Indolizidine and quinolizidine alkaloids

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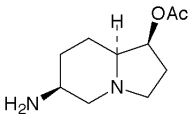
1 General reviews

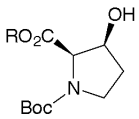
A review on quinolizidine alkaloids spanning the decade 1986–1996 has been published in a recent supplementary volume in the *Rodd's Chemistry of Carbon Compounds* series.[1] The review focuses on new quinolizidine alkaloids from terrestrial and marine plants and animals, as well as on the many syntheses published during the period under consideration. A recent book that deals with the biochemistry, ecology and medicinal applications of alkaloids includes relevant material in useful surveys of the alkaloids obtained from arthropods, vertebrates and marine animals,[2] and on the enzymology of alkaloid biosynthesis.[3] A short review on alkaloid chemosystematics contains some information on the distribution of quinolizidine alkaloids in higher plants.[4]

2 Slaframine

The previously communicated synthesis of (−)-slaframine **1** from the protected (2*R*,3*S*)-3-hydroxyproline esters **2** by Knight and Sibley,[5] outlined in an earlier review in this series,[6a] has now been published with full experimental details.[7]



1 (−)-Slaframine

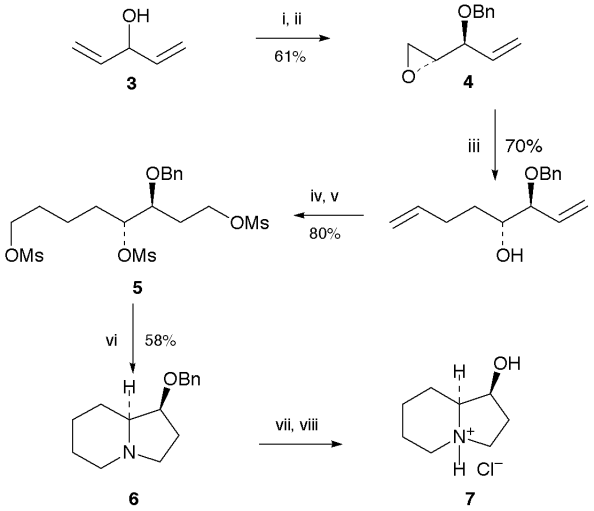


2 R = Me, Et

3 Hydroxylated indolizidine alkaloids

3.1 1-Hydroxyindolizidine and 1,2-dihydroxyindolizidines

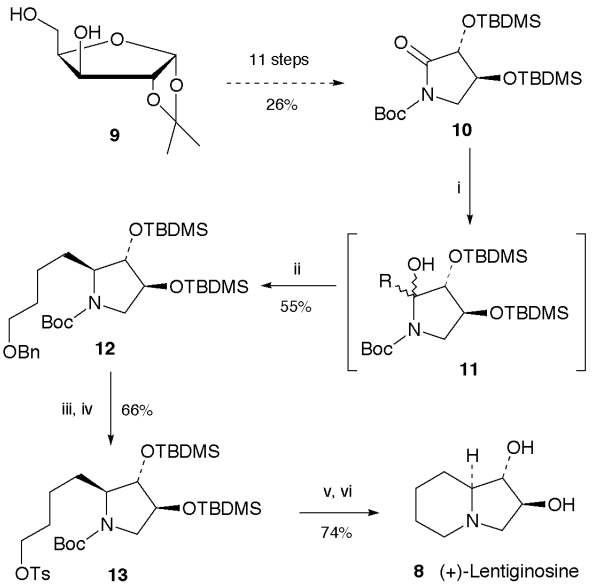
A new route to (1*S*,8a*S*)-1-hydroxyindolizidine, thought to be an intermediate in the biosynthesis of slaframine, used Sharpless asymmetric epoxidation of penta-1,4-dien-3-ol **3** with (+)-diisopropyl tartrate to introduce the required stereogenic centres at an early stage of the synthesis (Scheme 1).[8]



Scheme 1 *Reagents:* i, L-(+)-DIPT, Bu^{t}OOH, Ti(OPr^i)$_4$, 4 Å molecular sieves, CH_2Cl_2, −20 °C; ii, BnBr, NaH, Bu_4NI, THF, −20 °C; iii, $H_2C{=}CHCH_2MgCl$, CuI (10%), THF, −78 °C; iv, dicyclohexylborane (3 equiv.), THF, then 3 M NaOH, H_2O_2 (30% aq.); v, MsCl, py, CH_2Cl_2, rt; vi, aq. NH_3, K_2CO_3, MeOH, rt, 2 d; vii, H_2, $PdCl_2$, MeOH, rt; viii, HCl (g).

Conventional transformations of epoxide **4** led to the acyclic tris(mesylate) **5**, treatment of which with aqueous ammonia effected a very simple double ring closure to give the indolizidine **6** in 58% yield. After hydrogenolysis of the benzyl protecting group, the target compound was isolated as the hydrochloride salt **7**.

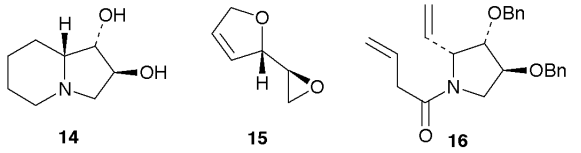
A synthesis of (+)-lentiginosine **8** by Yoda and co-workers, the second from this group, commenced by converting the commercially available 1,2-*O*-isopropylidene-D-xylofuranose **9** into the protected pyrrolidin-2-one **10** in eleven steps and 26% yield (Scheme 2).[9] Addition of 4-benzyloxybutylmagnesium bromide was followed by highly stereoselective (98:2) reductive deoxygenation of adduct **11** with triethylsilane in the presence of boron trifluoride–diethyl ether to yield the pyrrolidine **12**. The indolizidine nucleus was formed by ring closure of tosylate **13**, after which removal of the protecting groups completed the synthesis of the desired alkaloid **8**. The low optical rotation found for the product ($[\alpha]_D^{27}$ +3.20, *c* 0.27, MeOH) is in agreement with recently reported values, and adds



Scheme 2 *Reagents:* i, $BnO(CH_2)_4MgBr$, THF, −78 °C; ii, Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C; iii, Pd black, HCO_2H (4.4%) in MeOH, 40 °C; iv, *p*-TsCl, py; v, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −20 °C to 0 °C; vi, KOH, MeOH.

further weight to the body of evidence that has recently emerged for the absolute configuration of the natural product.

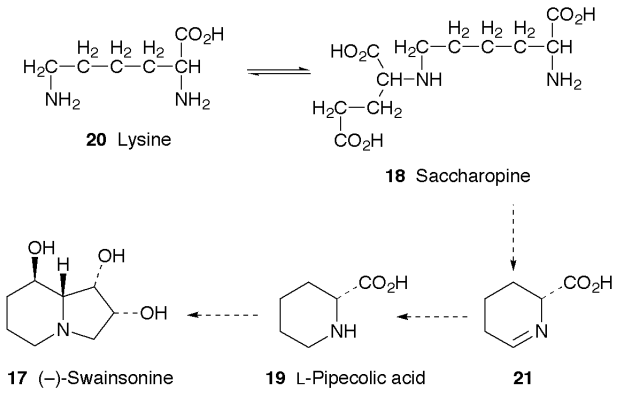
The unnatural lentiginosine epimer (−)-(1*S*,2*S*,8a*R*)-indolizine-1,2-diol **14** has been prepared from the homochiral epoxide **15** by a route involving ring-closing metathesis of diene intermediate **16**.[10]



3.2 Swainsonine and related compounds

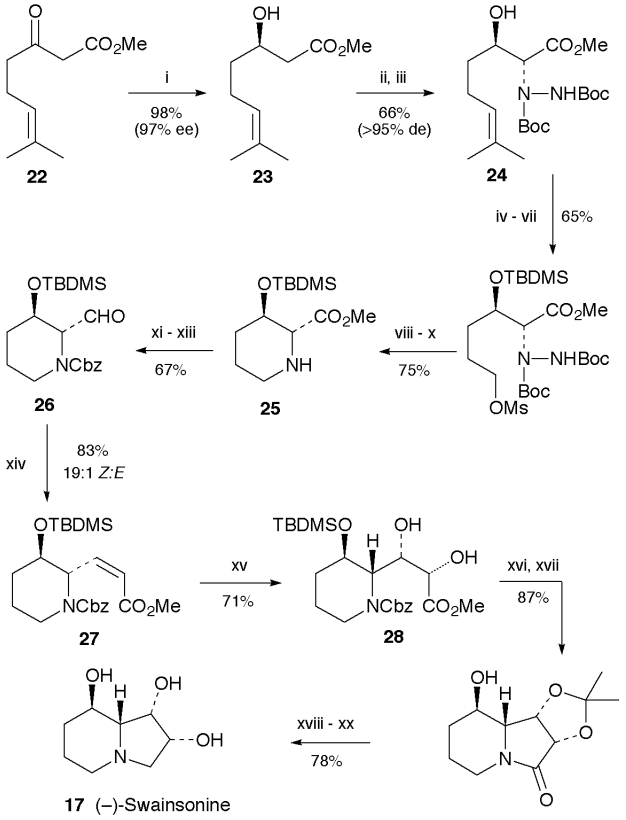
The outbreak in Mozambique of a lysosomal storage disease in goats feeding on *Ipomoea carnea* (family Convolvulaceae) has led to the isolation and identification of swainsonine **17** and two calystegines (polyhydroxylated tropanes) as the causative agents.[11] This is only the second time that swainsonine has been isolated from a higher plant belonging to a family other than the Leguminosae; the previous case involved Australian members of the genus *Ipomoea*.[12]

α-Aminoadipic acid, saccharopine **18** and L-pipecolic acid **19**, early metabolic precursors in the biosynthesis of (−)-swainsonine **17** by cultures of the filamentous fungus *Metarhizium anisopliae*, have been quantified by reversed-phase HPLC



analysis of mycelial extracts derivatised with 9-fluorenylmethyl chloroformate (FMOC).[13] Since the biosynthetic pathways leading to L-lysine **20** and (−)-swainsonine are thought to diverge after the formation of saccharopine, L-lysine was also assayed by the new technique. Previous studies have shown that culturing the fungus in a lysine-rich medium boosts production of swainsonine,[14] no doubt because catabolism of L-lysine also proceeds *via* saccharopine. The present study revealed an increase in intracellular levels of pipecolic acid **18** when the mycelium was grown in the presence of lysine, thereby adding support to an earlier hypothesis[15] that intermediates **18**, **19** and **21** are implicated in the biosynthesis of the alkaloid. However, swainsonine production was inhibited at pH 9 despite an increase in pipecolic acid levels; and attempts to generate mutant strains of the fungus capable of over-producing lysine, and hence swainsonine, failed even though saccharopine levels increased. In the meantime, other workers have improved fermentation conditions for *M. anisopliae* such that yields of swainsonine as high as 61 mg dm^{-3} have been obtained when using a modified starch–casein medium supplemented by DL-lysine.[16]

Enantioselective hydrogenation of keto-ester **22** over $RuBr_2$[(*R*)-BINAP] catalyst provided the asymmetric *entrée* into a new synthesis of (−)-swainsonine **17** (Scheme 3).[17] The

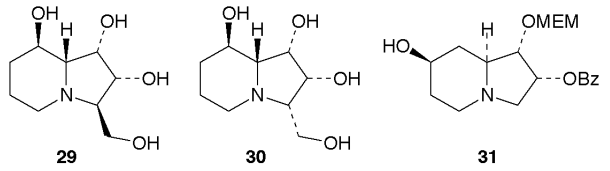


Scheme 3 *Reagents:* i, $RuBr_2$[(*R*)-BINAP], H_2 (1 atm), MeOH, 50 °C; ii, MeZnBr, THF, 0 °C; iii, LDA, THF, −78 °C, then $Bu^tO_2CN{=}NCO_2Bu^t$, THF, −78 °C; iv, 2,6-lutidine, TBDMS-OTf, CH_2Cl_2, −78 °C; v, O_3, CH_2Cl_2, −78 °C; vi, $BH_3{\cdot}SMe_2$, CH_2Cl_2, −78 °C to rt; vii, MsCl, py, 0 °C; viii, TFA, CH_2Cl_2, 0 °C to rt; ix, Raney Ni, H_2 (1 atm), MeOH, ultrasound, rt; x, Et_3N, CH_2Cl_2, rt; xi, BnO_2CCl, DMAP, MeCN, 0 °C to rt; xii, $Ca(BH_4)_2$ (6 equiv.), THF–EtOH (2:3), −20 °C to rt; xiii, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C; xiv, 18-crown-6, $(CF_3CH_2O)_2POCHCO_2Me^-\ K^+$, THF, −78 °C; xv, OsO_4 (0.2 equiv.), Me_3NO, Me_2CO–H_2O (19:1), ultrasound, rt; xvi, Pd/C, H_2 (1 atm), NaOAc, MeOH, rt to 35 °C; xvii, $(MeO)_2CMe_2$, Dowex 50W-400 (H^+), rt; xviii, $BH_3{\cdot}SMe_2$, THF, rt; xix, EtOH, reflux; xx, HCl (1 M), reflux, then Dowex 1X8-200 (OH^-).

enolate of the resulting alcohol **23** was diastereoselectively aminated with di-*tert*-butyl azodicarboxylate to give the *anti* hydrazine **24**. A further seven steps completed the synthesis of

the protected (2*R*,3*R*)-pipecolic ester **25**. Subsequent Horner–Wittig homologation of the aldehyde derivative **26** with the potassium salt of Still's methyl bis(trifluoroethyl)phosphonoacetate reagent yielded predominantly (19:1) the *Z*-alkenoate **27**, dihydroxylation of which then afforded diol **28**. At this point all the stereogenic centres of the target alkaloid had been introduced, and simple functional group transformations completed the synthesis of (−)-swainsonine **17**.

New synthetic analogues of swainsonine reported during the period under review include the two (−)-3-hydroxymethylswainsoninines **29** and **30**, both of which proved effective as



inhibitors of jack bean α-mannosidase (IC_{50} 1.2 and 45 μM respectively; *cf.* 0.1 μM for swainsonine itself).[18] As part of a study on the synthesis of enantiomerically pure *cis*-3,4-dihydroxypyrroline *N*-oxides by desymmetrising C_2-symmetric diols, the energetic research group of Goti, Brandi and coworkers has prepared the differentially protected indolizidine-1,2,7-triol **31** and its enantiomer *ent*-**31**.[19] Growing interest in the potential of swainsonine and its derivatives to function as antitumour agents has resulted in several patents describing the synthesis and activity of substituted swainsonines,[20,21] imino sugars related to the alkaloid,[22] and the easily formulated stable hydrohalide salts of swainsonine.[23]

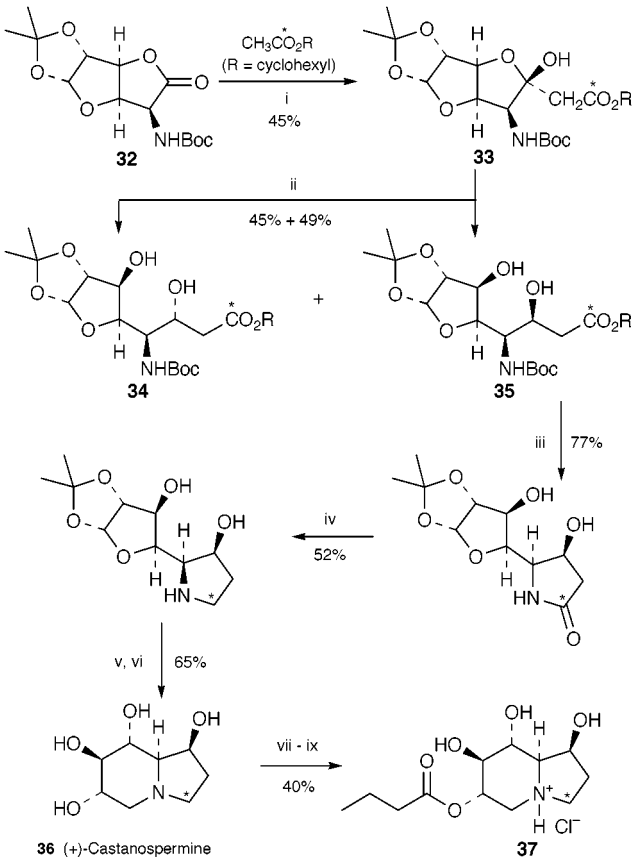
Swainsonine appears to be coming into its own as an antitumour agent, if the rapidly increasing number of publications on the topic is anything to go by. A review on the role of protein glycosylation inhibitors in cancer chemotherapy and the prevention of metastasis describes the alkaloid's most notable effects: blocking of pulmonary colonisation by tumour cells, stimulation of components of the immune system and of the growth of bone marrow cells, and amelioration of the toxicity of other chemotherapeutic agents.[24] A short review on similar themes has also appeared in Chinese.[25] The ability of swainsonine to maintain antimetastatic activity for several days after administration has been correlated with its retention in lymphoid tissue, especially the spleen.[26] Research from China has shown that administration of swainsonine increased splenocyte levels, decreased tumour volume and inhibited metastasis to the liver and peritoneum in nude mice orthotopically implanted with gastric carcinoma in the gastric wall,[27,28] while Korean workers have shown that swainsonine lowers the liposaccharide-induced humoral immune responses in mice.[29]

One of the most important papers published in the period under review describes phase IB clinical trials in terminally ill patients with advanced malignancies of various kinds.[30] The pharmacokinetics, toxicities and biochemical effects of orally administered swainsonine at increasing dose levels between 50–600 μg kg^{-1} were examined in sixteen cancer patients and two HIV-positive patients. The maximum tolerated dose was found to be about 300 μg kg^{-1} day^{-1}, after which abnormal serum aspartate transferase levels and breathing difficulties were observed in all patients. Other adverse effects included fatigue, anorexia and abdominal pain. The expected inhibition of lysosomal and Golgi mannosidases was evaluated by monitoring oligosaccharide markers, while changes in lymphocyte populations cast some light on the alkaloid's ability to increase natural killer cell activity. Although malignancies were too advanced for objective responses of the diseases to the drug regime to be evaluated, the study suggested the kinds of dosing schedules that should be followed in future investigations.

