## Pyrrolizidine alkaloids

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Pyrrolizidine alkaloids

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This review covers pyrrolizidine alkaloids isolated from natural sources. Topics include: aspects of structure, isolation, and biological/pharmacological studies; total syntheses of necic acids, necine bases and closely-related non-natural analogues. The literature from July 2001 to December 2012 is reviewed.

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Introduction

This review aims to continue the series of summaries of the field by D. J. Robins published in Natural Product Reports during 1984–1995 and continued in the same style by J. R. Liddell for six years from 1996. The current authors have focused on the synthetic aspects, and only complete total syntheses and identified formal syntheses have been included. The discussion is not limited to 1-azabicyclo[3.3.0]octane derivatives isolated from plants or sequestered from them in higher organisms; for example, ‘pyrrolizidines’ from bacterial and fungal sources, as well as those that bear little biosynthetic relationship to the plant pyrrolizidines are included. No pure methodology papers are discussed, nor are syntheses of non-natural and unlikely-ever-to-be-natural pyrrolizidines included. Selected syntheses of stereoisomers of known naturally-occurring polyhydroxylated pyrrolizidines are included. The review is structured as follows: first, selected aspects of pyrrolizidine structure, isolation, and biological studies are summarised; next, descriptions are given of the syntheses of necic acids, and then the synthesis of necine bases beginning with the important degradation product heliotridane and continuing with progressively more highly-hydroxylated molecules; finally, the syntheses are described of miscellaneous pyrrolizidines, that do not contain the hydroxymethyl pyrrolizidine motif common to the vast majority of the plant pyrrolizidines. Within each section, examples are described chronologically to convey a sense of developments over the review period.

Positions around the pyrrolizidine ring are numbered according to the IUPAC system recommended for the parent pyrrolozine:

Structural studies

Skvortsoy published several reviews compiling important findings on the stereochemical and conformational properties of pyrrolizidines, both natural and non-natural. Data compiled from several studies into the GLC separation of simple, isomeric
pyrrolizidine alcohols\(^2\) showed that the order of emergence of isomers is determined by the balance of intramolecular hydrogen bonds and hydrogen bonding with the column systems; this, in turn, depends on stereochemical features of each molecule. Accordingly, determining the proportions of these hydrogen bonds allows an assignment of the configuration of pyrrolizidine alcohols.

The effect of steric factors on the equilibrium between the cis- and trans- ring-fusion conformations of pyrrolizidines was discussed.\(^3\) N-unsubstituted examples exist predominantly in the cis- form due to angular strain present in the trans- conformer. Strong cross-ring non-bonding interactions, for example in C(3),C(5)-disubstituted pyrrolizidines, increases the proportion of the trans-form. This has relevance to the reactivity of pyrrolizidines, with functional groups lying inside the cage-like structure of the cis- form being less accessible to external reagents, and the outcome of reactions such as alkene hydrogenation that determine stereochemistry at the bridgehead position. The preferred conformation also influences the basicity of the nitrogen atom and physical characteristics such as IR stretches.

A third paper\(^4\) discusses the IR spectra (O–H stretching frequency) of simple pyrrolizidine alcohols, connecting these data to stereochemistry. Again, trends were ascribed to the presence and extent of intra- or intermolecular hydrogen bonding and interactions with the solvent.

The absolute configurations of the creatonotines and callimorphines, insect-specific pyrrolizidine alkaloids made by esterification of sequestered plant-derived necine bases, especially retronecine, with insect-derived necic acids, was determined by comparison with reference compounds.\(^5\) All possible stereoisomers of the necic acids were synthesised as their methyl esters and separated using GCMS, and retention times compared with those isolated from insects. Some variation in the stereochemistry of the C(2') position of the necic acids was observed in the samples isolated from insects, postulated to be due to epimerisation at this position after biosynthesis.

An NMR study conducted by Fleet’s group confirmed the structures of previously isolated australine-type alkaloids in order to be sure that all compounds were, in fact, distinct natural products.\(^5\) As part of this study, the group conducted a careful search for further pyrrolizidines in Castanospermum australe seeds, and discovered three new alkaloids (1–3). They also reported extensive biological testing of all isomers against a panel of glycosidase enzymes.

Confirmation of two related polyhydroxylated alkaloids was gained via single crystal X-ray diffraction structures for 3-epi-casuarine\(^7\) and 1-epi-alexine.\(^8\)

A detailed computational study of the conformational possibilities of a variety of N-fused azabicyclic compounds has been reported.\(^9\) Selected members of conformer libraries obtained by molecular mechanics (MM3) calculations were optimised at the MP2/6-31G* level; three stable cis-conformers and a trans-conformer were located using this approach.

**Isolation**

**New esters of known necine bases**

Retrohoustine 4, heliohoustine 5, and isoretrohoustine 6 were isolated along with lycopsamine from the leaves of Ageratum houstonianum, extracts of which are used in traditional Mexican Indian medicine for their anti-infective properties.\(^10\)

In a study into the alkaloids of Osyris alba, plant samples collected in France were shown to contain at least eight quinolizidine and eleven pyrrolizidine alkaloids, including the newly-identified ester janfesteine 7 ((7R)-hydroxyxychysin A).\(^11\) The pyrrolizidine alkaloids were, in general, found as their N-oxides.

New glycosides of thesinine have been reported: the glucoside 8, the first example of a glycosylated pyrrolizidine alkaloid to be isolated from the herb Borago officinalis,\(^12\) and the rhamnoside 9, isolated by two different groups. Thus, in 2008, 9 was reported to be present in the grass Lolium perenne as a ca. 1:1 mixture of E-
and Z-alkene isomers,\textsuperscript{13} it was isolated exclusively as the E-isomer (9′′) from the herb <i>Tephrosia kirilowii</i>.\textsuperscript{14} The stereochemistry of the necine base core was assigned in 9 based on the formation of (+)-isoretronecanol by saponification; this also corresponds to the absolute stereochemistry in thesinine isolated from <i>Borago officinalis</i>.\textsuperscript{15} Equivalent experiments were not reported for the other two glycosides (8 and 9′′).

A new macrocyclic pyrrolizidine alkaloid, acetylplatyphilline 10, was isolated from <i>Senecio arcticus</i> along with senecionine, platyphilline, and neoplatyphilline (amongst others).\textsuperscript{16}

Novel alkaloids 7,9-diangeloylplatynecine 11 and 8-epi-sarracine N-oxide 12 were among the pyrrolizidine alkaloids isolated from <i>Senecio macedonicus</i>.\textsuperscript{17} Another new compound, 8-epineosarracine, was detected by GC/MS analysis.

Among seven pyrrolizidine alkaloids obtained from the aerial parts of <i>Lithospermum canescens</i>, four were identified as new natural products and their structures determined to be the heliotridine esters 13–16 shown.\textsuperscript{18}

The same group also conducted analyses of a different species of the same genus, <i>Ligularia lankongensis</i>. First, two non-macrocyclic alkaloids lankongensisines A (22) and B (23)\textsuperscript{21} were identified; these appear to be transacylation products of alkaloids of the more common senecionine type. Later, another new diester pyrrolizidine was described, called simply lankongensisine 24.\textsuperscript{22} This cyclopentane-linked structure is unique among the pyrrolizidines; indeed, the pattern of substituents around the

Three related novel pyrrolizidines 17–19 were obtained from the aerial parts of <i>Onosma leptantha</i>.\textsuperscript{19} Two known alkaloids of the same type (echihumiline and its N-oxide) were also isolated from this source.

A study of the chemical constituents of <i>Ligularia tsangchanensis</i> resulted in the isolation and structural determination of three pyrrolizidine alkaloids. In addition to the known yamataimine, the novel <i>O</i>-acetyl derivative 20 was found, along with the corresponding <i>N</i>-oxide 21.\textsuperscript{20}

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cyclopentyl ring is unprecedented in the chemical literature.

Three new alkaloids were isolated from the roots of *Cynoglossum furcatum* and their structures assigned on the basis of spectroscopic evidence as isoechinatine 25, lactodine 26, a lactate ester of heliotridine, and viridinatine 27, a derivative of echinatine.

Further investigations by the same group on pollen isolated from *Senecio ovatus* suggested that the most prominent pyrrolizidine alkaloid present was the previously unreported metabolite, 2-hydroxysarracine 33.

Eight new pyrrolizidine esters (four, 34–37, of retronecine; one each of heliotridine, platynecine, isoretronecanol, and trachelanthamidine, 38–41, respectively) were isolated from *Anchusa strigosa* in two studies by the same group. All were tested for their antifeeding activity using lepidopteran larvae.

During efforts to find new muscarinic M3 receptor binding inhibitors, an extract from the dried bulbs of *Cremastra appendiculata* was found to be active. Isolation of its chemical constituents identified the new pyrrolizidine alkaloid cremastrine 42 as an active component.

An unusual pyrrolizidine medium-ring lactone, helindicine 43,
was isolated along with lycopsamine 44 from the roots of Heliotropium indicum. The authors report that this is the first example of a pyrrolizidine lactone from the genus Heliotropium. The authors noted the structural similarity of lycopsamine and helidicine and proposed that the latter derives from the former; perhaps of relevance to this proposal is that the two compounds are epimeric at the 2′-position.

Seven senecionine-type pyrrolizidine alkaloids were obtained from Senecio bicolor, ssp. cineraria, one of which was a novel compound assigned as O-acetyl jacobine 45.

An oxidised derivative of phenopyrrozin, p-hydroxy-phenopyrozin 46, was isolated from the marine fungus Chromocleista sp. alongside the parent compound. The structure was assigned on the basis of spectroscopic methods and the absolute stereochemistry determined by X-ray crystallography. This compound showed some antifungal activity (against Candida albicans, MIC = 25 µg mL⁻¹) but showed little antibacterial activity (against Staphylococcus aureus, MIC > 50 µg mL⁻¹), and no cytotoxicity against various cancer cell lines (at 5 µg mL⁻¹).

Senecivernine N-oxide 47 was isolated from a mixture of nine Bulgarian species of the Senecio genus. This compound was isolated as the N-oxide despite the inclusion of a reductive step during the isolation process, indicating incomplete reaction and a surprising stability of this N-oxide.

Phytochemical investigations into Brachyglottis hectori, a shrub separated from the Senecio genus, led to the isolation of five pyrrolizidine alkaloids. One of these was identified as a new structure, an O-angelyl regioisomer of petasinine 49 and named hectorine 48. The alkaloids are found mostly as their N-oxides in these plants and isolation was conducted after reduction with Zn dust.

The pyrrolic pyrrolizidine alkaloid 50 was isolated along with thirteen other compounds from whole-plant extracts of Cynoglossum gasuense. The structure was assigned on the basis of spectroscopic data, with the D-configuration of the glucopyranosyl moiety assumed on biogenetic grounds. A similar pyrrolizidine core was observed in the new pyrrolizidine glycoside 51 derived from the roots of Ligularia cymbulifera.

Two new pyrrolizidines were obtained from Senecio nemorensis and identified as petasinoside A 52 and N-chloromethylhectorine chloride 53 on the basis of NMR experiments, mass spectrometry, and combustion analysis. Although the authors make no reference to the possibility, it seems likely that the N-chloromethyl substituent (in 53) is introduced by alkylation of hectorine during the isolation process (extraction with dichloromethane).

Three new natural products were obtained from the roots of Paris verticillata, verticillatins A–C (54–56). Structural determination was achieved using a combination of NMR spectroscopy and hydrolysis to known components; MTPA ester derivatives were formed in order to determine the stereochemistry at hydroxylated
centres. These compounds, along with others isolated from the same source, were tested against four human tumour cell lines; verticillatins A–C showed weak cytotoxicity against the HCT15 cell line and were inactive against the other cell lines tested.

Along with sixteen known pyrrolizidines, the new alkaloid osyrisine 57 was identified in the semi-parasitic plant Osyris alba L. of Jordanian origin, the structure being assigned primarily on the basis of NMR spectroscopic analysis. This compound showed antiparasitic activity against Entamoeba histolytica and Giardia intestinalis.

Analysis of Crotalaria juncea L. led to the identification of three previously unknown alkaloids, found to be similar in structure to the macrocyclic pyrrolizidine juncine but differing in the ester substituent. These natural products were identified as diastereomers of one another and named isohemijunciines A–C (58). Interestingly, across all the alkaloids found in these plants, the roots and stems were found to contain almost exclusively the N-oxide form whereas the seeds contained a majority of the free base.

New pyrrolizidine cores

Two unprecedented pyrrolizidinone lactones CJ-16,264 59 and CJ-16,367 60 were isolated from the fermentation broth of the unidentified fungus CL39457. The structures were determined by NMR experiments but these did not allow an assignment to be made of the stereochemistry in CJ-16,367 (although it might reasonably be inferred by comparison with CJ-16,264). These compounds were found to inhibit the growth of a number multi-drug resistant Gram-positive bacterial strains as well as some Gram-negative bacteria. Both showed cytotoxicity against HeLa cells. Comparison of the activity of 59 and 60 indicated that the γ-lactone moiety was crucial for stronger antibacterial activity.

Soon after this report, closely-analogous pyrrolizidines UCS1025A 61 and B 66 were obtained from the fungus Acromonium sp. KY4917 and the structures assigned on the basis of NMR spectroscopy, modelling, and X-ray crystallographic analysis of a brominated derivative. UCS1025A was found to exist as a mixture of two keto-enol tautomers and a third form, a carboxylic acid, formed by β-elimination of the bridging lactone oxygen (cf. 60, above). UCS1025A could be converted into UCS1025B by oxidation with MCPBA and the authors proposed that this proceeds via epoxidation of the enedione; alternatively, direct hydroxylation of the enol form seems to offer a better electronic match between substrate and reagent. UCS1025A was shown to possess antimicrobial and telomerase inhibitory activity, and was antiproliferative against human tumour cell lines.

Analysis of the alkaloids in bulbs of Scilla socialis led to the discovery of seven new pyrrolizidine alkaloids 63–69 all showing similarity to known hyacinthacines but varying in their substitution pattern or stereochemistry around the pyrrolizidine core. Known pyrrolizidine hyacinthacine B3 was also isolated. Later, the same group identified more hyacinthacines 70–75 from the same source. The structure (73) assigned to hyacinthacine C4 is the same as that reported by the same authors for hyacinthacine C1 but the 13C NMR data do not match and they have opposite signs for specific rotation. Subsequent total syntheses of (+)-hyacinthacine B3 (70), (+)-hyacinthacine C3 (72), and (+)-hyacinthacine C5 (74) revealed inconsistencies between spectroscopic data for the synthetic samples and those reported for the natural products; therefore the structures assigned to these hyacinthacines do not seem to be secure. Some of these alkaloids showed selective glycosidase inhibitory activity.
the adhesion of HL–60 cells to Chinese hamster ovar y cells

Later, three new bohemamines 82–84 were isolated from marine-derived actinomycete, strain CNQ-583, a Streptomyces sp. The depicted structures indicate relative configurations; in some cases the absolute stereochemistry remains unconfirmed although Snider's total synthesis of both enantiomers of (+)-NP25302\(^{52}\) confirms the depiction shown for this alkaloid.

Three closely-related novel compounds, pumilines A–C, 85–87 were found in the seeds of the annual herb Crotalaria pumila as part of a study of pyrrolizidine alkaloid sequestration by Estigmene acrea and Grammia geneura larvae.\(^{53}\) Supinidine and subulacine were also identified. Assignments of the relative configuration in these alkaloids are incomplete and tentative.

A close examination of the components of the culture broth of Salinispora tropica strain CNB–392 led to the isolation of five pyrrolizidine lactams and two new salinosporamides, one of which (88) contains a pyrrolizidine core. This molecule is an apparent aza-Michael adduct of an enone analogue of the usual cyclohexene motif found in, for example, salinosporamide A.\(^{54}\)

Three new pyrrolizidine alkaloids were obtained from the whole plant extract of Echium glomeratum Poir.\(^{55}\) The structures of the three compounds 89–91 were determined by NMR experiments as diastereomers of a previously undescribed bridged pyrrolizidinium core. Both (4S,7S,8R)- and (4S,7S,8S)-petranine were identified conclusively, but the ring-junction stereochemistry of the third alkaloid 91 (= either ent-89 or ent-90) could not be confirmed due to loss of the sample before complete data acquisition (the reported \(^1\)H NMR data do not allow a distinction to be made). In light of the known ability of pyrrolizidines to undergo \(N\)-chloromethylation with dichloromethane, a solvent used extensively in the extraction

In a related study, further australine- and hyacinthacine-type alkaloids with extended side-chains (76–79) were isolated from Scilla peruviana bulbs.\(^{49}\) Some of these alkaloids showed potent inhibition of yeast \(\alpha\)-glucosidase (76: IC\(_{50}\) = 6.6 \(\mu\)M; 78: IC\(_{50}\) = 6.3 \(\mu\)M) or a bacterial \(\beta\)-glucosidase (78: IC\(_{50}\) = 5.1 \(\mu\)M).

A strain of Streptomyces sp., UMA-044, isolated from the sediment of a catfish pond, yielded a series of fractions with activity in a cell-cell adhesion inhibition assay.\(^{50}\) Isolation of active components of these fractions led to the identification of a new pyrrolizidine, NP25302 80, along with bohemamine 81, the known epoxy derivative of NP25302. Both were shown to inhibit the adhesion of HL-60 cells to Chinese hamster ovary cells expressing intercellular adhesion molecule ICAM-1. Later, three new bohemamines 82–84 were isolated from marine-derived actinomycete, strain CNQ-583, a Streptomyces sp.\(^{51}\)
process, these pyrrolizidines may be isolation artefacts formed from simpler alkaloids based on angeloyl-heliotridine or retronecine cores.

Three terpenyl-pyrrolizidine conjugates, bistellatazines A–C, 92–94, were identified in the extracts of a Stellatta sp (a marine sponge).56 The structures were identified by spectroscopic analysis and chemical degradation studies, and are the first reported examples of this structural type. A biosynthetic pathway was proposed, based on a Diels–Alder cycloaddition between C14- and either C11- or C14- fragments. The stereochemistry of the aminopyrrolizidine fragment was not assigned but this fragment is apparently a single enantiomer common to the three bistellatazines.

Investigations into the pyrrolizidine composition of Heliotropium transalpinum var. transalpinum Vell. led to the discovery of new natural product transalpinecine 95.57 Also isolated was the epoxypyrrolizidine 96 (the epoxide diastereomer of known subulacine, which was also isolated); this pyrrolizidine had been previously synthesised but not reported as a naturally product. The structures were assigned on the basis of spectroscopic data combined with computation to rationalise certain physical and spectroscopic characteristics of each compound.

An amide-substituted pyrrolizidine, pochonicine 97, was obtained from the fungal strain Pochonia suchlasporia var. suchlasporia TAMA 87.58 The structure was determined using NMR and MS techniques; the absolute stereochemistry was not determined. Pochonicine showed potent inhibition of a variety of β-N-acetylglucosaminidases, at a level comparable to that of nagstatin, a natural inhibitor; the authors state that this is the first report of GlcNAc-ase inhibition by a pyrrolizidine.

Full details were reported of the isolation and characterisation of 1-epi-alexine 98 from the Australian tree Castanospermum australe.59 This followed an earlier X-ray crystallographic analysis that also allowed assignment of the absolute stereochemistry.5 This new pyrrolizidine was found to be a weak inhibitor of Cellulomonas fim β-mannosidase.

Three unusual polyketide macrolactams, heronamides A–C, were isolated from a Streptomyces sp. (CMB-M0406) obtained from a sediment collected off Heron Island, Australia.60 Heronamide A (100) contains a pyrrolizidinone core but its biosynthesis is proposed to involve a transannular [π4, + π6s]-cycloaddition (which the authors refer to as a ‘4π + 6π tandem electrocyclization’) of an oxidised form of the macrolactam heronamide C (99). These new natural products and various synthetic derivatives showed no cytotoxicity (vs. HeLa and MDA-MB-231 cell lines) nor antibiotic activity (vs. three bacteria – Escherichia coli ATCC 11775, Bacillus subtilis ATCC 6051, Staphylococcus aureus ATCC 25923 – and a fungus, Candida albicans).
The new pyrrolizidine alkaloid 101 was isolated from Chinese Senecio vulgaris along with senecionine. The structure was determined based on NMR studies, with the absolute stereochemistry being assumed by analogy with other alkaloids obtained from this species. The authors note that since methanol was used in the extraction procedure, it is possible that the compound is an isolation artefact. The name proposed for this pyrrolizidine, vulgarine, had already been assigned to an unrelated alkaloid 31 from Echium vulgare.

Six new aromatic compounds – all esters of 2-(4-hydroxyphenyl)ethanol – were isolated from the endophytic fungus Colletotrichum sp. L10 from the tree Cephalotaxus hainanensis Li. One of these was assigned the pyrrolizidine lactam structure 102.

A new pyrrolizidine alkaloid was isolated along with eight known natural products from the roots of Ligularia achyrotricha, a plant used in Tibetan traditional medicine. The structure 103, an oxidised form (i.e. the 3-oxo-7a-hydroxy derivative) of bisline, was assigned on the basis of spectroscopic analysis of a 1.5 mg sample from 1.3 kg of air-dried roots; moderate cytotoxicity was found against HL-60 and SMMC-7721 cell lines (IC₅₀ ~12.0 µg mL⁻¹).

Revised Structures

By comparison with spectroscopic data of synthetic compounds, the structures of epohelmins A and B, lanosterol synthase inhibitors isolated from the fungal strain FKI-0929, were revised from epoxyazocanes 104 and 105 to pyrrolizidines 106 and 107, respectively. Key observations included discrepancies in the expected ¹H and ¹³C NMR shifts for the epoxide centres, along with the experimental observation that 4,5-epoxyazocanes readily cyclise to 1-hydroxy pyrrolizidines. A separate total synthesis effort confirmed this revised assignment.

The structures originally reported for three alkaloids obtained from the culture broth of Streptomyces sp. (strain HKI0297) and named jenamidines A–C (108–110) were called into question by Snider, based on his analysis of their reported and expected NMR data. Model piperidone structures were prepared which provided experimental support for the expected NMR data, but these differed significantly from those reported for the jenamidines. This led to a reassignment of the piperidone structures to the hydroxypyrrolizidinones 111–113 for jenamidines A–C, respectively. These reassignments were subsequently confirmed by total synthesis.
Uniflorines A and B were isolated in 2000 and were deduced to contain a 6,5-indolizidine core (114 and 115, respectively); however, the total synthesis of 114 in 2004 by Pyne et al. along with the syntheses of 1-epi- and 1,2-di-epi- analogues indicated otherwise and further investigation suggested that the structures are, in fact, pyrrolizidines 116 and 117.

This was soon followed up in Pyne’s group, who then reported a total synthesis of (+)-uniflorine A to prove unequivocally that the revised structures were correct.

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**Biological studies**

**Bioactivity**

Investigations into the use of SC-53116 as a 5-HT\(_4\) agonist for use as a gastrointestinal prokinetic agent found that, although active, SC-53116 showed toxicity deriving from oxidation of the pyrrolizidine ring. This could be avoided by methylation at the bridgehead position, this analogue (118) being synthesised as the racemate. Unfortunately, 118 was found to be significantly less potent than the parent natural product and was not taken forward. Further investigations on a wider variety of analogues led to the discovery of a number of effective and selective ligands for the 5-HT\(_4\) receptor and the interesting discovery that ent-SC-53116 does not show the same mutagenic toxicity.

Computational studies into diversification of the core scaffold of known nictonic acetylcholine receptor (nAChR) ligands PNU-282,987 and SSR180711 led to the identification of a novel pyrrolizidine-containing scaffold 127 which, along with three other novel compounds, showed strong inhibition of the receptor. The known ligands were partial agonists of the receptor, but pyrrolizidine 127 was found to be a non-competitive antagonistic ligand, possibly causing blockade of the receptor channel.
The safety of the traditional Chinese herbal medicine Chuan Zi Wan (CZW) was explored with respect to its pyrrolizidine alkaloid content potentially deriving from the *Ligularia* species involved in its preparation. An HPLC-ESI analysis identified 26 potentially toxic pyrrolizidine alkaloids, which, apart from clivorine (the major alkaloid present), ligularine, hodgsonine, and ligularizine, had not been previously observed in this preparation. The total pyrrolizidine alkaloid content was found to be ~8.0 mg g⁻¹ of the dried extract, a level that could pose a health threat to users of CZW.

