Synthesis of 1,2-Dihydronaphtho[2,1-*b*]furans. Reactions of 1,2-Dioxines and Stabilised Phosphorus Ylides

A Thesis Submitted Towards the Degree of
Doctor of Philosophy

By
Martyn Jevric B.Sc. (Hons)

ADELAIDE UNIVERSITY

Department of Chemistry
Adelaide University
April 2004

Index

Statement of Originality

This work contains no material which has been accepted for the award of any other degree or diploma in any other university or other tertiary institution and, to the best of my knowledge and belief, this thesis contains no material previously published or written by any other person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University library, being available for loan or photocopying.

Martyn Jevric

12/1/05

Date

Abstract

Cyclopropane products are formed in high diastereomeric excess when 1,2-dioxines are treated with stabilised phosphorus ylides. The key intermediate in these reactions is the *cis*-γ-hydroxyenone which undergoes 1,4-addition by the ylide. *Cis*-γ-hydroxyenones are formed in a Kornblum-DeLaMare reaction by base catalysed rearrangement of 1,2-dioxines, in this case the ylide behaves as a base.

The area of interest was the reactions of 1,2-dioxines annulated to a naphthalene template. It was envisaged that upon the 1,4-addition to the *cis*-γ-hydroxyenone in order to form cyclopropyl products dearomatisation of the naphthalene portion must occur. Instead, it was expected that this would give rise to a new methology of synthesising dihydronaphthofurans.

This turned out to be the case and this work also resulted in the synthesis of two other dihydronaphthofuran products arising from the 1,2-dioxines. One of these dihydronaphthofurans arose from the Wittig / Oxa-Michael reaction of 1-(β-keto)-2-naphthols. 1-(β-Keto)-2-naphthols were a result of the base catalysed aromatisation of the-γ-hydroxyenone. These compounds were interesting in their own right, not only did they give rise to a regioisomeric set of dihydronaphthofurans, but underwent autoxidation to afford spiroepoxide products.

A cyclisation reaction of some of these dihydronaphthofurans with hydride abstracting reagent DDQ lead to the formation of an extra heterocyclic ring through the reactive naphthylic position. An interesting oxygen migration to the naphthylic position is also reported.

Ackowledgments

Let me take the time to give some thanks, ...in the context of how long this took to come to fruition it is but a blink of an eye. You learn not only just about the chemistry but also many of life's lessons by the interactions with past and present peoples on the journey, some good, some amusing and some disturbing but in essence all are character building experiences. I think I'll get myself another Wild Turkey, no ice, please.

Academically, there are many people to thank in the Chemistry Department. My supervisor Assc. Prof. Dennis Taylor, Dr Simon Pyke and Phil Clements (NMR), Dr Tiekink (X-ray) and any other staff that crossed my path. Oh yeah, and thanks to Prof. Bruce for giving an opportunity to experience some inorganic chemistry.

Socially, many people to mention and the chances are I'll leave someone out. Special thanks goes out to Ben (and Tasma) for making me pull my finger out, and teaching me some finer points of grammar like not to put a comma before the word 'and'. All the past and present brew buddies of the yerba mate, Jason "dugong", Oska "Heff", Tomas "Mogg Dogg", Thomas "the man with the appetite for 2 kilo steaks" , Smurto "Smutto" list goes on.... To all the lads I work security with and train with (including the elusive Jonny Meatpuppet) whom have taught me some finer points in life, ie don't work security. Im glad Im out....soon.

Family, most special, my mum whom I think is very supportive of my cause. Meine Oma, ich habe es afgemacht (I hope I wrote that right). Me sister (and Justin) for many things, I know I haven't been much of a brother or anything else come to mention it. Peace out.

Nurofen Plus, for those headaches that just never go away.

Publications arising from this Work

Expeditious synthesis of dihydronaphthofurans utilising 1,2-dioxines and stabilised phosphorus ylides. Haselgrove, T. D.; Jevric, M.; Taylor, D. K.; Tiekink, E. R. T. *Tetrahedron* (1999), 55 (51), 14739-14762.

Ethyl (*E*)-4-(2-hydroxy-1-naphthyl)-2-methyl-2-butenoate. Jevric, M.; Taylor, D. K.; Tiekink, E. R. T. *Acta Crystallographica, Section E (*2001), E57 (5), o426-o427.

Crystal structure of 2-(2-hydroxy-1-napthyl)-1-phenyl-1-ethanone. Jevric, M.; Taylor, D. K.; Tiekink, E. R. T. *Zeitschrift fuer Kristallographie – New Crystal Structures* (2001), 216 (4), 541-542.

Crystal structure of 2-(1-methylnaphtho[2,1-*b*]furan-2-yl)acetic acid. Jevric, M.; Taylor, D. K.; Tiekink, E. R. T. *Zeitschrift fuer Kristallographie – New Crystal Structures* (2001), 216 (4), 543-544.

Crystal structure of 1-[(*E*)-2-[4-(trifluoromethyl)phenyl]-1-ethenyl]naphthalene. Jevric, M.; Taylor, D. K.; Tiekink, E. R. T. *Zeitschrift fuer Kristallographie – New Crystal Structures* (2001), 216 (4), 545-546.

Crystal structure of 1-(4-methoxyphenyl)-1,3a,4,11*c*-tetrahydro-3*H*-benzo[*f*]furo[3,4-*c*]chromen-3,4-dione. Greatrex, B. W.; Jevric, M.; Kimber, M. C.; Krivickas, S. J.; Taylor, D. K.; Tiekink, E. R. T. *Zeitschrift fuer Kristallographie – New Crystal Structures* (2002), 217 (4), 587-588.

A novel *bis*-lactonisation of naphtho- and phenanthro-1,2-dioxines with malonate nucleophiles. Greatrex, B. W.; Jevric, M.; Kimber, M. C.; Krivickas, S. J.; Taylor, D. K.; Tiekink, E. R. T. *Synthesis* (2003), (5), 668-672.

Abbreviations

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
Anal. Calcd.	analysis calculated
Ar	aromatic
Bu	butyl
Bu^t	*tert*-butyl
CAN	cerium ammonium nitrate
cat.	catalytic
COSY	Correlated Spectroscopy
DABCO	1,4-diazobicyclo[2.2.2]octane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
$DDQH_2$	dihydro-2,3-dichloro-5,6-dicyanobenzoquinone
de	diastereomeric excess
DIBAL-H	di*iso*butylaluminium hydride
DMF	*N,N*-dimethyl formamide
DMSO	dimethylsulphoxide
δ	chemical shift
Δ	heat
E	energy
ee	enantiomeric excess
Et	ethyl
equiv.	equivalent(s)
E/Z	refer to the stereochemistry about the C1 and C2 positions of 1,2-dihydronaphtho[2,1-*b*]furan products and stereochemistry about alkene products
HMBC	Heteronuclear Multiple Bond Connectivity
HMQC	Heteronuclear Multiple Quantum Coherence
HRMS	high resolution mass spectrometry
$h\upsilon$	irradiation
IR	Infrared
J	coupling

M	moles per litre
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeOH	methanol
MHz	megahertz
mmol	millimoles
Mp.	melting point
MS	Mass Spectrum
m/z	mass to charge ratio
NBS	*N*-bromosuccinimide
NMR	Nuclear Magnetic Resonance
Nu	nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Plot
ppm	parts per million
Ph	phenyl
PTSA	*para*-toluenesulphonic acid
R_f	Retention factor
ROESY	Rotating Frame Overhauser Effect Spectroscopy
RT	room temperature
S_N2	bimolecular nucleophilic substitution
$S_{RN}1$	Nucleophilic radical substition
TEMPO	(2,2,6,6)-tetramethyl-1-piperidinyloxy, free radical
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TPP	triphenylphosphine
TPPO	triphenylphosphine oxide
Triton B	tetrabutylammonium hydroxide

CHAPTER 1

INTRODUCTION

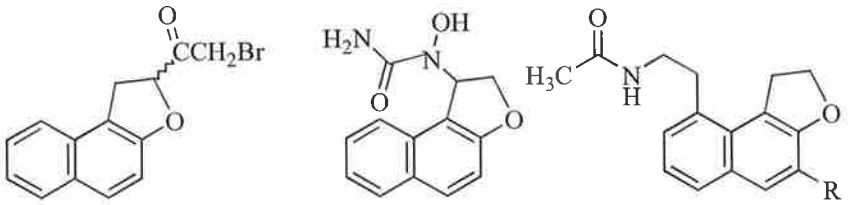
1.1 CURRENT SYNTHESIS OF 1,2-DIHYDRONAPHTHO[2,1-*b*]FURANS.

A modest number of examples of 1,2-dihydronaphtho[2,1-*b*]furans have been reported in the literature, some of which exhibit interesting biological properties.[1-4] As a result, much interest has been shown in developing methodologies for accessing these type of compounds. This study was an investigation into novel methods for the synthesis of 1,2-dihydronaphtho[2,1-*b*]furans, using an adapted protocol which has been employed for the synthesis of cyclopropanes.[5] The first part of this Chapter will focus upon some known bioactive 1,2-dihydronaphtho[2,1-*b*]furans and current synthetic methods employed in the synthesis of such compounds. The latter part will delve into the research which has been carried out in the Taylor group over the last few years and how this pertains to the novel synthesis of 1,2-dihydronaphtho[2,1-*b*]furans. Following this discussion, the aims of the project will be introduced.

Figure 1.1 contains a summary of some biologically active compounds containing a 1,2-dihydronaphtho[2,1-*b*]furan backbone. The simplest of these, **1**, has been reported to inhibit the activity of α-chymotrypsin.[6] In fact, some 1,2-dihydronaphtho[2,1-*b*]furans have been employed in the elucidation of the active site of α-chymotrypsin and those containing ester substitution at the C2 position can be effectively resolved by hydrolysis or deacylation.[1,7-9] Similarly, **2** is an effective inhibitor of 5-lipoxygenase[4] and amide **3** a Melatonin receptor ligand.[10] Some other analogues of **3** also show these same properties.[11-14] Interestingly, a large pool of benzofuran analogues of **1** have been reported in the literature and many are the subject of patents.[15-21]

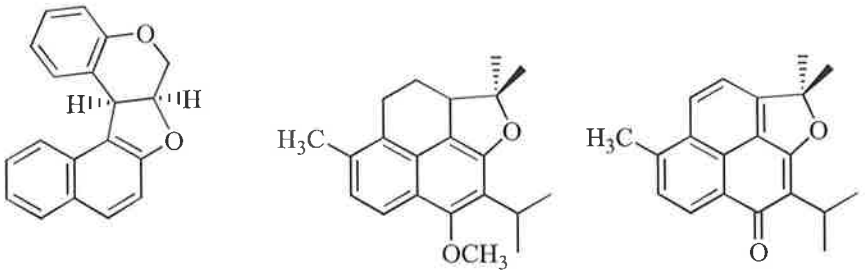
Compounds **4**, **5** and **6** are all naturally occurring compounds. Pterocarpans **4**, which contain a 1,2-dihydronaphtho[2,1-*b*]furan or 1,2-dihydrobenzofuran *bis* fused to a tetrahydronaphthopyran backbone have been shown to exhibit interesting biological properties.[2,22] Pterocarpans are produced by *leguminosae* plant species when subjected to fungal infections. It has also been reported that some Pterocarpans exhibit antitumor properties. Several strategies have been successfully employed in the synthesis of **4**.[2]

Figure 1.1 *Some interesting 1,2-dihydronaphtho[2,1-b]furans.*



1 2 3

R = H, F

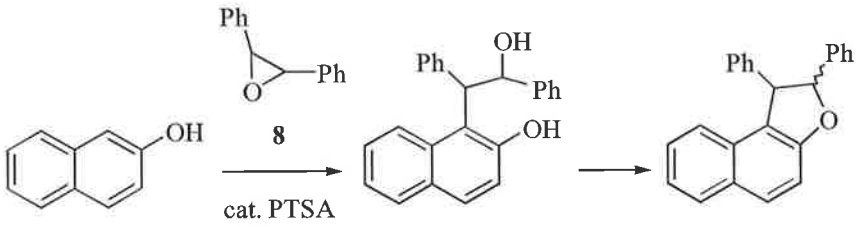


4 5 6

Prionitin **5** is believed to be an active component in Chinese medicine from the plant species, *salvia prionitis*.[23] Structurally similar salvilenone **6**, the de-aromatised analogue of **5**, has been isolated from a related species of plant *salvia miltiorrhiza* and has also been used in Chinese medicine to treat such ailments as heart disorders, hepatitis, and tuberculosis.[3] Salvilenone itself belongs to a class of compound called phenalenones, which occur infrequently in nature with the exception of some plants and fungi. Salvilenone **6** has been previously synthesised in a lengthy multi-step sequence.[3,24]

One of the first syntheses of 1,2-dihydronaphtho[2,1-*b*]furans was reported over half a century ago and entailed the reaction of 2-naphthol **7** with stilbene oxide **8** under acid catalysed conditions to afford **10** (**Scheme 1.1**).[25] The first step of the reaction was thought to occur through the electron rich carbon at C1 to furnish the diol **9**. The second step was the acid catalysed S_N1 substitution of water to give a benzylic cation, which was quenched by naphthyl alcohol to afford **10**. Without the aid of NMR, the stereochemistry was not elucidated.

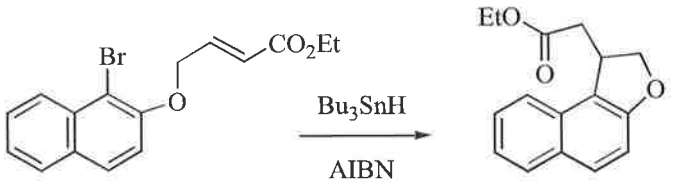
Scheme 1.1



7 8 cat. PTSA 9 **10** (70%)

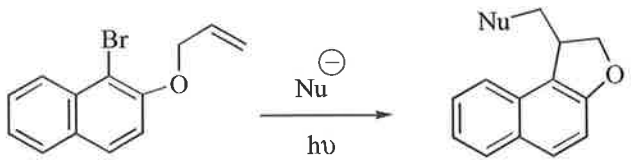
More recently, several approaches for the synthesis of 1,2-dihydronaphtho[2,1-*b*]furans, in particular using radical chemistry have been reported.[26,27] Many of these syntheses involve the radical catalysed ring closure reactions of 1-allylic naphthyl ethers such as **11** and **13** featured in **Schemes 1.2** and **1.3**. The reaction of the α,β–unsaturated esters have been reported to work quite well to give **12** in good yield.[27] Vaillard *et al.* demonstrated that in the presence of a nucleophile, a tandem ring closure / $S_{RN}1$ reaction could be used to obtain a host of functionalised 1,2-dihydronaphtho[2,1-*b*]furans **14**.[26] Tandem ring-closure / carboxylation reactions have also been reported in the synthesis 1,2-dihydronaphtho[2,1-*b*]furans, but not in good yield.[28]

Scheme 1.2



11 **12** (97%)

Scheme 1.3

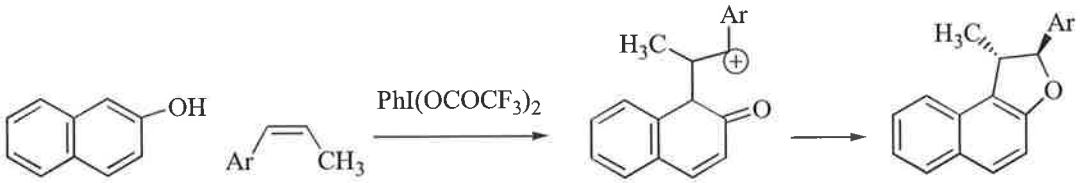


13 **14** (84-98%)

where Nu = $SnMe_3$, PPh_2, CH_2NO_2

Oxidative addition reactions can also be used to generate 1,2-dihydronaphtho[2,1-*b*]furans. The oxidation of **7** with iodobenzene *bis*-triflouroacetate in the presence of methyl substituted styrene **15** resulted in an annulation reaction affording *trans* 1,2-dihydronaphtho[2,1-*b*]furan **17** (**Scheme 1.4**).[29] These same reaction products could also be generated electrochemically. Presumably, electron rich 2-naphthol **7** is oxidised and an oxidative addition of the styrene occurs at C1 resulting in a benzylic stabilised carbocation intermediate **16**. Tautomerisation of **16** to the 1-substituted aromatised 2-naphthol and subsequent ring closure gives **17**.

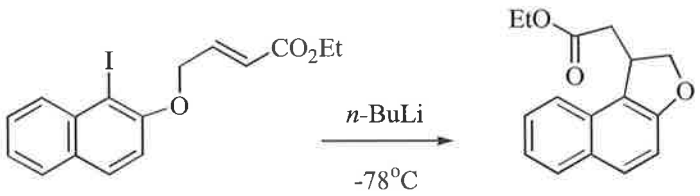
Scheme 1.4



7 **15** **16** **17** (39%)

Several other methodologies not employing radical chemistry have also been established, these are featured in **Schemes 1.5** and **1.6**. Weeratunga *et al.* explored the ring closure of the aryl iodide **18**. The reaction of **18** with *n*-butyl lithium gave the lithiated arene, which underwent Michael addition to effect ring-closure and afford **19** (**Scheme 1.5**).[30]

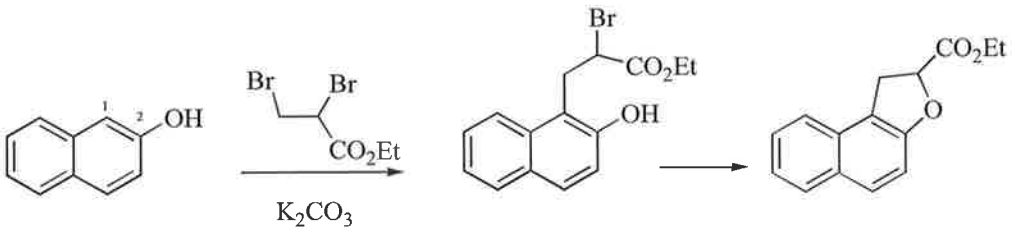
Scheme 1.5



18 **19**

The high reactivity of the C1-position of 2-naphthol **7** was exploited to effect an S_N2 reaction with a 2,3-dibromopropionate ester to afford intermediate **20**. This was followed by an intramolecular nucleophilic substitution giving **21** in good overall conversion.[31] This reaction has also been carried out with 3-amino-2-naphthol to afford the dihydronaphtho[2,1-*b*]furan in low yield.[32]

Scheme 1.6

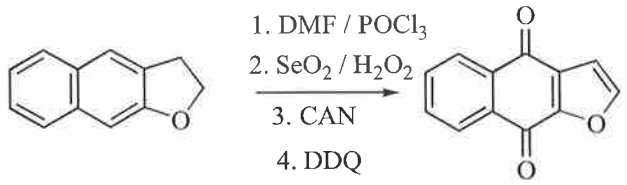


7 **20** **21** (71%)

Many compounds incorporating the furonaphthoquinone moiety have been reported in the literature and some exhibit interesting biological activity.[33-37] Godbole has demonstrated that the dihydronaphtho[3,2-*b*]furan **22** could be successfully transformed to the corresponding furo[3,2-*b*]naphthoquinone **23** (**Scheme 1.7**).[38]

Dihydronaphthofuran **22** was formylated at the 1-position in a Vilsmeier-Haack reaction. This was followed by conversion of the aldehyde to a naphthyl formate by a Baeyer-Villiger reaction. Oxidation using Cerium ammonium nitrate (CAN) acted to insert the second oxygen forming a quinone. The dihydrofuran is aromatised with DDQ resulting in furo[3,2-*b*]quinone **23**.

Scheme 1.7

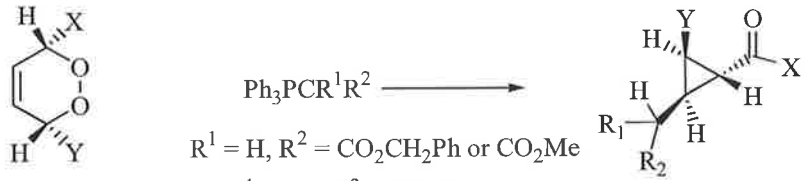


22 **23**

1.2 INTRODUCTION TO PREVIOUS WORK IN THE TAYLOR GROUP.

Early work in the Taylor group led to the serendipitous discovery by Rathbone that 1,2-dioxines such as **24** react with stabilised phosphorus ylides to afford novel cyclopropanes of the type **25**.[39] This reaction occurs with excellent diastereoselectivity giving cyclopropanes in high yield with triphenylphosphine oxide as the only byproduct. Both cyano and ester groups may be used to stabilise the phosphorane.[40] More recent work within the group has also demonstrated the efficiency of stabilised phosphonates in effecting the synthesis of these cyclopropanes.[41] The reaction mechanism has been investigated in some depth and will be presented later, but first, a discussion of the synthesis and chemistry of the 1,2-dioxine moiety is required.

Scheme 1.8



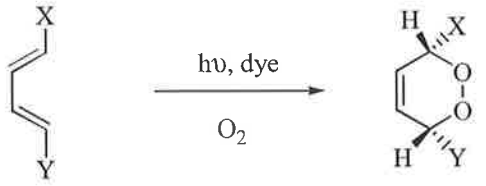
24 **25**

X and Y = H, aryl and alkyl 70-99% de>98%

1,2-Dioxines **24** can be conveniently synthesised by a [4π+2π] photosensitised Diels-Alder reaction of a 1,3-butadiene.[42,43] An example is shown in **Scheme 1.9** of the reaction of singlet oxygen with acyclic butadiene **26**. Singlet state oxygen can be generated by the use of specific dyes in these reactions when the reaction vessel is

irradiated with a light source specific to that dye. Dyes which have been reported include Chlorophyll *a*, Eosin, Methylene Blue, Tetraphenylporphine, and Rose Bengal.[44] Recently, Barrett has developed some new dyes far exceeding the singlet oxygen turnover rate with no light source required.[45]

Scheme 1.9



26 **24**

X and Y = H, aryl and alkyl

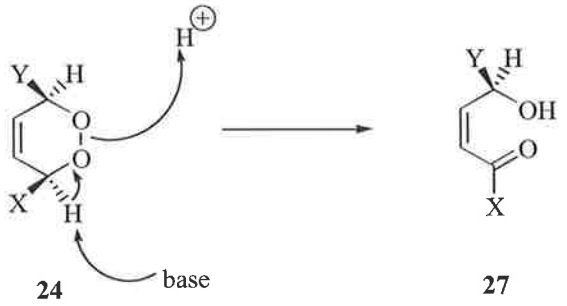
Using this protocol, a diverse range of 1,2-dioxines have been synthesised and cited in the literature. These include monocyclic[46], 1,2-dioxines affixed to polycycles[47-52] and even steroidal [53,54] 1,2-dioxines. The 1,2-dioxine can be constructed in the presence of such functionality as nitriles,[55] and even acid ahydrides.[56] There are some limitations as to what type of 1,3-butadienes can be used. One such problem being the 'ene' reaction, which can lead to hydroperoxide products when alkyl substituted 1,3-butadienes are used.[57]

1,2-Dioxines fall into a class of compounds known as organic peroxides, a class of compounds that contain a weak O-O linkage. Owing to the weakness of this bond, organic peroxides can be unstable under ordinary handling conditions, sometimes resulting in violent explosions. On the other hand, many of the literature 1,2-dioxines have been successfully characterised and are stable at ambient temperatures. 1,2-Dioxines can be manipulated to give a variety of 1,4-oxygen functionalised products. The discussion presented is centered about a few reactions relevant to this work, but possible manipulation includes selective reduction of either the olefin or the di-oxygen linkage,[58] and further epoxidation with *m*-CPBA.[59]

1,2-Dioxines can be treated under relatively mildly basic conditions to effect the formation of diketone products.[60,61] This reaction is facilitated by a Kornblum-DeLaMare rearrangement. The proposed mechanism for the Kornblum-DeLaMare reaction is presented (**Scheme 1.10** and **Scheme 1.11**).[60] Protons on the carbon α to the peroxide linkage are acidic, and the most acidic proton is removed by the base. This initiates a ring-opening process leading to the γ-hydroxyenone **27** (**Scheme 1.10**). In the

case of asymmetric 1,2-dioxines, the relative acidity of the C3 and C6 protons govern the regioselectivity of the ring-opening. When substituted with an aryl group, the acidity of the α proton increases. This means that regioselective Kornblum-DeLaMare reactions occur with aryl substituted 1,2-dioxines. For example when X is aryl and Y alkyl the ring-opening favours the product **27** in **Scheme 1.10**.

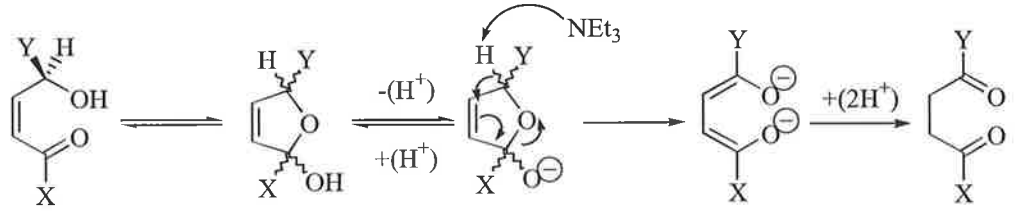
Scheme 1.10



24 **27**

Depending upon the nature of the γ-hydroxyenones, further reaction can occur to give diketones. Some steroidal and cyclic γ-hydroxyenones are reported to be stable,[62] whereas simpler systems tend not to be.[63] The mechanism for this process has been postulated as follows although it still warrants further investigation (**Scheme 1.11**).[5] It is believed that in a series of equilibria, γ-hydroxyenone **27** cyclises to give hemiacetal **28** and from there, the furanol anion **29** undergoes the rearrangement furnishing 1,4-diketone **30**. Under acidic conditions, both **27** and **30** would dehydrate to afford aromatised furan products.[63,64]

Scheme 1.11



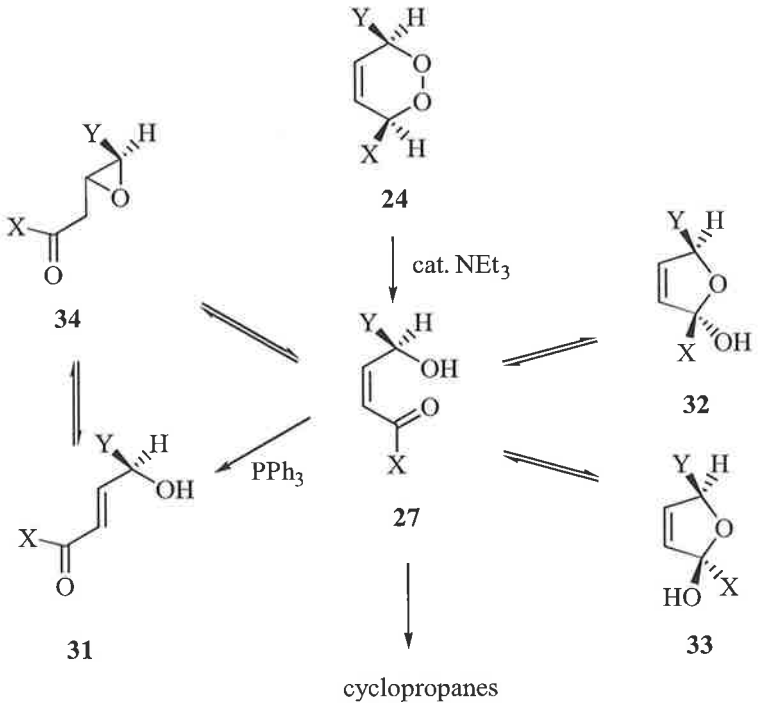
27 **28** **29** **30**

The reactive *cis* γ-hydroxyenone **27** was found to be the key intermediate in the cyclopropanation discussed previously.[5] In the course of investigating the cyclopropanation sequence, earlier members of the Taylor group developed methodologies for the synthesis of the *cis*-γ-hydroxyenones of the type **27**. Avery was the first to discover its role as an intermediate and that it was possible to generate it by

the base catalysed Kornblum-DeLaMare reaction of the 1,2-dioxine with a non-nucleophilic base, typically triethylamine (**Scheme 1.12**).[5] When subjected to the reaction conditions *cis*-γ-hydroxyenone **27** reacted with the same stabilised ylides to afford cyclopropanes identical to those derived from the analogous 1,2-dioxine.

Using ^{1}H NMR it was found that the *cis* γ-hydroxyenone **27** existed in equilibrium with hemiacetals **32** and **33**. Furthermore, upon treatment with TPP the *cis*-γ-hydroxyenone underwent quantitative rearrangement to the *trans* isomer **31**. *Trans*-γ-hydroxyenone was also isolated from the reaction of the dioxine and stabilised ylide. *Cis* to *trans* isomerisation occurred via an intramolecular cyclised intermediate **34** and the isomerisation was reversible in nature. Avery found that *trans* **31** did not undergo the cyclopropanation reaction with stabilised phosphorus ylides. It was also found that the cis-γ-hydroxyenone could be isomerised to the trans isomer when triphenylphosphine was used in conjunction with triethylamine.[5,65]

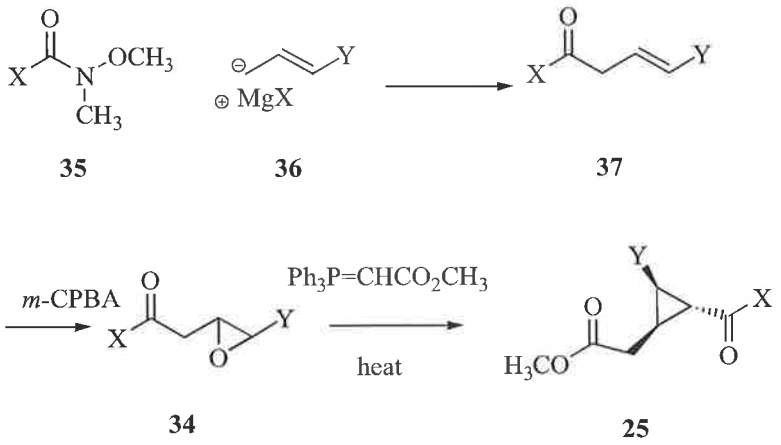
Scheme 1.12



Pain has explored the cyclopropanation arising from the base catalysed ring-opening of the β,γ-epoxy ketone **34** (**Scheme 1.13**) with stabilised phosphorus ylides.[66] It was possible to effect the formation of the *cis*-γ-hydroxyenone **27** by degradation of epoxide **34** with ylide. The enone intermediate underwent subsequent cyclopropanation. This synthesis involved generating β,γ-unsaturated ketone **37** by the treatment of a Weinreb amide **35** with an allylic Grignard reagent **36**. This was followed by an

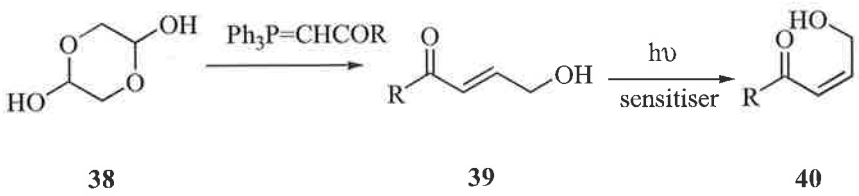
epoxidation of **37** with *m*-CPBA to give precursor **34**. Using this methodology, the inherent problems of using *m*-CPBA in the presence of the ketone sometimes led to Baeyer-Villiger oxidations in competition with the epoxidation. The success of this cyclopropanation route depended heavily upon the substituents adjacent to the ketone.

Scheme 1.13



Palmer utilised two different routes to prepare the *cis*-γ-hydroxyenone **40** and hence cyclopropanes.[67] In a one pot reaction of glycoaldehyde dimer **38** and a stabilised ketoylide, *trans*-γ-hydroxyenone **39** was obtained. *Trans*-γ-hydroxyenone **39** could be isomerised to **40** by photolysis in the presence of a sensitiser such as benzophenone. Derivatives **40** were suitable substrates for the cyclopropanation (**Scheme 1.14**). Infact, upon formation of **39**, it was possible to add the desired stabilised ester phosphorane to give cyclopropane under the photo-isomerising conditions in yields of up to 68%.

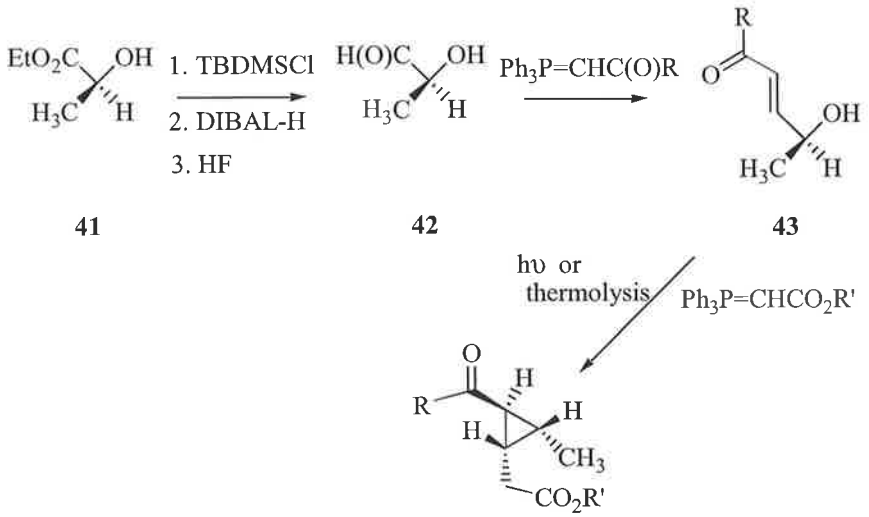
Scheme 1.14



The second approach involved the use of readily available chiral building blocks such as ethyl lactate **41** featured in **Scheme 1.15**.[67] This elaborate procedure involved the transformation of the ester **41** to the aldehyde **42**, via a silyl protected alcohol. This approach did not racemise the sole chiral centre. Aldehyde **42** was treated with ketone stabilised phosphorane giving **43**. *Trans*-γ-hydroxyenone **43** was isomerised in the

presence of a second ylide affording the cyclopropane product **44**. Unfortunately, this methodology does not embrace a large pool of potentially chiral starting materials.

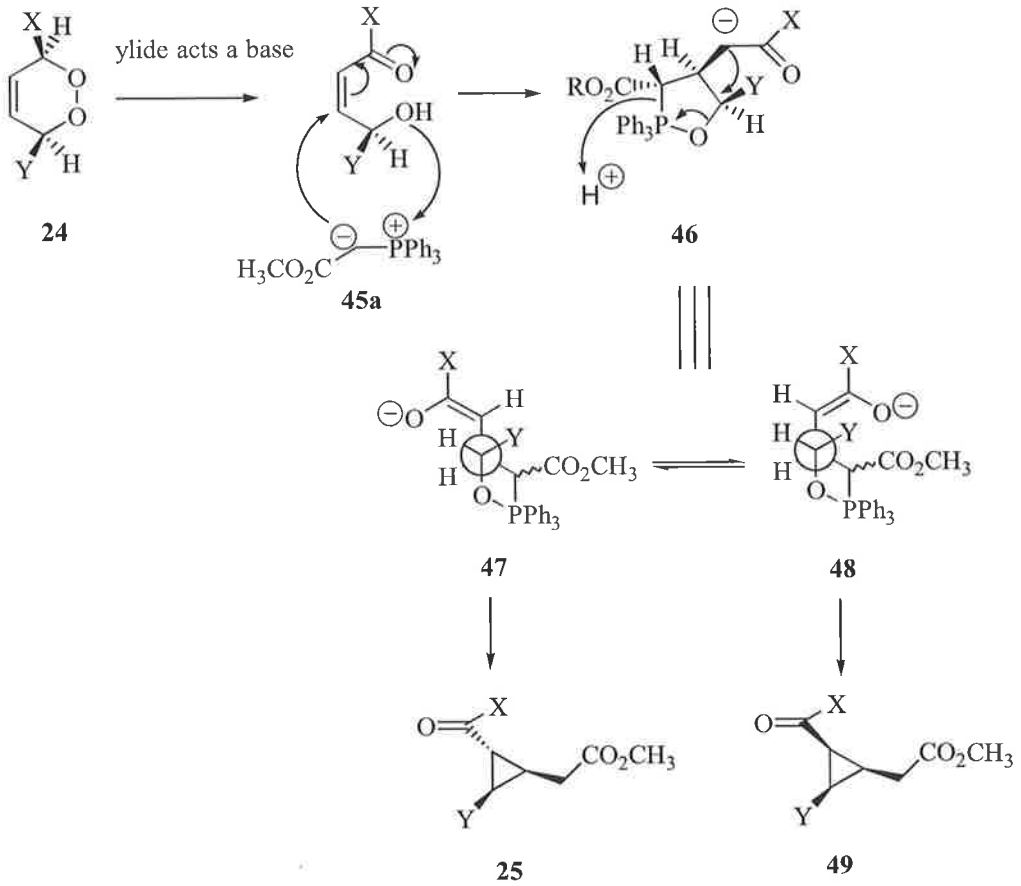
Scheme 1.15



44 (65% overall)

The mechanism of the cyclopropanation from the reaction of 1,2-dioxines and stabilised phosphoranes was proposed as follows (**Scheme 1.16**).[5] The phosphorane **45a** was thought to be bifunctional in nature. Its first purpose was its behavior to act as a mild base. Deprotonation of the most acidic proton α to the peroxide linkage initiates a Kornblum-DeLaMare reaction to furnish the *cis*-γ-hydroxyenone.

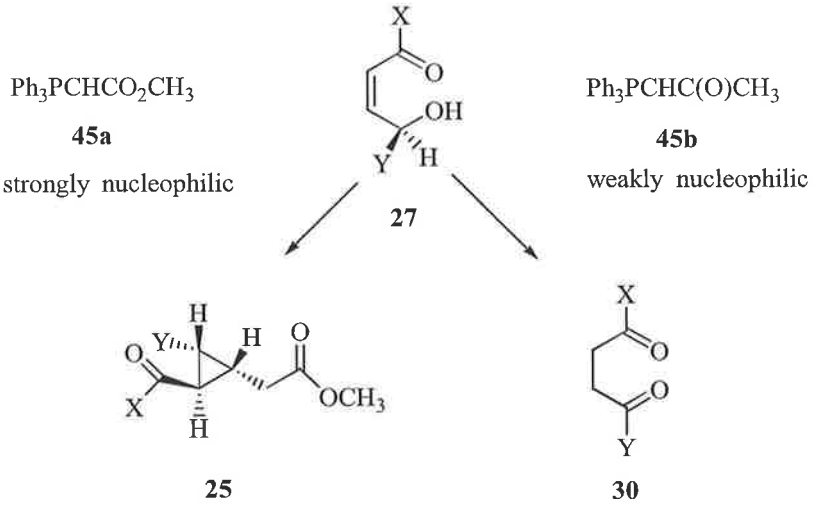
Scheme 1.16



The second function of the ylide was as a nucleophile. It is believed that the carbanion of the phosphorane undergoes a 1,4-addition, whilst at the same time the hydroxyl of the *cis* γ-hydroxyenone forms a covalent interaction with the phosphorus atom and in doing so forms a five membered ring intermediate represented by **46**. The addition of ylide to the enone is facially selective and the selectivity is governed by the *cis* enone conformation. It is thought that if intramolecular hydrogen bonding exists between the hydroxyl and ketone moieties, then both enhanced reactivity of the α,β-unsaturated ketone and facially selective addition upon the least hindered face would be expected for the *cis*-γ-hydroxyenones. In doing so, the single stereocentre of the *cis*-γ-hydroxyenone controls the relative stereochemistry of the introduced chiral centre. 1,4-Addition by phosphoranes have been previously reported in the literature.[68] The resulting oxaphospholane **46**, (a previously reported type of compound)[69-73] then undergoes an intramolecular S_N2 attack resulting in the expulsion of triphenylphosphine oxide. As demonstrated by the Newman projections, the stereochemistry of the third stereocentre is predetermined by the sterically least hindered orientation **47** resulting in the major product **25**, where the keto substituent is *trans* to the other two substituents. Minor cyclopropane **49** arises from the lesser favoured enolate conformation **48**.

It was found that the compatibility of a particular ylide with the 1,2-dioxine strongly depended on the nucleophilic characteristics of the ylide employed in the reaction. The rationale for the degradation of the γ-hydroxyenone to the diketone is based upon an argument which considers the relative nucleophilicity of the ylide; an example is depicted in **Scheme 1.17**. Both phosphoranes **45a** and **45b** are basic enough to induce the Kornblum-DeLaMare reaction to the *cis*-γ-hydroxyenone **27**. When the methyl ester phosphorane **45a** was employed, the strong nucleophilic character allowed for the 1,4-addition to **27**. The result is a successful cyclopropanation. On the other hand, the use of the methyl ketone phosphorane **45b**, where the carbanion was not as electron rich as **45a**, tended toward diketone products **30**. In this case, the nucleophilic character of this species was insufficient to undergo Michael addition. Thus, no cyclopropyl products were isolated when ketone ylides were used in place of ester ylides.

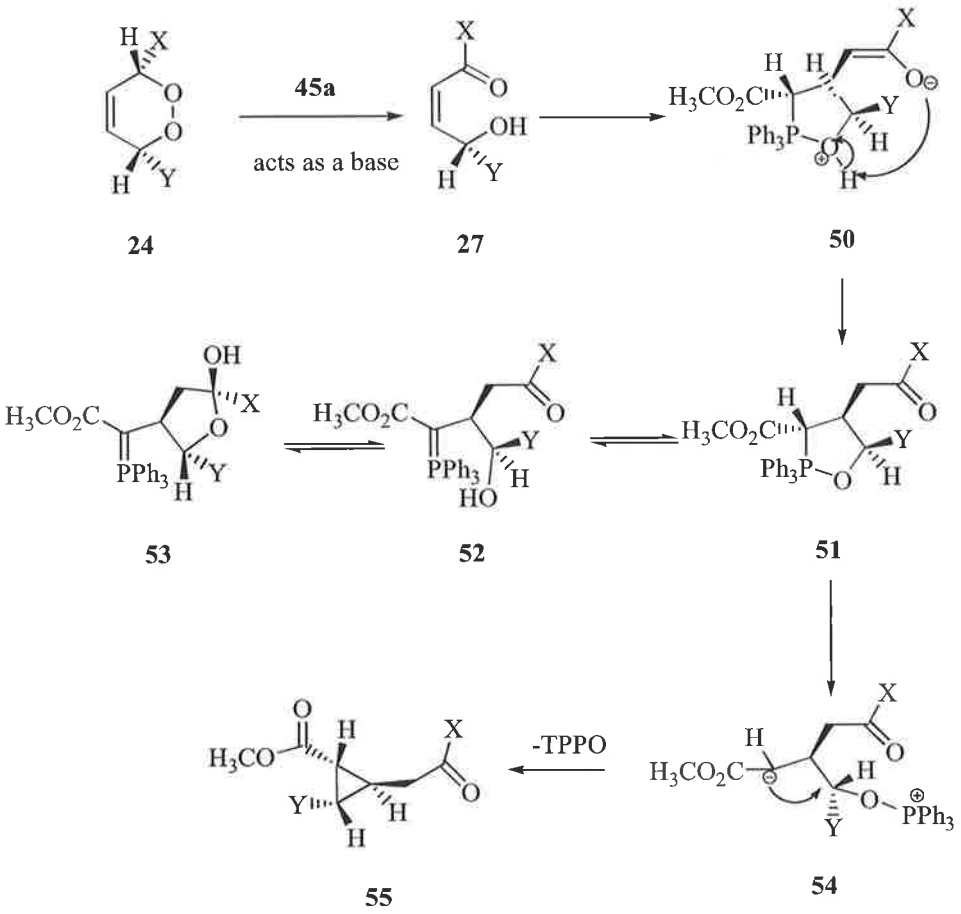
Scheme 1.17



The cyclopropanation described hitherto was found to be sensitive to the presence of ionic salts. In the presence of lithium bromide, the reaction of 1,2-dioxines with stabilised ylides yielded a novel class of cyclopropanes **55** (**Scheme 1.18**).[74] Lithium bromide has been shown to affect the equilibrium of the *cis-trans* conformation of **45a**, and also the stereochemistry of the oxaphospholane intermediate **50** in the Wittig reaction.[75] The same results could be obtained when using so-called bulky ylides. For example, when the *t*-butyl or the adamantyl substituted ester phosphorane were employed in the reaction, these novel cyclopropanes were also obtained. Mechanistically, it was thought that an intramolecular proton transfer occurs instead of the expulsion of TPPO to give **51**. **51** then undergoes ring-opening to give the equilibrium mixture of phosphorus containing intermediates **52** and the hemiacetal form

53. An X-ray structure verified the identity of **53**.[74] This equilibrium mixture slowly decays via **51** to its corresponding zwitterion **54**, which by intramolecular expulsion of TPPO affords **55**. Cyclopropane **55** now has the ester adjacent to the cyclopropane and a methylene bridging between the ketone and the cyclopropane with the ketone substituent *trans* to the other substituents.

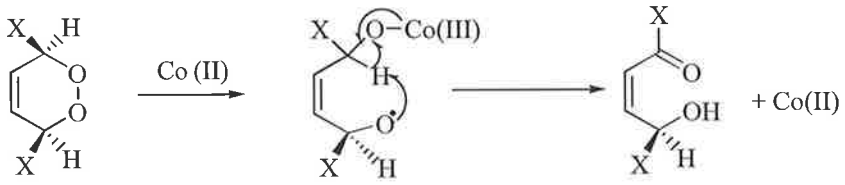
Scheme 1.18



It was found that enantio-enriched cyclopropanes could be generated when *meso* 1,2-dioxines **56** were allowed to react with Jacobsens, or structurally related chiral cobalt(II) catalyst (**Scheme 1.19**).[76] The mechanism of action firstly involved the homolytic cleavage of the O-O bond to afford the cobalt containing intermediate **57**.[63] This is then followed by a 1,5-hydrogen abstraction, which in turn regenerates the catalyst and affords enantiomerically enriched *cis*-γ-hydroxyenones **58**. Treatment of this intermediate with ylide afforded cyclopropanes with a high degree of enantiopurity. These ring-openings could be carried out in the presence of stabilised phosphoranes, as the rate of the base isomerisation by the phosphorane was insignificant in comparison to the catalytic radical opening process. A useful advantage to this approach was that the

catalyst did not cause the equilibrium to shift towards the unreactive *trans*-γ-hydroxyenone.

Scheme 1.19

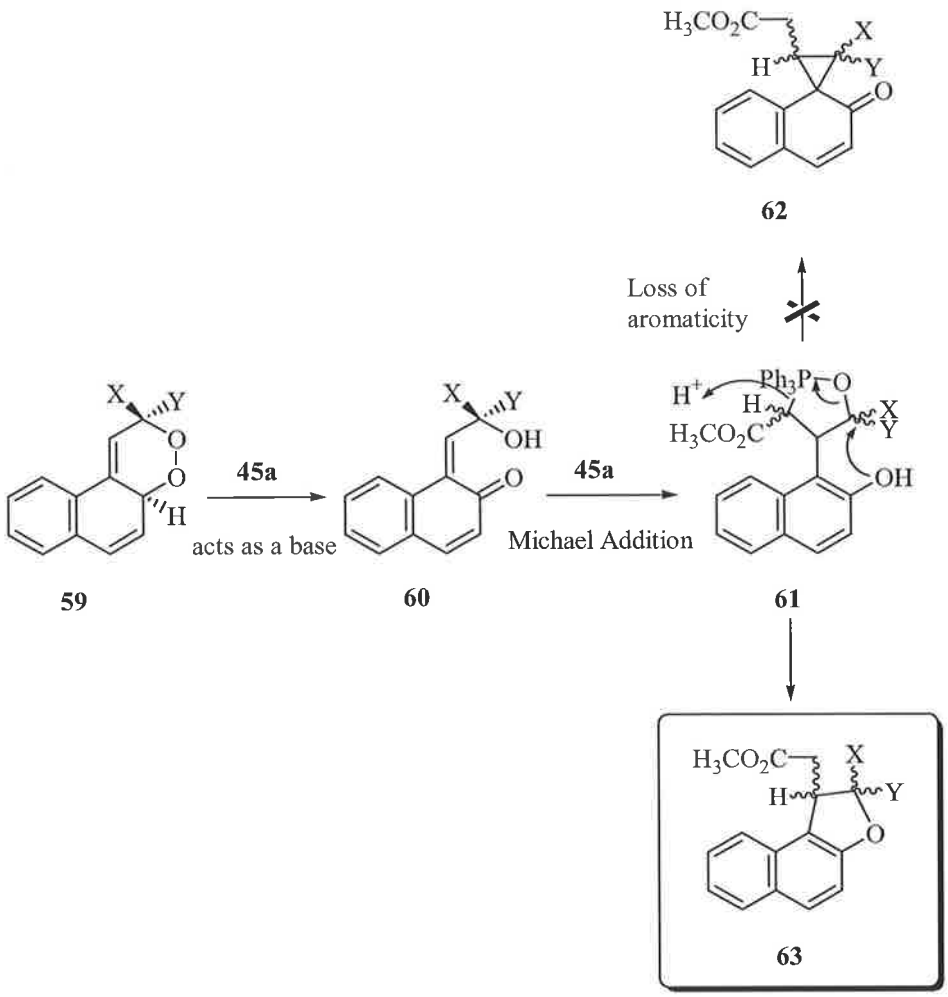


56 **57** **58**

1.2 SYNTHESIS OF 1,2-DIHYDRONAPHTHO[2,1-*b*]FURANS USING THE TAYLOR METHODOLOGY.

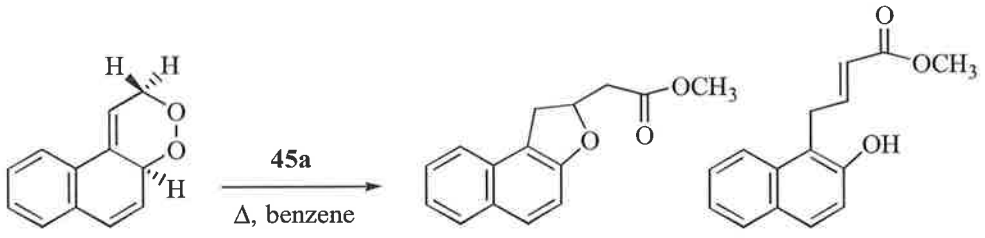
A preliminary examination of the reaction of fused 1,2-dioxines of the type mentioned in **Scheme 1.20** was carried out by Haselgrove.[77] This work was performed prior to the discovery of the mechanistic importance of the *cis* γ-hydroxyenone. The bi-functional nature of the phosphorane **45a** again initiated a Kornblum-DeLaMare reaction of 1,2-dioxine **59** to quinone methide **60**. It can now be envisaged that the intermediate γ-hydroxyenone **60** would undergo a facile 1,4-addition, the driving force being the rearomatisation of the naphthalene functionality. Once the system had been aromatised to the oxaphospholane **61**, it was thought that the cyclopropanation to **62** would not be favoured as it would require the dearomatisation of the naphthalene system. Instead, a furanisation process could give rise to 1,2-dihydronaphtho[2,1-*b*]furans **63**.

Scheme 1.20

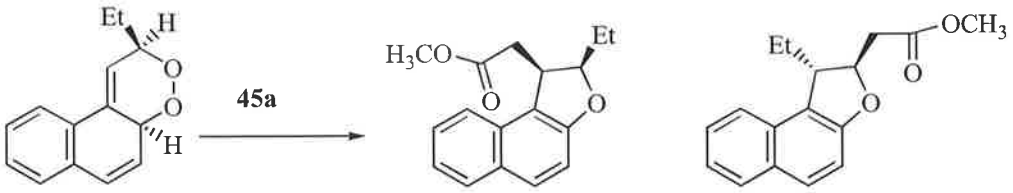


The preliminary research of Haselgrove, who investigated the reactions of 1,2-dioxines **64** and **67** with phosphorane **45a** featured in **Schemes 1.21** and **1.22**, led to the isolation of some 1,2-dihydronaphtho[2,1-*b*]furans. The results obtained from the parent system in **Scheme 1.21** did not agree with the proposed reaction. Instead, the reaction of **64** with ylide **45a** afforded a 1,2-dihydronaphtho[2,1-*b*]furan **65a** in 25% yield.

Scheme 1.21



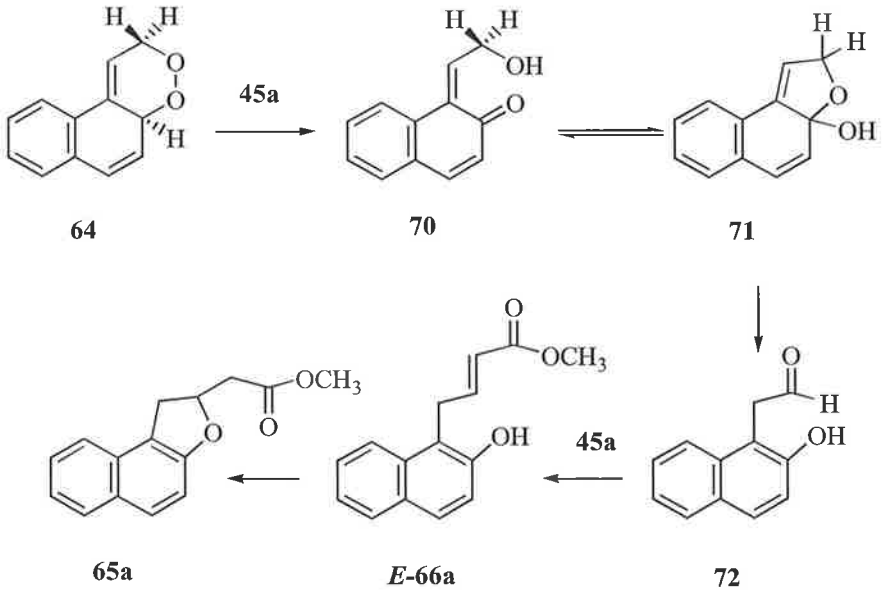
Scheme 1.22



67 ***E/Z*-68a** (31%) ***E/Z*-69a** (15%)

In the case of the parent system **64**, the two products seen, **65a** and ***E*-66a** more than likely had the same origins. In this case, ylide **45a** did not undergo 1,4-addition but instead, promoted the Kornblum-DeLaMare reaction to γ-hydroxyenone **70**. Further base catalysed degradation via cyclic intermediate **71** afforded aldehyde **72** capable of Wittig reaction to yield the alkene ***E*-66a** (**Scheme 1.23**). The furan **65a** was a direct result of an Oxa-Michael addition to the alkene ***E*-66a** catalysed by the basic character of **45a**.

Scheme 1.23



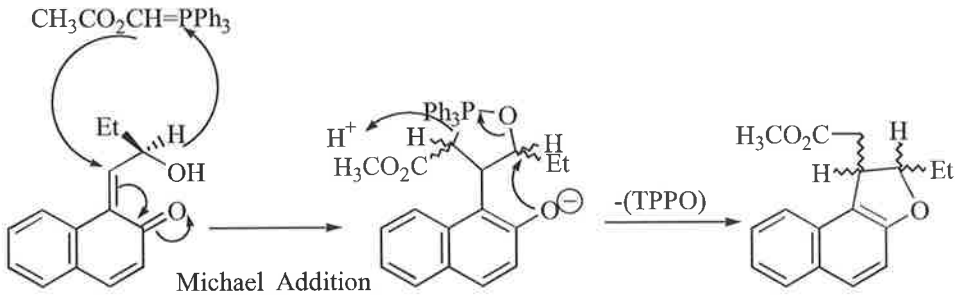
64 **70** **71**

65a ***E*-66a** **72**

The reaction of the ethyl substituted dioxine **67** in **Scheme 1.22** led to some interesting results. The proposed mechanism for the formation of the major product is shown in **Scheme 1.24**. In this case, ylide **45a** underwent a successful 1,4-addition to γ-hydroxyenone **73** followed by an intramolecular nucleophilic addition and expulsion of TPPO from the oxaphospholane **74** to afford ***E/Z*-68a**. ***E/Z*-68a** was formed in reasonably high *de* with the *cis* stereochemistry favoured. The minor 1,2-dihydronaphtho[2,1-*b*]furan ***E/Z*-69a** was believed to be another regioisomer where the

substituent positions were swapped, however, this compound was not formed with any significant diastereoselectivity.

Scheme 1.24



73 **74** ***E/Z*-68a**

It has been demonstrated that 1,2-dihydronaphtho[2,1-*b*]furans can be synthesised from aryl-fused 1,2-dioxines as precursors for the reactive *cis*-γ-hydroxyenones. The aims of this project were to extensively reinvestigate the reactions of a series of these fused 1,2-dioxines with a host of stabilised phosphorus ylides as an extension of Haselgroves work. 1,2-Dihydronaphtho[2,1-*b*]furans are relatively rare in the chemical literature and a unique opportunity exists to examine reactions of these compounds. Aromatic electrophilic substitutions on these compounds is of particular interest and another area that should be explored with this chemistry. Using the protocol established by Godbole,[38] this could provide a gateway into the synthesis of some new furonaphthoquinone products. The possibility of using this methodology depends greatly on where the electrophilic substitution takes place.

