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SYNTHETIC STRATEGIES TO THE ERGOLINE RING SYSTEM OF ERGOT ALKALOIDS

DAVID C. HORWELL
Lilly Research Centre Ltd., Erl Wood Manor, Windlesham, Surrey, England

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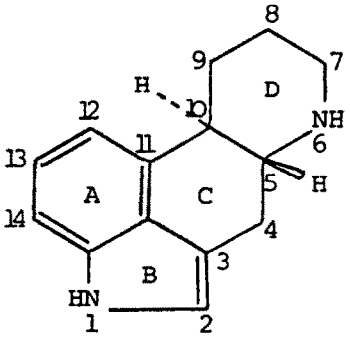
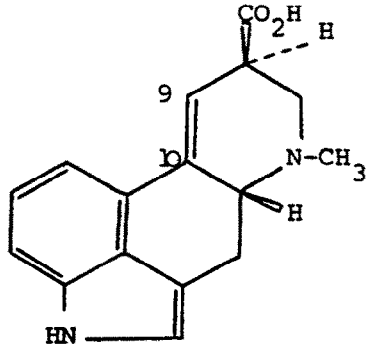
INTRODUCTION

The reviews available to date on the chemistry of ergot alkaloids adequately summarise their structural elucidation,[1,2] and the total syntheses of dihydrolysergic acid[1,2] and lysergic acid.[2–7] In addition, the biosynthesis,[5] history,[2,8,9] pharmacology,[8,10,11] and production by fermentation[12] of this unique class of indole alkaloids have been reviewed in detail. The chemistry and pharmacology of structural analogues of ergolines has also been summarised,[13] and further developed.[14,15]

The purpose of this article is to outline the synthetic problems that have been encountered not only in the total syntheses, but also in other modes of formation that may be adapted, or developed, to give the ergoline ring system (**1**). This unique heterocyclic ring system constitutes the basic skeleton in both the lysergamide (derivatives of lysergic acid (**2**)) and clavine classes of ergot alkaloids. It is hoped that this information will be of value when considering new approaches, or modifications to the ergoline ring system.[16] The total syntheses presently available do not offer commercially viable alternatives to the fermentation procedures that have been developed to produce ergot alkaloids.[5,6,12] However, the flexibility inherent in total synthesis does have an advantage in introducing novel substitution patterns which may not be readily attainable from the natural products. Such schemes will, for example, be of value in the discovery of new drugs based on chemical modification of this biologically active ring system.



ergoline (1)

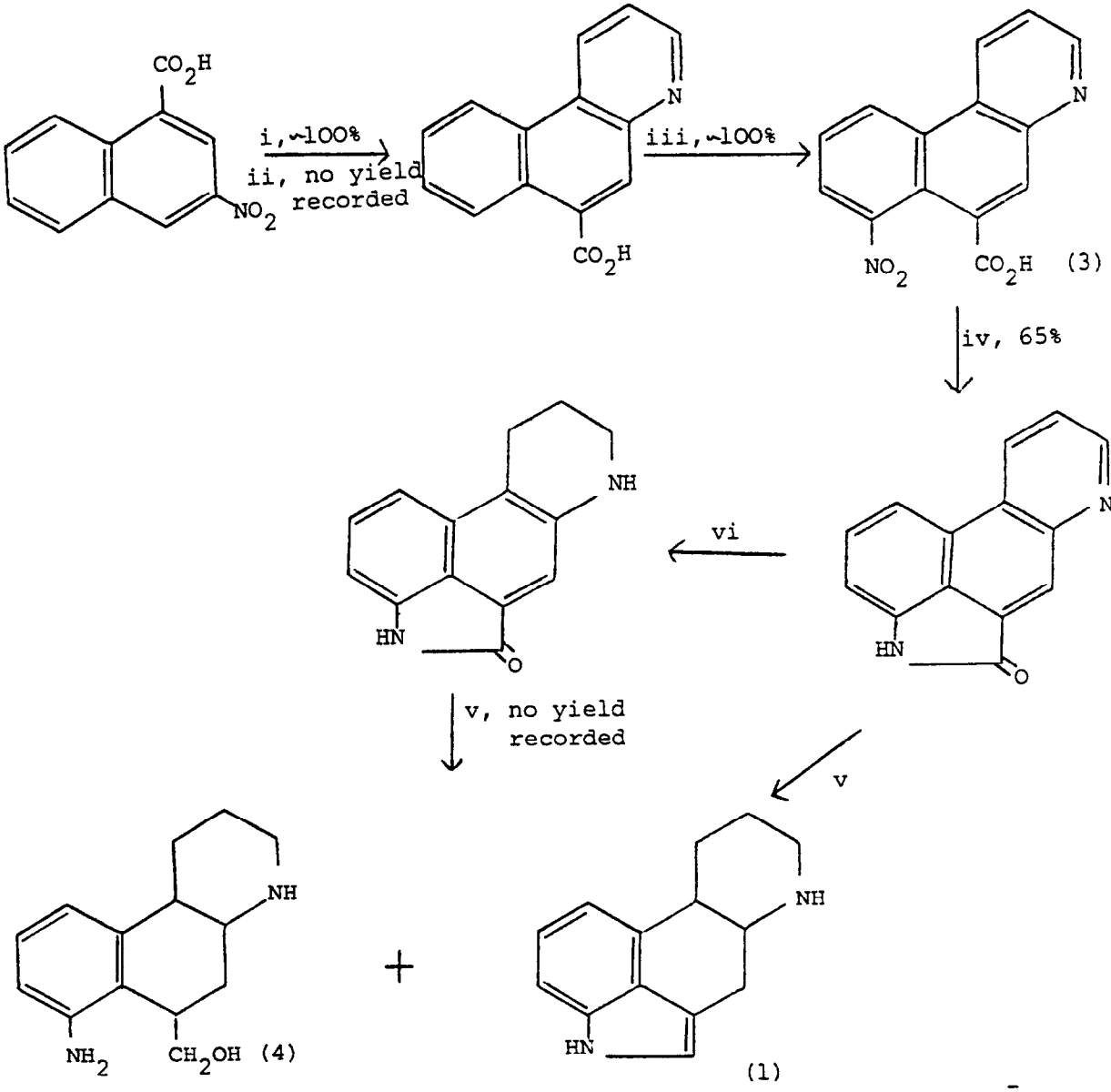


lysergic acid (2)-a$\Delta^{9,10}$-ergolene

The major synthetic problems encountered in the construction of the ergoline ring system are; (i) regiospecific formation of 4-substituted indoles, (ii) introduction of a high degree of strain in the molecule on fusion of the 6-membered ring C to the 4-position of indole and (iii) the instability of the naturally occurring ergolenes such as lysergic acid (**2**), which contain a $\Delta^{9,10}$-double bond. These $\Delta^{9,10}$-ergolenes readily isomerise to the resonance stabilised benz [c, d]indolines, involving irreversible aromatisation of ring C (e.g. **15** → **16**).

THE CHEMISTRY OF THE EARLY APPROACHES TO TOTAL SYNTHESIS

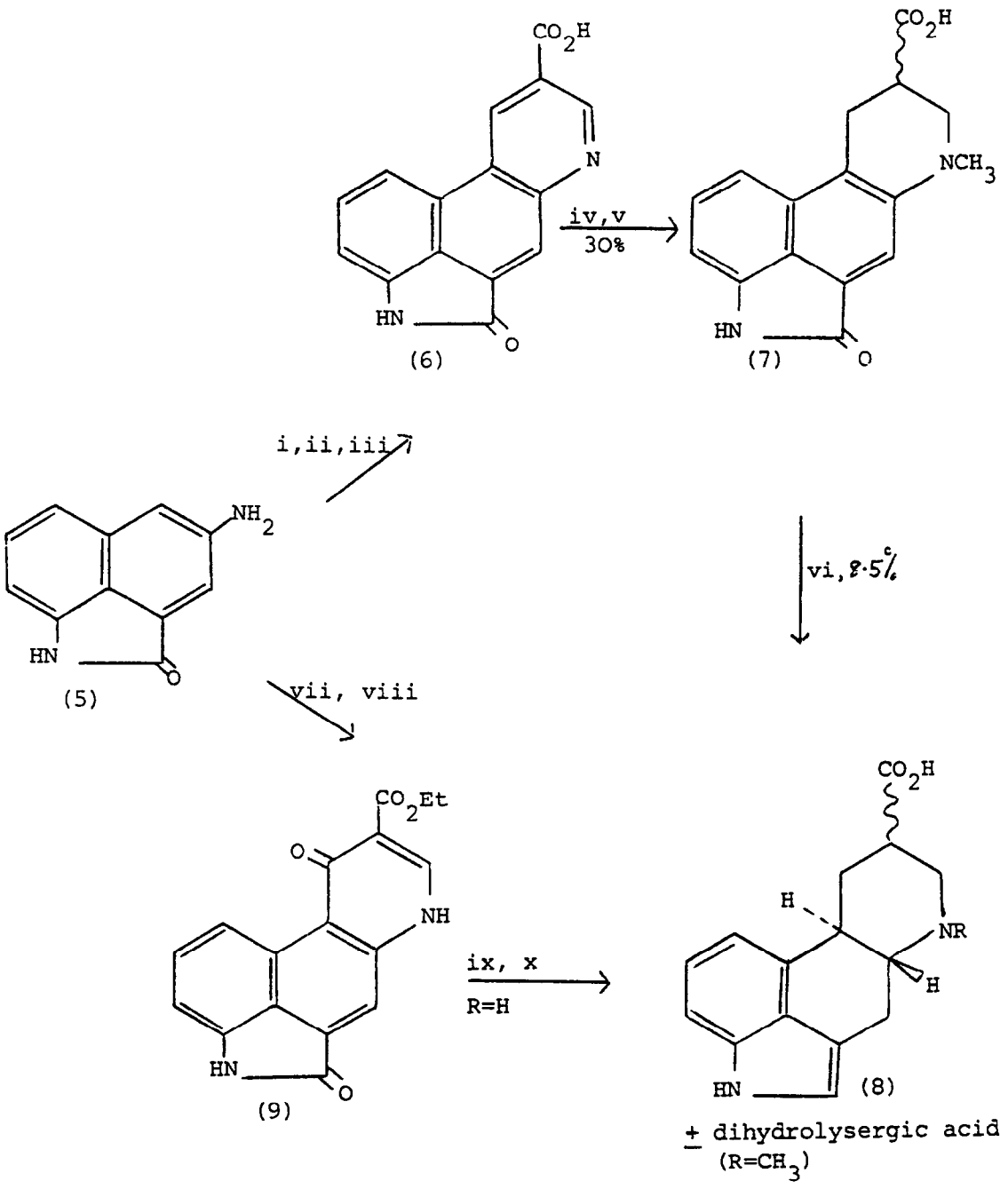
The early approaches to the synthesis of ergolines and ergolenes were designed to confirm the unique 4-substituted indole structure, the position of the carboxylic acid group, and the position of the $\Delta^{9,10}$-double bond of lysergic acid. Yields were, therefore, not necessarily optimised. The armamentarium of modern reagents and techniques, could undoubtedly be used to improve these routes. However, an outline of these approaches illustrate the problems encountered in ergoline chemistry.



Reagents: i, $FeSO_4^-$-NH_4OH; ii, Skraup synthesis; iii, HNO_3; iv, $FeSO_4^-$-NaOH; v, Na-BuOH; vi, H_2-Pt.

Scheme 1.

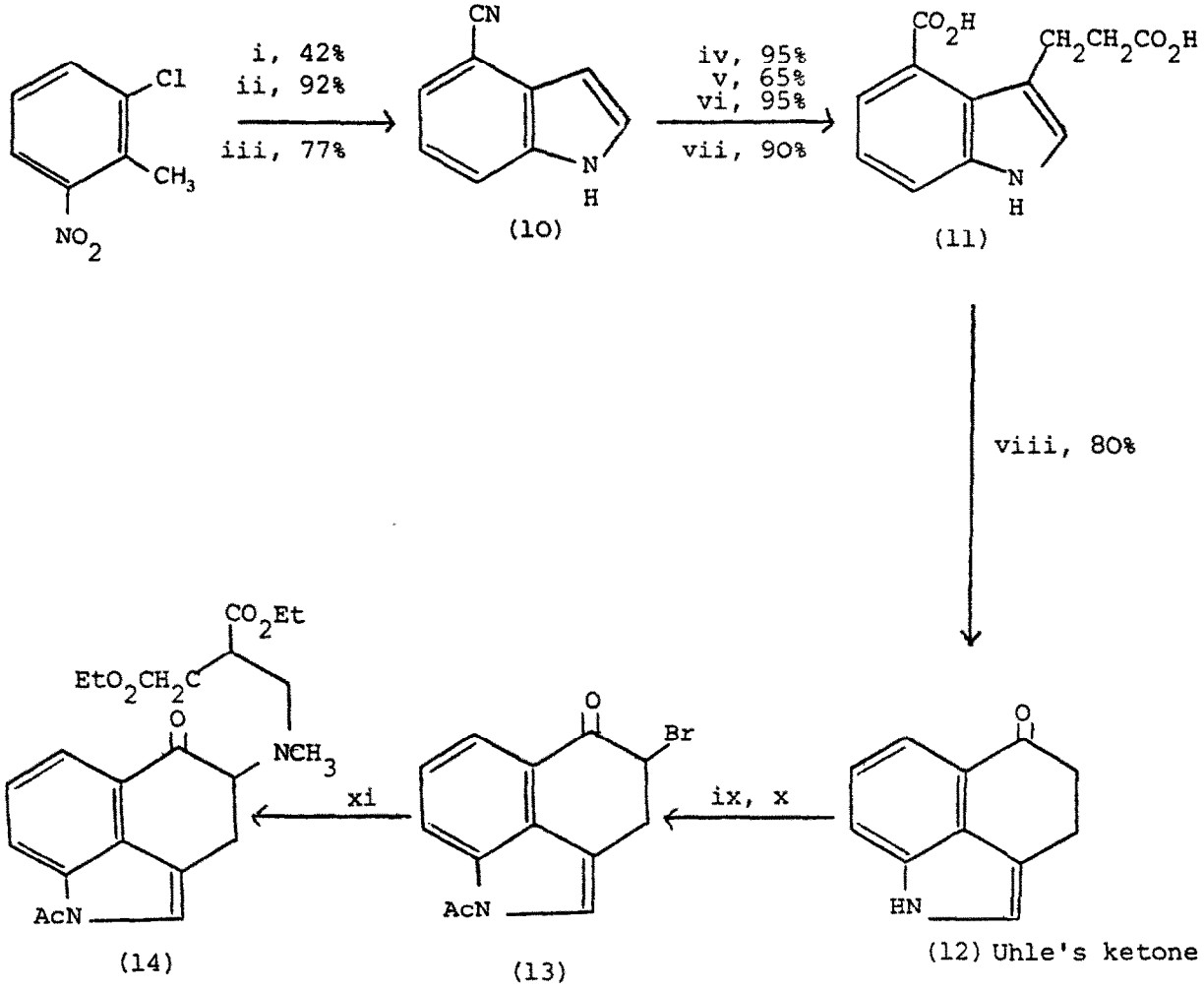
The ergoline ring system was named, and its structure proven by synthesis from 3-nitronaphthalene-1-carboxylic acid, by Jacobs and Gould in 1937 (Scheme 1).[17] A feature of this route is the remarkable regioselectivity and high yield of the nitration step to give **3**. However, the vigorous conditions necessary to saturate ring C and reduce the oxindole ring B, led to a mixture of the ring B cleaved aminoalcohol (**4**) as the major product, and ergoline (**1**). These products were separated by fractional crystallisation from ether in an unspecified, but presumably, low yield.



