The Synthesis and Evaluation of Some Anti-infective Agents

Robert William Allcock

A thesis submitted in partial fulfilment of the requirements of The Nottingham Trent University for the degree of Doctor of Philosophy

September 2000

Dedication

This thesis is dedicated to the memory of my father and mother.

William Allcock

22nd May 1935 - 5th June 1997

Iris Ann Allcock

28th May 1938 - 20th October 1981

Acknowledgements

The following people must be thanked for their contributions and help in completing this project. Special thanks to my supervisor Dr. I.G.C. Coutts for his tenacious and diplomatic guidance, and tireless efforts on my behalf; to Dr. P.R. Huddleston and Mr M. Wood, of the Organic Research laboratory at The Nottingham Trent University, for their technical support and friendship; to Dr. S.D. Mills of Zeneca Pharmaceuticals for his advice, encouragement, and interest; to Mr. M. Brice of the department of Life Sciences at The Nottingham Trent University for providing the antibacterial results; to Dr. A. Wookey and Dr. M. Betts, of AstraZeneca, for their helpful discussion of these results; to Dr. Hans Scheeren of the University of Nijmegen, Holland, for providing access to the high pressure facility and technical support during the high pressure cycloaddition reactions, and to BTG Ltd. for providing financial support during the patent development.

Finally, the preparation of this thesis would not have been possible without the love and understanding of Marta Solé Recasens and her parents, Joan and Maria.

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Abstract

Previous research at The Nottingham Trent University, directed towards the synthesis and evaluation of novel specific calmodulin antagonists, identified a series of compounds with the general structure Ar-O-$(CH_2)_nNR_2$ as possessing significant antifungal activity. In the present study the most potent, PCAB 300, has been subjected to a variety of structural modifications to improve its potency in a broad-spectrum human pathogenic fungal screen operated by Zeneca Pharmaceuticals.

A significant increase in potency was achieved by the substitution of the pyrrolidine moiety of PCAB 300 with methylamine. The investigation also established that the structural features required for optimal *in vitro* antifungal activity are a naphthalene ring substituted in the 6-position by bromine and in the 2-position by an alkoxy side chain, of eight to ten carbons long, possessing a terminal N-methyl substituent.

The results of this investigation are the subject of a patent application, UK-9922446.1 (1999), by BTG, and it is intended that selected potent inhibitors will undergo further *in vivo* and *in vitro* testing.

The palmarumycins are a structurally related and diverse class of biologically active natural products which contain a unique spiro-acetal moiety, formally derived from 1,8-dihydroxynaphthalene, linked to a second naphthalene ring at rich and varied levels of oxidation. Palmarumycin CP_1, structurally the least complex, was selected as a suitable synthetic target for both a synthetic and biological investigation.

A novel series of palmarumycin analogues were prepared, either by the direct oxidative cyclisation of aminonaphthyloxynaphthols, or by the cycloaddition of 3-oxo-2-pyrones to a novel series of quinone monoacetals. Thermal conditions gave poor to moderate yields, but high pressure led to quantitative conversion. Spectral data indicated that the cycloaddition reactions occurred with a high degree of site-, regio-, and stereo-selectivity which was dependant upon the substitution pattern of the quinone monoacetals. An account of this study has been published (Tetrahedron Letters, 2000, 41, 9105).

In general the quinone monoacetals and cycloaddition products that possessed an unsubstituted enone system showed significant activity against methicillin resistant *Staphylococcus aureus* (MRSA), with MIC values less than 10ppm. In contrast substituted cycloaddition products were inactive, which suggests that the biological activity of the compounds is reflected by their ability to act as Michael acceptors, and they are therefore unlikely to act as lead compounds for clinically useful antimicrobial agents.

Glossary

Bn	benzyl
^{t}BuLi	*tert*-butyllithium
COSY	correlated spectroscopy
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement through polarization transfer
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNPH	2,4-dinitrophenylhydrazine
ESI	electrospray ionization mass spectroscopy
EtOAc	ethyl acetate
EtOH	ethanol
LDA	lithium diisopropylamide
MeOH	methanol
m-CPBA	*meta*-chloroperoxybenzoic acid
MRSA	methicillin resistant *Staphylococcus aureus*
NBS	*N*-bromosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
THF	tetrahydrofuran
T.l.c	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	tetramethylsilane
TsOH	*para*-toluenesulfonic acid

1.0. Introduction.

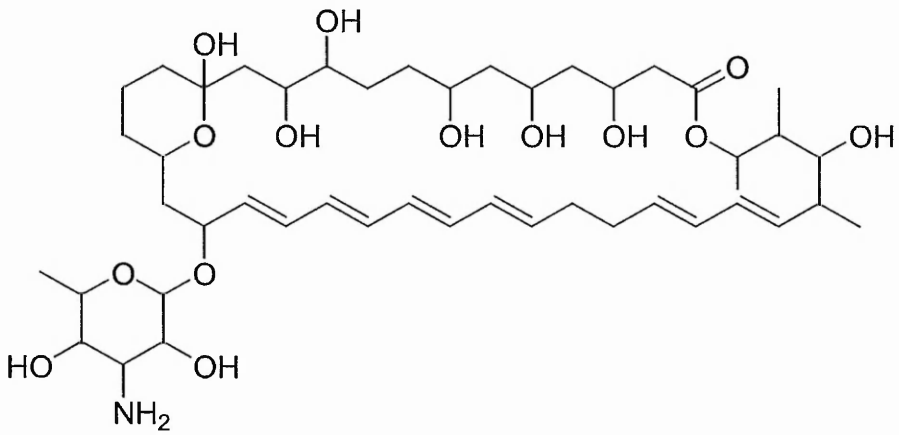
As the ability to treat bacterial infection improves it is inevitable that other disease targets should become more prominent. Viral, parasitic, and fungal diseases are being increasingly recognised as complications which need to be controlled.

Fungal infections in man cover a wide spectrum both in terms of severity and incidence. Whilst superficial infections such as athlete's foot are very common and in most cases are a minor problem systemic fungal infections can be debilitating and in some cases fatal. Recently, primarily as a result of the growing population of immuno-suppressed and immuno-compromised patients, arising from HIV infection and AIDS, transplant recipients, and cancer chemotherapy, both the number and severity of systemic fungal infections have increased[1, 2]. However, in contrast to the large number of available antibacterial drugs there are fewer antifungal agents, and none of which fulfills the urgent need for a non-toxic broad-spectrum systemic fungicidal agent.

Currently there are three main families of antifungal drugs:

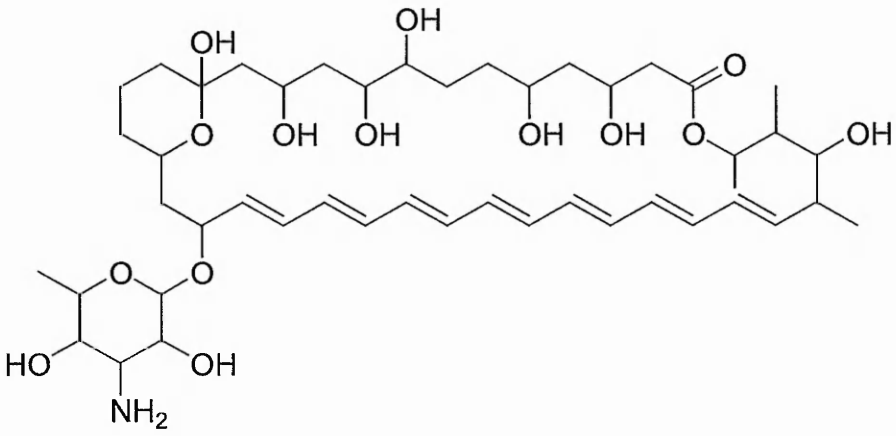
The polyenes:
Among the first potent broad-spectrum antifungal compounds are nystatin, Figure 1, and amphotericin B[2], Figure 2.

Figure 1.



Nystatin

Figure 2.



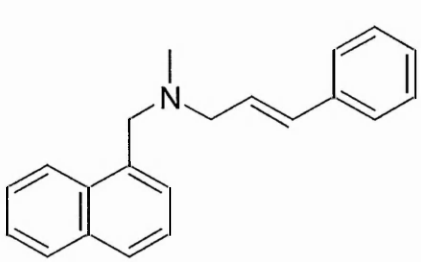
Amphotericin B.

The fungicidal activity of these polyenes is due to their ability to bind strongly with ergosterol, a fungal sterol of the cellular membrane, thereby generating lipid vesicles in the cellular membrane that are permeable to cations, which ultimately leads to cell lysis[3]. However, as fungal and mammalian cells are both eukaryotes the polyenes have a similar interaction with the constituent sterol of mammalian cell membranes, cholesterol, which gives rise to systemic toxicity. The pronounced toxicity associated with the polyenes has restricted the use of nystatin to topical and mucosal infections and amphotericin B to severe systemic infections only.

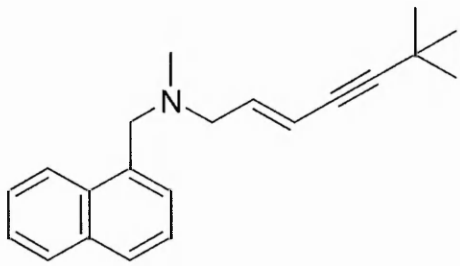
The Allylamines:

The allylamines naftifine[4] and its successor terbinafine[5], Figure 3, are moderate broad-spectrum antifungal compounds that are known to be reversible non-competitive inhibitors of squalene epoxidase[4], a membrane bound enzyme that is essential for the biosynthesis of ergosterol.

Figure 3.



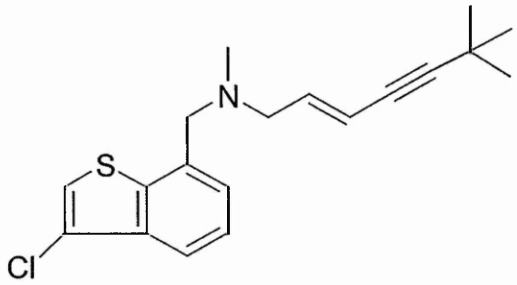
Naftifine



Terbinafine

More recently the replacement of the naphthalene moiety of terbinafine with 3-chloro-7-benzo[*b*]thiophene, to give SDZ 87-469 Figure 4, has afforded an allylamine with a broader spectrum of antifungal activity, with a higher potency in the inhibition of squalene epoxidase[6, 7].

Figure 4.

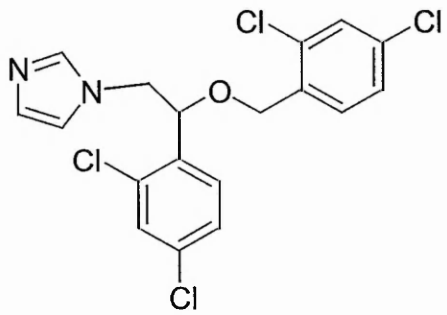


SDZ 87-469

The Azoles:

A significant advance in the treatment of cutaneous and systemic fungal infections was achieved in the early 1970s with the introduction of the imidazole miconazole, Figure 5[1,2].

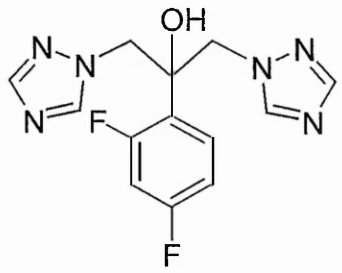
Figure 5.



Miconazole

Subsequently many imidazole and triazole derivatives have been found to possess antifungal activity. Currently, the leading triazole antifungal, with well over 50 million prescriptions to date[2], is fluconazole, Figure 6. Since its introduction in 1988 the success of fluconazole has been attributed to its clinical efficacy against *Candida albicans* and *Cryptococcus neoformans*, along with its availability in both oral and intravenous dosage forms[2].

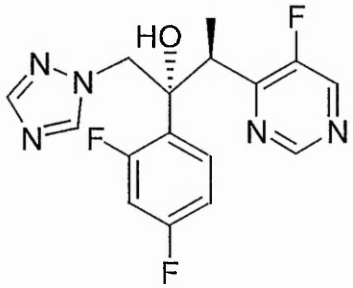
Figure 6.



Fluconazole

Like other azoles fluconazole prevents the biosynthesis of ergosterol by the inhibition of the fungal cytochrome P450-dependent enzyme, lanosterol 14α-demethylase. The depletion of ergosterol in the fungal cell membrane ultimately stops fungal replication and growth; thus the azoles are fungistatic but not fungicidal. However, fluconazole is less active against the two emerging *Candida* species *C. glabrata* and *C. krusei*, and is inactive against *Aspergillus fumigatus*, which, although uncommon, is frequently a life-threatening infection[2]. More recently this situation has been addressed by the introduction of Voriconazole, a pyrimidine derivative of fluconazole which has been shown to possess good *in vitro* activity against a wide range of fungal pathogens[8], Table 1.

Table 1[8].



Voriconazole

Pathogen	*Candida albicans*	*Candida glabrata*	*Candida krusei*	*Aspergillus fumigatus*	*Cryptococcus neoformans*
MIC* (μg/ml)	0.03	0.19	0.24	0.09	0.39

*MIC is defined as the minimum concentration of compound to inhibit replication of the pathogen *in vitro*.

However, in view of the emergence of azole-resistant *Candida albicans*[9] and the extensive use and dependence upon azole antifungals this class of compound could be further compromised in the long term.

Thus there is still a need for the identification of broad-spectrum antifungal compounds which are orally active with good toxicological profiles, and with divergent mechanisms of action[10].

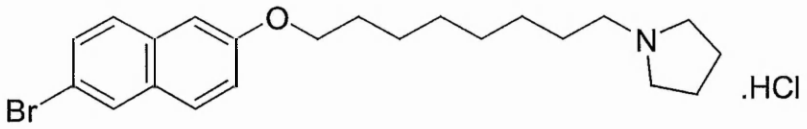
1.1. Calmodulin Antagonists as Potential Antifungal Agents.

The Ca^{2+} binding protein calmodulin (CaM) is found in a variety of eukaryote cells. Through its binding with calcium ions it undergoes conformational changes and activates many target enzymes[11] and has been implicated in many important cellular events such as cell motility, contractility, and division[12, 13].

Calmodulin proteins isolated from vertebrates, invertebrates, plants, and protazoa have been found to show a very high degree of sequence similarity, being more than 90% identical[14]. In comparison fungal calmodulin proteins have been shown to have a significant degree of divergence, only 60% identical for *Saccharomyces cerevisiae* [15,16,17], which raises the possibility that these proteins may be suitable targets for novel antifungal drugs[18, 19, 20].

Previous research at The Nottingham Trent University [21], directed towards the synthesis and evaluation of novel specific calmodulin antagonists, identified a series of compounds with the general structure Ar-O-$(CH_2)_nNR_2$ as possessing antifungal activity against the plant pathogen *Pythium ultimum*. This fungus is an oomycete, which does not synthesise ergosterol, and is thus unaffected by fungicides which inhibit sterol biosynthesis. This identified the possibility that these compounds could potentially be an important new class of antifungal agents[20]. Indeed the compound PCAB 300, Table 2, was shown to posses activity in both a calmodulin-dependent myosin light chain kinase screen with an IC_{50} value of 10μM and a broad-spectrum human pathogenic fungal screen Table 2[21].

Table 2[21].



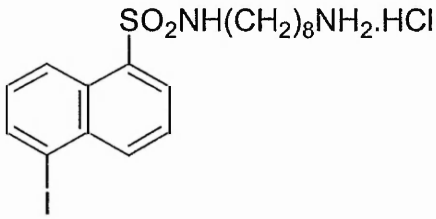
PCAB 300

Pathogen	*Candida albicans*	*C. albicans* Azole resist.	*Candida parapsilosis*	*Candida glabrata*	*Candida krusei*	*Candida tropicalis*
MIC (μg/ml)	4	4	8	2	0.5	4

Pathogen	*Cryptococcus neoformans*	*Sacch. cerevisiae*	*Aspergillus fumigatus*	*Trichophyton quinkeanum*
MIC (μg/ml)	0.5	8	4	1

Furthermore, J8 Figure 7, a potent and specific calmodulin antagonist[23] was also found to have significant activity against the plant pathogen *Pythium ultimum* with an IC_{50} value of 14.1mM[21].

Figure 7



J8

Thus, PCAB 300 was chosen as the primary lead compound for further development as an antifungal agent, possibly at the expense of calmodulin antagonism.

With access to a broad-spectrum human pathogenic antifungal screen operated by Zeneca Pharmaceuticals PCAB 300 was subjected to a systematic study of structural modifications in an attempt to optimise the antifungal potency. A second objective was to prepare the findings of the investigation for a potential patent application.

Also, J8, a potent and specific calmodulin antagonist[22], was prepared to test if the preliminary antifungal activity against the plant pathogen *Pythium ultimum* could be maintained in a broad-spectrum human pathogenic antifungal screen.

2.0. Chemical Discussion.

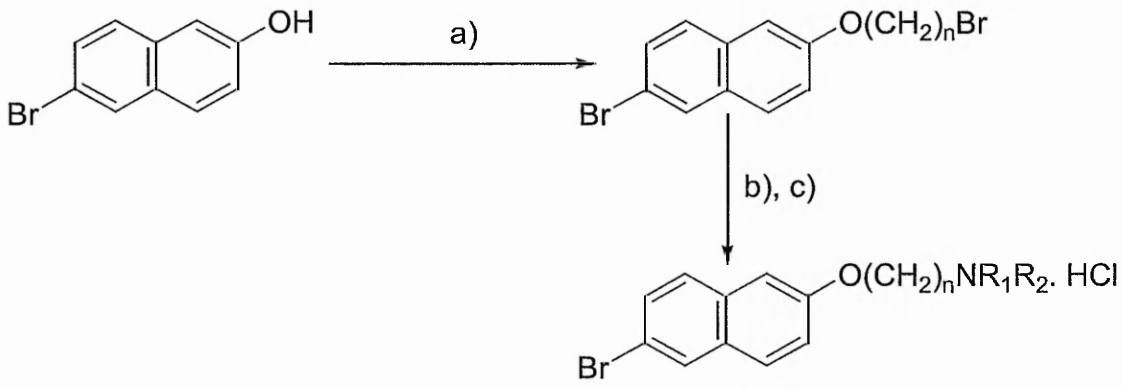
2.1. Development of PCAB 300.

PCAB 300 had primarily been developed as a CaM antagonist, but was also shown to exhibit significant activity against a broad-spectrum of human pathogenic fungi with IC_{50} values in the mM region[21].

The aim of this study was to develop the structural and functional characteristics of PCAB 300 to attain optimal antifungal activity, possibly at the expense of CaM antagonism.

The original synthetic route to these compounds is illustrated in Scheme 1, and was successfully modified for the preparation of analogous primary and secondary amines, compounds **8** and **9**, described below.

Scheme 1[21].



a) 5 eq. $Br(CH_2)_nBr$, 3 eq. K_2CO_3, butanone, reflux. b) 3 eq. R_1R_2NH, THF. c) CH_2Cl_2, 1M HCl diethyl ether.

2.1.1. Ether Synthesis.

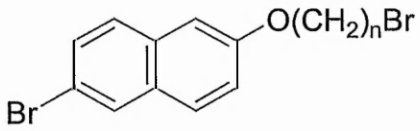
The Williamson ether synthesis is the best general method for the preparation of ethers. Excess dibromoalkane is required in order to obtain the mono-ether in high yield without any bis-ether or *C*-alkylation being observed. This statistical approach, which is in direct

contrast to the high dilution conditions required for the synthesis of crown ethers, has been found to be successful for a variety of aryloxides and dibromoalkanes. As dibromoalkanes are increasingly costly with increasing chain length the excess is conveniently recovered by reduced pressure kugelrohr distillation. After distillation the product is usually obtained as an oil, contaminated with residual dibromoalkane. Further purification is best achieved by trituration of the oil with petroleum ether to give the product as a solid, which is recrystallised from a suitable solvent.

The purity of the bromoalkyl-ether intermediates is crucial as the next synthetic transformation is amination and residual dibromo alkane would generate a complex mixture of products due to polyalkylation of the amino moiety. Also bromoalkanes act as indiscriminate alkylating agents in biological systems, so would interfere with the accuracy of subsequent biological assessment. The purity of the bromo-ether intermediates can be quickly assessed by comparison of the (-O-CH_2-) and (-CH_2-Br) integrals in the ^{1}H NMR spectrum.

In this manner the bromoalkyl-ethers, Table 3, were prepared.

Table 3.



Chain length (n)	2	6	8	9	10	12
Compound Number	**1**	**2**	**3**	**4**	**5**	**6**

2.1.2. Alkylation of Amines.

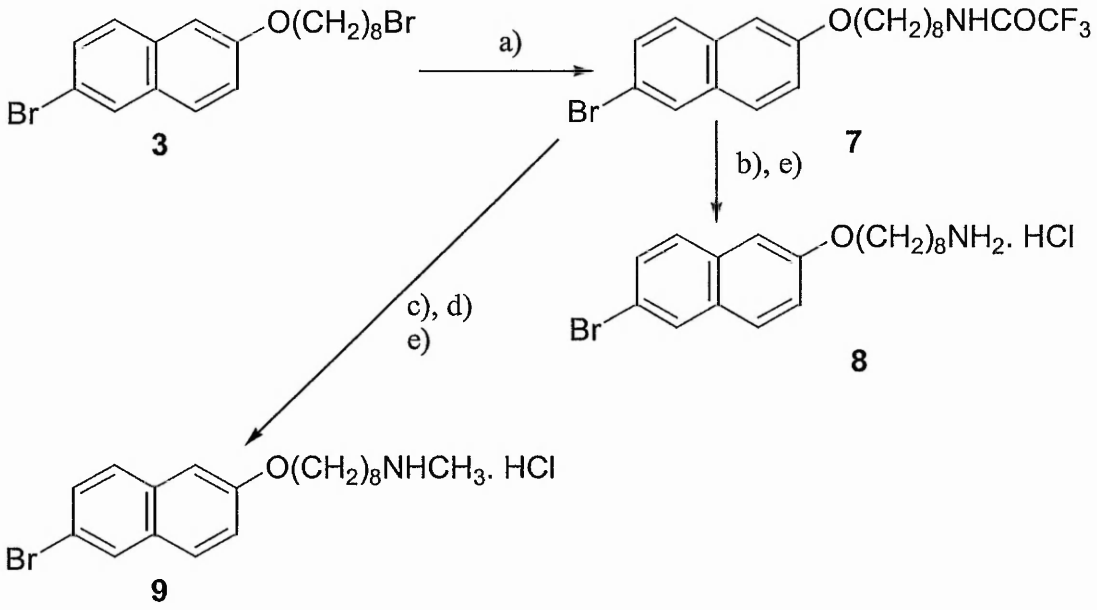
In general, the alkylation of amines is only of synthetic value for the preparation of tertiary amines and quaternary ammonium salts as the alkylation of ammonia or primary amines usually affords a complex mixture of products.

The classical method for converting alkyl halides into primary amines without polyalkylation is the Gabriel Phthalimide Synthesis[23]. This exploits the fact that amides

are weak bases with low nucleophilic character and must first be converted to their conjugate bases in order to react with alkyl halides. However, fairly vigorous acidic or basic conditions are required to hydrolyse the alkylated phthalimide to the product amine, and would be sufficient to cleave the alkyl-aryl ether linkages in the current series of compounds under investigation. Thus, a more compatable Gabriel synthon was required.

More recently, trifluoroacetamide has been described as an efficient Gabriel synthon[24]. The advantages of this reagent are that it is removed under mild conditions and would enable access to both primary and secondary amines from a common intermediate, Scheme 2.

Scheme 2.



a) 2 eq. CF_3CONH_2, 2 eq. NaH, DMF. b) 20% $NaOH_{(aq)}$, CH_3OH. c) 1.1 eq. NaH, CH_3I. d) 20% $NaOH_{(aq)}$, CH_3OH. e) CH_2Cl_2, HCl.diethyl ether.

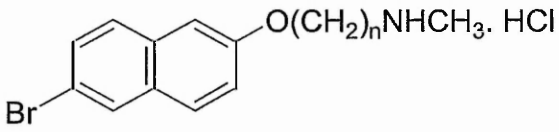
However, further synthetic studies revealed that secondary amines, but not primary amines, could be prepared in good yield by the statistical alkylation of an excess of the appropriate primary amine. This facilitated the synthesis of novel analogues of PCAB 300, employing a two step synthetic strategy from the appropriate phenol, in an analogous manner to that illustrated in Scheme 1.

2.1.3. Optimisation of the Alkyl Chain and Amino Moiety.

Initial investigations focused upon optimising the length of the alkyl side-chain and amino moiety.

Whilst investigating the length of the alkyl side-chain *N*-methylamine was chosen as the standard amino moiety and the following compounds, Table 4, were prepared by the two step synthetic methodology described above.

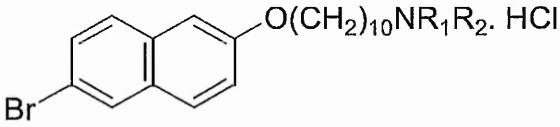
Table 4.



Chain length (n)	6	8	9	10	12
Compound Number	**10**	**9**	**11**	**12**	**13**

Whilst investigating the role of the amino moiety the standard length of the alkyl side-chain was C_{10}, and the following secondary and tertiary amines were prepared, Table 5 and Table 6 respectively.

Table 5. Secondary amines.



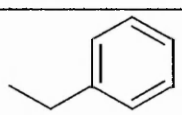
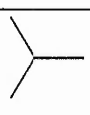
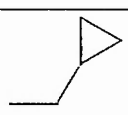
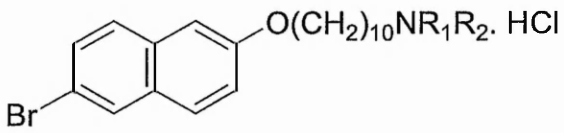
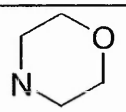
Compound	**14**	**15**	**16**	**17**
R_1	H	H	H	H
R_2	CH_2CH_3			

Table 6. Tertiary amines.

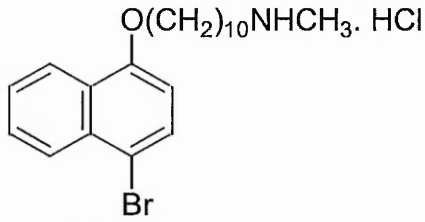


Compound	18	19	20
$R_1 = R_2$	CH_3	CH_2CH_3	

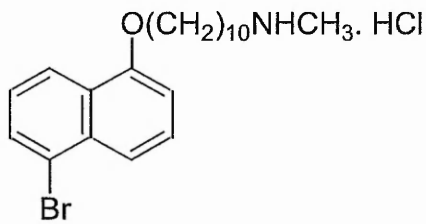
2.1.4. Positional Isomers of 6-bromo-2-naphthol.

To investigate the preferred orientation of the halogen and oxygen functions on the naphthalene nucleus compounds **21** and **22**, Figure 8, were chosen as suitable targets. This required the synthesis of the respective precursors 4-bromo-1-naphthol **23** and 5-bromo-1-naphthol **26**.

Figure 8.



21



22

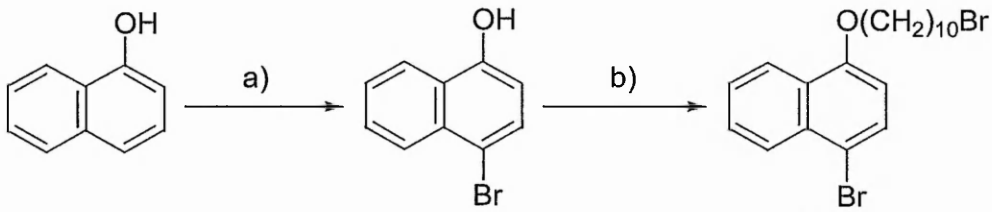
2.1.4.1 4-Bromo-1-naphthol.

Bromination of phenols can be achieved by a great variety of procedures, the treatment of phenol with bromine in different solvents being the most often used. However, the formation of polybrominated products and mixtures of regioisomers always occurs, leading to purification problems and poor yields of the required monobromophenols.

More recently, regioselective monobrominating systems have been successfully employed to obtain *para*-bromophenols in good yields. These include tetrabutylammonium tribromide in chloroform[25] and *N*-bromosuccinimide (NBS) in acetonitrile[26].

The latter method was successfully employed in the synthesis of 4-bromo-1-naphthol **23** from α-naphthol. The bromonaphthol was obtained in high yield providing that a 1:1 stoichiometry of naphthol to NBS was used, and that the commercially available NBS was recrystallised from water and dried prior to use. 4-Bromo-1-naphthol **23** was alkylated with an excess of 1,10-dibromodecane to give the intermediate bromoalkyl-ether **24**, Scheme 3, which was used to prepare compound **21** by the general method of amination.

Scheme 3.



23 **24**

a) 1 eq. *N*-bromosuccinimide, acetonitrile, r.t., 30min., 73%. b) 5 eq. $Br(CH_2)_{10}Br$, 3 eq. K_2CO_3, butanone, reflux, 78%.

2.1.4.2. 5-Bromo-1-naphthol.

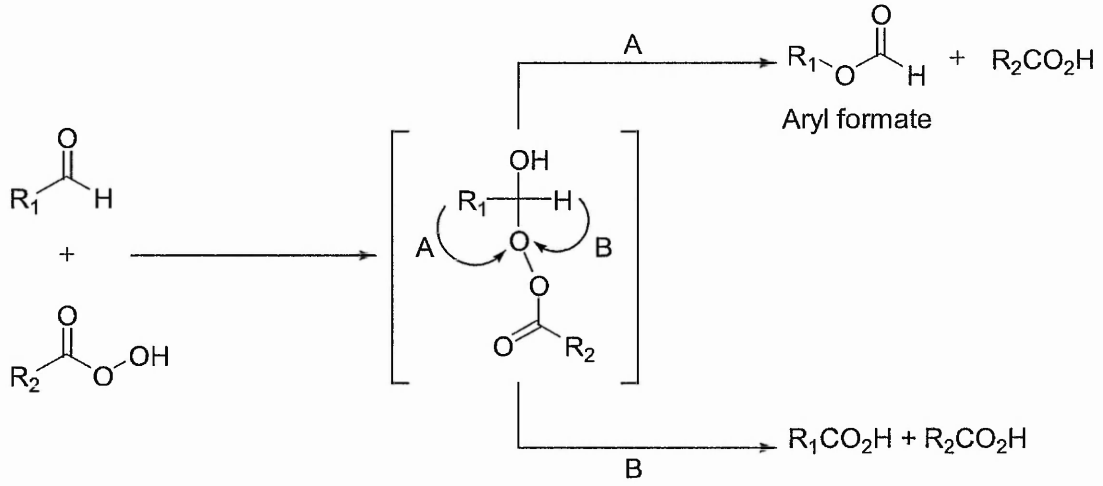
5-Bromo-1-naphthol cannot be prepared by bromination of α-naphthol due to the problems of regioselectivity and purification described above, thus an alternative synthetic strategy was sought.

A literature search revealed that 5-bromo-1-naphthol had been prepared in excellent yield by the Baeyer-Villiger oxidation of 5-bromo-1-naphthaldehyde using hydrogen peroxide activated by an organodiselenide catalyst[27]. However, previous attempts, at The Nottingham Trent University to prepare the organodiselenide catalyst were unsuccessful.

The mechanism of the Baeyer-Villiger oxidation, Scheme 4, can be described as the insertion of oxygen, and is accomplished by a sequence of steps involving nucleophilic addition of a peroxide to the carbonyl compound followed by migration of a specific group to the oxygen to form either an ester or a carboxylic acid. A major factor in determining which group migrates is the ability to accommodate a partial positive charge.

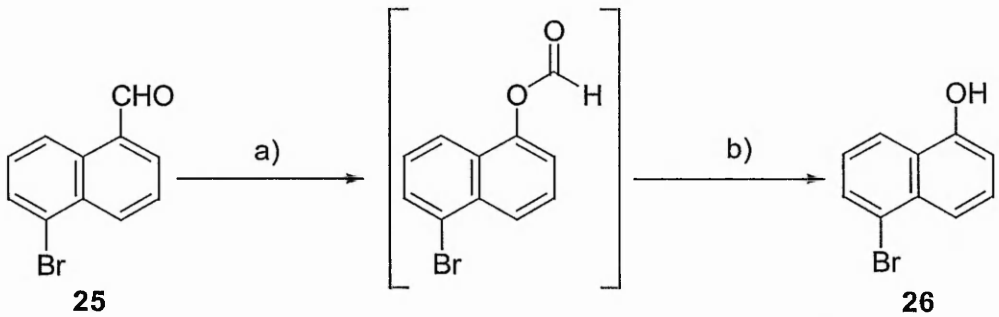
Thus, conventionally for aldehydes, hydrogen migrates, route B, to give the corresponding acid as the product. Migration of the aryl group, route A, to give the formate is normally observed only when electron-donating groups, *ortho* or *para* to the aldehyde, are present. This is known as the Dakin reaction, and is commonly employed to prepare phenols from activated aromatic aldehydes.

Scheme 4.



Further investigation of the literature revealed that little attention had been paid to the Baeyer-Villiger oxidation of polycyclic aromatic aldehydes. However, it was found that treatment of 5-bromo-1-naphthaldehyde **25**, prepared by the method described by Short and Wang[28], with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane at room temperature gave the corresponding naphthyl-formate in almost quantitative yield. Although the formate was stable to chromatography, the preparation of 5-bromo-1-naphthol **26** was achieved in higher yield by the immediate hydrolysis of the crude formate with dilute acid, Scheme 5.

Scheme 5.



25 **26**

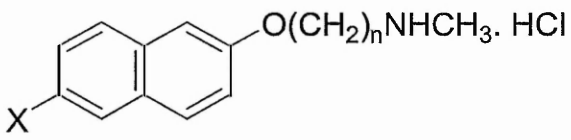
a) 1.1 eq. *m*-CPBA, chloroform, 48h., r.t. b) 2M HCl, methanol, 3h., r.t., 74%.

Thus, 5-bromo-1-naphthol **26** was alkylated with 1,10-dibromodecane to give the intermediate bromoalkyl-ether **27**, which was used to prepare compound **22** by the general method of amination.

2.2. Variation of Halogen.

In order to investigate the role of the naphthyl halogen substituent in the antifungal screen the de-halogenated, iodo, fluoro, and chloro analogues illustrated in Table 7 were prepared.

Table 7.



Compound	**28**	**29**	**30**	**31**
Chain length (n)	8	10	10	10
X	H	I	F	Cl

Compound **28**, a de-halogenated analogue of compound **9**, was readily prepared from β-naphthol employing the general methods of ether formation, to give the intermediate bromoalkyl-ether **32**, and amination.

2.2.1. Metal-Halogen Exchange.

Since neither 6-iodo-2-naphthol, 6-fluoro-2-naphthol, nor 6-chloro-2-naphthol are commercially available their synthesis was required.

A search of the literature revealed that 6-fluoro-2-naphthol had been prepared in four steps from β-methoxynaphthalene via the corresponding diazonium hexafluorophosphate[29], whilst 6-iodo-2-naphthol had been independently prepared, in one step, from 6-bromo-2-naphthol[30]. This had been achieved by heating the bromonaphthol with excess potassium iodide in the presence of nickel bromide and tributylphosphine. However, with the recent introduction of a variety of electrophilic fluorinating reagents, and the observation that

iodine and chlorine can be successfully introduced into aromatic nuclei by halogen-metal exchange[31a], it was anticipated that the halonaphthols could be prepared more conveniently from the appropriate naphthyl carbanion, providing that a suitable protecting group for the phenoxy function was employed.

Metal-halogen exchange is an important method for the preparation of organolithium reagents[31b]. The reaction proceeds in the direction of forming the more stable organolithium reagent, that is, the one derived from the more acidic organic structure, as illustrated by the equation in Figure 9.

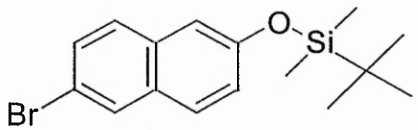
Figure 9.

$$ArX + RLi \rightleftharpoons ArLi + RX$$

Where X = Cl, Br, I.

The reaction is particularly useful for the conversion of aryl halides to the corresponding lithium compounds using *n*-butyllithium, as a result of the greater stability of the sp^2 carbanion in comparison to the sp^3 carbanion. However, it is also known that substituents, such as oxygen and nitrogen, on the aromatic nucleus are able to coordinate to the lithium ion, leading to *ortho*-lithiation. For this reason the *tert*-butyldimethylsilyl (TBDMS) ether of 6-bromo-2-naphthol, compound **33** Figure 10, was prepared.

Figure 10.



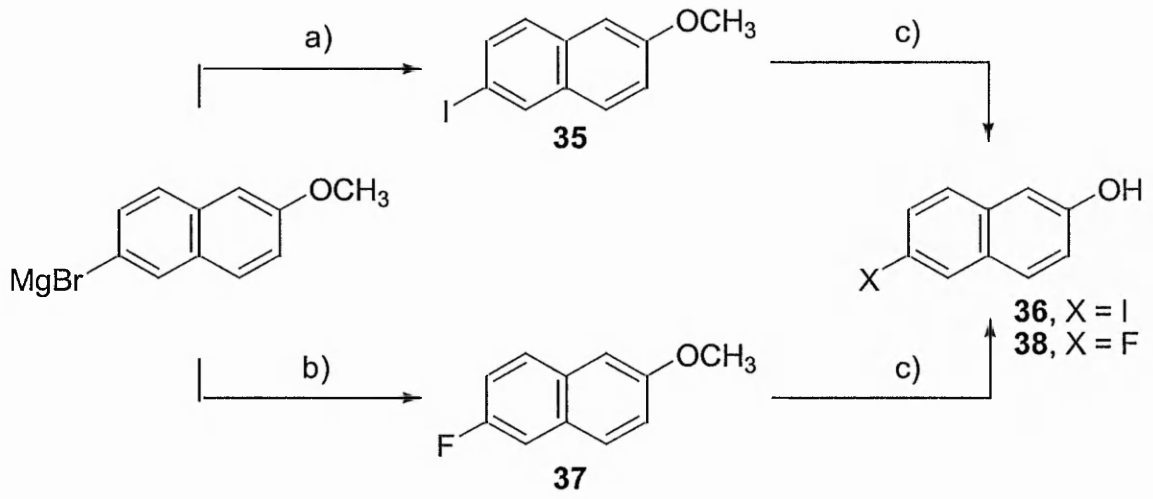
33

The TBDMS protecting group was chosen due to the ease at which it may be introduced and subsequently removed, but primarily it was also anticipated that the steric bulk of the protecting group would hinder *ortho* lithiation of the naphthalene nucleus, as could potentially occur in response to the directing power of the oxo substituent.

From a low temperature reaction of the TBDMS ether of 6-bromo-2-naphthol, **33**, with *n*-butyllithium, followed by the slow addition of an excess of elemental iodine, a complex mixture of products was obtained. It was reasoned that there were competing reactions in the formation of the aryllithium intermediate, possibly due to the unsuitable nature of the silyl protecting group, though no clear evidence was gained to confirm this.

However, treatment of 2-methoxy-6-naphthylmagnesium bromide, prepared from 2-methoxy-6-bromonaphthalene **34**, with an excess of iodine afforded 6-iodo-2-methoxynaphthalene **35** in good yield. The iodo-naphthalene was successfully demethylated with boron tribromide in dichloromethane to give 6-iodo-2-naphthol **36**. Scheme 6.

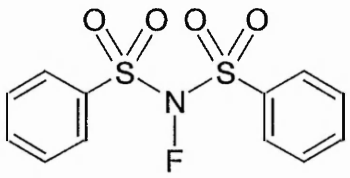
Scheme 6.



a) I_2, THF, 0°C to r.t., 1h., 56%. b) NFSI, THF, -35°C, 30min. c) 1M BBr_3, CH_2Cl_2.

In an analogous manner, *N*-fluorobenzenesulfonimide (NFSI)[32], Figure 11, an electrophilic fluorine reagent by the virtue of the Umpolung Principal, whereby the negative charge normally associated with fluorine is reversed by the electron withdrawing nature of the bis-sulfonamide functionality, was selected to quench 2-methoxy-6-naphthylmagnesium bromide in the anticipation of obtaining 6-fluoro-2-methoxynaphthalene.

Figure 11.

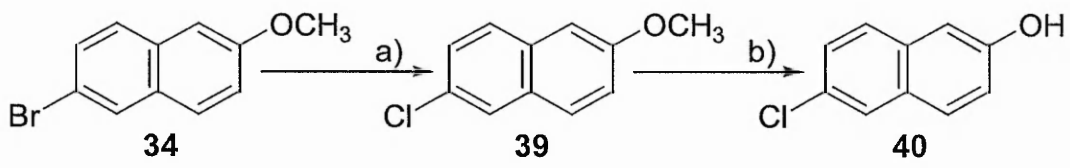


N-Fluorobenzenesulfonimide (NFSI)

Initially, the addition of 2-methoxy-6-naphthylmagnesium bromide to NFSI at 0°C in tetrahydrofuran resulted in a mild exotherm and gave a complex mixture of products that proved impossible to purify. Subsequently it was found that by maintaining an internal reaction temperature of -35°C during the addition of the Grignard reagent to NFSI, 6-fluoro-2-methoxynaphthalene **37** could be obtained, Scheme 6, although it was found to be contaminated with residual bromomethoxynaphthalene. Repeated attempts to purify **37** were unsuccessful and the crude fluoro-methoxynaphthalene was demethylated with boron tribromide in the anticipation that increasing the polarity of the mixture would aid the separation of the two compounds. Thus, after repeated recrystallisation from cyclohexane the fluoronaphthol was judged to be greater than 90% pure by analysis of its ^{1}H and ^{13}C NMR spectra.

In contrast to the TBDMS ether **33**, 6-chloro-2-methoxynaphthalene **39** was obtained in good yield from the addition of hexachloroethane[33] to a mixture of 6-bromo-2-methoxynaphthalene **34** and *n*-butyllithium at -70°C. The chloronaphthalene **39** was demethylated with boron tribromide to give 6-chloro-2-naphthol **40**, Scheme 7.

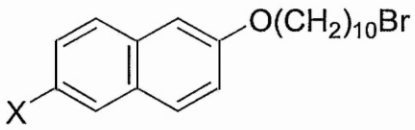
Scheme 7.



a) 1.05 eq. *n*-BuLi, THF, -70°C, 30min., Cl_3CCCl_3, 1h., 98%. b) 1M BBr_3, CH_2Cl_2, r.t., 18h., 86%.

Naphthols **36**, **38**, and **40** were alkylated with an excess of 1,10-dibromodecane to give the respective bromoalkyl-ether intermediates, **41**, **42**, and **43** Figure 12, which were used to prepare the iodo, fluoro, and chloro analogues, **29**, **30**, and **31**, by the general method of amination.

Figure 12.



41, X = I; **42**, X = F; **43**, X = Cl

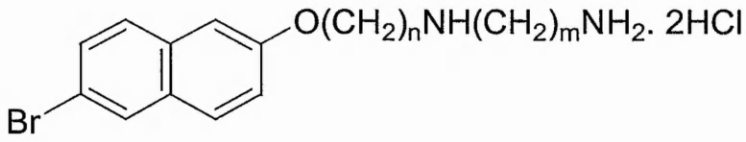
2.3. Introduction of Functionality into the Alkyl Chain.

An investigation into the incorporation of heteroatoms into the alkyl chain was initiated in an attempt to improve the aqueous solubility of the compounds, alter the spatial and geometric arrangement of the alkyl chain, and to provide additional sites for hydrogen bond donor and / or acceptor interactions.

2.3.1. Secondary Amine Functionality.

The secondary amine functionality was chosen due to its geometric similarity to carbon, being sp^3 hybridised and with bond angles of approximately 101°, its ability to ionise at physiological pH therefore aiding aqueous solubility, and its ability to act as both a hydrogen bond acceptor and / or donor. Thus compounds **44** and **45**, Figure 13, were chosen as a suitable targets.

Figure 13.



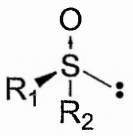
44, n = 2, m = 8; **45**, n = 6, m = 4.

Both compounds were prepared, in good yield, from the respective bromoalkyl-ether intermediates by the general method of amination with an excess of the appropriate, commercially available, diaminoalkane. The excess diaminoalkanes were removed by chromatography and the amino bis-hydrochloride salts were prepared by precipitation of the corresponding free base from dichloromethane by the addition of a solution of hydrogen chloride dissolved in diethyl ether

2.3.2. Introduction of Sulfoxide and Sulfone.

The nature of the S-O linkages of sulfoxides and sulfones has been argued for several decades, namely, whether the S-O bonds are semipolar single bonds or double bonds. X-ray crystallographic analysis, measurement of dipole moments, and infrared analysis support the semipolar single bond character with about 60% ionic character and should be best represented by the structures shown in Figure 14[34].

Figure 14.



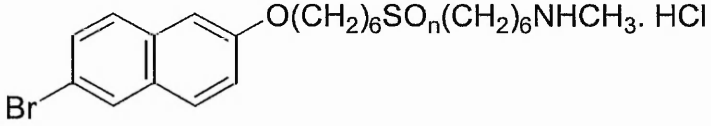
Sulfoxide

Resonance hybrid of the sulfone moiety.

It is also important to note that sulfoxides where $R_1 \neq R_2$ are chiral and although there are many methods to obtain enantiomerically pure sulfoxides[35] it was decided to initially investigate the sulfoxide as a racemic mixture.

In order to evaluate the pharmacological effects incurred by the incorporation of the sulfoxide and sulfone functional groups into the alkyl chain compounds **46** and **47**, Figure 15, were selected as suitable targets.

Figure 15.

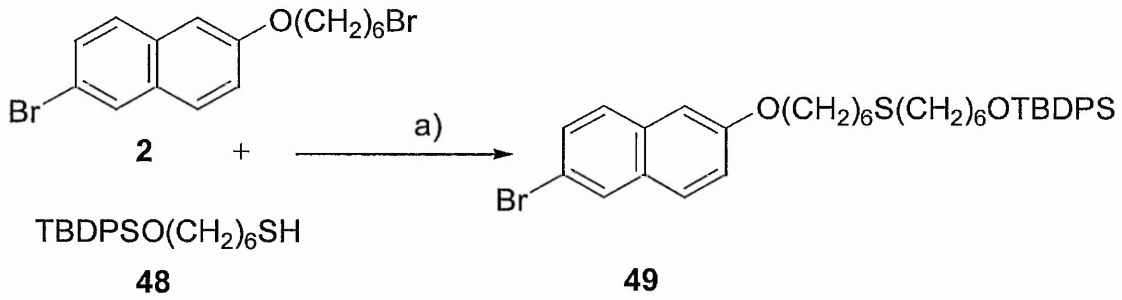


46, n = 1; **47**, n = 2

A C_6 alkyl spacer unit, either side of the sulfur atom, was initially selected as a suitable compromise between maintaining a reasonable distance between the sulfur atom and both the oxygen and nitrogen atoms without increasing the overall chain length by an unacceptable margin.

As both sulfoxides and sulfones can be obtained by the oxidation of sulfides a synthetic strategy was devised that would enable access to compounds **46** and **47** from a common intermediate, compound **49**, Scheme 8.

Scheme 8.



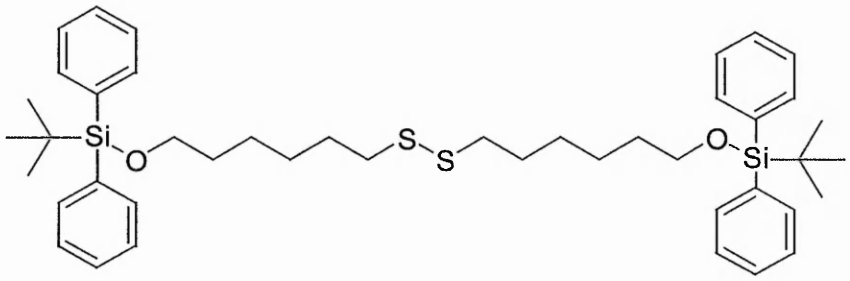
a) 3 eq. K_2CO_3, $Na_2S_2O_5$, butanone, reflux.

Commercially available 6-mercapto-1-hexanol was chosen as a convenient bifunctional synthon. However, its successful use depended largely upon the regioselective introduction of a protecting group to mask the hydroxyl function to prevent competing reaction between the chemically similar thiol and alcohol functions with the alkyl halide during the formation of the thioether.

Silyl ethers are known to be excellent protecting groups for alcohols due to the ease of their introduction, subsequent removal, and relative stability towards a variety of reaction conditions[36]. This is in contrast to the much weaker S-Si bond which is prone to hydrolysis during isolation. Thus *tert*-butyldiphenysilyl chloride was successfully used to prepare 6-mercapto-1-(*t*-butyldiphenylsilyloxy)hexane **48** in 70% yield.

The Williamson Ether Synthesis was initially used to prepare the thioether in moderate yield as the general reaction conditions resulted in the formation of disulfide, Figure 16.

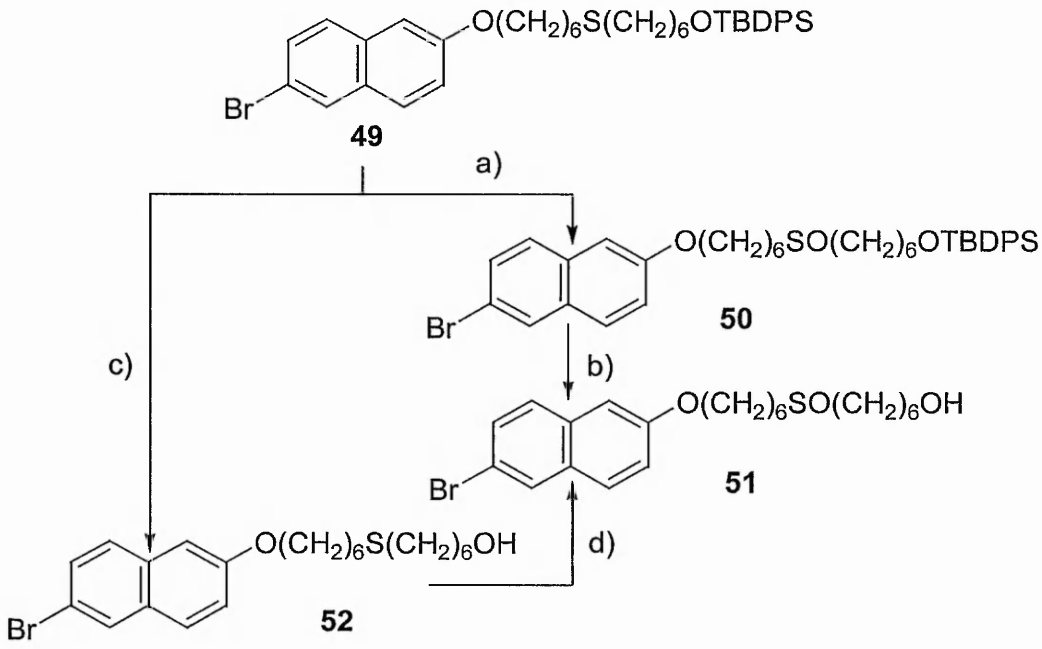
Figure 16.



This competing reaction was subsequently reduced to a minimum, to give the thioether in 78% yield, by the careful exclusion of oxygen from the reaction and the addition of a small quantity of sodium metabisulfite to maintain a reducing reaction medium.

Oxidation of the intermediate sulfide, **49** Scheme 9, to the sulfoxide was achieved in good yield with *m*-CPBA at -10°C in dichloromethane without any over oxidation to the sulfone being observed. However, removal of the silyl protecting group in the presence of the sulfoxide moiety proved to be problematic. It was subsequently found that the silyl protecting group could be removed more cleanly prior to oxidation of the sulfide to the sulfoxide, Scheme 9.

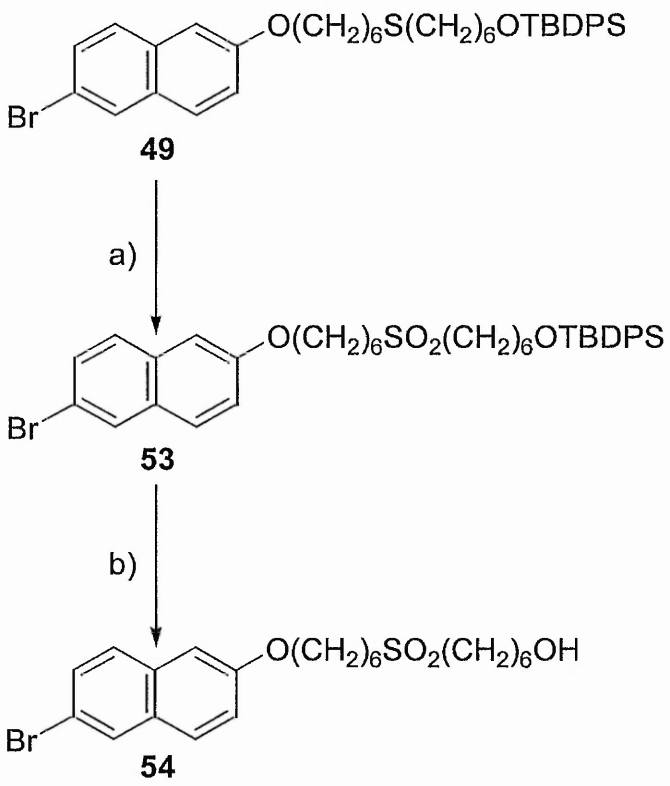
Scheme 9.



a) 1 eq. *m*-CPBA, CH_2Cl_2, -10°C, 2h., 97%. b) 1M TBAF, CH_2Cl_2, 60h., 45%. c) 1M TBAF, CH_2Cl_2, 60h., 94%. d) 1 eq. *m*-CPBA, CH_2Cl_2, -10°C, 2h., 98%.

In contrast, oxidation of sulfide **49** with 2.5 eq. of *m*-CPBA in refluxing dichloromethane afforded the sulphone **53**, and the silyl protecting group was removed cleanly in the presence of the sulphone to afford the hydroxy sulphone **54** in an overall good yield for the two synthetic transformations, Scheme 10.

Scheme 10.



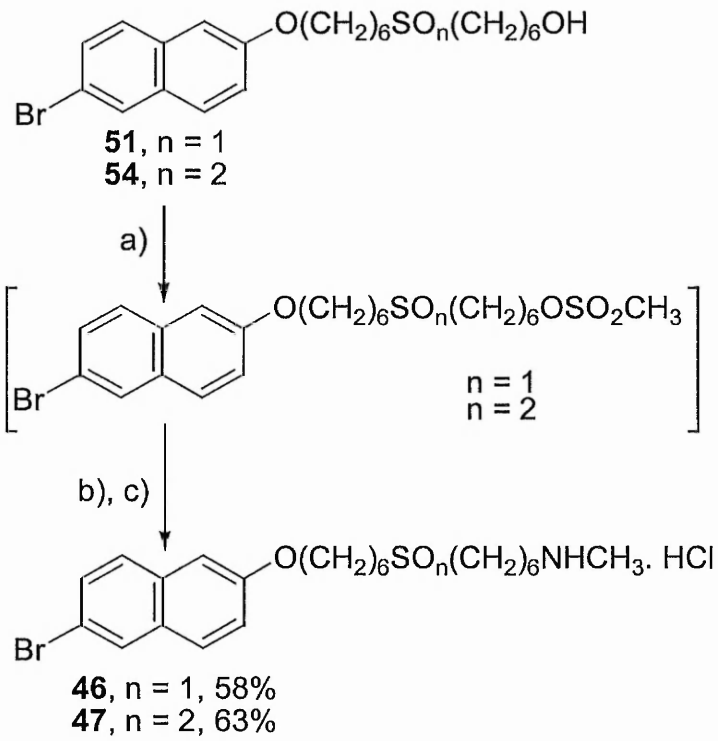
a) 2.5 eq. *m*-CPBA, CH_2Cl_2, reflux, 3h., 55%. b) 1M TBAF, CH_2Cl_2, 4Å molecular sieves, 60h., 90%.

Introduction of the methylamine moiety, for both the sulfoxide and sulphone intermediates **51** and **54** respectively, required the conversion of the hydroxy functionality into a suitable alkylating agent. This was achieved by formation of the corresponding mesylates, Scheme 11.

Initially this was achieved as a two step process, with chromatographic isolation of the mesylate. However, improved yields of the final product were obtained by a 'one - pot' strategy for the two synthetic transformations, whereby the formation of the mesylate was

judged complete by t.l.c. and the mixture was treated with an excess of methylamine in alcohol and allowed to stand for 18h. Thus, compounds **46** and **47** were obtained in acceptable yields.

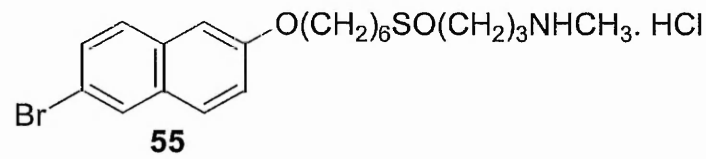
Scheme 11.



a) 1.1 eq. CH_3SO_2Cl, 1.5 eq. $(CH_3CH_2)_3N$, CH_2Cl_2. b) 33% CH_3NH_2 in EtOH. c) CH_2Cl_2, 1M HCl diethyl ether.

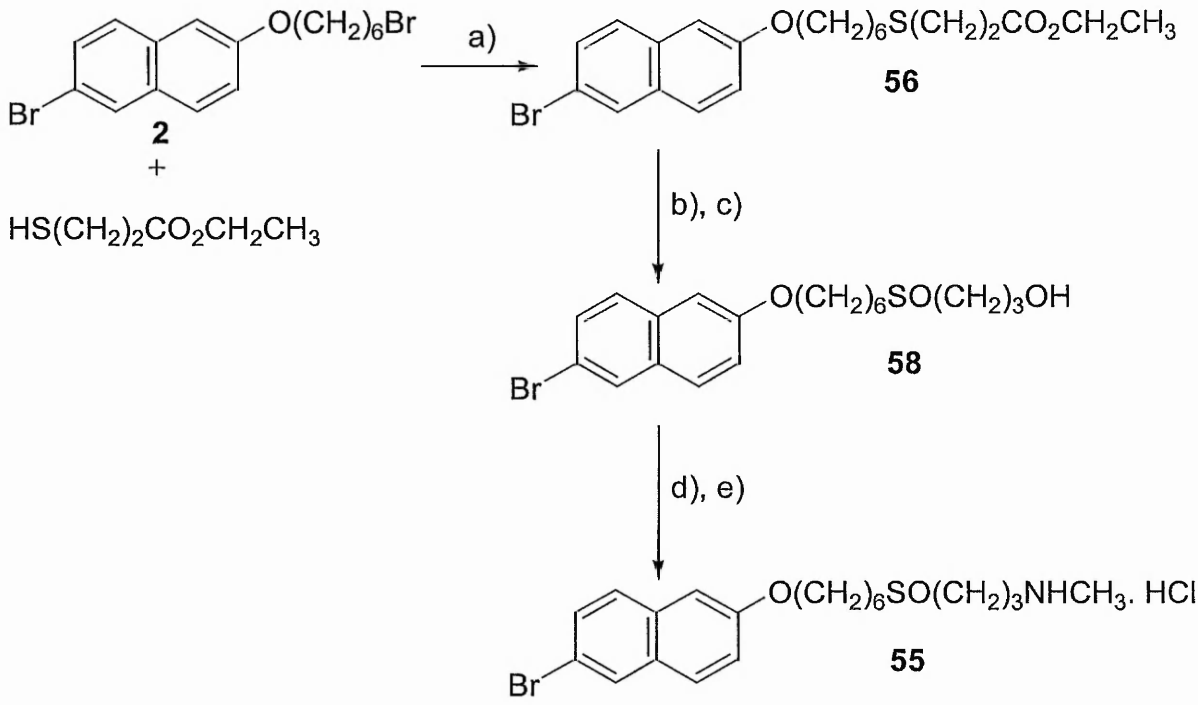
To evaluate the position of the sulfoxide functionality relative to the terminal alkyl methylamine moiety and the preferred chain length within the sulfoxide series compound **55** was prepared, Figure 17.

Figure 17.



Commercially available ethyl-3-mercaptopropionate was used as a convenient bifunctional synthon. The ethyl ester of compound **56** was reduced by lithium borohydride to afford the intermediate hydroxy sulfide **57**, which was oxidised to the sulfoxide **58** by *m*-CPBA, and compound 55 was obtained, via the corresponding mesylate Scheme 12, in a manner analogous to that described above.

Scheme 12.



a) 3 eq. K_2CO_3, butanone, reflux, 54%. b) 1.5 eq. $LiBH_4$, 1.5 eq. CH_3OH, THF, 83%. c) 1 eq. *m*-CPBA, CH_2Cl_2, r.t., 95%. d) i/ 1.1 eq. CH_3SO_2Cl, 1.5 eq. $(CH_3CH_2)_3N$, CH_2Cl_2. ii/ 33% CH_3NH_2 in EtOH, 82%. e) CH_2Cl_2, HCl diethyl ether.

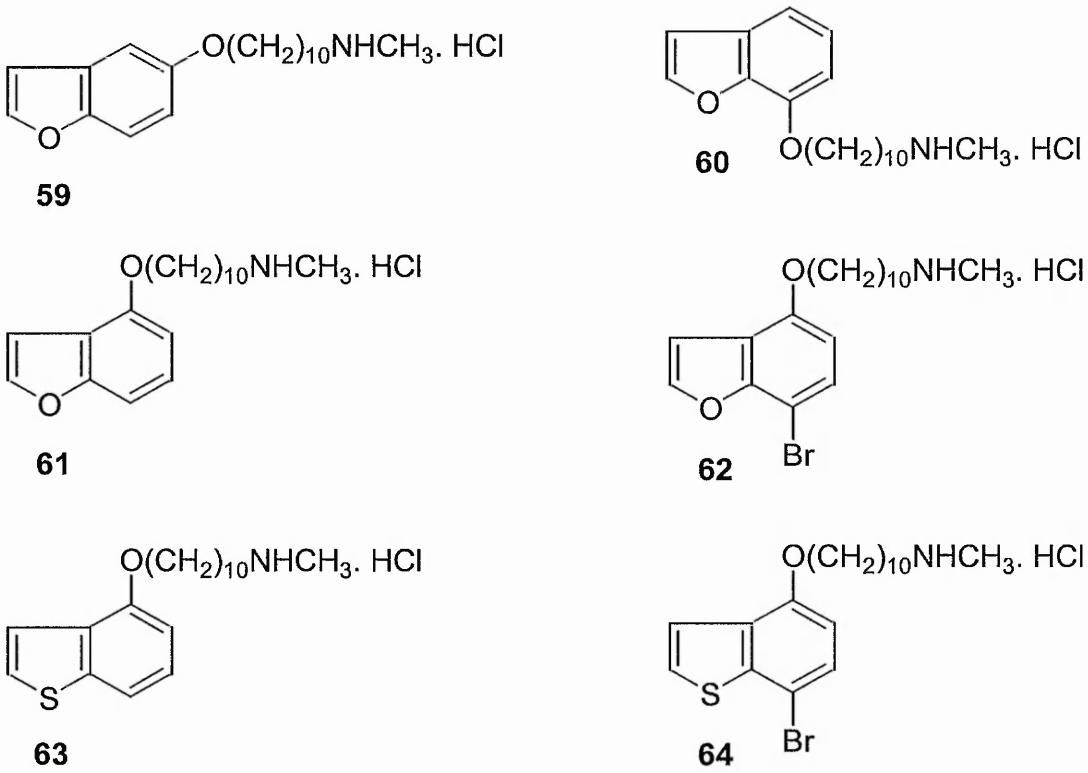
2.4. Benzo[*b*]thiophene and Benzo[*b*]furan Derivatives.

Bioisosterism is a lead modification approach that has been shown to attenuate toxicity, alter metabolism, and modify the activity of a lead compound. Thus, it was anticipated that a benzo[*b*]thiophene moiety could serve as a classical biostere for the naphthalene nucleus during an investigation into the relative pharmacological importance of the aromatic moiety.

Also, as oxygen is more electronegative than sulfur and does not have d-orbitals participating in bonding, an electronically divergent analogue of the benzo[*b*]thiophene nucleus is the benzo[*b*]furan system. Furthermore, the benzo[*b*]furan system was considered to be more amenable to the variation of the substitution patterns, and would therefore enable a more detailed structure-activity study to be completed on these aromatic systems.

Thus, the benzo[*b*]furans **59**, **60**, **61**, and **62**, and the benzo[*b*]thiophenes **63** and **64** were identified as suitable targets, Figure 18.

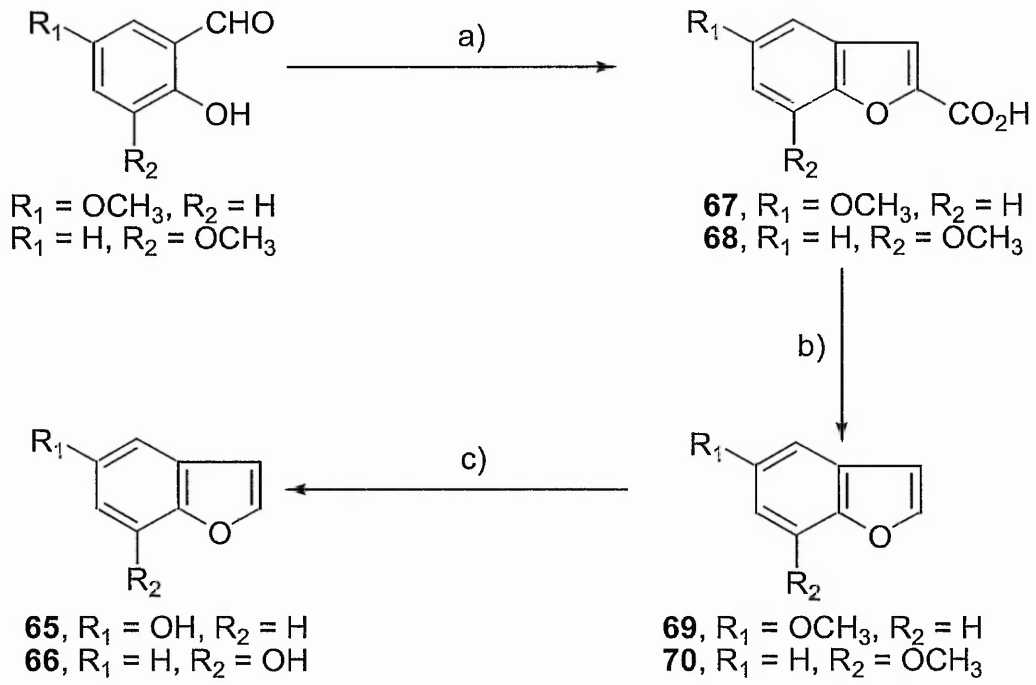
Figure 18.



2.4.1. Synthesis of Benzo[*b*]furan Analogues.

As none of the required hydroxybenzo[*b*]furans are commercially available their synthesis was required. A general synthesis of hydroxybenzo[*b*]furans from the appropriate commercially available methoxysalicylaldehydes, reported by René and Royer[37], was successfully used in for the preparation of 5-hydroxybenzo[*b*]furan **65** and 7-hydroxybenzo[*b*]furan **66**, Scheme 13.

