Pergamon

Tetrahedron Vol. 51, No. 18, pp. 5207-5236, 1995

0040-4020/95 $29.00+0.00

0040-4020(95)00247-2

TETRAHEDRON REPORT NUMBER 371

Annulation Reactions With Stabilized Phthalide Anions

Anthony S. Mitchell and Richard A. Russell*

School of Biological and Chemical Sciences, Deakin University, Geelong, Victoria, Australia, 3217.

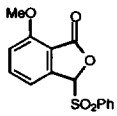
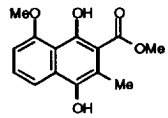
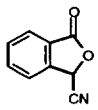
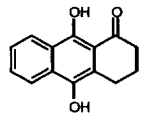
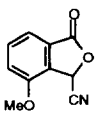
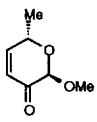
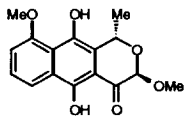
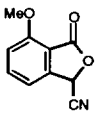
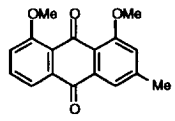
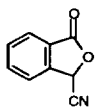
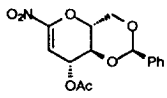
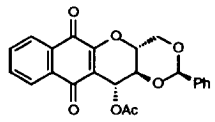
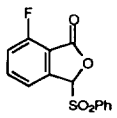
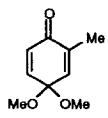
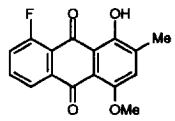
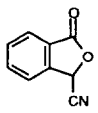
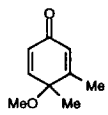
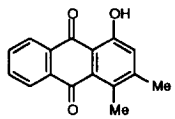
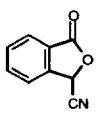
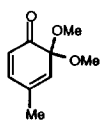
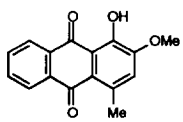
Contents

1. OVERVIEW

The widespread occurrence of the quinone nucleus in natural products has provided a focus for considerable synthetic endeavour. In the past decade, this has been accelerated by the discovery of a variety of quinonoid molecules exhibiting anti-neoplastic activity[1,2]. Whilst numerous new synthetic strategies have been proposed, few have proved to be more general or more widely accepted than the annulation of Michael

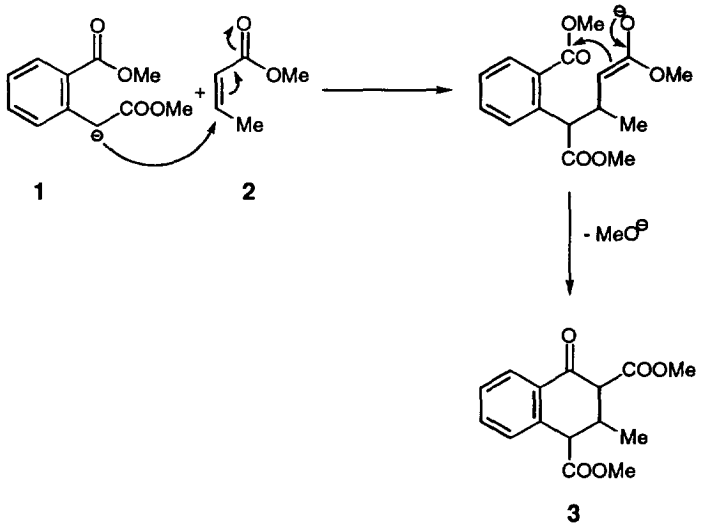
acceptors with stabilized phthalide anions. These anions, which are generated by treating the appropriate phthalide with a strong base (*e.g.* lithium diisopropylamide, dimsyl sodium or potassium *tert*-butoxide), undergo a wide variety of reactions, the scope of which is summarized in Table 1.

Table 1. Summary of Phthalide Anion Annulation Reactions.

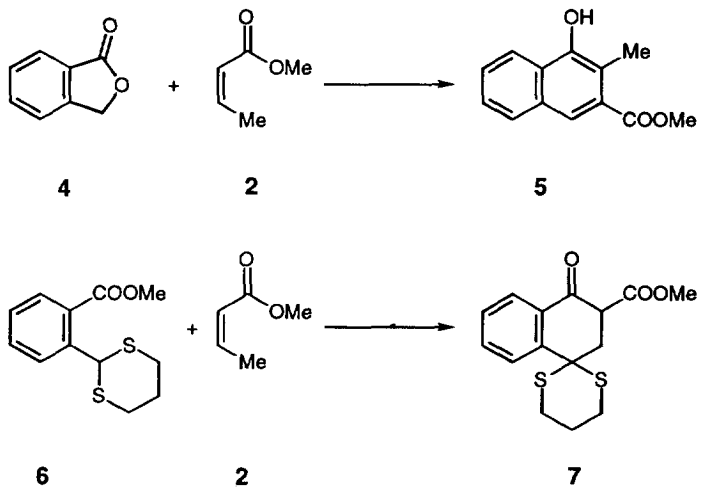
phthalide	substrate	product	% yield
			83
			60
			65
			30
			89
			74
			96
			79

2. BACKGROUND

The origins of the phthalide annulation sequence can be traced to the reaction between the anion of dimethyl homophthalate (1) and methyl crotonate (2) to afford the highly substituted tetralone (3), which was described by Schmid[3] in 1965. This reaction, which involves the combination of a Michael addition followed by a Claisen condensation, is somewhat reminiscent of the Robinson annulation (Scheme 1). Similar annulations of methyl crotonate (2) with the anion of phthalide[4] (4) to afford the naphthalene (5) and with the anion of methyl 2-(1,3-dithian-2-yl)benzoate[5] (6) to afford the substituted tetralone (7) have also been reported.



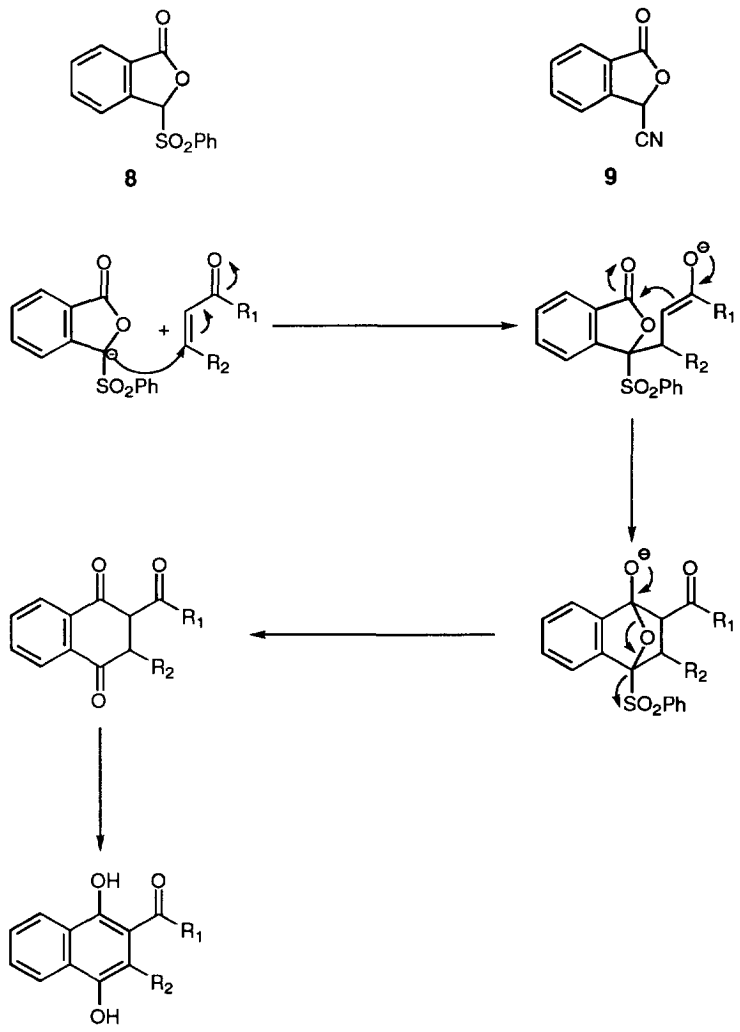
Scheme 1



3. REACTIONS OF PHTHALIDE ANIONS

3.1 Acyclic α,β-Unsaturated Carbonyl Compounds

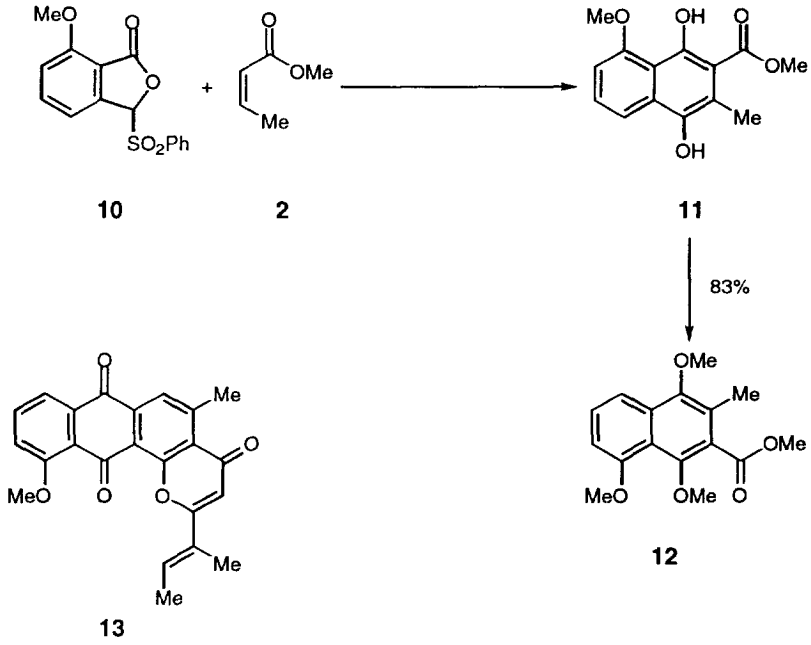
A fundamentally new route to highly substituted naphthalenes, based upon the annulation of Michael acceptors with the anion of 3-phenylsulfonylphthalide (8), was first published by Hauser[6] in 1978 (Scheme 2). In this synthesis the phenylsulfonylphthalide anion behaves as a bifunctional synthon and fulfills the role played by the homophthalate anion in Scheme 1. The function of the phenylsulfonyl group is twofold: prior to annulation it stabilizes the α-carbanion, and following annulation it acts as a leaving group, allowing the intermediate to aromatize. A similar reaction, using the anion of the cyano-substituted phthalide (9), was



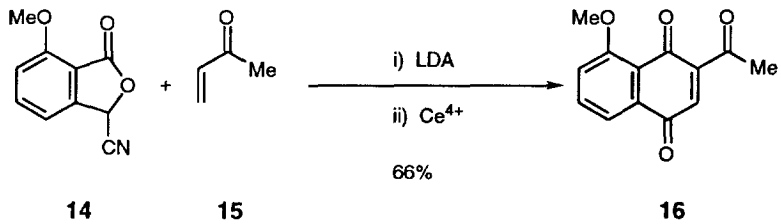
Scheme 2

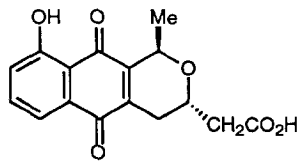
developed simultaneously by Kraus[7].

