Quinoline, quinazoline and acridone alkaloids

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1 Quinoline alkaloids

1.1 Occurrence

The new alkaloids reported in the period covered by this review are listed in Table 1 together with their sources.[1–16] The Table also includes a list of known alkaloids isolated from new sources. Since the characterisation of new compounds by spectroscopic methods is usually a matter of routine, only significant spectroscopic details will be mentioned in the ensuing discussion.

1.2 Non-terpenoid quinoline and quinolinone alkaloids from higher plants

The known compound 6-methoxykynurenic acid **1** has been found for the first time as a natural product in *Ephedra pachyclada* ssp. *sinaica*, where it occurs together with kynurenic acid **2** and 6-hydroxykynurenic acid **3**.[7] The compounds undoubtedly exist as a mixture of the 4-keto and 4-hydroxy tautomers. The structure of **1** was confirmed spectroscopically, by direct comparison with an authentic sample, and by conversion (with CH_3I–K_2CO_3–DMF) into methyl 4,6-dimethoxyquinoline-2-carboxylate **4**, which was also formed by methylation of **3**.

Separation of the quinolin-4-one and indoloquinazoline alkaloids from Chinese herbal preparations containing *Evodia* fruits has been achieved with the aid of capillary electrophoresis[17,18] and liquid chromatography.[19] A recent investigation of *Evodia rutaecarpa*, long known as a source of 2-alkylquinolin-4-ones, has yielded a suite of twelve alkaloids, five of which were claimed to be new.[8,9] The novel compounds include 1-methyl-2-dodecylquinolin-4-one **5** and the three alkaloids **6**–**8** bearing unsaturated side chains. The fifth compound, 2-tridecylquinolin-4-one **9**, has in fact been identified previously along with lower and higher homologues in an unseparated mixture of alkaloids from *Ruta graveolens*.[20] The representation of its structure in the quinolin-4-one form as illustrated is done for convenience; the amount of 4-hydroxyquinoline tautomer present depended on the medium in which spectra were recorded. The unsaturated compounds were more difficult to characterise because they were isolated as mixtures of positional isomers. For example, **8** was inseparable from the known alkaloid **10**; however, the *Z* geometry of both components was deduced from the ^{13}C NMR chemical shifts of the allylic carbon atoms (δ 26.9), and hydrogenation of the mixture yielded a single compound, the known alkaloid 1-methyl-2-undecylquinolin-4-one **11**. The positions of the double bonds were eventually determined by Lemieux–Johnson oxidation with osmium tetroxide and sodium periodate followed by HPLC detection of the resulting aldehydes (hexanal and pentanal, in the ratio 3:1) as 2,4-dinitrophenylhydrazone derivatives. Similarly, the new alkaloid **6** accompanied the known pentadec-10-enyl isomer **12** (1:1.2), and **7** was inseparable from evocarpine **13** (1:10).

A taxonomically problematic plant formally belonging to the family Simaroubaceae – probably the same as an eastern Australian species that has been placed at different times in at least four different genera and now accepted as showing an affinity to the species *Samadera bidwillii* – is the source of a unique combination of metabolites comprising a new quinolone alkaloid, two acridone alkaloids (see Section 3.1), a quassinoid, a limonoid and seven lignans.[14] Some of these are typical metabolites of the Simaroubaceae, while the alkaloids in particular are typical of the Rutaceae. Does the new species represent a primitive member of the order Rutales prior to the evolutionary separation into the two named families? The new quinolone is 1-acetoxymethyl-2-(10-acetoxyundecyl)quinolin-4-one **14**; the extremely rare substituent on nitrogen has previously been found only in the rutaceous genera *Boronia* and *Eriostemon* (*cf*. ref. 21*a*).

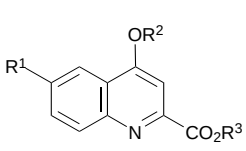
Further investigations on the effects of pure alkaloids and alkaloid mixtures from *Galipea longiflora* in the treatment of tropical diseases (*cf*. ref. 21*b*) have now been performed with BALB/c mice infected with *Leishmania amazonensis* and *L. venezuelensis*.[22] Both oral treatment and intralesional injection of chimanine B **15** reduced lesion weight and parasite loads substantially, showing improved performance over the reference drug Glucantime (*N*-methylglucamine antimonate). Intermediate antileishmanial activity resulted from oral administration of crude alkaloidal extracts from *G. longiflora* stem and bark. In addition, the purified alkaloids 2-propylquinoline **16** and 2-phenylquinoline **17** were reasonably effective when administered orally, as were 2-propylquinoline and 2-pentylquinoline **18** when administered by injection. The results suggest that chimanine B in particular would make a promising lead compound for the development of oral therapy against leishmaniasis.

An elaborate new synthesis of 2-substituted quinolines involved *ortho*-specific hydroxyalkylation of secondary anilines *via* *N*-alkylanilinochlorophenylboranes **19**, pyrolysis of the products **20** to give dihydroquinolines **21** (presumably by electrocyclisation of quinomethane imine intermediates), and finally deallylation of **21** induced by hydridotetrakis(triphenylphosphine)rhodium (Scheme 1).[23] Amongst the many products obtained were the three simple natural products 2-methylquinoline, 2-propylquinoline **16** and 2-phenylquinoline **17**. Other new routes to 2-phenylquinoline, which is frequently included amongst the targets when new methods for the synthesis of substituted quinolines are developed, include the Suzuki coupling of 2-chloroquinoline **22** and

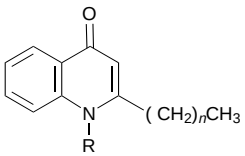
Table 1 Isolation and detection of quinoline alkaloids from plant, microbial and animal sources

Species	Alkaloid[a]	Ref.
Acronychia baeurlenii	Kokusaginine	1
	Pteleine	
Acronychia pubescens	Dictamnine	1
	Evolitrine	
	Kokusaginine	
Aegle marmelos	Integriquinolone	2,3
	4-Methoxy-*N*-methylquinolin-2-one	
Agathosma barosmaefolia	*N*-Methylhaplamine	4
	N-Methyl-4,6-dimethoxyquinolin-2-one	
	Skimmianine **53**	
Arthrobacter sp. strain YL-02729S	YM-30059[b] **55**	5
Chorilaena quercifolia	Skimmianine	6
Ephedra pachyclada ssp. *sinaica*	6-Hydroxykynurenic acid **3**	7
	Kynurenic acid **2**	
	6-Methoxykynurenic acid[b] **1**	
Evodia rutaecarpa	1-Methyl-2-dodecylquinolin-4-one[b] **5**	8
	(*Z*)-1-Methyl-2-(pentadec-9-enyl)quinolin-4-one[b] **6**	8,9
	(*Z*)-1-Methyl-2-(tridec-7-enyl)quinolin-4-one[b] **7**	8
	(*Z*)-1-Methyl-2-(undec-5-enyl)quinolin-4-one[b] **8**	
	(*Z*)-2-Tridecylquinolin-4-one[b] **9**	
Melicope erromangensis	Dutadrupine	10
	Flindersiamine	
	Kokusaginine	
	Skimmianine	
Penicillium sp. no. 410	(+)-Penigequinolones A and B[b] **56a**,**b**	11
Penicillium sp. NTC-47	(−)-3-Methoxy-4,5-dihydroxy-4-(4-methoxyphenyl)quinolin-2-one[b] **57**	12,13
	(−)-3-Methoxy-4-hydroxy-4-(4-methoxyphenyl)quinolin-2-one[b] **58**	12
	(+)-Penigequinolones A and B[b]	
aff. *Samadera* SAC-2825	2-(10-Acetoxyundecyl)-1-acetoxymethylquinolin-4-one[b] **14**	14
Scolopendra subspinipes mutilans	Jineol[b]	15
Ticorea longiflora	Dictamnine	16
	Evolitrine	
	γ-Fagarine **54**	
	4-Methoxy-*N*-methylquinolin-2-one	
	Skimmianine	

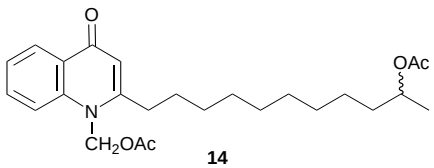
[a]Only new alkaloids and new records for a given species are listed in the Table. Structures of most known alkaloids may be found in previous reviews in this series. [b]New alkaloids.