**Metabolism**

A long-term study of riddelliine carcinogenicity found that male and female rats, and male mice, developed liver tumours after prolonged exposure, whereas female mice did not. The toxicokinetics of this pyrrolizidine alkaloid were determined by measurement of serum levels of the parent compound as well as the N-oxide and hydrolysis product, retronecine, after administration of riddelliine via oral gavage. High levels of the polar metabolites were observed in both genders of both species, suggesting extensive and rapid metabolism of the alkaloid. Although the observed toxicokinetics could explain the gross toxicity data in male and female rats, there must be other factors at play in the tumourogenicity of the drug, and the species/gender differences observed in this. Potentially, further metabolism of the N-oxide metabolite to a reactive pyrrolic species could be responsible. It was demonstrated that, under hypoxic conditions, metabolism of riddelliine N-oxide by rat liver microsomes leads to the same DNA adducts as seen with the dehydro-pyrrolizidine metabolite formed from the parent riddelliine. Rats dosed with 1.0 mg kg⁻¹ day⁻¹ of the N-oxide for three days showed a 2.6-fold lower level of DNA adducts than produced in animals dosed with riddelliine. Initial reduction of the N-oxide to the parent pyrrolizidine, and subsequent metabolism to the dehydro-pyrrolizidine was proposed; thus, riddelliine N-oxide is a progenotoxin leading to hepatocarcinogenesis.

An HPLC method was used to determine the fate of isolate (from *Ligularia duciformis*) in rat and mouse liver microsomal enzyme systems. Partial deacetylation occurred giving the known bisline (not shown) and a new structure, bisline lactone 128, the transacylation product of bisline. This compound and bisline (which interconvert at physiological pH) show lower in vivo hepatotoxicity than the parent isolate, implying a role for liver esterases in detoxifying this pyrrolizidine alkaloid.

Dehydromonocrotaline was found to be toxic to astrocytes at micromolar concentrations, and led to hypertrophy in the cells and increased glial fibrillary acidic protein (GFAP) expression even at sub-micromolar concentrations. Higher concentrations of the metabolite, from 10–500 µM, caused membrane damage and retraction of cellular processes, leading to lower GFAP expression. Condensed and fragmented chromat in these cells suggested apoptosis was induced at concentrations >100 µM.

Oxidation of retronecine-type pyrrolizidine alkaloids by CYP450 enzymes, reportedly in large part by the 3A and 2B isoforms, leads to formation of reactive pyrrolic metabolites which can interact with proteins and DNA resulting in various adducts and cross-linked species. This high reactivity, and thus short half-life, suggests that these metabolites could bind covalently to the P450 protein, thus acting as a mechanism-based or suicide inhibitor. Investigations into the effects of metabolism of monocrotaline and retrorsine found that, indeed, retrorsine was a mechanism-based inactivator of P450 3A4 in the presence of NADPH whereas monocrotaline was found not to inactivate any of the isoforms tested. Further work identified 3A4 and 2C19 as the major P450 isoforms responsible for metabolic activation of these two alkaloids.

An alternative metabolic pathway, direct N-glucuronidation of intact pyrrolizidine alkaloids, has been identified and studied. The extent of metabolism via this pathway was found to differ between species, with higher levels of N-glucuronidation seen, for example, in humans than in mice or rats, and the kinetics of the process also varied across species.

Metabolic activation of pyrrolizidine alkaloids to dehydropyrrolizidine alkaloids, followed by irradiation with UV light, generated reactive oxygen species (ROS), including singlet oxygen and superoxide ion, leading to peroxidation of lipid species. The parent pyrrolizidines or N-oxides did not mediate ROS formation, implicating the dehydro-metabolites as photosensitisers involved in the induction of skin cancer by these alkaloids.

These extensive researches by Fu and co-workers culminated in synthetic routes to chemical standards for the unambiguous identification of four DNA adducts produced during the metabolism of riddelliine in rats (as a validated model for human metabolism). These molecules, confirmed as the deoxyadenosinyl- and deoxyguanosinyl-dehydrosupinidine adducts 129–132, have potential application as biomarkers for pyrrolizidine alkaloid exposure and pyrrolizidine alkaloid-induced tumour formation.
Synthetic studies

Necic acids

Syntheses of the occasionally complex acid components of naturally-occurring pyrrolizidine alkaloid esters seldom appear; however, there were a variety of syntheses reported of (+)-nemorensic acid and its close derivatives and one of (+)-latifolic acid. The synthesis of (+)-latifolic acid was accomplished by Wood’s group, using diastereoselective Claisen rearrangement to establish the stereochemistry in α-hydroxyketoester 134 (Scheme 1). In this key step O-alkylation of (S)-pent-3-en-2-ol with the rhodium carbenoid derived from diazo compound 133 is followed by [3,3]-shift via the arrangement 139 shown. Lewis acid mediated [1,2]-shift of the pent-3-en-2-yl group in α-ketoester 140 via a chelated or H-bonded intermediate gave key intermediate 134 with dr = 4:1. A third diastereoselective step, chelation-controlled borohydride reduction, set the final stereogenic centre. The lactone was generated by ozonolysis of the alkene and TPAP oxidation of the lactol. Finally, hydrogenolysis of the benzyl ester provided (+)-latifolic acid 136. The semi-synthesis of (+)-latifoline 138 was then accomplished by sequential esterification of (+)-retronecine with angeloyl chloride and (+)-latifolic acid in activated form as the imidazolidine.

Scheme 1 Reagents and conditions: (a) (S)-pent-3-en-2-ol, Rh₂(TFA)₄, C₆H₆, reflux; (b) BF₃·OEt₂, C₆H₆; (c) NaBH₄, ZnCl₂, Et₂O, THF, –15 °C; (d) O₃, CH₂Cl₂, –78 °C then Me₂S; (e) TPAP, NMO, 3Å MS, CH₂Cl₂, 0 °C; (f) H₂, Pd/C, EtOAc; (g) TBSCl, imidazole, CH₂Cl₂; (h) BuLi, THF, 0 °C then angeloyl chloride; (i) SiF₄, CH₃CN; (j) 136-imidazolidine, CHCl₃.

The first two routes to (+)-nemorensic acid featured electron transfer redox steps as key elements of the syntheses. In Moeller’s route, (Scheme 2) selective reduction of the carboxylic acid in chiral monoester 141 led to lactonisation. Enolate methylation and then dehydration of the lactone carbonyl in the presence of propane-1,3-dithiol gave ketene thioacetal 142. An oxidation-methylation-oxidation-allylation sequence provided 3°-alcohol 143 as a 3:1 mixture of diastereomers that was taken through to the following step. Anodic oxidation resulted in loss of an electron from the ketene thioacetal; cyclisation of the hydroxyl group onto the so-formed radical cation proved highly stereoselective with complete 1,2-anti-stereocontrol with respect to the dithiane and 3-methyl substituents (→ 144). The epimers at the allylated centre were then separable and all that remained was to cleave one carbon from the alkene by ozonolysis and release the two carboxylic acids as shown.
stereogenic centre was installed by stereoselective hydrogenation from the less hindered face with accompanying hydrodebromination. To access the 4-hydroxy derivative, the alkenyl was first epoxidised from the exo-face, then Zn-mediated 1,2-elimination (Boord reaction) gave an allylic alcohol from which hydroxyl-directed hydrogenation with Crabtree’s catalyst completed the 3,4-trans-stereochemistry.

![Scheme 4](image)

Scheme 4 Reagents and conditions: (a) rt then ChCl, CH₂O, 0 °C to rt then Et₂N, Et₂O, 0 °C; (b) BrCH₂CH₂C(=CH₂)R⁺, (±)2-nemorensic acid, CH₂Cl₂; (c) H₂, Pd/C, MeOH; (d) LDA, THF, –78 °C then TMSCl; (e) O₃, CH₂Cl₂, –78 °C then aq HCO₂H, H₂O₂, reflux; (f) DMDO, acetone, CH₂Cl₂; (g) Zn, NaI, MeOH, 65 °C; (h) H₂ (60 psi), [Ir(cod)py(PCI)]PF₆, CH₂Cl₂; (i) LDA, THF, –78 °C then TMSCl; (j) O₃, CH₂Cl₂, –78 °C then aq HCO₂H, H₂O₂, reflux.

In a variant, the same oxonium ylid was trapped by allene to give exomethylene cycloheptanone 155 (Scheme 5). This was elaborated by similar routes, terminating in racemic 3-hydroxy-cis-nemorensic acid 156 and racemic nemorensic acid 145. Stereoselective epoxidation was performed on the ethylidene acetate of ketone 155 (to prevent Baeyer–Villiger oxidation), then hydride reduction and acetel hydrolysis set up the same ozonolysis route to the hydroxylated nematic. Alternatively, following ring-cleavage, hydrogenation from the ‘front’ face was achieved by direction from the ester(s), leading to 145.

![Scheme 5](image)

Scheme 5 Reagents and conditions: (a) allyl, Rh₂(OAc)₆, CH₂Cl₂, 0 °C; (b) ethylene glycol, CSA, CH₂Cl₂; (c) MCPBA, CH₂Cl₂; (d) LiAlH₄, THF; (e) HCl, aq THF; (f) LDA, THF, –78 °C then TMSCl; (g) O₃, CH₂Cl₂, –78 °C then aq HCO₂H, H₂O₂, reflux; (h) TMSClH₂, hexane, MeOH; (i) aq KOH; (j) LDA, THF, –78 °C then TMSCl; (k) DMDO, acetone, CH₂Cl₂, 0 °C; (l) NaIO₄ aq THF; (m) AgNO₃, NaOH, EtOH; (n)
CH₃CHN₂, Et₂O, 0 °C; (o) H₂ (60 psi), [Ir(cod)py(Ph₃P)]PF₆, CH₃Cl₂; (p) aq KOH.

At about the same time, Mascareñas employed a formally analogous strategy to access (+)-nemoresnic acid.⁹¹ Key to this approach was the diastereoselective intramolecular oxidopyrylium cycloaddition of chiral sulfoxide 158 (Scheme 6). The sulfoxide acted as an effective chiral auxiliary in this reaction to provide a 93:7 ratio of (5+2)-cycloaducts. Reductive cleavage of the C–S bonds with alkene hydrogenation and silyl shift all taking place in situ gave oxabicyclo[2.2.1]heptanone derivative 159. Pb(IV)-mediated reductive cleavage of the α-hydroxy ketone and Jones oxidation to the diacid completed the route.

Cycloaddition of a different kind featured in Ryu's synthesis of (+)-nemoresnic acid.⁹² The route began with a highly efficient (99% yield) and stereoselective (endo-xeo= 96:4; ee >99%) asymmetric Diels–Alder reaction between acrylate 161 and 2,5-dimethylfuran (162), catalysed by chiral oxazaborolidium species 165 (Scheme 7). This established all three stereogenic centres in a single step, leaving alkene oxidation and alcohol deoxygenation as strategic steps to complete the route. In order to extend from just one end of the alkene, the 1'-hydroxyl was used to trap the proximal aldehyde formed upon periodate cleavage of the diol from step c. Wittig reaction was selective for the 5-CHO (in preference to the lactol) then a further oxidation gave lactone 164. The route was completed by lactone hydrolysis with subsequent esterification, hydroboration and oxidation of the vinyl group, then three redox steps to provide the third methyl group and the two carboxylic acid functions.

### Scheme 6

Reagents and conditions: (a) SOCl₂, CHCl₃, 60 °C; (b) H₂, Pd, NaOAc, MeOH; (c) KOH, aq HCHO; (d) KOH, PMBCl, KI, acetone; (e) NaOAc, MeOH; (f) KOH, aq HCHO; (g) KOH, PMBCl, KI, acetone; (h) KOH, PMBCl, KI, acetone; (i) PhCH₂Br, NaH, THF; (j) PCC, celite, CH₂Cl₂; (k) CsOH, CH₂Cl₂; (l) Pb(OAc)₄ (60 psi), [Ir(cod)py(PCy₃)₂]PF₆; (m) TBAF·3H₂O, THF; (n) TMSCHN₂, PPh₃, imidazole, CH₂Cl₂; (o) CF₃COOH, aq citric acid, MeOH; (p) I₂, Ph₃P, imidazole, THF; (q) BH₃·THF, THF, 0 °C then NaOH, aq H₂O₂, 0 °C; (r) Zn, AcOH; (s) PCC, celite, CH₂Cl₂; (t) NaClO₂, NaH₂PO₄, aq t-BuOH, THF then aq NaOH.

### Scheme 7

Reagents and conditions: (a) 165, CH₂Cl₂, –95 °C; (b) LiAlH₄, THF, –30 °C; (c) OsO₄, NMO, aq t-BuOH, THF then NaIO₄; (d) Ph₃PCH₂Br, NaH, MeOH; (e) PCC, celite, CH₂Cl₂; (f) CsOH, CH₂Cl₂; (g) t-BuOH then TMSCHN₂, aq citric acid, MeOH; (h) i-Pr₂P, imidazole, THF; (i) BF₃·OEt₂, THF, 0 °C then NaOH, aq H₂O₂, 0 °C; (j) Zn, AcOH; (k) PCC, celite, CH₂Cl₂; (l) NaClO₂, NaH₂PO₄, aq t-BuOH, THF then aq NaOH.

### Heliotridane

Dieter's method for α-functionalisation of pyrrolidine carbamates was showcased in the synthesis of (+)-heliotridane along with (+)-isoretorecanol and (+)-curassanecine (Scheme 8).⁹³ Lithiation and transmetalation of N-Boc pyrrolidine (166) gave the α-(N-carbamoyl)alkyl cuprate which was coupled in situ with 4-bromo-2-iodobutene. The coupled product 167 was deprotected and cyclised to bicyclic compound 168 which served as a common intermediate for elaboration to the three alkaloids by standard methods. An asymmetric variant of the coupling chemistry was developed subsequently with the initial deprotonation being conducted in the presence of (+)-sparteine.⁹⁴ With this variation, the (+)-enantiomers of heliotridane and isoretorecanol were prepared along with (+)-laburnine (formal synthesis, illustrated in Scheme 9).

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Scheme 8 Reagents and conditions: (a) s-BuLi, TMEDA, THF, −78 °C then CuCN·2LiCl, −78 °C then 4-bromo-2-iodobutene, −78 °C; (b) TMSOTf, CHCl₃, −20 °C to rt; (c) H₂, Pd/C, CH₂Cl₂; (d) BH₃·THF, THF, 0 °C to rt then aq NaOH, H₂O₂, 0 °C to rt; (e) TMSCl, MeOH; (f) BF₃·OEt₂; (g) MCPBA, CH₂Cl₂; (h) aq HCl; (i) CsF, MeCN, reflux.

Scheme 9 Reagents and conditions: (a) s-BuLi, (−)-sparteine, Et₂O, −78 °C then CuCN·2LiCl, −78 °C then vinyl iodide, −78 °C; (b) CF₃CO₂Et, Et₂O, −20 °C to rt; (c) H₂, Pd/C, CH₂Cl₂, reflux; (d) aq KOH, reflux; (e) PPh₃, THF, 0 °C to rt then aq NaOH, H₂O₂, 0 °C to rt; (f) TMSCl, MeOH; (g) MCPBA, CH₂Cl₂; (h) aq HCl; (i) CsF, MeCN, reflux. Intermediates similar in structure to bromoalkene 167 were obtained by Kulinkovich by application of his eponymous reaction on proline derivative 175 (Scheme 10). The derived cyclopropanol 176 was mesylated allowing Lewis acid-mediated formal electrocyclic ring-opening and capture with bromide ion, generating allylic bromide 177. Homologation, then hydroxyl activation under Appel chlorination conditions gave the cyclised methylenepyrrolizidine 168. This was reduced with high diastereoselectivity (dr = 11:1) to (−)-heliotridane and its epimer (−)-pseudo-heliotridane.

Scheme 10 Reagents and conditions: (a) EtMgBr, Ti(Oi-Pr)₂, Et₂O; (b) H₂, Pd(OH)₃/C, MeOH; (c) CICO₂Et, Et₂N, CH₂Cl₂; (d) MeCl, Et₂N, Et₂O; (e) MgBr₂·OEt₂, CHCl₃, Et₂O, reflux; (f) Zn, (HCHO)₂, THF, reflux; (g) aq KOH, reflux; (h) PPh₃, CCl₄, Et₂N, DMF; (i) NaBH₄, NCl₃·6H₂O, MeOH (products isolated as picrate salts).

The Sc(III)-catalysed enantioselective addition of pyrroles to α,β-unsaturated 2-acyl imidazoles using chiral PyBOX ligands was applied to the synthesis of (+)-heliotridane. Thus, addition of pyrrole to substrate 182 (Scheme 11) at −40 °C gave adduct 183 with 95% ee; this compound was then cyclised to give pyrrolizidinone 184 in essentially enantiopure form. Hydrogenation then lactam reduction furnished (+)-heliotridane, which was purified by conversion to the picrate salt.

Scheme 11 Reagents and conditions: (a) (1–isopropyl-1H-imidazol-2-yl)lithium, THF; (b) (i) PPh₃, C₆H₆, reflux; (ii) aq NaHCO₃; (c) CH₂CHO, C₆H₆, rt to 80 °C; (d) pyrrole, 2 mol%; 185, 4 Å MS, CH₂CN, −40 °C (95% ee); (e) MeOTf, 4 Å MS, CH₂CN then i-PrNEt; (f) H₂, 5% Rh/Al₂O₃, EtOH (dr = 90:10); (g) LiAlH₄, THF then Na₂SO₄·10H₂O.

McNab’s systematic study of the hydrogenation of pyrrolizin-3-ones (such as 186, obtained by pyrolysis of the Knoevenagel adduct of 2-formylpyrrole and Meldrum’s acid) to pyrrolizidines showed that relatively mild conditions could be used to conduct this transformation compared to those required for unsubstituted pyrroles. This was ascribed to electron withdrawal by the N-acyl substituent, and hydrogenation of the pyrrole ring after reduction of the lactam did indeed proceed more slowly. With substrates bearing ring-substituents, it was found that the dr of the products was dependent upon catalyst, the solvent, and the location of the ring-substituent. The results of this study were applied to short syntheses of (±)-heliotridane, (±)-isoretrocanol, and (±)-retrocanol as summarised in Scheme 12. In each synthesis, removal of the minor diastereomer was achieved at the final stage by recrystallisation of the picrate salt. Although the authors’ assignment of the picrate salt of retrocanol is secure, the NMR spectra for the free-base showed significant discrepancies from previously published data; the authors do not account for this discrepancy but since no solvent is specified for the comparison NMR data, firm conclusions cannot be drawn.
Racemic pseudoheliotridane was prepared by a somewhat lengthy route building from an initial (3+2)-annulation between the α-sulfonylacetamide derivative 198 (Scheme 13) and the 2-bromocrotonate 197. Functional group manipulations gave a diene (the N-allyl isomer of 201) from which the second ring was formed by ring-closing metathesis; the use of Grubbs’ 2nd generation catalyst in this reaction led to a good yield of pyrrolizidine product 200, in contrast to reactions conducted with the 1st generation catalyst which returned primarily the open chain N-propen-1-yl isomer 201. Three reductive steps completed the route.

**Scheme 12** Reagents and conditions: (a) H$_2$ (45 psi), Rh/Al$_2$O$_3$, EtOH; (b) LiAlH$_4$, THF; (c) H$_2$ (45 psi), Rh/C, hexane; (d) H$_2$ (15 psi), Pd/C, MeOH; –20 °C then H$_2$ (45 psi), Pd/C, MeOH; (e) H$_2$ (45 psi), Rh/Al$_2$O$_3$, AcOH; (f) H$_2$ (45 psi), Rh/C, EtOAc.

Isoretonecanol and trachelanthamidine/laburnine

The simple 1-hydroxyethylpyrrolizidine isoretonecanol and its diastereomer trachelanthamidine/laburnine continue to be popular targets for exemplifying methods for 1,2-diasterecontrol and several new syntheses of these alkaloids were reported during the review period. The first, of the racemate, introduced the desired relative stereochemistry by intramolecular alklylation of the Pd π-allyl derived from acetate 202 (Scheme 14). The stereochemical outcome follows from a model in which the malonate nucleophile is delivered onto the tethering face (cis- to the C–NCOR bond) with the ester component of the Na⁺-chelated malonyl enolate situated in an exo-position in the transition state. Following this key step, the route to (±)-isoretonecanol simply required cyclohexene ring cleavage and appropriate activation of the hydroxypropyl fragment to enable cyclisation and completion of the pyrrolizidine ring system. With decarboxylation and N-deprotection steps, and adjustment of the oxidation level, this required seven further steps.

**Scheme 14** Reagents and conditions: (a) LiCl, LiOAc, 1,4-benzoquinone, Pd(OAc)$_2$, AcOH, pentane; (b) PMB-NH$_2$, Pd(OAc)$_2$, PPh$_3$, PhCH$_2$I; (c) MeO$_2$CCH$_2$COCl, Et$_3$N, CH$_2$Cl$_2$, 0 °C; (d) NaI, DMF then Pd(OAc)$_2$, dppe, DMF, 50 °C; (e) NaCl, DMSO, 155 °C; (f) Os$_4$O$_8$, Me$_3$NO·2H$_2$O, aq THF then NaO$_4$, MeOH then NaBH$_4$, MeOH; (g) TsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$; (h) CAN, aq CH$_3$CN, 0 °C; (i) NaI, THF, 0 °C to rt; (j) Bu$_3$NOAc, NaI, THF, 55 °C; (k) LiAlH$_4$, THF, 66 °C.

A second synthesis of the racemate was reported in the same year from serine-derived vinyl aziridine 205 (Scheme 15).
Photolytic aziridine ring-opening and azomethine ylid cycloaddition gave the cis-adduct 206 as the major diastereomer; the authors explained this stereocontrol to originate in the preference of both the CH=CHOEt and CO2Me groups to avoid the bulky N-trityl protecting group during the cycloaddition. N-Deprotection, alkene reduction, and lactamisation completed a formal synthesis of (±)-isoretronecanol, the final reduction of the lactam and ester carbonyl having been previously reported.

Scheme 15 Reagents and conditions: (a) methyl acrylate, CH3CN, hv, 0 °C; (b) CF3CO2H, CHCl3, MeOH; (c) H2, Pd/C, EtOAc; (d) PhCH2CN, reflux; (e) (not carried out in this work) LiAlH4. All the carbon atoms were brought together in a single step by stereoselective alkylation (product dr = 8:1) of 4-chlorobutyric acid derivative 208 with the acyl iminium ion generated in situ from N,O-acetal 211 (Scheme 16). The choice of thiazolidinethione as chiral auxiliary (rather than the more common oxazolidinone) was guided by its less problematic reductive cleavage with LiBH4. N-Deprotection and cyclisation upon basification completed this short synthesis.

Scheme 16 Reagents and conditions: (a) 211, TiCl4, i-Pr2NEt, CH2Cl2, –23 °C; (b) LiBH4, THF, MeOH, 0 °C; (c) CF3CO2H, Et3SiH, CH2Cl2; (d) NaHCO3, H2O.

In comparison, Yoda’s synthesis of (±)-isoretronecanol is rather lengthy, although most of the steps (Scheme 17) are very efficient. The key constructive step comprises a diasteroselective alkylation of the samarium enolate of N-p-methoxybenzyl succinimide to give 213 as the major diastereomer. Although the stereocontrol was only moderate, the isomers were readily separated and the synthesis continued on a single diastereomer. Formation of key intermediate 215 required eight steps as a result of protecting group manipulations and adjustment of the oxidation level. Subsequent blocking of the 1°-hydroxyl enabled sequential N-cyclisations to complete the pyrrolizidine motif.

Scheme 18 Reagents and conditions: (a) (E)-BnOCH=CHCH2Br, In, MeOH (dr = 9:1); (b) Cp2ZrCl2, CH2Cl2 then I2, CH2Cl2; (c) H2, ZrHCl, CH2Cl2, 0 °C.
Pd(OH)$_2$/C, MeOH; (d) TBAF, THF, 0 °C to rt; (e) CBr$_4$, PPh$_3$, Et$_3$N, CH$_2$Cl$_2$, 0 °C; (f) H$_2$, Pd(OH)$_2$/C, aq HCl, MeOH.

The most recent isoretronecanol synthesis, a formal synthesis of the (−)-enantiomer, was reported by Rao’s group along with the formal synthesis of (−)-trachelanthamidine.$^{104}$ The key constructive step here was ring-closing metathesis of diene 224 (Scheme 19) elaborated from 2-vinylpyrrolidine derivative 222, obtained from (S)-proline. Alkene hydrogenation was accompanied by hydrogenolysis of the O-benzyl ether to give diastereomers 226 and 227 (dr = 64:36) that were separated as their benzoate esters. These lactams had been previously converted into (−)-isoretronecanol and (−)-trachelanthamidine (= ent-laburnine, 174), respectively.

Scheme 19 Reagents and conditions: (a) LiAlH$_4$, THF, 0 °C to rt; (b) Swern oxidation; (c) Ph$_3$P=CH$_2$, THF, −10 °C; (d) OsO$_4$, NMO-H$_2$O, aq acetone, 0 °C to rt; (e) Bu$_3$SnO, PhCH$_2$I, reflux then BnBr, Bu$_3$P, CH$_2$Cl$_2$, 0 °C; (f) TEMPO, NaBr, NaOCl, NaHCO$_3$, acetone, 0 °C to rt; (g) Bu$_3$SnO, PhCH$_2$I, reflux; (h) LiAlH$_4$, THF, 0 °C to rt; (i) Na(Hg), Na$_2$PO$_4$, MeOH; (j) Swern oxidation; (k) Ph$_3$P=CH$_2$, THF, −78 °C; (l) Grubbs’ II, C$_2$H$_2$, reflux; (m) H$_2$, Pd/C, MeOH.