Reagents: i, OHCCH(CN)CHO; ii, $ZnCl_2$; iii, HCl-H_2O; iv, CH_3I-AgCl; v, H_2Pt-HCl; vi, Na-BuOH; vii, $EtOCH{=}C(CO_2Et)_2$-EtOH; viii, ΔH-260-265°-mineral oil; ix, Zn-HCl; x, Na-BuOH-H_2O.

Scheme 2.

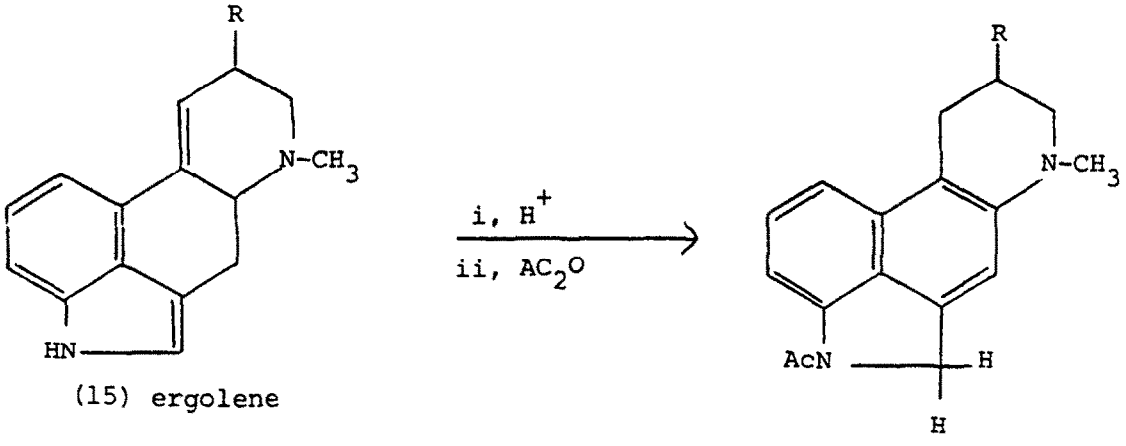
The position of the carboxylic acid group in racemic dihydrolysergic acid was verified by synthesis in 1945 by Jacobs and Uhle (Scheme 2).[18] 4-Aminonaphthostyril (**5**) was annelated under Friedel–Crafts conditions with cyanomalonic dialdehyde to give compound **6** having an aromatic ring D. By analogy with the original synthesis of ergoline, reduction of **7** by sodium in butanol gave the racemic dihydrolysergic acid (**8**), but only in 8.5% yield. Jacobs and Uhle were unable to resolve their synthetic compound (**8**, R=Me), in order to compare with the natural *d*(−)-dihydrolysergic acid, due to the limited quantity of material that they were able to obtain. Larger quantities of **8** were made available by a modification of the scheme from compound **5**.[19] In this route, annelation was achieved with ethoxymethylene diethylmalonate followed by thermolysis, to give the tetracyclic keto-enol (**9**). Clemmensen reduction of **9**, followed by treatment with sodium in butanol, gave a mixture of racemic dihydro- and isodihydronorlysergic acids (**8**, R=H). It was found essential to add water to the butanol before reduction in order to prevent conversion of the ester to the corresponding alcohol. The geometric isomers of **8**, (R=H) were separated as their methyl esters by chromatography.[20] Stoll later achieved the isolation of synthetic *d*(−)dihydrolysergic acid by resolution of the racemates via the L-norephidride.[21] This proved conclusively the structure of this acid, which is the basic constituent of the dihydrogenated naturally occurring lysergamide class of ergot alkaloids.



Reagents: i, $(CO_2Et)_2$-NaOEt; ii, $FeSO_4$-NH_4OH; iii, CuCN, quinolone, 237°; iv, AcOH-HCHO-Me_2NH; v, $CH_2(CO_2Et)_2$-NaOEt-$(CH_3)_2SO_4$; vi, 10% NaOH-H_2O, then ΔH; vii, KOH; viii, KCN-Ac_2O-ΔH, then 10% KOH; ix, Ac_2O; x Br_2; xi, $H_3CNHCH_2CH(CO_2Et)CH_2CO_2Et$.

Scheme 3.

The syntheses described above have given low yields of ergolines. This is because of the stepwise construction of the 4-substituted indoles from substituted naphthalenes, and because of the facile cleavage of the highly strained oxindole ring under the vigorous conditions necessary to reduce ring C. Uhle suggested that the $\Delta^{9,10}$ double bond of lysergic acid may be introduced by a completely different synthetic strategy, involving construction of a tricyclic ketone of the type **12** (Uhle's ketone).[22] This ketone would then allow the necessary α-functionalisation, e.g. via the bromoketone (**13**), followed by condensation with suitable active methylene groups, to give the $\Delta^{9,10}$ double bond directly, and unambiguously, on closure of ring D. The ketone was synthesised from 4-cyanoindole (**10**), by the intramolecular condensation of the diacid (**11**), under unusual conditions with potassium cyanide in acetic anhydride. Uhle later reported the preparation of the immediate precursor of ring D (**14**) in his 1951 paper[23] (Scheme 3). A limitation of this logical approach to lysergic acid is that condensation of the ketone (**14**) with active methylene groups would require either strong acid or base. These conditions would undoubtedly induce the known facile isomerisation of the $\Delta^{9,10}$ ergolene double bond to the benz[c, d]indoline (e.g. **15** → **16**), which is irreversible under these conditions.[1,2,24] The naphthalene derivative (**16**) is resonance stabilised by approximately 20 kcal/mole over the ergolene (**15**). This isomerisation has constantly thwarted many attempted syntheses of the ergolene ring system.

