

The synthesis of quinones

PETER T. GALLAGHER

Eli Lilly & Co. Ltd., Lilly Research Centre, Windlesham, Surrey GU20 6PH, UK

Reviewing the literature published between
1 January 1991 and 31 December 1995

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1 Synthesis of benzo-1,4-quinones

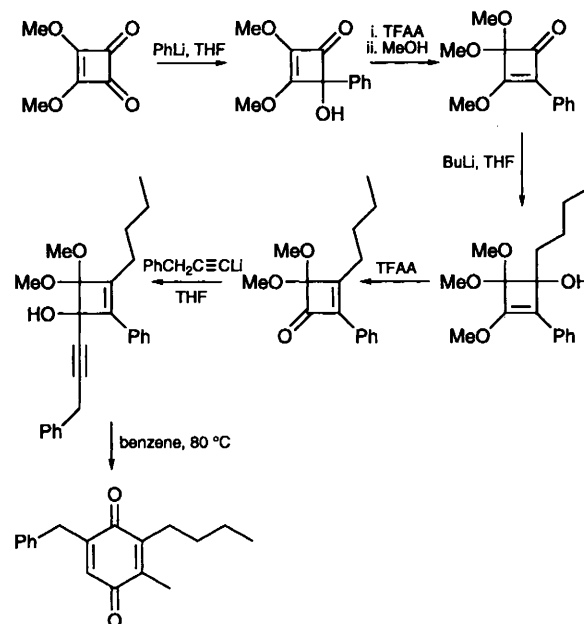
During the period under review developments in the synthesis of benzoquinones from squaric acid derivatives have occurred. From observations on the thermolysis of 3-alkoxy-4-alkynyl-4-hydroxycyclobutenones, this reaction has been generalised for the synthesis of a variety of substituted benzoquinones (**Scheme 1**).¹⁻³

Cyclobutenones may also be transformed in the presence of tributyltin methoxide to stannylquinones and these in turn undergo palladium-copper co-catalysed cross-coupling to give aryl and heteroaryl quinones in yields in the range 48–91% (**Scheme 2**).⁴

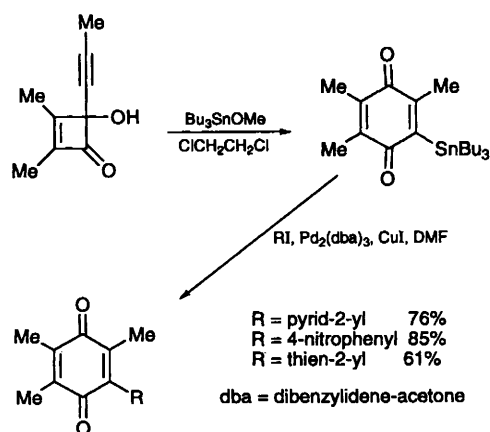
A route for the regioselective synthesis of poly-substituted quinones utilising a benzannulation reaction of alkenyl chromium carbene complexes and 1-phenyl-2-trimethylsilylethyne, followed by iodination and then Stille or Suzuki cross-coupling has been developed (**Scheme 3**).⁵

Similarly, ferrocenyl acetylene undergoes benzannulation with aryl and alkenyl chromium carbonyl complexes to produce ferrocenyl quinones.⁶ Other routes to quinones which have been developed include one to prenylated quinones involving lithiation of dimethylaminophenols and subsequent reaction with alkenals to produce prenyl alcohols which are hydrogenolysed and oxidised with Fremy's salt (potassium nitrosodisulfonate – ON(SO₃K)₂) to give quinones (**Scheme 4**).⁷

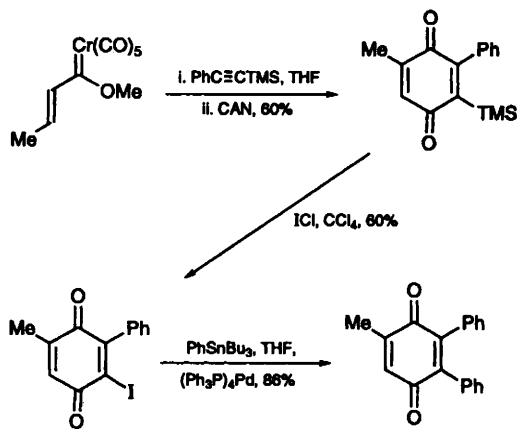
Facile double Michael addition induced cyclopropanation reactions of unsaturated esters have provided easy access to the tricyclo[5.1.0.0^{3,5}]octane-2,6-dione. These bis-halocyclopropyl diketones are readily ring opened to give quinones with tributyltin hydride (**Scheme 5**).⁸



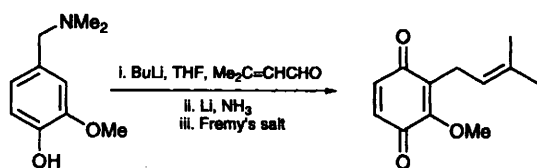
Scheme 1



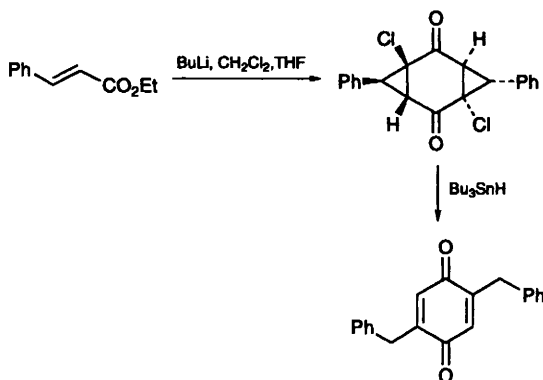
Scheme 2



Scheme 3



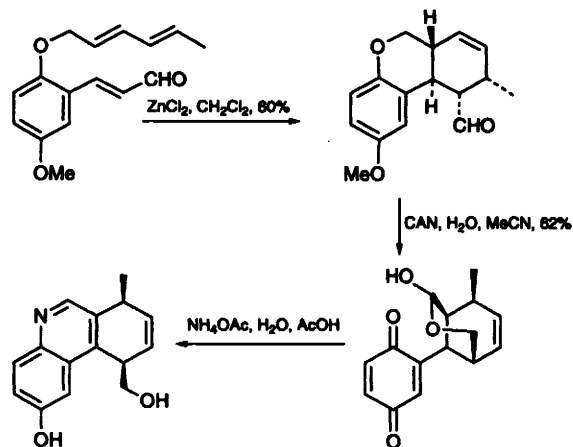
Scheme 4



Scheme 5

Pummerer type rearrangement of *p*-sulfinylphenol derivatives induced with trifluoroacetic anhydride gives a 1:1 mixture of the corresponding 1,4-quinone and the 1,4-dihydroquinone, which when subjected to mild oxidation provide high yields of the 1,4-quinones. A variety of substituents on sulfur are tolerated though low yields of quinone were reported with 4-nitrophenylsulfinylphenol.⁹

As part of efforts directed towards the synthesis of dynemicin A, Danishefsky utilised a 1,4-quinone to synthesise a quinoline precursor of dynemicin A. This required the synthesis of an appropriately substituted benzopyran, which was subjected to ceric ammonium nitrate (CAN) oxidation to provide a 1,4-quinone (Scheme 6).¹⁰

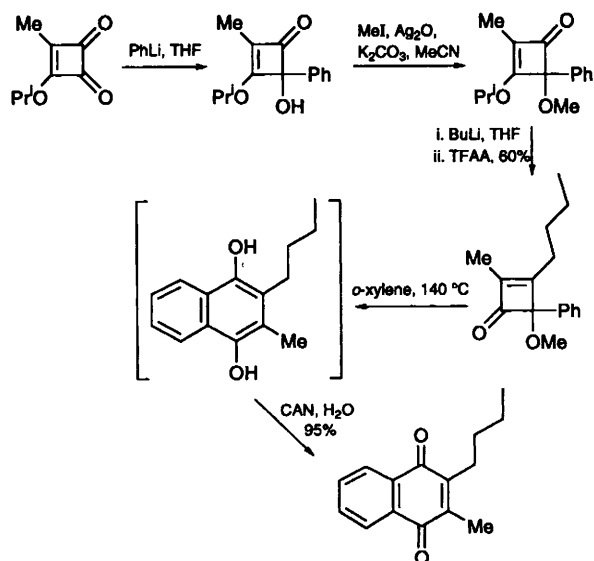


Scheme 6

2 Synthesis of naphthoquinones

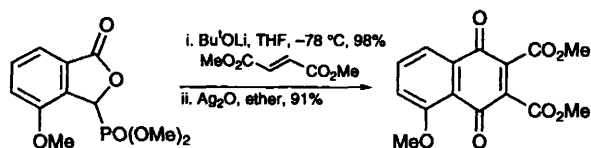
The synthesis of benzoquinones from cyclobutenediones (Scheme 1) is also amenable to the synthesis of naphthoquinones. Thus starting from a cyclobutenedione, consecutive addition of an aryllithium followed by an alkyl lithium and then thermal rearrangement at 140 °C produces a bis-1,4-naphthol which is readily oxidised with aqueous ceric ammonium nitrate (Scheme 7).

