

SYNTHESES OF INDOLIZIDINE ALKALOIDS - A REVIEW

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Dedicated to Professor Gilbert Stork on the occasion of his 65th birthday

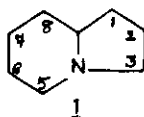
Abstract - Synthetic approaches to the indolizidine alkaloids as well as chiral syntheses of some members of this group published during 1979-1985 are reviewed.

The literature on the syntheses of indolizidine alkaloids upto the end of 1979 has been the subject of some reviews¹⁻⁴. Subsequently there have been a large number of publications⁵ on this subject and the present review covers the literature from 1979 to the end of 1985. A number of general methods have been developed for the syntheses of the basic skeleton of indolizidines and substituted indolizidines and these will be the subject of a separate review. The present review is restricted to syntheses of compounds of natural origin. For convenience, the review is presented according to the following plan.

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 - 2.1.1.2. Elaeocarpus alkaloids.
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1. Introduction

The indolizidine system 1 is present in many alkaloids isolated from plants, and also from fungal and animal sources. The alkaloids found among the Amaryllidaceae or Erythrina are not included in this review because of structural and biogenetic considerations. Securinega alkaloids are also not discussed here.



2.1. Simple Indolizidine Bases

2.1.1. Plant Origin

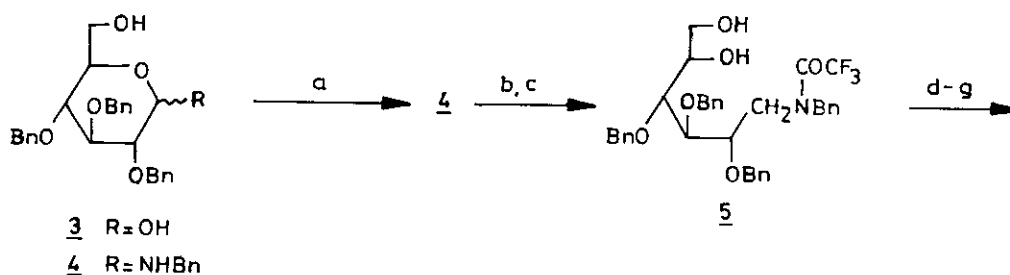
2.1.1.1. Castanospermum Alkaloids

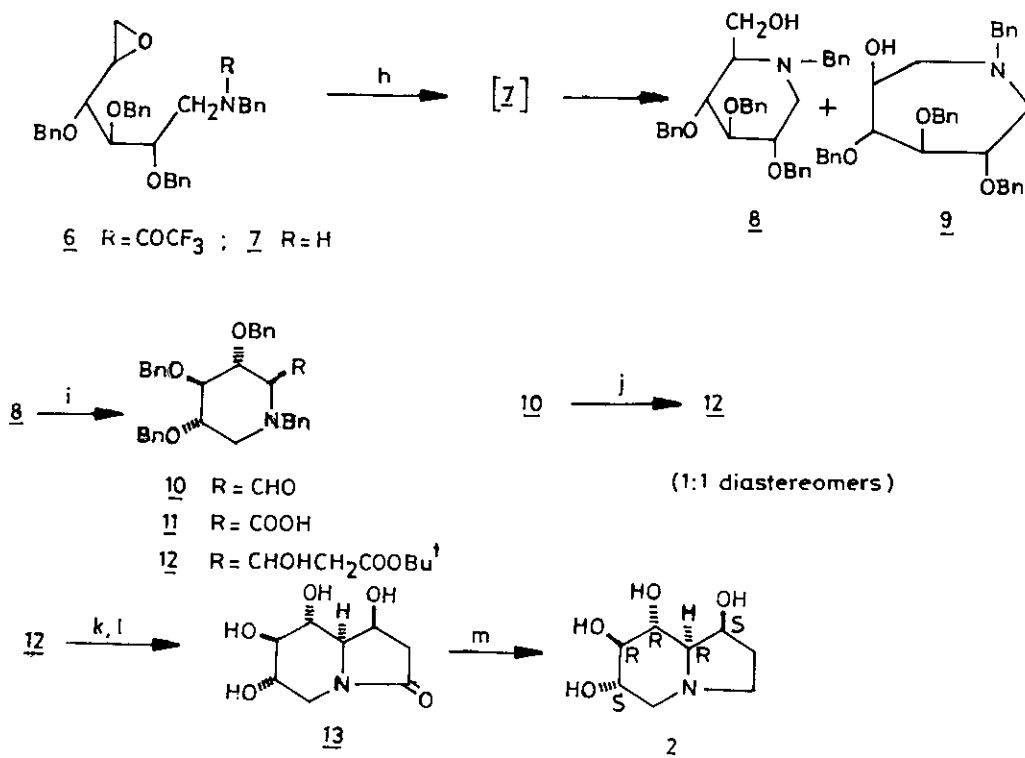
Castanospermine 2 isolated from the toxic seeds of Castanospermum australe⁶ is a potent inhibitor of numerous carbohydrate-processing enzymes. It is shown to inhibit α - and β -glucosidases in fibroblast extracts as well as the processing of oligosaccharide portions of influenza viral hemagglutinin⁷. The first and the only synthesis of castanospermine 2 is a chiral synthesis reported by Ganem and Bernotas⁷ starting from the chiral synthon α D-glucose according to Scheme 1. (+)-Castanospermine thus synthesised had $(\alpha)_D + 71^\circ$ (c, 0.27, H₂O).

2.1.1.2. Elaeocarpus Alkaloids

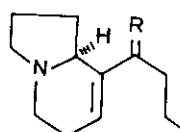
These alkaloids viz. elaeokanines A 14, B 15, C 16, D 17, E 18, elaeocarpine 19, and isoeleocarpine 20 have been isolated by Johns *et al.* from the leaves of Elaeocarpus species (Elaeocarpaceae) - rain forest trees which flourish in New Guinea^{3,8} and India⁸.

Scheme 1



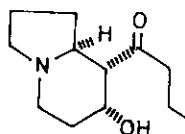


Reagents: a. Benzylamine; b. LAH, THF; c. (CF₃CO)₂O, Py; d. TBDMSCl, imidazole; e. MsCl, Et₃N, f. *n*-Bu₄NF, THF; g. CH₃ONa, MeOH; h. NaBH₄, EtOH, 40°C; i. (COCl)₂, DMSO; j. Lithio-*t*-butyl acetate; k. Hydrogenolysis; l. TFA, H₂O, 60°C, 3h; m. Dibal, THF.

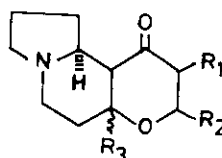


14 R = O

15 R = H, OH

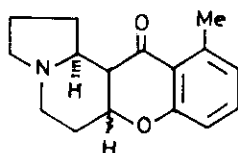


16



17 R₁ = H₂, R₂ = α-Me, R₃ = α-H

18 R₁ = H₂, R₂ = α-Me, R₃ = β-H

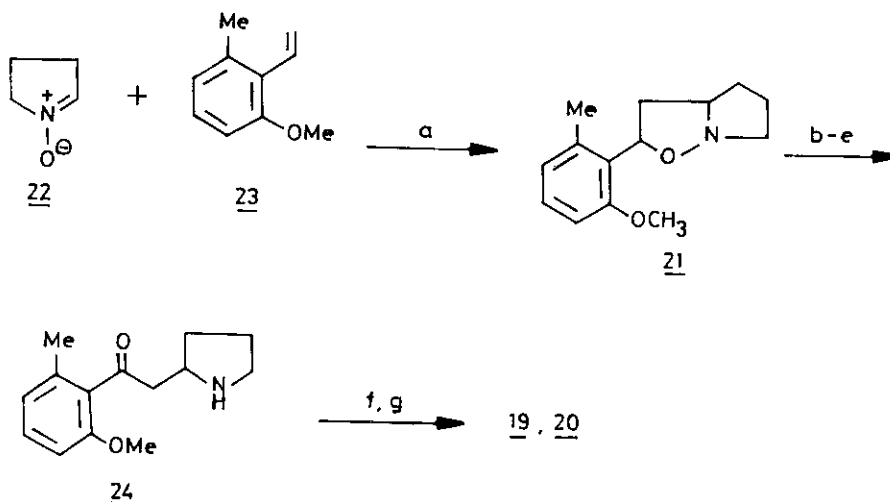


19 α-H

20 β-H

The synthesis of this series of alkaloids starting from nitrones was reported by Tufariello⁹. The isooxazolidine 21 was prepared by the addition of nitrone 22 to the hindered styrene 23 (Scheme 2). Elaeocarpine 19 and isoeleocarpine 20 were synthesised by this method.

Scheme 2



Reagents: a. Toluene, 85°C; b. H₂, PtO₂; c. BzOCOC1, Py; d. Collins reagent; e. H₂, Pd-C;

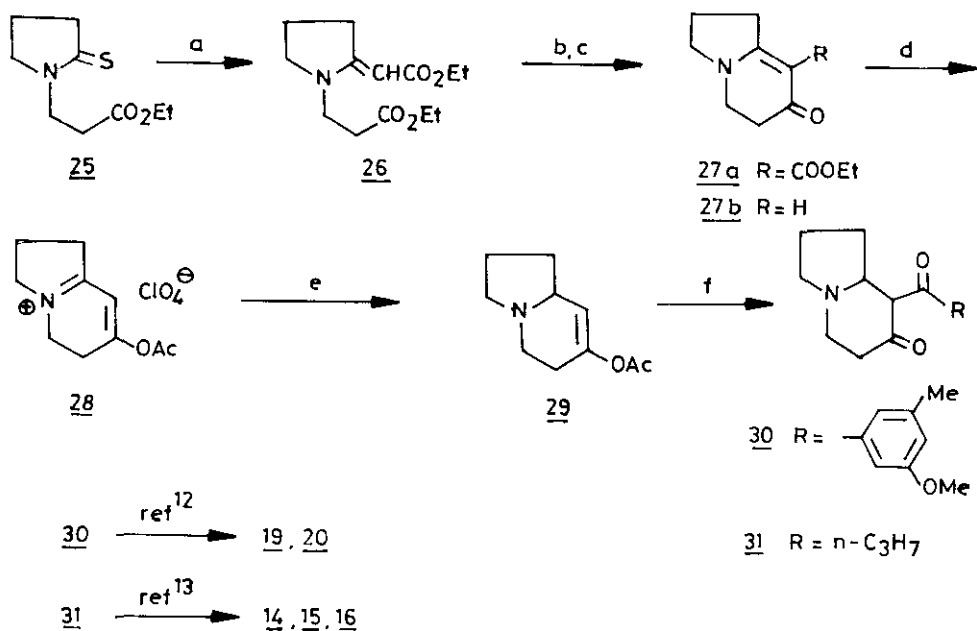
f. Acrolein; g. BBr₃

A formal synthesis of 14, 15 and 16 was reported by Howard and coworkers¹⁰. The substituted dehydroindolizidine 27 was synthesised from the exocyclic vinylogous urethane 26 via an acylative ring closure. Pyrrolidine-2-thione was alkylated on the nitrogen to yield 25 (CH₂=CHCOOEt, THF, NaOH (catalytic), 55°C, 98%) which was converted to the vinylogous urethane 26 using a sulphide contraction sequence¹¹ (Scheme 3).

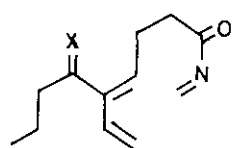
As an extension of Trost's method¹⁴ for the synthesis of quinolizine derivatives from iminoether and α,β -unsaturated ketones, 2-ethoxy-1-pyrrolidine and ethyl 3-oxopentanoate yielded 27 in 80% yield¹⁵ which was converted to elaeokanines A 14, B 15, and C 16 and also compounds 17, 19 and 20.

Weinreb and his team¹⁶ in their synthesis of elaeokanine A 14 have envisaged the iminedienophile as 32 and have constructed it in its 'masked form' to free it when needed for the intramolecular cycloaddition reaction. Thus, the 'masked iminedienophile 34' was prepared and was converted to elaeokanine A 14 (Scheme 4). Coniceine and tylophorine 210 were also synthesised by this method.

Scheme 3

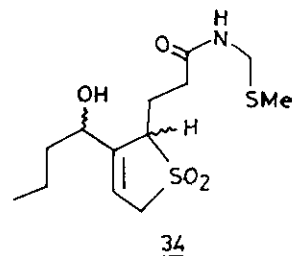


Reagents: a. $\text{CH}_2\text{BrCOOEt}$, CH_3CN , r.t., 16h; Ph_3P , Et_3N , CH_3CN , r.t.; b. Aq. NaOH (0.4M, 1 equiv.), reflux, 0.5h; c. Ac_2O , CH_3CN , r.t., 40h; d. CH_3COCl , AgClO_4 , CH_3CN , N_2 , dark, r.t., 1.5h; e. NaBH_4 , CH_3CN , r.t., 1h, gl.HOAc, reflux; f. MeLi , THF, N_2 , 0°C , 0.25h, RCOCl , THF, N_2 , 0°C .

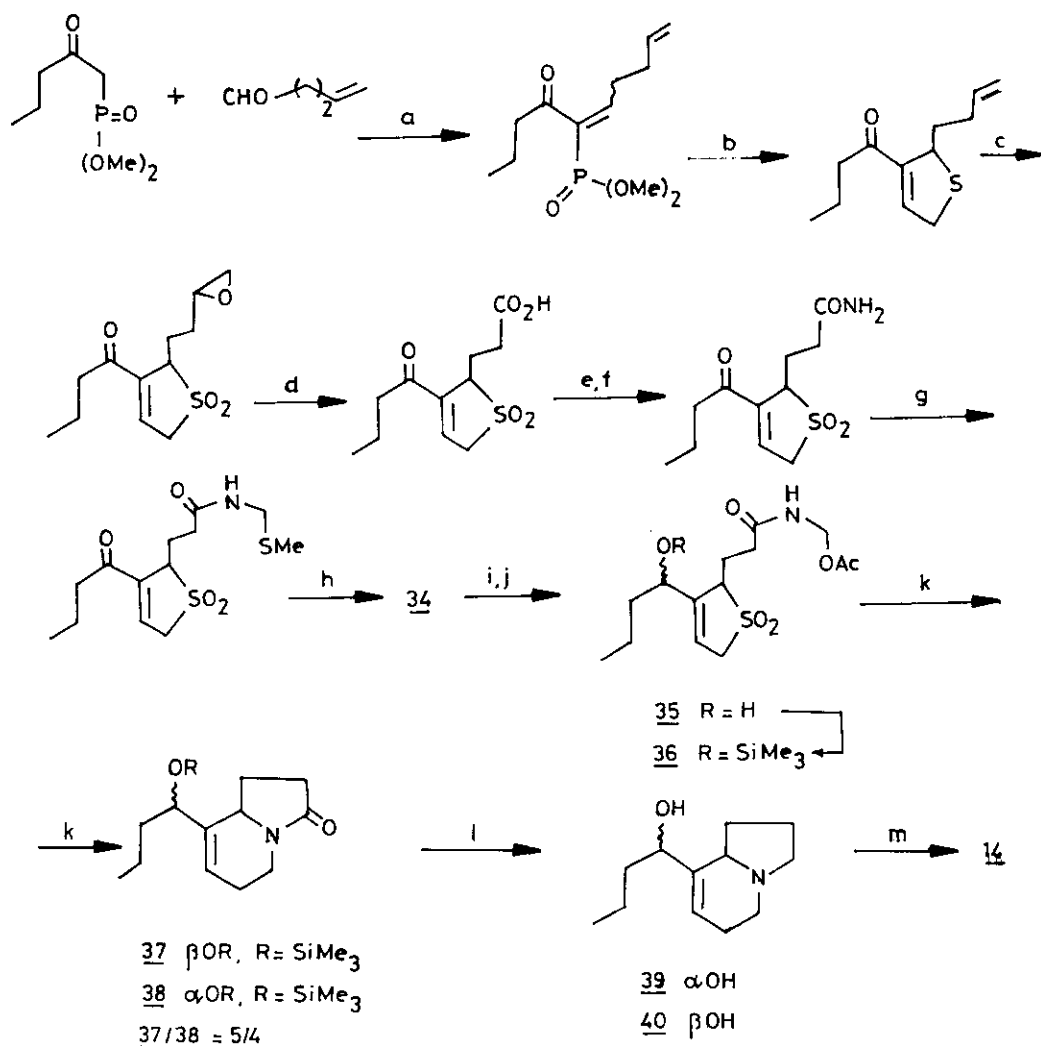


$\underline{32} \quad X = \text{O}$

$\underline{33} \quad X = \text{H, OR}$



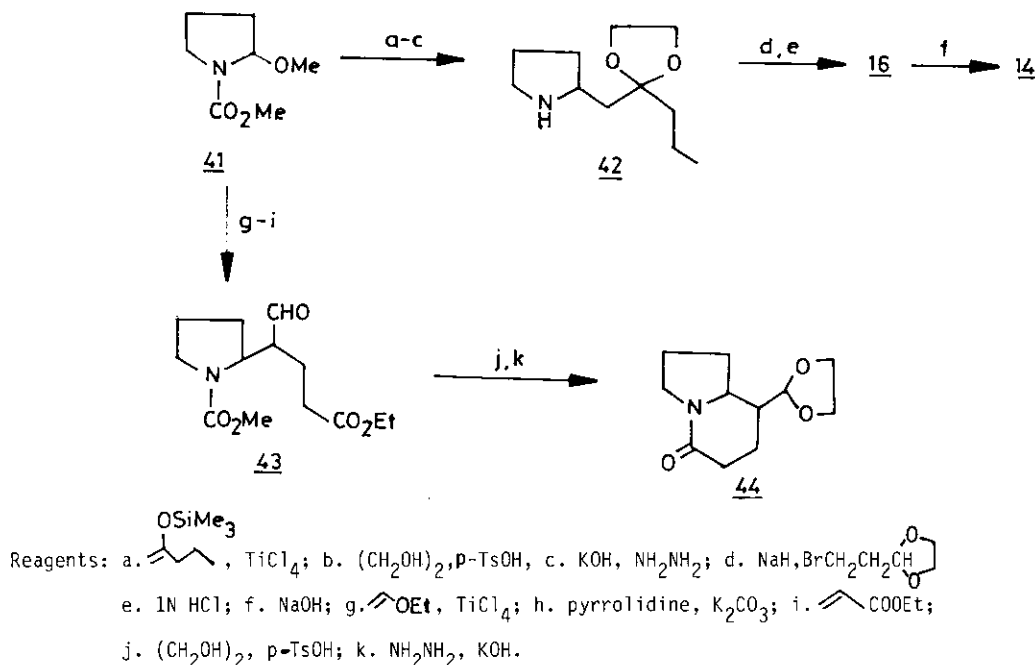
Scheme 4



Reagents: a. Piperidine, HOAc, C₆H₆; b. HSCH₂CHO, Et₃N; c. mCPBA, CH₂Cl₂; d. H₅IO₆, CrO₃, acetone, H₂O; e. EtOCOC₂Cl, Et₃N; f. NH₃; g. chloromethyl methylsulphide, CF₃COOH; h. NaBH₄, CeCl₃; i. Mercuric acetate, gl. HOAc; j. Silylation; k. Δ, 370°C, 1. Dibal, THF; m. CF₃COOH, DMSO.

