SYNTHETIC STUDIES TOWARDS PANACENE

A THESIS PRESENTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN CHEMISTRY AT MASSEY UNIVERSITY

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ABSTRACT

SYNTHETIC STUDIES TOWARDS PANACENE (1)

2-Trimethylsilyloxyfuran (23) and 2-acetyl-1,4-benzoquinone (6) were prepared according to published methods. The uncatalysed addition of 2-trimethylsilyloxyfuran (23) to the quinone (6) gave cis-3a,8b-dihydro-8-acetyl-7-hydroxyfuro-[3,2-b]benzofuran-2-(3H)-one (24) in 50% yield. The reaction of other 1,4-benzoquinones was investigated, establishing the necessity of an activating substituent at C-2 of the quinone. Attempts to reduce the acetyl group of cis-3a,8b-dihydro-8--acetyl-7-hydroxyfuro[3,2-b]benzofuran-2-(3H)-one (24) to the ethyl group present in panacene (1) were unsuccessful, although reduction of the ketone with sodium borohydride gave cis-3a,8b-dihydro-8-(1'-hydroxyethyl)-7-hydroxyfuro[3,2-b]-benzofuran-2-(3H)-one (51).

The conversion of cis-3a,8b-dihydro-8-acetyl-7-hydroxyfuro-[3,2-b]benzofuran-2-(3H)-one (24) to cis-3,3a,9b-trihydro-5-hydroxy-5-methylfuro[3,2-c][2]benzopyran-2,6,9-(5H)-trione (58) was carried out using ceric ammonium nitrate.

ACKNOWLEDGEMENTS

Firstly, I would like to thank my supervisor Dr Margaret Brimble for her enthusiasm and encouragement throughout my research. Thanks must also go to Professor Richard Hodges for running mass spectra on my compounds, and to Martin Hunt and Dr Geoffrey Lane of Applied Biochemistry Division, D.S.I.R. for providing one and two-dimensional ^{1}H and ^{13}C n.m.r. spectra and assisting in the interpretation. I also thank Dr Mark Brimble for proof-reading this thesis.

Secondly, I would like to mention my family who gave me their support in whatever I chose to do, and my fiancé Neill Haggarty, who has kept me on an even keel since I have known him.

CONTENTS

ABBREVIATIONS

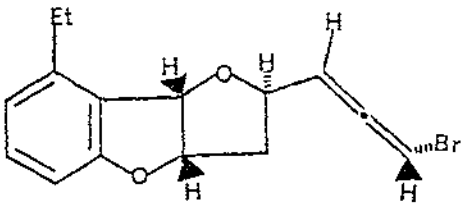
CAN	=	ceric ammonium nitrate
DMF	=	*N*,*N*-dimethylformamide
DMSO	=	dimethyl sulphoxide
NBS	=	*N*-bromosuccinimide
TES	=	triethylsilane
TFA	=	trifluoroacetic acid
TMSCl	=	chlorotrimethylsilane
Ts	=	*p*-toluenesulphonyl
p-TSA	=	*p*-toluenesulphonic acid

CHAPTER 1

INTRODUCTION

1.1 Panacene (1)

Panacene (1), a potent fish antifeedant, is one of several halogenated marine natural products isolated from Aplysia brasiliana in 1977 by Meinwald et al.[1]. Spectroscopic techniques revealed the presence of a bromo-allene moiety, and the uncommon cis-3a,8b-dihydrofuro[3,2-b]benzofuran ring system. This ring system has been reported in only one other natural product, the alkaloid rutagravine (2)[2], and in a decomposition product (3) of the naturally occurring coumarin micromelin (4).



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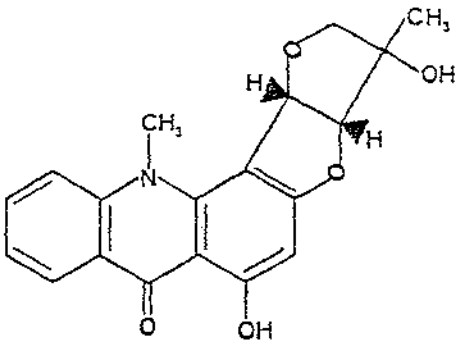

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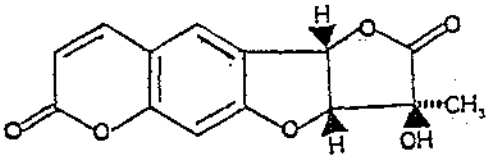

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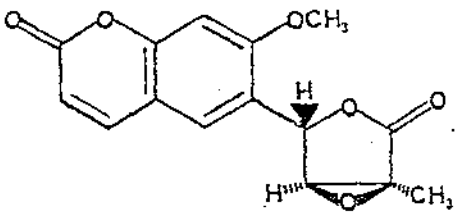
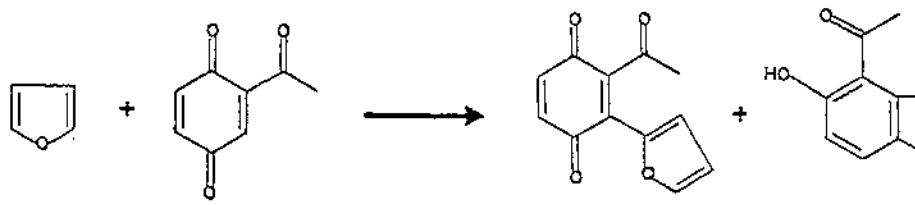


(4)

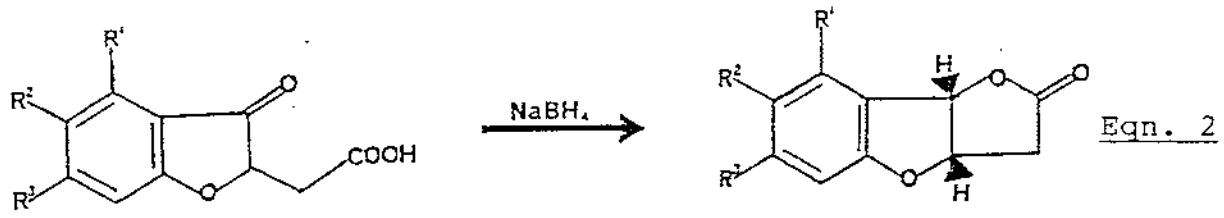
1.2 The cis-3a,8b-Dihydrofuro[3,2-b]benzofuran Ring System

Independently of the synthesis of panacene (1) itself, the parent cis-3a,8b-dihydrofuro[3,2-b]benzofuran ring system has been made by several groups[4,5,6]. In 1971, Eugster et al.[4] reacted furan (5) with 2-acetyl-1,4-benzoquinone (6), obtaining cis-3a,8b-dihydro-8-acetyl-7-hydroxyfuro-[3,2-b]benzofuran (7) in 7% yield (Eqn.1).



(5) (6) (7) (8) Eqn.1

In the same year, Arora and Brassard[5] reported the reduction of the substituted 2-coumaranonyl acetic acids (8) and (9) with sodium borohydride, to give high yields of the lactones (10) and (11) (Eqn.2).



Eqn. 2

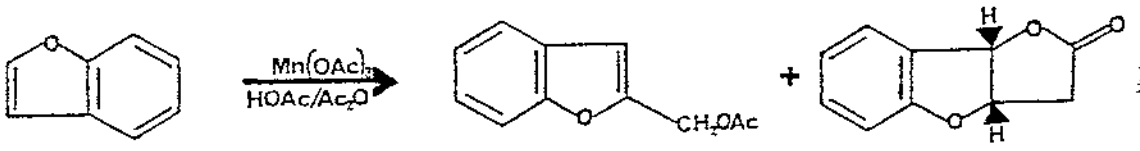
(8): $R^1=R^3=CH_3$; $R^2=H$.

(9): $R^1=R^2=$benzo; $R^3=H$.

(10): $R^1=R^3=CH_3$; $R^2=H$; 70% yield.

(11) $R^1=R^2=$benzo; $R^3=H$; 80% yield.

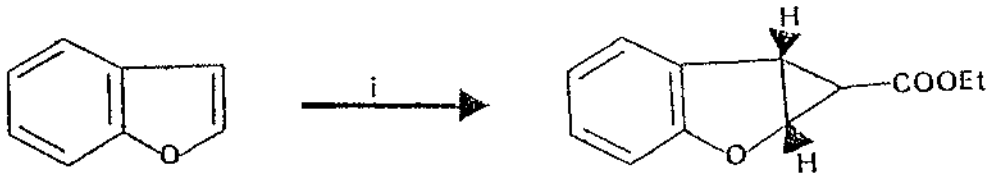
Later, in a study of the oxidation of benzofuran (12) with manganic acetate, Kasahara et al.[6] reported the isolation of the lactone cis-3a,8b-dihydrofuro[3,2-b] benzofuran-2-(3H)-one (13) in 21% yield (Eqn.3).



Eqn. 3

(12) (13), 21% 42%

More recently, Wenkert *et al.*[7] effected a Fétizon oxidation of the alcohol (14) to give the unsubstituted ring system (15) in 17% yield. The alcohol itself was a product of the copper-catalysed decomposition of ethyl diazoacetate in benzofuran (12), followed by reduction with lithium aluminium hydride (Scheme 1).



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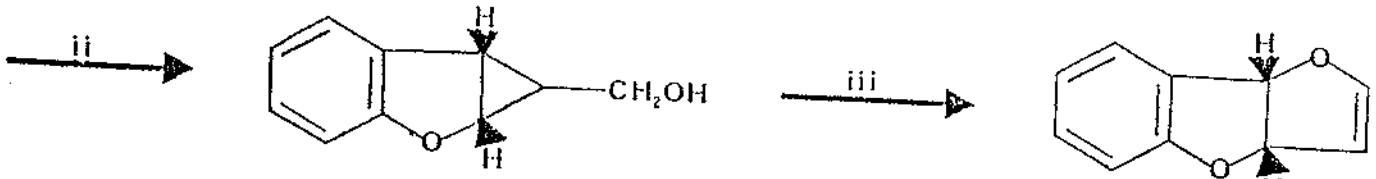


(14)

(15)

Reagents: (i) $N_2CHCOOEt$, Cu, heat; (ii) $LiAlH_4$; (iii) Ag_2CO_3 on celite, benzene (17% yield).

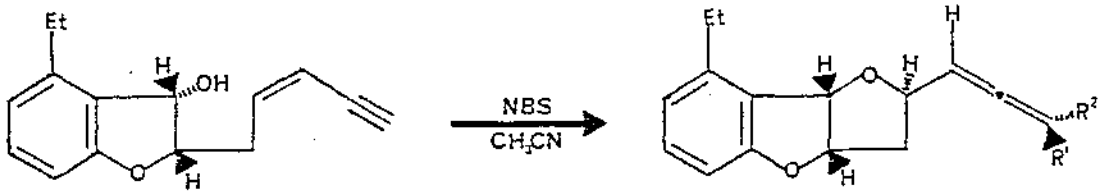
Scheme 1

1.3 Previous Syntheses of Panacene (1)

Studies towards the total synthesis of panacene (1) have led to the development of other reactions producing the cis-3a,8b-dihydrofuro[3,2-b]benzofuran ring system. To date, two syntheses of panacene (1) have been reported[8,9].

In 1982, Feldman et al.[8] published a total synthesis of panacene (1) and 1-epibromopanacene (16). The cis-dihydrobenzofuran (17), prepared from ethyl 6-ethylsalicylate (18), underwent smooth oxidative cyclisation upon treatment with N-bromosuccinimide to form the cis-3a,8b-dihydrofuro[3,2-b]-benzofuran ring system. The initial bromide (19) was converted in situ to the corresponding acetate, which upon hydrolysis and subsequent oxidation, afforded the aldehyde (20). Several more steps were then required to convert the aldehyde (20) into panacene (1) and 1-epibromopanacene (16) (Scheme 2).

Later that year, Feldman[9] published a biomimetic synthesis of panacene (1). In this case, the key step involved brominative cyclisation of the hydroxyenyne (21) to give a 1:1 mixture of panacene (1) and 1-epibromopanacene (16) in 62% yield (Eqn.4).

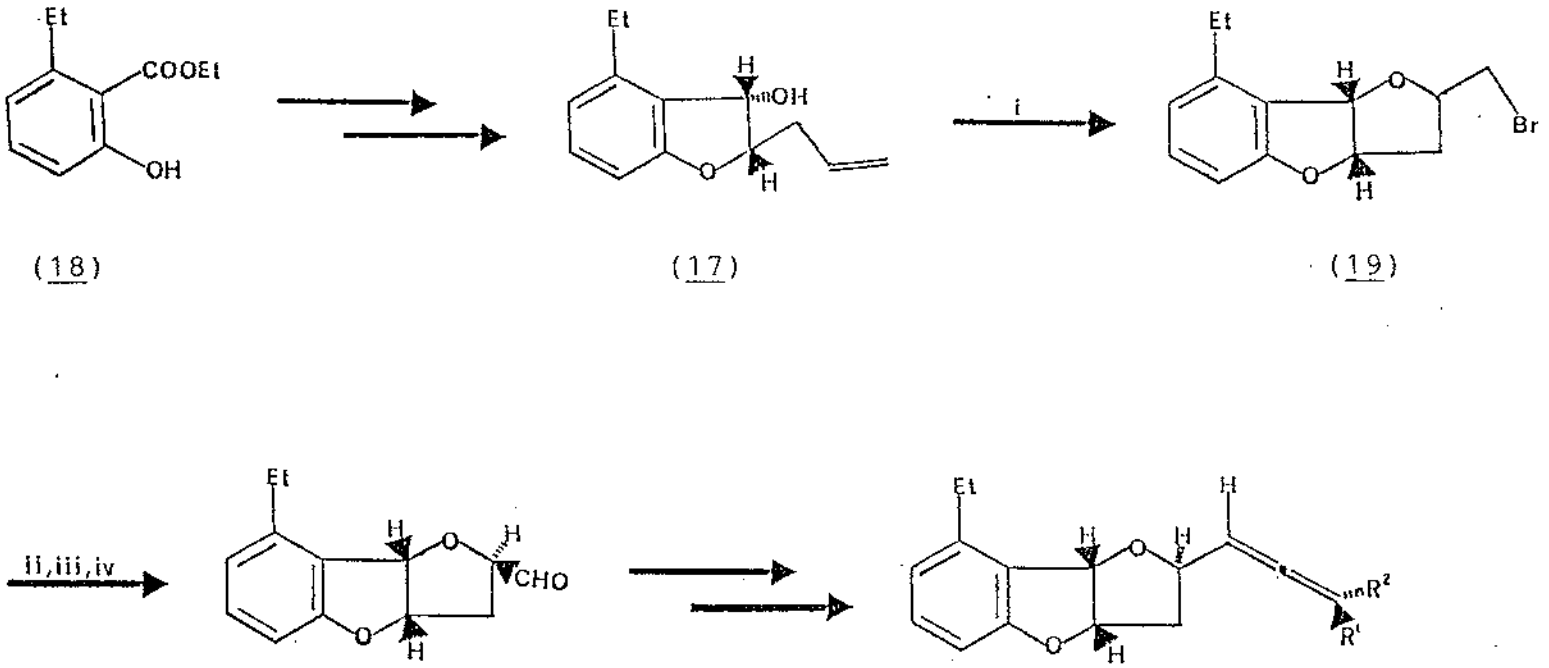


Eqn.4

(21)

(1): R^1=H, R^2=Br.

