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

JENNIFER JOY GIBSON

1987

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

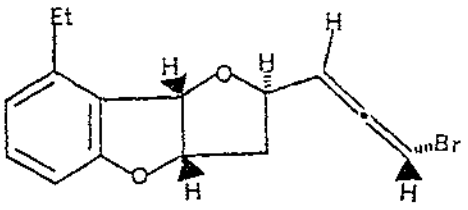
CAN	=	ceric ammonium nitrate
DMF	=	*N*,*N*-dimethylformamide
DMSO	=	dimethyl sulphoxide
NBS	=	*N*-bromosuccinimide
TES	=	triethylsilane
TFA	=	trifluoroacetic acid
TMSCl	=	chlorotrimethylsilane
Ts	=	*p*-toluenesulphonyl
p-TSA	=	*p*-toluenesulphonic acid

CHAPTER 1

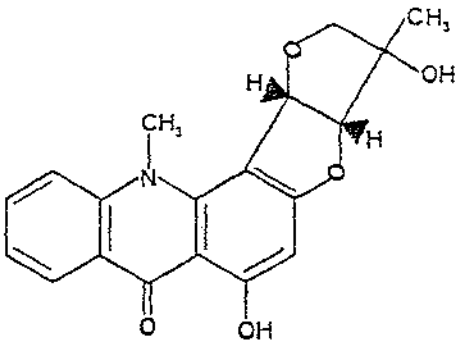
INTRODUCTION

1.1 Panacene (1)

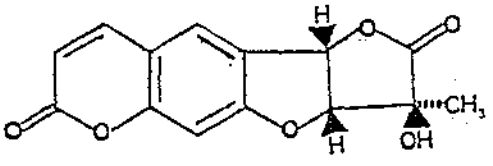
Panacene (1), a potent fish antifeedant, is one of several halogenated marine natural products isolated from Aplysia brasiliana in 1977 by Meinwald et al.[1]. Spectroscopic techniques revealed the presence of a bromo-allene moiety, and the uncommon cis-3a,8b-dihydrofuro[3,2-b]benzofuran ring system. 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).



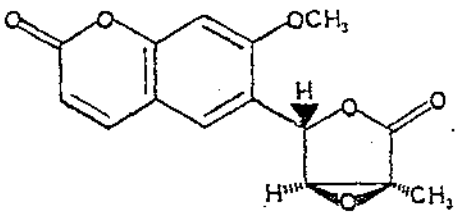
(1)



(2)



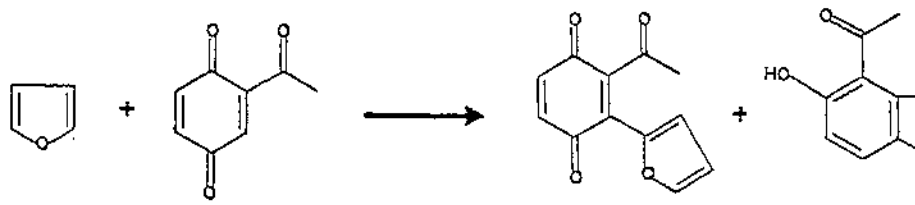
(3)



(4)

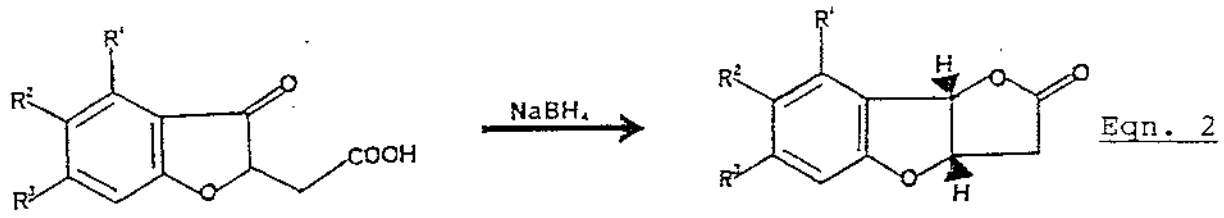
1.2 The cis-3a,8b-Dihydrofuro[3,2-b]benzofuran Ring System