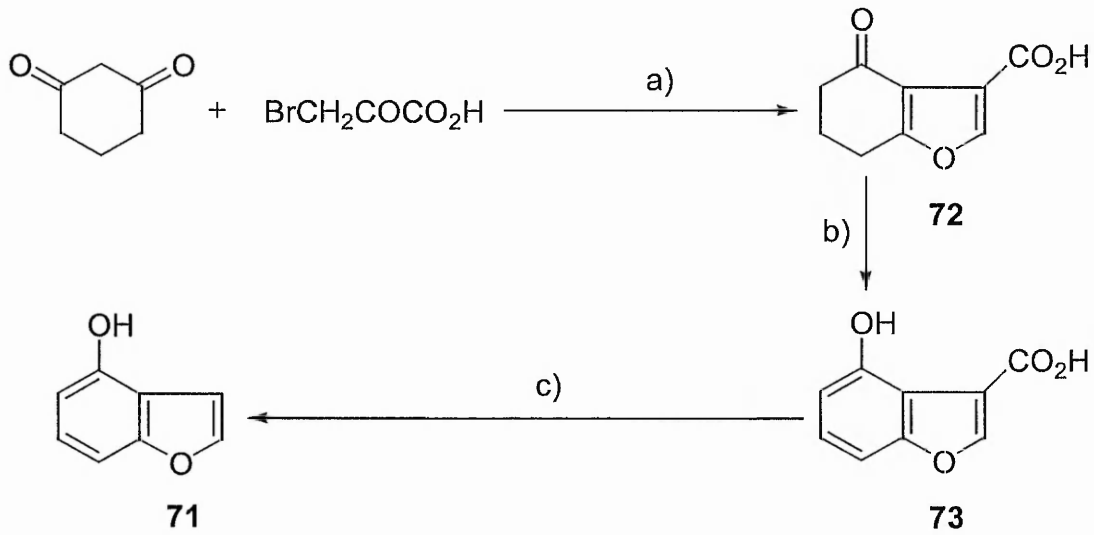
Scheme 13.



a) $ClCH_2CO_2Et$, K_2CO_3, DMF, reflux. b) Cu(0), quinoline. c) pyridine. HCl.

However, the preparation of 4-hydroxybenzo[*b*]furan (karanjol) **71** was achieved by a more efficient route described by Kneen and Maddocks [38], Scheme 14.

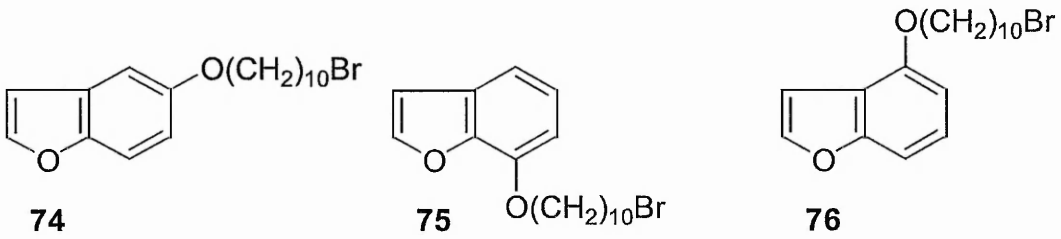
Scheme 14.



a) KOH, CH_3OH, H^+. b) Pd, decalin, dodecene. c) Cu(0), quinoline, reflux.

The hydroxybenzo[*b*]furans, **65**, **66**, and **71**, were alkylated with an excess of 1,10-dibromodecane to afford the bromoalkyl-ether intermediates, **74**, **75**, and **76** Figure 19, which were subsequently used to prepare compounds **59**, **60**, and **61** respectively by tretment with methylamine.

Figure 19.

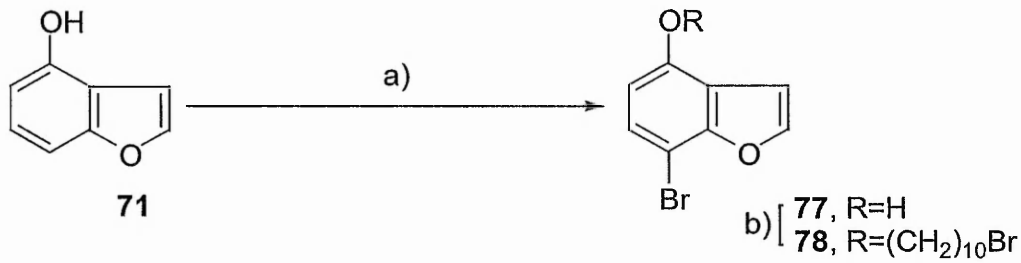


2.4.2. Bromination of 4-hydroxybenzo[*b*]furan.

7-Bromo-4-(8-bromooctyloxy)benzo[*b*]furan, had previously been prepared at The Nottingham Trent University by the bromination of the intermediate ω-bromoalkyloxybenzofuran with one equivalent of bromine at 0°C in carbon tetrachloride[21]. However, attempts to repeat this method for the analogous 10-bromodecanyl derivative, **76**, gave an inseparable mixture of brominated products.

However, the bromination of 4-hydroxybenzo[*b*]furan **71** with *N*-bromosuccinimide in acetonitrile was moderately successful and 7-bromo-4-hydroxybenzo[*b*]furan **77** was isolated in 23% yield after a tedious separation from a complex mixture of starting material and brominated products, Scheme 15.

Scheme 15.



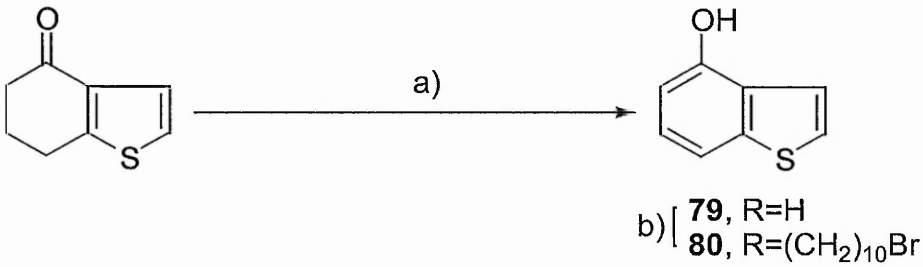
a) 1 eq. NBS, CH_3CN, 3.5h., r.t., 24%. b) 3 eq. K_2CO_3, 5 eq. $Br(CH_2)_{10}Br$, butanone, reflux.

7-Bromo-4-hydroxybenzo[*b*]furan **77** was successfully used to prepare compound **62**, via the intermediate bromoalkyl-ether **78**, by the general method of amination.

2.4.3. Synthesis of Benzo[*b*]thiophene Analogues.

4-Hydroxybenzo[*b*]thiophene **79** was prepared by the dehydrogenation of commercially available 4-keto-4,5,6,7-tetrahydrothianaphthene with sulfur[39], Scheme 16, and was used to prepare compound **63**, via the intermediate bromoalkyl-ether **80**, by the general method of amination.

Scheme 16.



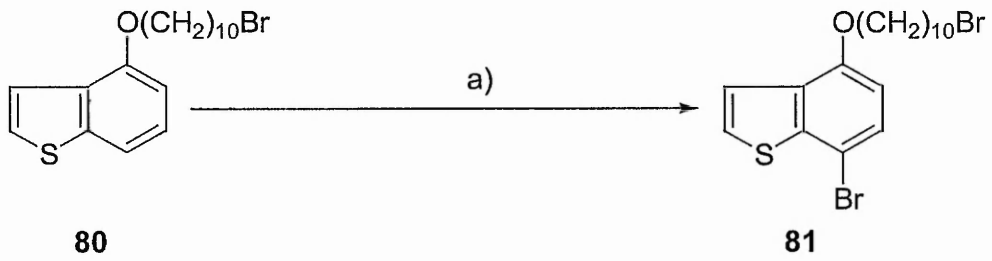
a) S, diphenyl ether 240°C, 4.5h., 57%. b) 3 eq. K_2CO_3, 5 eq. $Br(CH_2)_{10}Br$, butanone, reflux.

2.4.4. Bromination of ω-bromoalkyloxybenzo[*b*]thiophene.

Campaigne et al[40] reported that the bromination of 4-methoxybenzo[*b*]thiophene with bromine in carbon tetrachloride occurs regioselectively in the 7 position, and this method had been successfully used to prepare 7-bromo-4-(6-bromohexyloxy)benzo[*b*]thiophene by a previous researcher[21].

However, attempts to reproduce these results in the current investigation, by the bromination of the analogous 10-bromodecanyl derivative, **80**, consistently afforded an inseparable mixture of brominated products. However, further investigation of the bromination of the intermediate ω-bromoalkyloxybenzothiophene, **80**, with *N*-bromosuccinimide in acetonitrile regioselectively afforded 7-bromo-4-(10-bromo-decyloxy)benzo[*b*]thiophene, **81**, in 87 % yield, Scheme 17.

Scheme 17.



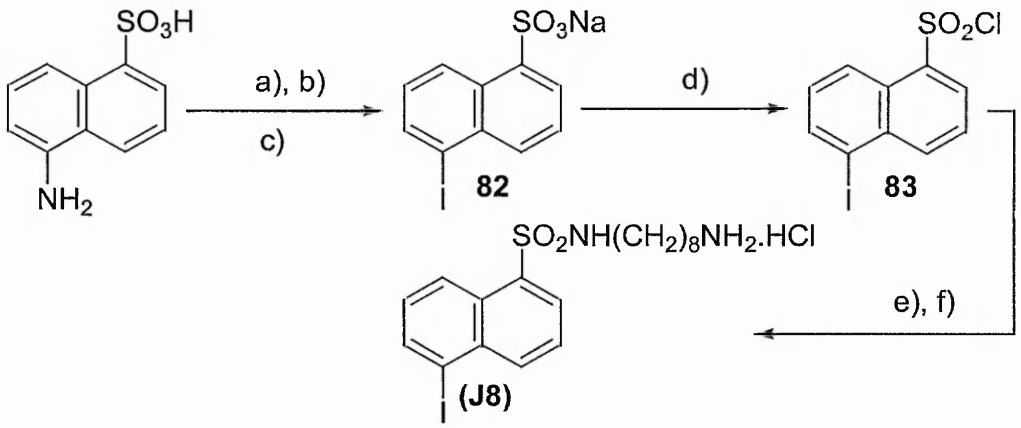
a) 1 eq. *N*-bromosuccinimide, acetonitrile, r.t., 24h., 87%.

Amination of **81** gave compound **64**.

2.5. Sulfonamides.

J8, a potent and specific CaM antagonist[22] has been shown to have significant antifungal activity against the plant pathogen *Pythium ultimum* with an IC_{50} value of 14.1mM[21]. To test if **J8** was able to maintain this level of activity in a broad-spectrum human pathogenic fungal screen, and become a suitable target for further development, initial work was directed towards the synthesis of J8. This was achieved by the classical chemical transformations illustrated in Scheme 18, as described by a previous researcher at Sheffield University [41].

Scheme 18.



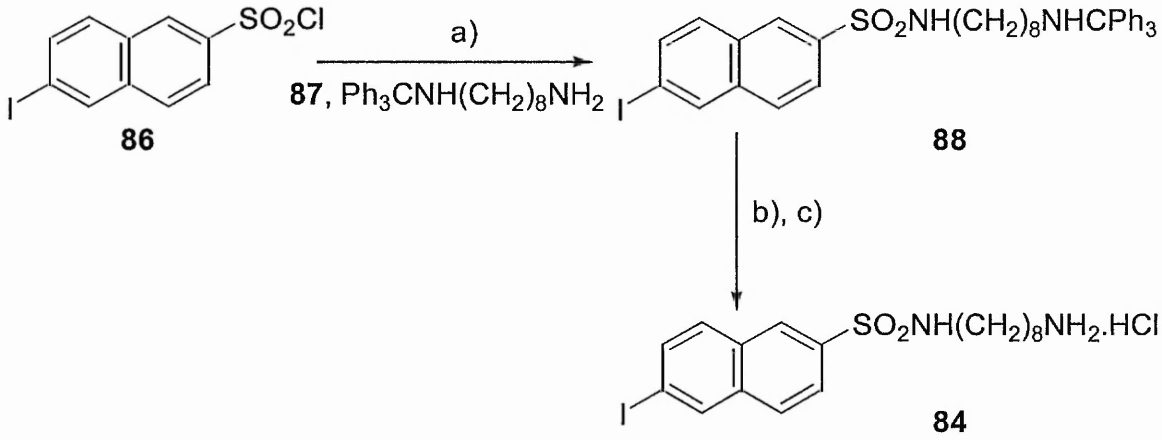
a) 2M NaOH, $NaNO_2$, conc. H_2SO_4. b) KI, H_2O, conc. H_2SO_4. c) $NaOH_{(aq)}$. d) $POCl_3$. e) 4eq. 1,8-diaminooctane, 1,4-dioxan. f) CH_2Cl_2, 1M HCl diethyl ether.

Previous research[21] had also shown that in a series of naphthalene compounds with the general structure Ar-O$(CH_2)_nNR_1R_2$ β-linkage produced greater antifungal activity in comparison to α-linkage. This initiated the synthesis of the β-substituted 6-iodo-2-sulfonyl analogue of **J8**, compound **84**.

The 6-iodo-2-naphthalene sulfonyl chloride **86** was prepared in an analogous manner to that described for **J8**, via the intermediate 6-iodo-2-naphthalene sodium sulfonate **85**, in small quantity due to the limited availability of 6-amino-2-naphthalene sulfonic acid.

The limited availability of the sulfonyl chloride **86** required the introduction of a protecting group strategy to minimise the wasteful consumption of the sulfonyl chloride by the competing formation of a bis-sulfonamide impurity, which was observed with the statistical amination method employed for the preparation of J8. This was achieved by the statistical mono protection of 1,8-diaminooctane with trityl chloride to afford the intermediate trityl bis-amine **87** in 64% yield, which was successfully used to prepare compound **84**, Scheme 19.

Scheme 19.



a) 1.5 eq. $(CH_3CH_2)_3N$, CH_2Cl_2. b) 2 eq. CF_3CO_2H, 1.1 eq. $(CH_3CH_2)_3SH$, THF. c) CH_2Cl_2, 1M HCl diethyl ether.

3.0. Results.

The synthesis of thirty two compounds has been completed. A total of thirty one compounds were evaluated in a broad-spectrum human pathogenic fungal screen, operated by Zeneca Pharmaceuticals Macclesfield. The known antifungal agents amphotericin B and fluconazole were included for comparison and the results are presented in Table 8, and, in collaboration with BTG International Ltd., are the subject of a patent application, UK-9922446.1, 1999.

A more detailed discussion of the pharmacological effects of the structural modifications undertaken are presented below by comparison of the MIC values, where MIC refers to the minimum concentration of a compound required to inhibit replication of the fungal pathogen.

3.1. Variation of Chain Length.

From Graph 1 it can be seen that whilst the C_{10} analogue, **12**, was found to be inactive against *Candida parapsilosis*, in general it was marginally more potent than the C_8 derivative, **9**. Whilst both the C_6 and C_9 analogues, **10** and **11** respectively, exhibited a progressive decrease in potency when compared to **9**, the C_{12} analogue, **13**, was almost completely inactive.

3.2. Variation of Amino Moiety.

As is illustrated by Graph 2, replacement of the terminal *N*-methyl moiety of **12** by NH_2 **8**, *N*-ethyl **14**, *N,N*-dimethyl **18**, and *N,N*-diethyl **19** had little effect, whilst the *N*-isopropyl compound **16** was slightly less active. In contrast, the *N*-benzyl and morpholino analogues, **15** and **20** respectively, were completely inactive. However, the N-cyclopropylmethyl analogue, **17**, showed a curious pattern, being inactive against most *Candida spp.*, but was particularly potent against *Cryptococcus neoformans*, *Aspergillus fumigatus*, and *Trichophyton quinkeanum*.

3.3. Variation of Substitution Pattern.

A marked decrease in activity was observed on going from the 2,6-substitution pattern of compound **12** to the 1,5 pattern of **22** and the 1,4 pattern of **21**, Graph 3.

3.4. Variation of Halogen.

The substitution of bromine in **12** by fluorine **30** caused a slight loss in activity, whilst a more significant loss in activity was observed with the unhalogenated analogue **28**, and the substitution of bromine for iodine, **29**, lead to an almost complete loss of activity, Graph 4.

3.5. Incorporation of Functionality into the Alkyl Chain.

The incorporation into the alkyl chain of a sulfoxide group gave water soluble compounds **46** and **55** with a reduction in activity. Whilst the bis-amino derivative, **45**, was slightly less active than the sulfoxides, both the isomeric bis-amine, **44**, and the sulfone, **47**, were virtually inactive, Graph 5.

3.6. Benzo[*b*]furan and Benzo[*b*]thiophene Analogues.

In general, the replacement of the naphthalene moiety by either benzo[*b*]furan or benzo[*b*]thiophene lead to a slight decrease in activity. The isomeric unhalogenated benzo[*b*]furans, **59**, **60**, and **61** were observed to be equipotent with the unhalogenated benzo[*b*]thiophene, **63**. Whilst the introduction of bromine, *para* to the ether linkage of the benzo[*b*]thiophene **63** to give compound **64**, resulted in a significant increase in activity, only a modest increase in activity was observed for the analogous bromo-benzo[*b*]furan, **62**, Graph 6.

3.7. Sulfonamides.

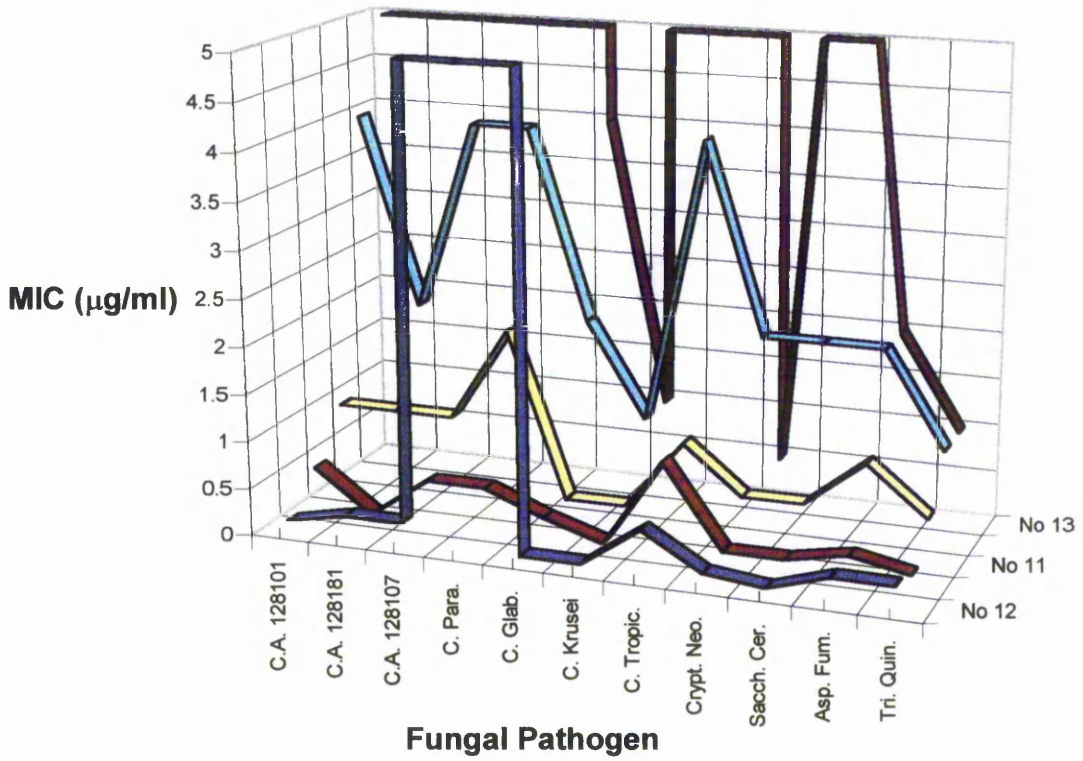
Both of the sulfonamides **J8** and the 2,6 positional isomer **84** were almost totally inactive in the fungal screen, Table 8.

Table 8.

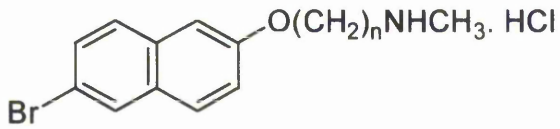
Pathogen MIC & IC_{50} (μg / ml)

	Candida albicans 128101		*Candida albicans* 128181		*Candida albicans* 128107		*Candida Parapsilosis* 138001		*Candida glabrata* 132002		*Candida krusei* 136001		*Candida tropicalis* 127001		*Cryptococcus neoformans* 184002		*Sacch. cerevisiae* 131001		*Aspergillus fumigatus* 173003		*Trichophyton quinkeanum* 133001	
Compound.	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}
Amphotericin	0.06	0.06	1	0.5	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.13	0.06	0.06	0.06
Fluconazole	128	8	128	128	128	32	1	0.06	128	16	128	32	128	0.13	16	1	128	2	128	128	32	2
12	0.13	0.13	0.25	0.13	0.25	0.13	128	0.25	0.06	0.06	0.06	0.06	0.50	0.50	0.13	0.13	0.06	0.06	0.25	0.25	0.25	0.13
9	0.50	0.25	0.06	0.06	0.5	0.25	0.50	0.25	0.25	0.25	0.06	0.06	1	1	0.13	0.13	0.13	0.13	0.25	0.13	0.13	0.06
8	0.50	0.25	1	1	0.50	0.25	1	0.25	0.25	0.13	0.25	0.06	0.50	0.50	0.25	0.13	0.25	0.13	1	0.25	0.50	0.25
14	1	0.5	1	0.25	1	0.5	128	0.5	0.13	0.13	0.25	0.06	2	2	0.25	0.25	0.5	0.25	0.13	0.13	0.25	0.25
11	1	1	1	0.5	1	0.5	2	1	0.25	0.25	0.25	0.08	1	1	0.5	0.5	0.5	0.5	1	0.5	0.5	0.25
19	1	1	1	0.25	2	1	4	0.5	0.5	0.5	0.5	0.25	1	1	0.25	0.25	0.5	0.5	1	1	0.5	0.5
64	1	1	1	1	2	2	2	0.13	0.6	0.5	0.5	0.25	2	2	0.5	0.25	1	1	1	0.26	2	1
18	1	1	1	0.5	2	1	2	1	0.6	0.5	0.5	0.5	1	1	0.5	0.5	1	0.5	1	1	0.5	0.5
30	4	2	4	2	4	4	8	2	0.5	0.5	0.5	0.25	2	0.5	0.5	0.25	1	1	1	1	0.125	0.06
16	8	4	4	1	4	4	8	2	1	1	0.50	0.25	4	2	0.50	0.13	0.50	0.50	4	1	1	0.25
10	4	2	2	0.60	4	2	4	1	2	1	1	0.5	4	4	2	1	2	1	2	1	1	0.5
22	4	4	8	2	4	2	128	4	2	0.5	1	0.5	64	4	1	0.25	2	1	1	1	1	0.5
62	4	4	4	4	8	8	8	4	2	2	1	0.5	4	4	1	0.5	2	1	2	0.25	2	1
59	8	2	8	2	16	8	16	4	4	1	2	0.25	16	4	4	1	4	2	2	1	2	1
28	16	4	4	1	8	8	16	4	4	2	2	0.50	16	4	0.25	0.25	4	4	4	1	2	1
60	16	4	8	1	8	4	8	4	4	4	1	0.5	8	4	2	1	2	2	4	0.5	4	1
61	8	4	8	4	8	8	16	4	4	2	2	0.5	8	4	0.5	0.5	4	4	2	0.25	4	2
63	8	4	8	4	8	8	8	2	4	4	2	0.25	8	8	1	1	2	2	4	1	4	2
46	8	4	4	4	8	8	16	4	4	2	2	1	8	8	1	1	4	4	4	2	4	4
55	16	8	8	8	16	16	16	4	8	8	4	2	8	8	4	2	8	8	16	4	8	8
45	32	16	16	4	32	32	16	8	8	8	8	2	8	8	4	1	16	16	128	16	8	4
21	8	8	8	4	8	4	128	4	8	2	1	0.25	128	128	1	1	4	1	8	0.6	2	0.25
17	128	64	32	1	128	64	128	64	0.5	0.25	0.25	128	128	64	0.25	0.13	0.5	0.25	0.5	0.13	0.06	0.06
29	128	16	128	8	128	64	128	128	4	2	2	0.5	128	128	1	1	2	1	128	16	0.5	0.25
13	128	32	128	8	128	64	128	128	16	4	16	1	128	128	1	0.50	32	8	64	2	4	1
47	128	16	128	4	128	128	128	16	8	4	2	2	128	32	2	2	128	4	128	32	8	8
44	128	16	16	4	128	128	32	8	8	8	8	2	128	8	2	1	16	16	128	128	32	16
20	128	128	128	64	128	128	128	32	128	32	128	2	128	128	1	0.5	128	128	128	32	128	8
15	128	128	128	128	128	128	128	128	128	128	128	128	128	128	128	0.5	128	128	128	128	128	128
84	128	128	128	128	128	128	128	128	128	64	128	4	128	128	128	32	128	128	128	64	128	128
J8	128	128	128	32	128	128	128	128	128	128	128	8	128	128	128	16	128	128	128	128	128	128

Graph 1. Variation of Chain Length.

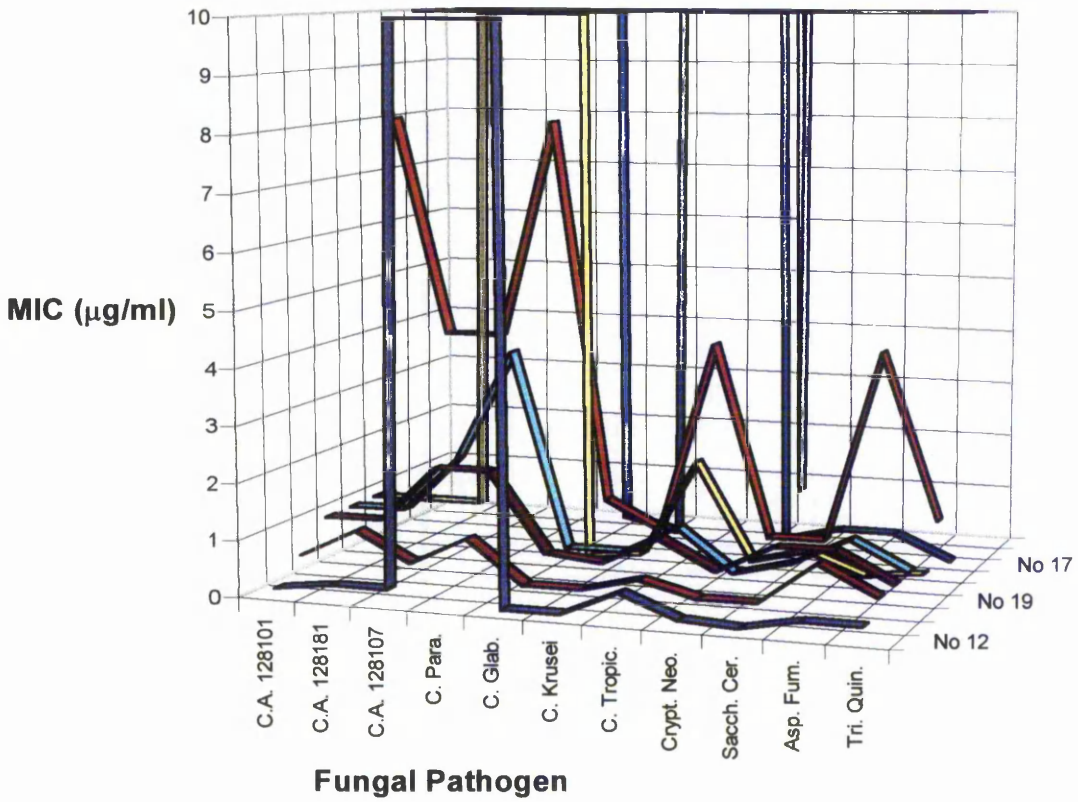


	C.A. 128101	C.A. 128181	C.A. 128107	C. Para.	C. Glab.	C. Krusei	C. Tropic.	Crypt. Neo.	Sacch. Cer.	Asp. Fum.	Tri. Quin.
No 12	0.13	0.25	0.25	128	0.06	0.06	0.5	0.13	0.06	0.25	0.25
No 9	0.5	0.06	0.5	0.5	0.25	0.06	1	0.13	0.13	0.25	0.13
No 11	1	1	1	2	0.25	0.25	1	0.5	0.5	1	0.5
No 10	4	2	4	4	2	1	4	2	2	2	1
No 13	32	8	64	128	4	1	128	0.5	8	2	1

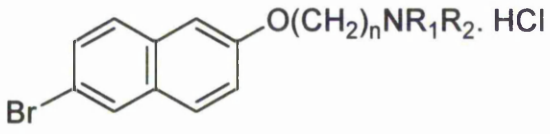


Compound Number	9	10	11	12	13
Chain length (n)	8	6	9	10	12

Graph 2. Variation of Amino Moiety.

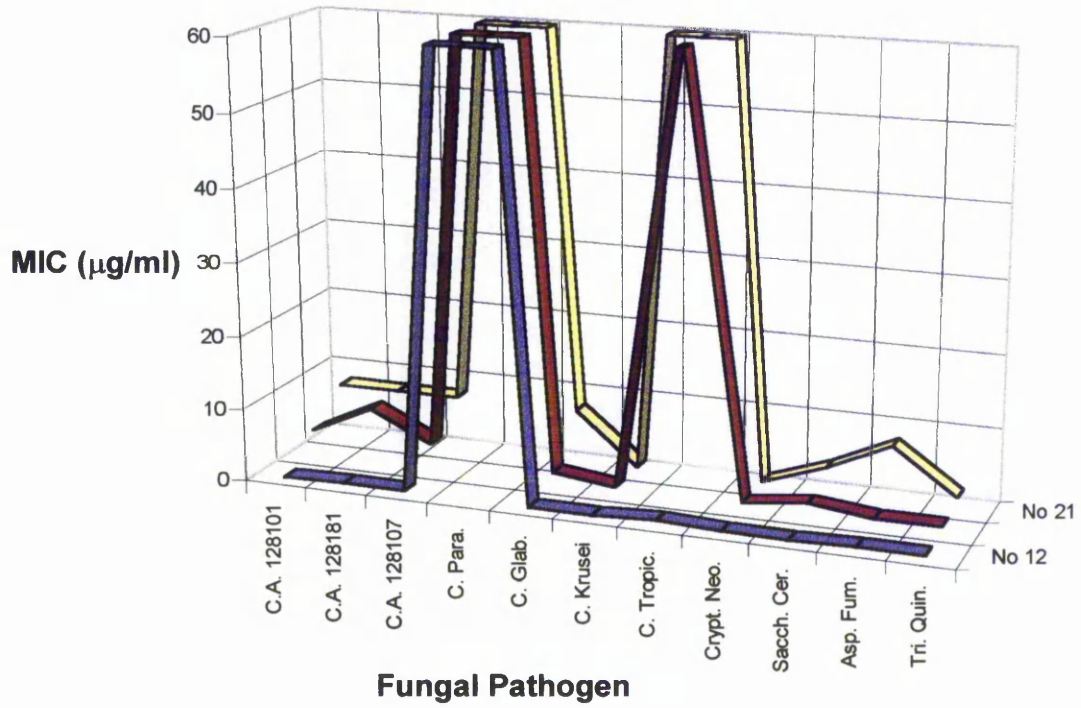


	C.A. 128101	C.A. 128181	C.A. 128107	C. Para.	C. Glab.	C. Krusei	C. Tropic.	Crypt. Neo.	Sacch. Cer.	Asp. Fum.	Tri. Quin.
No 12	0.13	0.25	0.25	128	0.06	0.06	0.5	0.13	0.06	0.25	0.25
No 8	0.5	1	0.5	1	0.25	0.25	0.5	0.25	0.25	1	0.5
No 18	1	1	2	2	0.6	0.5	1	0.5	1	1	0.5
No 19	1	1	2	4	0.5	0.5	1	0.25	0.5	1	0.5
No 14	1	1	1	128	0.13	0.25	2	0.25	0.5	0.13	0.25
No 16	8	4	4	8	1	0.5	4	0.5	0.5	4	1
No 17	128	32	128	128	0.5	0.25	128	0.25	0.5	0.5	0.06
No 20	128	128	128	128	128	128	128	1	128	128	128
No 15	128	128	128	128	128	128	128	128	128	128	128

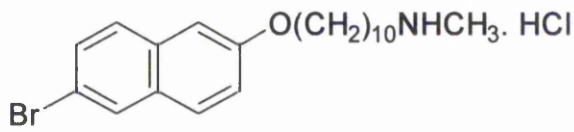


No	8	12	14	15	16	17	18	19	20
n	8	10	10	10	10	10	10	10	10
R_1	H	H	H	H	H	H	CH_3	Et.	Morpholino
R_2	H	CH_3	Et	$PhCH_2$	iPr.	$CH_2C(CH_2)_2$	CH_3	Et.	

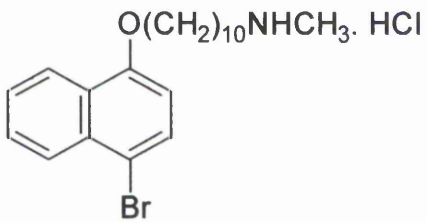
Graph 3. Variation of Substitution Pattern.



	C.A. 128101	C.A. 128181	C.A. 128107	C. Para.	C. Glab.	C. Krusei	C. Tropic.	Crypt. Neo.	Sacch. Cer.	Asp. Fum.	Tri. Quin.
No 12	0.13	0.25	0.25	128	0.06	0.06	0.5	0.13	0.06	0.25	0.25
No 22	4	8	4	128	2	1	64	1	2	1	1
No 21	8	8	8	128	8	1	128	1	4	8	2



12



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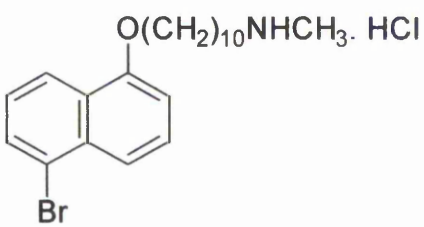
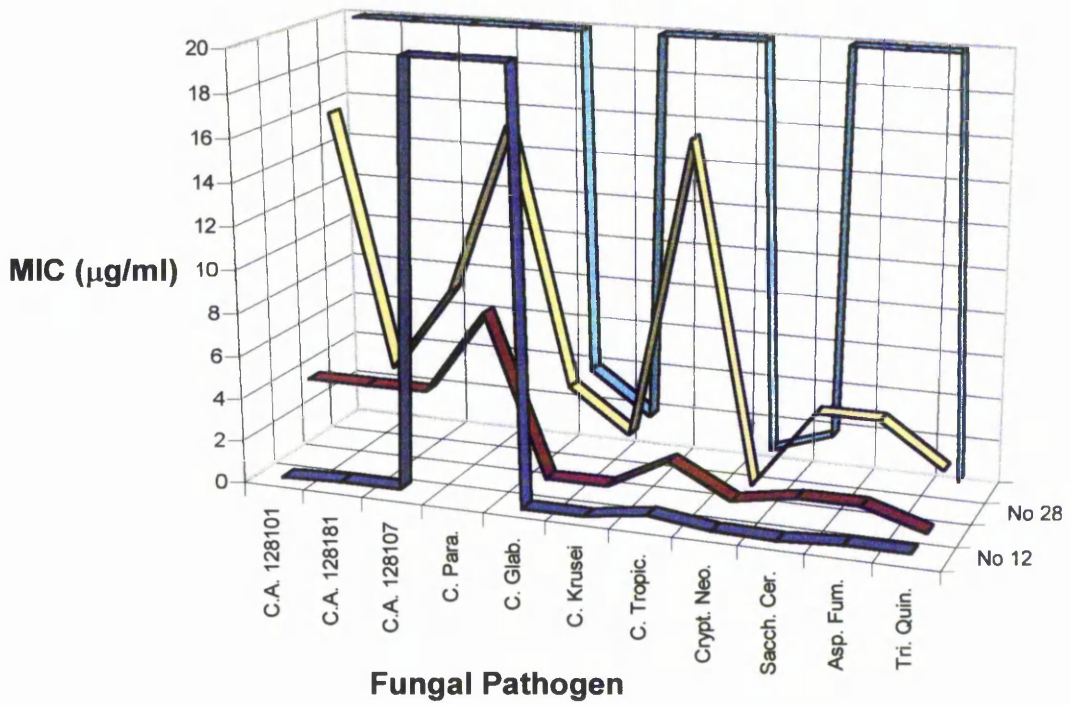
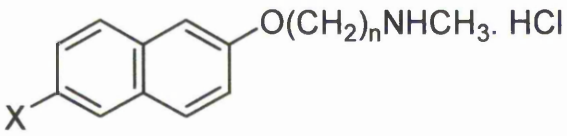


22

Graph 4. Variation of Halogen.



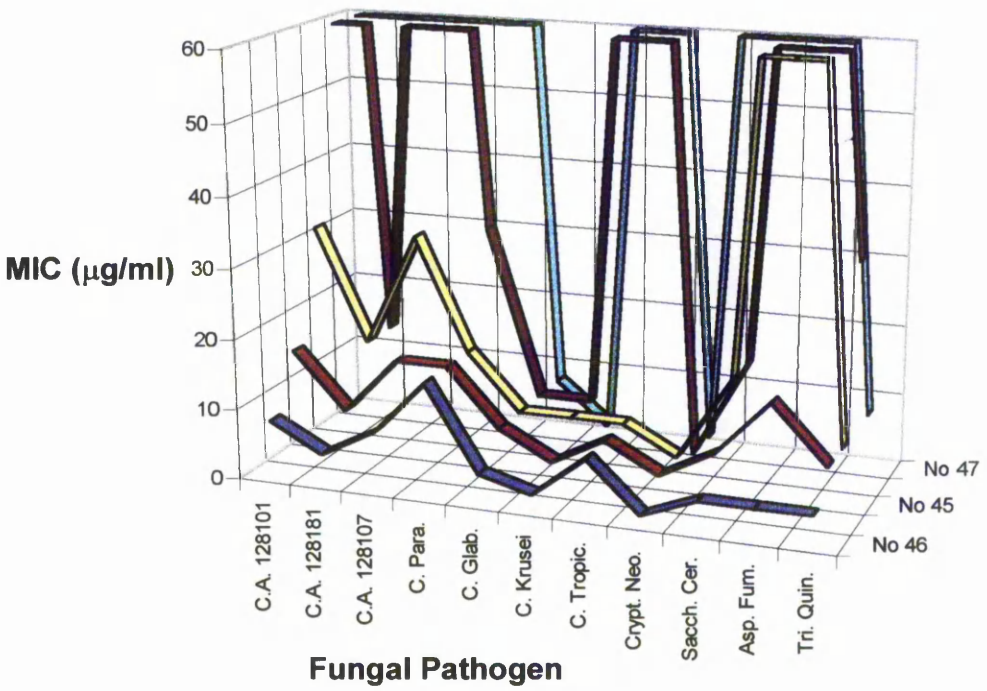
	C.A. 128101	C.A. 128181	C.A. 128107	C. Para.	C. Glab.	C. Krusei	C. Tropic.	Crypt. Neo.	Sacch. Cer.	Asp. Fum.	Tri. Quin.
No 12	0.13	0.25	0.25	128	0.06	0.06	0.5	0.13	0.06	0.25	0.25
No 30	4	4	4	8	0.5	0.5	2	0.5	1	1	0.125
No 28	16	4	8	16	4	2	16	0.25	4	4	2
No 29	128	128	128	128	4	2	128	1	2	128	0.5



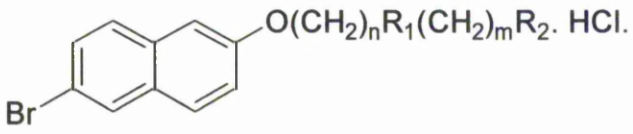
Compound	12	28	29	30	31*
Chain length (n)	10	8	10	10	10
X	Br	H	I	F	Cl

* Not tested.

Graph 5. Incorporation of Functionality into the Alkyl Chain.

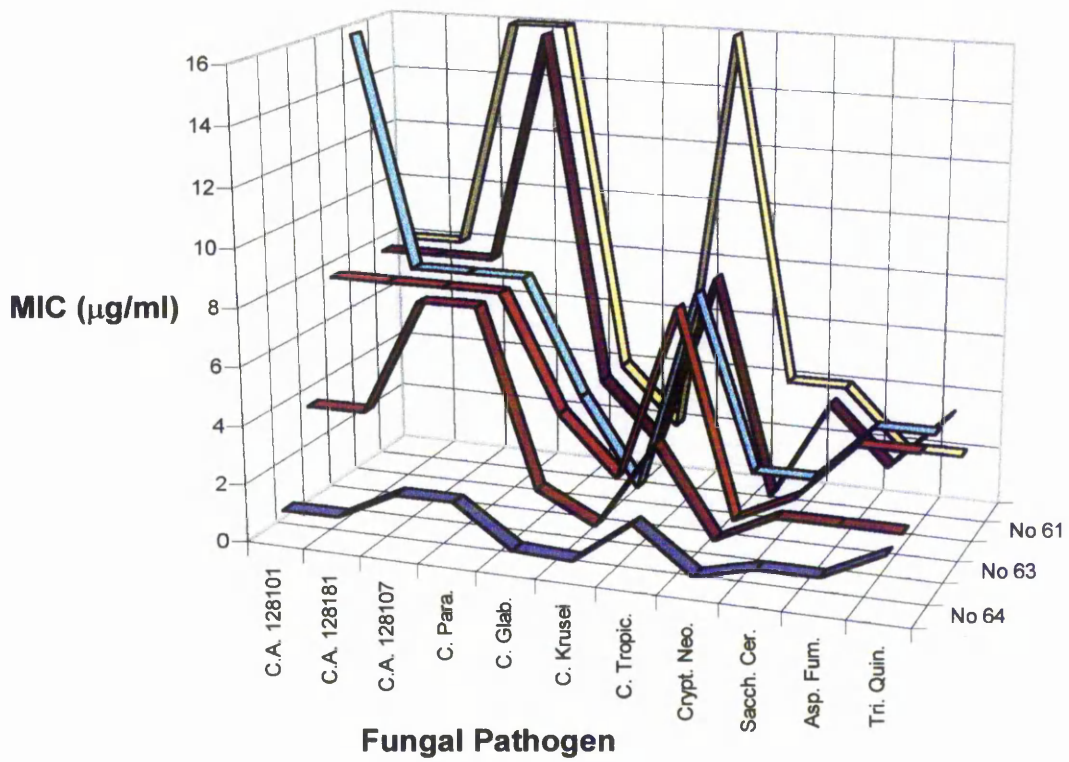


	C.A. 128101	C.A. 128181	C.A. 128107	C. Para.	C. Glab.	C. Krusei	C. Tropic.	Crypt. Neo.	Sacch. Cer.	Asp. Fum.	Tri. Quin.
No 46	8	4	8	16	4	2	8	1	4	4	4
No 55	16	8	16	16	8	4	8	4	8	16	8
No 45	32	16	32	16	8	8	8	4	16	128	8
No 44	128	16	128	32	8	8	128	2	16	128	32
No 47	128	128	128	128	8	2	128	2	128	128	8

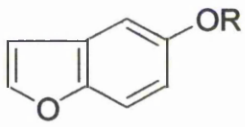


No	44	45	46	47	55
n	2	6	6	6	6
m	8	4	6	6	3
R1	NH	NH	SO	SO_2	SO
R2	NH_2	NH_2	$NHCH_3$	$NHCH_3$	$NHCH_3$

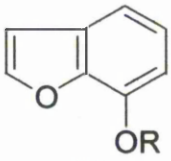
Graph 6. Benzo[*b*]furan and Benzo[*b*]thiophene Analogues.



	C.A. 128101	C.A. 128181	C.A. 128107	C. Para.	C. Glab.	C. Krusei	C. Tropic.	Crypt. Neo.	Sacch. Cer.	Asp. Fum.	Tri. Quin.
No 64	1	1	2	2	0.6	0.5	2	0.5	1	1	2
No 62	4	4	8	8	2	1	4	1	2	2	2
No 63	8	8	8	8	4	2	8	1	2	4	4
No 60	16	8	8	8	4	1	8	2	2	4	4
No 61	8	8	8	16	4	2	8	0.5	4	2	4
No 59	8	8	16	16	4	2	16	4	4	2	2



59



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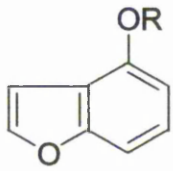

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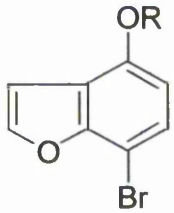

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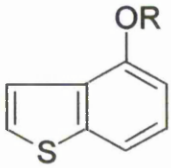
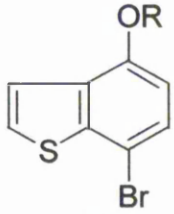


63



64

R = $O(CH_2)_{10}NHCH_3$. HCl.

4.0. Conclusion.

A total of thirty novel analogues of PCAB 300 have been prepared and evaluated in a broad-spectrum human pathogenic fungal screen operated by Zeneca Pharmaceuticals, and in collaboration with BTG are the subject of a patent application, UK-9922446.1, 1999.

A significant increase in potency was achieved by the substitution of the pyrrolidine moiety of PCAB 300 with methylamine. The investigation has also established that the structural features required for optimal *in vitro* antifungal activity are a naphthalene ring substituted in the six position by bromine and in the two position by an alkyloxy side chain, of eight to ten carbons long, possessing a terminal *N*-methyl substituent.

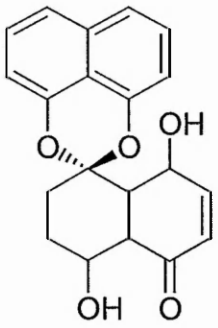
The variation in antifungal activity with small changes in structure suggests that the compounds are not simply acting as biocidal long chain amines, but it is not certain what is their mode of action. By comparison of their structure with PCAB 300 it is reasonable to assume that they are CaM antagonists but this is not a sufficient condition as the potent and specific CaM antagonist J8, and the 2,6 positional isomer **84**, were inactive in the fungal screen. However, the situation is complicated by the presence of iodine in the sulfonamides since the iodinated ether, **43**, also performed poorly in the fungal screen.

As a continuation of this work it is intended that BTG will conduct further *in vitro* and *in vivo* testing of selected potent inhibitors.

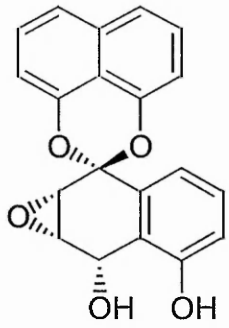
5.0. The Palmarumycin Family of Natural Products.

A structurally novel and diverse class of biologically active natural products was introduced by the isolation of MK3018 in 1989[42] and bipendensin in 1990[43], Figure 20.

Figure 20.



MK 3018

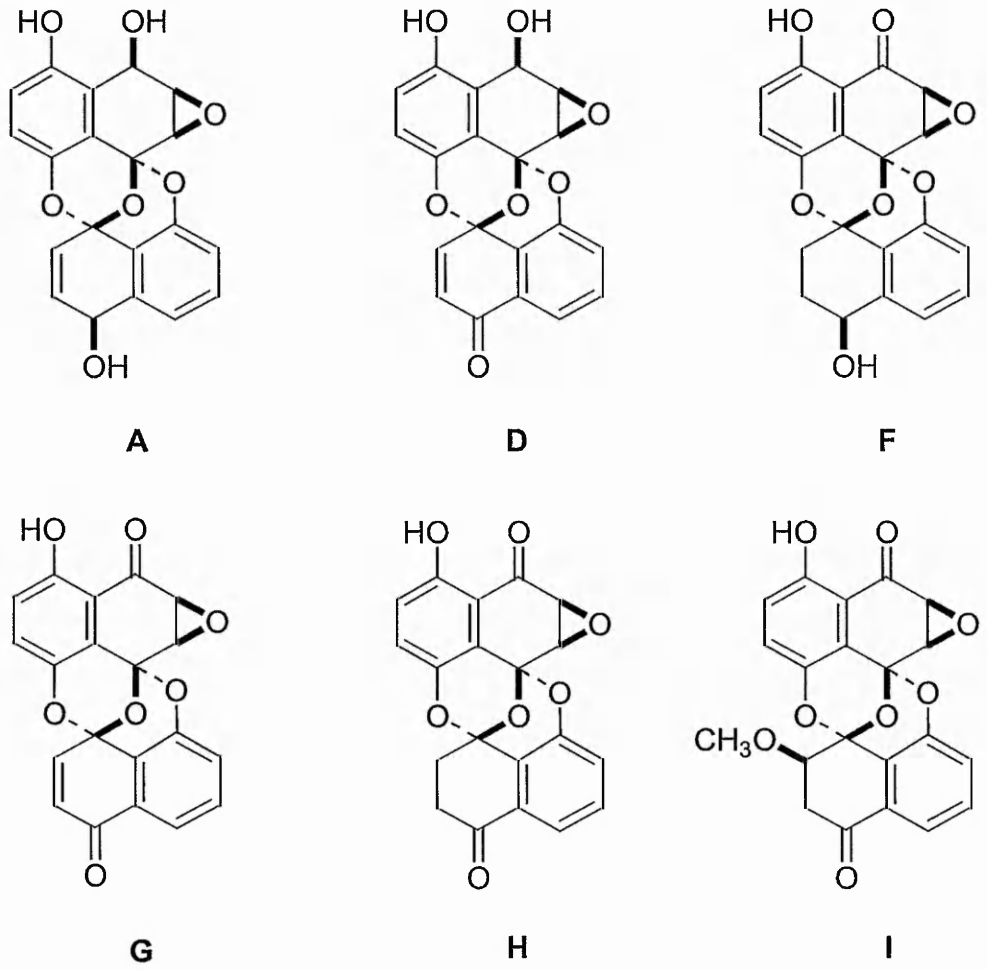


Bipendensin

The novel structural characteristics common to this class of compounds are a unique spiro-acetal, derived from 1,8-dihydroxynaphthalene, linked to a second naphthalene moiety at rich and varied levels of oxidation. Subsequently a number of related compounds were discovered.

The preussomerins, Figure 21, were isolated from the coprophilous fungus *Preussia isomera*[44, 45] in 1990 and the endophytic fungus *Harmonema dematioides*[46] in 1993. Although structurally related, they possess a more complex pattern of oxidation, with both of the naphthalene moieties being linked by a bis-spiro-acetal in which each acetal unit shares an oxo-bridge. Preussomerin **G** and **D** have been shown to inhibit *Ras* farnesyltransferase with IC_{50} values of 1.2μM[47] and are of interest as potential chemotherapeutic agents in the treatment of cancer. The precise mode of their inhibitory action is not known but as part of a structure activity study it was observed that the most active compounds possessed an epoxide in the upper half of the molecule and a conjugated ketone in the lower half. The enone functionality appeared to be critical for activity and its potential to serve as a Michael acceptor was demonstrated by the stereospecific addition of *N*-acetylcysteine[47].

Figure 21. The Preussomerins.

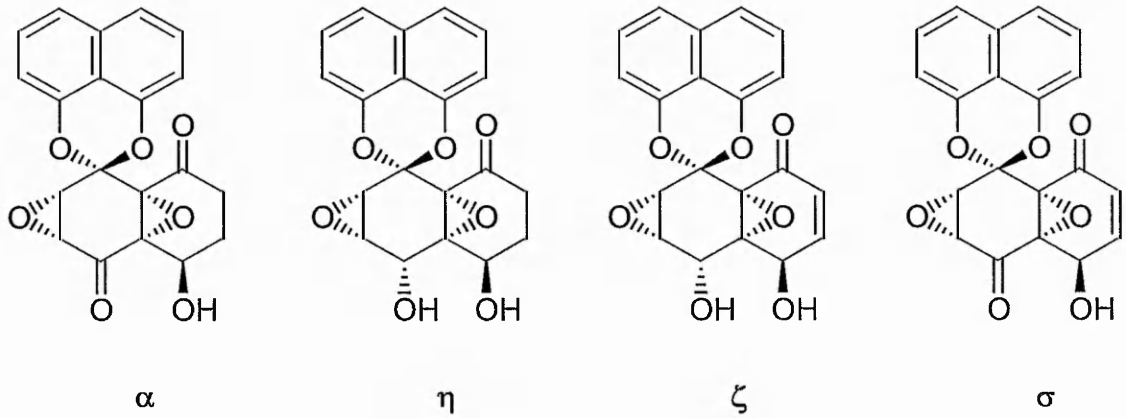


Diepoxins α, η, ζ, and σ, Figure 22, were isolated from the fermentation of a fungal culture, LL-07F275, in 1993 by Schlingmann et al[48]. The spiro-acetal bis-epoxides were characterised by spectroscopic methods and shown to exhibit varying degrees of antibiotic activity against a selection of bacteria and fungi. Diepoxin σ was observed to be the most potent having antifungal activity against *Candida albicans* in addition to antibacterial activities against a selected panel of bacteria in the range of 4 to 32 μg ml^{-1}. Diepoxins α and ζ were found to be active in the antibacterial screen only, being two to four times less active than diepoxin σ, whilst diepoxin η was almost completely inactive in both screens.

In the same year, Chu et al[49] also reported the isolation of diepoxin σ (Sch 49209) from the fermentation of a fungal culture, SCF-0642 *Nattrassia mangiferae*, and were able to establish its structure and relative stereochemistry from the synthesis and X-ray analysis of

Sch 50674, an acylated triepoxide derivative. It was also shown that diepoxin σ and its acylated derivative inhibited the invasion of fibrosarcoma cells through a matrigel membrane with IC_{50} values of 0.75mM and 0.25mM respectively, and were able to reduce the size of primary tumours and a number of metastases *in vivo*.

Figure 22. Diepoxins.



The palmarumycins **CP_1** to **CP_4** and **C_1** to **C_{16}**, Figure 23 and Figure 24 respectively, the largest group within the family of natural products, were isolated from the fermentation of the fungal cultures *Coniothyrium palmarum*[50] and an unidentified *Coniothyrium* species[51] respectively, in 1994 by Krohn et al. From preliminary biological evaluation studies, by agar diffusion tests, it was found that these compounds possessed antifungal, antibacterial, and herbicidal activities.

Figure 23. Palmarumycins CP_1 to CP_4.

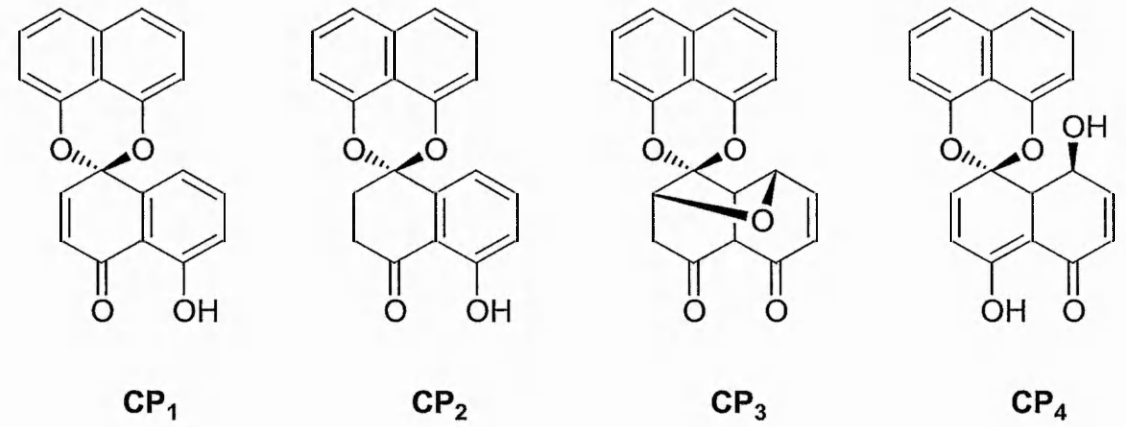
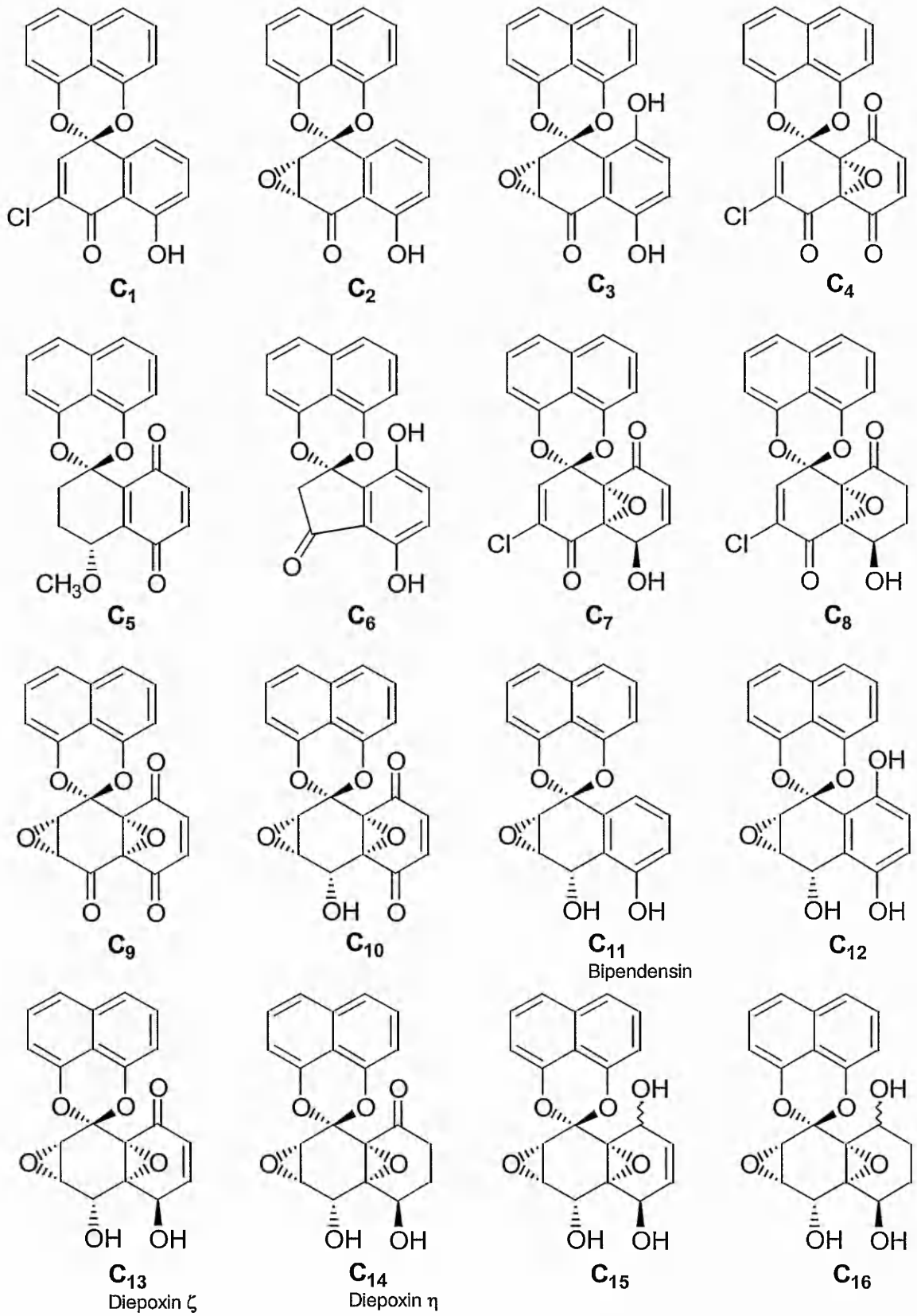


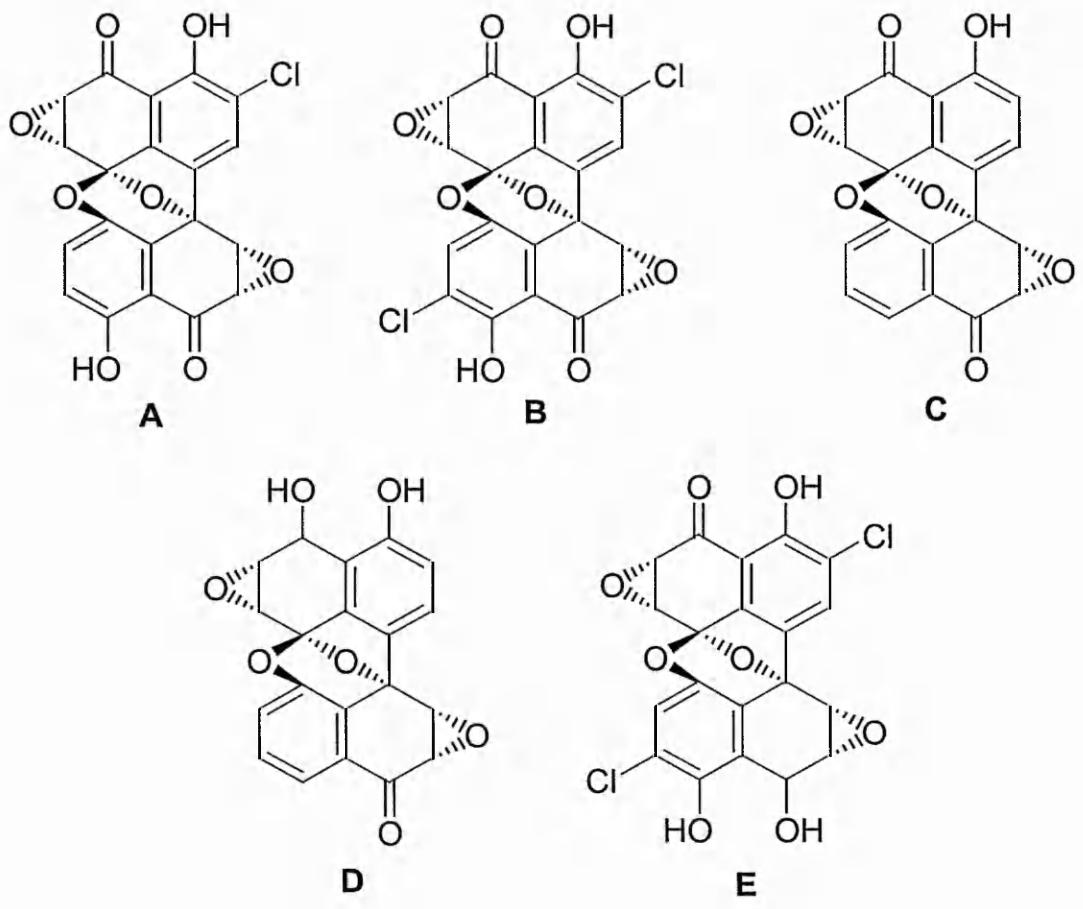
Figure 24. Palmarumycins C_1 to C_{16}.



Palmarumycin **CP_3** was the most active in the antifungal screen and had activity equal to that of **CP_4** against Gram-positive, *Bacillus megaterium*, and Gram-negative, *Escherichia coli*, bacteria, whilst **CP_1** and **CP_2** proved to be almost inactive. In comparison, the evaluation of palmarumycins **C_1** to **C_{16}** identified **C_3**, **C_{10}**, and **C_{12}** to have the highest antimicrobial activities within the particular series, being equally as active as **CP_3** in the fungal assay.

More recently a series of bisnaphthospiroacetal compounds, spiroxins **A**, **B**, **C**, **D**, and **E**, Figure 25, have been isolated form the culture of an unclassified marine-derived fungal strain LL-37H248 by McDonald et al[52]. Whilst the spiroxins are closely related to the preussomerins the principal distinguishing structural feature is the substitution of one of the oxo-bridges of the bis-spiroacetal unit found in the preussomerins with a carbon-carbon bond.

Figure 25. The Spiroxins.

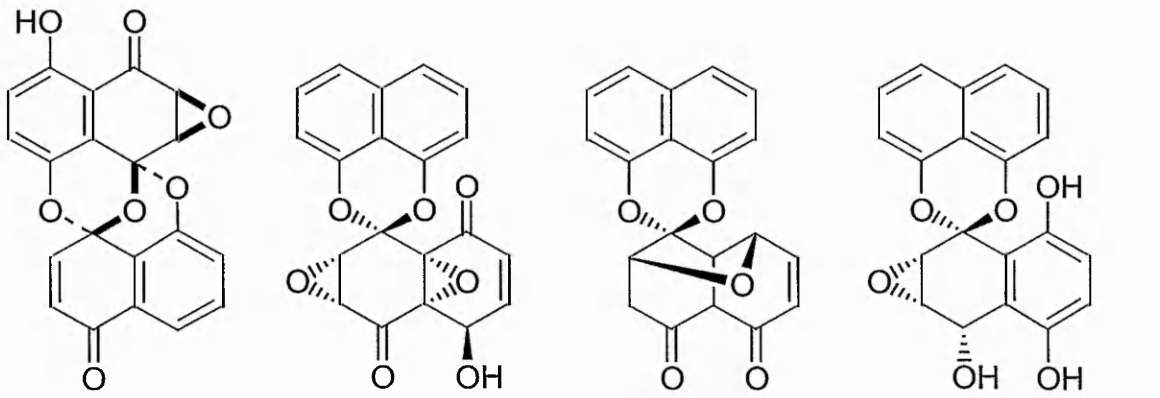


Spiroxin **A** was found to have some activity against Gram-positive bacteria, but only marginal activity against Gram-negative bacteria.

However, in a cytotoxicity assay spiroxin **A** exhibited a mean IC_{50} value of 0.09 μgml^{-1} against a panel of twenty five diverse cell lines and was active in a mouse xenograft model against human ovarian cancer showing 59% inhibition after twenty one days at a concentration of $1mgKg^{-1}$. As spiroxin **A** caused a concentration dependent nicking of pBR322 DNA in the presence of either dithiothreitol (DDT) or 2-mercaptoethanol the cleavage of single–stranded DNA was offered as a probable mechanism for its cytotoxic effects. It was also noted that the oxidation state of the spiroacetal carbon, essentially that of a masked ketone, could also enable the spiroxins to behave as quinone epoxides, thereby facilitating DNA cleavage under reducing conditions via an oxidative stress mechanism involving the formation of thiol conjugates.

By comparison of the structural features of the most biologically active compounds within each of the palmarumycin series, Figure 26, it is reasonable to assume that an enone functionality, or a masked quinone in the form of its dihydro precursor, in combination with an oxo substituent *peri* to the quaternary carbon of the spiro acetal are the principal components of the pharmacophore responsible for the biological activity.

Figure 26. The most active compounds within the palmarumycin series of natural products.



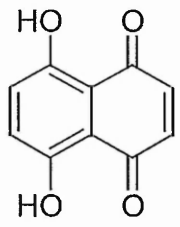
5.1. Quinone Cytotoxicity.

The molecular mechanisms of quinone cytotoxicity has been the subject of a recent review[53]. Whilst the cytotoxicity of quinones in rapidly dividing tumour cells was attributed to DNA modification, quinone toxicity in resting or non-dividing cells was due to the alkylation of essential protein thiol or amine groups and / or oxidative stress. This severely limits the use of the anthracycline drugs such as adriamycin and daunorubicin for the treatment of a wide range of human malignancies due to their dose-dependent cardiotoxicity that is attributed to futile redox cycling[54].

Oxidative stress arises when a quinone undergoes metabolic activation by various reductases or reduced cytochrome P450 to form a semiquinone radical which under aerobic conditions enters a redox cycle with molecular oxygen, reducing oxygen to superoxide radicals and regenerating the parent quinone. The formation of these powerful oxidising species is responsible for most of the damage to essential macromolecules. Whilst the higher redox potential benzoquinones and naphthoquinones are known to be the most toxic, the cytotoxicity exhibited by benzoquinones has been found to correlate with the extent of glutathione depletion by conjugate addition rather than oxidative cycling[55, 56, 57].

In general naphthoquinones, in particular hydroxynaphthoquinones such as naphthazarin, Figure 27, have been found to be comparatively more toxic even when their redox potential is lower than that of a benzoquinone. This is due to their ability to mediate oxidative stress by way of significantly increased oxygen activation, thereby overcoming the enzymatic defence mechanisms and / or inhibiting the defensive enzymes directly[53].

Figure 27.



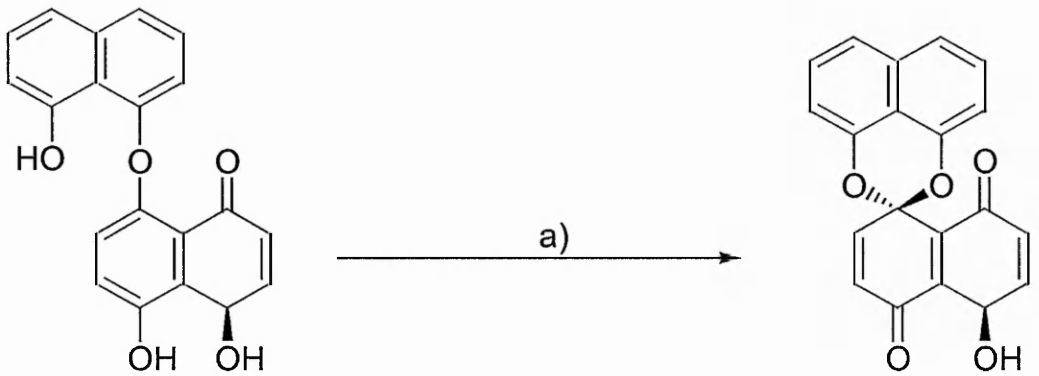
Naphthazarin

5.2. Recent Reported Syntheses of the Palmarumycin Series.

Prior to the initiation of this project synthetic studies towards the total synthesis of the palmarumycin family of natural products had received limited attention.