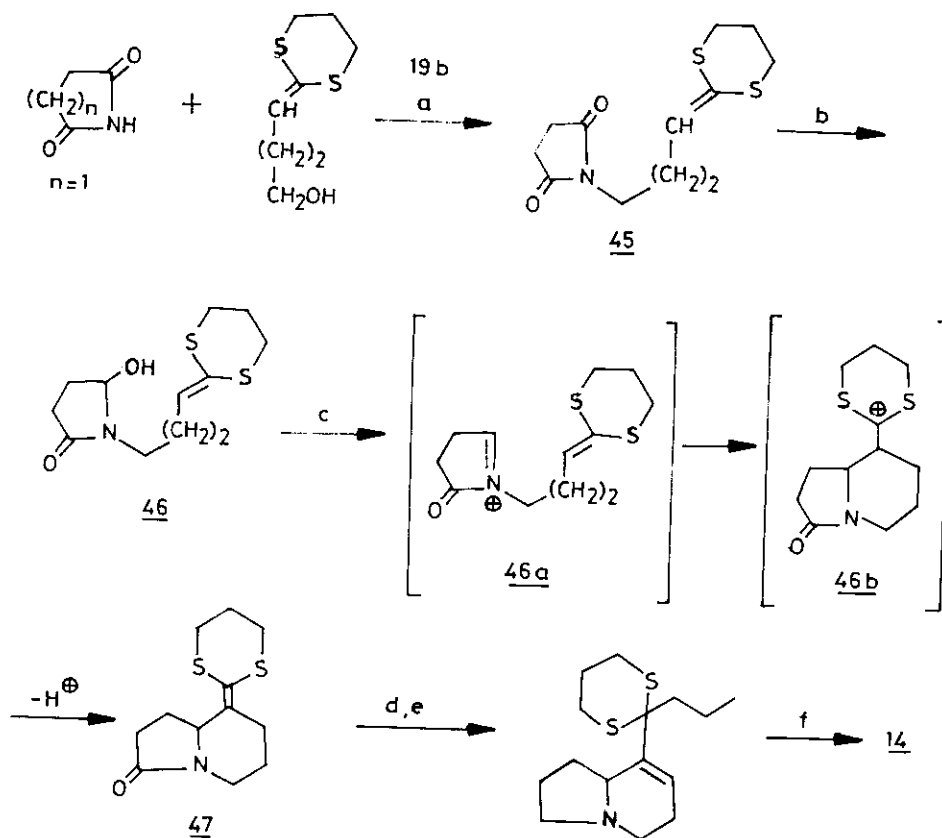
Shono and coworkers¹⁷ have synthesised *Elaeocarpus* alkaloids **14** and **16** by utilising anodically prepared 1-(alkoxycarbonyl)-2-methoxypyrrolidine **41**, as a key intermediate¹⁸ according to Scheme 5

Scheme 5



Chamberlin and coworkers^{19a} have utilised the ketenedithioacetal cyclisation for the synthesis of pyrrolizidine, indolizidine and quinolizidine alkaloids. Ketene dithioacetal group was used effectively as a new cationic (acyliminium) cyclisation terminator (as clearly depicted in Scheme 6). In addition, two modifications to the conventional methodologies for the acyliminium ion formation for this cyclisation were made. For the conversion of N-alkylimide 45 to the hydroxylactam 46, sodium borohydride reduction was carried out in methanol at -4°C. Over-reduction was prevented by simply pouring the reaction mixture into a stirred aqueous bicarbonate-methylenechloride mixture. The hydroxylactam recovered from the organic layer was suitable for the cyclisation step without further purification. Secondly, the formation of the iminium ion was done in non-acidic medium i.e. the hydroxylactam 46 was converted into the mesylate. This mesylate was not observed but undergoes rapid elimination to the acyliminium ion 46a followed by cyclisation to 46b which with the loss of a proton gives a new cyclic ketenedithioacetal 47 in good yield (Scheme 6). Conversion of 47 to 14 is depicted in the Scheme.

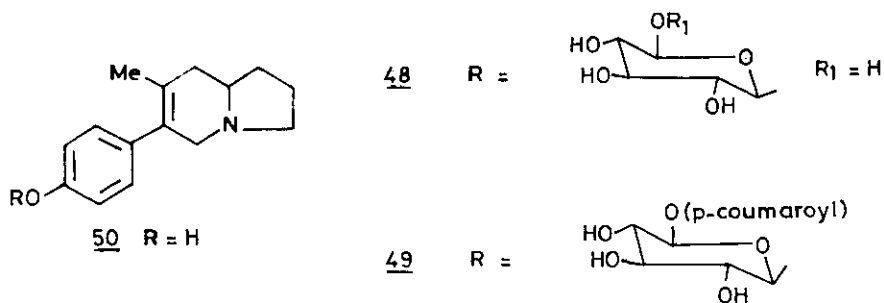
Scheme 6



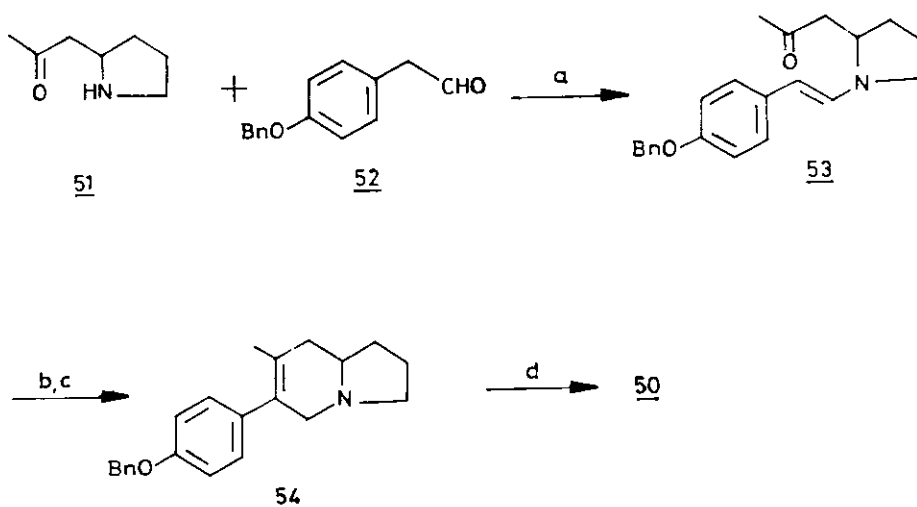
Reagents: a. Ph_3P , $COOEt-N=N-COOEt$; b. $NaBH_4$; c. $MsCl$, Et_3N , CH_2Cl_2 , $-20 \rightarrow 20^\circ C$; d. LAH; e. LDA, 1 ; f. Mercuric chloride, H_2

2.1.1.3. The Ipomoea Alkaloids

These alkaloids are isolated from the seeds of *Ipomoea alba*²⁰ and *Ipomoea muricata*^{21,22}. They are, two glycosides ipalbicine **48** and ipomine **49** and their aglycone ipalbidine **50**. Ipalbidine **50** is the only example of a naturally occurring indolizidine alkaloid having a unique structural feature of a C-methyl group on the hexahydroindolizidine nucleus²⁶. Several syntheses of ipalbidine are known upto 1979²³. Herbert and Hedges²⁴ have synthesised ipalbidine according to Scheme 7.



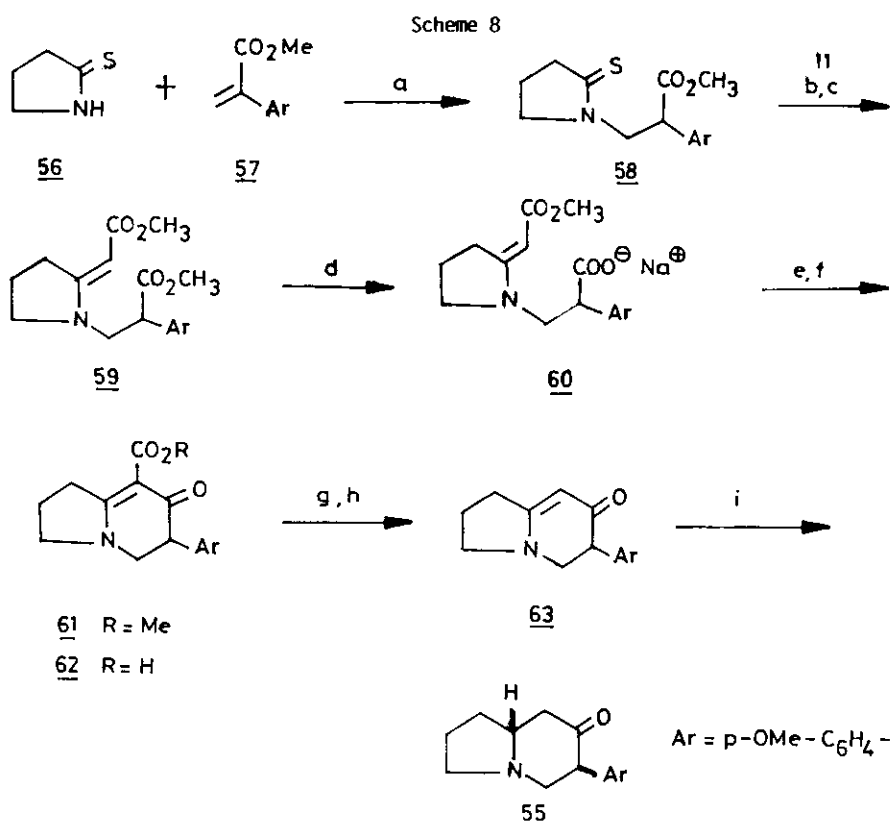
Scheme 7



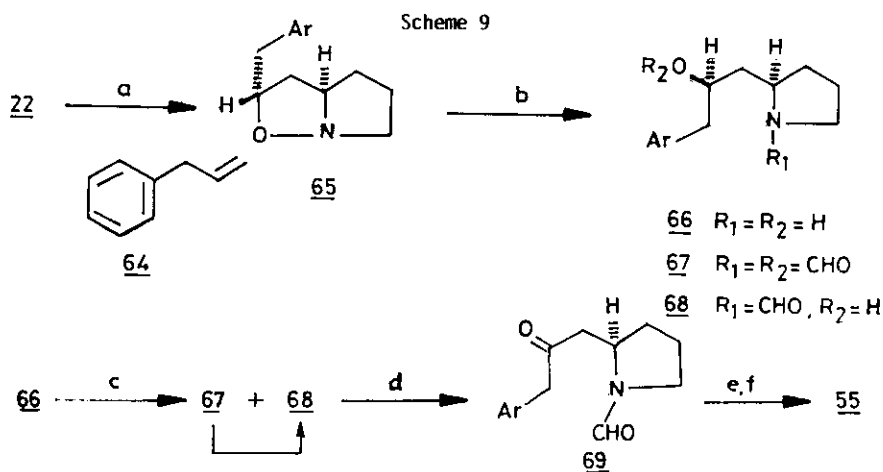
Reagents: a. Benzene, r.t.; b. MeOH; c. NaBH_4 , PrOH; d. HCl

Howard *et al.*²⁵ have synthesised the bicyclic ketone 55 by an acylative ring closure of the vinylogous urethane 60 through 61. Since the conversion of 55 to ipalbidine is a well known reaction, this completes the formal synthesis of ipalbidine 50 (Scheme 8).

Recently Iida *et al.*²⁶ have synthesised the bicyclic ketone 55 by intramolecular cyclisation of the N-formyl ketone 69 which was obtained via a (3+2) cycloaddition reaction of the cyclic nitron 22 with the olefine 64 (Scheme 9).



Reagents: a. NaOH(catalyst), THF; b. BrCH₂COOMe, THF; c. PPh₃, Et₃N, CH₃CN; d. NaOH (1 equiv.), H₂O; e. *n*-Bu₄NI; f. ClCOOMe, THF; g. KOH, H₂O, N₂; h. HCl; H₂O; i. LAH, THF.



Reagents: a. Toluene, reflux; b. Pd-C, H₂; c. HCOOH; d. Collins reagent; e. Aluminium isobutoxide; f. Li, liq. NH₃.

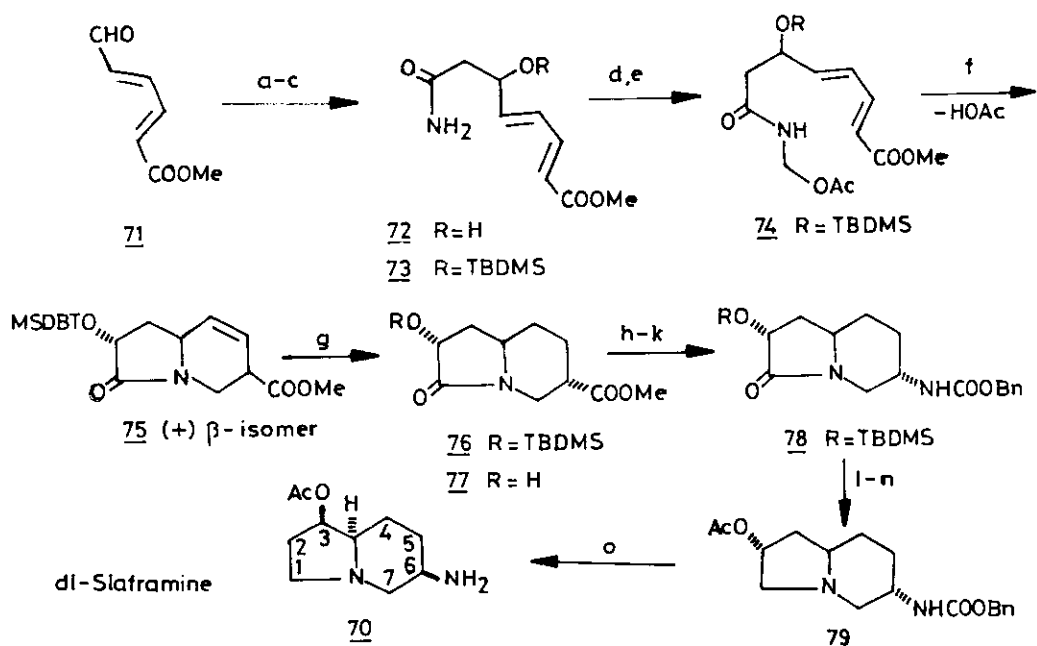
2.1.2. Fungal and Animal Origin

2.1.2.1. Alkaloids of *Rhizoctonia leguminicola*

2.1.2.1a. Slaframine

Slaframine **70** is a fungal toxin produced by *Rhizoctonia leguminicola*²⁷. It is responsible for excessive salivation of the livestock consuming mould-infested legume feeds. It is also a stimulator of the parasympathomimetic exocrine glands. The synthesis of the same was reported earlier by Rinehart *et al.*²⁸ with an overall yield of 0.1%, later by Christophel²⁹ with an overall yield of 0.3%. Weinreb and his team³⁰ have synthesised **70** from the diene aldehyde **71** through an intramolecular imino Diels-Alder reaction. The overall yield of **70** from **71** was 1.5% (Scheme 10).

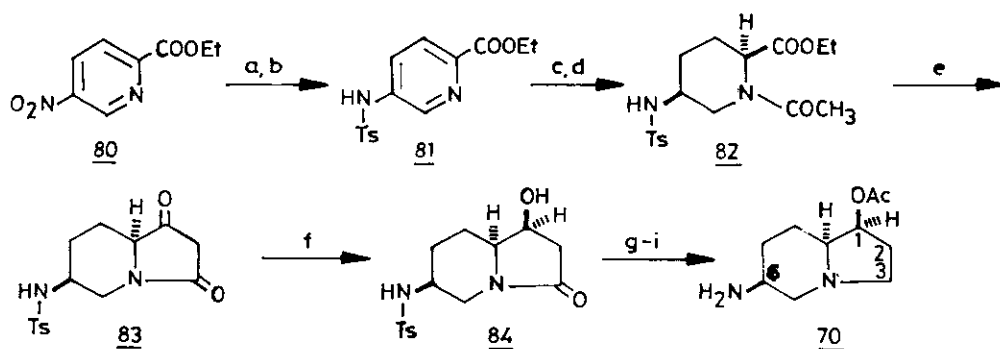
Scheme 10



Reagents: a. *n*-BuLi, trimethylsilylacetamide carbanion, -78°C ; b. H_3O^+ ; c. TBDMSCl, imidazole, DMF; d. $(\text{CH}_2\text{O})_n$, CsCO_3 , THF; e. Ac_2O , Py; f. Δ ; g. 9-BBN, THF, 0°C ; h. 5% KOH, MeOH; i. EtOCOCl , Py; NaN_3 , H_2O , 0°C ; j. THF; Δ ; k. $\text{C}_6\text{H}_5\text{CH}_2\text{OH}$, r.t.; l. B_2H_6 , THF; m. HCl, THF; n. Ac_2O , Py; o. 10% HOAc, MeOH

A stereoselective synthesis of (+)-slaframine was achieved by Schneider and Harris³¹. The key step in this synthesis is the formation of the octahydroindolizine nucleus via a potassium hydride cyclisation of the N-acetylpipecolate ester 82 to give a β -ketolactam 83. The stereochemistry of C₆ and C_{8a} of 70 was set during the catalytic reduction of 81 and this *cis*-relationship of substituents was retained during the cyclisation process. The relative configuration of C_{8a} was established via a stereoselective reduction of the β -ketolactam with L-selectride. The yield of (+)-slaframine 70 from 80 was 12% (Scheme 11).

