CHAPTER 2

RECENT SYNTHETIC STUDIES ON THE ERGOT ALKALOIDS AND RELATED COMPOUNDS

MASANORI SOMEI

Kanazawa University, Faculty of Pharmaceutical Sciences, Takara-machi, Kanazawa 920-8640, Japan

YUUSAKU YOKOYAMA AND YASUOKI MURAKAMI

Toho University, School of Pharmaceutical Sciences Funabashi, Chiba 274-8510, Japan

ICHIYA NINOMIYA, TOSHIKO KIGUCHI, AND TAKEAKI NAITO

Kobe Pharmaceutical University Higashinada, Kobe 658-8558, Japan

THE ALKALOIDS, VOL. 54
0099-9598/00 $35.00

I. Introduction

Ergot alkaloids are one of the most prolific groups of alkaloids derived from *Claviceps* species with respect to their structures and biological activity. Their structures are typically designated as an ergoline alkaloid having the characteristic structure of a tetracyclic indole ring system. The potential of this group of alkaloids as medicinal agents is very high based on their broad pharmacological activity, responding to such physiologically important biosubstances as noradrenaline, serotonin and/or dopamine and their receptors. Therefore, there have been a number of reviews written concerning their chemistry and synthesis and also their biological and metabolic aspects. The first review was written by two of the pioneers of ergot alkaloid chemistry, A. Stoll and A. Hoffmann in 1965, who originated the research and gave the first introduction to this group of natural products regrding their occurrence and distribution and opened the door to this group of alkaloids by shedding the light of modern chemistry *(1)*. Then a decade later in 1975, most of the ergot alkaloids presently known were summarized by two specialists in Basel, P.A. Stadler and P. Stutz, who triggered various aspects of the research which followed, including synthetic research on these alkaloids and the biological and pharmacological studies of ergot alkaloids *(2)*. By 1975, virtually all of the structures of the ergot alkaloids had been proposed, thereby making them attractive targets for synthesis and biological research on their development as medicinals. The decade from 1980 was that of synthesis, thus we enjoyed the very prolific results of the total syntheses of most of the ergoline alkaloids, as witnessed by the review articles written in the later years of the eighties. Then there came a time ripe for summarizing the synthetic works conducted in the decade of 1990.

We have reviewed all of the synthetic studies achieved since 1990, at the request of the editor of this series *(3)*. Then in 1998, this series presented an excellent review on the biochemistry of ergot alkaloids by Gröger and Floss, who assisted us to widen our sights further *(4)*.

For the synthetic achievement of ergot alkaloids, we were asked to review the addition of new results at the end of the 20th century. Here we will review the synthetic achievements of the last decade. The particular focus is on the studies of three Japanese groups including the groups led by Profs. Somei and Yokoyama, who have respectively poured their extensive efforts towards the exploitation of synthetic methodology on indole compounds, aiming at the establishment of the synthesis of ergot alkaloids.

II. Total Syntheses of Lysergic Acid

Lysergic acid (**1**) has stood out as the central figure in ergot alkaloid research throughout the twentieth century from the beginning of research on the ergot alkaloids.

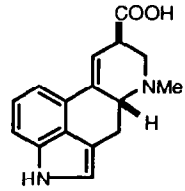
During this period, its structure was established by its total syntheses and its biological activity was well-studied. The total synthesis of lysergic acid (**1**) has attracted the significant attention of synthetic organic chemists, as witnessed by the number of total syntheses so far achieved, which now count to nine. All of these appeared in a short span of time in the nineties, except for the first one by Woodward and Kornfeld. Only one new addition to the list appeared since the previous review written in 1990 (*3*), where all the syntheses were well-documented, showing that the research in this decade has been focused in other directions. Here the authors want to mention briefly the total syntheses previously carried out simply for the basic strategies involved.

A. The First Total Synthesis by Kornfeld and Woodward (1956) (*5*)

This synthesis was achieved by the successful approach to the tricyclic ketone, what we have now called Kornfeld's ketone, which has been continuously playing a key role in the subsequent syntheses of many ergot alkaloid researchers, thus providing a number of improved syntheses. This synthesis was first reviewed by Stadler and Stutz in 1975 in Volume 15 of this series (*2*).

B. The Julia Synthesis (1969) (*6*)

Aiming at the formation of the C/D ring junction by the intramolecular attack of a stabilized allylic anion on an aryne generated from the A ring, the oxindole obtained from 5-bromoisatin was transformed to a mixture of stereoisomers which were further converted to the target molecule.



1 Lysergic acid

C. THE RAMAGE SYNTHESIS (1981) (*7*)

The suggestion by Woodward on the epimerization of lysergic acid (**1**) through an achiral tricyclic amine gave a hint to the authors for the synthesis of lysergic acid (**1**) via a route which involved a tricyclic amine as a key intermediate in their lengthy total synthesis. Similar routes were also followed by two other syntheses.

D. THE OPPOLZER SYNTHESIS (1981) (*8*)

By inventing an intramolecular imino-Diels-Alder cycloaddition of a diene formed by the thermolysis of an oxime-ether, the construction of the alkaloid skeleton, and the usefulness of this methodology, was successfully exemplified, first by the total synthesis of the benzo[*c*]phenanthridine alkaloid, chelidonine, and then in a beautiful total synthesis of lysergic acid (**1**).

E. THE NINOMIYA SYNTHESIS (1982) (*9,10*)

Irradiation of an enamide, which was readily prepared from the imine of the tricyclic Kornfeld's ketone by acylation with 3-furoyl chloride, in the presence of sodium borohydride, yielded the skeletal structure of the ergoline alkaloids, which was readily converted by conventional procedures to lysergic acid (**1**). This photochemical route offered a wide potential for application to variously substituted analogs of lysergic acid (**1**) having high synthetic interest.

F. THE REBEK SYNTHESIS (1983) (*11*)

By using *dl*-tryptophan as the starting unit, highly stereoselective steps via the tricyclic ketone completed the total synthesis of lysergic acid (**1**), thereby also paving a route for an enantioselective synthesis.

G. THE KURIHARA SYNTHESIS (1988) (*12*)

Modifying the synthesis of a key tricyclic aldehyde in the Ramage synthesis, subsequent Wittig-Horner reaction successfully linked their synthesis to the target lysergic acid (**1**).

H. The Cacchi Synthesis (1988) (*13*)

Also using the key intermediates in the Ramage synthesis, the newly developed oxidative addition of vinyl triflates to palladium(II) and the Heck reaction paved a way to lysergic acid (**1**).

I. The Vollhardt Synthesis (1994) (*14*)

Cocyclization of 4-ethynyl-3-indoleacetonitrile with an alkyne in the presence of a cupric complex gave rise to the ergoline skeleton, which was converted into lysergic acid diethylamide as discussed in Section III, C.

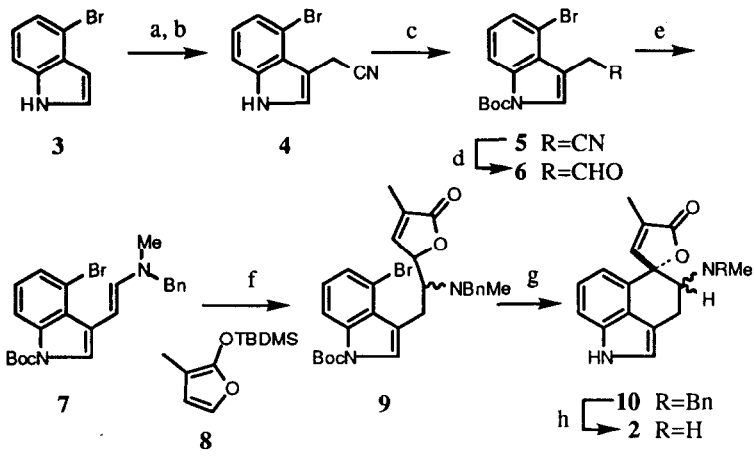
III. Total Synthesis of Ergot Alkaloids Other Than Lysergic Acid

Efforts toward the total synthesis of other members of the ergot alkaloid group have been carried out mostly by applying newly developed synthetic methodologies. Therefore, there are a number of new synthetic methodologies in the total synthesis and the syntheses aimed at the target alkaloids. The synthetic routes were often decorated by the author's own instinct. Although lysergic acid (**1**) has occupied a position at the center of interest for synthetic study, focus has also been directed toward other members of the ergot alkaloid group having non-ergoline structures.

A. Total Synthesis of Rugulovasines A and B

The alkaloids, rugulovasines A and B (**2**), were isolated in racemic form and were found to very easily interconvert upon warming. Rebek's group had succeeded in the enantioselective synthesis of (–)-rugulovasine early in 1980 and noticed its facile equilibration to form a mixture of the two alkaloids (*15–17*). A proposal for the intermediacy of an achiral structure in the facile interconversion of the two isomers in rugulovasines A and B (**2**) was confirmed by Rebek himself in the first enantioselective total synthesis (*15,16*). Martin's group have extensively studied its conversion aiming at the development of a new general synthetic methodology (*18*).

As a result, they have succeeded in using a vinylogous Mannich reaction as a method for the transformation applicable to the construction of a structural subunit common to different alkaloidal natural products. Starting from 4-bromoindole (**3**), a functionalized side chain was introduced into the 3-position



SCHEME 1. Reagents: a, aq. Me_2NH, aq. HCHO, AcOH; b, KCN, DMF-H_2O; c, $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2; d, DIBALH, CH_2Cl_2; e, BnNHMe, CH_2Cl_2; f, CSA, then **8**; g, *t*-BuOK, NH_3, *hv*; h, HCl, MeOH, H_2, $Pd(OH)_2$.

of the indole nucleus. This side chain was then converted into the corresponding 3-acetaldehyde. The reaction of the acetaldehyde **6** with benzylmethylamine furnished the enamine **7**, which was then treated *in situ* with the siloxyfuran **8** to give the adducts **9** as a diastereomeric mixture. Irradiation of the adducts in refluxing ammonia in the presence of potassium *t*-butoxide brought about smooth cyclization to give an inseparable mixture of the protected rugulovasines **10**. Though removal of the *N*-benzyl protecting group from the photocyclized product **10** was far more difficult than anticipated, after many attempts, it was found that hydrogenolysis of the hydrochloride over the Pearlman's catalyst furnished smooth debenzylation to complete the total synthesis of the two alkaloids **2** (Scheme 1).

B. SYNTHESIS OF CLAVICIPITIC ACID

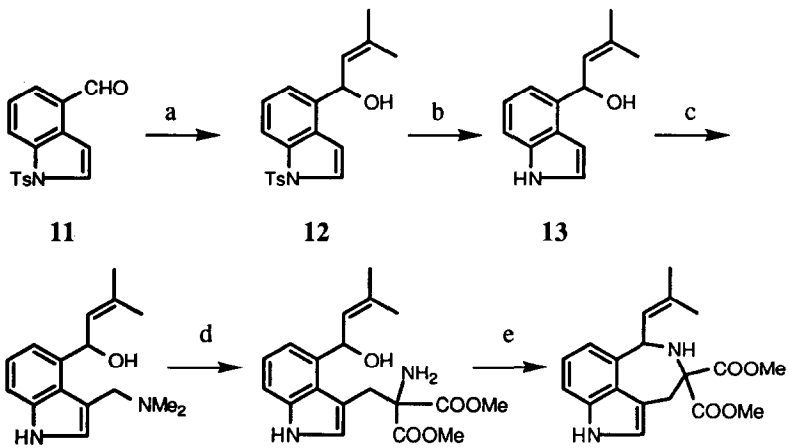
Clavicipitic acid and aurantioclavine are alkaloids having a fused seven-membered azepinoindole skeleton. As mentioned in the previous review (*3*), by 1988 clavicipitic acid had been synthesized by five groups, and aurantioclavine by two groups of chemists.

Clavicipitic acid is currently regarded as a derailment product of normal ergot metabolism (*4*). From its structural features of a seven-membered ring system, and also from biomimetic interest, this alkaloid has attracted the attention of many synthetic organic chemists. Therefore, a number of syntheses have been

reported of this particular alkaloid. As mentioned previously, there were already five by 1988, including Kozikowski and Greco (1982) (*19*), Munakata and Natsume (1983) (*20*), Kozikowski and Ohta again in 1985 (*21*), Matsumoto and Watanabe (1987) (*22*), Harrington (1987) (*23*), and Goto (1989), along with the synthesis of aurantioclavine by Somei (1985) (*24*), which were successively reported. Among, them, Kozikowski's biomimetic synthesis was entirely based on Floss' proposed sequence for the biosynthesis of the ergot alkaloid chanoclavine, as described in the previous review.

1. Formal Total Synthesis by Nichols group.

Nichols' group (*25*) successfully applied an acid-catalyzed intramolecular aminoalkylation reaction between an amine and alcohol to form the azepino ring system, the characteristic structure of this indolic amino acid in the route, via a functional equivalent of 10-hydroxylated DMAT **15**. This hypothetical biochemical precursor of the alkaloid, which was not prepared previously, was the key intermediate for their efficient synthesis to clavicipitic acid. Nichols' group first prepared the requisite alcohol **12** by the Grignard reaction of *N*-tosylated indole-4-carboxaldehyde **11** with 2-methyl-1-propenylmagnesium



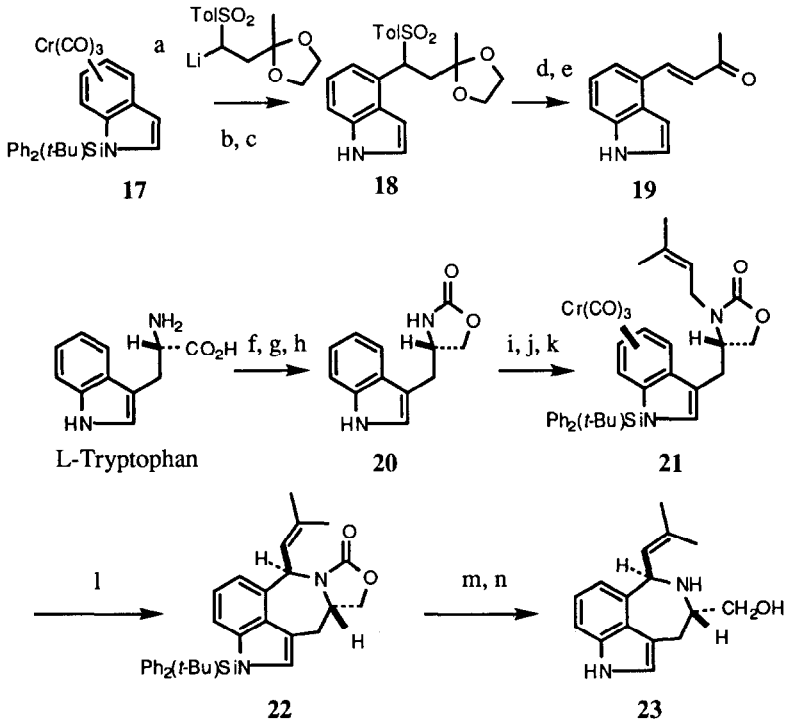
SCHEME 2. Reagents: a, $BrCH{=}C(Me)_2$, Mg, THF; b, Na-Hg, MeOH; c, HCHO, $HN(Me)_2$, AcOH; d, $H_2NCH(COOMe)_2$, $(n\text{-}Bu)_3P$, MeCN; e, TsOH, MeCN.

bromide. Deprotection of the indole nitrogen was smoothly achieved in nearly quantitative yield by the application of Trost's buffered amalgam method (*26*). Under classic Mannich conditions, the new indole **13** was converted to its gramine derivative **14**, which was then subjected to Somei's procedure (*27*) for conversion to the amino alcohol **15** in 80% yield. Cyclization of **15** was smoothly carried out by acid treatment giving the azepine **16** (Scheme 2).

The diester **16** has been shown to undergo decarbonylation to a *cis-trans* mixture of clavicipitic acids, thus furnishing a formal total synthesis of this alkaloid.

2. *Syntheses of Clavicipitic Acid by Somei's Group and Yokoyama's Groups*

Total syntheses of clavicipitic acid were achieved by two Japanese groups using their respective methodologies, as reviewed in Section IV.



SCHEME 3. Reagents: b, I_2; c, $(n\text{-Bu})_4NF$; d, cat. TsOH; e, Et_3N, f, $LiAlH_4$; g, NaOH; h, $COCl_2$; i, $Cr(CO)_3(MeCN)_3$; j, NaH, $Ph_2(t\text{-Bu})SiCl$; k, MeLi, $BrCH_2CH{=}C(Me)_2$; l, LDA, then I_2; m, $(n\text{-Bu})_4NF$; n, 3M KOH.

3. Attempted Synthesis by Semmelhack

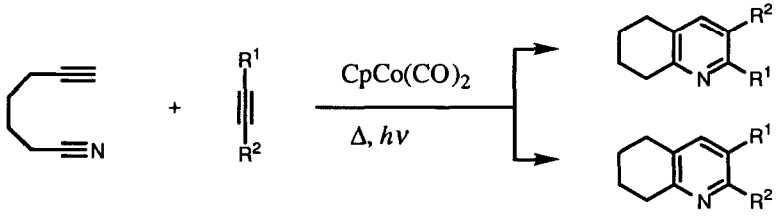
The activating effect of π-complexation of a $Cr(CO)_3$ complex allows for selective nucleophilic substitution in indoles, such as tryptophan, providing intermediates for the synthesis of clavicipitic acid. Indole was readily transformed into the corresponding tricarbonylchromium complex and silylated to the orange-colored complex **17**. The addition of **17** to a solution of the lithiated sulfone followed by oxidative quenching with iodine and desilylation furnished the C-4 substituted indole **18** in 90% yield. The conversion of **18** to the enone **19** was achieved in 78% yield by sequential acid and base treatment.

Reduction of L-tryptophan and the conversion of the resulting amino alcohol afforded the oxazolidinone **20** in good yield. By applying the activating effect of the π-complex **21**, formed with a tricarbonylchromium complex, an alkenyl side chain was introduced into the 4-position of the tryptophan ring to give the intermediate **22** for the synthesis of clavicipitic alcohol (**23**) (Scheme 3) (*28*).

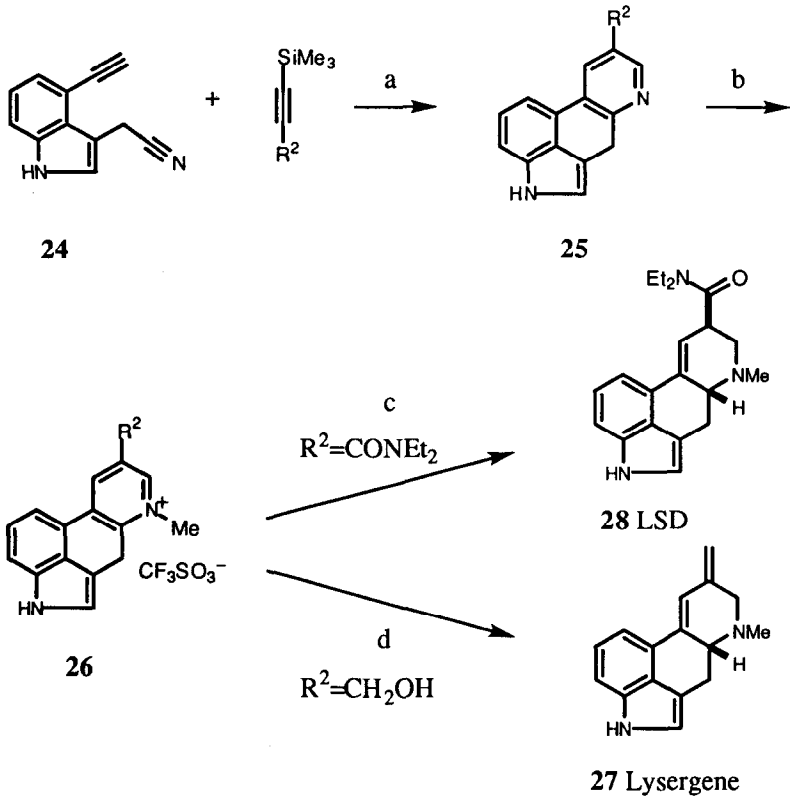
C. Total Synthesis of Lysergene and Lysergic Acid Diethylamide (LSD)

Vollhardt and coworkers (*14*) have developed the cocyclization reaction using a cobalt-catalyst, successfully applied the reaction to the construction of the ergoline skeleton, and then extended its application to the synthesis of ergoline alkaloids. They found that the η^5-cyclopentadienylcobalt-catalyzed cocyclization of α,ω-alkynenitriles with alkynes yielded the [2+2+2] cycloaddition products as shown in Scheme 4, thus showing the possibility for its application to the synthesis of nitrogen-containing polycyclic ring systems.

