Pyridoacridines in the 21st Century

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Abstract: This minireview summarizes the work developed during this Century with compounds containing the pyridoacridine scaffold in its different isomeric forms. The isolation of natural products, syntheses, bioactivities, chelation capacity, and other properties of compounds containing this framework are discussed. For reasons of length, only compounds containing a maximum of seven condensed rings have been considered, with a few exceptions.

Introduction

Interest in 'pyridoacridines', i.e. tetracyclic systems in which a pyridine ring is fused to an acridine – there are fifteen isomers – began with the isolation and structure determinations of marine alkaloids, many biologically active, based on some of these isomers.[1] We earlier summarised synthetic routes to pyridoacridines.[2] More recently, the following relevant aspects have been considered: '*ortho*-Directed metallation of π-deficient heterocycles in connection with palladium-catalyzed biaryl cross-coupling – synthesis of marine alkaloids of the pyridoacridine series',[3] 'Marine pyridoacridine alkaloids and synthetic analogues as antitumor agents',[4] 'Biological activities of pyridoacridines'[5] 'A mini review on pyridoacridines: prospective lead compounds in medicinal chemistry',[6] 'Alkaloids from marine invertebrates as important leads for anticancer drugs discovery and development',[7] 'Marine pyridoacridine alkaloids: biosynthesis and biological activities',[8] and 'New perspectives in the chemistry of marine pyridoacridine alkaloids'.[9]

In this review we consider all of the fifteen isomers, including natural product chemistry and synthesis reported in the 21st Century. Each isomer is named as a 'pyrido[A,B-*yz*]acridine' to emphasise the isomeric relationship, but where this name is not the systematic name, the Chemical Abstracts name is given in {brackets}. We do not cover in detail spectroscopic, other physico-chemical, or bioactive aspects. We have included extended examples but only up to hexacyclic systems, with some exceptions. The patent literature is not covered.

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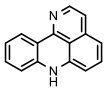
Prof John A. Joule did BSc, MSc, and PhD degrees in the University of Manchester, the last with George F. Smith. Following post-doctoral studies with Richard K. Hill (Princeton) and Carl Djerassi (Stanford) he returned to Manchester for his academic career. Joule's research there produced 250 papers on aspects of heterocyclic chemistry, especially indoles, and quinoxalines and pteridines related to the molybdenum cofactor. His textbook 'Heterocyclic Chemistry', co-authored with George Smith and latterly with Keith Mills, is now in its 5th Edition; 'Heterocyclic Chemistry at a Glance' is in its 2nd. He continues as Emeritus Prof at Manchester and acts as a Scientific Editor for *Arkivoc* and *Journal of Chemical Research* and as a Volume Editor for *Science of Synthesis*. He is co-Editor, with Gordon Gribble, of the annual *Progress in Heterocyclic Chemistry*.

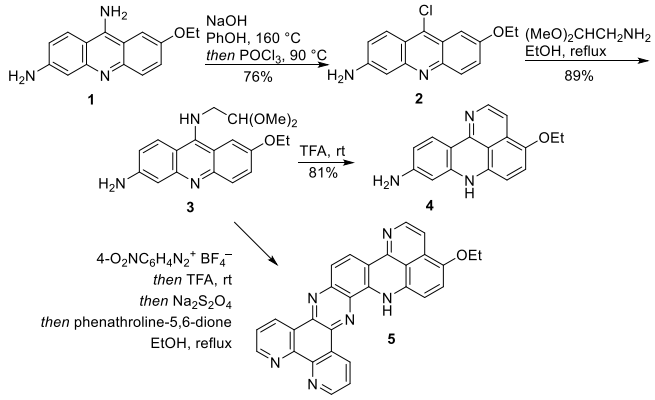


1. Pyrido[4,3,2-*kl*]acridine

Perhaps the obvious starting material for the construction of pyrido-acridines is a suitably functionalised acridine. For example, ethacridine **1** was transformed into chloro compound **2** and this into the 2,2-dimethoxyethanamine **3**, acid-catalysed closure of which produced (Scheme 1) a pyrido[4,3,2-*kl*]acridine **4**.[10]

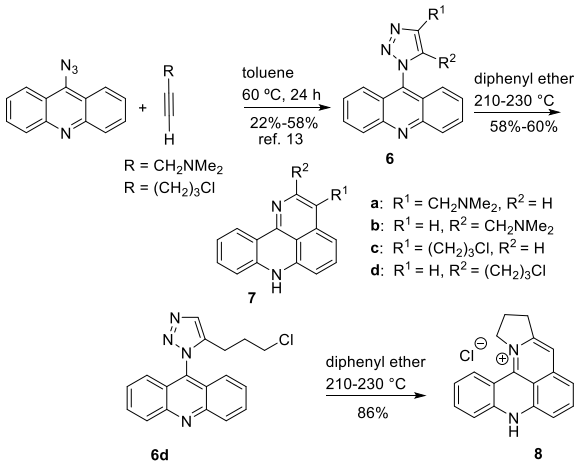
Electrophilic substitution of **3** with 4-nitrophenyldiazonium fluoroborate allows later introduction of an amine function by

reduction and thence by condensation with 1,10-phenanthroline-5,6-dione, formation of octacyclic analogue **5** of eilatin (Scheme 1) [9] (for structure of eilatin see Fig. 4)



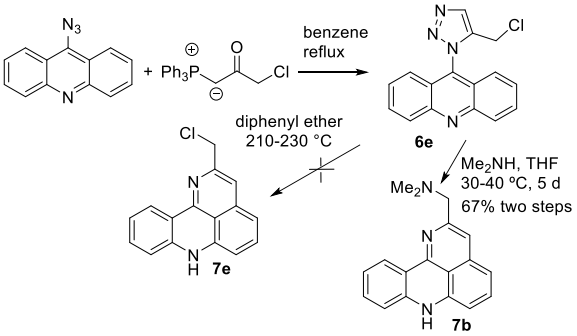
Scheme 1. Synthesis of a pyrido[4,3,2-*kl*]acridine from an acridine **1**; synthesis of **5**, analogue of eilatin.[10]

Alkylpyrido[4,3,2-*kl*]acridines **7** were prepared [11,12] using the previously described synthetic procedure.[13] The synthesis starts with a cycloaddition of dimethylaminoprop-2-yne (or 5-chloropent-1-yne) to 9-azidoacridine to give a regioisomeric mixture of triazolylacridines **6a** and **6b** (or **6c** and **6d**) (Scheme 2). The disadvantage of the cycloaddition method is that chromatographic separation of the mixture of isomeric triazoles is always required and the yield of the most hindered triazole is the lower. Thermolysis of **6a** and **6b** occurs with elimination of nitrogen to generate a reactive biradical or carbene species which cyclizes giving the pyridoacridines **7a** and **7b**. Different behavior of the regioisomeric acridines **6c** and **6d** was found in the thermolysis. Isomer **6c** cyclized to 3-(3-chloropropyl)pyridoacridine **7c**. The direct thermolysis of 3-chloropropyl derivative **6d** gave the water-soluble pentacyclic salt **8** via intramolecular cyclization of assumed chloropropylpyridoacridine intermediate **7d**.



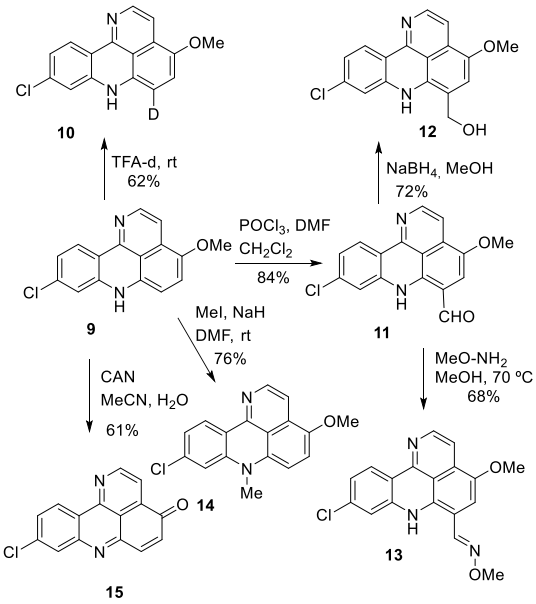
Scheme 2. Synthesis of 7*H*-pyrido[4,3,2-*kl*]acridines **7** and the acridinium salt **8**.[11,12]

A better yield of the acridine **7b** was achieved using an alternative procedure (Scheme 3) based on the reaction of 9-azidoacridine with chloroacetonyltriphenylphosphorane ylide to give the chloromethyltriazolylacridine **6e**. Attempts at thermolysis of the chloromethyl derivative **6e** were unsuccessful. However, acridine **6e** reacted smoothly with dimethylamine at 30-40 ºC to give pyridoacridine **7b**.[14]



Scheme 3. Synthesis of triazoloacridine **6e** and alternative synthesis of **7b**.[11,14]

In vitro biological evaluation of polycyclic acridines, the core heterocyclic framework of which is structurally related to bioactive marine natural products was performed.[29] Potentially the most interesting compound is the indolizino[7,6,5-*kl*]acridinium salt **8** (see Scheme 2). The intercalating ability at G-C DNA and inhibition of topo II were the most significant results. The water-soluble compound **8** is a potent inducer of apoptosis in lung and breast cancer cell lines.

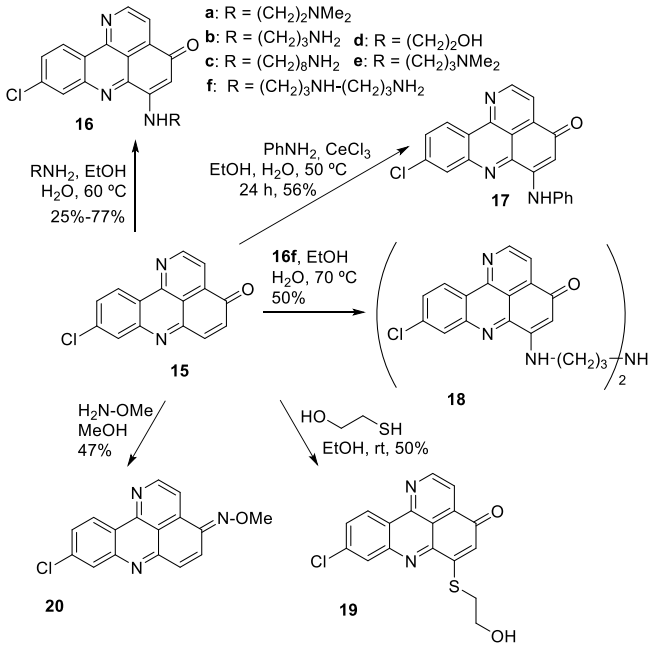


Scheme 4. Preparation of derivatives of pyridoacridine **9**.[15]

The reactivity of 4-methoxy-pyrido[4,3,2-*kl*]acridines as electron-rich aromatics allowed access to a series of 6-functionalized derivatives (Scheme 4).[15] The starting compound, 9-chloro-4-methoxypyrido[4,3,2-*kl*]acridine **9**, was obtained as described in previous work.[16] As shown in Scheme 4, H-D exchange in trifluoroacetic acid-*d* was performed at room temperature to give deuteration

regioselectively at position 6, compound **10**. Vilsmeier–Haack reaction using phosphoryl chloride with DMF proceeded smoothly to give the compound **11** with incorporation of one formyl group at the same position. Functional group interchange of the formyl group in **11** by reduction or reaction with methoxyamine afforded the derivatives **12** and **13**, respectively. *N*-Alkylation of **9** using methyl iodide and sodium hydride in DMF gave compound **14**. Oxidation of **9** with ceric ammonium nitrate (CAN) produced the pyridoacridone **15**.

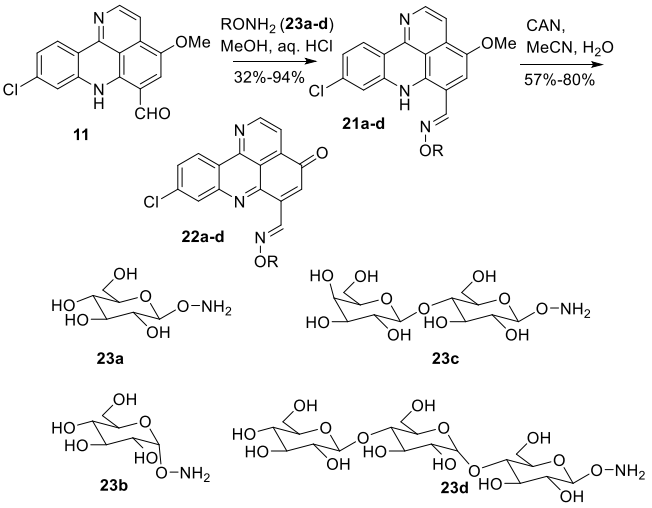
The reactivity of compound **15** with nucleophiles is characteristic of an iminoquinone, thus with an excess of primary amines and spontaneous oxidation of the initial Michael adduct, the enones **16** were produced (Scheme 5). Weaker nucleophiles such as aniline required Lewis acid catalysis to give, after one day, compound **17**. Coupling of compounds **15** and **16f** gave the dimeric structure **18**; this compound may act as a DNA-intercalator. Addition of β-mercaptoethanol at room temperature followed by spontaneous oxidation afforded compound **19**. In contrast to these conjugate additions, methoxyamine reacts to give the oxime ether **20**.



Scheme 5. Preparation of derivatives of pyridoacridone **15**.[15, 17]

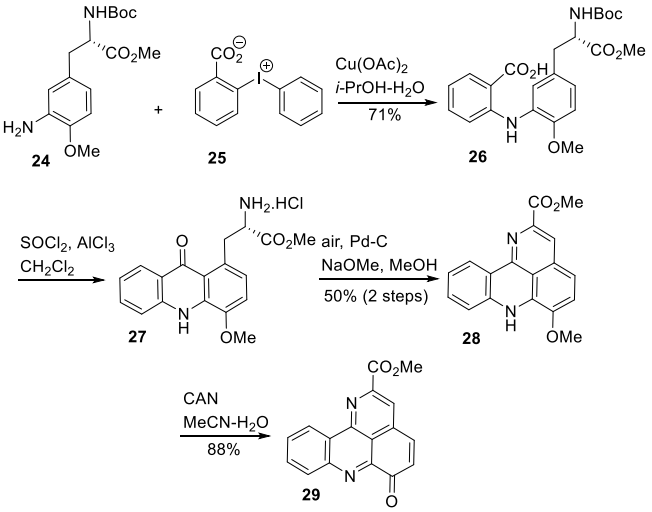
A series of glyco-conjugates derived from chloropyridoacridine **11** (Scheme 6) were prepared to test as potential antitumor agents.[17] The glycoconjugates **22** were obtained by chemoselective reaction of the aldehyde group in **11** with the aminooxy sugars **23** forming oximes **21**. Oxidation with CAN then led to the iminoquinones **22**.

The compounds **16** and **22** were tested against HT-29 cancer cells. The glycoconjugates are not cytotoxic compared to the amino conjugates that show cytostatic activity at micromolar concentration.



Scheme 6. Synthesis of glyco-conjugates **22a-d**.[17]

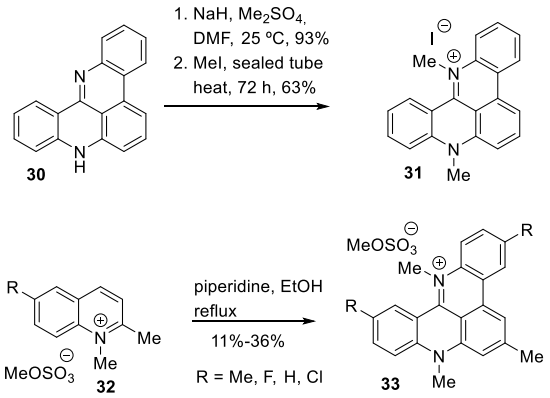
Studies on the biosynthesis of the fungal alkaloid necatorone using fluorine-labeled 3-(2-carboxyphenylamino)-L-tyrosine in feeding experiments demonstrated no incorporation of this amino acid.[18] However, the synthesis of the dideoxynecatorone derivative **29** using the protected aminotyrosine **24** was successful (Scheme 7).



Scheme 7. Synthesis of dideoxynecatorone derivative **29**.[18]

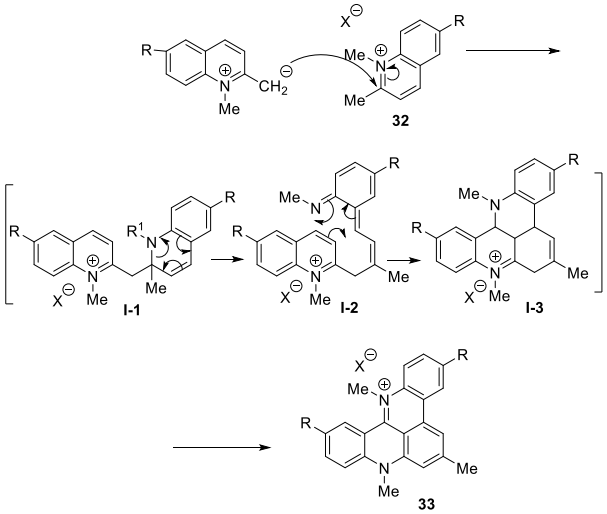
The amino acid **26** obtained by a copper(II) acetate mediated coupling reaction between **24** and the iodonium salt **25** underwent a cyclization in Friedel–Crafts conditions to give **27** and following basic conditions and air oxidation gave the pyridoacridine **28**. Oxidation of **28** with CAN afforded the natural product analogue **29**.

Two alternative synthetic routes were developed by the same group for the synthesis of acridinium salts **31** and **33** (Scheme 8).[19] A double *N*-alkylation of the quinolinoacridine **30** afforded the salt **31**. The second route is based in the reaction of *N*-methyl-2-methylquinolinium methyl sulfates **32** in ethanolic piperidine to give the salts **33**.



Scheme 8. Synthesis of acridinium salts **31** and **33**.[19]

The proposed mechanism for the formation of salts **33** is based on a betaine formation by reaction between the 2-methylquinolinium salt and piperidine base (Scheme 9). Subsequent addition of the betaine to a second equivalent of the starting quinolinium salt would give the dihydroquinoline intermediate **I-1** which, by an electrocyclic ring opening would proceed to the imine intermediate **I-2** from which, after electrocyclic ring closure (→ **I-3**) and oxidation, compound **33** would be obtained.



Scheme 9. Proposed mechanism for the formation of salts **33**.[19]

Compounds **33** (R = Me, F) are among the most potent telomerase inhibitors yet disclosed, with IC_{50} values < 0.5 μM.

