Quinoline, quinazoline and acridone alkaloids

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1 Quinoline alkaloids

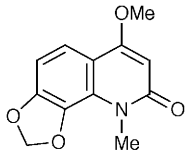
1.1 Occurrence

The new quinoline alkaloids reported in the period covered by this review are listed in Table 1 together with their sources.[1–23] The Table also includes several known alkaloids isolated from new sources. Significant details pertaining to the characterisation of the new compounds are given in the appropriate sections of the ensuing discussion.

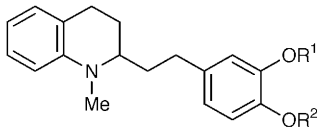
1.2 Non-terpenoid quinoline and quinolinone alkaloids from higher plants

Bioactivity-guided fractionation of an ethyl acetate extract of the seeds of *Casimiroa edulis*, a medicinal and food plant of Mexico and Central America, showed that the antimutagenic activity was due to the known alkaloid casimiroine **1**, among other metabolites.[1] Casimiroine not only inhibited 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced mutation of *Salmonella typhimurium*, but also displayed promising chemopreventive activity against cancer by significantly inhibiting DMBA-induced lesions in mouse mammary gland cultures.

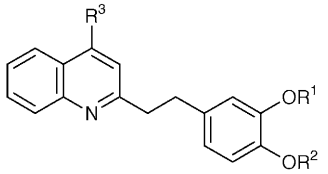
Two investigations on the constituents of Angostura bark (*Galipea officinalis*), published within a few months of each other, have brought to light the new 1,2,3,4-tetrahydroquinoline alkaloid **2**. The earlier publication assigned the name galipinine to the compound,[5] while the later publication, in which the isolation was based on bioactivity-guided fractionation against *Mycobacterium tuberculosis*, named it allocuspareine.[6] The former name should thus take precedence. The NMR spectroscopic data in the two publications are in broad agreement ($\delta_H \pm 0.3$ ppm, $\delta_C \pm 2$ ppm), although there are discrepancies in the assignment of signals. While galipinine was shown to be laevorotatory in the earlier study ($[\alpha]_D$ −33.4, *c* 0.0055, $CHCl_3$), a full CD spectrum reported in the latter study additionally proved that the new compound belongs to the same enantiomeric series as the related alkaloid cuspareine **3**, the absolute configuration of which is not known. Cuspareine was in fact also isolated in both investigations, as well as two other well-known alkaloids, cusparine **4** and galipine **5**. In addition, the presence of demethoxycusparine **6**, not previously known from this plant source, was reported in the earlier article, while 4-methoxy-2-pentylquinoline **7** and *N*-methylquinolin-2-one **8** were detected in the latter investigation. Despite the authors' claims to the contrary, alkaloid **8** is not a new natural product– it was, in fact, first detected in extracts of *G. officinalis* almost thirty years ago.[24] Both articles give previously unreported NMR spectroscopic data for cuspareine **3** and galipine **5**. As a postscript in the second investigation, the quinoline alkaloids were found to be more active against *M. tuberculosis* than the tetrahydroquinoline alkaloids, but the bulk of the activity resided in the unidentified polar basic fraction from the bark extract.



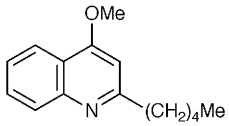
1 Casimiroine



2 Galipinine $R^1R^2 = CH_2$
3 Cuspareine $R^1 = R^2 = Me$



4 Cusparine $R^1R^2 = CH_2$, $R^3 = OMe$
5 Galipine $R^1 = R^2 = Me$, $R^3 = OMe$
6 $R^1R^2 = CH_2$, $R^3 = H$



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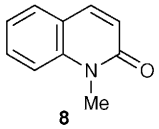

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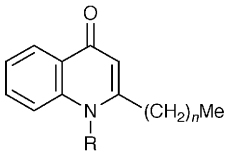
Although quinolin-4-one alkaloids bearing hydrocarbon chains at C-2 are not uncommon metabolites of certain rutaceous plants, the chains invariably possess an odd number of carbon atoms. A suite of quinolin-4-one alkaloids **9**–**16** isolated from *Ruta graveolens* is thus unusual in including all chain lengths between C_7 and C_{11}.[15] The *n*-octyl and *n*-decyl compounds **10**, **12** and **15** are new natural products, while 2-heptylquinolin-4-one **9** was previously known only as a

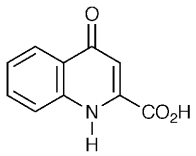
Table 1 Isolation and detection of quinoline alkaloids from microbial, plant and animal sources

Species	Alkaloid[a]	Ref
Casimiroa edulis	5-Hydroxy-1-methyl-2-phenylquinolin-4-one	1
	4-Methoxy-1-methylquinolin-2-one	
Clausena lansium	4-Methoxy-1-methylquinolin-2-one	2
Dictamnus dasycarpus	Dictangustine-A[b] **41**	3
	Isodictamnine **46**	
	Iso-γ-fagarine[b] **42**	
	N-Methylflindersine **38**	
	Preskimmianine	
	Skimmianine	
Evodia officinalis	Dihydroevocarpine	4
	Evocarpine	
	2-Hydroxy-4-methoxy-3-prenylquinoline **32** (see text)	
	1-Methyl-2-[(*Z*)-6-undecenyl]quinolin-4-one	
Galipea officinalis	Demethoxycusparine **6**	5
	(−)-Galipinine (Allocuspareine)[b] **2**	5,6
Glycosmis arborea	4,8-Dimethoxy-1-methyl-3-prenylquinolin-2-one	7
	(*O*-Methylglycosolone)	
Glycosmis trichanthera	Dictamnine **43**	8
(= *G. calcicola*), root bark	γ-Fagarine **44**	
	N-Methylatanine	
	Skimmianine	
Haliclona tulearensis	(+)-Halitulin[b] **87**	9
Mantella betsileo	*cis*-Decahydroquinoline 195A **111**	10
	cis-Decahydroquinoline 195J[b] **112**	
Melicope ptelefolia (= *Evodia lepta*)	Melicobisquinolinone A[b] **36**	11
	Melicobisquinolinone B[b] **37**	
	N-Methylflindersine	
Metrodorea flavida	γ-Fagarine	12
	Flindersiamine	13
	Kokusaginine	12
	Maculine	
Photuris versicolor	*N*-Methylquinolinium-2-carboxylate[b] **89**	14
Ruta graveolens	2-(*n*-Decyl)-1-methylquinolin-4-one[b] **15**	15
	2-(*n*-Decyl)quinolin-4-one[b] **12**	
	2-(*n*-Heptyl)quinolin-4-one **9**	
	2-(*n*-Nonyl)quinolin-4-one **11**	
	2-(*n*-Octyl)quinolin-4-one[b] **10**	
	2-(*n*-Undecyl)-1-methylquinolin-4-one **16**	
Severinia (= *Atalantia*) *buxifolia*	Severibuxine[b] **34**	16
Skimmia laureola	(+)-Methylisoplatydesmine[b] **35**	17
Solenopsis (*Diplorhoptrum*) *azteca*	Decahydroquinoline 5-epi-*cis*-275B′[b] **97**	18
	Decahydroquinoline 5-epi-*trans*-275B[b] **98**	
Solenopsis (*Diplorhoptrum*) sp. *picea* group	Decahydroquinoline *cis*-195A **111**	10
	Decahydroquinoline *cis*-195J[b] **112**	
Thamnosma africana	*N*-Methylatanine	19
Toddalia asiatica	Dictamnine	20
	γ-Fagarine	
	Haplopine **45**	
Zanthoxylum integrifolium	Atanine **33**	21
Z. monophyllum	γ-Fagarine	22
	Skimmianine	
Z. syncarpum	Skimmianine	23

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



9 R = H; *n* = 6
10 R = H; *n* = 7
11 R = H; *n* = 8
12 R = H; *n* = 9
13 R = H; *n* = 10
14 R = Me; *n* = 8
15 R = Me; *n* = 9
16 R = Me; *n* = 10



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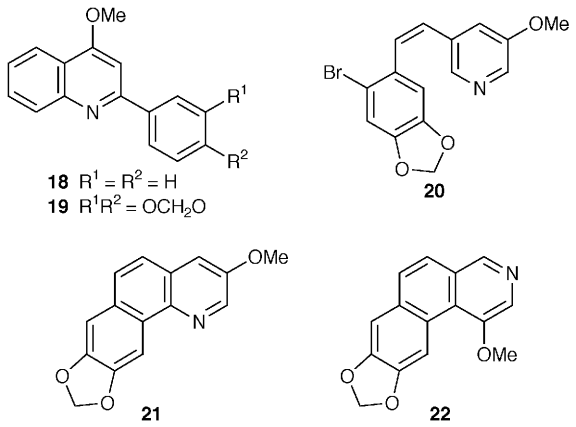
metabolite of microorganisms of the genus *Pseudomonas*. Not all of the alkaloids were separable, but MS measurements in some cases, and reversed-phase HPLC–MS in others, provided good evidence for the structures.

In last year's review,[25a] it was pointed out that the ostensibly new alkaloid transitorine **17** from *Ephedra transitoria* was, in fact, merely the keto tautomer of the well-known compound kynurenic acid. This fact has now been recognised by the authors,[26] who have withdrawn the trivial name transitorine (which actually appeared as 'transtorine' in the original publication[27]) from the literature.

Oxidation of 2-aryl-1,2,3,4-tetrahydroquinolin-4-ones with a relatively safe hypervalent iodine reagent, [hydroxy(tosyloxy)-iodo]benzene, in trimethyl orthoformate containing a trace of perchloric acid as catalyst provides a simple route to 2-aryl-4-methoxyquinolines, including the alkaloids **18** and **19** (graveolinine).[28] Radical cyclisation of the *cis*-stilbene-like precursor **20** with tributyltin hydride and AIBN in boiling benzene produced an equal mixture of the methyl ether **21** of the unusual benzo-[*h*]quinoline alkaloid toddaquinoline and its regioisomer **22** in 58% yield.[29]



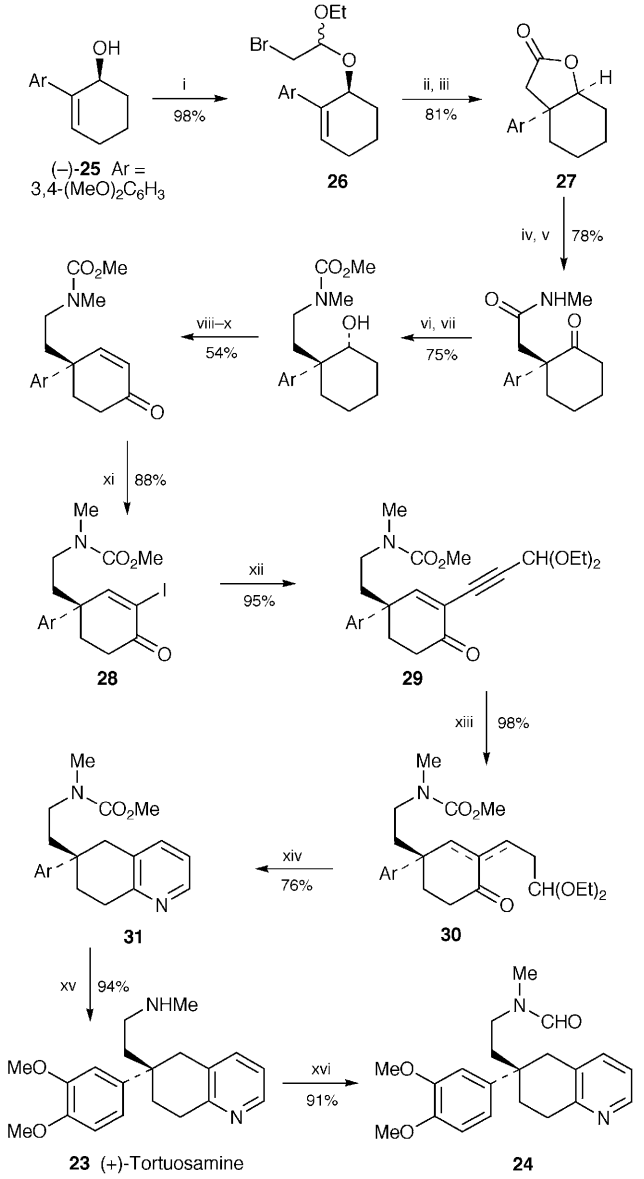
(+)-Tortuosamine **23** and its *N*-formyl analogue **24** are atypical alkaloids from the genus *Sceletium* (Amaryllidaceae). New enantioselective syntheses of these tetrahydroquinolines proceeded through the (−)-alcohol **25**, for which three different routes from the corresponding achiral 1-arylcyclohexene were developed.[30] Some significant later steps in the synthesis are shown in Scheme 1. One of these is the free radical cyclisation and oxidation of the bromoacetal **26**, which stereoselectively introduced the side chain adjacent to the aromatic ring into the product **27**. After a series of functional group interconversions and transpositions, the α-iodo enone **28** was subjected to palladium-mediated coupling with the diethyl acetal of propynal to give enyne **29**, partial hydrogenation of which over Lindlar catalyst produced a mixture of dienes **30**. Condensation of this mixture with ammonium acetate in acetic acid completed the construction of the tetrahydroquinoline core of the product **31**, which was readily converted into the target alkaloids (+)-**23** and (+)-**24**.

1.3 Terpenoid quinoline alkaloids, tricyclic derivatives and dimeric analogues

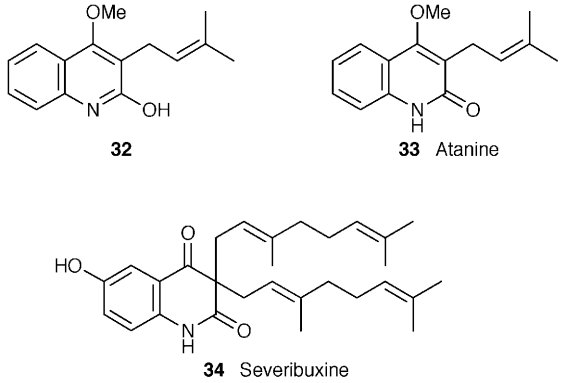
The ostensibly new alkaloid 2-hydroxy-4-methoxy-3-prenylquinoline **32**, isolated along with several known quinoline and carbazolo[1,2-*b*]quinazoline alkaloids from the fruits of *Evodia officinalis*,[4] is actually the hydroxy tautomer of the rather rare quinolin-2-one alkaloid atanine **33**. Confusion between hydroxyquinoline and quinolinone tautomers is a common pitfall for the unwary (*cf.* 'transitorine' in the previous section), and the prevailing tautomer depends on the medium in which spectra are recorded. The alkaloids isolated in this study (see Table 1) showed marginal cytotoxic activity against both human lung and colon carcinoma cells, but were inactive as topoisomerase inhibitors. Atanine from *Zanthoxylum integrifolium* has also proved to be a good inhibitor of platelet aggregation *in vitro*, and exhibited a strong vasorelaxing effect on the contraction of rat aorta induced by potassium ions or norepinephrine.[21]

Severibuxine **34**, a new member of the extremely rare class of monoterpenoid quinolinone alkaloids, is the first quinolinone alkaloid to have been found in the Chinese plant *Severinia buxifolia* (*Atalantia buxifolia*).[16] The usual metabolites from this source are acridone alkaloids, a number of which were also isolated on this occasion. The new compound and its acetate derivative were characterised spectroscopically. Severibuxine proved to be cytotoxic against P-388 murine leukaemia and various other cell lines, as were most of the accompanying acridones.