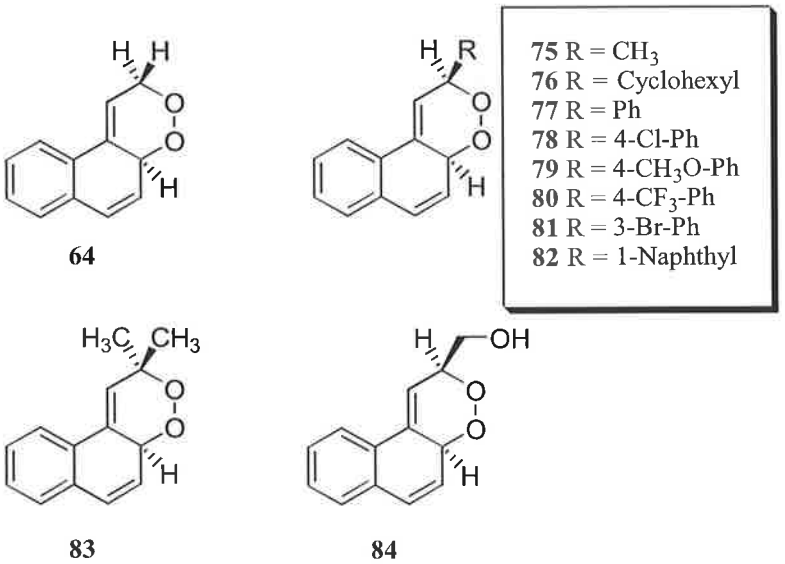
CHAPTER 2

REACTIONS OF 1,2-DIOXINES WITH STABILISED PHOSPHORUS YLIDES

2.1. THE 1,2-DIOXINES EMPLOYED IN THIS STUDY.

For the purposes of this study, a series of 1,2-dioxines with different groups in positions α to the peroxide bond were prepared (**Figure 2.1**). They included the unsubstituted parent system **64**, a variety of alkyl and aryl monosubstituted 1,2-dioxines **75** to **82** and disubstituted 1,2-dioxine **83**. In this area of research, the reactions of phosphoranes were not examined with all dioxines, instead, some are featured in a different aspect of the project. It was also of interest to examine the reactions of phosphoranes with hydroxyl bearing 1,2-dioxines; thus, **84** was also synthesised.

Figure 2.1 *1,2-dioxines employed in the study.*



The syntheses of these peroxides was accomplished using a general literature procedure.[5] This involved the photo-oxidation of the substituted vinyl naphthalenes with singlet state oxygen generated with photo-sensitiser Rose Bengal *bis*(triethylammonium salt). These vinyl naphthalenes were synthesised by the Wittig reaction of commercially available 1-naphthaldehyde with unstabilised phosphoranes using a general protocol established in the Taylor group.[65] The reaction protocol consisted of the addition of 1-naphthaldehyde to an ether solution of the phosphorane, generated by the treatment of the phosphonium salt with potassium *t*-butoxide. **Table 2.1** contains a summary of the alkenes and yields.

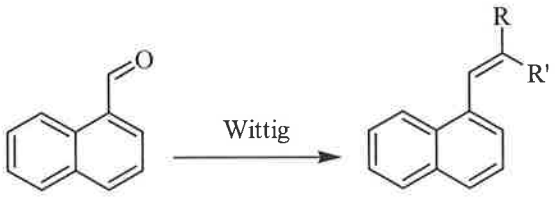
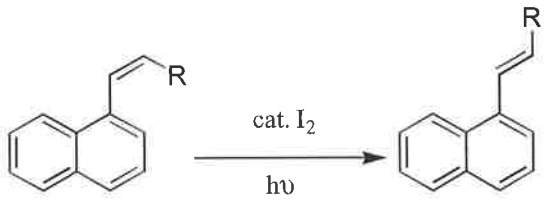


Table 2.1 *Reactions of 1-naphthaldehyde with phosphorus ylides.*

Entry	Ph_3P=CR(R')	Product	% Yield (*E* : *Z*)
1	R = H, R' = H	**85**	71
2	R = CH_3, R' = H	**86**	65 (35 : 65)
3	R = Cyclohexyl, R' = H	**87**	65 (32 : 68)
4	R = Phenyl, R' = H	**88**	94
5	R = 4-Chlorophenyl, R' = H	**89**	84
6	R = 4-Methoxyphenyl, R' = H	**90**	60
7	R = 4-Trifluoromethylphenyl, R' = H	**91**	84
8	R = 3-Bromophenyl, R' = H	**92**	75
9	R = 1-Naphthyl, R' = H	**93**	53
10	R = R' = CH_3	**94**	52

The reactions typically afforded mixtures of *cis* and *trans* alkenes and tended to favour the formation of the *cis* isomer. These substrates, with the exception of **86** and **87**, were used directly in the photo-oxidation step. It has been reported that the reaction of ***Z*-86** was sluggish for the [4π + 2π] reaction with singlet oxygen, with a competitive side [2π + 2π] reaction leading, via dioxetane and cleavage to 1-naphthaldehyde.[78] The *trans* isomer underwent a more rapid and efficient reaction with singlet state oxygen, thus it would be useful to synthesise predominantly the *trans* isomers. It has been reported that olefins may be isomerised using catalytic iodine in the presence of a light source.[79] For alkyl substituted alkenes **86** and **87**, it was possible to isomerise these mixtures to favour the *trans* isomer when the alkene mixtures were treated with a catalytic amount of iodine in the presence of sunlight (**Scheme 2.1**). Under these conditions, a 35 : 65 mixture of *trans* : *cis* **86** could be equilibrated to a 75 : 25 mixture. Likewise, a 32 : 68 mixture of *trans* : *cis* **87** was converted to 90 : 10, as determined by ^{1}H NMR.

Scheme 2.1

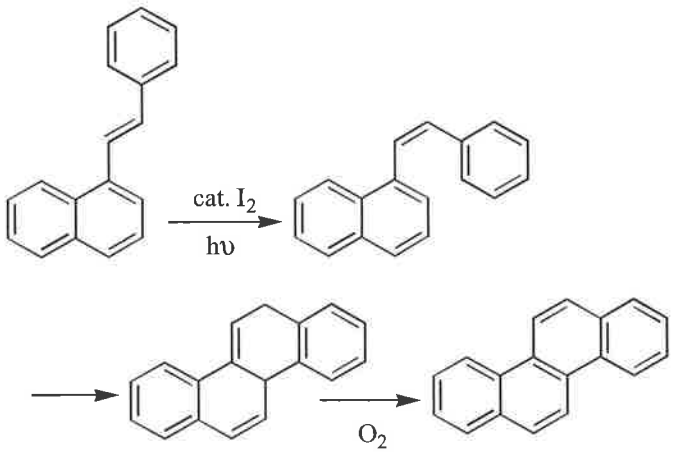


86 (*E* : *Z* = 35 : 65) **86** (*E* : *Z* = 75 : 25)

87 (*E* : *Z* = 32 : 68) **87** (*E* : *Z* = 90 : 10)

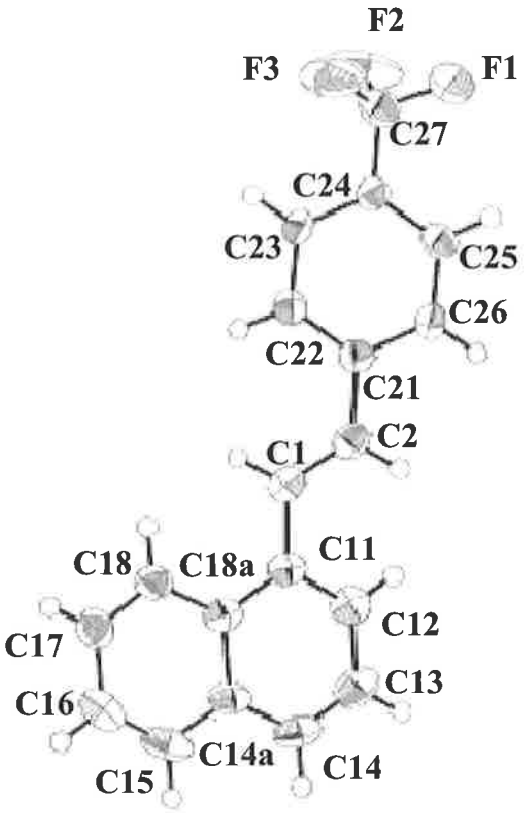
This methodology could not be extended to the aryl substituted alkene systems as these conditions have been reported to give rise to chrysenes (**Scheme 2.2**).[80] As a result the *E/Z* phenyl alkene mixtures were used in the photo-oxidation as synthesised as the isomerisation protocol could not be employed.

Scheme 2.2



It was possible to obtain an X-ray structure of the *trans* isomer of the 4-trifluoromethylphenyl substituted alkene **91** (**Figure 2.2**). In the solid state of ***E*-91**, both ring systems lay coplanar allowing for maximum conjugation.

Figure 2.2 *ORTEP diagram of E*-**91**.



The construction of the hydroxyl bearing alkene **96** was achieved in a two step process using a modified literature procedure described in **Scheme 2.3**. Methyl ester **95** was obtained by reaction of stabilised phosphorane with 1-naphthaldehyde, which resulted in the formation of the *trans* isomer exclusively. This was confirmed by comparison with the literature.[81] The reduction of the carbonyl moiety was then successfully achieved using DIBAL-H without affecting the adjacent alkene.[81] This approach was advantageous as only the *trans* isomer was formed which was a suitable precursor for the photo-oxidation reaction.

Scheme 2.3

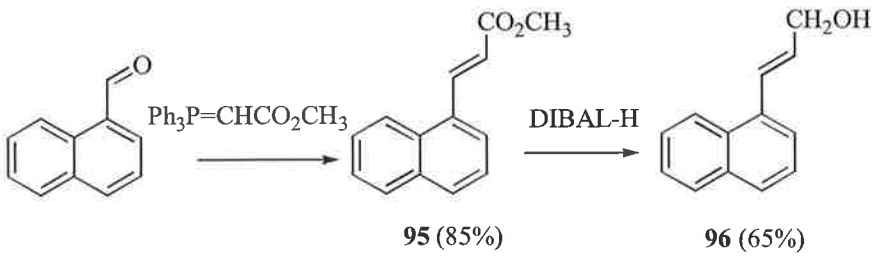


Table 2.2 contains a summary of yields obtained from the photo-oxidations of the series of alkenes **85** to **96**. The conditions for each reaction were identical using a protocol established in the Taylor group. A stream of oxygen gas was bubbled through a sinter into a dichloromethane solution of the requisite alkene in the presence of Rose Bengal *bis*(triethylammonium) salt. The reaction was performed in a jacketed vessel which was kept cool by the flow of ice cold water during the irradiation with two 500 W Tungsten Halogen lamps.[5] All dioxines could be purified by flash chromatography and the new 1,2-dioxines were characterised by both ^{1}H NMR and ^{13}C NMR.

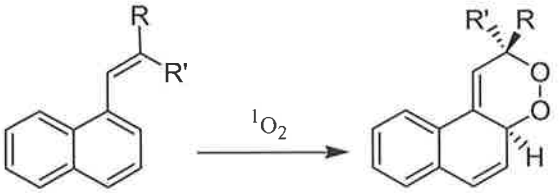


Table 2.2 *Photo-oxidations of alkenes* **85** *to* **96** *with singlet oxygen.*

Entry	Alkene	R	R'	Dioxine	Yield (%)
1	**85**	H	H	**64**	50
2	**86**	CH_3	H	**75**	84
3	**87**	Cyclohexyl	H	**76**	55
4	**88**	Ph	H	**77**	35
5	**89**	4-Cl-Ph	H	**78**	29
6	**90**	4-CH_3O-Ph	H	**79**	25
7	**91**	4-CF_3-Ph	H	**80**	40
8	**92**	3-Br-Ph	H	**81**	16
9	**93**	1-Naphthyl	H	**82**	24
10	**94**	CH_3	CH_3	**83**	30
11	**96**	CH_2-OH	H	**84**	78

The yields of the dioxines reported in **Table 2.2** are based upon recovered starting materials. In all systems, the alkene precursor failed to react to completion. In the case of the parent alkene **85** the crude yield showed only approximately 5% conversion to **64**, the remainder of which was starting material. Extended reaction times did not increase the conversion of **85** to **64**. An interesting feature of these reactions were that only one isomer was typically obtained from the mono-substituted alkene precursors. This was an indication that only the *trans* isomer was undergoing the Diels-Alder reaction with singlet oxygen. This held true with the exception of **86**, which gave small amounts of the *cis* adduct which was detectable by ^{1}H NMR. Dioxine

75 was isolated as an isomeric mixture in a ratio of 1 : 4, with consistent resonances for the ^{1}H NMR spectrum with that of the literature.[78] As one of the two stereocentres is removed in the Kornblum-DeLaMare reaction step, the relative conformation of 1,2-dioxine should not affect further reactions. This mixture was used as a mixture of diastereomers in further studies.

The ^{1}H NMR data for **77** was consistent with the literature and importantly indicated that ***E*-88** was the only isomer undergoing the reaction. For all the new aryl substituted dioxines, the ^{1}H NMR data was similar with that of **77**.[78] A key feature of these 1,2-dioxines, as observed by Matsumoto *et al.*, was an extensive long range coupling pattern amongst the non aromatic protons owing to the rigidity of these 1,2-dioxines. In conclusion, the reaction only seemed to be taking place with the *trans* alkene from the mixture. This was supported by the isolation of *cis* enriched alkene from the photolysis reaction mixture.

For dioxine **84**, no ROESY crosspeaks were observed between the hydroxymethyl and adjacent bridgehead proton at C2 with other protons which could be used to assign stereochemistry. As the starting material consisted of only the *trans* stereochemistry, based upon the mechanism of addition, the product must have *cis* stereochemistry. Extensive long range coupling was also present in the ^{1}H NMR of hydroxyl bearing dioxine **84**. The rationale for the lack of reactivity for the *cis* alkenes is clear. In order to undergo a successful Diels Alder reaction, the alkene must be in conjugation and in the *cissoid* conformation. In this conformation, there would be significant steric repulsion between the substituent at C2 and the *ortho* proton of the phenyl ring, thus making this arrangement unfavourable, and hence little or no cycloaddition results.

2.2. THE REACTIONS OF 1,2-DIOXINE 64 WITH STABILISED PHOSPHORANES.

To extend the work of Haselgrove, the parent system was reinvestigated. It was hoped that by modifying the conditions, one could favour the formation the desired 1,2-dihydronaphtho[2,1-*b*]furan **97**. In the previous work, the 1,2-dioxine **64** was allowed to react with the methyl ester phosphorane **45a**. Having a better understanding of the mechanisms involved, this study was to extend the reactions of **64** with a host of stabilised phosphorus ylides. The results and the mechanistic rationale are summarised

in **Scheme 2.4** and **Table 2.3.** The reactions typically involved the treatment of 100 mg of **64** with specified quantities of phosphorane in **Table 2.3**.

Scheme 2.4

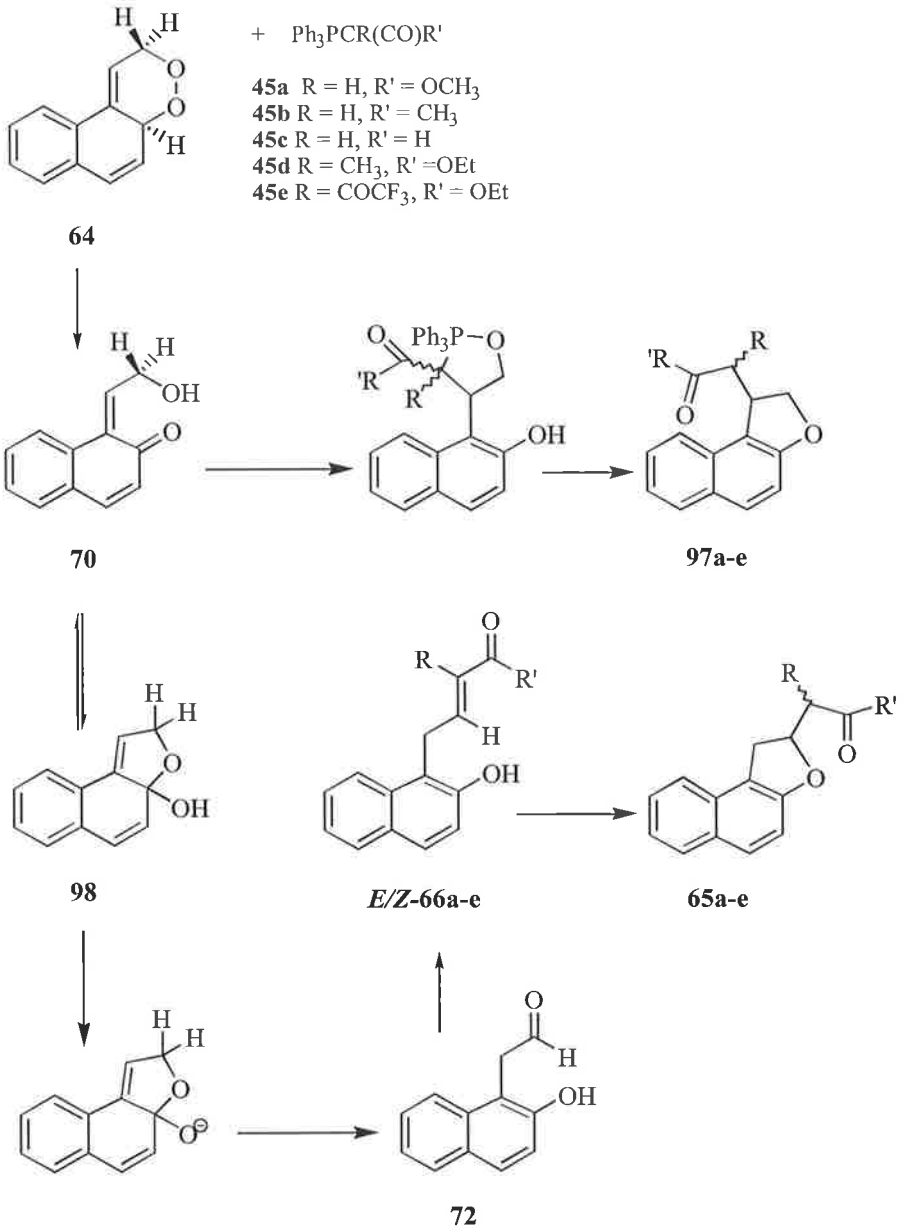


Table 2.3 *Reactions of stabilised ylides* **45a-e** *with* **64**.

Entry	Ylide (equiv.)	Temp.	Time	Products (%)
1	**45a** (1.05)	RT	24	**97a** (25) ***E*-66a** (38) ***Z*-66a** (7) **65a** (26)
			48	**97a** (34) ***E*-66a** (36) ***Z*-66a** (6) **65a** (36)
			96	**97a** (34) **65a** (64)
2	**45a** (4)	60	24	**97a** (23) ***E*-66a** (40) ***Z*-66a** (6) **65a** (36)
3	**45a** (1.05)	RT	96	**97a** (65) **65a** (33)

4	**45b** (1.05)	RT	48	**65b** (85)
5	**45c** (1.05)	RT	48	**65c** (98)
6	**45d** (1.05)	RT	62	***E*-66d** (88) ***Z*-66d** (8)
7	**45e**	RT	96	no reaction
8	**45e**	80	48	**72** (95)

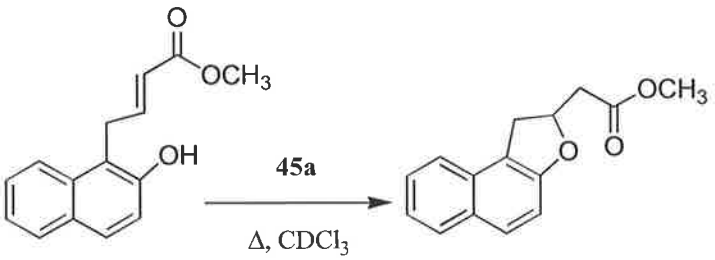
The reaction of phosphorane **45a** with dioxine **64** resulted in four main products, with the ratios depending upon the conditions employed (Entries 1-3). These were the two 1,2-dihydronaphtho[2,1-*b*]furans **97a** and **65a** and alkenes ***E*-66a** and ***Z*-66a**. Haselgrove had only discussed products arising from the base catalysed pathway, namely ***E*-66d** and ***Z*-66a** and **65a**.[77] The new features discovered for these reactions was that the concentration of phosphorane **45a** affected the product ratios. The optimal yields of the desired furan **97a** occurred when a large excess of phosphorane **45a** was used. This result highlights the ability of ylide **45a** to undergo a Michael addition with γ-hydroxyenone **70** contrary to the earlier findings. A rationale for the concentration dependence of this reaction could be explained if the rate of equilibration of the hemiketal **98** from γ-hydroxyenone **70** was comparable to the Michael addition step. The hemiketal **98** was a proposed intermediate in the irreversible formation of aromatised product **72**, thus, at higher concentrations of phosphorane **45a** the desired furan **97a** was preferentially formed. The reaction did not favour the formation of **97a** when heat was applied to the system, but actually resulted in the opposite furan **65a** being the major product.

The proton spectrum of **97a** agreed with the ^{1}H NMR data for the ethyl ester analogue featured in the literature.[30] In addition, the structure was confirmed by 2D NMR techniques such as the COSY experiment. In the ^{1}H NMR, two geminally coupled protons appeared downfield at δ 4.58 and 4.80 ppm and were assigned as the protons α to the furan oxygen. A second AB quartet was observed at δ 2.59 and 3.01 ppm and assigned as the methylene adjacent to the carbonyl. Another aliphatic proton was observed at δ 4.22 ppm, which coupled to both methylene groups. A ROESY crosspeak was also observed between the AB quartet adjacent to the carbonyl moiety and the *peri* proton of the naphthyl ring system. ^{13}C NMR data included 10 aromatic resonances, including a downfield signal, which at δ 157.52 ppm, represented the carbon attached to the oxygen of the furan. The analogous signal for **65a** occurred at δ 156.54 ppm. Other signals included an ester carbonyl at δ 172.61 ppm and four sp^3

resonances. The resonance at δ 77.21 ppm, represented the other carbon adjacent to the oxygen. A HMQC experiment confirmed the downfield AB quartet to reside upon this carbon. The Mass Spectrum of **65a** indicated a molecular ion corresponding to the formula $C_{15}H_{14}O_3$ and analysis agreed with the assignment.

The presence of the alkenes ***E/Z*-66a** and the furan **65a** were a result of a base catalysed rearrangement of γ-hydroxyenone **70** to afford aldehyde **72** (**Scheme 2.4**). This reaction occurred with a relatively similar rate to the desired furanisation as the product ratio could be manipulated by varying the amount of phosphorane **45a**. From these reactions, it was possible to isolate all products. It was confirmed that the opposite regioisomer **65a** originated from the alkenes ***E/Z*-66a** by treatment of the alkene with a catalytic amount of ylide and heat giving **65a** in quantitative yield (**Scheme 2.5**). It was possible to fully characterise and confirm the identities of these products as isolated by Haselgrove. As the minor alkene ***Z*-66a** was not stable for long periods, characterisation was performed directly after purification.

Scheme 2.5

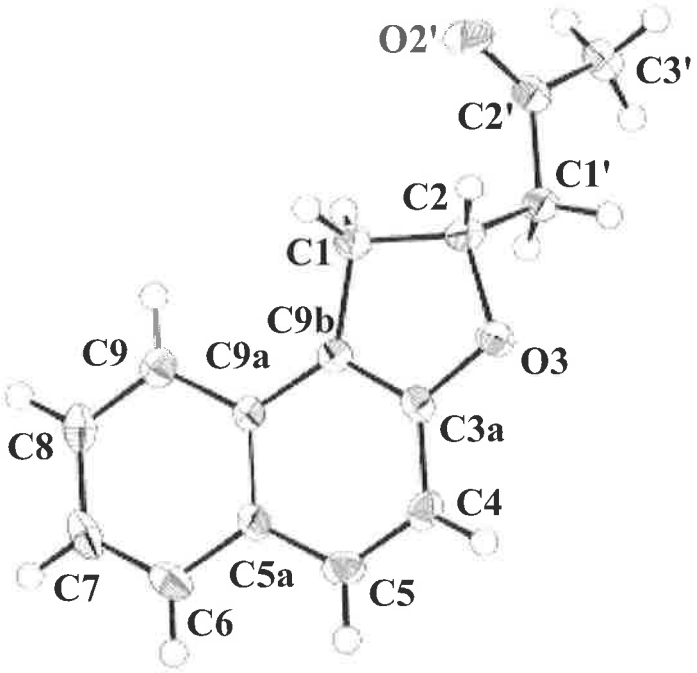


***E*-66a** **65a** quantitative

The reaction of the remaining stabilised ylides **45b** to **45e** were not successful in inducing the formation of the desired 1,2-dihydronaphtho[2,-*b*]furans **97b** to **97e** but favoured the formation of products derived from **72**. These phosphoranes, with the exception of the doubly stabilised ylide **45e**, were exceedingly basic and did not exhibit enough nucleophilic character to participate in the Michael addition to γ-hydroxyenone **70**. Doubly stabilised ylide **45e**, when heated to reflux in benzene only induced isomerisation of **64** to **70** (Entry 8). No further reaction was observed. On the other hand, the reaction of the aldehyde and the methyl ketone ylides **45b** and **45c** resulted in high yields of the other 1,2-dihydronaphtho[2,1-*b*]furans **65b** and **65c** (Entries 4 and 5). Interestingly, the reaction of the aldehyde ylide **45c** was quite clean and only small amounts of multiple adducts were detected. It has been reported that an enhancement in reactivity of α-hydroxy ketones towards stabilised phosphorus ylides occurs and

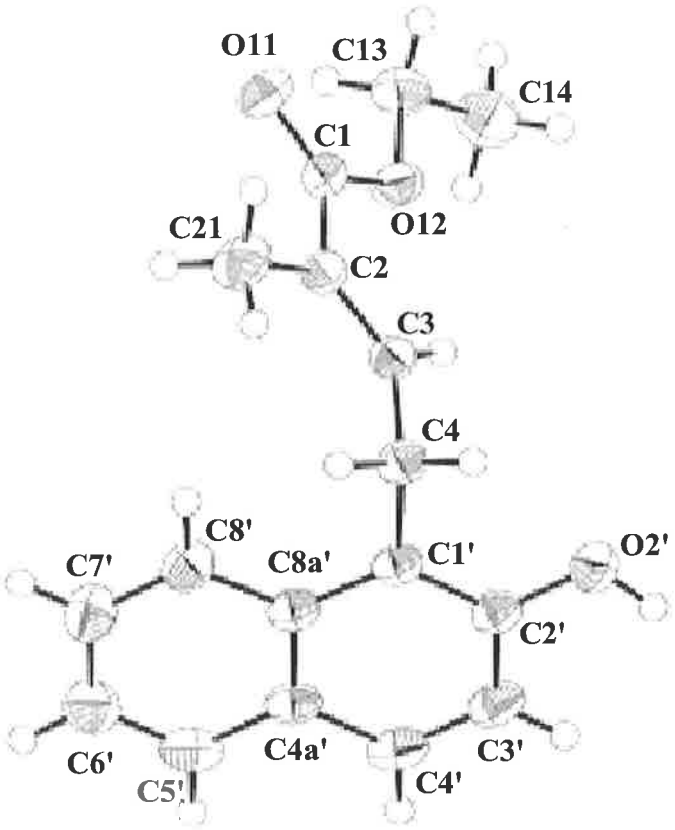
perhaps this suggests that the hydroxyl group of rearranged intermediate **72** plays a role in activating the carbonyl towards attack.[82] ^{1}H NMR data for **65b** and **65c** were analogous to that of **65a**, each with the presence of two sets of geminal protons bridged by a downfield resonance, δ 5.38 and 5.43 ppm for **65b** and **65c** respectively. It was possible to obtain an X-ray structure of **65b** (**Figure 2.3**). The tricyclic skeleton was essentially planar and the substituent was at right angles to the plane of the tricycle as expected.

Figure 2.3 *ORTEP diagram of* **65b**.



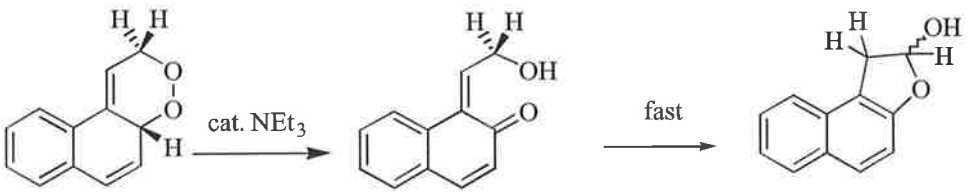
The reaction of **64** with **45d** resulted in no furan products, but afforded a clean reaction giving alkenes ***E*-66d** and ***Z*-66d**. **Figure 2.4** represents the ORTEP of ***E*-66d,** clearly showing the *trans* stereochemistry of the tertiary alkene. This could not be determined by ^{1}H NMR coupling. Some interesting spectroscopic patterns emerged between the *cis* and *trans* isomers and are discussed later in Chapter 2. It is noteworthy that the hydrogen of the hydroxyl moiety points away from the α,β-unsaturated ester in the solid state.

Figure 2.4 *ORTEP diagram of* ***E*-66d**.



In an attempt to reconfirm the identity of the base catalysed product **72**, a dichloromethane solution of **64** was treated with catalytic triethylamine (**Scheme 2.6**). The reaction was also monitored by ^{1}H NMR and was so fast that it was not possible to detect the presence of γ-hydroxyenone intermediate **70**. Presumably, the rate limiting step was the ring opening of the dioxine **64**.

Scheme 2.6

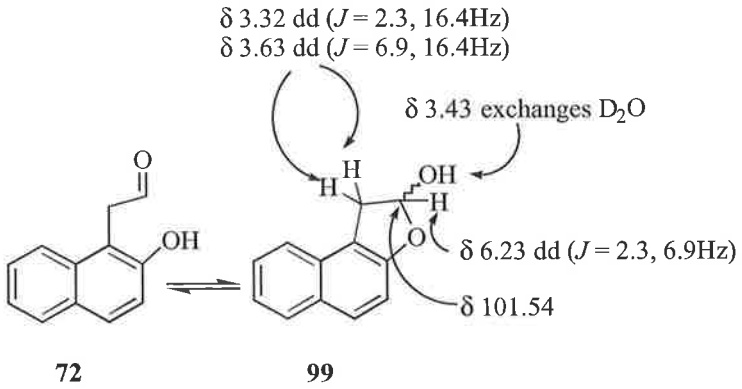


64 **70** **99** (95%)

Aldehyde **72** was isolated by chromatography using florisil as an adsorbent. The aldehyde (**Figure 2.5**) existed in solution entirely in the hemiacetal form **99** with no evidence of a carbonyl in either the ^{13}C NMR or the IR spectrum. The only informative peaks in the IR spectrum were a strong O-H stretching at 3462 cm^{-1} and aromatic peaks

at 1633 to 1518 cm^{-1}. The ^1H NMR showed a characteristic AB quartet at δ 3.32 to 3.63 ppm indicative of the furan methylene adjacent to a chiral centre coupled to a signal downfield at δ 6.23 ppm assigned as the CH proton of the hemiacetal. Also present was a singlet at δ 3.43 ppm, which underwent exchange with D_2O.

Figure 2.5 *Some NMR data of* **99**.



The hemiacetal **99** was a stable crystalline compound and likewise, could be treated with the same series of phosphoranes to afford product series **66** and **65** as observed in the reactions of **64**. The results of these reactions are summarised in **Table 2.4**.

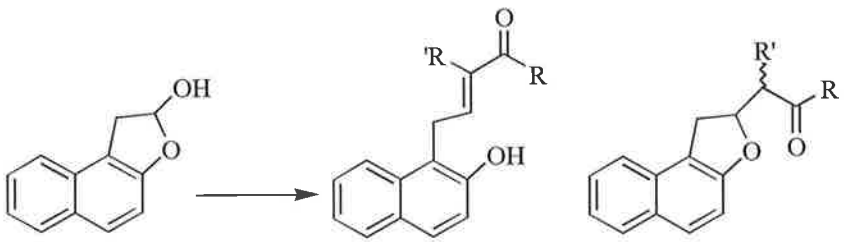


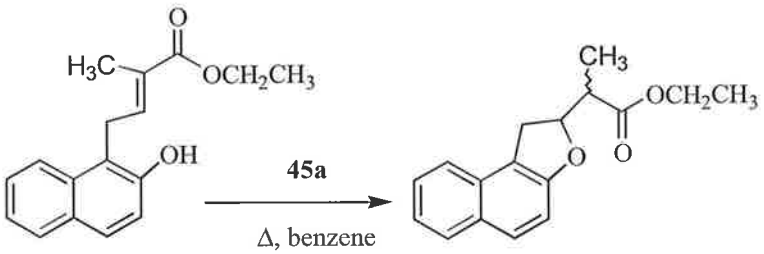
Table 2.4 *Reactions of* **72/99** *with stabilised ylides* **45a-45e**.

Entry	Ylide	Temperature °C	Time	Products (%)
1	**45a**	RT	30 minutes	***E*-66a** (75) ***Z*-66a**(17)
2	**45a**	60	24 hours	**65a** (90)
3	**45b**	RT	2 hours	**65b** (93)
4	**45c**	RT	2 hours	**65c** (79)
5	**45d**	RT	30 minutes	***E*-66d** (88) ***Z*-66d** (9)
6	**45d**	60	24 hours	***E*-66d** (88) ***Z*-66d** (9)
7	**45d**	80	24 hours	***E*-66d** (88) ***Z*-66d** (9)
8	**45e**	RT	30 minutes	no reaction
9	**45e**	80	96 hours	no reaction

The reaction of **99** at room temperature with one mole equivalent of **45a** (Entry 1) gave only the alkene **66a** seen previously. Only cyclic **65a** was observed when **99** was heated with an excess of **45a** (Entry 2). In the reactions of ylides **45b** to **45d** with **99** (Entries 3,4 and 5), the same products were obtained in similar yields as seen with dioxine **64**. Again, the aldehyde ylide **45c** led to a clean reaction giving a mono adduct. In all conditions examined, the reaction of **45d** with hemiacetal **99** afforded the identical products observed previously (Entries 5, 6 and 7) and in the case of Entry 7, the cyclisation to afford **65d**, did not occur. Phosphorane **45e** again failed to undergo any reaction, even when subjected to reflux in benzene for several days (Entry 9).

It was shown that ***E*-66d** could be cyclised when heated in the presence of methyl ester phosphorane **45a** to furnish **65d** as a mixture of isomers (**Scheme 2.7**). Some selectivity was observed in the cyclisation as a 36 : 64 mixture of diastereomers was obtained. It was thought that thermal instability of **45d** was the reason why **65d** did not form (Entries 6 and 7). These diastereomers could be separated by chromatography, however, due to freedom of bond rotation and almost identical spectroscopic data, it was not possible to assign the relative stereochemistry of these diastereomers. Both isomers exhibited similar characteristic ^{1}H NMR data as the simpler **65a** with the presence of the characteristic AB quartet representing the protons on the heterocycle along with a downfield resonance for the proton adjacent to the furan at δ 5.21 (major isomer) and 5.15 ppm (minor isomer).

Scheme 2.7



***E*-66d** **65d** (74%, 27%*de*)

2.3. THE REACTIONS OF 1,2-DIOXINE 75 WITH STABILISED PHOSPHORANES.

A more extensive investigation was carried using methyl substituted 1,2-dioxine **75**, the results of which are summarised in **Scheme 2.8** and **Table 2.5**. The ethyl substituted system in Haselgroves work had resulted in the formation of four 1,2-

dihydronaphtho[2-1-*b*]furan isomers. It was of interest to confirm the assignment of these products with a simpler system (methyl substitution) and to see whether it is possible to influence product ratios by varying the conditions as observed in the previous system. It was also of interest to examine the effects of lithium bromide and to determine whether the regioisomeric 1,2-dihydronaphtho[2,1-*b*]furans **68a** and **69a** seen in Haselgroves preliminary investigation have the same mechanistic origins as the lithium bromide induced cyclopropane series.[74,83]

Scheme 2.8

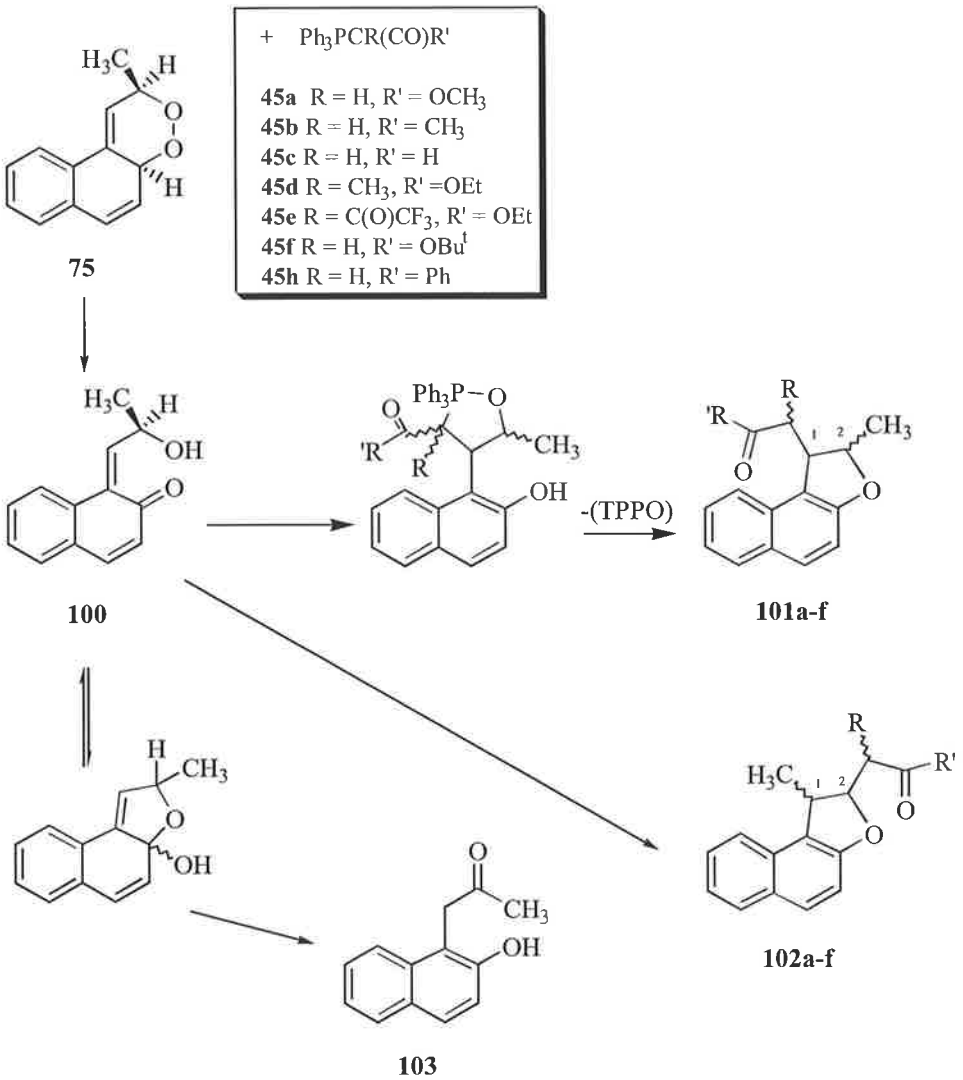


Table 2.5 *Reactions of* **75** *with stabilised ylides* **45a-45f**.

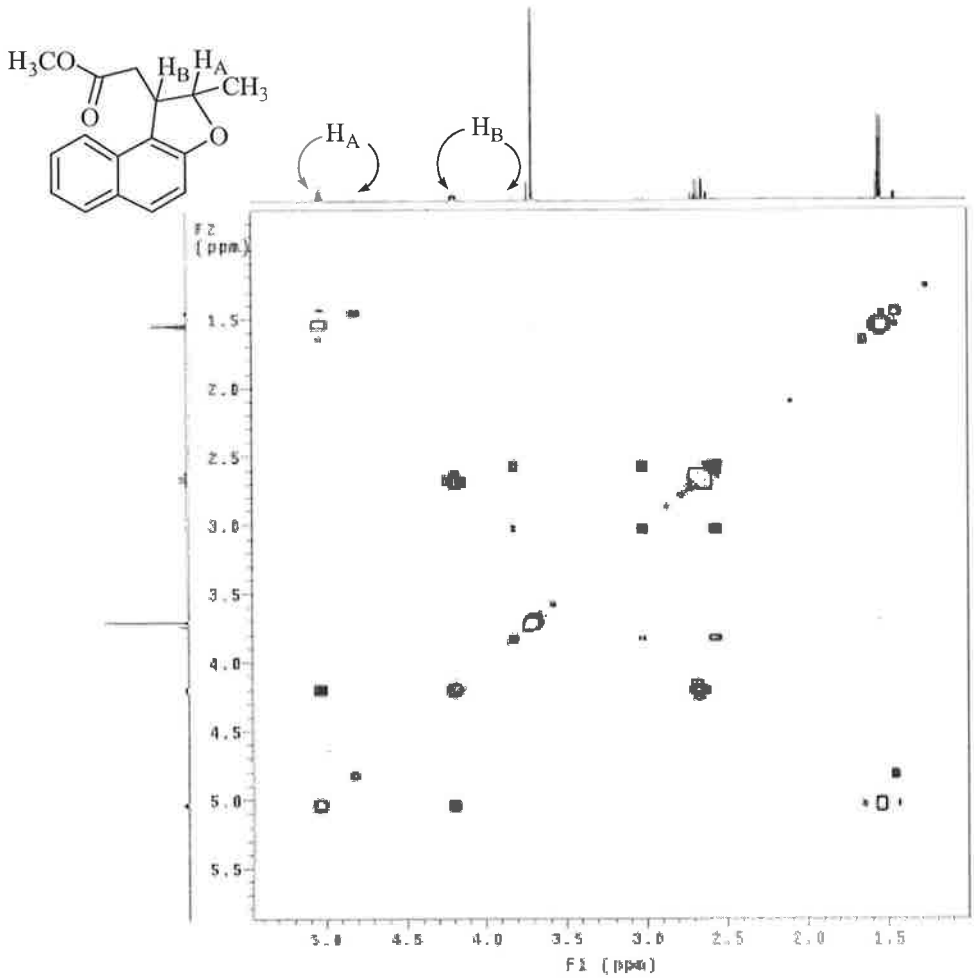
Entry	Ylide (Equiv.)	Conditions	Time	Products (%)
1	**45a**		72 hours	***E*-101a** (3) ***Z*-101a** (62) ***E*-102a** (11) ***Z*-102a** (8)
2	**45a** (2)		72 hours	***E*-101a** (4) ***Z*-101a** (66) ***E*-102a** (13) ***Z*-102a** (9)
3	**45a** (4)		72 hours	***E*-101a** (5) ***Z*-101a** (69) ***E*-102a** (15) ***Z*-102a** (10)

4	**45a** (4)	60 °C	72 hours	***E*-101a** (5) ***Z*-101a** (39) ***E*-102a** (12) ***Z*-102a** (7)
5	**45a**	LiBr	12 hours	***E*-101a** (44) ***Z*-101a** (10) ***E*-102a** (11) ***Z*-102a** (11)
6	**45b**		10 minutes	**103/104** (100)
7	**45c**		10 minutes	**103/104** (100)
8	**45e**	60 °C	24 hours	no reaction
9	**45f** (4)	60 °C	72 hours	***E*-101f** (10) ***Z*-101f** (37) ***E*-102f** (10) ***Z*-102f** (5)
10	**45f** (4)		72 hours	***E*-101f** (8) ***Z*-101f** (51) ***E*-102f** (24) ***Z*-102f** (7)
11	**45f** (4)	LiBr	12 hours	***E*-101f** (34) ***Z*-101f** (29) ***E*-102f** (24) ***Z*-102f** (17)

In the reactions of ester containing phosphoranes **45a** and **45f** (Entries 1, 2, 3 and 8, 9, 10) with dioxine **75**, the major product was identified as the 1,2-dihydronaphtho[2,1-*b*]furans ***Z*-101a** and ***Z*-101f** respectively (**Scheme 2.8**). These products were formed with high diastereoselectivity in agreeance with Haselgrove.[77] Diastereoselectivity favoured the *E* isomers ***E*-101a** and ***E*-101f** when the reaction was carried out in the presence of lithium bromide (Entries 5 and 11 respectively). Another regioisomeric series ***E/Z*-102a** and ***E/Z*-102f** was also identified in which the position of the substituents at C1 and C2 were inverted, analogous to that found in Haselgroves work. As with the reaction of **64**, the ketone and aldehyde phosphoranes **45b** and **45c** were too basic and thus resulted in the aromatised product **103** via the Kornblum-DeLaMare intermediate **100**. The ketone **103** existed in equilibrium with its hemiacetal form **104**, in a 2:1 ratio in $CDCl_3$ as reported in the literature.[84] In summary, as observed with **64** only the phosphoranes bearing ester functionality were compatible for the Michael addition in this system. An interesting feature of these reactions was that the bulkiness of the phosphorane **45f** did not have any significant influencing effect on the product ratios in comparison to **97a**. These types of reactions can sometimes be sensitive to the bulkiness of the phosphoranes substituents.[74]

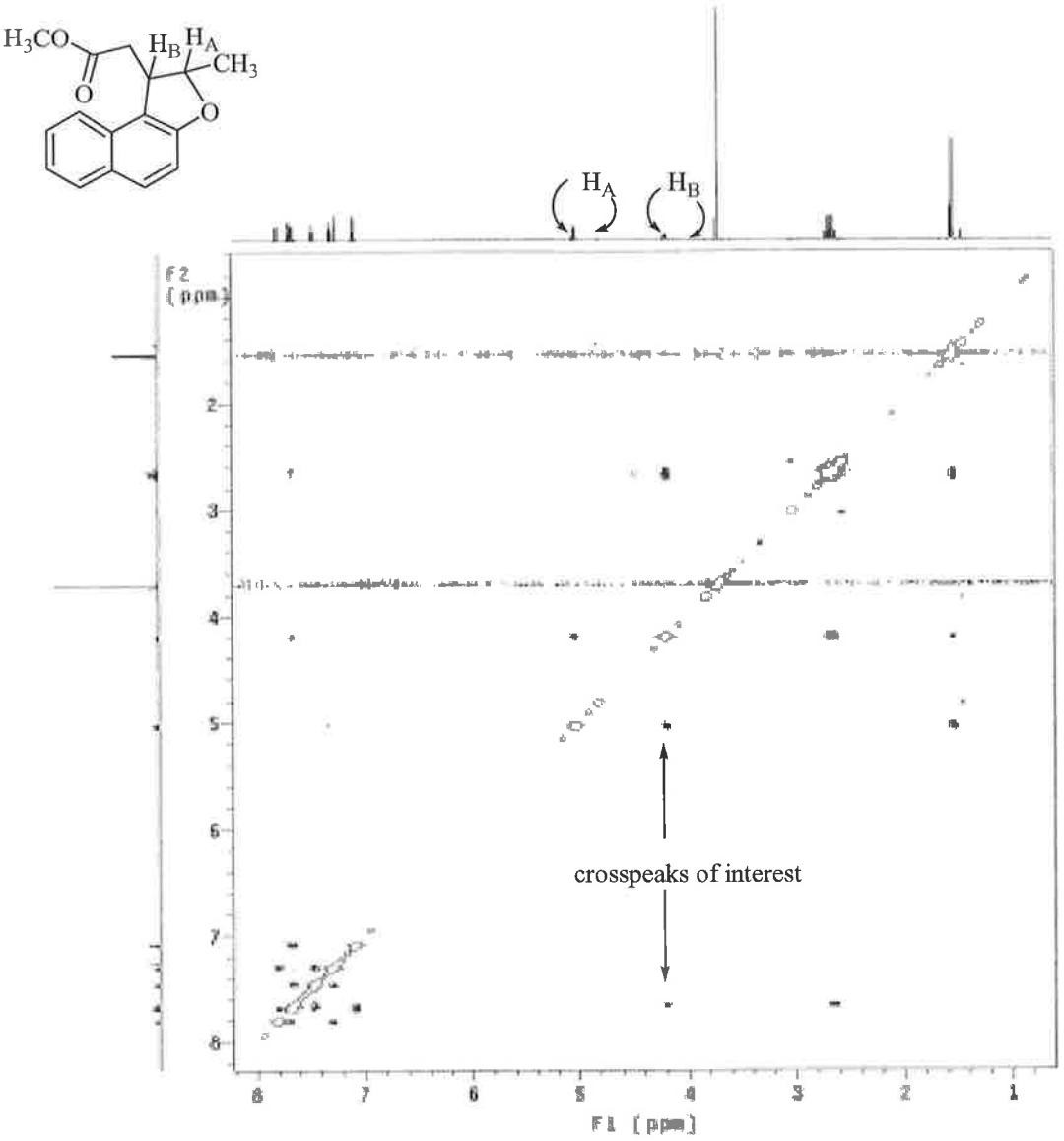
The structural connectivity of ***E*-101a** and ***Z*-101a** could be clearly seen in the COSY spectrum (**Figure 2.6**). It can be seen for both diastereomers that the methyl is adjacent to the downfield resonance assigned to the proton (H_A) adjacent to the oxygen of the furan ring. In addition, as observed in **97a**, the AB quartet representing the diastereotopic pair adjacent to the ester couples to the upfield proton (H_B) of the furan ring at C1.

Figure 2.6 *COSY spectrum of* ***E/Z*****-101a**.



The assignment of the stereochemistry was based on the analysis of the two isomers by 2D ROESY NMR (**Figure 2.7**). It can be seen that H_A (adjacent to furan oxygen) of the *cis* isomer shows strong through space interactions with the adjacent H_B of the furan moiety. A crosspeak between the methylene group within the side chain and the methyl group was also detected. However, H_A (adjacent to the furan oxygen) of the *trans* isomer displayed neither of these characteristic crosspeaks. Furthermore, the observed $^3J_{AB}$ coupling of 7.0 Hz for the *cis* isomer is greater than that found for the *trans* isomer $^3J_{AB}$ 2.6 Hz and is consistent with the trends cited in the literature.[85] An observable crosspeak was also detectable between H_B and the *peri* proton, thus supporting the assignment of the regioisomer and reconfirming the relative arrangement of the sp^3 carbon skeleton.

Figure 2.7 *ROESY spectrum of* ***E/Z*-101a**.



For the opposite regioisomer ***E/Z*-102a**, it was possible to establish connectivity by COSY experiment (**Figure 2.8**). In this case, it is now H_B which shows a correlation to the methyl group. The opposite also held true for the downfield signals as H_A now coupled to methylene group of the side chain. Both diastereomers gave a ROESY crosspeak for the methyl group with the *peri* proton in the aromatic system. The stereochemistry was confirmed as in the ROESY spectrum of ***E*-102a**, H_A exhibited a strong correlation to H_B. The coupling constants $^3J_{AB}$ for **102a** also followed the literature trend. This trend also extended to products ***E/Z*-101f** and ***E/Z*-102f** as summarized in **Table 2.6** where the *cis* coupling constant was approximately twice the *trans* coupling constant. Of note, the chemical shift for H_A was consistently observed at δ 5.0 ppm for all furan isomers.

Figure 2.8 *COSY spectrum of* ***E/Z*****-102a**.

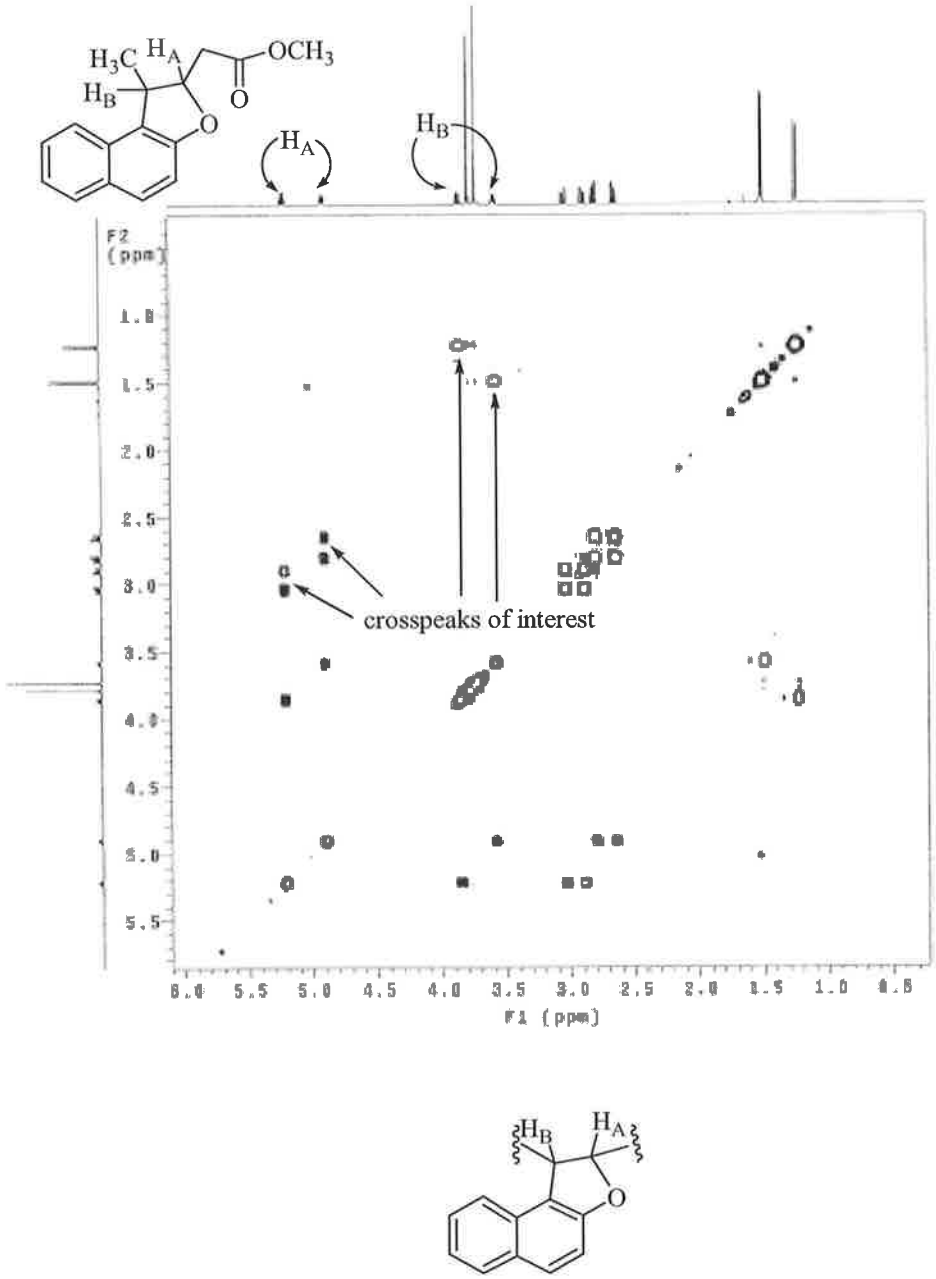


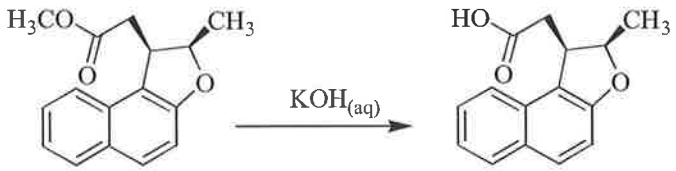
Table 2.6 *Coupling constants in the dihydronaphtho[2,1-b]furans* ***E/Z*****-101a/f** *and* ***E/Z*****-102a/f**.

Product	δ H_A	δ H_B	J_{AB} Hz
***E*-101a**	4.81	3.82	2.6
***Z*-101a**	5.03	4.20	7.0
***E*-102a**	4.90	3.58	3.5
***Z*-102a**	5.21	3.86	6.9
***E*-101f**	4.84	3.78	2.7
***Z*-101f**	5.03	4.16	6.6

***E*-102f**	4.84	3.61	3.5
***Z*-102f**	5.17	3.86	7.3

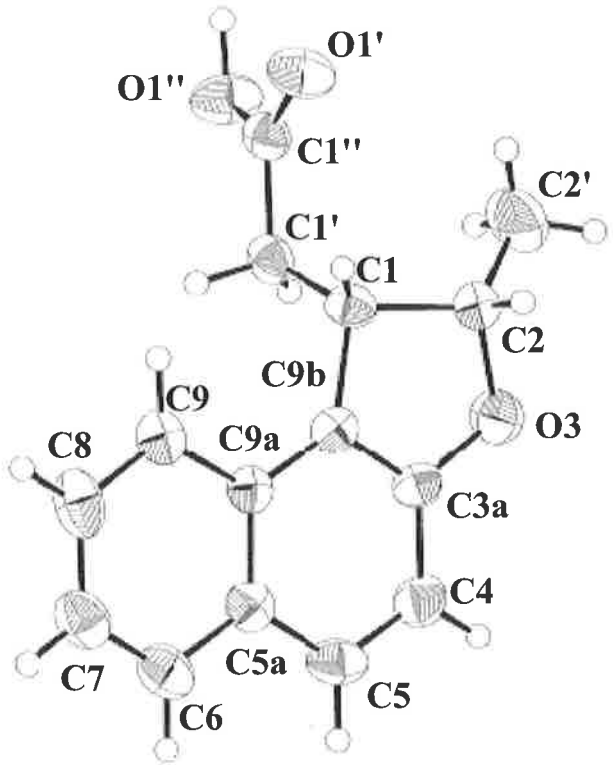
The identity and stereochemistry of the major product *Z*-**101a** from Entries 1 to 3 was reconfirmed by the synthesis of the acid derivative *Z*-**105** (**Scheme 2.9**) and the X-ray structure obtained (**Figure 2.10**). Although the preparation involved the hydrolysis of the mixture, it was possible to fractionally crystallise the *cis* isomer by thrice crystallising from chloroform and hexane. In the solid state, *Z*-**105** existed as a dimer with Hydrogen bonding between the carboxylic acids.

