Natural Product Reports

NPR

Pyrrolizidine alkaloids

Journal:	*Natural Product Reports*
Manuscript ID:	NP-REV-04-2014-000055.R1
Article Type:	Review Article
Date Submitted by the Author:	22-Jul-2014
Complete List of Authors:	Robertson, Jeremy; University of Oxford, Department of Chemistry Stevens, Kiri; University of Oxford, Department of Chemistry

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Pyrrolizidine alkaloids

Jeremy Robertson*[a] and Kiri Stevens[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

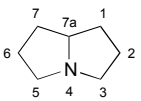
This review covers pyrrolizidine alkaloids isolated from natural sources. Topics include: aspects of structure, isolation, and biological/pharmacological studies; total syntheses of necic acids, necine bases and closely-related non-natural analogues. The literature from July 2001 to December 2012 is reviewed.[1]

Contents

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 pyrrolizine:

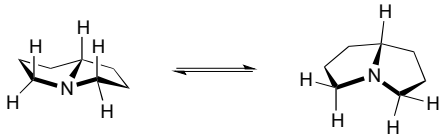


Structural studies

Skvortsov 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.

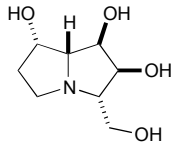


trans- *cis*-

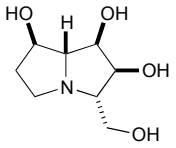
A third paper[4] discusses the IR spectra (O–H stretching frequency) of simple pyrrolizidine alcohols, connecting these data to stereochemistry. Again, trends were ascribed to the presence and extent of intra- or intermolecular hydrogen bonding and interactions with the solvent.

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.

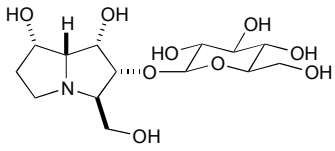
An NMR study conducted by Fleet's group confirmed the structures of previously isolated australine-type alkaloids in order to be sure that all compounds were, in fact, distinct natural products.[6] As part of this study, the group conducted a careful search for further pyrrolizidines in *Castanospermum australe* seeds, and discovered three new alkaloids (**1**–**3**). They also reported extensive biological testing of all isomers against a panel of glycosidase enzymes.



1, 2,3-di-*epi*-australine



2, 2,3,7-tri-*epi*-australine



3, 1-*epi*-australine 2-*O*-β-D-glucopyranoside

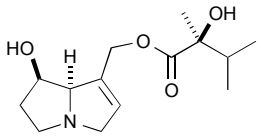
Confirmation of two related polyhydroxylated alkaloids was gained via single crystal X-ray diffraction structures for 3-*epi*-casuarine[7] and 1-*epi*-alexine.[8]

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.

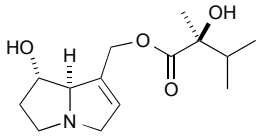
Isolation

New esters of known necine bases

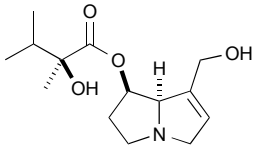
Retrohoustine **4**, heliohoustine **5**, and isoretrohoustine **6** were isolated along with lycopsamine from the leaves of *Ageratum houstonianum*, extracts of which are used in traditional Mexican Indian medicine for their anti-infective properties.[10]



4, retrohoustine

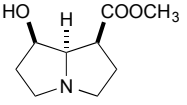


5, heliohoustine



6, isoretrohoustine

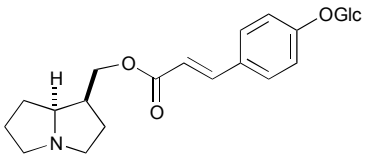
In a study into the alkaloids of *Osyris alba*, plant samples collected in France were shown to contain at least eight quinolizidine and eleven pyrrolizidine alkaloids, including the newly-identified ester janfestine **7** ((7*R*)-hydroxychysin A).[11] The pyrrolizidine alkaloids were, in general, found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



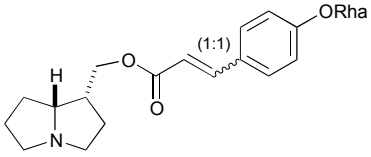
7, janfestine

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*-

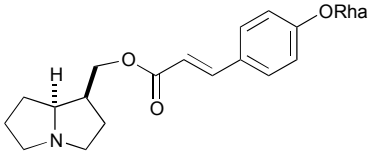
and *Z*- alkene isomers;[13] it was isolated exclusively as the *E*-isomer (**9′**) from the herb *Tephroseris kirilowii*.[14] The stereochemistry of the necine base core was assigned in **9** based on the formation of (+)-isoretronecanol by saponification; this also corresponds to the absolute stereochemistry in thesinine isolated from *Borago officinalis*.[15] Equivalent experiments were not reported for the other two glycosides (**8** and **9′**).



8, thesinine-4′-*O*-β-D-glucoside

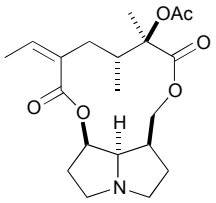


9, (*E,Z*)-thesinine-4′-*O*-α-rhamnoside



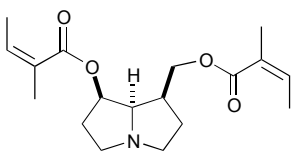
9′, (*E*)-thesinine-4′-*O*-α-L-rhamnoside

A new macrocyclic pyrrolizidine alkaloid, acetylplatyphylline **10**, was isolated from *Senecio arcticus* along with senecionine, platyphilline, and neoplatyphilline (amongst others).[16]

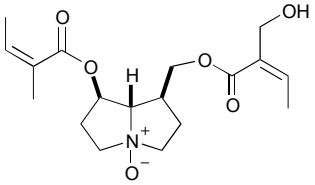


10, *O*-acetylplatyphilline

Novel alkaloids 7,9-diangeloylplatynecine **11** and 8-*epi*-sarracine *N*-oxide **12** were among the pyrrolizidine alkaloids isolated from the roots of *Senecio macedonicus*.[17] Another new compound, 8-epineosarracine, was detected by GC/MS analysis.

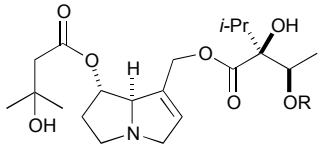


11, 7,9-diangeloylplatynecine

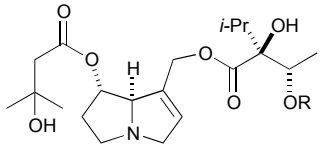


12, 8-*epi*-sarracine *N*-oxide

Among seven pyrrolizidine alkaloids obtained from the aerial parts of *Lithospermum canescens*, four were identified as new natural products and their structures determined to be the heliotridine esters **13**–**16** shown.[18]

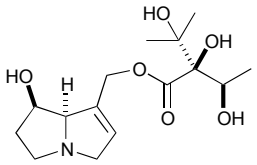


13, R = H, canescine
14, R = Ac, 13-*O*-acetylcanescine

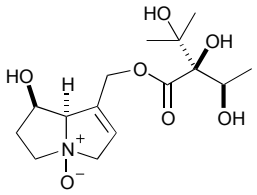


15, R = H, canescenine
16, R = Ac, 13-*O*-acetylcanescenine

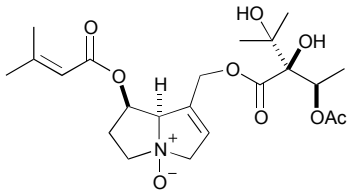
Three related novel pyrrolizidines **17**–**19** were obtained from the aerial parts of *Onosma leptantha*.[19] Two known alkaloids of the same type (echihumiline and its *N*-oxide) were also isolated from this source.



17, leptanthine

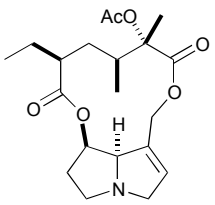


18, leptanthine *N*-oxide

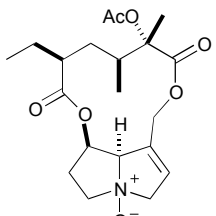


19, 3′-*O*-acetylechihumiline *N*-oxide

A study of the chemical constituents of *Ligularia tsangchanensis* resulted in the isolation and structural determination of three pyrrolizidine alkaloids. In addition to the known yamataimine, the novel *O*-acetyl derivative **20** was found, along with the corresponding *N*-oxide **21**.[20]



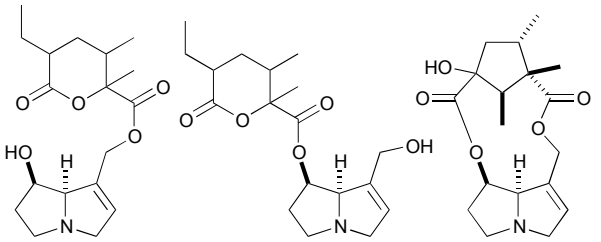
20, *O*-acetylyamataimine



21, *O*-acetylyamataimine *N*-oxide

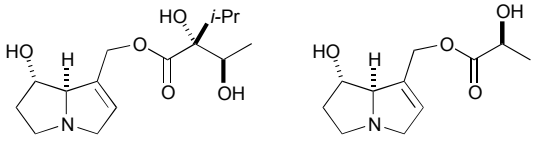
The same group also conducted analyses of a different species of the same genus, *Ligularia lankongensis*. First, two non-macrocyclic alkaloids lankongensisines A (**22**) and B (**23**)[21] were identified; these appear to be transacylation products of alkaloids of the more common senecionine type.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

cyclopentyl ring is unprecedented in the chemical literature.

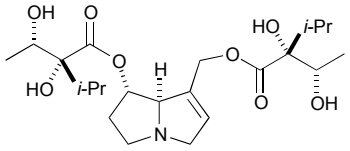


22, lankongensisine A **23**, lankongensisine B **24**, lankongensisine

Three new alkaloids were isolated from the roots of *Cynoglossum furcatum* and their structures assigned on the basis of spectroscopic evidence as isoechinatine **25**,[23] lactodine **26**, a lactate ester of heliotridine, and viridinatine **27**, a derivative of echinatine.[24]

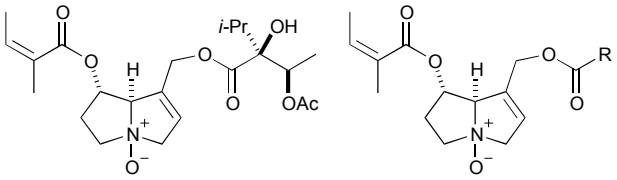


25, isoechinatine **26**, lactodine

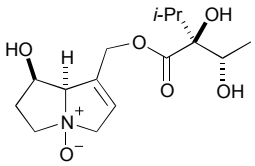


27, viridinatine

Work to develop solid-phase extraction methods and HPLC-ESI/MS profiling of pyrrolizidine alkaloids, using *Echium plantagineum* as a case study, identified higher ratios of pyrrolizidine *N*-oxides to free-bases than had previously been reported for this species.[25] Six pyrrolizidine alkaloids (or their *N*-oxides) were observed for the first time in this species; three of these **28**–**30** were new compounds. This work also discovered a higher proportion of acetylated *N*-oxides in the flower heads compared to the leaves.

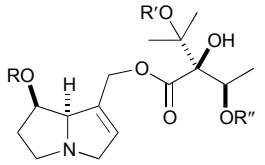


28, 3′-*O*-acetylechiumine *N*-oxide **29**, echiuplatine *N*-oxide (R = unspecified $C_6H_{13}O_2$)



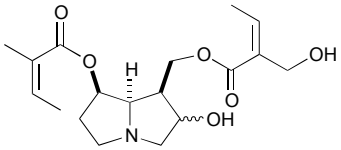
30, echimiplatine *N*-oxide

Two new pyrrolizidines, vulgarine **31** and 7-*O*-acetylvulgarine **32**, were found in pollen isolated from *Echium vulgare*, and their structures tentatively assigned on the basis of mass spectrometry and biogenetic considerations. The *N*-oxides of both were also observed.[26]



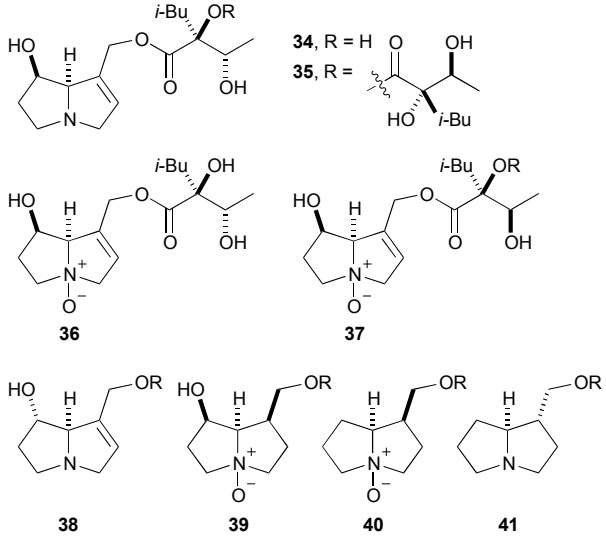
R′ or R″ = H or angelyl (unassigned)
31, R = H, vulgarine
32, R = Ac, 7-*O*-acetylvulgarine

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**.[27]



33, 2-hydroxysarracine

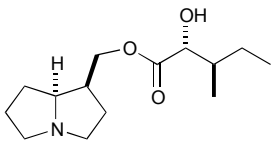
Eight new pyrrolizidine esters (four, **34**–**37**, of retronecine; one each of heliotridine, platynecine, isoretronecanol, and trachelanthamidine, **38**–**41**, respectively) were isolated from *Anchusa strigosa* in two studies by the same group.[28] All were tested for their antifeeding activity using lepidopteran larvae.



34, R = H
35, R =
36 **37**
38 **39** **40** **41**

For **38**–**41**, R as for **35**.

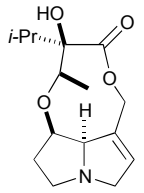
During efforts to find new muscarinic M3 receptor binding inhibitors, an extract from the dried bulbs of *Cremastra appendiculata* was found to be active. Isolation of its chemical constituents identified the new pyrrolizidine alkaloid cremastrine **42** as an active component.[29]



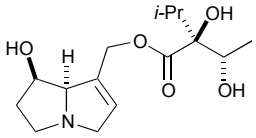
42, cremastrine

An unusual pyrrolizidine medium-ring lactone, helindicine **43**,

was isolated along with lycopsamine **44** from the roots of *Heliotropium indicum*.[30] 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 helindicine 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.

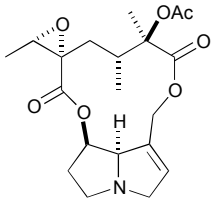


43, helindicine



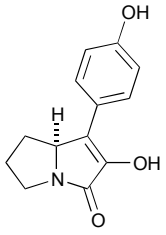
44, lycopsamine

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**.[31]



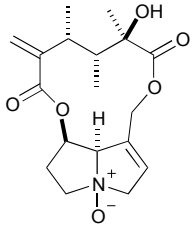
45, *O*-acetyl jacobine

An oxidised derivative of phenopyrrozin, *p*-hydroxy-phenopyrrozin **46**, was isolated from the marine fungus *Chromocleista* sp. alongside the parent compound.[32] 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}).



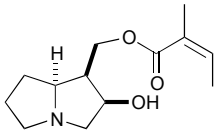
46, (+)-*p*-hydroxyphenopyrrozin

Senecivernine *N*-oxide **47** was isolated from a mixture of nine Bulgarian species of the *Senecio* genus.[33] 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.

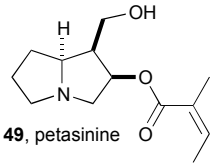


47, senecivernine *N*-oxide

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**.[34] The alkaloids are found mostly as their *N*-oxides in these plants and isolation was conducted after reduction with Zn dust.

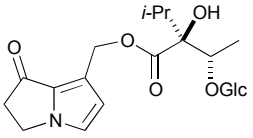


48, hectorine

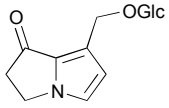


49, petasinine

The pyrrolic pyrrolizidine alkaloid **50** was isolated along with thirteen other compounds from whole-plant extracts of *Cynoglossum gasuense*.[35] 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*.[36]

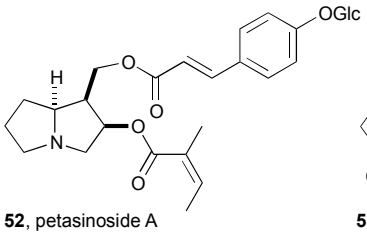


50

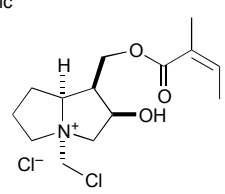


51

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.[37] 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).



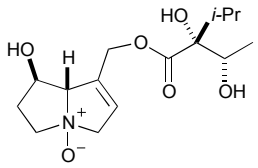
52, petasinoside A



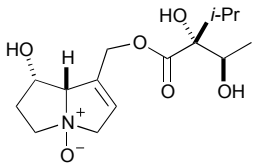
53, *N*-chloromethyl-hectorine chloride

Three new natural products were obtained from the roots of *Paris verticillata*, verticillatins A–C (**54**–**56**).[38] 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

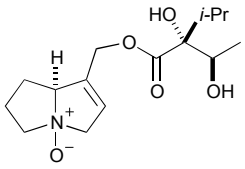
centres. These compounds, along with others isolated from the same source, were tested against four human tumour cell lines; verticillatins A–C showed weak cytotoxicity against the HCT15 cell line and were inactive against the other cell lines tested.



54, verticillatin A

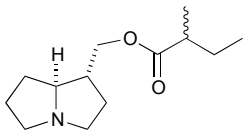


55, verticillatin B



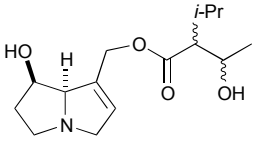
56, verticillatin C

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.[39] This compound showed antiparasitic activity against *Entamoeba histolytica* and *Giardia intestinalis*.



57, osyrisine

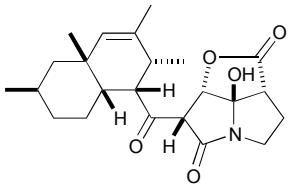
Analysis of *Crotalaria juncea* L. led to the identification of three previously unknown alkaloids, found to be similar in structure to the macrocyclic pyrrolizidine junceine but differing in the ester substituent.[40] These natural products were identified as diastereomers of one another and named isohemijunceines 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.



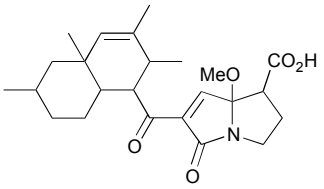
58, isohemijunceines A–C

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.[41] 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.

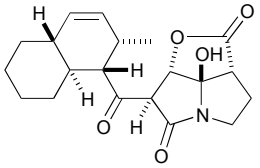


59, CJ-16,264

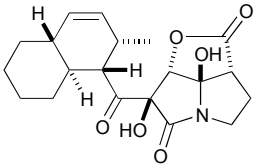


60, CJ-16,367

Soon after this report, closely-analogous pyrrolizidines UCS1025A **61** and B **66** were obtained from the fungus *Acremonium* sp. KY4917 and the structures assigned on the basis of NMR spectroscopy, modelling, and X-ray crystallographic analysis of a brominated derivative.[42] 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.

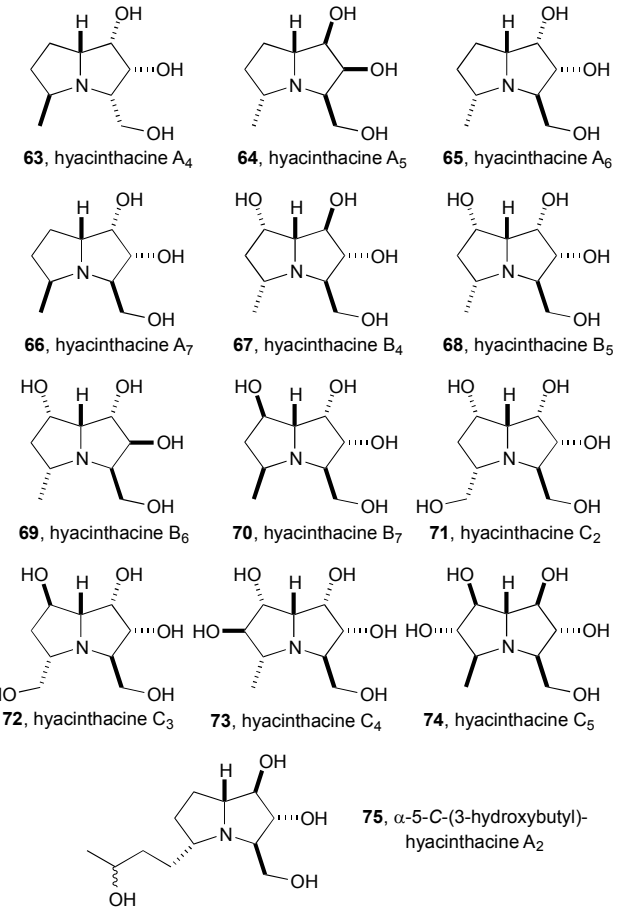


61, UCS1025A

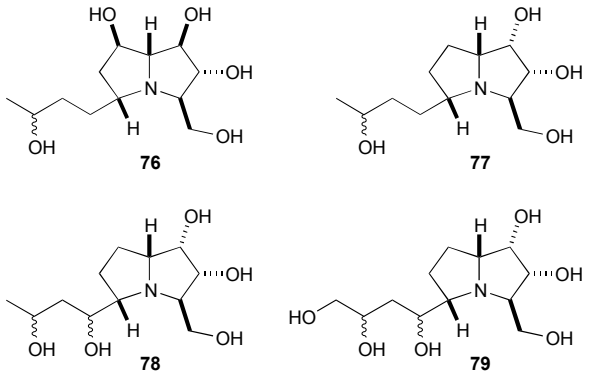


62, UCS1025B

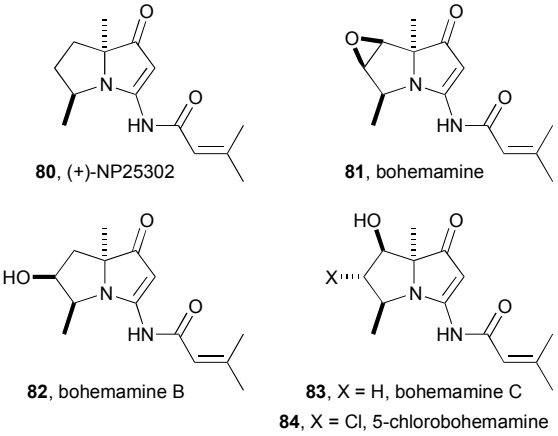
Analysis of the alkaloids in bulbs of *Scilla socialis* led to the discovery of seven new pyrrolizidine alkaloids **63**–**69** all showing similarity to known hyacinthacines but varying in their substitution pattern or stereochemistry around the pyrrolizidine core.[43] Known pyrrolizidine hyacinthacine B_3 was also isolated. Later, the same group identified more hyacinthacines **70**–**75** from the same source.[44] The structure (**73**) assigned to hyacinthacine C_4 is the same as that reported by the same authors for hyacinthacine C_1 but the ^{13}C NMR data do not match and they have opposite signs for specific rotation.[45] Subsequent total syntheses of (+)-hyacinthacine B_7 (**70**),[46] (+)-hyacinthacine C_3 (**72**),[47] and (+)-hyacinthacine C_5 (**74**)[48] 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.



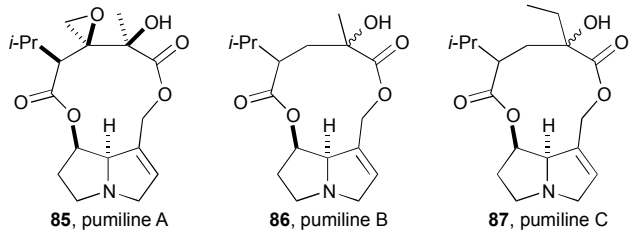
In a related study, further australine- and hyacinthacine-type alkaloids with extended side-chains (**76**–**79**) were isolated from *Scilla peruviana* bulbs.[49] Some of these alkaloids showed potent inhibition of yeast α-glucosidase (**76**: IC_{50} = 6.6 μM; **78**: IC_{50} = 6.3 μM) or a bacterial β-glucosidase (**78**: IC_{50} = 5.1 μM).



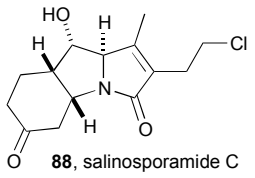
A strain of *Streptomyces* sp., UMA-044, isolated from the sediment of a catfish pond, yielded a series of fractions with activity in a cell-cell adhesion inhibition assay.[50] Isolation of active components of these fractions led to the identification of a new pyrrolizidine, NP25302 **80**, along with 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] 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.

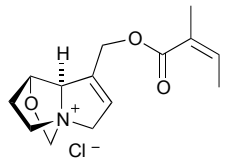


A close examination of the components of the culture broth of *Salinispora tropica* strain CNB-392 led to the isolation of five pyrrolidine lactams and two new salinosporamides, one of which (**88**) contains a pyrrolizidine core. This molecule is an apparent aza-Michael adduct of an enone analogue of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

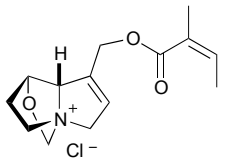


Three new pyrrolizidine alkaloids were obtained from the whole plant extract of *Echium glomeratum* Poir.[55] The structures of the three compounds **89**–**91** were determined by NMR experiments as diastereomers of a previously undescribed bridged pyrrolizidinium core. Both (4*S*,7*S*,8*R*)- and (4*S*,7*S*,8*S*)-petranine 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

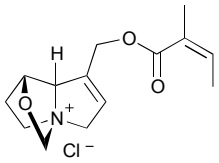
process, these pyrrolizidines may be isolation artefacts formed from simpler alkaloids based on angeloyl- heliotridine or retronecine cores.



89, (4*S*,7*S*,8*R*)-petranine



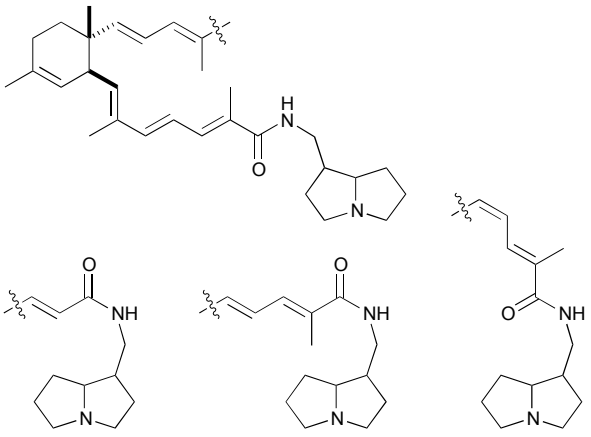
90, (4*S*,7*S*,8*S*)-petranine



91, (4*R*,7*R*)-petranine

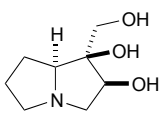
C(8), petranine numbering = C(7a), pyrrolizidine numbering.

Three terpenyl-pyrrolizidine conjugates, bistellettazines 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 C_{14}- and either C_{11}- or C_{14}- fragments. The stereochemistry of the aminopyrrolizidine fragment was not assigned but this fragment is apparently a single enantiomer common to the three bistellatazines.

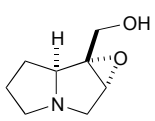


92, bistellettazine A **93**, bistellettazine B **94**, bistellettazine C

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.

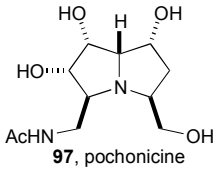


95, transalpinecine



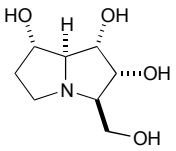
96, 1,2-di-*epi*-subulacine

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.



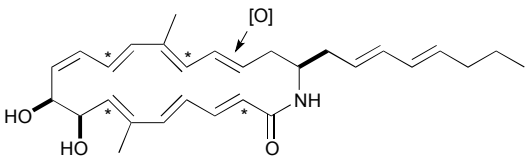
97, pochonicine

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.[8] This new pyrrolizidine was found to be a weak inhibitor of *Cellullomonas fimi* β-mannosidase.



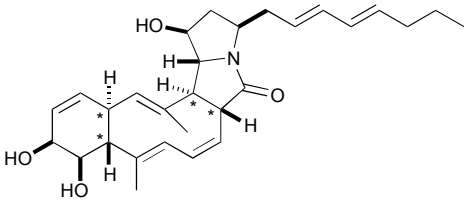
98, 1-*epi*-alexine

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 [$\pi4_s$ + $\pi6_s$]-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*).



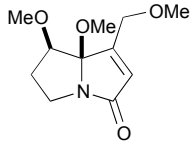
99, heronamide C

1) epoxidation
2) *N*-cyclisation
3) [4 + 6] cycloaddition (connecting *)



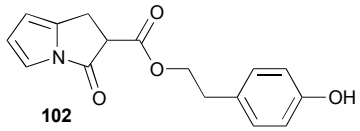
100, heronamide A

The new pyrrolizidine alkaloid **101** was isolated from Chinese *Senecio vulgaris* along with senecionine.[61] 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*.



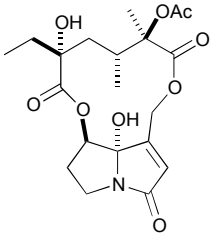
101, vulgarine

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.[62] One of these was assigned the pyrrolizidine lactam structure **102**.



102

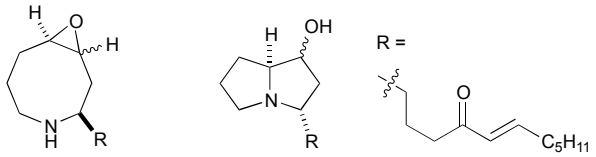
A new pyrrolizidine alkaloid was isolated along with eight known natural products from the roots of *Ligularia achyrotricha*, a plant used in Tibetan traditional medicine.[63] The structure **103**, an oxidised form (i.e. the 3-oxo-7a-hydroxy derivative) of bisline, was assigned on the basis of spectroscopic 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 (IC_{50} ~12.0 μg mL^{-1}).



103, ligulachyroine A

Revised Structures

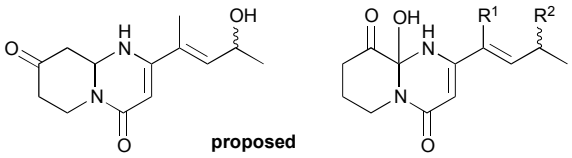
By comparison with spectroscopic data of synthetic compounds, the structures of epohelmins A and B, lanosterol synthase inhibitors isolated from the fungal strain FKI-0929, were revised from epoxyazocanes[64] **104** and **105** to pyrrolizidines **106** and **107**, respectively.[65] Key observations included discrepancies in the expected ^{1}H and ^{13}C NMR shifts for the epoxide centres, along with the experimental observation that 4,5-epoxyazocanes readily cyclise to 1-hydroxypyrrolizidines. A separate total synthesis effort confirmed this revised assignment.[66]



proposed **revised**

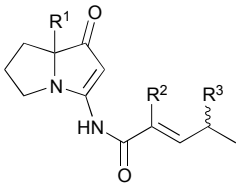
104, β-H, epohelmin A
105, α-H, epohelmin B
106, α-OH, epohelmin A
107, β-OH, epohelmin B

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.[67] 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.[52,68]



proposed

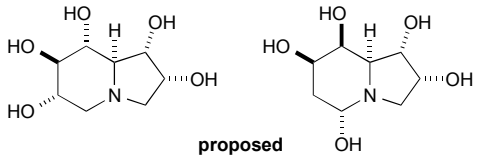
108, jenamidine A
109, R^1 = Me, R^2 = OH jenamidine B
110, R^1 = CH_2OH, R^2 = H jenamidine C



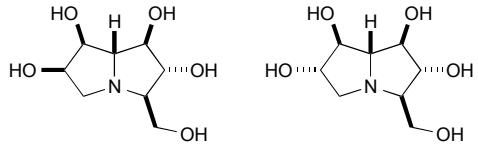
revised

111, R^1 = H, R^2 = Me, R^3 = OH, jenamidine A
112, R^1 = R^3 = OH, R^2 = Me, jenamidine B
113, R^1 = OH, R^2 = CH_2OH, R^3 = H, jenamidine C

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[69] indicated otherwise and further investigation suggested that the structures are, in fact, pyrrolizidines **116** and **117**.



114, uniflorine A **115**, uniflorine B



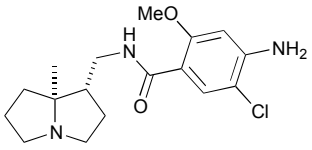
116, uniflorine A = 6-*epi*-casuarine **117**, uniflorine B = casuarine

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.[70]

Biological studies

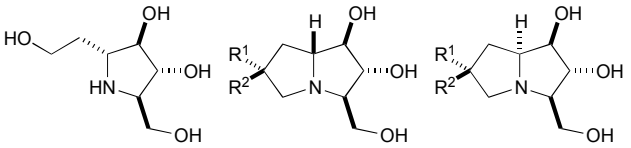
Bioactivity

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.[71] 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.[72]



118, (±)-methyl-SC-53116

7-Deoxycasuarine analogues **120**–**123** were designed as constrained analogues of the naturally-occurring chitin synthase inhibitor 6-deoxy-homo-DMDP (**119**).[73] The second ring was introduced in an effort to fix the orientation of the hydroxyethyl group of **119** since this group had been shown to be important for binding affinity. The bicyclic analogues were slightly more active glycosidase inhibitors; however, all showed lower levels of chitin synthase inhibition. The C(6) stereochemistry was found to influence binding affinity, with **120** being five times as active as its C(6) epimer **121**, and the C(7a) epimers **122** and **123** showed a ten-fold decrease in activity. Kinetic studies found that **120** bound in a different enzyme pocket to 6-deoxy-homo-DMDP and was a non-competitive inhibitor of the chitin synthase enzyme. The authors note that these results are the first reported examples of pyrrolizidine-type iminosugars acting as glycosyl-transferase inhibitors.



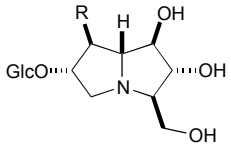
119 6-deoxy-homo-DMDP

120, R^1 = OH, R^2 = H
121, R^1 = H, R^2 = OH

122, R^1 = OH, R^2 = H
123, R^1 = H, R^2 = OH

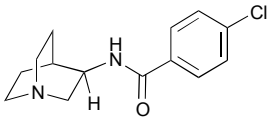
A review on the use of 8*H*-thieno[2,3-b]pyrrolizinones as anti-cancer agents has been published.[74]

Trehalose is insects' main blood sugar, being hydrolysed to glucose to give energy for flight; therefore, inhibition of trehalose hydrolysis offers a route to new insecticides. Casuarine 6-*O*-α-D-glucoside (**124**) is a known trehalase inhibitor, and its molecular conformation, in complex with the bacterial trehalase Tre37, has been reported. Within efforts to find more potent inhibitors, with selectivity for inhibition of insect trehalases, two new casuarine glucoside analogues (**125** and **126**) were prepared and tested against bacterial, mammalian kidney, and insect flight muscle trehalase enzymes.[75] Known inhibitor **124** was found to be the most potent compound, showing that the nature of the C(7) substituent has a strong bearing on inhibition. High selectivity was observed with **126**, with the IC_{50} for the insect trehalase significantly lower than for the other enzymes. A crystal structure of **126** bound to Tre37 was obtained, showing two additional hydrogen bonds between the C(7) substituent in **126** compared to **124**. All three compounds bound only very weakly to analogous human enzymes.

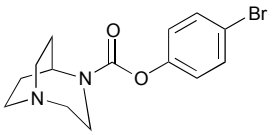


124, R = OH (casuarine 6-*O*-α-glucoside)
125, R = H
126, R = CH_2OH

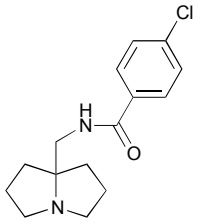
Computational studies into diversification of the core scaffold of known nictonic acetylcholine receptor (nAchR) ligands PNU-282,987 and SSR180711 led to the identification of a novel pyrrolizidine-containing scaffold **127** which, along with three other novel compounds, showed strong inhibition of the receptor.[76] 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.



PNU-282,987



SSR180711



127

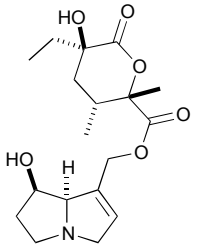
The safety of the traditional Chinese herbal medicine Chuan Zi Wan (CZW) was explored with respect to its pyrrolizidine alkaloid content potentially deriving from the *Ligularia* species involved in its preparation.[77] An HPLC-ESI analysis identified 26 potentially toxic pyrrolizidine alkaloids which, 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.[78] 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.[79] 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 pro-genotoxin leading to hepatocarcinogenesis.

An HPLC method was used to determine the fate of isoline (from *Ligularia duciformis*) in rat and mouse liver microsomal enzyme systems.[80] 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 isoline, implying a role for liver esterases in detoxifying this pyrrolizidine alkaloid.



128, bisline lactone

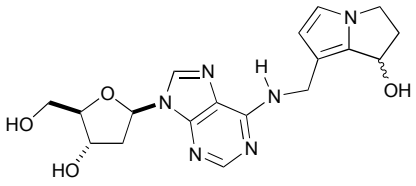
Dehydromonocrotaline was found to be toxic to astrocytes at micromolar concentrations, and led to hypertrophy in the cells and increased glial fibrillary acidic protein (GFAP) expression even at sub-micromolar concentrations.[81] Higher concentrations of the metabolite, from 10–500 μM, caused membrane damage and retraction of cellular processes, leading to lower GFAP expression. Condensed and fragmented chromatin 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.[82] Further work identified 3A4 and 2C19 as the major P450 isoforms responsible for metabolic activation of these two alkaloids.

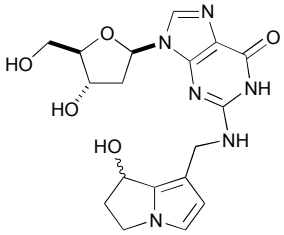
An alternative metabolic pathway, direct *N*-glucuronidation of intact pyrrolizidine alkaloids, has been identified and studied.[83] The extent of metabolism *via* this pathway was found to differ between species, with higher levels of *N*-glucuronidation seen, for example, in humans than in mice or 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.[84] 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).[85] 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.



129, β-OH, 'DHP-dA-3'
130, α-OH, 'DHP-dA-4'

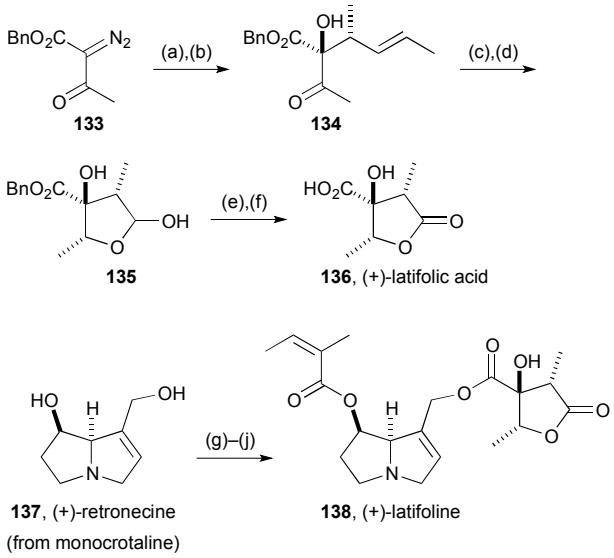


131, β-OH, 'DHP-dG-3'
132, α-OH, 'DHP-dG-4'

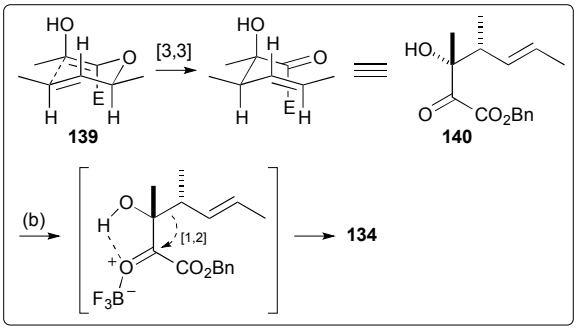
Synthetic studies

Necic acids

Syntheses of the occasionally complex acid components of naturally-occuring 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).[86] 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 imidazolide.



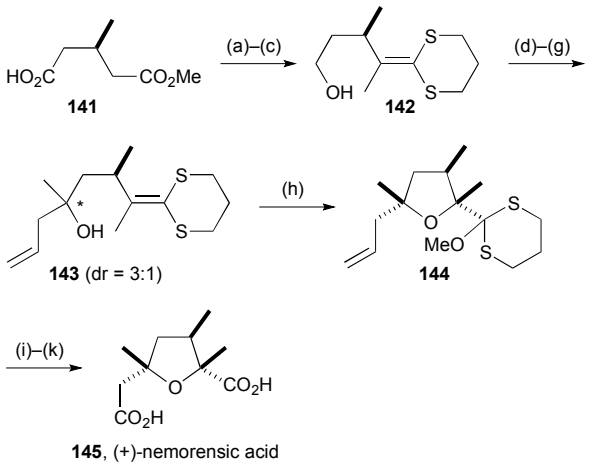
133 **134** **135** **136**, (+)-latifolic acid
137, (+)-retronecine (from monocrotaline) **138**, (+)-latifoline



139 **140** **134**

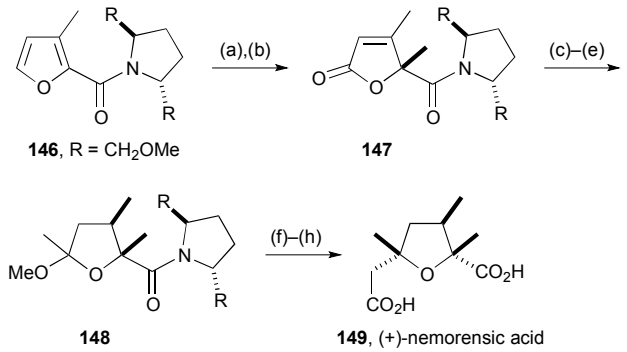
Scheme 1 Reagents and conditions: (a) (*S*)-pent-3-en-2-ol, $Rh_2(TFA)_4$, C_6H_6, reflux; (b) $BF_3{\cdot}OEt_2$, C_6H_6; (c) $NaBH_4$, $ZnCl_2$, Et_2O, THF, –15 °C; (d) O_3, CH_2Cl_2, –78 °C then Me_2S; (e) TPAP, NMO, 3Å MS, CH_2Cl_2, 0 °C; (f) H_2, Pd/C, EtOAc; (g) TBSCl, imidazole, CH_2Cl_2; (h) BuLi, THF, 0 °C then angeloyl chloride; (i) SiF_4, CH_3CN; (j) **136**-imidazolide, $CHCl_3$.

The first two routes to (+)-nemorensic acid featured electron transfer redox steps as key elements of the syntheses. In Moeller's route, (Scheme 2)[87] 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.



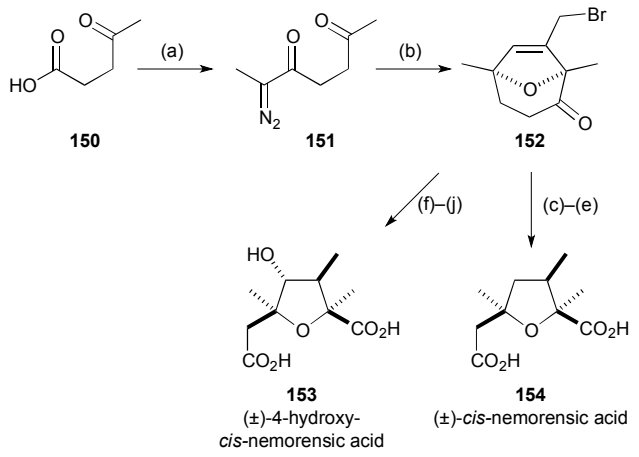
Scheme 2 Reagents and conditions: (a) $BH_3{\cdot}SMe_2$, THF; (b) LDA, MeI, THF; (c) $HS(CH_2)_3SH$, Me_3Al, CH_2Cl_2, reflux; (d) $(CF_3CO)_2O$, DMSO, CH_2Cl_2 then Et_3N; (e) MeLi, Et_2O; (f) $(CF_3CO)_2O$, DMSO, CH_2Cl_2 then Et_3N; (g) (–)-$Ipc_2BCH_2CH{=}CH_2$, Et_2O; (h) RVC anode, Pt cathode, undivided cell, Et_4NOTs, MeOH, THF; (i) O_3, CH_2Cl_2 then Me_2S; (j) $KMnO_4$, aq NaH_2PO_4, *t*-BuOH; (k) aq NaOH.

In Donohoe's synthesis,[88] published soon after Moeller's first communication, Birch reduction of furancarboxamide **146** (Scheme 3) with chiral auxiliary-controlled methylation gave butenolide **147** after allylic oxidation of the first-formed dihydrofuran. Alkene hydrogenation proceeded with good *syn*-diastereoselectivity (dr = 92:8) with respect to the amide functionality to set the correct 1,2-relationship of methyl groups. Petasis methylenation and controlled methanolysis of the enol ether gave acetal **148**. This was used as a precursor for allylation via the oxonium ion, with delivery of the allyl group following Woerpel's 'inside attack' stereoelectronic model. The synthesis was then easily completed by oxidative cleavage of the alkene and amide hydrolysis under forcing conditions.



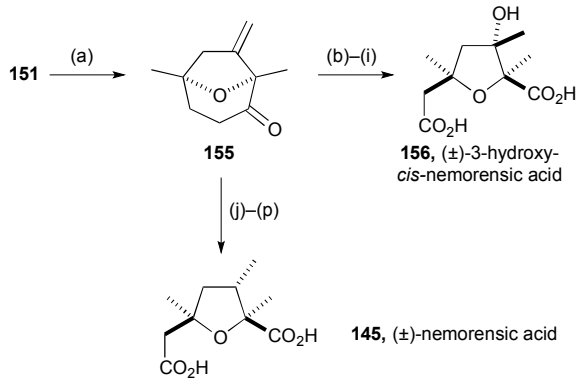
Scheme 3 Reagents and conditions: (a) Na, NH_3, –78 °C then MeI; (b) CrO_3, aq H_2SO_4, acetone, 50 °C; (c) H_2, $Pd(OH)_2/C$, EtOH; (d) Cp_2TiMe_2, THF, 70 °C; (e) HCl, $Me_2C(OMe)_2$, MeOH; (f) $CH_2{=}CHCH_2SiMe_3$, $TiCl_4$, CH_2Cl_2; (g) $RuCl_3{\cdot}xH_2O$, $NaIO_4$, aq CCl_4, CH_3CN; (h) aq. HCl, reflux.

Hodgson described routes to racemic *cis*-nemorensic acid (**154**, Scheme 4) and its 4-hydroxy derivative **153**.[89] Here, the oxonium ylid derived from diazoketone **151** was trapped in a cycloaddition with propargyl bromide, giving oxy-bridged cycloheptenone **152**. This established the 2,5-*cis*-disubstitution pattern in the target products, revealed later by ozonolysis (with oxidative work-up) of the silyl enol ether from **152**. The third methyl-bearing stereogenic centre was installed by stereoselective hydrogenation from the less hindered face with accompanying hydrodebromination. To access the 4-hydroxy- derivative, the alkene 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 Reagents and conditions: (a) *i*-BuOCOCl, Et_3N, Et_2O, 0 °C to rt then CH_3CHN_2, Et_2O, 0 °C; (b) $BrCH_2C{\equiv}CH$, $Rh_2(OAc)_4$, CH_2Cl_2; (c) H_2, Pd/C, MeOH; (d) LDA, THF, –78 °C then TMSCl; (e) O_3, CH_2Cl_2, –78 °C then aq HCO_2H, H_2O_2, reflux; (f) DMDO, acetone, CH_2Cl_2; (g) Zn, NaI, MeOH, 65 °C; (h) H_2 (60 psi), $[Ir(cod)py(PCy_3)]PF_6$, CH_2Cl_2; (i) LDA, THF, –78 °C then TMSCl; (j) O_3, CH_2Cl_2, –78 °C then aq HCO_2H, H_2O_2, reflux.

