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 up to 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.

![Indolizidine System](image)

2. Simple Indolizidine Bases

2.1. Plant Origin

2.1.1. 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 \(\alpha-\) and \(\beta-\)glucosidasess 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 \(\alpha\) D-glucose according to Scheme 1. \((+)-\)Castanospermine thus synthesised had \((\alpha)_{D} + 71^{0}\) \((c,0.27,\text{H}_{2}\text{O})\).

2.1.1.1. Elaeocarpus Alkaloids

These alkaloids viz. elaeokanines A \(^{14}\), B \(^{15}\), C \(^{16}\), D \(^{17}\), E \(^{18}\), elaeocarpine \(^{19}\), and isaelaeocarpine \(^{20}\) 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](image)

\(3\) \(R=\text{OH}\)

\(4\) \(R=\text{NHBn}\)
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R = COCF₃ ; 7 R = H

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. (COCI)₂, DMSO; j. Lithio-t-butyl acetate; k. Hydrogenolysis; l. TFA, H₂O, 60°C, 3h; m. Dibal, THF.

17 R₁ = H₂, R₂ = αMe, R₃ = α-H
18 R₁ = H₂, R₂ = αMe, R₃ = β-H

19 αH
20 βH
The synthesis of this series of alkaloids starting from nitrones was reported by Tufariello. The isooxazolidine was prepared by the addition of nitronet to the hindered styrene (Scheme 2). Elaeocarpine and isoelaeocarpine were synthesised by this method.

Scheme 2

Reagents: a. Toluene, 85%; b. H₂, PtO₂; c. BzOCOCI, 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 coworkers. The substituted dehydroindolizidine was synthesised from the exocyclic vinylogous urethane via an acylative ring closure. Pyrrolidine-2-thione was alkylated on the nitrogen to yield (CH₂=CHCOOEt, THF, NaOH (catalytic), 55°C, 98%) which was converted to the vinylogous urethane using a sulphide contraction sequence (Scheme 3).

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

Weinreb and his team in their synthesis of elaeokanine A 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 (Scheme 4). Coniceine and tylophorine were also synthesised by this method.
Scheme 3

Reagents:  

a. CH$_2$BrCOOEt, CH$_3$CN, r.t., 16h; Ph$_3$P, Et$_3$N, CH$_3$CN, r.t.;  
b. Aq. NaOH (0.4M, 1 equiv.), reflux, 0.5h;  
c. Ac$_2$O, CH$_3$CN, r.t., 40h;  
d. CH$_3$COCl, AgClO$_4$, CH$_3$CN, N$_2$, dark, r.t., 1.5h;  
e. NaBH$_4$, CH$_3$CN, r.t., 1h, gl. HOAc, reflux;  
f. MeLi, THF, N$_2$, 0°C, 0.25h, RCOCN, THF, N$_2$, 0°C.
Scheme 4

Reagents:

a. Piperidine, HOAc, C₆H₆; b. HSCH₂CHO, Et₃N; c. mCPBA, CH₂Cl₂; d. H₂O₂, CrO₃, ace-
tone, H₂O; e. EtOCOCl, Et₃N; f. NH₃; g. chloromethyl methylsulphide, CF₃COOH; h. NaBH₄, 
CeCl₃; i. Mercuric acetate, gl.HOAc; j. Silylation; k. Δ, 370°C; l. Dibal, THF; 
m. CF₃COOH, DMSO.

Shono and coworkers¹⁷ have synthesised **Elaeocarpus** alkaloids 14 and 16 by utilising anodically 
prepared **1-(alkoxycarbonyl)-2-methoxypyrrrolidine** 41, as a key intermediate¹⁸ according to Scheme 5.
Reagents: a. TiCl₄; b. (CH₂OH)₂, p-TsOH; c. KOH, NH₂NH₂; d. NaH, BrCH₂CH₂CH₂; e. 1N HCl; f. NaOH; g. (CH₂OH)₂, p-TsOH; h. pyrrolidine, K₂CO₃; i. COOEt; j. (CH₂OH)₂; p-TsOH; k. NH₂NH₂, KOH.

