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 reviews[1-4]. Subsequently there have been a large number of publications[5] 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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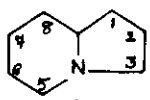
1. Introduction

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.



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2.1. Simple Indolizidine Bases

2.1.1. Plant Origin

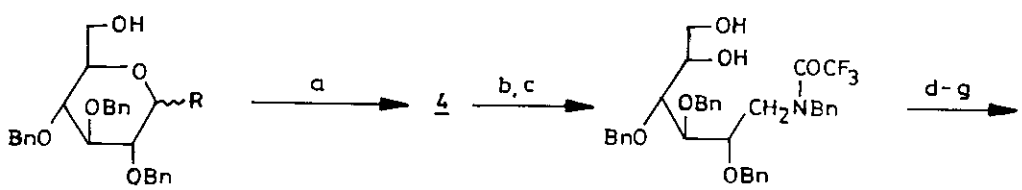
2.1.1.1. Castanospermum Alkaloids

Castanospermine 2 isolated from the toxic seeds of Castanospermum australe[6] 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 hemagglutinin[7]. The first and the only synthesis of castanospermine 2 is a chiral synthesis reported by Ganem and Bernotas[7] starting from the chiral synthon α D-glucose according to Scheme 1. (+)-Castanospermine thus synthesised had $(\alpha)_D$ + 71° (c,0.27,H_2O).

2.1.1.2. Elaeocarpus Alkaloids

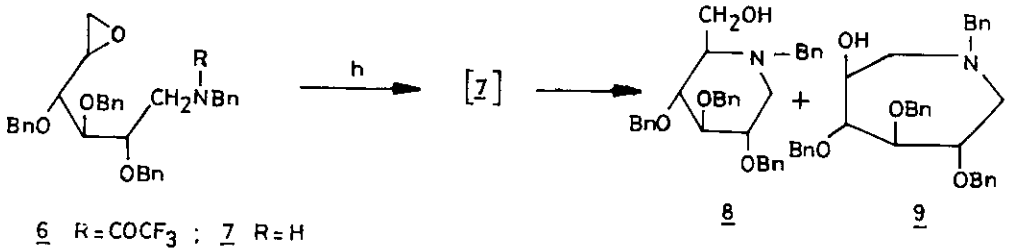
These alkaloids viz. elaeokanines A 14, B 15, C 16, D 17, E 18, elaeocarpine 19, and isoelaeocarpine 20 have been isolated by Johns et al. from the leaves of Elaeocarpus species (Elaeocarpaceae) - rain forest trees which flourish in New Guinea[3,8] and India[8].

Scheme 1

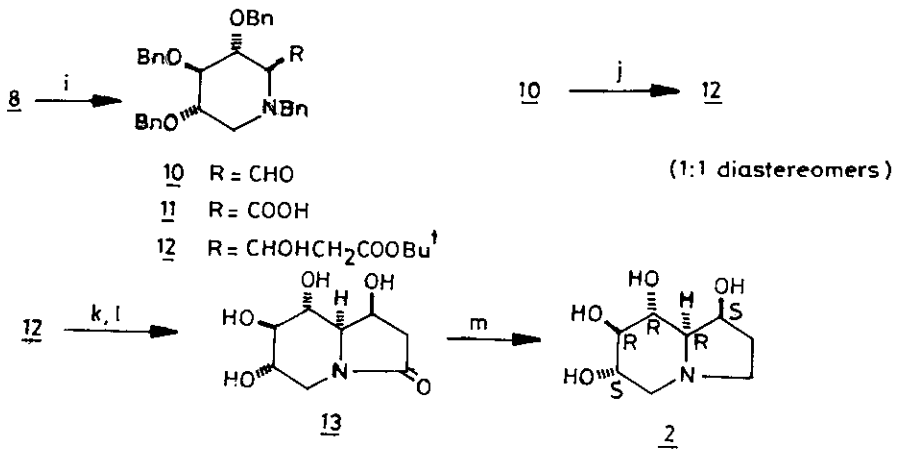


3 R=OH
4 R=NHBn

5

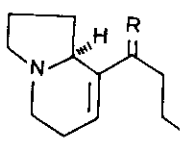


6 R = $COCF_3$; 7 R = H

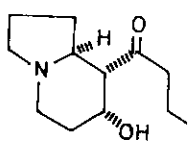


(1:1 diastereomers)

Reagents: a. Benzylamine: b. LAH,THF; c. $(CF_3CO)_2O$,Py; d. TBDMSCl, imidazole; e. MsCl, Et_3N, f. n-Bu_4NF, THF; g. CH_3ONa, MeOH; h. $NaBH_4$,EtOH, 40°C; i. $(COCl)_2$, DMSO; j. Lithio-t-butyl acetate; k. Hydrogenolysis; l. TFA, H_2O, 60°C, 3h; m. Dibal, THF.



14 R=O
15 R=H,OH



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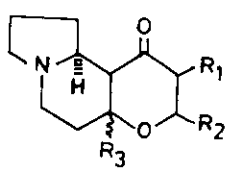
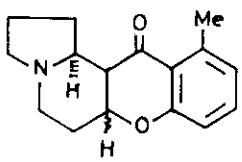


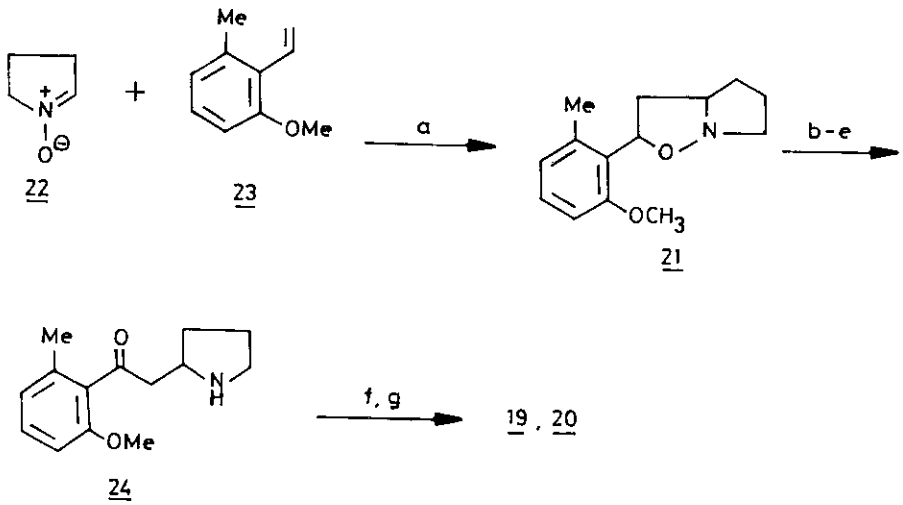
17 $R_1 = H_2$, R_2 = α-Me, R_3 = α-H
18 $R_1 = H_2$, R_2 = α-Me, R_3 = β-H



19 α-H
20 β-H

The synthesis of this series of alkaloids starting from nitrones was reported by Tufariello[9]. The isooxazolidine 21 was prepared by the addition of nitrone 22 to the hindered styrene 23 (Scheme 2). Elaeocarpine 19 and isoelaeocarpine 20 were synthesised by this method.

Scheme 2



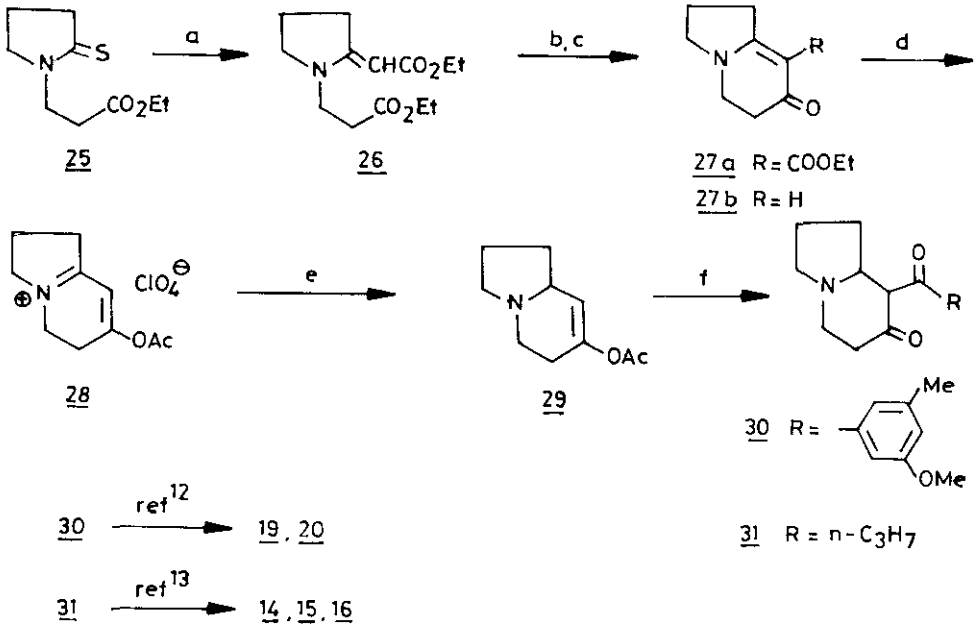
Reagents: a. Toluene, 85°C; b. H_2, PtO_2; c. BzOCOCl, Py; d. Collins reagent; e. H_2, Pd-C; f. Acrolein; g. BBr_3

A formal synthesis of 14, 15 and 16 was reported by Howard and coworkers[10]. 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 (CH_2=CHCOOEt, THF, NaOH (catalytic), 55°C, 98%) which was converted to the vinylogous urethane 26 using a sulphide contraction sequence[11] (Scheme 3).

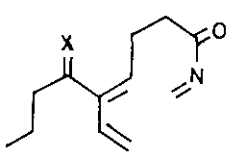
As an extension of Trost's method[14] for the synthesis of quinolizine derivatives from iminoether and α,β-unsaturated ketones, 2-ethoxy-1-pyrroline and ethyl 3-oxopentenoate yielded 27 in 80% yield[15] which was converted to elaeokanines A 14, B 15, and C 16 and also compounds 17, 19 and 20.

Weinreb and his team[16] 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

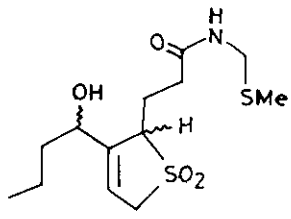


Reagents: a. $CH_2BrCOOEt$, CH_3CN, r.t., 16h; Ph_3P, Et_3N, CH_3CN, r.t; b. Aq.NaOH (0.4M, 1 equiv.), reflux, 0.5h; c. Ac_2O, CH_3CN, r.t., 40h; d. CH_3COCl, $AgClO_4$, CH_3CN, N_2, dark, r.t., 1.5h; e. $NaBH_4$, CH_3CN, r.t., 1h , gl.HOAc, reflux; f.MeLi, THF, N_2, 0^oC, 0.25h, RCOCN, THF, N_2, 0^oC.



32 X = O

33 X = H, OR



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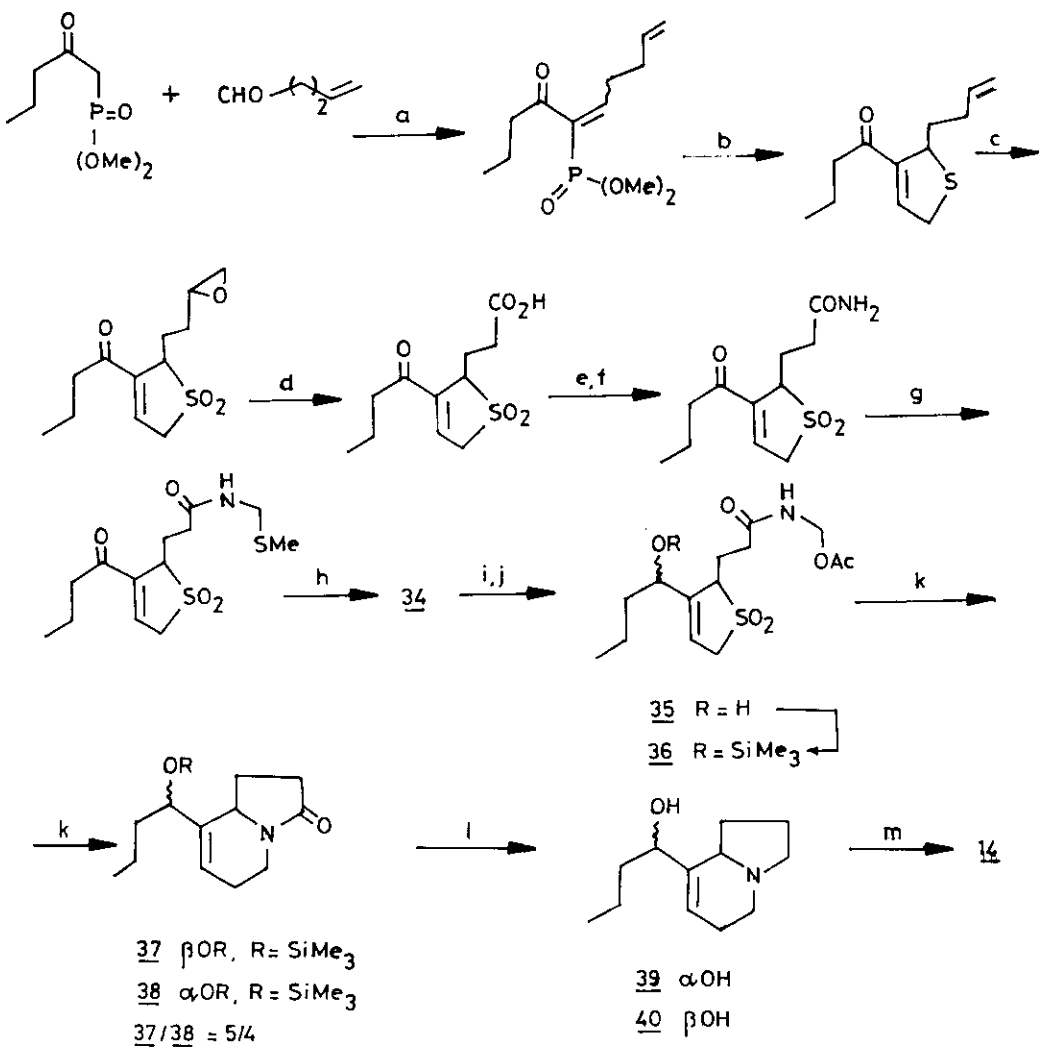
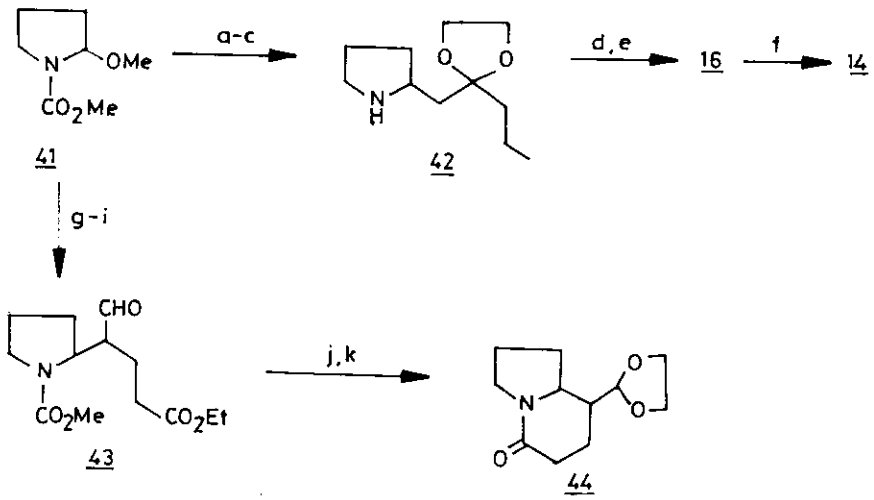
Scheme 4

