MARINE, NITROGEN-CONTAINING HETEROCYCLIC NATURAL PRODUCTS . STRUCTURES AND SYNTHESES OF COMPOUNDS CONTAINING QUINOLINE AND/OR ISOQUINOLINE UNITS

Mercedes Alvarez and Marisa Salas
Department of Pharmacology and Therapeutic Chemistry
Faculty of Pharmacy, University of Barcelona, Barcelona 08028, Spain
John A. Joule*
Chemistry Department, University of Manchester, Manchester M13 9PL, U.K.

Abstract - The structures, biological activities, and syntheses of marine, natural products containing quinoline and/or isoquinoline nuclei are reviewed.

The natural product chemistry of sea-dwelling organisms has been developed only over the last twenty years, or so.[1] In particular, during the last ten years, a fascinating variety of polycyclic nitrogenous heterocyclic natural products,[2] with novel structures, have been described. Many of these compounds, as well as being structurally novel, have been reported to have potentially valuable biological activities. Indeed, it has been pointed out[3] that since physical and behavioural defences are rare amongst sponges, and since they are sessile microphagic feeders susceptible to fouling by epizoic organisms and infection by external pathogenic microorganisms, it is probably not mere chance that many produce substances with antibacterial and/or antifungal activities. The interest of the medicinal chemist cannot help but be aroused by the possibilities provided by such naturally occurring 'lead' compounds.

The structural range and diversity of 'sea alkaloids' already described, and the prospect of those yet to come, present an extensive challenge both to the synthetic heterocyclic chemist and also to the bioorganic chemist, for it must be assumed that many of the structures are derived by elaboration of amino acid precursors, in ways which are different from the relatively familiar pathways established for the plant alkaloids.[4] Experimental study of the biosynthetic pathways leading to sea alkaloids is virgin territory.[5]

This Review covers the literature to the end of 1990, deals only with structure and synthesis, and is restricted to compounds in which a quinoline and/or an isoquinoline skeletal unit is present, at whatever oxidation level. Reported biological activity is

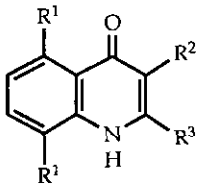
also mentioned. We have categorised substances according to structure, rather than on the basis of their biological origin, since this Review is targeted primarily at medicinal and synthetic chemists. Where a structure contains both quinoline and isoquinoline nuclei the compound is classified with the former.

1. Quinolines

(a) Simple Quinolones

Structures

Three yellow 4-quinolones have been described, uranidine[6] (**1a**), carboxylic acid (**1b**)[7] both from the sulphur-yellow sponge, *Verongia aerophoba* Schmidt, and antibacterial acid (**1c**)[8] from an Antarctic sponge *Dendrilla membranosa*.



1	R^1	R^2	R^3
a	OH	OH	H
b	H	OH	CO_2H
c	OH	H	CO_2H

The rapid darkening in colour which members of the *Verongidae* undergo on exposure to air can be attributed to oxidation of such 5,8-dihydroxyquinolones to the corresponding quinone, then oligomerisation of the quinone; the unstable blue quinone from **1a** was observed by ^1H nmr spectroscopy.

Syntheses

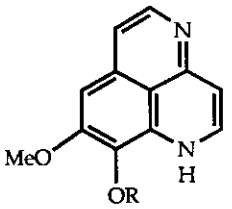
As part of the structure determination, an earlier synthesis,[9] in which ethyl 5,6-dimethoxy-4-quinolone-2-carboxylate was constructed by first condensing 2,5-dimethoxyaniline and diethyl oxaloacetate at 90°C then cyclising the resulting enamine by heating alone at 240°C, was repeated and the 4-quinolone ester converted into **1c** by alkaline hydrolysis.

(b) Benzo[d,e][1,6]naphthyridines

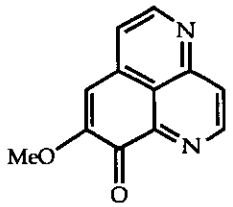
Structures

Three structurally related compounds have been isolated from the Okinawan sea sponge *Aaptos aaptos*, aaptamine (**2a**),[10] demethylaaptamine (**2b**), and oxidised variant (**3**).[11] It is not unreasonable to suppose that this group derives biogenetically from dihydroxyphenylalanine, condensed with, perhaps, asparagine. The third ring could then be formed by cyclising nucleophilic condensation *via* a quinone, as suggested by the structure of **3**. Aaptamine was shown[10,12] to have a powerful α-adrenoceptor blocking activity in vascular smooth muscle, **2b** was described[11] as

cytotoxic and antimicrobial, and 3 was the most potent of the trio in antimicrobial activity against Gram positive and Gram negative bacteria.

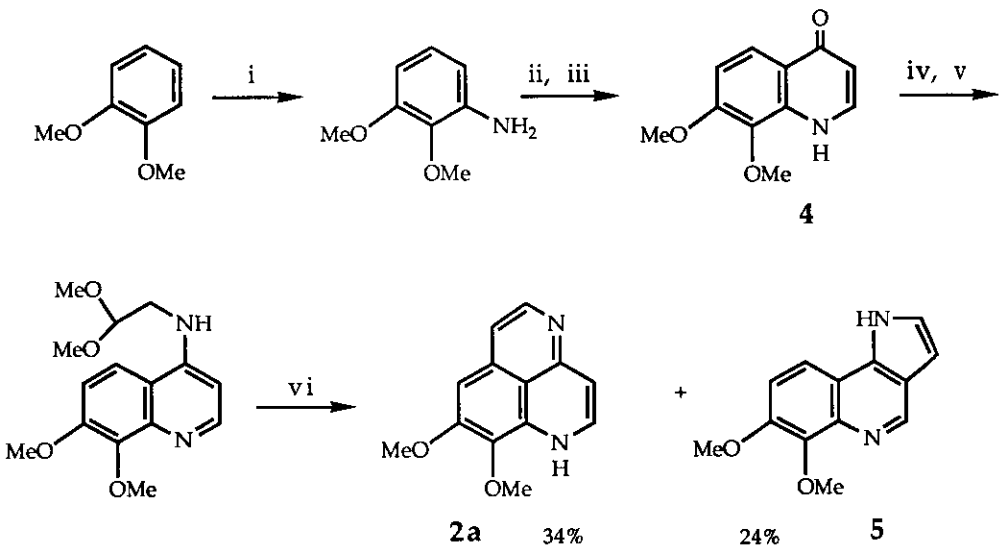


2		R
aaptamine	a	Me
demethylaaptamine	b	H



Syntheses

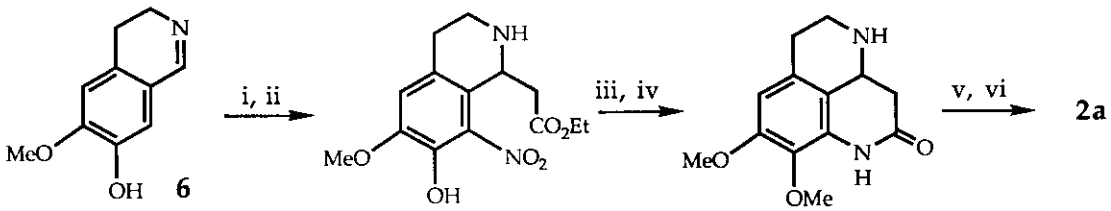
Seven different syntheses of aaptamine have been described[13] which variously started with the construction of a quinoline[13a,d,f] or an isoquinoline[13b,c,e,g] as a first stage. Scheme 1[13a] shows how ortho lithiation allowed preparation of 2,3-dimethoxyaniline for construction of quinolone (**4**). A protected aminoacetaldehyde side-chain was introduced for electrophilic cyclisation onto the benzene ring generating the desired product (aaptamine) (**2a**), but this was accompanied by the unexpected tricycle (**5**), apparently resulting from cyclising electrophilic attack on the pyridine ring.[14]



Scheme 1 Reagents : i, *n*-BuLi, TMEDA, 0→22°C, then $Me_3SiCH_2N_3$ (78%); ii, $HC{\equiv}CCO_2Me$, MeOH, 3 days, 22°C (73%); iii, Ph_2O, reflux, 25 min (91%); iv, $POCl_3$, 22°C, 24 h (86%); v, $H_2NCH_2CH(OMe)_2$, DMSO, 95°C, 5 days (52%); vi, TFA, CF_3SO_3H, SbF_5, 75-80°C, 3 min (34% plus 24% isomeric byproduct).

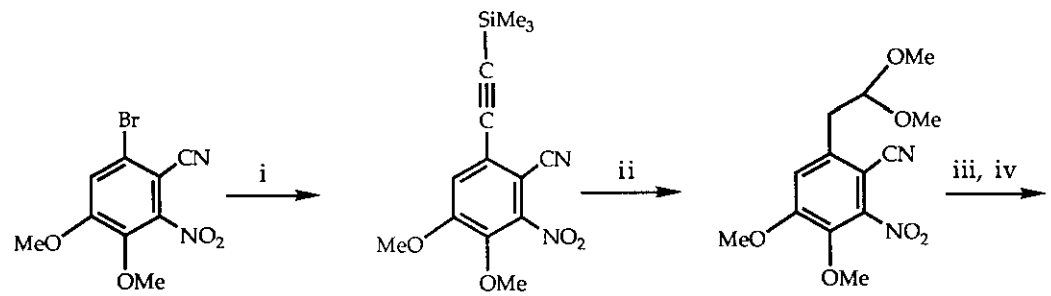
Scheme 2[13b] shows how the use of phenolic 3,4-dihydroisoquinoline (**6**) allowed both the required regioselective introduction of nitrogen, by nitration *via* nitrosation *ortho* to the phenolic hydroxyl, and then the insertion of the two carbon chain by

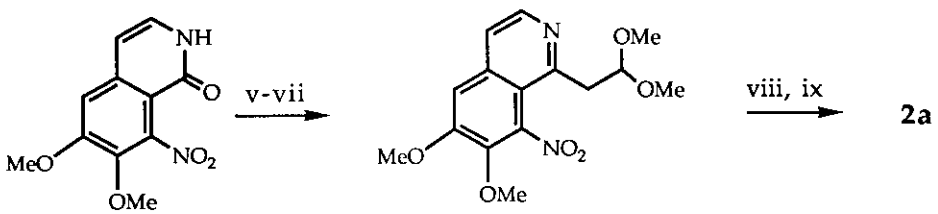
decarboxylative addition of ethyl hydrogen malonate to the imine group. After *O*-methylation, reduction of the nitro group permitted cyclisation to a lactam having the required ring system.



Scheme 2 Reagents : i, 40% HNO_3, $NaNO_2$ (cat.), 5°C (60%); ii, $HO_2CCH_2CO_2Et$, 120°C (70%); iii, CH_2N_2, Et_2O, CH_2Cl_2 (100%); iv, H_2, Pd-C, 10% HCl (65%); v, BH_3, THF (95%); vi, 5% Pd-C, xylene, reflux (60%).

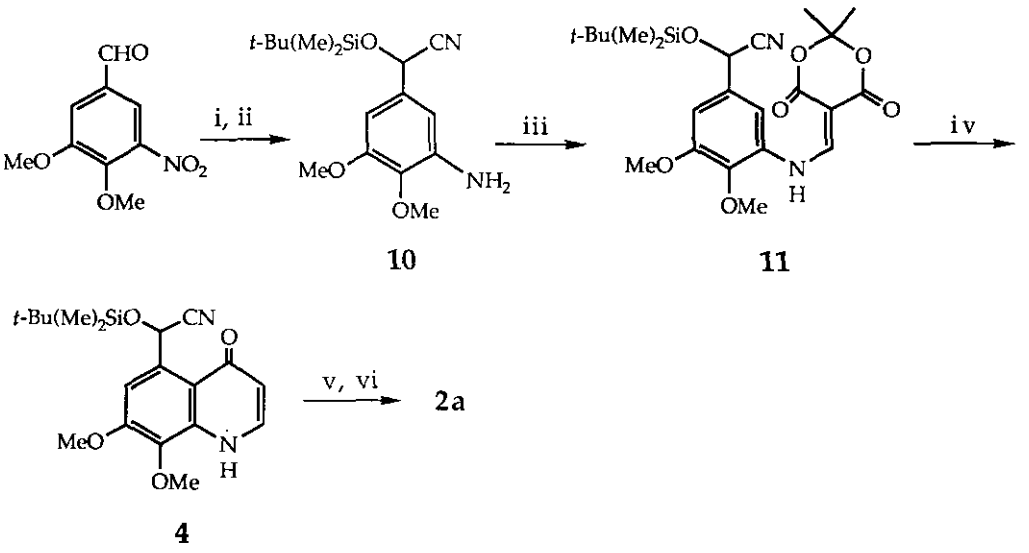
Palladium-catalysed couplings were a key feature of the route, Scheme 3[13c], which began with nitro nitrile (7), the two nitrogens present in **7** to be the ring nitrogens of final product. The two remaining two-carbon units required were introduced by Pd[0] couplings, in the steps producing 8 and 9.





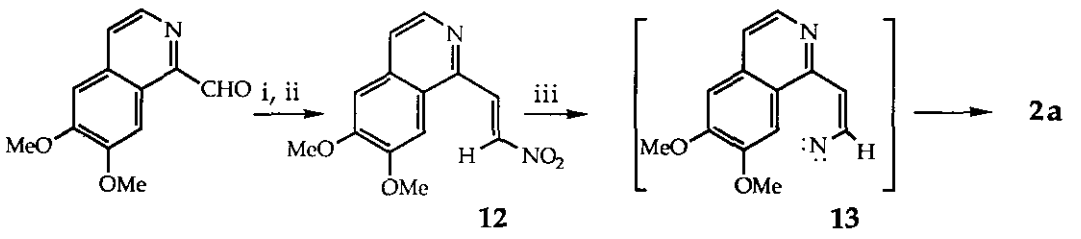
Scheme 3 Reagents : i, $HC{\equiv}CSiMe_3$ (TMSA), $Cl_2Pd[P(Ph)_3]_2$, CuI, DMF, 40-45°C (83%); ii, MeONa, MeOH, DMF, (67%); iii, H_2O_2, Na_2CO_3 (75 %): iv, *p*-TsOH (90%); v, $POCl_3$ (92%); vi, TMSA, "Pd" (85%); vii, NaOMe (63%); viii, H_2 /Pd-C (94%); ix, HCl (45%).

Difficulties in dehydrogenating a dihydroaaptamine, also encountered in another approach,[13b] led to the modified route shown in Scheme 4.[13d] The side chain of protected amine cyanohydrin (**10**) was later to be converted into a (silyl protected) ethanolamine thus providing for a final dehydration, rather than a dehydrogenation. A quinolone was constructed by thermolysis of the Meldrum's acid derivative (**11**) of **10**.



