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SYNTHETIC STUDIES IN DIHYDROINDOLE AND INDOLE ALKALOIDS

BY

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ABSTRACT

A synthetic approach toward the synthesis of vindoline (3) and a reinvestigation of the total synthesis of vincaminoridine (4) and epivincaminoridine (4a) is described.

The synthetic sequence involves alkylation with benzyl chloride of the monosodium salt of propane-1,3-diol to give γ-benzyloxypropanol (197). Treatment of 197 with thionyl chloride afforded benzyl-γ-chloropropyl ether (198). Alkylation of ethyl diethyl malonate with 198 provided diethyl γ-benzyloxypropylethyl malonate (134). Basic hydrolysis of 134 gave γ-benzyloxypropylethyl malonic acid (199), which upon decarboxylation provided 2-(γ-benzyloxypropyl)-butanoic acid (200). The monoacid (200) was esterified with ethanol to provide ethyl α-(γ-benzyloxypropyl)-butanoate (135). Alkylation of 135 with allyl bromide gave ethyl-α-(γ-benzyloxypropyl)-α-allyl-butanoate (201), which upon treatment with osmium tetroxide and sodium periodate gave ethyl α(γ-benzyloxypropyl)-α-(α-formylmethyl)-butanoate (140). Condensation of 140 with 6-methoxy tryptamine afforded the tetracyclic lactam (150). Lithium aluminum hydride reduction of the latter, followed by hydrogenolysis of the benzyl group gave two isomeric tetracyclic alcohols (204). These intermediates were converted via their mesylate derivatives to the quaternary salts (205), which upon treatment with potassium cyanide gave the isomeric cyanides (216). Acid hydrolysis of 216 gave the corresponding carbomethoxy derivative (151). Alkylation of 151

with methyl iodide provided dl-vincaminoridine (4) and dl-epivincaminoridine (4a). Transannular cyclization of the latter substances gave the pentacyclic aspidosperma-type system (195).

The degradation sequence involved acid hydrolysis of vindoline (3) to provide desacetyl vindoline (224), which upon catalytic hydrogenation gave desacetyldihydrovindoline (225). Pyrolysis of 225 afforded the ketone (86), which upon treatment with dimethyl carbonate provided the β-ketoester (226). Treatment of the sodium enolate of 226 with oxygen-hydrogen peroxide gave the hydroxy ketoester (227).

Treatment of desacetyldihydrovindoline (225) with N,N-thiocarbonyldiimidazole gave the thiocarbonate derivative (230), which upon desulfurization with Raney nickel afforded the unsaturated ester (231).

Catalytic hydrogenation of 231 gave the saturated ester (232), which upon treatment with lithium diisopropyl amide and oxygen-hydrogen peroxide provided the hydroxyester (234). The saturated ester 232 was converted to the alcohol derivative (237) by reduction with aluminum hydride. Oppenauer oxidation of 237 gave the aldehyde (238). Finally potassium permanganate oxidation of the unsaturated ester (231) gave 5-membered lactam (240), 6-membered lactam (241), N_a-formyl-5-membered lactam (242), and N_a-formyl-6-membered lactam (243).

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INTRODUCTION

1. General

In a broad sense, alkaloids are nitrogeneous bases which occur naturally in plants. They nearly always contain their nitrogen as part of a heterocyclic system and are often quite complex in structure. A particular alkaloid is usually restricted to certain genera and families of the plant kingdom, rarely being present in large groups of plants. In addition, the alkaloids usually show specific pharmacological activity. Alkaloids are most widely distributed among flowering plants, and rarely occur in animals, simple vascular plants, mosses, ferns, fungi and algae.[1]

More than three hundred thousand plant species are known, however, fewer than 35,000 have been examined for the presence of alkaloids. About 5,000 alkaloids have been isolated but many have been only partially characterized.[2,3]

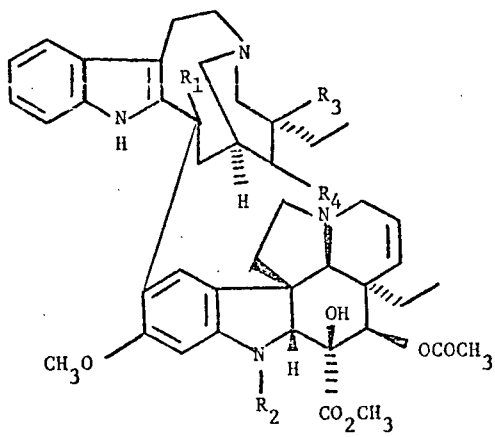
The curiosity of man regarding his natural world is evident in his earliest records, and it is no surprise, that his first exploration of the substances we now call natural products is lost in the mists of time. The exploration of the plants for chemical compounds of medicinal value has been going on for many centuries, herbalism and folk medicine, ancient and modern, have been the source of much useful therapy. A

new impetus was given to the search for medicinal plant principles by the discovery of the clinical usefulness of alkaloids of Rauwolfia species. This provided fresh stimulus for an enlarged and concentrated attack on the still unexplored botanical resources of the world. A great number of academic and industrial screening and evaluation programmes are now in existence, and many thousands of new plants are being studied. In recent years many new alkaloids have been discovered, and most of them have pharmacological activity. However, very few have successfully passed the screening and clinical testing in order to be accepted as useful drugs.

In the 1950's, the periwinkle plant Vinca rosea Linn. was studied because of its reputation as an oral hypoglycemic agent, but this has not survived scientific examination. However, extracts of this plant caused leukopenia rather than hypoglycemia in animals. Several research groups subsequently found such extracts to be active against experimental leukemia in mice.

Because of the interesting pharmacological activity of its alkaloidal fraction, Vinca rosea Linn. has been subjected to an examination as intense as has been recorded for the analgesics of the opium poppy, the muscle relaxants of curare, and the hypotensive-sedative agents of Rauwolfia. The importance of the alkaloids of Vinca rosea Linn. lies in potent antileukemic drugs, such as the dimeric alkaloids vinblastine (1) and vincristine (2). One of these, vincristine, is now being used clinically.[5] While no known drug, either natural or synthetic, is as effective as desired in the treatment of cancer, each new oncolytic drug, which has some positive effect in the treatment of clinical neoplasms, is another step of encouraging

progress. It has been shown that vinblastine and vincristine possess activity against lymphomas, Hodgkin's disease, lymphosarcoma, reticulum cell carcinoma, monocytic leukemia, and carcinomas of the breast.[6] However their application in clinical medicine is presently

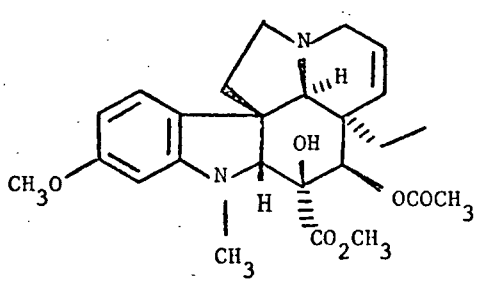


	R_1	R_2	R_3	R_4
(1)	CO_2CH_3	CH_3	OH	H
(2)	CO_2CH_3	CHO	OH	H

limited since vital information concerning the mode of action, the metabolism, and the structure-activity relationship of these drugs is lacking. The reasons for this situation are easily understood when one considers the present availability of these alkaloids. Vinca rosea Linn., from which these alkaloids are presently obtained, represents the only source of these drugs. The plant extract is extremely complex, with more than sixty alkaloids as natural constituents.

The difficult separation and the extremely low natural abundance of the above dimers makes these compounds available in minute amounts. This situation has prevented any detailed biological evaluation. In fact even for vinblastine (1) and vincristine (2) which are clinical drugs, there is virtually no information on the structural requirement for anti-tumor activity, specific mechanism of action, and metabolism. Another unanswered question is to what extent can the structure of the

dimeric system be modified either stereochemically or fractionally to provide novel drugs with increased pharmacological activity without side effects. It is clear that solutions for these problems, require a laboratory synthesis. A general and versatile laboratory synthesis of the monomeric indole and dihydro indole units and their relatives is essential for the dimer synthesis. Thus, the work described in this thesis is concerned with the chemistry of the indole and dihydroindole alkaloids of the Aspidosperma group, and with their biogenesis since this is relevant to the chemistry of the synthetic pathway employed. It is an approach toward the total synthesis of the dihydroindole unit present in vinblastine (1), namely vindoline (3), and related derivatives. As well, the total synthesis of dl-vincaminoridine (4) is presented, and represents an improvement over the sequence previously described.[7]



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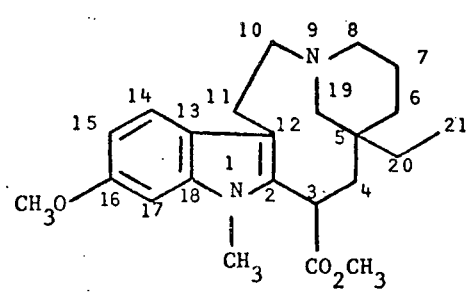

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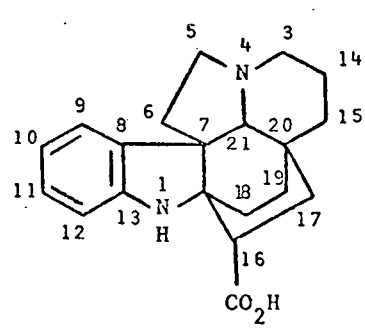

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Although a new numbering system, e.g. (5), has been proposed[8,9] for these alkaloids for the sake of clarity and consistency with previous publications we retain the numbering system originally employed in these families rather than adopting the more recent proposal.

2. Indole Alkaloids Biogenesis

Alkaloids are an extremely heterogeneous class of natural products. The structural types found in different classes of alkaloids are so diverse that it has been impossible to develop a single biogenetic hypothesis to include all alkaloids. Alkaloids have not been proven to have any definite function in plant metabolism, although several suggestions have been made. Some attempts were made to relate alkaloid formation to protein synthesis or to carbohydrate metabolism. Others have suggested, that they might serve as protecting agents against herbivorous animals.[10,11] The biogenesis of indole alkaloids, which are partially derived from the combination of tryptamine (6) and a C_9-C_{10} unit, has been the subject of ingenious speculation. Not only the biochemical origin of the C_9-C_{10} unit but its appearance in the well-known Corynanthe-Strychnos pattern (7) has provoked stimulating comment ever since Barger drew attention to a possible biogenesis of yohimbine in 1934.[15] Recent structural studies have increased the number of these alkaloids to more than 800, and two further main groups can be discerned in which the C_9-C_{10} unit (7) conforms to the Aspidosperma (8) and Iboga (9) skeletons.[1,16] Typical examples of these categories are ajmalicine (Corynanthe) (10), akuamicine (Strychnos) (11), vindoline (Aspidosperma) (3), and

catharanthine (Iboga) (12). In those alkaloids where only nine carbon atoms are present in addition to the tryptamine residue, it is invariably the carbon atom attached to C_{16} (see dotted line in structure 7, Figure 1) that is lost. The tryptamine portion of these molecules is derived *in vivo* from tryptophan,[17-20] and recent work has demonstrated that tryptamine is also an effective precursor of these alkaloids.[21-23] The remaining nine or ten skeletal carbon atoms appear in what at first sight seems a bewildering variety of different arrangements, but closer inspection allows the postulation that three main building units (7-9) are really involved to account for the vast majority of indole alkaloids (see Figure 1).

The biochemical building blocks for the C_9-C_{10} unit, prior to 1960, were obscure but a vigorous research program in several laboratories has provided considerable information in this direction. A brief summary of these experiments is now provided.

Origin of the C_9-C_{10} Unit

In contrast to the general agreement by different workers with regard to the "tryptophan" portion of the indole alkaloids, the biogenetic origin of the "non-tryptophan" or C_9-C_{10} unit, has been the subject of much controversy. Several theories have been proposed over the years. Barger[15] and Hahn[25] suggested in the early thirties that the indole alkaloids such as yohimbine (13, Figure 2) are formed by a Mannich reaction between tryptamine and 3,4-dihydroxyphenyl-acetaldehyde, or equivalent, and the condensed product (15) then undergoes a second Mannich reaction with formaldehyde to yield the yohimbinoid skeleton (16). To account for the carbomethoxy group in

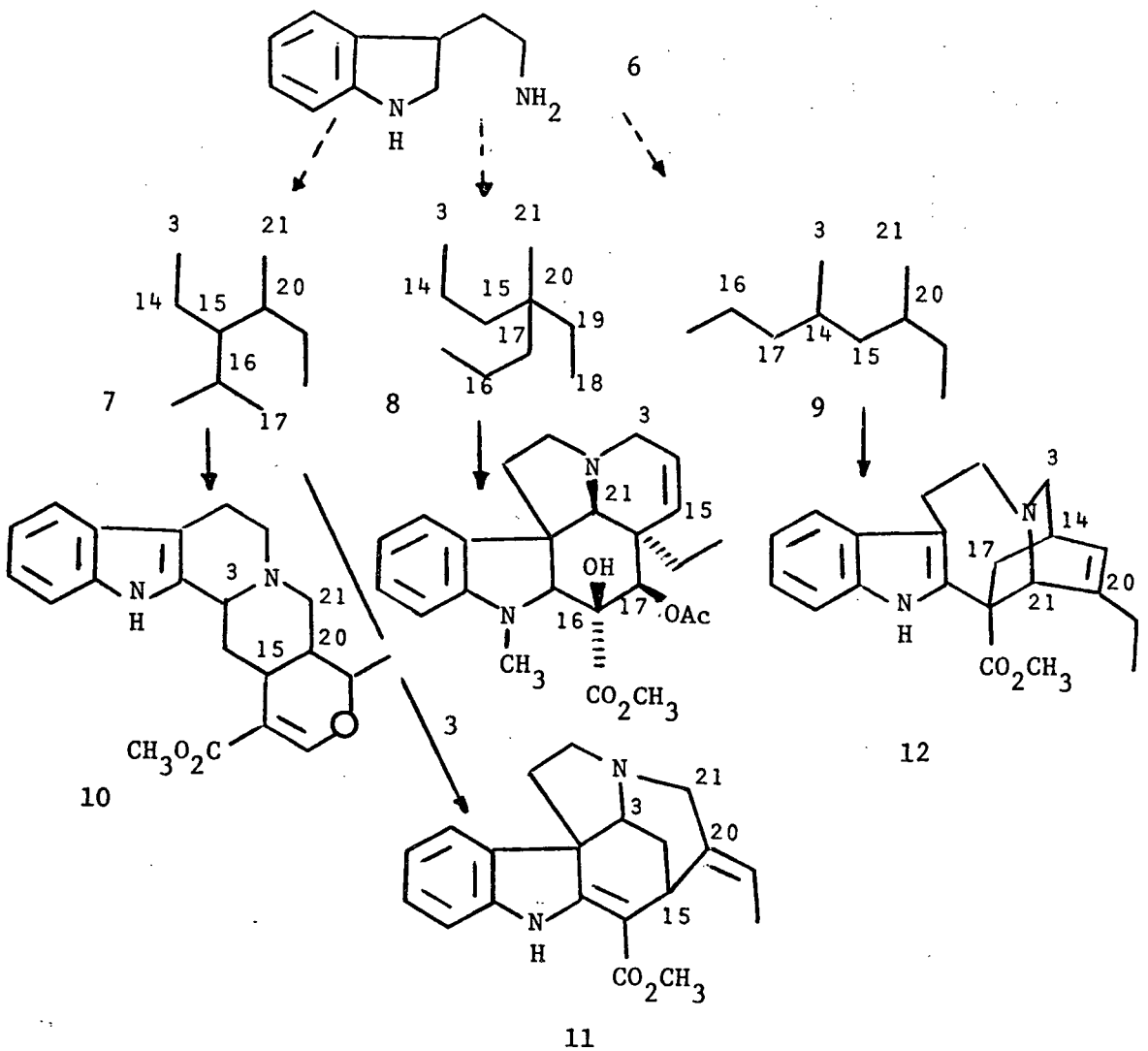

Figure 1. Proposed relationship between three main classes of indole alkaloids.

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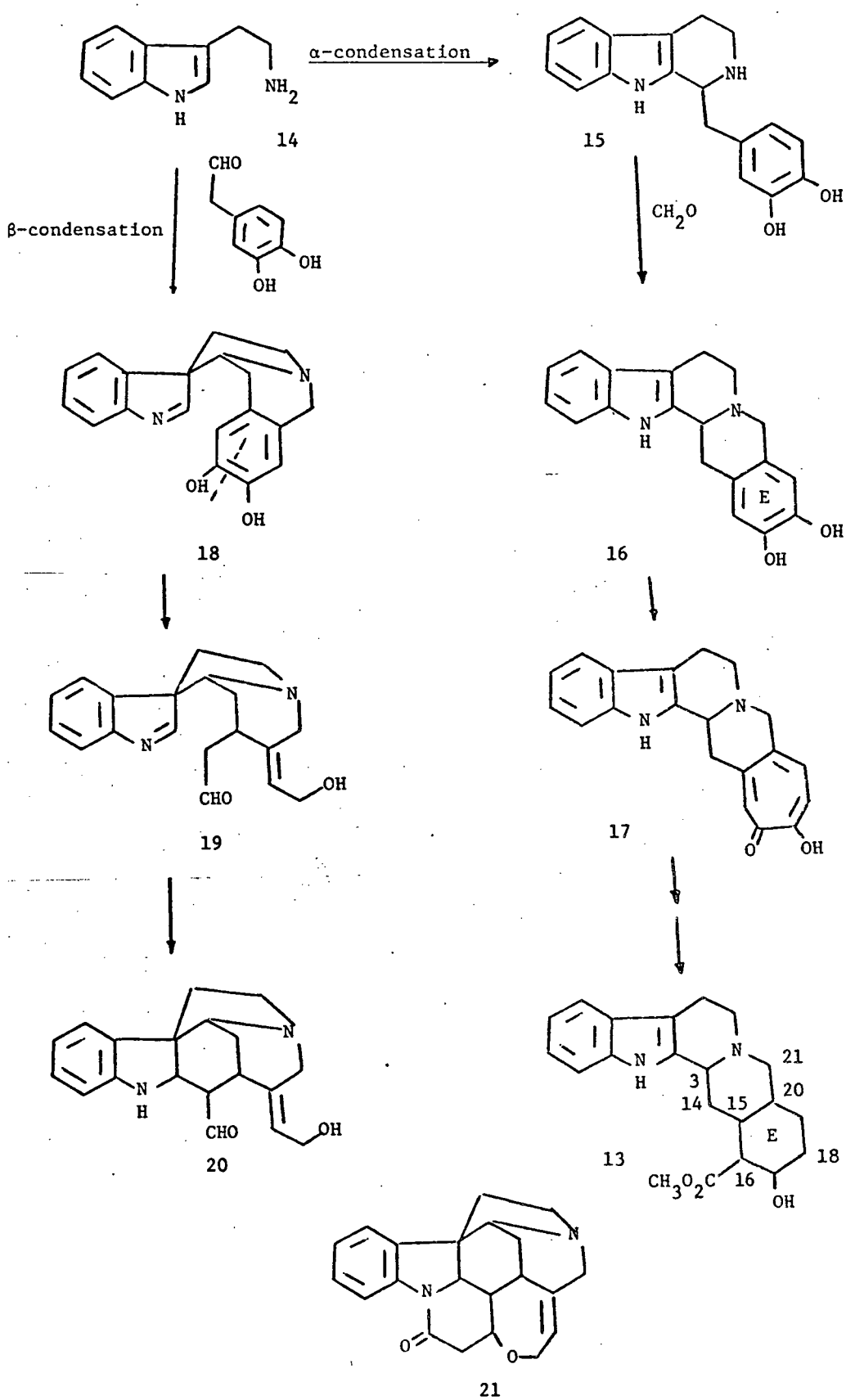
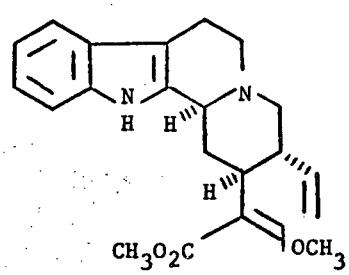


Figure 2. Barger-Hahn-Robinson-Woodward hypothesis.

ring E (13), it was suggested by Robinson[26] that it is also derived from formaldehyde through a tropolone intermediate (17). The Barger-Hahn hypothesis found support as a consequence of the ingenious suggestion by Woodward[27,28] in which instead of an α-condensation, there was condensation at the β-position with subsequent fission of the catechol type ring (18) to give strychnine (21) as indicated in Figure 2. This concept was applied to other indole alkaloids such as ajmalicine (10) and corynantheine (22). That hypothesis had a



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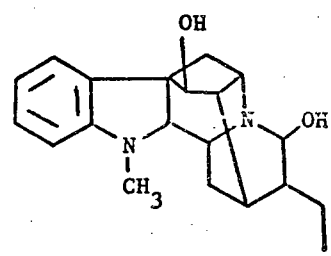

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number of deficiencies and in 1959 Wenkert[29-30] proposed an alternative, the prephenic acid hypothesis. In this hypothesis he suggested that the C_9-C_{10} unit is derived from carbohydrates via a pathway involving prephenic acid (24). Thus, the latter rearranges according to the scheme shown in Figure 3 to yield the key intermediate, the seco-prephenateformaldehyde (SPF) unit (29). This SPF unit can be incorporated into yohimibinoid alkaloids such as ajmalicine (10), corynantheine (22), and ajmaline (23). Although this hypothesis could account for the carboxyl group at the C_{16} position, and as the result of the stereospecific migration of the pyruvate side chain in compound (24), it also rationalizes the α-configuration of the hydrogen

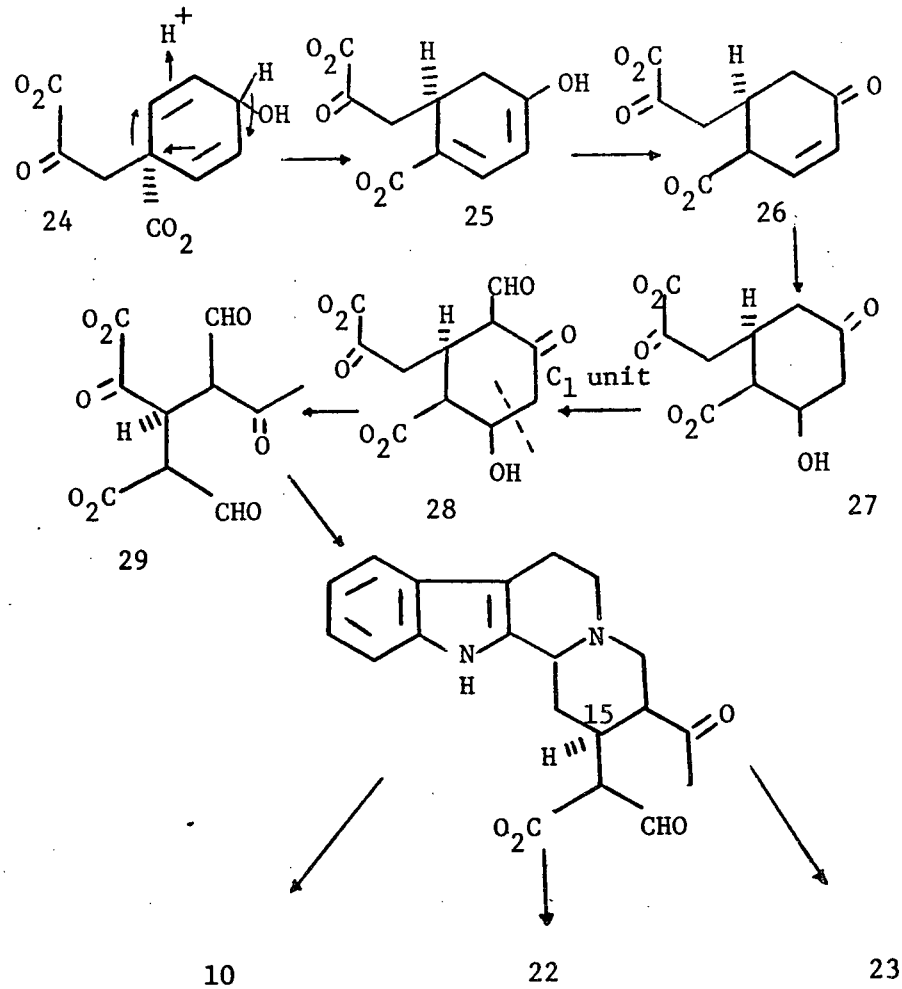


Figure 3. Wenkert's prephenic acid hypothesis.

atom at C_{15} found in yohimbine (13), and in almost all natural alkaloids, it did not stand up to experimental tests. Thus, feeding experiments with alanine-2-^{14}C to Rauwolfia serpentina plants, expected to convert the amino acid to prephenic acid and so on, showed that incorporation into ajmaline (23) was extremely poor. A third theory was then proposed by Schlitter and Taylor,[24] and Leete.[31-33] They suggested that three molecules of acetyl-coenzyme A condense to form a poly-β-keto chain (31) which by further condensation with formaldehyde and with carbonyl-coenzyme A, as indicated in Figure 4, forms an intermediate (32) very similar to Wenkert's SPF unit (29). This intermediate would then condense with tryptamine to give the various alkaloids in a manner similar to the latter part of Wenkert's hypothesis.

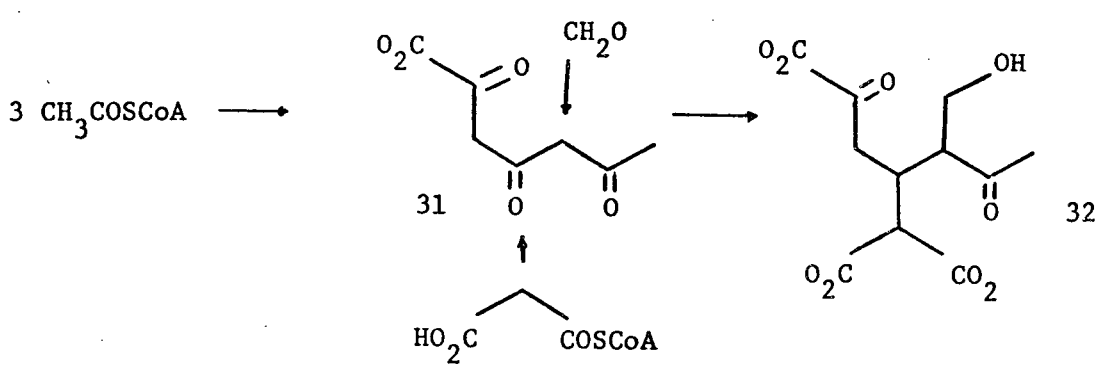


Figure 4. Schlittler-Taylor-Leete hypothesis.

The experimental support for this hypothesis[31,32] came by feeding sodium acetate-1-^{14}C (33), mevalonic-2-^{14}C acid (34), and tyrosine-2-^{14}C (35) to Rauwolfia serpentina plants. By administering acetate, radioactive ajmaline (23) equally labelled at C-3 and C-19 was isolated (Figure 5), but upon feeding mevalonic acid (34) or tyrosine (35), the ajmaline (23) isolated was completely inactive.

Battersby[34] also studied the biosynthesis of ajmaline (23) and found results in conflict to those of Leete, namely, incorporation of mevalonate took place.

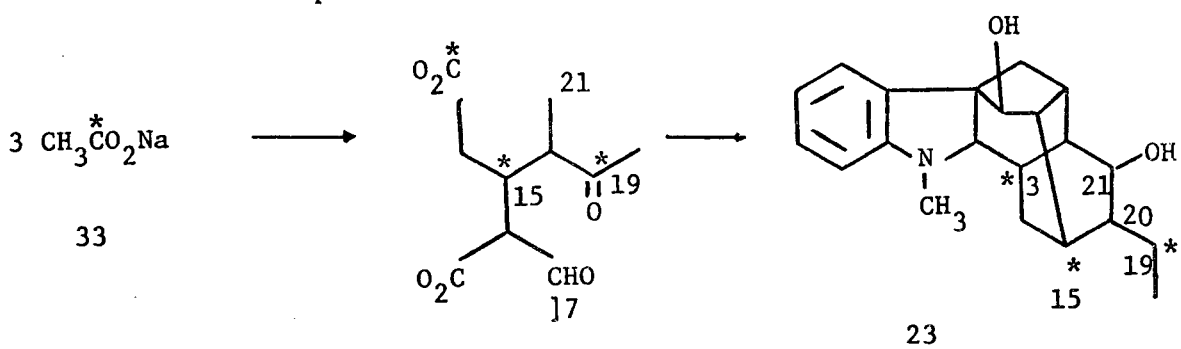
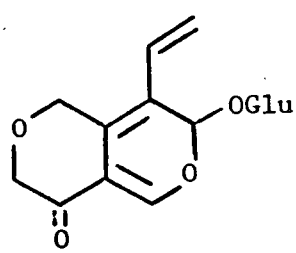


Figure 5. Incorporation of acetate into ajmaline.

Leete was unable to reproduce his original results,[19] and the failure to find radioactivity at C-15, as was expected from this hypothesis, as well as other results, would apparently exclude the acetate hypothesis.

The fourth hypothesis, the monoterpenoid hypothesis, was suggested independently by Thomas[35] and Wenkert.[36,37] The discovery of several non-alkaloidal glycosides such as gentiopicrin (36), bakankosin (37), and swertiamarin (38), and their remarkable similarities to the seco-prephenate-formaldehyde (SPF) unit, led them to suggest that the non-tryptophan portion of the indole alkaloids was monoterpenoid in origin. Thus on structural grounds, their derivation from non-nitrogeneous cyclopentanoid monoterpenes related to verbenalin (39), genepin (40), and asperuloside (41) would be readily explicable.



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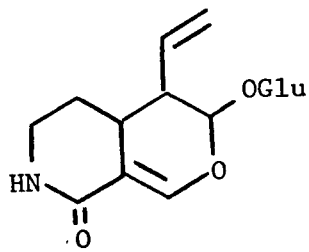

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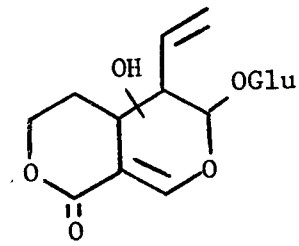

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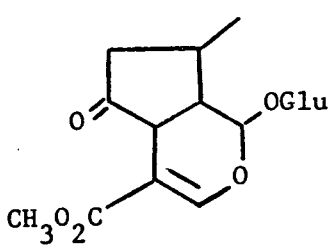

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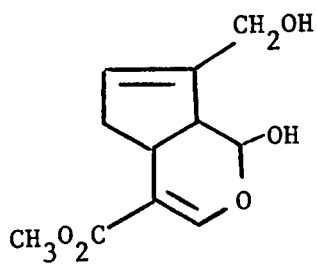

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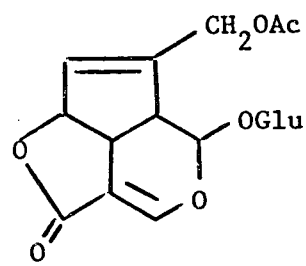

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Cleavage of the cyclopentane ring as indicated in Figure 6, would yield the carbon skeleton of the SPF unit having the required stereochemistry at C-15 (equivalent to C-4 in structure 45) in the indole alkaloids.

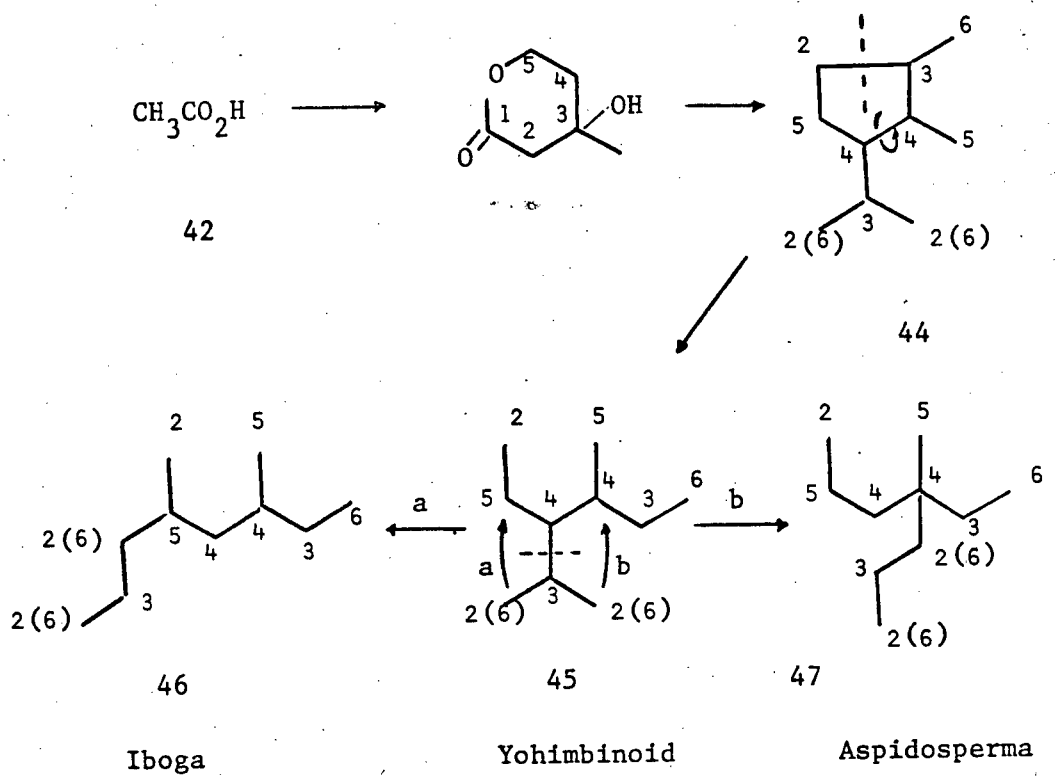


Figure 6. Thomas-Wenkert monoterpene hypothesis.

Many experiments published from different laboratories, particularly those of Arigoni, Battersby, Leete and Scott, provided results which gave a clear understanding of the proposed hypothesis. A recent review by Scott[14] provides a summary of these investigations. It has been proven beyond doubt that the first three hypotheses are incorrect. The only hypothesis in accordance with their findings is that due to Thomas and Wenkert, namely the monoterpene hypothesis. It was shown that all three types of the C_9-C_{10} unit (7), (8), and (9) are monoterpenoid in origin. Two residues of mevalonate (43) are used biologically in the normal head-to-tail combination of C_5 units, and the intermediacy of geraniol (48) was established.[38] The ^{14}C-labelling patterns were determined for representatives of the three types of alkaloids biosynthesized from labelled mevalonates which carried specific ^{14}C

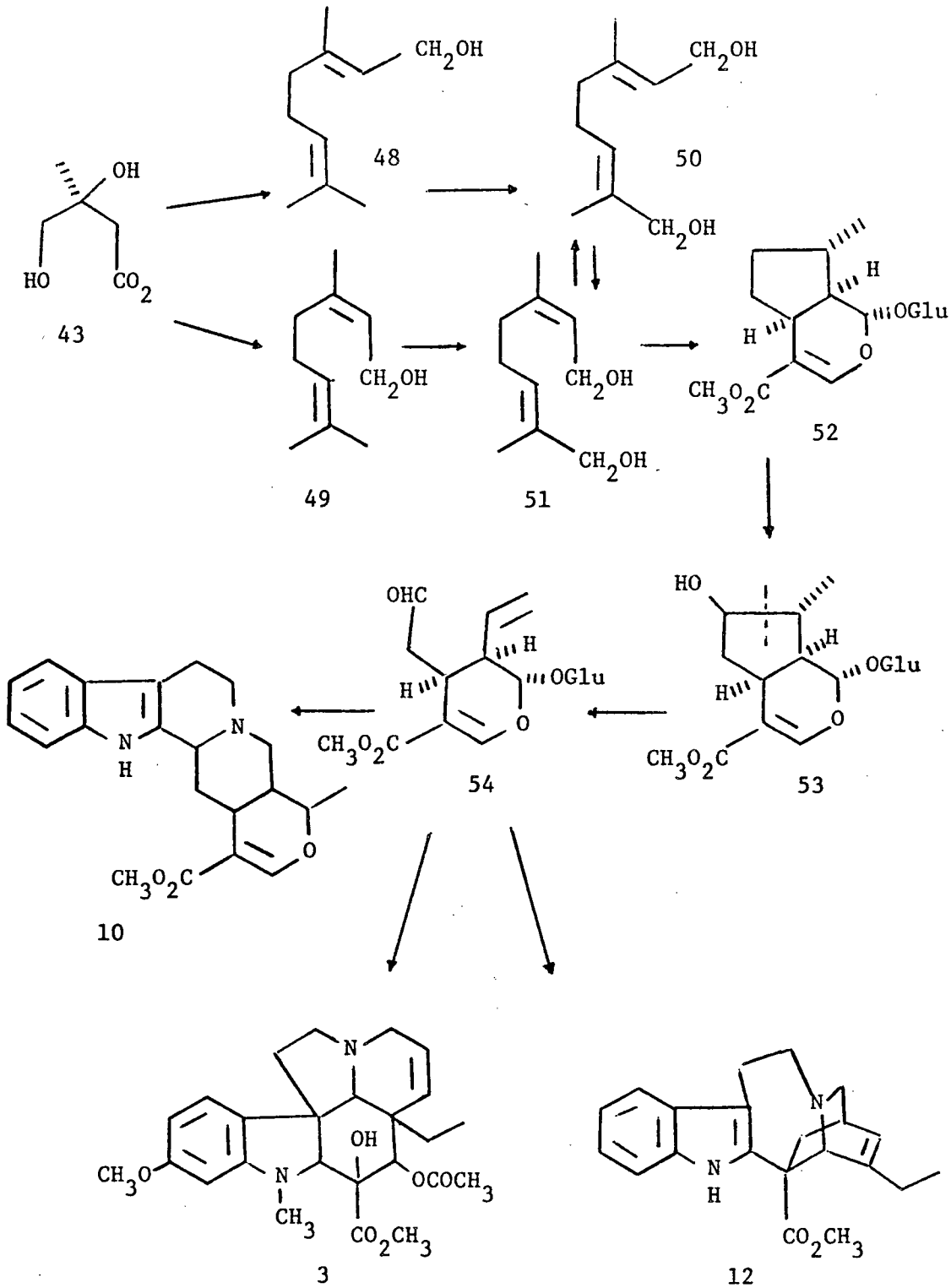
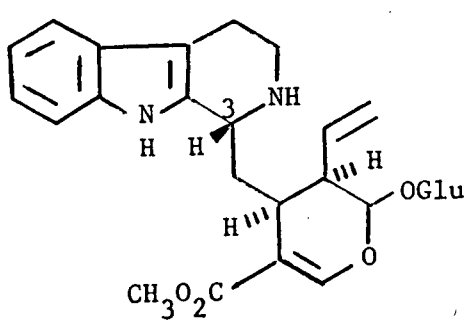


Figure 7. Biogenesis of the C_9-C_{10} unit of indole alkaloids.

labels at various known positions. The results were consistent with the proposal of Thomas and Wenkert, that 45 is generated by fission of some cyclopentane monoterpene (44) with rotation about the indicated single bond as shown in Figure 6. It was further recognized that unit 45 is structurally related to 46 and 47, and can be transformed into these other types by the bond fission and bond formation either at a or b, as shown in Figure 6, thus leading to the major families. The actual bio-intermediates corresponding to the cyclopentane monoterpene (44) were found to be loganin (53) and secologanin[39-42] (54). Desoxyloganin (52), hydroxygeraniol (50) and its cis-isomer hydroxynerol (51), were shown to be involved in the biosynthetic pathway.[43-46] Condensation of tryptamine with secologanin (54) opened the way to studies of the later stages of the biogenesis as discussed in the next section.

Later Stages of the Biogenesis

Two glucosides, vincoside (55) and isovincoside (56) (epimers at C-3) were obtained.[22,47] The stereochemistry at C-3 was uncertain. However, it has now been established by X-ray analysis that in vincoside (55) the hydrogen at C-3 has the β-orientation.[48,49]



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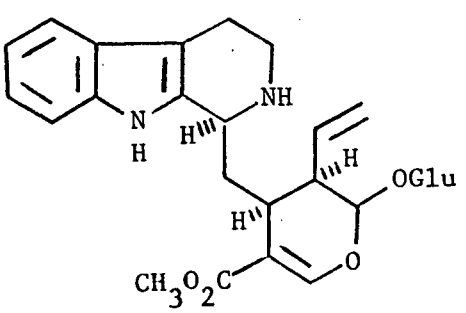

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Doubly labelled [ar-^{3}H,O-methyl-^{3}H]-vincoside was incorporated by Vinca rosea plants into all three types of indole alkaloids.[22,47] These results show that the main skeleton of vincoside (55) was built intact into the Corynanthe, Aspidosperma and Iboga systems. Isovincoside (56) was biologically inert and afforded no significant incorporations into any of the alkaloids.[50]

This result is unexpected from the point of view of the biosynthetic chemist because the configuration at C_3 of vincoside (55) is now opposite to that at the corresponding carbon of the next established intermediate, geissoschizine (57). It is not yet clear how this centre becomes epimerized in the biosynthesis but the following experimental facts have to be accounted for: Isovincoside (the C_3 epimer of vincoside) is not biologically active,[50] and the hydrogen at C_5 of loganin (54) (C_5 of loganin corresponds to C_3 of vincoside) is completely retained in the biosynthesis of the three main classes of indole alkaloids,[50] represented in Figure 7 by vindoline (3) (Aspidosperma), catharanthine (12) (Iboga), and ajmalicine (10) (Corynanthe).

Simultaneously and independently, vincoside (55) and isovincoside (56) were isolated from Vinca rosea,[22] and isovincoside (56) from Rhazya stricta.[51]

Before discussing the biosynthetic pathway beyond vincoside (55), it seems appropriate at this stage to consider two important points based upon structural relations at the alkaloidal level. Wenkert[29,36,37] recognized that there must be biosynthetic significance in the fact that there is almost complete stereochemical constancy at C_{15} in the

Corynanthe-Strychnos group, and it was proposed that the Strychnos, Aspidosperma and Iboga alkaloids could be derived from the Corynanthe system. A possible route from the Corynanthe to the Strychnos systems was put forth as shown in Figure 8 (pathway A). Later a second pathway was proposed by Scott[52] (Figure 8, pathway B), but no direct experimental evidence has yet been established to distinguish between these two mechanistic speculations.

Wenkert[29,36,37] had also proposed that the Strychnos system (67) was converted to both the Aspidosperma (71) and Iboga (72) types, as shown in Figure 9, via the cyclization of their iminium derivatives.

Returning to the pathway beyond vincoside (55), formation of the Corynanthe family requires no skeletal rearrangement and is regarded as involving enzymatic cleavage of the glucosidic residue followed by reductive condensation of the nascent aldehyde (73) as shown in Figure 10, Geissoschizine (57), corynantheine (22) and its aldehyde (75), and ajmalicine (10) could be reached via plausible steps.[22] Further evidence came from examination of the alkaloid content of seedlings of Vinca rosea, a technique used to obtain information about the sequence of alkaloidal transformations. It was found by Scott[53] that Corynanthe-type systems appeared before detectable amounts of Aspidosperma and Iboga alkaloids were formed. Direct feeding experiments[53-55] showed that the corynantheine aldehyde (75) was not significantly incorporated. However geissoschizine (57) was found to specifically label the Vinca rosea alkaloids including the Strychnos alkaloid akuammicine (11). These results indicated biological conversion of the corynanthe system of geissoschizine (57) into the

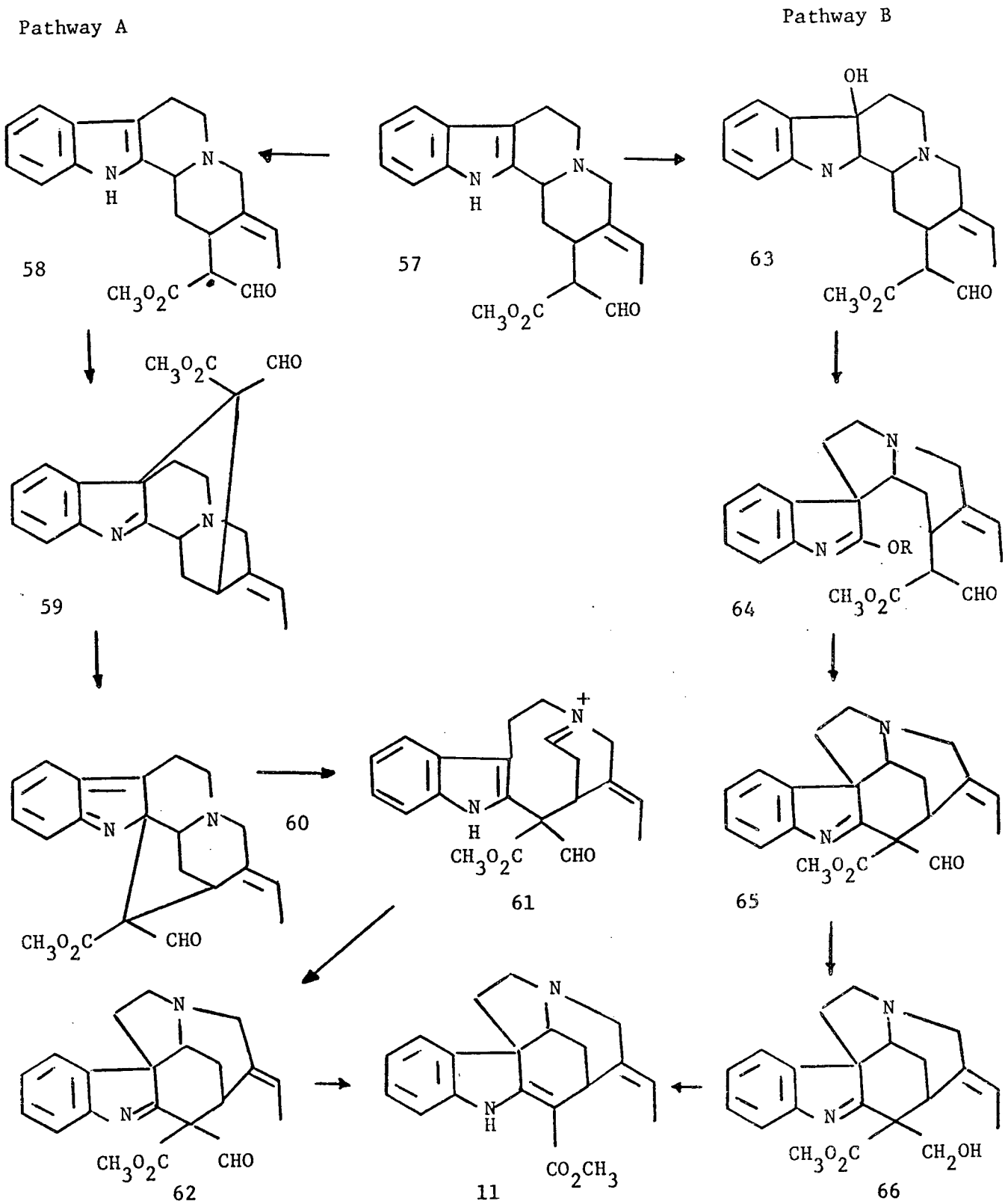


Figure 8. Proposed biogenesis of the Strychnos family.

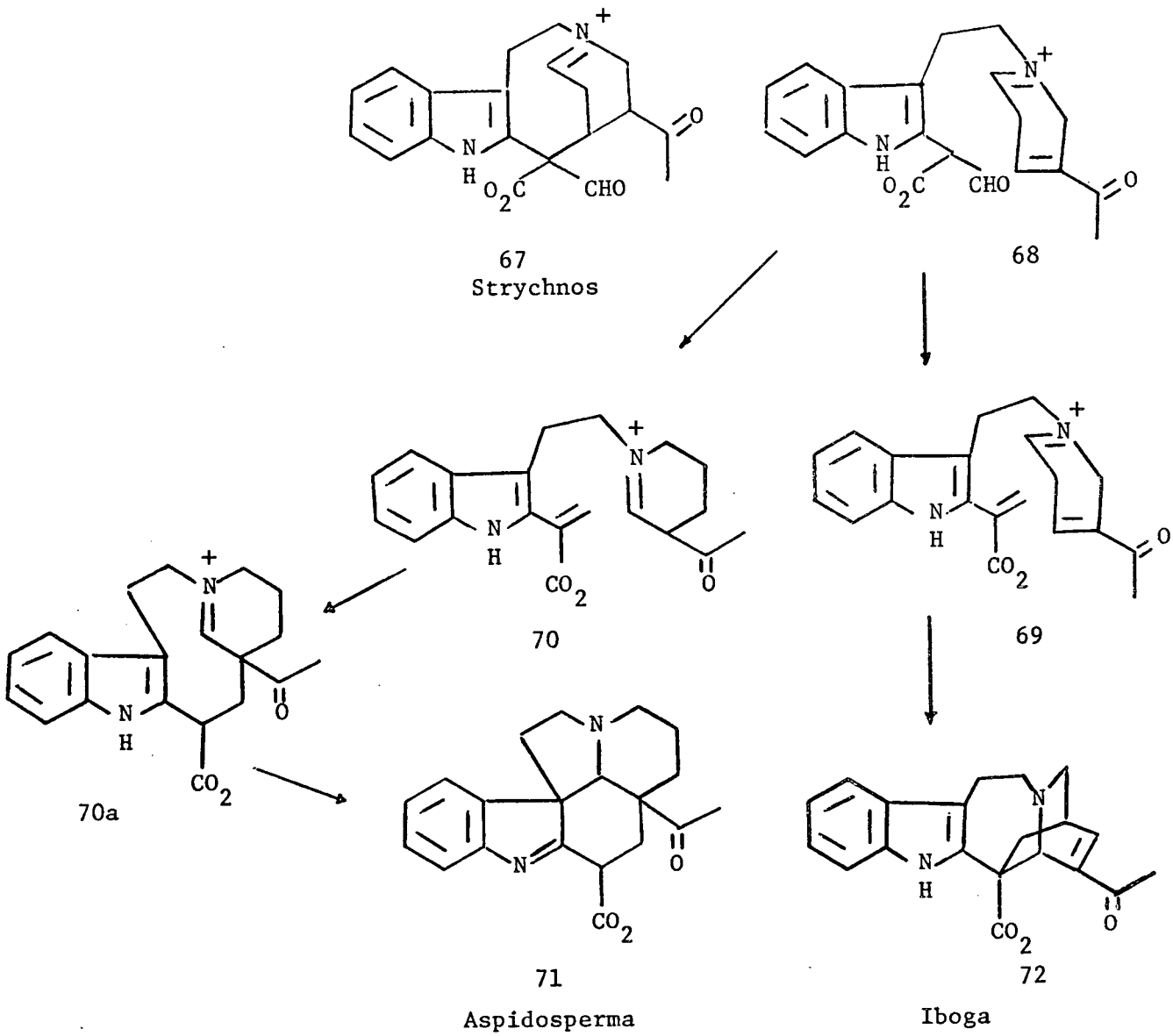


Figure 9. Wenkert's postulate for the biogenesis of the Aspidosperma and Iboga alkaloids.

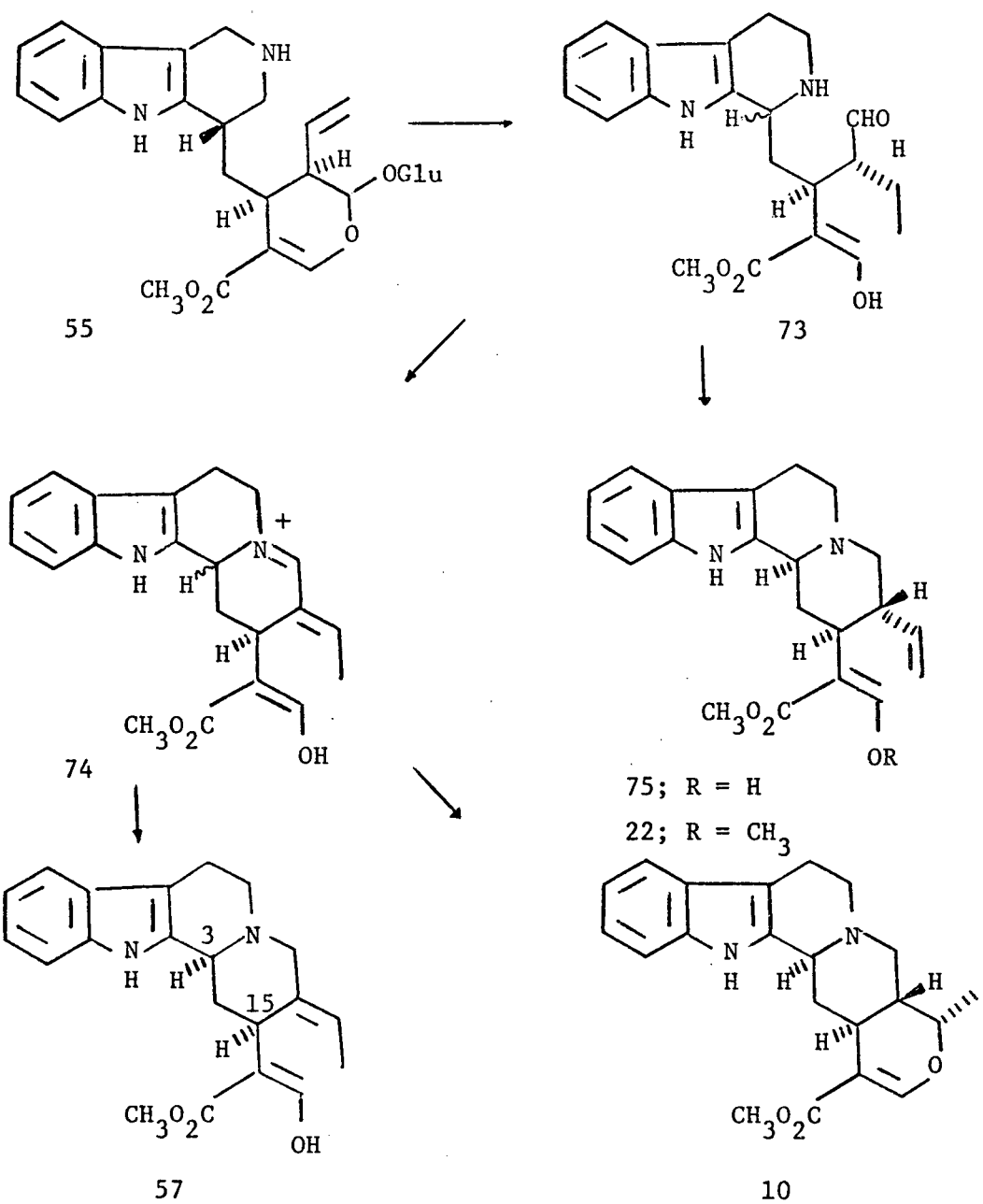


Figure 10. Biogenesis of the Corynanthe family.

rearranged Aspidosperma and Iboga skeletons, and that geissoschizine underwent an α,β-rearrangement to generate the Strychnos skeleton of akuammicine (11). Further evidence for the α,β-rearrangement came from incorporation of [ar-^{3}H]-vincoside (55) into akuammicine[54] (11).