2-Lithiofuran has also been used in this reaction when the products are benzo[*b*]furandiones.³ When a *tert*-butyl ether is used instead of an isopropyl ether in this type of synthesis, hydroxynaphthoquinones result. These, when subjected to Hooker oxidation (hydrogen peroxide–sodium carbonate–copper sulfate), are oxidatively rearranged to the isomeric hydroxyanthraquinones thereby allowing the synthesis of both hydroxylated regioisomers from the cyclobutenedione route.¹¹



Scheme 7

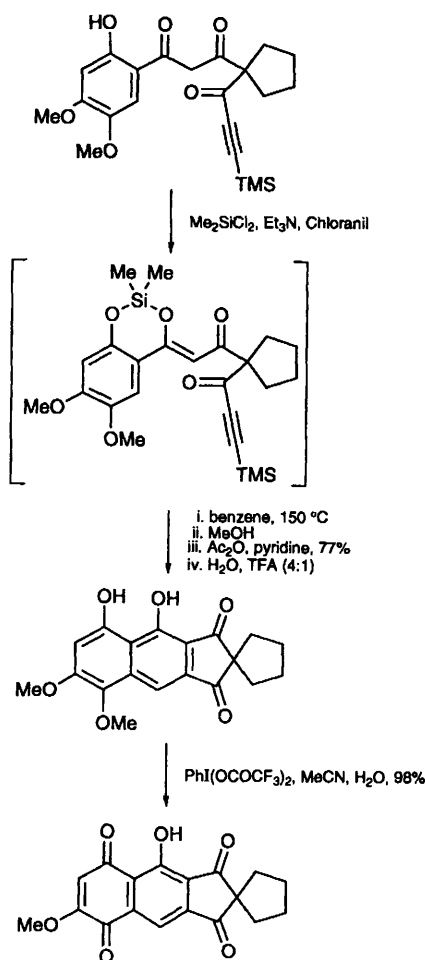
Naphtho-1,4-quinones are efficiently synthesised by regioselective reaction between dimethylphthalide-3-phosphonates and electron deficient alkenes (**Scheme 8**). A variety of alkenes may be used in this reaction: as well as fumarate (shown in the Scheme), maleate, acrylamides, vinyl ketones and unsaturated esters have all been successfully annulated.¹²



Scheme 8

A novel oxidative intramolecular cycloaddition of silylene protected dihydroxystyrene derivatives has provided a new route to the ABCD ring system of fredericamycin. The reaction appears quite general and the intermediate acetoxynaphthalene derivatives may also be isolated (**Scheme 9**).¹³

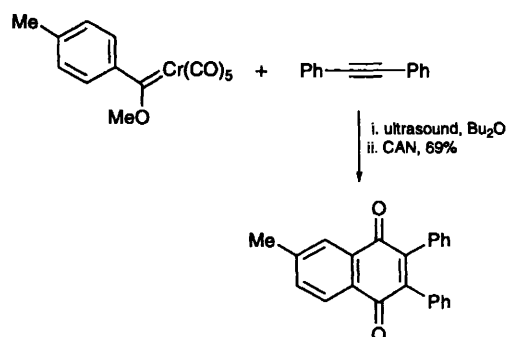
Construction of a hydroxynaphthalene prior to oxidation was the route taken to prepare



Scheme 9

aegyptinones A and B. Thus a photochemical aromatic annulation between diazoacetophenones and silyloxyacetylenes provides the hydroxy-naphthalenes, which were subjected to low temperature oxidation with oxygen to effect quinone formation.¹⁴

The Dötz chromium carbene annulation reaction has been enhanced by the application of ultrasound. Thus chromium carbonyls and alkynes can be transformed in minutes to naphthoquinones and furanoquinones in moderate to good yields (**Scheme 10**).¹⁵



Scheme 10

Intramolecular benzannulation reactions have also been reported utilising manganese carbene complexes in place of chromium.¹⁶

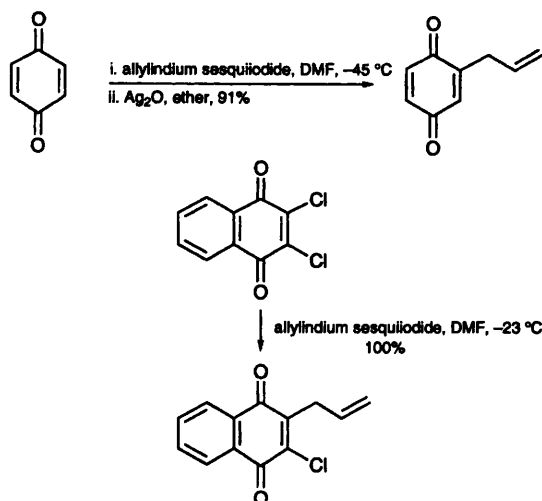
2.1 Substitution of benzoquinones and naphthoquinones

Substitution of quinones with allylic indium reagents has been shown to be a versatile way of introducing allyl, prenyl and geranyl groups to quinones. Reaction proceeds by allylation at the quinone carbonyl followed by facile [3,3]-sigmatropic rearrangement to the 2-allyl-1,4-naphthols which are routinely oxidised to the allylquinones. Direct displacement of chlorine from quinones may also be effected with allylindium sesquiodide (**Scheme 11**).¹⁷

Similarly allylation of quinones has been achieved with allyl(trifluoro)silanes and TBAF. Here, as with indium reagents, initial attack is at the quinone carbonyl followed by [3,3]-sigmatropic rearrangement; oxidation of the intermediate hydroquinone is with ferric chloride.¹⁸

2-Alkyl-naphtho-1,4-quinones may be synthesised by reacting trialkylboranes with unsubstituted naphthoquinones followed by oxidative work-up. Yields are variable and mono- and di-substitution may result.¹⁹ Arylation of quinones is achieved by reacting unsubstituted quinones with arylmercuric chlorides under lithium palladium chloride catalysis.²⁰

Displacement of halogen from electron deficient benzoquinones by dimethylaminobenzylidene anilines has also been reported. This reaction



Scheme 11

proceeds *via* a charge transfer complex and the products from this reaction are either monoanilino-trihalo benzoquinones or bisanilinodihalo benzoquinones.²¹ Unsubstituted quinones have been directly aminated with *O*-benzylhydroxylamine to provide aminoquinones. Alternative hydroxylamines were used but hydroxylamine, *O*-methylhydroxylamine and carboxymethoxylamine were found to be less effective.²²

In a novel two step process 2-hydroxynaphthoquinones have been synthesised by an initial [2 + 2] cycloaddition reaction between *N*-sulfinylarylamines (e.g. PhN=S=O) and naphthoquinone. This results in the formation of 2-(*N*-arylsulfinamoyl)-naphtho-1,4-quinones which in turn are easily hydrolysed with dilute hydrochloric acid to 2-hydroxynaphthoquinone.²³