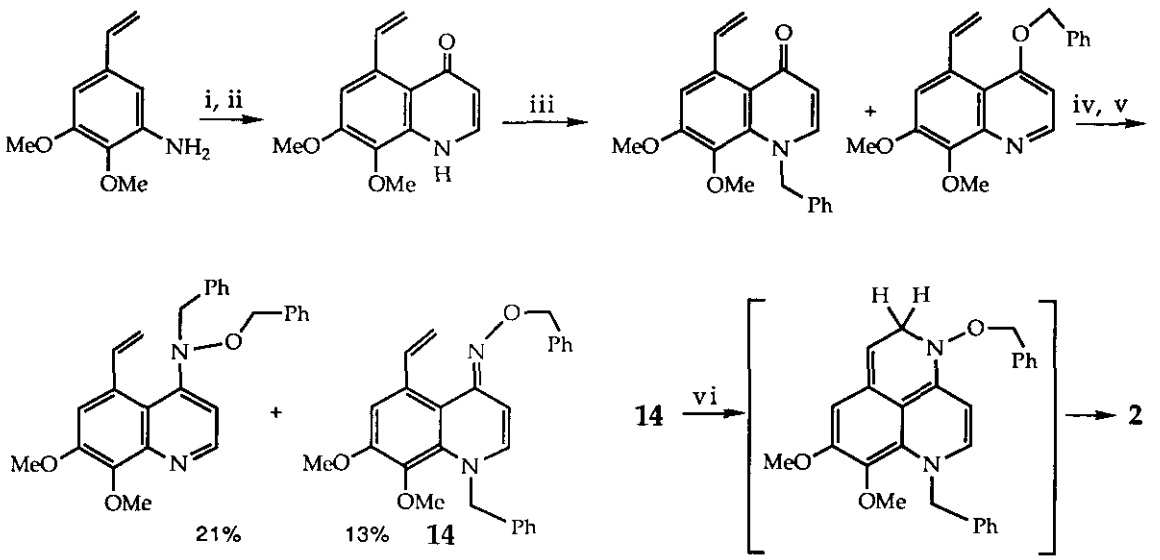
Scheme 4 Reagents : i, KCN, *t*-Bu(Me)$_2$SiCl, ZnI$_2$, MeCN, room temperature, (83%); ii, H$_2$/Ni (Raney), room temperature, 'pressure' (95%); iii, Meldrum's acid, HC(OMe)$_3$, reflux, 2 h (92%); iv, Ph$_2$O, reflux, 5 min (88%); v, H$_2$/Ni (Raney), MeOH, room temperature, 'pressure' (91%); vi, *p*-TsOH, HMDSA, sonication 15 min, then reflux, 12 h (51%).

A short route (Scheme 5)[13e] depended on the (presumed) intermediacy of a *Z* vinylnitrene (**13**) on heating the (*E*) nitroalkene (**12**) under deoxygenation conditions. The success is to be contrasted with the normal fate of aryl-vinylnitrenes - to be converted into aryl-acetonitriles.[15]



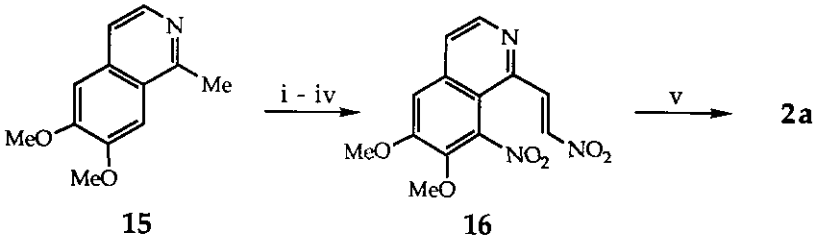
Scheme 5 Reagents : i, MeNO$_2$, Et$_2$NH, 0°C, 1 h; ii, pyridine, Ac$_2$O, 0°C, 14 h (85% overall i, ii); iii, (EtO)$_3$P, reflux, 2.5 h (58%).

The penultimate, key electrocyclic step in the route shown in Scheme 6[13f] required the synthesis of a 4-quinolone oxime, carrying a vinyl group, **14**. This could not be achieved by direct reaction of hydroxylamine with a 4-quinolone, but required a nucleophilic substitution on the corresponding 4-alkoxyquinoline.



Scheme 6 Reagents: i, $HCO\,CH_2CO_2Et$, room temperature, 14 h (62%); ii, Ph_2O, reflux, 40 min (30%); iii, $PhCH_2Br$, NaH, DMF, 30 min; iv, $NH_2OH.HCl$, EtOH, reflux, 1 h (33%); v, $PhCH_2Cl$, NaH, DMF, room temperature, 1 h; vi, *o*-$Cl_2C_6H_4$, reflux, 2 h (67%) then HCl conc., reflux, 2 h (de-*N*-benzylation) (90%).

The regioselective 8-nitration of isoquinoline (**15**) allowed the assembly of dinitroalkene (**16**), acidic reduction of which gave aaptamine (**2a**) (Scheme 7).[13g]

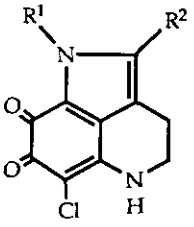


Scheme 7 Reagents : i, fuming HNO_3, -40°C (41%); ii, SeO_2, dioxan, reflux (54%); iii, $MeNO_2$, Al_2O_3 (84%); iv, Al_2O_3, PhH, reflux (-H_2O) (36%); v, Fe, AcOH (89%).

(c) Pyrrolo[3,2-d,e]quinolines

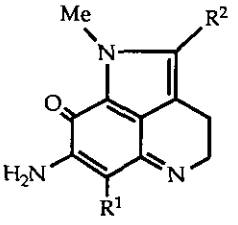
Structures

The three batzellines, A (**17a**), B (**17b**), and C (**17c**)[16a], and the isobatzellines A-D, (**18a-d**)[16b] were obtained from a Caribbean deep sea sponge, *Batzella* sp. and bear a strong structural similarity to the long known dehydrobufotenine, from the South American toad, *Bufo marinus*.[17] Isobatzelline A was converted into batzelline A by diazotisation and hydrolysis, and into isobatzelline D by catalytic hydrogenolytic removal of the halogen and sulphur[16b]. The isobatzellines, but not the batzellines, are cytotoxic (P388 leukemia cells) and also have moderate antifungal activity against *Candida albens*. It seems very likely that the skeleton derives from a closure of a tryptamine NH_2 onto the indole C-5, perhaps *via* an A-ring quinone.



batzellines A-C

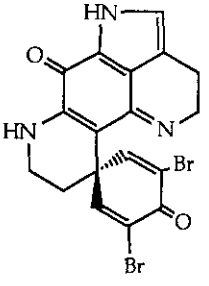
	R^1	R^2
17		
a	Me	SMe
b	H	SMe
c	Me	H



isobatzellines A-D

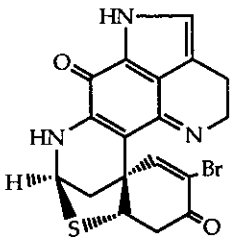
	R^1	R^2
18		
a	Cl	SMe
b	H	SMe
c	Cl	H
d	H	H

In a more elaborated form, this same tricyclic unit can be discerned in the discorhabdines A-D, and the prianosines A-D, but now with the incorporation of a tyrosine residue. The structurally simplest of this group is discorhabdine C[18,19] (**19**) in which the tyramine unit (probably after bromination) has been linked through nitrogen to the quinone, with a phenolic oxidative coupling to generate the spirocyclic dienone unit.

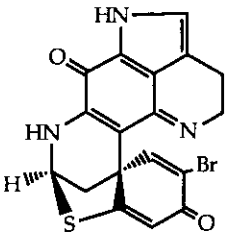


discorhabdine C
19

In discorhabdine A (same as prianosine A[20]) and discorhabdine B an additional sulphide bridge generates hexacyclic structures, (**20**) and (**21**).[19]

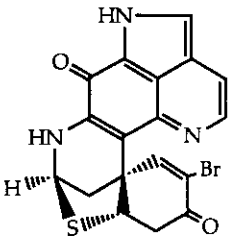


discorhabdine A
(= prianosine A)
20

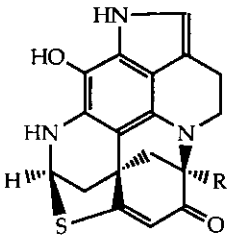


discorhabdine B
21

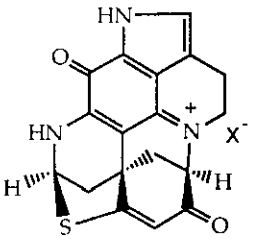
Prianosine B (**22**)[21] has an additional double bond compared with **20**, and prianosines C and D[18,21] (**23a**) and (**23b**), and discorhabdine D[22] (**24**), have an additional ring, making these the most complex of the series, as heptacyclic systems.



prianosine B
22



prianosines
C and D
23 R
a OH
b H

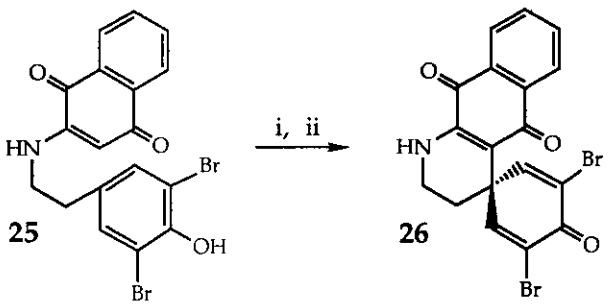


discorhabdine D
24

The discorhabdines were isolated from heavily pigmented sponges of *Latrunculia* species gathered in New Zealand waters, and the prianosines from *Prianos melanos*, a sponge gathered at Motobu Peninsula, Okinawa. Discorhabdine A has also been isolated independently from *P. melanos*. The discorhabdines A-C and the prianosines A-D have cytotoxic and antimicrobial activities; discorhabdine D has a lower cytotoxicity *in vitro*, but in contrast to the lack of activity of the other discorhabdines, a significant *in vivo* P388 activity.[22]

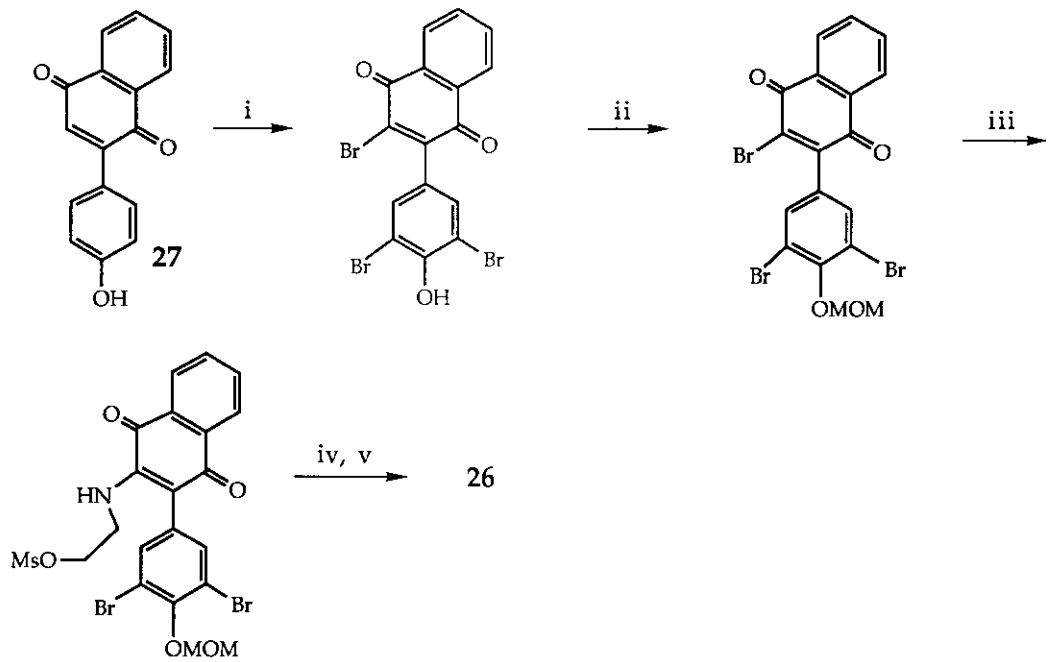
Syntheses

Three groups have described work towards the generation of the spirocyclic system of this group of alkaloids. Phenolic aminoquinone (**25**), available from reaction of 2,6-dibromotyramine with 2-methoxynaphthoquinone, was oxidatively coupled, better after *O*-silylation, using phenyliodosyl bis(trifluoroacetate) to produce spirocyclic quinone (**26**) (Scheme 8).[23]



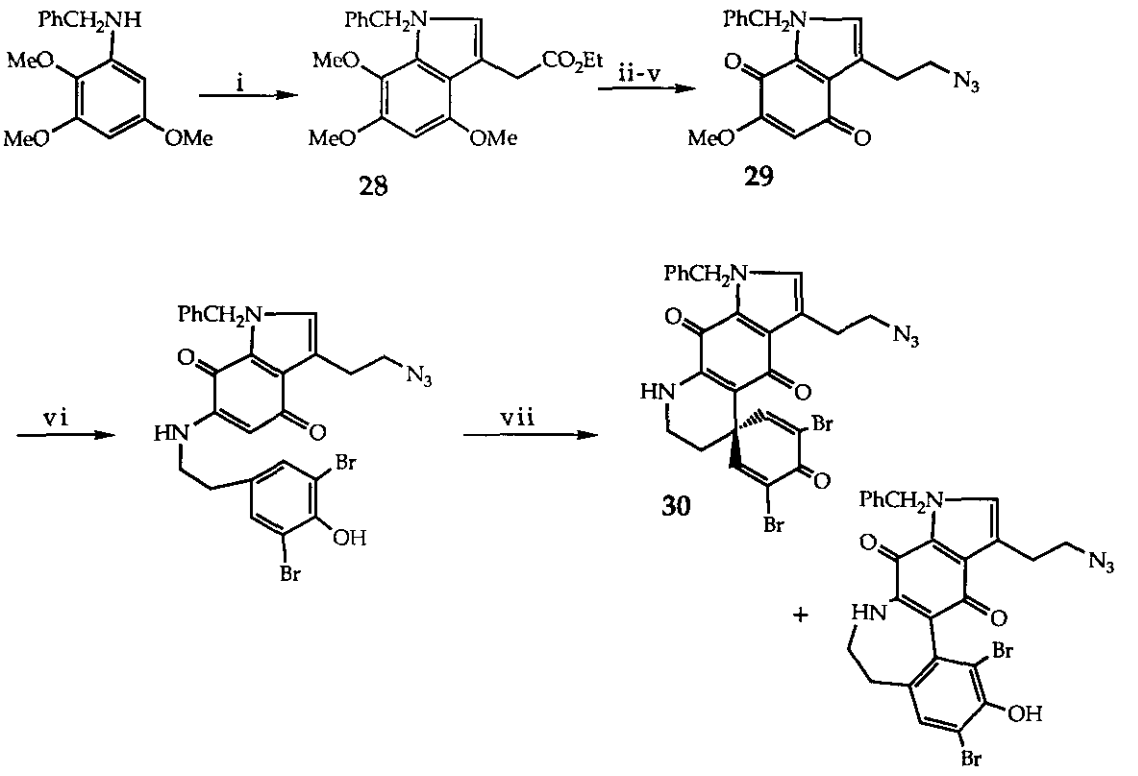
Scheme 8 Reagents: i, $MeCH{=}C(OMe)(OSiMe_3)$, CH_2Cl_2, 50°C, 5 h; ii, $PhI(OCOCF_3)_2$, CF_3CH_2OH, room temperature, 15 min (42% overall i, ii).