The isolation of stemmadenine (77), tabersonine (81) and preakuammicine (76) from young Vinca rosea seedlings,[53,55] (the first two were known from other sources, the last was new) gave further indication of the biosynthetic pathway beyond geissoschizine (57). Thus the status of the first two as late intermediates was established by showing that [O-methyl-^{3}H,11-^{14}C]-stemmadenine (77) was incorporated intact into tabersonine (81), vindoline (3), and catharanthine (12). Tabersonine (81) was also incorporated into vindoline (3) and catharanthine (12). Kutney[23] has confirmed the latter result by feeding [ar-^{3}H]-tabersonine to Vinca rosea and isolating radioactive vindoline (3) and catharanthine (12). These results support the sequence stemmadenine (77) → tabersonine (81) → catharanthine (12). At present there is no conclusive evidence as to the relationship between stemmadenine (77), preakuamicine (76) and akuammicine (11) or as to whether stemmadenine (77) appears on the pathway as a precursor to the Strychnos skeleton. However, mechanistic considerations as well as the timing of stemmadenine's appearance in growing seedlings[53,55] suggest that it follows, or is in equilibrium with the Strychnos system (76) as outlined in Figure 11.

Having reached the Strychnos family (76), let us now follow the series of biological transformations along the biosynthetic pathway which led to the remaining Aspidosperma and Iboga families.

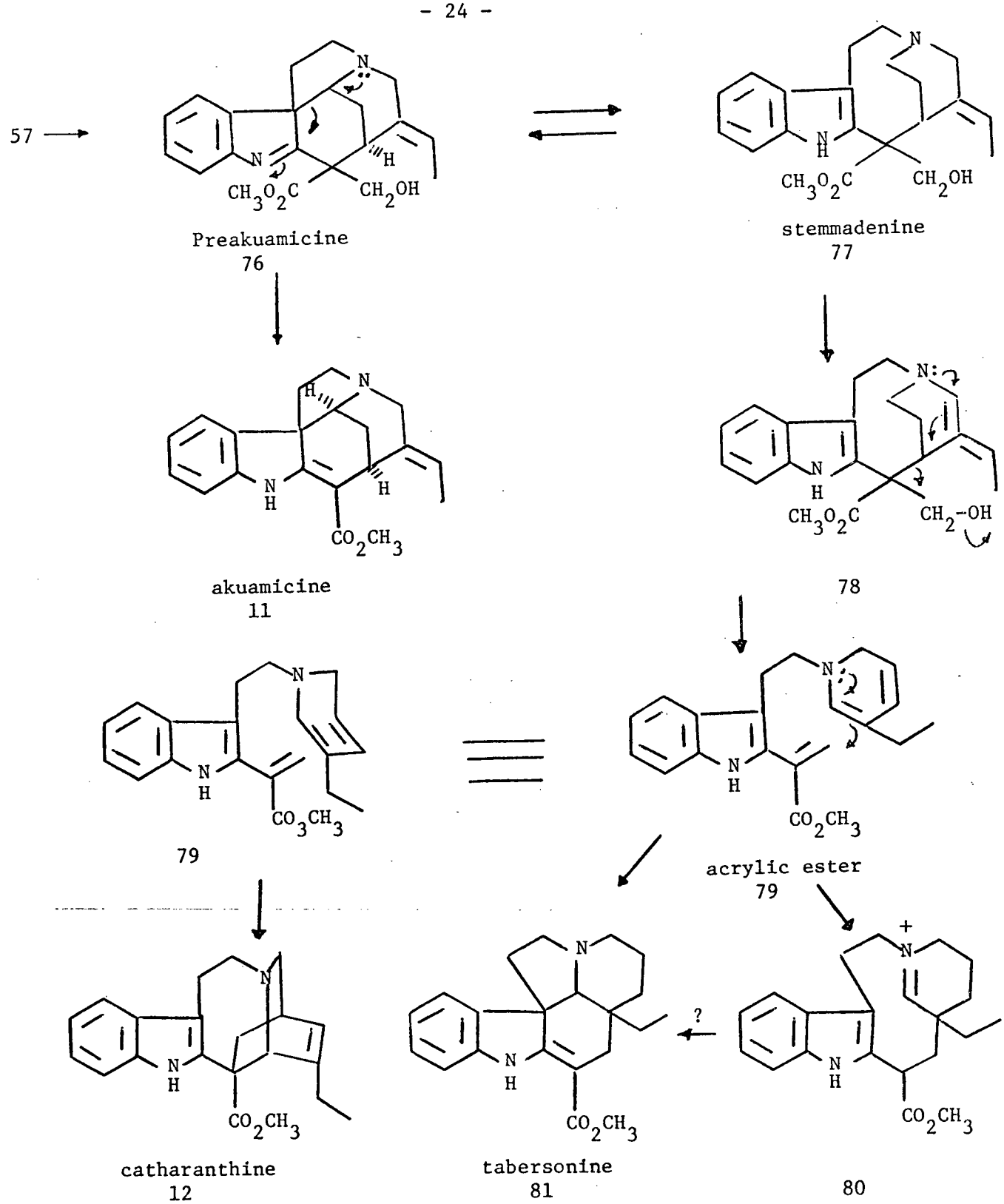
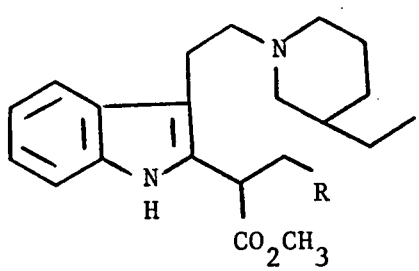
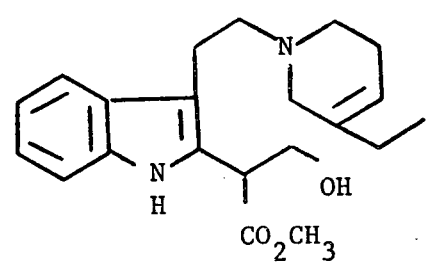


Figure 11. Biogenesis of the Strycnos, Aspidosperma, and Iboga systems.

A very interesting mechanism has been independently proposed by Scott[56] and Kutney[57] which involves skeletal fission and new bond formation as outlined in Figure 11. Thus isomerization of the exocyclic double bond of stemmadenine (77) to yield intermediate 78, could allow fragmentation to the acrylic ester (79) which can then ring close in the two indicated ways leading to tabersonine (81) and catharanthine (12). It is appropriate to note the similarity between the acrylic ester (79) and Wenkert's acrylic ester (70) contained in his original proposal.[36] Support for the formation of the acrylic ester (79) in the biological cleavage process came from the isolation of tetrahydrosecodine (82) from Rhazya stricta,[58,59] tetrahydrosecodin-17-ol (83) and the corresponding dihydro compound (84) from Rhazya orientalis.[58-60]



82; R = H
83; R = OH



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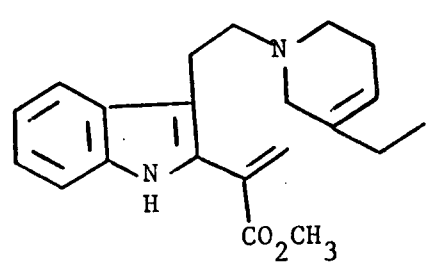


85

Further support for the acrylic ester (79), came from various plant investigations in Kutney's group.[61-64] Thus when [ar-^{3}H]secodin (85) (different from the proposed intermediate 79 only in the oxidation

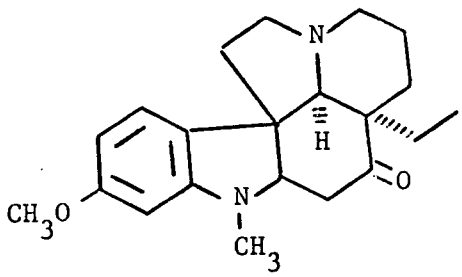
level of the piperidine ring) was fed to the V. rosea, V. minor and Aspidosperma pyricollum, low but definite incorporations were observed in the appropriate alkaloids present in these plants.

Furthermore, different labelled forms of secodine (85) were synthesized and fed to these plants.[61,62,64] These results showed that the secodine skeleton was incorporated intact and for the purpose of this discussion it is sufficient to indicate that the sequence 79 → vindoline (3) is now reasonably well established. It was the consideration of the later stages of the biosynthetic pathway, particularly the conversion 80 → 81 for example, which stimulated the synthetic plan which was chosen for vindoline (3).

3. Structure and Stereochemistry of Vindoline

Vindoline (3), is the major alkaloid in the leaves of the Apocynaceous plant Vinca rosea Linn., and was first isolated in 1958 by Kamat and co-workers,[65] who incorrectly assigned it the empirical formula $C_{27}H_{34}N_2O_6 \cdot 1/2H_2O$. Gorman et al.[66] subsequently determined the correct formula of the alkaloid, $C_{25}H_{32}N_2O_6$, and the base was shown to be pentacyclic and to contain an isolated double bond. Five of the oxygens were found to be present as hydroxyl, carbomethoxyl and acetoxyl functions. Careful comparison[67,68] of the mass spectra of ketone 86 obtained by pyrolysis of the hydrochloride of dihydrovindoline, and dihydrovindoline with that of N-methyl diacetylaspidospermine (87), indicates the presence of the latter ring system in vindoline (3) and its derivatives, since in all three compounds intense peaks were found at m/e 124, 174, 188 and 298. Further consideration of the nuclear magnetic resonance, mass and ultraviolet

spectra of vindoline (3) and its derivatives, led to the proposal of structure 88 for vindoline. Vindoline (3) and desacetylvindoline have



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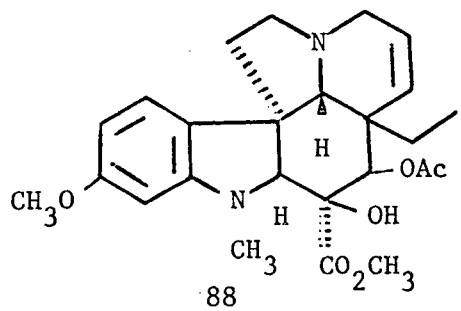

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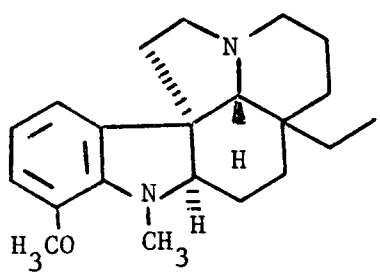


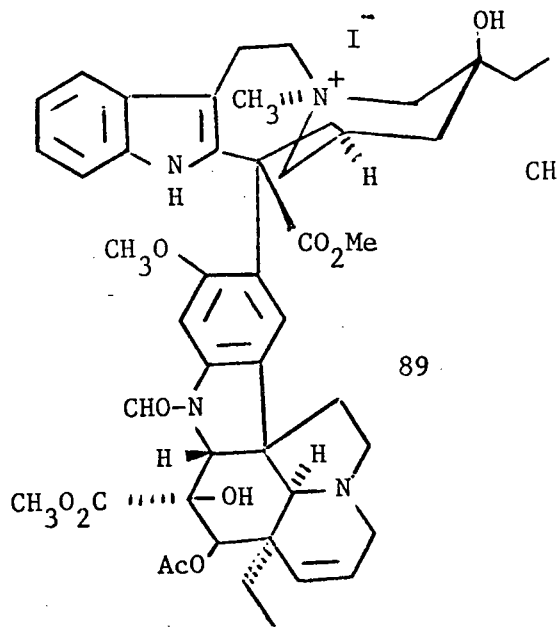
87

also been obtained from vincaleukoblastine,[68,70] leurosidine,[71] or leurosine[69] upon acid cleavage (concentrated hydrochloric acid, stannous chloride, tin-metal under reflux).

These dimeric indole-indoline alkaloids also present in the leaves of Vinca rosea Linn. (Catharanthus roseus G. Don), are powerful oncolytic agents whose biological properties have been thoroughly reviewed.[72] These compounds represent examples of indole-indoline alkaloids in which the indole moiety is linked through a C-C bond to the aromatic ring of the dihydro-indole portion of the molecule.

Finally an X-ray analysis[73] of vincristine methiodide (89) permitted the complete elucidation of the structure, stereochemistry and absolute configuration of vincaleukoblastine (1) and hence of vindoline (3), as a result of the known relationship[69] among these

molecules.



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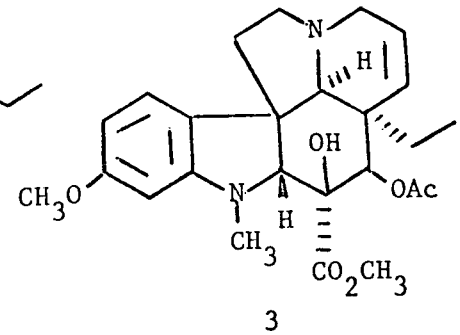


3

4. Syntheses of the Aspidosperma System

Although many alkaloids of complex structures belonging to the Aspidosperma family have been described,[74] the synthetic works are limited to several kinds of alkaloids and related compounds constituting the fundamental skeleton. The first total synthesis of the natural Aspidosperma system was reported by Stork.[75] In his successful synthesis of dl-aspidospermine (99), as well as that of dl-quebrachamine (101) (Figure 12) he utilized the Fischer indole synthesis[76] in order to achieve the construction of the desired pentacyclic skeleton. The required tricyclic intermediate 97 was obtained by employing the pyrolidine enamine reaction, which had previously been developed in Stork's laboratory, in the early stages of the sequence.

The stereochemistry of the various bicyclic and tricyclic intermediates utilized was left undefined since the authors felt that this stereochemical ambiguity was not significant here. The indolenine

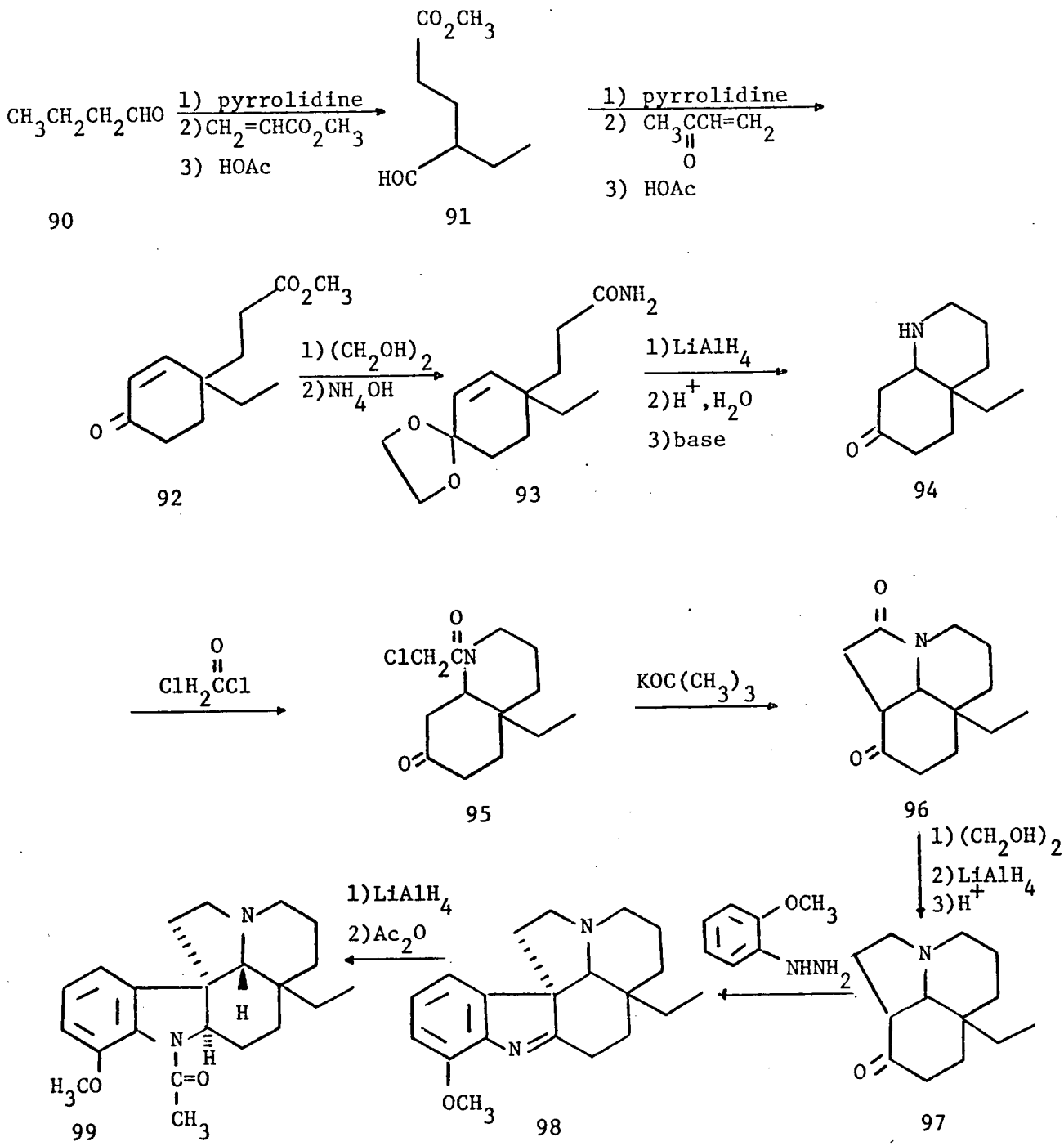
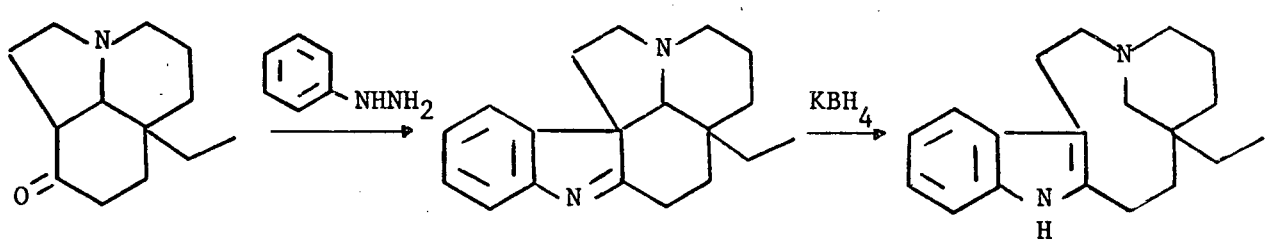


Figure 12. Stork's total synthesis of dl-aspidospermine.

98 being formed under equilibrating conditions would lead to equilibration at the two centers marked by asterisks via a reverse Mannich reaction.[77] The most stable relative arrangement of the two asymmetric centres of compound 98 would thus be expected to result whatever the stereochemistry of the intermediates or the detailed course of the indolenine cyclization process. Thus this most stable arrangement should coincide with that of dihydroaspidospermine (98). The identity of the synthetic material (99) as dl-aspidospermine was established by the identity of the infrared and mass spectra with those of the natural alkaloid.

Cyclization of the phenylhydrazone of 97 to a mixture containing 100, followed by reductive cleavage with potassium borohydride[78] permitted extension of the synthesis to yield dl-quebrachamine (101).



97 100 101

Another total synthesis of aspidospermine[79] (99) was reported by Ban and co-workers (Figure 13). Although the later steps were identical to those of Stork's synthesis,[75] these workers developed a different pathway to a bicyclic intermediate (107) which has the same planar structure as the corresponding one (94) prepared by Stork. However, the physico-chemical properties for the compound available from Ban's work, were quite different from those obtained by Stork,

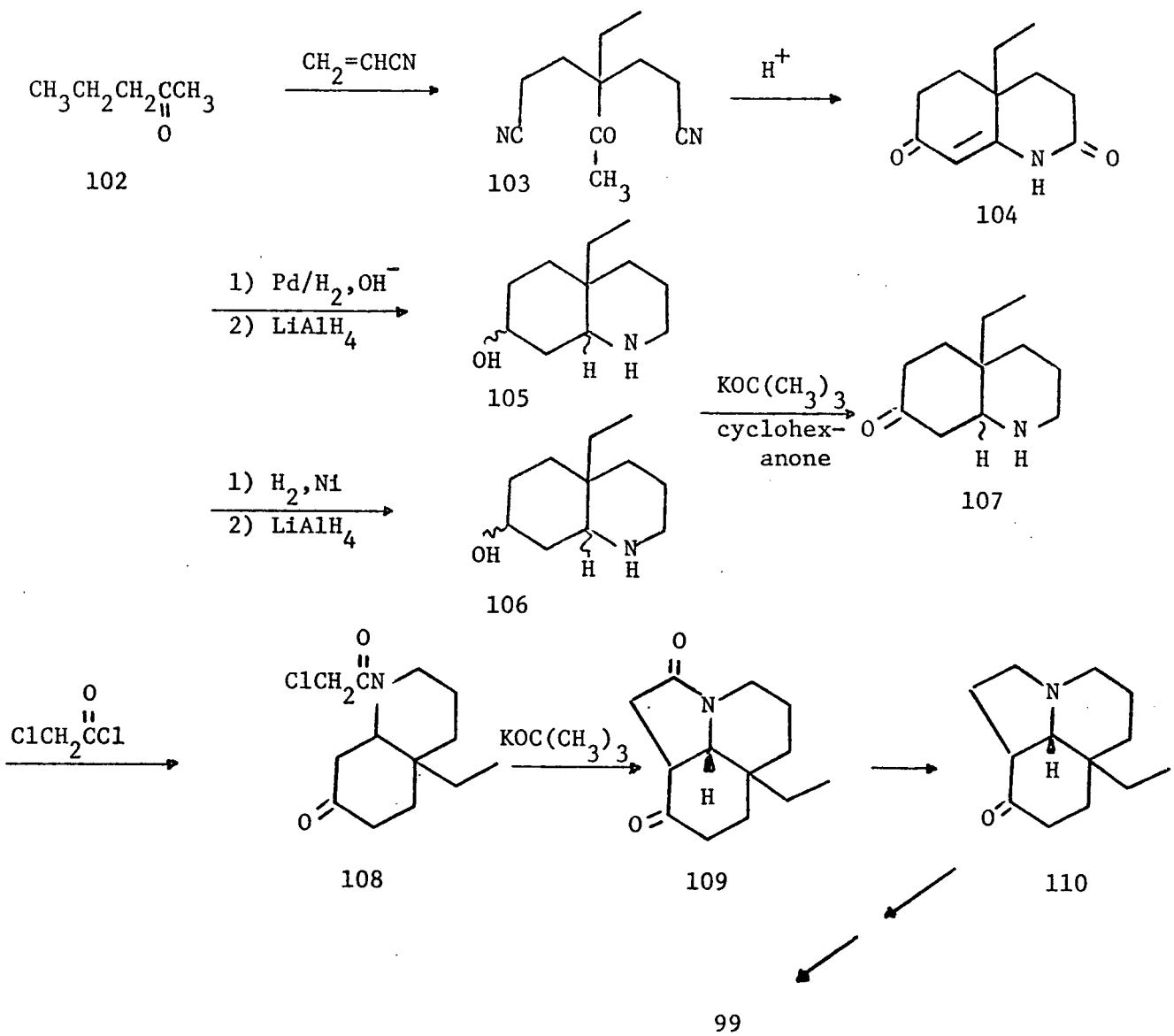
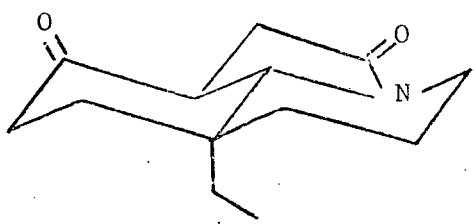


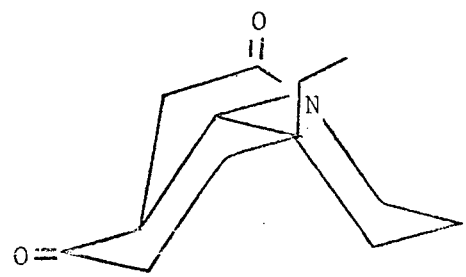
Figure 13. Ban's total synthesis of dl-aspidospermine.

and hence the following results led the authors to propose that they were diastereoisomers.

Thus conversion of 107 to 110 and the latter to dl-aspidospermine (99) in the same manner as indicated previously in the Stork synthesis (94 to 99) provided conclusive evidence that a series of intermediates was produced which were diastereomeric to those of Stork's synthesis. Moreover conformational analyses of the intermediates 96 and 109 allowed the assignment of the conformational structures of 96a and 109a.



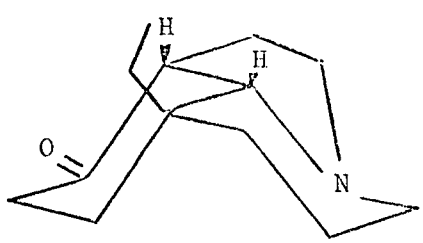
96a



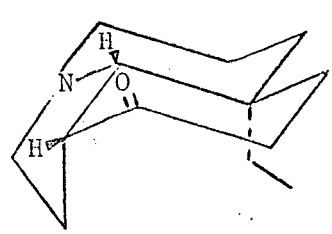
109a

The fact that dl-aspidospermine (99) was synthesized from either 97 or 110, supports Stork's proposal that equilibration occurs during the Fischer indole cyclization to the indolenine.[75]

Kuehne[80] has also synthesized the key tricyclic intermediate 97 with the stereochemistry as indicated in 97a and 97b.



97a



97b

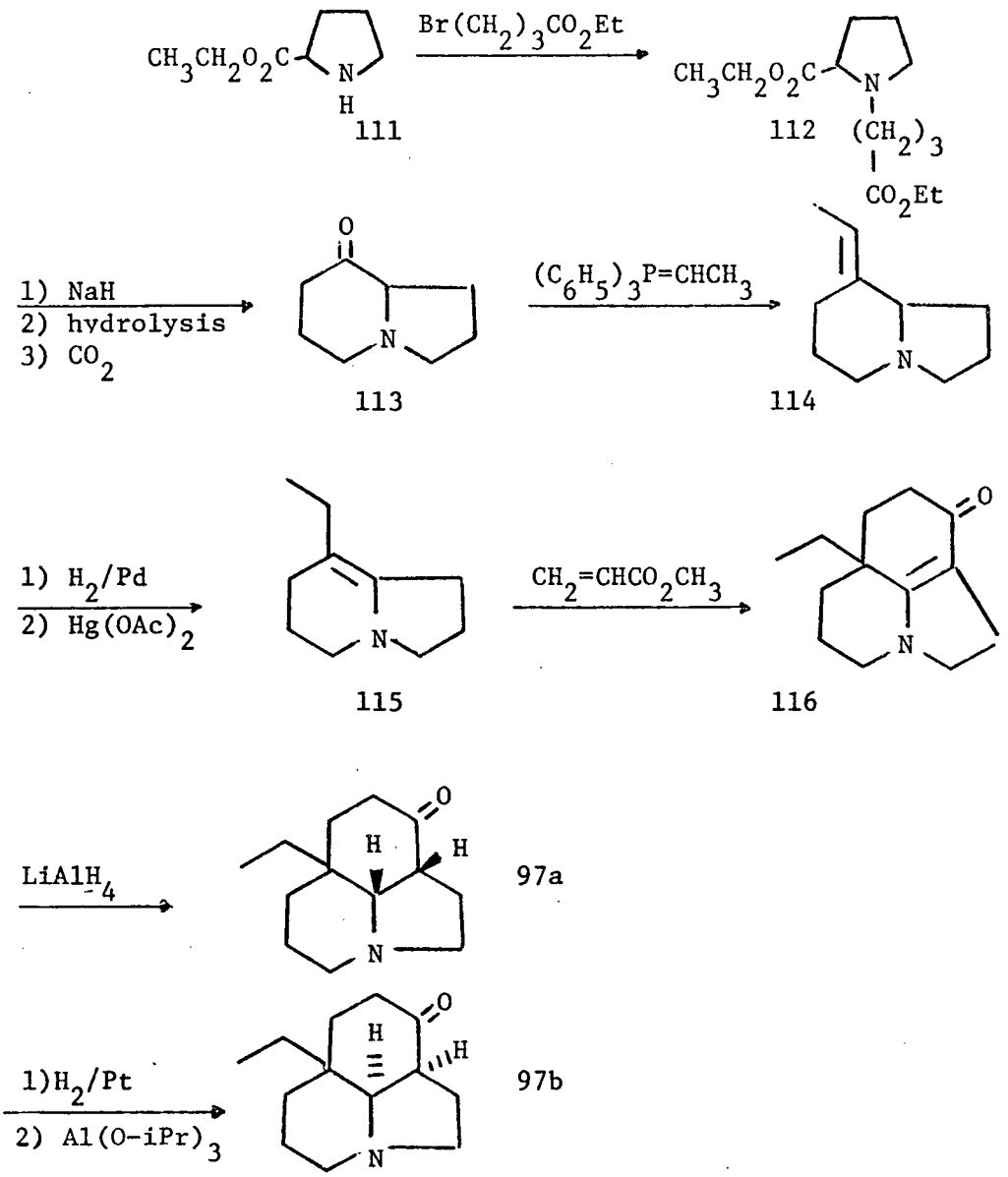
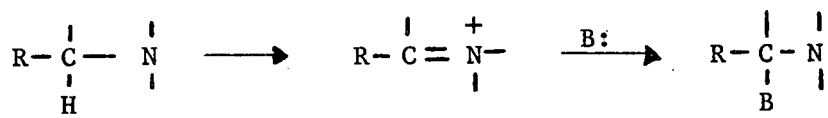


Figure 14. Kuehne's synthesis of the tricyclic aminoketone.

In his approach the starting material proline ethyl ester (111) was converted into compound 116 through the sequence shown in Figure 14. The enone (116) was then reduced to the desired tricyclic intermediate (97) either with lithium aluminum hydride or by catalytic hydrogenation followed by Oppenauer oxidation of the resulting amino alcohol.

Kutney and co-workers[83-87] undertook a totally different approach toward the synthesis of Aspidosperma and related alkaloids, placing emphasis on generality and versatility.

The reaction selected for this purpose involves the creation of an electrophilic center (iminium salt) in the original amine, followed by reaction of the latter intermediate with a nucleophile (B:) to yield the desired product, as indicated below.



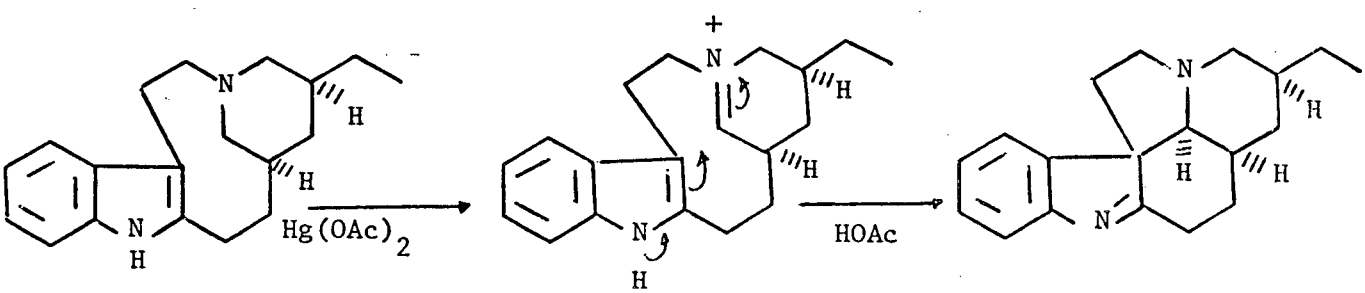
88 89 90

The participation of imines as possible intermediates in alkaloid biosynthesis has long been recognized.[81] Postulates on the possible biosynthetic pathways of indole alkaloids have proposed these imine intermediates[36] and their use in the synthesis of some indole alkaloids had already been demonstrated.[82] Thus, Kutney in his approach[83-87] utilized a transannular cyclization reaction of an appropriate nine-membered ring intermediate and was able to show that cleavamine (120) and quebrachamine (101) ring systems could be cyclized in a completely stereospecific manner to yield the necessary stereochemistry of the natural systems shown in 123 and 125. He has also shown that the

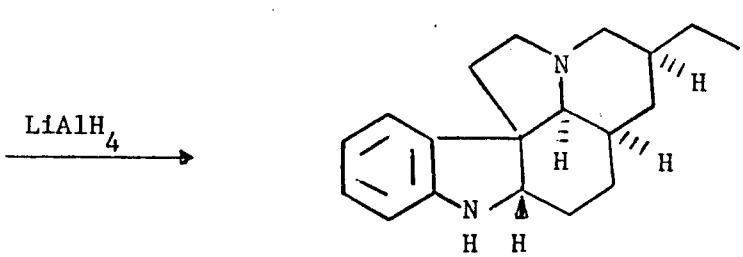
introduction of a carbomethoxy group at the appropriate position on the above systems (126 and 131) provided an alteration in the course of the cyclization process and an entry into the Aspidosperma (128) and Iboga alkaloids (130) (Figure 15). In his total synthesis[88,89] of dl-quebrachamine (101) and dl-aspidospermidine (125), he generated the nine-membered ring system by means of a reductive cleavage in the last step of the synthesis (Figure 16). In view of the previous conversion of dl-quebrachamine (101) to dl-aspidospermidine (125) via a transannular cyclization process he has also completed the total synthesis of the latter.

Further modifications of the synthetic sequence[90] in which tryptamine was condensed with the aldehydo ester (140) provided a considerable improvement over the sequence previously reported.[88] Moreover the versatility of this synthetic approach allowed the first total syntheses of a series of monomeric alkaloids in the Vinca family.

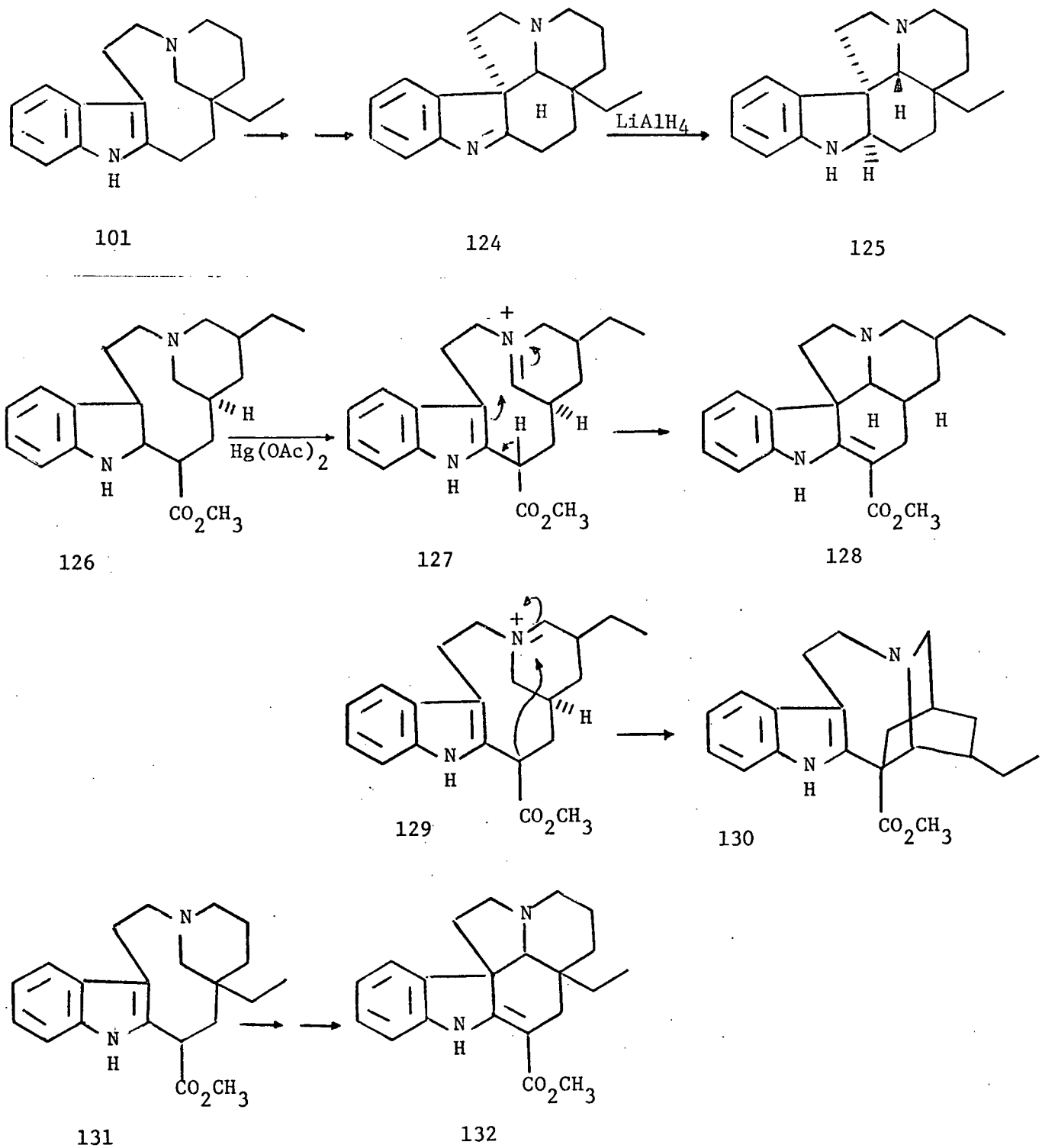
The quaternary mesylate (139) was a key intermediate. Thus treatment of 139 with potassium cyanide in dimethyl formamide afforded



120 12 122



123



101 124 125

126 127 128

129 130

131 132

Figure 15. Kutney's transannular cyclization of the cleavamine and quebrachamine systems.

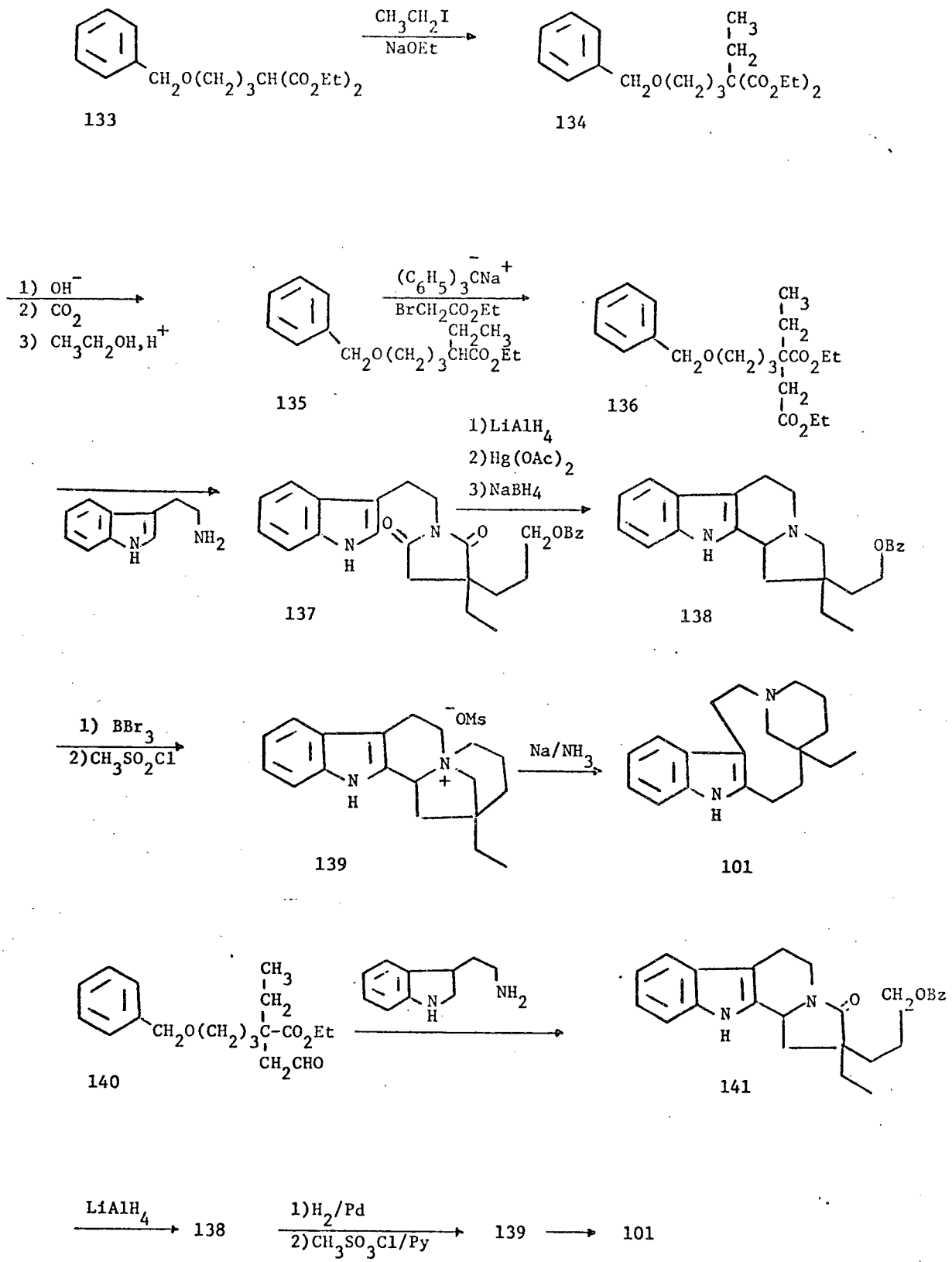


Figure 16. Kutney's total synthesis of dl-quebrachamine.

the nine-membered compound (142) possessing a cyano group at C_3 which upon hydrolysis followed by esterification with ethereal diazomethane provided dl-vincadine (143) and dl-epivincadine (144) as a minor component (epimers at C_3).

The synthesis of dl-vincadine also completes the total synthesis of dl-vincaminoreine (145) and dl-vincaminovine (146) in view of the already known interconversions.[91] The transannular cyclization approach applied to vincadine (143) and vincaminoreine (145) afforded vincadifformine (148) and minovine (147) respectively, and hence an entry into the pentacyclic series.

Kutney and co-workers[90] were also able to show that the transannular cyclization approach could be extended to the synthesis of alkaloids bearing oxygen functions, particularly methoxy groups on the aromatic ring. Condensation of 6-methoxytryptamine (149) with the aldehyde ester (140) afforded the tetracyclic lactone (150). Further elaboration of this intermediate in the same manner as indicated for compound 139 (Figure 17), afforded the total synthesis of 16-methoxyvincadine (151) and 16-methoxyepivincadine (152).

Harley-Mason and co-workers[92] reported another interesting synthesis of dl-aspidospermidine (125). The key step in this synthetic sequence was the acid catalyzed rearrangement of the tetracyclic hydroxy-lactam (155) to the pentacyclic aspidosperma type indolenine-lactam (156), which upon reduction with lithium aluminum hydride gave dl-aspidospermidine (125). Another synthesis of quebrachamine (101) and 3,4-dihydroquebrachamine (164) has been achieved by Ziegler and co-workers.[93] The approach employs the alkylation of 1-benzyl-3-ethyl-1,4,5,6-tetrahydro-

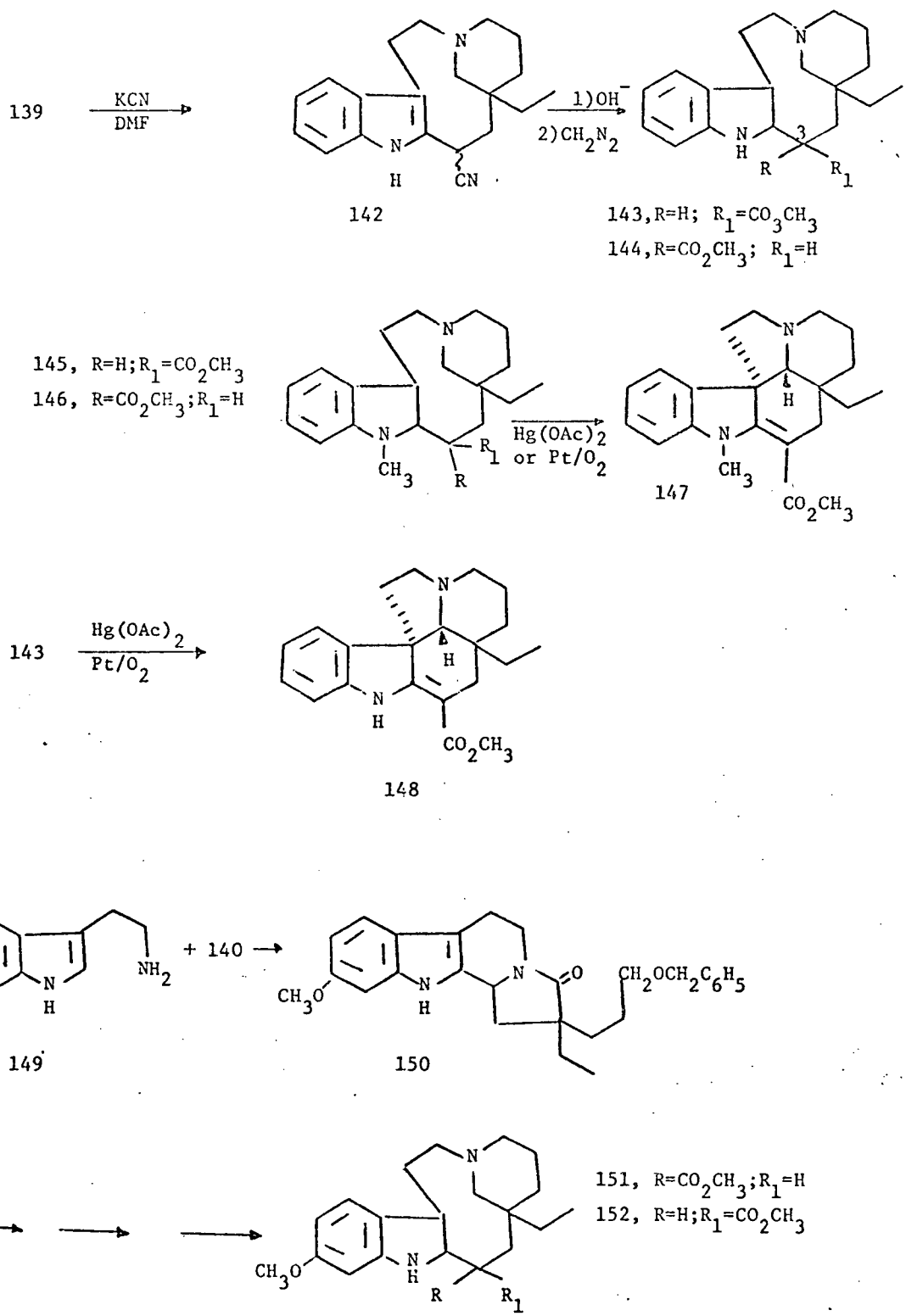


Figure 17. Kutney's total synthesis of some monomeric vinca alkaloids.

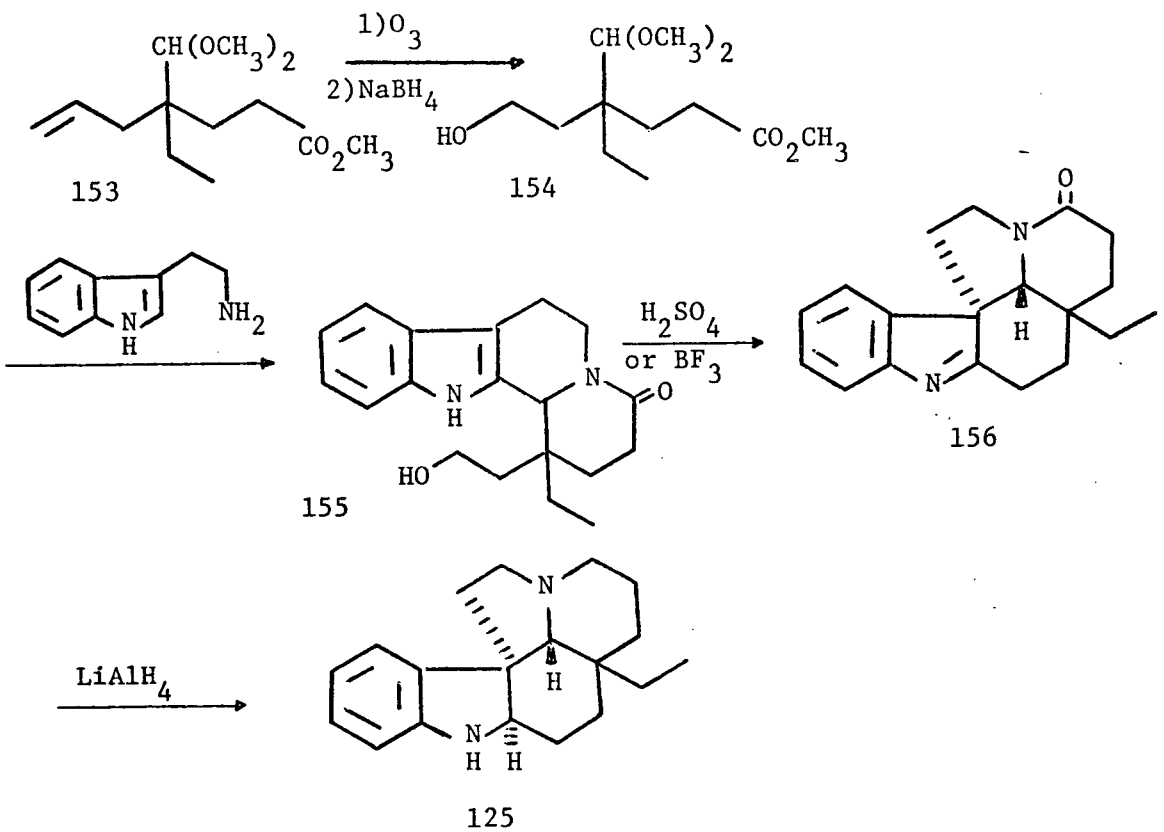


Figure 18. Harley-Mason's total synthesis of dl-aspidospermidine.

pyridine (160) with methyl haloacetates and subsequent cyclization to a nine-membered ring in high yield with polyphosphoric acid, as indicated in Figure 19. However the last step of the sequence was a very low yielding reaction, and his attempts toward the conversion of the compound (164) to quebrachamine (101) proved to be unsuccessful.

A similar approach has been utilized by Ziegler[94] in the total synthesis of dl-minovine (147). The most interesting aspect of the synthetic sequence involves the alkylation of the acrylic ester (167) with the enamine (160) followed by cyclization of the resultant iminium intermediate to afford the tetracyclic indole derivative (168).

Hydrogenolysis of 168 gave the secondary amine 169, and the ethylene bridge necessary to complete the synthesis was introduced in one operation by alkylation with ethylene dibromide. Wenkert and co-workers[95] reported an approach toward the construction of the Aspidosperma alkaloid skeleton. Sodium borohydride reduction of 170 followed by hydrolysis of the resultant nitrile with alkaline hydrogen peroxide yielded the amide (171). Catalytic hydrogenation of the latter with simultaneous cyclization at the β-position of the indole nucleus afforded the tetracyclic intermediate (172) similar in structure to that obtained by Ziegler.[94] The construction of the ethanamino-bridge (173) was performed by an intramolecular indole β-alkylation.