(16): R^1=Br, R^2=H.



(20)

(1): R^1=H, R^2=Br

(16): R^1=Br, R^2=H

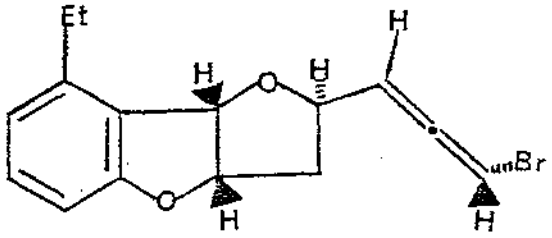
Reagents: (i) NBS, CH_3CN; (ii) KOAc, DMF; (iii) $NaOCH_3$, CH_3OH; (iv) $(COCl)_2$, Me_2SO, TEA, CH_2Cl_2. (i-iv): 64% yield

Scheme 2

It should be noted that both syntheses of panacene (1) produced a racemic mixture, and both involved stepwise construction of the cis-3a,8b-dihydrofuro[3,2-b]benzofuran ring system.

1.4 The Proposed Synthesis of Panacene (1)

Retrosynthetic analysis suggested that the ethyl-lactone (22) would be useful for the total synthesis of panacene (1) (Scheme 3).



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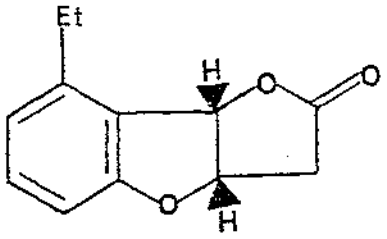

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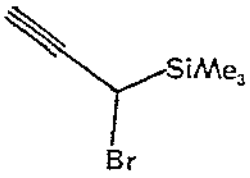


Scheme 3

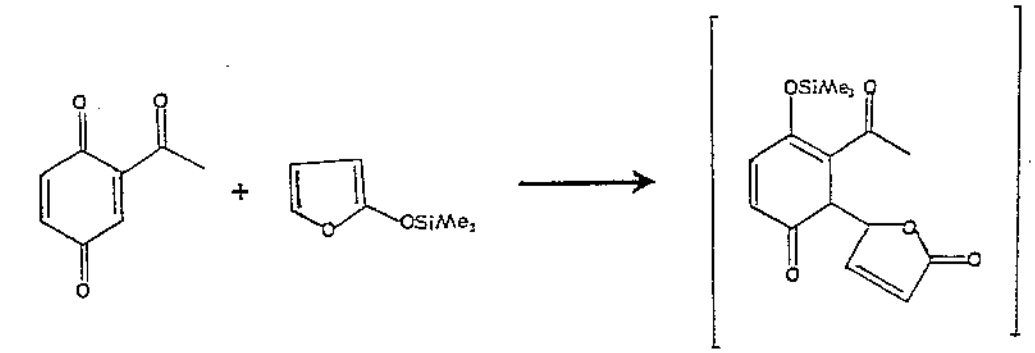
Based on the work by Pelter *et al.*[10], and other groups[11,12,13], it was proposed that the 1,4-addition of 2-trimethylsilyloxyfuran (23) to 2-acetyl-1,4-benzoquinone (6) might be a useful starting point for the synthesis of the required lactone (22) (Scheme 4). Thus, after initial 1,4-addition of 2-trimethylsilyloxyfuran (23) *ortho* to the ketone substituent on the quinone ring, a second 1,4-addition of the resulting phenoxy group onto the neighbouring butenolide moiety might occur, giving the 8-acetyl-7-hydroxylactone (24). Reduction of the ketone to an ethyl group, and removal of the hydroxy group would then give the 8-ethyllactone (22).

1.5 Other Additions to Quinones

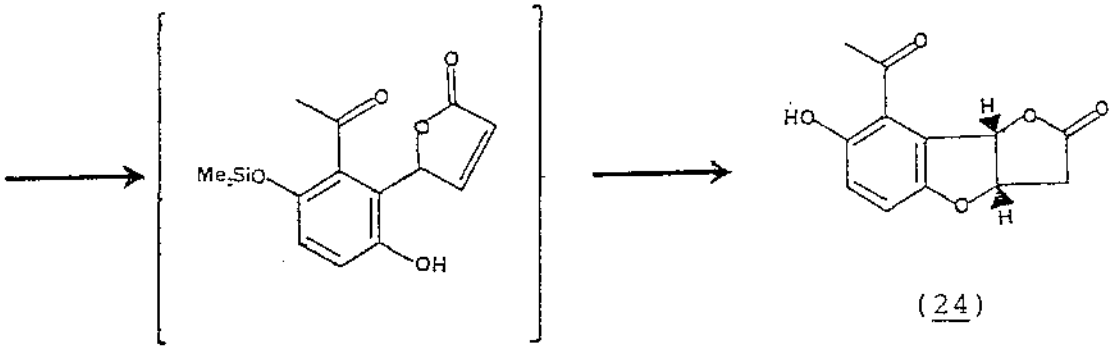
Additions to quinones have been reviewed in detail[14]. The addition of enol ethers, allylsilanes, and 2-*t*-butoxyfuran to quinones is particularly relevant to the proposed synthesis.

Eugster *et al.*[4] have reported the 1,4-addition of furan (5) itself to 2-acetyl-1,4-benzoquinone (6), in which aromatisation and attack of the phenolic oxygen onto the dihydrofuran moiety occurred only to a limited extent (Eqn.1, p.2).

In 1978, the 1,4-addition of 2-*t*-butoxyfuran (25) to 2-acetyl-1,4-naphthoquinone (26) was carried out by Kraus *et al.*[12] (Scheme 5). In this case, tautomerisation was followed by methylation, which blocked the phenoxy group. Furthermore, the robust nature of the *t*-butoxy group prevented formation of a butenolide moiety and subsequent



(6) (23)



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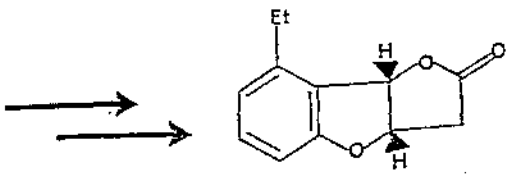
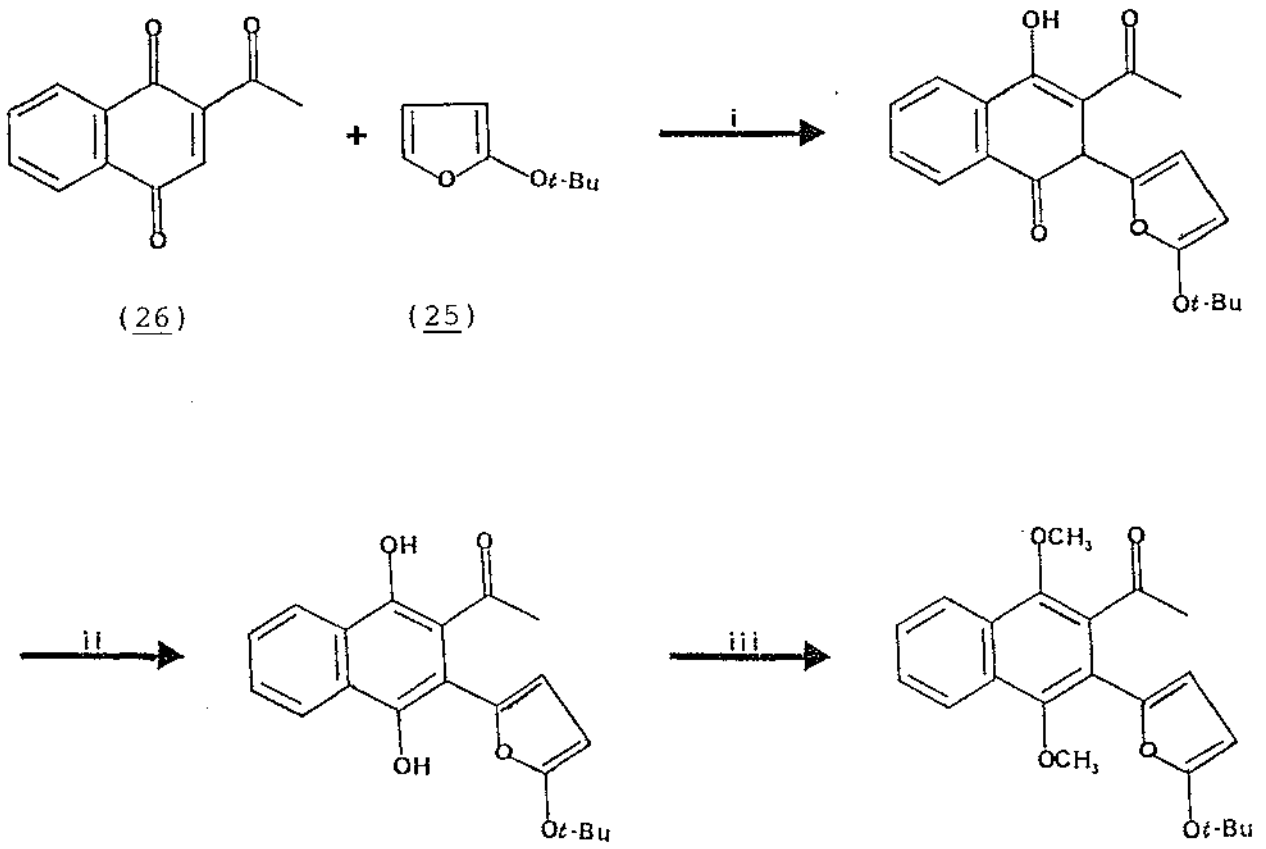


(22)

Scheme 4



(26) (25)

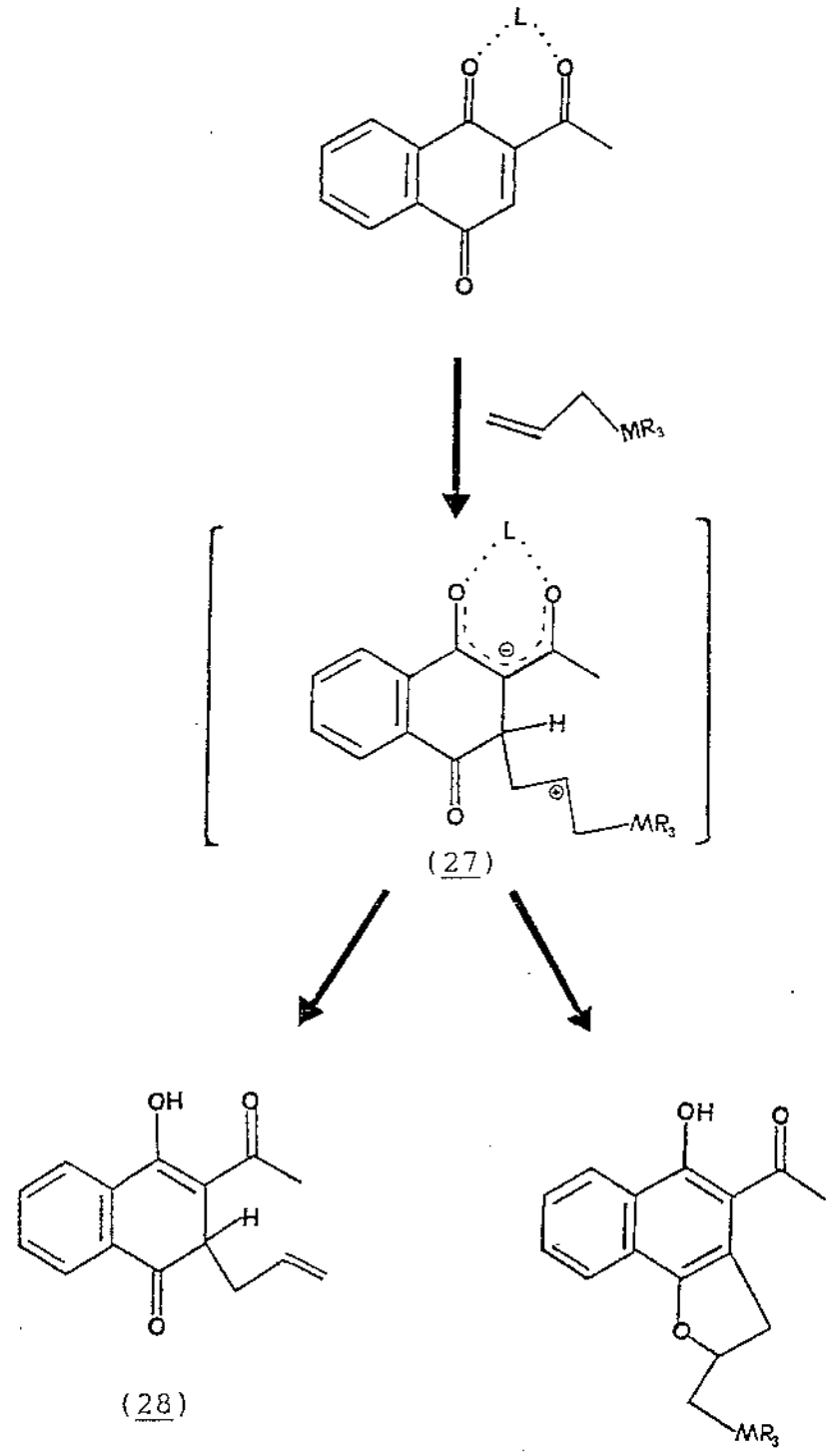
Reagents: (i) $PhCH_3$, 0 or -78°C; (ii) acid or base; (iii) $(CH_3)_2SO_4$, K_2CO_3, acetone. (i-iii): 62% yield.