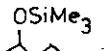


Reagents: a. Piperidine, HOAc, C_6H_6; b. $HSCH_2CHO$, Et_3N; c. mCPBA, CH_2Cl_2; d. H_5IO_6, CrO_3, acetone, H_2O; e. EtOCOCl, Et_3N; f.NH_3; g. chloromethyl methylsulphide, CF_3COOH; h.$NaBH_4$, $CeCl_3$; i. Mercuric acetate, gl.HOAc; j. Silylation; k. △, 370°C, l. Dibal, THF; m. CF_3COOH, DMSO.

Shono and coworkers[17] have synthesised Elaeocarpus alkaloids 14 and 16 by utilising anodically prepared 1-(alkoxycarbonyl)-2-methoxypyrrolidine 41, as a key intermediate[18] according to Scheme 5

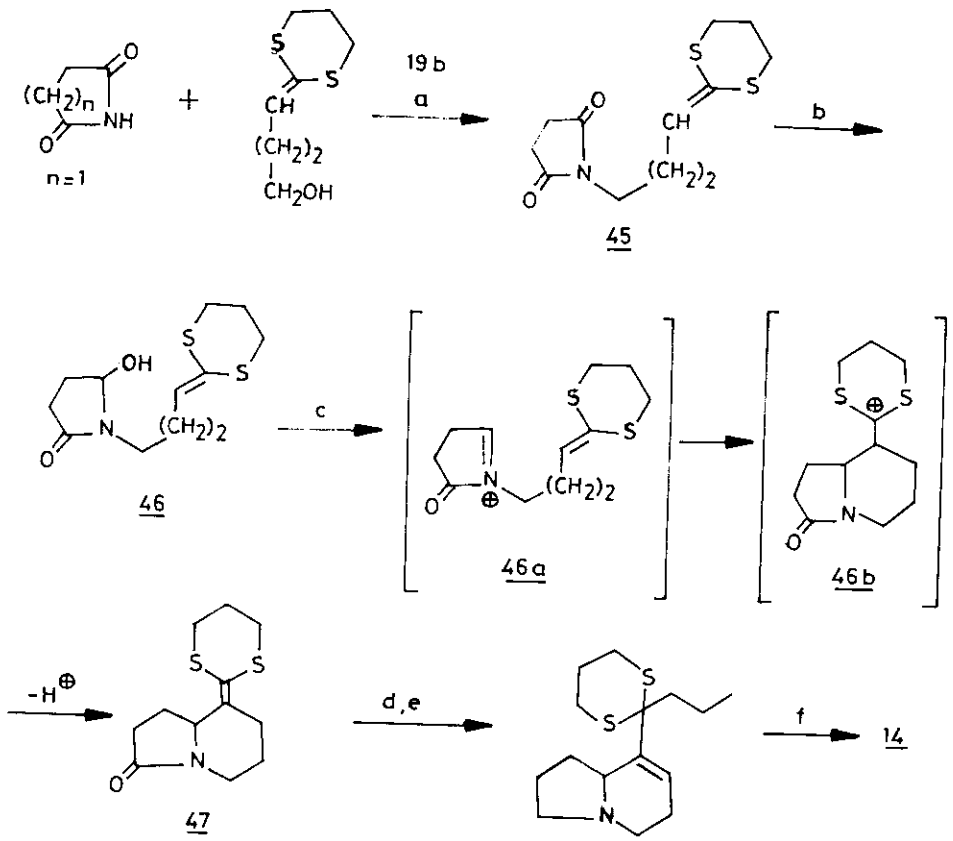
Scheme 5



Reagents: a.  , $TiCl_4$; b. $(CH_2OH)_2$, p-TsOH, c. KOH, NH_2NH_2; d. NaH, $BrCH_2CH_2CH$; e. 1N HCl; f. NaOH; g.  , $TiCl_4$; h. pyrrolidine, K_2CO_3; i.  ; j. $(CH_2OH)_2$, p-TsOH; k. NH_2NH_2, KOH.

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-methylene chloride 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.

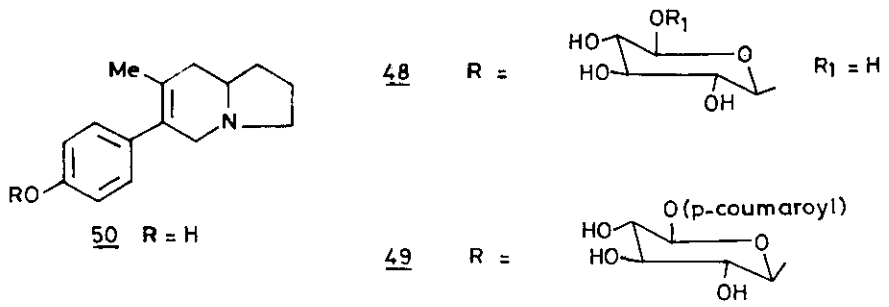
Scheme 6



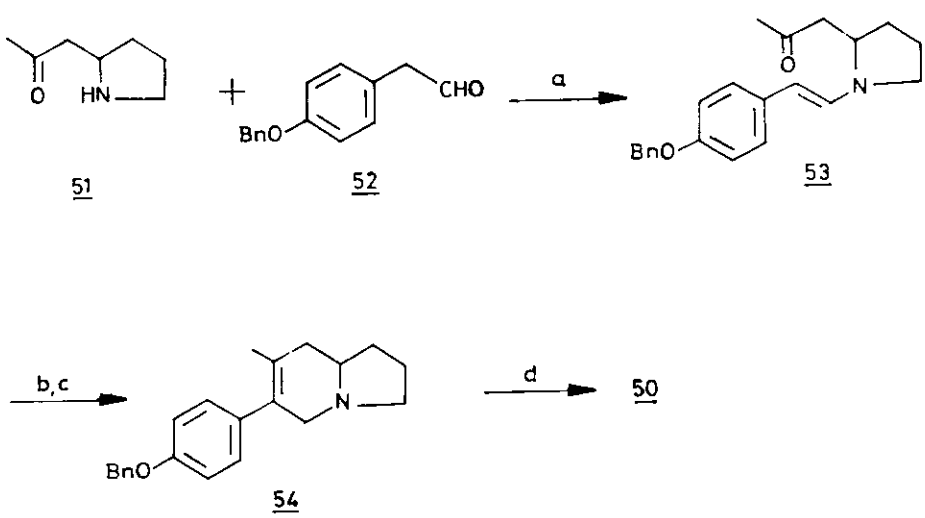
Reagents: a. Ph_3P, COOEt-N=N-COOEt; b. $NaBH_4$; c. MsCl, Et_3N, CH_2Cl_2, -20 → 20°C; d. LAH; e. LDA, I⁄⁄ ; f. Mercuric chloride, H_2

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 ipalbine 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 hexahydroindolizine nucleus[26]. Several syntheses of ipalbidine are known upto 1979[23]. Herbert and Hedges[24] have synthesised ipalbidine according to Scheme 7.



Scheme 7

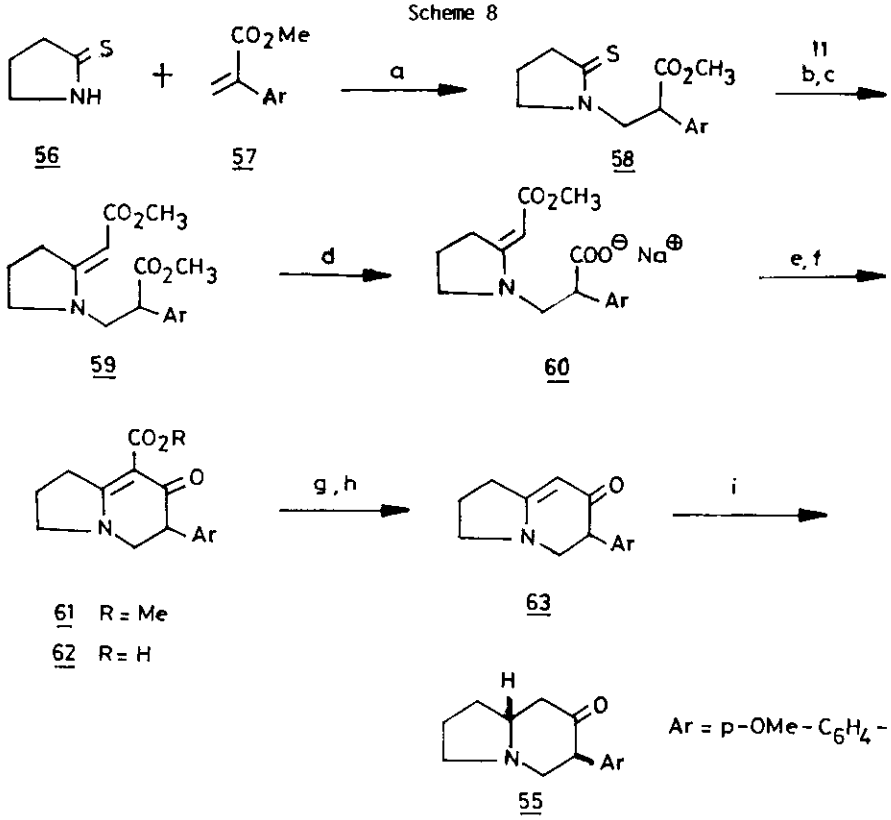


Reagents: a. Benzene, r.t.; b. MeOH; c. $NaBH_4$, PrOH; d. HCl

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 nitrone 22 with the olefine 64 (Scheme 9).

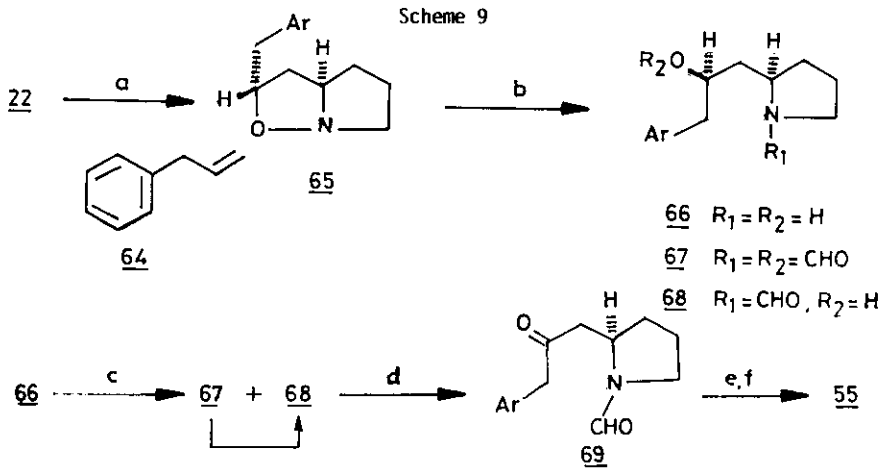
Scheme 8



56 57 58 59 60 61 R = Me 62 R = H 63 55

Reagents: a. NaOH(catalyst), THF; b. $BrCH_2COOMe$, THF; c. PPh_3, Et_3N, CH_3CN; d. NaOH (1 equiv.), H_2O; e. n-Bu_4NI; f. ClCOOMe, THF; g. KOH, H_2O, N_2; h. HCl; H_2O; i. LAH, THF.