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

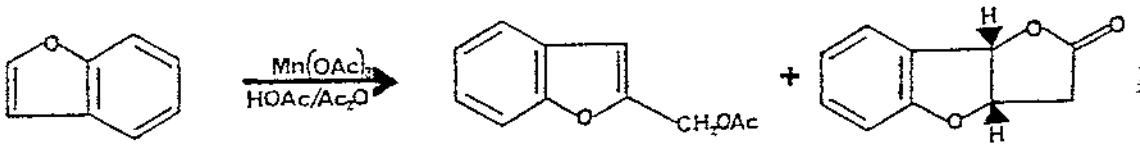
(8): $R^1=R^3=CH_3$; $R^2=H$.

(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.

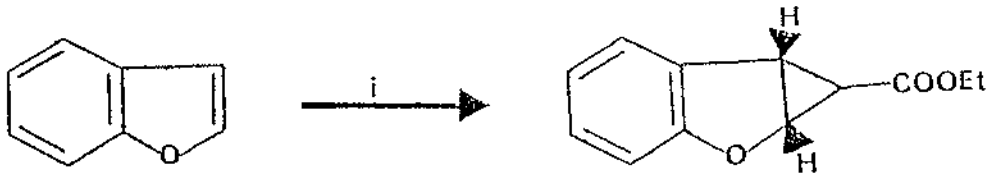
Later, in a study of the oxidation of benzofuran (12) with manganic acetate, Kasahara et al.[6] reported the isolation of the lactone cis-3a,8b-dihydrofuro[3,2-b] benzofuran-2-(3H)-one (13) in 21% yield (Eqn.3).



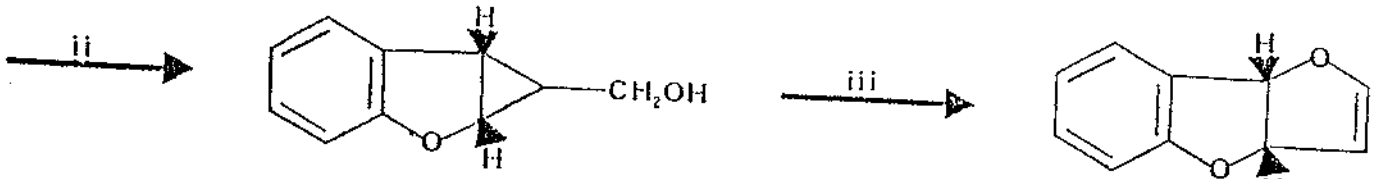
Eqn. 3

(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).



(12)



(14)

(15)

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

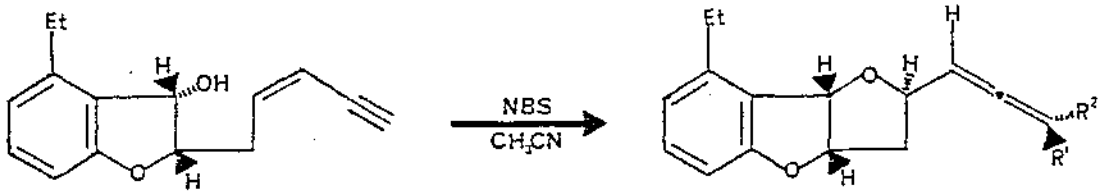
Scheme 1

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).