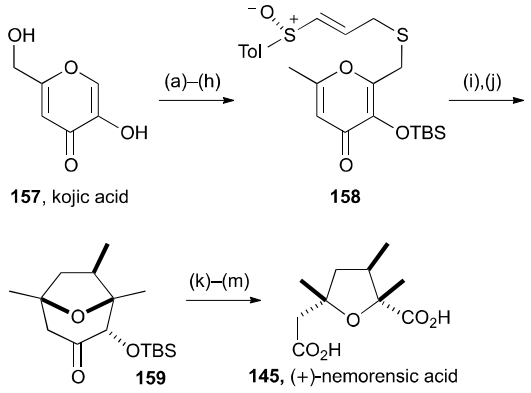
In a variant, the same oxonium ylid was trapped by allene to give exomethylene cycloheptanone **155** (Scheme 5).[90] This was elaborated by similar routes, terminating in racemic 3-hydroxy-*cis*-nemorensic acid **156** and racemic nemorensic acid **145**. Stereoselective epoxidation was performed on the ethylene acetal of ketone **155** (to prevent Baeyer–Villiger oxidation), then hydride reduction and acetal hydrolysis set up the same ozonolysis route to the hydroxylated necic acid. Alternatively, following ring-cleavage, hydrogenation from the 'front' face was achieved by direction from the ester(s), leading to **145**.

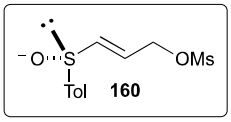


Scheme 5 Reagents and conditions: (a) allene, $Rh_2(OAc)_4$, CH_2Cl_2, 0 °C; (b) ethylene glycol, CSA, CH_2Cl_2; (c) MCPBA, CH_2Cl_2; (d) $LiAlH_4$, THF; (e) HCl, aq THF; (f) LDA, THF, –78 °C then TMSCl; (g) O_3, CH_2Cl_2, –78 °C then aq HCO_2H, H_2O_2, reflux; (h) $TMSCHN_2$, hexane, MeOH; (i) aq KOH; (j) LDA, THF, –78 °C then TMSCl; (k) DMDO, acetone, CH_2Cl_2, 0 °C; (l) $NaIO_4$, aq THF; (m) $AgNO_3$, NaOH, EtOH; (n)

CH_3CHN_2, Et_2O, 0 °C; (o) H_2 (60 psi), $[Ir(cod)py(PCy_3)]PF_6$, CH_2Cl_2; (p) aq KOH.

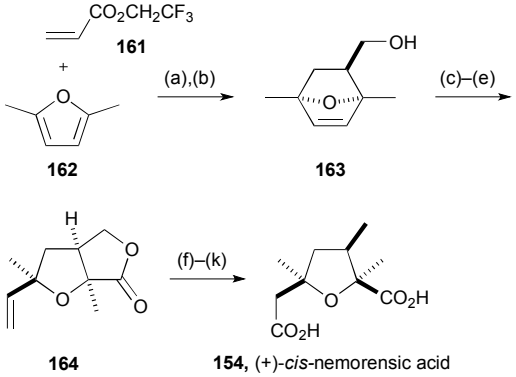
At about the same time, Mascareñas employed a formally analogous strategy to access (+)-nemorensic acid.[91] Key to this approach was the diastereoselective intramolecular oxidopyrylium cycloaddition of chiral sulfoxide **158** (Scheme 6). The sulfoxide acted as an effective chiral auxiliary in this reaction to provide a 93:7 ratio of (5+2)-cycloadducts. 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 oxidative cleavage of the α-hydroxy ketone and Jones oxidation to the diacid completed the route.

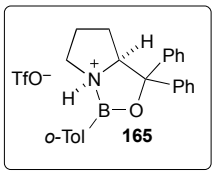




Scheme 6 Reagents and conditions: (a) $SOCl_2$, $CHCl_3$, 60 °C; (b) H_2, Pd, NaOAc, MeOH; (c) KOH, aq HCHO; (d) KOH, PMBCl, KI, acetone; (e) CBr_4, PPh_3, THF; (f) **160**, Ph_3SiSH, Cs_2CO_3, PPh_3, THF; (g) CF_3CO_2H, CH_2Cl_2; (h) TBSCl, imidazole, CH_2Cl_2; (i) $PhCH_3$, 160 °C; (j) Raney Ni, THF; 60 °C; (k) TBAF·$3H_2O$; (l) $Pb(OAc)_4$, MeOH; (m) CrO_3, H_2SO_4, aq acetone.

Cycloaddition of a different kind featured in Ryu's synthesis of (+)-*cis*-nemorensic acid.[92] The route began with a highly efficient (99% yield) and stereoselective (*endo*-:*exo*- = 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.

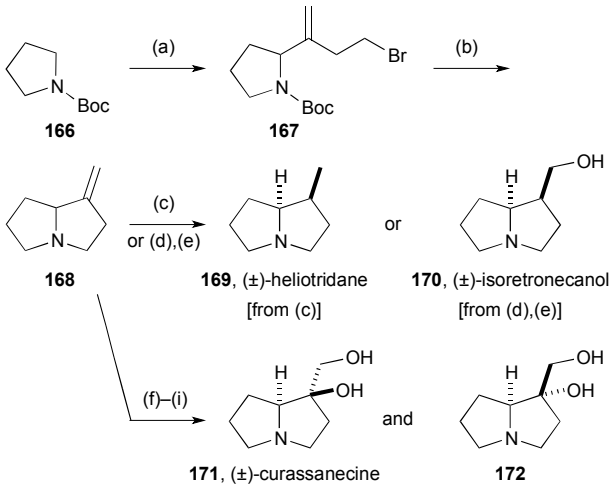




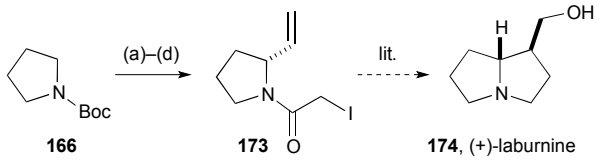
Scheme 7 Reagents and conditions: (a) **165**, CH_2Cl_2, –95 °C; (b) $LiAlH_4$, THF, –30 °C; (c) OsO_4, NMO, aq *t*-BuOH, THF then $NaIO_4$; (d) $Ph_3P^+CH_3\ Br^-$, NaHMDS, THF, 0 °C; (e) PCC, celite, CH_2Cl_2; (f) CsOH, *t*-BuOH then $TMSCHN_2$, aq citric acid, MeOH; (g) I_2, Ph_3P, imidazole, THF; (h) BH_3·THF, THF, 0 °C then NaOH, aq H_2O_2, 0 °C; (i) Zn, AcOH; (j) PCC, celite, CH_2Cl_2; (k) $NaClO_2$, NaH_2PO_4, 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 (±)-isoretronecanol and (±)-curassenecine (Scheme 8).[93] Lithiation and transmetallation 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 isoretronecanol were prepared along with (+)-laburnine (formal synthesis, illustrated in Scheme 9).

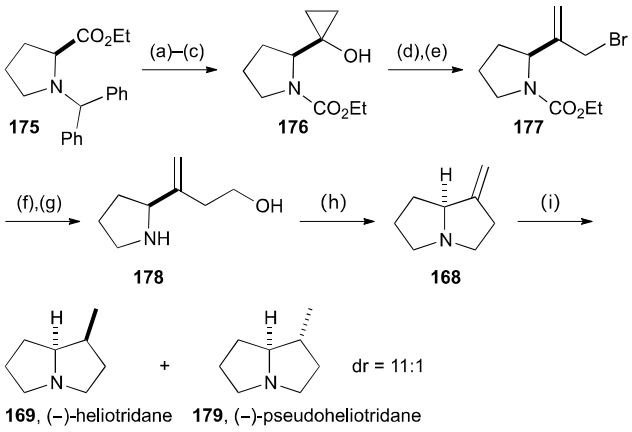


Scheme 8 Reagents and conditions: (a) *s*-BuLi, TMEDA, THF, −78 °C then CuCN·2LiCl, −78 °C then 4-bromo-2-iodobutene, −78 °C; (b) TMSOTf, CH_2Cl_2, −20 °C to rt; (c) H_2, Pd/C, CH_2Cl_2; (d) BH_3·THF, THF, 0 °C to rt then aq NaOH, H_2O_2, 0 °C to rt; (e) TMSCl, MeOH; (f) BF_3·OEt_2; (g) MCPBA, CH_2Cl_2; (h) aq HCl; (i) CsF, MeCN, reflux.



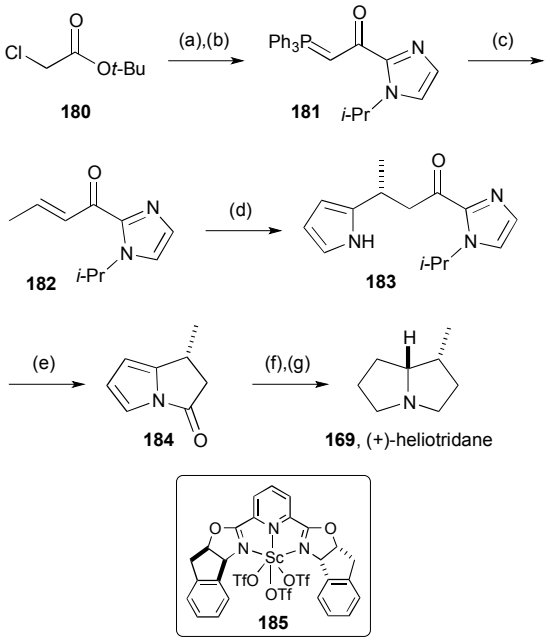
Scheme 9 Reagents and conditions: (a) *s*-BuLi, (–)-sparteine, Et_2O, −78 °C then CuCN·2LiCl, −78 °C then vinyl iodide, −78 °C; (b) CF_3COOH, CH_2Cl_2; (c) $ClCH_2COCl$, Et_3N, CH_2Cl_2; (d) NaI, CH_3CN.

Intermediates similar in structure to bromoalkene **167** were obtained by Kulinkovich by application of his eponymous reaction on proline derivative **175** (Scheme 10).[95] 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 (–)-pseudoheliotridane.



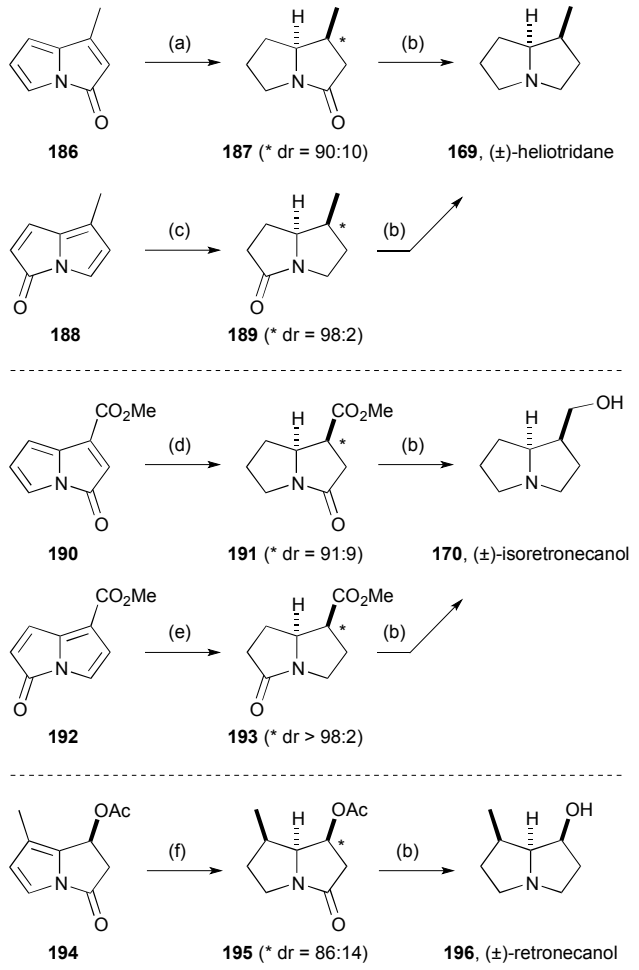
Scheme 10 Reagents and conditions: (a) EtMgBr, Ti(O*i*-Pr)$_4$, Et_2O; (b) H_2, $Pd(OH_2)$/C, MeOH; (c) $ClCO_2Et$, Et_3N, CH_2Cl_2; (d) MsCl, Et_3N, Et_2O; (e) $MgBr_2$·OEt_2, $CHCl_3$, Et_2O, reflux; (f) Zn, $(HCHO)_n$, THF, reflux; (g) aq KOH, reflux; (h) PPh_3, CCl_4, Et_3N, DMF; h) $NaBH_4$, $NiCl_2$·$6H_2O$, 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.[96] 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 pyrrolizinone **184** in essentially enantiopure form. Hydrogenation then lactam reduction furnished (+)-heliotridane, which was purified by conversion to the picrate salt.



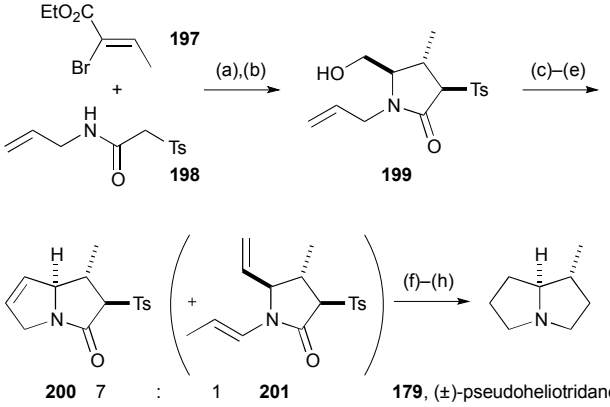
Scheme 11 Reagents and conditions: (a) (1-isopropyl-1*H*-imidazol-2-yl)lithium, THF; (b) (i) PPh_3, C_6H_6, reflux; (ii) aq $NaHCO_3$; (c) CH_3CHO, C_6H_6, rt to 80 °C; (d) pyrrole, 2 mol% **185**, 4Å MS, CH_3CN, –40 °C (95% ee); (e) MeOTf, 4Å MS, CH_3CN then *i*-Pr_2NEt; (f) H_2, 5% Rh/Al_2O_3, EtOH (dr = 90:10); (g) $LiAlH_4$, THF then Na_2SO_4·$10H_2O$.

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.[97] 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, (±)-isoretronecanol, and (±)-retronecanol 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 retronecanol 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.



Scheme 12 Reagents and conditions: (a) H_2 (45 psi), Rh/Al_2O_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_2O_3, AcOH; (f) H_2 (45 psi), Rh/C, EtOAc.

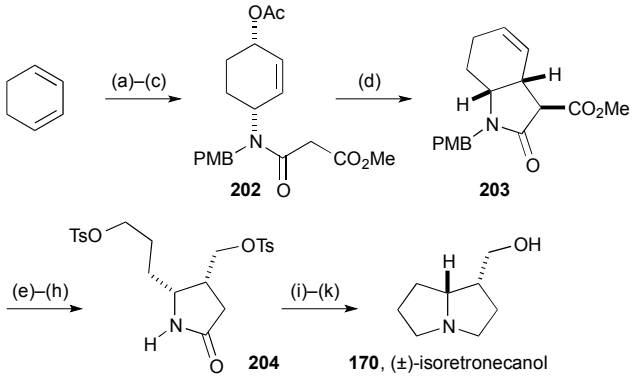
Racemic pseudoheliotridane was prepared by a somewhat lengthy route building from an initial (3+2)-annulation between the α-sulfonylacetamide derivative **198** (Scheme 13) and the 2-bromocrotonate **197**.[98] Functional group manipulations gave a diene (the *N*-allyl isomer of **201**) from which the 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 13 Reagents and conditions: (a) NaH, THF; (b) $NaBH_4$, EtOH; (c) Swern oxidation; (d) $Ph_3P^+Me\ I^-$, BuLi, HMPA, THF, –78 °C; (e) Grubbs' II, DCE, reflux; (f) Na(Hg), MeOH; (g) H_2, Pd/C, MeOH; (h) $LiAlH_4$, THF.

Isoretronecanol and trachelanthamidine/laburnine

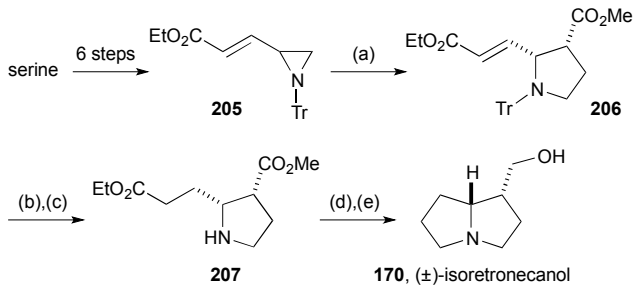
The simple 1-hydroxymethylpyrrolizidine isoretronecanol and its diastereomer trachelanthamidine/laburnine continue to be popular targets for exemplifying methods for 1,2-diastereocontrol and several new syntheses of these alkaloids were reported during the review period. The first, of the racemate, introduced the desired relative stereochemistry by intramolecular alkylation of the Pd π-allyl derived from acetate **202** (Scheme 14).[99] 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 (±)-isoretronecanol simply required cyclohexene ring cleavage and appropriate activation of the hydroxypropyl fragment to enable *N*-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, $PhCH_3$; (c) MeO_2CCH_2COCl, Et_3N, CH_2Cl_2, 0 °C; (d) NaH, DMF then $Pd(OAc)_2$, dppe, DMF, 50 °C; (e) NaCl, DMSO, 155 °C; (f) OsO_4, $Me_3NO{\cdot}2H_2O$, aq THF then $NaIO_4$, MeOH then $NaBH_4$, MeOH; (g) TsCl, Et_3N, DMAP, CH_2Cl_2; (h) CAN, aq CH_3CN, 0 °C; (i) NaH, THF, 0 °C to rt; (j) Bu_4NOAc, NaI, THF, 55 °C; (k) $LiAlH_4$, THF, 66 °C.

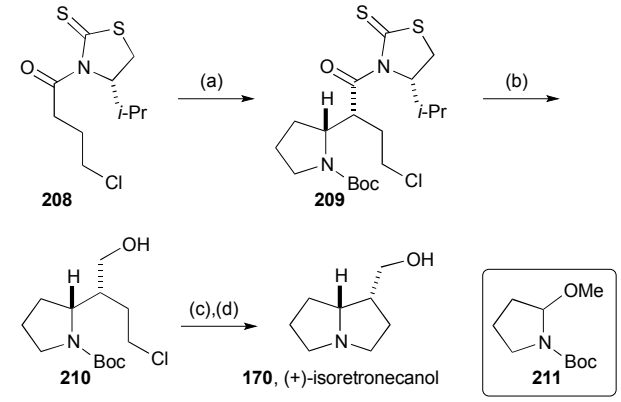
A second synthesis of the racemate was reported in the same year from serine-derived vinyl aziridine **205** (Scheme 15).[100]

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 $CH{=}CHCO_2Et$ and CO_2Me 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.



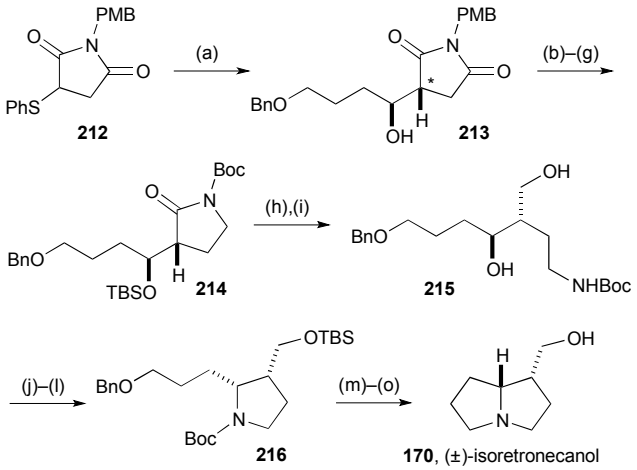
Scheme 15 Reagents and conditions: (a) methyl acrylate, CH_3CN, hν, 0 °C; (b) CF_3CO_2H, $CHCl_3$, MeOH; (c) H_2, Pd/C, EtOAc; (d) $PhCH_3$, reflux; (e) (not carried out in this work) $LiAlH_4$, THF.

One of the most concise syntheses of isoretronecanol, also notable for providing the (+)-isomer, was reported by Pilli's group.[101] 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 $LiBH_4$. *N*-Deprotection and cyclisation upon basification completed this short synthesis.



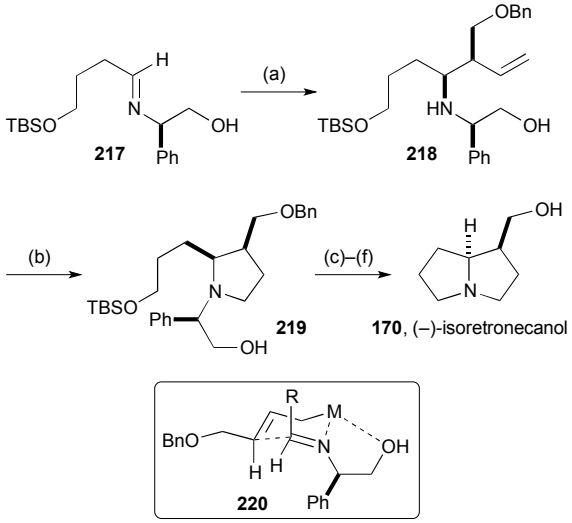
Scheme 16 Reagents and conditions: (a) **211**, $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, –23 °C; (b) $LiBH_4$, THF, MeOH, 0 °C; (c) CF_3CO_2H, Et_3SiH, CH_2Cl_2; (d) $NaHCO_3$, H_2O.

In comparison, Yoda's synthesis of (±)-isoretronecanol is rather lengthy, although most of the steps (Scheme 17) are very efficient.[102] The key constructive step comprises a diastereoselective 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 17 Reagents and conditions: (a) $BnO(CH_2)_3CHO$, SmI_2, HMPA, THF (* dr = 3:1); (b) TBSCl, imidazole, DMF; (c) $NaBH_4$, MeOH; (d) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –40 °C; (e) CAN, aq CH_3CN; (f) TBSCl, imidazole, DMF; (g) Boc_2O, DMAP, Et_3N, CH_2Cl_2; (h) $NaBH_4$, MeOH; (i) TBAF, THF; (j) TBSCl, Et_3N, CH_2Cl_2; (k) MsCl, Et_3N, CH_2Cl_2; (l) *t*-BuOK, THF; (m) H_2, Pd/C, EtOH; (n) MsCl, Et_3N, CH_2Cl_2; (o) CF_3CO_2H, CH_2Cl_2, 0 °C.

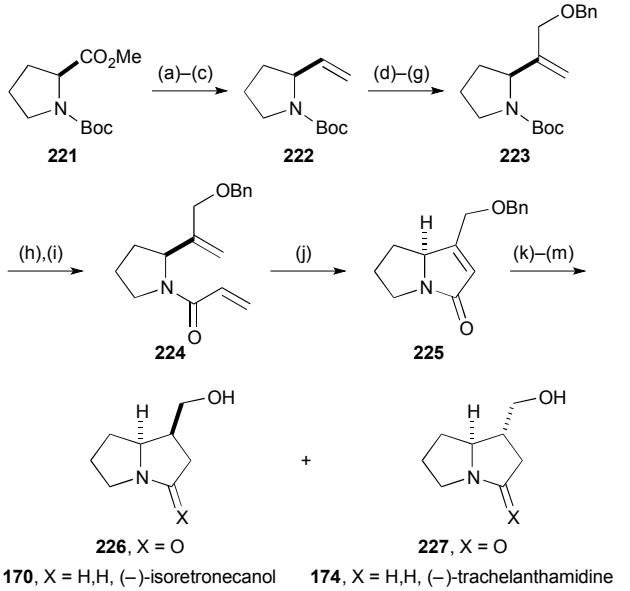
For Szymoniak's synthesis of (–)-isoretronecanol,[103] chiral auxiliary-controlled diastereoselective allylic transfer to imine **217** (Scheme 18) gave 1,2-*syn* diastereomer **218** with dr = 9:1. The stereochemical outcome was explained by delivery of the functionalised allyl indium to the face opposite the phenyl substituent in a chelated intermediate as shown (**220**). Overall formal 5-*endo*-*trig* hydroamination of aminoalkene **218** was achieved by hydrozirconation with excess Schwartz reagent, iodination of the C–Zr bond, then *N*-cyclisation (5-*exo*-*tet*) generating *cis*-disubstituted pyrrolidine **219**. Hydrogenolysis proved to be selective for the chiral auxiliary, and *N*-cyclisation followed under Appel conditions. Final debenzylation of the 1°-alcohol completed this short synthesis.



Scheme 18 Reagents and conditions: (a) (*E*)-$BnOCH_2CH{=}CHCH_2Br$, In, MeOH (dr = 9:1); (b) Cp_2ZrHCl, CH_2Cl_2 then I_2, CH_2Cl_2; (c) H_2,

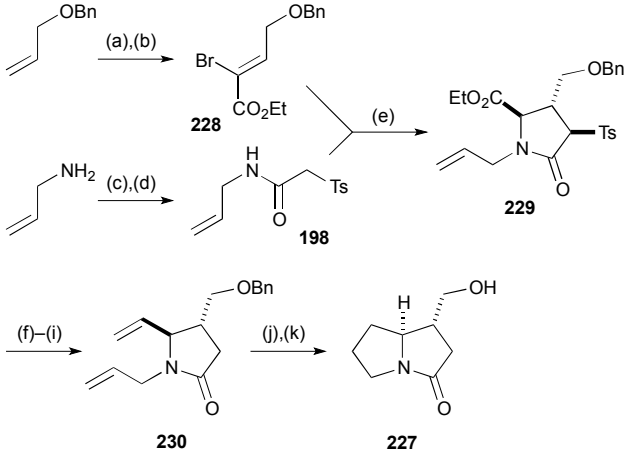
$Pd(OH)_2/C$, MeOH; (d) TBAF, THF, 0 °C to rt; (e) CBr_4, PPh_3, Et_3N, CH_2Cl_2, 0 °C; (f) H_2, $Pd(OH)_2/C$, aq HCl, MeOH.

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.



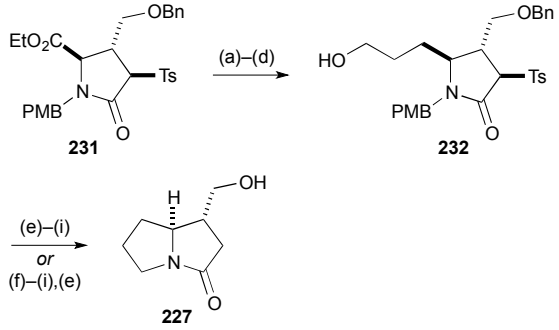
Scheme 19 Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C to rt; (b) Swern oxidation; (c) $Ph_3P{=}CH_2$, THF, –10 °C; (d) OsO_4, $NMO{\cdot}H_2O$, aq acetone, 0 °C to rt; (e) Bu_2SnO, $PhCH_3$, reflux then BnBr, Bu_4NI, $PhCH_3$, reflux; (f) TEMPO, NaBr, NaOCl, $NaHCO_3$, aq 2-butanone, $PhCH_3$, 0 °C; (g) $Ph_3P{=}CH_2$, THF, –10 °C; (h) CF_3CO_2H, Et_3N, CH_2Cl_2, 0 °C; (i) acryloyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C; (j) Grubbs' II, C_6H_6, 90 °C; (k) H_2, Pd/C, MeOH; (l) PhCOCl, Et_3N, DMAP, CH_2Cl_2, 0 °C then separate diastereomers; (m) K_2CO_3, 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 bromoenoate **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) $Ph_3P{=}C(Br)CO_2Et$; (c) $ClCH_2COCl$, Et_3N; (d) NaTs; (e) NaH, THF, reflux; (f) $LiAlH_4$, THF, 0 °C to rt; (g) Na(Hg), Na_3PO_4, MeOH; (h) Swern oxidation; (i) $Ph_3P{=}CH_2$, THF, –78 °C; (j) Grubbs' II, C_6H_6, reflux; (k) H_2, Pd/C, MeOH.

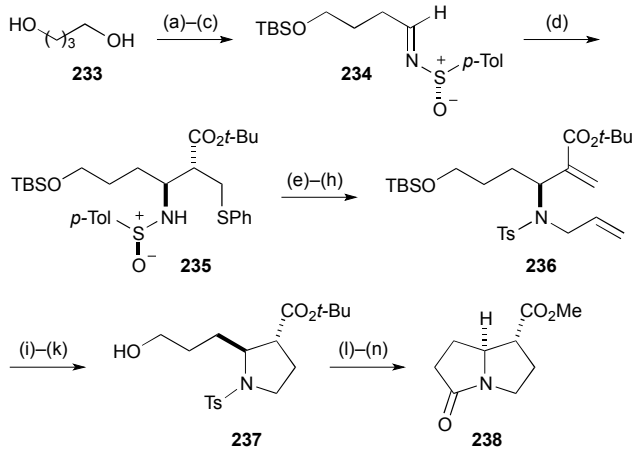
Chang effected a second formal synthesis of the racemate, building on the previous route, but forming the second ring by *N*-cyclisation rather than ring-closing metathesis.[106] From pyrrolidone **231** (Scheme 21, *cf.* Scheme 20), extension from the ester, reductive removal of the sulfonyl group, 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.



Scheme 21 Reagents and conditions: (a) $NaBH_4$, LiCl, MeOH; (b) Swern oxidation; (c) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2; (d) $LiAlH_4$, THF; (e) Na(Hg), MeOH; (f) MsCl, pyridine, CH_2Cl_2; (g) CAN, aq CH_3CN; (h) NaH, THF, reflux; (i) H_2, Pd/C, MeOH.

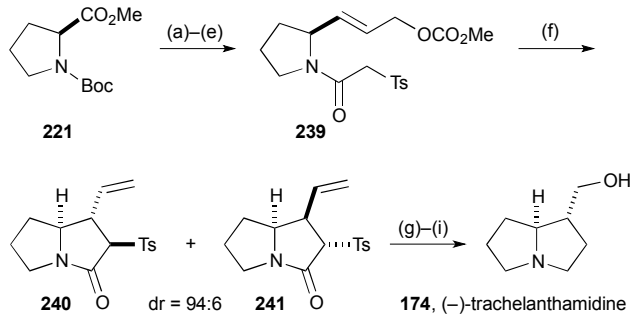
A formal synthesis of the (–)-enantiomer was developed from adduct **235** (Scheme 22).[107] Thus, tandem conjugate thiolation of *tert*-butyl acrylate and enolate addition to sulfinamine **234** gave adduct **235** (dr = 85:15). The formation of the minor diastereomer was attributed to epimerisation at the ester (as opposed to being the result of moderate asymmetric induction). The formal aza-Baylis–Hillman adduct **236** was then obtained by sulfoxide elimination, oxidation of the sulfinyl substituent to sulfonyl, and *N*-allylation. Ring-closing metathesis generated the pyrroline 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.



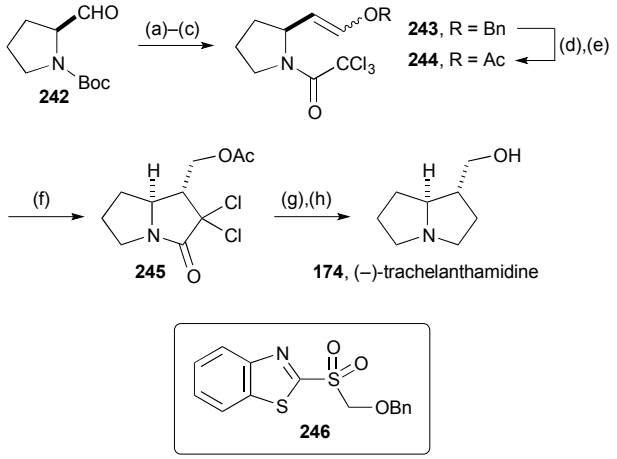
Scheme 22 Reagents and conditions: (a) TBSCl, *t*-BuOK, cyclopentyl methyl ether; (b) Swern oxidation; (c) (*S*)-*p*-toluenesulfinamide, $Ti(OEt)_4$, CH_2Cl_2, reflux; (d) MeMgBr/PhSH, *tert*-butyl acrylate, CH_2Cl_2, −50 °C; (e) MCPBA, CH_2Cl_2, 0 °C; (f) $PhCH_3$, 110 °C; (g) MCPBA, CH_2Cl_2; (h) allyl 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*- stereochemistry in **240** (with respect to the pyrrolidinone 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, triisopropyl phosphite 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, $PhCH_3$, –78 °C; (b) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2; (c) DIBAL, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C to 0 °C; (d) CF_3CO_2H, CH_2Cl_2 then $TsCH_2CO_2H$, PyBOP, *i*-Pr_2NEt, CH_2Cl_2; (e) $ClCO_2Me$, pyridine, DMAP, CH_2Cl_2; (f) $Pd_2(dba)_3$, $P(Oi\text{-}Pr)_3$, CH_3CN; (g) O_3, CH_2Cl_2, −78 °C then Me_2S then $NaBH_4$, aq EtOH; (h) Na(Hg), MeOH, −15 °C; (i) $LiAlH_4$, THF, reflux.

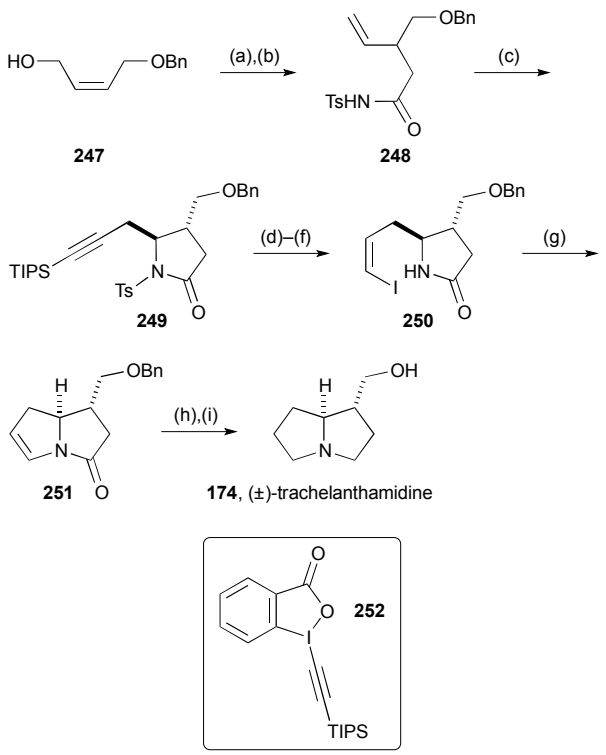
(*S*)-Proline also served as the source of chirality and one of the rings in Ishibashi's synthesis of (–)-trachelanthamidine in which the second ring was introduced by stereoselective radical cyclisation.[109] The *O*-benzyl enol ether **243** (Scheme 24), prepared by Julia olefination of *N*-Boc prolinal **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) **246**, LHMDS, THF, 0 °C to rt; (b) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (c) Cl_3CCOCl, Et_3N, CH_2Cl_2, 0 °C; (d) HCl, aq THF; (e) Ac_2O, KOAc, Et_3N, 120 °C; (f) 1,4-dimethylpiperazine, reflux; (g) H_2, Pd/C, NaOAc, EtOH; (h) $LiAlH_4$, THF, reflux.

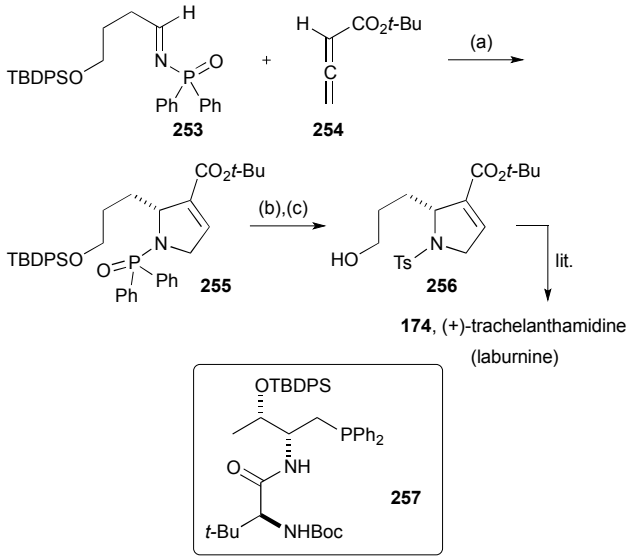
More recently, a palladium-catalysed aminoalkynylation strategy was applied to the synthesis of (±)-trachelanthamidine.[110] The cyclisation substrate, acyl sulfonamide **248** (Scheme 25), was prepared by Johnson–Claisen rearrangement of mono-*O*-benzyl diol **247**. The combination of LiCl and $PdCl_2$ 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 aminopalladation 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 hydroindiation. 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.



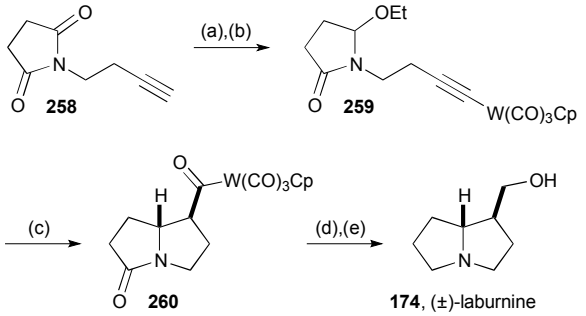
Scheme 25 Reagents and conditions: (a) $CH_3C(OEt)_3$, $EtCO_2H$, 100 °C to 160 °C then KOH, MeOH, reflux; (b) TsNCO, Et_3N, THF; (c) $PdCl_2$, LiCl, **252**, EtOH, (dr = 83:17); (d) Li/naphthalene, THF, −78 °C; (e) TBAF, THF, 0 °C to rt; (f) $InCl_3$, DIBAL then Et_3B then I_2, THF, −50 °C; (g) CuI, Cs_2CO_3, *N,N'*-dimethylethylenediamine, $PhCH_3$, 85 °C; (h) H_2, Pd/C, MeOH; (i) $LiAlH_4$, THF, reflux.

A carefully-orchestrated (3+2)-annulation of imine **253** (Scheme 26) and allenoate **254** led directly to pyrroline **255** with 96% ee.[111] 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.



Scheme 26 Reagents and conditions: (a) **257**, 5Å MS, Et_2O, 0 °C; (b) $BF_3{\cdot}OEt_2$, MeOH, CH_2Cl_2, 0 °C; (c) TsCl, Et_3N, CH_2Cl_2, 0 °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, **174**, 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.

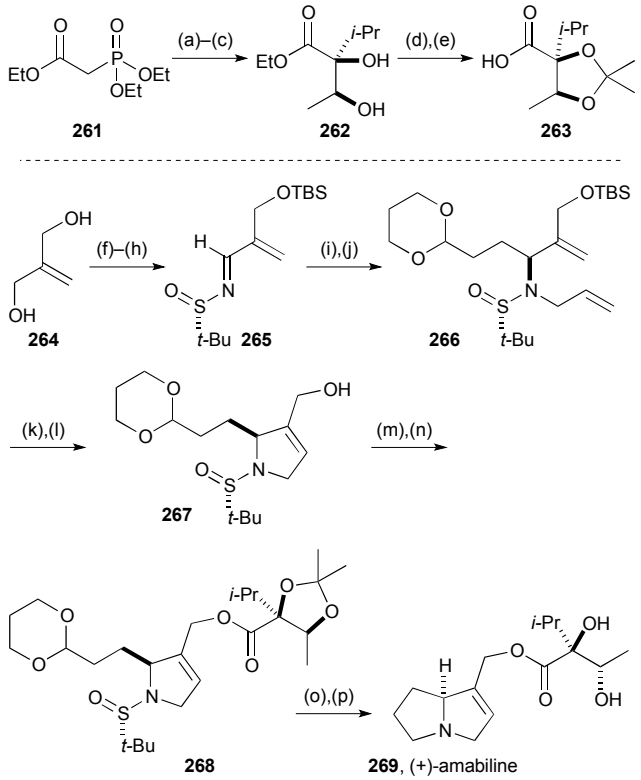


Scheme 27 Reagents and conditions: (a) DIBAL, CH_2Cl_2, –78 °C then EtOH, aq HCl; (b) $CpW(CO)_3Cl$, CuI, Et_2NH; (c) $BF_3{\cdot}OEt_2$, Et_2O, –78 °C to rt; (d) BnOH, I_2, CH_2Cl_2, –78 °C to rt; (e) $LiAlH_4$, THF, 0 °C to 65 °C.

Amabiline and cremastrine

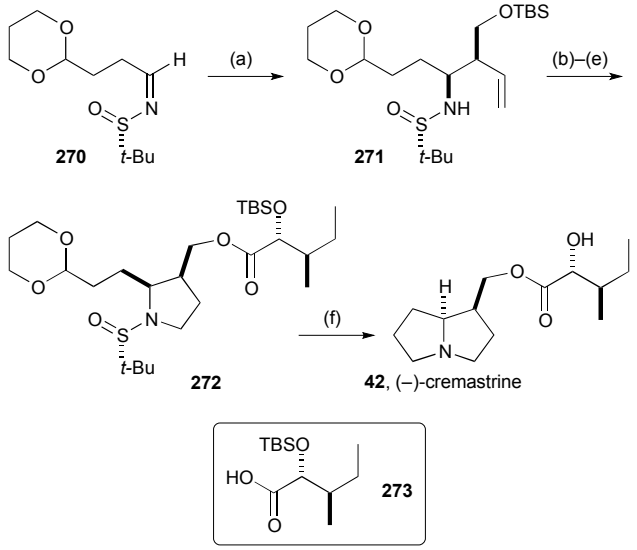
Lindsley's group described the syntheses of two complete pyrrolizidines (+)-amabiline and (–)-cremastrine based on diastereoselective 1,2-addition to chiral sulfoximine intermediates.[113] In both syntheses, and unusually, the pyrrolizidine ring system was generated *after* the necic acid side chain 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 ether deprotection afforded pyrroline **267** whose relative stereochemistry was confirmed by X-ray crystallography. Esterification with masked viridifloric acid derivative **263** gave

268 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-$BH(OAc)_3$ to complete the first total synthesis of (+)-amabiline.



Scheme 28 Reagents and conditions: (a) *i*-PrI, *t*-BuOK, DMSO, 0 °C; (b) LHMDS, CH_3CHO, THF, –78 °C; (c) AD-mix-α, aq *t*-BuOH, 0 °C; (d) $Ba(OH)_2$, H_2O, 50 °C; (e) $Me_2C(OMe)_2$, aq HCl; (f) TBSCl, imidazole, DMF, 0 °C to rt; (g) MnO_2, CH_2Cl_2; (h) (*S*)-*t*-$BuSONH_2$, $CuSO_4$, CH_2Cl_2; (i) (1,3-dioxan-2-yl)ethylmagnesium bromide, THF, –78 °C; (j) LHMDS, allyl bromide, DMF, –20 °C; (k) Grubbs' II, CH_2Cl_2; (l) TBAF, THF, 0 °C to rt; (m) TsCl, Et_3N, CH_2Cl_2, 0 °C; (n) **263**, K_2CO_3, DMF; (o) aq CF_3CO_2H; (p) MP-$B(OAc)_3H$, DCE.

The synthesis of (–)-cremastrine (Scheme 29) followed strategically similar lines.[114] 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.

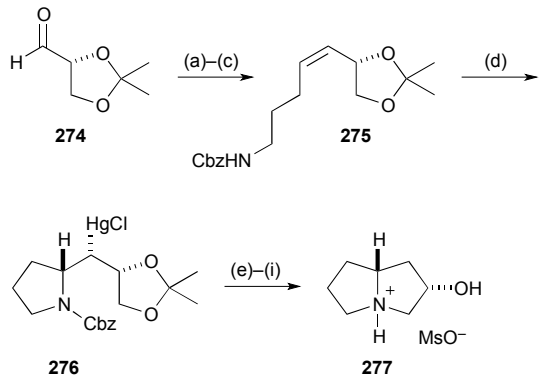


Scheme 29 Reagents and conditions: (a) (*E*)-$TBSOCH_2CH{=}CHCH_2Br$, In, NaBr, H_2O; (b) 9-BBN, CH_2Cl_2 then aq NaOH, H_2O_2; (c) DEAD, PPh_3, THF; (d) TBAF, THF; (e) **273**, EDCI, DMAP, CH_2Cl_2; (f) aq CF_3CO_2H then Et_3SiH.

Simple hydroxypyrrolizidines

Mono-

A synthesis of the simple 2-hydroxypyrrolizidine **277** (reported as the 3-isomer)[115] 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-hydroxypyrrolizidine.

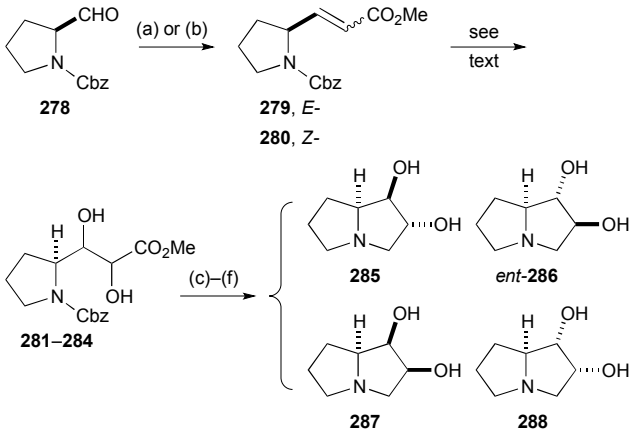


Scheme 30 Reagents and conditions: (a) 3-cyanopropyltriphenyl phosphonium bromide, NaHMDS, THF, 0 °C; (b) $LiAlH_4$, Et_2O, reflux; (c) CbzCl, Et_3N, THF, 0 °C to rt; (d) $Hg(OAc)_2$, CH_2Cl_2 then aq NaCl; (e) Bu_3SnH, AIBN, $PhCH_3$, rt to 70 °C; (f) aq AcOH; (g) MsCl, Et_3N, CH_2Cl_2, 0 °C; (h) H_2, Pd/C, EtOH.

Di-

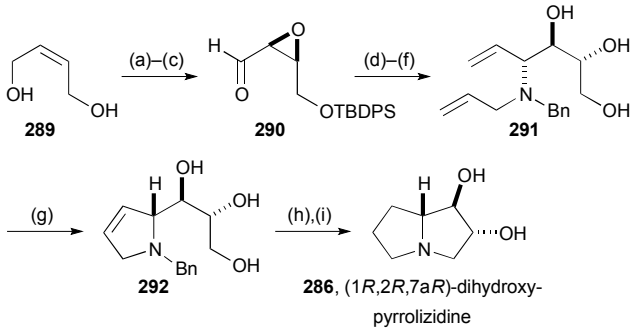
Six syntheses of the pyrrolizidine lower homologue of (–)-lentiginosine, (1*R*,2*R*,7a*R*)-dihydroxypyrrolizidine **286**, and its enantiomer (*ent*-**286**, Scheme 31) were reported during the review period. The first exploited general Wittig olefination/dihydroxylation/ring-closure methodology that had been developed for higher pyrrolizidines, see below.[116] In this

example, *E*- or non-selective Wittig reaction was conducted in dichloromethane or methanol, respectively; in the latter case the Z-enoate 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.



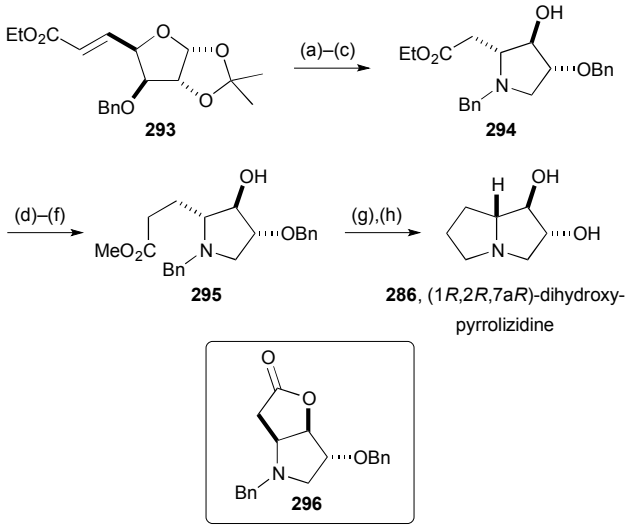
Scheme 31 Reagents and conditions: (a) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2 (→ *E*-); (b) $Ph_3P{=}CHCO_2Me$, MeOH (→ *E*-/*Z*- 1.3:1); (c) H_2, Pd/C, MeOH then NaOMe, MeOH, reflux; (d) NaH, BnBr, DMSO; (e) $LiAlH_4$, Et_2O, reflux; (f) H_2, Pd/C, aq HCl, MeOH then Amberlite IRA-400, MeOH.

In the first synthesis of the (–)-enantiomer,[117] 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 pyrroline **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* (IC_{50} = 27.3 and 25.5 μg mL^{-1}, respectively).