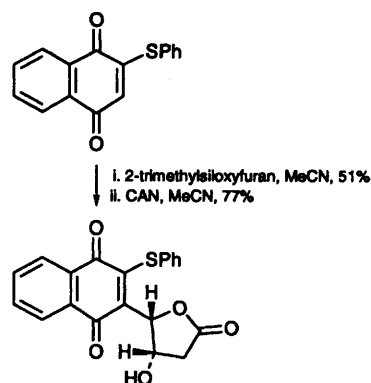
Titanium catalysed arylation of quinones has been shown to occur with cyclopropylbenzene derivatives. Arylation occurs from the 4-position of the cyclopropylbenzene to the 2-position of quinones and yields are enhanced by the presence of a trimethylsilyl substituent on the cyclopropyl ring.²⁴ A general arylation of bromoquinones with arylstannanes under palladium catalysis has been reported to provide aryl quinones in high yields.²⁵

A new synthesis of 5'-deoxyjuglinomycin A has been achieved utilising the facile addition of 2-trimethylsiloxyfuran to 2-phenylthionaphthoquinones to produce intermediate furo[3,2-*b*]naphtho[2,1-*d*]furans which are oxidised with CAN to the quinone (Scheme 12). Reductive removal of the sulfur substituent provides the juglinomycin derivative.²⁶

3 Synthesis of heterocyclic quinones

3.1 Synthesis of five-membered heteroaromatic quinones

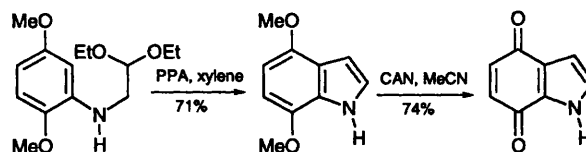
The ubiquitous nature of fused heterocyclic quinones, their biological properties and attendant commercial reward has resulted in them becoming



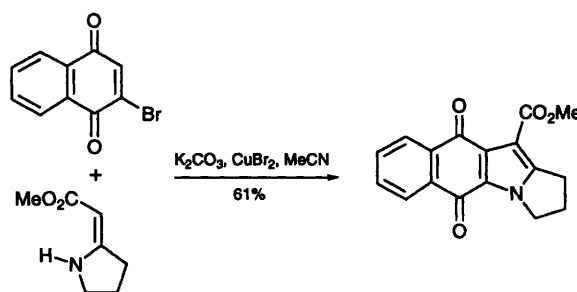
Scheme 12

targets for synthesis. Quinones are the active pharmacophore in antitumour agents, antibacterial and antimalarial agents and a rapid two step synthesis of both indoloquinones, and benzo-*[b]*thienoquinones has been reported.²⁷ Thus amino- or thio-acetals may be cyclised with PPA in xylene to give 4,7-substituted indoles and benzo-*[b]*thiophenes respectively. These in turn may be oxidised with CAN to give quinones (Scheme 13).

A one pot annulation reaction of bromo quinones to vinylogous carbamates has provided a facile synthesis of pyrroloindoloquinones which was extended to the synthesis of 7-methoxymitosene (Scheme 14).²⁸



Scheme 13



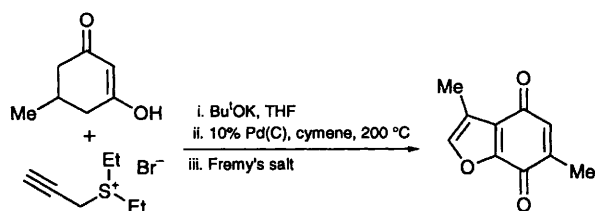
Scheme 14

This approach has also proved useful in the synthesis of the ABCD ring system of the originally proposed structure for kinamycin.²⁹ The mitosenes and murrayaquinones contain the indolo-4,7-quinone substructure and a novel approach to this system has been the construction of a 4-formyl-7-methoxyindole and subsequent oxidative degradation with Fremy's salt.³⁰ Alternatively as in

the synthesis of the topoisomerase II inhibitor BE 10988, a 4-benzyloxyindole may be debenzylated and oxidised with Fremy's salt to provide an indoloquinone.³¹

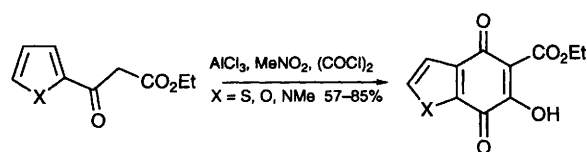
Carbazoloquinones have also been synthesised by direct palladation of anilinoquinones and naphthoquinones followed by oxidative cyclisation.^{32–34}

Furanoquinones may be synthesised in an analogous fashion to naphthoquinones from cyclobutenones (*cf.* Section 2).³⁵ They are also accessible from alkynylsulfonium salts by reaction with the enolates of cyclic 1,3-diketones. The first formed dihydrobenzofuranone is firstly dehydrogenated to the phenol and subsequently oxidised with Fremy's salt to the furanoquinone (Scheme 15).³⁶



Scheme 15

A general synthesis of hydroxynaphthoquinones and the analogous thiophene, pyrrole and furan quinones has been effected by bis-acylation of β -keto esters with oxalyl chloride. The resultant hydroxy esters are then hydrolysed and decarboxylated to give the hydroxy quinones (Scheme 16).³⁷

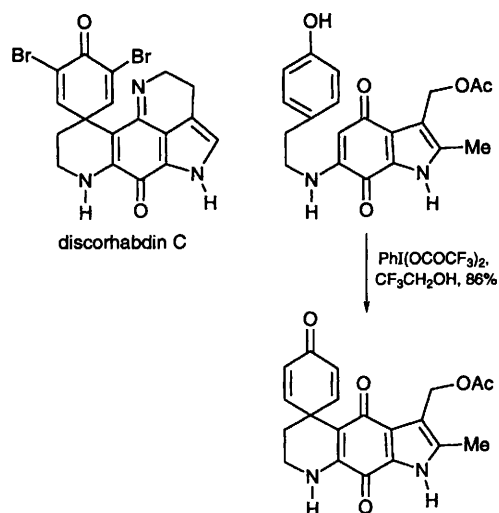


Scheme 16

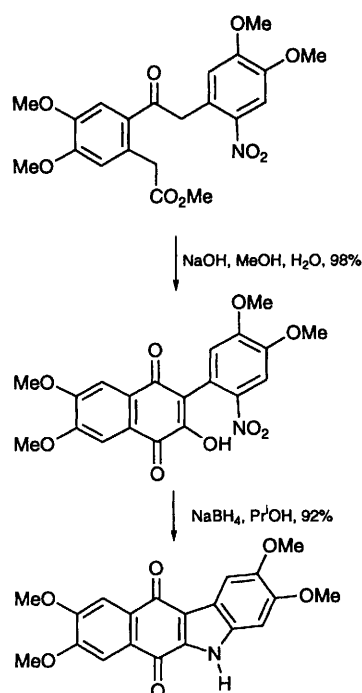
The cytotoxic antitumour agent discorhabdin C has proven to be a challenging target but an approach providing a general route to azacarbo-cyclic spirodienes has been developed utilising the hypervalent iodine oxidation of phenol derivatives with bis(trifluoroacetoxy)iodobenzene (Scheme 17).³⁸

Benzo-1,4-quinones bearing electron donating (*e.g.* amino or thio) substituents undergo dipolar cycloaddition reactions with diazomethane to produce indazoloquinones in moderate yield. Naphthoquinones also undergo this reaction.³⁹

An efficient synthesis of benzo[*b*]carbazoles has been reported by base catalysed ring closure of 2-(2-nitrophenyl)phenylacetic acids, the first formed hydroxynaphthoquinone is reduced with sodium borohydride in isopropanol to give the carbazole (Scheme 18).⁴⁰