In 1994, as part of a biosynthetic postulate, Krohn et al[51] proposed that the oxidative coupling of a hydroxynaphthalene linked by a diaryl ether to a phenolic base unit derived from a penta- or hexaketide could account for the formation of the novel quinone monoacetal unit. This hypothesis was subsequently supported, by the same group in 1997[58], by the isolation of the diaryl ether **89** from the fermentation of *Coniothyrium palmarum* and its oxidative cyclisation to the unknown quinone monoacetal **90** in 67% yield, Scheme 20.

Scheme 20.



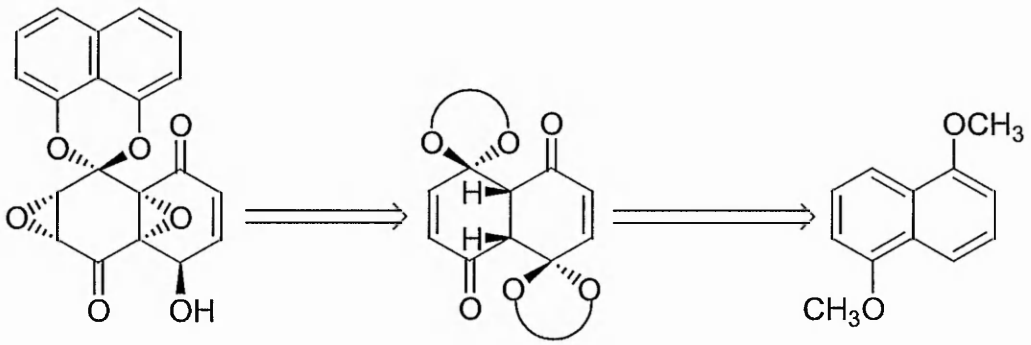
89 **90**

a) Ag_2O, toluene, methanol.

Subsequently the biosynthesis of cladospirone bisepoxide (cladospirone bisepoxide [59, 60], diepoxin ζ[48], palmarumycin C_{13}[51], Sch 53514[61]) has been investigated by feeding ^{13}C-labeled acetate to growing cultures of the fungus *Sphaeropsidales sp.*[62]. These studies have provided, by ^{13}C N.M.R. analysis, direct evidence that both naphthalene rings of the natural product are derived from the same pentaketide precursor via a fungal polyketide synthase.

Also during 1997, Wipf and Jung[63] reported the dipole-controlled nucleophilic addition of methyllithium to a bis-naphthoquinone acetal during model studies towards the asymmetric synthesis of diepoxin σ. From a retrosynthetic analysis of diepoxin σ, Figure 28, it was anticipated that chiral acetals such as **91** would be required to differentiate the prochiral faces of 1,5-dimethoxynaphthalene **92**.

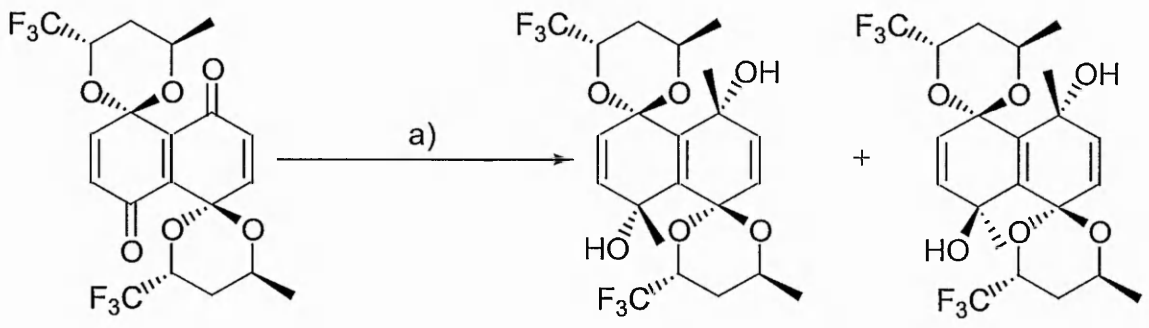
Figure 28. Retrosynthetic analysis of diepoxin σ.



Diepoxin σ **91** **92**

The investigation demonstrated the close agreement between the experimental and theoretical facial selectivity of the nucleophilic addition of methyllithium *anti* to the trifluoromethyl substituents of the acetal **93** Scheme 21, 9:1 and 12:1 respectively. The facial selectivity was also shown to be enhanced by increasing the polarity of the solvent, which further confirmed the remarkable long range electrostatic control of the addition.

Scheme 21. Dipole controlled diastereoselective 1,2-addition.



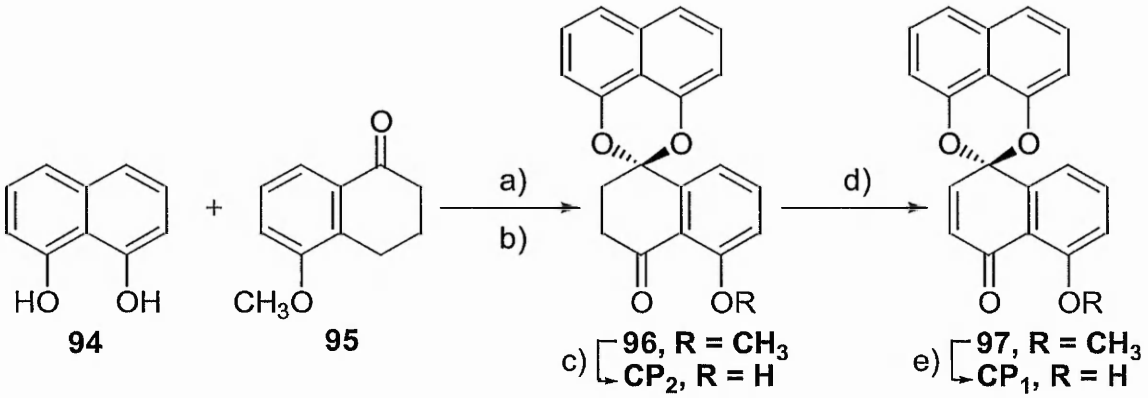
93 9:1

a) Methyllithium, diethyl ether, -78°C.

However, during the course of the practical investigation of this project several reports of the total synthesis of the palmarumycin family of natural products appeared in the literature.

Initially the total synthesis of palmarumycin $\mathbf{CP_1}$, and $\mathbf{CP_2}$ were independently published by Barrett[64] and Taylor[65, 66]. Both research groups obtained the spiro acetal from the forced acid catalysed condensation of 1,8-dihydroxynaphthalene **94** with 5-methoxytetralone **95**, followed by benzylic oxidation to afforded methoxy CP_2 **96** which could either be demethylated or oxidised further to methoxy CP_1 **97**, Scheme 22.

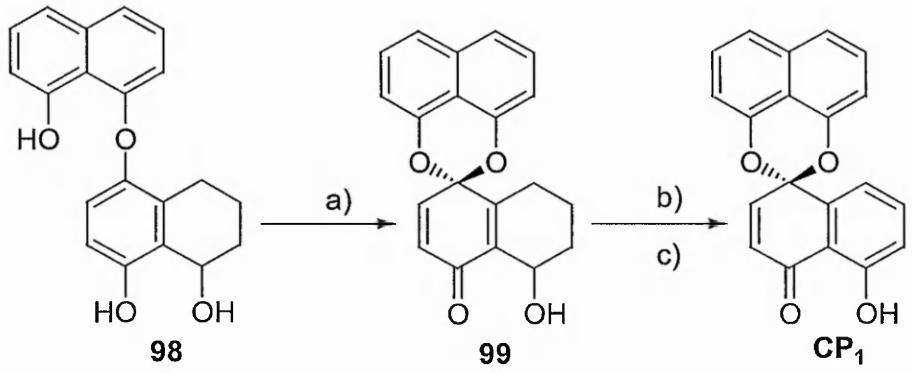
Scheme 22.



a) $TsOH_{(cat)}$, PhH, Dean-Stark, reflux, 48h., 86%. b) CrO_3.HCl.bipy., ^tBuOOH, PhH, r.t., 10h., 61%. c) MgI_2, PhH, reflux, 1.5h., 84%. d) DDQ, PhH, reflux, 10h., 65%. e) β-bromocatecholborane, DBU, CH_2Cl_2, 5°C, 10 min., 50%.[64].

Subsequently Wipf and Jung[67] obtained $\mathbf{CP_1}$ from the oxidative cyclisation of phenol **98** with phenyliodosyl diacetate, Scheme 23, and subsequent two step oxidation of **99** with Dess Martin periodinane and manganese dioxide without isolating the intermediate ketone. It is interesting to note that phenol **98** was obtained in five steps from the Ullmann coupling of the relatively inaccessible 8-iodo-1-methoxynaphthalene and 5-hydroxy-8-methoxytetralone.

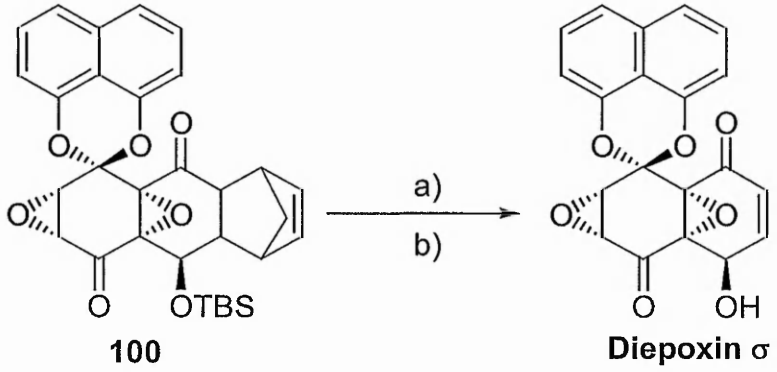
Scheme.23.



a) $PhI(OAc)_2$, CF_3CH_2OH, 87%. b) Dess-Martin periodinane, CH_2Cl_2. c) MnO_2, CH_2Cl_2, 60%.

Wipf and Jung[68] subsequently adapted this methodology to the elaborate preparation of (±)-diepoxin σ from 5-hydroxy-8-methoxy-1,4-napthoquinone in ten steps, which included a remarkable high temperature cycloreversion of the pentacyclic intermediate **100** as the penultimate step, Scheme 24.

Scheme 24.

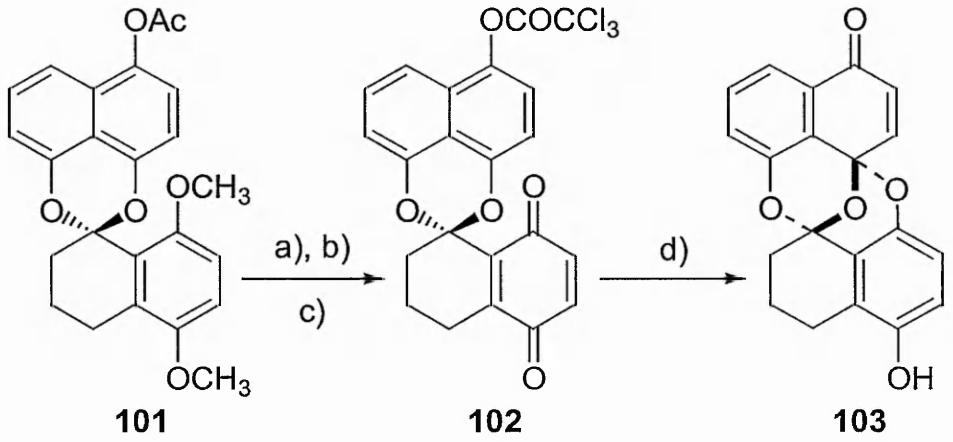


a) PhOPh, reflux, 250 to 260°C. b) HF, CH_3CN / H_2O, 0°C to r.t., 73%

Most recently the total syntheses of (±)-preussomerins **G** and **I** have been described by Heathcock and Chi[69]. The initial spiro acetal moiety was introduced by the acid catalysed condensation of 4-acetoxy-1,8-dihydroxynaphthalene with the methyl enol ether of 5,8-dimethoxytetralone to give intermediate **101**, Scheme 25, which by a process of

deprotection, protection, and oxidation was transformed to the quinone **102**. Hydrolysis of the trichloroacetate ester afforded the bis-acetal **103** as the only observable product, Scheme 25. This remarkable reaction was described as either a 'ring chain tautomerisation' or as a '1,6-addition of a phenoxide to the oxygen end of the quinone carbonyl group'. The resonance energy gained from the formation of two isolated benzene rings was proposed to be the driving force for the transformation.

Scheme 25.



a) 4M $NaOCH_3$, CH_3OH, 98%. b) $(Cl_3CCO)_2O$, TEA, 93%. c) $Ce(NH_4)_2(NO_3)_6$, 70% aq. CH_3CN, CH_2Cl, 87%. d) LiOH, $THF-H_2O$, 97%.

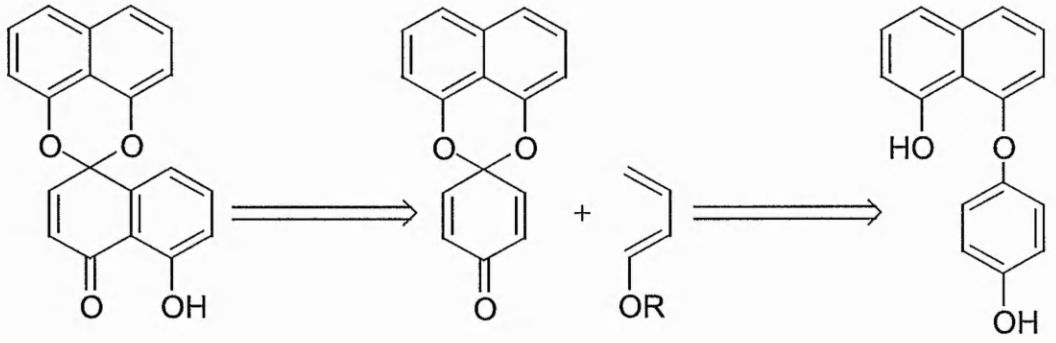
5.3. Synthetic Strategy.

In view of the continued interest at The Nottingham Trent University both in the development of novel antimicrobial and antifungal agents, and in the preparation of quinone monoacetals the palmarumycin family of natural products were selected as suitable lead compounds for both a synthetic and biological investigation.

Although palmarumycin $\mathbf{CP_1}$, structurally the least complex, is known to possess modest antimicrobial activity it was selected as a suitable synthetic target in order to establish a general protocol for the preparation of the palmarumycin skeleton. An important consideration in selecting a suitable synthetic strategy was the ease in which additional functionality could be selectively introduced. In particular, the subsequent introduction of an oxo substituent *peri* to the quaternary acetal carbon was desirable in view of the

functional groups present in the previously described pharmacophore. With these considerations in mind a retrosynthetic analysis of palmarumycin **CP_1**, Figure 29, revealed the potential of employing a cycloaddition reaction for the construction of the lower naphthyl ring. In comparison to the recently published total syntheses of palmarumycin CP_1, this was considered to be a particularly novel and attractive sequence that offered the potential to be able to manipulate the functional groups in both the diene and dienophile, thereby enabling rapid access to numerous analogues.

Figure 29. Retrosynthetic analysis of palmarumycin CP_1.

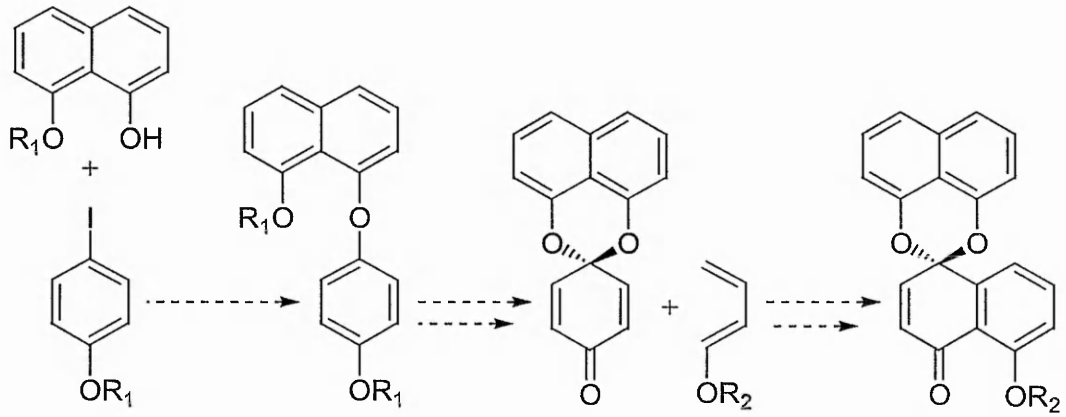


6.0. Chemical Discussion.

6.1. Introduction.

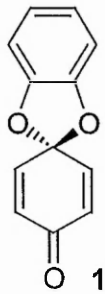
It was anticipated that palmarumycin CP_1 could be obtained by an investigation of the synthetic strategy illustrated in Figure 30.

Figure 30.



In comparison to the recently published total syntheses of CP_1 [64, 65, 66, 67] this strategy centred upon the construction of the lower naphthyl moiety by the regioselective cycloaddition of a suitably activated diene to a novel quinone monoacetal dienophile. The introduction of additional functionality in both the diene and dienophile components, and variation of the oxidation state of the adducts, potentially offered the advantageous isolation of numerous analogues for biological evaluation from comparatively accessible intermediates.

Although the preparation of quinone monoacetals by oxidative cyclisation of *para*-(aryloxy)phenols traditionally occurs in modest yield an investigation into the preparation of the known monoacetal **104**[70] was initiated to identify optimal conditions, Section 6.3.



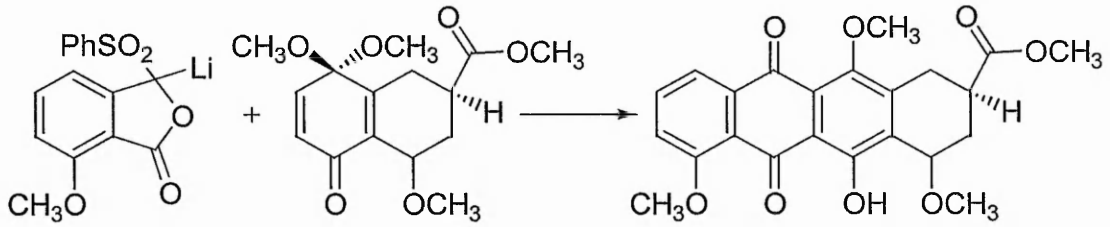
104

In contrast to quinones the cycloaddition chemistry of quinone monoacetals has received limited attention but are known to undergo regioselective addition to activated dienes under a variety of conditions, Section 6.6.2.

6.2. Chemistry Of Quinone Monoacetals.

Quinone monoacetals are attractive compounds as regiospecific quinone equivalents in organic synthesis and have served as synthetic precursors to various types of natural products such as tropolones[71], ryandol[72], α-tocopherol[73], and anthracyclines[74]. An example of the last is the regiospecific route to the daunomycinone, adriamycinone type aglycons by annulation of the quinone monoacetal **106** with the lithiated lactone **105**, Scheme 26[75].

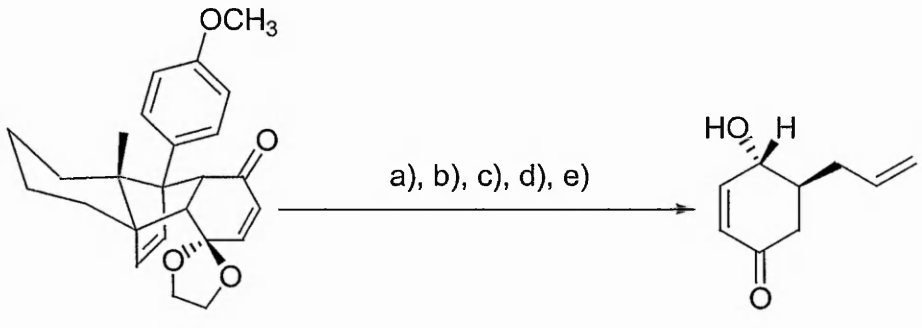
Scheme 26.



105 **106**

More recently the hydroxy enone **108**, an enantiomer of a chiral building block used in the preparation of manzamine A[76], was obtained from a chiral quinone monoacetal **107** by a regioselective and stereoselective reduction-alkylation-reduction procedure followed by hydrolysis of the spiro-acetal and cycloreversion[77], Scheme 27.

Scheme 27.

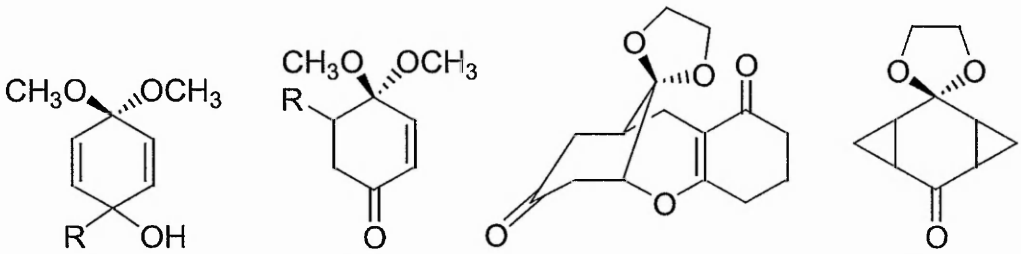


107 **108**

a) Zn, $NiCl_2$, propanol / H_2O, ultrasound. b) LDA, allyl bromide, -78°C. c) $LiAlH_4$, -40°C, diethyl ether. d) 6M HCl, acetone. e) 300°C, 10^{-2} mbar.

The general chemistry of quinone monoacetals has been the subject of several reviews[78, 79] and may be summarised as : 1,2-additions of organolithium and Grignard reagents to the carbonyl group to give protected *para*-quinol derivatives such as **109** Figure 31; regioselective Michael additions of oxygen, nitrogen, and sulfur nucleophiles to afford 1,4-addition products **110**; annelations which can either be nucleophilic β,β^1 additions to give compounds represented by **111**, or β,α additions resulting from initial nucleophilic β addition followed by intramolecular reaction of the nucleophilic centre generated at the α position with an electrophilic centre to give compounds depicted by **112**; reactions with derivatives of ammonia which constitutes a method for the replacement of a phenolic hydroxyl group by NO, NNPh, NH_2, or H; and Diels-Alder cycloaddition reactions, Section 6.6.2.

Figure 31.



6.2.1. General Methods For The Preparation of Quinone Monoacetals.

In general the direct preparation of quinone monoacetals has been achieved by the chemical oxidation of *para*-alkoxyphenols and / or *para*-(hydroxyphenoxy)phenols with the following oxidising agents : ferric chloride[80], copper(II) species[81], ceric ammonium nitrate[82, 83], *N*-bromosuccinimide[82, 83], manganese dioxide[70], dichlorodicyanobenzo-quinone (DDQ) [70], silver oxide[58, 70], thallium(III) nitrate (TTN)[84], and more recently phenyliodosyl bis(trifluoacetate) (PIFA)[85, 86], and the less expensive phenyliodosyl diacetate (PIDA)[87, 88]. They have also been obtained indirectly by i/ the electrochemical oxidation of 4-alkoxyphenols followed by mono-hydrolysis of the quinone bis-acetals[79, 89, 90]; ii/ by Lewis acid promoted diol exchange between a dimethyl quinone monoacetal and several aliphatic diols[91], iii/ from the hydrolysis of *N*-sulfonyl quinone-imine monoacetals by alumina[92], iv) and from the oxidation of *para*-(aminophenoxy)-phenols[93].

Table 9 serves to illustrate the application of the various methods described above in the preparation of quinone monoacetals.

Table 9.

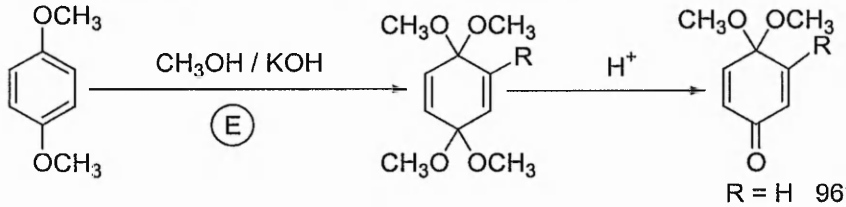
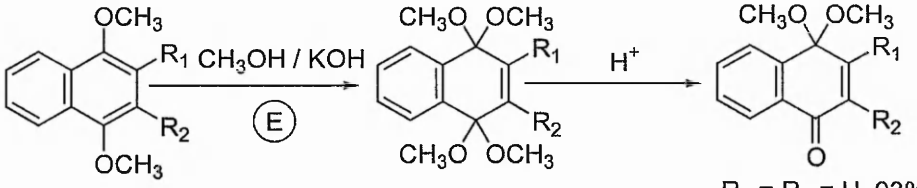
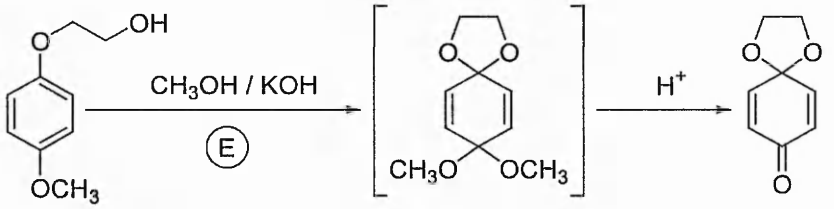
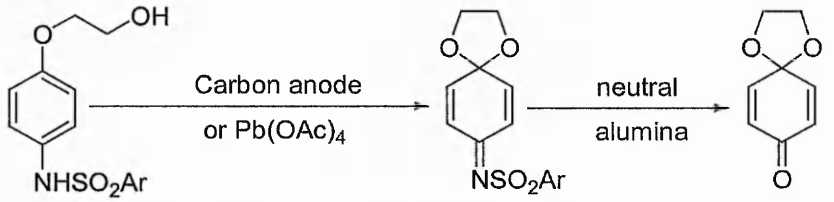
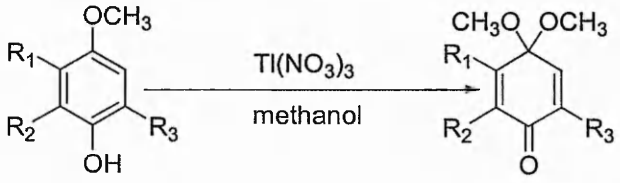
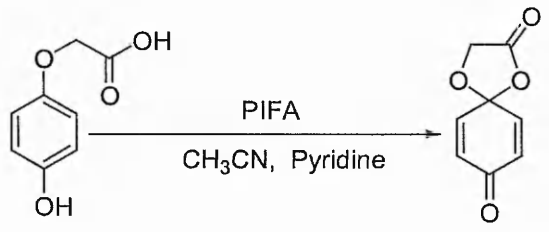
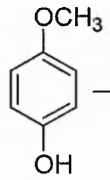
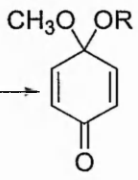
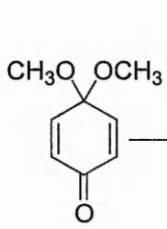
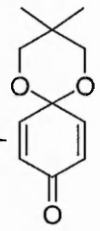
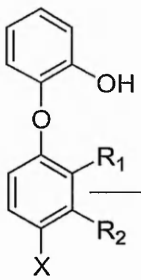
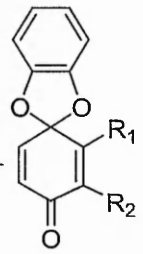
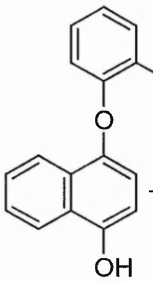
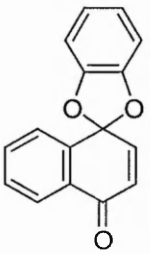
Entry	Reactant	Products
1[79, 90]		R = H 96% R = Br 62% R = OCH_3 77%
2[79, 89]		R_1 = R_2 = H 93% R_1 = Br, R_2 = H 85% R_1 = OCH_3, R_2 = H 27%
3[90]		95%
4[92]		54%
5[84]		R_1 = R_2 =R_3 = H 97% R_1 = Br, R_2 = R_3 = H 91% R_1 = R_3 = CH_3, R_2 = H 87%
6[85]		80%

Table 9 continued.

Entry	Reactant	Products
7[88]		
8[91]		
9[70, 93]		
10[70]		

(E) = Electrochemical oxidation

A general method for the preparation of quinone monoacetals in excellent yield by the oxidation of *para* alkoxyphenols with phenyliodosyl bis(trifluoroactate) (PIFA) was introduced in 1989 by Kita et al[85], Table 9 entry 6. It was effectively demonstrated that quinone monoacetals could be obtained by the oxidation of appropriate *para*-alkoxyphenols with PIFA either by intermolecular coupling in a nucleophilic solvent or by intramolecular coupling in a non-nucleophilic solvent. Analogous results were independently reported by Pelter et al[87], and Morrow[88], with the less expensive phenyliodosyl diacetate (PIDA) oxidant. More recently, from an investiagtion into the oxidative cyclisation of *N*-acyltyramines with PIFA described by Kita et al[86], the range

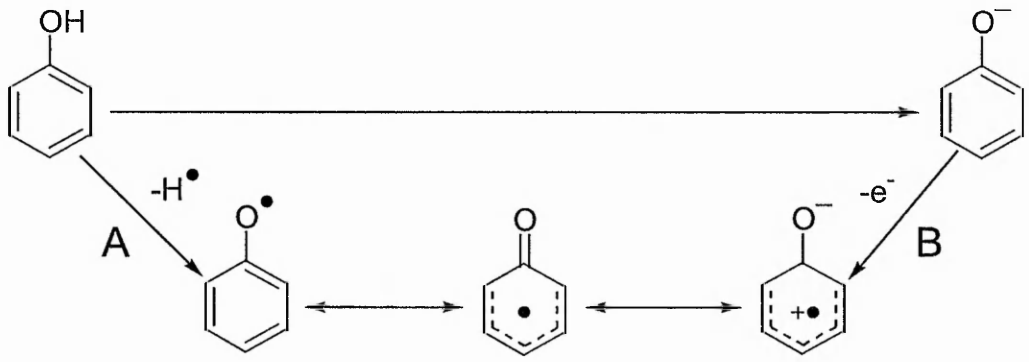
of compatable solvents has been extended to include 2,2,2-trifluoroethanol or dichloromethane with potassium carbonate as base.

Thus , there is currently a variety of chemical and electrochemical methods for the efficient preparation of *para*-alkoxy benzoquinone and naphthoquinone monoacetals. In contrast, prior to the recent publications on the total syntheses of the palmarumycin family of natural products, Section 5.2, the preparation of quinone monoacetals in which the acetal oxygens are derived from dihydric phenols or naphthols has received limited attention and are usually obtained in variable yields (Table 9 entries 9 and 10).

6.2.2. Mechanistic Considerations of Quinone Monoacetal Formation.

The oxidation of monohydric phenols by oxidising agents capable of one electron abstraction such as lead dioxide, silver oxide, manganese dioxide, and ferric or ceric ions results in the formation of resonance stabilised radical intermediates. These intermediates are generated either by the homolytic cleavage of the O-H bond of the phenol, route A Figure 32, or by the loss of one electron from the corresponding phenoxide anion, route B[94].

Figure 32.

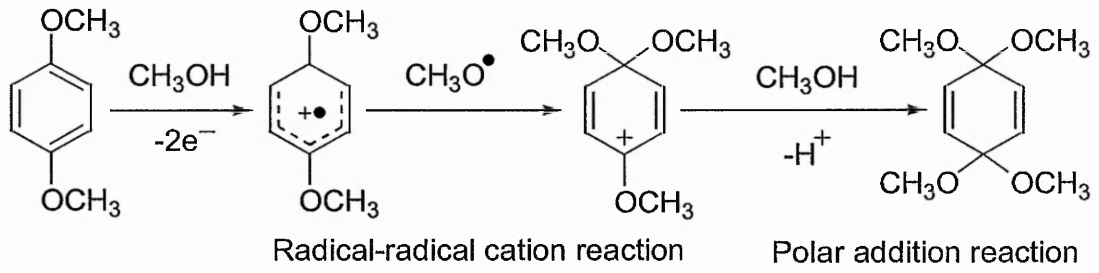


Direct evidence for the existence of these intermediates has been obtained from chemical reactivity studies, magnetic suceptability measurements, and the analysis of spectral data from infrared, ultra-violet, nuclear magnetic resonance, and electron spin resonance studies. From these studies it has been shown that the relative spin density for the unpaired electron follows the sequence O > C-4 > > C-2, C-6 > C-1, C-3, C-5. This is an observation which is supported by the experimentally observed preference for phenoxy

radicals to undergo coupling reactions predominantly *para* to the oxo substituent, though the particular products obtained for a given reaction are dependent upon both, the nature and position of substituents on the phenol, and the reaction conditions[95].

An analogous radical cation intermediate has been proposed for the formation of quinone bis acetals by the anodic oxidation of 1,4-dimethoxybenzene, Figure 33[96, 97].

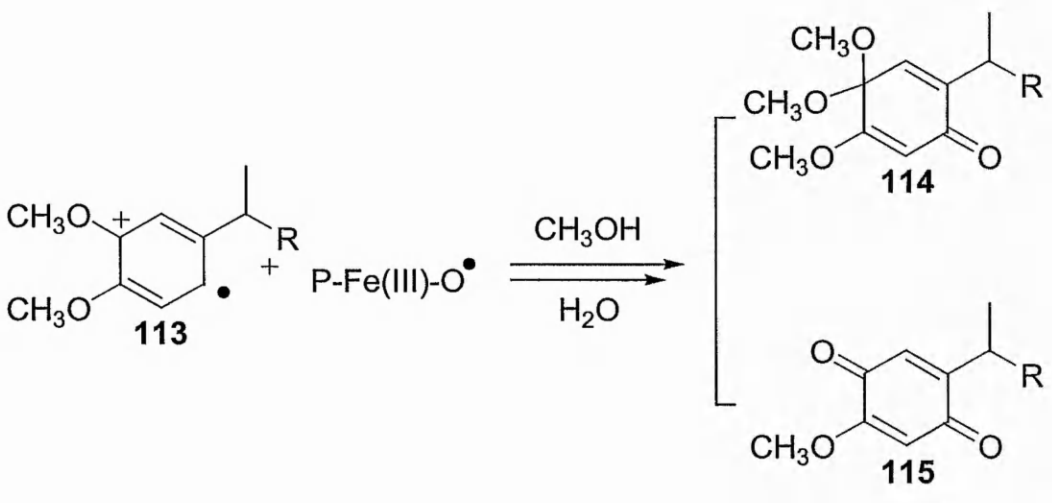
Figure 33.



The sequence is described by two electrochemical steps occurring at the anode followed by the combination of the methoxy radical with the radical cation and subsequent polar addition of methanol, an EECrCp mechanism.

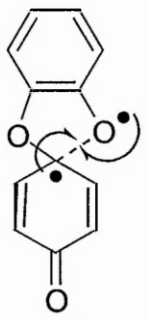
Similary, from an investigation into the biomimetic metalloporphyrin catalysed oxidation of an insect selective cytochrome P450 inhibitor, Verbutin[98], a radical cation intermediate, **113** Figure 34, was proposed to account for the formation of quinone monoacetal **114** and quinone **115** by its combination with a ferryloxy porphyrin and subsequent polar addition of either methanol or water respectively.

Figure 34.

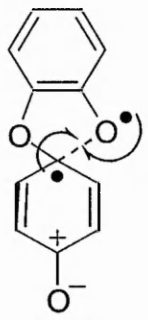


Thus it is conceivable that formation of the quinone monoacetal **104** with manganese dioxide could occur either by the intramolecular radical-radical combination **116** and / or the intramolecular radical-radical cation combination **117**, Figure 35, though the former is more probable in neutral non-polar solvents.

Figure 35.



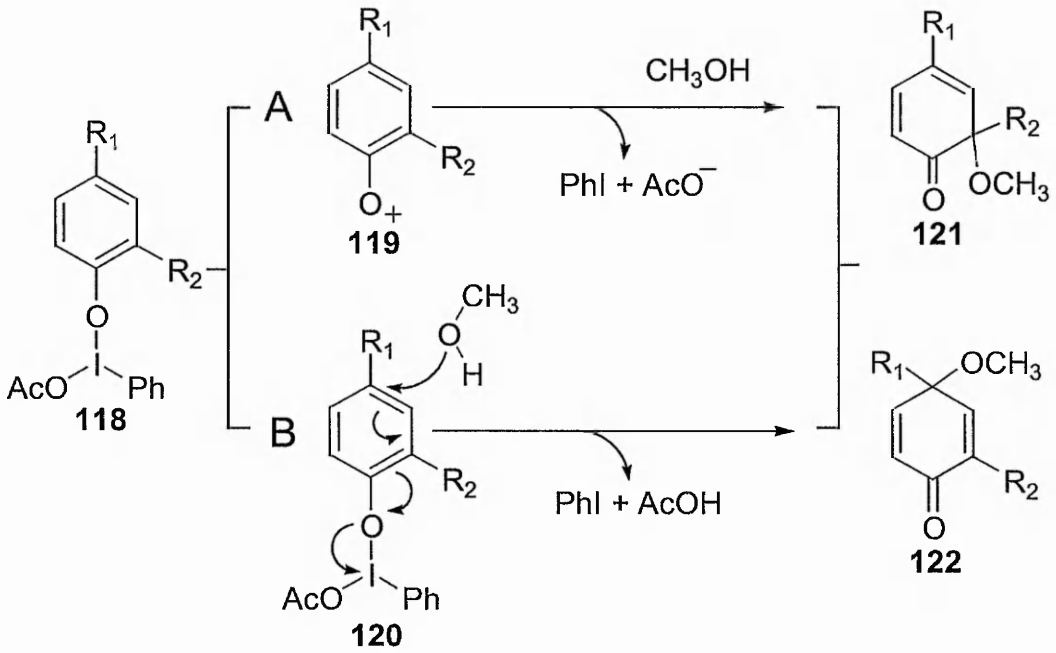
116



117

In contrast, two mechanistic pathways have recently been proposed for the oxidation of phenols with phenyiodonium(III) reagents from a common intermediate[99], Figure 36. Path A requires the dissociation of intermediate **118** to give a solvated phenoxenium ion which undergoes a polar addition with methanol, whereas path B requires the direct attack upon intermediate **118** by methanol and follows a concerted mechanism.

Figure 36.

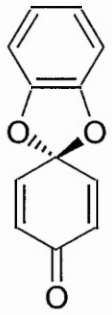


Subsequently, close agreement between the experimentally observed patterns of substitution and those predicted by the calculated charge distributions and LUMO coefficients for the respective phenoxenium ions were found, and it was also noted that no chiral induction was attained when a chiral phenyliodonium oxidant was used. From these results it was concluded that phenoxenium ions are the most probable intermediates for the oxidation of phenols with phenyliodosyl diacetate, thereby favouring the electronically controlled pathway A[100].

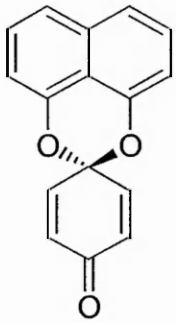
6.3. Preparation of spiro[benzo[d][1,3]dioxole-2,1′-(2′,5′-cyclohexadiene)]-4′-one.

Prior to commencing the synthesis of the quinone monoacetal **123**, Figure 37, the preparation of the known quinone monoacetal **104** was undertaken with the primary aim to re-investigate and identify optimal conditions for the oxidative cyclisation of 2,4′-dihydroxydiphenyl ether. The monoacetal **104** was also required for the subsequent investigation into the cycloaddition reaction and as an intermediate for the construction of a novel analogue of palmarumycin CP_1.

Figure 37.



104



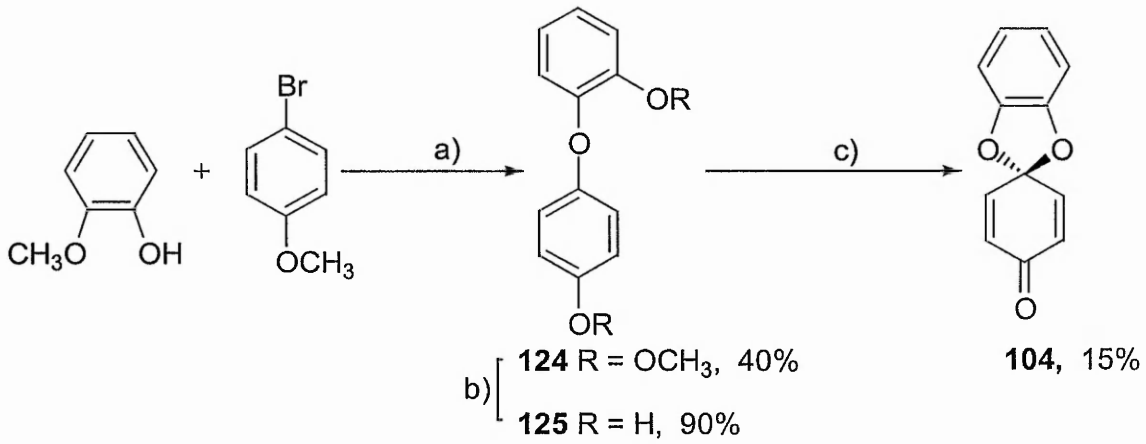
123

The quinone monoacetal **104** was originally prepared in 1969 by Coutts et al[70] by the methodology illustrated in Scheme 28.

An Ullmann ether synthesis procedure was employed for the copper promoted coupling of 2-methoxyphenol with *para*-bromoanisole, and the subsequent Lewis acid mediated demethylation of **124** afforded the dihydroxy diaryl ether **125**. Treatment of a 0.08M solution of **125** in refluxing benzene with manganese dioxide originally afforded quinone monoacetal **104** in 15% yield with 1,4-benzoquinone as the major product and polymeric

material. However, it was subsequently found that **104** could be consistently obtained in 40% yield by the application of a Soxhlet procedure, which had the added advantage of reducing the volume of toxic solvent required.

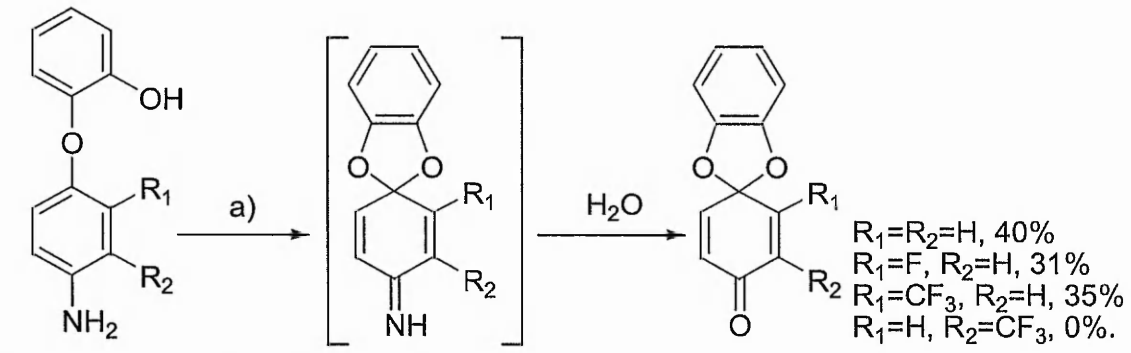
Scheme 28.



a) Copper bronze, pyridine, K_2CO_3, 150°C. b) $AlCl_3$, PhH, reflux. c) 5 eq. MnO_2, PhH, reflux.

More recently **104** has been prepared in comparable yield by the oxidation of 2-(4-aminophenoxy)phenol with manganese dioxide in an analogous manner[93]. The measured water content of two separate sources of oxidant was found to be 25% and was proposed to be sufficient for the hydrolysis of the intermediate quinone-imine. It was also observed that the oxidative cyclisation of the hydroxy anilines was sensitive to the nature and position of substituents. In particular, no quinone monoacetal was obtained when an electron withdrawing substituent *meta* to the ether linkage was present, Scheme 29.

Scheme 29.



a) 5eq. MnO_2, PhH, Soxhlet, reflux.

In initial experiments, quantities of **104** were obtained by the oxidation of **125** with manganese dioxide by the Soxhlet procedure. Best results were obtained when the commercial manganese dioxide was azeotroped with benzene for two hours in a Dean and Stark apparatus, which was then replaced by a Sohxlet extractor containing **125**.

In considering alternative methods for the oxidative cyclisation of **125** the impressive results obtained for the oxidation of *para* alkoxyphenols with hypervalent iodine reagents[85, 86, 87, 89] merited further investigation. The results obtained for the oxidation of **125** with PIDA are summarised in Table 10. In all cases 1.1 eq of PIDA dissolved in the minimum amount of acetonitrile or dichloromethane was added slowly to a solution of **125**.

Table 10.

Entry	Conc. Of **125**	Solvent	Base	% Yield of **104**
1	0.2M	2,2,2-trifluroethanol	-	25
2	0.2M	2,2,2-trichloroethanol	-	27
3	0.07M	2,2,2-trichloroethanol	-	24
4	0.02M	CH_2Cl_2	Li_2CO_3	42

Although intramolecular reactions are in general favoured by a dilute concentration of the solute it was considered uneconomical to adopt this technique for the oxidation of **125** in trifluoroethanol due to the expense of the solvent. Interestingly comparable yields of the quinone monoacetal **104** were obtained when the less expensive, but incredibly viscous, trichloroethanol was employed as a substitute solvent, both when the solute concentration was 20% and 7%. These disappointing results were attributed to a high concentration of the solute in the case of trifluoroethanol, leading to polymeric material, and the comparatively insoluble nature of **125** in trichloroethanol. Subsequently a more respectable yield of **104** was obtained when a combination of dichloromethane and lithium carbonate with a 0.02M concentration of **125** was employed.

In all cases monitoring of the oxidations by t.l.c. indicated the formation of a three component mixture and polymeric base-line material. In ascending order of polarity the first and major component was the quinone monoacetal **104** followed by 1,4-

benzoquinone as a trace impurity, whilst the third, a major impurity, was found to be a complex mixture of aromatic products by analysis of the ^{1}H N.M.R. spectrum. In conclusion, although the yield of **104** was not improved by the application of phenyliodosyl diacetate as the oxidant the investigation resulted in the successful identification of an alternative procedure that is as efficient as manganese dioxide for the oxidative cyclisation of **125**.

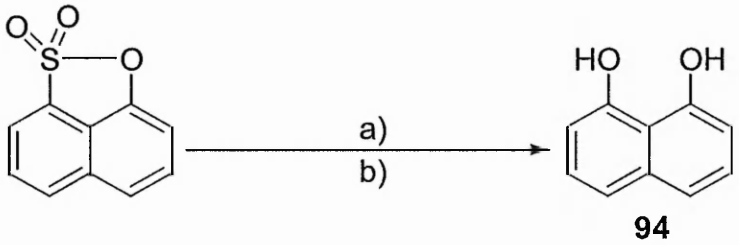
6.4. Preparation of Quinone Monoacetals Derived from 1,8-dihyroxynaphthalene.

It was anticipated that the naphthyl quinone monoacetal **123** would be obtained by the chemical oxidation, with either manganese dioxide or PIDA, of a dihydroxy intermediate in an analogous manner described for the preparation of **104**. However, as neither 1,8-dihydroxynaphthalene nor its monomethyl ether are commercially available, and would therefore be in limited supply, an investigation into a more efficient procedure for the preparation of the diaryl ether was required.

6.4.1. Preparation of 1,8-dihydroxynaphthalene 94.

1,8-Dihydroxynaphthalene **94** is usually obtained by the fusion of potassium hydroxide with 1,8-naphthosultone followed by acidification, as originally described in 1888 by Erdmann[101], Scheme 30.

Scheme 30.



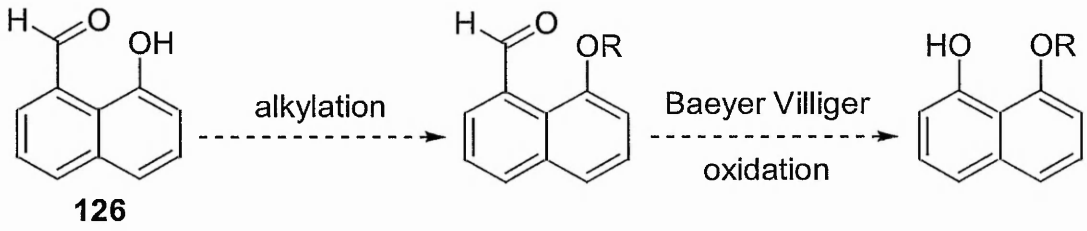
94

a) KOH, >200°C. b) Dilute HCl.

However, repeated attempts to prepare 1,8-dihydroxynaphthalene **94** by this method consistently afforded polymeric material. Thus, in view of these disappointing results an alternative synthetic strategy for the preparation of **94** was required.

As the subsequent diaryl ether synthesis would require a mono protected derivative of 1,8-dihydroxynaphthalene it was reasoned that 1-hydroxy-8-naphthaldehyde **126** could be employed as a suitable synthon, Scheme 31.

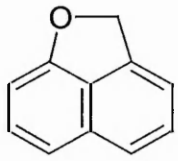
Scheme 31.



126

A search of the literature revealed that 1-hydroxy-8-naphthaldehyde **126** had originally been prepared by the oxidation of 2H-naphtho[1,8-bc]furan, Figure 38, with lead tetra-acetate[102].

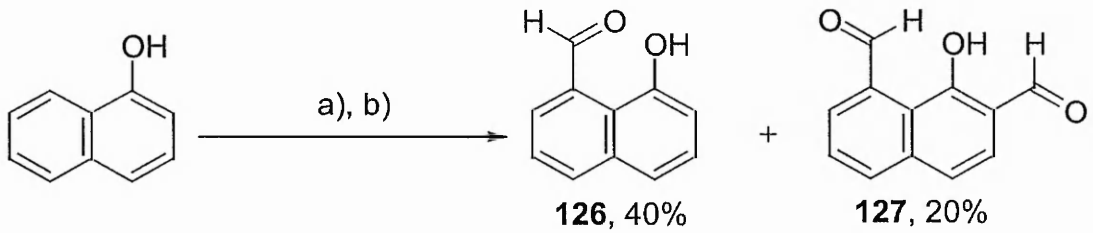
Figure 38.



2H-naphtho[1,8-bc]furan.

However, a more direct approach, subsequently described by Saá et al in 1988[103], was achieved by the *peri* lithiation of 1-naphthol, quenching with dimethylformamide to afford 1-hydroxy-8-naphthaldehyde **126** and 1-hydroxynaphthalene-2,8-dicarboxaldehyde **127** in a ratio of 2:1 respectively, Scheme 32.

Scheme 32.



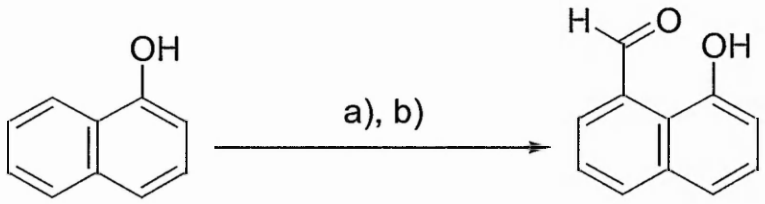
126, 40% **127**, 20%

a) 1.25 eq. 2M ^{t}BuLi, tetrahydropyran, 50°C to r.t., 4h. b) 0°C, dimethyl-formamide, 3h.

More recently the peri lithiation of polyhydric phenolic compounds, with 3 eq. of *n*-butyllithium per hydroxyl unit with TMEDA as the solvent, has been reported by Saá et al[104]. It was also reported that under the improved reaction conditions 1-naphthol was observed to undergo *peri* lithiation exclusively.

Using these conditions, 1-hydroxy-8-naphthaldehyde **126** was reliably obtained in excellent yield and on a multigram scale, Scheme 33.

Scheme 33.

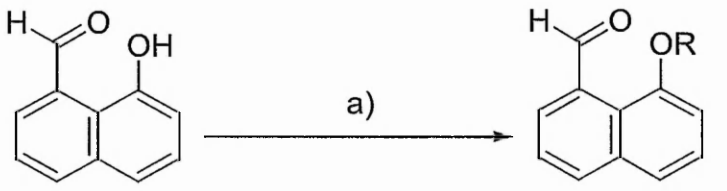


126

a) 3 eq. 2M *n*-butyllithium, 10 eq. TMEDA, r.t., sonicate 2h. b) -40°C, DMF, 1h., 85%.

However, repeated attempts to alkylate the hydroxynaphthaldehyde **126** with either methyl iodide or benzyl bromide afforded the corresponding ethers, **128** and **129** Scheme 34, in poor yield, which discouraged further investigation of this strategy.

Scheme 34.



126

128, R = CH_3, 15%.
129, R = CH_2Ph, 17%.

a) Methyl iodide or benzyl bromide, 2 eq. K_2CO_3, 2-butanone, r.t.

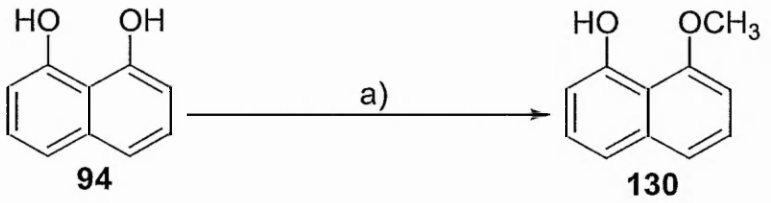
These results prompted the re-investigation of the preparation of 1,8-dihydroxy-naphthalene from the fusion of potassium hydroxide with 1,8-naphthosultone, and by

adopting the method recently described by Taylor et al[66], 1,8-dihydroxynaphthalene was successfully prepared in 89% yield.

6.4.2 Preparation of 1-methoxy-8-naphthol 130.

The methylation of diol **94** with dimethyl sulfate in aqueous alkali has been reported to afford the monomethyl ether and smaller quantities of the dimethylated product[105]. The authors, Buu-Hoï and Lavit, proposed that the monomethyl ether was preferentially obtained as a result of its cryptophenolic nature, thereby being insoluble in aqueous alkali and evading further methylation. In contrast, repeated attempts to reproduce this procedure during the current investigation resulted in the isolation of the dimethyl ether as the sole product. Subsequently, 1-methoxy-8-naphthol **130** was obtained in 82% yield from a statistical phase transfer alkylation procedure[106], Scheme 35.

Scheme 35.



a) 10% w/w $NaOH_{(aq)}$, CH_2Cl_2, *n*-$^tBu_4N^+Br^-$, CH_3I, 37°C, 20h., 82%.

6.4.3. Attempted Preparation of 1-methoxy-8(4-methoxyphenoxy)naphthalene.

The copper catalysed substitution of an aromatic halide by phenols has provided a general method for the preparation of diaryl ethers since its introduction by Ullmann[107] and has been the subject of several reviews [108, 109]. Typically the Ullmann ether synthesis requires prolonged heating at temperatures between 120 to 200°C in polar and often toxic solvents and / or co-solvents such as pyridine, dimethylformamide, or collidine. Variable yields of the diaryl ethers are obtained, especially with substituted reactants, and the aryl halide is often subject to competitive reductive dehalogenation and homocoupling.

A variety of copper species in oxidation states ranging from Cu(0) to Cu(III) have been observed to promote the reaction though Cu(I) is generally accepted to be the active

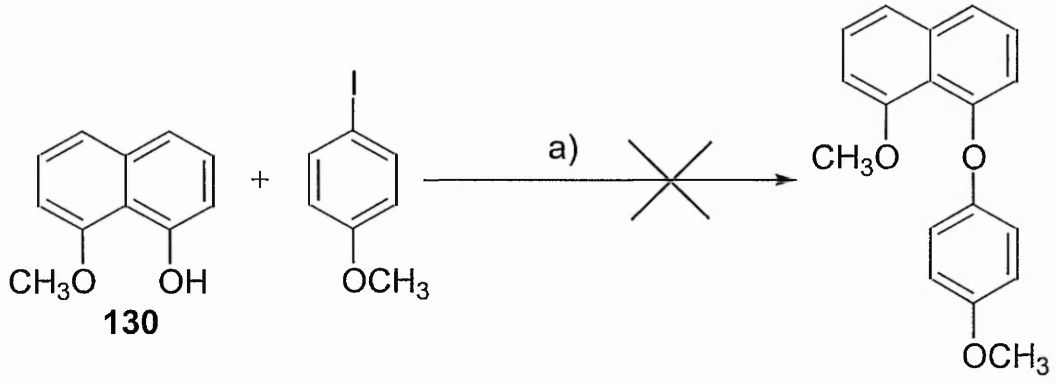
species. The reaction is subject to dramatic solvent effects and is generally promoted by those that contain a heteroatom. It has been postulated that the co-ordination of the copper catalyst by the lone pairs of the heteroatom of the solvent aids its dissolution and complex formation with the reactants and can be regarded as a co-catalyst[110, 111]. This observation has been supported by a more recent investigation into the substitution of bromobenzene in a concentrated solution of sodium methoxide where the cuprate intermediate $Na^+[Cu(OCH_3)_2]^-$ was proposed to be the active catalytic species[112].

More recently improved yields and reaction conditions for the copper catalysed synthesis of diaryl ethers have been reported by the application of ultrasound[113] and phosphazene P_4-^{t}Bu base[114]. Furthermore, the arylation of phenols with arylboronic acids in the presence of $Cu(OAc)_2$ has also been reported to be a particularly mild method for the preparation diaryl ethers[115, 116].

A particularly general and efficient procedure that employs cesium carbonate in toluene, with 5mol% of ethyl acetate, in the presence of catalytic quantities of copper catalyts such as CuCl, CuBr, CuI, $CuBr_2$, or $CuSO_4$ has been reported by Buchwald et al[117]. Although it was found that $(CuOTf)_2$·benzene complex gave slightly accelerated reaction rates cesium carbonate was identified as the key element responsible for the improved reaction conditions which were suitable for the coupling of unactivated aryl halides with *ortho* substituted phenols.

In view of both the commercial availability of the catalyst and base, along with the general applicability of the Ullmann procedure described by Buchwald, the method was selected for an investigation into the coupling of *para*-iodoanisole and 1-methoxy-8-naphthol **130**, Scheme 36. However, from an initial attempt to reproduce these results, with $(CuOTf)_2$·benzene complex as the catalyst, no detectable reaction was observed after 16 hours in refluxing toluene. Although this disappointing result could be attributed to a number of steric and / or reactivity factors, the subsequent comparison of the commercially obtained catalyst with the literature data[118] revealed a discrepancy in its appearance. As a result a catalytic quantity of CuBr was added to the original mixture and refluxed for a further 6 hours. Examination of the reaction mixture by t.l.c. indicated the formation of a complex mixture of products streaking from the baseline and the experiment was abandoned.

Scheme 36.



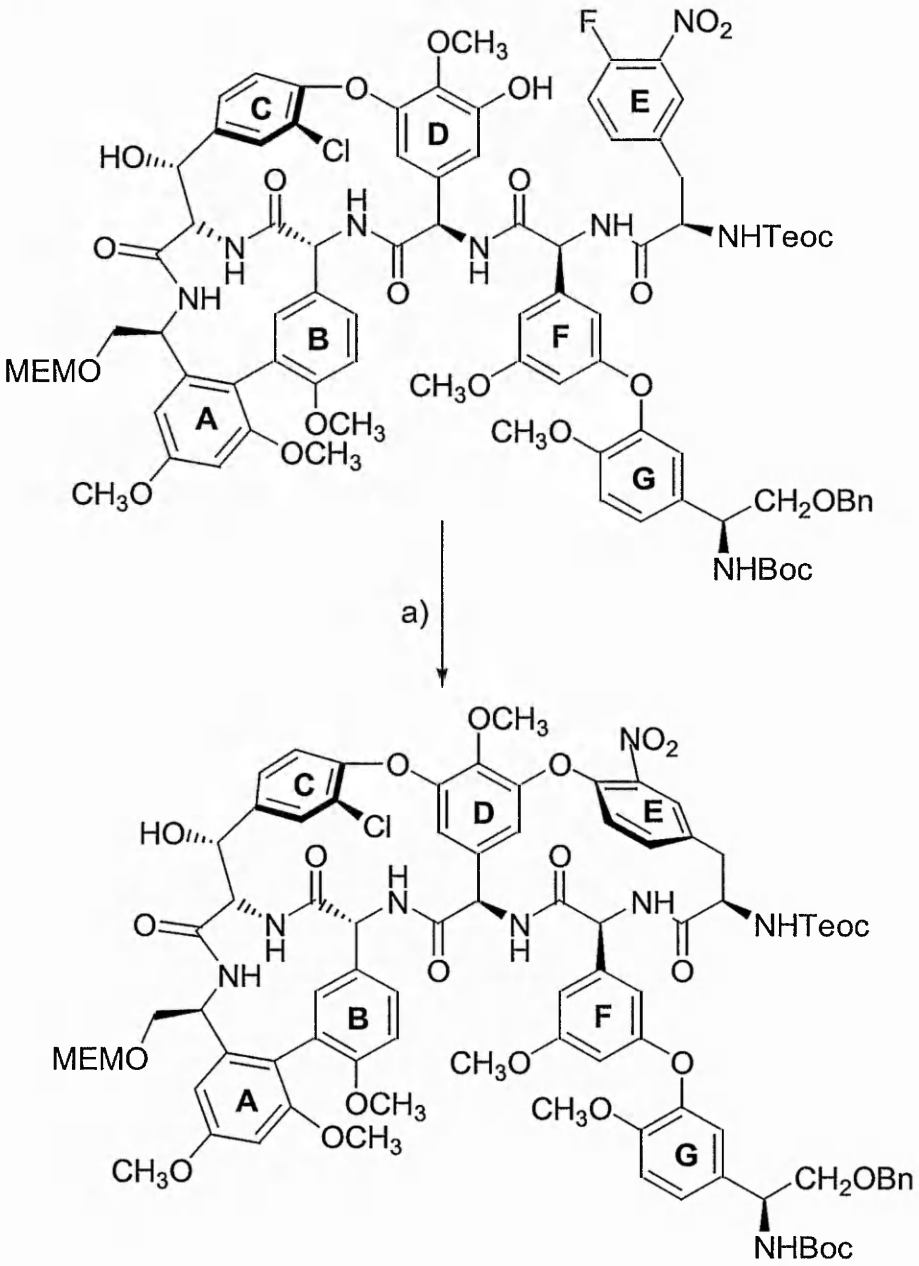
a) 0.2 eq. $(CuOTf)_2$·benzene, 0.05 eq. ethyl acetate, toluene, reflux, 16h.

Furthermore, analogous results were obtained when a mixture of *para*-iodoanisole, naphthol **130**, and cesium carbonate in dimethylformamide were heated at 120^0C for 2 hours in the presence of a catalytic quantity of CuO. Though no direct evidence was obtained, and the reactions had been conducted under an atmosphere of nitrogen, it was suspected that the conditions employed were sufficient for the oxidative decomposition of naphthol **130**. This assumption appeared even more probable in view of the reported observation that 1,8-dihydroxynaphthalene **94** is prone to rapid oxidative polymerisation when its solutions are not carefully protected from air[106]. Before continuing the investigation of the Ullmann approach it appeared prudent to explore the potential for the preparation of the diaryl ether moiety by an uncatalysed process.

6.4.4. Nucleophilic Aromatic Substitution (S_NAr).

The formation of the diaryl ether linkages of the vancomycin family of natural products have recently been achieved in excellent yield by a nitroaromatic based nucleophilic aromatic substitution (S_NAr) procedure[119, 120, 121]. These are particularly impressive results in view of the sensitivity and complexity of the vancomycin structure and can be exemplified by the formation of the 16-membered DE diaryl ether ring by a macrocyclic S_NAr of an *ortho*-fluoronitroaromatic, Scheme 37, during the recent total synthesis of the teicoplanin aglycon described by Boger et al[122].

Scheme 37.

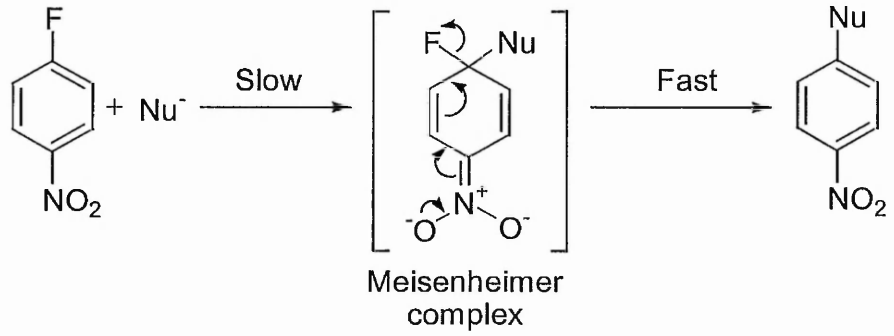


a) CsF, DMSO, 25°C, 80%.

The preparation of diaryl ethers by the S_NAr procedure is characterised by the addition of a phenolate to an electron deficient aromatic electrophile. Efficient aromatic electrophiles typically contain one or more electron-withdrawing group such as NO_2, CF_3, CN, CHO, CO_2H, *ortho* and / or *para* to a leaving group. The reactivity of the leaving group is generally observed to follow the sequence F > NO_2 > OTs > SOPh > Cl, Br, I > N_3, NR_3^+>OAr, OR, SR, NH_2[123], which contrasts with the order observed for the S_N1 and S_N2 mechanisms where fluorine is a poor leaving group. This has been explained by a

two step mechanism for the substitution reaction via a resonance stabilised intermediate known as a Meisenheimer complex, Figure 39.

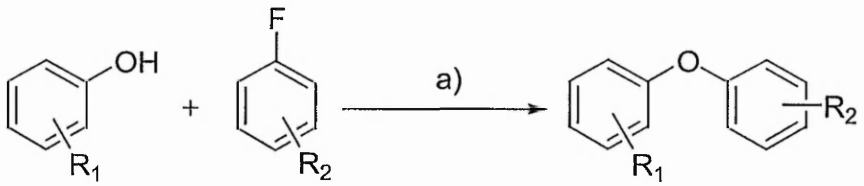
Figure 39.



Thus, the first step is rate determining and is promoted by groups that are able to generate a more electropositive carbon at the site of substitution[124].

The practical utility of the S_NAr reaction has recently been expanded to include the preparation of diaryl ethers from aromatic nucleophiles and electrophiles possessing unfavourable functionality and substitution patterns by the introduction of potassium fluoride-alumina complex ($KF.Al_2O_3$) and catalytic quantities of 18-crown-6 in acetonitrile or dimethyl sulfoxide[125]. In particular, dimethyl sulfoxide at a temperature of 140°C was observed to promote the coupling of electronically unfavourable 3-chlorobenzonitrile with 3-methoxyphenol to form the corresponding diaryl ether in 66% yield. The range of electron-withdrawing groups was also shown to include nitro, cyano, formyl, acetyl, ester, amide, and even aryl, Table 11.

Table 11[125].