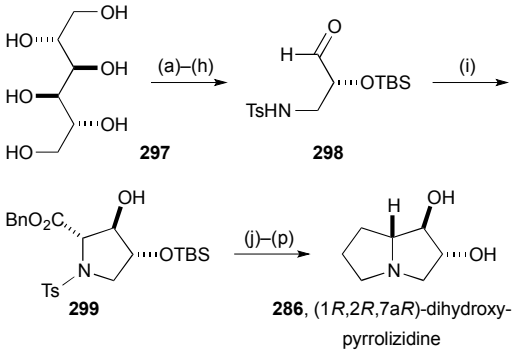
Scheme 32 Reagents and conditions: (a) BuLi, TBDPSCl, THF, −78 °C then reflux; (b) Ti(O*i*-Pr)$_4$, (−)-DET, *t*-BuOOH, 4Å MS, CH_2Cl_2, −23 °C; (c) IBX, DMSO; (d) $BnNH_2$, 4Å MS, Et_2O then $CH_2{=}CHMgBr$, $BF_3{\cdot}OEt_2$, −78 °C; (e) H_2SO_4, aq dioxane, reflux; (f) allyl bromide, K_2CO_3, aq THF; (g) Grubbs' I, CH_2Cl_2, reflux; (h) H_2, Pd/C, aq HCl, MeOH; (i) PPh_3, CCl_4, Et_3N, DMF.

Soon after, Dhavale reported a synthesis of similar length from enoate **293** (Scheme 33), prepared in five steps from D-glucose.[118] 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 Arndt–Eistert homologation (→ **295**), then hydrogenolysis of both benzyl groups and reduction of the resulting lactam completed the route.



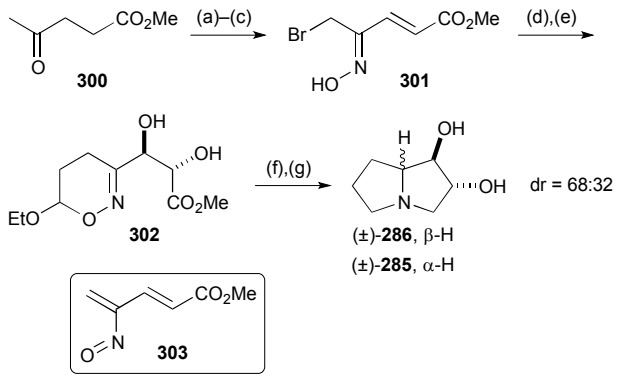
Scheme 33 Reagents and conditions: (a) aq CF_3CO_2H, 0 °C to rt; (b) $NaIO_4$, aq acetone, 0 °C to rt; (c) $BnNH_2$, AcOH, $NaBH_3CN$, MeOH, –20 °C to rt; (d) LiOH, aq MeOH, 0 °C to rt; (e) EtO_2CCl, Et_3N, THF, 0 °C to rt then CH_2N_2, Et_2O; (f) $PhCO_2Ag$, Et_3N, MeOH; (g) HCO_2NH_4, Pd/C, MeOH, reflux; (h) $LiAlH_4$, THF, reflux.

Building on a general method for the preparation of multifunctionalised pyrrolidines, Angle's group reported an enantiospecific synthesis of (1*R*,2*R*,7a*R*)-dihydroxypyrrolizidine from D-mannitol (**297**, Scheme 34).[119] 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 N_2 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.



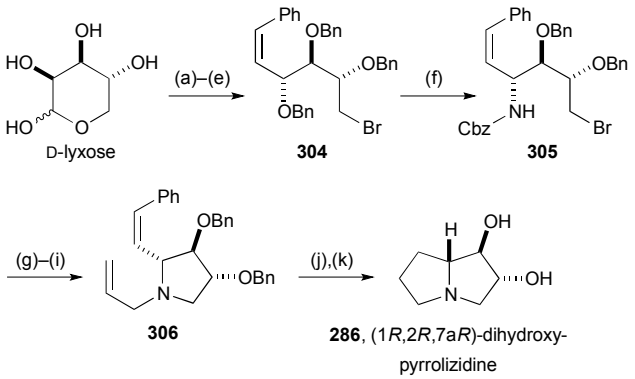
Scheme 34 Reagents and conditions: (a) $(MeO)_2CMe_2$, $SnCl_2$, DME, reflux; (b) $HC(OMe)_2NMe_2$, CH_2Cl_2; (c) MeI, $PhCH_3$, reflux; (d) Amberlyst 15, MeOH; (e) Bu_2SnO, $PhCH_3$, reflux then TsCl; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (g) NaNHTs, DMSO, 80 °C; (h) O_3, CH_2Cl_2, –78 °C then thiourea, 0 °C; (i) benzyl diazoacetate, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C; (j) MEMCl, *i*-Pr_2NEt, $CHCl_3$, reflux; (k) $NaBH_4$, EtOH; (l) Swern oxidation then $Ph_3P{=}CHCO_2Me$; (m) H_2, Pd/C, EtOAc; (n) Mg, MeOH; (o) $LiAlH_4$, THF, reflux; (p) CBr_4, MeOH, reflux.

A synthesis of racemic **286** was completed by nitroso-Diels–Alder reaction between diene **303** (generated in situ from levulenic 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**, dr = 82:18) but the relative stereochemistry was not determined. Combined hydrogenation, hydrogenolysis, 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.



Scheme 35 Reagents and conditions: (a) Br_2, Et_2O, –5 °C; (b) Et_3N, CH_2Cl_2, –35 °C; (c) $NH_2OH{\cdot}HCl$, aq $CHCl_3$; (d) Na_2CO_3, ethyl vinyl ether, *t*-BuOMe; (e) $KMnO_4$, $MgSO_4$, EtOH, –45 °C; (f) H_2, Pd/C, MeOH; (g) $BH_3{\cdot}SMe_2$, THF.

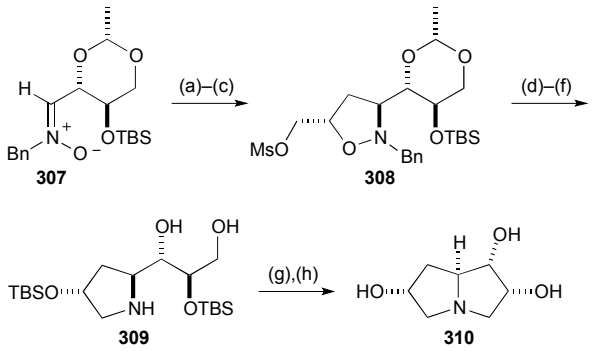
The most recent synthesis of (–)-**286** was an enantiospecific route from D-lyxose (Scheme 36).[121] The 1,2-diol stereochemistry originated in the 3,4-stereogenic centres in the starting sugar but the 7a-stereochemistry derived by selective amination of the allylic benzyl ether (step f). The authors 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_Ni reaction; in this particular case, the resulting diastereoselectivity was high at 26:1. Following this key step (→ **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.



Scheme 36 Reagents and conditions: (a) $SOCl_2$, MeOH; (b) NaH, BnCl, Bu_4NI, DMF; (c) H_2SO_4, aq dioxane, 60 °C; (d) NaH, $Ph_3P^+Bn\ Cl^-$, DMSO, THF, 45 °C; (e) CBr_4, Ph_3P, Et_3N, CH_2Cl_2, 0 °C; (f) $ClSO_2NCO$, Na_2CO_3, $PhCH_3$, 0 °C then aq Na_2SO_3; (g) *t*-BuOK, THF, 0 °C; (h) Et_3SiH, $Pd(OAc)_2$, Et_3N, CH_2Cl_2, reflux; (i) allyl bromide, K_2CO_3, THF, 45 °C; (j) Grubbs' II, $PhCH_3$, reflux; (k) H_2, Pd/C, aq HCl, EtOH then Dowex 50WX8 (H^+ form), aq NH_3.

Tri-

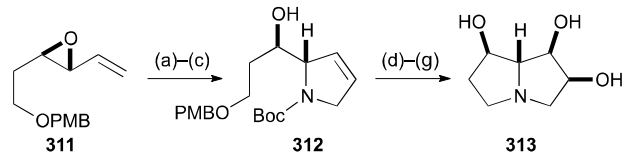
Three diverse routes were reported for accessing 1,2,6- and 1,2,7-trihydroxypyrrolizidines. The first employed a dipolar cycloaddition between methyl acrylate and nitrone **307** (Scheme 37), derived in six steps from D-glucose.[123] Apparently, this cycloaddition gave the diastereomer shown exclusively; the same reaction performed on the nitrone lacking the TBS protecting group was far less stereoselective, returning a 48:29:15:5 ratio of diastereomers. Ester reduction then mesylation of the 1°-hydroxyl gave intermediate **308**, setting up *N*-cyclisation and debenzylation upon cleavage of the N–O bond (step d). Following protecting group manipulations, cyclisation to form the second ring was effected by selective mesylation of the 1°-hydroxyl to give the 1,2,6-trihydroxypyrrolizidine **310** upon desilylation.



Scheme 37 Reagents and conditions: (a) $CH_2{=}CHCO_2Me$, $PhCH_3$, 110 °C; (b) DIBAL, THF, –10 °C; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt; (d) H_2, $Pd(OH)_2/C$, MeOH; (e) TBSCl, Et_3N, CH_2Cl_2; (f) aq AcOH, 80 °C; (g) MsCl, Et_3N, CH_2Cl_2, –10 °C to rt; (h) NH_4F, TBAF, aq THF.

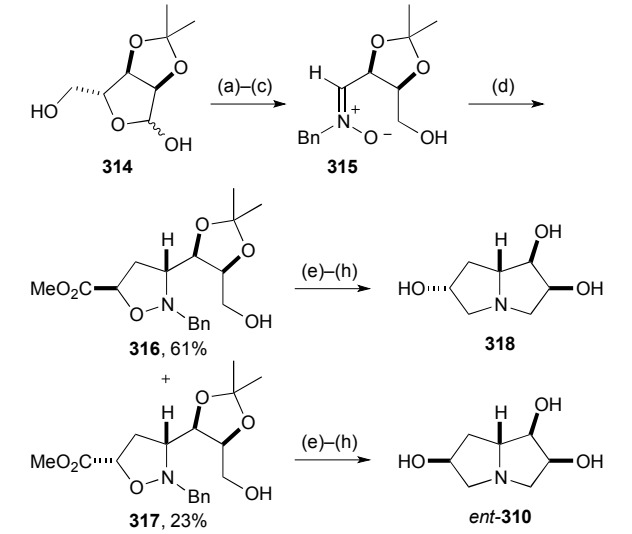
Pine's group disclosed an early application of their vinyl epoxide opening and ring-closing metathesis methodology in the synthesis of the 1,2,7-trihydroxypyrrolizidine **313** shown in Scheme 38.[124] The initial aminolysis of epoxide **311** required forcing conditions (refluxing toluene, 4 days) but proceeded efficiently. The rest of the synthesis was uneventful, with dihydroxylation of pyrroline **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, $PhCH_3$, 110 °C; (b) Boc_2O, Et_3N, THF; (c) Grubbs' I, CH_2Cl_2, reflux; (d) OsO_4, NMO, aq acetone; (e) CF_3CO_2H, anisole, CH_2Cl_2; (f) DEAD, Ph_3P, pyridine then Ac_2O, pyridine, 0 °C; (g) K_2CO_3, MeOH.

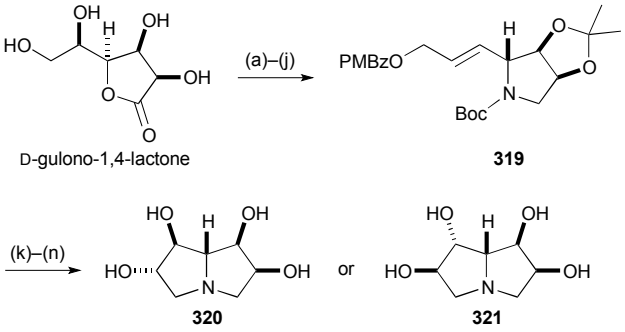
The diastereomeric cycloadducts **316** and **317** (Scheme 39) of D-ribose-derived nitrone **315** and methyl acrylate were separated and taken through a standard four-step sequence resulting in 1,2,6-trihydroxypyrrolizidine epimers **318** and *ent*-**310**.[125]



Scheme 39 Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C to rt; (b) $NaIO_4$, aq *t*-BuOH; (c) BnNHOH, Et_3N, CH_2Cl_2; (d) CH_2=$CHCO_2Me$, reflux; (e) H_2, Pd/C, MeOH; (f) PBu_3, 1,1′-(azodicarbonyl)dipiperidine, THF; (g) BH_3·SMe_2, THF; (h) TsOH, MeOH.

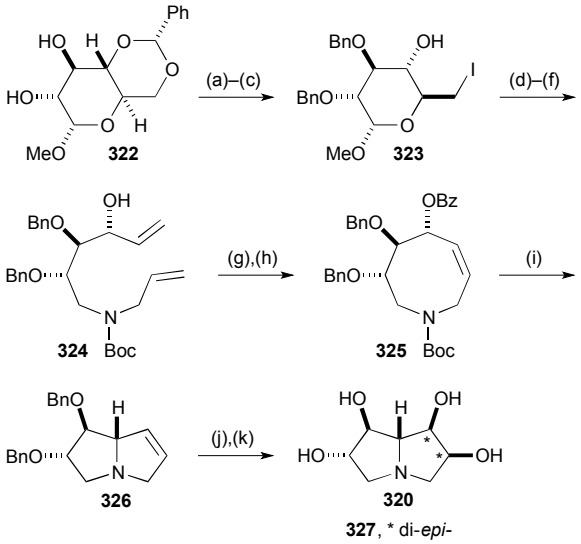
Tetra-

Developing from an enantiospecific route to indolizidines,[126] D-gulonolactone (Scheme 40) was elaborated through a sequence originally established by Fleet to a dihydroxyprolinal derivative (→ step g).[127] 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 *N*-cyclisation followed after deprotection of the Boc and acetonide protecting groups. Pyrrolizidine **320** showed moderate but specific inhibition of *Rhizopus* sp. amyloglucosidase (IC_{50} = 130 μM, K_i = 120 μM); the 6,7-diepimer (**321**) was rather weaker-acting ((IC_{50} = 200 μM, K_i = 180 μM).



Scheme 40 Reagents and conditions: (a) $Me_2C(OMe)_2$, TsOH, acetone; (b) $LiAlH_4$, THF, Et_2O; (c) MsCl, DMAP, pyridine; (d) $BnNH_2$, 70 °C; (e) aq AcOH, 50 °C; (f) H_2, $Pd(OH)_2$/C, Boc_2O, MeOH; (g) $Pb(OAc)_4$, $NaHCO_3$, CH_2Cl_2, –78 °C; (h) Ph_3P=$CHCO_2Et$, CH_2Cl_2; (i) DIBAL, CH_2Cl_2, –15 °C; (j) 4-$MeOC_6H_4COCl$, Et_3N, DMAP, CH_2Cl_2; (k) AD-mix-α (for **320**) or AD-mix-β (for **321**); (l) NaOMe, MeOH; (m) TsCl, pyridine, –20 °C; (n) aq CF_3CO_2H then aq NH_3.

Liotta's approach to the same 1,2,6,7-tetrahydroxypyrrolizidine motif was based on ring-closing metathesis and transannular S_N2 cyclisation.[128] The readily-available D-glucose derivative **322** (Scheme 41) was elaborated to iodide **323** by standard methods then a 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**.

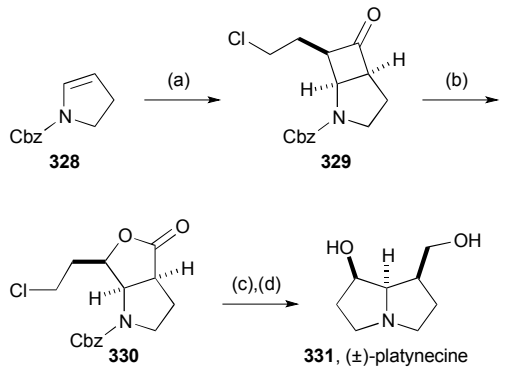


Scheme 41 Reagents and conditions: (a) KOH, BnBr, $PhCH_3$, reflux; (b) I_2, MeOH, reflux; (c) PPh_3, I_2, imidazole, $PhCH_3$, 50 °C; (d) allylamine, Zn, $NaBH_3CN$, aq PrOH, THF, reflux; (e) HCl, aq MeOH, CH_2Cl_2 then aq NaOH; (f) Boc_2O, dioxane; (g) Grubbs' II, CH_2Cl_2, reflux; (h) BzCl, pyridine; (i) CF_3CO_2H, CH_2Cl_2; (j) OsO_4, NMO, *t*-BuOH, acetone; (k) H_2, Pd/C, aq HCl, EtOH.

Platynecine and turneforcidine[129]

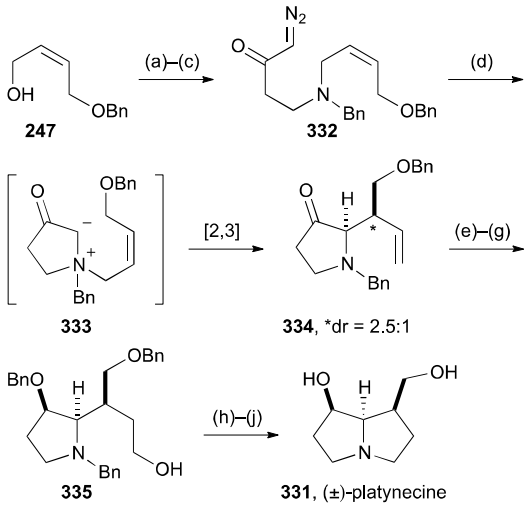
Three syntheses of racemic platynecine were recorded in the first

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-pyrroline (**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 cleaving O–O bond appropriately. Regardless, *N*-deprotection was accompanied by formation of the second pyrrolidine ring, and lactone reduction completed the 4-step sequence.



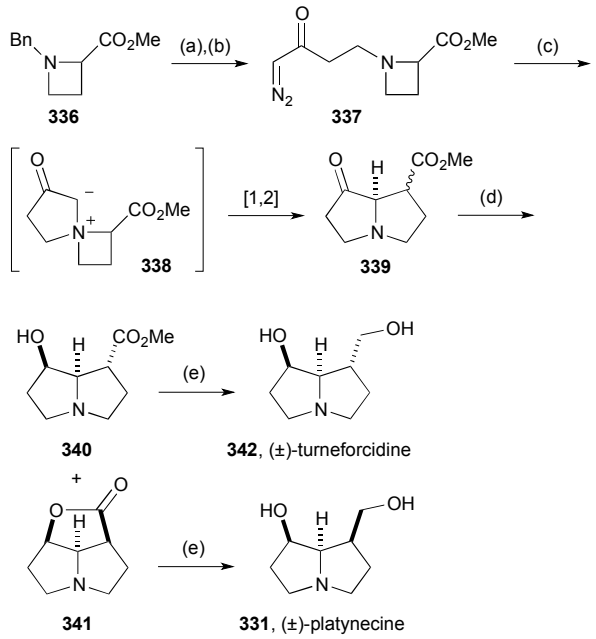
Scheme 42 Reagents and conditions: (a) 4-chlorobutyryl chloride, Et_3N, C_6H_{12}, reflux; (b) MCPBA, $NaHCO_3$, CH_2Cl_2; (c) H_2, $Pd(OAc)_2$, MeOH; (d) $LiAlH_4$, THF.

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.



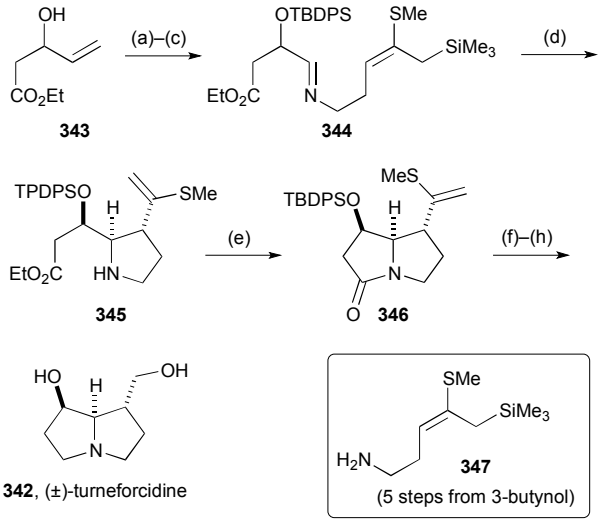
Scheme 43 Reagents and conditions: (a) MsCl, Et_3N, EtOAc; (b) $BnNH_2$, Et_3N, THF; (c) 4-bromo-1-diazobutan-2-one, Et_3N, EtOAc; (d) $Ru^{II}(TTP)(CO)$, $PhCH_3$, 50 °C; (e) $NaBH_4$, MeOH, 0 °C; (f) NaH, BnBr, THF, 0 °C; (g) 9-BBN, THF, reflux then H_2O_2, aq NaOH; (h) HCO_2NH_4, Pd/C, MeOH, reflux; (i) PPh_3, CCl_4, Et_3N, 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 α-diastereomer of ester **339** dominating. Hydrogenation of the ketone allowed easy separation of the diastereomers as a result of lactonisation (→ **341**) in the β-ester diastereomer. Final ester/lactone reduction gave the pyrrolizidines turneforcidine and platynecine, epimeric at C(1).



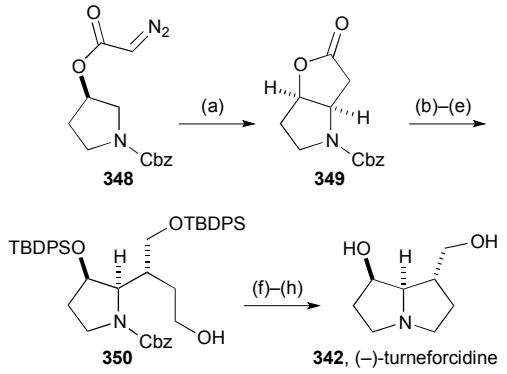
Scheme 44 Reagents and conditions: (a) HCO_2NH_4, Pd/C, MeOH, reflux; (b) 4-bromo-1-diazobutan-2-one, *i*-Pr_2NEt, CH_3CN; (c) $Cu(acac)_2$, $PhCH_3$, 85 °C; (d) H_2, PtO_2, MeOH; (e) $LiAlH_4$, THF, reflux.

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 envisaged to take place *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 45 Reagents and conditions: (a) TBDPSCl, imidazole, DMF; (b) O_3, CH_2Cl_2, –78 °C then Me_2S; (c) **347**, 4Å MS, CH_2Cl_2; (d) $TiCl_4$, CH_2Cl_2, –78 °C to –20 °C; (e) $AlMe_3$, CH_2Cl_2, 0 °C; (f) Oxone, aq MeOH; (g) $RuCl_3$, $NaIO_4$, aq CCl_4, CH_3CN; (h) $LiAlH_4$, THF, reflux.

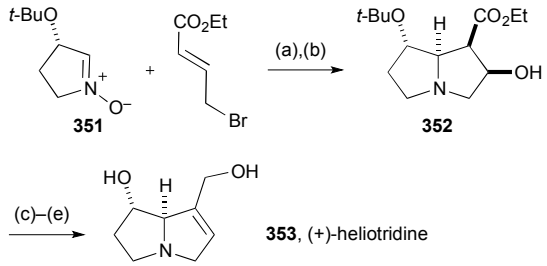
(–)-Turneforcidine was obtained in an enantiospecific synthesis from (*R*)-3-pyrrolidinol, which was converted into diazoester **348** (Scheme 46) by two standard steps.[134] Rhodium(II) carbenoid formation and C–H insertion to generate (–)-Geissman–Waiss lactone **349** proceeded in essentially quantitative yield. Catalyst screening for this transformation identified Rh_2(4*R*-MPPIM)$_4$ as the optimal catalyst, avoiding the undesired dimeric side-products seen with other catalysts (including the catalyst with 4*S*-MPPIM ligands). Continuation from this lactone to (–)-turneforcidine required a further seven steps, key among these being *exo*-diastereoselective enolate allylation to set the C(1) stereochemistry. The second ring was cyclised by mesylate displacement following release of the free pyrrolidine. Fluoride-mediated cleavage of both silyl substituents completed the route.



Scheme 46 Reagents and conditions: (a) Rh_2(4*R*-MPPIM)$_4$, DCE, 60 °C; (b) LHMDS, allyl bromide, HMPA, THF, −78 °C to −45 °C; (c) $NaBH_4$, EtOH, 0 °C; (d) TBDPSCl, imidazole, DMF; (e) OsO_4, $NaIO_4$, aq Et_2O then $NaBH_4$, EtOH, 0 °C; (f) MsCl, Et_3N, CH_2Cl_2; (g) cyclohexene, Pd/C, MeOH, reflux then K_2CO_3; (h) TBAF, THF.

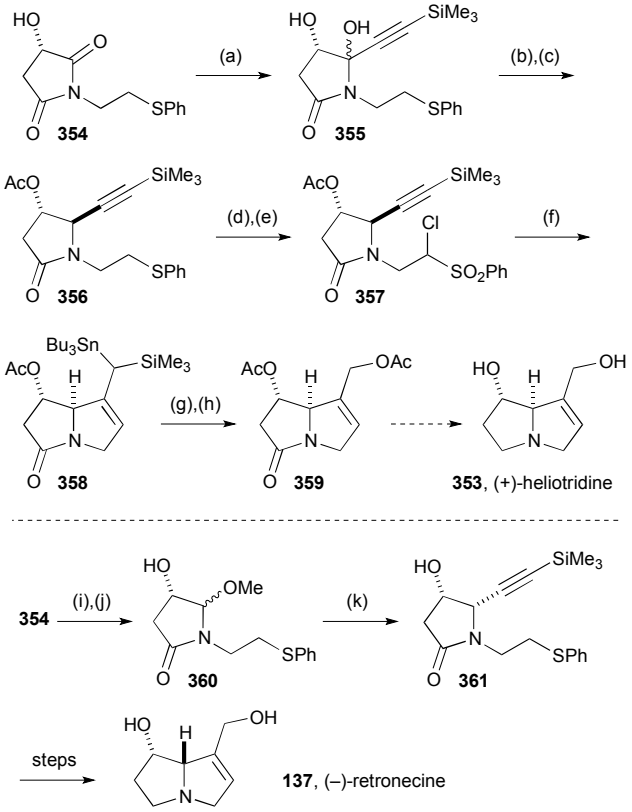
Heliotridine and retronecine

Continuing previous work on (−)-rosmarinecine and other, non-natural pyrrolizidines, Brandi and Cordero used a cycloaddition strategy to synthesise (+)-heliotridine from chiral nitrone **351** (Scheme 47), derived from diethyl (*S*)-malate in five steps.[135] The 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.



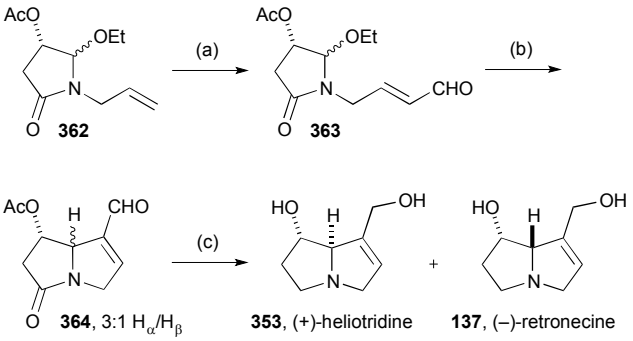
Scheme 47 Reagents and conditions: (a) $PhCH_3$, 0 °C to rt; (b) (i) H_2, Raney Ni, EtOH; (ii) Ambersep 900 OH; (c) NsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt; (d) DIBAL, CH_2Cl_2, 0 °C; (e) (i) aq CF_3CO_2H; (ii) Dowex 50WX8–200.

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.[136] 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.[137] 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.



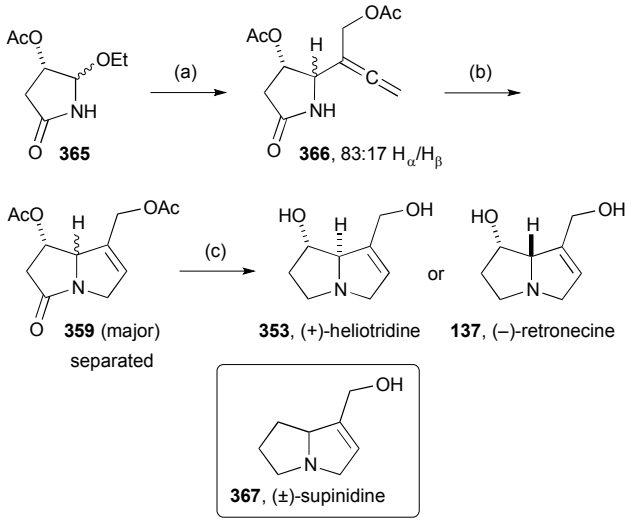
Scheme 48 Reagents and conditions: (a) $LiC{\equiv}CSiMe_3$, THF, −78 °C; (b) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C to 0 °C; (c) Ac_2O, DMAP, Et_3N, CH_2Cl_2; (d) NCS, CCl_4; (e) MCPBA, CH_2Cl_2; (f) Bu_3SnH, AIBN, C_6H_6, reflux; (g) PhSeBr, LiBr, CH_3CN, −40 °C to rt; (h) KOAc, 18-crown-6, aq CH_3CN; (i) $NaBH_4$, THF, EtOH, 0 °C; (j) TsOH, MeOH; (k) $Et_2Si(C{\equiv}CSiMe_3)Cl$, Et_3N, DMAP, CH_2Cl_2 then $TiCl_4$, −78 °C.

(–)-Malic acid was also the starting material for Aggarwal's synthesis of (+)-heliotridine and (–)-retronecine (Scheme 49); here, a Morita–Baylis–Hillman type coupling of an acyliminium ion and a tethered enal generated a 3:1 diastereomeric mixture of cyclised products **364**.[138] These isomers were separated following global reduction of the carbonyl groups.



Scheme 49 Reagents and conditions: (a) acrolein, Hoveyda–Grubbs' catalyst, CH_2Cl_2; (b) TMSOTf, $BF_3{\cdot}OEt_2$, Me_2S, MeCN; (c) $LiAlH_4$, THF, reflux.

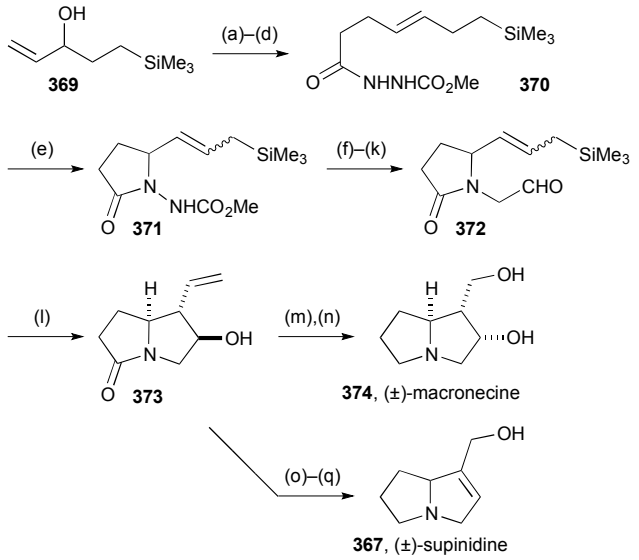
A combination of acyliminium trapping and Au(I)-mediated cyclisation featured as key steps in the most recent synthesis of heliotridine and retronecine, again starting from from malic acid.[139] Addition of (acetoxymethyl)propargyltrimethylsilane (**368**) afforded the allenyl product **366** (Scheme 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(7a)-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.



Scheme 50 Reagents and conditions: (a) **368** (see text), $BF_3{\cdot}OEt_2$, CH_3CN; (b) $ClAuPPh_3/AgBF_4$, CH_2Cl_2; (c) $LiAlH_4$, THF.

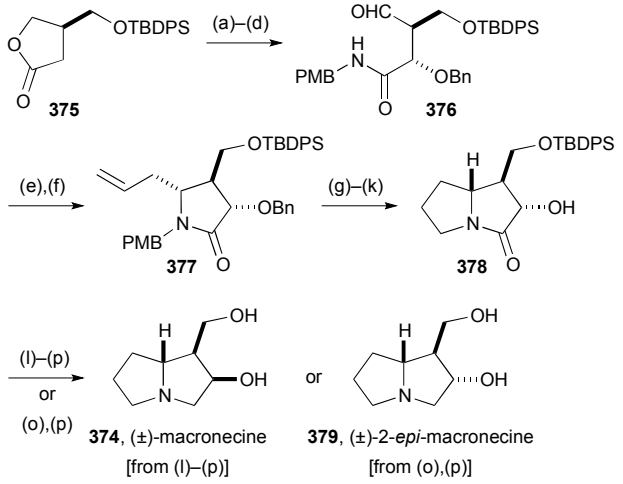
Macronecine

Intramolecular aza-ene reaction and aldehyde allylation were used in combination to create the two rings in (±)-macronecine and (±)-supinidine.[140] Acyl hydrazide **370** (Scheme 51) was prepared from allylic alcohol **369** (3 steps from 3-chloropropan-1-ol) via Johnson–Claisen rearrangement. Mild oxidation of the hydrazide 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 allylation. 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.



Scheme 51 Reagents and conditions: (a) $CH_3C(OEt)_3$, $EtCO_2H$, $PhCH_3$, reflux; (b) NaOH, MeOH; (c) NaH, $(COCl)_2$, pyridine, C_6H_6, 0 °C; (d) NH_2NHCO_2Me, Et_3N, CH_2Cl_2; (e) MnO_2, DCE,))), 0 °C; (f) NaH, MeI, THF, 0 °C; (g) Li/NH_3, –33 °C then EtOH; (h) BuLi, $BrCH_2CO_2Me$, HMPA, THF; (i) NaOH, MeOH; (j) EtSH, DCC, DMAP, CH_2Cl_2, 0 °C to rt; (k) Et_3SiH, Pd/C, CH_2Cl_2; (l) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –20 °C to rt; (m) 4-$NO_2C_6H_4CO_2H$, PPh_3, DEAD, THF, 0 °C to rt; (n) O_3, CH_2Cl_2, −78 °C then Red-Al, THF, –78 °C to rt to reflux; (o) 4-$NO_2C_6H_4COCl$, DMAP, CH_2Cl_2; (p) O_3, CH_2Cl_2, −78 °C then PPh_3, rt; (q) Red-Al, THF, –78 °C to rt to reflux.

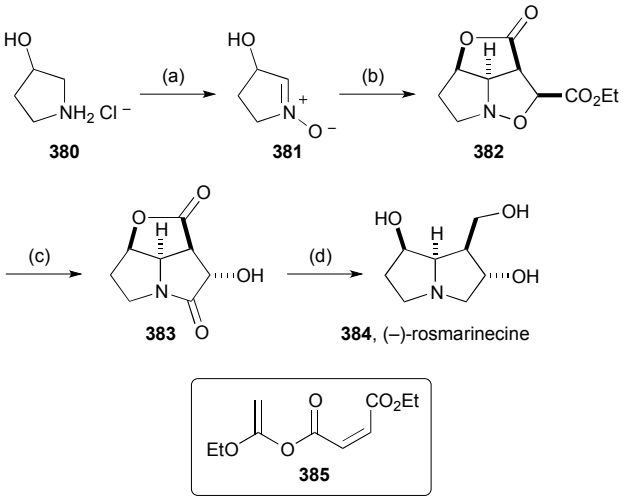
A second synthesis of (±)-macronecine, and its 2-epimer (**379**) was achieved from dihydroxyacetone dimer.[141] Following a 5-step route (not shown), racemic γ-lactone **375** (Scheme 52) was hydroxylated with almost exclusive *trans*- diastereoselectivity, with the minor *cis*- isomer being easily 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) BnBr, Ag_2O, EtOAc; (c) $PMBNH_2$, MeOH; (d) Swern oxidation; (e) $BF_3{\cdot}OEt_2$, THF, 0 °C; (f) allyltrimethylsilane, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C to –20 °C; (g) 9-BBN, THF then H_2O_2, aq NaOH, 0 °C; (h) TsCl, pyridine; (i) CAN, aq CH_3CN; (j) NaH, THF, 0 °C to rt; (k) H_2, $Pd(OH)_2$/C, EtOH; (l) Tf_2O, pyridine, CH_2Cl_2; (m) CsOAc, 18-crown-6, $PhCH_3$; (n) K_2CO_3, MeOH; (o) $BH_3{\cdot}THF$, THF; (p) HCl, MeOH.

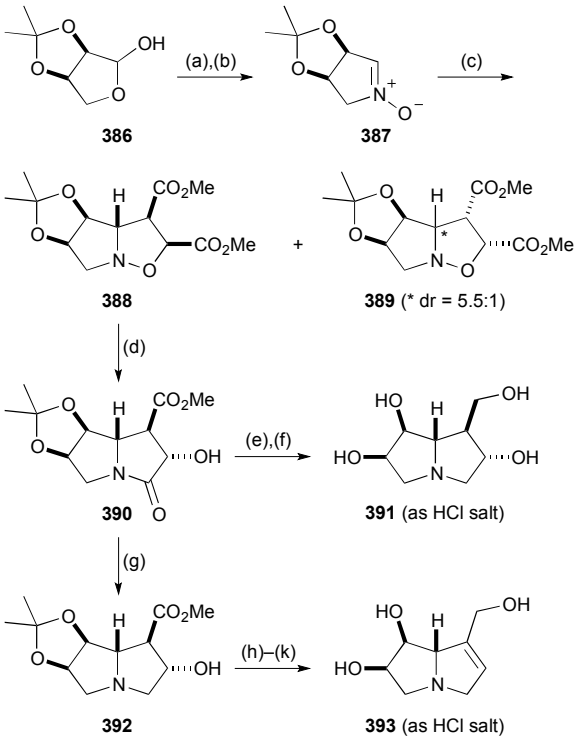
Rosmarinecine

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 hydroxynitrone **381** and vinyl ester **385** gave the intramolecular nitrone cycloadduct **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 subsequently[143] shortened (to that shown in Scheme 53) by the discovery of alternative conditions for generating the starting nitrone.



Scheme 53 Reagents and conditions: (a) Davis' oxaziridine, *t*-$BuNH_2$, aq CH_3CN; (b) **385**, CAL-B, MeCN, 5 °C; (c) H_2, $Pd(OH)_2$, MeOH; (d) Red-Al, THF, reflux.

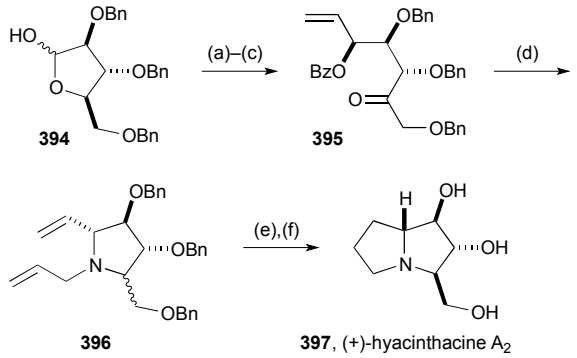
Nitrone cycloadditions featured in Goti's synthesis of the rosmarinecine analogue **391** and 7a-*epi*-crotanecine **393** (Scheme 54).[144] Nitrone **387**, obtainable from erythorbic acid via D-erythrose acetonide **386** gave major diastereomer **388** upon cycloaddition with dimethyl maleate. Hydrogenolysis 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 acetonide cleavage. Alternatively, selective reduction, maintaining the ester (→ **392**), facilitated regioselective dehydration via the mesylate; subsequent reduction and hydrolysis provided 7a-*epi*-crotanecine **393**.



Scheme 54 Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, 3Å MS, pyridine then (b) MsCl, pyridine (one pot); (c) dimethyl maleate, CH_2Cl_2; (d) H_2, $Pd(OH)_2$/C, MeOH; (e) $LiAlH_4$, THF, 65 °C; (f) HCl, MeOH; (g) $BH_3{\cdot}SMe_2$, THF, 65 °C; (h) MsCl, CH_2Cl_2; (i) DBU, CH_2Cl_2; (j) DIBAL, CH_2Cl_2, 0 °C; (k) HCl, MeOH.

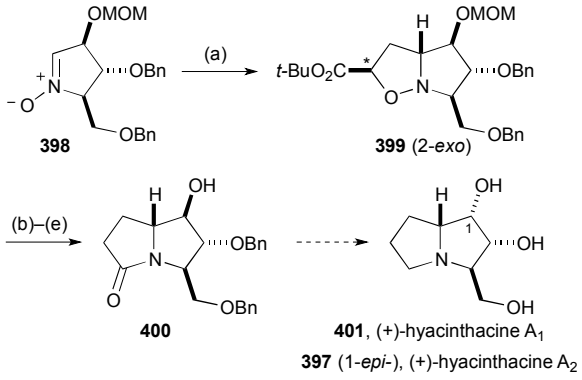
Hyacinthacines

The first total synthesis of (+)-hyacinthacine A_2, by Martin's group,[145] began with stereoselective (Cram chelate model) vinyl addition to commercially-available D-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 A_2 in confirmation of the assigned structure for this natural product.



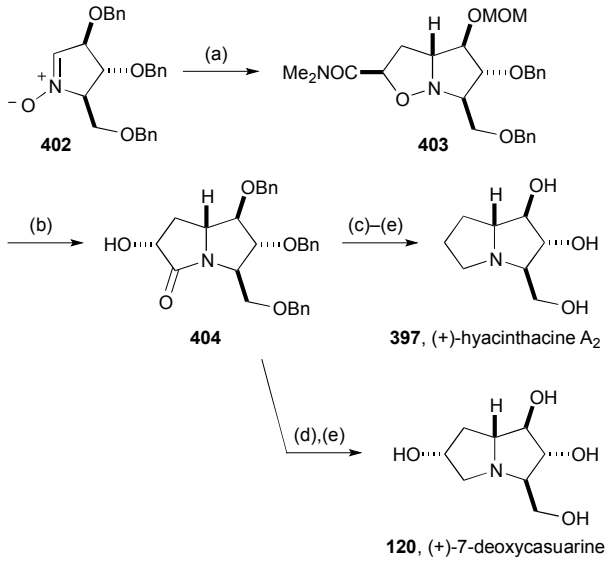
Scheme 55 Reagents and conditions: (a) divinylzinc, $MgBr_2$, THF; (b) BzCl, Bu_4NI, NaOH, aq CH_2Cl_2, 0 °C; (c) $(CF_3CO)_2O$, DMSO, Et_3N, CH_2Cl_2, –78 °C to rt; (d) allylamine, AcOH, $NaBH_3CN$, 3Å MS, MeOH, 0–40 °C; (e) Grubbs' I, $PhCH_3$, 60 °C; (f) H_2, Pd/C, aq HCl, MeOH, THF.

A (3+2)-cycloaddition approach to the synthesis of (+)-hyacinthacines A_1 and A_2 was reported,[146] from nitrone **398** (Scheme 56), derived from L-xylose. The nitrone was treated with *tert*-butyl acrylate leading to a 2:1 ratio of epimers at the starred position, with the major 2-*exo* isomer **399** being required for the synthesis. Lactam **400**, a potential late-stage intermediate to both hyacinthacines A_1 and A_2, was obtained in four steps from the cycloadduct.



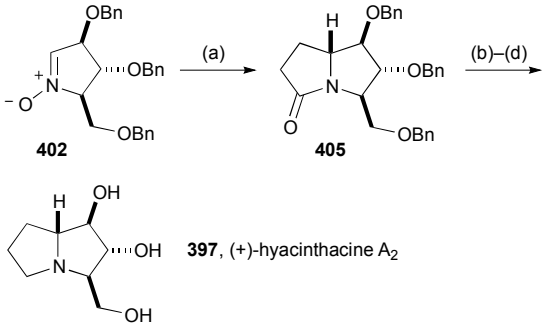
Scheme 56 Reagents and conditions: (a) *tert*-butyl acrylate, C_6H_6; (b) Zn, aq AcOH, 90 °C; (c) phenyl chlorothionoformate, pyridine, DMAP, CH_2Cl_2; (d) Bu_3SnH, AIBN, C_6H_6, reflux; (e) HCl, aq MeOH, 50 °C.

Goti's group used a similar strategy to access hyacinthacine A_2 and 7-deoxycasuarine, starting from tri-benzyl-protected nitrone **402** (Scheme 57).[147] In this work, **402** was derived from either L-xylose or D-arabinose, the latter being preferred due its lower cost. With the sterically-demanding dipolarophile dimethyl acrylamide, exclusive formation of the *anti*-*exo* product **403** was observed, installing the desired stereochemistry at C(6). This intermediate was cleaved reductively to give lactam **404** that was taken on to both (+)-hyacinthacine A_2 and (+)-7-deoxycasuarine. The same methodology was applied more recently to the synthesis of four analogues and five 6-*O*-α-glucosides of casuarine,[148] in order to assess their biological activity against glucoamylase.[75] Using alternative dipolarophiles, C- or Si-substituents were included at C(7), allowing introduction of hydroxymethyl- or hydroxyl- groups at this position.



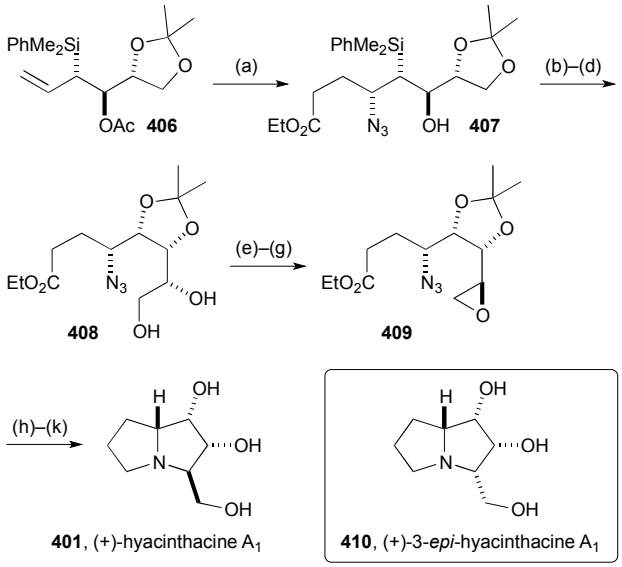
Scheme 57 Reagents and conditions: (a) dimethyl acrylamide, CH_2Cl_2; (b) Zn, aq AcOH, 50 °C; (c) MsCl, Et_3N, CH_2Cl_2; (d) $LiAlH_4$, THF, relux; (e) H_2, Pd/C, MeOH.

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.[149] Lactam reduction and hydrogenolysis of the benzyl ethers gave short access to (+)-hyacinthacine A_2.



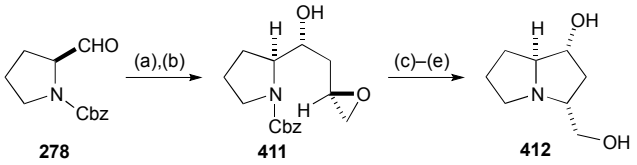
Scheme 58 Reagents and conditions: (a) ethyl acrylate, SmI_2, aq THF, −78 °C to rt then K_2CO_3, aq EtOH; (b) $LiAlH_4$, THF, 66 °C; (c) H_2, Pd/C, aq HCl, MeOH, THF; (d) Dowex 1X8 (OH^- form), H_2O.

The first total synthesis of (+)-hyacinthacine A_1 was achieved by stereocontrolled carboazidation of allylsilane **406** (Scheme 59), obtained by diastereoselective addition to glyceraldehyde acetonide (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.[150] 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 *N*-cyclisation onto pendant epoxide and ester functionality from **409**; lactam reduction and acetonide deprotection completed the route. By performing the double *N*-cyclisation following step (f), (+)-3-*epi*-hyacinthacine A_1 **410** was also prepared.



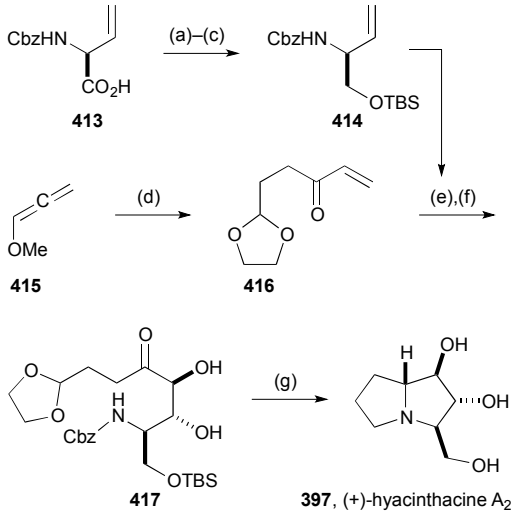
Scheme 59 Reagents and conditions: (a) $EtO_2CCH_2SCS.OEt$, $(Bu_3Sn)_2$, *t*-BuON=NO*t*-Bu, 3-pyridylsulfonyl azide, C_6H_6, 60 °C; (b) AcOOH, KBr, NaOAc, AcOH; (c) Dowex 1X10, MeOH; (d) $Me_2C(OMe)_2$, TsOH, CH_2Cl_2; (e) $Zn(NO_3)_2{\cdot}6H_2O$, CH_3CN, 50 °C; (e) TBSCl, pyridine; (f) MsCl, pyridine; (g) TBAF, THF then K_2CO_3, MeOH; (h) H_2, Pd/C, MeOH; (i) Et_3N, MeOH, reflux; (j) $LiAlH_4$, THF, 0 °C to reflux; (k) aq HCl, MeOH, reflux then Dowex 1X10 (OH^- form), H_2O.