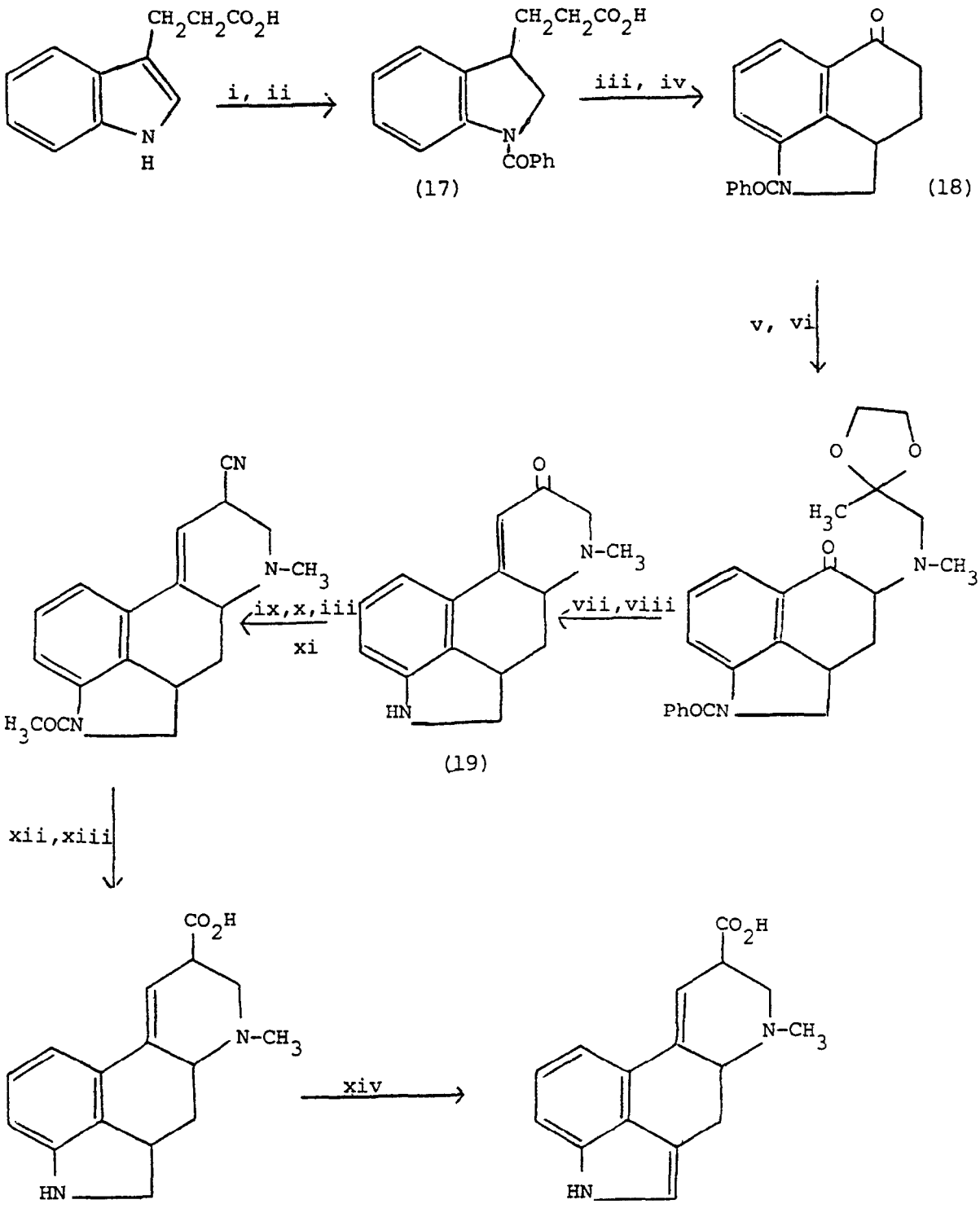


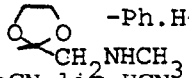
(15) ergolene

(16) benz[cd]indoline

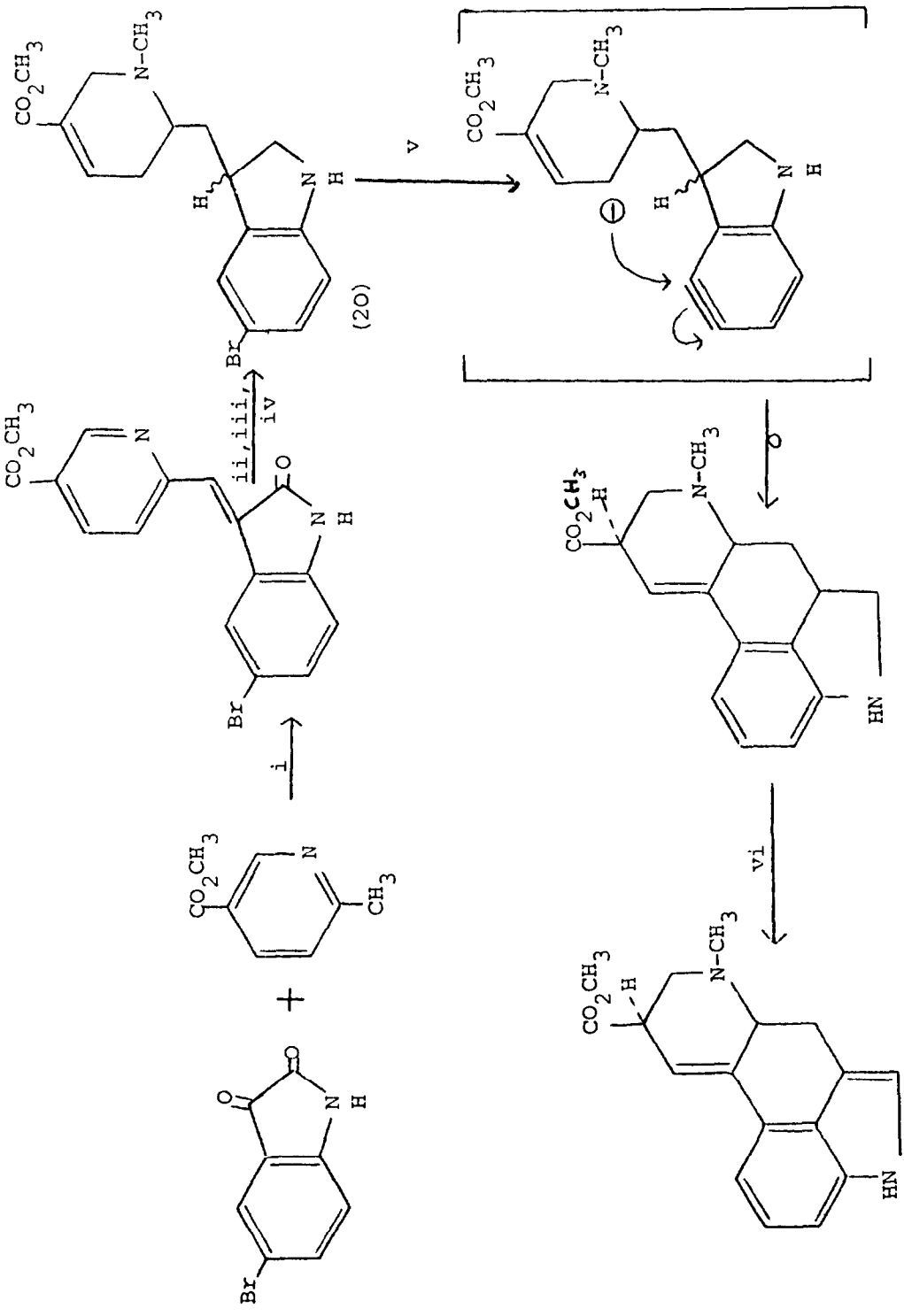
R = CO_2H, CO_2CH_3, CH_2OAc

The total synthesis of racemic lysergic acid was finally achieved by the Kornfeld–Woodward group at the Lilly laboratories. Scheme 4 summarises this route, which starts from indole propionic acid.[25] This approach avoids the problem of the ergolene isomerisation to the benz [c, d] indoline, by protecting the indole ring as the benzoyl indoline propionic acid derivative (**17**). Regeneration of the 2,3-indole double bond is left until the very last step of the reaction sequence. A further consequence of working at the indoline oxidation level, is that the intramolecular Friedel–Crafts acylation is obliged to undergo substitution in the 4-position to give **18**. Electrophilic substitution would otherwise take place in the extremely labile 2-position, at the indole oxidation level. This elegant approach to the formation of ring C thus avoids all the major problems that had previously been encountered in constructing the ergolene ring system. The tricyclic ketone (Kornfeld's ketone) **18** is still, perhaps, the most versatile intermediate for the synthesis of ergolines. It has all the elements necessary for further elaboration to ring D at all the oxidation levels found in the natural lysergamide and clavine alkaloids. For example, Kornfeld has further exploited the tetracyclic ketone (**19**), derived from **18**, in a two stage synthesis of racemic isosetoclavine.[26] Furthermore, lysergic acid has been transformed into penniclavine and elymoclavine by a procedure involving reduction of the carboxylic acid, and isomerisation of the $\Delta^{9,10}$- to the $\Delta^{8,9}$-double bond.[27]



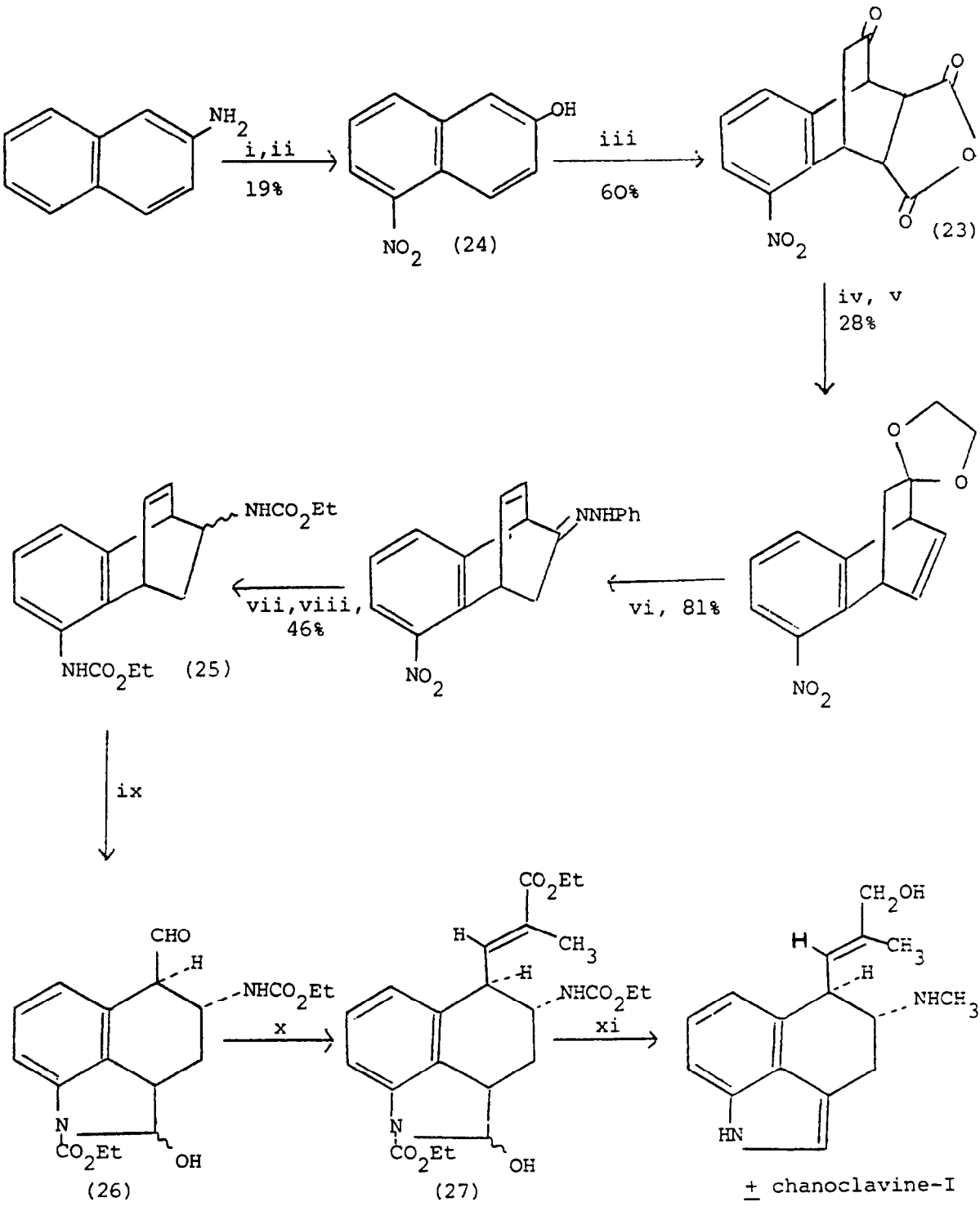
Reagents: i, NaOH-Raney Ni-H_2-3-4,000 psi,30hr; ii, NaOH-PhCOCl, iii, $SOCl_2$ iv, $AlCl_3$-CS_2; v, Br_2; vi  -Ph.H-ΔH; vii, H^+; viii, $NaOCH_3$; ix, Ac_2O; x, $NaBH_4$; xi, NaCN-liq.HCN; xii. MeOH-H_2SO_4; xiii, NaOH xiv, Raney Ni-H_2O-Na_2HAsO_4

Scheme 4.



Reagents: i, base; ii, B_2H_6; iii, CH_3I; iv, $NaBH_4$; v, $NaNH_2$-NH_3; vi, MnO_2

Scheme 5.



Reagents: i, HNO_3; ii, $NaNO_2$-H_2SO_4-ΔH; iii, maleic anhydride-160°-24 hr;
iv $\left[\begin{matrix}OH\\OH\end{matrix}\right.$-$H^+$; v, $Pb(OAc)_4$ or anodic oxidation-pyridine;
iv, 2NHCl-EtOH-Δ-2 hr, then H_2NNHPh; vii, Al-EtOH; viii, $ClCO_2Et$;
ix, O_3; x, $CH_3\overset{PPh_3}{\underset{}{}}CO_2Et$; xi, $(CO_2H)_2$-HOAc, then $LiAlH_4$

Scheme 6.

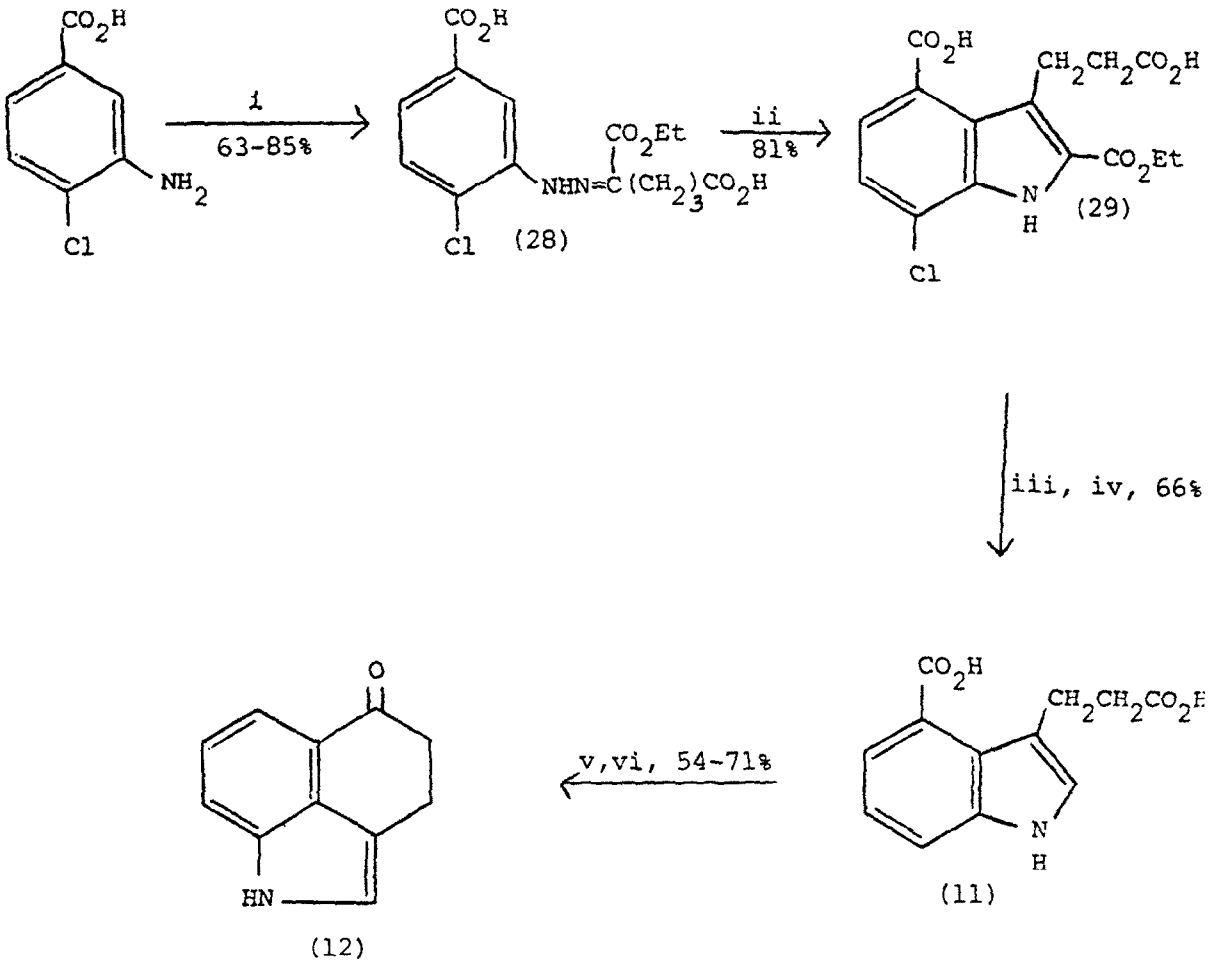
A second total synthesis of racemic lysergic acid involves a completely different conceptual approach, where ring C is generated by a remarkable intramolecular coupling reaction (Scheme 5).[28] Sodium in liquid ammonia generates both an allylic anion at C-5 of a tetrahydronicotinic acid and an aryne at C-4 of the indoline, which couple in only one of the isomers of **20**. The strongly basic medium also induces isomerisation of the double bond to the $\Delta^{9,10}$ position, to give the product **21**, on acylation, in 15% yield. The indole ring is then generated by dehydrogenation with manganese dioxide, to give the known methyl ester of racemic lysergic acid (**22**). The patent literature describes further refinements of this procedure.[6]

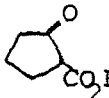
The total synthesis of racemic chanoclavine-I, an intermediate in the biosynthesis of ergot alkaloids, has several interesting features (Scheme 6).[29,30] The key intermediate bicyclo[2.2.2]octanone (**23**), is formed by a Diels–Alder reaction between the naphthol (**24**) and maleic anhydride in 60% yield. Ozonolysis of the derived dicarbamate (**25**) provides all the elements necessary for the formation of ring B, as well as a free aldehyde group. Further elaboration of the aldehyde by a Wittig reaction generates the side chain (**26** → **27**). The final reduction of **27** with lithium aluminium hydride gives the alcohol, N-Me group, and indole ring of racemic chanoclavine-I, all in one step! The yield from **25** is 28%. A major limitation to this elegant route, is the poor yields of the oxidative decarboxylation, and the stepwise production of (**23**) from the undesirable starting material, β-naphthylamine.