Scheme 2.9



***Z*-101a** ***Z*-105** (66%)

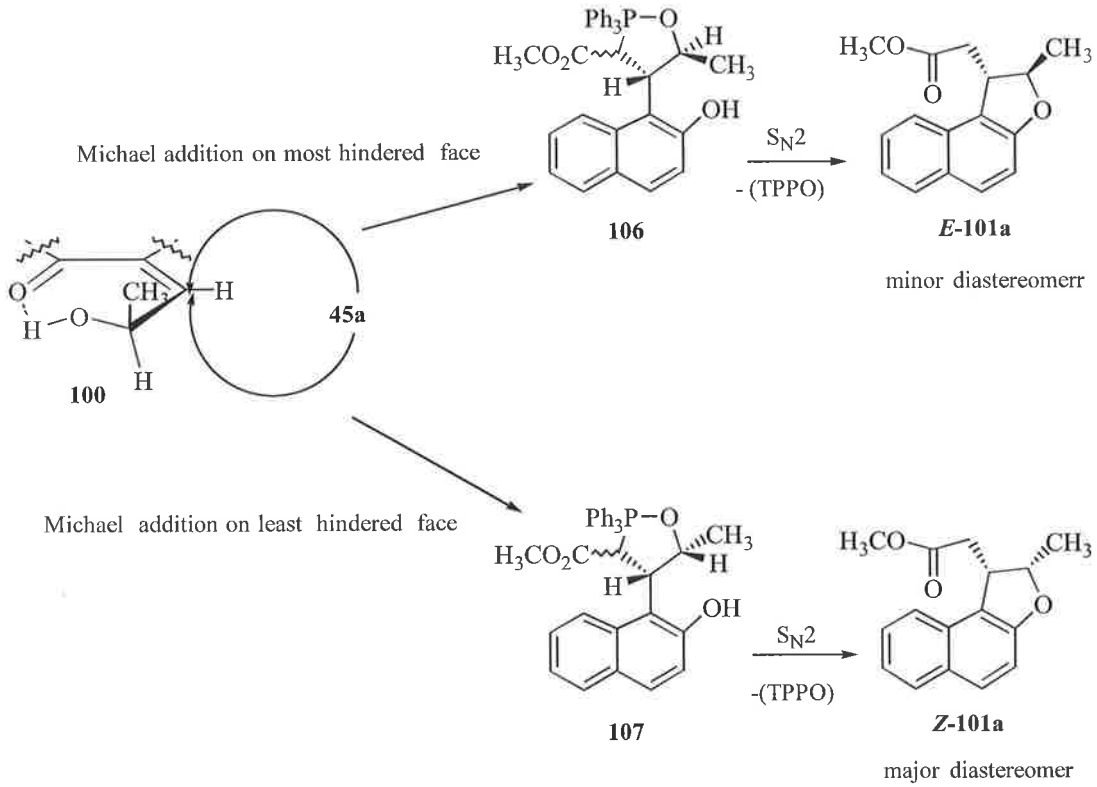
Figure 2.10 *ORTEP Diagram of* ***Z*-105**.



A plausible mechanism for the formation of ***Z*-101a** and ***E*-101f** is as follows (**Scheme 2.11**). It is proposed that once the Kornblum-DeLaMare reaction has taken

place, an intramolecular Hydrogen bond exists between the hydroxyl and carbonyl moieties, thus holding the hydroxyl group within the plane of the naphtho-skeleton. At this point it is now possible for the phosphorane **45a** or **45f** to undergo 1,4-addition from two inequivalent faces. One face bears the sterically hindered methyl substituent and one face bears a hydrogen atom. Therefore, attack predominates upon the face bearing the hydrogen. The resulting aromatised oxaphosphelane intermediate **107** undergoes an S_N2 reaction that expels TPPO and ensures that the relative stereochemistry is preserved. The minor isomer with the *trans* stereochemistry arises from intermediate **106**.

Scheme 2.11



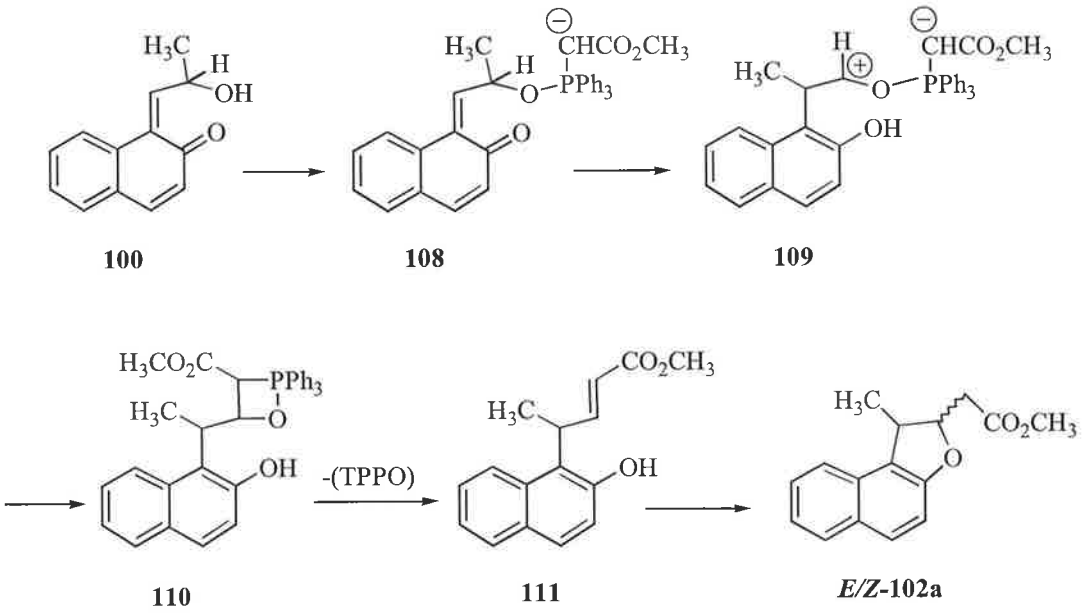
The mechanistic rationale for the effect of lithium bromide favouring the *trans* dihydronaphtho[2,1-*b*]furan ***E*-101a/f** probably does not parallel the mechanistic observance as seen with the cyclopropane reaction. It has been reported that the equilibrium conformation of the zwitterion ylide is affected by lithium bromide.[75] In the presence of lithium bromide the equilibrium lies with the ylide preferring *trans* stereochemistry about the enolate partial double bond. An increased rate of reaction was seen in the presence of lithium bromide with reaction times reduced from three days to 12 hours. This held true for reactions with **75**, as the reactions were completed in less than a day, compared to several days in the absence of lithium bromide. The bulkier *t*-butyl ester ylide **45f**, which had been shown to alter the reaction pathway in

the cyclopropanation manifold, especially in conjunction with lithium bromide, did not give any observable difference as compared to the reaction of **75** with non-bulky **45a**.

The effect of lithium bromide may be to direct the initial Michael addition, as this was where the stereochemistry was thought to have been set up. As with the cyclopropane reactions, once the Michael addition had occurred, it was not possible for epimerisation to occur, due to the fixture of the two stereo centres relative to one another. One could also speculate that the bromide has a competitive role in the displacement of TPPO, which could be followed by the intramolecular attack by the alkoxide to afford, by double inversion, the *trans* isomer. Further investigations are required to determine this mechanism.

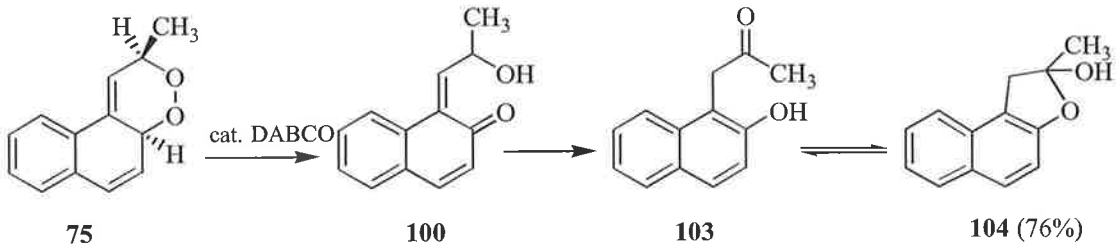
A plausible mechanism to describe the formation of the opposite regioisomeric series **102a** and **102f** involves a cationic rearrangement, whereby an initial complexation of the phosphorus to the hydroxyl moiety of the γ-hydroxyenone **100** occurs to give **108 (Scheme 2.12)**. A methyl migration occurs with the driving force for the reaction being the aromatisation of the naphthalene forming **109**. A stabilised cation adjacent to the oxygen is free to form an oxaphosphetane **110**, which degrades losing TPPO identical to a Wittig reaction. The resulting α,β-unsaturated ester **111** then undergoes an intramolecular Michael addition to afford the opposite regioisomer ***E/Z*-102a/f**. The Michael addition itself displayed some stereoselectivity resulting in the slight diastereomeric excess of the *trans* dihydronaphtho[2,1-*b*]furan **102a/f**. Whilst this proposed reaction pathway gave the correct products a 1,2-hydride shift could give rise to a more stable tertiary carbocationic intermediate over the secondry described. This mechanism indeed needs further investigation, perhaps being concerted in nature.

Scheme 2.12



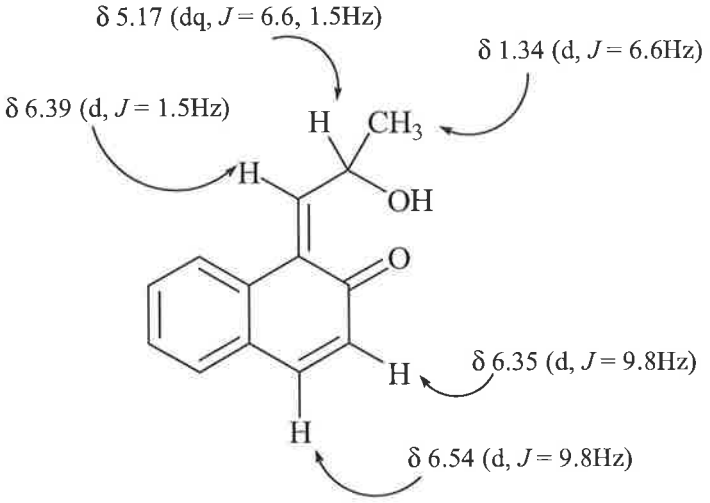
As observed with the reaction of the basic ylides **45b** and **45d** with **75**, a base catalysed degradation via the γ-hydroxyenone **100** reaction could be efficiently induced by the treatment of a dichloromethane solution of the dioxine **75** with a catalytic amount of DABCO to afford the mixture of **103** in equilibrium with hemiacetal **104** (**Scheme 2.13**).

Scheme 2.13

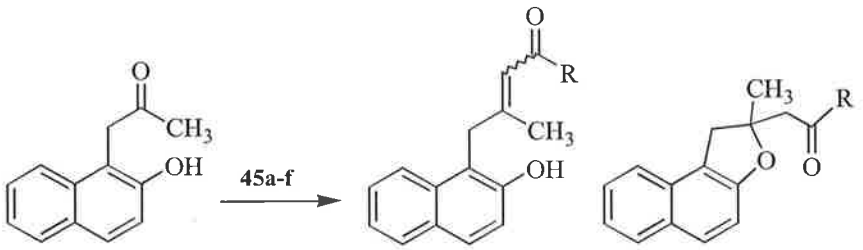


It was possible to detect and characterise the γ-hydroxyenone intermediate **100** when the reaction was carried out on an NMR scale on the 600 MHz spectrometer (**Figure 2.13**). Unfortunately, as the lifetime of this intermediate was in the order of minutes it was not possible to obtain any other data.

Figure 2.13 *^{1}H NMR assignment of* **100**.



As reported in the literature,[86] the base rearranged product **103** actually existed as an equilibrium with hemiacetal form **104**. Interestingly, it was possible to shift the equilibrium exclusively to the open form upon the addition of a small amount of DABCO to the $CDCl_3$ solution. The preparation of the aromatised products **103/104** gave an opportunity to generate a third regioisomeric series of 1,2-dihydronaphtho[2,1-*b*]furans. The reactions of **103/104** with stabilised phosphorus ylides **45a,b,c,f** afforded a new series of 1,2-dihydronaphtho[2,1-*b*]furans **112a-f** (**Table 2.7**).



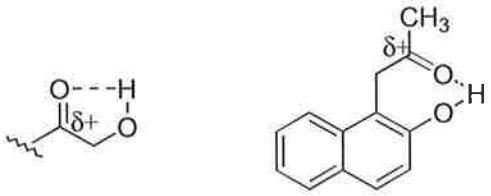
103/104 ***E/Z*-112a-f** **113a-f**

Table 2.7 *Reaction of* **103/104** *with stabilised ylides.*

Entry	Ylide (Equiv.)	Temperature °C	Time	Products (%)
1	**45a**	RT	1 hour	***E*-112a** (45) ***Z*-112a** (21)
			48 hours	***E*-112a** (59) ***Z*-112a** (31)
2	**45a** (2)	60	24 hours	**113a** (94)
3	**45b**	60	24 hours	**113b** (50)
4	**45c**	60	24 hours	Complex mixture
5	**45e**	60	24 hours	No reaction
6	**45f** (2)	60	24 hours	***E*-112f** (50) ***Z*-112f** (38)
				113f (7)

The Wittig reaction of **103/104** with **45a** (Entry 1) proceeded quite rapidly at room temperature. The rate of reaction was fast considering that elevated temperatures and sometimes pressure are required to accomplish the reaction of a ketone with a stabilised phosphorane.[87-89] The presence of the hydroxyl group was thought to be of assistance in enhancing the reactivity of the carbonyl. There is literature precedence for this effect described for the high reactivity of α-hydroxyketones.[82] Mechanistically this involves intramolecular hydrogen bonding polarising the carbonyl toward nucleophilic attack (**Figure 2.14**). The elevated reactivity was comparable to what was observed with the selective reaction of the aldehyde phosphorane **45c** with parent hemiacetal **99**.

Figure 2.14



The formation of the cyclised product **113a-f** could be achieved upon heating **103/104** in the presence of excess **45a** (Entry 2). The reaction of ylide **45b** (Entry 3) was sluggish in affording furan **113b** and no sign of any intermediate alkene **112b** was detected. The reaction of **103/104** with phosphorane **45c** gave an inseparable multi-component mixture (Entry 4), the reaction only occurring when refluxed in chloroform. Presumably, multiple addition of phosphorane to the aldehyde product **113c** occurred.

As ***E*** and ***Z*-66a** were 1,2-disubstituted alkenes, stereochemical assignment was possible by measuring the vicinal alkene coupling constants in the ^{1}H NMR. The stereochemistry of the uncyclised alkene products ***E/Z*-112a** and ***E/Z*-112f** could not be assigned upon the basis of coupling constant, but exhibited similar data to that of ***E/Z*-66a**. **Table 2.8** contains a summary of some of the characteristic data found for these products. The ^{1}H NMR chemical shift of the hydroxyl proton was consistently dependent upon the stereochemistry of the product. The chemical shifts for the *cis* alkenes typically featured between δ 8 to 9 ppm whilst for the *trans* alkenes the hydroxyl appeared between δ 5 to 6 ppm. The Wittig reaction of aldehydes with stabilised phosphorus ylides favour the *trans* isomer.[90] The ratio of the alkene products ***E/Z*-112a** and ***E/Z*-112a** agree with the forementioned phenomenon. The significant spectroscopic differences may be a result of intramolecular hydrogen bonding between the hydroxyl and the ester group. This effect could also explain the lowering of the

stretching observed in the IR spectrum for the C=O by some 30 cm^{-1} than the expected value for the ester. Of note, the crystal structure of *E*-**66d** gave no indication that this hydrogen bonding was present in the solid state.

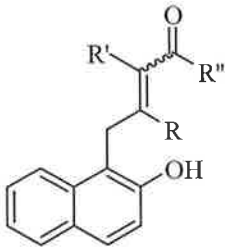


Table 2.8 *Some spectral data for some alkenes.*

Compound	δ (O-**H**)	δ (-CH_2-)	δ =C**H**	IR (C=O)	IR (O-H)
***E*-66a**	6.18	3.95	5.76, 7.23	1680	3300
***Z*-66a**	8.47	4.31	5.89, 6.54	1695	3327
***E*-66d**	5.17	3.94	6.80	1674	3390
***Z*-66d**	8.83	4.15	6.18	1685	3294
***E*-112a**	5.05	3.91	5.43	1714	3405
***Z*-112a**	8.67	4.33	5.85	1689	3290
***E*-112f**	5.39	3.87	5.32	1676	3263
***Z*-112f**	9.10	4.28	5.76	1675	3257

The third 1,2-dihydronaphtho[2,1-*b*]furan regioisomer series of **113a**, **113b**, and **113f** were easily identified by spectroscopic techniques. The ^{1}H NMR of **113a,b,f** all indicated two sets of isolated AB quartets for the protons. The AB quartets represented the methylene adjacent to the carbonyl moiety and the methylene of the furan at C1. These compounds also exhibited a definitive weak quaternary ^{13}C NMR signal at about δ 90 ppm for C2. The data is summarised in **Table 2.9**.

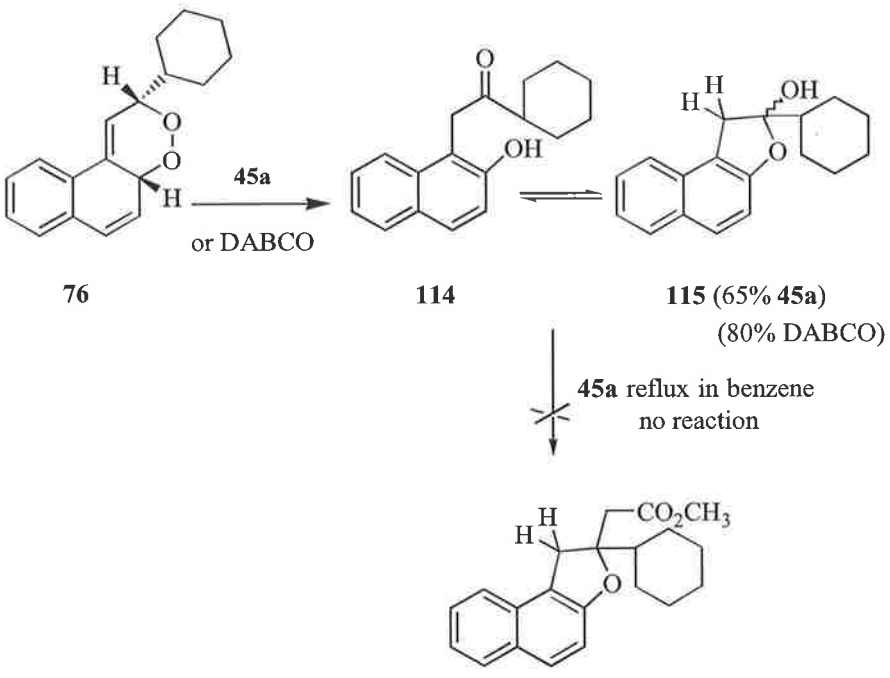
Table 2.9 *Characteristic ^{1}H NMR and ^{13}C NMR for* **113a-f.**

Product	δ H_a/H_b (J_{ab})	δ H_c/H_d (J_{cd})	δ C2
113a	3.29 and 3.60 (15.0Hz)	2.83 and 2.85 (15.6Hz)	86.90
113b	3.35 and 3.47 (15.6Hz)	2.98 and 3.02 (15.6Hz)	87.38
113f	3.29 and 3.69 (15.6Hz)	2.73 and 2.80 (14.4Hz)	87.21

2.4. A BRIEF INVESTIGATION INTO THE REACTIVITY OF 1,2-DIOXINE 76.

A brief investigation was made into the chemistry of the cyclohexyl dioxine **76**. In the reaction of **76** with **45a**, unlike the previous two systems studied, no such Michael addition occurred resulting in the base catalysed isomerisation to product **114** after seven days (**Scheme 2.13**). As substrate **76** and its corresponding intermediate γ-hydroxyenone were electronically similar to **75**, the reasons behind the lack of reactivity lay with steric bulk of the cyclohexyl group preventing the Michael addition before further base isomerisation could occur giving **114/115**. As seen with **102/103**, **114/115** existed in solution as an equilibrium of open chain **114** and hemiacetal **115** in a ratio of 1 : 1. As exhibited with **104**, hemiacetal **115** contained an AB quartet in the ^{1}H NMR at δ 3.26 and 3.53 ppm (J = 16.8 Hz). **114/115** was also obtained in good yield from the base catalysed degradation of **76** by catalytic DABCO. Treatment of **114/115** with excess **45a** under reflux in benzene did not result in the formation of 1,2-dihydronaphtho[2,1-*b*]furan **116** (**Scheme 2.13**). These conditions resulted in the recovery of the unreacted starting material **114/115**.

Scheme 2.13

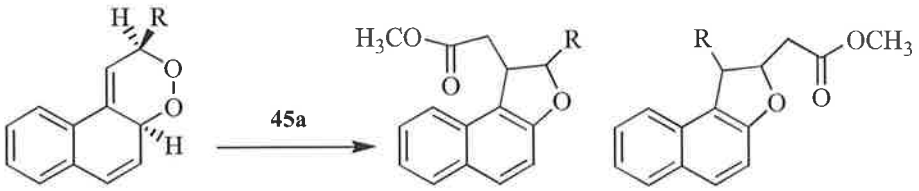


76 **114** **115** (65% **45a**) (80% DABCO)

116

2.5. REACTIONS OF 1,2-DIOXINES 77 TO 80 WITH PHOSPHORANE 45a.

A series of phenyl substituted dioxines **77** to **80** were reacted with **45a** under a variety of conditions. The results of these reactions are summarised in **Table 2.10**. This included reactions of phosphorane **45a** with electron donating 4-methoxyphenyl substituted dioxine **79** and electron withdrawing 4-trifluoromethyl substituted dioxine **80**.



77 R = Ph	***E/Z*-117a**	***E/Z*-118a**
78 R = 4-Cl-Ph	***E/Z*-119a**	***E/Z*-120a**
79 R = 4-MeO-Ph	***E/Z*-121a**	***E/Z*-122a**
80 R = 4-CF_3-Ph	***E/Z*-123a**	***E/Z*-124a**

Table 2.10 *Reactions of Dioxines* **77-80** *with stabilised ylide* **45a**.

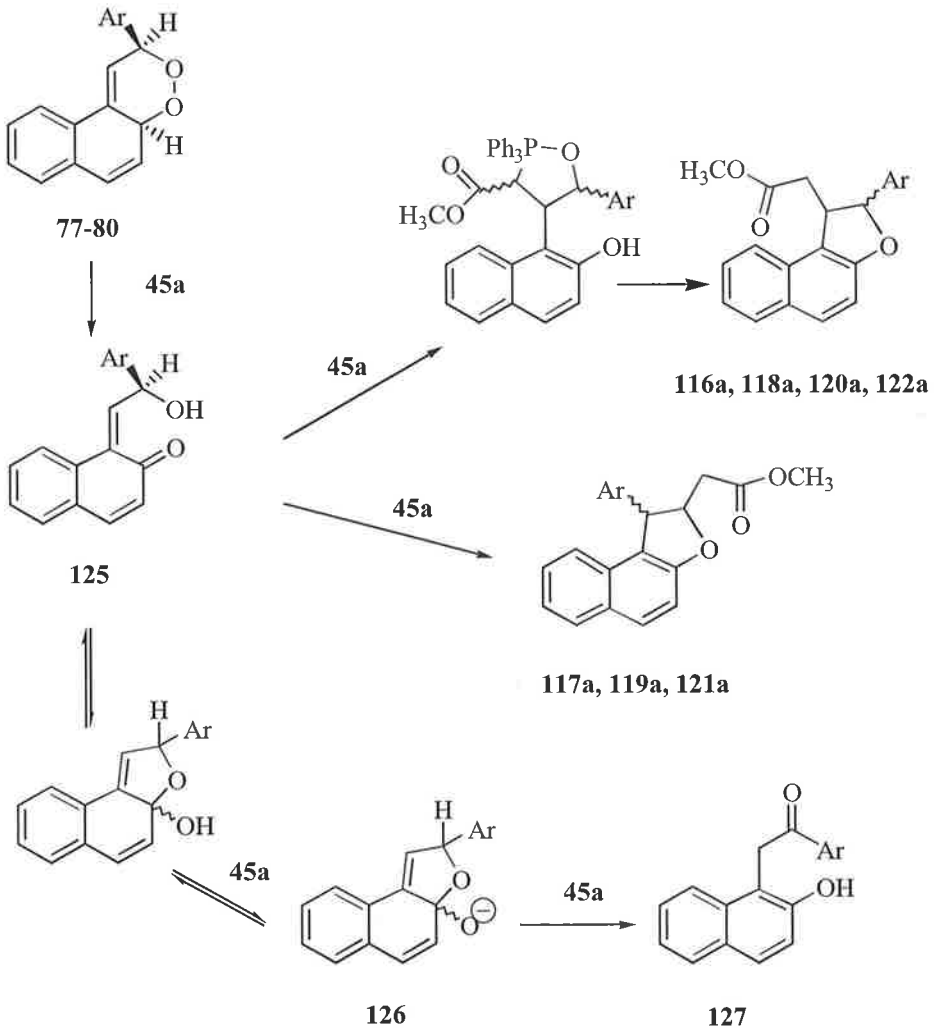
Entry	Dioxine	Equiv.Ylide **45a**	Time	Products (%)
1	**77**		6 days	***E*-117a** (-) ***Z*-117a** (30) ***E*-118a** (17) ***Z*-118a** (5)
2	**77**	4	6 days	***E*-117a** (-) ***Z*-117a** (31) ***E*-118a** (18) ***Z*-118a** (5)
3	**77**	2 + LiBr	1 day	***E*-117a** (8) ***Z*-117a** (6) ***E*-118a** (24) ***Z*-118a** (15)
4	**78**		6 days	***E*-119a** (2) ***Z*-119a** (13) ***E*-120a** (10) ***Z*-120a** (4)
5	**78**	4	6 days	***E*-119a** (1) ***Z*-119a** (11) ***E*-120a** (7) ***Z*-120a** (2)
6	**78**	2 + LiBr	1 day	***E*-119a** (8) ***Z*-119a** (3) ***E*-120a** (12) ***Z*-120a** (8)
7	**79**		6 days	***E*-121a** (4) ***Z*-121a** (10) ***E*-122a** (20) ***Z*-122a** (8)
8	**79**	4	6 days	***E*-121a** (5) ***Z*-121a** (10) ***E*-122a** (24) ***Z*-122a** (7)
9	**79**	2 + LiBr	1 day	***E*-121a** (19) ***Z*-121a** (3) ***E*-122a** (12) ***Z*-122a** (8)
10	**80**		6 days	***E*-123a** (-) ***Z*-123a** (10) ***E*-124a** (-) ***Z*-124a** (-)
11	**80**	4	6 days	***E*-123a** (-) ***Z*-123a** (10) ***E*-124a** (-) ***Z*-124a** (-)

The reactions of these dioxines **77** to **80** afforded the desired 1,2-dihydronaphtho[2,1-*b*]furans, **117a**, **119a**, **121a** and **123a** but typically in low

conversion. As observed for the reaction of **75** with **45a**, the *Z* isomer was formed in high diastereomeric excess. Infact, for the reaction of dioxine **77**, ***E*-117a** could not be identified in the crude ^{1}H NMR (Entries 1 and 2). Regardless of the quantities of **45a** used in the reaction, product ratios were not influenced. It was only possible to detect ***E*-117a** when lithium bromide was an additive (Entry 3). The second regioisomeric 1,2-dihydronaphtho[2,1-*b*]furan series **118a**, **120a**, and **122a** were identified by analogy to the second regioisomer seen in the reactions of **75** with **45a** (**Scheme 2.7**).

Accompanying the formation of the 1,2-dihydronaphtho[2,1-*b*]furan products were the base rearranged phenyl ketones of the type **127** represented in **Scheme 2.14**. The phenyl ketones precipitated from solution as byproducts and with the exception of 4-trifluoromethylphenyl substituted ketone **128** (**Scheme 2.15**), did not participate in further reactions. In the case of the reaction of electron withdrawing trifluoromethyl substituted dioxine **80** with **45a**, only a very small percentage was converted to the desired ***Z*-123a** and the bulk of the product was derived from the base degradation to the 1-(β-keto)-2-naphthol. This shall be discussed shortly.

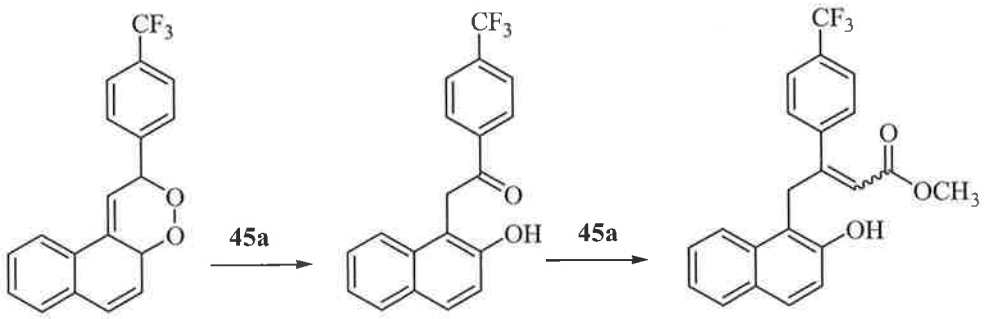
Scheme 2.14



There is an obvious relationship between the electron density on the carbon bearing the hydroxyl moiety and the rate at which the base catalysed degradation of the γ-hydroxyenone to the aromatised products occurs. As the electron density decreases at this site, the relative rate of base catalysed rearrangement increases. It is plausible that an electron withdrawing substituent upon the phenyl ring could favour the base promoted tautomerisation of **126** to aromatised product **127**. Comparatively, the reaction of **45a** with electron donating substituted dioxine **79** gave more furan products than was observed with electron withdrawing substituted dioxine **80**. Interestingly, the diastereoselectivity was very high for the Michael addition products irrespective of the quantities of ylide employed (Entries 1, 2, 4, 5, 7, 8, 10 and 11).

Only with the 4-trifluoromethanephenyl substituted system was there any evidence of the Wittig reaction taking place upon the 1-(β-keto)-2-naphthol **128**. This resulted in the formation of ***E/Z*-129a** (**Scheme 2.15**). In this case, the ketone was electron deficient enough to be attacked by the phosphorane at room temperature.

Scheme 2.15

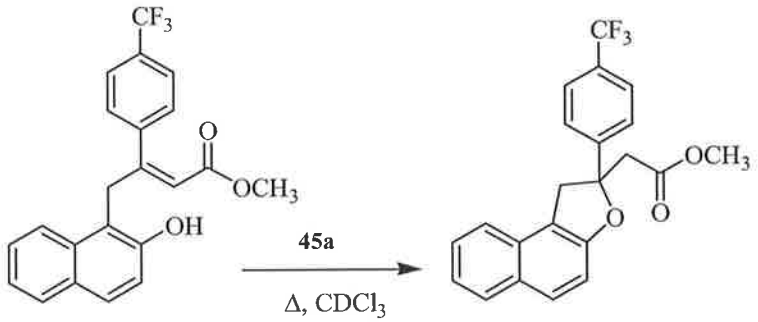


80 **128** ***Z*-129a** (22%) ***E*-129a** (15%) Entry 10

***Z*-129a** (49%) ***E*-129a** (26%) Entry 11

Alkene ***Z*-129a** could be cyclised upon treatment of excess ylide and heat to afford the 1,2-dihydronaphtho[2,1-*b*]furan **130a** in quantitative conversion (**Scheme 2.16**).

Scheme 2.16



***Z*-129a** **130a** quantitative

The use of lithium bromide in the reactions of **77** to **79** afforded the *trans* furans **117a**, **119a** and **121a** in good diastereomeric excess. In the case of the ***E/Z*-117a** and ***E/Z*-119a** systems, the diastereomeric excess was less than that seen in the methyl system generating **101a**. In the reactions with lithium bromide, both the diastereoselectivity and regioselectivity were affected. This suggests that lithium bromide was influencing multiple reaction pathways.

With the aid of a 2D ROESY experiment along with the coupling trends observed, it was possible to clearly distinguish *trans* (major isomer) from the *cis* isomer. In the ROESY spectrum of *E*-**118a**, a crosspeak was seen between the naphthylic proton and the geminal protons adjacent to the carbonyl. No such crosspeak was evident in the ROESY spectra of ***Z*-118a**. Conclusively, these furans exhibited the

same characteristic spectral data as shown in the ***E/Z*-102a**. All products could be easily identified by their characteristic ^{1}H NMR spectra. Diastereomer sets (***E/Z*-118a**), (***E/Z*-120a** and ***Z*-121a**) and (***E/Z*-122a**) could not be separated by chromatographic means, but it was possible to assign the peaks in the sp^3 region in the ^{1}H NMR as no coincidental resonances were observed. Elemental analysis supported the assignment of these furan mixtures.

In **Scheme 2.12** a cationic mechanism was proposed to account for the formation of a rearranged 1,2-dihydronaptho[2,1-*b*]furan. On the basis of this proposed mechanism, an enhancement in the amount of rearranged material would be expected with an enhanced migratory aptitude in the migrating group. Methoxy-phenyl substituted furan **122a** was formed in higher yield than 4-triflouromethylphenyl substituted furan **124a** which supports the proposed mechanism.

The coupling data for the protons on the furan ring were consistent with the values obtained with the methyl dioxine system. In agreeance with literature, the coupling constants of the furan ring protons could be used in the assignment of stereochemistry. **Table 2.11** summarised these values. It is noteworthy that as observed with ***E/Z*-101a/f** and ***E/Z*-102a/f** the chemical shifts of H_A and H_B were consistently higher for the *cis* isomer of all 1,2-dihydronaphtho[2,1-*b*]furans mentioned here.

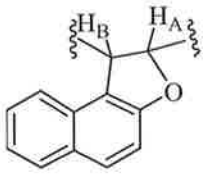


Table 2.11 *Furan coupling constants in* **117a-123a**.

Product	δ H_A	δ H_B	J_{AB}
***E*-117a**	5.74	4.17	2.7
***Z*-117a**	6.04	4.56	8.0
***E*-118a**	5.11	4.69	5.7
***Z*-118a**	5.53	5.01	9.0
***E*-119a**	5.71	4.11	2.4
***Z*-119a**	5.99	4.55	8.4
***E*-120a**	5.06	4.68	5.7
***Z*-120a**	5.50	4.99	8.8
***E*-121a**	5.68	4.16	2.6
***Z*-121a**	5.99	4.51	8.4
***E*-122a**	5.06	4.65	5.4

***Z*-122a**	5.48	4.97	8.4
***Z*-123a**	6.07	4.60	7.8

The base catalysed degradation reaction could be successfully carried out upon all the aryl substituted 1,2-dioxines **77** to **82**, where in most cases, the aromatised product precipitated pure from solution in good yield (**Table 2.12**). Some precautions were employed in handling these products in the solution state as decomposition to a new set of compounds otherwise occurred, the results of that study are discussed in Chapter 4.

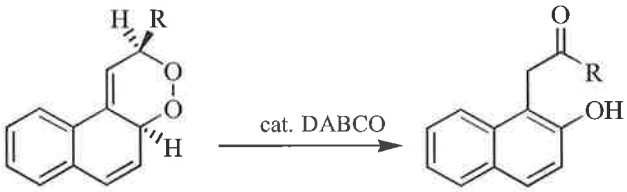
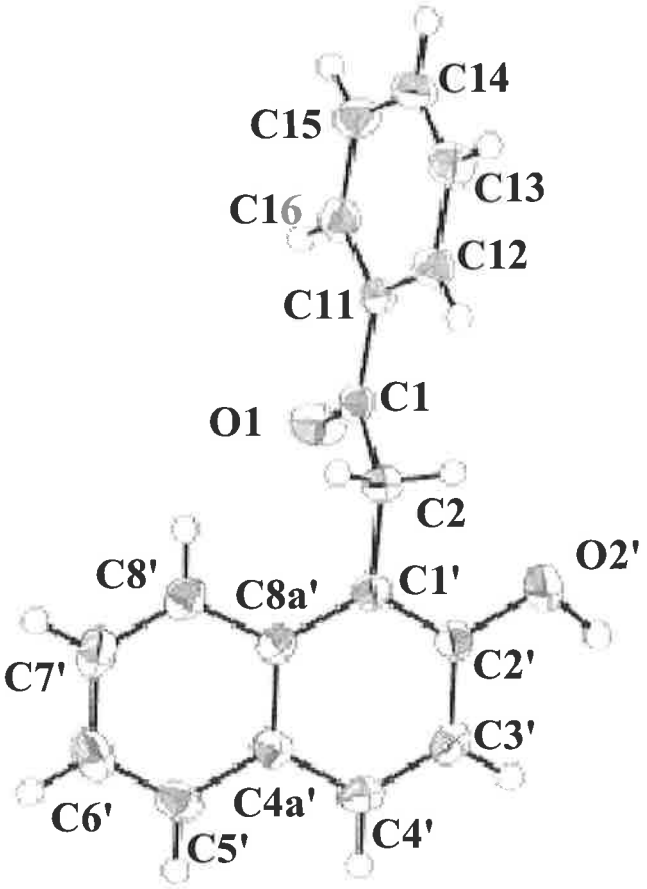


Table 2.12 *The base catalysed degradation of dioxines* **77-82**.

Entry	Dioxine	Solvent	Time	Product	Yield %
1	**77**	CH_2Cl_2	1 hour	**131**	88
2	**78**	CH_2Cl_2	1 hour	**132**	89
3	**79**	Benzene	1 hour	**133**	82
4	**81**	Benzene	1 hour	**134**	84
5	**82**	CH_2Cl_2	16 hours	**135**	68

A crystal structure was obtained of **131** (**Figure 2.15**), showing that in the solid state, this compound existed in the open form. In the solid state, the phenyl ring occupied space at approximate right angles to the naphtha-skeleton. By ^{1}H NMR and ^{13}C NMR analysis there was no evidence of an equilibrium with a hemiacetal form for any of these products. **Table 2.13** contains a summary of characteristic data for these compounds.

Figure 2.15 *ORTEP diagram of* **131**.



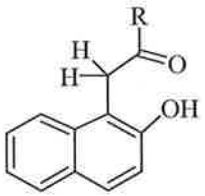
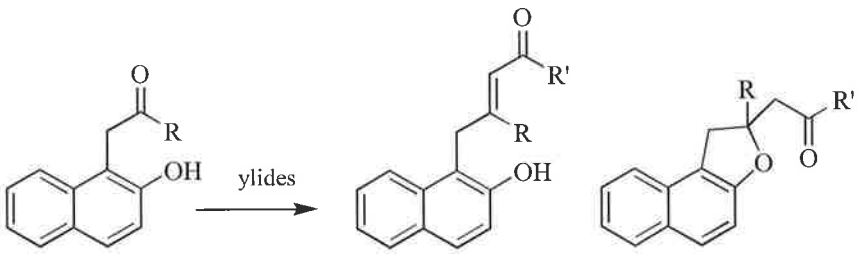


Table 2.13 *Some spectral data for* **131-135**.

Product	R	δ CH_2 (s)	δ C=O	δ C-OH	IR C=O	IR O-H
131	Ph	4.74	198.20	153.46	1676	3409
132	4-ClPh	4.70	197.26	153.32	1674	3421
133	4-MeOPh	4.70	197.18	152.59	1670	3419
134	3-BrPh	4.70	196.65	152.22	1681	3428
135	2-naphthyl	4.82	204.68	153.41	1684	3575

It was possible to treat these ketones with stabilised ylide to either afford the uncyclised alkene or the 1,2-dihydronaphtho[2,1-*b*]furans depending upon the conditions employed (**Table 2.14**). For the reactions of **131** and **132** with excess **45a** at

reflux in benzene (Entries 2 and 6) the cyclised furan products were formed exclusively. When heated to 50 °C with 1.1 equivalents of **45a** it was possible to obtain the uncyclised alkenes in good yield (Entries 1 and 5). This selectivity was not observed with reaction of **135** with excess **45a**, where refluxing overnight resulted in a mixture of cyclised and uncyclised products (Entry 8).



131	***E/Z*-136a**	**137a**
132	***E/Z*-138a**	**139a**
133	***E/Z*-140a**	**141a**
134	***E/Z*-142a**	**143a**

Table 2.14 *Reactions of* **131-134** *with phosphoranes.*

Entry	Substrate	Ylide (Equiv.)	Temperature	Products (%)
1	**131**	**45a** (1.1)	50	***Z*-136a** (53) ***E*-136a** (33)
2	**131**	**45a** (2)	80	**137a** (78)
3	**131**	**45g** (2)	80	**137g** (80)
4	**131**	**45h** (2)	80	**137h** (32)
5	**132**	**45a** (1.1)	50	***Z*-138a** (50) ***E*-138a** (35)
6	**132**	**45a** (2)	80	**139a** (74)
7	**133**	**45a** (2)	80	**141a** (79)
8	**134**	**45a** (2)	80	***Z*-142a** (41) ***E*-142a** (35) **143a** (17)

Using this methodology, the tertiary alkenes were not synthesised with a high degree of stereoselectivity. A property which assisted the characterisation of these structures was the chemical shift of the hydroxyl proton in the ^{1}H NMR. Discussed earlier, the hydroxyl proton appeared up to three ppm further downfield in the *cis* isomer, for example ***Z*-66a**. In this case the same phenomenon was observed for the *E*-isomers as the priority groups have changed. In effect this phenomenon was observed when a *syn* relationship existed between the carbonyl moiety and the 2-naphthol substituent. **Table 2.15** contains a summary of the relative ratios of isomers along with chemical shift data for the hydroxyl proton. Also of note was the long-range coupling seen in the *Z*-isomer of the alkenes between the olefinic proton and the methylene group.

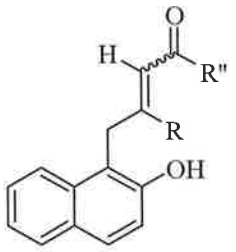


Table 2.15 *Data for the uncyclised Wittig adducts.*

Compound	δ (O-**H**)	δ -C**H**$_2$- (*J* Hz)	δ =C**H** (*J* Hz)	IR (C=O)	IR (O-H)
***E*-136a**	8.44	4.69	6.02	1689	3290
***Z*-136a**	5.10	4.19 (d, 1.6)	5.49 (t, 1.6)	1722	3579
***E*-138a**	8.20	4.68	6.01	1691	3300
***Z*-138a**	5.04	4.14 (d, 1.5)	5.49 (t, 1.5)	1722	3579
***E*-142a**	8.22	4.67	6.01	1691	3297
***Z*-142a**	5.23	4.10 (d, 2.1)	5.44 (t, 2.1)	1723	3580
***E*-129a**	8.17	4.70	6.01	1712	3311
***Z*-129a**	5.45	4.15 (d, 2.1)	5.53 (t, 2.1)	1724	3581

Characteristic data of the 1,2-dihydronaphtho[2,1-*b*]furans were analogous to those synthesised earlier in the project. **Table 2.16** contains a summary of characteristic data exhibited by these products, including an AB quartet for the diastereotopic furan protons in the ^{1}H NMR and a weak resonance of the quaternary sp^3 carbon of the adjacent carbon in the ^{13}C NMR at C2.

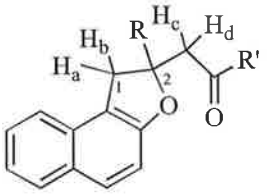


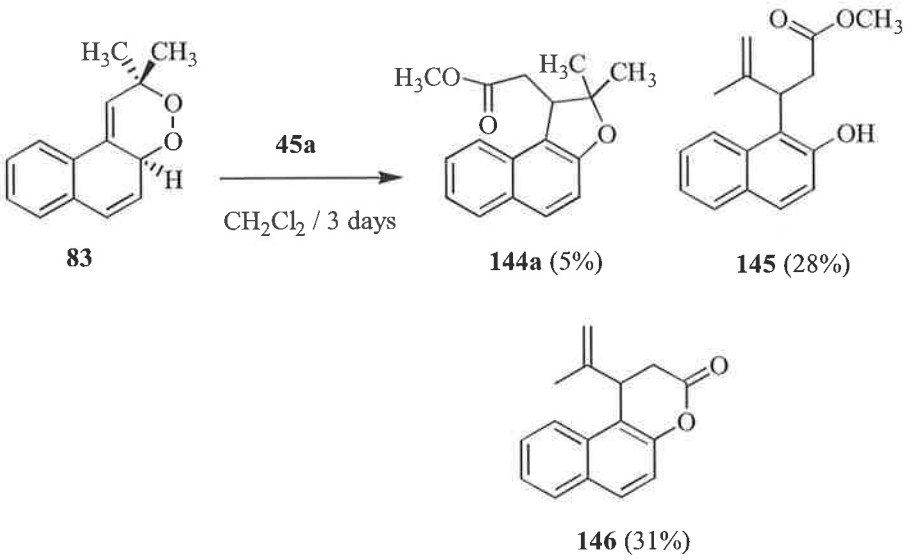
Table 2.16 *^{1}H NMR and ^{13}C NMR data for some 1,2-dihydronaphtho[2,1-b]furans.*

Product	δ H_a/H_b (J_{ab} Hz)	δ H_c/H_d (J_{cd} Hz)	δ C2
137a	3.77, 4.14 (15.7)	3.13, 3.16 (14.6)	80.72
137g	3.86, 4.19 (16.0)	3.81 (16.0)	90.62
137h	3.74, 4.12 (15.6)	3.17, 3.20 (14.4)	89.65
139a	3.73, 4.11 (15.6)	3.11, 3.14 (14.9)	89.25
141a	3.82, 4.09 (15.6)	3.10, 3.20 (14.4)	88.95
143a	3.73, 4.12 (15.6)	3.10, 3.14 (14.9)	N/A
130a	3.51, 3.73 (15.6)	3.15, 3.17 (14.9)	89.22

2.6. THE REACTION OF 1,2-DIOXINE 83 WITH PHOSPHORANE 45a.

The reaction of the disubstituted dioxine **83** with **45a** gave a mixture of products, including the expected dihydronaphtho[2,1-*b*]furan **144a** in 5% yield (**Scheme 2.17**). Two unexpected structurally related products **145** and **146** were the major reaction products.

Scheme 2.17

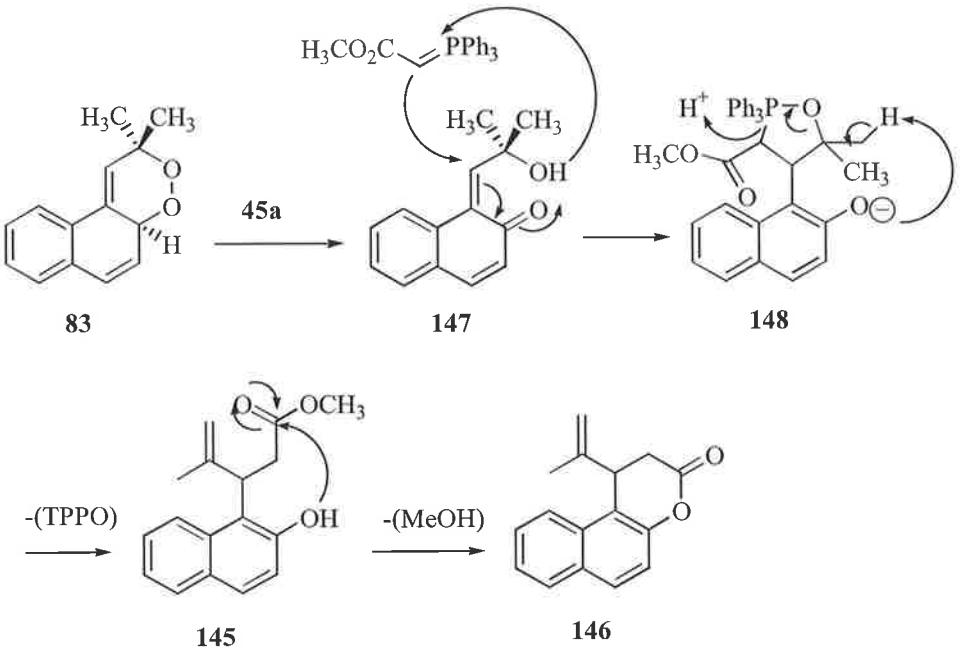


83 **144a** (5%) **145** (28%)

146 (31%)

This result supported the hypothesis that the most acidic proton in these dioxines was located at the ring junction. The rationale behind the formation of the lactone was that the tertiary substitution of the carbinol carbon prevented S_N2 attack and the elimination of TPPO was the more accessible pathway, described by **Scheme 2.18**. Lactone **146** was then given by the intramolecular cyclisation and expulsion of methanol.

Scheme 2.18



83 **147** **148**

145 **146**

1,2-Dihydronaphtho[2,1-*b*]furan **144a** exhibited similar characteristic data as the preceding systems. The ^{1}H NMR contained the usual AB quartet at δ 2.65 and 2.79 ppm for the diastereotopic protons adjacent to the carbonyl moiety. Both protons coupled to the proton of the furan ring and also of note, was the presence of two methyl singlet resonances at δ 1.47 and 1.52 ppm integrating as three hydrogens each representing the two inequivalent methyl groups. The ^{13}C NMR exhibited a weak resonance for the quaternary sp^3 carbon of the furan at C2 at δ 89.28 ppm along with the carbonyl at δ 173.24 ppm.

Ester **145** was shown by mass spectroscopy to have the same molecular formula as that of **144a**. The key to elucidating the structure of **145** was the ^{1}H NMR. An unusually upfield broad singlet was observed for the vinyl protons at δ 5.21 ppm. The methylene appeared as an AB quartet at δ 2.95 and 3.24 ppm as they were adjacent to the solitary chiral centre. The proton present at this centre at δ 4.70 ppm coupled to both protons of the AB quartet. The downfield signal at δ 6.90 ppm underwent exchange with deuterium oxide, indicative of a phenolic type of alcohol. The infrared spectrum complemented the assignment as both stretching for the O-H at 3446 cm^{-1} and the carbonyl moiety at 1736 cm^{-1} attributed to the ester were seen.

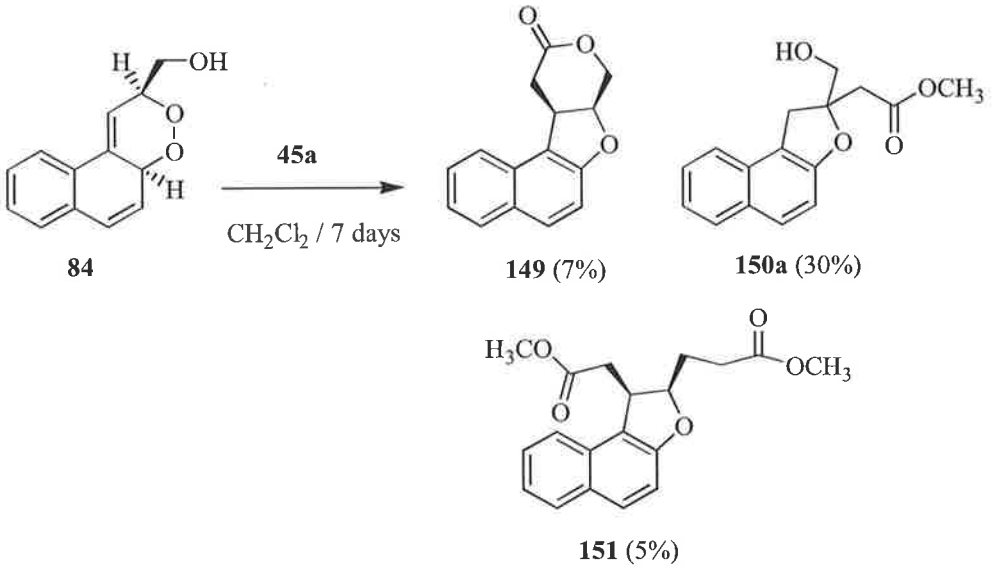
By mass spectrometry, **146** was shown to be 32 mass units smaller than **145**, indicative of a loss of methanol. This was supported by an absence of both the downfield methyl singlet and the exchangeable hydroxyl peak in the ^{1}H NMR. In addition to this, the ^{1}H NMR gave a more resolved upfield set of signals for the vinyl

protons at δ 4.54 and 4.88 ppm with a ^2J geminal coupling of 0.7 Hz. The Infrared spectrum contained the desired stretching for a lactone at 1765 cm^{-1} and the C=C at 1647 cm^{-1}.

2.7. THE REACTION OF 1,2-DIOXINE 84 WITH PHOSPHORANE 45a.

The last system investigated was the reaction of the α-hydroxy substituted 1,2-dioxine **84** with ylide **45a**. The reaction afforded a complex mixture of products, of which, the following products could be isolated from the crude reaction mixture by means of chromatography (**Scheme 2.19**).

Scheme 2.19

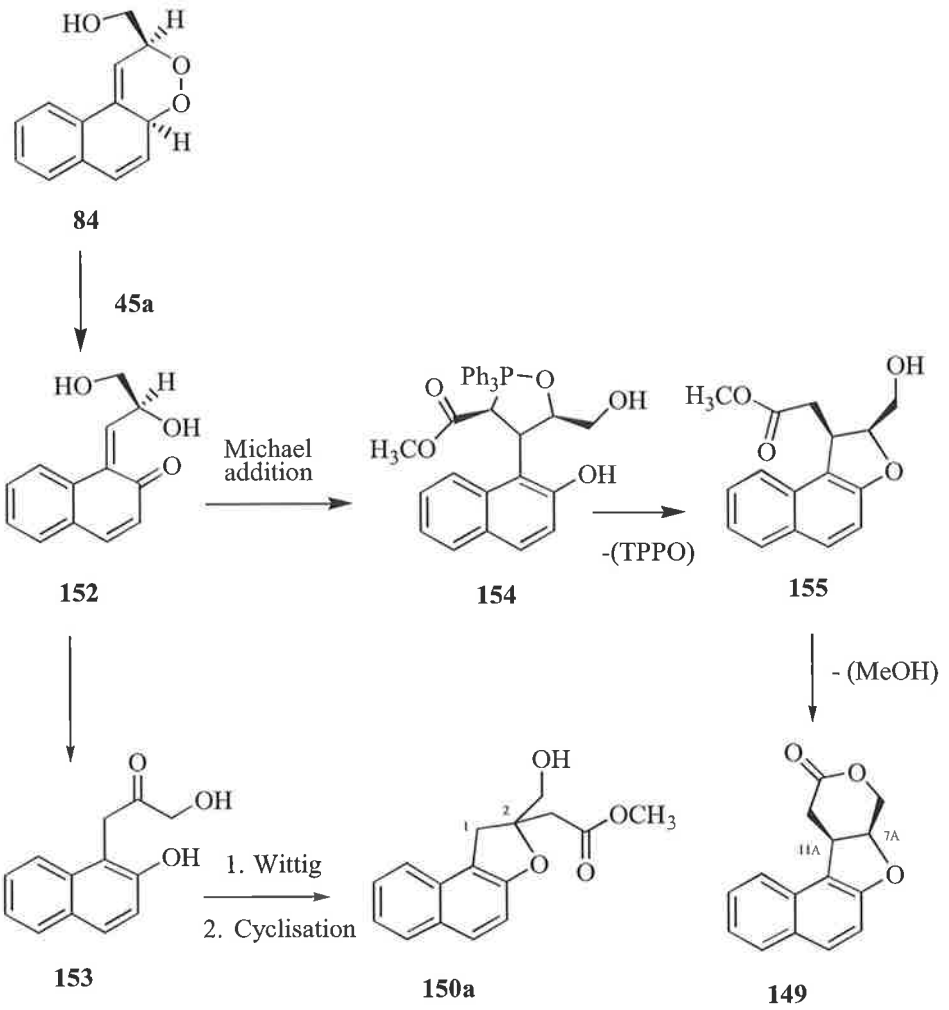


84 **149** (7%) **150a** (30%)

151 (5%)

The formation of both **149** and **150a** proceeded through the previously described routes (**Scheme 2.20**). Dihydronaphthofuran **150a** arose from the Wittig reaction of 1-(β-keto)-2-naphthol **153** with **45a** followed by intramolecular cyclisation. 1,2-Dihydronaphtho[2,1-*b*]furan **149** was the result of a Michael addition to give the oxaphospholane **154**, where in this case, the expulsion of TPPO was through the S_N2 mechanism. Intramolecular cyclisation of **155** resulted in the expulsion of methanol to give the cyclic ester **149**.