A synthesis of dl-tabersonine (81) was reported by Ziegler[96] in which he utilizes the previously developed approach[97] for the synthesis of the key intermediate 146. The remaining steps of the synthetic sequence, were basically the same approach that has been

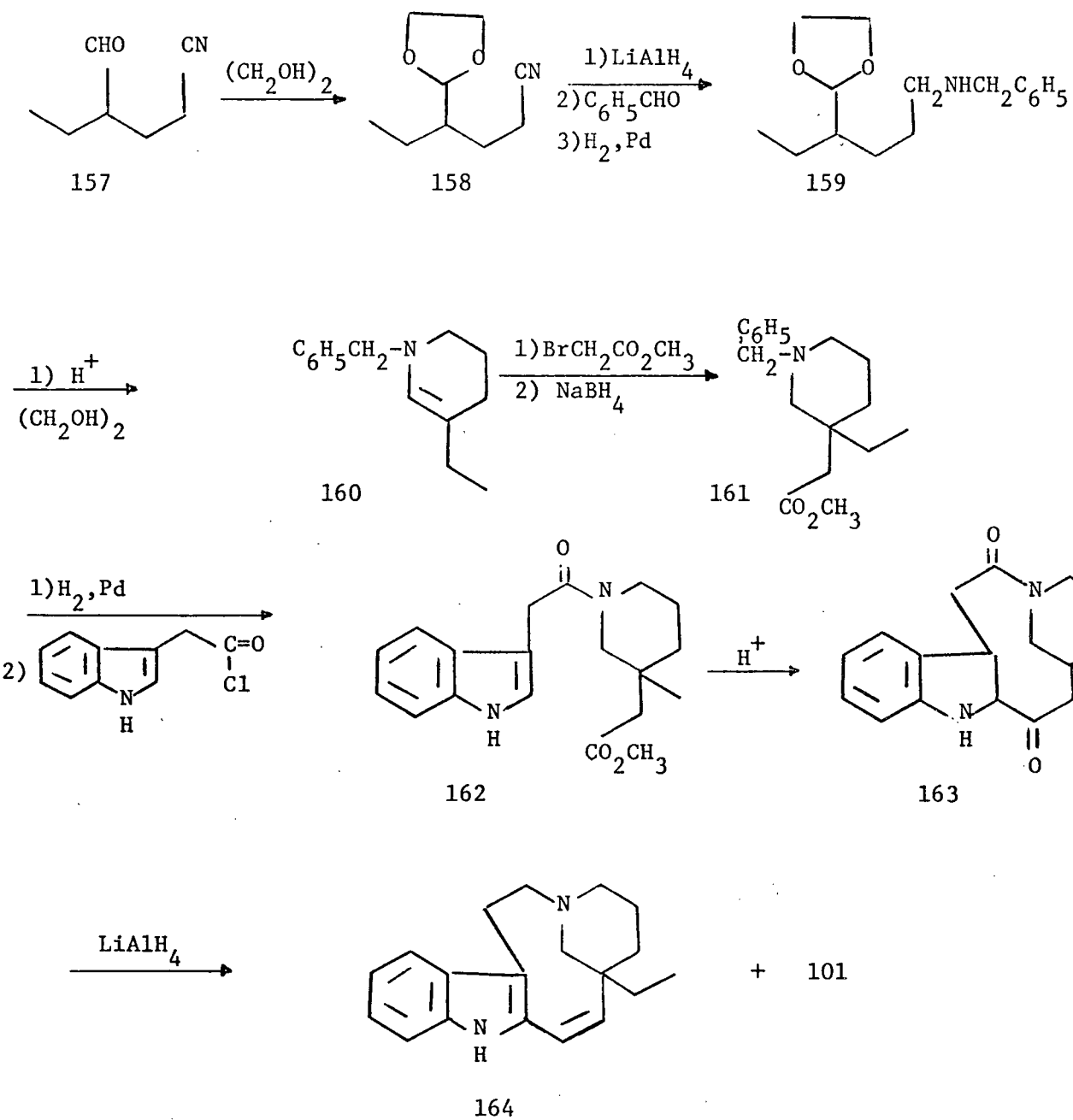


Figure 19. Ziegler's synthesis of quebrachamine.

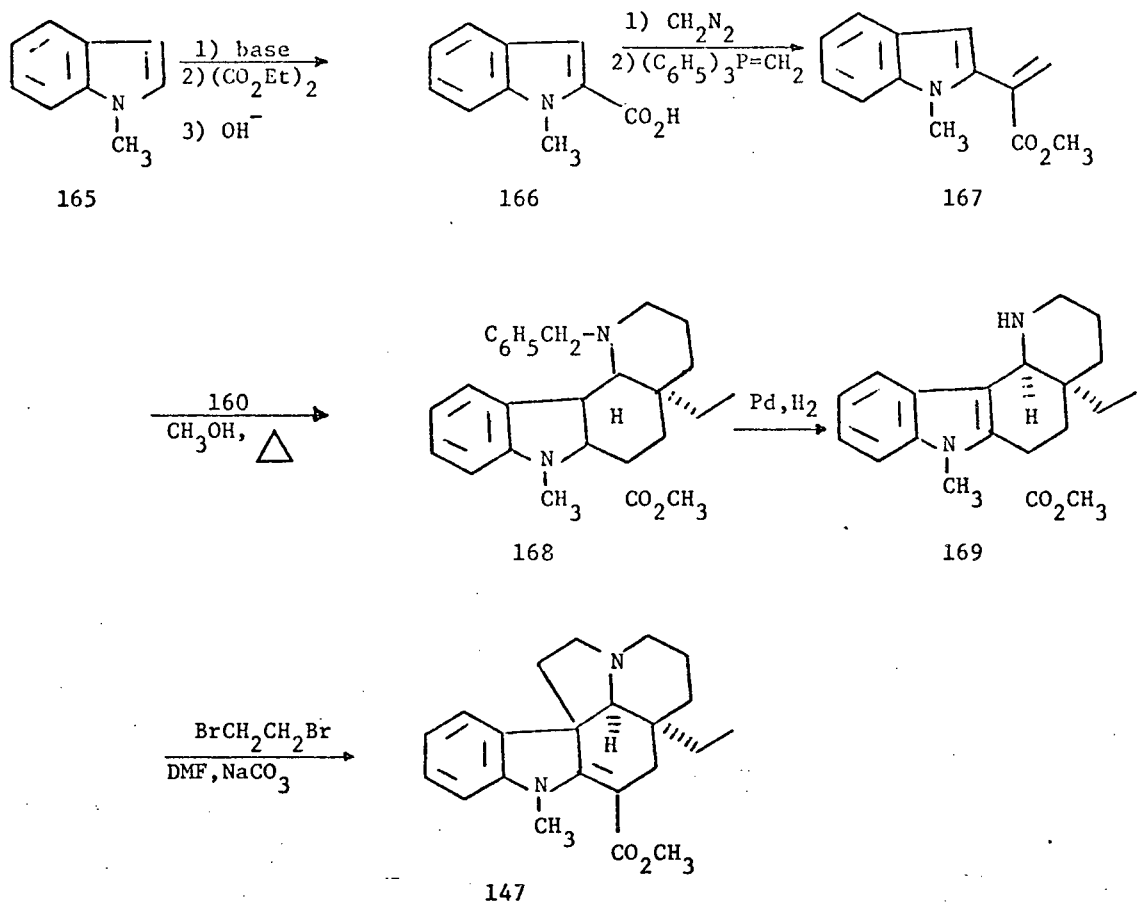


Figure 20. Ziegler's synthesis of dl-minovine.

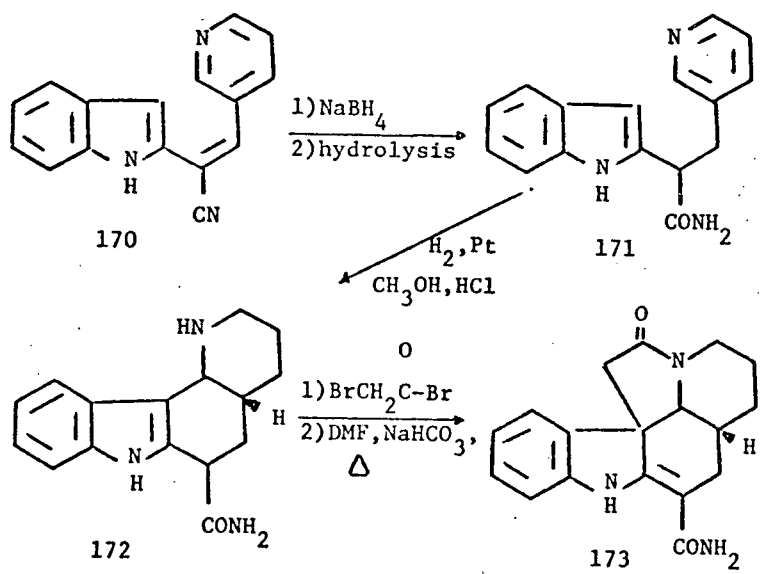


Figure 21. Wenkert's approach to aspidosperma alkaloid skeleton.

taken by Kutney in his synthesis of the monomeric Vinca alkaloids.[80,90,98]

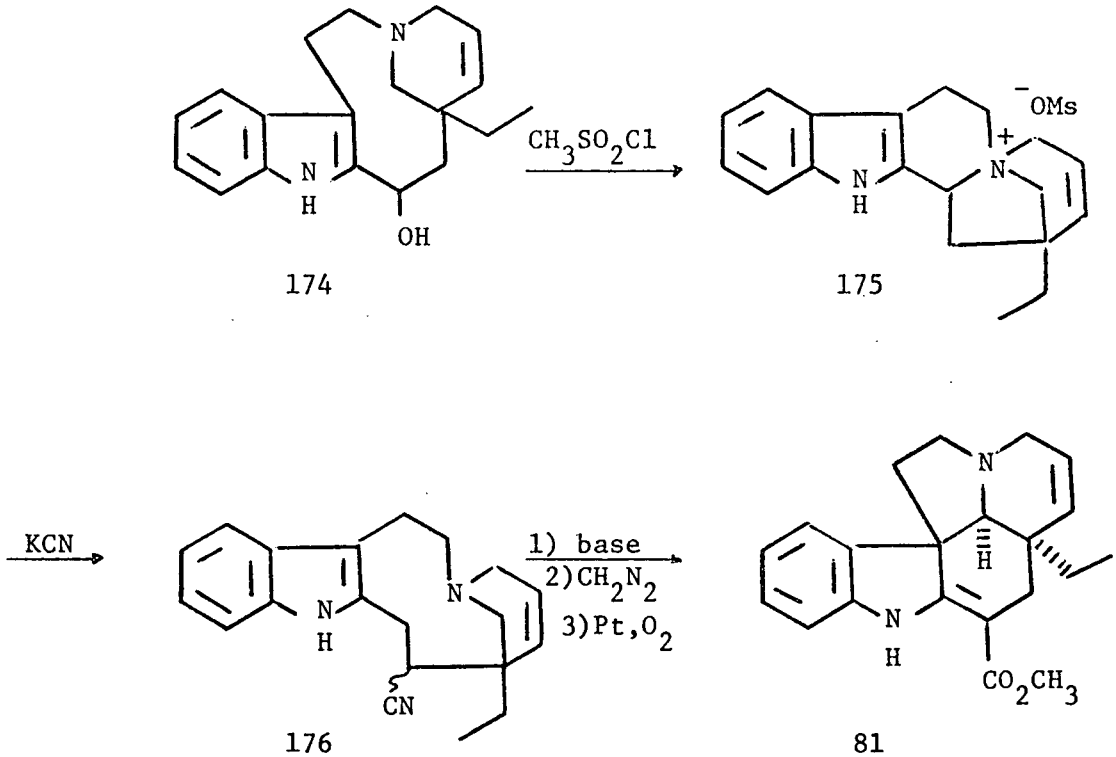


Figure 22. Ziegler's total synthesis of dl-tabersonine.

A new method for the synthesis of an established[75,79] hydrolulolidone Aspidosperma alkaloid precursor (187) has been reported by Stevens.[99] It involves the acid-catalyzed thermal rearrangement of a cyclopropyl imine (179) to a 2-pyrroline (180) as a key step.

Buchi and co-workers[100] have reported the total synthesis of vindorosine (194), a highly functionalized Aspidosperma alkaloid. The first step of his synthetic sequence involves an interesting boron trifluoride catalyzed cyclization of compound 188 to yield the tetracyclic indoline (189) as a major product. The intermediate 189 was then converted to the pentacyclic keto ester (192) via the synthetic operations indicated in Figure 24. The required stereochemistry and functionalization of ring C was then achieved via an interesting hydroxylation reaction.

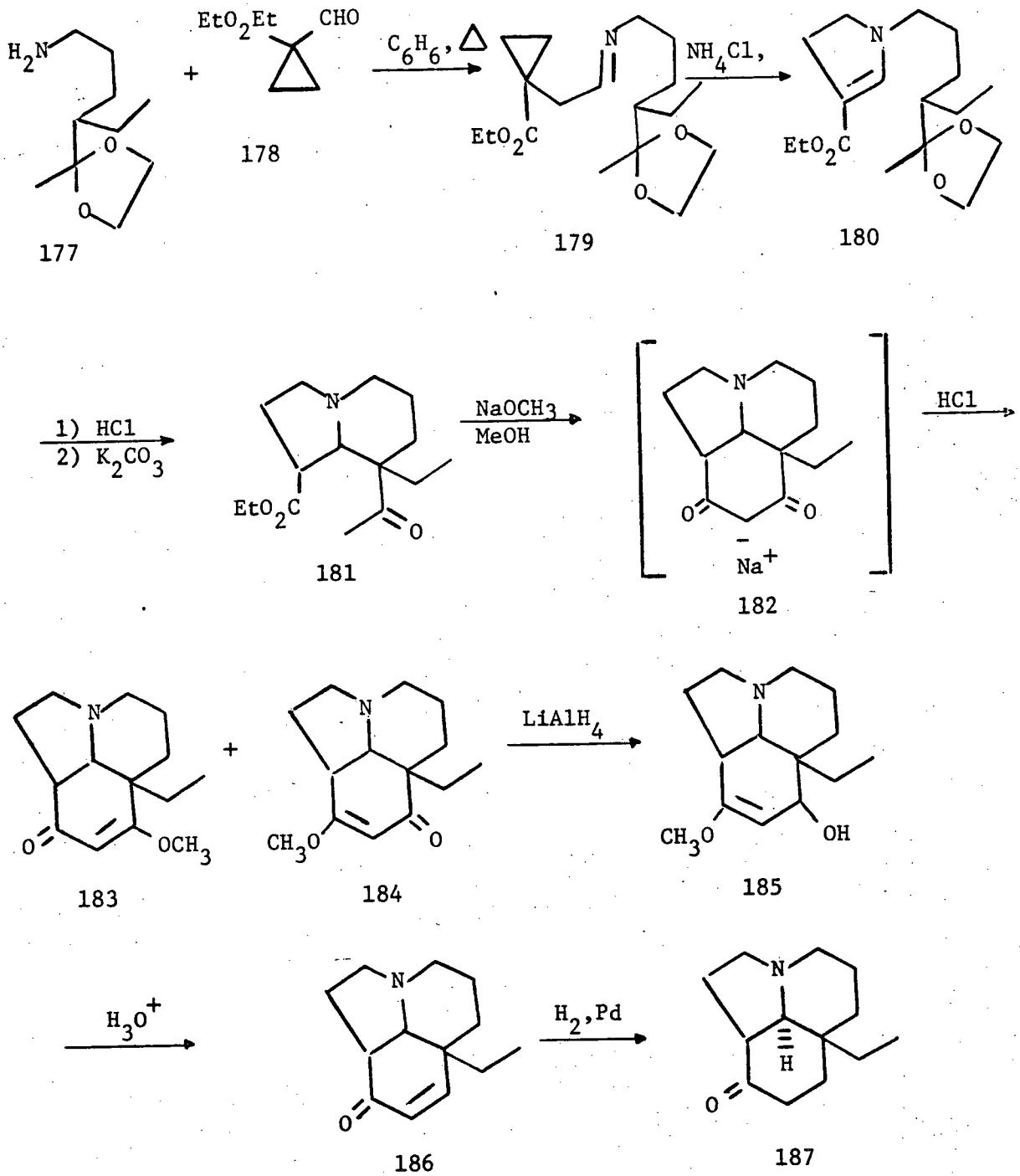


Figure 23. Steven's synthesis of the hydrolulolidone.

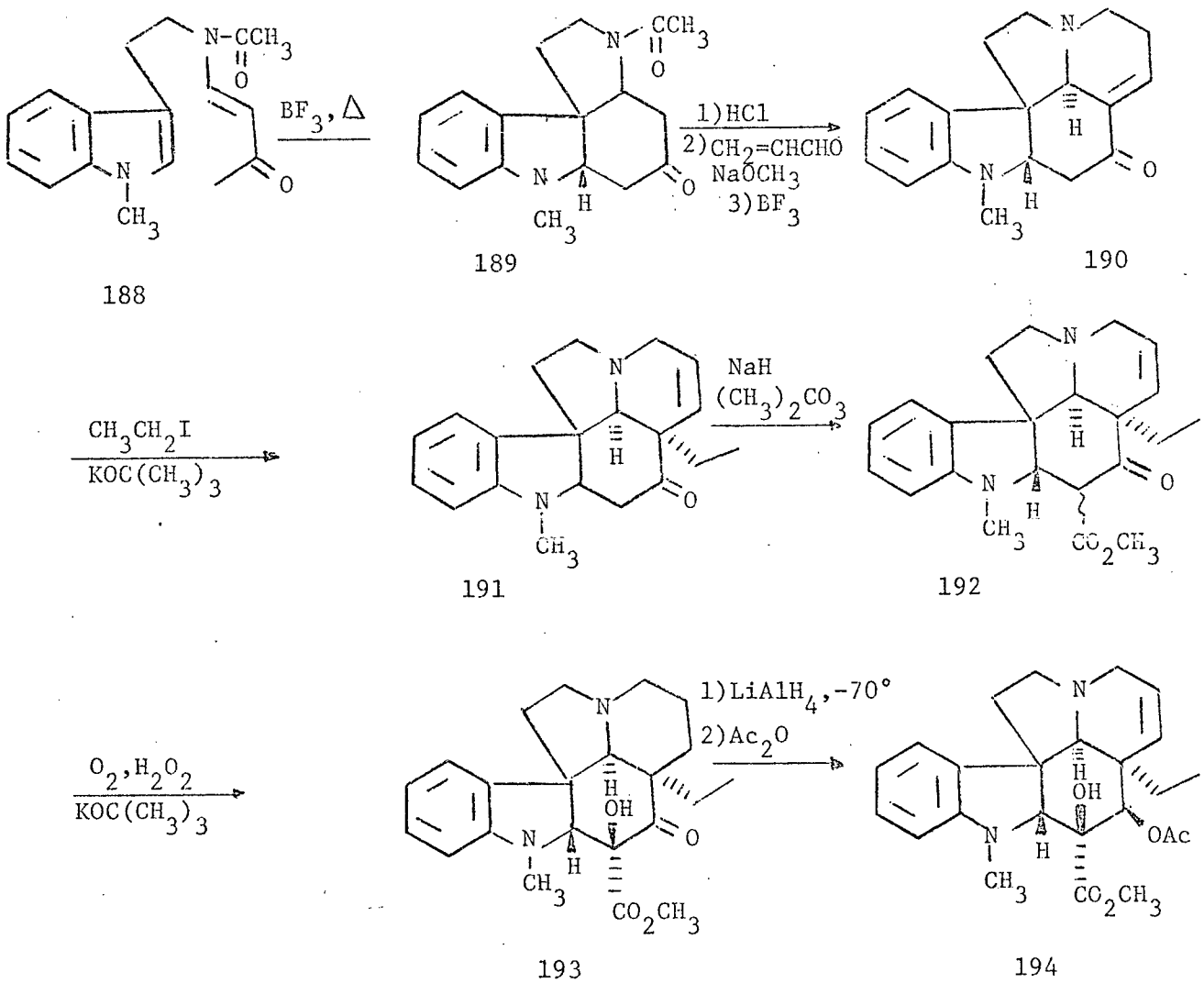


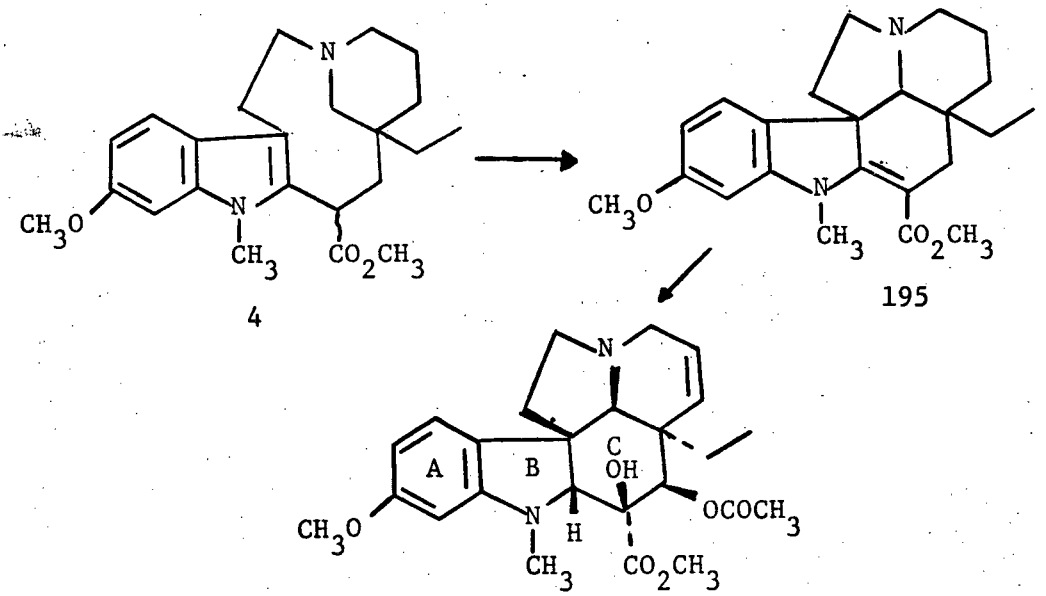
Figure 24. Buchi's total synthesis of dl-vindorosine.

Thus treatment of 192 with oxygen-hydrogen peroxide in the presence of base gave the hydroxy keto ester (193) which upon reduction followed by acetylation yielded dl-vindorosine (194).

DISCUSSION PART I

1. The Total Synthesis of dl-Vincaminoridine (4) and its Epimer

On inspection of the structural formula presented[73] for vindoline (3), it is obvious that the most difficult part of any synthetic approach to this interesting alkaloid would involve the construction of ring C, containing the six asymmetric centres. It was decided that from the number of possible pathways which might be employed in the construction of these functionality, the conversion of compound 4 to the pentacyclic intermediate 195, via a transannular cyclization reaction was attractive and potentially efficient. The use of nine-membered compounds to generate the desired pentacyclic aspidosperma skeleton has been proposed in biogenetic hypotheses, and Kutney and



co-workers[83-90] were able to carry out such a conversion. Having obtained the aspidosperma skeleton (195) the remaining functionality would then be elaborated via appropriate synthetic operations. The starting material which was chosen for the synthesis of the required crucial intermediate (4) was ethyl α-(γ-benzyloxypropyl)butanoate (135) which was prepared according to known procedures.[88,103] The reaction sequence is outlined in Figure 25 and only a brief mention of some experimental details are made here. Thus γ-benzyloxypropanol (197) was prepared[101] in 66% yield by condensation of the monosodium salt of propane-1,3-diol (196) with benzyl chloride in xylene. Treatment of 197 with thionyl chloride in dimethylaniline gave rise to benzyl γ-chloropropyl ether (198) in 80% yield.[102] Alkylation of ethyl diethyl malonate with 198 in absolute ethanol in the presence of sodium ethoxide gave diethyl γ-benzyloxypropylethyl malonate (134) in 54% yield.

Hydrolysis of the malonic ester derivative (134) with aqueous potassium hydroxide in ethanol, gave the desired γ-benzyloxypropylethyl malonic acid (199) as a viscous oil, which was crystallized from n-hexane-ether to provide a colorless solid in 81% yield. In order to complete the synthesis of the desired monoester derivative (135), we now proceeded as follows; γ-benzyloxypropylethyl malonic acid (199) was smoothly decarboxylated at 160°C to provide the 2-(γ-benzyloxypropyl)-butanoic acid (200) as a yellow viscous oil, which was used for the subsequent reaction without further purification. The crude monoacid (200) was esterified with ethanol and sulfuric acid to provide ethyl 2-(γ-benzyloxypropyl)-butanoate (135) as a clear oil in 76% yield (b.p. 135°/1.5 mm).

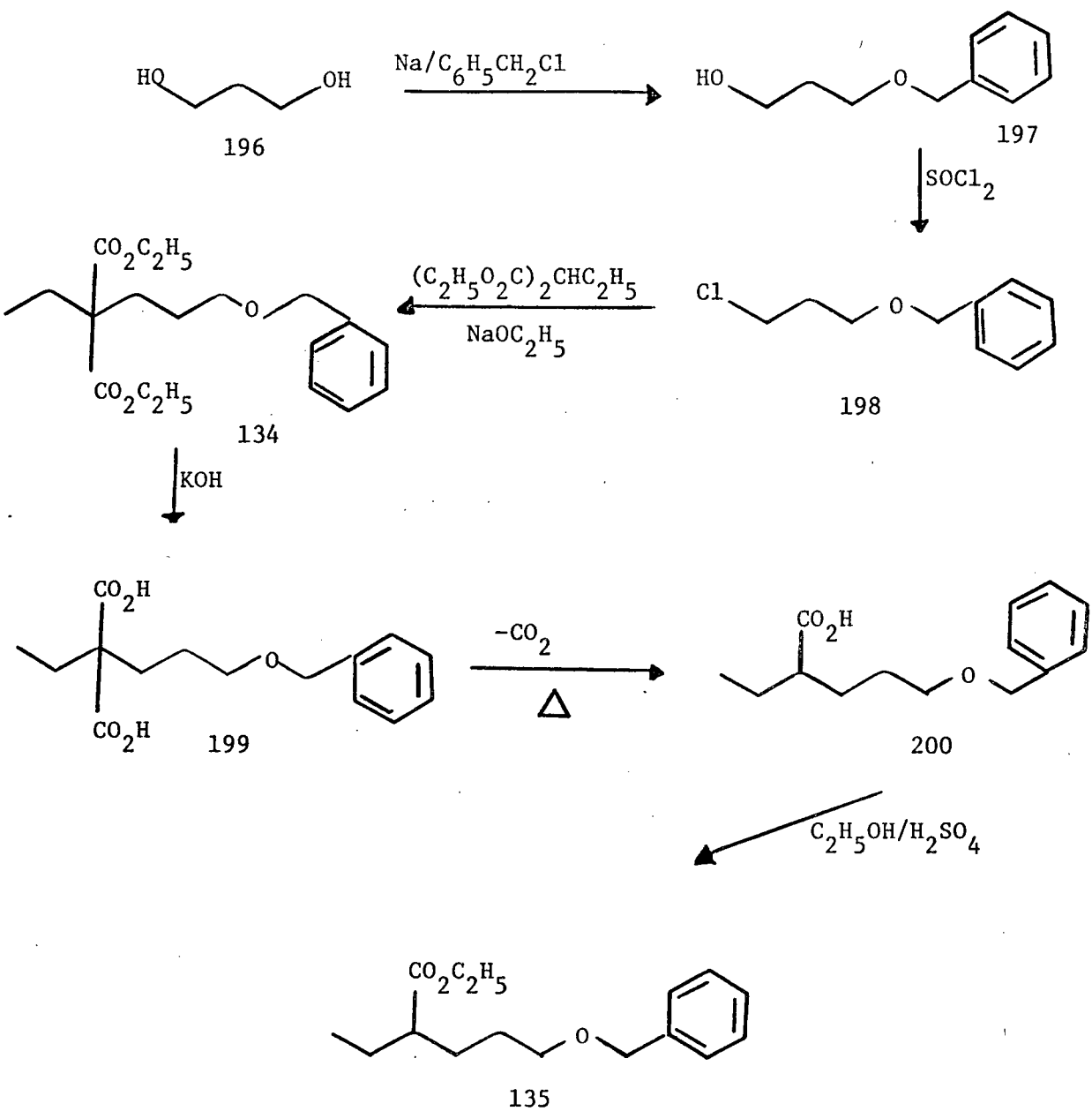


Figure 25. Preparation of the monoester (135).

Having obtained the monoester derivative (135), it became necessary at this point, bearing in mind the initially proposed synthetic approach, to direct our efforts toward the synthesis of the equivalent to the "non-tryptophan" unit of the aspidosperma skeleton, namely the aldehydoester (140). The sequence followed[7,90] is shown in Figure 26.

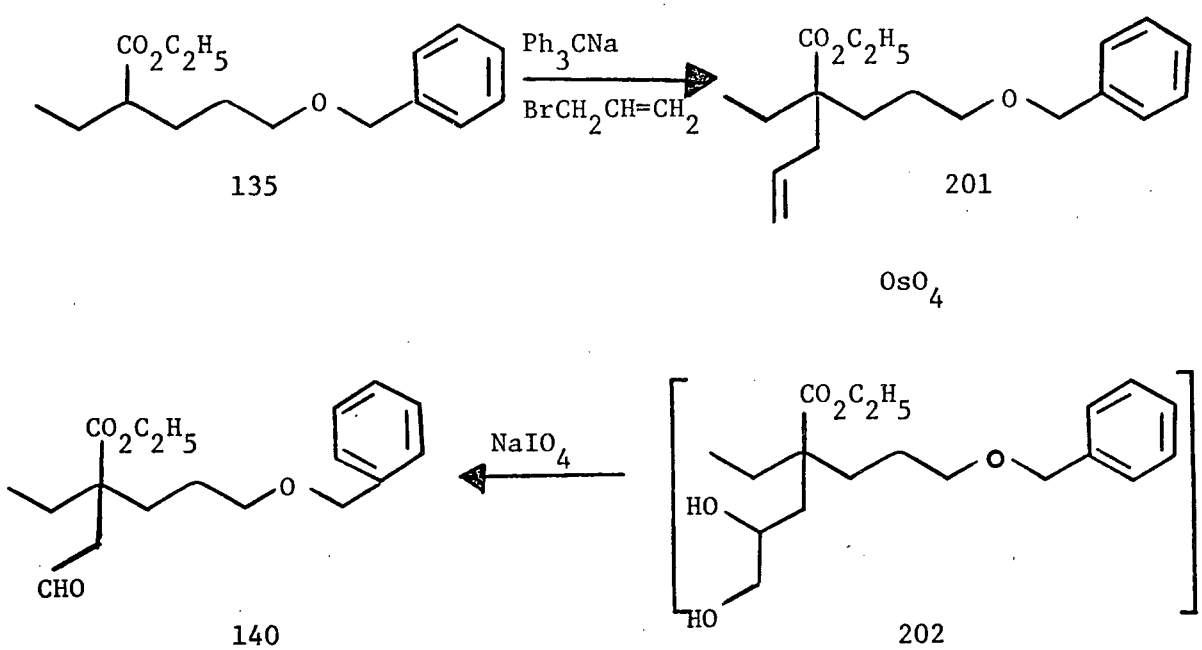


Figure 26. Preparation of aldehydoester (140).

Alkylation of 135 with allyl bromide in ether in the presence of triphenylmethyl sodium gave a yellow oil. After purification by fractional distillation under reduced pressure, the corresponding alkylated product 201 was obtained in 83% yield (b.p. 132-134°/0.15 mm).

The one step preparation of aldehydes from the corresponding allyl compounds is a well known reaction. Thus treatment of 201 with osmium tetroxide and sodium periodate, added successively to the reaction

mixture at room temperature, gave the desired aldehydoester (140), after purification by vacuum distillation in 70% yield (b.p. 174-176°/0.75 mm).

It is perhaps worthwhile to mention that once this aldehydoester (140) has been prepared, it was immediately utilized in the next condensation reaction due to its known instability.

Having obtained the synthetic intermediate (140) we next considered a Pictet-Spengler reaction,[104] namely the condensation of 140 with 6-methoxy tryptamine (149) to provide the required tetrahydro-β-carboline ring system (150) (Figure 27). The tryptamine derivative (149) was available from previous experiments and had been prepared according to a known procedure.[105]

When 140 was refluxed with 6-methoxy tryptamine (149) in glacial acetic acid for 1.5 hours followed by the conventional workup of the reaction mixture, a yellow residue was obtained.[7] This material was purified by column chromatography on alumina to give, in 98% yield, the lactam (150) as a yellowish glass. This intermediate (150) was a mixture of the two expected diastereoisomers, but no attempts to separate them at this stage were necessary for our purpose. The structure assigned to compound 150, was fully substantiated by spectral data.[7] Even though the spectral data have already been presented and discussed,[7] it is necessary for clarity in discussing further work to briefly mention it again from this stage of the sequence. The presence of the lactam was evident from the strong carbonyl absorption at 1670 cm^{-1}. The presence of the methoxy indole was evident in the ultraviolet spectrum (335, 321, 295, 272, 264, 227 nm). The mixture of the expected diastereoisomers (cis and trans with respect to C-3 and C-15) was submitted to nmr spectroscopy (Figure 28). The most characteristic features were a triplet at τ 5.25 (J = 8 cps) which was assigned to the

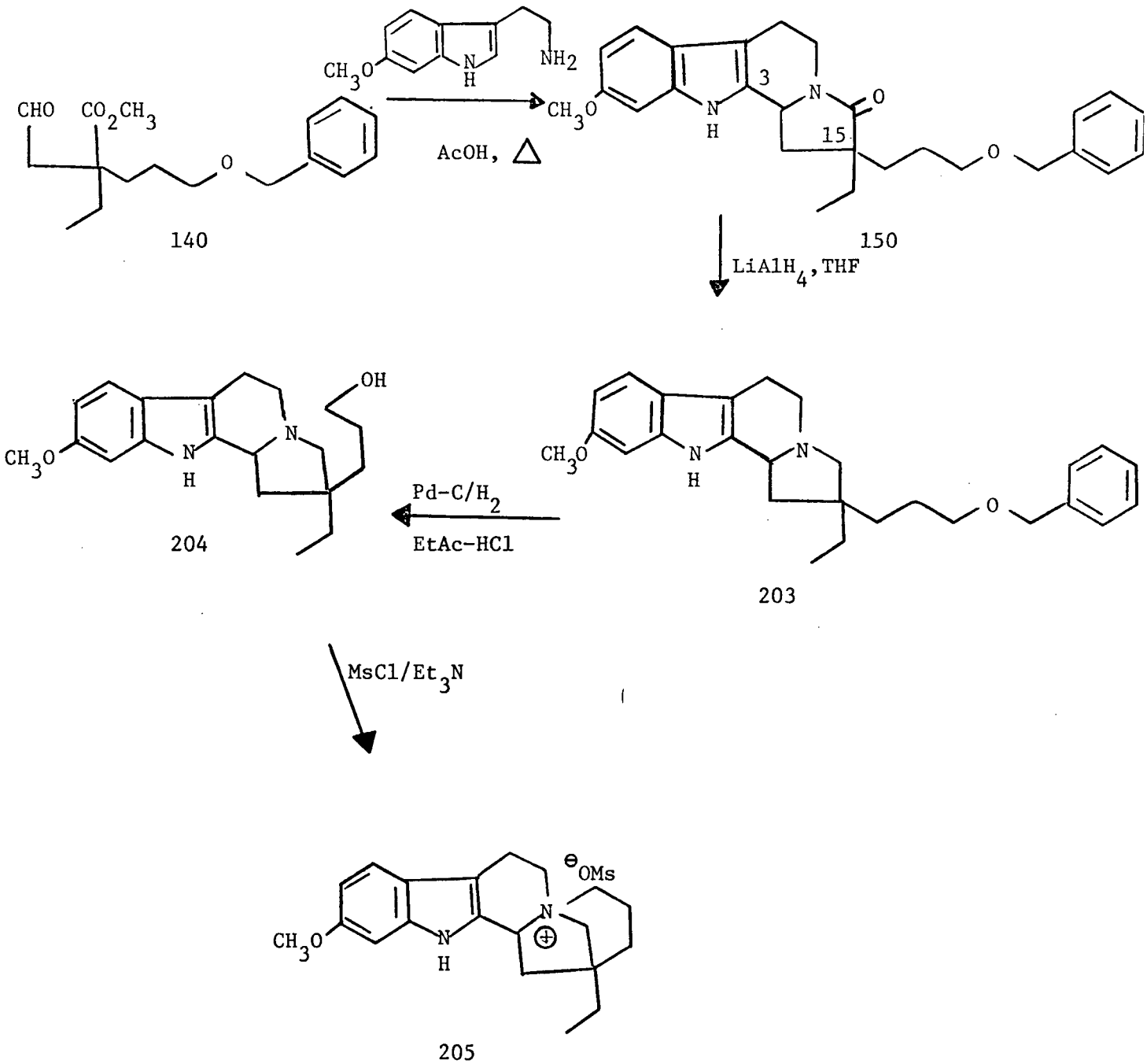


Figure 27. Preparation of the mesylate (205).

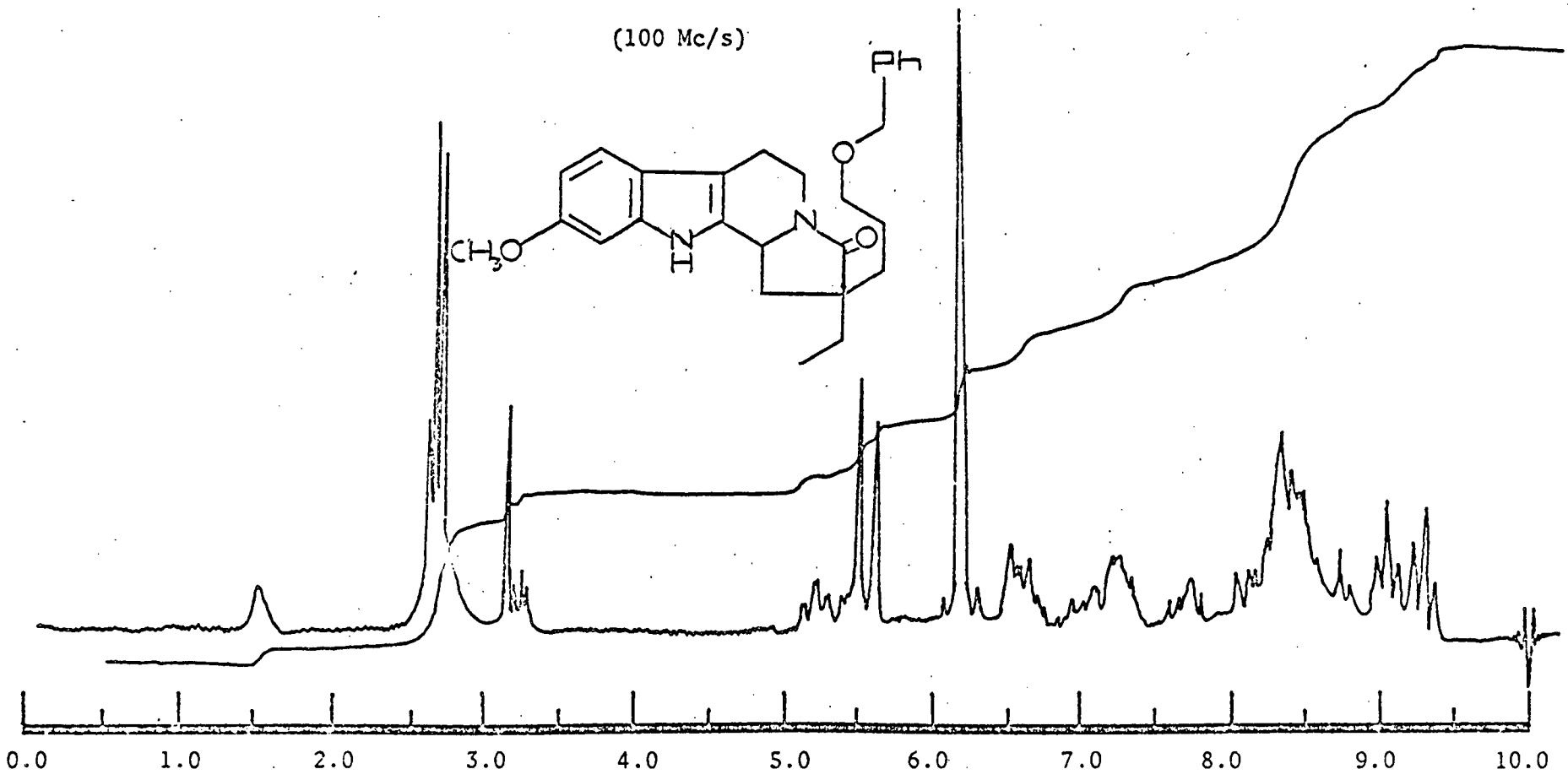


Figure 28. Nmr of the lactam ether (150). (Taken from C. Gletsos Ph.D. thesis)

C-3 proton, and the absence of signals for the proton on the indole ring, which indicated that the cyclization at the α position of the indole ring had taken place. In the mass spectrum (Figure 29) in addition to the molecular peak at m/e 432 and the base peak at m/e 91 (tropylium ion fragment), the other important peaks were at m/e 341, 281, 263 and 149. Tentative assignment for these fragments are indicated in Figure 30. The molecular formula, $C_{27}H_{32}O_3N_2$, was established by elemental analysis and high resolution mass spectrometry.

The next step was the conversion of 150 to the desired benzylether amine (203), which was achieved by lithium aluminum hydride reduction in refluxing tetrahydrofuran. The isolated crude product was purified by column chromatography on alumina to afford a mixture of the two diastereoisomers as a yellow amorphous material in 92% yield. The ultraviolet spectrum was that of a typical methoxy indole (230, 263, 270 and 300 nm), while the carbonyl absorption in the infrared spectrum was now absent. The nmr spectrum (Figure 31) showed a diamagnetic shift of the distorted triplet due to the C-3 proton now located at τ 5.93. All other signals were also in agreement with the proposed structure (203). The mass spectrum (Figure 29) showed significant fragments at m/e 91, 149, 240, 327 and 418 (M^+) according to our expectations. The molecular formula, $C_{27}H_{34}O_2N_2$, was established by high-resolution mass spectrometry and elemental analysis.

Having prepared the benzylether amine (203), we now turned our attention to the preparation of a key intermediate, the tetracyclic amino alcohol 204. Thus the benzyl group was removed by catalytic hydrogenolysis (10% palladium on charcoal, ethyl acetate, concentrated

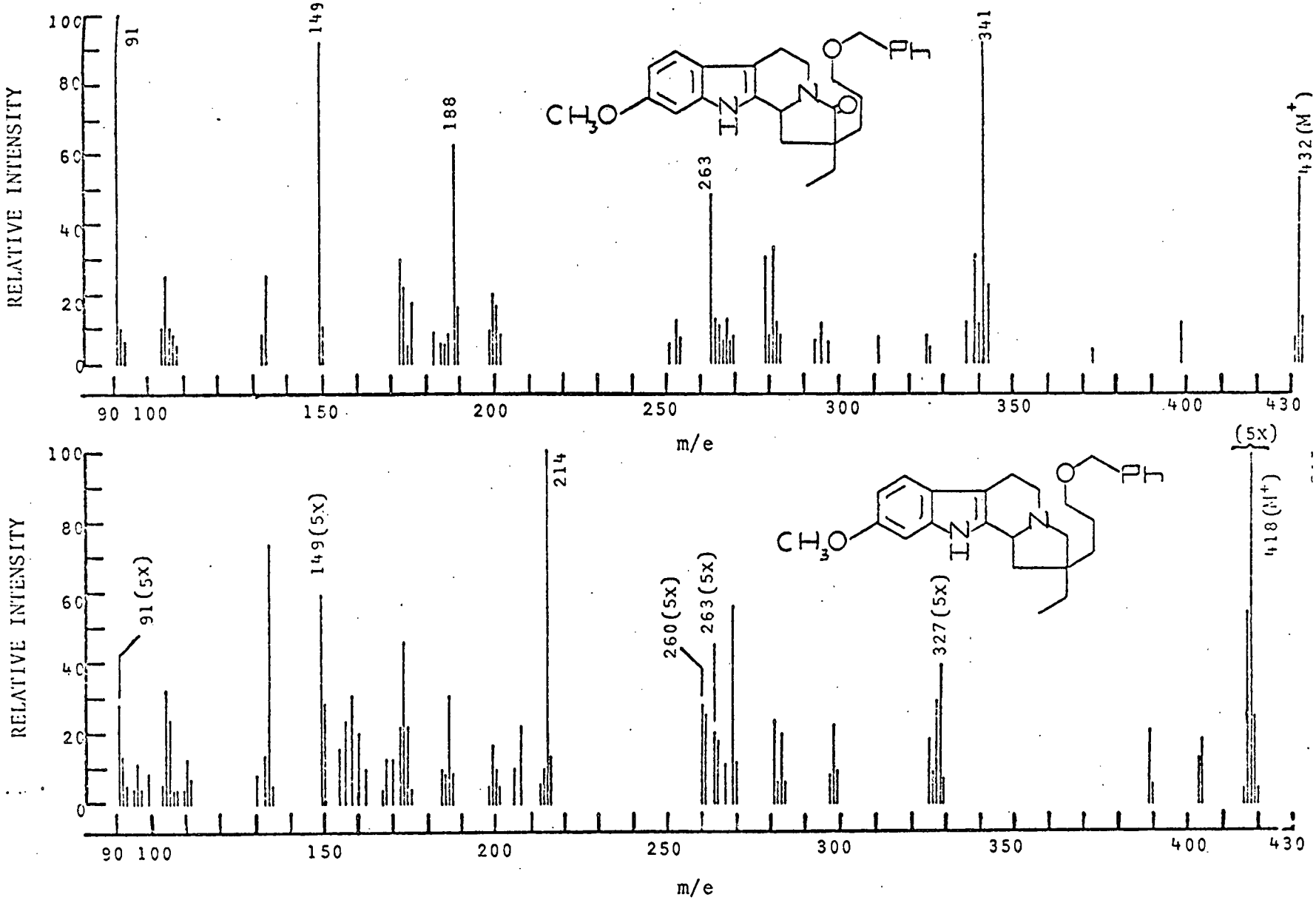


Figure 29. Mass spectra of the lactam ether (150) and amino ether (203). (Taken from C. Gletsos Ph.D. thesis)

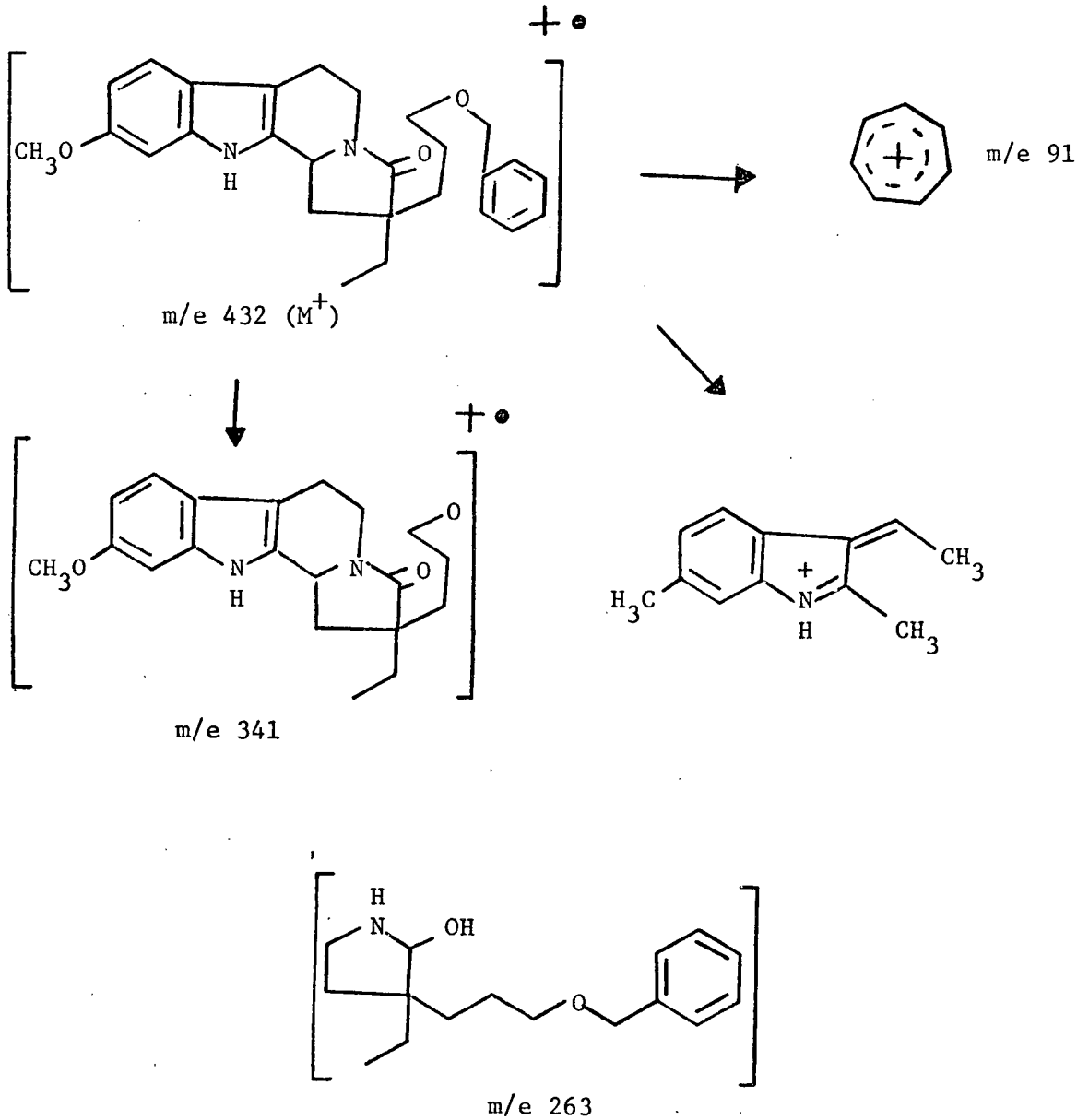


Figure 30. Fragmentation of the lactam ether (150).

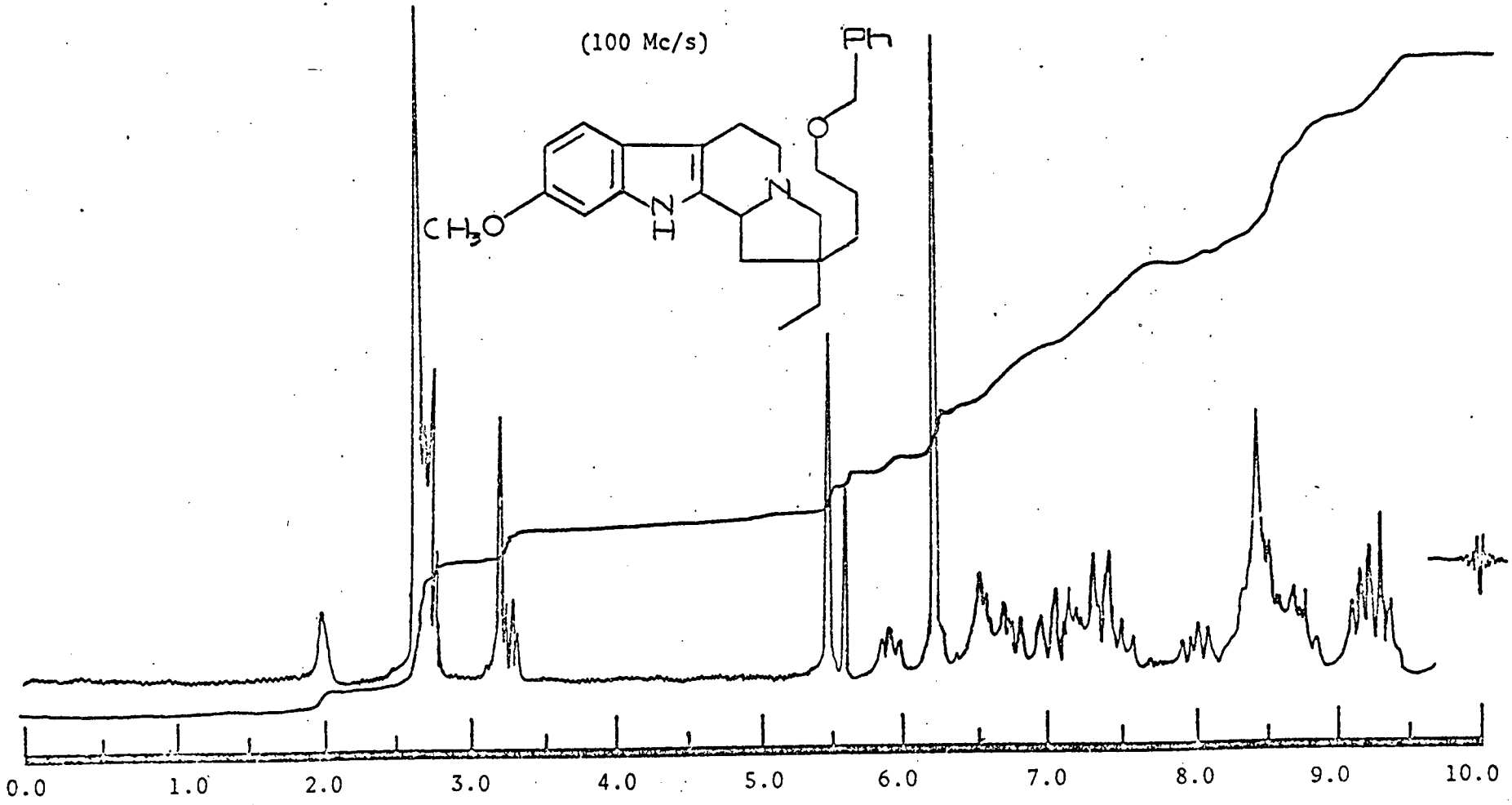
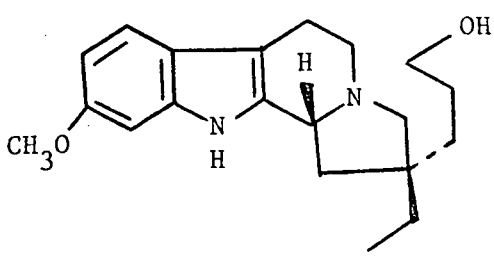


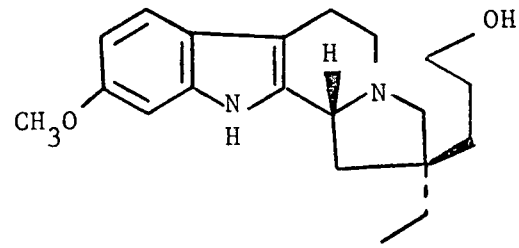
Figure 31. Nmr of the aminoether (203). (Taken from C. Gletsos Ph.D. thesis)

hydrochloric acid) to provide after the conventional workup a yellowish solid. Chromatography on aluminum allowed the isolation of the two isomeric alcohols (204) in 64% yield. Elution with ethyl acetate-ethanol (98:2) gave the less polar alcohol-I (24%) while elution with ethyl acetate-ethanol (9:1) afforded alcohol-II (40%). At this point it is appropriate to discuss some stereochemical relationships between these two diastereoisomeric alcohols. Since we are dealing with two dl-pairs it is not proper to refer to different functional groups of the molecule as being α or β, since the α stereochemistry in one case becomes β-oriented in the mirror image of the same dl-pair. Therefore we will adopt a "cis-trans" nomenclature as shown in Figure 32 in the ensuing discussion. For the sake of discussion we will refer to the dl-pair in which the proton at C-3 is in a "cis" relationship with the ethyl side chain (206 and 208) as "cis", while in the "trans" dl-pair these two asymmetric centers have a "trans" orientation (207 and 209). Let us assume that ring C is in the most favored half-chair conformation in both amino alcohols.