ALTERNATIVE APPROACHES TO RING C

Many alternative approaches to form ring C have concentrated on working at the indole or oxindole oxidation level of ring B. The indole ring is preferably protected, either as the N-acetyl[23,31,32] or as the less base labile tosyl-[33] or carbamoyl derivatives.[30] These groups go some way to stabilise the indole ring, and reduce the likelihood of both aromatisation of ring C and electrophilic substitution in the 2-position.[31,32] The necessary transformation of oxindoles to indoles in these systems has been investigated. Treatment of tetrahydronaphthostyril with triethyloxonium tetrafluoroborate, followed by reduction of the resultant 2-ethoxyindole with diborane, has given the corresponding indole in 61% yield.[34] Lithium aluminium hydride can also effect the conversion in one step, but the yields are only fair to moderate.[35,36] More often, in this variable reaction, lithium aluminium hydride or diborane give the indoline as the major product.[28,37–39] Working at the indoline level involves the limitations inherent in the Kornfeld–Woodward synthesis of lysergic acid (Scheme 4). These are, namely, the four steps necessary to hydrogenate the indole, protect the unstable indoline by benzoylation, hydrolysis, and especially, the low and variable yields of the dehydrogenation step to regenerate the indole ring. Many reagents have been tried to improve the yield in this last reaction, of which activated manganese dioxide appears to be the preferred reagent.[28,40] However, this reagent is notorious for its erratic results. Catalytic exchange with strained olefins may offer advantages.[41] A further modification to this route has been to replace carbon disulphide with methylene chloride as solvent in the Friedel–Crafts step (**17** → **18**).[+2] Both substituted and unsubstituted indole propionic acids are now available by several alternative routes.[43–46] Conditions for reduction of the indoles to indolines have been developed, which avoid the high pressures used in the original synthesis of lysergic acid.[47–49]

Improvements to the synthesis of Uhle's ketone (**12**) have been described. A novel route which has been applied on a kilogram scale, is described by Bowman *et al.* (Scheme 7).[33] The Fischer indole cyclisation (**28** → **29**) is obliged to occur *ortho-* to the 3-carboxylic acid group, by virtue of blocking the 6-position with a Cl atom. The chlorine is removed at a later stage by hydrogenolysis. The final cyclisation (**11** → **12**) gives Uhle's ketone (**12**) in 54% yield. Uhle had earlier obtained a yield of 71% on a small scale by adding 0.25 mole of potassium acetate to the reaction medium.[50] Catalysis by this salt was found to give more reproducible results than the original conditions using acetic anhydride-potassium cyanide (Scheme III). Interestingly, addition of 1 mole of potassium acetate completely aromatises ring C to give **30**. A similar cyclisation of the amino acid (**31**) has also given the aromatised compound (**32**) in 58% yield.[31] Grob has succeeded in isomerising the aromatic naphthol (**33**) with palladium in a tetralin-xylene mixture under an hydrogen atmosphere to give Uhle's ketone in excellent yield (87–97%)[51,52] This systematic study does, therefore, indicate that the benz[c,d]indoline → ergolene isomerisation may indeed be readily achieved under the correct experimental conditions. Plieninger has transformed various Diels–Alder adducts of substituted

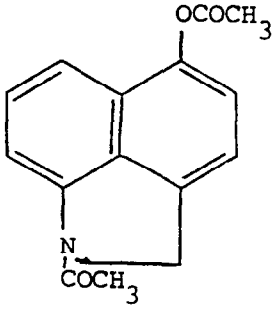


Reagents: i, HNO_2-HCl, then  ; ii, BF_3-HOAc; iii, KOH-aq-2 hr; iv; H_2-Pd-C-30 at; v, KCN-Ac_2O or NaOAc or KOAc (0.25 moles)-Ac_2O vi; NaOH-MeOH.

Scheme 7.

naphthalenes to Uhle's ketone.[53] Benzene ring A substituted[54] and unsubstituted[55] 1,3,4,5-tetrahydrobenz[c,d]indoles are also available by total synthesis.

The attempted direct cyclisation of indole propionic acid with polyphosphoric acid has not given Uhle's ketone. The only product identified has been **34**, in low yield, which is the result of electrophilic substitution in the 2-position.[56] Blocking the 2-position has met with success in directing substitution to the 4-position, but the yields tend to be only moderate. Thus, compound **35** has given **36** in 32% yield. Perhaps more generally applicable, is that 2-carbethoxyindole propionic acid has given Uhle's ketone after Friedel–Crafts cyclisation in 28% yield, followed by hydrolysis and decarboxylation in 5.3% yield.[32] The propionic acid is readily available by a Fischer indole synthesis. The poor yield of the decarboxylation step could undoubtedly be improved (c.f. decarboxylation of **29**, Scheme 7).



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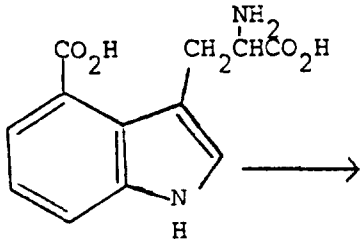

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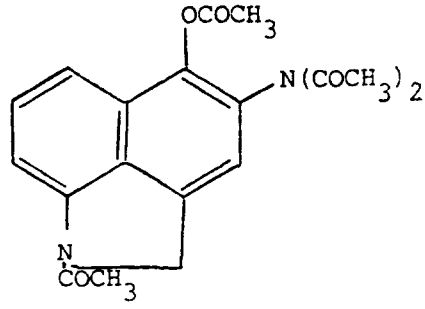

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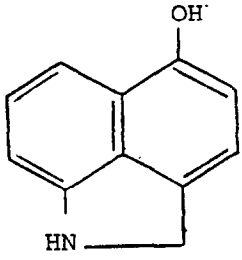

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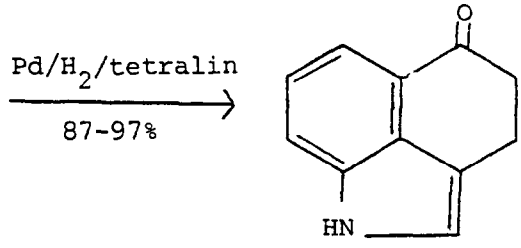

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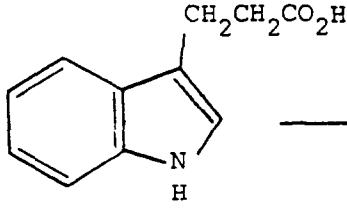

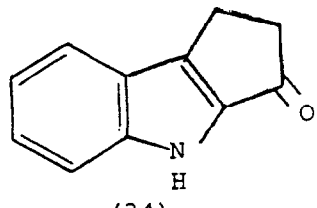

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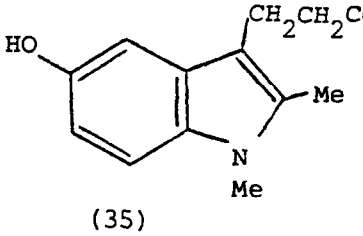

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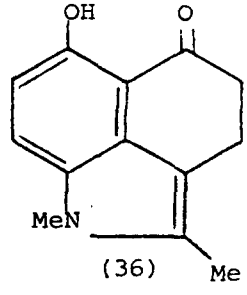

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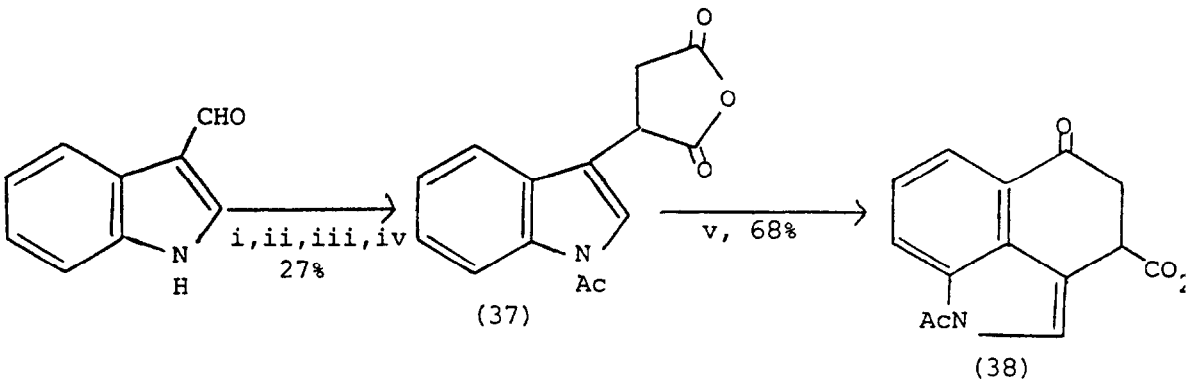
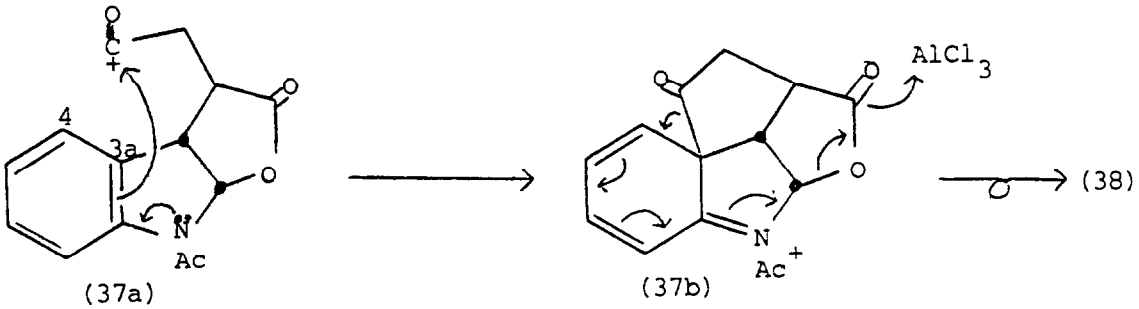


Reagents: i, $CH_2(CN)CO_2Et$-piperidine; ii, KCN-EtOH; iii, KOH-H_2O-ΔH;

iv, $H_3C-\overset{OAc}{C}=CH_2-H^+$, then AcOH-$Ac_2O$; v, $AlCl_3$-CH_2Cl_2

Scheme 8.

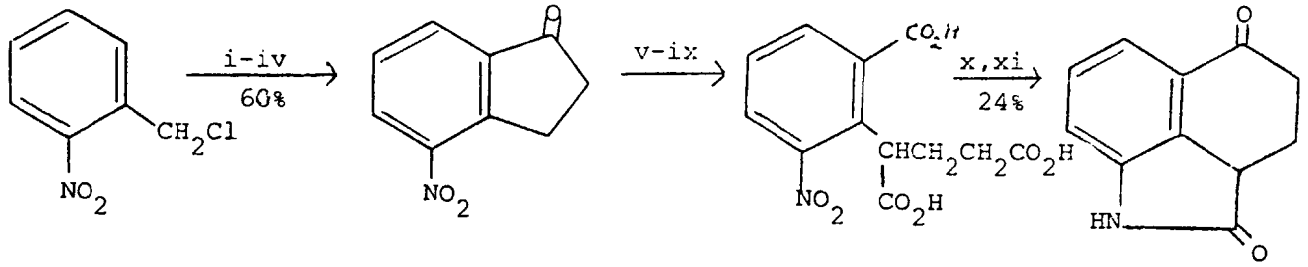
Szmuszkovicz describes what appears to be the only recorded example of an indole with an unsubstituted 2-position (**37**) undergoing the intramolecular Friedel–Crafts reaction in the 4-position to give the keto-acid **38** (Scheme 8).[58] Closely related species still give only 2-substitution.[32] The mechanism of this unique reaction may warrant further investigation. The indole 2,3-double bond may be protected by involving an intermediate such as **37a**. The acylating species may then be oriented towards the 3a-position. The surprisingly strain free intermediate **37b** may then undergo a [1,2] sigmatropic shift to the 4-position. (cf. **86** → **85**, Ref. 96).



Treatment of the readily available oxindole-3-propionic acid[59–63] under Friedel–Crafts conditions has given only an amorphous white solid of unknown structure. No product corresponding to the desired ketone (**39**) has been found in this reaction.[63] The ketone (**39**)[63] and its transposed isomer (**40**)[64] have, however, been synthesised by alternative routes (Scheme 9). Grob has elaborated the isomer (**40**) to ring D derivatives, but with concomitant aromatisation of ring C (see Section 3).

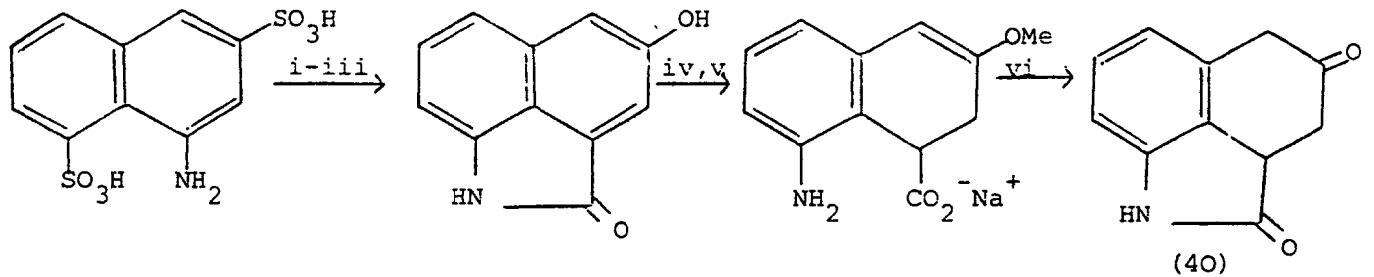
Several investigations have been directed towards the corresponding intramolecular cyclisation of ketonic species, in order to generate ring C and unsaturation suitable for elaboration to the $\Delta^{9,10}$ double bond of ergolene. For example, treatment of the model compounds **41** under Friedel–Crafts conditions has given small amounts of the cyclised products **42** (R=Me, R^1=H)[65,66] (R=CO_2Et, R^1=OMe).[67] The unsubstituted indoles (R=H) have given only the products of electrophilic substitution in the 2-position (**43**).[67] Treatment of the condensation product of diketene and 1,2-dimethylindole with polyphosphoric acid, has given **44** in 51% yield.[68]

Intramolecular cyclisation of the stabilised enol (**45**) gives **47** in good yield, in the presence of sulphuric acid. This cyclisation gives ring C prior to the formation of ring B, which represents a novel strategy to the methyl ester of the Uhle intermediate **6** (Scheme 10).[69] This scheme therefore