Aerial parts of *Skimmia laureola*, a medicinal plant native to Kashmir and northern Pakistan, yielded the new dihydrofuro-[2,3-*b*]quinoline alkaloid (+)-methylisoplatydesmine **35**, which was characterised fully by spectroscopic techniques.[17] Its absolute configuration was not ascertained.

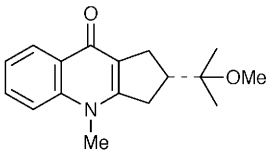


Scheme 1 *Reagents*: i, $H_2C{=}CHOEt$, NBS, Et_2O, 0 °C to rt; ii, Bu_3SnCl (cat.), $NaBH_4$, AIBN (cat.), Bu^{t}OH, reflux; iii, MCPBA, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt; iv, Me_2NH_2Cl, Me_3Al, THF, reflux; v, Swern oxidation; vi, $LiAlH_4$, THF, reflux; vii, MeOCOCl, Et_3N, CH_2Cl_2, rt; viii, CS_2, NaH, MeI, THF, rt; ix, 1,2-$Cl_2C_6H_4$, reflux; x, CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, −15 °C; xi, I_2, pyridine, CCl_4, rt; xii, $HC{\equiv}CCH(OEt)_2$, $PdCl_2(Ph_3P)_2$ (cat.), CuI (cat.), Pr^i_2NH, THF, 0 °C; xiii, H_2, Lindlar catalyst, EtOAc, rt; xiv, NH_4OAc, AcOH, 100 °C; xv, 50% KOH–EtOH (1 : 2) reflux; xvi, AcOCHO, 0 °C.

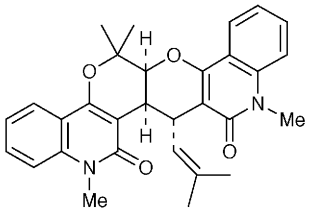


Two dimeric quinolinone alkaloids, melicobisquinolinones A and B, **36** and **37**, were isolated from leaf extracts of the Vietnamese medicinal plant *Melicope ptelefolia* together with one of the constituent moieties, *N*-methylflindersine **38**.[11]

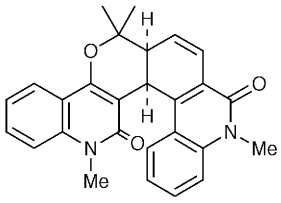
Dimers of prenylated quinolinone alkaloids are extremely uncommon, and most of them can be envisaged as formal Diels–Alder adducts formed from 'monomers' such as *N*-methylflindersine and a prenylquinolinone precursor **39**, as in the case of melicobisquinolinone A. Indeed, the new alkaloid **36** is a regioisomer of paraensidimerine D **40**, another formal Diels–Alder adduct of **38** and **39**, which has been known for almost two decades. Both **36** and **37** were characterised with the help of very thorough NMR spectroscopic studies in which two-dimensional correlations and NOE effects were used to establish connectivities and spatial relationships, as well as the half-chair or twisted conformations for the dihydropyran rings. Since neither of the bismelicoquinolinones showed Cotton effects in their CD spectra, they are thought to be racemic. Alkaloids **37** and **38** inhibited mycelial growth of the fungus *Cladosporium cucumerinum* at nanomolar concentrations, but **36** was inactive.



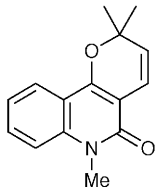
35 Methylisoplatydesmine



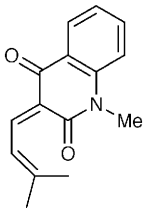
36 Melicobisquinolinone A



37 Melicobisquinolinone B



38 *N*-Methylflindersine



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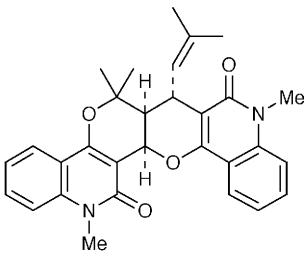


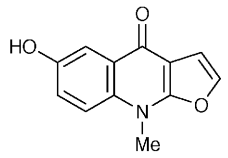
40 Paraensidimerine D

1.4 Furoquinoline alkaloids

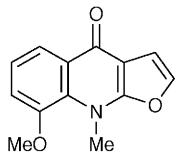
The simple new furoquinoline alkaloids dictangustine-A **41** and iso-γ-fagarine **42** were isolated from the root bark of Chinese *Dictamnus angustifolius* together with several other more common members of this class.[3] The positions of the substituents on ring A were determined by means of NOESY experiments.

Dictamnine **43**, γ-fagarine **44** and haplopine **45**, isolated from *Toddalia asiatica* by bioassay-guided fractionation, showed complete inhibitory activity at 100 μg ml^{-1} towards arachidonic acid-induced platelet aggregation *in vitro*.[20]

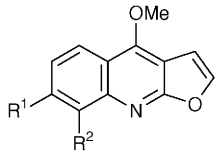
A new synthetic approach to the furoquinoline alkaloids in which the key step involves rhodium-mediated dipolar cycloaddition of diazoquinolinediones is exemplified by the synthesis of isodictamnine **46** (Scheme 2).[31] Cycloaddition of the diazo compound **47** with trimethylsilylacetylene was catalysed by rhodium pivalate and a few drops of ethanolic hydrochloric acid in fluorobenzene at 55 °C, and gave the 'angular' adduct **48** and the desired 'linear' adduct **49** in yields of 57% and 18% respectively. Desilylation of the separable adducts with tetrabutylammonium fluoride afforded the unnatural compound pseudoisodictamnine **50** (87%) and the target alkaloid



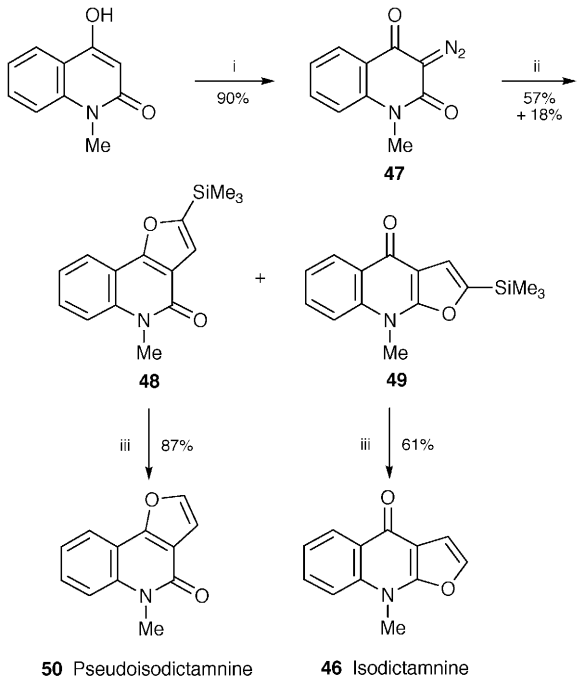
41 Dictangustine-A



42 Iso-γ-fagarine



43 Dictamnine $R^1 = R^2 = H$
44 γ-Fagarine $R^1 = H$; $R^2 = OMe$
45 Haplopine $R^1 = OH$; $R^2 = OMe$



50 Pseudoisodictamnine **46** Isodictamnine

Scheme 2 *Reagents*: i, Et_3N, $MeSO_2N_3$, EtOH, 0 °C to rt; ii, $HC{\equiv}C\text{-}SiMe_3$, $Rh_2(OCOCMe_3)_4$ (0.01 mol%), cat. HCl in Et_2O (1 M), C_6H_5F, 55 °C; iii, Bu_4NF, THF (1 M), rt.

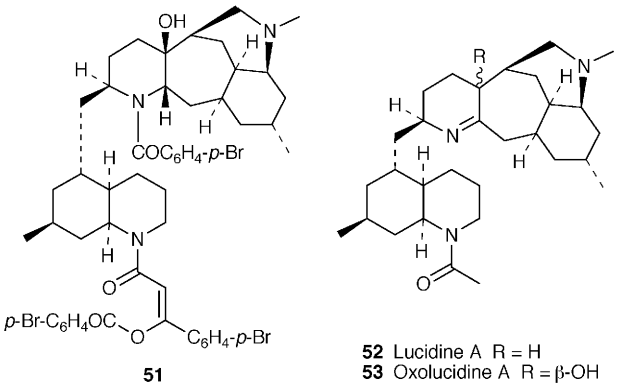
46 (61%). In general, the ratio of angular to linear adducts was found to vary markedly depending on the diazo compound, the dipolarophile and the presence of hydrochloric acid. The method is thus unlikely to be generally useful for preparing naturally occurring furo[2,3-*b*]quinolines and related 2,3-dihydro analogues.

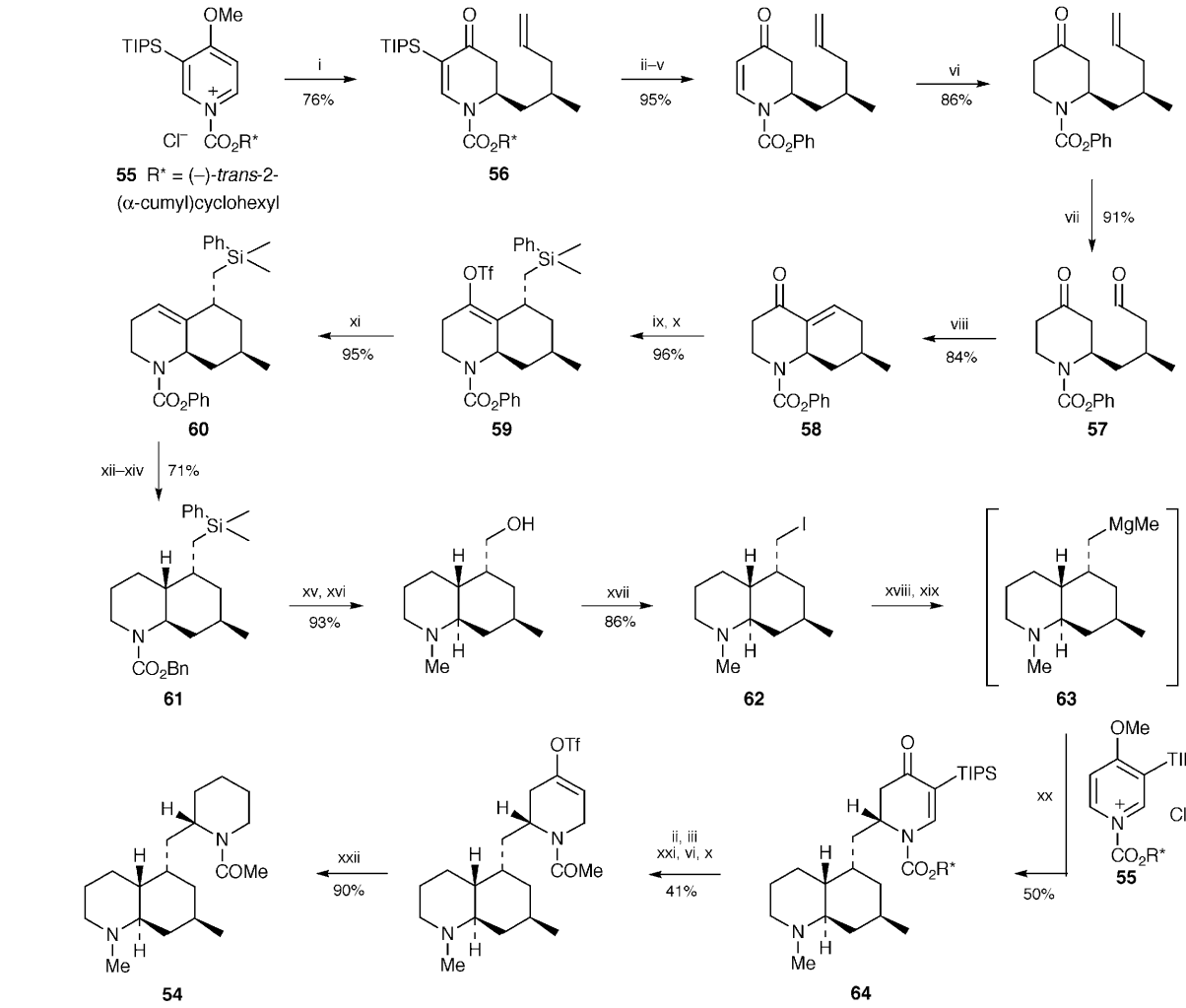
1.5 Decahydroquinoline alkaloids of the genus *Lycopodium*

Most of the alkaloids belonging to the genus *Lycopodium* (clubmosses) are polycyclic compounds commonly possessing $C_{10}N$, $C_{16}N_2$ or $C_{30}N_3$ skeletons. However, several decahydroquinolines bearing additional heterocyclic rings as substituents are known. The structures of two of these compounds, lucidine A and oxolucidine A, have hitherto been only partially elucidated because of the complexity of their NMR spectra. A recent reinvestigation of the extracts of *L. lucidulum* has now resulted in the almost complete assignment of the structures.[32] Separation of four alkaloids, lucidines A and B and oxolucidines A and B, was achieved by countercurrent distribution followed by chromatography on alumina and, finally, reversed-phase HPLC. A chemical correlation between lucidines A and B and the two oxolucidines was established by formation of the latter two from the former on exposure to air. Oxolucidine A was reduced to a dihydro derivative upon treatment with sodium

borohydride in methanol. An unusual tris(*p*-bromobenzoate) derivative of the reduced product gave crystals suitable for X-ray diffraction analysis, which revealed the structure **51**, the absolute configuration of which is as depicted. The structures of lucidine A and oxolucidine A were thus inferred to be **52** and **53**, respectively, and the only remaining uncertainty is the configuration of lucidine A at C-14. The structures of the compounds in the B series remain undetermined.