Three further formal syntheses and five further total syntheses of trachelanthamidine were reported during the review period. The first formal synthesis, of the racemate, featured ring-closing metathesis to construct the ‘left hand’ ring (as drawn).$^{105}$ Double deprotonation of amide 198 (Scheme 20) set up stepwise conjugate addition to bromoenolate 228; proton exchange and N-cyclisation with displacement of bromide established the desired 1,2-trans-dialkyl arrangement in lactam 229. Conversion of the ester functionality into a vinyl substituent enabled ring-closing metathesis of diene 230 to complete the ring system. Simultaneous alkene hydrogenation and benzyl ether hydrogenolysis afforded 3-oxotrachelanthamidine (227), completing the formal synthesis.

Scheme 20 Reagents and conditions: (a) ozonolysis; (b) Ph$_3$P=CHBr$_2$, Et$_2$O; (c) CICH$_2$COCl, Et$_3$N; (d) NaTs$_2$, (e) NaH, THF, reflux; (f) LiAlH$_4$, THF, 0 °C to rt; (g) Na(Hg), Na$_2$PO$_4$, MeOH; (h) Swern oxidation; (i) Ph$_3$P=CH$_2$, THF, −78 °C; (j) Grubbs’ II, C$_2$H$_2$, reflux; (k) H$_2$, Pd/C, MeOH.

Chang effected a second formal synthesis of the racemate, building on the previous route, but forming the second ring by N-cyclisation rather than ring-closing metathesis.$^{106}$ From 45 pyrrolidone 231 (Scheme 21, cf. Scheme 20), extension from the ester, reductive removal of the sulfonyl group, and N-cyclisation onto the mesylate (or the chloride since this was also generated during the mesylation step) gave lactam 227. Alternatively, the N-cyclisation could be effected prior to desulfonylation, both five-step routes from intermediate 232 proceeding in comparable yield.

A formal synthesis of the (−)-enantiomer was developed from adduct 235 (Scheme 22).$^{107}$ Thus, tandem conjugate thiolation of tert-butyl acrylate and enolate addition to sulfinamine 234 gave adduct 235 (dr = 85:15). The formation of the minor diastereomer was attributed to epimerisation at the ester (as opposed to being the result of moderate asymmetric induction). The formal azabays–Hillman adduct 236 was then obtained by sulfoxide elimination, oxidation of the sulfinyl substituent to sulfonyl, and N-allylation. Ring-closing metathesis generated the pyrrole in high yield; this was desilylated and hydrogenated to give the trans-disubstituted pyrrolidine 237 with dr = 86:14. Interestingly, hydrogenation with the silyl ether in place gave a 1:1 mixture of
cis- and trans- products which led the authors to conclude that the free hydroxyl group was important in directing the approach of the alkene to the catalyst surface. From this point, the sequence was concluded by oxidation and lactamisation, to provide pyrrolizidine 238 that had been converted into (−)-trachelanthamidine by Nagao in 1990.

Scheme 22 Reagents and conditions: (a) TBSCI, t-BuOK, cyclopentyl methyl ether; (b) Swern oxidation; (c) (S)-p-toluenesulfinamide, Ti(OEt)_4, CH_2Cl_2, reflux; (d) MeMgBr/PhSH, tert-butyl acrylate, CH_2Cl_2, −50 °C; (e) MCPBA, CH_2Cl_2, 0 °C; (f) PhCH_2H, 110 °C; (g) MCPBA, CH_2Cl_2; (h) allyl bromide, K_2CO_3, DMF; (i) Grubbs’ II, CH_2Cl_2, reflux; (j) CSA, CH_2Cl_2, MeOH; (k) H_2, Pd/C, MeOH; (l) PDC, DMF; (m) SOCl_2, MeOH, reflux; (n) Mg, MeOH, reflux.

A total synthesis of (−)-trachelanthamidine featured palladium-catalysed intramolecular allylation methodology that had been developed for the synthesis of substituted pyrrolidines.108 The α-sulfonyl amide substrate 239 (Scheme 23) was assembled from (S)-proline using straightforward chemistry. The key cyclisation, however, gave predominantly the trans,trans- stereocchemistry in 240 (with respect to the pyrrolidine ring); in the earlier acyclic amide substrates, cis,trans-pyrrolidinones had been preferred and the authors proffered a rationale to explain the different outcomes. A weaker π-donating ligand with a smaller cone angle was required in order to generate a sufficiently reactive π-allyl complex to allow the production of the relatively-strained pyrrolizidine; for this, trisopropyl phosphate was used in place of tris(2,4,6-trimethoxyphenyl)phosphine. From the major diastereomer 240, the vinyl substituent was truncated by ozonolysis with a two-stage reductive work-up. Reductive cleavage of the sulfonyl group and reduction of the lactam completed the synthesis.

Scheme 23 Reagents and conditions: (a) DIBAL, PhCH_2H, −78 °C; (b) Ph,P=CHCO_2Et, CH_2Cl_2; (c) DIBAL, BF_3·Et_2O; CH_2Cl_2, −78 °C to 0 °C; (d) CF_3CO_2H, CH_2Cl_2, then TsCH_2CO_2H, PyBOP, iPr_2NEt, CH_2Cl_2; (e) CICO_2Me, pyridine, DMAP, CH_2Cl_2; (f) Pd(dba)_2, P(Oi-Pr)_3, CH_2CN; (g) O_3, CH_2Cl_2, −78 °C then Me_S then NaBH_4aq EtOH; (h) Na(Hg), MeOH, −15 °C; (i) LiAlH_4, THF, reflux.

(5)-Proline also served as the source of chirality and one of the rings in Ishibashi’s synthesis of (−)-trachelanthamidine in which the second ring was introduced by stereoselective radical cyclisation.109 The O-benzyl enol ether 243 (Scheme 24), prepared by Julia olefination of N-Boc prolinal 242, was found not to react effectively in the key cyclisation reaction (see below); therefore, hydrolysis and formation of the enol acetate 244 was undertaken. Upon heating this substrate in 1,4-dimethylpiperazine, electron transfer from the amine initiated radical formation (after loss of chloride ion) and 5-exo-trig cyclisation, giving the pyrrolizidine 245 as a single diastereomer. Two reductive steps completed the concise route.

Scheme 24 Reagents and conditions: (a) DIBAL, PhCH_2H, −78 °C to rt; (b) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (c) Cl_3CCOCI, EtN, CH_2Cl_2, 0 °C; (d) HCl, aq THF; (e) Ac_2O, KOAc, EtN, 120 °C; (f) 1,4-dimethylpiperazine, reflux; (g) H_2, Pd/C, NaOAc, EtOH; (h) LiAlH_4, THF, reflux.

More recently, a palladium-catalysed aminokynlation strategy was applied to the synthesis of (±)-trachelanthamidine.110 The cyclisation substrate, acyl sulfonamide 248 (Scheme 25), was prepared by Johnson–Claisen rearrangement of mono-O-benzyl diol 247. The combination of LiCl and PdCl_2 was found to be particularly effective for the key cyclisation step, and the authors proposed Li_2PdCl_4 as the active catalyst. Although the mechanistic details of the cyclisation reaction were not elucidated, a sequence of (potentially reversible) intramolecular annopalladation of the alkene, ligand exchange with the iodoxolone 252, and reductive elimination would account for the product; equally, alkynylation of an amidopalladium intermediate could precede cyclisation. Regardless, the trans-disubstituted pyrrolidinone 249 was produced in good yield with moderate stereoselectivity (dr = 83:17). From this, the alkyne was deprotected and converted into Z-iodoalkene 250 using Oshima’s method which proceeds via an initial hydroiodination. Buchwald coupling conditions were applied successfully for the intramolecular lactam/iodide coupling to give 251. Successive hydrogenation and carbonyl reduction steps led to the racemic...
natural product.

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\text{Scheme 25 Reagents and conditions: (a) CH}_3\text{C(OEt)}_3, \text{EtCO}_2\text{H}, 100 \, ^\circ\text{C to 160} \, ^\circ\text{C then KOH, MeOH, reflux; (b) TsNCO, Et}_3\text{N, THF; (c) PdCl}_2, \\
\text{LiCl, H}_2\text{O, EtOH, (dr = 83:17); (d) Li/naphthalene, THF, } -78 \, ^\circ\text{C; (e) TBAF, THF, 0} \, ^\circ\text{C to rt; (f) InCl}_3, \text{DIBAL then Et}_3\text{B then I}_2, \text{THF, } -50 \, ^\circ\text{C; (g) CuI, Cs}_2\text{CO}_3, \text{N,N'-dimethylethlenediamine, PhCH}_3, 85 \, ^\circ\text{C; (h) H}_2, \text{Pd/C, MeOH; (i) LiAlH}_4, \text{THF, reflux.}}
\]

A carefully-orchestrated (3+2)-annulation of imine 253 (Scheme 26) and allenoate 254 led directly to pyrroline 255 with 96\% ee.\(^{11}\) The authors propose that the enolate obtained by conjugate addition of phosphine catalyst 257 undergoes addition to imine 253 with dual H-bonded activation of the phosphinoyl oxygen to set the absolute stereochemistry. Removal of both O- and N-protecting groups, then N-tosylation afforded pyrroline 256, the enantiomer of an intermediate in an earlier formal synthesis of (−)-trachelanthamidine,\(^{107}\) that linked with Nagao’s synthesis from 1990.

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\text{Scheme 26 Reagents and conditions: (a) 257, } 5\text{Å MS, Et}_2\text{O, } 0 \, ^\circ\text{C; (b) BF}_3\text{-OEt}, \text{MeOH, CH}_2\text{Cl}_2, 0 \, ^\circ\text{C; (c) TsCl, Et}_3\text{N, CH}_2\text{Cl}_2, 0 \, ^\circ\text{C.}}
\]

Finally, Liu and co-workers reported alkynyl tungsten derivatives as competent nucleophiles for intramolecular iminium trapping, the alkynyl tungsten functionality being synthetically equivalent to an ester enolate. This methodology was applied to the synthesis of (±)-laburnine (= (±)-trachelanthamidine, Scheme 27).\(^{112}\) Thus, exposure of substrate 259 to Lewis acid-initiated ionisation to form an N-acyl iminium intermediate, and cyclisation. The resulting vinylidene tungsten intermediate was trapped, presumably by adventitious water, to generate acyl tungsten species 260. Oxidative demetallation gave a benzyl ester that was reduced along with the lactam to complete the synthesis.

\[
\text{Scheme 27 Reagents and conditions: (a) DIBAL, CH}_2\text{Cl}_2, -78 \, ^\circ\text{C then EtOH, aq HCl; (b) CpW(CO)}_3\text{Cl, Cul, Et}_3\text{NH; (c) BF}_3\text{-OEt, Et}_2\text{O, } -78 \, ^\circ\text{C to rt; (d) BnOH, I}_2, \text{CH}_2\text{Cl}_2, -78 \, ^\circ\text{C to rt; (e) LiAlH}_4, \text{THF, } 0 \, ^\circ\text{C to 65} \, ^\circ\text{C.}}
\]

Amabiline and cremastrine

Lindsley’s group described the syntheses of two complete pyrrolizidines (+)-amabiline and (−)-cremastrine based on diastereoselective 1,2-addition to chiral sulfoximine intermediates.\(^{113}\) In both syntheses, and unusually, the pyrrolizidine ring system was generated after the necic acid side chain had been introduced. In the first synthesis, Grignard addition to sulfoximine 265 (Scheme 28) afforded sulfoxamide 266 with dr >>9:1. Ring-closing metathesis and silyl deprotection afforded pyrroline 267 whose relative stereochemistry was confirmed by X-ray crystallography. Esterification with masked viridifloric acid derivative 263 gave
which was subjected to global cleavage of acid-labile protecting groups and the chiral auxiliary. The so-formed iminium intermediate was reduced in situ with the polymer-supported hydride reducing agent MP-BH(OAc)₂ to complete the first total synthesis of (+)-amabiline.

The synthesis of (–)-cremastrine (Scheme 29) followed strategically similar lines.²⁵ Here, the two stereogenic centres in the necine base were installed by diastereoselective allylation of sulfoximine 270 (dr = 4:1). Alkene oxidation, then cyclisation and esterification afforded functionalised pyrrolidine 272; deprotection and intramolecular reductive amination generated (–)-cremastrine, the first total synthesis.⁶

Simple hydroxypyrrolizidines

Mono-
A synthesis of the simple 2-hydroxypyrrolizidine 277 (reported as the 3-isomer)²⁶ was achieved in nine steps from d-glyceraldehyde acetonide 274 as shown in Scheme 30. Wittig olefination, reduction, and N-protection led to amino alkene 275, this was cyclised to organomercurial 276 with dr >10:1. Following reductive demercuration, acetonide cleavage, and activation of the 1'-alcohol as the mesylate, hydrogenolysis released the free amine which cyclised giving the mesylate salt of (+)-2-hydroxyprrolizidine.

Di-
Six syntheses of the pyrrolizidine lower homologue of (–)-lentiginosine, (1R,2R,7aR)-dihydroxyprrolizidine 286, and its enantiomer (ent-286, Scheme 31) were reported during the review period. The first exploited general Wittig olefination/dihydroxylation/ring-closure methodology that had been developed for higher pyrrolizidines, see below.²⁶ In this

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Scheme 28 Reagents and conditions: (a) i-PrL, t-BuOK, DMSO, 0 °C; (b) LHMDS, CH₃CHO, THF, −78 °C; (c) AD-mix-α, aq t-BuOH, 0 °C; (d) Me₂SO, 50 °C; (e) Me₂SO, 50 °C; (f) TBSCl, imidazole, CH₂Cl₂, −78 °C; (g) K₂CO₃, THF; (h) t-BuONa, DMSO, 0 °C; (i) (1,3-dioxan-2-yl)ethylmagnesium bromide, THF, −78 °C; (j) LHMDS, CH₂Cl₂, 0 °C to rt; (k) TsCl, Et₃N, CH₂Cl₂, −20 °C; (l) Grubbs' II, CH₂Cl₂, 0 °C to rt; (m) (1,3-dioxan-2-yl)ethylmagnesium bromide, THF, −78 °C; (n) LHMDS, CH₂Cl₂, 0 °C to rt; (o) LiAlH₄, THF; (p) aq CF₃CO₂H; (q) MP-B(OAc)₂,H, DCE.

Scheme 29 Reagents and conditions: (a) (E)-TBSOCH₂CH=CH₂Br, In, NaBr, H₂O; (b) 9-BrBBN, CH₂Cl₂, then aq NaOH, H₂O; (c) DEAD, PPh₃, THF; (d) TBAF, THF; (e) t-BuONa, DMSO, 0 °C to rt; (f) TBSCl, imidazole, DMF, 0 °C to rt; (g) MnO₂, CH₂Cl₂; (h) (S)-t-BuSONH₂, CuSO₄, CH₂Cl₂, 0 °C to rt; (i) (1,3-dioxan-2-yl)ethylmagnesium bromide, THF, −78 °C; (j) LHMDS, allyl bromide, DMF, −20 °C; (k) Grubbs' II, CH₂Cl₂; (l) t-BuONa, DMSO, 0 °C; (m) TsCl, Et₃N, CH₂Cl₂, 0 °C; (n) (t-BuO)₂SiH, CuSO₄, CH₂Cl₂, 0 °C, then aq NaOH, H₂O; (o) aq CF₃CO₂H; (p) MP-B(OAc)₂,H, DCE.

Scheme 30 Reagents and conditions: (a) 3-cyanopropyltriphenylphosphonium bromide, NaHMDMS, THF, 0 °C; (b) LiAIH₄, Et₂O, reflux; (c) CbzCl, Et₃N, THF, 0 °C to rt; (d) Hg(OAc)₂, CH₂Cl₂, then aq NaCl; (e) Bu₂SnH, AIBN, PhCH₃, rt to 70 °C; (f) aq AcOH; (g) MscI, Et₃N, CH₂Cl₂, 0 °C; (h) H₂, Pd/C, EtOH.
example, E- or non-selective Wittig reaction was conducted in dichloromethane or methanol, respectively; in the latter case the Z-enolate was separated from its isomer for further elaboration. Dihydroxylation of these alkenes (279, 280) under either Upjohn catalysis conditions or α-/β-AD-mix gave all four diastereomeric diols (281–284) in pairs (varying ratios) that were separated and characterised after lactamisation (step c). Benzylation of the hydroxyl groups increased the efficiency of the subsequent carbonyl reduction, with deprotection affording ent-286 and its three diol diastereomers.

Soon after, Dhavale reported a synthesis of similar length from enolate 293 (Scheme 33), prepared in five steps from d-glucose. After acetonide hydrolysis, periodate cleavage led to an aldehyde intermediate from which reductive amination and aza-Michael cyclisation gave trisubstituted pyrrolidine 294. The C(2)-epimer was also produced in this reaction (~40:60 ratio with 294 minor) and this was easily separated as the lactone 296. The side chain was extended by Armdt–Eistert homologation (~295), then hydrogenolysis of both benzyl groups and reduction of the resulting lactam completed the route.

Scheme 31 Reagents and conditions: (a) Ph₃P=CHCO₂Me, CH₂Cl₂ (→ E-); (b) Ph₃P=CHCO₂Me, MeOH (→ E/Z: 1.3:1); (c) H₂, Pd/C, MeOH then NaOMe, MeOH, reflux; (d) NaH, BnBr, DMSO; (e) LiAlH₄, Et₂O, reflux; (f) H₂, Pd/C, aq HCl, MeOH then Amberlite IRA-400, MeOH.

In the first synthesis of the (−)-enantiomer, the absolute stereochemistry was set by Sharpless asymmetric epoxidation of a diol 289 (Scheme 32) as its mono-silyl ether, then diastereoselective vinyl Grignard addition to the intermediate benzyl imine proceeded with chelation control. Epoxide hydrolysis (→ 291) and elaboration via ring-closing metathesis afforded pyrrolidine 292. The second ring was closed by N-deprotection then activation of the 1°-hydroxyl group under Appel conditions with cyclisation taking place in situ. This compound displayed comparable activity to (−)-lentiginosine in inhibiting the amyloglucosidase from Aspergillus niger (IC₅₀ = 27.3 and 25.5 μg mL⁻¹, respectively).

Scheme 32 Reagents and conditions: (a) BuLi, TBDPSCI, THF, −78 °C then reflux; (b) Ti(Oi-Pr)₄, (−)-DET, 2BuOOH, 4A MS, CH₂Cl₂, −23 °C; (c) IBX, DMSO; (d) BnNH₂, 4A MS, EtO then CH₂=CHMgBr, BF₃·OEt₂, −78 °C; (e) H₂SO₄, aq dioxane, reflux; (f) allyl bromide, K₂CO₃, aq THF; (g) Grubbs’ 1, CH₂Cl₂, reflux; (h) H₂, Pd/C, aq HCl, MeOH; (i) PPh₃, CCl₄, Et₂N, DMF.

Building on a general method for the preparation of multifunctionalised pyrrolidines, Angle’s group reported an enantiospecific synthesis of (1R,2R,7αR)-dihydroxy-pyrrolizidine from d-mannitol (297, Scheme 34). An eight-step sequence was used to access isoserinal derivative 298, the substrate for the key step (step i). Lewis acid mediated Felkin–Anh mode addition of the diazoacetate into the aldehyde and stereoselective N-cyclisation gave trans,trans-disubstituted pyrrolidine 299 along with some product of N₂ elimination (not shown). From this key intermediate (that was also employed in a synthesis of (−)-lentiginosine) the synthesis followed conventional lines to install the second ring; viz., Wittig extension of the ester substituent, alkene reduction and lactamisation, carbonyl reduction, and removal of the O-protecting groups.
A synthesis of racemic 286 was completed by nitroso-Diels–Alder reaction between diene 303 (generated in situ from levulinic acid derivative 301) and ethyl vinyl ether (Scheme 35).\(^{[120]}\) Cis-dihydroxylation of the adduct was surprisingly stereoselective with respect to the acetal centre (302, \(\text{dr} = 82:18\)) but the relative stereochemistry was not determined. Combined hydrogenation, hydrolysis, and reductive amination afforded a lactam that was reduced further with borane to give the 7a-epimers (±)-286 and 285 in ~2:1 ratio. Two simple non-hydroxylated pyrrolizidines were prepared by analogous methods.

The most recent synthesis of (−)-286 was an enantiospecific route from D-lyxose (Scheme 36).\(^{[121]}\) The 1,2-diol stereochemistry originated in the 3,4-stereogenic centres in the starting sugar but the 7a-stereochemistry derived by selective amination of the allylic benzyl ether (step f). The authors did not comment on this process but a subsequent report\(^{[122]}\) by the group suggested, on the basis of results from a deuterated substrate, a retentive \(S_n\) reaction; in this particular case, the resulting diastereoselectivity was high at 26:1. Following this key step (\(\rightarrow 305\)), the rest of the route was straightforward with \(N\)-cyclisation forming the first ring (in 306) under basic conditions, and ring-closing metathesis furnishing the pyrrolizidine.

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**Scheme 34** Reagents and conditions: (a) \((\text{MeO})_3\text{CMe}_2\), \(\text{SnCl}_2\), DME, reflux; (b) \(\text{HC(OMe)}_3\text{NMe}_2\), \(\text{CH}_2\text{Cl}_2\); (c) \(\text{MeI}, \text{PhCH}_3\), reflux; (d) Amberlyst 15, MeOH; (e) \(\text{Bu}_3\text{SnO}, \text{PhCH}_3\), reflux then \(\text{TsCl};\) (f) TBSOTf, 2,6-lutidine, \(\text{CH}_2\text{Cl}_2\), 0 °C; (g) \(\text{NaNNH}_2\), DMSO, 80 °C; (h) \(\text{OsO}_4, \text{CH}_2\text{Cl}_2\), −78 °C then thiourea, 0 °C; (i) benzyl diazoacetate, \(\text{BF}_3\cdot\text{Et}_2\text{O}, \text{CH}_2\text{Cl}_2\), −78 °C; (j) MEMCl, \(\text{t}-\text{PrNEt}, \text{CHCl}_3\), reflux; (k) \(\text{NaBH}_4, \text{EtOH};\) (l) Swern oxidation then \(\text{Ph}_3\text{P=CHCO}_2\text{Me};\) (m) \(\text{H}_2, \text{Pd/C}, \text{EtOAc};\) (n) \(\text{Mg, MeOH};\) (o) \(\text{LiAIH}_4, \text{THF},\) reflux; (p) \(\text{CBr}_3, \text{MeOH},\) reflux.

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**Scheme 35** Reagents and conditions: (a) \(\text{Br}_2, \text{Et}_2\text{O}, -5 °C\); (b) \(\text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2\), −35 °C; (c) \(\text{NH}_2\text{OH.HCl}, \text{aq CHC}_\text{H}_3\); (d) \(\text{NaCO}_3, \text{ethyl vinyl ether, t-BuOMe};\) (e) \(\text{KMnO}_4, \text{MgSO}_4, \text{EtOH}, -45 °C\); (f) \(\text{H}_2, \text{Pd/C}, \text{MeOH};\) (g) \(\text{LiAIH}_4, \text{THF},\) reflux; (h) \(\text{CBr}_3, \text{MeOH},\) reflux.

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**Scheme 36** Reagents and conditions: (a) \(\text{SOCl}_2, \text{MeOH};\) (b) \(\text{NaH}, \text{BnCl}, \text{Bu}_3\text{Ni}, \text{DMF};\) (c) \(\text{H}_2\text{SO}_4, \text{aq dioxane}, 60 °C\); (d) \(\text{NaH, Ph}_3\text{P/Bn Cl, DMSO, THF, 45 °C; (e) CBr}_3, \text{PhP, EtN, CH}_2\text{Cl}_2, 0 °C; (f) CISO}_3\text{NCO, Na}_2\text{CO}_3, \text{PhCH}_3, 0 °C then aq NaSO}_3; (g) \(\text{t-BuOK, THF, 0 °C; (h) Et}_3\text{SiH, Pd(OAc)}_2, \text{EtN, CH}_2\text{Cl}_2, \text{reflux; (i) allyl bromide, K}_2\text{CO}_3, \text{THF, 45 °C; (j) Grubbs’ II, PhCH}_3\), reflux; (k) \(\text{H}_2, \text{Pd/C, aq HCl, EtOH then Dowex 50WX8 (H}^+\text{ form), aq NH}_3\).