In an alternative approach, based on intramolecular phenol alkylation, phenol-quinone (**27**) was tribrominated, an aminoethanol unit introduced, and thence spirocyclic quinone (**26**) generated (Scheme 9).[24]



Scheme 9 Reagents: i, pyridinium bromide perbromide, pyridine, 0°C→room temperature (87%); ii, MOMCl, base (67%); iii, $H_2N(CH_2)_2OH$, DMF, then MsCl, pyridine, CH_2Cl_2, room temperature (67%); iv, 6N HCl (90%); v, *t*-BuOK , DMF, 80°C (33%).

Scheme 10[25] shows how the indole (**28**), produced from a precursor aniline by reaction with ethyl 4-chloroacetoacetate, after elaboration of a nitrogen-containing side chain and oxidation (→ **29**), was coupled with 2,6-dibromotyramine and oxidatively cyclised producing **30**.

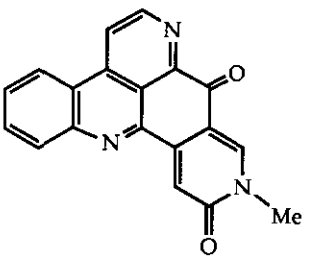


Scheme 10 Reagents: i, ethyl 4-chloroacetoacetate, EtOH, reflux (80%); ii, $LiAlH_4$, THF, 25°C (100%); iii, MsCl, Et_3N, CH_2Cl_2, 0°C; iv, NaN_3, DMF, 60°C (99% overall iii, iv); v, CAN, 50% aq. MeCN (68%); vi, 3,5-dibromotyramine hydrobromide, $NaHCO_3$, EtOH, reflux (69%); vii, *e.g.* anodic oxidation, MeOH, $LiClO_4$ (24% + 9% isomeric byproduct).

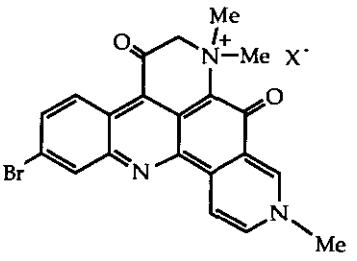
(d) Dibenzo[f,ij][2,7]naphthyridines

Structures

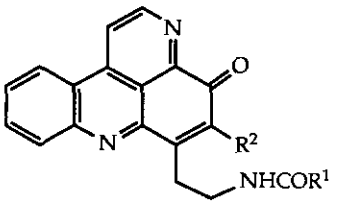
By far the largest sub-group of quinoline-containing sea alkaloids are those in which a dibenzo[f,ij][2,7]naphthyridine unit is present. Amphimedine (**31**), from a Pacific sponge *Amphimedon* sp., was the first to be described;[26] later, a quaternary salt with the same skeleton but different oxidation level, petrosamine (**32**) from a *Petrosia* sp. sponge from Belize, was reported; in solution this alkaloid exists as its enol.[27]



amphimedine
31

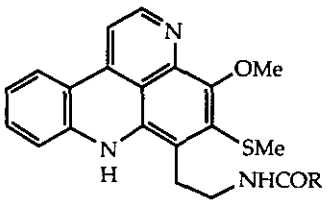


petrosamine
32



cystodytines A-C

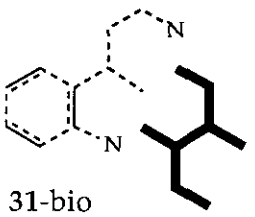
33	R^1	R^2	
a	$CH=C(Me)_2$	H	
b	C(Me)=CHMe	H	
c	$CH_2C(OH)(Me)_2$	H	
diplamine			
d	Me	SMe	



varamines A and B

34	R	
a	Et	
b	Me	

It is tempting to analyse the structure of these alkaloids in terms of a possible biosynthesis: diagram **31**-bio suggests how a tryptamine residue (dotted), in which the pyrrole ring has been opened, could be rationally combined with a C_8-unit (bold) which corresponds structurally to a reverse-Claisen ring-cleaved orsellinic acid.

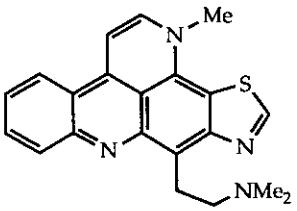


31-bio

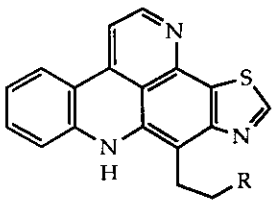
The cystodytines, A, B and C (**33a**, **b**, and **c**)[28] are clearly closely related to amphimedine, but with one less skeletal carbon; they have antineoplastic and powerful Ca-releasing activities and were isolated from the Okinawan tunicate *Cystodytes dellechiajei*. There is an obvious chemical pathway for the carbon 'lost' in comparison with amphimedine, in a retro-Claisen process. This 'nor-amphimedine' theme appears in several other variations, for example diplamine (**33d**),[29] from the tunicate *Diplosoma* sp., which is cytotoxic towards L1210 murine leukemia cells and also antimicrobial, and the varamines, A and B (**34a** and **b**),[30] which represent the same structural theme, but at a lower oxidation level; they also are cytotoxic towards L1210 murine leukemia cells.

This lower oxidation level of the dibenzo[f,ij][2,7]napthyridine theme occurs in several other variations which have in common the incorporation of an extra sulphur-containing ring : dercitine (35),[31] and dercitamine, nordercitine and dercitamide (**36a-c**)[32] from Bahamian deep water sponges of the family *Pachastrellidae* , *Stelletta* sp. and *Dercitus* sp., with a thiazole moiety, are examples. The violet-coloured dercitine was described as antitumour, antiviral, and immunomodulatory *in vitro* and

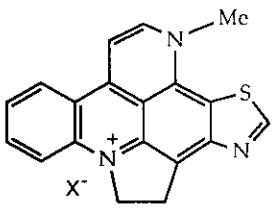
antitumour *in vivo*.[31] Further elaboration which seems to have involved intramolecular *N*-alkylation provides the quaternary salt cyclodercitine (**37**).[32] Isomerically fused thiazoles, kuanoniamines A, B, C, and D (**38** and **39 a-c**)[33] were obtained from a Micronesian tunicate and its predator, a prosobranch mollusk, *Chelynotus semperi*.



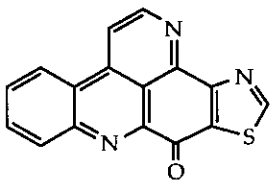
dercitine
35



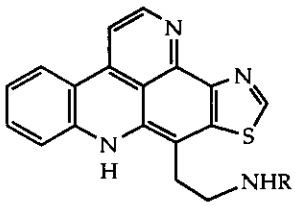
	36	R
dercitamine	**a**	NHMe
nordercitine	**b**	$N(Me)_2$
dercitamide	**c**	NHCOEt



cyclodercitine
37



kuanoniamine A
38

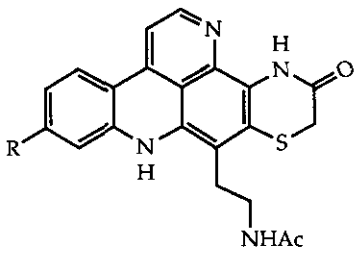


kuanoniamines B-D

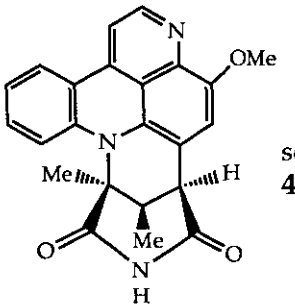
39	R
b	$COCH_2CH(Me)_2$
c	$COCH_2Me$
d	COMe

This alternative relative orientation of nitrogen and sulphur was found in 1,4-thiazine-fused alkaloids shermilamines A (**40a**)[34] and B (**40b**),[33,35] which were isolated from the tunicate *Trididemnun* sp. (collected in Pago Bay, Guam) and from an unidentified purple colonial tunicate, collected in Mante Channel, Pohnpei; shermilamine B was also obtained from a Red Sea tunicate *Eudistoma* sp. and named debromoshermilamine.[36] From this same tunicate were obtained[36,37] variations in which an isoprene unit and an additional nitrogen have been incorporated in one of two ways, to generate the hexacyclic systems found in segolines A and B (**41a** and **b**) on the one hand, and isosegoline (**42**) on the other.

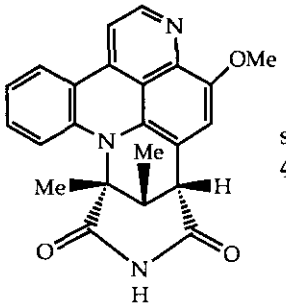
Alkaloids in which a further loss of one and two carbons respectively has occurred are norsegoline (**43**), from *Eudistoma* sp.[36] and kuanoniamine A (**38**).[33] The symmetrical eilatin (**44**),[38] also from *Eudistoma* sp. can be viewed (**44**-bio) as being comprised of two tryptamine residues (dotted) and two two-carbon units (bold).



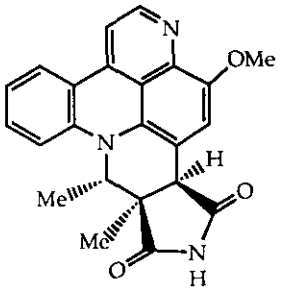
shermilamines
A and B
40 R
a Br
b H



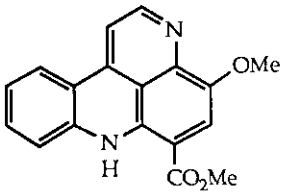
segoline A
41a



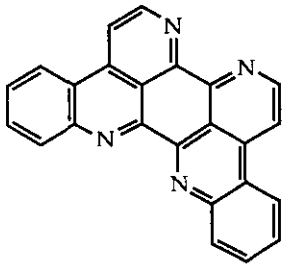
segoline B
41b



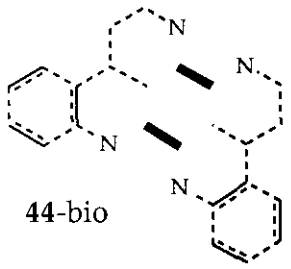
isosegoline
42



norsegoline
43

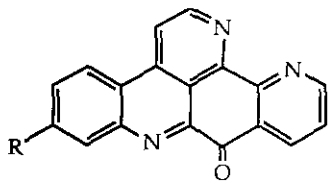


eilatine
44



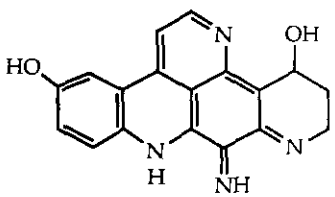
44-bio

2-Bromoleptoclinidinone (**45a**)[39] from an ascidian, *Leptoclinides* sp. and its de-bromo-analogue, ascididemine (**45b**),[40] from the Okinawan tunicate *Didemnum* sp., represent a rather different variant on the theme; here a fifth, pyridine ring is fused, but in a different orientation to the pyridone ring in amphimedine. 2-Bromoleptoclinidinone is described as mildly cytotoxic and ascididemine as having antineoplastic acitivity

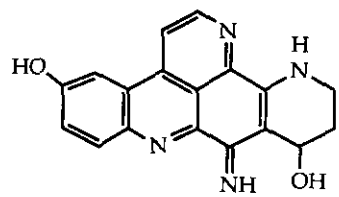


2-bromoleptoclinidinone
45a R=Br
ascididemine
45b R=H

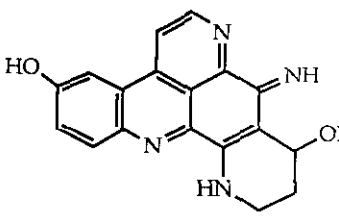
Calliactine, the pigment of the sea anemone *Calliactis parasitica*, first reported in 1940,[41] was reexamined recently and four alternative structures (**46a-d**) were considered, each including a dibenzo[f,ij][2,7]naphthyridine nucleus, of which **46a** was preferred;[42] it may be relevant that **46b** has a skeleton identical with that of **45/48**, and that **46d** has a skeleton identical with that of meridine/isomeridine (**47**).