1 R^1 = OMe; R^2 = R^3 = H
2 R^1 = R^2 = R^3 = H
3 R^1 = OH; R^2 = R^3 =H
4 R^1 = OMe; R^2 = R^3 = Me



5 R = Me; *n* = 11
9 R = H; *n* = 12
11 R = Me; *n* = 10



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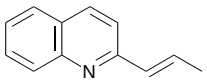

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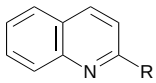
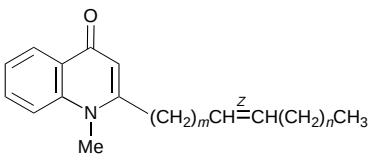


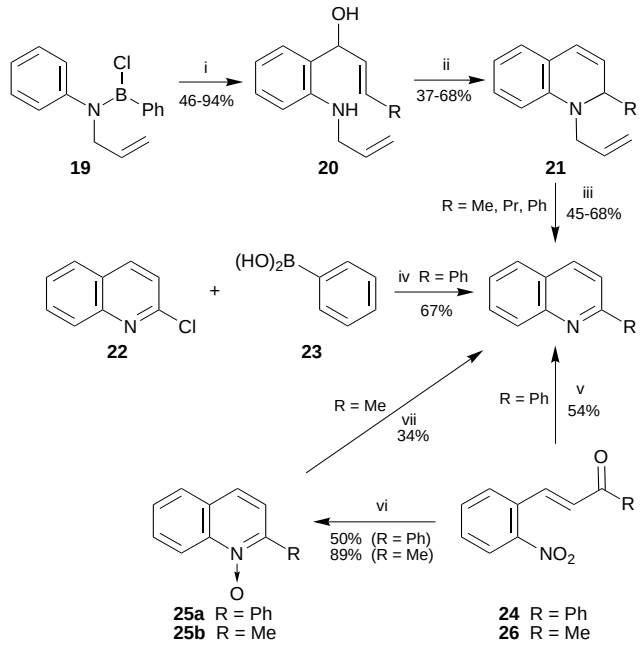
16 R = *n*-propyl
17 R = Ph
18 R = *n*-pentyl



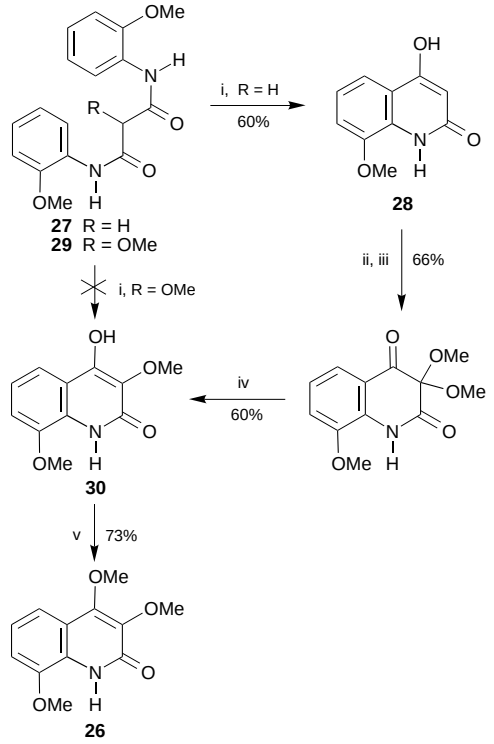
6 *m* = 8; *n* = 4
7 *m* = 6; *n* = 4
8 *m* = 4; *n* = 4
10 *m* = 5; *n* = 3
12 *m* = 9; *n* = 3
13 *m* = 7; *n* = 3

phenylboronic acid **23**,[24] and the titanium-mediated reduction of the nitrochalcone **24a**.[25] Ruthenium-catalysed carbonylation of the same nitrochalcone in the presence of a rigid diimine ligand yielded a mixture of 2-phenylquinoline (57%) and 2-benzoylindole (43%).[26] An alternative reduction of nitrochalcone **24a** with bakers' yeast stopped at the quinoline *N*-oxide stage **25a**; with the methyl analogue **24b**, further reduction of the *N*-oxide **25b** to 2-methylquinoline took place.[27]

The recently described[28] *Eriostemon* alkaloid 3,4,8-trimethoxy-2-quinolone **26** has been synthesised as shown in Scheme 2.[29] Eaton's reagent (methanesulfonic acid–phosphorus pentoxide) provided a superior medium for cyclising the malonic acid-derived dianilide **27** to the 4-hydroxyquinolin-2-one **28**. However, cyclisation of the methoxy-substituted analogue **29** to give the target alkaloid **26** directly failed, necessitating the less direct approach illustrated in the Scheme.

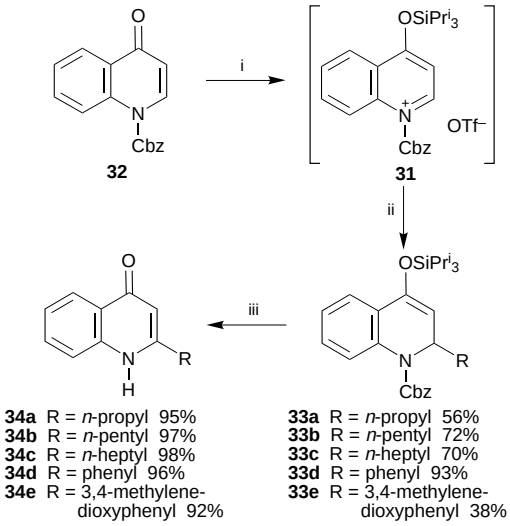


Scheme 1 *Reagents:* i, RCH=CHCHO, $ClCH_2CH_2Cl$, Pr^i_2NEt, −20 °C to 0 °C; ii, *p*-xylene, reflux; iii, $Rh(PPh_3)_4H$, TFA, EtOH, reflux; iv, $Pd(PPh_3)_4$, BHT, $Ba(OH)_2{\cdot}3H_2O$, THF, 75 °C; v, $TiCl_4$, Zn, THF, reflux, then add **24**, rt; vi, bakers' yeast, NaOH, H_2O–EtOH (7:3), reflux, 1 h; vii, bakers' yeast, NaOH, H_2O–EtOH (7:3), reflux, 24 h



Scheme 2 *Reagents:* i, P_2O_5 (10%) in $MeSO_3H$, 150–155 °C; ii, SO_2Cl_2, dioxane, rt; ii, NaOMe, MeOH, reflux, 5 min; iv, Zn, AcOH, EtOH, reflux; v, $(MeO)_2SO_2$, $NaHCO_3$, H_2O, rt

A versatile new route to 2-substituted quinolin-4-one alkaloids exploited regioselective addition of Grignard reagents to the *N*-Cbz-4-triisopropylsilyloxyquinolinium triflate **31**, prepared *in situ* from quinolin-4-one **32** and triisopropylsilyl triflate (Scheme 3).[30] Removal of the benzyloxycarbonyl protecting group from the adducts **33** by hydrogenolysis over a palladium–carbon catalyst simultaneously effected dehydrogenation of the heterocyclic ring. This short sequence provided easy access to five representative alkaloids **34**, including norgraveoline **34e**.

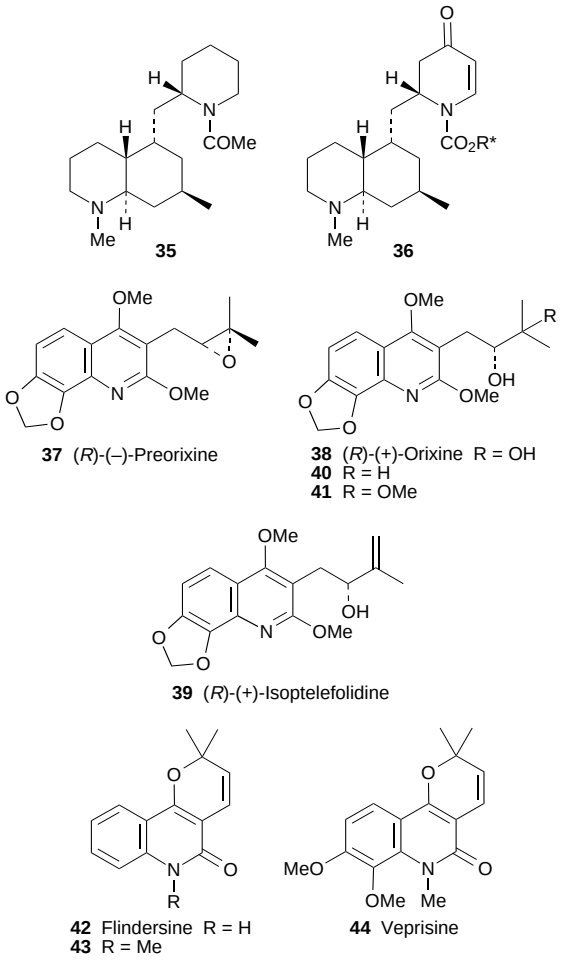


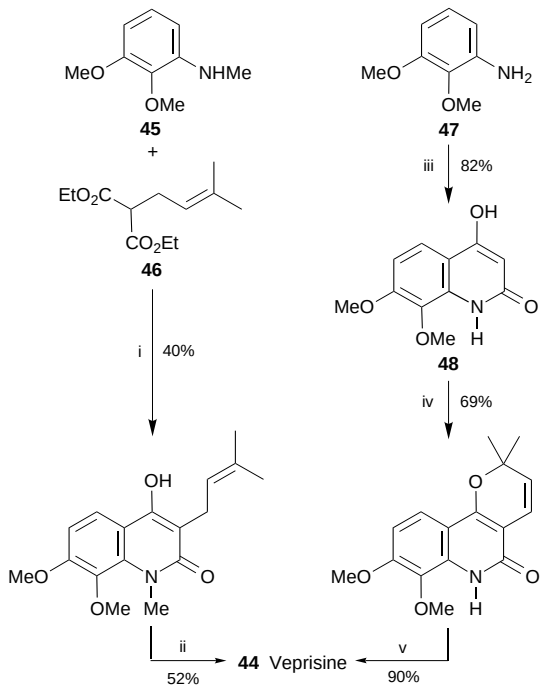
Scheme 3 *Reagents:* i, Pr^i_3SiOTf, 20 °C; ii, 2,6-lutidine (2.0 equiv.), CH_2Cl_2, RMgBr (1 M in THF; 2.0 equiv.), rt; iii, H_2 (1 atm), 10% Pd/C, MeOH, rt

A strategy for the synthesis of the decahydroquinoline *Lycopodium* alkaloid phlegmarine **35** has been described in a published conference contribution by Comins and co-workers.[31] Applications of this team's dihydropyridone methodology have so far culminated in the preparation of the advanced intermediate **36**. Completion of what promises to be the first asymmetric synthesis of this type of *Lycopodium* alkaloid is awaited with interest.

