# SYNTHESIS OF 4-SUBSTITUTED INDOLES AND THEIR ELABORATION TO THE ERGOT ALKALOIDS

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All of the synthetically important methods which have been developed for the preparation of 4-substituted indoles are reviewed. The use of these materials in the construction of the ergot alkaloids is discussed.

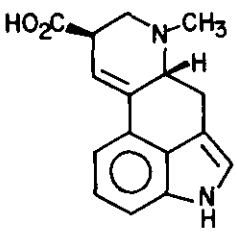
CONTENTS



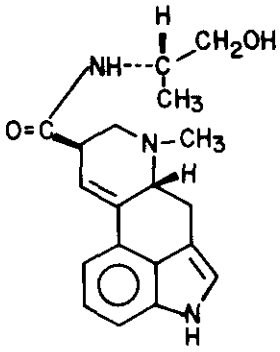
## 1. Summary of the pharmacological properties of the ergots.

The ergot alkaloids represent a structurally fascinating class of compounds which possess a range of important biological properties. These compounds are produced as the metabolic products of various species of the parasitic fungus Claviceps.[1] The infamous hallucinogen lysergic acid diethylamide (LSD) has, of course, been implemental in the development of the field of psychopharmacology. The ergots also presently find use in the treatment of postpartum hemorrhage (ergonovine and methylergonovine), hypertension, and of poor peripheral and cerebral blood circulation (nicergoline), migraine attacks (methysergide), and prolactin-dependent disorders such as galactorrhea, puerperal mastitis, and prolactin-dependent mammary carcinoma (2-bromo-α-ergokryptine and lergotrile).[2]

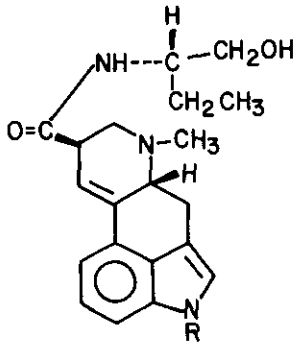
This group of compounds still holds a challenge for the practicing synthetic organic chemist. The development of new pathways to these products is valuable in the search for new ergot-based agents that show new or improved



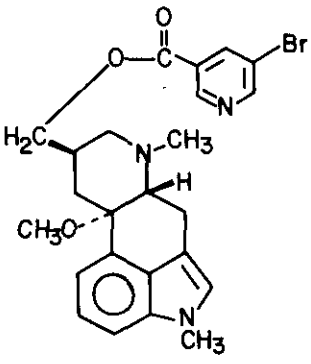
Lysergic acid



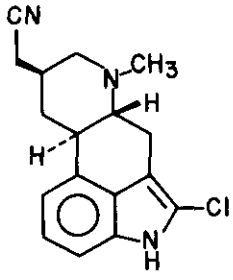
Ergonovine



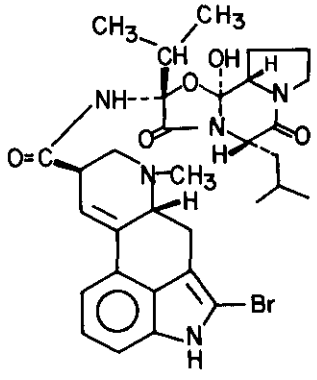
R = H, Methylergonovine
R = $CH_3$, Methysergide



Nicergoline



Lergotrile



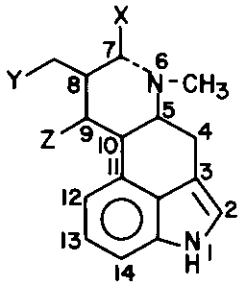
2-Bromo-α-ergokryptine

pharmacological activity.

In this review, the various schemes that have been devised for generating the important class of precursor molecules to these substances, the 4-substituted indoles, will be examined. The application of these compounds to the construction of the ergoline ring system will then be discussed in turn.

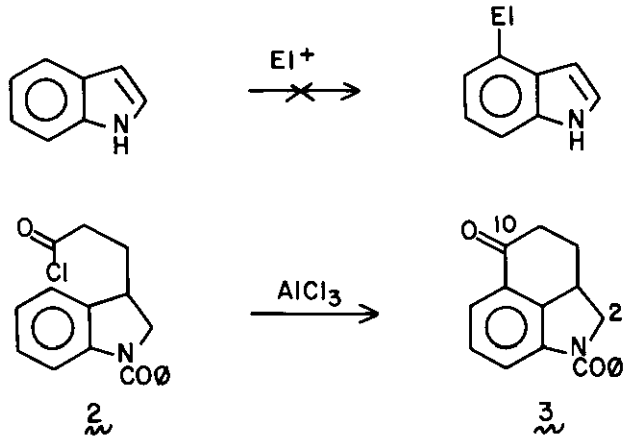
## 2. Methods of synthesis of 4-substituted indoles.

In planning a synthesis of the ergot alkaloids, one must eventually decide how the bond linking carbon atoms 10 and 11 will be made. The direct



1

introduction of a carbon unit as an electrophile into the 4-position of indole is, of course, difficult to achieve, for this position is more electron deficient than other available sites.[3] Kornfeld and Woodward were able to solve this problem in an elegant manner simply by carrying out an intramolecular Friedel-Crafts acylation

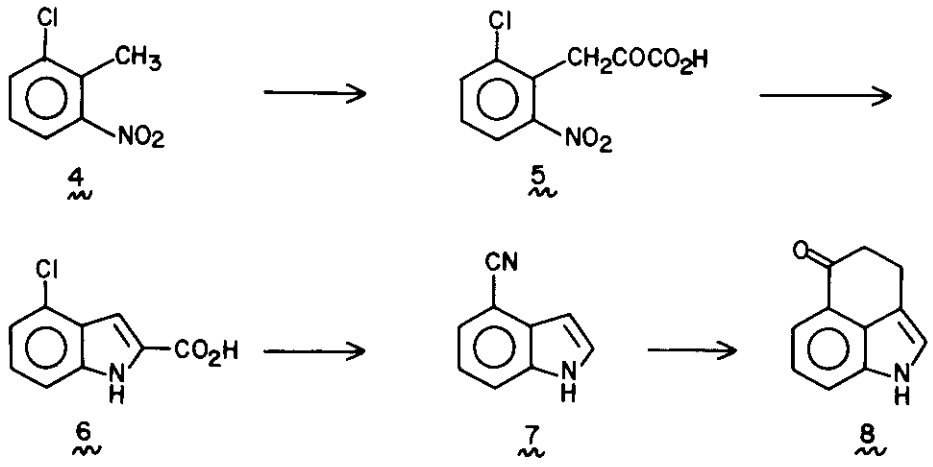


2 3

reaction on the reduced and N-protected derivative of 3-(indol-3-yl)propionic acid, the N-benzoylindoline 2, thus avoiding competing acylation at C-2.[4] This strategy does require regeneration of the indole by oxidation during the final stages of the ergoline synthesis. While such a strategy is effective for accomplishing functionalization at the 4-position of the indole, it is nonetheless limited in the sense that diverse functionality cannot be introduced easily into the C-10 position so as to gain rapid access to the entire gamut of known ergot structures.

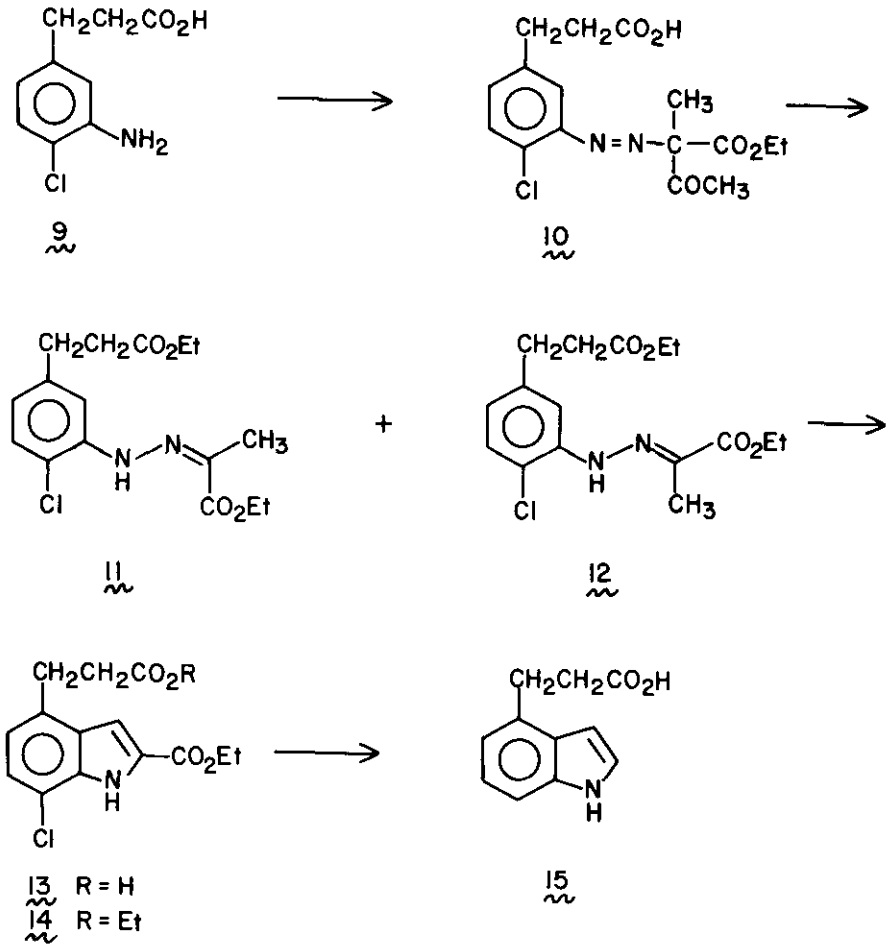
The more popular solution to this problem of generating C-4 functionalized indoles has involved direct synthesis from appropriately substituted arenes. One of the earliest, workable methods to be recorded was designed by Uhle and was based on an extension of the Reissert indole synthesis.[5]

The readily available dyestuff, 2-chloro-6-nitrotoluene, was condensed with ethyl oxalate to afford a pyruvic acid derivative 5 which was then reduced with ferrous hydroxide to 4-chloro-2-indolecarboxylic acid (6). Decarboxylation and replacement of halogen by cyanide occurred on refluxing 6 with cuprous cyanide in




quinoline. The resulting 4-cyanoindole (7) was characterized by hydrolysis to indole-4-carboxylic acid. Compound 7 was further transformed to tricyclic ketone 8, an important ergot precursor that is generally designated as Uhle's ketone.