By choosing appropriately substituted phthalides and Michael acceptors, the regiochemistry of the sole product can be predicted, and complex molecules can be assembled in a single step without ambiguity in the substitution pattern. Furthermore, these molecules can be subjected to additional chemical manipulations, enabling the construction of highly substituted natural products which may otherwise be difficult to prepare. For example, annulation of methyl crotonate (2) with the anion of the methoxy substituted phenylsulfonylphthalide (10) afforded the highly substituted naphthalene (11), which was isolated as the dimethyl ether (12) in 83% yield[8,9]. This latter compound was subsequently converted in several steps to *O*-methylkidamycinone (13), the methyl ether of aromatic moiety of the *C*-glycosyl antibiotic kidamycin[8,9].

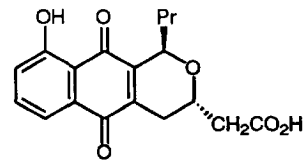


The initial products formed from the annulation of α,β–unsaturated carbonyl compounds with stabilized phthalide anions are 1,4-dioxygenated naphthalenes, which can be converted into naphthoquinones by oxidation. Reaction of the anion of cyanophthalide (14) with methyl vinyl ketone (15), followed by oxidation with ceric ammonium nitrate, afforded the acetyl naphthoquinone (16), a key intermediate in the synthesis of the naphthopyran antibiotic nanayomycin A (17)[10]. Deoxyfrenolicin (18), was prepared in an identical manner from propyl vinyl ketone[10].



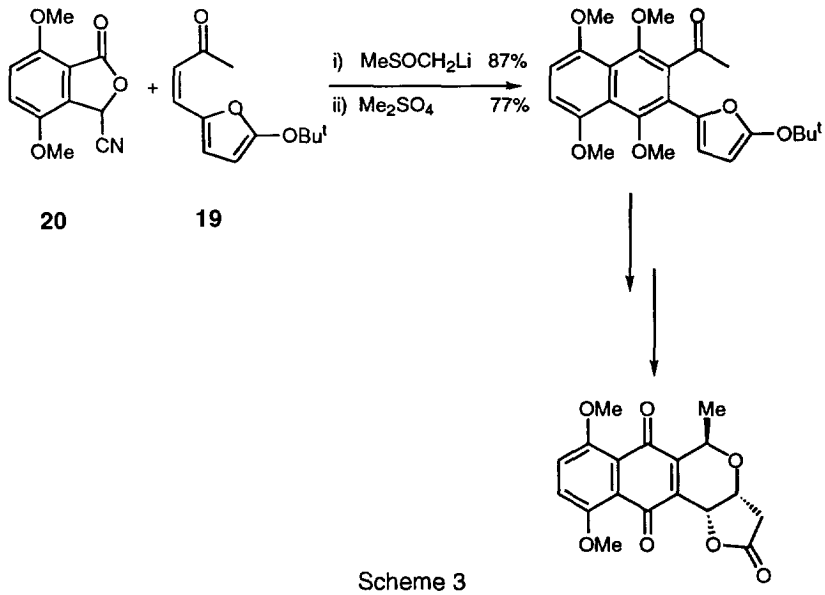


17



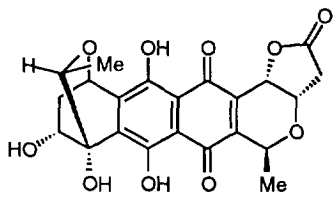
18

The annulation sequence is tolerant of monosubstitution at the β-position of the α,β-unsaturated carbonyl group[11,12], illustrated by the synthesis of the naphthopyran skeleton[11] from 4-(4-*tert*-butoxyfuran-1-yl)but-3-en-2-one (19) and the anion of cyanophthalide (20), as shown in Scheme 3. (±)-Granaticin (21), a complex naphthopyran antibiotic, was prepared using the highly substituted cyanophthalide (22) in a similar sequence of reactions[13].

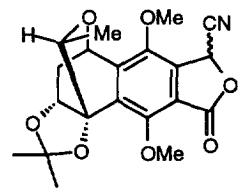


20 19

Scheme 3

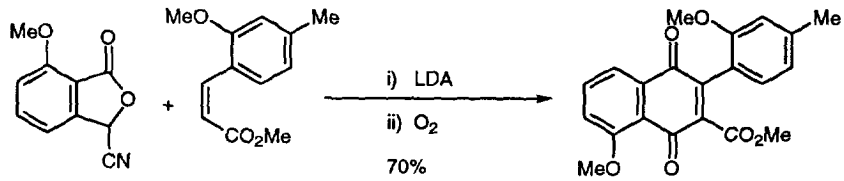


21

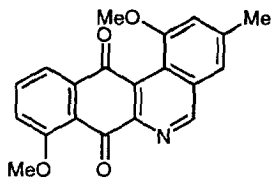


22

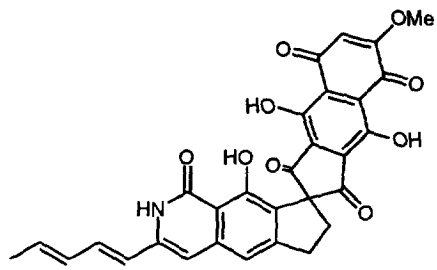
Cinnamic esters also undergo annulation. The phenylnaphthoquinone (23), prepared by addition of the anion derived from cyanophthalide (14) to the substituted cinnamate (24), was converted to the benzo[*b*]phenanthridine (25), the aglycone of the anti-tumour compound phenanthroviridin[14,15].



14 24 23

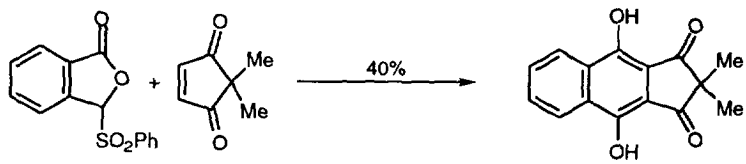


25



26

The antibiotic frederikamycin (26) contains a unique spirocyclopentane unit. A model study involving 2,2-dimethylcyclopent-4-ene-1,3-dione (27) and the anion of phenylsulfonylphthalide (8) demonstrated the feasibility of synthesizing such a structure using a phthalide anion strategy (Scheme 4)[16]. A total synthesis of racemic frederikamycin using this approach has recently been reported[17].

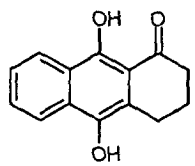


8 27

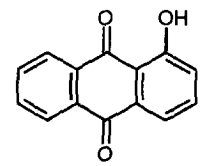
Scheme 4

3.2 Cyclohexenones

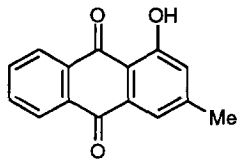
The anthraquinones, the most numerous of the naturally occurring quinones, are accessible by a range of phthalide anion strategies. Thus, annulation of cyclohexenone with the anion of 3-phenylsulfonylphthalide[6,18] or 3-cyanophthalide[12] afforded the tricyclic species (28), which was subsequently oxidized with N-bromosuccinimide[12,18] to afford 1-hydroxyanthraquinone (29).



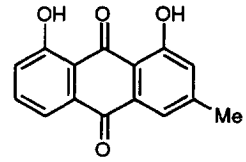
28



29

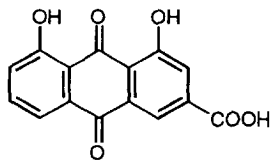


30

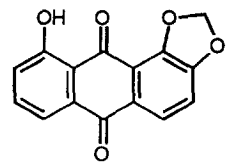


31

The regiospecific syntheses of pachybasin (30), chrysophanol (31), rhein (32) and morindiparvin A (33) have also been achieved by direct application of these methods using suitably substituted cyclohexenones and phthalide anions[12,18,19].

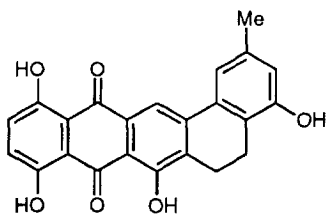


32

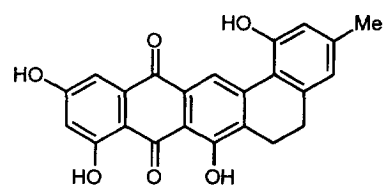


33

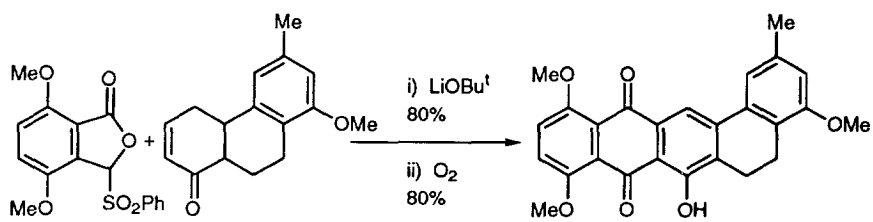
The pigment G2N, which contains the benzo[*a*]naphthacene nucleus, was isolated from a culture of the actinomycete *Frankia* G2 (ORS 020604), and assigned the structure (34)[20]. The trimethyl ether of (34) was subsequently synthesized by Hauser and Caringal by phenylsulfonylphthalide anion annulation of the hydrophenanthrone (35) followed by aerial oxidation of the initial product (Scheme 5)[20]. The synthetic product (36) had different physical and spectral properties to the trimethyl ether of the naturally occurring pigment, and on the basis of these results the structure of G2N was revised to (37)[20].



34



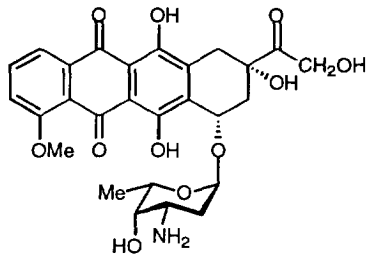
37



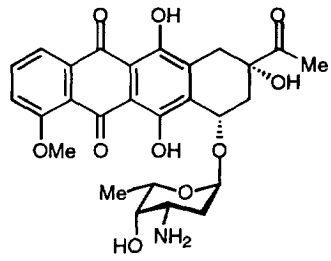
35 36

Scheme 5

The anthracyclines are a diverse group of pigments that have been isolated from the fermentation broths of various species of *Streptomyces*. A number of anthracyclines possess significant anti-cancer activity, and several of this group have now progressed from the laboratory into clinical practice. Adriamycin (38), and to a lesser extent daunomycin (39), are particularly active, and adriamycin is used as a front-line agent in many cancer chemotherapy regimens.