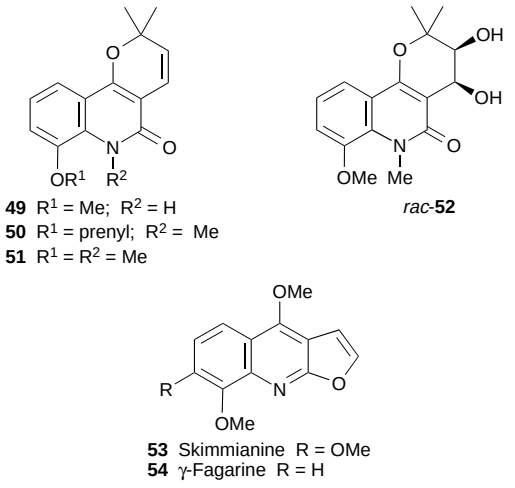
1.3 Hemiterpenoid quinoline alkaloids, tricyclic derivatives and furoquinoline alkaloids

When (−)-preorixine, a metabolite of *Orixa japonica*, was first reported some years ago,[32] its absolute configuration was assigned as *S* (*i.e.*, *ent*-**37**) after its conversion into (*R*)-(+)-orixine **38** by hydrolysis of the epoxide ring with putative inversion (*cf.* ref. 21*c*). However, NMR analysis of (*R*)- and (*S*)-α-methoxy-α-trifluoromethylphenylacetic acid esters (Mosher esters) of various alcohols derived from (−)-preorixine has now served to prove that this assignment was incorrect.[33] Two hydrolysis products, (+)-orixine and (+)-isoptelefolidine **39** – which, incidentally, accompanied (−)-preorixine when it was isolated – were unambiguously shown to possess the *R* configuration with the aid of this technique. (+)-Orixine could also be derived from (−)-preorixine by opening the epoxide ring at the more substituted site with formic acid followed by cleavage of the formate ester intermediate, a process that does not involve an inversion of configuration. Moreover, the stereogenic centre of (−)-preorixine is not affected when it is dehydrated to give (+)-isoptelefolidine. The accumulated evidence strongly suggests that (−)-preorixine must also have *R* configuration as shown in **37**. Additional evidence was obtained by reducing (−)-preorixine with diborane and lithium borohydride to yield **40**, the *R* configuration of which was again proved by NMR analysis of its two Mosher esters. (*R*)-(+)-3′-*O*-Methylpreorixine **41**, a minor constituent of the *O. orixa* extracts, was suspected to be an artefact of the isolation procedure, since it was easily prepared from (−)-preorixine and methanol in the presence of acid.





Scheme 4 *Reagents:* i, Ph_2O, 230–255 °C; ii, DDQ, C_6H_6, reflux; iii, malonic acid, $POCl_3$; iv, 3-methylbut-2-enal, pyridine, $MgSO_4$, reflux; v, NaH, THF, rt, then MeI



Flindersine **42**, *N*-methylflindersine **43** and veprisine **44**, isolated from the bark of the medicinally important East African tree *Fagara chalybea*, are active as SRS-A antagonists.[34] In this work, veprisine was prepared in two steps (21% yield) from 2,3-dimethoxy-*N*-methylaniline **45** and diethyl prenylmalonate **46** (Scheme 4). Other workers have recently made veprisine from 2,3-dimethoxyaniline **47** and malonic acid; heating the intermediate quinolinone **48** with 3-methylbut-2-enal in pyridine followed by *N*-methylation yielded the target alkaloid in an efficient 51% overall yield.[35] Adaptations of this procedure also resulted in syntheses of the related alkaloids **49**, **50** and **51** (zanthobungeanine); oxidation of the latter with osmium tetroxide afforded the *cis*-diol **52** in 42% yield. It is of interest that the two hydroxy groups in the naturally occurring diol from *Zanthoxylum simulans* have recently been shown to be *trans*.[36]

The accumulation of the furoquinoline alkaloids skimmianine **53** and γ-fagarine **54** in cell suspension cultures of *Fagara zanthoxyloides* showed a marked dependence on exogenous growth regulators.[37] Removal of the auxin α-naphthylacetic acid from the growth medium slightly stimulated the accumulation of the alkaloids (by 1.2 and 1.9 times respectively) relative to a control culture. However, the absence of the cytokinin benzylaminopurine brought about a ninefold decrease in alkaloid production. Removal of both phytohormones decreased alkaloid accumulation by 3.5 and 2.1 times respectively. The results show that the cytokinin plays an essential role in alkaloid biosynthesis within the cells, but the auxin inhibits biosynthesis.

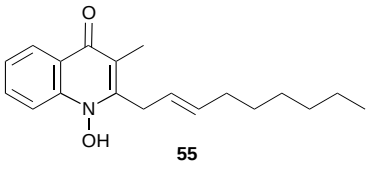
1.4 Quinoline alkaloids from microbial sources

YM-30059, an antibacterial and cytotoxic compound isolated from *Arthrobacter* sp. YL-02729S, has been formulated as the *N*-hydroxyquinolin-4-one **55** on the basis of its spectroscopic features.[5] It showed moderate activity against Gram-positive bacteria, including *Bacillus subtilis* and multiple-drug resistant *Staphylococcus aureus* and *S. epidermidis.* The metabolite was also a potent inhibitor of lipoxygenase.

Two active inhibitors of pollen-growth have been located by bioassay in the mycelial mats of *Penicillium* sp. No. 410.[11] The active fraction was obtained as an amorphous yellow powder by repeated chromatography of the acetone extract of the mats. This dextrorotatory product proved to be an inseparable mixture of two diastereoisomers **56a**,**b** in the ratio 2:1, though it was not possible to tell which was the major isomer. The structures and relative configurations of penigequinolones A and B, as the compounds were named, were assigned after extensive NMR work in which the ROESY technique proved crucial in permitting the complete assignment of the relative stereochemistry and the chair conformation of the tetrahydropyran ring. The styryl substituent on this ring is axial. The absolute configurations remain undetermined. The

demonstrable inhibition of the growth of tea pollen tubes by the isolated penigequinolones, complete at 100 mg l^{-1}, offers the possibility of developing these and related compounds as herbicides.

Interestingly enough, an independent group of workers has isolated the same two diastereoisomers **56a**,**b**, albeit in a different but unspecified ratio, from a culture of the fungus *Penicillium* sp. NTC-47 grown on an okara medium (the insoluble residue of whole soybean).[12] The compounds, unnamed in this work, were detected by a bioassay based on toxicity to the brine shrimp *Artemia salina*; when purified, they displayed an LC_{50} of 0.90 μg ml^{-1}. The results were reported in a published conference proceeding that also contains information on two related metabolites, the dihydroquinolinones **57** and **58**. Full details of the isolation and spectroscopic characterisation of the latter two compounds have since been published.[13] X-Ray crystallography complemented the usual battery of NMR studies on **57**, and confirmed its relative, but not its absolute, stereostructure. Dihydroquinolinone **57** was less toxic in the brine shrimp assay than the diastereoisomeric penigequinolone mixture (LC_{50} 20.0 μg ml^{-1}), but its deoxy analogue **58** was inactive.



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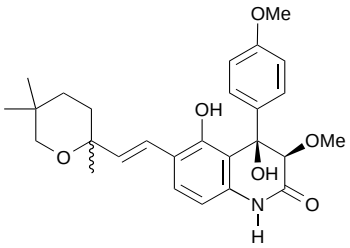
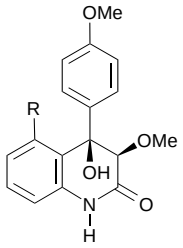