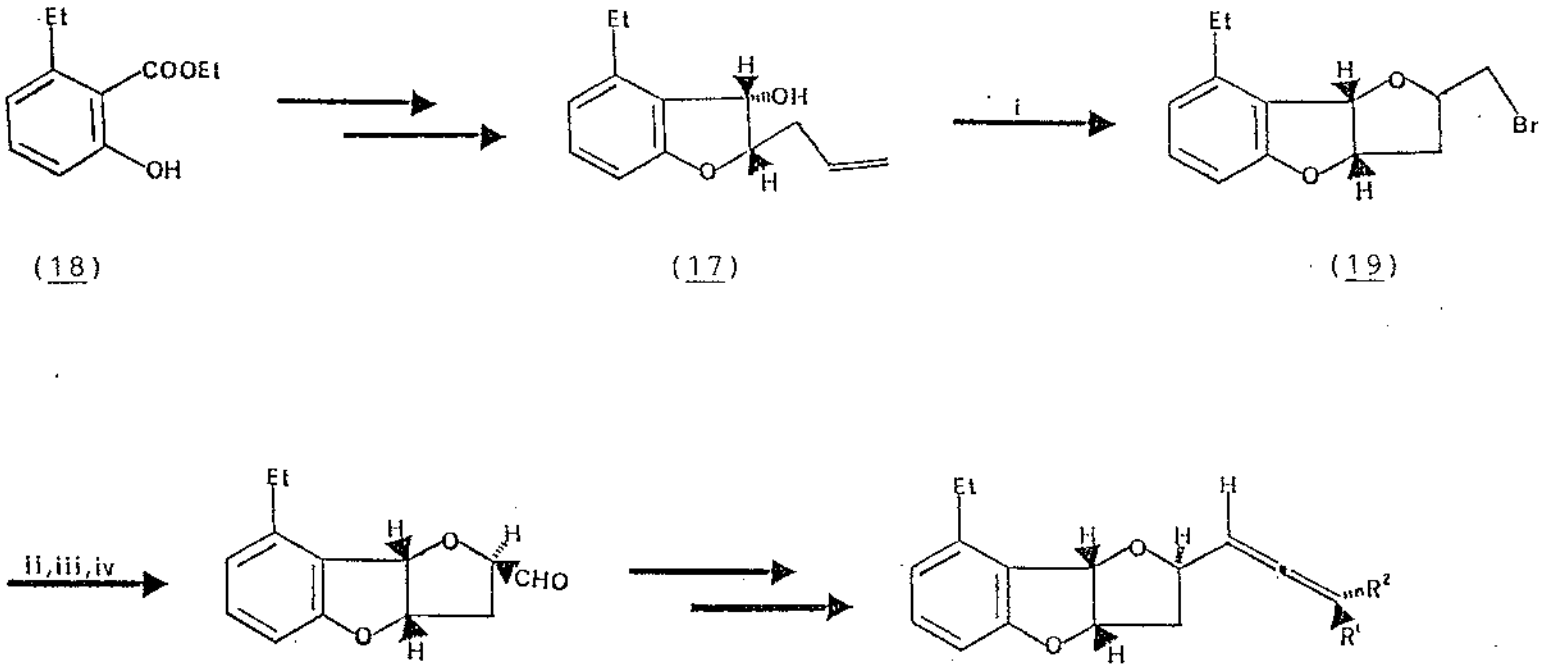


Eqn.4

(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

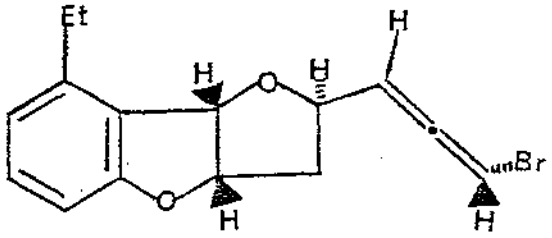
Reagents: (i) NBS, CH_3CN; (ii) KOAc, DMF; (iii) $NaOCH_3$, CH_3OH; (iv) $(COCl)_2$, Me_2SO, TEA, CH_2Cl_2. (i-iv): 64% yield

Scheme 2

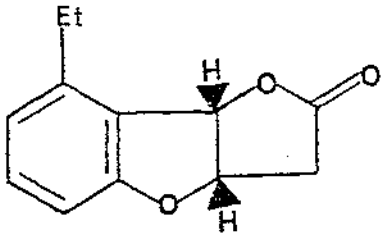
It should be noted that both syntheses of panacene (1) produced a racemic mixture, and both involved stepwise construction of the cis-3a,8b-dihydrofuro[3,2-b]benzofuran ring system.