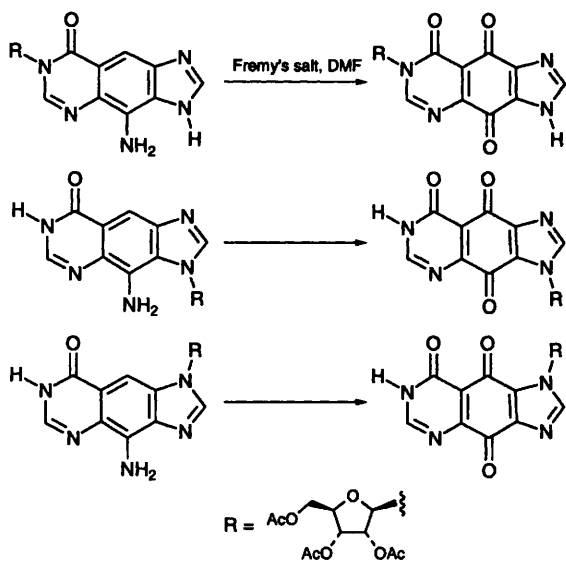
Scheme 17



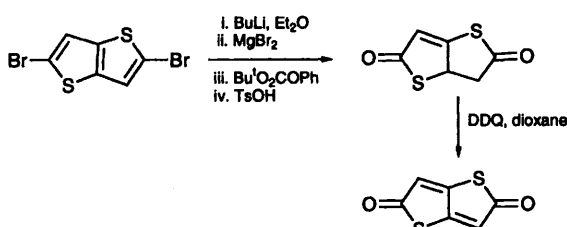
Scheme 18

Imidazo[4,5-*g*]quinazolinequinone nucleosides have been studied for their ability to be functionalised into enzyme directed reductive alkylating agents. They are accessible by a chemoselective Fremy's salt oxidation of ribosylated aminoimidazo[4,5-*g*]quinazolines (Scheme 19).⁴¹

Driven by the need to find alternative quinone functionalised nuclei as acceptors in place of tetracyano-*p*-quinone dimethane (TCNQ) in charge transfer complexes with tetrathiofulvalene, efficient syntheses of thieno[2,3-*b*]naphtho-1,4-quinones were required. Thus microwave assisted cyclisation of several thienoylbenzoic acid derivatives were studied and the most efficient catalyst was found to be Montmorillonite K-10 freed of quartz and feldspar.⁴²



Scheme 19



Scheme 20

Alternatives to TCNQ were also cited as the reason for the synthesis of thieno[3,2-*b*]thiophene-2,5-quinone (**Scheme 20**).⁴³

3.2 Synthesis of six-membered heteroaromatic quinones

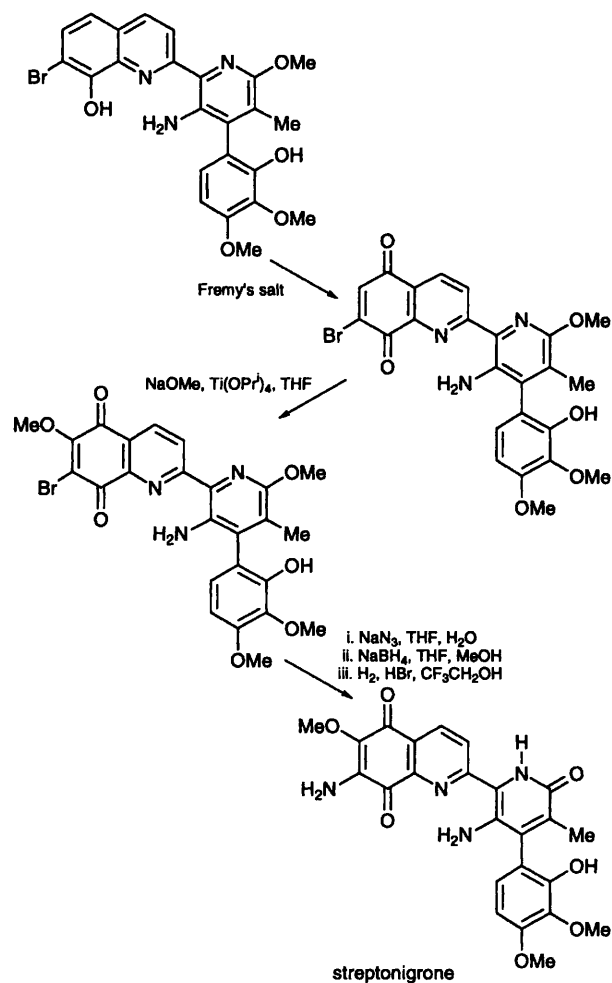
New 7-aminomethyl-6-chloroquinoline-5,8-quinones have been synthesised by Mannich reaction of 6-chloroquinoline-5,8-quinone and formaldehyde with secondary amines. Yields are moderate (38–80%) and the products possess amoebicidal activity.^{44,45} 6-Chloroquinoline-5,8-quinone is the common precursor for novel oxazolo- and thiazolo-quinolinediones which are formed by reaction of the chloro quinone with amides and thiourea respectively.⁴⁶

Homophthalic anhydride has been shown to react regiospecifically with 6-bromo-1-chloro-4-methylisoquinoline-5,8-quinone under basic conditions (sodium hydride, THF) to produce, in 77% yield, 1-chloro-6-hydroxy-4-methylnaphtho[2,3-g]isoquinoline-5,12-quinone, a precursor to antitumour aminonaphthoisoquinolinequinones. The corresponding unbrominated isoquinoline-5,8-quinone showed no regioselectivity.⁴⁷

Perfragillin B, a cytotoxic isoquinoline quinone isolated from *M. perfragillis*, has been synthesised by

hetero Diels–Alder reaction of 1,3-bis(*tert*-butyldimethylsiloxy)-2-azabutadiene and 2,3-bis(methylthio)benzoquinone followed by hydrolysis, oxidation and methylation.⁴⁸

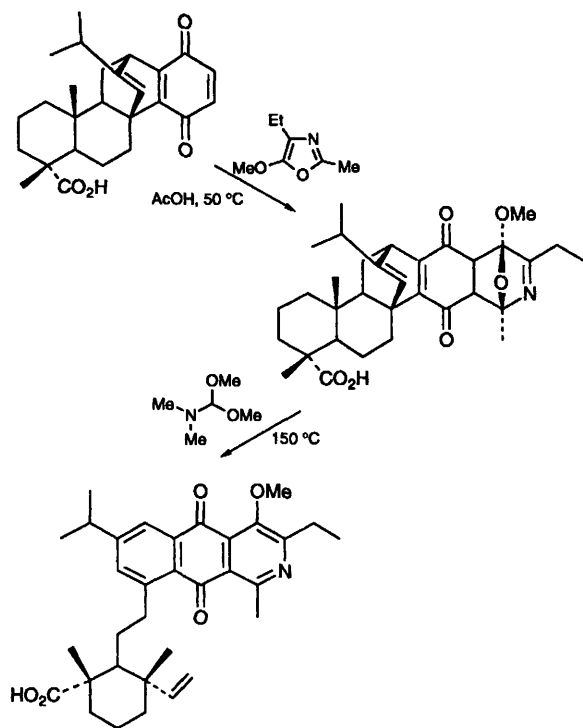
During the period under review the first total synthesis of streptonigrone was achieved. Significant steps in the synthesis of this antitumour antibiotic are the room temperature inverse electron demand Diels–Alder reaction of an *N*-sulfonylazabutadiene with a ketene acetal, chemoselective oxidation of an hydroxyquinoline to a quinone in the presence of a phenol and the introduction of a methoxy group to the quinone with titanium tetraisopropoxide. These last steps are shown in **Scheme 21** together with the final steps of the synthesis.⁴⁹



Scheme 21

Streptonigrin has also been a target of interest and a new synthesis of the quinolinequinone moiety has been published as has a convergent synthesis of streptonigrin and lavendamycin analogues.^{50,51}

An entry into the field of azaanthraquinones is possible by the Diels–Alder reaction between 2-methyl-4-ethyl-5-methoxyoxazole and quinopimaric acid.⁵² The initial adduct may then be cleaved in dimethylformamide dimethyl acetal at elevated temperature to give the azaanthraquinone in 82% yield (**Scheme 22**).