Although of comparable potency as telomerase inhibitors, compound **33** (R = Me) is 30-fold more growth inhibitory than **33** (R = H) in the NCI 60 cell panel. The same group described the recognition and stabilization of the pentacyclic methylacridinium cation **RHPS4** (Fig. 1) with d(TTAGGGT)$_4$ DNA quadruplex producing a potent telomerase inhibition.[20]

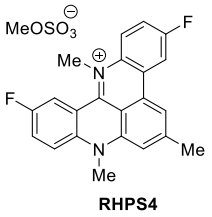
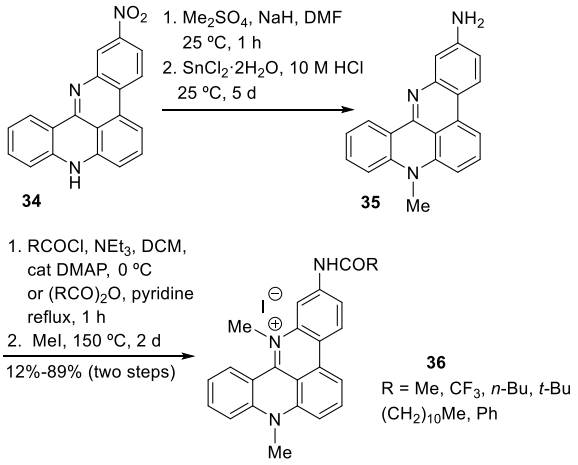


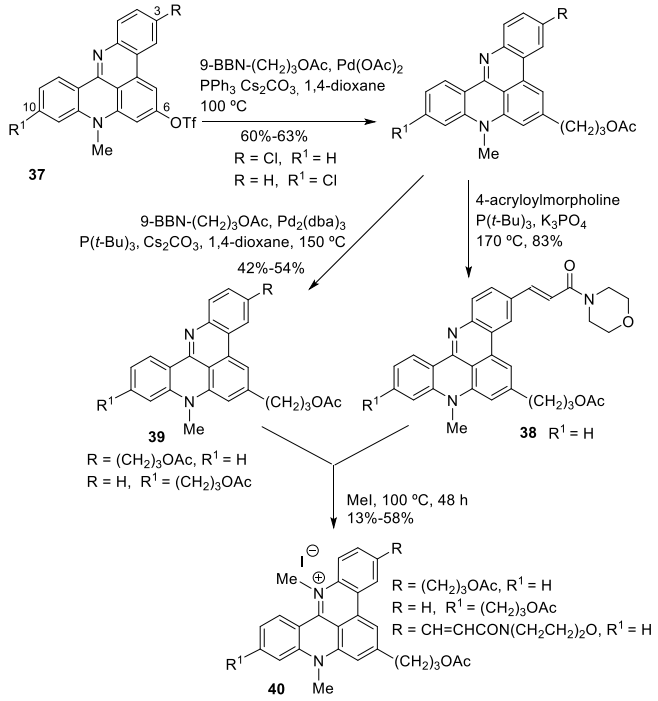
Figure 1. Structure of **RHPS4**.[20]

Using similar chemistry, the amine **35**, obtained by *N*-methylation and reduction of the nitroacridine **34**, gave the acridinium salts **36** in two steps – amine acylation of **35** and *N*-methylation, as shown in Scheme 10.[21]



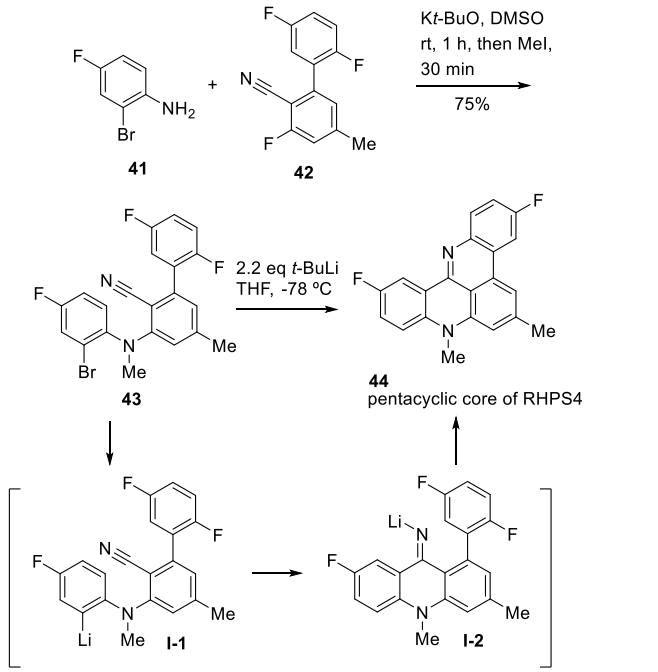
Scheme 10. Synthesis of acridinium salts **36**.[21]

The introduction of bulky saturated (3-acetoxy)propyl or (*E*)-3-(morpholin-4-yl)-3-oxopropenyl substituents in the 3-, 6-, or 10-positions of the pentacyclic nucleus was tested with the aim of enhancing the affinity to G-quadruplex structures.[22,23] Suzuki–Miyaura and Heck reactions were used for the synthesis of the functionalized pentacyclic acridines **38** and **39** (Scheme 11). Alkylboranes, prepared by interaction of 9-borabicyclo[3,3,1]nonane (9-BBN) and allyl acetate, or *N*-acryloylmorpholine, were used for two successive cross–coupling reactions starting originally from quinolinoacridine **37** to give compounds **38** and **39**. Quaternization of **38** and **39** afforded the acridinium salts **40**.



Scheme 11. Synthesis of substituted pentacyclic acridines **38** and **39** and acridinium iodides **40**.[22-24]

Extensive studies of compound stability and metabolic stability of pentacyclic acridinium salts in the presence of cytochrome P450 enzymes, as well as intracellular drug localization, suggested that the salts are selective inhibitors of telomerase.

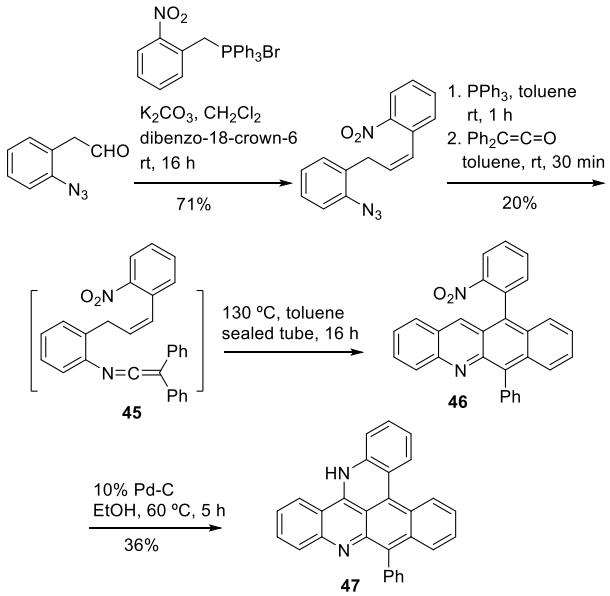


Scheme 12. Synthesis of pentacyclic core of **RHPS4** by an anionic ring–closing cascade.[26]

Quantification of relative quadruplex and duplex binding affinity constants places some of these ligands among the most selective quadruplex DNA interactive agents reported to date.[24,25]

A convergent synthesis of the telomerase inhibitor **RHPS4** (see Fig. 1) was described by construction of the pentacyclic framework via an anionic ring-closing cascade in which two new rings are formed (Scheme 12).[26] The key intermediate aminonitrile **43** was obtained by nucleophilic aromatic substitution of the fluorine situated *ortho* to the cyano group in **42** by the potassium salt of **41** followed by in situ quenching of the resulting diarylamine anion with methyl iodide. Treatment of **43** with *tert*-butyllithium results in double cyclization by exchange of bromine by lithium (→ **I-1**), addition of the resulting organolithium to the cyano group (→ **I-2**) and final nucleophilic substitution of fluorine by the generated imine anion to give **44**.

A benzo[*b*]acridine **46**, obtained by an intramolecular [4+2] cycloaddition reaction of a ketenimine **45**, was the synthetic intermediate for the preparation of acridine **47** (Scheme 13). Reduction of the nitro group of **46** gave an amine which, by means of an intramolecular amination of the pyridine ring, gave an hexacyclic system which was spontaneously oxidized to **47**.[27]

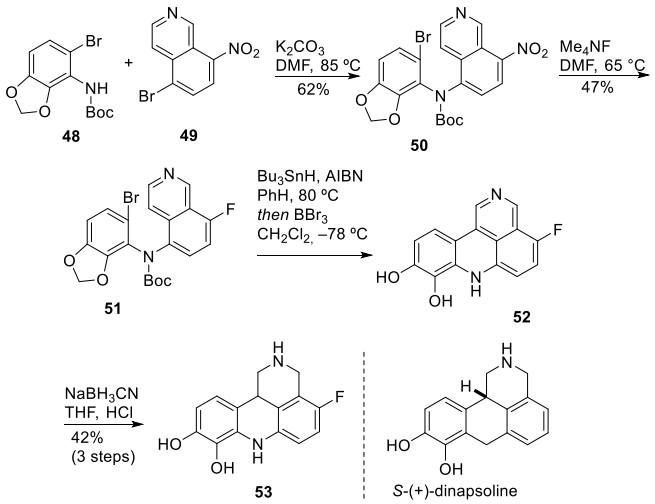


Scheme 13. Synthesis of hexacyclic system **47** *via* [4+2] cycloaddition.[27]

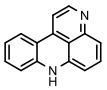
2. 7*H*-Pyrido[3,4,5-*kl*]acridine

Although no natural products incorporating this skeleton have been reported, structure **53** was prepared as an analogue of *S*-(+)-dinapsoline,[28] which has anti-Parkinson activity with significant metabolic and pharmacological advantages over other D_1 agonists.

The synthesis of **53** (Scheme 14) started with a nucleophilic aromatic substitution of the *para*-nitro-activated quinolinyl bromide **49** with a Boc-protected arylamine **48** giving **50**. Following displacement of the nitro group with fluoride (→ **51**), a radical induced cyclisation provided a tetracycle, from which the diol and the amine protections were removed leaving **52**. Reduction of **52** with sodium cyanoborohydride produced the dinapsoline analogue **53**.[29]



Scheme 14. Structure of dinapsoline and synthesis of an analogue **48**.[29]

3.  Pyrido[2,3,4-*kl*]acridine

This pyridoacridine isomer is by far the most frequently encountered in the naturally occurring marine alkaloids. For this reason we have arbitrarily divided the coverage into sections based on the number of rings present. This leads to some overlap in that the pyrido[2,3,4-*kl*]acridine skeleton occurs in compounds with more than one ring size by virtue of having other rings, benzene or pyridine, fused to it.

3.1. Tetracyclic systems

Pyridoacridine alkaloids isodiplamine, cystodytin K and lissoclinidine were isolated from the New Zealand ascidian *Lissoclinum notti* (Fig. 2).[30] Their biological activities, including antitumour and antibiotic, were assessed.

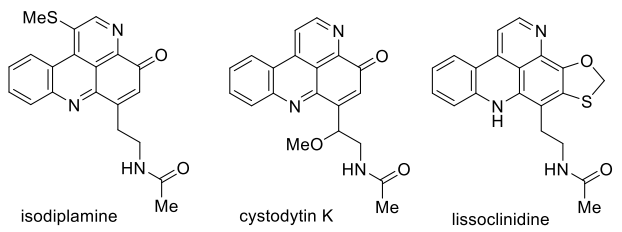
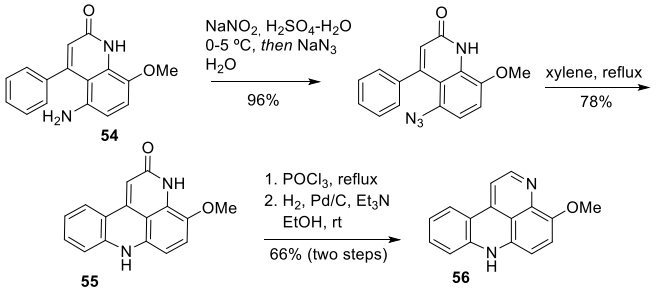


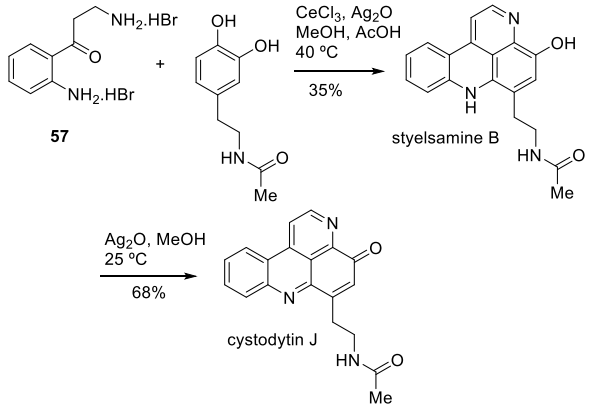
Figure 2. Structures of isodiplamine, cystodytin K and lissoclinidine.[30]

The synthesis of some marine alkaloids, with tetracyclic skeletons, was developed using, as starting material, the substituted quinolone **54**.[31] Transformation of amino into azide and thermal cyclization afforded the tetracyclic acridone **55**. Reduction of **55** to acridine **56** was achieved by transformation into the chloroacridine and then catalytic hydrogenolysis (Scheme 15).



Scheme 15. Synthesis of pyridoacridine **56**.[31]

A biomimetic synthesis of styelsamine B was described[32] by a reaction between kynuramine dihydrobromide **57** and *N*-acetyl dopamine (Scheme 16). A cascade process produced a fast entry to styelsamine B. This compound was oxidised to cystodytin J using silver oxide in methanol. The authors point out that this is a formal total synthesis of diplamine because the transformation of cystoditin J into diplamine had been described.[33]

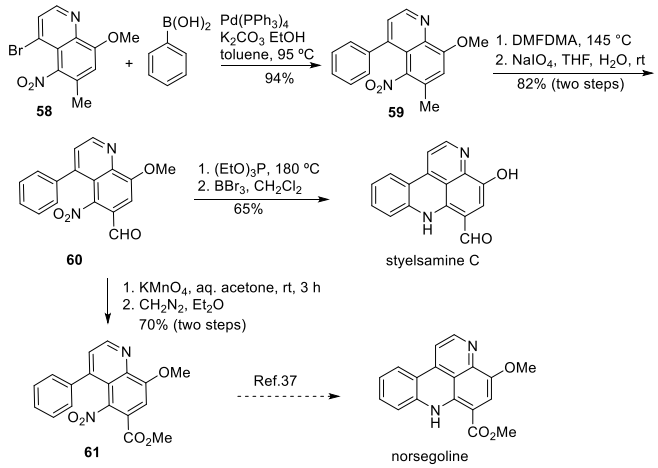


Scheme 16. Synthesis of styelsamine B[32] and cystodytin J.[33]

The procedure described previously[31] for the synthesis of the alkaloids styelsamine B and cystodytin J was followed exactly for the preparation of analogues in which only the *N*-acyl group was varied.[34]

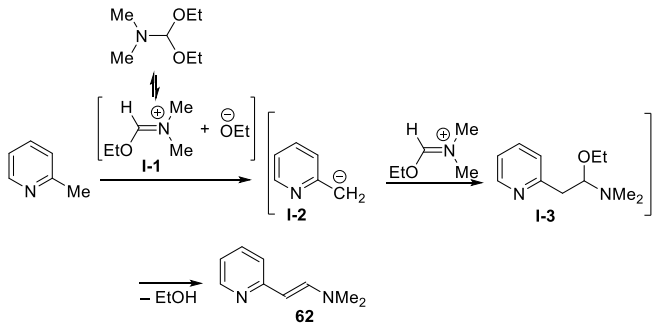
A total synthesis of styelsamine C and the formal synthesis of norsegoline utilized as the key step a biaryl cross-coupling reaction.[35,36] Suzuki reaction between 4-bromoquinoline **58** and phenylboronic acid gave the 4-phenylquinoline **59** in excellent yield (Scheme 17). Transformation of **59** into the aldehyde **60** was accomplished in two steps, based on the formation of an enamine by reaction of **59** with dimethylformamide dimethyl acetal (DMFDMA) (cf. Scheme

18) followed by oxidative cleavage. The intramolecular nitrene insertion reaction of **60** using triethyl phosphite gave the tetracyclic compound and final demethylation furnished styelsamine C. Oxidation of aldehyde **60** to carboxylic acid followed by methyl ester formation gave the nitro ester **61**. The synthesis of norsegoline from **61** was previously described by Kubo et al.[37]



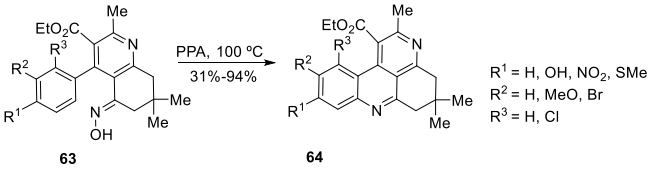
Scheme 17. Total synthesis of styelsamine C and formal synthesis of norsegoline.[36]

The functionalization of a pyridine- or quinoline-2- or 4-methyl group using dimethylformamide diethyl (or dimethyl) acetal (DMFDEA or DMFDMA) has been employed several times in pyridoacridine chemistry, Scheme 18 illustrates the mechanism using 2-methylpyridine. Briefly, dissociation of the reagent provides an alkoxide that deprotonates the methyl group forming a carbanion **I-2** that reacts with the electrophilic iminium ion **I-1**. Final loss of ethanol from **I-3** gives an enamine **62** – the reaction equivalent of a 2-pyridinyl-acetaldehyde or, by oxidative cleavage of the double bond, a source of 2-pyridinecarbaldehyde.



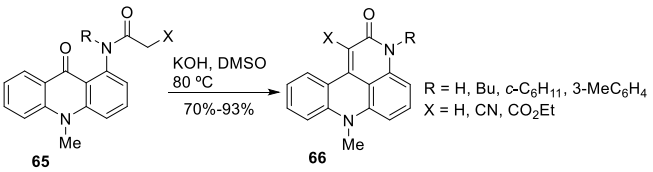
Scheme 18. Mechanism of action of DMFDEA with a 2- (or 4-)methylpyridine.

Studies of oxotetrahydroquinoline oximes **63** under conditions typical of Beckmann reaction provided a different entry for the synthesis of dihydropyridoacridines **64** (Scheme 19).[38]



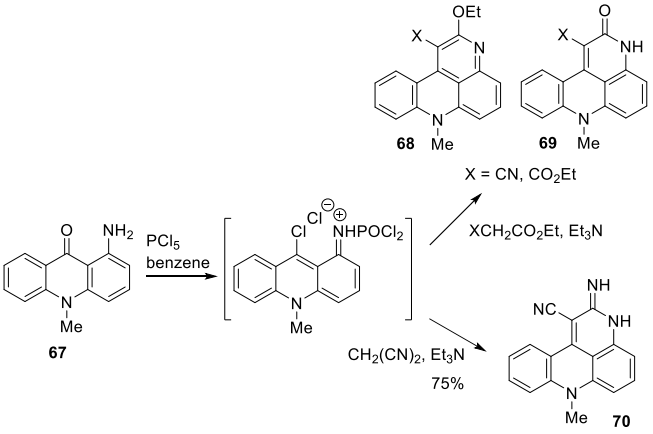
Scheme 19. The use of typical Beckmann reaction conditions for synthesis of dihydro-pyrido[2,3,4-*kl*]acridines **64**.[38]

Intramolecular cyclization of 1-(*N*-acylamino)acridones **65** forming pyridoacridones **66** was achieved in basic conditions.[39] Only secondary amides **65** (R = H) containing an activating substituent (X = CN, CO_2Et) in the acyl group cyclize with potassium hydroxide in DMF to pyridoacridones **66** (X = CN, CO_2Et). However, tertiary amides **65** (R = alkyl) underwent cyclization in the same conditions even without an activating substituent in the acyl group (Scheme 20).



Scheme 20. Cyclization of *N*-acylaminoacridones **66**.[39]

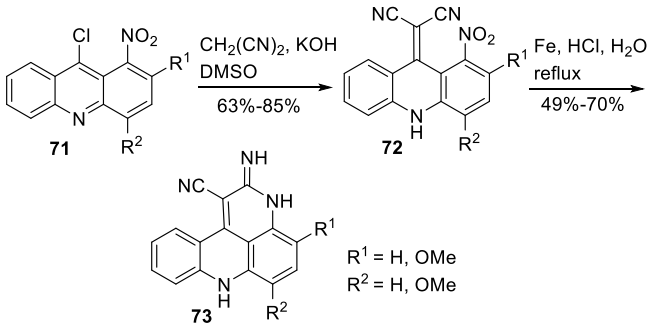
Treatment of aminoacridone **67** with phosphorus pentachloride in benzene and then with a malonic acid derivative, in the presence of a base, directly gave pyrido[2,3,4-*kl*]acridine derivatives **68** and **69**. With ethyl cyanoacetate as active compound acridine **68** (X = CN) and acridin-2-one **69** (X = CN) were obtained in a ratio ~3 : 1 (Scheme 21).[40] In the case of ethyl malonate, the same conditions yielded a mixture of **68** and **69** (X = CO_2Et) in approximately the same ratio. With malononitrile as reactant, a cyclization onto the cyano group gave a product that was assigned the cyanoacridine amidine structure **70**, as the sole product.