Scheme 5

cyclisation to give the cis-3a,8b-dihydrofuro[3,2-b]benzofuran ring system. It was also found that under no circumstances would 2-t-butoxyfuran (25) add to unactivated quinones such as 1,4-naphthoquinone, or benzoquinone. 1,4-Addition to activated benzoquinones was not examined.

The addition of allylsilanes and allystannanes to 2-alkanoyl-1,4-quinones was reported in 1986 by Uno et al.[13] (Scheme 6). The cation (27) produced initially, underwent two competing reactions. Allylstannanes tended to cause formation of the metal elimination product (28), whereas, allylsilanes increased the proportion of intramolecular electrophilic attack on the carbonyl oxygen atom, with concommitant rearomatisation. This is analogous to the proposed attack of a phenoxy group onto a butenolide moiety.

It can be seen that the proposed use of 2-trimethylsilyloxyfuran (23) in the synthesis of the lactone (22) (Scheme 4, p.11) is supported in several ways. It has been shown that addition of furan (5) to 2-acetyl-1,4-benzoquinone (6)[4] resulted in limited formation of both the desired ring system (7), and the uncyclised product (29) (Eqn.1, p.2). Use of a modified furan, such as an enol ether, would enhance the initial 1,4-addition reaction[12] (Scheme 5, p.12). Furthermore, a silyloxyfuran, being more labile than an alkoxyfuran, would be expected to encourage butenolide formation, and hence favour subsequent cyclisation (Scheme 4, p.11).



(27)

(28)

L: Lewis acid

M: Sn or Si

R: Me or Ph

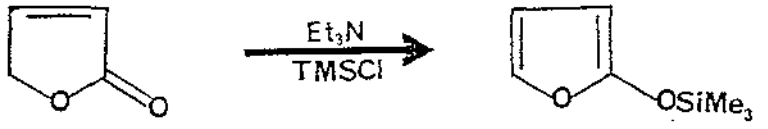
Scheme 6

Whilst the 1,4-addition of various nucleophiles to quinones has been demonstrated[4,12,13,14], the potential of this addition-aromatisation-addition sequence, for generating the cis-3a,8b-dihydrofuro[3,2-b]benzofuran ring system from an activated quinone and 2-trimethylsilyloxyfuran (23), has not been realized. The aim of this thesis, therefore, is to investigate this novel furofuran annulation reaction, and to explore its use as the basis of a new synthetic route to panacene (1).

CHAPTER 2

DISCUSSION

The investigation of the proposed furofuran annulation (Scheme 5, p.13) required the synthesis of 2-trimethylsilyloxyfuran (23) and 2-acetyl-1,4-benzoquinone (6). 2-Trimethylsilyloxyfuran (23) itself is made by silylation of the enolate anion of furan-2-(5H)-one (30) (Eqn.5).

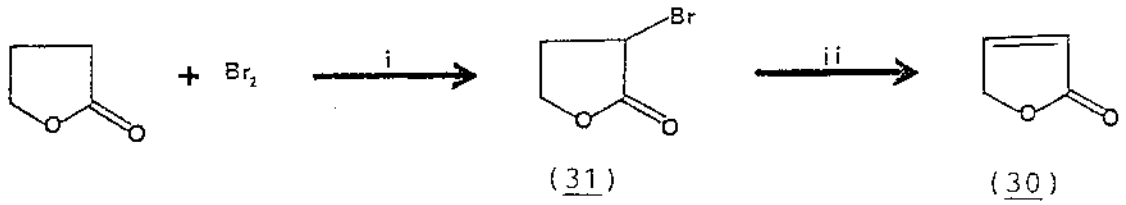


Eqn. 5

(30) (23)

2.1 Synthesis of 2-Trimethylsilyloxyfuran (23)

Until 1974, the best method known of synthesising furan-2-(5H)-one (30) had an overall yield of only 33%, and involved handling the irritant α-bromo-γ-butyrolactone (31) as an intermediate[15] (Scheme 7).

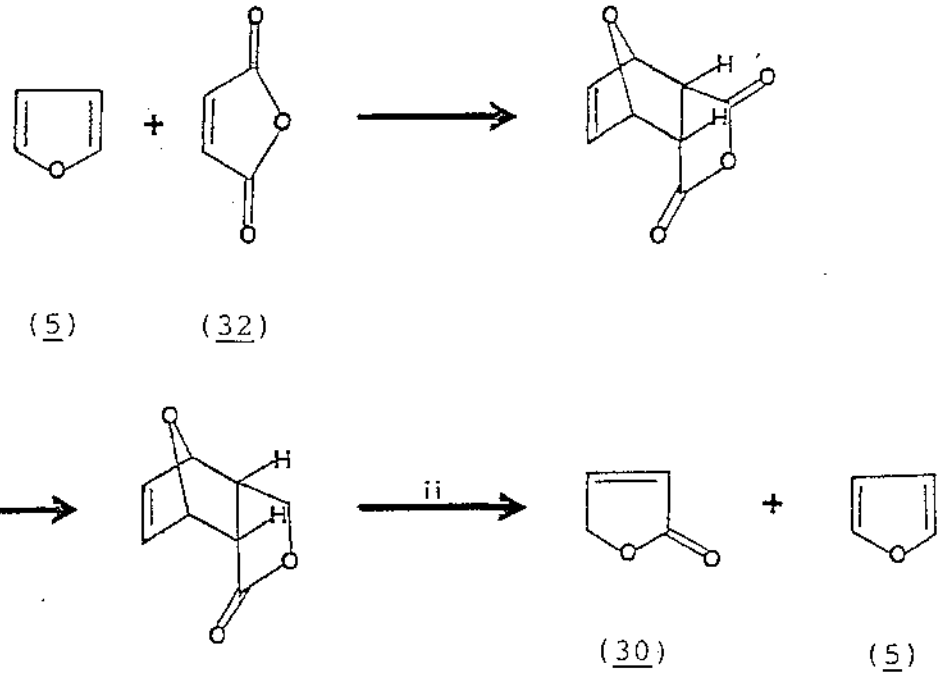


(31) (30)

Reagents: (i) P(55% yield); (ii) Et_3N(60% yield).

Scheme 7

Since that time, two more satisfactory preparations have been developed[16,17]. Takano et al.[16] made furan-2-(5H)-one in 65% yield from furan (5) and maleic anhydride (32). The three steps involved were a Diels-Alder reaction, selective reduction, and a retro-Diels-Alder reaction (Scheme 8).



(5) (32)

(30) (5)

Reagents: (i) $NaBH_4$, EtOH (80% yield); (ii) 140-150°C/ 20 mm Hg (79% yield).

Scheme 8

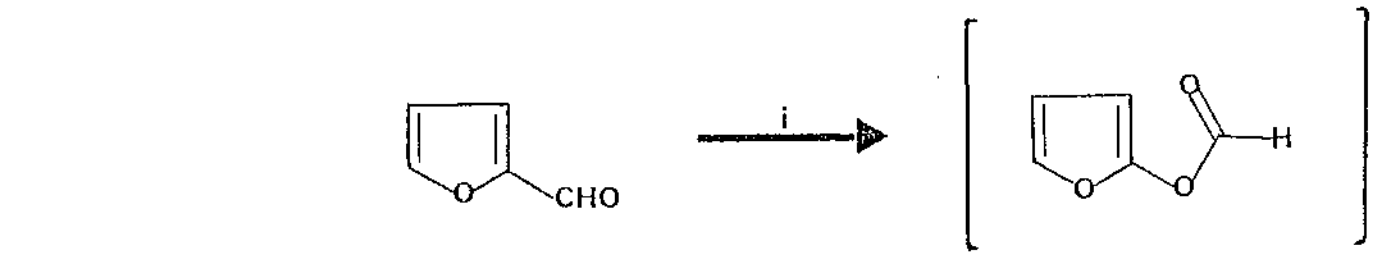
More recently, Näsman *et al.*[17] reported a simple one-pot preparation of furan-2-(5H)-one (30) from furfural (33), in 54% yield, (Scheme 9).

In view of the shorter time required, the one-pot procedure[17] was chosen in preference to the higher-yielding three-step synthesis[16].

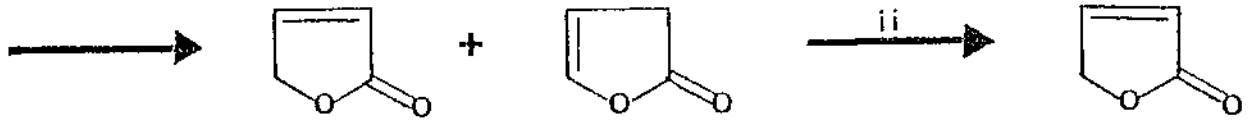
Reaction of furfural (33) with formic acid in aqueous hydrogen peroxide produced the formate ester (34), which was hydrolysed *in situ* to give a 1:4 mixture of the isomers (30) and (35). Treatment of the organic phase with triethylamine, after removal of dichloromethane and formic acid, effected isomerisation of the non-conjugated isomer (35) to furan-2-(5H)-one (30). Distillation under reduced pressure gave the pure product (30), identified by its boiling point and ^{1}H n.m.r. spectrum[17]. Due to the moisture sensitivity of the next reaction, furan-2-(5H)-one (30) was dried over magnesium sulphate, then redistilled before use.

An early study[18] showed the most satisfactory preparation of silyl enol ethers to be reaction of the carbonyl compound with a base such as triethylamine, to form the enolate anion, followed by excess chlorotrimethylsilane to give the *O*-silylated product. The preparation of 2-trimethylsilyloxyfuran (23) itself was not reported until 1977. Asaoka *et al.*[19] treated the butenolide, furan-2-(5H)-one (30), with triethylamine and chlorotrimethylsilane, at room temperature, to give 2-trimethylsilyloxyfuran (23) in 90% yield (Eqn.5, p.16).

More recently, Ricci *et al.*[20] used *N*,*N*-diethylaminotrimethylsilane in ether, to convert the butenolide (30) to 2-trimethylsilyloxyfuran (23) in 80% yield. As this reagent was not readily available, the method of Asaoka *et al*. was used. Few experimental details were given,



(33) (34)



(30) (35) (30)

Reagents: (i) HCOOH, H_2O_2, H_2O, CH_2Cl_2, Na_2SO_4, K_2CO_3; (ii) Et_3N, toluene.
(i-ii) 54% yield.

Scheme 9

and attempts to perform the reaction were fraught with difficulties.

Early procedures involved the addition of ice-cooled, dry triethylamine to the butenolide (30), stirred in an ice--salt bath, under an atmosphere of nitrogen. This was followed by addition of dry chlorotrimethylsilane. After standing at room temperature for varying lengths of time (2-16 h.), the product was directly distilled from the solid mass, under reduced pressure. Codistillation of the salt, triethylamine hydrochloride, with the product (23) was a major problem. Asaoka et al.[19] had made no mention of removal of triethylamine hydrochloride by filtration prior to distillation. Indeed, filtration would not remove all of the finely divided salt effectively. Attempts to extract the solid mass with pentane or ether before distillation, also met with little success.

It was hoped that a basic resin might be a viable alternative to triethylamine, with the hydrochloride becoming bound to the resin, and the organic product being easily extracted. The butenolide (30) and chlorotrimethylsilane were added to the weakly basic resin, Biorad AG3-X4A (Ph-NR_2), in dichloromethane. The reaction was monitored by ^1H n.m.r. spectroscopy. After six days stirring at room temperature, no reaction had occurred. Heating under reflux for 3 h. resulted in disappearance of the butenolide (30), but no 2-trimethylsilyloxyfuran (23) was observed. Use of a strongly basic resin, AGIX-2 (Ph-CH_2NR_2), was also investigated. Again, no reaction occurred at room temperature, and none of the desired product (23) was formed after heating under reflux for 16 h.

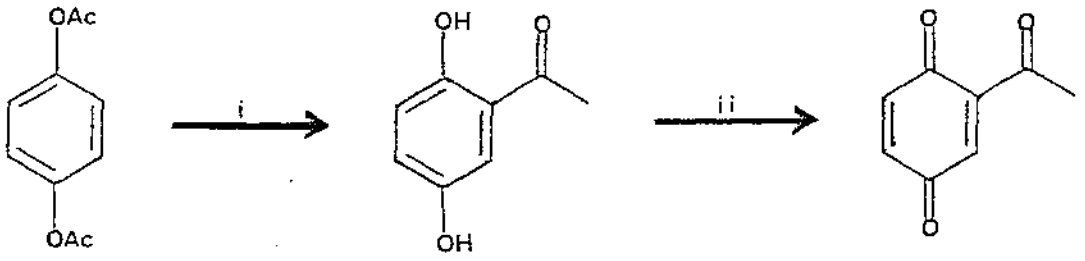
Experimental details were then obtained from Asaoka[21]. This led to the reaction being carried out in dry ether. The presence of solvent increased the extent of reaction

compared to that of earlier reactions carried out in the absence of solvent. Most of the triethylamine hydrochloride was filtered off before distillation of the reaction mixture. Several distillations were required to obtain pure material for the proposed furofuran annulation. The maximum yield obtained under these conditions, after three distillations, was 38%. 2-Trimethylsilyloxyfuran (23) was identified by its ^{1}H n.m.r. spectrum, and its boiling point, which was in agreement with the value given by Asaoka et al.[19].

2.2 Addition of 2-Trimethylsilyloxyfuran (23) to 2-Acetyl--1,4-benzoquinone (6)

With the preparation of 2-trimethylsilyloxyfuran (23) accomplished, attention was turned to the preparation of 2-acetyl-1,4-benzoquinone (6).

2,5-Dihydroxyacetophenone (36) was prepared via a Fries rearrangement of hydroquinone diacetate (37), using aluminium chloride[22]. Recrystallisation from 95% ethanol, followed by oxidation with silver oxide[23], gave 2-acetyl--1,4-benzoquinone (6) (Scheme 10). The melting point of the product (6) was in agreement with that in the literature[23].



(37) (36) (6)

Reagents: (i) $AlCl_3$ (58% yield); (ii) Ag_2O, benzene (91% yield).