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).

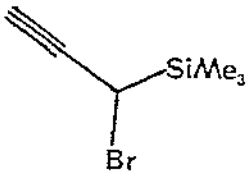


(1)



(22)

+



Scheme 3

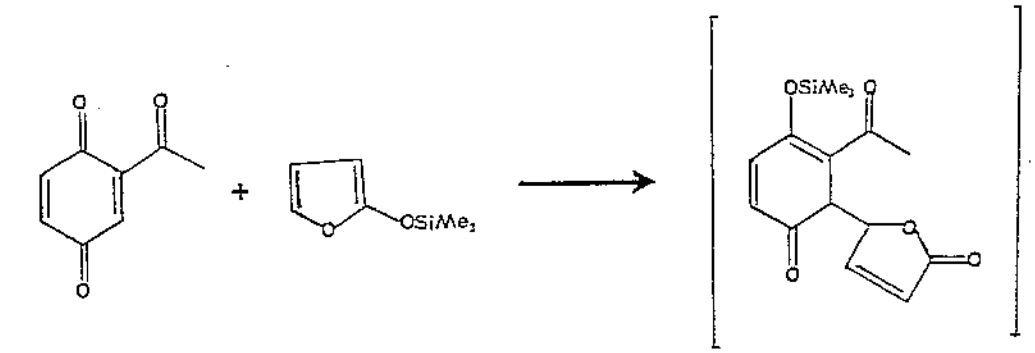
Based on the work by Pelter *et al.*[10], and other groups[11,12,13], it was proposed that the 1,4-addition of 2-trimethylsilyloxyfuran (23) to 2-acetyl-1,4-benzoquinone (6) might be a useful starting point for the synthesis of the required lactone (22) (Scheme 4). Thus, after initial 1,4-addition of 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

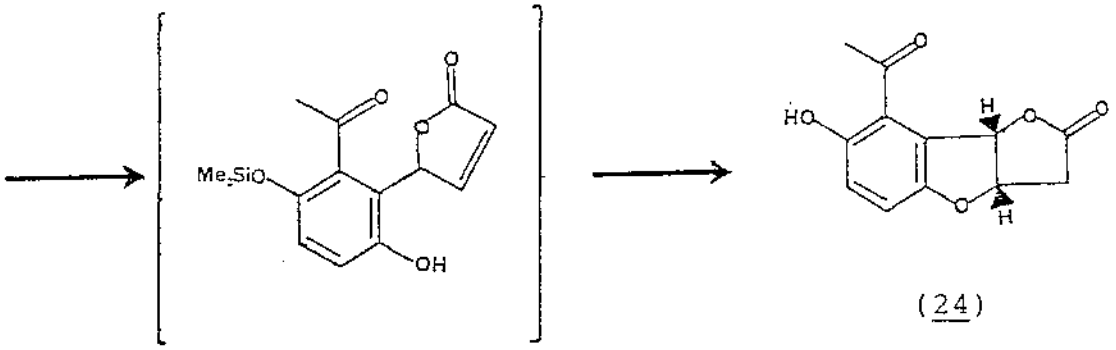
Additions to quinones have been reviewed in detail[14]. The addition of enol ethers, allylsilanes, and 2-*t*-butoxyfuran to quinones is particularly relevant to the proposed synthesis.

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).