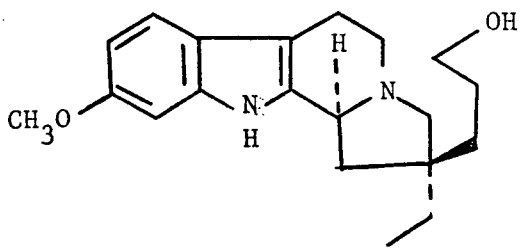
At this point the infrared spectrum was very helpful in assigning the relative positions of the C-3 proton and the lone pair of electrons on the nitrogen atom. Bohlmann[106] has shown that in certain quinolizidine alkaloids, infrared bands in the C-H region appear when hydrogen atoms on a carbon atom adjacent to a nitrogen atom are trans and anti-parallel to the unshared pair of electrons on the hetero atom. This technique has proven to be a useful tool in stereochemical assignments in several alkaloids.[107-110] Since in both of our amino alcohols (204) no



206, cis dl-pair



207, trans dl-pair



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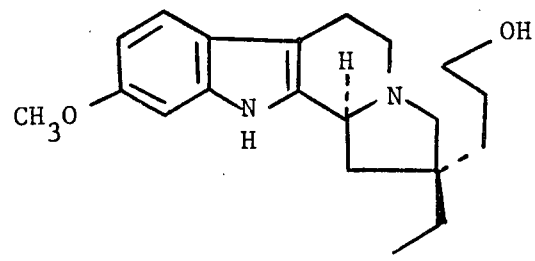


209

Figure 32. The two diastereoisomeric dl-pairs of alcohols.

Bohlmann bands between 2700 and 2800 cm^{-1} were apparent in the infrared spectra, this would support the situation in which the C-3 proton is not in a co-planar and trans relationship with the unshared pair of electrons on the nitrogen atom of the heterocyclic ring.

It is necessary to recognize that in either the "cis" or "trans" dl-pairs, one of the members must have a 3α-H orientation, while the enantiomer will have the 3β-H stereochemistry. In other words we can have a 3α-"cis" isomer and a 3α-"trans" isomer, or a 3β-"cis" isomer and a 3β-"trans" one. Consequently any given environment of the C-3 proton with respect to the indole ring and the nitrogen atom is available in either the "cis" or "trans" dl-pairs. On this basis

any special shielding or deshielding of the C-3 proton by the indole ring or adjacent nitrogen atom is similar in both series. It is of interest to note however that the chemical shift of the C-3 proton in the two isolated alcohols-I and II is not identical.

Therefore we must consider the "cis" or "trans" relationship of the C-3 proton in conjunction with the ethyl side chain in order to be able to explain the observed nmr spectra. Molecular models provided some information about the stereochemistry of these amino-alcohols. When the C-3 proton is cis to the lone pair of electrons on the nitrogen atom, the ethyl chain of the trans isomer (207a and 209a) will be lying above the indole ring and far away from the unshared pair of electrons on the nitrogen. As a result of that, one can expect the C-3 proton to be deshielded by the nitrogen atom, while the ethyl group in turn is shielded by the indole ring. Therefore the "trans" dl-pair has the C-3 proton multiplet at low field (τ 5.82) and the methyl triplet at high field (τ 9.28). However in the "cis" isomers (206a and 208a), the ethyl group is not lying over the indole ring, but is in reasonably close proximity to the N-electrons and to the C-3 proton. Therefore we feel that the C-3 proton would be shielded by the ethyl group while the latter in turn is deshielded by the nitrogen atom. As a result the "cis" dl-pair has the C-3 proton multiplet at higher field (τ 5.90) and the methyl triplet at lower field (τ 9.14). Support for these assignments was available from the literature. Rosen and Schoolery[111] in their work on Rauwolfia alkaloids assumed that axial protons absorb at higher field than the corresponding equatorial ones and on this basis they made their

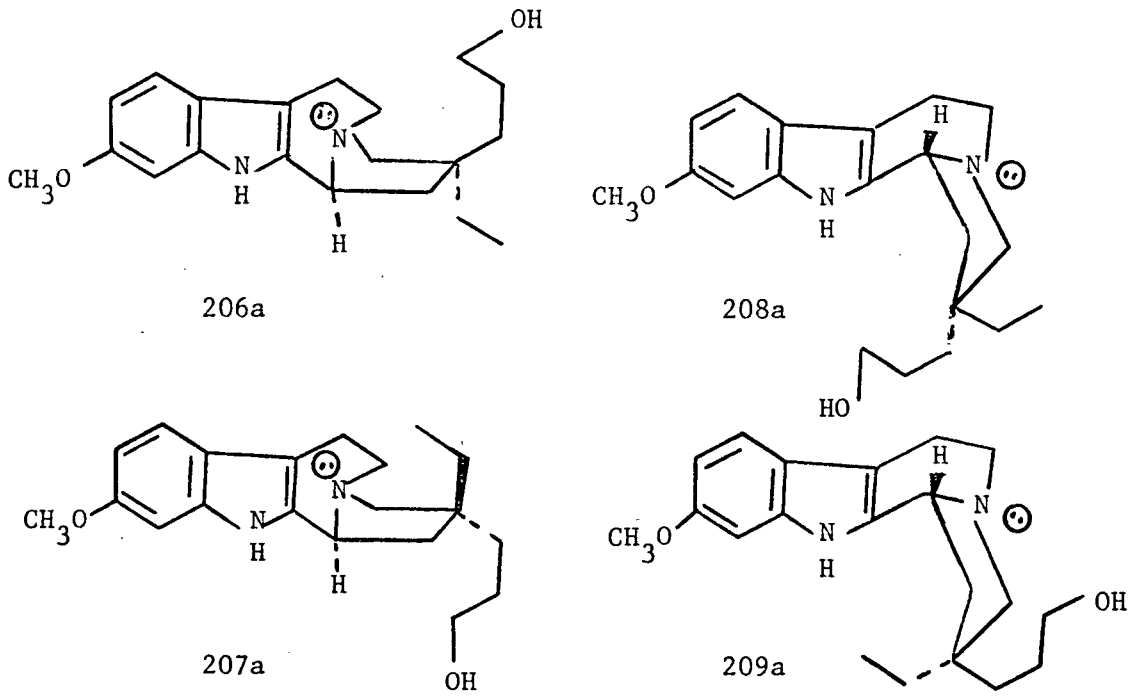
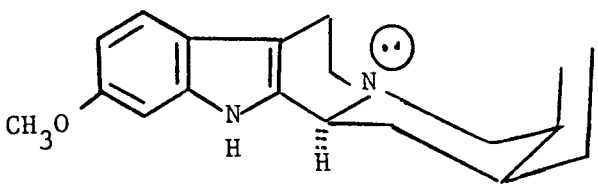


Figure 33. Conformation of the isomeric alcohols I (206a,208a) and II (207a,209a).

assignments. For in their study, an alkaloid family having the partial structure 210 was considered. In this case the C-3 proton is in a diaxial anti-parallel relationship to the unshared pair of electrons on the nitrogen atom, the C-3 proton signal was always found above τ 6.2. On the other hand, when the C-3 proton is in an equatorial cis relationship (partial structure 211), it resonates around τ 5.6.

By analogy with these results we may expect in our case, both isomers to have C-3 protons of the latter type (τ 5.82 and 5.90). Furthermore these authors[111] have also accounted for the lack of resolved fine structure in the C-3 proton signal in cases where the

lone pair on the nitrogen atom is in close proximity to it as, "due to spin coupling to the nitrogen atom, which often smears the peak due to quadrapole relaxation of the nitrogen".



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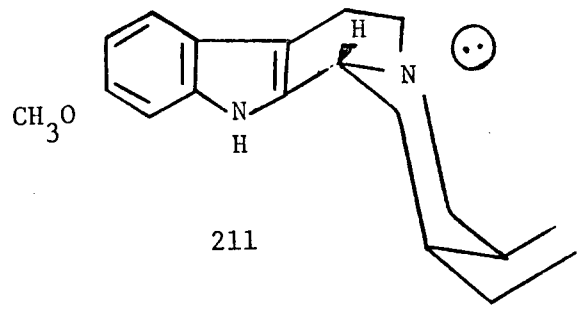

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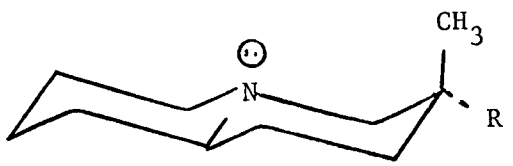
The same argument has been used by Wenkert et al.[112] in the stereochemical elucidation of the isomeric alkaloids ajmalicine (10) and tetrahydroalstonine. Again the equatorial and cis-oriented C-3 proton had a lower field resonance (τ 5.55). During the structural elucidation of corynantheidine type alkaloids using ir, nmr, ord and cd, Beckett et al.[113] have used extensively the already proposed argument for the C-3 proton and its electronic environment.

They have also discussed the relative effect of the unshared pair of electrons on the nitrogen atom upon the methyl group in some quinolizidine compounds. For instance in 212 the methyl signal was found at τ 8.9, whereas in 213 it was at τ 9.16. This result indicated that the methyl signal shifted downfield (τ 0.26), by changing it from the "cis" 1,3-diaxial to 1,3-axial-equatorial orientation.

Further support for our proposed assignment came from Wenkert's[82] nmr studies concerning the conformational implications in several flavopereirine derivatives, where again arguments pertinent to the C-3 proton and the methyl group of the ethyl side chain were made. These authors accept even larger limits between an axial and an equatorial

C-3 proton, anticipating a difference as large as τ 1.26. Partial structure (214) and (215) are given for these alkaloids.



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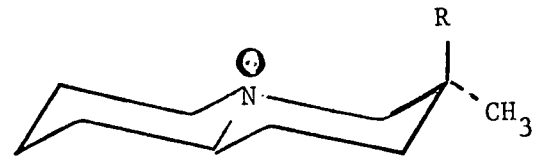

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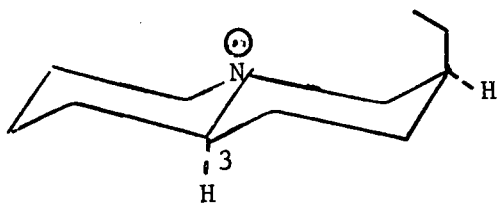

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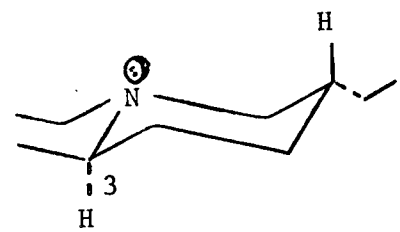

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Based on what we have discussed, we felt that alcohol-I is the "cis" dl-pair (206a) and (208a), whereas alcohol-II is the "trans" dl-pair (207a) and (209a) in Figure 33. Alcohol-I was crystallized from methylene chloride-hexane, mp 154-155°. The ultraviolet spectrum had a typical indole chromophore (227.5, 268, 297 nm), while the nmr spectrum (Figure 34) showed a multiplet at τ 5.90 due to the C-3 proton. The methyl protons of the ethyl side chain resonated as a triplet at τ 9.14, and the aromatic region had only three protons instead of eight as noted in the starting material 203. The mass spectrum (Figure 35) had fragments at m/e 149, 186, 199 and 328 (M^+) as expected. The molecular formula for this compound, $C_{20}H_{28}O_2N_2$, was established by elemental analysis and high resolution mass spectrometry.

The more polar isomer alcohol II, was more easily crystallized from

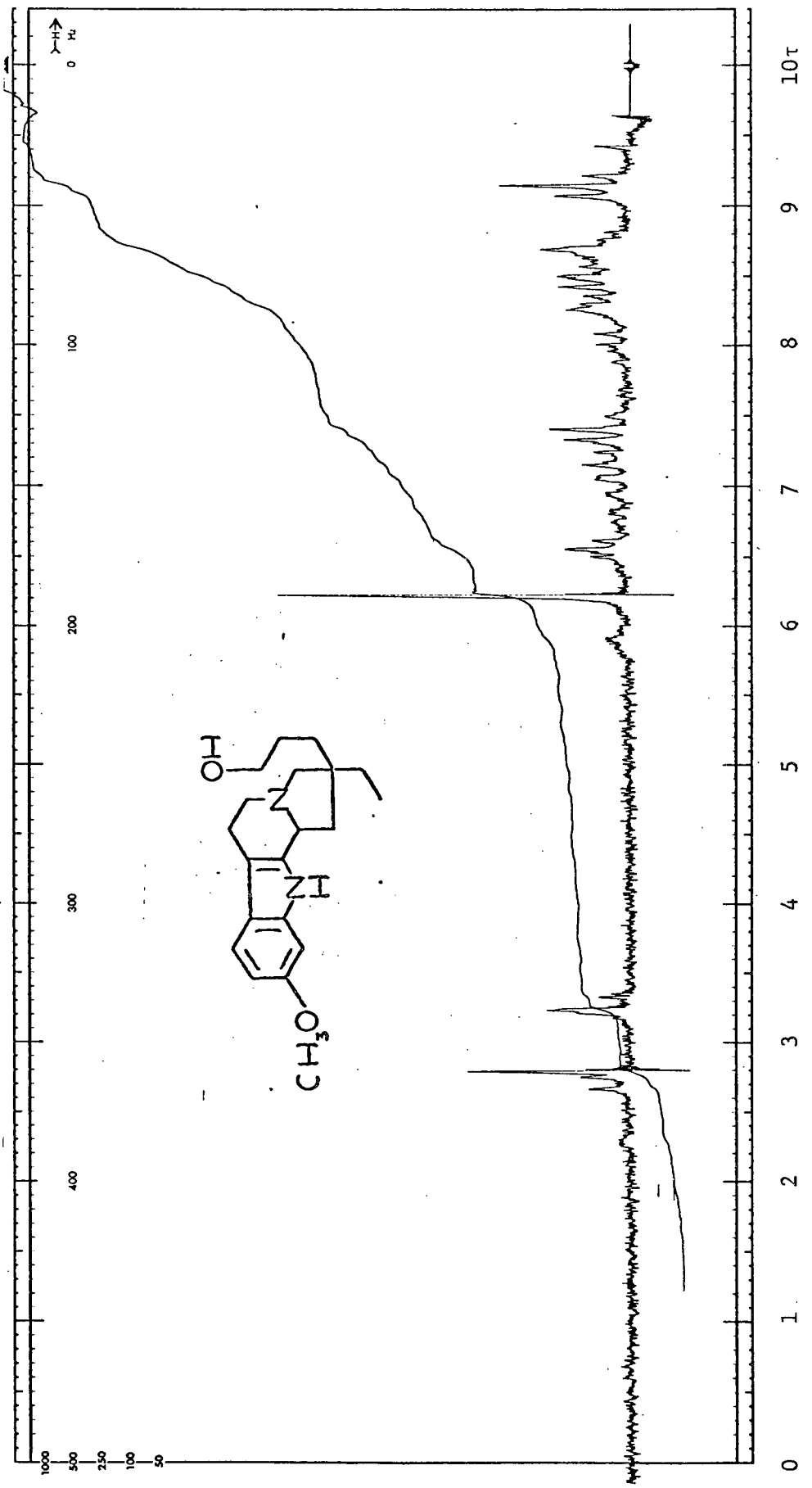


Figure 34. Nmr of alcohol I (206a and 208a).

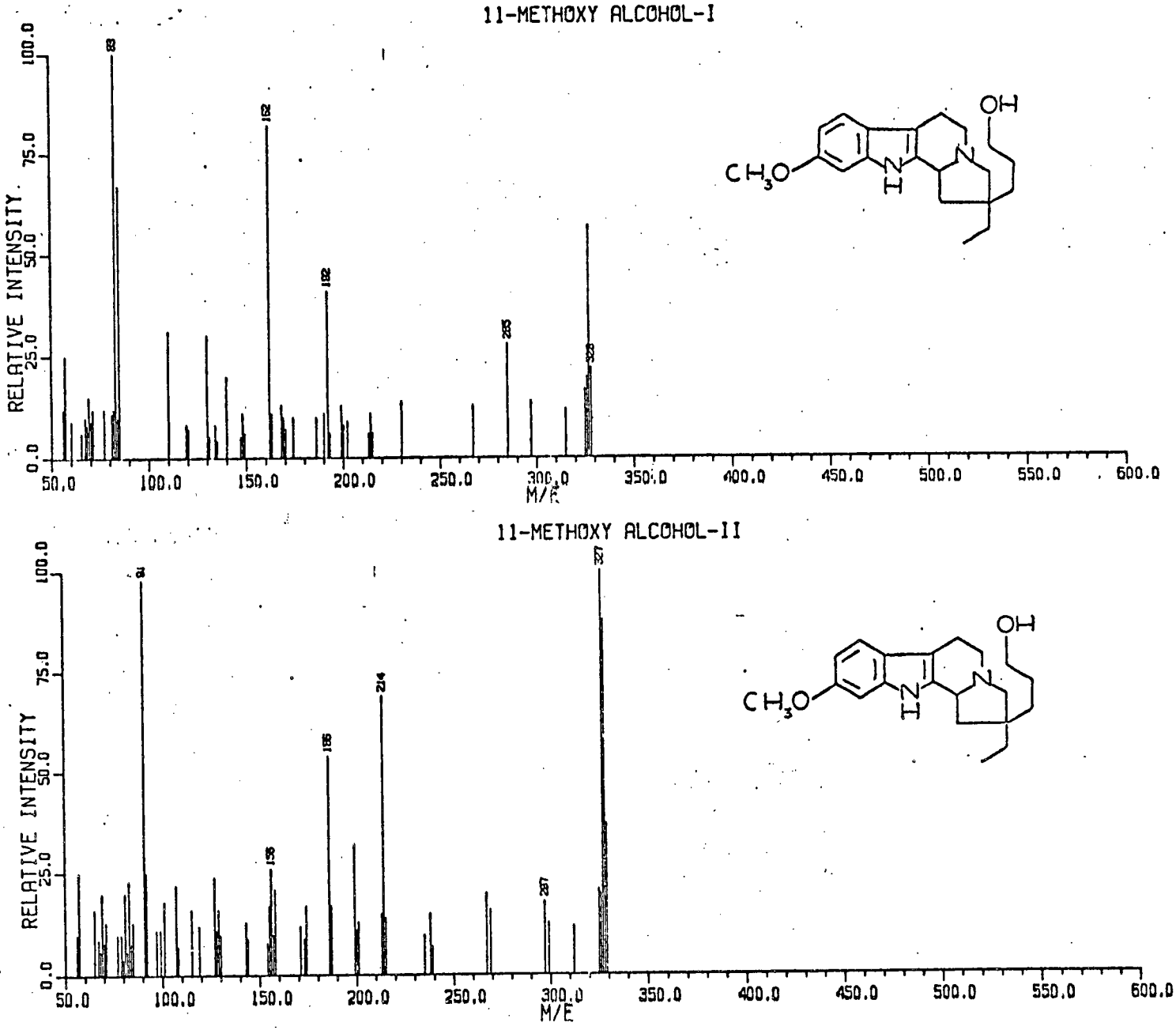


Figure 35. Mass spectra of alcohol I and alcohol II.

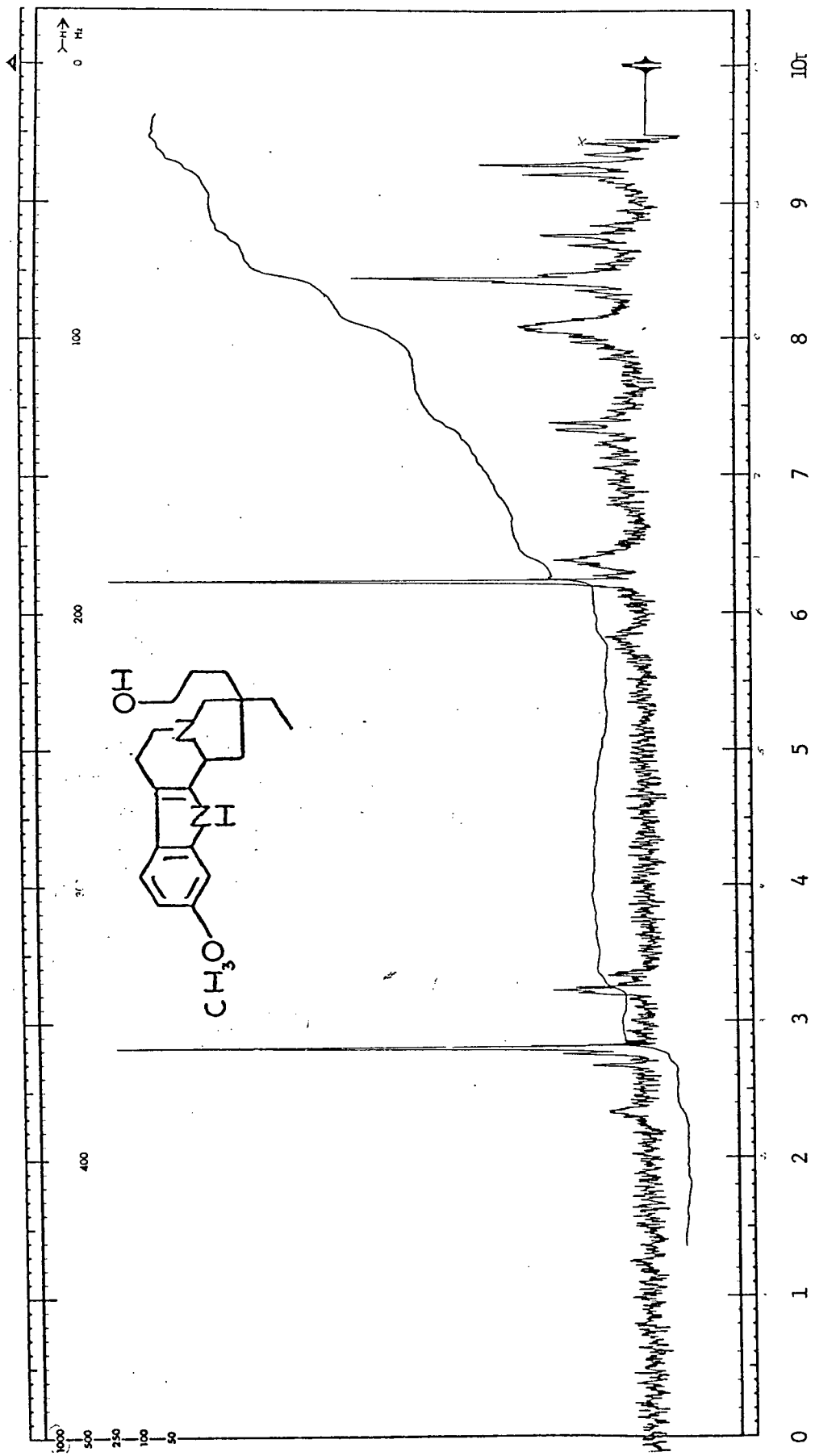


Figure 36. Nmr of alcohol II (207a and 209a).

methylene chloride to afford an analytical sample, mp 168-169°. The isomeric nature of both alcohols was established beyond doubt by elemental analysis as well as mass spectrometry. The infrared spectrum of this compound was almost superimposable with that of alcohol I. The nmr spectrum (Figure 36) was consistent with that of alcohol I but now the C-3 proton was seen as a multiplet at τ 5.82 while the methyl protons of the ethyl group resonated at higher field (τ 9.28). The mass spectrum (Figure 35) had the same pattern of fragmentation as was found for alcohol I, therefore each isomer exhibited spectral data in complete accord with the assigned structures.

Having obtained the required intermediate (204), our next aim was the generation of the nine-membered ring compound bearing the appropriate functional group at C-3, which would provide the basic Aspidosperma skeleton. The synthetic approach in which the piperidine ring was formed *via* intramolecular nucleophilic displacement of a mesyl group, is outlined in Figures 27 and 37. The resulting quaternary ammonium salt (205) upon nucleophilic attack at the carbon atom adjacent to the quaternary center, underwent a ring cleavage reaction with simultaneous introduction of the necessary functionality at C-3 to generate the vincaminoridine ring system (206) (Figure 37). Thus treatment of each of the isomeric alcohols (204) with methane sulfonyl chloride in the presence of triethylamine at 0°, provided a quantitative yield of the corresponding mesylates (205). These compounds were not completely characterized. When either of the mesylates of alcohol-I or alcohol-II was treated with potassium cyanide in dimethylformamide at 150° (bath temperature) followed by

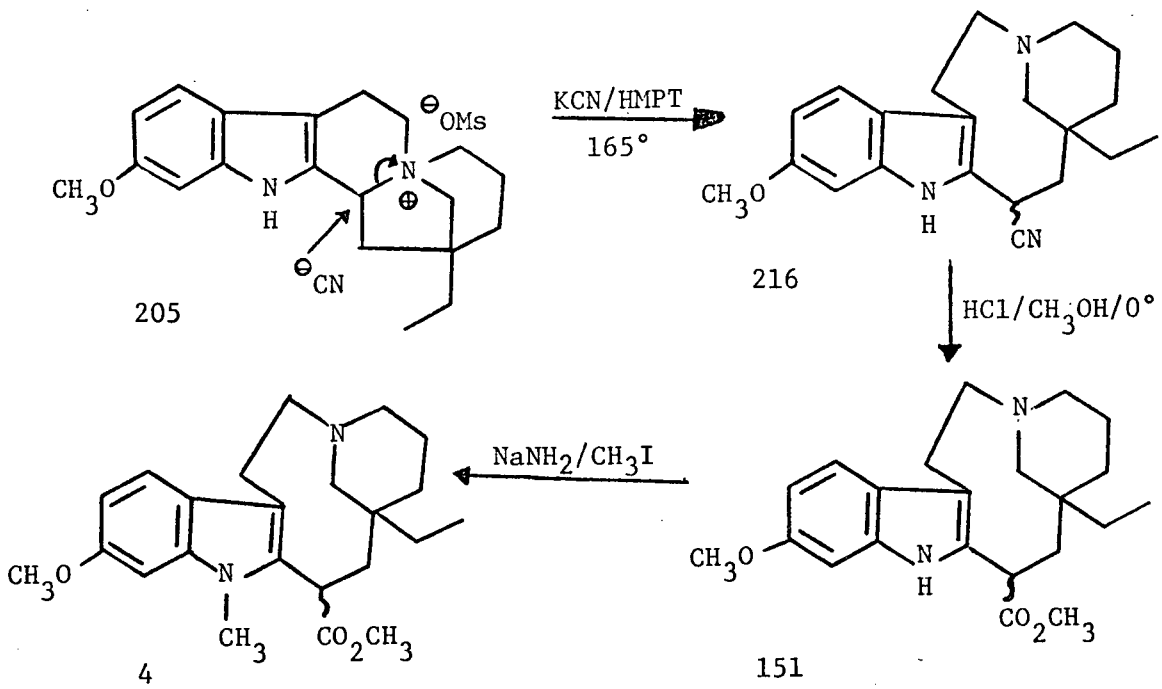


Figure 37. Preparation of dl-vincaminoridine (4) and its epimer.

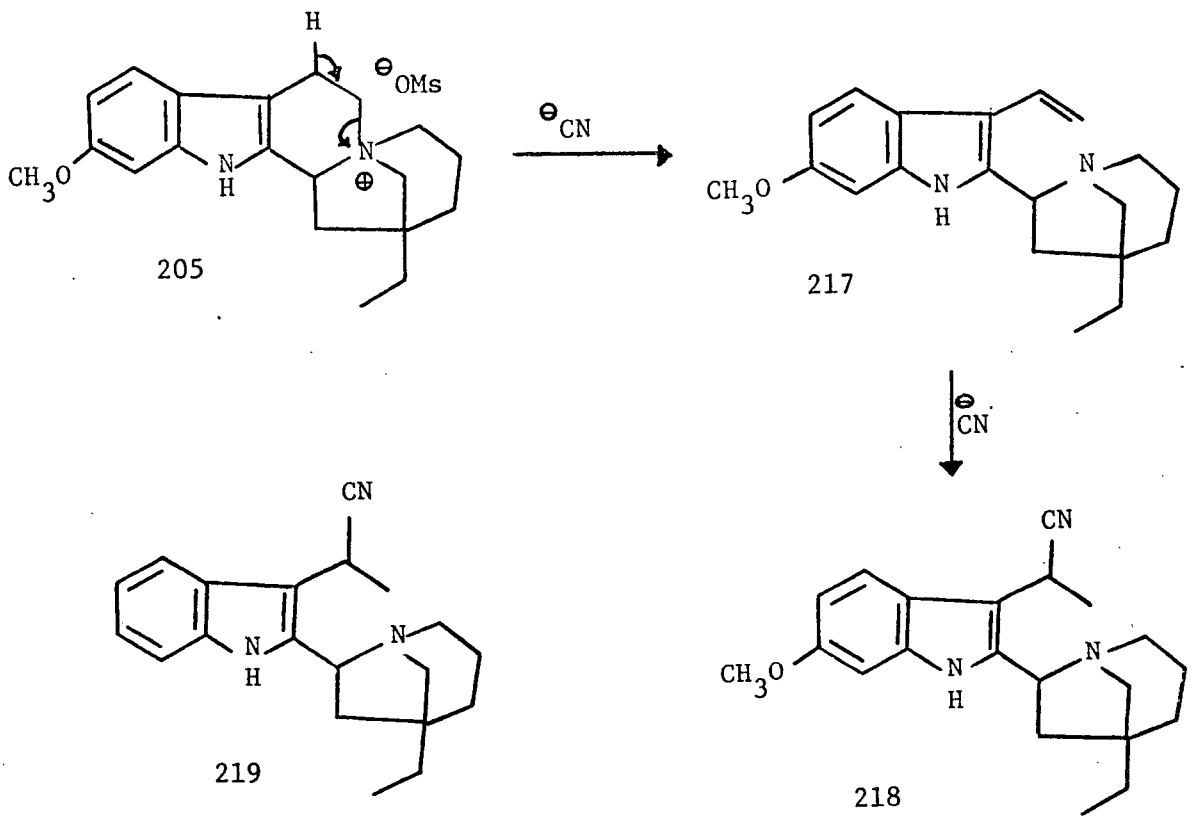
conventional workup of the reaction mixture, a dark gummy product was obtained. Investigation of the product mixture from either mesylate by means of tlc showed them to be identical. Chromatography of the crude product gave some starting material (205), and the two desired isomeric cyanides possessing the formula (216) but in unsatisfactory yield. Initial attempts to prepare these cyanides (216) failed or gave other products when the reaction was carried out in solvents such as diethylene glycol, dimethyl sulfoxide and dimethyl acetamide. In most of the cases, starting material (205) was recovered unreacted. A wide variation of reaction conditions (temperature, time, concentration, solvent) was attempted. A summary of these preliminary

investigations using 100 mg of the starting material (205) is given in Table I.

Table I.

Solvent	Temperature (°C)	Time (hr)	mg of CN containing product
DMSO	60	48	3
DMSO	60-110	48	20
DMSO	reflux	48	20
DMF	150	6	26
DMF	reflux	24	20
DMF/10% CH_3OH	reflux	24	15
HMPT	180	24	50

Perhaps the reason for the low yield of the reaction is due to the steric interference of the ethyl side chain. However it was obvious that the solvent effect plays a decisive role. It was clear from other investigations in our laboratory[7] that one of the most serious side reactions in this type of reaction is the ability of the cyanide ion to act as a base, and to perform a Hofmann elimination. That is, the intermediate 3-vinylindole derivative (217) resulting from the Hofmann reaction undergoes addition of cyanide to yield compounds of type 218. In a parallel series of investigations[7] on intermediates lacking the methoxyl group in the indole ring, such reactions did compete and the resulting product (219) was completely



characterized. On the basis of these results, it was clear that an increase in the yield of the conversion of 205 to 216 (Figure 37), was possible if we were to increase the nucleophilicity of the cyanide ion. Since dimethyl formamide showed some encouraging results we decided to turn our attention to other dipolar aprotic solvents. Hexamethylphosphoramide (HMPT) is a member of this class of reagents. To understand the special properties of HMPT as a reaction medium, one must be aware of the distinction between protic and dipolar aprotic solvents, which is extensively reviewed in the literature.[114] Protic solvents are proton donors such as water, alcohols, and formamide.

Dipolar aprotic solvents are characterized by dielectric constants[15] ε 7 , dipole moments at 7.3 D, and an inability to act as proton donors.[114] To a first approximation, cations are solvated by both classes of solvents fairly well by ion-dipolar interactions. However, anions are best solvated by molecules that can form H bonds and HMPT, like all dipolar aprotic solvents, lacks this characterization.

Hence, solvation of anions in these solvents is greatly reduced; not only do anions have a higher activity in HMPT[115,116] but bimolecular reactions will be considerably accelerated. On the basis of the above argument we decided on the use of HMPT as a solvent in order to increase the nucleophilicity of the cyanide ion.

Indeed when intermediate 205 was treated with potassium cyanide in HMPT at 165° for 7 hours, followed by conventional workup, we were able to isolate after column chromatography two cyanides (216) in 49% yield, as well as some unreacted starting material (205). The isomeric nature of these cyanides was established by elemental analysis and high resolution mass spectrometry which indicated the formula $C_{21}H_{27}ON_3$. An analytical sample was obtained by high pressure liquid chromatography (Figure 38). Cyanide I was crystallized from n-hexane-acetone, then methylene chloride (19%), mp 186-187°. The infrared spectrum showed the nitrile band at 2225 cm^{-1}, while the ultraviolet spectrum had maxima at 226, 277 and 298 nm. The nmr spectrum (Figure 39) showed a quartet at τ 6.12 (J_{AB} = 10 cps, J_{AC} = 3 cps) due to the C-3 proton (-CHCN), and a triplet at τ 9.07 (J = 7 cps) assigned to the methyl group of the ethyl side chain. The main fragments in the mass spectrum (Figure 40) were found at m/e 124,

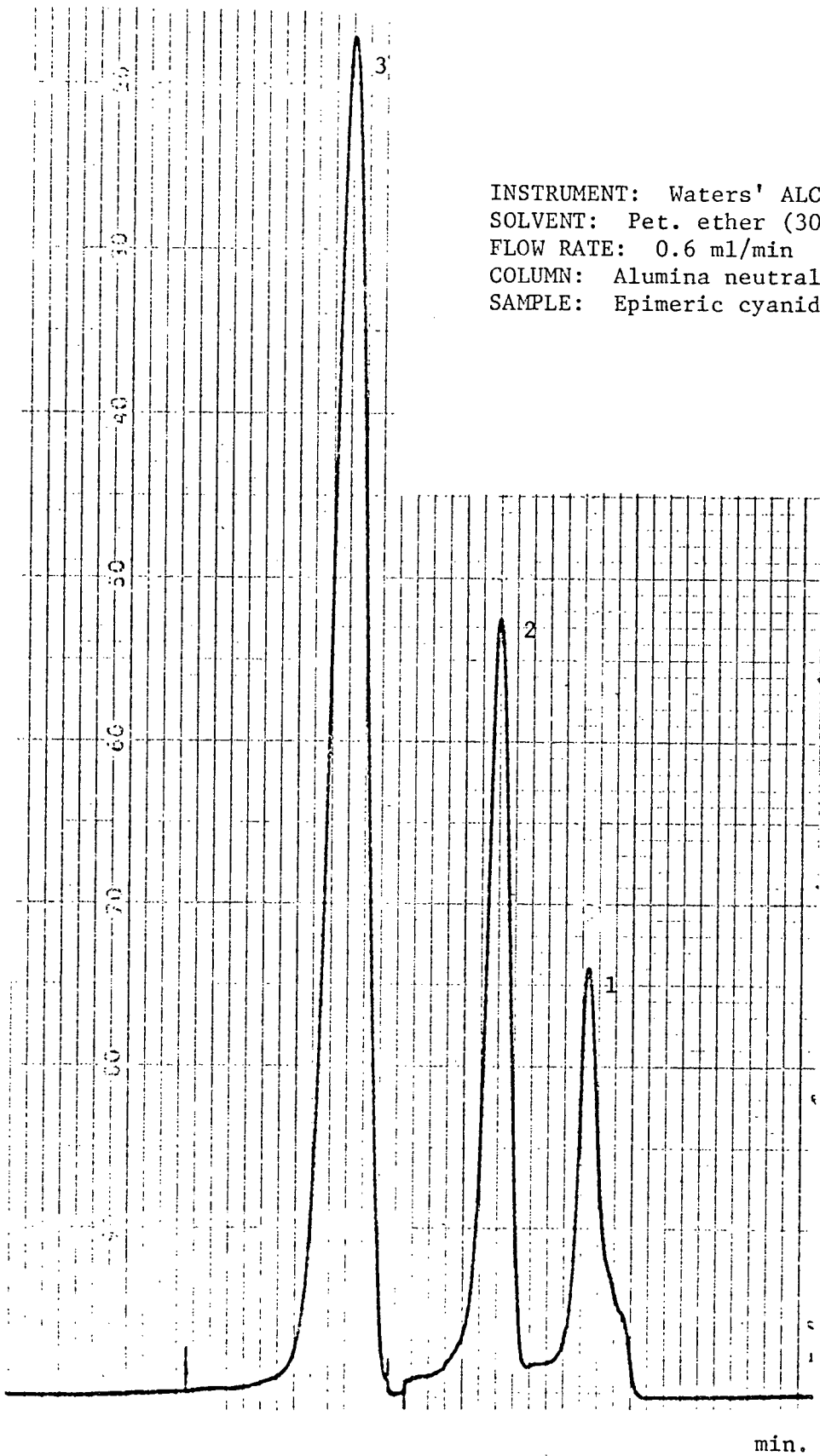


Figure 38. High pressure liquid chromatography of cyanide I and II. 2. Cyanide-I (20 min); 3. Cyanide-II (29 min).

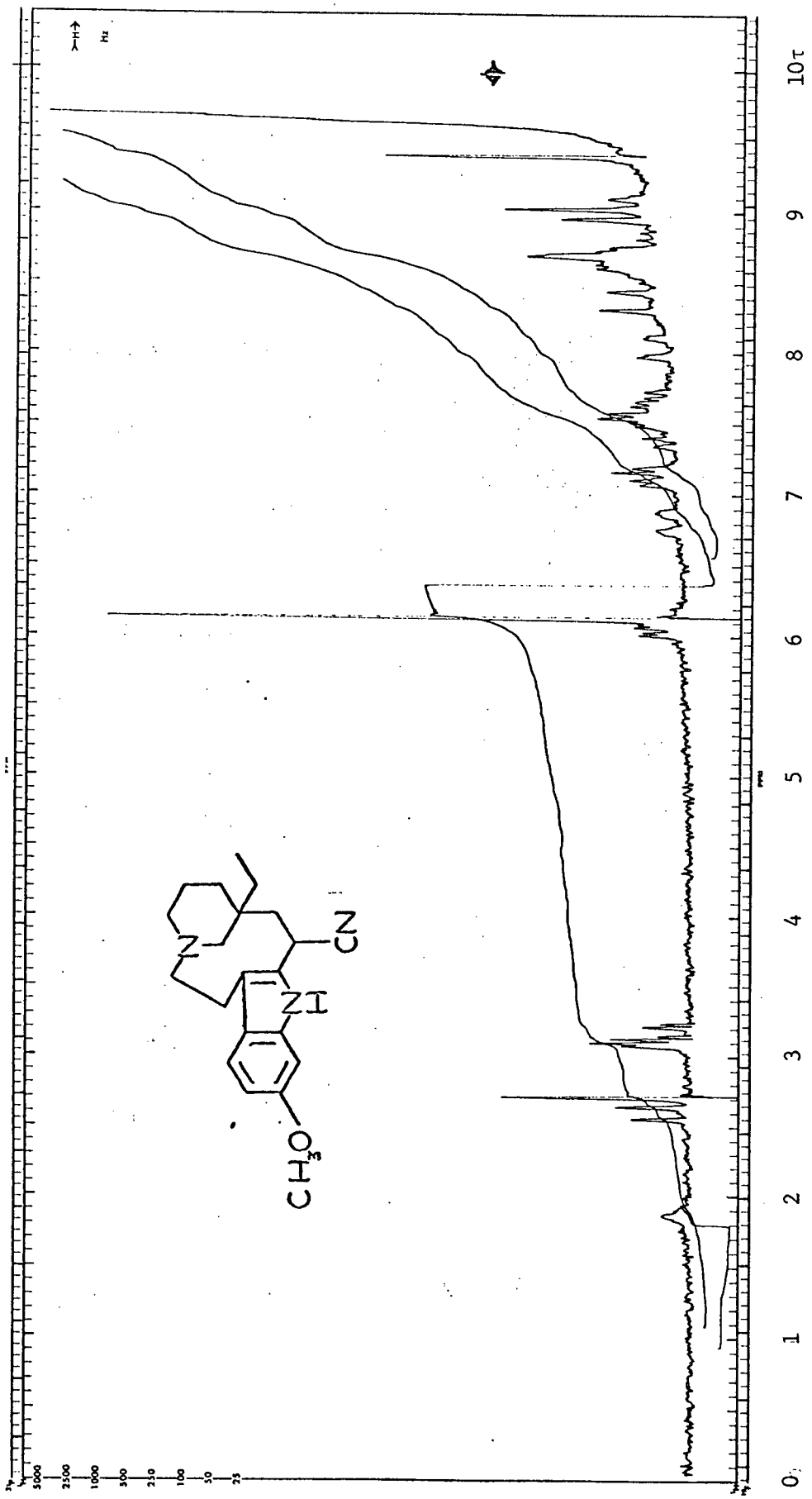


Figure 39. Nmr spectrum of 16-methoxy cyanide I (220).

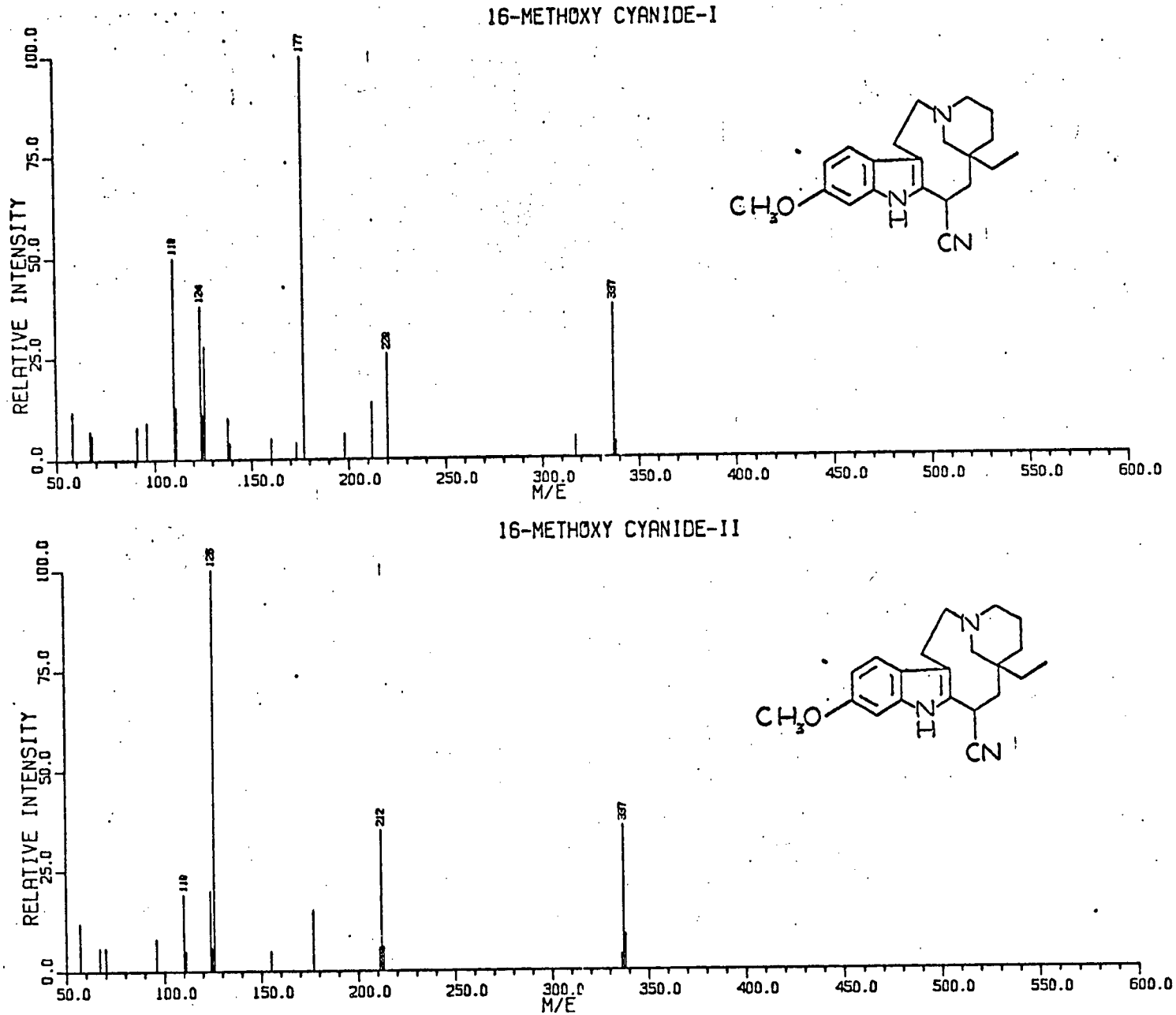


Figure 40. Mass spectra of 16-methoxy cyanide I and II.

126, 177, 212, and 337 (M^+). These fragments are depicted in Figure 41, and are in agreement with expectation.[117,118]

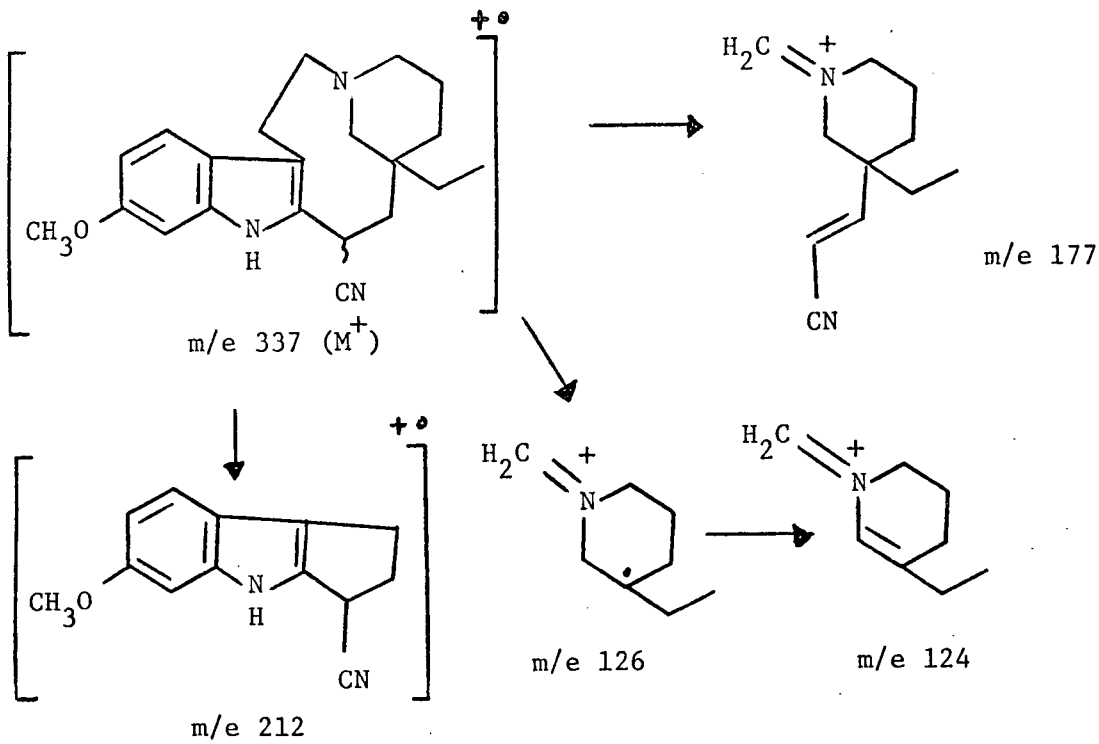


Figure 41. Fragmentation of cyanide I and cyanide II.

The cyanide II was crystallized from methanol (30%), mp 191-192°. The infrared spectrum was almost superimosable with that of cyanide I. The nmr spectrum (Figure 42) showed a quartet at τ 4.03 (J_{AB} = 10 cps, J_{AC} = 3 cps) assigned to the C-3 proton, while the methyl protons of the ethyl side chain resonated as a triplet at τ 9.34 (J = 7 cps). The mass spectrum (Figure 40) of this compound showed the same pattern of fragmentation as the less polar cyanide I.

The chemical shift of the C-3 proton for the cyanides I and II can be explained by considering several conformations similar to those

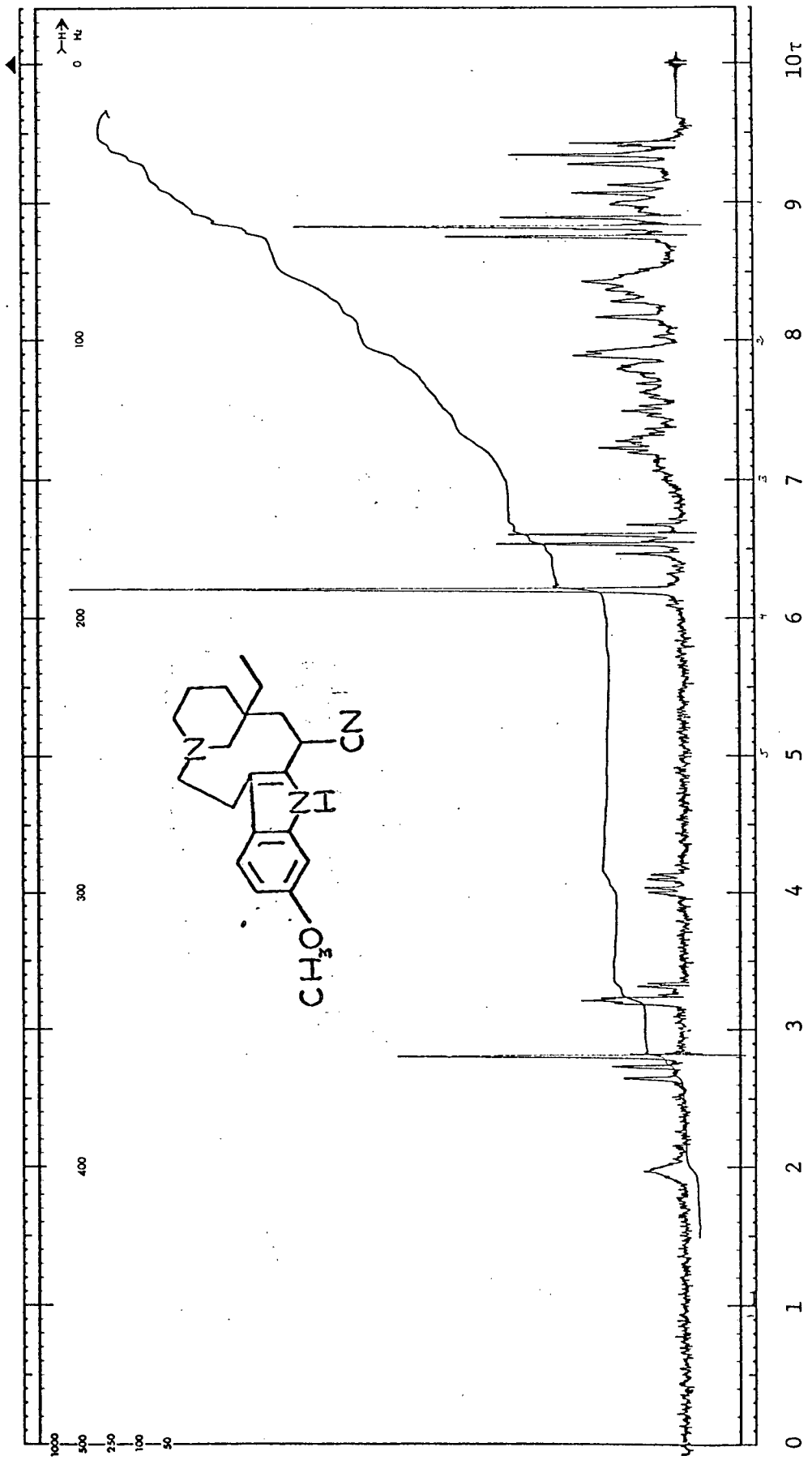
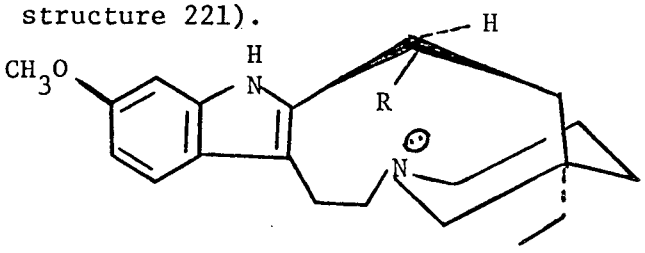


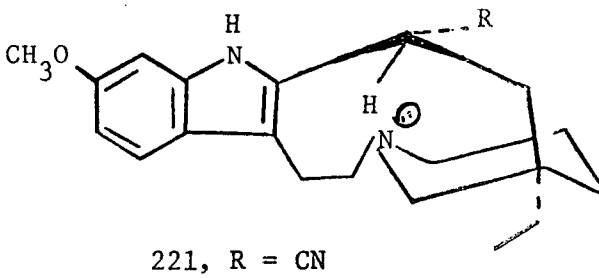
Figure 42. Nmr spectrum of 16-methoxy cyanide II (221).

proposed by Kompis.[119] According to his proposal, the C-3 proton is away from the lone pair of electrons on the nitrogen in the case of cyanide I resulting in no special effect by the nitrogen atom and a more normal position for this type of proton (τ 6.12, structure 220), while in the case of cyanide II the C-3 proton is close to the nitrogen resulting in magnetic deshielding of this proton (τ 4.03, structure 221).