Scheme 9



64 65 66 $R_1 = R_2 = H$ 67 $R_1 = R_2 = CHO$ 68 $R_1 = CHO$, $R_2 = H$ 69

Reagents: a. Toluene, reflux; b. Pd-C,H_2; c. HCOOH; d. Collins reagent; e. Aluminium isobutoxide; f. Li, liq.NH_3

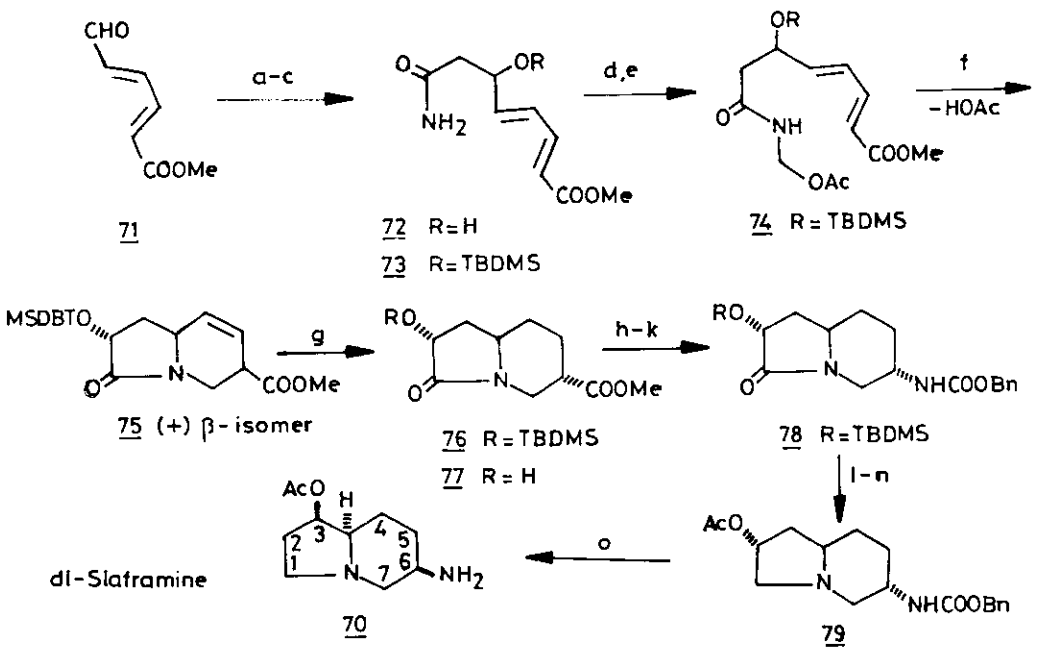
2.1.2. Fungal and Animal Origin

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 Christophel[29] with an overall yield of 0.3%. Weinreb and his team[30] 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).

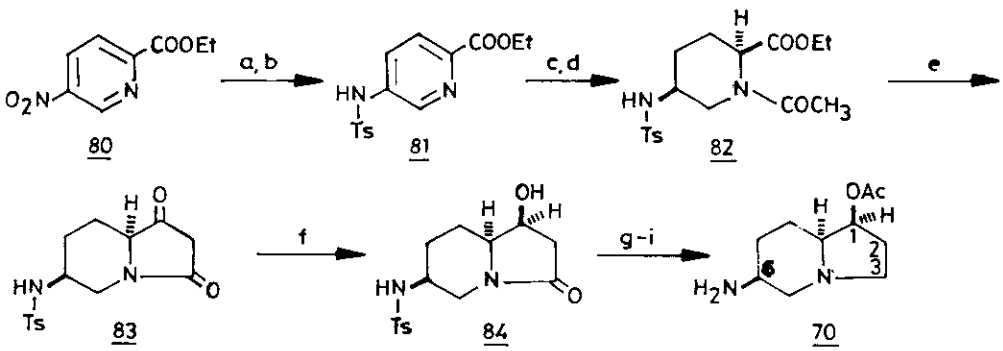
Scheme 10



Reagents: a. n-BuLi, trimethylsilylacetamide carbanion, -78°C; b. H_3O^+; c. TBDMSCl, imidazole, DMF; d. $(CH_2O)_n$, $CsCO_3$, 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. $C_6H_5CH_2OH$,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 Harris[31]. 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 C_6 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



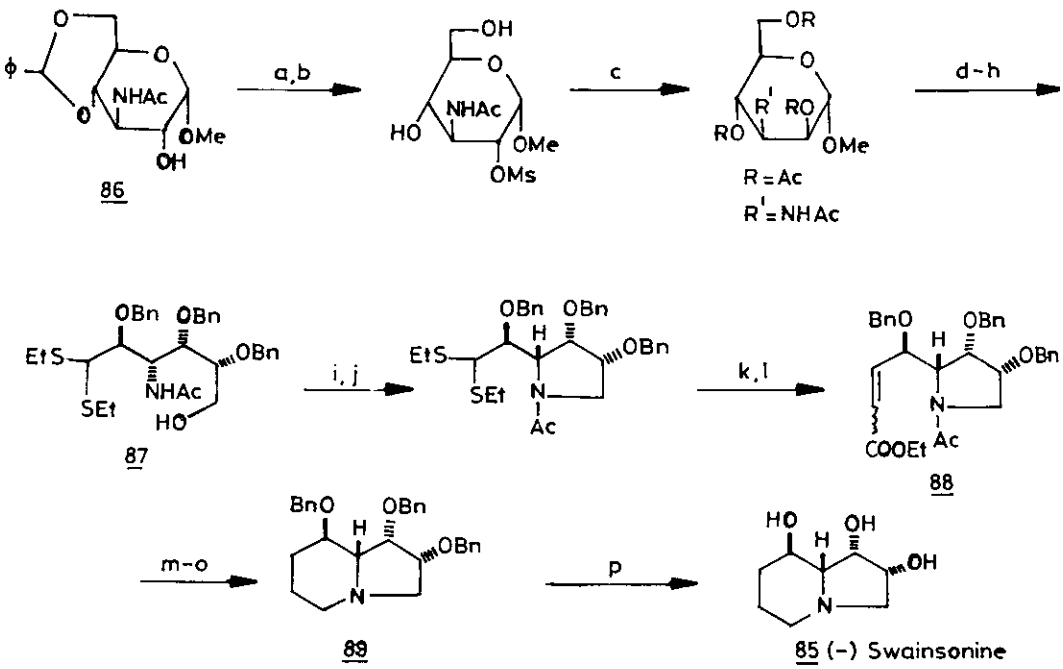
Reagents: a. H_2,Pd-C; b. pTsCl,Py; c. H_2,PtO_2, HOAc,Ac_2O; d. Ac_2O; e. KH; f. L-Selectride reduction; g. BH_3,THF; h. Na,NH_3; i. HOAc, HCl

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 F3622[34]. The alkaloid induces conditions similar to mannosidosis in cattle which graze on pastures containing these weeds[35]. Several chiral syntheses of this alkaloid are reported recently.

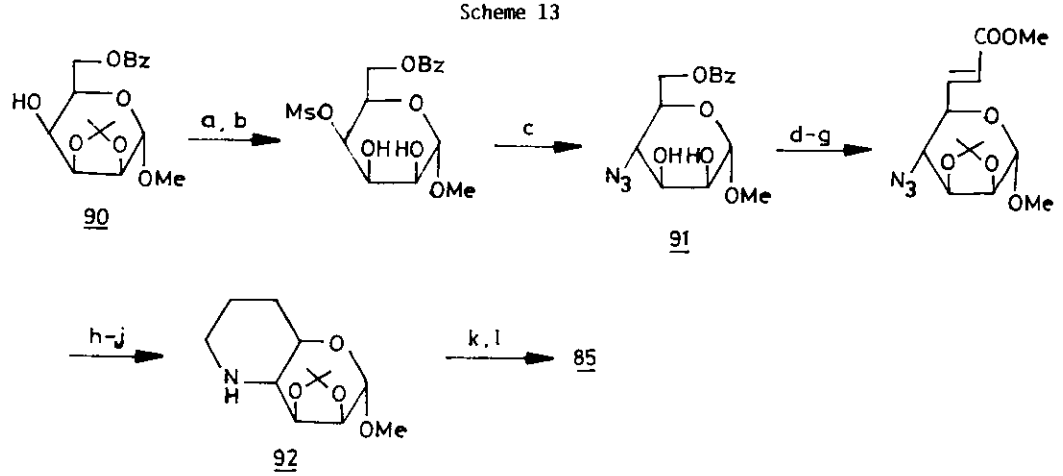
Suami and coworkers[36] have synthesised (-) - swainsonine 85 from D-mannose by a 15 step sequence starting from 86. The overall yield of (-) - swainsonine 85 $(\alpha)_D^{25}$ - 81.7° (c,0.6,MeOH) from the chiral precursor 86 was 2.3% (Scheme 12). Takaya et al.[34] have utilised D-mannose for the synthesis of(-)-swainsonine 85 $(\alpha)_D^{25}$ - 84.7° (c,0.53,MeOH). The intermediate 90[37] was obtained in 3 steps from D-mannose. The configuration of C_4 was inverted at the fourth step to yield 91 (Scheme 13)

Scheme 12



Reagents: a. $MsCl,Et_3N$; b. MeOH, 0.06M HCl; c. NaOAc, methoxyethanol; d. NaOMe; e. $EtSH,H^+$; f. TrCl, p-DMAP; g. BnBr,DMF,NaH; h. H^+; i. p-TsCl,Py; j. NaOH, reflux; k. $HgCl_2$, $CaCO_3$; l. Diethyl ethoxycarbonylmethylphosphonate, NaH; m. Raney Ni, H_2; n. Aq.EtOH,KOH; o. LAH,THF; p. $Pd(OH)_2$-C,H_2

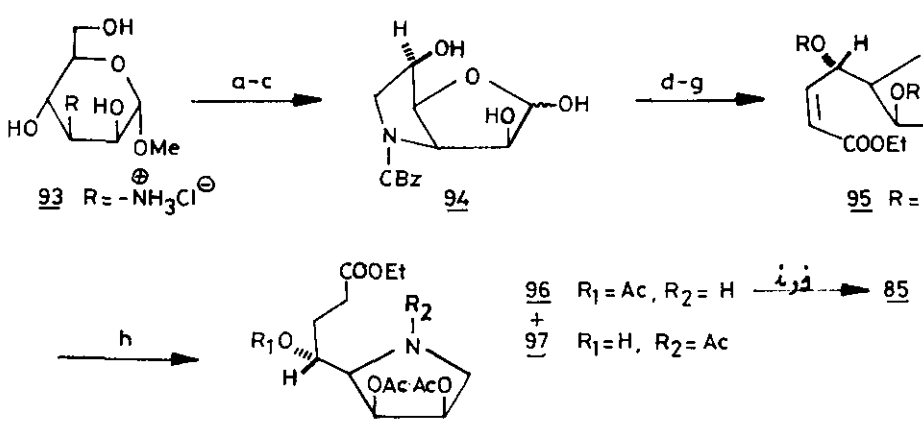
Scheme 13



Reagents: a. MsCl,Py; b. CF_3COOH,MeOH; c. NaN_3,DMF; d. p-TsOH-$Me_2C(OMe)_2$, acetone; e. KOH,MeOH; f. DMSO,Py-SO_3-Et_3N; g. $Ph_3P=CHCOOMe$, THF; h. H_2, Pd-C, MeOH; i. MeOH, reflux; j. BH_3,THF; k. BCl_3,CH_2Cl_2; l. $NaBH_3CN$,H_2O-MeOH.

Richardson and coworkers[38] have synthesised 85, $(\alpha)_D$ -84°(MeOH), from the chiral synthon methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride 93 which was readily available from methyl-α-D-glucopyranoside[39] in 20-25% yield. (-)-Swainsonine 85 was obtained from 93 in 11 steps (Scheme 14).

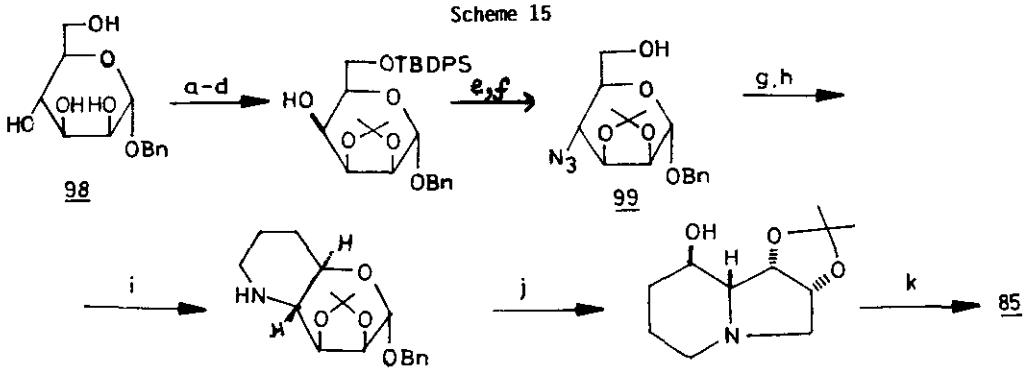
Scheme 14



Reagents: a. Benzyloxy carbonylation; b. p-TsCl,Py;Pd-C,H_2; EtOH,NaOAc; Benzyloxy carbonylation; c.H^+,reflux; d. Ethanethiol, HCl; e. Ac_2O,Py; f. $HgCl_2$, $CaCO_3$; g. Ethoxycarbonyl-methylenetriphenylphosphorane; h. Pd-C,H_2; i. BH_3-DMS; j. NaOMe, MeOH.

Total synthesis of (-)-swainsonine 85 $(\alpha)_D^{20}$-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 C_4 with the retention of configuration (99) by oxidising the hydroxyl group at C_4 followed by reduction. The overall yield of 85 from 98 was 26% (Scheme 15).