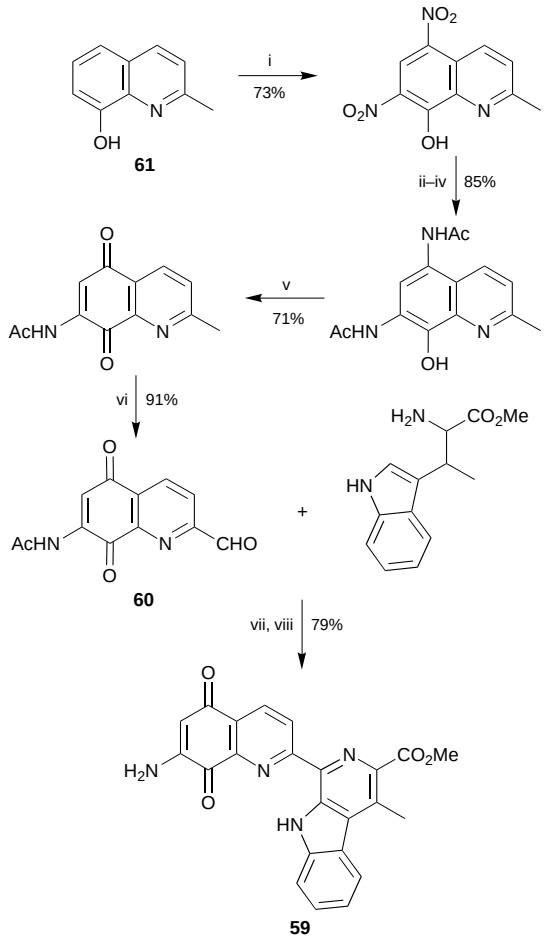
56a,b Penigequinolines A, B



57 R = OH
58 R = H

A major review on alkaloids containing quinolinequinone and quinolinequinonimine units includes a substantial section giving the most complete account to date of the isolation, characterisation, synthesis, biosynthesis and biological activity of the microbial metabolites lavendamycin, streptonigrin, streptonigrone and related compounds.[38] At the heart of the most recent synthesis of lavendamycin methyl ester **59** is a new and efficient five-step synthesis of 7-acetamidoquinolinequinone **60** from the commercially available 8-hydroxy-2-methylquinoline **61** (Scheme 5).[39] Compound **60** was readily converted into the target as shown, thereby making available gram quantities of the antibiotic in overall yields of 37–43%. The sequence was easily adapted for the preparation of aminoquinolinequinone derivatives related to **60**, which are interesting in their own right as potent antitumour agents.

An important synthesis of racemic virantmycin **62** that established its previously disputed relative stereochemistry once and for all was reported in a communication in 1991 by Morimoto *et al.*[40] (*cf.* ref. 21*d*). Full details of this synthesis and those of the racemic diastereoisomer **63** and the model compounds **64**–**67** have now been published together with particulars of the significant NOE studies on which the relative stereochemical assignments were based.[41] Moreover, an enantioselective synthesis of unnatural (+)-(2*S*,3*S*)-virantmycin, *ent*-**62**, has also appeared recently.[42] In this route, the key to stereocontrol lay in the Sharpless asymmetric epoxidation of allylic alcohol **68**, the product **69** in turn being transformed



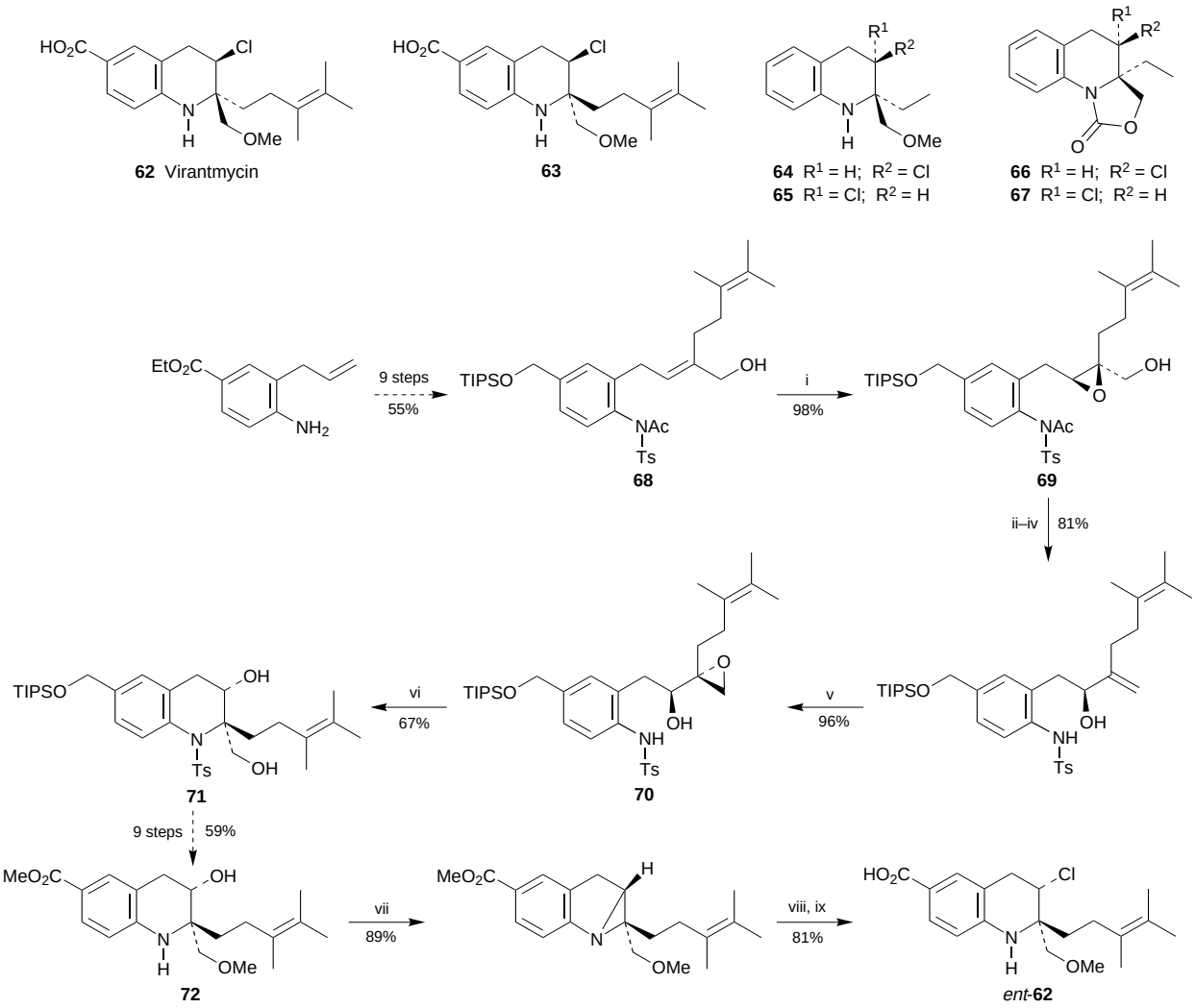
Scheme 5 *Reagents:* i, HNO_3–H_2SO_4 (7:3 v/v), 0 °C; ii, H_2 (30 psi), 5% Pd/C, HCl (10% aq.), rt; iii, Na_2SO_3, NaOAc, H_2O, then Ac_2O, rt; iv, MeOH–H_2O (10:1), reflux; v, $K_2Cr_2O_7$, HOAc, H_2O, rt; vi, SeO_2, dioxane, H_2O, reflux; vii, xylene, reflux; viii, H_2SO_4, H_2O (3:4), 0 °C to 60 °C

into another epoxide **70**, which underwent cyclisation to yield the tetrahydroquinoline **71** (Scheme 6). A further nine steps afforded alcohol **72**, the absolute configuration of which was confirmed by applying the exciton chirality method to its 4-dimethylaminobenzoate ester. The synthesis of (+)-virantmycin was completed as illustrated. Natural (−)-(2*R*,3*R*)-virantmycin and the synthetic racemate showed excellent antiviral activity in a test involving the growth inhibition of influenza virus. However, the antiviral activities of the unnatural (+)-enantiomer and the racemic diastereoisomer **63** were negligible.

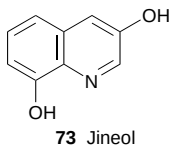
1.5 Quinoline alkaloids from animals

The centipede *Scolopendra subspinipes mutilans* has traditionally been used in Korea for the treatment of various disorders, including convulsions and seizures. Bioactivity-guided fractionation of the ethanolic extract of this animal has now yielded a very simple new alkaloid, 3,8-dihydroxyquinoline **73**, which has been given the trivial name jineol.[15] Its structure was deduced from a thorough spectroscopic study of the native metabolite and its methyl and acetyl derivatives. The 3-hydroxyquinoline moiety, rare in nature, is apparently unique in a metabolite from an animal source. Jineol proved to be moderately cytotoxic in five human tumour cell models; it was less effective than cisplatin, but more effective than carboplatin, 3,8-dimethoxyquinoline and 3,8-diacetoxyquinoline.