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**Scheme 37** Reagents and conditions: (a) \(\text{CH}_2=\text{CHCO}_2\text{Me}, \text{PhCH}_3\), 110 °C; (b) \(\text{DBAL, THF, -10 °C; (c) MeCl, EtN, CH}_2\text{Cl}_2, 0 °C to rt; (d) \(\text{H}_2, \text{Pd(OH)}_2\text{Cl, MeOH; (e) TBSCl, EtN, CH}_2\text{Cl}_2; (f) aq AcOH, 80 °C; (g) MeCl, EtN, CH}_2\text{Cl}_2, -10 °C to rt; (h) NH}_3\text{F, TBAF, aq THF.}

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Pine’s group disclosed an early application of their vinyl epoxide opening and ring-closing metathesis methodology in the synthesis of the 1,2,7-trihydroxypyrrolizidine 313 shown in Scheme 38.\(^{[124]}\) The initial amination of epoxide 311 required forcing conditions (refluxing toluene, 4 days) but proceeded efficiently. The rest of the synthesis was uneventful, with dihydroxylation of pyrrolidine 312 proceeding anti-to the 2-substituent, and final ring-closure
being achieved under Mitsunobu conditions (step f).

Scheme 38 Reagents and conditions: (a) allylamine, TsOH, toluene, PhCH₂, 110 °C; (b) Boc₂O, Et₃N, THF; (c) Grubs’ I, CH₂Cl₂, reflux; (d) OsO₄, NMO, aq acetone; (e) CF₃CO₂H, anisole, CH₂Cl₂; (f) DEAD, Ph₂P, pyridine then Ac₂O, pyridine, 0 °C; (g) K₂CO₃, MeOH.

The diastereomeric cycloadducts 316 and 317 (Scheme 39) of d-ribose-derived nitronate 315 and methyl acrylate were separated and taken through a standard four-step sequence resulting in 1,2,6-trihydroxypyrrolizidine epimers 318 and ent-310.¹²⁵

Scheme 39 Reagents and conditions: (a) NaBH₄, MeOH, 0 °C to rt; (b) NaIO₄, aq t-BuOH; (c) BnNH₂, Et₃N, CH₂Cl₂; (d) CH₂=CHCO₂Me, reflux; (e) H₂, Pd/C, MeOH; (f) PBU₃, 1,1′-(azodicarbonyl)dipiperidine, THF; (g) BH₂-SMe₂, THF; (h) TsOH, MeOH.

Tetra-

Developing from an enantiospecific route to indolizidines,¹²⁶ d-gulonolactone (Scheme 40) was elaborated through a sequence originally established by Fleet to a dihydroxyproline derivative (⇒ step g).²² Wittig olefination, reduction and esterification with para-methoxybenzoyl chloride gave allylic ester 319 that was an excellent substrate for asymmetric dihydroxylation giving both possible cis-diol diastereomers (dr = 95:5 and >99.5:0.5 using AD-mix-α or AD-mix-β, respectively). The 1°-alcohol formed by ester hydrolysis was activated by sulfonylation, then AD-mix-α (for 320) or AD-mix-β (for 321); (l) NaOMe, MeOH; (m) TsCl, pyridine, –20 °C; (n) aq CF₃CO₂H then aq NH₄Cl.

Lioja’s approach to the same 1,2,6,7-tetrahydroxypyrrolizidine motif was based on ring-closing metathesis and transannular S₄N₂ cyclisation.¹²⁶ The readily-available d-glucose derivative 322 (Scheme 41) was elaborated to iodide 323 by standard methods then one-pot fragmentation/reductive-amination sequence afforded diene 324 after N-protection. Ring-closing metathesis was effective in generating the medium ring 325 in refluxing dichloromethane but at a higher temperature (refluxing toluene) the alkene isomerised, giving an enamine. The transannular substitution occurred spontaneously (⇒ 326) following removal of the Boc group. Dihydroxylation gave an approximately 2:1 ratio of diols in favour of that shown (in 320); the diol diastereomers were separated and debenzylated to afford the final pyrrolizidines 320 and 327.

Scheme 40 Reagents and conditions: (a) Me₂C(O)Me₂, TsOH, acetic; (b) LiAlH₄, THF, Et₂O; (c) MsCl, DMAP, pyridine; (d) BnNH₂, 70 °C; (e) aq Ac₂O, 50 °C; (f) H₂, Pd(OH)₂/C, Boc₂O, MeOH; (g) Pb(OAc)₄, NaHCO₃, CH₂Cl₂, –78 °C; (h) Ph₂P=CHCO₂Et, CH₂Cl₂; (i) Dibal, CH₂Cl₂, –15 °C; (j) 4-MeOCH₂CO₂H, Et₃N, DMAP, CH₂Cl₂; (k) AD-mix-α (for 320) or AD-mix-β (for 321); (l) NaOMe, MeOH; (m) TsCl, pyridine, –20 °C; (n) aq CF₃CO₂H then aq NH₄Cl.

Platyneicine and turneforcidine¹²⁹

Three syntheses of racemic platyneicine were recorded in the first

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half of the review period. The first, a concise route from Correia’s group, built on a highly stereoselective [2+2]-
cycloaddition of chloroethyl ketene with N-Cbz-2-pyrrole (328) (Scheme 42).\(^{130}\) Subsequent Baeyer–Villiger oxidation of the so-
formed ketone proved surprisingly regioselective, giving only lactone 330. The authors ascribed this selectivity to localised
strain-activation of the migrating bond although, in this
compressed system, the regioselectivity could be simply a
consequence of accessible conformations that position the
\(\text{C}-\text{O} \) bond appropriately. Regardless, \(N\)-deprotection
was accomplished by formation of the second pyrrolidine ring,
and lactone reduction completed the 4-step sequence.

Scheme 42 Reagents and conditions: (a) 4-chlorobutyl chloride, Et\(_3\)N,
\(\text{CH}_2\text{Cl}_2\), reflux; (b) MCPBA, NaHCO\(_3\), Et\(_3\)N; (c) H\(_2\), Pd(OAc)\(_2\), MeOH;
(d) LiAlH\(_4\), THF.

The second synthesis of (±)-platynecine\(^{131}\) was based on [2+3]-
sigmatropic rearrangement of ammonium ylid 333 (Scheme 43),
formed in situ from diazoketone 332 upon exposure to Ru(II)
catalysis. The syn- and anti- diastereomers of 334 were obtained
in equal proportion immediately following the reaction, but this
ratio increased to 2.5:1, in favour of the syn- isomer, following
purification on silica. After ketone reduction (step e), the two
diastereomers were separable and the syn- isomer was carried
forward to the natural product in five steps.

Scheme 43 Reagents and conditions: (a) MeCl, Et\(_3\)N, EtOAc; (b) BnNH\(_2\),
Et\(_3\)N, THF; (c) 4-bromo-1-diazobutan-2-one, Et\(_3\)N, EtOAc; (d) Ru\(_2\)(TTP)(CO), PhCH\(_3\), 50 °C; (e) NaBH\(_4\), MeOH, 0 °C; (f) NaH, BnBr,
THF, 0 °C; (g) 9-BBN, THF, reflux then H\(_2\)O\(_2\), aq NaOH; (h) HCO\(_2\)H, Pd/C, MeOH, reflux; (i) PPh\(_3\), CCl\(_3\), Et\(_3\)N, DMF; (j) H\(_2\), PdCl\(_2\), MeOH.

A closely-related rearrangement formed the cornerstone of
West’s route to (±)-platynecine and (±)-turneforcidine.\(^{132}\) Here,
the ammonium ylid (338, Scheme 44) was embedded in a spiro-
fused azetidine and, with a saturated migrating chain, Stevens-
type [1,2]-rearrangement ensued. Two diastereomers of the
pyrrolizidine were obtained, with the \(\alpha\)-diastereomer of ester 339
dominating. Hydrogenation of the ketone allowed easy separation
of the diastereomers as a result of lactonisation (\(\rightarrow\) 341) in the \(\beta\)-
estere diastereomer. Final ester/lactone reduction gave the
pyrrolizidines turneforcidine and platynecine, epimeric at C(1).

Scheme 44 Reagents and conditions: (a) HCO\(_2\)NH\(_2\), Pd/C, MeOH, reflux;
(b) 4-bromo-1-diazobutan-2-one, \(i\)-Pr\(_2\)NEt, CH\(_2\)CN; (c) Cu(acac)\(_2\),
PhCH\(_3\), 85 °C; (d) H\(_2\), PdO\(_2\), MeOH; (e) LiAlH\(_4\), THF, reflux.

Two further syntheses of turneforcidine appeared at the beginning
of the review period, the papers being received on consecutive
months. The first, of the racemate, featured intramolecular
metalloiminium allylation of substrate 344 (Scheme 45).\(^{133}\) The
cyclisation was highly diastereoselective and the authors
proposed a conformationally biased model in which allylation is
envisioned to take place \(\text{anti}\) to the bulky TBDPSO- substituent.
Although, in other cases, the second cyclisation occurred
spontaneously, in this case further Lewis acid activation (of ester
345) was necessary in order to complete the pyrrolizidine core in
346. From this point, the vinylsulfide had to be clipped
oxidatively, giving the carboxylic acid at C(1). The route was
completed by reduction of both carbonyls and desilylation, all of
which were accomplished upon treatment with LiAlH\(_4\) under
relatively forcing conditions.

Scheme 34 Reagents and conditions: (a) 4–bromo–1–diazobutan–2–one, \(i\)-Pr\(_2\)NEt,
CH\(_2\)CN; (c) Cu(acac)\(_2\), PhCH\(_3\), 85 °C; (d) H\(_2\), PdO\(_2\), MeOH; (e) LiAlH\(_4\), THF, reflux.

Two further syntheses of turneforcidine appeared at the beginning
of the review period, the papers being received on consecutive
months. The first, of the racemate, featured intramolecular
metalloiminium allylation of substrate 344 (Scheme 45).\(^{133}\) The
cyclisation was highly diastereoselective and the authors
proposed a conformationally biased model in which allylation is
envisioned to take place \(\text{anti}\) to the bulky TBDPSO- substituent.
Although, in other cases, the second cyclisation occurred
spontaneously, in this case further Lewis acid activation (of ester
345) was necessary in order to complete the pyrrolizidine core in
346. From this point, the vinylsulfide had to be clipped
oxidatively, giving the carboxylic acid at C(1). The route was
completed by reduction of both carbonyls and desilylation, all of
which were accomplished upon treatment with LiAlH\(_4\) under
relatively forcing conditions.
1,3-dipolar cycloaddition with ethyl 4-bromocrotonate proceeded with complete regio- and diastereoselectivity to give the endo-product (not shown) exclusively. N-O reduction, and cyclisation onto the primary bromide was effected in a one-pot procedure (step b) to give the pyrrolizidine core (352), then dehydration, ester reduction, and deprotection gave (+)-heliotridine.

Scheme 47 Reagents and conditions: (a) PhCH₂, 0 °C to rt; (b) (i) H₂, Raney Ni, EtOH; (ii) Ambersep 900 OH; (c) NaI, DMAP, Et₃N, CH₂Cl₂, 0 °C to rt; (d) DIBAL, CH₂Cl₂, 0 °C; (e) (i) aq CF₃CO₂H; (ii) Dowex 50WX8-200.

Other recently-published syntheses of this natural product rely on α-functionalisation of maleimide-derived starting materials. The first of these began with acetylide addition to imide 354 (Scheme 48), available from (−)-malic acid in four steps. The hemiaminal product 355 was produced as a diastereomeric mixture but deoxygenation proceeded stereoselectively, with the silane reagent directed by the adjacent hydroxyl group. After further functionalisation of the N-alkyl substituent, cyclisation from 357, to give the second ring, was effected via a radical reaction; destannylation of the product (358) and oxidation gave diacetate 359, an intermediate in a previous synthesis of (+)-heliotridine. A slight modification of this procedure was used to furnish (−)-retronecine; here, the adjacent hydroxyl group was used to deliver the acetylene group intramolecularly to an acyliminium ion generated from hemiaminal 360, obtaining the cis-diastereomer 361. From here, the synthesis was completed following steps analogous to those used to prepare (+)-heliotridine.

Heliotridine and retronecine

Continuing previous work on (−)-rosmarinecine and other, non-natural pyrrolizidines, Brandi and Cordero used a cycloadition strategy to synthesise (+)-heliotridine from chiral nitrone 351 (Scheme 47), derived from diethyl (S)-malate in five steps. The
global reduction of the carbonyl groups. This journal is © The Royal Society of Chemistry [year].

A combination of acyliminium trapping and Au(I)-mediated cyclisation featured as key steps in the most recent synthesis of heliotridine and retronecine, again starting from malic acid. Addition of (acetoxymethyl)propargyltrimethylsilane (368) afforded the allenyl product 366 (Scheme 50) as an 83:17 ratio of diastereomers. Allene activation with a Au(I)/Ag(I) co-catalyst initiated efficient 5-endo mode cyclisation; the diastereomeric pyrrolizidine products (359 and its C(7α)-epimer) were separated at this point and carried through independently to (+)-heliotridine and (–)-retronecine by reduction. (+)-Supinidine was also synthesised by an analogous route from maleimide.

Macronecine

Intramolecular aza-ene reaction and aldehyde alkylation were used in combination to create the two rings in (+)-macronecine and (+)-supinidine. Acyl hydrazone 370 (Scheme 51) was prepared from allylic alcohol 369 (3 steps from 3-chloroprop-1-ol) via Johnson–Claisen rearrangement. Mild oxidation of the hydrazone to the corresponding diazo intermediate led to intramolecular ene reaction directly, with the proportion of Z-alkene varying considerably (E/Z, dr = 95:5 to 70:30). Reductive cleavage of the N–N bond (in lactam 371) followed by installation of the tethered aldehyde gave substrate 372 for intramolecular alkylation. Cyclisation was achieved in moderate yield following removal of three minor isomers (373, original dr = 86.4:5.8:4.4:3.4). Mitsunobu esterification then ozonolysis with a strongly reductive work-up generated (+)-macronecine directly. Alternatively, standard esterification then ozonolysis with a milder reductive work-up (to the aldehyde) effected elimination of the 2°-hydroxyl at C(2); hydride reduction then afforded (+)-supinidine.
A second synthesis of (±)-macronecine, and its 2-epimer (379) was achieved from dihydroxyacetone dimer.141 Following a 5-step route (not shown), racemic γ-lactone 375 (Scheme 52) was hydroxylated with almost exclusive trans- diastereoselectivity, with the minor cis-isomer being easily removed after benzyl protection. Aminolysis and oxidation gave amino aldehyde 376 which cyclised upon Lewis acid treatment. The so-formed hydroxylactam was allylated under standard conditions to give 377. The remainder of the synthesis followed conventional lines, with the second ring being formed by alkene oxidation, activation, and N-cyclisation following oxidative removal of the PMB group. 2-Epi-macronecine was obtained from pyrrolizidinone 378 after lactam reduction and cleavage of the silyl group but access to macronecine itself required a 3-step alcohol inversion sequence, via the triflate.

Scheme 52 Reagents and conditions: (a) LHMDS, 2-phenylsulfonyl-3-phenyloxaziridine, THF, −78 °C; (b) BuBr, Ag2O, EtOAc; (c) PMBNO2, MeOH; (d) Swern oxidation; (e) BF3·OEt2, THF, 0 °C; (f) allyltrimethylsilane, BF3·OEt2, CH2Cl2, −78 °C to −20 °C; (g) 9-BBN, THF then H2O2, aq NaOH, 0 °C; (h) TsCl, pyridine; (i) CAN, aq CH3CN; (j) NaH, THF, 0 °C to rt; (k) H2, Pd(OH)2/C, EthOH; (l) Tf2O, pyridine, CH2Cl2; (m) Cs2CO3, 18-crown-6, PhCH2Cl; (n) K2CO3, MeOH; (o) BH3·THF, THF; (p) HCl, MeOH.

Rosmarinecine

It was known that nitrones of the form 381 (Scheme 53) undergo partial racemisation during, for example, Mitsunobu esterification; this had caused problems during Goti’s synthesis of (–)-rosmarinecine described previously.1 This property was exploited by effecting esterification with activated maleic acid esters enzymatically since this could be run as a dynamic kinetic resolution. Thus, mediated by Candida antarctica lipase (CAL-B), racemic hydroxynitrite 381 and vinyl ester 385 gave the intramolecular nitrene cycladduct 382 directly in 91% ee.142 This adduct was recrystallised to give a single enantiomer then, following Goti’s route, reductive cleavage of the N-O bond and lactamisation generated tricyclic pyrrolizidine lactone 383. Reduction of both carbonyl groups gave (–)-rosmarinecine in excellent yield and enantiopurity. The overall route was subsequently143 shortened (to that shown in Scheme 53) by the discovery of alternative conditions for generating the starting nitrene.
Nitrone cycloadditions featured in Goti’s synthesis of the rosmanicine analogue 391 and 7α-epi-crotanecine 393 (Scheme 54). Nitrone 387, obtainable from erythorbic acid via δ-erythrose acetonide 386 gave major diastereomer 388 upon cycloaddition with dimethyl maleate. Hydrogenolysis of the N-O bond gave lactam 390, the common intermediate for the two pyrrolizidine analogues. The first, 391, was obtained following lactam and ester reduction then acetamide cleavage. Alternatively, selective reduction, maintaining the ester (→ 392), facilitated regioselective dehydration via the mesylate; subsequent reduction and hydrolysis provided 7α-epi-crotanecine 393.

Hyacinthacines

The first total synthesis of (+)-hyacinthacine A2, by Martin’s group, began with stereoselective (Cram chelate model) vinyl addition to commercially-available δ-arabinose derivative 394 (Scheme 55). Regioselective benzoylation of the so-formed diol proceeded in a 3.5:1 ratio favouring the allylic benzoate; subsequent oxidation of the remaining alcohol gave ketone 395. Under the conditions of reductive amination with allylamine, the allylic benzoate was also displaced leading to pyrrolidine derivative 396, dr = 75:25 in favour of the β-benzyloxymethyl substituent. Ring-closing metathesis was effected in low yield on the hydrochloride salt of 396 in order to minimise catalyst deactivation. Finally, hydrogenation of the newly-formed pyrroline ring afforded (+)-hyacinthacine A2 in confirmation of the assigned structure for this natural product.
From the same nitrone (402), Sm(II)-mediated reductive addition of ethyl acrylate furnished bicyclic lactam 405 (Scheme 58) with dr = 90:10, reflecting preferred addition anti to the proximal benzyloxy substituent. Lactam reduction and hydrolysis of the benzyl ethers gave short access to (+)-hyacinthacine A$_2$.

The first total synthesis of (+)-hyacinthacine A$_1$ was achieved by stereocontrolled carboazidation of allylsilane 406 (Scheme 59), obtained by diastereoselective addition to glyceraldehyde acetone (prepared, in turn, from d-mannitol). The carboazidation was efficient with this diastereomer, leading to an 84:16 ratio of syn,anti- (407) and anti,anti-adducts. The conversion of this intermediate into the natural product required ten further steps, key among them being Fleming–Tamao oxidative cleavage of the C–Si bond, and double $\Delta$-cyclisation onto pendant epoxide and ester functionality from 409; lactam reduction and acetone deprotection completed the route. By performing the double $\Delta$-cyclisation following step (f), (+)-3-epi-hyacinthacine A$_1$ 410 was also prepared.

Blechert’s group applied an approach strategically similar to their earlier synthesis of xenovenine to a synthesis of (+)-hyacinthacine A$_1$. In this case, cross-metathesis of alkene 414 (Scheme 61), derived from racemic vinyl glycine, and masked 1,4-diacetyl 416 led to diol 417 after asymmetric dihydroxylation. A one-pot sequence—hydrogenolysis of the Chz protecting group and reductive cyclisation onto the ketone, acid-mediated direct conversion of the acetal into a bicyclic iminium, hydrogenation, and formation of the free-base—gave the natural product in six steps by the longest linear route from (S)-vinyl glycine derivative 413.
paralleled that used, for example, in Donohoe’s synthesis of reductive amination, from Cbz–(chain adducts in variable diastereomers was achieved using a chemoenzymatic procedure.

This overall 19-step route to (–)–5–extension then stereoselective reductive amination completing an overall 19-step route to (–)–5–epi-hyacinthacine A₄.

Key pyrrolidine intermediates for the synthesis of hyacinthacines were obtained from D-glucose via reductive cyclisation of azides such as 419 (Scheme 62).154 From pyrrolidine 420, the route paralleled that used, for example, in Donohoe’s synthesis of hyacinthacines A₆ and A₇ (see below, Scheme 68) with Wittig extension then stereoselective reductive amination completing an overall 19-step route to (–)–5–epi-hyacinthacine A₄.

A concise synthesis of (–)-hyacinthacine A₂ and three diastereomers was achieved using a chemoenzymatic procedure. L-Rhamnulose 1-phosphate aldolase (RhuA/Pase) catalysed the aldol addition of dihydroxyacetone phosphate (DHAP) to either enantiomer of N-Cbz prolinal the diastereomers 422 and 423 were isolated with dr = 45:55.

In situ Cope–House cyclisation of hydroxylamine intermediate 433 (Scheme 64), obtained by stereoselective Grignard addition to nitro 402, formed the key step in a synthesis of (+)-5-epi-hyacinthacine A₃ and (–)-5-epi-hyacinthacine A₅ from 2,4-diphenylpropan-2-one (Dipp–2)157. Deoxygenation of the N-oxide was achieved in the same step as global deprotection, resulting in a short synthesis of these polyhydroxylated pyrrolizidines.

The group followed up on this, with the synthesis of twelve tri- and tetrahydroxylated pyrrolizidines 121, 397, and 423–432 from prolinal derivative 278 and its 3- and 4-hydroxy derivatives.56 This revealed an assignment error in the results presented in Scheme 63; thus compound 410 was corrected to 425 and compound 423 was corrected to 432.
The first non-chiral pool synthesis of (+)-hyacinthacine A₁ was reported in 2008, using (S)-Stericol (437, Scheme 65) as a chiral auxiliary. Elaboration of this alcohol to lactam 438 was conducted using a previously reported procedure (see the section on amorphogynines) which involved [2+2]-cycloaddition of dichloroketene as a key step. Copper-catalysed Grignard addition to derived aminoacetal 439 gave the trans-2,5-dialkylpyrrolidine 440 preferentially (dr = 6:1). The rest of the synthesis followed conventional lines with the cis-diol motif in 432 being introduced by Chugaev elimination of alcohol 441 and dihydroxylation.

**Scheme 64** Reagents and conditions: (a) 3-butenylmagnesium bromide, THF, −78 °C; (b) CHCl₃; (c) H₂, Pd/C, aq HCl, MeOH, THF.

The first asymmetric syntheses of (+)-hyacinthacines B₁ and B₂ were reported in 2008. The enantiospecific routes initiated from (5)-pyroglutamic acid which was converted into lactam 446 (Scheme 67) by known methods. Addition of butenylmagnesium bromide was followed by hydride reduction which gave high levels of the desired epimer (dr = 95:5) at high dilution in ethanol. Mesylation and N-cyclisation gave pyrrolidone 447. Sharpless asymmetric dihydroxylation was carried out in both enantiomeric ligand series [dr (step h) = 71:29; dr (step i) = 19:81] to give samples enriched in either mesylate epimer (448/449). Release of the free amine in both diastereomeric series, N-cyclisation and deprotection steps gave access to the natural products 445 and 450.

**Scheme 65** Reagents and conditions (incomplete information available): (a) Boc₂O, DMAP, Et₃N; (b) LiEt₂BH, TeOH, MeOH; (c) PhMe₂SiCH₂MgCl, CuBr·SMe₂, BF₃·OEt₂; (d) Sia₂BH then H₂O; (e) Dess–Martin periodinane; (f) NaClO₂ then CH₂N₂; (g) TMSOTf; (h) PhCH₂OH, heat; (i) CF₃CO₂H; (j) KH then CS₂ then MeI; (k) heat; (l) OsO₄, NMO, acetone; (m) HBF₄·OMe₂, KF then MCPBA; (n) BH₃·SMe₂.

The authors later reported the elaboration of lactam 442 into (+)-hyacinthacine B₁ (Scheme 66), with installation of the additional hydroxymethyl substituent at C(5) being achieved from cyanoamine 443 by iminium generation, and capture by the silylated Grignard reagent employed in the synthesis of 401.

**Scheme 66** Reagents and conditions (incomplete information available): (a) TESCl, imidazole; (b) DIBAL, BuLi then TMSCN; (c) PhMe₂SiCH₂MgCl, THF/Et₂O; (d) TBAF; (e) HBF₄·OMe₂ then aq KOH then H₂O₂, KF, DMF.