Scheme 15

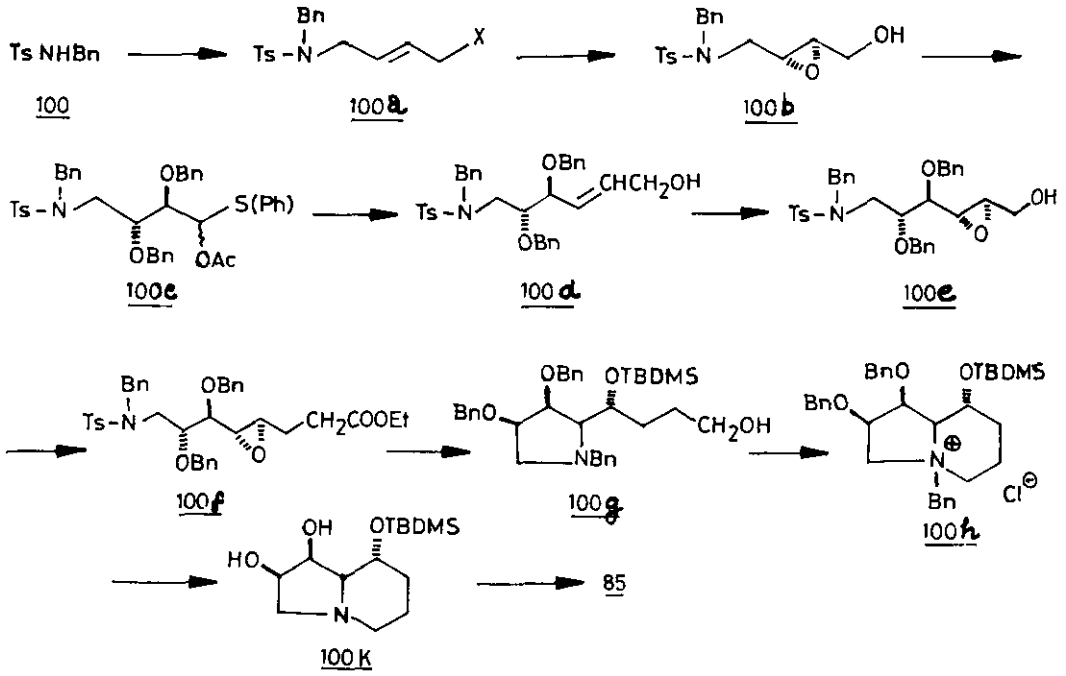


Reagents: a. tert-Butyldiphenylsilyl chloride, imidazole; b. acetone, $Me_2C(OMe)_2$, camphor sulphonic acid; c. PCC, powdered mol. sieves, CH_2Cl_2; d. $NaBH_4$; e. Triflic anhydride, Py,CH_2Cl_2; f. NaN_3, DMF, r.t.; n-Bu_4NF, DMF; g. PCC, powdered mol. sieves, CH_2Cl_2; h. Ph_3P=CHCHO; i. 10% Pd-C, H_2,MeOH; j. Pd-black, HOAc, r.t., 3 days; k. CF_3COOH, 80% D_2O.

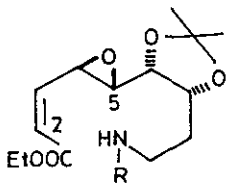
Sharpless et al.[41a] have reported a total synthesis of (-)-swainsonine 85, $(\alpha)_D^{25}$ -73.8° (c,0.21, EtOH), in 21 steps and in 6.6% overall yield from trans-1,4-dichloro-2-butene and N-benzyl-p-toluenesulphonamide. It is the first reported non-carbohydrate route to this alkaloid. It was well 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 (-)-diisopropyl tartrate 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 debenzylation gave the amido alcohol 100k in quantitative yield. Desilylation using Dowex 50W-X8(H^+ form) yielded (-)-swainsonine 85.

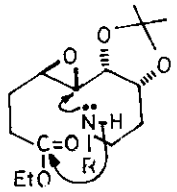
Scheme 16



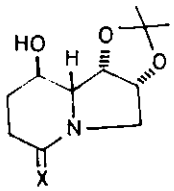
A short enantiospecific synthesis of 85 from D-mannose has been achieved by Hashimoto et al.[42] by a route involving a one step cyclisation of the epoxyamino ester 101c to the lactam 102a followed by the reduction of the lactam 102a to the protected swainsonine 102b. It was found that the conjugated ester 103a was reduced with $NaBH_4$ in trifluoroethanol through 101a to



103

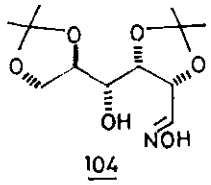


101



102 a X = O

102 b X = H_2



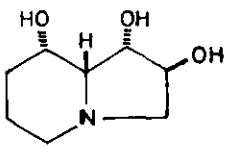
104

a R = CBz

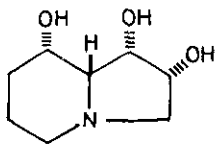
b R = CF_3CO

c R = H

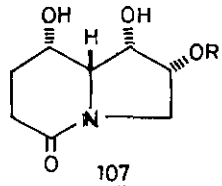
102a and further to 102b. The compound 103c could be generated via a $NaBH_4$ treatment by appropriately protecting the amino group (eg. CF_3CO-) by a direct conversion of 103b to 102b through a synchronous occurrence of a sequence of reactions viz. i) reduction and deprotection of 103b to 101c ii) *double cyclisation of 101c to 102a iii) reduction of 102a to 102b. Therefore, an* extremely short enantiospecific total synthesis of 85 [$(\alpha)_D^{25}$ -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-mannose[43]. 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 derivative[44] 107 (Scheme 17,18)



105



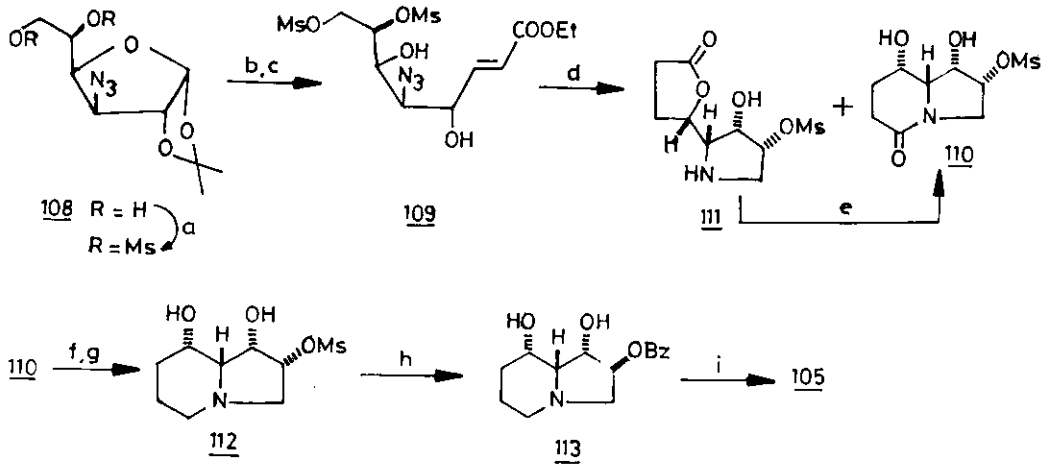
106



107

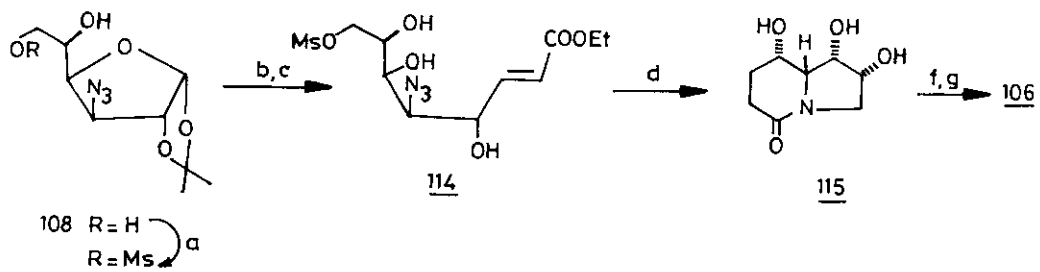
R = Ms or H

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. △, 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

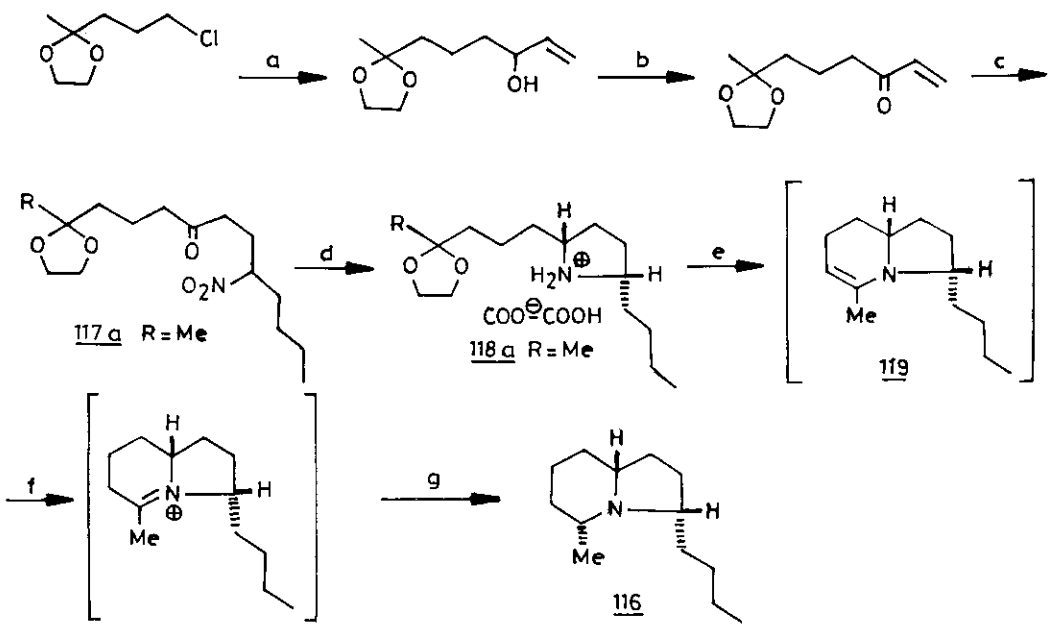


Reagents:a. MsCl,Py; b. $CF_3COOH,H_2O(9:1)$; c. Ph_3P=CH-COOEt, THF; d.H_2, 10% Pd-C, MeOH; e. △, DMF-EtOH(1:4); f. $[(CH_3)_3Si]_2$-$NH(CH_3)_3SiCl$; g. $BH_3(CH_3)_2S$, THF

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 earlier[46]. Lee and Robert[47] 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. monomerinel 116.

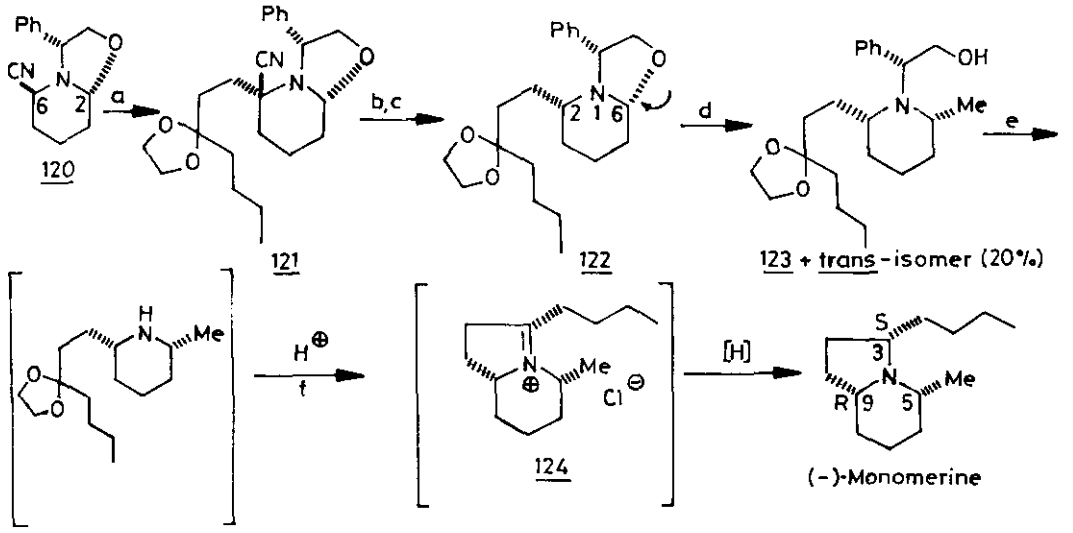
Scheme 19

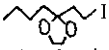


Reagents: a. Mg,THF; CH_2=CHCHO; b. PCC or MnO_2, CH_2Cl_2; c. Nitropentane, TMG; d.10% $PdSO_4$, anhyd.Na_2SO_4; e. H_3O^+; f. pH 3.8-5.4; g. $NaBH_3CN$, MeOH.

Recently Husson and Royer[48] 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 aminonitrile 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

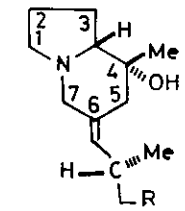


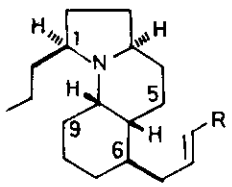
Reagents: a. LDA;  ; b. $AgBF_4$; c. $Zn(BH_4)_2$; d. MeMgBr-ether; e. H_2, Pd-C, MeOH; f. HCl 1%. (-)-Monomerine so obtained had $(\alpha)_D^{20}$ -35.8° (c, 1.35, n-Hexane). The natural monomerine being dextrorotary, the absolute configuration of monomerine was assigned as 3R,5S and 9S based on their previous results.

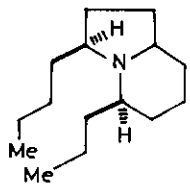
2.1.2.3. Alkaloids of the Dendrobatidae

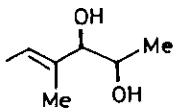
A number of alkaloids 125-131 that possess interesting pharmacological properties have been isolated[50] in minute quantities from the skin extracts of frogs belonging to Dendrobatid family. They are divided into batrachotoxin, histrioniotoxin, pumiliotoxin and gephyrotoxin classes of alkaloids. Of these the indolizidine alkaloids pumiliotoxins, gephyrotoxin 223A are bicyclic whereas gephyrotoxins are tricyclic indolizidine alkaloids. There are several syntheses, stereospecific or starting from a chiral synthon or using a chiral auxiliary, which will be discussed here.