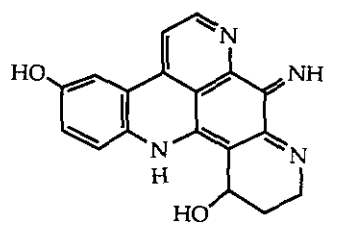
46a



46b

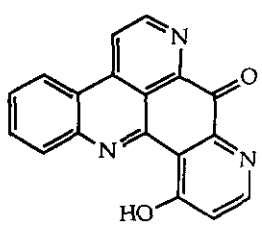


46c

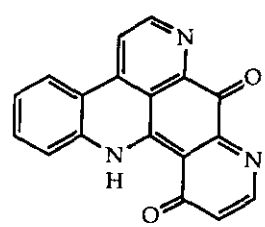


46d

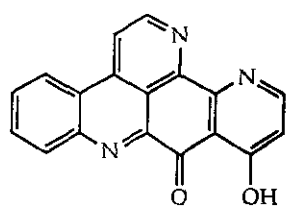
Cytotoxic meridine (**47a**) and its isolable tautomer (**47b**) were obtained from the ascidian *Amphicarpa meridiana*, from the waters off South Australia, together with a base for which structure **48** was proposed. Spectroscopic comparisons between these, related alkaloids, and a degradation product of calliactine led to the view that **46b** is to be preferred for the latter.[43]



meridine
47a



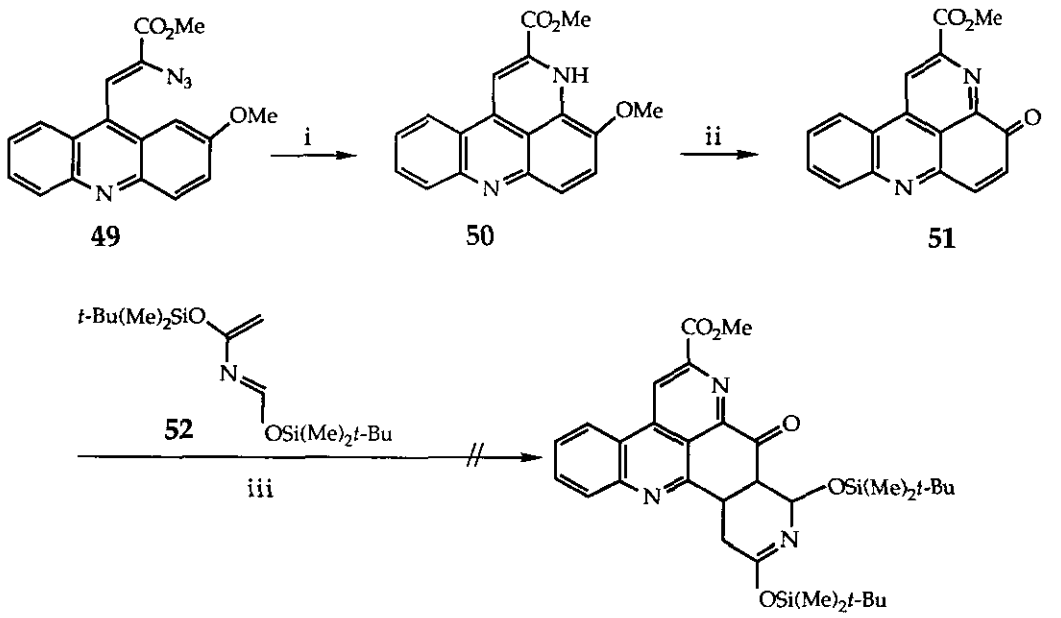
isomeridine
47b



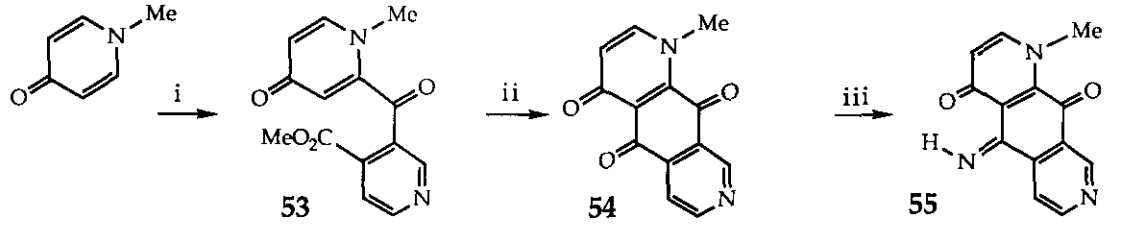
48

Syntheses

As well as approaches which went part way to amphimedine[44] three completed total syntheses have been described.[45] Oxidation of the methyl group in 2-methoxy-9-methylacridine and condensation with methyl azidoacetate gave **49**, thermolysis of which generated a nitrene which selectively inserted (4:1) into the peri position *ortho* to the methoxyl, producing tetracycle (**50**). Oxidation to the quinone-imine (**51**) was to be followed by completion of the final ring *via* an aza-Diels Alder, with Ghosez' azadiene (**52**), which however was unsuccessful (Scheme 11).[44a]



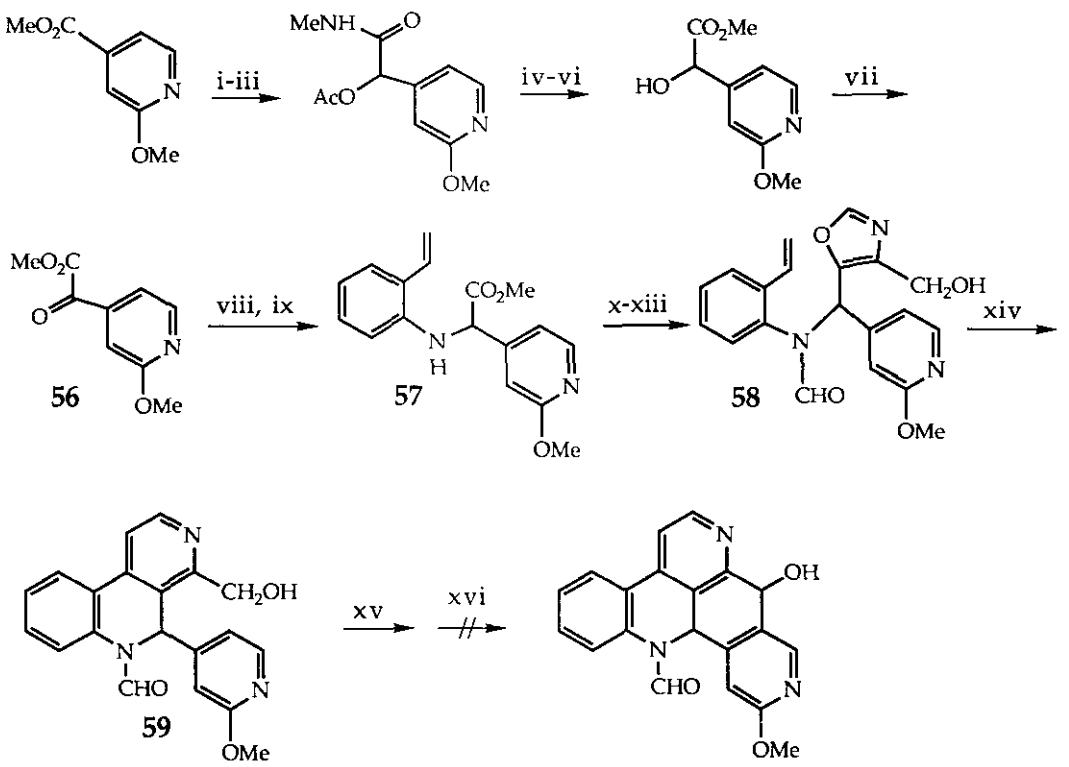
Scheme 11 Reagents : i, xylene, 140°C (97%); ii, MnO_2, 35% H_2SO_4 , 0°C (75%); iii, several conditions.



Scheme 12 Reagents : i, *n*-BuLi, THF, -78°C, then 4-methoxycarbonylpyridine-3-ylcarboxylic acid chloride (44%); ii, oleum, 200°C, 5 h (61%); iii, aq. NH_3, MeOH (100%).

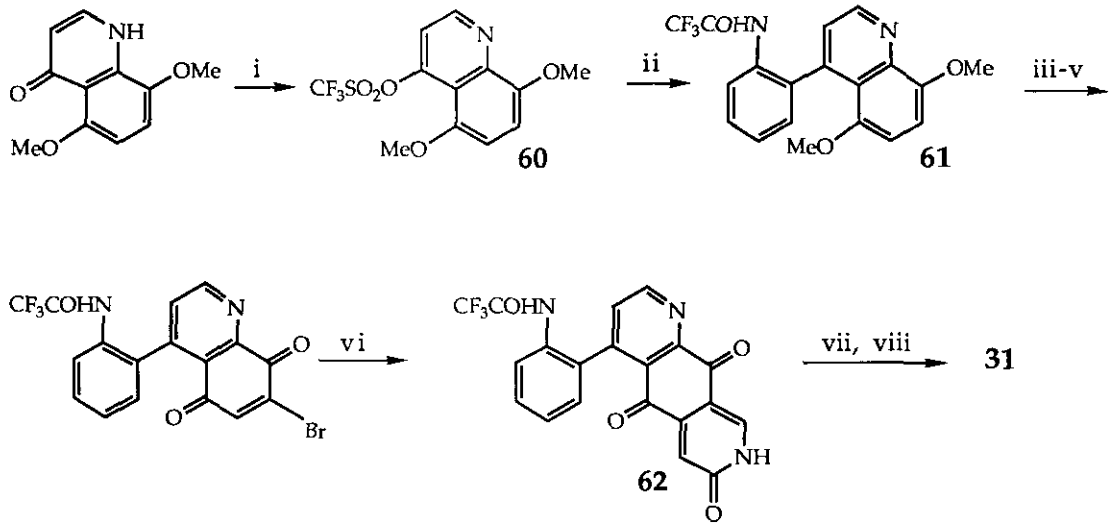
Scheme 12 shows the condensation of 2-lithio-1-methyl-4-pyridone with 4-methoxycarbonylpyridine-3-carboxylic acid chloride to give **53** which produced tricyclic quinone (**54**) in oleum. The third nitrogen was introduced *via* a regioselective reaction with ammonia, but attempts to add the remaining benzenoid ring to **55** have not yet been successful.[44b]

An intramolecular Diels-Alder addition of alkene to oxazole was central to the route[44c] shown in Scheme 13. Methyl 2-methoxypyridine-4-carboxylate was converted into α-keto ester (**56**) from which an imine with 2-vinylaniline was prepared and this reduced to afford **57**. Conversion of ester into oxazolylalcohol (**58**) set up the opportunity for intramolecular cycloaddition, **58** → alcohol (**59**), but attempts to close the final ring *via* electrocyclisation of the corresponding aldehyde, were frustrated by decarbonylation or reduction of the formyl group.

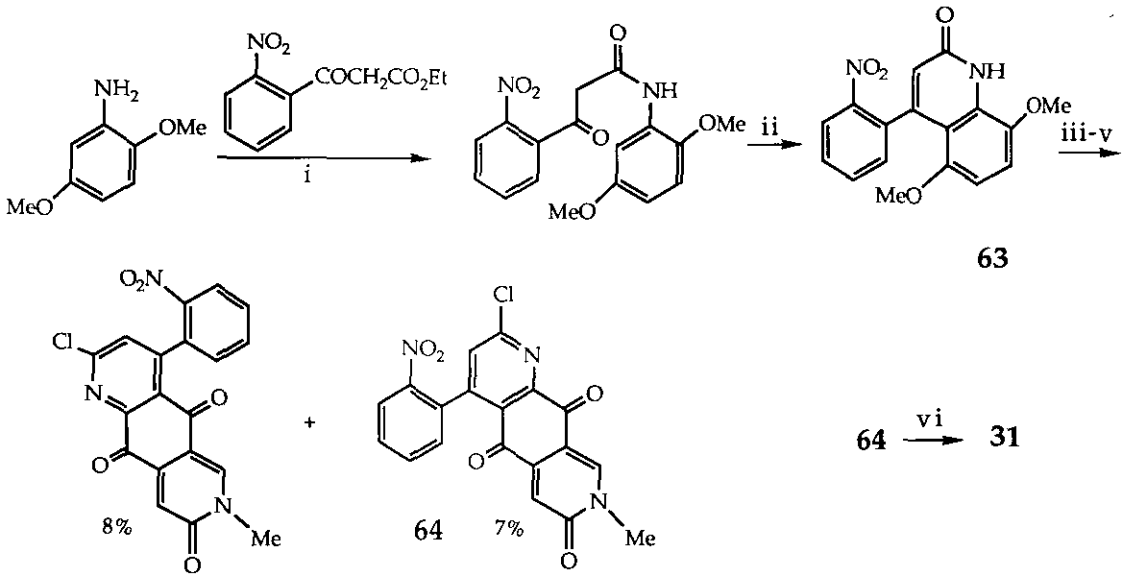


Scheme 13 Reagents : i, $Ca(BH_4)_2$ (80%); ii, CrO_3-pyridine (94%); iii, MeNC, AcOH, MeOH, 60°C (77 %); iv, $NaNO_2$, Ac_2O, AcOH; v, Na_2CO_3, CCl_4; vi, NaOMe, MeOH, 0°C, 10 min (85% overall iv-vi); vii, CrO_3-pyridine; viii, 2-vinylaniline, *p*-TsOH, PhMe; ix, $NaB(CN)H_3$, AcOH (78%); x, $Me_2AlSeMe$, PhMe; xi, $CNCH_2CO_2Me$, NEt_3, Cu_2O, THF; xii, $Ca(BH_4)_2$; xiii, HCO OCO Me, THF, 0°C→ room temperature, 15 h (82% overall xiii, xiv); xiv, *o*-$Cl_2C_6H_4$, reflux, DBN (71%) ; xv, MnO_2, $CHCl_3$, room temperature (67%); xvi, hν.

Scheme 14 shows how triflate (60) was coupled to give 4-arylquinoline (**61**), selective *O*-demethylation then allowing monobromination, the corresponding quinone undergoing an aza-Diels-Alder cycloaddition to give quinone (**62**), deprotection and pyridone *N*-methylation then producing the alkaloid.[45a]



Scheme 14 Reagents : i, Tf_2O, CH_2Cl_2, 2,6-lutidine, DMAP, 0→23°C (92%); ii, *o*-$C_6H_4(SnMe_3)(NHCOCF_3)$, 1,4-dioxane, $Pd(PPh_3)_4$, LiCl, 7 h (71 %); iii, LiI, 2,6-lutidine, 150°C (64 %); iv, Br_2, AcOH, $CHCl_3$; v, CAN, MeCN, H_2O, 0°C (59% overall iv, v); vi, **52**, THF, 23°C, 21 h (47%); vii, HCl, THF, 80°C, 3 h (86%); viii, Me_2SO_4, K_2CO_3, DMF, 23°C (96%).

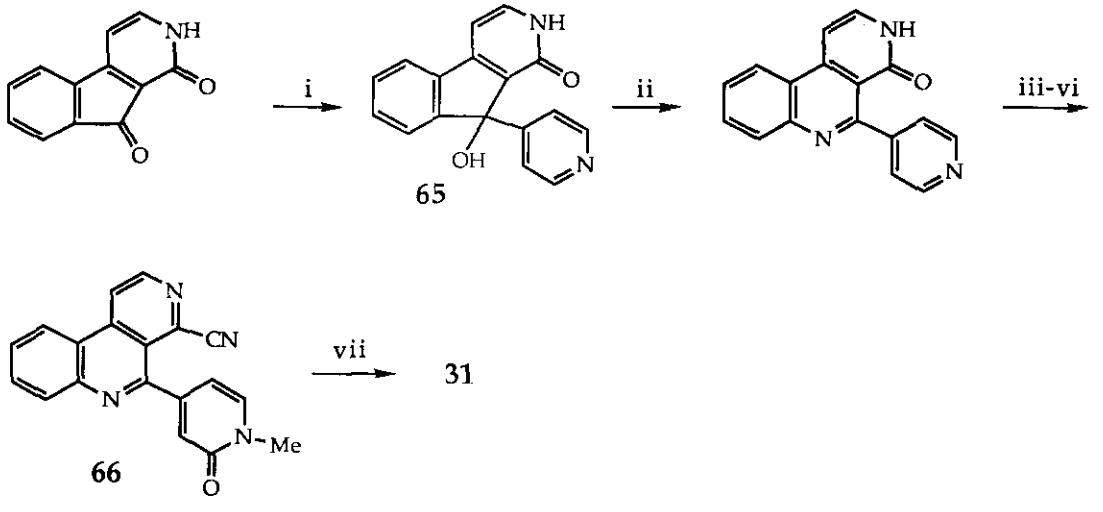


Scheme 15 Reagents : i, PhMe, pyridine, 140°C, 6 h (100%); ii, 80% H_2SO_4, 75°C, 30 min (53%); iii, PCl_5, $POCl_3$, 70°C, 45 min (66%); iv, CAN, aq. MeCN, 0°C, 15 min (77%); v, **52**, $CHCl_3$, 35°C, 8

h, then MeI, K_2CO_3, tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1), DMF, room temperature, 1 h; vi, H_2, 10% Pd-C, Et_3N, MeOH, room temperature, 20 h (13%).