(39)

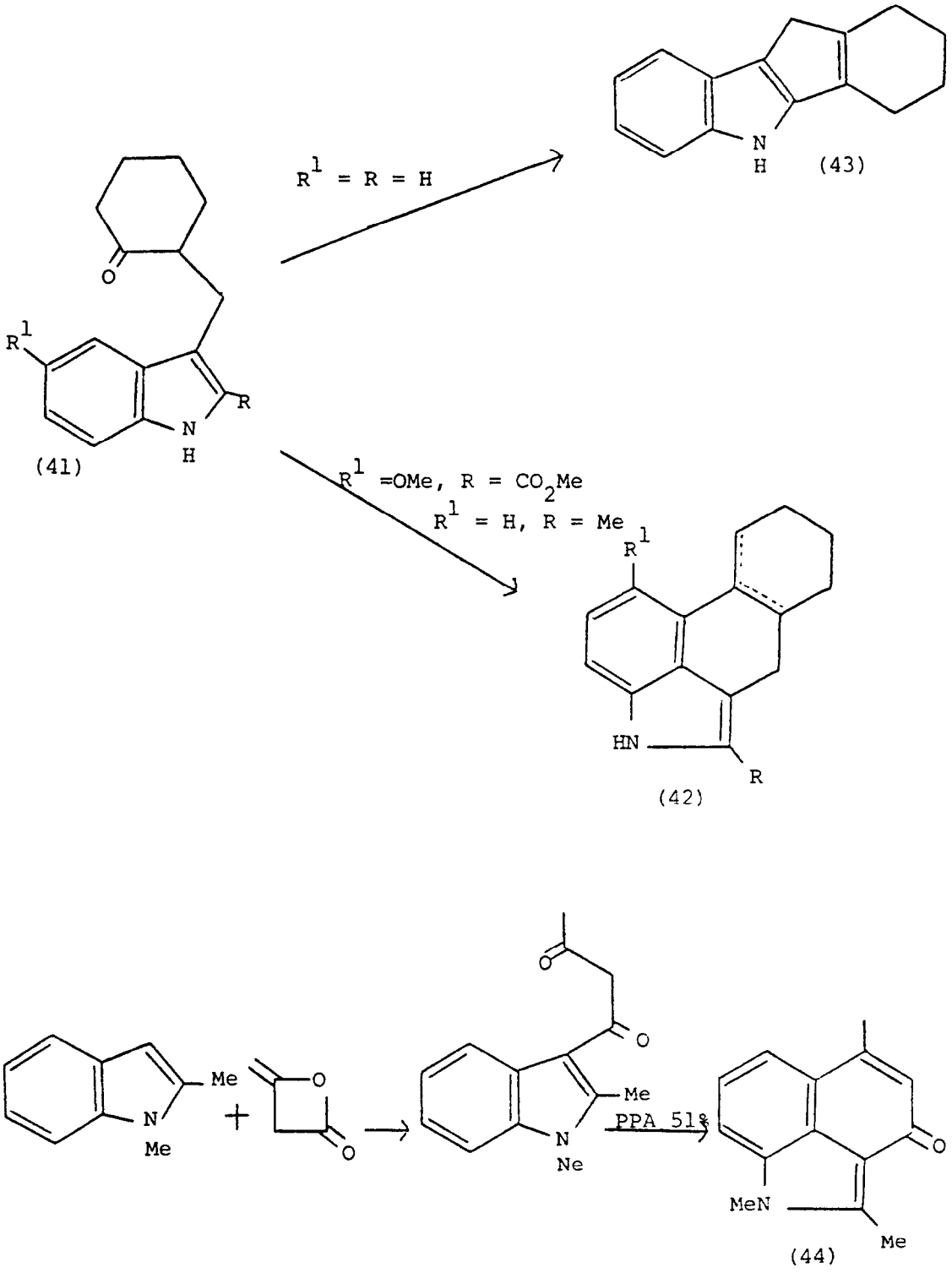
Reagents: i, $CH_2(CO_2Et)_2$-$Mg(OEt)_2$; ii, conc.HCl-Δ H; iii, $SOCl_2$; iv, $AlCl_3$; v, iso AmNO-EtOH-HCl; vi, Ac_2O; vii, MeOH-Na_2CO_3; viii, Triton B-35°, ix, HOAc-HCl-H_2O-Δ H-24 hr; x, $FeSO_4^-$-NH_4OH; xi, Ac_2O-NaOAc-Δ H, then HCl-MeOH-ΔH.



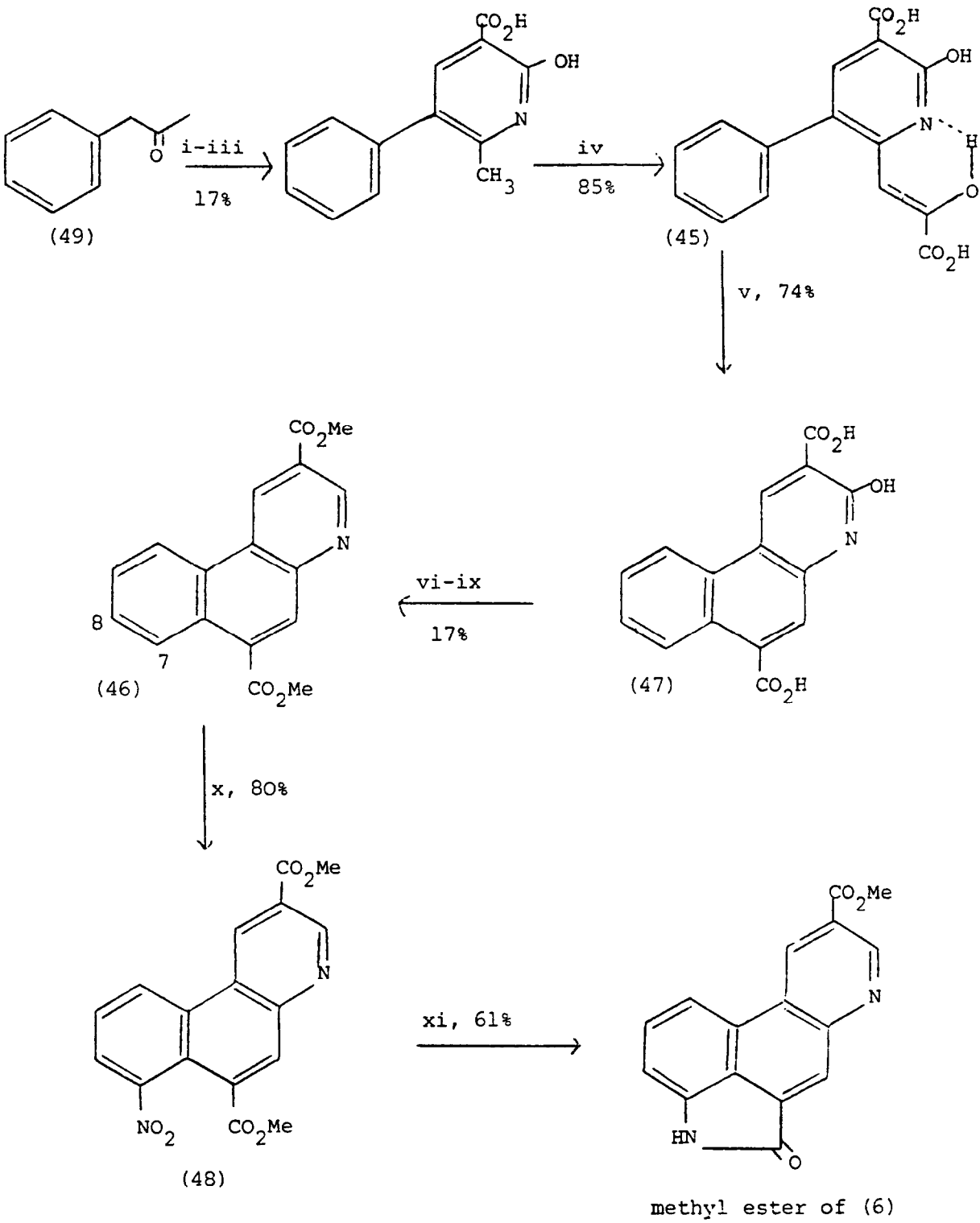
(40)

Reagents: i, HNO_2; ii, Cu_2CN; iii, KOH; iv, $(CH_3)_2SO_4$; v, Na-Hg-150 min-140°; vi, conc.HCl-50 min-90°.

Scheme 9.



constitutes a new total synthesis of racemic dihydrolysergic acid. The success of this approach is dependent on the fact that the nitration of **46** occurs in the 7-position, to give **48** in high yield and isomeric purity. This regioselectivity of nitration is in common with the original synthesis of ergoline (Scheme 1). Compound **48** is then reductively cyclised to the oxindole ring B derivative in good yield. The overall yield of the methyl ester of **6** from **49** is only 1.3 %, due to the poor stage (ii), and the several stages (vi–ix) necessary to remove the 2-OH group from **47**. Unlike **46**, compound **47** was shown to undergo nitration predominantly in the 8-position. Later work has indicated that analogues of compound **46** with a non-aromatic ring D, also do not nitrate selectively in the 7-position (see Ref. 76).



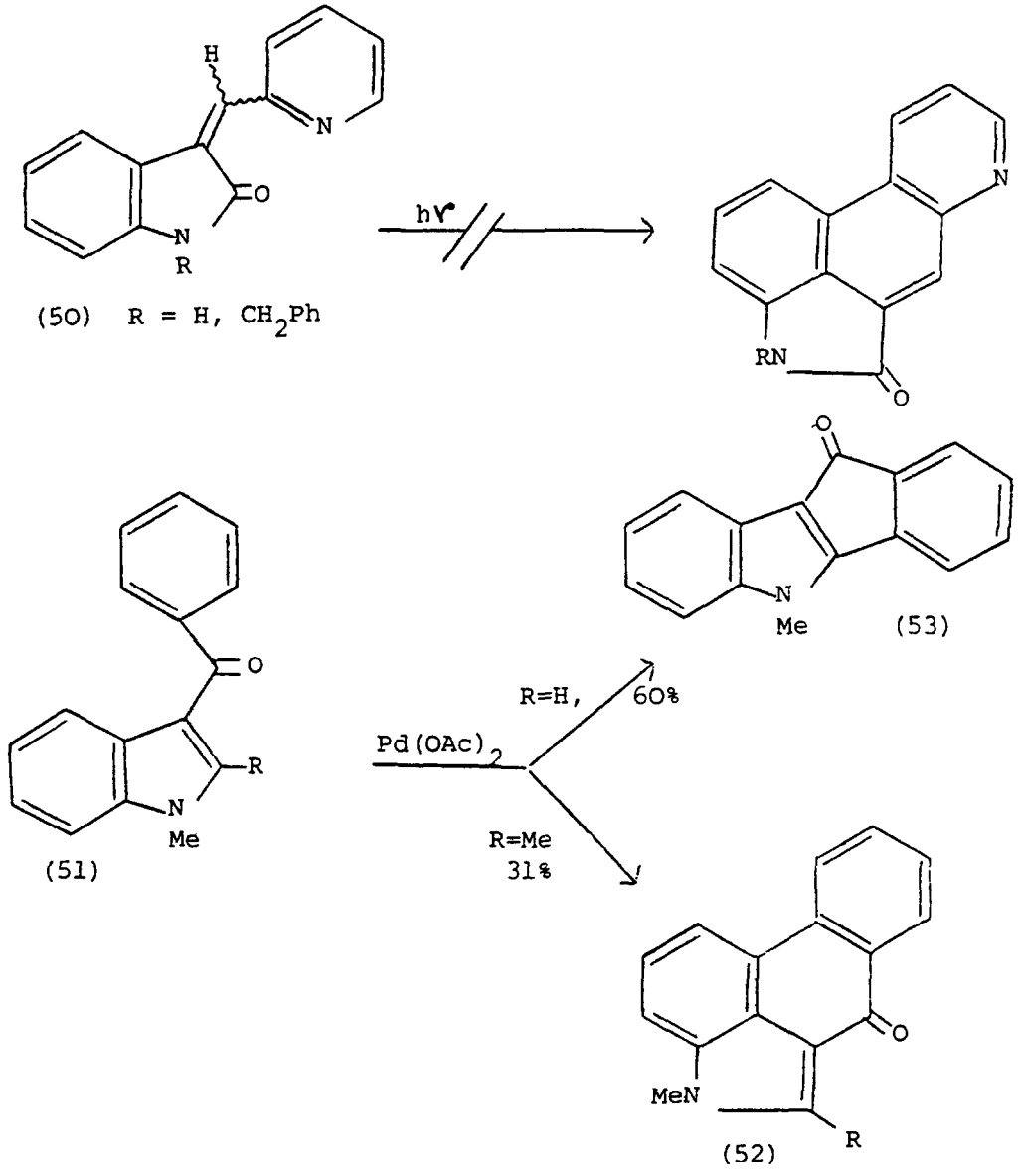
Reagents: i, NaOMe-HCO_2Et; ii, EtO_2CCH_2CN-pyridine; iii, conc.HCl; iv, $(COCl)_2$-$POCl_3$, then H_2O; v, conc.H_2SO_4-RT-2 days; vi, PCl_5-$POCl_3$, vii, MeOH; viii, $NaBH_4$ in MeOH; ix, Pd-xylene-ΔH-1 hr; x, HNO_3; xi, H_2-Pd-HOAc.