Scheme 21. Synthesis of pyrido[2,3,4-*kl*]acridines **68-70** from 1-aminoacridone **67**.[40]

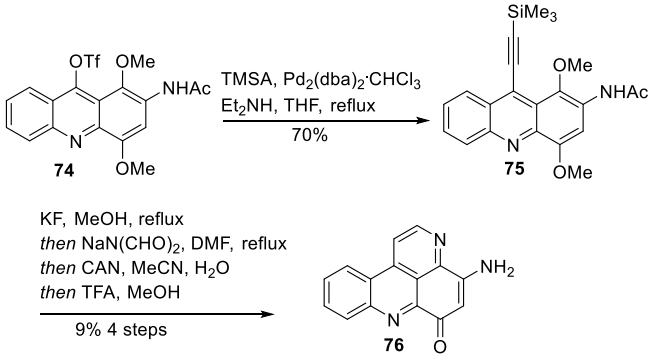
9-Chloro-1-nitroacridines **71** containing substituents in the nitro-benzene ring react with malononitrile in DMSO in the presence of potassium hydroxide yielding 9-dicyanomethyli-denes **72** (Scheme 22).[40] Subsequent reduction of the nitro

group was accompanied by cyclization to 4- or 6-methoxy-substituted 1-cyano-2-iminopyrido[2,3,4-*kl*]acridines **73**, though the alternate tautomer with an amino-pyridine unit was not considered.



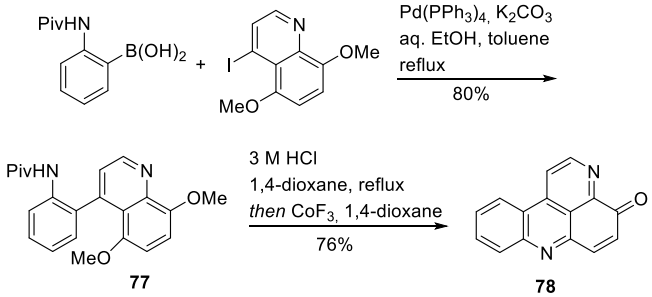
Scheme 22. Synthesis of 1-cyano-2-iminopyrido[2,3,4-*kl*]acridines **73** from the acridines **71**.[40]

The key steps in the assembly of the amino-quinone-imine **76** are the palladium-catalysed Sonogashira cross-coupling of triflate **74** with trimethylsilylacetylene (TMSA) giving **75** (Scheme 23). Later formation of the new pyridine ring in **76** was afforded in one pot and four steps by silyl group removal, incorporation of a diformyl protected amino group (cf. similar use of sodium diformylamide and discussion of mechanism in Schemes 32 and 33), oxidation and cyclization with concomitant amino group deprotection.[41]



Scheme 23. Synthesis of 4-amino-6*H*-pyrido[2,3,4-*kl*]acridin-6-one **76**.[41]

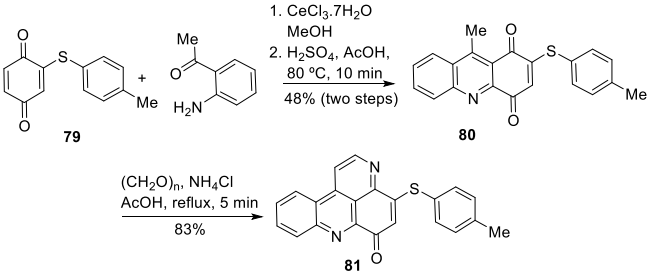
An alternative route (Scheme 24)[42] to a tetracyclic quinone-imine system **78** also started with a palladium-catalysed coupling, to generate the 4-(2-aminophenyl)quinoline **77**.



Scheme 24. Synthesis of the pyridoacridone **78**.[42]

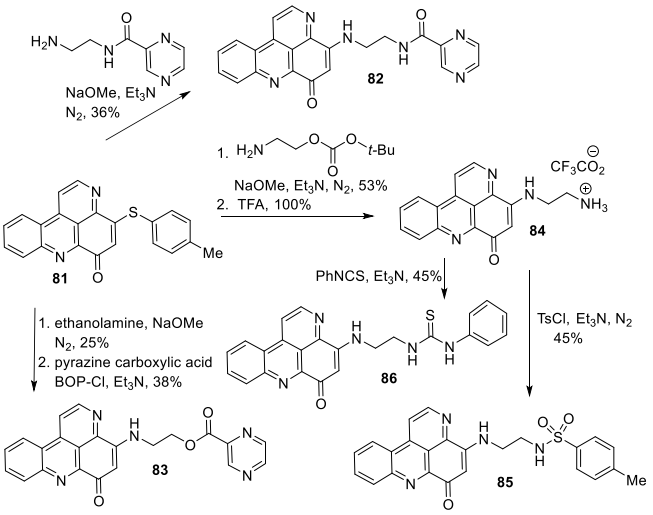
Amide hydrolysis then oxidation to the quinone (not isolated) level led directly to the tetracycle **78**.

The synthesis and biological evaluation of a series of pyrido[2,3,4-*kl*]acridin-6-ones were developed looking for novel therapeutics to treat tuberculosis infections. Interesting compounds were **82** and **83** (Scheme 26), which were found to inhibit the growth of *Mycobacterium tuberculosis* at micromolar concentration, but were not cytotoxic towards Vero and P388 cells.[43] The common synthetic intermediate for all the series is the dihydroacridine-1,4-dione **81**. Oxidative coupling of the benzoquinone **79** with 2-aminoacetophenone and subsequent acid-catalyzed cyclisation led to acridinequinone **80**. The last ring of the pyridoacridone **81** was introduced by a one-pot annulation using paraformaldehyde and ammonium chloride in glacial acetic acid (Scheme 25).



Scheme 25. Synthesis of pyrido[2,3,4-*kl*]acridone **81**.[43]

The propensity of the tolylthio group in **81** to be substituted by nucleophiles was used for the preparation of active compounds **82** and **83** (Scheme 26). Amide **82** was prepared by direct reaction of **81** with *N*-(2-aminoethyl)pyrazine-2-carboxamide in basic conditions. Using the same reaction conditions with the aminoethyl *tert*-butylcarbonate as nucleophile and subsequent removal of the protecting group, the diaminopyridoacridone salt **84** was obtained.



Scheme 26. Syntheses of pyrido[2,3,4-*kl*]acridones **82**, **83**, **85**, and **86**.[43]

The primary amine of **84** was reacted with tosyl chloride or phenylisothiocyanate to give derivatives **85** and **86**,

respectively. Finally, using ethanolamine as reagent with **81** followed by ester formation with pyrazine carboxylic acid, using bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) as coupling agent, product **83** was obtained.

3.2 Pentacyclic systems

3.2.1 *Natural product isolations*

Bioactive pyridoacridines have been isolated from four phyla (Porifera, Chordata-Subphylum Tunicata, Mollusca and Cnidaria) leading to the suggestion that they are actually produced by associated symbionts. Now, a study of the locality of a typical pyridoacridine alkaloid, dercitamide (= kuanoniamine C) in bacteria-free sponge cells in the marine sponge *Oceanapia sagitaria* (Sollas), strongly suggests that the alkaloids are probably not produced by intracellular symbiotic organisms. The study concludes that the localisation of dercitamide in significant concentrations in specific cells throughout the sponge means that it has important biological and ecological functions, such as chemical defence against predators and possibly against pathogens.[44]

A study of the temporal variation in the production of shermilamine B and kuanoniamine D (Fig. 3) by the purple morph of the ascidian *Cystodytes* sp. showed there to be no statistically significant seasonal variation.[45]

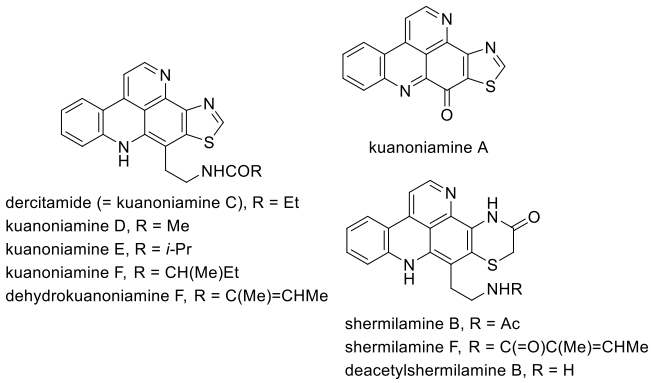


Figure 3. Structures of some kuanoniamines and some shermilamines.

Kuanoniamines A and C (Fig. 3), isolated from the marine sponge *Oceanapia sagittaria* (Sollas) collected from the Gulf of Thailand, were evaluated for their cytotoxic effect against five human tumour cell lines and one human non-tumour cell line. Kuanoniamine A proved to be a potent growth inhibitor of all the human tumor cell lines as well as the nontumour cell line. Though kuanoniamine C was found to be much less potent than kuanoniamine A, it was found to possess a high selectivity toward the estrogen dependent breast cancer cell line.[46] Kuanoniamine E (R = *i*-Pr) and kuanoniamine F (R = CH(Me)Et) (Fig. 3) were isolated from a Singaporean ascidian along with other pyridoacridines, including ascididemine (Fig. 4) and the 'ring-opened' variant **87** drawn to suggest its structural relationship to other pyridoacridine alkaloids.[47] The Australian ascidian *Polysyncraton echinatum* contains 12-deoxyascididemine, along with ascididemine and the heptacyclic eilatin.

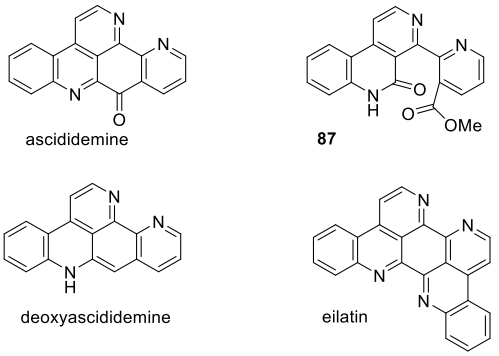


Figure 4. Structures of ascididemine, eilatin and related compounds.[47]

From a *Xestospongia* sp. collected from the Philippines and Palau, deoxyamphimedine was obtained,[48] along with neoamphimedine.[49] Demethyldeoxyamphimedine was obtained from the purple chromotype of the Western Mediterranean ascidian *Cystodytes dellechiajei*.[50] The 5-methoxy derivative of neoamphimedine (R = OMe) was obtained together with neoamphimedines Y (R = H) and Z (R = Me) accompanied by a new skeleton in alpkinidine (Fig. 5), from *Xestospongia carbonaria* and *Xestospongia exigua*, drawn in such a way as to suggest its possible relationship to the other compounds from this source.[51]

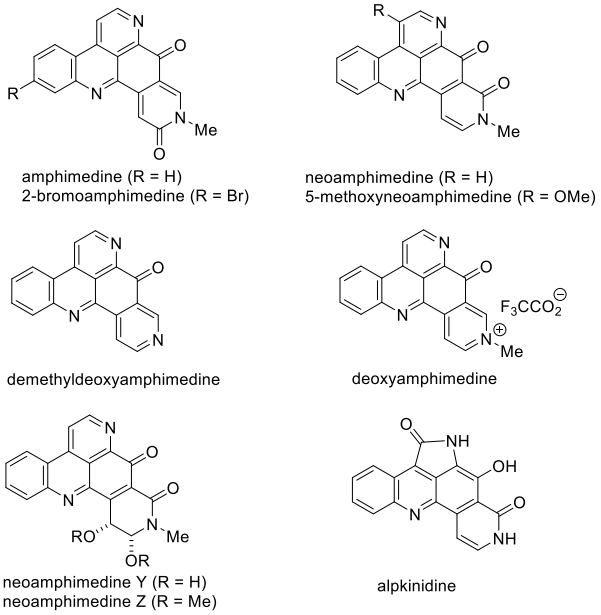


Figure 5. Structures of amphimedine, neoamphimedine, alpkinidine, and related substances.[48-51]

Examinations of various chromotypes of the western Mediterranean ascidian *Cystodytes dellechiajei* all revealed the presence of several known pyridoacridine alkaloids and from the purple colored morph collected in Catalonia, *N*-deacetylshermilamine B (R = H, Fig. 3) and from the green colored morph collected in the Balearic Islands, variants cystodimine A (R = H) and cystodimine B (R = OH) (Fig. 6).[52] Isocystodamine (R = H), *N*-methylisocystodamine (R = Me)

and *N*-methoxymethylisocystodamine (R = CH_2OMe) induce the erythroid differentiation of human leukemia K562 cells with an ED50 value of 5 nM. They were isolated from a sponge *Biemna* sp. dredged at a depth of 150 m on a sea knoll named Oshima-Shinsone, Southern Japan.[53]

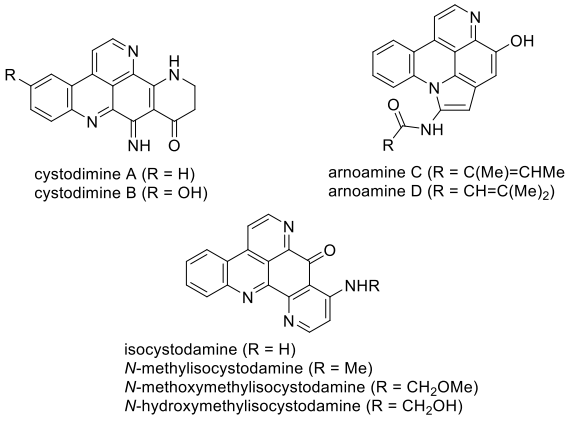


Figure 6. Structures of cystodamines, isocystodamines and arnoamines.[52, 53]

Purification of the bioactive extract of the ascidian *Cystodytes violatinctus* (Solomon Islands) led to the isolation and identification of two known alkaloids and shermilamine F (R = C(=O)C(Me)=CHMe, Fig. 3), dehydrokuanoniamine F (R = C(Me)=CHMe, Fig. 3) and arnoamines C (R = C(Me)=CHMe, Fig. 6) and D (R = $CH=CMe_2$).[54] The Indonesian marine sponge *Biemna fortis* yielded a substance named labuanine A (Fig. 7).[55] It has activity as a neuronal differentiation inducer against a murine neuroblastoma cell line, Neuro 2A. Two cell differentiation inducing pyridoacridines from the same sponge proved to be *N*-hydroxymethylisocystodamine (Fig. 6) and neolabuanine A (a tautomer of labuanine, Fig. 7) and co-occur with other pyridoacridine natural products.[56]

Three alkaloids from the ascidian *Lissoclinum* cf. *badium* collected off the coast of Papua New Guinea, were identified as inhibitors of the Hdm2 E3 activity. Two of them contain the pyrido[2,3,4-*kl*]acridine subunit, tetracyclic diplamine B, and pentacyclic lissoclinidine B. The most biologically interesting is lissoclinidine B which inhibits ubiquitylation and degradation of p53, and selectively kills transformed cells harboring wild-type p53 (Fig. 7).[57]

Petrosamine B is an inhibitor of the *Helicobacter pylori* enzyme aspartyl semialdehyde dehydrogenase and was isolated from the Australian sponge *Oceanapia* sp (Fig. 8).[58] The compound is isomeric (position of the bromine) with petrosamine, also from a sponge, *Petrosia* sp.[59] In analysis of petrosamine B, these workers found no evidence for the dicarbonyl form reported for petrosamine.

However, in another study of petrosamine, isolated from a Thai marine sponge *Petrosia* sp., it was shown to exist in the dicarbonyl form in DMSO-d_6 solution.[60] Along with petrosamine, a new variant, 2-bromoamphimedine, was obtained.

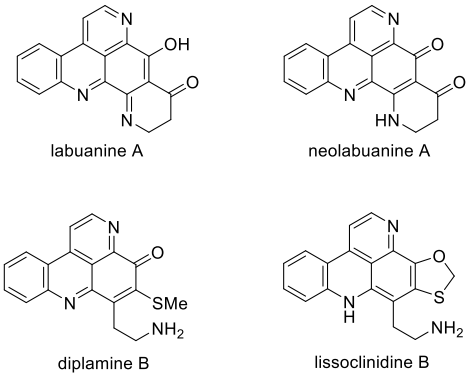


Figure 7. Structures of labuanine A, neolabuanine A, diplamine B and lissoclinidine B.[54]

Petrosamine has potent anticholinesterase activity, six times higher than that of the reference galanthamine. In a computational docking study, using the enzyme from the electric eel *Torpedo californica* (TcAChE), a major contribution was shown to be due to interaction with the *N,N*-dimethyl ammonium group of the alkaloid.[59]

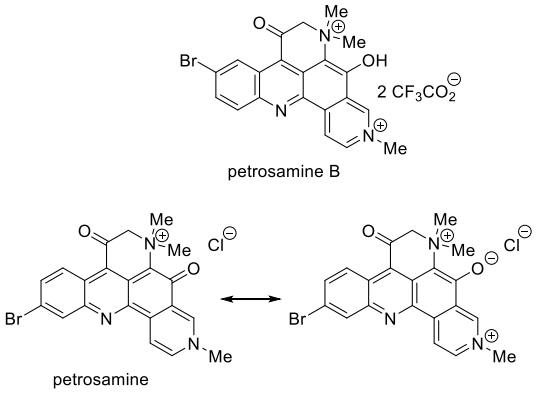
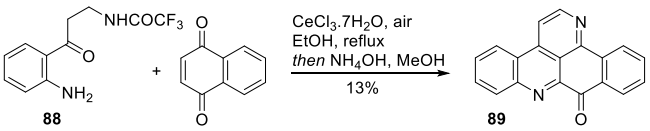


Figure 8. Structures of two petrosamines.[58]

3.2.2 Syntheses

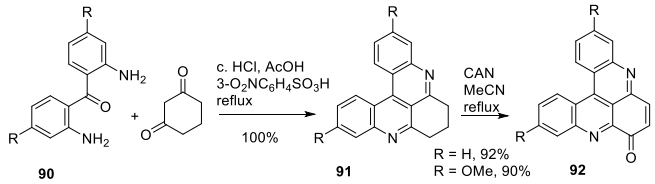
1,4-Naphthoquinone has been used to generate pentacyclic systems and compounds with more than five rings.[61] Thus, reaction with TFA-protected kynuramine, **88**, leads in two steps and in one pot to the pentacyclic quinoneimine **89** containing the pyrido[2,3,4-*kl*]acridine nucleus (Scheme 27).



Scheme 27. Synthesis of 4-deaza-ascididemine **89**.[61]

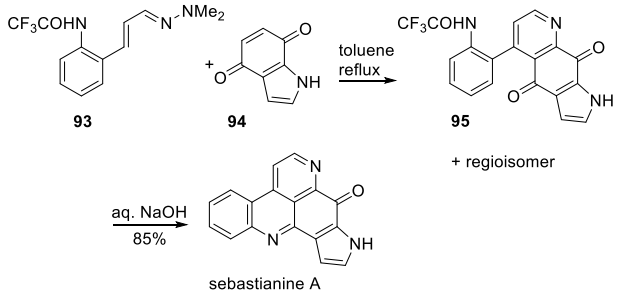
The keto-diamine **90** reacts with cyclohexane-1,3-dione to generate partially reduced versions **91** quantitatively.[60] These can be oxidised to the quinone-imines **92** which react

with bromine with substitution of both hydrogens of the quinone-imine ring (Scheme 28).



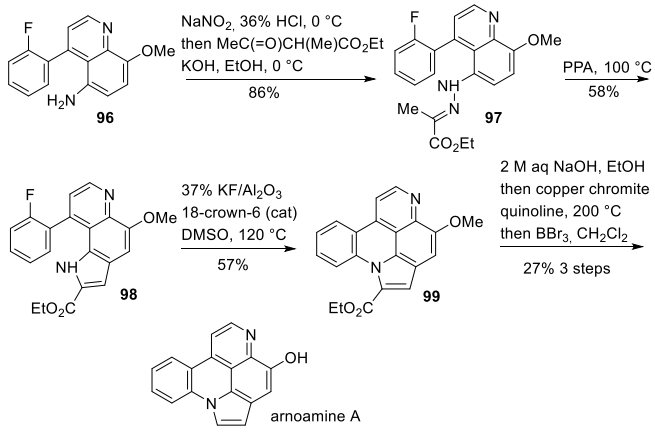
Scheme 28. Synthesis of quinone-imines **92**.[61]

A total synthesis of sebastianine A was achieved (Scheme 29) starting with a Diels–Alder cycloaddition of **93** with 4,7-dimethoxyindole-derived quinone **94**.[62] The yields in the Diels–Alder step were very low. Cyclization in basic conditions of regioisomer **95** gave sebastianine A.