220, R = CN

151a, R = CO_2CH_3



221, R = CN

151b, R = CO_2CH_3

Since it was known from previous experiments[7] that the alkaline hydrolysis of cyanide-I and cyanide-II gave the desired carbomethoxy derivative (151) in only 30% yield and decarboxylation may be a serious side reaction, it was felt that hydrolysis under acidic conditions might provide the ester derivative (151) in better yield. It would also provide us with some information about the stereochemistry at C-3 under these conditions. We first sought to carry out such a transformation by using a limited amount of hydrochloric acid, that had been generated in situ by solvolysis of acetyl chloride in anhydrous methanol.

Thus a mixture of the epimeric cyanides (216) was treated as indicated above, and stirred for 94 hours, followed by the conventional workup. The reaction product was isolated either by preparative tlc or high pressure liquid chromatography. However we found that this

approachhad been unsuccessful as far as the conversion of the cyano to the carbomethoxy group was concerned. Instead we had promoted an epimerization of cyanide-II to cyanide-I, completely reversing the ratio cyanide-I/cyanide-II initially present in the starting material (see Figure 38). We next increased the acid concentration and were able after conventional workup to isolate the desired carbomethoxy derivative (151) in 20% yield. Finally we decided to perform the hydrolysis in methanol that had been saturated with anhydrous hydrogen chloride.

Thus when the mixture of epimeric cyanides (216) was treated according to the above conditions we were able to isolate 16-methoxy-dl-vincadine (151a) and its C-3 epimer in 26% and 9% yield respectively. We observed that purification on alumina or silica gel resulted in poor recovery and decomposition of the desired esters. Perhaps it is appropriate to note that 16-methoxy-dl-vincadine (the major isomer) had the stereochemical features of cyanide-I (the minor isomer in the previous step of the synthetic sequence), as can be seen in the nmr spectra (Figures 39 and 43). It had a typical methoxy indole ultraviolet spectrum (228, 278 and 301 nm) and its infrared spectrum showed a strong carbonyl absorption at 1725 cm^{-1}. The nmr spectrum (Figure 43) was most informative. A new three-proton singlet due to the protons of the carbomethoxy group could be seen at τ 6.31, while an unresolved quartet at τ 6.35 was assigned to the C-3 proton. The methyl group of the ethyl side chain was found at τ 9.18.

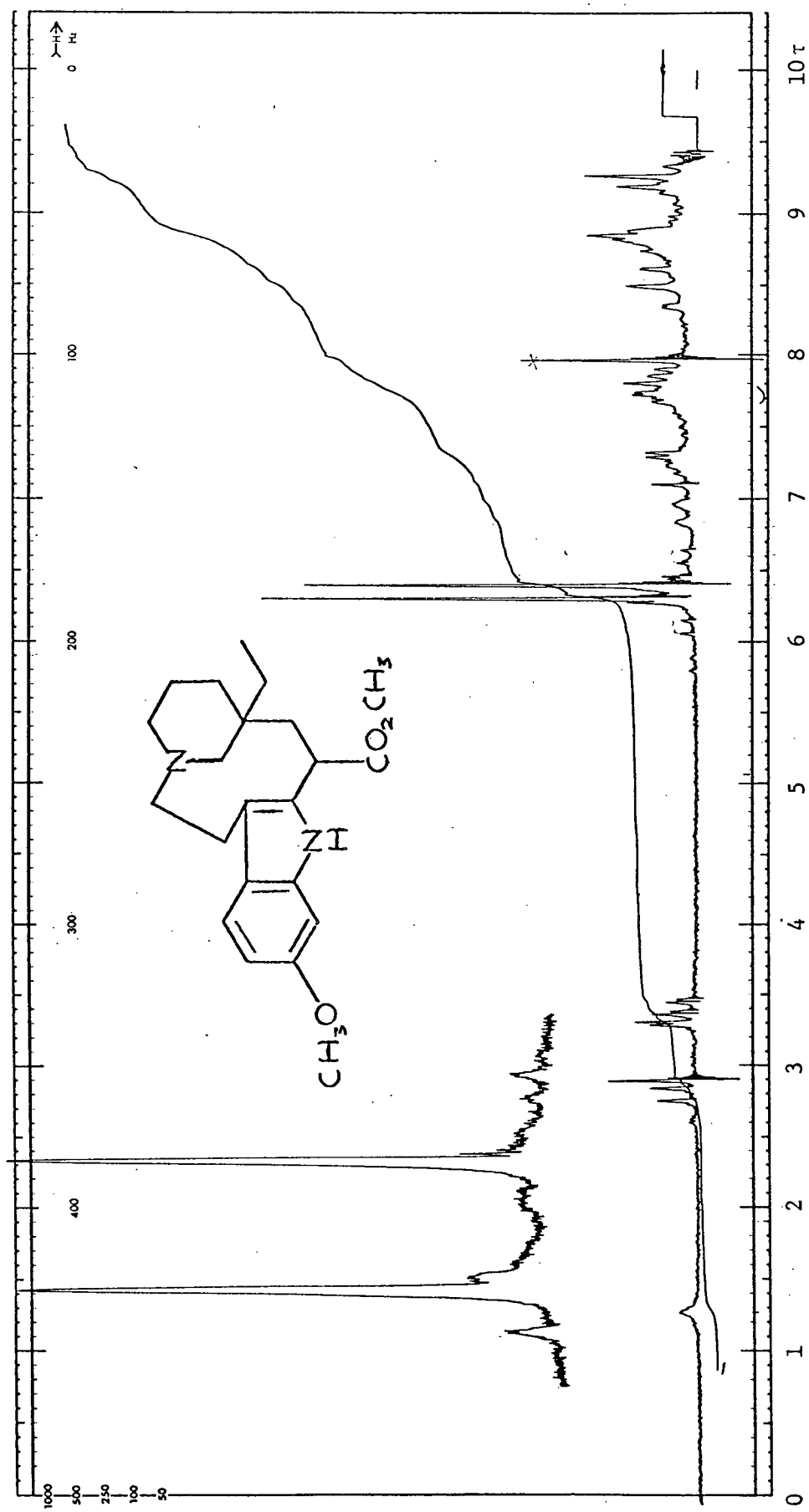


Figure 43. Nmr of 16-methoxy-dl-vincadine (151a).

The main fragments in the mass spectrum (Figure 44) were present at m/e 124, 138, 210, 245, and 370 (M^+). A rationalization for some of the fragments is presented in Figure 45. High resolution mass spectrometry established the formula $C_{22}H_{30}O_3N_2$ (found: 370.225; calc.: 370.225).

The minor isomer had also a methoxy indole chromophore and an infrared spectrum which was almost superimposable with that of the major isomer. However the nmr spectrum (Figure 46) now had the C-3 proton quartet (J_{AB} = 12 cps, J_{AC} = 2 cps) at τ 4.49. The three-proton singlet due to the carbomethoxy group was found at τ 6.38, while the methyl protons of the ethyl side chain were found as a triplet at τ 9.36. The mass spectrum (Figure 44) was similar to that of 16-methoxy vincadine. The isomeric nature of these two diastereo-isomers was confirmed by high resolution mass spectrometry.

The next step in the synthetic sequence in order to achieve the required intermediate 4, was the methylation of the indole nitrogen atom of the ester derivatives (151). This was done via the previously published procedure.[120] Thus treatment of 151 with sodium amide in liquid ammonia, followed by alkylation of the resulting anion with methyl iodide, gave the N-methyl compound (4) in good yield. The reaction product after conventional workup and purification by preparative tlc on silica gel gave the dl-epimers in 62% yield. The more polar of these dl-pairs on silica gel chromatoplates, had an infrared spectrum with no NH absorption and a strong carbonyl absorption (CO_2CH_3) was present at 1735 cm^{-1}. The ultraviolet spectrum (232, 288, 300 nm) was in good agreement with that reported in the literature.[16,119] The nmr

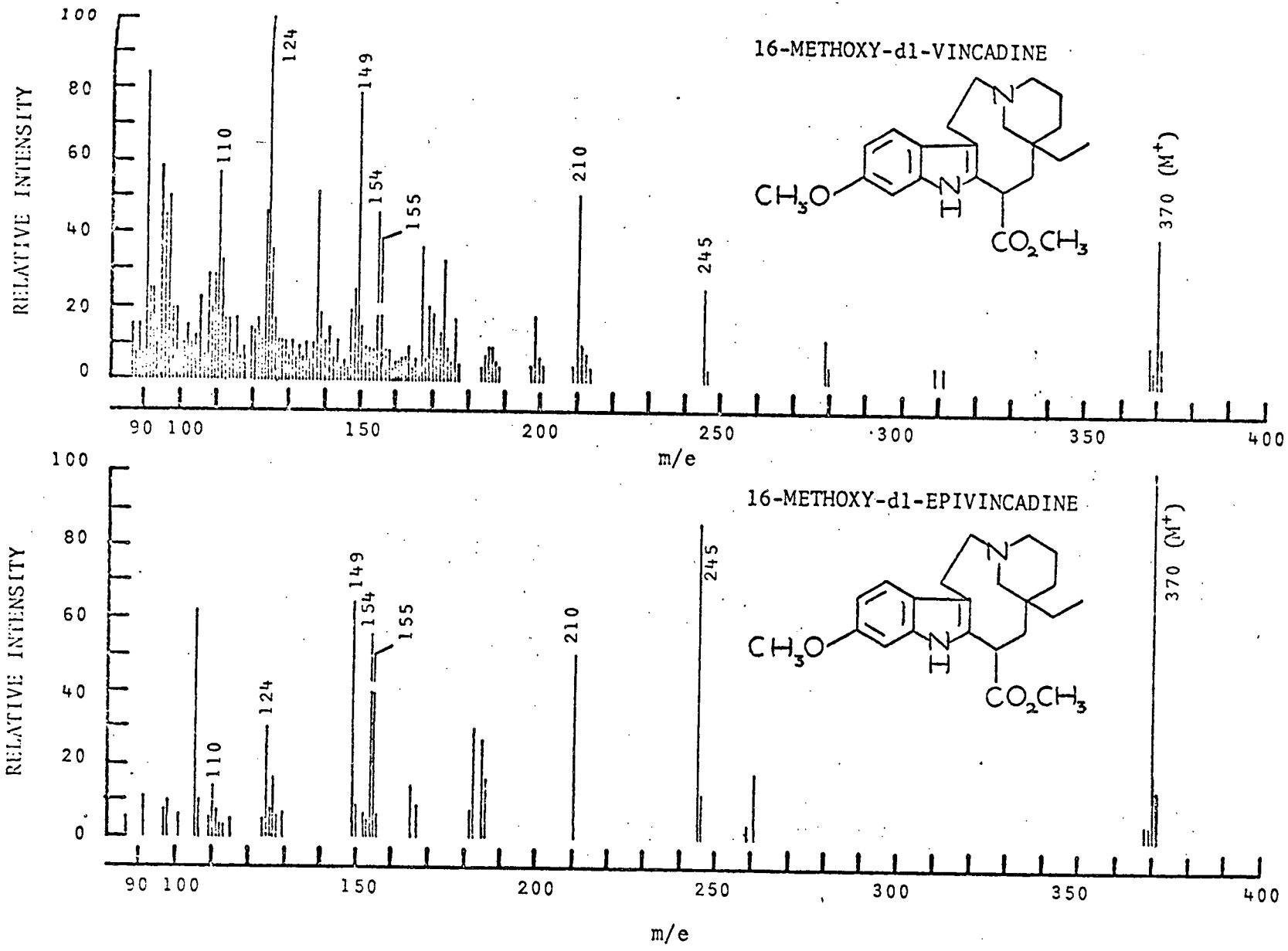


Figure 44. Mass spectra of 16-methoxyvincadine and its epimer.

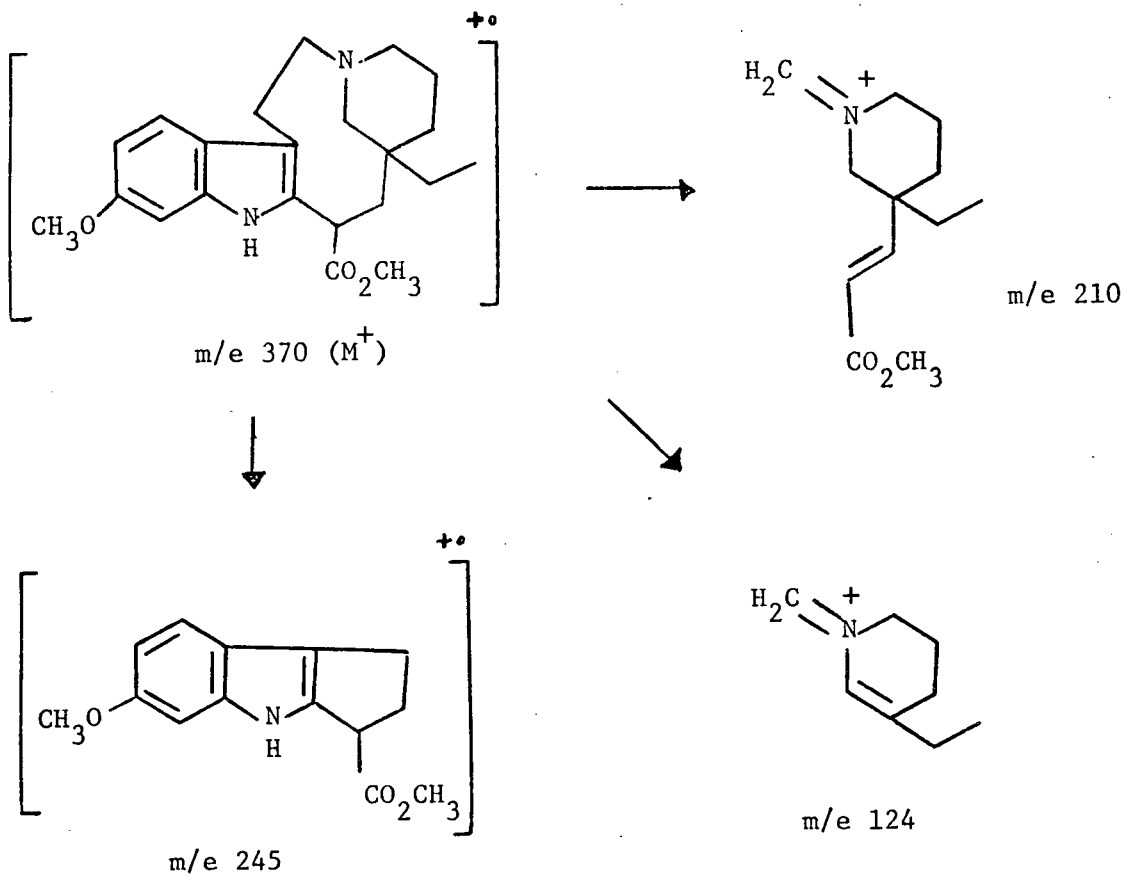


Figure 45. Fragmentation of 16-methoxyvincadine and its epimer upon electron impact.

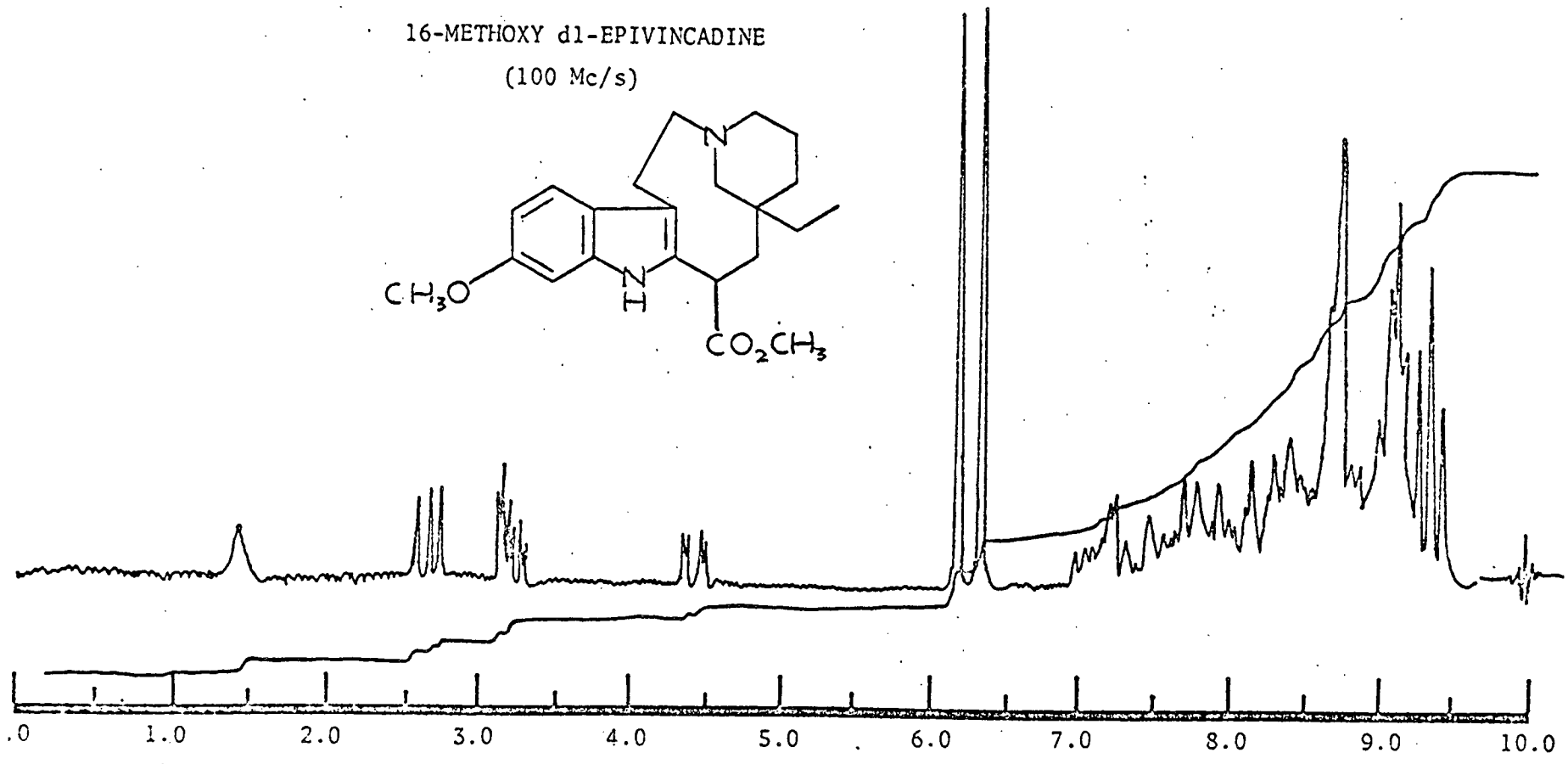


Figure 46. Nmr spectrum of 16-methoxy-dl-epivincadine (151b).
(Taken from C. Gletsos Ph.D. thesis)

spectrum (Figure 47) showed the absence of the signal due to the N-H proton, and a new singlet at τ 6.56 was assigned to the N-methyl group. The C-3 proton was found at τ 6.20 as a multiplet overlapping with one of the methoxy signals. The formula $C_{23}H_{32}O_3N_2$ for this compound was established by high resolution mass spectrometry (found: 384.239, Calcd.: 384.241). The mass spectrum (Figure 48) showed the expected fragments at m/e 124, 210, 259, and 384 (M^+). The less polar dl-pair had an infrared spectrum almost superimposable to that of the above compound. The ultraviolet spectrum was also a typical indole chromophore (232, 288, 298 nm). The nmr spectrum (Figure 49) showed the absence of signals due to the NH proton, and the N-methyl protons were found at τ 6.46. The C-3 proton was present as a multiplet at τ 3.90. The mass spectrum (Figure 48) had the expected peaks at m/e 124, 210, 259 and 384 (M^+). Comparison of the spectral data[121] of the natural vincaminoridine, an alkaloid isolated from Vinca rosea Linn. which has been assigned[119] the structure 4, with those of the above diastereoisomers confirmed the identity of our less polar isomer (C-3 proton at τ 3.90) with the natural alkaloid.

Having obtained the required nine-membered ring intermediate (4), the next obvious step in order to achieve the synthesis of the pentacyclic aspidosperma-type system (195) would be the transannular cyclization reaction. Although the pentacyclic structure (195) has not yet been isolated from natural sources, it was felt to be a valuable intermediate for the total synthesis of vindoline (3), and therefore would provide an entry into the dimeric series as well.

However, the transannular cyclization process (4 to 195) via the

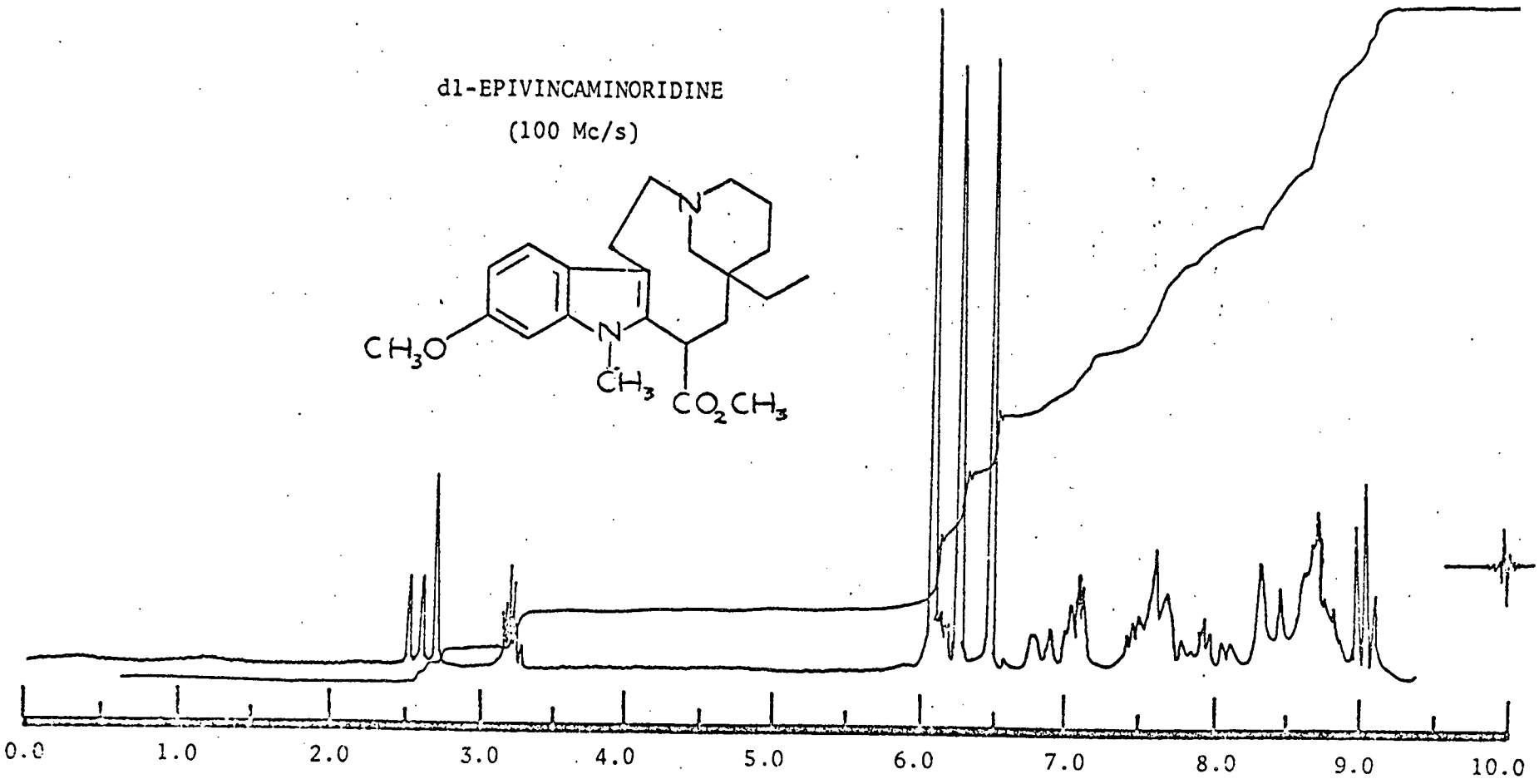


Figure 47. Nmr of dl-epivincaminoridine (4a). (Taken from C. Gletsos Ph.D. thesis)

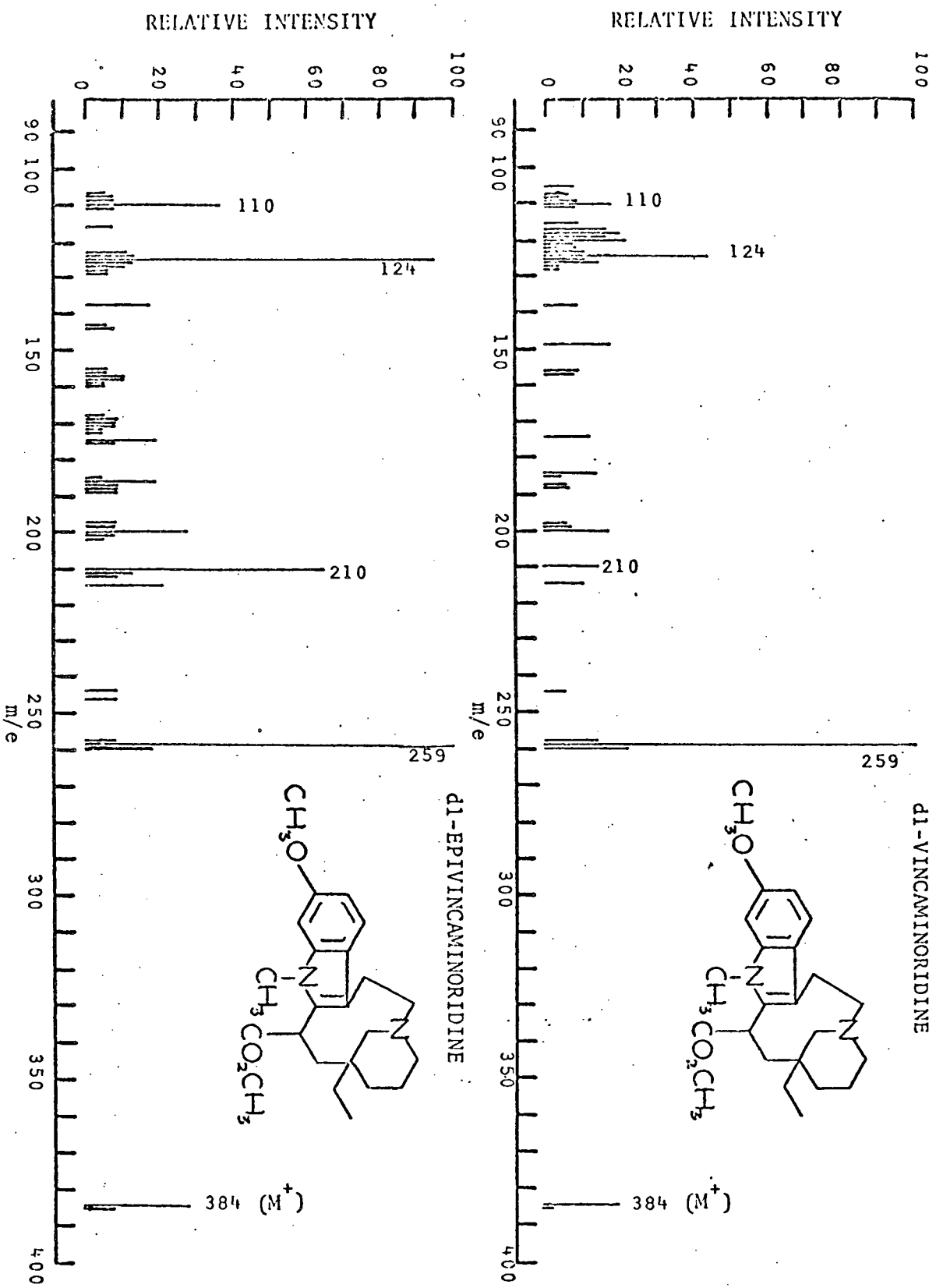


Figure 48. Mass spectra of dl-vincaminoridine and its epimer.

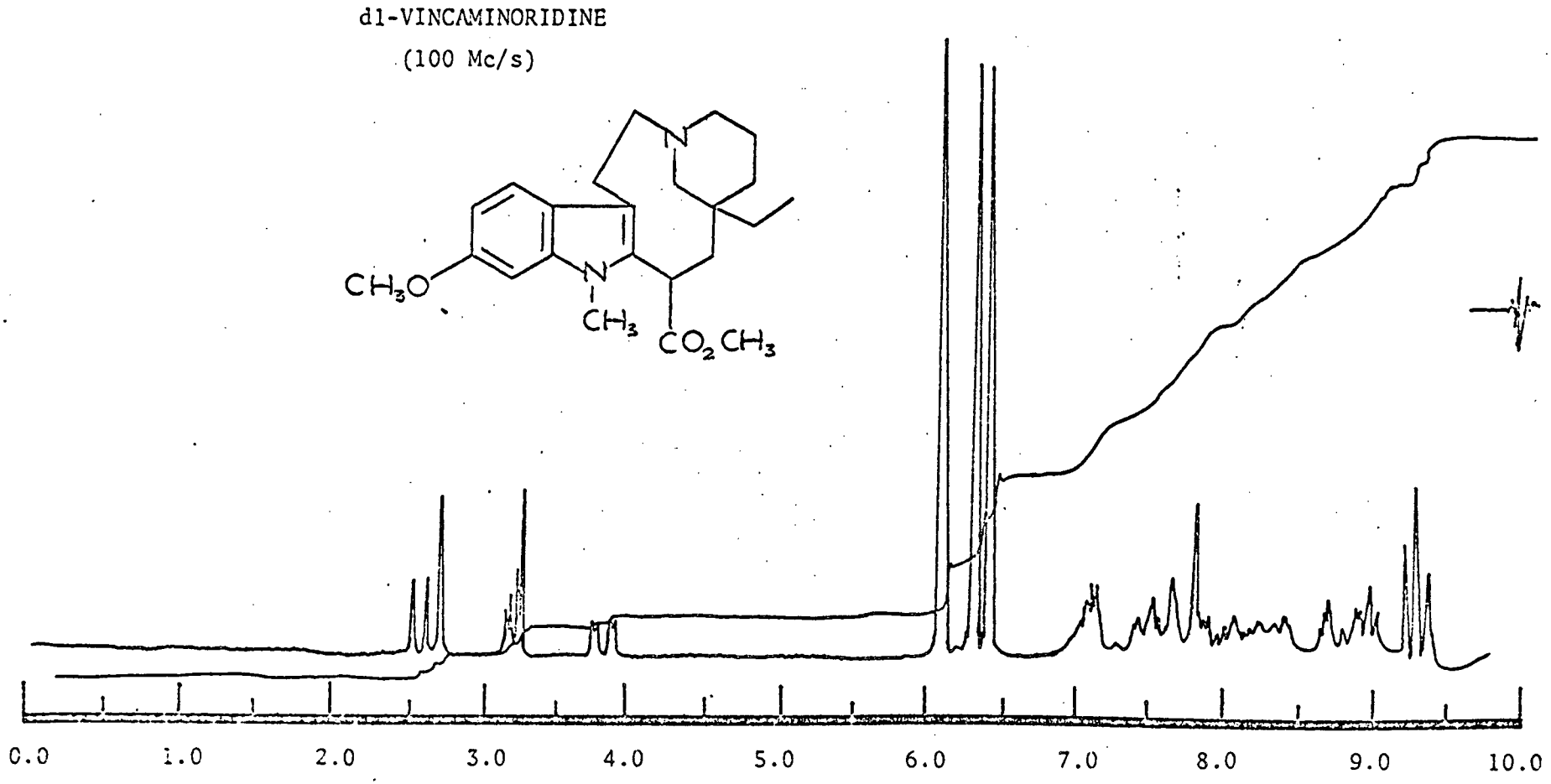


Figure 49. Nmr spectrum of dl-vincaminoridine (4). (Taken from C. Gletsos Ph.D. thesis)

iminium intermediate has important stereochemical implications. The necessary "folding" of the nine-membered ring system (4) requires a definite stereochemistry in the end product (195). Although this process has received considerable application particularly in our laboratory, and to a lesser extent in other groups, the overall importance of the stereochemistry at C-3 has not been ascertained. Preliminary investigation of the conversion of 4 to 195 using mercuric acetate oxidation in glacial acetic acid at room temperature on a mixture of the epimeric carbomethoxy derivatives gave a reaction product which was purified by preparative tlc on alumina. Two semi-crystalline materials in 11% (less polar component) and 24.5% (more polar component) yields were obtained. The infrared spectra of both of these compounds were superimposable. Mass spectra of this material had fragments at m/e 149, 202, 263, and 382 (M^+). High resolution mass spectrometry established the formula, $C_{27}H_{32}O_4N_2$ (found: 382.224; Calc.: 382.255). The ultraviolet spectrum of the less polar compound had maxima at 225, 310 (infl.) and 335 nm, while the more polar had maxima at 225, 310 (infl.) and 340 nm. The above results suggested that they were the desired cyclization product (195), but the small amount of material available did not allow us to take an nmr spectrum.

Since our synthetic approach led predominantly to one epimer (4) and we were not sure which stereoisomer would undergo the transannular cyclization reaction in better yield, we decided to investigate the possibility of epimerization of the major isomer. Indeed dl-epivincaminoridine upon treatment with sodium methoxide in refluxing methanol for 48 hours, followed by the conventional workup and isolation by

thin layer chromatography, provided dl-vincaminoridine and dl-epivincaminoridine in a 2:3 ratio.

At this point it was decided that we should turn our efforts toward another series of investigations that involved the degradation of vindoline (3). The degradation sequence could provide a feasible high yielding route to the pentacyclic intermediate 195. It would also give us an opportunity to compare our totally synthetic materials, presently in racemic form, with the appropriate optically active templates. These latter substances would not only help us in the identification and characterization of the synthetic products, but they might be utilized as relays for further synthetic work. Furthermore the degradation sequence would also provide, in optically active form, appropriate dihydroindole units that would be invaluable in other synthetic areas. Those modified templates could perhaps lead to the synthesis of new dimers related to vinblastine (1) and vincristine (2) but with different pharmacological activity.

A discussion of these experiments is present in Part II of this thesis.

EXPERIMENTAL I

Melting points were determined on a Kofler block and are uncorrected. Ultraviolet spectra were measured in 95% ethanol or methanol on a Cary model 15 spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer 21 or 137 spectrophotometer. Nuclear magnetic resonance spectra (nmr) were taken in deuterochloroform solution on Varian Associates spectrometers, models T-60, HA-100 or XL-100. Line positions are given in the Tiers τ scale, with tetramethylsilane as an internal standard. The types of protons, integrated areas, multiplicity and spin coupling constant J are indicated in parentheses. Mass spectra were recorded on an Atlas CH-4B or Associated Electrical Industries MS-902 spectrometer, high resolution measurements being determined on the latter instrument.

Silica gel G and alumina Woelm containing 2% by weight of a fluorescent indicator were used for thin-layer chromatoplates. As spraying reagent a solution 1:2 of antimony pentachloride in carbon tetrachloride, or a solution of ceric sulfate in aqueous sulfuric acid were used extensively. Unless otherwise specified column chromatography was performed using either Woelm grade silica or neutral alumina, and deactivated as required with the correct amount of water. Distilled solvents were used. High pressure liquid chromatography was performed either on a Waters ALC-100 or ALC-202 instrument.

Elemental analyses were performed by Mr. P. Borda of the Microanalytical Laboratory, University of British Columbia.

Synthesis of Aldehydo Ester (140)

The initial experiments involving the preparation of the aldehydo ester (140) were performed according to the previously established procedure.[7,88,103] Details of the quantities used and the yields obtained in this work, for the various steps are given below. Also where small differences in conditions and/or yields were observed these are indicated.

γ-Benzyloxy propanol (197)

The monosodium salt of propane-1,3-diol (500 g) in xylene was treated with benzyl chloride under the conditions outlined in the literature.[101] The product was obtained as a clear oil (254.4 g, 66% yield). bp 95-100°/1-2 mm (lit. 145-150°/13 mm).

Benzyl γ-Chloropropyl Ether (198)

γ-Benzyloxy propanol (197) (234 g) was treated with thionyl chloride (190 g) in dimethyl aniline, according to the known procedure.[102] The product was obtained as a colorless oil (200 g) in 80% yield, bp 95-100°/1 mm (lit. 129°/16 mm).

Diethyl γ-Benzyloxypropylethyl Malonate (134)

Ethyl diethyl malonate (81 g) was alkylated with benzyl γ-chloropropyl ether (198) (81 g) in the presence of sodium ethoxide in absolute ethanol according to the literature procedure.[88] The desired product,

was obtained as a colorless oil (76 g) in 54% yield, bp 140-150°/0.1 mm.

γ-Benzyloxypropylethyl Malonic Acid (199)

Diethyl γ-benzyloxypropylethyl malonate (134) 976 g) was treated with potassium hydroxide in ethanol/water according to the literature procedure.[88] The product was crystallized from n-hexane-ether as colorless mass in (51 g) 81% yield, mp 117-120°.

2-(γ-Benzyloxypropyl)-butanoic Acid (200)

γ-Benzyloxypropylethyl malonic acid (51 g) (199) was decarboxylated[88] to give the desired product as a yellow viscous oil (43 g). The product was not further purified but subjected to the next reaction.

Ethyl α-(γ-benzyloxypropyl)-butanoate (135)

A solution of 2-(γ-benzyloxypropyl)-butanoic acid (40 g) (200) in absolute ethanol was esterified according to the literature procedure.[88] The desired product was obtained as a clear oil (38 g) in 76% yield, bp 135°/1.5 mm.

Ethyl α-(γ-Benzyloxypropyl)-α-allylbutanoate (201)

Ethyl α-(γ-benzyloxypropyl)-butanoate (24 g) (135) in ether, was alkylated with allyl bromide (11.6 g) in the presence of sodium triphenyl methane as indicated in the literature.[7,90] The desired alkylated product was obtained as a colorless oil (22 g) in 83% yield, bp 132-134°/0.15 mm.

Ethyl α-(γ-benzyloxypropyl)-α-(α-formylmethyl)-butanoate (140)

A solution of the allyl compound (24 g) (201) in tetrahydrofuran was treated with osmium tetroxide and sodium metaperiodate according to the literature procedure.[7,90] Purification by vacuum distillation, gave the desired aldehydo ester (168) in 70% yield as a colorless oil, bp 174-176°/0.75 mm.

Preparation of 11-methoxycyclic lactam (150)

6-Methoxy tryptamine (149) (7 g, 36.8 mmole) and the aldehyde ester (140) (15 g, 49 mmole) in glacial acetic acid (25 ml) were refluxed for 1.5 hr, under an atmosphere of oxygen-free nitrogen. The acetic acid was removed under reduced pressure to give a yellow residue. Purification on a basic alumina column (Shawnigan, 400 g) and elution with pet. ether-ethyl acetate (2:3) gave the pure lactam (150) (16 g, 98%). This product was a mixture of the two expected diastereoisomers but no attempts to separate them at this stage were necessary for our purpose. Infrared (liq. film) 3250 (broad, hydrogen bonded NH), 1735 (small) and 1670 (strong, lactam) cm^{-1}. Ultraviolet; λ_{max} (log ε): 227 (4.12), 264 (sh, 3.73), 272 (sh, 3.72), 295 (3.75), 321 (3.47), 335 (3.39) nm. Nmr signals (100 MHz): τ 1.56 (broad singlet, 1H, NH), 2.75 (multiplet, 6H, aromatic), 3.20 (singlet, 1H, C-12 proton), 3.25 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-10 proton), 5.25 (broad triplet, J = 8 cps, 1H, C-3 proton), 5.55 and 5.66 (singlets, 2H, $C_6H_5CH_2O$-), 6.23 (singlet, 3H, CH_3O-), 9.05 and 9.28 (triplets, J = 7 and 7 cps, 3H, CH_3CH_2-). Mass spectrum, main peaks: m/e 91, 149, 188, 263, 341, 432 (M^+). Molecular weight: 432.241. Calc. for $C_{27}H_{32}O_3N_2$: 432.241. Found: C, 75.21; H, 75.21; H, 7.51; N, 6.52. Calcd. for

$C_{27}H_{32}O_3N_2$: C, 74.97; H, 7.46; N, 6.48.

Preparation of 11-methoxycyclic amine (203)

The lactam (150) (25 g, 0.051 mole) was dissolved in anhydrous tetrahydrofuran (150 ml, distilled from $LiAlH_4$ and stored over CaH_2) and slowly added with stirring to a solution of $LiAlH_4$ (16 g, 0.420 mole) in anhydrous tetrahydrofuran (450 ml). The reaction was performed under dry conditions and an atmosphere of oxygen-free nitrogen. Refluxing with adequate stirring for 72 hr followed. The reaction mixture was cooled to room temperature and then in an ice-water bath. Wet tetrahydrofuran (water in THF, 1:3) was added carefully with vigorous stirring to decompose the complex and excess $LiAlH_4$. The white sludge was stirred for 20 minutes more and it was filtered through a bed of celite. The cake was washed three times with hot tetrahydrofuran. The filtrate was dried over anhydrous magnesium sulfate. Filtration and removal of the solvent under reduced pressure gave a light yellow gum (24.5 g). This gum was chromatographed on a basic alumina column (Shawinigan, 400 g). Elution with benzene-ethyl acetate (20-100%) gave the desired product, a pure mixture of the two dl-epimers (22 g, 92%). Infrared (neat): no carbonyl absorption. Ultraviolet; λ_{max} (log ε): 230 (4.18), 263 (3.68), 270 (sh, 3.66), 300 (3.74) mm. Nmr signals (100 MHz): τ 2.04 (broad singlet, 1H, NH), 2.70 (multiplet, 6H, aromatic), 3.25 (singlet, 1H, C-12 proton), 3.30 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-10 proton), 5.53 and 5.65 (singlets, 2H, $C_6H_5\underline{CH}_2O$-), 5.93 (broad triplet, J = 6 cps, 1H, C-3 proton), 6.26 (singlet, 3H, CH_3O-), 9.16 and 9.30 (triplet, J = 7 cps and 7 cps, 3H, CH_3CH_2-). Mass spectrum; main peaks: m/e 91, 149, 214, 260, 327 and 418 (M^+). Molecular weight: 418.265. Calc. for

$C_{27}H_{34}O_2N_2$: 418.262. Found: C, 77.61; H, 8.21; N, 6.62. Calc. for $C_{27}H_{34}O_2N_2$: C, 77.47; H, 8.19; N, 6.69.

Debenzylation of the Mixture of dl-Epimeric Amines (203)

To the mixture of amines (203) (20 g, 47.8 mmole) dissolved in ethyl alcohol (250 ml) and concentrated HCl (8 ml), 10% palladium on charcoal (2 g) was added. The mixture was stirred and hydrogenated at room temperature and 1 atm. pressure for 6.5 hr. When no more uptake of hydrogen was noted the reaction was stopped. The catalyst was removed by filtration, through a bed of celite and the cake was washed several times with methanol. The filtrate was concentrated under reduced pressure at room temperatre and then basified by careful addition of a saturated solution of sodium carbonate. To the resulting basic solution (litmus paper), water (150 ml) was added and extraction with methylene chloride (6 x 100 ml) followed. The combined organic layers were washed with water (2 x 200 ml) and dried over anhydrous sodium sulfate, filtration and removal of the solvent under reduced pressure afforded a yellowish solid (15 g). This material was dissolved in a minimum amount of ethyl acetate. To the solution was added a few grams of alumina and the ethyl acetate was evaporated off from the slurry. The alumina coated with the same was then transferred to the top of a column filled with alumina (Shawinigan, 650 g) in benzene. Gradient elution with ethyl acetate-ethanol (98:2) gave alcohol-I (less polar) and with ethyl acetate-ethanol (9:1) afforded alcohol-II.

11-Methoxy Alcohol-I - Amorphous solid (3.73 g, 24%). It was crystallized from methylene chloride-n-hexane (3:1), washed with cold

acetone and recrystallized once more from wet methanol, mp 154-155°. Infrared (KBr): absence of strong benzylic bands between 770-690 cm^{-1}. Ultraviolet: λ_{max} (log ε): 227.5 (4.42), 268 (3.66), 297 (3.73) mm. Nmr signals (100 MHz): τ 2.28 (broad singlet, 1H, NH), 2.71 (doublet, J_{ortho} = 9 cps, 1H, C-9 proton), 3.22 (doublet, J_{meta} = 2 cps, 1H, C-12 proton), 3.30 (quartet, J_{meta} = 2 cps, J_{ortho} = 9 cps, 1H, C-10 proton), 5.90 (multiplet, 1H, C-3 proton), 6.22 (singlet, 3H, CH_3O-), 6.55 (triplet, 2H, $-CH_2OH$), 9.14 (triplet, 3H, CH_3CH_2-). Mass spectrum; main peaks: m/e 149, 186, 199, 214 and 328 (M^+). Molecular weight: 328.215. Calc. for $C_{20}H_{28}O_2N_2$: 328.215. Found: C, 72.89; H, 8.69; N, 8.60. Calcd. for $C_{20}H_{28}O_2N_2$: C, 73.13; H, 8.59; N, 8.53.

11-Methoxy Alcohol-II - Amorphous solid (6.31 g, 40%). Crystallized easier than alcohol-I from methylene chloride, mp 168-169°. Infrared (KBr): absence of strong benzylic bands between 770-690 cm^{-1} and similar with that of alcohol-I. Ultraviolet: λ_{max} (log ε): 227 (4.50), 269 (3.71), 297 (3.79) mm. Nmr signals (100 MHz): τ 2.16 (distorted singlet, 1H, NH), 2.70 (doublet, J_{ortho} = 9 cps, 1H, C-9 proton), 3.21 (doublet, J_{meta} = 2 cps, 1H, C-12 proton), 3.30 (quartet, J_{meta} = 2 cps, J_{ortho} = 9 cps, 1H, C-10 proton), 5.82 (multiplet, 1H, C-3, proton), 6.23 (singlet, 3H, CH_3O-), 6.38 (triplet, 2H, $-CH_2OH$), 9.28 (triplet, 3H, CH_3CH_2-). Mass spectrum; main peaks: m/e 199, 214 and 328 (M^+). Molecular weight: 328.216. Calc. for $C_{20}H_{28}O_2N_2$: 328.215. Found: C, 72.82; H, 8.85; N, 8.63. Calc. for $C_{20}H_{28}O_2N_2$: C, 73.13; H, 8.59; N, 8.53.

Preparation of 11-Methoxy Mesylates (205)

(a) 11-Methoxy alcohol-I (204) (600 mg, 1.82 mmole) was dissolved in a mixture of dry triethylamine (10 ml, distilled over sodium hydroxide) and chloroform (26 ml) and cooled to -10-0°C (ice-rock salt bath). Keeping anhydrous conditions, freshly distilled methane sulfonyl chloride (500 mg, 4.37 mmole, distilled over P_2O_5) was added dropwise with efficient stirring. The reaction mixture was allowed to come slowly to room temperature and let stand for 44 hours. The solvent was removed at room temperature and reduced pressure to give a deep red gum. This gum was dissolved in chloroform (20 ml) and extracted with aqueous ammonium hydroxide (4 N, 4 x 15 ml) and once with water (15 ml). The combined aqueous layers were washed with a little chloroform (5 ml) and the water was removed under reduced pressure and moderate heating. Any remaining water in the resulting yellow solid was azeotroped several times with dry benzene. The residue was extracted with dry hot chloroform (4 x 10 ml) which dissolved only the mesylate but not the inorganic material. The chloroform solution was filtered and the filtrate was evaporated to dryness under reduced pressure to give the pure mesylate (723 mg, 98%) as a light yellow foam, and it was used for the subsequent steps without further purification. Infrared (neat): 3448 (NH), 1639 (C=C) cm^{-1}. Nmr signals (100 MHz): τ 2.82 (doublet, J_{ortho} = 8 cps, 1H, C-9 proton), 2.93 (doublet, J_{meta} = 2 cps, 1H, C-12 proton), 3.31 (quartet, J_{meta} = 2 cps, J_{ortho} = 8 cps, 1H, C-10 proton), 4.95 (multiplet, 1H, C-3 proton), 6.24 (singlet, 3H, $C\underline{H}_3O$-), 9.15 (triplet, 3H, $C\underline{H}_3CH_2$-).

(b) 11-Methoxy alcohol-II (204) was mesylated exactly as is described above to give the pure mesylate (205) in quantitative yield.

Again this material was used for the next step without further purification Infrared (neat): 3448 (NH), 1645 (C=C) cm^{-1}. Nmr signals (100 MHz): -0.84 (singlet, 1H, N<u>H</u>), 2.78 (doublet, J_{ortho} = 8 cps, 1H, C-9 proton), 3.03 (doublet, J_{meta} = 2 cps, 1H, C-12 proton), 3.36 (quartet, J_{meta} = 2 cps, J_{ortho} = 8 cps, 1H, C-10 proton), 5.08 (multiplet, 1H, C-3 proton), 6.28 (singlet, 3H, C<u>H</u>$_3$O-), 9.24 (triplet, 3H, C<u>H</u>$_3$CH$_2$-).

Preparation of 16-Methoxy Cyanides (216)

(a) To a solution of mesylate alcohol-I (450 mg) in dry dimethylformamide (25 ml) pulverized potassium cyanide (330 mg) was added. The reaction was performed in dry nitrogen atmosphere. The reaction mixture was heated at 155° (bath temperature) and stirred for 6 hours. The dark reaction mixture was cooled to room temperature and 6 N aqueous ammonium hydroxide (40 ml) was added to it under stirring. The resulting basic solution was extracted with benzene (5 x 35 ml). The combined benzene extracts were washed with brine (2 x 15 ml). The organic layer was dried over anhydrous sodium sulfate, filtration and removal of the solvent under reduced pressure at room temperature gave 190 mg of a brown gum. Chromatography of the crude product on alumina neutral Woelm, activity III, using benzene as eluent gave 120 mg of a mixture of the epimeric cyanides.

(b) To a solution of the mesylate of alcohol-II (205) (1.265 g, 3.11 mmole) in dry hexamethylphosphoamide (40 ml), pulverized potassium cyanide (1.170 g, 18 mmole) was added. The resulting mixture was heated at 175° (bath temperature) and stirred for 7.5 hr under an atmosphere of oxygen-free nitrogen. The dark reaction mixture was cooled to room temperature and aqueous ammonium hydroxide (80 ml, 5 N) was added to it

with stirring. The resulting basic solution was extracted with ethyl ether (6 x 40 ml). The combined ethereal extracts were washed with water (3 x 15 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure at room temperature to afford 600 mg of a yellowish foam.

(c) The mesylate of alcohol-I (205) (2.276 g, 5.60 mmole) was treated exactly as indicated above to afford 1.000 g of a yellowish foam and checking the reaction products (tlc, ir, nmr information) it was shown that both mesylates gave the same mixture of epimeric cyanides.

The crude reaction products (600 mg) were chromatographed on alumina neutral column (40 g, Woelm, activity III). Elution with pet. ether-benzene (3:2) gave cyanide-I and further elution with the same solvent system (1:1) afforded cyanide-II.

16-Methoxy Cyanide-I - Amosphous solid (199 mg, 19%). Recrystallized from n-hexane-acetone and methylene chloride, mp 186-187°C. Infrared (KBr): 3346 (strong, NH) and 2252 (medium, -CN) cm^{-1}. Ultraviolet; λ_{max} (log ε): 227 (4.48), 275 (3.69), 300 (3.81) mm. Nmr signals (100 MHz): τ 1.80 (broad multiplet, 1H, NH), 2.69 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.20 (singlet, 1H, C-17 proton), 3.27 (quartet, J_{orhto} = 8 cps, J_{meta} = 2 cps, 1H, C-15 proton), 6.12 (quartet, J_{AB} = 4 cps, J_{AC} = 2 cps, 1H, C-3 proton), 6.21 (singlet, 3H, CH_3O-), and 9.07 (triplet, J = 7 cps, 3H, CH_3CH_2-). Mass spectrum; main peaks: m/e 124, 126, 177, 212 and 337 (M^+). Molecular weight: 337.218. Calc. for $C_{21}H_{27}ON_3$: 337.215. Found: C, 74.61; H, 8.52; N, 12.39. Calc. for $C_{21}H_{27}ON_3$: C, 74.74; H, 8.07; N, 12.45.

16-Methoxy Cyanide-II - Amorphous solid (320 mg, 30%). Recrystallized from methanol and n-hexane, mp 191-192°. Infrared (KBr): 3356 (strong, NH), 2232 (medium, -CN) cm^{-1}. Ultraviolet; λ_{max} (log ε): 226 (4.45), 277 (3.37), 298 (3.83) mm. Nmr signals (100 MHz): 1.94 (broad singlet, 1H, NH), 2.64 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.15 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 3.23 (quartet, J_{meta} = 2 cps, J_{ortho} = 8 cps, 1H, C-15 proton), 4.03 (quartet, J_{AB} = 10 cps, J_{AC} = 3 cps, 1H, C-3 proton), 6.18 (singlet, 3H, CH_3O-), 9.34 (triplet, J = 7 cps, 3H, CH_3CH_2-). Mass spectrum; main peaks: m/e 124, 126, 177, 212, 337 (M^+). Molecular weight: 337.216. Calc. for $C_{21}H_{27}ON_3$: 337.215. Found: C, 74.57; H, 8.31; N, 12.41. Calc. for $C_{21}H_{27}ON_3$: C, 74.74; H, 8.07; N, 12.45.

High Pressure Liquid Chromatography of the Epimeric Cyanides (216)

INSTRUMENT: Waters' ALC-202.