A partial hyacinthacine analogue **412** (Scheme 60) was prepared in five steps from *N*-Cbz (*S*)-prolinal (**278**).[151] Addition of allylindium bromide proved highly selective for the *Si*- face, and epoxidation (→ **411**) was also highly stereoselective, presumably being directed by the hydroxyl group. Hydrogenolysis of the Cbz group led directly to *ent*-2-deoxyhyacinthacine A_2 but temporary acetylation aided its isolation, purification, and characterisation.



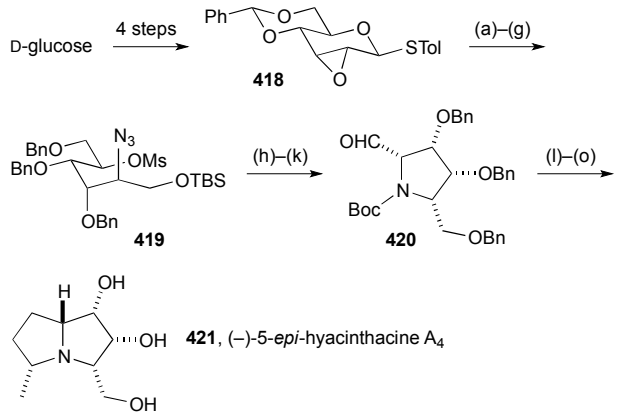
Scheme 60 Reagents and conditions: (a) In, allyl bromide, THF, −78 °C (dr = 95:5); (b) MCPBA, CH_2Cl_2; (c) H_2 (65 psi), Pd/C, MeOH; (d) Ac_2O, DMAP, pyridine; (e) NaOMe, MeOH.

Blechert's group applied an approach strategically similar to their earlier synthesis of xenovenine[152] to a synthesis of (+)-hyacinthacine A_2.[153] In this case, cross-metathesis of alkene **414** (Scheme 61), derived from racemic vinyl glycine, and masked 1,4-dicarbonyl **416** led to diol **417** after asymmetric dihydroxylation. A one-pot sequence—hydrogenolysis of the Cbz 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**.



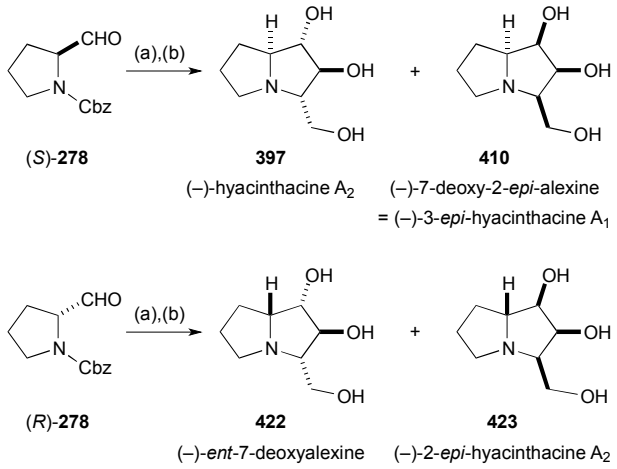
Scheme 61 Reagents and conditions: (a) $SOCl_2$, MeOH, 0 °C to rt; (b) $LiBH_4$, Et_2O; (c) TBSCl, imidazole, DMF, 0 °C to rt; (d) BuLi, THF, –35 °C then 2-(2-bromoethyl)-1,3-dioxolane, –78 °C to 0 °C, then aq HCl; (e) Hoveyda–Grubbs' II (Hoveyda–Blechert catalyst), CH_2Cl_2, 40 °C; (f) AD-mix-β, $NaHCO_3$, $MsNH_2$, $K_2OsO_4{\cdot}2H_2O$, aq *t*-BuOH; (g) H_2, Pd/C, MeOH then HCl then H_2, Pd/C then Amberlite IRA 401 (wet, OH^- form) then aq NH_3.

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 A_6 and A_7 (see below, Scheme 68) with Wittig extension then stereoselective reductive amination completing an overall 19-step route to (–)-5-*epi*-hyacinthacine A_4.



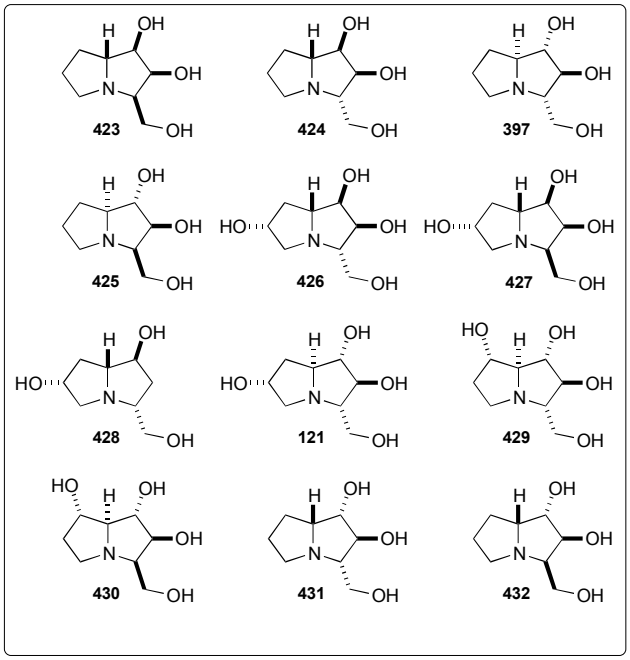
Scheme 62 Reagents and conditions: (a) NaN_3, NH_4Cl, DMSO, 85 °C; (b) TsOH, MeOH; (c) NaH, BnBr, DMF; (d) NBS, aq acetone, reflux; (e) $NaBH_4$, MeOH; (f) TBSCl, DMAP, pyridine; (g) MsCl, pyridine; (h) H_2, Pd/C, Et_3N, THF; (i) Boc_2O, Et_3N, CH_2Cl_2; (j) TBAF·$3H_2O$, THF; (k) Swern oxidation; (l) Ph_3P=CHCOMe, $PhCH_3$, reflux; (m) H_2 (1 atm.), Pd/C, MeOH; (n) HCl then Amberlite IRA-400 (OH^-); (o) H_2 (4 atm), Pd/C, MeOH.

A concise synthesis of (–)-hyacinthacine A_2 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 **278** (Scheme 63) to give open-chain adducts in variable *syn*-/*anti*- ratio.[155] Thus, following reductive amination, from Cbz-(*S*)-prolinal pyrrolizidines **397** and **410** were obtained with dr = 80:20, and from Cbz-(*R*)-prolinal the diastereomers **422** and **423** were isolated with dr = 45:55.

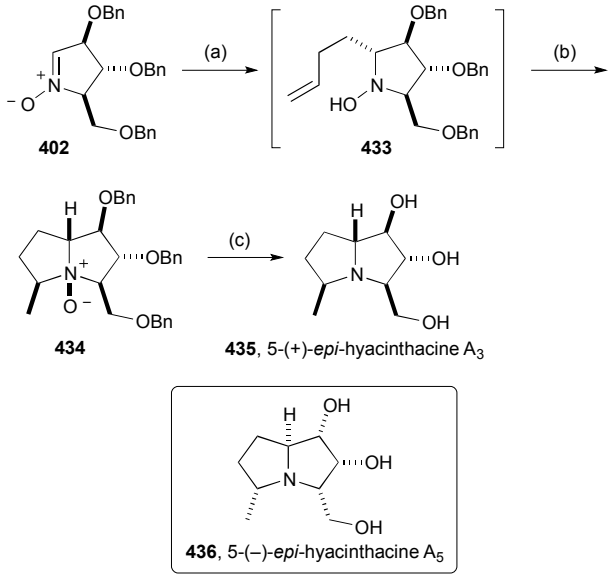


Scheme 63 Reagents and conditions: (a) RhuA/Pase, DHAP, aq DMF, pH 6.9, 4 °C; (b) H_2, Pd/C, aq EtOH.

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.[156] 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**.

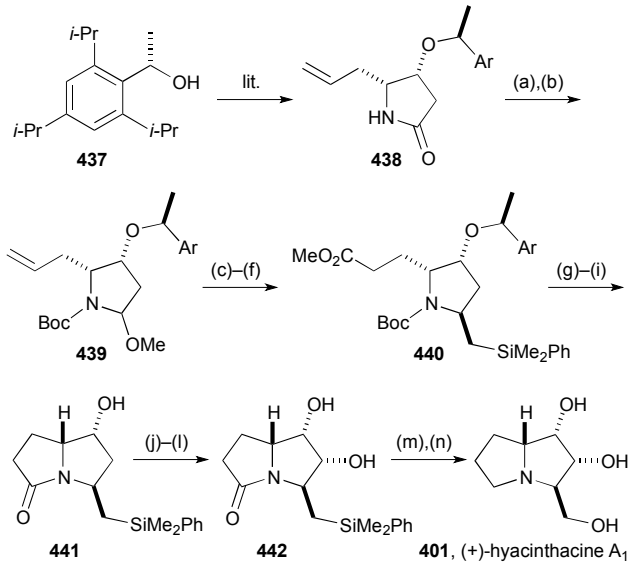


In situ Cope–House cyclisation of hydroxylamine intermediate **433** (Scheme 64), obtained by stereoselective Grignard addition to nitrone **402**, formed the key step in a synthesis of (+)-5-*epi*-hyacinthacine A_3 (and (–)-5-*epi*-hyacinthacine A_5 from 2,4-di-*epi*-**402**).[157] Deoxygenation of the *N*-oxide was achieved in the same step as global deprotection, resulting in a short synthesis of these polyhydroxylated pyrrolizidines.



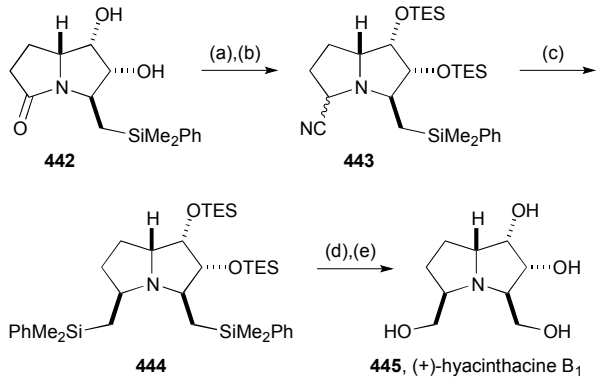
Scheme 64 Reagents and conditions: (a) 3-butenylmagnesium bromide, THF, −78 °C; (b) $CHCl_3$; (c) H_2, Pd/C, aq HCl, MeOH, THF.

The first non-chiral pool synthesis of (+)-hyacinthacine A_1 was reported in 2008, using (*S*)-Stericol® (**437**, Scheme 65) as a chiral auxiliary.[158] Elaboration of this alcohol to lactam **438** was conducted using a previously reported procedure (see the section on amphorogynines) 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 **342** being introduced by Chugaev elimination of alcohol **441** and dihydroxylation.



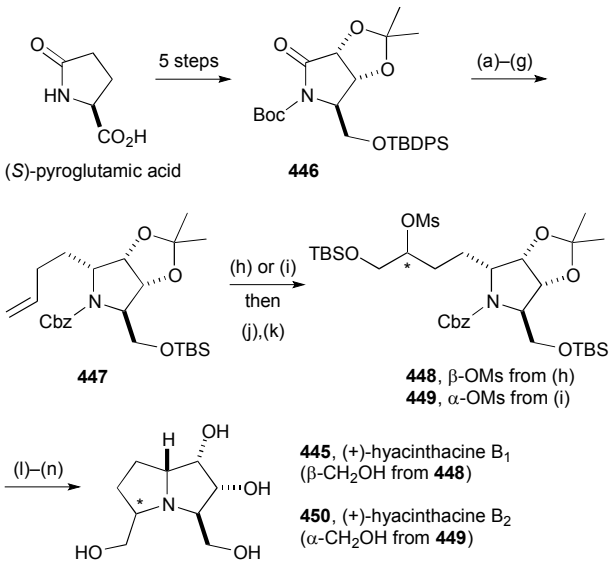
Scheme 65 Reagents and conditions (incomplete information available): (a) Boc_2O, DMAP, Et_3N; (b) $LiEt_3BH$, TsOH, MeOH; (c) $PhMe_2SiCH_2MgCl$, $CuBr{\cdot}SMe_2$, $BF_3{\cdot}OEt_2$; (d) Sia_2BH then H_2O_2; (e) Dess–Martin periodinane; (f) $NaClO_2$ then CH_2N_2; (g) TMSOTf; (h) $PhCH_3$, heat; (i) CF_3CO_2H; (j) KH then CS_2 then MeI; (k) heat; (l) OsO_4, NMO, acetone; (m) $HBF_4{\cdot}OMe_2$, KF then MCPBA; (n) $BH_3{\cdot}SMe_2$.

The authors later reported the elaboration of lactam **442** into (+)-hyacinthacine B_1 (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**.[159]



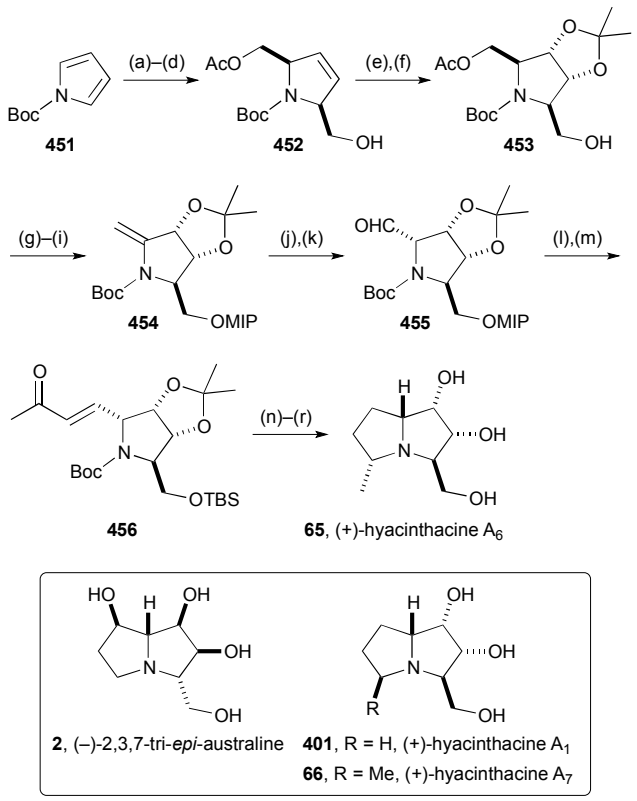
Scheme 66 Reagents and conditions (incomplete information available): (a) TESCl, imidazole; (b) DIBAL, BuLi then TMSCN; (c) $PhMe_2SiCH_2MgCl$, THF/Et_2O; (d) TBAF; (e) $HBF_4{\cdot}OMe_2$ then aq KOH then H_2O_2, KF, DMF.

The first asymmetric syntheses of (+)-hyacinthacines B_1 and B_2 were reported in 2008.[160] The enantiospecific routes initiated from (*S*)-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 pyrrolidine **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**.



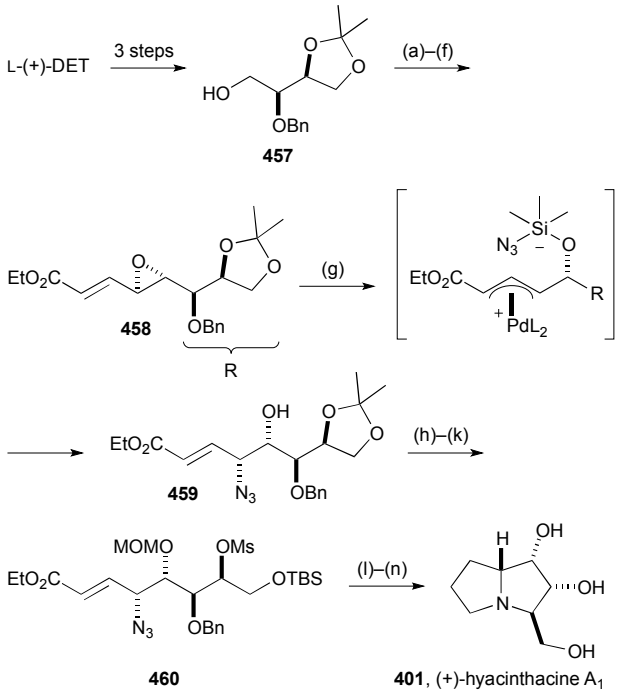
Scheme 67 Reagents and conditions: (a) $CH_2{=}CH(CH_2)_2MgBr$, THF; (b) $NaBH_4$, $CeCl_3$, EtOH, 0 °C; (c) MsCl, Et_3N, CH_2Cl_2; (d) *t*-BuOK, THF; (e) TBAF, THF; (f) NaH, THF then CbzCl, $NaHCO_3$, MeOH; (g) TBSCl, imidazole, DMF; (h) AD-mix-α, aq *t*-BuOH, 0 °C; (i) AD-mix-β, aq *t*-BuOH, 0 °C; (j) TBSCl, Et_3N, CH_2Cl_2; (k) MsCl, Et_3N, CH_2Cl_2; (l) H_2, Pd/C, EtOH; (m) TBAF, THF; (n) aq CF_3CO_2H.

Donohoe employed his established pyrrole reduction methodology (*cf.* Scheme 89) as the starting point for a general synthesis of polyhydroxylated pyrrolizidine alkaloids.[161] 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_1, (+)-hyacinthacine A_6, and (+)-hyacinthacine A_7. The synthesis of (+)-hyacinthacine A_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.



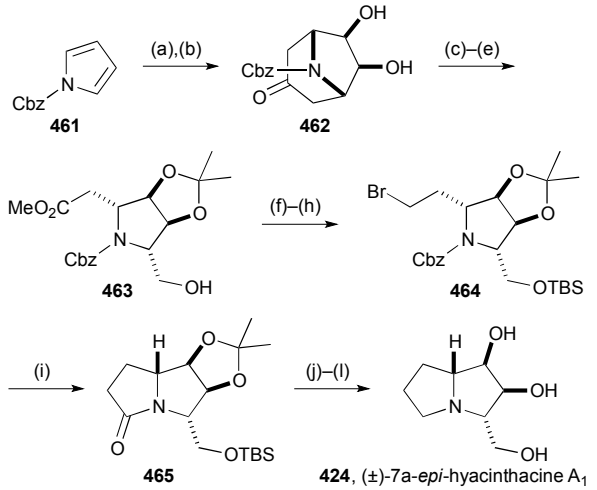
Scheme 68 Reagents and conditions: (a) LiTMP, $ClCO_2Me$, THF, –78 °C; (b) Li, DBB, THF, –78 °C then 2,6-di(*tert*-butyl)phenol; (c) Red-Al, THF, 0 °C; (d) *Pseudomonas* lipoprotein lipase, vinyl acetate, THF, 37 °C; (e) OsO_4, Me_3NO, CH_2Cl_2; (f) 2-methoxypropene, TsOH, DMF; (g) 2-methoxypropene, PPTS then K_2CO_3, MeOH; (h) Ms_2O, DMAP, CH_2Cl_2; (i) DBU, NaI, DME, reflux; (j) BH_3·THF, THF then NaOH, aq H_2O_2; (k) TPAP, NMO, 4Å MS, CH_2Cl_2; (l) NaH, $(EtO)_2PO.CH_2COMe$, THF, 0 °C to rt then aq HCl; (m) TBSCl, imidazole, DMF; (n) Bu-(*R*)-CBS reagent, BH_3·THF, THF, –17 °C; (o) H_2, PtO_2, EtOAc; (p) $ZnBr_2$, *p*-cresol, CH_2Cl_2; (q) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt; (r) HCl, MeOH.

In Chandrasekhar's synthesis of (+)-hyacinthacine A_1,[162] selectively-protected tetraol **457** (Scheme 69), derived from L-(+)-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 azidosiliconate 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_1.



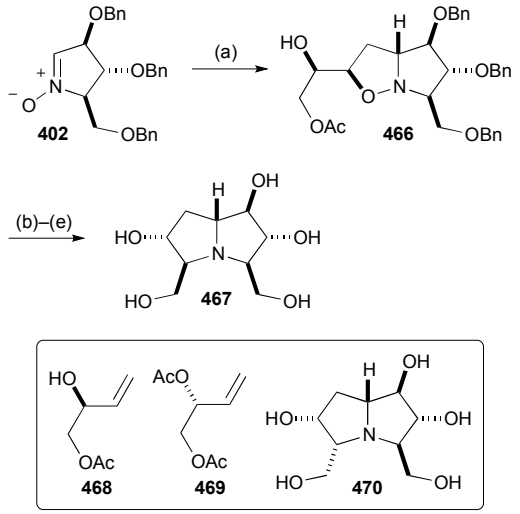
Scheme 69 Reagents and conditions: (a) IBX, EtOAc, reflux; (b) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 0 °C to rt; (c) DIBAL, THF, –10 °C to 0 °C; (d) *t*-BuOOH, (–)-DET, $Ti(Oi\text{-}Pr)_4$, CH_2Cl_2, –23 °C; (e) IBX, EtOAc, reflux; (f) $Ph_3P{=}CHCO_2Et$, C_6H_6, 0 °C to rt; (g) $TMSN_3$, $Pd(PPh_3)_4$, THF then citric acid, MeOH; (h) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; (i) PPTS, MeOH; (j) TBSCl, imidazole, CH_2Cl_2; (k) MsCl, Et_3N, CH_2Cl_2, −10 °C; (l) H_2, Pd/C, EtOH then K_2CO_3, aq EtOH, reflux; (m) TsOH, MeOH; (n) $LiAlH_4$, THF, reflux.

In an unusual approach to the synthesis of pyrrolizidine diastereomer (±)-7a-*epi*-hyacinthacine A_1, (4+3)-cycloaddition to pyrrole derivative **461** (Scheme 70) set the *cis*- relative stereochemistry across the 3- and 7a- positions in the final product.[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 alkyllithium 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 hydroxyester **463** in enantiomerically enriched form, opening a route to individual pyrrolizidine enantiomers.



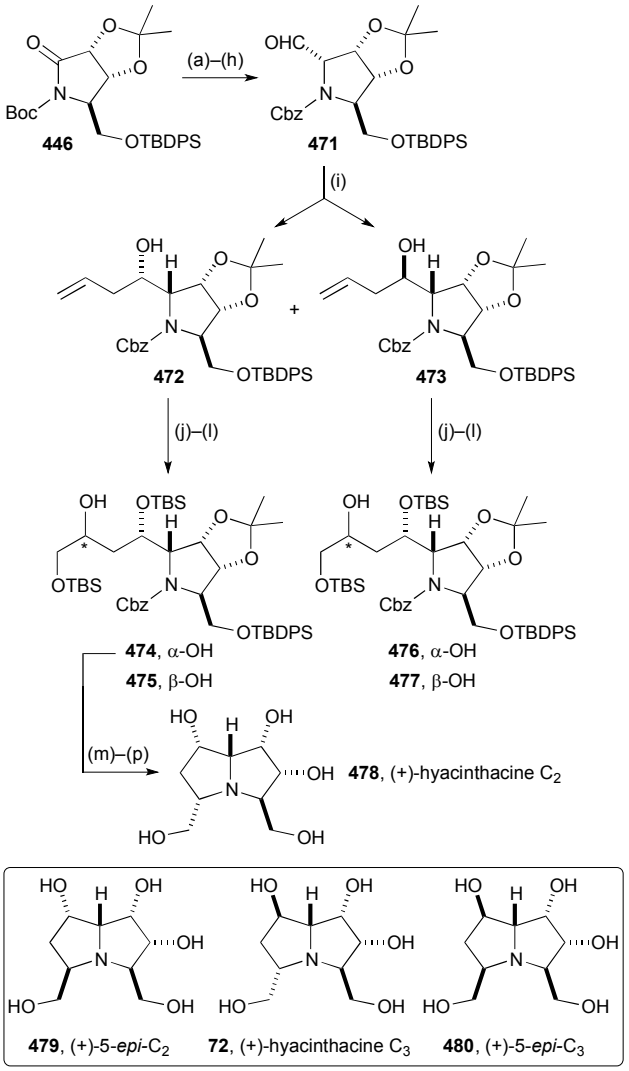
Scheme 70 Reagents and conditions: (a) 1,1,3,3-tetrabromoacetone, $ZnEt_2$, $PhCH_3$, –12 °C to rt; (b) $K_2OsO_4{\cdot}2H_2O$, NMO, aq acetone, *t*-BuOH; (c) $Me_2C(OMe)_2$, TsOH, acetone; (d) MCPBA, DCE, 2,4,6-(*t*-Bu)$_3C_6H_2OH$, 55 °C; (e) K_2CO_3, MeOH; (f) TBSCl, imidazole, DMF; (g) $LiAlH_4$, Et_2O; (h) CBr_4, PPh_3, CH_2Cl_2; (i) *t*-BuLi, THF, –80 °C; (j) $BH_3{\cdot}SMe_2$, THF then MeOH, reflux; (k) aq HCl, MeOH, reflux then Dowex 1X8 (OH^-) ion exchange chromatography.

Hyacinthacine $C_{2/3}$ analogues were prepared by nitrone cycloaddition of **402** with allylic alcohol **468** (→ **466**, Scheme 71) or allylic acetate **469** (en route to **470**).[164] The dipolarophiles were obtained by lipase mediated kinetic resolution of racemic 3-buten-1,2-diol and their cycloadditions found to afford predominantly one diastereromer 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 71 Reagents and conditions: (a) **468**, CH_2Cl_2, 70 °C (microwave); (b) MsCl, pyridine, CH_2Cl_2; (c) Zn, aq AcOH, 60 °C; (d) Ambersep 900 (OH), MeOH; (e) H_2, Pd/C, HCl then Dowex 50WX8, aq NH_3.

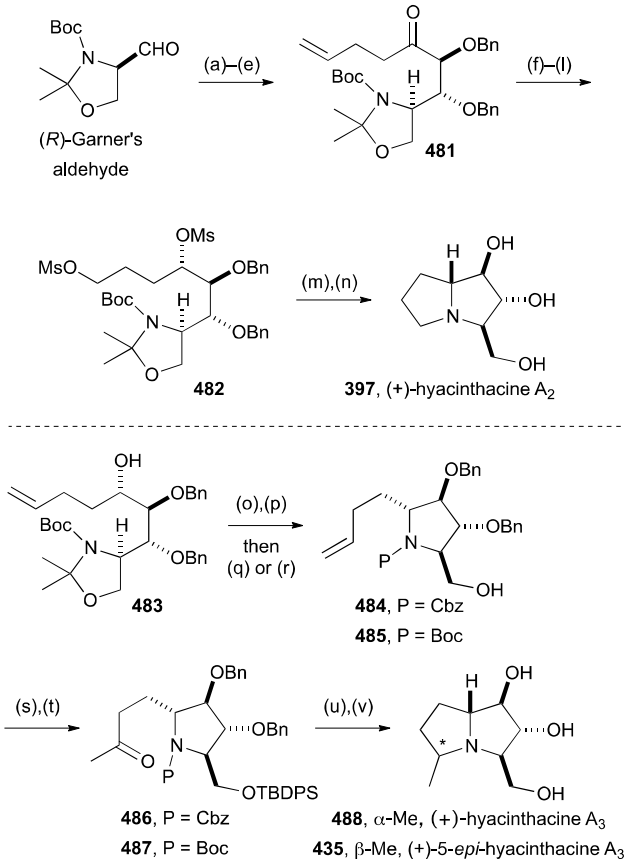
Aldehyde **471** (Scheme 72), prepared in eight steps from lactam **446** (*cf.* Scheme 67) served as common starting material for the first reported total syntheses of hyacinthacines C_2 and C_3, and their 5-*epi*- analogues.[47] Zinc-mediated allylation gave separable alcohols **472** and **473** in ca. 4:1 ratio, respectively. Each epimer was subsequently dihydroxylated and the stereochemistry at the newly-formed 2°-hydroxyl was established in all four cases (**474**–**477**) on the basis of ^{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_2 with identical sequences being used to access the other diastereomers shown. This work revealed discrepancies between the NMR data for synthetic (+)-hyacinthacine C_3 and those reported for the natural product and a revision of the structure of the latter is needed.



Scheme 72 Reagents and conditions: (a) CH_2=$CHMgBr$, THF, –78 °C; (b) $NaBH_4$, $CeCl_3$, MeOH, –20 °C; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C; (d) TBAF, THF, 0 °C then NaH; (e) CbzCl, $NaHCO_3$, MeOH; (f) TBDPSCl, imidazole, DMF; (g) OsO_4, NMO, aq acetone, *t*-BuOH; (h) $NaIO_4$, aq THF; (i) Zn, 3-bromopropene, NH_4Cl, aq THF; (j) TBSCl, imidazole, DMF; (k) OsO_4, NMO, aq acetone, *t*-BuOH; (l) TBSCl, imidazole, DMF; (m) MsCl, Et_3N, CH_2Cl_2; (n) H_2, Pd/C, EtOH; (o) TBAF, THF; (p) aq CF_3CO_2H.

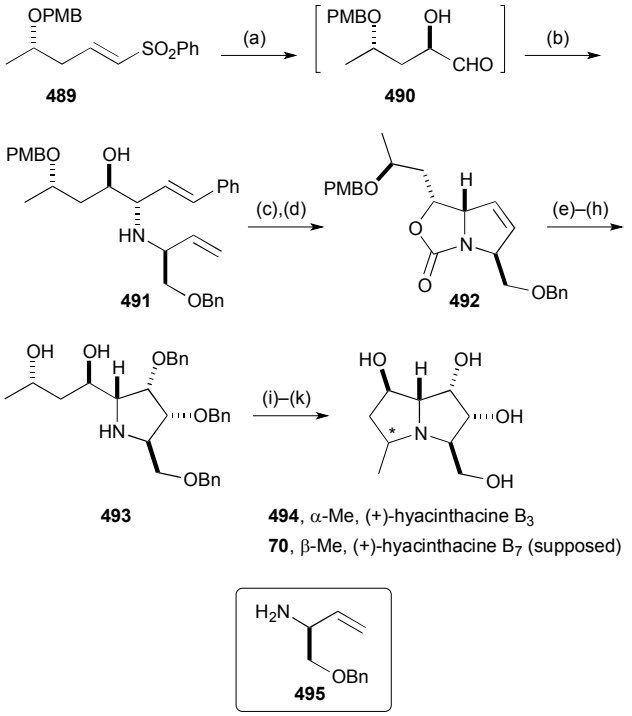
Hyacinthacines A_2, A_3 and 5-*epi*-hyacinthacine A_3 (Scheme 73) were synthesised from ketone **481**, derived from Wittig olefination of Garner's aldehyde then dihydroxylation and elaboration via the Weinreb amide.[165] Selective carbonyl

reduction then alkene cleavage and activation of the 5- and 7a-positions as their mesylates (in **482**) set up double *N*-cyclisation to (+)-hyacinthacine A_2 in the final step. For the synthesis of (+)-hyacinthacine A_3, the cyclisation steps were separated; cyclisation onto C(7a)- proceeded via the mesylate as before, then Wacker oxidation of **484** or **485**) allowed reductive amination to complete the pyrrolizidine ring system. From the Cbz-protected intermediate **486**, (+)-5-*epi*-hyacinthacine A_3 was obtained as a single diastereomer; from the Boc- analogue **487**, separable mixtures of (+)-hyacinthacine A_3 and its 5-epimer were obtained in proportions that varied markedly depending on precise reaction conditions.



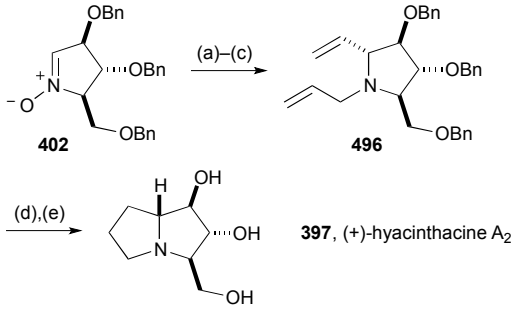
Scheme 73 Reagents and conditions: (a) $Ph_3P{=}CHCO_2Et$, THF, reflux; (b) AD-mix-β, $MsNH_2$, aq *t*-BuOH, 0 °C; (c) BnBr, Ag_2O, Et_2O; (d) (MeO)NHMe ·HCl, *i*-PrMgCl, THF, –10 °C; (e) 3-butenylmagnesium bromide, THF, 0 °C; (f) L-Selectride, THF, –78 °C; (g) TESCl, Et_3N, CH_2Cl_2; (h) OsO_4, NMO, aq *t*-BuOH, THF; (i) aq $NaIO_4$; (j) $NaBH_4$, MeOH, 0 °C; (k) TBAF, THF; (l) MsCl, Et_3N, CH_2Cl_2, 0 °C; (m) H_2, Pd/C, aq HCl, MeOH; (n) aq NH_3, MeOH; (o) MsCl, Et_3N, CH_2Cl_2, 0 °C; (p) CF_3CO_2H, CH_2Cl_2, 0 °C; (q) CbzCl, Na_2CO_3, aq THF; (r) Boc_2O, Et_3N, THF; (s) $PdCl_2$, CuCl, O_2, aq DMF; (t) TBDPSCl, imidazole, DMF; (u) H_2, Pd/C, aq HCl, MeOH; (v) aq NH_3, MeOH.

Building on their route to australine epimers (see below, Scheme 88) Pyne's group reported the first total synthesis of (+)-hyacinthacine B_3 (Scheme 74).[46] Sulfone **489**, prepared in two steps from (*S*)-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 B_3 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[44] for (+)-hyacinthacine B_7 but this synthesis showed that the original structural assignment requires revision.



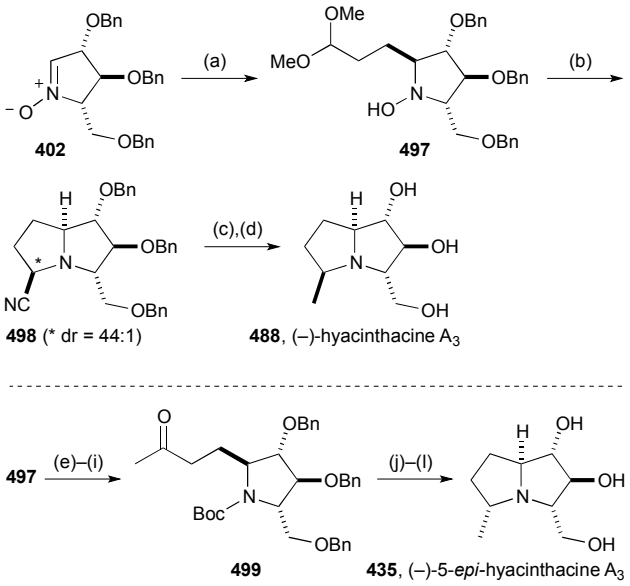
Scheme 74 Reagents and conditions: (a) DHDQ-IND-OsO_4, $MsNH_2$, aq *t*-BuOH; (b) PhCH=CHB(OH)$_2$, **495**, CH_2Cl_2; (c) triphosgene, Et_3N, CH_2Cl_2; (d) Grubbs' II, CH_2Cl_2, 90 °C (microwave); (e) $K_2OsO_4{\cdot}2H_2O$, NMO, aq acetone; (f) BnBr, NaH, Bu_4NI, THF; (g) DDQ, aq CH_2Cl_2; (h) NaOH, EtOH, 110 °C (microwave); (i) MsCl, Et_3N, CH_2Cl_2, 0 °C; (j) H_2, $PdCl_2$, MeOH; (k) ion-exchange chromatography.

A total synthesis of hyacinthacine A_2 was achieved in five steps from nitrone **402**, derived from D-arabinose (Scheme 75).[166] Vinyl Grignard addition proceeded with high *anti*-stereoselectivity with respect to the adjacent benzyloxy 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.



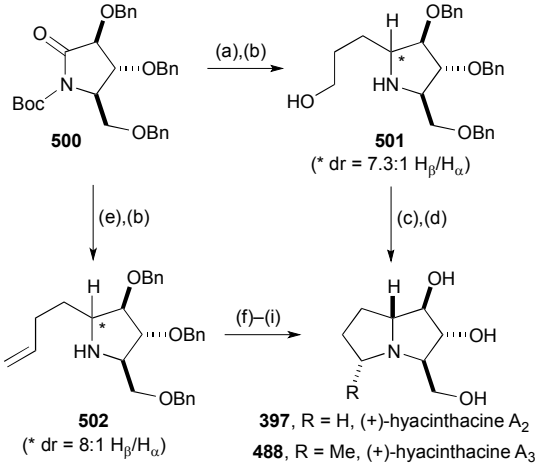
Scheme 75 Reagents and conditions: (a) $CH_2{=}CHMgBr$, Et_2O, 0 °C; (b) Zn, AcOH; (c) allyl bromide, K_2CO_3, Bu_4NI, DMF; (d) Grubbs' II, $PhCH_3$, 80 °C; (e) H_2, $Pd(OH)_2$/C, aq HCl, MeOH, HCl then Dowex 50WX8-200.

Grignard addition to the enantiomer of this nitrone (**402**, Scheme 76) was used in the synthesis of (−)-hyacinthacine A_3 and its C(5) epimer.[167] One-pot acetal hydrolysis, cyclisation, and cyanation gave aminonitrile **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 A_3. In the same work, (–)-5-*epi*-hyacinthacine A_3 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) $(MeO)_2CH(CH_2)_2MgBr$, THF; (b) KCN, aq HCl, 30 °C; (c) MeMgI, $AgBF_4$, CH_2Cl_2, Et_2O; (d) H_2, Pd/C, MeOH; (e) Zn, $Cu(OAc)_2$, AcOH, CH_2Cl_2; (f) Boc_2O, NaOH, aq dioxane; (g) TsOH, aq acetone, reflux; (h) MeMgI, Et_2O, 0 °C; (i) PCC, SiO_2, CH_2Cl_2; (j) CF_3CO_2H, CH_2Cl_2; (k) $NaBH_4$, MeOH, 0 °C; (l) H_2, Pd/C, MeOH.

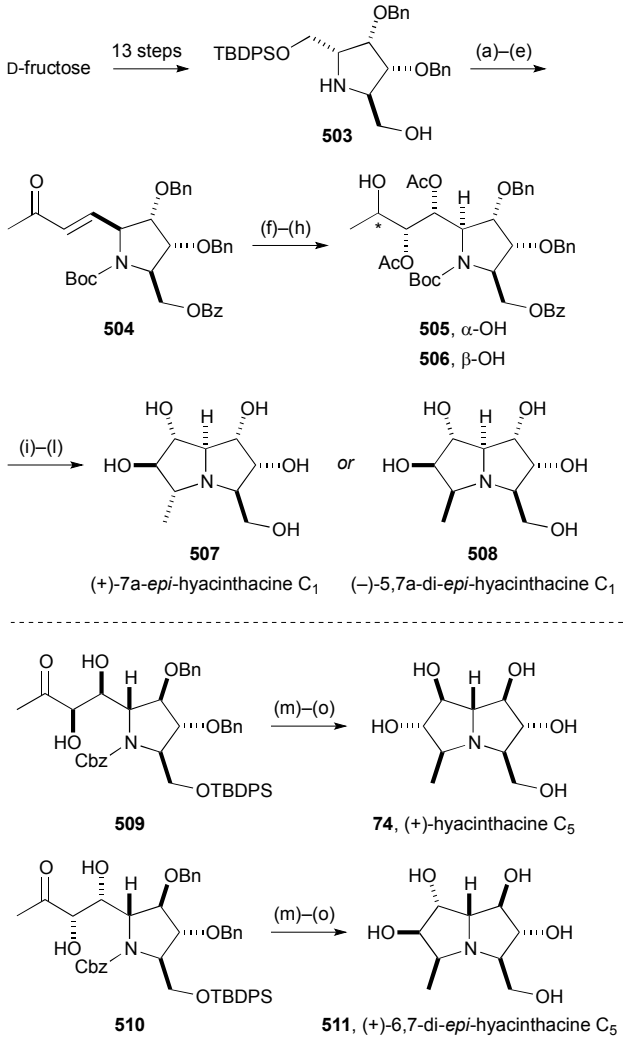
Lactam **500** (Scheme 77), obtained from lactam **521** (Scheme 81) by *N*-deprotection (CAN) and acylation (Boc_2O), was used as a common intermediate in syntheses of (+)-hyacinthacines A_2 and A_3 which differ by the presence (or absence) of a C(5)-methyl.[168] Grignard addition to the ring carbonyl and hemiaminal reduction afforded adduct **501** with reasonable diastereoselectivity. The major [β-H(7a)] diastereomer was cyclised under Appel conditions and deprotected, giving (+)-hyacinthacine A_2. For (+)-hyacinthacine A_3, adduct **502** was *N*-protected for the Wacker oxidation of the terminal alkene; 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**)).



Scheme 77 Reagents and conditions: (a) $TBSO(CH_2)_3MgBr$, CH_2Cl_2, –30 °C; (b) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C to rt; (c) PPh_3, CCl_4, Et_3N, DMF; (d) H_2, Pd/C, aq HCl, MeOH; (e) 3-butenyl-MgBr, THF, −30 °C; (f) CbzCl, K_2CO_3, aq THF; (g) O_2, $PdCl_2$, CuCl, aq DMF; (h) H_2, Pd/C, MeOH; (i) H_2, Pd/C, aq HCl, MeOH then Dowex 1X8 (OH^-).

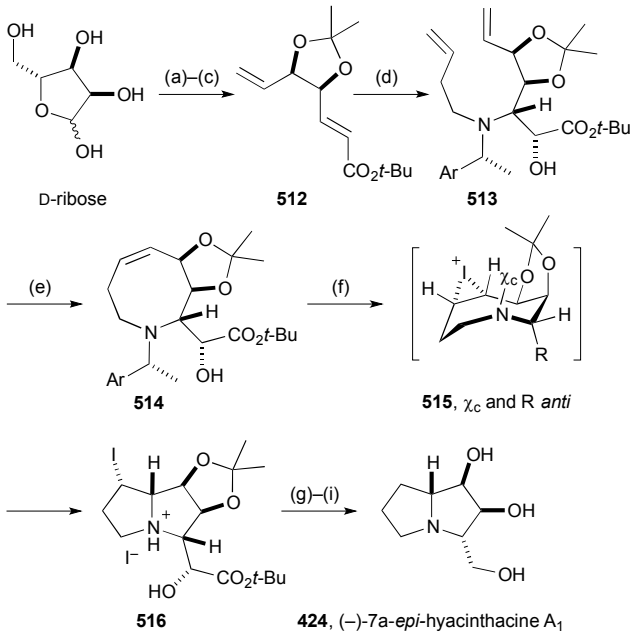
The route was recently improved by the use of a one-pot reductive alkylation procedure to install the butenyl side chain.[169] Thus, the *N*-PMB analogue of lactam **500** (i.e. **521**, Scheme 81) was treated with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine then 3-butenyl-MgBr followed by Hantzsch 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 7a-centre occurred during the Wittig olefination (step e).[170] 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*-dibenzyloxy variant of pyrrolidine enone **504**, gave a 1.4:1 ratio of diols **509** and **510**.[48] Both diastereomers gave the same C(5)-stereochemistry upon reductive amination (step l), presumably controlled by preferential hydrogenation of the intermediate iminium from the face *anti*- to the bulky $CH_2OTBDPS$ group. Desilylation and hydrogenolysis of the benzyl protecting groups afforded the alkaloid (+)-hyacinthacine C_5 and its 6,7-diepimer. Although firm conclusions were not drawn, it was noted that the ^{13}C NMR data in particular for synthetic hyacinthacine C_5 and those reported[44] differ; therefore, it is proposed that the structure of this natural product requires revision.



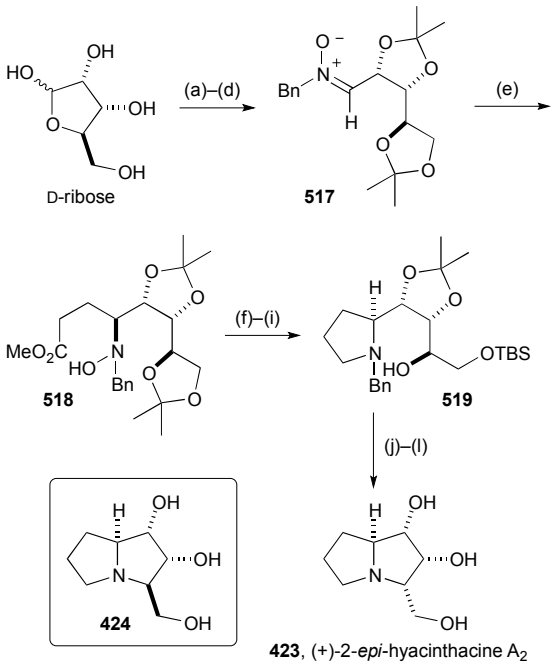
Scheme 78 Reagents and conditions: (a) Boc_2O, Et_3N, CH_2Cl_2; (b) BzCl, Et_3N, CH_2Cl_2; (c) TBAF·$3H_2O$, THF; (d) TPAP, NMO, 3Å MS, CH_2Cl_2; (e) Ph_3P=CHCOMe, $PhCH_3$, reflux; (f) OsO_4, NMO, acetone; (g) Ac_2O, pyridine; (h) $NaBH_4$, MeOH, 0 °C; (i) MsCl, Et_3N, CH_2Cl_2; (j) CF_3CO_2H, CH_2Cl_2; (k) Et_3N, THF, reflux then NaOMe; (l) H_2, Pd/C, aq HCl, MeOH then Amberlite IRA-400 (OH^-); (m) H_2, Pd/C, MeOH; (n) TBAF, THF; (o) H_2, Pd/C, aq HCl, MeOH then Amberlite IRA-400 (OH^-).

In Davies' recent synthesis of (–)-7a-*epi*-hyacinthacine A_1, 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).[171] Oxidation of the so-formed enolate in situ gave intermediate **513** as a single observable diastereomer. Ring-closing metathesis gave hexahydroazocine **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.



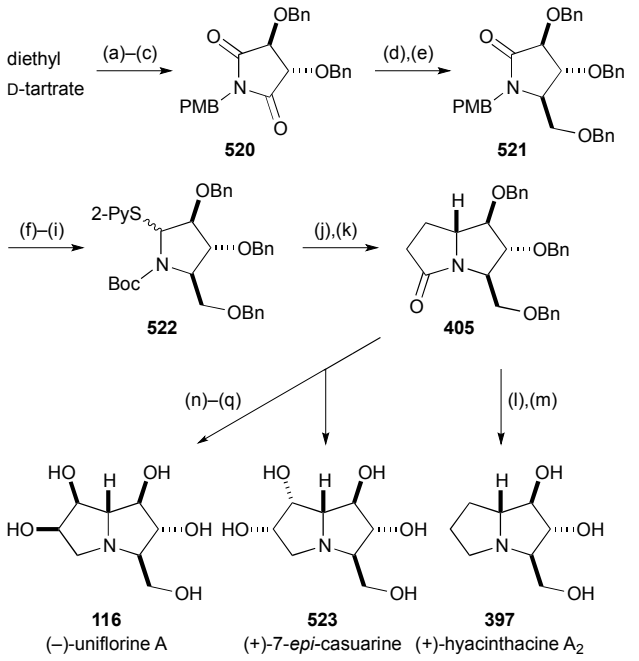
Scheme 79 Reagents and conditions: (a) acetone, HCl, aq MeOH, reflux; (b) I_2, PPh_3, CH_3CN, $PhCH_3$, 60 °C; (c) $(EtO)_2POCH_2CO_2t$-Bu, BuLi, THF, –78 °C to rt; (d) lithium (*R*)-but-3-enyl(α-methyl-*p*-methoxybenzyl)amide, THF, −78 °C then camphor-sulfonyloxaziridine, −78 °C to rt; (e) Grubbs' I, CH_2Cl_2, 30 °C; (f) I_2, $NaHCO_3$, CH_2Cl_2; (g) $LiAlH_4$, THF, –78 °C to rt; (h) $NaIO_4$, aq MeOH then $NaBH_4$; (i) HCl, aq MeOH, reflux then ion exchange chromatography. [Ar = PMB; χ_c = (*R*)-α-methyl-*p*-methoxybenzylamine]

D-Ribose was also employed as the starting material in a synthesis of the (+)-enantiomer of 2-*epi*-hyacinthacine A_2 (**423**, Scheme 80).[172] Here, the key constructive step, that established the C(7a)-stereochemistry, was achieved by Sm(II)-mediated reductive alkylation of nitrone **517** in a process related to, for example, Py's route to (+)-hyacinthacine A_2 (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 A_1 (**424**), by final ring-closure onto an epoxide, led instead to a trihydroxylated indolizidine.