More conventional applications of swainsonine relate to its use in characterising the murine lysosomal α-mannosidase[31] and α-mannosidases I and II from *Vigna umbellata* (rice beans).[32] Studies on the reversal of *Oxytropis sericea* locoweed poisoning (swainsonine intoxication) in sheep have shown that the half-life of the alkaloid is less than 20 hours in skeletal muscle, heart, brain and serum, but about 60 hours in liver, kidney and pancreas; animals destined for slaughter thus need to be kept for at least 25 days (10 $T_{1/2}$) to ensure that the toxin has been cleared from animal tissue.[33]

3.3 Castanospermine and related compounds

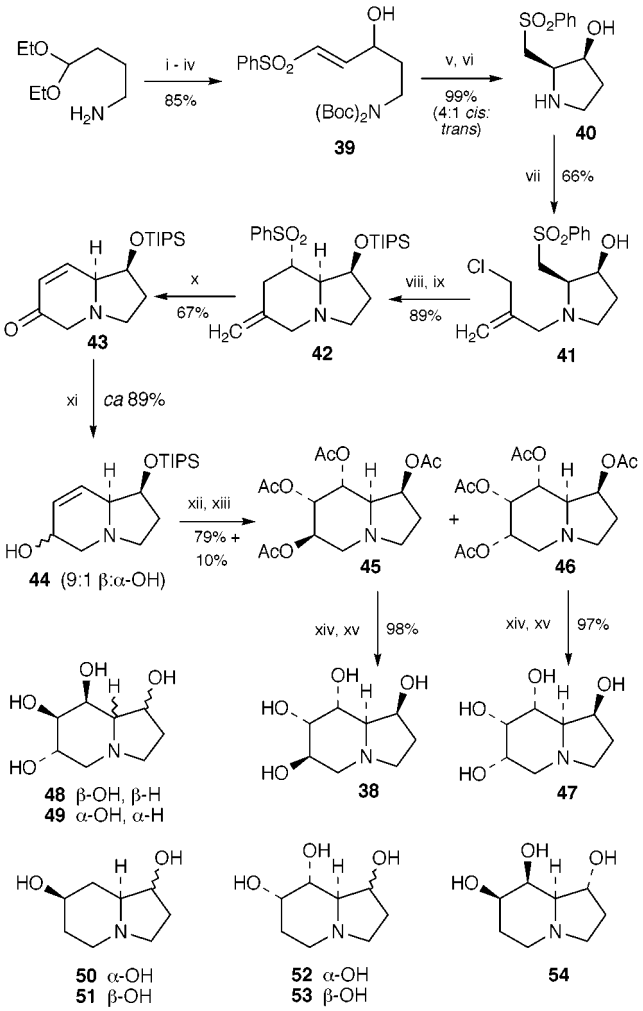
When a sample of ^{14}C-labelled 6-*O*-butyrylcastanospermine, a promising anti-HIV agent, was needed for pharmacokinetic studies, the synthetic route chosen commenced with a Claisen condensation between cyclohexyl [1-^{14}C]acetate and the bicyclic lactone **32**, which is derived from glucose (Scheme 4; the labelled site is indicated throughout by an asterisk).[34] This proved to be an inefficient reaction, but the labelled ester could be recovered and recycled several times to give hemiketal **33** in an overall yield of 45%. Subsequent reduction of the hemiketal showed no stereoselectivity, and flash chromatography was needed to separate the diastereoisomeric diols **34** and **35**. The ensuing reactions, however, were straightforward, and culminated in what is essentially a new synthesis of (+)-castanospermine **36**, albeit labelled with ^{14}C at C-3. The overall yield of this seven-step sequence was 5%, and the radiochemical purity of the labelled alkaloid was 100%. The hydrochloride salt of the target ester **37** itself was prepared by regiospecific esterification of [3-^{14}C]castanospermine at the C-6 hydroxy group according to the recently reported procedure of Furneaux *et al.*,[35] which



Scheme 4 *Reagents:* i, cyclohexyl [1-^{14}C]acetate, LDA, THF, −78 °C to −16 °C, then flash chromatography and recycling of labelled ester; ii, H_2 (1 atm), PtO_2, EtOAc; iii, HCO_2H, CH_2Cl_2, 0 °C to rt, then Dowex 1X2-100 (OH^-); iv, $LiAlH_4$, THF, 0 °C to reflux; v, TFA–H_2O (9:1), 0 °C to rt, then NaOH (1 M) to pH 9.75; vi, H_2 (1 atm), 5% Pt/C, then Dowex 50WX2-200 (H^+); vii, $(Bu_3Sn)_2O$, toluene, reflux, Dean–Stark apparatus; viii, $CH_3(CH_2)_2COCl$, toluene, −15 °C to 10 °C; ix, HCl in Et_2O (1 M).

involves selective derivatisation with bis(tributyltin) oxide followed by acylation with butyryl chloride at −15 °C.

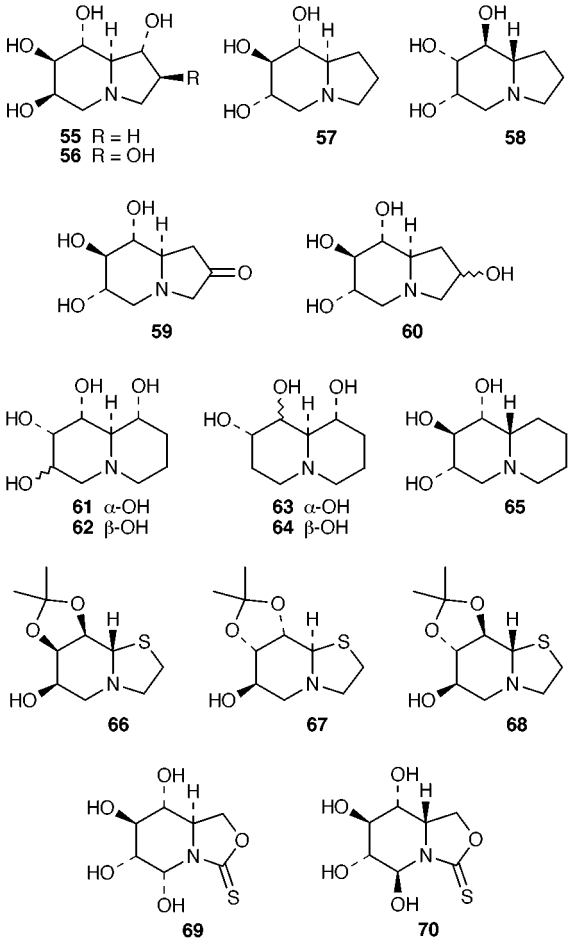
An early key transformation in the synthesis of the minor alkaloid 6,7-di-*epi*-castanospermine **38** by Carretero and co-workers[36] involved acid induced cyclisation of the unsaturated sulfone **39** to give a 4:1 mixture of the racemic 2,3-*cis*-disubstituted pyrrolidine **40** and its *trans* isomer (Scheme 5).



Scheme 5 *Reagents:* i, $(Boc)_2O$, CH_2Cl_2, 0 °C to rt; ii, BuLi, $(Boc)_2O$, THF, 0 °C; iii, AcOH–H_2O (2:1), rt; iv, $PhSO_2CH_2SO$-*p*-Tol, piperidine, CH_2Cl_2, 0 °C; v, TFA, CH_2Cl_2, rt; vi, Et_3N, THF, −78 °C; vii, $(ClCH_2)_2C{=}CH_2$, LiI, K_2CO_3, MeCN, 70 °C; viii, 2,6-lutidine, Pr^i_3Si-OTf, CH_2Cl_2, −78 °C to rt; ix, LHDMS, THF 0 °C; x, O_3, TFA, CH_2Cl_2, −20 °C, then Ph_3P, rt, then Et_3N, CH_2Cl_2, 0 °C to rt; xi, L-Selectride, THF, –78 °C; xii, OsO_4, TMEDA, CH_2Cl_2, −78 °C, then Na_2SO_3, THF, reflux; xiii, Ac_2O, py, DMAP, rt, then chromatography; xiv, aq. NaOH (10%), MeOH, rt; xv, Dowex 1X8-200 (OH^-).

The isomers were separated after *N*-alkylation with 3-chloro-2-chloromethylprop-1-ene. Silylation and base-initiated cyclisation of the major product **41** served to construct the indolizidine skeleton of **42**, following which ozonolysis and elimination of the sulfone group yielded another pivotal intermediate, the bicyclic enone **43**. Reduction of the carbonyl group with L-Selectride afforded an inseparable mixture of the two diastereoisomeric alcohols **44** (9:1), which were separated only after dihydroxylation with osmium tetroxide and peracetylation of the resulting tetrols. The synthesis of (±)-6,7-di-*epi*-castanospermine **38** was completed by hydrolysis of the tetraacetate **45**, while hydrolysis of the minor isomer **46** yielded the unnatural compound (±)-7-*epi*-castanospermine **47**, the (1*S*,6*S*,7*S*,8*R*,8a*R*) enantiomer of which was recently reported.[37] Manipulations of other intermediates prepared during this research resulted in the first reported syntheses of (±)-8,8a-di-*epi*-castanospermine **48** and (±)-1,8-di-*epi*-castanospermine **49**, as well as the 1,7-indolizidine-1,7-diols **50** and **51**, and the three indolizidine-1,7,8-triols **52**–**54**. Some related results were communicated in a published conference paper.[38]

Unnatural analogues of castanospermine remain popular as synthetic targets because of their potential to act as competitive inhibitors of glycosidases and glycoprotein processing. The period under consideration has seen syntheses of (−)-1,6-di-*epi*-castanospermine **55** and the pentahydroxy analogue **56**;[39] an



enantioselective synthesis of 1-deoxycastanospermine **57**[40] and two different approaches to (+)-1-deoxy-6-*epi*-castanospermine **58**;[41,42] and the preparation of (+)-2-oxo and 2-hydroxy variants **59** and **60**.[43] Carretero's approach to racemic polyhydroxylated indolizidines (Scheme 5) has been extended to include four quinolizidine analogues of castanospermine, **61**–**64**,[44] while the quinolizidine analogue of 1-deoxycastanospermine, **65**, has been prepared from an arabinofuranose derivative.[45] Amongst the large number of more exotic castanospermine lookalikes are several optically active 1-thiaindolizidinetriols, isolated as the ketals **66**–**68**;[46] and the bicyclic thiocarbamates **69** and **70**, which formally belong to the D-*gluco* and L-*ido* series respectively.[47] Only in the last case was any biological activity reported: **69** was a moderately good inhibitor of yeast α-glucosidase but not of almond β-glucosidase, thus showing a reversed linkage specificity compared with castanospermine itself. An application for a patent on the regioselective preparation of 6-*O*-monoesters of castanospermine has been filed.[48]

The diverse biological effects of castanospermine once again feature prominently in the recent literature. A review on plant-derived lead compounds for anti-HIV chemotherapy included the alkaloid and related indolizidines in the extensive line-up of novel drug candidates.[49] Another review dealing with the development of antiinflammatory drugs for the treatment of multiple sclerosis and related diseases of the central nervous

system described the antiinflammatory potential of castanospermine, which prevents the accumulation of leukocytes at inflammatory sites by inhibiting their passage through the subendothelial basement membrane.[50] Results on this theme have also been patented.[51] Despite reports that the alkaloid can inhibit the growth and metastasis of prostate cancer in mouse and rat models, recent *in vivo* studies failed to reveal cytotoxicity towards two rat prostate adenocarcinoma cell lines or effects on cell characteristics related to metastatic potential.[52] Intraperitoneal injection of castanospermine into streptozotocin-diabetic mice (150 μmol kg^{-1}) demonstrated the alkaloid's significant antihyperglycemic effects by reducing blood glucose levels by almost 50% after four hours.[53] Also of interest in this regard is the finding that castanospermine inhibited islet lysosomal acid glucan-1,4-α-glucosidase activity (EC_{50} 10^{-7} M) *in vitro* and, in parallel, functioned as a slow-acting inhibitor of glucose-induced insulin release.[54,55] The alkaloid has been used more conventionally as a glucosidase inhibiting tool for characterising the glucosidase I from mung bean seedlings,[56] in investigating oligosaccharide trimming in the assembly of nicotinic acetylcholine receptors,[57] and in exploring the endo-mannosidase pathway for the processing of viral envelope glycoprotein.[58]

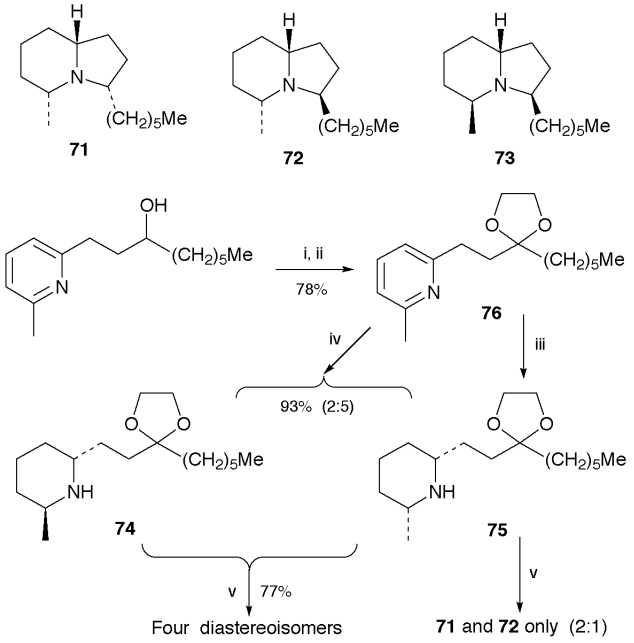
4 Alkaloids from ants

4.1 Occurrence

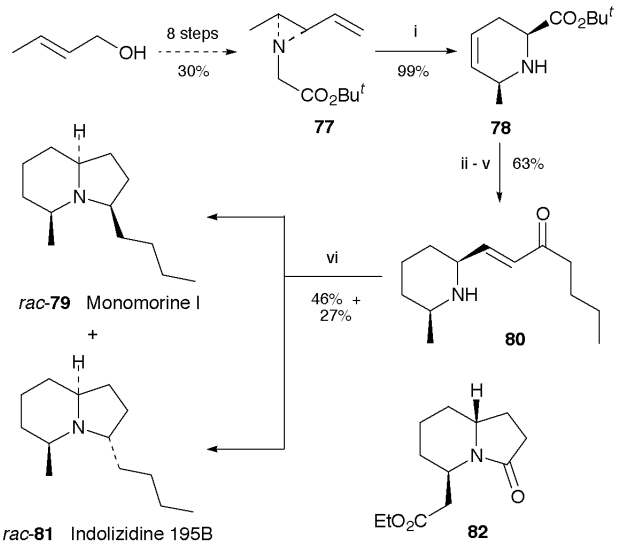
(5*Z*,9*Z*)-3-Hexyl-5-methylindolizidine **71**, a known constituent of the venom of thief ants of the genus *Solenopsis* (*Diplorhoptrum*), was reported as recently as 1996 as a caste-specific metabolite in queens of a species found in Puerto Rico.[59] Venom collected from worker ants of several populations of a taxonomically uncertain species (*S. molesta validiuscula*?) from California has now been shown to contain two of the remaining three diastereoisomers of **71**, *viz.*, the (5*E*,9*E*)- and (5*Z*,9*E*)-isomers **72** and **73**.[60] Fascinatingly, different populations contained either one or the other of the new alkaloids, plus in some cases a trace of the (5*Z*,9*Z*) isomer; the population-specific distribution may well have significance in resolving taxonomic ambiguities. The structures of the new compounds were ascertained in part from their mass spectra and GC-FTIR studies, the characteristic range of Bohlmann bands in the latter providing evidence for the stereochemical assignments. More importantly, direct comparison of the new alkaloids with all four diastereoisomers of 3-hexyl-5-methylindolizidine, synthesised by the unselective route shown in Scheme 6, provided incontrovertible evidence for the proposed structures. An important aspect of the chemical correlation was the unambiguous assignment of stereochemistry in the piperidine intermediates **74** and **75**; only the *cis* isomer **75** (the exclusive product of hydrogenation of the pyridine **76** over a rhodium catalyst) has Bohlmann bands in its IR spectrum. Reductive cyclisation of **75** in turn gave only **71** and **72**, while reductive cyclisation of a 2:5 mixture of piperidines **74** and **75** (produced by reducing pyridine **76** with sodium in ethanol) yielded all four of the indolizidine diastereoisomers.

4.2 Synthesis

Base-induced aza-[2,3]-Wittig rearrangement of (±)-aziridine **77**, prepared in eight steps from crotyl alcohol, was extremely efficient, giving the 2,6-*cis*-disubstituted unsaturated piperidine **78** in 99% yield. This intermediate was used by Somfai and co-workers[61] in a short synthesis of the Pharaoh ant trail pheromone monomorine I **79** (Scheme 7). The indolizidine nucleus was formed by reductive cyclisation of enone **80**. This reaction yielded a separable mixture of the racemic target alkaloid (±)-**79** (46%) and its diastereoisomer (±)-**81** (27%), which is the frequently synthesised amphibian skin alkaloid



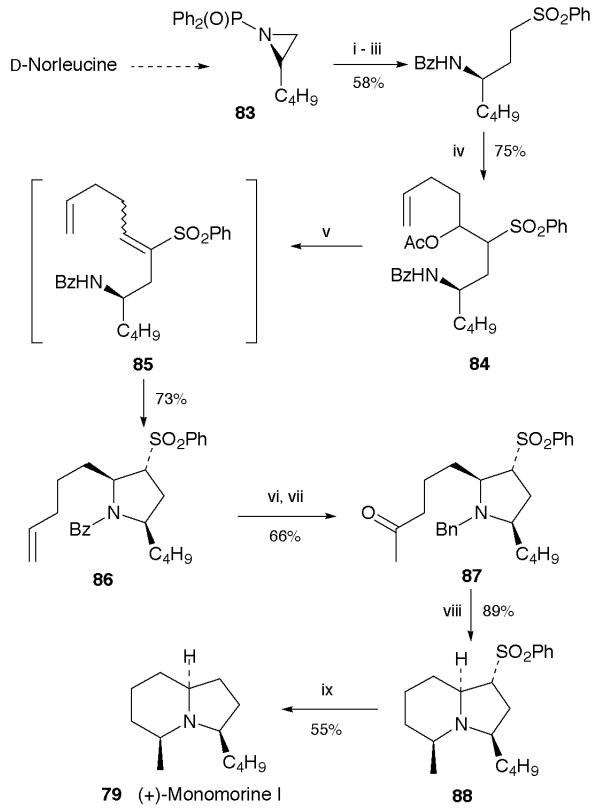
Scheme 6 *Reagents:* i, PDC, py, CH_2Cl_2, TFA, rt; ii, $(CH_2OH)_2$, *p*-TsOH, HCl, C_6H_6, reflux; iii, H_2 (3 atm), 5% Rh/Al_2O_3, EtOAc, rt; iv, Na, EtOH, reflux; v, HCl, THF–H_2O, rt, then $NaBH_3CN$.



Scheme 7 *Reagents:* i, LDA, THF, −78 °C; ii, H_2 (50 psi), 5% Rh/C, MeOH; iii, $LiAlH_4$, THF, 0 °C to rt; iv, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt; v, $(MeO)_2POCH_2COBu$, LiCl, Pr^i_2NEt, MeCN, rt; vi, H_2 (1 atm), 5% Pd/C, MeOH.

indolizidine 195B. A new route to indolizidinone **82**[62] also has implications for the synthesis of 3,5-disubstituted indolizidines such as those shown in Scheme 7.