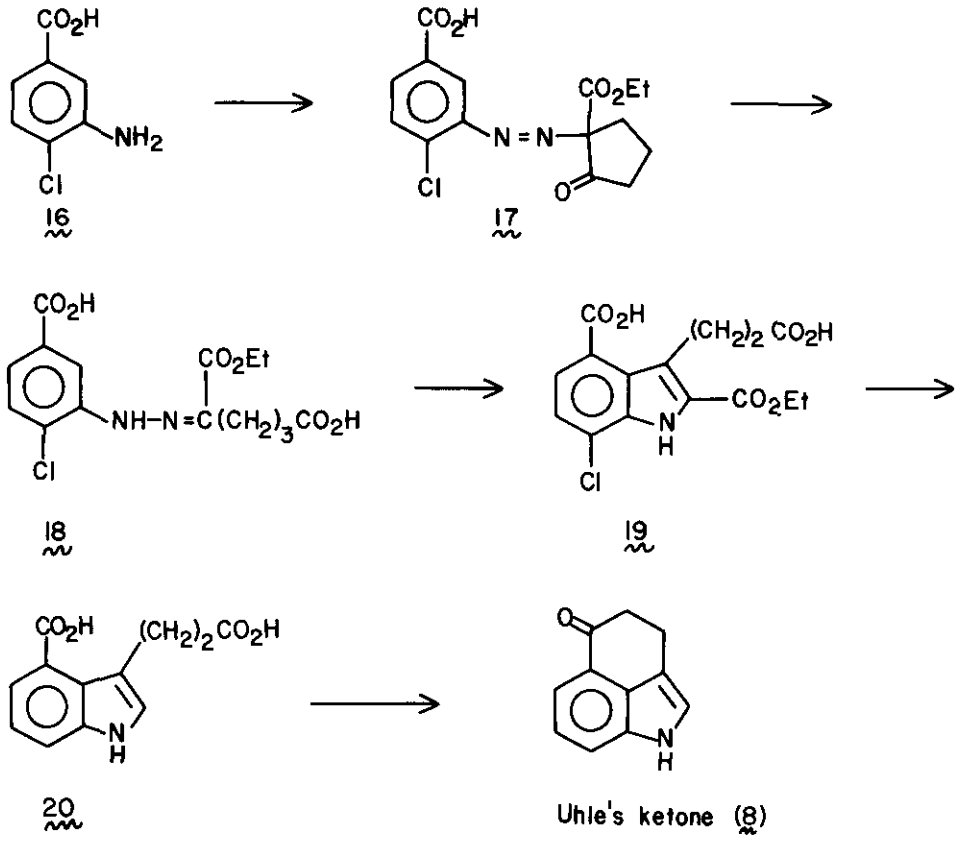
The Fischer indolization of phenylhydrazones containing a blocking chlorine substituent at one of the ortho positions has been shown to yield 4-substituted-7-chloroindoles. Japp-Klingeman reaction of the diazonium salt prepared from the aminoacid




9 with ethyl methylacetoacetate gave, for example, an azoester 10 which when refluxed in ethanol containing sulfuric acid furnished hydrazones 11 and 12. Fischer indolization ($ZnCl_2$, 'AcOH, reflux, 14 h) of the hydrazones yielded the 4-substituted indoles 13 and 14 in addition to the 6-substituted indole formed by the "abnormal" Fischer indolization. Saponification of the mixture of 13 and 14, decarboxylation with Cu/quinoline, and catalytic hydrogenation gave 3-(indol-4-yl)propionic acid (15).[6]

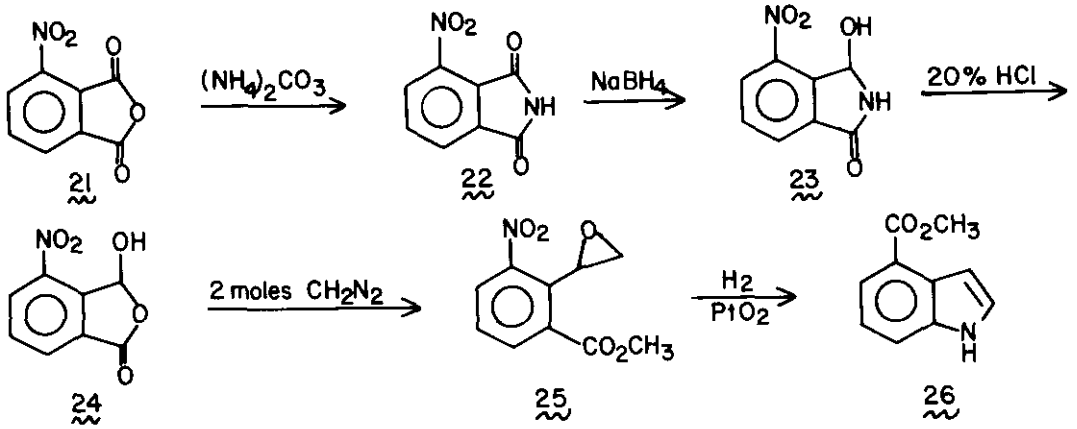
A similar sequence of reactions involving the Fischer indolization has been carried out to produce *3,4-dihydrobenz[cd]indol-5(1H)-one, Uhle's ketone.*[7] Thus, condensation of 5-carboxy-2-chlorobenzenediazonium chloride with ethyl 2-oxocyclopentanecarboxylate yielded azo compound 17, which was hydrolyzed to the monoester 18. Conversion

to indole 19 was effected by treatment with concentrated sulfuric acid in glacial acetic acid. Transformation of the indole diacid monoester 19 in 67% overall yield to 3-(4-carboxyindol-3-yl)propionic acid (20) was accomplished by a "one-pot" procedure involving hydrolysis and hydrogenolysis in alkaline solution to remove halogen, followed, after removal of catalyst, by decarboxylation at 240°C. Indole acid 20 was further transformed into Uhle's ketone 8 by reaction with sodium acetate in acetic anhydride followed by N-deacetylation with 2N sodium hydroxide.

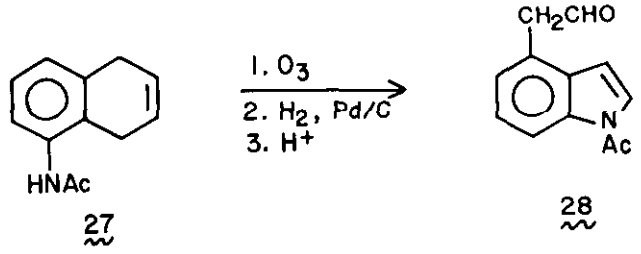



A report in 1972 provided a new route to indole-4-carboxylic acid starting from 3-nitrophthalic anhydride (21).[8] Treatment of this compound with ammonium carbonate effected conversion to 4-nitrophthalimide (22) which on reduction with sodium borohydride gave 3-hydroxy-4-nitrophthalimidine (23). Hydrolysis afforded 3-hydroxy-4-nitrophthalide (24) which on reaction with 2 equivalents of diazomethane gave 2-methoxycarbonyl-6-nitrostyrene oxide (25) in good yield. The oxide 25 was trans-

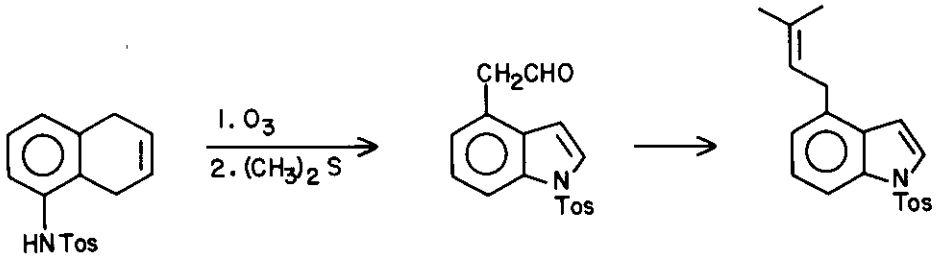
formed to methyl 4-indolecarboxylate (26) in one step by reductive cyclization over platinum oxide.




A relatively ingenious approach to 4-substituted indoles was executed by H. Plieninger in the mid 50's.[9] The starting compound, 1-acetamido-4,8-dihydronaphthalene (27), easily prepared from α-naphthylamine by reduction and N-acetylation, was found to undergo facile ozonolytic cleavage to generate after catalytic reduction and acid treatment 1-acetylindole-4-acetaldehyde (28). Compound 28 was characterized as its semicarbazone and was further transformed through its oxime to indole-4-acetonitrile and indole-4-acetic acid.