The enantiospecific routes initiated from (5)-pyroglutamic acid which was converted into lactam 446 (Scheme 67) by known methods. Addition of butenylmagnesium bromide was followed by hydride reduction which gave high levels of the desired epimer (dr = 95:5) at high dilution in ethanol. Mesylation and N-cyclisation gave pyrrolidone 447. Sharpless asymmetric dihydroxylation was carried out in both enantiomeric ligand series [dr (step h) = 71:29; dr (step i) = 19:81] to give samples enriched in either mesylate epimer (448/449). Release of the free amine in both diastereomeric series, N-cyclisation and deprotection steps gave access to the natural products 445 and 450.

**Scheme 67** Reagents and conditions: (a) CH₂=CH(CH₂)₂MgBr, THF; (b) NaBH₄, CeCl₃, EtOH, 0 °C; (c) McCl, Et₂N, CH₂Cl₂; (d) t-BuOK, THF; (e) TBAF, THF; (f) NaH, THF then CbzCl, NaHCO₃, MeOH; (g) TBSCl, imidazole, DMF; (h) AD-mix-a, aq t-BuOH, 0 °C; (i) AD-mix-β, aq t-BuOH, 0 °C; (j) TBSCl, Et₂N, CH₂Cl₂; (k) McCl, Et₂N, CH₂Cl₂; (l) H₂, Pd/C, EtOH; (m) TBAF, THF; (n) aq CF₃CO₂H.
Donohoe employed his established pyrrole reduction methodology (cf. Scheme 89) as the starting point for a general synthesis of polyhydroxylated pyrrolizidine alkaloids.\textsuperscript{61} Dihydropyrrole 452 (Scheme 68) was obtained in >98% ee in four steps from N-Boc pyrrole, and dihydroxylation of this alkene was achieved with high diastereoselectivity (dr>20:1). Protection of the diol led to pyrrolidine 453, a common intermediate in the synthesis of four naturally-occurring pyrrolizidines: (−)-2,3,7-tri-epi-australine, (+)-hyacinthacine A\textsubscript{1}, (+)-hyacinthacine A\textsubscript{6}, and (−)-hyacinthacine A\textsubscript{1}. The synthesis of (+)-hyacinthacine A\textsubscript{6}, detailed in the scheme, is representative. Thus, MIP-protection of the 1°-alcohol and acetate hydrolysis enabled dehydration, giving enamide 454. This was hydroborated from the exo-face and oxidised to aldehyde 455. Olefination, asymmetric reduction of resulting ketone 456, and alkene hydrogenation were followed by mild N-deprotection (step p). Activation of the pro-C(5) hydroxyl group as its mesylate was accompanied by N-cyclisation to complete the pyrrolizidine core. The natural product 65 was generated by acidic hydrolysis of the hydroxyl protecting groups.

\[ \text{Scheme 68 Reagents and conditions: (a) LiTMP, CICO}_{2}\text{Me, THF, }\text{−78} ^\circ \text{C}; (b) Li, DBB, THF, }\text{−78} ^\circ \text{C to }\text{2,6-di}(\text{tert-buty})\text{phenol}; (c) Red-Al, THF, 0 ^\circ \text{C}; (d) }\text{Pseudomonas lipoprotein lipase, vinyl acetate, THF, 37} ^\circ \text{C}; (e) OsO}_{4}, \text{MeNO, CH}_{2}\text{Cl}_{2}; (f) 2-methoxypropene, TSOH, DMF; (g) 2-methoxypropene, PPTS then K\textsubscript{3}CO\textsubscript{3}, MeOH; (h) }\text{MsO, DMAP, CH}_{2}\text{Cl}_{2}; (i) DBU, NaI, DME, reflux; (j) BH\textsubscript{3}-THF, THF then NaOH, aq H\textsubscript{2}O\textsubscript{2}; (k) TPAP, NMO, 4A MS, CH\textsubscript{2}Cl\textsubscript{2}; (l) NaN\textsubscript{3}, (EtO\textsubscript{2})\textsubscript{3}PO, CH\textsubscript{2}Cl\textsubscript{2}, THF, 0 °C to rt then aq HCl; (m) TBSCl, imidazole, DMF; (n) Bu\textsubscript{3}SnH, reflux, p-cresol, CH\textsubscript{2}Cl\textsubscript{2}; (o) MsCl, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C to rt; (r) HCl, MeOH.

In Chandrasekhar’s synthesis of (+)-hyacinthacine A\textsubscript{6}, selectively-protected tetraol 457 (Scheme 69), derived from 1-(+) diethyl tartrate, was elaborated in six straightforward steps to epoxy ester 458. Lewis acid activation combined with Pd(0)-catalysis generated allylic azide 459 by intramolecular delivery of azide from the azidosilicate to the Pd-π-allyl presumed to be in the extended conformation shown. From this point 459, protecting group manipulations and activation set up double cyclisation following alkene hydrogenation and azide and benzyl ether hydrogenolysis. The so-formed pyrrolizidinone (not shown) was subjected to final deprotection and lactam reduction to give (+)-hyacinthacine A\textsubscript{1}.

In an unusual approach to the synthesis of pyrrolizidine diastereomer (−)-7α-epi-hyacinthacine A\textsubscript{1}, (4+3)-cycloadDITION to pyrrrole derivative 461 (Scheme 70) set the cis- relative stereochemistry across the 3- and 7α- positions in the final product.\textsuperscript{163} Ring cleavage by Baeyer–Villiger oxidation gave pyrrolidine 463 which was then elaborated to bromide 464. The second ring was closed somewhat unconventionally by metal-halogen exchange and intramolecular acylation of the so-formed alkylithium onto the Cbz carbonyl. Lactam reduction (in 465) and release of the hydroxyl groups gave the target pyrrolizidine 424. The authors showed that lipase-mediated resolution was effective for the generation of hydroxyster 463 in enantiomerically enriched form, opening a route to individual pyrrolizidine enantiomers.
Hyacinthacine C\textsubscript{2,3} analogues were prepared by nitrone cycloaddition of 402 with allylic alcohol 468 (\(\rightarrow\) 466, Scheme 71) or allylic acetate 469 (en route to 470).\textsuperscript{166} The dipolarophiles were obtained by lipase mediated kinetic resolution of racemic 3-buten-1,2-diol and their cycloadditions found to afford predominantly one diastereomer in each case. From isoxazolidine 466, a standard sequence was followed (sulfonylation, N-O reduction and cyclisation, then two deprotection steps) to give pyrrolizidine 467. An analogous sequence from diacetate 469 gave the 5-epimer 470.

![Scheme 70](image)

**Scheme 70** Reagents and conditions: (a) 1,1,3,3-tetramethoxypropane, ZnEt\textsubscript{2}, PhH\textsubscript{2}, –12 °C to rt; (b) K \textsubscript{2}CO\textsubscript{3}, THF, aq HCl; (c) \textsubscript{1}MCPBA, DCE, 2,4,6-tri-\textsubscript{Bu}C\textsubscript{6}H\textsubscript{4}OH, 55 °C; (e) K \textsubscript{2}CO\textsubscript{3}, MeOH; (f) TBS, imidazole, DMF; (g) LiAlH\textsubscript{4}, Et\textsubscript{2}O; (h) CBr\textsubscript{4}, PPh\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}; (j) t-BuLi, THF, –80 °C; (k) BH\textsubscript{3}:Me\textsubscript{2}S, THF then MeOH, reflux; (l) aq HCl, MeOH, reflux then Dowex 1X8 (OH\textsuperscript{–}) ion exchange chromatography.

Aldehyde 471 (Scheme 72), prepared in eight steps from lactam 464, \textsuperscript{167} served as common starting material for the first reported total syntheses of hyacinthacines C\textsubscript{2} and C\textsubscript{3}, and their 5-epi-analogues.\textsuperscript{167} Zinc-mediated allylation gave separable alcohols 472 and 473 in ca. 4:1 ratio, respectively. Each epimer was subsequently dihydroxylated and the stereochemistry at the newly-formed 2\textsuperscript{°}-hydroxyl was established in all four cases (474–477) on the basis of \textsuperscript{13}C-NMR data of the derived 1,3-acetonides. The scheme gives reagents for the elaboration, by standard methods, of one of these epimers (474) to (+)-hyacinthacine C\textsubscript{2} with identical sequences being used to access the other diastereomers shown. This work revealed discrepancies between the NMR data for synthetic (+)-hyacinthacine C\textsubscript{3} and those reported for the natural product and a revision of the structure of the latter is needed.

![Scheme 71](image)

**Scheme 71** Reagents and conditions: (a) 468, CH\textsubscript{2}Cl\textsubscript{2}, 70 °C (microwave); (b) MsCl, pyridine; CH\textsubscript{2}Cl\textsubscript{2}; (c) Zn, aq AcOH, 60 °C; (d) Ambersep 900 (OH), MeOH; (e) H\textsubscript{2}, Pd/C, HCl then Dowex 50WX8, aq NH\textsubscript{3}.

Hyacinthacines A\textsubscript{2,3}, A\textsubscript{1} and 5-epi-hyacinthacine A\textsubscript{1} (Scheme 73) were synthesised from ketone 481, derived from Wittig olefination of Garner’s aldehyde then dihydroxylation and elaboration via the Weinreb amide.\textsuperscript{165} Selective carbonyl...
reduction then alkene cleavage and activation of the 5- and 7α-
positions as their mesylates (in 482) set up double N-cyclisation
to (+)-hyacinthacine A2 in the final step. For the synthesis of (+)-
hyacinthacine A3, the cyclisation steps were separated;
cyclisation onto C(7α)- proceeded via the mesylate as before, then
Wacker oxidation of 484 or 485 allowed reductive amination
to complete the pyrrolizidine ring system. From the Cb z-protected
intermediate 486, (+)-5-epi-hyacinthacine A1 was obtained as a
single diastereomer; from the Boc- analogue 487, separable
mixtures of (+)-hyacinthacine A1 and its 5-epimer were obtained
in proportions that varied markedly depending on precise reaction
conditions.

**Scheme 73** Reagents and conditions: (a) Ph-P=CHCO₂Et, THF, reflux;
(b) AD-mix-β, MeNH₂, aq t-BuOH, 0 °C; (c) PhCH=CHB(OH)₂, NaH, Bu₂OH, THF;
(d) triphosgene, Et₂O; (e) MeON(CH₂)₂HCl, i-PrMgCl, THF, –10 °C; (f) L-Selectride, THF, –78 °C; (g) TESCl, Et₂N, CH₂Cl₂;
(h) OsO₄, NaOCl, MeOH, THF; (i) aq NaH, Bu₂Ni, THF; (j) DDQ, aq CH₂Cl₂;
(k) NaOH, EtOH, 110 °C (microwave); (l) MsCl, Et₂N, CH₂Cl₂, 0 °C; (m) H₂,
PdCl₂, MeOH; (n) N-BOC, THF; then (o) or (f).

Building on their route to australine epimers (see below, Scheme
88) Pyne’s group reported the first total synthesis of (+)-
hyacinthacine B₃ (Scheme 74). Sulphone 489, prepared in two
steps from (5)-penten-2-ol, was dihydroxylated and the so-formed
aldehyde 490 trapped with amine 495 in a Petasis boronic acid
Mannich reaction to give diene 491. Ring-closing metathesis then
dihydroxylation gave pyrrolidine 493 after protecting group steps.
The synthesis of (+)-hyacinthacine B₃ was then completed by
selective mesylation and N-cyclisation at the less hindered
hydroxyl, then hydrogenolysis of the O-benzyl ethers. A parallel
sequence from (R)-penten-2-ol afforded the structure (70)
reported for (+)-hyacinthacine B₇ but this synthesis showed that
the original structural assignment requires revision.

**Scheme 74** Reagents and conditions: (a) DHDQ-IND-OsO₄, MsNH₂, aq t-
BuOH; (b) PhCH=CHB(OH)₂, 495, CH₂Cl₂; (c) triphosgene, Et₂N,
CH₂Cl₂; (d) Grubbs’ II, CH₂Cl₂, 90 °C (microwave); (e) K₂OsO₄·2H₂O,	NMO, aq acetone; (f) BnBr, NaH, Bu₂OH, THF; (g) DDQ, aq CH₂Cl₂;
(h) NaOH, EtOH, 110 °C (microwave); (i) MsCl, Et₂N, CH₂Cl₂, 0 °C; (j) H₂,
PdCl₂, MeOH; (k) ion-exchange chromatography.

A total synthesis of hyacinthacine A₂ was achieved in five steps
from nitron 402, derived from D-arabinose (Scheme 75). Vinyl Grignard
addition proceeded with high anti-stereoselectivity with respect to the adjacent benzoxyl group (dr
>99:1). The so-formed hydroxylamine (not shown) was
deoxygenated and N-alkylated to give diene 496 from which ring-
closing metathesis, alkene hydrogenation, and deprotection gave
the natural product (397) efficiently.
Grignard addition to the enantiomer of this nitrone (402, Scheme 76) was used in the synthesis of (−)–hyacinthacine A₃ and its C(5) epimer.¹¹⁰ One-pot acetal hydrolysis, cyclisation, and cyanation gave amidonitrile 498, predominantly as the endo- diastereomer shown. Modified Bruylants reaction with MeMgBr was effective only with added Ag(I) salt as Lewis acid (dr = 8:6:1). Hydrogenolysis completed the route to (−)-hyacinthacine A₃. In the same work, (−)-5-epi-hyacinthacine A₁ was obtained from Grignard adduct 497. Here, N-O bond cleavage and N-protection, then conversion of the terminal acetal to methyl ketone 499 set up reductive amination and deprotection steps to complete the route.

**Scheme 76** Reagents and conditions: (a) (MeO₂)₃CH(CH₂)₂MgBr, THF; (b) KCN, aq HCl, 30 °C; (c) MeMgl, AgBF₄, CH₂Cl₂, Et₂O; (d) H₂, Pd/C, MeOH; (e) Zn, Cu(OAc)₂, AcOH, CH₂Cl₂; (f) Boc₂O, NaOH, aq dioxane; (g) TsOH, aq acetone, reflux; (h) MeMgl, Et₂O, 0 °C; (i) PCC, SiO₂, CH₂Cl₂; (j) CF₃CO₂H, CH₂Cl₂; (k) NaBH₄, MeOH, 0 °C; (l) H₂, Pd/C, MeOH.

Lactam 500 (Scheme 77), obtained from lactam 521 (Scheme 81) by N-deprotection (CAN) and acylation (Boc₂O), was used as a common intermediate in syntheses of (+)-hyacinthacines A₂ and A₃, which differ by the presence (or absence) of a C(5)-methyl.¹¹⁸ Grignard addition to the ring carbonyl and hemiaminal reduction afforded adduct 501 with reasonable diastereoselectivity. The major [β-H(7a)] diastereomer was cyclised under Appel conditions and deprotected, giving (+)-hyacinthacine A₂. For (+)-hyacinthacine A₂ adduct 502 was N-protected for the Wacker oxidation of the terminal alken; cyclisation by reductive amination onto the so-formed ketone and benzyl ether hydrogenolysis completed the route (which also confirmed the identity of this alkaloid (488)).

The route was recently improved by the use of a one-pot reductive alkylation procedure to install the butenyl side chain.¹¹⁹ Thus, the N-PMB analogue of lactam 500 (i.e. 521, Scheme 81) was treated with TEO and 2,6-di-tert-butyl-4-methylpyridine then 3-butenyl-MgBr followed by Hantzsch ester to generate 502-PMB in a single operation (not shown). From this point, the route was continued as before.

Methodology developed for the synthesis of A-series hyacinthacines (see below, Scheme 85) was adapted for the synthesis of hyacinthacine C diastereomers. Thus, in one application, fructose-derived pyrrolidine 503 (Scheme 78) was elaborated to enone 504; epimerisation of the 7α-centre occurred during the Wittig olefination (step e).¹¹⁷ In this substrate, dihydroxylation under Upjohn conditions gave a single diol diastereomer. Acetylation then hydride reduction gave separable epimers 505 and 506 (dr = 1:1). Mesylation of the free alcohols in 505 and 506, then N-cyclisation and deprotection gave new pyrrolizidines 507 and 508, respectively. In related work, dihydroxylation of a trans-dienylboroxyl variant of pyrrolidine enone 504, gave a 1:4:1 ratio of diols 509 and 510.¹¹⁸ Both diastereomers gave the same C(5)-stereochemistry upon reductive amination (step I), presumably controlled by preferential hydrogenation of the intermediate iminium from the face anti- to the bulky CH₂OTBDPS group. Desilylation and hydrogenolysis of the benzyl protecting groups afforded the alkaloid (+)-hyacinthacine C₂ and its 6,7-diepimer. Although firm conclusions were not drawn, it was noted that the [¹³C] NMR data in particular for synthetic hyacinthacine C₃ and those reported¹²⁰ differ; therefore, it is proposed that the structure of this natural product requires revision.
In Davies’ recent synthesis of (−)-7a-epi-hyacinthacine A₁, d-ribose was converted in three steps to a substrate 512 (Scheme 79) for doubly diastereoselective (matched) conjugate addition of a chiral ammonia equivalent (step d).

Oxidation of the so-formed enolate in situ gave intermediate 513 as a single observable diastereomer. Ring-closing metathesis gave 514, a substrate for transannular iodoamination (with accompanying loss of the N-protecting group) via favoured conformer 515. The extra carbon in the side-chain was excised by ester reduction, periodate cleavage, and a second reduction; acetonide hydrolysis then generation of the free-base completed the route.

D-Ribose was also employed as the starting material in a synthesis of the (+)-enantiomer of 2-epi-hyacinthacine A₂ (423, Scheme 80). Here, the key constructive step, that established the C(7a)-stereochemistry, was achieved by Sm(II)-mediated reductive alkylation of nitrone adduct 516 in a process related to, for example, Py’s route to (+)-hyacinthacine A₂ (Scheme 58). From adduct 518, the rest of the route followed established lines. Cleavage of the N-O bond then reduction of the so-formed lactam gave pyrrolidine 519 after selective acetonide hydrolysis and silylation of the 1°-hydroxyl. The second ring was closed via the mesylate, and deprotection liberated the pyrrolizidine (423). An attempt to extend this general route for the preparation of (+)-7a-epi-hyacinthacine A₁ (424), by final ring-closure onto an epoxide, led instead to a trihydroxylated indolizidine.
A total synthesis of (+)-hyacinthacine C3 and two epimers was developed from nitrone 402 (Scheme 82).174 The strategy is related to that reported for the synthesis of (+)-5-epi-hyacinthacine A3 (see above, Scheme 64). Stereoselective addition of lithiated dithiane 526 then Cope–House cyclisation (step b) generated two diastereomers 524 and 525 (dr = 1:1) of the pyrrolizidine core following reduction of the N-oxide. The separated alcohol 524 was then taken through three standard steps to give pyrrolizidine 74 efficiently. By performing the carbonyl reduction (step e) after MOM-protection of the 2°-hydroxyl group, the cis-diol disposition in analogues 527 and 528 was attained. The isomers were assayed for inhibition of a variety of glycosidases, and 528 showed weak activity against α-glucosidases from rat intestinal maltase ($IC_{50} = 58.5 \mu M$) and rice ($IC_{50} = 64.2 \mu M$).
Fox’s recent synthesis of (+)-hyacinthacine A₂ built on Madsen’s earlier route to the 7-hydroxy derivative, australine (see below, Scheme 90).

The key difference in this route (Scheme 83) was the mode of transannular cyclisation to clip across the eight-membered ring and form the pyrrolizidine. In Madsen’s work, this was achieved by epoxide ring-opening; in Fox’s route, transannular hydroamination was effected under mildly alkaline conditions (step g). The stereochemical aspects of this route are noteworthy: the Z-hexahydroazocine isomer 530 was converted into the E-isomer 531 by photoisomerisation in a flow reactor set up to trap the strained E-alkene by complexation with Ag(I), unreacted Z-alkene being cycled through the reactor. The planar chirality in the hexahydroazocine was then fully transferred to the pyrrolizidine in the final step.

Mention has already been made (see above, Scheme 78) of Izquierdo’s general approach to pyrrolizidines from D-fructose-derived functionalised pyrrolidines. During the review period, this strategy was first introduced in the context of the synthesis of (+)-7a-epi-hyacinthacine A₂ (432) and 5,7a-di-epi-hyacinthacine A₁ (540) from partially-protected 2,5-dideoxy-2,5-imino-D-glucitol (DGDP) 539 (Scheme 85). Wittig extension with either Ph₂P=CHCHO or Ph₂P=CHCOMe then reductive amination led to hyacinthacine isomers 432 and 540, respectively. Subsequently, analogous approaches were described for the synthesis of (+)-hyacinthacine A₁ (397), (+)-hyacinthacine A₂ (488), (+)-3-epi-hyacinthacines A₁ (541) and A₂ (425), the enantiomers of 3-epi-hyacinthacine A₃ (542 and 543), (+)-5-epi-hyacinthacines A₁ (436) and A₂ (421), and (–)-hyacinthacine A₁ (66) and its (–)-1-epimer (544). A further paper, describing the syntheses of (–)-hyacinthacine A₁ (401) and (–)-hyacinthacine A₆ (65), was retracted.

Parallelling earlier approaches to the hyacinthacines, Goti’s group described a synthesis of (+)-hyacinthacine A₁, its C(7a) epimer and two 6-hydroxylated analogues (Scheme 84). Thus, nitroene 532, derived from D-ribose, reacted with tert-butyl acrylate to give a 1.5:1 ratio of exo-anti (533) and exo-syn (534) diastereomers with complete regioselectivity. Following their separation, the two adducts were taken forward by the established N-O reductive cleavage / N-acylation process leading to 6-hydroxy-pyrrolizidinones 535 and 536, respectively. Standard transformations led, in a few steps, to the four pyrrolizidines shown.
Desvergnes and Py prepared the hyacinthacine homologue ‘8-homo-ent-(+)-hyacinthacine A₂’ (548, Scheme 86) from d-glucose as a potential UDP-galactopyranose mutase (UGM) inhibitor. Octyl tetra-benzyl d-glucose was hydrolysed, exposing the 1,4-hydroxylaldehyde from which nitro compound 546 was prepared by condensation and Sn₂-displacement steps. Sm(II)-mediated reductive alkylation with ethyl acrylate gave the N-hydroxyxypyrrolidine 547 essentially as a single diastereomer (the minor diastereomer was undetectable by NMR). From this point, it simply remained to reduce the hydroxylamine, cyclise under basic conditions, reduce the so-formed lactam, and cleave the benzyl protecting groups. This pyrrolizidine (548) and three other candidates) showed modest UGM inhibition (~40% at 25 mM).

**Australine and epimers**

The first reported synthesis of a member of this class during the review period featured an elegant tandem intermolecular nitroalkene Diels–Alder / intramolecular nitrene cycladdition to set four of the five stereogenic centres in the target, (+)-1-epi-australine (553, Scheme 87) which had been synthesised just twice previously. The cycladdition substrate 550 was assembled in three steps from disopropylchlorosilane by: (i) addition of butadienyllithium; (ii) conversion of the so-formed silane to the pyridine, 0 °C to rt (then separate isomers); (d) TBAF, THF; (c) H₂, Pd/C, aq HCl, MeOH then Amberite IRA-400 (OH⁻).

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Pyne’s synthesis of australine epimers began with the \textit{trans}-vinyl epoxide 554 (Scheme 88), available from 3-but-yn-1-ol in six steps via Sharpless asymmetric epoxidation. Ring-opening with allylamine 495 (from butadiene monoepoxide, 3 steps) and trimethyl orthoformate gave carbamate 555.\textsuperscript{185} Ring-closing metathesis, and dihydroxylation anti-to the benzylxymethyl group gave key intermediate 556. Protecting group manipulations then allowed removal of benzyl and acetyl protecting groups. The use of Zn–mediated fragmentations of the carbamate (→ 557) set up a final cyclisation under Mitsunobu conditions. Removal of benzyl and acetyl protecting groups then allowed the route to (\textit{+})-1,7-di-\textit{di-epi}-australine. Derivatisation of diol 556 as its cyclic sulfate allowed regioselective ring-opening with caesium benzoate en route to \textit{trans}-dioxygenated pyrroline 558. A sequence of steps similar to that used in the synthesis of the (\textit{+})-1,7-di-\textit{di-epi}-isomer generated (\textit{−})-7-\textit{epi}-australine. This strategy was used to prepare (\textit{−})-1-\textit{epi}-australine simply by varying the stereochemistry of the starting vinyl epoxide to 561\textsuperscript{.180} An attempt to extend this methodology to encompass a synthesis of (\textit{+})-australine itself was unsuccessful.

Donohoe’s synthesis of (\textit{+})-1-\textit{epi}-australine began with Birch reduction of pyrrole 562 (Scheme 89) with dienolate protonation under equilibrating conditions giving the \textit{trans}-diester 563.\textsuperscript{190,191} Dihydroxylation and acetonide protection allowed discrimination of the two esters with the sterically less-encumbered \textit{exo}-ester (i.e. \textit{anti}- to the acetonide) being reduced preferentially. DIBAL reduction of the remaining ester produced aldehyde 564 which was used as a substrate for stereoselective vinyl organometallic additions, the conditions shown (step g) providing the best compromise of desired selectivity and high conversion. Elaboration of the vinyl group and cyclisation under standard conditions completed the synthesis, 11 steps overall from pyrrole 562. The intermediate aldehyde 564 was also used in a synthesis of the 7-deoxy analogue, hyacinthacine A\textsubscript{1} (401). In this case, the chain was extended with Wittig olefination, then reduction steps and intramolecular N-alkylation completed the route (cf. Scheme 68).