Scheme 11



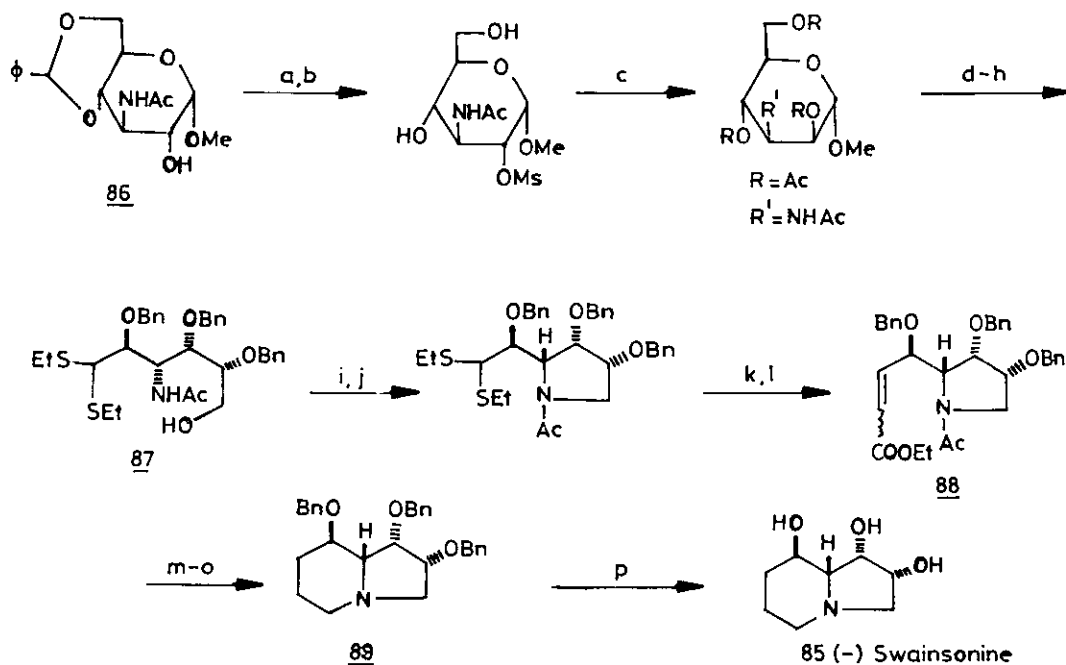
Reagents: a. H₂, Pd-C; b. pTsCl, Py; c. H₂, PtO₂, HOAc, Ac₂O; d. Ac₂O; e. KH; f. L-Selectride reduction; g. BH₃, THF; h. Na, NH₃; i. HOAc, HCl

2.1.2.1.b. Swainsonine

Swainsonine 85 is a potent inhibitor of mannosidase and disrupts the processing of glycoprotein. It has been isolated from *Swainsona canescens*³², from the locoweed *Astragalus lentiginosus*³³, from the fungus, *Rhizoctonia leguminicola*^{6b} and from cultured broth of the fungus *Metarhizium anisopliae* F3622³⁴. The alkaloid induces conditions similar to mannosidosis in cattle which graze on pastures containing these weeds³⁵. Several chiral syntheses of this alkaloid are reported recently.

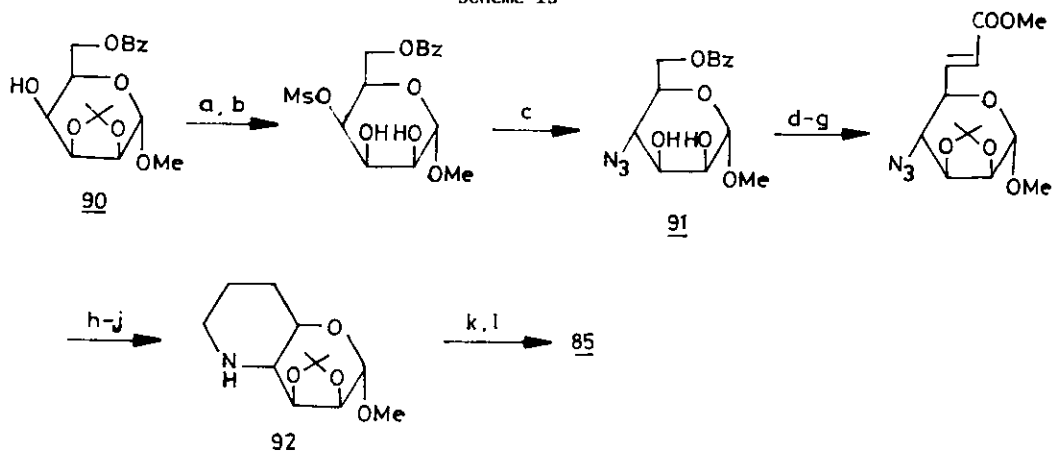
Suami and coworkers³⁶ have synthesised (-) - swainsonine 85 from D-mannose by a 15 step sequence starting from 86. The overall yield of (-) - swainsonine 85 (α)_D²⁵ - 81.7° (c, 0.6, MeOH) from the chiral precursor 86 was 2.3% (Scheme 12). Takaya *et al.*³⁴ have utilised D-mannose for the synthesis of (-)-swainsonine 85 (α)_D²⁵ - 84.7° (c, 0.53, MeOH). The intermediate 90³⁷ was obtained in 3 steps from D-mannose. The configuration of C₄ was inverted at the fourth step to yield 91 (Scheme 13)

Scheme 12



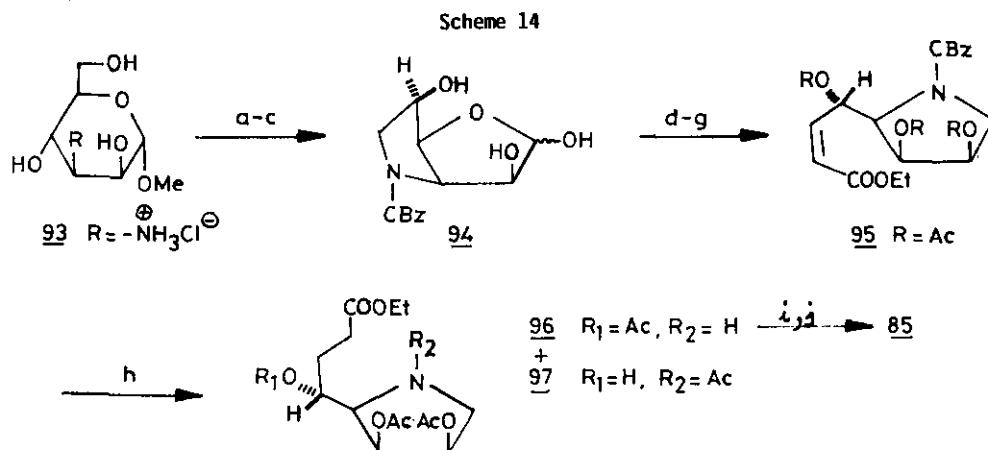
Reagents: a. $\text{MsCl}, \text{Et}_3\text{N}$; b. $\text{MeOH}, 0.06\text{M HCl}$; c. $\text{NaOAc}, \text{methoxyethanol}$; d. NaOMe ; e. EtSH, H^+ ; f. $\text{TrCl}, p\text{-DMP}$; g. $\text{BnBr}, \text{DMF}, \text{NaH}$; h. H^+ ; i. $p\text{-TsCl}, \text{Py}$; j. $\text{NaOH}, \text{reflux}$; k. $\text{HgCl}_2, \text{CaCO}_3$; l. Diethyl ethoxycarbonylmethylphosphonate, NaH ; m. Raney Ni, H_2 ; n. $\text{Aq. EtOH}, \text{KOH}$; o. LAH, THF ; p. $\text{Pd}(\text{OH})_2\text{-C}, \text{H}_2$

Scheme 13



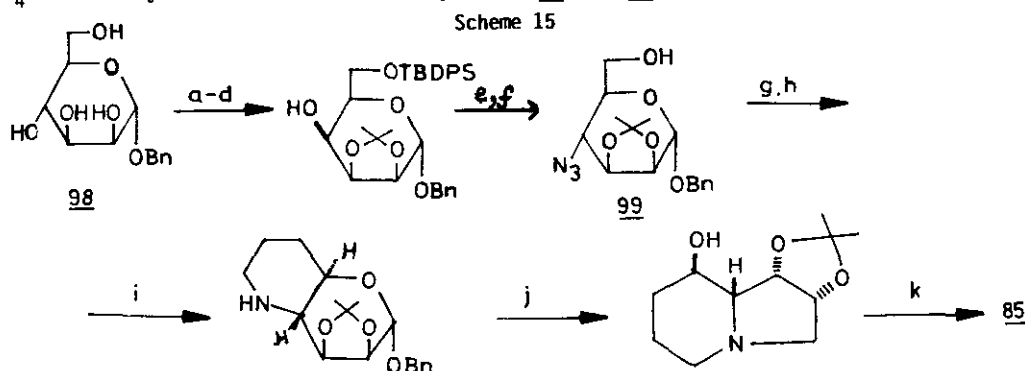
Reagents: a. MsCl, Py ; b. $\text{CF}_3\text{COOH}, \text{MeOH}$; c. NaN_3, DMF ; d. $p\text{-TsOH}-\text{Me}_2\text{C}(\text{OMe})_2$, acetone; e. KOH, MeOH ; f. $\text{DMSO}, \text{Py}-\text{SO}_3\text{-Et}_3\text{N}$; g. $\text{Ph}_3\text{P}=\text{CHCOOMe}, \text{THF}$; h. $\text{H}_2, \text{Pd-C}, \text{MeOH}$; i. $\text{MeOH}, \text{reflux}$; j. BH_3, THF ; k. $\text{BCl}_3, \text{CH}_2\text{Cl}_2$; l. $\text{NaBH}_3\text{CN}, \text{H}_2\text{O}-\text{MeOH}$.

Richardson and coworkers³⁸ have synthesised 85, (α)_D -84°(MeOH), from the chiral synthon methyl 3-amino-3-deoxy- α -D-mannopyranoside hydrochloride 93 which was readily available from methyl- α -D-glucopyranoside³⁹ in 20-25% yield. (-)-Swainsonine 85 was obtained from 93 in 11 steps (Scheme 14).



Reagents: a. Benzyloxy carbonylation; b. p-TsCl, Py; Pd-C, H₂; EtOH, NaOAc; Benzyloxy carbonylation; c. H⁺, reflux; d. Ethanethiol, HCl; e. Ac₂O, Py; f. HgCl₂, CaCO₃; g. Ethoxycarbonylmethylenetriphenylphosphorane; h. Pd-C, H₂; i. BH₃-DMS; j. NaOMe, MeOH.

Total synthesis of (-)-swainsonine 85 (α)_D -67.4°(c, 0.33, MeOH) was carried out by Smith et al.⁴⁰ starting from the chiral synthon benzyl- α -D-mannopyranoside 98. The azido group was introduced at C₄ with the retention of configuration (99) by oxidising the hydroxyl group at C₄ followed by reduction. The overall yield of 85 from 98 was 26% (Scheme 15).

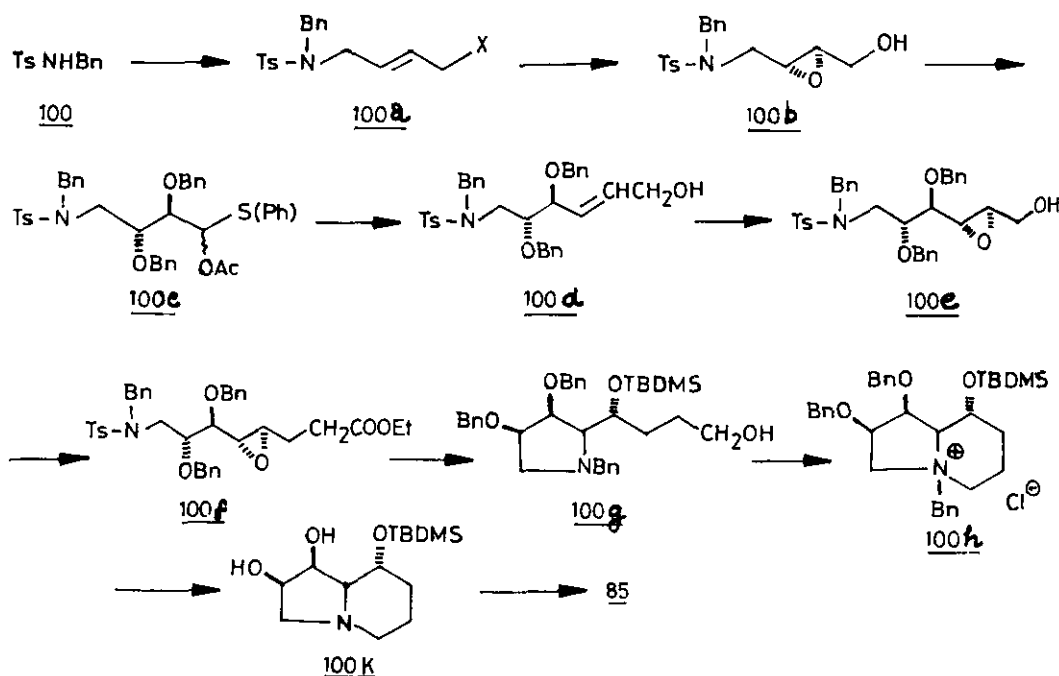


Reagents: a. *tert*-Butyldiphenylsilyl chloride, imidazole; b. acetone, Me₂C(OMe)₂, camphor sulphonic acid; c. PCC, powdered mol. sieves, CH₂Cl₂; d. NaBH₄; e. Triflic anhydride, Py, CH₂Cl₂; f. NaN₃, DMF, r.t.; g. n-Bu₄NF, DMF; h. PCC, powdered mol. sieves, CH₂Cl₂; i. Ph₃P=CHCHO; j. 10% Pd-C, H₂, MeOH; k. Pd-black, HOAc, r.t., 3 days; l. CF₃COOH, 80% D₂O.

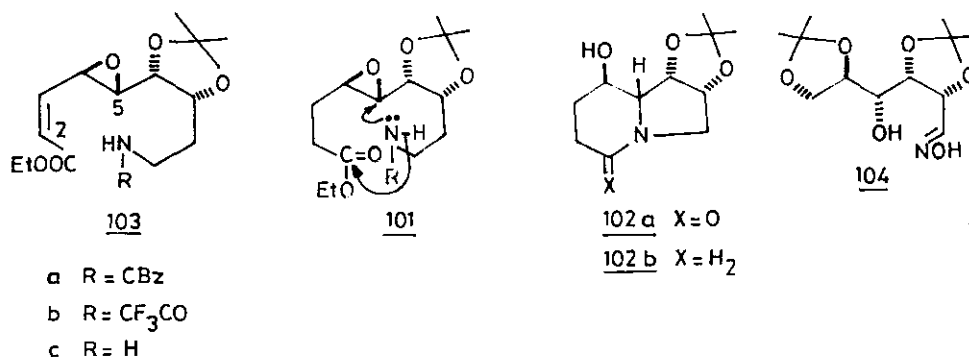
Sharpless *et al.*^{41a} have reported a total synthesis of (-)-swainsonine **85**, (α)_D²⁵-73.8° (c, 0.21, EtOH), in 21 steps and in 6.6% overall yield from *trans*-1,4-dichloro-2-butene and *N*-benzyl-*p*-toluenesulphonamide. It is the first reported non-carbohydrate route to this alkaloid. It was well demonstrated that suitably protected nitrogen was compatible with the asymmetric epoxidation and with the other transformations in the Masamune-Sharpless^{41b,41c} iterative process. The *N*-benzyl-*p*-toluenesulphonamide moiety met these requirements. The stereochemistry of the isomers was established via asymmetric epoxidation using (-)-diisopropyltartrate and Titanium IV isopropoxide.

Asymmetric epoxidation of **100a** under standard conditions^{41b} yielded the epoxy alcohol **100b**. Conversion of epoxy alcohol into **100e** was accomplished in 9 steps. The chemistry involved is similar to the one used for the total synthesis of hexoses^{41c}. The final two carbons required for swainsonine backbone were added by a Moffat oxidation of **100e** followed by direct addition of (ethoxycarbonylmethylene)-triphenyl phosphorane. Diimide reduction of the resultant α,β -unsaturated ester afforded **100f** in 74% yield from **100e**. Deprotection of the *p*-tosyl group of **100f** using sodium naphthalide followed by protection of the hydroxyl group using *tert*-butyldimethylsilyl triflate and reduction afforded the alcohol **100g**. Mesylation of **100g** followed by debenzoylation gave the amido alcohol **100k** in quantitative yield. Desilylation using Dowex 50W-X8(H⁺ form) yielded (-)-swainsonine **85**.

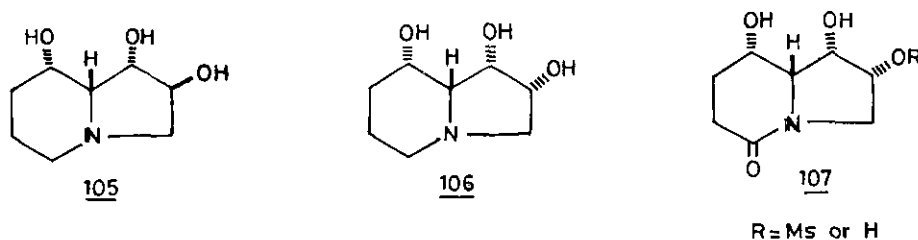
Scheme 16



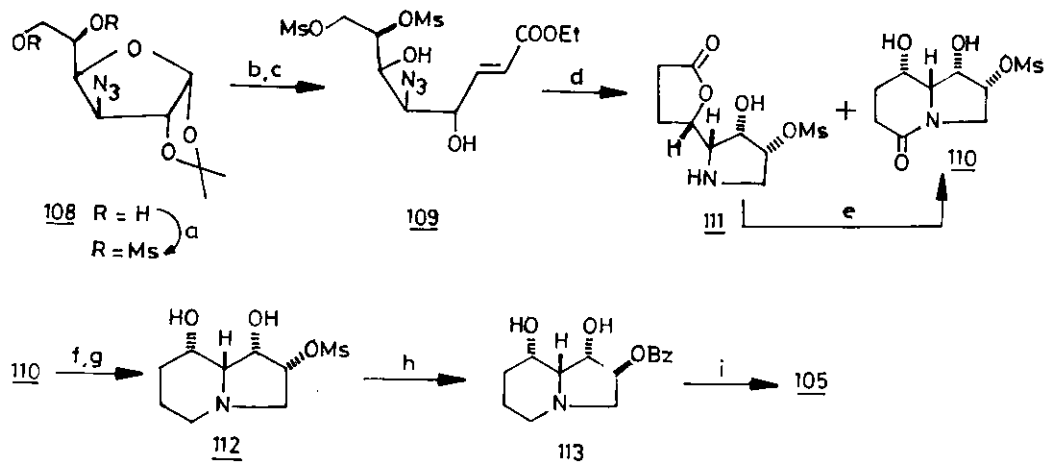
A short enantiospecific synthesis of 85 from D-mannose has been achieved by Hashimoto *et al.*⁴² by a route involving a one step cyclisation of the epoxyamino ester 101c to the lactam 102a followed by the reduction of the lactam 102a to the protected swainsonine 102b. It was found that the conjugated ester 103a was reduced with NaBH₄ in trifluoroethanol through 101a to



102a and further to 102b. The compound 103c could be generated via a NaBH₄ treatment by appropriately protecting the amino group (eg. CF₃CO-) by a direct conversion of 103b to 102b through a synchronous occurrence of a sequence of reactions viz. i) reduction and deprotection of 103b to 101c ii) double cyclisation of 101c to 102a iii) reduction of 102a to 102b. Therefore, an extremely short enantiospecific total synthesis of 85 [(α)_D²⁵-79.8°(c, 0.55, MeOH)] was developed by a route involving as a key step the conversion of 103a to 102b. The intermediate 103a was prepared in a straightforward manner from the oxime 104 from the readily accessible D-mannose⁴³. Two isomers of swainsonine(1S, 2S, 8S, 8aR)-1,2,8-trihydroxyoctahydroindolizidine 105 and the corresponding(1S, 2R, 8S, 8aR) derivative 106 were synthesised from D-glucose via a one step cyclisation to the 5-oxo-1,2,8-trihydroxyindolizidine derivative⁴⁴ 107 (Scheme 17,18)