The simpler *Lycopodium* alkaloid N_a-acetyl-N_b-methylphlegmarine **54** has been synthesised by Comins and coworkers by a route involving two different applications of their well-known methodology based on the use of chiral *N*-acylpyridinium salts as precursors for the preparation of versatile dihydropyridone intermediates (Scheme 3).[33] Firstly, stereoselective addition of (*R*)-2-methylpent-4-enylmagnesium chloride to the salt **55** gave the *N*-acyldihydropyridone **56** in 76% yield. Significant later steps included acid-induced intramolecular aldol condensation of keto-aldehyde **57** to create the hexahydroquinolin-4(1*H*)-one **58**, stereoselective introduction of an axial substituent at C-5 by conjugate addition and trapping of the enolate to form the silylated enol triflate **59**, and defunctionalisation of **59** with a palladium(0) catalyst and formic acid to yield the bridgehead alkene **60**. The ensuing hydrogenation of the alkene took place predominantly (89 : 11) on the face opposite to the silyl substituent, giving a *trans*-fused decahydroquinoline containing four of the target alkaloid's five stereogenic centres. Oxidative desilylation of **61** and manipulation of substituents then completed the synthesis of the key 5-iodomethyldecahydroquinoline **62**. Experience gained with model studies[34] suggested the transformation of **62** into the organomagnesium reagent **63**, which was added to a second equivalent of the salt **55** to produce the new dihydropyridone **64** in 50% yield along with the product of methyl addition (50%). A single crystal X-ray structure determination of **64** confirmed that all five stereogenic centres had been correctly installed. The synthesis of alkaloid **54** was completed as shown in Scheme 3. This route, the first asymmetric synthesis



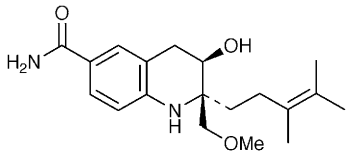


Scheme 3 *Reagents*: i, (*R*)-H_2C=$CHCH_2CH(Me)CH_2MgCl$, THF, −78 to −42 °C, then 10% aq. HCl; ii, NaOMe in MeOH (4.37 M), reflux; iii, 10% aq. HCl, THF, rt; iv, BuLi, THF, −78 °C; v, PhOCOCl, THF, −78 °C; vi, L-Selectride, $BF_3{\cdot}Et_2O$, THF, −78 °C; vii, O_3, MeOH, −78 °C, then Me_2S, −78 °C to rt; viii, *p*-TsOH·H_2O, C_6H_6, 40–50 °C; ix, $PhMe_2SiCH_2MgCl$, CuI, Et_2O–THF, 0 °C to rt; x, *N*-(5-chloro-2-pyridyl)triflimide, DMPU, Et_2O–THF, heat; xi, Bu_3N, HCO_2H, Ph_3P, $Pd(OAc)_2$, DMF, 60 °C; xii, KOH, Pr^iOH–H_2O, reflux; xiii, H_2 (1 atm), 5% Pd/C, AcOH, EtOH, rt; xiv, BnOCOCl, NaOH (1 M), 0 °C to rt; xv, 35% $MeCO_3H$ in AcOH, $Hg(OAc)_2$, rt; xvi, $LiAlH_4$, THF, reflux; xvii, $(Ph_2PCH_2)_2$, $(CH_2I)_2$, CH_2Cl_2, rt to reflux; xviii, Bu′Li (2 equiv.), Et_2O, −78 to −45 °C; xix, MeMgBr (1 equiv.), Et_2O; xx, salt **55**, PhMe, −78 °C; xxi, AcCl, K_2CO_3, THF, rt; xxii, H_2 (1 atm), 5% Pd/C, Li_2CO_3, EtOAc.

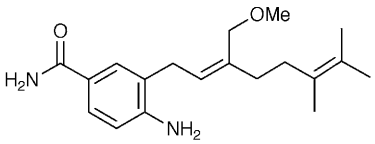
of (−)-N_a-acetyl-N_b-methylphlegmarine, established the (2′*S*, 4a*R*,5*S*,7*R*,8a*R*) absolute configuration of the alkaloid.

1.6 Quinoline alkaloids from fungal and microbial sources

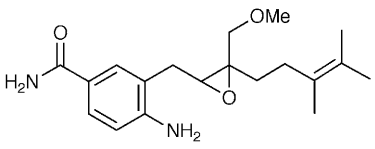
It has been suggested that the biogenesis of the *Streptomyces* metabolite benzastatin D **65** from the simpler benzastatin A **66** is *via* an epoxide such as **67**, which can undergo cyclisation to give either **65** or the alternative metabolite benzastatin E **68**.[35] In model studies designed to probe these options, the epoxides **69** and **70** were found to give exclusively the indoline products **71** and **72** after catalytic hydrogenation over a 10% palladium-on-carbon catalyst. However, it is possible that benzastatins D and E interconvert through an aziridine intermediate. This hypothesis was tested by the model reaction sequence shown in Scheme 4. Treatment of the aniline derivative **73** with iodine yielded the 3-iodotetrahydroquinoline **74**, which was converted into the aziridine **75** when exposed to DBU in toluene at 100 °C. Solvolysis of **75** with silver tetrafluoroborate in aqueous acetone yielded only the tetrahydroquinolin-3-ol **76**, but treatment with anhydrous hydrogen chloride produced a 1 : 1 mixture of the alternative products **77** and **78**.



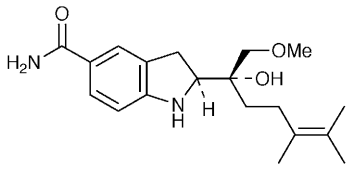
65 Benzastatin D



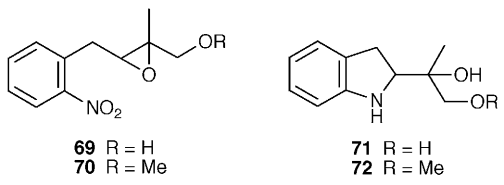
66 Benzastatin A



67



68 Benzastatin E

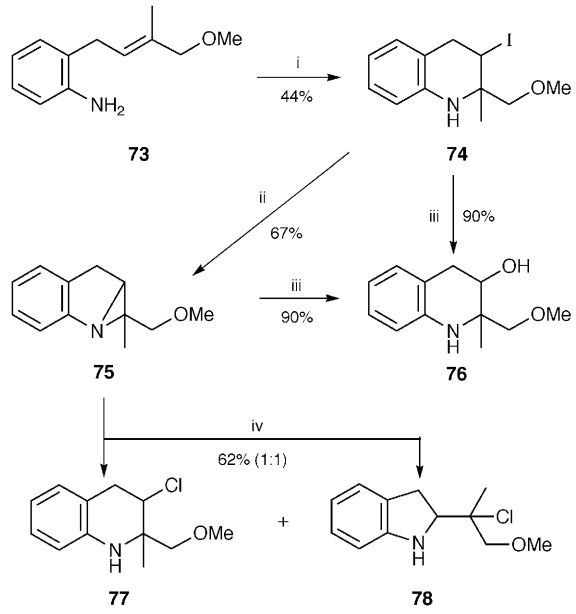


69 R = H
70 R = Me

71 R = H
72 R = Me

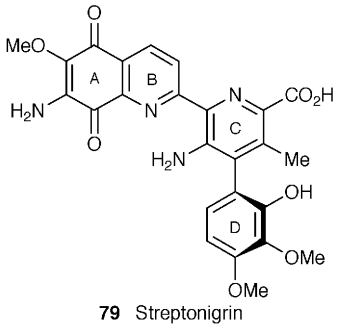
Further studies aimed at the total synthesis of the broad-spectrum antibiotic and antitumour compound streptonigrin **79** have focused on coupling strategies for building the CD ring system.[36] The best results were achieved by means of Suzuki coupling between the boronic ester **80** and 4-chloro-3-nitropyridine [$Pd(Ph_3P)_4$, K_2CO_3, DME, reflux], which gave the model biaryl system **81** in 81% yield.

The first total synthesis of luzopeptins A–C **82**–**84**, potent antitumour antibiotics isolated from the microorganism

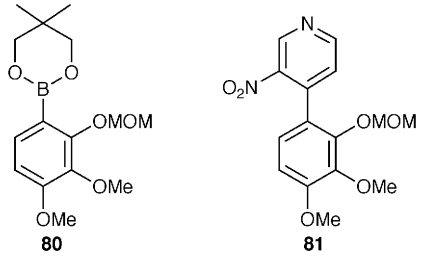


73 **74** **75** **76** **77** **78**

Scheme 4 *Reagents*: i, I_2, Na_2CO_3, CH_2Cl_2, rt; ii, DBU, PhMe, 100 °C; iii, $AgBF_4$, Me_2CO–H_2O, rt; iv, dry HCl, CH_2Cl_2, rt.



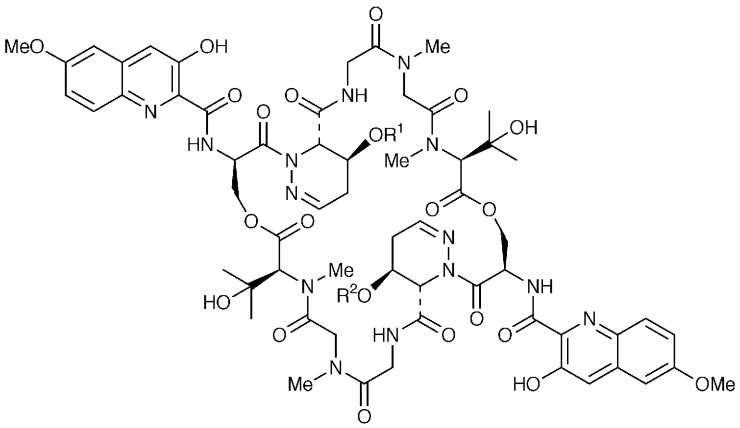
79 Streptonigrin



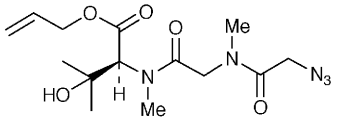
80 **81**

Actinomadura luzonensis almost twenty years ago, has been communicated by Boger and co-workers.[37] The challenges posed by the construction of the symmetrical decadepsipeptide core, obviously the main feature of the synthesis, will not be described here since they are only peripheral to the topic of this review. At the end of the synthesis, 3-hydroxy-6-methoxyquinoline-2-carboxylic acid was attached to free amine groups on the depsipeptide core by conventional amide formation to give luzopeptin C in 80% yield . Peracetylation followed by mild basic hydrolysis then yielded a mixture of luzopeptins A (50%) and B (20%). Ciufolini and co-workers have also described a synthetic approach to the luzopeptins in which the main objective was the assembly of the key tripeptide **85** in multigram amounts.[38]

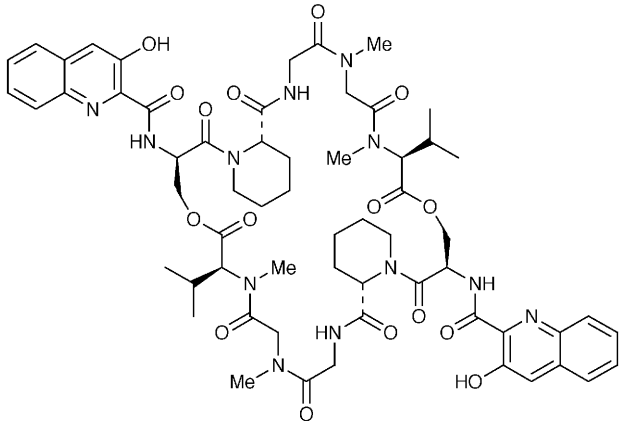
Boger and Saionz have reported further studies on the DNA-binding properties of the antitumour antibiotic sandramycin **86** and 23 synthetic analogues in which the intercalation chromophore was systematically varied[39] (*cf.* ref. 25*b*). The surface plasmon resonance technique was used to establish binding constants to the high-affinity bis-intercalation binding site 5′-$(GCATGC)_2$, and to evaluate the preference for sandramycin binding to 5′-$d(GCXXGC)_2$ (X = AT, TA, CG, GC). In general,



82 Luzopeptin A $R^1 = R^2 = Ac$
83 Luzopeptin B $R^1 = H$; $R^2 = Ac$
84 Luzopeptin C $R^1 = R^2 = H$



85



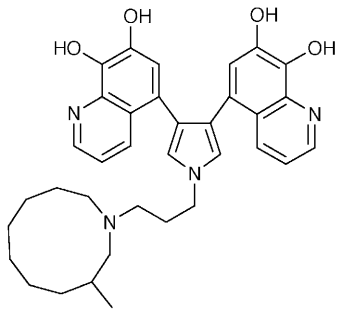
86 Sandramycin

results paralleled those previously obtained by fluorescence quenching measurements, but in addition it was found that complexes formed at the high-affinity bis-intercalation sites were exceptionally stable, as judged by the unusually slow off rates for binding dissociation. This feature appears to correlate with previously observed cytotoxicity.

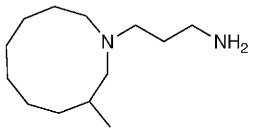
1.7 Quinoline alkaloids from animals

(+)-Halitulin, a marine metabolite possessing the unique 3,4-bis(quinolin-5-yl)pyrrole structure **87** (absolute configuration unknown), was isolated from the sponge *Haliclona tulearensis* collected in Sodwana Bay near Durban, South Africa.[9] This astonishing structure was revealed by a combination of spectroscopic and chemical analyses. In particular, the 7,8-dihydroxyquinoline unit, unprecedented in a natural product, was suggested by the formation of an unstable *ortho*-quinone on treatment with sodium periodate. Its position of attachment was inferred from NOE effects between 2-H on the pyrrole ring and 4-H and 6-H on the quinoline system. The azacyclodecane and aliphatic components were deduced after spectroscopic comparisons with haliclorensin **88**, a simpler metabolite recently reported from the same sponge. Halitulin forms an unstable tetraacetate, and is oxidised on exposure to air and light to a mixture of two azacyclodecane *N*-oxides, after which quinone formation apparently occurs. The new alkaloid showed cytotoxic activity towards cell cultures of P-388 murine leukaemia, A-549 human lung carcinoma, HT-29 human colon carcinoma and MEL-28 human melanoma (IC_{50} 0.025, 0.012, 0.012 and 0.025 μg cm^{-3}, respectively).