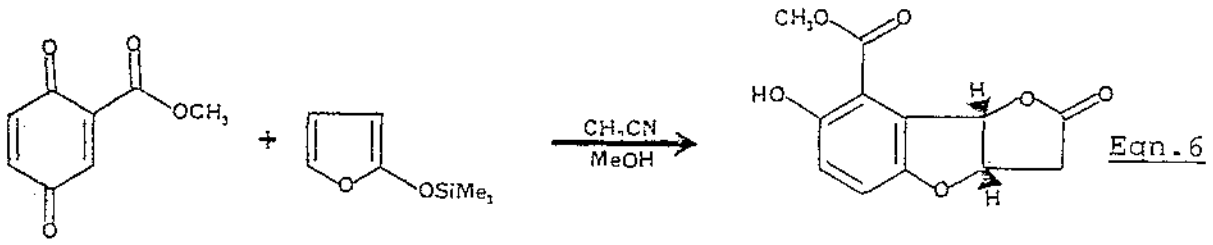
Scheme 10

Using acetonitrile as the solvent, 2-trimethylsilyloxyfuran (23) (2 equivalents) was reacted with 2-acetyl-1,4-benzoquinone (6) at 0°C, under an atmosphere of nitrogen. An immediate colour change to blood-red suggested a reaction had occurred. T.l.c. confirmed that no starting material remained. Subsequently, methanol was added to ensure complete hydrolysis of the trimethylsilyl group. After an aqueous work-up, purification by flash chromatography[24] afforded the desired 8-acetyl-7-hydroxylactone (24) in 50% yield (Scheme 4, p.1†).

The product analysed correctly for $C_{12}H_{10}O_5$, and the molecular ion, at m/z 234 in the mass spectrum, supported this as the molecular formula. The infra-red spectrum exhibited strong absorbances at 1765 and 1640 cm^{-1}, indicative of the carbonyl group of a γ-lactone and an o-hydroxyaryl ketone, respectively. In the ^1H n.m.r. spectrum, resonances at δ_H 5.37 and 6.26 were assigned to the bridgehead protons, 3a-H and 8b-H, based on panacene (1), where the analogous protons resonated at δ_H 5.29 and 5.80[1] (Table I, p.31). This was consistent with other

examples of the cis-3a,8b-dihydrofuro[3,2-b]benzofuran-2-(3H)--one ring system, where the bridgehead protons resonated in the range δ_H 4.84 to 6.30[3,5,6]. The resonance at δ_H 5.37 appears as a double double doublet and that at δ_H 6.26 as a doublet. Thus, the signal at δ_H 5.37 was assigned to 3a-H, which is coupled with 3-H_A, 3-H_B, and 8b-H, and that at δ_H 6.26 was assigned to 8b-H, which is coupled to only 3a-H. The coupling constant $J_{3a,8b}$ 6.2 Hz is indicative of cis-fusion of the two furan rings, which commonly gives rise to coupling constants of the order of 5-8 Hz[1,3,5-8]. The more unusual and highly strained trans-fusion is seen in the trans isomer of compound (3)[3] (p. 1), where the bridgehead protons resonated at δ_H 4.58 and 6.06, but the coupling constant was only 2 Hz. The ^{13}C n.m.r. spectrum (Table III, p.33) was in excellent agreement with other spectroscopic data. Assignment required comparison with the analogous 8-carbomethoxy adduct (38) (p.24) on which two-dimensional n.m.r. experiments were carried out. These will be detailed later.

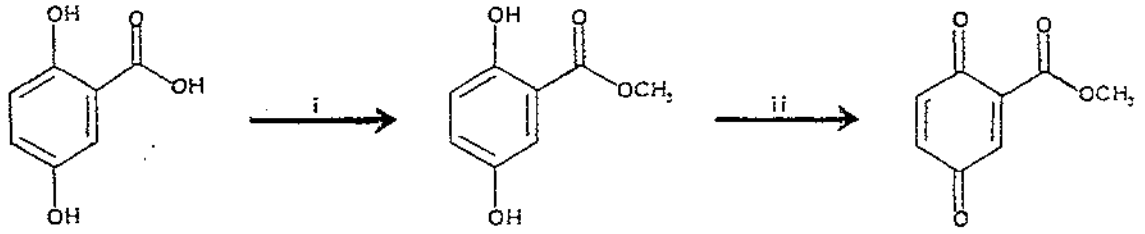
2.3 Synthesis of cis-3a,8b-Dihydro-8-carbomethoxy-7-hydroxy-furo[3,2-b]benzofuran-2-(3H)-one (38)



Eqn.6

(39) (23) (38)

Encouraged by the successful addition of 2-trimethylsilyloxyfuran (23) to 2-acetyl-1,4-benzoquinone (6), it was decided to attempt addition to an alternative activated quinone, 2-carbomethoxy-1,4-benzoquinone (39), to form the 8-carbomethoxy-7-hydroxylactone (38) (Eqn.6).



(40) (41) (39)

Reagents: (i) MeOH, H_2SO_4; (ii) MnO_2, benzene.

Scheme 11

The addition of 2-trimethylsilyloxyfuran (23) to 2-carbomethoxy-1,4-benzoquinone (39) was performed in the same way as the addition to 2-acetyl-1,4-benzoquinone (6) described earlier (p. 22). cis-3a,8b-Dihydro-8-carbomethoxy-7-hydroxyfuro[3,2-b]benzofuran-2-(3H)-one (38) was obtained in 75% yield. The product analysed correctly for $C_{12}H_{10}O_6$, with a molecular ion at m/z 250 in the mass spectrum. The infra-red spectrum exhibited a strong absorbance at 1770 cm^{-1}, assigned to the carbonyl group of the γ-lactone. Absorbances at 3600-3100 and 1680 cm^{-1} were due to the phenolic group and the o-hydroxyaryl ester, respectively. The ^1H n.m.r. spectrum was very similar to that of the 8-acetyl-7-hydroxylactone (24). A slight shift was observed in the signals of the bridgehead protons, the resonance of 3a-H shifted downfield from δ_H 5.37 to 5.47, and the resonance of 8b-H also downfield from δ_H 6.26 to 6.44 (Table I, p. 31). The bridgehead coupling constant, $J_{3a,8b}$, decreased slightly from 6.2 to 5.9 Hz. The change in coupling constants $J_{3a,3}$ 6.1 and 1.4 Hz* in the methyl ester adduct (38), suggested that the ring system was held in a slightly different conformation from that of the methyl ketone (24), where the corresponding coupling constants were $J_{3a,3}$ 3.6 and 1.8 Hz (Table II, p. 32).

* As it could not be determined which of the two protons bound to C-3 was which, both are referred to as 3-H, and two values given.

Some of the ^{13}C n.m.r. spectrum could be assigned on the basis of chemical shift and multiplicity. The triplet at δ_C35.0 was assigned to the $-CH_2-$ group of the lactone, the quartet at δ_C52.5 to the methyl group of the aryl ester, and the singlets at δ_C110.8 and 122.6, to C-8 and C-8a, respectively. This left uncertainty surrounding the absolute assignments of the bridgehead doublets, at δ_C82.0 and 83.8, the aromatic doublets, at δ_C117.4 and 121.1, and the aromatic singlets bound to oxygen, at δ_C153.7 and 154.6.

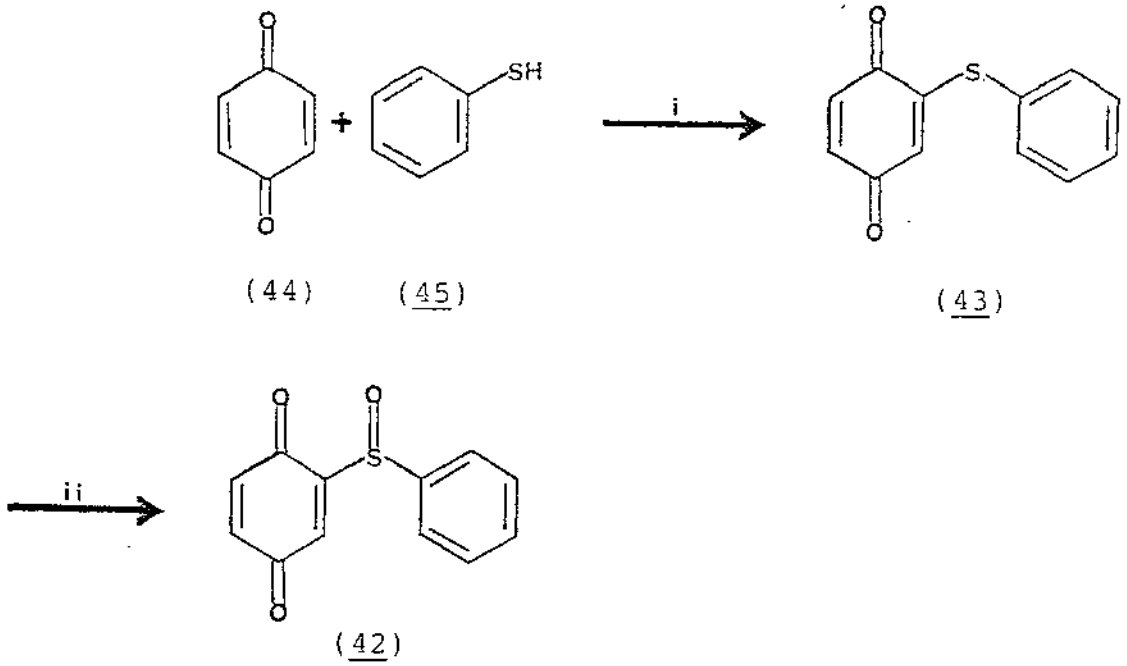
An XHCORRD experiment was performed on the ester adduct (38), involving decoupling of protons not attached to the same carbon nucleus, and correlation of C-H shifts. This enabled observation of one-bond C-H coupling. It was seen that the carbons resonating at δ_C82.0 and 83.8 were bonded to the protons resonating at δ_H5.47 and 6.44, respectively. Thus, the doublet at δ_C82.0 was assigned to C-3a, and that at δ_C83.8 to C-8b. One-bond coupling was observed between the aromatic carbon resonating at δ_C117.4 and the proton resonating at δ_H7.15, and also between the carbon resonating at δ_C121.1 and the proton resonating at δ_H6.99. However, it could not be determined which of these was at position 5 and which at position 6, since the absolute positions of the two aromatic protons were uncertain.

A COLOC experiment was then performed, with H-H decoupling and suppression of one-bond C-H coupling, allowing long-range C-H coupling to be observed. Due to the parameters used, the aromatic carbons could not be distinguished with any certainty. A long-range coupling was seen between the carbon resonating at δ_C154.6, and the phenolic proton. Thus, the singlet at δ_C154.6 was assigned to C-7, and that

at δ_C153.7 to C-4a. This was supported by the observation of long-range coupling between C-4a and 8b-H.

2.4 Use of a Sulphinyl Activating Group

The successful addition of 2-trimethylsilyloxyfuran (23) to two activated benzoquinones (6), (39), prompted the extension of this work to the use of a sulphoxide activating group. 2-Phenylsulphinyl-1,4-benzoquinone (42) was prepared by oxidation of the corresponding sulphide (43)[26], which was itself prepared by reacting 1,4-benzoquinone (44) with thiophenol (45), in methanol (Scheme 12)[27].



(44) (45) (43)

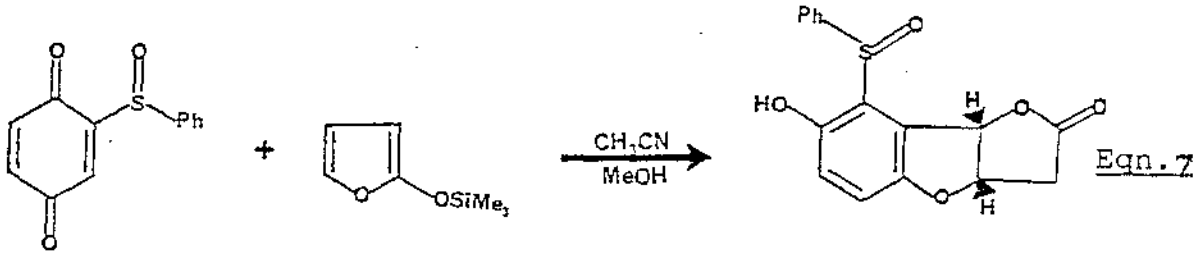
(42)

Reagents: (i) MeOH (97% yield); (ii) $CF_3COOH, H_2O_2, 0^oC$ (94% yield).

Scheme 12

Oxidation of sulphides to sulphoxides has been reviewed[28], with reagents such as hydrogen peroxide[29], peracids[30], and manganese dioxide[31] being in common use. It was decided to use a recently developed reagent, peroxytrifluoroacetic acid, which was reported to be rapid at low temperatures, and highly selective[26]. In addition the by-product, trifluoroacetic acid, was easily removed. The reaction was extremely clean, giving 2-phenylsulphinyl-1,4-benzoquinone (42) in 94% yield. The product analysed correctly for $C_{12}H_8O_3S$, and the appearance of a molecular ion, at m/z 216 in the mass spectrum supported this molecular formula. An absorbance at 1050 cm^{-1} in the infra-red spectrum indicated the presence of a sulphoxide group. The assigned structure was also supported by the ^1H n.m.r. spectrum. A multiplet at δ_H6.73-7.00 was assigned to 5-H and 6-H, and a multiplet at δ_H7.24-7.33 to 3-H, of the benzoquinone ring. The five aromatic protons resonated at δ_H7.47-7.63 and 7.70-7.87.

This sulphinylquinone (42) was then reacted with 2-trimethylsilyloxyfuran (23), in a manner analogous to the previous quinones, giving the 8-phenylsulphinyl-7-hydroxylactone (46) in 47% yield (Eqn. 7).

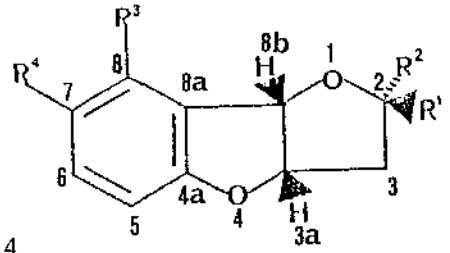


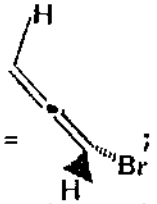
Eqn. 7

(42) (23) (46)

The nature of the adduct (46) was confirmed by the infrared spectrum, which showed the presence of a 5-membered lactone, a sulphoxide and a phenolic group, absorbing at 1765, 1050, and 3500-3100 cm^{-1}, respectively. The ^{1}H n.m.r. spectrum compared well with those of the methyl ketone (24) and the methyl ester (38) (Table I, p.31). In this case, the bridgehead protons resonated at δ_H5.49 and 6.69, with a coupling constant of 5.7 Hz. The coupling constants, $J_{3a,3}$ 6.5 and 1.3 Hz are closer in magnitude to those of the ester (38) than those of the ketone (24) (Table II, p.32). The ^{13}C n.m.r. spectrum was assigned by comparison with the ester (38), to which it was very similar (Table III, p.33).