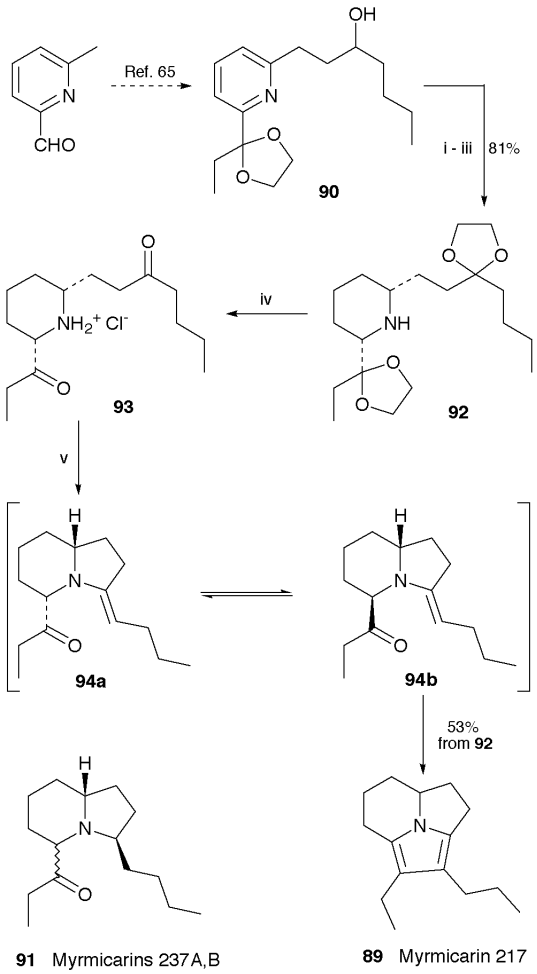
Another aziridine, the enantiopure compound **83** (made in two steps from commercially available D-norleucine), was used by Craig and co-workers in the synthesis of (+)-monomorine I **79** shown in Scheme 8.[63] In a pivotal step, base-induced elimination of acetic acid from sulfone **84** afforded the unsaturated intermediate **85**. Although isolable, **85** normally underwent an immediate 5-*endo-trig* cyclisation to give 2,5-*cis*-disubstituted pyrrolidine **86** as a single isomer (73% from **84**). The stereochemistry of **86** was confirmed by X-ray crystallography. Deoxygenation of the benzoyl protecting group followed by modified Wacker oxidation yielded ketone **87**, reductive cyclisation of which was accomplished by transfer hydrogenation over palladium on charcoal to give a single indolizidine isomer **88**. An alternative route involving deprotection of **86** followed by intramolecular aminomercuration was less stereoselective, and gave a mixture of C-5 epimers of **88**.



Scheme 8 *Reagents:* i, $PhSO_2Me$, BuLi, TMEDA, THF, −78 °C to rt; ii, $BF_3{\cdot}Et_2O$, CH_2Cl_2–MeOH (1:1), rt; iii, PhCOCl, py, CH_2Cl_2, rt, workup with $Me_2N(CH_2)_3NH_2$; iv, BuLi, TMEDA, THF, then hex-5-enal, −78 °C, then Ac_2O, −78 °C to rt; v, Bu^tOK (2.1 equiv.), Bu^tOH (10 equiv.), THF (0.033 M), rt; vi, DIBAL-H, CH_2Cl_2, −78 °C to rt; vii, $Hg(OAc)_2$, THF–H_2O (3:1), rt, then $PdCl_2$, $CuCl_2$, THF, rt; viii, cyclohexa-1,4-diene, 10% Pd/C, MeOH, reflux; ix, $NaC_{10}H_8$ (3.5 equiv.), THF, rt, 5 min.

The synthesis of (+)-monomorine **79** was completed by brief exposure of **88** to sodium naphthalenide, which effected desulfonylation in 55% yield.

The novel pyrrolo[2,1,5-*cd*]indolizine group of alkaloids isolated from the poison gland secretions of myrmecine ants was described in the previous review in this series (*cf.* ref. 6*b*). The first synthesis of one of these alkaloids, myrmicarin 217, **89**, has now been disclosed (Scheme 9).[64] Exhaustive hydrogenation of the pyridine **90** (previously prepared by the same research group during the synthesis of the simpler myrmecine alkaloids 237A and B, **91**[65]) followed by functional group manipulations afforded the 2,6-*cis*-disubstituted piperidine **92** in 81% overall yield. Deprotection with hydrochloric acid yielded the salt **93**, which was converted directly into the target alkaloid **89** on exposure to dilute aqueous sodium bicarbonate solution. The progress of this remarkably easy reaction was monitored by ^1H NMR spectroscopy, which showed that fast cyclisation to the 5,8a-*cis*-indolizidine **94a** was followed by rapidly-established equilibration with the C-5 epimer **94b**. The intramolecular condensation of isomers **94** leading to myrmicarin 217 was a much slower process. Interestingly, traces of compounds showing identical MS and GC properties to those of the isomers **94** could be detected in the defensive secretions of *Myrmicaria striata* and *M. opaciventris*, which are the sources of the new pyrrolo[2,1,5-*cd*]indolizine alkaloids (*cf.* ref. 6*b*).

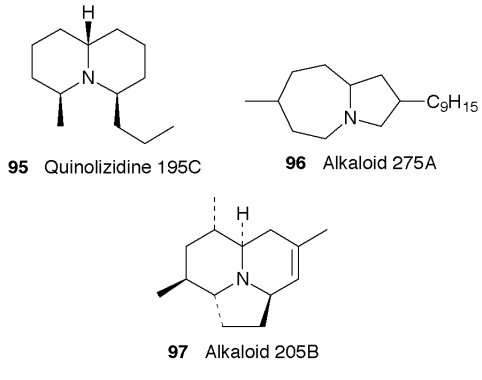


Scheme 9 *Reagents:* i, PDC, 4 Å molecular sieves, CH_2Cl_2, 20 °C; ii, $(CH_2OH)_2$, *p*-TsOH, toluene, reflux; iii, H_2 (25 atm), 10% Pd/C, EtOH, rt; iv, HCl (1 M), 70 °C; v, aq. $NaHCO_3$, Et_2O, 20 °C, then C_6H_6, 40 °C.

5 Alkaloids from amphibians

5.1 Occurrence

A short review by Daly, the doyen of investigators in the field of amphibian skin alkaloids, presents a personal account of thirty years of research in this area.[66] The article includes a brief history of some important discoveries in the field, as well as many seminal references to the literature. The coverage is essentially by structural class. An important point (also, significantly, highlighted in the title of the article) is that the compounds isolated from amphibian skins are actually *arthropod* alkaloids; it has become increasingly apparent that most of the metabolites are not biosynthesised by the amphibians, but are sequestered from dietary sources. This review includes some unpublished results on previously unidentified or incorrectly identified alkaloids. One can look forward in the forthcoming literature to the identification of a new class of quinolizidines as represented by quinolizidine 195C **95**, the correction of the structure of alkaloid 275A from a 4-methyl-6-nonynylquinolizidine to an unprecedented 4-methyl-9-nonynyl-1-azabicyclo[5.3.0]decane **96**, and the disclosure of a unique cyclic ether of the pumiliotoxin class, alkaloid 341A. The stereochemistry of tricyclic alkaloid 205B has also been revised slightly as shown in **97**.

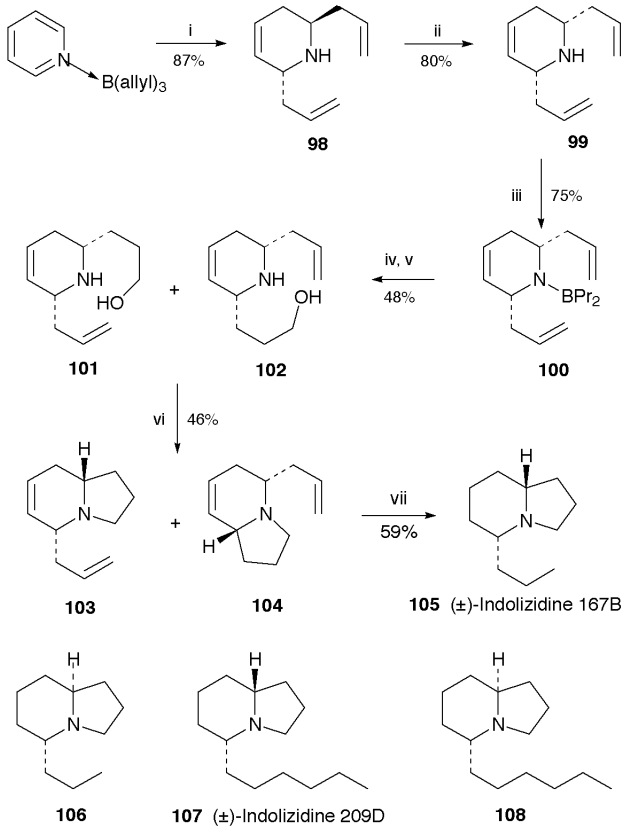


Daly has also written a short overview of the main classes of amphibian alkaloids for the semicentennial volume of the distinguished Academic Press series *The Alkaloids*.[67] This review, too, stresses the probable dietary origins of alkaloids akin to those found in arthropods, and highlights those classes for which unknown biological sources provide a challenge for further research. The same author and two collaborators of long standing have further emphasised the enigmatic origin of frog skin alkaloids in a short popular article.[68] It has also been shown that Madagascan frogs of the genus *Mantella*, like their dendrobatid cousins from the Americas, failed to produce skin alkaloids when raised in captivity, but sequestered indolizidine alkaloids when fed with alkaloid-dusted fruit flies.[69] A wild-caught specimen of *M. viridis* still contained pumiliotoxins even after 18 months of captivity on an alkaloid-free diet.

5.2 Synthesis

Recent advances in the synthesis of dendrobatid alkaloids have been reviewed by Kibayashi and Aoyagi,[70] whose own contributions in this field over the past few years have been substantial.

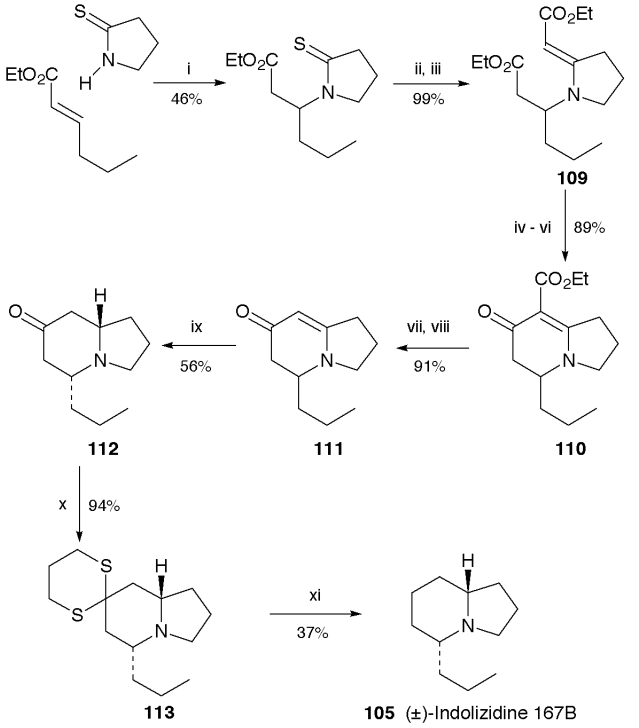
Four syntheses of the simple indolizidine alkaloid 167B, a popular target for illustrating novel methodology, were published during the period under review. Bubnov and co-workers converted the *trans*-2,6-diallyl-1,2,3,6-tetrahydropyridine **98**, a known product from the reaction of pyridine and triallylborane, into the *cis* isomer **99** by thermal equilibration with additional triallylborane (Scheme 10).[71] Hydroboration and oxidation of



Scheme 10 *Reagents:* i, Pr^{i}OH; ii, $(H_2C{=}CHCH_2)_3B$, 130 °C, then OH^-; iii, $Pr_2BCH_2CH{=}CH_2$, 130 °C; iv, $(Pr_2BH)_2$, THF, 0 °C; v, H_2SO_4, 0 °C, then H_2O_2, NaOH, −20 °C; vi, Ph_3P, CBr_4, CH_2Cl_2, 0 °C, then Et_3N; vii, H_2 (100 atm), Raney Ni, AcOH, 100 °C.

this isomer, unusually protected as the *N*-dipropylboryl derivative **100**, gave the isomeric alcohols **101** and **102** (48%), which were cyclised to the indolizidines **103** and **104** *via* the corresponding bromides. Catalytic hydrogenation of the mixture over Raney nickel completed the synthesis of the racemic target alkaloid (±)-**105**. A similar sequence of reactions on **98** afforded racemic 5-*epi*-indolizidine 167B (±)-**106**, while appropriate modifications of the route provided access to a related alkaloid, indolizidine 209D (±)-**107** and its 5-epimer **108**.

The key steps in another short synthesis of racemic indolizidine 167B are shown in Scheme 11.[72] These include preparation of the vinylogous urethane **109** by Eschenmoser

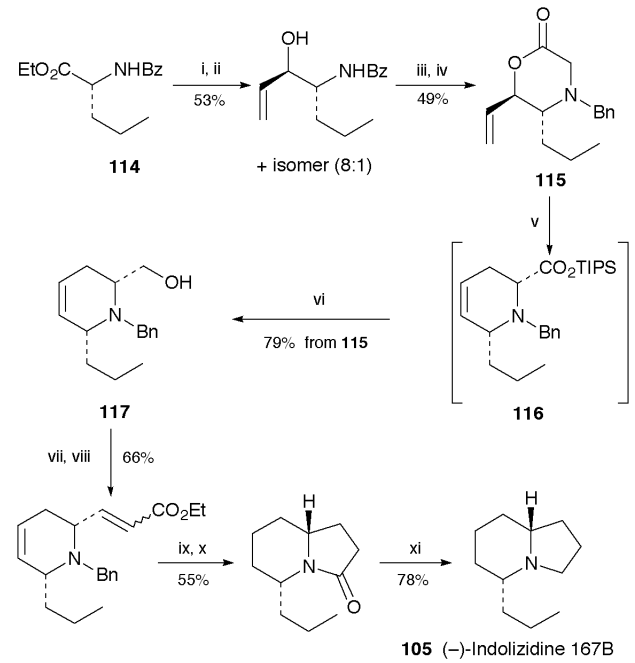


Scheme 11 *Reagents:* i, NaOH (cat.), THF, reflux; ii, $BrCH_2CO_2Et$, MeCN, rt; iii, Ph_3P, Et_3N, MeCN, rt; iv, NaOH, H_2O, reflux; v, Ac_2O, MeCN, rt; vi, MeCN, reflux; vii, KOH, H_2O, reflux; viii, HCl; ix, $LiAlH_4$, THF, 0 °C to rt; x, $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, TFA, rt; xi, Raney Ni W-2, EtOH, reflux.

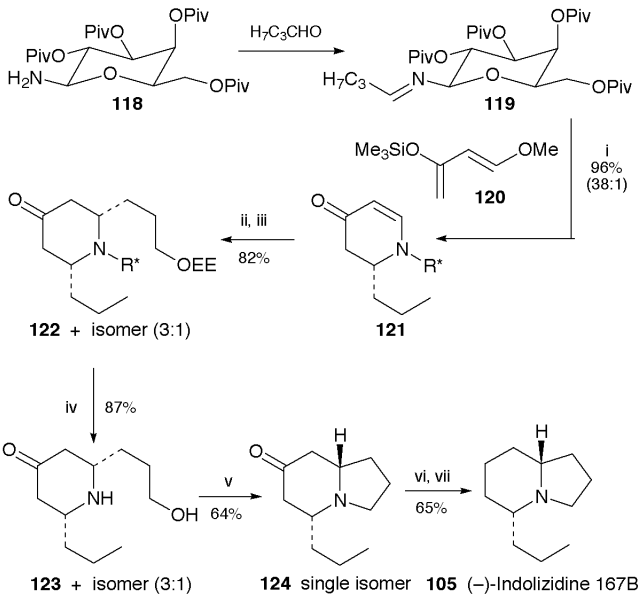
sulfide contraction, acylative ring closure to create the unsaturated indolizidine **110**, hydrolysis and decarboxylation to the bicyclic vinylogous amide **111**, and a stereoselective reduction with lithium aluminium hydride to give the ketone **112**. Defunctionalisation of this intermediate *via* the corresponding propylene dithioketal **113** completed the eight-step synthesis of the volatile racemic alkaloid (±)-**105** in an overall yield of 7.2% based on pyrrolidine-2-thione.

An enantioselective synthesis of (−)-indolizidine 167B by Angle and Henry commenced with *N*-benzoyl-D-norvaline ethyl ester **114**, which was converted in three steps and 26% yield into the oxazinone **115** (Scheme 12).[73] The triisopropylsilyl ketene acetal ether of this compound, prepared *in situ*, underwent spontaneous Claisen rearrangement; the resulting ester **116** was immediately reduced with lithium aluminium hydride to give the *cis*-2,6-disubstituted 1,2,3,6-tetrahydropyridine **117** in 79% yield from **115**. The straightforward transformations shown in the Scheme completed the synthesis of the target alkaloid (−)-**105** in nine steps and 5.8% overall yield from the amino ester **114**.

Tetra-*O*-pivaloyl-β-D-galactosylamine **118** was used as an unusual chiral auxiliary in the synthesis of (−)-indolizidine 167B shown in Scheme 13.[74] The aldimine derivative **119** underwent a highly diastereoselective aza Diels–Alder cycloaddition (38 : 1) with Danishefsky's diene **120** in the presence of zinc chloride to give the dihydopyridone **121** in 96% yield. The *R* absolute configuration at the site bearing the propyl substituent was confirmed by X-ray crystallography. However, conjugate addition of 3-(1-ethoxy)ethoxypropylcuprate to **121** in the presence of trimethylsilyl chloride showed poor diastereoselectivity (3 : 1), and resulted in the formation of predom-



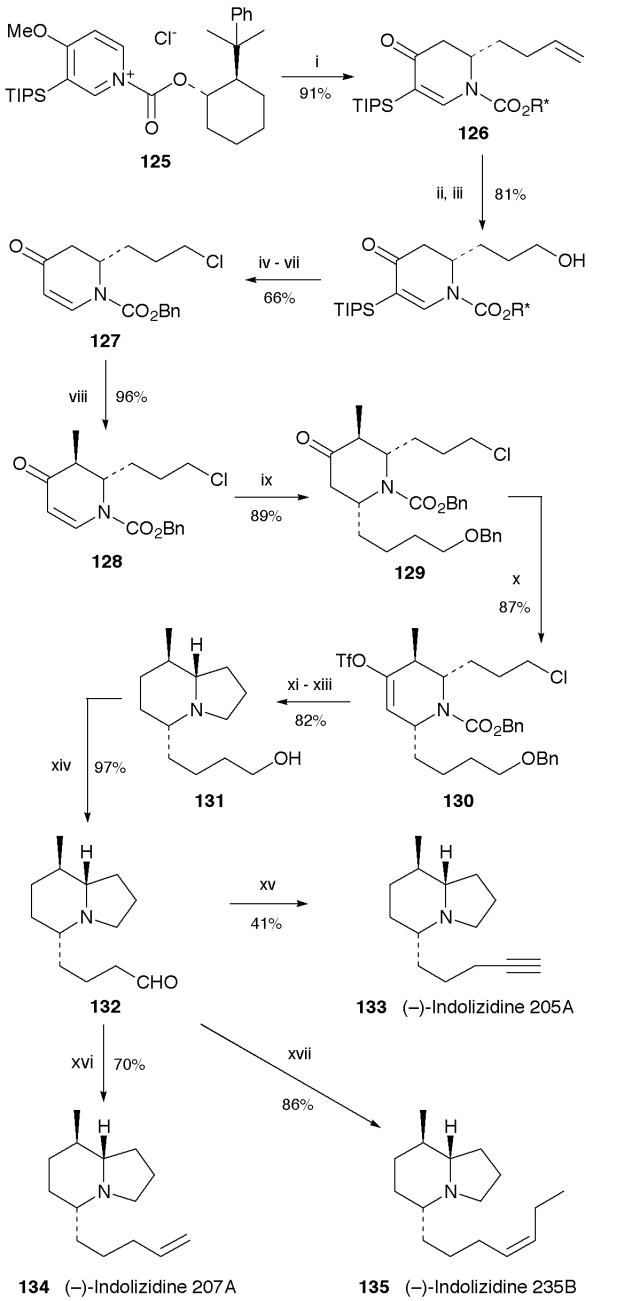
Scheme 12 *Reagents:* i, DIBAL-H, CH_2Cl_2, −78 °C; ii, H_2C=CHMgCl, THF, −75 °C to rt; iii, $LiAlH_4$, THF, 0 °C to reflux; iv, $BrCH_2CO_2Ph$, Pr^i_2NEt, MeCN, 0 °C to rt; v, TIPS-OTf, Et_3N, C_6H_6, rt; vi, $LiAlH_4$, Et_2O, 0 °C to rt; vii, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt; viii, $(EtO)_2POCH_2CO_2Et$, KH, THF, −78 °C to rt; ix, Pd/C (5%), Na_2CO_3, Et_2O, filter and repeat, then H_2 (30 psi), $Pd(OH)_2$/C, EtOH, 60 °C; x, Me_3Al, C_6H_6, 0 °C to reflux; xi, $LiAlH_4$, Et_2O, 0 °C to reflux.