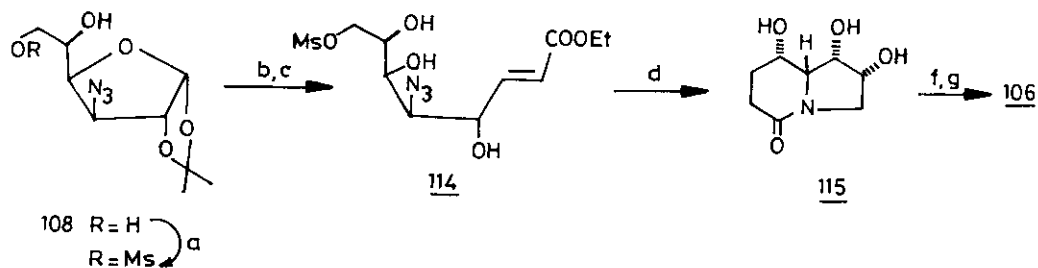


Scheme 17



Reagents: a. $MsCl, Py$; b. $CF_3COOH, H_2O(9:1)$; c. $Ph_3P=CH-COOEt$, THF; d. H_2 , 10% $Pd-C$, MeOH; e. Δ , DMF-EtOH(1:4); f. $[(CH_3)_3Si]_2NH(CH_3)_3SiCl$; g. $BH_3(CH_3)_2S$, THF; h. $BzONa$, DMF; i. $NaOMe$, NaOH

Scheme 18

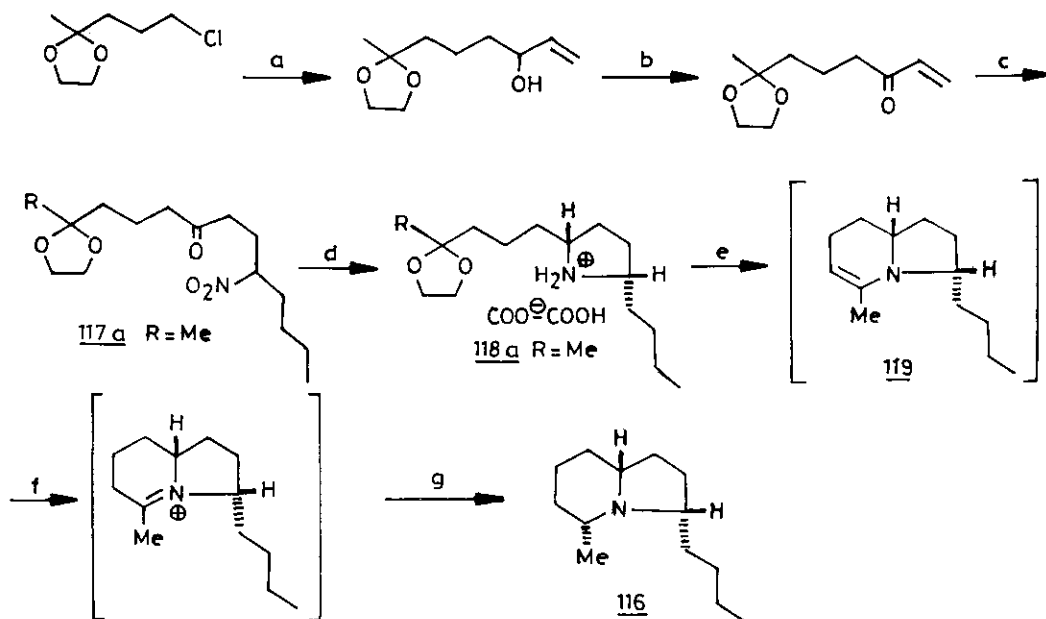


Reagents: a. $MsCl, Py$; b. $CF_3COOH, H_2O(9:1)$; c. $Ph_3P=CH-COOEt$, THF; d. H_2 , 10% $Pd-C$, MeOH; e. Δ , DMF-EtOH(1:4); f. $[(CH_3)_3Si]_2NH(CH_3)_3SiCl$; g. $BH_3(CH_3)_2S$, THF

2.1.2.2. Pheromones of the Pharoah ant

A trail substance of the Pharoah ant, *Monomorium pharaonis* (L) was isolated by Ritter *et al*⁴⁵. There are several non-stereoselective syntheses of monomerine I 116 reported earlier⁴⁶. Lee and Robert⁴⁷ have reported a stereospecific total synthesis of (±)-monomerine-I (Scheme 19). The key step in the synthesis is the reductive cyclisation of the nitroketone 117a to 118a. Sodiumcyanoborohydride reduction of the enamine 119 yielded only one isomer viz. monomerine I 116.

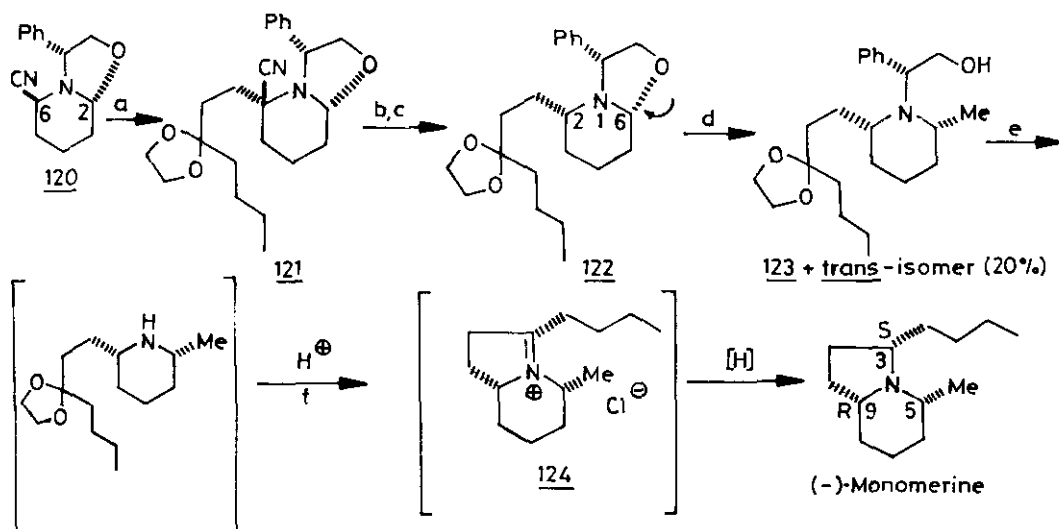
Scheme 19



Reagents: a. Mg, THF; $\text{CH}_2=\text{CHCHO}$; b. PCC or MnO_2 , CH_2Cl_2 ; c. Nitropentane, TMG; d. 10% PdSO_4 , anhyd. Na_2SO_4 ; e. H_3O^+ ; f. pH 3.8-5.4; g. NaBH_3CN , MeOH.

Recently Husson and Royer⁴⁸ have synthesised (-)-monomerine by an asymmetric synthesis using a chiral auxiliary 120 (2-cyano-6-oxazolopiperidine)⁴⁹ equivalent to 1,4-dihydropyridine. Reaction conditions were established in such a way that differentiated the reactivity of the amino-nitrile and aminoether moieties of the synthon, enabling the control of relative and absolute configurations over 2 and 6 positions. As chemo- and stereoselective reactions could be achieved either at C_2 or C_6 centres of the chiral synthon and as hydrogenolysis produced a secondary nitrogen centre capable of undergoing an intramolecular ring closure, this synthon represented an ideal starting point for the chiral synthesis of indolizidine alkaloids (Scheme 20).

Scheme 20

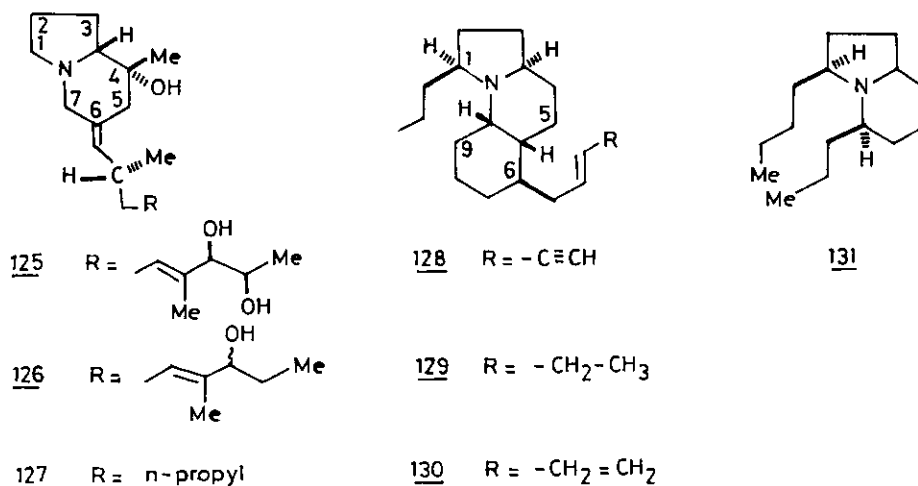


Reagents: a. LDA; $\text{BrCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br}$; b. AgBF_4 ; c. $\text{Zn}(\text{BH}_4)_2$; d. MeMgBr -ether; e. H_2 , Pd-C , MeOH ; f. HCl 1%. (-)-Monomerine so obtained had $(\alpha)_D^{20} -35.8^\circ$ (c, 1.35, *n*-Hexane). The natural monomerine being dextrorotary, the absolute configuration of monomerine was assigned as 3R,5S and 9S based on their previous results.

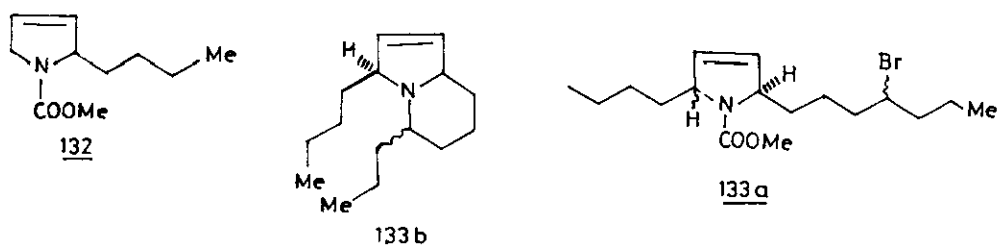
2.1.2.3. Alkaloids of the Dendrobatidae

A number of alkaloids 125-131 that possess interesting pharmacological properties have been isolated⁵⁰ in minute quantities from the skin extracts of frogs belonging to Dendrobatid family. They are divided into batrachotoxin, histrionitoxin, pumiliotoxin and gephyrotoxin classes of alkaloids. Of these the indolizidine alkaloids pumiliotoxins, gephyrotoxin 223A are bicyclic whereas gephyrotoxins are tricyclic indolizidine alkaloids. There are several syntheses, stereo-specific or starting from a chiral synthon or using a chiral auxiliary, which will be discussed here.

Gephyrotoxin-223 131 and its stereoisomers were synthesised⁵¹ via a $\text{N}_1\text{-C}_2$ -vicinal annelation of a 1,4-dibromoalkane on to a pyrroline ring system. 132 was alkylated exclusively at the primary carbon site with 1,4-dibromoheptane affording a 1:1 mixture of 4'-bromo stereoisomers

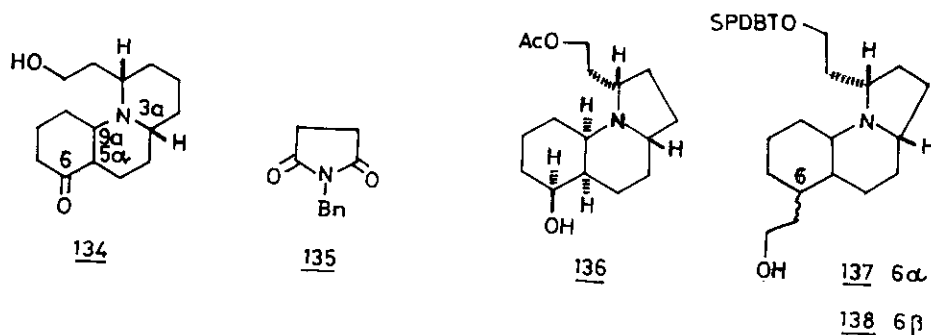


133a when treated with LDA (THF - 40°C). Decarboxymethylation and cyclisation of 133a gave 133b which on catalytic hydrogenation afforded a single stereoisomer 131.



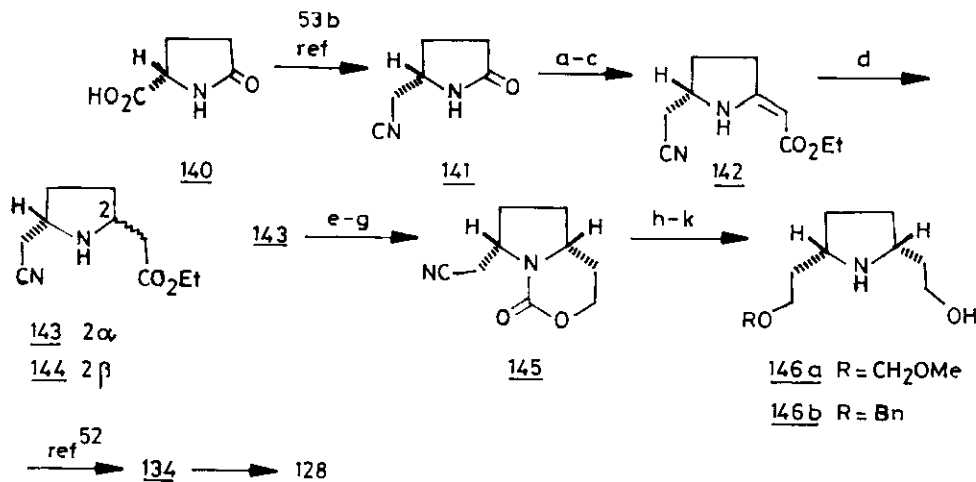
There were three groups headed by Freeman, Hart and Kishi who have almost simultaneously started their work on the synthesis of this group of alkaloids. Kishi *et al.*⁵² have synthesised (±)-gephyrotoxin 128 through the intermediate vinylogous amide 134. The unique aspect of this synthesis is that all the five asymmetric centres were introduced simultaneously through hydrogenation reactions. One of the key strategies involved the use of a hydroxyethyl sidechain to direct the stereochemical course of the hydrogenation of the vinylogous amide 134. The overall yield of 134 from 135 (the starting material) was about 20% in 14 steps. Hydrogenation of 134 using 5% platinum on alumina in ethyl acetate followed by acetylation gave 136 (61% from 134) which

was converted to 137 and 138 in seven steps. The ratio of diastereomeric alcohols varied accord-



ing to different reducing agents used (LAH or Pt on alumina or dissolving metal reduction). The compound 137 was converted to perhydrogephyrotoxin 129 in 4 steps. (PCC, CH_2Cl_2 , r.t.; $\text{CH}_3\text{CH}_2\text{CH}=\text{PPh}_3$, THF, 0°C ; 5% Rh on alumina, EtOH, 60 psi, H_2 , r.t.; $\text{Et-Bu}_4\text{NF}$, DMF, r.t.). Likewise 137 was converted to 128 in 6 steps (PCC, CH_2Cl_2 , r.t.; $\text{EtOCH}=\text{CHP}^+\text{Ph}_3\text{Br}^-$, NaOEt, r.t.; pTsoH, acetone, water, 0°C ; $\text{ClCH}_2\text{P}^+\text{Ph}_3\text{Cl}^-$, BuLi, THF; MeLi, THF; Me_3SiCl ; $\text{Et-Bu}_4\text{NF}$, DMF) in an overall yield of 45% from 137. Later Kishi *et al.*⁵³ have revised the structure of gephyrotoxin to 128, which was earlier assigned as 139 (C_1 & C_6 sidechain α in 128) by Daly *et al.*⁵⁰ by synthesising 128 from a chiral starting material viz., L-pyrroglutamic acid (Scheme 21).

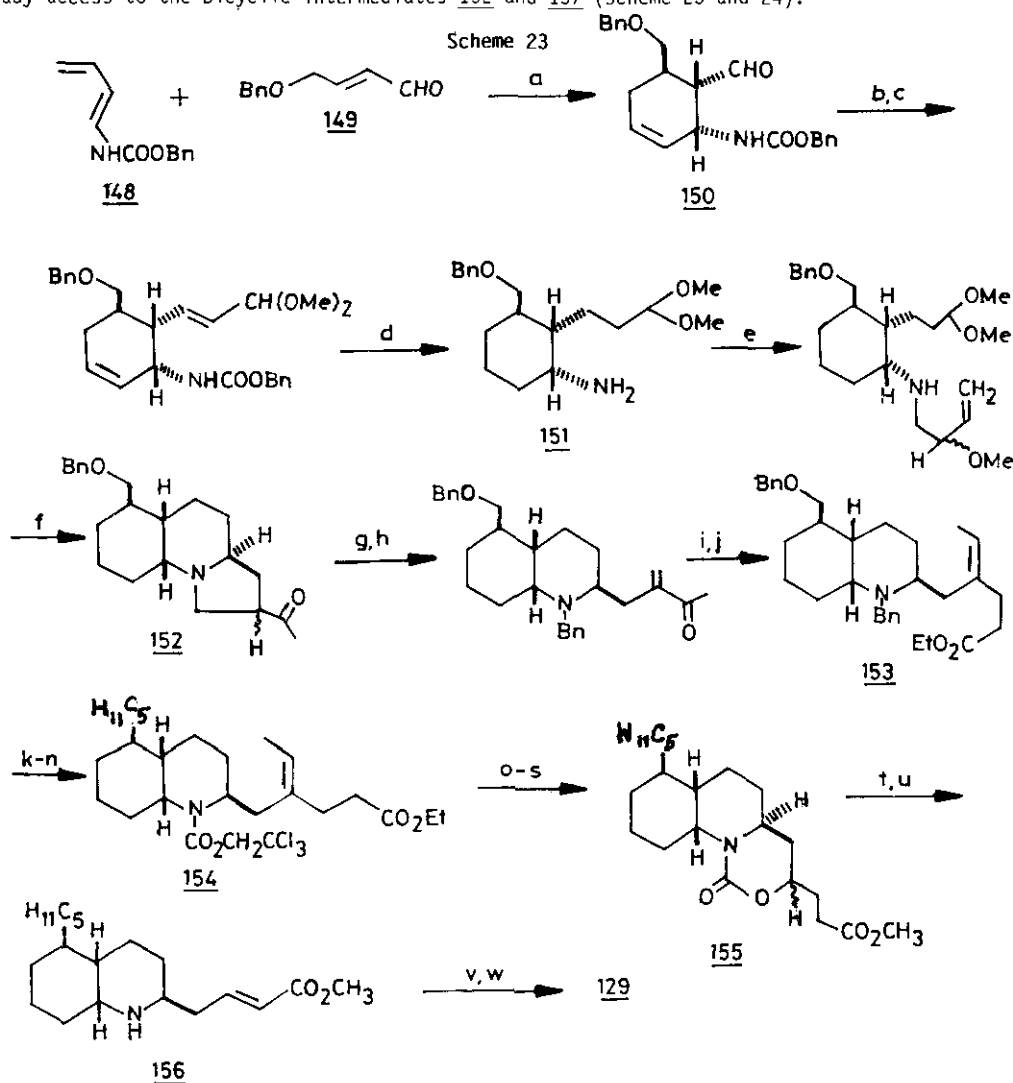
Scheme 21



Reagents: a. P_2S_5 , Py, 85°C ; b. MeOCHBrCOOEt , NaHCO_3 , r.t., reflux; c. 0.1N KOH, EtOH, 60°C ; d. H_2 (1 atm), 5% Pt-C, HClO_4 , MeOH, r.t.; e. $\text{C}_6\text{H}_5\text{COCl}$, Py, CH_2Cl_2 , r.t.; f. LiBH_4 , THF, r.t.; g. KH, THF, r.t.; h. Dibal, THF-toluene; i. NaBH_4 , DME, r.t.; j. MeOCH_2Br , $i\text{-Pr}_2\text{EtN}$, CH_2Cl_2 ; k. $\text{Ba(OH)}_2 \cdot \text{H}_2\text{O}$, reflux.