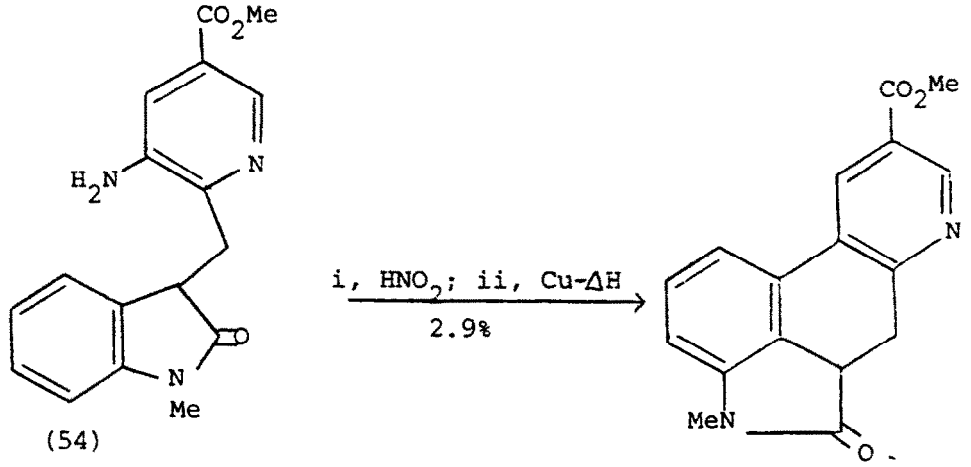
Scheme 10.

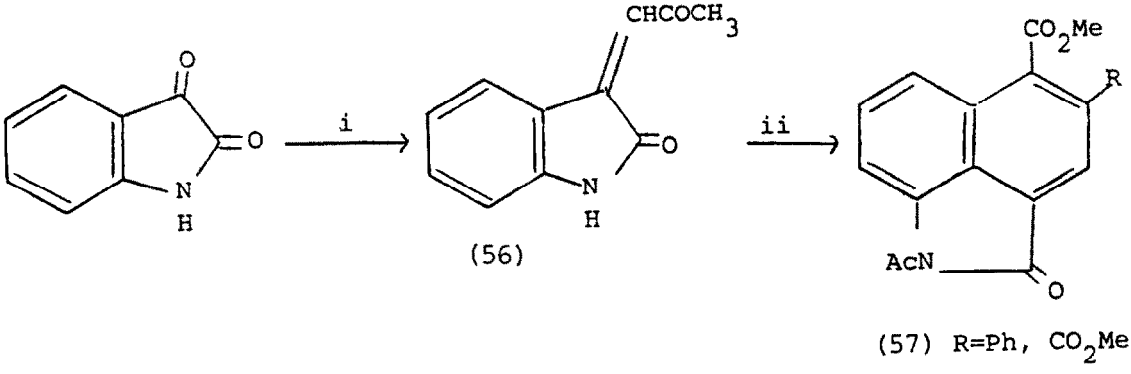
Other modes of intramolecular coupling of aromatic rings to the 4-position of indoles have also been investigated. The photolysis of the oxindolidene-2-pyridine (**50**), under many conditions, has given no evidence of ring C formation.[70] However, in a model system with the 3-benzoyl indole (**51**, R=Me), coupling of the 4-position of the indole ring with the 2-position of the benzene ring has given a 31% yield of **52**, (R=Me), in the presence of 0.5 equivalents of palladium acetate.[71] The unsubstituted compound **51**(R=H) gives the 2-substituted product (**53**) in 60% yield under these conditions. The intramolecular Pschorr reaction of **54** does give the dimethyl derivative (**55**) of the Uhle intermediate (**6**), but in very poor yield (2.9%).[72]

The readily available oxindolylacetone (**56**) has been shown to participate as the diene component in a Diels–Alder reaction with activated acetylenic, but no ethylenic, dienophiles. Thus, reaction of **56** with acetylene dicarboxylate and phenylpropiolate, has given the naphthostyril derivatives (**57**) in 16% (R=CO_2Me) and 10.6% (R=Ph) yield, respectively.[73] No adducts with 1,4-dihydro-N-methylnicotinamide or 1-methyl-2-pyridone-3-carboxamide, which would have generated rings C and D directly, were observed under these conditions.

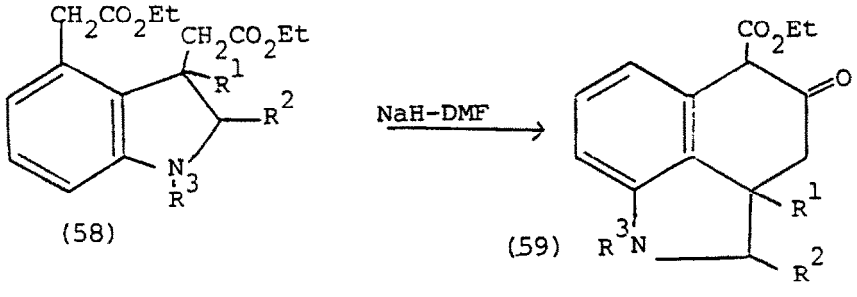
Dieckmann cyclisation of the diesters (**58**) with sodium hydride in dimethylformamide forms the ring C products (**59**) in excellent yield.[74] These compounds possess the β-tetralone part structure, and are more highly enolised than the isomeric Uhle (**12**) and Kornfeld (**18**) ketones, respectively. These β-ketoesters may have synthetic potential as precursors to ring D, provided a more direct route to **58** is found.







Reagents: i, CH_3COCH_3-Et_2NH; ii, $RC{\equiv}CCO_2Me$-Ac_2O-ΔH

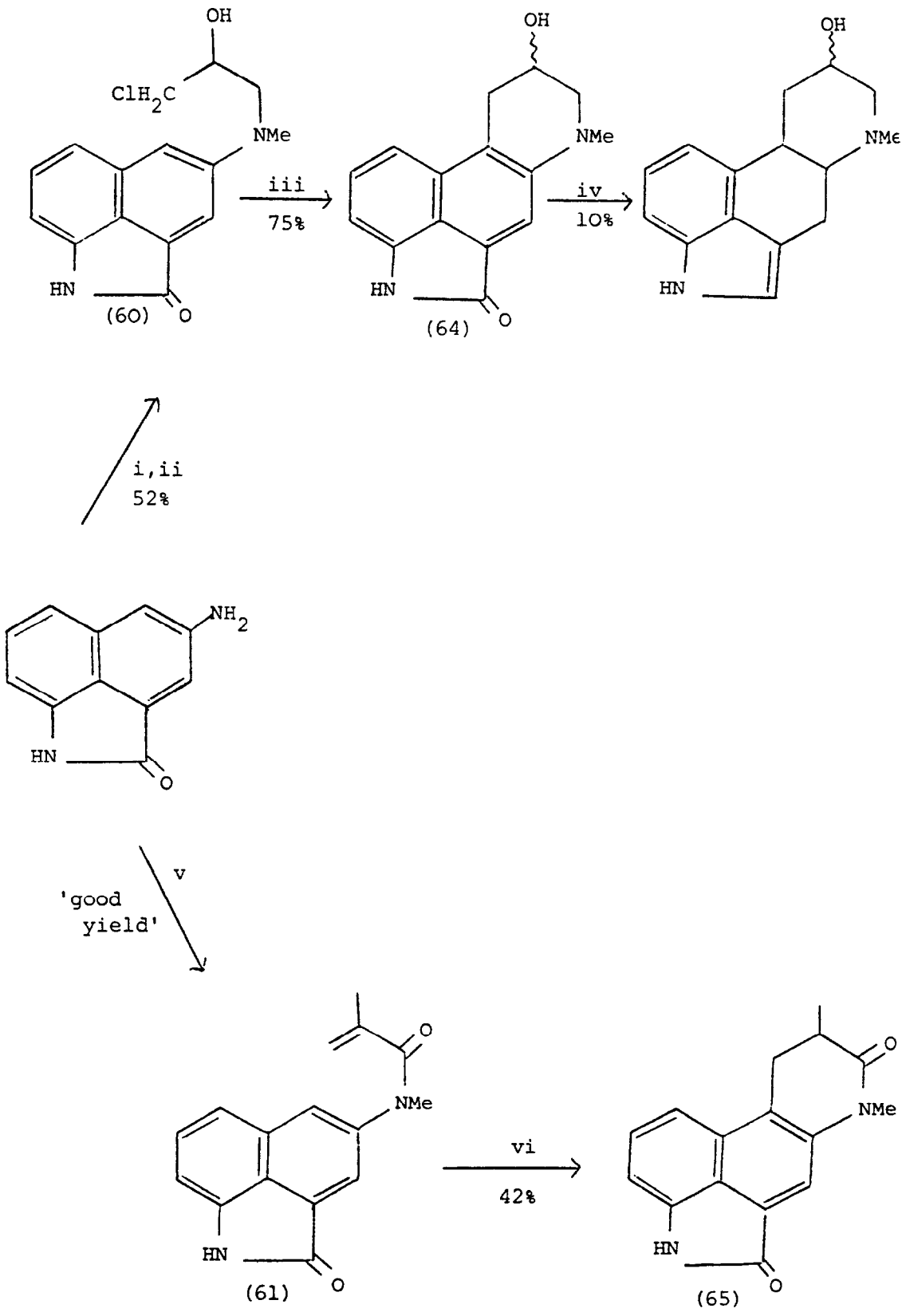


R^1=R^2= π-bond, R^3=H, yield:86%

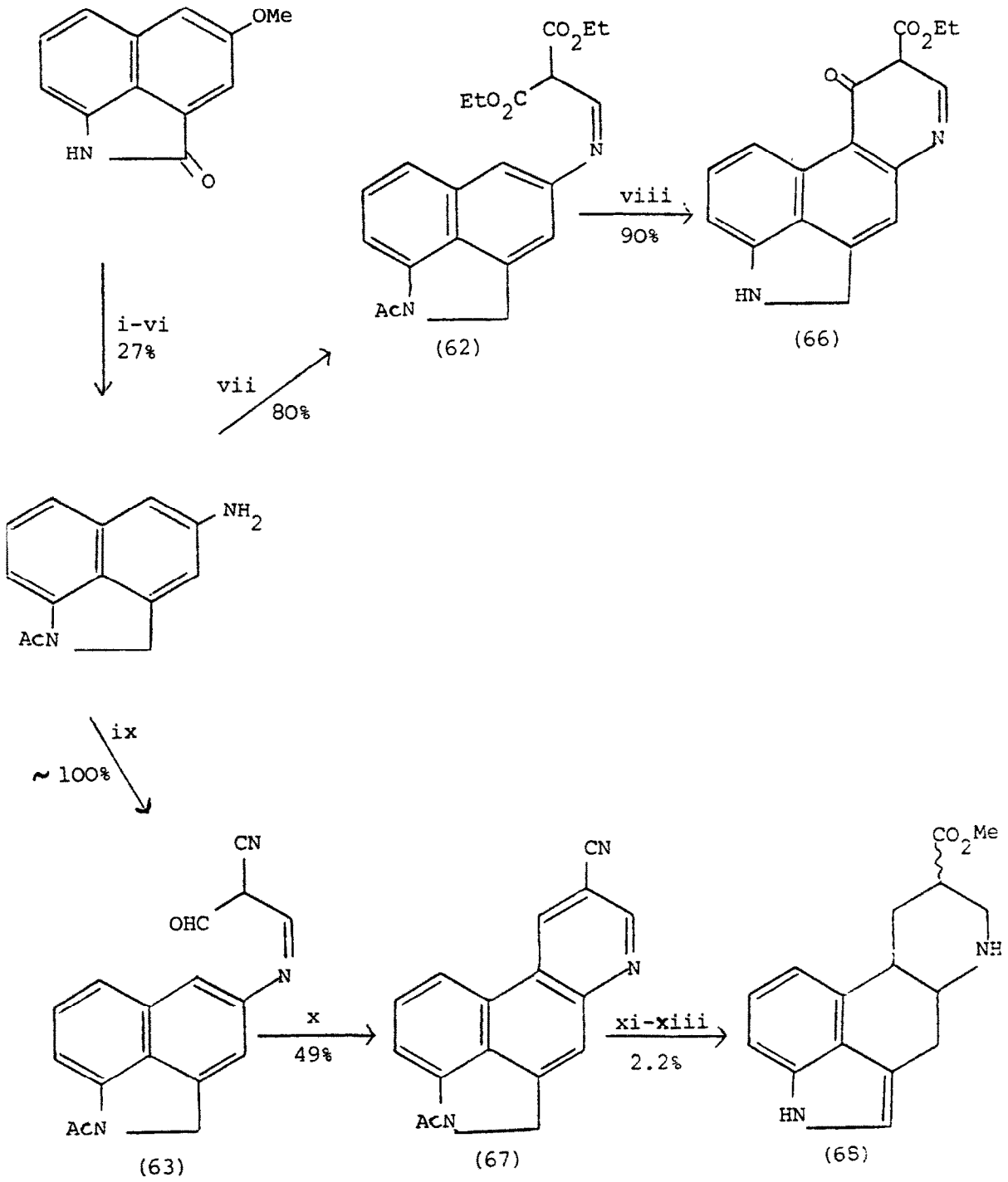
R^1=R^2=H, R^3=COPh; yield:90%

ALTERNATIVE APPROACHES TO RING D

Variations on the original routes to ring D have been developed, starting from 4-aminonaphthostyril,[75,76] 4-methoxy-[24,77] and 4-hydroxynaphthostyril,[77] 4-keto-tetrahydronaphthostyril derivatives,[78] and Uhle's ketone (**12**)[33,79] (Schemes 11–13). These routes are limited by the facile aromatisation of ring C under the reaction conditions, or by difficulty in saturating this aromatic ring in synthetically useful yields. However, the annelation of the naphthostyril derivatives