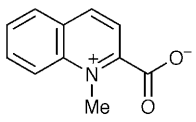
The much simpler alkaloid *N*-methylquinolinium-2-carboxylate **89**, a natural betaine isolated from whole-body extracts of the firefly *Photuris versicolor*, appears to participate in the



87 Halitulin



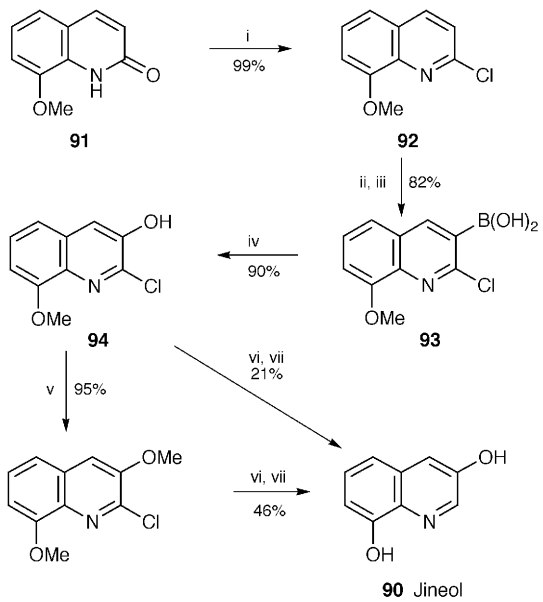
88 Haliclorensin



89

insects' arsenal of chemical defences against predators.[14] This is the first time that this known compound has been found as a natural product. The structure was deduced on the basis of its spectroscopic properties, and confirmed by synthesis following a reported procedure.[40]

Jineol (quinoline-3,8-diol) **90**, a cytotoxic alkaloid isolated from the centipede *Scolopendra subspinipes*, has been synthesised by a route in which directed *ortho*-lithiation of a 2-chloroquinoline is the principal step (Scheme 5).[41] 8-Methoxyquinolin-2-one **91**, prepared in three steps from *o*-anisidine, was converted into the 2-chloro derivative **92** by treatment with phosphorus oxychloride, following which lithiation with lithium tetramethylpiperidide and treatment with trimethyl borate afforded the quinoline-3-boronic acid **93** in 82% overall yield. Oxidation with peracetic acid to give the quinolin-3-ol **94** proceeded in excellent yield. Dechlorination of **94** with zinc in acetic acid followed by demethylation gave a poor overall yield (21%) of the target alkaloid **90**, but the yield was improved to 46% by forming the methyl ether of **94** before carrying out the



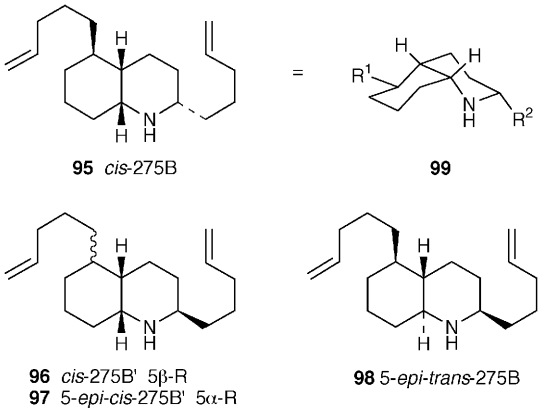
Scheme 5 *Reagents*: i, $POCl_3$, pyridine (cat.), C_6H_5Cl, reflux; ii, LiTMP, THF, −75 °C; iii, $B(OMe)_3$, THF, −75 °C, then H_2O–THF; iv, $MeCO_3H$ (32%), HOAc, 0 °C to rt, then $NaHSO_3$, H_2O; v, Me_2SO_4, K_2CO_3, Me_2CO, reflux; vi, Zn, HOAc, H_2O, 70 °C; vii, pyridine·HCl, 200–220 °C.

defunctionalisations. A number of ethers of jineol were also prepared for biological screening by alkylating **90** with haloalkanes in dimethyl sulfoxide containing powdered potassium hydroxide.

1.8 Decahydroquinoline alkaloids from ants and amphibians

A major new survey of the alkaloidal constituents isolated from the skins of frogs, toads and related amphibians by Daly, Garraffo and Spande provides a snapshot of the current state of knowledge in this rapidly expanding area of investigation.[42] The section on 2,5-disubstituted *cis*- and *trans*-decahydroquinoline alkaloids, almost 40 of which have been partially or fully characterised to date, covers the occurrence, biological activity, synthesis and spectroscopic identification of these compounds, and gives valuable information on their IR and MS behaviour in particular. Also mentioned briefly are some tentative tetrahydroquinoline and octahydroquinoline variants, and putative Diels–Alder dimers of the latter. The smaller family of gephyrotoxins, which possess a perhydropyrrolo[1,2-*a*]-quinoline core, is dealt with separately.

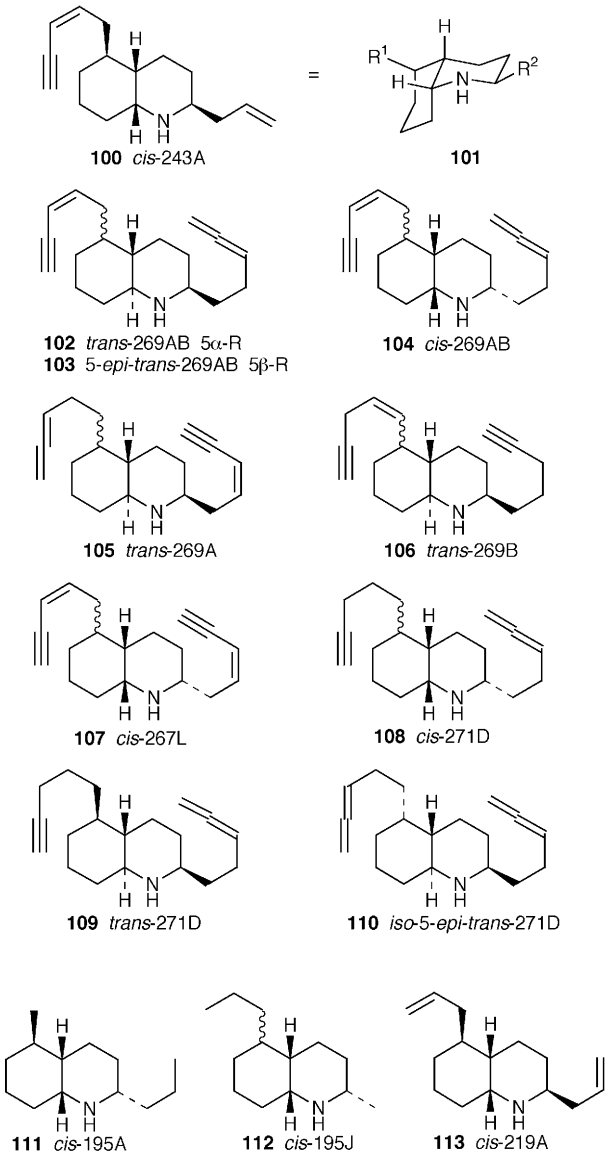
The hypothesis that most of the skin alkaloids of amphibians are derived from dietary sources has received a fillip from the discovery of decahydroquinoline alkaloids in ants, reported in two recent papers. Extracts from virgin queens of the myrmicine ant *Solenopsis* (*Diplorhoptrum*) *azteca* from Puerto Rico contained two new caste-specific alkaloids of molecular mass 275 in the ratio 1:9.[18] Mass spectrometric fragmentation patterns and FTIR spectra showed beyond doubt that these were decahydroquinolines bearing unsaturated side chains – the first compounds of this class ever detected in ants. Two related alkaloids of the same molecular mass isolated from Costa Rican populations of the frog *Dendrobates pumilio* had been known for some years, but had never previously been obtained in sufficient quantity for characterisation. Valuable spectroscopic comparisons between the four compounds proved that they were diastereomeric; in particular, the stereochemical relationships were inferred largely on the basis of Bohlmann bands and fingerprint absorptions in the IR spectra. The upshot is that the frog alkaloids (decahydroquinolines *cis*-275B and *cis*-275B′) have been assigned the structures **95** and **96**, respectively, while the new ant alkaloids (coded as 5-*epi*-*cis*-275B′ and 5-*epi*-*trans*-275B) are **97** and **98**. A substantial ^1H and ^{13}C NMR spectroscopic study of *cis*-275B **95** and its deuterium chloride salt, and extensive comparisons with synthetic model systems, permitted the determination of an '*N*-*endo*' conformation, as illustrated in **99**.



Furthermore, accumulated experience and recent advances in spectroscopic interpretation also allowed the authors to clarify the structures of several other amphibian decahydroquinolines that have hitherto been only tentatively identified. ^{13}C NMR spectroscopic data were obtained for the first time for *cis*-243A **100** from *D. auratus*; the '*N*-*exo*' conformation **101**, with the C-2 substituent equatorial and the C-5 substituent axial, appears to be favoured. The structure of *trans*-269AB from *D. pumilio* and various populations of *D. histrionicus* – actually, an inseparable mixture of **102** and its C-5 epimer **103** – was also based partly on NMR spectroscopic measurements, and is comparatively secure. Several minor stereoisomers in the 269AB complex have not yet been clarified, although a related compound from Costa Rican *D. granuliferus* seems to be an isomer of *cis*-269AB **104**. Some residual uncertainty also hangs over the configuration at C-5 of alkaloids *trans*-269A **105** and *trans*-269B **106** from *D. auratus*. A population of *D. pumilio* from Isla Colón, Panama produced the partly characterised *cis*-267L **107**, while a suite of decahydroquinolines of molecular mass 271 from *D. granuliferus* appeared to include *cis*-271D **108** and *trans*-271D **109** (in both of which the C-2 and C-5 side-chains might be interchanged), and *iso*-5-epi-*trans*-271D **110**. The paper contains a useful list of 36 known and tentative decahydroquinoline alkaloids and their amphibian sources.

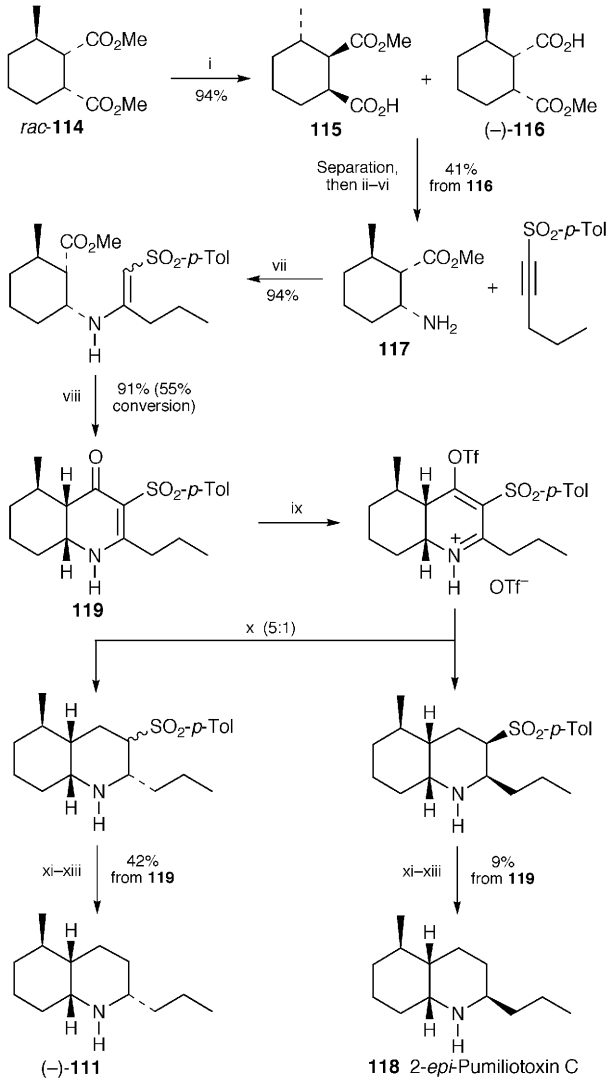
A Brazilian myrmicine ant species belonging to the *Solenopsis* (*Diplorhoptrum*) sp. *picea* group was found to contain three structurally isomeric alkaloids in the ratio 3:1:1.[10] The major component proved to be identical to a known amphibian 4-methyl-6-propylquinolizidine (also known as quinolizidine 195C). The minor components, characterised by GC-MS behaviour and FTIR spectroscopy, proved to be the well-known frog alkaloid *cis*-195A **111** (the inappropriately-named pumiliotoxin C, or *cis*-fused 5-methyl-2-propyldecahydroquinoline; *vide infra*) and a hitherto unknown stereoisomer. This isomer showed fingerprint absorptions in the IR spectrum typical of a *cis*-fused decahydroquinoline, as well as a Bohlmann band pattern indicative of *cis*-disposed hydrogen substituents at C-2 and C-8. The relative stereochemistry at C-5 was not determined. Structure **112** was proposed for the new product, which has been assigned the code designation *cis*-195J. Significantly, small quantities of the same triad of alkaloids have been found, among several others, in a number of populations of the Madagascan mantelline frog *Mantella betsileo*, which strongly suggests that ants related to the Brazilian species are likely dietary sources of the sequestered skin alkaloids.

An important communication by the Daly team describes the use of chemical ionisation tandem mass spectrometry (CI-MS/MS) with ammonia as the reagent gas for elucidating the structures of several classes of monocyclic and bicyclic amphibian



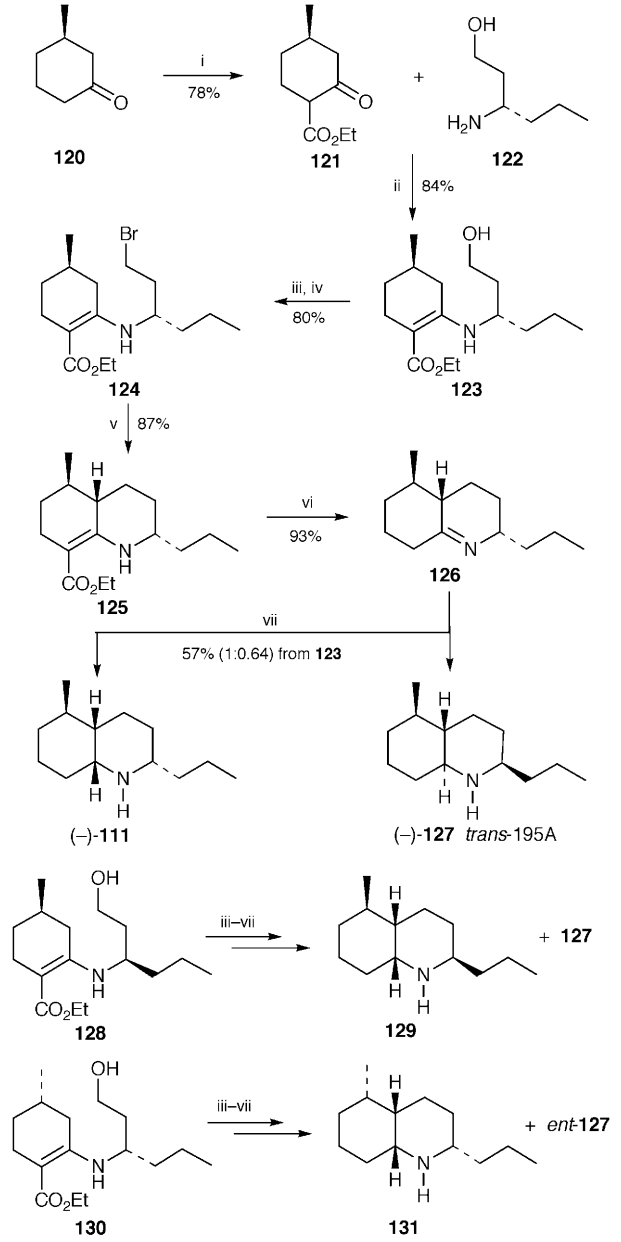
alkaloids, including decahydroquinolines.[43] The collision-induced dissociation of the initially generated $[M + H]^+$ ion, which is incapable of releasing a radical, results in markedly different fragmentation pathways when compared to conventional electron-impact methods, and casts new light on the structures of the alkaloids. The CI-MS/MS spectra of *cis*-195A **111** and *cis*-219A **113** were given to illustrate the application of the technique to decahydroquinoline systems.