Chamberlin and coworkers 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 to the hydroxylactam, 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-methylenchloride 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 was converted into the mesylate. This mesylate was not observed but undergoes rapid elimination to the acyliminium ion followed by cyclisation to which with the loss of a proton gives a new cyclic ketenedithioacetal in good yield (Scheme 6). Conversion of 47 to 44 is depicted in the Scheme.
Reagents: a. \( \text{Ph}_3\text{P}, \text{COOEt-NN'-COOEt} \); b. \( \text{NaBH}_4 \); c. \( \text{MsCl}, \text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2, -20 \to 20^\circ \text{C} \); d. \( \text{LAH} \); e. \( \text{LDA}, 1\% \); f. \( \text{Mercuric chloride}, \text{H}_2 \)

2.1.1.3. The Ipomoea Alkaloids

These alkaloids are isolated from the seeds of \( \text{Ipomoea alba}^{20} \) and \( \text{Ipomoea muricata}^{21,22} \). They are, two glycosides ipalbine \( 4\) 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.
Howard et al. 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. 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).

Reagents: a. Benzene, r.t.; b. MeOH; c. NaBH₄, PrOH; d. HCl
Reagents: a. NaOH (catalyst), THF; b. BrCH₂COOME, THF; c. PPh₃, Et₂N, 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 is a fungal toxin produced by Rhizoctonia leguminicola. 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. with an overall yield of 0.1%, later by Christophel with an overall yield of 0.3%. Weinreb and his team 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, trimethylsilylacetic acid, -78°C; b. H₃O⁺; c. TBDMS, imidazole, DMF; d. (CH₂O)₉, CsCO₃, THF; e. Ac₂O,Py; f. Δ; g. 9-BBN,THF, 0°C; h. 5% KOH, MeOH; i. EtOCON, Py; NaN₃, H₂O, 0°C; j. THF, Δ; k. C₆H₅CH₂OH,r.t.; l. B₂H₆,THF; m. HCl, THF; n. Ac₂O, Py; o. 10% HOAc,MeOH
A stereoselective synthesis of (+)-slaframine was achieved by Schneider and Harris. 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 C8a 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 C8 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, PdO2, 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, from the locoweed Astragalus lentiginosus, from the fungus, Rhizoctonia leguminicola, and from cultured broth of the fungus Metarhizium anisopliae F3622. The alkaloid induces conditions similar to mannosidosis in cattle which graze on pastures containing these weeds. Several chiral syntheses of this alkaloid are reported recently.

Suami and coworkers have synthesised (-) - swainsonine 85 from D-mannose by a 15 step sequence starting from 86. The overall yield of (-) - swainsonine 85 (α)25 - 81.7° (c, 0.6, MeOH) from the chiral precursor 86 was 2.3% (Scheme 12). Takaya et al. have utilised D-mannose for the synthesis of (-) - swainsonine 85 (α)25 - 84.7° (c, 0.53, MeOH). The intermediate 90 was obtained in 3 steps from D-mannose. The configuration of C4 was inverted at the fourth step to yield 91 (Scheme 13)
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Scheme 12

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

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Richardson and coworkers have synthesised 85, (α)\textsubscript{D}-84\textdegree (MeOH), from the chiral synthon methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride which was readily available from methyl-α-D-glucopyranoside\textsuperscript{39} in 20-25% yield. (-)-Swainsonine 85 was obtained from 93 in 11 steps (Scheme 14).

Scheme 14

![Scheme 14](image)

Reagents: a. Benzylxy carbonylation; b. p-TsCl,Py,Pd-C,H\textsubscript{2}; EtOH,NaOAc; Benzylxy carbonylation; c. H\textsuperscript{+}, reflux; d. Ethanethiol, HCl; e. Ac\textsubscript{2}O,Py; f. HgCl\textsubscript{2}, CaCO\textsubscript{3}; g. Ethoxycarbonylmethylenetriphenylphosphorane; h. Pd-C,H\textsubscript{2}; i. BH\textsubscript{3}-DMS; j. NaOMe, MeOH.