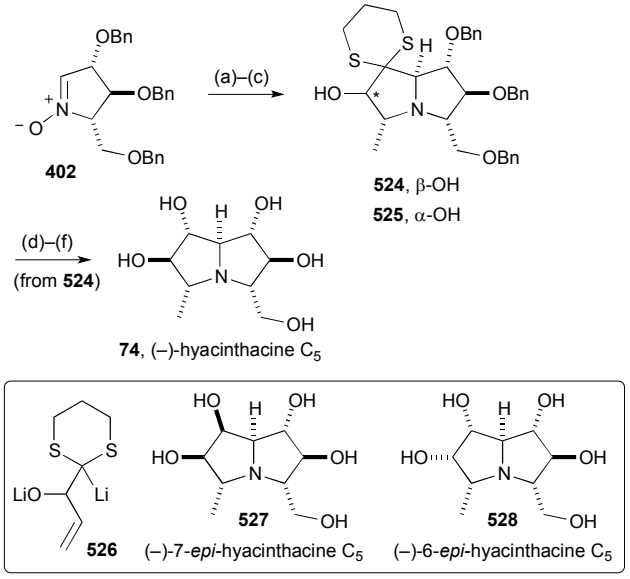
Scheme 80 Reagents and conditions: (a) *i*-PrSH, aq HCl; (b) $Me_2C(OMe)_2$, TsOH, THF, 60 °C; (c) $HgCl_2$, HgO, acetone, reflux; (d) BnNHOH, $MgSO_4$, CH_2Cl_2; (e) CH_2=$CHCO_2Me$, SmI_2, aq THF; (f) Zn, aq AcOH, 50 °; (g) $LiAlH_4$, THF, reflux; (h) aq AcOH, 40 °C; (i) TBSCl, imidazole, CH_2Cl_2; (j) MsCl, pyridine, –20 °C to rt; (k) KI, Et_3N, $PhCH_3$, 165 °C; (l) HCl, aq MeOH then Amberlite IRA-401, MeOH.

SmI_2 was used twice in a unified synthesis of (+)-hyacinthacine A_2, (−)-uniflorine and (+) -7-*epi*-casuarine.[173] To begin, diethyl D-tartrate was converted into the *N*-protected tartarimide **520** (Scheme 81) and the first Sm(II)-mediated reductive alkylation effected, giving lactam **521**. This was elaborated to the *N*,*S*-acetal **522** that was then used in the second Sm(II)-mediated reaction, this time conjugate addition to ethyl acrylate, with stereocontrol offered by the adjacent benzyloxy group. The cyclised adduct **405** served as a common intermediate for the synthesis, by standard methods, of the three pyrrolizidines shown.



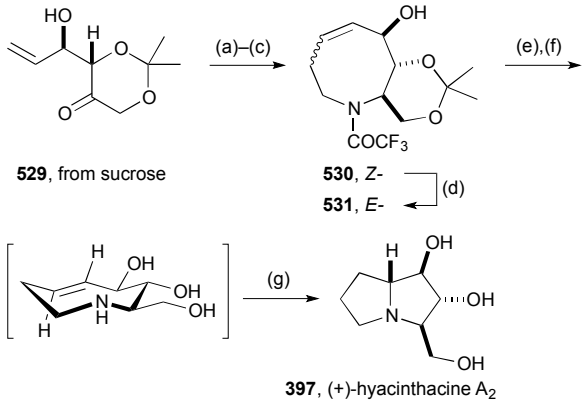
Scheme 81 Reagents and conditions: (a) NaH, BnBr, DMF, –20 °C to 0 °C; (b) LiOH, aq EtOH, 0 °C to 5 °C; (c) $PMBNH_2$, AcCl, CH_2Cl_2, reflux; (d) $BnOCH_2Cl$, SmI_2, $FeCl_3$, THF, 0 °C to rt; (e) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C to rt; (f) CAN, aq CH_3CN, 0 °C; (g) Boc_2O, Et_3N, DMAP, CH_2Cl_2; (h) $NaBH_4$, MeOH, –10 °C; (i) 2-PySH, $CaCl_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to rt; (j) ethyl acrylate, $BF_3{\cdot}OEt_2$, SmI_2, *t*-BuOH, THF, –60 °C; (k) HCl, aq EtOH then K_2CO_3, MeOH; (l) $LiAlH_4$, THF, 0 °C to 60 °C; (m) H_2, Pd/C, aq HCl, MeOH then Dowex 1X8 (OH^-); (n) LDA, PhSeBr, THF, –78 °C then H_2O_2, aq CH_2Cl_2; (o) OsO_4, NMO, citric acid, aq *t*-BuOH (dr = 60:40 in favour of β-diol) or $KMnO_4$, 18-C-6, CH_2Cl_2, –10 °C (dr = 14:86 in favour of α-diol); (p) $LiAlH_4$, THF, reflux; (q) H_2, Pd/C, MeOH.

A total synthesis of (–)-hyacinthacine C_5 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 A_3 (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 μM) and rice (IC_{50} = 64.2 μM).



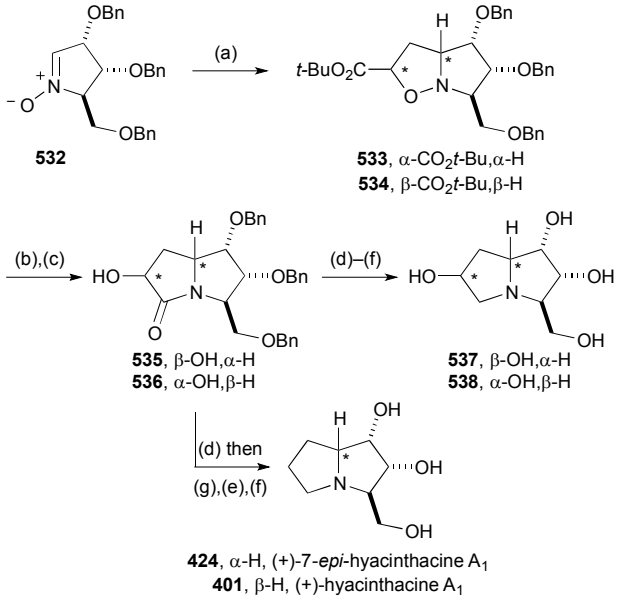
Scheme 82 Reagents and conditions: (a) **526**, TMEDA, THF, –30 °C; (b) $CHCl_3$; (c) Zn, HOAc; (d) NBS, $AgNO_3$, aq CH_3CN; (e) $NaBH_4$, MeOH; (f) H_2, Pd/C, aq HCl, MeOH.

Fox's recent synthesis of (+)-hyacinthacine A_2 built on Madsen's earlier route to the 7-hydroxy derivative, australine (see below, Scheme 90).[175] 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.



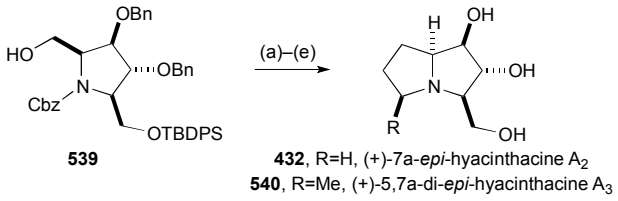
Scheme 83 Reagents and conditions: (a) 3-butenamine·HOAc, $NaBH_3CN$, 4Å MS, CH_3CN, 0 °C to rt; (b) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 0 °C to rt; (c) Grubbs' II, CH_2Cl_2 (d) hν (254 nm), hexanes, Et_2O cycle through $AgNO_3/SiO_2$ column; (e) MeLi, THF, –78 °C; (f) HCl, MeOH then aq HOAc; (g) aq NH_3 then adjust pH to 7.

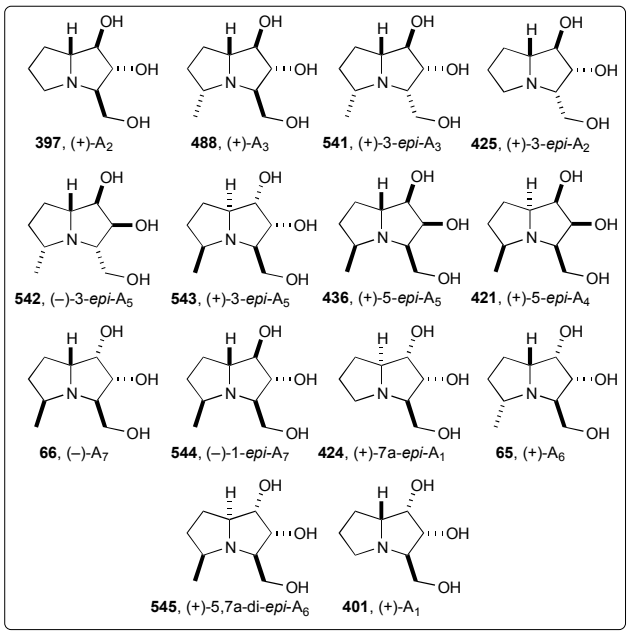
Paralleling earlier approaches to the hyacinthacines, Goti's group described a synthesis of (+)-hyacinthacine A_1, its C(7a) epimer and two 6-hydroxylated analogues (Scheme 84).[176] Thus, nitrone **532**, derived from D-ribose, reacted with *tert*-butyl acrylate to give a 1.5:1 ratio of *exo-anti* (**533**) 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-hydroxypyrrolizidinones **535** and **536**, respectively. Standard transformations led, in a few steps, to the four pyrrolizidines shown.



Scheme 84 Reagents and conditions: (a) *tert*-butyl acrylate, CH_2Cl_2; (b) Zn, aq AcOH, 60–65 °C; (c) Ambersep 900 OH, MeOH; (d) $LiAlH_4$, THF, reflux; (e) H_2, Pd/C, aq HCl, MeOH; (f) Dowex 50WX8–200; (g) MsCl, Et_3N, CH_2Cl_2.

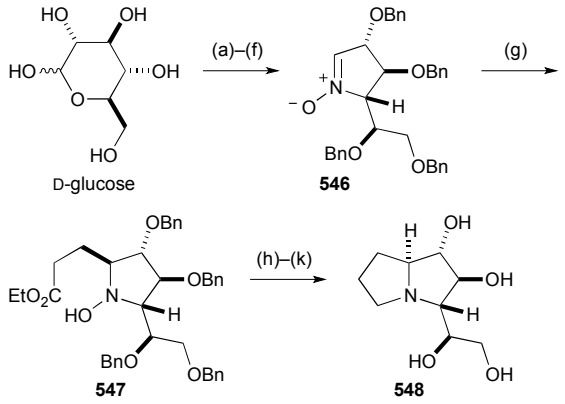
Mention has already been made (see above, Scheme 78) of Izquierdo's general approach to pyrrolizidines from D-fructose-derived functionalised pyrrolidines. During the review period, this strategy was first introduced in the context of the synthesis of (+)-7a-*epi*-hyacinthacine A_2 (**432**) and 5,7a-di-*epi*-hyacinthacine A_3 (**540**) from partially-protected 2,5-dideoxy-2,5-imino-D-glucitol (DGDP) **539** (Scheme 85).[177] Wittig extension with either Ph_3P=CHCHO or Ph_3P=CHCOMe then reductive amination led to hyacinthacine isomers **432** and **540**, respectively. Subsequently, analogous approaches were described for the synthesis of (+)-hyacinthacine A_2 (**397**);[178] (+)-hyacinthacine A_3 (**488**);[179] (+)-3-*epi*-hyacinthacines A_3 (**541**) and A_2 (**425**);[180] the enantiomers of 3-*epi*-hyacinthacine A_5 (**542** and **543**);[181] (+)-5-*epi*-hyacinthacines A_5 (**436**) and A_4 (**421**);[182] (–)-hyacinthacine A_7 (**66**) and its (–)-1-epimer (**544**);[183] (+)-7a-*epi*-hyacinthacine A_1 (**424**), (+)-hyacinthacine A_6 (**65**), and (+)-5,7a-di-*epi*-hyacinthacine A_6 (**545**).[184] A further paper, describing the syntheses of (+)-hyacinthacine A_1 (**401**) and (+)-hyacinthacine A_6 (**65**), was retracted.[185]





Scheme 85 Reagents and conditions: (a) TPAP, NMO, 4Å MS, CH_2Cl_2; (b) Ph_3P=CHCHO, CH_2Cl_2 or Ph_3P=CHCOMe, CH_2Cl_2, reflux, (c) H_2, Pd/C, MeOH; (d) TBAF, THF; (e) H_2, Pd/C, aq HCl, MeOH then Amberlite IRA-400 (HO^-).

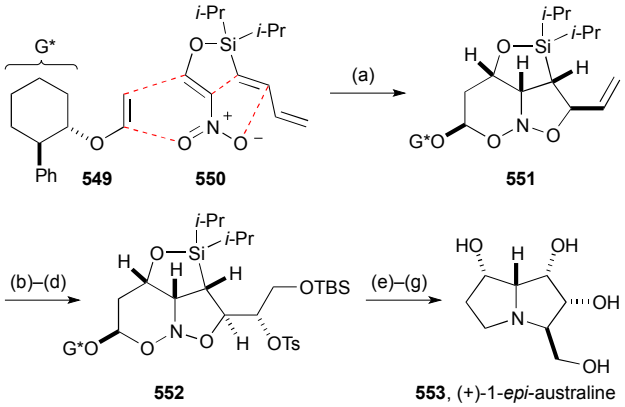
Desvergnes and Py prepared the hyacinthacine homologue '8-homo-*ent*-(+)-hyacinthacine A_2' (**548**, Scheme 86) from D-glucose as a potential UDP-galactopyranose mutase (UGM) inhibitor.[186] Octyl tetra-*O*-benzyl D-glucose was hydrolysed, exposing the 1,4-hydroxyaldehyde from which nitrone **546** was prepared by condensation and S_N2-displacement steps. Sm(II)-mediated reductive alkylation with ethyl acrylate gave the *N*-hydroxypyrrolidine **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).



Scheme 86 Reagents and conditions: (a) 1-octanol, $FeCl_3$, dioxane, 0 °C to rt; (b) NaH, BnBr, DMF, 0 °C to rt; (c) AcOH, aq H_2SO_4, 85 °C; (d) NH_2OTBS, $MgSO_4$, PPTS, $PhCH_3$, reflux; (e) MsCl, Et_3N, CH_2Cl_2; (f) Bu_4N^+ $Ph_3SiF_2^-$ (TBAT), 4Å MS, THF, reflux; (g) CH_2=$CHCO_2Et$, SmI_2, aq THF, –78 °C; (h) SmI_2, aq THF; (i) K_2CO_3, aq EtOH, 60 °C; (j) $LiAlH_4$, THF, reflux; (k) BCl_3, CH_2Cl_2, –78 °C to 0 °C.

Australine and epimers

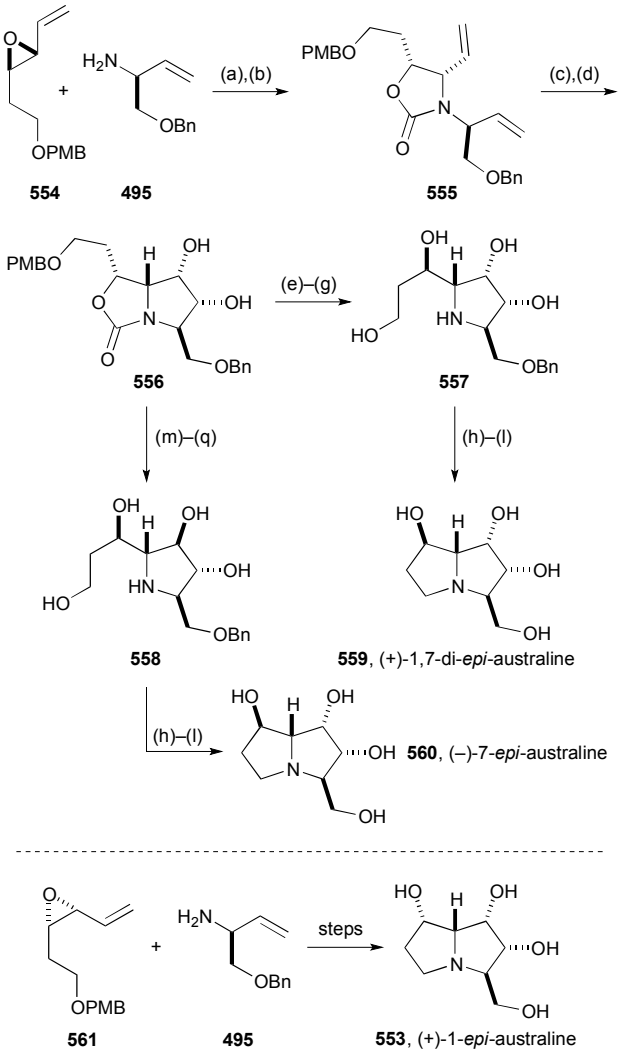
The first reported synthesis of a member of this class during the review period featured an elegant tandem intermolecular nitroalkene Diels–Alder / intramolecular nitrone cycloaddition to set four of the five stereogenic centres in the target, (+)-1-*epi*-australine (**553**, Scheme 87)[187] which had been synthesised just twice previously. The cycloaddition substrate **550** was assembled in three steps from diisopropylchlorosilane by: (i) addition of butadienyllithium; (ii) conversion of the so-formed silane to the chlorosilane; and (iii) *O*-silylation with the potassium enolate of nitroacetaldehyde. This was taken into the reaction with chiral vinyl ether **549** and cycloaddition effected with MAPh (from 2,6-diphenylphenol and trimethylaluminium) in toluene to give intermediate **551** as a single diastereomer. Alkene dihydroxylation proceeded naturally to give a 3:1 ratio in favour of the undesired 2°-alcohol epimer; this was turned round to a ~1:3 ratio using the Sharpless AD conditions shown (step b). Oxidative cleavage of the C–Si bond in compound **552** then hydrogenolysis of the N–O bonds set up reductive amination and intramolecular S_N2 reactions in situ to generate the pyrrolizidine after deprotection.



Scheme 87 Reagents and conditions: (a) MAPh, $PhCH_3$, –75 °C; (b) $K_2OsO_4{\cdot}2H_2O$, $K_3Fe(CN)_6$, DHQD-PHN, aq *t*-BuOH; (c) TBSOTf, pyridine, 0 °C to rt (then separate isomers); (d) Ts_2O, pyridine; (e) H_2O_2,

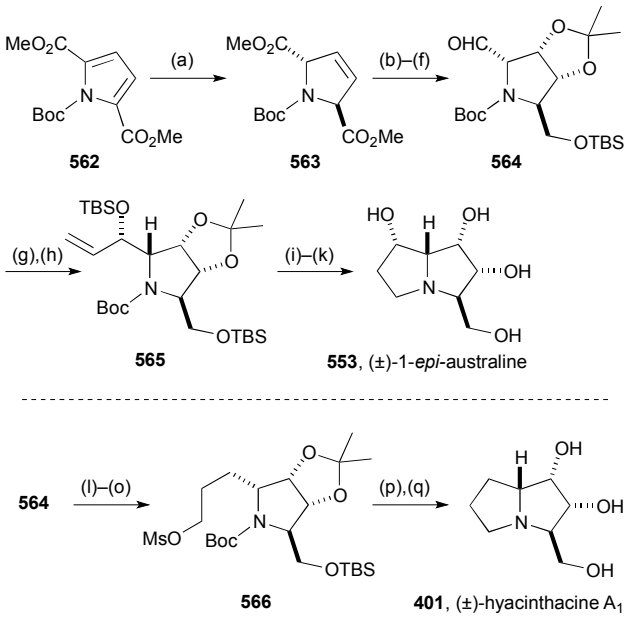
$KHCO_3$, aq THF, MeOH, 55 °C; (f) H_2, Raney Ni, MeOH; (g) HF, aq MeOH.

Pyne's synthesis of australine epimers began with the *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 *N*,*O*-diprotection gave carbamate **555**.[188] Ring-closing metathesis, and dihydroxylation *anti*-to the benzyloxymethyl group gave key intermediate **556**. Protecting group manipulations then ethanolysis of the carbamate (→ **557**) set up a final cyclisation under Mitsunobu conditions. Removal of benzyl and acetyl protecting groups completed the route to (+)-1,7-di-*epi*-australine. Derivatisation of diol **556** as its cyclic sulfate allowed regioselective ring-opening with caesium benzoate en route to *trans*-dioxygenated pyrrolidine **558**. A sequence of steps similar to that used in the synthesis of the (+)-1,7-di-*epi*- isomer generated (–)-7-*epi*-australine. This strategy was used to prepare (+)-1-*epi*-australine simply by varying the stereochemistry of the starting vinyl epoxide to **561**.[189] An attempt to extend this methodology to encompass a synthesis of (+)-australine itself was unsuccessful.



Scheme 88 Reagents and conditions: (a) LiOTf, CH_3CN, 120 °C; (b) triphosgene, Et_3N, CH_2Cl_2; (c) Grubbs' I, CH_2Cl_2, reflux; (d) $K_2OsO_4{\cdot}H_2O$, NMO, aq acetone; (e) Ac_2O, pyridine; (f) DDQ, aq CH_2Cl_2; (g) NaOH, EtOH, 70 °C; (h) DIAD, PPh_3, pyridine, 0 °C; (i) Ac_2O, pyridine; (j) H_2, $PdCl_2$, MeOH; (k) Ac_2O, pyridine; (l) NaOMe, MeOH; (m) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C; (n) $RuCl_3{\cdot}3H_2O$, $NaIO_4$, aq CCl_4, CH_3CN; (o) $PhCO_2H$, Cs_2CO_3, DMF, 40 °C then H_2SO_4 aq THF; (p) DDQ, aq CH_2Cl_2; (q) NaOH, EtOH, 70 °C.

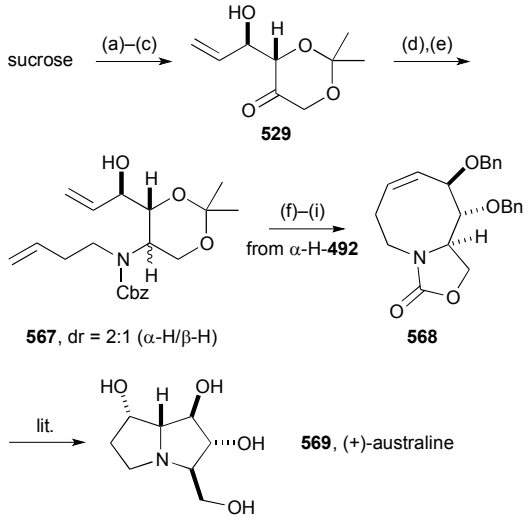
Donohoe's synthesis of (±)-1-*epi*-australine began with Birch reduction of pyrrole **562** (Scheme 89) with dienolate protonation under equilibrating conditions giving the *trans*-diester **563**.[190,191] Dihydroxylation and acetonide protection allowed discrimination of the two esters with the sterically less-encumbered *exo*-ester (i.e. *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_1 (**401**). In this case, the chain was extended by Wittig olefination, then reduction steps and intramolecular *N*-alkylation completed the route (*cf.* Scheme 68).



Scheme 89 Reagents and conditions: (a) Li, NH_3, THF, NH_4Cl, –78 °C; (b) OsO_4, Me_3NO, CH_2Cl_2; (c) 2,2-dimethoxypropane, TsOH, acetone; (d) $NaBH_4$, THF, MeOH; (e) TBSCl, imidazole, DMF; (f) DIBAL, CH_2Cl_2, –40 °C; (g) vinyl-MgBr, THF; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C to rt; (i) $BH_3{\cdot}THF$ then H_2O_2, aq NaOH, THF; (j) MsCl, Et_3N, CH_2Cl_2; (k) aq CF_3CO_2H; (l) $Ph_3P{=}CHCO_2Me$, $PhCH_3$, 110 °C; (m) H_2, PtO_2, MeOH; (n) DIBAL, CH_2Cl_2, –78 °C to rt; (o) MsCl, pyridine, 0 °C; (p) TESOTf, 2,6-lutidine, CH_2Cl_2, –78 °C to rt; (q) $(COCl)_2$, MeOH.

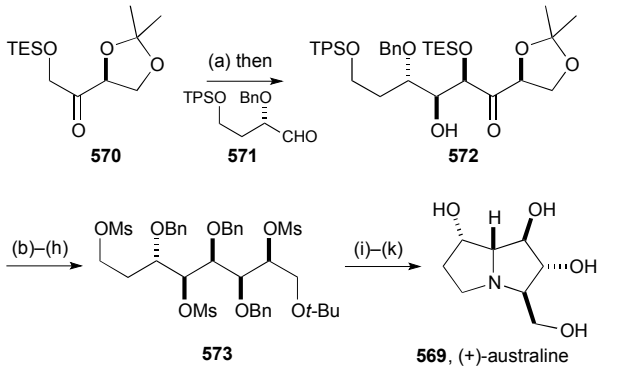
Towards the middle of the review period, Madsen completed enantiospecific formal syntheses of australine with the preparation of hexahydroazocine **568** (Scheme 90) by two routes, one from D-fructose, the other from sucrose; only the latter 'second generation' route will be described here.[192] Central to both routes was the use of Zn-mediated fragmentations of carbohydrate-derived precursors to give usefully-functionalised

enantiopure intermediates. Here, acetonide protection of sucrose cleaved the glucose and fructose residues, and the fructofuranoside moeity 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.[193] 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.



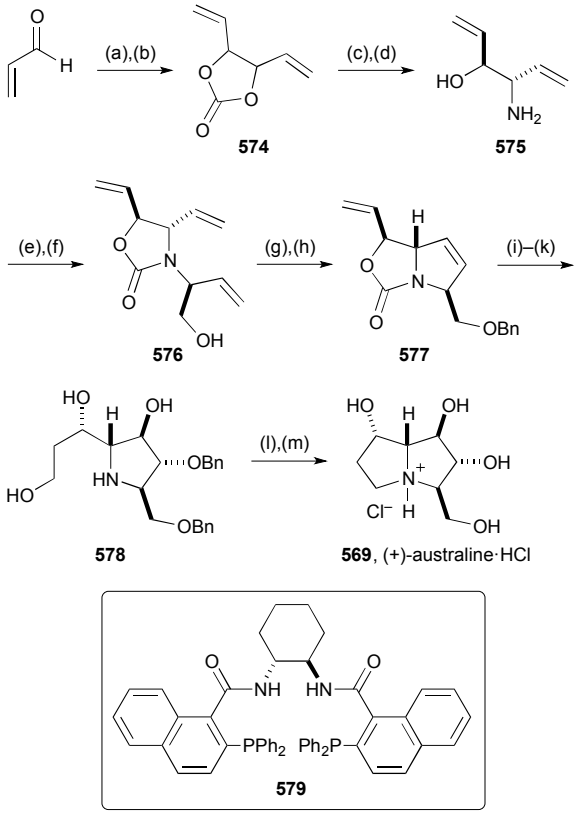
Scheme 90 Reagents and conditions: (a) 2,2-dimethoxypropane, $TsOH{\cdot}H_2O$, DMF; (b) I_2, PPh_3, imidazole, THF, 65 °C; (c) Zn, aq THF,))), 40 °C; (d) homoallylamine, $NaBH_3CN$, AcOH, 3Å MS, THF; (e) Cbz-Cl, $KHCO_3$, aq CH_2Cl_2; (f) Grubbs' II, CH_2Cl_2; (g) aq AcOH; (h) NaOMe, MeOH; (i) NaH, BnBr, THF.

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-erythrulose (2 steps) and (*S*)-malic acid (6 steps), respectively.[194] 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_N2-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**.



Scheme 91 Reagents and conditions: (a) Cy_2BCl, Et_3N, 0 °C; (b) SEMCl, *i*-Pr_2NEt, CH_2Cl_2; (c) $LiBH_4$, Et_2O, –90 °C; (d) DDQ, aq THF; (e) NaH, BnBr, THF, 40 °C; (f) $MeMgBr$, $PhCH_3$, Et_2O, reflux; (g) TBAF, THF; (h) MsCl, Et_3N, CH_2Cl_2; (i) $BnNH_2$, NaI, DMSO, 80 °C; (j) H_2, $Pd(OH)_2$, EtOH; (k) CF_3CO_2H, CH_2Cl_2 then aq NH_3.

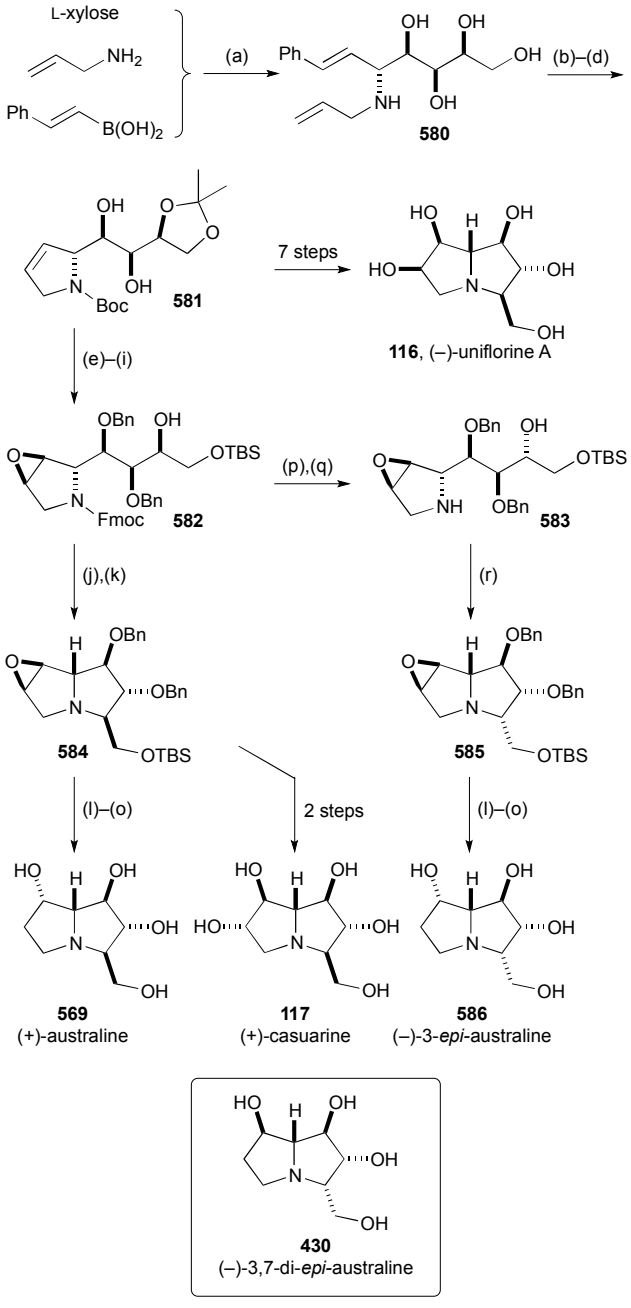
Marco's australine synthesis was soon followed by Trost's which featured sequential enantio- and diastereoselective allylic alkylation processes (Scheme 92).[195] The synthesis began with reductive dimerisation of acrolein and conversion to carbonate **574**, a mixture of diastereomers. With **579** as chiral ligand, Pd-mediated asymmetric allylation with *N*-phthalimide gave, after release of the free amine, aminoalcohol **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 (**579**). 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 92 Reagents and conditions: (a) Zn, aq NH_4Cl, THF; (b) $(EtO)_2CO$, K_2CO_3, 115 °C; (c) phthalimide, Na_2CO_3, π-allylpalladium(II) chloride dimer, **579**, CH_2Cl_2; (d) $H_2N(CH_2)_2NH_2$, EtOH; (e) triphosgene, pyridine, CH_2Cl_2; (f) butadiene monoepoxide, $Pd_2dba_3·CHCl_3$, **579**, DBU, CH_2Cl_2; (g) Grubbs' II, CH_2Cl_2, reflux; (h) benzyl 2,2,2-trichloroacetimidate, TfOH, CH_2Cl_2; (i) 9-BBN, THF then aq $NaBO_3·H_2O$, 0 °C; (j) Oxone, $(CF_3)_2CO$, Na_2CO_3, EDTA, aq CH_3CN, 0 °C; (k) BnOH, Dowex 1X8-50, 100 °C; (l) MsCl, Et_3N, CH_2Cl_2, –30 °C to rt; (m) H_2, $PdCl_2$, MeOH.

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 carbamate was followed by alkene epoxidation, generating **582** as a single diastereomer. This intermediate served as a second branching point leading to two parallel syntheses of (+)-australine and (–)-3-*epi*-australine. Cyclisation, to complete the pyrrolizidine skeleton, 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) $NaHSO_4$, CH_2Cl_2, reflux then water; (b) H_2, $PdCl_2$, MeOH). Thus, in appropriate envelope conformations that allow axial attack by hydride, the 7-position is hindered by pseudoaxial protons at C(1) and C(5). Mitsunobu inversion of the newly-formed 2°-alcohol and hydroxyl deprotection completed the route.

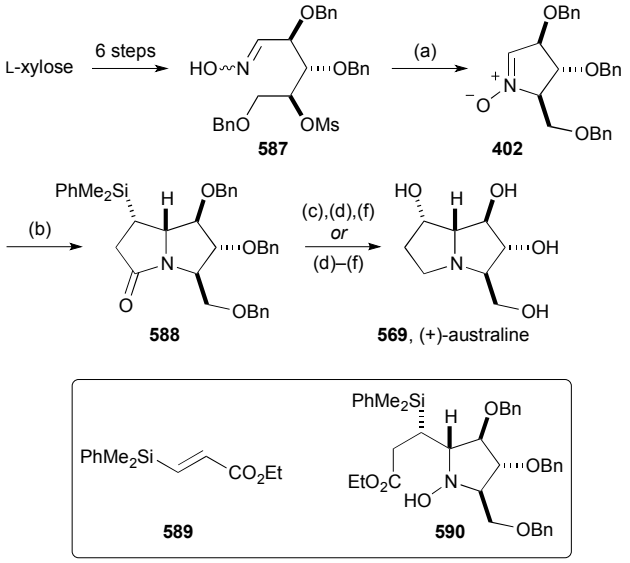
Access to (–)-3-*epi*-australine followed an analogous pathway after Mitsunobu inversion of the 3-OH (→ **583**). Non-natural (–)-3,7-di-*epi*-australine (**430**) was also prepared by retaining the C(7)-stereochemistry obtained upon hydride-mediated epoxide opening (*cf.* step l). The synthesis and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



Scheme 93 Reagents and conditions: (a) EtOH; (b) Boc_2O, Et_3N, MeOH; (c) $Me_2C(OMe)_2$, PPTS, acetone; (d) Grubbs' I, CH_2Cl_2, reflux; (e) NaH, BnBr, Bu_4NI, THF; (f) aq HCl, MeOH; (g) TBSCl, imidazole, DMAP, THF; (h) FmocCl, aq Na_2CO_3, THF; (i) CF_3COCH_3, Oxone, $NaHCO_3$, aq CH_3CN, 0 °C; (j) MsCl, Et_3N, CH_2Cl_2, 0 °C; (k) piperidine, CH_3CN; (l)

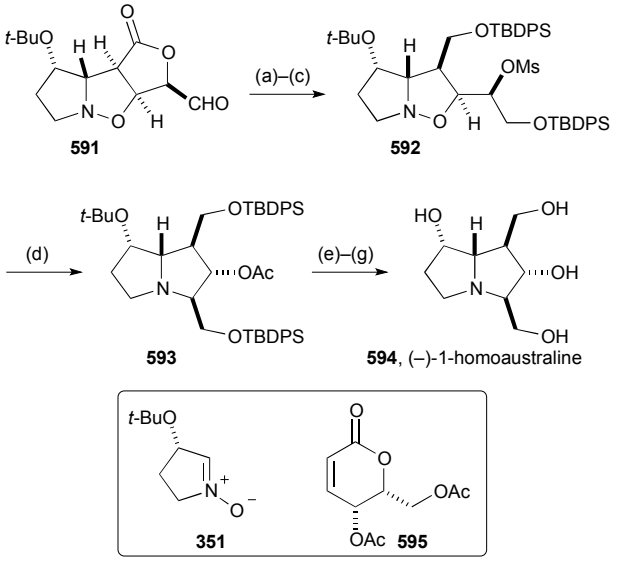
$LiAlH_4$, THF, 0 °C; (m) DIAD, PPh_3, 4-NO_2-$C_6H_4CO_2H$, $PhCH_3$, 80 °C; (n) K_2CO_3, MeOH; (o) H_2, $PdCl_2$, MeOH then ion-exchange chromatography; (p) DIAD, PPh_3, 4-NO_2-$C_6H_4CO_2H$, $PhCH_3$; (q) K_2CO_3, MeOH; (r) DIAD, PPh_3, $PhCH_3$, 80 °C.

Py's recent synthesis of (+)-australine (Scheme 94)[198] built on methodology developed for (+)-hyacinthacine A_2 (see above, Scheme 58). Thus, nitrone **402** was prepared in six steps from L-xylose. 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**).



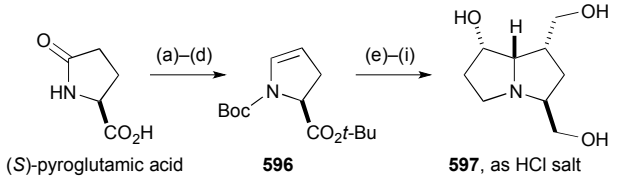
Scheme 94 Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, $NaHCO_3$, aq MeOH, 65 °C; (b) SmI_2, **589**, $(CF_3)_2CHOH$, LiBr, THF, –78 °C to –30 °C then Zn, AcOH; (c) cumyl hydroperoxide, KH, TBAF, DMF; (d) $BH_3{\cdot}SMe_2$, THF, reflux; (e) *t*-BuOOH, KH, TBAF, DMF; (f) H_2, Pd/C, THF, MeOH.

Chmielewski completed a synthesis of (–)-1-homoaustraline (Scheme 95), and evaluated its inhibitory activity against a panel of commercially-available α- and β-glucosidases.[199] The tricylic aldehyde **591** was obtained from the adduct of nitrone **351** (5 steps from (*S*)-malic acid) and lactone **595** (~4 steps from D-galactose) following transacylation and 1,2-diol cleavage. This was reduced, the 1°-alcohols silylated, and the remaining hydoxyl group activated by mesylation, giving **592**. Hydrogenolysis of the N–O bond resulted in cyclisation to generate the 1-homoaustraline 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) $LiBH_4$, THF; (b) TBDPSCl, Et_3N, DMAP, rt to reflux; (c) MsCl, Et_3N, CH_2Cl_2, –5 °C to rt; (d) H_2, Pd/C, EtOAc then Ac_2O, Et_3N, DMAP; (e) TBAF, THF then Ac_2O, pyridine; (f) CF_3CO_2H then Ac_2O, Et_3N, DMAP; (g) NH_3, MeOH.

The 1-*epi*-2-deoxy- derivative **597** (Scheme 96) of (–)-1-homoaustraline was prepared in nine steps overall from pyroglutamic acid.[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 $LiAlH_4$ reduction of the methyl ester at C(3).

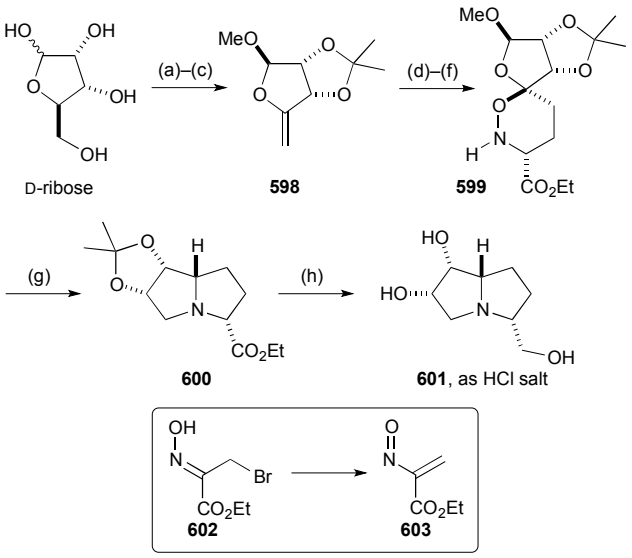


Scheme 96 Reagents and conditions: (a) *t*-BuOAc, $HClO_4{\cdot}2H_2O$; (b) Boc_2O, DMAP, CH_3CN; (c) DIBAL, $PhCH_3$, –78 °C; (d) $(CF_3CO)_2O$, 1,4-lutidine, $PhCH_3$, 0 °C to reflux; (e) 4-chlorobutyryl chloride, Et_3N, C_6H_{12}, reflux; (f) MCPBA, $NaHCO_3$, CH_2Cl_2; (g) 10% aq HCl then 5% aq NaOH; (h) H_2SO_4, MeOH, reflux; (i) $LiAlH_4$, THF, reflux then aq HCl.

Alexine(s)

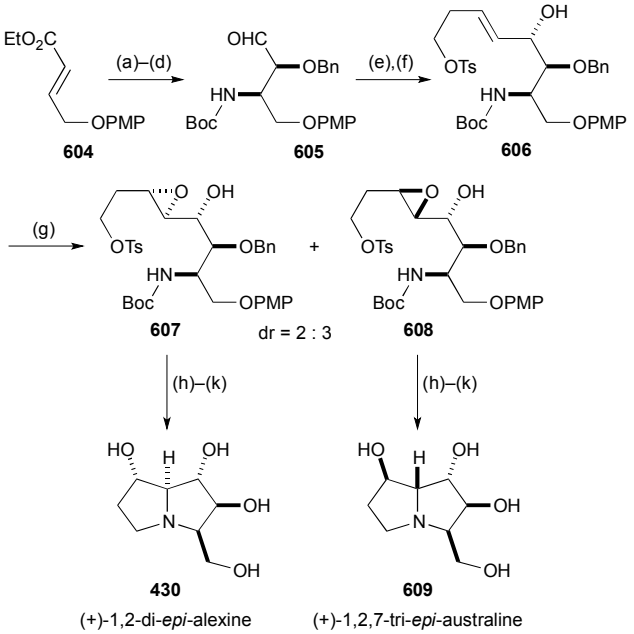
Early in the review period Gallos reported a hetero-Diels–Alder approach to a partially hydroxylated alexine analogue (**601**, Scheme 97).[201] Building on earlier precedent set separately by Gilchrist and Reissig, the nitrosoacrylate diene **603** was prepared by 1,4-elimination from bromooxime **602** and trapped in situ by Diels–Alder reaction with D-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 **600** exclusively. The target molecule (**601**) was then obtained by ester reduction and acetonide cleavage.



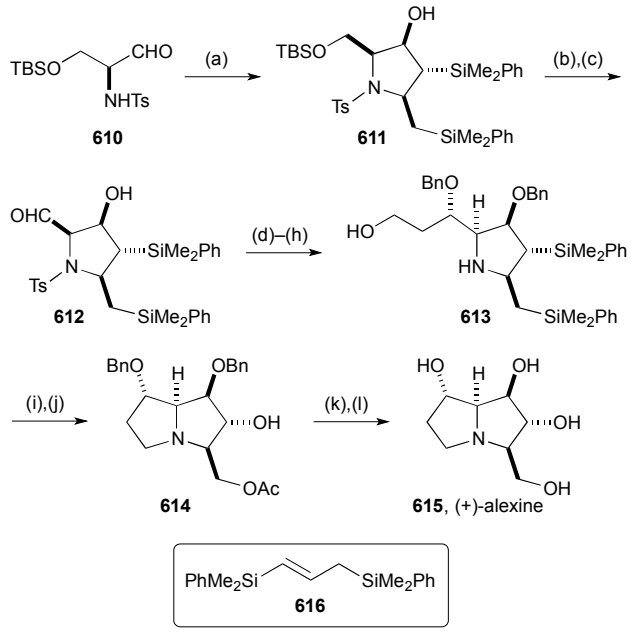
Scheme 97 Reagents and conditions: (a) HCl, acetone, MeOH, 60 °C; (b) I_2, PPh_3, imidazole, Et_2O, CH_3CN; (c) DBU, benzene, C_6H_6, reflux; (d) **602**, Na_2CO_3, CH_2Cl_2; (e) $NaBH_3CN$, AcOH; (f) Et_3N, $CHCl_3$, reflux; (g) H_2, Raney Ni, H_3BO_3, $MgSO_4$, MeOH; (h) $LiBH_4$, THF then HCl, MeOH.

The synthesis of two non-natural pyrrolizidines (+)-1,2-di-*epi*-alexine (**430** = *ent*-(–)-3,7-di-*epi*-australine, see above, Scheme 93) and (+)-1,2,7-tri-*epi*-australine (**609**, Scheme 98) was the first of these particular hydroxylated stereoisomers.[202] Sharpless asymmetric aminohydroxylation of unsaturated ester **604** gave an aminoalcohol intermediate, with ee >99% following one recrystallisation, that was carried forward to the aldehyde **605**. Vinyl Grignard addition (Cram chelate selectivity, dr = 4:1) and cross metathesis furnished allylic alcohol **606** that gave two inseparable epoxide diastereomers **607** and **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 **609** being consistent with those previously reported for the enantiomer.



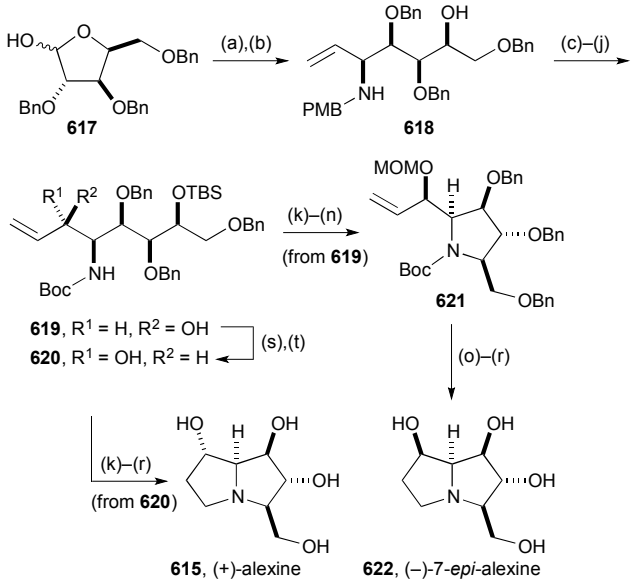
Scheme 98 Reagents and conditions: (a) $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2PHAL$, LiOH, *N*-bromoacetamide, aq *t*-BuOH, 4 °C; (b) NaH, BnCl, DMF, 0 °C; (c) Boc_2O, DMAP, THF, reflux then NH_2NH_2, MeOH; (d) DIBAL, CH_2Cl_2, –78 °C; (e) H_2C=CHMgBr, THF, –50 °C to rt; (f) H_2C=$CH(CH_2)_2OTs$, Grubbs' II, CH_2Cl_2; (g) $VO(acac)_2$, *t*-BuOOH, $PhCH_3$; (h) HCl, aq MeOH; (i) K_2CO_3, MeOH; (j) CAN, aq CH_3CN, 4 °C; (k) H_2, Pd/C, MeOH [products isolated as their HCl salts].

Two syntheses of natural (+)-alexine were reported in the same year. The first, an enantiospecific route from L-serine,[203] was constructed around a key (3+2)-annulation between aldehyde **610** and the bis(dimethylphenylsilyl)propene **616** (Scheme 99). In this process, developing positive charge β-to both silyl substituents is trapped by the attached sulfonamide resulting in heavily-functionalised pyrrolidine **611** (dr >40:1). Chelation-controlled allylation of aldehyde **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 **610**, stands as the first asymmetric, non-carbohydrate route to (+)-alexine.



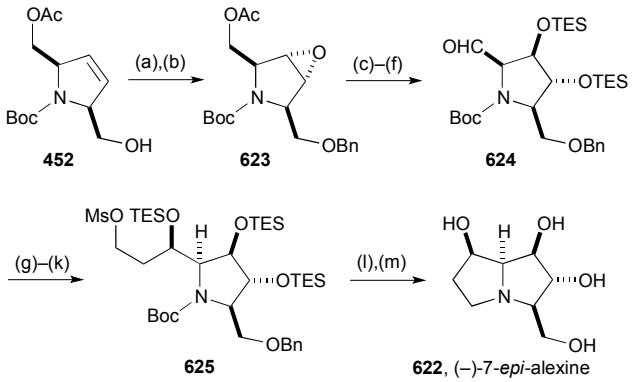
Scheme 99 Reagents and conditions: (a) **616**, $MeAlCl_2$, CH_2Cl_2, –78 °C; (b) AcOH, aq THF; (c) TEMPO, NaOCl, KBr, aq CH_2Cl_2; (d) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, –78 °C; (e) BnBr, KHMDS, THF, –78 °C; (f) OsO_4, $NaIO_4$, pyridine, aq CH_3CN; (g) $NaBH_4$, MeOH, 0 °C; (h) sodium naphthalenide, DME, –60 °C; (i) CBr_4, PPh_3, Et_3N, CH_2Cl_2; (j) $Hg(OTf)_2$, AcOOH, AcOH; (k) LiOH, aq THF; (l) H_2, Pd/C, EtOH.