Decahydroquinoline *cis*-195A, still referred to as pumiliotoxin C by most synthetic chemists (to the chagrin of the Daly group[42]), is the prototypical decahydroquinoline alkaloid from the skin secretions of dendrobatid frogs, and it remains a very popular target for synthesis. Some years ago, Back and Nakajima reported a short synthesis of the racemic alkaloid[44] (*cf.* ref. 25*c*); this route has now been modified as shown in Scheme 6 to yield the (−)-enantiomer **111**.[45] The key to enantioselectivity lay in the selective hydrolysis of the racemic diester **114** with pig liver esterase to give a 1 : 1 mixture of the two half-esters **115** and **116**. Although these compounds were difficult to separate, a combination of chemical transformations and recycling allowed recovery of the latter in a total yield of 67%. The (−)-half ester **116** was converted in four steps into the (−)-amino ester **117**, following which syntheses of (−)-**111** and the epimeric compound 2-*epi*-pumiliotoxin C **118** were completed *via* the bicyclic enaminone (+)-**119** by means of the methodology previously used for making the racemic compounds.

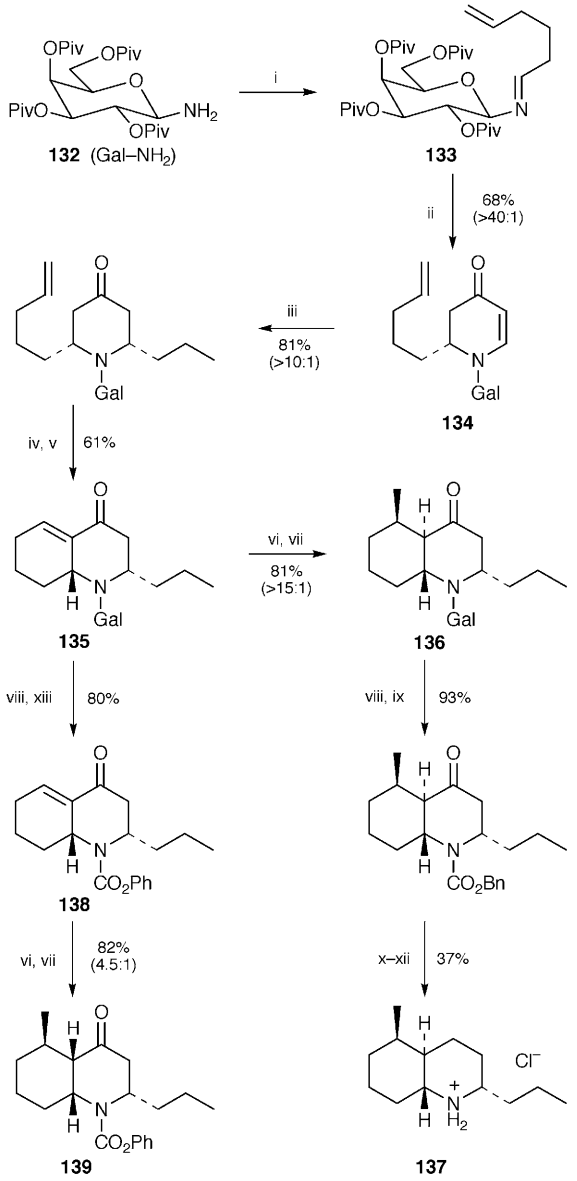


Scheme 6 *Reagents*: i, pig liver esterase, phosphate buffer (pH 8), rt; ii, CH_2N_2 in Et_2O, MeOH; iii, NaOH, H_2O, reflux, then HCl; iv, Ph_2PON_3, Et_3N, PhMe, reflux; v, BnOH, pyridine, reflux; vi, H_2 (1 atm), 10% Pd/C, HCO_2H, MeOH, rt; vii, EtOH, rt; viii, LDA, THF, −78 °C to rt; ix, Tf_2O, CH_2Cl_2, reflux; x, H_2 (100 atm), PtO_2, MeOH, 6 d; xi, BnOCOCl, aq. K_2CO_3, $CHCl_3$; xii, 5% Na–Hg, Na_2HPO_4, MeOH–THF (1 : 1), rt; xiii, H_2 (1 atm), 10% Pd/C, EtOH, rt.

Short complementary syntheses of (−)-pumiliotoxin C and several of its stereoisomers, devised by Habermehl and co-workers,[46] are illustrated in Scheme 7. Condensation of the kinetically-generated enolate of (*R*)-(+)-3-methylcyclohexanone **120** with diethyl carbonate yielded the keto ester **121**, after which reaction with (*S*)-(+)-3-aminohexanol **122** produced the 3-aminoacrylate **123**. Sequential replacement of the hydroxy group by tosylate and bromide gave **124**, stereoselective cyclisation of which was effected in 87% yield merely by heating in degassed DMF at 100 °C. The stereochemistry at C-4a in the product **125** is probably a result of steric effects during cyclisation. Removal of the ethoxycarbonyl blocking group was accomplished by heating **125** under reflux in a mixture of acetic acid, hydrochloric acid and pyridine. The imine functionality of the product **126** was hydrogenated over palladium on charcoal to produce a mixture of (−)-pumiliotoxin C **111** and the (−)-*trans*-fused epimer **127** in a ratio of about 1 : 0.64 and an overall yield of 57% based on **123**. Epimerisation of the propyl chain in the latter product was probably caused by isomerisation of the imine in the presence of the palladium catalyst. The products could be separated by chromatography on alumina, but characterisation, including X-ray crystallographic analysis, was performed on the more stable hydrochloride salts. The *trans*



Scheme 7 *Reagents*: i, $(EtO)_2CO$, LDA, THF, −78 °C to rt; ii, TFA (cat.), 4Å molecular sieves, PhMe, 100 °C; iii, *p*-$TolSO_2Cl$, DMAP, CH_2Cl_2, rt; iv, NaBr, DMF, rt; v, DMF, 4Å molecular sieves, 100 °C; vi, HOAc, pyridine, 20% aq. HCl, reflux; vii, H_2, 10% Pd/C, EtOH, then chromatography on Al_2O_3 (activity grade III).

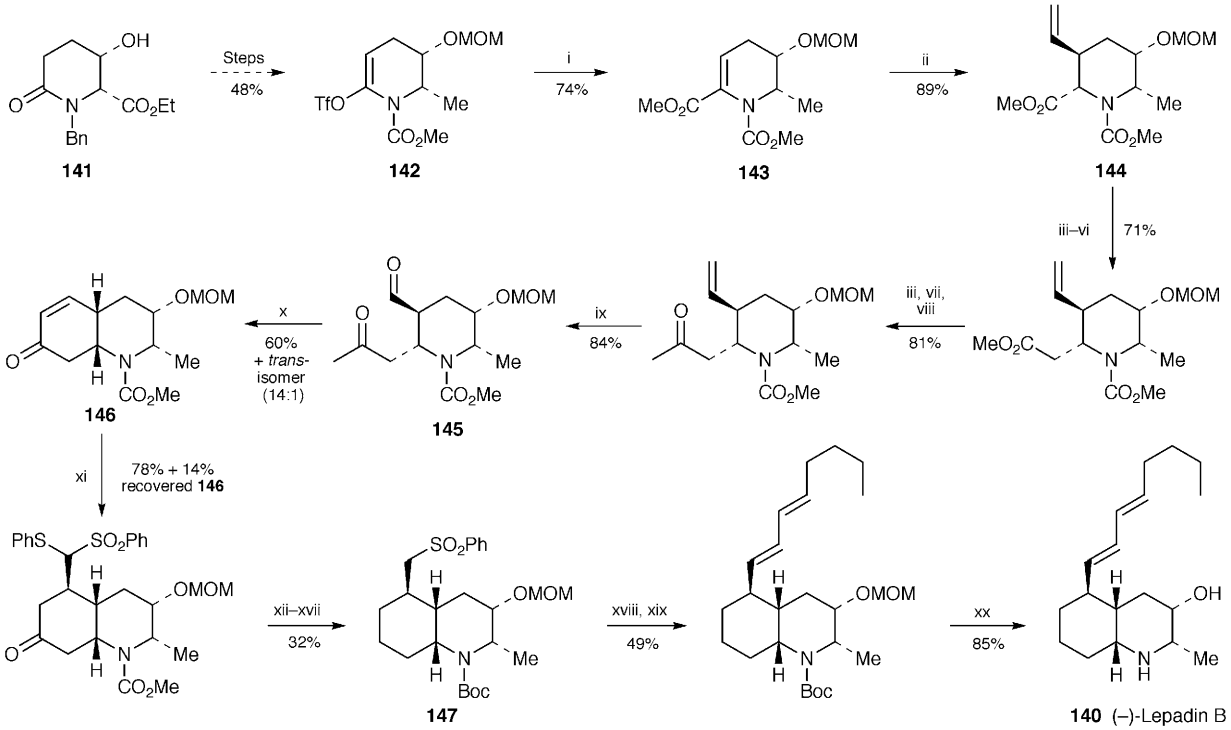


Scheme 8 *Reagents*: i, hex-5-enal, 4Å molecular sieves, pentane; ii, 1-methoxy-3-trimethylsilyloxybutadiene, $ZnCl_2{\cdot}Et_2O$, THF, −20 °C; iii, PrMgCl, CuCl, $BF_3{\cdot}Et_2O$, THF, −78 °C; iv, $NaIO_4$, K_2OsO_4 (cat.), aq. dioxane; v, NaOH, dibenzo-18-crown-6, C_6H_6; vi, Me_2CuLi, Me_3SiCl, THF, −78 °C; vii, Bu_4NF; viii, HCl (1 M), aq. MeOH (1:5); ix, BnO-COCl, $NaHCO_3$; x, $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$; xi, H_2, Raney Ni; xii, HCl; xiii, PhOCOCl.

compound would appear to be the same as the minor frog alkaloid *trans*-195A, the stereochemistry at C-5 of which was previously undetermined, but which has now apparently been clarified.[42] In the same manner, the aminoacrylate **128**, prepared from (*R*)-(+)-3-methylcyclohexanone **120** and (*R*)-(−)-3-aminohexanol *ent*-**122**, was transformed into a mixture of **127** and the new *cis*-fused pumiliotoxin C isomer **129**. Finally, aminoacrylate **130**, derived from (*S*)-(−)-3-methylcyclohexanone *ent*-**120** and (*S*)-(+)-3-aminohexanol **122**, yielded another new *cis*-fused stereoisomer **131** as well as *ent*-**127**, the enantiomer of the *trans*-fused product.

Another approach that resulted in the synthesis of both *cis*- and *trans*-fused decahydroquinolines of the pumiliotoxin C class employed 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosamine **132** as an unusual chiral auxiliary (Scheme 8).[47] The imine **133** derived from reaction between this sugar derivative and hex-5-enal underwent a stereoselective Diels–Alder cycloaddition with 1-methoxy-3-trimethylsilyloxybutadiene to give the dihydropiperidin-4-one **134** in 68% yield and a diastereomeric ratio (dr) of better than 40:1. A sequence of reactions similar to those used in the Comins *Lycopodium* synthesis (*cf.* Section 1.5, Scheme 3) produced the pivotal bicyclic enone **135**, after which stereoselective conjugate addition with lithium dimethylcuprate in the presence of trimethylsilyl chloride afforded the *trans*-fused decahydroquinolin-4-one **136** (81%, dr > 15:1). The structure of this product was substantiated by X-ray crystallography. The chiral auxiliary was removed with aqueous acid, after which standard transformations completed the synthesis of the hydrochloride salt of **137**, which is yet another stereoisomer of pumiliotoxin C. The interesting feature of this route is that the chiral auxiliary apparently steers the protonation of the enolate formed from **135** by conjugate addition. When the sugar moiety of **135** was replaced by phenoxycarbonyl to give **138**, the subsequent reaction with methylcuprate yielded the *cis*-fused product **139** in 82% yield and a dr of 4.5:1. Both **138** and **139** had previously featured in a synthesis of pumiliotoxin C by Comins and Dehghani.[48]

The first enantioselective total synthesis of the marine decahydroquinoline alkaloid lepadin B **140**, a metabolite of the



Scheme 9 *Reagents*: i, $Pd(PPh_3)_4$, PPh_3, Et_3N, MeOH, CO (balloon), DMF, rt; ii, $H_2C{=}CHLi$, CuI, Et_2O, −78 to −30 °C; iii, $LiOH{\cdot}H_2O$, MeOH–H_2O (3 : 1), 60 °C; iv, EtOCOCl, Et_3N, THF, 0 °C; v, CH_2N_2, Et_2O; vi, $PhCO_2Ag$, Et_3N, Et_2O; vii, Im_2CO, Et_3N, MeONHMe·HCl, CH_2Cl_2, 0 °C to rt; viii, MeMgBr, THF, 0 °C to rt; ix, OsO_4, $NaIO_4$, dioxane–H_2O (1 : 1), rt; x, DBU (4 equiv.), C_6H_6, reflux; xi, $PhSCH_2SO_2Ph$, BuLi, THF, −78 to −10 °C; xii, Bu_3SnH, AIBN, C_6H_6, reflux; xiii, $NaBH_4$, MeOH–CH_2Cl_2 (1 : 10), 0 °C; xiv, Im_2CS, $(CH_2Cl)_2$, reflux; xv, Bu_3SnH, PhMe, reflux; xvi, PrSLi, HMPA–THF, rt; xvii, $(Boc)_2O$, C_6H_6, reflux; xviii, BuLi, THF, −78 °C, then 2-heptenal, −78 to −50 °C; xix, Na–Hg, Na_2HPO_4, MeOH, rt; xx, conc. HCl, MeOH, reflux.

tunicate (sea-squirt) *Clavelina lepadiformis*, has been achieved by Toyooka *et al.* as shown in Scheme 9.[49] These workers once again commenced with the chiral building block **141**, which has featured in several of their previous alkaloid syntheses. In this case, the building block was converted in a number of steps into the vinyl triflate **142** (48% overall yield), which underwent palladium-catalysed methoxycarbonylation to produce the unsaturated ester **143**. The ensuing conjugate addition of a vinyl group gave the 2,3-*trans*-substituted ester **144** as a single isomer. After a series of standard transformations, the crucial intramolecular aldol condensation of keto-aldehyde **145** was achieved with DBU in boiling benzene. Some epimerisation of the aldehyde also occurred under these conditions, and the *cis*-fused bicyclic enone **146** was isolated in 60% yield as a 14 : 1 mixture with the *trans*-fused isomer. Conjugate addition of phenylthiomethyl phenyl sulfone at C-5 was followed by a series of defunctionalisations to give the sulfone-containing decahydroquinoline **147**. To complete the synthesis, Julia coupling of **147** with 2-heptenal followed by removal of the remaining protecting groups yielded lepadin B **140**. The spectra of the laevorotatory trifluoroacetate salt of the synthetic product ($[\alpha]_D^{26}$ −92.6, MeOH) were identical with those of the salt of natural lepadin B ($[\alpha]_D$ −96, MeOH). This synthesis verifies the (2*S*,3*S*,4a*S*,5*S*,8a*R*) absolute configuration of (−)-**140**.