Interest in the synthesis of the important frog skin alkaloid decahydroquinoline 195A (pumiliotoxin C) continues



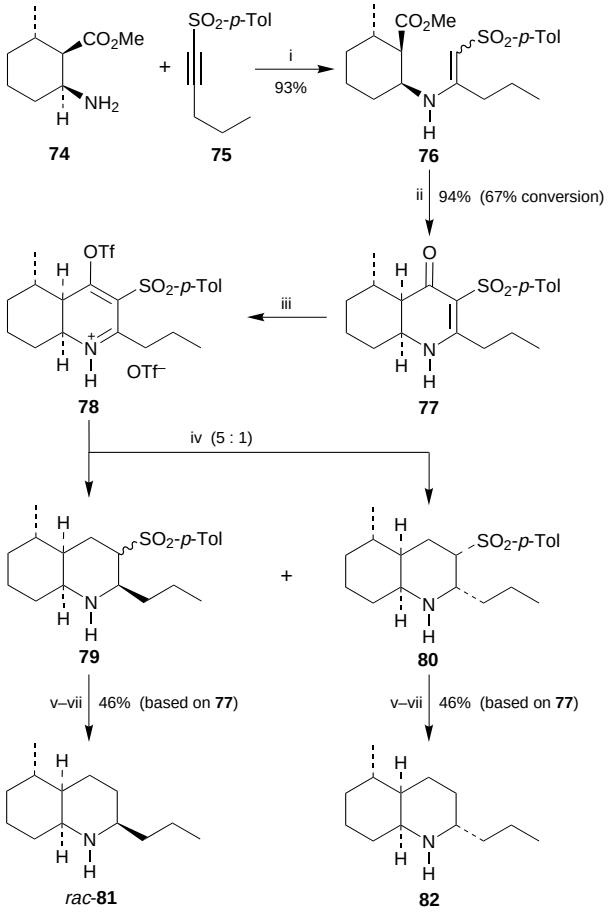
Scheme 6 *Reagents:* i, L-(+)-diethyl tartrate, $Ti(OPr^i)_4$, Bu^tOOH, CH_2Cl_2, −20 °C; ii, MsCl, NEt_3, CH_2Cl_2, 0 °C; iii, NaI (5 equiv.), Zn (2 equiv.), DMF, 100 °C; iv, DIBAL, toluene, −15 °C; v, Bu^tOOH, $VO(acac)_2$, CH_2Cl_2, 0 °C; vi, TFA (2 equiv.), toluene, rt; vii, DEAD, PPh_3, THF, rt; viii, NaOH, MeOH, reflux; ix, NEt_4Cl (20 equiv.), TFA (4 equiv.), CH_2Cl_2, −15 °C



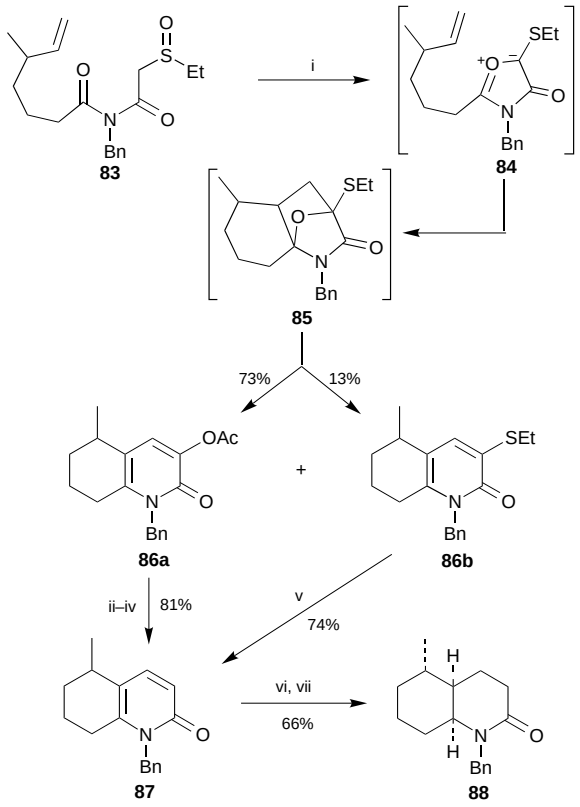
unabated. No fewer than four routes to this pharmacologically interesting compound, all involving new methodological developments, were reported during the period under review. In the approach of Back and Nakajima[43] (Scheme 7), the amino ester **74**, derived in several steps from the Diels–Alder adduct of piperylene and maleic anhydride, underwent conjugate addition to the alkynyl sulfone **75** to yield a 2:1 mixture of the *Z* and *E* isomers of **76**. Ring closure of **76** with LDA did not proceed to completion (33% of the substrate was recovered), but conversion to the octahydroquinolin-4-one **77** was efficient (94%). Reduction of the enol triflate **78** removed both the superfluous functionality at C-4 as well as the C2–C3 double bond, although the latter process afforded a mixture of diastereoisomers **79** and **80** in a 5:1 ratio. After chromatographic separation, these isomers were converted as shown into (±)-pumiliotoxin C **81** and (±)-2-epipumiliotoxin C **82**.

The approach of Kuethe and Padwa[44] (Scheme 8) employed a tandem Pummerer rearrangement–isomünchnone dipolar cycloaddition on substrate **83** *via* intermediates **84** and **85** to create the tetrahydroquinolinone nucleus of **86a** in an efficient 73% yield. A minor product, **86b**, was also isolated (13%). Both products were defunctionalised to the common intermediate **87**, which was readily reduced to the bicyclic lactam **88** with the required *cis* stereochemistry of ring fusion. Although the authors asserted that the preparation of lactam **88** completed a formal synthesis of racemic pumiliotoxin C, the references they cited[45,46] describe the *N*-debenzyl analogue of **88** rather than **88** itself.

A paper by Fukumoto and co-workers[47] gives full details of, and additional information on, a synthesis of (+)-pumiliotoxin C (the unnatural enantiomer, as shown in **81**) that was previously reported in a communication[48] (*cf.* ref. 21*e*). A key step was cyclisation of enyne **89**, made in fourteen steps from the chiral acrylate **90** and butadiene *via* optically pure cyclohexene alcohol **91** (Scheme 9). Under free radical conditions, cyclisation of **89** gave the bicyclic compound **92** in 99% yield. However, difficulties in the operating conditions prompted a search for an alternative cyclisation, which was achieved much more easily, though in poorer yield (61%), by a palladium-induced hydrosilylation. After several functional group manipulations, bicyclic ketone **93** was obtained. Beckmann rearrangement of a second bicyclic ketone, **94**, gave lactam **95**, which has the requisite decahydroquinoline skeleton of the target alkaloid. A more recent approach by the same research team[49] also proceeded by way of cyclohexene alcohol **91**, which was transformed in three steps and 34% yield



Scheme 7 *Reagents:* i, THF, rt; ii, LDA, THF; iii, Tf_2O, CH_2Cl_2, reflux; iv, H_2 (100 atm), PtO_2, MeOH; v, CbzCl, K_2CO_3, H_2O, $CHCl_3$, reflux; vi, 5% Na–Hg, Na_2HPO_4, MeOH-THF (1:1); vii, H_2, Pd/C, EtOH



Scheme 8 *Reagents:* i, Ac_2O, *p*-TsOH (cat.), reflux; ii, K_2CO_3, MeOH; iii, Tf_2NPh, NEt_3; iv, $Pd(OAc)_2$, Ph_3P, HCO_2H, NEt_3; v, Raney Ni, EtOH, 65 °C; vi, $LiB(Bu^i_3)_3H$; vii, H_2, PtO_2

into the nitro compound **96**. Treatment with *p*-chlorophenyl isocyanate induced intramolecular nitrile oxide cycloaddition, giving a tricyclic isoxazoline **97** that incorporated several of the stereochemical relationships required for the target alkaloid. Cleavage of the heterocyclic ring followed by functional group interconversions afforded **93**, at which point the two routes converged. Since both ketone **94** and lactam **95** have been prepared in racemic form by previous workers and converted into (±)-pumiliotoxin C,[45,46,50] the enantioselective synthesis of these two compounds in the present investigations can be viewed as completing a formal synthesis of (+)-pumiliotoxin C **81**.

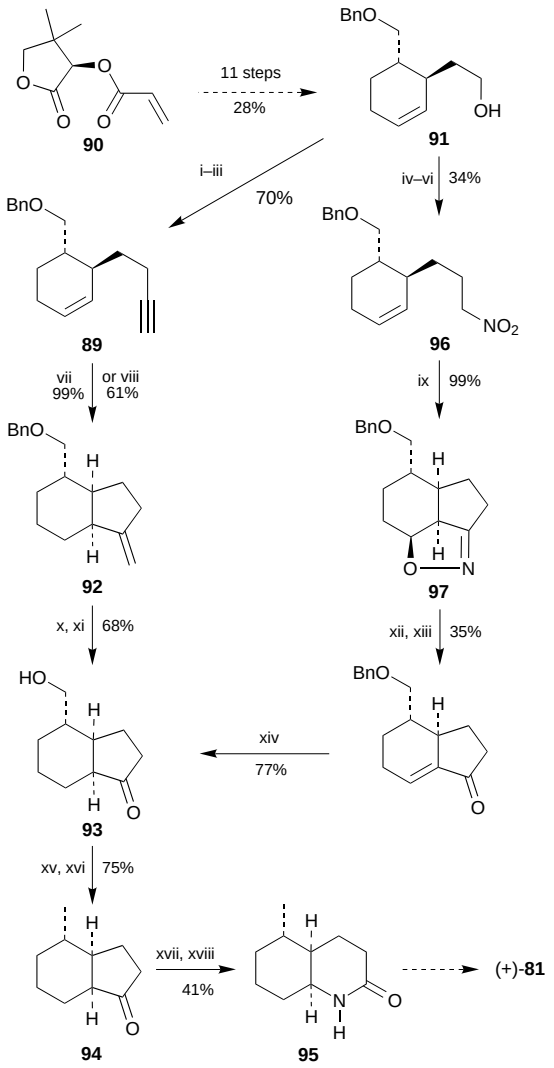
2 Quinazoline alkaloids

2.1 Occurrence and biological activity

1,3-Dimethylquinazoline-2,4-dione **98** has been identified as the sex pheromone of the pale-brown chafer beetle *Phyllopertha diversa*, a devastating turf pest in Japan.[51] Released in picogram quantities by females, this pheromone has long eluded detection. In this study, it was an almost unnoticed component when a biologically active ether extract was analysed by gas chromatography with an electroantennographic detector. Male beetles were successfully lured in significant numbers to field traps baited with a synthetic sample of the pheromone, made by methylating **99** with iodomethane and sodium hydroxide in DMSO. This is the first time that this simple alkaloid, which has antiinflammatory, anticonvulsant and analgesic properties, has been found as a natural product.