Scheme 2.20

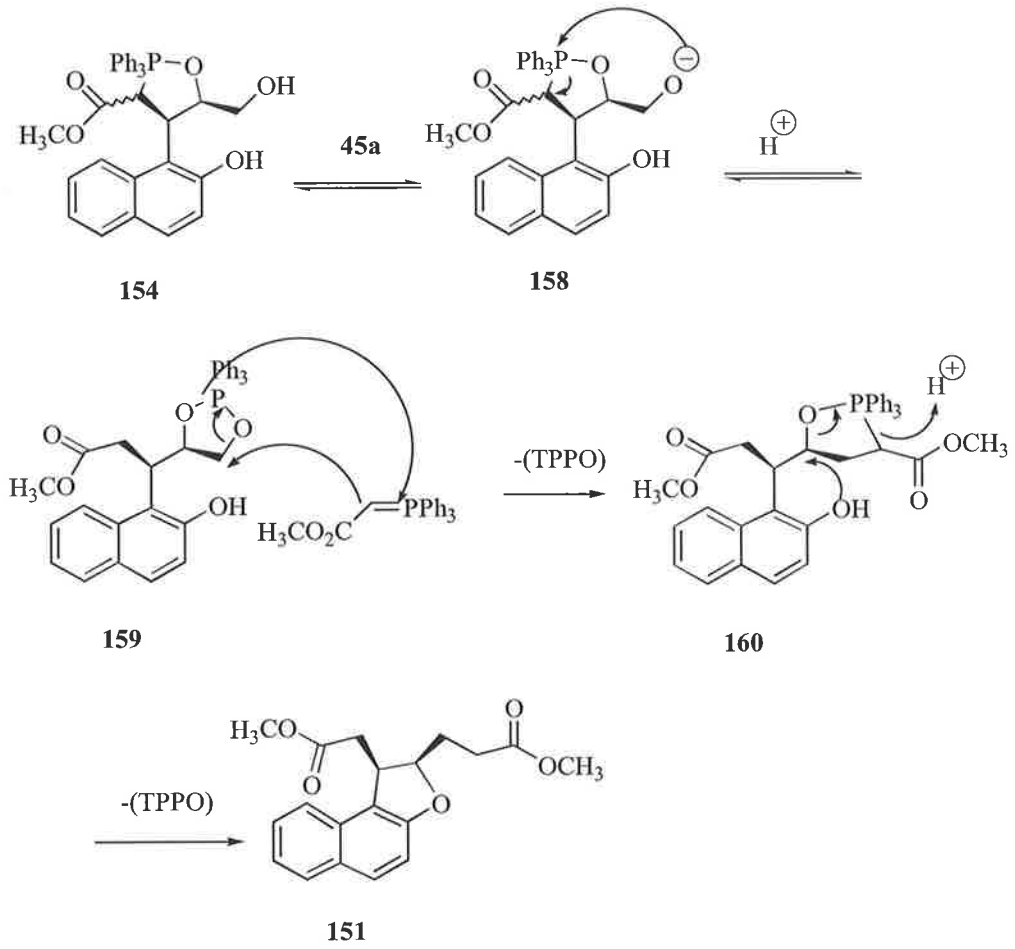


The infrared for **149** included the carbonyl stretching at 1780 cm^{-1} indicative of a lactone. The presence of a molecular ion (*m/z*) at 240 matched with the addition of the ylide **45a** and loss of methanol. In the ^{1}H NMR spectrum of **149** there was the presence of the protons of C11A and C7A at δ 4.30 and 5.14 ppm respectively. These coupled to each other with a large coupling constant of ^{3}J = 7.0 Hz as those observed with the *cis* 1,2-disubstituted furans like ***Z*-101a/f**. These protons exhibited a strong crosspeak in the 2D ROESY spectrum. In addition both these protons coupled to separate AB quartets.

Characteristic ^{1}H NMR data for **150a** consisted of two sets of independent AB quartet resonances assigned to the diastereotopic pairs of protons. These consisted of the pair adjacent to the ester functionality at δ 2.99 ppm and the ring protons of the dihydrofuran moiety at δ 3.47 ppm, agreeing with what had been seen with the phenyl and methyl substituted analogues **113a** and **137a**. An indicative weak resonance in the ^{13}C NMR at δ 89.11ppm confirmed the presence of the sp^{3} quaternary carbon of the furan at C2.

151 was not an expected product from this reaction. The presence of the extra hydroxyl group promoted the addition of two equivalents of ylide. A plausible mechanism describing its formation could involve initial Michael addition of ylide to the γ-hydroxyenone (**Scheme 2.21**). A proton transfer occurs, resulting in a primary alkoxide which then coordinates to the phosphorus forming a dioxaphospholane **159**. The dioxephospholane moiety is a previously described functionality which have been described as intermediates in tetrahydrofuran synthesis.[91,92] A second ylide attacks this *bis* oxy phosphorus species, expelling TPPO and an intramolecular cyclisation expels a second equivalent of TPPO to afford **151**.

Scheme 2.21

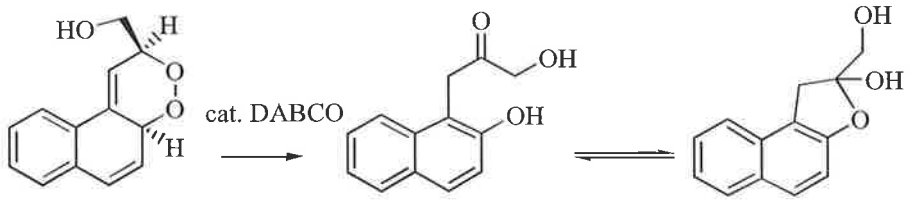


The structure of **151** was confirmed with the assistance of 2D NMR experiments. Firstly, a molecular ion at 328 (*m/z*) agreed with the proposed formula, although only one carbonyl stretching was observed in the IR spectra. This was complimented by the presence of two ester carbonyls in the ^{13}C NMR at δ 172.89 and 173.42 ppm. The connectivity of the structure in the ^{1}H NMR was such that of the three AB quartets, only two coupled to each other, yet both portions coupled to one of each

proton of the furan ring. There were significant crosspeaks between two of these AB quartets with the carbonyl resonances in the HMBC spectrum. The regiochemistry was confirmed by a ROESY experiment. A strong enhancement existed between the lone methylene and the *peri*-proton of the aromatic system, whereas the two adjacent methylenes gave rise to no enhancement with the aromatic protons. Finally, the stereochemistry was also confirmed by the ROESY interaction of the ring protons of the furan, which were quite strong and the small coupling constant, 3.6 Hz, between these two which also indicated a *cis* stereochemistry.

Likewise, a base catalysed degradation of dioxine **84** to the 1-(β-keto)-2-naphthol could be carried out efficiently upon treatment with DABCO giving a product which existed as an equilibrium mixture of **153** with the hemiacetal form **161** in a $CDCl_3$ solution with a small amount of d_6-DMSO as a 3:12 ratio (**Scheme 2.22**). **161** exhibited a characteristic AB quartet at δ 3.34 and 3.64 ppm with a geminal coupling of 17.4 Hz in addition to a second AB quartet in the ^1H NMR spectrum. This second set of signals, which was a complicated pattern, was resolved upon addition of D_2O to the solution. This signal was assigned to the methylene group adjacent to the alcohol. In the ^{13}C NMR spectrum, a resonance a δ 208.22 ppm attributed to the carbonyl of **153** was seen.

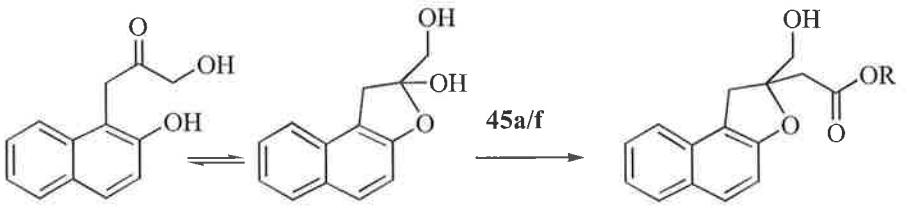
Scheme 2.22



84 **153** **161** (80%)

153/161 was reacted with phosphoranes **45a** and **45f** to afford the corresponding furans **150a** and **150f**. It was possible to obtain these reaction products under even milder condition than those used in the other systems (**Scheme 2.23**) by merely stirring together at room temperature overnight. The enhanced reactivity observed was due to the greater polarisation of the carbonyl owing to hydrogen bonding. This phenomenon has been previously reported in the literature for the reactions of ketones with stabilised phosphoranes.[82]

Scheme 2.23



153 **161**

150a (79%) R = CH_3

150f (78%) R = *t*-butyl

To conclude, much knowledge has been generated regarding the reactivity of these type of masked γ-hydroxyenones as Michael acceptors. The most logical approach to improving the reactivity of these systems hinges about the use of more nucleophilic species, such as Horner-Wittig reagents. This may improve the yields of dihydronaphtho[2,1-*b*]furan products and may even give Michael type addition products for the methylketone phosphonate. No-one has yet examined the effects of an ylide with more or less electron density upon the phosphorus in these types of reactions. This may alter the amount of migrated products seen in the reactions of monosubstituted dioxines and phosphorus ylides. Overall, this area of research has resulted in the syntheses of three regioisomers of 1,2-dihydronaphtho[2,1-*b*]furans originating from the same starting 1,2-dioxine. In some cases, the system could be manipulated to influence the formation of one product type over the other(s).

CHAPTER 3
MISCELLANEOUS REACTIONS OF 1,2-DIHYDRONAPHTHO[2,1-*b*]FURANS

Chapter 3 is centered about several useful reactions of some 1,2-dihydronaphtho[2,1-*b*]furan products derived from Chapter 2. This section covers some aromatic electrophilic substitution reactions of dihydronaphtho[2,1-*b*]furans and naphthofurans with the intention of developing routes into further functionalised naphtho[2,1-*b*]furan products. This investigation also uncovered a useful cyclisation reaction of some dihydronaphtho[2,1-*b*]furans utilising DDQ as a dehydrogenating reagent to afford tetrahydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-9-one products. These lactones have the potential to be used as templates for citric acid derivative synthesis.

3.1. AROMATISATION OF SOME 1,2-DIHYDRONAPHTHO[2,1-*b*]FURANS.

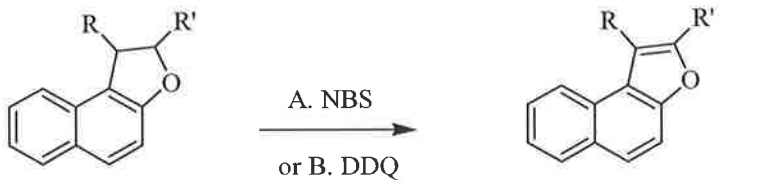
A short investigation was undertaken into electrophilic aromatic substitution reactions of some naphtho[2,1-*b*]furans and 1,2-dihydronaphtho[2,1-*b*]furan products from Chapter 2. One report was found dated over 30 years ago and pertained to the Friedel-Crafts acylation and the Vilsmeier-Haack formylation of 2-methylnaphtho[2,1-*b*]furan.[93] Another report pertaining to the electrophilic substitution of 2-acetylnaphtho[2,1-*b*]furan using nitric acid agreed with the earlier report whereby substitution occurred at C5.[94] Previous characterisation of these compounds were not thorough. No coupling data was given for the aromatic substitution pattern in the ^{1}H NMR. Furthermore, no examples of electrophilic substitution could be found for 1,2-dihydronaphtho[2,1-*b*]furans in the literature.

An aim of this project was to investigate this early work for the purposes of fully characterizing substituted products by current NMR techniques and to reconfirm these earlier findings. In addition, the established products from the electrophilic substitution of 1,2-dihydronaphtho[2,1-*b*]furans may find application in the synthesis of furonaphtho[2,1-*b*]quinones in the future. For this to be successful, electrophilic aromatic substitution must occur at C6 or C9 (*peri*-position) for the products to be oxidised to the quinone. The choice of electrophile was nitric acid and reactions were performed using conditions described in the literature.[94] It was hoped that the presence of this extremely electron withdrawing substituent would disperse signals in the ^{1}H

NMR sufficient for critical analysis. Furthermore, it was possible that nitro-substituted 1,2-dihydronaphtho[2,1-*b*]furans and naphtho[2,1-*b*]furans would provide crystalline material both for the purpose of stability and in the hope of obtaining X-ray quality crystals.

The desired naphthofurans **162** and **163** were synthesised using two different procedures, *N*-bromo succinimide (NBS) (Method A),[95] and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (Method B).[96] Both have been reported to facilitate an overall dehydrogenation leading to an aromatised product. When DDQ was employed for the oxidation of ***E/Z*-101a** and ***E/Z*-102a**, superior results were obtained when the reaction was carried out in THF. **Scheme 3.1** contains a summary of the yields obtained for these reactions. It seemed that for ***E/Z*-102a** NBS was the more effective reagent, whereas the opposite held true for ***E/Z*-101a**. The reaction of ***E/Z*-101a** with NBS was not clean and gave many side products, one of which **166** was isolated and shall be discussed shortly.

Scheme 3.1



***E/Z*-101a** R = $CH_2CO_2CH_3$, R' = CH_3 **162** A. (49%), B. (73%)

***E/Z*-102a** R = CH_3, R' = $CH_2CO_2CH_3$ **163** A. (59%), B. (52%)

Characterisation of **162** and **163** was possible using standard techniques as the two chiral centres were both removed in the aromatised products. A very simplified ^1H NMR was observed for these products owing to the loss of both chiral centres. The characteristic ^1H NMR data for these products included three singlets in the sp^3 region representing the methyl ester, the methyl attached to the furan and the methylene attached to the furan. Likewise, the ^{13}C NMR spectrum exhibited only three signals in the sp^3 region and also gave two resonances each for the furan carbons adjacent to the oxygen at δ 151.50 and 152.18 ppm for **162**, and δ 145.33 and 151.81 ppm for **163**. When **162** was hydrolysed to the corresponding acid **164**, it was possible to obtain crystals suitable for X-ray structure determination. As seen in **Figure 3.1**, acid **164** in the solid state existed as a dimeric species where Hydrogen bonding occurred between

two acids. Similarly, when **163** was hydrolysed to the corresponding acid **165**, the molecular structure could also be determined (**Figure 3.2**).

Figure 3.1 *ORTEP diagram of* **164**.

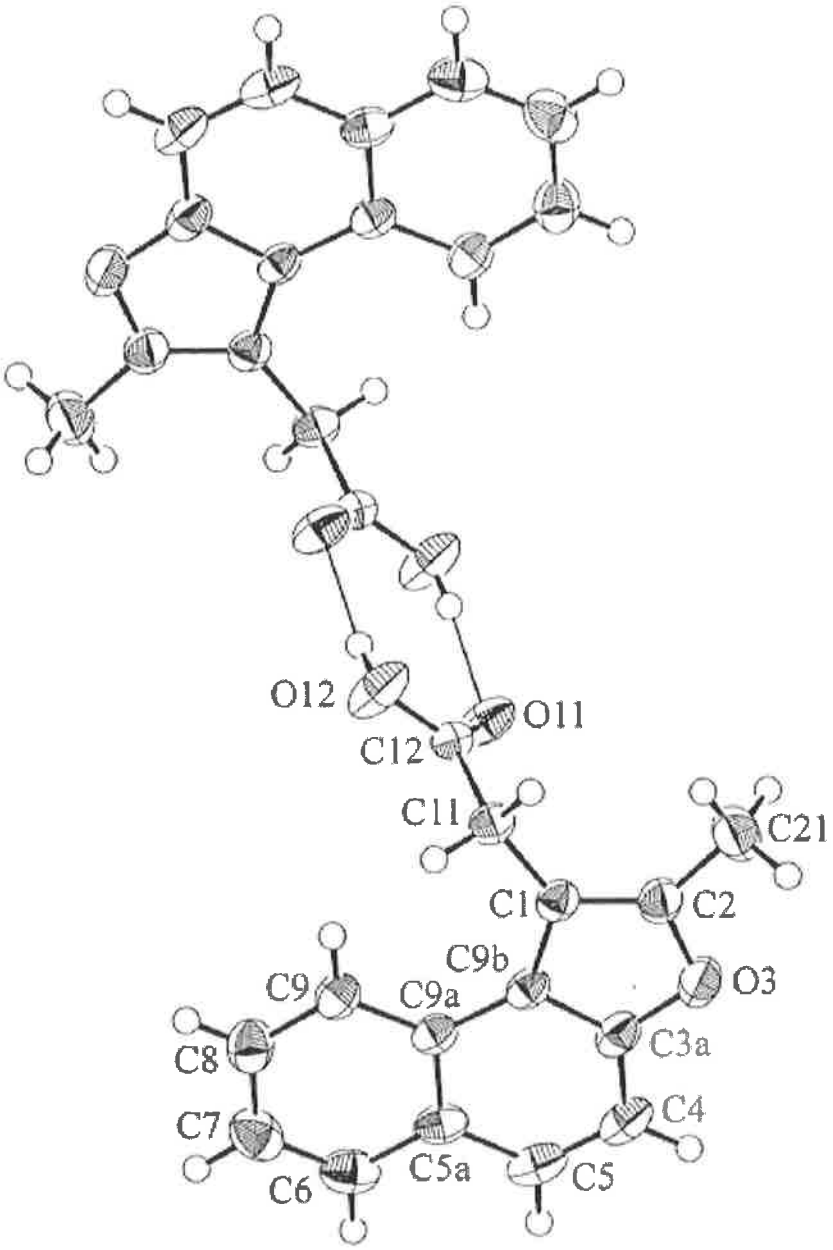
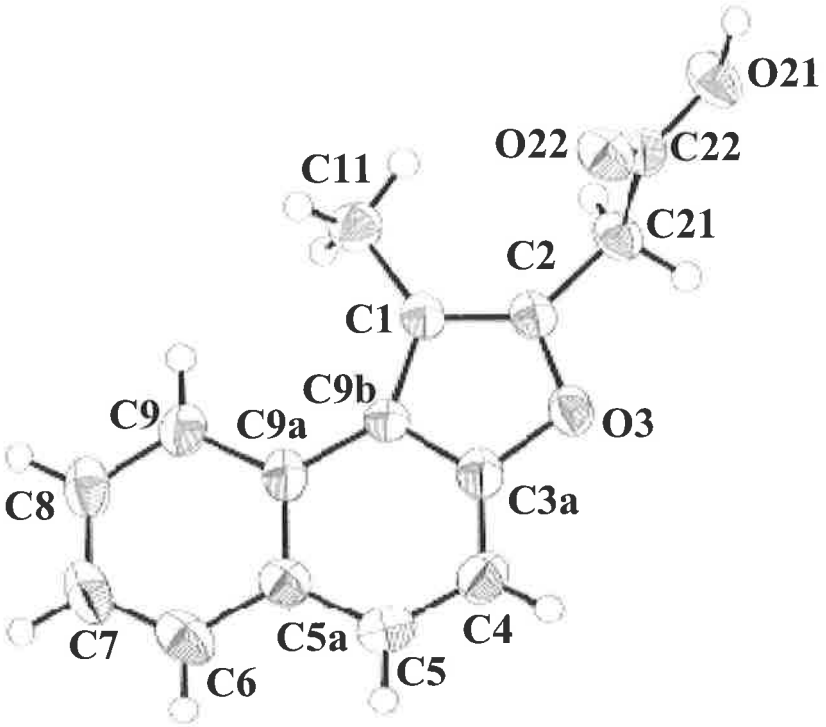
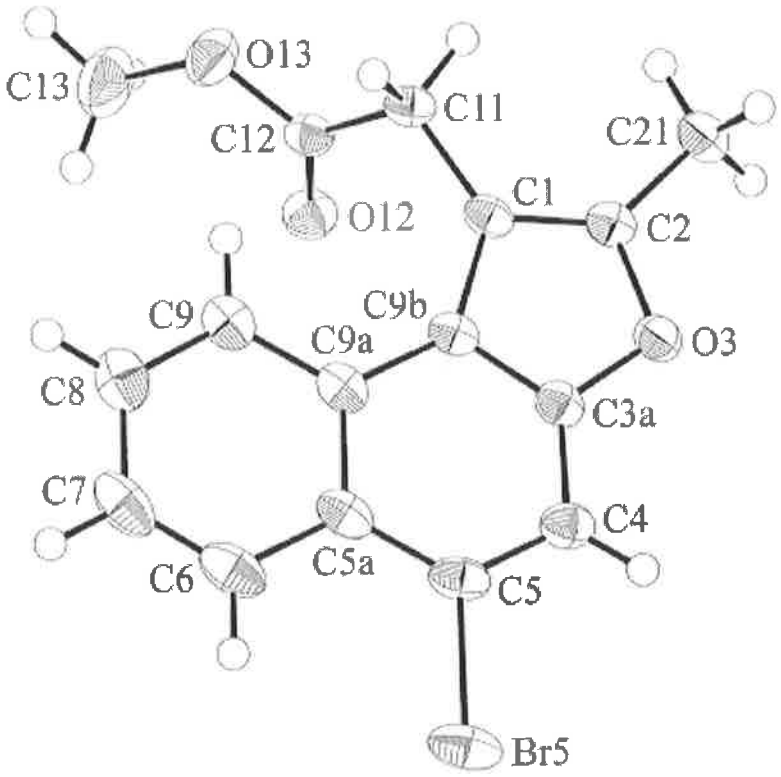


Figure 3.2 *ORTEP diagram of* **165**.



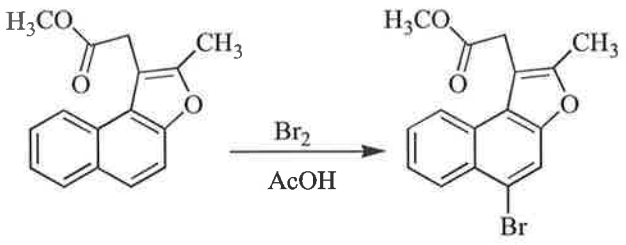
In the case of the synthesis of **162** using Method A, the reaction with NBS afforded a second isolable product **166**, whereby, it was believed that an electrophilic substitution of bromine had occurred (**Scheme 3.2**). This material made up some 12% of the reaction mixture. The mass spectrum of **166** indicated that one bromine had added to the molecule with the presence of a molecular ion (*m/z*) at 332. The ^{1}H NMR spectrum contained only five aromatic proton signals, two of which experienced two large *ortho* couplings and one singlet at δ 7.81 ppm. This coupling pattern indicated that an aromatic electrophilic reaction occurred on the ring adjoining the furan. Although all these signals were unobscured, it was not possible to assign the *peri* proton as no detectable crosspeak in the ROESY was observed. However, it was possible to obtain X-ray quality crystals of **166**. This clearly showed that an electrophilic substitution had occurred at C5 agreeing with the earlier literature report (**Figure 3.3**).[93,94]

Figure 3.3 *ORTEP diagram of* **166**.



Classical electrophilic bromination conditions were employed to optimize the yield of **166** to 88%.[97] Furan **162** was allowed to react with one molar equivalent of bromine in glacial acetic acid. This reaction resulted in one product spectroscopically identical to that of **166** isolated from the reaction of **101a** with NBS.

Scheme 3.2

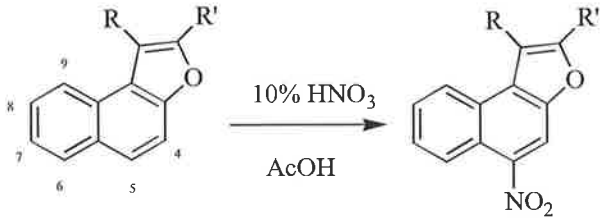


162 **166** (88%)

3.2. ELECTROPHILIC SUBSTITUTION REACTIONS OF 1,2-DIHYDRONAPHTHO[2,1-*b*]FURAN 113a AND NAPHTHO[2,1-*b*]FURANS 162 AND 163.

The next area of interest was the electrophilic substitution reactions of naphtho[2,1-*b*]furans **162** and **163** and 1,2-dihydronaphtho[2,1-*b*]furan **113a** with nitric acid. Several reports exist describing the mutagenic properties of 2-nitronaphtho[2,1-*b*]furans along with other interesting biological properties. In the same reports no such bioactivity was reported for the 5-nitro substituted analogues.[94,98] Reactions of **162** and **163** with a solution of 10% nitric acid in glacial acetic acid gave exclusively the 5-substituted nitro compounds **167** and **168** (**Scheme 3.3**).

Scheme 3.3

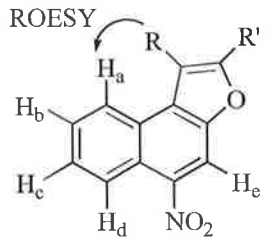


162 **167** (70%)

163 **168** (65%)

The reaction times for the nitration were short and to prevent multiple nitration, the contents of the reaction vessel were poured into excess water upon the disappearance of the starting material by TLC. These products could be conveniently purified by flash chromatography. Products **167** and **168** exhibited similar ^{1}H NMR patterns in the aromatic region as that seen for **166**. In these instances with the use of a 2D ROESY experiment, it was possible to assign the *peri*-proton in both products, where for **167** the ROESY crosspeak was observed with the methylene at δ 3.43 ppm. Unfortunately, in the case of **168**, the two *bis ortho* substituted protons (H_b and H_c) were coincidental. Again, neither a ROESY nor a COSY crosspeak was observed for H_d and H_e. **Figure 3.4** contains a summary of the ^{1}H NMR data, the *peri* proton assigned on the basis that a through space interaction was seen with the substituent at C1. A COSY experiment was used to identify all other aromatic protons.

Figure 3.4 *Some* ^1H *NMR data of* **167** *and* **168**.

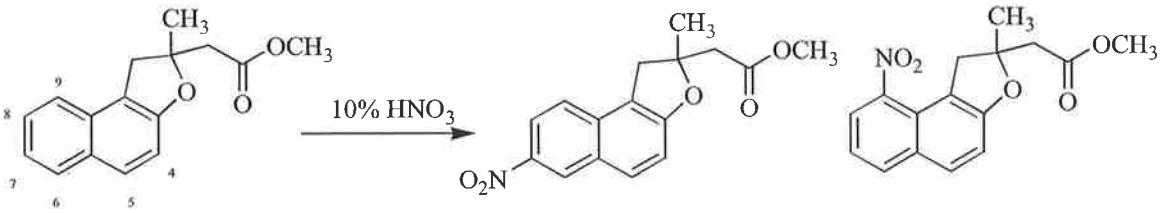


167	
Proton	δ (*J* Hz)
H_a	8.28 (8.4, 1.2)
H_b	7.30 (8.4, 7.2, 1.2)
H_c	7.22 (9.0, 7.2, 1.2)
H_d	8.71 (9.0, 1.2)
H_e	7.99 (s)

168	
Proton	δ (*J* Hz)
H_a	8.01 (7.8, 1.2)
H_b	7.21-7.26 (m)
H_c	7.21-7.26 (m)
H_d	8.70 (9.0, 1.2)
H_e	7.96 (s)

The reaction of the 1,2-dihydronaphtho[2,1-*b*]furan **113a** with nitric acid gave more complicated results (**Scheme 3.4**). Two products **169a** and **170a** formed in roughly similar quantities were separated by flash chromatography. Both **169a** and **170a** gave a molecular ion at 301, indicative that both products were a result of a single electrophilic substitution. In this case the reactivity lay within the C ring, unlike the aromatised furans **162** and **163** (the reaction occurring upon the B ring), the lone pair of oxygen was not delocalised into an aromatic ring. As a result a different distribution of electron density throughout the π network and hence different sites of electrophilic substitution.

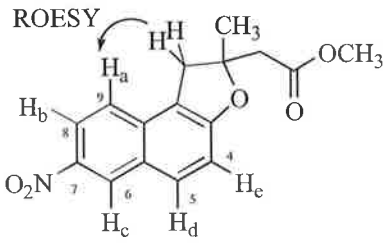
Scheme 3.4



113a **169a** (31%) **170a** (39%)

The position of the nitro group in **169a** was determined from the 2D ^1H NMR spectra. In reference to **Figure 3.5** in the aromatic region, the coupling pattern indicated that no protons were experiencing two *ortho* couplings and so the substitution could only have occurred at either C7 or C8. The 2D ROESY experiment made it possible to identify the *peri*-proton with a crosspeak seen between the AB quartet of the protons upon the furan ring and the aromatic at δ 7.19 ppm.

Figure 3.5 *Some* ^1H *NMR data for* **169a**.



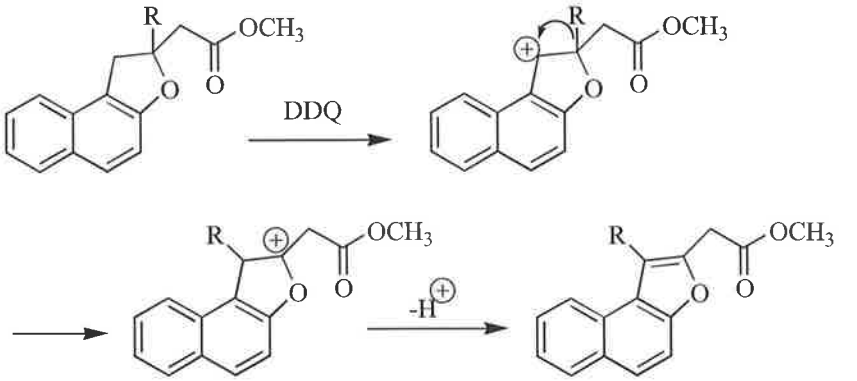
Proton	δ (*J* Hz)
H_a	7.19 (8.7)
H_b	7.85 (8.7)
H_c	8.74 (2.4)
H_d	8.21 (9.1, 2.4)
H_e	7.60 (9.1)

Product **170a** also exhibited an unobscured ^{1}H NMR spectrum in d_6-benzene. In this product, there was only one aromatic proton which exhibited two large couplings due to *ortho* protons. This is only possible if the electrophilic substitution had occurred either at the *peri* position C9 or at C6. The ROESY experiment of **170a** gave no additional information as neither crosspeaks were detected between the methylene of the furan ring with any aromatic signals, nor between the two independent sets of signals in the C4 and C5 positions. As a result of the failure of the 2D experiments, the aromatic protons were left unassigned. Fortunately, an X-ray structure of a derivative of **170a** featured later in this chapter confirmed the site of nitration to be at the *peri* position. This was an encouraging result for the pursuit of a synthesis of furonaphtho[2,1-*b*]quinones.

3.3. REACTIONS OF 1,2-DIHYDRONAPHTHO[2,1-*b*]FURANS WITH DDQ.

An investigation was carried out into the reactivity of some of the dihydronaphtho[2,1-*b*]furans with hydride abstracting reagents. It was envisaged that the furans **113a** and **137a (Scheme 3.5)**, with the use of a hydride abstracting agent, could undergo a Meerwein-Wagner cationic rearrangement to naphtho[2,1-*b*]furans. The driving force for the process would be the aromatisation caused by the loss of a proton, possible only from the rearranged carbocation.

Scheme 3.5



Preliminary calculations at the AM1 level of theory using the Spartan® suite of programs into the cation stabilities for the methyl and phenyl substituted furans (**Table 3.1**) both showed relatively small energy differences between the initial and rearranged carbocations marginally not in favour of the required rearrangement.[99] The question remained if the energy of the transition state was accessible. This was investigated empirically using some well known hydride abstractors.

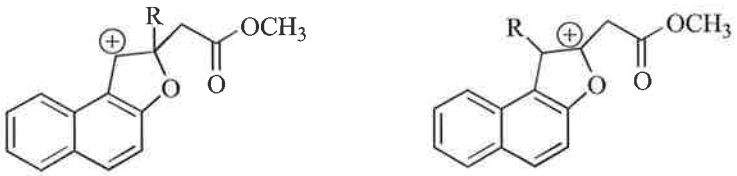
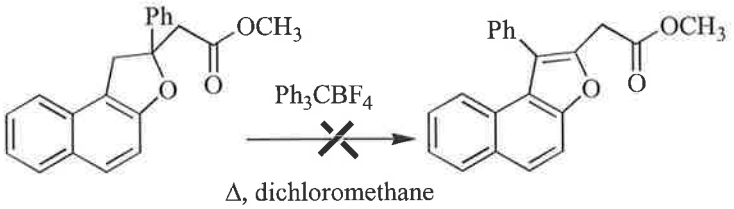


Table 3.1 *Energies of some carbocations.*

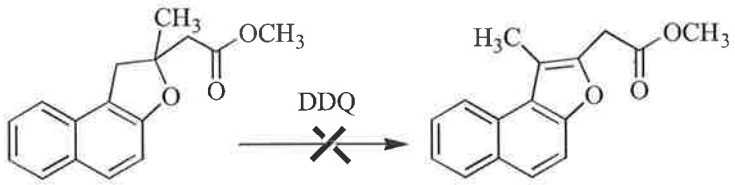
R	Energy Kcal/mol	Energy Kcal/mol	ΔE Kcal/mol
CH_3	108.29	113.27	-4.98
Ph	143.43	146.00	-2.57

Two well known hydride abstractors were used, namely DDQ[100] and trityl cation.[101] Infact, DDQ has been used previously in inducing a Meerwein-Wagner rearrangement leading to aromatised products.[102] Reactions on both 1,2-dihydronaphtho[2,1-*b*]furans **113a** and **137a** utilising both DDQ and trityl cation respectively, resulted in no reaction, even when the DDQ reaction was heated to reflux in chlorobenzene (**Scheme 3.6**).

Scheme 3.6



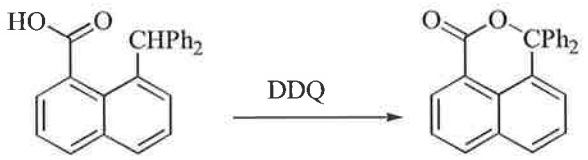
137a **171**



113a **163**

It was not known whether hydride abstraction was occurring, so in order to investigate this phenomenon further, a series of reactions were conducted upon the acid derivatives of some 1,2-dihydronaphtho[2,1-*b*]furans (**Scheme 3.8**). It was thought that in these cases, *cis*-lactones should be formed. These acids were conveniently synthesized by the base catalysed hydrolysis of esters synthesized in both Chapters 2 and 3. A general protocol was employed which is mentioned in the Experimental section along with characterisation data. It has been reported that the intramolecular cyclisation of naphthylic acid **172** was effected by the use of DDQ under anhydrous conditions to give **173** (**Scheme 3.7**).[103]

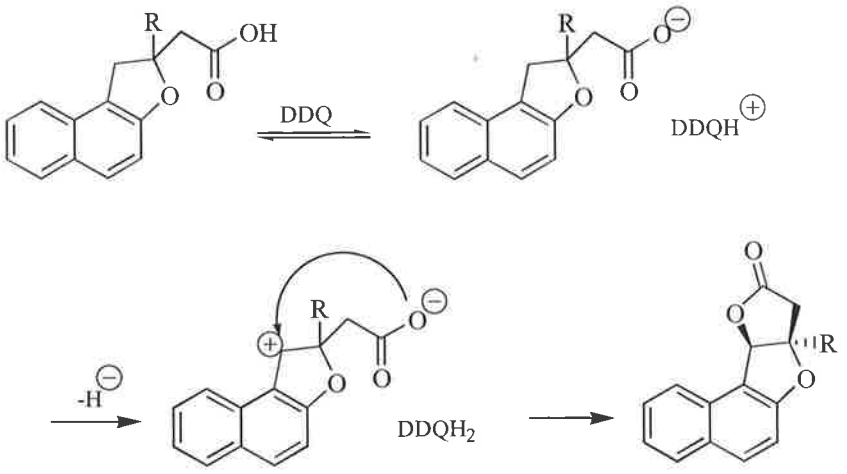
Scheme 3.7



172 **173** (85%)

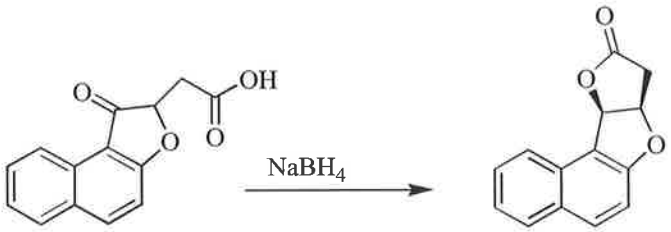
Mechanistically, as seen in **Scheme 3.8**, when DDQ has been protonated, it becomes more activated toward hydride abstraction. The driving force for the reaction, being the aromatisation of the $DDQH^+$ to $DDQH_2$. Acid catalysis for these types of reactions have been used often in the literature to enhance the activity of DDQ.

Scheme 3.8



Two other literature syntheses into similar bicylic lactones, without using acid catalysed esterification, have been described in the literature. One involved the reduction of ketoacid **174** with sodium borohydride. **174** itself was derived from an elaborately functionalised starting material (**Scheme 3.9**).[104]

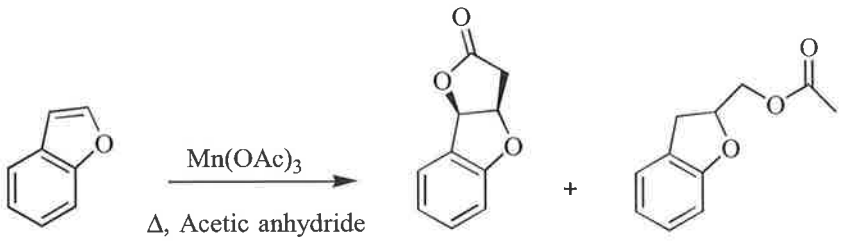
Scheme 3.9



174 **175** (80%)

Manganese (III) acetate was allowed to react with benzofuran **176**, the acetate radical adding to the electron rich double bond of **176** resulting in the formation of **177** as a minor product (**Scheme 3.10**).[105]

Scheme 3.10



176 **177** (21%) (42%)

The DDQ facilitated lactonisation of acids **178** to **181** was examined as these reactions should result in the formation of *cis*-lactones (**Table 3.2**). In all but one case, only mild conditions, heating to 50 °C in benzene, were required in order to stereo-selectively synthesise several lactones in good yield. Qualitatively, the progress of the reaction could be monitored by the formation of a precipitate of $DDQH_2$ and the colour of solution lightened. Typically (Entries 1, 2, and 4), no starting material was detectable by TLC after one hour. For the case of the nitro substituted acid, elevated temperatures (refluxing in benzene overnight) were required to afford the lactone **183** (Entry 3). Presumably, the electron withdrawing properties of the nitro moiety withdrew electron density from the benzylic position such that higher energies were required to attain the cationic intermediate. Importantly, only one isomer was detectable in the crude ^1H NMR.

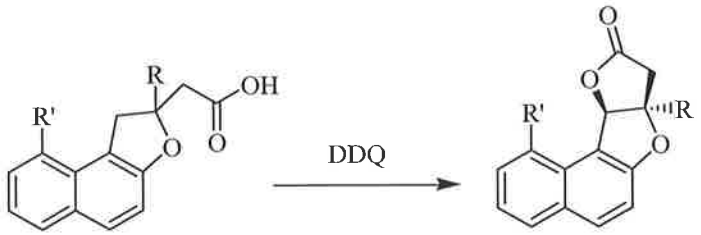


Table 3.2 *Reactions of dihydronaphtho[2,1-b]furan acids* **178-181** *with DDQ.*

Entry	Acid	R	R'	Temperature	Product	Yield %
1	**178**	H	H	50	**175**	38
2	**179**	CH_3	H	50	**182**	82
3	**180**	CH_3	NO_2	80	**183**	92
4	**181**	Ph	H	50	**184**	71

Some of the characteristic data for these lactones has been summarised in **Table 3.3**, including characteristic IR data for the carbonyl of the lactone. The ^1H NMR data obtained for **175** were in agreeance with that of the literature. It was possible to assign the furan carbons. In the cases of **182** to **184**, all ^{13}C NMR spectra contained a weak quaternary for C7A with a proximal signal for C10A. The assignment for C7A and C10A for **175** were confirmed by an HMQC experiment.

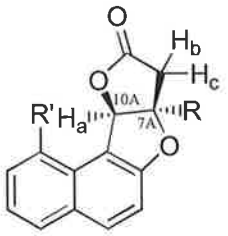
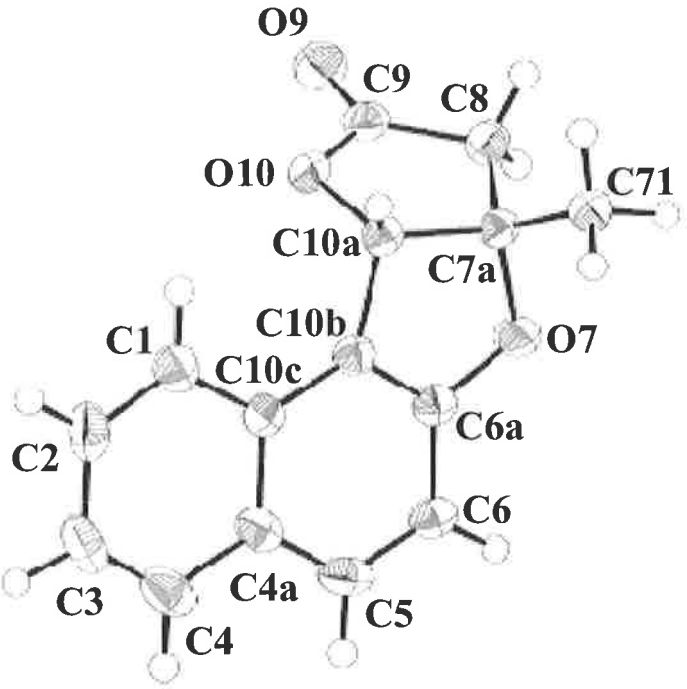


Table 3.3 *Characteristic data for lactones* **175** *and* **182-184**.

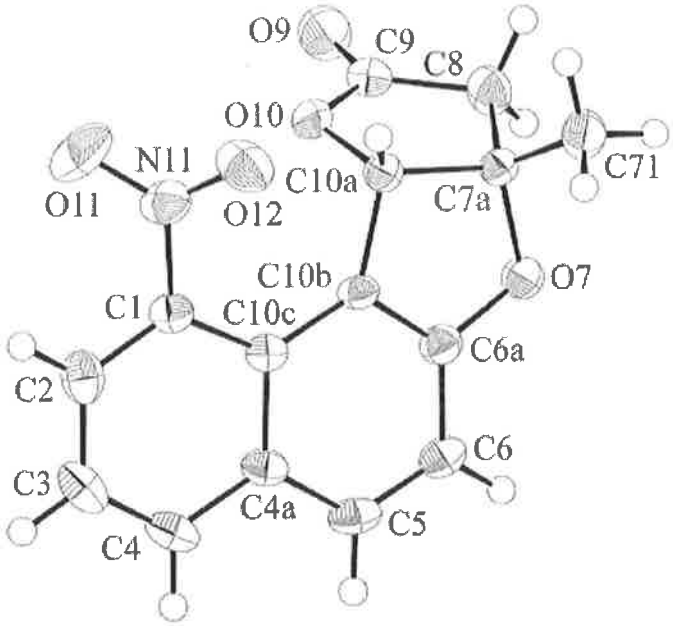
Compound	δ H_a (*J* Hz)	δ H_b/H_c (J_{bc} Hz)	δ C7A	δ C10A	IR (C=O)
175	6.46 (d, 6.6)	3.05 and 3.17 (19.0)	83.48	81.51	1783
182	6.06	2.93 and 3.22 (18.9)	90.19	88.05	1780
183	6.12	2.89 and 3.11 (19.2)	90.10	88.35	1784
184	6.35	3.38 and 3.53 (18.9)	93.21	89.78	1784

Figure 3.6 *ORTEP diagram of* **182**.



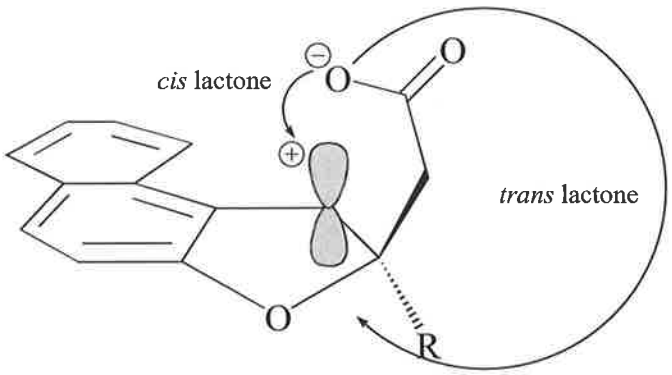
The stereochemistry of these products was confirmed by the X-ray structures of both **182** and **183** (**Figures 3.6** and **3.7**). It can be clearly seen that the nitro group was at the *peri* position. Although not clear, the nitro moiety was situated out of the plane of the naphthalene framework. This was more than likely a result of steric factors.

Figure 3.7 *ORTEP diagram of* **183**.



The mechanistic rationale into the stereoselectivity can be easily described by **Figure 3.8**, where it could be seen that facial attack of the carbocation was possible from only one face. Attack upon the opposite face would require severe ring strain.

Figure 3.8



The reactions of the esters were reinvestigated with the use of a catalytic amount of *p*-toluenesulphonic acid (PTSA) (**Table 3.4**). Using the same conditions in the presence of catalytic PTSA, the same products were obtained, similarly in good yield. Reaction times in these instances were identical to those observed with the corresponding carboxylic acids.

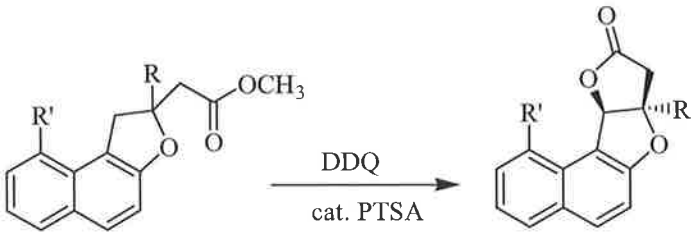
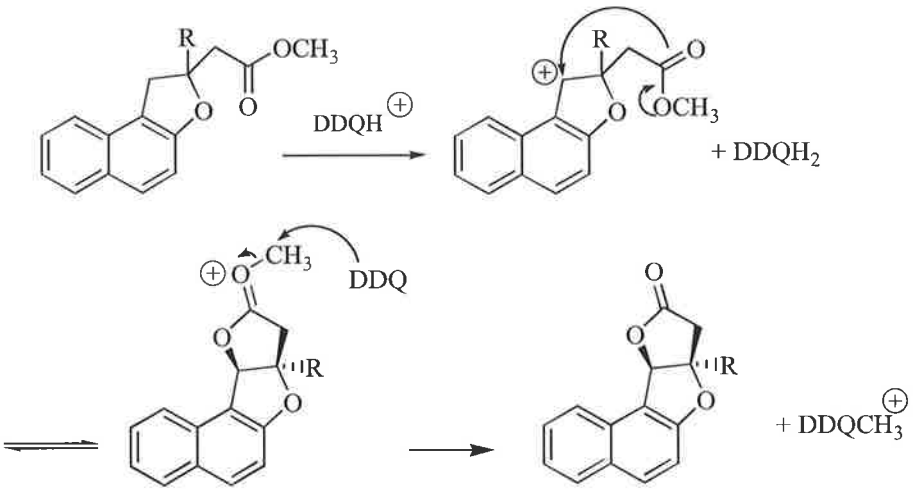


Table 3.4 *Reactions of dihydronaphtho[2,1-b]furan esters with DDQ.*

Entry	Substrate	R	R'	Temperature	Product	Yield %
1	**65a**	H	H	50	**175**	45
2	**113a**	CH_3	H	50	**182**	64
3	**169a**	CH_3	NO_2	80	**183**	85
4	**137a**	Ph	H	50	**184**	80
5	**139a**	4-ClPh	H	50	**185**	75

The mechanistic rationale for these results is similar to the reactions of the acids **178** to **181** **(Scheme 3.11)**. Under the acidic conditions, DDQ exists in equilibrium with the protonated form $DDQH^+$. This now activated species can effect a hydride abstraction to afford the benzylic carbocation, which results in cyclisation and $DDQH_2$. A new molecule of DDQ becomes methylated giving the lactone and another molecule of activated $DDQCH_3^+$. It is this species which can abstract another hydride and so on.

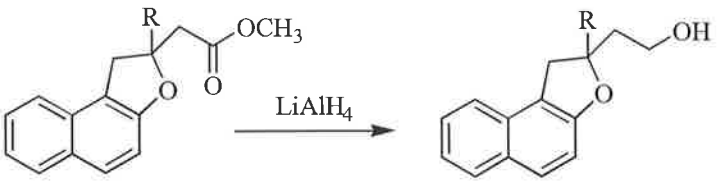
Scheme 3.11



1,2-Dihydronaphtho[2,1-*b*]furans **113a** and **139a** were reduced to give methyl substituted and 4-chlorophenyl substituted alcohols **186** and **187** in order to investigate the same reaction with the alcohol derivatives **(Scheme 3.12)**. This was easily achievable by the reduction of the ester with an excess of lithium aluminiumhydride.

These compounds were easily distinguishable using ^{1}H NMR. A complex coupling pattern was evident between two adjacent methylene groups.

Scheme 3.12

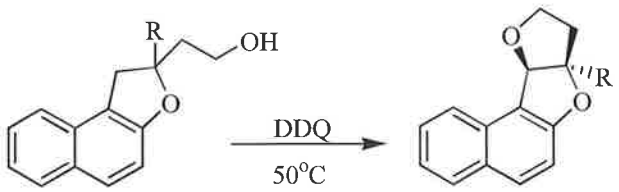


113a (R = CH_3) **186** (92%)

139a (R = 4-Cl-Ph) **187** (85%)

Some literature precedence exists for the formation of cyclic ethers by the intramolecular addition of an alcohol to an alkene facilitated by DDQ.[106,107] The reactions of the alcohols with DDQ resulted in the major product being the *cis*-cyclised difuran (**Scheme 3.13**). These products were easily identified using ^{1}H NMR spectroscopy. There was no sign of neither a resonance due to an alcohol group nor any sign of a downfield resonance of an aldehyde due to oxidation of the alcohol. Instead, a downfield singlet for the naphthylic proton was observed which indicated that the cyclisation giving the *bis* furans had occurred. These naphthylic signals appeared at δ 5.64 and 5.96 ppm for **188** and **189** respectively. Interestingly these reactions proceded with out the use of acid catalysis. Presumably the DDQ could still form an equilibrium with its activated $DDQH^+$ form in this reaction medium. Furthermore, these products were substantially less polar than their precursors and were easily purified by flash chromatography.

Scheme 3.13



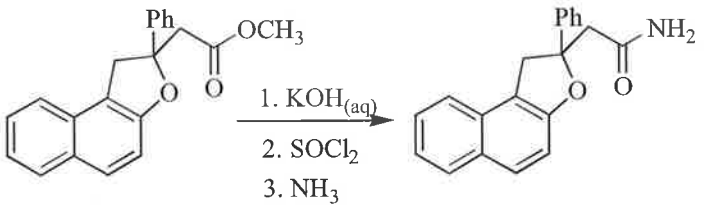
186 (R = CH_3) **188** (82%)

187 (R = 4Cl-Ph) **189** (88%)

The last reaction investigated was with the amide **190**. The synthesis of the amide **190** was achieved in good yield by the one pot reaction of the ester **137a**, firstly

base catalysed hydrolysis of the ester with potassium hydroxide. The acid chloride was generated by treatment of the crude acid with thionyl chloride. Ammonia was then condensed into the vessel at low temperature gave amide **190** (**Scheme 3.14**).

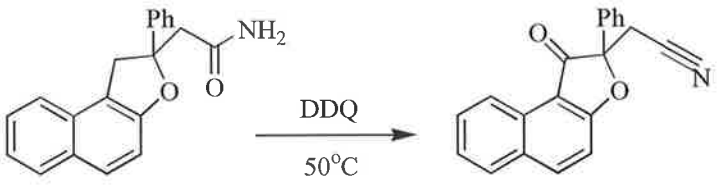
Scheme 3.14



137a **190** (76%)

The reaction of **190** with one equivalent of DDQ did not give the cyclic lactone or the amide, but instead conversion of half the material to the cyano compound **191** occurred along with recovery of the remainder of the starting material (**Scheme 3.15**). The optimal yield of **191** was obtained when two equivalents of DDQ were used. As can be seen by the comparison of the ^{1}H NMR (**Figure 3.8**), both the amide signals, and the protons on the carbon α to the naphthyl skeleton were no longer present in the reaction. Other characteristic data for **191** included the presence of only two carbon resonances in the sp^3 region in the ^{13}C NMR and the presence of a carbonyl signal at δ 197.30 ppm. The infrared spectrum contained both stretches at 1704 and 2258 cm^{-1} for the carbonyl and nitrile respectively.

Scheme 3.15

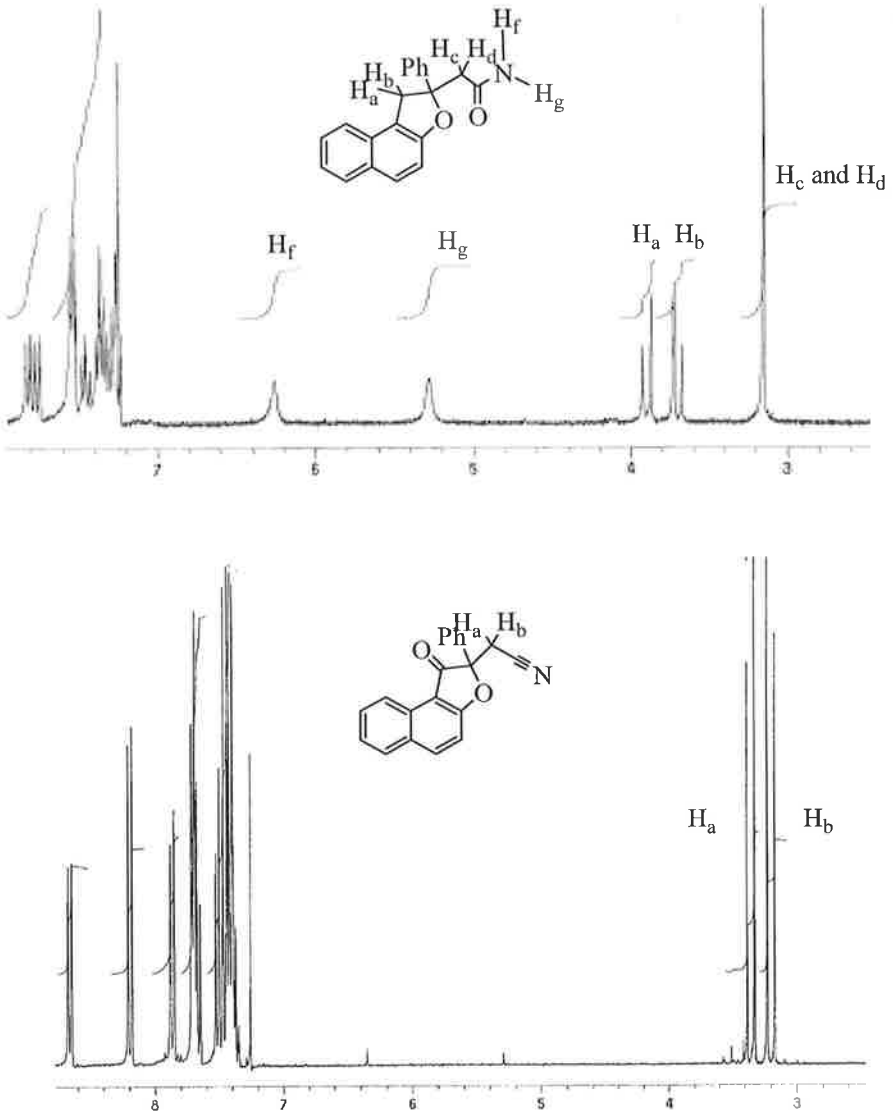


190 **191**

(45% conversion) 1 equiv.DDQ

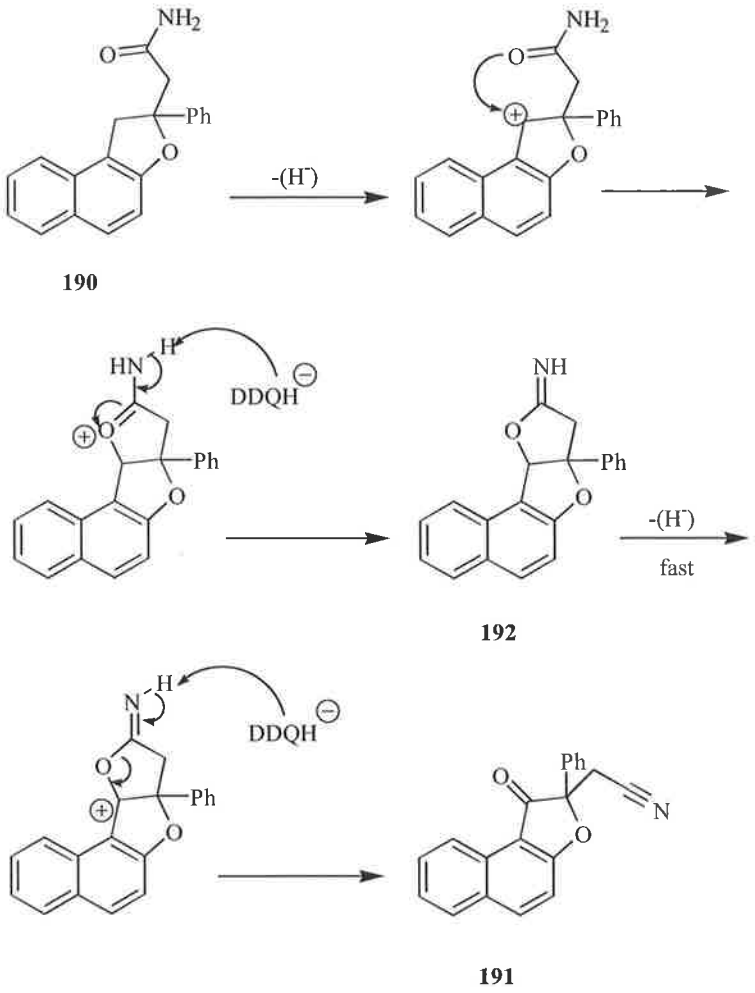
(90%) 2 equiv. DDQ

Figure 3.8 *^{1}H NMR spectra of* **190** *and* **191**.