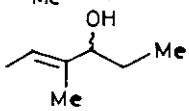
Gephyrotoxin-223 131 and its stereoisomers were synthesised[51] via a N_1-C_2-vicinal annelation of a 1,4-dibromoalkane on to a pyrroline ring system. 132 was alkylated exclusively at the primary carbon site with 1,4-dibromoheptane affording a 1:1 mixture of 4'-bromo stereoisomers







125 R = 

126 R = 

127 R = n-propyl

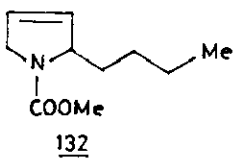
128 R = -C≡CH

129 R = $-CH_2-CH_3$

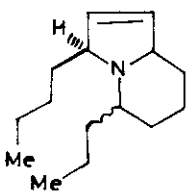
130 R = $-CH_2=CH_2$

131

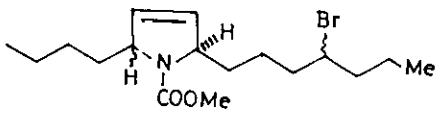
133a when treated with LDA (THF - 40°C). Decarboxymethylation and cyclisation of 133a gave 133b which on catalytic hydrogenation afforded a single stereoisomer 131.



132



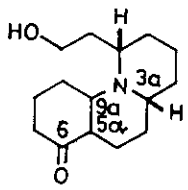
133b



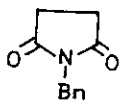
133a

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

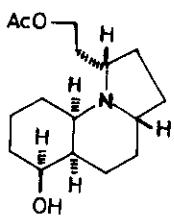
was converted to 137 and 138 in seven steps. The ratio of diastereomeric alcohols varied accord-



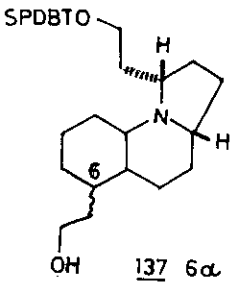
134



135



136

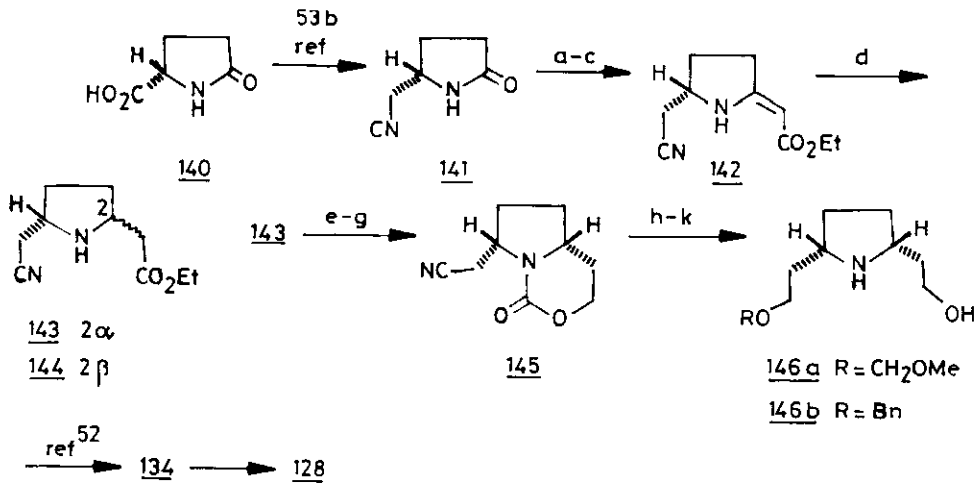


137 6α

138 6β

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.; $CH_3CH_2CH{=}PPh_3$, THF, 0°C; 5% Rh on alumina, EtOH, 60 psi, H_2, r.t.; n-Bu_4NF, DMF, r.t.). Likewise 137 was converted to 128 in 6 steps (PCC, CH_2Cl_2, r.t.; $EtOCH{=}CHP^+Ph_3\ Br^-$, NaOEt, r.t.; pTsOH, acetone, water, 0°C; $ClCH_2P^+Ph_3Cl^-$, BuLi, THF; MeLi, THF; Me_3SiCl; n-Bu_4NF, 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-pyroglutamic acid (Scheme 21).

Scheme 21

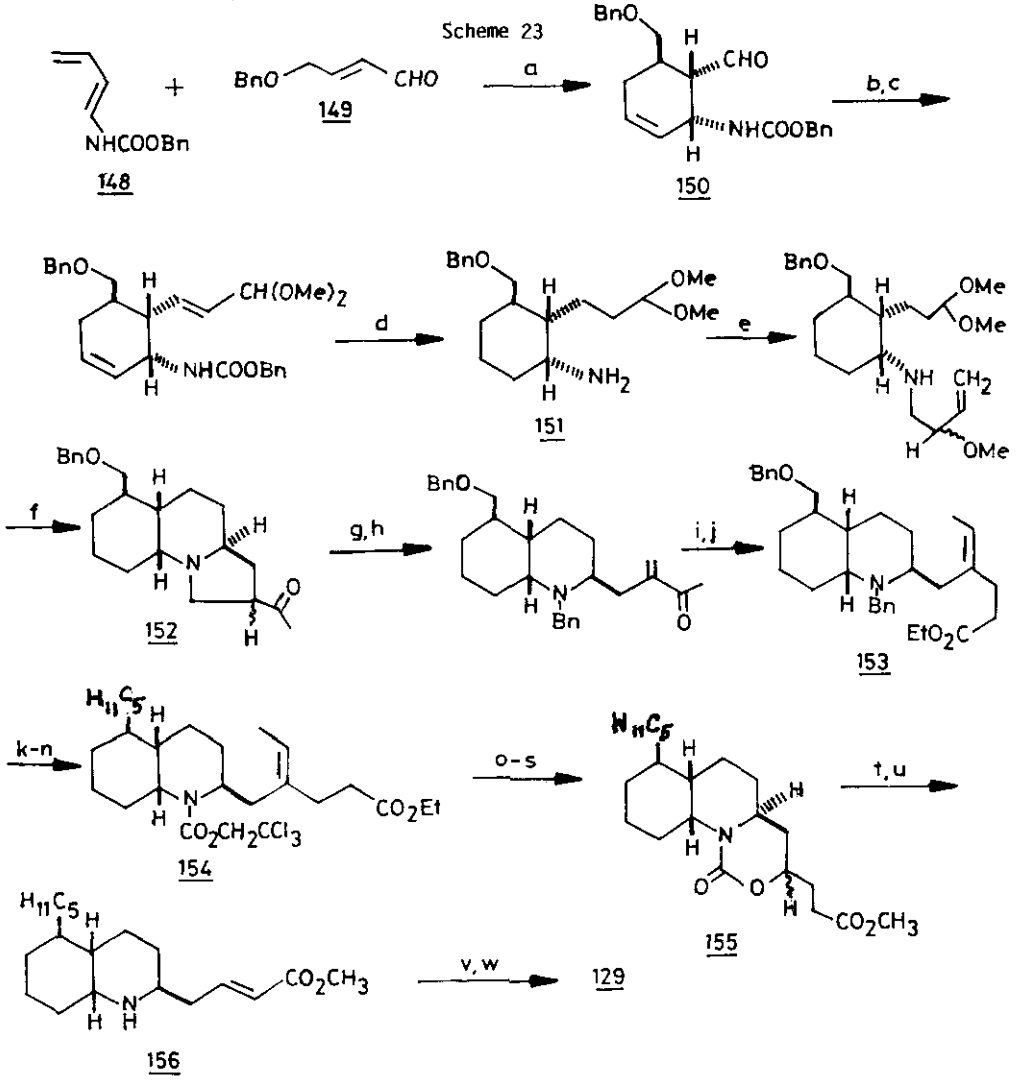


Reagents: a. P_2S_5, Py, 85°C; b. MeOCHBrCOOEt, $NaHCO_3$, r.t., reflux; c. 0.1N KOH, EtOH, 60°C; d. H_2(1 atm), 5% Pt-C, $HClO_4$, MeOH, r.t.; e. C_6H_5COCl, Py, CH_2Cl_2, r.t.; f. $LiBH_4$, THF, r.t.; g. KH, THF, r.t.; h. Dibal, THF-toluene; i. $NaBH_4$, DME, r.t.; j. $MeOCH_2Br$, $^iPr_2EtN, CH_2Cl_2$; k. $Ba(OH)_2, H_2O$, reflux.

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

Lee and Stevens[54] 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).

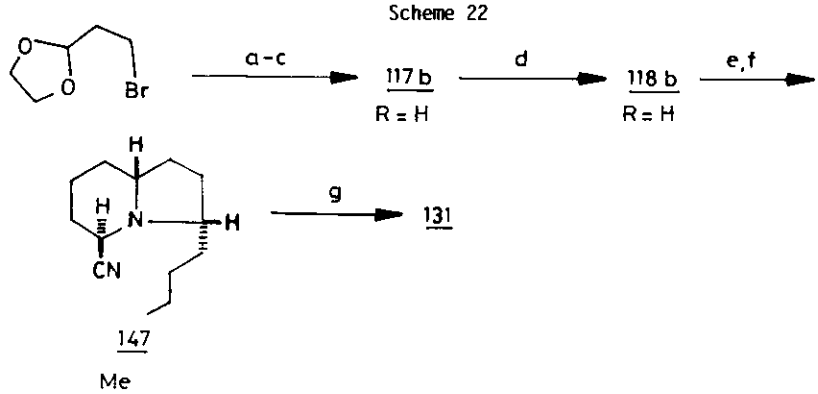
Scheme 23



Reagents: a. 110°C,Δ; 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, BF_3-Et_2O; l. Tosylation; m. $LiBu_2Cu$, ether, -20°C; n. Chloroformate debenzylation; 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.

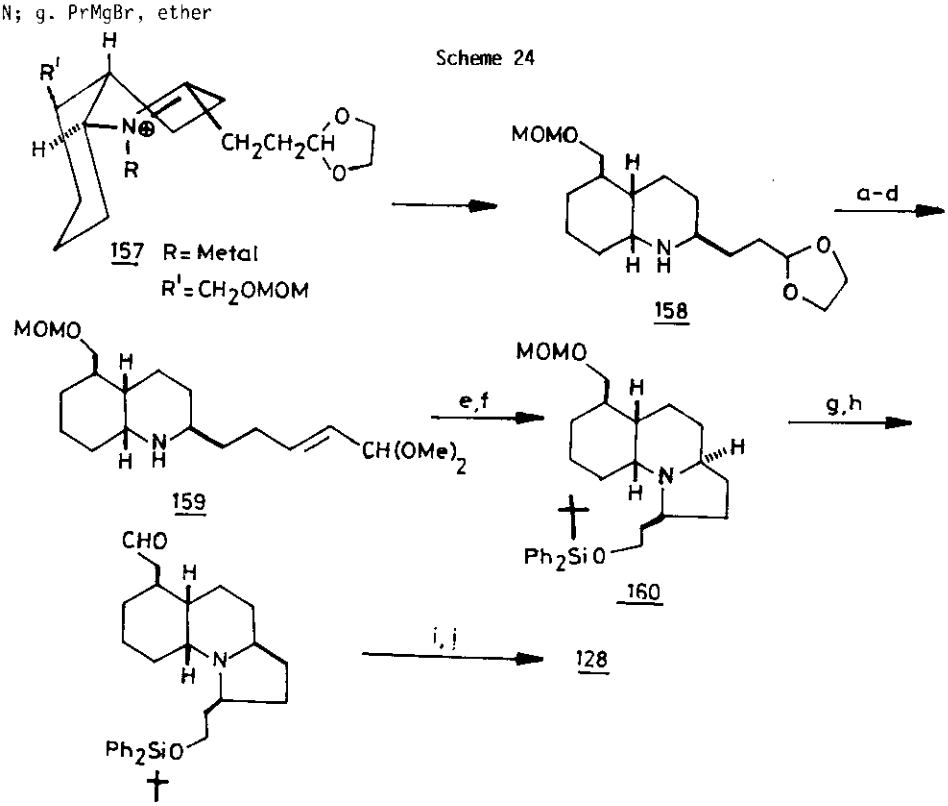
They have synthesised prehydrogephyrotoxin[55] 129 and gephyrotoxin[56] 128 by utilising trans-1,3-butadiene-1-carbamate 148 and trans-2-benzyl-2-butenal 149.

Scheme 22



Reagents: a. $CH_2(COCSOPh)_2$; b. refluxing, CCl_4; c. 1-Nitropentane, TMG; d. Raney Ni, H_2; e. H_3O^+; f. KCN; g. PrMgBr, ether

Scheme 24

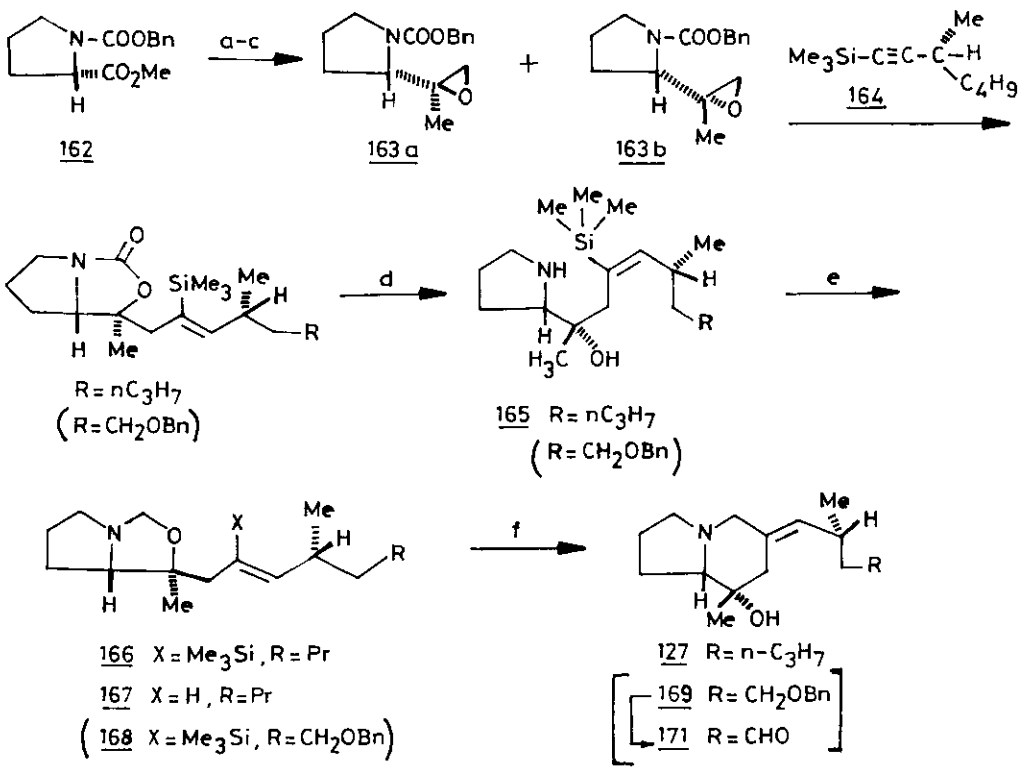


Reagents: a. $ClCOOCH_2CCl_3$, 1,2,2,6,6-pentamethylpiperidine, CCl_4; b. $HClO_4$, THF; Formylmethylenetriphenylphosphorane; c. Pyridinium p-toluenesulphonate, MeOH; d. KOH, MeCHOHMe, H_2O; e. 1M HCl, THF, NaOMe; $NaBH_4$, MeOH; f. TBDPSCl, Et_3N, pDMAP, CH_2Cl_2; g. HBr, DME, 50°C; h. $(COCl)_2$, DMSO; i. $^{i}Pr_3SiCH_2C{\equiv}CSiPr_3^{i}$, BuLi, THF, - 78°C→r.t.; j. n-Bu_4NF