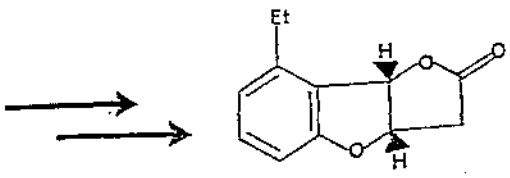
In 1978, the 1,4-addition of 2-*t*-butoxyfuran (25) to 2-acetyl-1,4-naphthoquinone (26) was carried out by Kraus *et al.*[12] (Scheme 5). In this case, tautomerisation was followed by methylation, which blocked the phenoxy group. Furthermore, the robust nature of the *t*-butoxy group prevented formation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



(6) (23)

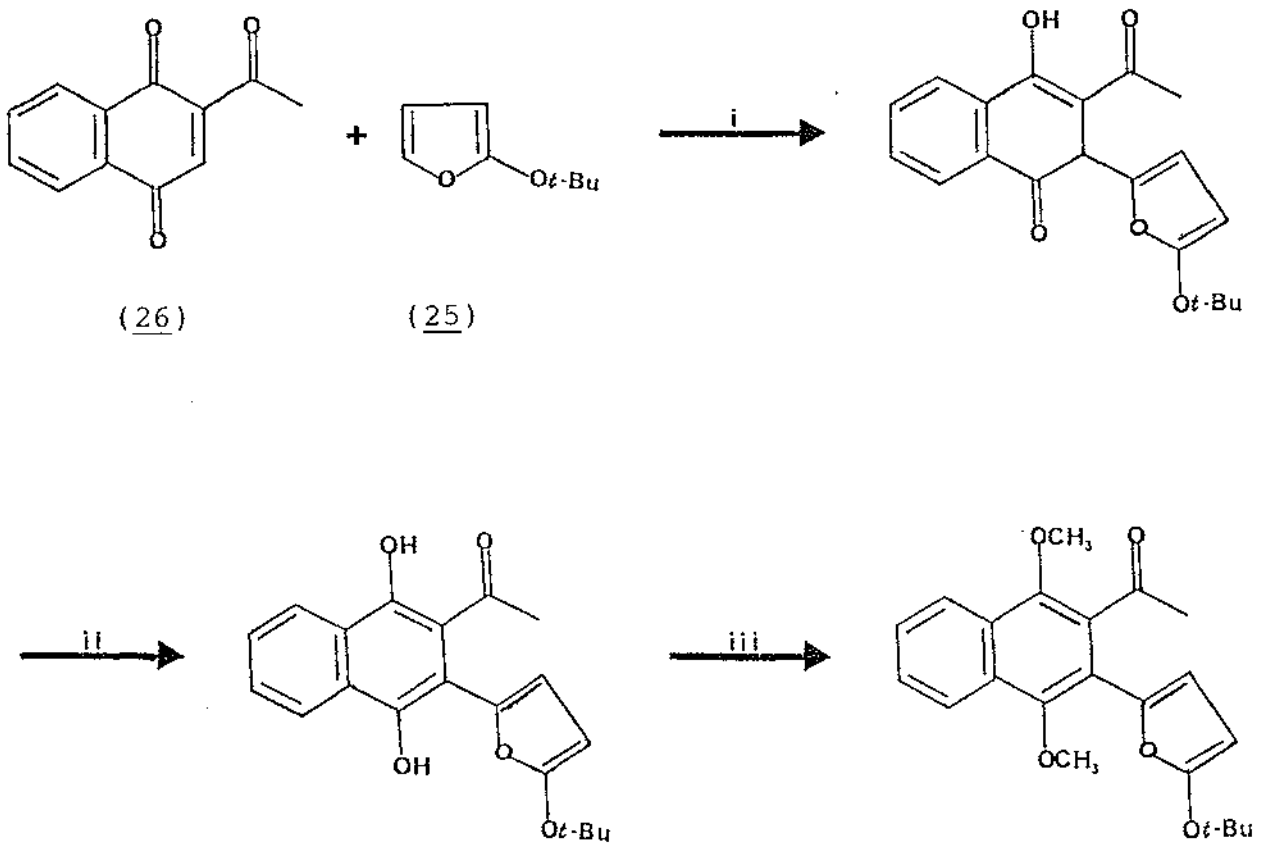


(24)



(22)

Scheme 4



(26) (25)