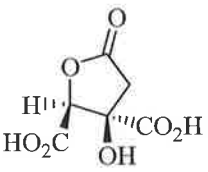
The mechanism describing this reaction (**Scheme 3.16**) was similar to the reaction of the esters in **Table 3.4**. The cyclic intermediate **192** is more readily oxidized by DDQ than the first hydride abstraction. The second carbocation, more stable than the first, collapses by the loss of a proton from the imine to give the cyano compound. As one equivalent of DDQ resulted in the formation of 50% product the rate determining step was the first hydride abstraction. It has been reported in the literature that when oxygen is in the benzylic position the rate of hydride abstraction increases.[108] This fact supports the findings of the double oxidation.

Scheme 3.16

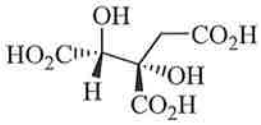


Using this established methodology it may be possible to synthesise enantiomerically pure citric acid derivatives like (+)-hibiscus acid **193**,[109] structurally similar acyclic (-)-*allo*-hydroxycitric acid **194** and newly discovered amino acid residue **195** (**Figure 3.9**).[110] (+)-Hibiscus acid **193** has been isolated from *Hibiscus sabdriffa*, which is used as Roselle tea in some Asian countries, and been shown to be an inhibitor of porcine pancreatic α-amaylase.[111] (-)-*Allo*-hydroxycitric acid **194**, isolated from *Garcinia cambogia* possesses some interesting biological properties.[112] Diol **194**, structurally differing to **193** by virtue of hydrolysis of the lactone, has been shown to be an effective inhibitor of ATP-citrate lysase, resulting in depression in fatty acid synthesis.[113,114] Proline analogue **195** was identified in a cyclic peptide isolated from a *Streptomyces* culture, which was believed to effect apoptosis in human pancreatic carcinoma AsPC-1 cells.[110]

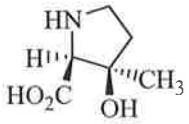
Figure 3.9



193



194

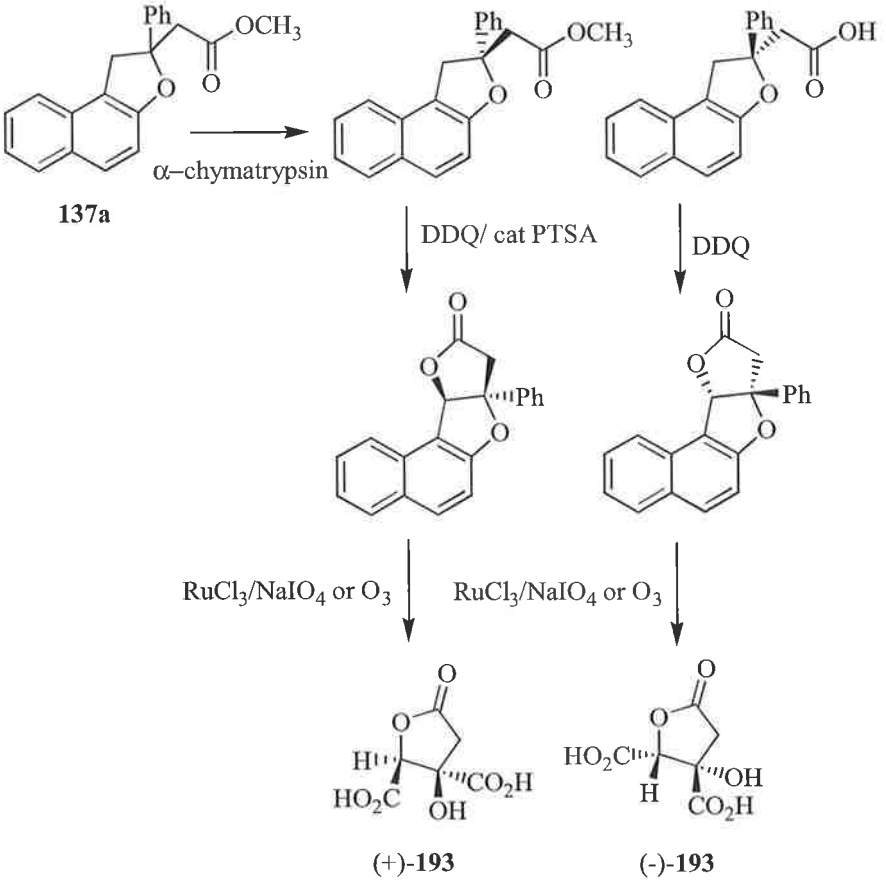


195

The synthesis of **193** and **194** could be achieved by the enzymatic cleavage of the methyl ester by α chymotrypsin, to give opposite sets of enantiomers of both acid and unreacted ester (**Scheme 3.17**). α-Chymotrypsin has been shown to resolve enantiomers of 2-ester substituted 1,2-dihydronaphtho[2,1-*b*]furans efficiently. The synthesis of enantiopure amino acids has been accomplished by the ruthenium tetroxide mediated oxidative degradation of enantiopure tetrahydroindolenes and indolenes.[115,116]

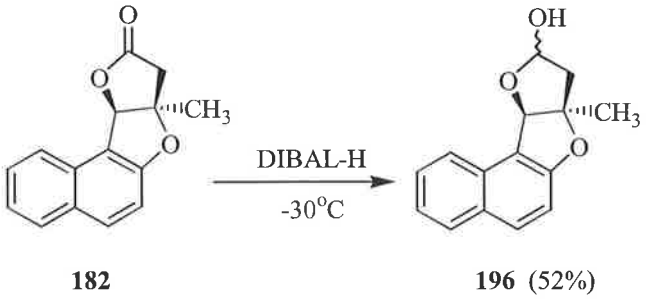
It is envisaged that both the enantiopure ester and acid could be reacted with DDQ to give enantiomerically pure lactones in a single step. The final step would then be either ruthenium tetroxide facilitated cleavage to afford the enantiopure citric acid derivative **193**. This process could also be obtained by the use of ozone.[117] Thus the use of the naphthalene template would make it possible to observe stereochemical control. Hydrolysis of (-)-**193** would then afford bio-active citric acid derivative **194**. For the synthesis of **195**, this methodology would need to be extended to the cyclisation of amines. All these natural products would be highly desirable targets in synthesis owing to their biological properties. It is envisaged that amino acid **195** could be derived from 1,2-dihydronaphtho[2,1-*b*]furan **113a** by first converting the ester to the primary amine followed by a cyclisation effected by DDQ and subsequent ozonolysis.

Scheme 3.17



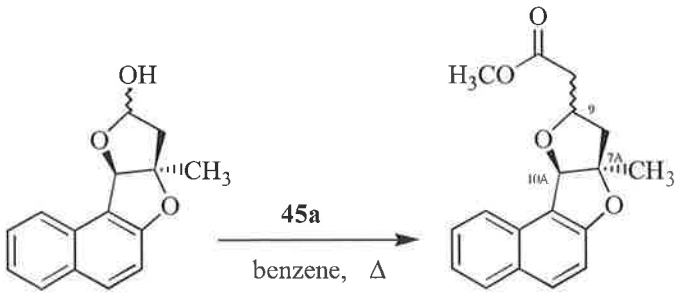
One final aspect of this investigation was the conversion of the lactone **182** to its corresponding lactol **196**. This was achieved using DIBAL-H, at low temperatures, in moderate yield (**Scheme 3.18**).

Scheme 3.18



Lactol **196** in solution existed in the hemiacetal form, as a mixture of diastereomers. Due to its innate instability and the complexity of the NMR data, the hemiacetal was immediately reacted with an excess of **45a** in refluxing benzene overnight to afford the diastereomeric mixture of difurans *cis/trans* **197** (**Scheme 3.19**).

Scheme 3.19



196 **197** (74%)

The reaction occurred with a high degree of stereoselectivity (80% *de*). Unfortunately, using a ROESY experiment, it was not possible to determine the stereochemistry of the third chiral centre as no indicative crosspeaks were observed. The two diastereomers could not be separated by chromatography. In the ^{1}H NMR, the signals for both diastereomers were unobscured and it was possible to identify the naphthylic protons at δ 5.68 and 5.48 ppm (both singlets) for the major isomer and minor isomers respectively. The proton upon the newly formed chiral centre at C9 appeared downfield for both isomers at δ 4.13 (major isomer) and 4.51 ppm (minor isomer) and experienced coupling from four neighbouring protons. With the use of 2D NMR experiments, namely HMQC and HMBC, the naphthylic and the adjacent quaternary carbons could also be assigned for both isomers from the ^{13}C NMR. The major isomer exhibited resonances at δ 87.46 (C10A), 96.18 (C7A) and 73.94 ppm for the carbon of the new chiral centre of the newly formed tetrahydrofuran at C9. Likewise, for the minor isomer δ 87.99 (C10A), 96.56 (C7A) and the new chiral carbon C9 at 75.44 ppm.

In conclusion, this work has the potential to be extended upon in several areas. The major product of the electrophilic substitution of the 1,2-dihydronaphtho[2,1-*b*]furan **113a** had substitution at the C9 position and could therefore be further reacted to give furonaphthoquinone products. If one utilizes the work of Godbole,[38] it should be possible to access these furonaphthoquinones barring any unforeseen complications with the proximity of the 9-substituent with the furan ring. In any respect, this needs to be investigated. High yielding reaction conditions have been described for the oxidative cyclisation of 1,2-dihydronaphtho[2,1-*b*]furans utilising DDQ. The oxygen migration reaction forming the nitrile needs further investigating. The scope of the rearrangement should be investigated to determine if there is broad applicability. And finally, the utility of α-chymotrypsin needs to be examined due to potential application to the synthesis of

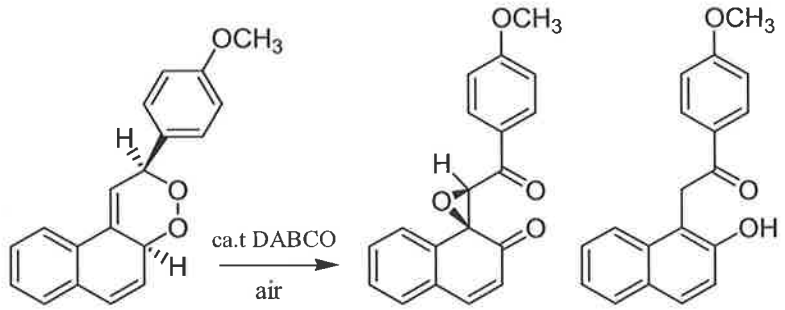
targets such as (+)-hibiscus acid **193** and (-)-*allo*-hydroxycitric acid **194**. This approach would be the first from naphthalene derived starting materials.

CHAPTER 4

SYNTHESIS OF SOME SPIROEPOXIDES.

A serendipitous discovery was made whilst investigating the base catalysed rearrangement of the 1,2-dioxine **79**. When **79** was allowed to react with a catalytic amount of DABCO in dichloromethane overnight (**Scheme 4.1**) spiroepoxide **198** was obtained as the major product. A small amount of the aromatised product **133** was also isolated by chromatography. 1-(β-Keto)-2-naphthol **133** did not precipitate from the solution when dichloromethane was the reaction solvent, however, the conditions employed did not preclude the presence of either oxygen or water as the vessel was left open to aerial exposure.

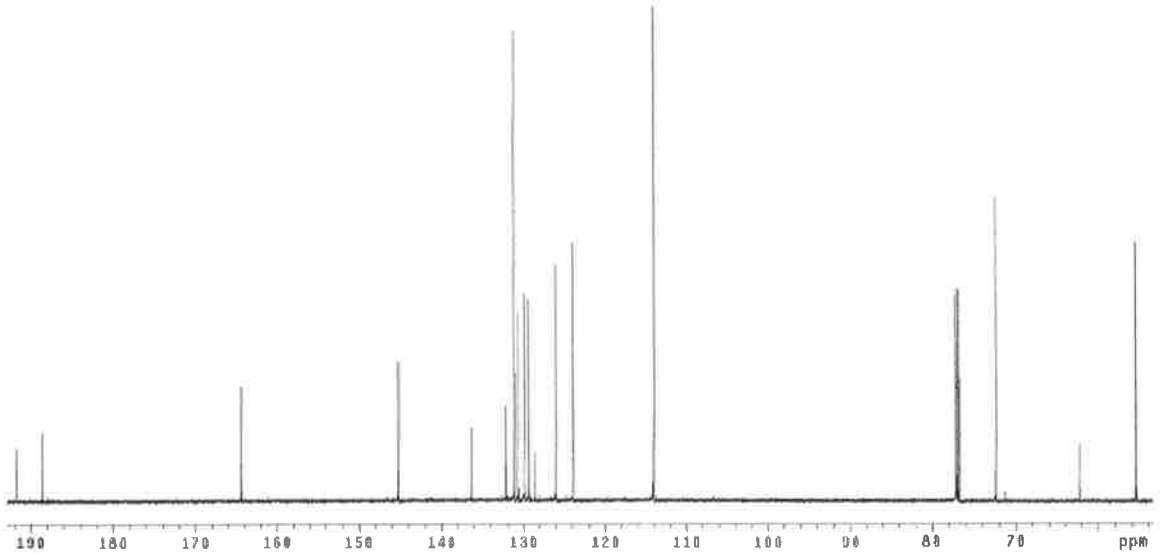
Scheme 4.1



79 **198** (61%) **133** (11%)

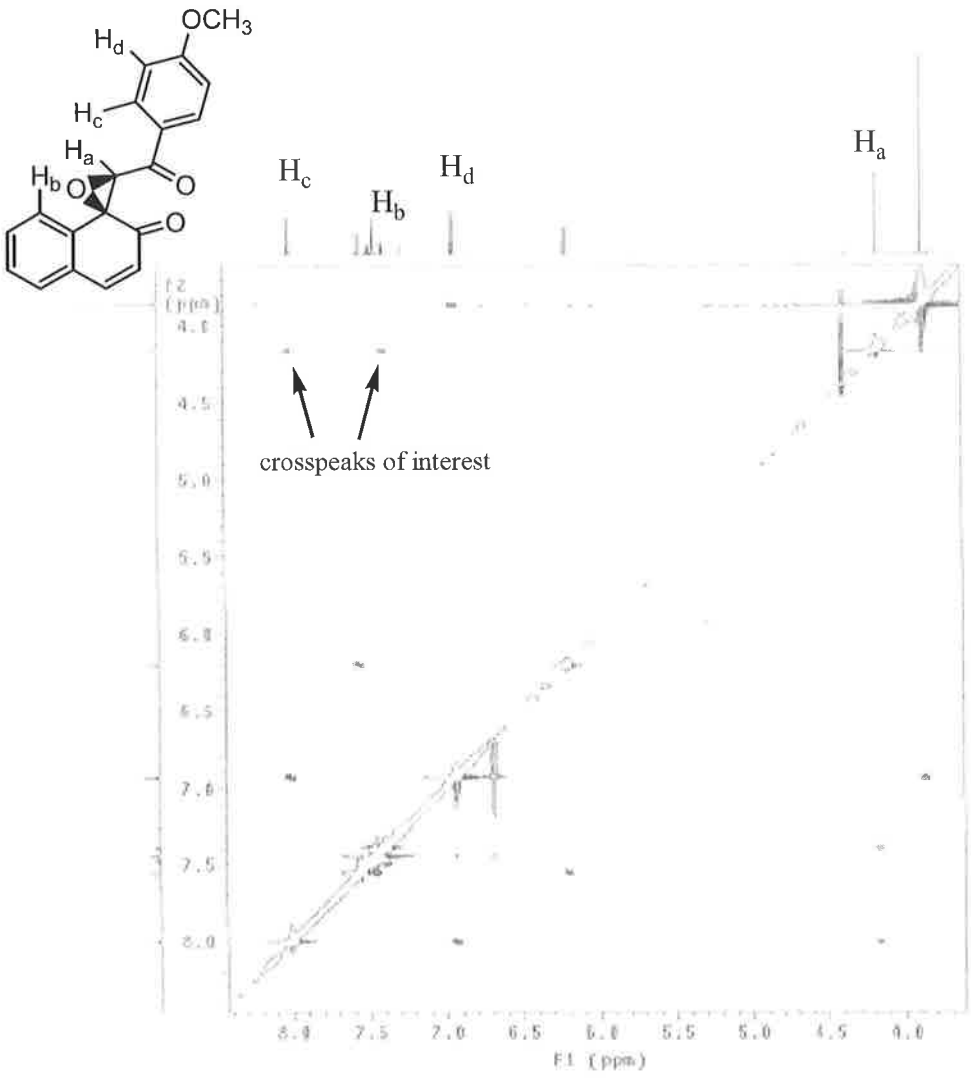
Characteristic data for **198** included a singlet in the ^{1}H NMR at δ 4.16, which integrated as one for the solitary epoxide proton. A doublet at δ 6.20 was assigned to the α-proton in the α,β-unsaturated ketone. The IR spectrum showed only one broad stretching in the carbonyl region at 1682 cm^{-1}. The ^{13}C NMR spectrum (**Figure 4.1**) revealed carbonyl signals at δ 188.61 and 191.71 ppm and three sp^3 carbon resonances. One sp^3 carbon was due to the methoxy group and the other two sp^3 signals were due to the carbons of the epoxide. The epoxide pair consisted of a strong signal at δ 62.22 ppm, along with the partner quaternary weak resonance at δ 72.37 ppm. The structural framework of **198** was confirmed by the use of 2D NMR techniques. In the HMBC of **198**, there were observed between the epoxide proton H_a at δ 4.16 with both the carbonyl signals and the quaternary carbon of the epoxide at δ 62.17 ppm in the ^{13}C NMR.

Figure 4.1 *^{13}C NMR of* **198**.



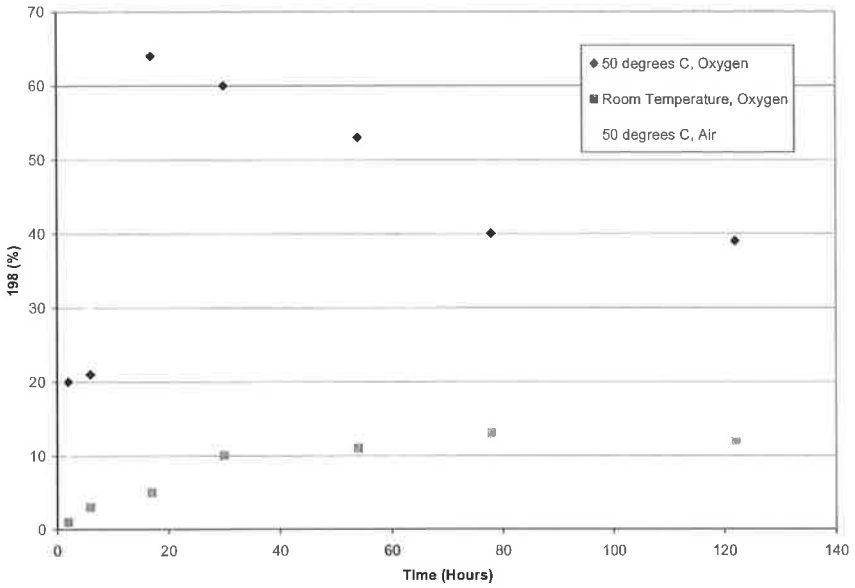
The stereochemical assignment about the two chiral centres of the epoxide could be clearly determined from the ROESY spectrum. This was possible due to the rigid nature of the product and a crosspeak observed between the epoxide singlet and the *peri*-proton of the aromatic ring. (**Figure 4.2**). This was valid as it was easy to see the signals owing to the *p*-methoxy substituted aromatic ring in the ^{1}H NMR, which were clearly the most intense signals in the ^{13}C NMR.

Figure 4.2 *ROESY spectrum of* **198**.



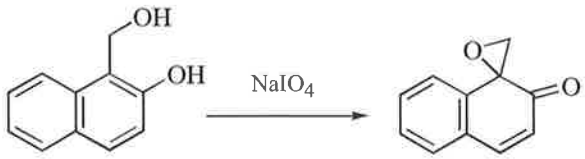
The reaction was repeated upon an NMR scale, a variety of conditions were employed and are presented in **Figure 4.3**. For reactions carried out under an oxygen atmosphere, a balloon filled with oxygen was attached to a luer lock and a needle perforated through the NMR tube lid. By these means, it was possible to keep the system under positive pressure for the required duration of the reaction. The plot of the time relationship (**Figure 4.3**) indicated that the best conversions could be obtained when the reaction was allowed to proceed for about 20 hours in the presence of both DABCO and an oxygen atmosphere with warming to 50 °C. Quantities of **198** present in solution gradually decreased after this time. Interestingly, the formation of the precipitates typical of the Kornblum-DeLaMare products, and their subsequent disappearance with time suggested that these were key intermediates in the oxidation. In these reactions, 1,3,5-trimethylbenzene was used as an internal standard.

Figure 4.3 *Reactions of dioxine* **79** *with DABCO.*



Upon examination of the literature, it was discovered that few examples of these types of compounds and processes leading to the formation of such products, have been reported. The synthesis typically involved the oxidation of aromatic alcohols. The synthesis of naphthospiroepoxide **200** was achieved by the oxidation of electron rich 1-methyl alcohol substituted 2-naphthol **199** with the use of sodium periodate (**Scheme 4.2**).[118] This type of reaction has also been reported with benzo-analogues[119-122] and the reaction could also be performed using iodobenzene diacetate as the oxidant.[123]

Scheme 4.2

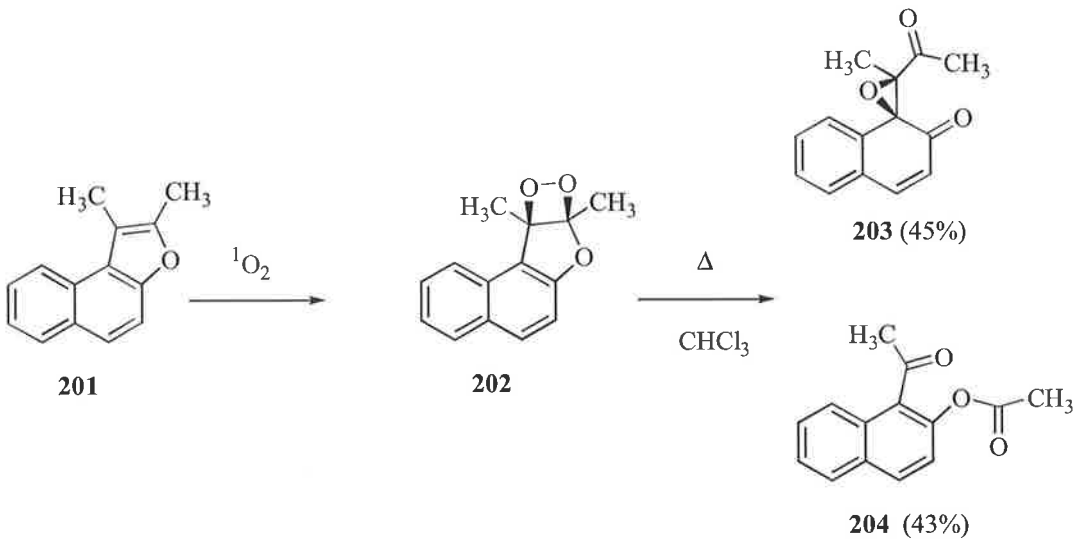


199 **200** (61%)

The research group of Adam utilised several methodologies in the synthesis of spiroepoxides from furan precursors.[124,125] The treatment of naphtho[2,1-*b*]furan **201** with singlet oxygen afforded isolable dioxetane **202** (**Scheme 4.3**). Thermal decomposition resulted in a rearrangement to give the spiroepoxide **203** and [2π + 2π] retro Diels-Alder cleavage product **204**. This reaction was performed upon a variety of naphthofurans and several benzofurans. In an independent study, the reaction of phenanthrafurans with singlet oxygen afforded analogous spiroepoxide products.[126]

Catalytic addition of bromide anion has also been employed in the decomposition of these dioxetanes to give spiroepoxides.[127]

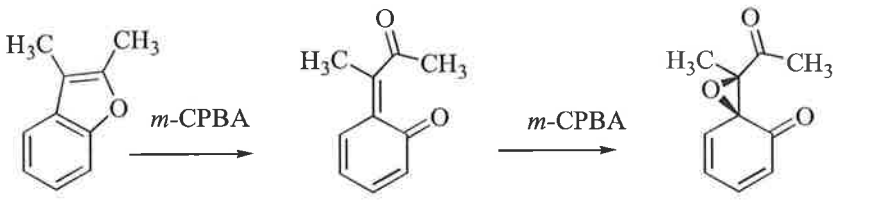
Scheme 4.3



201 **202**

Oxidation to the spiroepoxide **207** could also be effected by the treatment of benzofurans **205** with *m*-CPBA (**Scheme 4.4**). It was proposed that first the furan ring opens to give a quinone methide **206**, which is subsequently epoxidised. These products were reported to be thermally unstable leading to either rearrangement to an aromatised acetal or dimerisation products. These reactive spiroepoxides could be trapped as Diels-Alder adducts.

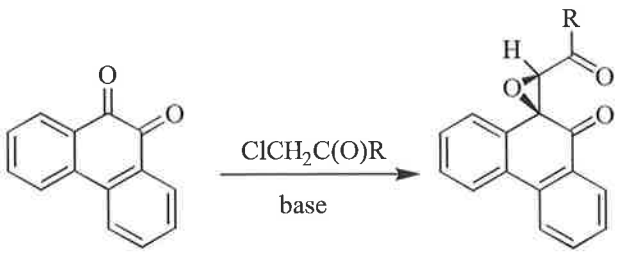
Scheme 4.4



205 **206** **207** (59-68%)

Utilising a different strategy, Awad *et al.* accomplished the synthesis of the anthracene analogues **209** by the Darzens condensation of phenanthraquinone **208** (**Scheme 4.5**) with various substrates.[128,129] These products were all isolated with the same stereochemistry as for that observed in the oxidation of **79**. It was thought that this was a result of the remote ketone capable of enolisation, thus giving **209** as the thermodynamic product with the acyl group facing away from the *peri*-proton. Analogous products could be obtained when the reaction was performed with chrysenequinone.[130]

Scheme 4.5

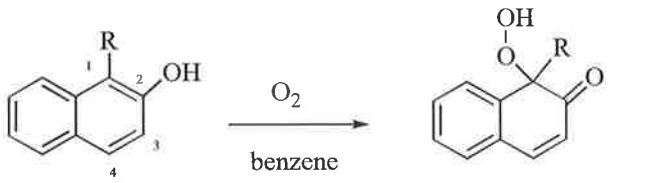


208 R = substituted phenyl **209** (39-79%)

No autoxidation reactions have been reported for 1,2-dioxines leading to such products. Many autoxidation reactions are known which result in the formation of hydroperoxides.[131] These can occur unassisted in the presence of oxygen, but some require the use of catalytic conditions such as strong base or light to initiate the process.[131] The following discussion contains a brief overview of some known autoxidations and formation of hydroperoxides which are relevant to our discovery.

Several reports have been published regarding autoxidations of electron rich aromatic alcohols.[132-138] Carnduff *et al.* was the earliest to report this phenomenon, with the autoxidations of 1-substituted 2-naphthols **210** which lead to the formation of dearomatised hydroperoxides **211 (Scheme 4.6)**.[133]

Scheme 4.6



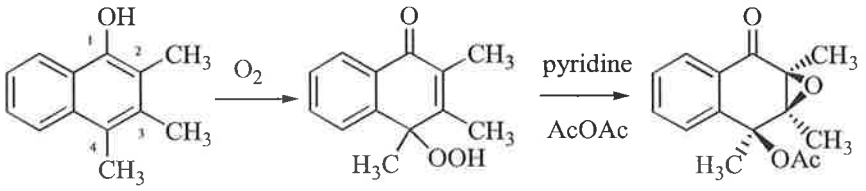
210 R = alkyl **211** (85-94%)

The tendency was that the larger the alkyl substituent the faster the autoxidation proceded. The rationale was that in order to relieve the *peri*-strain existing between the proton at C8 and the alkyl group at C1, sp^3 hybridisation occurred via a radical chain mechanism, leading to the dearomatisation and incorporation of oxygen into the structure. Infact, this process was reported to have occurred in the absence of an initiator or light, the hydroperoxide precipitating from the benzene solution. Interestingly, the autoxidation of 1-phenyl-2-naphthol did not occur. Carnduff has also reported that when these hydroperoxides were exposed to basic conditions, the

hydroperoxide underwent several reactions including an intramolecular Michael addition of the hydroperoxy anion to the α,β-unsaturated ketone.[139,140]

Greenland *et al.* reported the autoxidation of 3,4-disubstituted 1-hydroxynaphthalene **212** along with various other similar substrates, giving rise to hydroperoxide **213** as outlined in **Scheme 4.7**.[136] It was found that in the absence of a substituent at C4 no autoxidation occurred in these systems. Thus, this work supported Carnduffs findings where the driving force for the process seemed to be dependent upon the relief of the *peri*-strain. As found in the work by Carnduff these reactions also occurred without the use of catalysts and in the absence of light. This hydroperoxide could also be used to stereospecifically direct an intramolecular epoxidation under basic conditions to afford **214**.

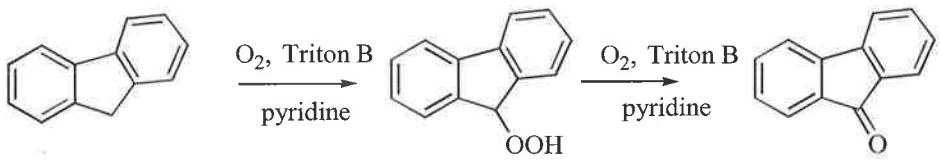
Scheme 4.7



212 **213** (58%) **214**

Benzylic autoxidations have also been reported.[131,141] One notable reaction is the autoxidation of fluorene **215** in pyridine in the presence of catalytic Triton B (**Scheme 4.8**). Triton B, a quaternary ammonium hydroxide, is a source of soluble hydroxide in pyridine. It is believed that the autoxidation proceeds via an ionic mechanism, where fluorene is deprotonated to afford an aromatic anion which reacts with molecular oxygen to afford isolable hydroperoxide **216**. Further reaction of the hydroperoxide **216** leads to the formation of fluorenone **217**.

Scheme 4.8

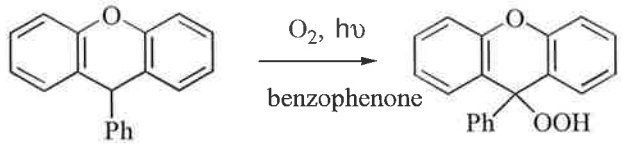


215 **216** **217**

Other benzylic oxidations have been reported to occur with oxygen to also afford α-hydroperoxides. In these cases, a catalyst such as 9,10-dicyanoanthracene

(DCA) / methyl viologen (MV^{2+}) or benzophenone had to be used in the presence of light.[142-144] These type of hydroperoxides also had to be considered potential intermediates in the spiroepoxide formation. **Scheme 4.9** contains an example of this process. Light is required to facilitate the reaction of a benzophenone–sensitised oxidation of phenyl xanthene **218** to hydroperoxide **219**.[143]

Scheme 4.9

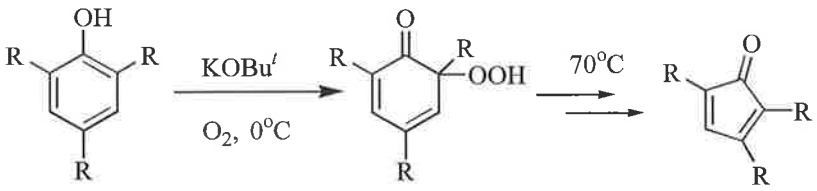


218 **219**

There have been many reports covering autoxidation of organic compounds facilitated by singlet state oxygen, but as our initial study had involved the use of DABCO, a well known singlet oxygen quencher,[145] its involvement in the process was highly unlikely and so shall not be discussed further.

Phenols of the type **220** can be oxidised under basic conditions in an oxygen atmosphere to afford hydroperoxide products **221** (**Scheme 4.10**).[146] When this reaction is performed at elevated temperatures further reactions occur resulting in the formation of ring contracted cyclopentadienones **222**.[146,147] This same kind of reaction has been reported to have occurred when the phenol was treated with hydrogen peroxide in the presence of sodium bicarbonate or by treatment of **220** with transition metal catalysts in the presence of molecular oxygen.[148]

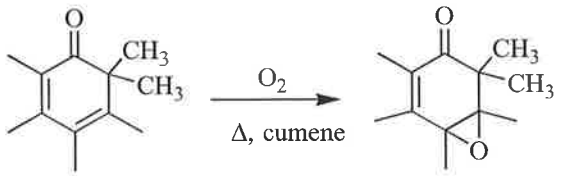
Scheme 4.10



220 **221** **222**

Other relevant oxidations that have been reported in the literature are the epoxidation γ,δ-double bond in **223**. Heating of the unsaturated ketone **223** in cumene at 110 °C under an oxygen atmosphere afforded **224** (**Scheme 4.11**).[149] An interesting feature of the report was the unreactivity of the olefin adjacent to the ketone.

Scheme 4.11



223 **224** (90-95%)

The aims of this work were therefore to further explore the generality of this new spiroepoxidation reaction and to examine the involvement of the 1-(β-keto)-2-naphthols as intermediates in this process. It was also of interest to determine the scope of substrates that would undergo this process.

It was decided that a larger pool of 1-(β-keto)-2-naphthol products from Chapter 2 should be subjected to the catalytic DABCO conditions (**Table 4.1**). 1-(β-Keto)-2-naphthols **103/104**, **114/115**, **131** to **135**, and **153/161** obtained by the DABCO catalysed degradation of dioxines **75-84** were allowed to react using a general protocol. All reactions in **Table 4.1** were performed upon a 50 mg scale, by stirring vigorously either as a suspension or as a solution in *d*-chloroform under an atmosphere of oxygen. It was found that when these 1-(β-keto)-2-naphthols were treated under the same conditions, the spiroepoxide could be obtained in similar, if not better yields. This was true with the exception of **153/161** (Entry 8), where no such reaction occurred. **Table 4.2** contains a summary of characteristic spectral data for the unusual spiroepoxides **198** and **225** to **230**.

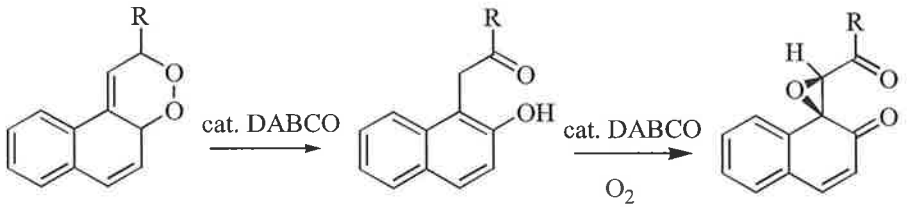


Table 4.1 *Reaction of 1-(β-keto)-2-naphthols with DABCO in the presence of oxygen.*

Entry	Dioxine	R	1-(β-keto)-2-naphthol	Product	Yield %
1	**75**	CH_3	**103/104**	**225**	58
2	**76**	cyclohexyl	**114/115**	**226**	85
3	**77**	Ph	**131**	**227**	73
4	**78**	4-Cl-Ph	**132**	**228**	64
5	**79**	4-CH_3O-Ph	**133**	**198**	68
6	**81**	3-Br-Ph	**134**	**229**	74
7	**82**	1-naphthyl	**135**	**230**	81

8	**84**	CH_2OH	**153/161**	No reaction	-

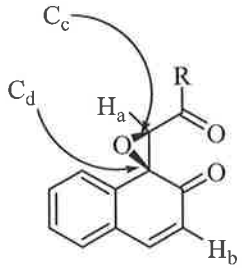


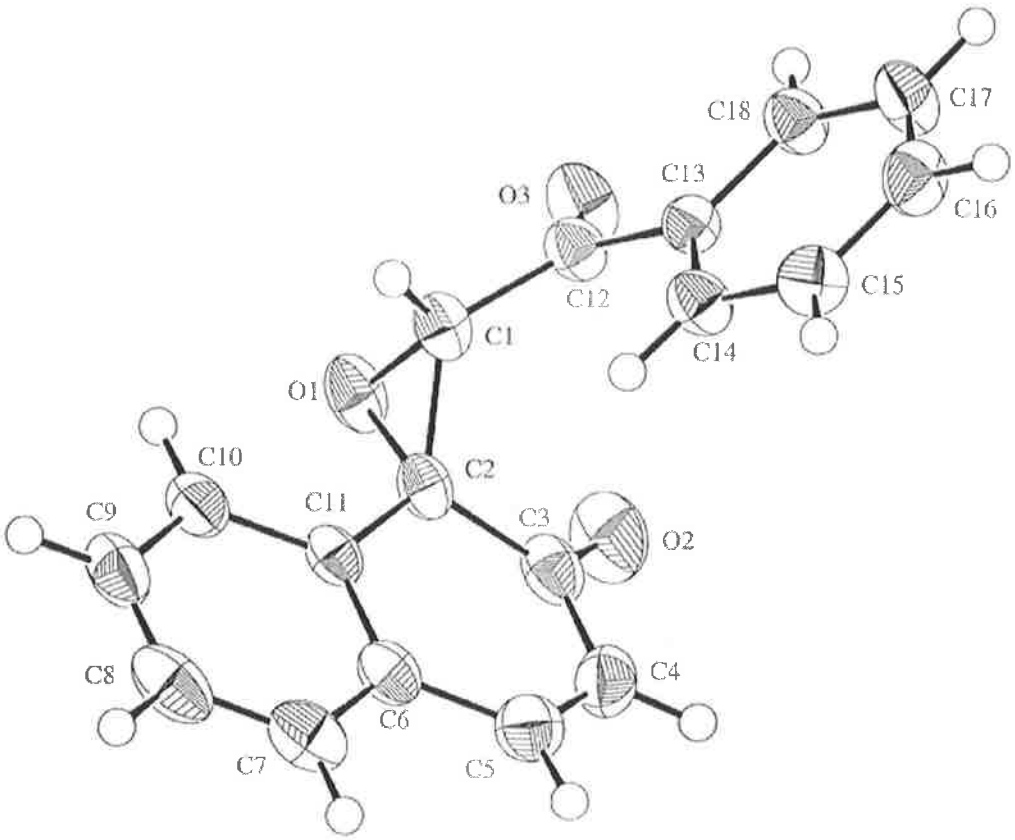
Table 4.2 *Characteristic data for spiroepoxide products.*

Epoxide	δ H_a	δ H_b (*J* Hz)	δ C_c	δ C_d	δ C=O	IR (C=O)
225	3.67	6.26 (9.9)	73.22	62.66	192.38, 202.30	1716, 1680
226	3.77	6.24 (10.0)	72.02	62.44	192.38, 206.43	1707, 1678
227	4.22	6.22 (9.9)	72.21	62.23	190.31, 191.56	1699, 1678
228	4.18	6.23 (9.9)	71.87	62.08	189.70, 191.55	1699, 1678
198	4.16	6.20 (10.2)	72.37	62.17	188.43, 191.53	1682
229	4.18	6.22 (9.9)	71.72	62.09	189.73, 191.66	1702, 1678
230	4.38	6.25 (10.2)	72.50	62.95	191.90, 192.83	1676

It was of interest to note that the substituent adjacent to the ketone did not have to be an aryl group but could also be simple alkyl substituents. Additionally, the substrate bearing the extra hydroxyl group did not undergo the reaction. A report extending upon Carnduffs work had found that when the hydroxyl group of the 2-position was involved in hydrogen bonding, in their case with fluoride, no autoxidation was observed in 2-naphthols.[150] It is plausible that an intramolecular hydrogen bonding effect could be enhanced in the presence of the extra hydroxyl group. Otherwise, the lack of reactivity could extend to the poor solubility of **153/161** in chloroform. To examine this further, the reaction was repeated for **153/161** in d_6-DMSO under identical conditions, however, starting material was again recovered.

It was possible to obtain an X-ray structure of **227**, thus supporting the earlier assignment of the stereochemistry about the epoxide (**Figure 4.4**).

Figure 4.4 *ORTEP diagram of* **227**.



As 1-(β-keto)-2-naphthols **103/104**, **114/115** and **131** to **135** were confirmed to be intermediates, it was decided to examine the reaction under a range of conditions to elucidate the mechanism. **Table 4.3** describes the various conditions to which the 1-(β-keto)-2-naphthols were subjected. Typically, these reactions were performed on a 30 mg scale with vigorous stirring in *d*-chloroform unless specified. Vigorous stirring was often required as some substrates had poor solubility. No effort was made to determine relative rates of reaction; with the exception of Entry 6. These reactions were typically left overnight and the products purified by chromatography using florisil as the adsorbent.

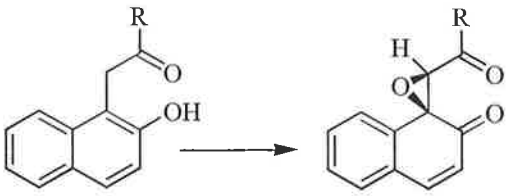


Table 4.3 *Reactions of 1-(β-keto)-2-naphthols under different conditions.*

Entry	Substrate	Conditions	Product	Yield %
1	**132**	Dark, DABCO	**228**	67
2	**132**	Methanol	**228**	35

3	**132**	Acetonitrile	**228**	61
4	**103/104**	-	**225**	55
5	**132**	Imidazole	**228**	87
6	**103/104**	TEMPO, DABCO	**225**	55
7	**131**	1,4-Dinitrobenzene, DABCO	**227**	72
8	**131**	$POEt_3$, DABCO	Complicated mixture	-
9	**132**	*N*-Methylmorpholine *N*-oxide	**228**	Trace
10	**132**	Urea Hydroperoxide	**228**	5

The reaction seemed to take place equally as well in the dark (Entry 1), suggestive of a Carnduff like hydroperoxide intermediate. It was thought that the role of DABCO was merely as a base catalyst, and entries 2, 3, and 4 demonstrate that this process occurs in the absence of base, although not to the extent seen with the use of an amine base. This suggests that the mechanism of autoxidation is not ionic in nature as discussed in **Scheme 4.8**. The use of imidazole gave an excellent yield of the spiroepoxide **228** (Entry 5). The crude ^{1}H NMR of this reaction exhibited the presence of what seemed to be the opposite diastereomer, with an extra set of minor signals for the epoxy proton and characteristic doublet for the α proton of the α,β-unsaturated ketone. Purification by chromatography, however, only resulted in the isolation of the one diastereomer. Presumably the minor diastereomer epimerised by the reported enolisation as in the anthracene analogues.[128]

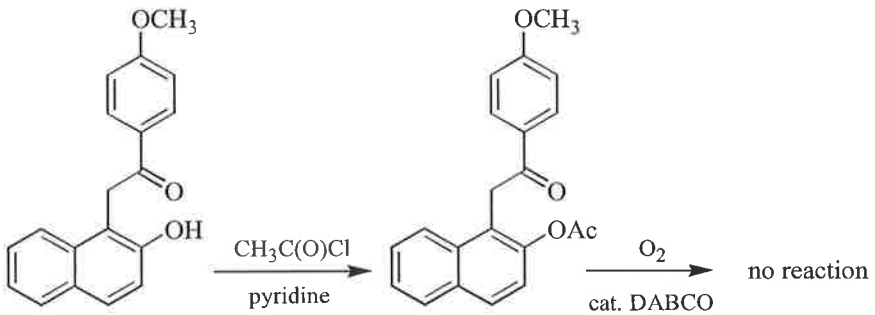
The reaction of **103/104** in the presence TEMPO (Entry 6) indicated that the reaction was temporarily retarded, in comparison to the control experiment yet still affording a good conversion to the spiroepoxide. Carnduff had examined the effects of 2,4,6-tri-*t*-butylphenol in this manner and observed the same results with the formation of the hydroperoxides. The use of 1,4-dinitrobenzene (Entry 7) exhibited no effect upon the reaction. From this result it can be concluded that the process does not favour an $S_{RN}1$ mechanism as 1,4-dintrobenzene is an efficient inhibitor of $S_{RN}1$ reactions.[151]

The reaction was also carried out in the presence of triethylphosphite (Entry 8) in the hope that the proposed intermediate hydroperoxide could be trapped as its alcohol, but unfortunately, this reaction was not clean and lead to decomposition. The reaction of substrate **132** with *N*-methylmorpholine-*N*-oxide was examined (Entry 9) under a nitrogen atmosphere, to determine whether the delivery of the oxygen could be facilitated in this manner, or perhaps that DABCO *N*-oxide was forming and was involved in the oxidation of the 2-naphthols. The reaction only lead to a small amount

of **228**, presumably this was a result of the system containing a low concentration of oxygen in the solvent. Finally, the reaction of **132** with multiple equivalents of urea hydroperoxide under an inert atmosphere (Entry 10) also resulted in a low conversion to **228**. This implied that this reaction does not occur with hydrogen peroxide as a source of oxygen.

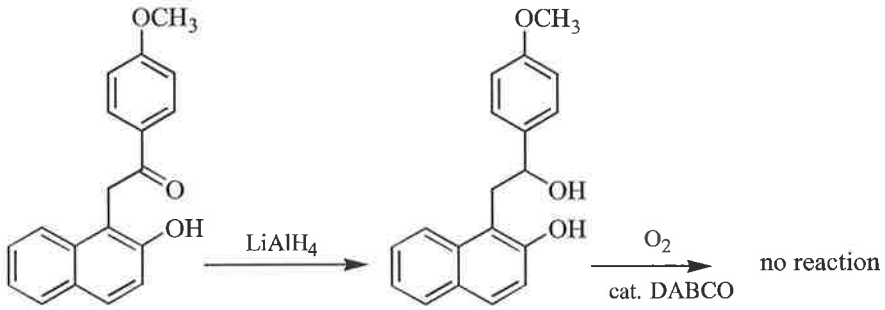
Some derivatives of the **133** were synthesised and examined for reactivity with DABCO in the presence of oxygen (**Schemes 4.12** and **4.13**). No sign of autoxidation occurred when the hydroxyl group was protected as the acetate **231**, suggesting that the mechanism favoured a hydroperoxide intermediate. Diol **232** also did not undergo autoxidation, presumably due to the same grounds of the unreactivity of **153/161**.

Scheme 4.12



133 **231** (72%)

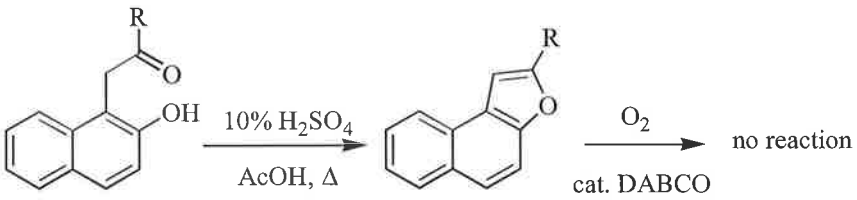
Scheme 4.13



133 **232** (76%)

1-(β-Keto)-2-naphthols **131** and **132** were dehydrated by warming in sulphuric acid diluted in glacial acetic acid (**Scheme 4.14**). The reactions of naphtho[2,1-*b*]furans **233** and **234** using the same conditions employed in the synthesis of the spiroepoxides from the 2-naphthols also resulted in no reaction. As DABCO is reported to be a quencher of singlet oxygen, it seemed that neither the dehydrated naphtho[2,1-*b*]furan, nor the dioxetane, as described by Adam was an intermediate in the autoxidative process.

Scheme 4.14

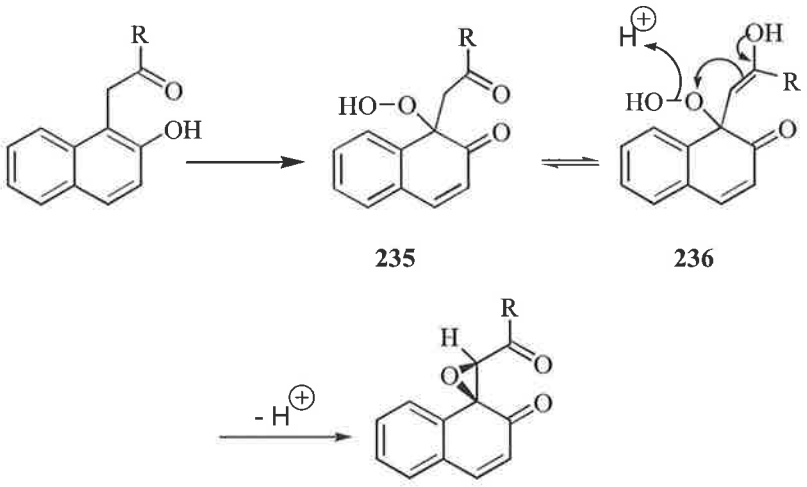


131 R = Ph **233** (59%)

132 R = 4-Cl-Ph **234** (77%)

In summary, based upon the data obtained in this study and the literature precedence, it was possible to propose a mechanism of the formation of these spiroepoxide products (**Scheme 4.15**). The disruption to the aromaticity occurs first with the formation of a hydroperoxide intermediate **235**, akin to those observed by Carnduff.[133] Enolisation promoted by the amine base gives the reactive enolate **236**, which undergoes intramolecular ring-closure to furnish the spiroepoxide and the loss of water. Epoxidation reactions resulting in the expulsion of hydroxide from a hydroperoxide by a carbanion have been reported.[136]

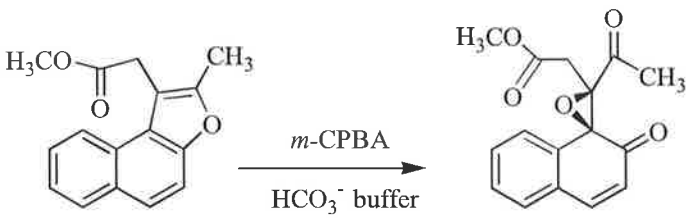
Scheme 4.15



235 **236**

It was of interest to synthesise more functionalised spiroepoxides like **237** (**Scheme 4.16**). Using the chemistry developed by Adam for the reactions of furans and benzofurans,[124] spiroepoxide **237** was synthesised successfully. This was achieved by the treatment of functionalised naphtho[2,1-*b*]furan **162** with excess *m*-CPBA using an aqueous bicarbonate buffer. Interestingly, no sign of other products were present in the crude ^{1}H NMR, including Baeyer-Villager oxidation of the ketones. This methodology provided an alternate pathway to spiroepoxides.

Scheme 4.16



162 **237** (55%)

The ^{1}H NMR spectrum of **237** included the same characteristic doublet at δ 6.11 ppm as observed in all the spiroepoxides synthesised, attributed to the α proton of the α,β-unsaturated ketone. The methylene adjacent to the ester now appeared as an AB quartet at δ 2.50 and 3.06 ppm. The ^{13}C NMR indicated three signals for the carbonyls at δ 169.22, 194.39 and 207.18 ppm and two weak resonances for the quaternary carbons of the epoxide at δ 73.36 and 68.93 ppm. The infrared also confirmed the presence of multiple carbonyls, exhibiting stretches at 1741, 1712, and 1684 cm^{-1}. Thus, complementary to the work of Adam, functionalised spiroepoxides derived from naphtho[2,1-*b*]furans can be synthesised using the methodology described here.

In conclusion, the future directions for this work lie in several areas and could include the transformation of the spiroepoxides, using a literature procedure, to afford aromatised acetals.[125] Further mechanistic data could also be obtained by carrying out the autoxidation upon the substrates with the ketone masked as a thioacetal, in the hope that one could trap the hydroperoxide by an intramolecular oxidation to the sulphoxide. The chemistry pioneered by Adam could be used in conjunction with some more functionalised naphtho[2,1-*b*]furans derived from 1,2-dioxines to give a broader and more functionalised range of spiroepoxides such as **237**.

CHAPTER 5

EXPERIMENTAL SECTION

GENERAL. Solvents were dried by appropriate methods wherever needed.[152] All organic extracts were dried over anhydrous magnesium sulfate. All hemiacetals were purified by column chromatography utilising silica gel (40-63 μm) or florisil (60-100 U.S. mesh) as adsorbent purchased from Merck. Thin-layer used chromatography (TLC) aluminum sheets silica gel 60 F_{254} (40 x 80 mm) from Merck. Melting points were taken on a Reichert Thermovar Kofler apparatus and are uncorrected. Infrared spectra were recorded on a ATI Mattson Genesis Series FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR and ^{19}F NMR spectra were recorded in $CDCl_3$ solution on a Varian INOVA (600 MHz) or on a Varian Gemini 2000 (300 MHz or 200 MHz) instrument, TMS (0.00 ppm) and $CDCl_3$ (77.00 ppm) as internal standards unless otherwise specified. All yields reported refer to isolated material judged to be homogeneous by TLC and NMR spectroscopy unless otherwise specified. Micro analysis were performed at the University of Otago, New Zealand. Accurate mass measurements were made at either at by Kratos at the University of Tasmania, or at Monash University. X-ray crystallography was performed courtesy of Dr E. R. T. Tiekink at the University of Adelaide upon a Rigaku AFC-7*R* diffractometer or at the University of Singapore upon a Bruker AXS SMART CCD diffractometer. Otherwise X-ray crystallography was performed at a Nonius Kappa instrument at Monash University courtesy of Dr G. Fallon. The following materials were purchased from Aldrich and used without further purification. Triphenylalkylidenephosphoranes **45a-h**, 1-naphthaldehyde, Rose Bengal, *bis* (triethylammonium)salt, DDQ, Lithium aluminiumhydride, DIBAL-H (1.5M in toluene), thionyl chloride. All calculations were performed at the AM1 level of theory, using the Spartan® suite of programs.[99]

General Procedure for the Preparation of the Prerequisite Alkenes

The unstabilised phosphorus ylide was generated by the treatment of a suspension of the corresponding phosphonium salt in dry ether with potassium *t*-butoxide. The mixture was stirred ten minutes before the addition of the aldehyde. After 30 minutes, the solution was triturated with hexane and filtered. The solvent was removed from the filtrate and residue subjected to chromatography (silica) to afford the alkene mixture. The requisite vinylic naphthalenes were acquired as follows; 1-vinylnaphthalene[153] **85** was prepared in 71% yield from the action of methylene(triphenyl)phosphorane on 1-

naphthaldehyde; 1-(1-propenyl)naphthalene[154] **86** (*E* : *Z*; 35 : 65) was prepared in 65% yield from the action of ethylene(triphenyl)phosphorane on 1-naphthaldehyde; 1-[(*E/Z*)-2-cyclohexyl-1-ethenyl]naphthalene **87** (*E* : *Z*; 30 : 70) was prepared in 65% yield from the action of cyclohexylmethylene(triphenyl)phosphorane on 1-naphthaldehyde; 1-[(*E/Z*)-2-phenyl-1-ethenyl]naphthalene[155] **88** was prepared in 94% yield from the action of triphenyl(phenylmethylene)phosphorane on 1-naphthaldehyde; 1-[(*E/Z*)-2-(4-chlorophenyl)-1-ethenyl]naphthalene[80] **89** was prepared in 84% yield from the action of [(4-chlorophenyl)methylene](triphenyl)phosphorane on 1-naphthaldehyde; 1-[(*E/Z*)-2-(4-methoxyphenyl)-1-ethenyl]naphthalene[156] **90** was prepared in 60% yield from the action of [(4-methoxyphenyl)methylene](triphenyl)phosphorane on 1-naphthaldehyde; 1-{(*E/Z*)-2-[4-(trifluoromethyl)phenyl]-1-ethenyl}naphthalene[157] **91** was prepared in 84% yield from the action of {[4-(trifluoromethyl)phenyl]methylene} (triphenyl)phosphorane on 1-naphthaldehyde; 1-[(*E/Z*)-2-(3-bromophenyl)-1-ethenyl]naphthalene[158] **92** was prepared in 75% yield from the action of [(3-bromophenyl)methylene](triphenyl)phosphorane on 1-naphthaldehyde; 1-[(*E/Z*)-2-(1-naphthyl)-1-ethenyl]naphthalene[159] **93** was prepared in 53% yield from the action of (1-naphthylmethylene)(triphenyl)phosphorane on 1-naphthaldehyde; 1-(2-methyl-1-propenyl(naphthalene)[160] **94** was prepared in 52% yield from the action of isopropylene(triphenyl)phosphorane on 1-naphthaldehyde.