The largest difference between the three ^{13}C n.m.r. spectra is seen in the signal for C-8 which shifts downfield from δ_C116.3 for the ketone (24), to δ_C110.8 for the ester (38), to δ_C127.8 for the sulphoxide adduct (46). Larger differences are seen between the resonances of the aromatic carbons, due to changes in the C-8 substituent, than between the carbons at the lactone end of the molecule, where the structure undergoes minor conformational changes only. The ^{13}C resonances of panacene (1), differ from those of the synthetic adducts, reflecting the presence of a bromo-allene instead of a lactone at C-2, and an ethyl group instead of an electron-withdrawing group at C-8.



panacene (1): R^1=  ; R^2=H; R^3=Et; R^4=H.

cis-3a,8b-dihydro-8-acetyl-7-hydroxyfuro[3,2-b]benzofuran-2-(3H)-one(24): R^1=R^2=O; R^3=COMe; R^4=OH.

cis-3a,8b-dihydro-8-carbomethoxy-7-hydroxyfuro[3,2-b]benzofuran-2-(3H)-one(38): R^1=R^2=O; R^3=COOMe; R^4=OH.

cis-3a,8b-dihydro-8-phenylsulphinyl-7-hydroxyfuro[3,2-b]benzofuran-2-(3H)-one(46): R^1=R^2=O; R^3=SOPh; R^4=OH.

cis-3a,8b-dihydro-8-(1'-hydroxyethyl)-7-hydroxyfuro[3,2-b]benzofuran-2-(3H)-one(51): R^1=R^2=O; R^3=$\underset{\underset{OH}{|}}{CHCH_3}$; R^4=OH.

TABLE I

^{1}H Chemical Shifts[a] For the cis-3a,8b-Dihydrofuro[3,2-b]benzofuran Ring System

Compound	3-H_A, 3-H_B	3a-H	5-H	6-H	8b-H	OH
(1)[b]	2.01, 2.48	5.29	6.64	7.19	5.80	-
(24)[c]	3.00-3.07	5.37	7.03	7.03	6.26	12.44
(38)[d]	2.93-3.17	5.47	6.99[f]	7.15[f]	6.44	10.51
(46)[d]	2.68-3.40	5.49	6.89	6.89	6.69	not available
(51)[d]	2.78, 3.19	5.15-5.48	6.55-6.84	6.55-6.84	6.14 / 6.32[e]	8.5

a. Expressed in parts per million downfield from TMS (δ_H).

b. Reported from 270 MHz ^{1}H n.m.r. spectrum in $CDCl_3$[1].

c. Obtained from 80 MHz ^{1}H n.m.r. spectrum in $CDCl_3$.

d. Obtained from 80 MHz ^{1}H n.m.r. spectrum in d^6-acetone.

e. Chemical shift for the minor diastereomer.

f. Assignment of the aromatic protons to positions 5 or 6 cannot be decided unambiguously.

TABLE II

Coupling Constants[a] For the cis-3a,8b-Dihydrofuro[3,2-b]-benzofuran Ring System

Compound	$J_{3a,3}$	$J_{3a,8b}$
(1)[b]	5.65, 0.8	5.98
(24)[c]	3.6, 1.8	6.2
(38)[c]	6.1, 1.4	5.9
(46)[c]	6.5, 1.3	5.7
(51)[c]	1.9, 0.4	5.8

a. Expressed in Hz.

b. Reported from 270 MHz ^1H n.m.r. spectrum in $CDCl_3$[1].

c. Obtained from 80 MHz ^1H n.m.r. spectra in d^6-acetone.

TABLE III

^{13}C Chemical Shifts[a] For the cis-3a,8b-Dihydrofuro[3,2-b]benzofuran Ring System

Compound	2	3	3a	4a	5	6	7	8	8a	8b
(1)[b]	73.4	40.4	85.4	160.7	107.0	130.8	120.3	143.3	123.2	82.3
(24)[c]	173.1	35.3	80.7	153.9	123.3[f]	119.5[f]	158.8	116.3	120.2	84.2
(38)[d]	175.1	35.0	82.0	153.7	121.1[f]	117.4[f]	154.6	110.8	122.6	83.8
(46)[e]	175.1	35.7	81.7	150.6	120.9[f]	114.6[f]	156.6	127.8	122.4	83.8

a. Expressed in parts per million downfield from TMS (δ_c).

b. Ref. 1.

c. Obtained from 20 MHz ^{13}C n.m.r. spectrum in $CDCl_3$.

d. Obtained from 20 MHz ^{13}C n.m.r. spectrum in d^6-DMSO.

e. Obtained from 20 MHz ^{13}C n.m.r. spectrum in d^6-acetone.

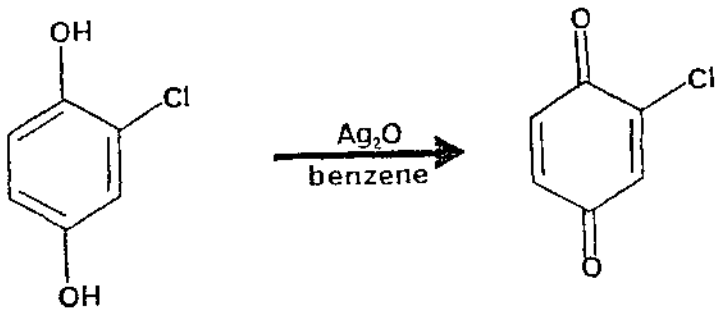
f. Assignment of the resonances of positions 5 and 6 cannot be decided unambiguously.

2.5 Addition of 2-Trimethylsilyloxyfuran (23) to Unactivated Quinones

A more detailed picture of this novel furofuran annulation (Scheme 4, p. 11) was desired. Thus, the addition of 2-trimethylsilyloxyfuran (23) to several unactivated benzoquinones was investigated, using the conditions already established. The use of 1,4-benzoquinone (44) itself, resulted in a complex mixture of products, none of which were identified as the desired adduct by ^{1}H n.m.r. spectroscopy.

The addition of 2-trimethylsilyloxyfuran (23) to 2-thiophenyl-1,4-benzoquinone (43) also gave a complex mixture of products. ^{1}H n.m.r. spectroscopy showed that none of the fractions obtained after flash chromatography contained the desired product.

Finally, 2-chloro-1,4-benzoquinone (47) was prepared from 1-chloro-2,5-dihydroxybenzene (48) using silver oxide under the same conditions as 2,5-dihydroxyacetophenone (36)[23,32] (Eqn.8).



Eqn 8

(48) (47)

Addition of 2-trimethylsilyloxyfuran (23) to the chloroquinone (47) gave none of the desired product. ^{1}H n.m.r. spectroscopy indicated that the crude reaction mixture consisted mainly of furan-2-(5H)-one (30) and the quinone (47).

These results suggested that this uncatalysed addition of 2-trimethylsilyloxyfuran (23) to quinones required the presence of an electron-withdrawing group at C-2 of the quinone, to activate them.

2.6 Attempted Conversion of cis-3a,8b-Dihydro-8-acetyl-7-hydroxyfuro[3,2-b]benzofuran-2-(3H)-one (24) to cis-3a,8b-Dihydro-8-ethyl-7-hydroxyfuro[3,2-b]benzofuran-2-(3H)-one (22)

Having successfully synthesised the 8-acetyl-7-hydroxylactone (24) in order to use this adduct in the proposed synthesis of panacene (1) (Scheme 4, p.11), it remained to reduce the methyl ketone to an ethyl group, and remove the phenolic substituent.

A wide variety of reagents have been used to reduce aromatic ketones to hydrocarbons[33]. The two most traditional methods, the Clemmensen and Wolff-Kishner reductions, involve prolonged heating with acid and base, respectively. For that reason it was decided to by-pass these and try reagents which would be less likely to cleave the γ-lactone ring (Table IV, p.40).

Triethylsilane is effective in reducing ketones to hydrocarbons when used in conjunction with a Lewis, or protic acid, which activates the carbonyl group[34]. Doyle *et al.*[35] reported high selectivity, short reaction time, and lack

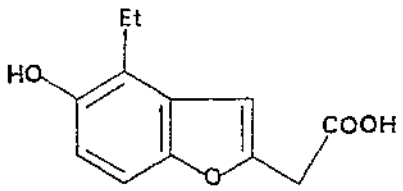
of competing reactions as advantages of the triethylsilane/ trifluoroacetic acid combination.

Triethylsilane was added dropwise to a solution of the ketone (24) in trifluoroacetic acid. The reaction was monitored by t.l.c. After 45 minutes, no starting material remained. An agueous work-up was followed by flash chromatography, affording a yellow crystalline product in 51% yield. Spectroscopic data showed the product to be 4-ethyl--5-hydroxybenzofuran-2-ylacetic acid (49). The mass spectrum contained a peak at m/z 220, assigned to the molecular ion. Absorbances at 3380 and 1700 cm^{-1} in the infra-red spectrum were assigned to a phenolic group and the carbonyl group of a carboxylic acid, respectively. The ^{1}H n.m.r. spectrum confirmed the nature of the product. The resonances of the bridgehead protons were no longer apparent. A triplet at δ_H 1.05-1.30 and a quartet at 2.60-3.00 were assigned to the ethyl protons. The methylene protons next to the carboxylic acid resonated at δ_H 3.80, and the aromatic protons at δ_H 6.6-7.1.

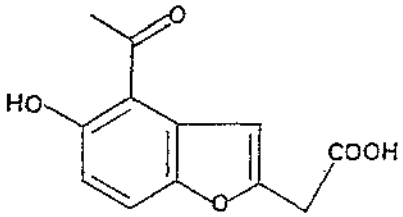
Closer investigation showed that triethylsilane, in the absence of trifluoroacetic acid, had no effect on the lactone ring, but failed to reduce the methyl ketone. Trifluoroacetic acid alone gave 4-acetyl-5-hydroxybenzofuran-2-ylacetic acid (50) in 73% yield. An absorbance at 1695 cm^{-1} in the infra-red spectrum was assigned to the carbonyl group of the carboxylic acid, and one at 1610 cm^{-1} showed the presence of an o-hydroxyaryl ketone. The methylene protons of the $-CH_2COOH$ group resonated at δ_H3.85. A downfield shift was observed in the resonance of the methyl protons, from δ_H 1.05-1.30 in the ethyl-substituted acid (49) to δ_H 2.75 in the keto-acid (50). 6-H and 7-H resonated at δ_H 6.65-6.85 and 7.40-7.60, reflecting the presence of an aryl ketone rather than an alkyl substituent at C-4. A singlet at δ_H 6.80 was assigned to 3-H.

Thus, while the acid was required for reduction, its presence was causing ring-opening to occur as a competing reaction. p-Toluenesulphonic acid, and acetic acid were each tried as alternatives to trifluoroacetic acid. In both cases no reaction occurred at room temperature, but heating under reflux yielded the keto-acid (50).

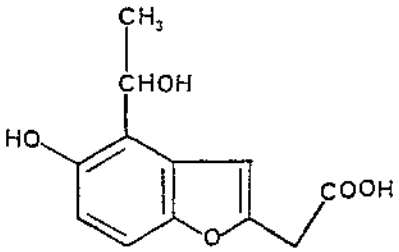
Several groups[36,37] have activated ketones towards triethylsilane with boron trifluoride. Due to the unavailability of gaseous boron trifluoride[36], the reaction was attempted using boron trifluoride ethereate[37]. Stirring in dry ether at 0°C, for 1 h., gave only starting material and the keto-acid (50).



(49)



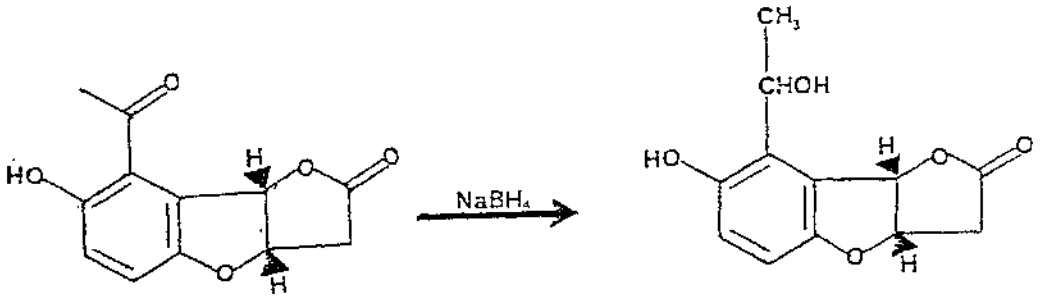
(50)



(52)

Having difficulty in finding an acid which would activate the ketone without cleaving the lactone, attention turned to different types of reducing agents.

Sodium borohydride is a common reducing agent for conversion of ketones to alcohols[38]. It has also been used in conjunction with other reagents to convert ketones or alcohols to hydrocarbons[39,40]. Before trying some of the reported combinations, it was important to make sure that sodium borohydride on its own would not cause ring-opening. The ketone (24) was stirred with sodium borohydride, in methanol, at room temperature, for 1 h. An aqueous work-up was followed by flash chromatography, giving cis-3a,8b--dihydro-8-(1-hydroxyethyl)-7-hydroxyfuro[3,2-b]benzofuran--2-(3H)-one (51) in 58% yield (Eqn. 9). The product gave a peak in the mass spectrum at m/z 236, corresponding to the molecular formula $C_{12}H_{12}O_5$. Peaks at 3370-3320 and 1753 cm^{-1} in the infra-red spectrum, were assigned to the phenolic group and the carbonyl group of the γ-lactone, respectively. The ^1H n.m.r. spectrum confirmed the structure of the product. T.l.c. indicated the presence of two diastereomers, having very similar R_f, but forming different coloured complexes with vanillin. When an excess of sodium borohydride was used, and the reaction time increased, the proportion of the minor diastereomer increased. ^1H n.m.r. spectroscopy showed a very slight difference in the resonance of the methyl group, from δ_H1.52 for the major diastereomer to δ_H1.51 for the minor diastereomer. A larger difference was visible in the resonance assigned to 8b-H, from δ_H6.14 in the major product to δ_H6.32 in the minor product (Table I, p.31). The coupling constants J_{gem}18.8Hz, $J_{3,3a}$0.4 and 1.9 Hz, and $J_{8b,3a}$ 5.8 Hz, were the same in both diastereomers (Table II, p.32).