Gephyrotoxin obtained by synthesis had an $[\alpha]_D^{20} + 50^\circ$ (c, 1 EtOH). As the naturally occurring alkaloid was a levorotatory one, the structure of gephyrotoxin was revised as 128. (However, the structure of this alkaloid remains unsettled)⁵⁰.

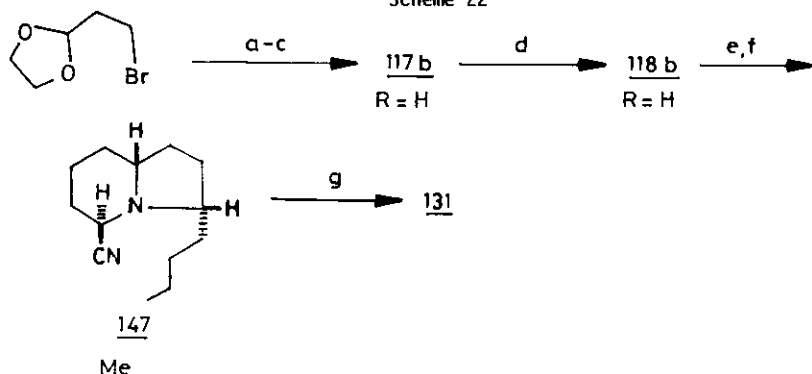
Lee and Stevens⁵⁴ have reported a stereospecific total synthesis of gephyrotoxin-223 131 (Scheme 22). The sequence of reactions are similar to the one mentioned earlier for monomerine - I 116. The dienamide approach previously developed was adopted by Overman *et al.*^{55,56} to provide a ready access to the bicyclic intermediates 152 and 157 (Scheme 23 and 24).



Reagents: a. $110^{\circ}\text{C}, \Delta$; b. Formylmethyltriphenylphosphorane, THF; c. Acetalisation with pyridinium-p-tosylate, MeOH; d. Pd-C, H_2 , MeOH, 1 atm; e. 2-methoxy-2-methyl-3-butenal, NaBH_4 ; f. Δ , benzene, p-TsOH; g. BnBr, CHCl_3 reflux; h. 2% NaOH; i. NaBH_4 ; j. Orthoester Claisen rearrangement; k. Ethanethiol, $\text{BF}_3 \cdot \text{Et}_2\text{O}$; l. Tosylation; m. LiBu_2Cu , ether, -20°C ; n. Chloroformate debenzoylation; o. Ozone; p. NaBH_4 ; q. LiOH; r. NaH; s. CH_2N_2 ; t. SeO_2 ; u. Zn, HOAc, 90°C ; v. NaOMe, NaOH reflux; w. LAH.

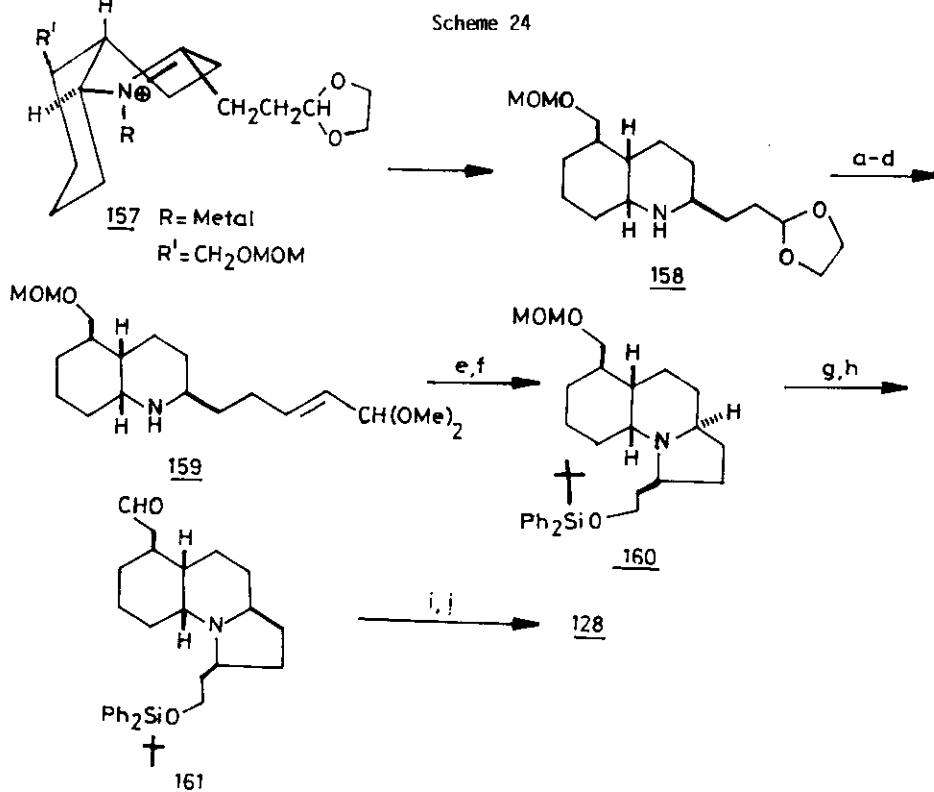
They have synthesised prehydrogephyrotoxin⁵⁵ 129 and gephyrotoxin⁵⁶ 128 by utilising trans-1,3-butadiene-1-carbamate 148 and trans-2-benzyl-2-butenal 149.

Scheme 22



Reagents: a. $\text{CH}_2\text{CO}_2\text{SOPh}$; b. refluxing, CCl_4 ; c. 1-nitropentane, TMG; d. Raney Ni, H_2 ; e. H_3O^+ ; f. KCN; g. PrMgBr , ether

Scheme 24

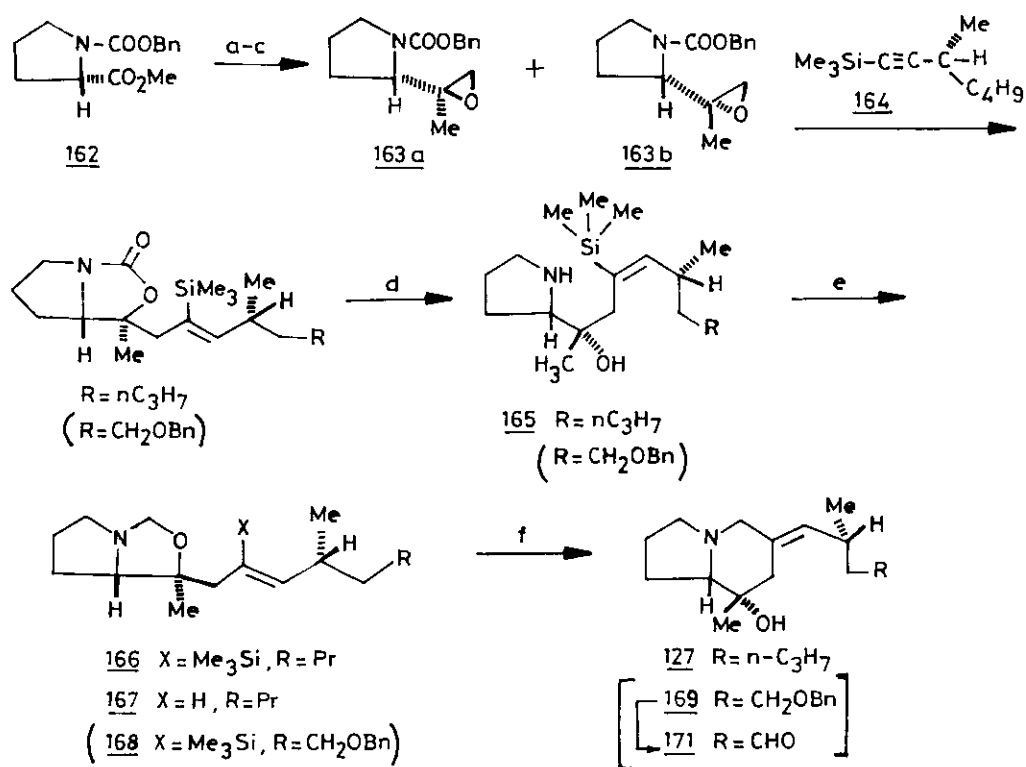


Reagents: a. $\text{ClCOOCH}_2\text{CCl}_3$, 1,2,2,6,6-pentamethylpiperidine, CCl_4 ; b. HClO_4 , THF; Formylmethylenetriphenylphosphorane; c. Pyridinium p-toluenesulphonate, MeOH; d. KOH, MeCHOHMe , H_2O ; e. 1M HCl, THF, NaOMe; NaBH_4 , MeOH; f. TBPSCl, Et_3N , pMAP, CH_2Cl_2 ; g. HBr, DME, 50°C ; h. $(\text{COCl})_2$, DMSO; i. $^i\text{Pr}_3\text{SiCH}_2\text{C}\equiv\text{CSiPr}_3$, BuLi, THF, $-78^\circ\text{C} \rightarrow \text{r.t.}$; j. $n\text{-Bu}_4\text{NF}$

Likewise a total synthesis of (±)-gephyrotoxin 128 was achieved⁵⁶ in 6.5% overall yield from the readily available trans-1,3-butadienecarbamate 148. The key step in the reaction is the reduction of the bicycliciminium ion 157 from the more hindered α -face to provide 158 with LAH under controlled temperature. This reaction yielded 158 and its α -isomer in the ratio of 12:1.

A highly convergent, concise and prochiral route for the chemical synthesis of pumiliotoxin 251D^{57,58} 127 and pumiliotoxin B⁵⁸ 126 was developed by Overman *et al.* via a stereospecific iminiumion-vinylsilane cyclisations starting from the chiral synthon viz., L-proline ester 162. The mixture of epoxides 163a and 163b (1:2) were obtained in 2 steps from L-proline ester 162 (Scheme 25).

Scheme 25

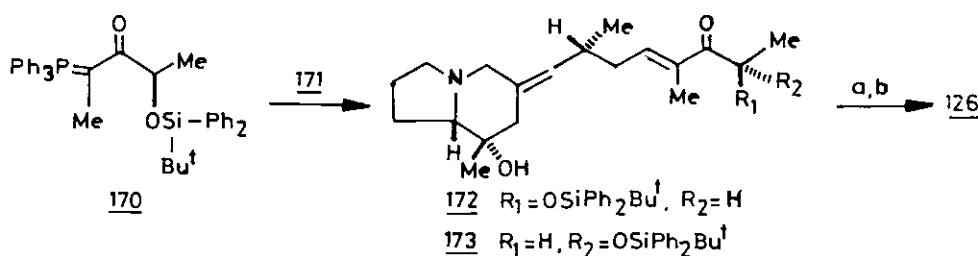


Reagents: a. MeMgI; b. SOCl_2 , Py; c. m-CPBA, hexane, 25°C; d. 3M EtOH-KOH; e. $(\text{CH}_2\text{O})_n$; f. EtOH, camphorsulphonic acid, reflux.

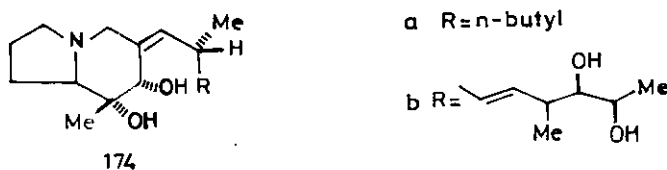
Thus the total synthesis of (+)-pumiliotoxin 251D hydrochloride 127 (α)_D²⁵+28° (c, 0.62, MeOH) was achieved by a convergent sequence in 9 steps in an overall yield of 6.3% from S-1-heptyn-3-ol and 3.6% from N-benzoyloxycarbonyl-L-proline 162.

The side chain¹⁷⁰ of pumiliotoxin B was introduced to compound ¹⁷¹ (Scheme 26) which was prepared according to Scheme 25 mentioned earlier. The compound ¹⁷⁰ was prepared from ethyl L-lactate in 4 steps in 18% overall yield. Thus Pumiliotoxin B, (α)_D + 19.3° (C, 1.00, MeOH) was obtained in 13 steps in an overall yield of 1.8% from L-proline ester. This synthesis unambiguously established the complete stereostructure of this potentially important cardiac agent. Allo-pumiliotoxin-A, (276A) ^{174a} and (339B) ^{174b} were also synthesised using the chiral synthon L-proline carboxylate^{58a}.

Scheme 26

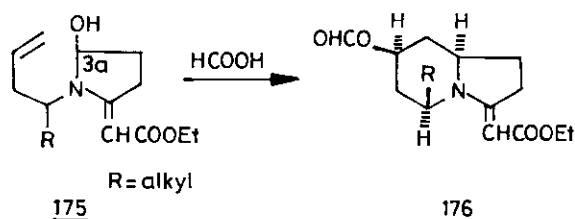


Reagents: a. Threoselective reduction using LAH; b. $n\text{-Bu}_4\text{NF}$, DMF.

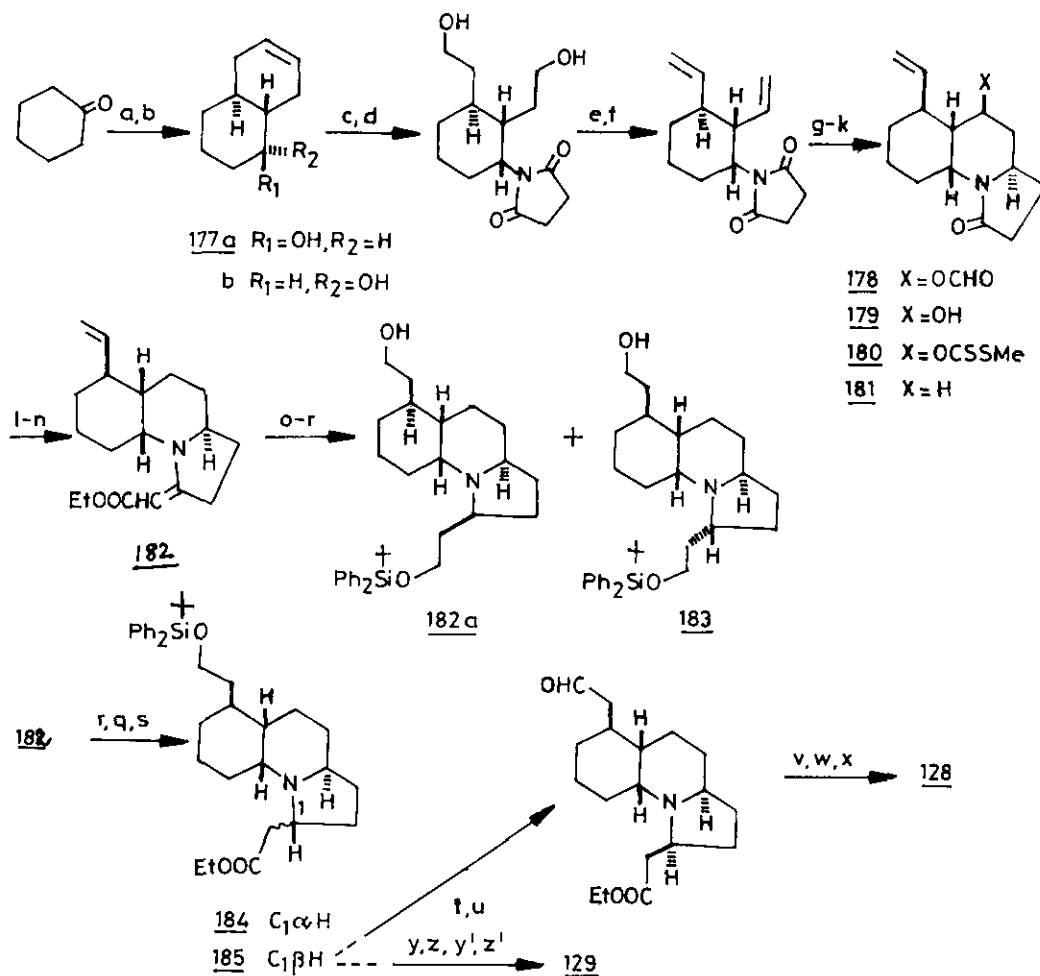


Hart⁵⁹ and Tsai have synthesised depentenylperhydrogephyrotoxin⁵⁹, gephyrotoxin-223AB ¹³¹ and its isomer⁶⁰, gephyrotoxin ¹²⁸, dehydrogephyrotoxin ¹³⁰⁶¹ by introducing the asymmetric centre at C_{3a} through a formic acid induced vinylogous-N-acyliminium cyclisation of carbinolamides^{59,60} of the type ¹⁷⁵ to ¹⁷⁶ (Scheme 27).

Scheme 27



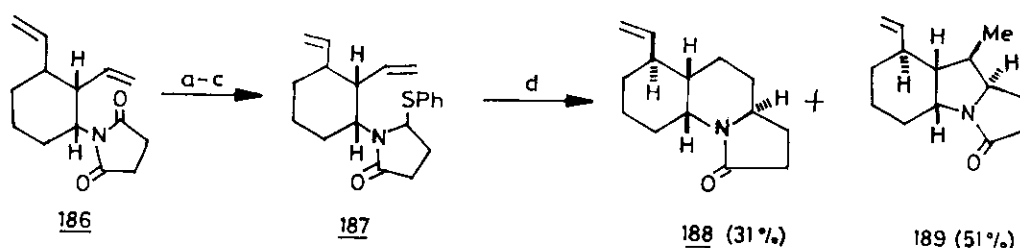
Scheme 28



Reagents: a. 1, 3-Butadiene, AlCl₃; b. LAH, -70°C; c. Succinimide-Mitsunobu condition; d. Ozone, MeOH, NaBH₄; e. Bu₃P, p-nitrophenyl selenocyanate; f. H₂O₂; g. Dibal; h. HCOOH, CH₂Cl₂; i. NaOH; j. Xanthate formation; k. Bu₃SnH; l. Lawesson reagent^{61b}; m. Ethyl bromoacetate; n. Et₃N, Ph₃P; o. NaBH₃CN, Ph₄; p. LAH; q. TBDPSCl; r. Disiamylborane, H₂O₂; s. Pt on Al₂O₃, EtOAc-hexane; t. n-Bu₄NF, THF; u. (COCl)₂, Me₂SO, Et₃N; v. 1-(Trimethylsilyl)-3-*t*-butyldimethylsilyl-1-propyne, *t*-BuLi; w. Dibal; x. n-Bu₄NF, DMF; y. Pinacol-E-1-trimethylsilyl-1-propene-3-boronate, CH₂Cl₂, r.t.; z. Hydrolysis; y'. Dibal; z'. KH in THF.