A second (+)-alexine synthesis, reported a few months later,[204] began with vinyl Grignard addition to the imine formed from 4-methoxybenzylamine and xylose derivative **617** (Scheme 100). The resulting amine **618**, formed as a single diastereomer, was carried through a sequence of protecting group manipulations then oxidative cleavage of the alkene. A second vinyl Grignard addition generated alcohol **619** essentially as a single 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_N2-type cyclisation. The pyrrolizidine ring system was completed by hydroboration 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) $PMBNH_2$, 4Å MS, $PhCH_3$, reflux; (b) H_2C=CHMgCl, THF, –78 °C to 0 °C; (c) BzCl, CH_2Cl_2; (d) CAN, MeOH; (e) TBSCl, imidazole, DMF; (f) Boc_2O, Et_3N, DMAP, CH_2Cl_2; (g) $(Me_2N)_2C$=NH, 130 °C; (h) OsO_4, NMO, acetone; (i) $NaIO_4$, aq THF; (j) H_2C=CHMgCl, THF, –78 °C; (k) MOMCl, *i*-Pr_2NEt; (l) TBAF, THF; (m) MsCl, Et_3N, CH_2Cl_2; (n) *t*-BuOK, THF; (o) 9-BBN, THF then H_2O_2, aq NaOH; (p) MsCl, Et_3N, CH_2Cl_2; (q) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –20 °C; (r) HCO_2H, Pd/C, MeOH, reflux; (s) TPAP, NMO, 4Å MS, CH_2Cl_2; (t) $NaBH_4$, $CeCl_3$, MeOH, –45 °C.

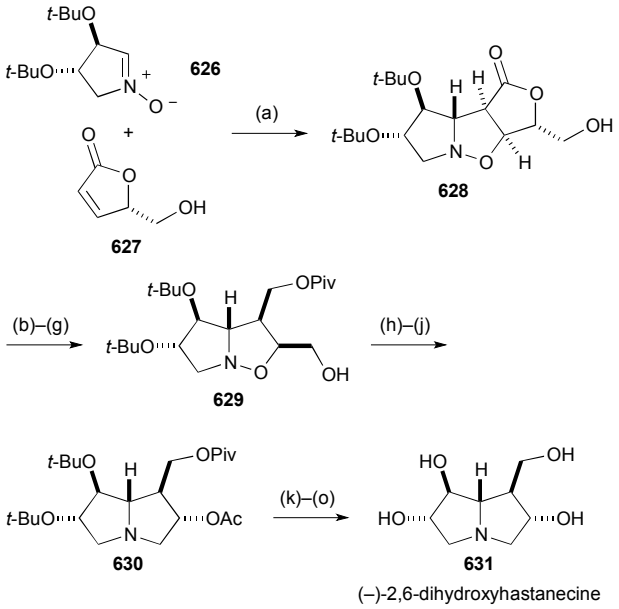
Donohoe's group achieved a synthesis of (–)-7-*epi*-alexine from monoacetate **452**, prepared as in Scheme 68.[205] The *trans*-1,2-diol motif present in the final product was installed by Lewis acid mediated epoxide opening in compound **623** (Scheme 101) by the neighbouring acetate group followed by methanolysis 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) BnBr, Ag_2O, 4Å MS, CH_2Cl_2; (b) CF_3COCH_3, Oxone, EDTA, $NaHCO_3$, aq CH_3CN, 0 °C; (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –50 °C; (d) K_2CO_3, MeOH; (e) TESCl, Et_3N, DMAP, CH_2Cl_2; (f) Swern oxidation; (g) H_2C=$CHCH_2MgBr$, THF, –78 °C; (h) TESCl, Et_3N, DMAP, CH_2Cl_2; (i) O_3, CH_2Cl_2, –78 °C then PPh_3; (j) $NaBH_4$, MeOH, CH_2Cl_2, 0 °C; (k) Ms_2O, 2,6-lutidine, DMAP, CH_2Cl_2; (l) TESOTf, 2,6-lutidine, CH_2Cl_2 then MeOH; (m) H_2, Pd/C, aq HCl, MeOH.

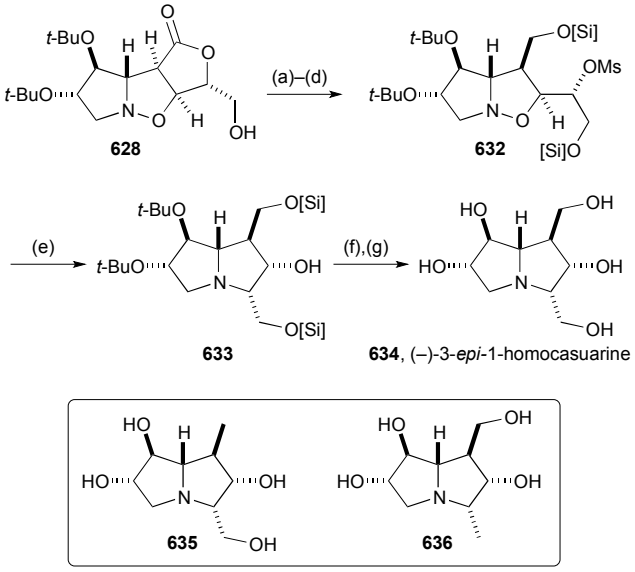
Dihydroxyhastanecine

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 nitrone **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 nitrone cycloaddition with unfunctionalised furan-2(5*H*)-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) TBDPSCl, imidazole, CH_2Cl_2, −15 °C to rt; (c) $BH_3{\cdot}SMe_2$, THF; (d) PivCl, DMAP, CH_2Cl_2, −15 °C to rt; (e) TBAF, THF; (f) $NaIO_4$, MeOH; (g) $NaBH_4$, MeOH; (h) MsCl, Et_3N, CH_2Cl_2, −15 °C to rt; (i) H_2, Pd/C, EtOAc/MeOH; (j) Ac_2O, Et_3N; (k) $LiAlH_4$, Et_2O; (l) Ac_2O, Et_3N; (m) CF_3COOH; (n) Ac_2O, Et_3N; (o) NH_3, MeOH.

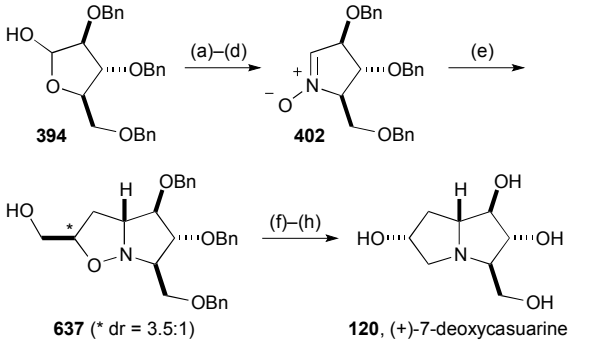
The same group applied an analogous strategy to the synthesis of (–)-3-*epi*-1-homocasuarine (**634**, Scheme 103) and two reduced derivatives **635** and **636**.[208] Omission of the periodate cleavage (step f, Scheme 102) retained what would become the 3-hydroxymethyl group, and deoxygenation of the 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) TBDPSCl, imidazole, CH_2Cl_2, −15 °C to rt; (b) $BH_3{\cdot}SMe_2$, THF; (c) TBDPSCl, imidazole, CH_2Cl_2, −15 °C to rt; (d) MsCl, Et_3N, CH_2Cl_2, −15 °C to rt; (e) H_2, Pd/C, EtOAc, MeOH; (f) TBAF, THF then Ac_2O, Et_3N, –5 °C; (g) NH_3, MeOH. [Si] = TBDPS.

Casuarines

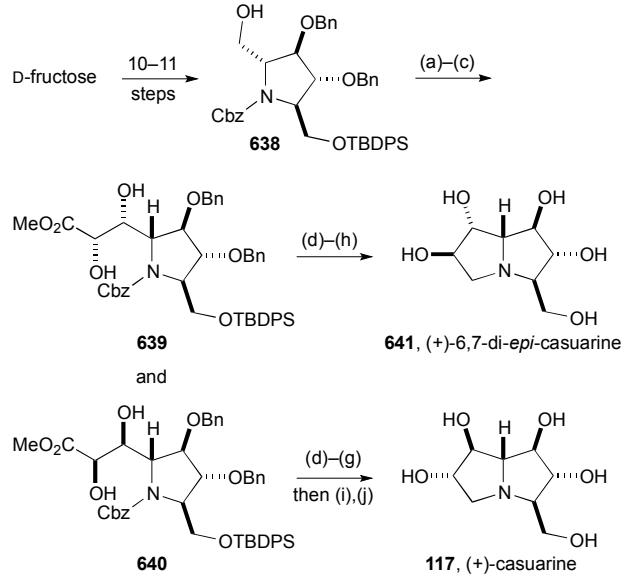
Nitrone **402**, derived from D-arabinose derivative **394** (Scheme 104), reacted with allyl alcohol to give nitrone cycloadduct **637** in 73% yield following separation of the epimer at the starred carbon.[209] Mesylation of the 1°-hydroxyl set up *N*-cyclisation in situ under the conditions employed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



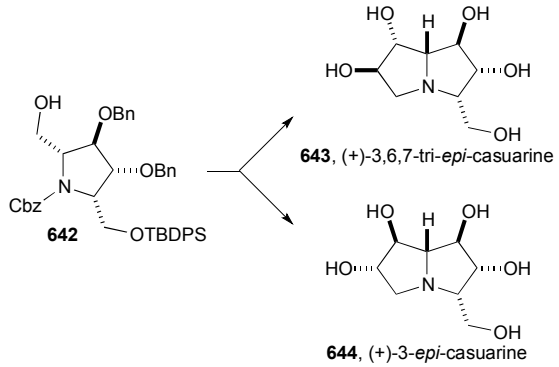
Scheme 104 Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, NaOMe, MeOH; (b) TBDPSCl, pyridine; (c) PPh_3, I_2, imidazole, $PhCH_3$, reflux; (d) TBAF, $PhCH_3$, reflux; (e) allyl alcohol, $PhCH_3$, reflux; (f) MsCl, pyridine, CH_2Cl_2; (g) $Mo(CO)_6$, aq CH_3CN, reflux; (h) H_2, Pd/C, aq HCl, MeOH.

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 hyacinthacine diasteromers 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)hydroquinine, 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*-pyrrolidine diastereomer **642** led to the two casuarine isomers **643** and **644** shown in Scheme 106.[211]

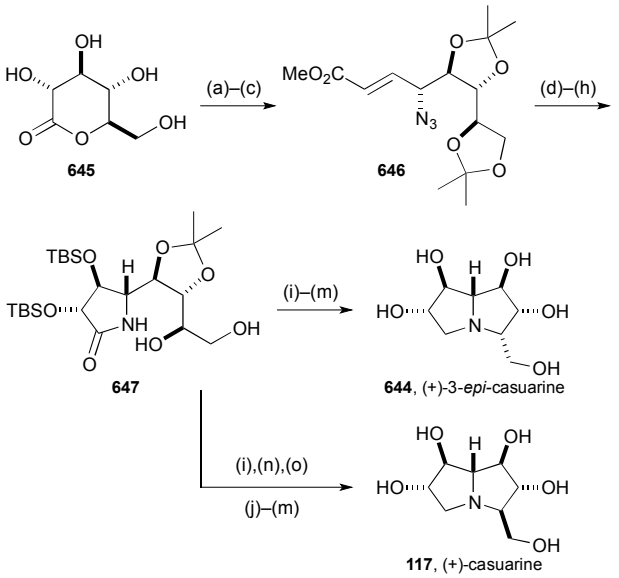


Scheme 105 Reagents and conditions: (a) TPAP, NMO, 4Å MS, CH_2Cl_2; (b) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2; (c) see text; (d) H_2, Pd/C, MeOH; (e) NaOMe, MeOH; (f) $BH_3{\cdot}SMe_2$, THF then MeOH, heat; (g) TBAF, THF; (h) H_2, Pd/C, aq HCl, MeOH then Amberlite IRA-400 (OH^- form); (i) as (h) then Ac_2O, pyridine, DMAP; (j) NaOMe, MeOH.



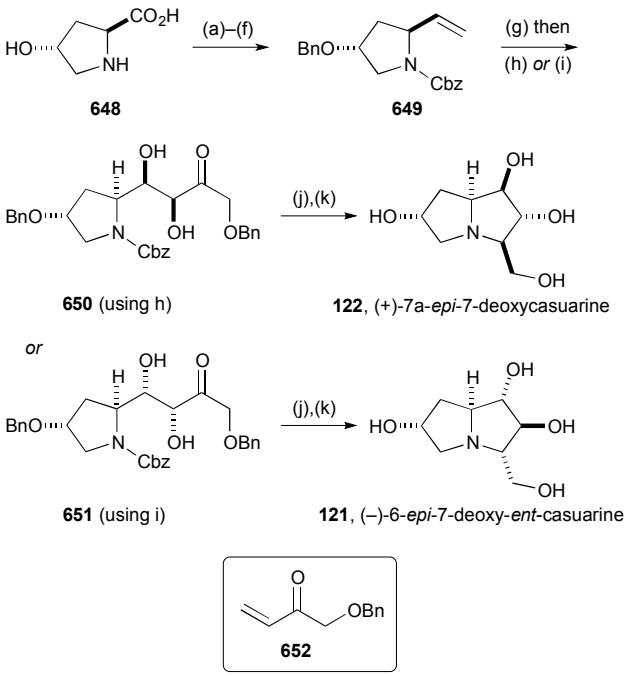
Scheme 106

Following confirmation by crystallography of the structure of (+)-3-*epi*-casuarine,[7] Fleet's group completed total syntheses of this pyrrolizidine and (+)-casuarine, in part to provide spectroscopic data for direct comparison.[212] Protection of D-gluconolactone (**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 pyrrolizidines 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) $Me_2C(OMe)_2$, TsOH, MeOH then Tf_2O, pyridine, CH_2Cl_2; (b) NaN_3, DMF; (c) DIBAL, $PhCH_3$, –78 °C then MeOH, –78 °C to rt then $Ph_3P{=}CHCO_2Me$; (d) OsO_4, NMO, aq acetone; (e) H_2, $Pd(OH)_2$/C, THF; (f) $PhCH_3$, reflux; (g) TBSCl, imidazole, THF, reflux; (h) AcOH, aq MeOH, reflux; (i) TBSCl, pyridine; (j) MsCl, Et_3N, CH_2Cl_2; (k) $BH_3{\cdot}THF$, THF, reflux; (l) aq CF_3CO_2H, reflux; (m) aq NaOAc then aq NH_3, Amberlite CG120(H^+); (n) Tf_2O, pyridine, CH_2Cl_2, –50 °C to 0 °C; (o) CF_3CO_2Cs, 2-butanone, 50 °C then K_2CO_3.

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 pyrrolidine **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.

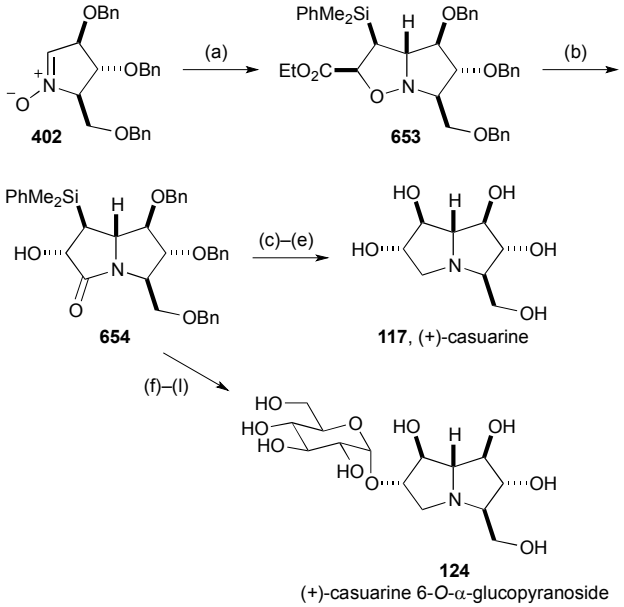


648 **649** **650** (using h) **122**, (+)-7a-*epi*-7-deoxycasuarine **651** (using i) **121**, (–)-6-*epi*-7-deoxy-*ent*-casuarine

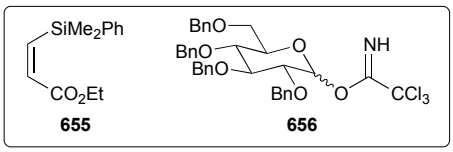
652

Scheme 108 Reagents and conditions: (a) $SOCl_2$, MeOH; (b) Cbz-Cl, K_2CO_3, aq THF; (c) *O*-benzyl trichloroacetimidate, TfOH, CH_2Cl_2, hexane; (d) $NaBH_4$, LiCl, THF, EtOH; (e) Swern oxidation; (f) $Ph_3P^+Me\ Br^-$, BuLi, THF, –78 °C to rt; (g) **652**, Hoveyda–Grubbs' II (Hoveyda–Blechert catalyst), CH_2Cl_2, reflux; (h) AD-mix-β, $NaHCO_3$, $MeSO_2NH_2$, aq acetone; (i) AD-mix-α, $NaHCO_3$, $MeSO_2NH_2$, aq acetone; (j) H_2, Pd/C, MeOH then aq HCl; (k) Amberlite IR 410 (OH^- form).

The popular nitrone method formed the basis of a second synthesis of (+)-casuarine during the review period.[214] 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 incorporated in the cycloaddition partner **655** (Scheme 109) in 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-*O*-glucoside **124**. Here, the free hydroxyl group in intermediate **654** was acetylated, the C–Si bond cleaved oxidatively as before and the resulting free hydroxyl protected as its benzyl ether. Deacetylation under basic conditions released the 6-OH for glucosylation with trichloroacetimidate-activated **656**, and lactam reduction and hydrogenolysis of all eight benzyl ethers completed the route.



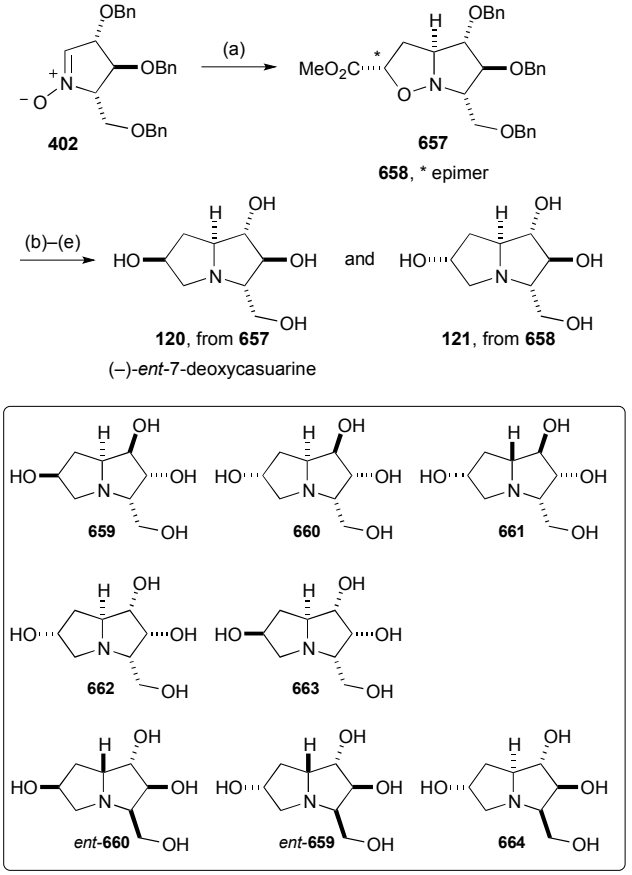
402 **653** **654** **117**, (+)-casuarine **124** (+)-casuarine 6-*O*-α-glucopyranoside



655 **656**

Scheme 109 Reagents and conditions: (a) **655**, CH_2Cl_2; (b) Zn, aq AcOH, 65 °C; (c) $Hg(O_2CCF_3)_2$, CF_3CO_2H, AcOH, AcOOH, $CHCl_3$; (d) $LiAlH_4$, THF, reflux; (e) H_2, Pd/C, aq HCl, MeOH; (f) Ac_2O, pyridine; (g) $Hg(O_2CCF_3)_2$, CF_3CO_2H, AcOH, AcOOH, $CHCl_3$; (h) *O*-benzyl trichloroacetimidate, TfOH, Et_2O; (i) Ambersep 900 OH, MeOH; (j) **656**, TMSOTf, Et_2O, –20 °C; (k) $LiBH_4$, BH_3·THF, THF; (l) H_2, Pd/C, aq HCl, MeOH.

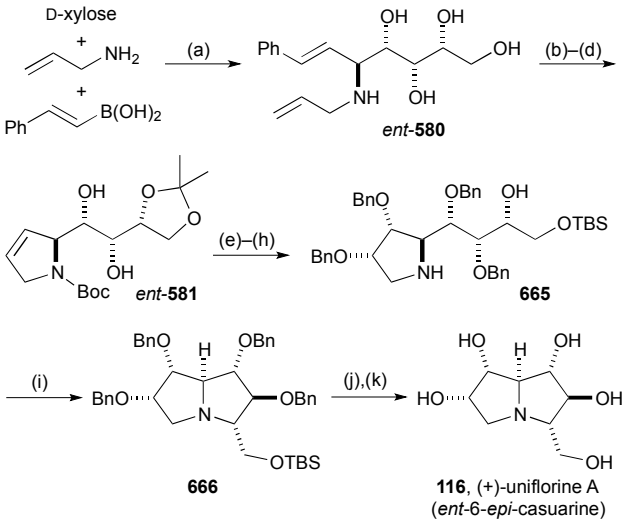
An equivalent approach was used to prepare (–)-*ent*-7-deoxycasuarine (**120**) and its 6-epimer from nitrone **402** (from D-xylose) (Scheme 110).[215] Following the nitrone cycloaddition (→ **657**), the pyrrolizidine ring-system was completed by ester reduction and mesylation of the so-formed 1°-alcohol 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.



Scheme 110 Reagents and conditions: (a) CH_2=$CHCO_2Me$, THF (dr = 80:20); (b) DIBAL, THF, –10 °C to rt; (c) MsCl, Et_3N, CH_2Cl_2; (d) Zn, aq AcOH; (e) H_2, Pd/C, aq HCl, MeOH then Dowex 50WX8.

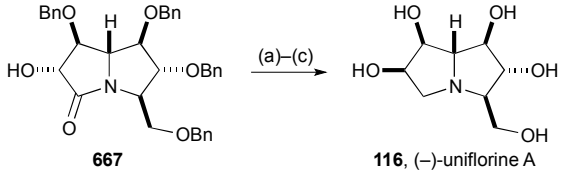
Uniflorines

Pyne's group proposed revised structures for the uniflorines and then effected a total synthesis of uniflorine A in confirmation of these new structures.[70] 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 (*E*)-styrene boronic acid gave tetraol *ent*-**580** (*cf*. Scheme 93) which was protected, and cyclised using ring-closing metathesis. Subsequent dihydroxylation *anti*- to the pyrroline substituent provided a single diastereomer; protecting group manipulation (→ **665**) and *N*-cyclisation under Mitsunobu conditions gave pyrrolizidine **666**. Two-stage global deprotection 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 L-xylose to produce the natural enantiomer, (–)-uniflorine.[196]



Scheme 111 Reagents and conditions: (a) EtOH; (b) Boc_2O, Et_3N, MeOH; (c) $Me_2C(OMe)_2$, PPTS, acetone; (d) Grubbs' I, CH_2Cl_2, reflux; (e) $K_2OsO_4{\cdot}H_2O$, NMO, aq acetone; (f) NaH, BnBr, Bu_4NI, THF; (g) HCl, MeOH; (h) TBSCl, DMAP, Et_3N, CH_2Cl_2; (i) DIAD, PPh_3, pyridine; (j) HCl, MeOH; (k) H_2, $PdCl_2$, MeOH then ion exchange purification.

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).[214,216] The route was analogous to the casuarine synthesis with the exception that an inversion at C(6) was required (step a).

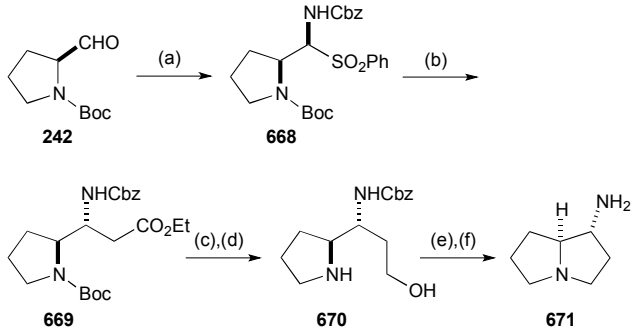


Scheme 112 Reagents and conditions: (a) BzOH, DIAD, THF; (b) $LiAlH_4$, THF, reflux; (c) H_2, Pd/C, aq HCl, MeOH then Dowex 50WX8.

A third synthesis of (–)-uniflorine A was summarised earlier (Scheme 81).[173]

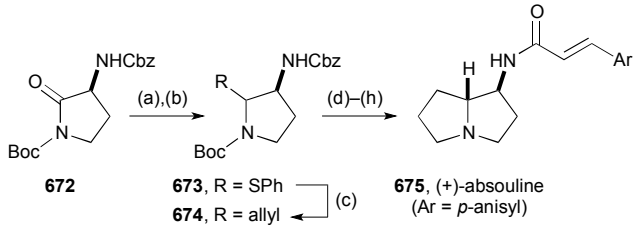
Aminopyrrolizidines

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**.[217] 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.



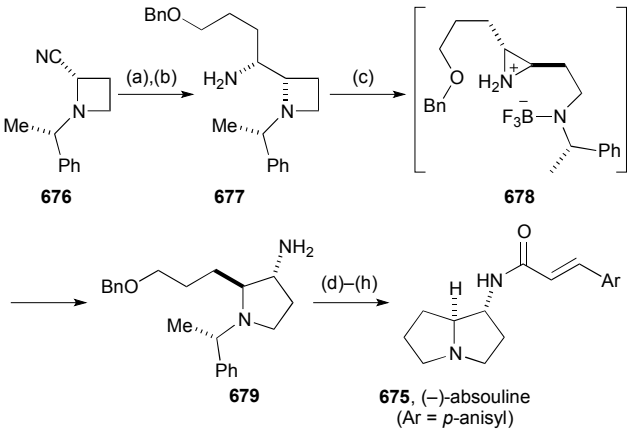
Scheme 113 Reagents and conditions: (a) $CbzNH_2$, $PhSO_2H$, $MgSO_4$, CH_2Cl_2; (b) EtOAc, LDA, THF, –78 °C; (c) $NaBH_4$, $CaCl_2$, EtOH-THF; (d) aq HCl, THF; (e) MsCl, Et_3N, CH_2Cl_2; (f) H_2, Pd/C, MeOH.

The first asymmetric synthesis of natural (+)-absouline was reported the following year.[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.



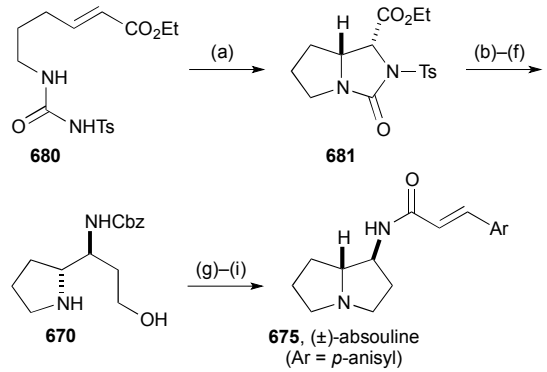
Scheme 114 Reagents and conditions: (a) $NaBH_4$, MeOH, –15 °C; (b) PhSH, TsOH, PPTS, CH_2Cl_2; (c) BuLi, Li-naphthalenide, $CH_2{=}CHCH_2I$, THF, –78 °C; (d) $BH_3{\cdot}SMe_2$, hexane, 30 °C then aq NaOH, H_2O_2; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C; (f) aq HCl, dioxane, then aq NaOH; (g) H_2, Pd/C, aq HCl; (h) $ArCH{=}CHCO_2H$, DCC, DMAP, CH_2Cl_2.

A synthesis of the non-natural enantiomer, (–)-absouline, was reported towards the end of the same year.[219] Here, (*S*)-α-methylbenzylamine served as the source of chirality via cyanoazetidine **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*-aminopyrrolidine **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.



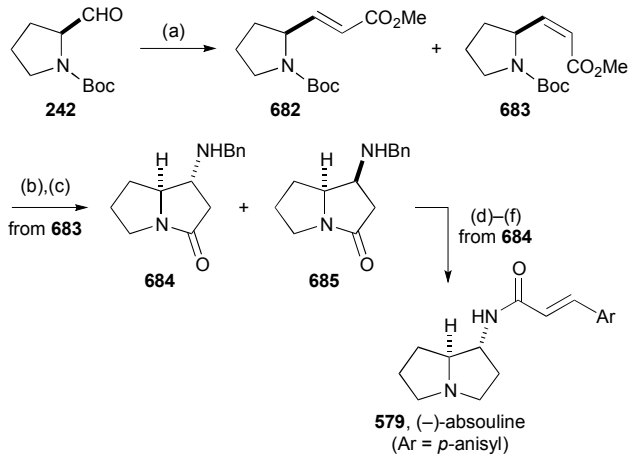
Scheme 115 Reagents and conditions: (a) $Li(CH_2)_3OBn$, $Et_2O/PhCH_3$; (b) $NaBH_4$, MeOH; (c) $BF_3{\cdot}OEt_2$, CH_3CN, reflux; (d) Boc_2O, EtOAc; (e) H_2, Pd/C, MeOH; (f) PPh_3, CCl_4, Et_3N, DMF; (g) CF_3CO_2H, CH_2Cl_2, 0 °C; (h) $ArCH{=}CHCO_2H$, DCC, DMAP, CH_2Cl_2, 0 °C.

Muñiz applied intramolecular oxidative diamination methodology to a synthesis of (±)-absouline.[220] The substrate for the key reaction, *N*-sulfonyl urea derivative **680** (Scheme 116), was prepared in three steps from pent-4-enenitrile. Following Pd(II)-mediated diamination (step a), the carboxyl group was homologated and reduced; the tosyl group was then removed by ethanolysis, and the urea cleaved under acidic conditions to generate intermediate **670**. This pyrrolidine was taken on to the racemic natural product using known chemistry (see above, Scheme 113).



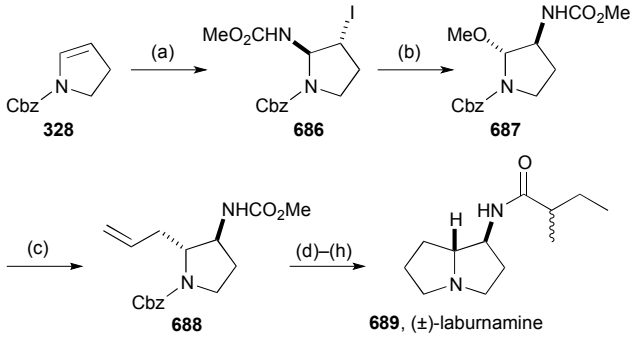
Scheme 116 Reagents and conditions: (a) $Pd(OAc)_2$, $CuBr_2$, Na_3PO_4, DMF, 40 °C; (b) NaOMe, aq MeOH; (c) Arndt–Eistert homologation; (d) $BH_3{\cdot}SMe_2$, THF; (e) $Mg(OEt)_2$, EtOH, 65 °C then CF_3CO_2H, CH_2Cl_2; (f) CbzCl, Et_3N, CH_2Cl_2; (g) MsCl, Et_3N, CH_2Cl_2; (h) H_2, Pd/C, MeOH; (i) $ArCH{=}CHCO_2H$, DCC, DMAP, CH_2Cl_2.

The most recent synthesis of absouline exemplifies a general approach to aminopyrrolizidine synthesis based on conjugate amination of proline-derived unsaturated esters.[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.



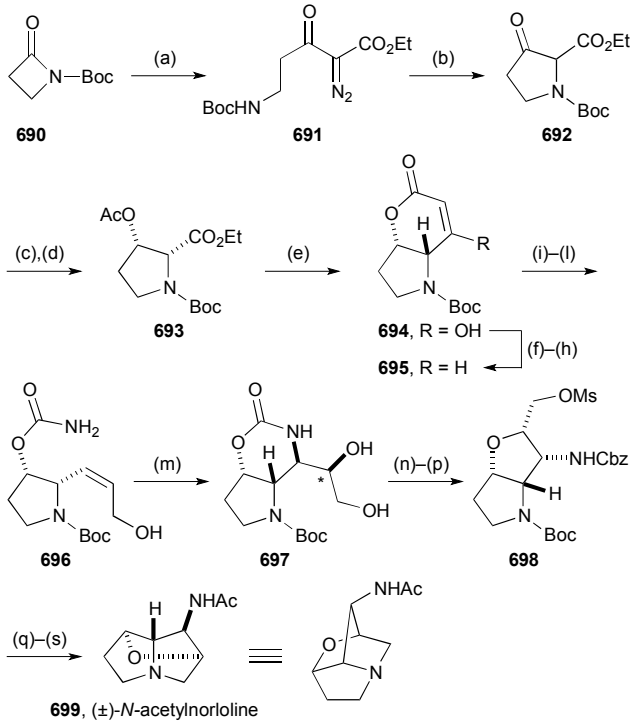
Scheme 117 Reagents and conditions: (a) $(MeO)_2POCH_2CO_2Me$, LiCl, *i*-Pr_2NEt, CH_3CN; (b) $BnNH_2$, EtOH, 80 °C; (c) CF_3CO_2H, Me_2S, CH_2Cl_2 then Et_3N, EtOH; (d) $BH_3{\cdot}SMe_2$, THF, 66 °C; (e) H_2, Pd/C, MeOH, HCl; (f) $ArCH{=}CHCO_2H$, DCC, DMAP, CH_2Cl_2.

1-Aminopyrrolizidine **671** was also an intermediate in the only synthesis of laburnamine (**689**, Scheme 118) to be reported during this period.[222] Iodocarbamation of 1-pyrroline 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*-acyliminium 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 absouline) to deliver (±)-laburnamine.



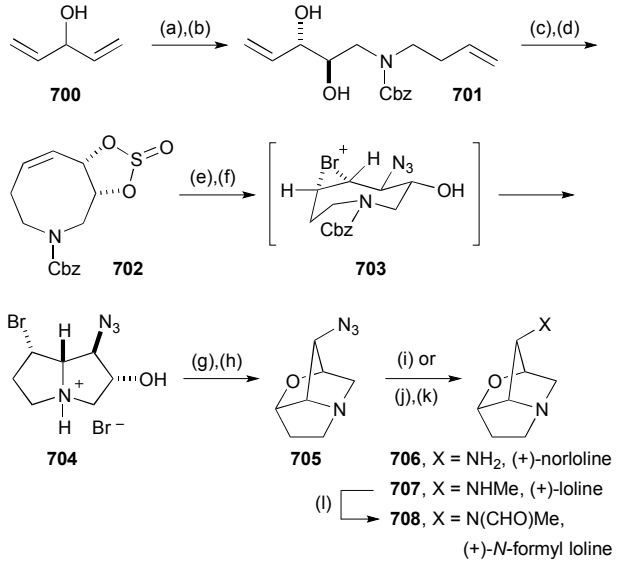
Scheme 118 Reagents and conditions: (a) $MeOCONH_2$, I_2, THF, –78 °C; (b) NaHMDS, MeOH, THF, –78 °C; (c) $CH_2{=}CHCH_2SiMe_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (d) $BH_3{\cdot}SMe_2$, THF then aq NaOH, H_2O_2, 40 °C; (e) TsCl, pyridine, $CHCl_3$; (f) H_2, Pd/C, EtOH; (g) TMSI, $CHCl_3$, 60 °C then MeOH; (h) (±)-2-methylbutyryl chloride, Et_3N, THF.

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.[1] More recently, a synthesis of another member of the loline class of alkaloids, (±)-*N*-acetylnorloline (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 $A^{1,3}$-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 pyrrolidine ring, then deprotection and acetylation completed the synthesis.



Scheme 119 Reagents and conditions: (a) $N_2{=}CHCO_2Et$, LHMDS, THF, –78 °C; (b) $Rh_2(OAc)_4$, $PhCH_3$, 90 °C; (c) $NaBH_4$, MeOH; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (e) LHMDS, THF, –78 °C to –20 °C; (f) *t*-$BuNH_2{\cdot}BH_3$, citric acid, MeOH, 0 °C; (g) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (h) DBU, CH_2Cl_2; (i) LiOH, aq THF; (j) MeI, K_2CO_3, DMF; (k) $Cl_3CCONCO$, CH_2Cl_2, 0 °C then $NaHCO_3$, MeOH; (l) DIBAL, CH_2Cl_2, –78 °C; (m) K_2OsO_4, *t*-BuOCl, NaOH, aq. PrOH; (n) MsCl, pyridine; (o) CbzCl, Et_3N, THF; (p) Cs_2CO_3, MeOH; (q) CF_3CO_2H, CH_2Cl_2, 0 °C then Et_3N, MeOH; (r) H_2, Pd/C, MeOH, EtOAc; (s) Ac_2O, $CHCl_3$.

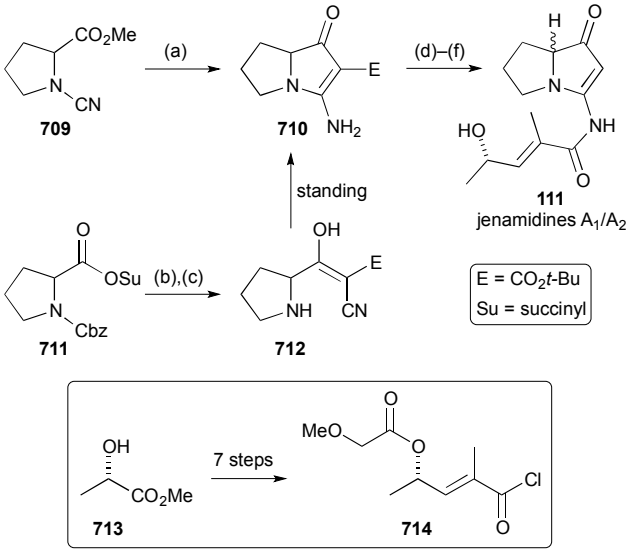
Soon after this synthesis appeared, Trauner reported an efficient eight-step route to azide **705** (Scheme 120) which was then converted into the natural products (+)-loline, (+)-*N*-formyl loline, and temuline ((+)-norloline).[225] The synthesis began with Sharpless asymmetric epoxidation of divinyl carbinol (**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 stereoselective 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 Boc_2O, and reduction of the carbamate gave loline and then *N*-formylloline.



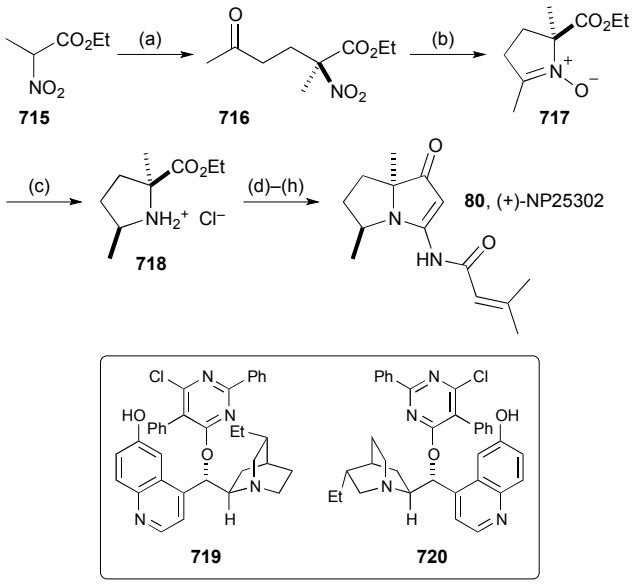
Scheme 120 Reagents and conditions: (a) *t*-BuOOH, Ti(O*i*-Pr)$_4$, L-(+)-DIPT, CH_2Cl_2, –25 °C; (b) CH_2=$CH(CH_2)_2NH_3^+Cl^-$, *i*-Pr_2NEt, MeOH, 45 °C then CbzCl, aq Na_2CO_3; (c) Grubbs' II, CH_2Cl_2, 45 °C; (d) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C; (e) LiN_3, DMF, 130 °C; (f) Br_2, MeOH, 0 °C; (g) LiCl, DMF, 105 °C then aq NaOH; (h) K_2CO_3, MeOH, 150 °C (microwave); (i) H_2, Pd/C, MeOH; (j) H_2, Pd/C, Boc_2O, THF; (k) $LiAlH_4$, THF, reflux; (l) AcNHCHO (from HCO_2H and Ac_2O).

Following Snider's revision of the structures of jenamidines A and B (**111** and **112**),[67] the same group completed a short synthesis of jenamidines A_1/A_2[226] from the reduced 3-aminopyrrolizin-1-one **710** (Scheme 121) for which two synthetic routes were devised.[52,68] In the first route, cyanamide **709** (obtained in two steps from proline) was subjected to crossed Claisen condensation with the lithium enolate of *t*-butyl acetate. 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*-butyl cyanoacetate, 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 methoxyacetate 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*-butyl 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 (4*S*,7*S*)-isomer shown.[52] 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**.

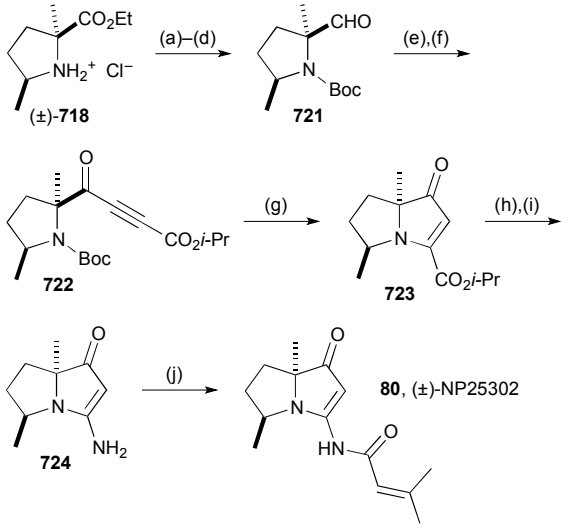


Scheme 121 Reagents and conditions: (a) *t*-BuOAc/LDA, THF, –45 °C then LHMDS; (b) NaH/*t*-butyl cyanoacetate, C_6H_6; (c) H_2, Pd/C, MeOH; (d) NaH, **714**, THF; (e) CF_3CO_2H, CH_2Cl_2, 0 °C; (f) Na_2CO_3, MeOH, 0 °C.



Scheme 122 Reagents and conditions: (a) MVK, **720**, CH_2Cl_2, –20 °C; (b) H_2 (1 atm), Pd/C, EtOH; (c) H_2 (3.3 atm), Pd/C, aq HCl, EtOH; (d) BrCN, $NaHCO_3$, EtOH; (e) *t*-BuOAc/LDA, –45 °C to rt; (f) *t*-BuOK, *t*-BuOH, 135 °C; (g) NaH, 3-methylbut-2-enoyl chloride, THF; (h) CF_3CO_2H, CH_2Cl_2.

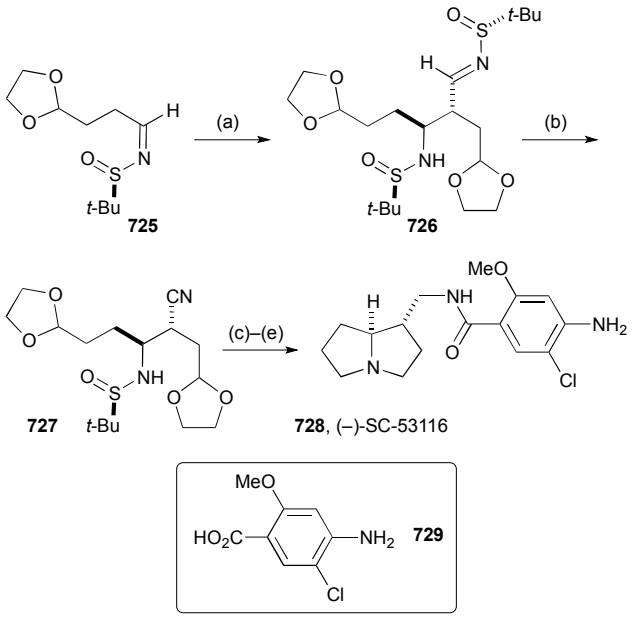
A second synthesis of NP25302 followed from the same dimethylproline derivative **718**.[227] Key steps in this route included addition of lithiated isopropyl propiolate to aldehyde **721** (Scheme 123), 5-*endo*-*dig* cyclisation to form the second ring (**722** → **723**), and Curtius rearrangement (step i) to install the vinylogous urea functionality present in the natural product.



Scheme 123 Reagents and conditions: (a) Boc_2O, DMAP, CH_3CN; (b) LiOH, aq MeOH; (c) BH_3·THF, THF; (d) Dess–Martin periodinane, CH_2Cl_2, 0 °C; (e) LiC≡CCO_2i-Pr, THF, –40 °C to 0 °C; (f) Dess–Martin periodinane, CH_2Cl_2; (g) TMSOTf, CH_2Cl_2, –30 °C then aq $NaHCO_3$; (h) KOH, aq CH_3CN then $(PhO)_2PON_3$, DMF, 0 °C; (i) aq AcOH, reflux; (j) NaH, 3-methylbut-2-enoyl chloride, THF.

SC-53116

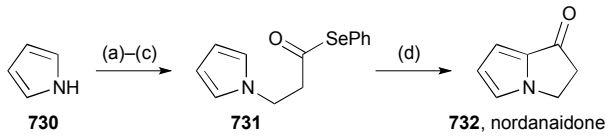
An unexpected self-condensation side-reaction, observed during the attempted metallation and alkylation of *N*-sulfinyl aldimines, was applied to the synthesis of SC-53116 (**728**, Scheme 124), a synthetic serotonin 5-HT_4 antagonist.[228] Various conditions for this reaction were surveyed, and a combination 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**.



Scheme 124 Reagents and conditions: (a) LHMDS, DMPU, THF, −48 °C; (b) 150 °C (microwave), CH_3CN; (c) BH_3·SMe_2, THF, reflux; (d) **729**, DCC, HOBt, DMF; (e) H_2, PtO_2, CF_3CO_2H, aq EtOH.

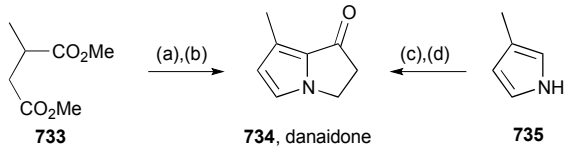
Danaidone and nordanaidone

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.[229]



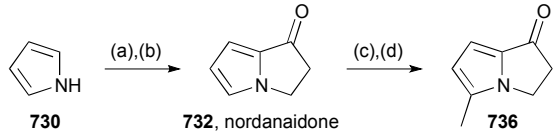
Scheme 125 Reagents and conditions: (a) NaH, DMF then $Br(CH_2)_2CO_2Me$, 0 °C to rt; (b) LiOH, aq EtOH; (c) PhSeSePh, PBu_3, CH_2Cl_2; (d) Bu_3SnH, AIBN, cyclohexane, reflux.

In the first of two routes to danaidone, dimethyl methylsuccinate (**733**, Scheme 104) was reduced and the dialdehyde trapped directly with β-alanine ethyl ester. Intramolecular Friedel–Crafts acylation proved regioselective in favour of the desired regioisomer. In this work, the obtained danaidone was further elaborated to bifunctional alkylating agents for cross-linking DNA.[230] The second synthesis of danaidone served as an extension of the authors' methodology for hydroalkoxylation of activated alkenes.[231] Conjugate addition of 3-methylpyrrole (**735**) to acrylonitrile was effected with DBU as catalyst then Friedel–Crafts acylation as before completed the route.



Scheme 126 Reagents and conditions: (a) DIBAL, CH_2Cl_2, –78 °C then β-alanine ethyl ester hydrochloride; (b) BBr_3, CH_2Cl_2, 0 °C; (c) acrylonitrile, DBU then HCl(g), $ZnCl_2$, Et_2O; (d) aq Na_2CO_3.

An equivalent route was employed more recently in the synthesis of nordanaidone and a danaidone regioisomer (**736**, Scheme 127).[232]



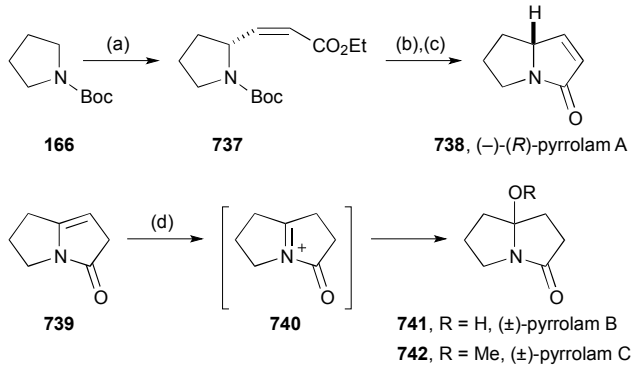
Scheme 127 Reagents and conditions: (a) acrylonitrile, Triton B, H_2O, 12 °C; (b) $AlCl_3$, KCl, NaCl, 130 °C then H_2O, 0 °C to 90 °C; (c) NBS, THF, –50 °C to –10 °C; (d) $MeB(OH)_2$, $Pd(OAc)_2$, RuPhos, Cs_2CO_3, aq $PhCH_3$, 130 °C.