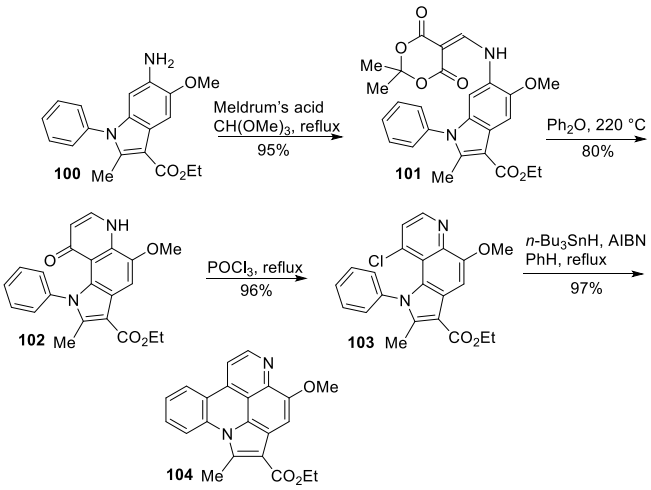
Scheme 29. Synthesis of sebastianine A.[62]

Another compound with a fused pyrrole ring is arnoamine A, a synthesis of which (Scheme 30) can be traced back to the quinoline **96**.[63] Conversion of amine into diazonium salt and reaction with a 1,3-keto-acid (the Japp–Klingemann reaction) produced the arylhydrazone **97** which was then transformed into pyrido-indole **98** *via* a Fischer indole synthesis. Rather vigorous conditions induced intramolecular indole-*N*-arylation to form **99** now requiring simple adjustments to arrive at arnoamine A.



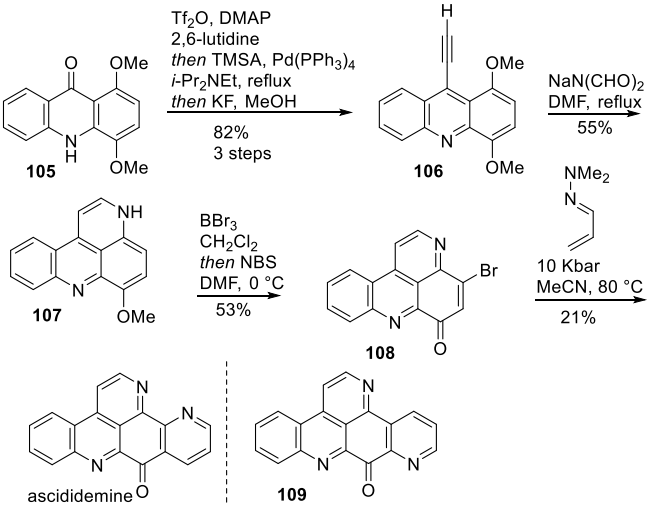
Scheme 30. Synthesis of arnoamine A.[63]

The arnoamine skeleton **104** was also produced via a different strategy (Scheme 31) in which a preformed *N*-phenyl indole **100** was the starting point.[64] Construction of the 4-quinolone unit in **102** via thermolysis of the Meldrum's acid structure **101** and reaction with phosphoryl chloride gave the chloro compound **103**. Formation of the final bond relied on an intramolecular radical substitution. Work employing this final step also led to arnoamine B itself.[65,66]

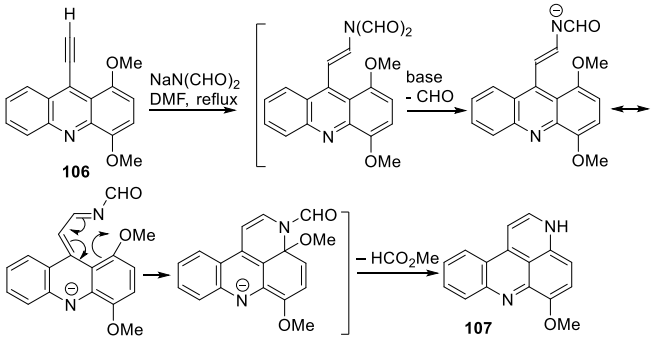


Scheme 31. Synthesis of arnoamine A skeleton from an indole.[65, 66]

The Authors' synthesis of ascididemine began with the acridone **105** (Scheme 32)[67] converted as shown into ethynyl-acridine **106**. The next step was entirely novel involving reaction with sodium diformylamide and producing the 'top' pyridine ring directly **107**. Transformation into a bromo-quinone-imine **108** allowed an aza-Diels–Alder sequence to complete the synthesis. Analogous methodology also produced the non-natural ascididemine isomer **109**. A tentative mechanism for the key ring-forming step giving **107** is detailed in Scheme 33.

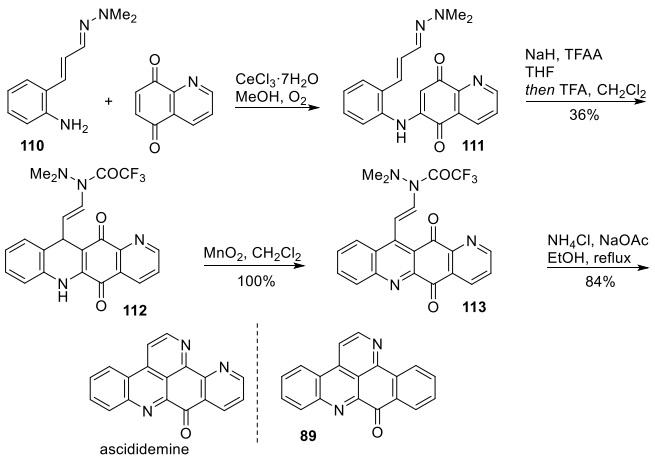


Scheme 32. Synthesis of ascididemine and an isomer **109**.[67]



Scheme 33. Proposed mechanism of pyridine ring formation from alkyne **106** with sodium diformylamide.

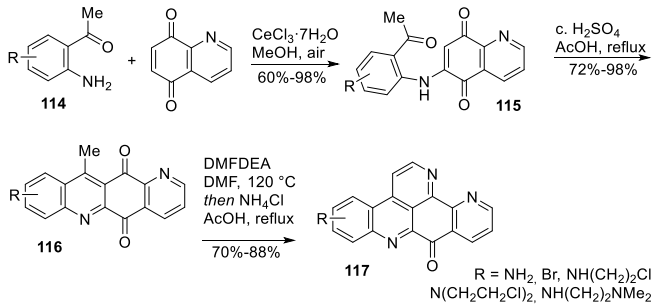
Another synthesis of ascididemine, based on oxidative amination of a quinone, began with a regioselective reaction between quinoline-5,8-dione and the aniline **110** (Scheme 34) in the presence of air to oxidise the initial Michael addition intermediate to **111**. Cyclisation of **111** to the tetracycle **112** resulted from successive reactions with trifluoroacetic acid anhydride and then trifluoroacetic acid.



Scheme 34. Synthesis of ascididemine from quinoline-5,8-dione and structure of 4-deaza-ascididemine **89**.[68]

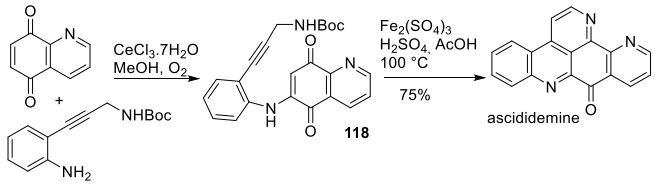
The quinoline-5,8-dione employed in Scheme 34 was also used in the synthesis of non-natural analogues **117** (Scheme 35).[69] The quinone was reacted with various *ortho*-aminoacetophenones **114** to provide variation in the benzene ring, and the products **115** closed to tetracycles **116** with strong acid. The 'top' ring was constructed by functionalization of the pyridine-4-methyl group using DMFDEA and then reaction with ammonia (cf. Scheme 18).

For several of the products, the antitumor activity (determined *in vitro*) and tolerability (determined *in vivo*) were superior to those of the alkaloids of which they are analogues. Several analogues, as well as ascididemine, bromo-leptoclinidinone, neocalliactine acetate, and 11-hydroxy-ascididemine themselves, were produced via a Brønsted acid-promoted tandem annulation (Scheme 36 – only the intermediates for ascididemine itself are shown).[70]



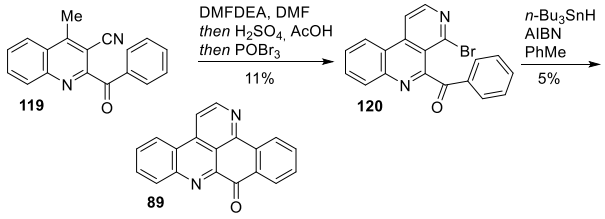
Scheme 35. Synthesis of ascididemine analogues **117** from quinoline-5,8-diones **115**.[69]

Again here, amino-quinoline-quinones e.g. **118** were utilised and prepared, as previously, by amination of the quinone in the presence of an oxidising trap. Of several conditions assessed, the best to bring about the conversion of **118** into the final products proved to be ferric sulfate and sulfuric acid with acetic acid at 100 °C.



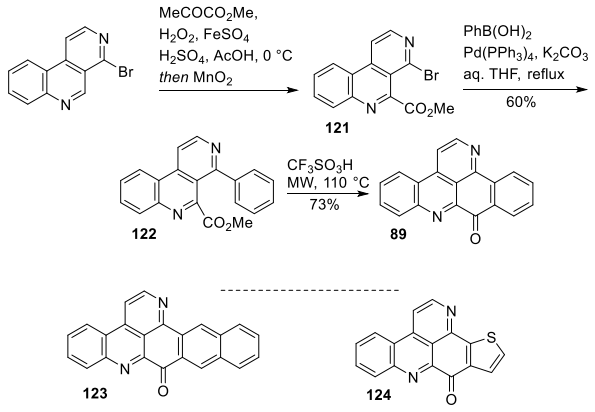
Scheme 36. Synthesis of ascididemine via a tandem annulation.[70]

In the light of the bioactivity of ascididemine, several other reports describe analogues (only those with a pyrido[2,3,4-*kl*]acridine unit are described here). For example, the 4-deaza-ascididemine **89** was constructed using **119** as starting material. Using the Minisci reaction, 4-methyl-3-cyanoquinoline was converted into the ketone **119**. Functionalisation of the methyl group produced a 2-pyridone unit and conversion into halide **120** allowed a radical, but low yielding, substitution to complete the pentacycle (Scheme 37).[71]



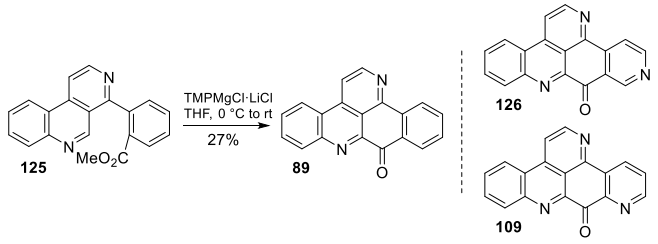
Scheme 37. Synthesis of 4-deaza-ascididemine **89** via a radical aromatic substitution.[71]

Adapting the approach further, naphthyridine ester **121** was produced *via* Minisci substitution, which was cross-coupled with various aryl- and hetarylboronic acids (only product **122** from phenylboronic acid is shown) to give materials ready for a final strong acid-promoted closure, in this case giving **89** (Scheme 38).[72] Amongst several other structures produced in this way were **123** and **124**.



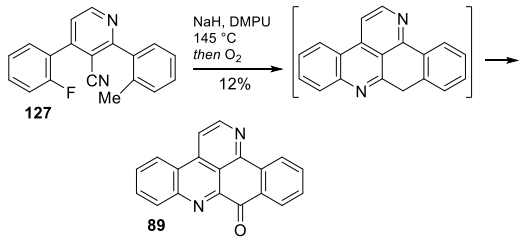
Scheme 38. Synthesis of 4-deaza-ascididemine **89** and structures of analogues **123** and **124**.[72]

Reversing the sequence of bond formations, the ester **125**, and substituted variants (not shown), were made by cross-coupling 4-bromobenzo[*c*][2,7]naphthyridine with aryl esters carrying an *ortho* boronic acid, and the last ring made via metallation at the N=CH with 2,2,6,6-tetramethylpiperidinyl-magnesium chloride lithium chloride complex (TMPMgCl·LiCl), though in only moderate yields (Scheme 39).[73] The isomers **126** and **109** of ascididemine were also made in this way.



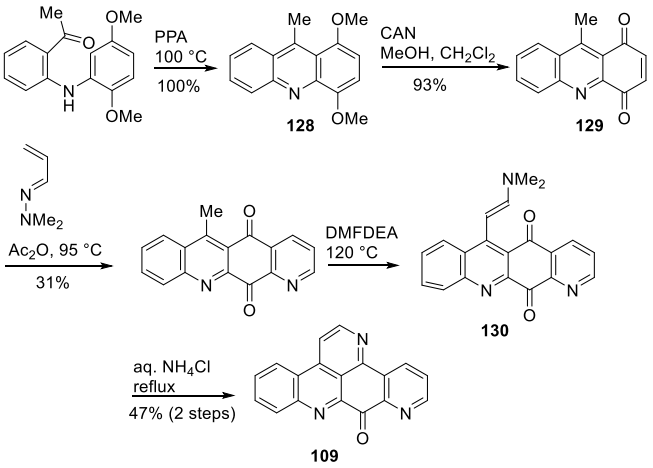
Scheme 39. Synthesis of 4-deaza-ascididemine **89** and structures of ascidemine isomers **126** and **109**.[73]

The base-promoted closure of two rings using sodium hydride in *N,N′*-dimethylpropyleneurea (DMPU) from the fluoro-nitrile **127** neatly leads directly to 4-deaza-ascididemine **89**, with formation of two rings, though the yields in this example and substituted variants, were only moderate (Scheme 40).[74] The mechanism of the anionic ring closure is detailed in Scheme 12.



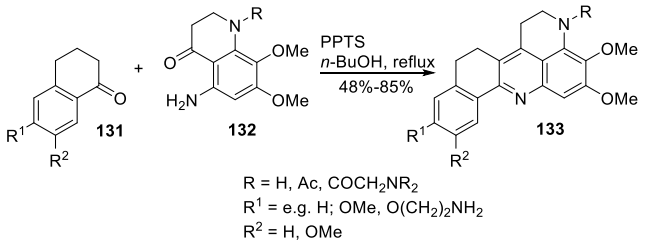
Scheme 40. Synthesis of 4-deaza-ascididemine **89**.[74]

The non-natural isomer **109** of ascididemine was also prepared as shown in Scheme 41.[75] Firstly the dimethoxy-methylacridine **128** was constructed and converted into the corresponding quinone **129**. Aza-Diels–Alder reaction with acrolein *N,N*-dimethylhydrazone added the next pyridine ring. Functionalisation of the methyl group by reaction with DMFDEA (→**130**) and then simple treatment with aqueous ammonia completed the task (Scheme 41).



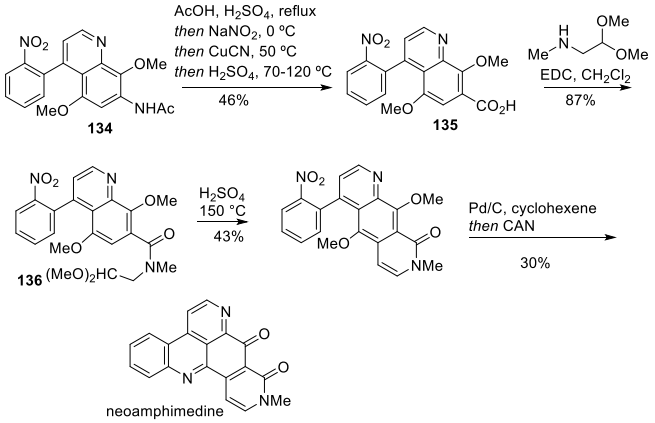
Scheme 41. Synthesis of non-natural isomer **109** of ascididemine.[75]

Somewhat further away from natural structures, the hydro-pyrido[2,3,4-*kl*]acridines **133** were prepared (Scheme 42) and shown to be cytotoxic, but no strict correlations with their DNA binding affinity and effects on topoisomerases were observed.[76-78] The construction was very straightforward, having in hand the amino-ketones **132** and ketones **131**, comprising a standard Friedländer quinoline synthesis.



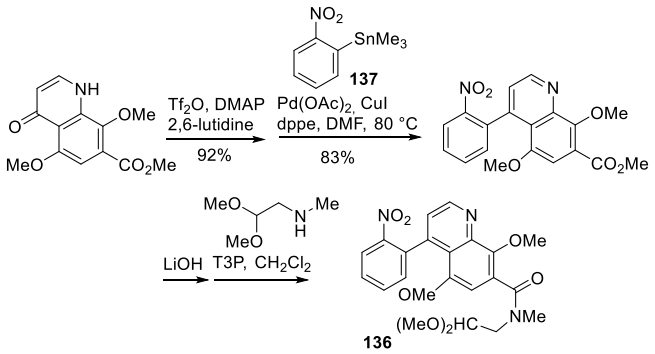
Scheme 42. Synthesis of pentacyclic pyridoacridines **133**.[77]

The first total synthesis (Scheme 43)[79] of neoamphimedine proceeded with the construction of the 4-(2-nitrophenyl)dimethoxyquinoline **134** originating from 4-methoxy-2-nitrophenol in seven steps. Transformation of the acetylamino group of **134** into carboxylic acid **135** and formation of an amide with *N*-methylaminoacetaldehyde dimethylacetal gave **136**, which was ring closed in acidic media. Nitro-group reduction and then reaction of the resulting aniline with the quinone, produced by oxidation with CAN of the dimethoxybenzene, gave the last heterocyclic ring of neoamphimedine.



Scheme 43. First synthesis of neoamphimedine.[79]

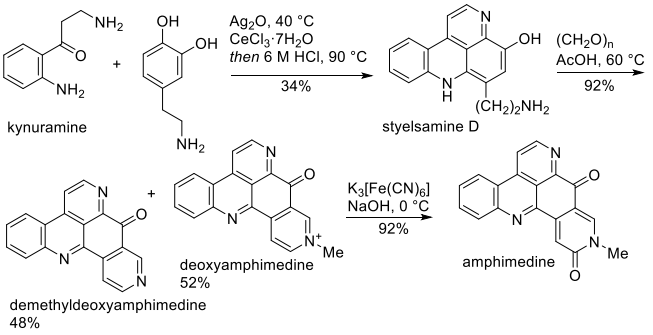
In a somewhat shorter route to neoamphimedine, described as an ATP-competitive inhibitor of topoisomerase IIα and potent anticancer agent, key intermediate **136** was constructed *via* a triflate cross-coupling with stannane **137** (Scheme 44).[80] Hydrolysis of ester then formation of amide bond was achieved by reaction *N*-methylaminoacetaldehyde dimethyl acetal using as activating agent propylphosphonic anhydride (T3P). Arguably, neoamphimedine is one of the most potent antitumor agents of the pyridoacridine family.[6]



Scheme 44. Improved steps in a synthesis of neoamphimedine.[80]

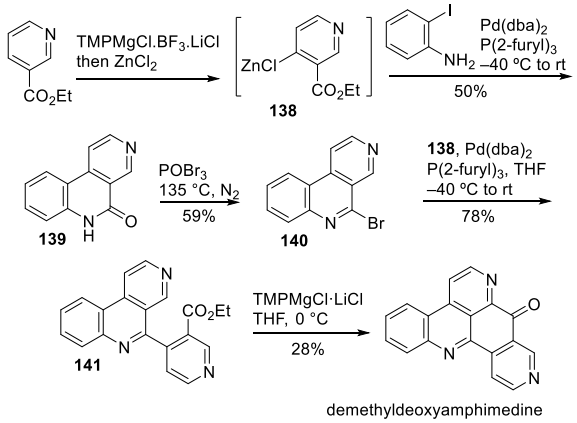
In a delightfully short synthesis (Scheme 45)[81] of amphimedine, kynuramine gained from tryptamine *via* an improved route, was converted directly into styelsamine D. Next, reaction with formaldehyde generated a mixture of demethyldeoxyamphimedine and deoxyamphimedine. The final step was the oxidation of the pyridinium salt with ferricyanide – fortunately this occurred on the desired side of the quaternary nitrogen giving amphimedine.