E/Z-**87**

A colourless oil. R_f 0.60 (hexane). Anal.Calcd for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found C, 91.51; H, 8.25.

***Z*-87**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13-1.93, m, 10H; 2.20-2.40, m, 1H; 5.81, dd (*J* = 11.4, 10.2 Hz), 1H; 6.82, d (*J* = 11.4 Hz), 1H; 7.42-7.56, m, 4H; 7.71-8.00, m, 2H; 8.08, dd (*J* = 6.3, 3.6 Hz), 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.32, 25.95, 33.26, 37.08, 125.01, 125.11, 125.32, 125.65, 125.67, 126.04, 127.00, 128.23, 132.03, 133.48, 135.34, 140.34.

***E*-87**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13-1.93, m, 10H; 2.20-2.40, m, 1H; 6.24, dd (*J* = 15.9, 7.2 Hz), 1H; 7.15, d (*J* = 15.9 Hz), 1H; 7.42-7.56, m, 4H; 7.71-8.00, m, 2H; 8.18, d (*J* = 6.6 Hz), 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.68, 26.19, 33.03, 41.51,

123.40, 123.93, 124.36, 125.54, 125.62, 127.10, 128.41, 131.20, 133.61, 135.88, 140.18, 1 C masked.

X-ray quality crystals of ***E*-91** were grown from the slow evaporation of a hexane solution. The crystal data was obtained upon on a Rigaku AFC-7*R* diffractometer.

Isomerisation of *E/Z*-86 and *E/Z*-87 with iodine

The same procedure was employed for both alkene mixtures, whereby the isomeric mixture (3.0 g) was dissolved in benzene (100 mL) and to this solution added 1 crystal of iodine. The vessel was stoppered and exposed to sunlight for one day. The resulting solution was filtered through a short pad of silica and the solvent removed *in vacuo* to afford the *E* enriched alkene mixture, as reported in **Scheme 2.1**.

Methyl (*E*)-3-(1-naphthyl)-2-propenoate[161] ***E*-95** was synthesised by the action of methylesterphosphorane **45a** upon 1-naphthaldehyde and subsequently purified by chromatography (85%).

(*E*)-3-(1-Naphthyl)-2-propen-1-ol[81] ***E*-96** was made via current literature procedure involving the reduction of ***E*-95** with DIBAL-H (65%).

General Procedure for the Preparation of the 1,2-Dioxines

All 1,2-dioxines were prepared by the Rose Bengal *bis(*triethylammonium)salt sensitised ($4\pi + 2\pi$) cycloaddition of singlet oxygen to the corresponding substituted vinylic naphthalenes. The appropriate vinylic naphthalene (3.0 g) and Rose Bengal, *bis*(triethylammonium)salt (30 mg) were dissolved in dry dichloromethane (100 mL) and the reaction vessel semi-immersed in an ice bath so that the reaction mixture maintained a temperature *ca.* 5-10 °C. A stream of oxygen was then passed through the solution, whilst irradiating with two tungsten halogen lamps (500 W) at a distance of 10 cm from the reaction vessel for *ca.* 5 hr. The volatiles were then removed *in vacuo* and the residue subjected to flash chromatography. All solid 1,2-dioxines prepared in this work were manipulated with teflon coated spatulas to prevent premature decomposition.

2,4*a*-Dihydronaphtho[2,1-*c*][1,2]dioxine[78] 64

50% yield based on recovered **85**. R_f 0.45 (10% ethyl acetate / hexane). Mp: 79-79.5 °C, (Lit. Mp: 67-68 °C).

(±) (2*S*,4a*R*)-2-Methyl-2,4*a*-dihydronaphtho[2,1-*c*][1,2]dioxine[78] 75

84% yield based on recovered **86**. R_f 0.36 (6% ethyl acetate / hexane).

(±) (2*R*,4a*R*)-2-Cyclohexyl-2,4a-dihydronaphtho[2,1-*c*][1,2]dioxine 76

55% yield based on recovered **87**. A pale yellow oil. R_f 0.70 (30% dichloromethane / hexane). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.83-0.89, m, 1H; 1.00-1.38, m, 5H; 1.67, broad d (J = 12.4 Hz), 1H; 1.70-1.72, m, 2H; 1.90-1.98, m, 1H; 2.11, broad d (J = 12.9 Hz), 1H; 4.12, ddd (J = 7.7, 3.0, 3.0 Hz), 1H; 5.76, ddd (J = 7.7, 3.0, 3.0 Hz), 1H; 5.86, dddd (J = 4.0, 3.0, 3.0, 2.3 Hz), 1H; 6.14, ddd (J = 4.0, 3.0, 0.8 Hz), 1H; 6.40-6.42, m, 1H; 7.02, dd (J = 7.2, 1.9 Hz), 1H; 7.18-7.22, m, 2H; 7.41, dd (J = 6.6, 2.1 Hz), 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.76, 25.93, 26.27, 29.27, 29.66, 42.74, 78.69, 84.85, 120.95, 123.73, 123.84, 127.19, 128.31, 128.57, 128.95, 131.32, 131.89, 134.80. MS *m/z* (%): 268 (M^+, 50), 171 (97), 157 (91), 128 (35), 83 (100). HRMS, $C_{18}H_{20}O_2$: calcd, 268.1463; found 268.1464.

(±) (2*R*,4a*R*)-2-Phenyl-2,4a-dihydronaphtho[2,1-*c*][1,2]dioxine[78] 77

35% yield based on recovered **88**. A white solid. Mp: 101-103 °C (Lit. Mp: 104.0-104.3 °C). R_f 0.32 (30% dichloromethane / hexane). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.47 dd (J = 3.6, 3.6 Hz), 1H; 5.80, ddd (J = 10.2, 2.4, 1.2 Hz), 1H; 6.03, dddd (J = 3.6, 3.0, 3.0, 2.4 Hz), 1H; 6.20, ddd (J = 3.0, 3.0, 0.6 Hz), 1H; 6.46, dd (J = 10.2, 3.0 Hz), 1H; 7.07, dd (J = 7.2, 1.2 Hz), 1H; 7.21-7.27, m, 2H; 7.31-7.41, m, 3H; 7.47-7.51, m, 3H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 79.05, 81.74, 119.94, 123.79, 124.05, 127.39, 128.42, 128.47, 128.50, 128.52, 129.01, 129.18, 131.09, 132.15, 135.83, 139.50.

(±) (2*R*,4a*R*)-2-(4-Chlorophenyl)-2,4a-dihydronaphtho[2,1-*c*][1,2]dioxine 78

29% yield based on recovered **89**. A light yellow solid. Mp: 78-82 °C. R_f 0.32 (30% dichloromethane / hexane). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.52 dd (J = 3.0, 3.0 Hz), 1H; 5.78, dd (J = 10.2, 2.4 Hz), 1H; 6.02, dddd (J = 3.0, 3.0, 3.0, 2.4 Hz), 1H; 6.15, ddd (J = 3.0, 3.0, 1.2 Hz), 1H; 6.45, dd (J = 10.2, 3.0 Hz), 1H; 7.08, dd (J = 7.8, 1.2 Hz), 1H; 7.22-7.28, m, 2H; 7.32-7.34, m, 2H; 7.38-7.48, m, 3H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 80.93, 82.00, 119.28, 123.55, 124.08, 127.44, 128.57, 128.59, 129.19, 129.28, 129.91, 130.86, 132.15, 134.40, 136.33, 138.02. MS *m/z* (%): 296 (M^+, 20), 278 (57), 265 (32), 139 (100), 111 (31). HRMS, $C_{18}H_{13}O_2Cl$: calcd, 296.0604; found 296.0610.

(±) (2*R*,4a*R*)-2-(4-Methoxyphenyl)-2,4a-dihydronaphtho[2,1-*c*][1,2]dioxine 79

25% yield based on recovered **90**. A white solid. Mp: 136-138 °C. R_f 0.43 (50% dichloromethane / hexane). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.79, s, 3H; 5.49, dd (J = 2.7, 2.7 Hz), 1H; 5.80, dd (J = 10.2, 1.8 Hz), 1H; 6.00, dddd (J = 3.0, 2.7, 2.7, 1.8 Hz), 1H; 6.16, dd (J = 2.7, 2.7 Hz), 2H; 6.46, dd (J = 10.2, 3.0 Hz), 1H; 6.88-6.90, m, 2H; 7.07, dd (J = 7.8, 1.2 Hz), 1H; 7.20-7.28, m, 2H; 7.40-7.43, m, 2H; 7.47, d (J = 7.8 Hz), 1H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 55.26, 79.02, 81.33, 113.76, 120.20, 123.95, 124.04, 127.35, 128.47, 128.94, 129.11, 130.14, 131.17, 131.68, 132.15, 135.70, 159.80. MS *m/z* (%): 292 (18, M^+), 274 (98), 259 (48), 231 (17), 202 (15), 135 (100). HRMS, $C_{19}H_{17}O_3$ ($[M+H]^+$): calcd, 293.1178; found 293.1161.

(±) (2*R*,4a*R*)-2-(4-Trifluoromethanephenyl)-2,4a-dihydronaphtho[2,1-*c*][1,2]dioxine 80

40% yield based on recovered **91**. A colourless oil. R_f 0.32 (30% dichloromethane / hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.59, dd (J = 3.6, 3.6 Hz), 1H; 5.77, dd (J = 9.9, 2.2 Hz), 1H; 6.03, dddd (J = 3.8, 3.6, 3.0, 2.2 Hz), 1H; 6.19, ddd (J = 3.8, 3.8, 0.8 Hz), 1H; 6.46, dd (J = 9.9, 3.0 Hz), 1H; 7.07, dd (J = 7.2, 1.6 Hz), 1H; 7.06-7.09, m, 1H; 7.23-7.28, m, 2H; 7.47-7.50, m, 1H; 7.63, broad s, 4H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 79.13, 80.88, 118.82, 123.32, 124.03 q ($^1J_{CF}$ = 272 Hz), 124.05, 125.36 q ($^3J_{CF}$ = 3.7 Hz), 127.45, 128.50, 128.57, 129.25, 129.33, 130.43 q ($^2J_{CF}$ = 33.2 Hz), 130.71, 132.12, 136.63, 143.45. MS *m/z* (%): 330 (M^+, 26), 301 (30), 173 (30), 157 (100), 128 (46). HRMS, $C_{19}H_{13}O_2F_3$: calcd, 330.0868; found 330.0864.

(±) (2*R*,4a*R*)-2-(3-Bromophenyl)-2,4a-dihydronaphtho[2,1-*c*][1,2]dioxine 81

16% yield based on recovered **92**. A colourless oil, that slowly decomposes. R_f 0.32 (30% dichloromethane / hexane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.51 dd (J = 3.0, 3.0 Hz), 1H; 5.79, dd (J = 10.2, 2.2 Hz), 1H; 6.03, dddd (J = 3.0, 3.0, 3.0, 3.0 Hz), 1H; 6.17, ddd (J = 3.0, 3.0 Hz), 1H; 6.45, dd (J = 10.2, 3.0 Hz), 1H; 7.06-7.10, m, 1H; 7.20-7.28, m, 3H; 7.44-7.49, m, 3H; 7.65, s, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 79.13, 80.92, 118.97, 122.59, 123.49, 124.10, 126.98, 127.46, 128.57, 129.23, 129.31, 130.00, 130.80, 131.40, 131.46, 132.18, 136.52, 141.87. MS *m/z* (%): 342 (M^+, 13), 340 (M^+, 22), 338 (10), 324 (65), 322 (63), 171 (100), 157 (86).

(±) (2*R*,4a*R*)-2-(1-Naphthyl)-2,4a-dihydronaphtho[2,1-*c*][1,2]dioxine 82

24% yield based on recovered **93**. A white solid. Mp: 133-136 °C. R_f 0.43 (30% dichloromethane / hexane). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.78 ddd (*J* = 10.2, 3.0, 0.6 Hz), 1H; 6.08, dddd (*J* = 3.6, 3.0, 3.0, 3.0 Hz), 1H; 6.32, ddd (*J* = 3.0, 3.0, 0.6 Hz), 1H; 6.38, dd (*J* = 3.6, 3.6 Hz), 1H; 6.46, dd (*J* = 10.2, 3.0 Hz), 1H; 7.09, dd (*J* = 7.2, 1.2 Hz), 1H; 7.25, m, 2H, 7.41-7.43, m, 1H; 7.49-7.61, m, 3H; 7.68, dd (*J* = 7.2, 1.2 Hz), 1H; 7.84, d (*J* = 8.4 Hz), 1H; 8.13, d (*J* = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 77.73, 79.37, 119.97, 123.20, 123.92, 124.18, 125.03, 125.69, 126.58, 127.39, 127.98, 128.53, 128.85, 129.05, 129.13, 131.15, 131.49, 132.19, 133.95, 134.53, 136.65. MS *m/z* (%): 312 (M^+, 17), 294 (27), 280 (23), 155 (100), 127 (60). HRMS, $C_{22}H_{16}O_2$: calcd, 312.1150; found 312.1156.

2,2-Dimethyl-2,4a-dihydronaphtho[2,1-*c*][1,2]dioxine[78] 83

30% yield based on recovered **94**. R_f 0.43 (6% ethyl acetate / hexane).

(±) (2*R*,4a*R*)-2,4a-Dihydronaphtho[2,1-*c*][1,2]dioxin-2-yl methanol 84

78% yield based on recovered **96**. A colourless oil. R_f 0.31 (4% ethyl acetate / dichloromethane). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.36, dd (*J* = 3.0, 2.4 Hz), 1H; 3.80, ddd (*J* = 11.4, 8.4, 3.0 Hz), 1H; 4.08, ddd (*J* = 11.4, 7.8, 2.4 Hz), 1H; 4.62, ddd (*J* = 8.4, 7.8, 3.0 Hz), 1H; 5.75, dd (*J* = 10.2, 2.4 Hz), 1H; 5.94-5.97, m, 2H; 6.42, dd (*J* = 10.2, 3.0 Hz), 1H; 7.03, dd (*J* = 7.2, 1.2 Hz), 1H; 7.20-7.25, m, 2H; 7.42. d (*J* = 7.2 Hz), 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 63.99, 79.26, 82.11, 117.24, 127.41, 128.58, 129.15, 129.36, 130.77, 131.87, 137.31. MS *m/z* (%): 216 (42), 198 (31), 185 (41), 169 (34), 157 (100), 141 (38), 128 (66), 115 (30). HRMS, $C_{13}H_{12}O_3$: calcd, 216.0786; found 216.0785.

Reactions of dioxine 64 with phosphoranes 45a-e

A general procedure was employed in all these reactions, whereby to a solution of the dioxine (approximately 100 mg scale) in dichloromethane was added the stabilised phosphorus ylide under the conditions outlined in **Table 2.3**. The solvent was then removed *in vacuo* and the residue subjected to column chromatography (silica) to afford the listed products.

Methyl 2-(1,2-dihydronaphtho[2,1-*b*]furan-1-yl)acetate 97a

A colourless oil. R_f 0.42 (14% ethyl acetate / hexane). IR (CH_2Cl_2) 3055, 2955, 1735, 1631, 1598, 1521 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.59, dd (*J* = 16.5, 11.0 Hz), 1H; 3.01, ddd (*J* = 16.5, 3.3, 1.1 Hz), 1H; 3.73, s, 3H; 4.22, dddd (*J* = 11.0, 8.4, 3.3, 2.9 Hz), 1H; 4.58, dd (*J* = 9.5, 2.9 Hz), 1H; 4.80, ddd, (*J* = 9.5, 8.4, 1.1 Hz), 1H; 7.09-7.84, m, 6H. ^{13}C NMR ($CDC1_3$, 150 MHz) δ 38.19, 38.36, 51.84, 77.21, 112.30, 120.22, 121.86, 122.93, 126.99, 129.14, 129.58, 129.97, 130,20, 157.52, 172.61. MS *m/z* (%): 242 (M^+, 21), 169 (100), 141 (41), 114 (12). Anal. Calcd for $C_{15}H_{14}O_3$: C, 45.36; H, 5.82. Found: C, 74.12; H, 5.99.

Methyl (*E*)-4-(2-hydroxy-1-naphthyl)-2-butenoate *E*-66a

A colourless oil that decomposes over several days. R_f 0.35 (5% ethyl acetate / dichloromethane). IR (CH_2C1_2) 3300, 1680, 1620, 1600 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.68, s, 3H; 3.95, dd (*J* = 6.3, 1.6 Hz), 2H; 5.76, dt (*J* = 15.7, 1.6 Hz), 1H; 6.18, bs (exch. D_2O), 1H; 7.00-7.04, m, 1H; 7.23, dt (*J* = 15.7, 6.3 Hz), 1H; 7.29-7.79, m, 5H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 27.69, 51.42, 115.53, 117.61, 121.57, 122.79, 123.37, 126.92, 128.74, 128.84, 129.45, 133.24, 147.07, 151.00, 167.38. MS *m/z* (%): 242 (M^+, 68), 214 (26), 181 (100), 156 (35), 115 (23). HRMS, $C_{15}H_{14}O_3$: calcd, 242.0943; found, 242.0933.

Methyl (*Z*)-4-(2-hydroxy-1-naphthyl)-2-butenoate *Z*-66a

A colourless oil that decomposes over several days. R_f 0.73 (5% ethyl acetate / dichloromethane). Mp: 87-89 °C. IR (CH_2C1_2) 3327, 1695, 1641, 1622, 1601, 1215 cm^{-1}. ^1H NMR ($CDC1_3$, 300 MHz) δ 3.85, s, 3H; 4.31, dd (*J* = 8.7, 1.2 Hz), 2H; 5.89, dt (*J* = 11.4, 1.2 Hz), 1H; 6.54, dt (*J* = 11.4, 8.7 Hz), 1H; 7.16-7.l4, m, 6H; 8.47, s (exch. D_2O), 1H. ^{13}C NMR ($CDC1_3$, 150 MHz) δ 25.11, 52.13, 113.25, 118.77, 119.34, 121.91, 122.88, 12678, 128.91, 128.94, 129.26, 133.02, 146.53, 153.54,169.77. MS *m/z* (%): 242 (M^+, 55), 210 (12), 181 (100), 168 (80), 152 (22). HRMS, $C_{15}H_{14}O_3$: calcd, 242.0943; found, 242.0934.

Methyl 2-(1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetate 65a

A white solid. R_f 0.35 (14% ethyl acetate / hexane). Mp: 76-76.5 °C. IR (CH_2C1_2) 1737, 1632, 1602, 1522 cm^{-1}. ^1H NMR ($CDC1_3$, 300 MHz) δ 2.76, dd (*J* = 15.0, 6.3Hz), 1H; 2.95, dd (*J* = 15.3, 6.9 Hz), 1H; 3.70, dd (*J* = 15.3, 9.6 Hz), 1H; 3.75, s, 3H; 5.36, dddd (*J* = 9.6, 7.2, 6.9, 6.3 Hz), 1H; 7.08-7.78, m, 6H. ^{13}C NMR ($CDC1_3$,

150 MHz) δ 34.29, 40.84, 51.85, 79.45, 112.11, 117.65, 122.63, 122.94, 126.71, 128.69, 129.13, 129.30, 130.76, 156.54, 170.92. MS *m/z* (%): 242 (M^+, 55), 181 (12), 168 (100), 141 (8). HRMS, $C_{15}H_{14}O_3$: calcd, 242.0943; found, 242.0941.

Ethyl (*E*)-4-(2-hydroxy-1-naphthyl)-2-methyl-2-butenoate *E*-66d

A pale yellow solid. R_f 0.13 (dichloromethane). Mp: 128.5-129.5 °C. IR (NUJOL) 3390, 1674, 1630, 1599, 1513 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23, t (*J* = 7.2 Hz), 3H; 2.13, d (*J* =1.2 Hz), 3H; 3.94, d (*J* = 6.8 Hz), 2H; 4.14, q (*J* = 7.2 Hz), 2H; 5.17, s (exch. D_2O), 1H; 6.80, dt (*J* = 6.8, 1.2 Hz), 1H; 7.02-7.84, m, 6H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.75, 14.23, 24.82, 60.52, 117.31, 117.68, 122.87, 123.29, 126.77, 128.22, 128.38, 128.68, 129.45, 133.30, 140.20, 150.70, 168.15. MS *m/z* (%): 270 (M^+, 32), 224 (53), 195 (62), 181 (100, 169 (14). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.53; H, 6.50. X-ray quality crystals of ***E*-66d** were grown from the slow evaporation of a dichloromethane solution. The crystal data was obtained upon on a Rigaku AFC-7*R* diffractometer.

Ethyl (*Z*)-4-(2-hydroxy-1-naphthyl)-2-methyl-2-butenoate *Z*-66d

A colourless oil. R_f 0.71 (dichloromethane). IR (CH_2Cl_2) 3294, 1685, 1643, 1622, 1599, 1520 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37, t (*J* = 6.9 Hz), 3H; 1.88, d (*J* = 1.2 Hz), 3H; 4.15, d (*J* = 8.9 Hz), 2H; 4.34, q (*J* = 7.5 Hz), 2H; 6.18, dt (*J* = 8.9, 1.2 Hz), 1H; 7.17-7.95, m, 6H; 8.83, s (exch. D_2O), 1H; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.14, 20.31, 25.56, 61.51, 113.91, 119.27, 121.89, 122.65, 126.55, 126.89, 128.57, 128.84, 129.14, 132.98, 139.69, 153.61, 170.50. MS *m/z* (%): 270 (M^+, 69), 225 (72), 224 (72), 196 (82), 183 (100), 168 (41). HRMS, $C_{17}H_{18}O_3$: calcd, 270.1256; found, 270.1249.

1-(1,2-Dihydronaphtho[2,1-*b*]furan-2-yl)acetone 65b

A white solid. R_f 0.31 (14% ethyl acetate / hexane). Mp: 69-69.5 °C. IR (NUJOL) 1703, 1630, 1599 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.26, s, 3H; 2.85, dd (*J* = 16.8, 6.5 Hz), 1H; 3.11, dd (*J* = 15.7, 6.6 Hz), 1H; 3.14, dd (*J* = 16.8, 7.0 Hz), 1H; 3.72, dd (*J* = 15.7, 9.4 Hz), 1H; 5.38, dddd (*J* = 9.4, 7.0, 6.6, 6.5 Hz), 1H; 7.07-7.78, m, 6H. ^{13}C NMR ($CDCl_3$ 150 MHz) δ 30.72, 34.51, 49.82, 79.25, 112.11, 117.89, 122.70, 123.00,126.79, 128.75, 129.17, 129.34, 130.86, 156.66, 206.30. MS *m/z* (%): 226 (M^+, 8), 181 (24), 168 (100), 139 (24), 115 (10), 69 (21). Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.66; H, 6.19. found: C, 79.40: H, 6.35. X-ray quality crystals of **65b** were grown

from an evaporating ethyl acetate / hexane (1 : 3) solution at 278 K. Crystal data was obtained upon a Nonius Kappa CCD diffractometer.

2-(1,2-Dihydronaphtho[2,1-*b*]furan-2-yl)acetaldehyde 65c

A colourless oil. R_f 0.47 (dichloromethane). IR (CH_2Cl_2) 1726, 1631, 1602, 1581 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.89, ddd (*J* = 17.5, 5.7, 1.2 Hz), 1H; 3.09, dd (*J* = 17.5, 7.2, 1.5 Hz), 1H; 3.16, dd (*J* = 15.6, 6.9 Hz), 1H; 3.74, dd (*J* = 15.6, 9.6 Hz), 1H; 5.43, dddd (*J* = 9.6, 7.2, 6.9, 5.7 Hz), 1H; 7.08-7.82, m, 6H; 9.91, d (*J* = 0.9 Hz), 1H. ^{13}C NMR ($CDCl_3$ 150 MHz) δ 34.56, 50.06, 81.39, 111.96, 117.57, 122.63, 123.07, 126.83, 128.73, 129.29, 129.37, 130.74, 156.49, 199.70. MS *m/z* (%): 212 (M^+, 100), 181 (28), 168 (52), 141 (16), 115 (15). Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.26; H, 5.66. Found: C, 79.12; H, 5.61.

Cyclisation of methyl (*E*)-4-(2-hydroxy-1-naphthyl)-2-butenoate *E*-66a

To an NMR tube containing **66a** (15 mg, 0.062 mmol) in the presence of 1,3,5-trimethylbenzene (3.0 mg, internal standard) in *d*-chloroform (0.5 mL) was added **45a** and the contents of the tube heated to 60 °C overnight. Examination of the contents by ^1H NMR indicated quantitative conversion of ***E*-66a** to **65a**.

Synthesis of 1,2-Dihydronaphtho[2,1-*b*]furan-2-ol 99

To a solution of dioxine **2.1** (400 mg, 2.15 mmol) in chloroform (15 mL) at 5 ^0C was added triethylamine (11 mg, 0.05 equiv. in chloroform, 2 mL) and the mixture kept at this temperature overnight. The volatiles were then removed *in vacuo* and the residue subjected to flash chromatography on florisil (14% ethyl acetate / hexane) to afford pure **99** as a crystalline white solid (380 mg, 95%).

R_f 0.23 (14% ethyl acetate / hexane). Mp: 115-116°C. IR (NUJOL) 3462, 1633, 1601, 1576, 1518 cm^{-1}. ^1H NMR ($CDCl_3$ + 1 drop D_2O, 300 MHz) δ 3.32, dd (*J* = 16.4, 2.3 Hz), 1H; 3.43, s (exch. D_2O), 1H; 3.63, dd (*J* = 16.7, 6.9 Hz), 1H; 6.23, dd (*J* = 6.9, 2.3 Hz), 1H; 7.14-7.83, m, 6H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 36.86, 101.54, 112.06, 116.64, 122.80, 123.20, 126.80, 128.76, 129.22, 129.59, 130.72, 155.17. MS *m/z* (%): 186 (M^+, 100), 157 (51), 130 (48). Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.56; H, 5.60.

Reactions of 99 with phosphoranes 45a-e

A general procedure was employed in all these reactions. To a solution of **99** (approximately 50 mg scale) in dichloromethane was added the stabilised phosphorus ylide and left under the prescibed conditions as outlined in **Table 2.4**. The solvent was then removed *in vacuo* and the residue subjected to column chromatography (silica) to afford the listed products.

Synthesis of Ethyl 2-(1,2-dihydronaphtho[2,1-*b*]furan-2-yl)propanoate 65d

To a solution of ethyl ***E*-66d** (64 mg, 0.237 mmol) in dry benzene (4 mL) was added **45a** (62 mg, 0.195 mmol). The resulting solution was heated under reflux overnight. The solvent was removed *in vacuo* and the crude residue purified by flash chromatography to give **65d** (minor isomer) (17 mg, 27%) as a colourless oil and **65d** (major isomer) (30 mg, 47%) as a white crystalline solid.

65d (minor isomer): R_f 0.42 (8% ethyl acetate / hexane). IR (CH_2Cl_2) 1730, 1633, 1601, 1579, 1522 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25, t (J = 7.1 Hz), 3H; 1.36, d (J = 6.9 Hz), 3H; 2.85, dq (J = 6.9, 6.9 Hz), 1H; 3.27, dd (J = 15.7, 7.4 Hz), 1H; 3.63, dd (J = 15.7, 9.6 Hz), 1H; 4.18, q (J = 7.1 Hz), 2H; 5.15, ddd (J = 7.4, 9.6, 6.9 Hz), 1H; 7.08-7.11, m, 1H; 7.26-7.33, m, 1H; 7.44-7.49, m, 1H; 7.56-7.59, m, 1H; 7.66-7.69, m, 1H; 7.79-7.81, m, 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.17, 14.17, 31.50, 44.83, 60.69, 84.15, 112.02, 117.83, 122.58, 122.86, 126.67, 128.70, 129.04, 129.22, 130.68, 156.98, 173.86. MS *m/z* (%): 270 (M^+, 3375), 181 (21), 168 (100), 141 (21), 102 (46), 74 (23). HRMS, $C_{17}H_{18}O_3$: calcd, 270.1256; found 270.1256.

65d (major isomer): Mp 57-58 °C. R_f 0.50 (8% ethyl acetate / hexane); IR (CH_2Cl_2) 1728, 1633, 1603, 1583, 1521 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27, d (J = 7.4 Hz), 3H; 1.28, t (J = 7.1 Hz), 3H; 2.94, dq (J = 7.4, 7.4 Hz), 1H; 3.27, dd (J = 15.9, 8.0 Hz), 1H; 3.57, dd (J = 9.8, 15.9 Hz), 1H; 4.20, q (J = 7.1 Hz), 2H; 5.21, ddd (J = 7.4, 8.0, 9.8 Hz), 1H; 7.09-7.12, m, 1H; 7.28-7.33, m, 1H; 7.43-7.48, m, 1H; 7.55-7.58, m, 1H; 7.65-7.68, m, 1H; 7.78-7.81, m, 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.13, 14.16, 32.79, 45.37, 60.68, 84.09, 111.91, 117.97, 122.64, 122.85, 126.65, 128.67, 129.02, 129.22, 130.73, 156.90, 173.81. MS *m/z* (%): 270 (M^+, 78), 181 (30), 168 (100), 141 (21), 102 (22). Anal.Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found C, 75.75; H, 6.86.

Reactions of 75 with phosphoranes 45a-f

These reactions were performed upon either a large scale or on an NMR scale. The conditions employed were universal for every reaction system and are described in **Table 2.5**. A typical procedure was as follows. To a solution of dioxine **75** (300 mg, 1.50 mmol) in anhydrous dichloromethane (20 mL) was added ylide **45a** (560 mg, 1.68 mmol) and the reaction allowed to stir for three days, after which time the solvent was removed *in vacuo* and the residue purified by flash chromatography (silica) to afford diastereomeric mixtures of ***E/Z*-101a** (260 mg, 60%) and ***E/Z*-102a** (64 mg, 15%), both as colourless oils. NMR reactions were performed in *d*-chloroform upon a 30 mg scale and phenyltrimethylsilane was employed as the internal standard, the conditions also described in **Table 2.5**.

Reactions of 75 with phosphoranes 45a/f in the presence of lithium bromide.

These reactions were performed upon an NMR scale of approximately 30 mg of dioxine under the same described conditions, except the lithium bromide (5 equivalents) was added prior to the addition of the stabilised ylide. The exact conditions are described in **Table 2.5**. After the introduction of the ylide the NMR tube was sonicated for 90 minutes then left at ambient temperature for up to a day.

Diastereomeric mixture of (±) Methyl (1*R*,2*S* and 1*R*,2*R*)-2-(2-methyl-1,2-dihydronaphtho [2,1-*b*] furan-1-yl) acetate *E/Z*-101a

A colourless oil. R_f 0.39 (10% ethyl acetate / hexane). Anal. Calcd for $C_{16}H_{16}O_3$ (mixture): C, 74.98; H, 6.29. Found: C, 74.97; H, 6.42.

***Z*-101a**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.55, d (J = 7.0 Hz), 3H; 2.63, dd (J = 17.0, 3.6 Hz), 1H; 2.69, dd (J = 17.0, 9.6 Hz), 1H; 3.70, s, 3H; 4.20, ddd (J = 9.6, 7.0, 3.6 Hz), 1H; 5.03, dq (J = 7.0, 7.0 Hz), 1H; 7.08-7.09, m, 1H; 7.29-7.31, m, 1H; 7.45-7.48, m, 1H; 7.64-7.70, m, 2H; 7.80-7.82, m, 2H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.95, 33.60, 40.60, 51.90, 83.15, 112.14, 122.01, 122.23, 122.90, 126.93, 129.11, 129.60, 129.69, 130.09, 156.79, 173.00.

***E*-101a**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.45, d (J = 6.5 Hz), 3H; 2.57, dd (J = 16.8, 11.2 Hz), 1H; 3.02, dd (J = 16.8, 3.1 Hz), 1H; 3.74, s, 3H; 3.82, ddd (J = 11.2, 3.1, 2.6 Hz), 1H; 4.81, dq (J = 6.5, 2.6 Hz), 1H; 7.08-7.09, m, 1H; 7.29-7.31, m, 1H; 7.45-7.48, m, 1H; 7.64-7.70, m, 2H; 7.80-7.82, m, 2H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.46,

30.89, 38.42, 51.73, 85.93, 112.65, 121.79, 122.20, 122.76, 126.90, 129.10, 129.48, 130.01, 130.62, 151.14, 173.17.

Diastereomeric mixture of (±) methyl (1*R*,2*S* and 1*R*,2*R*)-2-(1-methyl-1,2-dihydronaphtho [2,1-*b*] furan-2-yl) acetate *E/Z*-102a

A colourless oil. R_f 0.32 (10% ethyl acetate / hexane). Anal. Calcd for $C_{16}H_{16}O_3$ (mixture): C, 74.98; H, 6.29. Found: C, 74.93; H, 6.29. ^{13}C NMR ($CDCl_3$, mixture, 150 MHz) δ 14.49, 20.42, 35.02, 38.15, 39.94, 41.87, 51.83, 52.02, 82.90, 86.75, 112.23, 112.49, 122.02, 122.18, 122.26, 122.84, 122.87, 124.51, 126.66, 126.69, 129.02, 129.03, 129.16, 129.52, 129.70, 129.71, 130.22, 130.59, 155.71, 155.78, 171.07, 171.38.

***Z*-102a**: ^1H NMR ($CDCl_3$, 600 MHz) δ 1.23, d (*J* = 6.9 Hz), 3H; 2.89, dd (*J* = 16.2, 6.9 Hz), 1H; 3.04, dd (*J* = 16.2, 6.9 Hz), 1H; 3.79, s, 3H; 3.86, dq (*J* = 6.9, 6.9 Hz), 1H; 5.21, ddd (*J* = 6.9, 6.9, 6.9 Hz), 1H; 7.08-7.10, m, 1H; 7.28-7.30, m, 1H; 7.43-7.46, m, 1H; 7.65-7.69, m, 2H; 7.78-7.80, m, 1H.

***E*-102a**: ^1H NMR ($CDCl_3$, 600 MHz) δ 1.49, d (*J* = 6.9 Hz), 3H; 2.65, dd (*J* = 16.0, 6.5 Hz), 1H; 2.81, dd (*J* = 16.0, 7.2 Hz), 1H; 3.58, dq (*J* = 6.9, 3.5 Hz), 1H; 3.73, s, 3H; 4.90, ddd (*J* = 7.2, 6.5, 3.5 Hz), 1H; 7.08-7.10, m, 1H; 7.28-7.30, m, 1H; 7.43-7.46, m, 1H; 7.65-7.69, m, 2H; 7.78-7.80, m, 1H.

Diastereomeric mixture of (±) *tert*-butyl (1*R*,2*S* and 1*R*,2*R*)-2-(2-methyl-1,2-dihydronaphtho [2,1-*b*] furan-1-yl) acetate *E/Z*-101f

A colourless oil. R_f 0.43 (5% acetone / hexane). Anal.Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found C, 76.23; H, 7.65.

***Z*-101f**: ^1H NMR ($CDCl_3$, 600 MHz) δ 1.45, s, 9H; 1.57, d (*J* = 6.6 Hz), 3H; 2.58-2.60, m (AB portion of ABX), 2H; 4.16, dd (*J* = 6.6, 6.6Hz, X portion of ABX), 1H; 5.03, dq (*J* = 6.6, 6.6 Hz), 1H; 7.06-7.08, m, 1H; 7.27-7.31, m, 1H; 7.44-7.47, m, 1H; 7.65-7.70, m, 2H; 7.79-7.80, m, 1H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 15.14, 27.99, 35.04, 40.56, 80.73, 83.29, 112.10, 122.16, 122.42, 122.83, 126.83, 126.86, 129.07, 129.50, 129.57, 130.11, 156.71, 171.77.

***E*-101f**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.46, s, 9H; 1.46, d (J = 6.4 Hz), 3H; 2.48, dd (J = 16.4, 11.3 Hz), 1H; 2.92, dd (J = 16.4, 3.2 Hz), 1H; 3.78, ddd (J = 2.7, 3.2, 11.3 Hz), 1H; 4.84, dq (J = 2.7, 6.4 Hz), 1H; 7.08-7.09, m, 1H; 7.27-7.31, m, 1H; 7.44-7.47, m, 1H; 7.65-7.70, m, 2H; 7.79-7.80, m, 1H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.53, 28.11, 39.87, 44.99, 80.96, 85.69, 112.60, 119.46, 121.94, 122.69, 126.80, 129.04, 129.45, 129.83, 130.65, 156.33, 171.40.

Diastereomeric mixture of (±) *tert*-butyl (1*R*,2*S* and 1*R*,2*R*)-2-(1-methyl-1,2-dihydronaphtho [2,1-*b*] furan-2-yl) acetate *E/Z*-102f

A colourless oil. R_f 0.38 (5% acetone / hexane). ^{13}C NMR ($CDCl_3$, mixture, 150 MHz) δ 14.47, 20.51, 28.10, 28.13, 36.32, 38.09, 41.39, 41.66, 81.09, 81.19, 83.19, 87.13, 112.28, 112.49, 122.28, 122.40, 122.73, 122.77, 124.65, 126.59, 126.60, 129.01, 129.04, 129.40, 129.62, 130.24, 130.62, 130.98, 155.87, 155.90, 169.49, 169.84, 1 C masked. Anal.Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found C, 76.82; H, 7.42.

***Z*-102f**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.24, d (J = 7.1 Hz), 3H; 1.35, s, 9H; 2.84, dd (J = 16.2, 7.3 Hz), 1H; 2.98, dd (J = 16.2, 7.3 Hz), 1H; 3.86, dq (J = 7.1, 7.3 Hz), 1H; 5.17, ddd (J = 7.3, 7.3, 7.3 Hz), 1H; 7.06-7.07, m, 1H; 7.27-7.30, m, 1H; 7.44-7.47, m, 1H; 7.65-7.70, m, 2H; 7.78-7.81, m, 1H.

***E*-102f**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.40, s, 9H; 1.50, d (J = 6.8 Hz), 3H; 2.57, dd (J = 15.6, 7.0 Hz), 1H; 2.71, dd (J = 15.6, 6.8 Hz), 1H; 3.61, dq (J = 6.8, 3.5 Hz), 1H; 4.84, ddd (J = 7.0, 6.8, 3.5 Hz), 1H; 7.09-7.10, m, 1H; 7.27-7.30, m, 1H; 7.44-7.47, m, 1H; 7.65-7.70, m, 2H; 7.78-7.81, m, 1H.

Synthesis of the equilibrium mixture of 1-(2-hydroxy-1-naphthyl)acetone 103 and 2-methyl-1,2-dihydronaphtho[2,1-*b*]furan-2-ol 104

To a solution of dioxine (500 mg, 2.5 mmol) in anhydrous dichloromethane (60 mL) under nitrogen at 5 °C was added DABCO (56 mg, 0.5 mmol). After 10 hours the volatiles were removed *in vacuo* and the residue subjected to flash chromatography R_f 0.28 (5% ethyl acetate / dichloromethane) to afford pure **103/104** (380 mg, 76%) as a crystalline white solid.

Mp: 149.5-151 °C (Lit.[86] Mp: 151-152 °C). IR (NUJOL) 3412, 3236, 1694, 1659, 1630, 1583, 1512, 1274, 1175, 1048, 816, 755 cm^{-1}. ^{1}H NMR ($CDC1_3$, 300 MHz) δ

1.84, s, 3H; 2.26, s, 3H; 3.24, s (exch. D_2O), 1H; 3.48, s, 2H; 4.14, s, 2H; 6.88, s (exch. D_2O), 1H; 7.10-7.14, m, 1H; 7.31-7.38, m, 1H; 7.46-7.67, m, 1H; 7.69-7.72, m, 1H; 7.77-7.82, m, 1H; 7.83-7.88, m, 1H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 27.41, 29.71, 40.67, 41.63, 77.20, 109.95, 112.12, 112.68, 117.25, 118.63, 122.18, 122.70, 123.07, 123.32, 126.76, 127.06, 128.77, 128.81, 129.20, 129.33, 129.3,130.75, 133.05, 152.60, 155.04, 209.56. Anal. Calcd for $C_{13}H_{12}O_2$ (mixture): C, 77.98; H, 6.04. Found: C, 77.99; H, 6.28.

(±) (1*R*,2*R*)-2-(2-Methyl-1,2-dihydronaphtho[2,1-*b*]furan-1-yl)acetic acid *Z*-105

The *Z* enriched methyl ester **101a** was treated to literature conditions to afford each corresponding acid.[162] A white crystaline solid recrystalised thrice from chloroform and hexane (66%). Mp: 175.5-176.5 °C. IR (CH_2Cl_2) 3200-2600, 1710, 1630, 1599, 1581 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.61, d (*J* = 6.6 Hz), 3H; 2.74-2.77, AB portion of ABX, 2H; 4.16-4.24, X portion of ABX, 1H; 5.06, dq (*J* = 6.6, 6.6 Hz), 1H; 7.08-7.11, m, 1H; 7.30-7.35, m, 1H; 7.46-7.51, m, 1H; 7.68-7.72, m, 1H; 7.81-7.84, m, 1H; 11.60, broad s (exch D_2O), 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.06, 33.40, 40.34, 83.04, 112.17, 121.82, 122.99, 127.06, 129.90, 129.67, 129.85, 130.00, 177.98, 1C masked. MS *m/z* (%): 242 (M^+, 36), 183 (100), 155 (37), 115 (10). Anal.Calcd for $C_{15}H_{12}O_3$: C, 74.36; H, 5.82. Found C, 74.47; H, 5.83. X-ray quality crystals of ***Z*-105** were grown from an evaporating *d*-chloroform / *n*-heptane (1 : 4) solution at 278K. The crystal data was obtained upon on a Rigaku AFC-7*R* diffractometer.

Reactions of 103/104 with stabilised phosphoranes

The reactions were typically performed upon a 50 mg scale, the conditions employed described in **Table 2.7**. A typical procedure was as follows. To a solution of hemiacetal **103/104** (50 mg, 0.25 mmol) in dry chloroform (15 mL) under a nitrogen atmosphere was added ylide **45a** (125 mg, 0.37 mmol) and the reaction heated under reflux overnight. The volatiles were removed *in vacuo* and the residue purified by column chromatography to afford **2.37a** (60 mg, 94%) as a colourless oil.

Methyl (*E*)-4-(2-hydroxy-1-naphthyl)-3-methyl-2-butenoate *E*-112a

A white solid. R_f 0.40 (20% ethyl acetate / hexane): Mp: 96-97 °C. IR (CH_2C1_2) 3579, 3405, 1714, 1949, 1630, 1602, 1585, 1566 cm^{-1}. ^1H NMR ($CDC1_3$, 300 MHz) δ 2.33, s, 3H; 3.60, s, 3H; 3.91, s, 2H; 3.91, s, 2H; 5.05, s (exch. D_2O), 1H; 5.43, s, 1H; 7.05-7.08, m, 1H; 7.33-7.36, m, 1H; 7.41-7.47, m, 1H; 7.68-7.79, m, 3H. ^{13}C NMR ($CDC1_3$,

150 MHz) δ 19.28, 35.73, 50.71, 108.1, 115.68, 117.68, 123.08, 123.42, 126.91, 128.65, 129.03, 129.49, 133.72, 151.36, 158.22, 167.28. MS m/z (%): 256 (M^+, 36), 224 (16), 195 (61), 182 (100), 181 (95), 152 (12), 129 (11). HRMS, $C_{16}H_{16}O_3$: calcd, 256.1099; found, 256.1096.

Methyl (*Z*)-4-(2-hydroxy-1-naphthyl)-3-methyl-2-butenoate *Z*-112a

A white solid. R_f 0.49 (20% ethyl acetate / hexane). Mp: 93-93.5 °C. IR (CH_2C1_2) 3290, 1689, 1641, 1601, 1581 cm^{-1}. ^1H NMR ($CDC1_3$, 300 MHz) δ 1.79, s, 3H; 3.84, s, 3H; 4.33, s, 2H; 5.85, s, 1H; 7.15-7.18, m, 1H; 7.29-7.34, m, 1H; 7.47-7.53, m, 1H; 7.67-7.70, m, 1H; 7.77-7.80, m, 1H; 8.01-8.04, m, 1H; 8.67, s (exch. D_2O), 1H. ^{13}C NMR ($CDC1_3$, 150 MHz) δ 24.74, 28.18, 52.02, 113.19, 116.19, 118.94, 122.52, 122.77, 126.41, 128.87, 129.01, 129.21, 133.74, 154.04, 158.46, 170.25. MS *m/z* (%): 256 (M^+, 40), 224 (15), 195 (62), 182 (100), 181 (92), 152 (12). HRMS, $C_{16}H_{16}O_3$: calcd, 256.1099; found, 256.1103.

Methyl 2-(2-methyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl) acetate 113a

A colourless oil. R_f 0.53 (20% ethyl acetate / hexane). IR (NEAT) 1753, 1631, 1599, 1522 cm^{-1}. ^1H NMR ($CDC1_3$ 300 MHz) δ 1.64, s, 3H; 2.83 and 2.85, AB_q (J_{AB} = 15.0 Hz), 2H; 3.29 and 3.60, AB_q (J_{AB} = 15.6 Hz), 2H; 3.63, s, 3H; 7.06-7.07, m, 1H; 7.26-7.29, m, 1H; 7.42-7.45, m, 1H; 7.53-7.55, m, 1H; 7.64-7.66, m, 1H; 7.76-7.78, m, 1H. ^{13}C NMR ($CDC1_3$, 150 MHz) δ 26.65, 40.15, 45.00, 51.54, 86.90, 112.15, 117.89, 122.60, 122.75, 126.57, 128.62, 129.01, 129.16, 130.91, 155.66, 170.54. MS *m/z* (%): 256 (M^+, 60), 195 (12), 182 (100), 181 (30), 153 (7). HRMS, $C_{16}H_{16}O_3$: calcd, 256.1099; found, 256.1089.

1-(2-Methyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl acetone 113b

A white solid. R_f 0.60 (dichloromethane). Mp: 80-81 °C. IR (CH_2C1_2) 1714, 1631, 1598, 1579, 1522 cm^{-1}. ^1H NMR ($CDC1_3$, 600 MHz) δ 1.62, s, 3H; 2.21, s, 3H; 2.98 and 3.02, AB_q (J_{AB} = 15.6 Hz), 2H; 3.35 and 3.47, AB_q (J_{AB} = 15.6 Hz), 2H; 7.06-7.08, m, 1H; 7.29-7.32, m, 1H; 7.44-7.47, m, 1H; 7.55-7.56, m, 1H; 7.68-7.70, m, 1H. ^{13}C NMR ($CDC1_3$, 150 MHz) δ 26.72, 31.66, 40.39, 53.69, 87.38, 112.15, 118.17, 122.69, 122.87, 126.71, 128.68, 129.12, 129.21, 152.02, 155.53, 206.52. MS *m/z* (%): 240 (M^+, 12), 182 (100), 165 (6), 129 (5). HRMS, $C_{16}H_{16}O_2$: calcd, 240.1150; found, 240.1136.

tert-Butyl (_E_) (4-(2-hydroxy-1-naphthyl)-3-methyl-2-butenoate _E_-112f

A colourless oil. R_f 0.73 (dichloromethane). IR (NUJOL) 3263, 1676, 1641, 1599, 1583, 1520 cm^{-1}. ^1H NMR ($CDCl_3$ 300 MHz) δ 1.41, s, 9H; 2.27, s, 3H; 3.87, s, 2H; 5.32, s, 1H; 5.39, s (exch. D_2O), 1H; 7.03-7.06, m, 1H; 7.34-7.37, m, 1H; 7.47-7.50, m, 1H; 7.64-7.67, m, 1H; 7.74-7.80, m, 2H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 24.48, 28.00, 28.19, 82.01, 113.36, 118.28, 119.00, 122.40, 122.76, 126.30, 128.83, 128.91, 129.14, 133.81, 154.15, 156.24, 169.56. MS *m/z* (%): 298 (M^+, 5), 242 (68), 225 (26), 195 (58), 182 (97), 181 (100), 157 (10), 129 (21), 69 (43), 57 (64). Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.62; H, 7.45.

tert-Butyl (_Z_)-4-(2-hydroxy-1-naphthyl)-3-methyl-2-butenoate _Z_-112f

A white crystaline solid. R_f 0.36 (dichloromethane). Mp: 184.5-185.5 °C. IR (NUJOL) 3336, 3257, 1675, 1645, 1630, 1516 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.56, s, 9H; 1.73, s, 3H; 4.28, s, 2H; 5.76, s, 1H; 7.15-7.18, m, 1H; 7.27-7.32, m, 1H; 7.45-7.50, m, 1H; 7.66-7.69, m, 1H; 7.75-7.78, m, 1H; 8.00-8.03, m, 1H; 9.10, s (exch. D_2O), 1H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 19.15, 28.24, 35.82, 79.85, 115.71, 117.75, 117.85, 123.16, 123.26, 126.74, 128.53, 128.85, 129.85, 129.38, 133.72, 151.49, 155.92, 166.57. MS *m/z* (%): 298 (M^+, 13), 242 (89), 225(26), 195(62), 182(98), 181 (100), 152(7), 57(31). HRMS, $C_{19}H_{22}O_3$: calcd, 298.1569; found, 298.1569.

tert-Butyl 2-(2-methyl-1,2-dihydronaphtho[2,1-_b_]furan-2-yl)acetate 113f

A colourless oil. R_f 0.85 (dichloromethane). IR (CH_2Cl_2) 1722, 1631, 1601, 1521, 1466 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35, s, 9H; 1.64, s, 3H; 2.73 and 2.80, AB_q (J_{AB}=14.4 Hz), 2H; 3.29 and 3.69, AB_q (J_{AB}=15.6 Hz), 2H; 7.06-7.07, m, 1H; 7.28-7.30, m, 1H; 7.44-7.47, m, 1H; 7.55-7.57, m, 1H; 7.66-7.68, m, 1H; 7.78-7.80, m, 1H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 27.22, 27.93, 40.02, 46.90, 80.91, 87.21, 112.22, 118.12, 122.63, 122.72, 126.61, 128.68, 128.99, 129.18, 131.02, 155.93, 169.48. MS *m/z* (%): 298 (M^+, 35), 241 (54), 195 (82), 182 (100). HRMS, $C_{19}H_{22}O_3$: calcd, 298.1569; found, 298.1567.

Reaction of 76 with phosphorane 45a

To a solution of 1,2-dioxine **76** (221 mg, 0.825 mmol) in dry dichloromethane (20 mL) under a nitrogen atmosphere was added ylide **45a** (627 mg, 1.88 mmol) and the reaction allowed to stir for one week at ambient temperature. The solvent was then

removed *in vacuo* and the residue purified by flash chromatography (silica) to give **114 /115** (144 mg, 65%) as a white solid.

Equilibrium mixture of 1-cyclohexyl-2-(2-hydroxy-1-naphthyl)-1-ethanone 114 and 2-cyclohexyl-1,2-dihydronaphtho[2,1-*b*]furan-2-ol 115

To a solution of **76** (66.5 mg, 0.248 mmol) in dry benzene (10 mL) at 0 °C under a nitrogen atmosphere was added DABCO (1 mg, 0.009 mmol) and the reaction was allowed to stir for one hour. The solvent was reduced to a few mL, cooled in cold water then filtered. The collected precipitate was washed quickly with cold benzene, then with hexane to afford **114/115** as a white crystaline solid (53 mg, 80%).

Mp 155-157 °C. IR (CH_2Cl_2) 3577, 3265, 2935, 2856, 1684, 1639, 1624, 1599 1520 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 1.14-1.32, m, 4H; 1.36-1.42, m, 1H; 1.64-1.72, m, 1H; 1.76-1.94, m, 4H; 2.05-2.07, m, 1H; 2.61, tt (J = 3.3, 7.7 Hz), 1H; 2.98, broad s, 1H; 3.26 and 3.53, AB_q (J_{AB} = 16.8 Hz), 2H; 4.18, s, 2H; 7.10-7.11, m, 1H; 7.16-7.17, m, 1H; 7.28-7.34, m, 2H; 7.44-7.46, m, 1H; 7.49-7.52, m, 1H; 7.56-7.59, m, 2H; 7.68-7.69, m, 2H; 7.77-7.79, m, 1H; 7.86-7.87, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.52, 25.71, 25.95, 26.25, 26.82, 27.31, 28.35, 37.72, 37.92, 50.72, 112.08, 112.90, 113.28, 117.11, 119.20, 121.97, 122.66, 122.94, 123.10, 126.66, 126.82, 128.73, 128.87, 129.05, 129.20, 129.30, 129.41, 132.92, 153.38, 155.23, 215.22. MS *m/z* (%): 268 (48, M^+), 250 (100), 207 (74), 157 (62), 128 (65), 83 (71). Anal.Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found C, 80.32; H, 7.29.

Reaction of 114/115 with phosphorane 45a

114/115 (34.5 mg, 0.129 mmol) and **45a** (168 mg, 0.503 mmol) were heated under reflux in benzene (10 mL) under a nitrogen atmosphere, for one week, after which time the volatiles were removed *in vacuo* and the residue purified by flash chromatography (silica, 10% ethyl acetate / hexane) to return **114/115** (28.9 mg) unreacted.

Reactions of 77 to 80 with phosphorane 45a

A series of NMR scale reactions were performed on the 1,2-dioxines (typically upon 30 mg scale), treated with ylide **45a**, to a variety of conditions, those which were summarised in **Table 2.10**. In all these reactions phenyltrimethylsilane was employed as an internal standard. These reactions were monitored over two weeks by ^1H NMR.

For purification and characterisation purposes, all relevant reactions were combined, solvent removed and purified by flash chromatography.

(±) Methyl 2-[(1*R*,2*S*)-2-phenyl-1,2-dihydronaphtho[2,1-*b*]furan-1-yl]acetate *Z*-117a

A white solid. Mp. 128-130 °C. R_f 0.37 (12% acetone / hexane). IR (CH_2Cl_2) 1734, 1631, 1599, 1579 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.33, dd (*J* = 16.5, 9.9 Hz), 1H; 2.50, dd (*J* = 16.5, 4.1 Hz), 1H; 3.28, s, 3H; 4.56, ddd (*J* = 9.9, 8.0, 4.1 Hz), 1H; 6.04, d (*J* = 8.0 Hz), 1H; 7.21-7.26, m, 1H; 7.31-7.50, m, 7H; 7.69-7.71, m, 1H; 7.75-7.78, m, 1H; 7.83-7.86, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.11, 42.39, 51.47, 88.15, 112.33, 121.84, 122.16, 123.13, 127.05, 127.18, 128.03, 128.22, 129.15, 129.95, 130.20, 136.29, 156.69, 172.15. MS *m/z* (%): 318 (M^+, 42), 244 (100), 217 (27). Anal.Calcd for $C_{21}H_{18}O_3$: C, 79.23; H, 5.70. Found C, 78.97; H, 5.78.

(±) Methyl 2-[(1*R*,2*R*)-2-phenyl-1,2-dihydronaphtho[2,1-*b*]furan-1-yl]acetate *E*-117a

A white solid. Mp. 127-128.5 °C. R_f 0.37 (12% acetone / hexane). IR (CH_2Cl_2) 1733, 1632, 1600, 1579, 1521, 1492 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 2.75, dd (*J* = 11.4, 17.1 Hz), 1H; 3.10, dd (*J* = 3.0, 17.1 Hz), 1H; 3.77, s, 3H; 4.17, ddd (*J* = 2.7, 3.0, 11.4 Hz), 1H; 5.74, d (*J* = 2.7 Hz), 1H; 7.25-7.33, m, 5H; 7.41-7.47, m, 3H; 7.58-7.61, m, 1H; 7.76-7.78, m, 1H; 7.82-7.85, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 38.80, 46.78, 51.83, 89.26, 112.13, 119.07, 121.85, 123.00, 125.16, 127.00, 127.78, 128.47, 129.13, 129.80, 130.29, 141.76, 157.09, 172.43. MS *m/z* (%): 318 (M^+, 26), 244 (100), 217 (27), 202 (18). HRMS, $C_{21}H_{18}O_3Na$: calcd, 341.1154; found 341.1154.

Diastereomeric mixture of (±) (1*R*,2*S* and 1*R*,2*R*)-Methyl 2-(1-phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetate *E/Z*-118a

A colourless oil. R_f 0.45 (12% acetone / hexane). ^{13}C NMR ($CDCl_3$, mixture, 50 MHz) δ 38.83, 40.28, 50.63, 51.99, 52.10, 54.02, 83.61, 88.42, 112.31, 112.56, 117.91, 120.25, 122.98, 123.12, 123.21, 123.25, 125.39, 126.45, 126.95, 127.01, 127.43, 127.58, 127.98, 128.93, 129.01, 129.10, 129.14, 129.18, 130.08, 130.24, 130.52, 130.64, 130.85, 138.48, 142.61, 157.28, 157.38, 170.91, 171.46. Anal.Calcd for $C_{21}H_{18}O_3$: C, 79.23; H, 5.70. Found C, 78.79; H, 5.83.