Table 2 Isolation and detection of quinazoline alkaloids

Species	Alkaloid[a]	Ref
Aspergillus ochraceus	(−)-Circumdatin C[b] **151**	50
	(−)-Circumdatin D[b] **152**	51
	(−)-Circumdatin E[b] **153**	
	(−)-Circumdatin F[b] **154**	
Calanthe aristurifera, C. discolor, C. reflexa	Tryptanthrin **165**	52
Evodia officinalis	Evodiamine	4
	Rutaecarpine **161**	
Glycosmis cf. chlorosperma	(*E*)-Bogorin[b] **150**	53
	(*Z*)-Bogorin[b] **148**	
Penicillium sclerotigenum	Sclerotigenin[b] **157**	54
Penicillium thymicola	(+)-Alantrypinone[b] **158**	55
	(−)-Fumiquinazoline F **159**	
Phellodendron amurense (callus cultures)	(−)-7,8-Dihydroxyrutaecarpine[b] **162**	56
	(+)-7-Hydroxyrutaecarpine **161**	
Zanthoxylum integrifolium	14-Formylrutaecarpine	21

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

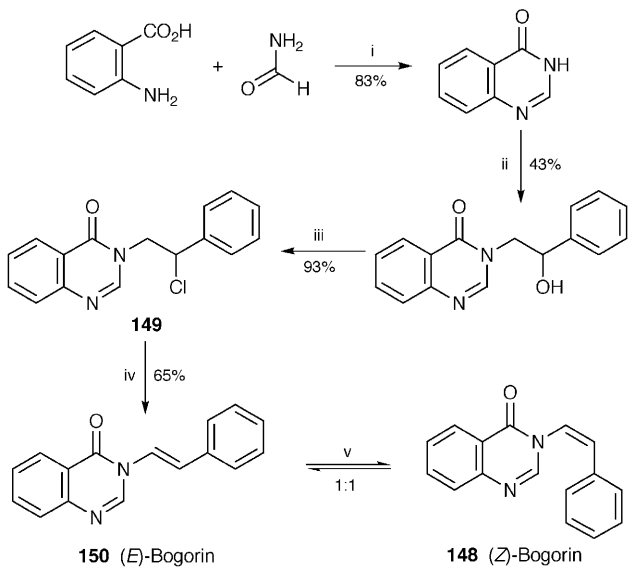
2 Quinazoline alkaloids

2.1 Occurrence, characterisation and biological activity

New quinazoline alkaloids isolated during the period under review are listed in Table 2 together with known alkaloids isolated from new sources.[4,21,50–56]

(*Z*)-Bogorin **148**, a new quinazolone alkaloid isolated from Javanese *Glycosmis cf. chlorosperma*, was obtained in quantities too small for confirmation of its structure by two-dimensional NMR spectroscopic experiments.[53] The putative structure was therefore substantiated by the short synthesis shown in Scheme 10. Base-induced elimination of hydrogen chloride from **149** produced exclusively (*E*)-bogorin **150**, which proved to be identical to another trace alkaloid in the plant extract. Photochemical isomerisation of **150** yielded a separable 1 : 1 mixture of (*E*)- and (*Z*)-bogorins, the latter of which gave ^1H and ^{13}C NMR spectroscopic signals identical to those of natural **148**. (*Z*)-Bogorin showed antifungal activity towards *Cladosporum herbarium* (IC_{50} 40 μg cm^{-3}), and was moderately cytotoxic towards *Artemia salina* (brine shrimp). The (*E*)-isomer and the synthetic precursors were significantly less active.

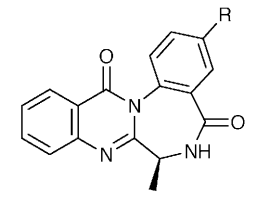
New peptide-like quinazolinone alkaloids derived from anthranilic acid together with other simple amino acids continue to turn up in fungal extracts. Circumdatin C **151** and the



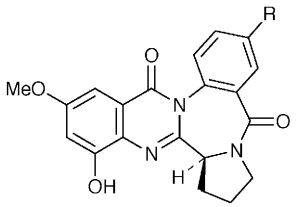
Scheme 10 *Reagents*: i, 130 °C, 2.5 h; ii, styrene oxide, pyridine (cat.), Pr^{i}OH, reflux; iii, $SOCl_2$, C_6H_6, reflux; iv, DBU, C_6H_6, reflux; v, *hv* (high pressure Hg lamp), cyclohexane, rt.

minor metabolites **152**–**154**, named circumdatins D, E and F respectively, are quinazolino[3,2-*a*][1,4]benzodiazepinediones from a terrestrial isolate of *Aspergillus ochraceus* (subgenus *Circumdati*, section *Circumdati*).[50,51] The compounds, formally biosynthesised from two substituted anthranilate units and either L-alanine or L-proline, were accompanied by two unusual zwitterionic benzodiazepines, circumdatins A **155** and B **156**. All structures were elucidated on the basis of spectroscopic measurements, with two-dimensional NMR experiments playing the expected dominant role. The simpler quinazolinobenzodiazepine sclerotigenin **157**, obtained from extracts of the sclerotia (reproductive structures) of *Penicillium sclerotigenum*, is derived from anthranilic acid and glycine.[54] This compound, which first appeared in the literature over twenty years ago as a purely synthetic material,[57] gave NMR spectra at ambient temperatures consistent with the presence of atropisomers, a phenomenon that has been observed with related 1,4-benzodiazepines. Variable temperature NMR measurements indicated an interconversion barrier of about 20 kcal mol^{-1}. Sclerotigenin appears to be largely responsible for the observed antiinsectan activity of the fungal extract towards the crop pest *Helicoverpa zea* (the corn earworm).

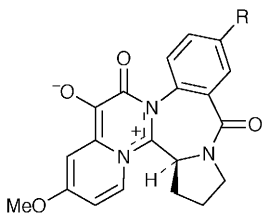
Two major metabolites isolated from a new *Penicillium* species, *P. thymicola*, are the novel alkaloid, (+)-alantrypinone



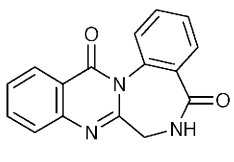
151 Circumdatin C R = OH
154 Circumdatin F R = H



152 Circumdatin D R = OMe
153 Circumdatin E R = H

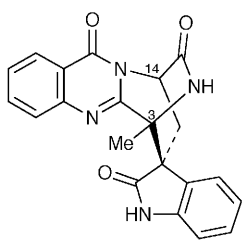


155 Circumdatin A R = OMe
156 Circumdatin B R = H

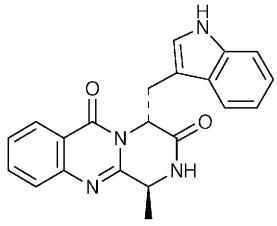


157 Sclerotigenin

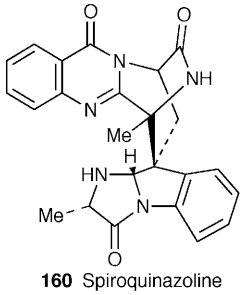
158 and a known compound, fumiquinazoline F **159**.[55] In addition to the usual complement of spectroscopic methods used for characterising the new compound, X-ray crystallographic analysis revealed the (3*R*,14*R*) absolute configuration shown in **158**. The implication is that alantrypinone incorporates L-alanine and the unusual amino acid D-tryptophan, as do fumiquinazoline F and the closely related spiroquinazoline **160**. The authors feel, however, that modular peptide synthases are probably responsible for the biosynthesis of these compounds, and that the configuration of the more likely precursor L-tryptophan is reversed during an enzymatic reaction.



158 Alantrypinone

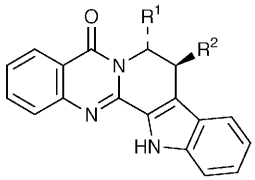


159 Fumiquinazoline F



160 Spiroquinazoline

Callus cultures of *Phellodendron amurense*, the bark of which is used as a traditional medicine in China, produce indolopyridoquinazoline alkaloids related to the well-known compound rutaecarpine **161**. In the latest investigation of the chemical constituents of the cultures, the new metabolite (−)-7,8-dihydroxyrutaecarpine **162** and a known alkaloid, (+)-7-hydroxyrutaecarpine **163**, were isolated from methanolic extracts of callus tissue.[56] The only noteworthy feature in an otherwise unexceptional spectroscopic structural elucidation was the relatively small coupling constant between 7-H and 8-H (*J* 2 Hz), which suggests a *trans*-diequatorial arrangement of these protons, and hence a *trans*-diaxial arrangement of the two hydroxy groups.

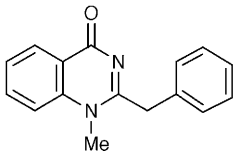


161 Rutaecarpine $R^1 = R^2 = H$
162 $R^1 = R^2 = OH$
163 $R^1 = OH$; $R^2 = H$

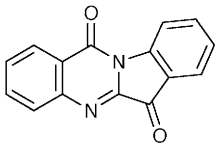
The rather uncommon quinazoline alkaloid arborine **164** has been identified as the component responsible for the inhibition of juvenile hormone III-biosynthesis in the field cricket (*Gryllus bimaculatus*) by leaf extracts of *Glycosmis pentaphylla*.[58] A review on the search for natural products and analogues with antitubercular activity has once again highlighted the importance of tryptanthrin **165** as a lead compound.[59]

2.2 Structural and synthetic studies

A recent book chapter dealing with applications of transition



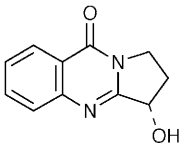
164 Arborine



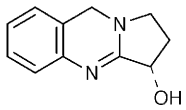
165 Tryptanthrin

metal-catalysed carbonylations in the synthesis of alkaloids includes a short section on quinazoline alkaloids.[60]

In 1996 Joshi *et al.* indisputably demonstrated the (3*S*) absolute configuration of (−)-vasicinone **166** by means of X-ray crystallography, but reported that NMR spectroscopic analysis of the (+)- and (−)-Mosher's esters of the alkaloid gave a contradictory result[61] (*cf.* ref. 25*d*). They have now acknowledged that they fell into the trap of assuming that, for example, the (*R*)-Mosher's acid chloride [α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride] gives rise to an ester that also has the (*R*) configuration.[62] In fact, in terms of the Cahn–Ingold–Prelog sequence rules, the ester must have (*S*) configuration because the priorities of the substituents change once chlorine is replaced by oxygen. There is thus no contradiction in the results from the spectroscopic analysis of the Mosher's esters, and the (3*S*) configuration of (−)-vasicinone has been fully vindicated. NMR spectroscopic analysis of the (+)- and (−)-Mosher's esters of (−)-vasicine **167** likewise confirms that this alkaloid, too, has the (3*S*) configuration.



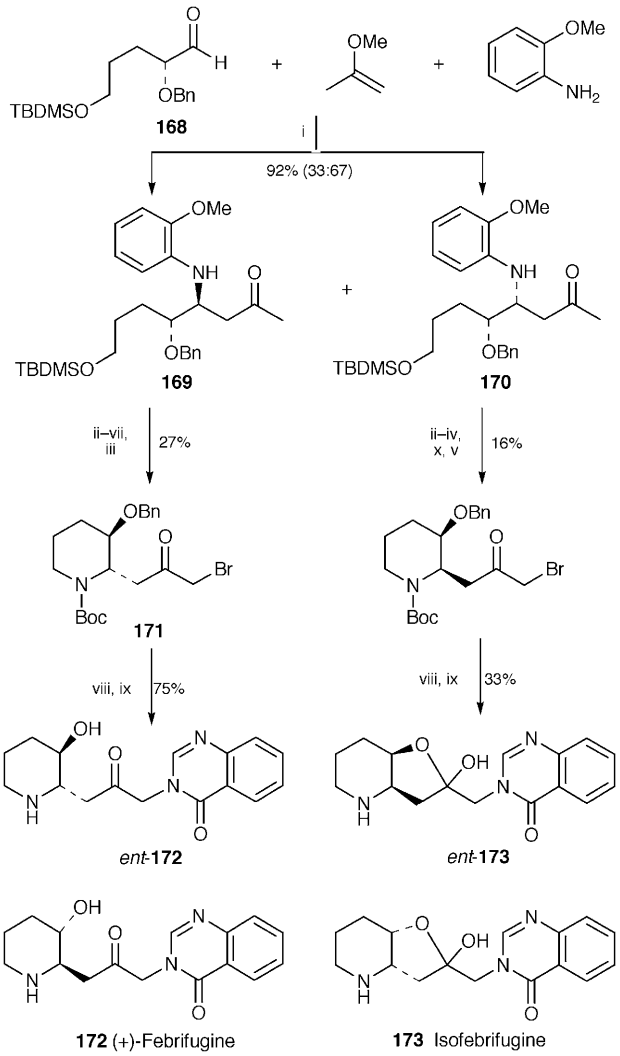
166 (–)-Vasicinone



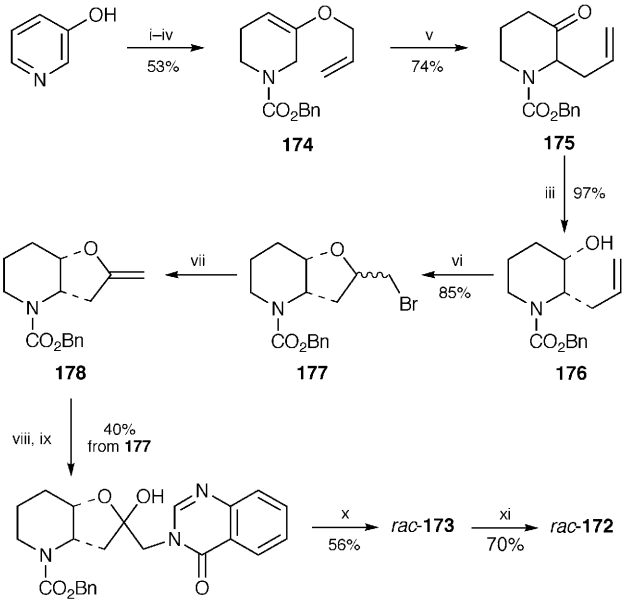
167 (–)-Vasicine

The alkaloids febrifugine and isofebrifugine, first reported over fifty years ago, have moved into the limelight recently in view of their powerful antimalarial activity. The natural products have long been assumed to have the (2′*S*,3′*R*) and (2′*R*,3′*R*) absolute configurations, respectively. However, the first asymmetric total synthesis of the two alkaloids, by Kobayashi *et al.*, has now shown that these absolute configurations must be reversed.[63] Part of their synthesis of (2′*S*,3′*R*)-febrifugine is shown in Scheme 11. Condensation between 2-methoxyaniline, 2-methoxypropene and the (*R*)-aldehyde **168** (prepared by an enantioselective tin-mediated aldol condensation) was catalysed by ytterbium(III) triflate in aqueous medium, and gave the Mannich-type adducts **169** and **170** in 92% yield and a ratio of 33:67. The *anti* adduct **169** was converted in several steps into the bromomethyl ketone **171**, reaction of which with the anion of 4(3*H*)-quinazolinone (4-hydroxyquinazoline) followed by removal of the protecting groups completed the synthesis of the (−)-enantiomer of febrifugine, *ent*-**172**. Natural febrifugine is dextrorotatory, and therefore must have the (2′*R*,3′*S*) configuration. By commencing with the (*S*)-enantiomer of aldehyde **168**, the authors were able to prepare (2′*R*,3′*S*)-(+)-febrifugine **172**, the data for which were identical in all respects with those reported for the natural product. A similar sequence of reactions on the *syn*-diastereomer **170** led to the formation of unnatural (2′*R*,3′*R*)-isofebrifugine *ent*-**173**, while the natural enantiomer **173** was once again obtained when the (*S*)-aldehyde *ent*-**168** was used in the synthesis.