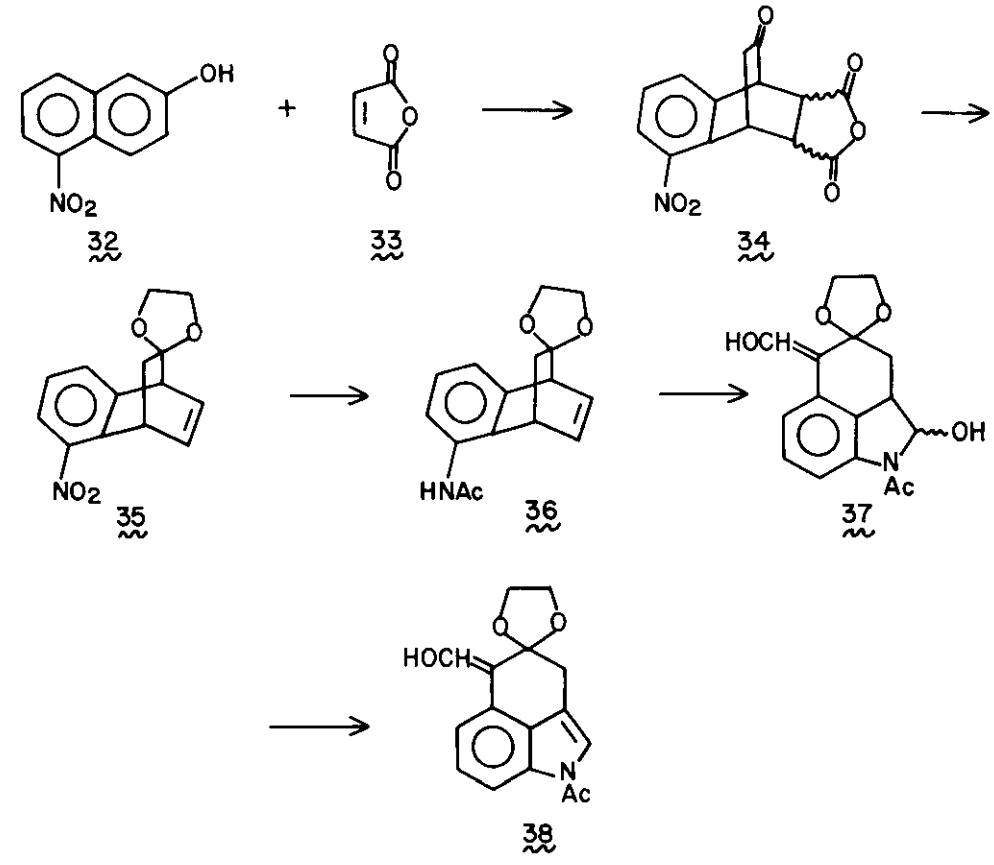



A similar sequence of reactions was carried out on 1-(tosylamino)-5, 8-dihydronaphthalene (29) to generate the more stable 1-tosylindole-4-acetaldehyde (30).[10] Reaction of 30 with various Wittig reagents gave chain elongated materials (e.g., 31).




29 30 31

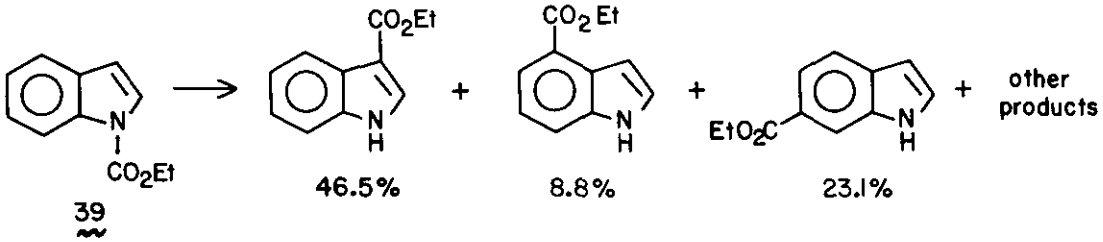
A related route to a more advanced ergot precursor designed by Plieninger started with the Diels-Alder cycloadduct 34 prepared from 5-nitro-2-naphthol (32) and maleic anhydride.[11] Conversion of 34 to its corresponding diester, followed by carbonyl group protection, ester hydrolysis and oxidative bis-decarboxylation afforded 35. The




32 33 34 35 36 37 38

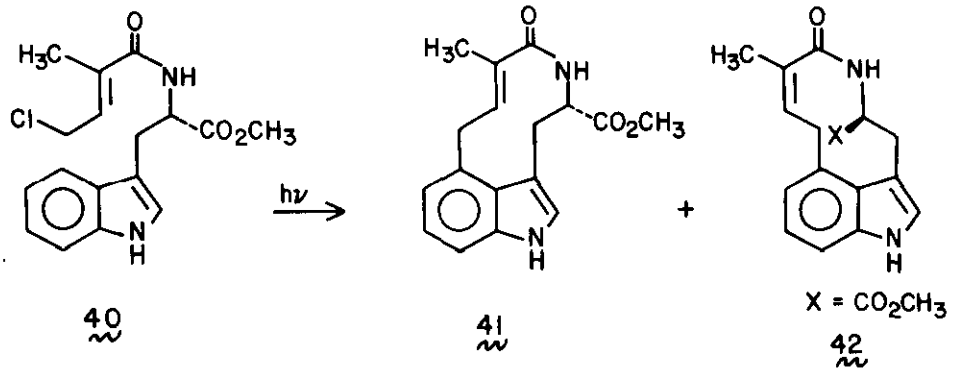
nitro group was reduced, the resulting amine N-acetylated, and the bridging double bond cleaved by ozonolysis to produce 37 on reductive workup. Subjection of 37 to acid catalyzed dehydration completed the preparation of the tricyclic indole derivative 38. The application of this chemistry to the synthesis of chanoclavine I will be discussed in the next section.

A rather interesting but inefficient route to the 4-substituted indoles reported by M. Somei consisted of subjecting 1-substituted indoles to a photochemical Fries-type rearrangement.[12] Thus, 1-ethoxycarbonylindole (39) was irradiated with a 450 W Hanovia high-pressure mercury lamp to afford the 3-,4-,and 6-ethoxycarbonylindoles and diindolylmethane in 46.5%, 8.8%, 23.1% and 1.4% yields, respectively. Other examples of the reaction process have been studied. This route differs from the majority




of those discussed previously in that indole itself serves as the starting material.

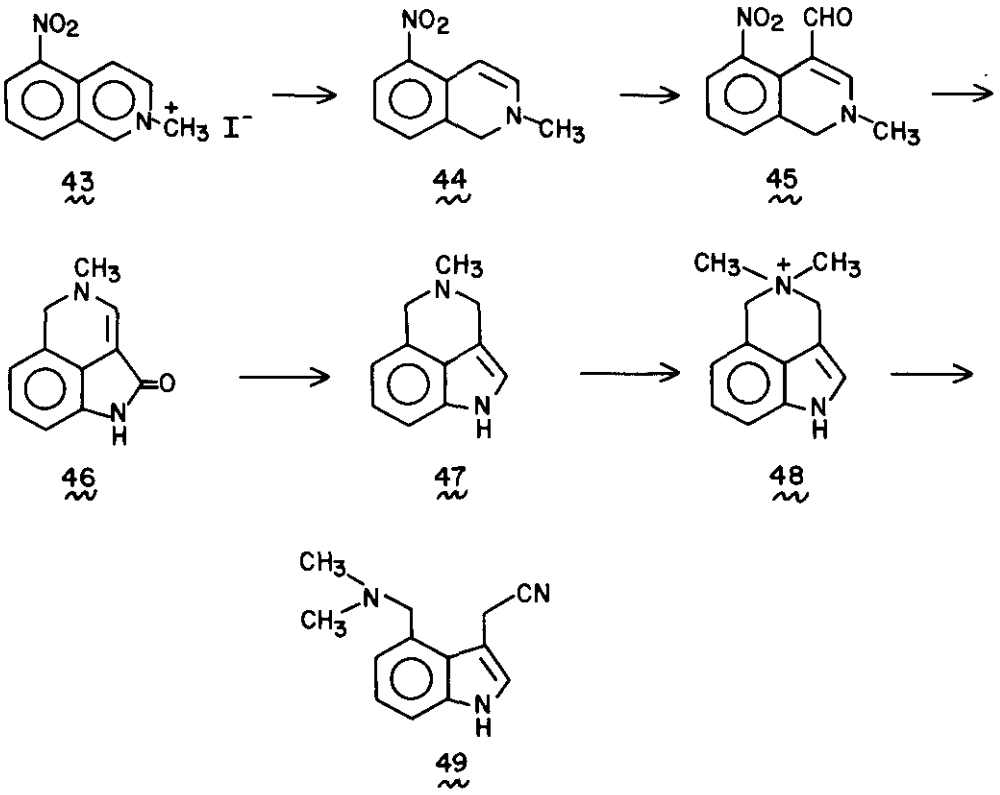
An examination of a Büchi model of α-chlorotiglyl L-tryptophan methyl ester 40 in its cis-form reveals that the tiglyl side chain can be placed directly above C-4 of the indole. Prompted by the photochemical studies of Yonemitsu and Witkop, R. G. Lawton prepared 40 and irradiated it at 2537 Å for 6 h.[13] The tiglyl lactam 41 and the angelyl lactam 42 were produced in yields of 33.2% and 19.3%




40 41 42

respectively. These compounds have all the elements of the ergoline skeleton, with the exception of the C-D ring fusion bond.

The synthesis of 3,4-disubstituted indoles has been accomplished in a novel way from 5-nitroisoquinoline.[14] Accordingly, reduction of 2-methyl-5 nitroisoquinolinium iodide (43) with sodium borohydride followed by Vilsmeier reaction afforded 4-formyl-1,2-dihydro-2-methyl-5-nitroisoquinoline (45). Treatment of 45 in turn with triethylphosphite followed by borane reduction and acid treatment gave 4-methyl-1,3,4,5-tetrahydropyrrolo [4,3,2-de]isoquinoline (47). Fragmentation of this material was accomplished by reacting its methiodide with potassium cyanide to give 3-cyanomethyl-4-dimethylaminomethylindole (49).