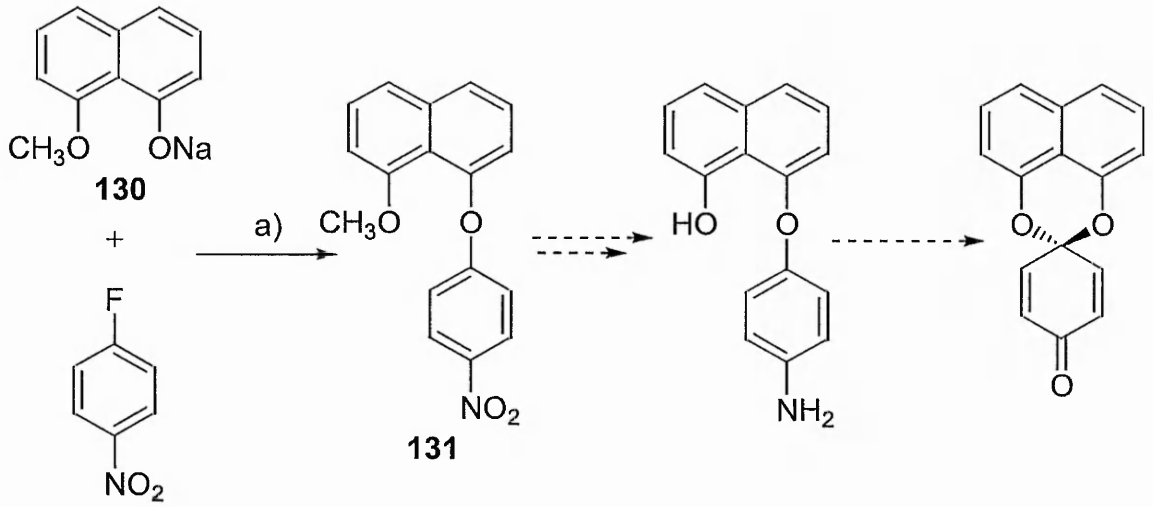
a) $KF.Al_2O_3$, 18-crown-6, DMSO, 140°C.

R_1	H	H	H	3-OCH_3	3-OCH_3
R_2	CHO	4-CO_2Et	2-$CONH_2$	4-CH_3CO_2	4-Ph
Time (h.)	16	124	48	16	172
% Yield	81	82	66	70	19

The adoption of the S_NAr methodology for the current investigation required the judicious selection of an appropriately functionalised electrophile. Essentially a fluorobenzene substituted with a *para* electron-withdrawing group that would have to be able to both promote the substitution reaction and be amenable to its subsequent transformation into the ketone function of the quinone monoacetal **123**. Initial considerations focused upon the aldehyde group as an indirect method for the preparation of a phenol by means of the Bayer-Villiger oxidation. However, as quinone monoacetals have also been obtained from the the oxidation of *para*-(aminophenoxy)phenols, Table 9 entry 9, the potential of a more facile route by way of the nitro diaryl ether was realised.

Preference for *para* fluoronitrobenzene as the electrophile, over the corresponding benzaldehyde, was primarily given on the basis that the former are known to be the most efficient electrophiles for the S_NAr reaction. Also, in view of the analogous yields of **104** obtained from the oxidative cyclisation of either the respective phenol or aniline intermediates, no significant advantage was envisaged to be achieved from the preparation of the dihydric diaryl ether intermediate which would require the Bayer-Villiger oxidation of the aldehyde as an additional step. Thus, an investigation into the preparation of the naphthyl quinone monoacetal **123** by the oxidative cyclisation of the *para* (aminophenoxy)naphthol was initiated as illustrated in Figure 40.

Figure 40.

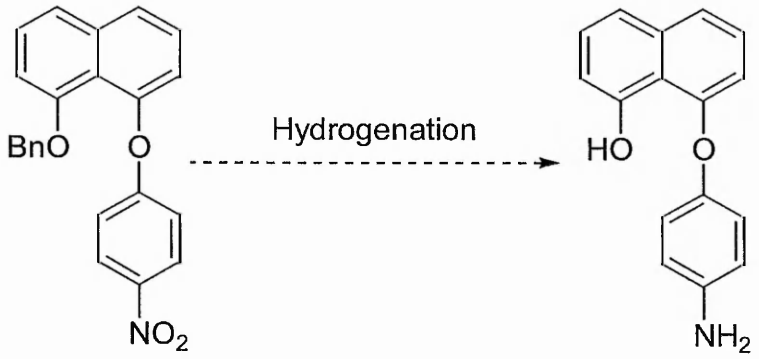


a) DMSO, 80°C.

Initially from the addition of *para* fluoronitrobenzene to a degassed solution of sodium 8-methoxy 1-naphthoate in dimethyl sulfoxide at room temperature, followed by heating to 80°C for 3h. a 53% yield of the nitro diaryl **131** ether was obtained. However, analysis of the ^{1}H N.M.R. spectrum of the crude reaction mixture revealed the presence of an aromatic ethyl ether impurity. It was concluded that residual sodium ethoxide used to prepare the sodium salt of naphthol **130** had competitively reacted with the electrophile, a situation that was quickly resolved by the preparation of the salt with sodium hydride. Thus, the nitro diaryl ether **131** was subsequently obtained in 83% yield and established an efficient general methodology for the preparation of the diaryl ether moiety.

As the conditions typically employed for the deprotection of methyl ethers are frequently harsh[126] combined with the relative sensitivity of electron rich anilines to undergo oxidative degradation it was considered prudent to attempt to cleave the methyl ether prior to the reduction of the nitro group. However, from the addition of boron tribromide to a solution of **131** at -70°C in dichloromethane and then allowing it to attain room temperature the formation of a complex mixture of products was indicated by t.l.c. Isolation of the major component and subsequent analysis of its ^{1}H N.M.R. spectrum revealed the loss of the methyl ether signal at δ 3.59 ppm and an aromatic region which suggested the presence of more than one compound. It was concluded that the potential of the nitrophenoxy moiety to behave as a leaving group combined with the sensitivity of the nitro functionality towards Lewis acids precluded further investigation of this approach. However, it was quickly realised that a more elegant approach could be attained by use of the benzyl ether protecting group which would enable the generation of both the hydroxy and aniline functional groups in a single step by catalytic hydrogenation, Figure 41.

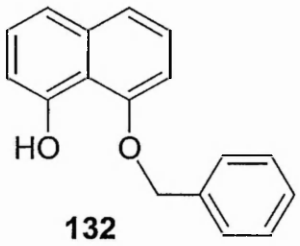
Figure 41.



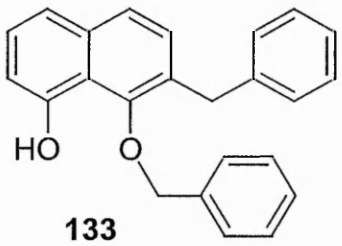
However, initial attempts to prepare the novel 8-benzyloxy-1-naphthol **132**, Figure 42, by means of the previously described phase transfer alkylation procedure, with benzyl bromide, afforded a two component mixture by t.l.c. Both products were indicated to be phenolic by a positive reaction with a neutral solution of ferric chloride and although reasonable separation of the two components was observed by t.l.c, attempts to separate them by chromatography resulted in their co-elution. From the subsequent analysis of the ^{1}H N.M.R. spectrum two distinct benzylic signals at δ 5.18ppm and δ 4.09ppm in conjunction with a complex aromatic region and two exchangeable acidic protons at δ 9.37ppm and δ 9.62ppm were observed, which indicated a mixture of *O*- and *C*-benzylated naphthols repectively. Reduced pressure kugelrohr distillation of the mixture gave a black residue consisting of degradation products and a distillate consisting of both components. Trituration of the distillate with a mixture of methanol and cyclohexane gave a white precipitate, in low yield, that possessed ^{1}H and ^{13}C N.M.R spectra that were consistent with **132**.

Under alternative conditions often employed for the Williamson ether synthesis, 2-butanone, potassium carbonate, at room temperature for 18 hours, and the discovery of an improved chromatographic procedure, the benzyl ether **132** was subsequently obtained in 64% yield. The improved separation also afforded the less polar impurity as a viscous oil which possessed ^{1}H and ^{13}C N.M.R. spectra that were consistent with the *O*- and *C*-dibenzyl naphthol **133**, Figure 42 .

Figure 42.



132



133

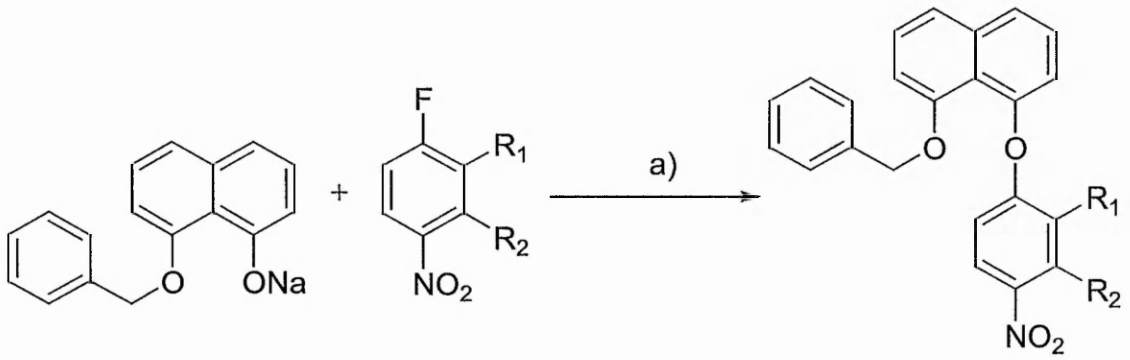
The formation of **133** is not too surprising in view of the relative stability of the benzyl carbonium ion under the polar reaction conditions and the electron rich nature of dihydroxynaphthalenes, and although electrophilic scavengers such as anisole or thioanisole could have been employed to prevent its formation it was subsequently

observed that the formation of the benzyl ether **132** is complete after 6 hours with an isolated yield of 90%.

In an analogous manner to that previously described for the preparation of **131** the nitro diaryl ethers **134**, **135**, and **136**, , were prepared from the coupling of the appropriate *para*-fluoronitrobenzenes with the sodium salt of 8-benzyloxy-1-naphthol **132** and the results are summarised in Table 12.

4-Fluoro-2-methoxynitrobenzene **137** was obtained by the alkylation of commercial 5-fluoro-2-nitrophenol with methyl iodide and potassium carbonate in 2-butanone.

Table 12.



a) DMSO.

Compound	R_1	R_2	Reaction Temp. / Time	% Yield
134	H	H	60°C / 2 h.	90
135	CF_3	H	20°C / 3 h.	95
136	H	OCH_3	60°C / 2.5h.	91

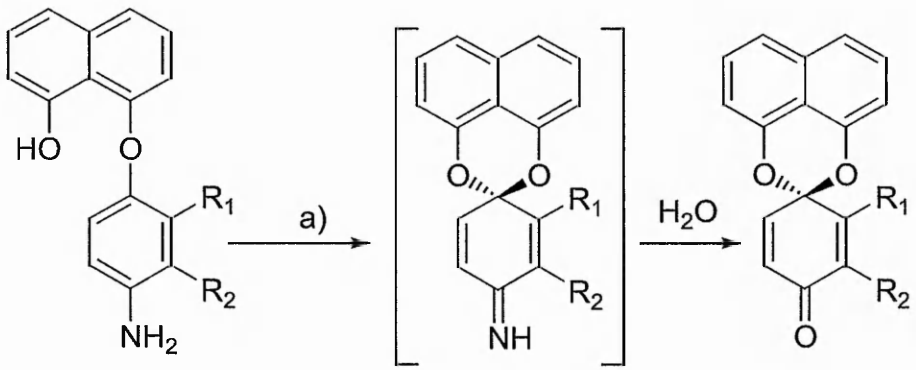
In view of the sterically congested nature of naphthol **133** the impressive yields of the nitro diaryl ethers further underlined the utility of the S_NAr methodology for the efficient preparation of the diaryl ether moiety. Although a detailed investigation of various substitution patterns within the fluoronitrobenzenes was not performed the substitution reaction occurred smoothly at room temperature when the electrophile was further activated with a trifluromethyl group *ortho* to the fluorine. Also the incorporation of an electron-donating group *meta* to the fluorine did not have a noticeable deactivating effect upon the formation of the diaryl ether **136**.

Catalytic hydrogenation of the nitro diaryl ethers with 10% Pd-C suspended in a mixture of ethyl acetate and ethanol under an atmospheric pressure of hydrogen afforded the corresponding *para*-(aminophenoxy)naphthols **138**, **139**, and **140** in near quantitative yield. Although the naphthyloxy anilines could be chromatographed for optimal purity, oxidative degradation of the compounds was observed by the formation of black oils within hours if not kept cold under an atmosphere of nitrogen, and so in general they were immediately subjected to oxidative cyclisation upon isolation without further purification.

6.4.5. Oxidative Cyclisation of *para*-(aminophenoxy)naphthols.

Based largely upon the results obtained from previous investigations at The Nottingham Trent University[93] the oxidative cyclisation was achieved by refluxing a 0.02M solution of the *para*-(aminophenoxy)naphthol in benzene with five equivalents of 85% activated manganese dioxide under an atmosphere of nitrogen, Table 13. As residual water in the commercial manganese dioxide was required for the *in situ* hydrolysis of the intermediate quinone-imines the oxidant was not azeotroped with the solvent prior to the addition of the *para*-(aminophenoxy)naphthols as previously described for the oxidation of the dihydroxy diaryl ether **125**.

Table 13.



a) 5 eq. 85% MnO_2, PhH, reflux.

Quinone monoacetal	R_1	R_2	Time	% Yield
123	H	H	2h.	86
141	CF_3	H	5.5h.	25
142	H	OCH_3	3.5h.	58

In agreement with earlier observations the oxidations were observed to be sensitive to the substituents on the aniline component, though an electron-donating group *meta* to the ether linkage can be seen to exert less of an effect than an *ortho* electron-withdrawing group. In comparison of the yields for the unsubstituted quinone monoacetals **104** and **123**, 40% and 86% respectively, it is evident that the formation of a quinone monoacetal formally derived from 1,8-dihydroxynaphthalene is clearly favoured over one derived from catechol.

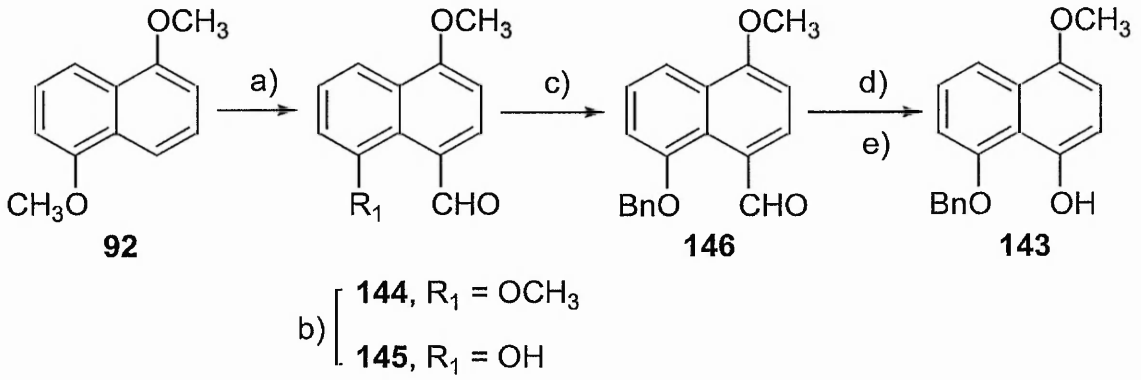
6.5. The Direct Preparation of Palmarumycin CP_1 Analogues.

The combination of the successful identification of an efficient methodology for the preparation of naphthyl quinone monoacetals and the availability of 1-fluoro-4-nitronaphthalene[127] prompted an investigation into the direct formation of the palmarumycin skeleton via the corresponding *para*-nitro dinaphthyl ethers.

An alternative electrophile, 1-fluoro-4-naphthaldehyde, has previously been shown to undergo efficient and regioselective aromatic nucleophilic substitution reactions with oxygen, nitrogen, and sulfur nucleophiles, with the products being subsequently transformed into naphthols by the Baeyer Villiger oxidation of the aldehyde[128]. It is also known that *para*-(hydroxyaryloxy)naphthol, prepared by the Ullmann coupling of 2-methoxyphenol with 1-bromo-4-methoxynaphthalene followed by demethylation, can be oxidised with DDQ to afforded the quinone monoacetal in quantitative yield, Table 9 entry 10[70]. However, as the application of the current nitro-aromatic methodology would eliminate the need for an additional functional group interconversion the coupling of 8-benzyloxy-1-naphthol **132** with 1-fluoro-4-nitronaphthalene was investigated. It was also anticipated that the substitution of naphthol **132** with 8-benzyloxy-4-methoxy-1-naphthol **143** would enable the preparation of a regioisomer of CP_1 and further extend the general utility of the nitro-aromatic methodology.

The preparation of **143** was achieved in six steps from commercial 1,5-dihydroxy-naphthalene **92** by a modification of the original method described by Hart and Mannino[129], Scheme 38.

Scheme 38.



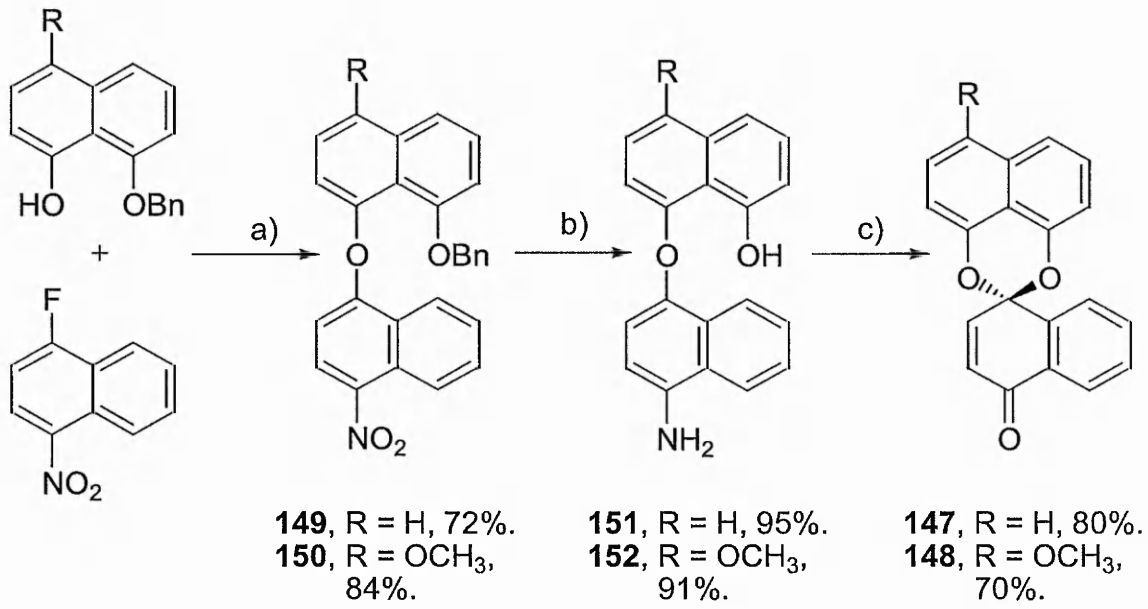
a) DMF, $POCl_3$, $PhCH_3$, 98%. b) BBr_3, CH_2Cl_2, 0°C to r.t., 81%. c) BnBr, K_2CO_3, 2-butanone, 90%. d) *m*-CPBA, $CHCl_3$. e) conc. HCl, EtOH-THF, 70%.

In an analogous manner to that described by Rapoport et al[130] 8-hydroxy-4-methoxy-1-naphthaldehyde was prepared by a Vilsmeier-Haack formylation of 1,5-dimethoxy-naphthalene followed by a regioselective demethylation with boron tribromide. Although the methyl ether *para* to the aldehyde is in the less sterically congested environment co-ordination of the Lewis acid to the carbonyl function of the aldehyde was proposed to account for the remarkable selectivity.

In contrast to the previously described problems encountered with the benzylation of 1,8-dihydroxynaphthalene, formation of an *O*- and *C*- dibenzyl impurity was not observed with the benzylation of naphthol **145**, which is probably due to a combination of the deactivating effect of the aldehyde substituent and the lack of a second oxy anion. In view of the sensitivity of dihydroxy naphthalenes in basic solutions to undergo oxidative degradation the original method for the transformation of **146** to **143**, which involved the basic hydrolysis of the intermediate formate ester[129], was changed to an acidic procedure which afforded naphthol **143** in comparable yield.

As illustrated in Scheme 39 the *para* nitro dinaphthyl ethers were obtained in good yield and were successfully employed in the efficient preparation of a deoxy analogue of palmarumycin CP_1 **147** and a regioisomer of methoxy palmarumycin CP_1 **148**.

Scheme 39.



a) DMSO, 0°C to r.t. b) 10% Pd-C, EtOAc-EtOH, 1 atm. $H_{2(g)}$, r.t. c) 5 eq MnO_2, PhH, reflux.

In considering the application of this methodology to the preparation of palmarumycin CP_1 it was quickly realised that this approach would be severely hampered by the inaccessible nature of a suitably substituted electrophile. For example, one of the most suitable electrophiles would be 1-fluoro-5-methoxy-4-nitronaphthalene, or alternatively the respective chloro analogue. Also if the oxidative cyclisation of a dihydroxy intermediate was considered then the aldehyde function could be employed to replace the nitro group as a masked hydroxyl but once again the trisubstituted naphthalenes in both the fluoro and chloro series are difficult to access.

6.6. Introduction to Cycloaddition Chemistry.

With the formation of two new σ-bonds in a single step cycloaddition reactions have found broad application in the preparation of complex molecules since its introduction by Diels and Alder in 1928[131], and the following characteristics of the reaction have been repeatedly observed:

1/ For normal electron demand cycloadditions electron-donating substituents X in the diene accelerate the reaction, and electron-withdrawing substituents Z retard it, whereas, Z groups in the dienophile accelerate the reaction and X groups retard it. As the name suggests, the opposite applies for inverse electron demand cycloadditions.

2/ Cyclic dienes react faster than the corresponding acyclic dienes and dienes fixed into a trans conformation are unreactive.

3/ The cycloaddition of an unsymmetrical diene with an unsymmetrical dienophile generally occurs with a high degree of regioselectivity.

4/ Almost all cycloadditions follow suprafacial bond formation for both diene and dienophile. Thus the stereochemical relationships in 1,4-disubstituted dienes and disubstituted dienophiles are preserved, thereby enabling the prediction of upto four new stereogenic centres.

5/ When the conjugated systems of both diene and dienophile have at least three atoms there are two possible all-suprafacial approaches and thus, two possible products termed *endo* and *exo* arise.

6/ Cycloadditions that have transition structures involving a total number of (4n+2) electrons, such as [4+2], [8+2], and [6+4], are thermally induced. This is analogous to the number of electrons required for an aromatic transition state, while [2+2], [4+4], and [6+6] cycloadditions are almost only found to be induced photochemically.

These observations and the ability to predict which cycloadditions are thermally or photochemically allowed have been rationalised by 'the principal of conservation of orbital symmetry' described by Woodward and Hoffmann[132]. The Woodward-Hoffmann rules are based on the assumption that an orbital in the starting material must feed into an orbital of the same symmetry in the product in order to preserve the elements of symmetry observed for some reactions.

The importance of orbital symmetry was also recognised by Fukui[133], who proposed that the majority of chemical reactions should occur at the position of, and in the direction of,

maximium overlap between the highest occupied molecular orbital (HOMO) of one component and the lowest unoccupied molecular orbital (LUMO) of the other component. These orbitals are collectively known as the frontier orbitals and are responsible for the most significant contribution to the lowering of the transition state energy. The frontier orbital theory has been the subject of several reviews[134].

The effects of substituents on both the diene and dienophile has important consequences for the observed regioselectivities and stereoselectivies of most cycloadditions between unsymmetrical components, and is most clearly seen by considering the sizes of the atomic orbital coefficients that are part of the frontier orbitals. As is the case with HOMO and LUMO energies the orbital coefficients can be obtained experimentally from photoelectron spectroscopy studies[135] or estimated by computational methods[136, 137].

For example, the cycloaddition of 1-methoxybuta-1,3-diene **153** with acrolein **154** has the potential to form a mixture of four isomers, Figure 43, two regioisomers, *ortho* and *meta*, and two stereoisomers for each regioisomer, *endo* and *exo*.

The selectivity for a particular regioisomer can be estimated conventially by identifying the charge distribution of each component, but is more conclusively evident from the analysis of the frontier orbital coefficients[137], Figure 44.

Figure 43.

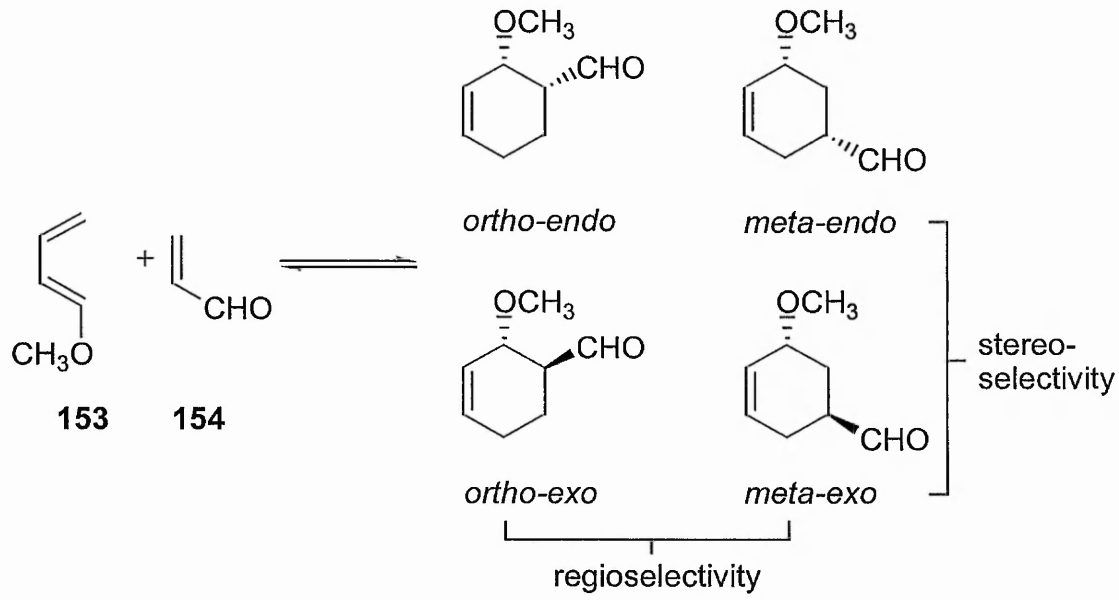
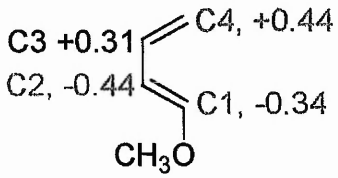
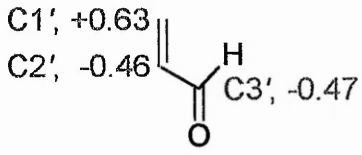


Figure 44.



HOMO orbital coefficients

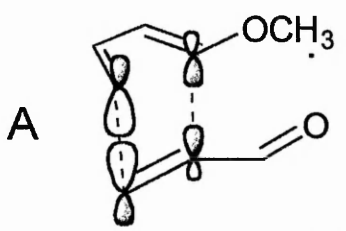


LUMO orbital coefficients

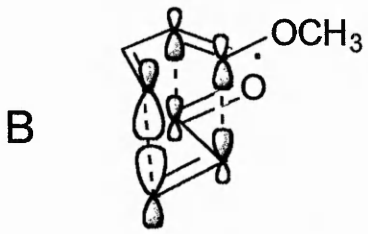
As the largest coefficient of the diene, C-4, will interact most strongly with the largest coefficient of the dienophile, C-1′, the *ortho* adduct is predicted to be the major regioisomer. It is also interesting to note that the respective sizes of the orbital coefficients will be reflected in the transition state, with initial overlap of the frontier orbitals occurring between C-4 of the diene and C-1′ of the dienophile before C-1 and C-2′ respectively. This implies that although bond formation for most cycloadditions are concerted, the extent of orbital overlap in the transition state is often asynchronous. In general, 1,3-butadienes substituted at C-1 with electron-donating substituents favour the *ortho* adduct and, whilst less tightly controlled, substitution at C-2 on the diene favours the *para* adduct.

In contrast the stereoselectivity is frequently less strongly controlled. The *exo* stereoisomer is obtained from a transition state where the electron-withdrawing substituent on the dienophile is furthest away from the conjugated system of the diene, whereas the *endo* stereoisomer is obtained from a transition state where the substituent is underneath the the conjugated system. Thus by comparing the two possible transition states for the cycloaddition of 1-methoxybuta-1,3-diene with acrolein, Figure 45, the *exo* transition state A suffers the least amount of steric repulsion and so should be the major isomer.

Figure 45.



exo- transition state



endo- transition state

However, in many cases the *endo* isomer is obtained as the major product. Only small amounts of the *exo* isomer are obtained unless the mixture is subjected to prolonged heating thereby establishing the thermodynamic equilibrium in its favour by a process of cycloreversion and re-addition. Secondary orbital interactions (SOI) in the transition state have been proposed to account for the high degree of *endo* selectivity[138], the product of kinetic control, observed for many cycloadditions. Futher analysis of the *endo* transition state B Figure 45, in conjunction with the frontier orbital coefficients Figure 44, reveals the potential for a favourable secondary orbital overlap between C-2 of 1-methoxy-buta-1,3-diene and C-3′ of acrolein. Although this interaction does not result in the formation of a new bond it has the potential to contribute to the lowering of the transition state energy.

6.6.1. Cycloadditions at High Pressure.

The general theoretical considerations and practical applications of organic synthesis at high pressure in liquid systems, typically between one and twenty Kbar (0.1 to 2Mpa), have been the subject of several reviews[139, 140, 141].

In summary, the technique is beneficial for reactions:

1) where the molecularities of the reactants decrease in the products;
2) that proceed through a cyclic transition state;
3) that occur by a dipolar transition state;
4) that are inhibited by steric hinderance.

The activation volume of a reaction ΔV^*, the volume change on converting reagents into the transition state, can be expressed by the thermodynamic equation 1.

Equation 1.

$$\Delta V^* = - RT \left(\frac{\delta \ln k}{\delta p} \right)$$

Therefore reactions that possess a negative volume of activation will be accelerated by increased pressure.

In general, cycloadditions exhibit a large increase in reaction rate under conditions of applied pressure. The application of pressure to a cycloaddition may also result in large changes in both the regio- and stereo-selectivity of a reaction as pressure favours the forward reaction over cycloreversion thereby changing thermodynamic control into kinetic control. Cycloadditions are known to have volumes of activation, ΔV^*, similar in magnitude to volumes of reaction, ΔV^{**}, in the range of -35 ± 5 cm^3 mol^{-1}[142]. This is consistent with an ordered single-step cycloaddition with a compact transition structure which has similar volume properties to the product. However, the cycloadditions of maleic anhydride with dienes **A** to **C**, Table 14, have been found to have volumes of activation more negative than the volumes of reaction, whereas the opposite trend was observed with the acetylenic dienophile **D**[143].

Table 14[143].

Entry	Diene (Dienophile)	ΔV^* cm^3 mol^{-1}	ΔV^{**} cm^3 mol^{-1}
A	isoprene (maleic anhydride)	-39.0 ±0.8	-35.9 ±0.9
B	trans-1-methoxy-1,3-butadiene (maleic anhydride)	-43.9±2.0	-30.4 ±0.9
C	1,3-cyclohexadiene (maleic anhydride)	-39.6 ±0.8	-30.3 ±0.9
D	dimethyl acetylene-dicarboxylate (cyclopentadiene)	-30.2 ±0.7	-33.8 ±0.8

ΔV^* is the change in activation volume and ΔV^{**} is the change in reaction volume.

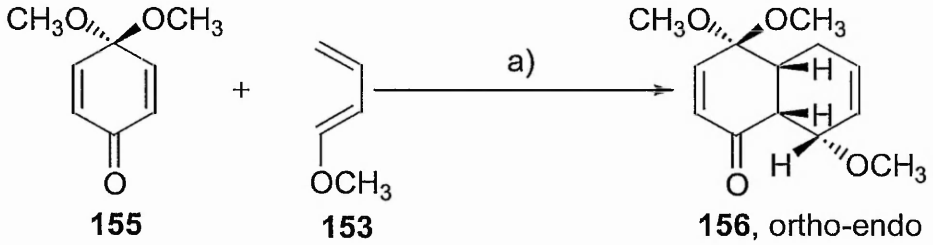
It was also noted that the difference between the partial molar volumes of the *endo* and *exo* adducts, ≈ 0.5 cm^3 mol^{-1}, were too small to account for the more negative volumes of activation of the transition states. Thus, secondary orbital interactions, which cannot occur with dienophile **D** and cyclopentadiene, were proposed to account for the more compact transition structures observed with dienophiles **A** to **C** and maleic anhydride. This postulate was supported by a subsequent investigation into the correlations between the extent of volume contraction and the strength of the secondary orbital interaction in the transition state by Seguchi et al[144]. It was concluded that a large volume contraction due

to the operation of a secondary orbital interaction can be expected in a strongly *endo*-orientating cycloaddition reaction.

6.6.2. Quinone Monoacetals as Dienophiles.

As part of an investigation into the preparation of tetracyclic anthracyclinone derivatives reported by Fariña et al[145] the cycloaddition of 1-methoxybuta-1,3-diene **153** with an unsymmetrical quinone equivalent, 4,4-dimethoxycyclohex-2,5-dien-1-one **155**, was found to afford the *ortho-endo* adduct **156** exclusively, Scheme 39.

Scheme 39.

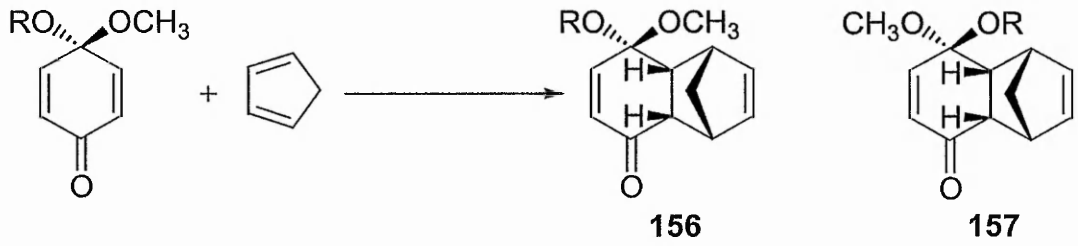


a) PhH, 80°C, 50h., 66%.

The anticipated *ortho* regiochemistry, predicted by consideration of both the electronic and steric properties of the reactants, and the *endo*-stereochemistry of the cycloadduct were determined from the analysis of the ^{1}H N.M.R. spectrum in conjunction with a lanthanide shift reagent and decoupling experiments. Directly comparable results were subsequently obtained by Swenton from a mixture of identical reactants at room temperature after a period of ten days[79].

Centred upon the principal of steric control[146] Fariña et al[145] further demonstrated that additional stereoselectivity at the quaternary carbon of unsymmetrical quinone monoacetals could be achieved during the cycloaddition reactions. It was shown that the larger alkoxy group of a mixed acetal directed the approach of the cyclic diene to the less sterically hindered face of the pro-chiral dienophile, with exclusive retention of the *endo*-stereochemistry, to afford an enriched mixture of stereoisomers, Scheme 40.

Scheme 40.



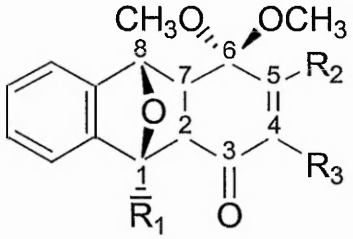
R	Time / hr.	% Yield	Isomer ratio **156** : **157**
ethyl	160	72	1.4 :1
iso-propyl	480	63	5 : 1

However, the ratios were subsequently observed to significantly decrease when the acyclic diene 1-methoxybuta-1,3-diene was used[147].

The results independently obtained by Fariña[145, 147] and Swenton[79] demonstrate the highly selective nature of normal electron demand cycloaddition reactions of quinone monoacetals in preference for the *ortho-endo* regio- and stereo-isomers. However, the cycloadditions typically required long reaction times with high temperatures to afford the adducts in modest yields, which is indicative of the relatively unreactive nature of quinone monoacetals as dienophiles.

In contrast the cycloaddition of a variety of 1-substituted isobenzofurans to quinone monoacetals bearing alpha or beta substituents has been reported to occur in near quantitative yields at room temperature[148]. The cycloadditions were also observed to be highly site-, regio-, and stereo-specific, whereby addition occurred on the unsubstituted side of the dienophile to form the *ortho-endo* adducts illustrated in Figure 46.

Figure 46.

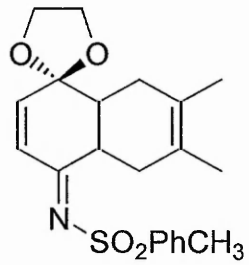


$R_1 = R_2 = R_3 = H$
$R_1 = R_3 = H\ R_2 = OCH_3$
$R_1 = CO_2CH_3\ R_2 = R_3 = H$
$R_1 = CH_3\ R_2 = OCH_3\ R_3 = H$

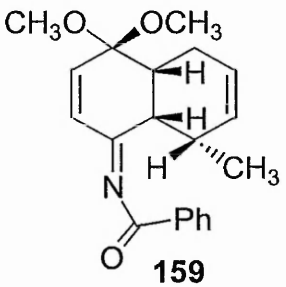
The regiochemistry of the adducts was determined by the selective deuteriation of H-2, using sodium in deuterated methanol, which was observed not to interfere with the coupling of H-5 to H-7 or H-7 to H-8. Furthermore, the coupling constant of H-7 to H-8, $J_{7\text{-}8}$ 5.5Hz, enabled the assignment of the *endo*-stereochemistry of the adducts.

The cycloaddition chemistry of *N*-sulfonyl[149] and *N*-benzoyl[150] quinone-imine monoacetals has also been described. Whilst the *N*-sulfonyl derivative was observed to afford adducts, represented by **158** Figure 47, in modest yield after two days in refluxing benzene the *N*-benzoyl derivative failed to react with a variety of dienes after three days at a temperature of 150°C.

Figure 47.



158



159

However, the *N*-benzoyl derivative was observed to react smoothly with a variety of dienes under an external pressure of 13Kbar at room temperature to afford the corresponding adducts, represented by **159** Figure 47, in high yield. The high pressure cycloaddition reactions were also observed to be highly regio- and stereo-selective by the formation of the *ortho-endo* adducts as was determined by the correlations in the NOESY spectrum between the *ortho* protons of the benzoate group and the protons of the newly formed cyclohexene ring.

In an analogous manner, Kerr et al further extended their original work with the *N*-benzoyl quinone-imine monoacetals to include the high pressure cycloaddition reactions of quinone monoacetals[151]. Whilst both furan and Danishefsy's diene failed to react cleanly, 1-*tert*-butylsilyloxybuta-1,3-diene afforded the *ortho-endo* adduct **160** in 67% yield after one day at room temperature and a pressure of 13Kbar. The *endo* stereochemistry of the adduct was determined by the observed close agreement between the experimental coupling constant of H-4a to H-5, *J*4.6 Hz, and the calculated values,

J_{endo} 2 to 5 Hz and J_{exo} 16 Hz. It was also shown that exposure of the adduct to a catalytic quantity of acid resulted in its aromatisation to a *para* methoxynaphthol derivative, **161** Scheme 41, by the elimination of methanol and the silyloxy group.

Scheme 17.

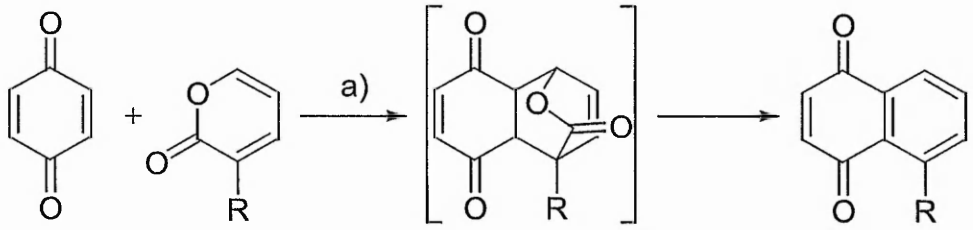
160 **161**

a) $PhCH_3$, cat. *para*-toluenesulfonic acid, 24h.

6.6.3. Selection of an Appropriate Diene.

Historically the formation of a substituted aromatic ring by a cycloaddition methodology with *para*-quinone dienophiles has been achieved with derivatives of 2-pyrone. Aromatisation typically occurred by the *in situ* thermal oxidative elimination of carbon dioxide from the tricyclic lactone adducts and can best be illustrated by the formation of 1,4-naphthoquinone and 5-methoxyjuglone from the cycloaddition of 1,4-benzoquinone with either 2-pyrone or 3-methoxy-2-pyrone respectively, Scheme 42, as described by Bosshard et al in 1964[152].

Scheme 42.



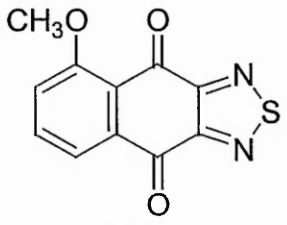
2-pyrone, R=H
3-methoxy-2-pyrone, R=OCH_3

1,4-naphthaquinone, R=H
5-methoxyjuglone, R=OCH_3

a) PhH, reflux.

Similarly novel analogues of anthraquinone, illustrated by **162** Figure 48, have been prepared in good yields, though it was noted that these cycloadditions failed when 3-hydroxy-2-pyrone was used as the dienophile[153].

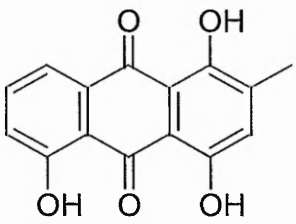
Figure 48.



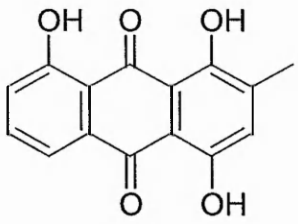
162

In contrast, the preparation of the anthraquinones islandicin and digitopurpone, **163** and **164** Figure 49, have been achieved by the regiospecific cycloaddition of 3-hydroxy-2-pyrone with the respective 6- or 7-chloro-2-methylnaphthazarins, **165** and **166**[154]. However, initially a dihydro derivative of the dienophile was isolated as an impurity. This was rationalised by the formation of the intermediate tricyclic lactone adduct, followed by the spontaneous elimination of carbon dioxide to give a bicyclic diene, which was immediately aromatised in the presence of unreacted naphthazarin, which in turn was reduced. The side reaction was successfully eliminated by the subsequent addition of lead dioxide to the cycloaddition reactions. The regioselectivity of the reactions was described as being controlled by the electron-donating power of the hydroxy substituent of the diene, which is known to be nucleophilic at C-6 as described by Corey et al[155]. Therefore C-6, possessing the largest HOMO coefficient, was predicted to combine with the unsubstituted carbon of the quinone system which was predicted to have the largest LUMO coefficient as directed by the alpha chlorine atom.

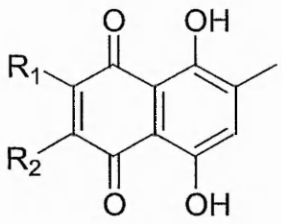
Figure 49.



163



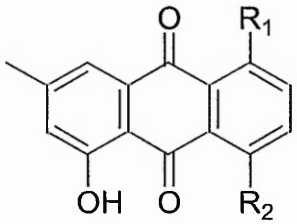
164



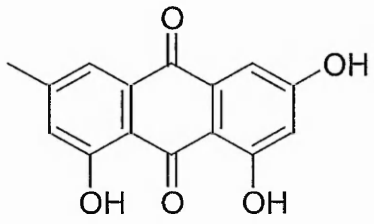
165 $R_1 = H$, $R_2 = Cl$
166 $R_1 = Cl$, $R_2 = H$

In an analogous manner the natural products pachybasin **167** Figure 50, helminthosporin **168**, chrysophanol **169**[156, 157], and emodin **170**[158] have been prepared from the appropriate 1,4-naphthoquinone and 6-methoxy-4-methyl-2-pyrone.

Figure 50.



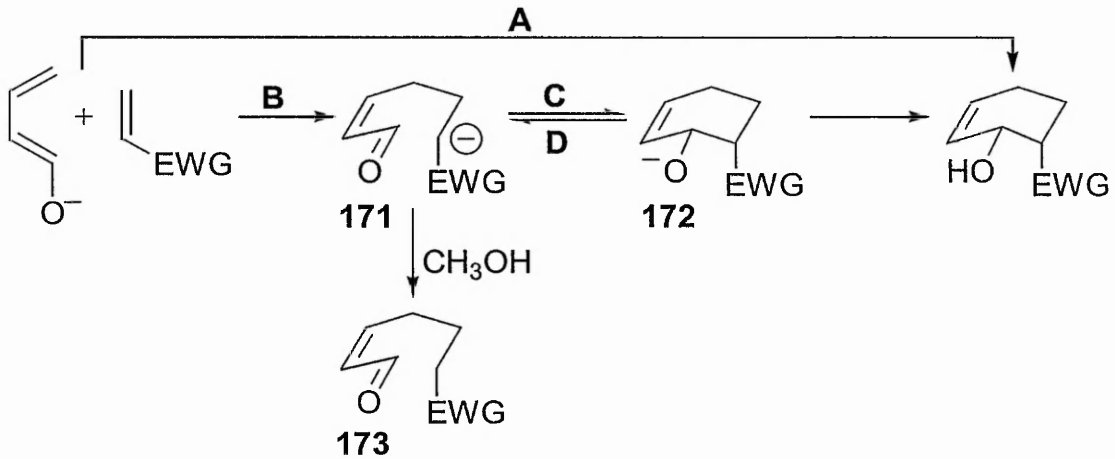
167 $R_1 = R_2 = H$ = Pachybasin
168 $R_1 = R_2 = OH$ = Helminthosporin
169 $R_1 = H$ $R_2 = OH$ = Chrysophanol



170 emodin

More recently the base catalysed cycloaddition reactions of 3-hydroxy-2-pyrone with various electron deficient dienophiles has been reported by Nakatani et al[159] to afford the corresponding lactone adducts in near quantitative yield at room temperature. Whilst complete regioselectivity was observed with methyl vinyl ketone and methyl acrylate by the exclusive formation of the *ortho* adducts the respective stereochemical ratios were found to be 1.3:1 and 11:1 in favour of the *endo* isomers. In agreement with an earlier report by Koener and Rickborn[160] the base catalysed cycloaddition reactions were believed to have proceeded via a concerted mechanism, path **A** Figure 51, rather than the alternative stepwise tandem Michael-aldol reaction, path **B** and **C**.

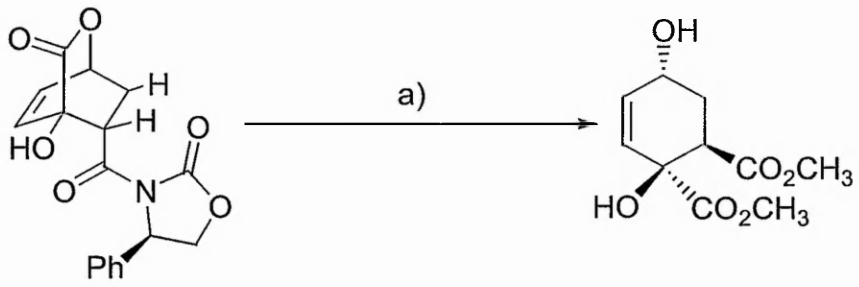
Figure 51.



It was argued that, as the reactions were conducted in a methanol-triethylamine mixture, the intermediate enolate, **171** path **B**, would have been quenched by methanol to afford the Michael adduct **173**, and, although some Michael adduct was detected, Kroener and Rickborn had previously confirmed that these adducts were formed by a retro-aldol reaction of the cycloadducts **172**.

Subsequently Nakatani et al further extended the base catalysed cycloaddition reactions of 3-hydroxy-2-pyrone to the asymmetric synthesis of lactone adducts, up to 95%de, with *N*-acryloyl oxazolidinone dienes in the presence of a chiral base[161]. The homochiral bicyclolactone adducts were subsequently treated with sodium methoxide in methanol to afford highly functionalised cyclohexenes, which offered the additional potential for further use as practical substrates for the asymmetric synthesis of complex molecules, Scheme 43.

Scheme 43.



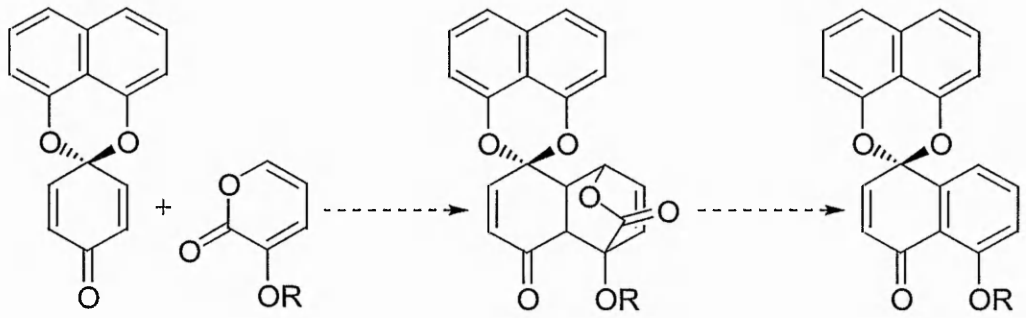
a) CH_3ONa, CH_3OH.

3-Hydroxy-2-pyrone has also been shown to undergo regioselective cycloaddition to a variety of electron deficient dienophiles at a pressure of 20 to 40 Kbar to afford the lactone adducts with varying degrees of stereoselectivity in preference for the *endo* isomer[162]. However, the adduct obtained with methyl vinyl ketone, along with several others, were observed to partially decompose upon attempted purification by column chromatography.

Thus in comparison to dienes, such as 1-methoxybuta-1,3-diene, 3-hydroxy-2-pyrone and its methyl ether were envisaged to offer significant advantages. Primarily, being cyclic the dienes are fixed into a cis-conformation and would therefore be predicted to be more reactive than the corresponding acyclic analogues. Also, the well described

regioselective nature of the dienes, being nucleophilic at C-6, would be predicted to combine with quinone monoacetals with a high degree of regioselectivity in favour of the required *ortho* adduct. The dienes also contain a leaving group in the form of the lactone functionality which would be expected to aid the aromatisation of the newly formed cyclohexene ring, but with the retention of the oxo substituent, thereby facilitating access to palmarumycin CP_1 or its methyl ether, Figure 52.

Figure 52.



3-hydroxy-2-pyrone, R = H

3-methoxy-2-pyrone, R = CH_3

Furthermore, by the application of alternative procedures to the conventional thermal techniques, such as base catalysis or high pressure, the highly functionalised lactone adducts may be accessed, which in both the *ortho* and *meta* regioisomers would possess an oxo substituent *peri* to the quarternary carbon of the acetal, and would be of interest both for further chemical modification and biological evaluation.

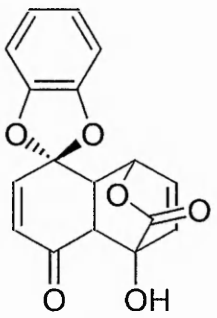
6.6.4. Base Catalysed Cycloaddition.

3-Hydroxy-2-pyrone **174** was prepared by the pyrolysis of commercial mucic acid at 150°C in the presence of potassium dihydrogen phosphate and phosphorus pentoxide as described by Watt et al[163].

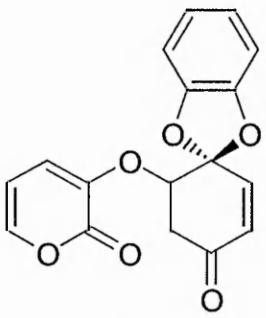
Adopting the base catalysed procedure described by Nakatani et al[159] exposure of quinone monoacetal **104** to an equimolar mixture of diene **174** and triethylamine in dichloromethane at room temperature over a period of twenty four hours, resulted in the

formation of a new compound of intermediate polarity by t.l.c. From the analysis of the infrared spectrum a hydroxy group at 3342cm^{-1} and two carbonyl functions at 1708cm^{-1} and 1686cm^{-1} were identified and observed to be consistent with the cycloaddition product **175** Figure 53. However, analysis of the ^{1}H N.M.R. spectrum revealed the presence of an upfield twelve line ABX system consisting of three well defined double doublets centred at δ 3.64ppm, δ 3.21ppm, and δ 2.83ppm. The coupling constants of the ABX system were observed to be characteristic of a substituted cyclohexane ring with a geminal constant of *J*18Hz, a vicinal axial-axial constant of *J*12Hz, and a vicinal axial-equitorial constant of *J*4.6Hz. The presence of the hydroxy function was confirmed by the presence of a broad singlet at δ 6.34ppm that exchanged with deuterium oxide, only two separately coupled pairs of doublets, at δ 6.48ppm δ 6.11ppm *J*7.3Hz and δ 6.87ppm δ 6.23ppm *J*10.2Hz, with chemical shifts corresponding to vinylic protons were observed. Thus due to the absence of a downfield allylic proton, required for cycloadduct **175**, combined with the presence of the ABX system and hydroxyl proton the spectral data gave best agreement with the unusual aromatised Michael adduct **177,** and not the alternatives **175** or **176**.

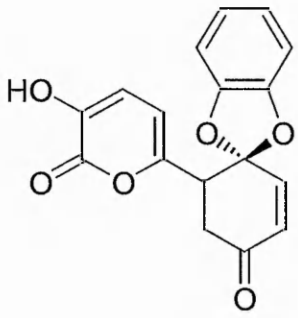
Figure 53.



175



176



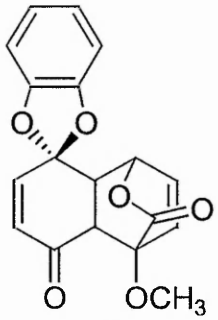
177

6.6.5. Thermal Cycloaddition.

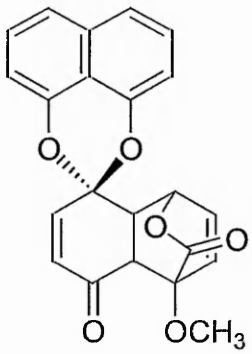
As previously described, Section 6.6.3, the thermal cycloaddition reactions of 3-hydroxy-2-pyrone **174** with quinones has been observed to be problematic. Thus 3-methoxy-2-pyrone **178**, obtained by the methylation of **174**[163], and was used for an investigation into the thermal cycloaddition reactions of the quinone monoacetals **104** and **123**.

In both cases a stoichiometric quantity of diene and dienophile in benzene were refluxed for five days, whereby the reaction mixtures had darkened significantly and were indicated by t.l.c. to be a three component mixture of starting materials and a new compound. Chromatographic purification of the crude reaction mixtures afforded, in ascending order of polarity, recovery of the respective quinone monoacetal and a cycloaddition product. The respective yields of the cycloaddition products **179** and **180** Figure 54, obtained from dienophiles **104** and **123** respectively, were 55% and 27%; if the quantities of recovered acetals are considered the adjusted yields are 86% and 89%.

Figure 54.



179



180

In an attempt to optimise the adduct yields the reactions were repeated in xylene at a temperature of 150°C, whereby the mixtures were observed to slowly darken. After a period of six hours t.l.c indicated the disappearance of both starting materials and the formation of a complex mixture of degradation products.

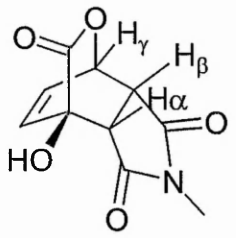
6.6.6. Structural Characteristics of Adducts 179 and 180.

For both of the adducts, **179** and **180**, the clarity of the signals in the ^{1}H and ^{13}C N.M.R. spectra, and in particular the occurrence of a single signal corresponding to the methyl ether, were indicative of the formation of a single regio- and stereo-isomer. Evidence for the retention of the lactone functionality of the diene and the ketone functionality of the dienophile was obtained from the corresponding characteristic carbonyl absorption bands at $1764cm^{-1}$ and $1695cm^{-1}$ in the infrared spectra, which were supported by the appropriate signals in the ^{13}C spectra at δ 170ppm and δ 191ppm.

Although reports concerning the isolation of the intermediate lactone adducts arising from the cycloaddition chemistry of 2-pyrones are limited it has been established that the *endo* and *exo* stereochemistry of the adducts may be deduced from the magnitude of the H_α–H_β coupling constants in the ^1H N.M.R. spectra. In general these coupling constants for adducts derived from 3-oxo-2-pyrones have been reported to be in the range of 1.1 to 1.5Hz for the *exo* adducts and 2.0 to 4.5Hz for the *endo* adducts[164]. It was also noted that in certain instances the regiochemistry of the adducts can be inferred by the respective chemical shifts of H_α and H_β.

For comparative purposes the spectral data of the *endo* and *exo* stereoisomer of a tricyclic lactone adduct, prepared from 3-hydroxy-2-pyrone and *N*-methylmaleimide, are presented in Figure 55[159].

Figure 55[159].

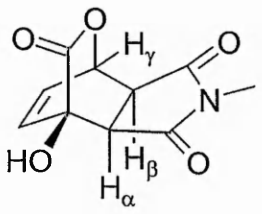


endo

H_α 3.13(1H, d, *J*8.1Hz)

H_β 3.77(1H, dd, *J*4.8, 8.2Hz)

H_γ 5.59(1H, m)



exo

H_α 3.20(1H, d, *J*9.2Hz)

H_β 3.27(1H, dd, *J*2.2, 9.2Hz)

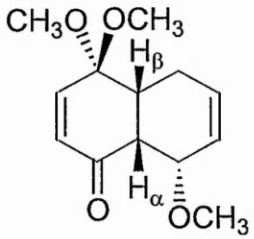
H_γ 5.60(1H, m)

Thus, although H_α and H_β of the adducts illustrated in Figure 55 are both alpha to an amide function, it is evident that the chemical shift corresponding to the double doublet of H_β is further downfield than the doublet of H_α, which can be ascribed to the deshielding effect that H_β experiences from the direction of the lactone functionality, ie. H_β is alpha to the acyloxy functionality of the lactone and not to its carboxylate function.

In contrast the chemical shift of H_β in the *ortho* regioisomer illustrated in Figure 56 was observed to be further upfield than H_α[147], which, in agreement with the general trends

observed for chemical shifts in ^{1}H N.M.R. spectra, confirms that the carbonyl function of the enone has a greater deshielding effect than the acetal group.

Figure 56.



endo

H_α 3.30ppm, H_β 2.72ppm

The respective ^{1}H N.M.R. spectral data obtained for the cycloadducts **179** and **180** is presented in Table 15. In both cases the double doublet was shown to couple to the other two protons by analysis of a two dimensional correlated spectroscopy spectrum (COSY).

Table 15.

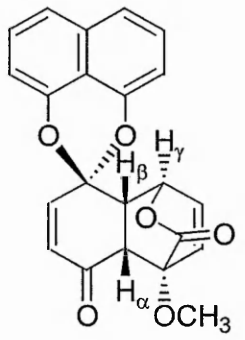
Adduct	Chemical shift ppm.		
179	5.50(1H, m)	3.67(1H, dd, *J*4.6, 8.6Hz)	3.45(1H, d, *J*8.9Hz)
180	5.62(1H, m)	3.74(1H, dd, *J*4.6, 8.6Hz)	3.42(1H, d, *J*8.6Hz)

Although the observed coupling constants of the double doublets, *J*4.6Hz, strongly suggested the *endo* stereochemistry of the adducts, the assignment of H_α and H_β by comparison of the chemical shifts with the published data did not in the first instance appear possible in view of the different nature of the structures. However, by comparing the two structures representing the *ortho-endo* and *meta-endo* adducts, illustrated for adduct **180** Figure 57, tentative assignment of the regiochemistry was made possible.

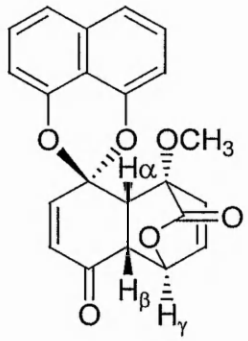
For example, in the *ortho-endo* adduct the signal in the ^{1}H N.M.R spectrum corresponding to H_β would experience the strong deshielding effect of the acyloxy function of the lactone and would be predicted to appear as a double doublet with a chemical shift further downfield, but close to, the doublet of H_α which is deshielded by the carbonyl function of the enone. However, for the *meta* adduct the double doublet of H_β would experience the deshielding effects of both the lactone function and the carbonyl

of the enone system simultaneously and would, therefore, be predicted to have a chemical shift closer to that of Hγ. Furthermore, by comparison with the *ortho* adduct, H_α in the *meta* adduct would be shifted further upfield, and so the difference between the chemical shifts of H_β and H_α in the *meta* adduct would be predicted to be greater than in the *ortho* adduct. Therefore as the difference between the chemical shifts of H_β and H_α for adducts **179** and **180** were observed to be 0.2 to 0.3 ppm the spectral data was considered to be consistent with the *ortho-endo* regio- and stereo-chemistry.

Figure 57.



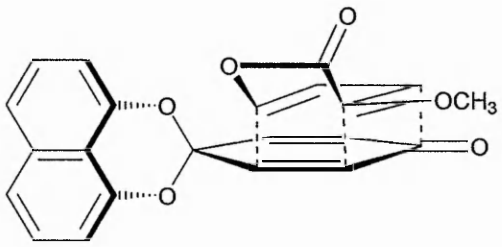
180a, *ortho-endo*,



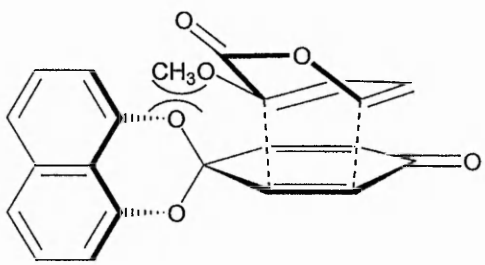
180b, *meta-endo*.

Further evidence in support of the *ortho-endo* regio-and stereo-isomer can be gained from the known regio- and stereo-selective nature of both quinone monoacetals and 3-methoxy-2-pyrone. It was also noted that as the H_β-H_γ coupling constants of *J*4.6Hz were in agreement with the *endo* stereochemistry, by comparing the *endo* transition states for both the *ortho* and *meta* adducts, illustrated for cycloadduct **180** Figure 58, the transition state of the *meta* regioisomer was predicted to be significantly higher in energy, and therefore less probable, due to the steric repulsion between the methoxy substituent and the acetal group.

Figure 58.



ortho-endo



meta-endo

6.6.7. Attempted Cycloaddition by Lewis Acid Catalysis.

It is known that a variety of Lewis acids, such as zinc dibromide, diethylaluminum chloride, and boron trifluoride etherate, are able to catalyse both normal and inverse electron demand cycloadditions by their co-ordination to heteroatoms of the dienophile or diene respectively[165].

However, the addition of 3-methoxy-2-pyrone **178** to a solution of boron trifluoride etherate and dienophile **104** at -70°C resulted in the slow decomposition of the diene after the reaction mixture had attained room temperature, whilst the presence of a cycloaddition product was not detected by t.l.c. It was also observed that repetition of the procedure, using either tin (IV) or titanium (IV) chloride as the catalyst resulted in the rapid decomposition of both components of the reaction mixture.

Although only a brief investigation into the catalysis of the cycloaddition reaction by Lewis acids was completed it was concluded that in view of the highly oxygenated nature of the dienophile and diene, with numerous sites for the co-ordination of the Lewis acid, further investigation of the procedure was envisaged to be problematic and was therefore rejected in favour of the comparatively neutral conditions of cycloadditions at high pressure.

6.6.8. Cycloaddition at High Pressure.

Although eamples are limited, it is known that the cycloaddition reactions of quinone monoacetals are enhanced by the application of high pressure techniques, Section 6.6.2. Thus with the co-operation of Dr. Hans Scheeren, who provided access to the excellent high pressure facilities within the Department of Organic Chemistry at the University of Nijmegen Holland, an investigation of the cycloaddition reactions of the quinone monoacetals **104**, **123**, **141**, and **142** with dienes **174** and **178** at high pressure was undertaken, and the results are presented in Table 16.

As can be seen the cycloadditions were observed to occur smoothly to afford the cycloadducts in near quantitative yield and repetition of experiment two at a reduced pressure of 12Kbar had no significant effect upon the yield of adduct **180**.

Table 16.

Exp. No	Diene	Dienophile	Pressure Kbar	Time hr.	Adduct	Yield
1	**178**	**104**	15	24	**179**	92
2a	**178**	**123**	15	24	**180**	88
2b	**178**	**123**	12	24	**180**	85
3	**178**	**141**	15	24	**181**	96
4	**178**	**142**	15	24	**182**	90
5	**174**	**104**	15	24	**183**	D.*

*Decomposed.

For experiments 1, 2, and 3 the spectral data obtained for the corresponding adducts were observed to be indicative of the formation of a single regio- and stereo-isomer. The chemical shifts of H_α, H_β, and H_γ, and the coupling constant of H_β-$H\gamma$, were found to be directly comparable to the adducts obtained from the thermal cycloadditions, which inferred the *ortho-endo* geometry of the adducts. A surprising result was obtained for experiment 3, where the trifluoromethyl substituent of dienophile **141**, *ortho* to the quarternary carbon of the acetal, had been predicted to direct the addition of the diene to the substituted face. Further evidence in support of the addition of the diene to the unsubstituted face of **141** was obtained by the characteristic singlet, corresponding to the alpha proton of the enone, at δ 6.77ppm in the ^{1}H N.M.R. spectrum. It seems that for experiment 3 the cycloaddition reaction, where complete site, regio-, and stereo-selectivity was observed, was subject to steric control by the trifluoromethyl substituent in preference to its electron-withdrawing nature.

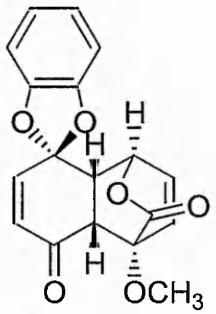
As was anticipated, the electron-donating methoxy substituent of dienophile **142**, Table 16 experiment 4, directed the cycloaddition of the diene to the unsubstituted face of the dienophile. The *ortho* regioselectivity of the cycloaddition was inferred by the characteristic chemical shifts corresponding to H_α, H_β, and H_γ in the ^{1}H N.M.R. spectrum. However, in contrast to the results of the previous experiments the coupling constant of H_β-H_γ was observed to be 1.3Hz, which in comparison to the literature values strongly inferred the *exo*-stereochemistry. This was an unexpected result in view of the known preference for cycloadditions that are *endo* orientating, by virtue of the secondary orbital interactions between the diene and dienophile, to be particularly selective at high

pressures favouring the kinetic product via the more compact *endo* transition state, Section 6.6.1.

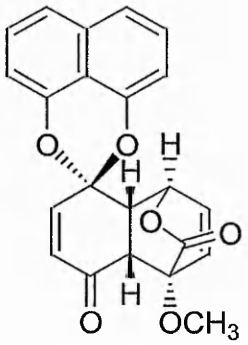
It was also shown, by the analysis of the ^{1}H N.M.R. of the crude reaction mixture, that the cycloaddition between dienophile **104** and 3-hydroxy-2-pyrone, **174**, occurred smoothly at an applied pressure of 15Kbar to afford the *ortho* adduct in near quantitative yield. However, the appropriate stereochemistry of the adduct was not determined, as, prior to purification the adduct was observed to have reverted to the respective starting materials after being stored at 4°C for a period of four weeks. The instability of the hydroxy adduct is in agreement with the observed degradation of some adducts derived from 3-hydroxy-2-pyrone reported by Gladysz et al[162].

In agreement with the observations of Kerr et al[151] the cycloaddition reactions of the quinone monoacetals **104**, **123**, **141**, and **142** with dienes **174** and **178** were observed to occur efficiently at high pressure to form the respective adducts illustrated in Figure 59 in a highly site-, regio-, and stereo-selective manner, as was deduced from the analysis of the spectral data.

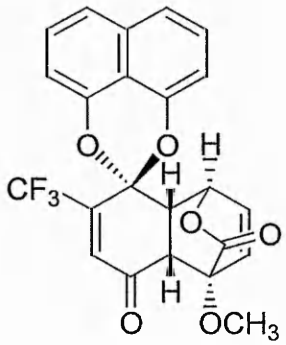
Figure 59.



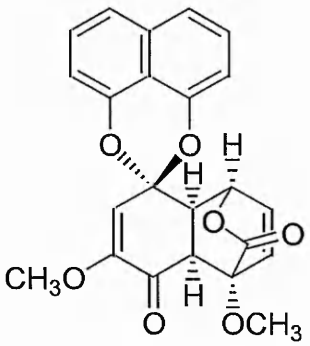
179, *ortho-endo*



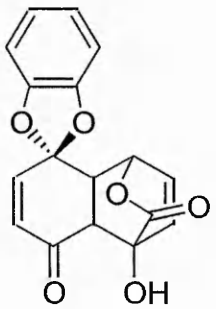
180, *ortho-endo*



181, *ortho-endo*



182, *ortho-exo*



183, *ortho*

6.7. Molecular Modelling.

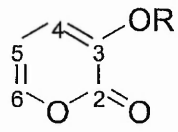
In an attempt to further rationalise the interesting results of the cycloaddition reactions a computational molecular modeling investigation of the reactants and products was undertaken.