The utility of this cocyclization was shown in the synthesis of the ergoline framework when an ethynylic indole was employed, as in Scheme 5. The requisite 4-ethynyl-3-indoleacetonitrile (**24**) was prepared readily from the 4-bromoindole precursor followed by palladium-catalyzed trimethylsilyl-ethynylation-deprotonation.



Scheme 4

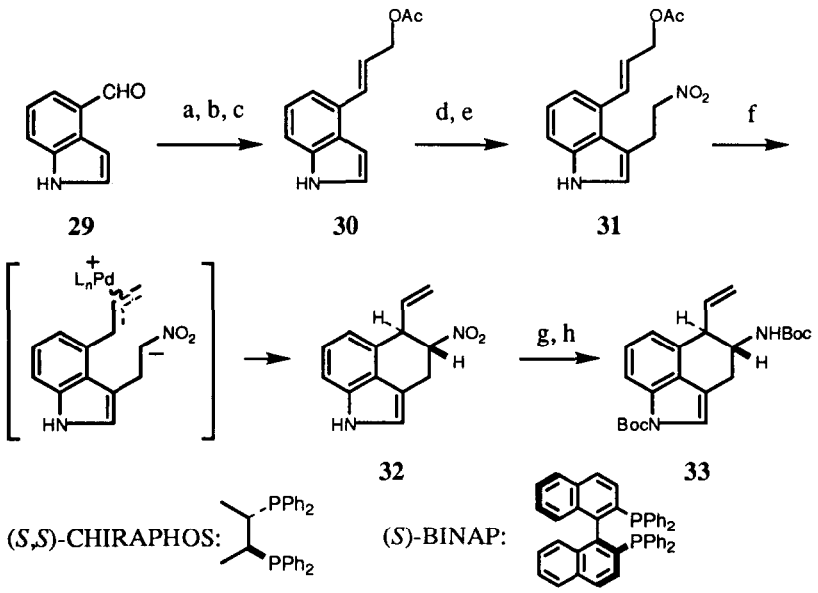


SCHEME 5. Reagents: a, $CpCo(CO)_2$, Δ, *hν*; b, CF_3SO_2Me, THF; c, 3-4 eq. $NaBH_4$, MeOH; d, excess $NaBH_4$, CD_3CN.

The compound **25**; R^2=CH_2OH in these products, which carries a pyridine ring, was quaternized with methyl iodide and then reduced to give the tetrahydropyridine moiety, thereby completing a short total synthesis of lysergene (**27**) (Scheme 5). Similarly, LSD (**28**) was conveniently synthesized from the cycloaddition product **25** with a carboxamide group on the ring.

D. SYNTHESIS OF (–)-CHANOCLAVINE I

As mentioned in the previous review, chanoclavine I was synthesized previously in the last decade by several groups. The first total synthesis was achieved by Plieninger's group (*29*) which was followed by the syntheses of

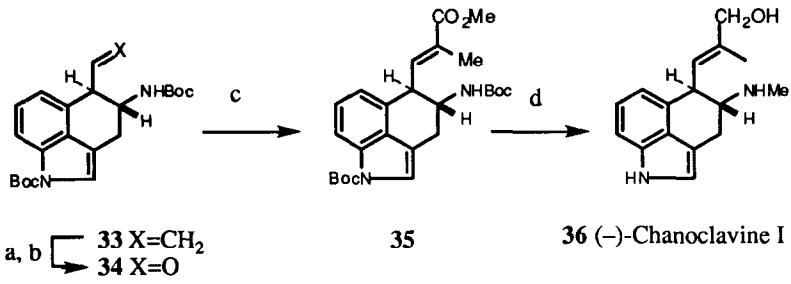


SCHEME 6. Reagents: a, $(MeO)_2P(O)CH_2CO_2Me$; b, DIBALH; c, Ac_2O; d, $Me_2NCH{=}CHNO_2$; e, $NaBH_4$; f, $Pd(dba)_2$, K_2CO_3, (*S*,*S*)-CHIRAPHOS, or $Pd(OAc)_2$, K_2CO_3, (*S*)-BINAP; g, Zn-Hg, HCl; h, $(Boc)_2O$.

Natsume (*30*), Kozikowski (*31*), Oppolzer (*32*), and Ninomiya (*33*), in addition to the synthesis of secoergolines by Somei's group (*34*).

The first enantioselective total synthesis of (–)-chanoclavine I (**36**) was reported by French chemists (*35,36*), who invented an unique method of constructing the ring system, including the C ring, together with the enantioselective introduction of two side chains into the D ring, by the application of an intramolecular palladium-catalyzed allylation of a nitroacetate. Genet *et al.* selected 4-formylindole (**29**) as the bifunctional starting compound. The Horner-Emmons reaction of the aldehyde **29** with trimethyl phosphonoacetate in the presence of potassium carbonate in refluxing tetrahydrofuran yielded the unsaturated ester **30** in 95% yield, which was reduced with DIBALH to the allylic alcohol, and then converted into the allylic acetate **30**.

The C-3 functionalization of **30** was achieved in two steps, that is, first, treatment with 1-dimethylamino-2-nitroethylene to the unsaturated nitroacetate **31** and then reduction of the double bond with sodium borohydride in tetrahydrofuran-methanol to furnish the desired nitroacetate **31** in 50% overall yield from the aldehyde **29**. Asymmetric formation of the C-5, C-10 bond of the nitroacetate **31** was achieved by using the palladium (0) complex catalyst. The best results of this key cyclization were obtained using $Pd(dba)_2$ and (*S*,*S*)-



SCHEME 7. Reagents: a, OsO_4, NMO; b, $NaIO_4$; c, $Ph_3P{=}C(Me)CO_2Me$; d, $LiAlH_4$.

CHIROPHOS, or $Pd(OAc)_2$ and (*S*)-BINAP as the chiral diphosphine, at room temperature. The desired enantiomer 5*R*-**32** was obtained under mild conditions in 60% yield, and with diastereo- and enantioselectivity of up to 95% (Scheme 6).

For the synthesis of (–)-chanoclavine I (**36**), they applied the same methodology devised by Kozikowski (*31*) and Oppolzer (*32*). The nitro group in **32** was reduced to the primary amine with amalgamated zinc, and then the two nitrogens were converted to the corresponding dicarbamate **33** with $(Boc)_2O$ in acetonitrile at room temperature. The carbamate **33** was then treated with a catalytic amount of osmium tetroxide in the presence of NMO in aqueous acetone to furnish the crude diol, which was cleaved with sodium periodate to yield the unstable key aldehyde **34**. The Wittig reaction of the aldehyde **34** afforded the unsaturated ester **35**, which was then reduced with lithium aluminum hydride under reflux to give (–)-chanoclavine I (**36**) in 13% yield upon chromatography, thereby completing the first total asymmetric synthesis of (–)-chanoclavine I (**36**) from the optically active nitro compound **32** (Scheme 7). This methodology could be applied to the synthesis of analogous ergot alkaloids, including 6,7-secoagroclavine, (+)-paliclavine, or the rugulovasines.

IV. Research on the Synthesis of Ergot Alkaloids by Three Japanese Groups

In the past decade, two Japanese groups, led by Somei and Yokoyama, respectively, have concentrated their synthetic interests and efforts on the ergot alkaloids by exploiting respective methodologies and achieving the total synthesis of clavicipitic acid and many related alkaloids. Originally, they had

directed their interests to the chemistry and reactions with the intention to apply their methods to the synthesis of natural indole alkaloids, particularly ergot alkaloids. During the course of their extensive research on indole alkaloids, reactions were developed and knowledge on the chemistry and reactions of indole derivatives was generated. Therefore, here we summarize our results and offer a perspective on the research outcomes.

Iwao's group has independently established an efficient methodology for the synthesis of 3,4-differentially substituted indoles. Their contributions in the total synthesis of ergot alkaloids are also reviewed.

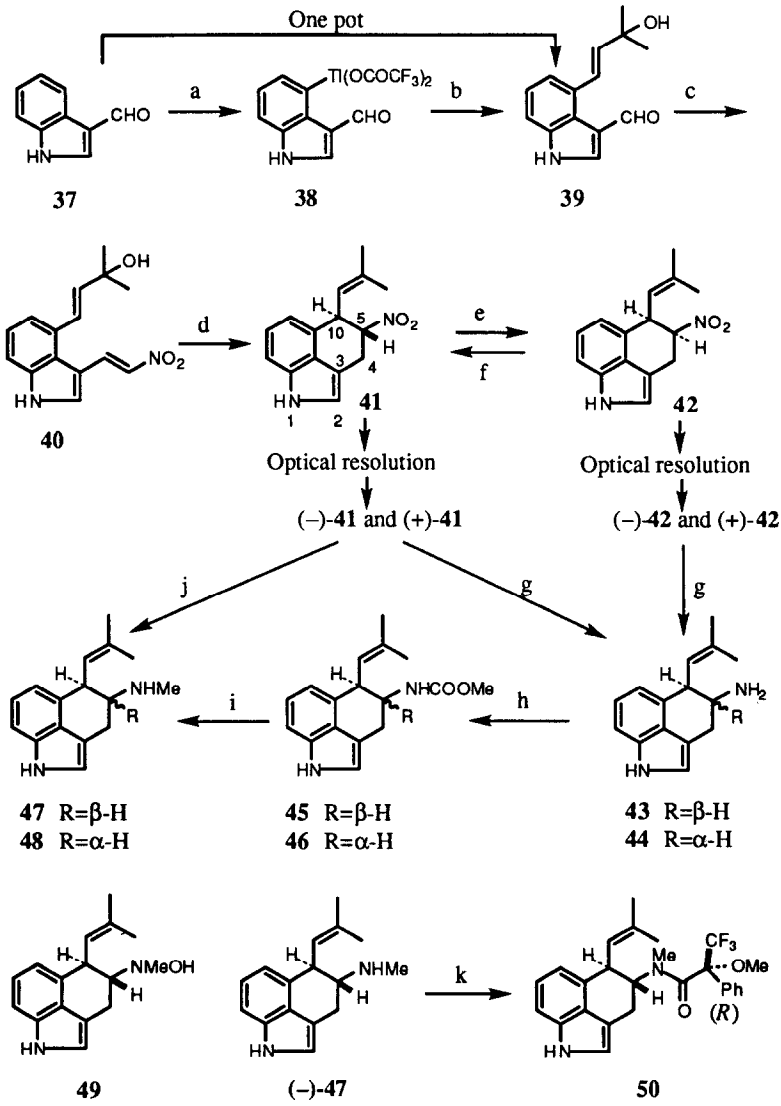
A. Synthetic Studies by Somei's Group

As already mentioned in the previous review (*3*), Somei *et al.* began their involvement in the synthesis of ergot alkaloids with the intention of applying two new reactions, a palladium-catalyzed tin-thall reaction and the intramolecular cyclization by nitronate anions for the construction of the ergoline skeleton. In the past decade, Somei *et al.* further extended their reactions and chemistry into the ergot alkaloids in order to carry out the synthesis with the least number of steps in the common synthetic route (*37*).

1. Synthesis of 6,7-Secoagroclavines, Chanoclavine I, Isochanoclavine I, Norchanoclavine I, Chanoclavine II, Norchanoclavine II, and Their Enantiomers

The synthetic methodologies, consisting of the routes shown in Schemes 8, 9, and 10 (*37*), were demonstrated to be effective for the total syntheses of a number of (–)-ergot alkaloids and their (+)-enantiomers (*38*). The alkaloids synthesized in this manner were (–)-6,7-secoagroclavine, (–)-chanoclavine I, (–)-isochanoclavine I, (–)-norchanoclavine I, (–)-chanoclavine II, (–)-norchanoclavine II, (–)-agroclavine, (–)-agroclavine I, and their (+)-enantiomers. All of the syntheses started from 3-formylindole (**37**). They first prepared the 4-substituted indole **39** by the procedure of a one-pot tin-thall reaction (*39*) which proceeded via the formation of (3-formylindol-4-yl)thallium bis(trifluoroacetate) (**38**), followed by palladium-catalyzed reaction with tri-*n*-butyl (3-hydroxy-3-methyl-1-butenyl)stannane (*40*).

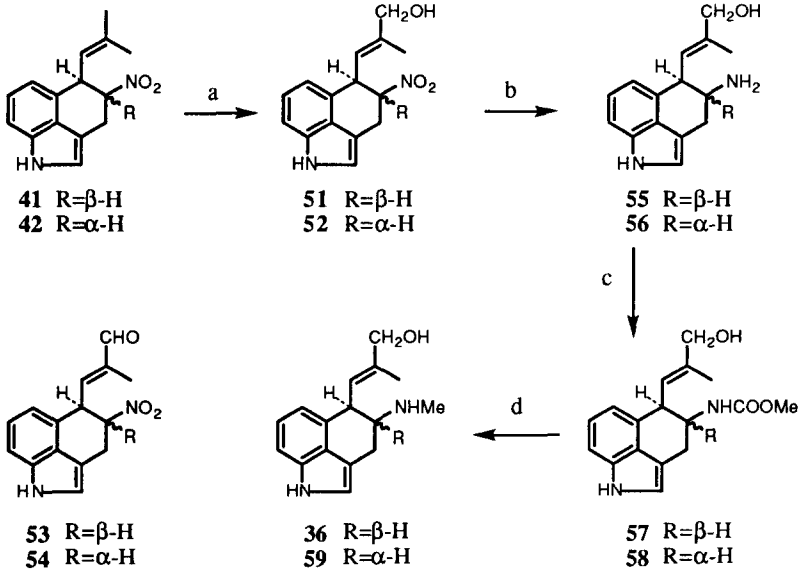
Aldol condensation of **39** with nitromethane afforded the nitrovinylindole **40**, which was then reduced with sodium borohydride in methanol followed by acid treatment (*41*) in a one-pot procedure to bring about the stereospecific cyclization to the tricyclic *trans* isomer **41**. This *trans* isomer **41** was readily isomerized to the *cis* isomer **42** by treatment with sodium methoxide in methanol, while the reverse isomerization of *cis* **42** to *trans* **41** was achieved by treatment with triethylamine in benzene (*37*).



SCHEME 8. Reagents: a, $Tl(OCOCF_3)_3$, CF_3COOH; b, $(n\text{-}Bu)_3SnCH{=}CHC(OH)Me_2$, $Pd(OAc)_2$, DMF; c, $MeNO_2$, NH_4OAc; d, $NaBH_4$, MeOH, then $HCl\text{-}H_2O$; e, NaOMe, MeOH; f, Et_3N, benzene; g, Zn-Hg, HCl, H_2O, MeOH; h, ClCOOMe, Et_3N, CH_2Cl_2; i, $LiAlH_4$, THF; j, MeMgI, THF, then Zn-HCl, MeOH; k, $ClCOCPh(CF_3)(OMe)$.

Optical resolution of the key intermediates, *trans* **41** and *cis* **42**, was achieved, with base-line resolution, by chiral column chromatography on a chiralpak AS column, to afford (–)-*trans* **41**, (+)-*trans* **41**, (–)-*cis* **42**, and (+)-*cis* **42** on a semi-preparative scale. The first total syntheses of (–)-6,7-secoagroclavine [(–)-*trans* **47**] and its (+)-enantiomer [(+)-*trans* **47**] were completed in a one-pot operation by the reaction of (–)- and (+)-*trans* **41** with an excess of methylmagnesium iodide, respectively, followed by reduction of the resulting methylhydroxylamines [(–)- and (+)-*trans* **49**], with zinc in methanolic hydrochloric acid.

Alternatively, three-step syntheses of (–)-6,7-secoagroclavine [(–)-**47**] and its (+)-enantiomer [(+)-**47**] were also achieved (*38*). Reduction of both (–)- and (+)-*trans* **41** with amalgamated zinc in methanolic hydrochloric acid afforded the respective (–)- and (+)-*trans* isomers **43**, which were then treated with methyl chloroformate to afford the corresponding carbamates [(–)- and (+)-*trans* **45**], respectively. These respective carbamates were then reduced with lithium aluminum hydride to give the enantiomeric *N*-methyl amines **47**. This series of conversions was also applied to the corresponding optically active *cis*-compounds **44**, **46**, and **48**, as shown in Scheme 8 (*38*). The structures of these products were unambiguously determined from the X-ray crystallographic



41 R=β-H
42 R=α-H

51 R=β-H
52 R=α-H

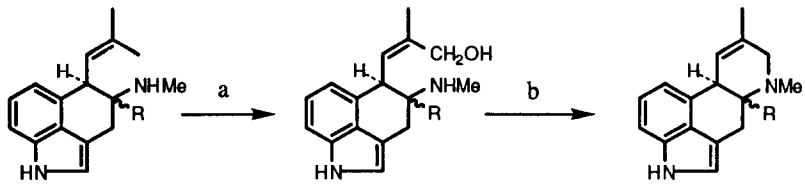
55 R=β-H
56 R=α-H

53 R=β-H
54 R=α-H

36 R=β-H
59 R=α-H

57 R=β-H
58 R=α-H

SCHEME 9. Reagents: a, SeO_2, dioxane, H_2O; b, Zn-Hg, HCl, H_2O, MeOH; c, ClCOOMe, Et_3N, CH_2Cl_2; d, $LiAlH_4$, THF.



47 R=β-H
48 R=α-H

60 R=β-H
61 R=α-H

62 R=β-H
63 R=α-H

SCHEME 10. Reagents: a, SeO_2, dioxane, H_2O; b, $POCl_3$, K_2CO_3.

analysis of the compound **50**, which was prepared by the *N*-acylation of (–)-**47** with (*R*)-(+)-2-methoxy-2-trifluoromethylphenyl-acetyl chloride (*40*).

Oxidation of (–)-*trans* **41** with *t*-butyl hydroperoxide in the presence of 5% selenium dioxide on silica gel (*42*) in dioxane, followed by reduction of the resulting mixture of (–)-*trans* **51** and the overoxidized aldehyde [(–)-*trans* **53**] with sodium borohydride, afforded the (–)-(*E*)-hydroxymethyl compound [(–)-*trans* **51**]. Similarly, (+)-*trans* **41** was converted to the (+)-(*E*)-hydroxymethyl compound [(+)-*trans* **51**]. The subsequent reduction of (–)- and (+)-*trans* **51** with amalgamated zinc in methanolic hydrochloric acid afforded (–)- and (+)-norchanoclavine I (**55**), respectively, which were then converted to the (–)- and (+)-*trans* methyl carbamates (**57**) by reaction with methyl chloroformate.

Total syntheses of the *N*-methyl derivatives, (–)-chanoclavine I [(–)-**36**] and its enantiomer [(+)-**36**] were achieved, respectively, by the reduction of these carbamates with lithium aluminum hydride, which completed the total synthesis of (–)-chanoclavine I [(–)-**58**] and its enantiomer [(+)-**58**], respectively. Application of this series of conversions to the corresponding optically active *cis*-compounds [(–)- and (+)-*cis* **52**] completed the total syntheses of norchanoclavine II [(–)-**56**] and chanoclavine II [(–)-**59**] (*43*), and their enantiomers, through **58**, as shown in Scheme 9.

Oxidation of the *Z*-methyl of the isobutenyl group of (–)-**47** with selenium dioxide in dioxane produced (–)-isochanoclavine I [(–)-**60**], as shown in Scheme 10. This regioselective functionalization can be explained by the coordination of the methylamino group at the 5-position to selenium, bringing the selenium dioxide molecule close to the *Z*-methyl group (*44*).

2. *Synthesis of* (–)- *and* (+)-*Agroclavines, and of* (–)- *and* (+)-*Agroclavine I*

Syntheses of the enantiomeric agroclavines [(–)- and (+)-**62**] were achieved, respectively, as shown in Scheme 10, starting from enantiomeric **47**. Oxidation of the *Z*-methyl of the isobutenyl group of (–)- and (+)-**47** with selenium

dioxide in dioxane afforded (–)-isochanoclavine I [(–)-**60**] and (+)-**60**, respectively. Subsequent cyclization of both enantiomers [(–)- and (+)-**60**] proceeded smoothly with phosphorus oxychloride in the presence of potassium carbonate to give (–)-agroclavine [(–)-**62**] and (+)-agroclavine [(+)-**62**], respectively. Since (–)-agroclavine **62** was previously converted to festuclavine, costaclavine, isosetoclavine, and setoclavine (*45*), the formal total syntheses of these ergoline alkaloids were completed.