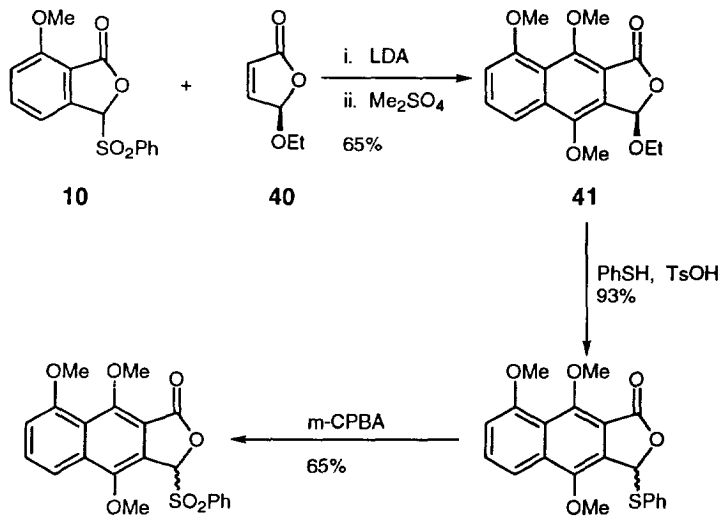
38



39

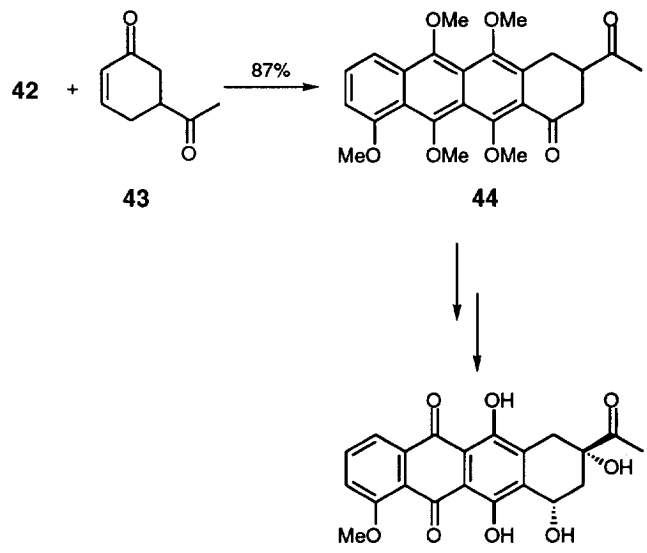
The construction of anthracyclines presents a considerable synthetic challenge, and has been the subject of intensive effort over the last two decades. Many approaches to these complex molecules have been published. It is perhaps not surprising that the regiochemical control afforded by phthalide anion chemistry has lead to a number of partial and total syntheses of anthracyclines being based on this methodology[11-30].

An elegant technique for the construction of the rhodomycinone system, using a recursive annulation strategy, was described by Hauser[21,22]. Annulation of furanone (40) with the anion of phenylsulfonylphthalide (10) afforded the lactone (41), which was readily converted into the ring homologated phthalide (42) by acid catalyzed condensation of (41) with thiophenol and oxidation of the phenylsulfide group to the phenylsulfone with *meta*-chloroperbenzoic acid. Annulation of



10 40 41

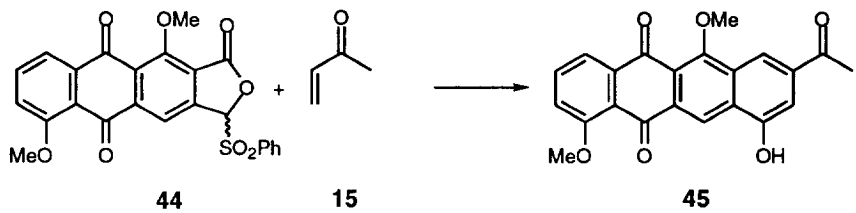
42



Scheme 6

5-acetylcyclohexenone (43) with the anion of (42) afforded the anthracyclinone precursor (44) with complete regiochemical control (Scheme 6).

An alternative approach, employing the anion of the quinonoid phenylsulfonylphthalide (44), has recently been applied to the synthesis of the aromatic anthracyclinone (45), as shown in Scheme 7.



Scheme 7

Retrosynthetic analysis of the 11-deoxyanthracyclinone system suggests the use of phthalide anion annulation of (4H)-naphthalenones (Figure 1), and a similar scheme can be envisaged for the 9-deoxyanthracyclinone system. Indeed, a number of syntheses based on this idea have been reported; they each reflect different approaches towards the non-trivial construction of the (4H)-naphthalenone moiety.

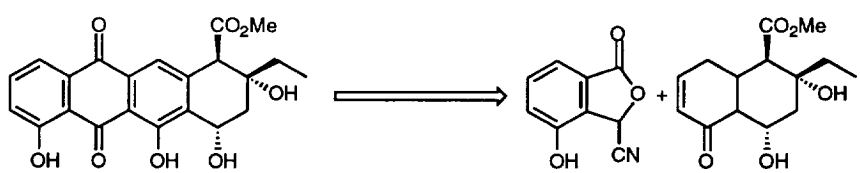
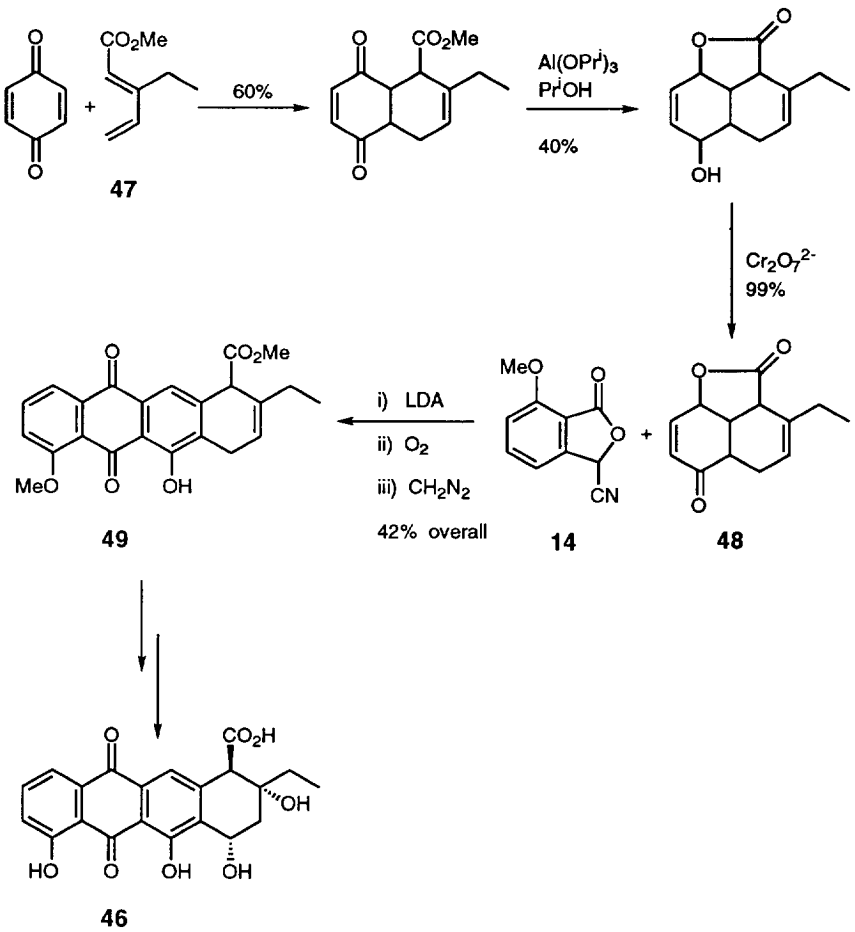


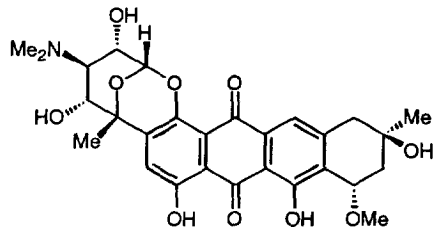
Figure 1. Retrosynthetic analysis of 11-deoxyanthracyclines

This method is exemplified by the elegant regioselective and stereoselective total synthesis[23,24] of racemic aklavinone (46) by Li *et al.*, shown in Scheme 8. Meerwein-Ponndorf-Verley reduction of the Diels-Alder adduct of dienoate (47) and benzoquinone, followed by Jones oxidation of the allylic alcohol, afforded the functionalized naphthalenone (48). Subsequent annulation of (48) with the anion of cyanophthalide (14) followed by aerial oxidation afforded the naphthacenequinone (49) which was further elaborated to (±)-aklavinone (46).

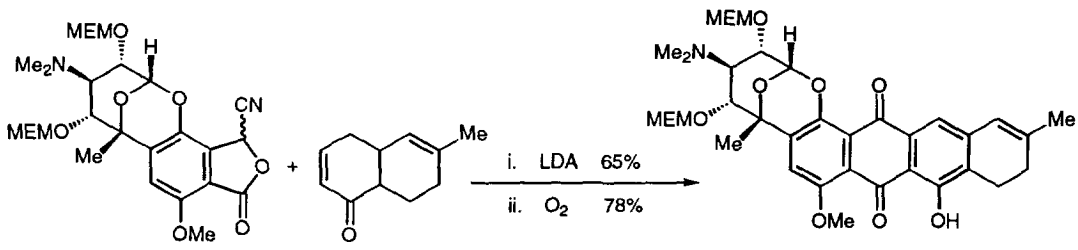


Scheme 8

A similar concept has been exploited by Hauser, who has developed general routes for the convergent, regiospecific synthesis of 9-deoxyanthracyclines, based on the annulation of hydronaphthalenones[25-37]. A further example of the utility of these reactions is shown in Scheme 9, with the synthesis of the *C*-glycoside anti-tumour antibiotic (±)-7-*con*-*O*-methylnogarol (50). The key synthetic reaction was the annulation of the hydronaphthalenone (51) with the racemic cyanophthalide (52)[38] to afford the hexacyclic intermediate (53). Elaboration of (53) to (±)-7-*con*-*O*-methylnogarol was accomplished using standard techniques.



50

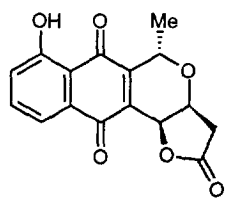


52 51 53

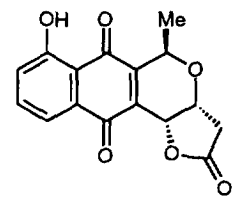
Scheme 9

3.3 Pyranones

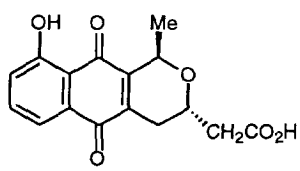
A number of naphtho[2,3-*c*]pyran-5,10-diones have been isolated from *Streptomyces* species, and some have been shown to possess significant anti-microbial activity and potential anti-tumour activity[39]. These include nanayomycin D (54) and its enantiomer kalafungin (55), nanayomycin A (17), deoxyfrenolicin (18), granaticin (21) and the *C*-glycosyl pyranonaphthoquinone medermycin (56).