Eqn. 9.

(24) (51)

Palladium (II) chloride has been used with sodium borohydride to reduce aryl ketones and benzyl alcohols to hydrocarbons[40]. The reaction is reported to be fast and highly selective. Sodium borohydride was added to a suspension of palladium chloride and the ketone (24) in methanol. The mixture was stirred at room temperature for 1 h. Following an aqueous work-up, t.l.c. of the crude product showed the presence of the alcohol (51) and a more polar compound. ^{1}H n.m.r. spectroscopy indicated that none of the desired product was present. Based on its u.v. activity, polarity, and molecular weight, the polar compound was assumed to be the alcohol-substituted acid (52), arising from cleavage of the γ-lactone ring by palladium chloride.

A similar reducing system for aryl ketones and benzylic alcohols is sodium cyanoborohydride with zinc iodide[41]. Stirring these with the ketone (24), in 1,2-dichloroethane for 4.5 h. gave no reaction. The mixture was subsequently heated under reflux for 12 h. Using an aqueous work up, it proved difficult to recover organic material from the reaction.

TABLE IV

Attempted Reductions of cis-3a,8b-Dihydro-8-acetyl-7-hydroxyfuro[3,2-b]benzofuran-2-(3H)-one (24)

REAGENT	CONDITIONS	RESULT
TES/TFA	25°C, 0.75 h.	4-ethyl-5-hydroxybenzofuran-2-ylacetic acid (49)
TFA	25°C	4-acetyl-5-hydroxybenzofuran-2-ylacetic acid (50)
TES	25°C, 3 days	no reaction
	64°C, 2 h., MeOH	no reaction
TES/pTSA	25°C, 1 h.	no reaction
	64°C, 3 h., MeOH	4-acetyl-5-hydroxybenzofuran-2-ylacetic acid (50)
TES/AcOH	25°C, 18 h.	no reaction
	64°C, 2 h., MeOH	4-acetyl-5-hydroxybenzofuran-2-ylacetic acid (50)
TES/$BF_3.Et_2O$	0°C, 1 h.	4-acetyl-5-hydroxybenzofuran-2-ylacetic acid (50)
$NaBH_4$	25°C, 1-2 h., MeOH	alcohol-lactone (51)
$NaBH_4/PdCl_2$	25°C, 1 h., MeOH	alcohol-lactone (51) and a polar product (52)
$NaCNBH_3/ZnI_2$	25°C, 5 h., MeOH	no reaction
	83°C, 12 h, 1,2-dichloroethane	organic material difficult to recover
(i) $TsNHNH_2$ (ii) $NaBH_4$	(i) 64°C, 6 h., MeOH (ii) 64°C, 8.5 h., MeOH	complex mixture

A less direct way in which sodium borohydride can be used to reduce ketones to hydrocarbons is by reduction of their tosylhydrazone derivatives[42].

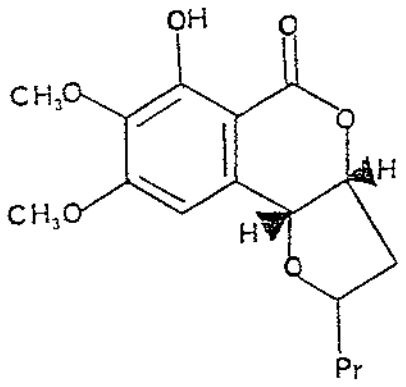
Tosylhydrazine was prepared by the method of Friedman et al.[43], then heated under reflux with the ketone (24) in methanol, for 6 h., to form the derivative. The reaction was monitored by t.l.c. Sodium borohydride was added and heating continued for 8.5 h., after which time an aqueous work-up yielded a complex mixture of products.

In view of the difficulty in reducing the methyl ketone (24) to an ethyl group without disrupting the cis-3a,8b-dihydro furo[3,2-b]benzofuran-2-(3H)-one ring system, it was evident that the proposed route to panacene (1) was not practicable.

2.7 Further Work

Since the synthesis of panacene (1) from the 8-acetyl-7-hydroxylactone (24) (Scheme 4, p.11) was no longer feasible, attention turned to another potential use for the lactones generated by the addition of 2-trimethylsilyloxyfuran (23) to activated quinones.

The 5H-furo[3,2-c][2]benzopyran ring system is seen in the antifungal and insecticidal monocerin (53)[44], and in the isochromane antibiotics, such as kalafungin (54)[45].



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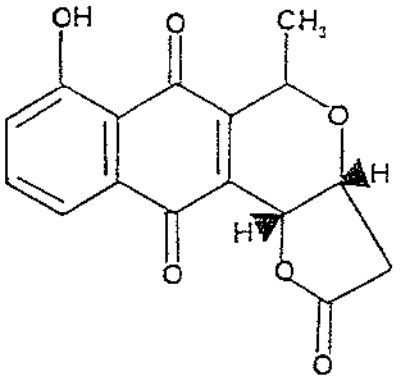
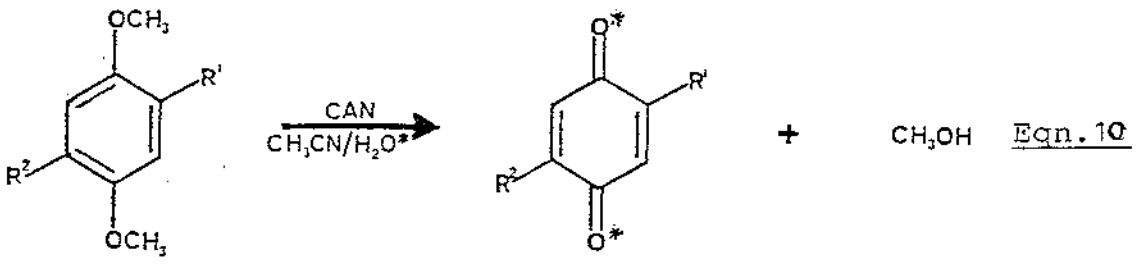


(54)

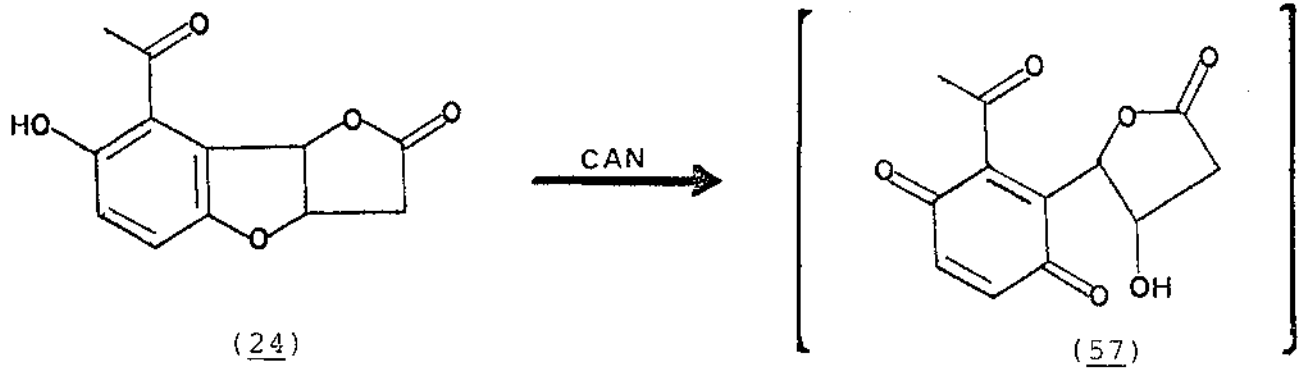
It was proposed that the conversion of the 8-acetyl-7--hydroxylactone (24) to a 5H-furo[3,2-c][2]benzopyran-2-(5H)--one could be the basis of a new synthetic route to the whole series of antibiotics related to kalafungin (54).

Castagnoli, Jr. et al.[46] have reported that ceric ammonium nitrate in aqueous acetonitrile can be used to oxidise a variety of hydroquinone methyl ethers (55) to the corresponding quinones (56). ^{18}O labelling showed that it was the aryl-oxygen, rather than the methyl-oxygen bond which was cleaved, giving methanol as a by-product (Eqn.10).



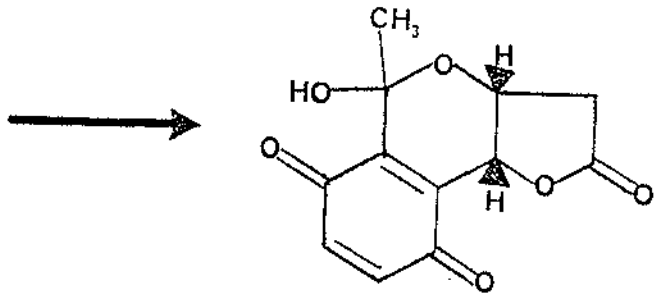
(55) (56) Eqn.10

On this basis, it was thought that the 8-acetyl-7-hydroxy-lactone (24), as a cyclic ether of a hydroquinone, might undergo an analogous oxidative dealkylation reaction to give the ß-hydroxylactone (57). Subsequent nucleophilic attack of the hydroxyl group onto the methyl ketone would give rise to the hemi-ketal (58) (Scheme 13).



(24)

(57)



(58)

Scheme 13

An excess of aqueous ceric ammonium nitrate was added to the 8-acetyl-7-hydroxylactone (24) in acetonitrile. Extraction with dichloromethane, followed by flash chromatography, gave cis-3,3a,9b-trihydro-5-hydroxy-5-methylfuro-[3,2-c][2]benzopyran-2,6,9-(5H)-trione (58) as predicted. Identification of the product was carried out by spectroscopic techniques. No molecular ion was apparent in the mass spectrum, however a very intense signal at m/z 235 corresponded to M-CH_3, a common fragmentation for hemiketals.

The infra-red spectrum contained peaks at 3370, 1760 and 1653 cm^{-1}, assigned to an alcohol, and the carbonyl groups of a γ-lactone and quinone, respectively. The ^1H n.m.r. spectrum showed an upfield shift in the resonances of the bridgehead protons. The double doublet at δ_H4.89 was assigned to H-3a, and the doublet at δ_H5.16 to H-9b. These positions were consistent with those observed in monocerin (53) and its derivatives[44], where the resonances of the bridgehead protons are found in the region δ_H4.46 to 5.38. The coupling constant of $J_{3a,9b}$2.9 Hz, supports the presence of a cis-fused 5H-furo[3,2-c][2]benzopyran system, which commonly has a bridgehead coupling constant of 3 Hz[44,45]. The position at which the methyl protons resonated had also moved upfield from δ_H2.76 to 1.75, consistent with them being adjacent to an sp^3 hybridised carbon rather than a carbonyl group.

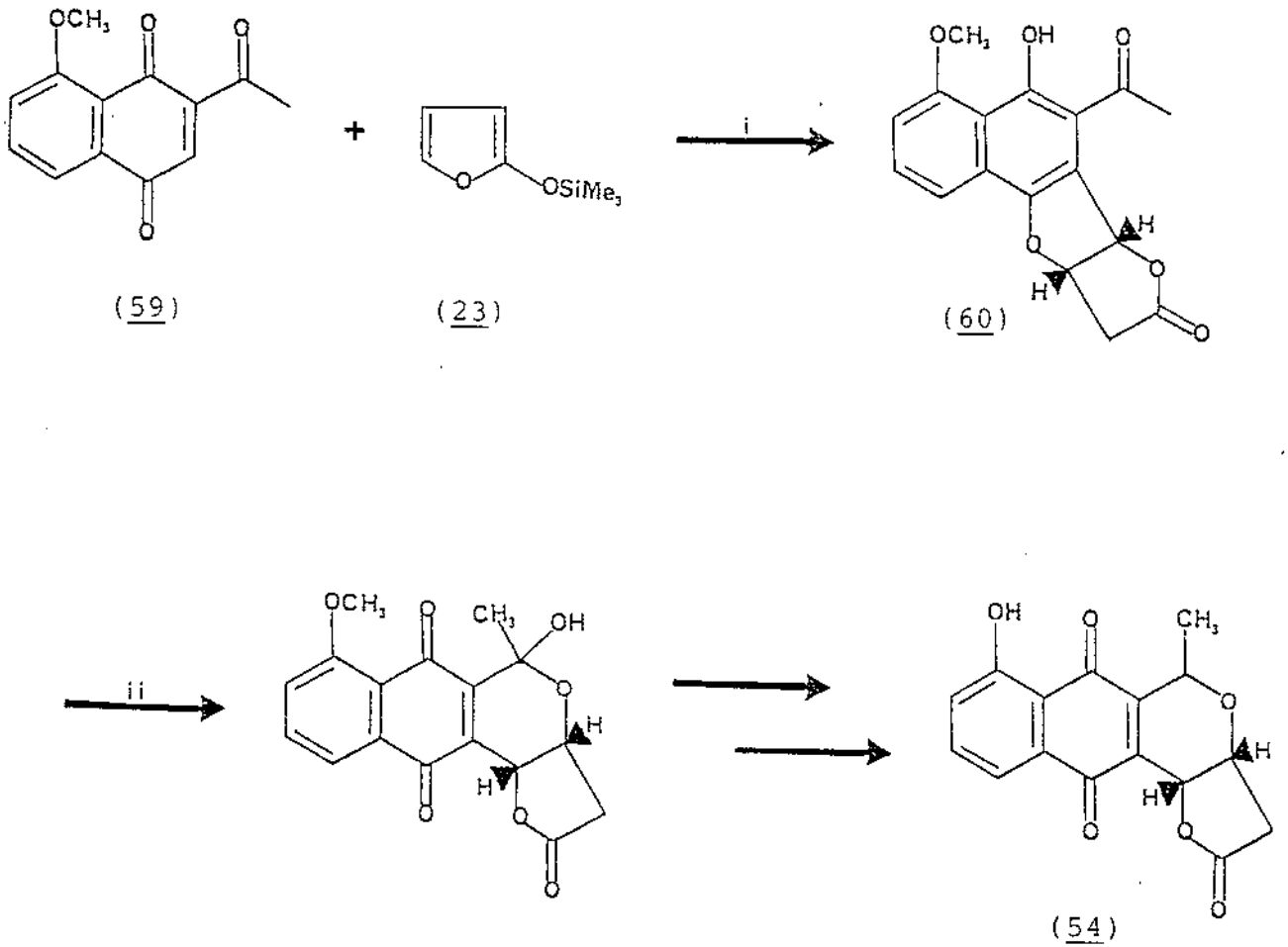
A more polar by-product gave an infra-red spectrum containing peaks at 3400 and 1775 cm^{-1}, showing the presence of a hydroxyl group and a γ-lactone, respectively. Two peaks at 1672 and 1650 cm^{-1} were consistent with the presence of the carbonyl groups of a quinone and a ketone, but these could not be assigned with certainty.