Somei *et al.* also succeeded in the first total synthesis of (–)-agroclavine I [(–)-**63**] and the determination of the absolute configuration of this alkaloid (*46*). They prepared (–)-*cis* **61** and its enantiomer [(+)-*cis* **61**] by applying their regioselective allylic oxidation with 30% selenium dioxide on celite. It was found that the sign of the optical rotation changed upon the ring closure of (–)-*cis* **61** with phosphorus oxychloride in the presence of potassium carbonate, giving rise to (+)-agroclavine I [(+)-**63**]. Similarly, (+)-*cis* **61** yielded (–)-agroclavine I [(–)-**63**]. As a result, the compound [(+)-*cis* **42**] was determined to have the [5*R*,10*S*] absolute configuration, and consequently (–)-agroclavine I [(–)-**63**] has the [5*R*,10*S*] configuration (*40*).

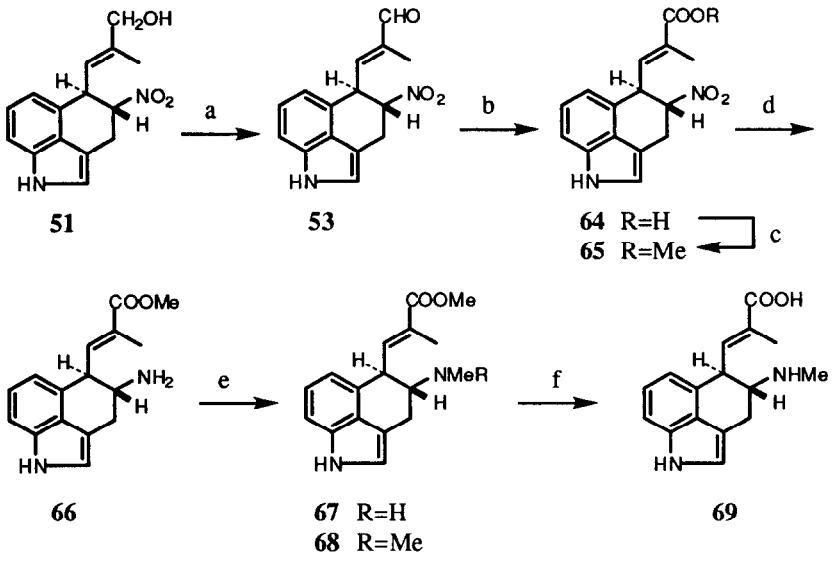
3. Synthesis of (±)-*Chanoclavine I Acid*

The first total synthesis of chanoclavine I acid (*47*), a major alkaloid in the seeds of *Ipomea violacea* (*48*), was completed by Somei *et al.* who employed the key intermediate **51** for the formation of chanoclavine I (**36**), and also for the synthesis of chanoclavine I acid (**69**). Compound **51** was oxidized with pyridinium chlorochromate in dichloromethane to give the aldehyde **53**, which was further oxidized to the carboxylic acid **64** by employing sodium hypochlorite in the presence of 2-methyl-2-butene (*49*), as shown in Scheme 11.

Methylation of **64** with ethereal diazomethane afforded the methyl ester **65**, which was then reduced with amalgamated zinc and hydrochloric acid to give the amine **66**. Methylation of the primary amine with dimethyl sulfate in the presence of potassium carbonate afforded a mixture of the monomethylamine **67** and the dimethylamine **68**, which were separated. Alkaline hydrolysis of **67** in methanol and subsequent column chromatography on Amberlite IRA-120 completed the total synthesis of (±)-chanoclavine I acid (**69**).

4. Synthesis of (±)-*Chanoclavine I and of* (–)- *and* (+)-*KSU 1415*

Application of the primary amine **66**, obtained as shown in Scheme 11, to an alternative synthesis of (±)-chanoclavine I (**36**) was carried out as an example to demonstrate the potential of employing a common intermediate for the synthesis of a wide variety of ergoline alkaloids (*47*). The route for applying the key intermediate **66** to this synthesis consisted of a series of conventional reactions:



SCHEME 11. Reagents: a, pyridinium chlorochromate, CH_2Cl_2; b, NaOCl, NaH_2PO_4, $(Me)_2C{=}CHMe$; c, CH_2N_2, MeOH; d, Zn-Hg, HCl, H_2O, MeOH; e, Me_2SO_4, K_2CO_3; f, NaOH, MeOH.

treatment of the primary amine **66** with methyl chloroformate in the presence of triethylamine produced the carbamate **70**, which was then reduced with lithium aluminum hydride in tetrahydrofuran to give (±)-chanoclavine I (**36**) (Scheme 12).

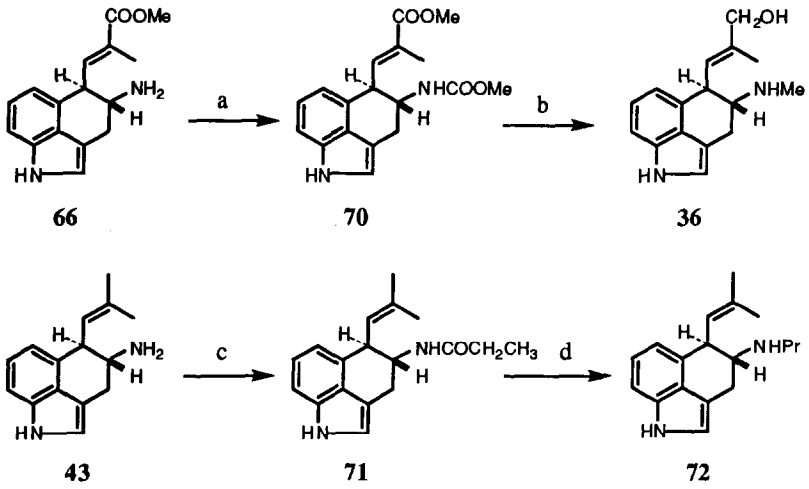
Somei *et al.* also disclosed that (±)-6-nor-6-propyl-6,7-secoagroclavine [(±)-**72**, KSU 1415] showed potent dopamine agonistic activity (*50*).

In continuing research, (–)- and (+)-KSU 1415 [(–)- and (+)-**72**] were similarly prepared by the reaction of the respective enantiomers [(–)- and (+)-**43**] with propionyl chloride followed by reduction of the resulting enantiomeric **71** with lithium aluminum hydride in tetrahydrofuran (*40*) (Scheme 12). The biological evaluations of these compounds have not been reported.

5. Total Synthesis of (±)-*Clavicipitic Acid*

Somei *et al.* developed two further synthetic methodologies by manipulating the substituents at the 3-position of indoles, as shown in Scheme 13.

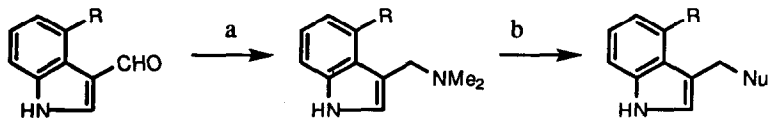
The first was a route for the formation of the gramine **74**, which was obtained directly from the 3-formylindoles **37** and **73**, by reaction with sodium borohydride in 50% dimethylamine and methanol (*51*). The other was a route including selective monoalkylation of the gramine **74** with active methylene



SCHEME 12. Reagents: a, ClCOOMe, Et_3N; b, $LiAlH_4$, THF; c, propionyl chloride, Et_3N, CH_2Cl_2; d, $LiAlH_4$, THF.

compounds, using tri-*n*-butylphosphine as a catalyst, to give the compounds **75** (*27*). They applied the gramine synthesis to the compound **39** and succeeded in synthesizing **76** in two steps from 3-formylindole (**37**), as shown in Scheme 14. The compound **77** was then prepared by selective monoalkylation of the gramine **76** with methyl nitroacetate as an active methylene compound.

Application of the amino-cyclization method (*52*) to the compound **77** was also developed by Somei *et al.* Reduction of the nitroester **77** with amalgamated zinc in hydrochloric acid yielded the seven-membered ring system as a mixture



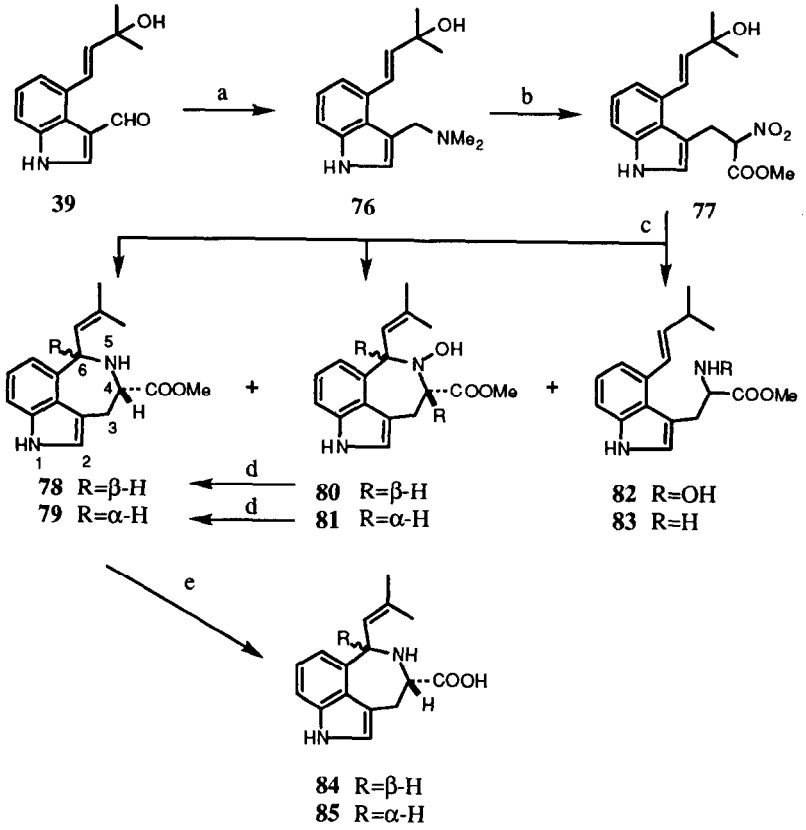
37 R=H
73 R=NO_2, CN, I, OMe

74 **75**

SCHEME 13. Reagents: a, $NaBH_4$, Me_2NH, MeOH ; b, nucleophiles (Nu=$CHNO_2$, $C(COOEt)_2NHAc$, $CH(COOMe)_2$, etc.), (*n*-Bu)$_3$P, MeCN.

of stereoisomeric isomers of (±)-*cis* **78** and *trans* **79** (*53*). *trans*-Clavicipitic acid methyl ester (**79**) was obtained as the major product, together with other products, *N*-hydroxy compounds as the racemates *cis* **80** and *trans* **81**, and the

noncyclized products (**82** and **83**) (Scheme 14). Treatment of (±)-*cis* **80** and *trans* **81** with aqueous titanium(III) chloride brought about dehydroxylation on nitrogen to afford (±)-*cis* **78** and *trans* **79**, respectively, which were known previously from the synthesis of *cis*- and *trans*-clavicipitic acid (**84**,**85**) by Natsume *et al.* (*54*).

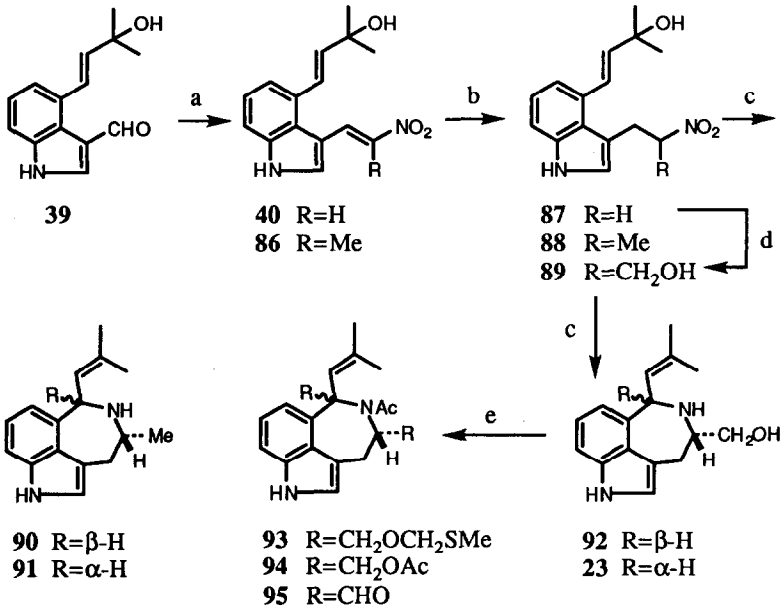


SCHEME 14. Reagents: a, $NaBH_4$, Me_2NH, MeOH; b, O_2NCH_2COOMe, $(n\text{-}Bu)_3P$, MeCN; c, Zn-Hg, HCl, MeOH; d, $TiCl_3$, H_2O, MeOH; e, NaOH, MeOH, H_2O.

6. Syntheses of Clavicipitic Acid Analogs

Somei *et al.* further applied the above synthetic route for clavicipitic acid, to the preparation of analogs of (±)-clavicipitic acid (*53*). Aldol condensation of **39** with nitromethane and nitroethane afforded the nitroalkenes **40** and **86**, respectively, which were reduced with sodium borohydride to give the nitroalkanes **87** and **88** in high yields, ready for the amino-cyclization method, as shown in Scheme 15. Amino-cyclization of **87** and **88** was similarly carried out employing amalgamated zinc in hydrochloric acid to afford *cis* **90** and *trans* **91**, the 4-methyl analogs of clavicipitic acid. Application of this cyclization to the compound **89**, obtained by reacting **87** with formaldehyde in the presence of potassium *t*-butoxide, gave *cis* **92** and *trans* **23**, the 4-hydroxymethyl analogs.

Contrary to the expectation that the hydroxymethyl group at the 4-position of **23** would be readily oxidized to a carboxyl group, and thereby was expected to provide another route to *trans*-clavicipitic acid, it resisted various oxidative conditions. On the other hand, oxidation of **23** with acetic anhydride and



39

40 R=H
86 R=Me

87 R=H
88 R=Me
89 R=CH_2OH

90 R=β-H
91 R=α-H

93 R=CH_2OCH_2SMe
94 R=CH_2OAc
95 R=CHO

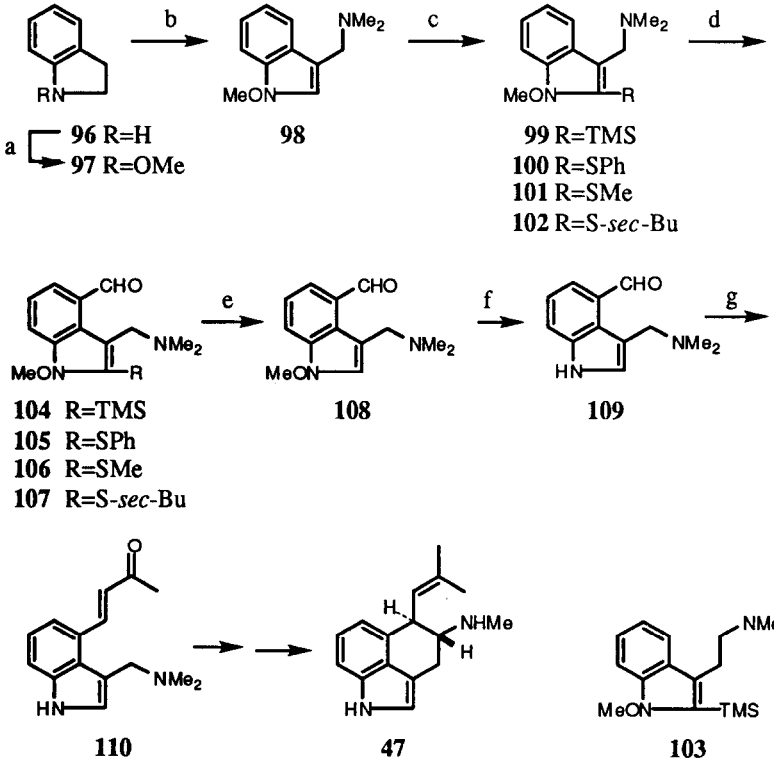
92 R=β-H
23 R=α-H

SCHEME 15. Reagents: a, RCH_2NO_2, NH_4OAc; b, $NaBH_4$, MeOH; c, Zn-Hg, HCl, MeOH; d, CH_2O, *t*-BuOK; e, Ac_2O, DMSO.

dimethyl sulfoxide yielded the analogous *N*-acetates, (±)-*trans* **93**, **94**, and **95** (*53*).

7. *Synthesis of (±)-6,7-Secoagroclavine, (±)-Aurantioclavine, and (±)-Clavicipitic Acid*

Somei *et al.* investigated the lithiation of 2-substituted 1-methoxy-3-dimethylaminomethylindoles at the 4-position, expecting that the introduction of a bulky 2-substituent would force the dimethylamino group in the desired direction (*55*). Suitable substrates **99–102** with a bulky substituent at the 2-position were prepared from indoline **96** in a series of reactions: 1) oxidation of



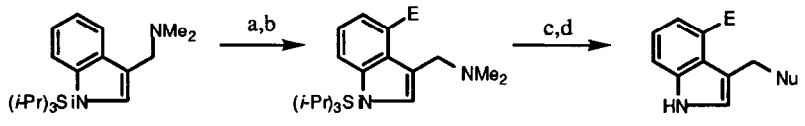
SCHEME 16. Reagents: a, Na_2WO_4, 30% H_2O_2, then CH_2N_2; b, CH_2O, Me_2NH, AcOH; c, *n*-BuLi, THF, then TMSCl, Ph_2S_2, Me_2S_2, or $(sec\text{-}Bu)_2S_2$; d, *n*-BuLi, ether, then DMF; e, $(n\text{-}Bu)_4NF$; f, $h\nu$, EtOH; g, acetone, NaOH, H_2O.

96 with sodium tungstate and 30% hydrogen peroxide, followed by methylation with diazomethane, 2) Mannich reaction, and 3) regioselective lithiation of **98** at the 2-position, followed by reaction with electrophiles, as shown in Scheme 16. They found when the solvent was ether, lithiation of **99–102** took place smoothly at the 4-position, while as long as tetrahydrofuran was used, lithiation did not occur. Lespedamine derivative **103**, a homolog of **99**, was not lithiated at the 4-position at all.

Based on the above results, Somei *et al.* developed a novel synthetic route for multi-functionalized 4-substituted indoles starting from indoline **96**, and applied it to the synthesis of ergot alkaloids (*55*). Lithiation of 1-methoxy-3-dimethylaminomethylindoles **99–102** with *n*-butyllithium in ether, followed by trapping with *N*,*N*-dimethylformamide, afforded **104–107** in good yields. Subsequent treatment of **104** or **105–107** with tetra-*n*-butylammonium fluoride or Raney nickel, respectively, afforded **108**. Ultraviolet irradiation removed the 1-methoxy group to afford 4-formylgramine (**109**), which was then converted to **110** by aldol condensation with acetone. Compound **110** had been already converted to (–)-6,7-secoagroclavine [(–)-**47**], (±)-aurantioclavine and (±)-clavicipitic acid through **41** and **76**, respectively (*38,56*).

B. Synthetic Studies by Iwao's Group

Iwao *et al.* introduced an efficient methodology for the synthesis of 3,4-disubstituted indoles **113** (*57*). Their strategy comprises two sequential steps: 1) selective functionalization of 1-silyl-3-dimethylaminomethylindole (**111**) at the 4-position by directed lithiation, followed by quenching with electrophiles, for the preparation of 4-dimethylamino-substituted indole **112** (*58*); 2) substitution of the dimethylamino group of **112** for various nucleophiles giving **113** upon desilylation through quaternization followed by a fluoride ion-induced elimination-addition reaction (Scheme 17) (*59*).