Scheme 13 *Reagents:* i, $ZnCl_2$, THF–CH_2Cl_2(1:1), −78 °C to −20 °C, then HCl (aq., 1 M); ii, $CH_3CH(OEt)OCH_2CH_2CH_2MgBr$, CuBr·$SMe_2$, Me_3SiCl, THF, −78 °C; iii, Bu_4NF, THF, rt; iv, HCl (aq., 1 M), MeOH, rt, then Na_2CO_3; v, Et_3N, CCl_4, Ph_3P, MeCN, 0 °C to rt; vi, $(CH_2SH)_2$, BF_3·Et_2O, CH_2Cl_2, 0 °C to rt; vii, H_2, Raney Ni, Pr^iOH, 70 °C

inantly the *cis*-2,6-disubstituted piperidinone **122**. Mild acidic hydrolysis removed the protecting group and the sugar auxiliary from this product, after which the liberated heterocycle **123**—still as a 3:1 mixture of isomers—was converted *via* ketone **124** into the target alkaloid (−)-**105** by standard reactions. Interestingly, only the pure *cis* bicyclic ketone **124** was isolated in the cyclisation step.

Further developments in the enantioselective synthesis of indolizidine alkaloids *via N*-acyldihydropyridone intermediates have been reported by Comins and his team. The incorporation of a chiral auxiliary, (+)-*trans*-2-(α-cumyl)cyclohexyl (TCC), into pyridinium salt **125** provided the key to the excellent asymmetric induction seen in their new synthesis of three 5,8-disubstituted amphibian indolizidine alkaloids (Scheme 14).[75] Addition of but-3-enylmagnesium bromide to **125**



Scheme 14 *Reagents:* i, H_2C=$CH(CH_2)_2MgBr$, THF, −78 °C; ii, OsO_4 (cat.), $NaIO_4$, H_2O-THF (1:1), rt; iii, L-Selectride, THF, −78 °C; iv, NaOMe, MeOH, reflux; v, HCl (10% aq.), rt; vi, BuLi, THF −78 °C, then BnOCOCl; vii, Ph_3P, NCS, CH_2Cl_2, −42 °C to rt; viii, LiHMDS, THF, −78 °C, then MeI, −78 °C to rt; ix, $BnO(CH_2)_4MgBr$, CuBr·SMe_2, BF_3·Et_2O, THF −78 °C; x, LiHMDS, THF, −78 °C, then *N*-(2-pyridyl)trifilimide; xi, H_2 (1 atm), 5% Pt/C, EtOH, rt; xii, H_2 (1 atm), 20% $Pd(OH)_2$/C, EtOH, rt; xiii, Na_2CO_3, EtOH, reflux; xiv, Dess–Martin periodinane, CH_2Cl_2, rt; xv, $(MeO)_2POCHN_2$, $KOBu^t$, THF, −78 °C; xvi, Ph_3P=CH_2, THF, 0 °C to rt; xvii, Ph_3P=$CHCH_2CH_3$, THF, −78 °C to rt.

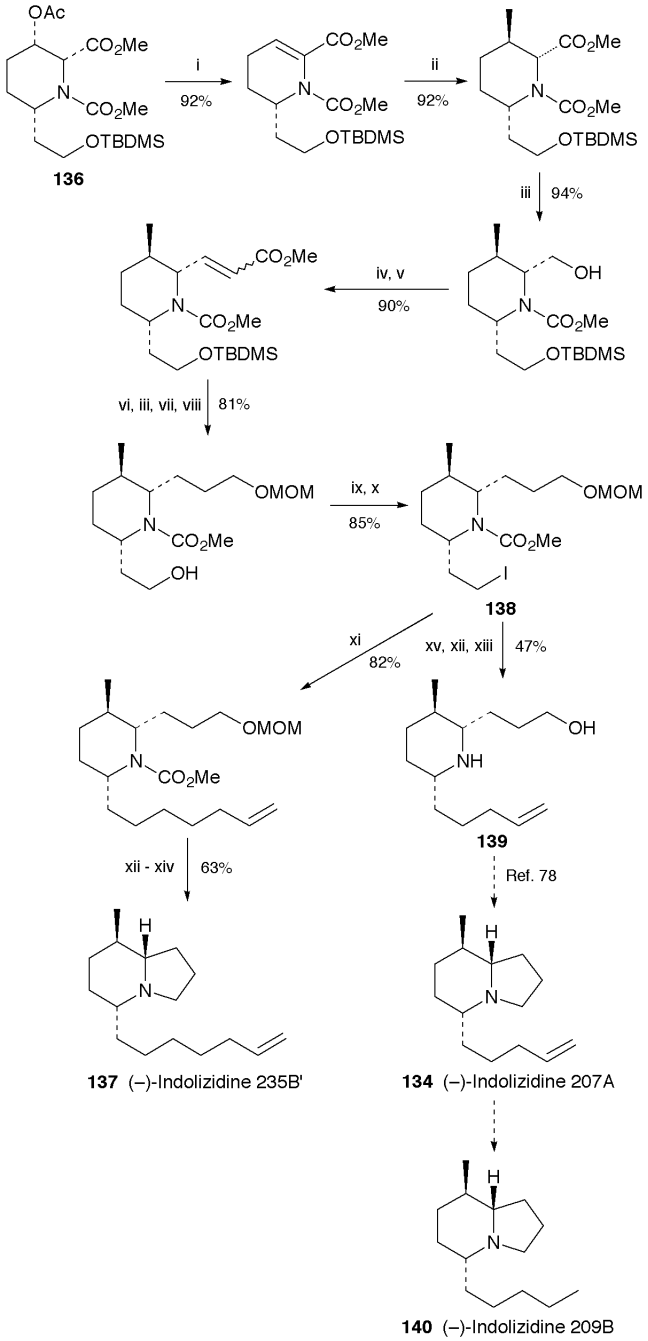
yielded the dihydropyridone **126** as a single diastereoisomer in 91% yield after recrystallisation. After a series of functional group manipulations, the alkyl groups destined to become the substituents at C-8 and C-5 of the targets were introduced stereoselectively by enolate alkylation (**127** → **128**) and conjugate addition (**128** → **129**) respectively. The indolizidine nucleus was formed from vinyl triflate **130** in a one-pot sequence involving defunctionalisation of the vinyl triflate, removal of benzyl protecting groups and cyclisation to give the

amino alcohol **131**. This sequence of reactions took place in a noteworthy overall yield of 82%. Dess–Martin oxidation of this compound yielded aldehyde **132**, which served as a common precursor for the three target alkaloids, (−)-indolizidine 205A **133**, (−)-indolizidine 207A **134** and (−)-indolizidine 235B **135**. The products were found to have identical MS, FTIR and GC properties to the natural compounds.

Momose and Toyooka previously communicated a rather lengthy synthesis of 5,8-dialkylindolizidine alkaloids from the substituted piperidine **136**[76] (*cf.* ref. 6*c*). A full paper, which also generalises and extends the approach to include related 1,4-disubstituted quinolizidine alkaloids, has now been published.[77] Some key steps in the synthesis of (−)-indolizidine 235B′ **137** are shown in Scheme 15. Copper(I)-induced cross-coupling of iodide **138** with pent-4-enylmagnesium bromide served to introduce the unsaturated C-5 chain of the target alkaloid. An alternative coupling with allylmagnesium chloride yielded the trisubstituted piperidine **139**, thereby converging with Kibayashi's previously reported synthesis[78] of two related alkaloids, (−)-indolizidines 207A **134** and 209B **140**. Suitable modifications to the illustrated route also provided access to (−)-indolizidine **141**, the preparation of which is especially interesting as it has helped to clarify the possible structures of two very minor amphibian indolizidines which have hitherto not been available in sufficiently large amounts for full characterisation. The IR spectrum of the synthetic compound was virtually identical to that of indolizidine 223J, the Bohlmann bands in particular suggesting that the natural product has, at least, the same relative configuration between C-5 and C-9. By contrast, natural indolizidine 223I lacks Bohlmann bands; 5-H and 8a-H are thus likely to be *trans* to each other, and the atypical structure **142** is now proposed for this alkaloid. In addition, an adaptation of the illustrated synthetic route yielded the (−)-quinolizidine **143**, which turned out to have different GC and MS properties to the minor, and imperfectly characterised, quinolizidine alkaloid 207I. Since both, however, have very similar patterns of Bohlmann bands, the relative stereostructure of quinolizidine 207I has now been revised to the new tentative structure **144**.

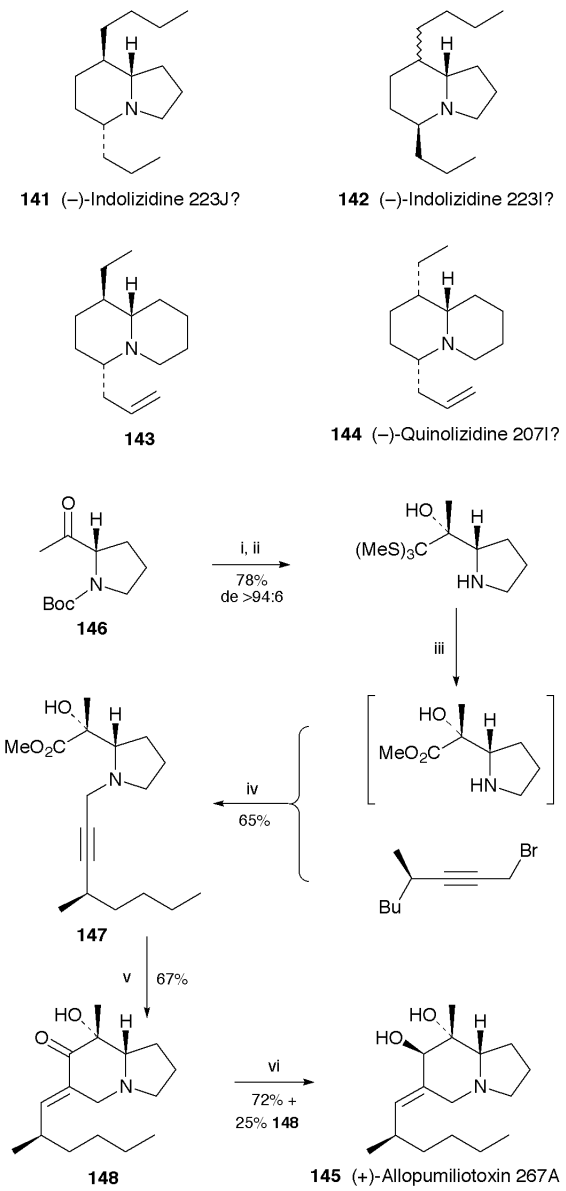
The shortest synthesis of (+)-allopumiliotoxin 267A **145** to date has been reported by Sato and co-workers.[79] Conversion of the L-proline derivate **146** (also used by Overman in his 1992 synthesis of the alkaloid[80]) into the pivotal intermediate **147** as shown in Scheme 16 set the scene for a novel cyclisation mediated by titanium(IV) isopropoxide and isopropylmagnesium chloride, which is actually the main theme of the report. This combination of reagents appears to generate an (η^2-propenyl)titanium(II) species *in situ*. The organometallic intermediate then reacts with the alkyne group of **147** to produce a putative titanacyclopropene. Subsequent intramolecular nucleophilic substitution with the strategically placed ester group results in the formation of indolizidinone **148** in 67% overall yield after workup. Since Overman's earlier route to (+)-allopumiliotoxin 267A[80] also proceeded *via* **148**, the two syntheses converge again at this point. Reduction of the ketone group with tetramethylammonium triacetoxyborohydride and glacial acetic acid in acetone (Overman's conditions) gave the target alkaloid **145** in 72% yield (96% based on recovered **148**). This noteworthy route to (+)-allopumiliotoxin 267A required only seven steps from Boc-protected L-proline, and the overall yield was 27%.

The first total synthesis of (+)-homopumiliotoxin 223G **149** (and, indeed, the first total synthesis of a homopumiliotoxin alkaloid) has been accomplished by Kibayashi and co-workers as shown in Scheme 17.[81] Lewis acid-initiated addition of 1-isopropyl-1-trimethylsilylallene to the ketone **150** afforded homopropargylic alcohol **151** as the sole diastereoisomer in almost quantitative yield. The configuration of the newly established stereogenic centre was confirmed by NOE measurements on the cyclic carbamate derived from the Boc-protected



Scheme 15 *Reagents:* i, NaH, DMF, C_6H_6, 0 °C to 50 °C; ii, Me_2CuLi, Et_2O, −78 °C to −30 °C; iii, Super-hydride, THF, 0 °C; iv, $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C to 0 °C; v, $(EtO)_2POCH_2CO_2Me$, NaH, THF, 0 °C; vi, H_2 (4 atm), 5% Pd/C, MeOH, rt; vii, MOM-Cl, Pr^i_2NEt, CH_2Cl_2, 0 °C to rt; viii, Bu_4NF, THF, 0 °C to rt; ix, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0°C; x, NaI, Me_2CO, 50 °C; xi, $H_2C{=}CH(CH_2)_3MgBr$, CuI, THF, −40 °C to −30 °C; xii, LiSPr, HMPA, THF, 0 °C to rt; xiii, HCl (conc., cat.), MeOH, reflux; xiv, CBr_4, Ph_3P, Et_3N, CH_2Cl_2, 0 °C; xv, $H_2C{=}CHCH_2MgCl$, CuI, THF, −40 °C to −30 °C.

compound **152**, hydrostannylation of which gave a mixture (3.6 : 1) of the (*Z*)-alkenylstannane **153** and its regioisomer **154**. Once the former product had been transformed into the corresponding iodoalkene **155**, a remarkably efficient (99% yield) palladium-catalysed carbonylation gave the lactone **156**, which was readily converted into the target alkaloid (+)-(1*S*,9a*S*)-**149** as illustrated. The reaction sequence proceeded in eleven steps and an overall yield of 27% from *N*-Cbz-L-pipecolic acid. Comparison of spectroscopic data showed that the synthetic and natural products were identical, thereby resolving some residual uncertainty about the relative configuration of the two stereogenic centres in the alkaloid. However, the natural product's absolute configuration remains unknown



Scheme 16 *Reagents:* i, TFA, anisole, CH_2Cl_2, rt; ii, $(MeS)_3CH$–BuLi, −78 °C to −40 °C; iii, $Hg(ClO_4)_2{\cdot}3H_2O$, MeOH, $CHCl_3$, rt; iv, Pr^i_2NEt, THF, rt; v, $Ti(OPr^i)_4$, Pr^iMgCl, Et_2O, −78 °C to −50 °C to −5 °C; vi, Me_4N^+ $BH(OAc)_3^-$, HOAc, Me_2CO.

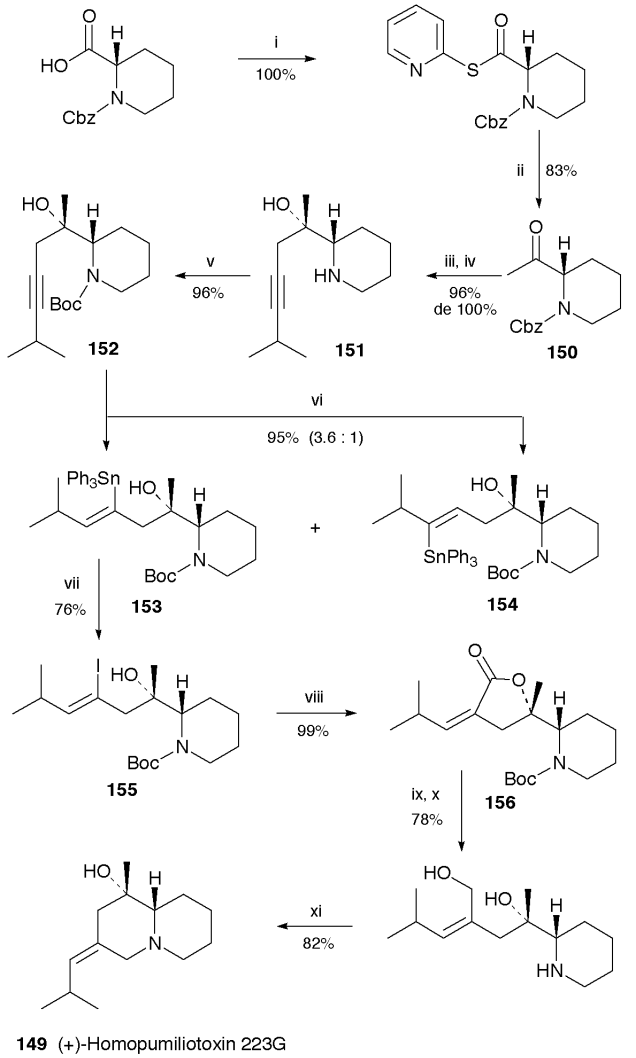
because too little has been isolated for comprehensive characterisation.