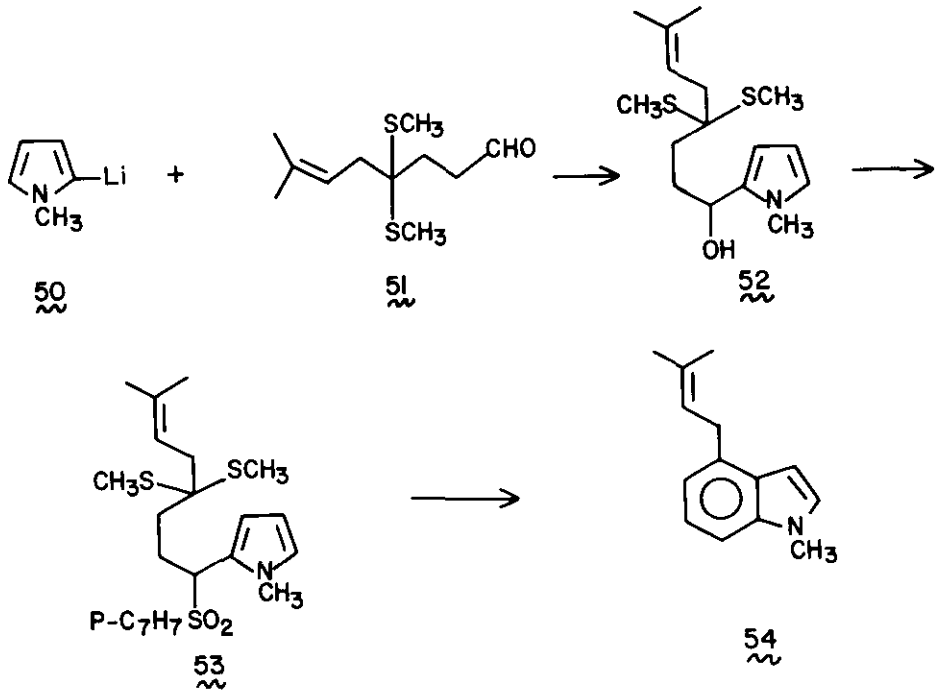

43 44 45

46 47 48

49

A scheme which differs conceptually from the majority of those already discussed in that it starts with a pyrrole ring to which is then fused the substituted arene ring has been developed by B. Trost.[15] The unstable alcohol 52, prepared from aldehyde 51 and 2-lithio-N-methylpyrrole, was reacted with p-toluenesulfinic acid at room temperature to give sulfone 53. Resubjection of this compound to p-toluenesulfinic

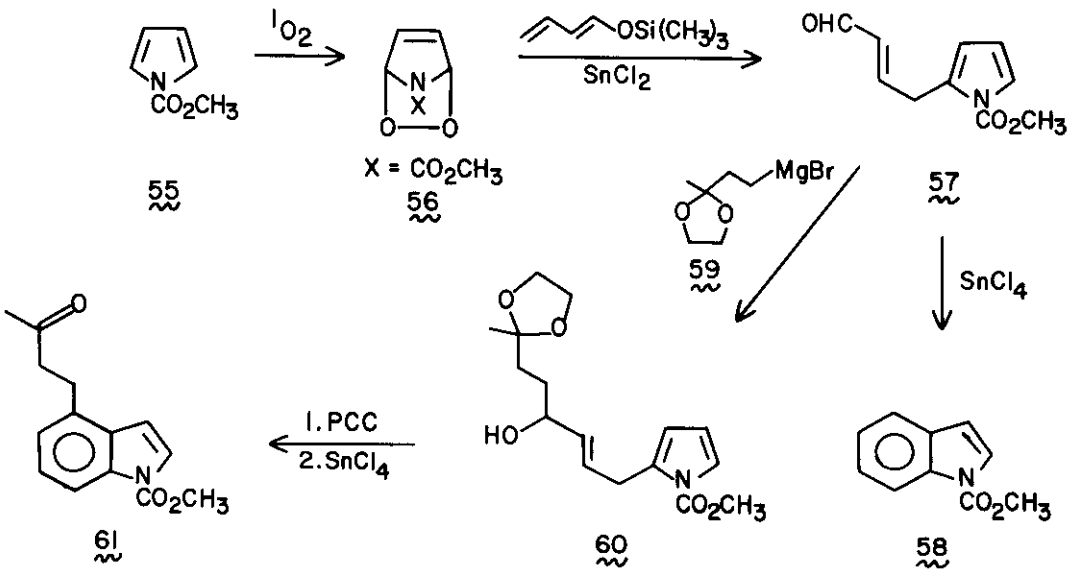
acid at 50°C in acetonitrile effected cyclization with formation of 1-methyl-4-(3-methyl-2-butenyl)indole (54).



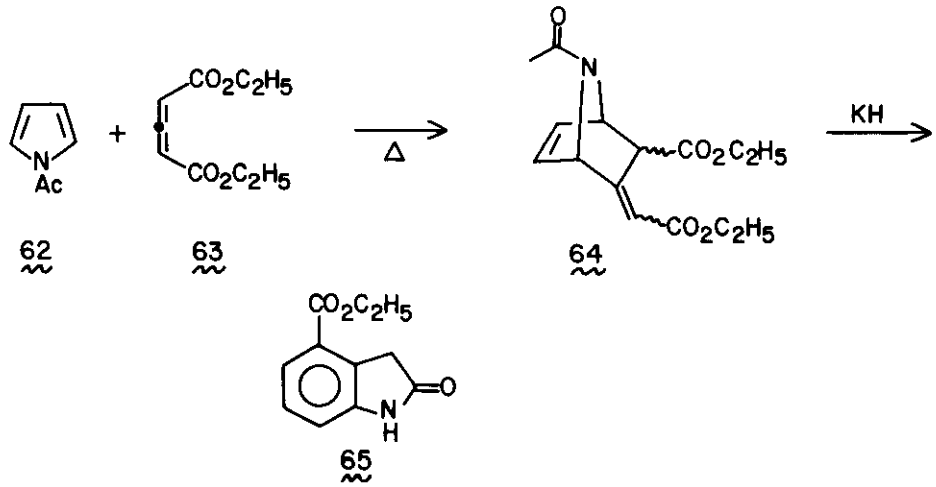

50 51 52 53 54

A related synthesis of 4-alkylindoles starting from N-methoxycarbonylpyrrole has been reported by M. Natsume.[16] The pyrrole 55 was photooxygenated at low temperature, and the endoperoxide 56 obtained was condensed with a nucleophile such as the trimethylsilyl enol ether of crotonaldehyde in the presence of stannous chloride to afford the 2-substituted pyrrole 57 as the major product. Lewis acid catalyzed cyclization of this compound took place to give 58 in 69% yield.

Alternatively, prior reaction of 57 with the Grignard reagent 59, followed by oxidation and stannic chloride catalyzed cyclization with concomitant cleavage of the dioxolane provided the 4-substituted N-methoxycarbonylindole 61. The application of this synthesis to the construction of a chanoclavine precursor will be discussed in the following section.

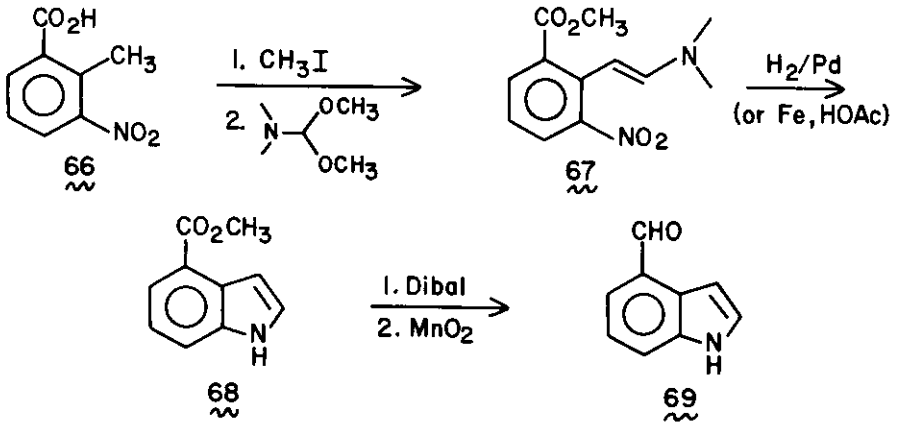



We have reported a rather novel reorganization reaction for the preparation of 4-ethoxycarbonyloxindole (65).[17] The process involved treating the Diels-Alder product 64 derived from the reaction of 1,3-dicarboethoxyallene (63) and N-acetylpyrrole (62)