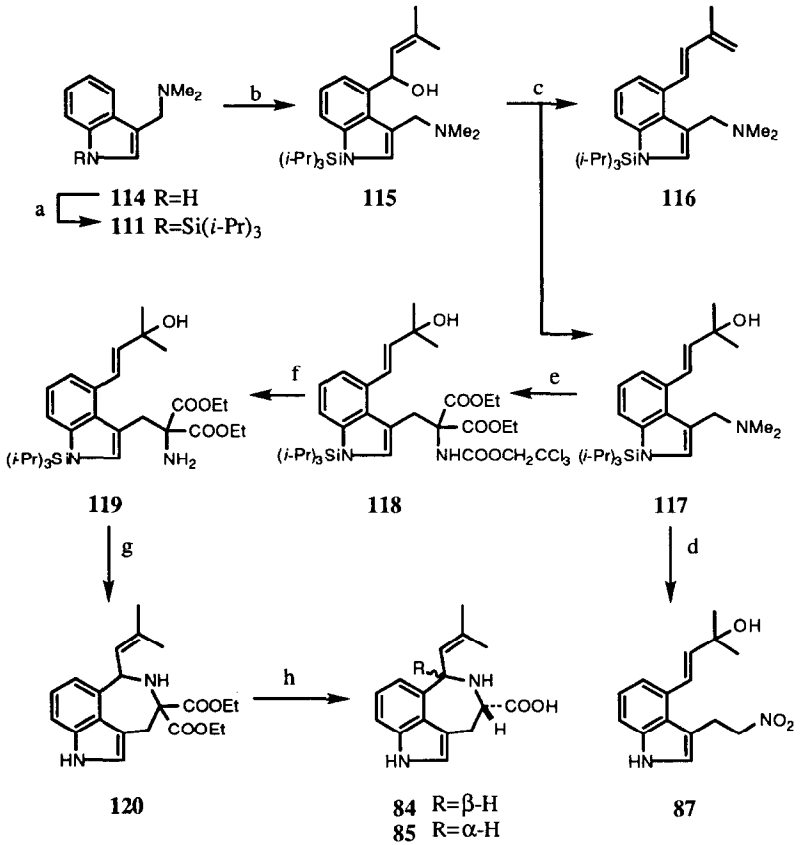
111 **112** **113**

Scheme 17. Reagents: a, *t*-BuLi, ether; b, electrophiles (E=Me_3Si, PhS, I, CHO, Me_2C=CHCHOH, etc.); c, MeI; d, nucleophiles (Nu=$CHNO_2$, $C(TrocNH)(COOEt)_2$, etc.), $(n\text{-}Bu)_4NF$.

1. Synthesis of (±)-6,7-Secoagroclavine, (±)-Aurantioclavine, and (±)-Clavicipitic Acid

Iwao *et al.* applied the above methodology to the total syntheses of ergot alkaloids (*58,59*).

3-Dimethylaminomethylindole (**114**) was silylated on nitrogen, first by metalation with *n*-butyllithium in tetrahydrofuran followed by silylation with triisopropylsilyl chloride. Lithiation of **111** with *t*-butyllithium in ether at



SCHEME 18. Reagents: a, *n*-BuLi, $(i\text{-Pr})_3SiCl$; b, *t*-BuLi, ether, then $Me_2C{=}CHCHO$; c, 85% H_3PO_4, dioxane; d, MeI, benzene, then $MeNO_2$, $(n\text{-Bu})_4NF$; e, MeI, benzene, then $Cl_3CCH_2OCONHCH(COOEt)_2$, $(n\text{-Bu})_4NF$, THF; f, Zn, THF, 1M KH_2PO_4; g, PPTS, CH_2Cl_2; h, 2M KOH, MeOH, then 2M HCl, and then aqeous EtOH, reflux.

–78°C occurred regioselectively at the 4-position due to the steric hindrance of a bulky substituent on the 1-position. The resulting 4-lithiated intermediate was reacted with 3-methyl-2-butenal to afford the alcohol **115**. Acid-catalyzed allylic rearrangement of **115**, by treatment with 85% phosphoric acid in dioxane, produced **117**, together with **116** as a minor product. Quaternization of **117** with methyl iodide in benzene, and subsequent reaction of the methiodide with nitromethane as a nucleophile in the presence of tetra-*n*-butylammonium fluoride, afforded **87** in an excellent yield, thereby establishing for Iwao's group alternative formal total syntheses of (–)-6,7-secoagroclavine [(–)-**47**] and (±)-aurantioclavine. Somei's group had already succeeded in the synthesis of the same alkaloids employing **87** as a key intermediate (*37,38*).

Similarly, the methiodide was reacted with diethyl (2,2,2-trichloroethoxycarbonyl)aminomalonate as a nucleophile to give **118**, which was then converted to the amine **119** by deprotection of the 2,2,2-trichloroethoxycarbonyl group with zinc and potassium dihydrogen phosphate. Dehydrative cyclization of **119** to the azepinoindole **120** was achieved by heating **119** in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate in dichloromethane. Hydrolysis of **120** with potassium hydroxide in methanol yielded the malonic acid derivative which was then readily decarboxylated on heating in aqueous ethanol to accomplish total syntheses of (±)-*cis*- and (±)-*trans*-clavicipitic acid (**84,85**) in a ratio 3 : 2 (Scheme 18) (*57*).

C. Synthetic Studies by Yokoyama and Murakami's Group

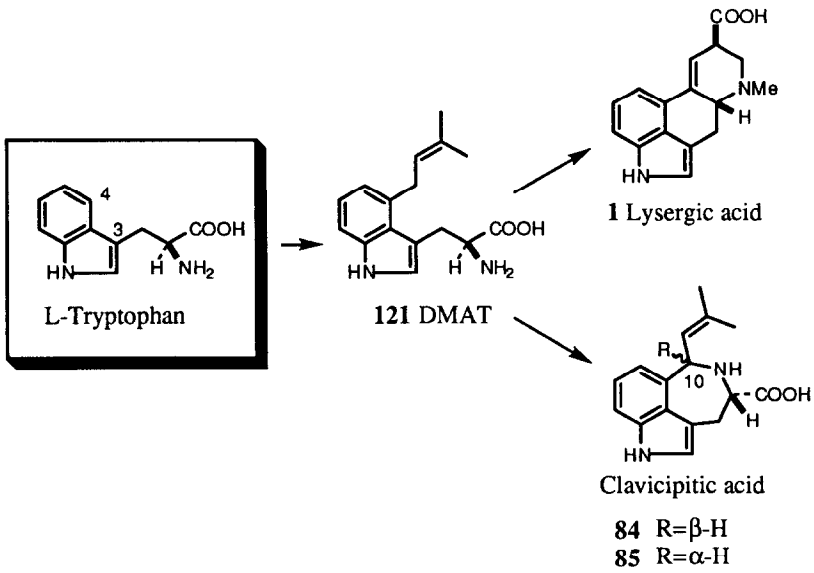
Yokoyama *et al.* have carried out extensive synthetic studies on nitrogen-containing heterocyclic compounds with a particular focus on the indole ring system. In a continuation of their work, following synthetic work on the benzo[*c*]phenanthridine alkaloids, they initiated synthetic studies by tackling the synthesis of ergoline alkaloids. Their approach to this group of alkaloids has been based on the exploitation of the chemistry and reactions of tryptophan.

Tryptophan, existing as an optically active form, and commercially available in the L-form, has been known as one of the important essential amino acids, and is also regarded as the important key intermediate in the biosynthesis of many important biological compounds. Ergot alkaloids, as represented by lysergic acid (**1**) and clavicipitic acid (**84,85**), are known to be biosynthesized from L-tryptophan through a common intermediate, 4-(γ,γ-dimethylallyl)tryptophan (DMAT) (**121**) (Scheme 19) (*4*).

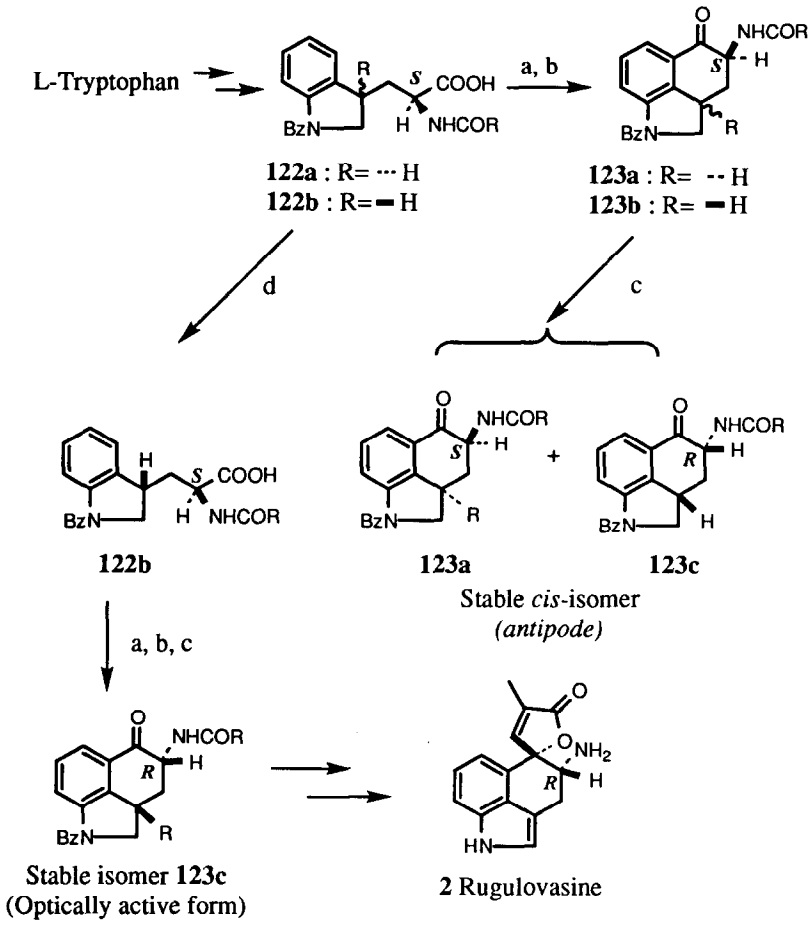
However, many ideas and then studies have been based on the effective use of tryptophan as the synthetic starting material for substitution at the 4-position of the ring system, but so far without much success in the synthesis of the optically active form of the ergot alkaloids. The reason for the failure of its application to the synthesis has been regarded as the facile racemization which

occurred during substitution at the 4-position, together with the poor reactivity of the 4-position of tryptophan.

For example, Rebek (*15–17*) and Varie (*60*) reported that intramolecular Friedel-Crafts acylation of a diastereomeric mixture of dihydrotryptophans **122a** and **122b** prepared from L-tryptophan yielded the ketone as a mixture of diastereomers **123a** and **123b**, and they also noticed that one of the isomers **123b** was readily epimerized to give the stable *cis* isomer **123c**, thus giving rise to the racemates **123a** and **123c** as the cyclization product. In order to obtain enantiomerically pure isomer **123c**, it was necessary to isolate **123b** from the diastereomeric mixture of **123a** and **123b**. Rebek *et al.* thus succeeded in synthesizing optically pure rugulovasine (**2**) from **123c** (Scheme 20). This is the only complete synthesis of an optically active ergot alkaloid from L-tryptophan thus far achieved. In order to establish a higher level of synthetic chemistry in the ergoline alkaloids, Yokoyama and Murakami's group has carried out research by making an effective use of tryptophan, to open this area to asymmetric synthesis, and to bring it closer to biochemical importance.



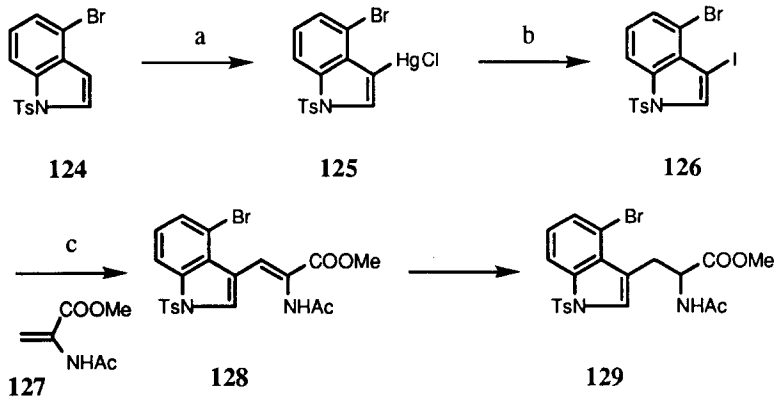
SCHEME 19. Biogenetic route for the ergot alkaloids.



SCHEME 20. Reagents: a, $(COCl)_2$; b, $AlCl_3$; c, epimerization; d, separation of diastereomers.

1. Use of Optically Active 4-Bromotryptophan as the Key Synthetic Intermediate

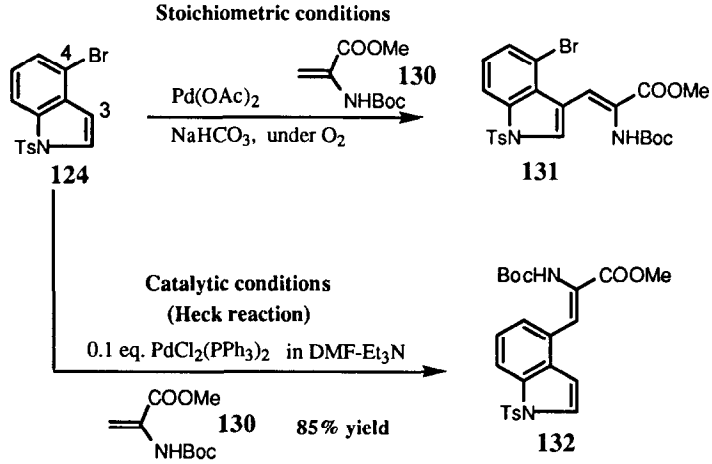
The use of 4-bromotryptophan was regarded as having a high potential for the synthesis of a variety of 4-substituted derivatives for further conversion into many biologically important compounds, though not many promising results were available until 1995.



SCHEME 21. Reagents: a, $HgCl_2$; b, I_2; c,15 mol% $Pd(OAc)_2$.

Hegedus reported the synthesis of *dl*-4-bromotryptophan **129** from *N*-tosyl-4-bromoindole **124** as a precursor for ergot alkaloid synthesis (*23*) (Scheme 21). 4-Bromodehydrotryptophan **128** was prepared from the *N*-protected 4-bromoindole **124** in a three-step synthesis, which involved a mercuration-iodination reaction followed by chemoselective palladium-catalyzed vinylation of 4-bromo-3-iodo-1-tosylindole **126** with *N*-acetyldehydroalanine methyl ester **127**. Although this route was short and applicable to the preparation of variously substituted dehydrotryptophans, the use of a hazardous mercury reagent during the synthetic process turned attention to other methods, for example, the one-step synthesis of *N*-Boc-4-bromodehydrotryptophan methyl ester (**131**) from the same starting material **124** (*61,62*).

Vinylation of **124** with *N*-Boc-dehydroalanine methyl ester (**130**) occurred only at the 3-position in the presence of a stoichiometric amount of $Pd(OAc)_2$. This reaction was interesting because vinylation occurred chemoselectively only at the 3-position, in spite of the presence of a reactive carbon-bromine bond, while the C-4 vinylated product **132** was obtained in the presence of a catalytic amount of $PdCl_2(PPh_2)_2$ according to the Heck reaction. Thereby the two reactive positions of 3 and 4 were completely distinguishable towards vinylation by changing the reaction conditions (Scheme 22). The yield of **131** was markedly improved by the addition of chloranil, as shown in Table I. On the assumption that chloranil acts as an oxidizing agent to recycle palladium(0) to palladium(II), the role of a catalytic amount of $Pd(OAc)_2$ was deduced, and thus employed, though the yield of **131** stayed only at 38% under these condition (Scheme 22). Other oxidizing reagents such as DDQ, MnO_2, Ag_2CO_3, $(Coşalen)_2$-O_2, and $Cu(OAc)_2$ were found to be not as effective as chloranil.



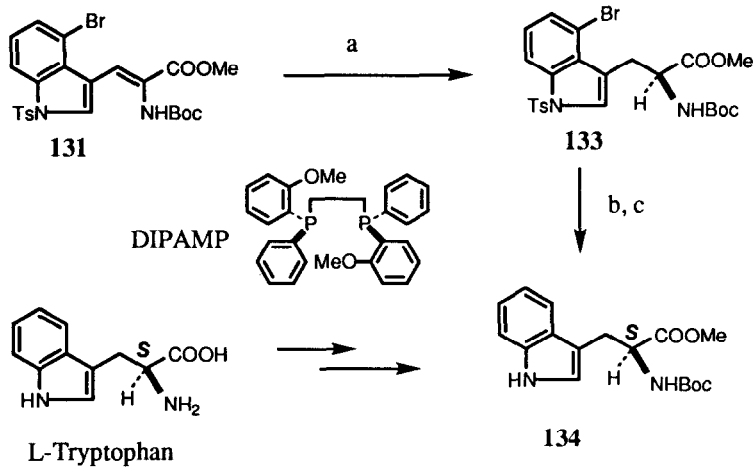
SCHEME 22

Asymmetric reduction of **131** was carried out using DIPAMP as a chiral phosphine ligand to give the 4-bromotryptophan derivative **133** with high optical purity (94% ee). The absolute configuration was determined as *S* by the conversion of **133** into *N*-Boc-tryptophan methyl ester (**134**), which was correlated with a sample synthesized from L-tryptophan. Although there have been numerous reports of the asymmetric reduction of *N*-acetyl- or *N*-benzoyl-protected dehydroamino acids with high enantiomeric excess, there are only a limited number of reports of the asymmetric reduction of a *N*-urethane-protected dehydroamino acid such as **131**. Schmidt recorded the highest optical yield (95% ee) by the asymmetric reduction of *N*-Boc-dehydrotryptophan using a rhodium-DIPAMP complex (*63*) (Scheme 23).

TABLE I. SYNTHESIS OF 4-BROMODEHYDROTRYPTOPHAN (**131**)

Expt.	$Pd(OAc)_2$ eq.	chloranil eq.	time (h)	temp.(°C)	solvent	Yield of 131 (%)
1	1.0	–	3	70	CH_2ClCH_2Cl	41[a)]
2	1.0	0.25	7.5	70	CH_2ClCH_2Cl	74
3	1.0	1.0	7	90	TCB	85
4	0.25	1.0	3	90	TCB	38

a) under Ar TCB=1,2,4-trichlorobenzene

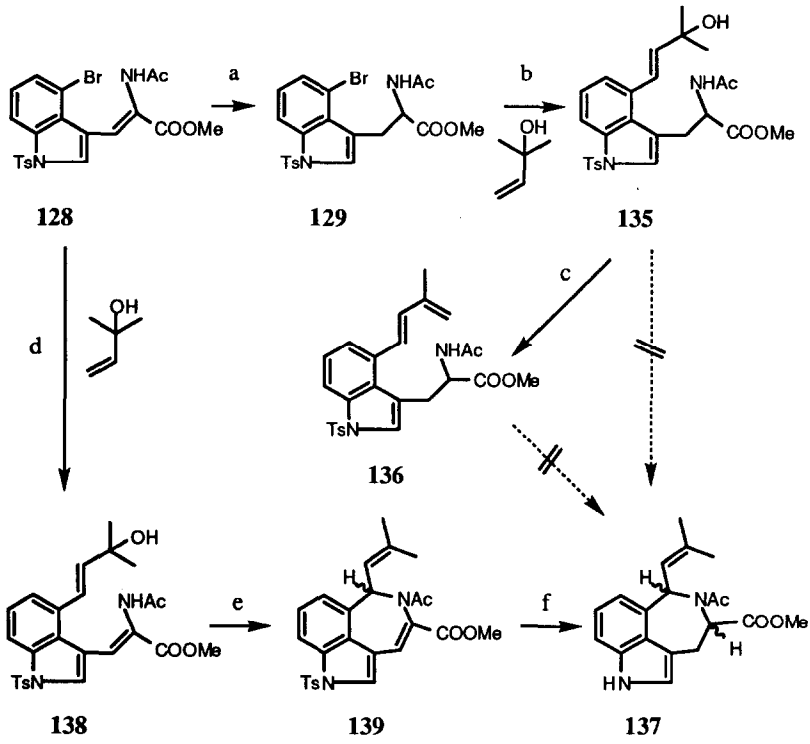


SCHEME 23. Reagents: a, H_2, $Rh(COD)_2BF_4$, DIPAMP; b, Pd-C, H_2; c, Mg, MeOH.