In all cases the lowest energy conformation of a structure, corresponding to the global minimum, was obtained from a Monte Carlo (semi-random) search by the application of the MM2[166] force field, whereby the lowest energy conformer was generated more than once. The structures obtained from the conformation search were then minimised with the MOPAC-AM1[167] semi-empirical program to obtain the data presented below.

6.7.1. Molecular Orbital Coefficients.

The molecular orbital coefficients corresponding to the HOMO of the dienes are presented in Table 17.

Table 17.



174, R = H
178, R = CH_3

Diene	C-2	C-3	C-4	C-5	C-6
174	-0.083	-0.492	-0.328	+0.420	+0.435
178	-0.096	-0.475	-0.384	+0.383	+0.448

In contradiction to the known reactivity of dienes **174** and **178**, where C-6 has been identified as the nucleophilic centre Section 6.6.3, the largest orbital coefficients were calculated to be situated at C-3. Although the difference between the values obtained for C-3 and C-6 could be considered marginal, C-3 would be predicted to interact more strongly with either C-2 or C-6 of dienophile **104**, Table 20, to afford preferentially the *meta* regioisomer. Although a similar discrepancy between the experimentally observed regioselective nature of a diene and the calculated orbital coefficients has been reported

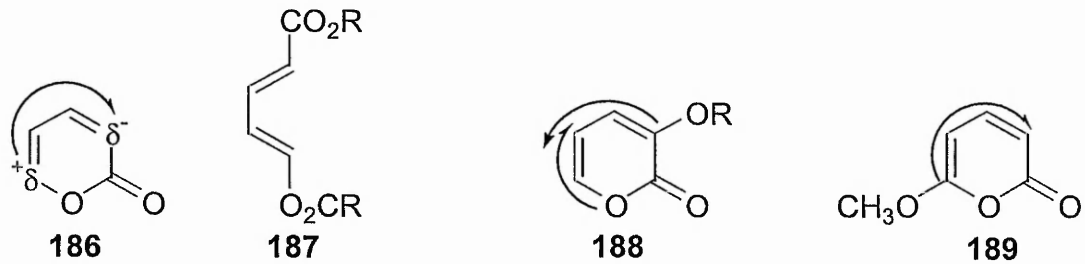
for piperylene, and was attributed to the incorrect evaluation of the donor character of the methyl substituent[168], the molecular orbital coefficients of 2-pyrone **184** and 6-methoxy-2-pyrone **185** were calculated for comparison, Table 18.

Table 18.

Diene	C-2	C-3	C-4	C-5	C-6
184	+0.061	+0.517	+0.233	-0.509	-0.444
185	+0.079	+0.536	+0.180	-0.574	-0.354

For 2-pyrone and 6-methoxy-2-pyrone the largest coefficients of the bonding termini of both dienes is located at C-3, which in conjunction with the results obtained for the 3-oxo-2-pyrones, **174** and **178** Table 17, suggests that the general electron distribution of 2-pyrones is controlled by the lactone functionality, generating a partial negative charge on C-3 and a partial positive charge on C-6, **186** Figure 60. Thus the lactone functionality can be regarded as both an electron-withdrawing carboxylate and an electron-releasing acyloxy group where the respective separate pull-push effects can be considered to operate in the same, clockwise, direction from C-6 to C-3 of the cyclic system. This may be more clearly seen by comparison with the acyclic analogue **187** Figure 60. Therefore, based on the results of the molecular orbital coefficients, it could be argued that an electron-donating substituent at C-3 of 2-pyrone would be in conflict with the inherent electron distribution of 2-pyrones, **188** Figure 60, whereas, an electron-donating substituent at C-6 could be argued to operate in synergy with the inherent electron distribution of 2-pyrones, **189** Figure 60.

Figure 60.



Further evidence in support of these observations was obtained from the calculated electrostatic derived atomic charges, Table 19, where, in considering the bonding

termini, C-3 and C-6, of 2-pyrone, 6-methoxy-, and 3-methoxy-2-pyrone, the nucleophilic centre for all three dienes was situated at C-3.

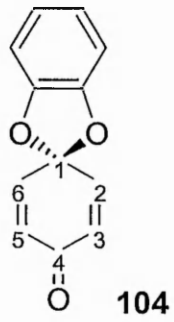
Table 19.

Diene	C-2	C-3	C-4	C-5	C-6	ΔC-6, C-3
2-pyrone	+0.524	-0.514	+0.139	-0.457	+0.065	0.579
6-methoxy-2-pyrone	+0.482	-0.526	+0.124	-0.598	+0.406	0.932
3-methoxy-2-pyrone	+0.441	-0.144	+0.008	-0.417	+0.003	0.147

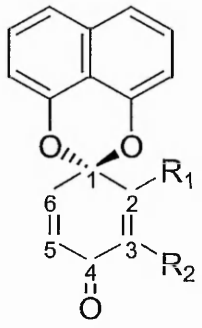
It was also noted that by calculating the difference between the values of C-6 and C-3, 3-methoxy-2-pyrone was significantly less polarised than the other two dienes. When combined with the results obtained for the orbital coefficients, 3-methoxy-2-pyrone, in contrast to the literature precedence, would be predicted to be the least regioselective of the three dienes, with a marginal preference for the *meta* adduct, while in comparison 6-methoxy-2-pyrone would be predicted to exhibit a high degree of regioselectivity in preference for the *ortho* adduct.

The molecular orbital coefficients corresponding to the LUMO of the dienophiles are presented in Table 20.

Table 20.



104

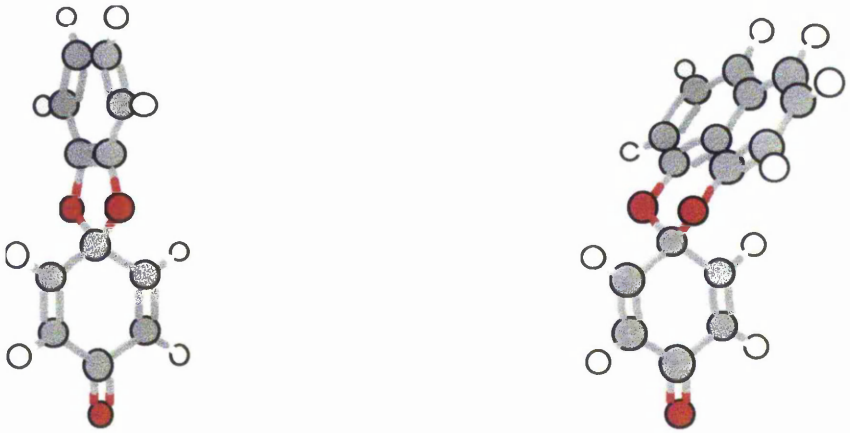


123, $R_1 = R_2 = H$
141, $R_1 = CF_3$ $R_2 = H$
142, $R_1 = H$ $R_2 = OCH_3$

Dienophile	C-1	C-2	C-3	C-4	C-5	C-6
104	+0.189	+0.411	-0.321	-0.412	-0.321	+0.411
123	-0.196	-0.377	+0.298	+0.378	+0.299	-0.380
141	+0.150	+0.447	-0.414	-0.384	-0.242	+0.346
142	-0.122	-0.033	+0.015	+0.026	-0.125	-0.155

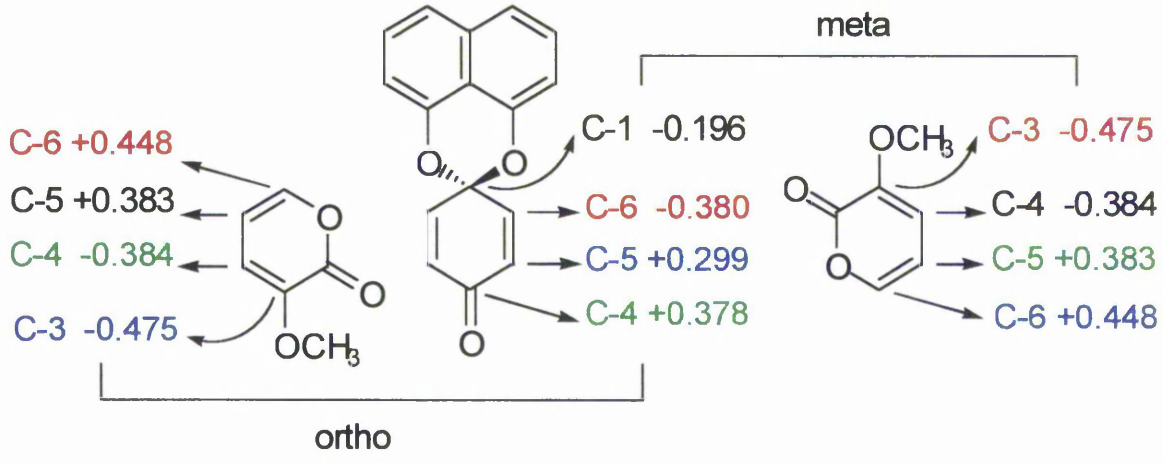
In considering the data obtained for the dienophiles the largest coefficient of the LUMO was observed to be located at the beta carbon with respect to the carbonyl group of the quinone, which is in agreement with the regioselective nature of quinone monoacetals described by Fariña et al[145]. Though marginal, it was noted that for dienophile **123** there was a slight discrepancy in the size of the orbital coefficients calculated for C-2 and C-6, with C-6 being slightly larger. By comparing the minimised structures of **104** and **123**, Figure 61, it can be seen that the acetal function of dienophile **123** is slightly distorted, with the naphthalene ring leaning away from the perpendicular line bisecting C-1 and C-4 of the quinone system in the direction of C-2.

Figure 61.



Therefore, based solely on the orbital coefficients obtained for the dienes and dienophiles, Figure 62, the regiochemistry of the adducts would be predicted to be *meta*.

Figure 62.



However, whilst there is the potential for a positive secondary orbital interaction between C-4 of the diene and C-1 of the dienophile in the *meta-endo* transition state, the potential energy gain from this interaction would be predicted to be more than offset by the steric repulsion experienced by the methoxy substituent of the diene and the acetal function of the dienophile. Therefore, in contrast to the spectral stereochemical assigment of adducts **179**, **180**, and **181**, the stereoselectivity of the *meta* regioisomer would be predicted to be *exo*. If it is assumed either that the electron donating power of the methoxy substituent of 3-methoxy-2-pyrone has been underestimated and that C-6 is the nucleophilic centre, or that 3-methoxy-2-pyrone is considered to be an indiscriminate diene, then the regioselectivity of the cycloaddition would be subject to steric control imparted by the acetal group of the dienophile. Thus, the preferred conformation of the adducts **179**, **180**, and **181** would be predicted to be *ortho-endo* which is in agreement with the regio-and stereo-chemical assignment of the adducts based upon their spectral data.

For dienophile **141**, as was anticipated from the electron-withdrawing nature of the trifluoromethyl substituent the largest orbital coefficient was calculated to be at C-2, Table 20, which in contrast to the spectral data obtained for adduct **181** would have predicted cycloaddition to have occurred on the substituted face of the dienophile.

For dienophile **142**, which possesses a methoxy substituent alpha to the carbonyl function, the largest coefficient was calculated to be at C-6 and in agreement with the spectral data of adduct **182** cycloaddition would be predicted to occur on the unsubstituted face. Furthermore, it was also noted that in comparison to dienophiles **123** and **141** the orbital coefficient of C-4 for **142** was significantly smaller, which would suggest that the secondary orbital interaction between the diene and dienophile would be comparatively less. Therefore it could be argued that with no significant reduction in the transition state energy to be gained from a strong secondary orbital interaction the less sterically congested *exo* transition state would be energetically more favourable. This observation could be used to rationalise the unexpected experimental results.

6.7.2. Regio- and Stereo-chemical Conformational Analysis of Cycloadduct 180.

In order to gain an appreciation of the regio- and stereo-chemical conformations of the cycloaddition products adduct **180** was selected as a representative structure and all four

possible isomers were minimised in an analogous manner to that described for the dienes and dienophiles. As well as the respective energies of each isomer the dihedral angle of H_β-H_γ was measured and used to estimate the respective vicinical coupling constants by the application of the Karplus equations[169]:

$$J_{\beta\gamma} = J^{0} \cos^2 \phi \qquad (0^\circ \leq \phi \leq 90^\circ)$$
$$J_{\beta\gamma} = J^{180} \cos^2 \phi \qquad (90^\circ \leq \phi \leq 180^\circ)$$

Where ϕ is the dihedral angle and $J^0 = 10$Hz and $J^{180} = 16$Hz[170].

The results obtained for all four isomers are presented in Table 21 and graphically in Figure 63.

Table 21.

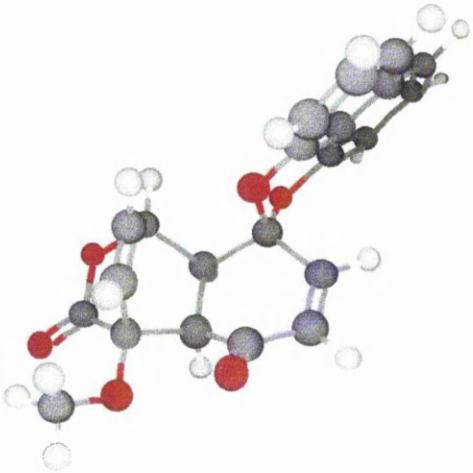
Isomer	ΔH_f Kcal / mole	SE Kcal / mole	ϕ $H_{\beta\gamma}$	$JH_{\beta\gamma}$ Hz.
Ortho-endo	-97.9	43.4	61.4	2.29
Ortho-exo	-95.7	46.5	72.4	0.91
Meta-endo	-97.3	43.9	62.6	2.12
Meta-exo	-96.1	44.9	71.3	1.03

Where ΔH_f = the heat of formation.
SE = the steric energy.
ϕ = the dihedral angle between H_β and H_γ.
$J_{\beta\gamma}$ = the calculated coupling constant for H_β-H_γ.

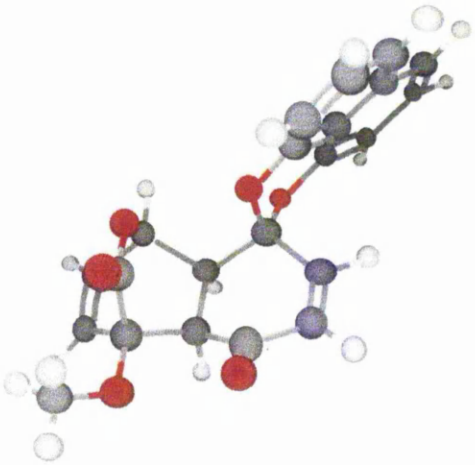
Only marginal differences between the *ortho* and *meta* regioisomers were observed when the heats of formation and steric energies of the respective stereoisomers were compared, and were considered too small to attribute any significant preference for a particular conformation of the cycloadducts. In contrast, the estimated coupling constants obtained for H_β-H_γ, although not directly comparable in magnitude to the experimental values, were found to follow the general trend of the literature values, 1.1 to 1.5Hz for the *exo* adducts and 2.0 to 4.5Hz for the *endo* adducts[164]. This afforded greater confidence in the correct assignment of the stereochemistry of the adducts. However, as the dihedral angles of H_β – H_γ for a particular stereoisomer were found to be comparable for both the *ortho*

and *meta* regioisomers, *ortho-endo* ϕ $H_{\beta\gamma}$ 61.4° *meta-endo* ϕ $H_{\beta\gamma}$ 62.6°, no further evidence in support of the regiochemistry of the adducts could be inferred.

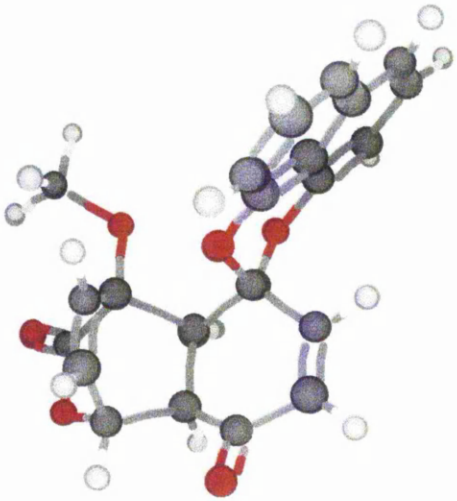
Figure 63.



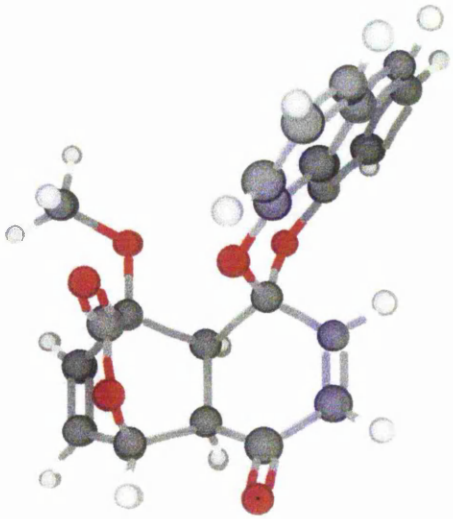
180a, *ortho-endo*



180b, *ortho-exo*



180c, *meta-endo*



180d, *meta-exo*

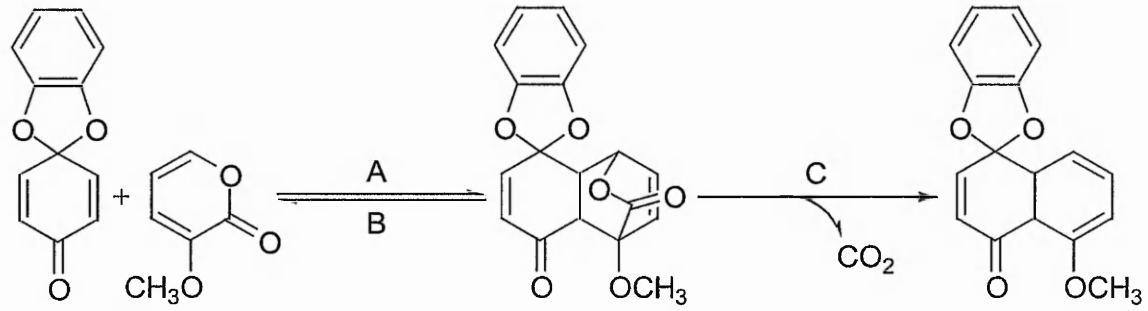
6.8. Attempted Aromatisation of Cycloadduct 179.

Only a brief investigation into the aromatisation of cycloadduct **179** was completed.

In contrast to the preparation of 5-methoxyjuglone and the anthraquinones described in Section 6.6.3, where aromatisation of the intermediate lactone adducts was effected thermally in the presence of an oxidant, exposure of cycloadduct **179** to manganese dioxide in refluxing benzene for a period of eight hours afforded a mixture of adduct **179**

and the cycloreversion products 3-methoxy-2-pyrone **178** and quinone monoacetal **104**. Furthermore, in agreement with the results obtained from the thermal cycloaddition investigation, Section 6.6.5, exposure of adduct **179** to manganese dioxide at a temperature of 150°C afforded a complex mixture of degradation products after a period of two hours. These disappointing results were rationalised by the observation that the lactone adducts have the potential to follow either of the two [4+2] cycloreversion pathways, B or C, illustrated in Figure 64.

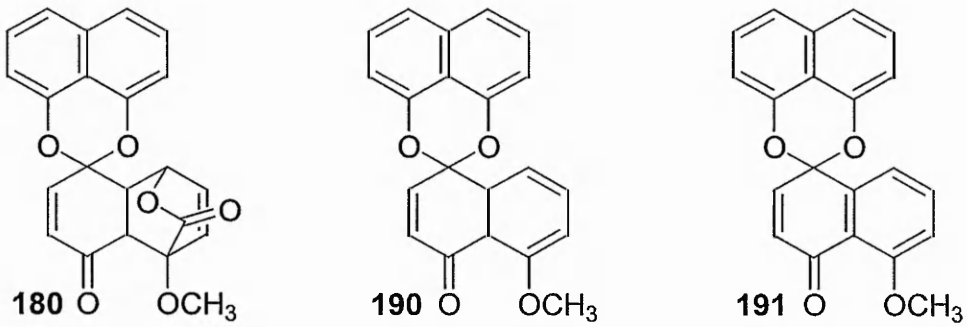
Figure 64.



Thus, although in general pathway C is favoured by the loss of stable molecules, such as acetylene, carbon dioxide, or nitrogen, it will only be followed when the activation energy of the process is lower than that of route B.

However, during the routine analysis of adduct **180** by electrospray ionisation mass spectrometry (E.S.I.) the MH^+ ions corresponding to the un-ionized structures illustrated in Figure 65, were observed at an injection temperature of 140°C.

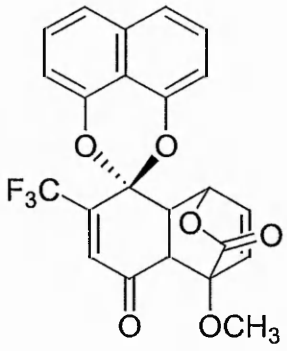
Figure 65.

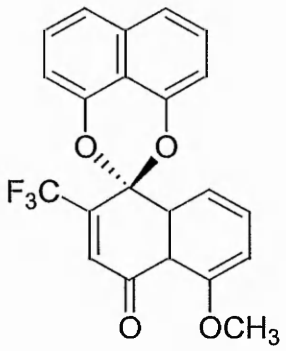


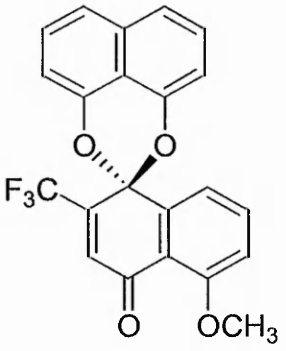
Fw:	376.4	332.3	330.3
m/z (ESI):	376.7 (MH, 100%)	333.3 (MH^+, 85%)	331.5 (MH^+, 50%)

By further experimentation it was subsequently found that by increasing the injection temperature to 190°C the relative abundance of the molecular ions corresponding to adduct **180**, diene **190**, and methoxy palmarumycin CP_1 **191** were 35%, 50%, and 100% respectively. Analogous results were also observed for the trifluoromethyl cycloadduct **181**, Figure 66.

Figure 66.







Fw:	444.4	400.4	398.3
m/z (ESI):	444.6 (MH, 20%)	401.1 (MH^+, 100%)	399.1 (MH^+, 75%)

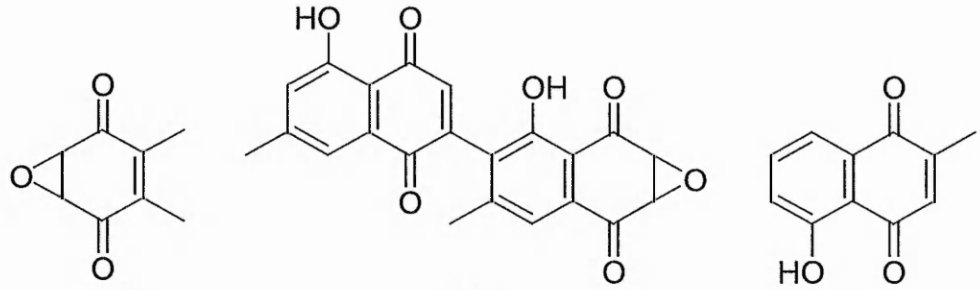
Therefore, although no further attempts to aromatise the lactone adducts were made, the results obtained from the mass spectrometry indicate that the required transformation may potentially be achieved on a preparative scale by an investigation into the chemical or electrochemical ionisation of the adducts in conjunction with flash vacuum pyrolysis.

7.0. Antimicrobial Activity of Quinone Monoacetals.

There are accounts scattered through the literature of the antimicrobial activity of simple quinones, although often without quantitative minimum inhibitory concentration (MIC) values.

1,4-Benzoquinone itself is mildly active against *Staphylococcus aureus* with an MIC of 800ppm, while 2,6-dimethoxy-1,4-benzoquinone, MIC 200ppm, is the active antibacterial substance in bamboo[171]. Terreic acid, **194** Figure 67, has MIC values of 25 to 200ppm against a range of Gram-positive and Gram-negative organisms[172]. The bis-naphthoquinone monoepoxide diosquinone **195** shows considerably greater activity against a number of pathogens, MIC 3 to 30ppm Gram positive and 15 to 60ppm for Gram negative, than did the simpler plumbagin **196**[173].

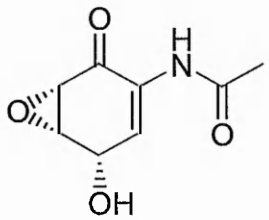
Figure 67.



194 **195** **196**

Among quinone derivatives, the Streptomyces metabolite LL-C10037a, **197** Figure 68, is the simplest example of the epoxyquinol antibiotics, the manumycins[174]. The antimicrobial activity of the functionalised quinone monoacetals, the palmarumycins, has been discussed in Section 5.0.

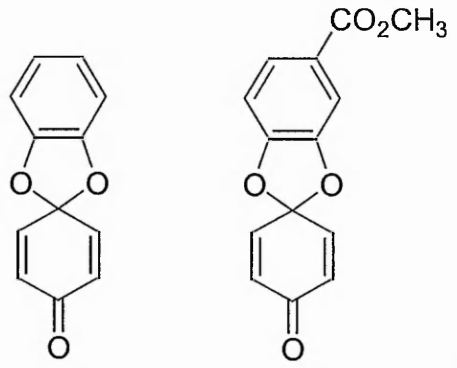
Figure 68.



197

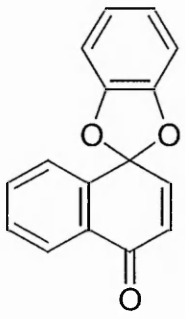
As a result of previous collaborations, four quinone monoacetals, **104**, **198**, **199**, and **200** had been screened for antibacterial activity by Zeneca Pharmaceuticals and the results are presented in Table 22.

Table 22.

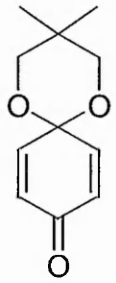


104

198



199



200

Compound	Sau Ox.	Sau Nov.	Sau *in vivo*.	Sau MRQS.	Sau MRQR.	CNS MS.	CNS MR.	Spy.	Bsu.	Efa.	Can a.
104	2	2	4	4	4	1	4	4	4	8	4
198	8	16	16	16	16	8	16	16	16	32	16
199	0.5	0.5	2	1	1	0.25	1	1	2	4	4
200	8	8	32	32	32	8	32	16	8	64	16

Key to Table 22.

Sau = *Staphylococcus aureus*.

CNS = coagulase negative *Staphylococci*

Spy = *Streptococcus pyogenes*

Bsu = *B. subtilis*

Efa = *E. faecalis*

Can a. = *Candida albicans*

Ox = Oxford.

Nov = novobiocin resistant.

MR = methicillin resistant.

MS = methicillin sensitive.

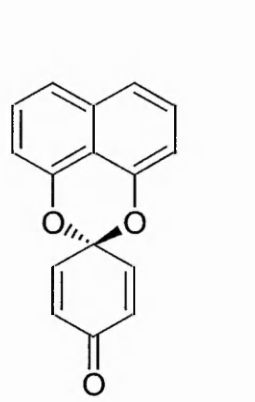
QR = quinolone resistant.

QS = quinonlone sensitive.

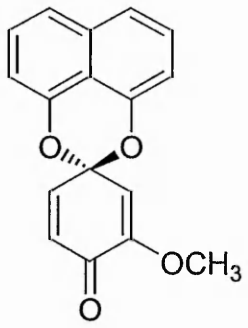
This screen has now been discontinued, but the significant activity of **104** and **199**, much greater than that of the parent quinones, and the marked reduction in potency of **200** prompted us to conduct a limited assay of selected quinone monoacetals prepared in this

study. In collaboration with the Life Sciences department at The Nottingham Trent University, a manual version of the automated Zeneca protocol was used to determine the MIC values of a number of compounds against a strain of methicillin resistant *Staphylococcus aureus* (MRSA) and the results are summarised in Table 23.

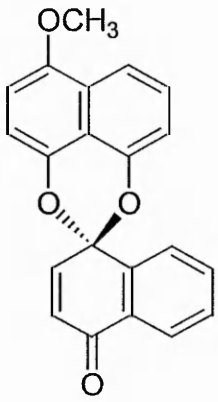
Table 23. Activity of Quinone Monoacetals against MRSA.



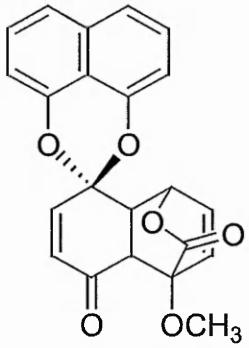
123



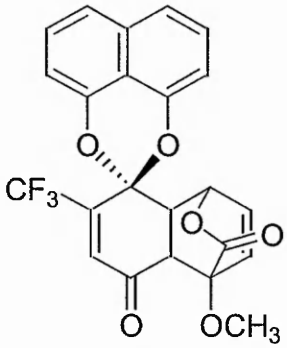
142



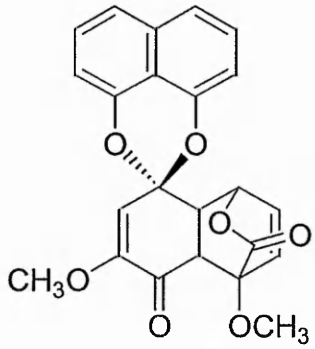
148



180



181



182

Compound	**104**	**200**	**199**	**123**	**142**	**148**	**180**	**181**	**182**
MIC (ppm)	8	64	2	4	2-4	~2*	4	>128	>128

*Partially insoluble in medium.

Although the MIC values for **104** and **199** differ slightly from those obtained in the professional assay, Table 22, this may simply reflect differences in the growth medium and inoculum size, and are within one dilution.

With the exception of **200** all the simple quinone monoacetals show significant activity, with MIC values below 10ppm, and the most potent, the naphthoquinone **199**, is active

against sensitive organisms at concentrations below 1ppm. They are thus considerably more active than the parent quinones.

The quinone monoacetals derived from catechol and the less accessible 1,8-dihydroxynaphthalene are equipotent, and the combination of a methoxy derivative of the latter diol with naphthoquinone in compound **148**, our nearest approach to a palmarumycin, gives a product of poor solubility.

The results obtained with the pyrone adducts derived from **123** are informative. Compound **180**, containing an unsubstituted enone system, is as potent as **123**, but the substituted derivatives **181** and **182** are inactive. This strongly suggests that the biological activity of the compounds reflects their ability as enones to act as Michael receptors. The inductive effect of the trifluoromethyl group in **181** would diminish the polarisation, and hence the electrophilicity of the enone, while the methoxy substituent in **182** offers steric hindrance to nucleophilic attack.

Support for this suggestion is also provided by the MIC values of 4ppm for acetals **104** and **198** against the eukaryotic fungus *Candida*, implying a non-specific mode of action. It is noteworthy that many of the antimicrobial quinones and derivatives described in the literature are also reported to have antifungal and cytotoxic properties.

Thus, though the quinone monoacetals prepared in this investigation have significant activity against MRSA, and have been useful vehicles for developing synthetic strategies, they are unlikely to act as lead compounds for clinically useful antimicrobials.

8.0. Conclusion.

A general methodology for the preparation of a novel and highly functionalised series of palmarumycin CP_1 analogues has been developed by the cycloaddition of 3-methoxy-2-pyrone to a novel series of quinone monoacetals under both thermal conditions, with moderate to poor yields, and at high pressure with almost quantitative conversion. The cycloaddition reactions were observed to occur with a high degree of regio- and stereo-chemical control with the exclusive formation of a single isomer in each case. The unsubstituted quinone monoacetal dienophiles afforded the *ortho-endo* adducts. Additional site-selectivity was incurred by a trifluoromethyl substituent, *ortho* to the quarternary carbon of the acetal, to afford the *ortho-endo* adduct on the unsubstituted face of the dienophile, whilst a *meta* methoxy substituent resulted in the total reversal of the stereochemistry of the cycloaddition to afford the *ortho-exo* adduct on the unsubstituted face of the dienophile.

A molecular modelling study of the dienes, dienophiles, and cycloaddition products revealed a discrepancy in the known regioselective nature of the dienes, 3-hydroxy- and 3-methoxy-2-pyrone, by virtue of the estimated molecular orbital coefficients, and was attributed to the incorrect evaluation of the donor ability of the oxo substituents by the semi-empirical MOPAC-AM1 program. Although no additional information in support of either the *ortho* or *meta* regiochemistry of the cycloaddition products was obtained from the molecular modelling study, support for the *ortho* regiochemistry of the adducts was argued on the basis of the spectral data obtained, and by the comparison of the transition states, where the *ortho-endo* transition state was predicted to be the more energetically favorable when compared to the *meta-endo*. However, greater confidence in the correct assignment of the stereochemistry of the adducts was given, due to the close agreement between the H_β-H_γ coupling constants obtained from the 1H NMR spectra with those reported in the literature, which were further supported by the estimated values obtained from the molecular modelling study.

In general the quinone monoacetals and cycloaddition products that possessed an unsubstituted enone system showed significanty activity against methicillin resistant *Staphylococcus aureus* (MRSA), with MIC values less than 10ppm. In contrast the cycloaddition products that were substituted with either a trifluoromethyl or methoxy

group were inactive, which suggests that the biological activity of the compounds is reflected by their ability to act Michael acceptors.

Thus, although the quinone monoacetals prepared in this investigation have significant activity against MRSA it is concluded that they are unlikely to act as lead compounds for clinically useful antimicrobial agents.

9.0. Experimental.

NMR spectra were recorded on JEOL GX-270 instrument, using tetramethylsilane (TMS) as the internal standard; samples were dissolved in cloroform-*d*, unless otherwise indicated. Two dimensional Correlated Spectroscopy (COSY), ^{1}H-^{13}C COSY, and Distorsionless Enhancement through Polarization Transfer (DEPT) experiments were completed where necessary. Melting points were recorded on a Gallankamp melting point apparatus and are uncorrected. Infrared spectra were recorded an a Perkin Elmer Fourier Transform spectrometer (FTIR) either by thin film (deposited samples were prepared by dissolving solids or oils in a small volume of chloroform and forming a thin film on a sodium chloride plate by allowing the solvent to evaporate), or by the preparation of a KBr disc. Low resolution Electrospray Ionization (ESI) mass spectra were recorded on a LCQ Finnigan spectrometer. Elemental analyses were carried out at The University of Nottingham.

Chromatography is flash column chromatography and was performed using Merk silica gel 60 (5735) using the eluant specified. Thin layer chromatography was carried out using pre-prepared plates, Merk silica gel 60 F-254. Technical grade petroleum ether (bp. 40-60°C) and ethyl acetate were distilled prior to use. Anhydrous diethyl ether and benzene were prepared by distillation from lithium aluminum hydride powder. Analytical grade dimethylformamide was dried over 4Å molecular sieves. Aldrich anhydrous dimethyl sulfoxide (27,685.5) was used as supplied. Anhydrous acetonitrile was prepared by distillation from phosphorus pentoxide, tetrahydrofuran was dried by distillation from sodium-benzophenone ketyl. TMEDA, and dichloromethane were dried by distillation from calcium hydride immediately before use. Triethylamine was dried by distillation from potassium hydroxide. *N*-bromosuccinimide was purified by recrystallisation from water and dried over 4Å molecular sieves in *vacuo*. All other reagents were purchased from commercial sources and used without further purification.

9.1. The Preparation of PCAB 300 Analogues.

General Methods

A. Williamson Ether Synthesis

To the appropriate phenol (1eq) and powdered potassium carbonate (3eq) suspended in 2-butanone (0.3M) at room temperature under an atmosphere of nitrogen was added the

appropriate α,ω-dibromoalkane (5eq). The heterogenous mixture was stirred vigorously and gently refluxed until the reaction was judged complete by t.l.c., allowed to cool, and the solvent was removed in *vacuo*. The residue was suspended in dichloromethane, filtered, and sequentially partitioned with 2M NaOH and saturated sodium chloride. The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. Excess α,ω-dibromoalkane was removed by kugelrohr distillation at reduced pressure and the residue was triturated with 1 to 5 % ethanolic petroleum ether to give a precipitate that was recrystallised from an appropriate solvent.

B. Alkylation of Amines.

To the appropriate alkyl halide (1eq) and triethylamine (2eq) dissolved in dimethylformamide (0.1M), at room temperature under an atmosphere of nitrogen, was added the appropriate amine (10eq)*. The mixture was stirred at room temperature for 18 h. and the solvent removed in *vacuo*. The residue was dissolved in ethyl acetate and sequentially partitioned, twice with water, and saturated sodium chloride. The organic fraction was dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The residue was purified by chromatography eluting with ethyl acetate : methanol : 880 NH_3, 90:(10 to 15): 3. Fractions containing the product were combined and concentrated in *vacuo* to give the desired amine as the free base.

*Methylamine was used as a 33% solution in ethanol; ethylamine was used as a 2M solution in methanol; and dimethylamine was used as a 2M solution in methanol.

C. Preparation of Hydrochloride Salts.

To the appropriate amine dissolved in the minimum amount of dichloromethane at room temperature was slowly added an excess of ethereal hydrogen chloride. The mixture was cooled to 0°C, filtered, and the hydrochloride salt was purified by recrystallisation from an appropriate solvent.

NAPHTHALENE DERIVATIVES.

Preparation of 6-bromo-2(ω-bromoalkyloxy)naphthalenes.

The ethers were prepared from commercially available 6-bromo-2-naphthol and the appropriate α,ω-dibromoalkane by the General method A.

6-Bromo-2(2-bromoethyloxy)naphthalene **1**.

% Yield : 74. M.p. 130-132°C. δ ^{1}H 7.88 (1H, d, ArH), 7.64-7.46 (3H, m, ArH), 7.15 (1H, dd, ArH), 7.04 (1H, d, ArH), 4.34 (2H, t, O***CH***$_2$CH$_2$Br), 3.67 (1H, t, OCH$_2$***CH***$_2$Br); δ ^{13}C 156.24, 132.79, 130.20, 129.72, 129.63, 128.71, 128.37, 119.71, 117.39, 106.93, 67.78, 28.93.

6-Bromo-2(6-bromohexyloxy)naphthalene **2**.

% Yield : 71. M.p. 55-56°C. δ ^{1}H 7.89 (1H, d, ArH), 7.64-7.46 (3H, m, ArH), 7.15 (1H, dd, ArH), 7.06 (1H, d, ArH), 4.04 (2H, t, O***CH***$_2$(CH$_2$)$_5$Br), 3.42 (2H, t, O(CH$_2$)$_5$***CH***$_2$Br), 1.92-1.82 (4H, m, OCH$_2$***CH***$_2$(CH$_2$)$_2$***CH***$_2$CH$_2$Br), 1.55-1.49 (4H, m, O(CH$_2$)$_2$(***CH***$_2$)$_2$ (CH$_2$)$_2$Br); δ ^{13}C 157.28, 133.04, 129.92, 129.61, 129.54, 128.43, 128.32, 119.99, 116.91, 106.45, 67.76, 33.82, 32.65, 29.13, 27.92, 25.34.

6-Bromo-2(8-bromooctyloxy)naphthalene **3**.

% Yield : 78. M.p. 59-60°C. δ ^{1}H 7.89 (1H, d, ArH), 7.63-7.45 (3H, m, ArH), 7.16 (1H, dd, ArH), 7.06 (1H, d, ArH), 4.03 (2H, t, O***CH***$_2$(CH$_2$)$_7$Br), 3.40 (2H, t, O(CH$_2$)$_7$***CH***$_2$Br), 1.88-1.80 (4H, m, OCH$_2$***CH***$_2$(CH$_2$)$_4$***CH***$_2$CH$_2$Br), 1.49-1.36 (8H, m, O(CH$_2$)$_2$(***CH***$_2$)$_4$ (CH$_2$)$_2$Br); δ ^{13}C 57.34, 133.06, 129.90, 129.61, 129.50, 128.41, 128.32, 120.03, 116.87, 106.45, 67.96, 34.02, 32.76, 29.31, 29.13, 28.68, 28.09, 25.98.

6 - Bromo - 2 (9 - bromononyloxy) naphthalene **4**.

% Yield : 69. M.p. 62-63°C. δ ^{1}H 7.91 (1H, d, ArH), 7.64-7.55 (2H, m, ArH), 7.49 (1H, dd, ArH), 7.13 (1H, dd, ArH), 7.04 (1H, d, ArH), 4.03 (2H, t, O***CH***$_2$(CH$_2$)$_8$Br), 3.41 (2H, t, O(CH$_2$)$_8$***CH***$_2$Br), 1.88-1.82 (4H, m, OCH$_2$***CH***$_2$(CH$_2$)$_5$***CH***$_2$CH$_2$Br), 1.55-1.30 (10H, m, O(CH$_2$)$_2$(***CH***$_2$)$_5$(CH$_2$)$_2$Br); δ ^{13}C 157.35, 133.06, 129.88, 129.59, 129.50, 128.39, 128.30, 120.03, 116.85, 106.45, 67.99, 34.03, 32.78, 29.45, 29.25, 28.68, 28.12, 26.12, 26.04, 24.74.

6-Bromo-2(10-bromodecyloxy)naphthalene **5**.

% Yield : 76. M.p. 70-72°C. δ ^{1}H 7.90 (1H, d, ArH), 7.64-7.46 (3H, m, ArH), 7.17 (1H, dd, ArH), 7.08 (1H, d, ArH), 4.05 (2H, t, O***CH***$_2$(CH$_2$)$_9$Br), 3.41 (2H, t, O(CH$_2$)$_9$***CH***$_2$Br), 1.88-1.81 (4H, m, OCH$_2$***CH***$_2$(CH$_2$)$_6$***CH***$_2$CH$_2$Br), 1.55-1.33 (12H, m, O(CH$_2$)$_2$(***CH***$_2$)$_6$ (CH$_2$)$_2$Br); δ ^{13}C 157.37, 133.08, 129.90, 129.61, 129.52, 128.41, 128.32, 120.05, 116.85, 106.47, 68.03, 34.03, 32.79, 29.43, 29.33, 29.16, 28.73, 28.14, 26.06.

6-Bromo-2(12-bromododecyloxy)naphthalene **6.**

% Yield : 82. M.p. 69-71°C. δ ^{1}H 7.90 (1H, d, ArH), 7.64-7.46 (3H, m, ArH), 7.16 (1H, dd, ArH), 7.08 (1H, d, ArH), 4.05 (2H, t, O***CH***$_2$(CH$_2$)$_{11}$Br), 3.40 (2H, t, O(CH$_2$)$_{11}$***CH***$_2$Br), 1.88-1.81 (4H, m, OCH$_2$***CH***$_2$(CH$_2$)$_8$***CH***$_2$CH$_2$Br), 1.56-1.29 (16H, m, O(CH$_2$)$_2$***(CH2)***$_8$ (CH$_2$)$_2$Br); δ ^{13}C 157.39, 133.08, 129.90, 129.61, 129.52, 128.39, 128.32, 120.07, 116.85, 106.47, 68.07, 34.09, 32.83, 29.52, 29.42, 29.38, 29.18, 28.75, 28.16, 26.07.

Preparation of 6-bromo-2(ω-methylaminoalkyloxy)naphthalene hydrochlorides.

The amine hydrochloride derivatives were prepared from the appropriate ω-bromoalkyl-6-bromo-2-naphthyl ether and excess methylamine by the General methods B and C respectively

6-Bromo-2(6-methylaminohexyloxy)naphthalene HCl. **10.**

% Yield : 85. M.p. 179-180°C. δ ^{1}H 7.88 (1H, d, ArH), 7.62-7.54 (2H, m, ArH), 7.48 (1H, dd, ArH), 7.13 (1H, dd, ArH), 7.04 (1H, d, ArH), 4.00 (2H, t, O***CH***$_2$(CH$_2$)$_5$NHCH$_3$), 2.94 (2H, t, O(CH$_2$)$_5$***CH***$_2$NHCH$_3$), 2.67 (3H, s, O(CH$_2$)$_6$NH***CH***$_3$), 1.90-1.80 (4H, m, OCH$_2$***CH***$_2$(CH$_2$)$_2$***CH***$_2$CH$_2$NHCH$_3$), 1.51 (4H, m, O(CH$_2$)$_2$***(CH$_2$)***$_2$(CH$_2$)$_2$NHCH$_3$); δ ^{13}C 157.18, 133.01, 129.90, 129.59, 129.54, 128.43, 128.35, 119.94, 116.93, 106.47, 67.58, 49.33, 32.88, 28.89, 26.42, 25.84, 25.61. (Found : C, 54.85; H, 6.46; N, 3.60. C$_{17}$H$_{23}$BrClNO requires : C, 54.78; H, 6.22; N, 3.76 %)

6-Bromo-2(8-methylaminooctyloxy)naphthalene HCl. **9.**

% Yield : 72. M.p. 163-165°C. δ ^{1}H 7.88 (1H, d, ArH), 7.62-7.55 (2H, m, ArH), 7.49 (1H, dd, ArH), 7.15 (1H, dd, ArH), 7.06 (1H, d, ArH), 4.02 (2H, t, O***CH***$_2$(CH$_2$)$_6$ CH$_2$NHCH$_3$), 2.91 (2H, t, O(CH$_2$)$_7$***CH***$_2$NHCH$_3$), 2.66 (3H, s, O(CH$_2$)$_8$NH***CH***$_3$), 1.83-1.81 (4H, m, OCH$_2$***CH***$_2$(CH$_2$)$_4$***CH***$_2$CH$_2$NHCH$_3$), 1.37 (8H, m, O(CH$_2$)$_2$***(CH$_2$)***$_4$(CH$_2$)$_2$NHCH$_3$); δ ^{13}C 157.32, 133.04, 129.88, 129.59, 129.50, 128.41, 128.34, 120.02, 116.87, 106.47, 67.89, 49.40, 32.83, 29.29, 29.09, 28.95, 26.59, 25.95, 25.86. (Found : C, 57.14; H, 6.75; N 3.30. C$_{19}$H$_{27}$BrClNO requires : C, 56.94; H, 6.79; N, 3.49 %)

6-Bromo-2(9-methylaminononyloxy)naphthalene HCl **11.**

% Yield : 76. M.p. 160-161°C. δ ^{1}H 7.87 (1H, d, ArH), 7.62-7.58 (2H, m, ArH), 7.48 (1H, dd, ArH), 7.16 (1H, dd, ArH), 7.06 (1H, d, ArH), 4.01 (2H, t, O***CH***$_2$(CH$_2$)$_8$NHCH$_3$),

2.91 (2H, t, $O(CH_2)_8\boldsymbol{CH_2}NHCH_3$), 2.66 (3H, s, $O(CH_2)_9NH\boldsymbol{CH_3}$), 1.84-1.81 (4H, m, $OCH_2\boldsymbol{CH_2}(CH_2)_5\boldsymbol{CH_2}CH_2NHCH_3$), 1.34 (10H, m, $O(CH_2)_2\boldsymbol{(CH_2)_5}(CH_2)_2NHCH_3$); δ ^{13}C 157.36, 133.08, 129.90, 129.60, 129.52, 128.41, 128.35, 120.05, 116.87, 106.47, 67.96, 49.40, 32.79, 29.31, 29.24, 29.15, 28.97, 26.65, 26.02, 25.88. (Found : C, 58.02; H, 7.16; N, 3.08. $C_{20}H_{29}BrClNO$ requires : C, 57.91; H, 7.05; N, 3.38 %)

6-Bromo-2(10-methylaminodecyloxy)naphthalene HCl **12.**

% Yield : 73. M.p. 154-156°C. δ ^1H 7.89 (1H, d, ArH), 7.64-7.59 (2H, m, ArH), 7.49 (1H, dd, ArH), 7.16 (1H, dd, ArH), 7.07 (1H, d, ArH), 4.03 (2H, t, $O\boldsymbol{CH_2}(CH_2)_9NHCH_3$), 2.87 (2H, t, $O(CH_2)_9\boldsymbol{CH_2}NHCH_3$), 2.66 (3H, s, $O(CH_2)_{10}NH\boldsymbol{CH_3}$), 1.85-1.80 (4H, m, $OCH_2\boldsymbol{CH_2}(CH_2)_6\boldsymbol{CH_2}CH_2NHCH_3$), 1.31 (12H, m, $O(CH_2)_2\boldsymbol{(CH_2)_6}(CH_2)_2NHCH_3$); δ ^{13}C 157.37, 133.08, 129.90, 129.61, 129.52, 128.41, 128.34, 120.07, 116.87, 106.47, 68.01, 49.42, 32.78, 29.43, 29.31, 29.18, 29.02, 26.67, 26.07, 25.89. (Found : C, 58.75; H, 7.22; N, 3.17. $C_{21}H_{31}BrClNO$ requires : C, 58.82; H, 7.29; N, 3.27 %)

6-Bromo-2(12-methylaminododecyloxy)naphthalene HCl. **13.**

% Yield : 68. M.p. 152-155°C. δ ^1H 7.90 (1H, d, ArH), 7.65-7.89 (2H, m, ArH), 7.50 (1H, dd, ArH), 7.17 (1H, dd, ArH), 7.08 (1H, d, ArH), 4.04 (2H, t, $O\boldsymbol{CH_2}(CH_2)_{11}NHCH_3$), 2.91 (2H, t, $O(CH_2)_{11}\boldsymbol{CH_2}NHCH_3$), 2.67 (3H, s, $O(CH_2)_{12}NH\boldsymbol{CH_3}$), 1.86-1.81 (4H, m, $OCH_2\boldsymbol{CH_2}(CH_2)_8\boldsymbol{CH_2}CH_2NHCH_3$), 1.27 (16H, m, $O(CH_2)_2\boldsymbol{(CH_2)_8}(CH_2)_2NHCH_3$); δ ^{13}C 157.54, 133.21, 130.04, 129.65, 129.56, 128.41, 128.32, 120.07, 116.93, 106.85, 68.23, 49.33, 29.53, 29.47, 29.36, 29.24, 29.02, 26.70, 26.09, 25.81. (Found : C, 60.52; H, 7.90; N, 3.10. $C_{23}H_{35}BrClNO$ requires : C, 60.46; H, 7.72; N, 3.07 %)

Preparation of compounds with the general structure Ar-O-$(CH_2)_nNR_1R_2$ where Ar is 6-bromo-2-naphthyl.

Primary amine

Preparation of 6-bromo-2(8-aminooctyloxy)naphthalene HCl **8.**

a) Preparation of *N*1-[8-(6-bromo-2-naphthyloxy)octyl]-2,2,2-trifluoroacetamide **7.**

To a suspension of NaH (60% in oil, 0.21g, 5.3 mmol) in dry dimethylformamide (25ml), at room temperature under an atmosphere of nitrogen, was added a solution of

trifluoroacetamide (0.59g, 5.2mmol) in dimethylformamide (5ml) over a period of 5 min. The mixture was stirred for 1h. A solution of intermediate **3** (1.2g, 2.9mmol) in dimethylformamide (5ml) was added and the mixture was gently refluxed for 3h. T.l.c, petroleum ether:ethyl acetate, 7:3, indicated disappearance of starting material (Rf 0.49) and formation of a new compound (Rf 0.23). The mixture was allowed to cool and was quenched by the dropwise addition of methanol (2ml). The solvent was removed in *vacuo* and the residue dissolved in ethyl acetate (50ml) and partitioned with water (2×20ml) and saturated sodium chloride (15ml). The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The crude solid was purified by chromatography, gradient elution with petroleum ether:ethyl acetate, 20:1 to 4:1. Fractions containing the product were combined and concentrated in *vacuo* to give compound **7** as a white solid, 0.66g (51%). M.p. 84-86°C. δ ^{1}H 7.89 (1H, d, ArH), 7.65-7.56 (2H, m, ArH), 7.49 (1H, dd, ArH), 7.16 (1H, dd, ArH), 7.08 (1H, d, ArH), 4.04 (2H, t, $O\boldsymbol{CH_2}(CH_2)_7NHCOCF_3$), 3.37 (2H, q, $O(CH_2)_7\boldsymbol{CH_2}NHCOCF_3$), 1.85-1.80 (2H, m, $O(CH_2)_6\boldsymbol{CH_2}CH_2NHCOCF_3$), 1.61-1.47 (4H, m, $OCH_2\boldsymbol{CH_2}(CH_2)_3\boldsymbol{CH_2}CH_2CH_2NHCOCF_3$), 1.40-1.36 (6H, m, $O(CH_2)_2\boldsymbol{(CH_2)_3}(CH_2)_3NHCOCF_3$); δ ^{13}C 157.45, 157.34, 156.91, 133.08, 129.90, 129.61, 129.52, 128.41, 128.34, 120.03, 117.99, 116.89, 113.75, 106.47, 67.94, 29.18, 29.13, 29.06, 28.91, 26.58, 25.98.

b) Preparation of compound **8**.

Intermediate **7** (0.34g, 0.8mmol) was suspended in a mixture of 20% NaOH (10ml) and methanol (4ml) at room temperature and stirred vigorously for 6 h. T.l.c., petroleum ether : ethyl acetate, 4:1, indicated disappearance of starting material (Rf 0.27) and formation of baseline material. The mixture was extracted with dichloromethane (2×20ml) and the combined organics were partitioned with saturated sodium chloride (15ml). The organic fraction was dried over Na_2SO_4, filtered, and concentrated in vacuo to give a white solid. The hydrochloride salt was prepared by the General method C to give compound **8** as a white crystalline solid, 0.21g (71%). M.p. 179-182°C. δ ^{1}H 8.10 (1H, d, ArH), 7.84-7.77 (2H, m, ArH), 7.58 (1H, dd, ArH), 7.35 (1H, d, ArH), 7.23 (1H, dd, ArH), 4.06 (2H, t, $O\boldsymbol{CH_2}(CH_2)_7NH_2$), 2.76 (2H, t, $O(CH_2)_7\boldsymbol{CH_2}NH_2$), 1.77 (2H, m, $OCH_2\boldsymbol{CH_2}(CH_2)_6NH_2$), 1.58 (2H, m, $O(CH_2)_6\boldsymbol{CH_2}CH_2NH_2$), 1.44 (2H, m, $O(CH_2)_2\boldsymbol{CH_2}(CH_2)_3NH_2$), 1.31 (6H, m, $O(CH_2)_3\boldsymbol{(CH_2)_3}(CH_2)_2NH_2$); δ ^{13}C 157.07, 133.03, 129.65, 129.40, 129.26, 128.99, 128.66, 120.02, 116.23, 106.72, 67.69, 38.58, 28.68, 28.59, 27.01, 25.92, 25.56. (Found : C, 56.05; H, 6.46; N, 3.71. $C_{18}H_{25}BrClNO$ requires : C, 55.90; H, 6.52; N, 3.62 %)

Secondary Amines.

The following secondary amine hydrochlorides were prepared from intermediates **3** or **5** and the appropriate primary amine by the General methods B and C respectively.

6-Bromo-2(10-ethylaminodecyloxy)naphthalene HCl **14.**

% Yield : 62. M.p. 155-157°C. δ ^{1}H 8.10 (1H, d, ArH), 7.84-7.76 (2H, m, ArH), 7.57 (1H, dd, ArH), 7.35 (1H, d, ArH), 7.22 (1H, dd, ArH), 4.07 (2H, t, O***CH$_2$***$(CH_2)_9$ $NHCH_2CH_3$), 2.91-2.82 (4H, m, $O(CH_2)_9$***CH$_2$***NH***CH$_2$***CH_3), 1.77 (2H, m, OCH_2***CH$_2$*** $(CH_2)_8NHCH_2CH_3$), 1.58 (2H, m, $O(CH_2)_8$***CH$_2$***$CH_2NHCH_2CH_3$),1.45 (2H, m, OCH_2CH_2 ***CH$_2$***$(CH_2)_7NHCH_2CH_3$), 1.29 (10H, m, $O(CH_2)_3$***(CH$_2$)$_5$***$(CH_2)_2NHCH_2CH_3$); δ ^{13}C 157.37, 133.08, 129.90, 129.59, 129.50, 128.41, 128.34, 120.05, 116.85, 106.47, 68.03, 50.46, 45.84, 28.88, 28.79, 28.72, 28.58, 28.54, 26.10, 25.54, 22.90, 8.38. (Found : C, 59.72; H, 7.53; N, 3.14. $C_{22}H_{33}BrClNO$ requires : C, 59.67; H, 7.51; N, 3.16 %)

6-Bromo-2(10-benzylaminodecyloxy)naphthalene HCl **15.**

% Yield : 69. M.p. 173-175°C. δ ^{1}H 8.10 (1H, d, Ar_{nap}), 7.83-7.76 (2H, m, Ar_{nap}), 7.57-7.53 (3H, m, $Ar_{Bn\times2}$, $Ar_{nap\times1}$), 7.44-7.41 (3H, m, Ar_{Bn}), 7.35 (1H, d, Ar_{nap}), 7.22(1H, dd, Ar_{nap}), 4.11 (4H, m, O***CH$_2$***$(CH_2)_9NH$***CH$_2$***Ph), 2.85 (2H, t, $O(CH_2)_9$***CH$_2$***$NHCH_2Ph$), 1.80 (2H, m, OCH_2***CH$_2$***$(CH_2)_8NHCH_2Ph$), 1.77 (2H, m, $O(CH_2)_8$***CH$_2$***CH_2NHCH_2Ph), 1.45 (2H, m, OCH_2CH_2***CH$_2$***$(CH_2)_7NHCH_2Ph$), 1.27 (10H, m, $O(CH_2)_3$***(CH$_2$)$_5$***$(CH_2)_2NHCH_2$ Ph); δ ^{13}C 158.49, 139.23, 134.57, 129.94, 129.59, 129.50, 128.81, 128.26, 127.93, 127.87, 126.80, 121.93, 117.00, 106.90, 67.85, 52.77, 50.99, 30.02, 29.79, 29.68, 29.22, 29.06, 28.70, 27.28, 25.66. (Found : C, 56.05; H, 6.46; N, 3.71. $C_{27}H_{33}BrClNO$ 1/4 H_2O requires : C, 55.90; H, 6.52; N, 3.62 %)

6-Bromo-2(8-isopropylaminooctyloxy)naphthalene HCl **16.**

% Yield : 74. M.p. 147-149°C. δ ^{1}H 8.10 (1H, d, ArH), 7.84-7.76 (2H, m, ArH), 7.58 (1H, dd, ArH), 7.36 (1H, d, ArH), 7.20 (1H, dd, ArH), 4.08 (2H, t, O***CH$_2$***$(CH_2)_7NH$ $CH(CH_3)_2$), 3.22 (1H, m, $O(CH_2)_8NH$***CH***$(CH_3)_2$), 2.82 (2H, t, $O(CH_2)_7$***CH$_2$***$NHCH(CH_3)_2$), 1.78 (2H, m, OCH_2***CH$_2$***$(CH_2)_6NHCH(CH_3)_2$), 1.63 (2H, m, $O(CH_2)_6$***CH$_2$***CH_2NHCH $(CH_3)_2$), 1.46-1.33 (8H, m, $O(CH_2)_2$***(CH$_2$)$_4$***$(CH_2)_2NHCH(CH_3)_2$), 1.25-1.22 (6H, d, $O(CH_2)_8NHCH$***(CH$_3$)$_2$***); δ ^{13}C 157.00, 132.94, 129.90, 129.35, 129.18, 128.88, 128.57, 119.93, 116.23, 106.69, 67.60, 49.24, 43.74, 28.88, 28.58, 28.50, 26.04, 25.66, 25.47,

18.57. (Found : C, 58.83; H, 7.21; N, 3.02. $C_{21}H_{30}BrClNO$ requires : C, 58.96; H, 7.07; N, 3.27 %)

6-Bromo-2(10-cyclopropylmethylaminodecyloxy)naphthalene HCl **17.**

% Yield : 55. M.p. 173-175°C. δ ^{1}H 7.89 (1H, d, ArH), 7.63-7.58 (2H, m, ArH), 7.54 (1H, dd, ArH), 7.15 (1H, dd, ArH), 7.06 (1H, d, ArH), 4.02 (2H, t, O***CH₂***$(CH_2)_9$NH $CH_2CH(CH_2)_2$), 2.99 (2H, t, $O(CH_2)_9$***CH₂***$NHCH_2CH(CH_2)_2$), 2.83 (2H, m, $O(CH_2)_{10}$NH ***CH₂***$CH(CH_2)_2$), 1.85-1.79 (4H, m, OCH_2***CH₂***$(CH_2)_6$***CH₂***$CH_2NHCH_2CH(CH_2)_2$), 1.48 (2H, m, $O(CH_2)_2$***CH₂***$(CH_2)_7NHCH_2CH(CH_2)_2$), 1.31 (11H, m, $O(CH_2)_3$***(CH₂)₅***$(CH_2)_2$NH CH_2***CH***$(CH_2)_2$), 0.71 (2H, d, $O(CH_2)_{10}NHCH_2CH$***(CH₂)₂***), 0.46 (2H, d, $O(CH_2)_{10}NHCH_2$ CH***(CH₂)₂***); δ ^{13}C 157.37, 133.08, 129.90, 129.59, 129.50, 128.41, 128.34, 120.05, 116.85, 106.47, 68.01, 52.04, 46.99, 29.45, 29.38, 29.33, 29.18, 29.09, 26.92, 26.07, 25.97, 6.90, 4.73. (Found : C, 61.31; H, 7.56; N, 3.19. $C_{24}H_{35}BrClNO$ requires : C, 61.48; H, 7.52; N, 2.99 %)

Tertiary amines

The following tertiary amine hydrochlorides were prepared from 6-bromo-2(10-bromodecyloxy)naphthalene **5** and the appropriate secondary amine by the General methods B and C respectively.

6-Bromo-2(10-dimethylaminodecyloxy)naphthalene HCl **18.**

% Yield : 76. M.p. 138-140°C. δ ^{1}H 7.90 (1H, d, ArH), 7.65-7.57 (2H, m, ArH), 7.49 (1H, d, ArH), 7.17 (1H, dd, ArH), 7.09 (1H, d, ArH), 4.05 (2H, t, O***CH₂***$(CH_2)_9N(CH_3)_2$), 2.96 (2H, t, $O(CH_2)_9$***CH₂***$N(CH_3)_2$), 2.80 (6H, d, $O(CH_2)_{10}N$***(CH₃)₂***), 1.86-1.81 (4H, m, OCH_2***CH₂***$(CH_2)_6$***CH₂***$CH_2N(CH_3)_2$), 1.49 (2H, m, $O(CH_2)_2$***CH₂***$(CH_2)_7N(CH_3)_2$), 1.33 (10H, m, $O(CH_2)_3$***(CH₂)₅***$(CH_2)_2N(CH_3)_2$); δ ^{13}C 157.39, 133.08, 129.90, 129.61, 129.52, 128.41, 128.35, 120.07, 116.87, 106.50, 68.01, 58.06, 42.80, 29.36, 29.24, 29.15, 28.98, 26.63, 26.02, 24.22. (Found : C, 59.57; H, 7.54; N, 3.18. $C_{22}H_{33}BrClNO$ requires : C, 59.67; H, 7.51; N, 3.16 %)

6-Bromo-2(10-diethylaminodecyloxy)naphthalene HCl **19.**

% Yield : 64. M.p. 112-114°C. δ ^{1}H 8.10 (1H, d, ArH), 7.84-7.76 (2H, m, ArH), 7.58 (1H, dd, ArH), 7.35 (1H, d, ArH), 7.19 (1H, dd, ArH), 4.07 (2H, t, O***CH₂***$(CH_2)_9$

$N(CH_2CH_3)_2$), 3.04 (4H, m, $O(CH_2)_{10}N(\boldsymbol{CH_2}CH_3)_2$), 2.94 (2H, t, $O(CH_2)_9\boldsymbol{CH_2}N(CH_2CH_3)_2$), 1.78 (2H, t, $OCH_2\boldsymbol{CH_2}(CH_2)_8N(CH_2CH_3)_2$), 1.75 (2H, m, $O(CH_2)_8\boldsymbol{CH_2}CH_2N(CH_2CH_3)_2$), 1.45 (2H, m, $OCH_2CH_2\boldsymbol{CH_2}(CH_2)_5(CH_2)_2N(CH_2CH_3)_2$), 1.29 (10H, m, $O(CH_2)_3\boldsymbol{(CH_2)_5}(CH_2)_2N(CH_2CH_3)_2$), 1.20 (6H, t, $O(CH_2)_{10}N(CH_2\boldsymbol{CH_3})_2$); δ ^{13}C 157.41, 133.10, 129.91, 129.62, 129.56, 128.86, 128.37, 119.91, 116.85, 106.51, 68.01, 50.46, 45.84, 28.88, 28.79, 28.72, 28.58, 28.54, 26.10, 25.54, 22.90, 8.38. (Found : C, 60.51; H, 7.99; N, 2.71. $C_{24}H_{37}BrClNO$ 1/4H_2O requires : C, 60.63; H, 7.95; N, 2.95 %)

6-Bromo-2(10-morpholinodecyloxy)naphthalene HCl **20.**

% Yield : 72. M.p. 157-159°C. δ ^{1}H 8.11 (1H, d, ArH), 7.85-7.78 (2H, m, ArH), 7.59 (1H, dd, ArH), 7.36 (1H, d, ArH), 7.25 (1H, dd, ArH), 4.11 (2H, t, $O\boldsymbol{CH_2}(CH_2)_9N(CH_2CH_2)_2O$), 3.94-3.86 (4H, m, $O(CH_2)_{10}N(CH_2\boldsymbol{CH_2})_2O$), 3.41 (2H, t, $O(CH_2)_9\boldsymbol{CH_2}N(CH_2CH_2)_2O$), 3.07-3.00 (4H, m, $O(CH_2)_{10}N(\boldsymbol{CH_2}CH_2)_2O$), 1.83-1.71 (4H, m, $OCH_2\boldsymbol{CH_2}(CH_2)_6\boldsymbol{CH_2}CH_2N(CH_2CH_2)_2O$), 1.47 (2H, m, $OCH_2CH_2\boldsymbol{CH_2}(CH_2)_7N(CH_2CH_2)_2O$), 1.32 (10H, m, $O(CH_2)_3\boldsymbol{(CH_2)_5}(CH_2)_2N(CH_2CH_2)_2O$); δ ^{13}C 157.36, 132.81, 129.47, 129.18, 129.02, 128.70, 128.41, 119.75, 115.98, 106.72, 67.53, 62.97, 55.74, 50.71, 28.70, 28.56, 28.45, 28.31, 25.90, 25.38, 22.47. (Found : C, 59.18; H, 7.44; N, 3.13. $C_{24}H_{35}BrClNO_2$ requires : C, 59.45; H, 7.27; N, 2.89 %)

Preparation of 4-bromo-1-naphthyloxy and 5-bromo-1-naphthyloxy derivatives.

Preparation of 4-bromo-1(10-methylaminodecyloxy)naphthalene HCl **21.**

a) Preparation of 4-bromo-1-naphthol **23**.

To a solution of 1-naphthol (0.72g, 5.0mmol) in dry acetonitrile (20ml) at room temperature under an atmosphere of nitrogen was added *N* - bromosuccinimide (0.89g, 5.0mmol) in one portion to give a deep red homogenous mixture which was stirred for 30 min. T.l.c, petroleum ether : ethyl acetate, 4:1, indicated the presence of a new compound with an Rf value similar to that of 1–naphthol (Rf 0.23). The solvent was removed in *vacuo*, and the residue was dissolved in dichloromethane (50ml) and partitioned with water (2×20ml) and saturated sodium chloride (15ml). The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude solid. The solid was purified by chromatography eluting with petroleum ether:ethyl acetate, 5:1. Fractions containing the product (Rf 0.22) were combined and concentrated in *vacuo* to

give compound **23** as a crimson solid, 0.71g (63%). M.p. 116-118°C, [lit. [175]m.p. 121°C]. δ ^{1}H 8.19 (2H, dd, ArH), 7.59-7.56 (3H, m, ArH), 6.71 (1H, d, ArH), 5.38 (1H, br.s., disappeared on D_2O shake, ArO***H***); δ ^{13}C 151.25, 132.68, 129.38, 127.87, 126.04, 125.59, 122.15, 113.42, 109.16.

b) Preparation of 4-bromo-1(10-bromodecyloxy)naphthalene **24**.