Central to the middle of the review period, Madsen completed enantiospecific formal syntheses of australine with the preparation of hexahydroazocine 568 (Scheme 90) by two routes, one from \textit{d}-fructose, the other from sucrose; only the latter ‘second generation’ route will be described here.\textsuperscript{192} Central to both routes was the use of Zn-mediated fragmentations of carbohydrate-derived precursors to give usefully-functionalised

\begin{equation}
\text{Scheme 88 Reagents and conditions: (a) LiOTf, CH}_2\text{CN, 120 °C; (b) triphosgene, Et}_3\text{N, CH}_2\text{Cl}_2; (c) Grubbs' I, CH}_2\text{Cl}_2, reflux; (d) K}_2\text{OsO}_4, \text{H}_2\text{O}, \text{NMO, aq acetone; (e) Ac}_2\text{O, pyridine; (f) DDQ, aq CH}_3\text{Cl}_2; (g) NaOH, EtOH, 70 °C; (h) DIAD, PPh}_3, pyridine, 0 °C; (i) Ac}_2\text{O, pyridine; (j) H}_2, \text{PdCl}_2, \text{MeOH; (k) Ac}_2\text{O, pyridine; (l) NaOMe, MeOH; (m) SOCl}_2, \text{Et}_3\text{N, CH}_2\text{Cl}_2, 0 °C; (n) RuCl}_3\cdot3\text{H}_2\text{O, NaOCl, aq CCL}_4, \text{CH}_2\text{CN; (o) PhCO}_2\text{H, Cs}_2\text{CO}_3, \text{DMF, 40 °C then H}_2\text{SO}_4, aq THF; (p) DDQ, aq CH}_3\text{Cl}_2; (q) NaOH, EtOH, 70 °C.}
\end{equation}

\begin{equation}
\text{Scheme 89 Reagents and conditions: (a) Li, NH}_3, \text{THF, NH}_3\text{Cl, –78 °C; (b) Os}_2\text{O}_7, \text{Me}_2\text{NO, CH}_2\text{Cl}_2; (c) 2,2-dimethoxypropane, TsoH, acetone; (d) NaBH}_4, \text{THF, MeOH; (e) TBDSCI, imidazole, DMF; (f) Dibal, CH}_2\text{Cl}_2, –40 °C; (g) vinyl-MgBr, THF; (h) TBSOTf, 2,6-lutidine, CH}_2\text{Cl}_2, –78 °C to rt; (i) BH}_2\cdot\text{THF then H}_2\text{O}, aq NaOH, THF; (j) \text{MeCl, Et}_3\text{N, CH}_2\text{Cl}_2; (k) aq CF}_3\text{CO}_2\text{H; (l) Ph}_2\text{P=CHCO}_2\text{Me, PhCH}_2\text{Cl, 110 °C; (m) H}_2, \text{PtO}_2, \text{MeOH; (n) Dibal, CH}_2\text{Cl}_2, –78 °C to rt; (o) \text{MeCl, pyridine, 0 °C; (p) TESOTf, 2,6-lutidine, CH}_2\text{Cl}_2, –78 °C to rt; (q) (COCl)}_2, \text{MeOH.}
\end{equation}
enantiopure intermediates. Here, acetone protection of sucrose cleaved the glucose and fructose residues, and the fructosefuranoside moiety was then iodinated and fragmented to provide protected ketotriol 529. Reductive amination with homoallylamine gave 567 as a 2:1 mixture in favour of the desired epimer which was carried forward into the next step. From this point the route paralleled White’s synthesis of (+)-australine. Ring-closing metathesis proceeded efficiently, then three protecting group manipulation steps gave bicyclic carbamate 568 which had previously been converted to (+)-australine in three steps.

Scheme 90 Reagents and conditions: (a) 2,2-dimethoxypropane, TsOH H2O, DMF; (b) Li, PPh3, imidazole, THF, 65 °C; (c) Zn, aq THF, 40 °C; (d) homoallylamine, NaBH4, BnBr, THF, 40 °C; (e) MeMgBr, PhCH3, Et2O, reflux; (f) TBAF, THF; (g) MeSOCl, Et2O, reflux; (h) NaH, BnBr, THF, 40 °C; (i) DDQ, aq THF; (j) NaH, BnBr, THF, 40 °C; (k) MsCl, Et3NEt, CH2Cl2, –90 °C; (l) BH3, CH2Cl2; (m) LiBH4, aq CH2Cl2; (n) SEMCl, i-Pr2NEt, CH2Cl2; (o) LiBH4, Et2O, –90 °C; (p) DDQ, aq THF; (q) NaH, BnBr, THF, 40 °C; (r) MeMgBr, PhCH3, Et2O, reflux; (s) TBAF, THF; (t) MsCl, Et3NEt, CH2Cl2; (u) BnNH2, NaI, DMSO, 80 °C; (v) H2, Pd(OH)2, EtOH; (w) CF3CO2H, CH2Cl2; (x) then aq NH3.

Marco’s australine synthesis was soon followed by Trost’s which featured sequential enantio- and diastereoselective allylic alklylation processes (Scheme 92). The synthesis began with reductive dimerisation of acrolein and conversion to carbonate 574, a mixture of diastereomers. With 579 as chiral ligand, Pd-mediated asymmetric allylation with N-phthalimide gave, after release of the free amine, aminolcohol 575 in >99% ee. The derived carbamate then entered into a palladium-mediated diastereoselective ring-opening of racemic butadiene monoepoxide in the presence of the same ligand 577. This reaction proved to be totally ligand-controlled with ent-579 affording the epimeric epoxide-opening product with essentially the same dr and ee. Ring-closing metathesis generated the first pyrrolidine ring (in 577) then, after hydroboration and oxidation of the vinyl group, exo-face selective epoxidation and regioselective alcoholysis set up the trans-diol stereochemistry and cleaved the carbamate, giving 578. The synthesis was then completed by N-cyclisation onto the 1°-mesylate formed in situ, and hydrogenolysis of the benzyl ethers.

Scheme 91 Reagents and conditions: (a) Cy2BCl, EtN, 0 °C; (b) SEMCl, i-Pr2NEt, CH2Cl2; (c) LiBH4, Et2O, –90 °C; (d) DDQ, aq THF; (e) NaH, BnBr, THF, 40 °C; (f) MeMgBr, PhCH3, Et2O, reflux; (g) TBAF, THF; (h) MsCl, Et3NEt, CH2Cl2; (i) BnNH2, NaI, DMSO, 80 °C; (j) H2, Pd(OH)2, EtOH; (k) CF3CO2H, CH2Cl2; (l) then aq NH3.

The first total synthesis of (+)-australine completed during the review period was based on syn-selective boron aldol reaction between two fragments 570 and 571 (Scheme 91), derived from L-erythrose (2 steps) and (S)-malic acid (6 steps), respectively. After OH protection (of 572), low-temperature hydride reduction of the ketone gave the alcohol product (not shown) with dr >95:5. Protecting group manipulation and mesylation of the three free hydroxyl groups gave intermediate 573 which, upon reaction with benzylamine, underwent three consecutive S$_{N}$2-type displacements (first at the 1°-position, then 2 x 5-exo-tet cyclisations) to give the pyrrolizidine ring system. Hydrogenolysis of the benzyl protecting groups, removal of the tert-butyl substituent under acidic conditions, and basification gave (+)-australine in 11% overall yield based on ketone 570.
protons at C(1) and C(5). Mitsunobu inversion of the newly-formed 2'-alcohol and hydroxyl deprotection completed the route.

Access to (−)-3-epi-australine followed an analogous pathway after Mitsunobu inversion of the 3-OH (→ 583). Non-natural (−)-3,7-di-epi-australine (430) was also prepared by retaining the C(7)-stereochemistry obtained upon hydride-mediated epoxide opening (cf. step 1). The synthesis and glycosidase inhibitory activity of these and related indolizidine alkaloids was summarised in a separate publication.197

Following on from Pyne’s syntheses of australine epimers (see above, Scheme 88), the group reported a unified synthesis of two pairs of pyrrolizidine epimers: (+)-australine and its 3-epimer 586, and (−)-uniflorine A (which is discussed separately, below) and its 6-epimer, (+)-casuarine (Scheme 93).196 The four syntheses developed from a common intermediate, pyrroline 581, that was prepared in short order by Petasis boron Mannich reaction then ring-closing metathesis as key steps. Selective hydroxyl protection, leaving just the 3-OH exposed, then blocking of the nitrogen as a base-labile Fmoc carb amate was achieved in both routes by mesylation of the free OH. En route to (+)-australine, treatment with piperidine cleaved the Fmoc group, and N-alkylation followed in situ. The regioselectivity of hydride ring-opening of the epoxide in 584 was not discussed but presumably fits the explanation given for the regioselective hydrolysis that gives the trans-diol in casuarine (from 584: (a) NaHSO₄, CH₂Cl₂, reflux then water; (b) Hz, PdCl₂, MeOH). Thus, in appropriate envelope conformations that allow axial attack by hydride, the 7-position is hindered by pseudoaxial
Py’s recent synthesis of (+)-australine (Scheme 94)\textsuperscript{198} built on methodology developed for (+)-hyacinthine A\textsubscript{2} (see above, Scheme 58). Thus, nitrone 402 was prepared in six steps from L-xylene. In the key step, this was subjected to reductive coupling with β-silylacrylate 589, the ester being delivered to the face opposite the ring substituents flanking the C=N bond, and with chelation between the ester carbonyl and nitrone oxygens establishing the 1,7a- relative stereochemistry in 590. Further reduction (Zn in step b)cleaved the hydroxylamine N–O bond and closed the pyrrolizidine ring, giving 588. The C–Si bond was then cleaved oxidatively, the lactam reduced, and the free hydroxyl groups released to furnish the natural product (569).

Scheme 94 Reagents and conditions: (a) NH\textsubscript{3}OH·HCl, NaHCO\textsubscript{3}, aq MeOH, 65 °C; (b) SmI\textsubscript{2}, 589, (CF\textsubscript{3})\textsubscript{2}CHOH, LiBr; THF, −78 °C to −30 °C then Zn, AcOH; (c) cumyl hydroperoxide, KH, TBAF, DMF; (d) BH\textsubscript{3}·SMe\textsubscript{2}, THF, reflux; (e) t-BuOOH, KH, TBAF, DMF; (f) H\textsubscript{2}, Pd/C, THF, MeOH.

Chmielewski completed a synthesis of (−)-1-homoaustrialine (Scheme 95), and evaluated its inhibitory activity against a panel of commercially-available α- and β-glucosidases.\textsuperscript{199} The tricyclic aldehyde 591 was obtained from the adduct of nitrone 351 (5 steps from (S)-malic acid) and lactone 595 (~4 steps from β-galactose) following transacylation and 1,2-diol cleavage. This was reduced, the 1°-alcohols silylated, and the remaining hydroxyl group activated by mesylation, giving 592. Hydrogenolysis of the N–O bond resulted in cyclisation to generate the 1-homoaustrialine core in 593. Standard removal of silyl, t-Bu, and acetyl protecting groups delivered the australine homologue 594; this compound showed only weak glucosidase inhibitory activity.

Scheme 95 Reagents and conditions: (a) LiBH\textsubscript{4}, THF; (b) TBDPSCI, Et\textsubscript{3}N, DMAP, rt to reflux; (c) MsCl, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, −5 °C to rt; (d) H\textsubscript{2}, Pd/C, Et\textsubscript{3}OAc then Ac\textsubscript{2}O, Et\textsubscript{3}N, DMAP; (e) TBAF, THF then Ac\textsubscript{2}O, pyridine; (f) CF\textsubscript{3}CO\textsubscript{2}H then Ac\textsubscript{2}O, Et\textsubscript{3}N, DMAP; (g) NH\textsubscript{3}, MeOH.

The 1-epi-2-deoxy- derivative 597 (Scheme 96) of (−)-1-homoaustrialine was prepared in nine steps overall from pyroglutamic acid.\textsuperscript{200} Reduction and dehydration of the lactam carbonyl gave pyrroline 596 that was elaborated to the pyrrolizidine analogue following a parallel route to that used in the synthesis of (±)-platynecine (see above, Scheme 42). Thus [2+2]-cycloaddition and selective Baeyer–Villiger rearrangement set the 1,7,7a-stereochemistry, with the second ring closure being effected by cyclisation onto the chloroalkyl side chain upon N-deprotection and basification (step g). The sequence was completed by LiAlH\textsubscript{4} reduction of the methyl ester at C(3).

Scheme 96 Reagents and conditions: (a) t-BuOAc, HClO\textsubscript{4}, H\textsubscript{2}O; (b) Boc\textsubscript{2}O, DMAP, CH\textsubscript{2}CN; (c) DIBAL, PhCH\textsubscript{2}O, −5 °C to rt; (d) H\textsubscript{2}, Pd/C, Et\textsubscript{3}OAc then Ac\textsubscript{2}O, Et\textsubscript{3}N, DMAP; (e) TBAF, THF then Ac\textsubscript{2}O, pyridine; (f) CF\textsubscript{3}CO\textsubscript{2}H then Ac\textsubscript{2}O, Et\textsubscript{3}N, DMAP; (g) NH\textsubscript{3}, MeOH.

Alexine(s)

Early in the review period Gallos reported a hetero-Diels–Alderman approach to a partially hydroxylated alexine analogue (601, Scheme 97).\textsuperscript{201} Building on earlier precedent set separately by Gilchrist and Reissig, the nitrosoacrylate diene 603 was prepared by 1,4-elimination from bromoxime 602 and trapped in situ by Diels–Alderman reaction with L-ribose-derived enol ether 598. The cycloaddition proceeded with excellent exo-face selectivity, but the subsequent imine reduction was poorly stereoselective; fortunately, base-catalysed equilibration of the ester led to complete conversion to the epimer 599 shown (ester equatorial, THF C–O bond axial). Reduction of the N–O bond was
accompanied by double reductive amination to give pyrrolizidine \textbf{600} exclusively. The target molecule \textbf{(601)} was then obtained by ester reduction and acetonide cleavage.

\begin{equation}
\text{D-ribose} \quad \text{598} \quad \text{599} \quad \text{Scheme 97 Reagents and conditions: (a) HCl, acetone, MeOH, 60 °C; (b) \text{I}_2, \text{PPh}_3, \text{imidazole, EtO}, \text{CH}_3\text{CN}; (c) \text{DBU, benzene, C}_2\text{H}_4, \text{reflux; (d) 602, NaHCO}_3, \text{CH}_2\text{Cl}_2; (e) \text{NaBH}_3, \text{AcOH; (f) Et}_3\text{N, CHCl}_3, \text{reflux; (g) H}_2, \text{Raney Ni, H}_3\text{BO}_3, \text{MgSO}_4, \text{MeOH; (h) LiBH}_4, \text{THF then HCl, MeOH.}})
\end{equation}

The synthesis of two non-natural pyrrolizidines (\text{+})-1,2-di-epi-alexine (\textbf{430} = \text{ent-(--)-3,7-di-epi-australine, see above, Scheme 93}) and (\text{+})-1,2,7-tri-epi-australine (\textbf{609}, Scheme 98) was the first of these particular hydroxylated stereoisomers.\textsuperscript{202} Sharpless asymmetric aminohydroxylation of unsaturated ester \textbf{604} gave an aminoalcohol intermediate, with ee >99% following one recrystallisation, that was carried forward to the aldehyde \textbf{605}. Vinyl Grignard addition (Cram chelate selectivity, dr = 4:1) and cross metathesis furnished allylic alcohol \textbf{606} that gave two inseparable epoxide diastereomers \textbf{607} and \textbf{608} with little stereoselectivity. The isomers were separated following the double cyclisation reaction (step i), and deprotection completed the syntheses with the spectroscopic data of \textbf{609} being consistent with those previously reported for the enantiomer.

\begin{equation}
\text{Scheme 98 Reagents and conditions: (a) K}_2\text{OsO}_4\cdot2\text{H}_2\text{O, (DHQD)}_2\text{PHAL, LiOH, N-bromoacetamide, aq }\text{-BuOH, 4 °C}; (b) NaH, BnCl, DMF, 0 °C; (c) Boc}_2\text{O, DMAP, THF, reflux then NH}_2\text{NH}_2, \text{MeOH; (d) DIBAL, CH}_2\text{Cl}_2, -78 °C; (e) H}_2\text{C=CHMgBr, THF, -50 °C to rt; (f) H}_2\text{C=CH(CH}_2)_2\text{OTs, Grubbs` II, CH}_2\text{Cl}_2; (g) VO(acac)_2, }\text{t-BuOOH, PhCH}_3; (h) \text{HCl, aq MeOH; (i) K}_2\text{CO}_3, \text{MeOH; (j) CAN, aq CH}_3\text{CN, 4 °C; (k) H}_2, \text{Pd/C, MeOH [products isolated as their HCl salts].}}
\end{equation}

Two syntheses of natural (\text{+})-alexine were reported in the same year. The first, an enantiospecific route from \text{L}-serine,\textsuperscript{203} was constructed around a key (3+2)-annulation between aldehyde \textbf{610} and the bis(dimethylphenylsilyl)propene \textbf{616} (Scheme 99). In this process, developing positive charge \beta-to both silyl substituents is trapped by the attached sulfonamide resulting in heavily-functionalised pyrrolidine \textbf{611} (dr >40:1). Chelation-controlled allylation of aldehyde \textbf{612} set the remaining stereogenic centre, and the synthesis was completed by cyclisation under Appel conditions, Fleming–Tamao oxidation of the silyl groups, and deprotection. The synthesis, twelve steps from aldehyde \textbf{610}, stands as the first asymmetric, non-carbohydrate route to (\text{+})-alexine.
A second (+)-alexine synthesis, reported a few months later, began with vinyl Grignard addition to the imine for protection and selective silyl group cleavage, the first pyrrolidine diastereomer, the stereochemistry being determined retrospectively at the end of the synthesis. Following hydroxyl protection and selective silyl group cleavage, the first pyrrolidine ring (in 621) was formed by intramolecular S$_{1,2}$-type cyclisation. The pyrrolizidine ring system was completed by hydrogenation and oxidation of the alkene, then activation and cyclisation under standard conditions. Hydrogenolysis of the three benzyl groups afforded (-)-7-epi-alexine 622. Alternatively, from alcohol 619, an oxidation/reduction sequence generated epimer 620 which was converted into the natural product, (+)-alexine, by an analogous series of reactions.

Scheme 100 Reagents and conditions: (a) PMBNH$_2$, 4 Å MS, PhCH$_3$, reflux; (b) H$_2$=CHMgCl, THF, –78 °C to 0 °C; (c) BrCl, CH$_2$Cl$_2$; (d) CAN, MeOH; (e) TBSCI, imidazole, DMF; (f) Boc$_2$O, Et$_3$N, DMAP, CH$_2$Cl$_2$; (g) (Me$_2$N)$_2$C=NH, 130 °C; (h) OsO$_4$, NMO, acetone; (i) NaIO$_4$, THF; (j) H$_2$=CHMgCl, THF, –78 °C; (k) MOMCl, i-Pr$_2$NEt; (l) TBAF, THF; (m) MsCl, Et$_3$N, CH$_2$Cl$_2$; (n) t-BuOK, THF; (o) 9-BBN, THF then H$_2$O, aq NaOH; (p) MsCl, Et$_3$N, CH$_2$Cl$_2$; (q) BF$_3$:Et$_2$O, CH$_2$Cl$_2$, –20 °C; (r) HCO$_2$H, Pd/C, MeOH, reflux; (s) TPAP, NMO, 4 Å MS, CH$_2$Cl$_2$; (t) NaBH$_4$, CeCl$_3$, MeOH, –45 °C.

Donohoe’s group achieved a synthesis of (+)-7-epi-alexine from monoacetate 452, prepared as in Scheme 68. The trans-1,2-diol motif present in the final product was installed by Lewis acid mediated epoxide opening in compound 623 (Scheme 101) by the neighbouring acetate group followed by methanolation of the so-formed acetate regioisomers. Allyl addition to aldehyde 624, to install the final stereogenic centre, turned out to be chelated by the NBoc group, leading to the incorrect stereochemical outcome for natural (+)-alexine. This sense of stereoinduction could not be overturned and the authors had to settle for a synthesis of the 7-epimer 622, following conventional lines after step g.

Scheme 101 Reagents and conditions: (a) Br$_2$, Ag$_2$O, 4 Å MS, CH$_2$Cl$_2$; (b) CF$_3$CO$_2$H, Ozone, EDTA, NaHCO$_3$,aq CH$_3$CN, 0 °C; (c) BF$_3$:Et$_2$O, CH$_2$Cl$_2$, –50 °C; (d) K$_2$CO$_3$, MeOH; (e) TESCl, Et$_3$N, DMAP, CH$_2$Cl$_2$; (f) Swern oxidation; (g) H$_2$=CHCH$_3$MgBr, THF, –78 °C; (h) TESCl, Et$_3$N, DMAP, CH$_2$Cl$_2$; (i) O$_2$, CH$_2$Cl$_2$, –78 °C then PPh$_3$; (j) NaBH$_4$, MeOH, CH$_2$Cl$_2$, 0 °C; (k) Ms$_2$O, 2,6-lutidine, DMAP, CH$_2$Cl$_2$; (l) TESOTf, 2,6-lutidine, CH$_2$Cl$_2$ then MeOH; (m) H$_2$, Pd/C, aq HCl, MeOH.
Dihydroxyhastanece

2,6-Dihydroxyhastanecine (631, Scheme 102), a non-natural analogue of hastanecine, was synthesised from 628 (cf. 591, Scheme 95), the 1,3-dipolar cycloadduct of nitrene 626 (5 steps from (R,R)-tartaric acid) and lactone 627 (3 steps from d-mannitol).\(^{206}\) Earlier investigations into the cycloaddition of various γ-lactones and pyrrolidine nitrones\(^{207}\) had shown that the reaction between 626 and 627 gave just a single diastereomer of adduct 628. The synthesis progressed via lactone reduction and periodate cleavage to remove the extraneous hydroxymethyl functionality. Although extra protection and deprotection steps were required to achieve this sequence, an analogous nitrene cycloaddition with unfunctionalised furan-2(5H)-one (in place of 627) was less stereoselective (dr = 93:7). From the truncated adduct 629, N–O bond cleavage and re-cyclisation following the usual strategy gave pyrrolizidine 630, five deprotection steps completed the route.

Scheme 102 Reagents and conditions: (a) PhCH\(_3\), (b) TBDPSCI, imidazole, CH\(_2\)Cl\(_2\), −15 °C to rt; (c) BH\(_3\), SMco, THF; (d) PivCl, DMAP, CH\(_2\)Cl\(_2\), −15 °C to rt; (e) TBAF, THF; (f) NaIO\(_4\), THF; (g) LiAlH\(_4\), THF; (h) NaBH\(_4\), Et\(_2\)O; (i) BH\(_3\), MeOH; (j) TBDPS, THF; (k) NaBH\(_4\), MeOH; (l) Ac\(_2\)O, THF; (m) CF\(_3\)COOH; (n) Ac\(_2\)O, Et\(_2\)N; (o) NH\(_3\), MeOH.

The same group applied an analogous strategy to the synthesis of (−)-3-epi-1-homocasuarine (634, Scheme 103) and two reduced derivatives 635 and 636.\(^{208}\) Omission of the periodate cleavage (step f, Scheme 102) retained what would become the 3-hydroxymethyl group, and deoxygenation of the 1- or 3-hydroxymethyl substituents (giving 635 and 636, respectively) was achieved by Super-hydride reduction of the corresponding mesylate. The 3-methyl derivative (636) of (−)-2,6-dihydroxyhastanecine showed weak inhibition of almond β-D-glucosidase (IC\(_{50}\) = 13 mM); 634 and 635 showed no activity against this and a range of other glycosidases.

Scheme 103 Reagents and conditions: (a) TBDPSCI, imidazole, CH\(_2\)Cl\(_2\), −15 °C to rt; (b) BH\(_3\), SMco, THF; (c) TBDPSCI, imidazole, CH\(_2\)Cl\(_2\), −15 °C to rt; (d) NaIO\(_4\), THF, Et\(_2\)O, EtOAc; (e) MeOH; (f) TBAF, THF then Ac\(_2\)O, Et\(_2\)N, −5 °C; (g) NH\(_3\), MeOH. [Si] = TBDPS.