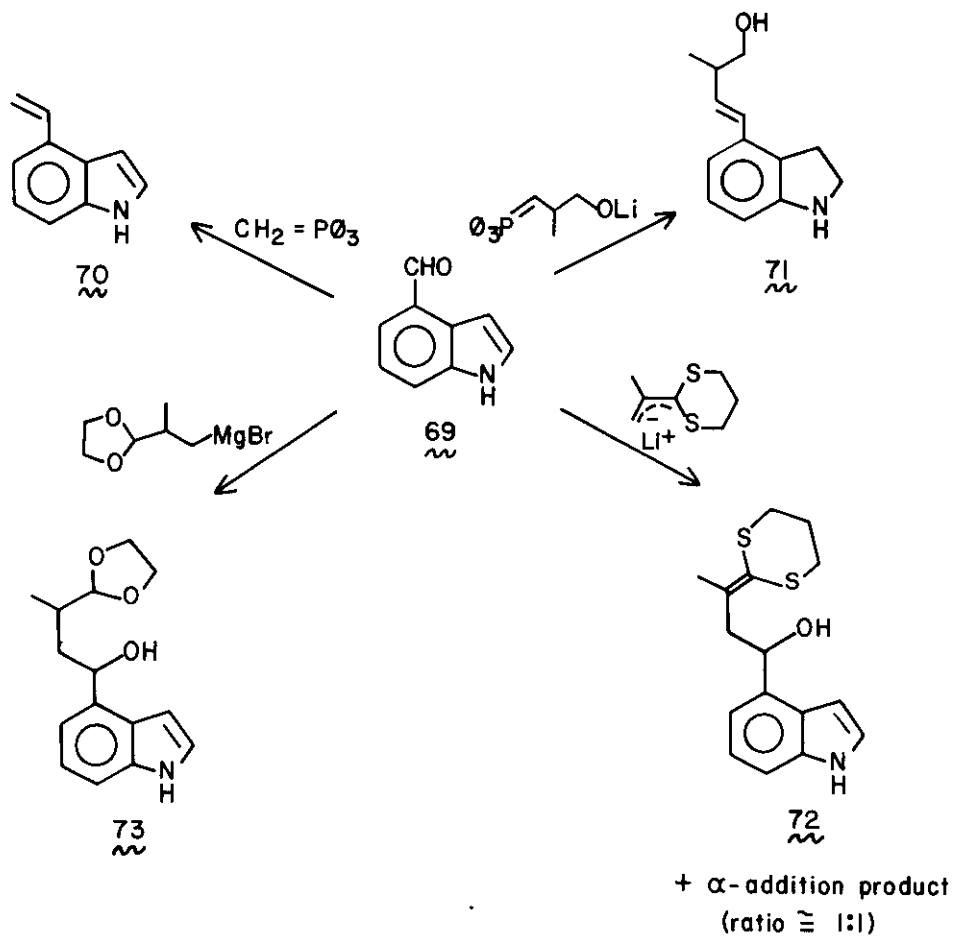


with excess potassium hydride in tetrahydrofuran. By starting with N-acetyl-2-methylpyrrole, the scheme can be used to prepare 5-methyl-4-ethoxycarbonyloxindole in a regiospecific fashion. Since oxindoles can be transformed to indoles by reduction, the chemistry does constitute a new entry into this important class of compounds.

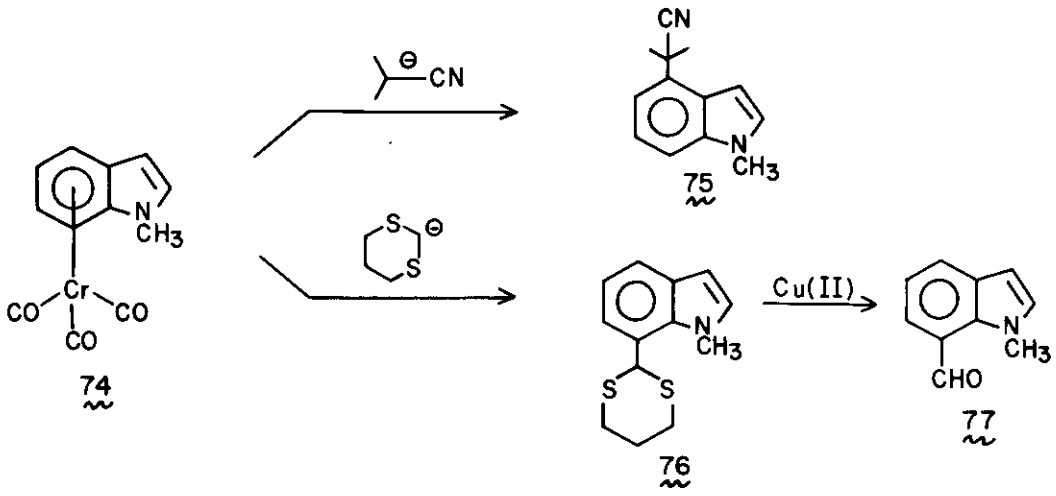
Perhaps the most convenient process for the synthesis of 4-substituted indoles to have been developed to date was that reported by Kozikowski, Ishida, and Chen and by Ponticello and Baldwin at Merck, Sharp and Dohme.[18] The commercially available compound, 2-methyl-3-nitrobenzoic acid served as the starting material. Conversion of the acid to its ester followed by treatment with excess N,N-dimethylformamide dimethylacetal yielded the isolable enamine 67. Catalytic hydrogenation of the nitro group gave 4-methoxycarbonylindole (68) on acid workup.




The ester could be converted to indole-4-carboxaldehyde (69) by reduction to the alcohol followed by oxidation to aldehyde with manganese dioxide. The aldehyde was in turn transformed to a host of other 4-substituted indoles by reaction with phosphoranes and organolithium reagents. Some of these reactions are summarized in the following scheme.




The only procedure to have been developed that accomplishes the direct fuctionalization of indole at its 4-position (in the intermolecular mode) was that which relied on the activation of the indole nucleus through formation of its π-chromium complex.[19] The reaction of N-methylindoletricarbonyl chromium with the anion of isobutyronitrile led directly to the 4-substituted indole 75. When 74 was reacted with the anion derived from 1,3-dithiane, the 7-substituted indole 76 was formed instead. Copper (II) promoted hydrolysis of the dithiane group of 76 provided the indolecarboxaldehyde 77. The regiochemistry of the reaction process was thus dependent on the




nature of the nucleophile employed. Further studies are, however, needed in order to ascertain whether such chemistry can lead to serviceable types of 4-substituted indoles.

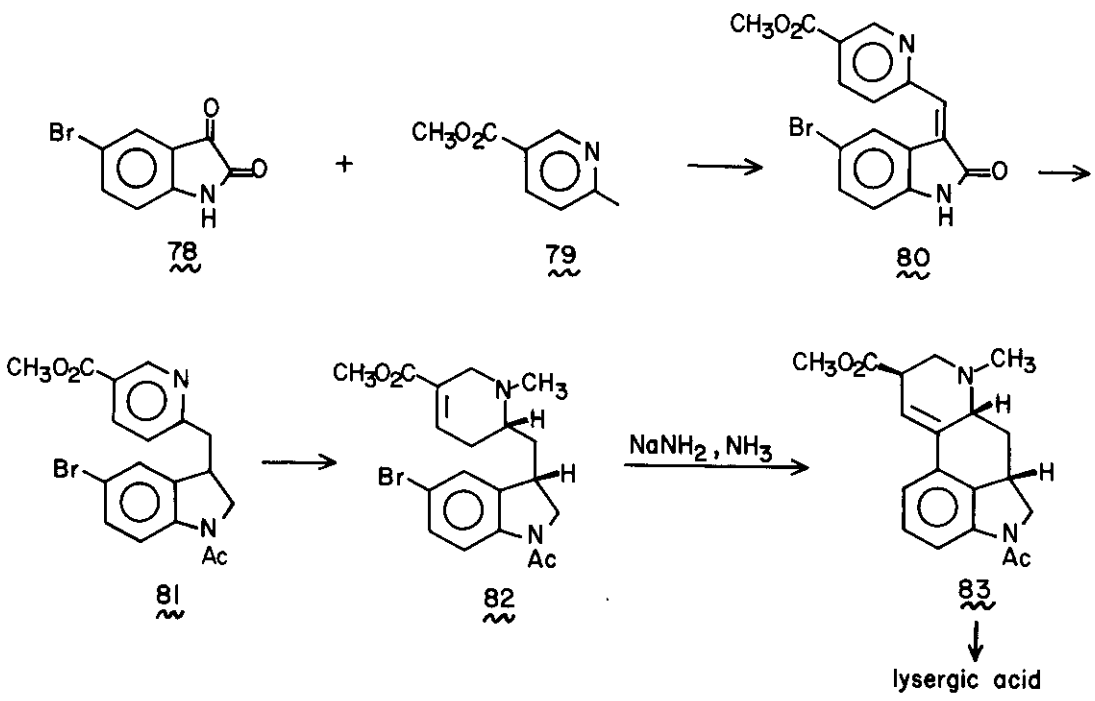
3. Elaboration to the ergots.

The Kornfeld group synthesis of lysergic acid relied on the use of the N-benzoyl-2,3-dihydroindole 3 prepared by intramolecular Friedel-Crafts acylation as outlined in the previous section.[4] Since this synthesis appears in many reviews, it will not be repeated here. Likewise, the classical synthetic work of Stoll and Uhle in the ergot area has been reviewed, and the reader is directed to these articles.[20]

The only other important synthetic efforts on the ergots have been conducted by Julia, Ramage, Cassady, Plieninger, Kozikowski, Rebek and Natsume. A summary of these endeavors follows.