Likewise a total synthesis of (±)-gephyrotoxin 128 was achieved[56] 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 B[58] 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

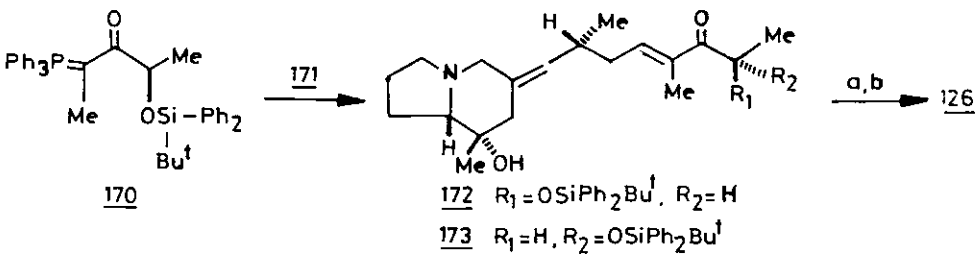


Reagents: a. MeMgI; b. $SOCl_2$,Py; c. m-CPBA, hexane, 25°C; d. 3M EtOH-KOH; e. $(CH_2O)_n$; f. EtOH, camphorsulphonic acid, reflux.

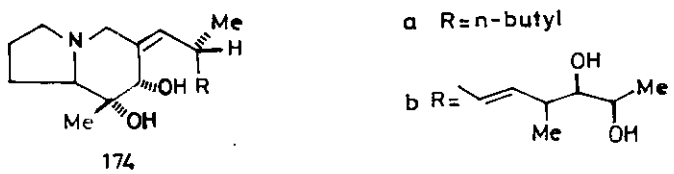
Thus the total synthesis of (+)-pumiliotoxin 251D hydrochloride 127 $(\alpha)_D^{25}+28^0$ (c, 0.62, MeOH) was achieved by a convergent sequence in 9 steps in an overall yield of 6.3% from S-1-heptyn-3-ol and 3.6% from N-benzyloxycarbonyl-L-proline 162.

The side chain 170 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, $(\alpha)_D$ + 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. Allopumiliotoxin-A, (276A) 174a and (339B) 174b were also synthesised using the chiral synthon L-proline carboxylate [58a].

Scheme 26

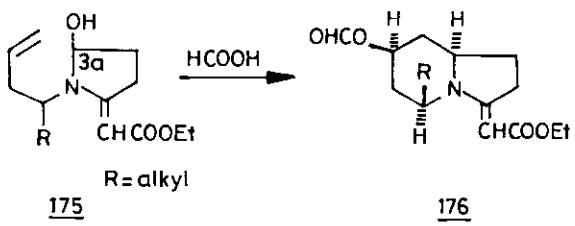


Reagents: a. Threoselective reduction using LAH; b. n-Bu_4NF,DMF.

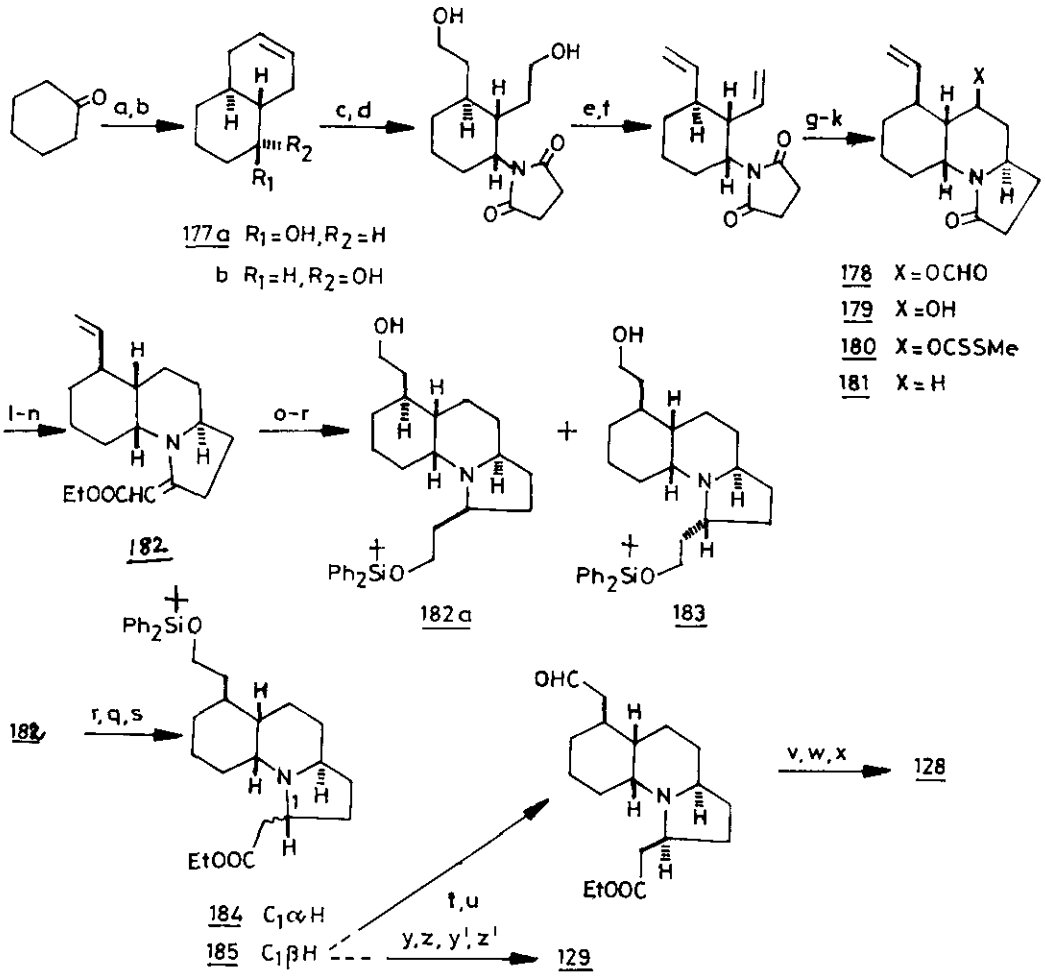


Hart[59] and Tsai have synthesised dependentylperhydrogephyrotoxin[59], gephyrotoxin - 223AB 131 and its isomer[60], gephyrotoxin 128, dehydrogephyrotoxin 130[61] by introducing the asymmetric centre at C_{3a} through a formic acid induced vinylogous-N-acyliminium cyclisation of carbinolamides[59,60] of the type 175 to 176 (Scheme 27).

Scheme 27



Scheme 28

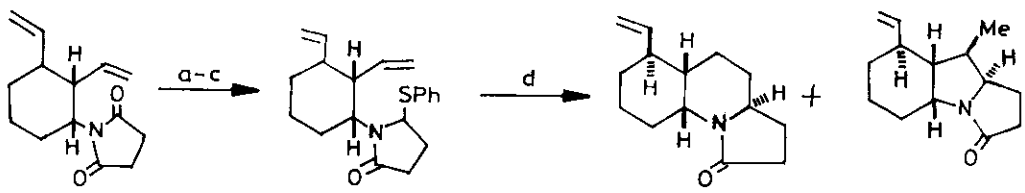


Reagents: a. 1, 3-Butadiene, $AlCl_3$; b. LAH,-70°C; c. Succinimide-Mitsunobu condition; d. Ozone, MeOH, $NaBH_4$; e. Bu_3P, p-nitrophenyl selenocyanate; f. H_2O_2; g. Dibal; h. $HCOOH,CH_2Cl_2$; i. NaOH; j. Xanthate formation; k. Bu_3SnH; i. Lawesson reagent[61b]; m.Ethyl bromoacetate; n. Et_3N,Ph_3P; o. $NaBH_3CN$,pH4;p.LAH; q. TBDPSCl; r. Disiamylborane, H_2O_2; s. Pt on Al_2O_3, EtOAc-hexane; t.n-Bu_4NF,THF; u. $(COCl)_2$, Me_2SO, Et_3N; v. 1-(Trimethylsilyl)-3-t-butyldimethylsilyl-1-propyne, t-BuLi; w. Dibal; x.n-Bu_4NF, DMF; y. Pinacol-E-1-trimethylsilyl-1-propene-3-boronate, CH_2Cl_2, r.t.; z. Hydrolysis; y'. Dibal; z'. KH in THF.

As a typical example, synthesis of gephyprotoxin 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.

Hart[62] has synthesised the intermediate 188 for the synthesis of gephyrotoxin using an α-acylimino radical cyclisation (Scheme 29)

Scheme 29



186 187 188 (31%) 189 (51%)

Reagents: a. $NaBH_4$; b. EtOH,HCl; c. PhSH, TsOH; d. Bu_3SnH, AIBN, PhH.

Ibuka et al.[63] have synthesised (±)-perhydrogephyrotoxin 129 starting from 1,3-bis-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).

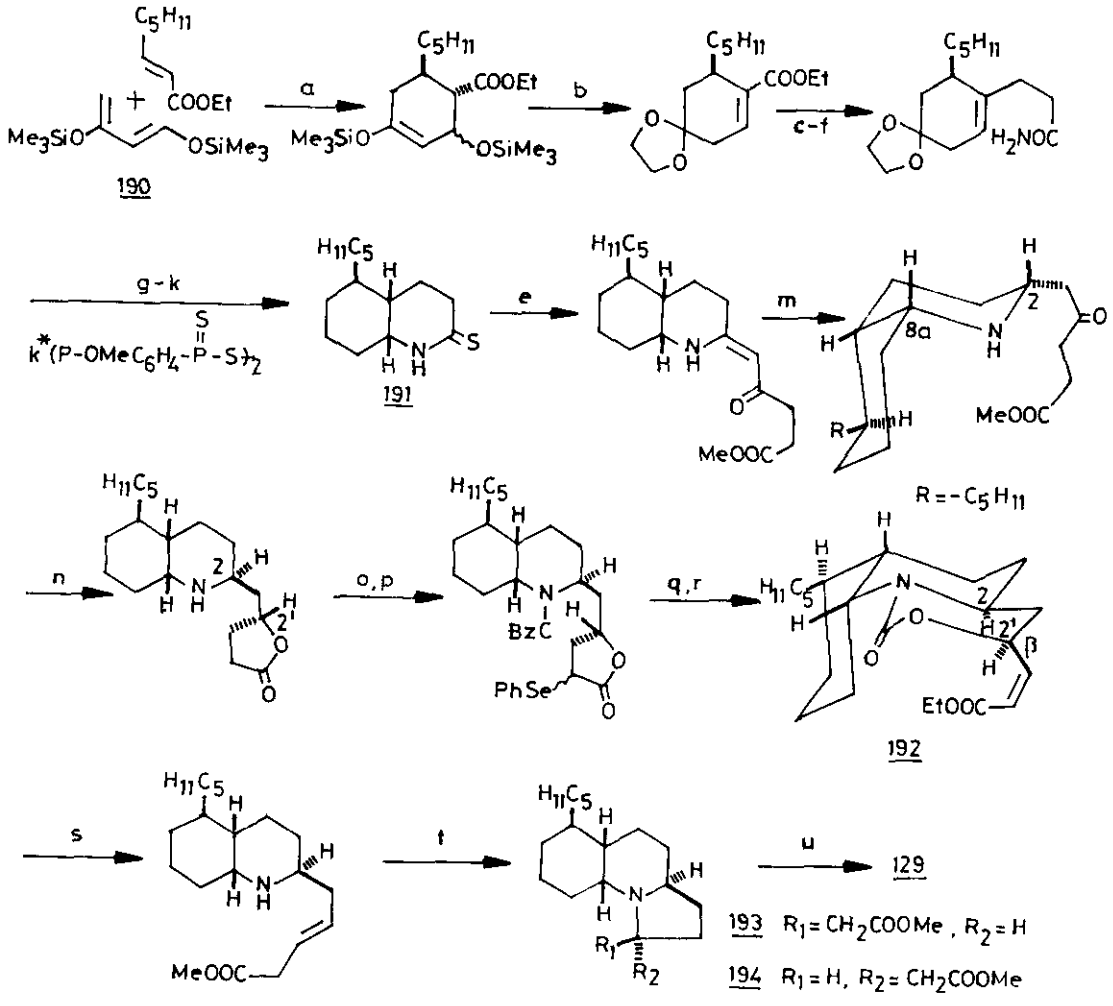
Recently Husson and Royer[64] have clearly established the absolute configuration of gephyrotoxin-223AB 131 by utilising the chiral auxiliary 120 mentioned earlier. The compound 131 was prepared following a variation of the scheme used for the synthesis of (-)-monomerine I 116. The critical step of this 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° (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 perfumery[65]. The isomer 198a was synthesised from a 2,3-disubstituted cyclopentenone oxime 199 by Lalonde and coworkers[66]. Beckmann rearrangement of 199 gave a 6-substituted piperidone 200. Epoxidation of 200 followed by

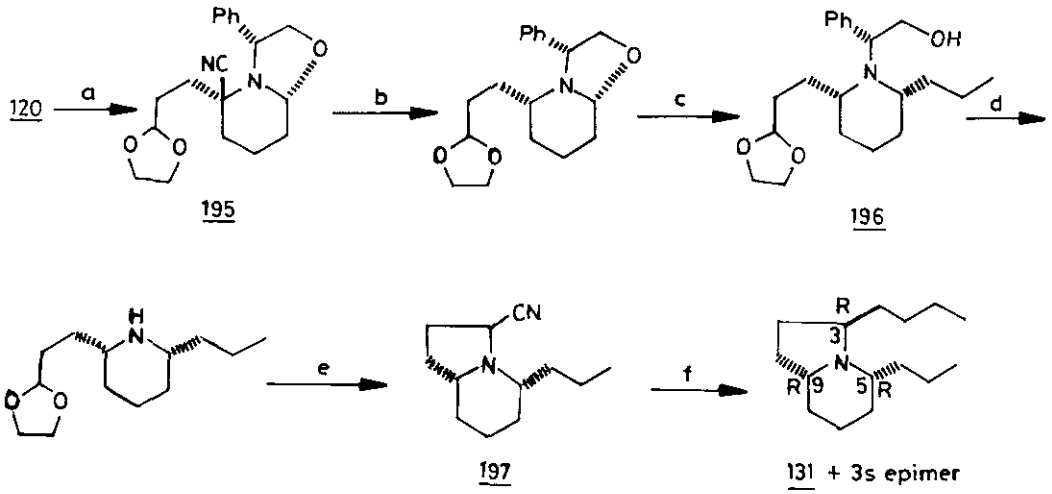
refluxing with sodium hydride in benzene gave the bicyclic intermediate 202. Conversion of 202 to 198 is given in Scheme 32.