SOLVENT: Pet. ether (30-60°)-chloroform (1:1).

FLOW RATE: 0.6 ml/min.

COLUMN: Alumina neutral Woelm 6 ft. x 2 mm O.D.

SAMPLE LOAD: 10 mg, total.

RETENTION TIME: Cyanide-I (20 min), cyanide-II (29 min).

Epimerization of the Isomeric Cyanides (216)

To a cooled solution (ice-water bath) of the isomeric cyanides (120 mg, 0.356 mmole) in anhydrous methanol, acetyl chloride (0.2 ml) was added under stirring. After 10 minutes distilled water (0.1 ml) was added and the reaction mixture was allowed to come slowly to room temperature. Stirring was continued for 94 hours. The solvent was

then removed under reduced pressure without heating. The residue was taken up in ether (10 ml) and neutralized with saturated sodium bicarbonate solution, and extracted with ether (3 x 10 ml). The combined organic extracts were washed with brine (10 ml) and dried over anhydrous sodium sulfate. Filtration and removal of the solvent gave 175 mg of a yellowish solid. Purification of the crude reaction mixture either by column chromatography on alumina neutral Woelm (10 g, activity III) using pet. ether-benzene (1:1) as eluent or high pressure liquid chromatography (Waters' ALC 100, pet. ether-chloroform (3:1), 9 ml/min, alumina neutral Woelm, 4 ft x 3/8" O.D.), afforded 62 mg of cyanide-I (15 min) and 12 mg of cyanide-II (33 min).

Preparation of 16-Methoxy-dl-vincadine (151a) and its Epimer

(a) To a cooled solution of the epimeric cyanides (216) (18 mg) in anhydrous methanol (10 ml), acetyl chloride (7 ml) was added. The reaction mixture was allowed to come slowly to room temperature and let stand for 48 hours, when distilled water (0.1 ml) was added. After an additional 24 hours, the solvent was removed under reduced pressure without heating. The residue was taken up in ether, neutralized with saturated sodium bicarbonate solution, and extracted with ether (3 x 15 ml). The combined organic extracts were dried over anhydrous sodium sulfate. Filtration and removal of the solvent gave 16 mg of a gum. Purification of this crude reaction product by high pressure liquid chromatography (Waters' ALC-100, pet. ether-chloroform (3:1), 9 ml/min, alumina neutral Woelm 4 ft. x 3/8" O.D., 16-methoxy-dl-vincadine, 5 min; 16-methoxy-dl-epivincadine, 8 min) gave (6 mg) of the desired carbomethoxy derivative (151) in 20% yield.

(b) To a solution of 16-methoxy cyanide-II (216) (280 mg, 0.83 mmole) in anhydrous methanol (20 ml), water (0.2 ml) was added. The solution was cooled (ice-water bath) and saturated with anhydrous hydrogen chloride (20 min). The reaction mixture was then allowed to come slowly to room temperature and left standing for 96 hours. The solvent was removed under reduced pressure without heating and the residue was taken up in a small volume of dichloromethane and neutralized by the addition of a saturated solution of sodium bicarbonate. The resulting solution was then extracted with methylene chloride (3 x 10 ml). The combined organic layers were dried over sodium sulfate. Filtration and removal of the solvent gave 222 mg of a brown gum.

The above reaction was repeated with a mixture of both cyanides and an identical mixture of diastereoisomeric carbomethoxy derivatives was obtained.

Separation was obtained by preparative tlc on silica gel Woelm, developed with a mixture of benzene-ethyl acetate (4:1). 16-Methoxy dl-epivincadine: amorphous solid (9%), resisted crystallization, leading to decomposition products. Infrared ($CHCl_3$): 3370 (small, N<u>H</u>), 1725 (strong, CO_2CH_3) cm^{-1}. Ultraviolet: λ_{max} (log ε): 228 (4.43), 278 (3.65), 300 (3.76) mm. Nmr signals (100 MHz): 1.49 (singlet, 1H, N<u>H</u>), 2.70 (doublet, 1H, J_{ortho} = 8 cps, 1H, C-14), 3.20 (doublet, J_{meta} = 2.5 cps, 1H, C-17 proton), 3.30 (quartet, J_{ortho} = 8 cps, J_{meta} = 2.5 cps, 1H, C-15 proton), 4.49 (quartet, J_{AB} = 11 cps, J_{AC} = 2 cps, 1H, C-3 proton), 6.23 (singlet, 3H, $C\underline{H}_3O$-), 6.38 (singlet, 3H, CO_2CH_3), 9.36 (triplet, J = 7 cps, 3H, $C\underline{H}_3CH_2$-). Mass spectrum; main peaks: m/e 124, 126, 210, 245, and 370 (M^+). Molecular weight: 370.224. Calc. for $C_{22}H_{30}O_3N_2$: 370.225.

16-Methoxy dl-vincadine - amorphous solid (25%), resisted crystallization, leading to decomposition products. It was more polar on silica gel chromatographic plates developed with benzene-ethyl acetate (4:1). Infrared ($CHCl_3$): 3370 (medium sharp, NH), 1730 (strong, CO_2CH_3) cm^{-1}. Ultraviolet; λ_{max} (log ε): 228 (4.43), 278 (3.65), 301 (3.76) mm. Nmr signals (100 MHz): 1.16 (broad singlet, NH), 2.70 (doublet, J_{ortho} = 8 cps, 1H, C-14), 3.21 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 3.30 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-15 proton), 6.22 (singlet, 3H, CH_3O-), 6.31 (singlet, 3H, CO_2CH_3), 6.35 (multiplet, 1H, C-3 proton), and 9.18 (triplet, 3H, CH_3CH_2-). Mass spectrum; main peaks: m/e 124, 138, 210, 245 and 370 (M^+). Molecular weight: 370.225. Calc. for $C_{22}H_{30}O_3N_2$: 370.225.

N_a-Methylation of 16-Methoxy dl-vincadine (151a) and its Epimer (151b)

Sodium amide (0.25 mmole) was prepared from redistilled liquid ammonia (4-5 ml) and freshly cut sodium metal (5.85 mg, 0.25 mmole). A trace of ferric nitrate was added as a catalyst to the solution of sodium amide in liquid ammonia, kept under highly purified nitrogen and efficient stirring. A solution of epimeric esters (151) (58 mg, 0.15 mmole) in dry tetrahydrofuran (1 ml) was added with a syringe. The dark solution was kept in a dry ice-acetone bath and stirring continued for 30 minutes more. Methyl iodide (16 ml, 0.25 mmole) in a few drops of tetrahydrofuran was added with a syringe. The reaction mixture was kept cold and stirred for 25 minutes more and then the ammonia allowed

to evaporate slowly under a stream of nitrogen. The removal of ammonia was enhanced by blowing a stream of warm air around the reaction vessel. The dark residue was taken into a mixture of aqueous ammonium chloride-ethyl ether (10 ml, 1:1) and extracted several times with ethyl ether. The combined organic layers, after washing with water were dried over anhydrous sodium sulfate. Filtration of the inorganic agent and removal of the solvent under reduced pressure at room temperature gave 55 mg of a yellow gum. Preparative tlc on silica gel chromatoplates developed with benzene-ethyl acetate (4:1) gave the two N-methylated epimers (62%).

dl-Vincaminoridine (4): As an amorphous solid (9 mg). Infrared ($CHCl_3$): No NH absorption and 1735 (strong, CO_2CH_3) cm^{-1}. Ultraviolet; λ_{max} (log ε): 232 (4.47), 288 (3.78), 299 (3.82) nm. Nmr signals (100 MHz): 2.65 (doublet, J_{ortho} = 9 cps, 1H, C-14 proton), 3.25 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-17 proton), 3.90 (quartet, J_{AB} = 10 cps, J_{AC} = 2 cps, 1H, C-3 proton), 6.16 (singlet, 3H, $C\underline{H}_3O$-), 6.38 (singlet, 3H, $CO_2C\underline{H}_3$), 6.46 (singlet, 3H, $C\underline{H}_3N$), and 9.33 (triplet, J = 6 cps, 3H, $C\underline{H}_3CH_2$-). Mass spectrum; main peaks: m/e 124, 210, 259 and 384 (M^+). Molecular weight: 384.240. Calc. for $C_{23}H_{32}O_3N_2$: 384.241.

dl-Epivincaminoridine (4a): Amorphous solid (32 g). This was the more polar epimer in silica gel chromatoplates developed with benzene-ethyl acetate (4:1). Infrared ($CHCl_3$): No NH absorption and 1725 (strong, CO_2CH_3) cm^{-1}. Ultraviolet; λ_{max} (log ε): 232 (4.53), 288 (3.78), and 300 (3.81) nm. Nmr signals (100 MHz): 2.66 (doublet, J_{ortho} = 9 cps, 1H, C-14 proton), 3.30 (quartet, J_{ortho} = 9 cps, J_{meta} =

2 cps, 1H, C-15 proton), 3.31 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 6.15 (singlet, 3H, $C\underline{H}_3O$-), 6.20 (distorted quartet, 1H, C-3 proton), 6.34 (singlet, 3H, $CO_2C\underline{H}_3$), 6.56 (singlet, 3H, $C\underline{H}_3N$), and 9.08 (triplet, J = 7 cps, 3H, $C\underline{H}_3CH_2$-). Mass spectrum; main peaks: m/e 124, 210, 259 and 384 (M^+). Molecular weight: 384.239. Calc. for $C_{23}H_{32}O_3N_2$: 384.241.

Epimerization of dl-Epivincaminoridine (4a) to dl-Vincaminoridine (4)

To a stirred freshly prepared solution of sodium methoxide in absolute methanol dl-epivincaminoridine (23 mg) was added. The solution of sodium methoxide was made by addition of 14 mg of freshly cut sodium in absolute methanol (12 ml) under a dry nitrogen atmosphere and efficient stirring. After the addition of dl-epivincaminoridine (4a) the reaction mixture was refluxed under dry nitrogen for 48 hours. The cooled solution was concentrated under reduced pressure and the residue taken up in chloroform. Filtration and removal of the solvent gave 32 mg of a yellowish gum. Preparative tlc on silica gel chromatoplates developed with benzene-ethyl acetate (4:1) gave 7.3 mg of dl-vincaminoridine (4) and 11.5 mg of dl-epivincaminoridine (4a).

Transannular Cyclization of dl-Vincaminoridine (4a) and its Epimer

A mixture of dl-vincaminoridine and its epimer (22 mg, 5.75 mmole) in glacial acetic acid (11 ml), and mercuric acetate (96 mg, 30.25 mmole) was stirred for 43 hours at room temperature under an atmosphere of nitrogen. The formed mercurous acetate was filtered off and the filtrate was basified by careful addition of a 10% aqueous solution of sodium bicarbonate. The resulting basic solution was

extracted with methylene chloride and the combined organic layers were washed with water, dried over anhydrous sodium sulfate. Filtration and removal of the solvent gave 17 mg of an amorphous solid. Preparative tlc on alumina neutral Woelm, developed with chloroform-ethyl acetate (1:1) gave two isomeric products. The less polar of them (2.0 mg, 11%) was obtained as an amorphous solid. Infrared ($CHCl_3$): 1715 (strong, α,β-unsaturated ester), 1660 (strong, C=C in conjugation) cm^{-1}. Ultraviolet; λ_{max}: 225, 310 (infl.) and 335 nm. The more polar compound (4.5 mg, 24%) was also obtained as an amorphous solid. Infrared ($CHCl_3$): 1715 (strong, α,β-conjugated ester), 1660 (strong, C=C in conjugation) cm^{-1}. Ultraviolet, λ_{max} 225, 310 (infl.) and 340 nm. The mass spectra of both compounds had main peaks at m/e 124, 149, 263 and 382 (M^+). Molecular weight: 382.224. Calc. for $C_{23}H_{30}O_3N_2$: 382.225.

DISCUSSION PART II

1. Partial Synthesis of Appropriate Dihydroindole Units

For the reasons presented in the end of the discussion of Part I we directed our efforts toward the degradation sequence which could provide the relay compounds 225, 226 and 195. One of the required intermediates, ketone 86, had been previously obtained by Gorman[67] via either a soda lime distillation of vindoline (3) at 325°, or in better yield by another process. Hydrogenation of vindoline yields dihydrovindoline (222) which could then be converted to an amorphous hygroscopic hydrochloride. Pyrolysis of this salt at 195-200° in vacuum gave a distillate from which the ketone 86 was obtained in 15% overall yield (Fig. 50).

Since desacetyldihydrovindoline (225) was the required intermediate that would eventually lead us to the synthesis of the relay compound 195, we decided to obtain the ketone 86, via a slightly modified sequence of reactions (Fig. 51). Thus the natural alkaloid vindoline (3) was refluxed in concentrated hydrochloric acid for a short period of time on a pre-heated bath, followed by conventional workup of the reaction mixture. Desacetylvindoline (224) was obtained in quantitative yield as a foam, which crystallized upon addition of ether. Recrystallization from methanol gave colorless plates, m.p. 160-162°. The nmr spectrum

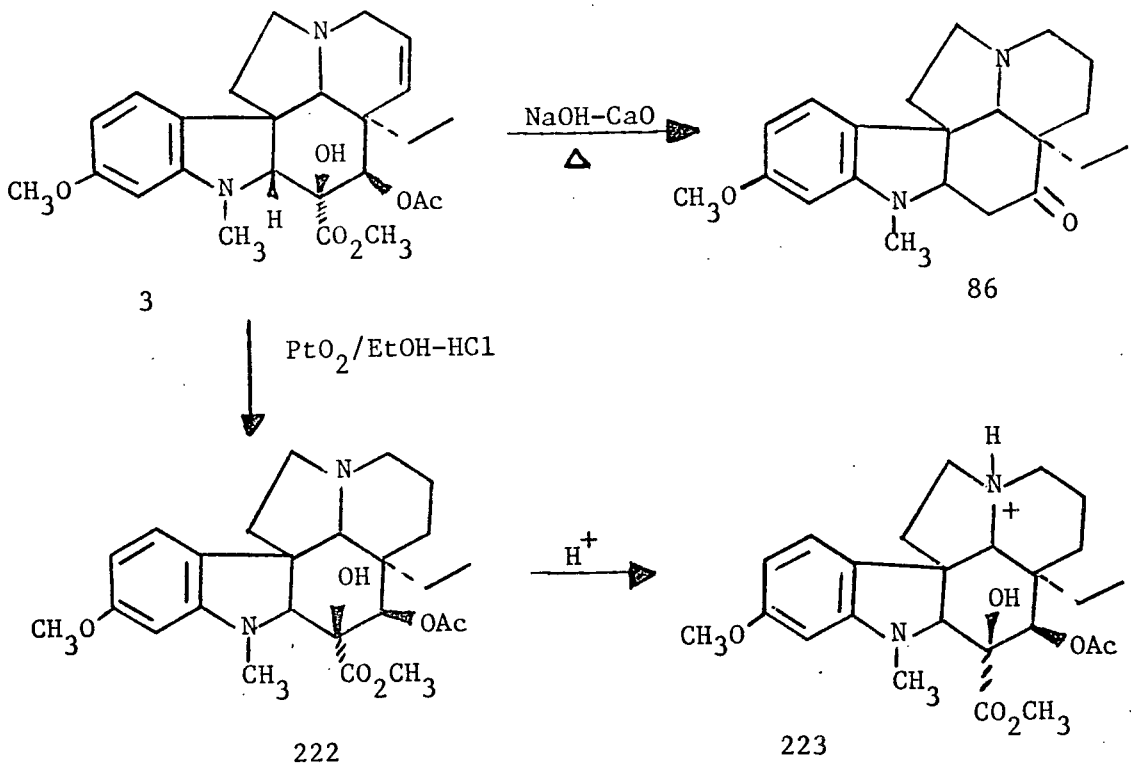


Fig. 50. Gorman's preparation of ketone 86.

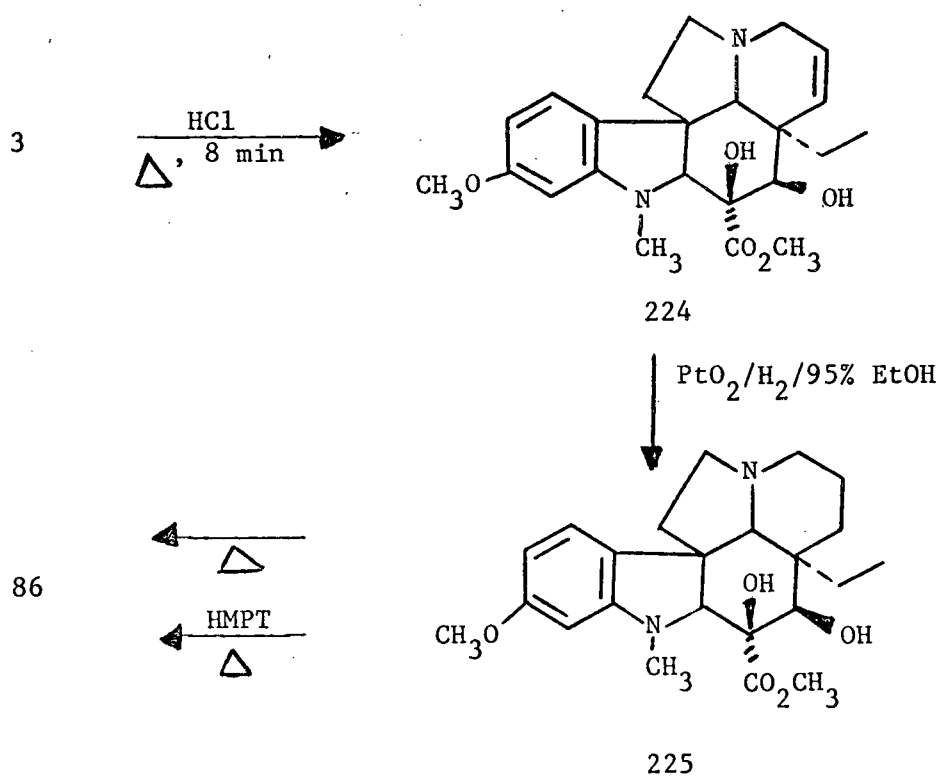


Fig. 51. Preparation of ketone 86.

(Fig. 52) showed clearly that only the acetate group had been removed (singlet at τ 7.93 in the starting material). The mass spectrum (Fig. 53) had significant and expected fragments at m/e 107, 121, 135, 174, 188, and 414 (M^+).[122]

The molecular formula, $C_{23}H_{30}O_5N_2$, was confirmed by elemental analysis and high resolution mass spectrometry. The next step was the catalytic hydrogenation of the double bond present in ring D. When desacetylvindoline (224) was hydrogenated in 95% ethanol in the presence of Adam's catalyst (PtO_2), desacetyldihydrovindoline (225) was obtained as an oil in 95% yield. Crystallization from ether, and recrystallization from methanol gave an analytical sample, m.p. 181-183°. In the nmr spectrum (Fig. 54) the signals due to the vinylic protons (τ 4.22, Fig. 52) were now absent. The mass spectrum (Fig. 53) had the main fragments at m/e 124, 188, 242, 298, and 416 (M^+), which are characteristic of the aspidospermine type skeleton.[122] The formula, $C_{23}H_{32}O_5N_2$, was confirmed by elemental analysis and high resolution mass spectrometry. We next attempted the pyrolysis of desacetyldihydrovindoline in a pyrex tube heated at 280-290°. After purification of the crude product by chromatography on neutral alumina the desired ketone 86 was obtained in 30% yield (based on recovered starting material). However when we tried to increase the amount of the compound in the pyrolysis the yield was lower. At this point we decided to try a more efficient way to perform such a conversion, without having to limit the amount of compound to be pyrolyzed in each run. Monson[123] reported that primary and secondary alcohols were dehydrated by treatment with hexamethylphosphoric triamide at 220-240°. Lomas et al.,[124] have also shown that

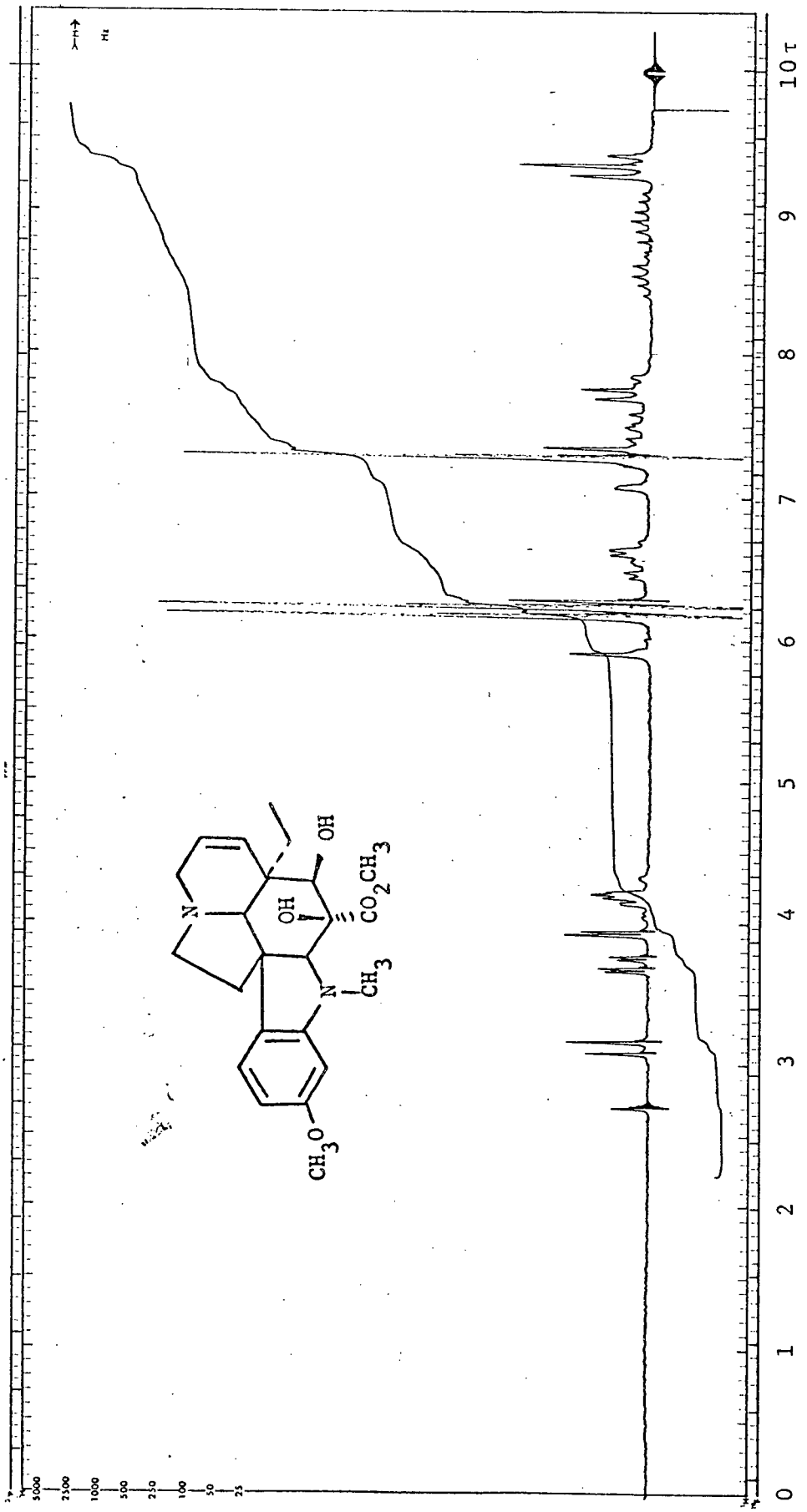


Figure 52. Nmr spectrum of desacetylvindoline.

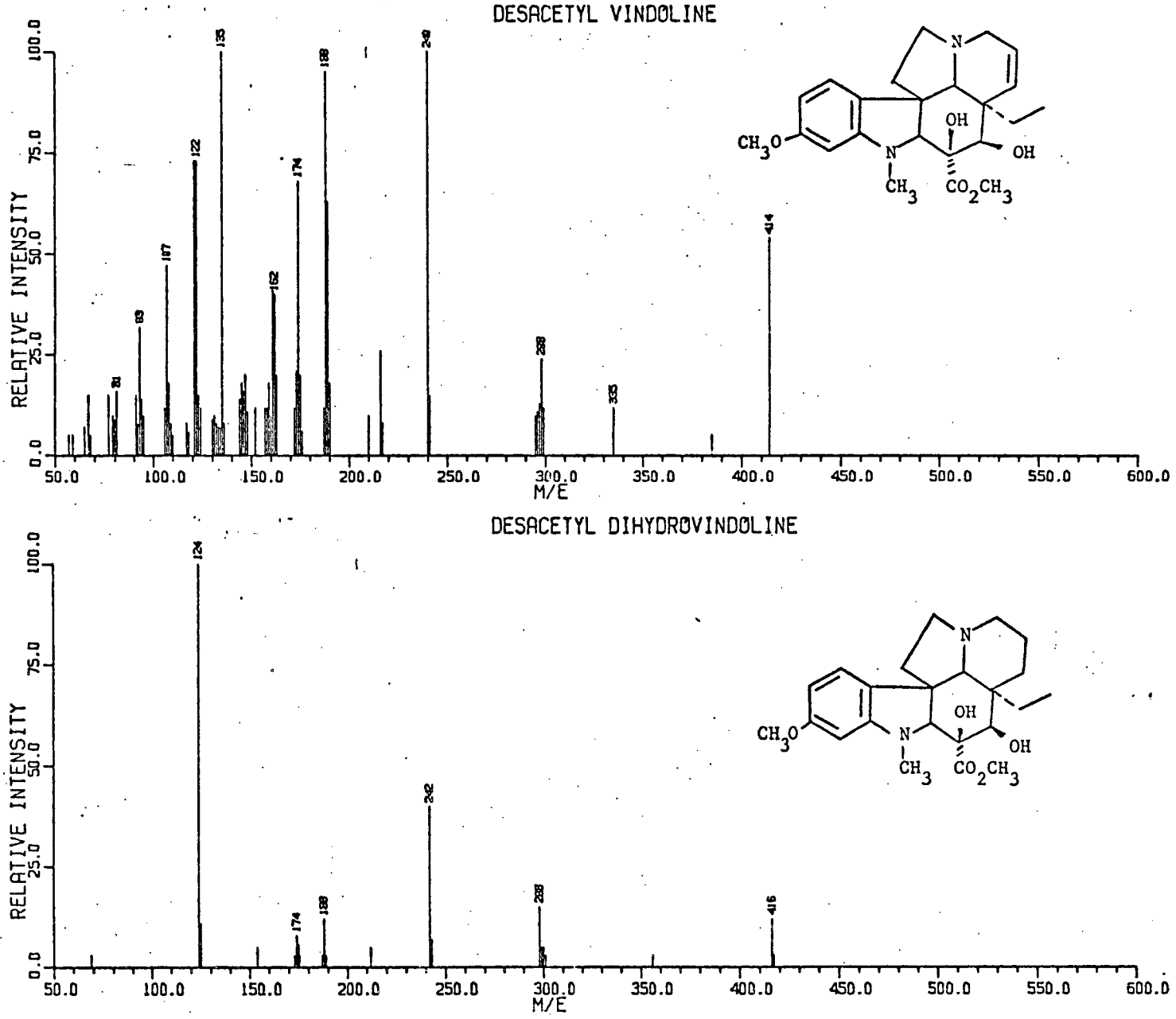


Figure 53. Mass spectra of desacetylvindoline (224) and desacetyldihydrovindoline (225).

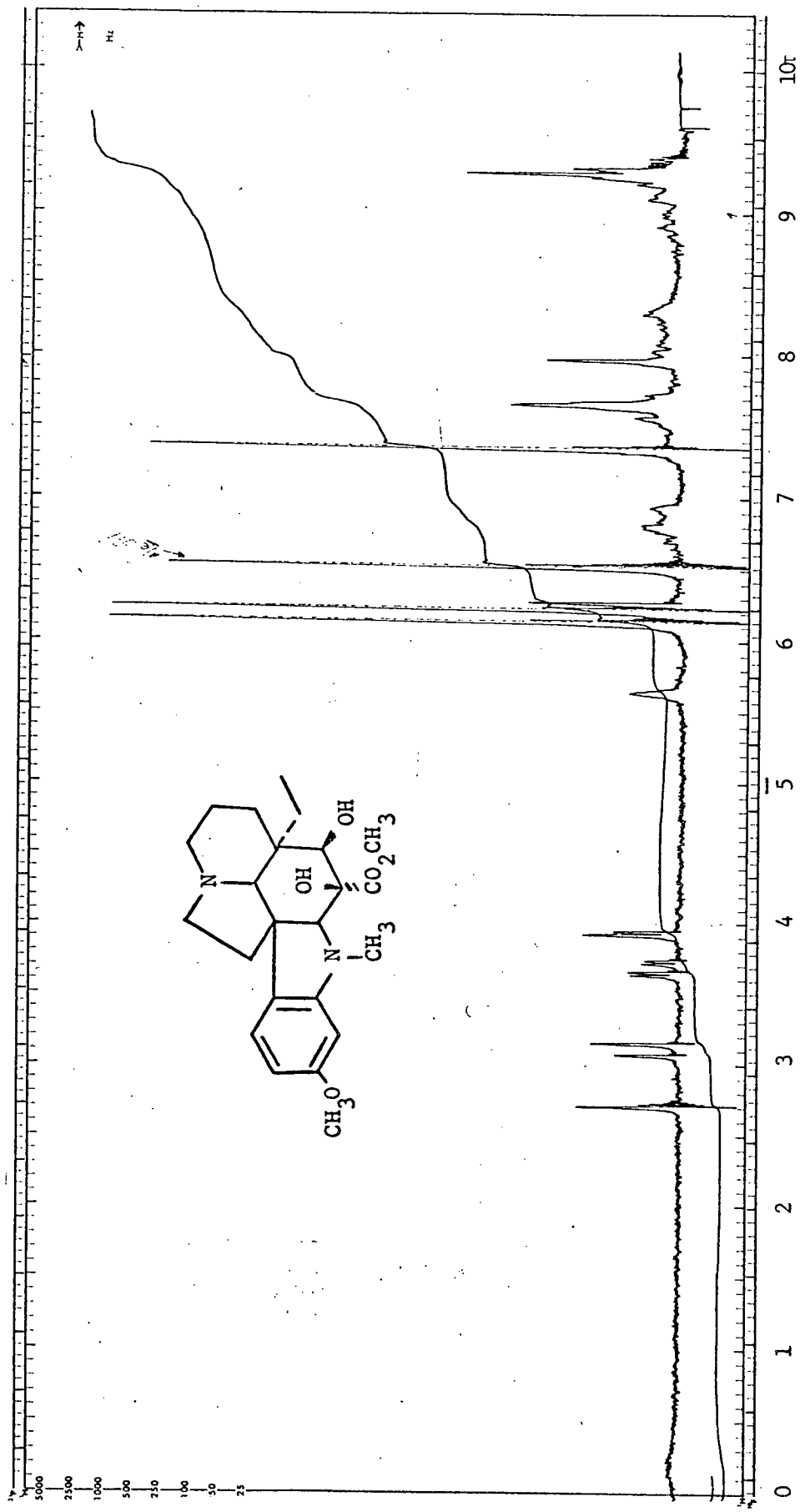


Figure 54. Nmr spectrum of desacetyldihydrovindoline (225).

tertiary alcohols can be dehydrated by this method. On this basis we decided to apply this procedure hoping to be able to prepare the β-keto ester (226, Fig. 55) directly from desacetyldihydrovindoline (225) without having to go via the intermediate ketone 86. However, when preliminary investigations were performed at different temperatures, they showed that no conversion at all had taken place below 170°, and that the ketone 86 was formed at 170° without production of any detectable amount (by tlc) of the β-ketoester (226). Since the reaction proceeded slowly at 170°, we therefore raised the temperature to 220°C. We were gratified to find that the ketone 86 was obtained, after conventional work-up and purification by chromatography on neutral alumina, in 40% yield. This method was better than the previous one utilized by Gorman[67] (15% yield). Recrystallization from methanol gave an analytical sample, m.p. 135-137°. The spectral properties were in complete accord with the assigned structure.[67] Thus, the infrared spectrum showed a strong carbonyl absorption at 1701 cm^{-1}, while the ultraviolet spectrum (213, 252, and 305 nm) had a typical 16-methoxy dihydroindole chromophore. In the nmr spectrum (Fig. 55) the absorptions due to the C-4 proton, and the methyl protons of the carbomethoxy group (τ 5.66 and 6.27, Fig. 54) were now absent. The mass spectrum (Fig. 56) had the expected fragments at m/e 124, 174, 188, 298, and 340 (M^+). The molecular formula, $C_{21}H_{28}O_2N_2$, was confirmed by elemental analysis and high resolution mass spectrometry, (found: 340.211, calculated for $C_{21}H_{28}O_2N_2$: 340.215). Having obtained the ketone 86, we concerned ourselves with the introduction of the carbomethoxy group which would provide us with the required β-ketoester (226, Fig. 57). This was successfully accomplished by condensation of the ketone 86 with dimethyl carbonate in the presence of sodium hydride.[125]

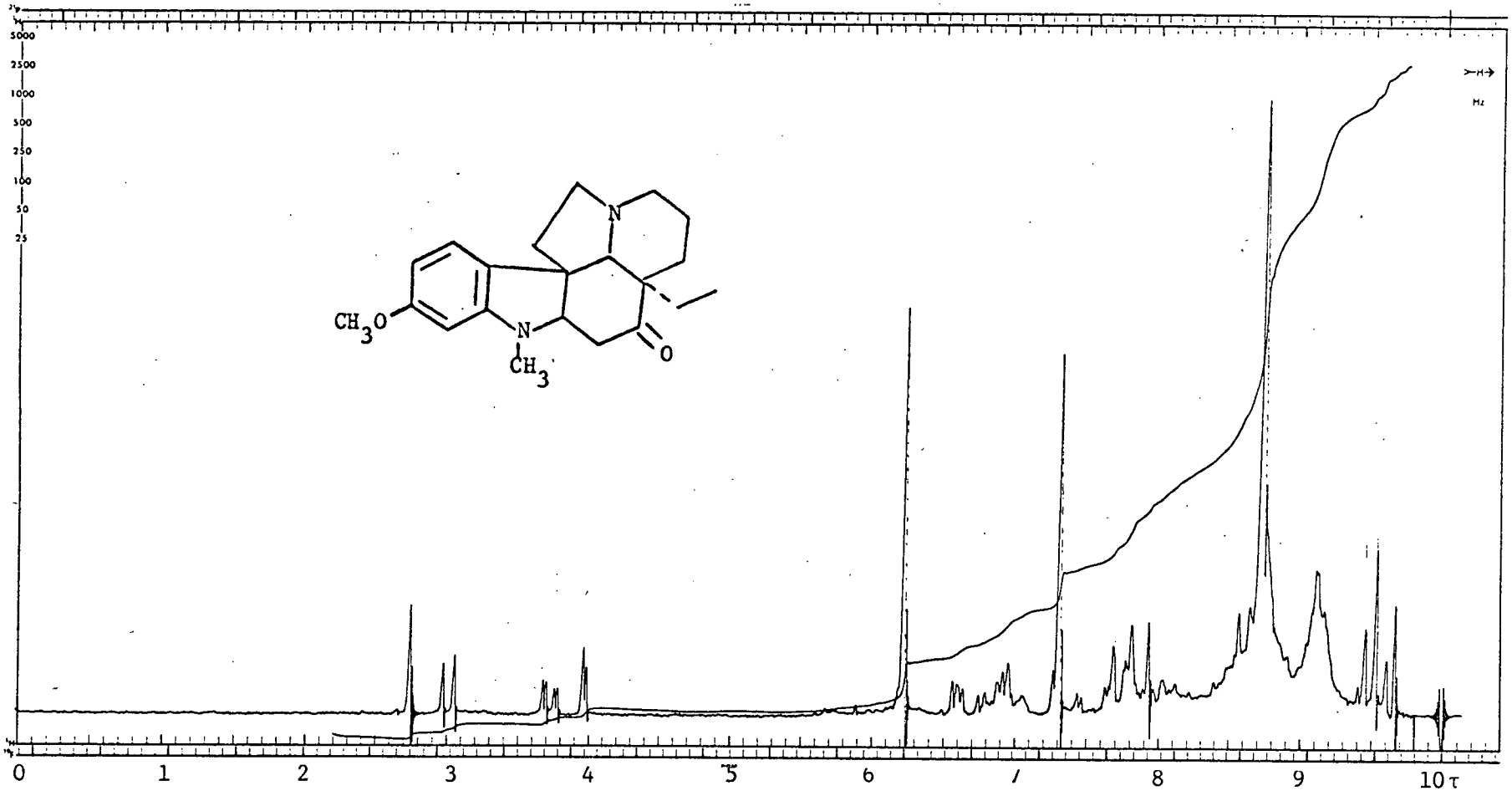


Figure 55. Nmr spectrum of ketone 86.

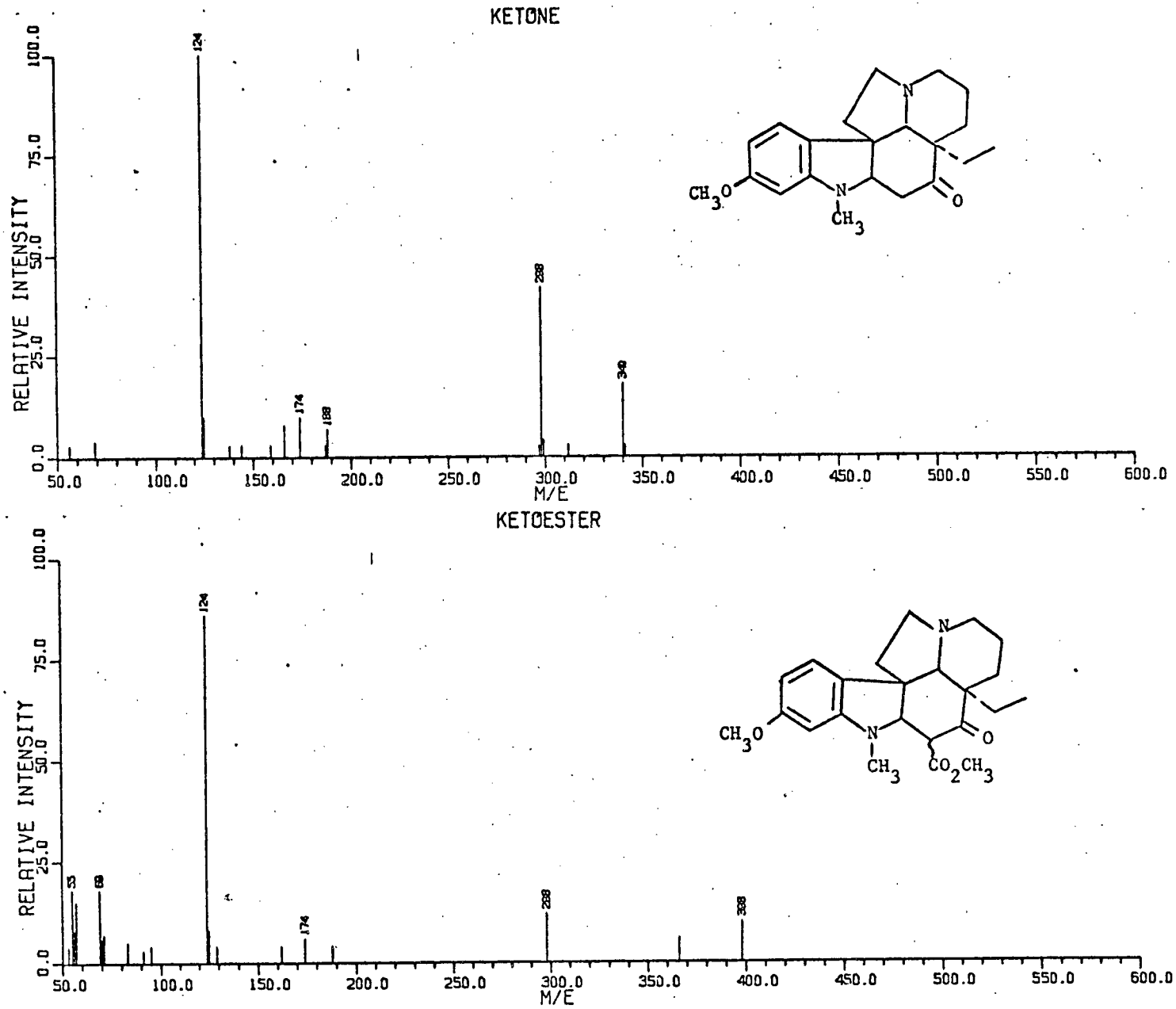


Figure 56. Mass spectra of the ketone 86 and β-ketoester 226.

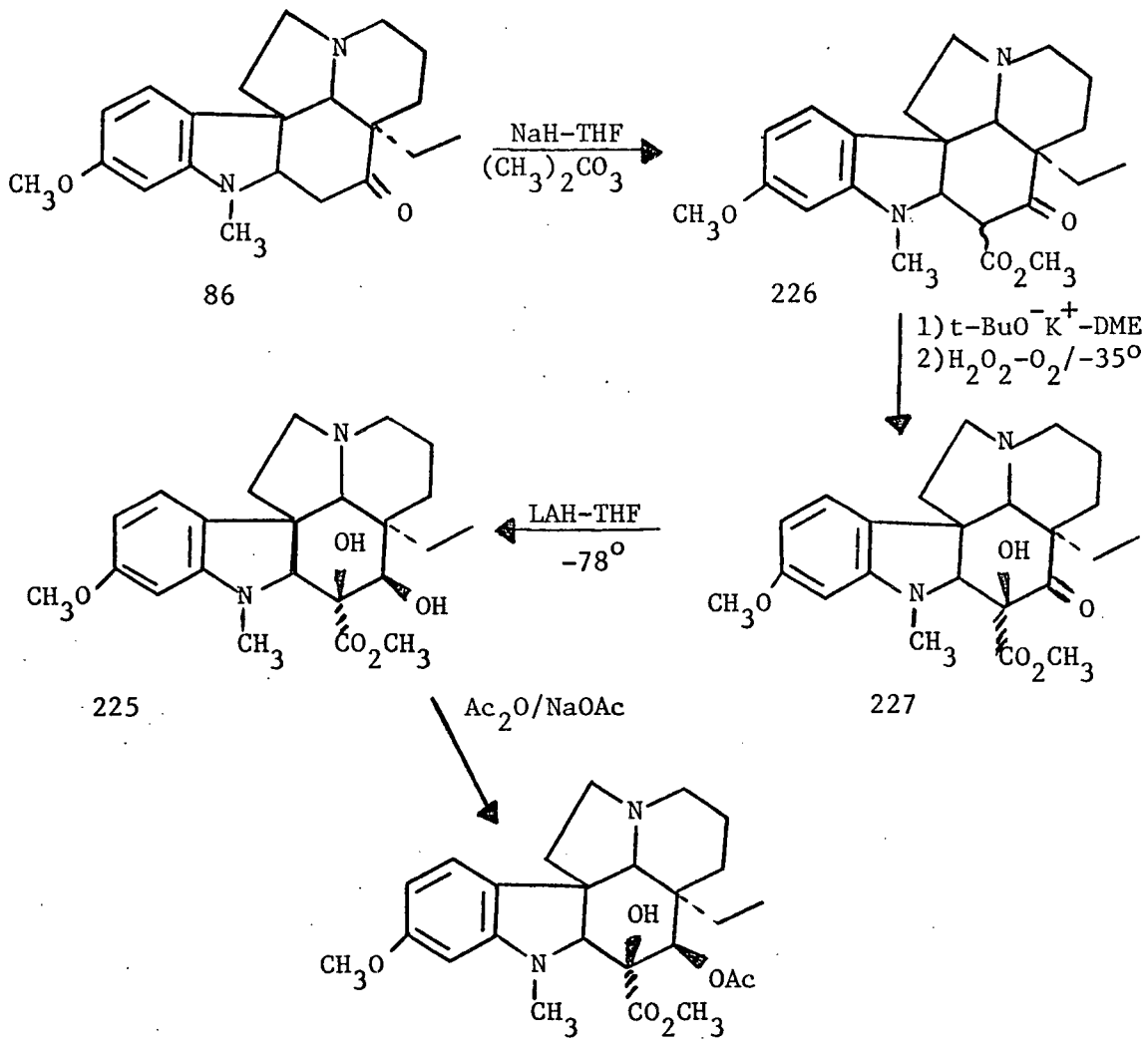


Figure 57. Partial synthesis of dihydrovindoline (222).

A mixture of the β-ketoester (226) and its enol tautomer was obtained in 71% yield after conventional work-up and purification by chromatography on silica gel. No attempts were made to isolate the tautomeric forms since in the next step the stereochemistry, whatever it might be, is going to be destroyed by generation of the enolate. The infrared spectrum had two strong carbonyl absorptions at 1725 and 1700 cm^{-1}, while the ultraviolet spectrum had maxima at 212 (4.39), 252 (3.88), and 304 (3.58) nm. The mixture of keto and enol tautomeric forms was evident in the nmr spectrum (Fig. 58). The most characteristic features were a singlet at τ -3.62 which was assigned to the C-3 proton of the enol form, a singlet at τ 5.7 due to C-2 proton of the enol form, and two doublets at τ 5.82 and 6.00 (J_{AB} = 4 and 6 cps) resulting from the C-3 proton of the keto form. The mass spectrum (Fig. 56) had the expected fragmentation pattern, and the main fragments were found at m/e 124, 174, 188, 298, and 398 (M^+). An assignment for these fragments is outlined in Fig. 59. The molecular formula, $C_{23}H_{30}O_4N_2$, was established by high resolution mass spectrometry (Found: 398.220, calculated for $C_{23}H_{30}O_4N_2$: 398.218).

Having obtained the β-ketoester derivative (226) in satisfactory yield, we now directed out efforts toward the introduction of the hydroxy group at the C-3 position. At this time Buchi and co-workers[100] published their total synthesis of vindorosine (194) in which they applied an interesting hydroxylation reaction, we therefore decided to utilize their procedure. When a solution of the β-ketoester (226) in tert-butyl alcohol-1,2-dimethoxyethane containing potassium tert-butoxide was treated with 98% hydrogen peroxide and molecular oxygen at -35°, we were able to isolate after conventional work-up and

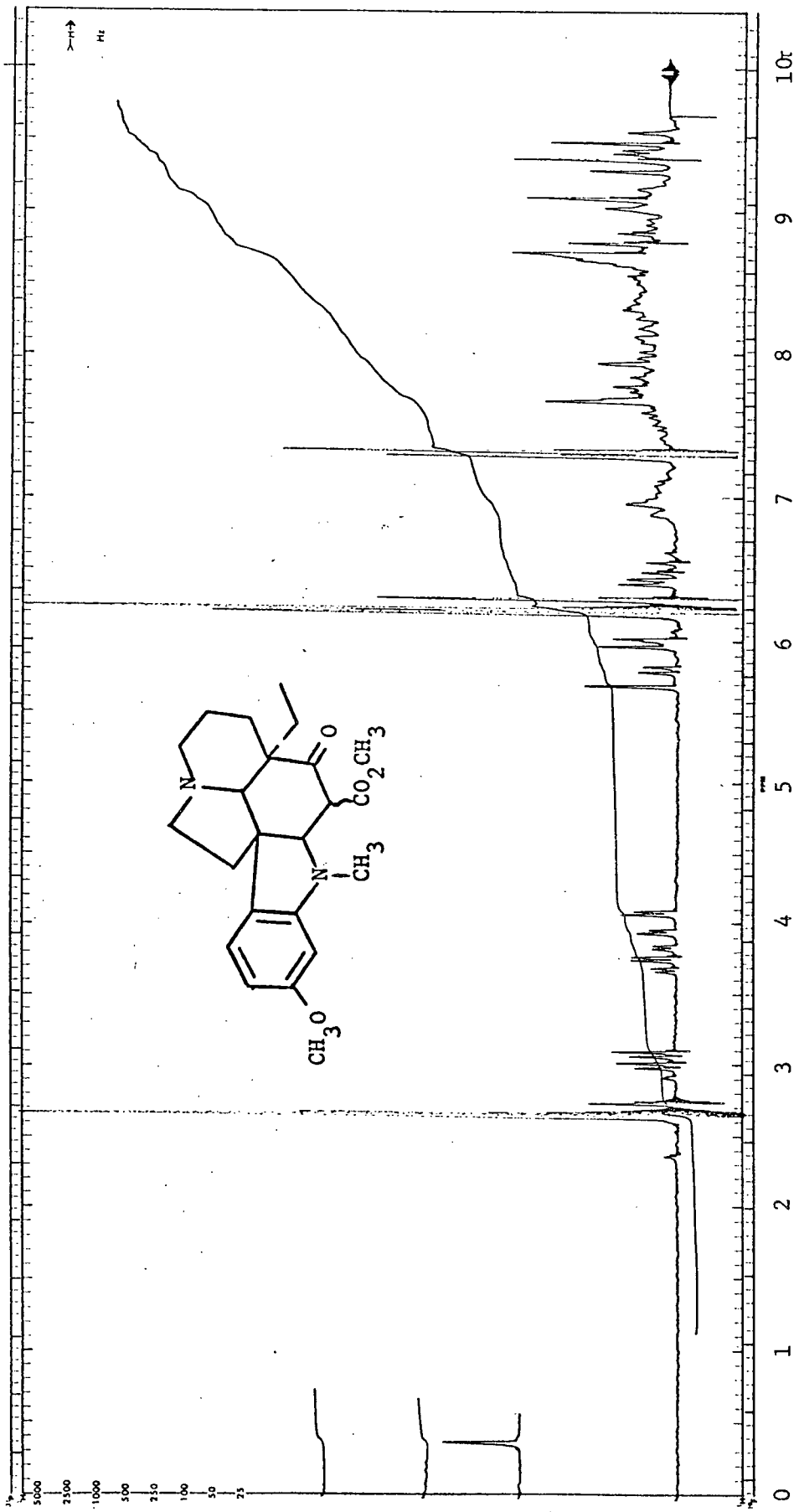


Figure 58. Nmr spectrum of β-ketoester 226.