As a typical example, synthesis of gephyrotoxin 128^{61a} is given in Scheme 28. An interesting feature of this 23 step stereoselective synthesis is that no protecting, deprotecting reaction sequences were involved. Compound 183 was compared with the sample provided by Dr. Kishi. Hart⁶² has synthesised the intermediate 188 for the synthesis of gephyrotoxin using an α -acylimino radical cyclisation (Scheme 29)

Scheme 29



Reagents: a. NaBH_4 ; b. EtOH, HCl ; c. PhSH, TsOH ; d. $\text{Bu}_3\text{SnH}, \text{AIBN}, \text{PhH}$.

Ibuka *et al.*⁶³ have synthesised ($\pm$)-perhydrogephyrotoxin 129 starting from 1,3-bis- α -trimethylsilyloxybuta-1,3-diene 190. An efficient new decarboxylative reduction of γ -carbomoyloxy- α,β -enoate 192 by lithium dibutyl cuprate is a new feature in this synthesis (Scheme 30).

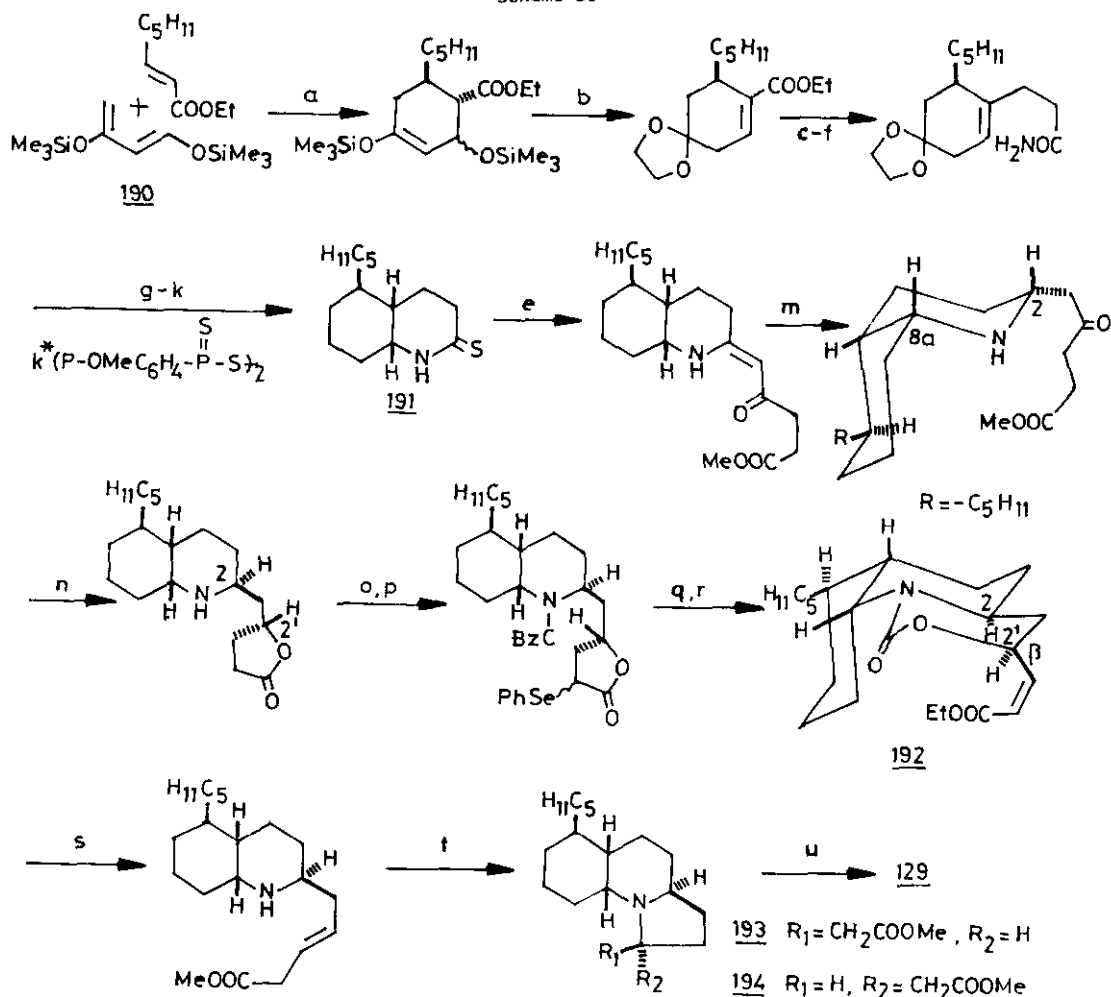
Recently Husson and Royer⁶⁴ have clearly established the absolute configuration of gephyrotoxin-223AB 131 by utilising the chiral auxiliary 120 mentioned earlier. The compound 131 was prepared following a variation of the scheme used for the synthesis of (-)-monomerine I 116. The critical step of this synthesis was the stereoselective introduction of the butyl chain at C_3 of 197 via the intermediate iminium ion. As the synthetic material 131 exhibited the same sign of rotation $[(\alpha)_D^{20} -101^\circ \text{ (c.2.3, n-hexane)}]$ as the natural product, it was then deduced that the absolute configuration of the natural (-)-gephyrotoxin 223AB as 3R, 5R and 9R (Scheme 31).

2.1.2.4 The Alkaloids of Castor fiber

The nupharindolizidine alkaloid 198 is a minor constituent from *Castoreum* (dried scent glands of the Canadian beaver) an article of commerce used in perfumery⁶⁵. The isomer 198a was synthesised from a 2,3-disubstituted cyclopentenone oxime 199 by Lalonde and coworkers⁶⁶. Beckmann rearrangement of 199 gave a 6-substituted piperidone 200. Epoxidation of 200 followed by

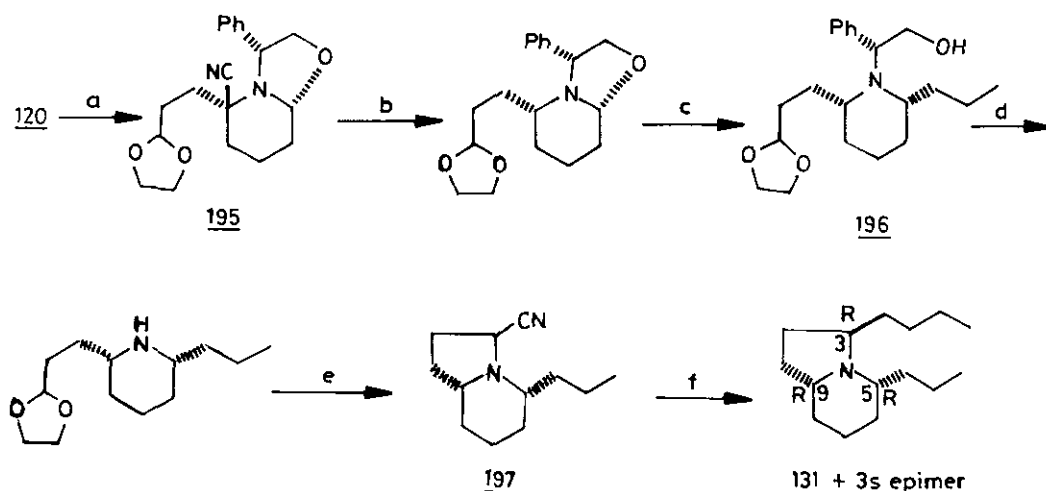
refluxing with sodium hydride in benzene gave the bicyclic intermediate 202. Conversion of 202 to 198 is given in Scheme 32.

Scheme 30



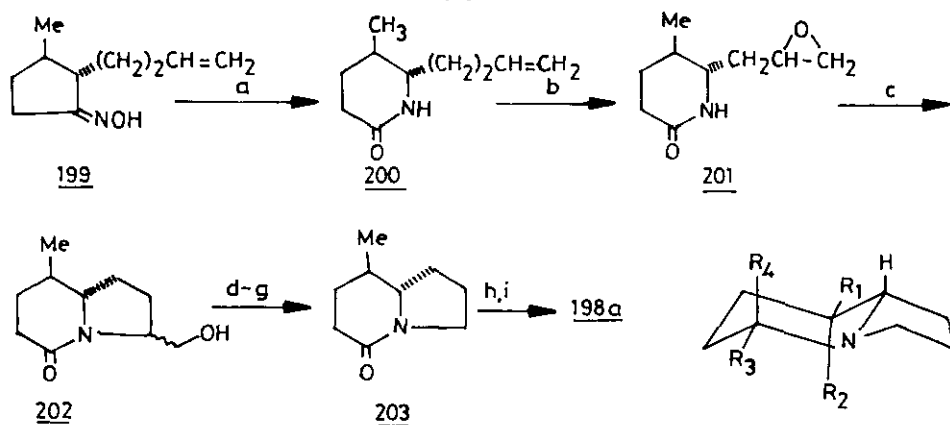
Reagents: a. 175°C , 48h; b. $(\text{CH}_2\text{OH})_2$, p-TsOH, C_6H_6 reflux, 10h; c. Dibal, Hexane-Toluene, -73°C , 3h; d. BuLi, THF, HMPT (2:1), -73°C ; p-TsCl, $-73^\circ \rightarrow 0^\circ\text{C}$; e. CuCH_2CN , THF, $-73 \rightarrow -30^\circ\text{C}$; f. 30% H_2O_2 , 25% aq. KOH, r.t., 12h; g. 5% aq. HCl; h. 5% NaOMe, MeOH, 65°C ; i. $(\text{CH}_2\text{SH})_2$, $\text{BF}_3\text{-Et}_2\text{O}$, CHCl_3 , r.t.; j. Raney W-2 Ni, EtOH, 78°C ; k. k*-xylene, 140°C ; l. $\text{BrCH}_2\text{COCH}_2\text{CH}_2\text{COOMe}$, CHCl_3 , $\text{Ph}_3\text{P}(\text{CH}_2\text{CH}_2\text{NMe})_2$, 61°C ; m. NaBH_3CN , 5% aq. HCl, MeOH; n. NaBH_3CN , MeOH, -20°C ; p-TsOH, benzene, reflux, 1h; o. ClCOOPh , Py, p-DMAP, r.t.; p. Lithium cyclohexyl isopropylamide, THF, HMPT, -73°C ; q. PhSeCl, LiOH, MeOH, H_2O , reflux; CH_2N_2 ; r. 30% H_2O_2 , Py, CH_2Cl_2 , 0°C ; s. LiBu_2Cu , THF; t. NaOMe, MeOH, reflux; u. Dibal, hexane-toluene, $-60 \rightarrow -30^\circ\text{C}$.

Scheme 31



Reagents: a. LDA, $\text{I}-\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{I}$; b. AgBF_4 , THF, $\text{Zn}(\text{BH}_4)_2$; c. PrMgBr , ether; d. H_2 , Pd-C, MeOH; e. CH_2Cl_2 , HCl; KCN; f. $n\text{-BuMgBr}$, ether.

Scheme 32

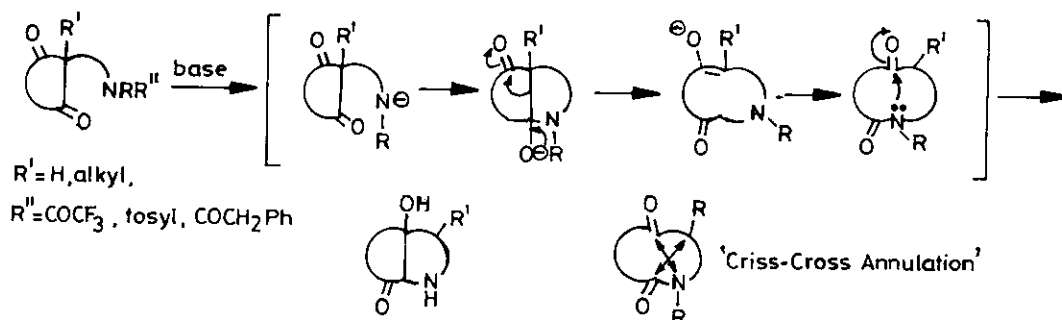


198 a $\text{R}_1=\text{Me}$, $\text{R}_2=\text{H}$, $\text{R}_3=\text{Furyl}$, $\text{R}_4=\text{H}$
 b $\text{R}_1=\text{Me}$, $\text{R}_2=\text{R}_3=\text{H}$, $\text{R}_4=\text{Furyl}$
 c $\text{R}_1=\text{R}_4=\text{H}$, $\text{R}_2=\text{Me}$, $\text{R}_3=\text{Furyl}$
 d $\text{R}_1=\text{R}_3=\text{H}$, $\text{R}_2=\text{Me}$, $\text{R}_4=\text{Furyl}$

Reagents: a. PCl_5 , ether, p-TsCl, Py; b. m-CPBA; c. NaH, benzene, reflux; d. CrO_3 , H_2SO_4 , acetone; e. $\text{Pb}(\text{OAc})_2$, $\text{Cu}(\text{OAc})_2$, H_2O ; Py, N_2 , Δ ; f. H_2 , Pd, MeOH; g. NaBH_3CN , pH 3.0, MeOH, 25°C ; h. 3-Furyllithium, ether; i. NaBH_3CN , MeOH, pH 3.0.

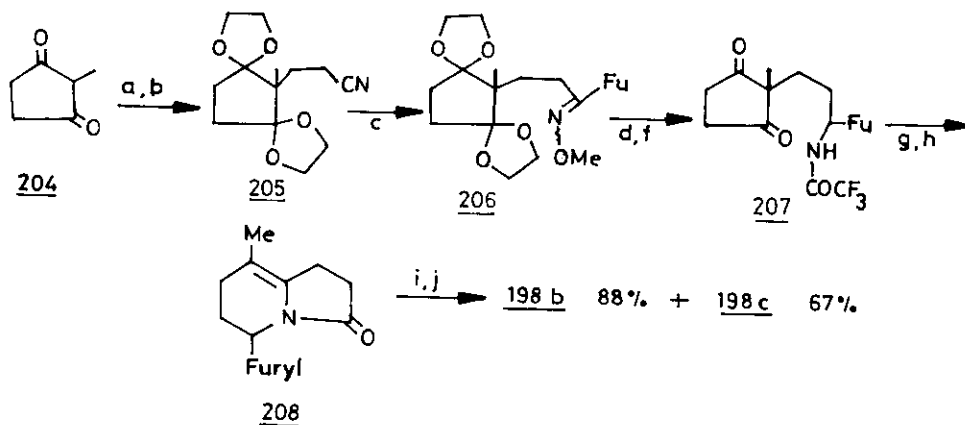
Ban *et al.*⁶⁷ have used a novel type of reaction which they named as 'Criss-cross Annulation'⁶⁸ for the synthesis of 198. Scheme 33 clearly depicts this 'Criss-cross Annulation'.

Scheme 33



The application of this method to the synthesis of the isomers 198b and 198c is given in Scheme 34.

Scheme 34



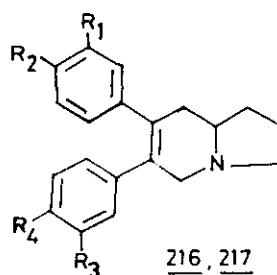
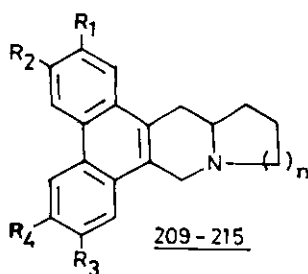
Reagents: a. Acrylonitrile; b. $(\text{CH}_2\text{OH})_2$, CSA; c. Furyllithium, H_2O , NH_2OMe ; d. LAH, THF; e. $(\text{CF}_3\text{CO})_2\text{O}$, Py; f. aq. CF_3COOH ; g. LiOH, aq. MeOH, 65°C ; h. aq. HCl, MeOH; i. NaBH_3CN , MeOH, pH 3.0; j. LAH, THF.

2.2 Phenanthroindolizidine Alkaloids:

The phenanthroindolizidine alkaloids have been the subject of numerous biological and chemical studies¹⁻². Several of these natural products are powerful vesicants, often highly toxic, and can modulate the growth of various normal and abnormal mammalian tissues. The reviews¹⁻² mentioned summarise the efforts towards the chemical structure, stereochemistry and synthesis upto

1979.

In the most commonly reported synthetic methods, the heterocyclic residue is coupled with the phenanthrene residue through a 9-halomethyl moiety. The completion of the skeleton proceeded under Friedel-Crafts conditions. Thus, many phenanthroindolizidines using proline esters have been prepared by this approach^{1,69,70}. In all cases racemic products resulted due to the drastic conditions employed for the ring closure into the phenanthrene. Simple phenanthroindolizidine skeleton 209, tylophorine 210 and 6-methoxyphenanthroindolizidine 211 were synthesised by this method.