Casuarines

Nitrone 402, derived from D-arabinose derivative 394 (Scheme 104), reacted with allyl alcohol to give nitrene cycloadduct 637 in 73% yield following separation of the epimer at the starred carbon.\(^{209}\) Mesylation of the 1°–hydroxyl set up N-cyclisation in situ under the conditions employed for reductive cleavage of the N–O bond. The 7-deoxy analogue of casaurine was then simply obtained by hydrogenolysis (cf. Scheme 57).

Scheme 104 Reagents and conditions: (a) NH\(_2\)OH·HCl, NaOMe, MeOH; (b) TBDPSCI, pyridine; (c) PPh\(_3\), I\(_2\), imidazole, PhCH\(_3\), reflux; (d) TBAF, PhCH\(_3\), reflux; (e) allyl alcohol, PhCH\(_3\), reflux; (f) NaIO\(_4\), pyridine, CH\(_2\)Cl\(_2\); (g) Mo(CO)\(_6\), aq CH\(_2\)CN, reflux; (h) H\(_2\), Pd/C, aq HCl, MeOH.

The natural product itself, (+)-casuarine, was first synthesised during the review period by Izquierdo’s group based on Wittig olefination and dihydroxylation.\(^{210}\) The strategy paralleled that used by the group for the synthesis of numerous hyacinthine diastereomers as described earlier (cf. Schemes 78 and 85). Thus, from D-fructose, a lengthy sequence of standard transformations and protecting group manipulations led to partially protected pyrrolidine 638 (Scheme 105). Oxidation and immediate Wittig olefination gave exclusively the E-alkene product. Subsequent Sharpless asymmetric dihydroxylation generated, as the major
diastereomer, 639 or 640 using ligands O-(4-
chlorobenzoyl)hydroquinidine or O-(4-chlorobenzoyl)hydro-
quinine, respectively (step c, dr ~2:1); use of standard Upjohn
conditions gave a 1:1 ratio. Each diol diastereomer was then
taken through a straightforward lactamisation/reduction sequence,
affording (+)-casuarine and its 6,7-di-epi- analogue (641) after
deprotection. Essentially identical chemistry, deriving from the
cis-pyrrrolidine diastereomer 642 led to the two casuarine isomers
643 and 644 shown in Scheme 106.211

Scheme 105 Reagents and conditions: (a) TPAP, NMO, 4Å MS, CH₂Cl₂;
(b) Ph₃P=CHCO₂Me, CH₂Cl₂; (c) see text; (d) H₂, Pd/C, MeOH; (e)
NaOMe, MeOH; (f) BH₃·SMe₂, THF then MeOH, heat; (g) TBAF, THF;
(h) H₂, Pd/C, aq HCl, MeOH then Amberlite IRA-400 (OH⁻ form); (i) as
(h) then Ac₂O, pyridine, DMAP; (j) NaOMe, MeOH.

Scheme 106

Following confirmation by crystallography of the structure of (+)-
3-epi-casuarine,7 Fleet’s group completed total syntheses of this
pyrrrolidine and (+)-casuarine, in part to provide spectroscopic
data for direct comparison.212 Protection of D-glucolactone
(645, Scheme 107) as its diacetonide released just the 2-OH for
azide displacement of triflate; ester reduction and Wittig
olefination gave allylic azide 646. Dihydroxylation gave a 4:1
ratio of diastereomeric diols, from which the major isomer was
elaborated routinely to lactam 647. Selective silylation of the 1°-
hydroxyl group, O-sulfonylation, and N-cyclisation following
lactam reduction gave (+)-3-epi-casuarine 644. By inverting the
2°-hydroxyl after step i, (+)-casuarine 117 was obtained by the
same four-step final sequence. The two pyrrrolizidines showed
very different ¹H NMR spectra in water at pH 8.3–9.3 and
conformational models were proposed to explain these data.
Connected with this are significantly different glycosidase
inhibition profiles, with (+)-casuarine being, in general, the more
active except against almond β-D-glucosidase.

Scheme 107 Reagents and conditions: (a) Me₃C(O)Me₂, TsOH, MeOH
then Tf₂O, pyridine, CH₂Cl₂; (b) NaN₃, DMF; (c) Dibal, PhCH₃, -78 °C
then MeOH, -78 °C to rt then Ph₃P=CHCO₂Me; (d) OsO₄, NMO, aq
acetic acid; (e) H₂, Pd(OH)₃/C, THF; (f) PhCH₃, reflux; (g) TBSCI,
imidazole, THF, reflux; (h) Ac₂O, aq MeOH, reflux; (i) TBSCI, pyridine;
(j) MsCl, Et₃N, CH₂Cl₂; (k) BH₃·THF, THF, reflux; (l) aq CF₃CO₂H,
reflux; (m) aq NaOAc then aq NH₃, Amberlite CG120(H⁺); (n) Tf₂O,
pyridine, CH₂Cl₂, -50 °C to 0 °C; (o) CF₃CO₂Cs, 2-butaneone, 50 °C then
K₂CO₃.

More casuarine analogues were prepared by Blechert in a
sequence (Scheme 108)213 that has parallels with later steps in
Izquierdo’s strategy. Thus, a key feature of the route is
stereodivergent dihydroxylation of an α,β-unsaturated carbonyl
system with the key difference being the mode of olefination
(cross metathesis vs. Wittig) and, in the Blechert synthesis, the
dihydroxylation takes place across the pro-1,2-alkene (vs. across
the pro-6,7-alkene in the Izquierdo work). Thus, vinyl pyrrrolidine
649 was prepared from the chiral pool starting material 648 and
subjected to cross metathesis with enone 652. The so-formed
enone (not shown) was dihydroxylated in poor to moderate yield
with either AD-mix-β or -α to give diols 650 or 651, respectively.
The parallel sequences were completed simply by reductive
amination, and hydrogenolysis of all protecting groups.
The popular nitrone method formed the basis of a second synthesis of (+)-casuarine during the review period. The strategy parallels that used by Izquierdo in the synthesis of the 7-deoxy analogue and begins with the same arabinose-derived nitrone 402; here, though, an extra hydroxyl group is masked form as a silane. Subsequent Fleming–Tamao cleavage of the C–Si bond in pyrrolizidine lactam 654, then carbonyl reduction and deprotection gave (+)-casuarine. Notably in this work the authors also completed the first total synthesis of the naturally-occurring 6-deoxycasuarine (120) and its 6-epimer from nitrone 402 (from d-xylose) (Scheme 110). Following the nitrone cycloaddition (→ 657), the pyrrolizidine ring-system was completed by ester reduction and mesylation of the so-formed 1°-alcohol so that N-O bond cleavage was accompanied by N-cyclisation. The free pyrrolizidine 120 was released by deprotection and ion-exchange chromatography. Elaboration of the minor cycloadduct 658 afforded analogue 121. Eight further diastereomers were also prepared, from the appropriate stereoisomeric nitrones: 659–661 from d-arabinose, 662 and 663 from d-ribose, and ent-660, ent-659, and 664 from L-arabinose.
Uniflorines

Pyne’s group proposed revised structures for the uniflorines and then effected a total synthesis of uniflorine A in confirmation of these new structures. This enantiospecific synthesis (Scheme 111) started with D-xylose and provided the non-natural (+)-enantiomer of uniflorine A. Petasis boronic acid Mannich reaction with allylamine and (ent-580) furnished (+)-uniflorine, which established the relative and absolute configuration of the natural product by comparison of NMR and specific rotation data. The synthesis was subsequently repeated, starting from t-xylose to produce the natural enantiomer, (−)-uniflorine.

A second synthesis of (−)-uniflorine was elaborated from pyrrolizidine 667 (Scheme 112) that had been used in the preparation of (+)-casuarine (see above, Scheme 109). The route was analogous to the casuarine synthesis with the exception that an inversion at C(6) was required (step a).

A third synthesis of (−)-uniflorine A was summarised earlier (Scheme 81).

Aminopyrrolizidines

Petrini’s synthesis of (−)-1-aminopyrrolizidine 671 (Scheme 113), the first synthesis of a single enantiomer of this amine, initiated with α-amidoalkylsulfone 668 obtained from (S)-prolinal derivative 242. Treating this sulfone with the lithium enolate of ethyl acetate effected sulfinate elimination and addition to the so-formed N-acylimine, resulting in a 90:10 ratio in favour of the anti-isomer 669. Ester reduction and N-deprotection, followed by cyclisation and release of the 1-amino group, completed the route that also constitutes a formal synthesis of (−)-absouline and (−)-laburnamine.
The first asymmetric synthesis of natural (+)-absouline was reported the following year.\textsuperscript{218} The carbonyl group in aminopyrrolidinone 672 (Scheme 114), derived from (S)-aspartic acid, was converted into sulfide 673. Deprotonation of the carbamate and metallation gave a dianion that was quenched with allyl iodide to give anti-674 as a single isomer. Elaboration of the terminal olefin, then cyclisation and N-deprotection under standard conditions gave (+)-aminopyrrolizidine 671 that was acylated to complete the first synthesis of the natural enantiomer of absouline.

A synthesis of the non-natural enantiomer, (−)-absouline, was reported towards the end of the same year.\textsuperscript{219} Here, (S)-α-methylbenzylamine served as the source of chirality via cyanoaetidines 676 (Scheme 115). Organometallic addition and reduction of the imine intermediate in situ provided diamine 677 in high diastereomeric excess (dr >25:1). The key step in the synthesis achieved a swap of amine substituents through two stereospecific internal substitutions via protonated aziridine 678, affording anti-aminopyrrolizidine 679 (dr >25:1). With the stereochemistry established, completion of the synthesis of (−)-absouline was achieved in five straightforward steps, the second ring being formed under Appel conditions.

The most recent synthesis of absouline exemplifies a general approach to aminopyrrolizidine synthesis based on conjugate amination of proline-derived unsaturated esters.\textsuperscript{221} Thus N-Boc (S)-prolinal 242 (Scheme 117) was subjected to olefination under a variety of conditions to yield esters 682 and 683 in ratios ranging from 3:1 to 1:2, respectively. Conjugate addition with benzylamine generally favoured the formation of the syn-diamine (en route to 684) irrespective of the alkene geometry in the starting material; however, the highest yield (92%) and dr (7:2) was obtained from the Z-isomer 683. Following cyclisation, the separated desired diastereomer 684 was reduced, deprotected and acylated to afford (−)-absouline.
1-Aminopyrrolizidine 671 was also an intermediate in the only synthesis of laburnamine (689, Scheme 118) to be reported during this period. Isodocarbazone of 1-pyrrolone derivative 328 and methanolysis of the N-acylaziridine formed from 686 upon treatment with base gave aminoacetal 687. Allylation of this intermediate, via the N-acylaminium ion, was moderately trans-selective (dr = 77:23), and the separated trans-688 was carried through a sequence analogous to that described in Scheme 114 (for the preparation of absolane) to deliver (±)-laburnamine.

White’s synthesis of (±)-loline, the first asymmetric synthesis of this cyclised aminopyrrolidine,223 falls within the period of this review but was summarised previously. More recently, a synthesis of another member of the loline class of alkaloids, (±)-N-acetylloline (Scheme 119), was described.224 The first pyrrolidine ring was produced by amination of the Rh(II)-carbenoid derived from diazo-β-ketoester 691. Stereoselective ketone reduction, and elaboration of the ester via Dieckmann product 694, gave carbamate 696. Tethered aminohydroxylation afforded diol 697 as a single diastereomer, with stereocontrol explained on the basis of minimisation of A15-strain. Mesylation of both hydroxyls and N-acylation enabled methanolysis of the cyclic carbamate to set up O-cyclisation by displacement at the starred carbon in 697, giving 698. Removal of the N-Boc substituent led to formation of the second pyrroline ring, then deprotection and acetylation completed the synthesis.

Soon after this synthesis appeared, Trauner reported an efficient eight-step route to azide 705 (Scheme 120) which was then converted into the natural products (±)-loline, (±)-N-formyl loline, and temuline ((+)-norloline).225 The synthesis began with Sharpless asymmetric epoxidation of divinyl carbinal (700). Epoxide opening and ring-closing metathesis from the so-formed dienyl aminodiol 701 gave hexahydroazocine derivative 702 after activation of the diol as its cyclic sulfite. Introduction of the azide, by selective nucleophilic substitution at the activated allylic centre, set up a stereoelectronic transannular bromoamination reaction. This key step generated the pyrrolizidine core apparently as a single diastereomer (via conformation 703 with pseudoequatorial azide and hydroxyl substituents); the isolation of benzyl methyl carbonate supports a mechanism in which the Cbz-substituent is cleaved by attack at the carbonyl group immediately following cyclisation. Formation of the cyclic ether required a double inversion sequence from bromide 704; first, bromide was displaced with chloride then the final cyclisation, to complete the loline core, was effected under basic conditions with microwave heating. Azide reduction of this intermediate (705) gave norloline; repetition of this reaction in the presence of Boc₂O, and reduction of the carbamate gave oiline and then N-formylloiline.
asymmetric Michael addition using bifunctional catalysts

Scheme 120 Reagents and conditions: (a) t-BuOOH, Ti(Oi-Pr)₄, L-(+)-DIPT, CH₂Cl₂, -25 °C; (b) CH₂=CH(CHOH)₂NH₂·Cl⁻, i-Pr₂NEt, MeOH, 45 °C then CbzCl, aq Na₂CO₃; (c) Grubs’ II, CH₂Cl₂, 45 °C; (d) SOCl₂, Et₂N, CH₂Cl₂, 0 °C; (e) LiN₂, DMF, 130 °C; (f) Br₂, MeOH, 0 °C; (g) LiCl, DMF, 105 °C then aq NaOH; (h) K₂CO₃, MeOH, 150 °C (microwave); (i) Bu₂Pd/C, MeOH; (j) H₂, Pd/C, Boc₂O, THF; (k) LiAlH₄, THF, reflux; (l) AcNHCHO (from HCO₂H and AcOH).

Following Snider’s revision of the structures of jenamidines A and B (111 and 112), the same group completed a short synthesis of jenamidines A₁/A₂ from the reduced 3-aminopyrrolizin-1-one 710 (Scheme 121) for which two synthetic routes were devised. In the first route, cyanamide 709 (obtained in two steps from proline) was subjected to crossed Claisen condensation with the lithium enolate of t-buty lactate. Treatment of the so-formed β-ketoester with more base in the same reaction vessel resulted in cyclisation to the desired vinylogous urea 710, albeit in low yield. In the second route, from proline derivative 711, crossed Claisen condensation, this time with the sodium enolate of t-buty lactoacetae, and N-deprotection gave the α-cyano-β-ketoester 712 as a complex tautomeric mixture. Fortunately, this cyclised slowly on standing to give the intermediate 710 in improved overall yield. The methoxycetate protecting group for the side-chain hydroxyl in acid chloride 714 was chosen because it offered sufficient resilience to provide a good yield in the acylation, survived acid-mediated tert-buty ester hydrolysis and decarboxylation, and allowed straightforward deprotection under mildly basic conditions to complete the synthesis.

A sequence analogous to the first route, above, enabled access to the related natural product NP25302 in racemic and both enantiomeric forms which established the natural product to be the (4S,7S)-isomer shown. The syntheses of both ethyl 2,5-dimethylprolinate enantiomers (718, Scheme 122) initiated with asymmetric Michael addition using bifunctional catalysts 719 and 720. Following chemistry optimised in the racemic series, reduction and cyclisation were effected in two stages via nitrone 717.

Scheme 121 Reagents and conditions: (a) t-BuOAc/LDA, THF, -45 °C then LHMDS; (b) NaH/t-buty lactoacetae, C₂H₅; (c) H₂, Pd/C, MeOH; (d) NaH, 714, THF; (e) CF₃CO₂H, CH₂Cl₂, 0 °C; (f) Na₂CO₃, MeOH, 0 °C.

Scheme 122 Reagents and conditions: (a) MVK, 720, CH₂Cl₂, -20 °C; (b) H₂ (1 am), Pd/C, EtOH; (c) H₂ (3.3 atm), Pd/C, aq HCl, EtOH; (d) BrCN, NaHCO₃, EtOH; (e) t-BuOAc/LDA, -45 °C to rt; (f) t-BuOK, t-BuOH, 135 °C; (g) NaH, 3-methylbut-2-enyl chloride, THF; (h) CF₃CO₂H, CH₂Cl₂.

A second synthesis of NP25302 followed from the same dimethylproline derivative 716. Key steps in this route included addition of lithiated isopropyl propionate to aldehyde 721 (Scheme 123), 5-endo-dig cyclisation to form the second ring (722 → 723), and Curtius rearrangement (step i) to install the vinylogous urea functionality present in the natural product.
Danaidone and nordanaidone

Butterfly pheromone pyrrolizidines nordanaidone (Scheme 125) and danaidone (Scheme 126) were prepared by short routes. The simpler compound, nordanaidone, was obtained by acyl radical cyclisation and oxidative aromatisation in situ from selenide 731, prepared as shown from pyrrole.

SC-53116

An unexpected self-condensation side-reaction, observed during the attempted metallation and alkylation of N-sulfinyl aldimines, was applied to the synthesis of SC-53116 (728, Scheme 124), a synthetic serotonin 5-HT₄ antagonist. Various conditions for this reaction were surveyed, and a combination of LHMDS and DMPU as additive was found to give high efficiency and diastereoselectivity. Application to the succindialdehyde derivative 725 gave three diastereomers of dimer 726 (dr = 91:5:4) from which nitrile 727 was separated as a single diastereomer following sulfoxide elimination. Nitrile reduction, amide formation, and reductive amination gave the target molecule in only five steps from sulfoximine 725.

Pyrrolams

The synthesis and biological activity of pyrrolams A–D were reviewed recently.

In 2004, an asymmetric synthesis of (R)-pyrrolam A was reported based on asymmetric deprotonation of N-Boc pyrrolidine 166 (Scheme 128) and coupling with ethyl (Z)-3-iodoacrylate. The conditions for N-deprotection and
lactamisation had to be carefully optimised in order to obtain (–)-pyrrolam A with high ee and free from alkene isomers and the hydroxylated pyrrolizidine, pyrrolam B. Eventually it was found that addition of a dichloromethane solution of the hydrochloride (corresponding to pyrrolidine 737 lacking the Boc group) to a rapidly-stirred saturated solution of NaHCO₃ gave reproducible results. The isomeric enamide 739 was obtained from the same hydrochloride by treatment with LHMDS (THF, –78 °C) and this was found to be converted into pyrrolams B and C as shown. On this basis it was concluded that pyrrolams B–D, also obtained from Streptomyces olivacus, and a dimer (Scheme 129), often isolated in conjunction with pyrrolam A, are most probably artefacts rather than naturally-occurring metabolites.

Scheme 128 Reagents and conditions: (a) s-BuLi, (–)-sparteine, CuCN·2LiCl, (Z)-ICH=CHCO₂Et, Et₂O, THF, –78 °C to rt; (b) TMSCI, MeOH; (c) dissolve in CH₂Cl₂ then add to aq NaHCO₃; (d) EtOAc, wet SiO₂, EtOAc (→ 741) then MeOH, dry SiO₂ (→ 742).

A telescoped oxidation/in situ Wittig sequence was used by Tilve to construct (S)-pyrrolam A from (S)-prolinol derivative 745 (Scheme 129). This sequence proved to be more efficient than a stepwise alternative. Alkene hydrogenation and N-deprotection followed by lactamisation gave pyrrolizidinone 747 which was converted to the enantiomer of the natural product by selenoxide elimination.

Scheme 129 Reagents and conditions: (a) PCC, NaOAc, Ph,P=CHCO₂Et, CH₂Cl₂; (b) H₂, Pd/C, EtOH; (c) NaOME, EtOH, reflux; (d) LDA, PhScCl, THF, –78 °C; (e) H₂O₂, AcOH, aq THF, 0 °C to rt.

Wittig olefination was also used to construct the same C1–C2 bond in Schobert’s synthesis of (R)-pyrrolam A. Here, exposure of benzyl (R)-prolinate (748, Scheme 130) to solid-supported cumulated ketene-ylid 751 produced 1-benzoxypyrrlam A 749 directly, the resin-bound phosphine oxide being easily removed by filtration. Deoxygenation of this molecule required four steps comprising enol ether hydrolysis, regioselective and stereoselective carbonyl reduction, then elimination of the derived mesylate. The route provided the natural product with 95% ee.

Scheme 130 Reagents and conditions: (a) 751, THF, 60 °C; (b) H₂, Pd/C, MeOH; (c) NaBH₄, AcOH, CH₂Cl₂, 0 °C; (d) MeCl, Et₂N, CH₂Cl₂; (e) Et₂N, CH₂Cl₂, reflux.

A related intramolecular Wittig olefination strategy was used in Tilve’s second synthesis of (S)-pyrrolam A. The phosphonium salt generated from bromoacetamide 753 (Scheme 131) was deprotonated to generate ylid 754 from which (S)-pyrrolam A followed. Unsurprisingly, separation of the pyrrolizidine from triphenylphosphine oxide generated in the final step proved troublesome and reverse phase HPLC was necessary; however, alternative methods for conducting the Wittig reaction, including the use of polystyrene-bound triphenylphosphine, were not successful.

Scheme 131 Reagents and conditions: (a) BrCH₂COCl, NaOAc, aq acetone, 0 °C to rt; (b) PCC, CH₂Cl₂; (c) PPh₃, C₆H₆; (d) NaH, THF, 0 °C.

The most recent synthesis of (R)-pyrrolam A took advantage of diastereoselective addition of the enolate derived from allyl α-diazoacetoacetate (760) to chiral sulfinimine 755 (Scheme 132) which gave a 98.5:1.5 ratio in favour of the isomer shown. In order to avoid complications from the sulfinyl group, which
decomposes under the conditions for photochemical Wolff rearrangement (step d), the N-substituent was swapped to Boc (→ 756). With this modification, rearrangement and ketene trapping via 757 proceeded reasonably efficiently. Palladium(0)-mediated deallylation and decarboxylation, followed by removal of the Boc group, gave vinylpyrrolidinone 759. The synthesis was completed by lactam reduction, N-acylation, and ring-closing metathesis.

Scheme 132 Reagents and conditions: (a) LHMDS, 760 (see text), CH₂Cl₂, −78 °C; (b) CF₃CO₂H, MeOH, 0 °C; (c) BocO, Et₃N, DMAP, THF, 0 °C; (d) hv (λ >300 nm), 500 W, C₆H₆, 35 °C; (e) Pd(PPh₃)₄, morpholine, THF, 0 °C; (f) Pd(0), THF, reflux; (b) CH₂=CHCOCl, K₂CO₃, aq EtOAc, 0 °C; (i) Grubbs’ II, PhCH₂Cl, 80 °C.

Hydroxyphenopyrazin

(+)-p-Hydroxyphenopyrazin, recently isolated from three different fungi, was synthesised, along with (+)-phenopyrazin (the non-natural enantiomer), from (S)-proline using Suzuki coupling to install the requisite aryl group.²³ Hydroxyphenopyrazin (Scheme 133) gave a mixture of both alkenic geometries; therefore, the alkene was reduced to allow cyclisation of both isomers. The α-hydroxy group was introduced via enolate oxidation with dissolved oxygen, with the intermediate peroxide being broken down using Na₂SO₄. In the case of the phenyl analogue 767, further oxidation occurred upon standing to give (+)-phenopyrazin directly, whereas the p-hydroxy analogue 768 required separate oxidation and deprotection steps to furnish (+)-p-hydroxyphenopyrazin.

Scheme 133 Reagents and conditions: (a) CDI, THF, 0 °C to rt then KO₂, C₂H₅O₂Et, MgCl₂, THF, 50 °C; (b) TMSO₂K, Et₃N, THF, −65 °C to −40 °C; (c) PhB(OH)₂, or p-HO-C₆H₄-B(OH)₂, Pd(PPh₃)₄, Na₂CO₃, aq dioxane; (d) H₂, Pd–BaSO₄, EtOAc; (e) H₂, PdO, MeOH, EtOAc; (f) aq CF₃CO₂H, CH₂Cl₂; (g) aq NH₄OH, sealed tube, 75 °C; (h) LDA, O₂, P(OMe)₃, HMPA, THF, −75 °C to −65 °C; (i) TBSCl, AgNO₃, pyridine, THF; (j) for 767: upon standing; (k) for 768: RuCl₃, NaIO₄, aq CCl₄, MeCN; (l) TBABF, THF, −40 °C.