Scheme 22

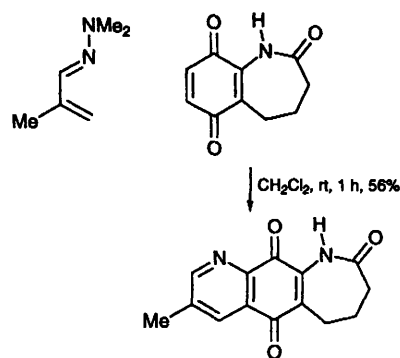
Ultrasound irradiation has been shown to assist the Diels–Alder reaction of 1-azadienes and quinones which may be converted to azaanthraquinones.⁵³ 5-Deazaflavin-6,9-quinones are regarded as hybrids of 5-deazaflavin and coenzyme Q and their synthesis has been achieved by heating 6-alkylaminouracils and 2,3-dimethoxybenzaldehyde in DMF. The resultant methoxydeazaflavin is then oxidised in moderate yield with Fremy's salt to the quinone.⁵⁴ A series of quinazoline-5,8-diones have been synthesised to evaluate their *in vitro* cytotoxicity towards L1210 leukaemia cells.⁵⁵

3.3 Synthesis of saturated heterocyclic quinones

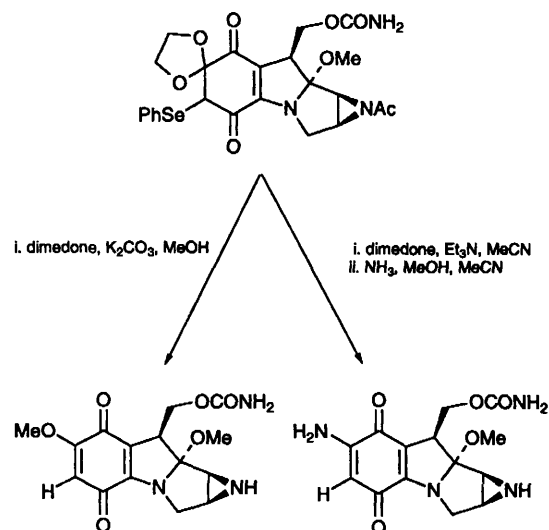
2,3,4,5-Tetrahydro-1*H*-1-benzazepine-2,6,9-trione has been synthesised by the ring expansion of 5-methoxytetralone, demethylation and oxidation with Fremy's salt. This trione has been used in Diels–Alder and hetero Diels–Alder reactions and when reacted with methacrolein dimethylhydrazone the product is a quinolinotrione (**Scheme 23**).^{56–58}

A study attempting to find less toxic analogues of the antitumour agent mitomycin C has been published, wherein a facile removal of a phenyl-seleno group with the soft carbon nucleophile dimedone resulted in easy access to demethylated analogues of mitomycin (**Scheme 24**).^{59,60}

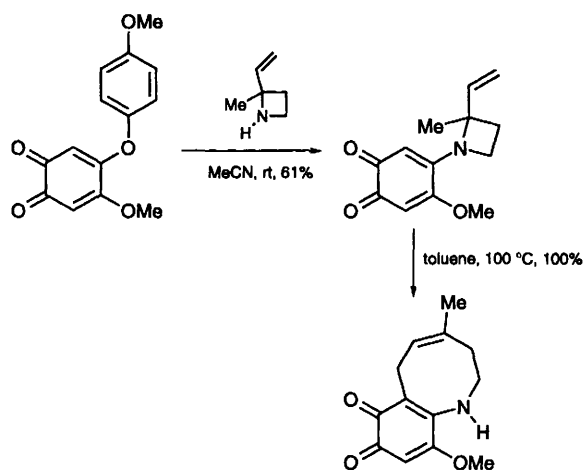
4-Hydroxyanisole can be oxidised with copper in the presence of oxygen to a methoxyphenoxy *ortho*-quinone. Reaction with vinylazetidine displaces 4-methoxyphenol to give an azetidyl quinone which can then be thermally rearranged ([3,3]-sigmatropic)



Scheme 23



Scheme 24

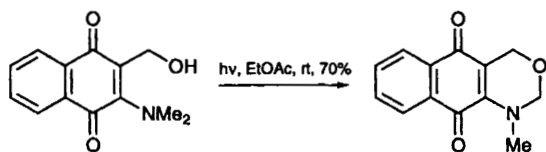


Scheme 25

to a tetrahydrobenzazocinequinone, a structure analogous to the natural pigment maesanine (**Scheme 25**).⁶¹

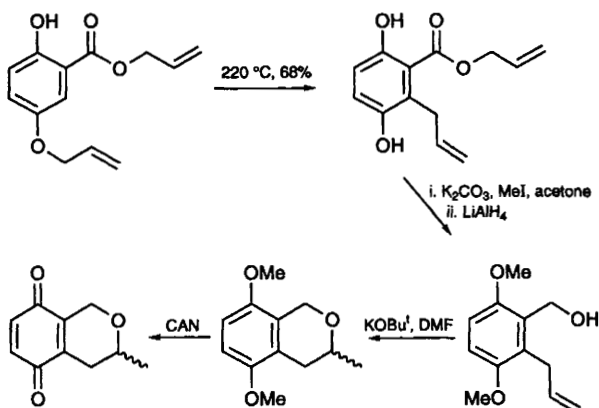
The appearance of quinolone resistant bacteria has prompted a search for novel quinolone

structures with antibacterial activity. Whilst attempting to synthesise analogues of 3-amino-naphtho-1,4-quinone-2-carboxylic acid a novel photochemical cyclisation of 2-hydroxymethyl-3-dialkylaminonaphtho-1,4-quinones was discovered which provides novel dihydro-5,10-dioxo-1*H*-naphth[2,3-*d*][1,3]oxazines in yields in the range 42–70% (**Scheme 26**).⁶²



Scheme 26

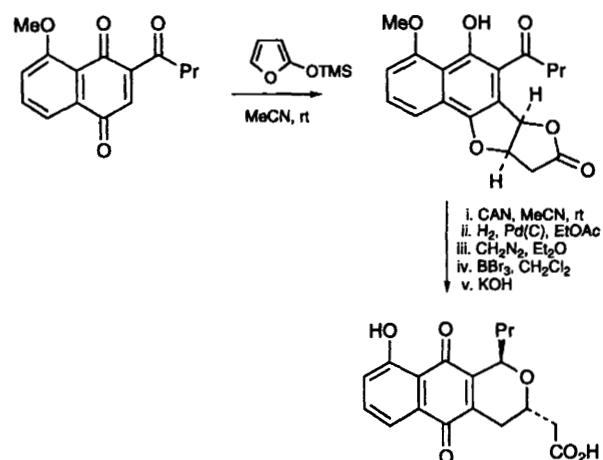
Benzo- and naphtho-pyranquinones have remained targets for synthesis throughout the period of this review. Base catalysed cyclisations of allyl alcohols to pyran derivatives with potassium *tert*-butoxide in DMF⁶³ have been applied to the synthesis of both benzopyranquinones,⁶⁴ and to the naphthopyranquinones, ventiloquinones G and E (**Scheme 27**).⁶⁵