***Z*-118a**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.35, dd (J = 16.5, 6.0 Hz), 1H; 2.61, dd (J = 16.5, 7.8 Hz), 1H; 3.66, s, 3H; 5.01, d (J = 9.0 Hz), 1H; 5.53, ddd (J = 9.0, 7.8, 6.0 Hz), 1H; 7.18-7.30, m, 9H; 7.74-7.79, m, 2H.

***E*-118a**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.84, dd (J = 15.9, 6.0 Hz), 1H; 2.95, dd (J = 15.9, 7.8 Hz), 1H; 3.72, s, 3H; 4.69, d (J = 5.7 Hz), 1H; 5.11, ddd (J = 7.8, 6.0, 5.7 Hz), 1H; 7.18-7.30, m, 9H; 7.74-7.79, m, 2H.

(±) Methyl 2-{(1*R*,2*R*)-2-[4-chlorophenyl]-1,2-dihydronaphtho[2,1-*b*]furan-1-yl}acetate *Z*-119a

A colourless oil. R_f 0.50 (15% ethyl acetate / hexane). IR (CH_2Cl_2) 1734, 1631, 1600, 1580, 1521, 1491 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.29, dd (J = 16.8, 10.2 Hz), 1H; 2.51, dd (J = 16.8, 3.6 Hz), 1H; 3.32, s, 3H; 4.55, ddd (J = 10.2, 3.6, 8.4 Hz), 1H; 5.99, d (J = 8.4 Hz), 1H; 7.20-7.25, m, 1H; 7.29-7.36, m, 3H; 7.44-7.52, m, 3H; 7.68-7.73, m, 1H; 7.84-7.85, m, 1H; 7.94-7.95, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 34.96, 42.39, 51.51, 87.40, 112.22, 121.59, 122.09, 123.26, 127.15, 128.37, 128.63, 129.17, 129.89, 130.07, 133.87, 134.87, 134.88, 156.46, 172.03, 1 C masked. MS *m/z* (%): 352 (M^+, 27), 278 (100), 215 (28), 139 (12). HRMS, $C_{21}H_{17}O_3Cl$: calcd, 352.0892; found 352.0869.

(±) Methyl 2-{(1*R*,2*R*)-2-[4-chlorophenyl]-1,2-dihydronaphtho[2,1-*b*]furan-1-yl}acetate *E*-119a

A colourless oil. R_f 0.48 (15% ethyl acetate / hexane). IR (NUJOL) 1733, 1632, 1600, 1579, 1521, 1492 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.74, dd (J = 16.5, 11.7 Hz), 1H; 3.10, dd (J = 16.5, 3.0 Hz), 1H; 3.78, s, 3H; 4.11, ddd (J = 11.7, 2.7, 2.4 Hz), 1H; 5.71, d (J = 2.4 Hz), 1H; 7.24-7.48, m, 7H; 7.56-7.59, m, 1H; 7.76-7.79, m, 1H; 7.83-7.85, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 38.57, 46.79, 51.90, 88.56, 112.08, 118.79, 121.82, 123.19, 126.83, 127.16, 128.64, 129.20, 129.90, 130.26, 130.47, 133.56, 140.36, 156.87, 172.53. MS *m/z* (%): 352 (M^+, 28), 278 (100), 251, (8), 215 (28). HRMS, $C_{21}H_{17}O_3ClNa$: calcd, 375.0764; found 375.0762.

Diastereomeric mixture of (±) (1*R*,2*S* and 1*R*,2*R*)-Methyl 2-{1-[4-chlorophenyl]-1,2-dihydronaphtho[2,1-*b*]furan-2-yl}acetate *E/Z*-120a

A colourless oil. R_f 0.45 (15% ethyl acetate / hexane). ^{13}C NMR ($CDCl_3$, mixture, 150 MHz) δ 36.41, 39.94, 49.74, 51.84, 51.93, 53.08, 83.14, 87.96, 112.10, 112.35, 119.51, 121.49, 122.57, 122.68, 123.15, 123.19, 126.44, 126.67, 126.81, 128.34, 128.58, 128.63, 129.09, 129.89, 129.90, 130.19, 130.23, 130.28, 130.47, 130.56, 133.02, 133.22, 136.83, 140.96, 157.06, 157.14, 171.60, 170.03. Anal.Calcd for $C_{20}H_{17}O_3Cl$: C, 71.49; H, 4.86. Found C, 71.25; H, 4.68.

***Z*-120a**: ^1H NMR ($CDCl_3$, 600 MHz) δ 2.35, dd (*J* = 16.6, 6.8 Hz), 1H; 2.63, d (*J* = 16.6, 7.6 Hz), 1H; 3.67, s, 3H; 4.99, d (*J* = 8.8, 7.6, 6.8 Hz), 1H; 5.50, ddd (*J* = 8.8 Hz), 1H; 7.13-7.15, m, 2H; 7.18-7.23, m, 2H; 7.25-7.30, m, 3H; 7.76-7.81, m, 3H.

***E*-120a**: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.83, dd (*J* = 15.8, 6.1 Hz), 1H; 2.94, dd (*J* = 15.8, 7.3 Hz), 1H; 3.78, s, 3H; 4.68, d (*J* = 5.5 Hz), 1H; 5.06, ddd (*J* = 7.3, 6.1, 5.5 Hz), 1H; 7.13-7.15, m, 2H; 7.18-7.23, m, 2H; 7.25-7.30, m, 3H; 7.76-7.81, m, 3H.

(±) Methyl 2-{(1*R*,2*R*)-2-[4-methoxyphenyl]-1,2-dihydronaphtho[2,1-*b*]furan-1-yl}acetate *E*-121a

A colourless oil. R_f 0.39 (20% ethyl acetate / hexane). IR (CH_2Cl_2) 1735, 1631, 1614, 1599, 1582 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 2.74, dd (*J* = 16.6, 11.3 Hz), 1H; 3.09, dd (*J* = 16.6, 3.1 Hz), 1H; 3.75, s, 3H; 3.76, s, 3H; 4.16, ddd (*J* = 11.3, 3.1, 2.6 Hz), 1H; 5.68, d (*J* = 2.6 Hz), 1H; 6.82-6.84, m, 2H; 7.22-7.23, m, 1H; 7.29-7.33, m, 3H; 7.44-7.46, m, 1H; 7.60-7.61, m, 1H; 7.75-7.76, m, 1H; 7.82-7.84, m, 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.76, 46.60, 51.87, 55.24, 89.26, 112.21, 113.87, 119.15, 121.86, 122.98, 126.56, 127.00, 129.15, 129.72, 130.25, 130.30, 133.93, 157.01, 159.24, 172.51. MS *m/z* (%): 348 (M^+, 28), 316 (13), 274 (100), 259 (14). HRMS, $C_{22}H_{20}O_4$: calcd, 348.1362; found 348.1362.

Mixture of (±) (1*R*,2*S* and 1*R*,2*R*)-Methyl 2-{1-[4-methoxyphenyl]-1,2-dihydronaphtho[2,1-*b*]furan-2-yl}acetate *E/Z*-122a and (±) Methyl 2-{(1*R*,2*S*)-2-[4-methoxyphenyl]-1,2-dihydronaphtho[2,1-*b*]furan-1-yl}acetate *Z*-121a

Anal.Calcd for $C_{19}H_{22}O_4$: C, 75.83; H, 5.79. Found C, 75.94; H, 5.57.

***Z*-121a**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.35, dd (J = 17.0, 10.2 Hz), 1H; 2.49, dd (J = 17.0, 4.2 Hz), 1H; 3.32, s, 3H; 4.51, ddd (J = 10.2, 8.4, 4.2 Hz), 1H; 5.99, d (J = 8.4 Hz), 1H; 7.11-7.13, m, 2H; 6.82-7.85, m, 10H.

***E*-122a**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.82, dd (J = 15.6, 5.4 Hz), 1H; 2.93, dd (J = 15.6, 7.8 Hz), 1H; 3.77, s, 3H; 4.65, d (J = 5.4 Hz), 1H; 5.06, ddd (J = 7.8, 5.4, 5.4 Hz), 1H; 6.82-7.85, m, 10H.

***Z*-122a**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.36, dd (J = 16.8, 6.6 Hz), 1H; 2.59, dd (J = 16.8, 8.8 Hz), 1H; 3.67, s, 3H; 4.97, d (J = 8.4 Hz), 1H; 5.48, ddd (J = 8.8, 8.4, 6.6 Hz), 1H; 6.82-7.85, m, 10H.

(±) Methyl 2-{(1*R*,2*S*)-2-[2-(4-trifluoromethyl)phenyl]-1,2-dihydronaphtho[2,1-*b*]furan-1-yl}acetate *Z*-123a

A white solid. Mp 149-151 °C. R_f 0.29 (10% ethyl acetate / hexane). IR (CH_2Cl_2) 1734, 1633, 1621, 1599, 1580, 1521 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.28, dd (J = 16.8, 10.2 Hz), 1H; 2.51, dd (J = 16.8, 3.6 Hz), 1H; 3.25, s, 3H; 4.60, ddd (J = 10.2, 7.8, 3.6 Hz), 1H; 6.07, d (J = 7.8 Hz), 1H; 7.22-7.23, m, 2H; 7.34-7.36, m, 1H; 7.48-7.51, m, 1H; 7.62-7.70, m, 4H; 7.77-7.79, m, 1H; 7.85-7.86, m, 1H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 34.87, 42.36, 51.48, 87.28, 112.22, 121.45, 122.04, 123.37, 124.04 q ($^1J_{CF}$ = 270 Hz), 125.09 q ($^3J_{CF}$ = 3.8 Hz), 127.24, 127.68, 129.20, 129.93, 129.96, 130.18, 130.29 q ($^2J_{CF}$ = 32.3 Hz), 140.36, 156.36, 171.93. ^{19}F NMR ($CDCl_3$, 564 MHz) δ 63.45. MS *m/z* (%): 386 (33, M^+), 312 (100), 285 (34), 215 (30). HRMS, $C_{22}H_{17}O_3F_3$: calcd, 386.1130; found 386.1127.

Methyl (*Z*)-4-(2-hydroxy-1-naphthyl)-3-[4-(trifluoromethyl)phenyl]-2-butenoate *Z*-129a

A colourless oil. R_f 0.38 (25% ethyl acetate / hexane). IR (CH_2Cl_2) 3581, 1724, 1649, 1630, 1616, 1587, 1518 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.45, s, 3H; 4.15, d (J = 2.1 Hz), 1H; 5.45, s (exch D_2O), 1H; 5.53, t (J = 2.1 Hz), 2H; 7.00-7.02, m, 1H; 7.34-7.37, m, 1H; 7.41-7.43, m, 2H; 7.47-7.50, m, 1H; 7.63-7.64, m, 2H; 7.68-7.70, m, 1H; 7.74-7.75, m, 1H; 7.78-7.80, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.52, 51.10, 114.79, 117.51, 117.87, 122.69, 123.41, 124.18 q ($^1J_{CF}$ = 270 Hz), 125.02 q ($^3J_{CF}$ = 4.0 Hz), 127.06, 127.38, 128.71, 129.25, 129.34, 129.77 q ($^2J_{CF}$ = 32.0 Hz), 133.47, 144.71, 151.38, 157.11, 166.29. ^{19}F NMR ($CDCl_3$, 564 MHz) δ 63.60. MS *m/z* (%):

386 (M^+, 46), 325 (73), 354 (13), 312 (100), 181 (46). HRMS, $C_{22}H_{17}O_3F_3$: calcd, 386.1130; found 386.1142.

Methyl (*E*)-4-(2-hydroxy-1-naphthyl)-3-[4-(trifluoromethyl)phenyl]-2-butenoate *E*-129a

A colourless oil. R_f 0.53 (25% ethyl acetate / hexane). IR (CH_2Cl_2) 3311, 1712, 1693, 1624, 1601, 1520 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 3.90, s, 3H; 4.70, s, 1H; 6.01, s, 1H; 7.10-7.12, m, 3H; 7.17-7.19, m, 2H; 7.31-7.33, m, 2H; 7.48-7.50, m, 1H; 7.60-7.62, m, 1H; 7.64-7.66, m, 1H; 8.17, s (exch D_2O), 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.83, 52.39, 112.61, 118.70, 119.45, 122.00, 122.61, 123.81 q ($^1J_{CF}$ = 270 Hz), 124.84 q ($^3J_{CF}$ = 3.8 Hz), 126.04, 127.43, 128.48, 128.98, 129.23, 130.21 q ($^2J_{CF}$ = 32.2 Hz), 133.30, 144.38, 153.68, 158.24, 169.50. ^{19}F NMR ($CDCl_3$, 564 MHz) δ 63.28. MS *m/z* (%): 386 (M^+, 50), 354 (12), 325 (72), 312 (100), 181 (46). HRMS, $C_{22}H_{17}O_3F_3$: calcd, 386.1130; found 386.1132.

Methyl 2-{2-[4-(trifluoromethyl)phenyl]-1,2-dihydronaphtho[2,1-*b*]furan-2-yl}acetate 130a

A colourless oil. R_f 0.29 (15% acetone / hexane). IR (CH_2Cl_2) 1738, 1634, 1620, 1603, 1580, 1522 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.15 and 3.17, AB_q (J_{AB} = 14.9 Hz), 2H; 3.51, s, 3H; 3.73 and 4.13, AB_q (J_{AB} = 15.6 Hz), 2H; 7.23-7.26, m, 1H; 7.29-7.34, m, 1H; 7.43-7.49, m, 1H; 7.55-7.58, m, 1H; 7.61-7.75, m, 5H; 7.79-7.82, m, 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.54, 46.13, 51.68, 89.22, 111.99, 117.26, 122.64, 123.25, 124.03 q ($^1J_{CF}$ = 270 Hz), 125.45 q ($^3J_{CF}$ = 4.0 Hz), 126.89, 128.77, 129.52, 129.61, 129.88 q ($^2J_{CF}$ = 32.4 Hz), 130.62, 148.73, 155.67, 169.56, 1 C masked. ^{19}F NMR ($CDCl_3$, 564 MHz) δ 63.50. MS *m/z* (%): 386 (M^+, 19), 325 (18), 312 (100), 181 (11). HRMS, $C_{22}H_{17}O_3F_3$: calcd, 386.1130; found 386.1125.

Base catalysed rearrangements of dioxines 77-79 and 81-82

A general procedure was employed in the synthesis of **131** to **135**, the exact conditions described in **Table 2.12**. A typical procedure was as follows. To a stirring solution of the **77** (1.25 g, 4.77 mmol) in dichloromethane (30 mL) was added a solution of DABCO (50 mg, 0.45 mmol) in 5mL dichloromethane. The reaction was left stirring for one hour. The resulting mixture was filtered and the solid washed several times with cold dichloromethane to give **131** as a powdery white solid (1.10 g, 88%).

In the case of the reaction of **78**, the product **132** also precipitated from dichloromethane. In the case of **79** and **81**, products **133** and **134** respectively were precipitated from benzene. **135** had to be purified by column chromatography (florisil, 10% ethyl acetate / hexane).

1-Phenyl-2-(2-hydroxy-1-naphthalenyl)-1-ethanone 131

A white solid. R_f 0.37 (25% ethyl acetate / hexane). Mp: 213-217 °C (decomposes). IR (NUJOL) 3409, 1676, 1595, 1579, 1513 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.74, s, 2H; 7.18-7.21, m, 1H; 7.30-7.38, m, 2H; 7.48-7.55, m, 3H; 7.60-7.63, m, 1H; 7.71-7.74, m, 1H; 7.77-7.80, m, 1H; 7.90-7.93, m, 1H; 8.16-8.19, m, 2H. ^{13}C NMR (d_6-acetone, 50 MHz) δ 36.51, 114.86, 118.59, 123.39, 124.05, 127.09, 129.05, 129.21, 129.32, 129.41, 129.88, 133.67, 135.30, 138.33, 153.46, 198.20. MS *m/z* (%): 262 (M^+, 72), 157 (75), 129 (49), 105 (100), 77 (33). Anal.Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found C, 82.39; H, 5.47. X-ray quality crystals of **131** were grown from tetrahydrofuran / methanol solution at 278 K. Crystal data was obtained upon a Rigaku AFC-7*R* diffractometer.

1-(4-Chlorophenyl)-2-(2-hydroxy-1-naphthalenyl)-1-ethanone 132

A white solid. Mp: 212-220 °C (decomposes). IR (NUJOL) 3421, 1674, 1630, 1587, 1570, 1518 cm^{-1}. ^1H NMR ($CDCl_3$/d_6-DMSO, 300 MHz) δ 4.70, s, 2H; 7.20-7.27, m, 2H; 7.37-7.44, m, 3H; 7.64-7.75, m, 3H; 8.09-8.11, m, 1H; 9.18, s, 1H. ^{13}C NMR ($CDCl_3$/d_6-DMSO, 75 MHz) δ 35.92, 112.70, 117.86, 122.24, 122.41, 126.14, 128.37, 128.13, 128.34, 129.56, 133.63, 135.02, 138.79, 152.32, 197.26, 1C masked. MS *m/z* (%): 296 (M^+, 32), 157 (100), 139 (67), 128 (45). Anal.Calcd for $C_{18}H_{13}ClO_2$: C, 72.85; H, 4.42; Cl, 11.95. Found C, 72.64; H, 4.34; Cl, 12.18.

2-(2-hydroxy-1-naphthalenyl)-1-[4-(methoxy)phenyl]-1-ethanone 133

A white solid. Mp: 200-205 °C (decomposes). R_f 0.40 (40% ethyl acetate / hexane). IR (NUJOL) 3419, 1670, 1630, 1602, 1578, 1502 cm^{-1}. ^1H NMR ($CDCl_3$/d_6-DMSO, 300 MHz) δ 3.87, s, 3H; 4.70, s, 2H; 6.93-6.96, m, 2H; 7.21-7.28, m, 2H; 7.36-7.40, m, 1H; 7.63-7.66, m, 1H; 7.72-7.78, m, 2H; 8.13-8.16, m, 2H; 9.06, s, 1H. ^{13}C NMR ($CDCl_3$/d_6-DMSO, 50 MHz) δ 35.50, 55.19, 113.43, 118.21, 122.27, 122.63, 126.10, 128.19, 128.24, 128.57, 129.87, 130.51, 133.59, 133.78, 152.59, 163.21, 197.18. MS *m/z* (%): 292 (M^+, 12), 274 (100), 259 (36), 135 (68). Anal.Calcd for $C_{19}H_{16}O_3$: C, 79.23; H, 5.70. Found C, 78.97; H, 5.78.

1-(3-Bromophenyl)-2-(2-hydroxy-1-naphthalenyl)-1-ethanone 134

A white solid. Mp: 192-197 °C (decomposes). R_f 0.38 (25% ethyl acetate / hexane). IR (NUJOL) 3428, 1681, 1630, 1581, 1566, 1548 cm^{-1}. ^1H NMR ($CDCl_3$ / d_6-DMSO, 300 MHz) δ 4.70, s, 2H; 7.21-7.28, m, 2H; 7.35-7.42, m, 2H; 7.51-7.55, m, 1H; 7.63-7.75, m, 3H; 8.07-8.10, m, 1H; 8.25-8.27, m, 1H; 9.42, s, 1H. ^{13}C NMR ($CDCl_3$ / d_6-DMSO, 50 MHz) δ 35.69, 112.25, 117.62, 121.98, 122.12, 122.16, 125.89, 126.41, 127.88, 128.05, 128.09, 129.63, 130.75, 133.42, 135.06, 138.32, 152.22, 196.65. MS *m/z* (%): 324 (M^+, 64), 322 (M^+, 67), 215 (41), 157 (100), 139 (24), 127 (90). Anal.Calcd for $C_{18}H_{13}O_2Br$: C, 63.36; H, 3.84. Found C, 63.77; H, 4.30.

2-(2-Hydroxy-1-naphthyl)-1-(1-naphthyl)-1-ethanone 135

A white solid. Mp: 155-158 °C. R_f 0.47 (15% ethyl acetate / hexane). IR (CH_2Cl_2) 3575, 1684, 1631, 1597, 1576, 1510 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.82, s, 2H; 7.19-7.21, m, 1H; 7.30-7.32, m, 1H; 7.38-7.57, m, 5H; 7.75-7.88, m, 4H; 8.00-8.03, m, 1H; 8.18-8.21, m, 1H; 8.45-8.48, m, 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.33, 113.39, 119.05, 122.29, 123.18, 124.34, 125.77, 126.63, 126.85, 128.16, 128.44, 128.81, 129.44, 129.49, 129.77, 130.30, 133.15, 133.35, 133.97, 135.41, 153.41, 204.68. MS *m/z* (%): 312 (M^+, 10), 294 (40), 155 (100), 127 (64). HRMS, $C_{22}H_{16}O_2$: calcd, 312.1150; found 312.1149.

Reactions of 131-134 with phosphoranes

A general procedure was employed, typically upon a 50 mg scale but could be performed equally well on larger scales. The exact conditions are described in **Table 2.14**. The following is an example. A mixture of **46g** (124 mg, 3.02 mmol) and **131** (42.0 mg, 0.160 mmol) in dry chloroform (15 mL) was heated under reflux for one day under a nitrogen atmosphere. The solvent was removed *in vacuo* and the crude residue purified by flash chromatography (20% ethyl acetate / hexane) to give **137g** as a colourless oil (50.4 mg, 80%).

Methyl (*E*)-4-(2-hydroxy-1-naphthyl)-3-phenyl-2-butenoate *E*-136a

A colourless oil. R_f 0.44 (25% ethyl acetate / hexane). IR (CH_2Cl_2) 3290, 1689, 1626, 1601, 1520 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.90, s, 3H; 4.69, s, 2H; 6.02, s, 1H; 7.05-7.18, m, 8H; 7.52-7.67, m, 3H; 8.44, s (exch D_2O), 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.06, 52.26, 113.12, 118.58, 118.83, 122.34, 122.88, 125.75, 126.98, 127.87, 128.22, 128.33, 128.98, 133.44, 140.92, 153.88, 159.91, 170.07. MS *m/z* (%): 318 (M^+,

37), 286 (17), 257 (67), 244 (100), 181 (26). HRMS, $C_{21}H_{18}O_3$: calcd, 318.1256; found 318.1252.

Methyl (*Z*)-4-(2-hydroxy-1-naphthyl)-3-phenyl-2-butenoate *Z*-136a

A colourless oil. R_f 0.33 (25% ethyl acetate / hexane). IR (CH_2Cl_2) 3579, 1722, 1645, 1631, 1601, 1587, 1492 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.48, s, 3H; 4.19, d (J = 1.6 Hz), 2H; 5.49, t (J = 1.6 Hz), 1H; 5.10, broad s (exch D_2O), 1H; 7.05-7.08, m, 1H; 7.34-7.42, m, 6H; 7.50-7.52, m, 1H; 7.70-7.73, m, 1H; 7.79-7.81, m, 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.76, 50.91, 115.37, 117.11, 117.69, 122.97, 123.44, 126.91, 126.98, 127.83, 128.10, 128.64, 129.46, 133.54, 140.86, 151.27, 157.86, 166.39. MS *m/z* (%): 318 (M^+, 29), 286 (14), 257 (53), 244 (100), 181 (27). HRMS, $C_{21}H_{18}O_3$: calcd, 318.1256; found 318.1252.

Methyl 2-(2-phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetate 137a

A colourless oil. R_f 0.46 (20% ethyl acetate / hexane). IR (CH_2Cl_2) 1738, 1633, 1601, 1579, 1522, 1494 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.13 and 3.16, AB_q (J_{AB} = 14.6 Hz), 2H; 3.48, s, 3H; 3.77 and 4.14, AB_q (J_{AB} = 15.7 Hz), 2H; 7.26-7.50, m, 6H; 7.58-7.62, m, 3H; 7.72-7.75, m, 1H; 7.81-7.83, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 41.26, 46.47, 51.60, 89.72, 112.08, 117.74, 122.72, 123.00, 124.85, 128.70, 129.23, 130.73, 144.82, 155.95, 169.97. MS *m/z* (%): 318 (M^+, 32), 286 (22), 257 (2), 244 (100), 181 (11). HRMS, $C_{21}H_{18}O_3$: calcd, 318.1256; found 318.1255.

Benzyl 2-(2-phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetate 137g

A colourless oil. R_f 0.33 (17% ethyl acetate / hexane). IR (CH_2Cl_2) 1734, 1633, 1601, 1579, 1522, 1497 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.17 and 3.20, AB_q (J_{AB} = 14.4 Hz), 2H; 3.74 and 4.12, AB_q (J_{AB} = 15.6 Hz), 2H; 4.91, s, 2H; 7.06-7.08, m, 1H; 7.20-7.36, m, 9H; 7.42-7.46, m, 1H; 7.52-7.55, m, 3H; 7.68-7.71, m, 1H; 7.78-7.81, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 41.36, 46.69, 66.42, 89.65, 112.05, 117.65, 122.70, 122.96, 124.80, 126.65, 127.50, 128.03, 128.12, 128.33, 128.44, 128.69, 129.22, 129.45, 130.70, 135.45, 144.86, 155.93, 169.29. MS *m/z* (%): 394 (M^+, 48), 303 (28), 257 (100), 244 (96). Anal.Calcd for $C_{27}H_{22}O_3$: C, 82.21; H, 5.62. Found C, 81.96; H, 5.81.

1-Phenyl-2-(2-phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)ethanone 137h

A pale yellow oil. R_f 0.50 (8% ethyl acetate / hexane). IR (CH_2Cl_2) 1691, 1674, 1633, 1599, 1579, 1521, 1495 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.86 and 4.19, AB_q (J_{AB} = 16.0 Hz), 2H; 3.81, AB_q (J_{AB} = 16.0 Hz), 2H; 7.04-7.07, m, 1H; 7.25-7.39, m, 5H; 7.45-7.50, m, 3H; 7.58-7.65, m, 4H; 7.76-7.83, m, 3H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 41.02, 49.44, 90.62, 111.96, 118.07, 122.80, 122.98, 125.13, 126.68, 127.49, 128.31, 128.35, 128.41, 128.66, 129.15, 129.42, 130.73, 132.99, 137.59, 145.11, 155.76, 197.04. MS *m/z* (%): 364 (M^+, 84), 362 (73), 244 (100), 215 (42), 105 (74), 91 (18), 77 (53). HRMS, $C_{26}H_{20}O_2$: calcd, 364.1463; found 364.1463.

Methyl (*E*)-3-(4-chlorophenyl)-4-(2-hydroxy-1-naphthalenyl)-2-butenoate *E*-138a

A colourless oil. R_f 0.33 (20% ethyl acetate / hexane). IR (CH_2Cl_2) 3300, 1691, 1626, 1600, 1520 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.90, s, 3H; 4.68, s, 2H; 6.01, s, 1H; 6.97-7.12, m, 4H; 7.19-7.26, m, 3H; 7.60-7.68, m, 3H; 8.20, s (exch D_2O), 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.76, 52.33, 112.96, 118.79, 118.98, 122.56, 122.66, 126.06, 128.11, 128.38, 128.51, 129.03, 129.14, 133.34, 134.36, 139.23, 153.76, 158.47, 169.76. MS *m/z* (%): 352 (M^+, 15), 320 (22), 291 (74), 278 (100), 181 (59). HRMS, $C_{21}H_{17}O_3Cl$: calcd, 352.0866; found 352.0860.

Methyl (*Z*)-3-(4-chlorophenyl)-4-(2-hydroxy-1-naphthalenyl)-2-butenoate *Z*-138a

A white solid. Mp: 134-137 °C. R_f 0.24 (20% ethyl acetate / hexane). IR (CH_2Cl_2) 3579, 1722, 1647, 1630, 1595, 1518 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.46, s, 3H; 4.14, d (J = 1.5 Hz), 2H; 5.04, s (exch D_2O), 1H; 5.49, t (J = 1.5 Hz), 1H; 7.02-7.05, m, 1H; 7.25-7.28, m, 2H; 7.34-7.39, m, 3H; 7.47-7.52, m, 1H; 7.70-7.82, m, 3H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.59, 51.00, 115.11, 117.56, 117.63, 122.82, 123.47, 127.06, 128.28, 128.44, 128.69, 129.22, 129.42, 133.49, 133.72, 139.13, 151.19, 156.91, 166.20. MS *m/z* (%): 352 (M^+, 15), 320 (22), 291 (76), 278 (100), 181 (72). HRMS, $C_{21}H_{17}O_3Cl$: calcd, 352.0866; found 352.0860.

Methyl 2-[2-(4-chlorophenyl)-1,2-dihydronaphtho[2,1-*b*]furan-2-yl]acetate 139a

A pale yellow viscous oil. R_f 0.49 (20% ethyl acetate / hexane). IR (NEAT) 1738, 1633, 1601, 1579, 1521 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.11 and 3.14, AB_q (J_{AB} = 14.9 Hz), 2H; 3.51, s, 3H; 3.73 and 4.11, AB_q (J_{AB} = 15.6 Hz), 2H; 7.21-7.24, m, 1H;

7.29-7.36, m, 3H; 7.44-7.52, m, 3H; 7.56-7.59, m, 1H; 7.71-7.74, m, 1H; 7.79-7.82, m, 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.40, 46.27, 51.68, 89.25, 112.02, 117.47, 122.67, 123.16, 126.45, 126.82, 128.59, 128.75, 129.40, 129.54, 130.65, 133.47, 143.27, 155.71, 169.74. MS *m/z* (%): 352 (M^+, 19), 291 (22), 278 (100), 181 (20). HRMS, $C_{21}H_{17}O_3Cl$: calcd, 352.0866; found 352.0860.

Methyl 2-(2-(4-methoxyphenyl)-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetate 141a

A colourless oil. R_f 0.36 (25% ethyl acetate / hexane). IR (CH_2Cl_2) 1736, 1633, 1612, 1581, 1514 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.10 and 3.20, AB_q (J_{AB} = 14.4 Hz), 2H; 3.48, s, 3H; 3.77, s, 3H; 3.82 and 4.09, AB_q (J_{AB} = 15.6 Hz), 2H; 6.87-6.90, m, 2H; 7.2-7.22, m, 1H; 7.26-7.31, m, 1H; 7.44-7.49, m, 1H; 7.56-7.59, m, 1H; 7.68-7.71, m, 1H; 7.77-7.80, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 41.10, 46.42, 51.54, 55.19, 89.55, 112.03, 113.70, 117.81, 122.68, 122.91, 126.10, 126.62, 128.65, 129.14, 129.37, 130.69, 136.71, 155.84, 158.89, 170.02. MS *m/z* (%): 348 (M^+, 42), 316 (20), 287 (37), 274 (100), 181 (16). HRMS, $C_{22}H_{20}O_4$: calcd, 348.1366; found 348.1372.

Methyl (*Z*)-3-(3-bromophenyl)-4-(2-hydroxy-1-naphthalenyl)-2-butenoate *Z*-142a

A colourless oil. R_f 0.42 (20% ethyl acetate / hexane). IR (CH_2Cl_2) 3580, 1723, 1648, 1630, 1592, 1560, 1517 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.46, s, 3H; 4.10, d (J = 2.1 Hz), 2H; 5.23, s (exch D_2O), 1H; 5.44, t (J = 2.1 Hz), 1H; 7.00-7.03, m, 1H; 7.24-7.26, m, 2H; 7.34-7.39, m, 1H; 7.46-7.53, m, 3H; 7.68-7.82, m, 3H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.53, 51.06, 114.95, 117.56, 117.77, 122.06, 122.80, 123.44, 125.80, 127.06, 128.68, 129.23, 129.38, 129.57, 129.87, 130.74, 133.47, 142.93, 151.32, 156.41, 166.21. MS *m/z* (%): 398 (28, M^+), 396 (28, M^+), 366 (11), 364 (11), 337 (63), 335 (59), 324 (79), 322 (83), 255 (24), 226 (36), 181 (100), 128 (68). HRMS, $C_{21}H_{17}O_3Br$: calcd, 396.0362; found 396.0355.

Methyl (*E*)-3-(4-bromophenyl)-4-(2-hydroxy-1-naphthalenyl)-2-butenoate *E*-142a

A colourless oil. R_f 0.54 (20% ethyl acetate / hexane). IR (CH_2Cl_2) 3297, 1691, 1628, 1600, 1560, 1519 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.90, s, 3H; 4.67, s, 2H; 6.01, s, 1H; 6.88-6.90, m, 2H; 7.10-7.13, m, 1H; 7.16-7.28, m, 4H; 7.58-7.67, m, 3H; 8.22, s (exch D_2O), 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.73, 52.36, 112.71, 118.72, 119.19, 121.90, 122.54, 122.68, 125.76, 125.99, 128.47, 129.03, 129.20, 129.39, 130.10, 131.24, 133.32, 142.70, 153.77, 158.03, 169.68. MS *m/z* (%): 398 (M^+, 30), 396 (M^+,

30), 366 (23), 364 (23), 337 (70), 335 (65), 324 (96), 322 (99), 255 (22), 226 (25), 181 (100), 128 (43). HRMS, $C_{21}H_{17}O_3Br$: calcd, 396.0362; found 396.0373.

Methyl 2-[2-(3-bromophenyl)-1,2-dihydronaphtho[2,1-*b*]furan-2-yl]acetate 143a

A colourless oil. R_f 0.65 (20% ethyl acetate / hexane). IR (CH_2Cl_2) 1738, 1633, 1595, 1579, 1568, 1521 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.10 and 3.14, AB_q (J_{AB} = 14.9 Hz), 2H; 3.51, s, 3H; 3.73 and 4.12, AB_q (J_{AB} = 15.6 Hz), 2H; 7.22-7.34, m, 4H; 7.40-7.44, m, 1H; 7.47-7.50, m, 1H; 7.56-7.59, m, 1H; 7.72-7.74, m, 2H; 7.79-7.82, m, 1H. MS *m/z* (%): 398 (M^+, 25), 396 (M^+, 25), 366 (3), 364 (3), 337 (18), 335 (15), 324 (99), 322 (100), 215 (23), 181 (28). HRMS, $C_{21}H_{17}O_3Br$: calcd, 396.0362; found 396.0373.

Reaction of Dioxine 83 with ylide 45a: A typical procedure

To a solution of **83** (130 mg, 0.61 mmol) in anhydrous dichloromethane (5 mL) under a nitrogen atmosphere was added ylide **45a** (250 mg, 0.75 mmol). The mixture was allowed to stir at ambient temperature for five days after which time the volatiles were removed *in vacuo* and the residue subjected to silica gel chromatography. Elution with a mixture of 10% ethyl acetate / hexane afforded **144a** (9 mg, 5%) as a crystalline solid, **145** (46 mg, 28%) as a colourless oil and **146** (45 mg, 31%) as a crystalline solid.

Methyl 2-(2,2-dimethyl-1,2-dihydronaphtho[2,1-*b*]furan-1-yl) acetate 144a

A white solid. Mp: 76.5-78.5 °C. R_f 0.40 (10% ethyl acetate / hexane). IR (CH_2Cl_2) 1736, 1630, 1599, 1581 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.47, s, 3H; 1.52, s, 3H; 2.65, dd (J = 17.5, 10.3 Hz), 1H; 2.79, dd (J = 17.5, 3.3 Hz), 1H; 3.73, s, 3H; 3.98, dd (J = 10.3, 3.3 Hz), 1H; 7.05-7.08, m, 1H; 7.27-7.33, m, 1H; 7.44-7.50, m, 1H; 7.64-7.71, m, 2H; 7.80-7.83, m, 1H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.16, 28.50, 35.31, 46.03, 51.83, 89.28, 112.69, 121.16, 121.88, 122.71, 126.90, 129.24, 129.56, 129.82, 130.62, 155.56, 173.24. MS *m/z* (%): 270 (M^+, 38), 197 (100), 181 (12), 169 (9), 141 (15). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.67; H, 6.72.

Methyl 3-(2-hydroxy-1-naphthyl)-4-methyl-4-pentenoate 145

A colourless oil. R_f 0.34 (10% ethyl acetate / hexane). IR (CH_2C1_2) 3446, 1736, 1641, 1621, 1600 cm^{-1}. ^1H NMR ($CDC1_3$, 300 MHz) δ 1.66, s, 3H; 2.95, dd (J = 16.2, 7.1 Hz), 1H; 3.24, dd (J = 16.2, 7.1 Hz), 1H; 3.60, s, 3H; 4.70, dd (J = 7.1, 7.1 Hz), 1H; 5.21, s, 2H; 6.90, s (exch. D_2O), 1H; 7.09-7.12, m, 1H; 7.34-7.36, m, 1H; 7.44-7.48, m, 1H; 7.66-7.69, m, 1H; 7.76-7.78, m, 1H; 8.09-8.12, m, 1H. ^{13}C NMR ($CDCl_3$, 150

MHz) δ 22.72, 36.05, 39.57, 51.91, 111.15, 118.19, 119.82, 122.45, 123.23, 126.53, 128.93, 129.41, 129.86, 132.96, 148.25, 153.45, 173.73. MS *m/z* (%): 270 (M^+, 42), 238 (20), 197 (100), 181 (56), 169 (21), 141 (22); HRMS, $C_{17}H_{18}O_3$: calcd, 270.1256; found, 270.1262.

1-Isopropenyl-2,3-dihydro-1*H*-benzo[*f*]chromen-3-one 146

A white solid. Mp: 155-156 °C. R_f 0.20 (10% ethyl acetate / hexane). IR (CH_2Cl_2) 1765, 1647, 1626, 1601 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.87, s, 3H; 2.94, dd (*J* = 15.9, 7.0 Hz), 1H; 3.10, dd (*J* = 15.9, 1.8 Hz), 1H; 4.24, dd (*J* = 7.0, 1.8 Hz), 1H; 4.54, d (*J* = 0.7 Hz), 1H; 4.88, d, (*J* = 0.7 Hz), 1H; 7.24-7.28, m, 1H; 7.46-7.48, m, 1H; 7.52-7.55, m, 1H; 7.80-7.87, m, 3H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 20.52, 34.02, 39.08, 106.89, 114.09, 117.48, 123.08, 125.19, 127.32, 128.80, 129.68, 131.10, 131.19, 143.30, 149.64, 167.70. MS *m/z* (%): 238 (M^+, 100), 223 (8), 195 (72), 181 (78), 165 (22), 141 (33), 115 (35); Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.73; H, 5.91.

Reaction of 84 with phosphorane 45a

To a solution of **84** (150 mg, 0.694 mmol) in dry dichloromethane under a nitrogen atmosphere was added **45a** (285 mg, 0.85 mmol) and the reaction allowed to stir for one week at ambient temperature. The solvent was then removed *in vacuo* and the residue purified by flash chromatography (silica) to give ***Z*-149** (12 mg, 7%) as a white solid, ***Z*-151** (11 mg, 5%) as a white solid and **150a** (57 mg, 30%) as a colourless oil.

(±) (7a*S*,10a*R*)-7a,10,11,11a-Tetrahydro-8*H*-naphtho[1',2':4,5]furo[2,3-*c*]pyran-10-one *Z*-149

A white solid. Mp: 177-179 °C. R_f 0.60 (dichloromethane). IR (CH_2Cl_2) 1780, 1624, 1601, 1514 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 2.68, dd (*J* = 17.4, 3.6 Hz), 1H; 3.40, dd (*J* = 17.4, 9.0 Hz), 1H; 4.14, dd (*J* = 12.0, 2.4 Hz), 1H; 4.30, ddd (*J* = 9.0, 7.0, 3.6 Hz), 1H; 4.50, dd (*J* = 12.0, 4.2 Hz), 1H; 5.14, ddd (*J* = 7.0, 4.2, 2.4 Hz), 1H; 7.14-7.16, m, 1H; 7.44-7.47, m, 1H; 7.56-7.59, m, 1H; 7.65-7.67, m, 1H; 7.72-7.74, m, 1H; 7.85-7.86, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.43, 36.95, 64.96, 76.17, 114.12, 118.94, 121.71, 124.14, 127.13, 129.18, 129.35, 130.18, 131.79, 152.25, 175.33. MS *m/z* (%): 240 (M^+, 100), 197 (25), 181 (26), 169 (12), 152 (11). HRMS, $C_{15}H_{12}O_3Na$: calcd, 263.0684; found 263.0685.

Methyl 2-(2-(hydroxymethyl)-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetate 150a

A colourless oil. R_f 0.25 (5% ethyl acetate / dichloromethane). IR (CH_2Cl_2) 3593, 1736, 1633, 1603, 1579, 1522 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.32, t (J = 5.1 Hz), 1H; 2.94 and 3.05, AB_q (J_{AB} = 15.0 Hz), 2H; 3.42 and 3.53, AB_q (J_{AB} = 15.9 Hz), 2H; 3.66, s, 3H; 3.89, d (J = 5.4 Hz), 2H; 7.07-7.10, m, 1H; 7.31-7.35, m, 1H; 7.47-7.50, m, 1H; 7.56-7.59, m, 1H; 7.67-7.70, m, 1H; 7.79-7.81, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.62, 40.25, 51.82, 66.81, 89.11, 112.01, 117.94, 122.65, 123.12, 126.79, 128.66, 129.23, 129.36, 130.78, 155.47, 170.65. MS *m/z* (%): 272 (28), 240 (41), 198 (48), 181 (100), 157 (29). HRMS, $C_{16}H_{16}O_4$: calcd, 272.1049; found 272.1053.

(±) (1*R*,2*R*)-2-Methyl-3-[1-(2-methoxy-2-oxoethyl)-1,2-dihydronaphtho[2,1-*b*]furan-2-yl]propanoate *Z*-151

A colourless oil. R_f 0.35 (5% ethyl acetate / dichloromethane). IR (CH_2Cl_2) 1736, 1631, 1597, 1581, 1521 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 2.08-2.24, m, 2H; 2.58-2.64, m, 2H; 2.68-2.76, m, 2H; 3.70, s, 3H; 3.72, s, 3H; 4.24, ddd (J = 9.6, 7.0, 4.2 Hz), 1H; 4.83, ddd (J = 10.6, 7.0, 3.6 Hz), 1H; 7.07-7.08, m, 1H; 7.29-7.32, m, 1H; 7.45-7.48, m, 1H; 7.65-7.66, m, 1H; 7.68-7.70, m, 1H; 7.80-7.81, m, 1H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 25.10, 31.28, 40.36, 51.72, 52.00, 86.03, 112.17, 122.03, 122.06, 123.00, 126.98, 129.12, 129.66, 129.78, 129.98, 156.43, 172.89, 173.42. MS *m/z* (%): 328 (M^+, 23), 254 (18), 240 (7), 195 (9), 181 (100). HRMS, $C_{19}H_{20}O_5Na$: calcd, 328.1208; found 351.1206.

Equilibrium mixture of 1-hydroxy-3-(2-hydroxy-1-naphthyl)acetone 153 and 2-(hydroxymethyl-1,2-dihydronaphtho[2,1-*b*]furan-2-ol 161

To a solution of **84** (330 mg, 1.53 mmol) in dry dichloromethane (10 mL) was added DABCO (5 mg, 0.04 mmol) and the solution allowed to stir at ambient temperature for one hour under a nitrogen atmosphere. The volatiles were removed *in vacuo* and the crude residue purified by chromatography (florisil, 20% ethyl acetate / dichloromethane) to afford **153/161** as a cream coloured solid (281 mg, 85%).

Mp 109-111 °C. R_f 0.51 (20% ethyl acetate / dichloromethane). IR (NUJOL) 3296, 1633, 1599, 1580, 1521 cm^{-1}. ^1H NMR ($CDCl_3$/d_6-DMSO, 600 MHz) δ 3.34 and 3.64, AB_q (J_{AB} = 17.4 Hz), 2H; 3.78, dd (J = 11.4, 4.2 Hz), 1H; 3.82, dd (J = 11.4, 4.2 Hz), 1H; 4.04, t (J = 3.6 Hz, exch D_2O), 1H; 4.16, s, 2H; 4.27, d (J = 3.6 Hz), 2H; 4.34, t (J = 4.2Hz), 1H; 6.62, s, 1H; 7.09-7.11, m, 1H; 7.21-7.23, m, 1H; 7.27-7.30, m, 2H; 7.42-

7.46, m, 2H; 7.58-7.59, m, 1H; 7.64-7.68, m, 2H; 7.73-7.79, m, 3H; 9.39, s, 1H. ^{13}C NMR ($CDCl_3$/d_6-DMSO, 150 MHz) δ 35.45, 36.40, 65.61, 66.76, 110.40, 111.06, 111.42, 117.25, 117.40, 121.80, 121.97, 122.08, 122.10, 125.92, 127.78, 127.87, 127.91, 128.08, 128.33, 130.09, 131.26, 132.99, 152.41, 154.92, 208.22, 1 C masked. MS *m/z* (%): 216 (20, M^+), 198 (5), 157 (100), 144 (17), 128 (60). Anal.Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59, Found C, 72.10; H, 5.55.

Reaction of 153/161 with phoshoranes 45a and 45f

The same protocol was employed as for the reactions of **153/161** with both **45a** and **45f**, which were typically performed upon a 30 mg scale. The conditions employed are those that were described in **Scheme 2.23**.

***tert*-Butyl 2-(2-(hydroxymethyl)-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetate 150f**

A colourless oil. R_f 0.33 (dichloromethane). IR (CH_2Cl_2) 3587, 1724, 1633, 1603, 1579, 1522 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31, s, 9H; 2.04, t (J = 6.3 Hz), 1H; 2.39, s, 2H; 3.41, d (J = 16.2 Hz), 1H; 3.57, d (J = 16.2 Hz), 1H; 3.87, d (J = 6.3 Hz), 2H; 7.07-7.10, m, 1H; 7.29-7.34, m, 1H; 7.44-7.50, m, 1H; 7.56-7.59, m, 1H; 7.66-7.69, m, 1H; 7.78-7.81, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.85, 35.37, 42.22, 67.33, 81.35, 89.31, 112.02, 118.15, 122.63, 123.03, 126.76, 128.66, 129.14, 129.30, 130.81, 155.76, 169.46. MS *m/z* (%): 314 (M^+, 36), 281 (9), 240 (24), 181 (62), 44 (100). Anal.Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found C, 72.87; H, 6.85.

Synthesis of Naphtho[2,1-*b*]furans 162 and 163 using NBS: Method A

The typical procedure employed was general to both systems. *N*-Bromosuccinimide (77 mg, 0.433 mmol) was added to a solution of the ***E/Z*-101a** (104 mg, 0.406 mmol) in carbon tetrachloride (10 mL). A small crystal of benzoyl peroxide was added and the mixture heated under reflux for one hour and then allowed to cool to ambient temperature. The mixture was filtered through cotton and the solvent removed *in vacuo* to give a crude residue, which was further purified by flash chromatography (12% acetone / hexane) to afford **162** (50.5 mg, 49%) as a pale yellow oil, along with Methyl 2-(5-bromo-2-methylnaphtho[2,1-*b*]furan-1-yl) acetate **166** (16 mg, 12%) as a pale yellow solid.

Synthesis of the Naphthofurans 162 and 163 using DDQ: Method B[163]

A typical procedure was as follows. To a stirring solution of ***E/Z*-101a** (1.91 g, 7.46 mmol) in dry THF (50 mL) was added DDQ (1.81 g, 7.97 mmol) and the vessel heated under reflux for one day under a nitrogen atmosphere. The solution was allowed to cool to room temperature, diluted with water and extracted twice with dichloromethane (100 mL). The organic phase was dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography (10% acetone / hexane) to give the pure **162** (1.39 g, 74%).

Methyl 2-(2-methylnaphtho[2,1-*b*]furan-1-yl)acetate 162

A yellowish solid. Mp: 76-78 °C. R_f 0.41 (10% acetone / hexane). IR (CH_2Cl_2) 1738, 1620, 1581, 1525, 804 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.52, s, 3H; 3.70, s, 3H; 3.98, s, 2H; 7.45-7.48, m, 1H; 7.56-7.60, m, 2H; 7.65-7.68, m, 1H; 7.92-7.94, m, 1H; 8.23-8.26, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.95, 31.51, 52.24, 109.45, 112.12, 122.21, 122.78, 123.96, 124.60, 126.10, 128.01, 129.05, 130.80, 151.50, 152.18, 171.58. MS *m/z* (%): 254 (M^+, 76), 195 (100), 181 (31), 165 (27), 152 (22). HRMS, $C_{16}H_{14}O_3$: calcd, 254.0943; found 254.0942.

Methyl 2-(1-methylnaphtho[2,1-*b*]furan-2-yl)acetate 163

(59%). R_f 0.33 (12% acetone / hexane). IR (CH_2Cl_2) 1741, 1618, 1577, 1523 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.55, s, 3H, 3.72, s, 3H, 3.85, s, 2H; 7.43-7.67, m, 4H; 7.88-7.93, m, 1H; 8.31-8.36, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.29, 32.35, 52.30, 122.68, 122.85, 123.93, 125.01, 126.02, 128.80, 128.91, 130.64, 145.33, 151.81, 169.62. MS *m/z* (%): 254 (M^+, 26), 195 (100), 165 (29), 152 (23). HRMS, $C_{16}H_{14}O_3$: calcd, 254.0943; found 254.0932.

Methyl 2-(5-bromo-2-methylnaphtho[2,1-*b*]furan-1-yl) acetate 166

Mp: 118-120 °C. R_f 0.24 (12% acetone / hexane). IR (CH_2Cl_2) 1739, 1618, 1577, 1521 cm^{-1}. ^1H NMR (d_6-benzene, 600 MHz) δ 2.00, s, 3H; 3.21, s, 3H; 3.41, s, 2H; 7.27, ddd (J = 7.0, 7.0, 1.2 Hz), 1H; 7.38, ddd (J = 7.0, 7.0, 1.2 Hz), 1H; 7.81, s, 1H; 8.36, dd (J = 7.0, 1.2 Hz), 1H; 8.46, dd (J = 7.0, 1.2 Hz), 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.93, 31.41, 52.29, 109.47, 116.49, 118.11, 122.27, 123.13, 125.23, 126.87, 128.31, 128.40, 128.77, 150.74, 152.87, 171.30. MS *m/z* (%): 332 (M^+, 100), 273 (93), 259 (25), 194 (37), 165 (62). HRMS, $C_{16}H_{13}BrO_3$: calcd, 332.0049; found 332.0062. X-ray quality

crystals of **166** were grown from an evaporating *n*-heptane solution at 278 K. The crystal data was obtained upon on a Bruker AXS SMART CCD diffractometer.

Synthesis of carboxylic acids 164 and 165.

Esters **162** and **163** was treated to literature conditions to afford the corresponding acids **164** and **165** respectively.[162] All acids were subsequently crystallised to afford pure material.

2-(2-methylnaphtho[2,1-*b*]furan-1-yl)acetic acid 164

A white solid, recrystallised from ethanol (75%). Mp: 178-182 °C (decomposes, sealed tube). IR (NUJOL) 1699, 1622, 1579, 1525 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.51, s, 3H; 4.00, s, 2H; 7.44-7.69, m, 4H; 7.91-7.94, m, 1H; 8.21-8.23, m, 1H; Carboxylic proton not detected. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.92, 31.12, 108.84, 112.13, 122.00, 122.70, 124.03, 126.21, 127.90, 129.09, 130.80, 151.55, 152.44, 175.45. MS *m/z* (%): 240 (M^+, 39), 195 (100), 165 (13), 152 (13), 69 (37). Anal.Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found C, 74.92; H, 4.98. X-ray quality crystals of **164** were grown from ethanol solution at 278K. The crystal data was obtained upon on a Bruker AXS SMART CCD diffractometer.

2-(1-methylnaphtho[2,1-*b*]furan-2-yl)acetic acid 165

A white solid, recrystallised from hot dichloromethane / hexane (1 : 1) (75%). Mp: 194-195 °C (sealed tube). IR (NUJOL) 1714, 1697, 1622, 1579, 1523 cm^{-1}. ^1H NMR ($CDCl_3$/d_6-DMSO 300 MHz) δ 2.61, s, 3H; 3.86, s, 2H; 7.45-7.48, m, 1H; 7.53-7.68, m, 3H; 7.92-7.95, m, 1H; 8.36-8.39, m, 1H; Carboxylic proton not detected. ^{13}C NMR ($CDCl_3$/d_6-DMSO 50 MHz) δ 11.30, 32.46, 112.25, 114.38, 122.74, 122.84, 123.79, 124.70, 125.88, 128.78, 128.82, 130.54, 146.18, 151.70, 171.43. MS *m/z* (%): 240 (M^+, 88), 195 (100), 165 (12), 152 (12). Anal.Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found C, 74.74; H, 5.03. X-ray quality crystals of **165** were grown from a cooling dichloromethane / hexane / methanol (1 : 1 : 0.1) solution. The crystal data was obtained upon on a Rigaku AFC-7*R* diffractometer.

Reaction of 162 with Bromine

To a solution of **162** (107 mg, 0.42 mmol) in glacial acetic acid (5 mL) was added bromine (0.48 M, 1.0 mL, 0.48 mmol) and the solution heated to 30 °C for 15 minutes. The solution was poured onto ice water and the mixture extracted twice with

dichloromethane. The organic phase was dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (12% acetone / hexane) to furnish **166** as a light yellow solid (124 mg, 88%).

Reaction of naphthofurans 162 and 163 with nitric acid

To a stirring solution of **162** (452 mg, 1.78 mmol) in glacial acetic acid (25 mL) in an ice water bath was added nitric acid (2 mL) and the contents allowed to stir for 15 minutes. The solution was poured onto ice water and the mixture extracted twice with dichloromethane (50 mL). The organic phase was dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography (20% acetone / hexane) to give **167** (373 mg, 70%) as a bright yellow solid.

Methyl-2-(2-methyl-5-nitronaphtho[2,1-*b*]furan-1-yl)acetate 167

A yellow solid. Mp: 166-167 ^{o}C. R_f 0.27 (20% ethyl acetate / hexane). IR (CH_2Cl_2) 1739, 1608, 1579, 1531, 1516, 1336 cm^{-1}. ^{1}H NMR (d_6-benzene, 600 MHz) δ 1.95, s, 3H; 3.23, s, 3H; 3.43, s, 2H; 7.22, ddd (J = 9.0, 7.2, 1.2 Hz), 1H; 7.30, ddd (J = 8.4, 7.2, 1.2 Hz), 1H; 7.99, s, 1H; 8.28, dd (J = 8.4, 1.2 Hz), 1H; 8.71, dd (J =9.0, 1.2 Hz), 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.38, 31.28, 52.47, 110.41, 111.22, 123.07, 123.34, 124.53, 127.14, 127.41, 127.93, 128.18, 143.07, 148.27, 158.17, 170.80. MS *m/z* (%): 299 (M^+, 100), 240 (30), 209 (16), 194 (25), 165 (14). Anal.Calcd for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38, N, 4.68. Found C, 64.33; H, 4.37; N, 4.77.

Methyl-2-(1-methyl-5-nitronaphtho[2,1-*b*]furan-2-yl)acetate 168

A yellow solid. Mp: 132-135 ^{o}C. R_f 0.32 (25% ethyl acetate / hexane). IR (CH_2Cl_2) 1743, 1672, 1626, 1579, 1530, 1518, 1338 cm^{-1}. ^{1}H NMR (d_6-benzene, 600 MHz) δ 1.99, s, 3H; 3.28, s, 3H; 3.35, s, 2H; 7.21-7.26, m, 2H; 7.96, s, 1H; 8.01, dd (J = 7.8, 1.2 Hz), 1H; 8.70, dd (J = 9.0, 1.2 Hz), 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.35, 32.55, 52.61, 111.33, 115.45, 122.82, 123.46, 124.42, 127.06, 127.37, 128.47, 128.77, 143.38, 148.50, 151.11, 168.79. MS *m/z* (%): 299 (M^+, 100), 240 (70), 210 (44), 194 (23), 165 (29). HRMS, $C_{16}H_{13}NO_5$: calcd, 299.0794; found 299.0789.

Reaction of 113a with nitric acid

To a stirring solution of **113a** (325 mg, 1.27 mmol) in glacial acetic acid (20 mL) in an ice water bath was added nitric acid (4 mL, 50% in glacial acetic acid). The vessel was warmed to 30 °C and left one hour stirring at ambient temperature. The solution was poured onto ice water and the mixture extracted twice with dichloromethane. The organic phase was dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography (20% ethyl acetate / hexane) to give methyl 2-(2-methyl-7-nitro-1,2-dihydronaphtho[2,1-*b*]furan-2-yl) acetate **169a** (120 mg, 31%) as a bright yellow oil and methyl 2-(2methyl-9-nitro-1,2-dihydronaphtho[2,1-*b*]furan-2-yl) acetate **170a** (150 mg, 39%) as a yellow orange oil.

169a: R_f 0.33 (20% ethyl acetate / hexane). IR (CH_2Cl_2) 1738, 1626, 1603, 1537, 1506, 1338 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 1.66, s, 3H; 2.86 and 2.89, AB_q (J_{AB} = 15.3 Hz), 2H; 3.33 and 3.66, AB_q (J_{AB} = 16.2 Hz), 2H; 3.66, s, 3H; 7.19, d, (J = 8.7 Hz), 1H; 7.60, d (J = 9.1 Hz), 1H; 7.85, d, (J = 8.7 Hz); 8.21, dd (J = 9.1, 2.4 Hz); 8.74, d (J = 2.4 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.97, 39.65, 44.81, 51.67, 88.18, 114.36, 119.01, 120.19, 123.74, 125.65, 127.25, 131.78, 133.60, 143.06, 159.17, 170.18. MS *m/z* (%): 301 (M^+, 17), 227 (100), 181 (38), 152 (22). HRMS, $C_{16}H_{15}NO_5$: calcd, 301.0950; found 301.0941.