Quinazoline-2,4-dione **99** has itself been isolated from dyer's woad, *Isatis tinctoria*, and shown to have antiinflammatory and antihypertensive properties.[52] Although this was claimed to be the first isolation of **99** from a natural source, its isolation from *Strobilanthes cusia* has previously been reported in this series of reviews (*cf*. ref. 21*f*). The related plant *Isatis indigotica*, the principal source of the antipyretic and antiviral Chinese drug 'Ban-Lan-Gen', yielded the known alkaloid qingdainone (candidine) **100** and several new natural products, amongst them 3-(2-carboxyphenyl)-4(3*H*)-quinazolinone **101**[53] and 3-(2-hydroxyphenyl)-4(3*H*)-quinazolinone **102**.[54] Both were previously known as synthetic compounds. The carboxylic acid **101** showed endotoxic activity *in vitro* in the limulus amoebocyte lysate test. The most interesting new metabolite in the present group is the pyrrolo[2,1-*b*]quinazolinone isaindigotone **103**,[54] the tricyclic core of which is reminiscent of the medicinally important vasicine group of alkaloids. The HMBC spectrum of **103** unambiguously indicated the location of the arylidene unit at C-3, while NOE difference spectra established the (*E*) configuration and the positions of the hydroxy and methoxy substituents.

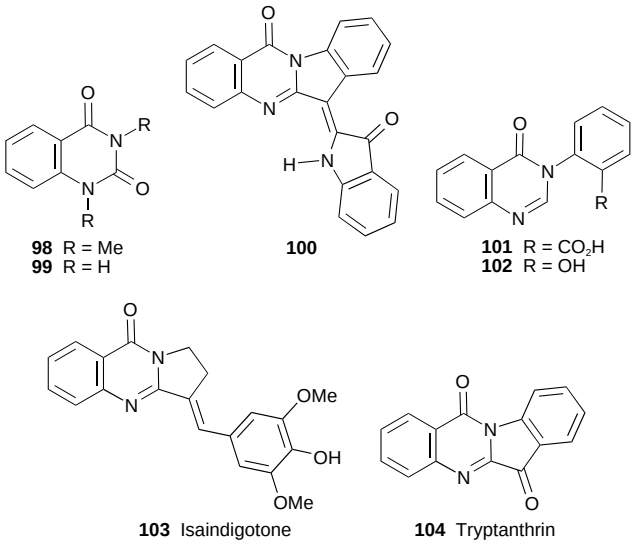
Tryptanthrin **104** has been obtained from the Indian medicinal plant *Wrightia tinctoria*.[55] The better-known Ayurvedic medicinal plant *Adhatoda vasica* has yielded the new pyrroloquinazolinone alkaloids desmethoxyaniflorine **105** and 7-methoxyvasicinone **106**, as well as 5-methoxyvasicinone **107**, which appears to be new as a natural product.[56] The metabolites were characterised by means of spectroscopic studies; in addition, the structure of desmethoxyaniflorine was confirmed by X-ray crystallography. As a matter of interest, the crystal structure of 7-methoxyvasicinone[57] was reported in the previous review in this series (*cf*. ref. 21*g*). The present work assigns the *R* absolute configuration at C-3 to both **106** and **107** without presenting convincing evidence for the assignment. It appears that the configurational assignment may have been assumed on the basis of a widely accepted 3*R* assignment



Scheme 9 *Reagents:* i, CBr_4, Ph_3P, CH_2Cl_2, 0 °C to rt; ii, $LiC{\equiv}CSiMe_3$, HMPA, THF, −78 °C to rt; iii, NaOH (1 M), MeOH, rt; iv, TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt; v, $MeNO_2$, KF, Bu_4NCl, toluene, rt; vi, Ac_2O, pyridine, rt, then $NaBH_4$, EtOH, 0 °C; vii, Bu_3SnH, AIBN, C_6H_6, reflux, then SiO_2, CH_2Cl_2, rt; viii, $(dba)_3Pd_2$, $CHCl_3$, *N*,*N*′-bis(benzylidene)ethylenediamine, polymethylhydrosiloxane, AcOH, $ClCH_2CH_2Cl$, rt; ix, *p*-chlorophenyl isocyanate, NEt_3, toluene, sealed tube, 60 °C; x, Na, NH_3, THF, −78 °C; xi, O_3, MeOH–CH_2Cl_2 (3:1), −78 °C, then Me_2S; xii, H_2, Raney Ni(W2), $(MeO)_3B$, MeOH–H_2O (15:1), rt; xiii, *p*-TsOH, C_6H_6, 60 °C; xiv, H_2, 10% Pd/C, EtOAc, rt; xv, $(imid)_2CS$, DMAP, CH_2Cl_2, reflux; xvi, Bu_3SnH, AIBN, C_6H_6, reflux; xvii, $NH_2OH{\cdot}HCl$, NaOAc, MeOH, rt; xviii, *p*-TsCl, NaOH, THF–H_2O (2:3), 0 °C to rt

for vasicine alkaloids. However, as was pointed out in the previous review, there is excellent recent evidence[58] to suggest that the traditional 3*R* assignment for alkaloids in the vasicine/vasicinone manifold is wrong (*cf.* ref. 21*g*; see also Section 2.2 below).

The known fungal metabolite fiscalin B **108** and two new tremorgenic principles have been isolated from the ethyl acetate extract of the ascomycete *Corynascus setosus* cultivated on sterilised rice.[59] Extensive NMR data were reported for all three compounds. The spectroscopic properties of the new compounds were very similar to those of the known *Aspergillus* metabolites tryptoquivaline **109** and nortryptoquivaline **110** respectively, the major differences in chemical shift being observed for C-26 and C-27. The CD spectra were also similar to those of the tryptoquivalines except for extra positive Cotton effects near 280 nm. The implication was that the new compounds were probably diastereoisomers of the



98 R = Me
99 R = H

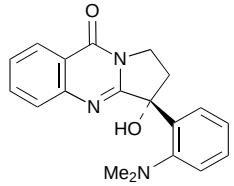
100

101 R = CO_2H
102 R = OH

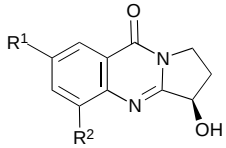
103 Isaindigotone

104 Tryptanthrin

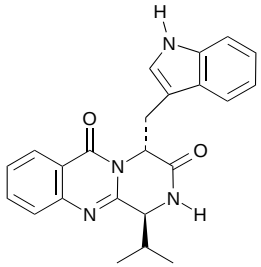
tryptoquivalines. This hypothesis was confirmed for the tryptoquivaline analogue, the relative stereochemistry of which was established by means of X-ray crystallography. On the reasonable assumption that the absolute configurations of the new alkaloids are the same as those of tryptoquivaline and nortryptoquivaline except at C-27, the compounds were identified as 27-*epi*-tryptoquivaline **111** and 27-*epi*-nortryptoquivaline **112**, both having 2*S*,3*S*,12*R*,15*S*,27*R* configuration. On intraperitoneal injection of 50 mg kg^{-1} of the metabolites in mice, **111** and **112** caused weak tremor with paralysis, which appeared at about 30 and 120 min after injection and lasted for about 120 and 30 min respectively. In comparison, after about 60 min tryptoquivaline **109** induced a similar response that lasted for about 90 min, while nortryptoquivaline **110** was inactive.



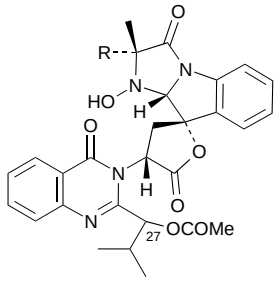
105 Desmethoxyaniflorine



106 R^1 = OMe; R^2 = H
107 R^1 = H; R^2 = OMe



108 Fiscalin B

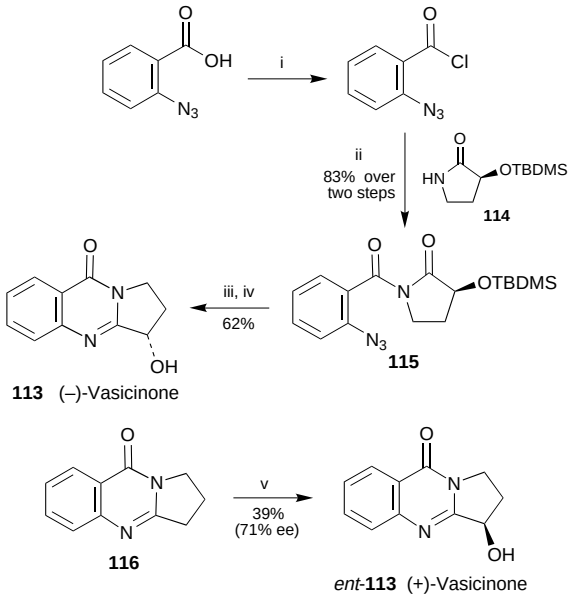


109 Tryptoquivaline R = Me; 27*S*
110 Nortryptoquivaline R = H; 27*S*
111 R = Me; 27*R*
112 R = H; 27*R*

2.2 Synthesis

The recent reversal of the accepted stereochemistry for vasicine and related alkaloids[58] has already been mentioned in this review (see Section 2.1). An important report describing the first asymmetric syntheses of both enantiomers of vasicinone