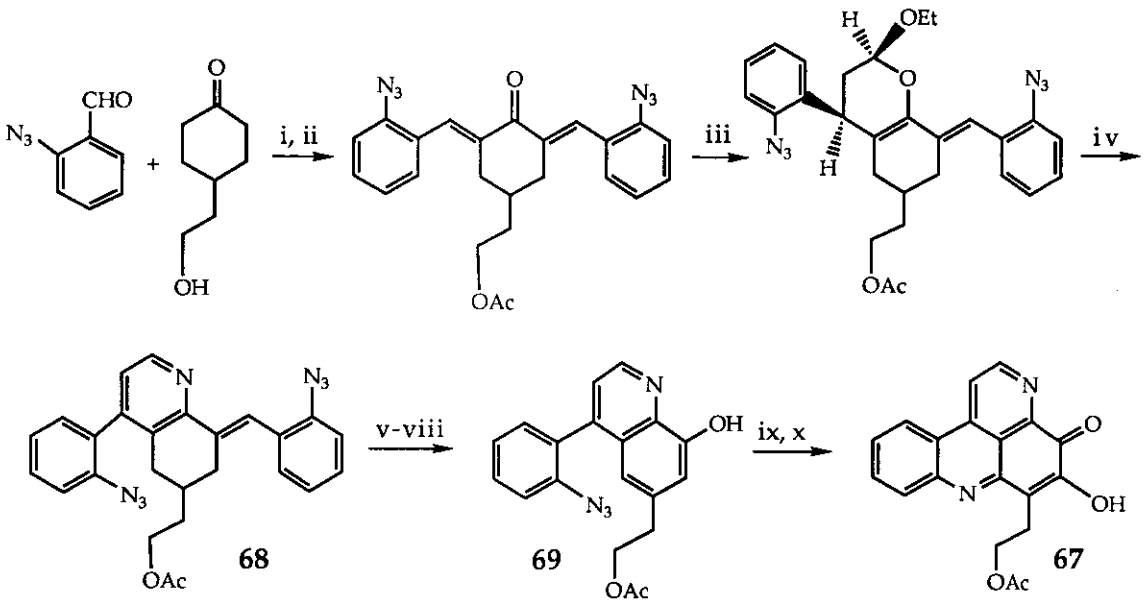
In another synthesis reported in 1988 (Scheme 15),[45b] 4-aryl-2-quinolone (**63**) was synthesised by a classical route. Conversion to quinone and an aza-Diels-Alder process, again using Ghosez' aza-diene, producing **64** and its regioisomer, hydrogenation/hydrogenolysis then allowing the formation of the final ring.

A quite different route (Scheme 16)[45c] depended on the Schmidt reaction of aza-fluorenol (**65**) with migration of the most electron-rich ring, which allowed the assembly of four of the five rings required. Regioselective *N*-methylation and oxidation converted the pendant pyridine to the pyridone oxidation level, and the final, quinonoid ring was created by an apparently regioselective Friedel-Crafts type acylation of the pyridone, *para* to its carbonyl, using nitrile (**66**).

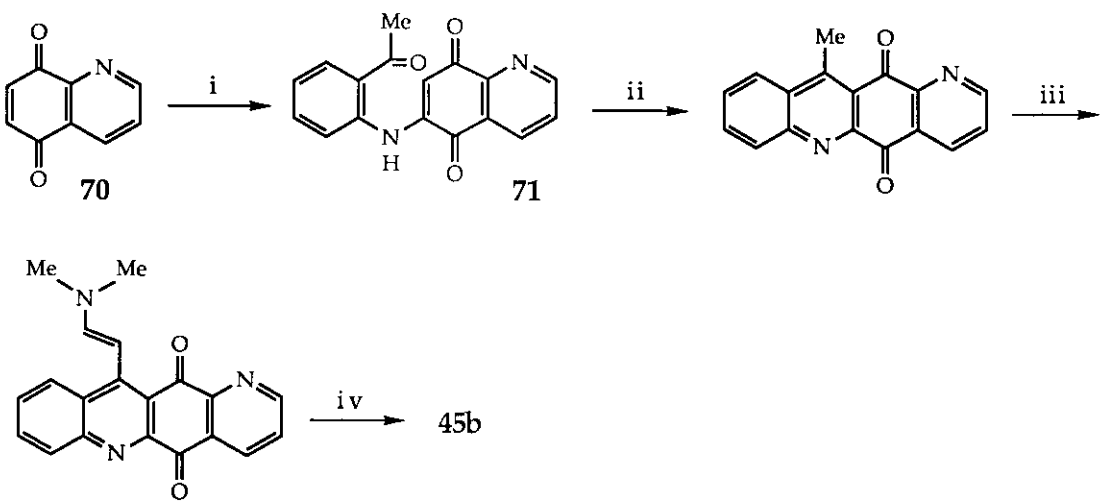


Scheme 16 Reagents : i, Me_3SiCl, Et_3N, THF, 60°C, 1 h, then 4-bromopyridine, *n*-BuLi, -40 → -20°C (87%); ii, NaN_3, PPA, 45°C, 20 h (69%); iii, PCl_5, cat. DMF , $POCl_3$, 180°C, 20 h (90%); iv, $MeOSO_2F$, 20°C, 40 min; v, KOH, $K_3Fe(CN)_6$, 20°C, 10 h (61% overall iv, v); vi, CuCN, DMSO, 150°C, 4 h, (70%); vii, PPA, 90°C, 5 h (35%).

Work on a route to the tetracyclic cystodytine A has progressed to the quinone-imine (**67**).[46] Scheme 17 illustrates the construction of tetrahydroquinoline (**68**), oxidation and aromatisation producing 69. Oxidation to *ortho*-quinone then thermolysis of this azide allowed nitrene insertion to provide **67**.



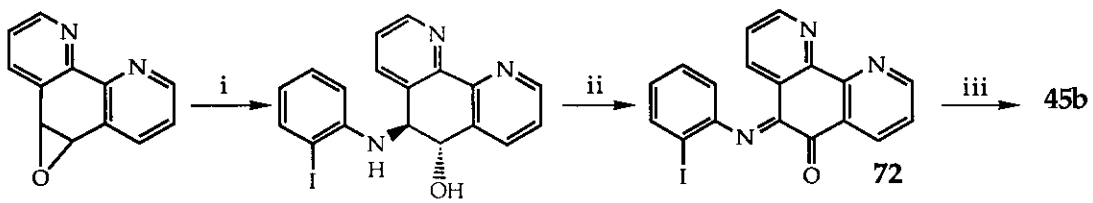
Scheme 17 Reagents : i, 10% aq. NaOH, EtOH, 0°C; ii, Ac_2O, pyridine (88% overall i, ii); iii, CH_2=CH-OEt, $(CH_2Cl)_2$, Yb(fod)$_3$, reflux, (68%); iv, $NH_2OH.HCl$, MeCN, reflux (77%); v, O_3, MeOH, -78°C, then Me_2S (76%); vi, isopropenyl acetate, cat. TfOH; vii, DDQ, PhMe, reflux, 15 min; viii, aq. $NaHCO_3$, MeOH, 25°C, (56% overall v-viii); ix, $ON(SO_3K)_2$ (Frémy's salt), MeOH, phosphate buffer, 25°C (65%); x, PhMe, reflux (74%).



Scheme 18 Reagents : i, 2-aminoacetophenone, $CeCl_3.7H_2O$, EtOH, air, 20°C, 16 h (78%); ii, H_2SO_4-AcOH (1:10), reflux, 10 min (94 %); iii, $Me_2NCH(OEt)_2$, DMF, 120°C, 1 h; iv, NH_4Cl, AcOH, reflux, 1 h (59%).

Both ascididemine and 2-bromoleptoclinidinone have been synthesised by the route shown in Scheme 18,[47a,b] and the former by an alternative shown in Scheme 19.[47c] Quinoline-quinone (**70**) underwent regioselective, oxidative addition with 2-aminoacetophenone to give ketone (**71**); acid-catalysed cyclisation and functionalisation of activated methyl then allowed construction of the final pyridine ring.[47a]

In a commendably short route, quinone-imine (**72**), produced *via* nucleophilic ring opening of phenanthroline epoxide with 2-iodoaniline, was photo-cyclised to produce ascididemine.[47c]

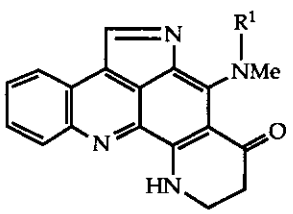


Scheme 19 Reagents : i, 2x2-iodoaniline, Et_3Al, CH_2Cl_2 (79%); ii, $BaMnO_4$, CH_2Cl_2 (83%); iii, hν, conc. H_2SO_4 (32%).

(e) Pyrrolo[2,3,4-kl]acridines

Structures

Three pentacyclic substances from the Fijian sponge *Plakortis* sp. may be related to the compounds in section (d) but are here classified separately. It may be relevant that if the five membered ring were six-membered then that skeleton is identical with one structure (**46c**), considered for calliactine. Plakinidines A, B,[48] and C[49] (**73a** and **b** and **74**), were cytotoxic towards L1210 murine leukemia cells, and the first two had *in vitro* activity against the parasite *Nippostrongylus brasiliensis*.

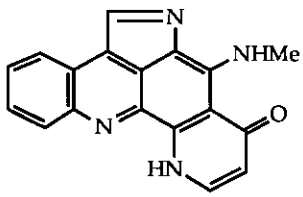


plakinidines A and B

73 R^1

a H

b Me



plakinidine C **74**

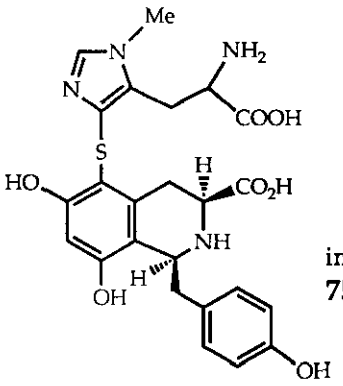
2. Isoquinolines

Relatively few isoquinoline-unit-containing sea alkaloids, other than those in which there is also a quinoline unit and which have been discussed in Section 1, have been described.

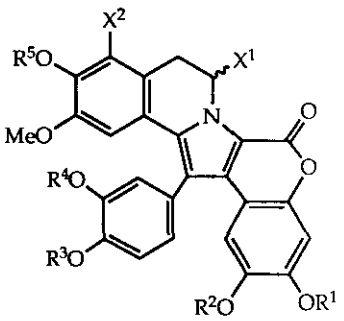
(a) Simple isoquinolines

Structures

Imbricatine (**75**)[50] from the starfish *Dermasterias imbricata* seems to be comprised of two phenylalanine-derived residues and a thio-*N*-methylated histidine, and indeed such thio-amino acids have been isolated from the starfish, *Evasterias troschelii*.[51] Imbricatine showed significant activity in antineoplastic assays.

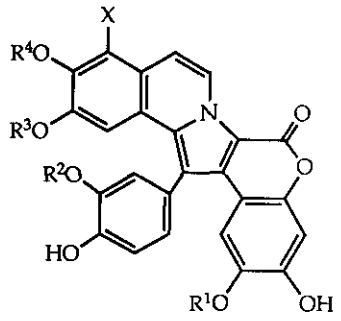


imbricatine
75



lamellarines A , C and E-G

76	R^1	R^2	R^3	R^4	R^5	X^1	X^2
a	H	Me	H	Me	Me	OH	OMe
b	H	Me	H	Me	Me	H	OMe
c	H	Me	Me	H	Me	H	OH
d	H	Me	Me	Me	Me	H	OH
e	Me	H	Me	H	H	H	H



lamellarines B, D and H

77	R^1	R^2	R^3	R^4	X
a	Me	Me	Me	Me	OMe
b	Me	Me	Me	H	H
c	H	H	H	H	H

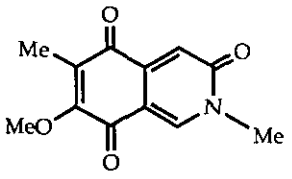
The lamellarins A-H (**76a-e** and 77a-c) were obtained from a prosubranch mollusk, *Lamellaria* sp. (A-D) and a marine ascidian, *Didemnon chartaceum* (E-H); one may speculate that they are derived from three DOPA residues, combined in a novel manner.[52]

(b) Isoquinoline quinones

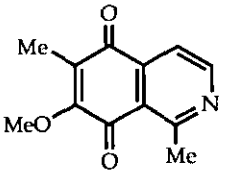
Structures

The bright blue sponges of *Reniera* sp. have yielded a group of isoquinoline quinones, and elaborated 'dimers' thereof. Some of these substances have also been isolated from microbial sources; other, structurally very similar compounds have been reported only from microbial sources. These microbial structures are not included here, though synthetic work on such compounds is discussed, since the structural similarity makes it relevant to the marine compounds.

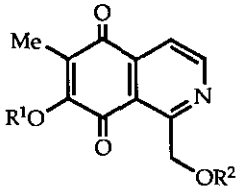
Mimosamycine (**78**)[53,54] and quinone (**79**) are the simplest of the isoquinoline-quinones described, with renierone (**80a**)[54,55] which has antibacterial activity, *O*-demethylrenierone (**80b**) and *N*-formyl-1,2-dihydrorenierone (**81a**) only marginally more complex.[55] The alcohol-quinone corresponding to renierone, rather confusingly named renierol (**80c**) was isolated, along with mimosamycine, from *Xestospongia*



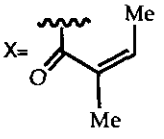
mimosamycine
78

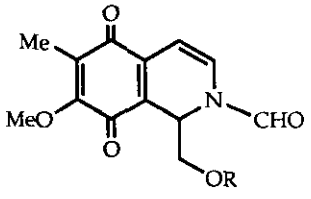


79

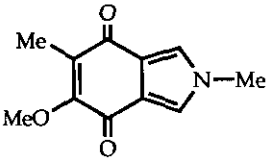


80	R^1	R^2
renierone	**a** Me	X
O-demethylrenierone	**b** H	X
renierol	**c** Me	H
renierol acetate	**d** Me	COMe
renierol propionate	**e** Me	COEt





81	R
a	X
b	COMe
c	COEt

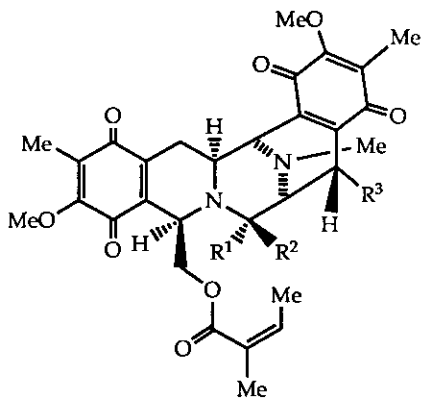


82

caycedoi,[56] and renierol acetate (**80d**) and propionate (**80e**), accompanied by *N*-formyl-1,2-dihydroisoquinoline-quinones (**81b** and **81c**), from a *Xestospongia* sp.[57]

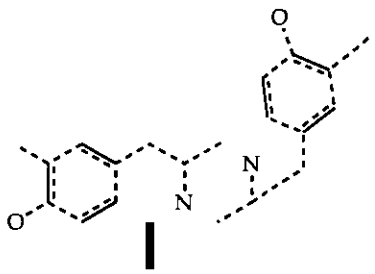
and from the nudibranch *Junura funebris*. These four isoquinoline quinones showed activity against *Bacillus subtilis* and *Staphylococcus aureus*. Also isolated from a *Reniera sp.* was isoindole-quinone (**82**).