In the ^{1}H n.m.r. spectrum, the appearance of a double doublet at $\delta_H 4.90$, and a doublet at $\delta_H 5.16$, with a coupling constant of 3 Hz, showed the presence of the cis-fused 5H--furo[3,2-c][2]benzopyran ring system. However, a double double doublet at $\delta_H 5.62$, and a doublet at $\delta_H 6.35$, with a coupling constant of 5.9 Hz indicated the co-existence of the cis-fused furo[3,2-b]benzofuran ring system. These results are consistent with the more polar product being a dimer. Support for this idea was also provided by Castagnoli, Jr. et al.[46], who report competitive dimerisation in the case of hydroquinones which lack substitution at either the 2 or 5 position on the benzene ring. Potentially, this supposed dimer could be recycled, or conditions changed to slow its rate of formation relative to that of the desired product.

Whilst the synthesis of panacene (1) from the lactone (24) has not been realised, this novel conversion of the ring system into the 5H-furo[3,2-c][2]benzopyran ring system may provide an entry into the pyranonaphthoquinone antibiotics.

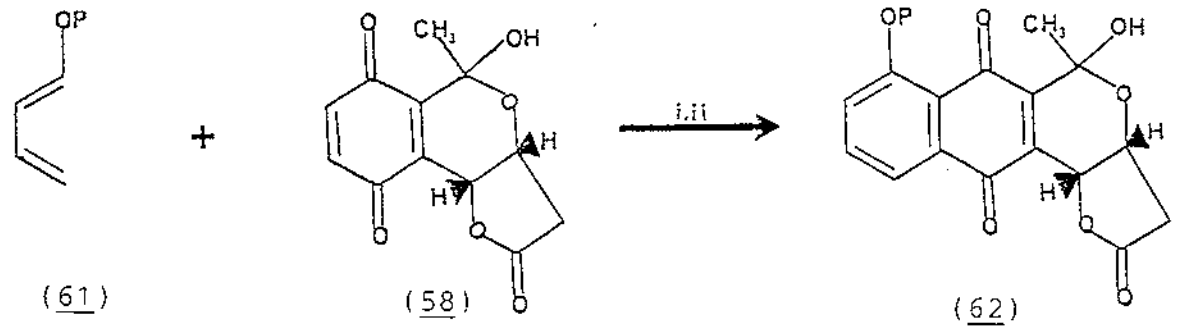
Two possible routes to kalafungin (54) itself, present themselves. Firstly, 2-trimethylsilyloxyfuran (23) could be added to the activated naphthoquinone (59) to give the adduct (60). Oxidative dealkylation with ceric ammonium nitrate, followed by reduction of the lactol group, and cleavage of the methyl ether, would then give rise to kalafungin (54) (Scheme 14).

Secondly, based on the work by Yoshii et al.[47], the hemiketal (58) could be treated with an ether of 1,3-butadiene (61), to give the cycloaddition product (62). Again, reduction of the lactol, and removal of the protecting group, would give kalafungin (54) (Scheme 15).

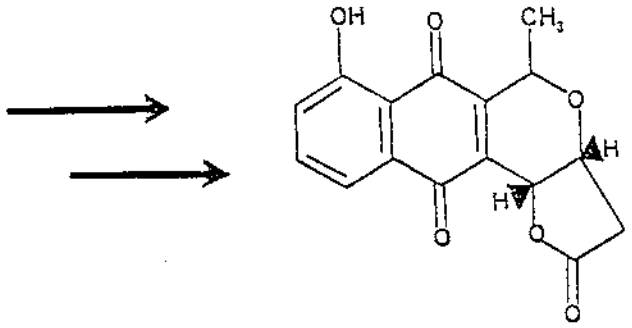


Reagents: (i) MeOH, CH_3CN; (ii) CAN.

Scheme 14



(61) (58) (62)



(54)

Reagents: (i) toluene; (ii) Na_2CO_3 in EtOH (aq).

Scheme 15

CHAPTER THREE

EXPERIMENTAL

General Details

Melting points were determined on a hot-stage melting point apparatus, and are uncorrected.

Elemental analyses were carried out by Professor A.D. Campbell and Associates, University of Otago, Dunedin.

Ultra-violet spectra were recorded on a Shimadzu U.V.160 spectrophotometer. Absorption maxima are reported in wavelengths (nm), followed by the molar absorptivity (log ε).

Infra-red spectra were recorded on a Pye Unicam SP3-200S spectrophotometer as nujol mulls between sodium chloride discs. Absorption maxima are given in wavenumbers (cm^{-1}) relative to a polystyrene standard, and are described with the following abbreviations:

s = strong
m = medium
br. = broad

^1H nuclear magnetic resonance (n.m.r.) spectra were obtained at 60 MHz using a Varian T-60 spectrometer, and at 80 MHz using a Bruker WP-80SY.
^1H n.m.r. data are expressed as parts per million downfield shift from tetramethylsilane as internal reference, and are reported as positions (δ_H), relative integral, multiplicity (s = singlet, m = multiplet, d = doublet, dd = double doublet, ddd = double double doublet, t = triplet, q = quartet, br. = broad), coupling constant (J Hz), and assignment.

^{13}C n.m.r. spectra were obtained at 20 MHz on a Bruker WP-80SY. The ^{13}C n.m.r. data are expressed as parts per million downfield shift from tetramethylsilane as internal reference, and are reported as position (δ_C), multiplicity in the single frequency off-resonance decoupled (s.f.o.r.d.) spectrum, and assignment.

Mass spectra and accurate mass measurements were recorded on an A.E.I. MS9 mass spectrometer with an ionisation potential of 70 eV. Major fragmentations are given as percentages relative to the base peak intensity.

Flash chromatography was performed according to the procedure of Still et al.[24] using Merck Kieselgel 60 (230-400 mesh) with the solvents described.

Analytical thin layer chromatography was carried out on precoated silica gel plates (Merck Kieselgel $60F_{254}$), and compounds were visualised by u.v. fluorescence, iodine vapour, or vanillin in methanolic sulphuric acid.

Solvents were purified and dried according to the methods of Perrin, Perrin and Armarego[48].

'Ether' refers to diethyl ether.

Furan-2-(5H)-one (30)

30% aqueous hydrogen peroxide (75 ml) was added to a mixture of furfural (33) (96.0 g, 1 mol), formic acid (92.1 g, 2 mol), sodium sulphate (100 g), and potassium carbonate (35 g) in dichloromethane (500 ml). After stirring vigorously for 0.5-0.8 h., 30% hydrogen peroxide (125 ml) was added dropwise over 3 h., and the reaction mixture left to stir for a further 16 h. The organic layer was separated and the inorganic phase washed with dichloromethane (200 ml). Following solvent removal under reduced pressure, toluene (200 ml) was added and the formic acid removed by azeotropic distillation. To the residual solution was added triethylamine (2.5 ml) in toluene (200 ml). After standing for 1 h., distillation under vacuum afforded furan-2-(5H)-one (30) (43 g, 51%) as a yellow liquid, b.p. 96-102°C/20 mm Hg (lit.,[17] b.p. 95-96°C/19 mm Hg).

2-Trimethylsilyloxyfuran (23)

To a solution of furan-2-(5H)-one (30) (11 g, 0.11 mol) in diethyl ether (50 ml), cooled in an ice-salt bath, under an atmosphere of nitrogen, was added ice-cold triethylamine (13.8 g, 0.14 mol), followed by chlorotrimethylsilane (15.2 g, 0.14 mol). After standing for 16 h., the reaction mixture was filtered to remove most of the triethylamine hydrochloride. Three distillations afforded 2-trimethylsilyloxyfuran (23) (7.8 g, 38%) as a colourless liquid, b.p. 44-46°C/17 mm Hg (lit.,[19] b.p. 34-35°C/9-10 mm Hg).

2,5-Dihydroxyacetophenone (36)

2,5-Dihydroxyacetophenone (36) was prepared according to the method of Vogel[22], affording yellow crystals, m.p. 204-205°C (lit.,[22] m.p. 202-203°C).

2-Acetyl-1,4-benzoquinone (6)

Silver oxide (3.7 g, 16 mmol, prepared according to the method of Vogel[49]) was added to a mixture of 2,5-dihydroxyacetophenone (36) (500 mg, 3.3 mmol) and sodium sulphate (900 mg) in sodium-dried benzene (400 ml). After stirring for 2 h., the reaction mixture was filtered through sodium sulphate over celite. Solvent was removed under reduced pressure to give 2-acetyl-1,4-benzoquinone (6) (347 mg, 70%) as an orange crystalline solid, m.p. 62-64°C (lit.,[23] m.p. 64.0-65.5°C).

cis-3a,8b-Dihydro-8-acetyl-7-hydroxyfuro[3,2-b]benzofuran--2-(3H)-one (24)

A solution of 2-trimethylsilyloxyfuran (23) (672 mg, 4.30 mmol) in acetonitrile (12 ml) was added dropwise to an ice-cooled solution of 2-acetyl-1,4-benzoquinone (6) (320 mg, 2.13 mmol) in acetonitrile (25 ml), under an atmosphere of nitrogen. Immediately the orange solution turned red. After 5 minutes, methanol (2.5 ml) was added, and the reaction mixture allowed to warm to room temperature over 0.5 h. Following dilution with dichloromethane (60 ml), the solution was washed with 1 M hydrochloric acid (30 ml) then water (30 ml). Drying over magnesium sulphate and

removal of solvent on the rotary evaporator gave a red oil. Purification by flash chromatography, using hexane:ethyl acetate as eluant, gave cis-3a,8b-dihydro-8-acetyl-7-hydroxyfuro[3,2-b]benzofuran-2-(3H)-one (24) (250 mg, 50%). Recrystallisation from chloroform-hexane gave yellow neddles, m.p. 164-165°C (Found: C, 61.97; H, 4.29; M^+, 234.0524. $C_{12}H_{10}O_5$ requires C, 61.54; H, 4.30; M^+ 234.0529); λ_{max} (EtOH) 228 (log ε 4.1), and 365 nm (3.6); υ_{max} (nujol) 1765 (s, γ-lactone C=0), and 1640 cm^{-1} (s, o-hydroxyaryl ketone); δ_H (80 MHz; $CDCl_3$) 2.76 (3H, s, $-CH_3$), 3.00-3.07 (2H, m, 3-H_A and 3-H_B), 5.37 (1H, ddd, $J_{3a,8b}$ 6.2, $J_{3a,3}$ 3.6 and 1.8 Hz, 3a-H), 6.26 (1H, d, $J_{3a,8b}$ 6.2, 8b-H), 7.03 (2H, s, 5-H and 6-H), and 12.44 (1H, s, -OH); δ_C (20 MHz; $CDCl_3$) 30.5 (q, $-CH_3$), 35.3 (t, C-3), 80.7 (d, C-3a), 84.2 (d, C-8b), 116.3 (s, C-8), 119.5 (d, C-5 or C-6), 120.2 (s, C-8a), 123.3 (d, C-6 or C-5), 153.9 (s, C-4a), 158.8 (s, C-7) 173.1 (s, C-2), and 203.1 (s, -COMe); m/z 234 (M^+, 97%), 219 (M-CH_3, 100), 189 (M-COOH, 27), and 175 (M-CH_2COOH, 20).

Methyl 2,5-Dihydroxybenzoate (41)

A mixture of 2,5-dihydroxybenzoic acid (40) (5.0g, 32 mmol), methanol (10 g, 0.32 mol) and concentrated sulphuric acid (1.3 ml) was heated under reflux for 4 h. Excess methanol was removed under reduced pressure. After extraction of the residual solution with ether (2 x 8 ml), the combined ethereal phases were washed with saturated aqueous sodium bicarbonate. Drying over magnesium sulphate, followed by removal of solvent on the rotary evaporator, gave methyl 2,5-dihydroxybenzoate (42) (5.2 g, 96%) as a white solid, m.p. 86-88°C (lit.,[50] m.p. 86-87°C).

2-Carbomethoxy-1,4-benzoquinone (39)

A mixture of methyl 2,5-dihydroxybenzoate (41) (1.0 g, 5.9 mmol) and sodium sulphate (1.5 g) in sodium-dried benzene (50 ml), was stirred with manganese dioxide (7.8 g, 90 mmol, prepared according to the method of Vogel[51]) for 0.5 h. After filtration through sodium sulphate over celite, solvent was removed at reduced pressure to give 2-carbomethoxy-1,4-benzoquinone (39) (750 mg, 76%) as an orange crystalline solid, m.p. 52-54°C (lit.,[25] m.p. 53.5-54.0°C).

cis-3a,8b-Dihydro-8-carbomethoxy-7-hydroxyfuro[3,2-b]benzofuran-2-(3H)-one (38)

A solution of 2-trimethylsilyloxyfuran (23) (0.76 g, 4.9 mmol) in acetonitrile (15 ml) was added to an ice-cooled solution of 2-carbomethoxy-1,4-benzoquinone (38) (0.40 g, 2.4 mmol) in acetonitrile (30 ml), under an atmosphere of nitrogen. The solution immediately changed colour from orange to red.

After 5 minutes, methanol (3 ml) was added, and the reaction mixture warmed to room temperature over 0.5 h. Following addition of dichloromethane (75 ml), the reaction mixture was washed with 1 M hydrochloric acid (2 x 35 ml), and water (2 x 35 ml). After drying over magnesium sulphate, solvent was removed on the rotary evaporator. The resulting red oil was purified by flash chromatography using hexane:ethyl acetate as eluant, to give cis-3a,8b-dihydro--8-carbomethoxy-7-hydroxyfuro[3,2-b]benzofuran-2-(3H)-one (38) (450 mg, 75%) as a white crystalline solid.