Total synthesis of (-)-swainsonine 85 (α)\textsubscript{D}20 67.4\textdegree (c,0.33,MeOH) was carried out by Smith et al.\textsuperscript{40} starting from the chiral synthon benzyl-α-D-mannopyranoside 98. The azido group was introduced at C\textsubscript{4} with the retention of configuration (99) by oxidising the hydroxyl group at C\textsubscript{4} followed by reduction. The overall yield of 85 from 98 was 26% (Scheme 15).

Scheme 15

![Scheme 15](image)

Reagents: a. tert-Butyldiphenylsilyl chloride, imidazole; b. acetone, Me\textsubscript{2}C(OMe)\textsubscript{2}, camphor sulphonic acid; c. PCC, powdered mol. sieves, CH\textsubscript{2}Cl\textsubscript{2}; d. NaBH\textsubscript{4}; e. Triflic anhydride, Py,CH\textsubscript{2}Cl\textsubscript{2}; f. NaN\textsubscript{3}, DMF, r.t.; n-Bu\textsubscript{4}NF, DMF; g. PCC, powdered mol. sieves, CH\textsubscript{2}Cl\textsubscript{2}; h. Ph\textsubscript{3}P=CHCHO; i. 10% Pd-C, H\textsubscript{2},MeOH; j. Pd-black, HOAc, r.t., 3 days; k. CF\textsubscript{3}COOH, 80% D\textsubscript{2}O.
Sharpless et al.\(^{41a}\) have reported a total synthesis of \((-\)-swainsonine \(85, (\text{c.0.21, EtOH})\), in 21 steps and in 6.6% overall yield from \(\text{trans-1,4-dichloro-2-butene}\) and \(\text{N-benzyl-p-toluene sulphonamide}\). 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 \(\text{N-benzyl-p-toluene sulphonamide}\) 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 \((\text{ethoxycarbonylmethylene})\)-triphenyl phosphorane. Diimide reduction of the resultant \(\alpha,\beta\)-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-butylidimethylsilyl 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.\textsuperscript{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 $102a$ and further to $102b$. The compound $103c$ could be generated via a NaBH$_4$ treatment by appropriately protecting the amino group (e.g., CF$_3$CO-)$ 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)$_D^{25}$$-79.8^\circ$ (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.\textsuperscript{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-trihydroxindolizidine derivative\textsuperscript{44} $107$ (Scheme 17,18)
Reagents: a. MsCl, Py; b. CF₃COOH, H₂O (9:1); c. Ph₃P=CH-COOEt, THF; d. H₂, 10% Pd-C, MeOH; e. Δ, DMF-EtOH (1:4); f. [(CH₃)₃Si]₂NH(CH₃)₃SiCl; g. BH₃(CH₃)₂S, THF; h. BzONa, DMF; i. NaOMe, NaOH

Scheme 17

Reagents: a. MsCl, Py; b. CF₃COOH, H₂O (9:1); c. Ph₃P=CH-COOEt, THF; d. H₂, 10% Pd-C, MeOH; e. Δ, DMF-EtOH (1:4); f. [(CH₃)₃Si]₂NH(CH₃)₃SiCl; g. BH₃(CH₃)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. There are several non-stereoselective syntheses of monomerine I reported earlier. Lee and Robert have reported a stereospecific total synthesis of (+)-monomerine I (Scheme 19). The key step in the synthesis is the reductive cyclisation of the nitroketone to sodiumcyanoborohydride reduction of the enamine yielded only one isomer viz. monomerine I.

Scheme 19

Reagents: a. Mg,THF; CH₂=CHCHO; b. PCC or MnO₂, CH₂Cl₂; c. Nitropentane, TMG; d.10% PdSO₄, anhydr.Na₂SO₄; e. H₂O⁺; f. pH 3.8-5.4; g. NaBH₃CN, MeOH.