The title compound was prepared from 4-bromo-1-naphthol **23** and 1,10-dibromodecane by the General method A. % Yield : 78. M.p. 53-55°C. δ ^{1}H 8.28 (1H, d, ArH), 8.14 (1H, d, ArH), 7.65-7.51 (3H, m, ArH), 6.68 (1H, d, ArH), 4.10 (2H, t, O***CH$_2$***$(CH_2)_9Br$), 3.40 (2H, t, $O(CH_2)_9$***CH$_2$***Br), 1.94-1.82 (4H, m, OCH_2***CH$_2$***$(CH_2)_6$***CH$_2$***CH_2Br), 1.55 (2H, m, $O(CH_2)_2$***CH$_2$***$(CH_2)_7Br$), 1.39-1.32 (10H, m, $O(CH_2)_3$***(CH$_2$)$_5$***$(CH_2)_2Br$); δ ^{13}C 154.68, 132.43, 129.50, 127.67, 126.95, 126.83, 125.82, 122.50, 112.88, 105.23, 68.34, 34.07, 32.79, 29.45, 29.36, 29.33, 29.16, 28.73, 28.16, 26.20.

c) Preparation of 4-bromo-1(10-methylaminodecyloxy)naphthalene_HCl **21**.

The title compound was prepared from intermediate **24** and an excess of 33% methylamine in ethanol by the General methods B and C respectively. % Yield : 52. M.p. 107-109°C. δ ^{1}H 8.23 (1H, d, ArH), 8.13 (1H, d, ArH), 7.64-7.50 (3H, m, ArH), 6.66 (1H, d, ArH), 4.09 (2H, t, O***CH$_2$***$(CH_2)_9NHCH_3$), 2.87 (2H, t, $O(CH_2)_9$***CH$_2$***$NHCH_3$), 2.66 (3H, s, $O(CH_2)_{10}NH$***CH$_3$***), 1.91-1.87 (4H, m, OCH_2***CH$_2$***$(CH_2)_6$***CH$_2$***CH_2NHCH_3), 1.53 (2H, m, $O(CH_2)_2$***CH$_2$***$(CH_2)_7NHCH_3$), 1.38-1.33 (10H, m, $O(CH_2)_3$***(CH$_2$)$_5$***$(CH_2)_2NHCH_3$); δ ^{13}C 154.77, 132.56, 129.56, 127.69, 127.10, 126.86, 125.86, 122.55, 112.99, 105.43, 68.48, 49.58, 33.14, 29.45, 29.33, 29.22, 29.06, 26.77, 26.24, 26.00. (Found : C, 58.98; H, 7.12; N, 2.86. $C_{21}H_{31}BrClNO$ requires : C, 58.82; H, 7.29; N, 3.27 %)

Preparation of 5-bromo-1(10-methylaminodecyloxy)naphthalene HCl **22**.

a) Preparation of 5-bromo-1-naphthaldehyde **25**[176].

To a solution of 1-naphthaldehyde (10.0g, 64mmol) in chloroform (20ml) at room temperature was added bromine (3.30 ml, 64mmol) and the mixture was refluxed until the evolution of HBr had ceased. The mixture was allowed to cool and the solvent was removed in *vacuo* to give an orange residue. The residue was extracted with boiling toluene (50ml) and filtered. The filtrate was allowed to cool, stirred vigorously with saturated $Na_2S_2O_5$ (70ml) for 1h, and allowed to stand at room temperature for 18h. The

pale yellow heterogeneous mixture was filtered and the solid bisulfite complex was suspended in a 10% solution of $NaCO_3$ (45ml), stirred vigorously for 3h and filtered. The pale yellow solid was recrystallised from ethanol to give compound **32** as a white solid, 6.90g (69%). M.p. 98-100°C, [lit. [176]m.p. 105°C]. δ ^{1}H 10.37 (1H, s, ArC***H***O), 9.22 (1H, d, ArH), 8.55 (1H, d, ArH), 7.99 (1H, d, ArH), 7.85 (1H, d, ArH), 7.73-7.67 (1H, m, ArH), 7.52-7.46 (1H, m, ArH); δ ^{13}C 192.92, 137.94, 134.14, 131.46, 131.18, 129.29, 128.44, 126.20, 124.85, 124.65, 123.34.

b) Preparation of 5-bromo-1-naphthol **26**.

i/ Preparation of 5-bromo-1-naphthyl formate.

To a solution of 5-bromo-1-naphthaldehyde **25** (3.0g, 12.8mmol) in chloroform (80ml) at room temperature was added a solution of *m*-chloroperoxybenzoic acid (50%, 8.8g, 25.5mmol) over a period of 5 min. The mixture was stirred at room temperature for 48h. T.l.c., petroleum ether : ethyl acetate, 4 : 1, indicated the disappearance of starting material (Rf 0.41) and the formation of a new compound (Rf 0.35). The mixture was partitioned with saturated $NaHCO_3$ (2×25ml), saturated sodium chloride (25ml), and the organic phase was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give the crude formate as a grey solid, 2.27g (71%), which was used without further purification. M.p. 73-75 °C.

ii/ Preparation of 5-bromo-1-naphthol **26**.

To a solution of the naphthyl formate (1.98g, 7.9mmol) suspended in methanol (40ml) at room temperature was added 2M HCl (5ml) and the heterogenous mixture was stirred for 3h. T.l.c, petroleum ether:ethyl acetate, 4:1, indicated the disappearance of the formate (Rf 0.35) and the formation of a new compound (Rf 0.24). The solvent was removed in *vacuo* and the residue was dissolved in ethyl acetate (50ml) and partitioned with saturated sodium chloride (20ml). The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude solid that was purified by chromatography eluting with petroleum ether:ethyl acetate, 4:1. Fractions containing the product were combined and concentrated in *vacuo* to give compound **26** as a buff coloured solid, 1.30g (74%). M.p. 134-136°C, [lit. [27]m.p. 138°C]. δ ^{1}H 8.20 (1H, d, ArH), 7.84-7.77 (2H, m, ArH), 7.40 (1H, m, ArH), 7.29 (1H, m, ArH), 6.86 (1H, d, ArH), 5.37 (1H, br.s., disappeared on D_2O shake, ArO***H***); δ ^{13}C 151.41, 133.24, 130.64, 127.67, 127.13, 125.26, 122.60, 121.67, 119.93, 109.38.

c) Preparation of 5-bromo-1(10-bromodecyloxy)naphthalene **27**.

The title compound was prepared from 5-bromo-1-naphthol **26** and 1,10-dibromodecane by the General method A. % Yield : 77. M.p. 61-63°C. δ ^{1}H 8.26 (1H, d, ArH), 7.80-7.49 (2H, m, ArH), 7.46-7.43 (1H, m, ArH), 7.31-7.25 (1H, m, ArH), 6.86 (1H, d, ArH), 4.12 (2H, t, O***CH***$_2$(CH$_2$)$_9$Br), 3.40 (2H, t, O(CH$_2$)$_9$***CH***$_2$Br), 1.94-1.81 (4H, m, OCH$_2$***CH***$_2$(CH$_2$)$_6$***CH***$_2$CH$_2$Br), 1.55 (2H, m, OCH$_2$CH$_2$***CH***$_2$(CH$_2$)$_7$Br), 1.42-1.31 (10H, m, O(CH$_2$)$_3$***(CH$_2$)$_5$***(CH$_2$)$_2$Br); δ ^{13}C 154.80, 132.97, 130.46, 127.38, 126.99, 125.21, 122.41, 122.05, 118.96, 105.25, 68.37, 34.05, 32.79, 29.43, 29.36, 29.33, 29.20, 28.73, 28.14, 26.20.

d) Preparation of 5-bromo-1(10-methylaminodecyloxy)naphthalene HCl **22**.

The title compound was prepared from **27** and an excess of 33% methylamine in ethanol by the General methods B and C respectively. % Yield : 63. M.p. 157-159°C. δ ^{1}H 8.29 (1H, d, ArH), 7.80-7.76 (2H, m, ArH), 7.46 (1H, t, ArH), 7.26 (1H, m, ArH), 6.85 (1H, d, ArH), 4.11 (2H, t, O***CH***$_2$(CH$_2$)$_9$NHCH$_3$), 2.88 (2H, t, O(CH$_2$)$_9$***CH***$_2$NHCH$_3$), 2.65 (3H, s, O(CH$_2$)$_{10}$NH***CH$_3$***), 1.93-1.85 (4H, m, OCH$_2$***CH***$_2$(CH$_2$)$_6$***CH***$_2$CH$_2$NHCH$_3$), 1.54 (2H, m, OCH$_2$CH$_2$***CH***$_2$(CH$_2$)$_7$NHCH$_3$), 1.33 (10H, m, O(CH$_2$)$_3$***(CH$_2$)$_5$***(CH$_2$)$_2$NHCH$_3$); δ ^{13}C 154.89, 132.90, 130.47, 127.33, 127.06, 125.25, 122.42, 122.08, 119.01, 105.34, 68.43, 49.40, 32.74, 29.43, 29.31, 29.24, 29.02, 26.68, 26.24, 25.88. (Found : C, 58.81; H, 7.38; N, 3.13. C$_{21}$H$_{31}$BrClNO requires : C, 58.82; H, 7.29; N, 3.27 %).

Preparation of 2-naphthol, 6-iodo-2-naphthol, 6-fluoro-2-naphthol, and 6-chloro-2-naphthol derivatives.

Preparation of 2-(8-methylaminooctyloxy)naphthalene HCl **28**.

a) Preparation of 2-(8-bromooctyloxy)naphthalene **32**.

The title compound was prepared from 2-naphthol and 1,8-dibromooctane by the General method A. % Yield : 78. M.p. 128-129°C. δ ^{1}H 7.77-7.70 (3H, m, ArH), 7.45-7.39 (1H, t, ArH), 7.35-7.31 (1H, t, ArH), 7.16-7.12 (2H, d, ArH), 4.07 (2H, t, O***CH***$_2$(CH$_2$)$_7$Br), 3.41 (2H, t, O(CH$_2$)$_7$***CH***$_2$Br), 1.89-1.81 (4H, m, OCH$_2$***CH***$_2$(CH$_2$)$_4$***CH***$_2$CH$_2$Br), 1.54-1.38 (8H, m, O(CH$_2$)$_2$***(CH$_2$)$_4$***(CH$_2$)$_2$Br); δ ^{13}C 157.05, 134.59, 129.31, 128.86, 127.62, 126.66, 126.29, 123.47, 118.99, 106.50, 67.91, 34.02, 32.78, 29.20, 28.70, 28.10, 26.02.

b) Preparation of 2-(8-methylaminooctyloxy)naphthalene.HCl **28**.

The title compound was prepared from **32** and an excess of 33% methylamine in ethanol by the General methods B and C respectively. % Yield : 76. M.p. 162-163°C. δ ^{1}H 7.76-7.70 (3H, m, ArH), 7.45-7.39 (1H, m, ArH), 7.34-7.26 (1H, m, ArH), 7.14 (2H, d, ArH), 4.04 (2H, t, $OCH_2(CH_2)_7NHCH_3$), 2.89 (2H, t, $O(CH_2)_7CH_2NHCH_3$), 2.64 (3H, s, $O(CH_2)_8NHCH_3$), 1.85-1.79 (4H, m, $OCH_2CH_2(CH_2)_4CH_2CH_2NHCH_3$), 1.48-1.38 (8H, m, $O(CH_2)_2(CH_2)_4(CH_2)_2NHCH_3$); δ ^{13}C 157.01, 134.57, 129.29, 128.84, 127.60, 126.68, 126.27, 123.45, 118.99, 106.50, 67.80, 49.36, 32.76, 29.11, 28.95, 28.72, 26.58, 25.97, 25.84. (Found : C, 70.28; H, 8.68; N, 4.23. $C_{19}H_{28}BrClNO$ 1/4H_2O requires : C, 69.92; H, 8.80; N, 4.29 %).

Attempted preparation of 6-iodo-2(*tert*-butyldimethylsilyloxy)naphthalene.

a) Preparation of 6-bromo-2(*tert*-butyldimethylsilyloxy)naphthalene **33**.

6-Bromo-2-naphthol (2.50g, 11.2mmol), imidazole (3.81g, 56.0mmol), and *tert*-butyldimethylsilyl chloride (3.89g, 25.8mmol) were dissolved in dichloromethane (40ml) at room temperature under an atmosphere of nitrogen and stirred for 18h. T.l.c., petroleum ether : ethyl acetate : methanol, 4 : 1 : 0.25, indicated the disappearance of starting material (Rf 0.32) and formation of a new compound (Rf 0.72). The mixture was partitioned with 2M sodium hydroxide (20ml), water (20ml), and saturated sodium chloride (15ml) to give a homogeneous organic layer. The organics were dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a viscous oil that solidified on cooling. The crude solid was recrystallised from ethanol to give compound **33** as a white amorphous solid, 3.06g (81%). δ ^{1}H 7.66 (1H, d, ArH), 7.37 (1H, d, ArH), 7.25 (2H, m, ArH), 6.90 (1H, d, ArH), 6.85 (1H, d, ArH), 0.77 (9H, s, $ArOSi(CH_3)_2C(CH_3)_3$), 0.0 (6H, s, $ArOSi(CH_3)_2C(CH_3)_3$); δ ^{13}C 153.80, 133.03, 130.24, 129.56, 129.38, 128.43, 128.30, 123.06, 117.25, 114.86, 25.66, 18.22, -4.36.

b) Attempted preparation of 6-iodo-2(*tert*-butyldimethylsilyloxy)naphthalene.

6-Bromo-2(*tert*-butyldimethylsilyloxy)naphthalene **33** (1.00g, 2.96mmol) was dissolved in anhydrous tetrahydrofuran (30ml) at room temperature under an atmosphere of nitrogen and cooled to -70°C. *n*-Butyl lithium (2M, 1.63ml, 3.26mmol) was added maintaining a temperature below -65°C to give a pale yellow mixture. The mixture was stirred for 20min. and iodine (1.13g, 8.89mmol) dissolved in tetrahydrofuran (4ml) was added maintaining a temperature below -65°C. The mixture was allowed to attain room

temperature and stirred for 3h. The solvent was removed in *vacuo* to give a black oil that was dissolved in ethyl acetate (50ml) and partitioned with a 10% solution of sodium metabisulfite (2×30ml), water (20ml), and saturated sodium chloride (15ml). The organics were dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude brown oil, 0.98g. T.l.c., petroleum ether : ethyl acetate, 40 : 1, indicated the presence of starting material (Rf 0.52), an impurity (Rf 0.15), and intense base line material. The crude oil was purified by chromatography eluting with petroleum ether:ethyl acetate, 10:0.1. Fractions containing the product (Rf 0.42) were combined and concentrated in *vacuo* to give a white solid, 0.42g (37%). Analysis of the product by N.M.R. indicated it to be a mixture of starting material **33**, as the major component, and 6-iodo-2(t-butyldimethylsilyloxy)naphthalene. Experiment abandoned.

Preparation of 6-iodo-2(10-methylaminodecyloxy)naphthalene HCl **43**.

a) Preparation of 6-bromo-2-methoxynaphthalene **34**.

To a suspension of 6-bromo-2-naphthol (5.00g, 22.4mmol) and powdered potassium carbonate (7.74g, 56.0mmol) in 2-butanone (100ml) at room temperature under an atmosphere of nitrogen, was added methyl iodide (2.80ml, 44.8mmol). The heterogenous mixture was stirred at room temperature for 24h. T.l.c., petroleum ether:ethyl acetate, 4:1, indicated the disappearance of starting material (Rf 0.26) and formation of a new compound (Rf 0.54). The solvent was removed in *vacuo* and the residue was suspended in ethyl acetate (75ml), filtered, and partitioned with 2M NaOH (2×20ml), 10% $Na_2S_2O_5$ (20ml), and saturated sodium chloride (15ml). The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a white solid. The solid was recrystallised from ethanol to give compound **34** as a white solid, 4.40g (83%).M.p. 109-110°C, [lit. [177]m.p. 108-111°C]. δ ^{1}H 7.89 (1H, d, ArH), 7.59-7.56 (2H, m, ArH), 7.49 (1H, dd, ArH), 7.15 (1H, dd, ArH), 7.06 (1H, d, ArH), 3.89 (3H, s, ArO***CH*$_3$**); δ ^{13}C 157.86, 133.04, 129.99, 129.65, 129.61, 128.48, 128.37, 119.76, 117.02, 105.73, 55.33.

b) Preparation of 6-iodo-2-methoxynaphthalene **35**.

To a suspension of magnesium (0.45g, 18.6mmol) in dry tetrahydrofuran (4ml) at room temperature under an atmosphere of nitrogen, was added 1ml of intermediate **34** (4.00g, 16.9mmol) dissolved in tetrahydrofuran (12.0ml). The reaction was initiated by the addition of a crystal of iodine, with gentle heating, and once initiated the remaining

solution of **34** was added at such a rate to maintain reflux. Upon complete addition, 15 min., the mixture was maintained at gentle reflux for a further 30 min. to give a pale yellow homogenous mixture. The mixture was cooled to 0°C and iodine (4.28g, 33.7mmol) was added in one portion. The mixture was allowed to attain room temperature and stirred for 1h., quenched by the addition of methanol (1ml), and the solvent was removed in *vacuo*. The residue was dissolved in ethyl acetate (50ml) and partitioned with 10% $Na_2S_2O_5$ (20ml), 2M HCl (20ml), and saturated sodium chloride (15ml). The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a pale yellow solid. The solid was recrystallised from ethanol to give compound **35**, 2.70g (56%). M.p. 143-145°C, [lit. [30]m.p. 141-142°C]. δ ^{1}H 8.12 (1H, d, ArH), 7.67-7.62 (2H, m, ArH), 7.48 (1H, dd, ArH), 7.14 (1H, dd, ArH), 7.07 (1H, d, ArH), 3.90 (3H, s, ArO***CH*$_3$**); δ ^{13}C 157.99, 136.24, 134.73, 133.33, 130.60, 128.39, 128.34, 119.55, 105.68, 88.07, 55.33.

c) Preparation of 6-iodo 2-naphthol **36**.

To a solution of intermediate **35** (1.20g, 4.20mmol) in dichloromethane (22ml) at -78°C (acetone / dry ice bath) under an atmosphere of nitrogen, was added a solution of 1M boron tribromide in dichloromethane (4.30ml, 4.30mmol). The mixture was allowed to attain room temperature and stirred for 3h. T.l.c., petroleum ether:ethyl acetate, 4:1, indicated the disappearance of starting material (Rf 0.53) and the presence of a new compound (Rf 0.23). The mixture was slowly added to a slurry of ice (20ml) and 2M HCl (15ml) and stirred for 30 min. The mixture was extracted with dichloromethane (35ml), separated, and the organic fraction was partitioned with water (20ml) and saturated sodium chloride (15ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude solid. The solid was purified by chromatography eluting with petroleum ether:ethyl acetate, 4:1, to give compound **36** as a pale yellow crystalline solid, 0.65g (57%). M.p. 136-138°C, [lit. [30]m.p. 135-136°C]. δ ^{1}H 8.13 (1H, d, ArH), 7.65-7.60 (2H, m, ArH), 7.42 (1H, d, ArH), 7.10-7.07 (2H, m, ArH), 5.10 (1H, s, disappeared on D_2O shake, ArO***H***); δ ^{13}C 153.73, 136.39, 134.93, 133.30, 130.60, 128.88, 128.03, 118.54, 109.56, 88.23.

d) Preparation of 6-iodo-2(10-bromodecyloxy)naphthalene **41**.

The title compound was prepared from 6-iodo-2-naphthol **36** and 1,10-dibromodecane by the General method A. % Yield : 74. M.p. 76-77 °C. δ ^{1}H 8.12 (1H, d, ArH), 7.63-7.59 (2H, m, ArH), 7.47 (1H, d, ArH), 7.16-7.11 (1H, dd, ArH), 7.06 (1H, d, ArH), 4.05 (2H, t,

$OCH_2(CH_2)_9Br$), 3.41 (2H, t, $O(CH_2)_9CH_2Br$), 1.87-1.80 (4H, m, $OCH_2CH_2(CH_2)_6CH_2CH_2Br$), 1.55-1.33 (12H, m, $O(CH_2)_2(CH_2)_6(CH_2)_2Br$); δ ^{13}C 157.52, 136.24, 134.66, 133.40, 130.53, 128.35, 128.26, 119.85, 106.41, 87.91, 68.03, 34.07, 32.79, 29.43, 29.33, 29.16, 28.73, 28.14, 26.06.

e) Preparation of 6-iodo-2(10-methylaminodecyloxy)naphthalene HCl **29**.

The title compound was prepared from intermediate **41** and an excess of 33% methylamine in ethanol by the General methods B and C respectively. % Yield : 85. M.p. 191-193°C. δ ^1H 8.12 (1H, d, ArH), 7.66-7.58 (2H, m, ArH), 7.46 (1H, d, ArH), 7.15-7.12 (1H, dd, ArH), 7.06 (1H, d, ArH), 4.04 (2H, t, $OCH_2(CH_2)_9NHCH_3$), 2.55 (2H, t, $O(CH_2)_9CH_2NHCH_3$), 2.42 (3H, s, $O(CH_2)_{10}NHCH_3$), 1.83 (2H, m, $OCH_2CH_2(CH_2)_8NHCH_3$), 1.47-1.30 (14H, m, $O(CH_2)_2(CH_2)_7CH_2NHCH_3$); δ ^{13}C 157.52, 136.22, 134.64, 133.40, 130.53, 128.35, 128.25, 119.85, 106.41, 87.89, 68.05, 52.22, 36.57, 29.94, 29.56, 29.51, 29.38, 29.16, 27.33, 26.07; *m/z* (ESI) 440.3 (MH^+, 100%).

Preparation of 6-fluoro-2(10-methylaminodecyloxy)naphthalene HCl **30.**

a) Preparation of 6-fluoro-2-methoxynaphthalene **37**.

To a stirred solution of *N*-fluorobenzenesulfonimide (5.85g, 18.6mmol) in tetrahydrofuran (10ml) at -35°C (acetonitrile / dry ice bath) under an atmosphere of nitrogen, was added a solution of 2-methoxy-6-naphthylmagnesium bromide in tetrahydrofuran (8.0ml, 8.4mmol) over a period of 15 min. The mixture was stirred at -35°C for 30 min., allowed to attain room temperature, quenched by the addition of methanol (5ml), and the solvent was removed in *vacuo*. The residue was suspended in ethyl acetate (50ml) and partitioned with 2M HCl (20ml) and saturated sodium chloride (15ml). The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude solid, **37**. The solid was recrystallised from ethanol and used without further purification. M.p. 51-53°C, [lit. [29]m.p. 59-60°C].

b) Preparation of 6-fluoro-2-naphthol **38**.

To a solution of crude 6-fluoro-2-methoxynaphthalene **37** (1.56g, 8.9mmol) in dry dichloromethane (40ml) at -78°C (acetone / dry ice bath) under an atmosphere of nitrogen, was added 1M boron tribromide (9.0ml, 9.0mmol). The mixture was allowed to attain room temperature and stirred for 18h. T.l.c., petroleum ether:ethyl acetate, 4:1, indicated the disappearance of starting material (Rf 0.57) and formation of a new

compound (Rf 0.28). The mixture was slowly added to a slurry of ice (20ml) and 2M HCl (15ml), and stirred for 30 min. Dichloromethane was removed in *vacuo* and the aqueous was extracted with ethyl acetate (2×25ml). The combined organics were partitioned with water (20ml) and saturated sodium chloride (15ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude solid. The solid was purified by chromatography eluting with petroleum ether:ethyl acetate, 4:1, to give compound **38** as a white solid, 0.72g (50%). M.p. 111-113°C, [lit. [29]m.p. 116-117.5°C]. δ ^{1}H 7.70-7.64 (2H, m, ArH), 7.41-7.37 (1H, d, ArH), 7.25-7.11 (3H, m, ArH), 4.97 (1H, br.s., disappeared on D_2O shake, ArO***H***); δ ^{13}C 161.02, 157.45, 156.83, 131.46, 129.07, 129.00, 128.50, 128.37, 126.54, 118.79, 117.03, 116.66, 111.00, 110.69, 109.67.

c) Preparation of 6-fluoro-2(10-bromodecyloxy)naphthalene **42**.

Compound **42** was prepared from 6-fluoro-2-naphthol **38** and 1,10-dibromodecane by the General method A. % Yield : 82. M.p. 65-66°C. δ ^{1}H 7.71-7.65 (2H, m, ArH), 7.39 (1H, dd, ArH), 7.21-7.18 (3H, m, ArH), 4.05 (2H, t, O***CH$_2$***$(CH_2)_9Br$), 3.40 (2H, t, $O(CH_2)_9$***CH$_2$***Br), 1.88-1.80 (4H, m, OCH_2***CH$_2$***$(CH_2)_6$***CH$_2$***CH_2Br), 1.49-1.33 (12H, m, $O(CH_2)_2$***(CH$_2$)$_6$***$(CH_2)_2Br$); δ ^{13}C 161.02, 157.45, 156.83, 131.44, 129.23, 128.75, 128.53, 128.41, 126.66, 120.09, 116.60, 116.22, 110.94, 110.64, 106.67, 68.01, 34.07, 32.81, 29.45, 29.34, 29.22, 28.73, 28.16, 26.07.

c) Preparation of 6-fluoro-2(10-methylaminodecyloxy)naphthalene HCl **30**.

The title compound was prepared from intermediate **42** and an excess of 33% methylamine in ethanol by the General methods B and C respectively. % Yield : 88. M.p. 140-143°C. δ ^{1}H 7.71-7.66 (2H, m, ArH), 7.39 (1H, dd, ArH), 7.21-7.11 (3H, m, ArH), 4.04 (2H, t, O***CH$_2$***$(CH_2)_9NHCH_3$), 2.55 (2H, t, $O(CH_2)_9$***CH$_2$***$NHCH_3$), 2.43 (3H, s, $O(CH_2)_{10}NH$***CH$_3$***), 1.86-1.81 (2H, m, OCH_2***CH$_2$***$(CH_2)_8NHCH_3$), 1.49-1.31 (14H, m, $O(CH_2)_2$***(CH$_2$)$_7$***CH_2NHCH_3); δ ^{13}C 161.02, 157.46, 156.58, 131.46, 129.23, 128.75, 128.53, 128.46, 126.27, 120.11, 116.60, 116.22, 110.94, 110.64, 106.67, 68.05, 52.24, 36.57, 29.96, 29.58, 29.54, 29.40, 29.24, 27.35, 26.11; *m/z* (ESI) 332.4 (MH^+, 100%).

<u>Preparation of 6-chloro-2(10-methylaminodecyloxy)naphthalene HCl **31**.</u>

a) Preparation of 6-chloro-2-methoxynaphthalene **39**.

To a solution of 6-bromo-2-methoxynaphthalene **34** (2.0g, 8.44mmol) in tetrahydrofuran (40ml) at -70°C (acetone / dry ice) under an atmosphere of nitrogen was added

butyllithium (2.5M in hexane, 3.5ml, 8.8mmol) over a period of 10 min. The pale yellow mixture was stirred for a further 30 min. and a solution of hexachloroethane (3.99g, 16.9mmol) in tetrahydrofuran (5ml) was added dropwise over a period of 10 min. The mixture was stirred at -70°C for 1h., allowed to attain room temperature, and quenched by the slow addition to a mixture of ice (20ml) and 2M HCl (20ml). The mixture was diluted with water (30ml) and extracted with ethyl acetate (3 × 20ml). The combined organics were partitioned with water (2×15ml) and saturated sodium chloride (15ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a pale brown solid. The crude solid was purified by recrystallisation from ethanol to give compound **39** as a white solid, 1.60g (98%). M.p. 64-65°C. δ ^{1}H 7.73 (1H, d, ArH), 7.67-7.62 (2H, m, ArH), 7.39-7.35 (1H, dd, ArH), 7.18-7.14 (1H, dd, ArH), 7.08 (1H, d, ArH), 3.90 (3H, s, ArO***CH$_3$***); δ ^{13}C 157.77, 132.81, 129.45, 129.05, 128.52, 128.21, 127.15, 126.38, 119.80, 105.69, 55.31.

b) Preparation of 6-chloro-2-naphthol **40.**

To a solution of intermediate **39** (1.30g, 6.8mmol) in dry dichloromethane (27ml) at -78°C (acetone / dry ice bath) under an atmosphere of nitrogen, was added 1M boron tribromide (7.1ml, 7.1mmol). The mixture was allowed to attain room temperature and stirred for 18h. The mixture was slowly added to a slurry of ice (20ml) and 2M HCl (15ml), and stirred for 30 min. Dichloromethane was removed in *vacuo* and the aqueous was extracted with ethyl acetate (2×25ml). The combined organics were partitioned with water (20ml) and saturated sodium chloride (15ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude solid. The solid was purified by chromatography eluting with petroleum ether:ethyl acetate, 4:1, to give compound **40** as a white solid, 1.04g (86%). M.p. 118-120°C, [lit. [178]m.p. 115°C].

c) Preparation of 6-chloro-2(10-bromodecyloxy)naphthalene **43.**

Compound **43** was prepared from 6-chloro-2-naphthol **40** and 1,10 - dibromodecane by the General method A. M.p. 123-124°C. δ ^{1}H 7.73 (1H, d, ArH), 7.67-7.63 (2H, m, ArH), 7.38-7.34 (1H, dd, ArH), 7.18-7.14 (1H, dd, ArH), 7.09 (1H, d, ArH), 4.05 (2H, t, O***CH$_2$***$(CH_2)_9Br$), 3.41 (2H, t, $O(CH_2)_9$***CH$_2$***Br), 1.88-1.80 (4H, m, OCH_2***CH$_2$***$(CH_2)_6$***CH$_2$*** CH_2Br), 1.52-1.33(12H, m, $O(CH_2)_2$***(CH$_2$)$_6$***$(CH_2)_2Br$); δ ^{13}C 157.67, 132.81, 129.42, 129.05, 128.44, 128.17, 127.08, 126.36, 120.11, 106.47, 68.05, 34.07, 32.81, 29.45, 29.36, 29.18, 28.75, 28.16, 26.07.

d) Preparation of 6-chloro-2(10-methylaminodecyloxy)naphthalene.HCl **31**.

The title compound was prepared from intermediate **43** and an excess of 33% methylamine in ethanol by the General methods B and C respectively. M.p. 141-143°C. δ ^{1}H 7.99 (1H, d, ArH), 7.85-7.79 (2H, m, ArH), 7.47-7.43 (1H, dd, ArH), 7.35 (1H, d, ArH), 7.23-7.19 (1H, dd, ArH), 4.06 (2H, t, $OCH_2(CH_2)_9NHCH_3$), 2.40 (2H, t, $O(CH_2)_9CH_2NHCH_3$), 2.23 (3H, s, $O(CH_2)_{10}NHCH_3$), 1.81-1.71 (2H, m, $OCH_2CH_2(CH_2)_8NHCH_3$), 1.43-1.25 (14H, m, $O(CH_2)_2(CH_2)_7CH_2NHCH_3$); δ ^{13} 156.95, 132.78, 129.00, 128.74, 128.57, 127.75, 126.70, 126.11, 119.98, 106.63, 67.59, 51.67, 36.27, 29.31, 29.01, 28.79, 28.61, 26.89, 25.56; m/z (ESI) 348.4 (MH^+, 100%).

Preparation of compounds with the general formula Ar-O-$(CH_2)_m$NH$(CH_2)_n$NH$_2$ 2HCl where Ar is 6-bromo-2-naphthol.

Preparation of *N*1-[2-(6-bromo-2-naphthyloxy)ethyl]-1,8-octanediamine 2HCl **44.**

The title compound was prepared from intermediate **1** and 1,8-diaminooctane by the general methods B and C respectively. % Yield : 81. M.p. >200°C; (Found : C, 51.35; H, 6.49; N, 5.94. $C_{20}H_{31}BrCl_2N_2O$ requires : C, 51.52; H, 6.70; N, 6.01 %).

Preparation of *N*1-[6-(6-bromo-2-naphthyloxy)hexyl]-1,4-butanediamine 2HCl **45.**

The title compound was prepared from intermediate **2** and 1,4-diaminohexane by the General methods B and C respectively. % Yield : 55. M.p. >200°C; (Found : C, 51.92; H, 6.65; N, 5.68. $C_{20}H_{31}BrCl_2N_2O$ requires : C, 51.52; H, 6.70; N, 6.01 %).

Preparation of compounds with the general formula Ar-O-$(CH_2)_m$S(O)$_n(CH_2)_p$ NHCH$_3$ HCl where Ar is 6-bromo-2-naphthol.

Preparation of *N*1-methyl-6-[6-(6-bromo-2-naphthyloxy)hexylsulfinyl]-1-hexanamine HCl **46.**

a) Preparation of 6-mercapto-1-(*tert*-butyldiphenylsilyloxy)hexane **48**.

To a mixture of 6-mercapto-1-hexanol (5.0ml, 36.7mmol) and imidazole (3.00g, 44.0mmol) in dimethylformamide (88ml) at room temperature, under an atmosphere of

nitrogen, was added *tert*-butyldiphenylsilyl chloride (11.3ml, 44.0mmol). The homogeneous mixture was stirred at room temperature for 24h. T.l.c., petroleum ether : ethyl acetate, 4 : 1 indicated the disappearance of t-butyldiphenylsilyl chloride (Rf 0.53) and formation of a new compound (Rf 0.39). The solvent was removed in *vacuo* and the residue was dissolved in ethyl acetate (50ml) and partitioned with water (30ml), 0.1M HCl (15ml), and saturated sodium chloride (15ml). The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude oil. The oil was purified by flash column chromatography eluting with petroleum ether:ethyl acetate, 4:1. Fractions containing the product were combined and concentrated in vacuo to give compound **48** as a viscous oil, 8.40g (61%). δ ^{1}H 7.68-7.65 (4H, dd, ArH), 7.39 (6H, m, ArH), 3.66 (2H, t, $HS(CH_2)_5\boldsymbol{CH_2}OSi(Ph)_2C(CH_3)_3$), 2.47 (2H, m, $HS\boldsymbol{CH_2}(CH_2)_5OSi(Ph)_2C(CH_3)_3$), 1.58-1.53 (4H, m, $HSCH_2\boldsymbol{CH_2}(CH_2)_2\boldsymbol{CH_2}CH_2OSi(Ph)_2C(CH_3)_3$), 1.38-1.27 (5H, m, $\boldsymbol{H}S(CH_2)_2\boldsymbol{(CH_2)_2}(CH_2)_2OSi(Ph)_2C(CH_3)_3$, 1×H exchanged on D_2O shake); δ ^{13}C 135.52, 134.03, 129.49, 127.69, 63.74, 33.46, 32.34, 28.21, 26.85, 25.21, 24.53, 19.17.

b) Preparation of 6-[6-(6-bromonaphthyloxy)hexylsulfanyl]-1-(*tert*-butyldiphenylsilyloxy) hexane **49**.

6-Mercapto-1-(*tert*-butyldiphenylsilyloxy)hexane **48** (2.90g, 7.80mmol), intermediate **2** (3.00g, 7.70mmol), powdered potassium carbonate (3.76g, 27.2mmol), and sodium metabisulfite (0.02g) were suspended in degassed 2-butanone (50ml) at room temperature under an atmosphere of nitrogen, and heated at reflux for 7h. T.l.c., petroleum ether:ethyl acetate, 40:1 indicated the disappearance of intermediate **2** (Rf 0.46) and the formation of a new compound (Rf 0.29). The solvent was removed in *vacuo* and the residue was dissolved in dichloromethane (50ml), filtered, and the filtrate was partitioned with water (30ml) and saturated sodium chloride (15ml). The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude oil. The oil was purified by chromatography eluting with petroleum ether:ethyl acetate, 40:1. Fractions containing the product were combined and concentrated in *vacuo* to give compound **49** as a viscous oil, 4.10g (78%). δ ^{1}H 7.88 (1H, d, ArH), 7.68-7.65 (4H, dd, ArH), 7.62-7.54 (2H, m, ArH), 7.48-7.41 (1H, dd, ArH), 7.40-7.36 (6H, m, ArH), 7.16-7.12 (1H, dd, ArH), 7.06 (1H, d, ArH), 4.03 (2H, t, $ArO\boldsymbol{CH_2}(CH_2)_5S(CH_2)_6OSi(Ph)_2C(CH_3)_3$), 3.65 (2H, t, $O(CH_2)_6S(CH_2)_5\boldsymbol{CH_2}OSi(Ph)_2C(CH_3)_3$), 2.52 (4H, m, $O(CH_2)_5\boldsymbol{CH_2}S\boldsymbol{CH_2}(CH_2)_5OSi(Ph)_2C(CH_3)_3$), 1.84 (2H, t, $OCH_2\boldsymbol{CH_2}(CH_2)_4S(CH_2)_6OSi(Ph)_2C(CH_3)_3$), 1.63-1.47 (10H, m, $O(CH_2)_2\boldsymbol{CH_2}CH_2\boldsymbol{CH_2}CH_2SCH_2\boldsymbol{CH_2}CH_2\boldsymbol{(CH_2)_2}CH_2OSi(Ph)_2C(CH_3)_3$, 1.38-1.33 (4H, m,

$O(CH_2)_3\boldsymbol{CH_2}(CH_2)_2S(CH_2)_2\boldsymbol{CH_2}(CH_2)_3OSi(Ph)_2C(CH_3)_3)$, 1.05 (9H, s, $O(CH_2)_6S(CH_2)_6$ $OSi(Ph)_2C\boldsymbol{(CH_3)_3}$); δ ^{13}C 157.32, 135.54, 134.07, 133.04, 129.88, 129.59, 129.49, 128.39, 128.30, 127.87, 127.56, 120.02, 116.85, 106.45, 67.87, 63.81, 32.42, 32.11, 32.08, 29.67, 29.60, 29.40, 29.07, 28.64, 26.86, 25.77, 25.41, 19.19.

Method 1. Preparation of 6-[6-(6-bromonaphthyloxy)hexylsulfinyl]-1-hexanol **51**

a) Preparation of 6-[6-(6-bromonaphthyloxy)hexylsulfinyl]-1-(*tert*-butyldiphenylsilyloxy) hexane **50**.

To a solution of **49** (1.00g, 1.48mmol) in dichloromethane (25ml) at -5°C under an atmosphere of nitrogen was added a solution of m-CPBA (50%, 0.50g, 1.48mmol) in dichloromethane (15ml) maintaining a temperature below 0°C. The mixture was stirred at 0°C for 2h. whereby t.l.c., petroleum ether:ethyl acetate, 4:6, indicated the disappearance of starting material (Rf 0.62) and the formation of a new compound (Rf 0.10). The mixture was partitioned with saturated sodium bicarbonate (30ml), water (20ml), and saturated sodium chloride (20ml). The organics were dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give compound **50** as a crisp foam, 1.00g (97%). δ ^{1}H 7.90 (1H, d, ArH), 7.68-7.64 (4H, m, ArH), 7.61-7.56 (2H, m, ArH), 7.49 (1H, dd, ArH), 7.42-7.37 (6H, m, ArH), 7.15 (1H, dd, ArH), 7.06 (1H, d, ArH), 4.05 (2H, t, $O\boldsymbol{CH_2}(CH_2)_5SO$ $(CH_2)_6OSi(Ph)_2C(CH_3)_3)$, 3.66 (2H, t, $O(CH_2)_6SO(CH_2)_5\boldsymbol{CH_2}OSi(Ph)_2C(CH_3)_3)$, 2.64 (4H, m, $O(CH_2)_5\boldsymbol{CH_2}SO\boldsymbol{CH_2}(CH_2)_5OSi(Ph)_2C(CH_3)_3)$, 1.85-1.72 (6H, m, $OCH_2\boldsymbol{CH_2}(CH_2)_2$ $\boldsymbol{CH_2}CH_2SOCH_2\boldsymbol{CH_2}(CH_2)_4OSi(Ph)_2C(CH_3)_3)$, 1.58-1.54 (6H, m, $OCH_2)_2\boldsymbol{CH_2}(CH_2)_3SO$ $(CH_2)_3\boldsymbol{(CH_2)_2}CH_2OSi(Ph)_2C(CH_3)_3)$, 1.43-1.37 (4H, m, $O(CH_2)_3$ $\boldsymbol{CH_2}(CH_2)_2SOCH_2)_2$ $\boldsymbol{CH_2}(CH_2)_3OSi(Ph)_2C(CH_3)_3)$, 1.04 (9H, s, $O(CH_2)_6SO(CH_2)_6OSi(Ph)_2C\boldsymbol{(CH_3)_3}$); δ ^{13}C 157.27, 135.56, 134.10, 134.01, 133.06, 129.94, 129.63, 129.54, 128.46, 128.34, 127.60, 119.99, 116.94, 106.49, 67.85, 63.67, 52.43, 52.29, 32.43, 32.24, 32.13, 32.09, 29.09, 28.93, 28.63, 26.86, 25.83, 22.61, 19.23.

b) Preparation of 6-[6-(6-bromonaphthyloxy)hexylsulfinyl]-1-hexanol **51**.

To a mixture of **50** (1.00g, 1.44mmol) and 4A molecular sieves (1.00g) in dichloromethane (25ml) at room temperature under an atmosphere of nitrogen, was added 1M tetrabutylammonium fluoride, in tetrahydrofuran (3.6ml, 3.60mmol). The heterogenous mixture was stirred at room temperature for 60h. T.l.c, ethyl acetate:methanol, 10:0.2, indictaed the disappearance of starting material (Rf 0.52) and the formation of a new compound (Rf 0.16). The mixture was partitioned with water

(2×20ml) and saturated sodium chloride (15ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude oil. The oil was purified by chromatography gradient eluting with ethyl acetate:methanol, 10:0.2 to 10:1, fractions containing the product were combined and concentrated in *vacuo* to give compound **51** as a white solid, 0.30g (45%). M.p. 82-83°C. δ ^{1}H 7.90 (1H, d, ArH), 7.65-7.56 (2H, m, ArH), 7.17-7.12 (1H, dd, ArH), 7.08 (1H, d, ArH), 4.06 (2H, t, $O\boldsymbol{CH_2}(CH_2)_5SO(CH_2)_6OH$), 3.63 (2H, t, $O(CH_2)_6SO(CH_2)_5\boldsymbol{CH_2}OH$), 2.72-2.59 (4H, m, $O(CH_2)_5\boldsymbol{CH_2}SO\boldsymbol{CH_2}(CH_2)_5OH$), 1.84-1.71 (7H, m, $OCH_2\boldsymbol{(CH_2)_2}(CH_2)_3SO(CH_2)_4\boldsymbol{CH_2}CH_2O\boldsymbol{H}$, 1×H exchanged on D_2O shake), 1.58-1.50 (6H, m, $O(CH_2)_4\boldsymbol{CH_2}CH_2SOCH_2\boldsymbol{CH_2}CH_2\boldsymbol{CH_2}(CH_2)_2OH$), 1.47-1.38 (4H, m, $O(CH_2)_3\boldsymbol{CH_2}(CH_2)_2SO(CH_2)_2\boldsymbol{CH_2}(CH_2)_3OH$); δ ^{13}C 157.28, 133.06, 129.95, 129.63, 129.58, 128.46, 128.35, 120.00, 116.94, 106.50, 67.73, 62.60, 52.33, 32.38, 28.93, 28.59, 25.80, 25.37, 22.64, 22.61. (Found : C, 57.78; H, 6.95. $C_{22}H_{31}BrO_3S$ requires : C, 58.02; H, 6.86 %).

Method 2. Preparation of 6-[6-(6-bromonaphthyloxy)hexylsulfinyl]-1-hexanol **51**

a) Preparation of 6-[6-(6-bromo-2-naphthyloxy)hexylsulfanyl]-1-hexanol **52**.

To a mixture of **49** (0.35g, 0.50mmol) and 4A molecular sieves (1.00g) in dichloromethane (10ml) at room temperature under an atmosphere of nitrogen, was added 1M tetrabutylammonium fluoride, in tetrahydrofuran (10ml, 10.0mmol). The heterogenous mixture was stirred at room temperature for 60h. T.l.c, petroleum ether:ethyl acetate, 1:1, indictaed the disappearance of starting material (Rf 0.81) and the presence of a new compound (Rf 0.33). The mixture was diluted with dichloromethane (40ml), filtered, and the filtrate was partitioned with water (2×20ml) and saturated sodium chloride (15ml). The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude oil. The oil was purified by chromatography eluting with petroleum ether:ethyl acetate, 3:2. Fractions containing the product were combined and concentrated in *vacuo* to give compound **52** as a white solid, 0.26g (94%). M.p. 60-62°C. δ ^{1}H 7.90 (1H, d, ArH), 7.65-7.60 (2H, m, ArH), 7.56-7.50 (1H, dd, ArH), 7.17-7.13 (1H, dd, ArH), 7.08 (1H, d, ArH), 4.05 (2H, t, $O\boldsymbol{CH_2}(CH_2)_5S(CH_2)_6OH$), 3.64 (2H, t, $O(CH_2)_6S(CH_2)_5\boldsymbol{CH_2}OH$), 2.55-2.49 (4H, m, $O(CH_2)_5\boldsymbol{CH_2}S\boldsymbol{CH_2}(CH_2)_5OH$), 1.85 (2H, m, $OCH_2\boldsymbol{CH_2}(CH_2)_4S(CH_2)_6OH$), 1.65-1.48 (10H, m, $O(CH_2)_2\boldsymbol{CH_2}CH_2\boldsymbol{CH_2}CH_2SCH_2\boldsymbol{CH_2}$ $CH_2\boldsymbol{(CH_2)_2}CH_2OH$), 1.42-1.36 (5H, m, $O(CH_2)_3$ $\boldsymbol{CH_2}(CH_2)_2S(CH_2)_2\boldsymbol{CH_2}(CH_2)_3O\boldsymbol{H}$, 1×H exchanged on D_2O shake); δ ^{13} 157.34, 133.06, 129.92, 129.61, 129.54, 128.43, 128.32,

120.03, 116.89, 106.49, 67.91, 62.87, 32.61, 32.09, 29.60, 29.07, 28.64, 25.77, 25.37. (Found : C, 60.35; H, 7.26. $C_{22}H_{31}BrO_2S$ requires : C, 60.13; H, 7.11 %).

b) Preparation of 6-[6-(6-bromonaphthyloxy)hexylsulfinyl]-1-hexanol **51**.

To a solution of **52** (0.63g, 1.40mmol) in dichloromethane (25ml) at -10°C (salt / ice bath) under an atmosphere of nitrogen, was added a solution of *m*-chloroperoxybenzoic acid (50%, 0.50g, 1.50mmol) in dichloromethane (15ml) over a period of 15 min. The mixture was stirred for 2h. T.l.c., ethyl acetate:methanol, 10:0.2, indicated the disappearance of starting material (Rf 0.65) and the presence of a new compound (Rf 0.13). The mixture was partitioned with water (20ml) and saturated sodium chloride (15ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give compound **51** as a white solid, 0.64g (98%). Spectral data were found to be identical to those obtained for compound **51** from method 1.

c) Preparation of *N*1-methyl-6-[6-(6-bromo-2-naphthyloxy)hexylsulfinyl]-1-hexanamine HCl **46**.

i/ Preparation of 6-[6-(6-bromonaphthyloxy)hexylsulfanyl)hexyl methanesulfonate.

To a solution of **51** (0.60g, 1.30mmol) and triethylamine (0.30ml, 2.20mmol) in dichloromethane (7.0ml) at -25°C (acetonitrile / dry ice) under an atmosphere of nitrogen, was added methanesulfonyl chloride (0.10ml, 1.50mmol) over a period of 5 min. The mixture was stirred for 10 min. T.l.c, ethyl acetate:methanol, 10:0.2, indicated the disappearance of starting material (Rf 0.19) and the presence of a new compound (Rf 0.26).

ii/ Preparation of compound **46**.

To the mesylate solution at -25°C was added a solution of triethylamine (0.30ml, 2.20mmol) and 33% methylamine in ethanol (15ml) over a period of 5 min. The mixture was allowed to attain room temperature and stirred for 18h. T.l.c., ethyl acetate:methanol:880ammonia, 9:1:0.2, indicated the disappearance of the mesylate (Rf 0.59) and the presence of a new compound (Rf 0.11). The mixture was diluted with dichloromethane (40ml) and partitioned with 2M NaOH (20ml) and saturated sodium chloride (15ml), dried over Na_2SO_4, filtered, and concentrated in *vacuo* to give a crude solid. The solid was purified by chromatography eluting with ethyl acetate:methanol:880 ammonia, 9:1.5:0.2. Fractions containg the product were combined and concentrated in *vacuo* to give the free base as a white solid, 0.36g (58%).

iii/ The hydrochloride salt was prepared by the General method C. M.p. 87-89°C dec. δ ^{1}H 7.90 (1H, d, ArH), 7.65-7.57 (2H, m, ArH), 7.51-7.47 (1H, dd, ArH), 7.17-7.13 (1H, dd, ArH), 7.08 (1H, d, ArH), 4.06 (2H, t, O***CH₂***$(CH_2)_5SO$ $(CH_2)_6NHCH_3$), 2.71-2.62 (4H, m, $O(CH_2)_5$***CH₂***SO***CH₂***$(CH_2)_5NHCH_3$), 2.56 (2H, t, $O(CH_2)_6SO(CH_2)_5$***CH₂***$NHCH_3$), 2.43 (3H, s, $O(CH_2)_6SO(CH_2)_6NH$***CH₃***), 1.83-1.75 (4H, m, OCH_2***CH₂***$(CH_2)_4SO(CH_2)_4$***CH₂*** CH_2NHCH_3), 1.57-1.42 (12H, m, $O(CH_2)_2$***(CH₂)₃***CH_2SOCH_2***(CH₂)₃***$(CH_2)_2NHCH_3$); δ ^{13}C 157.27, 133.06, 129.94, 129.63, 129.58, 128.46, 128.34, 120.00, 116.94, 106.49, 67.71, 67.62, 52.42, 52.33, 51.93, 36.51, 29.61, 28.93, 28.81, 28.63, 26.94, 25.80, 22.61. (Found : C, 54.72; H, 6.80; N, 2.75. $C_{23}H_{35}BrClNO_2S$ requires: C, 54.71; H, 6.99; N, 2.77 %).

Preparation of *N*1-methyl-6-[6-(6-bromo-2-naphthyloxy)hexylsulfonyl]-1-hexanamine HCl **47.**

a) Preparation of 6-[6-(6-bromo-2-naphthyloxy)hexylsulfonyl]-1-(*tert*-butyldiphenylsilyl-oxy)hexane **53**.

To a solution of **49** (2.50g, 3.70mmol) in dichloromethane (20ml) at room temperature under an atmosphere of nitrogen, was added a solution of *m*-chloroperoxybenzoic acid (50%, 2.56g, 7.40mmol) in dichloromethane (10ml). The mixture was gently refluxed for 3h. T.l.c., petroleum ether:ethyl acetate, 40:1, indicated the disappearance of intermediate **55** (Rf 0.48) and the formation of a new compound (Rf 0.28). The mixture was allowed to cool, diluted with dichloromethane (20ml) and partitioned with saturated sodium hydrogen carbonate (15ml) and saturated sodium chloride (15ml). The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude oil. The oil was purified by chromatography eluting with petroleum ether:ethyl acetate, 40:1. Fractions containing the product were combined and concentrated in *vacuo* to give compound **53** as viscous oil, 1.45g (55%). δ ^{1}H 7.89 (1H, d, ArH), 7.68-7.66 (4H, m, ArH), 7.65-7.55 (2H, m, ArH), 7.49-7.41 (2H, m, ArH), 7.40-7.37 (5H, m, ArH), 7.15 (1H, dd, ArH), 7.07 (1H, d, ArH), 4.04 (2H, t, O***CH₂***$(CH_2)_5SO_2(CH2)_6OSi(Ph)_2C(CH_3)_3$), 3.65 (2H, t, $O(CH_2)_6SO_2(CH_2)_5$***CH₂***$OSi(Ph)_2C(CH_3)_3$), 2.95-2.87 (4H, m, $O(CH_2)_5$***CH₂*** SO_2***CH₂***$(CH_2)_5OSi(Ph)_2C(CH_3)_3$), 1.86-1.83 (6H, m, OCH_2***(CH₂)₂***$(CH_2)_3SO_2(CH_2)_4$***CH₂*** $CH_2OSi(Ph)_2C(CH_3)_3$), 1.56-1.54 (6H, m, $O(CH_2)_4$***CH₂***$CH_2SO_2CH_2$***CH₂***CH_2***CH₂***$(CH_2)_2$ $OSi(Ph)_2C(CH_3)_3$), 1.40 (4H, m, $O(CH_2)_3$***CH₂***$(CH_2)_2SO_2(CH_2)_2$***CH₂***$(CH_2)_3OSi(Ph)_2C$ $(CH_3)_3$), 1.05 (9H, s, $O(CH_2)_6SO_2(CH_2)_6OSi(Ph)_2C$***(CH₃)₃***); δ ^{13}C 157.21, 135.54, 133.94, 133.03, 129.94, 129.61, 129.56, 128.46, 128.34, 127.62, 119.96, 116.94, 106.45, 67.60,

63.54, 52.74, 52.52, 32.11, 28.82, 28.27, 26.86, 25.70, 25.34, 21.92, 21.85, 21.06, 19.21, 14.20.

b) Preparation of 6-[6-(6-bromo-2-naphthyloxy)hexylsulfonyl]-1-hexanol **54**.

To a mixture of **53** (1.05g, 1.50mmol) and 4A molecular sieves (1.0g) in dichloromethane (15ml) at room temperature under an atmosphere of nitrogen, was added 1M tetrabutylammonium fluoride in tetrahydrofuran (3.0ml, 3.0mmol). The mixture was stirred at room temperature for 60h. T.l.c., petroleum ether:ethyl acetate, 7:3, indicated the disappearance of starting material (Rf 0.73) and the presence of a new compound (Rf 0.16). The mixture was diluted with dichloromethane (40ml) and partitioned with water (20ml) and saturated sodium chloride (15ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude solid. The solid was purified by chromatography eluting with petroleum ether:ethyl acetate, 4:1. Fractions containing the product (Rf 0.28) were combined and concentrated in *vacuo* to give compound **54** as a white solid, 0.63g (90%). M.p. 106-108°C. δ ^{1}H 7.91 (1H, d, ArH), 7.66-7.57 (2H, m, ArH), 7.50 (1H, dd, ArH), 7.17-7.13 (1H, dd, ArH), 7.07 (1H, d, ArH), 4.06 (2H, t, $O\boldsymbol{CH_2}(CH_2)_5SO_2(CH_2)_6OH$), 3.65 (2H, t, $O(CH_2)_6SO_2(CH_2)_5\boldsymbol{CH_2}OH$), 3.00-2.92 (5H, m, $O(CH_2)_5\boldsymbol{CH_2}SO_2\boldsymbol{CH_2}(CH_2)_5O\boldsymbol{H}$, 1×H disappeared on D_2O shake), 1.91-1.83 (6H, m, $OCH_2\boldsymbol{(CH_2)_2}(CH_2)_3SO_2(CH_2)_4\boldsymbol{CH_2}CH_2OH$), 1.61-1.42 (10H, m, $O(CH_2)_3\boldsymbol{(CH_2)_2}CH_2SO_2CH_2\boldsymbol{(CH_2)_3}(CH_2)_2OH$); δ ^{13}C 157.23, 133.53, 129.95, 129.63, 129.61, 128.50, 128.35, 119.96, 116.98, 106.50, 67.62, 62.62, 52.65, 32.26, 28.82, 28.27, 25.71, 25.27, 21.89.

c) Preparation of *N*1-methyl-6-[6-(6-bromo-2-naphthyloxy)hexylsulfonyl]-1-hexanamine HCl **47**.

i/ Preparation of 6-[6-(6-bromonaphthyloxy)hexylsulfanyl)hexyl methanesulfonate.

To a solution of **54** (0.51g, 1.10mmol) and triethylamine (0.23ml, 1.60mmol) in dichloromethane (7.0ml) at -25°C (acetonitrile / dry ice) under an atmosphere of nitrogen, was added methanesulfonyl chloride (0.09ml, 1.20mmol) over a period of 5 min. The mixture was stirred for 15 min. T.l.c, ethyl acetate:petroleum ether, 7:3, indicated the disappearance of starting material (Rf 0.20) and the formation of a new compound (Rf 0.35).

ii/ Preparation of compound **47**.

To the mesylate solution at -25°c was added 33% methylamine in ethanol (15ml) over a period of 5 min. The mixture was allowed to attain room temperature and stirred for 18h.

T.l.c., ethyl acetate:methanol:880ammonia, 9:1:0.2, indicated the disappearance of mesylate (Rf 0.88) and the presence of a new compound (Rf 0.17). The mixture was diluted with dichloromethane (40ml) and was partitioned with 2M NaOH (20ml) and saturated sodium chloride (15ml), dried over Na_2SO_4, filtered, and concentrated in *vacuo* to give a crude solid. The solid was purified by chromatography eluting with ethyl acetate:methanol:880ammonia, 9:1:0.2. Fractions containing the product were combined and concentrated in *vacuo* to give the free base as a white solid, 0.35g (63%).

iii/ The hydrochloride salt was prepared by the General method C.
M.p. 156-158°C. δ ^{1}H 7.90 (1H, d, ArH), 7.66-7.50 (2H, m, ArH), 7.47 (1H, dd, ArH), 7.17-7.13 (1H, dd, ArH), 4.06 (2H, t, $O\boldsymbol{CH_2}(CH_2)_5SO_2(CH_2)_6NHCH_3$), 2.97 (4H, m, $O(CH_2)_5\boldsymbol{CH_2}SO_2\boldsymbol{CH_2}(CH_2)_5NHCH_3$), 2.56 (2H, t, $O(CH_2)_6SO_2(CH_2)_5\boldsymbol{CH_2}NHCH_3$), 2.43 (3H, s, $O(CH_2)_6SO_2(CH_2)_6NH\boldsymbol{CH_3}$), 1.89-1.82 (6H, m, $OCH_2\boldsymbol{CH_2}(CH_2)_2\boldsymbol{CH_2}CH_2SO_2CH_2$ $\boldsymbol{CH_2}(CH_2)_4NHCH_3$), 1.58-1.35 (10H, m, $O(CH_2)_2\boldsymbol{(CH_2)_2}(CH_2)_2SO_2(CH_2)_2\boldsymbol{(CH_2)_3}CH_2NH$ CH_3); δ ^{13}C 157.23, 133.04, 129.95, 129.63, 129.59, 128.48, 128.35, 119.98, 116.98, 106.49, 67.62, 52.72, 52.60, 51.86, 36.51, 29.52, 28.82, 28.45, 28.28, 26.81, 25.71, 21.90, 21.87. (Found : C, 52.65; H, 6.73; N, 2.91. $C_{23}H_{35}BrClNO_2S1/4H_2O$ requires : C, 52.57; H, 6.81; N, 2.67 %).

Preparation of *N*1-methyl-3-[6-(6-bromo-2-naphthyloxy)hexylsulfinyl]-1-propanamine HCl **55.**

a) Preparation of ethyl-3-[6-(6-bromo-2-naphthyloxy)hexylsufanyl]propanoate **56**.
Intermediate **2** (3.08g, 7.77mmol), powdered potassium carbonate (2.68g, 19.4mmol), and ethyl-3-mercaptopropionate (2.68g, 20.0mmol) were suspended in degassed 2-butanone (50ml) at room temperature under an atmosphere of nitrogen. The heterogenous mixture was gently refluxed for 3.5h. T.l.c., petroleum ether:ethyl acetate, 4:1, indicated the disappearance of starting material (Rf 0.46) and the presence of a new compound (Rf 0.34). The mixture was allowed to cool and the solvent was removed in *vacuo*. The residue was suspended in dichloromethane (50ml), filtered, and the filtrate was partitioned with water (25ml) and saturated sodium chloride (15ml). The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude oil. The oil was purified by chromatography eluting with petroleum ether:ethyl acetate, 10:1. Fractions containg the product (Rf 0.20) were combined and concentrated in *vacuo* to give compound **56** as a white solid, 1.80g (54%). M.p. 45-46°C. δ ^{1}H 7.90 (1H, d, ArH),

7.65-7.57 (2H, m, ArH), 7.50-7.46 (1H, dd, ArH), 7.17-7.13 (1H, dd, ArH), 7.08 (1H, d, ArH), 4.19-4.12 (2H, q, $O(CH_2)_6S(CH_2)_2CO_2\boldsymbol{CH_2}CH_3$), 4.05 (2H, t, $O\boldsymbol{CH_2}(CH_2)_5S(CH_2)_2CO_2CH_2CH_3$), 2.82-2.76 (2H, t, $O(CH_2)_6SCH_2\boldsymbol{CH_2}CO_2CH_2CH_3$), 2.62-2.53 (4H, m, $O(CH_2)_5\boldsymbol{CH_2}S\boldsymbol{CH_2}CH_2CO_2CH_2CH_3$), 1.87-1.82 (2H, m, $OCH_2\boldsymbol{CH_2}(CH_2)_4S(CH_2)_2CO_2CH_2CH_3$), 1.67-1.59 (2H, m, $O(CH_2)_4\boldsymbol{CH_2}CH_2S(CH_2)_2CO_2CH_2CH_3$), 1.53-1.47 (4H, m, $O(CH_2)_2\boldsymbol{(CH_2)_2}(CH_2)_2S(CH_2)_2CO_2CH_2CH_3$), 1.26 (3H, t, $O(CH_2)_6S(CH_2)_2CO_2CH_2\boldsymbol{CH_3}$); δ ^{13}C 172.02, 157.32, 133.06, 129.92, 129.81, 129.52, 128.43, 128.32, 120.03, 116.89, 106.47, 67.85, 60.66, 34.93, 32.06, 29.45, 29.07, 28.57, 27.01, 25.75, 14.21.

b) Preparation 3-[6-(6-bromo-2-naphthyloxy)hexylsufanyl]-1- propanol **57**.

To a solution of intermediate **56** (1.50g, 3.41mmol) and methanol (0.21ml, 5.12mmol) in dry tetrahydrofuran (17ml), at room temperature under an atmosphere of nitrogen, was added lithium borohydride (0.11g, 5.12mmol) over a period of 5 min. The mixture was heated to 50°C and stirred for 1h. T.l.c., petroleum ether:ethyl acetate, 3:2, indicated the disappearance of starting material (Rf 0.46) and the presence of a new compound (Rf 0.23). The mixture was allowed to cool and slowly added to a mixture of ice (30ml) and 2M HCl (10ml) over a period of 10 min. and stirred for a further 30 min. The volume of the solvent was reduced by 30% in *vacuo* and extracted with dichloromethane (2×25ml). The organic fractions were combined and partitioned with water (20ml) and saturated sodium chloride (15ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude solid. The solid was recrystallised from ethanol to give compound **57** as a white solid, 1.13g (83%). M.p. 52-53°C. δ ^{1}H 7.90 (1H, d, ArH), 7.65-7.49 (2H, m, ArH), 7.46 (1H, dd, ArH), 7.17-7.13 (1H, dd, ArH), 7.08 (1H, d, ArH), 4.05 (2H, t, $O\boldsymbol{CH_2}(CH_2)_5S(CH_2)_3OH$), 3.76 (2H, t, $O(CH_2)_6S(CH_2)_2\boldsymbol{CH_2}OH$), 2.67-2.53 (4H, m, $O(CH_2)_5\boldsymbol{CH_2}S\boldsymbol{CH_2}(CH_2)_2OH$), 1.90-1.80 (4H, m, $OCH_2\boldsymbol{CH_2}(CH_2)_4SCH_2\boldsymbol{CH_2}CH_2OH$), 1.70-1.62 (3H, m, $O(CH_2)_4\boldsymbol{CH_2}CH_2S(CH_2)_3O\boldsymbol{H}$, 1×H disappeared on D_2O shake), 1.55-1.46 (4H), m, $O(CH_2)_2\boldsymbol{(CH_2)_2}(CH_2)_2S(CH_2)_3OH$); δ ^{13}C 157.32, 133.06, 129.92, 129.61, 129.54, 128.43, 128.32, 120.03, 116.89, 106.47, 67.87, 61.98, 32.02, 31.86, 29.45, 29.07, 28.89, 28.63, 25.75.

c) Preparation 3-[6-(6-bromo-2-naphthyloxy)hexylsufinyl]-1-propanol **58**.

To a solution of intermediate **57** (0.75g, 1.89mmol) in dichloromethane (20ml) at -10°C (salt/ice bath), under an atmosphere of nitrogen, was added a solution *m*-chloroperoxy-benzoic acid (50%, 0.66g, 1.91mmol) in dichloromethane (10ml) over a period of 10

min. The mixture was stirred for 2h. T.l.c., ethyl acetate:methanol, 10:0.2, indicated the disappearance of starting material (Rf 0.60) and the presence of a new compound (Rf 0.13). The mixture was allowed to attain room temperature and partitioned with saturated sodium hydrogen carbonate (15ml) and saturated sodium chloride (15ml). The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give an amorphous solid upon exposure to high vacuum, 0.74g (95%). M.p. 110-112°C. δ ^{1}H 7.90 (1H, d, ArH), 7.65-7.56 (2H, m, ArH), 7.50-7.46 (1H, dd, ArH), 7.17-7.12 (1H, dd, ArH), 7.07 (1H, d, ArH), 4.05 (2H, t, $O\boldsymbol{CH_2}(CH_2)_5SO(CH_2)_3OH$), 3.75 (2H, t, $O(CH_2)_6SO(CH_2)_2\boldsymbol{CH_2}$ OH), 3.26 (1H, br.s, disappeared on D_2O shake, $O(CH_2)_6SO(CH_2)_3O\boldsymbol{H}$), 2.88-2.66 (4H, m, $O(CH_2)_5\boldsymbol{CH_2}SO\boldsymbol{CH_2}(CH_2)_2OH$), 2.11-2.05 (2H, m, $O(CH_2)_6SOCH_2\boldsymbol{CH_2}CH_2OH$), 1.86-1.82 (4H, m, $OCH_2\boldsymbol{CH_2}(CH_2)_2\boldsymbol{CH_2}CH_2SO(CH_2)_3OH$), 1.57 (4H, m, $O(CH_2)_2\boldsymbol{(CH_2)_2}(CH_2)_2$ $SO(CH_2)_3OH$); δ ^{13}C 157.25, 133.04, 129.92, 129.61, 129.56, 128.46, 128.34, 119.98, 116.93, 106.47, 67.67, 61.01, 51.81, 49.70, 28.89, 28.55, 26.65, 25.79, 22.70.

d) Preparation of *N*1-methyl-3-[6-(6-bromo-2-naphthyloxy)hexylsulfinyl]-1-propanamine HCl **55**.

i/ Preparation 3-[6-(6-bromo-2-naphthyloxy)hexylsufinyl]propyl methanesulfonate.

To a solution of intermediate **58** (0.60g, 1.45mmol) and triethylamine (0.30ml, 2.18mmol) in dichloromethane (7.0ml) at -25°C (acetonitrile/dry ice), under an atmosphere of nitrogen, was added methanesulfonyl chloride (0.12ml, 1.60mmol) over a period of 5 min. The mixture was stirred for a further 15 min. T.l.c, ethyl acetate:methanol, 10:0.2, indicated the disappearance of starting material (Rf 0.13) and the presence of a new compound (Rf 0.21).

ii/ Preparation of compound **55**.

To the mesylate solution at -25°C was added 33% methylamine in ethanol (15ml) over a period of 5 min. The mixture was allowed to attain room temperature and stirred for 18h. The mixture was diluted with dichloromethane (40ml) and partitioned with 2M NaOH (20ml) and saturated sodium chloride (15ml), dried over Na_2SO_4, filtered, and concentrated in *vacuo* to give a crude solid. The solid was purified by chromatography eluting with ethyl acetate:methanol:880ammonia, 9:1.5:0.3. Fractions containg the product were combined and concentrated in *vacuo* to give the free base as a white solid, 0.51g (82%).

iii/ The hydrochloride salt was prepared by the General method C.