6 *Elaeocarpus* alkaloids

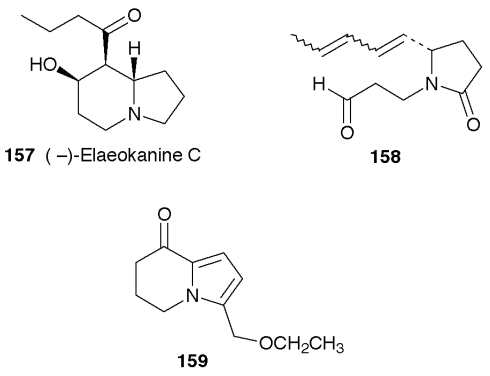
A formal synthesis of (−)-elaeokanine C **157** by a route employing a novel nickel-catalysed cyclisation of diene-aldehyde **158** was previously reported in a communication[82] that was highlighted in last year's review in this series (*cf.* ref. 6*d*). Full experimental details of this synthesis have now been provided in a paper that also includes examples of the application of the new method to the synthesis of pyrrolidines, piperidines, perhydroazepines and pyrrolizidines.[83]

7 Alkaloids from *Polygonatum sibiricum*

A new indolizidine alkaloid isolated from the rhizomes of *Polygonatum sibiricum* (Liliaceae)[84] is unusual for several reasons. Firstly, indolizidine alkaloids have never before been isolated from liliaceous species. Secondly, the new alkaloid, for which the structure **159** has been proposed, appears to be the first reported 5,6,7,8-tetrahydroindolizine (tetrahydropyr-



Scheme 17 *Reagents:* i, $(PyS)_2$, Ph_3P, MeCN, rt; ii, MeMgBr, THF, −20 °C; iii, H_2, Pd/C, TFA, MeOH; iv, 1-isopropyl-1-trimethylsilylallene, $TiCl_4$, CH_2Cl_2, −78 °C; v, $(Boc)_2O$, K_2CO_3; vi, Ph_3SnH, Et_3B, toluene, rt; vii, NIS; viii, CO, $Pd(OAc)_2$, Ph_3P, Bu_3N, HMPA, 100 °C; ix, TFA; x, DIBAL-H; xi, CBr_4, Ph_3P.

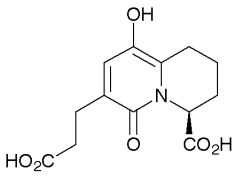


rolo[1,2-*a*]pyridine) from a natural source. The ethoxymethyl side chain is also a most curious substituent. The terse Chinese communication describing compound **159** contains sufficient spectroscopic data (IR, UV, MS; ^1H, ^{13}C and HETCOR NMR) to make the structural assignment appear reasonable. However, the proposed structure should perhaps be viewed with caution until independent evidence can be obtained.

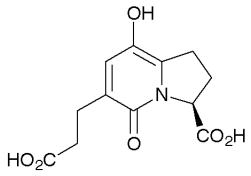
8 *Streptomyces* metabolites

A58365B **160**, an inhibitor of angiotensin-converting enzyme isolated from the fermentation broth of the bacterium *Strepto-*

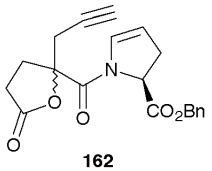
myces chromofuscus, was synthesised in racemic form some years ago by Clive and co-workers.[85] Full details of the synthesis were reported in this series of reviews (*cf.* ref. 6*e*). Essentially the same route has now been used for preparing the related 1,2,3,5-tetrahydroindolizine (±)-A58365A **161**.[86] As



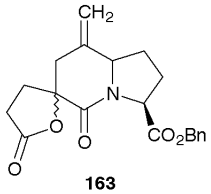
160 A58365B



161 A58365A



162



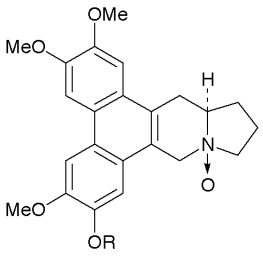
163

before, the crux of the synthesis was the enyne radical cyclisation of both diastereoisomers of enamide **162** with tributyltin hydride and AIBN in boiling toluene. Destannylation of the intermediate vinylstannanes with trifluoroacetic acid afforded diastereoisomic indolizidinones **163** in about 90% overall yield. Both isomers were readily transformed into the target alkaloid by ozonolysis of the methylene group, base-initiated cleavage of the lactone ring and hydrogenolysis of the benzyl ester.

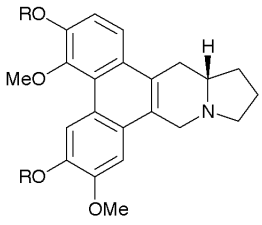
9 Phenanthroindolizidine alkaloids and seco analogues

Ten phenanthroindolizidine alkaloids, eight of them new, were isolated some years ago[87] from *Tylophora tanakae* (Asclepiadaceae), which is indigenous to the Ryukyu islands of Japan. Further phytochemical investigations on the leaves and caules of this species have now yielded another four new alkaloids.[88] (−)-Tylophorine *N*-oxide **164** and (−)-7-demethyltylophorine *N*-oxide **165** were found as additional metabolites in the previously investigated plant source, while (+)-3,6-didemethylisotylocrebrine **166** and (+)-14α-hydroxy-3,6-didemethylisotylocrebrine **167** accompanied the known alkaloid 14α-hydroxy-3-demethylisotylocrebrine **168** in the polar extract from a cultivated specimen. Full ^{1}H and ^{13}C NMR and other spectroscopic data were reported for the novel alkaloids. Although the absolute configurations of the new compounds were not specifically determined, they appear to have been assigned as illustrated by analogy with known alkaloids. Assays of the cytotoxicities of ten of the fourteen *Tylophora* alkaloids towards five different cancer cell lines showed a substantial diminution of activity in the *N*-oxides. Alkaloids with one free hydroxy group in the phenanthrene framework (*e.g.*, **168**) were more potent that those with two or no hydroxy groups [*e.g.*, **167** or (+)-isotylocrebrine **169**], while the introduction of the 14α-hydroxy group, as in **168**, also increased efficacy. An indication of greater activity in the (*S*) series of alkaloids (13β-H) as compared with the (*R*) group [13α-H, as represented by the prototypical *Tylophora* alkaloid (−)-tylophorine **170**] requires further study.

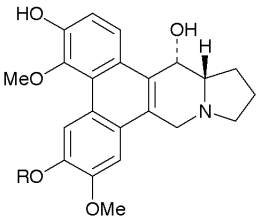
Pergularinine **171** and tylophorinidine **172**, phenanthroindolizidine alkaloids from the Indian herb *Pergularia pallida*, have shown promising antitumour activity in assays with thymidylate synthase (TS), a key target enzyme in cancer chemotherapy. The alkaloids were potently toxic and cytostatic towards *Lactobacillus leichmannii* cells, from which the enzyme was isolated and purified for model inhibition studies.[89] They appear to bind irreversibly to TS, probably through a covalent linkage;



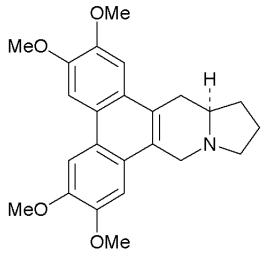
164 R = Me
165 R = H



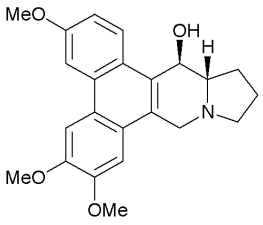
166 R = H
169 R = Me



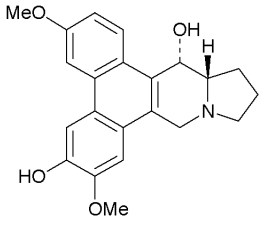
167 R = H
168 R = Me



170 (–)-Tylophorine



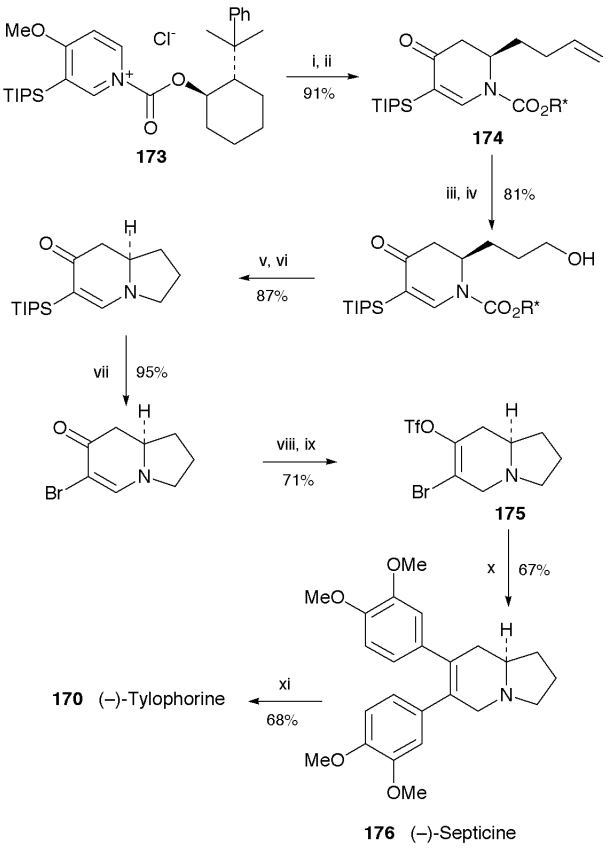
171 Pergularinine



172 Tylophorinidine

K_i values of 10×10^{-6} and 9×10^{-6} M respectively were determined for the two alkaloids, and the inhibition in both cases was of a simple linear non-competitive type. *In vitro* testing with human leukocytes isolated from the blood of patients suffering from either chronic myelocytic leukemia or acute lymphocytic leukemia showed that both alkaloids significantly lowered the abnormally high TS levels detected in the cells; in all cases, potent inhibition was apparent (IC_{50} *ca.* 50 μM).[90]

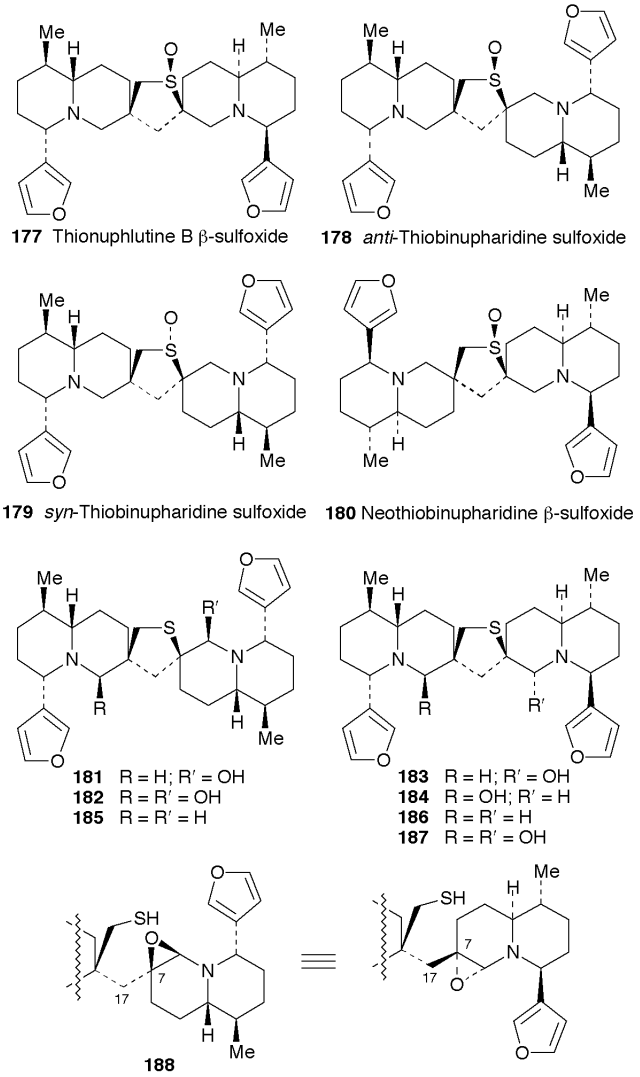
In 1991 Comins and Morgan reported syntheses of racemic tylophorine and its seco analogue septicine *via* dihydropyridone intermediates[91] (*cf.* ref. 6*f*). This strategy has been adapted with a high degree of stereocontrol to yield the laevorotatory alkaloids as shown in Scheme 18.[92] In contrast with the synthesis of the amphibian alkylindolizidines described in Section 5.2, the chiral auxiliary used here was (−)-*trans*-2-(α-cumyl)cyclohexanol. Addition of but-3-enylmagnesium bromide to pyridinium salt **173** yielded the dihydropyridone **174**, which was obtained as a single diastereoisomer in 91% yield after recrystallisation. Simple functional group interconversions led to the important bromovinyl triflate **175** (seven steps, 48% yield), into which both aryl groups were simultaneously introduced by palladium-catalysed cross-coupling with (3,4-dimethoxyphenyl)zinc bromide. The product, (−)-septicine **176**, was thus shown to possess *R* absolute configuration—an important conclusion, since the only previously reported enantioselective synthesis of (−)-septicine, which dates from 1969,[93] assigned the *S* absolute configuration to the laevorotatory alkaloid. The observed optical rotation ($[\alpha]_D^{28}$ −172) was also significantly higher than reported for the natural product ($[\alpha]_D$ −16 to −42). Further confirmation for the revised absolute stereochemistry of (−)-septicine was provided by oxidative coupling with vanadium(V) oxyfluoride, which afforded the known alkaloid (*R*)-(−)-tylophorine **170** in 68% yield and greater than 98% ee.



Scheme 18 *Reagents:* i, $H_2C{=}CH(CH_2)_2MgBr$, THF–toluene, −78 °C; ii, oxalic acid, H_2O, rt; iii, OsO_4 (cat.), HIO_4, THF–H_2O (1:1), rt; iv, L-Selectride, THF, −78 °C, then $NaBO_3{\cdot}4H_2O$, H_2O, rt; v, Ph_3P, NCS, CH_2Cl_2, −23 °C to 25 °C; vi, NaOMe, MeOH, reflux; vii, py·HBr_3, CH_2Cl_2, −23 °C to rt; viii, L-Selectride, THF, −23 °C; ix, 5-Cl-2-(NTf_2)pyridine, THF, –23 °C; x, 3,4-$(MeO)_2C_6H_3ZnBr$, $Pd(Ph_3P)_4$, THF, 25 °C to reflux; xi, VOF_3, TFA, CH_2Cl_2, 0 °C to rt.

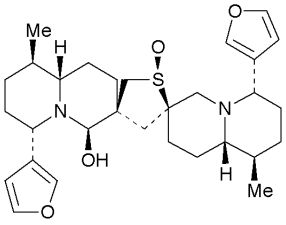
10 *Nuphar* alkaloids

The immunosuppressant activity of nine alkaloids from Chinese Nupharis Rhizoma, the medicinally valuable dried rhizomes of the waterlily *Nuphar pumilum* , was reported by Yamahara *et al.* in 1996[94] and discussed in last year's review (*cf.* ref. 6*g*). The same source has now yielded a further four biologically inactive metabolites:[95] thionuphlutine B β-sulfoxide **177**, *anti*-thiobinupharidine sulfoxide **178**, *syn*-thiobinupharidine sulfoxide **179** and neothiobinupharidine β-sulfoxide **180**—all of them known alkaloids. In this study, some stereochemical ambiguities in the structures of several dimeric hemiaminal alkaloids were resolved with the aid of 2D-NMR spectroscopic techniques. There appears to be no remaining doubt that the relative stereostructures of 6-hydroxythiobinupharidine **181**, 6,6′-dihydroxythiobinupharidine **182**, 6-hydroxythionuphlutine B **183** and 6′-hydroxythionuphlutine B **184** are as depicted in the diagrams. Furthermore, both **181** and **182** yielded thiobinupharidine **185** on reductive dehydroxylation with sodium borohydride, while **183** and **184** gave thionuphlutine B **186**. More interestingly, the hemiaminal alkaloids underwent rearrangement of the thiaspirane ring upon heating under reflux in chloroform solution for 24 hours. 6-Hydroxythiobinupharidine **181** and 6-hydroxythionuphlutine B **183** were found to interconvert; the former furnished a 6:4 mixture of the two alkaloids, while the latter produced a 1:9 mixture. Similar handling of 6,6′-dihydroxythiobinupharidine **182** produced a 65:35 mixture with 6,6′-dihydroxythionuphlutine B **187**. 6′-Hydroxythionuphlutine B **184** did not rearrange. It is postulated that the rearrangements proceed through epoxide intermediates such as **188**, after which free rotation about the C7–C17 bond permits attainment of conformations from which either product can be formed by recyclisation. Since the absolute stereostructure of thiobinupharidine **185** has previously been determined by X-ray crystallography, the interconversions reported serve to establish the absolute configurations of all the compounds described in this summary.

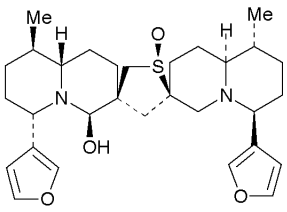


Four new dimeric sesquiterpene alkaloids of the thiaspirane sulfoxide class have been isolated from Chinese Nupharis Rhizoma by the same research group.[96] The structures of the new compounds [(−)-nupharpumilamines A–C, **189**–**191** and (+)-nupharpumilamine D **192**] were determined on the basis of chemical and spectroscopic evidence. The IR spectra of all four compounds showed the Bohlmann bands between 2750 and 2900 cm^{-1} that are characteristic of *trans*-fused quinolizidine rings, while skeletal connectivities and spatial relationships were elucidated by means of HMBC and NOE NMR experiments. The configurations of the sulfinyl groups were deduced by comparing NMR spectroscopic data with those of known alkaloids. In the case of the hemiaminal alkaloids **189** and **190**, reduction with sodium borohydride yielded products that were spectroscopically and chromatographically indistinguishable from authentic specimens of *anti*-thiobinupharidine sulfoxide **178** and thionuphlutine B β-sulfoxide **177** respectively.

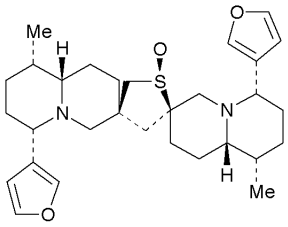
When the methanolic extract from rhizomes of another waterlily, *Nuphar japonicum*, proved to have insecticidal activity against larvae of the fly *Drosophila melanogaster*, bioassay-guided fractionation led to the isolation of four known alkaloids: (−)-castoramine **193**, (−)-7-epideoxynupharidine **194**, (−)-nupharolutine **195** and the piperidine alkaloid (−)-nuphamine **196**.[97] The isolation of (−)-castoramine is especially interesting, as its only natural source up to now has been the Canadian beaver *Castor fiber*, the scent glands of which contain



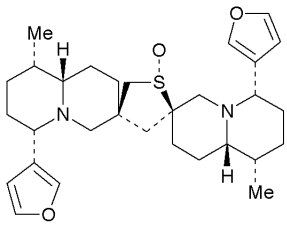
189 Nupharpumilamine A



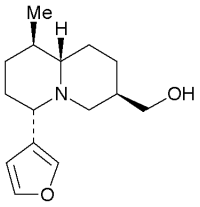
190 Nupharpumilamine B



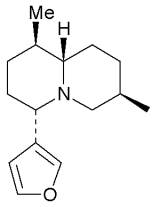
191 Nupharpumilamine C



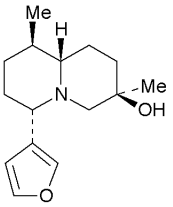
192 Nupharpumilamine D



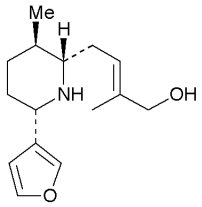
193 (–)-Castoramine



194 (–)-7-Epideoxynupharidine



195 (–)-Nupharolutine



196 (–)-Nuphamine

traces of this alkaloid and related *Nuphar*-like quinolizidines.[98] When the purified alkaloids were tested for insecticidal activity, the most active compound against larvae of *D. melanogaster* was (−)-castoramine (LC_{50} 1.00 μmol per ml of diet). However, (−)-7-epideoxynupharidine had the greatest acute toxicity towards adult flies (LD_{50} 0.86 μg per adult) and was also the most potent inhibitor of acetylcholinesterase isolated from the flies.