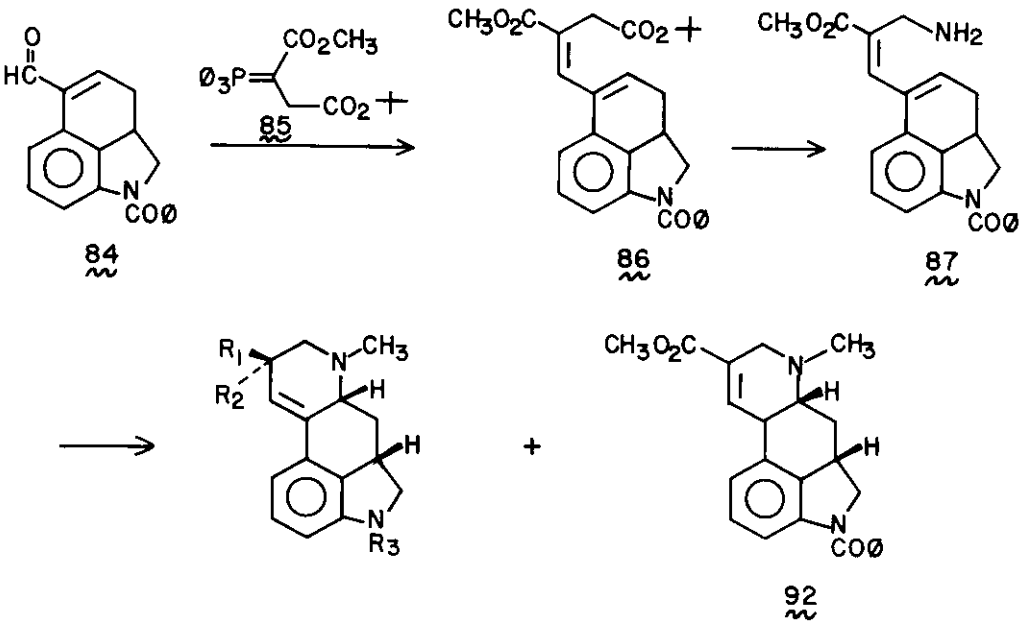
The Julia synthesis commenced by condensing 5-bromoisatin (78) with the methyl ester of 6-methylnicotinic acid (79).[21] Reduction of the oxindole derivative to indoline and N-acetylation were then carried out. The pyridine ring was reduced by treatment of the N-methylpyridinium salt with potassium borohydride, and the resulting tetrahydropyridine 82 was reacted with sodium amide in ammonia to generate the key tetracyclic system 83 in 15% yield. The synthetic scheme is thus related conceptually

to that used by Kornfeld in that the bond between atoms C-10 and C-11 was made by an intramolecular mechanism. Here, however, the strategic reaction consisted of the addition of a carbanion to an aryne. The synthesis of lysergic acid was completed by an acid promoted ester hydrolysis and N-deacetylation followed by oxidation of indoline to indole.




A new synthetic route to lysergic acid has been reported by a group at the Robert Robinson Laboratories.[22] The unsaturated aldehyde 84, prepared previously by Kornfeld and co-workers in the course of their synthetic studies towards lysergic acid, served as the starting material. Compound 84 was reacted with phosphorane 85 to give diester 86 which was in turn converted to the corresponding acid ester through removal of the tert-butyl group by the action of trifluoroacetic acid. Curtius degradation of the acid to the primary amine 87 followed by N-methylation gave a secondary amine which cyclized to a mixture of 88, 89 and 92. Separation of the mixture and subsequent treatment of pure 88 or a mixture of 88 and 89 with MeOH/HCl at reflux gave the same product which proved to be identical to that used in the first synthesis of lysergic acid. This sample was actually an epimeric mixture

of 90 and 91. The formal synthesis of lysergic acid was thus completed by a route which lends some credence to Woodward's proposal for the racemization of lysergic acid.



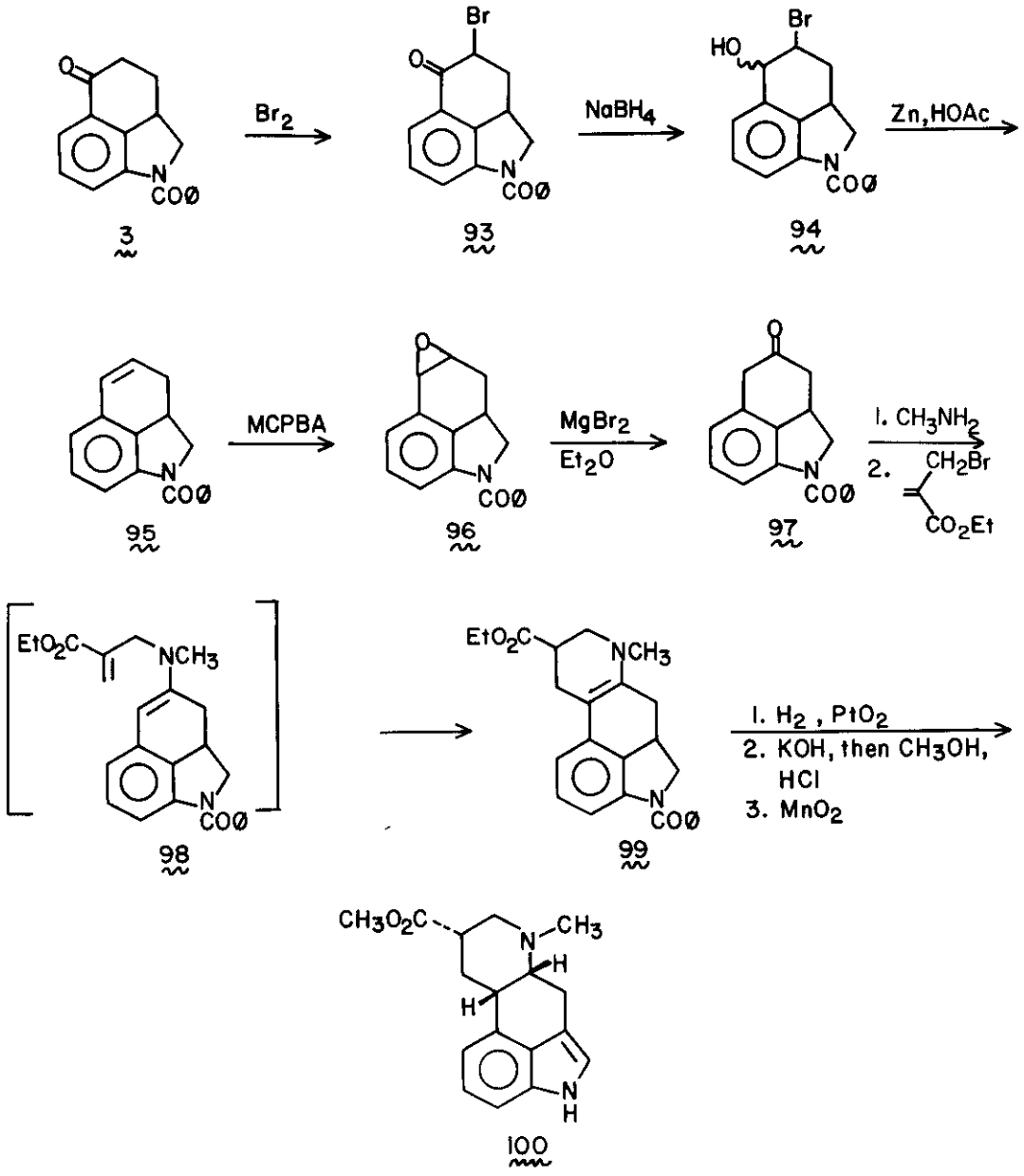

88 $R_1 = CO_2CH_3$, $R_2 = H$, $R_3 = COØ$

89 $R_1 = H$, $R_2 = CO_2CH_3$, $R_3 = COØ$

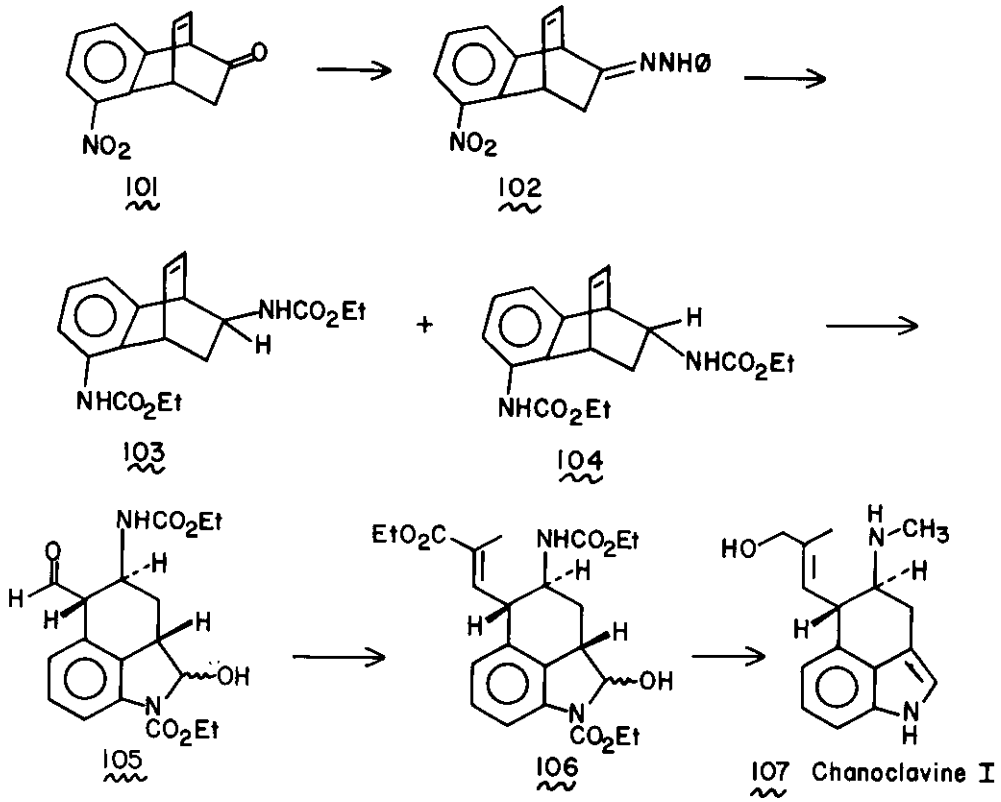
90 $R_1 = CO_2CH_3$, $R_2 = H$, $R_3 = H$

91 $R_1 = H$, $R_2 = CO_2CH_3$, $R_3 = H$

Cassady has designed a new strategy for construction of the ergoline ring system based on an annelation process developed by Grob.[23] The ketone 97, available from Kornfeld's tricyclic ketone 3 by the carbonyl transposition process outlined below, was reacted with methylamine and ethyl α-(bromomethyl)acrylate to afford tetracycle 99. Enamine 98 is a likely intermediate in this reaction scheme. Hydrogenation of 99 over $PtO_2$, removal of the N-benzoyl group, and oxidation with manganese dioxide to restore the indole gave racemic methyl dihydroisolysergate II (100).