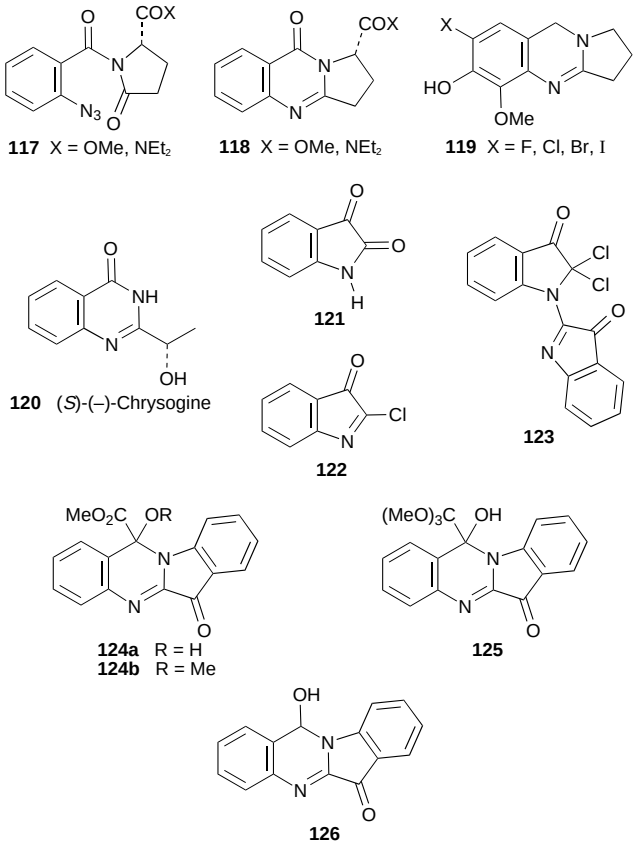
now provides indisputable evidence that the long-standing assignment of 3*R* configuration to (−)-vasicinone **113** is wrong.[60] In this work, Eguchi and co-workers first prepared (±)-vasicinone, *rac*-**113**, to establish the viability of their synthetic approach (Scheme 10, with racemic substrates) before embarking on the illustrated synthesis with the TBDMS-protected (3*S*)-3-hydroxypyrrolidin-2-one **114**, made in six steps from L-aspartic acid. The key step was the aza-Wittig cyclisation of **115**, after which the tricyclic product was deprotected to yield (*S*)-(−)-vasicinone **113** ($[\alpha]_D^{28}$ −58, *c* 0.45, $CHCl_3$) in 97% enantiomeric excess and 52% overall yield based on 2-azidobenzoic acid. With this reference compound in hand, the authors investigated the asymmetric oxidation of the anion derived from deoxyvasicinone **116** with (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine and its enantiomer (Davis reagents) as sources of electropositive oxygen. The best enantiomeric excess (71%) of (*R*)-(+)-vasicinone, *ent*-**113**, was obtained in THF at −78 °C with sodium hexamethyldisilazide as base and only half an equivalent of (−)-oxaziridine, although the isolated yield of the product was only 39%. Intramolecular aza-Wittig reaction on the azidolactams **117** has also been used to prepare the deoxyvasicinone derivatives **118**.[61] More conventional routes were employed to make the halogenated deoxyvasicine derivatives **119**, all of which showed good activity as bronchodilators.[62]



Scheme 10 *Reagents:* i, $SOCl_2$, reflux; ii, NaH, THF, 0 °C to rt; iii, Bu_3P, toluene, rt to reflux; iv, Bu_4NF, THF, 0 °C to rt; v, NaHDMS, THF, −78 °C, 1 h, then (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine, THF, −78 °C, 30 min

The synthesis of (*S*)-(−)-chrysogine **120** highlighted in last year's review (*cf*. ref. 21*g*) was claimed by the authors to be the first asymmetric synthesis of this mould metabolite. [63] Bergman has now pointed out[64] that his research group had already published essentially the same route to (*S*)-chrysogine in 1990.[65] The only difference was the base used in the final cyclisation step (Na_2CO_3 instead of NaOH). This earlier synthesis had, in fact, also been reviewed in these pages (*cf*. ref. 21*h*). The low optical rotation reported for the target in the more recent synthesis ($[\alpha]_D$ −27, *vs.* −41 in Bergman's work) may have been due to partial racemisation of the chiral starting material, (*S*)-2-acetoxypropanoyl chloride.

For well over a century it has been assumed that the structure of 'isatin chloride', formed by heating isatin **121** with phosphorus pentachloride, is **122**. Cornforth and his co-workers have now proved by spectroscopy and crystallography that the product is actually the dimer **123**.[66] Treatment of this dimer with dry methanol gave a mixture of indoloquinazolinones **124a**, **124b** and **125**. Compound **125** was photolabile, and deposited tryptanthrin **104** when kept for several days in deuterated chloroform. Several routes to the reduced tryptanthrin analogue **126** were also explored in this work, and persuasive evidence was adduced for the complex mechanisms involved in the transformations. Coincidentally, tryptanthrin (also known as couropitine A) **104** was recently prepared in 97% yield by heating isatin **121** with phosphoryl chloride and working up the reaction mixture with ice.[67]

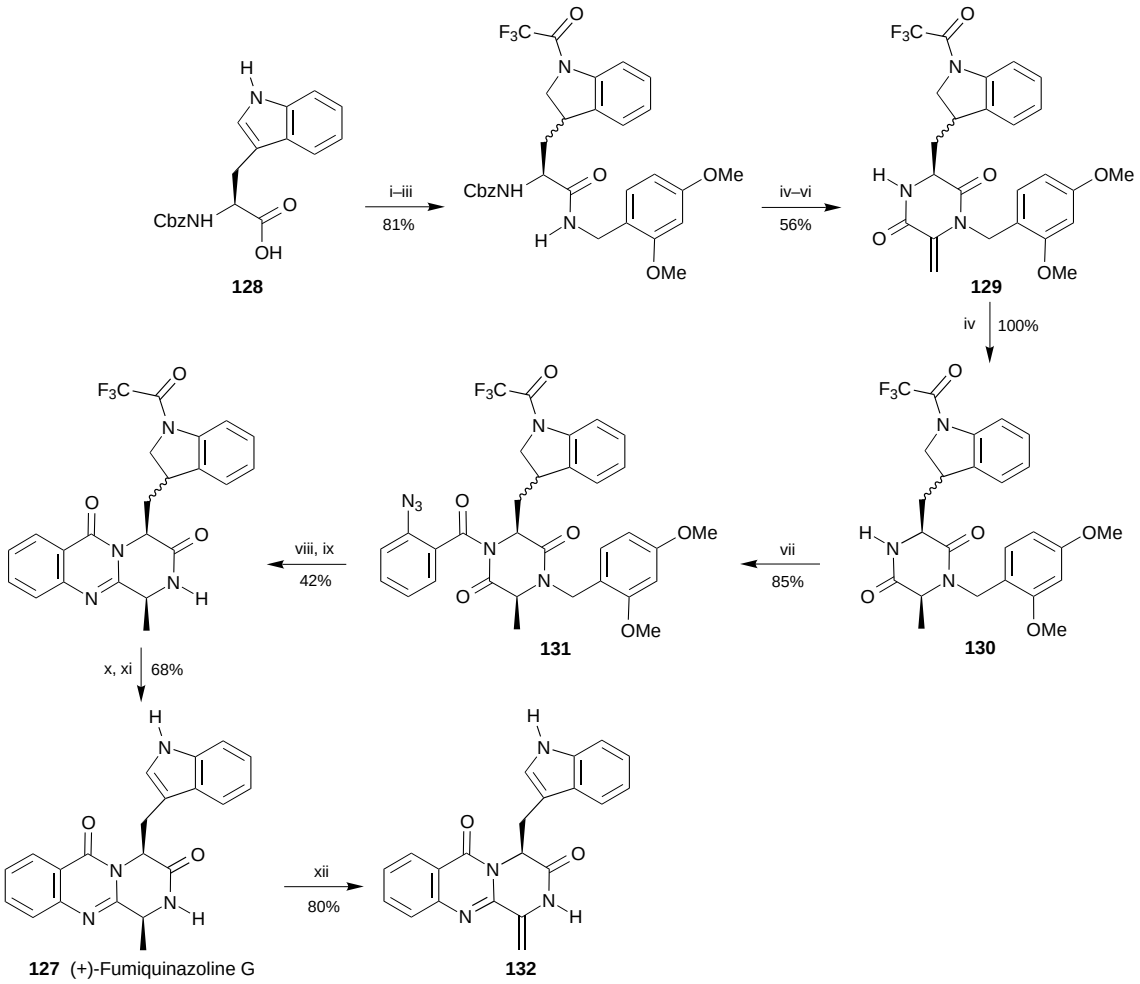


The first synthesis of (+)-fumiquinazoline G **127**, the enantiomer of the naturally occurring fungal metabolite, has been accomplished by He and Snider.[68] With the protected L-tryptophan derivative **128** as starting material, the diketopiperazine **129** was prepared in 45% yield over six steps as illustrated in Scheme 11. The diastereofacially selective hydrogenation of this product set up the second stereogenic centre with the correct relative stereochemistry. Acylation of the resulting compound **130** with 2-azidobenzoyl chloride yielded intermediate **131**, deprotection and aza-Wittig reaction of which created the quinazolin-4(3*H*)-one ring present in the final target. The synthesis, completed as shown, contains twelve steps in total and was achieved in an overall yield of 11%. Comparatively easy oxidation of fumiquinazoline G with manganese dioxide afforded the dehydro product **132**, thereby introducing useful functionality for the synthesis of more complex fumiquinazolines.