Another synthesis of demethyldeoxyamphimedine required, impressively, only four steps starting from ethyl nicotinate and 2-iodoaniline (Scheme 46).[82] Cross coupling of the 4-metallated ethyl nicotinate **138** with 2-iodoaniline produced the tricycle **139**.



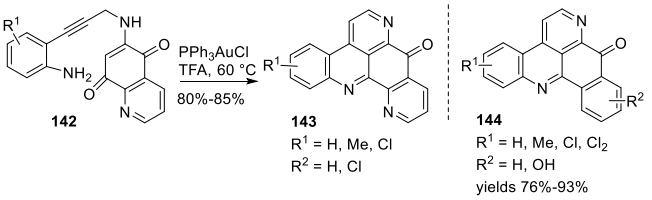
Scheme 45. Syntheses of styelsamine D, demethyldeoxyamphimedine, deoxyamphimedine, and amphimedine.[81]

Conversion into bromide **140** and cross coupling with the same metallated nicotinate produced **141** requiring only metallation of the pyridine moiety using TMPMgCl·LiCl, for intramolecular nucleophilic attack on the ester and the formation thereby of dimethyldeoxy-amphimedine.



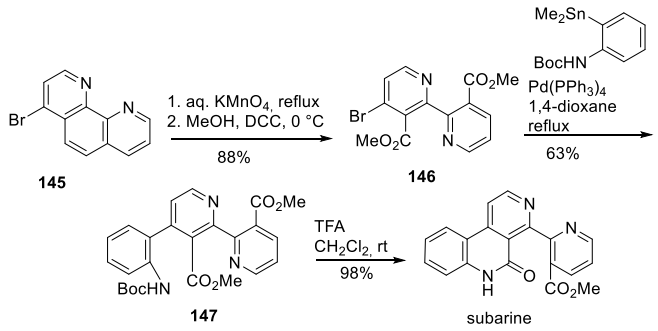
Scheme 46. Synthesis of demethyldeoxyamphimedine.[82]

An elegant use of gold catalysis with chloro(triphenylphosphine)gold(I) brings about ring closure (formation of two rings) of alkynyl-anilines **142** to iminoquinone **143** (Scheme 47).[83] The starting amino-quinones **142** were prepared from the quinoline-5,8-dione and the aralkynylmethylamine under oxidative conditions to trap initial adducts. Comparable deaza-analogues derived from naphthalene-1,4-diones led to pentacycles **144**.



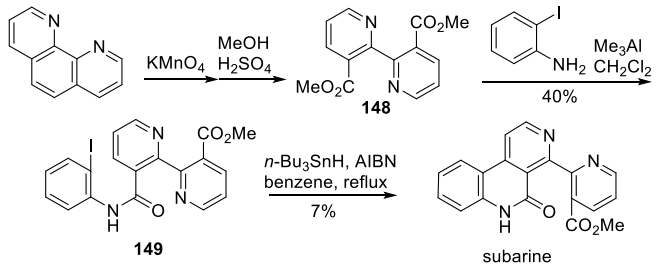
Scheme 47. Synthesis of compounds **142** and **144**.[83]

A simple synthesis of subarine from a Singapore ascidian[46] employs a cross-coupling as a key step (Scheme 48).[84] The structure is drawn in such a way as to suggest its relationship to the pentacyclic alkaloids of the ascididemine group, but with one ring 'missing' – hence its inclusion, though tricyclic, in this Section. Oxidative cleavage of the benzene ring in 4-bromo-1,10-phenanthroline **145** and esterification of the resulting di-acid gave di-ester **146**. Cross-coupling with *N*-(*tert*-butoxycarbonyl)-2-(trimethyl stannyl)aniline produced **147** then converted into the alkaloid with acid.



Scheme 48. Synthesis of subarine.[84]

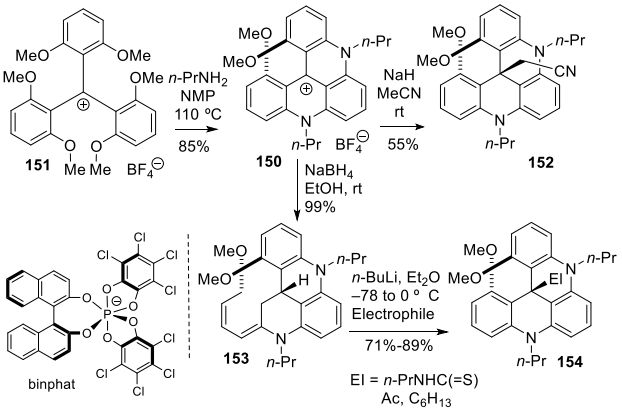
A second and somewhat shorter synthesis of subarine also began with an oxidative cleavage, leading to dimethyl [2,2'-bipyridine]-3,3'-dicarboxylate **148** (Scheme 49).[85] Amide formation with 2-iodoaniline to **149** and a final carbon–carbon bond-forming radical step gave the alkaloid, though only in 7% yield for the last step.[86]



Scheme 49. Second synthesis of subarine.[86]

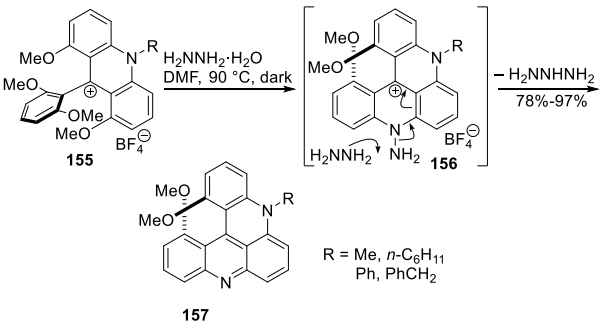
3.2.3. Helicenes and triazatriangulenium salts

The highly configurationally stable [4]heterohelicenium cations, e.g. **150**, can be prepared from the triaryl carbocation **151** by reaction with an amine, e.g. *n*-propanamine, four of the methoxy groups being thus displaced (Scheme 50).[87] The displacement of one pair of methoxy groups takes place at 50 °C.[88] Interference between the remaining methoxy groups in salts such as **150** ensures that the helicity is maintained. The salt **150** was shown to be configurationally stable up to 200 °C. Compound **150** was resolved by forming diastereomeric salts with binphat. Under strongly acidic conditions, e.g. PPA (polyphosphoric acid) or Eaton's reagent (phosphorous pentoxide in methanesulfonic acid), regioselective electrophilic substitution of salts such as **150**, e.g. acylations, sulfonylations, or alkylations, occurs at the extremity of the helical cores, *ortho* to a methoxyl group.[89] A range of nucleophiles, including aryl- and alkyllithiums, and hydride, react with these salts with attack at the central positively charged carbon, to produce neutral products, as in the examples **152** and **153** shown in Scheme 50. Derivatives with substituents at the central carbon such **154** can also be obtained via lithiation of the hydride reduction product **153**. The helicene salts were shown to bind to DNA, probably by intercalation.[90]



Scheme 50. Synthesis and reactions of [4]heterohelicenium cations.[87]

The use of hydrazine instead of a primary amine in reaction with carbocations **155** allows the synthesis of neutral products, with a fully aromatic acridine unit, but still chiral, quinacridines **157**.[91] As illustrated in Scheme 51, the products **155** of disubstitution with one primary amine unit, react with hydrazine giving intermediates believed to have structures **156** and then cleavage of the N–NH_2 bond brings about aromatization of the central pyridine ring (arrows on **156** are suggested). Quinacridines **157** are pink and when protonated (on the acridine nitrogen), the resulting cation is green.



Scheme 51. Synthesis of chiral 5*H*-quino[2,3,4-*kl*]acridines **157**.[91]

Under more extreme conditions, the triaryl carbenium ions **151** can be made to react with three equivalents of primary amines to produce cations called 'triazatriangulenium' ions (Fig. 9), e.g. the dark blue **158** (*n*-$PrNH_2$, NMP, 110 °C, 77%).[92]

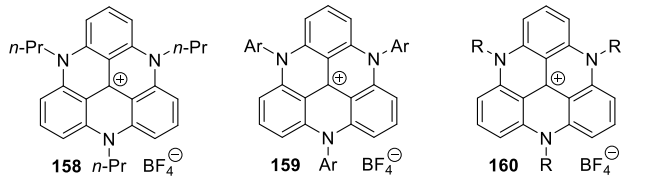
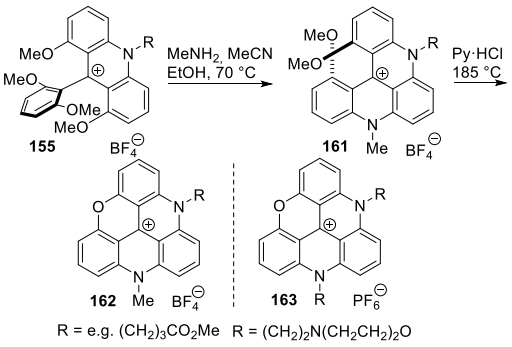


Figure 9. Typical triazatriangulenium cations **158-160**.[93]

Even more extreme conditions are required to introduce three arylamines, thus **151** tris(2,6-dimethoxyphenyl) methylium ion (DMP_3C^+) was heated in excess of various anilines, in the presence of sodium hydride, in a solvent-free reaction at 210 °C producing **159**.[93] Triazatriangulenium cations **160** with longer R groups, prepared with amines at 180 °C, can be used as phase-transfer catalysts.[94]

Aryl- and ethynyllithiums add easily to the central, positively charged carbon of triazatriangulenes, giving neutral products.[95] This process can be reversed photochemically.[96] Analogous systems, with one oxygen and two nitrogens as the bridging heteroatoms, can also be prepared, for example starting from salt **155**. Thus 'diazaoxatrianguleniums' **162** were made via demethylation of a methyl ether in a salt **161** then intramolecular displacement of the remaining methoxyl by the so-formed phenolic oxygen, as shown in Scheme 52.[97] Electrophilic substitution of diazaoxatriangulenes such as **162**, for example nitration and Vilsmeier formylation, occurs on the benzene ring with two nitrogens attached, and *ortho* to a nitrogen.[98] A study of the interaction of trianguleniums as optical probes for G-quadruplexes, showed **163** to be a unique fluorescence probe.[99] Interaction with a G-quadruplex from the promoter region of the c-myc oncogene revealed that they interact at 1:2 binding stoichiometry. Calculations showed that binding occurs mainly through π–π stacking between the polyaromatic core of the ligand and guanine residues of the outer G-quartets.[100]



Scheme 52. Synthesis of diazaoxatrianguleniums.[97]

3.3. Hexacyclic systems

Several hexacyclic alkaloids containing the pyrido[2,3,4-*kl*]acridine motif have been isolated during the 21st Century. Cycloshermilamine D was isolated from the marine tunicate *Cystodytes violatinctus*.[101] Segoline C possessing the benzo 1,6-diazaphenanthroline ring system was isolated from the Indian Ocean tunicate *Eudistoma bituminis* together with the known segoline A previously isolated from the Red Sea tunicate *Eudistoma* sp. (Fig. 10).[102]

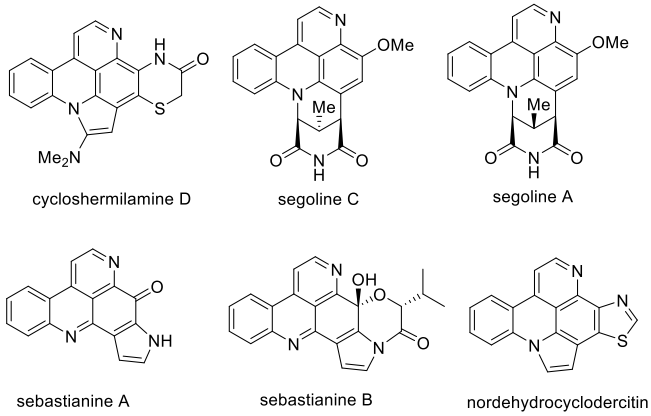
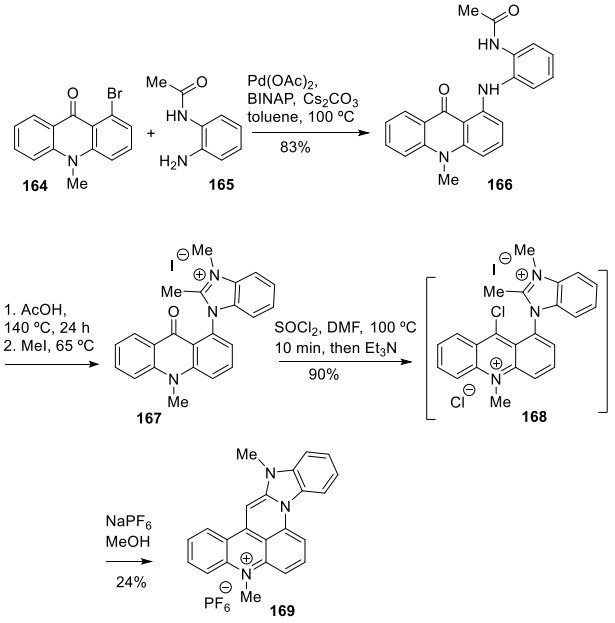


Figure 10. Structures of cycloshermilamine D, segolines A, C, sebastianines A, B and nordehydrocyclodercitin.[101-104]

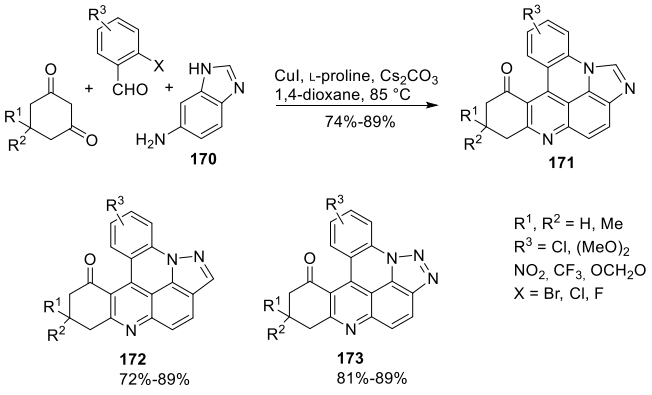
Sebastianine A (cf. Scheme 29 for synthesis) and sebastianine B were new alkaloids from the ascidian *Cystodytes dellechiajei* collected in Brazil.[103] Nordehydrocyclodercitin, from the ascidian *Aplidium cratiferum* was collected at Arab Reef, Great Barrier Reef, Australia.[104]

Hexacyclic acridine dye **169** possessing remarkable fluorescence properties and absorbing in the green area of the spectrum was synthesized from bromoacridone **164** (Scheme 53).[105] A palladium-catalysed Buchwald–Hartwig coupling between **164** and monoprotected *ortho*-phenylenediamine **165** produced **166**. Successive closure of the benzimidazole ring in refluxing acetic acid and quaternisation in refluxing methyl iodide gave the benzimidazolium-acridone **167**. Treatment of *N*-methylacridone **167** with a mixture of thionyl chloride and a few drops of anhydrous DMF gave the unstable 9-chloroacridinium chloride **168** that was converted in situ into the desired hexacyclic acridinium salt by addition of triethylamine which produced a 2-methylene-benzimidazole allowing attack on the acridine C-9 position. Dye **169** was finally isolated as a hexafluorophosphate salt by anion interchange after treatment with sodium hexafluorophosphate.



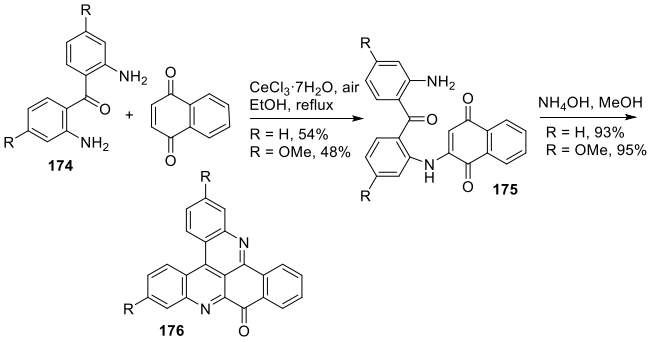
Scheme 53. Synthesis of acridine dye **169**.[105]

Imidazoquinolinoacridones **171** were obtained with good yields by a three-component reaction of 2-halo aromatic aldehydes, benzimidazol-6-amine **170** and cyclohexane-1,3-diones, catalyzed by copper(I) iodide and L-proline (Scheme 54).[106] The same domino reaction was applied for the syntheses of pyrazolo and triazolo derivatives **172** and **173** using as starting material a indazole-6-amine or a benzotriazole-6-amine, respectively. [107,108]



Scheme 54. Syntheses of imidazoquinolinoacridones **171** and structures of hexacyclic acridones **172** and **173**.[106-108]

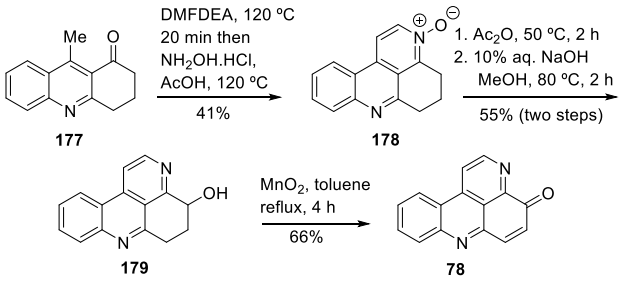
Reaction of 1,4-naphthoquinone with keto-diamine **174**, in the presence of an oxidizing agent, forms firstly **175**, which can be ring closed with ammonia, as a base, to the hexacyclic **176** (Scheme 55). In studies of electrophilic substitution, it was found that nitration occurs *ortho* to the methoxyl groups in **176** (R = OMe).[61]



Scheme 55. Synthesis of benzo[*b*]quino[4,3,2-*mn*]acridin-10-ones **176**.[61]

3.4. Heptacyclic systems

A total synthesis of the heptacyclic pyridoacridine alkaloid eilatin and its isomer isoeilatin was performed starting from pyridoacridones **78** or **181** respectively.[109] The pyridoacridone **78** was obtained (Scheme 56) by condensation of acridone **177** with DMFDEA (cf. Scheme 18) followed by ring closure with hydroxylamine hydrochloride to give the *N*-oxide **178**. Rearrangement of *N*-oxide **178** using acetic anhydride gave an acetoxy derivative, which was hydrolyzed to alcohol **179**. Subsequent oxidation of **179** gave the pyridoacridone **78**.

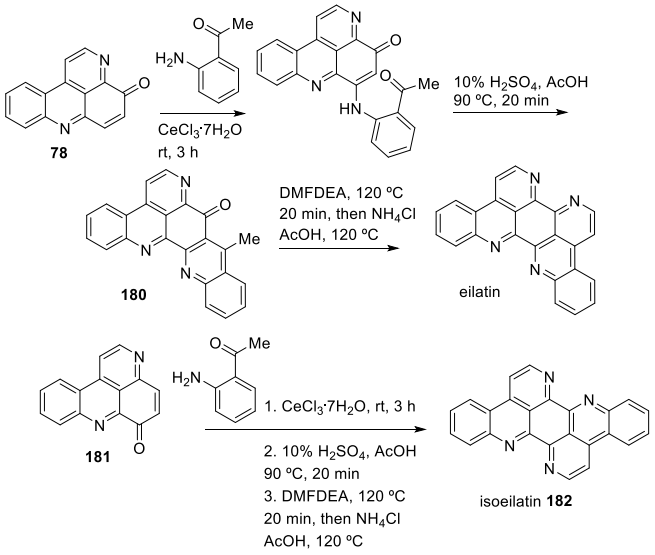


Scheme 56. Synthesis of 4*H*-pyrido[2,3,4-*kl*]acridin-4-one **78**.[109]

Oxidative amination of **78** with 2-aminoacetophenone using cerium(III) chloride catalyst followed by cyclization gave the hexacyclic pyridoacridone **180** which was transformed into eilatin by an annulation reaction using another DMFDEA procedure (Scheme 55).