2. *Synthesis of Optically Active Clavicipitic Acid*

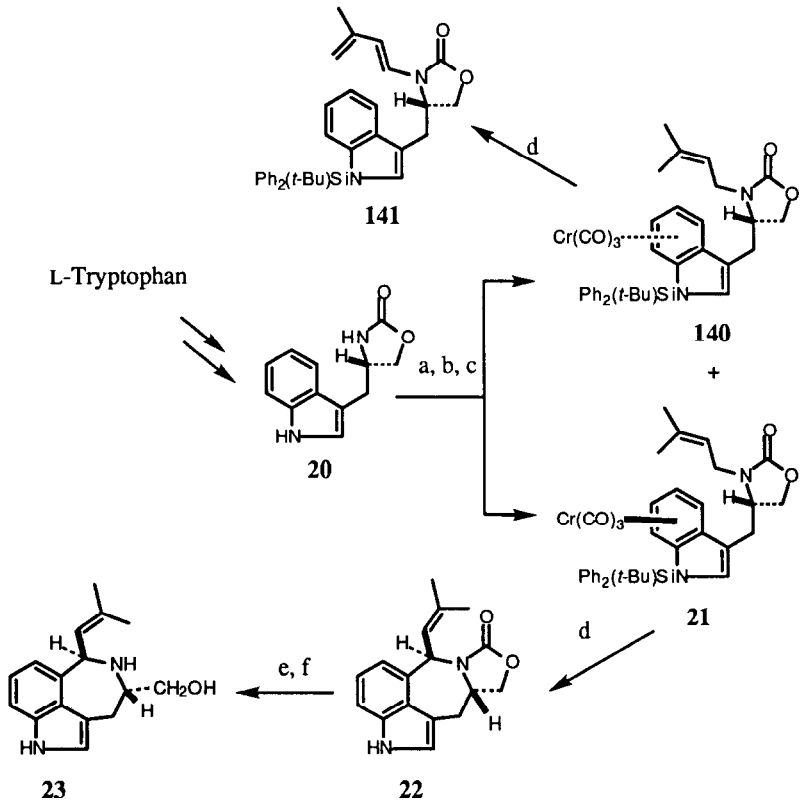
Clavicipitic acid (**84,85**) is an ergot alkaloid isolated from one of the *Claviceps* strains as a mixture of diastereomers, and has a unique ring system different from that of the ergoline alkaloids, including lysergic acid (**1**) (*64*). By the end of the last decade, a number of syntheses of this alkaloid had been reported (*19–23,28,47,53,57*) including two groups who reported the synthesis using a tryptophan derivative.

Hegedus *et al.* (*23*) reported an efficient vinylation of **129** with 1,1-dimethylallyl alcohol by the Heck reaction to give the C-4 vinylated product **135**, which was found to be unstable and readily dehydrated to give the diene **136**. The compounds **135** and **136** failed to give rise to cyclization to the tricyclic azepinoindole **137** under various conditions. However, the cyclization of the 4-vinylated dehydrotryptophan **138**, which was prepared by Heck reaction on the 4-bromodehydrotrytophan **128** with the palladium catalyst, proceeded smoothly on heating in the presence of stoichiometric or catalytic quantities of $PdCl_2(MeCN)_2$ to give the cyclized azepinoindole product **139** quantitatively. This facile cyclization of **138**, in contrast to **135** and **136**, could be attributed to the rigid conformation of the acetamidoacrylate side chain. Photochemical reduction of the cyclized compound **139** with sodium borohydride removed the tosyl group on nitrogen to give *N*-acetylclavicipitic acid methyl ester **137** as a mixture of diastereomers (Scheme 24).



SCHEME 24. Reagents: a, H_2, $Rh(PPh_3)_3$, MeOH; b, $Pd(OAc)_2$, $(o\text{-tol})_3P$; c, MeCOCl, pyridine; d, $Pd(OAc)_2$, $(o\text{-tol})_3P$; e, $PdCl_2(MeCN)$, MeCN; f, $NaBH_4$, Na_2CO_3, $h\nu$.

Semmelhack and coworkers (*28*) reported the synthesis of optically active clavicipitic alcohol (**23**) via the route involving an intramolecular cyclization of the chromium complex **21** starting from L-tryptophan. Although this cyclization proceeded smoothly to give the optically active azepinoindole **22** in good yield, the intermediary chromium complex was not isolated stereoselectively from the oxazolinone **20**. Compound **20** was reacted with $Cr(CO)_3(MeCN)_3$ followed by silylation and allylation to give a diastereomeric mixture of chromium complexes **21** and **140** in a 1:1 ratio. Each diastereomer showed contrasting behavior to cyclization, one isomer, **21**, rapidly cyclized to the pure tetracyclic product **22** in 77% yield, while the other isomer, **140**, gave only the diene **141** in 70% yield under the same conditions, as a result of dehydration of the product. The cyclized product **22** was then converted to clavicipitic alcohol (**23**) in 83% yield (Scheme 25).

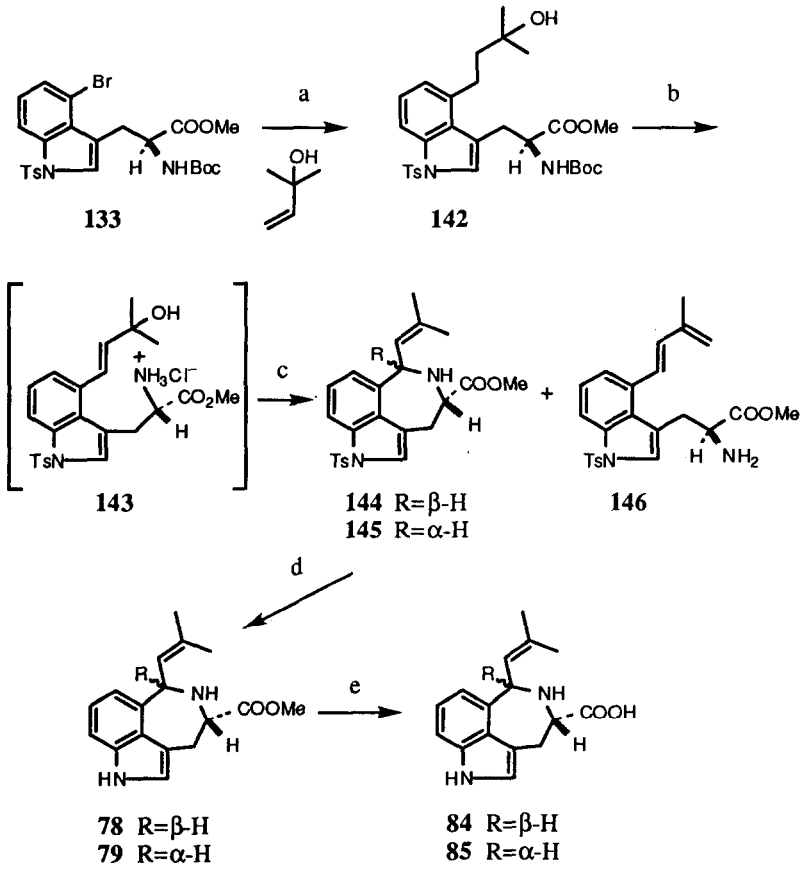


SCHEME 25. Reagents: a, $Cr(CO)_3(MeCN)_3$; b, NaH, $Ph_2(t\text{-Bu})SiCl$; c, MeLi, $(Me)_2C{=}CHCH_2Br$; d, LDA then I_2; e, $(n\text{-Bu})_4NF$; f, 3M KOH.

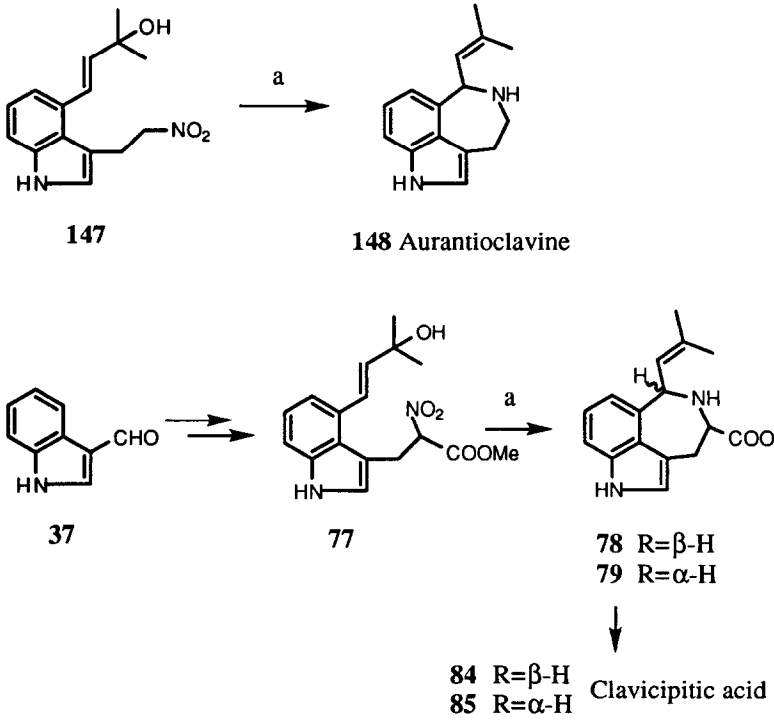
In 1995, Yokoyama and Murakami reported the first chiral synthesis of clavicipitic acid (**84**,**85**) using the optically active 4-bromotryptophan **133** as the starting compound with protection on nitrogen by a *t*-butoxycarbonyl group, which was later readily removed (*65*).

Vinylation of **133** under Heck conditions in the presence of silver carbonate proceeded smoothly to give the C-4 vinylated product **142** in 83% yield without racemization. This reaction in the absence of silver carbonate required higher temperature (120°C) and gave poor results with significant racemization (82% yield, 71% ee). When **142** was treated with acid, followed by neutralization using triethylamine, spontaneous cyclization of the resulting amine **143** took place giving a mixture of the *cis* and *trans* isomers **144** and **145** in 62% yield,

together with some of the dehydrated diene **146**, in 29% yield. This result was in sharp contrast to Hegedus's results, and could be explained by the effect of the substituent in the acetamide group which is poorly nucleophilic to attack by the double bond, thereby giving only the diene **136**. On the other hand, the free amine obtained from **142** was reactive enough to cause spontaneous cyclization under the reaction conditions. On the respective isomers *cis*-**144** and *trans*-**145**, detosylation with magnesium-methanol proceeded smoothly to give clavicipitic acid methyl esters as a mixture of *cis*-**78** and *trans*-**79**, which were purified by



SCHEME 26. Reagents: a, 0.1 eq. $PdCl_2(PPh_3)_2$, 1.0 eq. Ag_2CO_3, DMF-Et_3N, b. HCl, AcOEt; c, Et_3N; d. Mg, MeOH; e, KOH, MeOH-H_2O, Zn-Hg, HCl, MeOH-H_2O.

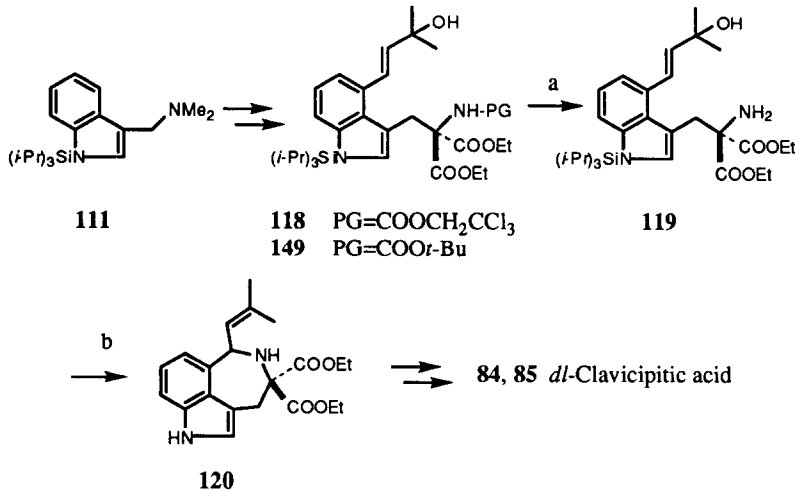


SCHEME 27. Reagents: a, Zn-Hg, HCl, MeOH-H_2O.

one recrystallization to give the pure samples, respectively. Alkaline hydrolysis of the esters **78** and **79** afforded pure clavicipitic acids (**84,85**), *cis* and *trans*, respectively. Their optical rotations were –195.3° (EtOH) for the *cis* isomer and –129.1° (EtOH) for the *trans* isomer (Scheme 26).

Somei's group (*24*) has reported a similar one-pot cyclization of the nitroolefin **147** by reductive amino-cyclization for the synthesis of *dl*-aurantioclavine (**148**). They later applied this method to the synthesis of *dl*-clavicipitic acids (**84,85**) (*47*). Nitroolefin **77**, prepared from 3-formylindole (**37**), was treated with amalgamated zinc in HCl and methanol to give the clavicipitic acid methyl esters (**78, 79**) (Scheme 27).

Recently, Iwao reported (*57*) the dehydrative cyclization of **119** in the total synthesis of *dl*-clavicipitic acid. Iwao prepared the diester **118**, having protected the amino group with a trichloroethoxycarbonyl group, which was then readily cleaved by treatment with zinc dust to recover the free amine **119** in



111 **118** PG=$COOCH_2CCl_3$ **119**
149 PG=COO*t*-Bu

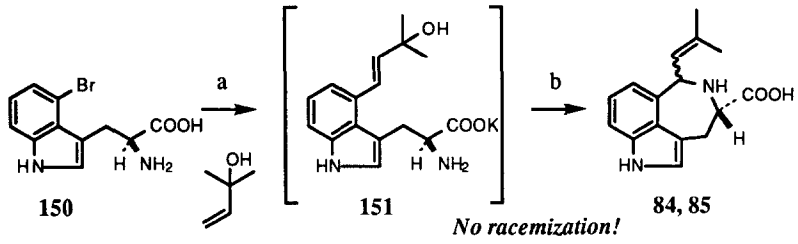
120

SCHEME 28. Reagents: a, Zn dust, KH_2PO_4; b, PPTS, CH_2Cl_2.

good yield. When the resulting amine **119** was heated in the presence of a catalytic amount of PPTS in refluxing dichloromethane, cyclization occurred smoothly to give the azepinoindole **120** in good yield (Scheme 28). In contrast to **118**, deprotection of the Boc group of **149** under acidic conditions (2M-HCl in dioxane or 98% HCOOH) gave only complex mixtures.

Although Yokoyama's synthetic route (*65*) was very efficient and practical, when compared to the other methods, it still required four steps from **133**, including three deprotecton steps. They have tried to improve further their synthetic route aiming at the one-pot synthesis of (–)-**84**, (–)-**85** from free (*S*)-4-bromotryptophan (**150**) without using any protective groups.

Heck reaction of **150** with 1,1-dimethylallyl alcohol was thoroughly investigated to find the conditions suitable for the one pot synthesis of the target alkaloid. Since the amino acid **150** is soluble only in water, the reaction of **150**, without using any protecting group on nitrogen was carried out in aqueous media using a water-soluble phosphine ligand, TPPTS, in the presence of potassium carbonate as a base. The product obtained was not the expected clavicipitic acid, but the potassium salt of the C-4 vinylated compound **151**, which had an uncyclized structure. This compound, **151**, was found to be stable under basic conditions and was isolated by ODS column chromatography. It smoothly cyclized under weakly acidic conditions to give a 1 : 1 mixture of diastereomeric clavicipitic acids (**84,85**) in 78% yield, thereby completing a two-step synthesis of **84,85**. Then, in order to establish the one-pot synthesis, after the vinylation of **150** in aqueous basic solution, the reaction mixture was



SCHEME 29. Reagents: a, 01 eq. $Pd(OAc)_2$, 0.2 eq. TPPTS, K_2CO_3, H_2O, in sealed tube; b, 50% AcOH.

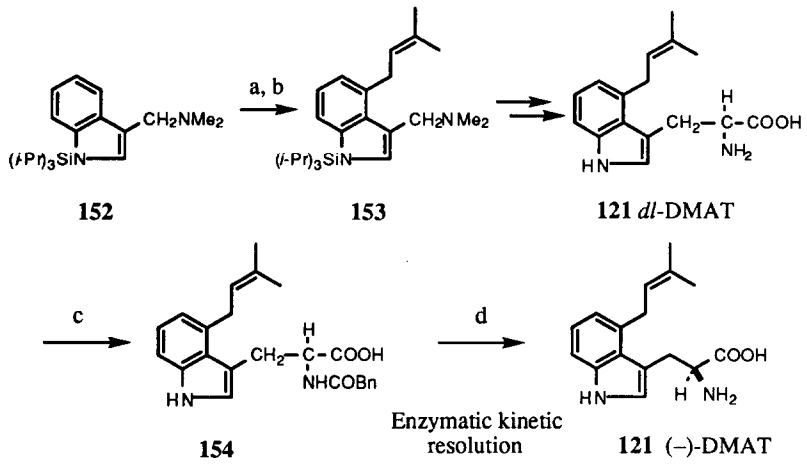
quenched with 60% aq. acetic acid and warmed to 50°C. Thus, the one-pot transformation from **150** to **84,85** was achieved smoothly to give clavicipitic acid (**84,85**) in 61% yield from **150** (Scheme 29). The optical purities of the intermediate **151** in this synthesis and clavicipitic acid (**84,85**) obtained (*cis* and *trans*) were 92% ee as determined by HPLC. During this process, no sign of racemization was detected and it was suggested that water played an important role for minimizing racemization under such strong basic conditions. Matsuo observed that facile racemization of amino acids occurs in 100% acetic acid, and that the rates of racemization were considerably lower in 50% aq. acetic acid than in 100% acetic acid (*66*).

3. Synthesis of Optically Active DMAT

DMAT (**121**) was first proposed (*1*) as an important key intermediate in the biosynthesis of ergot alkaloids, and this was confirmed later by isolation from the culture broth of *Claviceps* species (*67*). As studies have progressed, its importance became apparent from both the biosynthetic and the synthetic points of view (*4*).

The first synthesis of DMAT (**121**) was reported in 1967 by Plieninger's group (*68*) starting from 4-formylindole. This synthesis played an important role in the supply of DMAT (**121**) for biosynthetic research. In 1995, Nettekoven's group developed a method for the synthesis of optically active DMAT (*69*). They prepared 4-dimethylallylgramine (**153**) by selective C-4 lithiation of the *N*-silyl protected gramine **152** followed by treatment with dimethylallyl bromide. Then *dl*-DMAT (**121**) was synthesized from the above gramine **153** according to Plieninger's method (*68*). On conversion of *dl*-**121** to the phenacyl amide **154**, enzymatic kinetic resolution of **154** afforded enantiomerically pure (–)-DMAT (**121**) with 98% ee (Scheme 30).

Recently, Yokoyama and Murakami reported another synthesis of optically active DMAT (**121**) (*70*). Dehydration of **142** gave the unstable diene **155**



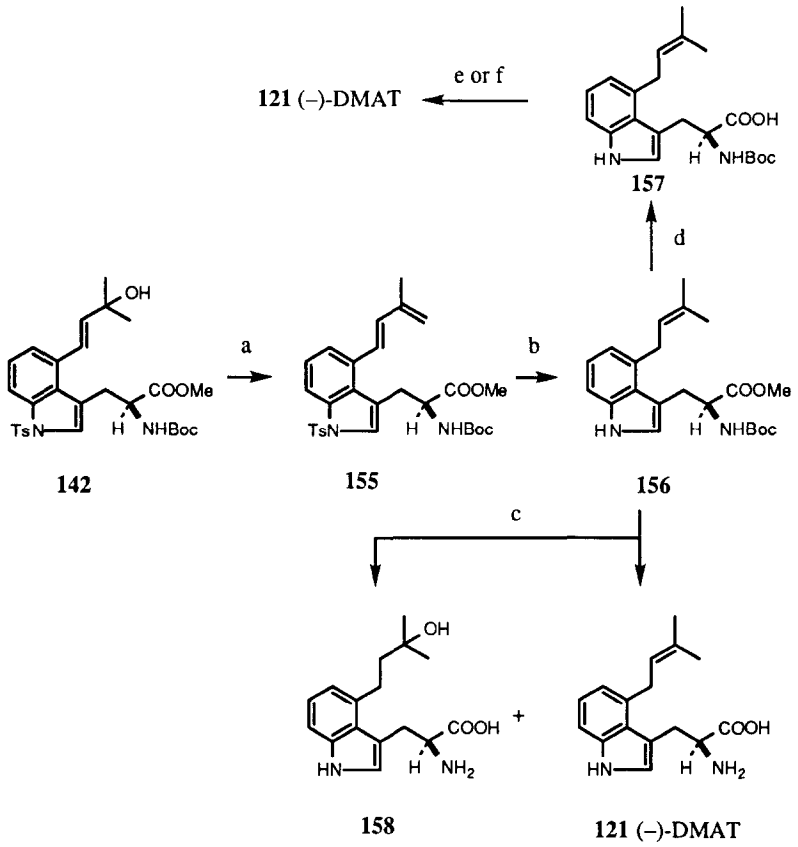
SCHEME 30. Reagents: a, *t*-BuLi; b, $BrCH_2CH{=}C(Me)_2$; c, BnCOCl; d, Penicillin G Acylase.

which was then treated with magnesium-methanol for reduction of the diene moiety in a 1,4 manner. Concomitant detosylation gave *N*-Boc-DMAT methyl ester (**156**). Since the optical purities of **142** and **156** were 93% and 91%, respectively, racemization was negligible. Alkaline hydrolysis of the ester **156** gave the acid **157** in 92% yield, and the Boc group was removed by heating in acetic acid at 120°C (Scheme 31).