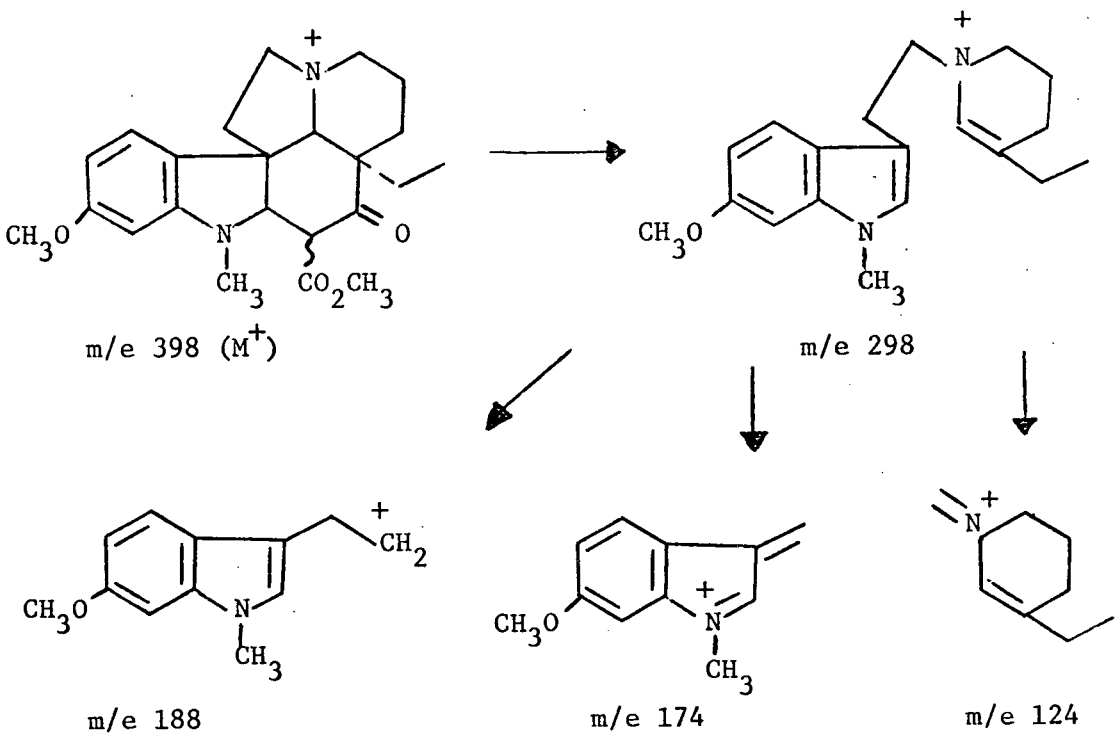


Fig. 59. Fragmentation of β-ketoester upon electron impact.

purification by tlc chromatography on silica gel, the desired hydroxy ketoester (227) in 59% yield. The infrared spectrum had two strong carbonyl absorptions at 1750 and 1712 cm^{-1}, while the ultraviolet spectrum had maxima at 213 (4.49), 248 (3.81), and 303 (3.67) nm. The nmr spectrum (Fig. 60) was consistent with the proposed structure (227). The methyl protons of the carbomethoxy and methoxy groups were found at τ 6.17 and 6.26, while the N-methyl group resonated at τ 7.37. In addition, the doublet due to the C-3 proton (present in the starting material 226) was now absent. The indicated stereochemistry (β-OH) was based upon comparison with an authentic sample obtained from Moffatt

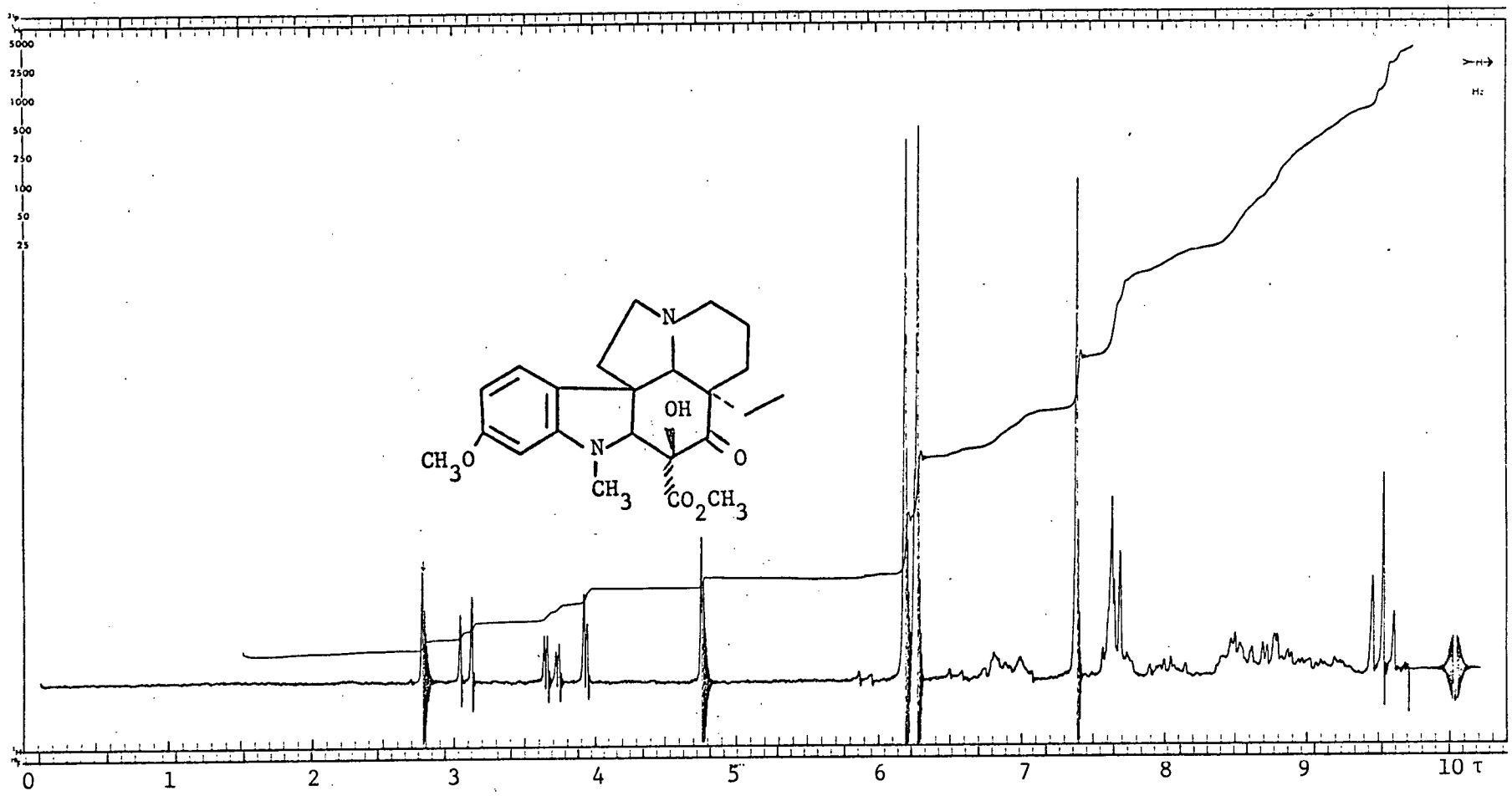


Figure 60. Nmr spectrum of hydroxy ketoester 227.

oxidation[126] of dihydrodesacetylvindoline (225), and kindly provided to us by Dr. Bunzli-Trepp of this laboratory. Both products were shown to be identical by spectral data and tlc chromatography. The mass spectrum (Fig. 61) had main fragments at m/e 124, 174, 188, 298, and 414 (M^+), which also locates the hydroxy group at the C-3 position. The molecular formula, $C_{23}H_{30}O_5N_2$, was established by high resolution mass spectrometry (found: 414.214, calculated for $C_{23}H_{30}O_5N_2$: 414.215). We have therefore completed the partial synthesis of dihydrovindole (222), since the last two remaining steps, namely the reduction of the carbonyl function to an alcohol having the required stereochemistry, followed by acetylation has already been accomplished in our laboratory[126] (see Fig. 57). Furthermore, since the functionalization of ring D of dihydrovindoline (222), namely the introduction of a double bond, has also been achieved in our laboratory,[126,127] as indicated in Figure 62, this also completes the partial synthesis of vindoline (3) (see Figures 57 and 62).

Having completed the latter stages of the total synthesis, we turn our attention to the connection between the intermediate 195 and the relay compound 226 in order to complete the total synthesis of vindoline (3). Our initial aim was to prepare the unsaturated ester 231 (Fig. 63) and the synthetic approach selected, was the one developed by Corey and co-workers,[128] namely olefin synthesis from 1,2-diols via a cyclic thiocarbonate derivative. Desacetyldihydrovindoline (225) was refluxed with N,N-thiocarbonyldiimidazole in butanone for 28 hours under an atmosphere of nitrogen. The crude reaction mixture after conventional work-up was purified by chromatography on silica gel. Continuous elution with ethyl acetate gave the desired thiocarbonate

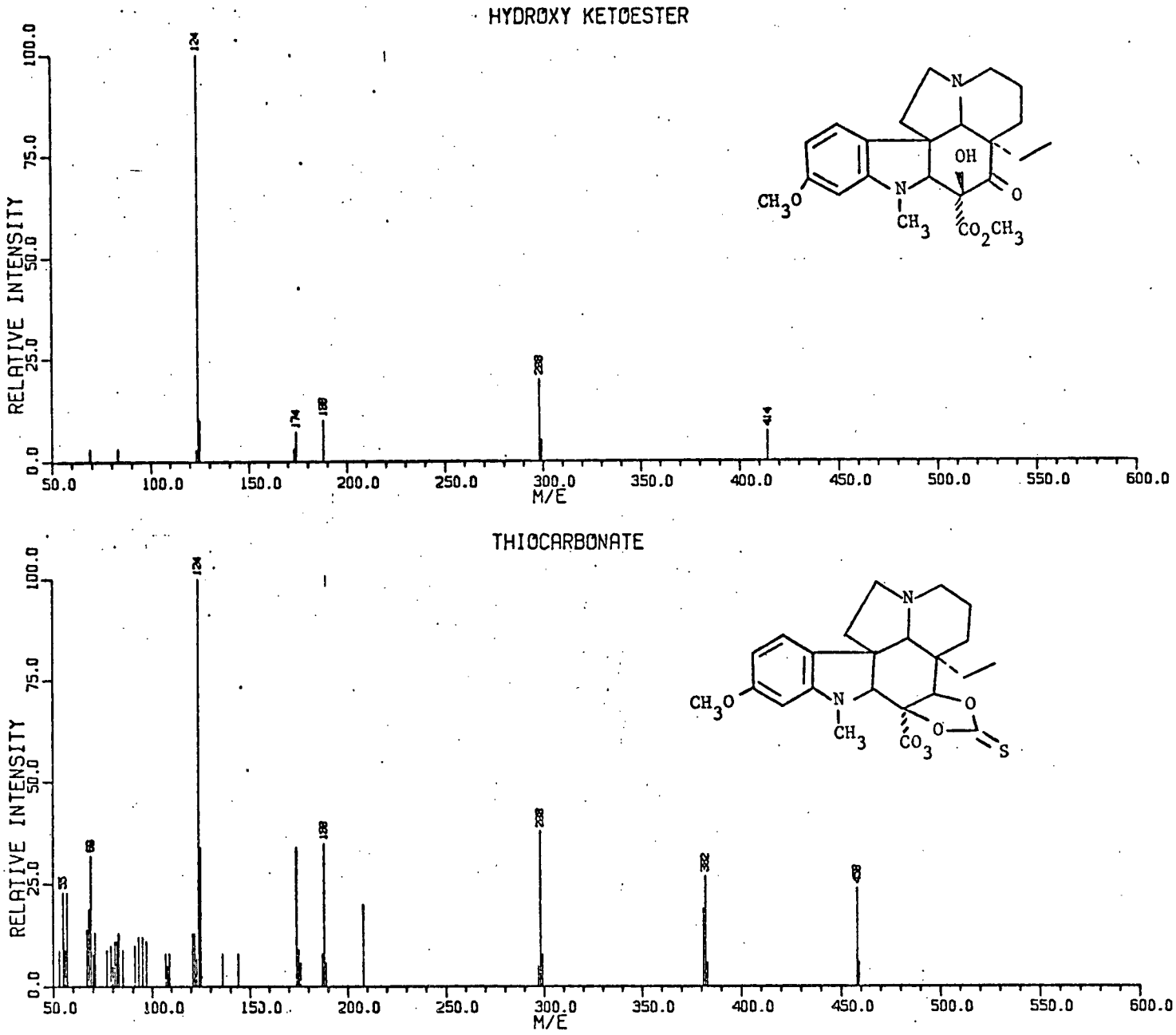


Figure 61. Mass spectra of hydroxy ketoester 227 and thiocarbonate derivative.

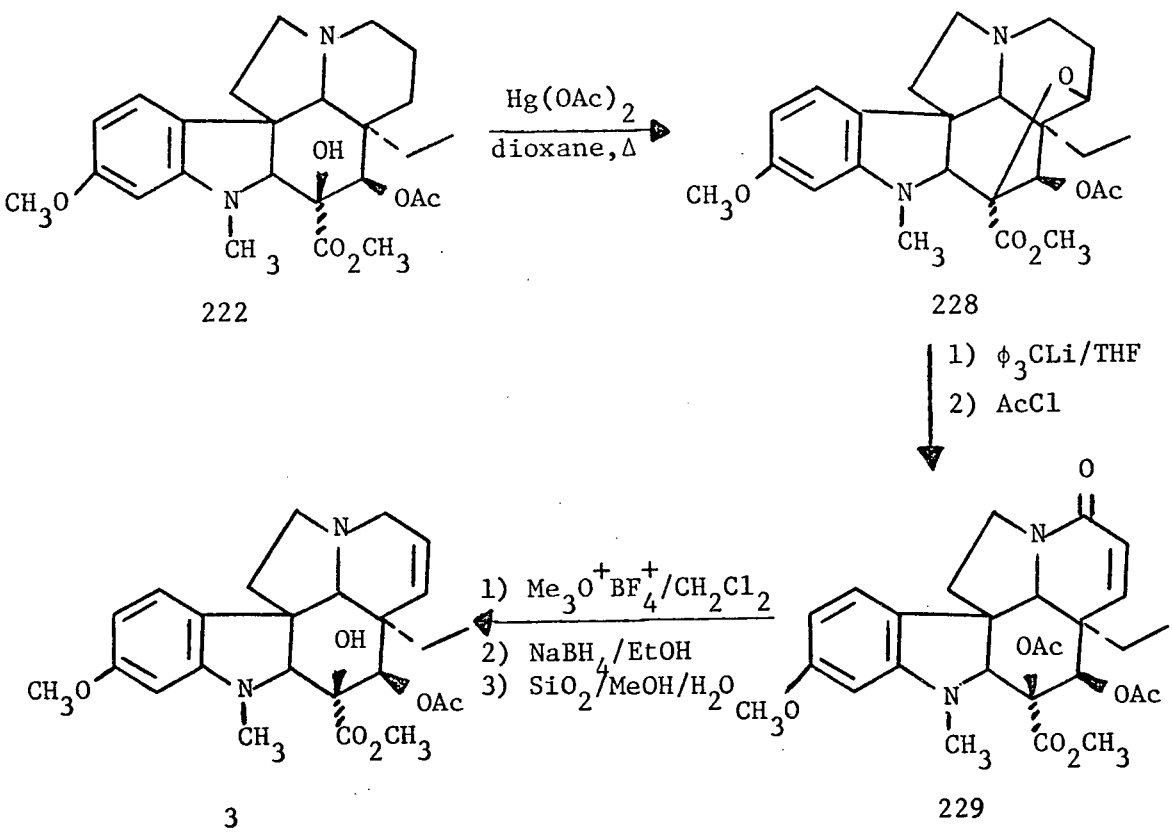


Figure 62. Partial synthesis of vindoline (3).

derivative (230, Fig. 63) in 88% yield. Recrystallization from ethyl acetate gave an analytical sample, m.p. 222-223°. The infrared spectrum showed strong bands at 1739 and 1304 cm^{-1} which were assigned respectively to carbonyl and thiocarbonyl groups. The ultraviolet spectrum had the 16-methoxyindole chromophore with maxima at 208 (4.53, 233 (4.33), and 298 (3.69) nm. The nmr spectrum (Fig. 64) was in good agreement with the proposed structure (230). The main features were a singlet at τ 4.69 assigned to the C-4 proton, a three proton singlet at τ 6.07 due to the methyl protons of the carbomethoxy group, and a one proton singlet at τ 6.20 arising from the C-2 proton. It is perhaps appropriate to note that the above signals were found at lower

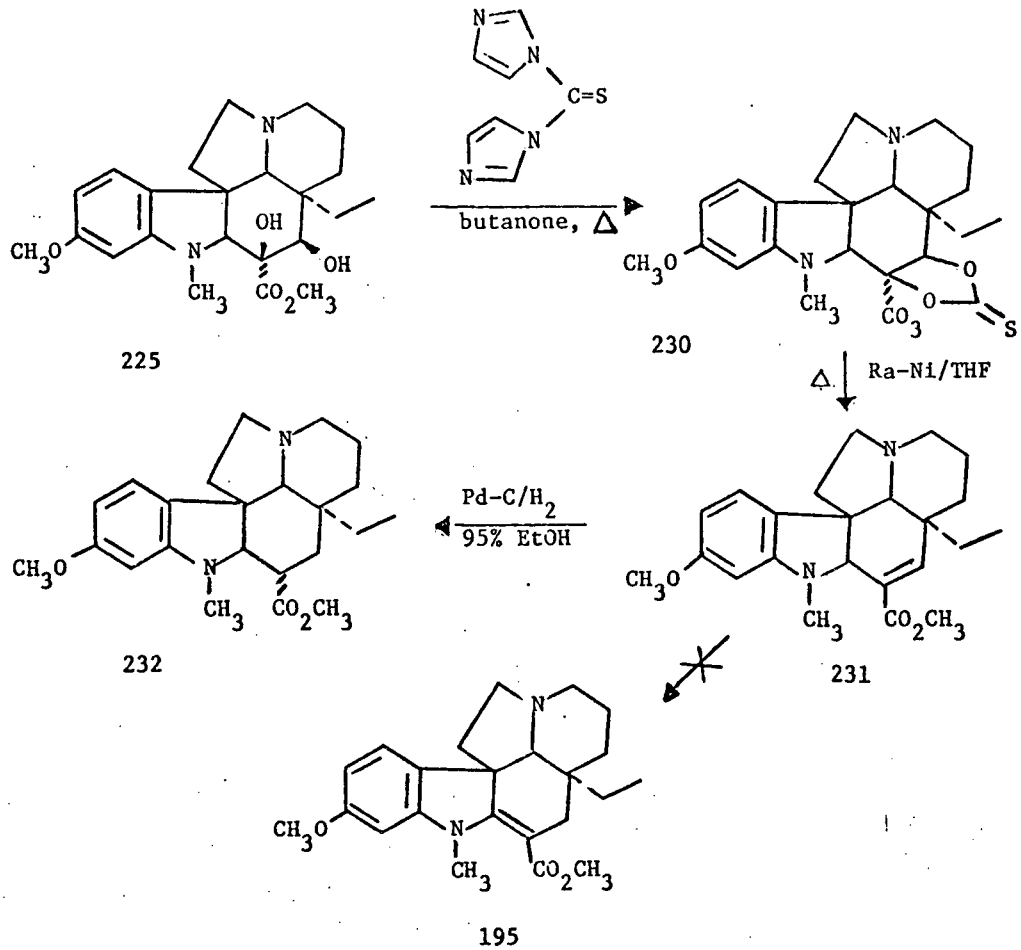


Figure 63. Preparation of the unsaturated ester (231).

field than in the starting material (225). The reason for this shift, at least in part, may be the deshielding effect of the thiocarbonate group. The mass spectrum (Fig. 61) had main fragments at m/e 124, 149, 298, 381, and 458 (M^+). The molecular formula, $C_{24}H_{30}N_2O_5S$, was established by elemental analysis.

The second part of the two-step synthesis of the unsaturated ester 231, which comprises the elimination of the thiocarbonate group with simultaneous formation of the double bond, was performed in the following way. The thiocarbonate derivative (230) in tetrahydrofuran and in the presence of Raney nickel was refluxed for 24 hours. After

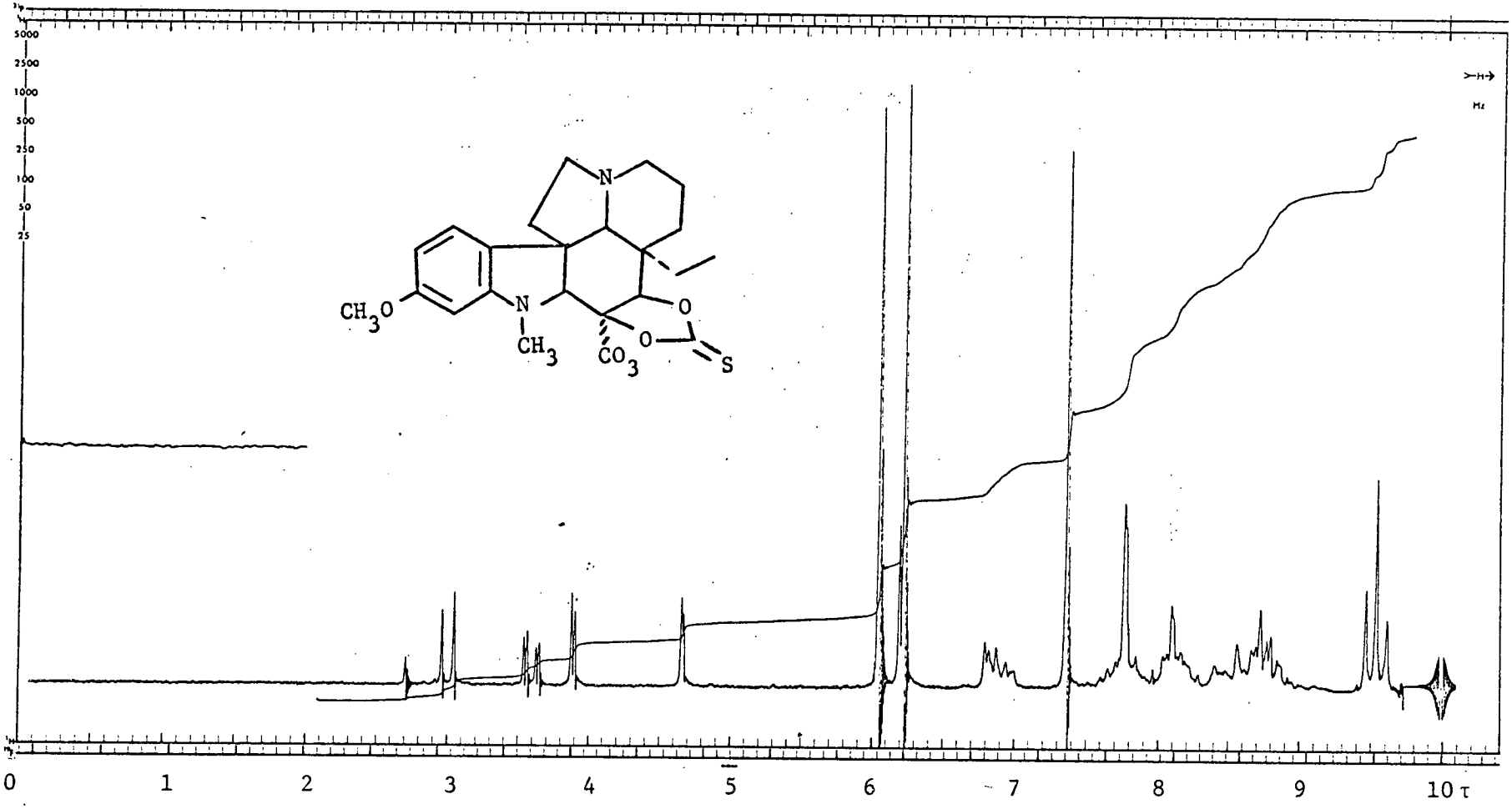


Figure 64. Nmr spectrum of thiocarbonate derivative (230).

usual work-up and purification of the crude reaction product by chromatography on silica gel, the desired product (231) was obtained in 81% yield. The spectra data were in good agreement with the assigned structure. The infrared spectrum had now a strong carbonyl absorption at 1703 cm^{-1} indicating clearly a shift caused by the conjugated double bond, while the ultraviolet spectrum had a typical 16-methoxydihydroindole chromophore. The nmr spectrum (Fig. 65) showed a one proton singlet at τ 2.77 due to the olefinic proton, and a one proton singlet at τ 5.73 was assigned to the C-2 proton. The molecular formula, $C_{23}H_{30}O_3N_2$, was established by elemental analysis and high resolution mass spectrometry (found: 382.222, calculated for $C_{23}H_{30}O_3N_2$: 382.225). Having obtained the α,β-unsaturated ester (231) we initially considered the possibility of isomerization of the double bond in order to obtain the relay compound 195 (Fig. 63). However since preliminary investigations[127] proved unsuccessful it was decided to attempt such a conversion via the saturated ester (232). This would provide us with an intermediate on which a good leaving group could be introduced at the α-position of the carbomethoxy group and subsequent elimination could eventually lead to the desired compound 195. Thus, catalytic hydrogenation of 231 with 10% palladium on charcoal in 95% ethanol gave after conventional work up and purification by chromatography on silica gel, the saturated ester 232 (Fig. 63) in 80% yield. The infrared spectrum showed a strong carbonyl absorption at 1735 cm^{-1}, while the ultraviolet spectrum had maxima at 212 (4.35), 253 (3.69), and 305 (3.53) nm. The nmr spectrum (Fig. 67) revealed the presence of a one proton doublet at τ 6.4 (J_{AB} = 2 cps) due to the C-2 proton and a one proton multiplet at τ 5.9 assigned to the C-3 proton. The α-stereochemistry of the

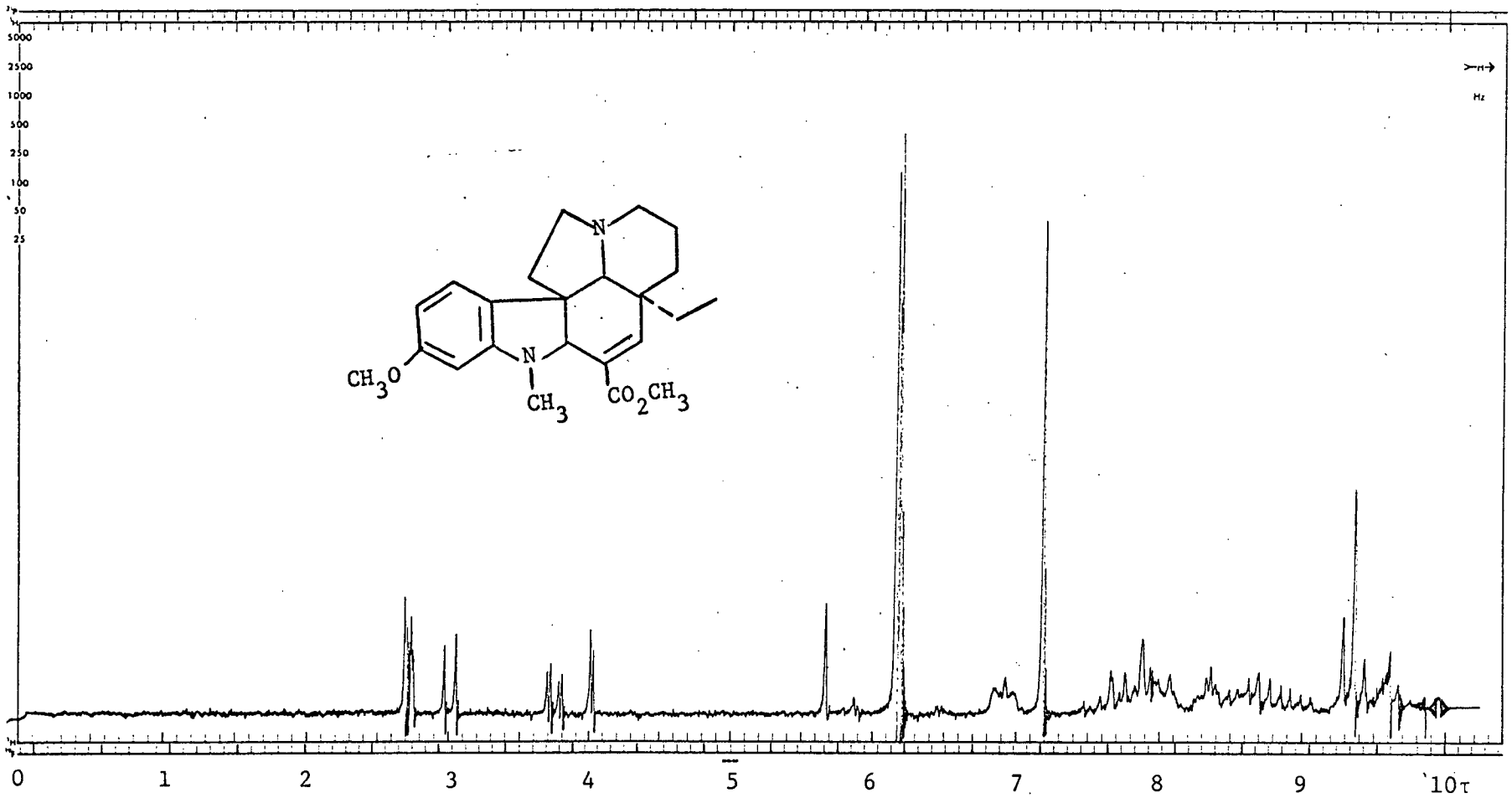


Figure 65. Nmr spectrum of the unsaturated ester (231).

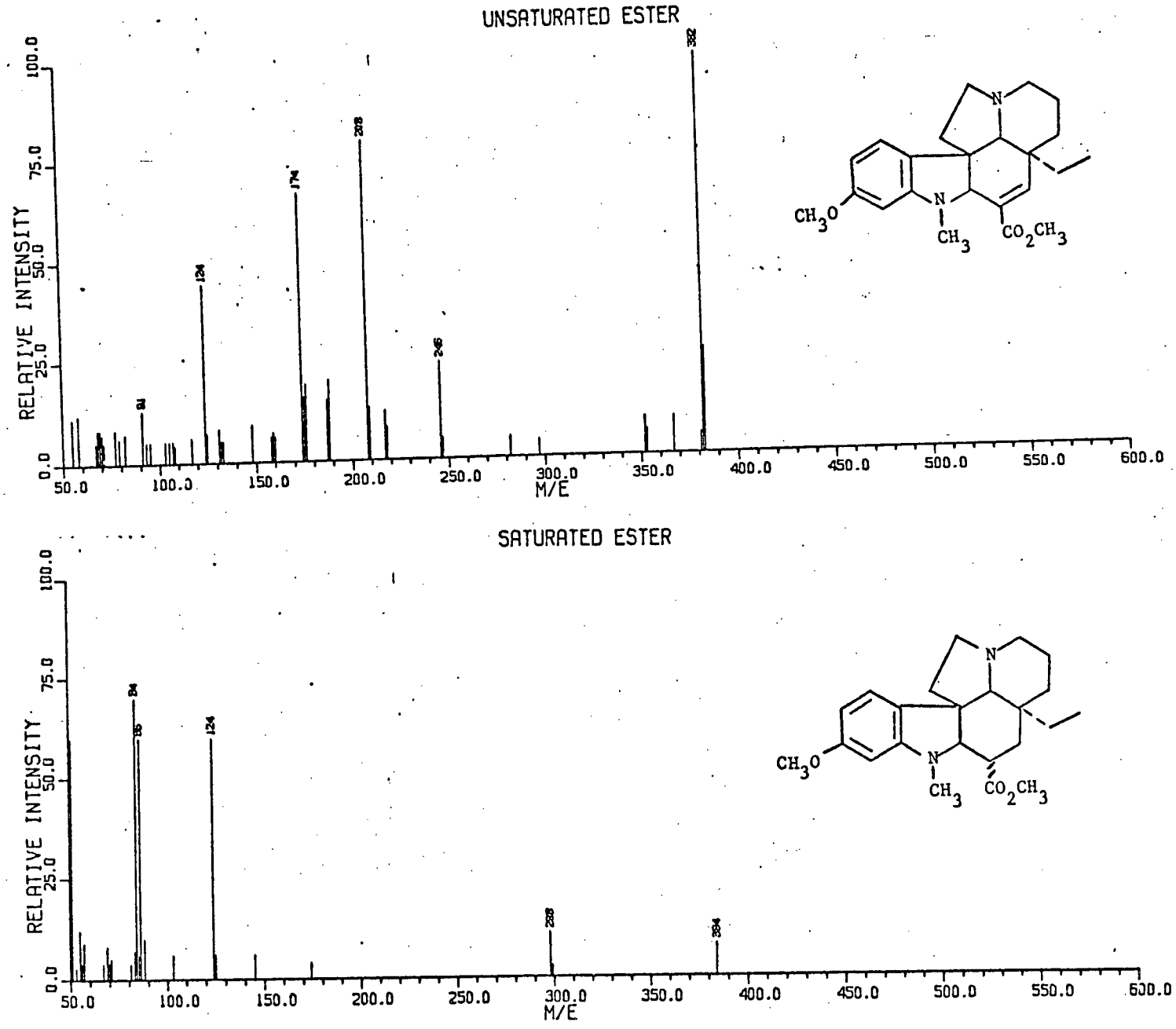


Figure 66. Mass spectra of the unsaturated ester (231) and saturated ester (232).

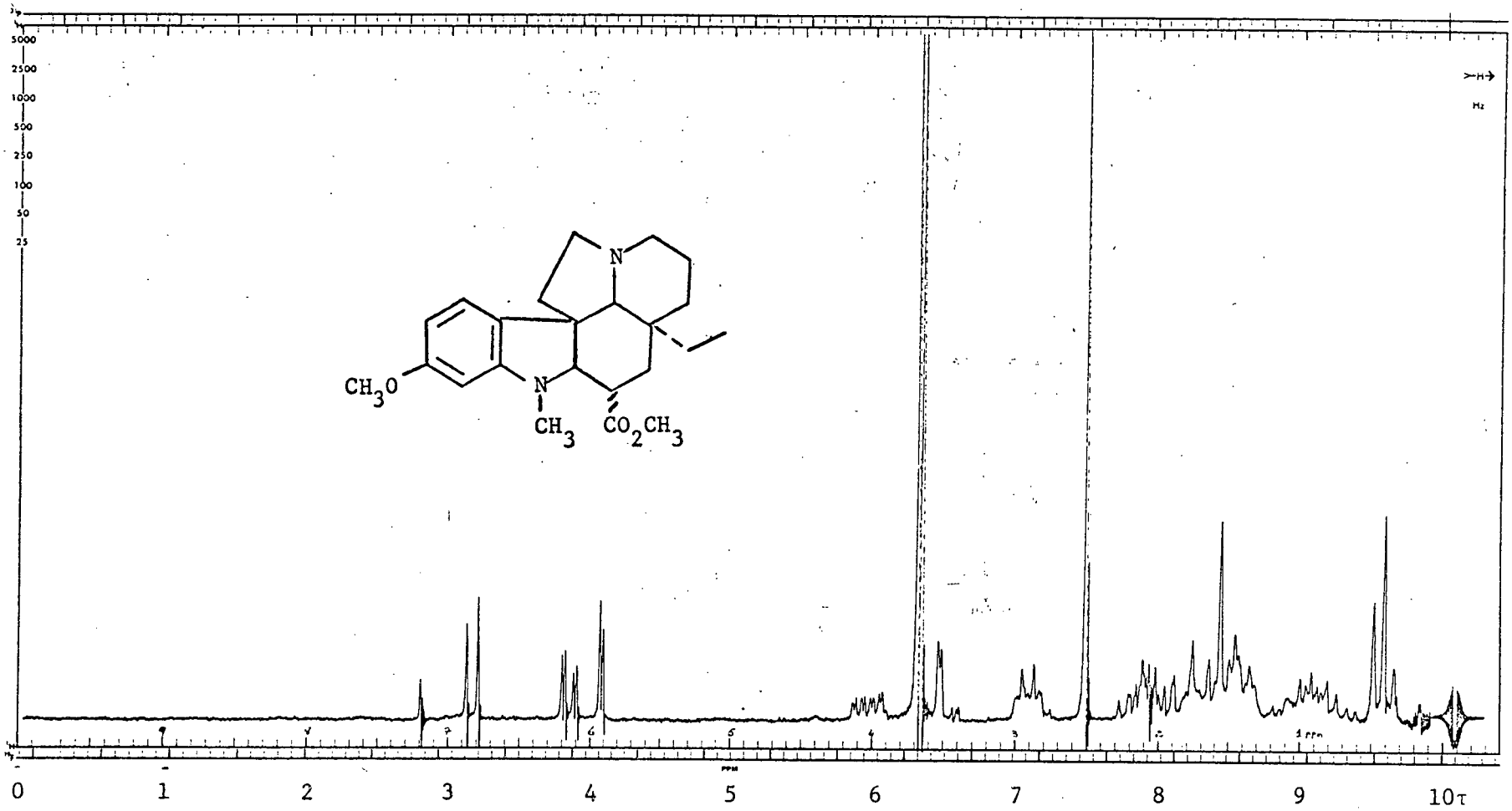


Figure 67. Nmr spectrum of saturated ester (232).

carbomethoxy group was based on the coupling constant of the vicinal protons on C-2 and C-3. A large vicinal coupling constant (8-14 cps) between protons is associated with an approximate diaxial orientation of the atoms, while smaller splittings (1-5 cps) are associated with axial-equatorial or diequatorial interactions.[129] Since the coupling constant found was 2 cps, this strongly suggests the assigned stereochemistry for the saturated ester (232). The mass spectrum (Fig. 66) showed the usual aspidospermine-like fragmentation and the main fragments were found at m/e 124, 210, 298, and 384 (M^+). The molecular formula, $C_{23}H_{32}O_3N_2$, was established by elemental analysis. Having obtain 232 we next considered the introduction of the leaving group. For this purpose an α-hydroxy ester derivative was our initial aim. At first we sought to perform such a synthetic operation via hydrogen peroxide oxidation of the enolate generated by treatment of intermediate 232 with potassium t-butoxide. This attempt proved to be unsuccessful; the reaction products after work up and isolation by tlc chromatography on silica gel were found to be the starting material (232, 8%) and its epimer at C-3 (233, 92%).

The latter compound 233, was recrystallized from methanol, m.p. 162-164°. The infrared spectrum had a strong carbonyl absorption at 1725 cm^{-1}, while the ultaviolet spectrum showed a 16-methoxyindole chromophore with maxima at 216 (4.42), 256 (3.80), and 307 (3.65) nm. The nmr spectrum (Fig. 68) showed a one proton doublet (J_{AB} = 10 cps) at τ 6.15 due to the C-2 proton. Such a large vicinal coupling constant may be associated with an approximate diaxial orientation[129] and therefore is in good agreement with the assigne d structure 233. The molecular formula $C_{23}H_{32}O_3N_2$, was established by elemental analysis.

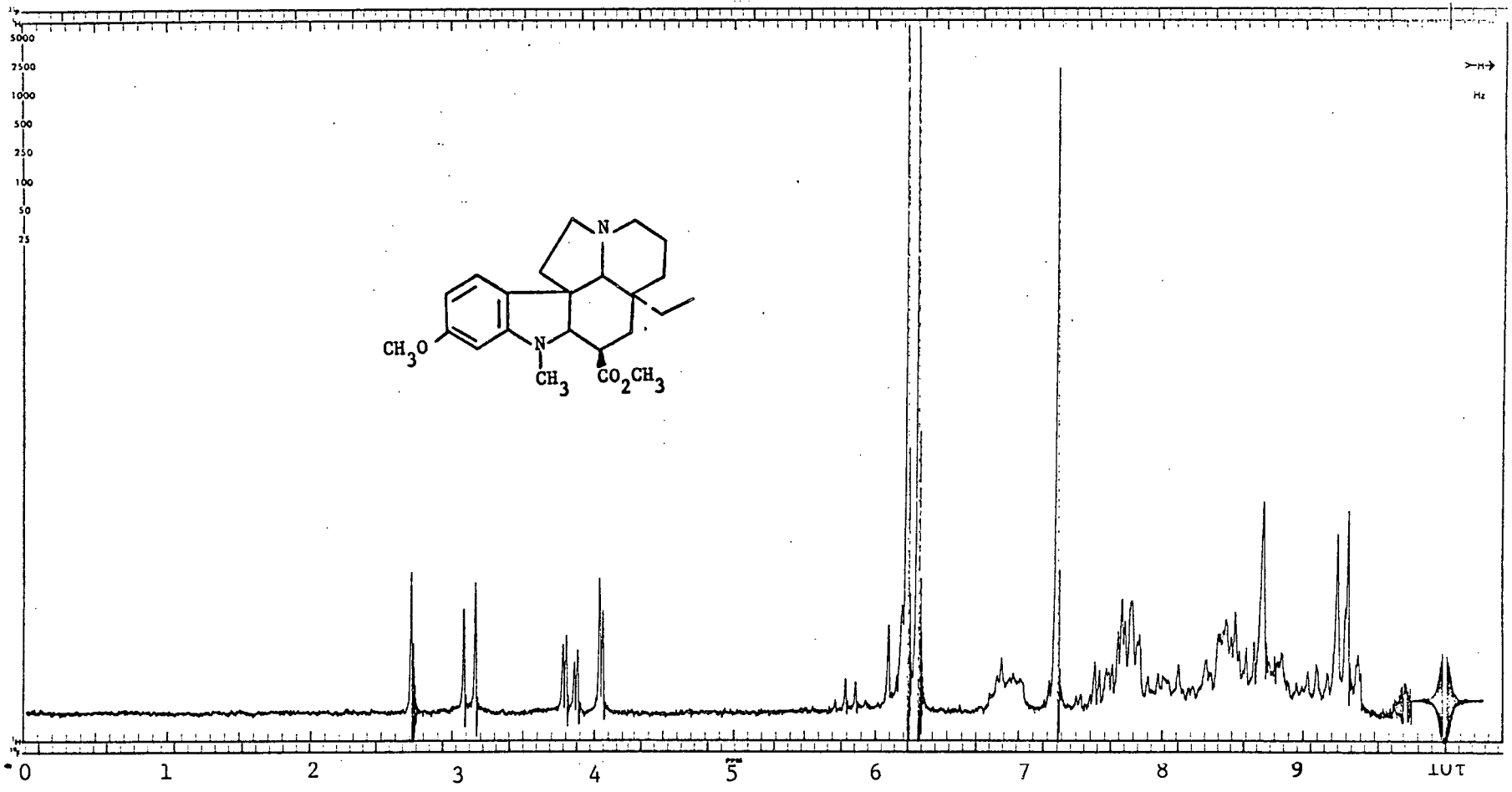


Figure 68. Nmr spectrum of saturated ester (233).

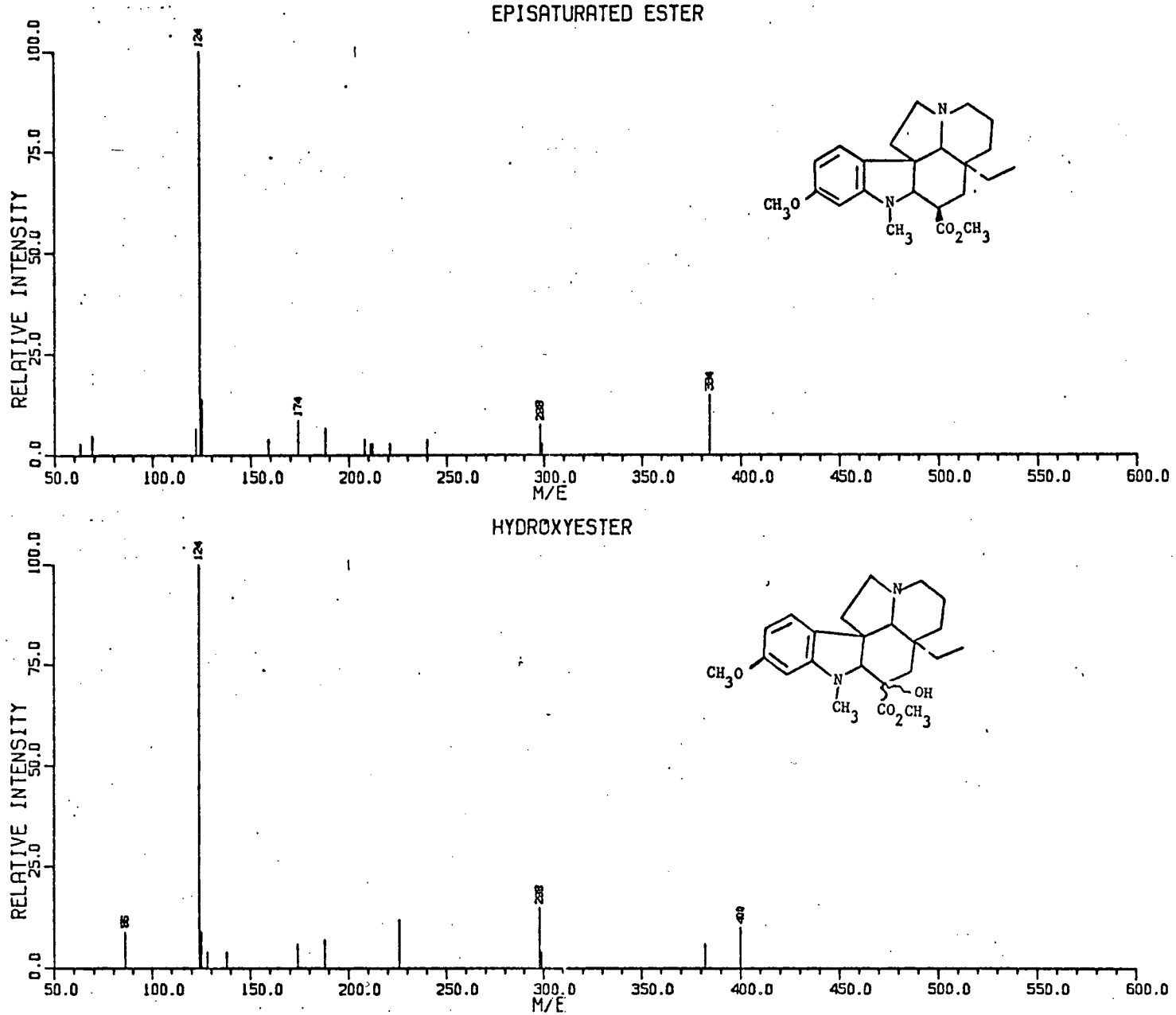
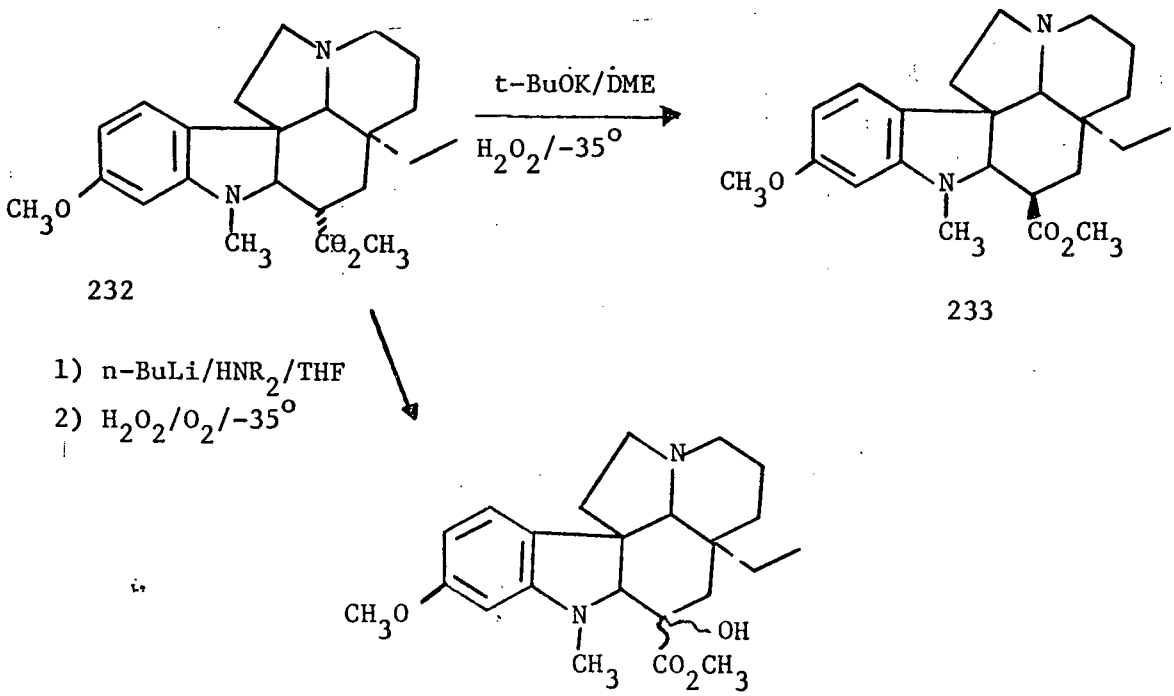


Figure 69. Mass spectra of saturated ester (233) and α-hydroxy ester (234).

It has been reported that the proton alpha to a carboxyl group[130] or ester function[131] can be abstracted with lithium dialkylamide reagents to generate the α-carbanion which on treatment with electrophilic reagents affords the corresponding α-substituted product.

At this point it was decided to attempt the use of lithium diisopropylamide as a base. This approach proved successful. Thus, reaction of 232 with hydrogen peroxide-molecular oxygen in the presence of lithium diisopropylamide in anhydrous tetrahydrofuran at room temperature for 18 hours, produced, in 54% yield (based on recovered starting material), the α-hydroxy ester (234). The nmr spectrum (Fig. 70) showed a one proton singlet at τ 6.13 due to the C-2 proton, while the three proton singlet assigned to the methyl protons of the carbomethoxy group was found at τ 6.13. There was an evident shift toward low field, as a result of the deshielding effect of the α-hydroxy substituent. The mass spectrum



232 233 234

Figure 70. Preparation of α-hydroxyester (234).

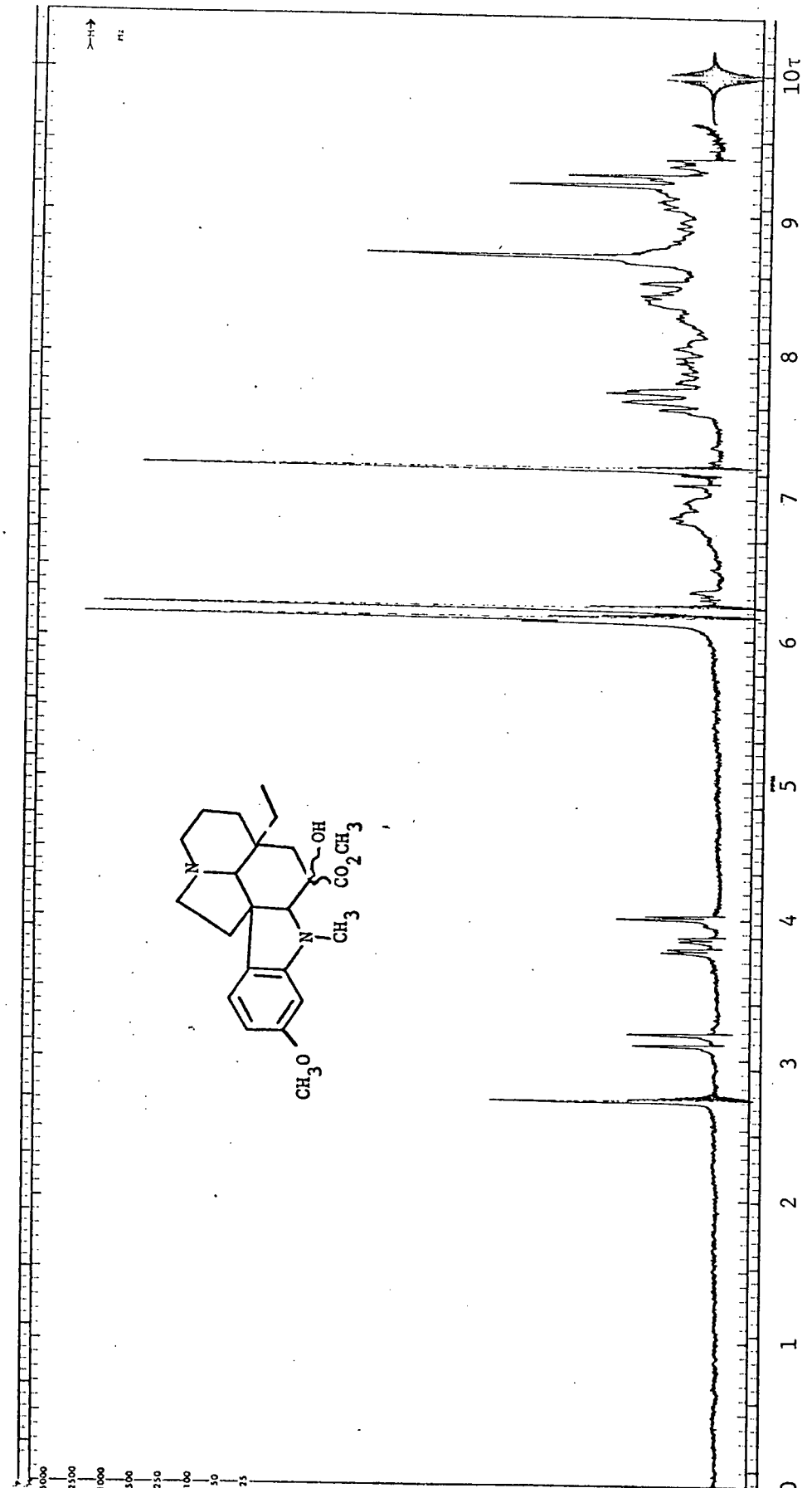
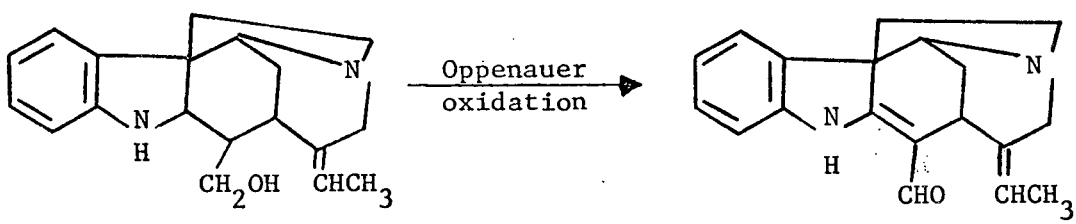


Figure 71. Nmr spectrum of α-hydroxyester (234).