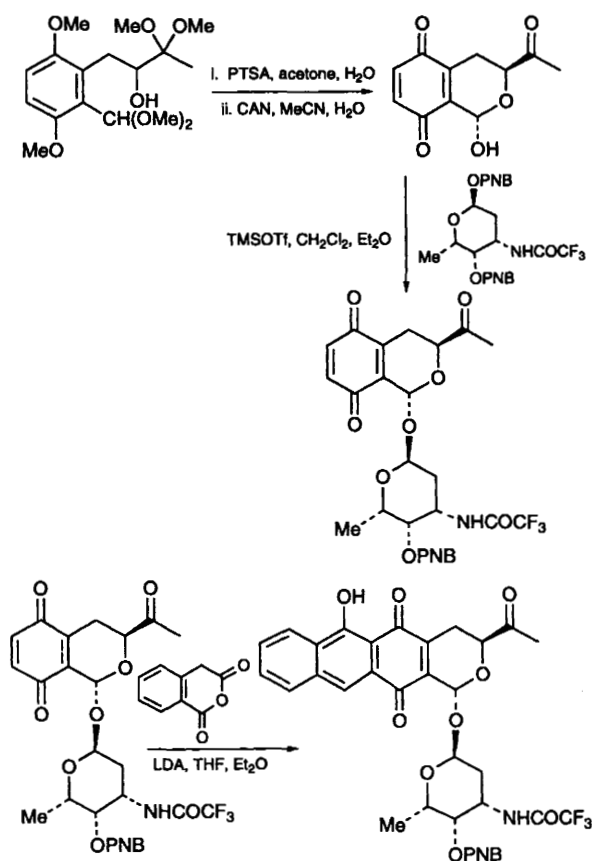
Scheme 27

An alternative approach to the naphthopyranquinone nucleus has been the addition of 1-trimethylsiloxyfuran to acynaphthoquinones to produce furonaphthofurans. These in turn have been oxidatively rearranged with CAN in aqueous acetonitrile to furonaphthopyrans and then converted to the antibiotic deoxyfrenolicin (**Scheme 28**).⁶⁶

Pyranquinones have themselves been used as precursors to anthracycline analogues of idarubicin. Thus acid catalysed cyclisation of hydroxy acetals followed by oxidation provides pyranquinones which on treatment with the lithium enolate of homophthalic anhydride provides analogues of idarubicin which have antitumour activity (**Scheme 29**).⁶⁷



Scheme 28

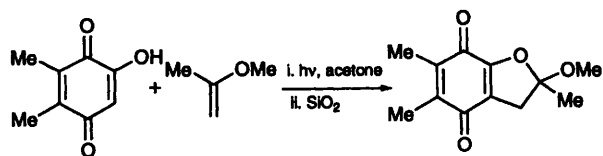


Scheme 29

Regioselective photoadditions between hydroxybenzoquinones and methyl vinyl ethers have been shown to produce benzofuran-4,7-diones in moderate yield (**Scheme 30**).⁶⁸

This type of photoaddition has also been reported between aminonaphthoquinones and methyl vinyl ethers when the products are 2,3-dihydro-1*H*-benz[*f*]indole-4,9-diones in 45–82% yields.⁶⁹

Two independent total synthesis of the potent antibiotics cervinomycins A₁ and A₂ (**Figure 1**) have been reported.^{70,71}



Scheme 30

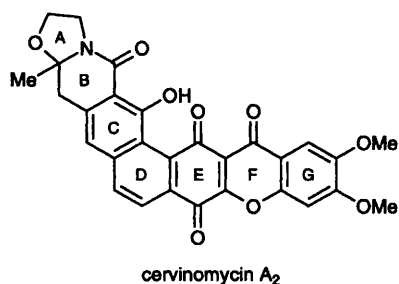


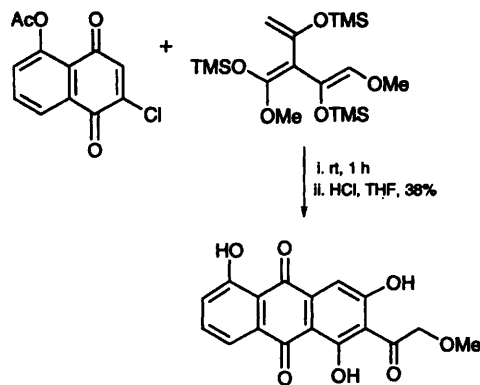
Figure 1

Both syntheses relied on the introduction of ring A in the final steps of the synthesis but differed in their construction of rings B–G. The approaches adopted were, respectively, mild photolytic oxidation to form ring D in the presence of iodine and nucleophilic attack by methyl 4,5-dimethoxy-salicylate on a bromo quinone followed by reduction of the quinone and acylation to form ring F. Both syntheses required oxidative demethylation to produce the quinone ring E.

4 Synthesis of anthraquinones and anthracyclinones

Anthraquinones and anthracyclinones remain attractive targets for synthesis primarily because of their biological activity which includes antitumour, antibacterial, anti-HIV, anti-osteoarthritic and antifungal.^{72–79} Consequently many strategies have been attempted in the synthesis of anthraquinones and of these the most versatile has been the Diels–Alder reaction between halonaphthoquinones and silyl dienol ethers or silyl ketene acetals. Brassard and co-workers have now extended their extensive studies in this area with the reaction of cross-conjugated dienes with halo quinones.⁸⁰ Thus at room temperature 1-methoxy-3-[methoxy-(trimethylsiloxy)methylene]-2,4-bis(trimethylsiloxy)penta-1,4-diene was reacted with 5-acetoxy-2-chloro-naphthoquinone and after acidic hydrolysis produced a (methoxyacetyl)anthraquinone in 38% yield (Scheme 31).⁸¹

Also utilising the Diels–Alder route to anthraquinones Kelly and co-workers have taken a styrylanthraquinone and cyclised this under palladium catalysed stannylation conditions to give benzo[*a*]naphthacenequinone pigments G-2N and G-2A.⁸²



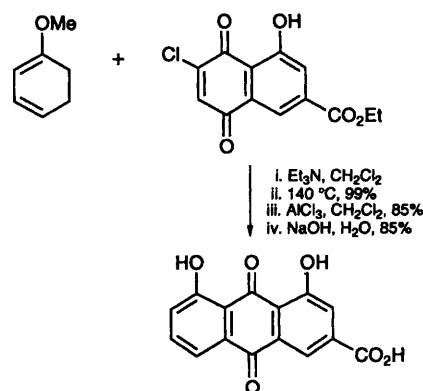
Scheme 31

A cycloaddition strategy has been used in the synthesis of iminodaunomycinones. Thus acyl derivatives of 10-amino-9-hydroxy-1,4-anthraquinone have been reacted with 1,3-bis(trimethylsiloxy)butadiene in high yield and good regioselectivity. Removal of the acyl protecting groups and hydrolysis of the silyl enol ether adduct followed by addition of ethenyl magnesium bromide and subsequent mercuric sulfate mediated hydrolysis of the alkyne produced the iminodaunomycinones.⁸³

Styrene derivatives have been also been shown to undergo thermal or ultrasound and Lewis acid catalysed cycloaddition reactions to benzoquinones. Thus 2-methylstyrene reacts with 2-methoxy-3-methylbenzoquinone to produce a dimethyl-methoxyphenanthra-1,4-quinone thereby assisting in the identification of naturally occurring phenanthraquinones of the *coleus* and *plectranthus* species.⁸⁴

The Diels–Alder route to anthraquinones has also found application in the synthesis of rhein (4,5-dihydroxyanthraquinone-2-carboxylic acid) the active metabolite of the anti-osteoarthritic drug diacetyl rhein, together with other naturally occurring anthraquinones, *e.g.* aloe-emodin (Scheme 32).⁸⁵

Cycloaddition of 2-hydroxymethylbuta-1,3-diene with a variety of quinones followed by oxidation to anthraquinone aldehydes has been reported. Anthraquinone aldehydes were required for