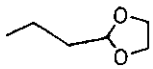
Scheme 30



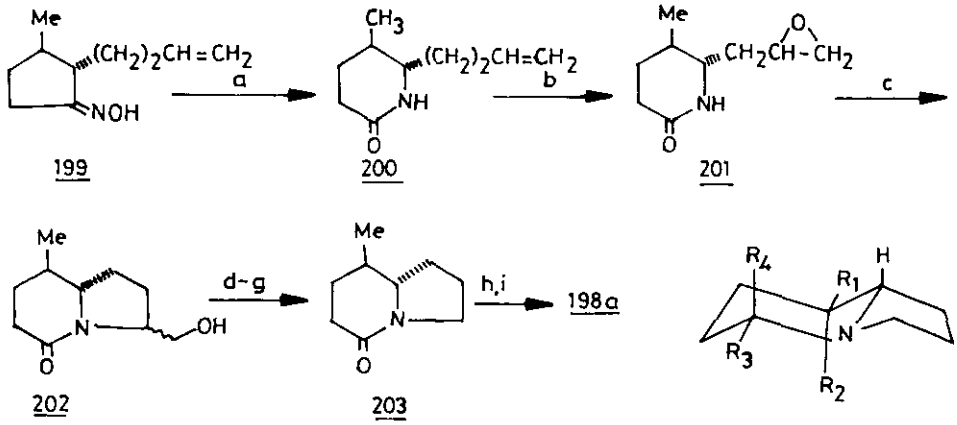
Reagents: a. 175°C, 48h; b. $(CH_2OH)_2$, p-TsOH, C_6H_6 reflux, 10h; c. Dibal, Hexane-Toluene, -73°C, 3h; d. BuLi, THF, HMPT (2:1), -73°C; p-TsCl, -73°→0°C; e. $CuCH_2CN$, THF, -73 → -30°C; f. 30% H_2O_2, 25% aq. KOH, r.t., 12h; g. 5% aq. HCl; h. 5% NaOMe, MeOH, 65°C; i. $(CH_2SH)_2$, BF_3-Et_2O, $CHCl_3$, r.t.; j. Raney W-2 Ni, EtOH, 78°C; k. k*-xylene, 140°C; l. $BrCH_2COCH_2CH_2COOMe$, $CHCl_3$, Ph_3P $(CH_2CH_2NMe)_2$, 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 → -30°C.

Scheme 31



Reagents: a. LDA, I  ; b; $AgBF_4$,THF, $Zn(BH_4)_2$; c. PrMgBr,ether; d. H_2,Pd-C, MeOH; e. CH_2Cl_2, HCl; KCN; f. n-BuMgBr, ether.

Scheme 32

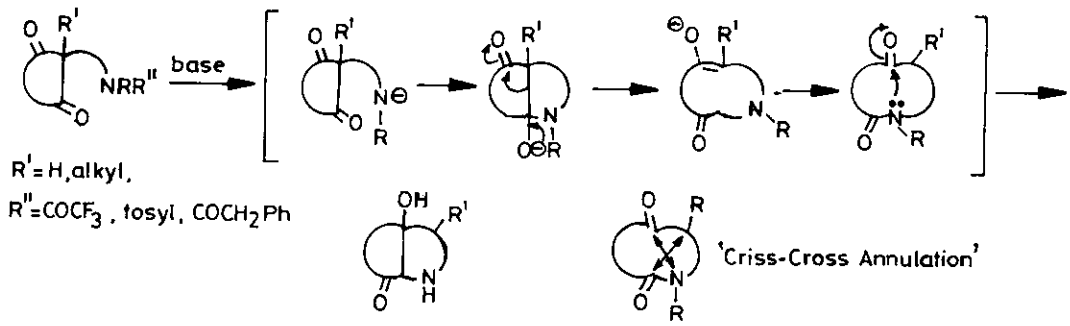


198 a R_1=Me, R_2=H, R_3=Furyl, R_4=H
b R_1=Me, R_2=R_3=H, R_4=Furyl
c R_1=R_4=H, R_2=Me, R_3=Furyl
d R_1=R_3=H, R_2=Me, R_4=Furyl

Reagents: a. PCl_5, ether, p-TsCl,Py; b. m-CPBA; c. NaH,benzene,reflux; d. CrO_3,H_2SO_4, acetone; e. $Pb(OAc)_2$, $Cu(OAc)_2$,H_2O; Py,N_2. △ ; 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.

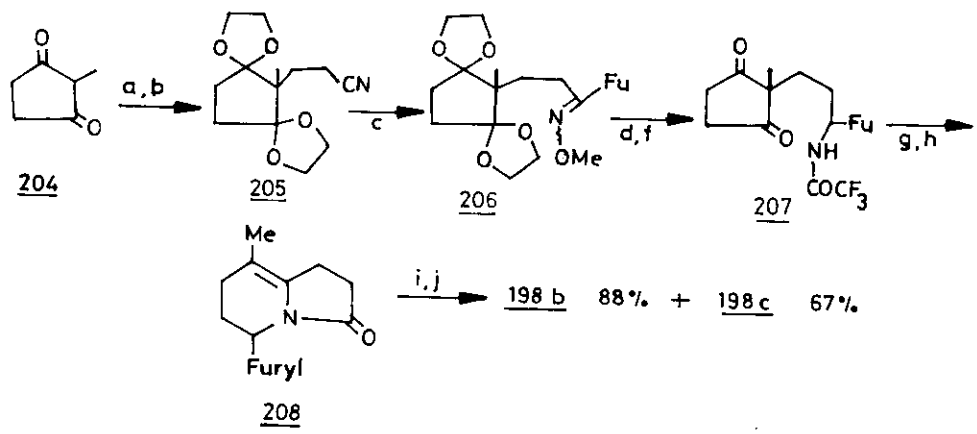
Ban et al.[67] have used a novel type of reaction which they named as 'Criss-cross Annulation'[68] for the synthesis of 198. Scheme 33 clearly depicts this 'Criss-cross Annulation'.

Scheme 33



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

Scheme 34



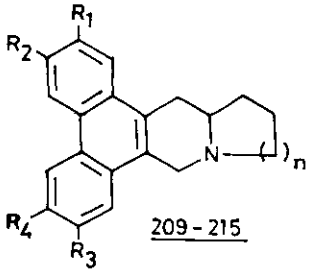
Reagents: a. Acrylonitrile; b. $(CH_2OH)_2$, CSA; c. Furyllithium, H_2O, NH_2OMe, d. LAH, THF, e. $(CF_3CO)_2O$, Py; f. aq.CF_3COOH; g. LiOH, aq. MeOH, 65°C; h. aq.HCl, MeOH, i. $NaBH_3CN$,MeOH, pH 3.0; j. LAH, THF.

2.2 Phenanthroindolizidine Alkaloids:

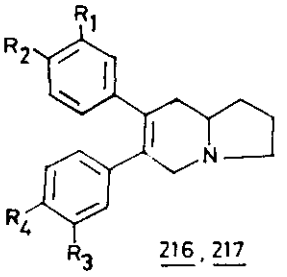
The phenanthroindolizidine alkaloids have been the subject of numerous biological and chemical studies[1-2]. Several of these natural products are powerful vesicants, often highly toxic, and can modulate the growth of various normal and abnormal mammalian tissues. The reviews[1-2] mentioned summarise 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 - 215



216, 217

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, Deoxytylophorinine

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

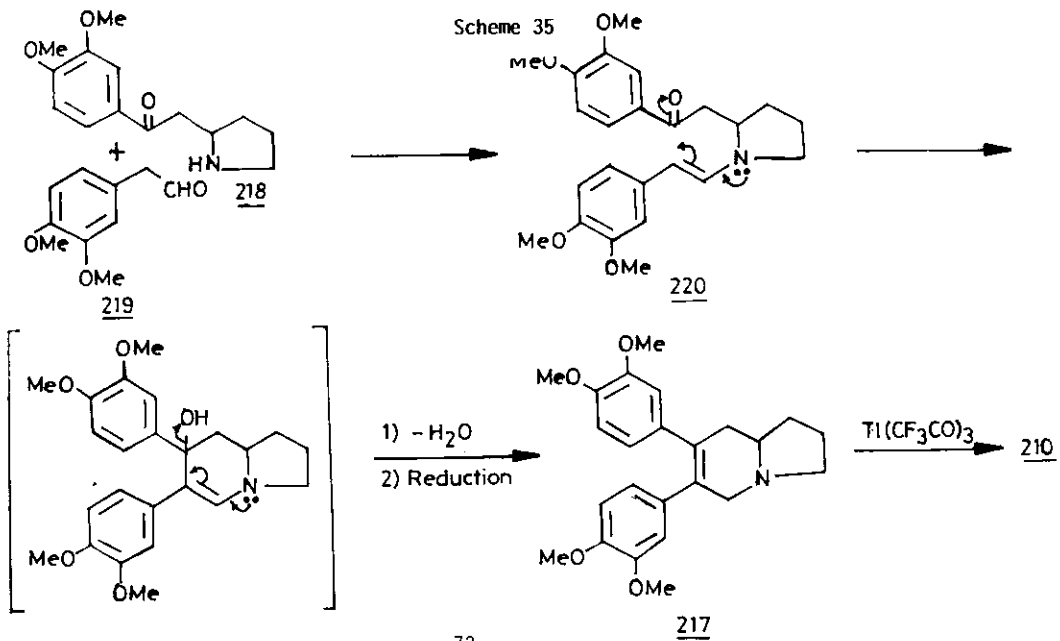
215 $R_1 = R_2 = OMe$, $R_4 = OH$, $R_3 = H$, n=1, Alkaloid C

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

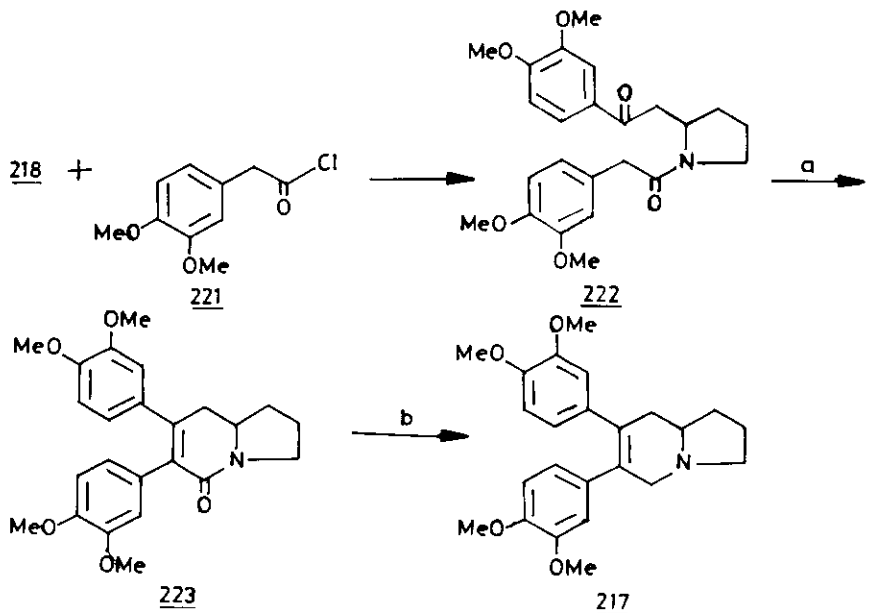
The biogenetically patterned sequence in which the condensation of phenacylpyrrolidine 218 with phenacylaldehydes 219 afforded the enamine 220. The enaminoketone condensation is effected in methanol at r.t. Cyclisation of the enamine and subsequent dehydration using selected Lewis acids[70,71] such as $SnCl_4$, $TiCl_4$ 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).