Br2
NaBH4
Zn,HOAc
MCPBA
MgBr2
Et2O
1. CH3NH2
2. CH2Br
CO2Et
EtO2C
NCH3
1. H2 , PtO2
2. KOH, then CH3OH, HCl
3. MnO2
CH3O2C
3
93
94
95
96
97
98
99
100

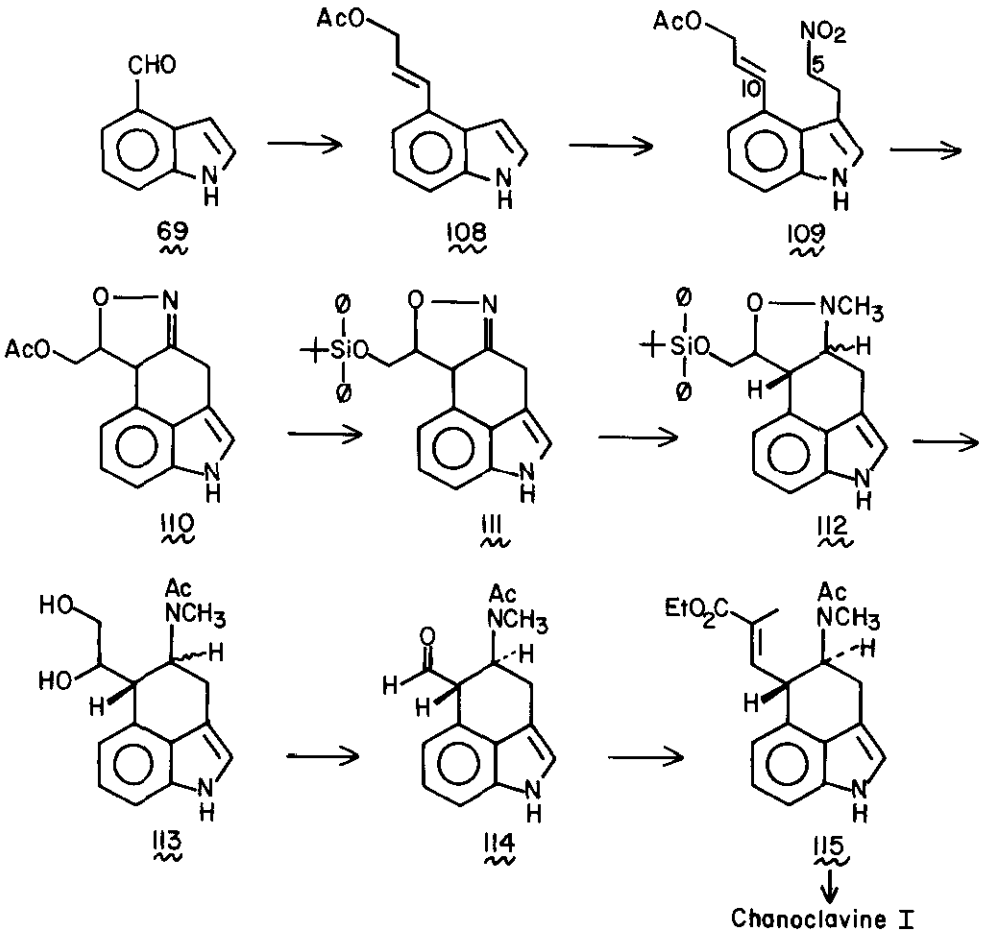
The research efforts of Plieninger have culminated in a total synthesis of chanoclavine I.[24] The tricyclic compound 101, available from the Diels-Alder product of 5-nitro-2-naphthol and maleic anhydride as discussed earlier, was converted to its phenylhydrazone 102 and reduced with activated aluminum to the diamine. This intermediate was treated with ethyl chloroformate in pyridine to generate the diurethanes 103 and 104 as a 1:3 mixture. The major isomer 104 was separated and ozonized to give the unstable aldehyde 105 on reductive workup. The aldehyde was immediately treated with ethyl 2-(triphenylphosphoranylidene)propionate to give the unsaturated ester 106 as a mixture of isomers at C-2. Oxalic acid promoted dehydration of 106 and reduction of ester to alcohol with concomitant deprotection of the indolic nitrogen and reduction of the urethane to the N-methyl group completed the synthesis of chanoclavine I (107).



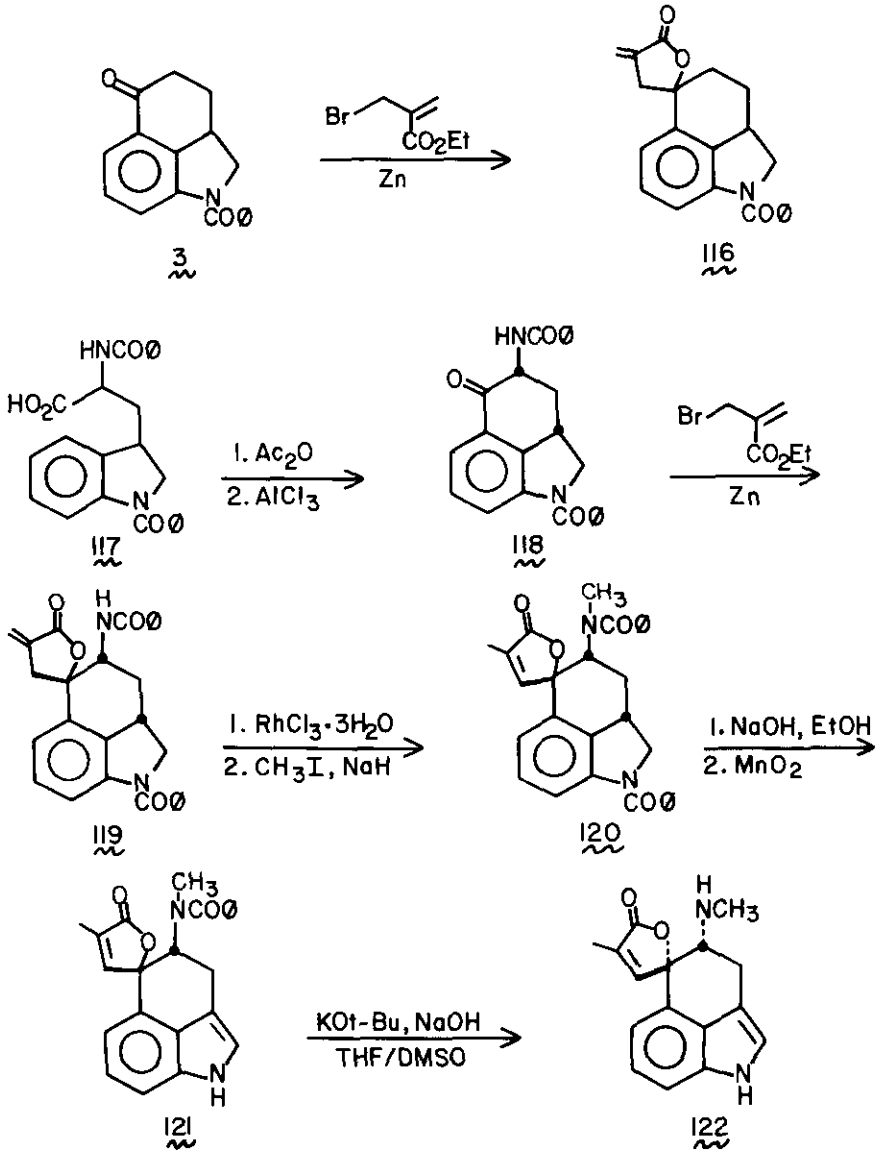

101 102 103 104 105 106 107 Chanoclavine I

Our own work in this area has led to the development of a very general scheme for ergot synthesis, a scheme by which many of the known ergot structures can be efficiently assembled.[25] The work has presently led to a total synthesis of chanoclavine I. The scheme differs from those already discussed in that the strategic step involves bond formation between carbon atoms 5 and 10. Indole-4-carboxaldehyde, prepared as