(Fig. 69) had the main fragments at m/e 124, 174, 188, 298 and 400 (M^+) supporting the proposed structure 234. High resolution mass spectrometry established the molecular formula $C_{23}H_{32}O_4N_2$ (found: 400.235, calculated for $C_{23}H_{32}O_4N_2$: 400.236). At this stage the work of Wieland et al.[132] and Grdinic and co-workers[133] in the curane alkaloids came to our attention. These authors were able to obtain the unsaturated aldehyde 236 via Oppenauer oxidation of the corresponding saturated alcohol 235. We therefore decided to attempt this alternative approach toward the synthesis of the intermediate 195. Thus 232 in anhydrous tetrahydrofuran



235 236

was refluxed with lithium aluminum hydride for 1 hour. Conventional work-up and purification of the crude reaction mixture by chromatography gave the amino alcohol 237 in 70% yield. The infrared spectrum had a broad absorption at 3500-3200 cm^{-1} due to the hydroxyl group, and no carbonyl absorption, while in the nmr spectrum (Fig. 73) the three proton singlet due to the methyl protons of the carbomethoxy group was absent. The mass spectrum (Fig. 74) showed main fragments at m/e 124, 174, 188, 220, 298, 338, and 356 (M^+) which substantiate the assigned structure 237. The molecular formula, $C_{22}H_{32}O_2N_2$, was established by high resolution mass spectrometry (found: 356.246, calculated for $C_{22}H_{32}O_2N_2$: 356.246). Having obtained the amino alcohol (237) in

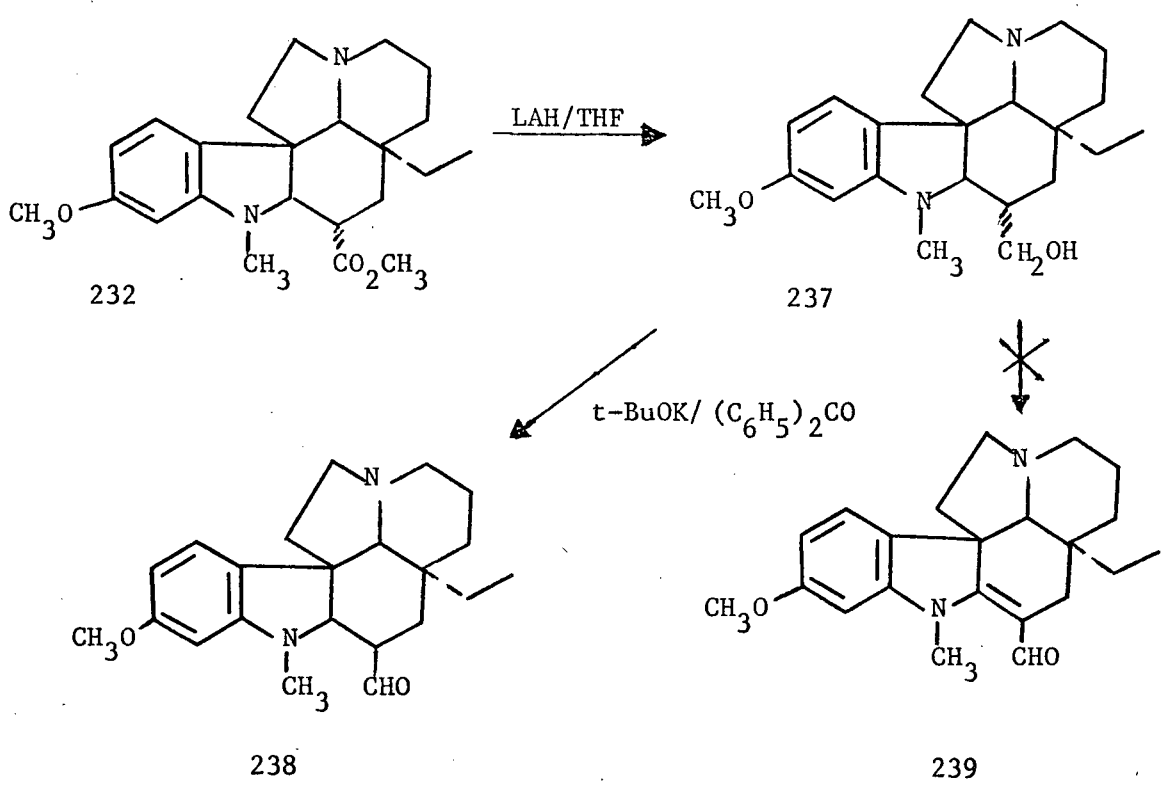


Figure 72. Preparation of aldehyde derivative 238.

satisfactory yield we then applied the Oppenauer oxidation to it, namely potassium t-butoxide and benzophenone in refluxing benzene. However we failed to obtain the desired α,β-unsaturated aldehyde (239). We were able to isolate only the saturated aldehyde (238) in high yield. The infrared spectrum had a strong carbonyl absorption at 1723 cm^{-1}, characteristic of a non-conjugated aldehydic carbonyl, while the ultraviolet spectrum had maxima at 213 (4.36), 255 (3.66), and 307 (3.54) nm, typical of the dihydroindole chromophore. The nmr spectrum (Fig. 75) showed a one proton singlet at τ 0.5 due to the aldehydic proton, a

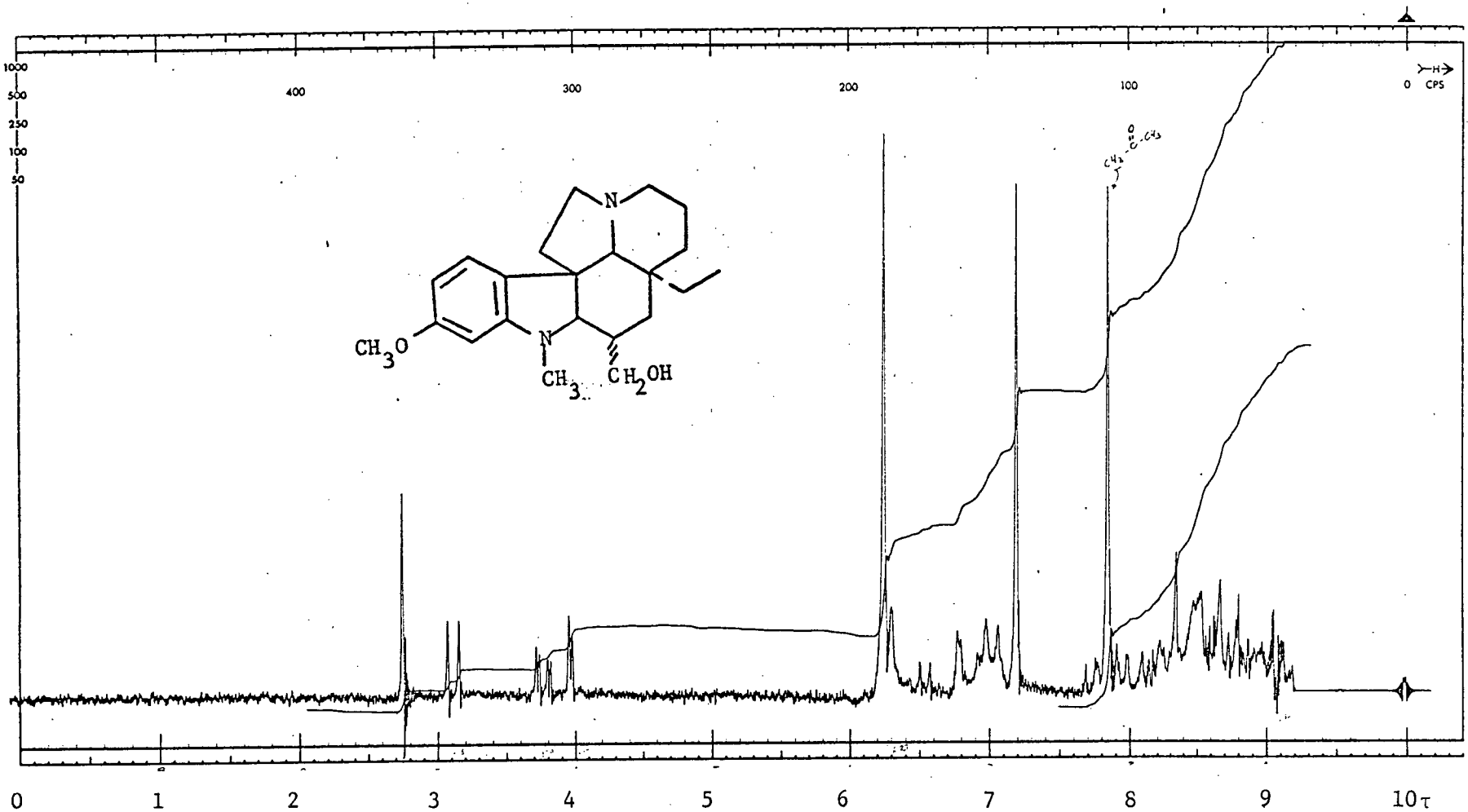


Figure 73. Nmr spectrum of aminoalcohol 237.

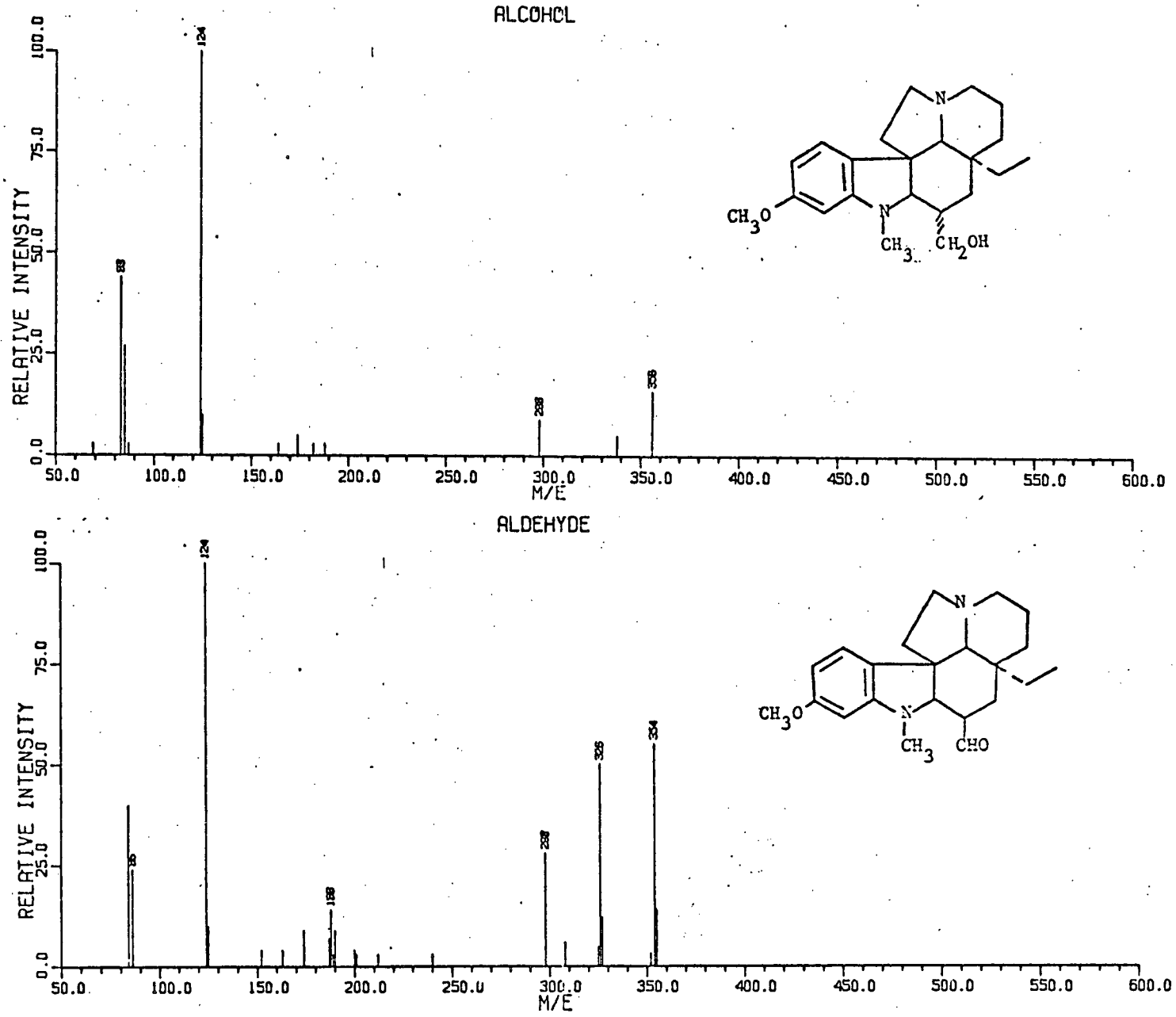


Figure 74. Mass spectra of aminoalcohol 237 and aldehyde derivative 238.

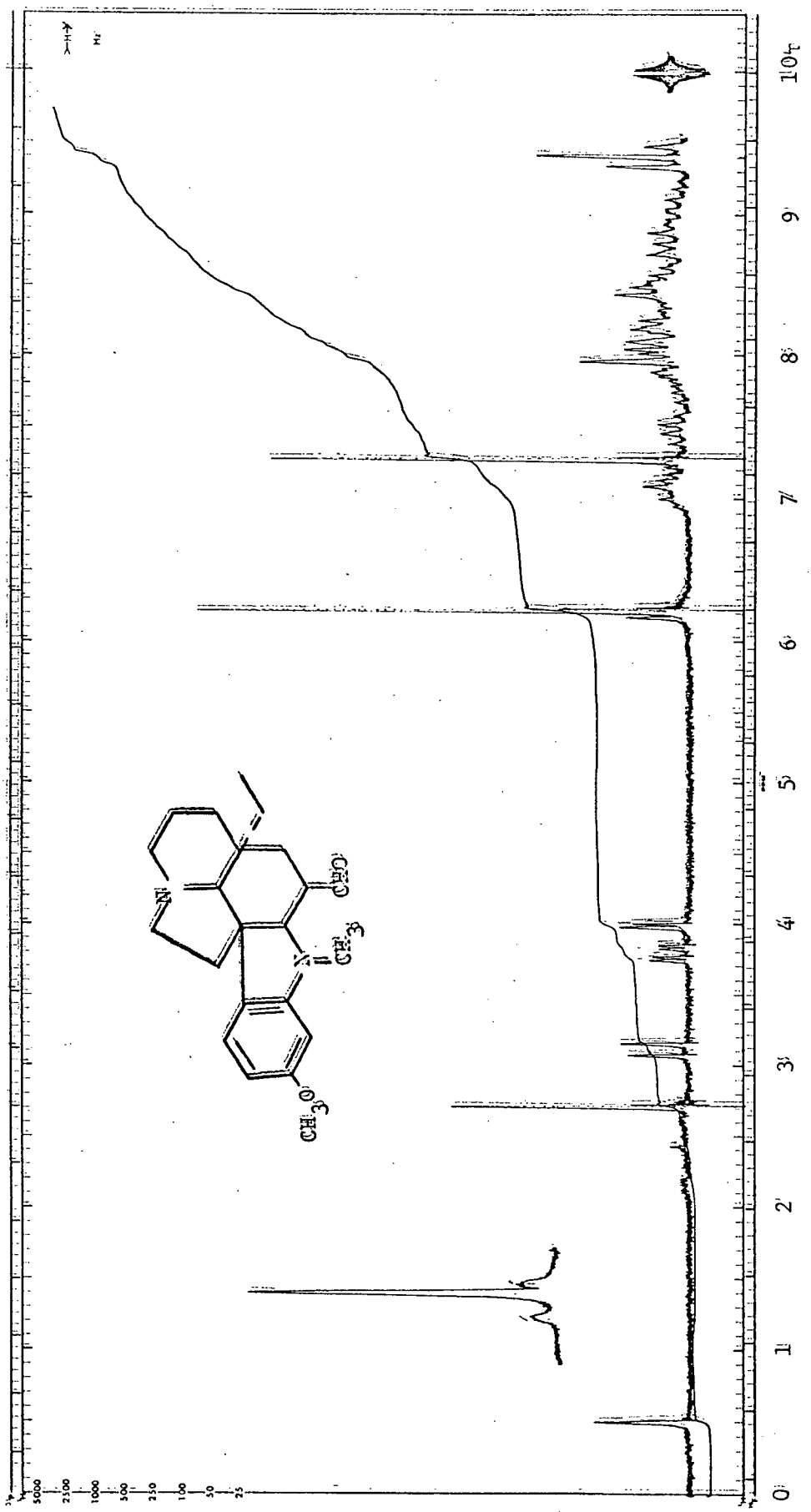
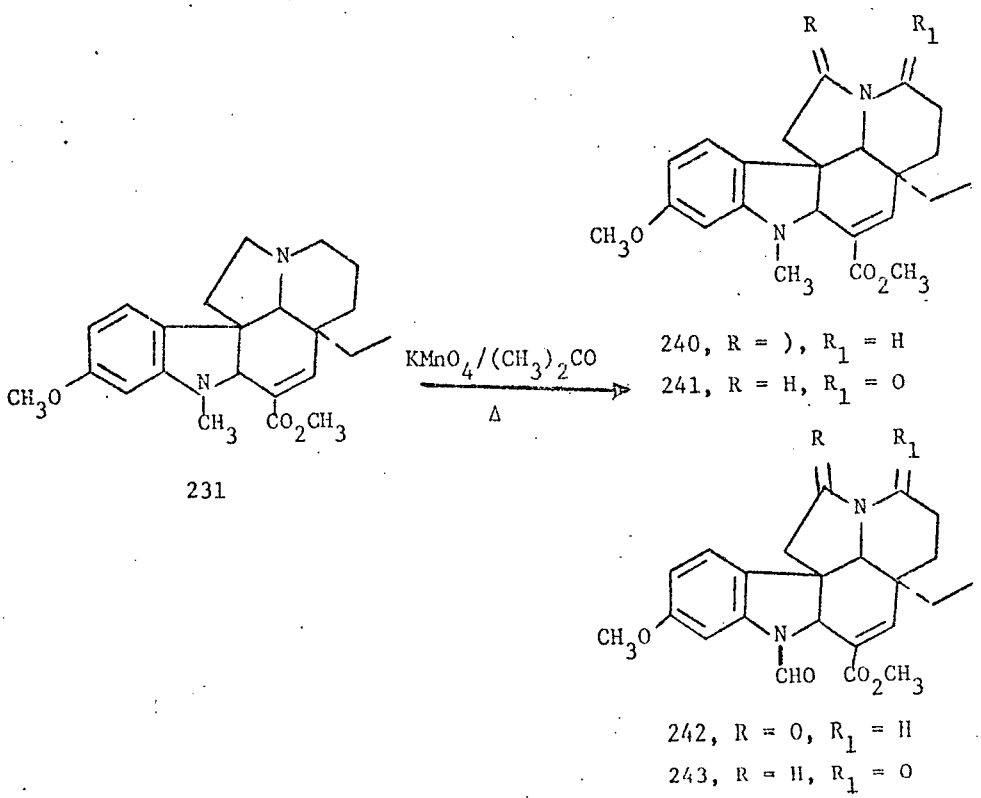


Figure 75. Nmr spectrum of aldehyde derivative 238.

one proton doublet at τ 6.20 assigned to the C-2 proton, and two three proton singlets at τ 6.22 and 7.28 assigned respectively to the methoxy and the N-methyl groups. The mass spectrum (Fig. 74) had the expected fragments at m/e 124, 188, 298, 326, and 354 (M^+). The molecular formula, $C_{22}H_{30}O_2N_2$, was established by elemental analysis.

Since the proposed mechanism[133] in which the saturated aldehyde (238), initially formed in the Oppenauer oxidation, dehydrogenates to give the corresponding α,β-unsaturated aldehyde (239) requires the formation of an iminium intermediate; we thought that perhaps the presence of the N-methyl group had prevented such formation. Therefore we decided to direct our efforts toward another series of investigations in which we had two objectives. Our first purpose would be to obtain the N-desmethyl derivatives, that could eventually lead to the desired relay compound 195. Our second aim would then be the synthesis of N-formyl derivatives to be utilized in the synthesis of vincristine (2) type compounds. Our preliminary investigation involved the potassium permanganate oxidation of the unsaturated ester (231). Thus, treatment of compound 231 with potassium permanganate in refluxing acetone followed by conventional work up and purification of the crude reaction mixture by tlc chromatography, we were able to isolate four compounds, here described by increasing order of polarity on silica gel chromatoplates developed with ethyl acetate: 5-membered ring lactam (240), 6-membered ring lactam (241), N_a-formyl-5-membered ring lactam (242), and N_a-formyl-6-membered ring lactam (243). It is hoped that the N-formyl derivatives can be cleaved to yield the N-desmethyl intermediate since there are several precedents for this in the literature.[134,135] The



resultant product 244 could then lead to the desired intermediate 195 via the reaction sequences outlined in Figure 76.

I have also discussed previously the synthesis of the α-hydroxyester 234 and it is now appropriate to reveal its usefulness as a starting material in an alternative synthesis of the desired intermediate 195. There is a variety of methods already known in the literature which may allow dehydration of 234 to 195 and some of them are outlined in Fig. 77. The above alternatives are under under investigation in our laboratory.

In conclusion, I would like to say that the synthetic sequence leading to dl-vincaminoridine (4) has been reinvestigated and improved (Figures 25, 26, 27, and 37). In addition, the above investigations have provided much of the chemistry essential in the completion of the highly oxygenated alkaloid vindoline (3), which forms the lower

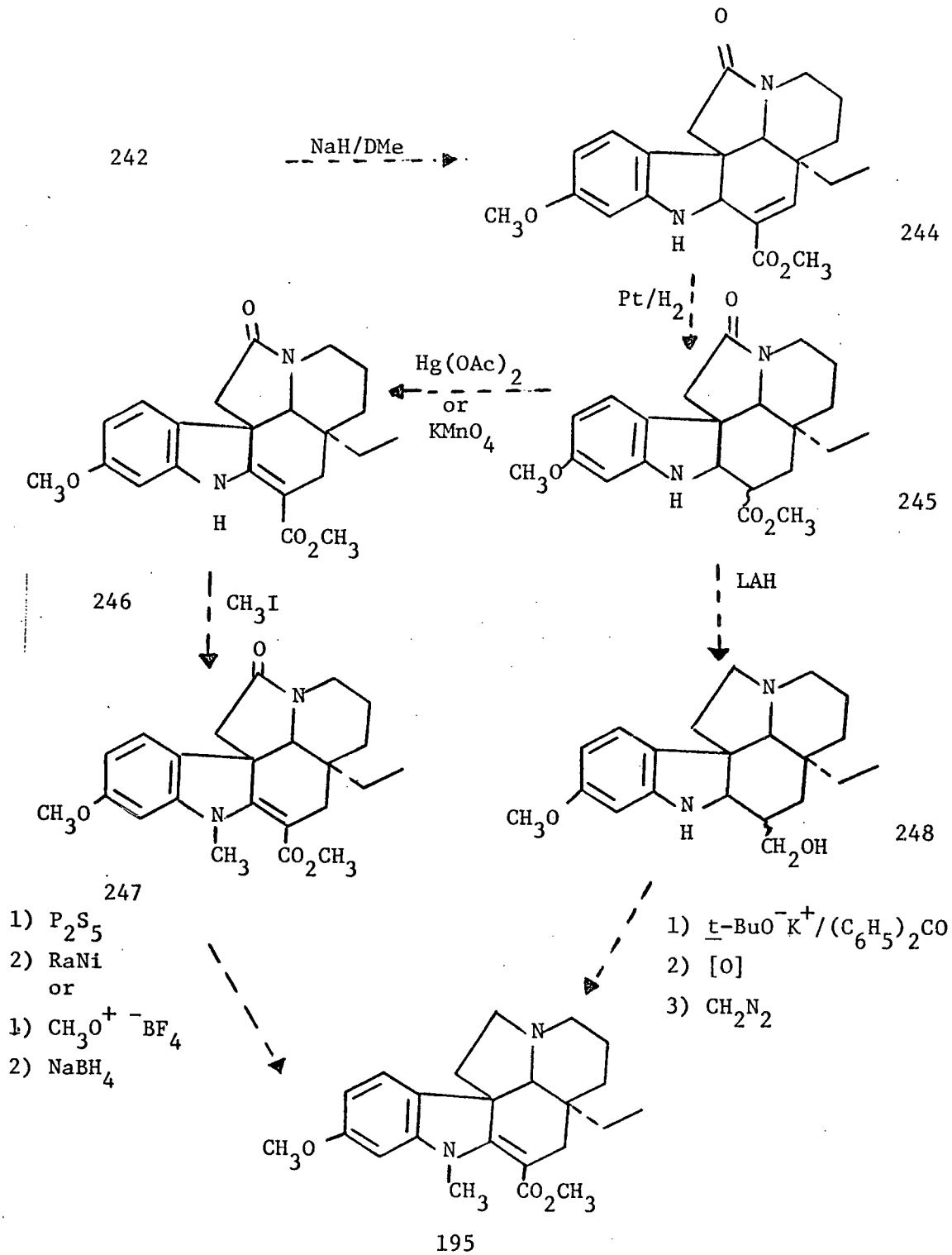


Figure 76. Proposal for the synthesis of intermediate 195.

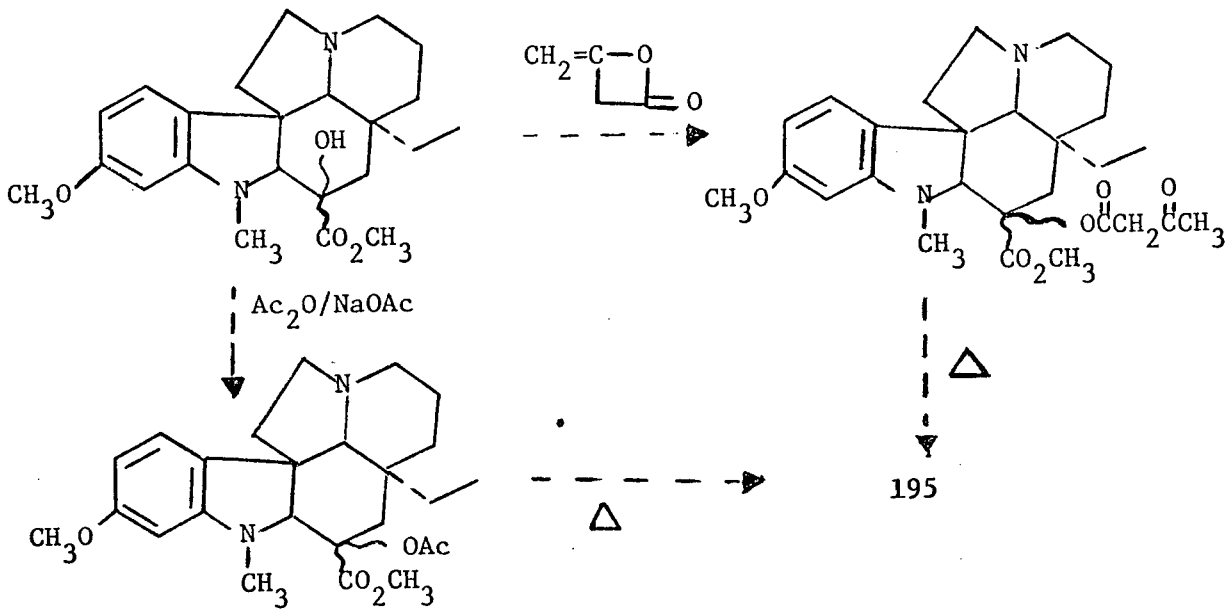


Figure 77. Alternative synthesis of intermediate **195**.

half of the biologically important Vinca alkaloids. A summary of the reactions as they relate to the vindoline synthesis is provided in Figure 78. The dotted arrows indicate the conversions which are presently incomplete.

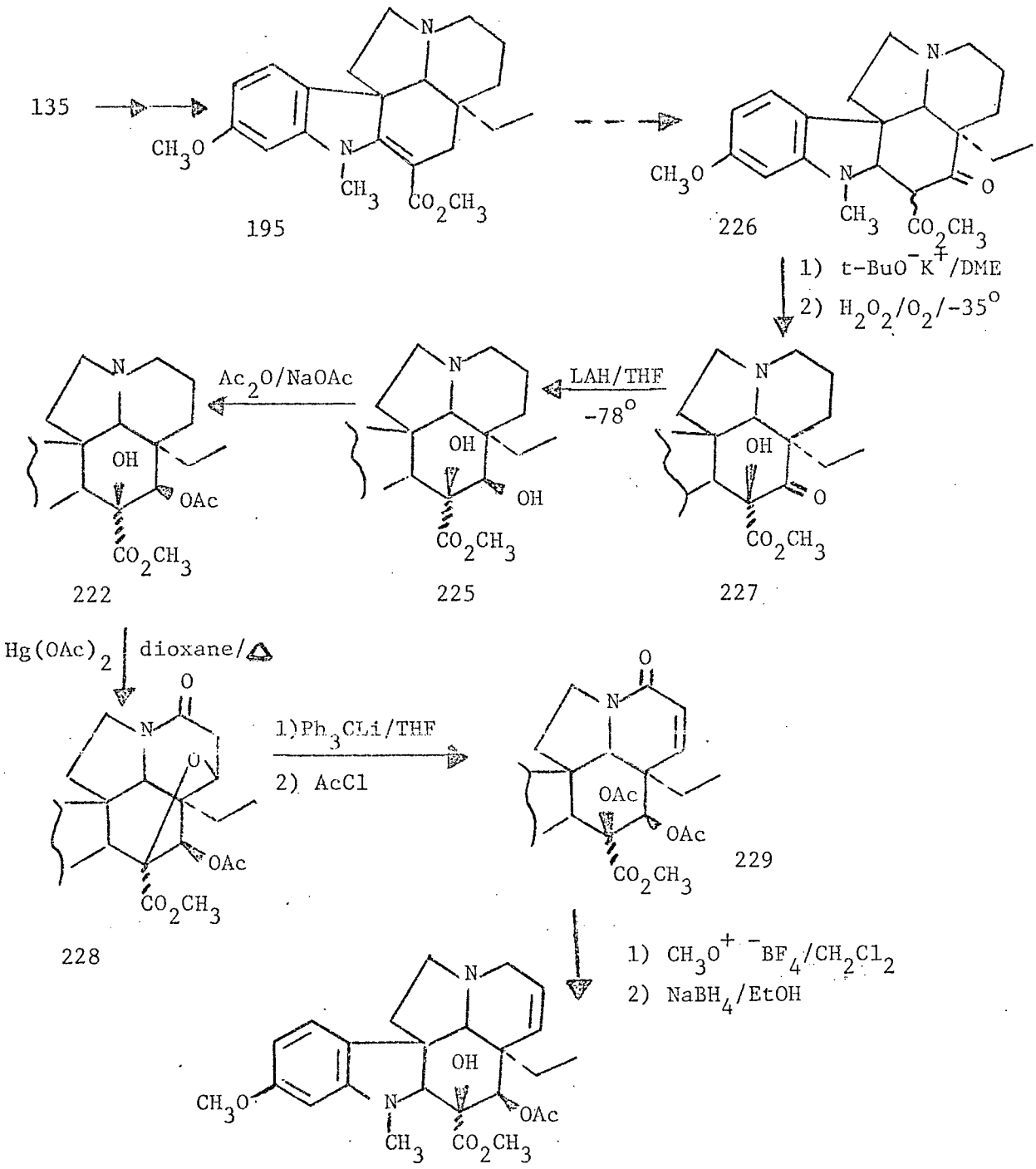


Figure 78. Summary of reactions which relate to the synthesis of vindoline.

EXPERIMENTAL PART II

For the general experimental information see page 91.

Preparation of Desacetylvindoline (224)

A solution of vindoline (3) (959 mg) in concentrated hydrochloric acid (30 ml) was brought to a gentle reflux for 8 min in an oil bath (previously preheated to 95-100°), under a nitrogen atmosphere. The solution was allowed to cool for 30 min, then cooled to 0° (ice bath), diluted with water (30 ml), and basified by careful addition of ammonium hydroxide (6 N). The resulting mixture was extracted with chloroform (3 x 30 ml), and the combined chloroform extracts washed with brine (2 x 10 ml) and dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure gave quantitative yield of desacetylvindoline (224) as a foam, which crystallized upon addition of diethyl ether. Recrystallization from methanol gave white plates, m.p. 160-162°C. Infrared ($CHCl_3$): 3600-3500 (medium, OH), 1727 (strong, CO_2OCH_3), 1616 (medium, C=C) cm^{-1}. Ultraviolet; λ_{max} (log ε): 214 (4.55), 254 (3.90), 306 (3.73) nm. Nmr signals (100 MHz): 3.14 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.72 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1 H, C-15 proton), 3.95 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 4.22 (multiplet, 2H, -CH=CH-), 5.93 (singlet, 1H, H-C-OH), 6.20 (singlet, 3H, CH_3O-), 6.27 (singlet, 3H, $-CO_2CH_3$), 6.40

(singlet, 3H, $C\underline{H}_3O$-), 6.27 (singlet, 3H, $-CO_2C\underline{H}_3$), 6.40 (singlet, 1H, $-NCH_3C\underline{H}$-), 6.58 (multiplet, 2H, $-NC\underline{H}_2CH$=), 7.32 (singlet, 3H, $-N-C\underline{H}_3$), 9.35 (triplet, J = 7.5 cps, 3H, $-CH_2C\underline{H}_3$). Mass spectrum, main peaks: m/e 107, 121, 135, 174, 188, 240, 298 and 414 (M^+). Molecular weight: 414.213. Calc. for $C_{23}H_{30}O_5N_2$: 412.215. Found: C, 66.58; H, 7.60; N, 6.55. Calc. for $C_{23}H_{30}O_5N_2$: C, 66.65; H, 7.30; N, 6.55.

Preparation of Desacetyldihydrovindoline (225)

Desacetylvindoline (224) (01.054 g) in 50 ml of ethanol (95%) was hydrogenated at room temperature and atmospheric pressure using 85 mg of platinum oxide catalyst. Absorption of hydrogen (58 ml) stopped after 1.25 h. The catalyst was removed by filtration and the solution was evaporated to a light oil. The product was crystallized from ether (1.001 g, 95%). Recrystallized from methanol, m.p. 181-183°C. Infrared ($CHCl_3$): 3570 (medium, OH), 1724 (strong, CO_2CH_3), 1613 (strong, C=C) cm^{-1}. Ultraviolet: λ_{max} (log ε): 214 (4.53), 251 (3.86), 303 (3.72) nm. Nmr signals (100 MHz): 3.13 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.70 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-15 proton), 3.95 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 5.66 (singlet, 1H, $\underline{H}COH$), 6.18 (singlet, 3H, $-OC\underline{H}_3$), 6.27 (singlet, 3H, $-CO_2C\underline{H}_3$), 6.29 (singlet, 1H, $H_3CN-C\underline{H}$), 7.39 (singlet, 3H, $\underline{H}_3CN$-), 9.31 (multiplet, 3H, $-CH_2C\underline{H}_3$). Mass spectrum, main peaks: m/e 124, 188, 242, 298, 416 (M^+). Molecular weight: 416.235. Calc. for $C_{23}H_{32}O_5N_2$: 416.231. Found: C, 66.02; H, 7.65; N, 6.78. Calc. for $C_{23}H_{32}O_5N_2$: C, 66.32; H, 7.74; N, 6.73.

Pyrolysis of Desacetyldihydrovindoline (225)

(a) Direct Method

477 mg of desacetyldihydrovindoline (225) in a pyrex tube was heated in a heating box for 3 h at 280-290°C under an atmosphere of nitrogen. The crude product was chromatographed on a neutral alumina column (Woelm, 15 g, activity II). Elution with benzene gave 100 mg (30% based on starting material recovered) of the desired ketone 86. Further elution with benzene-ether (4:1) gave 70 mg of the starting material. The ketone 86 was then recrystallized from methanol, m.p. 135-137°. Infrared ($CHCl_3$): 2890 (strong, CH), 1701 (strong, C=O), 1621 (strong, C=C) cm^{-1}. Ultraviolet; λ_{max} (log ε): 213 (4.48), 252 (3.81), 305 (3.73) nm. Nmr signals (100 MHz): 3.02 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.74 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-15 proton), 3.97 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 6.24 (singlet, 3H, $C\underline{H}_3O$-), 7.33 (singlet, 3H, $C\underline{H}_3N$-), 9.53 (triplet, J = 7 cps, 3H, $C\underline{H}_3CH_2$-). Mass spectrum; main peaks: m/e 124, 166, 174, 188, 298, and 340 (M^+). Molecular weight: 340.211. Calc. for $C_{21}H_{28}O_2N_2$: 340.215. Found: C, 74.25; H, 8.50; N, 8.09. Calc. for $C_{21}H_{28}O_2N_2$: C, 74.08; H, 8.29; N, 8.23.

(b) Using Hexamethylphosphoramide (HMPT)

530 mg of desacetyldihydrovindoline (225) in 8 ml of hexamethylphosphoramide was stirred and heated at 224°C (oil bath) for 2 h under an atmosphere of nitrogen. The resulting brown solution was cooled to room temperature and water (15 ml) was added. The reaction mixture was extracted with ether (5 x 20 ml), and the combined ethereal extracts were washed with water (2 x 5 ml) to remove residual HMPT, and dried

over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure at room temperature gave 578 mg of a yellow gum. The crude product was chromatographed on a neutral alumina column (Woelm, 20 g, activity I). Gradient elution with hexane-ether gave 143 mg (40% base on starting material recovered) of the desired ketone 86. Further elution with ether-methanol (19:1) gave 92 mg of the starting material. Considering the direct method (30%), this was slightly superior.

Preparation of the β-Ketoester (226)

To a suspension of sodium hydride (300 mg of 56% dispersion) in 20 ml of anhydrous tetrahydrofuran, a solution of ketone 86 (400 mg) in anhydrous tetrahydrofuran (5 ml) was added dropwise over a period of 20 min, under an atmosphere of nitrogen. The reaction mixture was stirred for 2.3 h and dimethyl carbonate (1.8 ml) was then added. After the addition of the dimethyl carbonate, the mixture was refluxed for 38 h, then cooled with an ice-water bath and the excess of sodium hydride destroyed by the addition of several drops of glacial acetic acid. The solution was taken up in water (20 ml), and extracted with ether (4 x 20 ml). The combined organic extracts were washed with aqueous sodium bicarbonate, then with brine, and dried over sodium sulfate. Filtration and removal of the solvent left 700 mg of a yellow gum, which was chromatographed on a silica gel column (Woelm, 20 g, activity II). Gradient elution with benzene-ether gave 336 mg (71%) of the desired β-ketoester (226). Infrared ($CHCl_3$): 1725 (strong, CO_2CH_3), 1700 (strong, C=O), 1610 (strong, C=C) cm^{-1}. Ultraviolet; λ_{max} (log ε):

212 (4.39), 252 (3.88), and 304 (3.59) nm. Nmr signals (100 MHz): -3.62 (singlet, 1H, C-3 proton, enol form), 3.04 and 3.08 (two doublets, J_{ortho} = 8 cps, 1H, C-14 proton, keto and enol forms), 3.74 and 3.82 (two quartets, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-15 proton), 3.97 and 4.08 (two doublets, J_{meta} = 2 cps, 1H, C-17 proton), 5.7 (singlet, 1H, C-2 proton, enol form), 5.82 and 6.00 (two doublets, J_{AB} = 4 and 6 cps, 1H, C-3 proton, keto form), 6.22 and 6.24 (two singlets, 6H, $CO_2\underline{CH_3}$ and $\underline{CH_3}O$), 7.30 and 7.32 (two singlets, 3H, $N\underline{CH_3}$, keto and enol forms), 9.40 and 9.50 (two triplets, 3H, $\underline{CH_3}CH_2$, keto and enol forms). Mass spectrum; main peaks: m/e 124, 174, 188, 298, and 398 (M^+) and 398 (M^+). Molecular weight: 398.220. Calc. for $C_{23}H_{30}O_4N_2$: 398.218.

Preparation of the Hydroxy Ketoester (227)

To a solution of the β-ketoester (226) (70 mg, 0.175 mmole) in 1,2-dimethoxyethane (20 ml) and t-butanol (1 ml), potassium t-butoxide (7 ml of a solution prepared with 214 mg of potassium in 25 ml of anhydrous t-butanol) was added. The reaction mixture was stirred for 15 min at room temperature. The reaction flask was then cooled to -35°C (dry ice-benzyl chloride) and 0.08 ml of a 98% hydrogen peroxide solution was added. Molecular oxygen was then passed through the reaction mixture for a period of 21 hours. The reaction mixture was allowed to come slowly to room temperature. The solvent was removed under reduced pressure without heating. The residue was taken in brine (5 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic layers were dried over anhydrous sodium sulfate. Filtration and removal of the solvent gave 100 mg of a yellowish gum. Purification

of the crude reaction mixture by tlc chromatography on silica gel developed with benzene-ethyl acetate (1:1), provide 15 mg of the starting material (226) and the desired hydroxy ketoester 227 (35 mg) in 59% yield (based on recovered starting material). Infrared ($CHCl_3$): 3450 (medium, OH), 1750 (strong, CO_2CH_3), 1712 (strong, C=O), 1616 (C=C) cm^{-1}. Ultraviolet; λ_{max} (log ε): 213 (4.49), 248 (3.81), 303 (3.67) nm. Nmr signals (100 MHz): 3.14 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.68 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-15 proton), 3.92 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 6.17 (singlet, 3H, CO_2CH_3), 6.26 (singlet, 3H, CH_3O-), 7.37 (singlet, 3H, CH_3N), 9.50 (triplet, J = 7 cps, 3H, CH_3CH_2-). Mass spectrum; main peaks: m/e 124, 174, 188, 298, and 414 (M^+). Molecular weight: 414.214. Calc. for $C_{23}H_{30}O_5N_2$: 414.215.

Preparation of Desacetyldihydrovindoline Thiocarbonate (230)

To a solution of 2.1 g of desacetyldihydrovindoline (225) in 125 ml of anhydrous butanone, 5.4 g N,N'-thiocarbonyldiimidazole was added. The reaction mixture was then refluxed for 28 hours under an atmosphere of nitrogen. The solvent was removed under reduced pressure and the crude reaction product was chromatographed on silica gel column (500 g). Continuous elution with ethyl acetate gave the desired thiocarbonate derivative (230) in 88% yield (2.057 g). Recrystallization from ethyl acetate gave an analytical sample, m.p. 222-223°. Infrared ($CHCl_3$): 1739 (strong, CO_2CH_3), 1304 (C=S) cm^{-1}. Ultraviolet; λ_{max} (log ε): 208 (4.53), 233 (4.33), and 298 (3.69) nm. Nmr signals (100 MHz): 302 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.63 (quartet, J_{ortho} = 8 cps, J_{meta} = 2.3 cps, 1H, C-15 proton), 3.90 (doublet, J_{meta} = 2.3 cps,

1H, C-17 proton), 4.69 (singlet, 1H, C-4 proton), 6.07 (singlet, 3H, $CO_2\underline{CH_3}$), 6.20 (singlet, 1H, C-2 proton), 6.24 (singlet, 3H, $\underline{CH_3}O$), 7.37 (singlet, 3H, $N\underline{CH_3}$), 9.54 (triplet, J = 7 cps, 3H, $\underline{CH_3}CH_2$-). Mass spectrum; main peaks: m/e 124, 149, 298, 381, and 458 (M^+). Found: C, 63.16; H, 6.9; N, 5.97. Calc. for $C_{24}H_{30}N_2O_5S$: C, 62.87; H, 6.60; N, 6.11.

Preparation of the α,β-Unsaturated Ester (231)

Raney nickel active catalyst (W.R. Grace Co. #28, 12 g) was washed with acetone (6 x 25 ml), decanted after settling and the solvent discarded. The catalyst was then refluxed for 4 h in reagent actone. After cooling to room temperature, the acetone was decanted and the catalyst was washed with tetrahydrofuran (6 x 25 ml). Washed Raney nickel was suspended in 25 ml of tetrahydrofuran and to this was added a solution of 0.645 g of desacetyldihydrovindoline thiocarbonate (230) in small volumes of tetrahydrofuran. The reaction mixture was refluxed with magnetic stirring for 24 hours. Filtration of the catalyst and removal of the solvent under reduced pressure gave 453 mg of crude α,β-unsaturated ester (84% crude). Purification of the crude product by chromatography on silica gel column (500 g) eluted with ethyl acetate-methanol (97.5:2.5) provided the desired product (231) in 81% yield. Infrared ($CHCl_3$): 1703 (strong, C=C-CO_2CH_3) cm^{-1}. Ultraviolet; λ_{max} (log ε): 212 (4.53), 253 (3.82), and 307 (3.62) nm. Nmr signals (100 MHz): 2.77 (broad singlet, 1H, C-4 proton), 3.04 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.78 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-15 proton), 4.06 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 5.73 (singlet, 1H, C-2 proton), 6.22 (singlet, 3H, $CO_2\underline{CH_3}$), 6.25 (singlet,

3H, $C\underline{H}_3O$), 7.25 (singlet, 3H, $NC\underline{H}_3$), 9.41 (triplet, J = 7 cps, 3H, $C\underline{H}_3CH_2$). Mass spectrum; main peaks: m/e 124, 149, 174, 208, 263, and 382 (M^+). Molecular weight: 382.222. Calc. for $C_{23}H_{30}O_3N_2$: 382.225. Found: C, 72.29; H, 7.89; N, 7.30. Calc. for $C_{23}H_{30}O_3N_2$: C, 72.28; H, 7.87; N, 7.32.

Preparation of 3,4-Desoxydihydrovindoline (232)

10% Palladium on charcoal (360 mg) was added to a solution of the α,β-unsaturated ester 231 (438 mg) in 95% ethanol (10 ml) at room temperature under an atmosphere of nitrogen. The reaction mixture was then hydrogenated at room temperature and one atmosphere of hydrogen with continuous stirring for 72 hours. The catalyst was removed by filtration through a celite pad and the pad subsequently washed with warm methanol (3 x 10 ml). Removal of the solvent under reduced pressure gave a yellow viscous product which was chromatographed on a silica gel column (50 g). Elution with benzene-ethyl acetate (1:1) gave the desired saturated ester 232 (385 mg) in 80% yield. Infrared ($CHCl_3$): 1735 (strong, CO_2CH_3) cm^{-1}. Ultraviolet; λ_{max} (log ε): 212 (4.35, 253 (3.69), and 305 (3.53) nm. Nmr signals (100 MHz): 3.08 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.78 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-15 proton), 4.00 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 5.9 (multiplet, 1H, C-3 proton), 6.32 and 6.34 (two singlets, 6H, CO_2CH_3 and CH_3O), 6.4 (doublet, J_{AB} = 2 cps, 1H, C-2 proton), 7.45 (singlet, 3H, $NC\underline{H}_3$), 9.5 (triplet, J = 7 cps, 3H, $C\underline{H}_3CH_2$). Mass spectrum; main peaks: m/e 124, 210, 298 and 384 (M^+). Found: C, 71.93; H, 8.58; N, 7.41. Calc. for $C_{23}H_{32}O_3N_2$: C, 71.84; H, 8.39; N, 7.29.

Epimerization of 3,4-Desoxydihydrovindoline (232)

To a stirred solution of 3,4-desoxydihydrovindoline (232) (93 mg) in 1,2-dimethoxyethane (5 ml) and t-butanol (1 ml), potassium t-butoxide (53 mg) was added. The reaction mixture was stirred for a further 30 min at room temperature, cooled to -35°, and 98% hydrogen peroxide (0.03 ml) was added. Molecular oxygen was passed through the stirred solution for a period of 8 h. The reaction mixture was then allowed to come to room temperature and the solvent was removed under reduced pressure without heating. The residue was taken up in brine (5 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic layers were dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure gave 91 mg of a colorless gum. Purification of the crude reaction mixture by tlc on silica gel developed with benzene-ethyl acetate (1:1) gave 6 mg of 3,4-desoxydihydrovindoline (232) and 68 mg of epi-3,4-desoxydihydrovindoline (233). The latter was recrystallized from methanol, m.p. 162-164°. Infrared ($CHCl_3$): 1725 (CO_2CH_3) cm^{-1}. Ultraviolet; λ_{max} (log ε): 212 (4.42), 256 (3.80), and 307 (3.65) nm. Nmr signals (100 MHz): 3.13 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.84 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-15 proton), 4.06 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 6.15 (doublet, J_{AB} = 10 cps, 1H, C-2 proton), 6.24 and 6.31 (two singlets, 6H, $CO_2\underline{CH_3}$ and $\underline{CH_3}O$), 7.29 (singlet, 3H, $NC\underline{H_3}$), 9.33 (triplet, J = 7 cps, 3H, $C\underline{H_3}CH_2$-). Mass spectrum; main peaks: m/e 124, 188, 298, and 384 (M^+). Found: C, 71.65; H, 8.45; N, 7.04. Calc. for $C_{23}H_{32}O_3N_2$: C, 71.84; H, 8.39; N, 7.29.

Preparation of Hydroxyester (234)

Redistilled diisopropylamine (0.61 ml, 0.5 mmole) in anhydrous tetrahydrofuran (8 ml) was introduced into a nitrogen swept flask and cooled to 0-5°. Butyllithium in heptane solution (0.4 ml, 0.7 mmole) was introduced in a fine stream through a rubber septum with a syringe. The reaction mixture was then stirred for 15 min. A solution of 3,4-desoxydihydrovindoline (232) (95 mg, 0.25 mmole) in anhydrous tetrahydrofuran (2 ml) was added dropwise, followed by stirring for 30 min at 0-5° and then at room temperature for 1 h. Molecular oxygen was then bubbled into the solution for 18 h. Water (20 ml) was added and the resulting mixture extracted with ether (3 x 15 ml). The combined organic layers were washed with brine (10 ml) and dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure gave 109 mg of a yellowish gum. Purification by tlc on silica gel developed with benzene-ethyl acetate (1:1) gave 20 mg of unreacted starting material (232), 23 mg of its epimer (235), and 31 mg (54% based on recovered starting material) of the hydroxy ester (234). Nmr signals (100 MHz): 3.15 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.82 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-15 proton), 4.02 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 6.13 (singlet, 1H, C-2 proton), 6.16 (singlet, 3H, $CO_2C\underline{H}_3$), 6.22 (singlet, 3H, $C\underline{H}_3O$), 7.22 (singlet, 3H, $NC\underline{H}_3$), 9.32 (triplet, J = 7 cps, 3H, $C\underline{H}_3CH_2$). Mass spectrum; main peaks: m/e 124, 174, 188, 298, and 400 (M^+). Molecular weight: 400.235. Calc. for $C_{23}H_{32}O_4N_2$: 400.236.

Reduction of 3,4-Desoxydihydrovindoline (232) with Lithium Aluminum Hydride

Anhydrous tetrahydrofuran (12 ml) and lithium aluminum hydride (100 mg) were introduced into a nitrogen swept flask, and a solution of 3,4-desoxydihydrovindoline (183 mg) in anhydrous tetrahydrofuran (13 ml) was added dropwise with stirring. The reaction was then refluxed for 1 h under an atmosphere of nitrogen. The reaction mixture was cooled to 0^{o} (ice bath) and the excess reagent destroyed by careful addition of a saturated aqueous solution of sodium sulfate. The precipitate was removed by filtration and washed several times with hot tetrahydrofuran. The filtrate and washings were combined and dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure gave 181 mg of the crude product. Purification by tlc on silica gel developed with ether provided the desired alcohol 237 (118 mg), 70% yield. Infrared ($CHCl_3$): 3500-3200 (broad, OH). Nmr signals (100 MHz): 3.15 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.79 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-15 proton), 3.99 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 6.27 (singlet, 3H, $C\underline{H}_3O$), 7.21 (singlet, 3H, $NC\underline{H}_3$). Mass spectrum; main peaks: m/e 124, 174, 188, 220, 298, 338, and 356 (M^+). Molecular weight: 356.246. Calc. for $C_{22}H_{32}O_2N_2$: 356.246.

Oppenauer Oxidation of Alcohol 237

To a stirred solution of the alcohol 237 (118 mg, 0.33 mmole) and benzophenone (300 mg, 1.65 mmole) in anhydrous benzene (10 ml), potassium t-butoxide (t-BuOH free) was added under an atmosphere of nitrogen. The reaction mixture was then brought to reflux for 35 min. The reaction mixture was cooled to room temperature, diluted with water (20 ml) and

extracted with ether (3 x 10 ml). The combined organic layers were extracted with an aqueous 5% hydrochloric acid solution (4 x 10 ml). The combined aqueous extracts were washed with ether (2 x 10 ml) and poured into a mixture of ice and concentrated ammonium hydroxide solution. The resulting basic solution was extracted with ether (3 x 10 ml), and the ethereal extracts dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure gave 103 mg of the aldehyde 238 (88% yield). An analytical sample was obtained by tlc on fluorisil chromatoplates developed with ether-methanol (95:5). Infrared ($CHCl_3$): 1723 (strong, C=O) cm^{-1}. Ultraviolet; λ_{max} (log ε): 213 (4.36), 255 (3.66), and 307 (3.54) nm. Nmr signals (100 MHz): 0.5 (singlet, 1H, C$\underline{H}$O), 3.11 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.79 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-15 proton), 3.99 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 6.20 (doublet, 1H, C-2 proton), 6.22 (singlet, 3H, C$\underline{H}_3$O), 7.28 (singlet, 3H, NC$\underline{H}_3$), 9.41 (triplet, J = 7 cps, 3H, C$\underline{H}_3$CH$_2$-). Mass spectrum; main peaks: m/e 124, 188, 298, 326 and 354 (M^+). Found: C, 74.80; H, 8.77; N, 7.50. Calc. for $C_{22}H_{30}O_2N_2$: C, 74.54; H, 8.53; N, 7.90.

Potassium Permanganate Oxidation of the α,β-Unsaturated Ester (231)

To a refluxing solution of α,β-unsaturated ester 231 (53 mg) in acetone (10 ml), potassium permanganate (718 mg) was added portionwise over a 5 h period. The reaction mixture was cooled (ice-bath), ice added to it and sulfur dioxide was passed through. The resulting solution was basified with aqueous sodium bicarbonate solution and extracted with ether (4 x 20 ml). The combined organic extracts were washed with water (10 ml), brine (10 ml), and dried over anhydrous sodium

sulfate. Filtration and removal of the solvent under reduced pressure gave 38 mg of crude reaction product. Preparative tlc chromatography of this material on silica gel developed with ethyl acetate gave 1.5 mg of the starting material (231), 2.5 mg of the lactam (240), 135 mg of the lactam N_a-formyl (242), 1.5 mg of the lactam (241), and 7 mg of the lactam N_a-formyl (243).

5-Membered ring lactam (240): Infrared ($CHCl_3$): 1710, 1680 cm^{-1}. Mass spectrum, main peaks: m/e 149, 174, 258, 381, and 396 (M^+). Molecular weight: 396.202. Calc. for $C_{23}H_{28}N_2O_4$: 396.204.

6-Membered ring lactam (241): Infrared ($CHCl_3$): 1710, 1620 cm^{-1}. Mass spectrum; main peaks: m/e 174, 207, 234, 297, 367, 381, and 396 (M^+).

5-Membered ring lactam N_a-formyl (242): Infrared ($CHCl_3$): 1720, 1665, 1595 cm^{-1}. Nmr signals (100 MHz, F.T.): 1.37 (singlet, 1H, N_CHO), 2.25 (broad singlet, 1H, C-17 proton), 2.82 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 2.97 (broad singlet, 1H, C-4 proton), 3.28 (quartet, J_{meta} = 2.5 cps, J_{ortho} = 8 cps, 1H, C-15 proton), 4.86 (singlet, 1H, C-2 proton), 6.15 and 6.18 (two singlets, 6H, CH_3O, and CO_2CH_3), 9.32 (triplet, J = 7 cps, 3H, $-CH_2CH_3$). Mass spectrum; main peaks: m/e 78, 160, 321, 357, 382, and 410 (M^+). Molecular weight: 410.174. Calc. for $C_{23}H_{26}O_5N_2$: 410.184.

6-Membered ring lactam N_a-formyl (243): Infrared ($CHCl_3$): 1715, 1675, 1620 cm^{-1}. Nmr signals (100 MHz, F.T.): 1.15 (singlet, 1H, NCHO), 2.35 (broad singlet, 1H, C-17 proton), 2.92 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.11 (singlet, 1H, C-4 proton), 3.31 (quartet, J_{ortho} = 8 cps, J_{meta} = 2.5 cps, 1H, C-15 proton), 6.17 and 6.19 (two singlets,

6H, $C\underline{H}_3O$, and $-CO_2C\underline{H}_3$), 9.23 (triplet, J = 7 cps, $-CH_2C\underline{H}_3$). Mass spectrum; main peaks: m/e 160, 173, 251, 283, 321, 367, 382, and 410 (M^+).

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