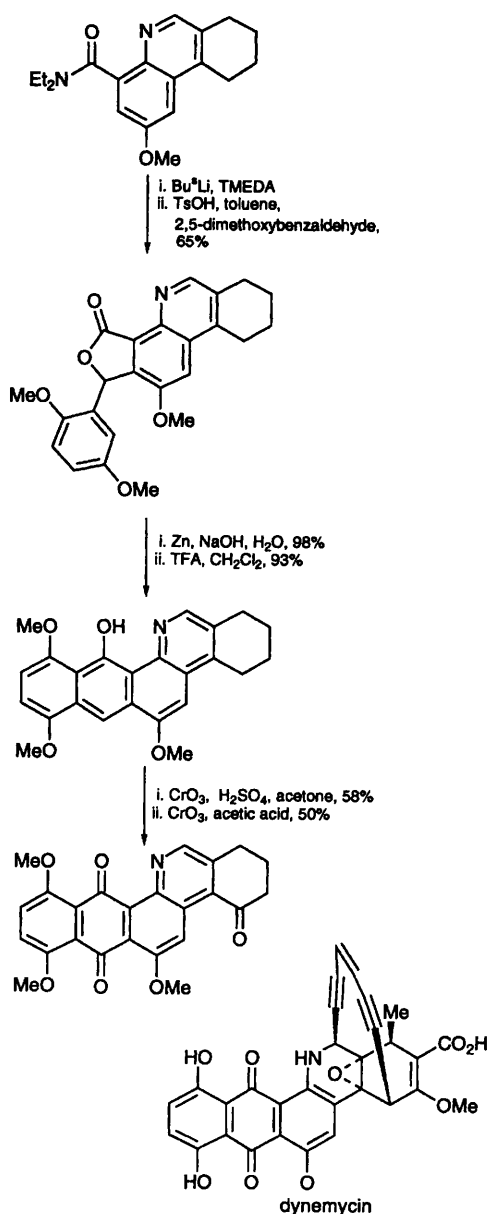


Scheme 32

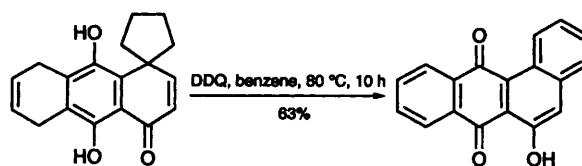
incorporation into porphyrins as models for the light-initiated charge separation which occurs in photosynthetic reaction centres.⁸⁶

Dynemycin, an enediyne anthraquinone, has anti-tumour and antibacterial properties and has as a consequence attracted much synthetic effort. One approach to the anthraquinone framework has been to *ortho*-lithiate a tetrahydrophenanthridine-carboxamide and to react this with 2,5-dimethoxybenzaldehyde (Scheme 33). The resultant phthalide is reduced to the acid and cyclised to the hydroxylated naphthophenanthridine. This is subsequently oxidised to the quinone with chromium trioxide.⁸⁷

Angucyclines have recently attracted attention due to their biological activity, and a facile one step synthesis from spirocyclic naphthoquinones has been reported. Thus oxidative rearrangement of spirocyclic naphthoquinones with DDQ in benzene



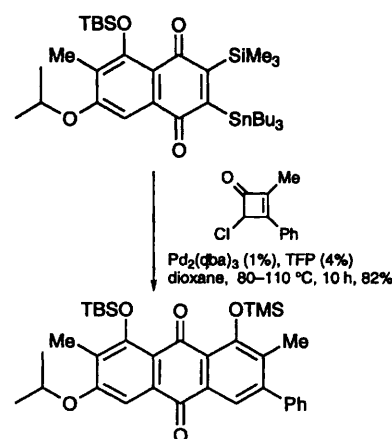
Scheme 33



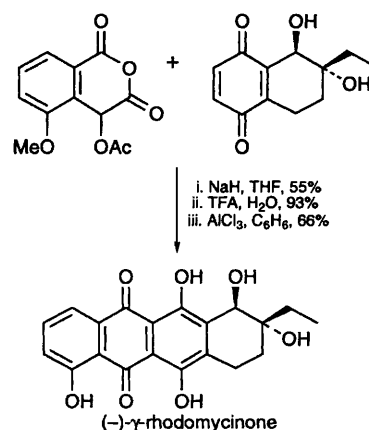
Scheme 34

benz[*a*]anthraquinones in moderate to good yield (Scheme 34).⁸⁸

In what promises to be a widely applicable synthesis of anthraquinones Liebeskind and co-workers have reacted 2-trimethylsilyl-3-tributylstannylquinones with a range of chlorinated cyclobutenones in good yield (Scheme 35). The reaction is carried out under palladium catalysis and the reaction is presumed to proceed *via* initial reaction between the tin and chlorine residues followed by thermal rearrangement to the benzannulated quinone.⁸⁹



Scheme 35

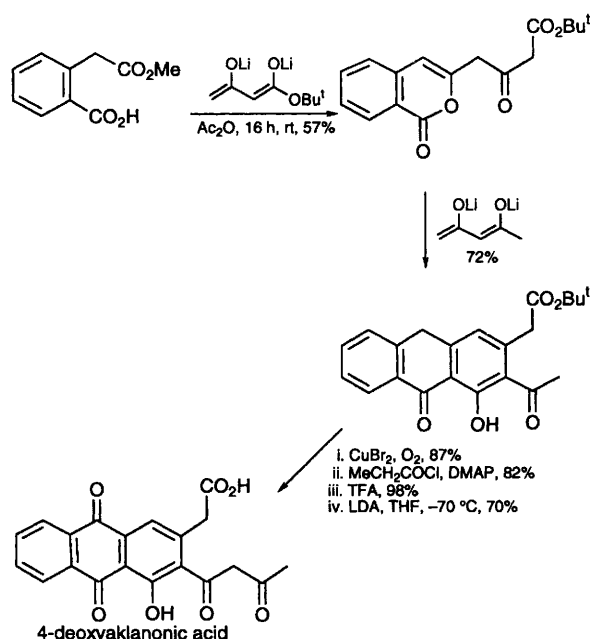


Scheme 36

Rhodomycinones (Scheme 36) have become targets for synthesis because of their antitumour properties. A new quinone synthon has been introduced by Fujioka and co-workers who have

exploited the facile addition of homophthalic anhydrides to this quinone. Subsequent rearrangement of the first formed tetrahydronaphthacene adduct (5,12- to 6,11-quinone) and demethylation of the aryl methyl ether provided an economical synthesis of (–)- γ -rhodomycinone. The quinone synthon is formed from 5,8-dimethoxy-1,2-dioxotetraline 1-[(2*S*,3*S*)-1,4-dimethoxy-2,3-butylene]acetal by alkylation with ethylmagnesium chloride followed by acid hydrolysis. The resultant ketone is reduced and finally demethylated to produce (5*R*,6*R*)-6-ethyl-5,6-dihydroxy-5,6,7,8-tetrahydronaphtho-1,4-quinone.⁹⁰

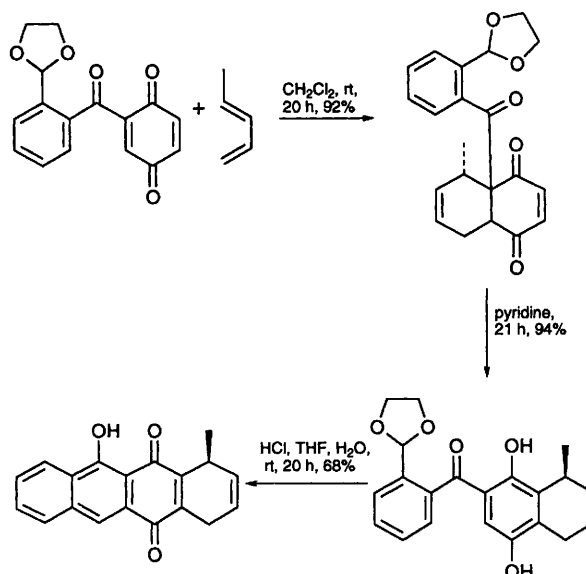
The biosynthesis of anthracyclinones structurally related to rhodomycinone has been studied. Thus 4-deoxyaklanonic acid has been synthesised and biotransformed with mutant S727 of *Streptomyces galileus* to anthracyclinones. Homophthalate monoester is reacted with *tert*-butyl acetoacetate dianion and cyclised with acetic anhydride to produce a coumarin. The dilithio anion of acetylacetone produced the anthrone in 72% yield and this was oxidised and esterified to produce an intermediate propionate, which was in turn rearranged with LDA to produce 4-deoxyaklanonic acid in 70% yield (Scheme 37).⁹¹