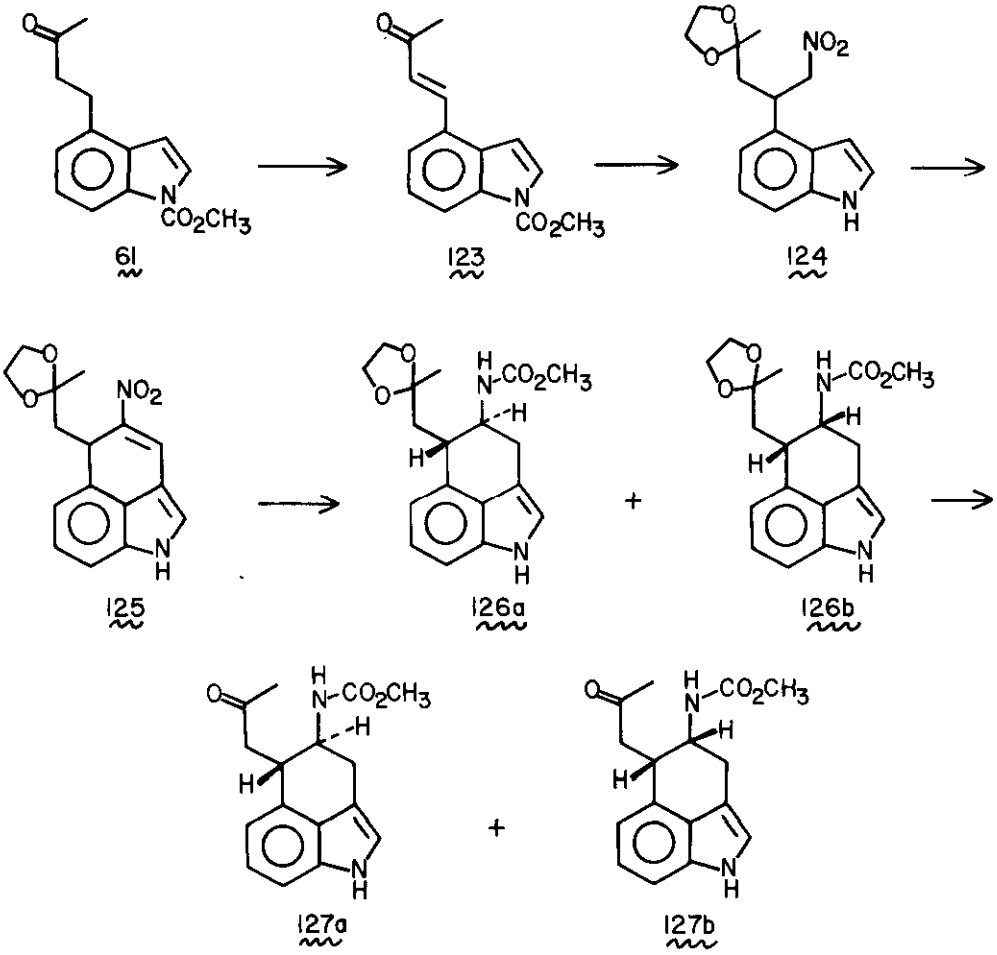
described previously from 2-methyl-3-nitrobenzoic acid, served as the starting material. This aldehyde was converted to 108 by reaction with the anion of ethyl diethylphosphonoacetate followed by aluminum hydride reduction and O-acetylation. Reaction of vinylindole 108 sequentially with N,N-dimethyliminium chloride and nitromethane in the presence of excess dimethyl acetylenedicarboxylate gave the 3,4-disubstituted indole 109 in good yield. On stirring with phenyl isocyanate, the nitro group of 109 was converted to a nitrile oxide which was intercepted by the neighboring unsaturated linkage to afford an isoxazoline. After interchange of the hydroxyl protecting group (110 → 111), the isoxazoline was transformed to isoxazolidine 112 by N-methylation followed by sodium borohydride reduction. Scission of the N-O bond of 112 by catalytic reduction, acetylation of the amine, and periodate cleavage of the diol unit gave the sensitive key aldehyde 114. Condensation of this aldehyde with ethyl 2-(triphenylphosphoranylidene)propionate, N-deacetylation and aluminum hydride reduction of the ester completed the synthesis.



An extension of the Kornfeld ergot strategy has been carried out by Rebek to prepare the tricyclic compound 118 from tryptophan.[26] Reformatsky reaction of the Kornfeld compound 3 with ethyl α-(bromomethyl)acrylate had previously been shown to provide the methylenelactone 116.[27] Application of this same chemistry to 118, followed by isomerization of methylenelactone 119 to butenolide 120 ($RhCl_3 \cdot 3H_2O$), N-methylation of the amine group, deprotection of the indoline by mild base hydrolysis, and oxidation of indoline to indole gave the N-benzoylrugulovasine 121. The N-benzoyl group was removed by the Gassman procedure (KOt-Bu, NaOH, THF/DMSO) to provide rugulovasine A (122), an ergot first isolated from strains of Penicillium concavo-rugulosum.



The novel procedure for the preparation of 4-alkylindoles from N-methoxycarbonylpyrroles has been used by Natsume to synthesize a fully functionalized precursor to the chanoclavines.[28] The 4-(3-oxo-1-butyl)indole 61 was brominated with N-bromosuccinimide and then passed through an alumina column to give the corresponding enone 123. Conjugate addition of nitromethane to the enone followed by protection of the ketone group as its ethylene ketal and deprotection of the indolic nitrogen by hydrolysis with mild alkali yielded 124. Formylation of intermediate 124 with the Vilsmeier-Haack reagent and cyclization with base afforded the tricyclic product 125. Reduction of this material with lithium aluminum hydride and derivatization of the amino group as its carbamate yielded two separable isomers 126a and 126b. Deprotection of the ketone gave compounds 127a and 127b. Extension of the carbonyl group by one carbon atom followed by a few other functional group manipulations should complete a synthesis of chanoclavines I and II.[29]



## 4. Future prospects.

To date, ergot alkaloids are produced by fermentation of the ergot fungus, by isolation from field-cultivated ergot and by partial synthesis. While chemical modification of lysergic acid is used to produce many commercial products, the total synthesis approach has not presently become feasible for economic reasons.

The generation of efficient total synthesis routes to the ergots is thus valuable in accomplishing several objectives: (a) The intermediates generated during the course of the synthesis offer a new source of materials for biological screening. These intermediates may show new types of activity or greater selectivity; (b) The new procedures which emerge as an outgrowth of the synthetic efforts may find use in chemically modifying the naturally derived ergots; (c) A truly short and high yielding ergot synthesis could well supplant the somewhat erratic and low yielding fermentation process; and (d) The new chemistry devised in pursuit of a total synthesis strategy may find use in other areas of synthesis design.

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References


1. For an excellent review on the biosynthesis of the ergot alkaloids and related compounds, see H. G. Floss, Tetrahedron, 1976, 32, 873.
2. For a review on the pharmacology of these compounds, see B. Berde and H. O. Schild, Eds., "Ergot Alkaloids and Related Compounds", Springer-Verlag, Berlin, 1978.
3. R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, 1970.
4. E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones and R. B. Woodward, J. Am. Chem. Soc., 1956, 78, 3087. Also, see T. Nagasaka and S. Ohki, Chem. Pharm. Bull., 1977, 25, 3023.
5. F. C. Uhle, J. Am. Chem. Soc., 1949, 71, 761; F. C. Uhle, C. M. McEwen, H. Schroter, C. Yuan and B. W. Baker, ibid., 1959, 82, 1200.
6. T. Nagasaka, T. Yuge and S. Ohki, Heterocycles, 1977, 8, 371.
7. R. E. Bowman, T. G. Goodburn and A. A. Reynolds, J. Chem. Soc., Perkin Trans. I, 1972, 112. R. E. Bowman, D. D. Evans, J. Guyett, H. Nagy, J. Weale, D. J. Weyell and A. C. White, ibid., 1972, 1926.
8. T. Watanabe, F. Hamaguchi, and S. Ohki, Chem. Pharm. Bull., 1972, 20, 2123.
9. H. Plieninger and K. Suhr, Chem. Ber., 1956, 89, 270.
10. H. Plieninger, E. Meyer, F. S.-Nassirian and E. Weidmann, Liebigs Ann. Chem., 1976, 1475.
11. H. Plieninger and W. Lehnert, Chem. Ber., 1967, 100, 2427; H. Plieninger, W. Lehnert and D. Mangold, ibid., 1967, 100, 2421.
12. M. Somei and M. Natsume, Tetrahedron Lett., 1973, 2451.
13. N. G. Anderson and R. G. Lawton, Tetradedron Lett., 1977, 1843.
14. M. Somei, K. Hashiba, F. Yamada, T. Maekawa, T. Kimata and C. Kaneko, Chem. Lett., 1978, 1245.
15. B. M. Trost, M. Reiffen and M. Crimmin, J. Am. Chem. Soc., 1979, 101, 257.
16. M. Natsume and H. Muratke, Tetrahedron Lett., 1979, 3477.
17. A. P. Kozikowski and M. P. Kuniak, J. Org. Chem., 1978, 43, 2083.
18. A. P. Kozikowski, H. Ishida and Y. Y. Chen, J. Org. Chem., 1980, 45, 2236.
19. A. P. Kozikowski and K. Isobe, J. Chem. Soc., Chem. Commun., 1978, 1076. The regiochemistry reported in this paper for the isobutyronitrile anion is incorrect. Further studies have revealed that nucleophilic substitution with this particular anion actually occurs at C-4 and not at C-7, M. F. Semmelhack, personal communication.

20. A. Stoll and A. Hofmann, in "The Alkaloids", Vol. VIII, Academic Press, New York, 1965, pp. 725-783; J. P. Kutney, in "The Total Synthesis of Natural Products", Vol. 3, Wiley-Interscience, New York, 1977, pp. 298-307.

21. M. Julia, F. Le Goffic, J. Igolen, and M. Baillarge, Tetrahedron Lett., 1969, 1569.

22. V. W. Armstrong, S. Coulton and R. Ramage, Tetrahedron Lett., 1976, 4311.

23. J. M. Cassady, G. S. Li, E. B. Spitzner and H. G. Floss, J. Med. Chem., 1974, 17, 300.

24. H. Plieninger and D. Schmalz, Chem. Ber., 1976, 109, 2140.

25. A. P. Kozikowski and H. Ishida, J. Am. Chem. Soc., 1980, 102, 4265.

26. J. Rebek and H. Shue, J. Am. Chem. Soc., 1980, 102, 5426.

27. E. Ohler, K. Reininger, and U. Schmidt, Angew. Chem. Internat. Ed., 1970, 9, 457.

28. M. Natsume and H. Muratake, Heterocycles, 1980, 14, 445.

29. After submission of this article, the following two relevant papers appeared: "Additional Studies on the Synthesis of 4-Alkylindoles from 2-Methyl-5-nitroisoquinolinium Iodide"; M. Somei, Y. Karasawa and C. Kaneko, Chemistry Lett., 1980, 813. "The Total Synthesis of (±)-6,7-Secoagroclavine"; M. Natsume and H. Muratake, Heterocycles, 1980, 14, 1101.

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