Although (–)-**121** was obtained as the sole product in 57% yield, serious racemization occurred (25% ee). On investigation it was found that hydrolysis of the ester **156** in 50% aq. acetic acid proceeded smoothly at lower temperature (80°C) to give (–)-DMAT (**121**) without racemization (94% ee) and in good yield (90%) (Scheme 31). Low temperature treatment thus might minimize both the racemization and the addition of water to the double bond **158**.

4. Synthesis of Optically Active Chanoclavine I

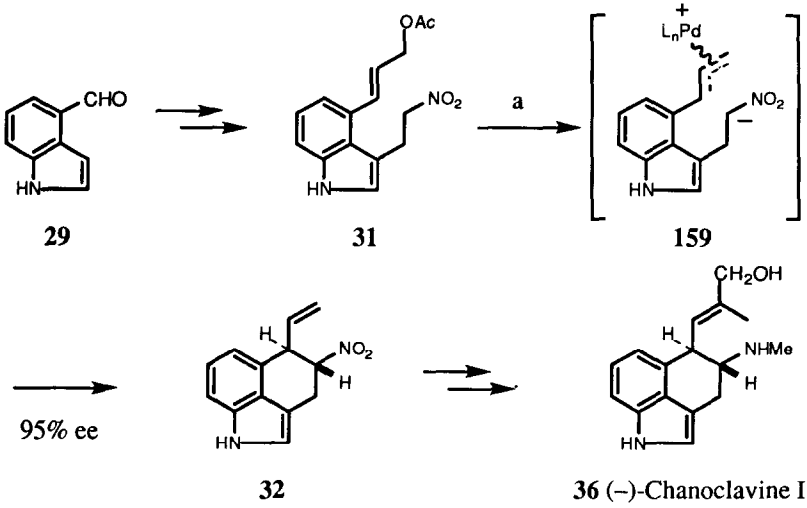
Chanoclavine I belongs to a class of 6,7-secoagroclavines having a tricyclic ring system. Its occurrence has a special significance since it is an important intermediate in the biosynthesis of tetracyclic ergolines, including lysergic acid (**1**) (*4*). Although *dl*-chanoclavine I (**36**) was synthesized previously by several groups (*29–33*), there were only a few reports on the synthesis in optically active form. In 1994, French chemists (*35,36*) reported the first asymmetric total synthesis of chanoclavine I (**36**) in 12 steps involving a process of the formation of C ring by asymmetric palladium-catalyzed cyclization as the key



SCHEME 31. Reagents: a, TsOH, benzene; b, Mg, MeOH; c, 50% aq. AcOH, sealed tube; d, 4% KOH-dioxane; e, 120°C, AcOH; f, 80°C, 50% aq. AcOH.

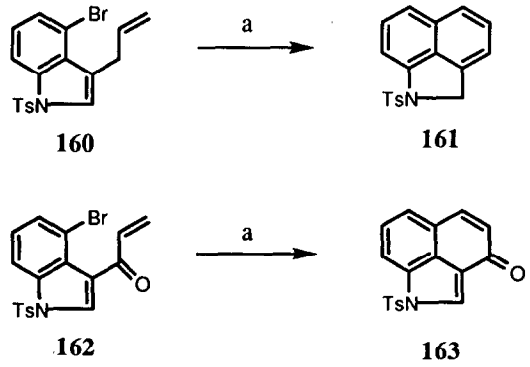
step via the π-allyl complex **159** with a chiral phosphine ligand (Scheme 32).

In order to use tryptophan as the starting material for the construction of an ergoline skeleton, it was necessary to develop an intramolecular cyclization for the formation of cyclohexa[*cd*]indole. For this purpose, there were several methods reported, particularly through the formation of a cyclohexa[*cd*]indole. Hegedus's group (*71*) developed a route by applying the Heck reacton to the cyclization of 3-allyl-4-bromo-*N*-tosylindole (**160**). Although they succeeded in synthesizing a tricyclic ring system, rearrangement of the double bond in the product occurred to form the more stable naphthalene derivative **161**. Further, Hegedus (*72*) attempted a similar cyclization of the α,β-unsaturated ketone **162**

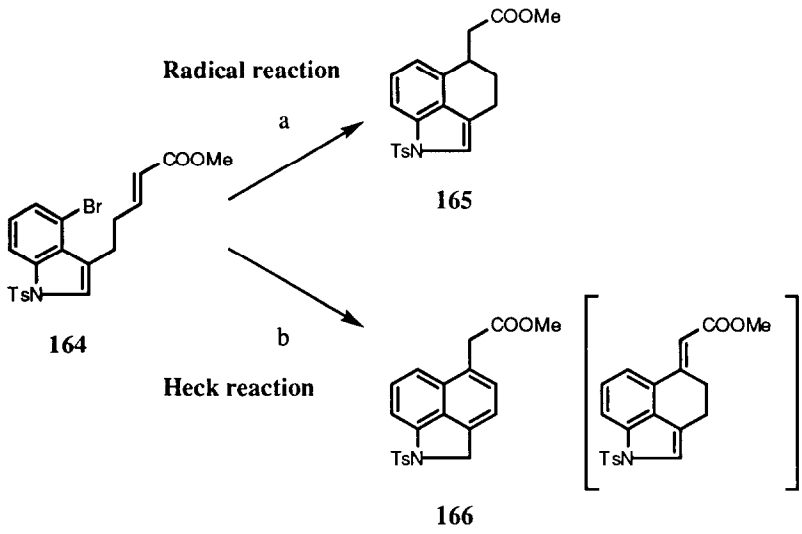


SCHEME 32. Reagents: a, $Pd(OAc)_2$, K_2CO_3, (*S*)-BINAP, THF.

to synthesize the tricyclic ketone **163** (Scheme 33). The presence of a keto group blocked rearrangement to the benz[*cd*]indoline system.



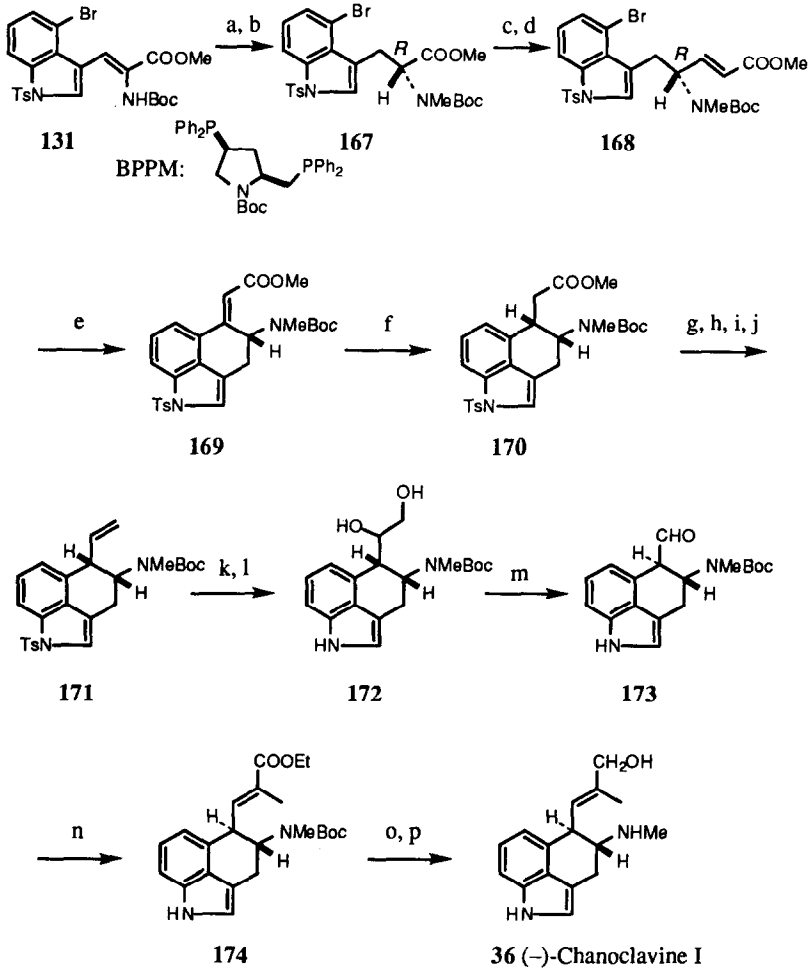
SCHEME 33. Reagents: a, $Pd(OAc)_2$, (*o*-tol)$_3$P, Et_3N in CH_3CN.



SCHEME 34. Reagents: a, $(n\text{-Bu})_3SnH$, AIBN, toluene; b, 0.1 eq. $PdCl_2(PPh_3)_2$, DMF-Et_3N.

Yokoyama *et al.* (*73,74*) also attempted an intramolecular palladium-catalyzed vinylation (Heck reaction) or radical reaction of the 4-bromoindole derivative **164** carrying an α,β-unsaturated ester group in the 3-substituent. Though the Heck reaction on this compound **164** was unsuccessful to give **166**, radical cyclization of **164** resulted in the desired tricyclic ring system **165** in moderate yield (Scheme 34). Accumulating the information on the reactions and results of these reactions, including the Heck reaction, aimed at the synthesis of chanoclavine I (**36**), the strategy for the synthesis of this alkaloid by the cyclization of tryptophan derivatives finally allowed completion of the total synthesis.

Optically active, doubly-protected 4-bromo-*N*-methyltryptophan **167** was prepared by asymmetric reduction of the corresponding dehydrotryptophan derivative **131**. The optical yield, however, was 55% ee, when BBPM was used as a chiral phosphine ligand. The absolute configuration of **167** was *R*, opposite to that of the natural amino acid, but this configuration was required for the synthesis of the natural ergoline alkaloids. Palladium-catalyzed intramolecular cyclization of the optically active conjugated ester **168**, which was prepared from **167**, proceeded smoothly in the presence of 1,3-bisdiphenylphosphino-propane (BPPP) and tribasic silver phosphonate-calcium carbonate to give the expected tricyclic ester **169** in good yield.



SCHEME 35. Reagents: a, MeI, Ag_2CO_3; b, $[Rh(COD)_2]BF_4$, BPPM, H_2, 5 atm; c, DIBALH; d, $Ph_3P{=}CHCO_2Me$; e, 0.1 eq. $PdCl_2$-BPPP, Ag_3PO_4, $CaCO_3$, DMF; f, H_2, 10% Pd-C; g, Li[Bu(*iso*-Bu)$_2$AlH], THF; h, $NaBH_4$, EtOH; i, *o*-NO_2PhSeCN, (*n*-Bu)$_3$P, pyridine-THF; j, $NaIO_4$, THF-H_2O; k, OsO_4 (cat.), NMO, Acetone-H_2O; l, Mg, MeOH; m, $NaIO_4$, MeOH-H_2O; n, $Ph_3P{=}C(Me)COOEt$, CH_2Cl_2; o, TFA, $CHCl_3$; p, DIBALH, THF.

On the other hand, radical cyclization of **168** by heating with tri-*n*-butyltin hydride and AIBN did not occur, only recovering the starting material. These

confusing results compared to the above preliminary experiment might be explained by a rigid conformation of the C ring due to the presence of a bulky protective group on the amino group in **168**. Catalytic reduction of the tricyclic compound **169** gave the homogeneous product **170** with an undesired *cis* configuration. Conversion of the ester **170** to the olefin **171** was accomplished smoothly by a straightforward four-step sequence of reactions including one-pot reduction, selenylation and *syn*-elimination. The optical purities of the products **168** and **171** were both 55% ee determined by HPLC, thus proving that no racemization was involved in the processes of the conversion [**167** to **168**] and cyclization steps [**168** to **169**] (Scheme 35).

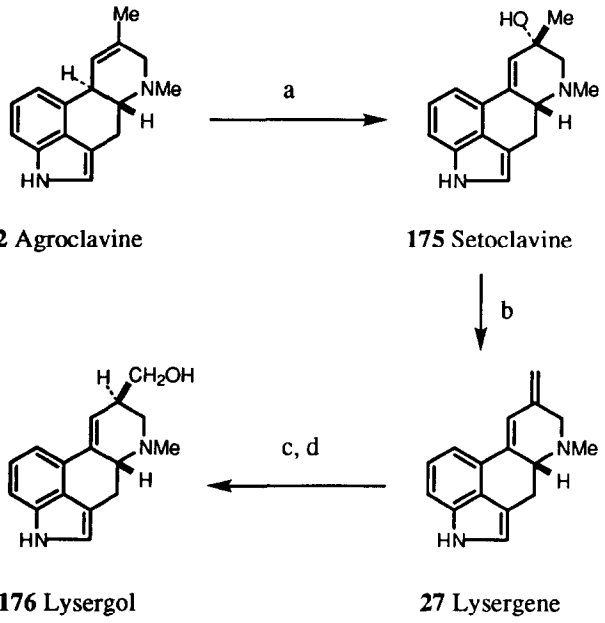
Oxidation of the olefin **171** with osmium tetroxide-NMO, followed by deprotection of the tosyl group with magnesium-methanol and cleavage of the diol with sodium periodate, gave the unstable aldehyde **173** which was immediately converted to the ester **174** by the Wittig reaction. Ready isomerization to the stable *trans* isomer **173** brought about the sole formation of the product with a *trans* configuration. Finally, the conversion of **174** to chanoclavine I (**36**) was carried out according to Oppolzer's procedure (*32*). The synthetic compound, which showed 75% ee after one recrystallization, had the same optical rotation as the natural alkaloid.

V. Interconversion of Ergoline Alkaloids

Most of the important conversions and interconversions of ergoline alkaloids were reported in the previous review (*3*). However, some further conversions were described in the literature based on a need for supply of the alkaloids.

A. Conversion of Agroclavine to Lysergol

Based on the previous results of the oxidative conversion of setoclavine (**175**) to lysergene (**27**), agroclavine (**62**), now readily available by the fermentation of *Claviceps purpurea* AA218, was successfully converted into lysergol (**176**) by functionalizing the 8-methyl group of agroclavine (**62**) (*75*). Regioselective dehydration of setoclavine (**175**) to lysergene (**27**) was achieved by heating **175** under reflux with predried Woelm alumina N-super 1 (type W200) in 1,2-dichloroethane to give lysergene (**27**). Then the exocyclic double bond was selectively hydroborated with 9-BBN at 60°C in tetrahydrofuran. Treatment of the adduct with aqueous sodium hydroxide and 30% hydrogen peroxide gave lysergol (**176**) (Scheme 36).



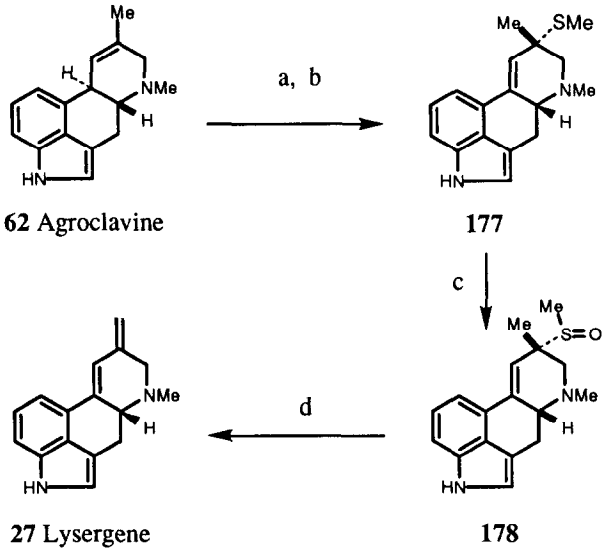
62 Agroclavine **175** Setoclavine

176 Lysergol **27** Lysergene

SCHEME 36. Reagents: a, $K_2Cr_2O_7$, c H_2SO_4, aq. acetone; b, Woelm alumina, $ClCH_2CH_2Cl$; c, 9-BBN, THF; d, NaOH, H_2O_2.

B. CONVERSION OF AGROCLAVINE TO LYSERGENE AND LYSERGINE

Ready availability of one of the most useful ergoline alkaloids agroclavine (**62**) has continuously drawn attention for its conversion to other ergot alkaloids (*76*). The hydrogen at C-10 of agroclavine (**62**) was readily removed by *n*-butyllithium to form an ambident carbanion which was then treated with a range of electrophiles to yield 10-substituted agroclavines, 8-substituted lysergines and isolysergic acid derivatives, one of which, 8-methylthio-lysergine (**177**), was prepared by the addition of dimethyl sulfide to agroclavine (**62**). The 8-methylthiolysergine (**177**) was then oxidized with sodium periodate to the sulfoxide **178**, and the methylthio group was eliminated in 40% yield to give the lysergene (**27**) (Scheme 37).



62 Agroclavine **177**

27 Lysergene **178**

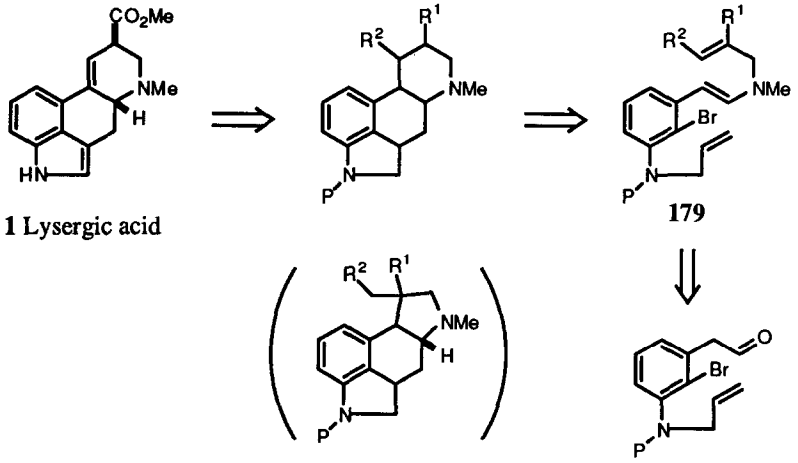
SCHEME 37. Reagents: a, *n*-BuLi, THF; b, MeSSMe; c, $NaIO_4$, aq, MeOH; d, heat.

VI. Reactions Developed for the Synthesis of Ergoline Alkaloids

Development of reactions designed or intended for the synthesis of ergot alkaloids and their analogs are summarized in this section, though successful invention and application of new synthetic methodologies were described in the section of new syntheses of ergoline alkaloids (Sections III and IV). There have been many reports describing the accumulated efforts and ideas aimed at the synthesis of natural products by new methods. In this section we have tried to collect these ideas in order to give chemists some concepts of the routes that have been investigated.

A. TANDEM RADICAL CYCLIZATION FOR THE CONSTRUCTION OF THE ERGOLINE SKELETON

Parsons *et al.* have developed a new free radical cyclization with the potential for application to the construction of the lysergic acid framework by a reaction



1 Lysergic acid

179

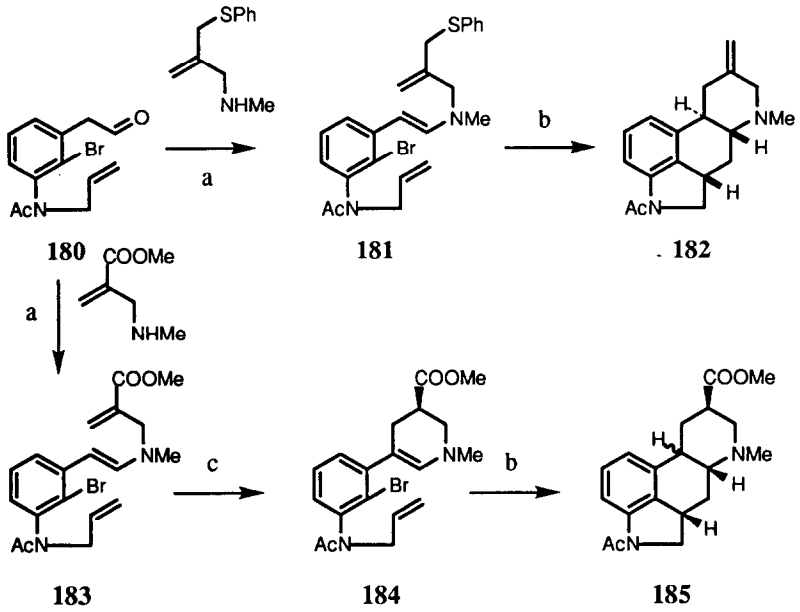
SCHEME 38. Retrosynthetic analysis.

involving the homolytic cleavage of a carbon-bromine bond, mediated by tri-*n*-butyltin hydride (*77*). This led to the development of a method for the construction of 3,4-disubstituted dihydroindoles via a single cyclization; hexahydrobenz[*cd*]indoles via double tandem cyclizations, and both octahydroindolo[6,5,4-*cd*]indoles and decahydroindolo[4,3-*fg*]quinolines via triple radical cyclizations of **179**. These synthetic ideas can be appreciated readily from the retrosynthetic scheme shown (Scheme 38).