Recrystallisation from acetone afforded an analytical sample, m.p. 171.5-172.0°C (Found: C, 57.03; H, 3.88; M^+,

250.0471. $C_{12}H_{10}O_6$ requires C, 57.61; H, 4.03; $\underline{M}^+$, 250.0477); λ_{max}(EtOH) 308 (log ε 3.0), and 349 nm (3.8); υ_{max}(nujol) 3600-3100 (s, -OH), 1770 (s, γ-lactone C=O), and 1680 cm^{-1} (s, o-hydroxyaryl ester C=O); δ_H (80 MHz; d^6-acetone) 2.93-3.17 (2H, m, 3-H_A and 3-H_B), 4.01 (3H, s, $-CH_3$), 5.47 (1H, ddd, $J_{3a,8b}$ 5.9, $J_{3a,3}$ 6.1 and 1.4 Hz, 3a-H), 6.44 (1H, d, $J_{3a,8b}$ 5.9 Hz, 8b-H), 6.99 (1H, d, $J_{5,6}$ 9.0 Hz, 5-H or 6-H), 7.15 (1H, d, $J_{5,6}$ 9.2 Hz, 6-H or 5-H), and 10.51 (1H, s, -OH); δ_c (20 MHz, d^6-DMSO) 35.0 (t, C-3), 52.5 (q, $-OCH_3$), 82.0 (d, C-3a), 83.8 (d, C-8b), 110.8 (s, C-8), 117.4 (d, C-5 or C-6), 121.1 (d, C-6 or C-5), 122.6 (s, C-8a), 153.7 (s, C-4a), 154.6 (s, C-7), 167.9 (s, aryl ester), and 175.1 (s, C-2); m/z 250 ($\underline{M}^+$, 55%), 218 ($\underline{M}-CH_3OH$, 100), 174 ($C_{10}H_6O_3$, 28), and 173 ($C_{10}H_5O_3$, 17).

2-Thiophenyl-1,4-benzoquinone (43)

To a finely divided suspension of 1,4-benzoquinone (44) (8.64 g, 80 mmol) in methanol (50 ml) was added a solution of thiophenol (45) (4.40 g, 40 mmol) in methanol (10 ml). After 5 minutes water (100 ml) was added, and the crude product filtered and washed with water to give 2-thiophenyl--1,4-benzoquinone (43) (8.4 g, 97%) as an orange solid. Recrystallisation from benzene gave orange-red needles, m.p. 113-114°C (lit.,[27] m.p. 114°C).

2-Phenylsulphinyl-1,4-benzoquinone (42)

2-thiophenyl-1,4-benzoquinone (43) (3.00 g, 0.0139 mol) was dissolved in trifluoroacetic acid (10 ml) and cooled to 0°C. A solution of peroxytrifluoroacetic acid was prepared by mixing 30% aqueous hydrogen peroxide (8.6 ml) with trifluoroacetic acid to give a final volume of 25 ml. This solution (3.48 ml, 0.0139 mol) was added dropwise to the sulphide solution. After standing at 0°C for 20 h., solvent was removed at reduced pressure. The residue was taken up in benzene (30 ml) and washed with 10% aqueous sodium bicarbonate. After drying over magnesium sulphate, solvent was removed to give 2-phenylsulphinyl-1,4-benzoquinone (42) (3.0 g, 93%) as a red solid, m.p. 118.5-119.5°C. (Found: C, 61.99; H, 3.51; S, 13.56; $\underline{M}^+$, 216.0216. $C_{12}H_8O_3S$ requires C, 62.07; H, 3.47; S, 13.81; $\underline{M}^+$, 216.0245); λ_{max} (MeOH) 206.0 (log ε 4.4), and 313.0 nm (3.6); υ_{max} (nujol) 1640 (s, C=O), and 1050 cm^{-1} (m, S=O); δ_H (80 MHz; d^6-acetone) 6.73-7.00 (2H, m, 5-H and 6-H), 7.24-7.33 (1H, m, 3-H), 7.47-7.63 (3H, m, Ar-H), and 7.70-7.87 (2H, m, Ar-H); δ_C (20 MHz; d^6-acetone) 126.73, 130.31, 132.55, 132.85, 137.40, 138.37, 143.33, 155.87, 176.0, 184.65, and 186.05; m/z 216 ($\underline{M}^+$, 100%), 188 ($\underline{M}$-CO, 12), and 187 ($\underline{M}$-CHO, 18).

cis-3a,8b-Dihydro-8-phenylsulphinyl-7-hydroxyfuro[3,2-b]-benzofuran-2-(3H)-one (46)

A solution of 2-trimethylsilyloxyfuran (23) (950 mg, 6.08 mmol) in acetonitrile (17 ml) was added slowly to an ice-cooled solution of 2-phenylsulphinyl-1,4-benzoquinone (42)

(706 mg, 3.04 mmol) in acetonitrile (35 ml) under an atmosphere of nitrogen. No colour change was observed. After 0.5 h., methanol (3.5 ml) was added, and the reaction mixture allowed to warm to room temperature over a further 0.5 h. Following dilution with dichloromethane (90 ml), the solution was washed with 1 M hydrochloric acid (45 ml), and water (45 ml). The organic phase was dried over magnesium sulphate, and the solvent removed under reduced pressure to give an orange oil. Purification by flash chromatography using hexane:ethyl acetate yielded cis-3a,8b-dihydro-8-phenylsulphinyl-7-hydroxyfuro[3,2-b]benzofuran-2--(3H)-one (46) (456 mg, 47%) as a white solid. Recrystallisation from acetone gave white needles, m.p. 154.5-155.5°C. (Found: M^+, 316.0408: $C_{16}H_{12}O_5S$ requires M^+, 316.0406); λ_{max} (MeOH) 205.5 (log ε 4.5), and 326.5 nm (4.0); υ_{max} (nujol) 3500-3100 (m, -OH), 1765 (s, C=0), and 1050 cm^{-1} (m, S=0); δ_H (80 MH_z; d^6-acetone) 2.68-3.40 (2H, m, 3-H_A and 3-H_B), 5.49 (1H, ddd, $J_{3a,8b}$ 5.7, $J_{3a,3}$ 6.5 and 1.3 Hz, 3a-H), 6.69 (1H, d, $J_{8b,3a}$ 5.7 Hz, 8b-H), 6.89 (2H, s, 5-H and 6-H), and 7.45-8.01 (5H, m, -SOPh); δ_C (20 MHz; d^6-acetone) 35.7 (t, C-3), 81.7 (d, C-3a), 83.8 (d, C-8b), 114.6 (d, C-5 or C-6), 120.9 (d, C-6 or C-5), 122.4 (s, C-8a), 126.4 (d, C-3'), 127.8 (s, C-8), 129.9 (d, C-2'), 132.1 (d, C-4'), 145.9 (s, C-1'), 150.6 (s, C-4a), 156.6 (s, C-7), and 175.1 (s, C-2); m/z 316 (M^+, 100%), 300 ($C_{16}H_{12}O_4S$, 43), 271 (M-COOH, 15), 253 ($C_{15}H_9O_2S$, 24), and 245 ($C_{13}H_9O_3S$, 25).

4-Ethyl-5-hydroxybenzofuran-2-ylacetic acid (49)

Triethylsilane (220 mg, 1.9 mmol) was added dropwise to a solution of cis-3a,8b-dihydro-8-acetyl-7-hydroxyfuro-[3,2-b]benzofuran-2-(3H)-one (24) (200 mg, 0.854 mmol) in trifluoroacetic acid (1.5 g, 13 mmol).

After 0.75 h. the reaction mixture was diluted with water (15 ml) and washed with diethyl ether (2 x 15 ml). Drying over magnesium sulphate, followed by solvent removal under reduced pressure gave a red oil. Flash chromatography using hexane:ether as eluant gave 4-ethyl-5-hydroxybenzofuran-2--ylacetic acid (49) (96 mg, 51%) as yellow needles, m.p. 125-130°C (Found: M^+, 220.0724. $C_{12}H_{12}O_4$ requires M^+, 220.0735); υ_{max} (nujol) 3380 (m, -OH), and 1700 cm^{-1} (s, -COOH); δ_H (60 MHz; $CDCl_3$) 1.05-130 (3H, t, $-CH_3$), 2.60-3.00 (2H, q, $-CH_2CH_3$), 3.80 (2H, s, $-CH_2COOH$), and 6.6-7.1 (3H, m, 3-H and Ar-H); m/z 220 (M^+, 100%), 205 ($M-CH_3$, 91), 176 ($M-CO_2$, 14), and 175 (M-COOH, 65).

4-Acetyl-5-hydroxybenzofuran-2-ylacetic acid (50)

cis-3a,8b-dihydro-8-acetyl-7-hydroxyfuro[3,2-b]benzofuran-2--(3H)-one (24) (100 mg, 0.427 mmol) was dissolved in trifluoroacetic acid. The red solution was diluted with water (10 ml) and washed with diethyl ether (2 x 10 ml). Drying over magnesium sulphate, followed by solvent removal at reduced pressure yielded 4-acetyl-5-hydroxybenzofuran-2-ylacetic acid (50) (73 mg, 73%) as an orange solid, m.p. 172-174°C (Found: M^+, 234.0533 . $C_{12}H_{10}O_5$ requires M^+, 234.0529); υ_{max} (nujol) 1695 (s, -COOH), and 1610 cm^{-1} (s, o-hydroxyaryl ketone); δ_H (60 MHz; $CDCl_3$) 2.75 (3H, s, $-CH_3$), 3.85 (2H, s, $-CH_2-$), 6.65-6.85 (1H, d, $J_{6,7}$ 4.5 Hz, 6-H or 7-H), 6.80 (1H, s, 3-H), and 7.40-7.60 (1H, d, $J_{7,6}$ 4.5 Hz, 7-H or 6-H); m/z 234 (M^+, 68%), 219 ($M-CH_3$, 100), 189 (M-COOH, 23), and 175 ($M-CH_2COOH$,3).

cis-3a,8b-Dihydro-8-(1'-hydroxyethyl)-7-hydroxyfuro[3,2-b]-benzofuran-2-(3H)-one (51)

Sodium borohydride (9 mg, 0.21 mmol) was added to a solution of cis-3a,8b-dihydro-8-acetyl-7-hydroxyfuro[3,2-b]benzofuran-2-(3H)-one (24) (100 mg, 0.43 mmol) in methanol (30 ml). After stirring at room temperature for 1 h., the mixture was taken up in saturated aqueous ammonium chloride (25 ml). To this was added 2 M sodium hydroxide (10 ml). The solution was left to stand for 0.25 h. Following acidification with 1 M hydrochloric acid (30 ml), the solution was extracted with ethyl acetate (2 x 30 ml). Drying over magnesium sulphate, and subsequent solvent removal under reduced pressure, afforded a pale brown solid. Flash chromatography using ethyl acetate as eluant gave cis-3a,8b-dihydro-8-(1'-hydroxyethyl)-7-hydroxyfuro[3,2-b]-benzofuran-2-(3H)-one (51) (57 mg, 57%), as white crystals, m.p. 184-186°C (Found: $\underline{M}^+$, 236.0696 . $C_{12}H_{12}O_5$ requires $\underline{M}^+$, 236.0685); λ_{max} (MeOH) 205.0 (log ε 3.4), 307.0 nm (2.7); υ_{max} (nujol) 3370-3320 (m, -OH), and 1753 cm^{-1} (s, γ-lactone C=0); δ_H (80 MHz; d^6-acetone) 1.52 (3H, d, $\underline{J}_{1',2'}$ 6.6 Hz, $-CH_3$), 2.78 (1H, dd, $\underline{J}_{gem}$ 18.8, $\underline{J}_{3,3a}$ 0.4 Hz, $3-H_A$), 3.19 (1H, dd, $\underline{J}_{gem}$ 18.8, $\underline{J}_{3,3a}$ 1.9 Hz, $3-H_B$), 5.15-5.48 (2H, m, 3a-H, 1'-H), 6.14 (1H, d, $\underline{J}_{8b,3a}$ 5.8 Hz, 8b-H), 6.55-6.84 (2H, m, Ar-H), and 8.5 (1H, br., -OH); $\underline{m}/\underline{z}$ 236 ($\underline{M}^+$, 100%), 235 ($\underline{M}$-H, 34), 219 ($\underline{M}$-OH, 59), and 218 ($\underline{M}-H_2O$, 71).

A minor diastereomer, having the same R_f value as the major product, was detected in the ^1H n.m.r. spectrum. Differences in chemical shift were observed for the methyl group, which resonated at δ_H1.51 instead of 1.52, and 8b-H, which resonated downfield from δ_H6.14, at δ_H6.32. All other chemical shifts, and the coupling constants appeared to be identical.

cis-3,3a,9b-Trihydro-5-hydroxy-5-methylfuro[3,2-c][2]benzopyran-2,6,9-(5H)-trione (58)

A solution of ceric ammonium nitrate (345 mg, 0.63 mmol) in water (5 ml) was added dropwise to cis-3a,8b-dihydro-8-acetyl-7-hydroxyfuro[3,2-b]benzofuran-2-(3H)-one (24) (50 mg, 0.21 mmol) dissolved in acetonitrile (15 ml). The solution was diluted with water (30 ml) and extracted with dichloromethane (50 ml). After the organic phase had been washed with water (30 ml) and dried over sodium sulphate, solvent was removed at reduced pressure to give a yellow oil. Flash chromatography using hexane:ethyl acetate as eluant afforded: cis-3,3a,9b-trihydro-5-hydroxy-5-methylfuro[3,2-c][2]benzopyran-2,6,9-(5H)-trione (58) (14 mg, 27%) as a yellow solid, which decomposed on heating; λ_{max} (EtOH) 204.5 (log ε 3.8), 244.5 (4.0), and 302.0 nm (3.2); υ_{max} (nujol) 3370 (br, -OH), 1760 (s, γ-lactone C=O), and 1653 cm^{-1} (s, quinone C=O); δ_H (80 MHz; d^6-acetone) 1.75 (3H, s, $-CH_3$), 2.44 (1H, d, J_{gem} 17 Hz, 3-H_A), 3.14 (1H, dd, J_{gem} 17, $J_{3,3a}$ 4.9 Hz, 3-H_B), 4.89 (1H, dd, $J_{3a,3}$ 4.9, $J_{3a,9b}$ 2.9 Hz, 3a-H), 5.16 (1H, d, $J_{9b,3a}$ 2.9 Hz, 9b-H), and 6.88 (2H, s, 7-H and 8-H), δ_c(20 MHz, d^6-acetone) 27.0 (q, $-CH_3$), 37.0 (t, C-3), 67.3 (d, C-3a or C-9b), 69.7 (d, C-9b or C-3a), 93.5 (s, C-5), 136.4 (d, C-7 or C-8), 138.6 (d, C-8 or C-7), 144.5 (s, C-5a or C-9a), 155.3 (s, C-9a or C-5a), 175.4 (s, C-2), 186.0 (s, C-6 or C-9), and 186.4 (s, C-9 or C-6); m/z 235 (M-CH_3, 100%), and 191 (M-CH_2COOH, 34%).

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