11 Lasubines, myrtine and epimyrtine

The short syntheses of the epimeric Lythraceae alkaloids lasubine I **197** and lasubine II **198** shown in Scheme 19 commenced with the β-hydroxyallylsilane **199**, which was prepared by indium-mediated allylation of veratraldehyde.[99] The key step was the intramolecular cyclisation of the allylsilane unit on to the *N*-acyliminium ion generated *in situ* from hydroxylactam **200**. When this reaction was performed with trifluoroacetic acid at −78 °C, the readily separable quinolizidinone diastereoisomers **201** and **202** were obtained in a ratio of 4:1; at 20 °C, the ratio swung to 0.55:1. Two routes to the target alkaloids were then investigated. Ozonolysis of **201** followed by reduction with lithium aluminium hydride yielded a 1.2:1 mixture of (±)-2-epilasubine I **203** and (±)-lasubine I **197**, while the same sequence of reactions converted **202** exclusively into (±)-2-epilasubine II **204**. Conformational analysis of the intermediate diones was used to rationalise the outcome of the reduction steps. When reduction of compounds **201** and **202** with lithium aluminium hydride preceded oxidative cleavage of the *exo*-methylene group, ketones **205** and **206** were formed in good yield. Reduction of **205** with sodium borohydride, although precedented, proved not to be diastereoselective, but the use of lithium tri-*sec*-butylborohydride (L-Selectride) gave (±)- lasubine **197** exclusively in 50% yield. The reductant of choice for the conversion of **206** into (±)-lasubine II **198** (60%) was lithium trisiamylborohydride (LS-Selectride). The overall yields of lasubines I and II by the second sequence of reactions (six steps) were 8% and 7.4% respectively based on **199**. Essentially the same approach (Scheme 19, with Me replacing Ar) has been applied to the synthesis of the simple *Vaccinium myrtillus* alkaloids (+)-myrtine **207** and (−)-epimyrtine **208**, the enantioselectivity arising from the use of (*S*)-**209** at the start of the reaction sequence.[100]

12 Alkaloids of the lupinine–cytisine–sparteine–matrine–*Ormosia* group

12.1 Occurrence, analysis, biological studies and chemical ecology

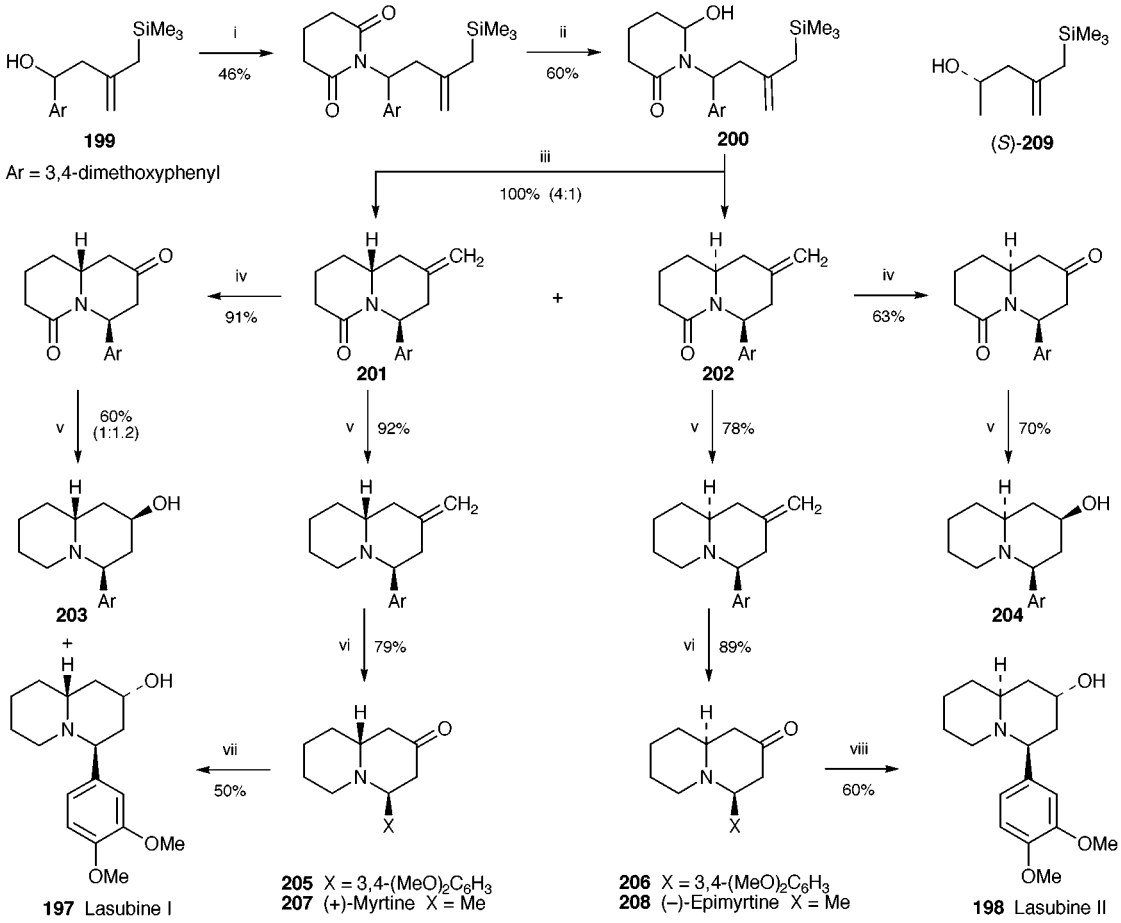
New alkaloids isolated from plants belonging to the Leguminosae, and new sources of known lupin alkaloids, are listed in Table 1.[101–105] As always, alkaloids previously recorded in a species are not included in the Table, even though they are often the major metabolites. A review in the Japanese literature dealing with the alkaloids found in plants of the genus *Maackia* also contains information on the probable biosynthesis of some of these unusual metabolites and implications for the chemotaxonomy of the genus.[106]

Efficient simultaneous solid-phase extraction and separation of both quinolizidine alkaloids and phenolics from a crude extract of *Lupinus albus* seedlings has been carried out on cartridges containing SCX-strong cation exchanger (benzenesulfonic acid groups) and C-18 reversed phase support linked in series.[107] Twenty alkaloids, including seven esters of 13-hydroxylupanine **210**, could be recognised in the eluate by GC-MS analysis. The technique was used to analyse changes in the alkaloid and isoflavonoid profiles during the defence reaction of plants evoked by abiotic and biotic elicitors. The Chinese literature contains details of the separation of ten alkaloids from the roots of *Sophora flavescens* by high-speed countercurrent chromatography.[108]

The mistletoe *Viscum cruciatum* is known to accumulate quinolizidine alkaloids in its leaves and stems by root parasitism on the host plant *Retama sphaerocarpa*. A new study has shown that two alkaloids, retamine **211** and lupanine **212**, are also present in both unripe and ripe fruits.[109] It is intriguing that more toxic alkaloids such as anagyrine **213**, cytisine **214** and *N*-methylcytisine **215**, all of which are sequestered in the leaves and stems of the hemiparasite, are not transported to the fruits. Since dissemination of the mistletoe's seeds is effected by consumption and rapid defecation by birds that feed on the berries, the apparent selection of less toxic alkaloids in the fruits may be considered as strategies both for the protection of the seeds and for their dissemination.

Alkaloid content and composition in sweet (alkaloid-poor) and bitter (alkaloid-rich) varieties of *Lupinus angustifolius* (narrow-leafed lupin) have been studied under simulated drought conditions in order to evaluate the factors limiting the utility of this lupin species as a useful fodder crop for livestock.[110] Another agriculturally-motivated study has shown that the alkaloid content of the alkaloid-deficient perennial *L. polyphyllus* (Washington lupin) remained stable over a three-year period, thus allaying some fears that cultivation leads to increasing alkaloid content.[111]

Profiles of the quinolizidine and dipiperidyl alkaloids found in various organs of Egyptian *Lygos* species have been established.[103] In addition, biological evaluations have been performed on some of the alkaloids. *N*-Methylcytisine **215** proved to have hypoglycemic activity, as shown by increased



Scheme 19 *Reagents:* i, glutarimide, DEAD, Ph_3P, THF, 0 °C to rt; ii, $LiEt_3BH$, CH_2Cl_2, −78 °C; iii, TFA, CH_2Cl_2, −78 °C, then flash chromatography; iv, O_3, CH_2Cl_2–MeOH (1:1), 5 min, −78 °C, then Me_2S; v, $LiAlH_4$, THF, reflux; vi, OsO_4 (cat.), $Na_3H_2IO_6$, AcOH (80%), 8 °C; vii, L-Selectride, THF, −78 °C; viii, LS-Selectride, THF, −78 °C.

plasma glucose levels in streptozotocin-induced diabetic mice. This alkaloid also enhanced amphetamine-induced sedation of locomotor activity, and exhibited significant antiinflammatory effect on prednisolone-induced edema in rat paw. Sparteine **216** increased induced smooth muscle contraction of isolated rat uterus, and both sparteine and cytisine increased histamine-initiated contraction of isolated guinea pig trachea.

12.2 Structural and spectroscopic studies

The seeds of *Lupinus albus* have yielded two new alkaloids, (+)-14-dehydro-10α-hydroxytermisine **217** and (−)-13α-hydroxy-5,6-dehydromultiflorine *N*-oxide **218**.[101] The customary spectroscopies were used for characterising the new compounds, and a range of NMR experiments provided evidence for the location and stereochemistry of the hydroxy groups in both metabolites. The NMR spectroscopic data were in excellent agreement with those obtained for the known alkaloids termisine **219** and 13α-hydroxy-5,6-dehydromultiflorine **220**. The final confirmation of the structure of **218** came from chemical correlation with **220**, into which it was easily converted by reduction with sulfur dioxide. The new alkaloid **218** could also be synthesised from **220** in 40% yield by oxidation with *m*-chloroperoxybenzoic acid.

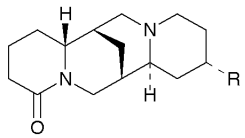
Full spectroscopic characterisation of a new alkaloid isolated from the seeds of *Lupinus varius* ssp. *orientalis* has led to the assignment of the structure as (−)-13β-hydroxymultiflorine **221**.[102] The equatorial disposition of the 13β-hydroxy group was confirmed by analysis of NMR spectra, NOE effects involving the axial 13α-H, and comparisons with the more common 13α-hydroxymultiflorine **222**, which was also isolated from the same plant source together with another twelve known alkaloids. (Incidentally, the article highlights the taxonomic confusion that frequently accompanies the identification of plants; *L. varius* is apparently a synonym for *L. digitatus*, *L. pilosus*, *L. hispanicus* and *L. micranthus*, all of which have appeared in this series of reviews at one time or another and have been used in good faith by the author of these reviews!) In the same study, thirteen alkaloids were isolated from the seeds of *L. hartwegii* (= *L. mexicanus*). These included two previously unknown metabolites, (+)-13α-hydroxyaphyllidine **223** and (+)-2β-hydroxyaphylline **224**. NMR analysis in particular facilitated the elucidation of the two structures, and spectroscopic comparisons with the known alkaloids (+)-aphyllidine **225** and (+)-aphylline **226**, also isolated in this work, clinched the assignments.

The unusual new alkaloid (+)-hupeol was isolated from Chinese *Maackia hupehensis* along with (−)-cytisine **214** as the main component (25% of total base) and seven other known alkaloids.[104] In methanolic solution, the new alkaloid exhibited two sets of NMR resonances in a 3:1 ratio; the spectra were very similar to those of cytisine apart from significant downfield shifts of the ^1H and ^{13}C signals at C-11 and C-13. The structures of the new compounds, assigned with the aid of a full complement of spectroscopic techniques, proved to be the epimeric (and probably equilibrating) hemiacetals **227**, with the dominant isomer possessing an axial OH group at the "anomeric" position. The absolute configuration of the new alkaloid was not determined. Hupeol is a biosynthetically interesting compound, since alkaloids of the cytisine class have long been regarded as the ultimate metabolites in the pathway of the lupin quinolizidines. The authors postulate that hupeol, which lacks a basic nitrogen, lies even further along the biosynthetic pathway for lupin alkaloids than does cytisine, and

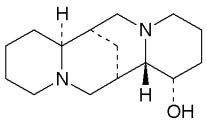
Table 1 Isolation and detection of alkaloids of the lupinine–cytisine–sparteine–matrine–*Ormosia* group[a]

Species	Alkaloid	Ref.
Lupinus albus (= *L. termis*)	(+)-14-Dehydro-10α-hydroxy-termisine[b] **217**	101
	(−)-13α-Hydroxy-5,6-dehydro-multiflorine *N*-oxide[b] **218**	
Lupinus hartwegii	(+)-13α-Hydroxyaphyllidine[b] **223**	102
	(−)-2β-Hydroxyaphylline[b] **224**	
Lupinus varius ssp. *orientalis*	(−)-5,6-Dehydromultiflorine	102
	(+)-Epilupinine	
	(+)-Epilupinine *N*-oxide	
	(−)-13α-Hydroxymultiflorine **222**	
	(−)-13β-Hydroxymultiflorine[b] **221**	
	(−)-Multiflorine *N*-oxide	
	(−)-13α-Tigloyloxymultiflorine	
Lygos (= *Retama*) *raetam*	Sparteine *N*(16)-oxide	103
Lygos raetam var. *bovei*	Anagyrine **213**	103
	Baptifoline	
	Cytisine **214**	
	5,6-Dehydrolupanine	
	N-Formylcytisine	
	Lupanine **212**	
	N-Methylcytisine **215**	
	Retamine **211**	
	Sparteine **216**	
Maackia hupehensis	(−)-Cytisine	104
	(−)-Epibaptifoline	
	Epilupinine	
	(−)-*N*-Formylcytisine	
	(+)-Hupeol[b] **227**	
	(−)-Lusitanine	
	(−)-*N*-Methylcytisine	
	N-(3-Oxobutyl)cytisine	
	Rhombifoline	
Sophora jaubertii	Allomatrine	105
	Anagyrine	
	Sophocarpine	
	Sophocarpine *N*-oxide	
	Sophoranol	
	Sophoridine	

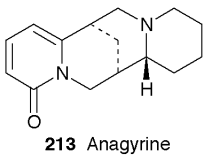
[a] Only new alkaloids and new records for a given species are listed in the Table. Structures of most known alkaloids may be found in previous reviews in this series. [b] New alkaloids.



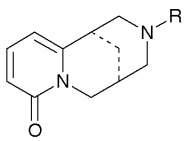
210 R = OH
212 Lupanine R = H



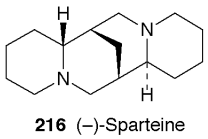
211 Retamine



213 Anagyrine



214 (–)-Cytisine R = H
215 R = Me

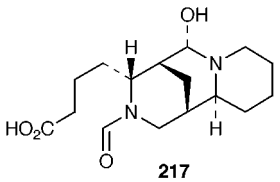


216 (–)-Sparteine

is perhaps an intermediate in the catabolism of lupin alkaloids to non-basic components.

Regioselective bromination of (−)-multiflorine **228** with *N*-bromosuccinimide (NBS) in dichloromethane gave the 3-bromo derivative **229** in 47% yield, while bromination with solid NBS yielded a 1:1 complex of **229** and succinimide (72%)—apparently the first reported example of a molecular complex formed between succinimide and a bisquinolizidine alkaloid.[112] X-Ray crystallography revealed that the imide was hydrogen bonded to N(16) as shown in **230**, with ring C of the alkaloid in the chair conformation expected for multiflorinium cations and a *cis* ring junction between rings C and D. Succinimide could be removed from the complex to give **229** in 76% yield by treating it with aqueous potassium carbonate solution. The crystal structure of **229** itself differed from that of the complex in that ring C adopted the typical boat conformation and *trans*-C/D ring junction found in alkaloids of the sparteine class. IR and NMR data were reported for both **229** and **230**, and analysis of coupling constants permitted an evaluation of the contribution of ring C chair conformations to the structures of both substances in solution.