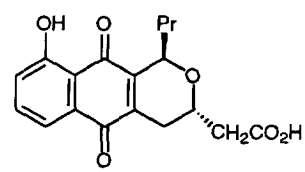
54



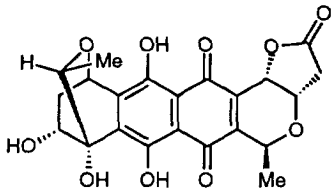
55



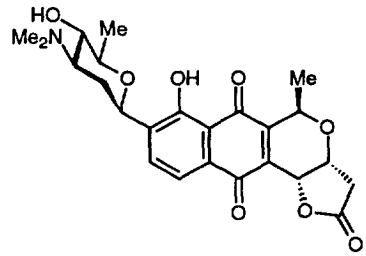
17



18

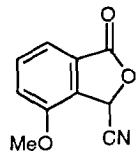


21

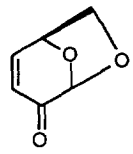


56

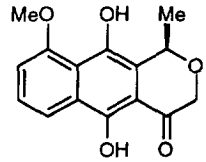
Phthalide anion annulation of α,β-unsaturated pyranones, which provides a rapid entry into the pyranonaphthoquinone system, was first reported by Kraus and Sugimoto[7]. Particularly useful is the reaction of carbohydrate derived enones, as this enables chiral molecules to be constructed. Laevoglucosenone (57) is a chiral pool intermediate readily available from the pyrolysis of starch or waste paper[40]. Annulation of laevoglucosenone (57) with the anion of cyanophthalide (58) afforded after several steps the naphthopyran (59), in which the methyl group has the same stereochemistry as the methyl group of kalafungin (17)[41].



58

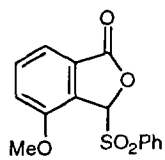


57

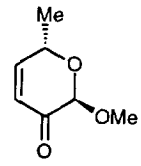


59

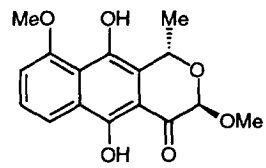
The enone (60) was prepared from methyl α-L-rhamnoside in three steps, and subsequent annulation of (60) with the anion of phenylsulfonylphthalide (61) afforded the chiral naphthohydroquinone (62) in 80% yield[39]. The naphthohydroquinone (62) was a key intermediate in the synthesis of kalafungin, nanayomycin A and nanayomycin D[39,42]. A similar reaction sequence involving the enantiomer of enone (58) (prepared from D-rhamnose) and the anion of the *C*-glycosylphenylsulfonylphthalide (63) afforded the chiral *C*-glycosylnaphthohydroquinone (64), which was further elaborated to medermycin (56)[43].



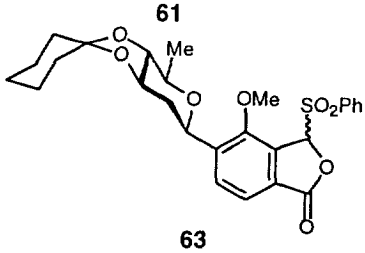
61



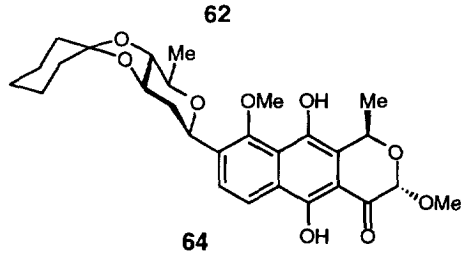
60



62

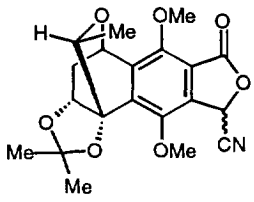


63

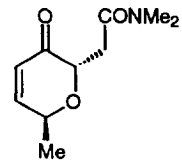


64

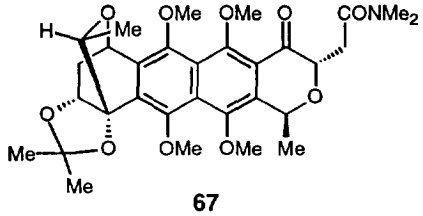
The homochiral enone (65), also derived from L-rhamnose, has been employed as the Michael acceptor in the enantioselective synthesis of granaticin (21)[44]. Reaction of (65) with the anion of the optically pure cyanophthalide (66) afforded the hexacyclic intermediate (67), which was elaborated to afford granaticin[44].



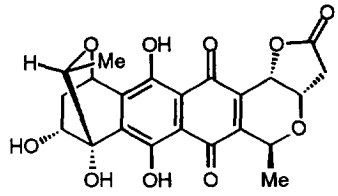
66



65



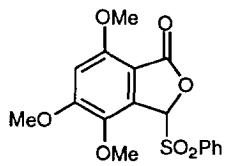
67



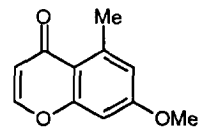
21

Hoffmann *et al.* have described the use of carbohydrate derived enones for the synthesis of isokalafungins and isonanayomycins[45].

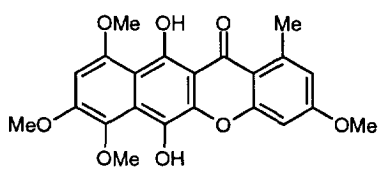
Benzopyranones also undergo phthalide anion annulation. Thus rapid entry into the benzo[*b*]xanthene-12-one system has been realized by annulation of the (4**H**)-benzopyranone (68) with the anion of phenylsulfonylphthalide (69), affording the bikaverin precursor (70) in 27% yield[46]. Oxidation of the hydroquinone system with silver carbonate on celite, and selective demethylation with lithium iodide in N,N-dimethylformamide afforded bikaverin (71), a red fungal pigment with specific antiprotozoal activity[46]. The poor yield of the annulation reaction reflects a general trend of the lower reactivity of sterically hindered phenylsulfonylphthalides. This limitation appears to be restricted to phenylsulfonylphthalide anions and in general the reaction of cyanophthalide anions is less influenced by substituents *peri* to the stabilizing group (*vide infra*).



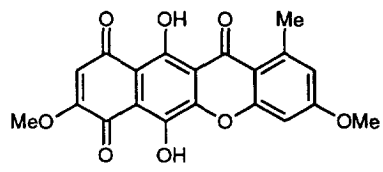
69



68

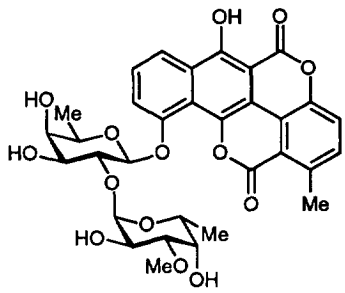


70

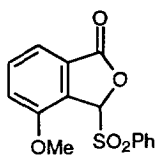


71

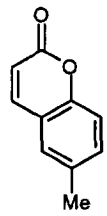
Chartreusin (72) is another *Streptomyces* antibiotic with significant anti-tumour activity[47]. The tetracyclic ring system (73) was easily prepared by annulation of the benzopyranone (74) with the anion of the phenylsulfonylphthalide (61). The fifth ring was elaborated by chloroformylation of the non-hydrogen bonded phenolic group of (73) with phosgene, followed by an intramolecular Friedel-Crafts acylation, affording the complex chartreusin aglycone (75) in few steps[48].



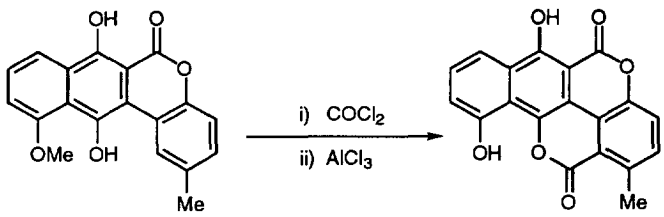
72



61



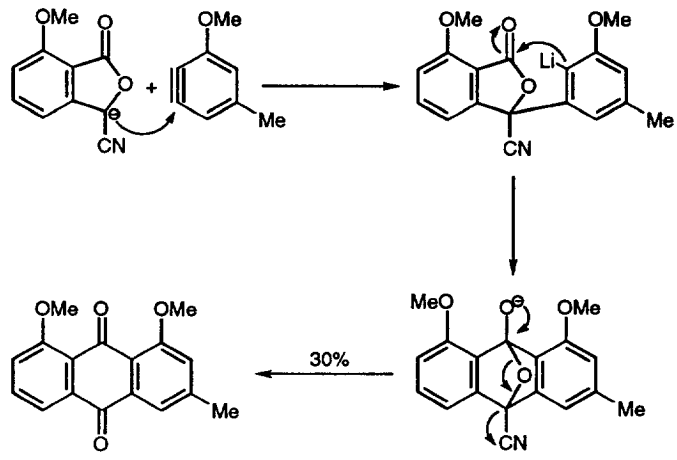
74



73 75

3.4 Arynes

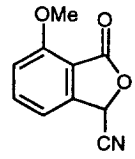
Sammes[49,50] has demonstrated that anthraquinones are formed by the annulation of arynes, with simple phthalide anions, followed by aerial oxidation of the intermediate product. Introduction of a leaving group on the three-position of the phthalide obviates the oxidation step and leads directly to anthraquinones[51-57]. A plausible mechanism for this transformation, illustrated by the synthesis of chrysophanol dimethyl ether (76), is shown in Scheme 10. This process avoids an additional oxidation step which is required when cyclohexenones are used as substrates.



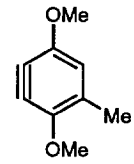
76

Scheme 10

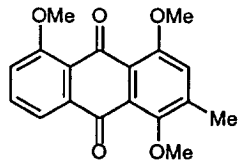
The presence of one methoxy group induces significant regiochemical control, indicating the more carbanionic character of the carbon *ortho* to the methoxy group; only trace amounts of the opposite regio-isomer were detected[51,56]. However, this regiochemical control is lost when the aryne is 1,4-dioxygenated; the asymmetrically substituted aryne (77) reacted with the anion of cyanophthalide (14) to afford almost equal amounts of the two regio-isomeric anthraquinones (78) and (79)[51,56].



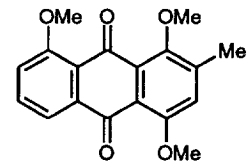
14



77

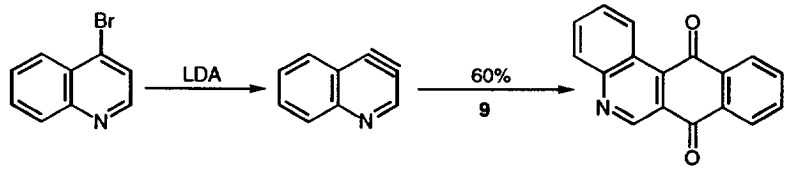


78

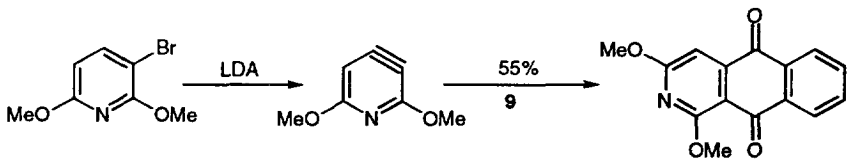


79

Several azaanthraquinones have been prepared from lithiated cyanophthalides and pyridynes[55]. The preparation of (80) and (81) are representative examples of this procedure.