Recently Husson and Royer have synthesised (-)-monomerine by an asymmetric synthesis using a chiral auxiliary (2-cyano-6-oxazolopiperidine) 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 C₂ or C₆ 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).
(-)-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 isolated$^{50}$ in minute quantities from the skin extracts of frogs belonging to Dendrobatid family. They are divided into batrachotoxin, histrionotoxin, 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 pyrrole ring system. 132 was alkylated exclusively at the primary carbon site with 1,4-dibromoheptane affording a 1:1 mixture of 4'-bromo stereoisomers.
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.\(^5\) 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 ethylacetate followed by acetylation gave 136 (61% from 134) which
was converted to 137 and 138 in seven steps. The ratio of diastereomeric alcohols varied according 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, CH₂Cl₂, r.t.; CH₃CH₂CH=PPH₃, THF, 0°C; 5% Rh on alumina, EtOH, 60 psi, H₂, r.t.; Ph₄BuNF, DMF, r.t.). Likewise 137 was converted to 128 in 6 steps (PCC, CH₂Cl₂, r.t.; (CH₂)₃CH=PhP⁺Br⁻, NaOEt, r.t.; pTsOH, acetone, water, 0°C; C₆H₅COCl, Py, CH₂Cl₂, r.t.; LiBH₄, THF, r.t.; KH, THF, r.t.; Dibal, THF-toluene; NaBH₄, DME, r.t.; MeOCH₂P₂EtN, CH₂Cl₂; Ba(OH)₂, H₂O, reflux). 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 (C₁ & C₆ sidechain α in 128) by Daly et al. ⁵⁰ by synthesising 128 from a chiral starting material viz., L-pyroglutamic acid (Scheme 21).

Reagents: a. P₂S₅, Py, 85°C; b. MeOCHBrCOOEt, NaHCO₃, r.t., reflux; c. 0.1N KOH, EtOH, 60°C; d. H₂(1 atm), 5% Pt-C, HClO₄, MeOH, r.t.; e. C₆H₅COCl, Py, CH₂Cl₂, r.t.; f. LiBH₄, THF, r.t.; g. KH, THF, r.t.; h. Dibal, THF-toluene; i. NaBH₄, DME, r.t.; j. MeOCH₂Br, ³Pr₂EtN, CH₂Cl₂, k. Ba(OH)₂, H₂O, reflux.

Geephyrotoxin obtained by synthesis had an [α]₀D₅₀ + 50º (c, 1 EtOH). As the naturally occurring alkaloid was a levorotatory one, the structure of geephyrotoxin was revised as 128 (However, the structure of this alkaloid remains unsettled). ⁵⁰
Lee and Stevens have reported a stereospecific total synthesis of gephyrotoxin-223 (Scheme 22). The sequence of reactions are similar to the one mentioned earlier for monomerine - I. The dienamide approach previously developed was adopted by Overman et al to provide a ready access to the bicyclic intermediates 152 and 157 (Scheme 23 and 24).

Reagents: a. 110°C, Δ; b. Formylmethyltriphenylphosphorane, THF; c. Acetalisation with pyridinium-p-tosylate, MeOH; d. Pd-C, H₂, MeOH, 1 atm; e. 2-methoxy-2-methyl-3-butenal, NaBH₄; f. Δ, benzene, p-TsOH; g. BNBr, CHCl₃ reflux; h. 2% NaOH; i. NaBH₄; j. Orthoester Claisen rearrangement; k. Ethanethiol, BF₃·Et₂O; l. Tosylation; m. LiBu₂Cu, ether, -20°C; n. Chloroformate debenzylation; o. Ozone; p. NaBH₄; q. LiOH; r. NaH; s. CH₂N₂; t. SeO₂; u. Zn, HNO₃, 90°C; v. NaOMe, NaOH reflux; w. LAH.
They have synthesised prehydrogephyrotoxin\textsuperscript{129} and gephyrotoxin\textsuperscript{128} by utilising trans-1,3-butadiene-1-carbamate 148 and trans-2-benzyl-2-butenal 149.