The absolute configuration of natural aloperine **231** has been established as (6*R*,7*R*,9*R*,11*S*) by crystallographic analysis of the native alkaloid and its dihydrochloride monohydrate.[113] Other crystal structures reported during the review period include those of dichloro[(−)-sparteine-*N*,*N*′]copper(II)[114] and 6-methyl-*N*(16)sparteinium iodide.[115] A more unusual study deals with the measurement of the absorption and vibrational circular dichroism spectra of (−)-sparteine **216**, and the



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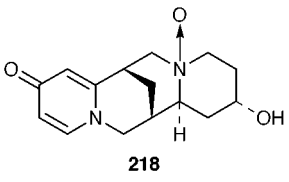

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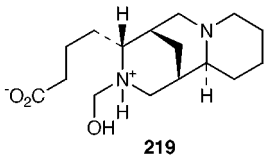

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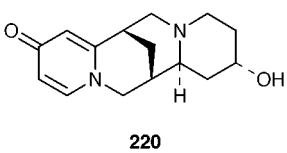

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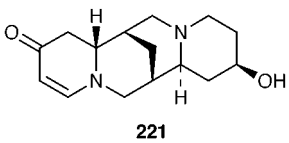

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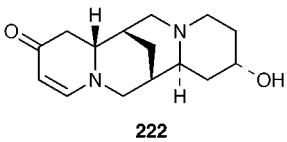

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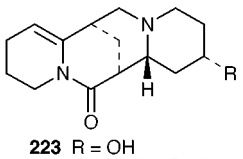
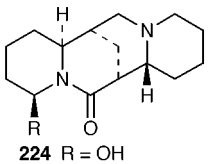
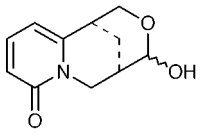


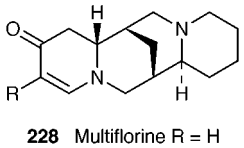
223 R = OH
225 Aphyllidine R = H



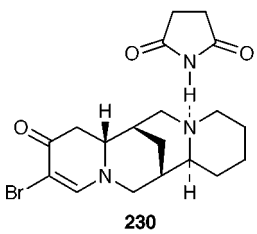
224 R = OH
226 Aphylline R = H



227 (+)-Hupeol



228 Multiflorine R = H
229 R = Br



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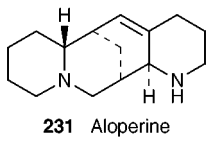


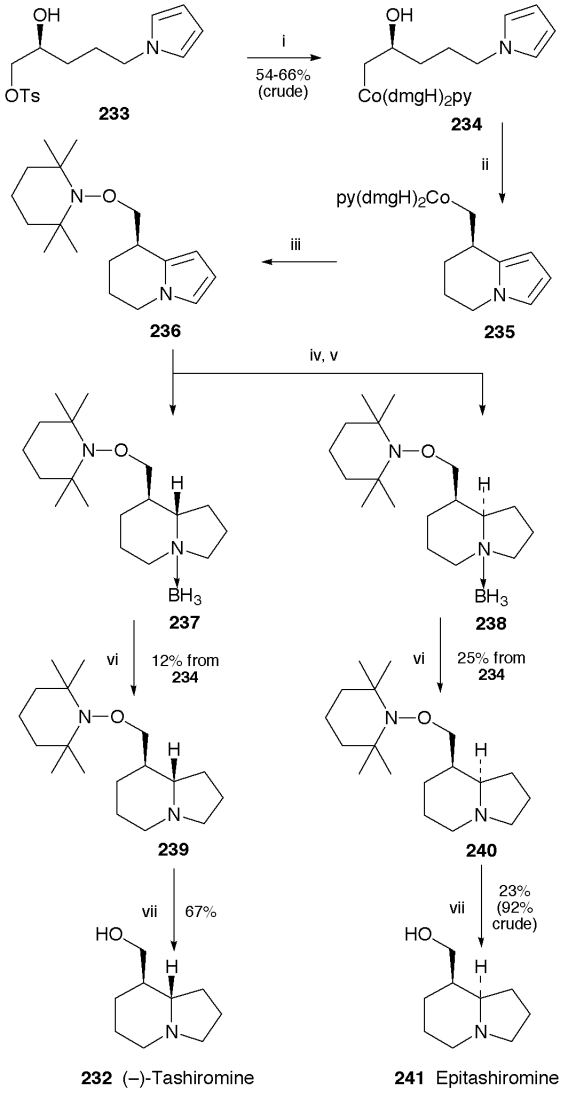
231 Aloperine

interpretation of the results on the basis of *ab initio* calculations.[116] Excellent agreement between experimental and theoretical frequencies and intensities was found in the mid-IR

region, and calculated geometries of the lowest energy conformers compared well with those known from X-ray crystallographic studies. The solution structures of the complexes formed between (−)-sparteine and other amine ligands on the one hand, and lithium 2,2,4,6,6-pentamethylpiperidide[117] and *n*-butyllithium[118] on the other, have been studied by ^{6}Li and ^{15}N NMR spectroscopy. Relative binding constants and energies were determined; and in the latter case the complex interactions between different ligands in mixed butyl-bridged dimers were evaluated.

12.3 Synthesis and other chemical studies

The use of a cobaloxime π-cation as a reactive intermediate is the feature of interest in a new synthesis of (−)-tashiromine **232** by Gage and Branchaud (Scheme 20).[119] The cobalt-containing



Scheme 20 *Reagents:* i, Na[Co(dmgH)$_2$)py], MeOH; ii, PPTS, $CHCl_3$; iii, TEMPO, *hv*, MeOH; iv, H_2, Rh/Al_2O_3, EtOH; v, BH_3·THF, THF; vi, EtOH, reflux; vii, Zn, HOAc–H_2O.

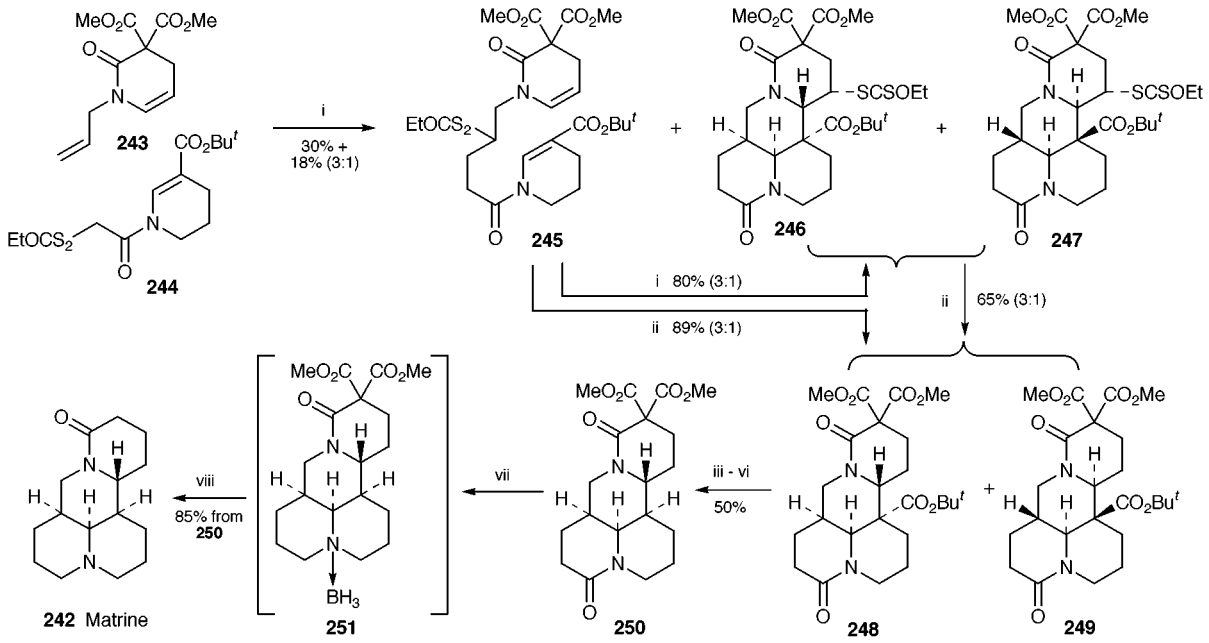
substituent was introduced by treating (*S*)-tosylate **233** (prepared in seven steps and 17% yield from L-glutamic acid; 96% ee) with Na[Co(dmgH)$_2$py]. The acid-sensitive product (*S*)-**234** was immediately treated with pyridinium toluene-*p*-sulfonate (PPTS) to form the desired cationic species *in situ*; highly enantioselective intramolecular capture by the pyrrole ring afforded the thermally unstable cobalt-containing tetrahydroindolizine **235**. Photochemically-induced oxygenative cleavage with 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO) provided (*R*)-**236**, catalytic hydrogenation of which yielded a mixture of two oxygen-sensitive diastereoisomeric products. *N*-Protection was accomplished by formation of borane complexes **237** and **238**, which proved to be separable by column chromatography. The protecting groups were removed by heating in ethanol to give the TEMPO-bound products **239** and **240** in overall yields of 12% and 25% respectively based on the cobaloxime **234**. Hydrogenolysis of the hydroxylamine N–O bond was effected with zinc dust and acetic acid to yield (−)-tashiromine **232** from **239** and the unnatural epitashiromine **241** from **240**. The enantiomeric purity of (−)-**232** was found to be 96% by ^{19}F NMR spectroscopic analysis of its Mosher esters. Additionally, since conversion of racemic epitashiromine into tashiromine has previously been demonstrated,[120] the preparation of **241** also represents a formal synthesis of (+)-tashiromine, *ent*-**232**.

The first new synthesis of matrine **242** in over a decade, by Zard and co-workers,[121] makes imaginative use of a stereocontrolled radical cascade for constructing the alkaloid's tetracyclic skeleton (Scheme 21). Heating a mixture of the *N*-allyllactam **243** (3 equiv.) and xanthate **244** (1 equiv.) in benzene with lauroyl peroxide as initiator gave the simple coupled product **245** (30%) and a mixture of the two stereoisomeric tetracyclic products **246** and **247** (ratio 3:1) in a yield of 18%. In this remarkable reaction, four C–C bonds and five contiguous stereogenic centres were created simultaneously with reasonable efficiency and fair stereoselectivity. Furthermore, re-exposure of **245** to lauryl peroxide also set off the radical cascade to give the same 3:1 mixture of tetracycles **246** and **247** in 80% yield. The major product has the requisite stereochemistry for matrine, while the minor product belongs to the allomatrine series. Removing the xanthate group from the tetracyclic mixture was also done with lauroyl peroxide, but in the presence of propan-2-ol as both solvent and hydrogen atom transfer reagent; the yield of products **248** and **249** was 65%. The combination of lauroyl peroxide and propan-2-ol also took the bicyclic compound **245** all the way to the 3:1 mixture of **248** and **249** in 89% yield. Chromatographic separation of the isomers was followed by selective hydrolysis of the bridgehead *tert*-butoxycarbonyl group of **248** and decarboxylation by Barton methodology, delivery of hydrogen taking place on the less hindered convex face to give the bislactam **250**. Chemoselective reduction of the lactam group in ring A with borane—dimethyl sulfide was achieved because the lactam in ring D is masked by the two adjacent ester groups. When heated with dilute hydrochloric acid, the intermediate borane–tertiary amine complex **251** underwent simultaneous decomplexation as well as hydrolysis and decarboxylation of the ester groups to give the hydrochloride salt of (±)-matrine **242** in 85% yield.

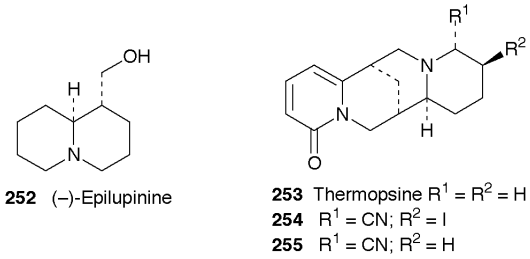
Experimental details of the enantioselective synthesis of (−)-epilupinine **252** by Naidu and West, communicated in 1994[122] (*cf.* ref. 6*h*), have been published in a full paper that also contains additional information on aspects of the stereoselectivity.[123] The biomimetic synthesis of alkaloids such as lupinine and sparteine *via* tetrahydropyridine intermediates by Wanner and Koomen, previously highlighted in these pages (*cf.* ref. 6*i*), has been revisited in symposium reports.[124,125] Treatment of thermopsine **253** with cyanogen iodide in boiling chloroform failed to give the expected von Braun degradation, yielding instead a mixture of the *trans*-15-cyano-14-iodo product **254** (55%) and the 15-cyano product **255** (5%), perhaps through an iminium ion intermediate.[126]

12.4 Enantioselective transformations mediated by (−)-sparteine

An important review by Hoppe and Hense deals with several aspects of enantioselective synthesis involving (−)-sparteine-complexed lithium–carbanion pairs.[127] Themes covered include syntheses with configurationally labile ion pairs (*e.g.*, lithiated allylic carbamates, benzylamine derivatives, indenides and

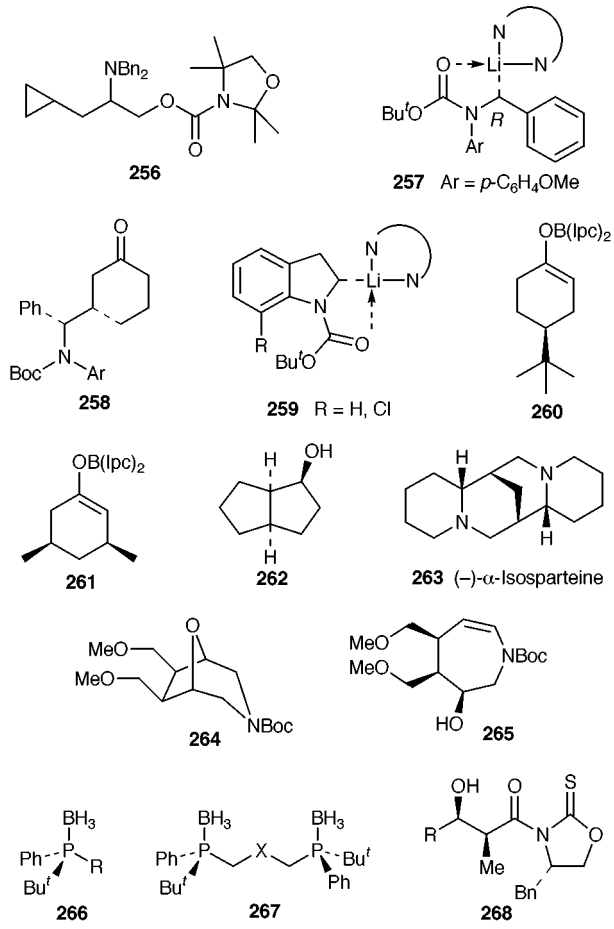


Scheme 21 *Reagents:* i, lauroyl peroxide (cat.), C_6H_6 (0.3 M in **244**), reflux; ii, lauroyl peroxide (cat.), Pr^iOH, reflux; iii, TFA, CH_2Cl_2; iv, $(COCl)_2$, CH_2Cl_2; v, *N*-hydroxy-4-methylthiazolinethione, Et_3N; vi, *tert*-dodecanethiol, C_6H_{12}, AIBN (cat.), reflux; vii, $BH_3{\cdot}Me_2S$, THF; viii, 2 M HCl, reflux.



252 (–)-Epilupinine

253 Thermopsine $R^1 = R^2 = H$
254 R^1 = CN; R^2 = I
255 R^1 = CN; R^2 = H



256

257 Ar = *p*-C_6H_4OMe

258

259 R = H, Cl

260

261

262

263 (–)-α-Isosparteine

264

265

266

267

268

cinnamic amides; homoenolates; α-thiocarbanions), syntheses with configurationally stable chiral ion pairs formed by kinetic deprotonation of achiral or racemic precursors (*e.g.*, alkyl carbamates and heteroatom-substituted alkyl carbamates, *N*-Boc pyrrolidines, 1-hydroxyalkyllithium derivatives, and substrates with axial or planar chirality), and sparteine-induced carbolithiation of alkenes. Hoppe's own papers on (−)-sparteine-mediated reactions published during the period under consideration include a synthesis of enantiomerically enriched β-cyclopropylalaninol derivatives from racemic carbamate **256**;[128] and enantioselective cyclocarbolithiation of alkenyl and alkynyl carbamates for the synthesis of enantiomerically pure cyclopentanols and 2-alkylidenecyclopentanols respectively.[129,130]

Beak and co-workers continue to make valuable contributions to the literature of enantioselective transformations mediated by (−)-sparteine **216**. Previously communicated studies on dynamic kinetic or thermodynamic resolution of lithiated intermediates in the enantioselective benzylic substitution reactions of *N*,*N*-diisopropyl-*o*-ethylbenzamide and *N*-pivaloyl-*o*-ethylaniline have been amplified in an important full paper.[131] In benzylic substitution reactions of *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine, it is the deprotonation step itself that is enantioselective; ^{6}Li and ^{13}C NMR spectroscopic studies established the monomeric stucture of the configurationally stable lithiated (*R*)-diastereoisomer **257**, which was formed in a 91 : 9 ratio with the alternative isomer when the substrate was treated with (−)-sparteine and *n*-butyllithium in toluene-d_8 at −78 °C.[132] The anions (and the cognate *N*-allyl systems) underwent highly diastereoselective and enantioselective conjugate addition to enones; with cyclohexenone, for instance, adduct **258** was formed as the sole diastereoisomer in 92% ee.[133] Deprotonation-substitution reactions of *N*-Boc indolines were also found to proceed through configurationally stable intermediates **259**.[134]

Several examples of sparteine-assisted deprotonations have been reported by other workers. Recent applications of Hoppe's methodology include syntheses of *N*-Boc-protected phenylglycines,[135] and of enantiopure 5-substituted butyrolactone intermediates *en route* to an algal nonaether.[136] Cuprates made from sparteine-complexed 2-lithio-*N*-Boc-pyrrolidine coupled efficiently with vinyl or propargyl iodides,[137] and copper(I)

cyanide catalysed the palladium-induced coupling of the same lithiated intermediate with aryl and vinyl iodides;[138] interestingly, the enantioselectivities of these processes were not determined. Other useful transformations involving (−)-sparteine-mediated deprotonation include a highly enantioselective enolborination of prochiral and racemic cyclohexanones to give products such as **260** and **261** (ee *ca.* 90%),[139] diastereoselective and enantioselective alkylation of the boron trifluoride complex of *N*-methylisoindoline (ee 64–89%),[140] and [2,3]-sigmatropic rearrangements of α-propargyloxyacetic acids to give allene-containing α-hydroxy acids (ee 5–49%).[141] The α-deprotonation and rearrangement of cyclooctene epoxide to the bicyclic alcohol (−)-**262** was more enantioselective with (−)-α-isosparteine **263** (ee 69–84% depending on base and temperature) than with (−)-sparteine (ee up to 78%), but the reverse was true for the epoxide of cyclodecene.[142] Ring opening of the 3-aza-8-oxabicyclo[3.2.1]octane **264** with *sec*-butyllithium and (−)-sparteine at −105 °C gave azepine **265** in 97% yield and 60% ee.[143] Enantioselective lithiation–substitution of heteroatomic hydrides has also been achieved, as in the high-yielding deprotonation and alkylation of racemic *tert*-butyl(phenyl)phosphine–borane complex to give *P*-chiral products of the form **266** (ee 82–95%) and **267** (ee >99%).[144] Related phosphine–borane complexes were the precursors in the synthesis of *P*-chiral bis(trialkyl)phosphine ligands for rhodium-catalysed enantioselective hydrogenations.[145]

(−)-Sparteine also exerts stereocontrol in addition reactions of anionic substrates to unsaturated acceptors. Representative examples demonstrating good to excellent selectivities include the addition of alkyllithiums[146] or 2-thiazolyllithium[147] to aldimines, aldol condensation between titanium enolates of *N*-acyloxazolidinethiones to give *syn*-diastereoisomers such as **268**,[148] and the reaction of benzothiazoyl(chloroalkyl)lithiums with aldehydes or ketones to give chlorohydrins and thence benzothiazolyl-substituted epoxides.[149] However, a sparteine-mediated Wadsworth–Horner–Emmons addition between diethyl benzylphosphonate and 4-*tert*-butylcyclohexanone gave only a 17% ee of the expected benzylidene product.[150] The presence of (−)-sparteine may influence the enantioselectivity of conjugate additions, as shown by reactions between lithium thiophenolate and methyl crotonate (ee 15%),[151] alkyllithiums and 2,6-di-*tert*-butyl-4-methoxyphenyl alkenoates (ee mostly >80%),[152] and aryllithiums and *tert*-butyl alkenoates (ee up to *ca.* 78%).[153] Examples of enantioselective polymerisations of alkenoates and related compounds in the presence of sparteine are too numerous to mention individually. Carbolithiation of acetals made from cinnamyl alcohol with alkyllithiums at −50 °C has been shown to give excellent yields of 2-alkyl-3-phenylpropanols (ee 85% or better); furthermore, when the lithiated intermediates were warmed to ambient temperature, enantiomerically pure *trans*-1-alkyl-2-phenylcyclopropanes were formed in yields of *ca.* 60%.[154] Other sparteine-assisted carbolithiations that proceeded with noteworthy selectivity include those of β-alkyl styrenes (ee 75% or better)[155] and the intramolecular reaction of *N*-lithiomethyl-*N*-(but-3-enyl)-amines to give substituted pyrrolidines (de 58–75%).[156] A more unusual reaction involved addition polymerisation of 3,3-dialkylcyclopropenes catalysed by (η^3-allyl)palladium complexes containing (−)-sparteine as ligand; partially stereoregular polycyclopropanes possessing a slight excess of meso units were obtained.[157]

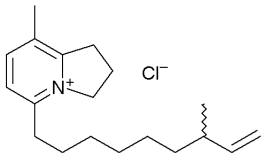
Katsuki and co-workers have shown that achiral manganese(III)–salen complexes are able to epoxidise styrene, indene and various chromenes asymmetrically (ee up to 73%) in a dichloromethane–water medium with iodosylbenzene as oxidant and 0.4 equivalents of (−)-sparteine as chiral modifier.[158] At this stage, yields remain very poor, but the transformation clearly has great potential. Asymmetric oxidation of methyl phenyl sulfide to the corresponding (*S*)-sulfoxide (ee 25%; yield 71%) was also demonstrated.