The pentacyclic renieramycines A-F (**83a-f**)[54,58] are clearly related to the simpler isoquinoline quinones; in addition to the angelic acid moiety, one may discern (dotted in **83**-bio) two identical 'methylated' tyrosine residues and a C_2-unit (bold).



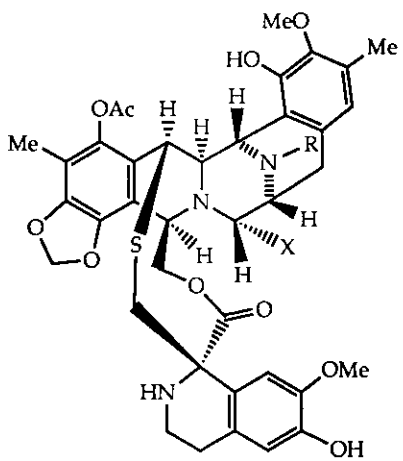
renieramycines A-F

83	R^1	R^2	R^3
a	H	H	OH
b	H	H	OEt
c	—O—		OH
d	—O—		OEt
e	OH	H	H
f	OH		OMe



83-bio

A bioassay-guided investigation of the Caribbean ascidian *Ecteinascidia turbinata* led to two potently antitumour sulphur-containing 'trimers'[59] shown to be identical with two of the ecteinascidines, 729, 743, 745, and 770 (**84a-d**) and 759A, 759B, probably *N*-oxides of 743, isolated in a complementary study of the same organism.[60] The relative stereochemistry of these complex molecules was shown to be the same as the renieriamycines[58] and microbial saframycins.[61] The saframycins have acylaminomethyl substituents where the marine substances have acyloxymethyl groups at the equivalent position, in the 'South West' of the molecule.

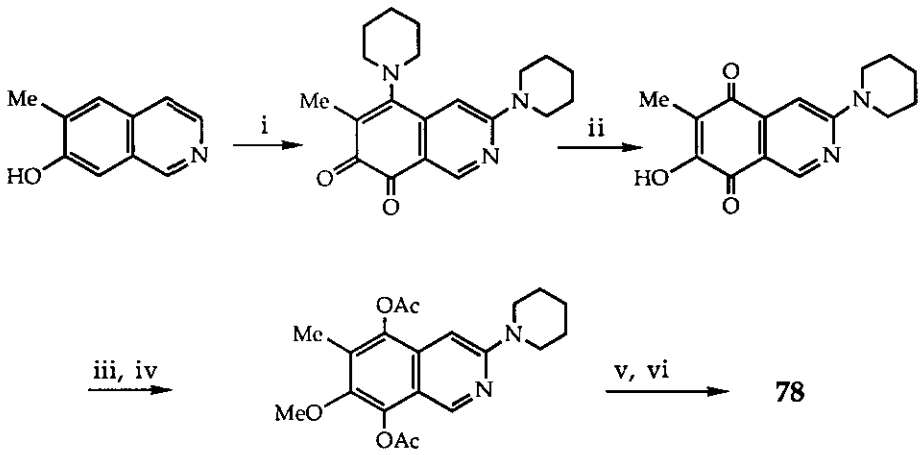


ecteinascidines

84	R	X
a	H	OH
b	Me	OH
c	Me	H
d	Me	CN

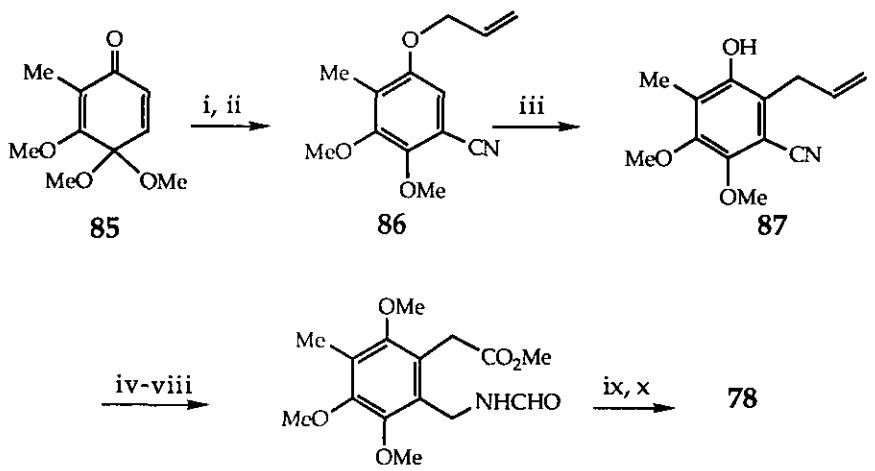
Syntheses

There have been three synthetic routes[62] to mimosamycine described, in the first of which mimosamycine, at the time only isolated from microbial sources, was produced (Scheme 20) by the oxidation of 7-hydroxy-6-methylisoquinoline using cupric acetate in the presence of a secondary amine (illustrated for dimethylamine). The *N*-methylation needed to be prefaced by temporarily reducing the quinone ring.[53a,b,62a]



Scheme 20 Reagents: i, O_2, piperidine, $Cu(OAc)_2$; ii, H_2SO_4, MeOH; iii, CH_2N_2; iv, Zn, AcONa, Ac_2O, AcOH; v, MeI; vi, silver oxide, MeOH.

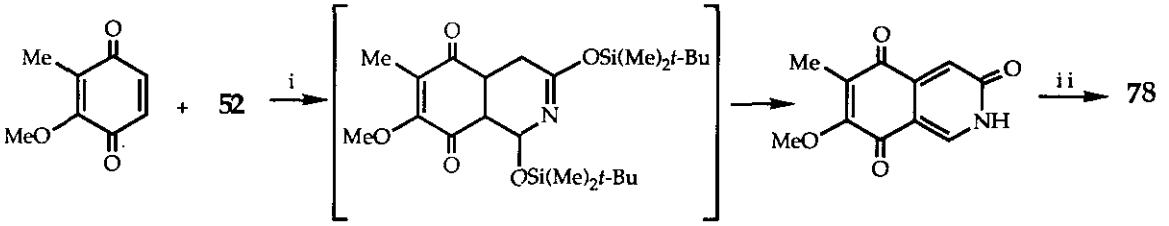
Mimosamycine has also been synthesised by the route shown in Scheme 21.[62b] The quinone acetal (**85**) was converted into the cyano-allyl ether (**86**) to allow introduction of the carbons of the hetero-ring *via* a Claisen rearrangement (→ **87**).



Scheme 21 Reagents: i, KCN, 18-crown-6, THF, 5.5 h (60%); ii, allyl bromide, K_2CO_3, acetone, reflux (97%); iii, DMA, reflux, 5-8 h (74%), iv, MeI, K_2CO_3 (88%); v, $KMnO_4$, TBAB, CH_2Cl_2, H_2O, AcOH (glacial); vi CH_2N_2 (70% overall v, vi); vii, H_2/Ni (Raney), 40 psi, room temperature; viii,

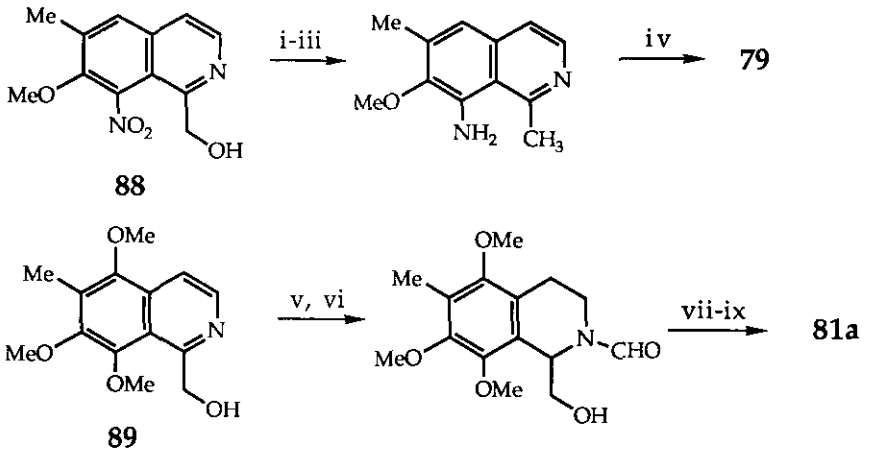
acetic formic anhydride, 5 days (82% overall vii, viii); ix, BH_3.THF, reflux, 1 h (55%); x, silver oxide, 6N HNO_3, dioxane, sonication (18%).

A quite different approach utilised the Ghosez aza-diene (**52**), to produce bisdemethyl-mimosamycin in one, well conceived, regioselective cycloaddition (Scheme 22).[62c]



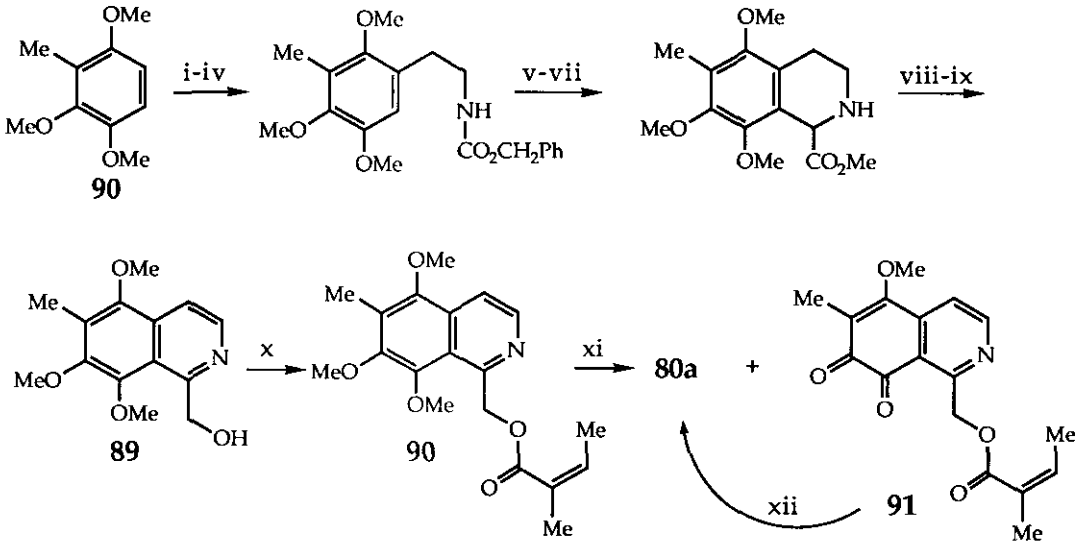
Scheme 22 Reagents: i, C_6H_6, then HCl (60%); ii, MeI, Na_2CO_3, DMF, tris[2-(2-methoxyethoxy)ethyl]amine (90%).

Renierol was converted into its propionate (**80d**) by reaction with the acid chloride in pyridine.[57] Renierol was also converted[63,64c] to the simple quinone (**79**) by *O*-tosylation, lithium triethylborohydride reductive deoxygenation and ceric ammonium nitrate oxidation; the same compound was also obtained by total synthesis from nitroisoquinoline (**88**), this route requiring Frémy's salt for the production of the *para*-quinone. Reduction of the heterocyclic ring in **89**, followed by *N*-formylation, *O*-acylation and CAN oxidation gave a 1,2,3,4-tetrahydroisoquinoline-quinone, Pd/C dehydrogenation of which affording[63,64c] the *N*-formyl-1,2-dihydroisoquinoline-quinone (**81a**). Scheme 23 shows these two syntheses.



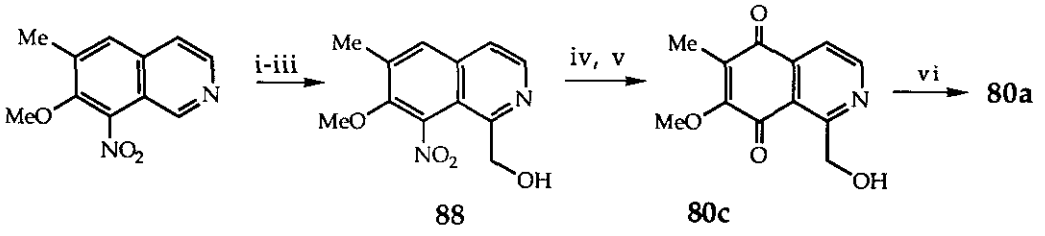
Scheme 23 Reagents: i, PhLi, TsCl, dioxane-ether, 0°C (85%); ii, $LiEt_3BH$, THF, room temperature, 30 min (57%); iii, H_2, Pd-C, MeOH, room temperature (78%); iv, $ON(SO_3K)_2$ (Frémy's salt) (83%); v, H_2, Pt_2O, AcOH; vi, HCO_2Et; vii, PhLi, (Z)-2-methylbut-2-enoyl chloride, THF, - 40°C (66%); viii, CAN (40%); ix, Pd-C, C_6H_6, reflux (59%).