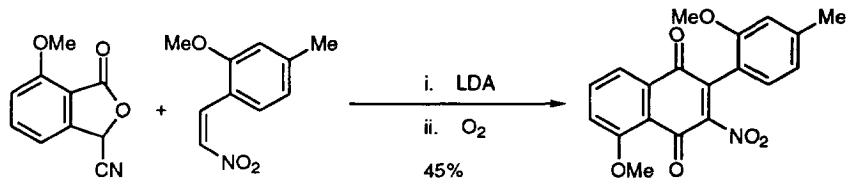
80



81

3.5 Nitroalkenes

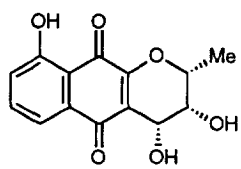
Although nitroolefins are well known as Michael acceptors, these have received only little attention as substrates for phthalide anion annulations. As part of a project directed towards the synthesis of the phenanthroviridin aglycone, the annulation of nitrostyrene (82) with the anion of cyanophthalide (14) was studied[15]. This is illustrated in Scheme 11. Although annulation of the corresponding methyl cinnamate was more efficient, the annulated nitro-adduct (83) was still isolated in 45% yield after oxidative work-up.



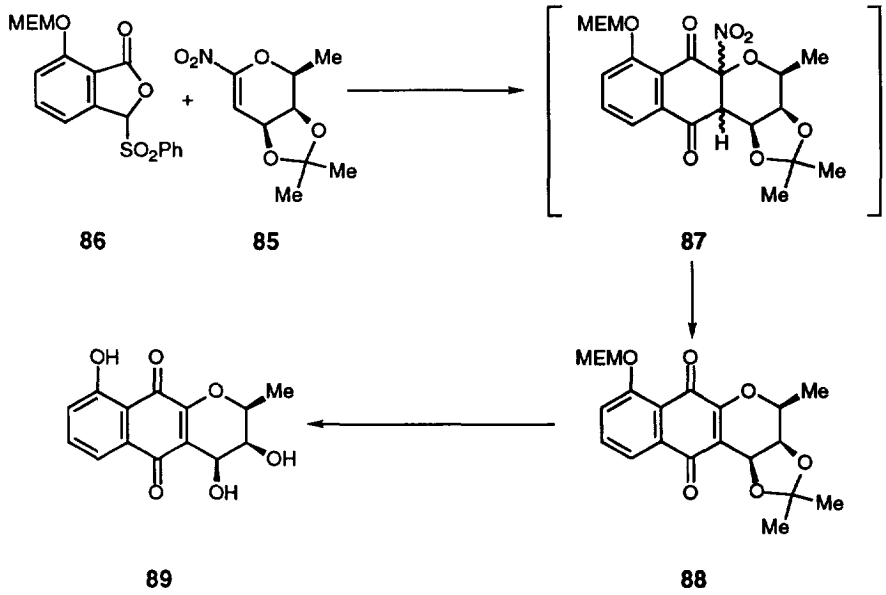
14 82 83

Scheme 11

(+)-Cryptosporin (84) is a metabolite of the fungus *Cryptospora pinicola*, and shows weak antibacterial activity towards *Gram*-positive bacteria. Brade and Vasella[58] have reported an elegant synthesis of (-)-cryptosporin based on the annulation of the L-fucose derived nitro-glycal (85) and the anion of 7-((2-methoxyethoxy)methoxy)phenylsulfonylphthalide (86). The intermediate (87) spontaneously eliminated nitrous acid to afford the naphthopyranoquinone (88) in 65% yield. (-)-Cryptosporin (89), was obtained by deprotection of the acetal groups.

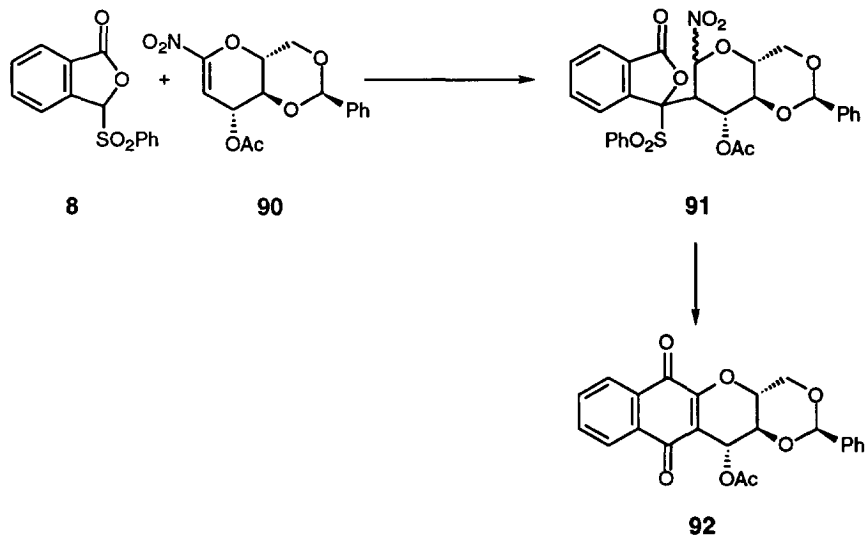


84



86 85 87 89 88

The reactivity of the anion of phenylsulfonylphthalide (8) towards the nitro-glycal (90) was also studied[58]. When the reaction mixture was quenched at 20° C, a mixture of epimeric Michael addition products (91) were isolated in 43% combined yield and the cyclized adduct (92) isolated in only 13% yield. However, briefly heating the reaction mixture to 40° C before quenching with acid afforded the annulated product (92) in excellent yield (89%).



8 90 91 92

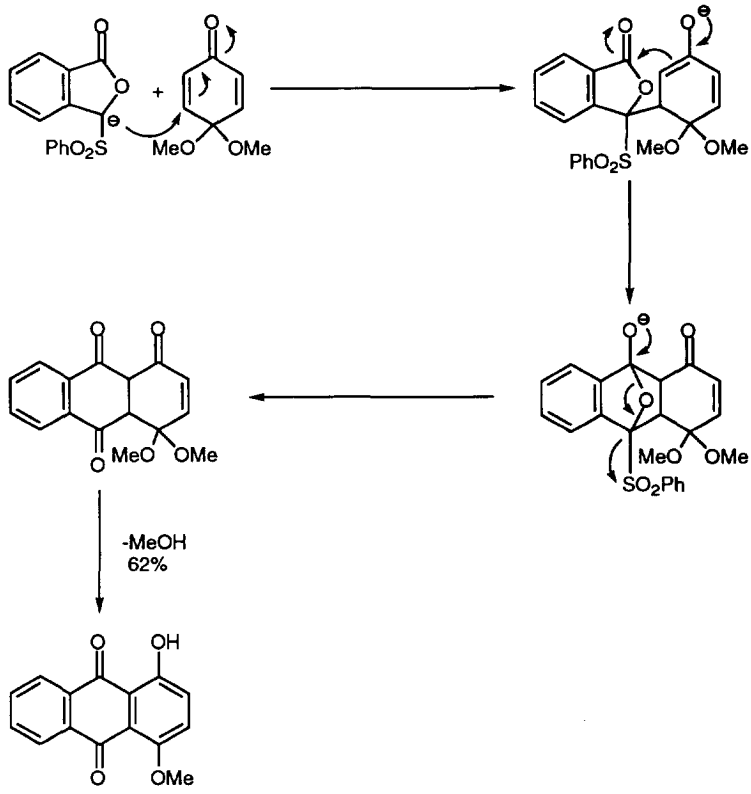
3.6 Quinones

The successful annulation of simple benzoquinones or naphthoquinones with phthalide anions has not been reported, even though these substrates are efficient Michael acceptors[59,60]. The failure of quinones to

annulate is probably caused by facile aromatization of the intermediate Michael adduct, with the resulting phenoxide anion being too poorly nucleophilic to attack the phthalide carbonyl group[56,61].

3.7 *para*-Quinone Monoketals

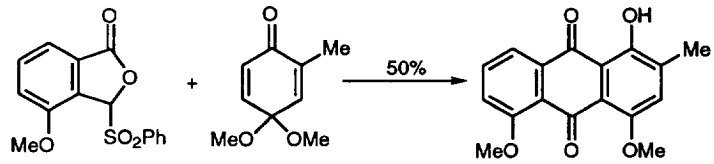
As shown in Section 3.2 the annulation of substituted cyclohexenones with cyanophthalide and phenylsulfonylphthalide anions provides easy access to 9- and 11-deoxyanthracyclines (*vide supra*). However, this methodology cannot readily be applied to the construction of the clinically important rhodomycinones which are based on a 1,4-dioxygenated anthraquinone. This limitation has been overcome by the introduction of quinone monoketals as substrates for the phthalide anion annulation reaction. Indeed the annulation of quinone monoketals with phthalide anions has now become a reaction of choice when assembling 1,4-dioxygenated anthraquinones and anthracyclines.



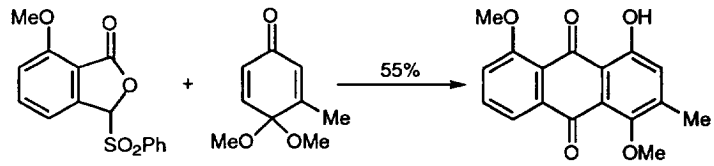
Scheme 12

Quinone monoketals, like arynes, afford anthraquinones directly, without requiring an additional oxidation step. However, unlike 1,4-dioxygenated arynes, which can give mixtures when annulated, quinone monoketals afford products of well-defined regiochemistry. A proposed mechanism for the annulation of benzoquinone monoketal with the anion of phenylsulfonylphthalide is outlined in Scheme 12. This route

towards 1,4-dioxygenated anthraquinones was first demonstrated by Russell and Warrener[56], and the versatility of the method was well illustrated by the synthesis of the anthraquinone (93) from the quinone monoketal (94) and 4-methoxyphenylsulfonylphthalide (61). The regio-isomeric anthraquinone (95) was prepared from the quinone monoketal (96) and 7-methoxyphenylsulfonylphthalide (10). The anthraquinones (93) and (95) were demethylated with boron tribromide, affording islandicin (97) by two complementary yet completely regioselective routes. This approach was reversed by annulating the dienones (94) and (96) with the anion of phenylsulfonylphthalides (10) and (61) respectively, to afford, after demethylation, digitopurpone (98), the regioisomer of islandicin.