209 $R_1 = R_2 = R_3 = R_4 = H$, ($n=1$), Simple phenanthroindolizidine

210 $R_1 = R_2 = R_3 = R_4 = OMe$ ($n=1$), Tylophorine; ($n=2$), Cryptopleurine 210a

211 $R_1 = R_3 = R_4 = H$, $R_2 = OMe$; $n=1$, 6-Methoxyphenanthroindolizidine

212 $R_2 = R_3 = R_4 = OMe$, $R_1 = H$; $n=1$, Deoxytylophorine

213 $R_2 = R_3 = OMe$, $R_4 = OH$, $R_1 = H$; $n=1$

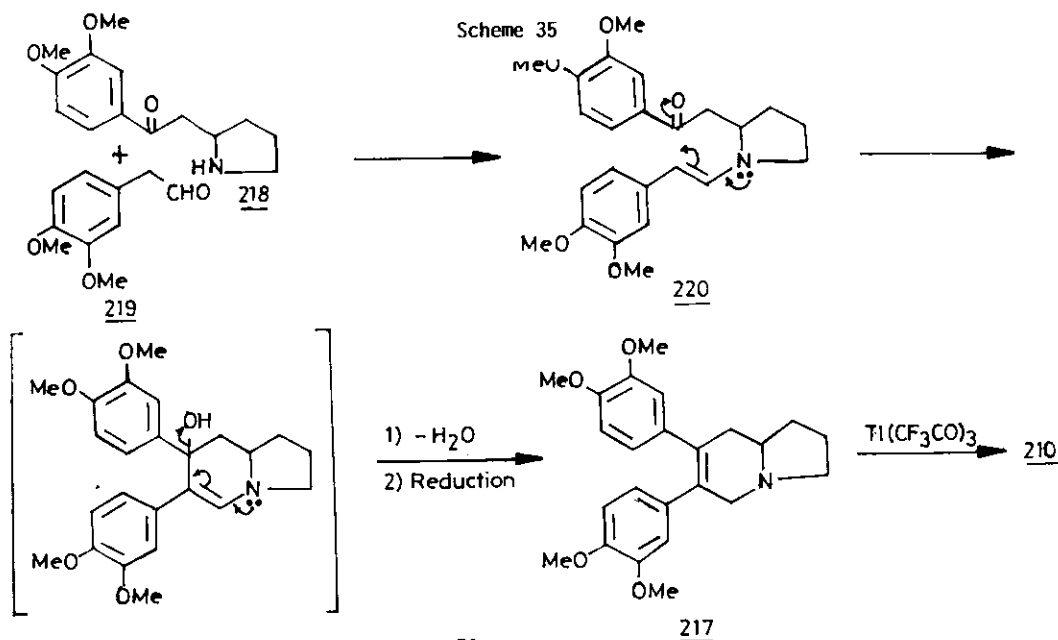
214 $R_1 = R_2 = R_4 = OMe$, $R_3 = H$, $n=1$, Antofine

215 $R_1 = R_2 = OMe$, $R_4 = OH$, $R_3 = H$, $n=1$, Alkaloid C

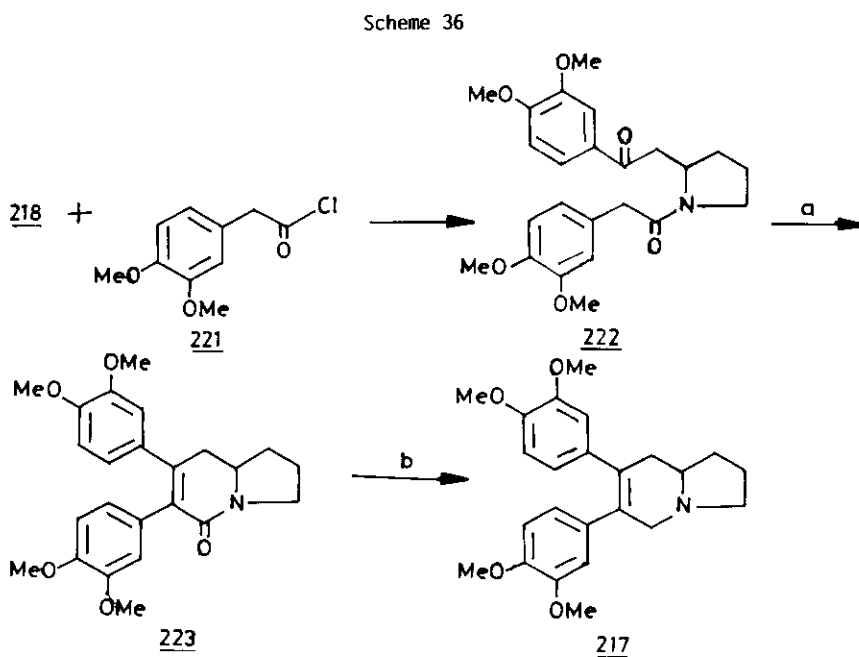
216 $R_1 = R_2 = R_3 = R_4 = OMe$, $n=1$, Septicine

217 $R_1 = R_2 = R_4 = OMe$, $R_3 = H$, Julandine

The biogenetically patterned sequence in which the condensation of phenacylpyrrolidine 218 with phenacylaldehydes 219 afforded the enamine 220. The enaminoketone condensation is effected in methanol at r.t. Cyclisation of the enamine and subsequent dehydration using selected Lewis acids^{70,71} such as $SnCl_4$, $TiCl_4$ in benzene or MgF_2 in ether led to the stilbene derivative which by choosing a suitable coupling agent for the biaryl formation yielded the corresponding phenanthroindolizidine derivatives. Julandine 217, septicine 216, 212 and 210 were synthesised by this method (Scheme 35).



Another biogenetically patterned sequence⁷² involved the treatment of 2-phenacylpyrrolidine 218 with the phenacyl chloride 221. The 2-phenacyl-N-phenylacetylpyrrolidine 222 so formed cyclised in the presence of 5% ethanolic alkali yielding the lactam 223. Reduction of 223 with LAH- $AlCl_3$ gave the secophenanthroindolizidine derivative 217 (Scheme 36)

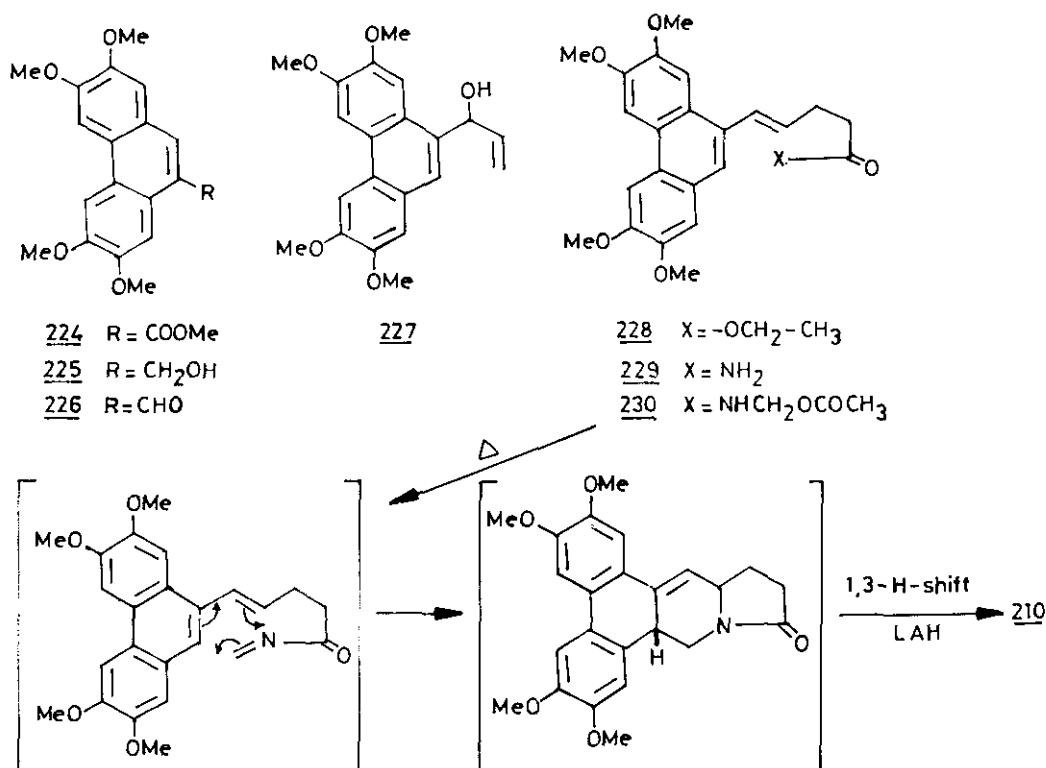


Reagents: a. Ethanolic alkali; b. LAH, $AlCl_3$

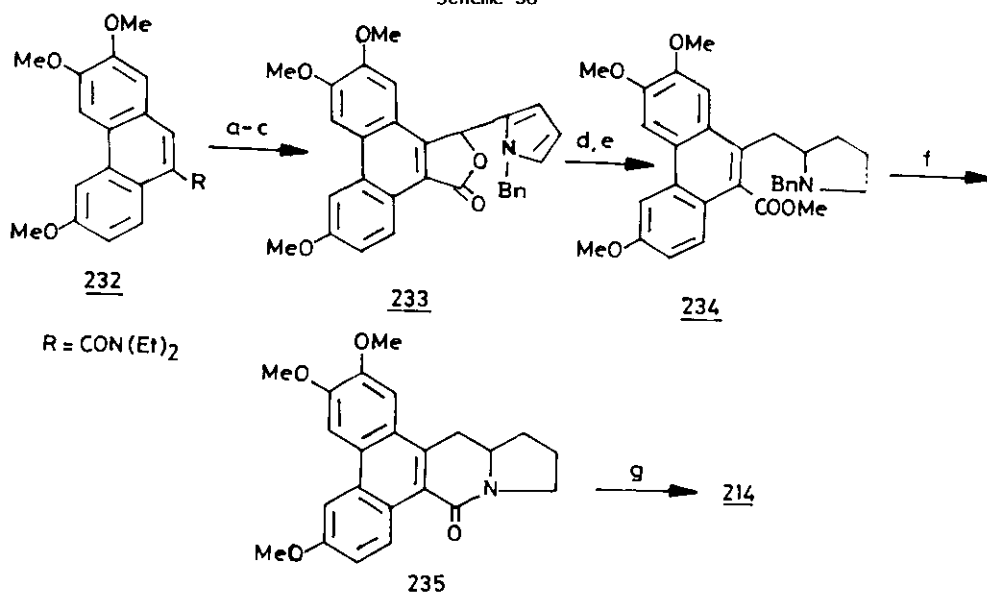
Antofine 214 and alkaloid C 215 were synthesised by the oxidation of the secophenanthroindolizidines like 217 with either MnO_2 or SiO_2 or $\text{CuCl}_2 \cdot \text{O}_2$, pyridine⁷³.

Using an intramolecular Diels-Alder strategy tylophorine 210 was synthesised¹⁶ in 8 steps from the known ester 224 in an overall yield of 5%. Reduction of 224 with LAH gave 225 which on PCC oxidation afforded 226 in good yield. Treatment of 226 with vinyl lithium in THF yielded 227 (79%). Orthoester Claisen rearrangement⁷⁴ of 227 gave the ester 228 which was converted to 229 with dimethylaluminium amide in refluxing methylene chloride. The compound 229 was converted to the arylimine precursor 230 by treatment with formaldehyde followed by acetylation. Heating 230 in bromobenzene at 210–220°C for 5 h produced 231 in 50% yield. Reduction of 231 with LAH gave racemic tylophorine 210 (Scheme 37). But this method could not be extended to more complicated examples.

Scheme 37

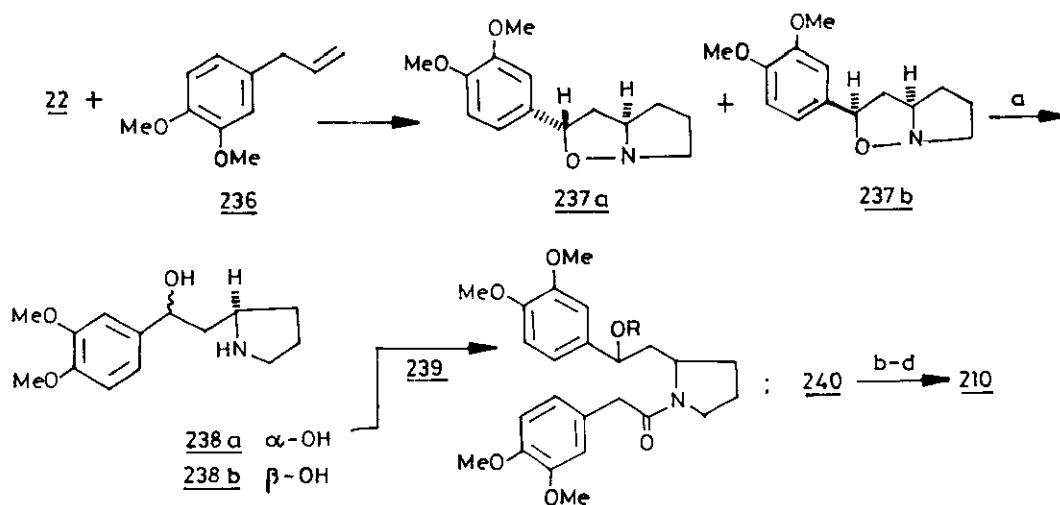


Scheme 38



Reagents: a. *Sec*-BuLi, TMEDA, ether, THF, -78°C; b. N-Benzylpyrrol-2-carboxaldehyde; c. Silica gel, CHCl₃, Δ; d. Zn-Cu, KOH, Py; e. CH₂N₂; f. H₂, Pt, HOAc; g. LAH, THF.

Scheme 39



239 3,4-(OMe)₂C₆H₃CH₂COCl

240 R = H

241 R = COCH₂C₆H₃(OMe)₂

Reagents: a. Zn, HOAc; b. NaOEt; c. LAH; d. hν, I₂

Metallation of phenanthrene carboxamide⁷⁵ followed by reaction with N-benzylpyrrole-2-carboxaldehyde has been applied for the synthesis of phenanthroindolizidines and quinolizidines. The phthalide intermediate 233 was converted to racemic antofine⁷⁶ (Scheme 38), in 38% yield.

The isoxazolidine available from the 1,3-dipolar addition of nitron to olefines^{9a} could be utilised as synthetic equivalents of β -amino alcohols and thus β -amino ketones which are claimed to be the biogenetic precursor of phenanthroindolizidine and quinolizidine alkaloids. Thus, 1,3-dipolar cycloaddition of 236 with 22 gave 237a and 237b (diastereomers, 93%). The mixture 237 on reductive cleavage with zinc and acetic acid gave the amino alcohols 238a and 238b. The conversion of 238a to tylophorine is given in the Scheme 39.

Tylophorine 210, cryptopleurine 210b, septicine 216 and julandine 217 were synthesised by this method⁷⁷.

In the synthesis of these alkaloids the formation of the biaryl linkage could be achieved from the corresponding stilbene derivatives by adopting any one of the corresponding methods.

i) Pschorr cyclisation: This is the first and foremost route to the formation of phenanthrene skeleton^{78a}. However, photochemical methods are preferable to these methods for the simplicity of operation.

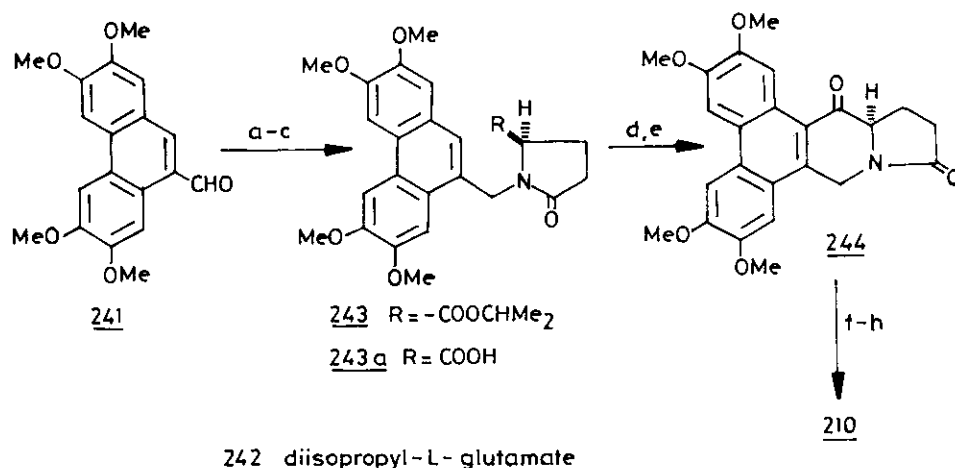
ii) Photocyclisation: This method yielded the desired phenanthrenes and also the unwanted isomers. However, these methods are superior to Pschorr cyclisation^{78b}.

iii) Anodic oxidation: This electrochemical method yielded the clean desired phenanthrene derivative⁷⁹.

iv) Phenolic oxidative coupling: The oxidising agents used are thallium III trifluoroacetate^{70,71} and VOF_3 in trifluoroacetic acid.^{80,69,81}

Finally chirally specific syntheses of S(+)-tylophorine 210 and cryptopleurine 210b were achieved⁸¹ by choosing α -amino acid such as the diisopropyl ester of L(+)-glutamic acid as a chiral educt. Reductive amination of the phenanthrene aldehyde 241 with the amine ester 242 followed by cyclisation gave 243, which on hydrolysis followed by Friedel-Crafts acylation gave 244 in nearly quantitative yield. This on catalytic hydrogenation followed by deoxygenation and LAH reduction gave S(+)-tylophorine, $(\alpha)_D^{20} +12.0^\circ$, mp 282-284°C. This is in discrepancy with the absolute configuration assigned to natural tylophorine on the basis of ozonolysis experiments⁸² and further work is in progress to settle the issue.

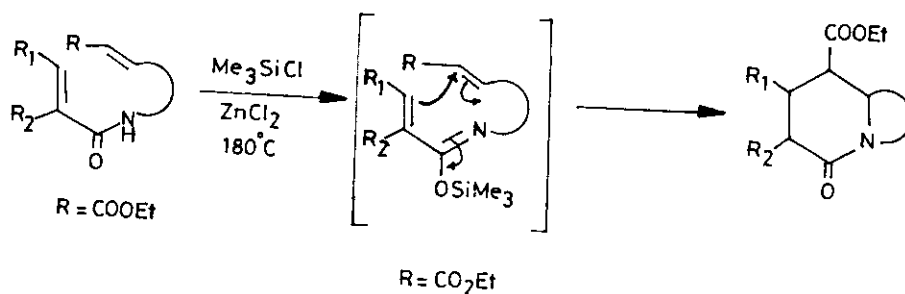
Scheme 40



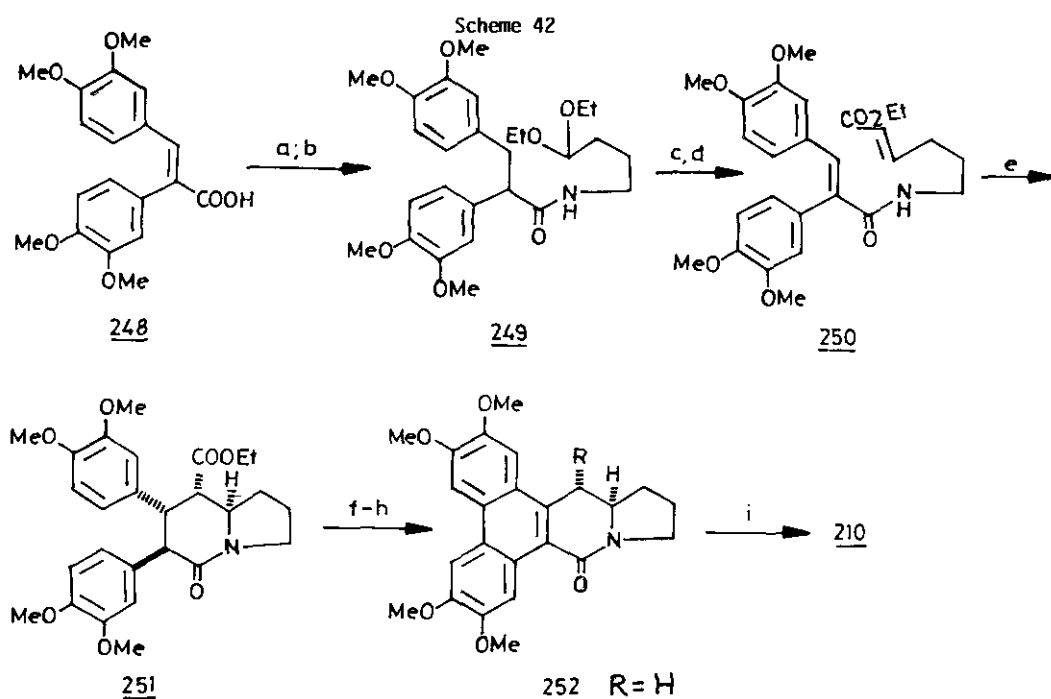
Reagents: a. 242; b. NaBH₃CN, MeOH; c. MeOH, HOAc; d. Hydrolysis; e. AlCl₃; f. Catalytic hydrogenation; g. Deoxygenation; h. LAH, THF.