Pyrrolams

The synthesis and biological activity of pyrrolams A–D were reviewed recently.[233]

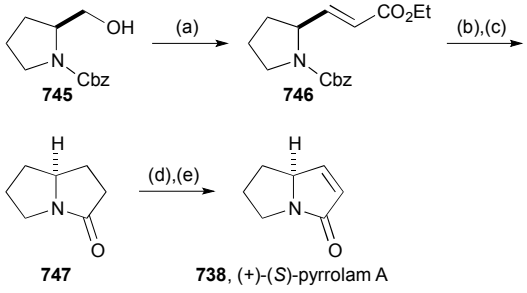
In 2004, an asymmetric synthesis of (*R*)-pyrrolam A was reported based on asymmetric deprotonation of *N*-Boc pyrrolidine **166** (Scheme 128) and coupling with ethyl (*Z*)-3-iodoacrylate.[234] The conditions for *N*-deprotection and

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 salt (corresponding to pyrrolidine **737** lacking the Boc group) to a rapidly-stirred saturated solution of $NaHCO_3$ 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 (**744**), often isolated in conjunction with pyrrolam A, are most probably artefacts rather than naturally-occurring metabolites.



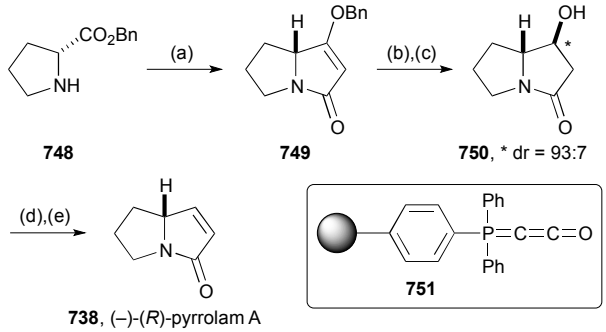
Scheme 128 Reagents and conditions: (a) *s*-BuLi, (−)-sparteine, CuCN·2LiCl, (*Z*)-ICH=CHCO$_2$Et, Et$_2$O, THF, −78 °C to rt; (b) TMSCl, MeOH; (c) dissolve in CH_2Cl_2 then add to aq $NaHCO_3$; (d) EtOAc, wet SiO_2, EtOAc (→ **741**) then MeOH, dry SiO_2 (→ **742**).

A telescoped oxidation/in situ Wittig sequence was used by Tilve to construct (*S*)-pyrrolam A from (*S*)-prolinol derivative **745** (Scheme 129).[235] 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.



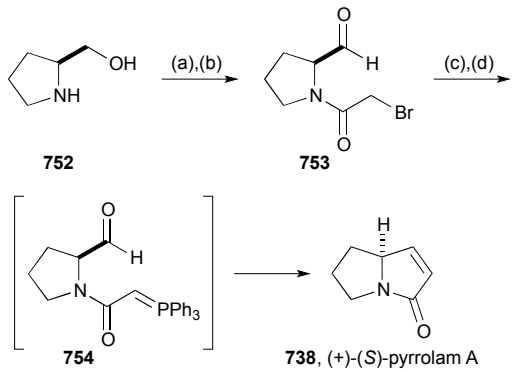
Scheme 129 Reagents and conditions: (a) PCC, NaOAc, Ph_3P=$CHCO_2Et$, CH_2Cl_2; (b) H_2, Pd/C, EtOH; (c) NaOEt, EtOH, reflux; (d) LDA, PhSeCl, THF, −78 °C; (e) H_2O_2, AcOH, aq THF, 0 °C to rt.

Wittig olefination was also used to contruct the same C(1)–C(2) bond in Schobert's synthesis of (*R*)-pyrrolam A.[236] Here, exposure of benzyl (*R*)-prolinate (**748**, Scheme 130) to solid-supported cumulated ketene-ylid **751** produced 1-benzyloxypyrrolam 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) H_2, Pd/C, MeOH; (c) $NaBH_4$, AcOH, CH_2Cl_2, 0 °C; (d) MsCl, Et_3N, CH_2Cl_2; (e) Et_3N, CH_2Cl_2, reflux.

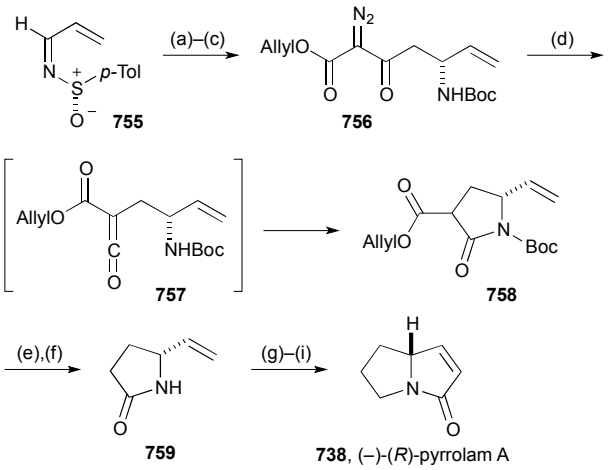
A related intramolecular Wittig olefination strategy was used in Tilve's second synthesis of (*S*)-pyrrolam A.[237] The phosphonium salt generated from bromoacetamide **753** (Scheme 131) was deprotonated to generate ylid **754** from which (*S*)-pyrrolam A followed. Unsurprisingly, separation of the 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) $BrCH_2COCl$, NaOAc, aq acetone, 0 °C to rt; (b) PCC, CH_2Cl_2; (c) PPh_3, C_6H_6; (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.[238] In order to avoid complications from the sulfinyl group, which

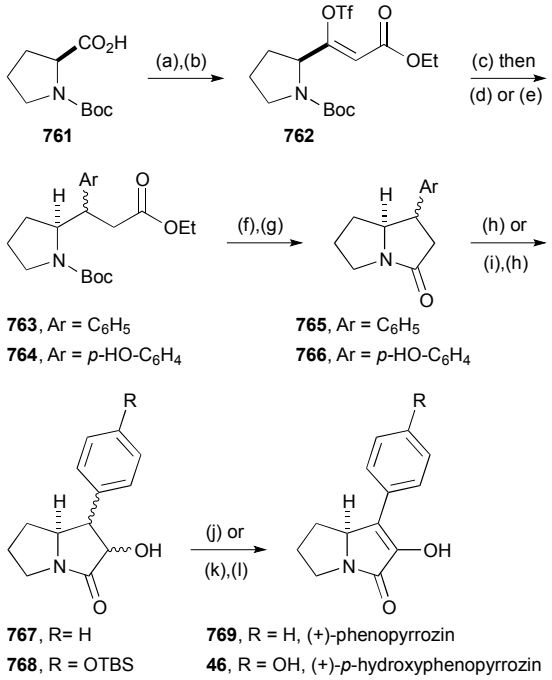
decomposes under the conditions for photochemical Wolff rearrangement (step d), the *N*-substituent was swapped to Boc (→ **756**). With this modification, rearrangement and ketene trapping via **757** proceeded reasonably efficiently. Palladium(0)-mediated deallylation and decarboxylation, followed 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), CH_2Cl_2, −78 °C; (b) CF_3CO_2H, MeOH, 0 °C; (c) Boc_2O, Et_3N, DMAP, THF, 0 °C; (d) hν (λ >300 nm), 500 W, C_6H_6, 35 °C; (e) $Pd(PPh_3)_4$, morpholine, THF; (f) CF_3CO_2H, CH_2Cl_2, 0 °C to rt; (g) $LiAlH_4$, THF, reflux; (h) CH_2=CHCOCl, K_2CO_3, aq EtOAc, 0 °C; (i) Grubbs' II, $PhCH_3$, 80 °C.

Hydroxyphenopyrrozin

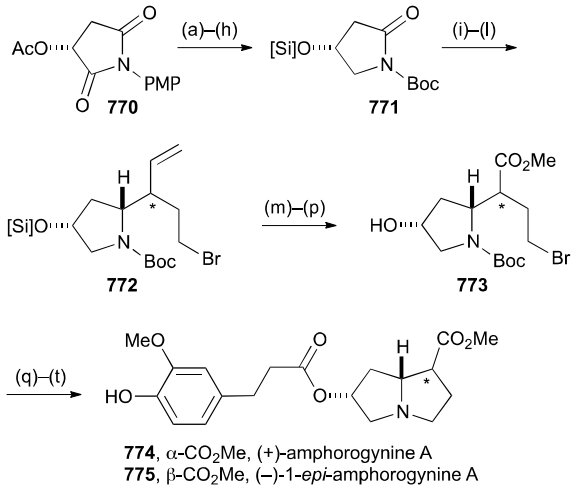
(+)-*p*-Hydroxyphenopyrrozin, recently isolated from three different fungi, was synthesised, along with (+)-phenopyrrozin (the non-natural enantiomer), from (*S*)-proline using Suzuki coupling to install the requisite aryl group.[239] Arylation of vinyl triflate **762** (Scheme 133) gave a mixture of both alkene geometries; therefore, the alkene was reduced to allow cyclisation of both isomers. The α-hydroxyl group was introduced *via* enolate oxidation with dissolved oxygen, with the intermediate peroxide being broken down using Na_2SO_3. In the case of the phenyl analogue **767**, further oxidation occurred upon standing to give (+)-phenopyrrozin directly, whereas the *p*-hydroxy analogue **768** required separate oxidation and deprotection steps to furnish (+)-*p*-hydroxyphenopyrrozin.



Scheme 133 Reagents and conditions: (a) CDI, THF, 0 °C to rt then $KO_2CCH_2CO_2Et$, $MgCl_2$, THF, 50 °C; (b) Tf_2O, Et_3N, THF, −65 °C to −40 °C; (c) $PhB(OH)_2$ or *p*-HO-C_6H_4-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, aq dioxane; (d) H_2, Pd-$BaSO_4$, EtOAc; (e) H_2, PtO_2, MeOH, EtOAc; (f) aq CF_3CO_2H, CH_2Cl_2; (g) aq NH_3, sealed tube, 75 °C; (h) LDA, O_2, $P(OMe)_3$, HMPA, THF, −75 °C to –65 °C; (i) TBSCl, $AgNO_3$, pyridine, THF; (j) for **767**: upon standing; (k) for **768**: $RuCl_3$, $NaIO_4$, aq CCl_4, MeCN; (l) TBAF, THF, −40 °C.

Amphorogynines

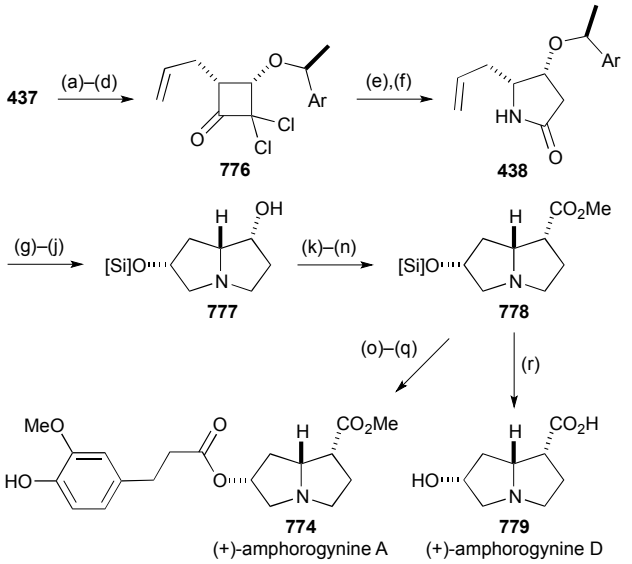
The amphorogynines from *Amphorogyne spicata* have an unusual 1,6-disposition of ester and oxy- functionality, accessed in the first total synthesis of amphorogynine A (Scheme 134), from D-(+)-malic acid, in confirmation of the assigned structure.[240] The derived imide **770** was taken through an eight-step 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**.



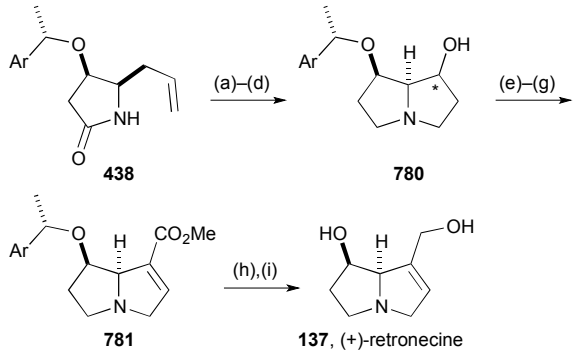
Scheme 134 Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C; (b) $BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, 0 °C; (c) K_2CO_3, MeOH; (d) BnBr, Ag_2O, DMF; (e) CAN, aq CH_3CN; (f) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C; (g) HCO_2H, Pd black, MeOH, 45 °C; (h) TBDPSCl, imidazole, CH_2Cl_2; (i) $NaBH_4$, MeOH, 0 °C; (j) $PMPO(CH_2)_2CH{=}CHCH_2SiMe_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C; (k) DDQ, aq CH_2Cl_2, 0 °C; (l) CBr_4, PPh_3, CH_2Cl_2; (m) OsO_4, NMO, aq acetone, 0 °C; (n) $NaIO_4$, aq Et_2O/THF; (o) Br_2, $NaHCO_3$, aq MeOH; (p) TBAF, THF, 0 °C; (q) 3-(*p*-benzyloxy-*m*-methoxyphenyl)propanoic acid, EDCI, DMAP, CH_2Cl_2, 0 °C; (r) $BF_3{\cdot}OEt_2$, CH_2Cl_2; (s) aq $NaHCO_3$; (t) H_2, Pd/C, EtOAc. [[Si] = TBDPS]

An overall slightly shorter synthesis of (+)-amphorogynine A was disclosed soon after and the approach was subsequently extended to (+)-amphorogynine D and (+)-retronecine.[241] The assembly of key intermediate lactam **438** (Scheme 135; also applied to the synthesis of (+)-hyacinthacines A_1 and B_1) began with the formation of the 1,2-dichloroethenyl ether of (*S*)-Stericol® (**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-dienol ether that, upon reaction with dichloroketene, afforded cyclobutanone **776**. 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°-alcohol as its tosylate allowed closure of the second ring (→ **777**). Oxidation, carbonylative cross-coupling of the derived enol triflate, and *exo*-face selective alkene reduction provided key intermediate pyrrolizidine **778**. Esterification and deprotection steps led to (+)-amphorogynine A; simple hydrolysis led to (+)-amphorogynine D.

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



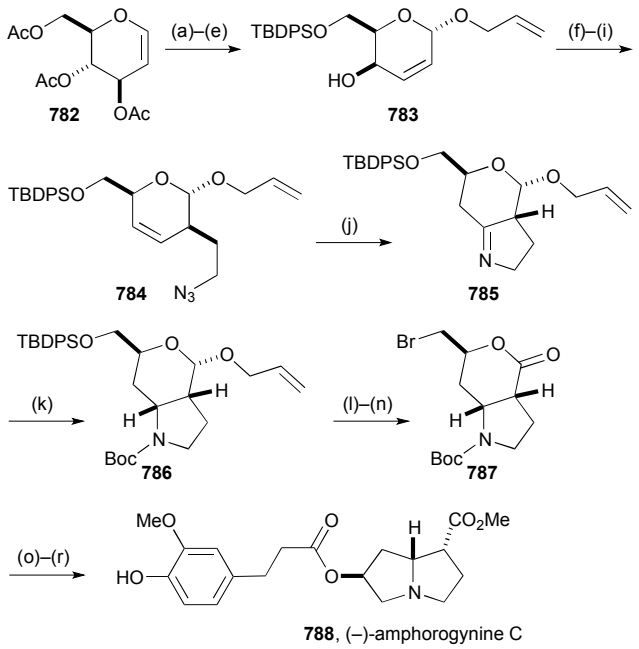
Scheme 135 Reagents and conditions: (a) KH, $Cl_2C{=}CHCl$, THF, –50 °C to rt; (b) BuLi, THF, –90 °C to –40 °C then allyl iodide, HMPA, 0 °C; (c) H_2, $Pd/BaSO_4$, $(CH_2NH_2)_2$, 1-hexene, DMF, 0 °C to rt; (d) Cl_3CCOCl, Zn(Cu), Et_2O; (e) $MesSO_2ONH_2$, CH_2Cl_2 then Al_2O_3, MeOH; (f) Zn(Cu), NH_4Cl, MeOH; (g) OsO_4, $Me_3N^+O^-$, aq *t*-BuOH; (h) Bu_2SnO, MeOH then TsCl, Et_3N; (i) TBDPSCl, imidazole, DMAP, DMF; (j) CF_3CO_2H, CH_2Cl_2; (k) Swern oxidation; (l) LHMDS, THF, –90 °C then *N*-(5-chloro-2-pyridyl)triflimide; (m) CO, $Pd(OAc)_2$, PPh_3, Et_3N, MeOH, DMF; (n) H_2, Pd/C, MeOH; (o) TBAF, THF; (p) 3-(*p*-TBSO-*m*-methoxyphenyl)propanoic acid, DIC, DMAP, CH_2Cl_2; (q) TBAF, THF; (r) aq HCl, dioxane. [Ar = 2,4,6-triisopropylphenyl; [Si] = TBDPS; Mes = mesityl (2,4,6-trimethylphenyl)]



Scheme 136 Reagents and conditions: (a) SeO_2, *t*-BuOOH, decane, DCE, reflux; (b) catecholborane, $Rh(PPh_3)_3Cl$, THF then NaOH, aq H_2O_2, 0 °C; (c) 2,4,6-(*i*-Pr)$_3C_6H_2SO_2Cl$, Et_3N, DMAP, pyridine, 0 °C to rt; (d) $BH_3{\cdot}SMe_2$, THF, reflux then Pd/C, Et_3N, MeOH (to decomplex the amine·borane); (e) Swern oxidation; (f) KHMDS, THF, –90 °C then *N*-(5-chloro-2-pyridyl)triflimide, –20 °C; (g) CO, $Pd(PPh_3)_4$, MeOH, DMF, 45 °C; (h) CF_3CO_2H, CH_2Cl_2, 0 °C; (i) DIBAL, CH_2Cl_2, –80 °C to –10 °C. [Ar = 2,4,6-triisopropylphenyl]

The 6-epimer of (+)-amphorogynine A, (–)-amphorogynine C (Scheme 137) was prepared for the first time recently.[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 acccompanied by loss of N_2 with [1,2]-H migration, giving bicyclic pyrroline **785**. Under the forcing conditions of the cycloaddition, imine epimerisation occurred giving the observed

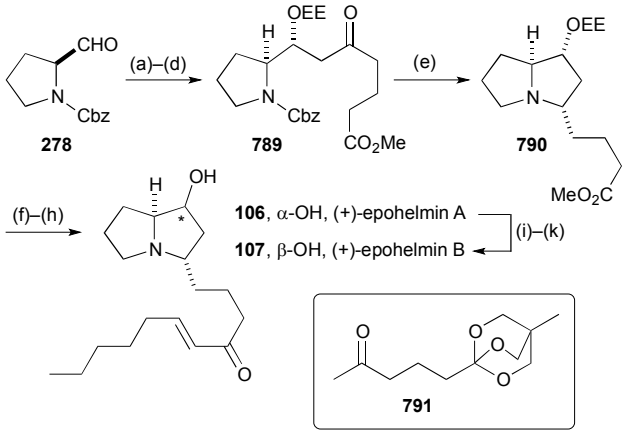
stereoisomer exclusively. The remainder of the synthesis required release of the lactol and its oxidation to the corresponding lactone, then desilylation and activation of the 1°-carbon by Appel reaction, giving bromolactone **787**. Upon deprotection of the amine, methanolysis of the lactone and *N*-cyclisation completed the pyrrolizidine core. The synthesis was completed by esterification followed by hydrogenolysis of the *O*-benzyl protecting group on the dihydroferulate side-chain.



Scheme 137 Reagents and conditions: (a) allyl alcohol, $FeCl_3$, CH_3CN *or* allyl alcohol, I_2, THF; (b) KOH, MeOH; (c) PPh_3, DIAD, $PhCO_2H$, THF; (d) NaOMe, MeOH; (e) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt; (f) $CH_3C(OMe)_3$, $EtCO_2H$, 140 °C; (g) $LiBH_4$, THF, MeOH, 0 °C to rt; (h) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt; (i) NaN_3, DMF, 60 °C; (j) $PhCH_3$, 140 °C; (k) $NaBH_4$, MeOH, 0 °C then Boc_2O, Et_3N, CH_2Cl_2, 0 °C to rt; (l) $PdCl_2$, aq THF; (m) CrO_3, H_2SO_4, $MgSO_4$, acetone, 0 °C to rt then TBAF, THF; (n) CBr_4, PPh_3, CH_2Cl_2, 0 °C to rt; (o) CF_3CO_2H, CH_2Cl_2; (p) NaOMe, MeOH; (q) 3-(*p*-benzyloxy-*m*-methoxyphenyl)propanoic acid, EDCI, DMAP, CH_2Cl_2; (r) H_2, Pd/C, EtOAc.

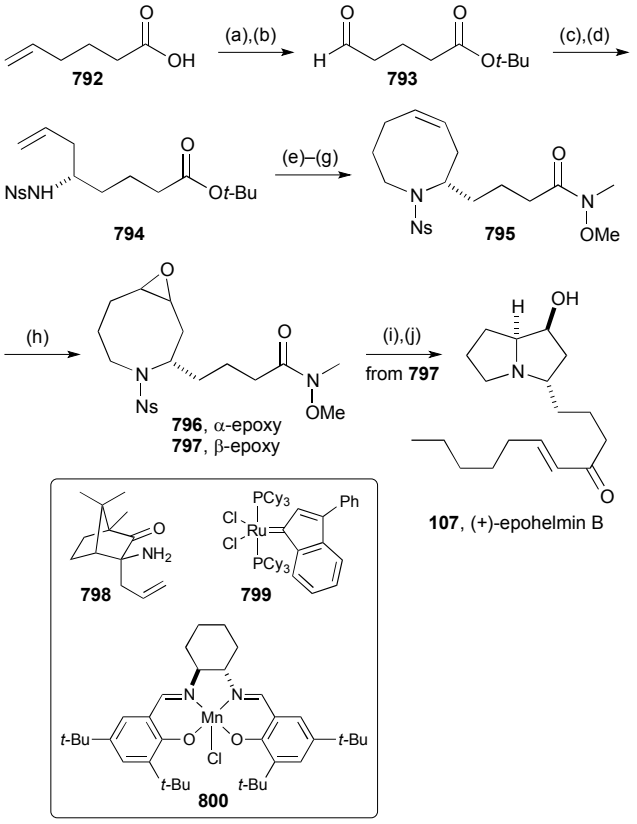
Epohelmins A and B

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 orthoester 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 stereocontrol 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.



Scheme 138 Reagents and conditions: (a) **791**, LDA, THF, –78 °C then **278**; (b) AcOH, aq THF; (c) K_2CO_3, MeOH; (d) $EtOCH{=}CH_2$, PPTS, CH_2Cl_2; (e) H_2, $Pd(OH)_2$, MeOH; (f) $(MeO)_2POCH_2Li$, 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, CH_2Cl_2.

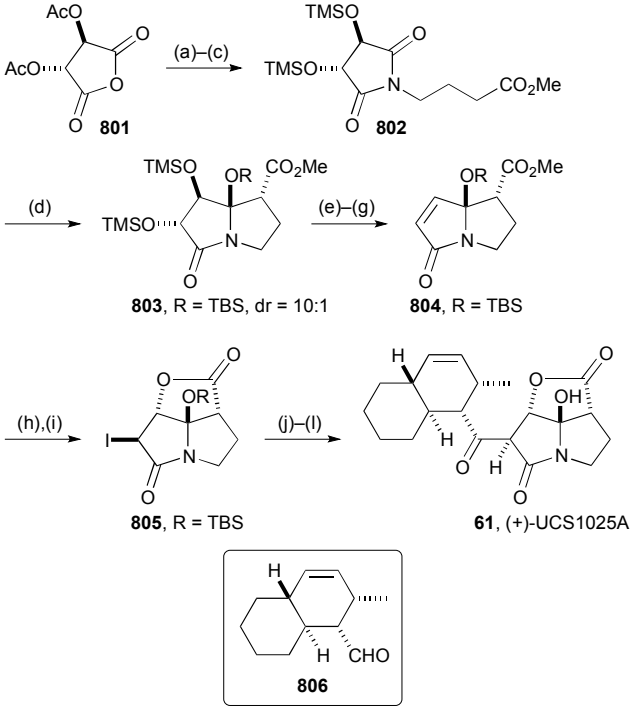
A more recent synthesis of (+)-epohelmin B was based on transannular cyclisation onto an azocane epoxide analogue of the structure originally-proposed for the epohelmins.[243] Absolute stereochemistry (ee = 94%) was established by azonia-Cope rearrangement of the imine formed from aldehyde **793** and 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 139 Reagents and conditions: (a) *t*-BuOH, DIC, DMAP, CH_2Cl_2; (b) O_3, CH_2Cl_2, –78 °C then Me_2S; (c) **798**, CSA, DCE, 0 °C then $NH_2OH{\cdot}AcOH$, MeOH, 50 °C; (d) NsCl, K_2CO_3, CH_2Cl_2, 0 °C to rt; (e) 5-bromo-1-pentene, K_2CO_3, DMF, 60 °C; (f) **799**, CH_2Cl_2; (g) CF_3CO_2H, CH_2Cl_2 then HN(OMe)Me·HCl, Et_3N, DCC, DMAP, CH_2Cl_2; (h) MCPBA, **800**, NMO, $AgPF_6$, CH_2Cl_2, –78 °C; (i) $HSCH_2CO_2H$, LiOH, DMF; (j) 1-iodo-1-heptene, *t*-BuLi, THF, –78 °C to –40 °C.

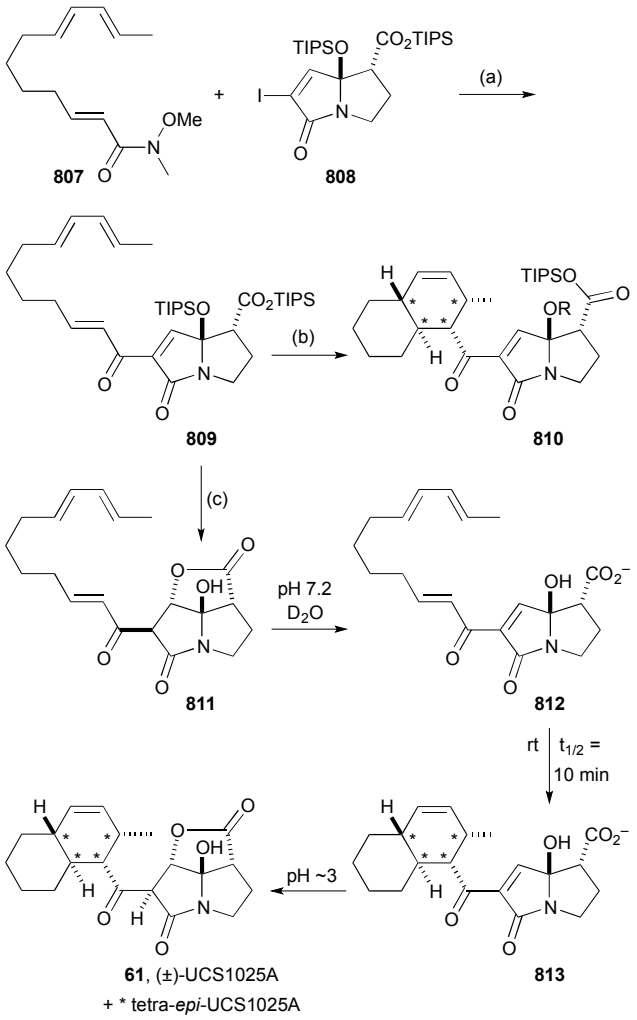
UCS1025A

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.[244] The successful route developed from chiral cyclic imide **802** (Scheme 140), obtained from L-(+)-tartaric acid. Intramolecular aldol-type addition under soft-enolisation conditions afforded adduct **803** in good yield and diastereoselectivity. Elimination of both trimethylsilyloxy groups was effected by desilylation, ditriflation 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 pyrrolizidinone **804**. Iodolactonisation then afforded iodide **805** that was coupled with aldehyde **806**, prepared using MacMillan's route.[245] The coupling reaction was described as a Reformatsky-type reaction 'which presumably passes through the intermediacy 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.



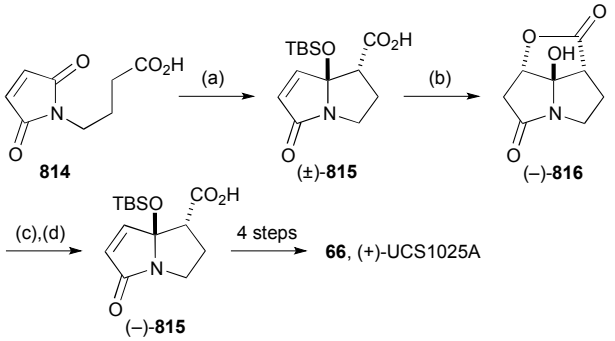
Scheme 140 Reagents and conditions: (a) $H_2N(CH_2)_3CO_2Me$, THF then AcCl, reflux; (b) AcCl, MeOH, 0 °C; (c) TMSCl, Et_3N, CH_2Cl_2; (d) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2, −78 °C to rt; (e) AcOH, HCl, aq THF; (f) Tf_2O, pyridine, CH_2Cl_2, −78 °C to rt then pyridine; (g) Bu_3SnH, $Pd(PPh_3)_4$, LiCl, THF, reflux; (h) $LiOH{\cdot}H_2O$, aq THF; (i) I_2, $NaHCO_3$, aq Et_2O, THF; (j) **806**, Et_3B, $PhCH_3$, –78 °C; (k) TBAF, THF, CH_2Cl_2; (l) Dess–Martin periodinane, CD_2Cl_2.

A proposed biomimetic synthesis of racemic UCS1025A was reported by Hoye and Dvornikovs soon after the Danishefsky paper.[246] 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 **807** (Scheme 141) with the Grignard reagent derived from iodopyrrolizidine **808**, 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 **811**, and was sensitive to the protecting groups present on the pyrrolizidine core. In all cases the cycloaddition showed no facial selectivity but the *exo*-/*endo*- preference was substrate controlled, with the *endo*- product dominating when the triene was linked to the pyrrolizidine core (triene **807** was shown to undergo cycloaddition only very slowly at 165 °C to give a 1:3 ratio of *endo*- and *exo*- adducts). Of most importance, it was found that the Diels–Alder reaction of the open carboxylate **812**, the major form of the compound under physiological conditions, was essentially spontaneous ($t_{1/2}$ 10 mins) and gave a 1:1 mixture of the natural product **61** and its tetraepimeric diastereomer (not shown).



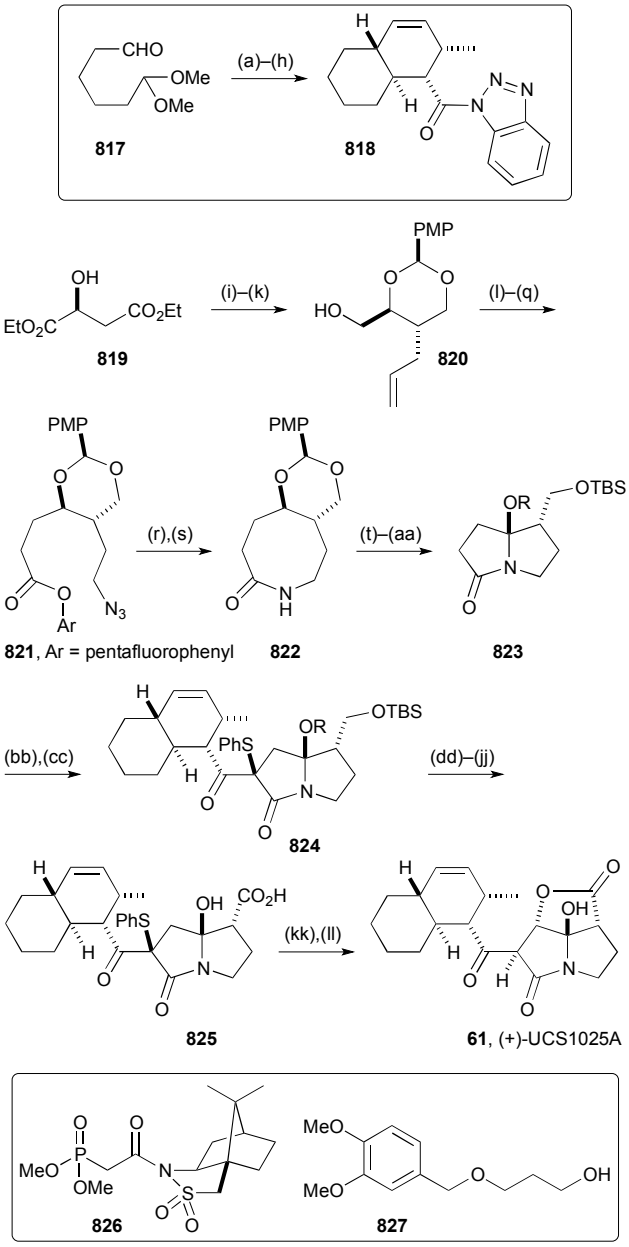
Scheme 141 Reagents and conditions: (a) *i*-PrMgCl, THF, Et_2O, −50 °C; (b) $CDCl_3$, 65 °C; (c) HF·pyridine, CH_3CN.

More recently, Christmann[247] demonstrated that racemic pyrrolizidine **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 (–)-**816** (≤ 62% ee), leaving **815** enriched in the (+)-enantiomer. Enantiomerically enriched (–)-**815** was then obtained from the lactone by β-elimination with DBU. The enantiopurity of (–)-**815** was then improved to 98.2% by trituration with pentane and this material was taken forward to give (+)-UCS1025A using Danishefsky's route.



Scheme 142 Reagents and conditions: (a) TBSOTf, Et_3N, $CDCl_3$ then K_2CO_3, MeOH; (b) quinine, CD_2Cl_2; (c) DBU; (d) triturate into hot pentane.

By way of contrast with the Christmann synthesis, the most recent synthesis of (+)-UCS1025A was lengthy at ~30 steps by the longest linear route.[248] The use of ethyl (*S*)-malate as starting material necessitated both chain-lenthening and chain-shortening steps to assemble the two arms of lactam precursor **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 **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 TBDPS 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 -CH_2OBz 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 **823** that was united with activated acid **818** and sulfenylated (→ **824**). A seven-step sequence was necessary to deprotect the bridgehead hydroxyl and convert the silyl ether into carboxylic acid **825**. Finally, oxidation of the sulfide and thermal elimination of the so-formed sulfoxide gave (+)-UCS1025A under the mildly-basic conditions of the thermolysis.

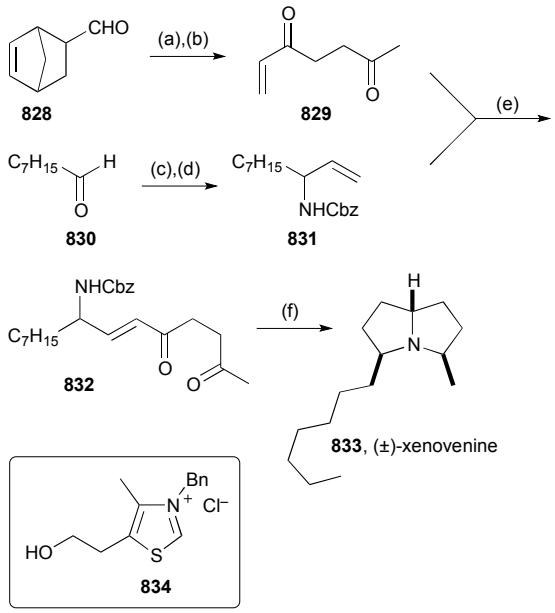


Scheme 143 Reagents and conditions: (a) (*E*-but-2-enyl)triphenylphosphonium bromide, LHMDS, THF; (b) aq HCl, THF; (c) **826**, Et_3N, LiCl, CH_3CN (dr = 1:1); (d) PhSSPh, THF, 90 °C (dr = 5:1 in favour of *E*-); (e) $EtAlCl_2$, CH_2Cl_2, 0 °C; (f) $LiAlH_4$, THF, 0 °C; (g) CrO_3, H_2SO_4, acetone, 0 °C; (h) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C then benzotriazole, Et_3N, 0 °C; (i) LDA, THF, –78 °C to –20 °C then allyl bromide, –78 °C to 0 °C (dr = 13:1); (j) $LiAlH_4$, THF, 50 °C; (k) *p*-$MeOC_6H_4CH(OMe)_2$, (+)-CSA, DMF; (l) IBX, 4Å MS, $Ph_3P{=}CHCO_2Me$, CH_2Cl_2; (m) O_3, MeOH, CH_2Cl_2, –78 °C then $NaBH_4$, –78 °C to 0 °C; (n) $NaBH_4$, $NiCl_2$, MeOH, 0 °C to rt; (o) $(PhO)_2PO.N_3$, DBU, $PhCH_3$, 80 °C; (p) $LiOH{\cdot}H_2O$, aq MeOH; (q) pentafluorophenol, EDCI, DMAP, CH_2Cl_2; (r) PBu_3, $PhCH_3$, 80 °C; (s) aq CH_3CN, reflux; (t) H_2, $Pd(OH)_2/C$, MeOH; (u) TBDPSCl, *i*-Pr_2NEt, *i*-PrOH, CH_2Cl_2; (v) TPAP, NMO, CH_2Cl_2; (w) TBAF, THF; (x) $(PhCO)_2O$, Et_3N, CH_3CN; (y) **827** (= ROH), (+)-CSA, $PhCH_3$ then Ac_2O, pyridine; (z) $LiOH{\cdot}H_2O$, MeOH; (aa) TBSCl, imidazole, CH_2Cl_2; (bb) LHMDS, **818**, THF, 0 °C; (cc) NaHMDS, PhSCl, THF, 0 °C; (dd) TBAF, AcOH, THF; (ee) 1-methyl-2-azaadamantane *N*-oxyl, $PhI(OAc)_2$, pH 7.2 phosphate buffer, CH_2Cl_2, 0 °C; (ff) K_2CO_3, allyl bromide, acetone; (gg) DDQ, aq CH_2Cl_2; (hh) Dess–Martin periodinane, CH_2Cl_2; (ii) pyrrolidine, AcOH, CH_2Cl_2; (jj) $Pd(PPh_3)_4$, CH_3CN; (kk) DMDO, CH_2Cl_2, 0 °C; (ll) $CaCO_3$, $PhCH_3$, 70 °C.

Xenovenine and related dialkyl pyrrolizidines

Xenovenine, also known as alkaloid 223H′, 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.

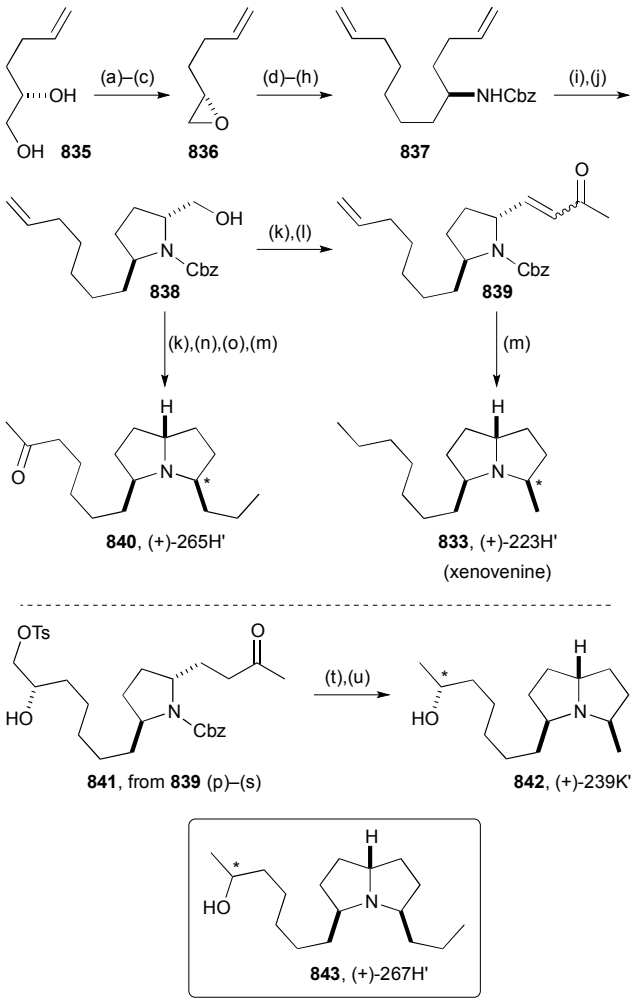
Blechert applied his group's sequential cross metathesis/reductive cyclisation methodology to a short synthesis of (±)-xenovenine (Scheme 144), in part to confirm the stereochemical course of the final imine reduction steps.[152] Alkenes **829**[249] and **831**,[250] prepared as shown, were coupled using the Hoveyda–Grubbs 2nd generation catalyst since this phosphine-free catalyst enabled approximately equimolar ratios of the two alkenes to be used. Following cross metathesis (→ **832**), alkene hydrogenation, *N*-deprotection, and double reductive amination were all effected within the same reaction to generate the racemic natural product.



Scheme 144 Reagents and conditions: (a) MVK, **834**, Et_3N, 65 °C; (b) FVP, 500 °C, 10 Torr; (c) $CbzNH_2$, $PhSO_2Na$, HCO_2H, aq THF; (d) vinylmagnesium bromide, THF, −20 °C; (e) Hoveyda–Grubbs' II (Hoveyda–Blechert catalyst), CH_2Cl_2, 40 °C; (f) H_2, Pd/C, MeOH.

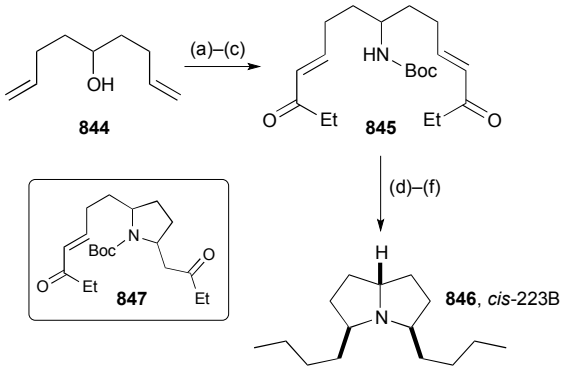
Takahata's group described syntheses of a group of related alkaloids previously shown to be present in certain Madagascan frogs (*Mantella* spp.).[251] The key intermediate in these syntheses, **838** (Scheme 145), was obtained from 1,5-hexadiene in eleven steps with the stereochemistry introduced at the outset by Sharpless asymmetric dihydroxylation (70% ee). Elaboration to epoxide **836**, Cu(I)-mediated ring-opening with a 5-hexenyl Grignard reagent, then introduction of the nitrogen via the azide led to carbamate **837**. Overall aminohydroxylation of the butenyl alkene, giving **838**, was achieved by acetoxymercuration and oxidative cleavage of the so-formed organomercurial; no *cis*-diastereomer was observed in this process. The first alkaloid 223H′ (xenovenine) was then obtained from pyrrolidine **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 pyrrolizidines 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). Pyrrolizidines 239K′ and 267H′ were reportedly isolated as epimeric mixtures at the hydroxylated carbon; therefore, the authors prepared both epimers in each series by appropriate choice of AD-mix reagent for asymmetric dihydroxylation of the heptenyl side-chain. For example, (6′*R*)-239K′ (**842**) required AD-mix-α; the hydroxyl groups were differentiated by selective 1°-sulphonation of a stannylene acetal, with Super Hydride-mediated reduction of the tosylate forming the final step in the route. The cyclisation by reductive amination in this sequence was apparently fully stereoselective, with no *trans*-isomer reported. (6′*S*)-239K′ was prepared using an analogous sequence featuring AD-mix-β, and the propyl versions (6′*R*)- and (6′*S*)-267H′ were obtained similarly. These alkaloids, and their enantiomers (prepared from *ent*-**835**, 80% ee), were evaluated for their affinity for nAChR of *Torpedo californica* electric organ; the enantiomers of alkaloid 223H′ (xenovenine) proved particularly active, with *K*i values of 0.067 and 0.050 μM for **833** and *ent*-**833**, respectively.



Scheme 145 Reagents and conditions: (a) $(MeO)_3CCH_3$, PPTS, CH_2Cl_2; (b) AcBr, Et_3N, CH_2Cl_2, 0 °C; (c) NaOH, MeOH, Et_2O; (d) 5-hexenyl-MgBr, CuI, THF, –40 °C; (e) MsCl, DMAP, pyridine, 0 °C to rt; (f) NaN_3, DMF, 45 °C; (g) $LiAlH_4$, THF, 0 °C; (h) CbzCl, aq NaOH, Et_2O, 0 °C; (i) $Hg(OAc)_2$, THF then aq $NaHCO_3$, aq KBr; (j) $NaBH_4$, O_2, DMF; (k) Swern oxidation; (l) dimethyl 2-oxopropylphosphonate, *i*-Pr_2NEt, LiCl, CH_3CN; (m) H_2, $Pd(OH)_2$, MeOH; (n) dimethyl 2-oxopentylphosphonate, *i*-Pr_2NEt, LiCl, CH_3CN; (o) O_2, $PdCl_2$, CuCl, aq DMF; (p) Red-Al, CuBr, 2-butanol, THF, –78 °C to –20 °C; (q) AD-mix-α, aq *t*-BuOH. 0 °C; (r) Bu_2SnO, $PhCH_3$, reflux; (s) TsCl, Et_3N; (t) H_2, $Pd(OH)_2$, MeOH; (u) Super Hydride, THF.

A single synthesis, and the first, of alkaloid *cis*-223B was 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 pyrrolidine **847** of unassigned relative configuration; however, under the conditions of the Boc-deprotection the products converged to a single pyrrolizidine stereoisomer, assigned by X-ray crystallographic analysis of a derivative. Mozingo-type deoxygenation of the carbonyl groups completed the route.

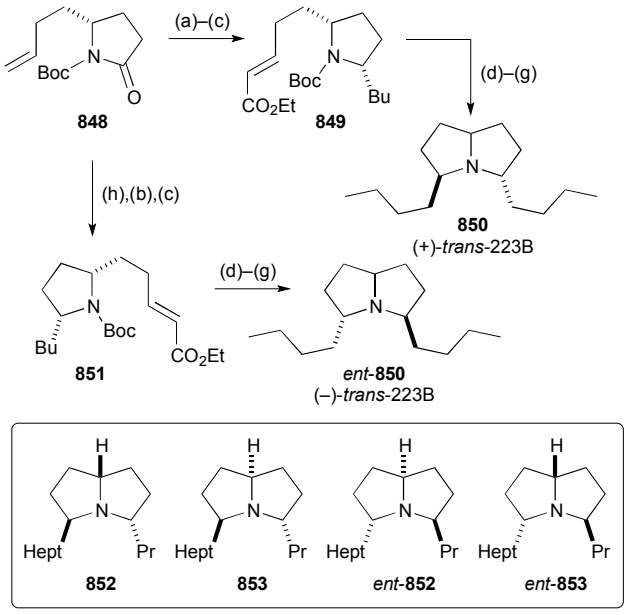


Scheme 146 Reagents and conditions: (a) SESNHBoc, DIAD, PPh_3, CH_2Cl_2; (b) CsF, CH_3CN, reflux; (c) ethyl vinyl ketone, Hoveyda–Grubbs' II (Hoveyda–Blechert catalyst), CH_2Cl_2; (d) CF_3CO_2H, CH_2Cl_2, 55 °C; (e) $HS(CH_2)_2SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (f) Raney Ni, EtOH, 80 °C.

γ-Lactam **848** (Scheme 147) is readily-available from (*S*)-pyroglutamic acid by reduction, activation, allylation, and *N*-Boc protection. This served as the starting point for an enantiodivergent synthesis of the enantiomers of the chiral diastereomer, *trans*-223B.[253] For the (+)-enantiomer, lactam ring-opening with BuMgBr and reductive amination set the stereochemistry (by pseudoaxial 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 *Melanophryniscus stelzneri*) since a chiral GC separation of the enantiomers was not achieved.

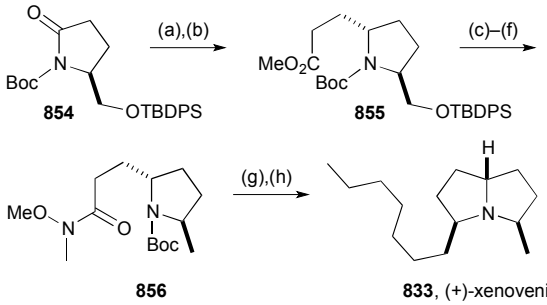
In the same paper, the authors disclosed the synthesis of four isomers—both enantiomers of pyrrolizidines **852** and **853**—as candidates for the structure of alkaloid 251O (found

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.