13 Alkaloids from marine sources

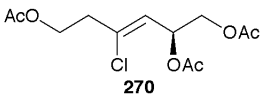
Specimens of the blue-green alga *Lyngbya gracilis* collected from the Palmyra atoll lagoon in Polynesia have yielded a single metabolite, (+)-louludinium chloride **269**.[159] The structure of this crystalline compound was elucidated spectroscopically, and full ^{1}H and ^{13}C NMR data were obtained. The absolute configuration is unknown. This is the first reported isolation of a 2,3-dihydro-1*H*-indolizinium system from a marine source.

The absolute configuration of (+)-halichlorine, a potent inhibitor of VCAM-1 induction, was not determined when its structure was revealed in 1996.[160] Methanolysis of the macrolide followed by ozonolysis and acetylation of the resulting product has now given the (*S*)-fragment **270**, the identity of which was established by direct comparison with both enantiomers of a synthetic sample made by lengthy routes from enantiomerically pure tartaric acids.[161] Since the relative stereochemistry of the alkaloid had previously been ascertained, the absolute stereochemistry must be as depicted in structure **271**. This is the mirror image of the originally proposed structure.

The previous review in this series described how an adaptation of the Mosher method permitted the determination of the 1*S*,2*S*,9*R*,10*R* absolute configurations of the sponge alkaloids saraine-1 and saraine-2 (*cf.* ref. 6*j*). Similar studies have now been performed on isosaraine-1 and isosaraine-2, the absolute configurations of which have been determined as 1*R*,2*R*,9*S*,10*R* (as shown in **272** and **273** respectively) by analysis of the Mosher esters of the alcohols formed by reducing the carbonyl groups.[162] The stereochemistry at C-3′ remains unknown. It is postulated that the two groups of alkaloids may be biogenetically linked by equilibration involving retro-Mannich/Mannich reactions through iminium ion intermediates such as **274** and the corresponding enamine **275**.



269 Louludinium chloride



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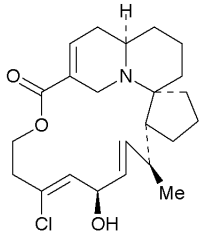
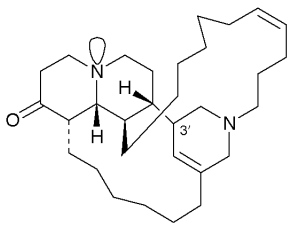
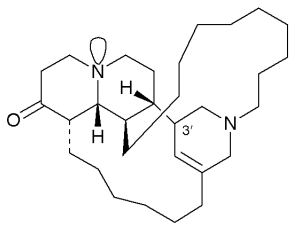


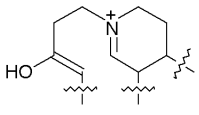
271 (+)-Halichlorine



272 Isosaraine-1



273 Isosaraine-2



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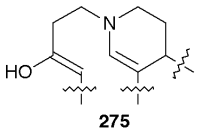
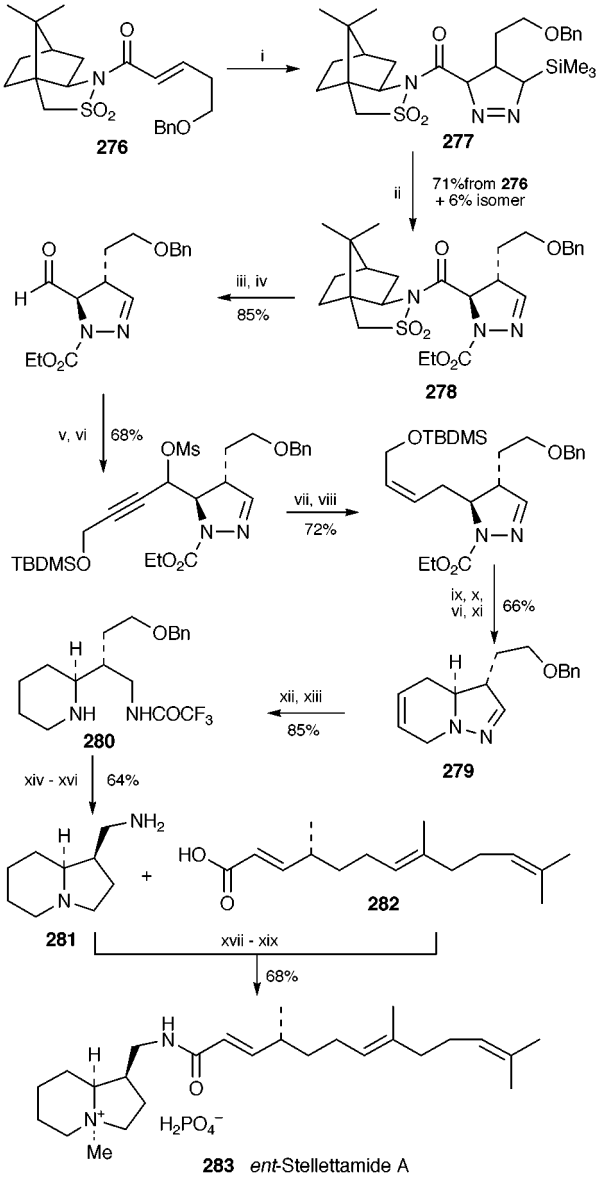


275

When the sponge metabolite stellettamide A (see below for structure) was first reported in 1990,[163] some antifungal and cytotoxic activity was also disclosed. A more comprehensive study has now revealed its ability to inhibit calmodulin, as demonstrated by a range of inhibition studies involving smooth muscle contraction, calmodulin-dependent enzymes and calmodulin itself.[164] In the meantime, the first total synthesis of

synthesis of stellettamide A (Scheme 22) has now provided evidence for the configuration of the stereogenic centre in the side chain as well as the compound's absolute stereochemistry.[165] Dipolar cycloaddition between (trimethylsilyl)diazomethane and the substituted acrylamide **276**, which incorporates the Oppolzer camphorsultam as chiral auxiliary, quantitatively yielded the pyrazoline adducts **277** as a 93:7 mixture of two diastereoisomers. Treatment with ethyl chloroformate and silver triflate induced loss of the nucleofugal silyl substituent and concomitant tautomerisation of the heterocycle to give **278** in 71% yield. Removal of the chiral auxiliary and construction of the piperidine ring as illustrated yielded the key bicyclic intermediate **279** (10 steps, 28% overall yield based on **278**). Completing this novel route to the indolizidine nucleus involved treating **279** with hydrogen and Raney nickel, which simultaneously reduced the C=C and C=N bonds and cleaved the N–N bond. Selective protection of the exposed primary amine group yielded **280**, which was converted in three simple steps into (1*R*,8a*S*)-1aminomethylindolizidine **281**, the heterocyclic core of the target alkaloid. Since the relative configuration of the side chain was unknown, both *R* and *S* versions of the trienoic acid **282** were prepared. DCC-mediated coupling of each acid with **281** followed by treatment of the products with iodomethane yielded two diastereoisomeric quaternary methiodide salts. Isomer **283**, prepared by anion exchange of the iodide salt with potassium dihydrogen phosphate, proved to have identical spectroscopic and chromatographic properties to those shown by natural stellettamide A, but its optical rotation had the opposite sign. Compound **283** is thus *ent*-stellettamide A; accordingly, the absolute configuration of the natural product must be (1*S*,4*S*,8a*R*,4′*S*).

A new total synthesis of clavepictines A and B, biologically active quinolizidine alkaloids from the tunicate *Clavelina picta*, proceeded *via* the enantiomerically pure lactam **284**, the absolute stereochemistry of which originated in the Sharpless asymmetric dihydroxylation of ethyl sorbate.[166] A significant step in the synthesis, the whole of which is outlined in Scheme 23, was the palladium-catalysed cross coupling of the vinyl triflate **285** with the enantiomerically pure alkyne **286**, made in three steps from (*S*)-(−)-glycidol. Reduction of the enamide product **287** with sodium cyanoborohydride in acidic medium resulted in the stereoselective introduction of the *trans*-2,6-substitution pattern into the piperidine ring of product **288**. Later steps of interest included the transformation of the propargyl alcohol **289** into the allenic ester **290** by orthoester Claisen rearrangement, and the novel silver(I)-mediated cyclisation of the δ-aminoallene **291** to produce a 7:1 mixture of quinolizidine **292** and its C6 epimer. The former, which contains the requisite stereogenic centres of the target alkaloids, was readily converted into (+)-clavepictine B **293** and the rather unstable (−)-clavepictine A **294** as shown. This route also provided confirmation for the absolute configurations of the alkaloids, which were assigned in a previous synthetic study as (3*R*,4*S*,6*S*,10*S*).[167] An interesting structural feature of the alkaloids is that they contain a rare *cis*-fused quinolizidine ring system, with axial methyl and oxygen substituents as shown in **295**.

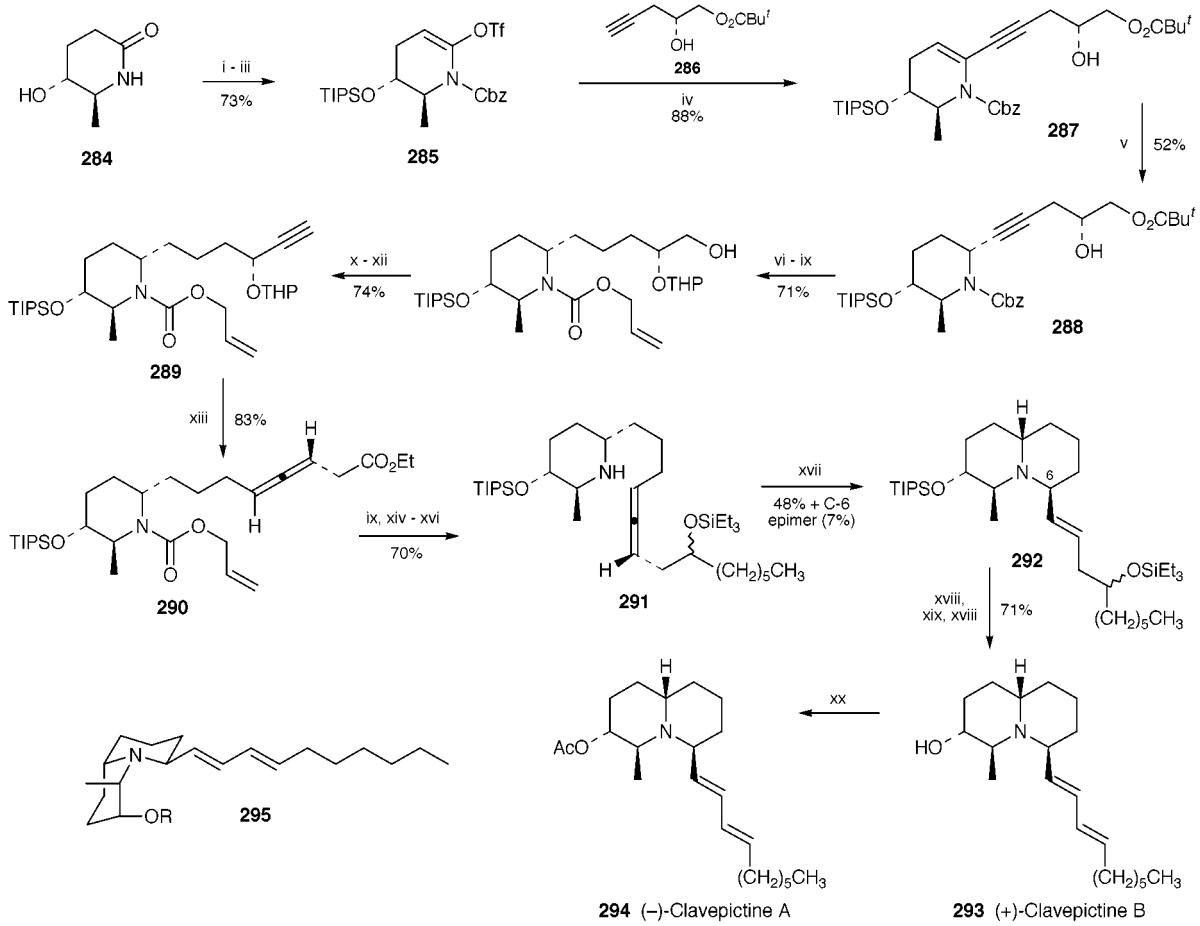


Scheme 22 *Reagents:* i, $N_2CHSiMe_3$, 4 Å molecular sieves, CH_2Cl_2–hexanes, rt; ii, EtOCOCl, AgOTf, CH_2Cl_2, 0 °C; iii, $LiAlH_4$, THF, −78 °C; iv, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to 0 °C; v, $TBDMSOCH_2C{\equiv}CMgBr$, THF, 0 °C to rt; vi, MsCl, Et_3N, CH_2Cl_2, 0 °C; vii, Bu_3P, $Pd_2(dba)_3$, NH_4O_2CH, C_6H_6; viii, H_2 (1 atm), $Pd/BaSO_4$, quinoline, MeOH, rt; ix, $Ba(OH)_2$, dioxane–H_2O, 100 °C; x, Boc_2O, aq. NaOH, THF, rt; xi, 10% H_2SO_4, dioxane, then 2M NaOH; xii, Raney Ni, H_2 (1 atm), EtOH, rt; xiii, CF_3CO_2Et, THF, 0 °C to rt; xiv, $Pd(OH)_2/C$, NH_4O_2CH, MeOH, reflux; xv, Ph_3P, CBr_4, Et_3N, MeCN, 0 °C to rt; xvi, 5% K_2CO_3, aq. MeOH, rt; xvii, DCC, DMAP, CH_2Cl_2, rt; xviii, MeI, K_2CO_3, MeOH, rt; xix, KH_2PO_4, 25% MeOH, then extract with CH_2Cl_2.

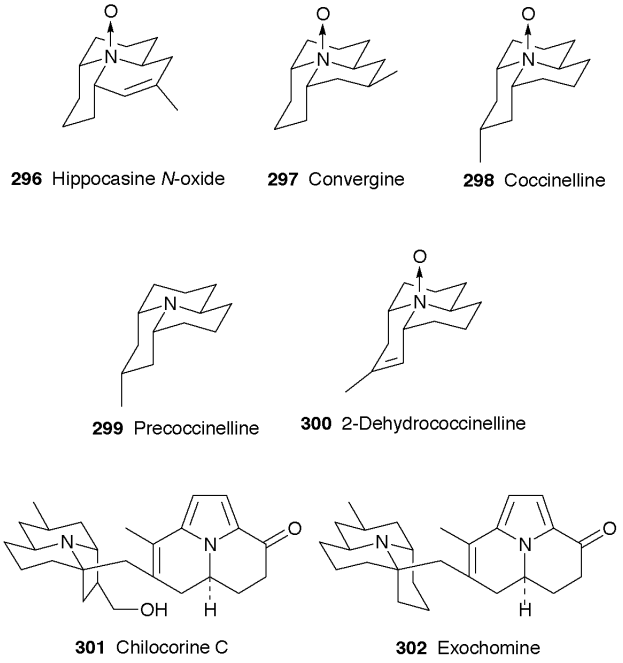
14 Alkaloids from coccinellid beetles

In a preliminary survey of the alkaloidal constituents of coccinellid beetles published in 1973, two unidentified minor alkaloids designated as AO1 (M^+, 191) and AO2 (M^+, 207) were detected in the European species *Anatis ocellata*.[168] A new isolation of (+)-AO2 from the same source has now resulted in its structural elucidation.[169] Spectroscopic studies, which included the determination of the skeletal connectivity by means of two-dimensional NMR experiments, suggested a structure similar to, but probably not identical with, the known alkaloid hippocasine *N*-oxide **296**. A comparison of ^{13}C NMR chemical shifts for the methine carbons adjacent to nitrogen with those of convergine **297** and coccinelline **298** indicated that AO2 had the same relative configuration as the latter. The matter was clinched by catalytic hydrogenation of AO2 over palladium on carbon in methanol, which resulted in the formation of precoccinelline **299**. Compound AO2 is thus proposed to be (+)-2-dehydrococcinelline **300**. It is likely that the minor alkaloid AO1 is the corresponding free base.

A new "dimeric" alkaloid, chilocorine C **301**, has recently been isolated as a minor constituent of the coccinellid beetle (ladybird) *Chilocorus cacti*.[170] The structure was determined on the basis of a range of spectroscopic experiments, especially long-range NMR spectroscopic correlations. The new natural product is unusual in that its saturated tricyclic moiety is a ring-contracted version of that found in the other three "dimeric" coccinellid alkaloids identified to date (*e.g.*, exochomine **302**)—and, in fact, of standard coccinellid 9b-azaphenalenes



Scheme 23 *Reagents:* i, TIPS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt; ii, BuLi, CbzCl, THF, −78 °C to −20 °C; iii, LiHMDS, THF, −78 °C , then 5-Cl-2-(NTf_2)pyridine; iv, $Pd(Ph_3P)_4$, CuI, Et_3N, THF, rt; v, $NaBH_3CN$, TFA, CH_2Cl_2, −30 °C to −15 °C; vi, H_2 (1 atm), 10% Pd/C, MeOH, rt; vii, $ClCO_2CH_2CH{=}CH_2$, Na_2CO_3, THF–H_2O, 0 °C; viii, dihydropyran, PPTS, CH_2Cl_2, rt; ix, DIBAL-H, CH_2Cl_2, −78 °C; x, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to 0 °C; xi, $(MeO)_2PCHN_2$, Bu^tOK, THF, −78 °C to 0 °C; xii, *p*-TsOH, MeOH, rt; xiii, $MeC(OEt)_3$, $EtCO_2H$ (cat.), 145 °C; xiv, $Me(CH_2)_5MgBr$, Et_2O, −78 °C; xv, Et_3Si-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C; xvi, $Pd(Ph_3P)_4$, dimedone, THF, rt; xvii, $AgNO_3$, acetone–H_2O, rt; xviii, Bu_4NF, THF, 0 °C; xix, Martin sulfurane, C_6H_6, rt; xx, Ac_2O, py.



such as those described in the preceding paragraph. The "missing" carbon atom appears as the hydroxymethyl branch, a unique feature in the coccinellid alkaloids that implies an unconventional step in the biosynthetic pathway.

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