Scheme 22

Reagents: a. CH\textsubscript{2}C\textsubscript{6}H\textsubscript{5}SOPh; b. refluxing, CCl\textsubscript{4}; c. 1-nitropentane, TMG; d. Raney Ni, H\textsubscript{2}; e. H\textsubscript{2}O\textsuperscript{+}; f. KCN; g. PrMgBr, ether

Scheme 24

Reagents: a. CICOOC\textsubscript{2}H\textsubscript{5}CCl\textsubscript{3}, 1,2,2,6,6-pentamethylpiperidine, CCl\textsubscript{4}; b. HClO\textsubscript{4}, THF, formylmethyleneetriphenylphosphorane; c. Pyridinium p-toluene sulphonate, MeOH; d. KOH, MeCHOHMe, H\textsubscript{2}O; e. 1M HCl, THF, NaOMe, NaBH\textsubscript{4}, MeOH; f. TBDPSCI, Et\textsubscript{3}N, pDMAP, CH\textsubscript{2}Cl\textsubscript{2}; g. HBr, DME, SO\textsubscript{2}Cl\textsubscript{2}; h. (COCl)\textsubscript{2}, DMSO; i. \text{t-Pr\textsubscript{3}}SiCH\textsubscript{2}C\equivCSiPr\textsubscript{3}, BuLi, THF, -78\degree C→r.t.; j. n-Bu\textsubscript{4}NF
Likewise a total synthesis of (t)-gephyrotoxin \( \text{128} \) was achieved\(^{56} \) in 6.5\% overall yield from the readily available trans-1,3-butadienecarbamate \( \text{148} \). The key step in the reaction is the reduction of the bicyclic iminium ion \( \text{157} \) from the more hindered \( \alpha \)-face to provide \( \text{158} \) with LAH under controlled temperature. This reaction yielded \( \text{158} \) and its \( \alpha \)-isomer in the ratio of 12:1.

A highly convergent, concise and prochiral route for the chemical synthesis of pumiliotoxin \( 2510^{57,58} \text{127} \) and pumiliotoxin \( A^{58} \text{126} \) was developed by Overman et al. via a stereospecific iminium-vinylsilane cyclisations starting from the chiral synthon viz., L-proline ester \( \text{162} \). The mixture of epoxides \( \text{163a} \) and \( \text{163b} \) (1:2) were obtained in 2 steps from L-proline ester \( \text{162} \) (Scheme 25).

![Scheme 25 diagram]

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

Thus the total synthesis of (t)-pumiliotoxin \( 2510 \) hydrochloride \( \text{127} \) \( \alpha \)\( \text{125 + 280} \) (\( \text{c, 0.62, MeOH} \)) was achieved by a convergent sequence in 9 steps in an overall yield of 6.3\% from 5-1-heptyn-3-ol and 3.6\% from N-benzylloxycarbonyl-L-proline \( \text{162} \).
The side chain 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, \((\alpha)_{D} + 19.3^\circ; c_{1}, 1.00, \text{MeOH}\) 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. Allomuniliotoxin-A, \((276A) 174a\) and \((339B) 174b\) were also synthesised using the chiral synthon L-proline carboxylate 58a.

Reagents: a. Threoselective reduction using LAH; b. \(n\)-Bu₄NF, DMF.

Hart\(^{59}\) and Tsai have synthesised depentenylperhydrogephyrotoxin\(^{59}\), gephyrotoxin-\(223\)AB \(^{131}\) and its isomer\(^{60}\), gephyrotoxin \(128\), dehydrogephyrotoxin \(130\)\(^{61}\) by introducing the asymmetric centre at \(C_{3a}\) through a formic acid induced vinlylogous-N-acyliminium cyclisation of carbinolamides\(^{59,60}\) of the type 175 to 176 (Scheme 27).
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. Bu₂SnH; l. Lawesson reagent; m. Ethyl bromoacetate; n. Et₃N, Ph₃P; o. NaBH₃CN, pH₄, p. LAH; p. TBDPSCI; q. Disiamylborane, H₂O₂; r. Pt on Al₂O₃, EtOAc-hexane; s. n-Bu₄NF, THF; t. (COCl)₂, Me₂SO, Et₃N; u. I-(Trimethylsilyl)-3-t-butylidimethylsilyl-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 129 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 \( \alpha \)-acylimino radical cyclisation (Scheme 29).