M.p. 130-132°C. δ ^{1}H 7.90 (1H, d, ArH), 7.65-7.57 (2H, m, ArH), 7.50 (1H, dd, ArH), 7.17-7.13 (1H, dd, ArH), 7.08 (1H, d, ArH), 4.05 (2H, t, $O\boldsymbol{CH_2}(CH_2)_5SO(CH_2)_3NHCH_3$), 2.78-2.72 (6H, m, $O(CH_2)_5\boldsymbol{CH_2}SO\boldsymbol{CH_2}CH_2\boldsymbol{CH_2}NHCH_3$), 2.45 (3H, s, $O(CH_2)_6SO(CH_2)_3NH\boldsymbol{CH_3}$), 1.99-1.96 (2H, m, $O(CH_2)_6SOCH_2\boldsymbol{CH_2}CH_2NHCH_3$), 1.86-1.80 (4H, m, $OCH_2\boldsymbol{CH_2}(CH_2)_2\boldsymbol{CH_2}CH_2SO(CH_2)_3NHCH_3$), 1.57 (4H, m, $O(CH_2)_2\boldsymbol{(CH_2)_2}(CH_2)_2SO(CH_2)_3NHCH_3$); δ ^{13}C 157.27, 133.06, 129.94, 129.63, 129.56, 128.46, 128.35, 120.00, 116.93, 106.49, 67.71, 52.38, 50.48, 50.15, 36.12, 28.91, 28.59, 25.80, 22.82, 22.62. (Found : C, 51.71; H, 6.51; N, 3.06. $C_{20}H_{29}BrClNO_2S$ requires : C, 51.90; H, 6.31; N, 3.03 %).

BENZO[*b*]FURAN DERIVATIVES.

Preparation of 5-(10-methylaminodecyloxy)benzo[*b*]furan HCl. **59**.

a) Preparation of 2-carboxy-5-methoxybenzo[*b*]furan **67**.

2-Hydroxy-5-methoxybenzaldehyde (5.0g, 32.8mmol), ethyl chloroacetate (4.82g, 39.4mmol), and freshly ground potassium carbonate (9.00g, 65.0mmol) were suspended in anhydrous dimethylformamide (75ml) at room temperature under an atmosphere of nitrogen. The heterogenous mixture was stirred vigorously and heated to reflux for 8h., allowed to cool, and poured onto crushed ice (200g). The resulting slurry was extracted with toluene (2×60ml), separated, and the organic fraction was partitioned with saturated sodium chloride (50ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give the crude decarboxylated product as an oil 1.30g. The aqueous phase was acidified with conc. HCl to precipitate the crude acid. Recrystallisation form a toluene / ethanol mixture gave compound **67** as a colourless crystalline solid, 2.70g (43%). M.p. 58-59°C, [lit. [37]m.p. 58°C].

b) Preparation of 5-methoxybenzo[*b*]furan **69**.

2-Carboxy-5-methoxybenzo[*b*]furan **67** (2.65g, 13.8mmol) and copper powder (0.90g, 13.8mmol) were suspended in quinoline (20ml) at room temperature under an atmosphere of nitrogen. The heterogenous mixture was stirred vigorously and heated to reflux for 1.5h. The mixture was cooled, poured into 2M HCl (200ml), and filtered. The filtrate was extracted with chloroform (3×100ml) and the combined organics were partitioned with water (80ml) and saturated sodium chloride (50ml). The residue was purified by

chromatography eluting with petroleum ether : ethyl acetate, 10:1 to give compound **69** as a colourless solid, 1.80g (90%). M.p. 56-57°C, [lit. [37]m.p. 58-59°C]. δ ^{1}H 7.57 (1H, d, ArH), 7.40-7.37 (1H,d, ArH), 7.04 (1H, d, ArH), 6.92-6.87 (1H, d, ArH), 6.69 (1H, s, ArH), 3.82 (3H, s, ArO***CH*$_3$**); δ ^{13}C 155.90, 149.92, 145.71, 127.94, 113.04, 111.79, 106.68, 103.45, 55.85.

c) Preparation of 5-hydroxybenzo[*b*]furan **65**.

5-Methoxybenzo[*b*]furan **69** (8.38g, 56.6mmol) and pyridine hydrochloride (20g) were combined at room temperature under an atmosphere of nitrogen and heated to 180°C for 2.5h. The mixture was allowed to cool, poured onto ice water (250ml), and acidified to pH 1 by the addition of conc. HCl. The aqueous mixture was extracted with ethyl acetate (2×100ml) and the combined organics were partitioned with 2M HCl (2×50ml) and saturated sodium chloride (50ml). The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a yellow oil. The residue was purified by chromatography eluting with petroleum ether : ethyl acetate, 8 : 1 to give compound **65** as a colourless solid, 7.30g (96%). M.p. 77-78°C, [lit. m.p. [37]79°C]. δ ^{1}H 7.58 (1H, d, ArH), 7.36-7.33 (1H, d, ArH), 7.00 (1H, d, ArH), 6.83-6.79 (1H, d, ArH), 6.65 (1H, s, ArH), 5.30 (1H, br.s., disappeared on D_2O shake, ArO***H***); δ ^{13}C 151.32, 150.04, 145.78, 128.28, 112.94, 111.80, 106.45, 106.14.

d) Preparation of 5-(10-bromodecyloxy)benzo[*b*]furan **74**.

Compound **74** was prepared from intermediate **65** and 1,10-dibromodecane by the General method A. %Yield : 78. M.p. 50-51°C. δ ^{1}H 7.57 (1H, s, ArH), 7.36 (1H, d, ArH), 7.04 (1H, d, ArH), 6.92-6.87 (1H, d, ArH), 6.69 (1H, d, ArH), 3.97 (2H, t, O***CH*$_2$**$(CH_2)_9$Br), 3.40 (2H, t, O$(CH_2)_9$***CH*$_2$**Br), 1.90-1.74 (4H, m, OCH$_2$***CH*$_2$**$(CH_2)_6$***CH*$_2$**CH_2Br), 1.47-1.32 (12H, m, O$(CH_2)_2$***(CH*$_2$*)$_6$**$(CH_2)_2$Br); δ ^{13}C 155.40, 149.86, 145.62, 127.90, 113.62, 111.71, 106.67, 104.38, 68.79, 34.07, 32.81, 29.45, 29.36, 28.73, 28.16, 26.07.

e) Preparation of 5-(10-methylaminodecyloxy)benzo[*b*]furan HCl. **59**.

Compound **59** was prepared from intermediate **74** and an excess of 33% methylamine in ethanol by the General methods B and C respectively. %Yield : 71. M.p. 130-131°C. δ ^{1}H 7.90 (1H, d, ArH), 7.47-7.43 (1H, d, ArH), 7.14 (1H, d, ArH), 6.90-6.87 (1H, d, ArH), 6.85 (1H, s, ArH), 3.97 (2H, t, O***CH*$_2$**$(CH_2)_9$NHCH$_3$), 2.81 (2H, t, O$(CH_2)_9$***CH*$_2$**NH CH_3), 2.49 (3H, s, O$(CH_2)_{10}$NH***CH*$_3$**), 1.72 (2H, m, OCH$_2$***CH*$_2$**$(CH_2)_8$NHCH$_3$), 1.61 (2H,

m, $O(CH_2)_8\boldsymbol{CH_2}CH_2NHCH_3$), 1.28 (12H, m, $O(CH_2)_2\boldsymbol{(CH_2)_6}(CH_2)_2NHCH_3$); δ ^{13}C 154.93, 149.13, 146.48, 127.80, 113.31, 111.53, 106.77, 104.53, 68.10, 48.09, 32.15, 28.80, 28.72, 28.66, 28.43, 25.86, 25.48, 25.19.

Preparation of 7-(10-methylaminodecyloxy)benzo[*b*]furan HCl. **60.**

a) Preparation of 2-carboxy-7-methoxybenzo[*b*]furan **68**.

Compound **68** was prepared from 2-hydroxy-7-methoxybenzaldehyde in an analogous manner to that described for intermediate **67**. %Yield : 41. M.p. 224-226°C, [lit. [179]m.p. >200°C]. δ ^{1}H 13.31 (1H, br.s., disappeared onD_2O shake, $CO_2\boldsymbol{H}$), 7.38 (1H, s, ArH), 7.08-6.96 (2H, m, ArH), 6.84-6.80 (1H, d, ArH), 3.69 (3H, s, $ArO\boldsymbol{CH_3}$); δ ^{13}C 160.02, 146.20, 145.39, 144.48, 128.39, 124.62, 114.68, 113.75, 109.13, 55.87.

b) Preparation of 7-methoxybenzo[*b*]furan **70**.

Compound **70** was prepared from intermediate **68** in an analogous manner to that described for intermediate **69**. 50%Yield as a colourless oil. δ ^{1}H 7.60 (1H, d, ArH), 7.19-7.10 (2H, m, ArH), 6.78-6.75 (1H, d, ArH), 6.73 (1H, d, ArH), 3.97 (3H, s, $ArO\boldsymbol{CH_3}$); δ ^{13}C 145.53, 144.92, 144.29, 129.09, 123.43, 113.48, 106.86, 106.25, 55.96.

c) Preparation of 7-hydroxybenzo[*b*]furan **66**.

Compound **66** was prepared from intermediate **70** in an analogous manner to that described for intermediate **65**. %Yield : 58, as a colourless oil. δ ^{1}H 7.58 (1H, d, ArH), 7.17-7.05 (2H, m, ArH), 6.86-6.82 (1H, d, ArH), 6.75 (1H, d, ArH), 6.02 (1H, br.s., disappeared on D_2O on shake, $ArO\boldsymbol{H}$); δ ^{13}C 144.85, 143.39, 141.11, 129.13, 123.72, 113.33, 110.51, 107.26.

d) Preparation of 7-(10-bromodecyloxy)benzo[*b*]furan **75**.

Compound **75** was prepared from intermediate **66** by the General method A.

%Yield : 75, as a pale brown oil. δ ^{1}H 7.61 (1H, d, ArH), 7.19-7.09 (2H, m, ArH), 6.80-6.77 (1H, d, ArH), 6.74 (1H, d, ArH), 4.16 (2H, t, $O\boldsymbol{CH_2}(CH_2)_9Br$), 3.39 (2H, t, $O(CH_2)_9\boldsymbol{CH_2}Br$), 1.90-1.78 (4H, m, $OCH_2\boldsymbol{CH_2}(CH_2)_6\boldsymbol{CH_2}CH_2Br$), 1.52-1.28 (12H, m, $O(CH_2)_2\boldsymbol{(CH_2)_6}(CH_2)_2Br$); δ ^{13}C 145.01, 144.80, 144.44, 129.13, 123.38, 113.24, 107.37, 106.83, 68.89, 34.00, 32.78, 29.56, 29.40, 29.27, 28.68, 28.10, 25.98.

e) Preparation of 7-(10-methylaminodecyloxy)benzo[*b*]furan HCl. **60**.

Compound **60** was prepared from intermediate **75** and an excess of 33% methylamine in ethanol by the General methods B and C respectively. %Yield : 74. M.p. 145-148°C. δ ^{1}H 7.94 (1H, d, ArH), 7.24-7.13 (2H, m, ArH), 6.95-6.91 (2H, m, ArH), 4.18 (2H, t, $OCH_2(CH_2)_9NHCH_3$), 2.85 (2H, t, $O(CH_2)_9CH_2NHCH_3$), 2.52 (3H, s, $O(CH_2)_{10}NHCH_3$), 1.81 (2H, m, $OCH_2CH_2(CH_2)_8NHCH_3$), 1.62 (2H, m, $O(CH_2)_8CH_2CH_2NHCH_3$), 1.49 (2H, m, $O(CH_2)_2CH_2(CH_2)_7NHCH_3$), 1.31 (10H, m, $O(CH_2)_3(CH_2)_5(CH_2)_2NHCH_3$); δ ^{13}C 145.45, 145.20, 144.84, 129.43, 123.36, 113.08, 107.73, 106.74, 68.30, 48.00, 32.08, 28.63, 28.58, 28.50, 28.27, 25.68, 25.29, 25.07. (Found : C, 66.56; H, 9.16; N, 4.26. $C_{19}H_{30}ClNO_2$ 1/4H_2O requires : C, 66.26; H, 8.93; N, 4.07 %).

Preparation of 4-(10-methylaminodecyloxy)benzo[*b*]furan HCl. **61**.

a) Preparation of 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]furan-3-carboxylic acid **72**.

To a solution of 1,3-cyclohexanedione (6.71g, 59.9mmol) in aqueous potassium hydroxide (3.40g, 61.1mmol, water, 12ml) cooled in an ice bath, was added a freshly prepared solution of bromopyruvic acid (10.0g, 59.9mmol) in methanol (30ml) over a period of 5 min. The red mixture was stirred st 5°C for 2h. and then allowed to attain room temperature. The methanol was removed in *vacuo* and the resulting slurry was diluted with water (60ml) and acidified to pH 1 by the dropwise addition of conc. HCl. The acidic mixture was stirred and heated to 100°C for 2h, a precipitate having formed after 30 min. The mixture was cooled in an ice bath, filtered, and the pale brown solid was recrystallised from ethanol with charcoaling to give compound **72** as a buff coloured solid, 8.42g (78%). M.p. 142-144°C, [lit. [38]m.p. 141-143°C]. δ ^{1}H 13.26 (1H, br.s., disappeared on D_2O shake, $CO_2\mathbf{H}$), 8.07 (1H, s, $OC\mathbf{H}=CH_2$), 3.01 (2H, t, $C\mathbf{H}_2$), 2.71 (2H, t, $C\mathbf{H}_2$), 2.31 (2H, m, $C\mathbf{H}_2$); δ ^{13}C 199.49, 170.78, 161.42, 150.19, 117.95, 117.23, 36.51, 23.23, 22.39.

b) Preparation of 4-hydroxybenzo[*b*]furan-3-carboxylic acid **73**.

Intermediate **72** (6.80g, 37.8mmol), dodecene (10ml, 45.0mmol), and palladium (10% on carbon, 3.40g) were suspended in decalin (80ml) at room temperature under an atmosphere of nitrogen. The black heterogeneous mixture was stirred vigorously and heated to reflux for 20h. (Caution : excessive bumping was observed). The mixture was allowed to cool and slowly diluted with ethanol (130ml), filtered through Arbosil,

washing with ethanol (2×30ml). The ethanol was removed in *vacuo* and the resulting slurry was cooled to 5°C. The white precipitate was collected by filtration and dried in *vacuo* to give compound **73** as a white solid, 5.42g (81%). M.p. 210-213°C, [lit. [38]m.p. 209-212°C]. δ ^{1}H 8.66 (1H, s, ArH), 7.30 (1H, t, ArH), 7.18 (1H, d, ArH), 6.74 (1H, d, ArH), 4.23 (1H, br.s., ArO**H**, disappeared on D_2O shake); δ ^{13}C 168.30, 156.48, 151.34, 151.21, 127.41, 114.50, 112.42, 109.29, 102.95.

c) Preparation of 4-hydroxybenzo[*b*]furan **71**.

3-Carboxy-4-hydroxybenzo[*b*]furan **73** (5.40g, 30.3mmol) and copper powder (5.40g, 85.0mmol) were suspended in quinoline (40ml) at room temperature under an atmosphere of nitrogen. The heterogenous mixture was stirred vigorously and heated to 220°C for 3.5h. T.l.c., diethyl ether:methanol, 10:1, confirmed the disappearance of **73** (Rf 0.13) and the presence of a new compound (Rf 0.74). The black mixture was allowed to cool to 100°C and poured onto crushed ice (300ml). The mixture was diluted with diethyl ether (200ml), filtered, and the two layers of the filtrate were separated. The organic fraction was partitioned with 2M HCl (2×80ml) and saturated sodium chloride (2×30ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a black viscous oil. The crude oil was purified by reduced pressure Kugelrohr distillation (bp. 130°C / 0.5mmHg) to give compound **71** as a pale yellow solid on cooling, 3.40g (84%). M.p. 51-53°C, [lit. [8]m.p. 55-56°C]. δ ^{1}H 7.51 (1H, d, ArH), 7.12 (2H, d, ArH), 6.86 (1H, d, ArH), 6.63 (1H, m, ArH), 6.23 (1H, br.s., disappeared on D_2O shake, ArO**H**); δ ^{13}C 156.64, 149.32, 143.72, 124.98, 116.71, 107.83, 104.49, 103.38.

d) Preparation of 4-(10-bromodecyloxy)benzo[*b*]furan **76**.

Compound **76** was prepared from intermediate **71** and 1,10-dibromodecane by the General method A. %yield : 78. M.p. 38-39°C. δ ^{1}H 7.52 (1H, d, ArH), 7.22-7.10 (2H, m, ArH), 6.87 (1H, d, ArH), 6.66 (1H, d, ArH), 4.09 (2H, t, O***CH*****$_2$**$(CH_2)_9$Br), 3.40 (2H, t, O$(CH_2)_9$ ***CH*****$_2$**Br), 1.90-1.80 (4H, m, OCH$_2$***CH*****$_2$**$(CH_2)_6$***CH*****$_2$**CH_2Br), 1.47-1.31 (12H, m, O$(CH_2)_2$ ***(CH*****$_2$**$)_6$$(CH_2)_2$Br); δ ^{13}C 156.26, 153.15, 143.34, 124.89, 117.84, 104.37, 104.10, 103.97, 68.30, 34.07, 32.81, 29.45, 29.36, 29.24, 28.75, 28.16, 26.07.

e) Preparation of 4-(10-methylaminodecyloxy)benzo[*b*]furan HCl. **61**.

Compound **61** was prepared from intermediate **76** and an excess of 33% methylamine in ethanol by the General methods B and C respectively. M.p. 107-108°C. δ ^{1}H 7.92 (1H, d,

ArH), 7.25-7.21 (2H, m, ArH), 6.92 (1H, d, ArH), 6.81 (1H, d, ArH), 4.13 (2H, t, $OCH_2(CH_2)_9NHCH_3$), 2.83 (2H, t, $O(CH_2)_9CH_2NHCH_3$), 2.52 (3H, s, $O(CH_2)_{10}NHCH_3$), 1.80 (2H, m, $OCH_2CH_2(CH_2)_8NHCH_3$), 1.61 (2H, m, $O(CH_2)_8CH_2CH_2NHCH_3$), 1.48 (2H, m, $OCH_2CH_2CH_2(CH_2)_7NHCH_3$), 1.30 (10H, m, $O(CH_2)_3(CH_2)_5(CH_2)_2NHCH_3$); δ ^{13}C 155.58, 152.58, 144.49, 125.23, 117.18, 104.53, 104.19, 103.90, 67.87, 48.11, 32.24, 28.90, 28.77, 28.67, 28.52, 25.92, 25.54, 25.32. (Found : C, 66.37; H, 9.15; N, 4.09. $C_{19}H_{30}ClNO_2$ 1/4H_2O requires : C, 66.26; H, 8.93; N, 4.07 %).

Preparation of 7-bromo-4-(10-methylaminodecyloxy)benzo[*b*]furan HCl. **62.**

a) Preparation of 7-bromo-4-hydroxybenzo[*b*]furan **77**.

4-Hydroxybenzo[*b*]furan **71** (1.00g, 7.45mmol) was dissolved in dry acetonitrile (30ml) at room temperature under an atmosphere of nitrogen and *N*-bromosuccinimide (1.33g, 7.45mmol) was added in one portion to give a dark red homogeneous mixture. The mixture was stirred at room temperature for 3.5h. to give a pale yellow mixture. T.l.c, petroleum ether:ethyl acetate, 4:1, indicated the presence of compound **71** (Rf 0.20) and the presence of two new compounds (Rf 0.27) and (Rf 0.19). The solvent was removed in *vacuo* to give a yellow viscous oil. The crude oil was dissolved in dichloromethane (50ml) and partitioned with water (2×15ml) and saturated sodium chloride (15ml). The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a pale brown solid. The solid was purified by chromatography eluting with petroleum ether:ethyl acetate, 5:1. Fractions containing the product (Rf 0.27) were combined and concentrated in *vacuo* to give compound **77** as a pale yellow solid, 0.38g (24%). Fractions containing the second compound (Rf 0.17) were combined and concentrated in *vacuo* to give a waxy solid, 0.43g, confirmed to be a complex mixture by N.M.R analysis. Compound **77**, M.p. 62-64°C. δ ^{1}H 7.54 (1H, d, ArH), 7.35 (1H, d, ArH), 7.04 (1H, d, ArH), 6.89 (1H, d, ArH), 5.79 (1H, br.s., disapppeared on D_2O shake, ArO***H***); δ ^{13}C 155.72, 145.82, 144.67, 126.93, 117.20, 105.53, 104.15, 102.05.

b) Preparation of 7-bromo-4-(10-bromodecyloxyl)benzo[*b*]furan **78**.

Compound **78** was prepared from intermediate **77** and 1,10-dibromodecane by the General method A. %Yield: 83, as a colourless oil. δ ^{1}H 7.55 (1H, d, ArH), 7.44-7.41 (1H, d, ArH), 7.14-7.10 (1H, d, ArH), 6.86 (1H, d, ArH), 4.22 (2H, t, $OCH_2(CH_2)_9Br$), 3.41 (2H, t, $O(CH_2)_9CH_2Br$), 1.85 (4H, m, $CH_2CH_2(CH_2)_6CH_2CH_2Br$), 1.57 (2H, m, $OCH_2CH_2CH_2$

$(CH_2)_7Br$), 1.33 (10H, m, $O(CH_2)_3$***$(CH_2)_5$***$(CH_2)_2Br$); δ ^{13}C 155.70, 149.43, 144.74, 128.44, 121.13, 108.12, 107.64, 104.53, 73.62, 34.09, 32.81, 30.15, 29.43, 29.34, 28.73, 28.16, 25.95.

c) Preparation of 7-bromo-4-(10-methylaminodecyloxy)benzo[*b*]furan HCl. **62**.

Compound **62** was prepared from intermediate **78** and an excess of 33% methylamine in ethanol by the General methods B and C respectively. % Yield : 72. M.p. 104-106°C. δ ^1H 8.05 (1H, d, ArH), 7.52-7.45 (1H, d, ArH), 7.33-7.30 (1H, d, ArH), 7.19 (1H, d, ArH), 4.30 (2H, t, $OCH_2(CH_2)_9NHCH_3$), 2.83 (2H, t, $O(CH_2)_9CH_2NHCH_3$), 2.52 (3H, s, $O(CH_2)_{10}NHCH_3$), 1.78 (2H, m, $OCH_2CH_2(CH_2)_8NHCH_3$), 1.62 (2H, m, $O(CH_2)_8CH_2$ CH_2NHCH_3), 1.52 (2H, m, $OCH_2CH_2CH_2(CH_2)_7NHCH_3$), 1.30 (10H, m, $O(CH_2)_3$***$(CH_2)_5$*** $(CH_2)_2NHCH_3$); δ ^{13}C 155.26, 148.79, 146.15, 128.16, 120.11, 107.51, 106.78, 104.87, 72.76, 48.11, 32.24, 29.55, 28.88, 28.75, 28.70, 28.52, 25.93, 25.39, 25.32. (Found : C, 54.19; H, 6.94; N, 3.22. $C_{19}H_{29}ClBrNO_2$ requires : C, 54.49; H, 6.98; N, 3.34 %).

BENZO[*b*]THIOPHENE DERIVATIVES.

Preparation of 4-(10-methylaminodecyloxy)benzo[*b*]thiophene HCl. **63.**

a) Preparation of 4-hydroxybenzo[*b*]thiophene **79**.

4,5,6,7-Tetrahydrobenzo[*b*]thiophene-4-one (3.25g, 21.35mmol) and sulfur (0.89g, 27.76mmol) were suspended in diphenyl ether (30ml) at room temperature under an atmosphere of nitrogen and heated to 240°C for 4.5h. to give a deep red homogeneous mixture. The mixture was allowed to cool, diluted with diethyl ether (80ml), and extracted with 2M NaOH (3×50ml). The basic aqueous layer was acidified to pH 3 with conc. HCl and extracted with dichloromethane (3×30ml). The organics were combined and partitioned with saturated sodium chloride (20ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a red oil that solidified on standing. The crude solid was purified by chromatography eluting with petroleum ether:ethyl acetate:methanol, 80:20:2.5. Fractions containing the product (Rf 0.30) were combined and concentrated in *vacuo* to give compound **79** as a yellow solid, 1.84g (57%). M.p. 78-82°C, [lit. [39]m.p. 80-82°C]. δ ^1H 7.48-7.45 (2H, m, ArH), 7.36 (1H, d, ArH), 7.24-7.16 (1H, m, ArH), 6.72-6.69 (1H, d, ArH), 5.29 (1H, br.s., disappeared on D_2O shake, ArO***H***); δ ^{13}C 150.69, 141.83, 129.18, 125.25, 125.04, 119.64, 115.22, 108.75.

b) Preparation of 4-(10-bromodecyloxy)benzo[*b*]thiophene **80**.

Compound **80** was prepared from intermediate **79** and 1,10-dibromodecane by the General method A. %Yield : 81. M.p. 52-54°C. δ ^{1}H 7.52-7.49 (1H, d, ArH), 7.45-7.43 (1H, d, ArH), 7.32-7.22 (2H, m, ArH), 6.74-6.71 (1H, d, ArH), 4.10 (2H, t, O***CH*****$_2$**$(CH_2)_9$Br), 3.40 (2H, t, O$(CH_2)_9$***CH*****$_2$**Br), 1.90-1.79 (4H, m, OCH$_2$***CH*****$_2$**$(CH_2)_6$***CH*****$_2$**CH_2Br), 1.54-1.49 (2H, m, O$(CH_2)_2$***CH*****$_2$**$(CH_2)_7$Br), 1.32-1.29 (10H, m, O$(CH_2)_3$***(CH*****$_2$*****)$_5$**$(CH_2)_2$Br); δ ^{13}C 154.55, 141.24, 130.65, 125.25, 124.33, 120.66, 114.57, 104.58, 68.07, 34.05, 32.79, 29.43, 29.34, 29.24, 28.81, 28.73, 28.14, 26.11.

c) Preparation of 4-(10-methylaminodecyloxy)benzo[*b*]thiophene HCl. **63**.

Compound **63** was prepared from intermediate **80** and an excess of 33% methylamine in ethanol by the General methods B and C respectively. %Yield : 67. M.p. 117-120°C. δ ^{1}H 7.52-7.50 (1H, d, ArH), 7.46-7.43 (1H, d, ArH), 7.32-7.22 (2H, m, ArH), 6.75-6.72 (1H, d, ArH), 4.10 (2H, t, O***CH*****$_2$**$(CH_2)_9$NHCH$_3$), 2.55 (2H, t, O$(CH_2)_9$***CH*****$_2$**NHCH$_3$), 2.42 (3H, s, O$(CH_2)_{10}$NH***CH*****$_3$**), 1.87 (2H, m, OCH$_2$***CH*****$_2$**$(CH_2)_8$NHCH$_3$), 1.50 (2H, m, O$(CH_2)_8$ ***CH*****$_2$**CH_2NHCH$_3$), 1.39-1.30 (12H, m, O$(CH_2)_2$***(CH*****$_2$*****)$_6$**$(CH_2)_2$NHCH$_3$); δ ^{13}C 154.57, 141.24, 130.65, 125.25, 124.31, 120.70, 114.55, 104.60, 68.10, 52.22, 36.57, 29.94, 29.52, 29.38, 29.25, 27.35, 26.15. (Found : C, 64.04; H, 8.85; N, 3.70. $C_{19}H_{30}ClNOS$ requires : C, 64.11; H, 8.49; N, 3.93 %).

Preparation of 7-bromo-4-(10-methylaminodecyloxy)benzo[*b*]thiophene HCl. **64.**

a) Preparation of 7-bromo-4-(10-bromodecyloxy)benzo[*b*]thiophene **81**.

Intermediate **80** (0.50g, 1.35mmol) was dissolved in a mixture of acetonitrile (7.0ml) and chloroform (0.5ml) at room temperature under an atmosphere of nitrogen. *N*-bromosuccinimide (0.24g, 1.35mmol) was added in one portion to give a pale yellow homogeneous mixture. The mixture was stirred at room temperature for 24h. T.l.c, petroleum ether:ethyl acetate, 40:1, indicated the disappearance of compound **80** (Rf 0.57) and the presence of a new compound (Rf 0.43). The solvent was removed in *vacuo* to give a pale brown oil. The crude oil was dissolved in ethyl acetate (50ml) and partitioned with water (2×20ml) and saturated sodium chloride (15ml). The organic fraction was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a black oil. The oil was purified by chromatography eluting with petroleum ether:ethyl acetate, 50:1. Fractions containing the product were combined and concentrated in *vacuo* to give

compound **81** as a colourless oil, 0.53g (87%). δ ^{1}H 7.58 (1H, d, ArH), 7.39-7.34 (2H, m, ArH), 6.65-6.61 (1H, d, ArH), 4.07 (2H, t, O***CH*****$_2$**$(CH_2)_9$Br), 3.40 (2H, t, O$(CH_2)_9$***CH*****$_2$**Br), 1.90-1.79 (4H, m, OCH$_2$***CH*****$_2$**$(CH_2)_6$***CH*****$_2$**CH_2Br), 1.50-1.29 (12H, m, O$(CH_2)_2$***(CH*****$_2$*****$)_6$** $(CH_2)_2$Br); δ ^{13}C 153.91, 142.62, 131.37, 127.67, 125.32, 121.83, 106.49, 105.98, 34.03, 32.79, 29.42, 29.33, 29.29, 29.13, 28.72, 28.14, 26.06.

b) Preparation of 7-bromo-4-(10-methylaminodecyloxy)benzo[*b*]thiophene HCl. **64**.
Compound **64** was prepared from intermediate **81** and an excess of 33% methylamine in ethanol by the General methods B and C respectively. %Yield : 82. M.p. 98-101°C. δ ^{1}H 7.60-7.58 (1H, d, ArH), 7.38-7.35 (2H, m, ArH), 6.65-6.62 (1H, d, ArH), 4.07 (2H, t, O***CH*****$_2$**$(CH_2)_9$NHCH$_3$), 2.55 (2H, t, O$(CH_2)_9$***CH*****$_2$**NHCH$_3$), 2.42, (3H, s, O$(CH_2)_{10}$NH***CH*****$_3$**), 1.90-1.80 (2H, m, OCH$_2$***CH*****$_2$**$(CH_2)_8$NHCH$_3$), 1.49-1.44 (4H, m, O$(CH_2)_2$***CH*****$_2$**$(CH_2)_5$***CH*****$_2$** CH_2NHCH$_3$), 1.30 (10H, m, O$(CH_2)_3$***(CH*****$_2$*****$)_5$**$(CH_2)_2$NHCH$_3$); δ ^{13}C 153.92, 142.62, 131.39, 127.67, 125.30, 121.85, 106.50, 105.98, 68.44, 52.22, 36.57, 30.10, 29.94, 29.56, 29.51, 29.34, 29.15, 27.33, 26.07. (Found : C, 50.43; H, 6.69; N, 3.49. $C_{19}H_{29}$ClBrNOSO H_2O requires : C, 50.39; H, 6.90; N, 3.09 %).

SULFONAMIDE DERIVATIVES.

Preparation of *N*1-(8-aminooctyl)-5-iodo-1-naphthalenesulfonamide HCl **J8**.

a) Preparation of sodium 5-iodo-1-naphthalenesulfonate **82**.
5-Amino-1-naphthalenesulfonic acid (22.3g, 0.1mol) dissolved in 2M sodium hydroxide (50ml) was added to a solution of sodium nitrite (8.0g, 0.116mol) in water (20ml). The mixture was added slowly to a vigorously stirred sloution of conc. sulfuric acid (30ml) in water (60ml) maintaining atemperature below 5°C to give a brown slurry that was stirred for a further 45min., and then filtered washing with cold saturated sodium chloride (20ml). The brown filter cake was added slowly to a vigorously stirred solution of potassium iodide (50g) dissolved in a solution of conc. sulfuric acid (20ml) in water (150ml) at a temperature of 40°C. After the evolution of nitrogen had ceased the brown slurry was heated to a temperature of 70°C and stirred for 1h., cooled to 0°C and filtered to give a brown solid. The crude solid was combined with solid sodium hydroxide (4.0g, 0.10mol) and dissolved in the minimum amount of boiling water, cooled and filtered to

give compound **82** as a pale crimson solid that was dried in *vacuo* over calcium chloride at 50°C for 18h., 18.3g (51%). M.p. >300°C. ν_{max} (KBr)/cm^{-1}: 1199, 1064.

b) Preparation of 5-iodo-1-naphthalenesulfonyl chloride **83**.

Sodium 5-iodo-1-naphthalenesulfonate (18.3g, 51.4mmol) was added, over a 10 minute period, to phosphoryl chloride (100ml, 1.07mol) at room temperature under an atmosphere of nitrogen. The black mixture was heated to 80°C and stirred for a further 2h. The mixture was allowed to cool to room temperature and added carefully (WARNING DELAYED EXOTHERM) to ice water (300ml) maintaining a temperature below 35°C. A pale purple solid was collected by filtration, and recrystallised from glacial acetic acid to give compound **83** as a dark brown solid, 11.5g (64%). M.p. 113-114°C. ν_{max} (KBr)/cm^{-1}: 1367, 1176. δ ^{1}H 8.84 (1H, d, ArH), 8.59 (1H, d, ArH), 8.45 (1H, d, ArH), 8.31 (1H, d, ArH), 7.69 (1H, t, ArH), 7.48 (1H, t, ArH); δ ^{13}C 141.22, 139.87, 139.59, 134.93, 130.13, 130.08, 128.25, 125.51, 124.83, 100.41.

c) *N*1-(8-aminooctyl)-5-iodo-1-naphthalenesulfonamide HCl **J8**.

To a solution of 1,8-diaminooctane (6.14g, 42.5mmol) in 1,4-dioxan (55ml) at room temperature was added a solution of **83** (2.50g, 7.1mmol) in 1,4-dioxan (30ml) over a period of 30min. The mixture was stirred at room temperature for a further 15min. and then slowly heated to 80°C and stirred for 1h. The cooled reaction mixture was diluted with water (80ml) and filtered. The pale crimson filter cake was extracted with hot methanol (100ml) and filtered. The filtrate was concentrated in *vacuo* to give a pale crimson solid that was dissolved in dichloromethane (20ml) and triturated with ethereal hydrogen chloride, cooled to 0°C, filtered, and recrystallised from ethanol to give **J8** as a white crystalline solid, 1.53g (43%). M.p. 222-223°C. ν_{max} (KBr)/cm^{-1}: 3278, 1316, 1160. δ ^{1}H (DMSO) 8.75 (1H, d, ArH), 8.35 (1H, d, ArH), 8.37 (1H, d, ArH), 8.23 (1H, d, ArH), 7.95 (2H, br. s, $ArSO_2NH(CH_2)_8\boldsymbol{NH_2}$), 7.81 (1H, t, ArH), 7.49 (1H, t, ArH), 3.39 (1H, br. s, $ArSO_2\boldsymbol{NH}(CH_2)_8NH_2$), 2.79 (2H, t, $ArSO_2NH\boldsymbol{CH_2}(CH_2)_7NH_2$), 2.71 (2H, t, $ArSO_2NH(CH_2)_7\boldsymbol{CH_2}NH_2$), 1.50 (2H, m, $ArSO_2NHCH_2\boldsymbol{CH_2}(CH_2)_6NH_2$), 1.27 (2H, m, $ArSO_2NH(CH_2)_6\boldsymbol{CH_2}CH_2NH_2$), 1.17 (2H, m, $ArSO_2NHCH_2CH_2\boldsymbol{CH_2}(CH_2)_5NH_2$), 1.02 (6H, m, $ArSO_2NH(CH_2)_3\boldsymbol{(CH_2)_3}(CH_2)_2NH_2$); δ ^{13}C (DMSO) 138.53, 137.07, 136.68, 134.68, 134.14, 129.29, 128.88, 128.47, 126.58, 125.64, 100.67, 42.23, 40.43, 28.84, 28.31, 28.14, 26.89, 25.68, 25.57. (Found : C, 43.48; H, 5.38; N, 5.51. $C_{18}H_{26}ClIN_2O_2S$ requires : C, 43.52; H, 5.27; N, 5.64%).

Preparation of *N*1-(8-aminooctyl)-6-iodo-2-naphthalenesulfonamide HCl **84.**

a) Preparation of sodium 6-iodo-2-naphthalenesulfonate **85**.

Sodium 5-iodo-2-naphthalenesulfonate **85** was prepared from 6-amino-2-naphthalene-sulfonic acid in an analogous manner to that described for compound **82**. M.p. >300°C. ν_{max} (KBr)/cm^{-1}: 1194, 1068.

b) Preparation of 6-iodo-2-naphthalenesulfonyl chloride **86**.

6-Iodo-2-naphthalenesulfonyl chloride **86** was prepared from compound **85** in an analogous manner to that described for compound **83**. M.p. 109-110°C. ν_{max} (KBr)/cm^{-1}: 1362, 1174. δ ^{1}H 8.59(1H, s, ArH), 8.46 (1H, s, ArH), 8.12 (1H, d, ArH), 8.01-7.96 (2H, m, ArH), 7.85 (1H, d, ArH); δ ^{13}C 142.82, 141.34, 135.78, 135.13, 130.24, 129.67, 128.39, 127.43, 123.5, 96.22.

c) Preparation of *N*1-trityl-1,8-octanediamine **87**.

To a mixture of 1,8-diaminooctane (20g, 139mmol) and triethylamine (10.6ml, 76mmol) dissolved in dimethylformamide (150ml) at room temperature under an atmosphere of nitrogen was added trityl chloride (19.3g, 69mmol), and the resulting white emulsion was stirred at room temperature for 18h. T.l.c., ethyl acetate:methanol:880ammonia, 93:15:3, indicated the presence of two new ninhydrin-positive compounds (Rf 0.29) and (Rf 0.80). The solvent was removed in *vacuo* to give a cream residue that was suspended in ethyl acetate (150ml) and partitioned with water (50ml) and saturated sodium chloride (50ml). The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a pale yellow viscous oil. The crude oil was purified by chromatography gradient eluting with ethyl acetate:methanol, 90:10, followed by ethyl acetate:methanol:880 ammonia, 93:15:3. The fractions containing product (Rf 0.29) were combined and concentrated in *vacuo* to give compound 87 as a pale yellow viscous oil, 11.5g (64%). υ_{max} (thin film)/cm^{-1}: 3278, 3055, 2922, 2852, 1665, 1595, 1555, 1488, 1448. δ ^{1}H 7.49 (6H, m, ArH), 7.25 (6H, m, ArH), 7.15 (3H, m, ArH), 2.64 (2H, t, $Ph_3CNH(CH_2)_7\boldsymbol{CH_2}NH_2$), 2.11 (2H, t, $Ph_3CNH\boldsymbol{CH_2}(CH_2)_7NH_2$), 1.51 (3H, br. s., $Ph_3C\boldsymbol{NH}(CH_2)_8\boldsymbol{NH_2}$), 1.46 (4H, m, $Ph_3CNHCH_2\boldsymbol{CH_2}(CH_2)_4\boldsymbol{CH_2}CH_2NH_2$), 1.25 (8H, m, $Ph_3CNH(CH_2)_2\boldsymbol{(CH_2)_4}(CH_2)_2NH_2$); δ ^{13}C 146.34, 128.62, 127.69, 126.09, 70.82, 43.52, 42.12, 32.57, 30.84, 29.58, 29.40, 27.28, 26.81.

d) Preparation of *N*1-(8-tritylaminooctyl)-6-iodo-2-naphthalenesulfonamide **88**.

To a mixture of *N*1-trityl-1,8-octanediamine **87** (1.54g, 3.97mmol) and triethylamine (0.83ml, 5.96mmol) dissolved in dichloromethane (20ml) at room temperature under an atmosphere of nitrogen, was added a solution of 6-iodo-2-naphthalenesulfonyl chloride **86** (1.40g, 3.97mmol) dissolved in dichloromethane (15ml) over a period of 45 minutes to give a dark red heterogeneous mixture. The mixture was stirred at room temperature for 18h. whereby t.l.c., ethyl acetate:methanol:880ammonia, 93:15:3, ninhydrin, indicated the disappearance of **87** (Rf 0.21) and the presence of a new compound (Rf 0.79). The mixture was partitioned with water (2×10ml) and saturated sodium chloride (15ml), dried over sodium sulfate, filtered, and concentrated in *vacuo* to give a crude grey amorphous solid upon exposure to high vacuum. The crude material was filtered through a pad of silica eluting with petroleum ether:dichloromethane:methanol, 70:30:1, and the filtrate was concentrated in *vacuo* to give compound **88** as a buff solid, 1.95g (70%). M.p. 100-102°C. ν_{max} (KBr)/cm^{-1}: 3279, 1665, 1324, 1159. δ ^{1}H 8.55 (1H, s, ArH), 8.42 (1H, s, ArH), 8.03 (1H, d, ArH), 7.98-7.95 (2H, m, ArH), 7.81, (1H, d, ArH), 7.51 (6H, m, ArH), 7.26 (9H, m, ArH), 4.64 (1H, br. s, $ArSO_2\boldsymbol{NH}(CH_2)_8NHCPh_3$), 2.86 (2H, m, $ArSO_2NH\boldsymbol{CH_2}(CH_2)_7NHCPh_3$), 2.07 (2H, t, $ArSO_2NH(CH_2)_7\boldsymbol{CH_2}NHCPh_3$), 1.52 (1H, br. s, $ArSO_2NH(CH_2)_8\boldsymbol{NH}CPh_3$), 1.36 (4H, m, $ArSO_2NHCH_2\boldsymbol{CH_2}(CH_2)_4\boldsymbol{CH_2}CH_2NHCPh_3$), 1.01 (8H, m, $ArSO_2NH(CH_2)_2\boldsymbol{(CH_2)_4}(CH_2)_2NHCPh_3$); δ ^{13}C 146.35, 139.73, 135.44 135.28, 130.39, 129.92, 129.42, 128.91, 128.39, 127.86, 127.24, 125.66, 123.59, 96.23, 70.82, 43.50, 42.22, 30.80, 29.40, 29.31, 28.81, 27.15, 26.25.

e) Preparation of *N*1-(8-aminooctyl)-6-iodo-2-naphthalenesulfonamide hydrochloride **84**.

To a mixture of *N*1-(8-tritylaminooctyl)-6-iodo-2-naphthalenesulfonamide **88** (1.90g, 2.70mmol) and triethylsilane (0.48ml, 2.97mmol) in dichloromethane (24ml) at room temperature under an atmosphere of nitrogen was added trifluoroacetic acid (0.42ml, 5.41mmol) over a period of 5 minutes and the resulting brown homogeneous mixture was stirred at room temperature for 20h. T.l.c., ethyl acetate:methanol:880ammonia, 93:15:3, ninhydrin, indicated the disappearance of starting material (Rf 0.84) and the presence of a new compound (Rf 0.19). The mixture was partitioned with 2M sodium hydroxide (10ml) and saturated sodium chloride (10ml), dried over sodium sulfate, filtered, and concentrated in *vacuo* to give a brown oil. The oil was dissolved in dichloromethane (20ml) and triturated with ethereal hydrogen chloride, cooled to 0°C, filtered, and

recrystallised from ethanol to give **84** as a white crystalline solid, 0.98g (73%). M.p. 219-221°C. ν_{max} (KBr)/cm^{-1}: 3278, 1316, 1160. δ ^{1}H (DMSO) 8.52 (1H, s, ArH), 8.44 (1H, s, ArH), 8.08 (1H, d, ArH), 7.97-7.91 (4H, br. m, 2×ArH, $ArSO_2NH(CH_2)_8\boldsymbol{NH_2}$), 7.88, (1H, d, ArH), 2.76-2.68 (4H, m, $ArSO_2NH\boldsymbol{CH_2}(CH_2)_6\boldsymbol{CH_2}NH_2$), 1.50 (2H, m, $ArSO_2NHCH_2\boldsymbol{CH_2}(CH_2)_6NH_2$), 1.44 (1H, br. s, $ArSO_2\boldsymbol{NH}(CH_2)_8NH_2$), 1.35 (2H, m, $ArSO_2NH(CH_2)_6\boldsymbol{CH_2}CH_2NH_2$), 1.14 (8H, m, $ArSO_2NH(CH_2)_2\boldsymbol{(CH_2)_4}(CH_2)_2NH_2$); δ ^{13}C (DMSO) 138.16, 136.23, 135.76, 135.47, 130.84, 130.50, 128.32, 127.30, 123.24, 95.87, 42.47, 40.42, 28.90, 28.36, 28.27, 27.04, 25.84, 25.27. (Found : C, 43.65; H, 5.29; N, 5.47. $C_{18}H_{26}ClIN_2O_2S$ requires : C, 43.52; H, 5.27; N, 5.64%).

9.2. Preparation of Palmarumycin Analogues.

Preparation of 1-methoxy-2-(4-methoxyphenoxy)benzene **124**.

4-Bromomethoxybenzene (93.5g, 0.50mol) 2-methoxyphenol (55ml 0,45mol) powdered anhydrous potassium carbonate (69.1g, 0.50mol) pyridine (10ml, 0.12mol) and copper bronze (10g, 0.16mol) were combined and thoroughly mixed at room temperature under an inert atmosphere to give a thick paste. The paste was refluxed at an external temperature 180°C for 2h., cooled to 80°C, copper bronze (10g, 0.16mol) and pyridne (10ml, 0.12mol) were added and the resultant heterogeneous mixture was refluxed for a further 5 hours. The cooled mixture was slowly treated with 2M HCl (400ml), diluted with ethyl acetate (250ml), and filtered through a plug of cotton wool. The two phase filtrate was separated and the acidic aqueous was partitioned with ethyl acetate (250ml). The combined organic phase was partitioned with 2M HCl (2×200ml), 2M NaOH (3×200ml), water (150ml), and saturated sodium chloride (100ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a red oil. The oil was diluted with petroleum ether (100ml) and cooled to -10°C, salt-ice bath, to give a pale brown precipitate. The crude solid was recrystallised from ethanol to give compound **124** as a buff solid, 39.9g, 35%. M.p. 73-75°C, [lit. [70, 180]m.p. 72-74°C, 77°C]. δ ^{1}H 6.95 (4H, m, H-2′, H-3′, H-5′, H-6′), 6.85 (4H, m, H-3, H-4, H-5, H-6), 3.86 (3H, s, 4′-OCH_3), 3.77 (3H, s, 1-OCH_3); δ ^{13}C 155.3 (C-4′), 150.8 (C-1), 150.7 (C-1′), 146.6 (C-2), 123.7 (C-4, C-5), 120.9 (C-3), 119.3 (C-2′), 119.1 (C-6′), 114.6 (C-3′, C-5′), 112.5 (C-6).

Preparation of 2-(4-hydroxyphenoxy)phenol **125**.

Compound **124** (34.5g, 0.15mol) was added to a suspension of aluminium trichloride (100g, 0.75mol) in benzene (100ml) at room temperature under an atmosphere of nitrogen. The pale yellow heterogeneous mixture was refluxed for 1.5 h. whereby t.l.c., petroleum ether : ethyl acetate, 8:3, indicated disappearance of **124** (Rf 0.39) and the formation of a new compound (Rf 0.16). The cooled mixture was slowly added to crushed ice (150ml), (caution : vigorous exotherm), diluted with 2M HCl (100ml) and subsequently extracted with ethyl acetate (3×80ml) and saturated sodium chloride (40ml) dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude solid. The crude solid was recrystallised from toluene to give compound **125** as a white solid, 28.6g, 94%. M.p. 163-165°C, [lit. [70]m.p. 164-165°C]. δ ^{1}H 8.66 (1H, br.s., 1-OH), 8.10 (1H, br.s., 1-OH), 6.96 (2H, m, H-3′, H-5′), 6.80 (6H, m, H-3, H-4, H-5, H-6, H-2′, H-6′); δ ^{13}C 153.1 (C-4′), 149.5 (C-1), 147.8 (C-1′), 145.4 (C-2), 123.5 (C-5), 119.7 (C-4), 119.6 (C-2′, C-6′), 118.3 (C-3), 116.6 (C-6), 116.1 (C-3′, C-5′).

Preparation of spiro[benzo[d][1,3]dioxole-2,1′-(2′,5′-cyclohexadiene)]-4′-one **104**.

Method 1. Oxidation with MnO_2.
Activated manganese dioxide (Aldrich 85%, 50g, 0.58mol) was suspended in benzene (350ml) at room temperature under an inert atmosphere and refluxed in a Dean and Stark apparatus for 2h. The Dean-Stark was replaced by a Soxhlet extractor with a thimble containing compound **125** (10.0g, 0.05mol). Extraction was performed at reflux with vigorous stirring under an inert atmosphere for 16h., t.l.c., petroleum ether : ethyl acetate, 9:1, indicated the presence of two compounds (Rf 0.27) and (Rf 0.15). The mixture was allowed to cool, filtered through Hyflo Super Cel, and the filtrate was concentrated in *vacuo* to give a brown viscous oil. The crude material was purified by chromatography eluting with petroleum ether : ethyl acetate, 9:1. Evaporation of the first clear-cut yellow fraction (Rf 0.27) gave compound **104**, 3.97g (40%) as a bright yellow solid. M.p. 142-144°C, [lit. [70]m.p. 143-144]. ν_{max}(KBr)/cm^{-1}: 3056, 1679, 1640, 1482, 1359, 1311, 1234, 1171, 1095, 1000, 926, 809, 747; δ ^{1}H 6.88 (4H, m, H-2, H-3, H-4, H-5), 6.87 (2H, d, *J*10.2, H-2′, H-6′), 6.29 (2H, d, *J*10.2, H-3′, H-5′); δ ^{13}C 184.3 (C-4′), 146.6 (C-1, C-6), 139.5 (C-2′, C-6′), 130.0 (C-2, C-5), 122.2 (C-3, C-4), 109.5 (C-3′, C-5′), 104.9 (C-1′); *m/z* (ESI) 200.3 (MH, 100%), 201.2 (MH$^+$, 17%). Evaporation of the second fraction (Rf

0.15) gave *p*-benzoquinone. M.p. 113-115°C, [lit. [70]m.p. 113-115°C]. δ ^{1}H 6.79 (4H, s, H-2, H-3, H-5, H-6); δ ^{13}C 187.2 (C-1, C-4), 136.5 (C-2, C-3, C-5, C-6).

Method 2. Oxidation with Phenyliodosyl diacetate.

Compound **125** (0.50g, 2.47mmol) and lithium carbonate (0.44g, 5.93mmol) were suspended in anhydrous dichloromethane (80ml) at room temperature under an inert atmosphere. Phenyliodosyl diacetate (0.88g, 2.72mmol) in dichloromethane (20ml) was added dropwise over a period of 30 minutes to give a bright red heterogeneous mixture which was stirred for a further 30 minutes. T.l.c., petroleum ether : ethyl acetate, 8:4, indicated a complex mixture with three principal components (Rf 0.52), (Rf 0.36), and (Rf 0.20). The mixture was treated with solid sodium bicarbonate (0.25g, 2.97mmol) stirred at room temperature for 5 minutes, and partitioned with water (2×30ml) and saturated sodium chloride (30ml). The organics were dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude black oil. The crude oil was purified by chromatography, gradient elution with petroleum ether : ethyl acetate, 9:1 to 1:1. The first fraction (Rf 0.52) gave compound **104** as a bright yellow solid, 0.21g (42%). M.p. : 142-144°C. Spectral data consistent with those obtained for compound **104** from Method 1. The second fraction (Rf 0.36) gave *p*-benzoquinone as a yellow solid, 0.04g. M.p. 112-114°C. The third fraction, 0.13g, was observed to be a complex mixture of aromatic compounds by ^{1}H N.M.R.

Peri lithiation of 1-naphthol.

Preparation of 8-Hydroxy-1-naphthaldehyde **126**.

1-Naphthol (4.33g, 30mmol) was dissolved in TMEDA (45ml, 300mmol) at room temperature under an atmosphere of nitrogen. n-Butyllithium (2M, 45.1ml, 90mmol) was added slowly over a period of 8 minutes to give a buff coloured precipitate. The heterogeneous mixture was sonicated for 2h., attaining an internal temperature of 50°C. The mixture was cooled to -40°C and anhydrous dimethylformamide (20ml) was added slowly, maintaining an internal temperature of -35°C, and left at -40°C for a further 1 hour. The mixture was allowed to attain room temperature and was quenched by the addition of 2M HCl, and diluted with water (100ml). T.l.c., petroleum ether : ethyl acetate, 4:1, indicated the disappearance of 1-naphthol (Rf 0.33) and the presence of a new compound (Rf 0.25) that gone a positive reaction with DNPH. The mixture was

extracted with ethyl acetate (2×70ml) and the combined organic phase was partitioned with water (2×30ml), saturated sodium chloride (2×20ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give an orange powder. The crude material was purified by chromatography eluting with petroleum ether : ethyl acetate, 4:1. Evaporation of the second fraction (Rf 0.24) gave compound **126** as an orange solid, 5.17g (85%). M.p. 90-91°C, [lit. [102, 103]m.p. 92-96°C, 88-90°C]. ν_{max}(KBr)/cm^{-1}: 3060, 2940, 1665, 1590, 1450, 1265, 1250, 1215, 1195, 1000, 975; δ ^{1}H 11.67 (1H, s, exchangeable with D_2O, OH), 9.83 (1H, s, CHO), 8.10 (1H, d, *J*9.9, H-4), 8.01 (1H, d, *J*8.6, H-2), 7.51 (2H, m, H-3, H-5), 7.39 (1H, d, *J*9.2, H-6), 7.17 (1H, d, *J*8.9, H-7); δ ^{13}C 197.84 (CHO), 155.13 (C-8), 142.93 (C-2), 139.10 (C-4), 136.22 (C-4a), 132.31 (C-3), 129.04 (C-6), 124.26 (C-1), 121.09 (C-5), 120.47 (C-8a), 115.94 (C-7).

Preparation of 8-methoxy-1-naphthaldehyde **128**.

8-Hydroxy-1-naphthaldehyde **126** (0.50g, 2.9mmol), and potassium carbonate (1.00g, 7.3mmol), were suspended in 2-butanone (10ml) at room temperature under an atmosphere of nitrogen. Methyl iodide (0.72ml, 11.6mmol) was added and the heterogeneous mixture was stirred at room temperature for 18 hours. T.l.c., petroleum ether : ethyl acetate, 4:1, indicated the disappearance of **126** (Rf 0.20) and the presence of a new compound (Rf 0.25) in *vacuo* and the residue was suspended in ethyl acetate (30ml) and filtered. The combined organics were partitioned with 1M HCl (15ml), water (15ml), and saturated sodium chloride (15ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude solid. The solid was purified by chromatography eluting with petroleum ether to ethyl acetate, 4:1. Evaporation of the first fraction gave compound **128** as an orange solid, 0.081g (15%). δ ^{1}H 11.09 (1H, s, CHO), 7.99-7.91 (2H, m, H-4, H-2), 7.53-7.45 (3H, m, H-3, H-5, H-6), 6.97 (1H, d, *J*8.3, H-7), 4.01 (3H, s, OCH_3);); δ ^{13}C 195.70 (CHO), 154.36 (C-8), 135.31 (C-2), 135.02 (C-4), 133.13 (C-4a), 127.26 (C-6), 126.52 (C-1), 125.75 (C-3), 123.45 (C-8a), 121.51 (C-5), 106.77 (C-7), 55.67 (OCH_3).

Preparation of 8-benzyloxy-1-naphthaldehyde **129**.

Compound **129** was prepared from **126** and benzyl bromide in an analogous manner to that described for compound **128**.

T.l.c., petroleum ether : ethyl acetate, 4:1, compound **129** (Rf 0.28) and compound **126** (Rf 0.20). %Yield : 17. δ ^{1}H 11.06 (1H, s, CHO), 7.95-7.90 (2H, m, H-2, H-4), 7.52-7.47

(2H, m, H-3, H-6), 7.42-7.33 (6H, m, H-7, H-2′, H-3′, H-4′, H-5′, H-6′), 6.99 (1H, d, *J*8.6, H-7), 5.21 (2H, s, $PhCH_2$-); δ ^{13}C 195.38 (CHO), 155.13 (C-8), 135.95 (C-1′), 135.58 (C-2), 135.34 (C-4), 134.57 (C-4a), 133.13 (C-5), 129.88 (C-3′), 128.95 (C-5′), 128.75 (C-4′), 127.81 (C-2′), 127.55 (C-6′), 126.36 (C-6), 125.71 (C-3), 124.90 (C-1), 121.78 (C-8a), 108.17 (C-7), 71.09 ($PhCH_2$-).

Preparation of 1,8-dihydroxynaphthalene **94**[66].

1,8-naphthasulfone (10g, 0.048mol) was intimately mixed with freshly ground potassium hydroxide (40g, 0.71mol) in a stainless steel beaker and covered with an asbestos mat. The mixture was heated to an internal temperature of 300°C (stainless steel thermocouple) with the evolution of white fumes to give a black tar that solidified on cooling to room temperature. A 1 : 2 mixture of concentrated hydrochloric acid and water was added with stirring until neutral pH was obtained. The black heterogeneous mixture was diluted with water (300ml) and extracted with ethyl acetate (3×150ml). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude black oil that was purified by chromatography with gradient elution, petroleum ether : ethyl acetate, 9:1 to 7:3. Fractions containing the product were combined and concentrated in *vacuo* to give compound **94** as a white solid, 6.94g, 89%, that slowly darkened upon exposure to air. M.p. 142-143°C, [lit. [66, 101]m.p. 141-142°C). ν_{max}(KBr)/cm^{-1}: 3150, 1612, 1407, 1283, 1032, 813; δ ^1H 10.30 (2H, br.s., 2-OH), 7.24 (4H, m, H-3, H-4, H-5, H-6), 6.77 (2H, br.s., *J*2.0 and *J*2.3, H-2, H-7); δ ^{13}C 154.2 (C-1, C-8), 136.9 (C-4a), 126.7 (C-3, C-6), 119.3 (C-4, C-5), 115.0 (C-8a), 108.6 (C-2, C-7).

Preparation of 1-methoxy-8-naphthol **130**.

a) 1,8-Dihydroxynaphthalene (5.0g, 31.2mmol) and tetra-n-butylammonium bromide (2.0g, 6.2mmol) were dissolved in a mixture of 10% w/w aqueous sodium hydroxide and dichloromethane (30ml) at room temperature. Methyl iodide (2.14ml, 34.3mmol) was added and the two phase mixture was stirred at a temperature of 37°C for 20h. to give a black emulsion. T.l.c., petroleum ether : ethyl acetate, 8:2, indicated the disappearance of 1,8-dihydroxynaphthalene (Rf 0.13) and the presence of a new compound (Rf 0.27) and baseline material. The dichloromethane was removed in *vacuo* and the residual aqueous was adjusted to pH 5.5 by the slow addition of 2M hydrochloric acid. The acidic mixture

was extracted with ethyl acetate (3×30ml) and the combined organic phase was partitioned with water (30ml), 10% aqueous sodium metabisulfite (20ml), and saturated sodium chloride (15ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a black oil that solidified upon standing. The crude solid was purified by chromatography eluting with petroleum ether : ethyl acetate, 8:2. Fractions containing the product were combined and concentrated in *vacuo* to give compound **130** as a buff solid, 4.46g (82%). M.p. 56°C, [lit. [53]m.p. 55-56°C]. ν_{max}(KBr)/cm^{-1}: 3359, 3057, 2948, 2843, 1629, 1612, 1583, 1452, 1403, 1306, 1262, 1197, 1158, 1119, 1076, 1028, 963, 812, 753; δ ^{1}H 9.32 (1H, br.s., 1-OH), 7.31 (4H, m, H-3, H-4, H-5, H-6), 6.87 (1H, d, *J*8.6, H-7), 6.73 (1H, d, *J*7.6, H-2), 4.01 (3H, s, 1-OCH_3); δ ^{13}C 156.1 (C-8), 154.5 (C-1), 136.7 (C-4a), 127.7 (C-3), 125.6 (C-6), 121.8 (C-4), 118.8 (C-5), 115.0 (C-8a), 110.4 (C-2), 103.9 (C-7).

Ullmann Ether Synthesis.

Attempted preparation of 1-methoxy-8-(4-methoxyphenoxy)naphthalene.

a) 1-Methoxy-8-naphthol **130** (2.04g, 6.0mmol), 4-iodoanisole (1.00g, 43mmol), and $(CF_3SO_3Cu)_2$.benzene complex (54mg, 1.1mmol) were suspended in a mixture of anhydrous toluene (40ml) and ethyl acetate (0.1ml) at room temperature under an atmosphere of nitrogen and refluxed for 16h. T.l.c., petroleum ether : ethyl acetate, 9:1 indicated the presence of 4-iodonisole (Rf 0.54) and 1-methoxy-8-naphthol (Rf 0.38). Copper(I) bromide (31mg, 0.2mmol) was added and the mixture was refluxed for a further 6 hours. T.l.c., petroleum ether : ethyl acetate, 9:1, indicated a complex mixture of products streaking from the baseline. Experiment abandoned.

b) 8-Methoxy-1-naphthol **130** (0.22g, 1.3mmol), 4-iodoanisole (0.25g, 1.1mmol), copper(II) oxide (15mg, 0.1mmol), and cesium carbonate (0.70g, 2.1mmol) were suspended in anhydrous dimethylformamide (10ml) at room temperature under an atmosphere of nitrogen. The heterogeneous mixture was stirred and heated to 120°C for 2h. T.l.c., petroleum ether : ethyl acetate, 9:1, indicated the disappearance of 1-methoxy-8-naphthol (Rf 0.38) and the formation of a complex mixture of products streaking from the baseline. Experiment abandoned.

Nucleophilic Aromatic Substitution (S_NAr) Reactions.

Preparation of 1-methoxy-8-(4-nitrophenoxy)naphthalene **131**.

Method 1.

Sodium (36mg, 1.6mmol) was added slowly to anhydrous ethanol (3ml) at room temperature under an atmosphere of nitrogen. 8-Methoxy-1-naphthol **130** (0.25g, 1.4mmol) was added slowly to give a pale green homogenous mixture. The solvent was removed in *vacuo* to give a pale yellow crisp foam that was dissolved in anhydrous dimethyl sulfoxide (3ml). The reaction flask was evacuated and purged with nitrogen and 4-fluoronitrobenzene (0.16ml, 1.5mmol) was added. The black homogeneous mixture was heated at 80°C for 3h. T.l.c., petroleum ether : ethyl acetate, 5:1, indicated the disappearance of 4-fluoronitrobenzene (Rf 0.41) and 8-methoxy-1-naphthol (Rf 0.23) and the presence of a new compound (Rf 0.25). The cooled reaction mixture was diluted with water (20ml) and extracted with ethyl acetate (2×15ml). The combined organics were partitioned with saturated sodium chloride (3×10ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a pale brown solid. The crude material was purified by chromatography eluting with petroleum ether : ethyl acetate, 6:1, to give compound **131** as a cream solid, 0.23g (54%). M.p. 100-102°C. ν_{max} (KBr)/cm^{-1}: 3075, 2927, 2836, 1591, 1574, 1508, 1487, 1381, 1339, 1266, 1162, 1109, 1073, 1026, 846, 751; δ ^{1}H 8.14 (2H, dd, *J*2.3 and *J*2.0, H-3′, H-5′), 7.75 (1H, d, *J*9.6, H-4), 7.45 (3H, m, H-3, H-5, H-6), 7.16 (1H, d, *J*8.6, H-2), 6.82 (2H, dd, *J*2.3 and *J*2.0, H-2′, H-6′), 6.77 (1H, d, *J*7.6, H-7); δ ^{13}C 165.4 (C-1′), 155.1 (C-1), 149.2 (C-8), 141.6 (C-4′), 137.5 (C-4a), 127.0 (C-6), 126.5 (C-3′, C-5′), 125.7 (C-3), 120.8 (C-7), 119.7 (C-4, C-5), 119.2 (C-8a), 115.3 (C-2′, C-6′), 106.3 (C-2).

Method 2.

8-Methoxy-1-naphthol **130** (0.25g, 1.44mmol) was dissolved in tetrahydrofuran (2ml) at room temperature under an atmosphere of nitrogen and sodium hydride (60mg, 60% in oil, 1.51mmol) was slowly added. After effervescence had ceased the solvent was removed in *vacuo* to give a pale yellow crisp foam. The foam was dissolved in dimethyl sulfoxide (4ml) and the flask was evacuated and purged with nitrogen. 4-nitro-fluorobenzene (0.16ml, 1.51mmol) was added to give a black homogeneous mixture that was heated to 60°C for 2h. T.l.c., petroleum ether:athyl acetate, 5:1, indicated the

disappearance of 8-methoxy-1-naphthol (Rf 0.23) and 4-nitrofluorobenzene (Rf 0.41) and the presence of a new compound (Rf 0.35). The cooled mixture was diluted with water (20ml) and extracted with ethyl acetate (2×15ml). The combined organic phase was partitioned with saturated sodium chloride (3×10ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a pale brown solid. The crude solid was triturated with petroleum ether, filtered, and washed with methanol (5ml) to give compound **131** as a cream solid, 0.35g, 83%. M.p. : 100-102°C. Spectral data were consistent with those of compound **131** obtained from method 1.

Preparation of 8-benzyloxy-1-naphthol **132**.

Method 1.

1,8-Dihydroxynaphthalene **94** (2.0g, 12.5mmol) and tetra-n-butylammonium bromide (0.8g, 2.5mmol) were dissolved in a mixture of 10% w/w aqueous sodium hydroxide and dichloromethane (20ml) at room temperature. Benzyl bromide (1.63ml, 13.7mmol) was added and the two phase mixture was stirred at room temperature for 20h. to give a black emulsion. T.l.c., petroleum ether : ethyl acetate, 7:3, indicated the disappearance of 1,8-dihydroxynaphthalene (Rf 0.23) and the presence of a new compound (Rf 0.47) and an impurity (Rf0.53). The mixture was adjusted to pH 5.5 by the slow addition of 2M hydrochloric acid and extracted with ethyl acetate (3×15ml) and the combined organic phase was partitioned with water (20ml), 10% aqueous sodium metabisulfite (20ml), and saturated sodium chloride (15ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a black oil. An attempt to purify the crude oil by chromatography eluting with petroleum ether : ethyl acetate, 9:1, resulted in the co-elution of the impurity (Rf0.35) with the product (Rf0.27). The mixed fractions were combined and concentrated in *vacuo* to give a crude orange oil, 2.7g. Analysis of the crude material by 1H N.M.R. indicated a 2:1 mixture of 8-benzyloxy-1-naphthol : an O- and C- dibenzyl naphthol impurity. δ ^{1}H 9.62 (s, 1×OH), 9.37 (s, 1×OH), 7.50 to 7.00 (9H + 14H, m), 6.82 (2H + 1H, m), 5.18 (s, 2H + 2H), 4.09 (s, 2H).

The crude oil was distilled at reduced pressure to afford a black residue consisting of degradation products and a yellow distillate consisting of 8-benzyloxy-1-naphthol (Rf0.27) and degradation products. Trituration of the distillate with a mixture of methanol and cyclohexane afforded **132** as a white precipitate, 0.20g (6%). M.p. 91-92°C. ν_{max} (KBr)/cm^{-1}: 3390, 3055, 2939, 1607, 1582, 1453, 1405, 1357, 1306, 1261, 1234, 1059,

811, 752; δ ^{1}H 9.37 (1H, br.s., 1-OH), 7.41 (7H, m, H-3, H-4, H-5, H-6, H-3′, H-4′, H-5′), 7.29 (2H, m, H-2′, H-6′), 6.83 (2H, dd, *J*7.3 and *J*7.3, H-2, H-7), 5.22 (2H, s, $PhCH_2$); δ ^{13}C 155.3 (C-1), 154.4 (C-8), 136.8 (C-4a), 135.3 (C-1′), 128.9 (C-4′), 128.8 (C-3, C-5), 128.5 (C-3′, C-6′), 127.9 (C-6), 125.5 (C-3), 122.0 (C-4), 118.9 (C-5), 115.2 (C-8a), 110.5 (C-7), 105.2 (C-2), 71.6 ($PhCH_2$). (Found : C, 81.24; H, 5.54. $C_{17}H_{14}O_2$ requires C, 81.58; H, 5.64%); *m/z* (ESI) 250.3 (MH, 100%), 251.8 (MH^+, 16%).

Method 2.