61 94 93

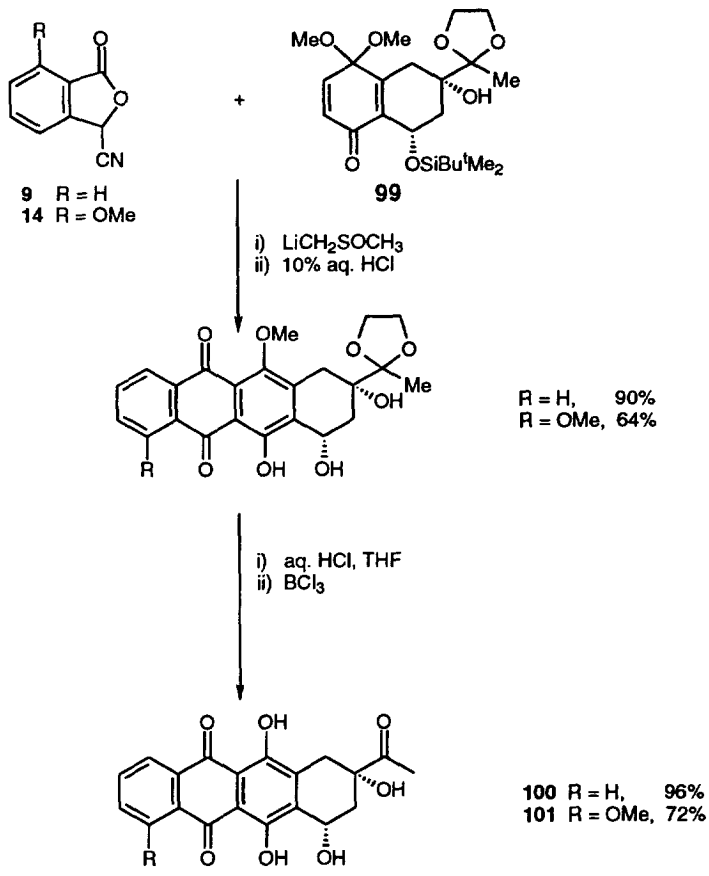


10 96 95

97 98

Two synthetic procedures that had a profound influence on syntheses directed towards the rhodomycinone skeleton were discovered in early anthracycline research. The first of these, the introduction of 7-hydroxyl group by benzylic bromination and solvolysis, was developed by Wong[62]. The second was the equilibration of C7 epimers to give daunomycinone enriched in the desired *cis* C7-C9 isomer[63]. As a consequence of these two results, many early syntheses of anthracyclines were directed to the preparation of the 7-deoxy-rhodomycinone system, with the knowledge that the 7-hydroxyl group could be introduced with the correct stereochemistry at a later stage. Indeed, a number of such syntheses of the 7-deoxy-rhodomycinone system, based on cyanophthalide anion or phenylsulfonyl anion annulation of suitable dienones, have been reported[64-69].

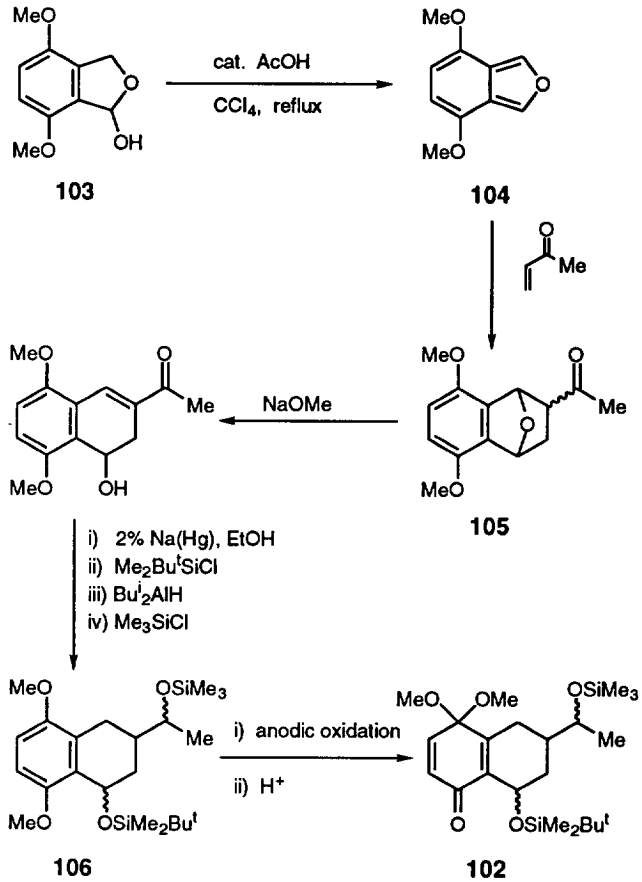
However, the success of the bromination-solvolysis procedure for introducing the A-ring benzylic oxygen group is highly dependant upon the substrate, and the equilibration and separation of C7-epimers is time-consuming and can be difficult to perform on a large scale. Swenton *et al.* have described the preparation of a fully oxygenated dienone[70-72] (99). Annulation of this dienone with the anion of cyanophthalide (9), followed by deprotection, afforded (+)-4-demethoxydaunomycinone (100) in 87% yield on a ten gram scale. (+)-Daunomycinone (101) was prepared from the anion of the methoxycyanophthalide (14), although the yields were lower for both the annulation and deprotection steps (Scheme 13).



Scheme 13

Keay and Rodrigo also have used the cyanophthalide anion route to prepare anthracyclinones[73,74]. Central to their synthesis was the quinone monoketal (102). As shown in Scheme 14, the acid catalyzed dehydration of phthalol (103) afforded the transient isobenzofuran (104) which readily undergoes $4\pi+2\pi$ cycloaddition with methyl vinyl ketone to afford a mixture of *endo* and *exo* Diels-Alder adducts (105). Base-induced retro-Michael reaction of these adducts afforded the α,β-unsaturated ketone, which was reduced and protected to afford the substituted tetralin (106). Anodic oxidation and selective monohydrolysis of (106)

afforded the anthracyclinone precursor (102). Further chemical manipulation of (102), of which a key step was the annulation of quinone monoketal (102) with the anion of cyanophthalide (14), afforded racemic daunomycinone[65,66].

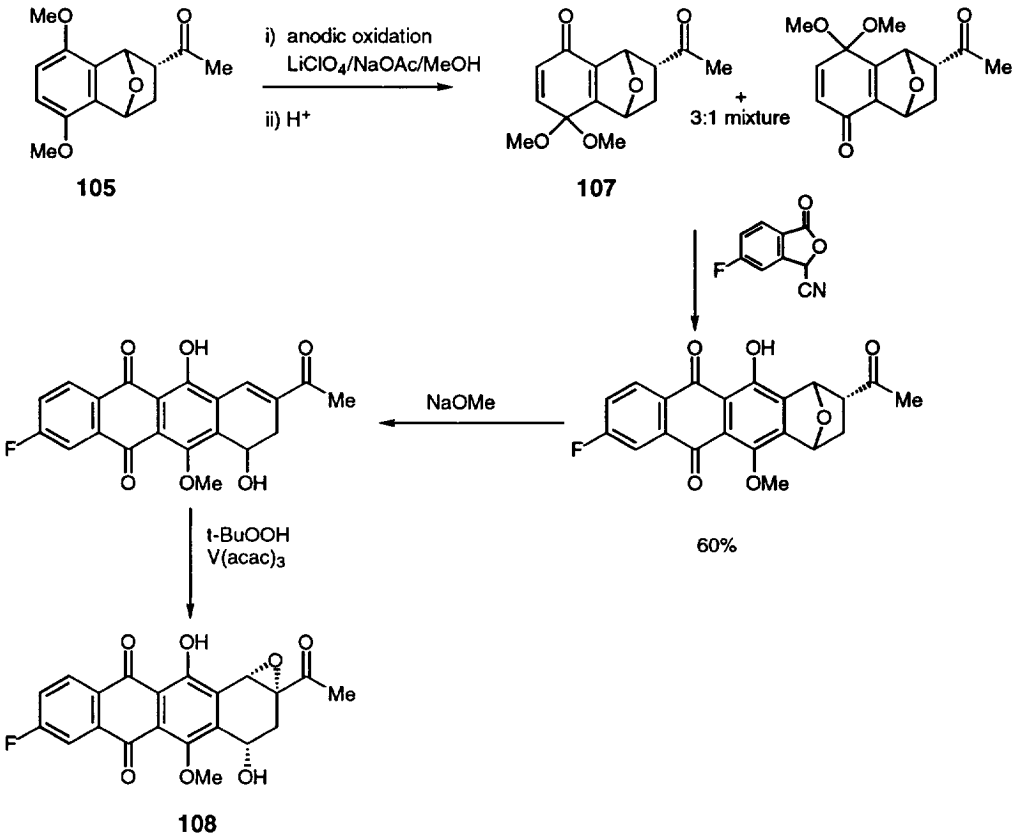


Scheme 14

Kim has creatively used the cyclic ether function in (105) to mask the double bond of an α,β–unsaturated ketone[75]. Thus precursor (105) was anodically oxidized to afford a regiomeric mixture of ketals. The major product (107) was elaborated *via* an annulation sequence to the anthracyclinone epoxide (108) (Scheme 15).

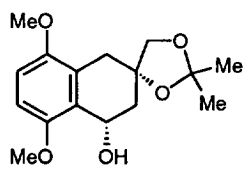
The above examples show simple synthetic routes to quinone monoketals related to the AB fragment of daunomycinone. The annulation of these quinone monoketals affords anthracyclinones in excellent yields, and enables the synthesis of a range of derivatives (such as fluorinated compounds) from a single AB fragment by simply changing the substitution of the phthalide anion. The major disadvantage of these procedures is that they are only suited to the preparation of racemic anthracyclinones. (Whilst Swenton *et al.*

did report the preparation of optically pure daunomycinone, the required resolution resulted in the loss of three-quarters of the starting material[72].)

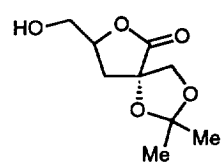


Scheme 15

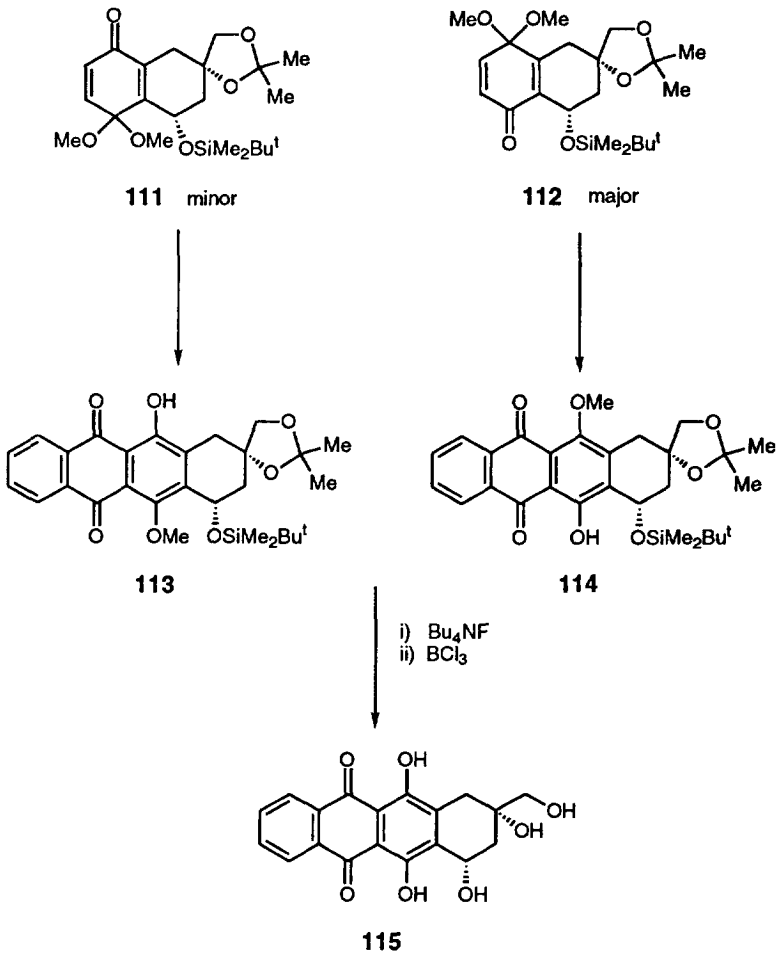
Monneret *et al.* have addressed this problem by preparing AB fragments with the required (7*S*,9*S*) stereochemistry from chiral pool intermediates[76,77]. The chiral precursor (109) was prepared from the commercially available α-D-isosaccharino-1,4-lactone (110) using a multi-step procedure. Protection of the benzylic alcohol of (109) and anodic oxidation afforded a near quantitative yield of the *bis*(ketal), which was selectively hydrolyzed to a 3:1 mixture of quinone monoketals (111) and (112). Annulation of the crude mixture of monoketals with the anion of cyanophthalide (9) afforded the regioisomeric anthracyclinone