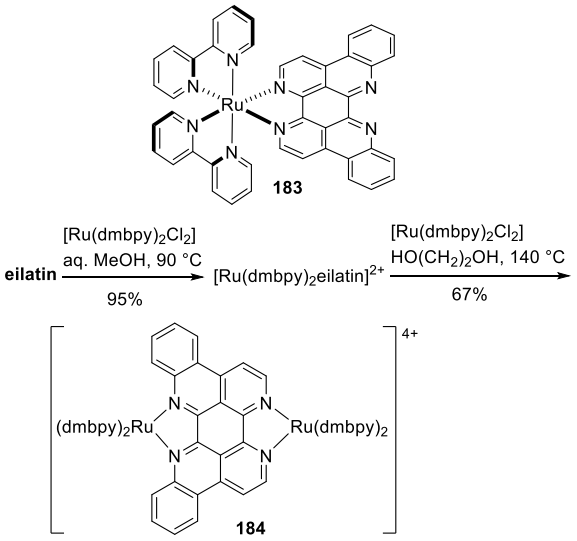
The same oxidative amination on pyridoacridone **181**, cyclization and annulation afforded isoeilatin **182** (Scheme 57).

There has been substantial interest in metal complexes of eilatin; structure **183** [Ru(bpy)$_2$eilatin] shows which nitrogens are used when the alkaloid acts as a mondentate ligand (Scheme 58).[110] However, the alkaloid can also act in a bidentate fashion, as in the complex **184**.[111] Eilatin Ru(II) complexes display anti-HIV activity and enantiomeric diversity in the binding of RNA.[112]

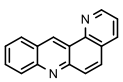


Scheme 57. Syntheses of eilatin and isoeilatin **182**.[109]

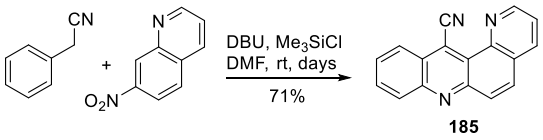
The cationic $[Fe(eilatin)_3]^{2+}$ effectively recognize (tris(tetrachlorobenzenediolato)phos-phate(V) (TRISPHAT) even in polar media such as 90% acetone–$CHCl_3$.[113]



Scheme 58. Structure of ruthenium complexes of eilatin in mono- and bidentate modes.[110, 111]

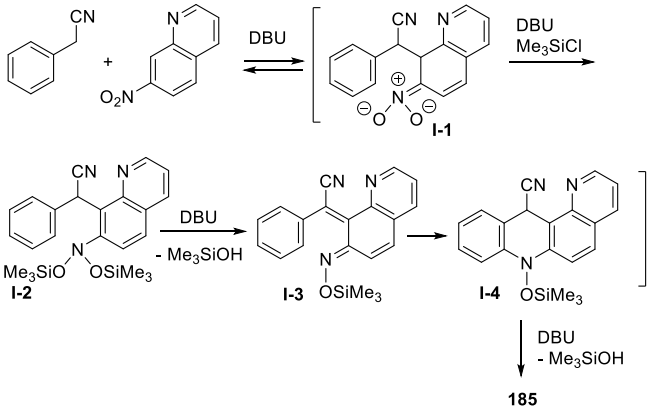
4.  Pyrido[2,3-*a*]acridine {benzo[*j*][1,7] phenan-throline}

There seem to be no natural products that include the pyrido[2,3-*a*]acridine nucleus however, there are synthetic examples. Benzylic carbanions react with nitroarenes under mild conditions in the presence of DBU and trialkylchlorosilanes to form tetra- and pentacyclic azaarenes. This process was used to construct the cyano-pyrido[2,3-*a*]acridine **185** as indicated in Scheme 59.[114]



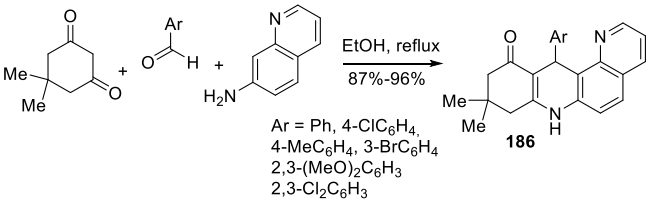
Scheme 59. Synthesis of a cyano-pyrido[2,3-*a*]acridine **185**.[114]

The proposed mechanism for the synthesis of pyridoacridine **185** is shown in Scheme 60. Addition of benzylic carbanion to the nitroquinoline gives **I-1** which was transformed *via* **I-2** into **I-3** ready for an electrocyclization and aromatization to afford the tetracyclic compound **185**.



Scheme 60. Proposed mechanism for the reaction of benzylic carbanions with nitroarenes.

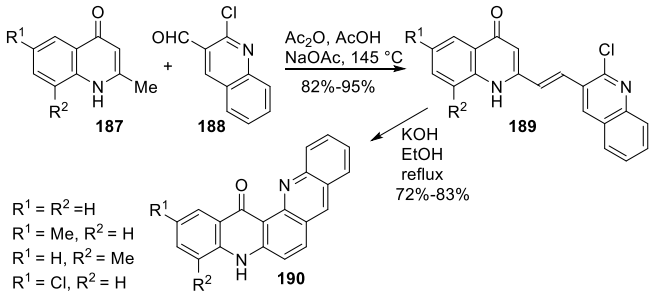
A three-component process involving an aromatic aldehyde, dimedone and 7-aminoquinoline produces hexahydropyrido [2,3-*a*]acridinones **186** (Scheme 61).[115]



Scheme 61. Synthesis of hexahydropyrido[2,3-*a*]acridinones **186**.[115]

Condensation of the quinolin-4-one **187** with 2-chloroquinoline-3-carbaldehyde **188** gave an alkene **189** which could be ring closed to **190** with base (Scheme 62).[116]

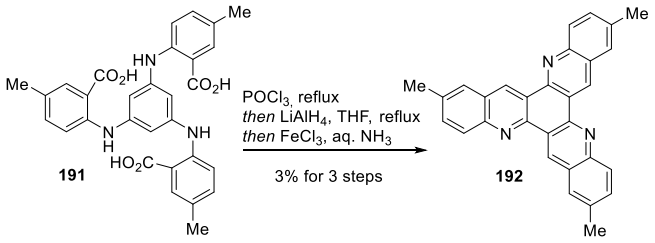
The synthesis of the heptacyclic 'triazatrinaphthylene' **192** (TrisK), a three-fold symmetry planar conjugated system with two-dimensional self-assembly properties, is an extension of the approach described for the synthesis of **220** (Scheme 76) and **288** (Scheme 95). In the present context, product **191** obtained by Buchwald-Hartwig cross-coupling between 1,3,5-tribromobenzene and 2-amino-5-methylbenzoic acid, triply cyclised with phosphoryl chloride leading to **192** via a heptacyclic triketone, reduced to a hexahydro-heptacycle then aromatized with iron(III) chloride (Scheme 63).[117]



Scheme 62. Synthesis of substituted dibenzo[*b,j*][1,7]phenanthrolin-14-ones **190**.[116]

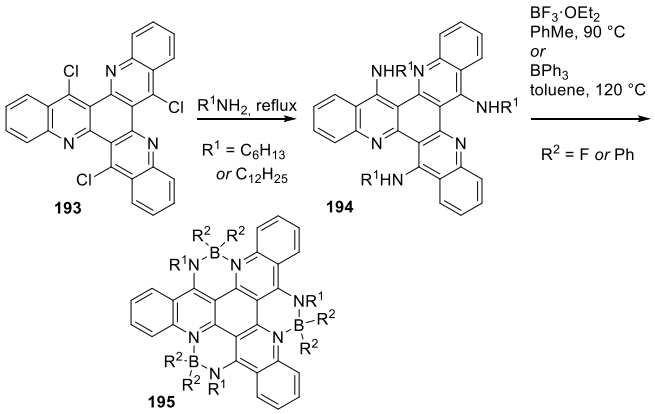
The structure actually contains three pyrido[2,3-*a*]acridine and three pyrido[2,3-*c*]acridine moieties. Exactly comparable triazatrinaphthylenes were prepared starting from 2-amino-5-alkoxy(C_3H_7O; $C_{10}H_{21}O$; $C_{12}H_{25}O$; $C_{16}H_{33}O$)benzoic acid.[118]

The compounds with propyloxy substituents, and its precursor still with three chlorine atoms (**193**, Scheme 64) were shown to form highly organized nanoporous honeycomb networks when adsorbed at the *n*-tetradecane/HOPG (highly oriented pyrolytic graphite) interface.[119]



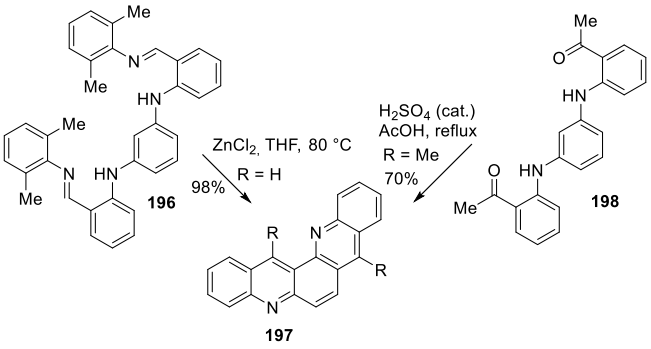
Scheme 63. Synthesis of a diquino[2,3-*a*:2',3'-*c*]acridine **192**.[117]

Displacements of the chlorines in **193** with amino-substituents (e.g. $NH(CH_2)_2NMe_2$) produced substances that recognize G-Quadruplex DNA.[120,121] The displacement of chlorines with other amines gave substances **194** that react (Scheme 64) with boron trifluoride or triphenylborane forming novel chromophores **195**.[122]



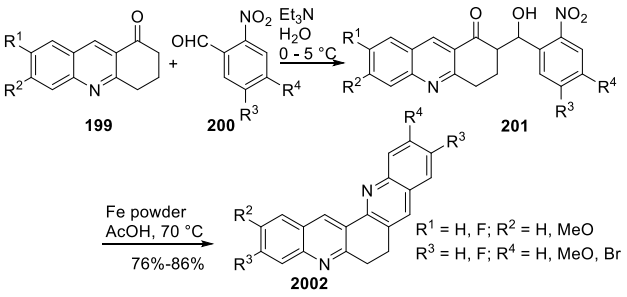
Scheme 64. Synthesis of triamino-diquino[2,3-*a*:2',3'-*c*]acridine boron adducts **195**.[122]

A variant on these ring closures, that provides fully aromatic products directly, depends on the use of *ortho*-arylaminophenyl Schiff bases.[123] Thus, in a general study, one example had **196** being converted into **197** (R = H). Perhaps even simpler, the diketone **198** was ring closed to **197** (R = Me) under acidic conditions (Scheme 65).[124]



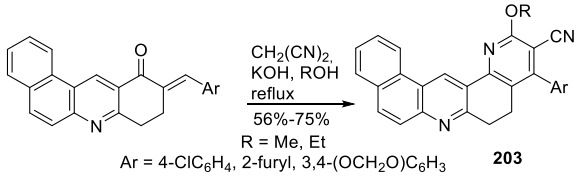
Scheme 65. Two approaches to dibenzo[*b,j*][1,7]phenanthrolines **197**.[124]

6,7-Dihydrodibenzo[*b,j*][1,7]phenanthrolines **202**, which contain both a pyrido[2,3-*c*]acridine unit and a pyrido[2,3-*a*]acridine moiety, can be assembled using an efficient two-step procedure, summarized in Scheme 66.[125] An aldol condensation between the tetrahydroacridone **199** and an *ortho*-nitro-araldehyde **200** giving an alcohol **201** is followed simply by conditions to reduce the nitro group to amine (iron and acetic acid), cyclisation and loss of water in the acidic conditions, in situ, completing the sequence. A selection from the twenty-five examples given in the paper is shown in the Scheme 66. Aromatisation of the remaining partially saturated ring was achieved with selenium dioxide in hot 1,4-dioxane.

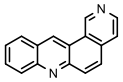


Scheme 66. Synthesis of substituted dihydro-dibenzo[*b,j*][1,7] phenanthrolines **202**.[125]

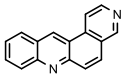
The pentacyclic compounds **203** were prepared as shown in Scheme 67. The luminescence spectra in solution and polycrystalline state were studied.[126]



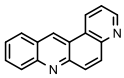
Scheme 67. Synthesis of dihydro-naphtho[2,1-*j*] [1,7]phenanthrolines **203**.[126]

5 .  Pyrido[3,4-*a*]acridine {benzo[*j*][2,7] phenanthroline}

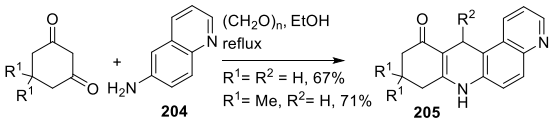
No natural products containing this tetracyclic system have been reported and there are no simple synthetic examples.

6.  Pyrido[4,3-*a*]acridine {benzo[*j*][3,7] phenanthroline}

There has been no synthetic work to produce this isomer, and no natural substances incorporating this skeleton have been reported.

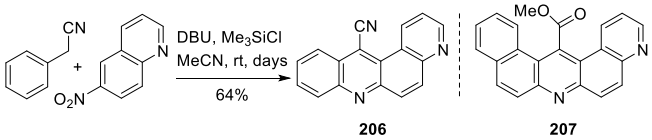
7.  Pyrido[3,2-*a*]acridine {benzo[*b*][4,7] phenanthroline}

Here again there are no natural substances that include this skeleton, however there are synthetic examples. The reaction of 6-aminoquinoline **204** with cyclohexane-1,3-diones and formaldehyde produces partially reduced pyrido[3,2-*a*]acridinones **205** (R^2 = H, Scheme 68).[127] Inclusion of an araldehyde in the reaction mixture, instead of the formaldehyde, produces corresponding products **205** (R^2 = Ar; 10 examples, 65-81%).[128]



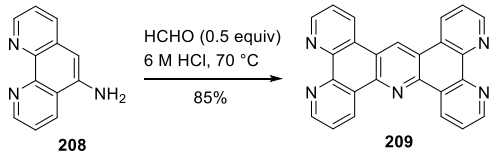
Scheme 68. A simple synthesis of hexahydropyrido[3,2-*a*]acridinones **205**.[127]

Benzylic carbanions react with nitroarenes under mild conditions in the presence of DBU and trialkylchlorosilanes to form tetra- and pentacyclic azaarenes. This reaction was used to make a range of fused systems from 6-nitroquinoline including cyano- **206** and methoxycarbonyl- **207** pyrido[3,2-*a*]acridines (Scheme 69).[114] For a discussion of the mechanism see Scheme 60.



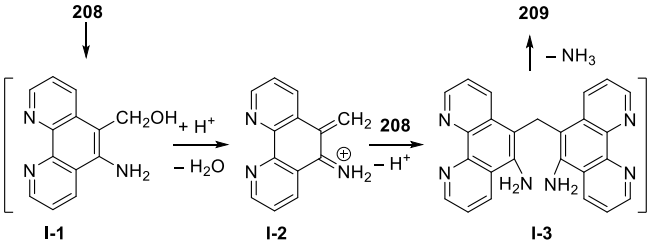
Scheme 69. The use of benzylic anions and 6-nitroquinoline to prepare pyrido[3,2-*a*]acridines and naphtho[1,2-*b*][4,7]phenanthrolines. [114]

Reaction of 5-amino-1,10-phenanthroline **208** with formaldehyde and acid produced the tetrapyrido[3,2-*a*:2',3'-*c*:3'',2''-*h*:2''',3'''-*j*]acridine **209** subsequently designated 'tpac' (Scheme 70).[129] The use of microwave heating reduced the synthesis reaction time from a week to 60 minutes – 70% yield.[130] The extended polycyclic bis-phenanthroline ligand led to the use of tpac in the formation of several metal complexes, in a monodentate or bidentate fashion (see below). Note: the structure of tpac comprises two pyrido[3,2-*a*]acridine units and also two pyrido[2,3-*c*]acridine units.



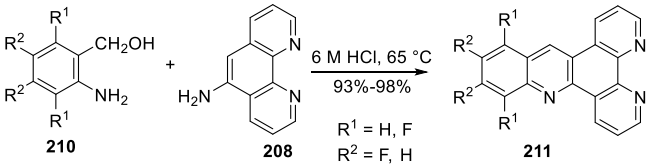
Scheme 70. Synthesis of tpac **209**.[129]

The synthesis is interpreted as beginning with electrophilic substitution *ortho* to the amino group of 5-amino-1,10-phenanthroline **208** leading to alcohol **I-1**, loss of water from which (→ **I-2**) and attack by a second equivalent of starting amine then producing **I-3**. Final acid-catalysed cyclising elimination of ammonia gives tpac **209** (Scheme 71).



Scheme 71. Postulated mechanism of the synthesis of tpac from 5-amino-1,10-phenanthroline

Analogous mono-dentate ligands **211**, the prototype being benzo[*b*]pyrido[3,2-*f*][1,7]phenanthroline (bpp) itself **211** (R^1 = R^2 = H), were prepared using 2-amino benzyl alcohols **210** with 5-aminophenanthroline **208**, as shown in Scheme 72.[131]

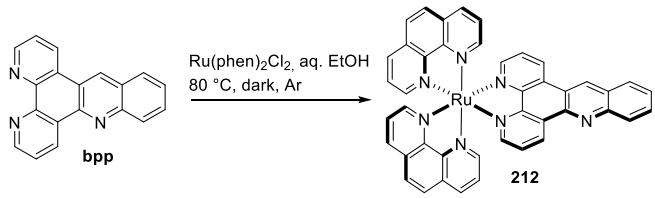


Scheme 72. Synthesis of benzo[*b*]pyrido[3,2-*f*][1,7]phenanthrolines **211**.[131]

Typical of the type of structure for complexes that have incorporated such ligands is **212**, $Ru(phen)_2(bpp)$ (Scheme 73).[131] Examples of the utility of complexes incorporating the ligands described above are the following: the complex $Cu(tpac)_2Cl$ was shown to cleave supercoiled pUC18 plasmid DNA in an oxidative manner by photoactivation with visible light;[132] the rigid dinuclear $[(tap)_2Ru(tpac)Ru(tap)_2]^{4+}$ complex (tap = 1,4,5,8-tetraazaphenanthrene) efficiently photodamages oligodeoxyribonucleotides containing guanine.[133] A review covers 'Ruthenium(II) complexes bearing fused polycyclic ligands: from fundamental aspects to

potential applications' and includes complexes involving ligands in this section, and others.[134]

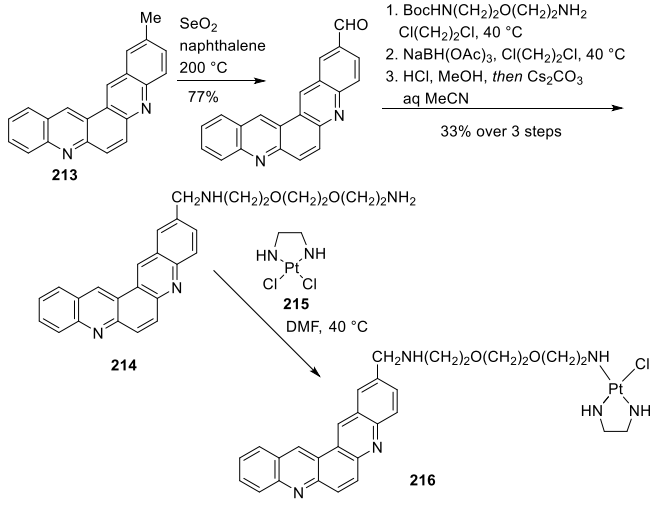
The complex $[Ru(bpp)(bpy)_2]^{2+}$, underwent $2e^-$ and $2H^+$ reduction, generating $[Ru(bppHH)(bpy)_2]^{2+}$, in response to visible light irradiation in solution in aqueous acetonitrile with triethylamine.[135] The pyridine ring of the acridine unit was regioselectively reduced to the 1,4-dihydro level.