3 Acridone alkaloids

3.1 Occurrence

The five new acridone alkaloids reported during the review period were isolated from rutaceous plants. They are listed in



Scheme 11 *Reagents:* i, 2,4-dimethoxybenzylamine (DMBn-NH_2), DCC; ii, BH_3, THF, TFA; iii, NEt_3, TFAA; iv, H_2, Pd/C; v, MeCOCOCl; vi, TFA, toluene, reflux; vi, H_2, Pd/C; vii, 2-azidobenzoyl chloride; viii, CAN, MeCN, H_2O; ix, Bu_3P, benzene; x, NH_3, MeOH; xi, MnO_2, EtOAc, 1 d; xii, excess MnO_2, EtOAc, several d

Table 2 together with known alkaloids from new plant sources.[14,69–72]

Two of the new alkaloids have surprisingly simple structures. 1-Hydroxy-3-methoxyacridone **133** was found with several related compounds by bioactivity-guided fractionation (brine shrimp test) of a bark extract from the African medicinal plant *Fagara macrophylla*, which is also known as *Zanthoxylum gillettii*.[71] 1-Methoxy-*N*-methylacridone **134**, which was isolated from the taxonomically puzzling *Samadera* specimen described previously (see Section 1.2),[14] is one of a mere handful of acridone alkaloids lacking the strongly hydrogen-bonding hydroxy substituent at C-1. It was accompanied by 1,8-dihydroxy-*N*-methylacridone **135**, an atypically substituted acridone alkaloid that was very recently found for the first time as a natural product in *Boronia lanceolata*.[73]

(−)-Margrapines A and B, **136** and **137**, two alkaloids of unknown relative and absolute stereochemistry isolated from the roots of the Marsh grapefruit, *Citrus paradisi*, are highly oxidised 4-prenylacridones.[70] The gross structures were assigned on the basis of comprehensive NMR data.

The bizarre new alkaloid fareanine **138** has been isolated from the leaves of the Australian tree *Medicosma fareana*.[72] Its inclusion amongst the acridone alkaloids is justified on the grounds of the postulated biogenesis for this compound, which the authors suggest is initiated by oxidative cleavage of the electron-rich aromatic ring of an acridone precursor such as normelicopicine **139**. Indeed, normelicopicine and related compounds were also isolated in this study. If one envisages the oxidation proceeding through a quinone ketal such as **140** – a type of intermediate for which precedent exists[74] – then cleavage of the C3–C4 bond followed by recyclisation between C2 and C4 will give rise to the new alkaloid's unique cyclopenta[*b*]quinoline skeleton.

3.2 Synthesis and biological studies

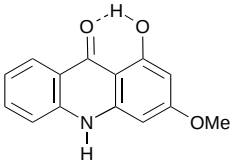
Clinical trials on the potent anticancer agent acronycine **141** have hitherto been hampered by the alkaloid's poor solubility in water. Modifications in the pyran ring have now been studied as a means of gaining access to more soluble derivatives.[75] Mild nitration (nitric acid, acetic acid, 0 °C) yielded **142** (90%), a variety of reductions on which provided access to the oxime **143** and the dihydroacronycine derivatives **144** and **145**. Further derivatives **146**–**148** could be prepared in turn from **145**. The nitro and oxime compounds **142** and **143** proved to be 300 and 10 times more active respectively than acronycine in inhibiting the proliferation of L1210 leukaemia cells, but **142** was inactive against P388 leukaemia and C38 colon adenocarcinoma in mice.

Condensation of synthetic 2-hydroxy-1,2-dihydroacronycine **149** with various glycoside donors has yielded a wide range of α-hexopyranosides, the antiproliferative activity of which has been tested in murine L1210 leukaemia cells.[76] While most of the products were about as active as acronycine itself, the azides **150** and **151** (as *R*/*S* mixtures at C-2 of the acronycine moiety) were approximately ten times more potent than the parent alkaloid in inhibiting cell proliferation. Since glycosides

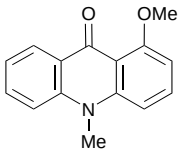
Table 2 Isolation and detection of acridone alkaloids

Species	Alkaloid[a]	Ref.
Bosistoa selwynii	Bosistine Citrusamine Junosine *N*-Methylataphylline *N*-Methylataphyllinine Yukocitrine	69
Citrus paradisi	(−)-Margrapine A[b] **136** (−)-Margrapine B[b] **137**	70
Fagara macrophylla (=*Zanthoxylum gillettii*)	Arborinine 1-Hydroxy-3-methoxyacridone[b] **133** 1-Hydroxy-3-methoxy-*N*-methylacridone Xanthoxoline	71
Medicosma fareana	Fareanine[b] **138** Melicopidine Normelicopicine **139** 1,3,4-Trimethoxy-*N*-methylacridone	72
aff. *Samadera* SAC-2825	1,8-Dihydroxy-*N*-methylacridone **135** 1-Methoxy-*N*-methylacridone[b] **134**	14

[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.



133



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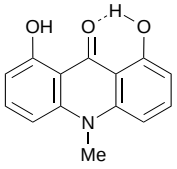

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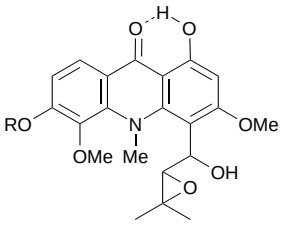
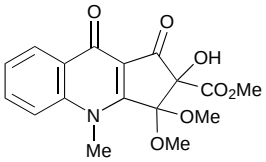
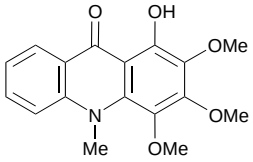


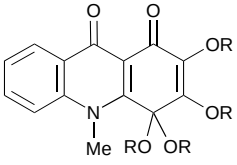
136 Margrapine-A R = H
137 Margrapine-B R = Me



138 Fareanine



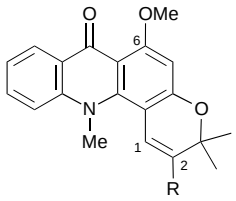
139 Normelicopicine



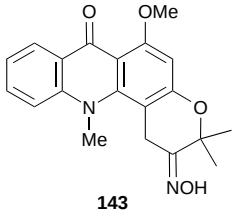
140

bearing amine substituents were only marginally active, it appears that activity may be related to lipophilicity of the sugar unit.

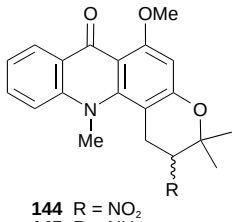
Synthetic 1,2-dihydroxy-1,2-dihydroacronycine **152**, made by treating acronycine with a catalytic quantity of osmium tetroxide and *N*-methylmorpholine *N*-oxide as reoxidant, has also been converted into a variety of derivatives for cytotoxic and antitumour investigations.[77] In this case, all of the products **153**–**157** were more active than acronycine itself when tested against L1210 leukaemia cells *in vitro*. However, removal of the methoxy group at C-6 rendered the compounds inactive. In addition, compounds **153**–**157** were active *in vivo* against murine P388 at doses four to sixteen times lower than with acronycine itself, while **154**, **156** and **157** were highly efficient in reducing the volume of colon 38 adenocarcinoma, which is normally a highly resistant solid tumour. Compound **154** in particular was remarkably active; all the treated mice were free of tumours after 23 days of treatment. These are the most promising results to date in the search for antitumour drugs based on acronycine as a lead compound.



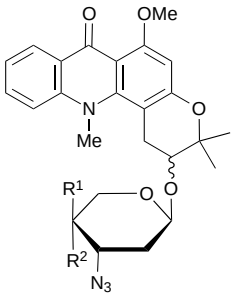
141 Acronycine R = H
142 R = NO_2



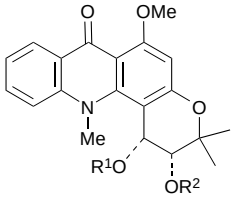
143



144 R = NO_2
145 R = NH_2
146 R = NMe_2
147 R = NHCOMe
148 R = NHCOPh
149 R = OH



150 R^1 = H; R^2 = OAc
151 R^1 = OAc; R^2 = H



152 R^1 = R^2 = H
153 R^1 = H; R^2 = COMe
154 R^1 = R^2 = COMe
155 R^1-R^2 = (C=O)
156 R^1 = H; R^2 = COPh
157 R^1 = COMe; R^2 = COPh

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