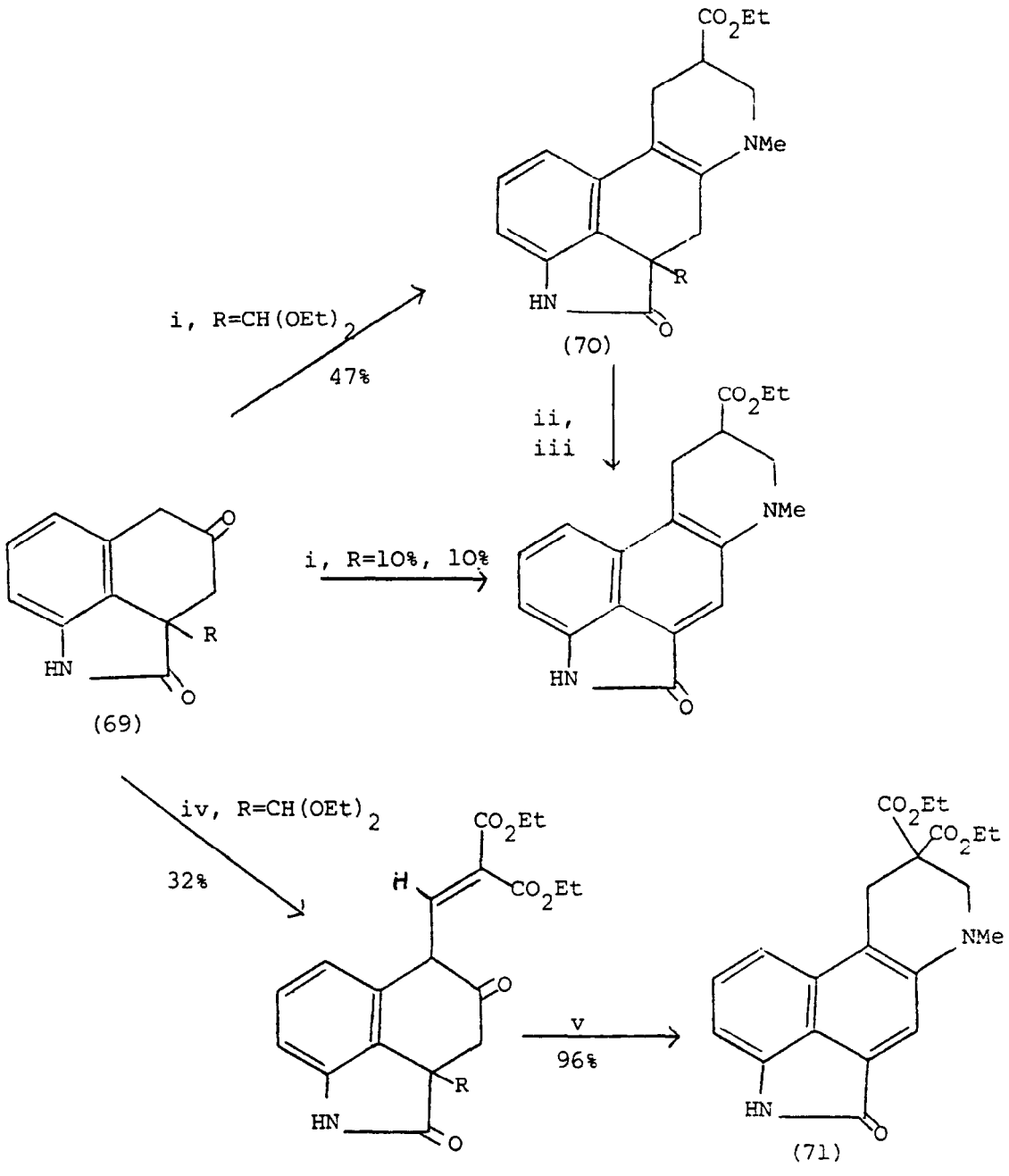


Reagents: i,  —CH_2Cl-EtOH-ΔH; ii, NaOAc-MeOH-MeBr; iii, $C_6H_5NEt_2$-ΔH; iv, Na-BuOH; v, COCl; vi, hν-C_6H_6-AcOH-96 hr.



Reagents: i, $LiAlH_4$; ii, Ac_2O; iii, HBr-HOAc; iv, Ac_2O-pyridine, v, Na_2CO_3-H_2O; vi, $(NH_4)_2SO_4$-NH_4OH-bomb; vii, $EtO{=}C(CO_2Et)_2$-EtOH-ΔH viii, Dowtherm; ix, NaH-CN (CHO, CHO); x, $ZnCl_2$-C_6H_5CN; xi, H_2SO_4-EtOH-NH_4Cl,ΔH; xii, Na-EtOH; xiii MeOH-HCl.

Scheme 11.

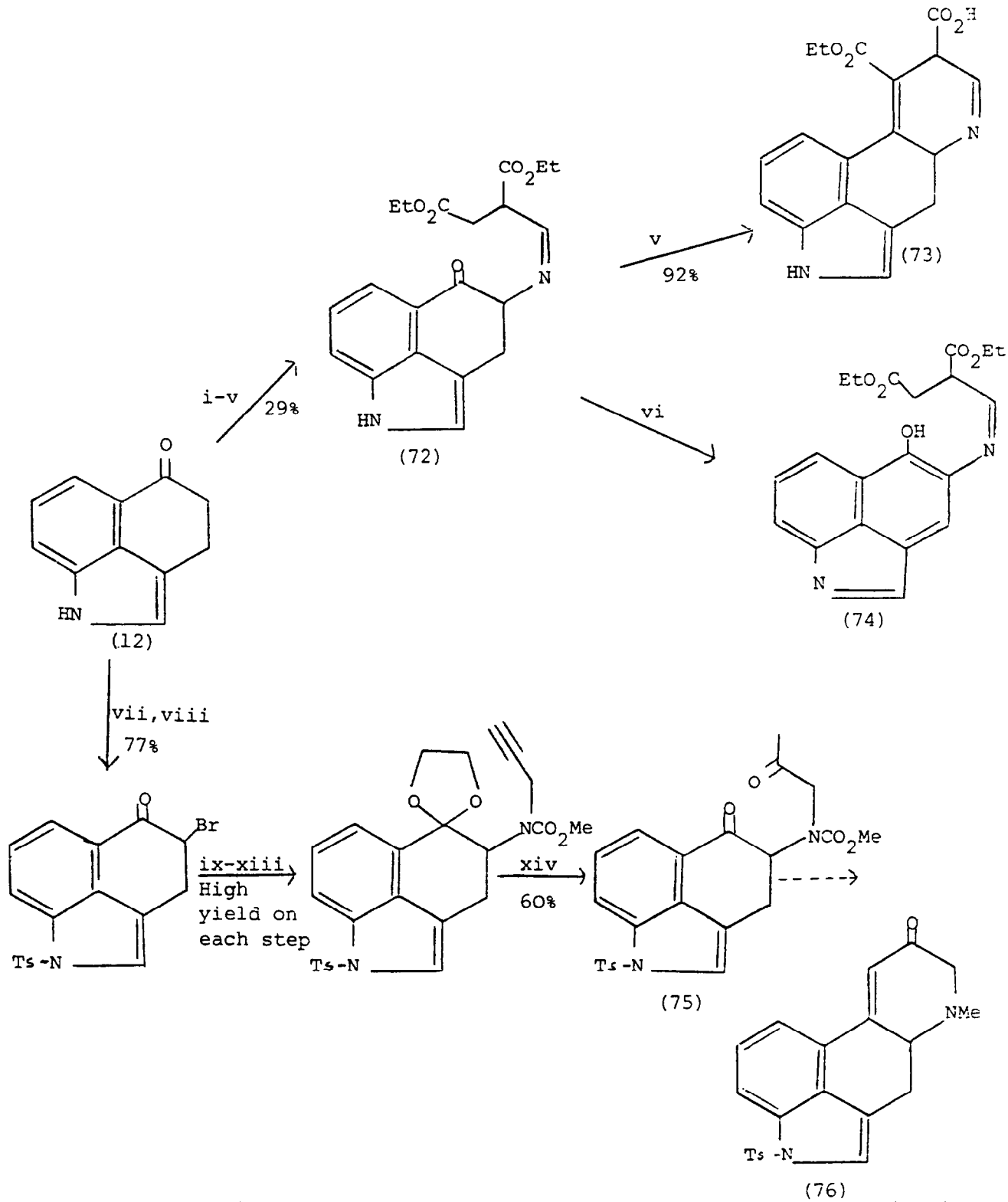


Reagents: i, $\overset{CH_2Br}{=}$ CO_2Et-H_2NMe-EtOH; ii, Ac_2O; iii, HCl;

iv, $EtO=\overset{CO_2Et}{\underset{CO_2Et}{<}}$-$KOBu^t$; v, HCHO-$HNMe_2$-NaOAc

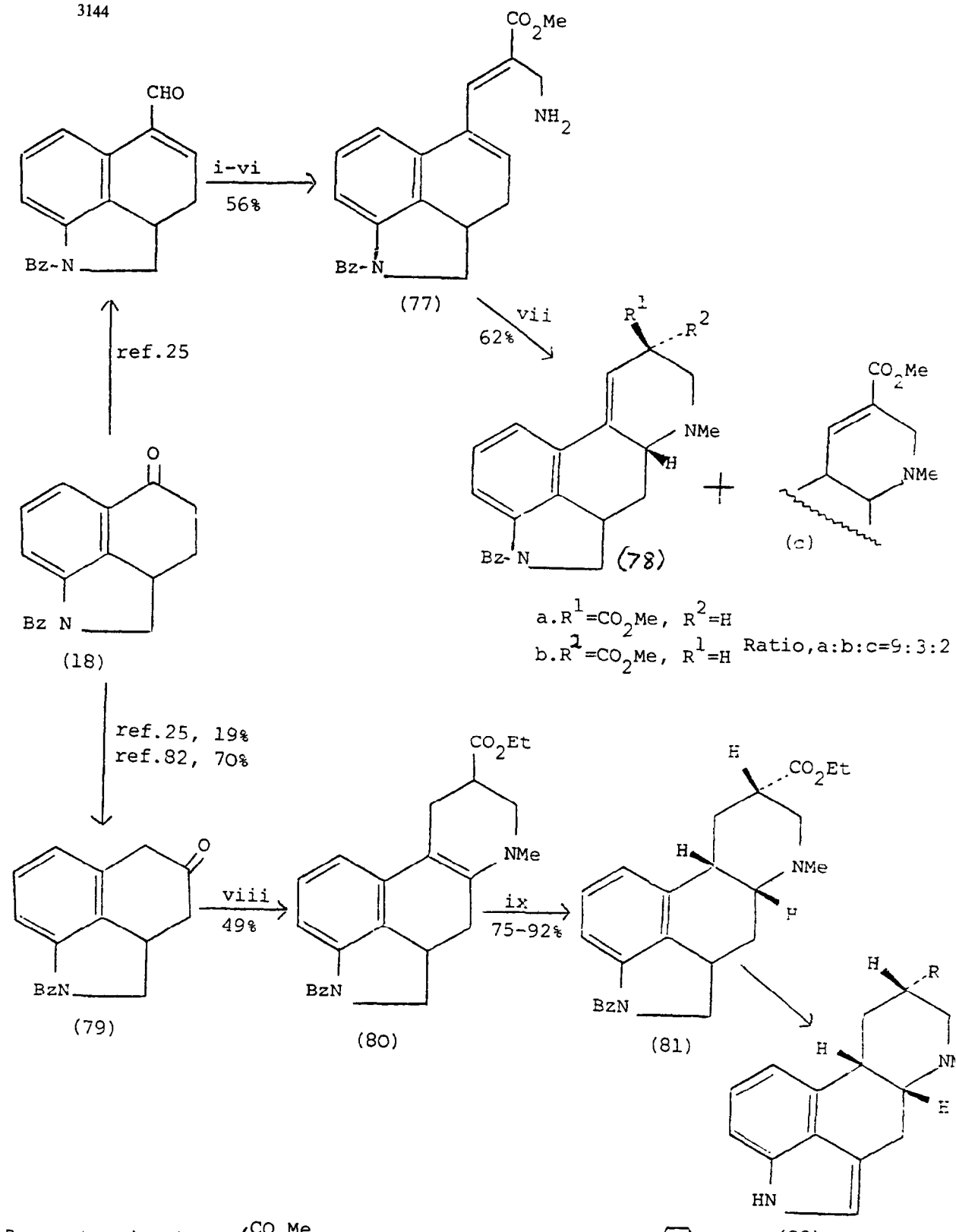
Scheme 12.

60,[75] **61**,[76] **62**[24] and **63**,[79] has given good yields of the aromatic ring C derivatives **64–67** respectively (Scheme 11). By conversion of the labile lactam of naphthostyril to the N-acetylbenz [c,d] indoline (**62**), it was hoped that the sodium in alcohol reduction would give better yields of the saturated ring C and D derivatives than the original routes (Schemes 1 and 2). However, the compound **67** could be converted to a mixture of the methyl esters of dihydro- and dihydroiso-norlysergic acids (**68**) in only 2.2% yield. Nevertheless, this procedure does constitute an alternative route to dihydrolysergic acid.



Reagents: i, $KOBu^t$; ii, AmONO; iii, Zn; iv, $OHC-CH(CO_2Et)_2$-NaOAc; v, $KOBu^t$-Bu^tOH; vi; Al_2O_3 column eluted with 1% EtOH in $CHCl_3$; vii $TsCl$-K_2CO_3; viii, $Me_3PhNH_4Br.Br_2$; ix, NaN_3-H_2SO_4; x, $[OH]_2$-BF_3Et_2O; xi, $LiAlH_4$; xii, $ClCO_2Me$; xiii, NaH-$BrCH_2C{\equiv}CH$; xiv, $HgSO_4$-H_2SO_4-H_2O.

Scheme 13.



Reagents: i, $Ph_3P=\langle^{CO_2Me}_{CO_2Bu}$ t-ΔH; ii, TFA; iii, Ph_2POCl-O NMe; iv, tetramethylgu anidinium-azide-CH_3CN; v, Δ H; vi, PTSA; vii, HCHO-HCO_2H-100°-1 hr; viii, $=\!\!-^{CO_2Et}_{CH_2Br}$-CH_3NH_2; ix, PtO_2-H_2-EtOAc.

Scheme 14.