109



110



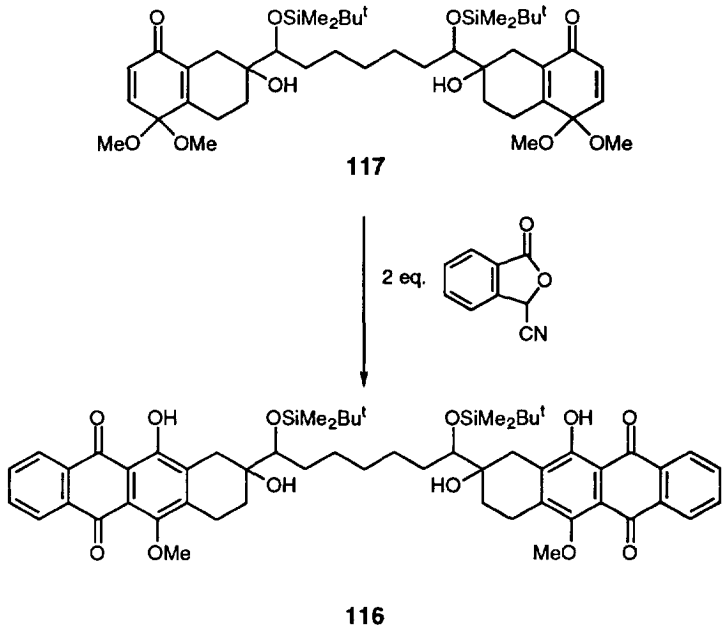
Scheme 16

precursors (113) and (114)[76]. Desilylation of this mixture with *tetra*-n-butylammonium fluoride followed by boron trichloride demethylation afforded the optically pure anthracyclinone (115) (Scheme 16)[76].

The cyanophthalide anion route is well suited to the preparation of derivatives in the rhodomycinone series. Indeed, by using a single chiral AB fragment, a number of D-ring modified derivates can be prepared by simply altering the substitution on the phthalide anion used for the annulation. This chemistry has been used to prepare adriamycin analogues and anthracycline precursors[78] that cannot be prepared by aerobic fermentation. Indeed, a number of synthetic A-ring fluorinated derivatives of anthracylines have been prepared using fluorinated phthalide anions as annulating reagents[79-82], and a ^{13}C-labelled cyanophthalide was used to prepare an isotopically labelled anthracycline[83].

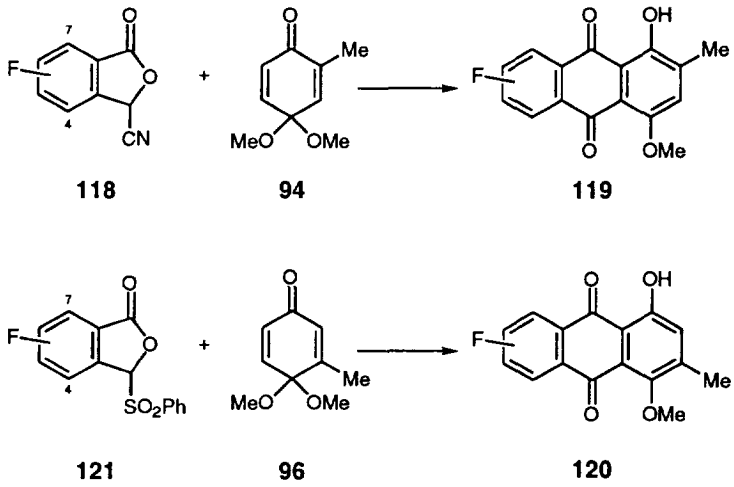
The phthalide anion annulation of *bis*(quinone monoketals) offers a rapid route to *bis*(anthraquinones) and *bis*(anthracyclines)[84-88]. A novel synthesis[84] of the *bis*(anthracycline) (116), which involved the cyanophthalide anion annulation of the *bis*(quinone ketal) (117), was reported by Russell *et al.*, and is

outlined in Scheme 17. This work has been further extended to include the synthesis of *bis*(anthraquinones) linked by polyamide[87,88] and polyether chains[88].



Scheme 17

An important result arising from a systematic study of the annulation reaction was the demonstration of the superiority of cyanophthalide anions over phenylsulfonylphthalide anions as annulating reagents[66,86]. In a series of reactions, the monofluorinated cyanophthalides (118) afforded consistently, and in some cases, quite markedly higher yields of anthraquinones (119) and (120) than the corresponding

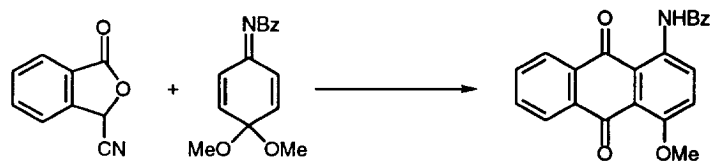


phenylsulfonylphthalides (121) when reacted with the dienones (94) and (96) respectively. This difference was even more pronounced when constructing tetracycles[66]. These results are summarized in Table 2.

Table 2. Comparison of the efficiency of cyanophthalide and phenylsulfonylphthalide anions as annulating reagents[66].

phthalide anion	dienone	% yield of anthraquinone from	
		phenylsulfonylphthalide	cyanophthalide
4-fluoro	(94)	45	76
5-fluoro	(94)	42	84
6-fluoro	(94)	44	73
7-fluoro	(94)	74	79
4-fluoro	(96)	53	82
5-fluoro	(96)	25	86
6-fluoro	(96)	51	93
7-fluoro	(96)	53	85

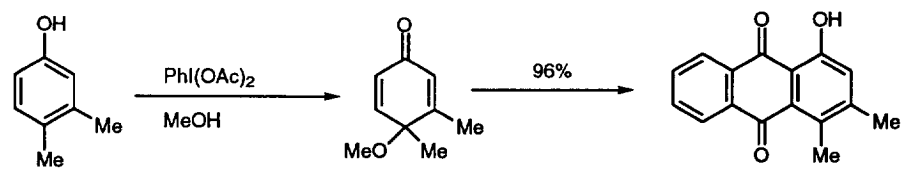
Annulation of the quinone imine acetal (122) with the anion of cyanophthalide (9) afforded the aminoanthraquinone (123)[89].



9 **122** **123**

3.8 2,5-Cyclohexadienones

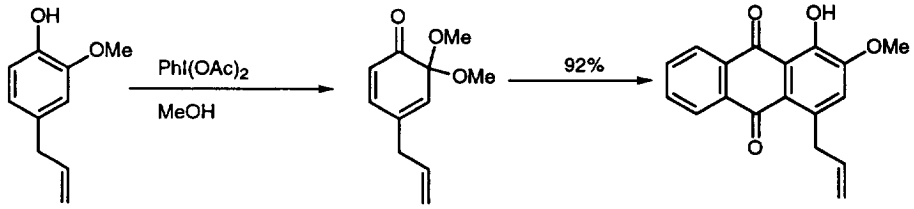
Direct extension of this chemistry has resulted from the observation that 4-substituted phenols can be oxidized with phenyliodonium diacetate or phenyliodonium *bis*(trifluoroacetate) in methanol solution to afford 4-methoxycyclohexa-2,5-dienones[90]. These products, like quinone monoketals, undergo a high yielding annulation with the anion of cyanophthalide (9) to afford the corresponding anthraquinones (Scheme 18)[90].



Scheme 18

3.9 *ortho*-Quinone Monoketals

A further extension of the reaction came with the discovery that some 2-methoxyphenols could afford *ortho*-quinone monoketals which resist self-dimerization sufficiently long enough to permit annulation (Scheme 19)[90]. Likewise, some 2-alkylphenols can be oxidized to 6-methoxy-2,4-cyclohexadienones which are also excellent substrates for the annulation reaction[90]. In short, these more recent developments have considerably extended the scope of the reaction to encompass a wide variety of substitution patterns.



Scheme 19

4. REFERENCES

1. Eckart, K. Quinones and Other Carbocyclic Antitumour Compounds. In *Antitumour Compounds of Natural Origin*; Aszalos, A. Ed.; CRC Press: Boca Raton, 1981; pp. 27-57.
2. El Khadem, H. S. Ed. *Anthracycline Antibiotics*; Academic Press: New York, 1982.
3. Eisenhuth, W.; Renfroe, H. B.; Schmid, H. *Helv. Chim. Acta*, **1965**, *45*, 375-379.
4. Broom, N. J. P.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.*, **1978**, 162-164.
5. Wadi, A.; Lopez-Calahora, F.; Alvarez, M.; Joule, J. A. *Tetrahedron Lett.*, **1992**, *33*, 3679-3682.
6. Hauser, F. M.; Rhee, R. P. *J. Org. Chem.*, **1978**, *43*, 178-180.
7. Kraus, G. A.; Sugimoto, H.*Tetrahedron Lett.*, **1978**, 2263-2266.
8. Hauser, F. M.; Rhee, R. P. *J. Am. Chem. Soc.*, **1979**, *101*, 1628-1629.
9. Hauser, F. M.; Rhee, R. P. *J. Org. Chem.*, **1980**, *45*, 3061-3068.
10. Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.*, **1987**, *52*, 1273-1276.
11. Nomura, K.; Okazaki, K.; Hori, K.; Yoshii, E. *Chem. Pharm. Bull.*, **1986**, *34*, 3175-3182.
12. Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh, S. *J. Org. Chem.*, **1983**, *48*, 3439-3444.
13. Nomura, K.; Okazaki, K.; Hori K.; Yoshii, E. *J. Am. Chem. Soc.*, **1987**, *109*, 3402-3408.
14. Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem.*, **1991**, *56*, 2289-2291.
15. Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem.*, **1992**, *57*, 2774-2783.
16. Parker, K. A.; Koziski, K. A.; Breault, G. *Tetrahedron Lett.*, **1985**, *26*, 2181-2182.
17. Saint-Jalmes, L.; Lila, C.; Xu, J. Z., Moreau, L.; Pfeiffer, B.; Eck, G.; Pelsez, L.; Rolando, C.; Julia, M. *Bull. Soc. Chim. Fr.*, **1993**, *130*, 447-449.
18. Hauser, F. M.; Prasana, S. *J. Org. Chem.*, **1982**, *47*, 383-384.
19. Rho, Y. S.; Park, S. H.; Kim, S.; Yun, Y. K.; Cho, I. H.; Kang, H. S. *Bull. Korean Chem. Soc.*, **1994**, *15*, 360-364, [*Chem. Abstr.*, **1994**, *121*, 133837s].