1,8-Dihydroxynaphthalene **94** (4.74g, 29.6mmol) and freshly ground potassium carbonate (8.18g, 59.2mmol) were suspended in 2-butanone (180ml) at room temperature under an atmosphere of nitrogen. Benzyl bromide (3.70ml, 31.1mmol) was added and the heterogeneous mixture was stirred at room temperature for 6h. T.l.c., petroleum ether : ethyl acetate, 8:2, indicated the disappearance of 1,8-dihydroxynaphthalene (Rf 0.13) and the formation of a new compound (Rf 0.39) with an impurity (Rf 0.54). The solvent was removed in *vacuo* and the residue was suspended in ethyl acetate (100ml) and filtered washing with ethyl acetate. The filtrate was partitioned with 1M Hydrochloric acid (3×25ml) and saturated sodium chloride (2×15ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a black oil. The crude material was purified by chromatography eluting with hexane : dichloromethane, 7:3. The first fraction (Rf0.23) was combined and concentrated in *vacuo* to give dibenzyl impurity **133** as a yellow oil, 0.20g. δ ^{1}H 9.61 (1H, br. s, OH), 7.40 (6H, m, H-3, H-4, H-5, H-6, H-4′, H-4″), 7.23 (8H, m, H-2′, H-3′, H-5′, H-6′, H-2″, H-3″, H-5″, H-6″), 6.85 (1H, d, *J*7.6, H-2), 5.24 (2H, s, $PhCH_2O$-), 4.10 (2H, s, $PhCH_2C$-); δ ^{13}C 155.2 (C-8), 151.3 (C-1), 141.3 (C-1″), 135.6 (C-4a), 135.2 (C-1′), 130.0 (C-6), 129.0 (C-2″, C-6″), 128.9 (C-3″, C-5″), 128.7 (C-3′, C-5′), 128.5 (C-4′), 128.3 (C-2′, C-6′), 128.0 (C-4″), 125.7 (C-3), 122.1 (C-5), 119.0 (C-7), 118.6 (C-4), 115.1 (C-8a), 105.3 (C-2), 71.6 ($PhCH_2O$-), 35.4 ($PhCH_2C$-).

The second fraction was combined and concentrated in *vacuo* to give compound **132** as a white solid, 6.67g (90%), whose spectral data were consistent with those of compound **132** obtained from method 1.

General method for the preparation of 1-benzyloxy-8-(4-nitrophenoxy)naphthalenes.

To a 2M solution of 8-benzyloxy-1-naphthol **132** (1eq) in tetrahydrofuran at room temperature under an atmosphere of nitrogen was added slowly sodium hydride (1.05eq,

60% in oil). After effervescence had ceased the solvent was removed in *vacuo* to give a crisp foam. The sodium salt was dissolved in dimethyl sulfoxide (0.5M) and the flask was evacuated and purged with nitrogen. The appropriate *para*-nitrofluorobenzene (1.05eq.) was added and the homogeneous mixture was stirred at the appropriate temperature until the reaction was judged to be complete by t.l.c. The cooled mixture was diluted with water and extracted with ethyl acetate three times. The combined organic phase was partitioned with saturated sodium chloride, three times, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The crude material was purified by chromatography eluting with the appropriate solvent, or by recrystallisation.

Preparation of 1-benzyloxy-8-(4-nitrophenoxy)naphthalene **134**.

Reaction temperature (time): 60°C (2 h.); T.l.c., petroleum ether:ethyl acetate, 4:1; 8-benzyloxy-1-naphthol **132** (Rf 0.53), 4-fluoronitrobenzene (Rf 0.61), compound **134** (Rf 0.49); Chromatography petroleum ether:ethyl acetate, 20:1, (Rf 0.22). Yield : 90% as a cream coloured solid. M.p. 106-108°C. ν_{max} (KBr)/cm^{-1}: 3058, 2926, 2879, 1596, 1573, 1507, 1489, 1373, 1333, 1269, 1109, 1058, 844, 748; δ ^{1}H 7.87 (2H, dd, *J*5.6 and *J*5.6, H-3″, H-5″), 7.76 (1H, d, *J*9.6, H-4), 7.46 (3H, m, H-3, H-6, H-5), 7.30 (1H, dd, *J*2.3 and *J*3.0, H-4′), 7.23 (2H, m, H-3′, H-5′), 7.12 (1H, d, *J*8.6, H-2), 7.05 (2H, dd, *J*4.6 and *J*3.6, H-2′, H-6′), 6.90 (1H, d, *J*7.6, H-7), 6.49 (2H, dd, *J*2.3 and *J*2.3, H-2″, H-6″), 4.86 (2H, s, $PhCH_2$); δ ^{13}C 165.0 (C-1″), 154.4 (C-1), 149.3 (C-8), 141.3 (C-4″), 137.6 (C-4a), 135.9 (C-1′), 128.3 (C-3′, C-4′, C-5′), 128.1 (C-2′, (C-6′), 126.9 (C-6), 126.6 (C-3), 125.5 (C-3″, C-5″), 121.0 (C-7), 119.8 (C-4, C-5), 119.5 (C-8a), 115.2 (C-2″, C-6″), 107.1 (C-2), 70.9 ($PhCH_2$). (Found : C, 74.07; H, 4.54; N, 3.73. $C_{23}H_{17}NO_4$ requires C, 74.38; H, 4.61; N, 3.77%).

Preparation of 1-benzyloxy-8-(4-nitro-2-trifluoromethylphenoxy)naphthalene **135**.

Reaction temperature (time) : 20°C (3 hours); T.l.c., petroleum ether:ethyl acetate, 4:1, 2-fluoro-5-nitrobenzotrifluoride (Rf 0.46), 8-benzyloxy-1-naphthol **132** (Rf 0.40), compound **135** (Rf 0.34); Recrystallised from ethanol; Yield : 95%. M.p. 168-169°C. ν_{max} (KBr)/cm^{-1}: 3062, 2936, 2879, 1627, 1599, 1579, 1522, 1481, 1344, 1278, 1137, 1063, 826, 758; δ ^{1}H 8.15 (1H, s, H-3″), 8.07 (1H, d, *J*9.2, H-5″), 7.80 (1H, d, *J*8.3, H-4), 7.50 (3H, m, H-3, H-5, H-6), 7.24 (1H, dd, *J*2.3 and *J*2.3, H-4′), 7.15 (3H, m, H-2, H-5′,

H-3′), 6.92 (3H, m, H-7, H-2′, H-6′), 6.55 (1H, d, *J*9.2, H-6″), 4.85 (2H, br.d., *J*31.3, $PhCH_2$); δ ^{13}C 154.2 (C-1″), 153.1 (C-1), 148.4 (C-8), 141.2 (C-4″), 137.5 (C-4a), 135.4 (C-1′), 128.4 (C-3′, C-4′, C-5′), 128.2 (C-2′, C-6′), 127.2 (C-6), 127.1 (C-5″), 126.7 (C-3), 123.7 (C-3″), 123.6 (C-6″), 120.9 (C-7), 119.6 (C-8a), 119.1 (C-2″), 115.1 (C-4, C-5), 107.1 (C-2), 70.9 ($PhCH_2$). (Found : C, 65.50; H, 3.67; N, 3.11. $C_{24}H_{14}F_3NO_4$ requires C, 65.60; H, 3.67; N, 3.19%).

Preparation of 4-fluoro-2-methoxy-1-nitrobenzene **137**.

5-Fluoro-2-nitrophenol (2.50g, 15.9mmol) and freshly ground potassium carbonate (4.40g, 31.8mmol) were suspended in anhydrous 2-butanone (50ml) at room temperature under an atmosphere of nitrogen. Methyl iodide (4.0ml, 63.7mmol) was added and the intense orange heterogeneous mixture was stirred at room temperature for 4 days to give a pale yellow mixture. T.l.c., petroleum ether:ethyl acetate, 4:1, indicated the disappearance of 5-fluoro-2-nitrophenol (Rf 0.47) and the presence of a new compound (Rf 0.26). The solvent was removed in *vacuo* and the residue was suspended in ethyl acetate (80ml) and filtered washing with ethyl acetate. The filtrate was partitioned with 2M hydrochloric acid (2×15ml) and saturated sodium chloride (15ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude oil that solidified on standing. The crude material was recrystallised from methanol to give compound **137** as a white crystaline solid, 1.98g (73%). M.p. 52-54°C. ν_{max} (KBr)/cm^{-1}: 3086, 2951, 1625, 1588, 1522, 1446, 1351, 1292, 1194, 1166, 1093, 1022, 956, 844, 749; δ ^1H 7.95 (1H, m, H-3), 6.79 (2H, m, H-5, H-6), 4.05 (3H, s, OCH_3); δ ^{13}C 169.3 (C-4), 156.1 (C-2), 136.4 (C-1), 128.3 (C-6), 107.5 (C-5), 101.6 (C-3), 56.8 (OCH_3).

Preparation of 1-benzyloxy-8-(3-methoxy-4-nitrophenoxy)naphthalene **136**.

Reaction temperature (time) : 60°C (2.5h.); T.l.c., petroleum ether:ethyl acetate, 8:3, 4-fluoro-2-methoxy-1-nitrobenzene **137** (Rf 0.66), 8-benzyloxy-1-naphthol **132** (Rf 0.57), compound **136** (Rf 0.47); Recrystallised from methanol / 5% toluene; Yield : 91% as a buff coloured solid. M.p. 121-123°C. ν_{max} (KBr)/cm^{-1}: 3085, 2926, 2856, 1614, 1574, 1508, 1445, 1374, 1350, 1286, 1268, 1196, 1166, 1096, 828, 764; δ ^1H 7.77 (1H, d, *J*8.3, H-4), 7.73 (1H, d, *J*9.2, H-5″), 7.45 (3H, m, H-3, H-5, H-6), 7.27 (3H, m, H-3′, H-4′, H-5′), 7.12 (3H, m, H-2, H-2′, H-6′), 6.92 (1H, d, *J*8.2, H-7), 6.19 (1H, s, H-2″), 5.97 (1H,

d, *J*11.6, H-6″), 4.90 (2H, s, $PhCH_2$), 3.60 (3H, s, OCH_3); δ ^{13}C 165.4 (C-1″), 155.5 (C-3″), 154.6 (C-1), 149.2 (C-8), 137.5 (C-4a), 135.9 (C-4″), 129.0 (C-1′), 128.4 (C-3′, C-4′, C-5′), 128.2 (C-2′, C-6′), 128.1 (C-5″), 126.9 (C-6), 126.6 (C-3), 121.0 (C-8a), 119.8 (C-5), 119.7 (C-4), 107.2 (C-6″), 106.0 (C-2), 100.8 (C-2″), 71.0 ($PhCH_2$), 56.1 (OCH_3). (Found : C, 72.18; H, 4.98; N, 3.21. $C_{24}H_{19}NO_5$ requires C, 71.81; H, 4.77; N, 3.49%).

General procedure for the preparation of aminophenoxy- and aminonaphthyloxy-naphthols.

1-Benzyloxy-8-(4-nitrophenoxy)- or (4-nitronaphthyloxy)-naphthalene (1part) and 10% Pd/C (0.5parts) were suspended in ethyl acetate at room temperature. The reaction flask was evacuated and purged with hydrogen and ethanol (2parts) was added. The black heterogeneous mixture was stirred at room temperature under an atmospheric pressure of hydrogen until judged complete by t.l.c. The mixture was filtered through Hyflo Super Cel, washing with ethanol, and the filtrate was concentrated in *vacuo* to give the 8-(4-aminophenoxy)- or (4-aminonaphthyloxy)-1-naphthols. These intermediates were immediately subjected to oxidative spiro-cyclisation without further purification.

Preparation of 8-(4-aminophenoxy)-1-naphthol **138**.

T.l.c., petroleum ether:ethyl acetate, 7:3, 1-benzyloxy-8-(4-nitrophenoxy)naphthalene **134** (Rf 0.58) and compound **138** (Rf 0.17); Yield : 96% as a crimson solid. M.p. 134-136°C. ν_{max} (KBr)/cm^{-1}: 3423, 3375, 3043, 2932, 1624, 1602, 1581, 1507, 1453, 1393, 1359, 1300, 1224, 1205, 1152, 1076, 1034, 843, 815, 751; δ ^{1}H 9.20 (1H, br. s, OH), 7.43 (1H, d, *J*8.3, H-6), 7.35 (2H, dd, *J*8.2 and *J*8.3, H-4, H-5), 7.19 (1H, dd, *J*8.9 and *J*8.3, H-3), 7.00 (2H, dd, *J*2.3 and *J*2.3, H-3′, H-5′), 6.93 (1H, d, *J*8.6, H-2), 6.72 (2H, dd, *J*2.0 and *J*2.0, H-2′, H-6′), 6.56 (1H, d, *J*7.6, H-7), 3.68(2H, br. s, NH_2); δ ^{13}C 156.4 (C-1′), 154.2 (C-1), 146.1 (C-8), 136.9 (C4a), 127.7 (C-6), 125.5 (C-3), 122.6 (C-3′, C-5′), 122.4 (C-2′, C-6′), 119.0 (C-7), 116.2 (C-4, C-5), 116.1 (C-8a), 108.8 (C-2). (Found : C, 76.61; H, 5.25; N, 5.53. $C_{16}H_{13}NO_2$ requires C, 76.48; H, 5.21; N, 5.57%).

Preparation of 8-(4-amino-2-trifluoromethylphenoxy)-1-naphthol **139**.

T.l.c., petroleum ether:ethyl acetate, 7:3, 1-benzyloxy-8-(4-nitro-2-trifluoromethyl phenoxy)naphthalene **135** (Rf 0.58) and compound **139** (Rf 0.26); Yield : 94% as a

crimson solid. M.p. 87-89°C. ν_{max} (KBr)/cm^{-1}: 3448, 3371, 3643, 2931, 1635, 1609, 1584, 1499, 1455, 1404, 1343, 1304, 1256, 1222, 1160, 1111, 1048, 1026, 834, 814, 755; δ ^{1}H 8.79 (1H, br s, OH), 7.47 (1H, d, *J*9.2, H-6), 7.37 (2H, dd, *J*8.2 and *J*8.3, H-4,H-5), 7.21 (1H, dd, *J*6.6 and *J*8.3, H-3), 6.97 (3H, m, H-2, H-3′, H-5′), 6.82 (1H, dd, *J*3.0 and *J*3.0, H-6′), 6.56 (1H, d, *J*8.6, H-7), 3.85 (2H, br s, NH_2); δ ^{13}C 155.4 (C-1), 153.8 (C-1′), 144.0(C-8), 143.9 (C-4′), 136.9 (C-4a), 127.8 (C-6), 125.4 (C-3), 123.8 (C-7), 123.4 (C-2′), 119.2 (C-6′), 115.5 (C-8a), 113.0 (C-5′), 112.9 (C-4), 112.8 (C-5), 110.9 (C-3′), 109.3 (C-2). (Found : C, 64.06; H, 3.80; N, 4.33. $C_{17}H_{12}F_3NO_2$ requires C, 63.95; H, 3.79; N, 4.39%).

Preparation of 8-(4-amino-3-methoxyphenoxy)-1-naphthol **140**.

T.l.c., petroleum ether:ethyl acetate, 8:3, 1-benzyloxy-8-(4-nitro-3-methoxyphenoxy)-naphthalene **136** (Rf 0.59) compound **140** (Rf 0.23); Yield : 96% as a crimson solid. M.p. 105-106°C. ν_{max} (KBr)/cm^{-1}: 3421, 3372, 3044, 2933, 1622, 1609, 1580, 1509, 1462, 1402, 1304, 1252, 1193, 1148, 1076, 1032, 940, 850, 813, 754; δ ^{1}H 9.19 (1H, br s, OH), 7.45 (1H, d, *J*9.2, H-6), 7.35 (2H, dd, *J*8.2 and *J*9.9, H-4, H-5), 7.20 (1H, dd, *J*7.3 and *J*7.9, H-3), 6.94 (1H, dd, *J*2.0 and *J*1.7, H-5′), 6.73 (1H, d, *J*8.6, H-2), 6.68 (2H, m, H-2′,H-6′), 6.59 (1H, d, *J*8.6, H-7), 3.81 (5H, br. s, NH_2, OCH_3); δ ^{13}C 156.5 (C-1), 154.2 (C-1′), 148.1 (C-3′), 145.9 (C-8), 136.9 (C-4a), 133.9 (C-4′), 127.7 (C-6), 125.6 (C-3), 122.6 (C-7), 119.0 (C-5′), 114.9 (C-4, C-5), 113.6 (C-8a), 110.5 (C-6′), 108.8 (C-2), 104.8 (C-2′), 55.7 (OCH_3). (Found : C, 72.66; H, 5.40; N, 4.77. $C_{17}H_{15}NO_3$ requires C, 72.58;H, 5.37; N, 4.98%).

General method for the oxidative spiro-cyclisation of aminophenoxy and aminonaphthyloxy naphthols.

The appropriate 8-(4-aminophenoxy)- or (4-aminonaphthyloxy)-1-naphthol (1eq, 0.02M) and of activated manganese dioxide (Aldrich 85%, 5eq) were suspended in anhydrous benzene under an atmosphere of nitrogen and gently refluxed until the reaction was judged complete by t.l.c.. The cooled mixture was filtered through Hyflo Super Cel, and the solid was washed with ethyl acetate. The pale yellow filtrate was concentrated in *vacuo* to give a crude solid. The crude material was purified by chromatography.

Preparation of spiro[2,5-cyclohexadiene-1,2′-naphtho[1,8-*de*][1,3]dioxine]-4-one **123**.

Reaction time : 2h.; t.l.c., (Chromatography), petroleum ether:ethyl acetate, 7:3, (20:1), 4-(8-aminophenoxy)-1-naphthol **138** Rf 0.17 and compound **123** Rf 0.61 (Rf 0.29); Yield : 86% as a bright yellow crystalline solid. M.p. 145-147°C. ν_{max} (KBr)/cm^{-1}: 3055, 2926, 1691, 1674, 1643, 1602, 1584, 1415, 1382, 1311, 1272, 1244, 1185, 1103, 1072, 1025, 950, 863, 823, 754; δ ^{1}H 7.54 (2H, d, *J*8.2, H-4′,H-5′), 7.45 (2H, dd, *J*7.6 and *J*8.3, H-3′, H-6′), 6.95 (4H, m, H-2, H-6, H-2′, H-7′), 6.31 (2H, d, *J*10.2, H-3, H-5); δ ^{13}C 184.3 (C-4), 146.4 (C-8′), 140.1 (C-2, C-6), 134.1 (C-4a), 129.9 (C-3, C-5), 127.6 (C-3′, C-6′), 121.3 (C-4′, C-5′), 113.5 (C-8a), 109.7 (C-2′, C-7′), 95.6 (C-1). (Found : C, 76.44; H, 4.10. $C_{16}H_{10}O_3$ requires 76.19; H, 4.10%).

Preparation of 2-trifluoromethylspiro[2,5-cyclohexadiene-1,2′-naphtho[1,8-*de*][1,3] dioxine]-4-one **141**.

Reaction time : 5.5h.; t.l.c., (Chromatography), petroleum ether:ethyl acetate, 8:3, (20:1), 8-(4-amino-2-trifluoromethylphenoxy)-1-naphthol **139**, Rf 0.21 and compound **141**, Rf 0.57 (Rf 0.23); Yield : 25% as a bright orange crystalline solid. M.p. 145-146°C. ν_{max} (KBr)/cm^{-1}: 3061, 2929, 1685, 1660, 1610, 1582, 1415, 1382, 1271, 1230, 1189, 1148, 1112, 1096, 1027, 992, 966, 923, 821, 804, 752; δ ^{1}H 7.54 (2H, d, *J*8.2, H-4′,H-5′), 7.45 (2H, dd, *J*7.6 and *J*8.3, H-3′, H-6′), 6.95 (4H, m, H-2, H-6, H-2′, H-7′), 6.31 (2H, d, *J*10.2, H-3, H-5); δ ^{13}C 184.3 (C-4), 146.4 (C-8′), 140.1 (C-2, C-6), 134.1 (C-4a), 129.9 (C-3, C-5), 127.6 (C-3′, C-6′), 121.3 (C-4′, C-5′), 113.5 (C-8a), 109.7 (C-2′, C-7′), 95.6 (C-1). (Found : C, 63.94; H, 2.92. $C_{17}H_9F_3O_3$ requires C, 64.16; H, 2.85%).

Preparation of 3-methoxyspiro[2,5-cyclohexadiene-1,2′-naphtho[1,8-*de*][1,3]dioxine]-4-one **142**.

Reaction time : 3.5h.; t.l.c., (Chromatography), petroleum ether:ethyl acetate, 8:3, (5:1), 8-(4-amino-3-methoxyphenoxy)-1-naphthol **140** Rf 0.22 and compound **142** Rf 0.39 (Rf 0.26); Yield : 58% as a bright yellow crystalline solid. M.p. 162-163°C. ν_{max} (KBr)/cm^{-1}: 2966, 2931, 1689, 1654, 1626, 1609, 1584, 1413, 1379, 1274, 1246, 1204, 1178, 1119, 1075, 1026, 980, 930, 854, 826, 768; δ ^{1}H 7.57 (2H, d, *J*8.3, H-4′, H-6′), 7.46 (2H, dd, *J*7.6 and *J*8.3, H-3′, H-6′), 6.98 (3H, m, H-6, H-2′, H-7′), 6.85 (1H, s, H-3), 6.24 (1H, d,

*J*12.5, H-6, H-5), 3.70 (3H, s, OCH_3); δ ^{13}C 183.3 (C-4), 147.5 (C-2), 145.6 (C-1′, C-8′), 139.5 (C-6), 134.1 (C-4a), 132.1 (C-5), 127.8 (C-3′, C-6′), 127.6 (C-3), 121.7 (C-4′, C-5′), 115.3 (C-8a), 110.0 (C-2′, C-7′), 95.4 (C-1), 55.5 (OCH_3). (Found : C, 73.01; H, 4.40. $C_{17}H_{12}O_4$ requires C, 72.85; H, 4.32%).

Preparation of 1,5-dimethoxynaphthalene **92**.

5-Hydroxy-1-naphthol (8.0g, 0.05mol) was dissolved in degassed ethanol (60ml) at 40°C under an atmosphere of nitrogen. Sodium hydroxide (5.0g, 0.13mol) dissolved in water (10ml) was added to give a pale yellow heterogeneous mixture. Dimethyl sulfate (11.8ml, 0.13mol) was added dropwise maintaining an internal temperature of 40-55°C. Upon complete addition of dimethylsulfate the mixture was refluxed for 2h. T.l.c., petroleum ether:ethyl acetate, 7:3, indicated the disappearance of 5-hydroxy-1-naphthol (Rf 0.28) and the presence of a new compound (Rf 0.56) with a trace impurity (Rf 0.41). Sodium hydroxide (1.4g, 0.04mol) in water (12ml) was added to the mixture at 40°C, and was stirred for a further 30 minutes, diluted with water (150ml) and chilled to give a grey precipitate that was collected by filtration and dried. The crude material was recrystallised from ethanol to give 1,5-dimethoxynaphthalene **92** as a cream coloured solid, 6.45g (69%). M.p. 183-185°C, [lit. [182]m.p. 183-184°C]. ν_{max} (KBr)/cm^{-1}: 3006, 2959, 2829, 1592, 1509, 1469, 1453, 1402, 1266, 1215, 1189, 1092, 1064, 1047, 865, 776; δ ^1H 7.83 (2H, d, *J*8.9, H-4, H-8), 7.36 (2H, t, *J*8.3 and *J*7.9, H-3, H-7), 6.83 (2H, d, *J*7.6, H-2, H-6), 3.98 (6H, s, 2 × OCH_3); δ ^{13}C 155.2 (C-1, C-5), 126.6 (C-4a, C-8a), 125.1 (C-3, C-7), 114.1 (C-4, C-8), 104.5 (C-2, C-6), 55.5 (2×OCH_3).

Preparation of 4,8-dimethoxy-1-naphthaldehyde **144**[130].

Compound **92** (6.0g, 32mmol) was made into a paste with dimethylformamide (3.7ml, 48mmol) and toluene (6.1ml, 57mmol) at room temperature under an atmosphere of nitrogen. To the paste at 0°C was added phosphoryl chloride (3.6ml, 39mmol) over a period of 6 minutes and the mixture was stirred at 0°C for a further 30 minutes. The heterogeneous mixture was heated to 100°C for 2h. to give a dark red homogeneous mixture. T.l.c., petroleum ether:ethyl acetate, 4:1, indicated the disappearance of compound **92** (Rf 0.46) and the presence of a new compound (Rf 0.14). The cooled

reaction mixture was poured into a mixture of 10% sodium hydroxide (90ml) and ice (30ml), with stirring, and was extracted with benzene (3×30ml). The combined organic phase was partitioned with 1M HCl (2×30ml), water (2×30ml), and saturated sodium chloride (30ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give compound **144** as a buff coloured solid, 6.36g (92%). M.p. 123-125°C, [lit. [130]m.p. 125-126°C]. ν_{max} (KBr)/cm^{-1}: 2934, 1665, 1588, 1518, 1465, 1413, 1332, 1271, 1226, 1065, 828, 800, 751; δ ^{1}H 11.04 (1H, s, CHO), 8.05 (1H, d, *J*8.3, H-2), 7.93 (1H, d, *J*9.6, H-5), 7.43 (1H, dd, *J*7.6 and *J*8.6, H-6), 6.99 (1H, d, *J*7.6, H-7), 6.87 (1H, d, *J*8.3, H-3), 4.03 (3H, s, OCH_3), 3.99 (3H, s, OCH_3); δ ^{13}C 194.6 (CHO), 159.5 (C-4), 156.3 (C-8), 129.4 (C-2), 127.7 (C-8a), 127.0 (C-1), 125.8 (C-6), 124.7 (C-4a), 115.3 (C-7), 107.7 (C-5), 103.9 (C-3), 55.9 (OCH_3), 55.6 (OCH_3).

Preparation of 8-hydroxy-4-methoxy-1-naphthaldehyde **145**[130].

Compound **144** (4.0g, 18.5mmol) was dissolved in dichloromethane (80ml) at room temperature under an atmosphere of nitrogen and cooled to -78°C (acetone/dry ice). Boron tribromide (1M in dichloromethane, 19.4ml, 19.4mmol) was added slowly and after complete addition the mixture was allowed to attain room temperature and stirred for 80 minutes. T.l.c., petroleum ether:ethyl acetate, 1:1, indicated the disappearance of compound **144** (Rf 0.50) and the presence of a new compound (Rf 0.43) with a trace impurity (Rf 0.34). The reaction mixture was poured into saturated sodium hydrogen carbonate (150ml), stirred vigorously for 30 minutes, and extracted with chloroform (3×50ml). The combined organic phase was partitioned with water (30ml) and saturated sodium chloride (30ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give an orange solid. The crude material was purified by chromatography eluting with petroleum ether:ethyl acetate, 7:3 (Rf 0.22). Evaporation of the first fraction gave compound **145** as a bright yellow solid, 3.04g (81%). M.p. 91-93°C, [lit. [130]m.p. 91-92°C]. ν_{max} (KBr)/cm^{-1}: 3439, 2692, 1650, 1618, 1571, 1519, 1461, 1407, 1373, 1311, 1280, 1219, 1172, 1097, 1029, 831, 795; δ ^{1}H 12.16 (1H, br s, OH), 9.60 (1H, s, CHO), 7.94 (1H, d, *J*8.3, H-2), 7.83 (1H, d, *J*9.6, H-5), 7.48 (1H, dd, *J*7.9 and *J*7.9, H-6), 7.17 (1H, d, *J*8.9, H-7), 6.85 (1H, d, *J*8.3, H-3), 4.10 (3H, s, OCH_3); δ ^{13}C 195.6 (CHO), 163.5 (C-8), 155.6 (C-4), 145.7 (C-2), 128.6 (C-6, C-1), 128.1 (C-8a), 125.4 (C-4a), 116.7 (C-7), 113.6 (C-5), 102.7 (C-3), 56.3 (OCH_3).

Preparation of 8-benzyloxy-4-methoxy-1-naphthaldehyde **146**[129].

Compound **145** (2.80g, 13.8mmol), benzyl bromide (2.0ml, 16.6mmol), and freshly ground potassium carbonate (8.61g, 62.3mmol) were suspended in 2-butanone (54ml) at room temperature under an atmosphere of nitrogen. The heterogeneous mixture was heated to a temperature of 60°C and stirred for 24h. T.l.c., petroleum ether:ethyl acetate, 7:3, indicated the disappearance of compound **145** (Rf 0.23) and the formation of a new compound (Rf 0.39). The cooled reaction mixture was filtered, the filter cake was washed with acetone, and the filtrate was concentrated in *vacuo*. The excess benzyl bromide was removed by kugelrohr distillation (80°C, 0.5mmHg) and the residue was recrystallised from ethanol to give compound **146** as a pale yellow solid, 3.28g (81%). M.p. 126-128°C, [lit. [129]m.p. 127-128°C]. ν_{max} (KBr)/cm^{-1}: 2937, 1666, 1616, 1588, 1570, 1515, 1444, 1414, 1354, 1330, 1271, 1222, 1168, 1096, 1051, 831, 798, 753; δ ^{1}H 11.04 (1H, s, CHO), 8.07 (1H, d, *J*8.3, H-2), 7.96 (1H, d, *J*9.2, H-5), 7.40 (6H, m, H-6, H-2′,H-3′,H-4′,H-5′,H-6′), 7.08 (1H, d, *J*8.9, H-7), 6.88 (1H, d, *J*8.3, H-3), 5.27 (2H, s, Ph*CH*$_2$), 4.04 (3H, s, OCH_3); δ ^{13}C 194.4 (CHO), 159.5 (C-8), 155.4 (C-4), 136.1 (C-1′), 129.6 (C-2), 128.8 (C-3′, C-4′, C-5′), 128.3 (C-2′, C-6′), 127.6 (C-1), 127.1 (C-8a), 125.7 (C-6), 124.8 (C-4a), 115.6 (C-7), 109.3 (C-5), 103.9 (C-3), 71.1 ($PhCH_2$), 55.9 (OCH_3).

Preparation of 8-benzyloxy-4-methoxy-1-naphthol **143**.

Compound **146** (3.00g, 10.3mmol) was dissolved in chloroform (100ml) at room temperature under an atmosphere of nitrogen and *meta*-chloroperoxybenzoic acid (70%, 5.30g, 21.6mmol) was added to give a pale yellow homogeneous mixture that was stirred at room temperature for 2h. T.l.c., petroleum ether:ethyl acetate, 7:3, indicated the disappearance of compound **146** (Rf 0.36, immediate reaction with DNPH) and the presence of a new compound (Rf 0.36, slow reaction with DNPH). The mixture was partitioned with 10% sodium thiosulfate (2×60ml), saturated sodium hydrogen carbonate (2×60ml), and saturated sodium chloride (30ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a red oil. The oil was dissolved in a mixture of ethanol and tetrahydrofuran (4:1, 40ml) and concentrated hydrochloric acid (5 drops) was added. The black homogeneous mixture was stirred at room temperature for 2h. T.l.c., petroleum ether:ethyl acetate, 8:2, indicated the disappearance of the intermediate formate (Rf 0.28) and the formation of a new compound (Rf 0.40). The mixture was concentrated in *vacuo*

to give a crude black solid that was purified by chromatography eluting with petroleum ether:ethyl acetate, 8:1. Evaporation of the first fraction (Rf 0.25) gave compound **143** as a white solid that rapidly darkened, 2.02g (70%). M.p. 113-115°C, [lit. [129]m.p. 112-114°C]. ν_{max} (KBr)/cm^{-1} : 3397, 2999, 2954, 1635, 1610, 1513, 1476, 1460, 1408, 1353, 1290, 1260, 1236, 1174, 1057, 984, 929, 886, 820, 802, 748; δ ^{1}H 8.99 (1H, br s, OH), 7.85 (1H, d, *J*8.6, H-5), 7.44 (5H, m, H-2′, H-3′, H-4′, H-5′, H-6′), 7.31 1H, dd, *J*7.9 and *J*8.3, H-6), 6.76 (2H, m, H-2, H-3), 5.25 (2H, s, Ph*CH*$_2$), 3.93 (3H, s, OCH$_3$); δ 155.1 (C-8), 148.1 (C-1), 147.9 (C-4), 135.3 (C-1′), 128.8 (C-3′, C-4′. C-5′), 127.9 (C-2′, C-6′), 125.1 (C-6), 118.7 (C-4a), 116.2 (C-7), 115.7 (C-8a), 109.1 C-5), 106.3 (C-2, C-3), 71.7 (Ph*C*H$_2$), 55.9 (OCH$_3$).

Preparation of 1-(8-benzyloxy-1-naphthyloxy)-4-nitronaphthalene **149**.

Compound **132** (1.20g, 4.79mmol) was dissolved in tetrahydrofuran (3.0ml) at room temperature under an atmosphere of nitrogen and sodium hydride (60% in oil, 0.20g, 5.03mmol) was added slowly. After effervescence had ceased the solvent was removed in *vacuo* to give a white solid. The sodium salt was dissolved in dimethyl sulfoxide (15ml) at room temperature and the flask was evacuated and purged with nitrogen and cooled to 5°C. 1-fluoro-4-nitronaphthalene[72] (0.92g, 4.79mmol) in dimethyl sulfoxide (5.0ml) was slowly added over a period of 5 minutes. The black homogeneous mixture was allowed to attain room temperature and stirred for 4h. T.l.c., petroleum ether:ethyl acetate, 8:2, indicated the disappearance of 1-fluoro-nitronaphthalene (Rf 0.47) compound **132** (Rf 0.40) and the presence of a new compound (Rf 0.35). The mixture was diluted with 1M HCl (40ml) and extracted with ethyl acetate (3×30ml), dried over MgSO$_4$, filtered, and concentrated in *vacuo* to give a crude solid. The crude material was purified by chromatography gradient eluting with petroleum ether:ethyl acetate, 10:1 to 6:4. Fractions containing the product were combined and concentrated in *vacuo* to give compound **149** as a pale green solid, 1.45g, 72%. M.p. 154-156°C. ν_{max} (KBr)/cm^{-1}: 2926, 1626, 1596, 1567, 1512, 1454, 1426, 1382, 1316, 1263, 1242, 1163, 1122, 1079, 1046, 1020, 962, 828, 763; δ ^{1}H 8.83 (1H, d, *J*8.9, H-3), 8.43 (1H, d, *J*8.6, H-8), 8.14 (1H, d, *J*8.9, H-5), 7.81 (1H, d, *J*7.9, H-6), 7.67 (1H, m, H-4″), 7.52 (2H, m, H-2″, H-6″), 7.43 (2H, m, H-3″, H-5″), 7.18 (1H, d, *J*7.3, H-4′), 6.91 (1H, m, H-7), 6.77 (3H, m, H-3′, H-5′, H-6′), 6.68 (2H, d, *J*7.3, H-2′, H-2), 6.27 (1H, d, *J*8.6, H-7′), 4.71 (2H, s, PhCH$_2$); δ ^{13}C 161.5 (C-1′), 154.5 (C-1), 149.6 (C-8′), 137.6 (C-4), 135.2 (C-4a′), 129.9 (C-1″), 127.9

(C-4a, C-6), 127.6 (C-4″), 127.4 (C-2″, C-6″), 127.0 (C-3″, C-5″), 126.8 (C-8a), 126.7 (C-3′), 126.6 (C-3, C-7), 125.3 (C-6′), 123.3 (C-8), 122.9 (C-8a′), 120.8 (C-2′, C-4′), 119.8 (C-5′), 107.1 (C-7′), 105.4 (C-2), 70.7 ($PhCH_2$). (Found : C, 76.70; H, 4.51; N, 3.30. $C_{27}H_{19}NO_4$ requires C, 76.95; H, 4.54; N, 3.32%).

Preparation of 5-benzyloxy-1-methoxy-4-(4-nitro-1-naphthyloxy)naphthalene **150**.

Compound **150** was prepared from 1-fluoro-nitronaphthalene and **132** by the method described for compound **149**. T.l.c., petroleum ether:ethyl acetate, 10:1, 1-fluoronitronaphthalene (Rf 0.55), compound **143** (Rf 0.38), and compound **150** (Rf 0.34). Yield : 84%. M.p. 129-130°C. ν_{max} (KBr)/cm^{-1}: 2929, 1628, 1598, 1571, 1512, 1454, 1427, 1412, 1385, 1364, 1320, 1269, 1239, 1199, 1158, 1072, 1051, 1022, 980, 886, 827, 767, 754; δ ^{1}H 8.69 (1H, d, *J*9.6, H-3), 8.38 (1H, d, *J*9.2, H-8), 8.16 (1H, d, *J*8.6, H-5), 7.95 (1H, d, *J*9.2, H-2), 7.67 (1H, t, H-6), 7.43 (1H, d, *J*7.3, H-6′), 7.38 (1H, d, *J*8.6, H-8′), 7.09 (1H, d, *J*8.3, H-7′), 6.86 (5H, m, H-2″, H-3″, H-4″, H-5″, H-6″), 6.66 (2H, d, *J*8.3, H-2′, H-3′), 6.29 (1H, d, *J*8.9, H-6′), 4.69 (2H, s, $PhCH_2$), 4.04 (3H, s, OCH_3); δ ^{13}C 162.0 (C-1), 154.3 (C-5′), 153.4 (C-1′), 142.6 (C-4′), 138.9 (C- 4), 135.2 (C-4a′), 129.8 (C-1″), 128.9 (C-4a, C-6), 127.7 (C-4″), 127.5 (C-2″, C-6″), 127.0 (C-3″, C-5″), 126.7 (C-7), 126.3 (C-3), 126.1 (C-8a), 123.3 (C-6′), 123.0 (C-7′, C-8), 120.1 (C-8a′), 119.3 (C-5), 114.9 (C-8′), 107.9 (C-2), 105.3 (C-2′), 104.3 (C-3′), 70.7 ($PhCH_2$), 55.9 (OCH_3). (Found : C, 74.75; H, 4.80; N, 2.86. $C_{28}H_{21}NO_5$ requires C, 74.49; H, 4.69; N, 3.10%).

Preparation of 8-(4-amino-1-naphthyloxy)-1-naphthol **151**.

Compound **151** was prepared from compound **149** by the general method of hydrogenation. T.l.c., petroleum ether:ethyl acetate, 8:3, compound **149** (Rf 0.59) and compound **151** (Rf 0.22). Yield : 95% as a white solid that slowly darkened. M.p. 163-165°C. ν_{max} (KBr)/cm^{-1}: 3382, 3047, 2927, 1605, 1512, 1465, 1400, 1304, 1281, 1256, 1199, 1155, 1114, 1066, 1022, 816, 754; δ ^{1}H 9.40 (1H, br. s, OH), 7.96 (1H, d, *J*7.9, H-8), 7.86 (1H, d, *J*7.9, H-5), 7.45 (5H, m, H-6, H-7, H-4′, H-5′, H-6′), 7.10 (3H, m, H-2, H-3, H-3′), 6.77 (1H, d, *J*7.9, H-2), 6.43 (1H, d, *J*8.6, H-7′), 4.25 (2H, br.s, NH_2); δ ^{13}C 156.8 (C-1′), 154.3 (C-1), 141.8 (C-8), 140.4 (C-4), 137.0 (C-8a, C-4a′), 127.8 (C-6′),

126.8 (C-7), 124.7 (C-3′), 122.6 (C-6), 121.5 (C-4a), 119.1 (C-8), 118.9 (C-5), 118.2 (C-4′, C-5′), 115.1 (C-8a′), 110.6 (C-3), 108.9 (C-2), 107.9 (C-2′). (Found : C, 74.94; H, 5.16; N, 4.30. $C_{20}H_{17}NO_3$ requires C, 75.22; H, 5.37; N, 4.39%).

Preparation of 8-(4-amino-1-naphthyloxy)-5-methoxy-1-naphthol **152**.

Compound **152** was prepared from compound **150** by the general method of hydrogenation. T.l.c., petroleum ether:ethyl acetate, 7:3, compound **150** (Rf 0.47) and compound **152** (Rf 0.15). Yield : 91% as a green amorphous solid. M.p. 72°C. ν_{max} (KBr)/cm^{-1}: 3381, 2927, 1611, 1516, 1465, 1394, 1250, 1228, 1153, 1062, 1039, 897, 808, 756; δ ^{1}H 9.46 (1H, br. s, OH), 8.10 (1H, d, *J*9.2, H-3), 7.86 (1H, d, *J*8.9, H-8), 7.78 (1H, d, *J*9.6, H-5), 7.47 (3H, m, H-6, H-7, H-7′), 7.10 (1H, d, *J*8.3, H-2), 7.03 (1H, d, *J*8.9, H-8′), 6.75 (1H, d, *J*8.3, H-3′), 6.44 (1H, d, *J*8.6, H-2′), 6.37 (1H, d, *J*8.6, H-6′), 4.13 (2H, br. s, NH_2), 3.88 (3H, s, OCH_3); δ ^{13}C 154.1 (C-1), 150.9 (C-1′), 150.3 (C-5′), 142.3 (C-4′), 140.1 (C-4), 132.6 (C-8a), 128.4 (C-4a), 127.3 (C-7), 126.7 (C-7′), 125.7 (C-4a′), 122.4 (C-6), 121.4 (C-8), 118.4 (C-5), 115.8 (C-8a), 113.4 (C-3, C-8′), 111.6 (C-2), 109.1 (C-2′), 108.2 (C-6′), 103.2 (C-3′), 55.7 (OCH_3). (Found : C, 73.82; H, 5.36; N, 3.93. $C_{21}H_{18}NO_{3.5}$ requires C, 74.11; H, 5.33; N, 4.12%).

Preparation of spiro[1,4-dihydronaphthalene-1,2′-naphtho[1,8-*de*][1,3]dioxine]-4-one **147**.

Compound **147** was prepared from compound **151** by the general method of oxidationwith activated manganese dioxide. T.l.c., (Chromatography), petroleum ether:ethyl acetate, 8:3 (20:1), compound **151** Rf 0.20 and compound **147** Rf 0.51 (Rf 0.26). Yield : 80% as a bright yellow solid. M.p. 193-194°C. ν_{max} (KBr)/cm^{-1}: 3056, 2926, 1668, 1634, 1600, 1412, 1376, 1326, 1301, 1270, 1157, 1130, 1094, 1070, 1027, 984, 942, 823, 755; δ ^{1}H 8.17 (1H, d, *J*8.9, H-8), 7.97 (1H, d, *J*9.2, H-5), 7.75 (1H, t, H-7), 7.65 (1H, d, *J*8.9, H-6), 7.57 (2H, d, *J*9.2, H-4′, H-5′), 7.46 (2H, t, H-3′, H-6′), 7.01 (1H, d, *J*10.6, H-2), 6.96 (2H, d, *J*8.3, H-2′, H-7′), 6.38 (1H, d, *J*10.6, H-3); δ ^{13}C 183.4 (C-4), 147.3 (C-1′, C-8′), 138.5 (C-2), 138.3 (C-8a), 134.1 (C-4a′), 133.9 (C-7), 130.3 (C-4a), 130.2 (C-3), 129.9 (C-8), 127.9 (C-5), 127.6 (C-3′, C-6′), 126.4 (C-6), 121.3 (C-4′, C-5′), 113.1 (C-8a′), 109.8 (C-2′, C-7′), 92.9 (C-1). (Found : C, 79.75; H, 4.08. $C_{20}H_{12}O_3$ requires C, 79.99; H, 4.03%).

Preparation of 4′-methoxyspiro[1,4-dihydronaphthalene-1,2′-naphtho[1,8-*de*][1,3]-dioxine]-4-one **148**.

Compound **148** was prepared from compound **152** by the general method of oxidation with activated manganese dioxide. T.l.c., (Chromatography), petroleum ether:ethyl acetate, 7:3 (10:1), compound **152** Rf 0.15 and compound **148** Rf 0.41 (Rf 0.25). Yield : 70% as a bright yellow solid. M.p. 206-208°C. ν_{max} (KBr)/cm^{-1}: 2934, 1676, 1612, 1509, 1467, 1418, 1383, 1300, 1266, 1158, 1130, 1077, 1059, 991, 948, 820, 802, 761; δ ^{1}H 8.19 (1H, d, *J*9.2, H-8), 7.98 (1H, d, *J*8.6, H-5), 7.88 (1H, d, *J*9.2, H-5′), 7.76 (1H, t, H-7), 7.63 (1H, t, H-6), 7.46 (1H, t, H-6′), 7.03 (1H, d, *J*8.3, H-7′), 7.00 (1H, d, *J*10.6, H-2), 6.90 (1H, d, *J*8.3, H-2′), 6.77 (1H, d, *J*8.2, H-3′), 6.37 (1H, d, *J*10.6, H-3), 4.00 (3H, s, OCH_3); δ ^{13}C 183.5 (C-4), 150.7 (C-4′), 147.4 (C-1′), 140.6 (C-8′), 138.7 (C-2), 133.9 (C-8a, C-8a′), 130.3 (C-3), 130.1 (C-4a), 129.9 (C-7), 127.9 (C-8), 126.9 (C-5), 126.3 (C-6), 125.8 (C-6′), 116.2 (C-7′), 113.6 (C-4a′), 110.8 (C-5′), 109.3 (C-3′), 104.9 (C-2′), 92.8 (C-1), 55.8 (OCH_3). (Found : C, 76.54; H, 4.24. $C_{21}H_{14}O_4$ requires C, 76.35; H, 4.27%).

Preparation of 3-hydroxy-2-pyrone **174**[163].

Mucic acid (30g, 0.14mol) and freshly ground potassium dihydrogen phosphate (30g, 0.22mol) were intimately mixed with phosphorus pentoxide (18g, 0.13mol) in a 250ml flask fitted with a still head and condenser. The mixture was vigorously heated from the top downwards, with charring, allowing the melt to run over the solid below. A pale yellow distillate (fraction b.p. 125-150°C) was collected over a period of 30 minutes. The distillate was adjusted to pH 6.6 by the addition of 1M potassium hydroxide and the basic aqueous mixture was continuously extracted with ether for 18 hours. The volume of the ethereal solution was reduced in *vacuo* and partitioned with saturated sodium chloride (2×15ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a pale yellow solid. The crude solid was purified by vacuum sublimation (110°C, 0.1mmHg) to give compound **174** as a white solid, 5.78g (36%). M.p. 89-91°C, [lit. [163, 181]m.p. 86-87°C, 92°C]. ν_{max} (KBr)/cm^{-1}: 3366, 3086, 1690, 1630, 1559, 1431, 1292, 1220, 1129, 1062, 770; δ ^{1}H 7.16 (1H, d, *J*6.9, H-4), 6.68 (1H, d, *J*8.9, H-6), 6.35 (1H, br.s., OH), 6.22 (1H, dd, *J*5.0 and *J*5.3, H-5); δ ^{13}C 161.7 (C-2), 142.5 (C-3), 142.2 (C-6), 114.9 (C-4), 107.3 (C-5).

Preparation of 3-methoxy-2-pyrone **178**[163].

3-Hydroxy-2-pyrone **174** (3.00g, 26.8mmol) and freshly ground potassium carbonate (7.40g, 53.5mmol) were suspended in 2-butanone (90ml) at room temperature under an inert atmosphere. Methyl iodide (6.7ml, 107mmol) was added and the heterogeneous mixture was stirred for 48h. T.l.c., petroleum ether : ethyl acetate, 1:1, indicated the disappearance of compound **174** (Rf 0.38) and the formation of a single product (Rf 0.21) contaminated with baseline material. The solvent was removed in *vacuo* and the cream residue was suspended in ethyl acetate (80ml) and filtered. The filtrate was partitioned with 1M NaOH (2×10ml) and saturated sodium chloride (15ml), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude white solid. The crude solid was purified by chromatography eluting with petroleum ether : ethyl acetate, 1:1. Evaporation of the second fraction (Rf 0.21) gave compound **178** as a white solid, 2.31g (68%). M.p. 59-61°C, [lit. m.p. [163, 181]58-60°C, 61°C]. ν_{max} (KBr)/cm^{-1}: 3116, 3014, 2952, 2843, 1720, 1634, 1570, 1465, 1364, 1268, 1132, 1081, 985, 886, 770; δ ^{1}H 7.19 (1H, d, *J*6.6, H-4), 6.49 (1H, d, *J*8.6, H-6), 6.21 (1H, dd, *J*5.0 and *J*5.3, H-5), 3.83 (3H, s, 3-OCH_3); δ ^{13}C 159.0 (C-2), 146.2 (C3), 142.8 (C-6), 112.3 (C-4), 105.7 (C-5), 56.0 (3-OCH_3).

Base Catalysed Cycloaddition.

Preparation of 6′-(oxo-2H-3-oxinyloxy)spiro[benzo[d][1,3]dioxole-2,1′-(2′-cyclohexene)]-4′-one **177**.

Compound **104** (0.54g, 2.70mmol) and 3-hydroxy-2-pyrone **174** (0.30g, 2.70mmol) were dissolved in anhydrous dichloromethane (27ml) at room temperature under an inert atmosphere. Triethylamine (0.37ml, 2.70mmol) was added and the pale yellow homogeneous mixture was stirred at room temperature for 24h. T.l.c., petroleum ether : ethyl acetate, 6:4, indicated the presence of compound **104** (Rf 0.53), the disappearance of **174** (Rf 0.20), the presence of a new compound (Rf 0.14), and baseline material. The pale red homogeneous mixture was partitioned with 1M HCl (10ml), water (10ml), and saturated sodium chloride (10 ml). The organic phase was dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give a crude buff coloured solid. The crude material was purified by chromatography, gradient eluting, with petroleum ether : ethyl acetate, 3:2 to 1:2. Evaporation of the first fraction gave compound **104** as a yellow solid, 0.06g.

Evaporation of the second fraction gave compound **177** as a buff coloured solid, 0.54g (64%, 72% corrected). M.p. 167-168°C. ν_{max}(KBr)/cm^{-1}: 3342, 3056, 2926, 1708, 1686, 1485, 1411, 1356, 1239, 1154, 1051, 909, 740; δ ^{1}H 6.87 (1H, d, *J*10.2, H-2′), 6.77 (4H, m, H-2″, H-3″, H-4″, H-5″), 6.48 (1H, d, *J*7.3, H-4), 6.29 (1H, s, OH), 6.23 (1H, d, *J*10.2, H-3′), 6.11 (1H, d, *J*7.4, H-5), 6.64 (1H, dd, J_{XB}12.0 and J_{XA}4.6, H_X-6′), 3.21 (1H, dd, J_{BA}18.0 and J_{BX}12.0, H_B-5′), 2.83 (1H, dd, J_{AB}18.0 and J_{AX}4.6, H_A-5′); δ ^{13}C 195.6 (C4′), 161.0 (C-2), 148.7 (C-6), 146.6 (C-1″, C-6″), 142.2 (C-2′), 141.2 (C-3), 131.9 (C-3′), 122.2 (C-3″, C-4″), 114.5 (C-4), 110.8 (C-5), 108.9 (C-2″, C-5″), 107.5 (C-1′), 46.5 (C-6′), 37.6 (C-5′); *m/z* (ESI) 313.3 (MH^+, 100%). (Found : C, 65.41; H, 3.87. $C_{17}H_{12}O_6$ requires C, 65.39; H, 3.87%).

Thermal Cycloadditions.

Preparation of 8′-methoxyspiro[benzo[d][1,3]dioxole-2,3′-(10-oxatricyclo[6.2.2.0^{2,7}]-dodeca -4′,11′-diene]-6′,9′-dione **179**.

Compound **104** (0.40g, 2.0mmol) and 3-methoxy-2-pyrone **178** (0.25g, 2.0mmol) were suspended in anhydrous benzene (10ml) at room temperature under an inert atmosphere. The heterogeneous mixture was heated to an internal temperature of 84°C, to give a pale yellow homogeneous mixture, and was gently refluxed for 66h. T.l.c., petroleum ether : ethyl acetate, 1:1, indicated the presence of compound **104** (Rf 0.60), formation of a new compound (Rf 0.45), and remaining 3-methoxy-2-pyrone **178** (Rf 0.16). The cooled reaction mixture was concentrated in *vacuo* to give a crude solid which was purified by chromatography eluting with petroleum ether : ethyl acetate, 7:3. Evaporation of the first fraction (Rf 0.46) gave compound **104** 0.18g as a yellow solid. Evaporation of the second fraction gave compound **179** as a buff coloured solid, 0.31g (55%, 86% corrected yield). M.p. 144-145°C. ν_{max}(KBr)/cm^{-1}: 3081, 2947, 1769, 1693, 1631, 1481, 1370, 1307, 1234, 1137, 1107, 752; δ ^{1}H 6.81 (4H, m, H-2, H-3, H-4, H-5), 6.61 (1H, d, *J*10.2, H-4′), 6.54 (1H, dd, *J*7.9 and *J*4.9, H-11′), 6.37 (1H, d, *J*7.9, H-12′), 6.29 (1H, d, *J*10.2, H-5′), 5.50 (1H, m, H-10′), 3.80 (3H, s, OCH_3), 3.67 (1H, dd, *J*4.6 and *J*8.6, H-2′), 3.45 (1H, d, *J*8.9, H-7′); δ ^{13}C 191.7 (C-6′), 170.1 (C-9′), 145.9 (C-1), 145.4 (C-6), 140.3 (C-4′), 136.4 (C-12′), 134.6 (C-11′), 129.7 (C-5′), 122.9 (C-3, C-4), 109.4 (C-2, C-5), 108.8 (C-3′), 81.8 (C-8′), 72.3 (C-10′), 54.4 (OCH_3), 46.9 (C-2′), 42.3 (C-7′). (Found : C, 66.09; H, 4.26. $C_{18}H_{14}O_6$ requires C, 66.26; H, 4.32%).

Preparation of 8′-methoxyspiro[naphtho[1,8-*de*][1,3]dioxine-2,3′-(10′-oxatricyclo-[6.2.2.$0^{2,7}$]dodeca-4′,11′-diene]-6′-9′-dione **180**.

Compound **123** (0.40g, 1.6mmol) and 3-methoxy-2-pyrone **178** (0.21g, 1.7mmol) were dissolved in anhydrous benzene (8.0ml) at room temperature under an atmosphere of nitrogen. The pale yellow homogeneous mixture was heated to an internal temperature of 85°C for 66h. T.l.c., petroleum ether:ethyl acetate, 8:3, indicated the presence of compound **123** (Rf 0.51), a new compound (Rf 0.19), and 3-methoxy-2-pyrone **178** (Rf 0.07). The sovent was removed in *vacuo* to give a crude oil that solidified on standing. The crude material was purified by chromatography eluting with petroleum ether:ethyl acetate, 8:3. Evaporation of the first fraction (Rf 0.51) gave compound **123** as a bright yellow solid, 0.28g. Evaporation of the second fraction gave compound **180** as a cream coloured solid, 0.16g (27%, 89% corrected yield). M.p. 176-177°C. ν_{max} (KBr)/cm^{-1}: 3080, 2992, 2951, 2846, 1759, 1697, 1631, 1610, 1586, 1411, 1378, 1315, 1273, 1254, 1213, 1142, 1099, 1051, 1010, 954, 935, 830, 822, 756; δ ^{1}H 7.50 (4H, m, H-3, H-4, H-5, H-6), 7.02 (1H, d, *J*7.6, H-2), 6.86 (1H, d, *J*10.6, H-7), 6.55(1H, m, H-11′), 6.51 (1H, d, *J*10.6, H-4′), 6.35 (1H, d, *J*8.3, H-13′), 6.20 (1H, d, *J*10.2, H-5′), 5.62 (1H, m, H-10′), 3.82 (3H, s, OCH3), 3.74 (1H, dd, *J*8.6 and *J*4.6, H-2′), 3.42 (1H, d, *J*8.6, H-7′); δ ^{13}C 191.9 (C-6′), 170.3 (C-9′), 145.8 (C-1), 145.6 (C-8), 140.9 (C-4′), 135.9 (C-5′), 134.3 (C-12′, C-4a), 129.9 (C-11′), 127.7 (C-3), 127.5 (C-6), 121.9 (C-4), 121.4 (C-5), 113.5 (C8a), 110.1 (C-2), 109.9 (C-7), 95.6 (C-3′), 81.9 (C8′), 71.7 (C-10′), 54.3 (OCH_3), 46.8 (C-2′), 42.8 (C-7′). (Found : C, 66.87; H, 4.34. $C_{24}H_{16}O_5$ requires C, 67.00; H, 4.60%); *m/z* (ESI, injection temp. 140°C) 376.7 (MH, 100%), 333.3 (-CO_2, 85%), 331.5 (-CO_2, -2H, 50%); *m/z* (ESI, injection temp. 190°C) 376.9 (MH, 35%), 333.3 (-CO_2, 50%), 331.6 (-CO_2, -2H, 100%).

High Pressure Cycloadditions.

General Method.

The appropriate quinone monoacetal (1eq) and 3-methoxy-2-pyrone **178** (1.05eq.) were dissolved in dichloromethane in a teflon reaction tube. The tube was sealed, excluding all air, with a tapered screw cap and was placed into the central bore of a pressure vessel filled with petroleum ether as the carrier medium. An external pressure of 15 Kbar was applied via a piston, fitted with rubber, teflon, and brass compression rings, connected

to an automatic hydraulic ram. After 24h. at room temperature the pressure was released slowly and the teflon reaction tube was recovered. The solvent was removed in *vacuo* to give a crude solid that was purified by chromatography.

Preparation of 8′-methoxyspiro[benzo[d][1,3]dioxole-2,3′-(10′-oxatricyclo[6.2.2.$0^{2,7}$]-dodeca-4′-11′-diene]-6′,9′-dione **179**.

Compound **179** was prepared from **104** and **178**.
Reaction conditions : 15kbar, 24h. T.l.c., (Chromatography), petroleum ether:ethyl acetate, 8:3 (8:3), indicated the disappearance of compound **104** (Rf 0.64) and the formation of a new compound (Rf 0.21). Yield : 92%. Spectral data were identical to those obtained for compound **179** obtained from the thermal cycloaddition.

Preparation of 8′-methoxyspiro[naphtho[1,8-*de*][1,3]dioxine-2,3′-(10′-oxatricyclo-[6.2.2.$0^{2,7}$]dodeca-4′,11′-diene]-6′-9′-dione **180**.

Compound **180** was prepared from **123** and **178**.
a) Reaction conditions : 15kbar, 24h.
b) Reaction conditions : 12kbar, 24h.
T.l.c., (Chromatography), petroleum ether:ethyl acetate, 8:3 (8:3), indicated the disappearance of compound **123** (Rf 0.57), the presence of a new compound (Rf 0.22), and a trace of 3-methoxy-2-pyrone **178** (Rf 0.07). Yield : a) 88%, b) 85 %. Spectral data for a) and b) were identical to those obtained for compound **180** obtained from the thermal cycloaddition.

Preparation of 8′-methoxy-4′-trifluoromethylspiro[naphtho[1,8-*de*][1,3]dioxine-2,3′-(10′-oxatricyclo[6.2.2.$0^{2,7}$]dodeca-4′,11′-diene]-6′-9′-dione **181**.

Compound **181** was prepared from **141** and **178**.
Reaction conditions : 15kbar, 24 hours. T.l.c., (Chromatography), petroleum ether:ethyl acetate, 8:3 (8:3), indicated the disappearance of compound **141** (Rf 0.64) and the presence of a new compound (Rf 0.40). Yield : 96%. M.p. 167-168°C. ν_{max} (KBr)/cm^{-1}: 3082, 2967, 2849, 1773, 1694, 1638, 1611, 1589, 1414, 1375, 1318, 1268, 1242, 1184, 1167, 1144, 1063, 1039, 994, 963, 822, 811, 758; δ ^{1}H 7.52 (4H, m, H-3, H-4, H-5, H-6),

7.12 (1H, d, *J*8.3, H-2), 6.94 (1H, d, *J*8.3, H-7), 6.77 (1H, s, H-5′), 6.61 (1H, dd, *J*8.2 and *J*4.9, H-11′), 6.37 (1H, d, *J*8.2, H-12′), 5.26 (1H, m, H-10′), 3.73 (3H, s, OCH3), 3.70 (1H, dd, *J*3.3 and *J*8.6, H-2′), 3.38 (1H, d, H-7′); δ ^{13}C 191.0 (C-6′), 169.3 (C-9′), 144.6 (C-1), 144.5 (C-8), 139.6 (C-4′), 136.4 (C-5′), 134.8 (C-4a), 134.2 (C-12′), 130.1 (C-11′), 127.9 (C-3), 127.7 (C-6), 122.4 (C-5), 122.1 (C-5), 112.2 (C-8a), 110.9 (CF_3), 110.3 (C-2), 109.9 (C-7), 95.4 (C-3′), 81.6 (C-8′), 71.0 (C-10′), 54.4 (OCH_3), 44.4 (C-2′), 43.1 (C-7′). (Found : C,,61.13; H, 3.34. $C_{24}H_{14}F_3O_6.0.5H_2O$ requires C, 60.93; H, 3.56%); *m/z* (ESI, injection temp. 190°C) 444.6 (MH, 20%), 401.1 (-CO_2, 100%), 331.6 (-CO_2, -2H, 75%).

Preparation of 5′,8′-dimethoxyspiro[naphtho[1,8-*de*][1,3]dioxine-2,3′-(10′-oxatricyclo-[6.2.2.0^{2,7}]dodeca-4′,11′-diene]-6′-9′-dione **182**.

Compound **182** was prepared from **142** and **178**.

Reaction conditions : 15kbar, 24 hours. T.l.c. (Chromatography), petroleum ether:ethyl acetate, 8:3 (8:3), indicated disappearance of compound **142** (Rf 0.58) and the presence of a new compound (Rf 0.27). Yield : 90%. M.p. 170-171°C. ν_{max} (KBr)/cm^{-1}: 3063, 2940, 2852, 1750, 1706, 1635, 1608, 1587, 1413, 1383, 1352, 1274, 1235, 1181, 1147, 1086, 1052, 1035, 990, 962, 910, 824, 800, 757; δ ^{1}H 7.48 (4H, m, H-3, H-4, H-5, H-6), 7.01 (1H, d, *J*7.26, H-2), 6.82 (1H, d, *J*7.6, H-7), 6.56 (1H, dd, *J*7.9 and *J*4.9, H-11′), 6.34 (1H, d, *J*7.9, H-12′), 5.56 (1H, m, H-10′), 5.39 (1H, s, H-4′), 3.80 (3H, s, 8′-OCH_3), 3.64 (1H, dd, *J*1.3 and *J*8.6, H-2′), 3.55 (1H, d, *J*8.6, H-7′), 3.48 (3H, s, 5′-OCH_3); δ ^{13}C 187.8 (C-6′), 170.1 (C-9′), 157.7 (C-5′), 145.9 (C-1), 144.3 (C-8), 134.2 (C-4a), 133.0 (C-12′), 130.6 (C-11′), 127.7 (C-3), 127.4 (C-6), 121.8 (C-4), 121.3 (C-5), 113.4 (C-8a), 110.0 (C-2), 109.8 (C-7), 107.5 (C-4′), 97.3 (C-3′), 82.3 (C-8′), 71.6 (C-10′), 55.9 (5′-OCH_3), 54.4 (8′-OCH_3), 46.0 (C-2′), 42.9 (C-7′). (Found : C, 66.19; H, 4.38. $C_{23}H_{18}O_7.0.5H_2O$ requires C, 66.50; H, 4.61%).

Preparation of 8′-hydroxyspiro[benzo[d][1,3]dioxole-2,3′-(10′-oxatricyclo[6.2.2.0^{2,7}] dodeca-4′,11′diene]-6′,9′-dione **183**.

Compound **183** was prepared from **104** and **174**.

Reaction conditions : 15kbar, 24h. T.l.c., petroleum ether:ethyl acetate, 8:3, indicated the disappearance of compound **104** (Rf 0.62) and 3-hydroxy-2-pyrone **174** (Rf 0.17), and

the formation of a new compound (Rf 0.08). The crude material was analysed by 60MHz ^{1}H NMR at the time of its preparation and then stored at 4°C for four weeks. Re-examination of the material by t.l.c., 8:3, prior to chromatography indicated that the material had reverted to the precursors **104** (Rf 0.62) and **174** (Rf 0.17) during storage. Crude compound **183**; δ ^{1}H (Bruker 100MHz, $CDCl_3$) 6.81 (4H, m, H-2, H-3, H-4, H-5), 6.61 (1H, d, H-4′), 6.54 (1H, dd, H-11′), 6.35 (1H, d, H-12′), 6.25 (1H, d, H-5′), 5.50 (1H, m, H-10′), 5.60 (1H, br. s, OH), 3.71 (1H, dd, H-2′), 3.05 (1H, d, H-7′).

Attempted aromatisation of cycloadduct **179**.

a) Compound **179** (0.10g, 0.31mmol) and manganese dioxide (0.08g, 0.92mmol) were suspended in anhydrous benzene (3.0ml) at room temperature under an atmosphere of nitrogen and heated to an external temperature of 85°C to give a black heterogeneous mixture. Heating was continued for 8h. T.l.c., petroleum ether:ethyl acetate, 8:3, indicated the presence of compound **104** (Rf 0.63), compound **179** (Rf 0.28), and 3-methoxy-2-pyrone **178** (Rf 0.11). The solvent was removed in *vacuo* to give a crude brown oil that was purified by chromatography eluting with petroleum ether:ethyl acetate, 8:3. Evaporation of the first fraction gave a bright yellow compound, 40mg, that was confirmed to be compound **104** by comparison of its melting point and ^{1}H NMR spectrum. Evaporation of the second fraction gave a buff coloured solid, 26mg, that was confirmed to be compound **179** by comparison of its melting point and ^{1}H NMR spectrum.

c) Experiment a) was repeated on an identical scale heating to an external temperature of 150°C for 2h. in anhydrous xylene. T.l.c., petroleum ether:ethyl acetate, 8:3, indicated the formation of a complex mixture of degradation products streaking from the baseline. Experiment abandoned.

9.3. Protocol for Antibacterial Assay.

Test Title: Antibacterial Test-*in vitro*

Objective: To Measure *in vitro* Antibacterial Activity

Study Details:

Method:	Agar dilution susceptibility test
Test Concentration:	1-128ug/ml (0.008-128ug/ml on request)

Study Details:

Vehicle:	2% DMSO in agar
Medium:	IsoSensitest agar
Incubation Time:	24 hours
Incubation Temperature:	37°C.

Organisms:	G+ve	*S. aureus*	601 078	Oxford
			601 122	novobiocin resistant
			601 155	*in vivo*
			607 003	MR QS
			607 004	MR QR
		coagulase	602 001	MS
		negative *staphylococci*	602 011	MR
		S. pyogenes	681 043	C2O3
		E. faecalis	683 026	
		B. subtilis	732 013	NCIMB 10263
		C. albicans	128 001	B2630 *in vivo*

Key:

MR methicillin resistant

MS methicillin sensitive

QR quinolone resistant

QS quinolone sensitive

Method:

On test day –1, the test organisms are inoculated into 10 ml volumes of IsoSensitest broth (IST) and incubated at 37°C overnight. At the same time fresh purity and quality assurance (QA) plates are prepared. Appropriate antibiotic sensitivity disks are placed on the QA plates and both sets of plates are incubated overnight at 37°C. On test day 1, the overnight purity and QA plates are checked and the cultures are diluted 1:100 in 10mls of IST broth.

Compounds are dissolved in 400µl of DMSO. Two hundred microlitres is used to prepare a two-fold dilution series in DMSO, in McCartney bottles. Molten agar, cooled to 56°C,

in 9.8ml volumes is dispensed into the bottles using a Perifill Dispenser, mixed and then poured into two-compartment petri dishes.

After drying, the plates are inoculated with 0.3ul of the diluted culture using a multipoint inoculator. The plated are incubated at 37°C overnight and the minimum inhibitory concentration determined as the lowest concentration to inhibit the growth of two or more colonies. A slight haze of growth is ignored.

Standard Compounds:

Methicillin M127155
Novobiocin M123971
The standards are tested at 0.008-128ug/ml.

Recording Results:

D = >128ug/ml
E = 128ug/ml
F = 64ug/ml
G = 32ug/ml
H = 16ug/ml
I = 8ug/ml
J = 4ug/ml
K = 2ug/ml
L = 1ug/ml
M = 0.5ug/ml
N = 0.25ug/ml
O = 0.13ug/ml
P = 0.06ug/ml
Q = 0.03ug/ml
R = 0.016ug/ml
S = <0.008ug/ml

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