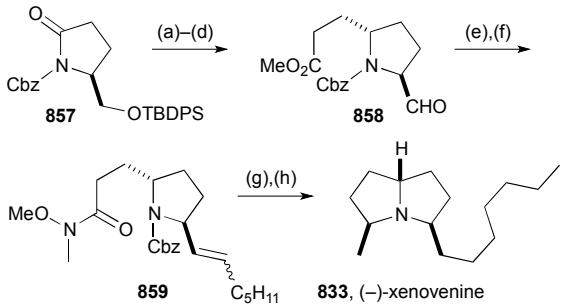
Scheme 147 Reagents and conditions: (a) BuMgBr, TMEDA, THF, –78 °C; (b) Ph_3SiH, $B(C_6F_5)_3$, CH_2Cl_2, –78 °C to rt; (c) ethyl acrylate, Grubbs' II, CH_2Cl_2, reflux; (d) $AlCl_3$, CH_2Cl_2 then K_2CO_3, CH_2Cl_2; (e) DIBAL, CH_2Cl_2, –50 °C; (f) $Ph_3P^+Et\ Br^-$, BuLi, THF, 0 °C to rt; (g) H_2, Pd/C, EtOAc; (h) H_2, Pd/C, EtOAc then 4-butenyl-MgBr, TMEDA, THF, –78 °C.

Huang's group developed a one-pot reductive coupling of *N*-acyl carbamates with activated alkenes and applied this to L-pyroglutamic acid derivative **854** (Scheme 148), obtaining pyrrolidine **855** with dr = 91:9 in favour of the 2,5-*trans* isomer.[254] Reduction of the primary alcohol generated the methyl substituent; then Grignard addition to the Weinreb amide **856** and a one-pot *N*-deprotection/imine reduction sequence provided (+)-xenovenine.



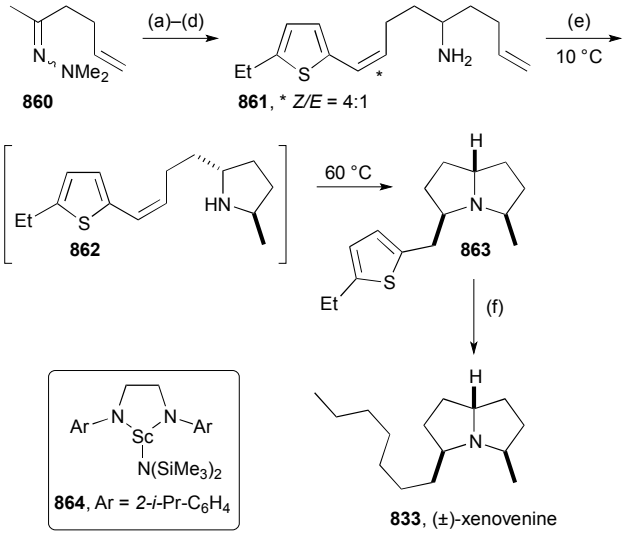
Scheme 148 Reagents and conditions: (a) DIBAL, THF, –78 °C; (b) methyl acrylate, SmI_2, $BF_3{\cdot}OEt_2$, *t*-BuOH, THF, –40 °C; (c) TBAF, THF; (d) I_2, PPh_3, imidazole, THF; (e) H_2, Pd/C, Et_3N, MeOH; (f) (MeO)NHMe·HCl, $AlMe_3$, CH_2Cl_2; (g) $C_7H_{15}MgBr$, THF, 50 °C; (h) HCl, EtOAc then NaOMe, MeOH then H_2, 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).[255]



Scheme 149 Reagents and conditions: (a) DIBAL, THF, –78 °C; (b) methyl acrylate, SmI_2, $BF_3{\cdot}OEt_2$, *t*-BuOH, THF, –40 °C [dr = 85:15]; (c) TBAF, THF, 0 °C to rt; (d) pyridine·SO_3, DMSO; (e) $C_6H_{13}P^+Ph_3Br^-$, BuLi, THF, −78 °C to rt; (f) (MeO)NHMe·HCl, $AlMe_3$, CH_2Cl_2; (g) MeLi, THF, −78 °C; (h) H_2, $Pd(OH)_2$/C, MeOH.

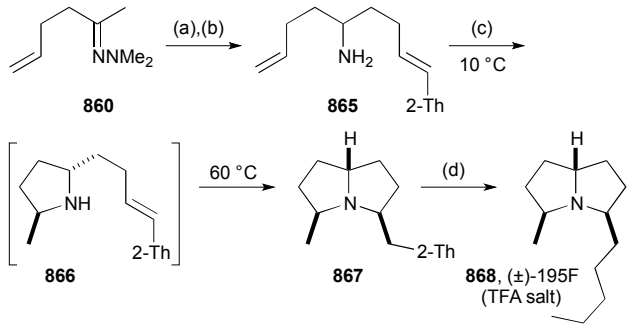
Building on his group's intramolecular alkene hydroamination methodology, Livinghouse noted that simple 1,2-disubstituted alkenes are 'reluctant participants' in this chemistry; indeed, an attempted *N*-cyclisation onto a dec-3-enyl substituent proceeded 'only with great lethargy' at 120 °C.[256] However, 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 desulfurisation. 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 pyrrolidine **862** with dr = 98:2. This intermediate then cyclised further to pyrrolizidine **863** upon heating, again with high stereoselectivity; C–S and alkene reduction completed the route.



Scheme 150 Reagents and conditions: (a) BuLi, THF, –78 °C to –15 °C then (*Z*)-BrCH=CH_2CH_2Br, –78 °C; (b) aq HCl, CH_2Cl_2; (c) 5-ethyl-thiophene-2-boronic acid, $Pd(PPh_3)_4$, LiCl, Na_2CO_3, DME, reflux; (d) NH_4OAc, $NaBH_3CN$, MeOH; (e) **864**, toluene-d_8, 10 °C then 60 °C; (f) H_2, Raney Ni, MeOH.

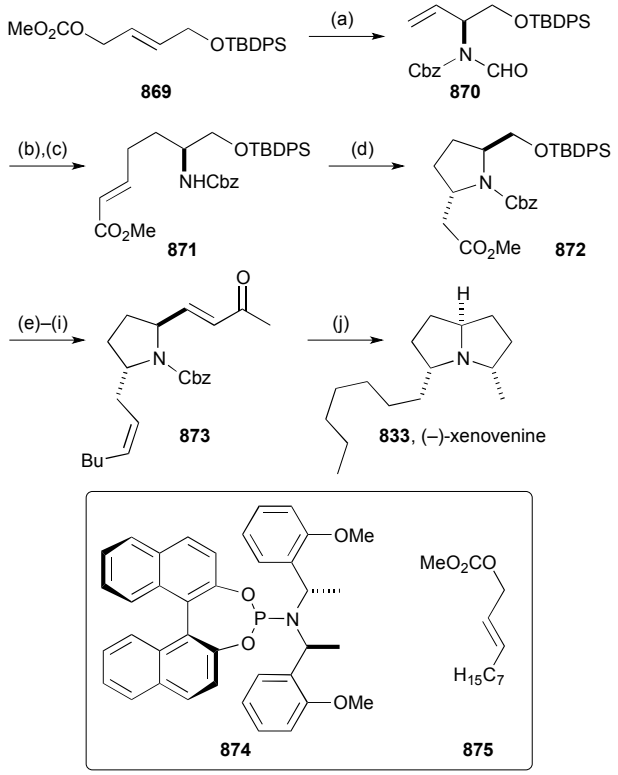
In closely-related work, Livinghouse showed that aminodiene

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*.



Scheme 151 Reagents and conditions: (a) BuLi, THF, –78 °C, add 2-thienyl-CH=CHCH$_2$Cl, –78 °C then aq HCl, CH_2Cl_2; (b) NH_4OAc, $NaBH_3CN$, MeOH; (c) **864**, toluene-d_8, 10 °C then 60 °C; (d) Raney Ni, MeOH, THF then CF_3CO_2H. [2-Th = 2-thienyl]

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 enoate **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.



Scheme 152 Reagents and conditions: (a) HN(CHO)Cbz, $[Ir(cod)Cl]_2$, **874**, 1,5,7-triazabicyclo[4.4.0]dec-5-ene, THF; (b) KOH, MeOH; (c) 9-BBN, THF, 50 °C then ICH=CHCO$_2$Me, Pd(dppf)Cl_2, Ph_3As, Cs_2CO_3, aq DMF; (d) KO*t*-Bu, THF, −78 °C; (e) DIBAL, CH_2Cl_2, –90 °C; (f) $Ph_3P^+C_5H_{11}\ Br^-$, KHMDS, THF, 0 °C; (g) TBAF·3H_2O, THF; (h) Swern oxidation; (i) Ph_3P=CHCOMe, $PhCH_3$, reflux; (j) H_2, Pd(OH)$_2$/C, MeOH.

Notes and references

[a] *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK. E-mail: jeremy.robertson@chem.ox.ac.uk; Tel: 44 1865 275660*

1 Previous article in this series: J. R. Liddell, *Nat. Prod. Rep.* 2002, **19**, 773.
2 I. M. Skvortsov, *Chem. Heterocycl. Comp.* 2003, **39**, 493.
3 I. M. Skvortsov, *Chem. Heterocycl. Comp.* 2006, **42**, 1247.
4 V. V. Tarasov, S. A. Kolesnikov, V. M. Levin and I. M. Skvortsov, *Chem. Heterocycl. Comp.* 2009, **45**, 929.
5 T. Beuerle, C. Theuring, N. Klewer, S. Schulz and T. Hartmann, *Insect Biochem. Mol. Biol.* 2007, **37**, 80.
6 A. Kato, E. Kano, I. Adachi, R. J. Molyneux, A. A. Watson, R. J. Nash, G. W. J. Fleet, M. R. Wormald, H. Kizu, K. Ikeda and N. Asano, *Tetrahedron: Asymmetry* 2003, **14**, 325.
7 C. Newton, J. van Ameijde, G. W. J. Fleet, R. J. Nash and D. J. Watkin, *Acta Crystallogr. E* 2004, **E60**, o1463.
8 A. L. Thompson, D. J. Watkin, Z. A. Gal, L. Jones, J. Hollinshead, S. F. Jenkinson, G. W. J. Fleet and R. J. Nash, *Acta Crystallogr. C* 2008, **C64**, o649.
9 A. M. Belostotskii and E. Markevich, *J. Org. Chem.* 2003, **68**, 3055.
10 H. Wiedenfeld and A. Andrade-Cetto, *Phytochemistry* 2001, **57**, 1269.
11 G. M. Woldemichael and M. Wink, *Biochem. Syst. Ecol.* 2002, **30**, 139.
12 M. Herrmann, H. Joppe and G. Schmaus, *Phytochemistry* 2002, **60**, 399.

13 A. Koulman, C. Seeliger, P. J. B. Edwards, K. Fraser, W. Simpson, L. Johnson, M. Cao, S. Rasmussen and G. A. Lane, *Phytochemistry* 2008, **69**, 1927.
14 Y.-H. Wang, J.-H. Wang, H.-P. He, H. Zhou, X.-W. Yang, C.-S. Li and X.-J. Hao, *J. Asian Nat. Prod. Res.*, 2008, **10**, 25.
15 C. D. Dodson and F. R. Stermitz, *J. Nat. Prod.* 1986, **49**, 727.
16 H. Wiedenfeld, D. Altanchimeg, A. Gantur and S. Narantuya, *J. Nat. Toxins* 2002, **11**, 187.
17 V. Christov, B. Mikhova, R. Alexandrova, D. Dimitrova, E. Nikolova and L. Evstatieva, *Z. Naturforsch.* 2002, **57c**, 780.
18 H. Wiedenfeld, A. Pietrosiuk, M. Furmanowa and E. Roeder, *Z. Naturforsch.* 2003, **58c**, 173.
19 O. Kretsi, N. Aligiannis, A. L. Skaltsounis and I. B. Chinou, *Helv. Chim. Acta* 2003, **86**, 3136.
20 A. Tan, Z. Wang, H. He, M. Zhang and X. Hao, *Heterocycles* 2003, **60**, 1195.
21 A. M. Tan, Y. S. Li, H. Yang, Z. T. Wang, H. P. He, M. Zhang and X. J. Hao, *Chin. Chem. Lett.* 2004, **15**, 68.
22 A. Tan, M. Zhang, Z. Wang and H. Zhang, *Heterocycles* 2011, **83**, 1611.
23 R. Ravikumar and A. J. Lakshmanan, *Indian J. Chem.* 2004, **43B**, 406.
24 S. Ravi, R. Ravikumar and A. J. Lakshmanan, *J. Asian Nat. Prod. Res.* 2008, **10**, 307.
25 S. M. Colegate, J. A. Edgar, A. M. Knill and S. T. Lee, *Phytochem. Anal.* 2005, **16**, 108.
26 M. Boppré, S. M. Colegate and J. A. Edgar, *J. Agric. Food Chem.* 2005, **53**, 594.
27 M. Boppré, S. M. Colegate, J. A. Edgar and O. W. Fischer, *J. Agric. Food Chem.* 2008, **56**, 5662.
28 (a) A. Braca, A. Bader, T. Siciliano, I. Morelli and N. De Tommasi, *Planta Med.* 2003, **69**, 835; (b) T. Siciliano, M. De Leo, A. Bader, N. De Tommasi, K. Vrieling, A. Braca and I. Morelli, *Phytochemistry* 2005, **66**, 1593.
29 Y. Ikeda, H. Nonaka, T. Furumai and Y. Igarashi, *J. Nat. Prod.* 2005, **68**, 572.
30 J. S. N. Souza, L. L. Machado, O. D. L. Pessoa, R. Braz-Filho, C. R. Overk, P. Yao, G. A. Cordell and T. L. G. Lemos, *J. Braz. Chem. Soc.* 2005, **16**, 1410.
31 H. Wiedenfeld, C. Montes, B. Tawil, A. Contin and R. Wynsma, *Pharmazie* 2006, **61**, 559.
32 Y. C. Park, S. P. Gunasekera, J. V. Lopez, P. J. McCarthy and A. E. Wright, *J. Nat. Prod.* 2006, **69**, 580.
33 N. Kostova, V. Christov, M. Cholakova, E. Nikolova and L. Evstatieva, *J. Serb. Chem. Soc.* 2006, **71**, 1275.
34 Y. Bai, M. Benn, N. Duke, W. Gul, Y. Y. Huang and H. Rüeger, *ARKIVOC* 2006, (iii), 34.
35 Y.-P. Jin, X.-N. Wei and Y.-P. Shi, *Helv. Chim. Acta* 2007, **90**, 776.
36 C.-M. Liu, H.-X. Wang, S.-L. Wei and K. Gao, *Helv. Chim. Acta* 2008, **91**, 308.
37 B.-J. Shi, A.-Z. Xiong, S.-S. Zheng, G.-X. Chou and Z.-T. Wang, *Nat. Prod. Res.* 2010, **24**, 1897.
38 K. H. Kim, K. H. Lee, S. U. Choi, K. R. Kim and K. R. Lee, *Heterocycles* 2010, **81**, 1493.
39 H. I. Al-Jaber, I. M. Mosleh, A. Mallouh, O. M. Abu Salim and M. H. Abu Zarga, *J. Asian Nat. Prod. Res.* 2010, **12**, 814.
40 S. M. Colegate, D. R. Gardner, R. J. Joy, J. M. Betz and K. E. Panter, *J. Agric. Food Chem.* 2012, **60**, 3541.
41 Y. Sugie, H. Hirai, H. Kachi-Tonai, Y.-J. Kim, Y. Kojima, Y. Shiomi, A. Sugiura, A. Sugiura, Y. Suzuki, N. Yoshikawa, L. Brennan, J. Duignan, L. H. Huang, J. Sutcliffe and N. Kojima, *J. Antibiot.* 2001, **54**, 917.
42 T. Agatsuma, T. Akama, S. Nara, S. Matsumiya, R. Nakai, H. Ogawa, S. Otaki, S.-i. Ikeda, Y. Saitoh and Y. Kanda, *Org. Lett.* 2002, **4**, 4387.
43 T. Yamashita, K. Yasuda, H. Kizu, Y. Kameda, A. A. Watson, R. J. Nash, G. W. J. Fleet and N. Asano, *J. Nat. Prod.* 2002, **65**, 1875.
44 A. Kato, N. Kato, I. Adachi, J. Hollinshead, G. W. J. Fleet, C. Kuriyama, K. Ikeda, N. Asano and R. J. Nash, *J. Nat. Prod.* 2007, **70**, 993.
45 A. Kato, I. Adachi, M. Miyauchi, K. Ikeda, T. Komae, H. Kizu, Y. Kameda, A. A. Watson, R. J. Nash, M. R. Wormald, G. W. J. Fleet and N. Asano, *Carbohydr. Res.* 1999, **316**, 95.
46 C. W. G. Au, R. J. Nash and S. G. Pyne, *Chem. Commun.* 2010, **46**, 713.
47 T. Sengoku, Y. Satoh, M. Takahashi and H. Yoda, *Tetrahedron Lett.* 2009, **50**, 4937.
48 J. A. Tamayo, F. Franco and F. Sanchez-Cantalejo, *Eur. J. Org. Chem*. 2011, 7182.
49 N. Asano, K. Ikeda, M. Kasahara, Y. Arai and H. Kizu, *J. Nat. Prod.* 2004, **67**, 846.
50 Q. Zhang, K. K. Schrader, H. N. ElSohly and S. Takamatsu, *J. Antibiot.* 2003, **56**, 673.
51 T. S. Bugni, M. Woolery, C. A. Kauffman, P. R. Jensen and W. Fenical, *J. Nat. Prod.* 2006, **69**, 1626.
52 J. R. Duvall, F. Wu and B. B. Snider, *J. Org. Chem.* 2006, **71**, 8579.
53 T. Hartmann, C. Theuring, T. Beuerle, L. Ernst, M. S. Singer and E. A. Bernays, *J. Chem. Ecol.* 2004, **30**, 229.
54 P. G. Williams, G. O. Buchanan, R. H. Feling, C. A. Kauffman, P. R. Jensen and W. Fenical, *J. Org. Chem.*, 2005, **70**, 6196.
55 F. Q. Alali, Y. R. Tahboub, E. S. Ibrahim, A. M. Qandil, K. Tawaha, J. P. Burgess, A. Sy, Y. Nakanishi, D. J. Kroll and N. H. Oberlies, *Phytochemistry* 2008, **69**, 2341.
56 M. El-Naggar, A. M. Piggott and R. J. Capon, *Org. Lett.* 2008, **10**, 4247.
57 J. C. M. Medina, G. F. Gauze, G. J. Vidotti, M. H. Sarragiotto, E. A. Basso and J. L. B. Peixoto, *Tetrahedron Lett.* 2009, **50**, 2640.
58 H. Usuki, M. Toyo-oka, H. Kanzaki, T. Okuda and T. Nitoda, *Bioorg. Med. Chem.* 2009, **17**, 7248.
59 L. Jones, J. Hollinshead, G. W. J. Fleet, A. L. Thompson, D. J. Watkin, Z. A. Gal, S. F. Jenkinson, A. Kato and R. J. Nash, *Phytochem. Lett.* 2010, **3**, 133.
60 R. Raju, A. M. Piggott, M. M. Conte and R. J. Capon, *Org. Biomol. Chem.* 2010, **8**, 4682.
61 W.-D. Xie, X. Li and K. H. Row, *Bull. Korean Chem. Soc.* 2010, **31**, 2715.
62 X. Lu, G. Chen, H. Hua, H. Dai, W. Mei, Y. Xu and Y. Pei, *Fitoterapia* 2012, **83**, 737.
63 L. Hua, J. Chen and K. Gao, *Phytochem. Lett.* 2012, **5**, 541.
64 Y. Sakano, M. Shibuya, Y. Yamaguchi, R. Masuma, H. Tomoda, S. Ōmura and Y. Ebizuka, *J. Antibiot.* 2004, **57**, 564.
65 M. Shibuya, B. B. Snider, Y. Sakano, H. Tomoda, S. Ōmura and Y. Ebizuka, *J. Antibiot.* 2005, **58**, 599.
66 B. B. Snider and X. Gao, *Org. Lett.* 2005, **7**, 4419.
67 B. B. Snider, J. R. Duvall, I. Sattler and X. Huang, *Tetrahedron Lett.* 2004, **45**, 6725.
68 B. B. Snider and J. R. Duvall, *Org. Lett.* 2005, **7**, 4519.
69 (a) A. S. Davis, S. G. Pyne, B. W. Skelton and A. H. White, *J. Org. Chem.* 2004, **69**, 3139; (b) A. S. Davis, T. Ritthiwigrom and S. G. Pyne, *Tetrahedron* 2008, **64**, 4868.
70 T. Ritthiwigrom and S. G. Pyne, *Org. Lett.* 2008, **10**, 2769.
71 D. P. Becker, D. L. Flynn and C. I. Villamil, *Bioorg. Med. Chem. Lett.* 2004, **14**, 3073.
72 D. P. Becker, D. L. Flynn, A. E. Moormann, R. Nosal, C. I. Villamil, R. Loeffler, G. W. Gullikson, C. Moummi and D.–C. Yang, *J. Med. Chem.* 2006, **49**, 1125.
73 (a) J.-B. Behr, A. Erard and G. Guillerm, *Eur. J. Org. Chem.* 2002, 1256; (b) J.-B. Behr, A. Gainvors-Claisse and A. Belarbi, *Nat. Prod. Res.* 2006, **20**, 1308.
74 C. Rochais, P. Dallemagne and S. Rault, *Anti-cancer Agents Med. Chem.* 2009, **9**, 369.
75 F. Cardona, A. Goti, C. Parmeggiani, P. Parenti, M. Forcella, P. Fusi, L. Cipolla, S. M. Roberts, G. J. Davies and T. M. Gloster, *Chem. Commun.* 2010, **46**, 2629.

76 N. Garcia-Delgado, S. Bertrand, K. T. Nguyen, R. van Deursen, D. Bertrand and J.-L. Reymond, *ACS Med. Chem. Lett.* 2010, **1**, 422.
77 J. Tang, M. Cheng and M. Hattori, *Anal. Methods* 2012, **4**, 2797.
78 L. Williams, M. W. Chou, J. Yan, J. F. Young, P. C. Chan and D. R. Doerge, *Toxicol. Appl. Pharm.* 2002, **182**, 98.
79 M. W. Chou, Y.-P. Wang, J. Yan, Y.-C. Yang, R. D. Beger, L. D. Williams, D. R. Doerge and P. P. Fu, *Toxicol. Lett.* 2003, **145**, 239.
80 J. Tang, M. Zhang, Z.-T. Wang, T. Akao, N. Nakamura and M. Hattori, *J. Anal. Toxicol.* 2004, **28**, 11.
81 R. A. Barreto, C. S. Sousa, V. D. A. Silva, A. R. Silva, E. S. Veloso, S. D. Cunha, M. F. D. Costa, R. S. El-Bachá and S. L. Costa, *Toxicol. in Vitro* 2008, **22**, 1191.
82 J. Dai, F. Zhang and J. Zheng, *Chem.-Biol. Interact.* 2010, **183**, 49.
83 Y.-Q. He, L. Yang, H.-X. Liu, J.-W. Zhang, Y. Liu, A. Fong, A.-Z. Xiong, Y.-L. Lu, L. Yang, C.-H. Wang and Z.-T. Wang, *Chem. Res. Toxicol.* 2010, **23**, 591.
84 Y. Zhao, Q. Xia, J. J. Yin, G. Lin and P. P. Fu, *Toxicol. Lett.* 2011, **205**, 302.
85 Y. Zhao, Q. Xia, G. Gamboa da Costa, H. Yu, L. Cai and P. P. Fu, *Chem. Res. Toxicol.* 2012, **25**, 1985.
86 I. Drutu, E. S. Krygowski and J. L. Wood, *J. Org. Chem.* 2001, **66**, 7025.
87 (a) B. Liu and K. D. Moeller, *Tetrahedron Lett.* 2001, **42**, 7163; (b) B. Liu, S. Duan, A. C. Sutterer and K. D. Moeller, *J. Org. Chem.* 2002, **124**, 10101.
88 T. J. Donohoe, J.-B. Guillermin and D. S. Walter, *J. Chem. Soc., Perkin Trans. 1* 2002, 1369.
89 D. M. Hodgson, T. D. Avery and A. C. Donohue, *Org. Lett.* 2002, **4**, 1809.
90 (a) D. M. Hodgson and F. Le Strat, *Chem. Commun.* 2004, 822; (b) D. M. Hodgson, F. Le Strat, T. D. Avery, A. C. Donohue and T. Brückl, *J. Org. Chem.* 2004, **69**, 8796.
91 F. López, L. Castedo and J. L. Mascareñas, *Chem. Eur. J.* 2002, **8**, 884.
92 J. Y. Sim, G.-S. Hwang, K. H. Kim, E. M. Ko and D. H. Ryu, *Chem. Commun.* 2007, 5064.
93 R. K. Dieter and R. Watson, *Tetrahedron Lett.* 2002, **43**, 7725.
94 R. K. Dieter, N. Chen and R. T. Watson, *Tetrahedron* 2005, **61**, 3221.
95 I. L. Lysenko and O. G. Kulinkovich, *Russ. J. Org. Chem.* 2005, **41**, 70.
96 D. A. Evans and K. R. Fandrick, *Org. Lett.* 2006, **8**, 2249.
97 X. L. M. Despinoy and H. McNab, *Org. Biomol. Chem.* 2009, **7**, 4502.
98 M.-Y. Chang, R.-T. Hsu, T.-W. Tseng, P.-P. Sun and N.-C. Chang, *Tetrahedron* 2004, **60**, 5545.
99 S. Lemaire, G. Giambastiani, G. Prestat and G. Poli, *Eur. J. Org. Chem.* 2004, 2840.
100 K. Ishii, T. Sone, Y. Shimada, T. Shigeyama, M. Noji and S. Sugiyama, *Tetrahedron* 2004, **60**, 10887.
101 (a) E. Pereira, C. de Fátima Alves, M. A. Böckelmann and R. A. Pilli, *Tetrahedron Lett.* 2005, **46**, 2691; (b) E. Pereira, C. de Fátima Alves, M. A. Böckelmann and R. A. Pilli, *Quim. Nova* 2008, **31**, 771.
102 M. Kabata, T. Suzuki, K. Takabe and H. Yoda, *Tetrahedron Lett.* 2006, **47**, 1607.
103 P.-O. Delaye, T. K. Pradhan, E. Lambert, J.-L. Vasse and J. Szymoniak, *Eur. J. Org. Chem.* 2010, 3395.
104 K. K. S. Reddy, B. V. Rao and S. S. Raju, *Tetrahedron: Asymmetry* 2011, **22**, 662.
105 M.-Y. Chang, D.-C. Wu and N.-C. Chang, *Heterocycles* 2005, **65**, 2865.
106 R.-T. Hsu, N.-C. Chang and M.-Y. Chang, *J. Chinese Chem. Soc.* 2006, **53**, 945.
107 S. Ishikawa, F. Noguchi and A. Kamimura, *J. Org. Chem.* 2010, **75**, 3578.
108 D. Craig, C. J. T. Hyland and S. E. Ward, *Synlett* 2006, 2142.
109 H. Ishibashi, M. Sasaki and T. Taniguchi, *Tetrahedron* 2008, **64**, 7771.
110 S. Nicolai, C. Piemontesi and J. Waser, *Angew. Chem. Int. Ed.* 2011, **50**, 4680.
111 X. Han, F. Zhong, Y. Wang and Y. Lu, *Angew. Chem. Int. Ed.* 2012, **51**, 767.
112 H.-L. Huang, W.-H. Sung and R.-S. Liu, *J. Org. Chem.* 2001, **66**, 6193.
113 T. J. Senter, O. O. Fadeyi and C. W. Lindsley, *Org. Lett.* 2012, **14**, 1869.
114 K. N. Hahn, O. O. Fadeyi, H. P. Cho and C. W. Lindsley, *Tetrahedron Lett.* 2012, **53**, 3577.
115 G. Enierga, M. Espiritu, P. Perlmutter, N. Pham, M. Rose, S. Sjöberg, N. Thienthong and K. Wong, *Tetrahedron: Asymmetry* 2001, **12**, 597.
116 I. Izquierdo, M. T. Plaza and J. A. Tamayo, *Tetrahedron: Asymmetry* 2004, **15**, 3635.
117 (a) T. Ayad, Y. Génisson, M. Baltas and L. Gorrichon, *Chem. Commun.* 2003, 582; (b) T. Ayad, Y. Génisson and M. Baltas, *Org. Biomol. Chem.* 2005, **3**, 2626.
118 V. D. Chaudari, K. S. A. Kumar and D. D. Dhavale, *Tetrahedron* 2006, **62**, 4349.
119 S. R. Angle, D. Bensa and D. S. Belanger, *J. Org. Chem.* 2007, **72**, 5592.
120 R. Zimmer, M. Collas, R. Czerwonka, U. Hain and H.-U. Reissig, *Synthesis* 2008, 237.
121 I. S. Kim, Q. R. Li, G. R. Dong, Y. C. Kim, Y. J. Hong, M. Lee, K.-W. Chi, J. S. Oh and Y. H. Jung, *Eur. J. Org. Chem.* 2010, 1569.
122 S. H. Lee, I. S. Kim, Q. R. Li, G. R. Dong and Y. H. Jung, *Tetrahedron Lett.* 2011, **52**, 1901.
123 J. Kubáň, A. Kolarovič, L. Fišera, V. Jäger, O. Humpa and N. Prónayová, *Synlett* 2001, 1866.
124 K. B. Lindsay, M. Tang and S. G. Pyne, *Synlett* 2002, 731.
125 N. G. Argyropoulos, P. Gkizis and E. Coutouli–Argyropoulou, *Tetrahedron* 2008, **64**, 8752.
126 A. T. Carmona, J. Fuentes and I. Robina, *Tetrahedron Lett.* 2002, **43**, 8543.
127 A. T. Carmona, J. Fuentes, P. Vogel and I. Robina, *Tetrahedron: Asymmetry* 2004, **15**, 323.
128 E. M. Sletten and L. J. Liotta, *J. Org. Chem.* 2006, **71**, 1335.
129 J. A. Vanecko and F. G. West, *Heterocycles* 2007, **74**, 125.
130 A. R. de Faria, E. L. Salvador and C. R. D. Correira, *J. Org. Chem.* 2002, **67**, 3651.
131 C.-Y. Zhou, W.-Y. Yu, P. W. H. Chan and C.-M. Che, *J. Org. Chem.* 2004, **69**, 7072.
132 J. A. Vanecko and F. G. West, *Org. Lett.* 2005, **7**, 2949.
133 D. K. An, D. Duncan, T. Livinghouse and P. Reid, *Org. Lett.* 2001, **3**, 2961.
134 A. G. H. Wee, *J. Org. Chem.* 2001, **66**, 8513.
135 F. Pisaneschi, F. M. Cordero and A. Brandi, *Eur. J. Org. Chem.* 2003, 4373.
136 J.-M. Huang, S.-C. Hong, K.-L. Wu and Y.-M. Tsai, *Tetrahedron Lett.* 2004, **45**, 3047.
137 J. M Dener and D. J Hart, *Tetrahedron* 1988, **44**, 7037.
138 E. L. Myers, J. G. de Vries and V. K. Aggarwal, *Angew. Chem. Int. Ed.* 2007, **46**, 1893.
139 A. C. Breman, J. Dijkink, J. H. van Maarseveen, S. S. Kinderman and H. Hiemstra, *J. Org. Chem.* 2009, **74**, 3798.
140 T. K. Sarkar, A. Hazra, P. Gangopadhyay, N. Panda, Z. Slanina, C.-C. Lin and H.-T. Chen, *Tetrahedron* 2005, **61**, 1155.
141 T. Sengoku, T. Suzuki, T. Kakimoto, M. Takahashi and H. Yoda, *Tetrahedron* 2009, **76**, 2415.
142 S. Akai, K. Tanimoto, Y. Kanao, S. Omura and Y. Kita, *Chem. Commun.* 2005, 2369.
143 H. Nemoto, K. Tanimoto, Y. Kanao, S. Omura, Y. Kita and S. Akai, *Tetrahedron* 2012, **68**, 7295.
144 S. Cicchi, M. Marradi, P. Vogel and A. Goti, *J. Org. Chem.* 2006, **71**, 1614.
145 L. Rambaud, P. Compain and O. R. Martin, *Tetrahedron: Asymmetry* 2001, **12**, 1807.
146 A. Toyao, O. Tamura, H. Takagi and H. Ishibashi, *Synlett* 2003, 35.

147 F. Cardona, E. Faggi, F. Liguori, M. Cacciarini and A. Goti, *Tetrahedron Lett.* 2003, **44**, 2315.
148 C. Bonaccini, M. Chioccioli, C. Parmeggiani, F. Cardona, D. L. Re, G. Soldaini, P. Vogel, C. Bello, A. Goti and P. Gratteri, *Eur. J. Org. Chem.* 2010, 5574.
149 S. Desvergnes, S. Py and Y. Vallee, *J. Org. Chem.* 2005, **70**, 1459.
150 L. Chabaud, Y. Landais and P. Renaud, *Org. Lett.* 2005, **7**, 2587.
151 I. Izquierdo, M. T. Plaza and V. Yáñez, *Tetrahedron: Asymmetry* 2005, **16**, 3887.
152 J. Gebauer, P. Dewi and S. Blechert, *Tetrahedron Lett.* 2005, **46**, 43.
153 P. Dewi-Wülfing and S. Blechert, *Eur. J. Org. Chem.* 2006, 1852.
154 L. Zhou, J. Chen and X.-P. Cao, *Synthesis* 2007, 1359.
155 J. Calveras, J. Casas, T. Parella, J. Joglar and P. Clapés, *Adv. Synth. Catal.* 2007, **349**, 1661.
156 X. Garrabou, L. Gómez, J. Joglar, S. Gil, T. Parella, J. Bujons and P. Clapés, *Chem. Eur. J.* 2010, **16**, 10691.
157 K. P. Kaliappan and P. Das, *Synlett* 2008, 841.
158 P. V. Reddy, A. Veyron, P. Koos, A. Bayle, A. E. Greene and P. Delair, *Org. Biomol. Chem.* 2008, **6**, 1170.
159 P. V. Reddy, P. Koos, A. Veyron, A. E. Greene and P. Delair, *Synlett* 2009, 1141.
160 T. Sengoku, Y. Satoh, M. Oshima, M. Takahashi and H. Yoda, *Tetrahedron* 2008, **64**, 8052.
161 T. J. Donohoe, R. E. Thomas, M. D. Cheeseman, C. L. Rigby, G. Bhalay and I. D. Linney, *Org. Lett.* 2008, **10**, 3615.
162 S. Chandrasekhar, B. B. Parida and C. Rambabu, *J. Org. Chem.* 2008, **73**, 7826.
163 O. Affolter, A. Baro, W. Frey and S. Laschat, *Tetrahedron* 2009, **65**, 6626.
164 J. A. Tamayo, F. Franco, D. L. Re and F. Sánchez-Cantalejo, *J. Org. Chem.* 2009, **74**, 5679.
165 C. Ribes, E. Falomir, M. Carda and J. A. Marco, *Tetrahedron* 2009, **65**, 6965.
166 I. Delso, T. Tejero, A. Goti and P. Merino, *Tetrahedron* 2010, **66**, 1220.
167 X.-G. Hu, Y.-M. Jia, J. Xiang and C.-Y. Yu, *Synlett* 2010, 982.
168 W.-J. Liu, J.-L. Ye and P.-Q. Huang, *Org. Biomol. Chem.* 2010, **8**, 2085.
169 J.-C. Liao, K.-J. Xiao, X. Zheng and P.-Q. Huang, *Tetrahedron* 2012, **68**, 5297.
170 J. A. Tamayo, F. Franco and F. Sanchez-Cantalejo, *Tetrahedron* 2010, **66**, 7262.
171 E. A. Brock, S. G. Davies, J. A. Lee, P. M. Roberts and J. E. Thomson, *Org. Lett.* 2011, **13**, 1594.
172 J. Rehák, L. Fišera, J. Kožíšek and L. Bellovičová, *Tetrahedron* 2011, **67**, 5762.
173 X.-K. Liu, S. Qiu, Y.-G. Xiang, Y.-P. Ruan, X. Zheng and P.-Q. Huang, *J. Org. Chem.* 2011, **76**, 4952.
174 W. Zhang, K. Sato, A. Kato, Y.-M. Jia, X.-G. Hu, F. X. Wilson, R. van Well, G. Horne, G. W. J. Fleet, R. J. Nash and C.-Y. Yu, *Org. Lett.* 2011, **13**, 4414.
175 M. Royzen, M. T. Taylor, A. DeAngelis and J. M. Fox, *Chem. Sci.* 2011, **2**, 2162.
176 G. D'Adamio, A. Goti, C. Parmeggiani, E. Moreno-Clavijo, I. Robina and F. Cardona, *Eur. J. Org. Chem* 2011, 7155.
177 I. Izquierdo, M. T. Plaza, R. Robles and F. Franco, *Tetrahedron: Asymmetry* 2001, **12**, 2481.
178 I. Izquierdo, M. T. Plaza and F. Franco, *Tetrahedron: Asymmetry* 2001, **14**, 3933.
179 I. Izquierdo, M. T. Plaza and F. Franco, *Tetrahedron: Asymmetry* 2002, **13**, 1581.
180 I. Izquierdo, M. T. Plaza and F. Franco, *Tetrahedron: Asymmetry* 2004, **15**, 1465.
181 I. Izquierdo, M. T. Plaza, J. A. Tamayo, M. Rodriguez and A. Martos, *Tetrahedron* 2006, **62**, 6006.
182 I. Izquierdo, M. T. Plaza, J. A. Tamayo and F. Sánchez-Cantalejo, *Tetrahedron: Asymmetry* 2007, **18**, 2211.
183 I. Izquierdo, M. T. Plaza, J. A. Tamayo, V. Yanez, D. Lo Re and F. Sánchez-Cantalejo, *Tetrahedron*, 2008, **64**, 4613.
184 I. Izquierdo, M. T. Plaza, J. A. Tamayo, F. Franco and F. Sánchez-Cantalejo, *Tetrahedron*, 2010, **66**, 3788.
185 I. Izquierdo, M. T. Plaza, J. A. Tamayo and F. Sánchez-Cantalejo, *Eur. J. Org. Chem.* 2009, 3809.
186 S. Desvergnes, V. Desvergnes, O. R. Martin, K. Itoh, H.-W. Liu and S. Py, *Bioorg. Med. Chem.* 2007, **15**, 6443.
187 S. E. Denmark and J. J. Cottell, *J. Org. Chem.* 2001, **66**, 4276.
188 M. Tang and S. G. Pyne, *J. Org. Chem.* 2003, **68**, 7818.
189 M. Tang and S. G. Pyne, *Tetrahedron* 2004, **60**, 5759 [erratum: M. Tang and S. G. Pyne, *Tetrahedron* 2004, **60**, 9527].
190 T. J. Donohoe and H. O. Sintim, *Org. Lett.* 2004, **6**, 2003.
191 T. J. Donohoe, H. O. Sintim and J. Hollinshead, *J. Org. Chem.* 2005, **70**, 7297.
192 A. Lauritsen and R. Madsen, *Org. Biomol. Chem.* 2006, **4**, 2898.
193 J. D. White and P. Hrnciar, *J. Org. Chem.* 2000, **65**, 9129.
194 C. Ribes, E. Falomir, M. Carda and J. A. Marco, *Org. Lett.* 2007, **9**, 77.
195 B. M. Trost, A. Aponick and B. N. Stanzl, *Chem. Eur. J.* 2007, **13**, 9547.
196 T. Ritthiwigrom, A. C. Willis and S. G. Pyne, *J. Org. Chem.* 2010, **75**, 815.
197 T. Ritthiwigrom, R. J. Nash and S. G. Pyne, *Tetrahedron* 2010, **66**, 9340.
198 P. Gilles and S. Py, *Org. Lett.* 2012, **14**, 1042.
199 D. Socha, K. Pasniczek, M. Jurczak, J. Solecka and M. Chmielewski, *Carbohydr. Res.* 2006, **341**, 2005.
200 M. S. Valle, P. Retailleau and C. R. D. Correia, *Tetrahedron Lett.* 2008, **49**, 1957.
201 J. K. Gallos, V. C. Sarli, C. I. Stathakis, T. V. Koftis, V. R. Nachmia and E. Coutouli-Argyropoulou, *Tetrahedron* 2002, **58**, 9351.
202 D. Chikkanna, O. V. Singh, S. B. Kong and H. Han, *Tetrahedron Lett.* 2005, **46**, 8865.
203 M. Dressel, P. Restorp and P. Somfai, *Chem. Eur. J.* 2008, **14**, 3072.
204 M. Takahashi, T. Maehara, T. Sengoku, N. Fujita, K. Takabe and H. Yoda, *Tetrahedron* 2008, **64**, 5254.
205 T. J. Donohoe, M. D. Cheeseman, T. J. C. O'Riordan and J. A. Kershaw, *Org. Biomol. Chem.* 2008, **6**, 3896.
206 S. Stecko, M. Jurczak, Z. Urbańczyk-Lipowska, J. Solecka and M. Chmielewski, *Carbohydr. Res.* 2008, **343**, 2215.
207 S. Stecko, K. Paśniczek, M. Jurczak, Z. Urbańczyk-Lipowska and M. Chmielewski, *Tetrahedron: Asymmetry* 2006, **17**, 68.
208 S. Stecko, J. Solecka and M. Chmielewski, *Carbohydr. Res.* 2009, **344**, 167.
209 A. T. Carmona, R. H. Whigtman, I. Robina and P. Vogel, *Helv. Chim. Acta* 2003, **86**, 3066.
210 I. Izquierdo, M. T. Plaza and J. A. Tamayo, *Tetrahedron* 2005, **61**, 6527.
211 I. Izquierdo, M. T. Plaza and J. A. Tamayo, *J. Carbohydr. Chem.* 2006, **25**, 281.
212 J. van Ameijde, G. Horne, M. R. Wormald, R. A. Dwek, R. J. Nash, P. W. Jones, E. L. Evinson and G. W. J. Fleet, *Tetrahedron: Asymmetry* 2006, **17**, 2702.
213 D. Koch, S. Maechling and S. Blechert, *Tetrahedron* 2007, **63**, 7112.
214 F. Cardona, C. Parmeggiani, E. Faggi, C. Bonaccini, P. Gratteri, L. Sim, T. M. Gloster, S. Roberts, G. J. Davies, D. R. Rose and A. Goti, *Chem. Eur. J.* 2009, **15**, 1627.
215 G. Podolan, L. Klešťíková, L. Fišera, J. Kožíšek and M. Fronc, *Synlett* 2011, 1668.
216 C. Parmeggiani, D. Martella, F. Cardona and A. Goti, *J. Nat. Prod.* 2009, **72**, 2058.
217 N. Giri, M. Petrini and R. Profeta, *J. Org. Chem.* 2004, **69**, 7303.
218 T. Tang, Y.-P. Ruan, J.-L. Ye and P.-Q. Huang, *Synlett* 2005, 231.
219 M. Vargas-Sanchez, F. Couty, G. Evano, D. Prim and J. Marrot, *Org. Lett.* 2005, **7**, 5861.
220 K. Muñiz, J. Streuff, P. Chávez and C. H. Hövelmann, *Chem. Asian J.* 2008, **3**, 1248.

221 E. J. Eklund, R. D. Pike and J. R. Scheerer, *Tetrahedron Lett.* 2012, **53**, 4644.
222 M. N. Matos, C. A. M. Afonso and R. A. Batey, *Tetrahedron* 2005, **61**, 1221.
223 P. R. Blakemore, S.-K. Kim, V. K. Schulze, J. D. White and A. F. T. Yokochi, *J. Chem. Soc., Perkin Trans. 1* 2001, 1831.
224 M. T. Hovey, E. J. Eklund, R. D. Pike, A. A. Mainkar and J. R. Scheerer, *Org. Lett.* 2011, **13**, 1246.
225 M. Cakmak, P. Mayer and D. Trauner, *Nature Chem.* 2011, **3**, 543.
226 The descriptors A_1 and A_2 reflect the fact that jenamidine A comprises two equilibrating diastereomers, epimeric at C(7a).
227 K. Stevens, A. J. Tyrrell, S. Skerratt and J. Robertson, *Org. Lett.* 2011, **13**, 5964.
228 L. B. Schenkel and J. A. Ellman, *Org. Lett.* 2004, **6**, 3621.
229 (a) S. M. Allin, W. R. S. Barton, W. R. Bowman and T. McInally, *Tetrahedron Lett.* 2001, **42**, 7887; (b) S. M. Allin, W. R. S. Barton, W. R. Bowman, E. Bridge (née Mann), M. R. J. Elsegood, T. McInally and V. McKee, *Tetrahedron* 2008, **64**, 7745.
230 S. Rajaraman and L. S. Jimenez, *Tetrahedron* 2002, **58**, 10407.
231 J. E. Murtagh, S. H. McCooey and S. J. Connon, *Chem. Commun.* 2005, 227.
232 G. Pinna, G. A. Pinna, G. Chelucci and S. Baldino, *Synthesis* 2012, 2798.
233 M. S. Majik and S. G. Tilve, *Synthesis* 2012, **44**, 2673.
234 R. T. Watson, V. K. Gore, K. R. Chandupatla, R. K. Dieter and J. P. Snyder, *J. Org. Chem.* 2004, **69**, 6105.
235 M. S. Majik, J. Shet, S. G. Tilve and P. S. Parameswaran, *Synthesis* 2007, 663.
236 R. Schobert and A. Wicklein, *Synthesis* 2007, 1499.
237 M. S. Majik, P. S. Parameswaran and S. G. Tilve, *Helv. Chim. Acta* 2008, **91**, 1500.
238 F. Mo, F. Li, D. Qiu and J. Wang, *Tetrahedron* 2010, **66**, 1274.
239 Y. Kothapalli, R. K. Puthukanoori and S. R. Alapati, *Tetrahedron Lett.* 2012, **53**, 1891.
240 H. Yoda, T. Egawa and K. Takabe, *Tetrahedron Lett.* 2003, **44**, 1643.
241 (a) C. Roche, P. Delair and A. E. Greene, *Org. Lett.* 2003, **5**, 1741; (b) C. Roche, K. Kadlecíková, A. Veyron, P. Delair, C. Philouze and A. E. Greene, *J. Org. Chem.* 2005, **70**, 8352.
242 I. de Miguel, M. Velado, B. Herradón and E. Mann, *Eur. J. Org. Chem.* 2012, 4347.
243 A. Fürstner and A. Korte, *Chem. Asian J.* 2008, **3**, 310.
244 T. H. Lambert and S. J. Danishefsky, *J. Am. Chem. Soc.* 2006, **128**, 426.
245 R. M. Wilson, W. S. Jen and D. W. C. MacMillan, *J. Am. Chem. Soc.* 2005, **127**, 11616.
246 T. R. Hoye and V. Dvornikovs, *J. Am. Chem. Soc.* 2006, **128**, 2550.
247 R. Marcia de Figueiredo, R. Fröhlich and M. Christmann, *Angew. Chem. Int. Ed.* 2007, **46**, 2883.
248 K. Uchida, T. Ogawa, Y. Yasuda, H. Mimura, T. Fujimoto, T. Fukuyama, T. Wakimoto, T. Asakawa, Y. Hamashima and T. Kan, *Angew. Chem. Int. Ed.* 2012, **51**, 12850.
249 H. Stetter and A. Landscheidt, *Chem. Ber.* 1979, **112**, 1410.
250 T. Mecozzi and M. Petrini, *J. Org. Chem.* 1999, **64**, 8970.
251 Y. Saito, S. Takahashi, N. Azer, A. T. Eldefrawi, M. E. Eldefrawi and H. Takahata, *Heterocycles* 2009, **79**, 1043.
252 J.-C. Legeay, W. Lewis and R. A. Stockman, *Chem. Commun.* 2009, 2207.
253 N. Toyooka, D. Zhou, H. Nemoto, Y. Tezuka, S. Kadota, N. R. Andriamaharavo, H. M. Garraffo, T. F. Spande and J. W. Daly, *J. Org. Chem.* 2009, **74**, 6784.
254 Y.-G. Xiang, X.-W. Wang, X. Zheng, Y.-P. Ruan and P.-Q. Huang, *Chem. Commun.* 2009, 7045.
255 X.-K. Liu, X. Zheng, Y.-P. Ruan, J. Ma and P.-Q. Huang, *Org. Biomol. Chem.* 2012, **10**, 1275.
256 T. Jiang and T. Livinghouse, *Org. Lett.* 2010, **12**, 4271.
257 T. Jiang, T. Livinghouse and H. M. Lovick, *Chem. Commun.* 2011, **47**, 12861.
258 M. Gärtner, R. Weihofen and G. Helmchen, *Chem. Eur. J.* 2011, **17**, 7605.