20. Hauser, F. M.; Caringal, Y. *J. Org. Chem.*, **1990**, *55*, 555-559.
21. Hauser, F. M.; Prasanna, S. *J. Org. Chem.*, **1979**, *44*, 2596-2598.
22. Hauser, F. M.; Prasanna, S. *J. Am. Chem. Soc.*, **1981**, *103*, 6378-6386.
23. Li, T.; Walsgrove, T. C. *Tetrahedron Lett.*, **1981**, *21*, 3741-3744.
24. Li, T.; Wu, Y.L. *J. Am. Chem. Soc.*, **1981**, *103*, 7007-7009.
25. Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.*, **1983**, *105*, 5688-5690.
26. Hauser, F. M.; Prasanna, S.; Combs, D. W. *J. Org. Chem.*, **1983**, *48*, 1328-1333.
27. Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.*, **1984**, *106*, 1098-1104.
28. Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.*, **1984**, *106*, 1862-1863.
29. Cho, I. H.; Rho, Y. S.; Sho, S. M.; Yoo, D. J.; Lee, J. Y.; Han, B. K. *J. Korean Chem. Soc.*, **1992**, *36*, 925-932, [*Chem. Abstr.*, **1993**, *119*, 95182y].
30. Cho, I. H.; Rho, Y. S.; Park, S. H.; Ahn, K. H.; Sin, H. S.; Han, B. K. *J. Korean Chem. Soc.*, **1993**, *37* 141-147, [*Chem. Abstr.*, **1993**, *119*, 72416p].
31. Hauser, F. M.; Mal, D. *Tetrahedron,* **1984**, *40*, 4711-4717.
32. Hauser, F. M.; Baghdanov, V.M. *Tetrahedron,* **1984**, *40*, 4719-4724.
33. Hauser, F. M.; Mal, D. *U. S. Pat.* 4,515,720 (7 May 1985), [*Chem. Abstr.*, **1985**, *103*, 123268w].
34. Hauser, F. M.; Hewawasam, P.; Mal, D. *J. Am. Chem. Soc.*, **1988**, *110*, 2919-2924.
35. Hauser, F. M.; Hewawasam, P.; Rho, Y. S. *J. Org. Chem.*, **1989**, *54*, 5110-5114.
36. Cho, I. H.; Chung, J. S.; Han, B. K.; Yoo, D. J.; Lee, J. Y. Rho, Y. S. *Taehan Hwahakhoe Chi*, **1989**, *33*, 644, [*Chem. Abstr.*, **1990**, *113*, 5997s].
37. Hauser, F. M.; Tommasi, R. A. *J. Org. Chem.*, **1991**, *56*, 5758-5759.
38. Hauser, F. M.; Chakrapani, S.; Ellenberger, W. P. *J. Org. Chem.*, **1991**, *56*, 5248-5250.
39. Tatsuta, K.; Akimoto, K.; Annaka, M.; Ohno, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.*, **1985**, *58*, 1699-1706.
40. Ward, R. B. in *Methods in Carbohydrate Chemistry*, Vol. 2,; Whistler, R. L. and Wolfram, M. L., Eds.; Academic Press: London, 1963; pp. 394-396.
41. Freskos, J. N.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.*, 1985, 658-659.
42. Umezawa, H.; Takeuchi, T.; Tatsuta, K.; Akimoto, K. *Jpn. Kokai Tokkyo Koho* 6,1172,882 (4 August1986), [*Chem. Abstr.*, 1987, **106**, 49880h].
43. Tatsuta, K.; Ozeki, H.; Yamaguchi, M.; Tanaka, M.; Okui, T. *Tetrahedron Lett.*, **1990**, *31*, 5495-5498.
44. Okazaki, K.; Nomura, K.; Yoshii, E. *J. Chem. Soc., Chem. Commun.*, **1989**, 354-356.
45. Hoffmann, B.; Schoenebaum, A.; Lackner, H. *Liebigs Ann. Chem.*, **1993**, 333-342.
46. Hauser, F. M.; Hewawasam, P.; Baghdanov, V. M. *J. Org. Chem.*, **1988**, *53*, 223-224.
47. McGovren, J. P.; Neil, G. L.; Crampton, S. L.; Robinson, M. I.; Douros, J. D. *Cancer Res.*, **1977**, *37*, 1666-1672.
48. Hauser, F. M.; Combs, D. W. *J. Org. Chem.*, **1980**, *45*, 4071-4073.
49. Sammes, P. G.; Dodsworth, D. J.; *J. Chem. Soc., Chem Commun.*, **1979**, 33-34.
50. Dodsworth, D. J.; Calcagno, M.-P.; Ehrmann, E.U.; Devadas, B.; Sammes, P. G. *J. Chem Soc., Perkin Trans. 1*, **1981**, 2120-2124.
51. Khanapure, S. P.; Thimma Reddy, R.; Biehl, E. R. *J. Org. Chem.*, **1987**, *52*, 5685-5690.
52. Khanapure, S. P.; Biehl, E. R. *J. Nat. Prod.*, **1989**, *52*, 1357-1359.
53. Bates, M. A.; Sammes, P. G.; Thomson, G. A. *J. Chem. Soc., Perkin Trans. 1*, **1988**, 3037-3045.

54. Khanapure, S. P.; Biehl, E. R. *Synthesis*, **1991**, 33-36.
55. Khanapure, S. P.; Biehl, E. R. *Heterocycles*, **1988**, *27*, 2643-2650.
56. Russell, R. A.; Warrener, R. N. *J. Chem. Soc., Chem. Commun.*, **1981**, 108-109.
57. Biehl, E. R.; Deshmukh, A. R.; Dutt, M. *Synthesis*, **1993**, 885-888.
58. Brade, W.; Vasella, A. *Helv. Chim. Acta*, **1988**, *72*, 1649-1657.
59. Kutyrev, A. A. *Tetrahedron*, **1991**, *47*, 8043-8065.
60. Finley, K. T. In *The Chemistry of the Quinonoid Compounds*, Vol. 1; Patai, S. Ed. John Wiley and Sons: London, 1974; pp. 877-1144.
61. Treub, W.; Eugster, C. H. *Helv. Chim. Acta*, **1972**, *55*, 969-973.
62. Wong, C. M.; Schwenk, R.; Popien, D.; Ho, T.-L. *Can. J. Chem.*, **1973**, *53*, 466-467.
63. Brockmann, H.; Niemeyer, J. *Chem. Ber.*, **1967**, *100*, 3578-3587.
64. Russell, R. A.; Krauss, A. S.; Irvine R. W.; Warrener, R. N. *Aust. J. Chem.*, **1985**, *38*, 179-187.
65. Russell, R. A.; Irvine, R. W.; Warrener, R. N. *Aust. J. Chem.*, **1985**, *38*, 189-195.
66. Russell, R. A.; Pilley, B. A.; Irvine, R. W.; Warrener, R. N. *Aust. J. Chem.*, **1987**, *40*, 311-323.
67. Russell, R. A.; Irvine, R. W.; Warrener, R. N. *J. Org. Chem.*, **1986**, *51*, 1595-1599.
68. Russell, R. A.; Crane, M. P. unpublished work
69. Russell, R. A.; Irvine, R. W.; Kraus, A. S., *Tetrahedron Lett.*, **1984**, *25*, 5817-5820.
70. Dolson, M. G.; Chernard, B. L.; Swenton, J. S., *J. Am. Chem. Soc.*, **1981**, *103*, 5263-5264.
71. Swenton, J. S. Regiospecific, Convergent Strategies for Anthracyclinone Synthesis Using Quinone Bis-And Monoketals. In *Anthracycline Antibiotics* ; El Khadem, H. S. Ed. Academic Press: New York 1982; pp. 167-196.
72. Swenton, J. S.; Freskos, J. N.; Morrow, G. W.; Sercel, A. D. *Tetrahedron*, **1984**, *40*, 4625-4632.
73. Keay, B. A.; Rodrigo, R. *Can. J. Chem.*, **1983**, *61*, 637-639.
74. Keay, B. A.; Rodrigo, R. *Tetrahedron*, **1984**, *40*, 4597-4607.
75. Kim, H. Y, Ping, G.; Russell, R. A. Unpublished results.
76. Genot, A.; Florent, J.-C.; Monneret, C. *J. Org. Chem.*, **1987**, *52*, 1057-1063.
77. Deguin, B.; Florent, J.-C.; Monneret, C. *J. Org. Chem.*, **1991**, *56*, 405-411.
78. Azadi-Ardakani, M.; Hayes, R.; Wallace, T. W. *Tetrahedron*, **1990**, *46*, 6851-6858.
79. Morrow, G. W.; Swenton, J. S.; Filppi, J. A.; Wolgemuth, R. L. *J. Org. Chem.*, **1987**, *52*, 713-719.
80. Swenton, J. S. ; Morrow, G. W.; Priebe, W. *U. S. Pat.* 4,697,005 (29 September 1987), [*Chem. Abstr.*, **1988**, *107*, 6348q].
81. Swenton, J. S.; Horton, D.; Priebe, W.; Morrow, G. W. *U. S. Pat.* 4,663,445 (5 May 1987), [*Chem. Abstr.*, **1989**, *110*, 134970q].
82. Irvine, R. W.; Kinloch, S. A.; Mc Cormick, A. S.; Russell, R. A.; Warrener, R. N. *Tetrahedron*, **1988**, *44*, 4591-4604.
83. Becker, A. M.; Irvine, R. W.; McCormick, A. S.; Russell, R. A.; Warrener, R. N. *Tetrahedron Lett.*, **1986**, *27*, 3431-3434.
84. Russell, R. A.; Day, A. I.; Pilley, B. A.; Leavy, P. J.; Warrener, R. N. *J. Chem. Soc., Chem. Commun.*, **1987**, 1631-1633.
85. Russell, R. A.; Leavy, P. J. unpublished results
86. Russell, R. A.; Pilley, B. A. unpublished results
87. Russell, R. A.; Longmore, R. W.; Warrener, R. N. *Aust. J. Chem.*, **1991**, *44*, 1691-1704.

88. Longmore, R. W. M. Sc. Thesis, Bond University, 1987.
89. Swenton, J. S.; Bonke, B. R.; Clark, W. M.; Chen, C.-P.; Martin, K. V. *J. Org. Chem.*, **1990**, *55*, 2027-2034.
90. Mitchell, A. S.; Russell, R.A. *Tetrahedron Lett.*, **1993**, *34*, 545-548.

(*Received* 14 *February* 1995)