**Scheme 29**

Reagents: a. \( \text{NaBH}_4 \); b. \( \text{EtOH}, \text{HCl} \); c. \( \text{PhSH}, \text{TsOH} \); d. \( \text{Bu}_3\text{SnH}, \text{AIBN}, \text{PhH} \).

Ibuka et al. 63 have synthesised \( (\pm) \)-perhydrogephyrotoxin 129 starting from 1,3-bis trimethylsilyloxybuta-1,3-diene 190. An efficient new decarboxylative reduction of \( \gamma \)-carbomoyloxy-\( \alpha,\beta \)-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 116. The critical step of this synthesis was the stereoselective introduction of the butyl chain at C3 of 197 via the intermediate iminium ion. As the synthetic material 131 exhibited the same sign of rotation \( [(\alpha)_0^{20\text{o}},101^\text{o} \text{ c,2,3,n-hexane}] \) 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 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 piperidine 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. (CH₂OH)₂, p-TsOH, C₆H₆; reflux, 10h; c. Dibal, Hexane-Toluene, -73°C; 3h; d. BuLi, THF, HMPT (2:1), -73°C; p-TsCl, -73° → 0°C; e. CuCH₂CN, THF, -73 → -30°C; f. 30% H₂O₂, 25% aq. KOH; r.t., 12h; g. 5% aq. HCl; h. 5% NaOMe, MeOH, 65°C; i. (CH₂SH)₂, BF₃·Et₂O, CHCl₃, r.t.; j. Raney W-2 Ni, EtOH, 70°C; k. k*-xylene, 140°C; l. BrCH₂COCH₂CH₂COOMe, CHCl₃, Ph₃P (CH₂CH₂NMe)₂, 61°C; m. NaBH₃CN, 5% aq. HCl, MeOH; n. NaBH₃CN, 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, H₂O, reflux; CH₂N₂; r. 30% H₂O₂, Py, CH₂Cl₂, 0°C; s. LiBu₂Cu, THF; t. NaOMe, MeOH, reflux; u. Dibal, hexane-toluene, -60 → -30°C.
Reagents: a. LDA, I; b. AgBF₄, THF, Zn(BH₄)₂; c. PrMgBr, ether; d. H₂, Pd-C, MeOH; e. CH₂Cl₂, HCl, KCN; f. n-BuMgBr, ether.

Reagents: a. PCl₅, ether, p-TsCl, Py; b. m-CPBA; c. NaH, benzene, reflux; d. CrO₃, H₂SO₄, acetone; e. Pb(OAc)₂, Cu(OAc)₂, H₂O; Py, N₂; f. H₂, Pd, MeOH; g. NaBH₃CN, pH 3.0, MeOH, 25°C; h. 3-Furyllithium, ether; i. NaBH₃CN, MeOH, pH 3.0.
Ban et al. have used a novel type of reaction which they named as 'Criss-cross Annulation' for the synthesis of 198. Scheme 33 clearly depicts this 'Criss-cross Annulation'.

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

Reagents: a. Acrylonitrile; b. (CH₂OH)₂, CSA; c. Furyllithium, H₂, NH₂OMe; d. LAH, THF, e. (CF₃CO)₂O, Py; f. aq.CF₃COOH; g. LiOH, aq. MeOH, 65°C; h. aq.HCl, MeOH, i. NaBH₃CN, MeOH, pH 3.0; j. LAH, THF.

2.2 Phenanthroindolizidine Alkaloids:

The phenanthroindolizidine alkaloids have been the subject of numerous biological and chemical studies. 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 mentioned summarise the efforts towards the chemical structure, stereochemistry and synthesis upto
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. 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.

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 such as SnCl₄, TiCl₄ in benzene or MgF₂ 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 sequence\textsuperscript{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\textsubscript{3} gave the secophenanthroindolizidine derivative 217 (Scheme 36).

Scheme 36

Reagents: a. Ethanolic alkali; b. LAH, AlCl\textsubscript{3}
Antofine 214 and alkaloid C 215 were synthesised by the oxidation of the secophenanthroindolizidines like 217 with either MnO₂, SiO₂ or CuCl₂, O₂, pyridine.