There have been four similar, but distinctly different approaches[64] to the total synthesis of renierone. Scheme 24 illustrates the assembly of an isoquinoline-alcohol (**89**), from trimethoxymethylbenzene (**90**); the final oxidative conversion to the desired *para*-quinone was accompanied by the formation of some *ortho*-quinone (**91**).[64a]



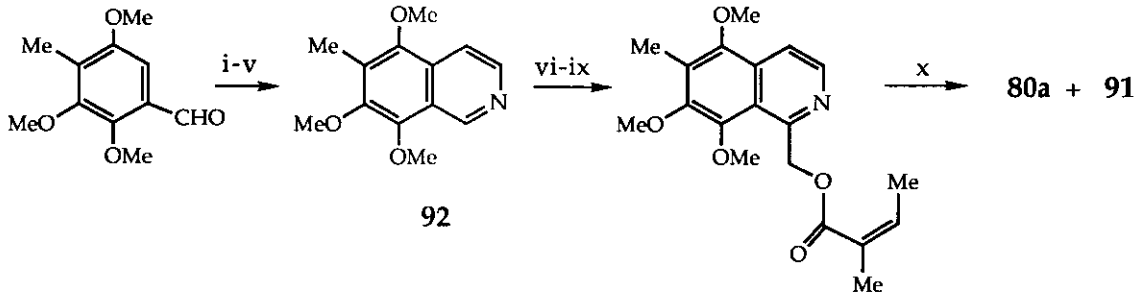
Scheme 24 Reagents: i, HCHO, HCl; ii, KCN, DMSO (75% overall i, ii); iii BH_3.THF; iv, $ClCO_2CH_2Ph$, K_2CO_3, $CHCl_3$ (50% overall iii, iv); v, Cl_2CHCO_2H, room temperature, 16 h; vi, CH_2N_2; vii, H_2, Pd-C, MeOH (80% overall v-vii); viii, chloranil, $PhMe_2$, 150°C (65%); ix, DIBAL, THF, 0°C, (70%); x, DCC-DMAP, (Z)-2-methylbut-2-enoic acid, ether (55%); xi, silver oxide, 6N HNO_3-dioxane (63%); xii, aq. H_2SO_4 then MeI/Ag_2O.

Scheme 25 shows how nitroisoquinoline-alcohol (**88**) was produced starting from 7-methoxy-6-methyl-8-nitroisoquinoline then converted through to renierone.[64b]



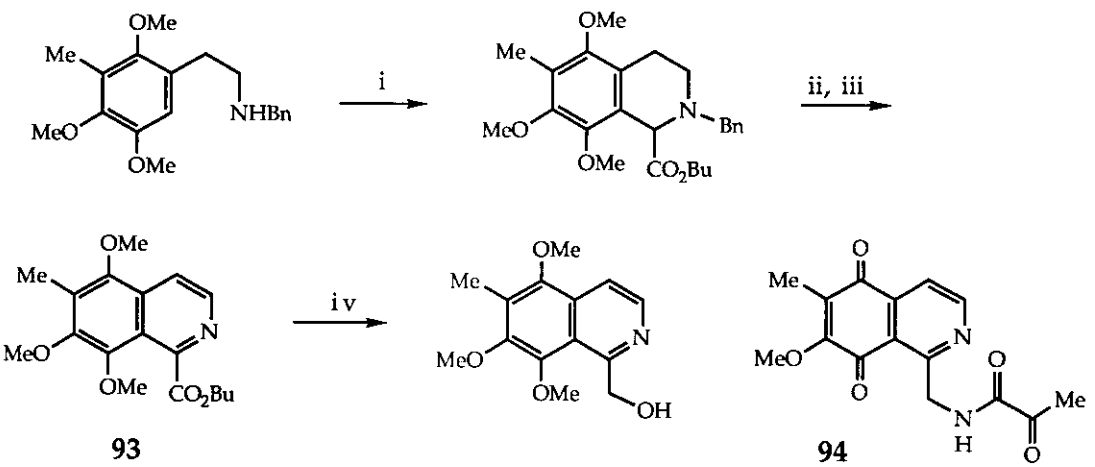
Scheme 25 Reagents: i, KCN, PhCO Cl, CH_2Cl_2, H_2O, 25°C (89%); ii, PhLi, HCHO (g), dioxane, ether, -20°C (61%); iii, NaOH, EtOH, 45°C, 5 min (90%); iv, H_2 Pd-C (92%); v, $ON(SO_3K)_2$ (63%); vi, PhLi, dioxane, ether, -20°C, then (Z)-2-methylbut-2-enoyl chloride (37%).

In a variation on the theme, the C-1-substitutent was introduced, again *via* Reissert chemistry, into trimethoxyisoquinoline (**92**), as shown in Scheme 26.[64c]



Scheme 26 Reagents: i, $H_2NCH_2CH(OMe)_2$, benzene, reflux (100%); ii, $NaBH_4$, MeOH, 5 min, room temperature (97%); iii, *p*-TsCl, pyridine, 20°C, 16 h (86%); iv, 6N HCl, dioxane, reflux, 1 h (97%); v, *t*-BuOK, *t*-BuOH, reflux, 5 min (99%); vi, KCN, PhCOCl, CH_2Cl_2, H_2O, room temperature, 1 h (73%); vii, BuLi, THF, -45°C, then HCHO (40%); viii, KOH, MeOH (93%); ix, PhLi, 0°C, (Z)-2-methylbut-2-enoyl chloride (78%); x, CAN[65], pyridine-2,6-dicarboxylic acid *N*-oxide, MeCN-H_2O, 0°C.

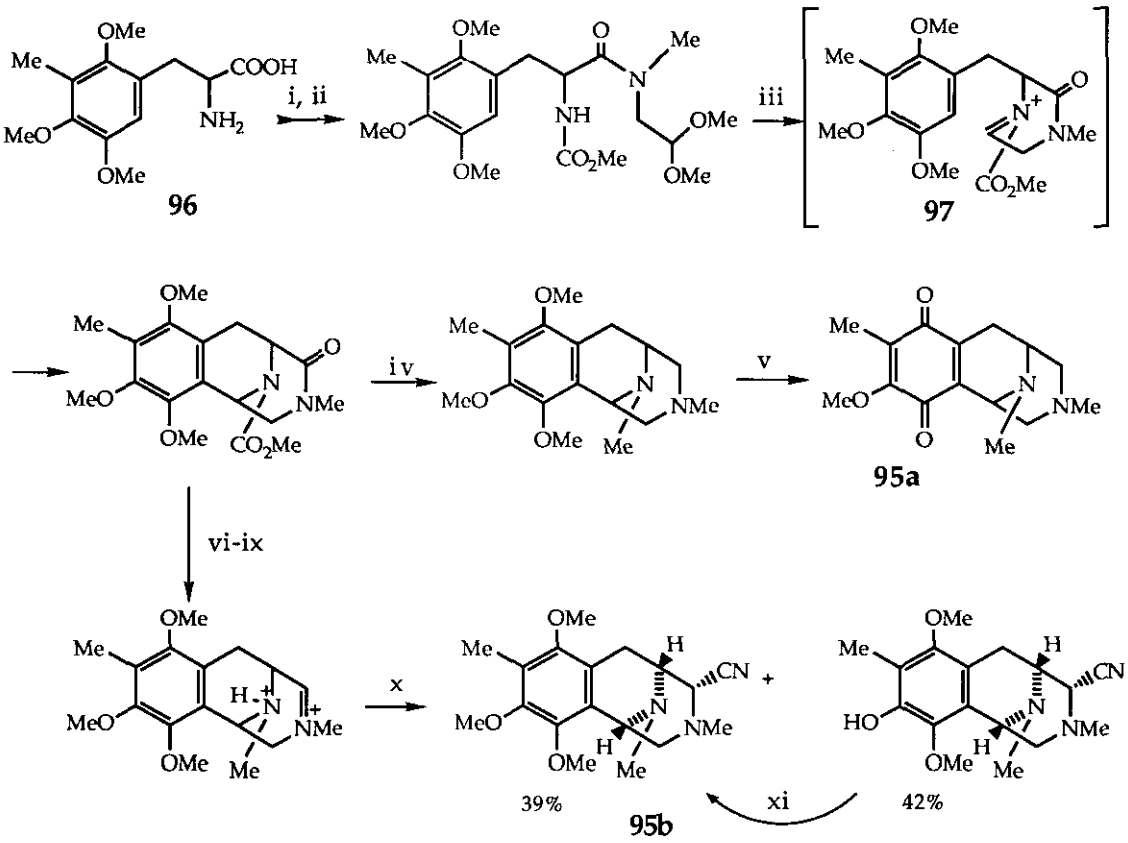
An alternative method (Scheme 27[64d]) for the production of an appropriately substituted isoquinoline produced ester (**93**), which was transformed into both renierone and also into the *Streptomyces* amino-methyl analogue, mimocin (**94**).[66]



Scheme 27 Reagents: i, $OCHCO_2n$-Bu, K_2CO_3, *n*-BuOH, room temperature, then TFA, room temperature (74 %); ii, H_2, Pd-C, HCO_2NH_4, MeOH (80%); iii, chloranil, *p*-xylene, 150°C (61%); iv, DIBAL, THF, 0°C (40%)

Reported synthetic work towards 'dimeric' species began with the microbial saframycins, but recently has been extended to a synthesis of (±)-renieramycin A.[67] The benzylic methoxyl group has been introduced into (±)-saframycin B by stereoselective oxidation with selenium dioxide in methanol; oxidation in water produced the corresponding alcohols, along with corresponding ketone, saframycin D.[68] Model work[69] and a total synthesis of (±)-saframycin A[70a] and two completed routes[70b,c] to (±)-saframycin B have been described. The tricyclic quinones (**95a**)[69b]

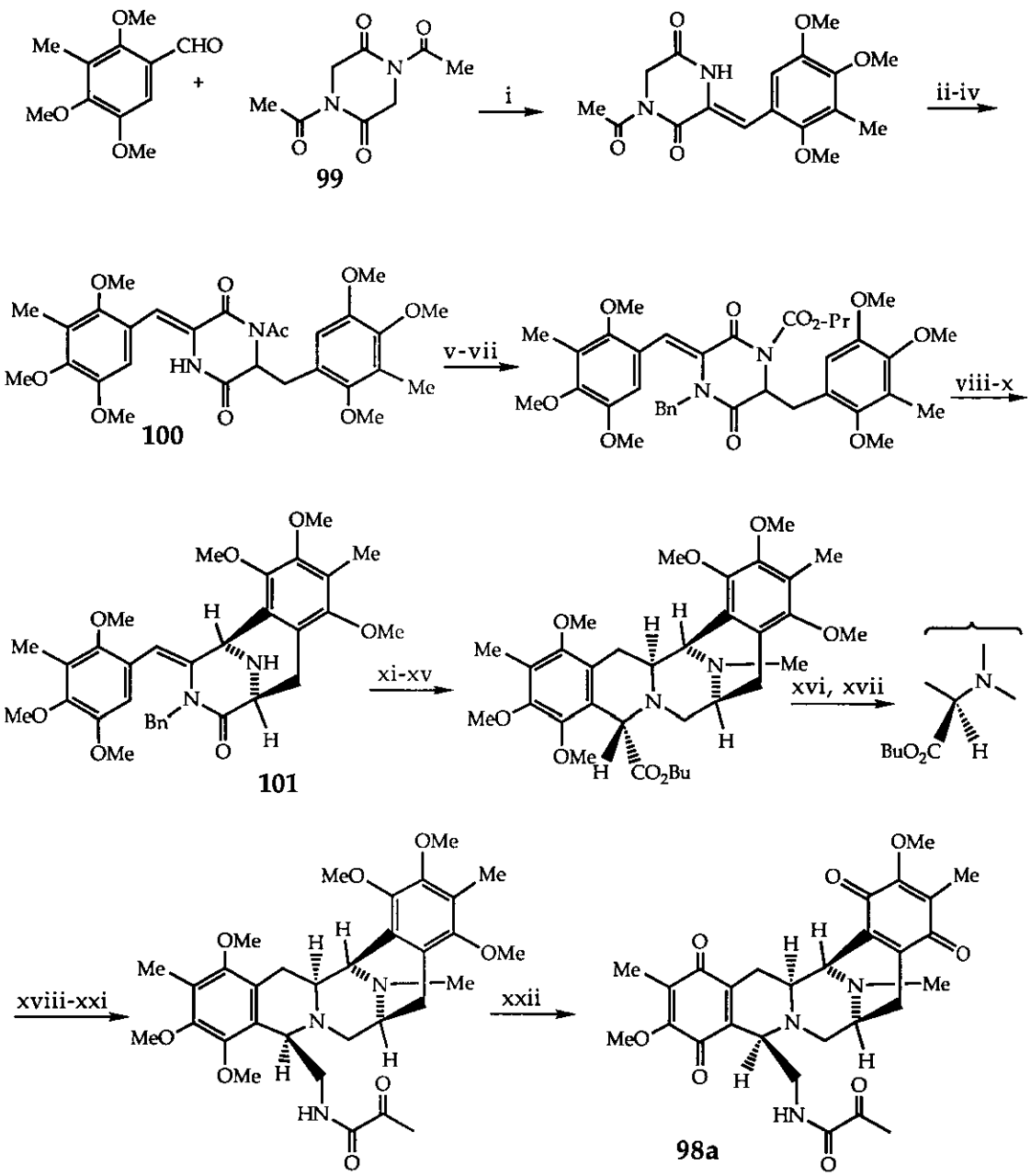
and cyano-derivative (95b)[69c] were constructed (Scheme 28) from amino acid (96), the key process for producing the target ring system presumably being an intramolecular acyliminium attack on the activated aromatic ring (*i.e. via* 97).



Scheme 28 Reagents: i, $ClCO_2Me$, NaOH, H_2O, room temperature, 2 h; ii, $ClCO_2i$-Bu, Et_3N, CH_2Cl_2, -15°C, 1 h, then $H_2NCH_2CH(OMe)_2$, -15°C→room temperature (80%); iii, TFA, reflux, 1.5 h (96%); iv, $LiAlH_4$, ether, reflux (87%); v, HNO_3 (71%); vi, NaOH, MeOH, reflux; vii, HCHO, HCO_2H, 100°C (50%); viii, DIBAL, toluene, -78°C (100%); ix, 12N HNO_3, <20°C; x, KCN, $NaHCO_3$, H_2O; xi, CH_2N_2, CH_2Cl_2, ether (100%).