Scheme 35



Another biogenetically patterned sequence[72] 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)

Scheme 36

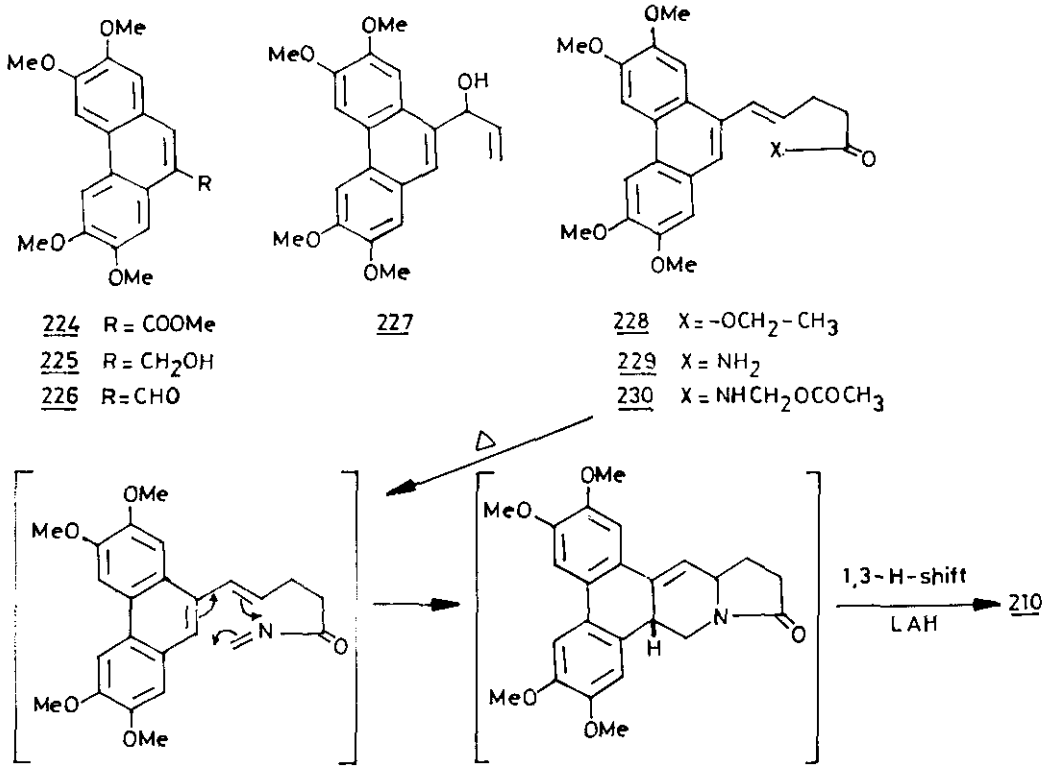


Reagents: a. Ethanolic alkali; b. LAH, $AlCl_3$

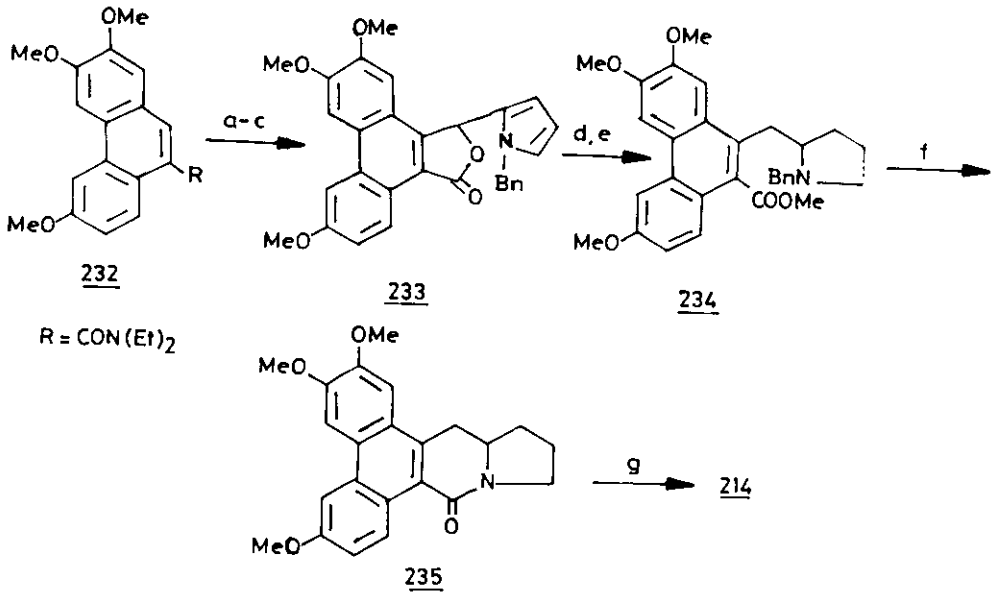
Antofine 214 and alkaloid C 215 were synthesised by the oxidation of the secophenanthroindolizidines like 217 with either MnO_2 or SiO_2 or $CuCl_2$,O_2, pyridine[73].

Using an intramolecular Diels-Alder strategy tylophorine 210 was synthesised[16] 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 vinyllithium in THF yielded 227 (79%). Orthoester Claisen rearrangement[74] 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

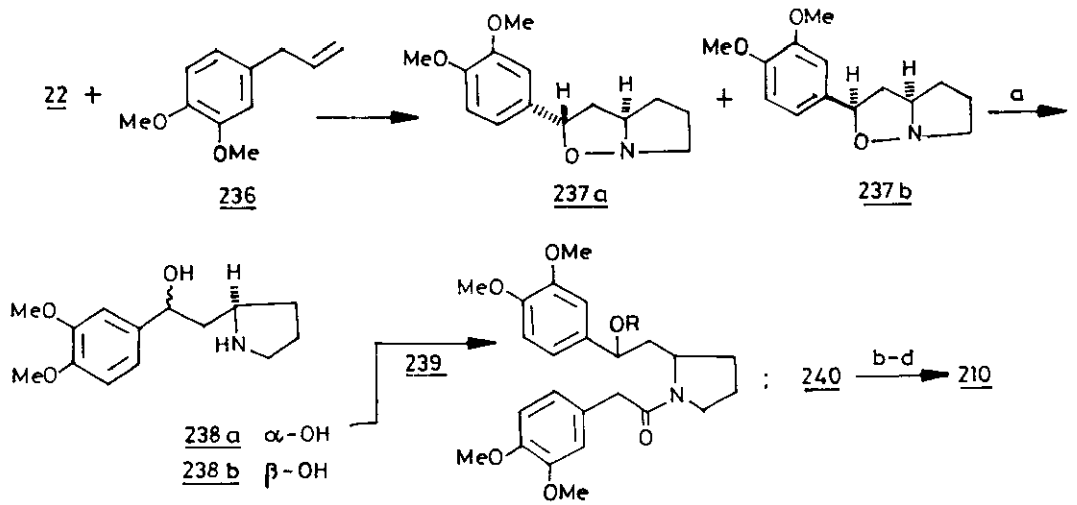


Scheme 38



Reagents: a. Sec-BuLi, TMEDA, ether, THF, -78°C; b. N-Benzylpyrrol-2-carboxaldehyde; c. Silica gel, $CHCl_3$, △; d. Zn-Cu, KOH,Py; e. CH_2N_2; f. H_2,Pt,HOAc; g. LAH, THF.

Scheme 39



239 3,4-$(OMe)_2$ $C_6H_3CH_2COCl$

240 R=H

241 $R=COCH_2C_6H_3(OMe)_2$

Reagents: a. Zn, HOAc; b. NaOEt; c. LAH; d. hυ, I_2

Metallation of phenanthrene carboxamide[75] 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 antofine[76] (Scheme 38), in 38% yield.

The isoxazolidine available from the 1,3-dipolar addition of nitrone 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.

Tylolphorine 210, cryptopleurine 210b, septicine 216 and julandine 217 were synthesised by this method[77].

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

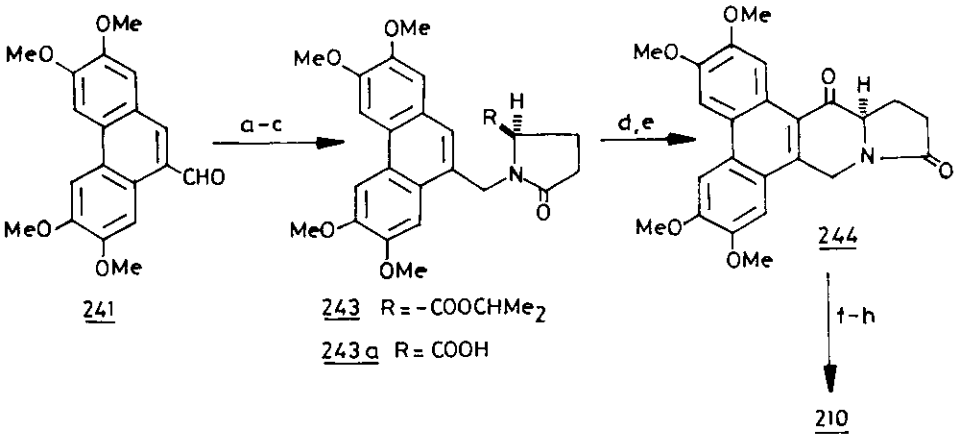
ii) Photocyclisation: This method yielded the desired phenanthrenes and also the unwanted isomers. However, these methods are superior to Pschorr cyclisation[78b].

iii) Anodic oxidation: This electrochemical method yielded the clean desired phenanthrene derivative [79].

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 achieved[81] 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, $(\alpha)_D$ +12.0°, mp 282 -284°C. This is in discrepancy with the absolute configfuration assigned to natural tylophorine on the basis of ozonolysis experiments[82] and further work is in progress to settle the issue.

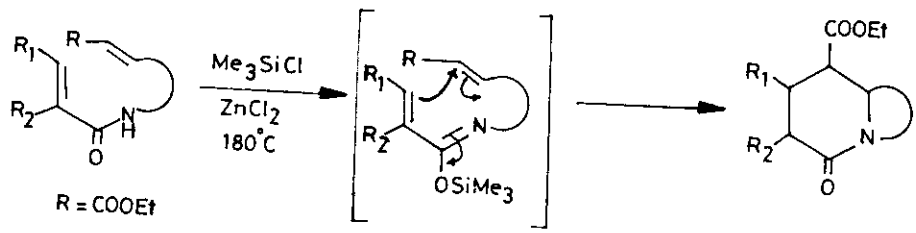
Scheme 40



Reagents: a. 242; b. $NaBH_3CN$,MeOH; c. MeOH,HOAc; d. Hydrolysis; e. $AlCl_3$; f. Catalytic hydrogenation; g. Deoxygenation; h. LAH, THF.

The recently reported[83] 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

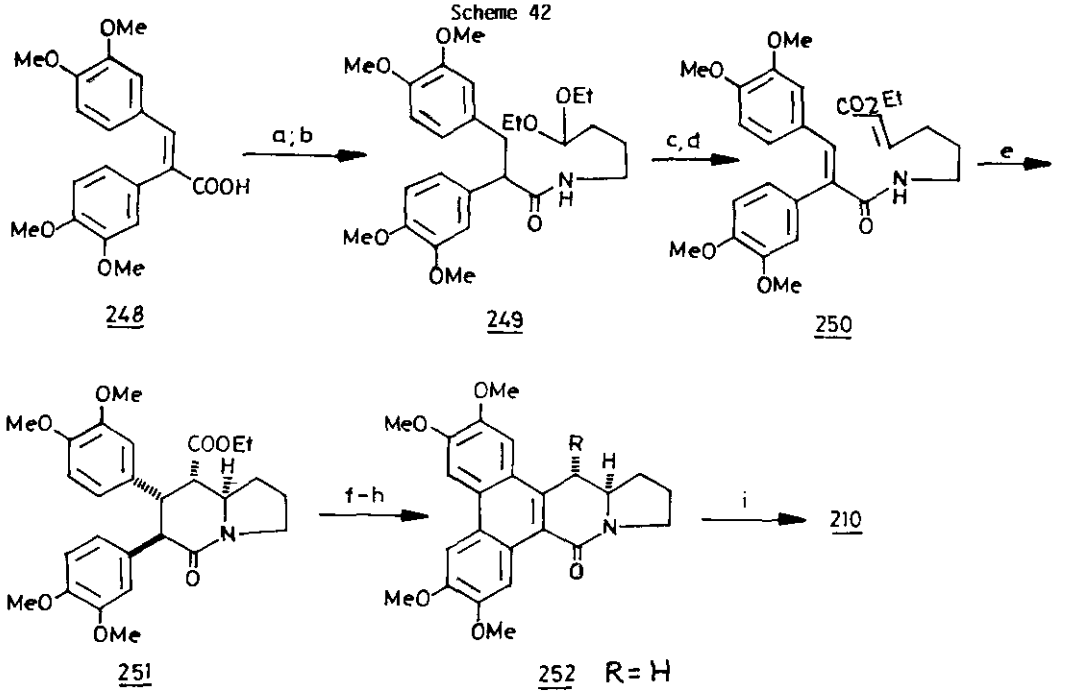
Scheme 41



R = CO_2Et

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 tributylsilyltrifluoromethane sulphonate (TBSOTf) and Et_3N in CH_2Cl_2 to yield 251 (68%). Conversion of 250 to tylophorine is given in Scheme 42.

Scheme 42



Reagents: a. $(COCl)_2$; b. $NH_2(CH_2)_3CH(OEt)_2$, $NaHCO_3$; c. HOAc,H_2O; d. Ph_3P=CHCOOEt; e. TBSOTf, Et_3N, r.t.; g.TTFA,BF_3-Et_2O, TFA; g.KOH,MeOH, h. HMPA, 230°C; i. $NaAl(OCH_2CH_2OMe)_2$,H_2

Abbreviations used in the review:

AIBN	azobisisobutyronitrile
Bn	benzyl
BnBr	benzyl bromide
Bz	benzoyl
mCPBA	m-chloroperbenzoic acid
CSA	camphorsulphonic acid
pDMAP	p-dimethylamino pyridine
DME	dimethoxyethane
HMPA	hexamethylphosphoramide
PCC	pyridinium chlorochromate
PpTSONa	pyridinium-p-toluenesulphonate
TBSOTf	tributylsilyltrifluoromethane sulphonate
TBDMS	tert-butyldimethylsilyl
TBDPS	tert-butyldiphenylsilyl
TMEDA	tetramethylethelenediamine

TMG	tetramethylguanidine
TrCl	trityl chloride
TTFA	thalium (III) trifluoroacetate

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