Scheme 73. Formation of a ruthenium complex **212** of bpp.[131]

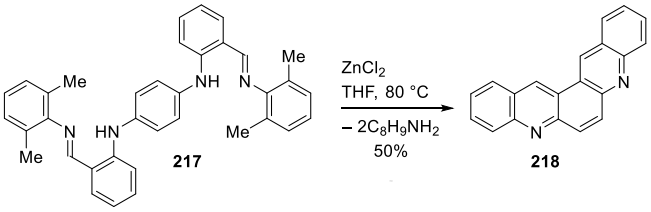
A complex containing a tpac unit was made by synthesis using a preformed ruthenium complex. Thus, $[(tap)_2Ru(5\text{-amino-}1,10\text{-phenanthroline}]$ gave $[(tap)_2Ru(tpac)]^{2+}$ by reaction with 5-amino-1,10-phenanthroline and formaldehyde promoted by 6 M hydrochloric acid at 90 °C (compare with the method in Scheme 70).[136]

An entirely different type of complex **216**[137] was prepared from primary amine **214** by reaction with platinum source **215**. Scheme 74 shows how 2-methyldibenzo[*b,j*][4,7] phenanthroline **213**[136] was converted into **216** in five steps. The complex **216** interacts with quadruplex DNA *via* a dual "noncovalent/covalent binding mode".



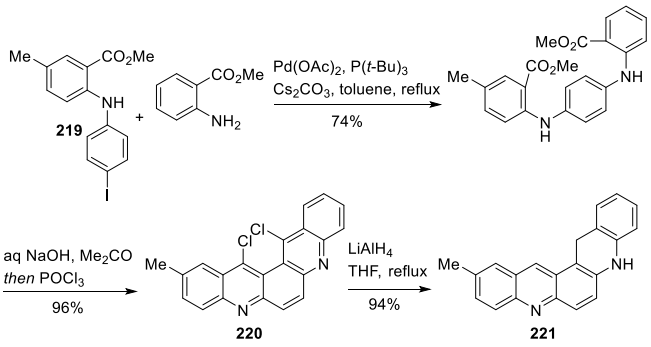
Scheme 74. Formation of a platinum complex **216**.[137]

Several polycyclic aza-aromatic compounds were produced via cyclization reactions of *ortho*-arylaminophenyl Schiff bases e.g. **217**, promoted by zinc chloride, one example producing the quinacridine **218**[123] (quinacridines are pyridoacridines with an extra fused benzene ring) as is shown in Scheme 75. Coordination of each imine nitrogen to zinc chloride activates the system for two intramolecular electrophilic cyclizations, with subsequent elimination of two equivalents of 2,6-dimethylaniline.



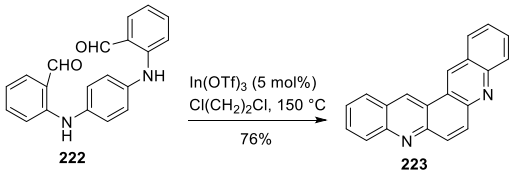
Scheme 75. Conversion of *ortho*-arylaminophenyl Schiff base **217** into a quinacridine **218**.[123]

Quinacridines can also be assembled in a stepwise fashion. Thus, Buchwald-Hartwig cross-coupling of iodoaniline **219** and methyl anthranilate produced a diester, double ring closure with phosphoryl chloride after ester hydrolysis then giving the dichloro-pentacycle **220**; the halogen could be removed but at the expense of reduction of one of the rings, affording **221**, but this is easily aromatized to give 2-methyldibenzo [*b,j*][4,7]phenanthroline (Scheme 76).[138]



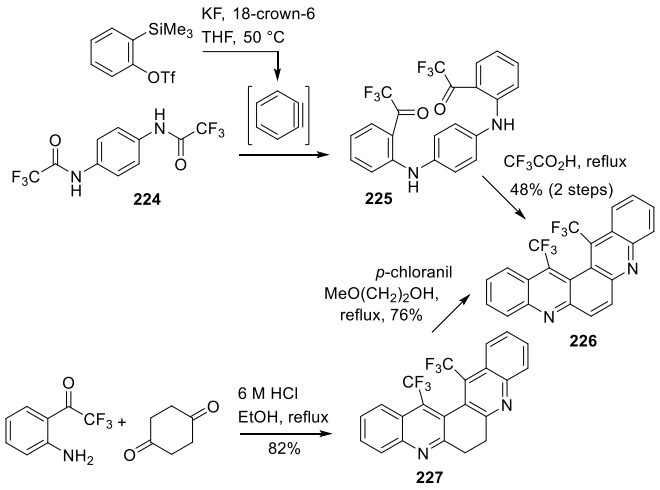
Scheme 76. The assembly of a dihydro-quinacridine **221** from methyl anthranilate.[138]

Making the same two bonds to reach quinacridine **223** can be achieved easily using dialdehyde **222** and indium triflate, albeit at high temperature (Scheme 77).[139]



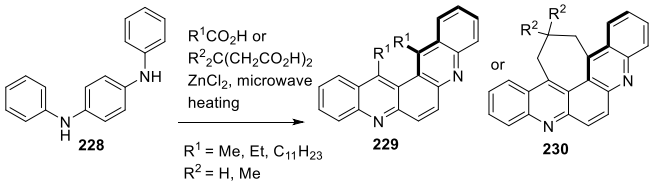
Scheme 77. A synthesis of dibenzo[*b,j*][4,7]phenanthroline **223**.[139]

The cyclisation substrate **225** was prepared by benzyne insertion into *para*-phenylenediamine-bis(trifluoroacetamide) **224**. Double ring closure to **226** was secured with hot trifluoroacetic acid.[140] An exactly comparable double ring closure but with methyl instead of trifluoromethyl, was brought about with catalytic sulfuric acid in refluxing acetic acid.[121] Product **226** can also be accessed via reaction of *ortho*-aminophenyl trifluoromethyl ketone with cyclohexane-1,4-dione giving **227**, easily dehydrogenated (Scheme 78). The formation of **227** can be seen as a double Friedländer reaction.

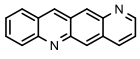


Scheme 78. Two syntheses of dibenzo[*b,j*][4,7]phenanthroline **226**.[140-141]

The condensing cyclisations of *N,N'*-diphenyl-*para*-phenylenediamine **228** with carboxylic acids or dicarboxylic acids, produces helical species, by virtue of the steric interference between the R^1 groups or constraint from the introduced ring; structures **229** and **230** are examples (Scheme 79).[140, 141]



Scheme 79. Syntheses of helical dibenzo[*b,j*][4,7]phenanthrolines **229** and **230**.[141]

8.  Pyrido[2,3-*b*]acridine

There is very little published work on simple (tetracyclic) examples of this ring structure. The patent literature contains many examples of elaborated versions with extra benzene/ pyridine ring(s) fused, but these are not discussed here.

Alkaloids such as deoxyascididemine and eilatin (Fig. 4) from the Australian ascidian *Polysyncraton echinatum*, contain both pyrido[2,3-*b*]acridine and pyrido[2,3,4-*kl*]acridine nuclei and all the other examples of this situation are considered under the latter heading.[142] Quinones **231**[143] and **232**[144] were amongst several re-prepared to assess antituberculosis activity (Fig. 11).[145]

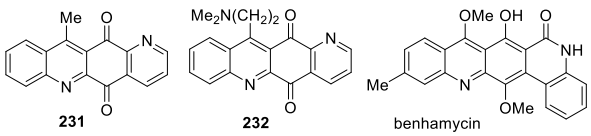
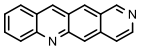
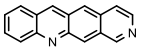


Figure 11. Structures of benhamycin and related compounds.[142-146]

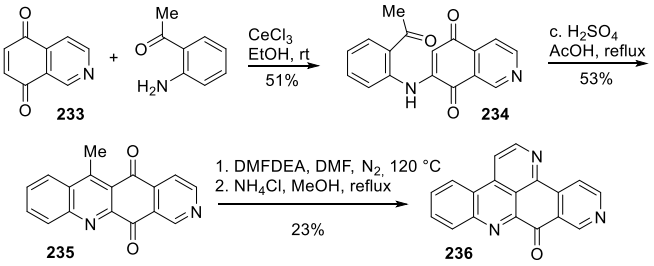
9.  Pyrido[3,4-*b*]acridine

There has been no synthetic work on this isomer, but there is an 'intensely yellow' alkaloid, isolated from a terrestrial *Streptomyces* sp., which incorporates the skeleton and was named benhamycin (Fig. 11).[146] The compound has an additional fused benzene ring in the pentacyclic structure which was established by spectroscopic analysis, including extensive ^{1}H and ^{13}C NMR measurements.

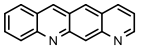
10.  Pyrido[4,3-*b*]acridine

There has been little synthetic work on this isomer, and no natural substances incorporating this skeleton have been reported.

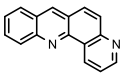
The quinone **235** was constructed from the isoquinoline-quinone **233**[147] thus, reaction with 2-aminoacetophenone in the presence of cerium trichloride produced **234** and this was ring closed to **235** in acid. A fifth ring was added utilizing the reactivity of the methyl group, located as it is at C-4 of the pyridine unit, and in the process producing a product **236** (Scheme 80) which now also has a pyrido[2,3,4-*kl*]acridine moiety and is an analogue of ascididemine.



Scheme 80. Construction of a pyrido[4,3-*b*]acridine-5,12-dione **235** and its conversion into 9*H*-quino[4,3,2-*de*][1,8]phenanthrolin-9-one **236**. [147]

11.  Pyrido[3,2-*b*]acridine

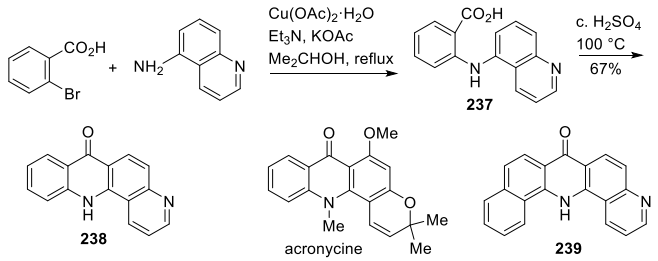
There are no relevant examples of compounds containing this structure and there are no natural products either.

12.  Pyrido[2,3-*c*]acridine {benzo[*b*][1,7-phenanthroline}

Note: the chemistry of tpac **209** (Scheme 70) which includes both two pyrido[2,3-*c*]acridine and two pyrido[3,2-*a*]acridine units, is dealt with in the pyrido[3,2-*a*]acridines, Section 7.

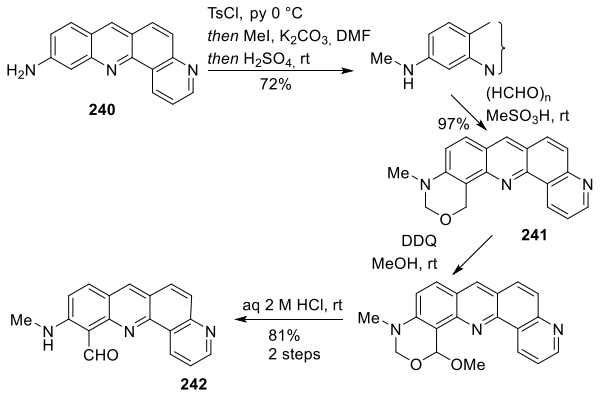
In work to prepare analogues of the pyranoacridone alkaloid acronycine, from*Acronychia baueri* Schott (Rutaceae), which has antitumor properties, the tetracyclic acridone **238** was assembled, the key step being the intramolecular aroylation

(**237→238)** (Scheme 81).[148] Using 1-bromonaphthalene-2-carboxylic acid instead of 2-bromobenzoic acid led to benzologue **239**.[149]



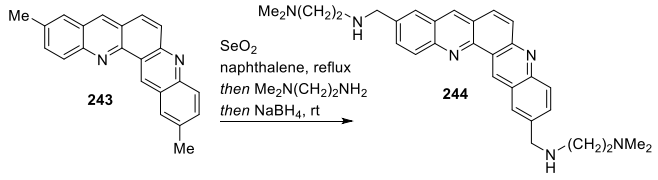
Scheme 81. Synthesis of an analogue **238** of acronycine.[148]

Amine **240**[150] was converted into the synthetically useful aldehyde **242** as shown in Scheme 82.[151] The formation of **241** illustrates the regioselectivity of electrophilic attack on the aminopyrido[2,3-*c*]acridine.

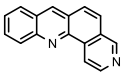


Scheme 82. Introduction of an aldehyde function at C-11 of a pyrido[2,3-*c*]acridine **242**.[151]

A range of diamine ligands, e.g. **244**, based on *meta*-quinacridine were prepared and evaluated for their G-quadruplex binding properties.[152] The Scheme 83 shows how methyl substituents were oxidized to aldehyde (55% for oxidation of **243**) and then reacted with various amines (*n*-$PrNH_2$, $Me_2N(CH_2)_2NH_2$, imidazol-3-yl$(CH_2)_2NH_2$, indol-3-yl$(CH_2)_2NH_2$, etc.) followed by sodium borohydride reduction; structure **244**, for example, one of thirteen prepared, was formed in 28% yield for the last two steps. Comparable diamines were attached to two aminoglycosides, one such exhibiting strong binding to the P6.1 element of human telomerase RNA.[153]



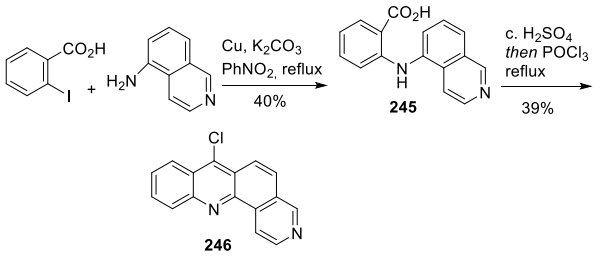
Scheme 83. Oxidation of methyl groups on a dibenzo[*b,j*][1,7]phenanthroline.[152]



13. Pyrido[3,4-*c*]acridine {benzo[*b*][1,8] phenanthroline}

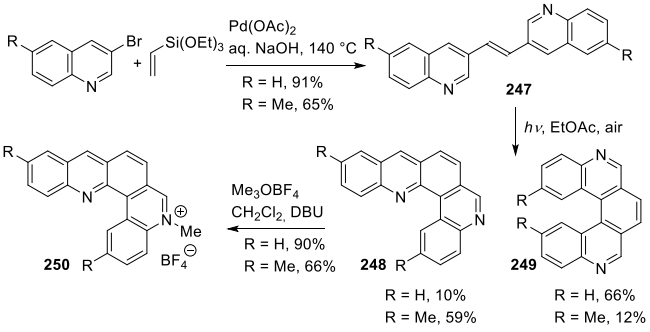
Note, that natural products related to amphimedine (Fig. 5), for example petrosamine B (Fig. 8) incorporate both pyrido[3,4-*c*]acridine *and* pyrido[2,3,4-*kl*]acridine units; they are dealt with in Section 3 on pyrido[2,3,4-*kl*]acridines.

Simple examples of pyrido[3,4-*c*]acridines were prepared, as potential amebicides,[154] as potential antitumor agents,[155] as antileukemia agents,[156] earlier than the period under review, but are usefully summarized briefly here. Each piece of work utilized essentially the same synthetic strategy, shown in Scheme 84. Compound **246** was obtained by Ullmann reaction of 2-iodobenzioc acid and 5-aminoisoquinoline to the acid **245**, ring closure with hot concentrated sulfuric acid and then conversion of the resulting ketone into **246** with phosphoryl chloride. The chlorine in **246** was displaced with various amines to produce the compounds of medicinal interest.



Scheme 84. Synthesis of a chloro-pyrido[3,4-*c*]acridine **246**.[155]

In the 21st Century, the ring system has been produced incidentally in studies of helical substances in the context of supramolecular chemistry and catalysis – various [5]heli-viologen isomers were produced by quaternisations.[157-159] The construction of precursors **247** for photochemical cyclisations was achieved with a Hiyama–Heck coupling of a 3-bromoquinoline and vinyltriethoxysilane. Two isomers **248** and **249** were formed in the photo-cyclisation and aerial oxidation (Scheme 85). The one with the embedded pyrido[3,4-*c*]acridine nucleus **248** underwent mono *N*-alkylation at the accessible nitrogen giving salt **250**, but required the presence of DBU to prevent protonation of the 'cove' nitrogen, possibly by adventitious fluoroboric acid.



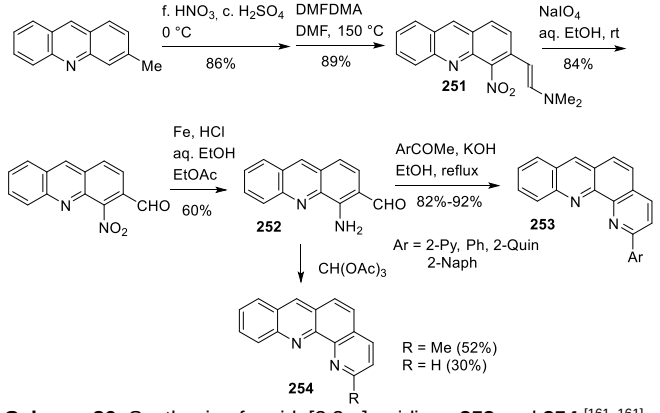
Scheme 85. Construction of a dibenzo[*b,k*][1,8]phenanthroline **248** and its quaternisation.[159]

14. Pyrido[4,3-*c*]acridine {benzo[*b*][1,9] phenanthroline}

There has been no synthetic work to produce this isomer and no natural substances incorporating this skeleton have been reported.

15. Pyrido[3,2-*c*]acridine {benzo[*b*][1,10] phenanthroline}

4-Aminoacridine-3-carbaldehyde **252** has been the starting point for the preparation of several pyrido[3,2-*c*]acridines and is itself prepared from 3-methylacridine, as shown in Scheme 86.[160] Regioselective nitration and reaction with DMFDMA (cf. Scheme 18) produces **251**. Next, periodate cleavage of the enamine double bond and reduction of the nitro gave **252**. Friedländer synthesis using **252** with aryl methyl ketones produces 2-aryl products **253** in high yields. Reaction of **252** with triacetylmethane gives a mixture of 2-methylpyrido[3,2-*c*]acridine (**254**, R = Me) and pyrido[3,2-*c*]acridine (**254**, R = H) itself.[161]



Scheme 86. Synthesis of pyrido[3,2-*c*]acridines **253** and **254**.[161, 161]

Extending the method further to benzo[*b*]cycloalkanones and 3,4-dihydro-1(2*H*)-anthracenone, produced structures **255** and **256**, respectively (Fig. 12);[162] aromatisation of **256** was achieved with Pd/C at 200 °C.

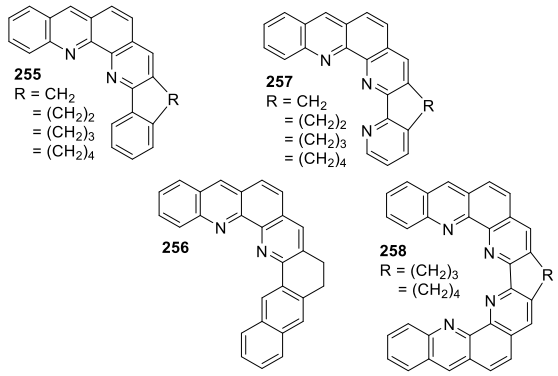


Figure 12. Structures of pyrido[3,2-*c*]acridines **255-258**.[162, 163, 165]

Extrapolation to pyrido[*b*]cycloalkanones similarly provided products **257** and full aromatization of the product with R = $(CH_2)_2$ was achieved with Pd/C in nitrobenzene at 200 °C.[163] A study of the reactions of ligands **257** with ruthenium(III) chloride trihydrate produced complexes of the form $[Ru(L)_2]^{2+}$ in favourable cases.[164] Reaction of two equivalents of the amino-aldehyde **253** with cycloheptane- and cyclooctane-1,2-diones produced structures **258**.[165] The use of simpler 1,2-diones gave complex mixtures from which some pyrido[3,2-*c*]acridine could be isolated.