The synthesis of racemic febrifugine and isofebrifugine by Takeuchi and co-workers shown in Scheme 12 employed an unusual Claisen rearrangement for the construction of the piperidinol segment.[64] The allyl enol ether **174**, prepared in four steps from 3-hydroxypyridine, rearranged in 74% yield to give the 2-allylpiperidin-3-one **175** merely on treatment with boron



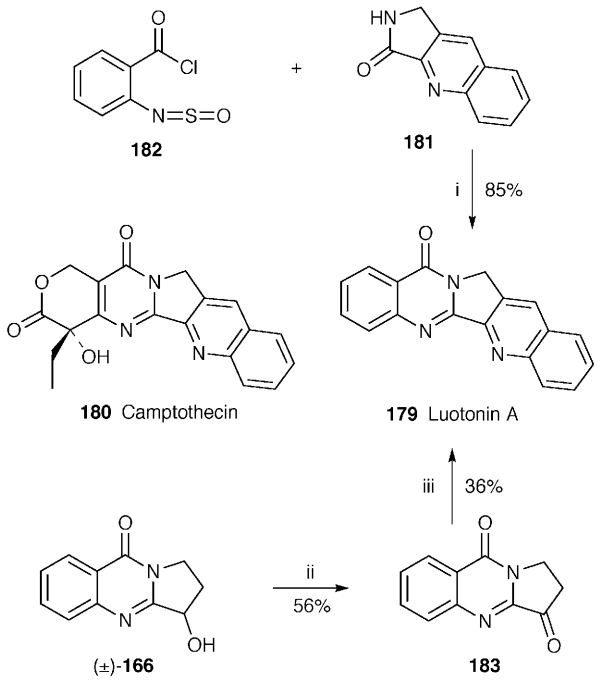
Scheme 11 *Reagents*: i, $Yb(OTf)_3$ (10%), THF–H_2O (9:1), 0–5 °C; ii, HF, THF; iii, Ph_3P, CBr_4, CH_2Cl_2; iv, CAN, MeCN, H_2O, 0 °C; v, Boc_2O; vi, $LiN(SiMe_3)_2$, THF, then Me_3SiCl; vii, MCPBA, CH_2Cl_2; viii, 4-hydroxyquinazoline, KOH; ix, HCl (6 M), reflux; x, Br_2, HBr, HOAc.



Scheme 12 *Reagents*: i, $PhCH_2Cl$, PhMe, reflux; ii, $H_2C{=}CHCH_2Br$, NaH, MeOH, reflux; iii, $NaBH_4$, MeOH, 0 °C; iv, BnOCOCl, THF, rt; v, $BF_3{\cdot}Et_2O$, MeCN, rt; vi, NBS, dry MeCN, rt; vii, Bu′OK, THF, reflux; viii, NBS, MeCN, H_2O, rt; ix, 4(3*H*)-quinazolinone, K_2CO_3, DMF, rt; x, H_2, 20% $Pd(OH)_2/C$, MeOH, rt; xi, EtOH, reflux, 2 h.

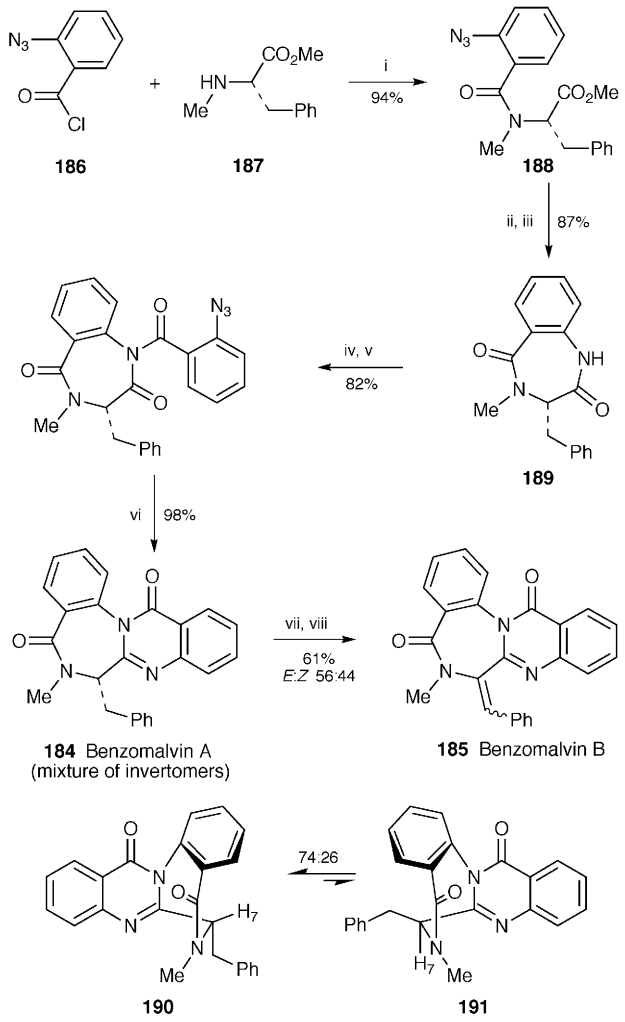
trifluoride etherate in acetonitrile at room temperature; rearrangement of the endocyclic double bond obviously precedes the Claisen rearrangement. Reduction of **175** with sodium borohydride in methanol gave the *cis*-2,3-disubstituted piperidin-3-ol **176** as the sole product. Bromoetherification then afforded the bicyclic compound **177** as a 3:1 mixture of diastereomers, an unimportant factor in view of the subsequent dehydrobromination to **178** under basic conditions. Bromohydration of **178** and reaction with 4(3*H*)-quinazolinone followed by removal of protecting groups completed the synthesis of (±)-isofebrifugine *rac*-**173**, following which thermal equilibration in boiling ethanol afforded (±)-febrifugine *rac*-**172**.

The recently discovered quino[2′,3′:3,4]pyrrolo[2,1-*b*]quinazolinone alkaloid luotonin A **179** bears a striking structural similarity to the topoisomerase I inhibitor camptothecin **180**, derivatives of which are used clinically for cancer chemotherapy. This structural similarity seems to underlie recent interest in the new alkaloid, which is effective against the murine leukaemia P-388 cell line (*cf.* ref. 25*e*). Luotonin A has rapidly succumbed to synthesis, and two short approaches published during the period under review are shown in Scheme 13. The first, by Wang and Ganesan,[65] employed the known lactam **181**, made in five steps and 9% overall yield from 2-nitrobenzaldehyde. Simple treatment of the anion of **181** with 2-sulfinylaminobenzoyl chloride **182** gave the target alkaloid **179** in 85% yield. The route devised by Kelly and co-workers[66] commenced with synthetic vasicinone (±)-**166**, prepared according to reported methods. Oxidation with Jones reagent afforded dione **183**, which underwent a Friedlander condensation with 2-aminobenzaldehyde to give luotonin A **179** in 36% yield.



Scheme 13 *Reagents*: i, $LiN(SiMe_3)_2$ (4.9 equiv.), THF, **182** (2.1 equiv.), rt, 2 h, then $LiN(SiMe_3)_2$ (2.5 equiv.), **182** (1.1 equiv.), rt, 1 h; ii, Jones oxidation; iii, 2-aminobenzaldehyde, Triton B, EtOH, reflux.

Syntheses of (−)-benzomalvin A **184** and benzomalvin B **185** by Eguchi and co-workers featured what has become known as the 'Eguchi protocol' (acylation of suitable precursors with 2-azidobenzoyl chloride **186** followed by intramolecular aza-Wittig reaction) to construct both heterocyclic rings (Scheme 14).[67] The present work expands on a previously published communication[68] (*cf.* ref. 25*f*), but includes noteworthy new results. In brief, reaction of **186** with *N*-methyl-L-phenylalanine methyl ester **187** yielded the intermediate azide

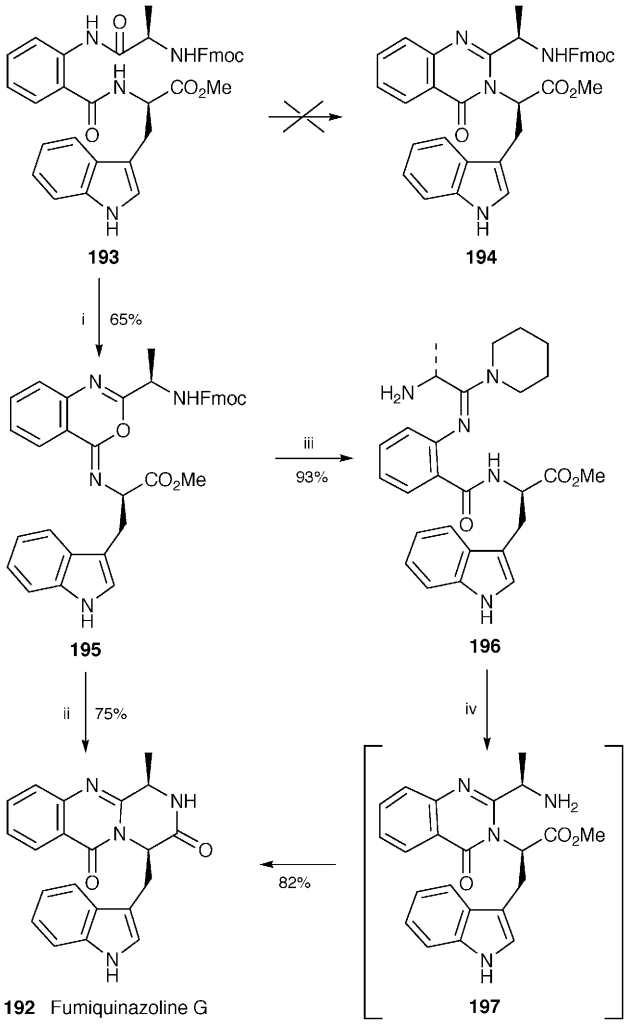


Scheme 14 *Reagents*: i, Et_3N, THF, 0 °C to rt; ii, Bu_3P, PhMe, rt to reflux; iii, TFA–H_2O–THF (1:1:12.5), rt; iv, $KN(SiMe_3)_2$, THF, −78 °C; v, **186**, THF, −78 °C to rt; vi, Ph_3P, PhMe, rt to reflux; vii, NBS, AIBN, CCl_4, reflux; viii, DBU, PhMe, reflux.

188 (ee 99.7%), after which treatment with tributylphosphine in boiling toluene followed by acidic work-up yielded the (−)-benzodiazepinedione **189** in 87% yield and undiminished optical purity. A second application of the 'Eguchi protocol' completed the synthesis of (−)-benzomalvin A **184** ($[\alpha]_D^{21}$ −109.8, *c* 1.0, MeOH). Incidentally, the claim that this is the first total synthesis of (−)-benzomalvin A is incorrect (*vide infra*). Benzomalvin B **185** was prepared from benzomalvin A as a mixture of (*E*) and (*Z*) isomers by a benzylic bromination–dehydrobromination sequence. An interesting feature of this study is that the conformation of benzomalvin A was found to change with time when studied by NMR spectroscopy, eventually attaining an equilibrium ratio of 76:24. The major conformer was identical with the natural product. NOE interactions between the *N*-methyl group and H-7 suggested the conformations shown in **190** and **191** for the major and minor invertomers respectively. Furthermore, an X-ray crystallographic study on a crystal of the minor conformer, which proved to be dextrorotatory ($[\alpha]_D^{23}$ +77.1, *c* 1.0, MeOH), confirmed the relative orientation of the diazepinone ring. The energy barrier between the two conformers was determined to be 5.9 kcal mol^{-1} by PM3 calculations. What is not clear from this work is whether the minor conformer is actually the same as (+)-benzomalvin D, a minor *Penicillium* metabolite reported in 1995[69] (*cf.* ref. 25*g*). Benzomalvin D was reported as displaying exactly the same kind of conformational interconversion with natural and synthetic samples of (−)-benzomalvin A as described by the Eguchi group, and conformational represent-

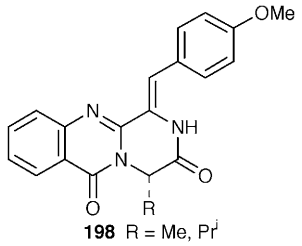
ations essentially the same as those illustrated in **190** and **191** (which are, in effect, atropisomers) were proposed. The authors of the present publication seem not to have been aware of these results, and it appears that they may have unwittingly synthesised benzomalvin D in the course of their work.