Allyl sulfides have been used in radical cyclization to control the regiochemistry in 6-endo ring closures. This, indeed was found to be the case when the enamine **181** was subjected to radical cyclization under high dilution conditions. The ergoline **182** was isolated after successful 5-*exo*-trig, 6-*endo*-trig, 6-*endo*-trig cyclization.

The uncyclized enamine **183** was treated in boiling toluene for 5 h. prior to radical cyclization, and then further treated with tri-*n*-butyltin hydride in boiling toluene. A successful tandem double 5-*exo*-trig, 6-*endo*-trig cyclization of the aryl radical generated from **184** afforded the tetrahydrolysergate **185** which was obtained as the only isolable product in 75% yield as a 3:1 mixture of two epimers at the 10-position (Scheme 39).

Although introduction of a 9,10-double bond in the lysergic acid framework remains unaccomplished, this tandem radical cyclization approach can be used for the synthesis of tetrahydrolysergic acid derivatives. With the appropriate choice of starting materials, the synthesis of other ergot alkaloids and their synthetic derivatives could be achieved using this novel approach.

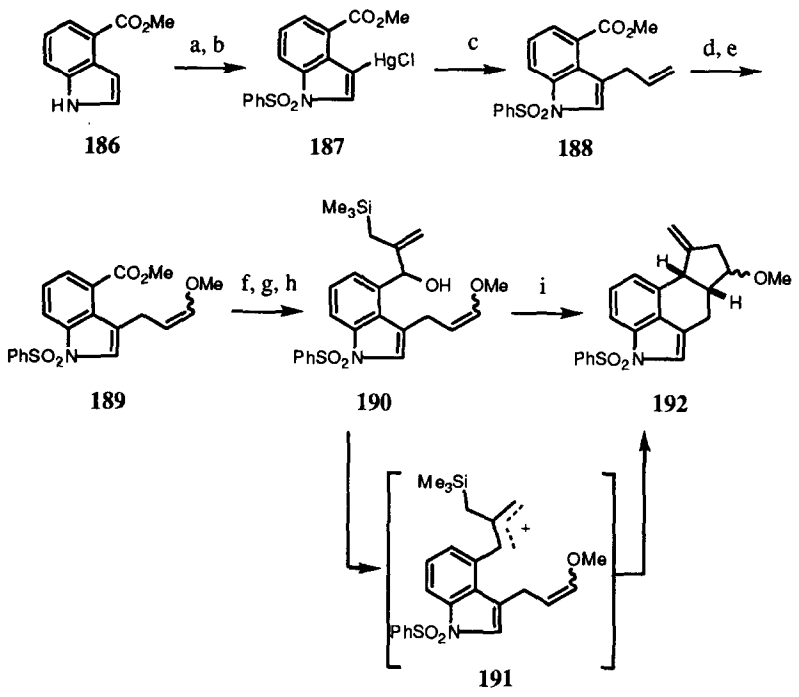


SCHEME 39. Reagents: a, molecular sieves, toluene; b, $(n\text{-Bu})_3SnH$; c, toluene [thermal cyclization].

B. INTRAMOLECULAR CYCLIZATION OF AN ALLYL CATION FOR THE SYNTHESIS OF THE ERGOLINE SKELETON

The intramolecular cyclization reaction involving the allyl cation **191** derived from the 3,4-disubstituted indole **190** was applied to the construction of the ergoline skeleton *(78)*.

4-Carbomethoxyindole (**186**) was reacted with benzenesulfonyl chloride in the presence of tetrabutylammonium hydroxide to yield the *N*-benzenesulfonamide in 95% yield. Treatment with mercuric acetate in acetic acid followed by aqueous sodium chloride yielded the indole-mercurichloride **187** quantitatively. Palladium-catalyzed coupling of the mercury salt with allyl bromide in the presence of Li_2PdCl_4 provided a fair yield of the 3-allylindole **188**. Cleavage of the alkene was achieved using catalytic osmium tetroxide and excess sodium periodate to form the desired aldehyde in 81% yield. This aldehyde was converted into the enol ether **189** in 95% yield, with a 1 : 1 ratio



SCHEME 40. Reagents: a, $PhSO_2Cl$, KOH, $(n\text{-}Bu)_4NOH$; b, $Hg(OAc)_2$, AcOH, cat. perchloric acid; c, allyl bromide, Li_2PdCl_4, MeOH; d, OsO_4, NMO then $NaIO_4$; e, $Ph_3PCHOMe{\cdot}HCl$, *t*-BuLi; f, DIBALH; g, MnO_2; h, Mg, 2-bromo-3-trimethylsilylpropene; i, $TiCl_4$, *N*-methylaniline.

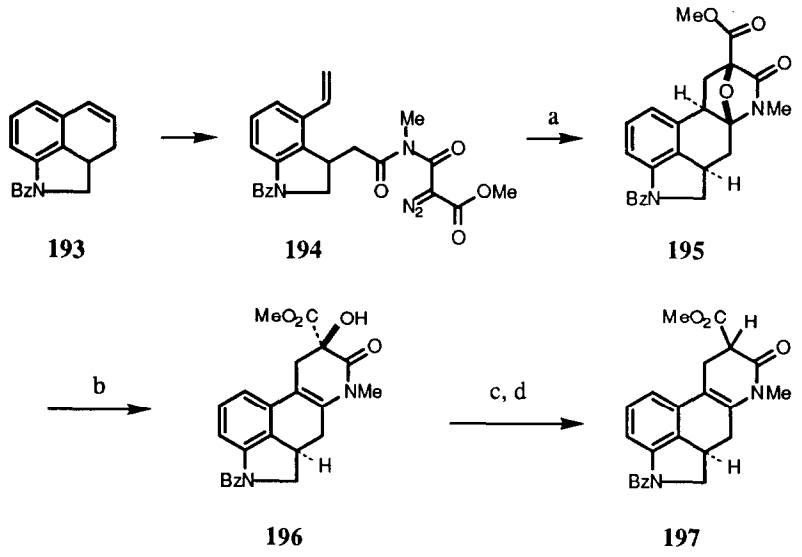
of the *cis* and *trans* mixed products, using methoxymethyltriphenylphosphonium chloride in conjunction with 2.2 equivalents of *t*-butyllithium. Finally, reduction of the ester **189** with DIBALH and reoxidation with manganese(IV) oxide provided the aldehyde in 84% yield. which was then reacted with the Grignard reagent formed from 2-bromo-3-trimethylsilylpropene to produce the key intermediate **190** in 62% yield. The intramolecular cycloaddition was achieved through reaction of **190** in the presence of $TiCl_4$ and *N*-methylaniline to yield a 1:1 mixture of two cycloadducts **192** (Scheme 40). This compound, **192**, was to serve as the synthetic precursor for the ergoline alkaloids.

C. Intramolecular Isomunchnone Cycloaddition Pathway to Lysergic Acid

As a viable approach to the synthesis of lysergic acid, intramolecular cycloaddition of alkenyl- and alkynyl-substituted diazoimides **194** across a transient isomunchnone dipole was investigated, aiming at the construction of the ring system of the quinoline ring system (C and D rings) of the ergot alkaloids (*79*).

Although the inability to carry out a double bond isomerization to the position required for lysergic acid is a drawback, this unique route of constructing the skeleton of the target alkaloid has the potential to become a new synthetic methodology for lysergic acid.

The known tricyclic olefin **193** was oxidatively ring opened at the olefinic ring to give an indoline derivative which was transformed to the starting prerequisite diazo imide **194**. The rhodium-catalyzed reaction of **194** proceeded smoothly, using rhodium(II) perfluorobutyrate as the catalyst, to give the cycloadduct **195** as the exclusive product in 93% yield. The conversion of the cycloadduct **195** to methyl paspalate was undertaken by treating **195** with



193 **194** **195**

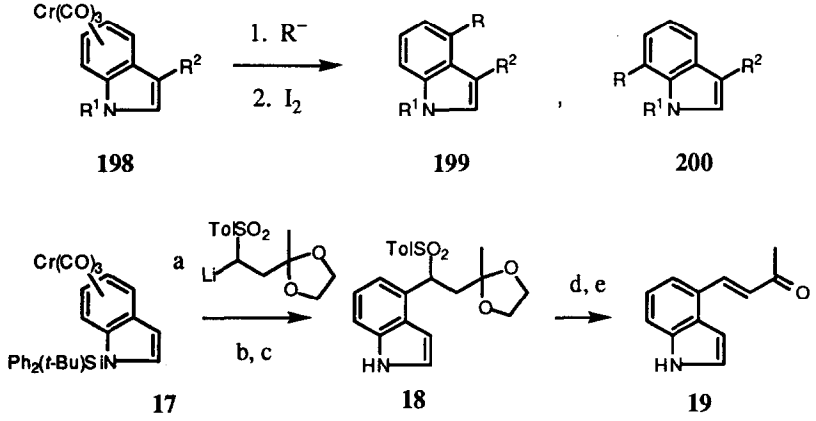
196 **197**

Scheme 41. Reagents: a, $[(CF_3CF_2CF_2CO_2)_2Rh]_2$, CH_2Cl_2; b, $BF_3{\cdot}OEt_2$, CH_2Cl_2; c, phenyl chloroformate; d, $(n\text{-}Bu)_3SnH$, AIBN, Δ.

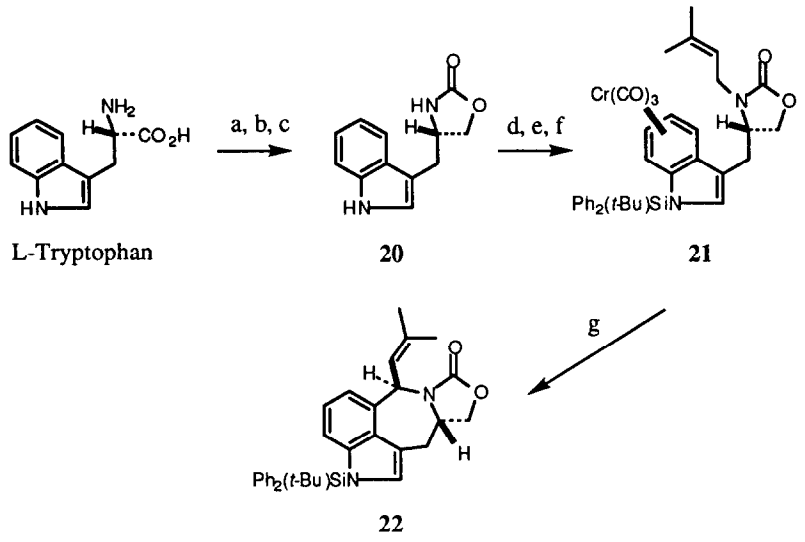
boron trifluoride etherate in dichloromethane to furnish the expected tetrasubstituted enamide **196** in quantitative yield. The Barton- McCombie reaction, using the phenyl thiocarbonate derivative with tri-*n*-butyltin hydride, afforded the expected deoxygenated amido ester **197** as a 2:1 mixture of diastereomers, which, however, resisted all attempts, using a variety of bases, to isomerize the double bond (Scheme 41).

D. Use of an Indole Chromium Complex for the Synthesis of Ergot Alkaloids

The activating effect of π-complexation of a $Cr(CO)_3$ unit allows selective nucleophilic substitution in indoles, including tryptophan derivatives, and thus provides intermediates for the synthesis of clavicipitic acid and related indole alkaloids. The addition of a nucleophile to an *N*-protected indole-$Cr(CO)_3$ complex **198** provided **199** and/or **200** for the regioselective introduction of a substituent at C-4 or C-7 on the indole ring, depending on the substituents at C-3 and N-1, as well as the nature of the nucleophile (*80*). This methodology was successfully applied to indole itself (*28*). Indole is readily transformed into the corresponding tricarbonylchromium complex and silylated with *t*-butylchloro-diphenylsilane to produce the crystalline complex **17**. The addition of **17** to a solution of the lithiated sulfone, followed by oxidative quenching with iodine and desilylation, furnished the C-4 substituted indole **18** in 90% yield. The indole **18** was converted to the enone **19** with the alkenyl side chain at the 4-position in 78% yield by sequential acid and base treatment (Scheme 42).



Scheme 42. Reagents: b, I_2; c, TBAF; d, cat. TsOH; e, Et_3N.



L-Tryptophan **20** **21**

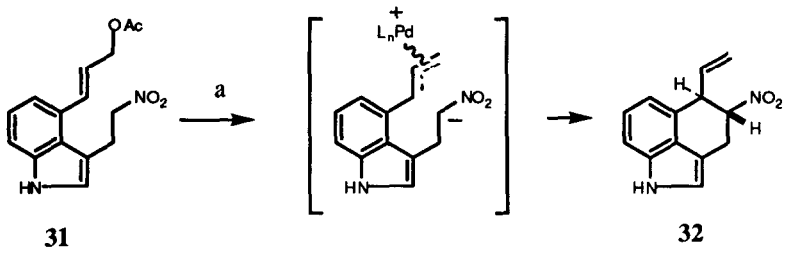
22

SCHEME 43. Reagents: a, $LiAlH_4$; b, NaOH; c, $COCl_2$; d, $Cr(CO)_3(MeCN)_3$; e NaH, $Ph_2(t\text{-Bu})SiCl$; f, MeLi, $(Me)_2C{=}C(H)CH_2Br$; g, LDA, then I_2.

A similar sequence of reactions was applied to L-tryptophan, and the subcequent conversion of the resulting amino alcohol into the oxazolidinone **20** proceeded in 82% yield (*28*). Following formation of the tricarbonylchromium complex **21**, treatment with LDA and iodine yielded the synthetic precursor **22** of clavicipitic acid (**84**,**85**) (Scheme 43).

E. ENANTIOSELECTIVE PALLADIUM-CATALYZED CARBOCYCLIZATION OF NITROACETATE FOR THE ERGOLINE SKELETON

Genet *et al.* (*35*) have developed an intermolecular, palladium-catalyzed alkylation of a nitroacetate, and applied the reaction to its intramolecular version using chiral ligands on the metal for the synthesis of the C ring of ergoline synthons in an optically active fashion. The preparation of these chiral synthons **32** was achieved by palladium-catalyzed enantioselective carbocyclization of the bifunctional nitroacetate **31**, synthesized from 4-formylindole. On exposing **31** to $Pd(dba)_2$ and (*S*)-CHIRAPHOS with potassium carbonate as the base, the chiral derivative **32** was obtained on a practical scale with an acceptable level of optical purity (69% ee). Genet *et al.* optimized these results by employing



31 **32**

SCHEME 44. Reagents: a, $Pd(OAc)_2$, K_2CO_3, (*S*)-BINAP.

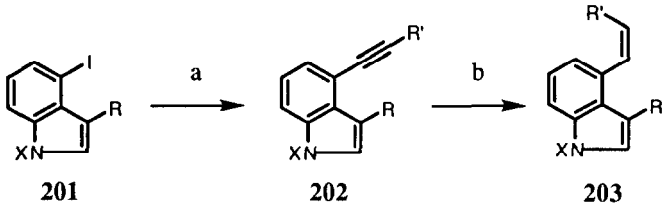
$Pd(OAc)_2$ and (*S*)-BINAP. The desired enantiomer **32** was obtained enantioselectively with a 95% ee (*36*) (Scheme 44).

This catalytic, enantioselective, palladium(0)-promoted C-5, C-10 ring closure provides a simple, direct and versatile synthesis of chiral ergoline compounds.

F. PALLADIUM-CATALYZED REACTIONS OF 3-ALKENYL-4-IODOINDOLES FOR THE SYNTHESIS OF 3,4-DISUBSTITUTED INDOLES

Palladium-catalyzed coupling of 4-iodoindoles with acetylenes established the smooth synthesis of 3,4-disubstituted indole derivatives suitable for the synthesis of ergoline alkaloids. Szántay *et al.* (*81*) thoroughly investigated the conditions of the relatively harsh conditions of the Heck reaction and succeeded in establishing satisfactory conditions for the substitution of 4-iodoindoles **201**. They examined four different 4-iodoindoles **201** with various electron densities in the aromatic ring, and three different palladium catalyst systems of $[Ph_3P]_4P$, $[Ph_3P]_2PdCl_2$, as well as $[Ph_3P]_4Pd$, generated *in situ* from Pd-C and triphenyl phosphine, for the addition of various acetylenes. As a result, they found that the reaction proceeded well on a scale of 1 mmol in DMF (ca. 20-30 mg/ml indole concentration) under argon atmosphere in the presence of 2 equivalents of triethylamine as base, in addition to the use of 2-5 equivalents of acetylene, 0.2 equivalents of cuprous iodide, and 0.02 equivalents of the palladium catalyst. The reactions were run at room temperature, giving mostly fair to good yields of chromatographically pure products (Scheme 45).

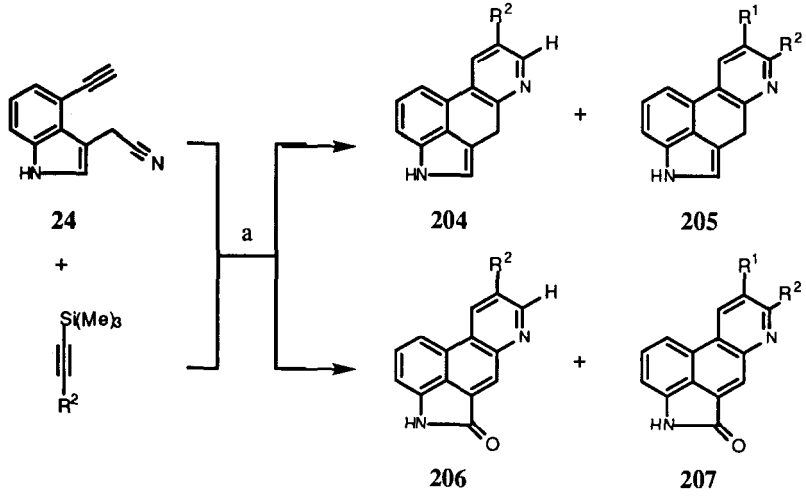
The acetylenic indoles **202** were partially saturated over the Lindlar catalyst to **203**, which was transformed previously to secoagroclavine by Somei *et al.* (*82*). Thus, these reaction conditions could provide a promising opportunity for the synthesis of many ergoline alkaloids.



SCHEME 45. Reagents: a, [Pd], CuI, Et_3N, DMF, H—≡—R' ; b, Lindlar catalyst.

G. COBALT-CATALYZED COCYCLIZATION OF 4-ETHYNYL-3-INDOLEACETONITRILES WITH ACETYLENES

4-Ethynyl-3-indoleacetonitriles (**24**), which were readily prepared from the corresponding 4-bromo precursors followed by palladium-catalyzed trimethylsilylethynylation-deprotection, were reacted with acetylenes in the presence of $CpCo(CO)_2$ catalyst to give rise to a mixture of the compounds **204–207** having the structure of the annelated tetracyclic ergot framework in one step (*14*) (Scheme 46). Although the formation of several products was not desired, this cocyclization reaction has several advantages for forming the ergoline skeleton in one step.



SCHEME 46. Reagents: a, $CpCo(CO)_2$, Δ, *hν*.

VII. Further Developments on the Synthetic Supply of Key Intermediates Useful in the Synthesis of Ergot Alkaloids

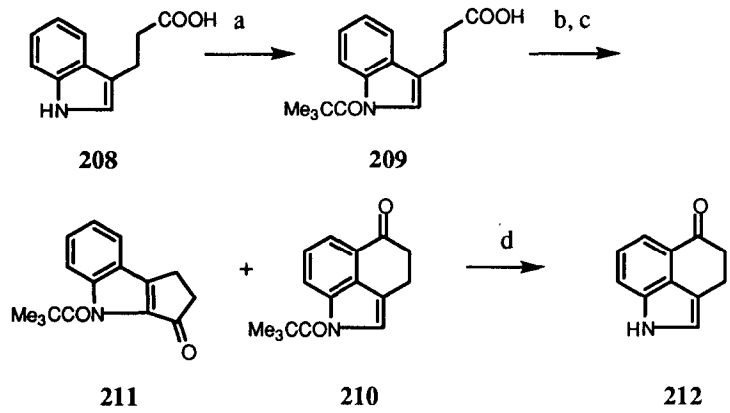
Due to the complexity of the structure of the ergot alkaloids and their remarkable biological potency, many synthetic approaches have accumulated. In addition, the establishment of convenient and facile synthetic procedures for the key synthetic intermediates have been sought as exemplified by the key intermediate tricyclic ketone in the synthesis by Woodward and Kornfeld. Actually, in many of the total syntheses of the ergot alkaloids, success has depended on the development of the convenient and efficient supply of the key intermediates.