Amphorogynes

The amphorogynes from Amphorogyne spicata have an unusual 1,6-disposition of ester and oxy- functionality, accessed in the first total synthesis of amphorogynine A (Scheme 134), from d-(-)-malic acid, in confirmation of the assigned structure.²⁴ The derived imide 770 was taken through an eight-step sequence to effect imide reduction to the lactam and swapping the O- and N-protecting groups. The defining step in this synthesis, allylsilane trapping of an acyliminium intermediate, proceeded with high cis-selectivity with respect to the silyloxy substituent but with only ~3:1 dr at the starred position in 772 (which probably reflects an ~3:1 E/Z-ratio in the allylic silane reagent). This diastereomeric mixture was elaborated first by alkene cleavage and oxidation to generate the methyl ester, then O-acylation with protected dihydroferulic acid (step q). Boc deprotection, cyclisation under basic conditions, and hydrogenolysis of the benzyl protecting group in the dihydroferulate side chain completed the route to amphorogynine and its 1-epi-analogue 775.
An overall slightly shorter synthesis of (+)-amphorogynine A was disclosed soon after and the approach was subsequently extended to (+)-amorphogynine D and (+)-retronecine.\textsuperscript{241} The assembly of key intermediate lactam 438 (Scheme 135; also applied to the synthesis of (+)-hyacinthaines A\textsubscript{1} and B\textsubscript{1}) began with the formation of the 1,2-dichloroethyl ether of (S)-Stericol\textsuperscript{1} (437, Scheme 65) which was then metallated and the intermediate lithium acetylide allylated in situ (step b). Partial hydrogenation of the skipped enyne gave a 1,4-dienyl ether that, upon reaction with dichloroketene, afforded cyclobutane 774. Ring-expansion by Beckmann rearrangement and reductive removal of the two chlorine substituents provided the lactam. The allyl group in 438 was dihydroxylated, and selective activation of the 1\textsuperscript{st} alcohol as its tosylate allowed closure of the second ring (→ 777). Oxidation, carboxylative cross-coupling of the derived enol triflate, and exo-face selective alkene reduction provided key intermediate pyrrolidine 788. Esterification and deprotection steps led to (+)-amorphogynine A; simple hydrolysis led to (+)-amorphogynine D.

Alternatively, allylic oxidation of the allyl group in 438 gave access to the 1,7-disposition of ester and hydroxy groups present in (+)-retronecine (Scheme 136).\textsuperscript{241b} The second ring was formed via a standard hydroboration-oxidation-activation sequence and the hydroxy group in 780 was oxidised in readiness for carboxylative cross-coupling as in the amorphogynine syntheses. Acid-mediated removal of the chiral auxiliary and ester reduction completed the route.

The 6-epimer of (+)-amorphogynine A, (-)-amorphogynine C (Scheme 137) was prepared for the first time recently.\textsuperscript{242} Glycal 782, readily-obtained from d-glucose (three steps) was taken through a five-step sequence to allyl glycoside 783 with overall conjugate displacement of acetate, and Mitsunobu inversion at C(4) as key steps. Johnson–Claisen rearrangement transferred the stereochemistry to C(2); subsequent azide cycloaddition (in 784) was accompanied by loss of N\textsubscript{2} with [1,2]-H migration, giving bicyclic pyrrolidine 785. Under the forcing conditions of the cycloaddition, imine epimerisation occurred giving the observed...
stereoisomer exclusively. The remainder of the synthesis required release of the lactol and its oxidation to the corresponding lactone, then desilylation and activation of the 1°-carbon by Appel reaction, giving bromolactone 787. Upon deprotection of the amine, methanolysis of the lactone and N-cyclisation completed the pyrrolizidine core. The synthesis was completed by esterification followed by hydrogenolysis of the O-benzyl protecting group on the dihydroferulate side-chain.

Epohelmins A and B

Snider called into question the azocane ring system assigned to epohelmins A and B (104 and 105, respectively), based on the proposal that the NMR chemical shifts associated with the supposed epoxy CH positions were more consistent with a pyrrolizidine ring system.65 The total synthesis that followed (Scheme 138) confirmed the pyrrolizidine formulation.66 The aldol addition of 791-enolate to prolinal 278 had not been expected to be usefully diastereoselective based on results with the lithium enolate of ethyl acetate but, in the event, high Felkin–Anh control was found. Following conversion of the organometallic reagent to the corresponding methyl ester, and OH protection (→ 789), reductive amination set the remaining stereogenic centre in pyrrolizidine 790. Again, the authors had not expected high stereoselectivity in this last step and it is presumed that the protected hydroxyl group blocks access to the back face of iminium/enamine intermediates. Continuation to epohelmin A was achieved by HWE olefination and deprotection. Finally, a simple redox sequence provided access to the epimer, epohelmin B, the stereoselectivity in the reduction step (step j) presumably arising from exo-face attack by the bulky hydride reducing agent. Both pyrrolizidines showed positive specific rotations, as their acetate salts, confirming the absolute stereochemistry of the natural products to be as depicted in Scheme 138.

A more recent synthesis of (+)-epohelmin B was based on transannular cyclisation onto an azacane epoxide analogue of the structure originally-proposed for the epohelmins.245 Absolute stereochemistry (ee = 94%) was established by azonia-Cope rearrangement of the imine formed from aldehyde 793 and camphor-derived homoallylamine 798 (Scheme 116). Ring-closing metathesis to the eight-membered ring proved most efficient with the ruthenium indenylidene catalyst 799. The ~1:3 stereoselectivity of α- and β-epoxides 796 and 797, respectively, obtained with MCPBA alone could be partially inverted to a 64:36 ratio under Jacobsen’s conditions with silver(I) added to ionise the salen pre-catalyst 800. Nosyl cleavage and alkyl displacement at the Weinreb amide afforded (+)-epohelmin B as well as a range of ketone analogues by variation of the organometallic reagent.

Scheme 138 Reagents and conditions: (a) 791, LDA, THF, −78 °C then 278; (b) AcOH, aq THF; (c) K2CO3, MeOH; (d) EtOH–CH2Br, PPTS, CH2Cl2; (e) H2, Pd(OH)2, MeOH; (f) (MeO)2POClLi, THF, −78 °C to rt; (g) NaH, hexanal, THF, 0 °C to rt; (h) aq AcOH; (i) Swern oxidation; (j) L-Selectride, THF; (k) Dess–Martin periodinane, CH2Cl2.

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stereoisomer of the coupled product (not shown) which was of a boron enolate’. This critical reaction generated a single type reaction which presumably passes through the intermediacy.

UCS1025A is an unusual pyrrolizidine–type alkaloid isolated from the fermentation broth of an *Acremonium* sp. fungus and exhibiting cancer cell antiproliferative activity through telomerase inhibition. Details of the first two syntheses of this compound were submitted for publication within one month of each other; Danishefsky’s was first. The successful route developed from chiral cyclic imide obtained from L-(+)-tartaric acid. Intramolecular aldol–type addition under soft–enolisation conditions afforded adduct in good yield and diastereoselectivity. Elimination of both trimethylsilyloxy groups was effected by desilylation, distillation and in situ elimination of the triflate β-to the lactam carbonyl, then palladium(0)-mediated reduction of the vinyl triflate, resulting in the α,β-unsaturated pyrrolizidine that was coupled with aldehyde, prepared using MacMillan’s route.

The coupling reaction was described as a Reformatsky–type reaction ‘which presumably passes through the intermediary of a boron enolate’. This critical reaction generated a single stereoisomer of the coupled product (not shown) which was desilylated and the 2°-alcohol oxidised to complete this convergent route to (+)-UCS1025A.

A proposed biomimetic synthesis of racemic UCS1025A was reported by Hoye and Dvornikovs soon after the Danishefsky paper. The proposal features an intramolecular Diels–Alder reaction to create the octalin component as essentially the final step. The substrate was assembled by coupling Weinreb amide with the Grignard reagent derived from iodopyrrolizidine, that was obtained by a route almost identical to that reported in Danishefsky’s work. The Diels–Alder reaction was found to occur at different rates for the different tautomers of, and was sensitive to the protecting groups present on the pyrrolizidine core. In all cases the cycloaddition showed no facial selectivity but the product dominating when the was shown.

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The coupling reaction was described as a Reformatsky–type reaction ‘which presumably passes through the intermediary of a boron enolate’. This critical reaction generated a single stereoisomer of the coupled product (not shown) which was desilylated and the 2°-alcohol oxidised to complete this convergent route to (+)-UCS1025A.

**Scheme 139** Reagents and conditions: (a) t-BuOH, DIC, DMAP, CH₂Cl₂; (b) O₂, CH₂Cl₂, −78 °C then Me₂S; (c) 798, CSA, DCE, 0 °C then NH₂OH·AcOH, MeOH, 50 °C; (d) NaCl, K₂CO₃, CH₂Cl₂, 0 °C to rt; (e) 5-bromo-1-pentene, K₂CO₃, CH₂Cl₂, 0 °C; (f) 799, CH₂Cl₂; (g) CF₃CO₂H, CH₂Cl₂, then HN(O)Me₂·HCl, Et₃N, DCC, DMAP, CH₂Cl₂; (h) MCPBA, 800, NMO, AgPF₆, CH₂Cl₂, −78 °C; (i) HSC(O)₂H₂, LiOH, DMF; (j) 1-iodo-1-heptene, BuLi, THF, −78 °C to −40 °C.

**UCS1025A**

**Scheme 140** Reagents and conditions: (a) H₂N(CH₂)₂CO₂Me, THF then AcCl, reflux; (b) AcCl, MeOH, 0 °C; (c) TMSCl, Et₃N, CH₂Cl₂; (d) TBSOTf, i-Pr₂NEt, CH₂Cl₂, −78 °C to rt; (e) AcOH, HCl, aq THF; (f) TfO, pyridine, CH₂Cl₂, −78 °C to rt then pyridine; (g) Bu₂SnH, Pd(PPh₃)₃, LiCl, THF, reflux; (h) LiOH·H₂O, aq THF; (i) t-Bu,NHCO₂H, aq Et₂O, THF; (j) 806, Et₂B, PhCH₂Cl, −78 °C; (k) TBAF, THF, CH₂Cl₂; (l) Dess–Martin periodinane, CDCl₃.

A proposed biomimetic synthesis of racemic UCS1025A was reported by Hoye and Dvornikovs soon after the Danishefsky paper. The proposal features an intramolecular Diels–Alder reaction to create the octalin component as essentially the final step. The substrate was assembled by coupling Weinreb amide with the Grignard reagent derived from iodopyrrolizidine, that was obtained by a route almost identical to that reported in Danishefsky’s work. The Diels–Alder reaction was found to occur at different rates for the different tautomers of, and was sensitive to the protecting groups present on the pyrrolizidine core. In all cases the cycloaddition showed no facial selectivity but the product dominating when the was shown.
More recently, Christmann\textsuperscript{247} demonstrated that racemic pyrrolizidine \textsuperscript{815} (Scheme 142), obtained in a single step as shown, could be resolved easily with quinine. Thus, exposure of the racemate to quinine led to a kinetic resolution in which the (–)-enantiomer cyclised to lactone (–)\textsuperscript{816} (≤ 62\% ee), leaving enriched in the (+)-enantiomer. Enantiomerically enriched (–)\textsuperscript{815} was then obtained from the lactone by β-elimination with DBU. The enantiopurity of (–)\textsuperscript{815} was then improved to 98.2\% by trituration with pentane and this material was taken forward to give (+)-UCS1025A using Danishefsky’s route.

By way of contrast with the Christmann synthesis, the most recent synthesis of (+)-UCS1025A was lengthy at ~30 steps by the longest linear route. The use of ethyl (S)-malate as starting material necessitated both chain-lengthening and chain-shortening steps to assemble the two arms of lactam precursor \textsuperscript{821}. The cyclisation (steps r,s) was achieved by an interesting application of a Staudinger aza-Wittig reaction followed by hydrolysis of the so-formed cyclic iminoether. Hydrogenolysis of the acetal (in \textsuperscript{822}), selective protection of the 1°-alcohol and oxidation of the 2°-alcohol gave a pyrrolizidinol as a 1:1 mixture of bridgehead alcohol diastereomers. In order to set this C(7a)-stereochemistry correctly, the TBDDS protecting group (introduced in step u) was replaced by benzoate. The authors needed to ensure that, in step y, the bridgehead –OR substituent would be installed anti to the \(-\text{CH}_2\text{OBz}\) group; that is, neighbouring group involvement of the benzoate carbonyl would shield one face of the iminium intermediate. Yet another protecting group swap (steps z, aa) afforded intermediate \textsuperscript{823} that was united with activated acid \textsuperscript{818} and sulfenylated (→ \textsuperscript{824}). A seven-step sequence was necessary to deprotect the bridgehead hydroxyl and convert the silyl ether into carboxylic acid \textsuperscript{825}. Finally, oxidation of the sulfide and thermal elimination of the so-formed sulfoxide gave (+)-UCS1025A under the mildly-basic conditions of the thermolysis.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_141.png}
\caption{Reagents and conditions: (a) i-PrMgCl, THF, EtO\textsubscript{2}, −50 °C; (b) CDCl\textsubscript{3}, 65 °C; (c) HF·pyridine, CH\textsubscript{3}CN.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_142.png}
\caption{Reagents and conditions: (a) TBSOTf, Et\textsubscript{3}N, CDCl\textsubscript{3} then K\textsubscript{2}CO\textsubscript{3}, MeOH; (b) quinine, CD\textsubscript{2}Cl\textsubscript{2}; (c) DBU; (d) triturate into hot pentane.}
\end{figure}
Xenovenine and related dialkyl pyrrolizidines

Xenovenine, also known as alkaloid 223H\textsuperscript{1}, is one of a group of (mainly 3,5-) dialkylpyrrolizidines isolated from, *inter alia*, arthropods and frogs/toads; evidence exists to show that some of these alkaloids are present by virtue of sequestration from dietary sources.

Blechert applied his group’s sequential cross metathesis/reductive cyclisation methodology to a short synthesis of (±)-xenovenine (Scheme 144), in part to confirm the stereochemical course of the final imine reduction steps.\textsuperscript{152}

Alkenes \textsuperscript{829,830} and \textsuperscript{831} prepared as shown, were coupled using the Hoveyda–Grubbs 2\textsuperscript{nd} generation catalyst since this phosphine-free catalyst enabled approximately equimolar ratios of the two alkenes to be used. Following cross metathesis (→ \textsuperscript{832}), alkene hydrogenation, N-deprotection, and double reductive amination were all effected within the same reaction to generate the racemic natural product.

Takahata’s group described syntheses of a group of related alkaloids previously shown to be present in certain Madagascan frogs (*Mantella* spp.). \textsuperscript{251} The key intermediate in these syntheses, \textsuperscript{838} (Scheme 145), was obtained from 1,5-hexadiene in eleven steps with the stereochernistry introduced at the outset by Sharpless asymmetric dihydroxylation (70% ee). Elaboration to epoxide \textsuperscript{836}, Cu(I)-mediated ring-opening with a 5-hexenyl Grignard reagent, then introduction of the nitrogen via the azide led to carbamate \textsuperscript{837}. Overall aminohydroxylation of the butenyl alkene, giving \textsuperscript{838}, was achieved by acetoxymercuration and oxidative cleavage of the so–formed organomercurial; no cis–diastereomer was observed in this process. The first alkali 223H\textsuperscript{1} (xenovenine) was then obtained from pyrrolidine \textsuperscript{838} in a three step sequence: oxidation to the aldehyde, Horner–Wadsworth–Emmons olefination, and reductive amination.

Stereocontrol at C(5) (starred) was moderate (dr = 85:15) but the 3,5-cis- and trans- isomers were separable by chromatography.
Alternatively, use of the oxopentyl phosphonate installed the 5-propyl substituent of pyrroloidines 265H' and 267H' that differ in the oxidation level in the heptyl side-chain. The ketone in 265H' was introduced in the penultimate step by Wacker oxidation, and hydrogenation completed the route with the 3,5-trans-isomer also being obtained (dr = 80:20). Pyrroloidines 239K' and 267H' were reportedly isolated as enantiomeric mixtures at the hydroxylated carbon; therefore, the authors prepared both enantiomers (prepared from the propyl versions (6239K) reported during the review period.252 This two-directional approach required seven steps overall from ethyl formate. The route features a double alkene cross metathesis to set up double cyclisation by sequential conjugate additions. The product 845 (Scheme 146) of the cross metathesis reaction was accompanied by pyrroloidine 847 of unassigned relative configuration; however, under the conditions of the Boc-deprotection the products converged to a single pyrroloidine stereoisomer, assigned by X-ray crystallographic analysis of a derivative. Mozingo-type deoxygenation of the carbonyl groups completed the route.

A single synthesis, and the first, of alkaloid cis-223B was reported during the review period.253 This two-directional approach required seven steps overall from ethyl formate. The route features a double alkene cross metathesis to set up double cyclisation by sequential conjugate additions. The product 845 (Scheme 146) of the cross metathesis reaction was accompanied by pyrroloidine 847 of unassigned relative configuration; however, under the conditions of the Boc-deprotection the products converged to a single pyrroloidine stereoisomer, assigned by X-ray crystallographic analysis of a derivative. Mozingo-type deoxygenation of the carbonyl groups completed the route.

\[
\text{Scheme 146 Reagents and conditions: (a) SESNNHboc, DIAD, PPh_3, CH_2Cl_2; (b) CsF, CH_2CN, reflux; (c) ethyl vinyl ketone, Hoveyda–Grubbs’ II (Hoveyda–Blecher catalyst), CH_2Cl_2; (d) C_F_3CO_2H, CH_2Cl_2, 55 °C; (e) HS(CH_2)_3SH, BF_3·OEt_2, CH_2Cl_2; (f) Raney Ni, EtOH, 80 °C.}
\]

\[\gamma\text{-Lactam 848 (Scheme 147) is readily-available from (S)-pyroglutamic acid by reduction, activation, alkylation, and N-Boc protection. This served as the starting point for an enantiodivergent synthesis of the enantiomers of the chiral diastereomer, trans-223B. For the (+)-enantiomer, lactam ring-opening with BuMgBr and reductive amination set the stereochemistry (by pseudoxiaxial delivery of hydride) of the Bu side chain in 849. Interestingly, cross metathesis and conjugate cyclisation gave the trans-isomer (cf. the stereochemical outcome in Scheme 146); the authors proposed a kinetic model to account for this sense of stereocontrol. Reduction to the aldehyde, Wittig olefination, and hydrogenation afforded (+)-trans-223B. By carrying out an initial hydrogenation of the butenyl side chain and then effecting Grignard addition (this time with 4-butenyl-MgBr) and reductive amination, the (+)-enantiomer (ent-850) was accessed. The authors did not determine which enantiomer corresponds to the natural product (as isolated from the frog \textit{Melanophryniscus stelzneri} since a chiral GC separation of the enantiomers was not achieved.

In the same paper, the authors disclosed the synthesis of four isomers—both enantiomers of pyrroloidines 852 and 853—as candidates for the structure of alkaloid 251O (found...
in three poison frog species and certain ants) using essentially the same chemistry as described for 
trans-223B but with appropriate variation in alkyl Grignard and Wittig reagents. Through these syntheses, the relative stereochemistry in the natural product was determined to be that shown in 853 but the absolute stereochemistry could not be assigned.

Reagents and conditions: (a) BuMgBr, TMEDA, THF, −78 °C; (b) Ph₂SiH, Br(C₂F₅)₂, CH₂Cl₂, −78 °C to rt; (c) ethyl acrylate, Grubbs’ II, CH₂Cl₂, reflux; (d) AlCl₃, CH₂Cl₂, then K₂CO₃, CH₃Cl; (e) DIBAL, CH₂Cl₂, −50 °C; (f) Ph₂PÉt Br, BuLi, THF, 0 °C to rt; (g) H₂, Pd/C, EtOAc; (h) H₂, Pd/C, EtOAc then 4-gethenyl-MgBr, TMEDA, THF, −78 °C.

Scheme 147 Reagents and conditions: (a) BuMgBr, TMEDA, THF, −78 °C; (b) Ph₂SiH, Br(C₂F₅)₂, CH₂Cl₂, −78 °C to rt; (c) ethyl acrylate, Grubbs’s II, CH₂Cl₂, reflux; (d) AlCl₃, CH₂Cl₂, then K₂CO₃, CH₃Cl; (e) DIBAL, CH₂Cl₂, −50 °C; (f) Ph₂PÉt Br, BuLi, THF, 0 °C to rt; (g) H₂, Pd/C, EtOAc; (h) H₂, Pd/C, EtOAc then 4-gethenyl-MgBr, TMEDA, THF, −78 °C.

Building on his group’s intramolecular alkene hydroamination methodology, Livinghouse noted that simple 1,2-disubstituted alkene are ‘reluctant participants’ in this chemistry; indeed, an attempted N-cyclisation onto a dec-3-enyl substituent proceeded ‘only with great lethargy’ at 120 °C. However, activation of the alkene by incorporation of a terminal aryl group allowed cyclisation to proceed more rapidly. With thienyl as the activating group, a route to saturated alkyl side-chains results following Raney nickel desulphurisation. Based on this idea, a short synthesis of (+)-xenovenine was achieved as shown in Scheme 150. The first, Sc(III)-catalysed, hydroamination step generated 2,5-trans-disubstituted pyrroline 862 with dr = 98:2. This intermediate then cyclised further to pyrrolidine 863 upon heating, again with high stereoselectivity; C–S and alkene reduction completed the route.

Reagents and conditions: (a) DIBAL, THF, −78 °C; (b) methyl acrylate, SmI₂, BF₃·OEt₂, t-BuOH, THF, −40 °C; (c) TBAF, THF; (d) I₂, P₂Ph₂, imidazole, THF; (e) H₂, Pd/C, Et₂N, MeOH; (f) (MeO)NHMe-HCl, AlMe₃, CH₂Cl₂; (g) C₆H₅MgBr, THF, 50 °C; (h) HCl, EtOAc then NaOEt, MeOH then H₂, Pd/C, MeOH.

The authors described a very similar sequence more recently in which the (−)-enantiomer was obtained by extending the hydroxymethyl substituent to provide the heptyl group and introducing the methyl group by organolithium addition to the Weinreb amide in 859 (Scheme 149).

Reagents and conditions: (a) DIBAL, THF, −78 °C; (b) methyl acrylate, SmI₂, BF₃·OEt₂, t-BuOH, THF, −40 °C [dr = 85:15]; (c) TBAF, THF, 0 °C to rt; (d) pyridine·SO₃, DMSO; (e) C₆H₅P⁺PhBr, B₃Li, THF, −78 °C to rt; (f) (MeO)NHMe-HCl, AlMe₃, CH₂Cl₂; (g) MeLi, THF, −78 °C, H₂, Pd(OH)₂/C, MeOH.

**Scheme 148** Reagents and conditions: (a) DIBAL, THF, −78 °C; (b) methyl acrylate, SmI₂, BF₃·OEt₂, t-BuOH, THF, −40 °C; (c) TBAF, THF; (d) I₂, P₂Ph₂, imidazole, THF; (e) H₂, Pd/C, Et₂N, MeOH; (f) (MeO)NHMe-HCl, AlMe₃, CH₂Cl₂; (g) C₆H₅MgBr, THF, 50 °C; (h) HCl, EtOAc then NaOEt, MeOH then H₂, Pd/C, MeOH.

**Scheme 150** Reagents and conditions: (a) BuLi, THF, −78 °C to −15 °C then (Z)-BrCH=CH₂CH₂Br, −78 °C; (b) aq HCl, CH₂Cl₂; (c) 5-ethylthiophene-2-boronic acid, Pd[PPh₃]₄, LiCl, Na₂CO₃, DME, reflux; (d) NH₂OAc, NaBH₄, CN, MeOH; (e) 864, toluene-d₈, 10 °C then 60 °C; (f) H₂, Raney Ni, MeOH.

In closely-related work, Livinghouse showed that aminodiene...
865 (Scheme 151), as one of six examples, cyclised slowly to 2,5-disubstituted pyrrolidine 866 with exclusive trans-stereochemistry.257 The second cyclisation was completed by raising the reaction temperature, and the cis-dialkyl product 867 was isolated with high selectivity. Reduction of the thiophene substituent completed the first total synthesis of alkaloid 195F from the arthropod Paratrechina amblyops.

Finally, both xenovenine enantiomers were obtained from simple allylic amines produced by asymmetric amination reactions.258 Thus, (−)-xenovenine was prepared from allylic carbonate 869 (Scheme 152), effecting the allylic displacement with N-formyl benzylcarbamate. This key step proceeded in ~97% ee but the yield was reduced because the achiral terminal amine regioisomer (not shown) was also present in ~1:2 ratio with the desired product 870. An eight-step sequence of transformations was then employed to extend one branch of the amine side-chain, effect kinetically-controlled trans-selective aza-Michael addition in enolate 871, and then further extend the side-chains in 872 by Wittig reactions. The pyrrolizidine was completed by one-pot N-deprotection, alkene hydrogenation, and reductive amination. The (+)-enantiomer was also prepared, by an analogous route starting with carbonate 875 in which the heptyl group is already present.

Notes and references

10 H. Wiedenfeld and A. Andrade-Cetto, Phytochemistry 2001, 57, 1269.
226 The descriptors $A_1$ and $A_2$ reflect the fact that jenamidine A comprises two equilibrating diastereomers, epimeric at C(7a).