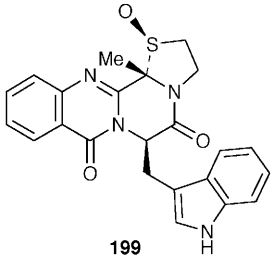
Wang and Ganesan recently reported a synthesis of fumiquinazoline G **192** in which cyclisation of the *N*-acylanthranilamide **193** to the 4-quinazolinone **194** was the key step[70] (*cf.* ref. 25*f*). He and Snider have now shown that the cyclisation does *not* produce the lactam **194**, but instead gives the lactim ether **195** (Scheme 15).[71] However, this does not invalidate the earlier study, since removal of the Fmoc protecting group with piperidine followed by chromatography on silica gel was accompanied by spontaneous cyclisation to yield fumiquinazoline G. Interestingly, removal of the Fmoc group with 4-dimethylaminopyridine yielded a free primary amine that failed to cyclise to the target alkaloid. With the aid of model studies, He and Snider were able to demonstrate that piperidine plays a role in the cyclisation over and above that of a deprotection agent. In their hands, an amidine carboxamide **196** proved to be an isolable intermediate. Exposure of this compound to silica gel induced spontaneous cyclisation to fumiquinazoline G through the putative quinazolinone intermediate **197**.

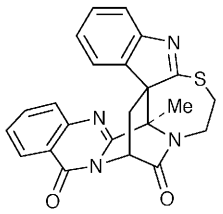


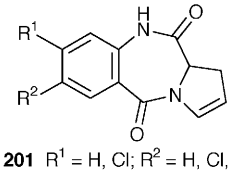
Scheme 15 *Reagents*: i, Ph_3P, I_2, Pr^i_2NEt, CH_2Cl_2, rt; ii, 20% piperidine in CH_2Cl_2, rt, then preparative TLC on SiO_2; iii, piperidine, EtOAc, rt; iv, SiO_2, EtOAc–MeOH (2:1), rt.

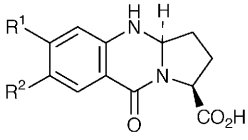
Several model studies designed to explore aspects of the synthesis of complex quinazoline alkaloids should be mentioned in conclusion. Synthetic approaches to the pyrazino[2,1-*b*]quinazoline core found in the ardeemins, fiscalins and fumiquinazolines have been evaluated by Cledera *et al.*, who showed that the 'Eguchi protocol' was the best of the four approaches studied for making products such as **198**.[72] Hart and Magomedov have examined an unusual cascade reaction in which the sulfoxide **199** rearranged to a mixture of products that included the spiroindoline **200** upon treatment with trifluoroacetic acid in chloroform.[73] The ultimate intention is to apply the novel process to the synthesis of the alkaloid spiroquinazoline **160**. On a simpler note, the benzodiazepinediones **201** were found to undergo rearrangement to the vasicinone-like carboxylic acids **202** in yields of 70–80% when heated in concentrated hydrochloric acid for a few minutes.[74]









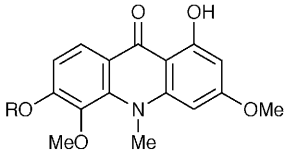


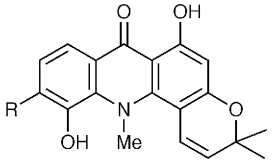
3 Acridone alkaloids

3.1 Occurrence and characterisation

A list of new acridone alkaloids, and known acridones isolated from new sources, is presented in Table 3.[8,16,75–79] The ^{13}C NMR spectrum of citpressine-I **203** has been reported for the first time, while certain reported ^{13}C NMR spectroscopic assignments for the pyrano[2,3-*c*]acridone **204** have been corrected.[75] The latter compound showed some antispasmodic activity by inhibiting acetylcholine-induced contraction on rabbit intestinal tissue. The known compound furacridone **205** is the first acridone alkaloid to have been isolated from the genus *Piper* (pepper) and, indeed, from the family Piperaceae.[79]

The new dimeric acridone alkaloid citbismine-F **206** was isolated as an optically inactive crystalline compound from the





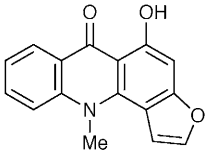
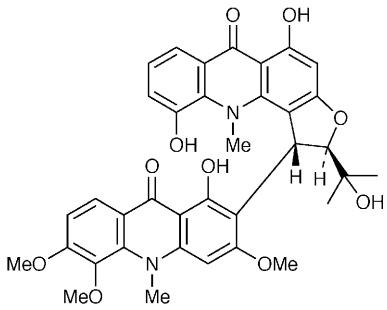


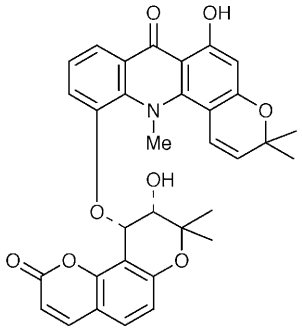
Table 3 Isolation and detection of acridone alkaloids

Species	Alkaloid[a]	Ref
Citrus deliciosa	Citpressine-I **203**	75
	6,11-Dihydroxy-10-methoxy-3,3,12-trimethyl-3,12-dihydro-7*H*-pyrano[2,3-*c*]acridin-7-one **204**	
Citrus paradisi	Citbismine-F[b] **206**	76
	(+)-Neoacrimarine-H[b] **208**	77
	(−)-Neoacrimarine-I[b] **209**	
	(−)-Neoacrimarine-J[b] **210**	
	Neoacrimarine-K[b] **211**	
Glycosmis trichanthera (= *G. calcicola*), stem bark	*N*-Desmethylnoracronycine **242**	8
	5-Hydroxynoracronycine **212**	
	Junosine	
	N-Methylatalaphylline	
	N-Methylatalaphyllinine **240**	
	Yukocitrine	
Melicope micrococca	Arborinine	78
Piper pedicellosum	Furacridone **205**	79
Severinia (= *Atalantia*) *buxifolia*	Atalaphylline	16

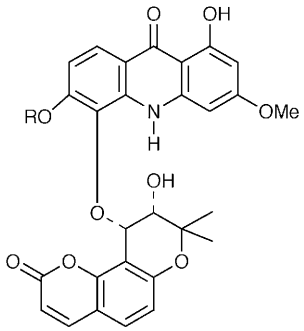
[a] Only new alkaloids and new records for a given species are listed in the table. Structures of most known alkaloids may be found in previous reviews in this series. [b] New alkaloids.



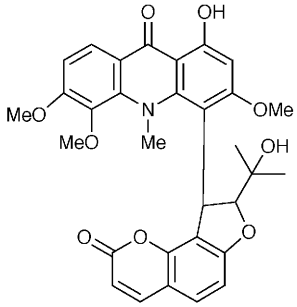
206 Citbismine-F



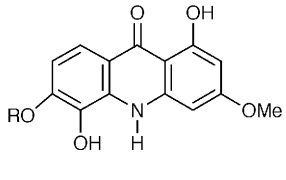
208 Neoacrimarine-H



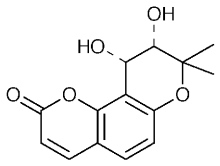
209 Neoacrimarine-I R = Me
210 Neoacrimarine-J R = H



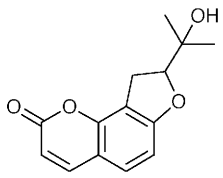
211 Neoacrimarine-K



213 Grandisine-I R = Me
214 R = H



215 *cis*-Khellactone

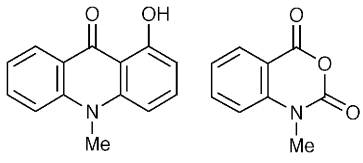


216 Columbianetin

roots of *Citrus paradisi* (Marsh grapefruit), and characterised with the assistance of the expected battery of one- and two-dimensional NMR spectroscopic techniques.[76] The alkaloid contains a dihydrofuro[2,3-*c*]acridone moiety that is not known as a natural product in its own right; the other constituent of the dimer is the well-known alkaloid citpressine-II **207**. The same plant species has also yielded four new acridone–coumarin dimers of the neoacrimarine class, *viz*. (+)-neoacrimarine-H **208**, (−)-neoacrimarine-I **209**, (−)-neoacrimarine-J **210**, and the optically inactive neoacrimarine-K **211**.[77] The nitrogen-containing moieties in **208**–**211** are 5-hydroxynoracronycine **212**, grandisine-I **213**, the previously unknown des-6-*O*-methyl analogue of grandisine-I **214** and citpressine-II **207**, respectively, while the coumarin units are *cis*-khellactone **215** in the first three alkaloids and columbianetin **216** in the fourth. The connectivities were established by means of NMR spectroscopic analyses, in particular heteronuclear multiple-bond correlation (HMBC) and NOE experiments. The absolute configurations of the alkaloids were not determined, but it is suspected that the observed optical rotations may indicate that neoacrimarine-H has the opposite stereostructure to neoacrimarines-I and -J in the *cis*-khellactone moiety.

3.2 Synthesis and biological studies

In what must surely be the shortest synthesis of an acridone alkaloid to date, 1-hydroxy-*N*-methylacridone **217** was prepared in a single step and 45% overall yield by condensing *N*-methylisatoic anhydride **218** with the potassium salt of cyclohexane-1,3-dione in DMSO at 110 °C over 18 hours.[80]



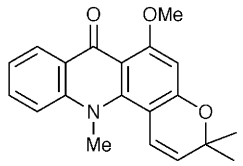
217 **218**

Sharpless asymmetric dihydroxylation of acronycine **219** with the commercially available AD-mix-α has given the (1*R*,2*R*)-(−)-*cis*-diol **220** in 40% enantiomeric excess (ee), while the enantiomeric diol *ent*-**220** was obtained in 70% ee when AD-mix-β was used.[81] The products could be purified by pre-

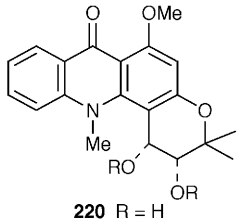
parative chiral HPLC. This suite of reactions has served to establish the absolute configuration of the naturally occurring (−)-*cis*-diol, an alkaloid that occurs in plants of the genus *Sarcomelicope*. Further confirmation of the configurations was provided by benzylic deoxygenation of **220** and *ent*-**220** with sodium cyanoborohydride in the presence of zinc iodide to give the known alcohols **221** and *ent*-**221**, respectively. Acetylation of the diols produced the diesters **222** and *ent*-**222**. The two enantiomers of the diester showed essentially the same potent cytotoxicity towards L-1210 leukaemia cells *in vitro* (IC_{50} 3.1 μM for **222** and 3.7 μmol for *ent*-**222**; *cf.* IC_{50} 3.4 μM for the racemate and 10.4 μmol for acronycine itself).

Further acronycine derivatives prepared for cytotoxicity studies include a range of racemic esters, ethers and amines **223**–**236**, the enol acetate **237** and ketone **238**, all derived by suitable manipulation of the racemic diol *rac*-**220**.[82] Access to the *trans*-series of compounds was obtained by equilibration of *rac*-**220** with methanolic hydrochloric acid. Most of the new compounds exhibited only marginal cytotoxicity towards L-1210 leukaemia cells, but the chloroacetate esters **229** and **232** showed activities comparable to those of racemic diesters such as *rac*-**222** (IC_{50} 1.47 and 5.2 μM respectively).

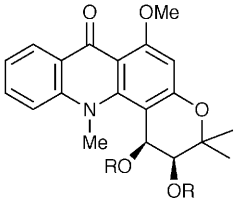
Two substantial studies on the effects of 15 different acridone and pyrano[2,3-*c*]acridone alkaloids on various cancer cells lines have cast light on the structural features needed for therapeutic efficacy. Four pyrano[2,3-*c*]acridone alkaloids in particular showed promising antiproliferative effects against tumour cell lines: atalaphyllidine **239**, 5-hydroxy-*N*-methylseverifoline (*N*-methylatalaphyllinine) **240**, atalaphyllinine **241** and des-*N*-methylnoracronycine **242**.[83] The IC_{50} values displayed by these compounds in tests with human lung carcinoma, melanin-producing mouse melanoma, T-cell leukaemia and human gastric cancer cell (lymph-node metastasised) were in the range 1.4–9.4 μM. Since these alkaloids had little effect on normal human cell lines, they may be useful as low-toxicity antitumour agents. Atalaphyllidine, des-*N*-methylnoracronycine and especially atalaphyllinine were able to induce differentiation of human promyelocytic leukaemia (HL-60) cells to produce characteristics of mature monocyte/macrophage cells, and also suppressed cell growth at 10 μM concentrations by 30, 65 and 94% respectively after four days of growth.[84] Interestingly, at concentrations of 2.5 μM, 5-hydroxynoracronycine **212** and alkaloids **239**–**241** stimulated cellular proliferation by 10–30% up to about the fourth day of growth.



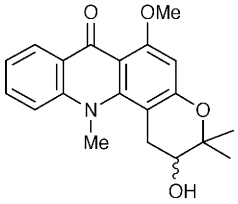
219 Acronycine



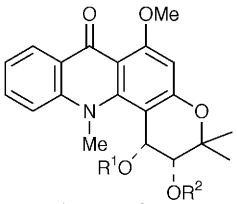
220 R = H
222 R = Ac



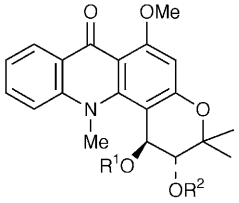
ent-**220** R = H
ent-**222** R = Ac



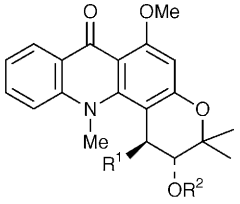
221 R = α-H
ent-**221** R = β-H



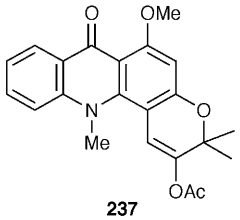
223 R^1 = Me; R^2 = H
224 R^1 = Me; R^2 = Ac
225 R^1 = Me; R^2 = $COCH_2Cl$
226 R^1 = Bn; R^2 = H



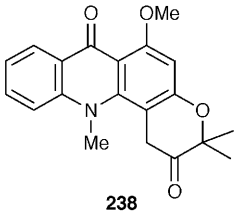
227 R^1 = Me; R^2 = H
228 R^1 = Me; R^2 = Ac
229 R^1 = Me; R^2 = $COCH_2Cl$
230 R^1 = Bn; R^2 = H
231 R^1 = Bn; R^2 = Ac
232 R^1 = Bn; R^2 = $COCH_2Cl$



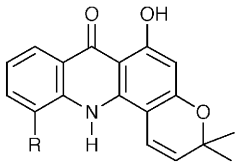
233 R^1 = NHMe; R^2 = Ac
234 R^1 = NHMe; R^2 = H
235 R^1 = N(Ac)Me; R^2 = Ac
236 R^1 = $NHNH_2$; R^2 = Ac



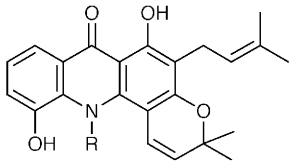
237



238



239 Atalaphyllidine R = OH
242 R = H



240 R = Me
241 Atalaphyllinine R = H

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