Therefore, for synthetic studies aimed at the development of new medicinals, some of the most important and useful synthetic methods for key synthetic intermediates are selected as follows.

A. Facile Synthesis of Uhle's Ketone

A facile synthesis of Uhle's ketone (**212**) starting from indolepropionic acid **208** was reported (*83*).

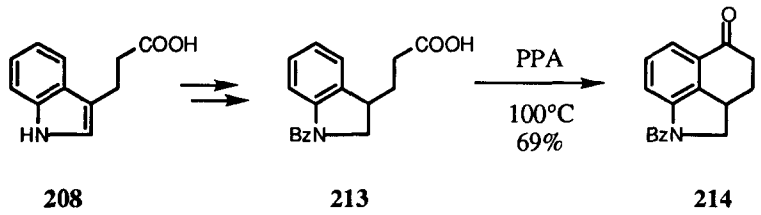
Uhle's ketone (**212**) was first synthesized from 6-chloro-2-nitrotoluene in eight steps by Uhle in 1949 (*84*), and has played an important key role in the synthesis of lysergic acid and many other indole derivatives. The increased importance of this ketone prompted the establishment of a facile synthetic supply of this ketone as one of the important starting compounds for the study of ergoline derivatives. Recently, Nakatsuka *et al.* (*83*) described a highly regioselective cyclization for the synthesis of Uhle's ketone from indolepropionic acid (**208**) using a novel Friedel-Crafts cyclization system. 3-(1-Trimethylacetylindol-3-yl)propionic acid (**209**) was prepared by trimethylacetylation of the starting indolepropionic acid **208** with *n*-butyllithium and trimethylacetyl chloride in tetrahydrofuran at –78°C in 91% yield. Compound **209** was treated with thionyl chloride to give the acid chloride which was then stirred with aluminum chloride in 1,2-dichloroethane at –10°C for 3 h. or at 10°C for 0.3 h. to give the cyclized products as a mixture of the two ketones **210** and **211**. Yields and relative ratios depended on the reaction temperature. The best result was obtained at 15°C for 1 h. in 83% combined yield and a 94:6 ratio. This cyclization was catalyzed by the reagent formed *in situ* from chloroacetyl chloride and aluminum chloride, which would generate a donor-acceptor complex species as an electron acceptor *in situ*. Removal of the trimethylacetyl moiety was achieved with catalytic sodium methoxide in methanol at 15°C for 10 min. giving Uhle's ketone (**212**) in 95% yield (Scheme 47).



SCHEME 47. Reagents: a, *n*-BuLi, Me_3CCOCl; b, $SOCl_2$; c, $AlCl_3$, additive ($ClCH_2COCl$), $ClCH_2CH_2Cl$; d, $NaHCO_3$, MeOH.

B. IMPROVED SYNTHESIS OF KORNFELD'S TRICYCLIC KETONE

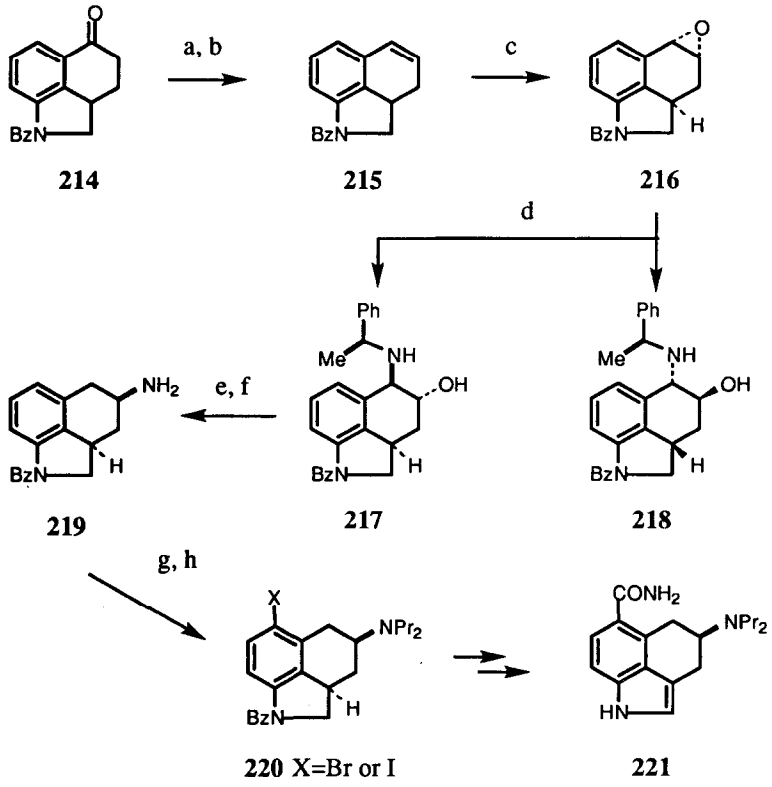
The tricyclic ketone (Kornfeld's ketone) **214** is well-known as the starting ketone in the first total synthesis of lysergic acid. Since then, a number of synthetic studies have employed this tricyclic ketone for the synthesis of lysergic acid and other ergoline alkaloids. This ketone **214** is now readily prepared from indolepropionic acid (**208**) according to the original route, but under improved reaction conditions (*85*) to give a good yield of this tricyclic ketone **214**. In practice the cyclization by polyphosphoric acid proceeded very smoothly at 100°C for 2 h. After cooling, the reaction mixture was simply poured into ice-water and extracted with dichloromethane, washed with water and dried. This simple and convenient procedure yields the ketone **214** in 69% (Scheme 48).



SCHEME 48

C. SYNTHESIS OF A TRICYCLIC AMINE DERIVED FROM KORNFELD'S KETONE

The utilities of Kornfeld's ketone **214** continues to attract interest, particularly for the synthesis of potential analogs related to the serotonin receptors. Martinelli and coworkers (*86*) have succeeded in synthesizing the aminotetralin derivatives which possess a tricyclic amine structure, and which are target drug candidates for clinical evaluation. They started their synthetic route from Kornfeld's ketone **214**, which was reduced with sodium borohydride. Subsequent dehydration afforded the crystalline olefin **215** in excellent yield. Epoxidation of this olefin with peracids proceeded highly



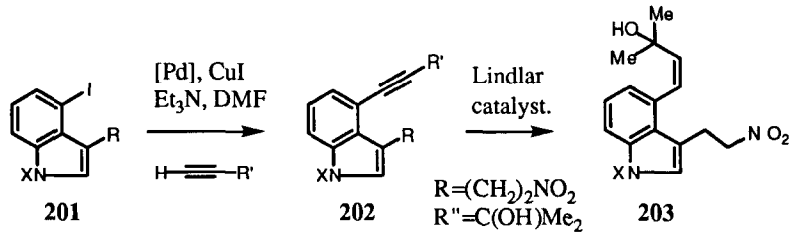
SCHEME 49. Reagents: a, $NaBH_4$; b, Amberlist 15; c, monomagnesium-peroxyphthalate, H_2O, *n*-BuOH; d, (*S*)-phenethylamine, *n*-BuOH; e, MsCl, Et_3N; f, Pd-C, H_2, H_3PO_4; g, Br_2, NaOAc or H_3IO_4; h, PrI, K_2CO_3.

stereoselectively affording primarily the *anti*-epoxides **216** with >96% de. Epoxide ring opening of **216** was best conducted in *n*-butanol at 110°C, thus fitting very well with the epoxide forming step above in the same solvent. Consequently, a solution of the racemic epoxide when reacted with an optically pure amine, such as (*S*)-α-phenethylamine, produced a 1:1 mixture of the diastereomers **217** and **218**, which, on cooling, provided the single isomer **217** in 43% yield. Mesylation of **217** was successfully carried out using methanesulfonyl chloride and triethylamine, giving rise to an aziridine which was then subjected to tandem benzylic hydrogenolysis in the presence of a palladium catalyst to give the optically active aminotetralin **219**. The usefulness of the tricyclic amine **219** was clear from its facile conversions, including regioselective, aromatic electrophilic *para*-substitution on the indoline moiety to afford the carbamoyl group substituted derivatives, and simple *N,N*-dialkylation to a variety of analogs. By utilizing the tricyclic amine **219**, a number of lysergic acid diethylamide analogs were synthesized (*86,87*) (Scheme 49).

D. Synthesis of 3,4-Disubstituted Indoles

Since the structural features of 3,4-disubstituted indoles are abundantly seen in the structures of various alkaloids, a number of synthetic approaches have appeared in the literature for the preparation of indole derivatives with the 3,4-disubstitution pattern. One of the recent methods was disclosed by Somei *et al.* (*37,88*) who took advantage of the reaction of thallium/iodination of a 3-carbonyl substituted indole, followed by the Heck reaction, for the preparation of a number of derivatives.

Szántay *et al.* (*81*) modified the original method by Somei by applying the



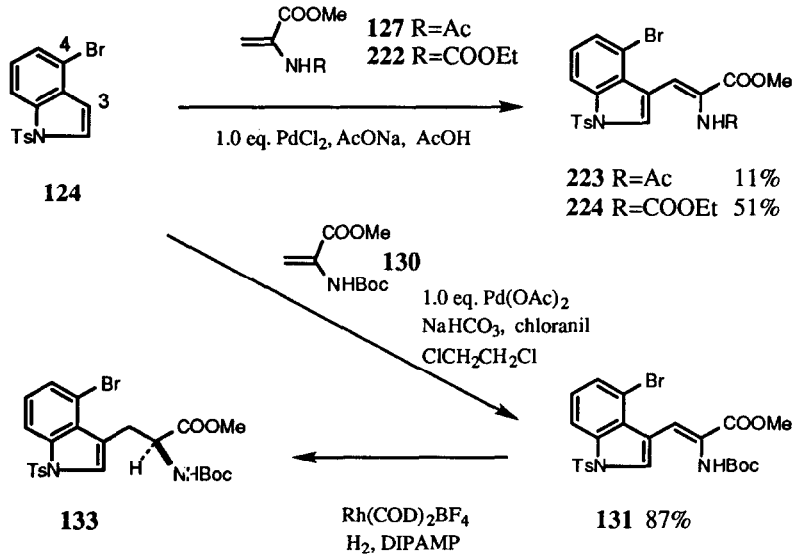
R=$(CH_2)_2NO_2$, $CH{=}CHNO_2$ (*E*)
R'=TMS, *n*-Bu, $C(OH)Me_2$

Scheme 50

Cu(I)-Pd(0) coupling of terminal acetylenes with the indole systems **201** at the 4-position, thereby improving the yield (Scheme 50). The ethynyl group in **202** was partially saturated over the Lindlar catalyst to afford the alkenes **203**, one of which was transformed previously to secoagroclavine (*82*).

E. Synthesis of 4-Bromotryptophan from 4-Bromoindole

In the course of studies aimed at the development of a method for introducing substituents into the indole ring, Yokoyama *et al.* (*61,62,65*) succeeded in a simple synthesis of 4-bromodehydrotryptophan **131** by the vinylation of *N*-tosyl 4-bromoindole (**124**) in the presence of a stoichiometric amount of palladium salt. Vinylation of *N*-acetyldehydroalanine methyl ester **127** and *N*-(ethoxycarbonyl)dehydroalanine methyl ester **222** with **124** occurred in the presence of a stoichiometric amount of $PdCl_2$ to give the corresponding 4-bromodehydrotryptophan **223** and **224**, respectively. This result opened the route for a simple synthesis of tryptophan derivatives. Actual preparation of the 4-bromotryptophan **133** was achieved by the vinylation of 4-bromoindole **124** with the *N*-Boc-dehydroalanine methyl ester **130** in the presence of a stoichiometric amount of $Pd(OAc)_2$. The literature conditions [1.0 equiv. of



Scheme 51

$Pd(OAc)_2$ in AcOH at 120°C for 2 h] (*62*) were not suited for this preparation. However, the compound **131** was obtained in 74-85% yield when the reaction was carried out in the presence of sodium hydrogen carbonate and chloranil as an oxidizing agent in an aprotic solvent, such as 1,2-dichloroethane or 1,2,4-trichlorobenzene. Asymmetric reduction in the presence of a rhodium-complex as catalyst afforded the 4-bromotryptophan **133** (Scheme 51).

VIII. MEDICINALS STRUCTURALLY RELATED TO ERGOLINES

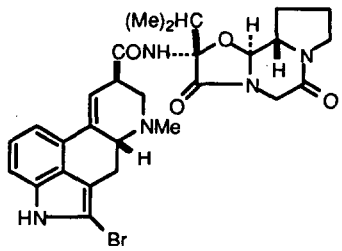
Originating from research on the development of medicinals structurally related to the natural ergoline-type of alkaloids, the ergoline-related major medicinals are summarized below.

The ergot alkaloids and their derivatives display such a diversified range of biological activities that they cannot be regarded within a single pharmacological or therapeutical entity. In spite of a great number of investigations on many derivatives and analogs of ergot alkaloids, aimed establishing the structure-activity relationships, much is yet to be done to reach appropriate conclusions. However, most of the ergoline derivatives, including the natural products and their synthetic analogs, generally exhibit both marked central and peripheral pharmacological activities. The generally non-selective interaction with the adrenalin, dopamine and serotonin receptors accounts for their wide spectra of pharmacological behaviors. The dopamine agonist components D_1 and D_2, which have many important clinical applications in the treatment of Parkinsonism, and the agonist/antagonist serotonergic components 5-HT_{1A}, 5-HT_{1C}, and 5-HT_{2C} with their documented connection with psychiatric disorders, such as depression and anxiety, have fostered interest in this class of compounds by a group of chemists led by Mantegani (*89–94*).

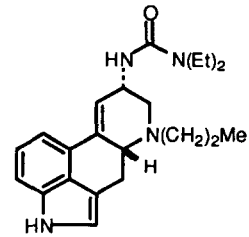
In this section, some of the medicinals with clinical applications are presented.

A. Bromocriptine

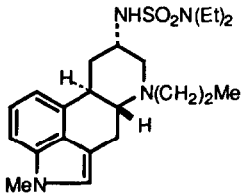
Bromocriptine (**225**) was first introduced in 1969 as a dopamine receptor agonist, produced from derivatives of the ergotoxine group of ergot alkaloids, prepared by the Sandoz group (Fluckiger *et al.*). Following research by many groups, its potentiality as a useful medicinal in the market was established (*95–*



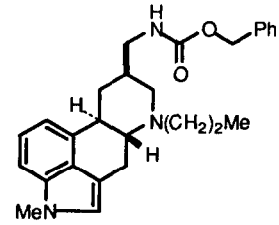
225 Bromocriptine



226 Lisuride



227 Mesulergine



228 Metergoline

97). The relationship between its stereochemistry and biological activity was established in 1980. Many aspects of its biological activity, including its endocrine profile, its usefulness as an immuno-modulator, in obstetrics and in gynecology, and in the treatment of pituitary tumors, have been described, along with clinical studies in the treatment Parkinson's disease.

Bromocriptine (**225**) is available as its methanesulfonate, known as Parlodel, Pravidel, or Serono-Bagren, and now is used as an enzymatic inhibitor for its prolactin and also for antiparkinsonian activity.

The chemisry and biology of bromocriptine (**225**) have been reviewed frequently, e.g. Ho and Thorner (*95*).

B. Lisuride

Structurally closely related to LSD, Lisuride (**226**) is a compound having a 3,3-dimethylureido substituent at the 9-position of the ergoline skeleton, and was first prepared in 1960 as a dopamine D_2-receptor agonist (*98*). Lisuride, as its acid maleate, is commercially available under the names of Cuvalit, Dopergin, Eunal, or Lysenyl, and is used clinically as an antimigraine and also as a prolactin inhibitor. The pharmacological activity and toxicity of lisuride were

reviewed previously in 1963 by L. Votava.

C. MESULERGINE

This compound, **227**, was first introduced by the Sandoz chemist Stutz, who not only had led research on the ergot alkaloids, but also contributed by writing the first review in "Manske's Alkaloids" series in 1982 (*2,99*). The principal structural feature is the *N*,*N*-dimethylsulfamide substituent on the 9-position of the ergoline skeleton, in addition to a methyl group on the indolic nitrogen. Mesulergine (**227**) has a variety of clinical activities, including central dopamine agonistic activity, hypotensive activity comparable to bromocriptine, inhibition of prolactin release, and antiparkinsonism.

D. METERGOLINE

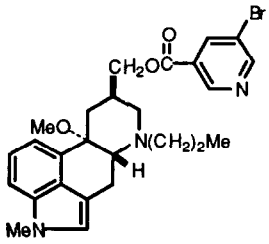
Developed by an Italian group in 1964, this compound, **228**, also known as Liserdol, has the structural features of an aminomethyl group protected by a benzyloxycarbonyl group at the 8-position, along with two methyl groups on both ring nitrogens, which provide a different pharmacological profile for this compound from most of the ergoline derivatives. It is used as an analgesic and antipyretic (*101*).

E. NICERGOLINE

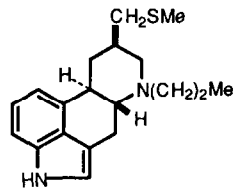
Also known as Nicotergoline and Nimergoline, this compound, **229**, has a characteristic structure at several points, including having a *trans* methanol adduct at the double bond at the 9-position, methyl groups on both ring nitrogens and the 8-hydroxymethyl group protected by a 5-bromonicotinate group. This compound, **229**, was attractive from the aspect of its dopaminergic activity and is used as a vasodilator (*99*).

F. PERGOLIDE

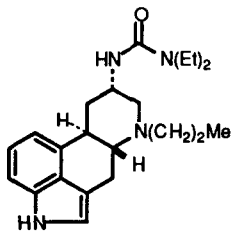
Introduced by Kornfeld and coworkers in 1979 as a dopaminergic agonist that also decreases plasma prolactin concentration, this compound, **230**, shows activity in the treatment of acute myocardial infarction with diastolic hypertension. It is also effective in the treatment of pituitary tumors secreting prolactin or growth hormone (*102*). Its clinical study revealed its effectiveness in Parkinson's disease, and it is now used clinically. This compound, **230**,



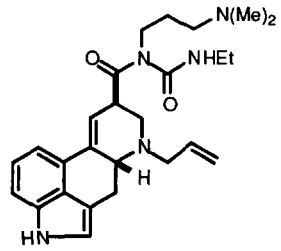
229 Nicergoline



230 Pergolide



231 Terguride



232 Cabergoline

induces the structural feature of a 8β-methylmercaptomethyl substituent, together with an ethyl group on the 6-nitrogen instead of a methyl group.

G. TERGURIDE

This is the dihydrogenated analog of lisuride (**226**) having the structure of 9,10-*trans*-dihydrolisuride, thereby exhibiting dopamine agonistic and antagonistic activities. Synthesized by Czechoslovakian chemists in 1972, this compound, **231**, is also called Dieonyl, Mysalfon, etc., and used in the form of the hydrogen maleate salt for its antiparkinsonian and antihyperprolactinemic activities (*103*).

H. CABERGOLINE

Selected from a group of dihydolysergylurea derivatives for its outstanding pharmacological and pharmacodynamic activity, carbergoline (**232**) has been used for its significant prolactin secretion inhibitory activity. This compound

was obtained by treatment of dihydrolysergic acid with an appropriate carbodiimide, or by the reaction of dihydrolysergamide with a large excess of an alkyl isocyanate (*104,105*). Carbergoline (**232**) is also recognized as a potent and selective D_2 receptor agonist, and is at least two-hundred fold more potent than bromocriptine in the prevention of the fertilized egg implantation in rats (ED_{50} 0.025 mg/Kg). It is devoid of the hypotensive activity and emesis present in almost all of the compounds in this therapeutic class.

IX. ADDENDUM

In nature, many types of natural products exist also in the form of glycosides, which, more importantly, are known to have potent and useful pharmacological activities. However, in the area of the ergot alkaloids, few ergot alkaloid glycosides are known, and their study remains in the future; a recent review mentioned the existence of elymoclavine fructoside and a few others (*106*).

Acknowledgments

The authors take this opportunity to express their appreciation to Dr. S. Mantegani for the kind offer of some of his most recent publications on ergot research.

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