Scheme 37

A rapid entry into the anthracyclinone ring system has been provided by the Diels–Alder reaction of *trans*-penta-1,3-diene with a benzoylbenzoquinone. Isomerisation of this adduct in pyridine produced the hydroquinone which under mild acid conditions was transformed to the naphthacenedione (Scheme 38).⁹²

The first total synthesis of an angucycline related antibiotic has been published during the period under review. Angucyclines (typified by aquaymycin)



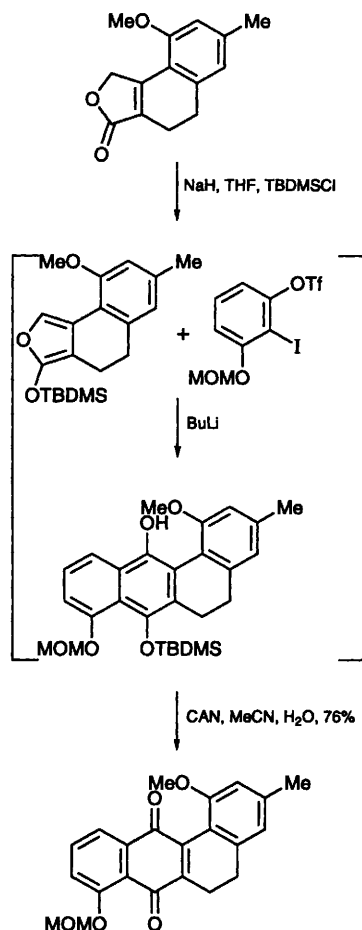
Scheme 38

are a growing class of antibiotics and the synthetic approach to an aromatic analogue of aquaymycin commenced with a cycloaddition between an *in situ* generated siloxyfuran and an *in situ* generated benzyne derived from an iodotriflate. Subsequent oxidation with CAN produced a benz[*a*]anthraquinone. The antibiotic was synthesised by an *ortho* glycosylation reaction on the deprotected MOM ether at the hydroquinone oxidation level followed by oxidation (Scheme 39).⁹³

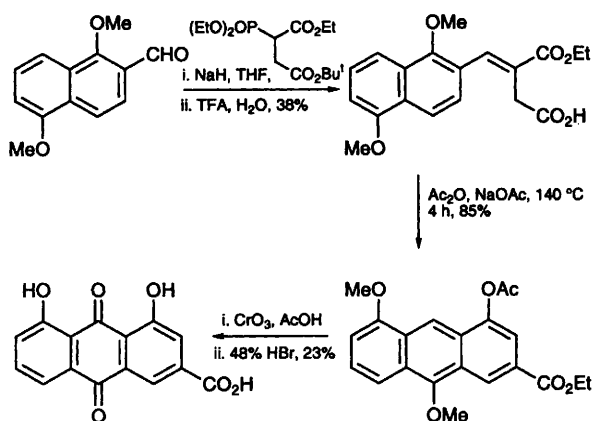
Related precursor aglycones of the angucyclines have been synthesised by cycloaddition between 5-hydroxynaphthoquinone and the silyl ketene acetal derived from ethyl 1-cyclohexeneacetate.⁹⁴ A similar approach to the construction of the carbon skeleton of angucyclines has been adopted by Krohn and co-workers but introduction of a pentamethyldisilane moiety early in their reaction sequence in the cyclohexene ring allowed photolytic conversion of the silane in the presence of oxygen to the tertiary alcohol required in the angucyclinones in the final steps of their synthesis.^{95,96}

One of the lesser known properties of certain anthraquinones is their ability to inhibit the progression of osteoarthritis; thus a synthesis of rhein which has allowed novel analogues of this anti-osteoarthritic has been reported. 1,5-Dimethoxy-2-naphthaldehyde was converted to a butenoic acid with a novel phosphonate and cyclised to an anthracene ester with acetic anhydride. This was subsequently oxidised and hydrolysed to rhein (Scheme 40).⁷⁸

A three step synthesis of anthra-1,4-quinones has been reported starting from phenylsulfonylphthalide. This was added to a bicyclic quinone in the presence of lithium *tert*-butoxide. Subsequent methylation and flash vacuum pyrolysis at 500 °C converted the extended bicyclic quinone to a anthra-1,4-quinone (Scheme 41).⁹⁷



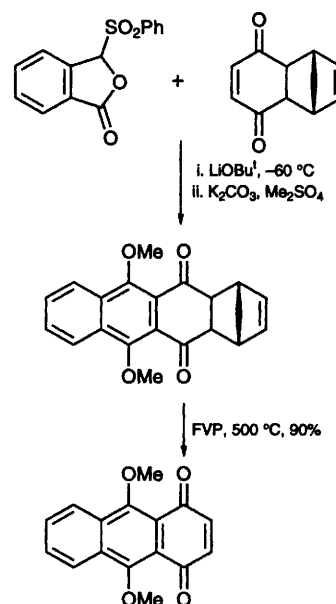
Scheme 39



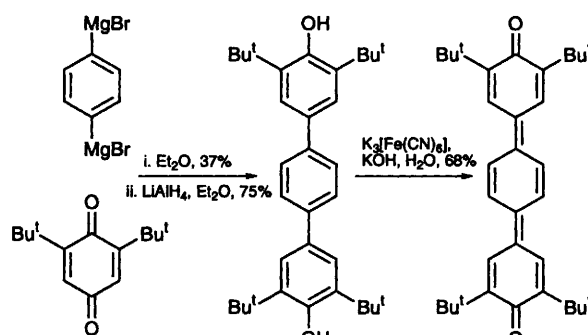
Scheme 40

5 Synthesis of other polycyclic quinones

Extended quinones have latterly been of interest because of their potential as organic semiconductors or as in electron acceptors in xerography.⁹⁸ As a consequence of this, extended arrays of quinones have been synthesised. One of these is *p*-terpheno-



Scheme 41

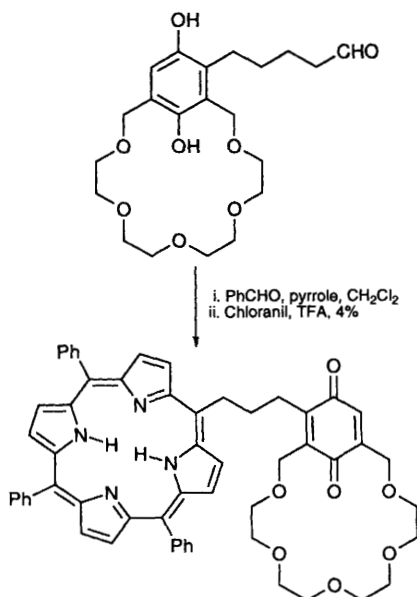


Scheme 42

quinone and Boldt and co-workers have recently synthesised the tetra-*tert*-butyl analogue (Scheme 42). Thus the bis-Grignard derived from 1,4-dibromobenzene is reacted with two equivalents of 2,6-di-*tert*-butylbenzoquinone followed by reduction and oxidation. The corresponding tetraphenyl analogue was too unstable to be isolated.⁹⁹

The other major area of interest with polycyclic quinones is in the synthesis of biomimetic photosynthetic model compounds. Currently porphyrin quinones are being studied where the quinone nucleus is oriented to allow the quinone access to the porphyrin. Such molecules have been synthesised in very low yield in a three component reaction with benzaldehyde and pyrrole and do display altered cyclic voltammetric properties in the presence of alkali metal ions (Scheme 43).¹⁰⁰

A fourfold bridged porphyrin quinone cyclophane has also been constructed which completely capped a single face of a porphyrin.¹⁰¹ Complex arrays are now being studied with porphyrin monomers, dimers, trimers and tetramers linked to



Scheme 43

quinones.^{100–105} A range of 1,10-*o*-benzo-[2.2]orthocyclophane-*o*-quinones have been synthesised to evaluate the intramolecular charge transfer interaction between the donor, a dimethoxybenzene, and the acceptor, an *o*-benzoquinone. Orthocyclophane-*o*-quinones are synthesised by [4 + 4] cycloadditions of *o*-quinodimethanes with anthracenes.¹⁰⁶

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