Condensation of the 4-ketotetrahydronaphthostyril derivative (**69**) with either bromomethylacrylate or diethylethoxymethylene malonate, has given the annelated products (**70** and **71**) respectively, in fair yields.[78] However, the facile aromatisation of ring C observed with the intermediates in these schemes led Grob to abandon this as an approach to lysergic acid (Scheme 12). It is worth noting that the double bond of the enamine (**70**) could be readily hydrogenated, to provide the corresponding saturated ring D derivative in high yield.

Condensation of the Schiffs base (**72**) derived from Uhle's ketone (**12**) is catalysed by potassium t-butoxide, to give the annelated product (**73**) in excellent yield. In contrast, passage of **72** through a column of alumina gives only the aromatised ring C derivative (**74**).[79] Bowman has developed a route to the 1,4-diketone (**75**) from Uhle's ketone, but by a rather long route (Scheme 13).[33] The tosyl group was found to be particularly effective in protecting the N–H group of the indole ring. This tosylation can now be effected under mild conditions by phase transfer catalysis.[80] Cyclisation of **75** to produce the target compound (**76**), had not been achieved at the time this work had to be terminated.

The Kornfeld tricyclic ketone (**18**) has also been further utilised in two novel routes to form ring D (Scheme 14). The key step in a new route to lysergic acid involves the cyclisation of **77** to **78**.[81] This procedure is formally based on the reverse of the mechanism proposed by Woodward to account for the ready epimerisation of lysergic acid and isolysergic acid. A four step conversion of the ketone (**18**) gives the transposed ketone (**79**).[25,82,83] This process has been improved.[82] Condensation of **79** with ethylbromomethylacrylate, has given the annelated product (**80**) in fair yield, in analogy with the Grob cyclisation procedure (cf. **69** → **70**). Catalytic hydrogenation of the enamine (**80**) gives the precursor (**81**) to a novel series of 5,10 *cis*-fused analogues of racemic dihydroisolysergic acid esters (**82**) and isodihydrolysergol (**83**).[83]

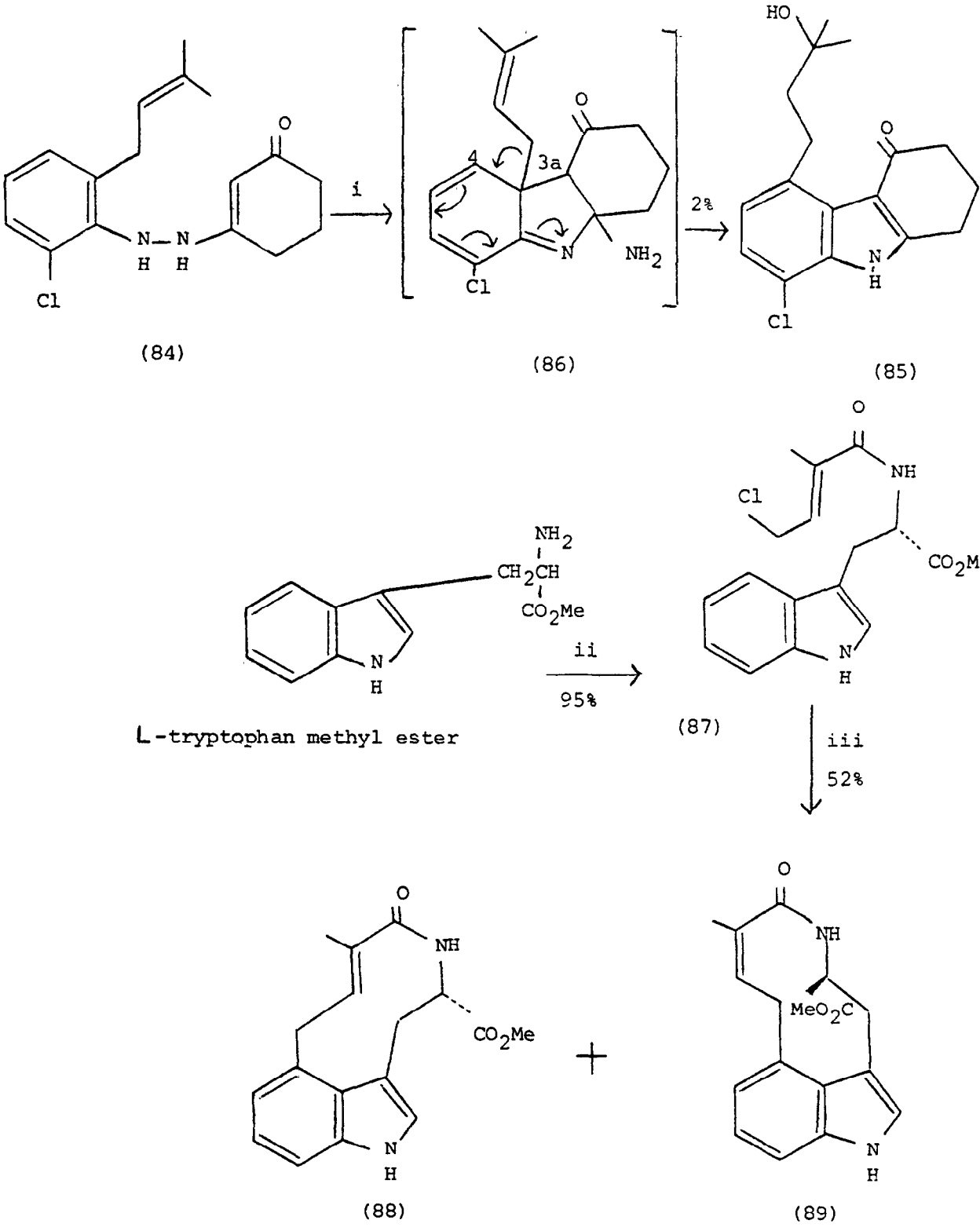
OTHER APPROACHES TO 4-SUBSTITUTED INDOLE DERIVATIVES

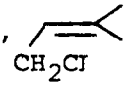
The development of new procedures to 4-substituted indole derivatives has been investigated, as precursors for both ergolines and other intermediates of ergot alkaloid biosynthesis.

The general syntheses of indoles has been adequately summarised elsewhere.[7,84–87] Plieninger and Hardegger have indicated a wide range of 4-substituted indoles which are available as potential intermediates for ergoline synthesis.[89–94] A new route to indoles, developed by Gassman, gives a "one pot" procedure to substituted 4-nitroindoles from 3-nitroanilines.[36] Grob has described the synthesis of 6-chloro-2-nitrophenylacetic acid in 84% yield from 2,3-dichloronitrobenzene.[95] Reduction and ring closure of this intermediate should offer a route to 4-chloroindole.

Synthetic strategies to 4-substituted indoles have been attempted by biomimetic procedures. Baldwin has suggested that a [1,2] sigmatropic shift of a prenyl group from the 3a- to 4-position may be the key step in the early stages of ergot alkaloid biosynthesis. Acid catalysed thermolysis of the model compound (**84**) effects the rearrangement to **85**, but only in 2% yield. The intermediate is presumed to be the 3a- prenyl compound (**86**).[96] Perhaps more synthetically attractive is the remarkably facile photochemical cyclisation of the readily available compound (**87**), which has given a mixture of the 10-membered lactams (**88** and **89**) in 33% and 19% yield respectively (Scheme 15).[97] Examination of a Drieding model of **87**, indicates that the ideal geometry for ring closure of this compound involves little strain in the system. This contrasts sharply with the intermediates used in annelation procedures to form the 6-membered ring C directly (e.g. compounds **20**, **41**, **50**, **51** and **54**). Strategies involving direct cyclisation of 3-substituted indoles to form larger ring C analogues may, therefore, warrant further investigation. This would involve transannular closure of such intermediates as **88** and **89**, or ring contraction of 7-, 8- or 9-membered ring C precursors.

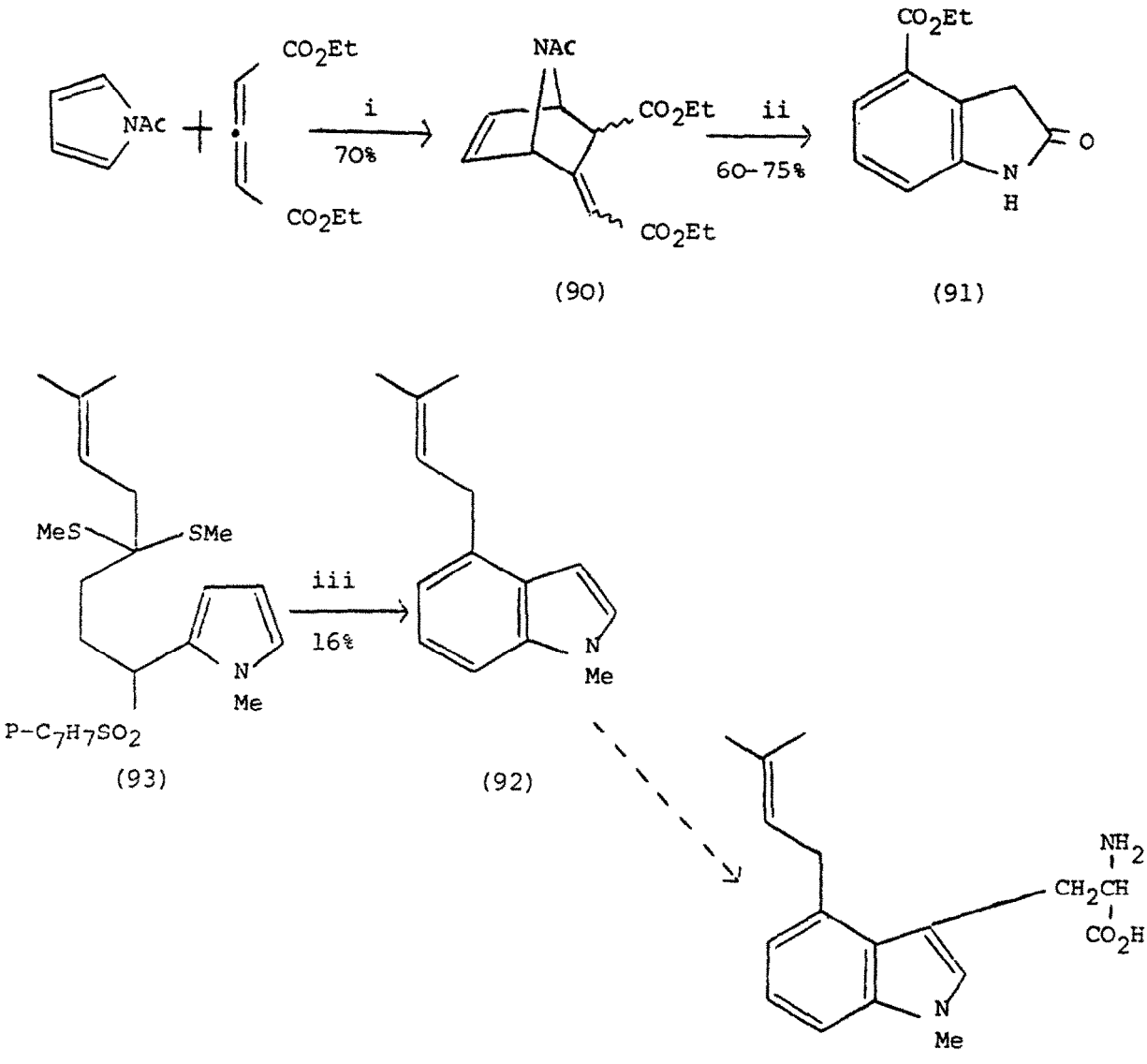
Two novel approaches have been developed by building 4-substituted indoles from pyrrole derivatives. Treatment of the Diels–Alder adduct (**90**) between N-acetylpyrrole and 1,3-dicarbethoxyallene with potassium hydride gives 4-carbethoxyoxindole (**91**) in good yield and under mild conditions.[98] The electron rich aromatic system of N-methylpyrrole allows the regiocontrolled cyclisation of a thionium ion, to give **92** in 16% yield.[99] The ion is derived from treatment of **93** with *p*-toluenesulphinic acid in refluxing acetonitrile. Further elaboration of **92**, in analogy with the work of Plieninger,[100] would give the 1-methyl derivative of dimethylallyltryptophan, the biosynthetic precursor of ergot alkaloids (Scheme 16).



Reagents: i, H_2SO_4 - H_2O - 102° - 15 min; ii,  - $(Pr^i)_2$ NEt;

iii, hν-vycor filter, 6 hr.

Scheme 15.



Scheme 16.

SUMMARY

The synthetic strategies to the ergoline ring system (I) have been outlined, and discussed in terms of their yields and limitations. The total syntheses of ergoline, racemic and natural dihydrolysergic acid, lysergic acid, isosetoclavine, penniclavine, elymoclavine and chanoclavine-I have been described. These illustrate the synthetic problems that have been encountered in ergoline chemistry. The role of key intermediates has been emphasised. Modification to the original schemes have not given yields or procedures that can compete with the production by fermentation of ergot alkaloids. However, it is hoped that the synthetic strategies discussed in this article will provide useful information, when considering new approaches, or modification, to the unique heterocyclic ring system of ergoline.

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Note added in proof. The transposed ketone (**79**) has been further utilised in the synthesis of the clavine alkaloids costaclavine, epi-costaclavine, and festuclavine by a modification to the route outlined in Scheme XIV.[101]

The addition of singlet oxygen to *N*-carbethoxypyrrole, followed by reaction with nucleophiles offers an alternative synthesis of 4-substituted indoles. The scheme has been extended to give precursors of 6,7-secoergolines,[103] further elaboration of which has given the first total synthesis of racemic 6,7-secoagroclavine,[104] an ergot alkaloid recently extracted from a fermentation broth of claviceps purpurea AA-218.[105] A new synthesis of chanoclavine I from 4-formylindole has also appeared.[106]