A series of model studies[69d] on the condensation of diketopiperazines with aromatic aldehydes paved the way for a route for a total syntheses of saframycin B (98a) which is summarised in Scheme 29.[70c] The approach centres on the use of *N,N'*-diacetyl-diketopiperazine (99) to provide the central ring of the natural products. The two aromatic rings were introduced by aldol condensations, α to the ring carbonyl groups, with subsequent reductions of the double bonds of the benzylidene derivatives thus produced. The benzylidenebenzyldiketopiperazine (100) was transformed into tricyclic intermediate (101) by selective partial reduction of ring imide carbonyl to allow *in situ* generation of an acyl iminium cation for intramolecular alkylation of the apposite aromatic ring. Functional group transformations at bridging nitrogen, and

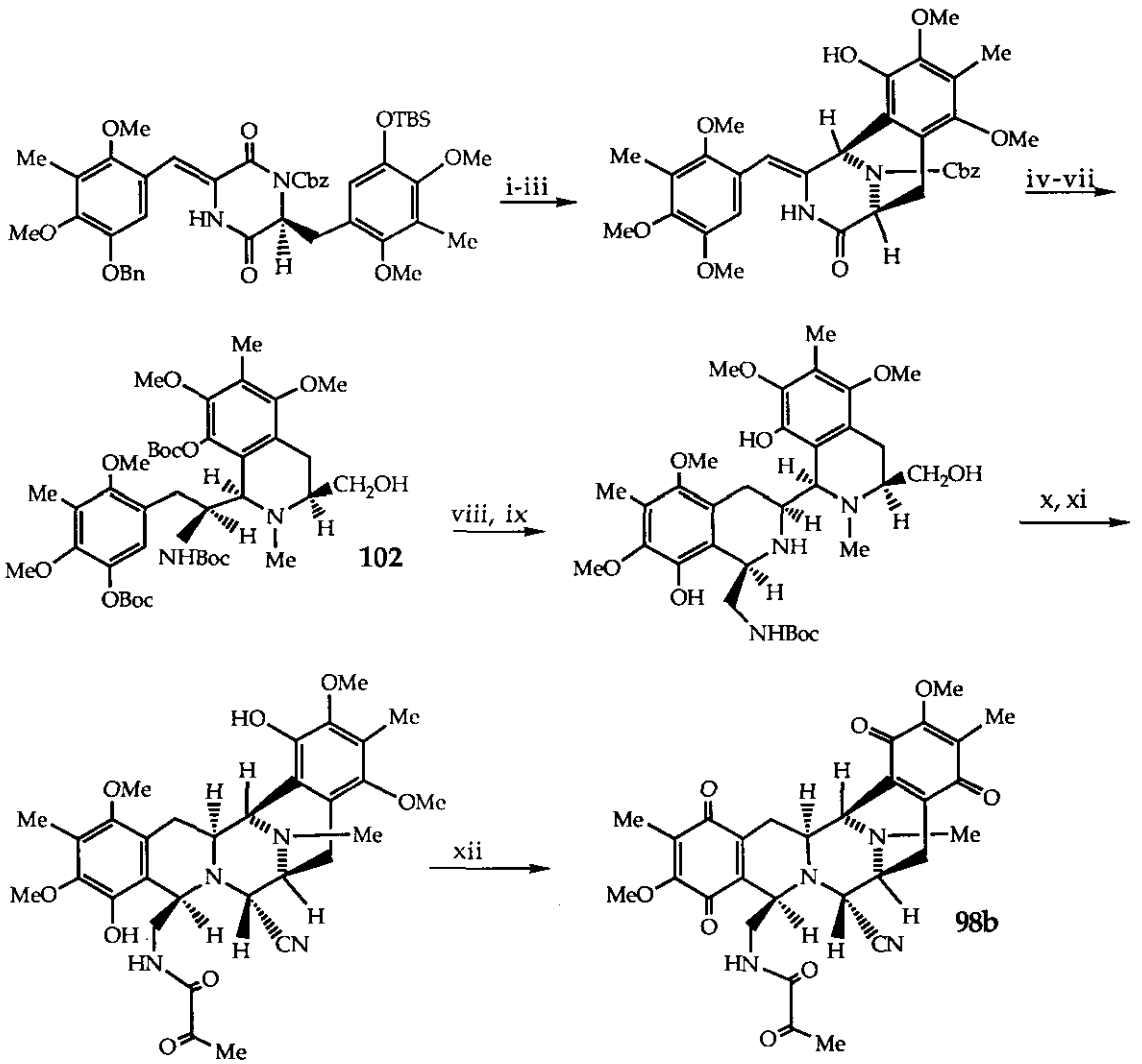
hydrogenation/hydrogenolysis produced an amine for closure of the hetero-ring of the final tetrahydroisoquinoline unit.



Scheme 29 Reagents: i, *t*-BuOK, *t*-BuOH, DMF, room temperature, 24 h (66%); ii, H_2, Pd-C, EtOH, DMF; iii, Ac_2O, 110°C, 4 h (80% overall ii,iii); iv, similar conditions to step i (54-84%); v, NaH, $PhCH_2Br$; vi, $H_2NNH_2.H_2O$ (94% overall v, vi); vii, $ClCO_2i$-Pr, Et_3N, DMAP, (94%); viii, $Li(t\text{-}BuO)_3AlH$ (21-69%); ix, HCOOH, 60°C (58-64%); x, H_2SO_4, TFA, room temperature (100%); xi, HCHO, HCO_2H, 70°C (96%); xii, AlH_3, THF, 0°C (93%); xiii, H_2, 20%Pd-C, EtOH, 4 atm, 80°C (99%);

xiv, HCO CO_2n-Bu (excess), K_2CO_3, n-BuOH, room temperature; xv, TFA, room temperature (70% overall xiv, xv); xvi, $Hg(OAc)_2$, 5% aq. AcOH, 90°C; xvii, $NaBH_4$, EtOH, H_2O, room temperature (71% overall xvi, xvii); xviii, $LiAlH_4$, THF, reflux (77%); xix, diethyl azodicarboxylate (DEAD), PhtNH, Ph_3P, THF, room temperature; xx, $H_2NNH_2.H_2O$, EtOH, reflux (76% overall xix, xx); xxi, ClCO CO Me, DMAP, Et_3N, CH_2Cl_2; xxii, BBr_3, CH_2Cl_2, -78→0°C, then 10M HNO_3 (41%).

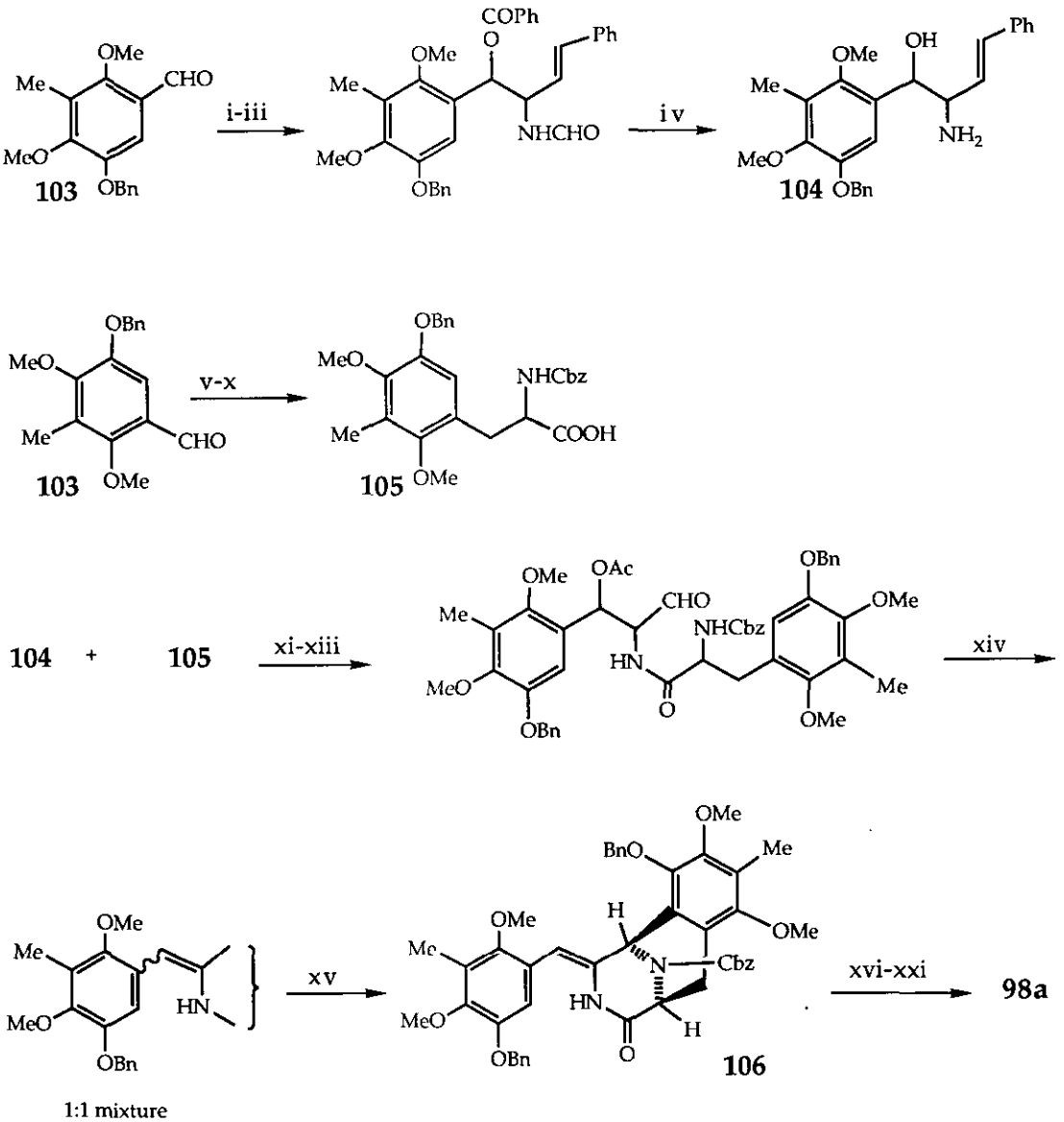
Saframycin A(**98b**) has also been produced[70a] by a route based on diketopiperazines; Scheme 30 shows the final stages of the synthesis. In order to insert the cyano group, it was necessary to open the central ring at a late stage (→ **102**) while the cyanide-bearing carbon was oxidised up to aldehyde level before reclosure.



Scheme 30 Reagents: i, $NaBH_4$, AcOH, EtOH, -25°C; ii, HCO_2H, 23°C; iii, n-$Bu_4N^+F^-$, THF, 23°C (85% overall i-iii); iv, H_2/Ni (Raney), EtOH, 1500 psi, 120°C; v, 37% HCHO, $NaBH_3CN$, TFA, MeOH, 23°C; vi, t-Boc_2O, DMAP, DMF, 60°C; vii, $NaBH_4$, EtOH, 0°C (75% overall vi, vii); viii,

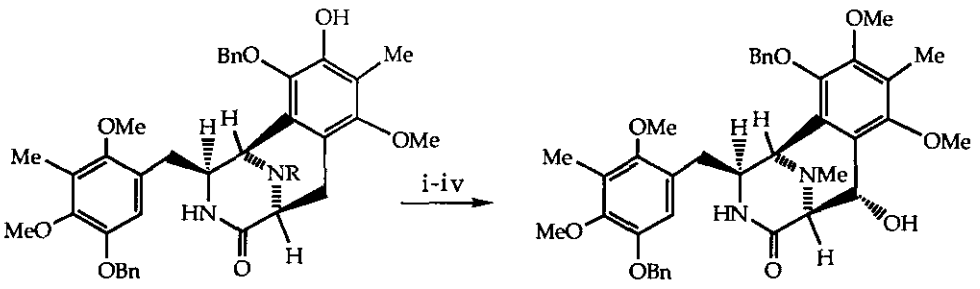
TFA, 23°C; ix, *t*-BocNHCH$_2$CHO, MeOH, 60°C (82% overall viii-ix); x, (COCl)$_2$, DMSO, CH$_2$Cl$_2$, Et$_3$N -78→23°C, then NaCN, MeOH, 23°C; xi, MeCOCOCl, NaHCO$_3$, CH$_2$Cl$_2$, 23°C (58% overall x, xi); xii, DDQ, acetone, H$_2$O, 0°C (60%).

The earliest total synthesis[70b] (Scheme 31) followed a quite different pattern. Recognising the symmetry in the saframycins, the aromatic aldehyde (**103**) was converted both into amino alcohol (**104**) and also into protected amino acid (**105**). Coupling **104** with **105** gave an amide the cinnamyl residue in which was oxidised to leave an aldehyde group for closure of the central piperazinone ring in an oxidation level required for intramolecular cyclisation giving **106**. Reduction and closure of the final heterocyclic ring then gave (±)-saframycin B.

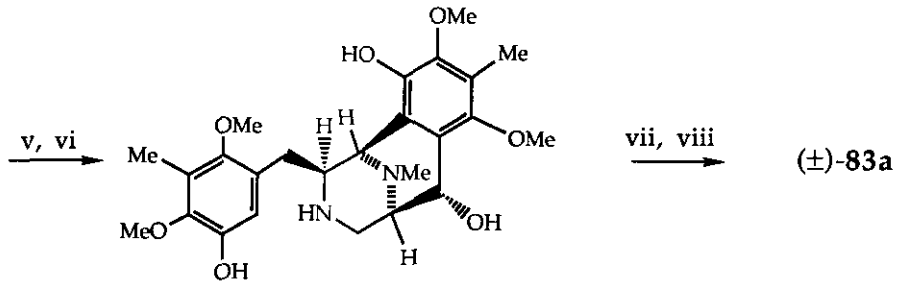


Scheme 31 Reagents: i, PhCH=CHNC, BuLi, -78°C; ii, PhCOCl, THF, -78→room temperature; iii, HCl, THF, room temperature (92% overall viii-x); iv, 3N NaOH, MeOH, room temperature (83%); v, $CNCH_2CO_2Et$, KH, THF, 0°C; vi, H_2/Ni (Raney), EtOH, 80°C, 1200 psi; vii, $PhCH_2Br$, K_2CO_3, DMF, 80°C; viii, HCl, EtOH, 60°C; ix, $PhCH_2OCO$ Cl, $PhNMe_2$, CH_2Cl_2, room temperature; x, 3N NaOH, MeOH, room temperature, acidic work-up (84% overall v-x); xi, DCC, CH_2Cl_2, room temperature (83%); xii, Ac_2O, pyridine, 60°C (98%); xiii, O_3, 50% MeOH, CH_2Cl_2, -78°C, then Me_2S; xiv, DBU, CH_2Cl_2 0°C; xv, HCO_2 H, 60°C, 20 min (74% overall xii-xv); xvi, H_2/Ni (Raney), EtOH, room temperature, 1000 psi (75%); xvii, AlH_3, THF, room temperature; xviii, $CbzNHCH_2CHO$, MeCN, 70°C, 45 min (75%); xix, H_2, 10% Pd-C, AcOH, room temperature, 1 atm; xx, MeCO COCl, $PhNMe_2$, CH_2Cl_2, room temperature (72%); xxi, CAN, THF, H_2O, 0°C (39%).

The total synthesis of(±)-renieramycin A[67] (final stages summarised in Scheme 32) followed the pattern shown in Scheme 29, to produce the tricyclic intermediate (**107**), it being found necessary to have a blocking group on the bridging nitrogen for the benzylic oxidation which was achieved stereospecifically in this work using DDQ.[71]



107 R = CO $O(CH_2)_2CO_2Me$



Scheme 32 Reagents: i, DDQ, aq. THF, 23°C; ii, MeI, K_2CO_3, DMF, 23°C; iii, DBU, MeOH, 23°C; iv, HCHO, $NaB(CN)H_3$, TFA, MeOH, 23°C (45% overall i-iv); v, AlH_3, THF, 23°C; vi, H_2, Pd/C, EtOH, 23°C (64% overall v, vi); vii, glycolaldehyde angelate, MeCN, 50°C (66%; mixture of epimers, 5:1 in favour of isomer shown); viii, DDQ, aq. Me_2CO, 23°C (48%).

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