Using an intramolecular Diels-Alder strategy tylophorine 210 was synthesised 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 rearrangement 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
Reagents: a. Sec-BuLi, TMEDA, ether, THF, -78°C; b. N-Binzylypyrrol-2-carboxaldehyde; c. Silica gel, CHCl₃, Δ; d. Zn-Cu, KOH,Py; e. CH₂₃H₂; f. H₂,Pt,HOAc; g. LAH, THF.

Scheme 39

Reagents: a. Zn, HOAc; b. NaOEt; c. LAH; d. h, D, I₂.
Metallation of phenanthrene carboxamide\textsuperscript{75} followed by reaction with N-benzylpyrrole-2-carboxaldehyde has been applied for the synthesis of phenanthroindolizidines and quinolizidines. The phthalide intermediate \textsuperscript{233} was converted to racemic antofine\textsuperscript{76} (Scheme 38), in 38\% yield.

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

Tylolphorine \textsuperscript{210}, cryptopleurine \textsuperscript{210b}, septicine \textsuperscript{216} and julandine \textsuperscript{217} were synthesised by this method\textsuperscript{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\textsuperscript{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\textsuperscript{78b}.

iii) Anodic oxidation: This electrochemical method yielded the clean desired phenanthrene derivative\textsuperscript{79}.

iv) Phenolic oxidative coupling: The oxidising agents used are thallium III trifluoroacetate\textsuperscript{70,71} and VOF\textsubscript{3} in trifluoroacetic acid\textsuperscript{80,69,81}.

Finally chirally specific syntheses of \(S(+)-\text{tylophorine} \textsuperscript{210}\) and cryptopleurine \textsuperscript{210b} were achieved\textsuperscript{81} by choosing \(\alpha\)-amino acid such as the diisopropyl ester of \(L(+)-\text{glutamic acid}\) as a chiral educt. Reductive amination of the phenanthrene aldehyde \textsuperscript{241} with the amine ester \textsuperscript{242} followed by cyclisation gave \textsuperscript{243}, which on hydrolysis followed by Friedel-Crafts acylation gave \textsuperscript{244} in nearly quantitative yield. This on catalytic hydrogenation followed by deoxygenation and LAH reduction gave \(S(+)-\text{tylophorine}, (\alpha )_D\text{+12.0}^\circ, \text{mp} 282-284^\circ C\). This is in discrepancy with the absolute configuration assigned to natural tylophorine on the basis of ozonolysis experiments\textsuperscript{82} and further work is in progress to settle the issue.
The recently reported\(^3\) 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.\(^4\) The acid 248 was converted to the acid chloride and then condensed with 4-aminobutyraldehyde diethylacetal to 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 Et\(_3\)N in CH\(_2\)Cl\(_2\) to yield 251 (68%). Conversion of 250 to tylophorine is given in Scheme 42.
Reagents: a. (COC)₂; b. NH₂(CH₂)₃CH(OEt)₂, NaHCO₃; c. HOAc, H₂O; d. Ph₃=P=COOEt; e. TBSOTf, Et₃N, r.t.; f. TFA, BF₃·Et₂O, TFA; g. KOH, MeOH; h. HMPA, 230°C; i. NaAl(OCH₂CH₂OMe)₂, H₂

Abbreviations used in the review:

AIBN azobisisobutyronitrile
Bn benzyl
BnBr benzyl bromide
Bz benzoyl
mCPBA m-chloroperbenzoic acid
CSA camphorsulphonic acid
pDMAP p-dimethylaminopyridine
DME dimethoxyethane
HMPA hexamethylyphosphoramide
PCC pyridinium chlorochromate
PpTSONa pyridinium-p-toluenesulphonate
TBSOTf tributylsilyl trifluoromethane sulphonate
TBOMS tert-butyldimethylsilyl
TBDPS tert-butyldiphenylsilyl
TMEDA tetramethylethylenediamine
REFERENCES


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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.
75. V. Snieckus, Heterocycles, 1980, 14, 1649.
b. C. K. Bradsher and H. Berger, J. Am. Chem. Soc., 1958, 80, 930,

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