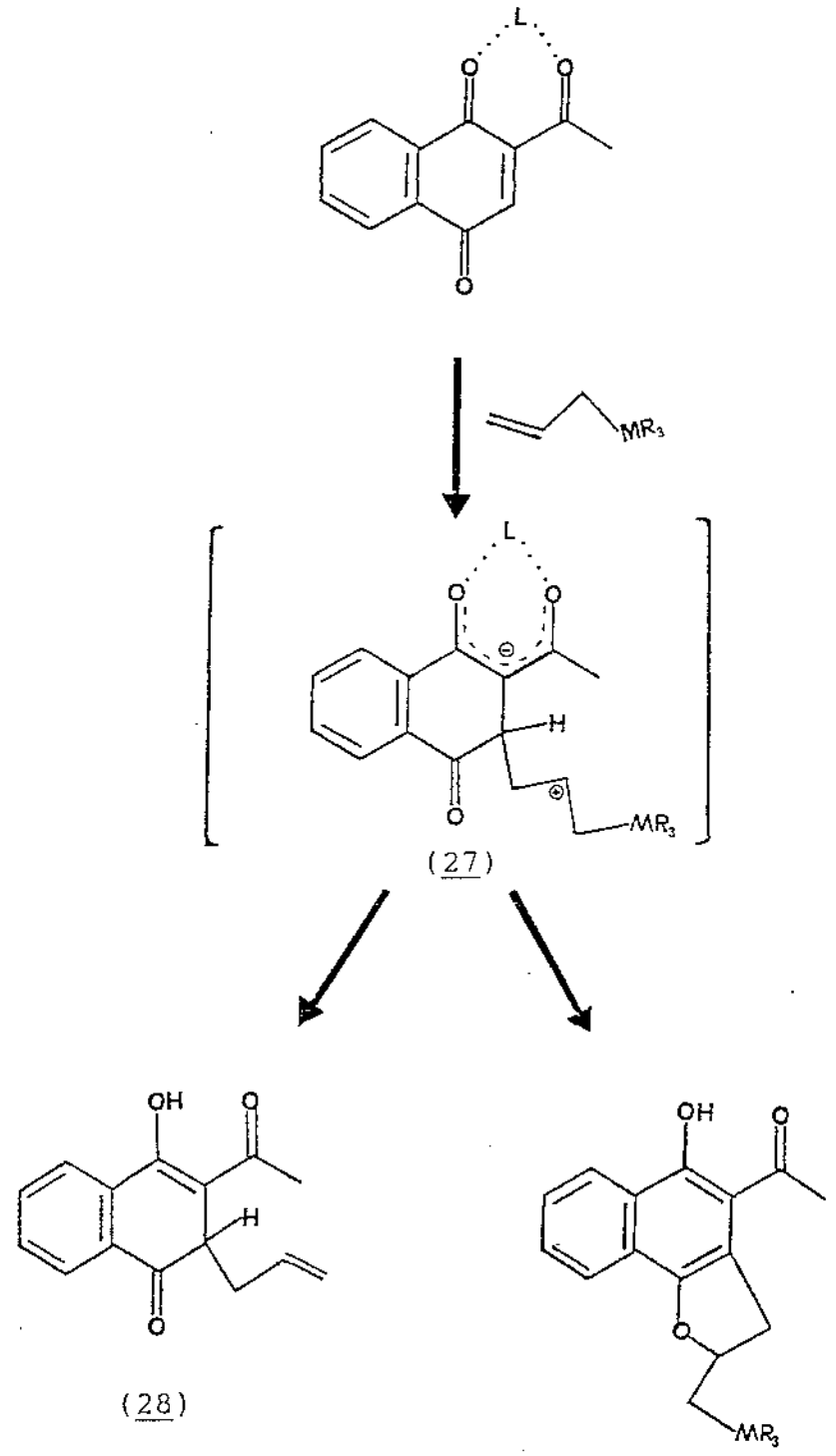
Reagents: (i) $PhCH_3$, 0 or -78°C; (ii) acid or base; (iii) $(CH_3)_2SO_4$, K_2CO_3, acetone. (i-iii): 62% yield.

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).