Diacetyl benzenes were also subjected to the Friedländer sequence with amino-aldehyde **252**. This produced intriguing ligands **259-261** (Fig. 13), from *ortho*-, *meta*- and *para*-diacetylbenzene, respectively.[166]

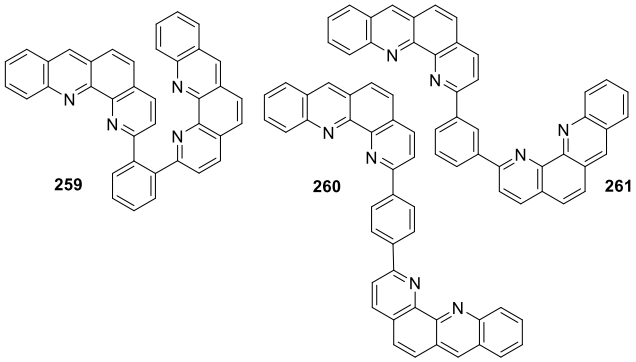
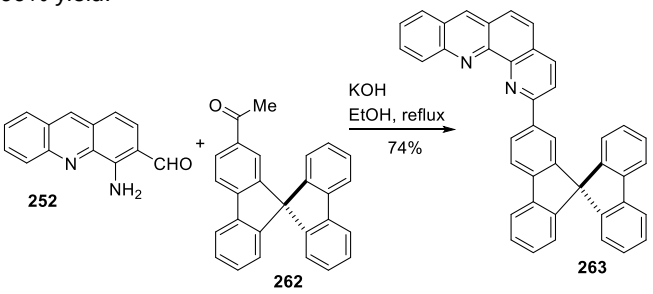


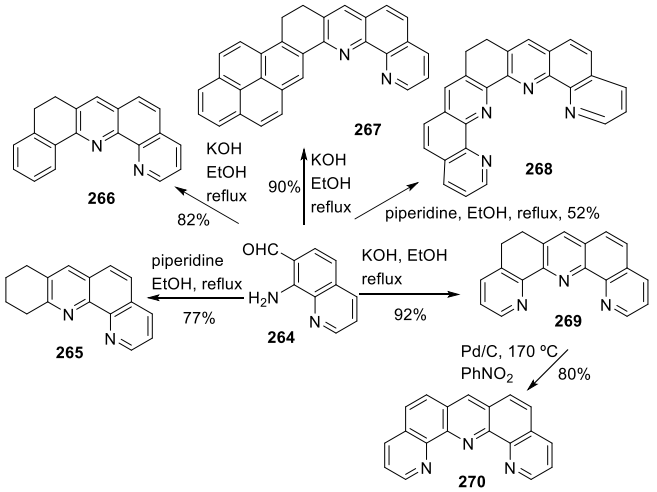
Figure 13. Products **259-261** from Friedländer reactions of diacetylbenzenes and 4-aminoacridine-3-carbaldehyde **252**.[166]

As a final example of the use of the Friedländer reaction using **252**, 2-acetyl-9,9'-spirobifluorene **262** was converted into **263** in 74% yield (Scheme 87).[167] Reaction with 2,2'-diacetyl-9,9'-spirobifluorene proceeded by analogy, at both side-chains, in 99% yield.[168]



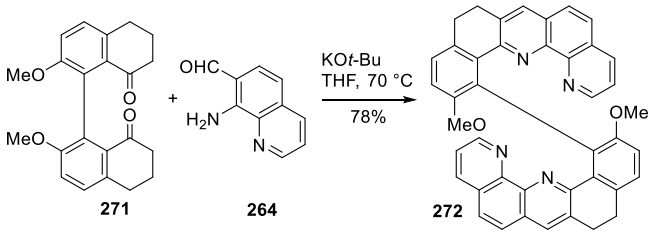
Scheme 87. Product **263** from Friedländer reaction of a spiroketone **262** with 4-aminoacridine-3-carbaldehyde **252**.[167]

8-Aminoquinoline-7-carbaldehyde **264** has also been used in Friedländer reactions to enter this series of pyridoacridines (Scheme 88). In the simplest case, with cyclohexanone, the tetrahydro-derivative **265** is formed.[169] With 1-tetralone, **266** is formed and with 9,10-dihydrobenzo[*a*]pyren-7(8*H*)-one, structure **267** results.[170] Cyclohexane-1,2-dione produces **268** incorporating two equivalents of **264**.[166] and reaction with 5,6,7,8-tetrahydroquinolin-8-one gives **269**,[170] precursor to dipyridoacridine **270**.



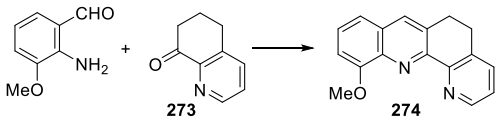
Scheme 88. The use of 8-aminoquinoline-7-carbaldehyde **264** and various six-membered ketones to prepare polycyclic ligands **265-270**.[169, 170, 173]

The amino-aldehyde **264** was combined with the bis-tetralone **271** to prepare the chiral helicene-like **272** and iron and ytterbium complexes therefrom (Scheme 89).[171]



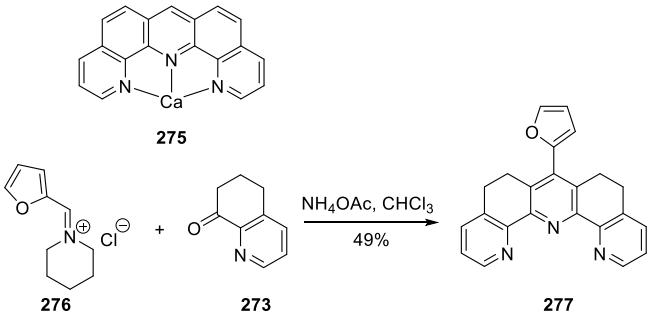
Scheme 89. Chiral product **272** from Friedländer reactions of a bis-tetralone **271** with 8-aminoquinoline-7-carbaldehyde **264**.[171]

2-Amino-3-methoxybenzaldehyde is a third *ortho*-amino-aldehyde that has been used to construct pyrido[2,3-*c*]acridines. Thus, with 5,6,7,8-tetrahydroquinolin-8-one **273** compound **274** was produced, with the idea that dehydrogenation and demethylation would produce a strong ligand in the tradition of 8-hydroxyquinoline (Scheme 90). Unfortunately, during attempted ether cleavage with hydrogen bromide, some dehydrogenation occurred producing an inseparable mixture.[172]



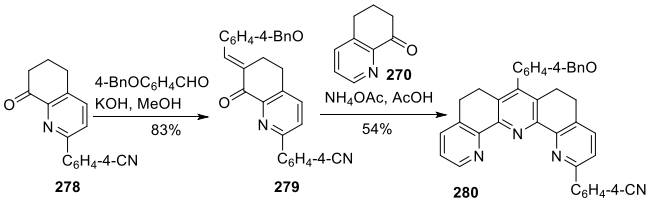
Scheme 90. Friedländer reaction of 5,6,7,8-tetrahydroquinolin-8-one **273** with 2-amino-3-methoxybenzaldehyde.[172]

Dipyrido[4,3-*b*;5,6-*b*]acridine[173] (dpa) **270**, often referred as 'dipyridoacridine', can be considered a tridentate homologue of 1,10-phenanthroline. The 'preorganised' donor nitrogens make for strong coordination to larger cations such as Ca^{2+} (structure **275**) and La^{3+}.[174] A furan-substituted tetrahydro-dpa **277** was made by reacting iminium salt **276** with two equivalents of tetrahydroquinolone **273** (Scheme 91).[175]



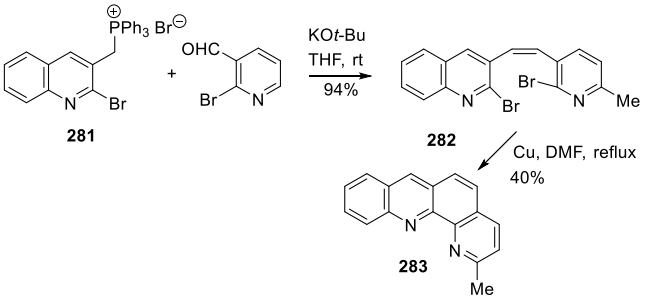
Scheme 91. Quino[8,7-*b*][1,10]phenanthrolines complex large cations.[175]

A classical pyridine ring synthesis (**279→280**) provided unsymmetrically substituted tetrahydro-dpas such as **280**, illustrated in the Scheme 92 with 5,6,7,8-tetrahydroquinolin-8-one itself and a 2-substituted-5,6,7,8-tetrahydroquinolin-8-one **278**.[175]



Scheme 92. Synthesis of tetrahydro-quino[8,7-*b*][1,10] phenanthroline **280**.[175]

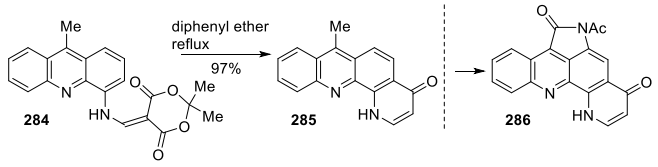
An entirely different route to the core system is illustrated in Scheme 93 which shows one example from six detailed.[176] Wittig reaction between the 2-bromoquinoline triphenylphosphonium salt **281** and 2-bromopyridine-3-carbaldehyde produced the *cis* alkene **282** which was cyclized to **283** by means of copper in hot DMF (Scheme 93).



Scheme 93. An alternative route for the construction of a pyrido[3,2-*c*]acridine **283**.[176]

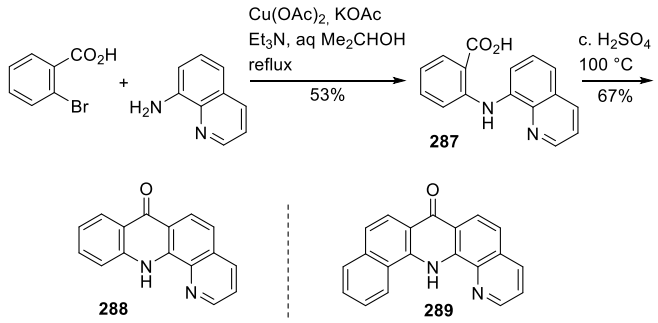
A route in which one of the pyridine rings of **285** was formed at a late stage started from 9-methylacridine (Scheme 94). 4-Nitration, reduction and then the amine was transformed into the cyclization precursor **284** by reaction with Meldrum's acid and trimethoxymethane. Thermolysis of **284** produced the

tetracyclic system **285** – an example of a standard route to 4-quinolones.[177] A comparable ring construction was even possible after prior construction of an extra five-membered lactam, giving product **286**, the work being relevant to the plakinidine alkaloids.[178]



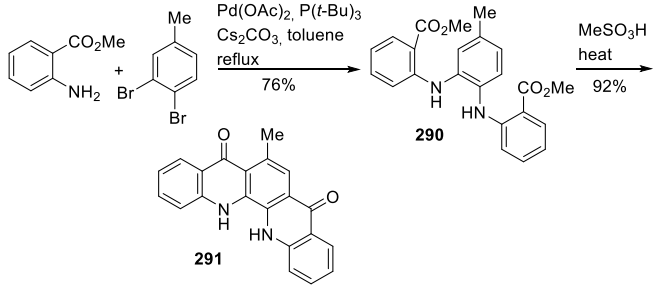
Scheme 94. Synthesis of a pyrido[3,2-*c*]acridone **285**.[177]

A copper-catalysed amination and a Friedel–Crafts cyclisation figured in the preparation of acid **287** and its conversion into the pyridoacridone **288** (Scheme 95).[148] An analogous sequence using 1-bromonaphthalene-2-carboxylic acid, instead of 2-bromobenzoic, led to **289**.[149]



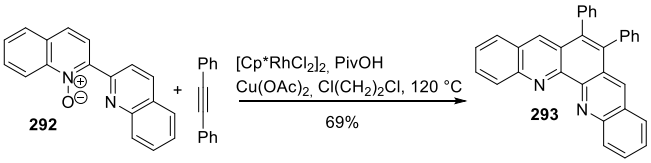
Scheme 95. Conversion of 8-aminoquinoline into a pyrido[3,2-*c*]acridone **288**.[148]

Moving to other methods for the construction of quinacridines (an extra benzene ring) the *ortho*-phenylene diamine derivative **290** was made by Buchwald-Hartwig double amination of an *ortho*-dibromobenzene with methyl anthranilate and the two pyridone rings in **291** made by a double Friedel–Crafts process (Scheme 96).[138] Reduction of the pyridones with sodium and then oxidation gave a fully aromatic quinacridine.



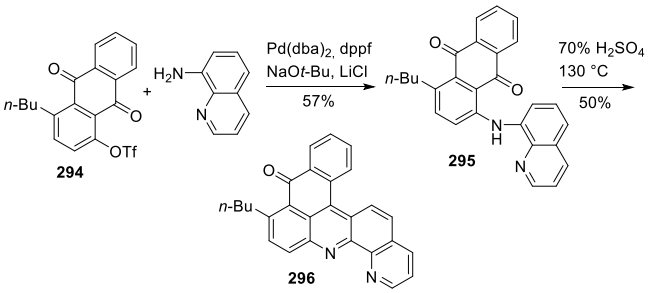
Scheme 96. Double acylative cyclisation to produce a dibenzo[*b,j*][1,10]phenanthroline-dione **291**.[138]

In studies of rhodium-catalysed reactions of pyridine *N*-oxides, a couple of examples produced extended pyrido[2,3-*c*]acridines, as in structure **293** from **292** (Scheme 97).[179]



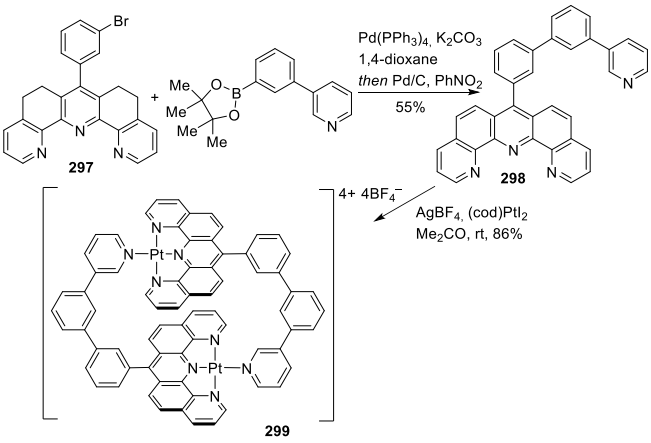
Scheme 97. Reaction of 2,2'-diquinoline *N*-oxide **292** with an acetylene.[179]

The quinone-triflate **294** was aminated by a Buchwald-Hartwig cross-coupling with 8-aminoquinoline and the product **295** closed to the heptacyclic compound **296** under strongly acidic conditions (Scheme 98).[180]



Scheme 98. A one-off route to a 9*H*-anthra[1,9-*bc*][1,10] phenanthrolinone **296**.[180]

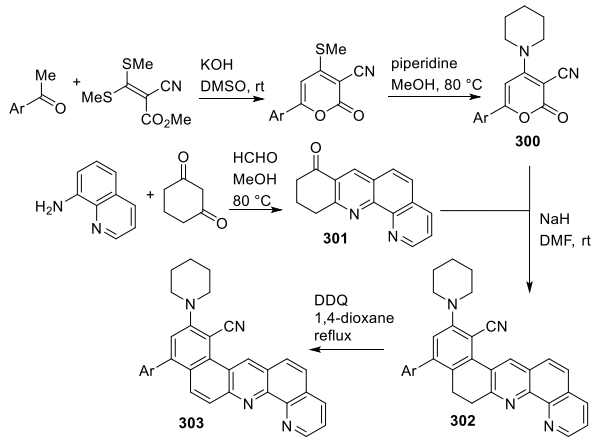
The extended ligand **298** (Scheme 99), synthesised as shown in Scheme 99 starting from **297**, was used to produce a bis-Pt(II) dimer **299** with an extended π-face contact area, which acts as a receptor with high affinity toward iodinated aromatic compounds.[181]



Scheme 99. The construction of a polycyclic system **298** and its platinum complex **299**.[181]

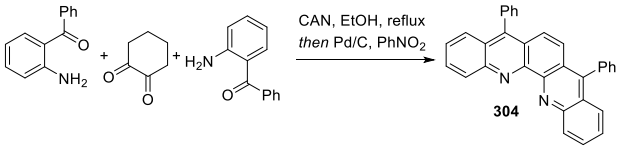
Naphtho[2,1-*b*][1,10]phenanthrolines **303**, termed NAPs, were synthesized as shown in Scheme 100. In particular, NAP-3 (Ar = 4-bromophenyl) was shown to be a dual colorimetric and ratiometric fluorescent probe for selective and

'direct' visualization of labile iron(III) pools in the multicellular organism, *Caenorhabditis elegans*.[182] The 2-pyrone **300** was prepared by a standard route then reacted with ketone **301** forming **302**, aromatization of which gave the NAPs **303**.



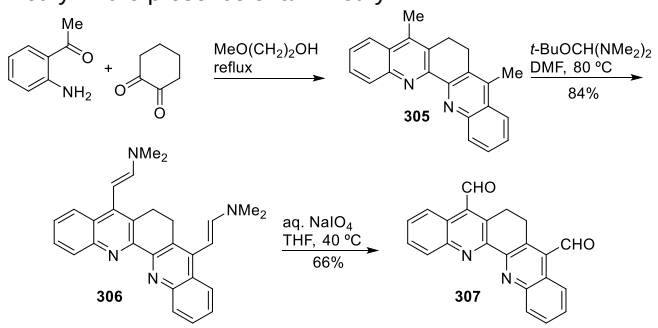
Scheme 100. Synthesis of naphtho[2,1-*b*][1,10]phenanthrolines **303**.[182]

Of the heteroleptic copper complexes made from various ligands, that with 5,8-diphenyl-6,7-dihydrodibenzo [*b,j*][1,10] phenanthroline **304** was the best photosensitizer in a photocatalytic Cu-Fe water reduction system.[183] Compound **304** was made from cyclohexane-1,2-dione and two equivalents of 2-aminobenzophenone (Scheme 101).



Scheme 101. Synthesis of quino[8,7-*b*][1,10]phenanthroline **304**.[183]

The conversion of pyridine (or quinoline) 2- or 4-methyl groups into enamines (cf. Scheme 18) can also be used, by subsequent oxidation, as a means for conversion into aldehyde groups. Thus, pentacycle **305** was reacted with Bredereck's reagent (*tert*-butoxybis(dimethylamino)methane) giving **306**, then oxidized to dialdehyde **307** (Scheme 102).[184] This work also showed preferential reaction of a pyridine 4-methyl in the presence of a 2-methyl.



Scheme 102. Conversion of quinoline methyl into aldehyde.[184]

Acknowledgments

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Keywords: Heterocycles • Acridine • Pyridine • Quinoline• Natural Products

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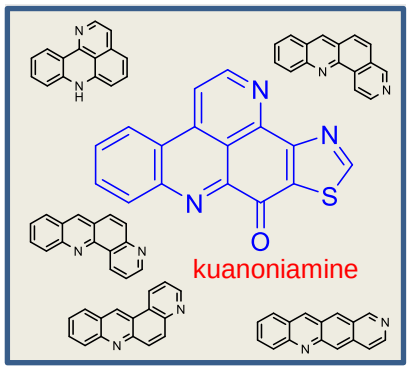
Layout 1:

MINIREVIEW

The pyridoacridines constitute a characteristic motif of a large family of heterocyclic compounds isolated mainly from marine sources. The new isolations, syntheses and biological evaluations performed during the 21st Century have been reviewed



Key Topic Pyridoacridines*

*John A. Joule and Mercedes Álvarez**

Page No. – Page No.

Title Pyridoacridines in the 21st Century

*Pyridoacridines, an important scaffold of bioactive Natural Products