The recently reported⁸³ new synthetic route to quinolizidine and indolizidine derivatives by intramolecular Diels-Alder reaction of 1-aza-1,3-dienes (Scheme 41) has been applied to the synthesis of tylophorine 210, an antineoplastic agent by Kametani *et al*⁸⁴. The acid 248 was converted to the acid chloride and then condensed with 4-aminobutyraldehyde diethylacetal to

Scheme 41



yield the amide 249. Deprotection of the acetal 249 using dilute acetic acid followed by Wittig reaction gave the enamide ester 250 (93%). This was subjected to annelation using tributylsilyl-trifluoromethane sulphonate (TBSOTf) and Et₃N in CH₂Cl₂ to yield 251 (68%). Conversion of 250 to tylophorine is given in Scheme 42.



Reagents: a. $(\text{COCl})_2$; b. $\text{NH}_2(\text{CH}_2)_3\text{CH}(\text{OEt})_2$, NaHCO_3 ; c. $\text{HOAc}, \text{H}_2\text{O}$; d. $\text{Ph}_3\text{P}=\text{CHCOOEt}$; e. $\text{TBSOTf}, \text{Et}_3\text{N}$, r.t.; f. $\text{TTFA}, \text{BF}_3\text{-Et}_2\text{O}$, TFA ; g. KOH, MeOH ; h. HMPA , 230°C ; i. $\text{NaAl}(\text{OCH}_2\text{CH}_2\text{OMe})_2, \text{H}_2$

Abbreviations used in the review:

AIBN	azobisisobutyronitrile
Bn	benzyl
BnBr	benzyl bromide
Bz	benzoyl
mCPBA	m-chloroperbenzoic acid
CSA	camphorsulphonic acid
pDMPA	p-dimethylaminopyridine
DME	dimethoxyethane
HMPA	hexamethylphosphoramide
PCC	pyridinium chlorochromate
PpTSONa	pyridinium-p-toluenesulphonate
TBSOTf	tributylsilyltrifluoromethane sulphonate
TBDMS	tert-butyltrimethylsilyl
TBDPS	tert-butyltriphenylsilyl
TMEDA	tetramethylethylenediamine

TMG	tetramethylguanidine
TrCl	trityl chloride
TTFA	thallium (III) trifluoroacetate

REFERENCES

1. T. R. Govindachari and N. Viswanathan, Heterocycles, 1978, 11, 587.
2. E. Gellert, J. Nat. Products, 1982, 45, 50.
3. S.R. Johns, J.A. Lamberton, in 'The Alkaloids' - Chemistry and Physiology, R. H. F. Manske, Ed., Academic Press, NY, 1973, Vol.XIV, pp 326.
4. D. J. Robins, "Advances in Heterocyclic Chemistry", A. R. Kartritzky and A. J. Boulton, Eds., Academic Press, NY, 1976, 23, pp. 152.
5. J. A. Lamberton, in 'The Alkaloids', Specialists Periodical Reports, M. F. Grunden, Ed., The Royal Society of Chemistry, London, 1982, Vol.12, Pg.69; 1981, 11, 59; 1980, 10, 63; 1979, 9, 67; Nat. Prod. Rep., 1984, 1, 245; 1985, 2, 234.
6. L.D. Hohenschutz, E. A. Bell, P. J. Jewess, D. P. Leworthy, R. J. Pryce, E. Arnold and J. Clardy, Phytochemistry, 1981, 20, 811; b. M.J. Schneider, F. S. Ungemach, H.P. Broquist and T. M. Harris, Tetrahedron, 1983, 39, 29; c. Idem, J.Am. Chem. Soc., 1983, 104, 6863; R. Saul, J. P. Chambers, R. J. Molyneux and A. D. Elbein, Arch. Biochem.Biophys., 1983, 221, 593.
7. R. C. Bernotas and B. Ganem, Tetrahedron Lett., 1984, 25, 165.
8. a. S. R. Johns, J. A. Lamberton, A. A. Sioumis and R. I. Willing, Aus. J. Chem., 1969, 22, 775; b. S. R. Johns, J. A. Lamberton and A. A. Sioumis ibid., 22, 793; c. S. R. Johns, J. A. Lamberton, A. A. Sioumis, H. Saures and R. L. Willing, ibid., 1971, 24, 1679; d. N. K. Hart, S. R. Johns and J. A. Lamberton, ibid., 1972, 25, 817; e. A. K. Barua, C. Dasgupta, S. Chakravarti, N. K. Choudhury and A. Ghosh, J. Ind. Chem. Soc., 1976, 53, 531; f. A. B. Ray, L. Chand and V. B. Pandey, Phytochemistry, 1979, 18, 700.
9. J. J. Tufariello, Accounts Chem. Res., 1979, 396; J. J. Tufariello and Sk. A. Ali, J. Am. Chem. Soc., 1979, 101, 7114.
10. A. S. Howard, G. C. Gerrans and C. A. Meerholz, Tetrahedron Lett., 1980, 21, 1373; A. S. Howard, C. A. Meerholz and J. P. Michael, Tetrahedron Lett., 1979, 20, 1339.
11. M. Roth, P. Dubs, E. Götschi and A. Eschenmoser, Helv. Chim. Acta, 1971, 54, 710.
12. T. Tanaka and I. Iijima, Tetrahedron, 1973, 29, 1285.
13. N. K.Hart, S. R. Johns and J. A. Lamberton, Aus. J. Chem., 1972, 25, 817.

14. B. M. Trost and R. A. Kunz, J. Am. Chem. Soc., 1975, 97, 7152.
15. T. Watanabe, Y. Nakashita, S. Katayama and M. Yamauchi, Heterocycles, 1980, 14, 1433; Idem, ibid., 1981, 16, 39.
16. a. N. A. Khatri, H. Schmitthenner, J. Shingarpure and S. M. Weinreb, J. Am. Chem. Soc., 1981, 103, 6387; b. N. A. Khatri, J. Shingarpure and S. M. Weinreb, J. Am. Chem. Soc., 1979, 101, 5073; c. S. M. Weinreb, J. Org. Chem., 1980, 45, 3372; d. S. M. Weinreb, Accounts Chem. Res., 1985, 18, 16.
17. T. Shono, Y. Matsumura, K. Uchida, K. Tsubata and A. Makino, J. Org. Chem., 1984, 49, 300.
18. T. Mukaiyama, Angew. Chem. Int. Ed. Engl., 1977, 16, 817.
19. a. A. R. Chamberlin, H. D. Nguyen and J. Y. L. Chung, J. Org. Chem., 1984, 49, 1682; b. O. Mitsunobu, Synthesis, 1981, 1.
20. J. M. Gourley, R. A. Heacock, A. G. L. McInnes, B. Nikolin and D. G. Smith, J. Chem. Soc. Chem. Commun., 1969, 709.
21. A. M. Dawida, F. Winternitz, and S. R. Johns, Tetrahedron, 1977, 33, 1733.
22. V. M. Chari, M. Jordan and H. Wagner, Planta Medica, 1978, 34, 93.
23. a. T. R. Govindachari, A. R. Sidhaye and N. Viswanathan, Tetrahedron, 1970, 26, 3829 - Dieckmann condensation.
b. A. E. Wick, P. A. Bartlett, and D. Dolphin, Helv. Chim. Acta., 1971, 54, 513.
c. R. V. Stevens, and Y. Luh, Tetrahedron Lett., 1977, 979 - Intramolecular cyclisation of enamine.
24. S. H. Hedges and R. B. Herbert, J. Chem. Res., 1979(S), 1, 413.
25. A. S. Howard, G. C. Gerrans, and J. P. Michael, J. Org. Chem., 1980, 45, 1713.
26. H. Iida, Y. Watanabe and C. Kibayashi, Chem. Lett., 1983, 1197; Idem, J. Chem. Soc. Perkin I, 1985, 261.
27. D. P. Rainey, E. B. Smalley, M. H. Crump and F. M. Strong, Nature, 1965, 205, 203; S. D. Aust and H. P. Broquist, ibid., 1965, 205, 204; R. A. Gardiner, K. L. Rinehart, J. J. Snyder, and H. P. Broquist, J. Am. Chem. Soc., 1968, 90, 5639.
28. D. Cartwright, R. A. Gardiner and K. L. Rinehart, J. Am. Chem. Soc., 1970, 92, 7615; W. J. Gensler and M. W. Hu, J. Org. Chem., 1973, 38, 3848.
29. W. Christophei, Ph.D. Thesis, Univ. of Illinois at Urbana, Champaign, 1976.
30. R. A. Grabo, M. L. Bremner and S. M. Weinreb, J. Am. Chem. Soc., 1982, 104, 7065.
31. M. J. Schneider and T. M. Harris, J. Org. Chem., 1984, 49, 3681.

32. S. M. Colegate, P. R. Dorling and C. R. Huxtable, Aus. J. Chem., 1979, 32, 2257.
33. R. J. Molyneux, and L. F. James, Science, 1982, 216, 190.
34. N. Yasuda, H. Tsutsumi and T. Takaya, Chem. Lett., 1984, 1201.
35. K. B. Locke, D. R. McEvan and I. J. Hamdorf, Aus. J. Chem., 1980, 56, 379.
36. T. Suami, K. Tadano, and Y. Iimura, Chem. Lett., 1984, 513.
37. M. E. Evans, Carbohydr. Res., 1977, 54, 105.
38. M. H. Ali, L. Hough and A. C. Richardson, J. Chem. Soc. Chem. Commun., 1984, 447.
39. A. C. Richardson, J. Chem. Soc., 1962, 373.
40. G. W. J. Fleet, M. J. Gough, and P. W. Smith, Tetrahedron Lett., 1984, 25, 1853.
41. a.C. E. Adams, F. J. Walker and K. B. Sharpless, J. Org. Chem., 1985, 50, 420.
b.T. Katsuki, and K. B. Sharpless, J. Am. Chem. Soc., 1980, 102, 5974; J. G. Hill, B. E. Rossiter, and K. B. Sharpless, J. Org. Chem., 1983, 48, 3607.
c.T. Katsuki, A. W. M. Lee, P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless, D. Tuddenham and F. J. Walker, J. Org. Chem., 1982, 47, 1373; S. Y. Ko, A. W. M. Lee, S. Masamune, L. A. Reed III, K. B. Sharpless and F. J. Walker, Science, 1983, 220, 949.
42. H. Setoi, H. Takeno, and M. Hashimoto, J. Org. Chem., 1985, 50, 3950.
43. A. Vasella, Helv. Chim. Acta, 1977, 60, 1273.
44. N. Yasuda, H. Tsutsumi and T. Takaya, Chem. Lett., 1985, 31.
45. F. J. Ritter, T. E. M. Rotgens, E. Talman, P. E. J. Verwiël, and F. Stein, Experientia, 1973, 29, 530; F. J. Ritter, and C. J. Persoons, Neth. J. Zool., 1975, 25, 261.
46. J. E. Oliver and P. E. Sonnet, J. Org. Chem., 1974, 39, 2662; *idem*, J. Heterocyclic. Chem., 1975, 12, 289; P. E. Sonnet, D. A. Netzet and R. Mondoza, *ibid.*, 1979, 16, 1041.
47. R. V. Stevens and A. W. M. Lee, J. Chem. Soc. Chem. Commun., 1982, 102.
48. R. Royer and H. P. Husson, J. Org. Chem., 1985, 50, 670.
49. L. Guerrier, J. Royer, D. S. Grierson and H. P. Husson, J. Am. Chem. Soc., 1983, 105, 7754.
50. a.For a recent review: J. W. Daly, Fortschr. Chem. Org. Naturst., 1982, 41, 205; B. Witkop and E. Gossinger, in 'The Alkaloids', A. Brossi, Ed., Academic Press, New York, 1983, Vol.21, Chapter 5.
b.Gephyrotoxin: T. Tokuyama, K. Uenoyama, G. Brown, J. W. Daly, and B. Witkop, Helv. Chim. Acta, 1974, 57, 2597; J. W. Daly, B. Witkop, T. Tokuyama, T. Nishikawa and I. L. Karle, Helv. Chim. Acta, 1977, 60, 1128 - The X-ray crystallographic assignment does not agree with the structure arrived at by a total synthesis of the same, starting from a chiral synthon (Ref.53).

- c. Gephyrotoxin 223: J. W. Daly, G. B. Brown, M. Mensah-Dwumah and C. W. Meyers, Toxicon, 1978, 16, 113; J. W. Daly, T. Tokuyama, G. Habermehl, I. L. Karle, and B. Witkop, Liebigs Ann. Chem., 1969, 729, 198; M. Mensah-Dwumah and J. W. Daly, Toxicon, 1978, 16, 189.
- d. Pumiliotoxins: J. W. Daly and C. W. Meyers, Science (Washington DC), 1967, 156, 970; J. W. Daly, T. Tokuyama, T. Fujiwara, R. J. Highet and I. L. Karle, J. Am. Chem. Soc., 1980, 102, 830; M. Uemura, K. Shimada, T. Tokuyama and J. W. Daly, Tetrahedron Lett., 1982, 23, 4369; L. E. Overman and R. J. McGready, ibid., 1982, 23, 2355; T. Tokuyama, K. Shimada, M. Uemura and J. W. Daly, ibid., 1982, 23, 2121.
51. T. L. Macdonald, J. Org. Chem., 1980, 45, 193.
 52. R. Fujimoto, Y. Kishi and J. F. Blount, J. Am. Chem. Soc., 1980, 102, 7154.
 53. a. R. Fujimoto, Y. Kishi and J. F. Blount, Tetrahedron Lett., 1981, 21, 4197.
b. R. B. Silberman, and M. A. Levy, J. Org. Chem., 1980, 45, 815.
 54. R. V. Stevens and A. W. M. Lee, J. Chem. Soc. Chem. Commun., 1982, 104.
 55. L. E. Overman and C. Fukaya, J. Am. Chem. Soc., 1980, 102, 1454.
 56. L. E. Overman, D. Lesuisse and M. Hashimoto, J. Am. Chem. Soc., 1983, 105, 5373.
 57. L. E. Overman and K. L. Bell, J. Am. Chem. Soc., 1981, 103, 1851.
 58. L. E. Overman, K. L. Bell and F. Ito, J. Am. Chem. Soc., 1984, 106, 4192.
a. L. E. Overman and S. W. Goldstein, ibid., 1984, 106, 5360.
 59. D. J. Hart, J. Am. Chem. Soc., 1980, 102, 397; J. Org. Chem., 1981, 46, 367.
 60. D. J. Hart and Y. Tsai, J. Org. Chem., 1982, 47, 4403.
 61. a. D. J. Hart and K. Kanai, J. Am. Chem. Soc., 1983, 105, 1255
b. B. S. Pederson, S. Scheibye and S. O. Lawesson, Bull. Soc. Belg., 1978, 87, 229.
 62. D. J. Hart and Y. Tsai ibid., 1982, 102, 1430.
 63. T. Ibuka, G. N. Chu and F. Yoneda, J. Chem. Soc. Chem. Commun., 1984, 597.
 64. J. Royer and H. P. Husson, Tetrahedron Lett., 1985, 26, 1515.
 65. R. Baurer and G. Ohloff, Helv. Chim. Acta, 1976, 59, 1169.
 66. R. T. Lalonde, N. Muhammad, C. F. Wong, E. R. Sturiale, J. Org. Chem., 1980, 45, 3664.
 67. T. Ohnuma, M. Tabe, K. Shiiya and Y. Ban, Tetrahedron Lett., 1983, 24, 4249.
 68. The proto-type of this annulation was reported earlier in the course of studies on the synthesis of mitomycins; T. Ohnuma, Y. Sekine, and Y. Ban, Tetrahedron Lett., 1979, 18, 2533, 2537.
 69. D. O. Shah and K. N. Trivedi, Indian J. Chem., 1977, 15B, 599.

70. J. E. Cragg, R. B. Herbert, F. B. Jackson, C. J. Moody and I. T. Nicolson, J. Chem. Soc. Perkin I, 1982, 2477; J. E. Cragg and R. B. Herbert, ibid., 1982, 2487.
71. R. B. Herbert, J. Chem. Soc. Chem. Commun., 1978, 794.
72. V. K. Mangala and D. S. Bhakuni, Ind. J. Chem., 1980, 19B, 931.
73. D. S. Bhakuni, and P. K. Gupta, Ind. J. Chem., 1982, 21B, 393.
74. W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brockson, T. Li, D. J. Faulkner and N. R. Paterson, J. Am. Chem. Soc., 1970, 92, 741.
75. V. Snieckus, Heterocycles, 1980, 14, 1649.
H. W. Gashwend and H. R. Rodriguez, 'Organic Reactions', John Wiley & Sons Inc. N.Y., 1979, 26, 1.
76. M. Iwao, Y. Watanabe, S. O. De Silva and V. Snieckus, Tetrahedron Lett., 1981, 22, 2349.
77. a.H. Iida, Y. Watanabe, M. Tanaka and C. Kubayashi, J. Org. Chem., 1984, 49, 2412.
b.T. Iwashita, M. Suzuki, T. Kusumi and H. Hakisawa, Chem. Lett., 1980, 383.
78. a.T. R. Govindachari, M. V. Lakshmikantham, K. Nagarajan and B. R. Pai, Tetrahedron, 1958, 4, 311.
b.C. K. Bradsher and H. Berger, J. Am. Chem. Soc., 1958, 80, 930,
T. R. Govindachari, B. R. Pai, S. Prabhakar and T. S. Savithri, Tetrahedron, 1965, 21, 2573.
L. Faber and W. Wiegand, Helv. Chim. Acta, 1976, 59, 2201.
H. Iida and C. Kubayashi, Tetrahedron Lett., 1981, 22, 1913.
H. Iida, C. Kubayashi and M. Tanaka, J. Chem. Soc. Chem. Commun., 1983, 271.
79. E. Kontani, M. Kitazawa and S. Tobinaga, Tetrahedron, 1974, 30, 3027 and references cited therein.
80. A. J. Lipa and R. E. J. Summons, J. Chem. Soc. Chem. Commun., 1977, 826;
A. McKillop, A. G. Turrel, and E. C. Taylor, J. Org. Chem., 1977, 42, 674; J. Chem. Soc. Chem. Commun., 1977, 538.
81. T. F. Buckley III and H. Rapoport, J. Org. Chem., 1983, 48, 4222.
82. T. R. Govindachari, T. G. Rajagopalan, and N. Viswanathan, J. Chem. Soc. Perkin I, 1974, 1161.
83. M. Ihara, T. Kirihaara, A. Kawaguchi, K. Fukumoto and T. Kametani, Tetrahedron Lett., 1984, 4541; M. Ihara, T. Kirihaara, K. Fukumoto and T. Kametani, Heterocycles, 1985, 23, 1097.
84. M. Ihara, M. Tsuruta, K. Fukumoto and T. Kametani, J. Chem. Soc. Chem. Commun., 1985, 1159.

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