170a: R_f 0.41 (20% ethyl acetate / hexane). IR (CH_2Cl_2) 1738, 1636, 1599, 1579, 1525, 1352 cm^{-1}. ^1H NMR (d_6-benzene, 600 MHz) δ 1.27, s, 3H; 2.37 and 2.39, AB_q, (J_{AB} = 15.0 Hz), 2H; 3.09 and 3.48, AB_q (J_{AB} = 16.2 Hz), 2H; 3.18, s, 3H; 6.60, dd (J = 8.2, 7.6Hz), 1H; 6.93, d (J = 8.8 Hz), 1H; 7.17, d (J =8.8 Hz), 1H; 7.25, dd (J = 7.6, 1.2 Hz), 1H; 7.31, dd (J = 8.2, 1.2 Hz), 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.61, 40.84, 44.83, 51.62, 87.35, 114.29, 114.74, 120.84, 122.61, 122.94, 130.40, 130.60, 133.43, 146.03, 159.09, 170.01. MS *m/z* (%): 301 (M^+, 25), 284 (22), 267 (28), 227 (100), 181 (79), 152 (47). HRMS, $C_{16}H_{15}NO_5$: calcd, 301.0950; found 301.0941.

Attempted synthesis of 163 from 113a

To a solution of **113a** (20 mg, 0.078 mmol) in dry chlorobenzene (5 mL) was added DDQ (18 mg, 0.079 mmol). The resulting solution was heated under reflux overnight under a nitrogen atmosphere. The solvent volume was reduced and the crude residue

purified by flash chromatography (10% acetone / hexane) to give back starting material (18 mg).

Attempted synthesis of 171 from 137a

To a solution of **137a** (41 mg, 0.13 mmol) in dry dichloromethane (5 mL) was added trityl tetrafluoroborate (43 mg, 0.13 mmol) and the mixture heated under reflux overnight under a nitrogen atmosphere. The solvent was removed *in vacuo* and the crude ^{1}H NMR indicated only the presence of starting material and the **137a** (36 mg) was recovered by chromatography (20% ethyl acetate / hexane).

Synthesis of carboxylic acids 178-181

Acids **178-181** were synthesised from their corresponding methyl esters using a literature procedure.[162] All acids were subsequently crystallised to afford pure material.

2-(1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetic acid 178

A white solid, recrystallised from chloroform (85%). Mp: 138.5-139.5 °C. IR (NUJOL) 2760, 1693, 1631, 1599, 1577, 1520 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.83, dd (J = 16.2, 6.0 Hz), 1H; 3.01, dd (J = 16.2, 7.2 Hz), 1H; 3.23, dd (J = 15.4, 6.9 Hz), 1H; 3.74, dd (J = 15.4, 9.6 Hz), 1H; 5.40, dddd (J = 9.6, 7.2, 6.9, 6.0 Hz), 1H; 7.11-7.14, m, 1H; 7.30-7.35, m, 1H; 7.45-7.51, m, 1H; 7.57-7.60, m, 1H; 7.68-7.71, m, 1H; 7.80-7.83, m, 1H; Carboxylic proton not detected. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 34.34, 40.61, 79.12, 112.12, 117.55, 122.65, 123.06, 126.80, 128.75, 129.27, 129.41, 130.77, 156.46, 175.19. MS *m/z* (%): 228 (M^+, 9), 168 (39), 69 (54), 55 (56), 41 (100). Anal.Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found C, 73.40; H, 5.03.

2-(2-Methyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetic acid 179

A light cream solid, recrystallised from *n*-heptane / dichloromethane (76%). Mp: 124-126 °C. IR (NUJOL) 2670, 1711, 1633, 1603, 1574 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.68, s, 3H; 2.91, s, 2H; 3.33 and 3.61, AB_q (J_{AB} = 15.9 Hz), 2H; 7.07-7.10, m, 1H; 7.27-7.33, m, 1H; 7.45-7.49, m, 1H; 7.56-7.59, m, 1H; 7.67-7.70, m, 1H; 7.79-7.82, m, 1H; Carboxylic proton not detected. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.57, 40.38, 44.96, 86.72, 112.26, 117.83, 122.66, 122.95, 126.72, 128.72, 129.20, 129.32, 130.93, 155.54, 175.36. MS *m/z* (%): 242 (M^+, 39), 144 (100), 105 (98), 77 (53). Anal.Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found C, 74.15; H, 5.74.

2-(2-Methyl-9-nitro-1,2-dihydronaphtho[2,1-*b*]furan-2-yl) acetic acid 180

A yellow solid, recrystallised from hot aqueous ethanol (81%). Mp: 160-162 °C. IR (NUJOL) 1709, 1624, 1595, 1576, 1522, 1500, 1331 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.64, s, 3H; 2.82 and 2.84, AB_q (J_{AB} = 15.3 Hz), 2H; 3.17 and 3.41, AB_q (J_{AB} = 16.2 Hz), 2H; 7.23, d (J = 8.8 Hz), 1H; 7.32, dd (J = 8.0 Hz), 1H; 7.80, dd (J = 1.1, 8.0 Hz), 1H; 7.81, d (J = 8.8 Hz), 1H; 7.99, dd (J = 1.1, 8.0 Hz), 1H; Carboxylic proton not detected. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.42, 41.14, 44.58, 87.14, 114.42, 114.71, 121.00, 122.74, 123.08, 130.57, 130.77, 133.53, 146.14, 159.01, 173.98. MS *m/z* (%): 287 (M^+, 53), 270 (57), 253 (53), 227 (85), 181 (100), 152 (72), 45 (90). Anal.Calcd for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88. Found C, 63.26; H, 4.69; N, 4.98.

2-(2-Phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetic acid 181

A white solid, recrystalised from hot dichloromethane / hexane (1 : 1) (62%). Mp: 154.5-155.5 °C. IR (NUJOL) 1722, 1657, 1603, 1577, 1521, 1496 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.17, AB_q (J_{AB} = 15.5 Hz), 2H; 3.74 and 4.03, AB_q (J_{AB} = 15.9 Hz), 2H; 7.24-7.37, m, 5H; 7.44-7.47, m, 1H; 7.53-7.56, m, 3H; 7.70-7.73, m, 1H; 7.78-7.81, m, 1H; Carboxylic proton not detected. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 41.69, 45.88, 52.69, 89.41, 112.09, 117.59, 122.71, 123.15, 124.81, 126.77, 127.71, 128.53, 128.73, 129.37, 129.57, 130.68, 144.24, 155.67, 173.57. MS *m/z* (%): 304 (M^+, 64), 257 (28), 244 (100), 181 (15). Anal.Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found C, 78.77; H, 5.44.

Reaction of 178-181 with DDQ

A general procedure was employed. The following is an example. To a stirring solution of **179** (120 mg, 0.496 mmol) in dry benzene (25 mL) under a nitrogen atmosphere,was added DDQ (113 mg, 0.498 mmol). The resulting solution was heated to 50 °C for one hour. The solution was allowed to cool, filtered and the volume of solvent reduced and chloroform was added. The crude mixture was filtered and the solution purified by flash chromatography (30% ethyl acetate / hexane) to give **182** as a white crystalline solid (97 mg, 82%).

(±) (7a*R*,10a*R*)-7a,8,9,10a-Tetrahydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-9-one 175

A white solid. Mp. 205-207 °C (lit.[104] 207-208 °C). R_f 0.58 (40% ethyl acetate / hexane). ^1H NMR ($CDCl_3$, 300 MHz) δ 3.05, dd (J = 19.0, 2.0 Hz), 1H; 3.17, dd (J = 19.0, 6.6 Hz), 1H; 5.56, ddd (J = 2.0, 6.6 Hz), 6.46, d (J = 6.6 Hz), 1H; 7.12-7.15, m,

1H; 7.38-7.43, m, 1H; 7.55-7.60, m, 1H; 7.83-7.89, m, 3H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.54, 81.51, 83.48, 112.13, 115.11, 122.13, 124.11, 128.11, 128.77, 129.63, 130.68, 133.48, 159.25, 174.72.

(±) (7a*R*,10a*R*)-7a-Methyl-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-9-one 182

A white crystaline solid. Mp. 147-149 °C. R_f 0.39 (30% ethyl acetate / hexane). IR (CH_2Cl_2) 1780, 1635, 1601, 1585, 1525 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.73, s, 3H; 2.93 and 3.22, AB_q (J_{AB} = 18.9 Hz), 2H; 6.06, s, 1H; 7.09-7.12, m, 1H; 7.37-7.42, m, 1H; 7.54-7.59, m, 1H; 7.83-7.88, m, 3H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.58, 41.22, 88.05, 90.19, 112.43, 114.66, 122.24, 123.99, 128.04, 128.79, 129.58, 131.01, 133.44, 158.57, 174.45. MS *m/z* (%): 240 (M^+, 12), 195 (17), 181 (39), 115 (23), 44 (100). Anal.Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found C, 75.08; H, 5.07. X-ray quality crystals of **182** were grown from an evaporating dichloromethane / hexane solution at 278 K. The crystal data was obtained upon on a Rigaku AFC-7*R* diffractometer.

(±) (7a*R*,10a*R*)-7a-Methyl-1-nitro-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-9-one 183

The same procedure was employed except the reaction mixture was refluxed overnight. A yellow solid. Mp: 190-195 °C (sealed tube, decomposes). R_f 0.58 (40% ethyl acetate / hexane). IR (CH_2Cl_2) 1784, 1628, 1599, 1579, 1529 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.78, s, 3H; 2.89 and 3.11, AB_q (J_{AB} = 19.2 Hz), 2H; 6.12, s, 1H; 7.25, d (J = 8.7 Hz), 1H; 7.44, dd (J = 7.8, 7.8 Hz), 1H; 7.98, d (J = 8.7 Hz), 1H; 7.99, dd (J = 7.8, 1.2 Hz), 1H; 8.07, dd (J = 8.7, 1.2 Hz), 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.54, 40.99, 88.35, 90.10, 112.18, 114.67, 122.29, 122.88, 125.27, 131.12, 134.24, 134.58, 145. 80, 161.60, 173.47. MS *m/z* (%): 285 (M^+, 100), 240 (8), 226 (64), 201 (48), 145 (65). HRMS, $C_{15}H_{11}NO_5Na$: calcd, 308.0535; found 308.0531. X-ray quality crystals of **183** were grown from an evaporating dichloromethane / hexane solution at 278 K. The crystal data was obtained upon on a Bruker AXS SMART CCD diffractometer.

(±) (7a*R*,10a*R*)-7a-Phenyl-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-9-one 184

A white solid. Mp: 171-172 °C. R_f 0.65 (30% ethyl acetate / hexane). IR (CH_2Cl_2) 1784, 1635, 1603, 1583, 1525, 1496 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.38 and 3.53, AB_q (J_{AB} = 18.9 Hz), 2H; 6.35, s, 1H; 7.26-7.29, m, 1H; 7.36-7.45, m, 4H; 7.52-7.57, m, 3H; 7.80-7.85, m, 2H; 7.90-7.93, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 43.40, 89.78, 93.21, 112.11, 114.65, 122.28, 124.17, 124.50, 128.12, 128.70, 128.82, 129.08, 129.85, 130.85, 133.64, 139.60, 158.95, 174.07. MS *m/z* (%): 302 (M^+, 14), 257 (100), 181 (49), 115 (42), 77 (60). Anal.Calcd for $C_{21}H_{16}O_3$: C, 79.46; H, 4.67. Found C, 79.14; H, 4.83.

Reaction of esters with DDQ

A general procedure was employed, the following is an example. To a stirring solution of **139a** (40.0 mg, 0.114 mmol) in dry benzene (8 mL) under a nitrogen atmosphere, was added DDQ (28.7 mg, 0.126 mmol). Anhydrous PTSA (2.0 mg in 0.5 mL dry benzene) was added to the homogenised solution and the vessel warmed to 50 °C for one hour. The solvent was reduced *in vacuo* and filtered through cotton. The crude residue chromatographed using flash chromatography (25% ethyl acetate / hexane) to give **185** (28.7 mg, 75%).

(±) (7a*R*,10a*R*)-7a-(4-Chlorophenyl)-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[1,2-*d*]furan-9-one 185

(85%). A white solid. Mp. 200-208 °C (decomposes). R_f 0.42 (20% ethyl acetate / hexane). IR (NUJOL) 1785, 1636, 1582, 1526, 1494 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.33 and 3.53, AB_q (J_{AB} = 19.2 Hz), 2H; 6.31, s, 1H; 7.25-7.28, m, 1H; 7.37-7.43, m, 3H; 7.47-7.58, m, 3H; 7.80-7.86, m, 2H; 7.91-7.93, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 43.28, 89.59, 92.73, 112.00, 114.48, 122.25, 124.32, 125.99, 128.22, 128.85, 129.28, 130.76, 133.79, 138.16, 158.73, 173.63. MS *m/z* (%): 336 (M^+, 46), 307 (59), 291 (100), 278 (38), 226 (26). Anal.Calcd for $C_{20}H_{13}O_3Cl$: C, 71.33; H, 3.89, Cl, 10.53. Found C, 71.05; H, 3.85; Cl, 10.27.

Synthesis of alcohols 186 and 187

Esters **113a** and **139a** were reduced using lithium aluminum hydride using a literature procedure.[164] Both products were purified by flash chromatography.

2-(2-Methyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)-1-ethanol 186

A colourless oil (92%). R_f 0.24 (10% ethyl acetate / dichloromethane). IR (CH_2Cl_2) 3614, 3566, 1632, 1599, 1586, 1522 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 1.71, broad s, 1H; 2.09, ddd (J = 14.5, 6.2, 5.4 Hz), 1H; 2.19, ddd (J = 14.5, 7.4, 5.6 Hz), 1H; 3.28 and 3.43, AB_q (J_{AB} = 15.3 Hz), 2H; 3.86, ddd (J = 11.5, 6.2, 5.6 Hz), 1H; 3.95, ddd (J = 11.5, 7.4, 5.4 Hz), 1H; 7.06-7.07, m, 1H; 7.29-7.32, m, 1H; 7.45-7.48, m, 1H; 7.55-7.57, m, 1H; 7.68-7.69, m, 1H; 7.80-7.81, m, 1H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.98, 41.23, 43.40, 59.54, 89.82, 112.48, 118.17, 122.84, 123.08, 126.90, 128.96, 129.37, 129.44, 131.20, 155.98. MS *m/z* (%): 228 (100), 209 (12), 195 (54), 183 (45). HRMS, $C_{15}H_{16}O_2$: calcd, 228.1150; found 228.1158.

2-[2-(4-Chlorophenyl)-1,2-dihydronaphtho[2,1-*b*]furan-2-yl]-1-ethanol 187

A colourless oil (85%). R_f 0.25 (5% ethyl acetate / dichloromethane). IR (CH_2Cl_2) 3683, 3608, 1633, 1603, 1579, 1522, 1491 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 1.94, broad s, 1H; 2.37, ddd (J = 14.7, 5.6, 5.6 Hz), 1H; 2.50, ddd (J = 14.7, 7.6, 6.0 Hz), 1H; 3.63-3.67, m, 2H; 3.73, ddd (J = 11.4, 7.4, 5.6 Hz), 1H; 3.79, d (J = 15.2 Hz), 1H; 7.20-7.22, m, 1H; 7.30-7.34, m, 3H; 7.43-7.46, m, 3H; 7.51-7.53, m, 1H; 7.72-7.74, m, 1H; 7.80-7.81, m, 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.35, 44.26, 59.02, 91.77, 111.83, 117.25, 122.54, 123.10, 126.19, 126.76, 128.59, 128.68, 129.37, 129.44, 130.59, 133.00, 143.69, 155.55. MS *m/z* (%): 324 (M^+, 100), 291 (81), 279 (49), 215 (27). Anal.Calcd for $C_{20}H_{17}O_2Cl$: C, 73.96; H, 5.28. Found C, 73.88; H, 5.33.

Synthesis of Difurans 188 and 189 using DDQ

The same procedure was employed as that of the acid series. Both **188** and **189** were purified by flash chromatography.

(±) (7a*R*,10a*R*)-7a-Methyl-7a, 8, 9, 10a-tetrahydrofuro[3,2-*b*]naphtho[1,2-*d*]furan 188

A white solid. (82%). Mp 63-65 °C. R_f 0.56 (20% ethyl acetate / hexane). IR (CH_2Cl_2) 1633, 1601, 1585, 1523 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 1.67, s, 3H; 2.11, ddd (J = 13.2, 11.1, 7.5 Hz), 1H; 2.37, ddd (J = 13.2, 4.9, 1.9 Hz), 1H; 3.59, ddd (J = 11.1, 7.5, 4.9 Hz), 1H; 3.98, ddd (J = 7.5, 7.5, 1.9 Hz), 1H; 5.64, s, 1H; 7.05-7.06, m, 1H; 7.31-7.34, m, 1H; 7.49-7.52, m, 1H; 7.76-7.81, m, 2H; 7.88-7.90, m, 1H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 23.43, 40.83, 66.58, 87.46, 96.02, 112.12, 116.28, 122.35, 123.21, 127.39,

128.64, 129.46, 131.43, 131.78, 158.48. MS *m/z* (%): 226 (M^+, 100), 195 (57), 181 (60), 171 (20). Anal.Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found C, 79.52; H, 6.46.

(±) (7a*R*,10a*R*)-7a-(4-Chlorophenyl)-7a, 8, 9, 10a-tetrahydrofuro[3,2-*b*]naphtho[1,2-*d*]furan 189

A gummy colourless oil. (88%). R_f 0.48 (15% ethyl acetate / hexane). IR (CH_2Cl_2) 3055, 1635, 1603, 1581, 1522, 1493 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 2.54, ddd (*J* = 13.5, 11.5, 7.3 Hz), 1H; 2.66, ddd (*J* = 13.5, 4.8, 1.3 Hz), 1H; 3.74, ddd (*J* = 8.0, 7.5, 4.8 Hz), 1H; 4.21, ddd (*J* = 8.0, 7.5, 1.3 Hz), 1H; 5.96, s, 1H; 7.19-7.21, m, 1H; 7.32-7.35, m, 3H; 7.49-7.52, m, 3H; 7.80-7.83, m, 2H; 7.86-7.87, m, 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.30, 67.21, 90.06, 98.37, 111.67, 115.71, 122.34, 122.50, 126.17, 127.53, 128.68, 129.78, 131.20, 132.09, 133.55, 140.24, 158.61. MS *m/z* (%): 323 (M^+, 100), 292 (97), 171 (40). Anal.Calcd for $C_{20}H_{13}O_3Cl$: C, 74.42; H, 4.68. Found C, 74.53; H, 4.68.

Synthesis of 2-(2-phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetamide 190

1,2-Dihydronaphtho[2,1-*b*]furan **137a** (516 mg, 1.62 mmol) was stirred overnight in ethanol (10 mL) and aqueous 10% potassium hydroxide (2 mL). The solution was acidified with 33% aqueous hydrochloric acid until the pH was less than 2. The aqueous phase was extracted with dichloromethane thrice (50 mL) and dried over sodium sulphate. The solution was filtered and the solvent removed *in vacuo*. The residue was taken up in dry dichloromethane (10 mL) under a nitrogen atmosphere and thionyl chloride added to the stirring solution. Stirring was maintained for 4 hours and the solvent was removed by a stream of nitrogen. The residue was taken up in dry ether (25 mL) and the vessel cooled to –78 °C and dry ammonia was condensed into the vessel for 5 minutes. The contents of the reaction were allowed to reach room temperature. Saturated brine was added to the mixture and the aqueous phase extracted twice with dichloromethane. The organic phase was dried over sodium sulphate, filtered and the solvent removed *in vacuo*. **190** was purified by chromatography (florisil, 30% ethyl acetate / dichloromethane) and was obtained as a cream coloured solid (352 mg, 76%).

Mp 155-158 °C. R_f 0.30 (30% ethyl acetate / dichloromethane). IR (CH_2Cl_2) 3510, 3398, 1685, 1633, 1589, 1495 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.15, s, 2H; 3.70 and 3.90, AB_q (J_{AB} = 15.6 Hz), 2H; 5.28, broad s, 1H; 6.27, broad s, 1H; 7.24-7.57, m,

9H; 7.75-7.83, m, 2H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 42.92, 48.27, 89.98, 111.75, 117.75, 122.80, 123.42, 124.64, 126.98, 127.76, 128.72, 129.55, 129.73, 130.73, 144.17, 155.20, 171.28, one carbon masked. MS *m/z* (%): 303 (M^+, 21), 278 (13), 244 (100), 215 (14). Anal.Calcd for $C_{20}H_{17}O_2N$: C, 79.19; H, 5.65; N, 4.62. Found C, 78.88; H, 5.75; N, 4.84.

Reactions of the 190 with DDQ

Method 1: To a solution of the **190** (34.1 mg 0.113 mmol) in dry benzene (10 mL) at 50°C under a nitrogen atmosphere was added DDQ (27.0 mg, 0.119 mmol) and the solution left overnight. Purification of the crude solution by flash chromatography yielded (1-oxo-2-phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)methyl cyanide **191** as a colourless oil (15.3 mg, 83%) with regard to recovered **190** (15.5 mg).

Method 2: An analogous procedure as above except **190** (44.5 mg, 0.147 mmol) in dry benzene (10 mL) was treated with DDQ (72.0 mg, 0.317 mmol). Following the same protocol, **191** (39.5 mg, 90%) was obtained.

(1-Oxo-2-phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)methyl cyanide 191

A yellowish oil. R_f 0.25 (25% ethyl acetate / hexane). IR (NUJOL) 2258, 1704, 1632, 1586, 1529, 1496 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.20 and 3.35, AB_q (J_{AB} = 23.1 Hz), 2H; 7.39-7.54, m, 5H; 7.68-7.73, m, 3H; 7.85-7.89, m, 1H; 8.17-8.22, m, 1H; 8.64-8.69, m, 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.61, 87.12, 111.31, 113.53, 114.79, 123.20, 124.67, 125.97, 128.73, 129.02, 129.27, 129.31, 129.80, 130.30, 134.47, 141.22, 174.02, 197.30. MS *m/z* (%): 299 (57), 259 (100), 231 (14), 126 (33). HRMS, $C_{20}H_{13}O_2N$: calcd, 299.0946; found 299.0954.

Synthesis of (±) (7a*R*,10a*R*)-7a-methyl-7a, 8, 9, 10a-tetrahydrofuro[3,2-*b*]naphtho[1,2-*d*]furan-9-ol 196

To a stirring solution of **182** (75.5 mg, 0.315 mmol) in dry THF (6 mL) at –78 °C, was added DIBAL-H (0.25 mL, 1.5 M in toluene) and the solution allowed to slowly warm to –20 °C. More DIBAL-H (0.10 mL) was added and stirred for 20 minutes. Ethyl acetate (1 mL) was added and the solution warmed to room temperature and the solvent removed *in vacuo*. Purification of the residue by flash chromatography afforded the hemiacetal **196** (40 mg, 52%), as a white solid. Due to the unstable nature of **196**, only ^{1}H NMR data was obtained.

Major diastereomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.72, s, 3H; 2.33, dd (J = 14.4, 5.4 Hz), 1H; 2.56, dd (J = 14.4, 4.8 Hz), 1H; 2.77, d (J = 1.8 Hz), 1H; 5.60, ddd (J = 5.4, 4.8, 1.8 Hz), 1H; 5.80, s, 1H; 7.05-7.06, m, 1H; 7.32-7.35, m, 1H; 7.50-7.53, m, 1H; 7.77-7.81, m, 2H; 7.83-7.84, m, 1H.

Minor diastereomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.65, s, 3H; 2.33, dd (J = 14.4, 2.4 Hz), 1H; 2.39, d (J = 4.8 Hz), 1H; 2.67, d (J = 14.4 Hz), 1H; 5.66, dd (J = 4.8, 2.4 Hz), 1H; 5.68, s, 1H; 7.09-7.11, m, 1H; 7.32-7.35, m, 1H; 7.50-7.53, m, 1H; 7.77-7.81, m, 2H; 7.88-7.89, m, 1H.

Synthesis of (±) methyl (7a*R*,10a*R*)-2-(7a-methyl-7a,8,9, 10a-tetrahydrofuro[3,2-*b*]naphtho[1,2-*d*]furan-9-yl) acetate 197

A solution of **196** (34.0 mg, 0.140 mmol) and **45a** (117 mg, 0.368 mmol) were heated under reflux in dry benzene (5 mL) under a nitrogen atmosphere for three days. The solvent was removed using a stream of nitrogen and the residue purified by flash chromatography (20% acetone / hexane) to give **197** (31.0 mg, 74%) as a colourless oil. R_f 0.35 (20% acetone / hexane). Anal.Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found C, 72.53; H, 5.96.

Major diastereomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.66, s, 3H; 1.84, dd (J = 13.2, 10.8 Hz), 1H; 2.54, dd (J = 15.0, 7.8 Hz), 1H; 2.60, dd (J = 13.2, 4.2 Hz), 1H; 2.74, dd (J = 15.0, 5.4 Hz), 1H; 3.62, s, 3H; 4.13, dddd (J = 10.8, 7.8, 5.4, 4.2 Hz), 1H; 5.68, s, 1H; 7.05-7.08, m, 1H; 7.31-7.34, m, 1H; 7.48-7.51, m, 1H; 7.77-7.81, m, 2H; 7.86-7.88, m, 1H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 23.57, 38.99, 46.18, 51.67, 73.94, 87.46, 96.18, 112.15, 116.22, 122.47, 123.22, 127.31, 128.62, 129.48, 131.43, 131.86, 158.50, 170.94.

Minor diastereomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.63, s, 3H; 2.23, dd (J = 13.2, 7.8 Hz), 1H; 2.41, dd (J = 16.2, 7.2 Hz), 1H; 2.50, dd (J = 13.2, 6.0 Hz), 1H; 2.57, dd (J = 16.2, 6.6Hz), 1H; 3.56, s, 3H; 4.51, dddd (J = 7.8, 7.2, 6.6, 6.0 Hz), 1H; 5.48, s, 1H, 7.05-7.08, m, 1H; 7.31-7.34, m, 1H; 7.48-7.51, m, 1H; 7.77-7.81, m, 2H; 7.86-7.88, m, 1H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 23.95, 39.66, 46.04, 51.50, 75.44, 87.99, 96.56, 112.69, 118.14, 122.69, 123.28, 127.34, 128.56, 129.35, 131.27, 131.95, 157.31, 171.38.

Initial synthesis of the (±) (2'*S*, 3'*S*)-3'-(4-methoxybenzoyl)spiro[naphthalene-1(2*H*), 2'-oxiran]-2-one 198

To a solution of **79** (100 mg, 0.342 mmol) in dichloromethane (10 mL) was added DABCO (5 mg, 0.045 mmol) and the mixture was allowed to stir over night at ambient temperature. The solvent was removed *in vacuo* and the crude residue purified by flash chromatography to give **198** (64 mg, 61%) as an orange oil and **133** (11 mg, 11%).

R_f 0.32 (40% ethyl acetate / hexane). IR 1682, 1600, 1575, 1513 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 3.86, s, 3H; 4.16, s, 1H; 6.20, d (J = 10.2 Hz), 1H; 6.92-6.94, m, 2H; 7.38-7.39, m, 1H; 7.44-7.49, m, 3H; 7.55, d (J = 10.2 Hz), 1H; 8.00-8.01, m, 2H. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 55.47, 62.22, 72.37, 114.02, 123.94, 125.96, 128.52, 129.30, 129.82, 130.63, 131.04, 132.13, 136.28, 145.21, 164.36, 188.61, 191.71. MS *m/z* (%): 306 (M^+, 7), 171 (52), 135 (100), 115 (12). HRMS, $C_{19}H_{14}O_4$: calcd, 306.0892; found 306.0892.

NMR reactions of 79 with DABCO

A series of reactions were carried out in an NMR tube upon a 15 mg scale, the conditions employed are presented in **Figure 4.3**. 1,3,5-Trimethylbenzene was utilised as an internal standard where the reaction variables were temperature and aerial exposure. In the case of reactions performed under an oxygen atmosphere, a balloon filled with oxygen was introduced to the tube by perforating the tube lid with a luer lock syringe adapter. The reaction which was exposed to air was done so by an open perforation to the NMR tube lid. The reactions at 50 °C were heated directly in a temperature controlled oil bath. The progress of these reactions was monitored by ^1H NMR.

General procedure for the synthesis of 198 and 225-230 from the 1-(β-keto)-2-naphthols

All spiroepoxides were synthesised using the same procedure as featured in **Table 4.1**. The following is an example. To a suspension of **131** (63.0 mg, 0.240 mmol) in chloroform-*d* (2.5 mL) under an oxygen atmosphere was added DABCO (17.8 mg, 0.15 mmol) and the contents stirred overnight at 50 °C. The solvent was removed *in vacuo* and the crude residue purified by chromatography to afford pure **227** as a white crystalline solid (48.2 mg, 73%).

Specific reactions mentioned in **Table 4.3** (Entries 1 to 8) were carried in the same fashion. Thus additives (1 mol equiv.) were introduced prior to dissolution of the naphthol. The workup and purification protocol were also the same. For Entries 9 and 10, the reactions were carried out under a nitrogen atmosphere, the workup was the same.

(±) (2'*S*, 3'*R*)-3'-Acetylspiro[naphthalene-1(2*H*), 2'-oxiran]-2-one 225

A colourless oil. R_f 0.39 (25% ethyl acetate / hexane). IR (CH_2Cl_2) 1716, 1680, 1633, 1606, 1597, 1568, 1531 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.50, s, 3H; 3.67, s, 1H; 6.26, d (J = 9.9 Hz), 1H; 7.20-7.26, m, 1H; 7.40-7.45, m, 3H; 7.55, d (J = 9.9 Hz), 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.55, 62.66, 72.33, 124.03, 125.74, 129.34, 129.78, 130.64, 132.02, 136.05, 145.63, 192.38, 202.30. MS *m/z* (%): 214 (M^+, 7), 171 (100), 144 (19), 115 (40), 83 (26). HRMS, $C_{13}H_{10}O_3$: calcd, 214.0630; found 214.0631.

(±) (2'*S*, 3'*S*)-3'-Cyclohexylcarboxylspiro[naphthalene-1(2*H*), 2'-oxiran]-2-one 226

A colourless oil. R_f 0.38 (15% ethyl acetate / hexane). IR (CH_2Cl_2) 2935, 2856, 1707, 1678, 1616, 1566 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16-1.27, m, 2H; 1.35-1.48, m, 3H; 1.69-1.73, m, 1H; 1.78-185, m, 3H; 2.17-2.20, m, 1H; 3.20, tt (J = 11.1, 3.3 Hz), 1H; 3.77, s, 1H; 6.24, d (J = 10.0 Hz), 1H; 7.25-7.27, m, 1H; 7.40-7.46, m, 3H; 7.54, d (J = 10.0 Hz), 1H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.81, 25.68, 25.95, 26.10, 29.03, 47.81, 62.44, 72.02, 124.03, 125.77, 129.22, 129.73, 130.55, 131.10, 132.03, 136.23, 145.50, 192.38, 206.43. MS *m/z* (%): 282 (M^+, 7), 171 (100), 115 (20), 83 (18). HRMS, $C_{18}H_{18}O_3$: calcd, 282.1256; found 282.1255.

(±) (2'*S*, 3'*S*)-3'-Benzoylspiro[naphthalene-1(2*H*), 2'-oxiran]-2-one 227

A white crystalline solid. Mp: 138-141 °C. R_f 0.31 (25% ethyl acetate / hexane). IR (CH_2Cl_2) 1699, 1678, 1614, 1599, 1581, 1566 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.22, s, 1H; 6.22, d (J = 9.9 Hz), 1H; 7.40-7.61, m, 8H; 8.00-8.03, m, 2H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 62.23, 72.21, 124.07, 125.93, 128.60, 128.73, 129.40, 128.87, 130.67, 132.18, 134.04, 135.38, 136.10, 145.29, 190.31, 191.56. MS *m/z* (%): 276 (M^+, 24), 172 (51), 106 (100), 77 (60). Anal.Calcd for $C_{18}H_{12}O_3$: C, 78.25; H, 4.38. Found C, 78.03; H, 4.20. X-ray quality crystals of **227** were grown from an evaporating ethyl

acetate / hexane (1 : 3) solution at 278 K. Crystal data was obtained upon a Nonius Kappa CCD diffractometer.

(±) (2'*S*, 3'*S*)-3'-(4-Chlorobenzoyl)spiro[naphthalene-1(2*H*), 2'-oxiran]-2-one 228

A white solid. Mp: 137.5-139 °C. R_f 0.38 (25% ethyl acetate / hexane). IR (CH_2Cl_2) 1699, 1678, 1616, 1589, 1568 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.18, s, 1H; 6.23, d (J = 9.9 Hz), 1H; 7.37-7.40, m, 1H; 7.45-7.52, m, 5H; 7.59, d (J = 9.9 Hz), 1H; 8.01-8.04, m, 2H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 62.08, 71.87, 124.04, 125.77, 129.04, 129.46, 129.92, 130.04, 130.70, 132.13, 133.95, 135.80, 140.52, 145.53, 189.70, 191.55. MS *m/z* (%): 310 (M^+, 6), 171 (100), 139 (13), 115 (55). Anal.Calcd for $C_{18}H_{11}O_3Cl$: C, 69.58; H, 3.57. Found C, 69.87; H, 3.71.

(±) (2'*S*, 3'*S*)-3'-(3-Bromobenzoyl)spiro[naphthalene-1(2*H*), 2'-oxiran]-2-one 229

A yellowish oil. R_f 0.45 (25% ethyl acetate / hexane). IR (CH_2Cl_2) 1702, 1678, 1616, 1590, 1567, 1523 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.18, s, 1H; 6.22, d (J = 9.9 Hz), 1H; 7.36-7.40, m, 2H; 7.45-7.52, m, 3H; 7.57-7.60, m, 1H; 7.70-7.75, m, 1H; 7.97-8.01, m, 1H; 8.19-8.20, m, 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 62.09, 71.72, 123.01, 124.12, 125.71, 127.20, 129.55, 130.02, 130.28, 130.77, 131.60, 132.11, 135.65, 136.84, 137.14, 145.75, 189.73, 191.66. MS *m/z* (%): 356 (4, M^+), 354 (4, M^+), 185 (7), 183 (7), 171 (100), 115 (22). HRMS, $C_{18}H_{11}O_3Br$: calcd, 353.9890; found 353.9879.

(±) (2'*S*, 3'*S*)-3'-(1-Naphthoyl)spiro[naphthalene-1(2*H*), 2'-oxiran]-2-one 230

A white solid. Mp: 130-132 °C. R_f 0.75 (50% ethyl acetate / hexane). IR (CH_2Cl_2) 1676, 1616, 1595, 1574, 1510 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.38, s, 1H; 6.25, d (J = 10.2 Hz), 1H; 7.41-7.69, m, 8H; 7.87-7.90, m, 1H; 8.04-8.07, m, 1H; 8.11-8.14, m, 1H; 8.87-8.90, m, 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 62.95, 72.50, 124.08, 124.19, 125.92, 126.06, 126.73, 128.40, 128.71, 129.38, 129.85, 130.10, 130.62, 130.66, 132.16, 134.09, 134.44, 136.14, 145.37, 191.90, 192.83, 1 C masked. MS *m/z* (%): 326 (M^+, 20), 171 (100), 155 (68), 127 (43), 115 (20). HRMS, $C_{16}H_{14}O_3$: calcd, 326.0948; found 326.0943.

1-[2-(4-Methoxyphenyl)-2-oxoethyl]-2-naphthyl acetate 231

A literature procedure was followed whereby a suspension of **133** (102.7 mg, 0.352 mmol) was treated with excess acetyl chloride in the presence of pyridine.[165] The crude

oil was purified by flash chromatography (25% ethyl acetate / hexane) to give **231** as a fluffy white solid (84.3 mg, 72%).

Mp 143-144 °C. R_f 0.38 (25% ethyl acetate / hexane). IR (NUJOL) 1769, 1671, 1599, 1513 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.27, s, 3H; 3.89, s, 3H; 4.62, s, 2H; 6.95-6.98, m, 2H; 7.24-7.26, m, 1H; 7.46-7.49, m, 2H; 7.81-7.88, m, 3H; 8.06-8.09, m, 2H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.93, 36.15, 55.50, 113.90, 121.39, 122.37, 123.92, 125.42, 126.86, 128.78, 129.81, 130.58, 131.98, 133.09, 147.08, 163.69, 169.33, 194.89, 1 C masked. MS *m/z* (%): 334 (M^+, 5), 316 (4), 292 (16), 274 (88), 182 (32), 157 (24), 135 (100). Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.42; H, 5.43. Found C, 75.32; H, 5.16.

1-[2-Hydroxy-2-(4-methoxyphenyl)ethyl]-2-naphthol 232

The general procedure featured in the synthesis of **186** and **187** was followed,[164] whereby **133** (48.1 mg, 0.165 mmol) was reduced using an excess of lithium aluminium hydride, resulting in the formation of diol **232** (37.0 mg, 76%) as a colourless oil after purification by chromatography (florisil, dichloromethane).

R_f 0.15 (dichloromethane). IR 3251 (broad), 1622, 1613, 1598, 1586, 1514, 1506 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.79, s (exch. D_2O), 1H; 3.41-3.52, m (AB portion of ABX), 2H; 3.87, s, 3H: 5.07-5.10, m (X portion of ABX), 1H; 6.96-7.00, m, 2H; 7.28-7.51, m, 5H; 7.74-7.86, m, 3H; 8.21, s (exch. D_2O), 1H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.45, 55.36, 76.66, 114.14, 117.35, 119.47, 122.14, 122.88, 126.36, 126.78, 128.66, 128.74, 129.45, 133.31, 135.87, 153.52, 159.53. MS *m/z* (%) 294 (M^+, 24), 276 (13), 158 (74), 137 (74), 84 (82), 49 (100): HRMS, $C_{19}H_{18}O_3Na$: calcd, 317.1154; found 317.1146.

Reactions of 231 and 232 with DABCO

The analogous conditions described earlier for the formation of **225-230** were employed. In both instances, no reaction was observed by ^1H NMR analysis.

Synthesis of Naphtho[2,1-*b*]furans 233 and 234

A general procedure was employed in the dehydration reaction, the following is an example. 1-(β-Keto)-2-naphthol **131** (47 mg, mmol) was heated to 100 °C in 10% sulphuric acid in glacial acetic acid (4 mL) until the substrate had completely

dissolved. The solution was poured into excess water and extracted thrice with dichloromethane. Drying over anhydrous sodium sulphate, filtering and removal of the solvent *in vacuo* gave the naphtho[2,1-*b*]furan **233** as a white crystalline solid (26 mg, 59%).

2-Phenylnaphtho[2,1-*b*]furan[166] 233

Mp. 145-146 °C (Lit. Mp: 146-147 °C). R_f 0.70 (12% acetone / hexane). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 100.89, 112.21, 123.40, 124.45, 124.70, 125.55, 125.86, 126.39, 127.60, 128.85, 129.09, 129.18, 130.49, 134.02, 152.49, 154.29.

2-(4-Chlorophenyl)naphtho[2,1-*b*]furan[167] 234

A white solid. Mp. 148-151 °C (Lit. Mp: 152.5-153.5 °C). R_f 0.67 (12% acetone / hexane). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 100.89, 112.21, 123.40, 124.45, 124.70, 125.55, 125.86, 126.39, 127.60, 128.85, 129.09, 129.18, 130.49, 134.02, 152.49, 154.29.

Synthesis of 237 using *m*-CPBA

A modified literature procedure was adopted,[124] where to a solution of *m*-CPBA (113 mg, 0.46 mmol) in a biphasic mixture of dichloromethane (3 mL) and saturated sodium bicarbonate (1mL), the vessel suspended in an ice bath, was added **162** (40.6 mg, 0.160 mmol) and allowed to slowly reach ambient temperature overnight. A solution of sodium sulphite (5 mL, 1 M), was added and the solution stirred for a further five minutes. The mixture was diluted with dichloromethane (20 mL) and the organic phase separated. The aqueous phase was extracted twice more with dichloromethane and the combined organics were dried over anhydrous sodium sulphate. The solution was filtered and the solvent removed *in vacuo*, where the residue was purified by chromatography (florisil, 40% ethyl acetate/hexane) to give **237** as a pale yellow oil (25.4 mg, 56%).

R_f 0.45 (40% ethyl acetate / hexane). IR (CH_2Cl_2) 1741, 1712, 1684, 1614, 1566 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 2.50 and 3.06, AB_q (J_{AB} = 16.8 Hz), 2H; 2.53, s, 3H; 3.69, s, 3H; 6.11, d (J = 10.2 Hz), 1H; 7.42-7.50, m, 5H. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.49, 34.71, 52.30, 68.93, 73.36, 125.30, 126.66, 129.45, 129.46, 129.90, 133.16, 133.47, 144.84, 169.22, 194.39, 207.18. MS *m/z* (%): 286 (12, M^+), 243 (100), 212

(17), 201 (17), 201 (92), 186 (34), 171 (30), 114 (32), 43 (22). HRMS, $C_{16}H_{14}O_5$: calcd, 286.0841; found 286.0845.

References

(1) Yamada, H.; Tanizawa, K.; Kanaoka, Y. *FEB* **1988**, *227*, 195.

(2) Santhosh, K. C.; Gopalsamy, A.; Balasubramanian, K. K. *Eur. J. Org. Chem.* **2001**, 3461.

(3) Zheng, G.; Kojima, T.; Kawisaka, H. *Heterocycles* **1988**, *27*, 1341.

(4) Adams, J. L.; Garigipati, R. S.; Sorenson, M.; Schmidt, S. J.; Brian, W. R.; Newton, J. F.; Tyrrell, K. A.; Garver, E.; Yodis, L. A.; Chabot-Fletcher, M.; Tzimas, M.; Webb, E. F.; Breton, J. J.; Griswold, D. E. *J. Med. Chem.* **1996**, *39*, 5035.

(5) Avery, T. D.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2000**, *65*, 5531.

(6) Pattabiraman, T. N.; Lawson, W. B. *Biochim. Biophys. Acta* **1972**, *258*, 548.

(7) Pattabiraman, T. N.; Lawson, W. B. *J. Biol. Chem.* **1972**, *247*, 3029.

(8) Rodgers, P. S.; Goaman, L. C. G.; Blow, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 6690.

(9) Tanizawa, K.; Yamada, H.; Kanaoka, Y. *Biochim. Biophys. Acta* **1987**, *916*, 205.

(10) North, P. C.; Ladlow, M. In *PCT Int. Appl.*; (Glaxo Group Ltd., UK). Wo, 1995, p 52 pp.

(11) Lesieur, D.; Depreux, P.; Leclerc, V.; Mansour, H. A.; Delagrange, P.; Renard, P. In *U.S.*; (Adir Et Compagnie, Fr.). Us, 2000, p 23 pp., Cont.-in-part of U.S. Ser. No. 124,197.

(12) Lesieur, D.; Depreux, P.; Leclerc, V. r.; Mansour, H. A.; Delagrange, P.; Renard, P. In *U.S.*; (Adir et Compagnie, Fr.). Us, 1999, p 25 pp., Cont.-in-part of U.S. 5,843,986.

(13) Lesieur, D.; Depreux, P.; Leclerk, V.; Ait Mansour, H.; Delagrange, P.; Renard, P. In *Eur. Pat. Appl.*; (Adir Et Compagnie, Fr.). Ep, 1996, p 38 pp.

(14) Leclerc, V.; Depreux, P.; Lesieur, D.; Caignard, D. H.; Renard, P.; Delagrange, P.; Guardiola-Lemaitre, B.; Morgan, P. *Bioorganic & Medicinal Chemistry Letters* **1996**, *6*, 1071.

(15) Burns, C. J.; Dankulich, W. P.; McGarry, D. G.; Volz, F. A. In *PCT Int. Appl.*; (Aventis Pharmaceuticals Products Inc., USA). Wo, 2001, p 107 pp.

(16) Burns, C. J.; Dankulich, W. P.; McGarry, D. G.; Volz, F. A. In *U.S. Pat. Appl. Publ.*; (Aventis Pharmaceuticals Inc., USA). Us, 2002, p 43 pp., Cont.-in-part of Appl. No. PCT/IB00/01562.

(17) Cheng, X.-m.; Filzen, G. F.; Geyer, A. G.; Lee, C.; Trivedi, B. K. In *PCT Int.*

Appl.; (Warner-Lambert Company Llc, USA). Wo, 2003, p 131 pp.

(18) Huebner, C. F. In *Ger. Offen.*; (Ciba-Geigy A.-G., Switz.). De, 1977, p 68 pp.

(19) Huebner, C. F. In *U.S.*; (Ciba-Geigy Corp., USA). Us, 1978, p 11 pp.

(20) Huebner, C. F. In *U.S.*; (Ciba-Geigy Corp., USA). Us, 1978, p 11 pp.

(21) Lavielle, G.; Hautefaye, P.; Atassi, G.; Pierre, A.; Kraus-Berthier, L.; Leonce, S. In *Eur. Pat. Appl.*; (Adir et Compagnie, Fr.). Ep, 1998, p 30 pp.

(22) Nakagawa, M.; Nakanishi, K.; Darko, L. L.; Vick, J. A. *Tetrahedron* **1982**, *23*, 3855.

(23) Reid, D. H. *Q. Rev. Chem. Soc.* **1965**, *19*, 274.

(24) Danheiser, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471.

(25) Guss, C. O.; Rosenthal, R.; Brown, R. F. *J. Am. Chem. Soc.* **1953**, *75*, 2393.

(26) Vaillard, S. E.; Postigo, A.; Rossi, R. A. *J. Org. Chem.* **2002**, *67*, 8500.

(27) Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52*, 4072.

(28) Olivero, S.; Dunach, E. *Eur. J. Org. Chem.* **1999**, 1885.

(29) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135.

(30) Weeratunga, G.; Jaworska-Sobiesiak, A.; Horne, S.; Rodrigo, R. *Can. J. Chem.* **1987**, *65*, 2019.

(31) Arrault, A.; Touzeau, F.; Guillaumet, G.; Merour, J. *Synthesis* **1999**, *7*, 1241.

(32) Touzeau, F.; Arrault, A.; Guillaumet, G.; Scalbert, E.; Pfeiffer, B.; Rettori, M.; Renard, P.; Merour, J. *J. Med. Chem.* **2003**, *46*, 1962.

(33) Rao, M. M.; Kingston, D. G. I. *J. Nat. Prod.* **1982**, *45*, 600.

(34) Inoue, K.; Inoue, H.; Chen, C. C. *Phytochem.* **1981**, *20*, 2271.

(35) Chitrananda, A.; Kumar, V.; Marshall, D. S.; Thomson, R. H.; Wikramaratne, D. B. N. *Phytochem.* **1991**, *30*, 941.

(36) Genevieve, L.; Pierre, D.; Pierre, B. J.; Rene, R.; Raymond, C. *Eur. J. Med. Chem.* **1982**, *17*, 253.

(37) Inbaraj, J. J.; Gandhidasan, R.; Murugesan, R. *J. Photochem. Photobiol. A* **1999**, *124*, 95.

(38) Godbole, H. M.; Ranade, A. A.; Joseph, A. R.; Paradkar, M. V. *Synth. Comm.* **2000**, *30*, 2951.

(39) Avery, T. D.; Haselgrove, T. D.; Rathbone, T. J.; Taylor, D. K.; Tiekink, E. R. T. *Chem. Commun.* **1998**, 333.

(40) Kimber, M. C.; Taylor, D. K. *Unpublished Results* **2001**.

(41) Kimber, M. C.; Taylor, D. K. *J. Org. Chem.* **2002**, *67*, 3142.

(42) Matsumoto, M.; Dobashi, S.; Kuroda, K.; Kondo, K. *Tetrahedron* **1985**, *41*, 2147.

(43) Takahashi, Y.; Wakamatsu, K.; Morishima, S.; Miyashi, T. *J. Chem. Soc. Perkin Trans. I* **1993**, 243.

(44) Denny, R. W.; Nickon, A. *Organic Reactions Volume 20*; John Wiley and Sons, Inc., 1973.

(45) Baum, S.; Trabanco, A. A.; Montalban, A. G.; Micallef, A. S.; Zhong, C.; Meunier, H. G.; Suhling, K.; Phillips, D.; White, A. J. P.; Williams, D. J.; Barrett, A. G. M.; Hoffman, B. M. *J. Org. Chem.* **2003**, *68*, 1665.

(46) Kondo, K.; Matsumoto, M. *Chem. Commun.* **1972**, 1332.

(47) Herz, W.; Juo, R.-R. *J. Org. Chem.* **1985**, *50*, 618.

(48) Matsumoto, M.; Dobashi, S.; Kondo, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 185.

(49) Matsumoto, M.; JKuroda, K.; Suzuki, Y. *Tetrahedron Lett.* **1981**, *22*, 3253.

(50) Schenck, G. O.; Dunlap, D. E. *Angewandte Chem.* **1956**, *68*, 248.

(51) Schenck, G. O.; Kinkel, K. G.; Mertens, H. J. *Ann.* **1953**, 125.

(52) Matsumoto, M.; Dobashi, S.; Kondo, K. *Tetrahedron Lett.* **1975**, *16*, 4471.

(53) Bladon, P. *J.Chem. Soc.* **1955**, 2176.

(54) Butenandt, A.; Paland, J. *Chem. Ber.* **1939**, *72*, 424.

(55) Oda, M.; Kitahara, Y. *Angewandte Chem. Eng. Ed.* **1969**, *8*, 673.

(56) Schenck, G. O.; Wirtz, R. *Naturwiss.* **1953**, *40*, 581.

(57) Ensley, H. E.; Balakrishnan, P.; Ugarkar, B. *Tetrahedron Lett.* **1983**, *24*, 5189.

(58) Campagnole, M.; Bourgeois, M.; Montuadon, E. *Tetrahedron* **2002**, *58*, 1165.

(59) Greatrex, B. W.; Jenkins, N. F.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2003**, *68*, 5205.

(60) Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880.

(61) Sengul, M. E.; Ceylan, Z.; Balci, M. *Tetrahedron* **1997**, *53*, 10401.

(62) Moore, R. N.; Lawrence, R. V. *J. Am. Chem. Soc.* **1959**, *81*, 458.

(63) O'Shea, K. E.; Foote, C. S. *J. Org. Chem.* **1989**, *54*, 3475.

(64) Suzuki, M.; Oda, Y.; Hamanaka, N.; Noyori, R. *Heterocycles* **1990**, *30*, 517.

(65) Avery, T. D. *Ph. D. Thesis, University of Adelaide* **2001**.

(66) Pain, H. *Honours Thesis, University of Adelaide* **1999**.

(67) Palmer, F. N.; Taylor, D. K. *J. Chem. Soc. Perkin Trans. I* **2000**, 1323.

(68) Vedejs, E.; Bershas, J. P. *Tetrahedron Lett.* **1975**, *16*, 1359.

(69) Okuma, K.; Tanaka, Y.; Shuzui, I.; Shioji, K. *Heterocycles* **1999**, *50*, 125-130.

(70) Okuma, K.; Hirabayashi, S.-i.; Ono, M.; Shioji, K.; Matsuyama, H.; Bestmann, H. J. *Tetrahedron* **1998**, *54*, 4243-4250.

(71) Okuma, K.; Tanaka, Y.-i.; Hirabayashi, S.-i.; Shioji, K.; Matsuyama, H. *Heterocycles* **1997**, *45*, 1385-1390.

(72) Okuma, K.; Tanaka, Y.; Ohta, H. *Tetrahedron Letters* **1993**, *34*, 4233-6.

(73) Bestmann, H. J.; Riemer, C.; Doetzer, R. *Chemische Berichte* **1992**, *125*, 225-9.

(74) Avery, T. D.; Fallon, G.; Greatrex, B. W.; Pyke, S. M.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2001**, *66*, 7955.

(75) Snyder, J. P. *Tetrahedron Lett.* **1971**, 215.

(76) Avery, T. D.; Jenkins, N. F.; Kimber, M. C.; Lupton, D. W.; Taylor, D. K. *Chem. Commun.* **2002**, 28.

(77) Haselgrove, T. D. *Honours Thesis, University of Adelaide* **1997**.

(78) Matsumoto, M.; Kondo, K. *Tetrahedron Lett.* **1975**, *45*, 3935.

(79) Courtot, P.; Auffret, J. *J. Chem. Res. Synop.* **1981**, *10*, 304.

(80) Leznoff, C. C.; Hayward, R. J. *Can. J. Chem.* **1972**, *50*, 528.

(81) Dickinson, J. M.; Murphy, J. A.; Patterson, C. W.; Wooster, N. F. *J. Chem. Soc. Perkin Trans. I* **1990**, 1179.

(82) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1987**, *52*, 2629.

(83) Greatrex, B. W. *Ph. D. Thesis, University of Adelaide* **2004**.

(84) Carnduff, J.; Marks, R. B. *J. Chem. Res. Synop.* **1977**, 201.

(85) Piero, D.-C.; Riccardo, S. *Org. Magn. Reson.* **1977**, *9*, 607.

(86) Carnduff, J.; Marks, R. B. *Tetrahedron Lett.* **1975**, *16*, 4073.

(87) Isaacs, N. S.; El-Din, C. N. *Tetrahedron Lett.* **1987**, *28*, 2191.

(88) Eguchi, T.; Aoyama, T.; Kakinuma, K. *Tetrahedron Lett.* **1992**, *33*, 5545.

(89) Abate, A.; Brenna, E.; Dei Negri, C.; Fuganti, C.; Serra, S. *Tetrahedron Asym.* **2002**, *13*, 899.

(90) Maercker, A. *hjyh*; John Wiley and Sons, Inc., 1965.

(91) Robinson, P. L.; Barry, C. N.; Kelly, J. W.; Evans Jr., S. A. *J. Am. Chem. Soc.* **1985**, *107*, 5210.

(92) Greatrex, B. W.; Taylor, D. K. *J. Org. Chem. In Press* **2004**.

(93) Chatterjea, J. N.; Lal, S.; Jha, U.; Rycroft, D. S.; Carnduff, J. *J. Chem. Res. Synop.* **1979**, 356.

(94) Einhorn, J.; Demerseman, P.; Royer, R.; Cavier, R. *Eur. J. Med. Chem.* **1983**, *18*, 175.

(95) Dunn, J. P.; Ackerman, N. A.; Tomolonis, A. J. *J. Med. Chem.* **1986**, *29*, 2326.

(96) Moskal, J.; Van Leusen, A. M. *J. Org. Chem.* **1986**, *51*, 4131.

(97) Monte, A. P.; Marona-Lewicka, D.; Parker, M. A.; Wainscott, D. B.; Nelson, D. L.; Nichols, D. E. *J. Med. Chem.* **1996**, *39*, 2953.

(98) Einhorn, J.; Demerseman, P.; Royer, R.; Cavier, R.; Gayral, P. *Eur. J. Med. Chem.* **1984**, *19*, 405.

(99) Wavefunction Inc., 18401 Von Karmen Ave., Suite 370, Irvine, CA 92715.

(100) Patai, S. *Chemistry of the Quinonoid Compounds*; Interscience: London : New York, 1974.

(101) J., D. H.; Gadecki, F. A.; Harmon, K. M.; Pearson, D. L. *J. Am. Chem. Soc.* **1957**, *79*, 4557.

(102) Braude, E. A.; Jackman, L. M.; Linstead, R. L.; Lowe, G. *J. Chem. Soc.* **1960**, 3123.

(103) Creighton, A. M.; Jackman, L. M. *J. Chem. Soc. Abs.* **1960**, 3138.

(104) Arora, P. C.; Brassard, P. *Can. J. Chem.* **1971**, *49*, 3477.

(105) Kasahara, A.; Izumi, T.; Suzuki, A.; Takeda, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3711.

(106) Campbell, I. M.; Caldazilla, C. H.; McCorkindale, N. J. *Tetrahedron Lett.* **1966**, 5107.

(107) Cardillo, G.; Cricchio, R.; Merlini, L. *Tetrahedron Lett.* **1969**, 907.

(108) Braude, E. A.; Linstead, R. L.; Woolridge, K. R. *J. Chem. Soc.* **1956**, 3070.

(109) Ibnusaud, I.; Thomas, P. T.; Rani, R. N.; Sasi, P. V.; Beena, T.; Hisham, A. *Tetrahedron* **2002**, *58*, 4887.

(110) Umezawa, K.; Nakazawa, K.; Uemura, T.; Ikeda, Y.; Kondo, S.; Naganawa, H.; Kinoshita, N.; Hashizume, H.; Hamada, M.; Takeuchi, T.; Ohba, S. *Tetrahedron Lett.* **1998**, *39*, 1389.

(111) Hanswadsi, C.; Kawabata, J.; Kasai, T. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 1041.

(112) Lewis, Y. S.; Neelakantan, S. *Phytochem.* **1965**, *4*, 619.

(113) Greenwood, M. R.; Cleary, M. P.; Gruen, R.; Blase, D.; Stern, J. S.; Triscari, J.; Sullivan, A. C. *Am. J. Physiol.* **1981**, *240*, 72.

(114) Hood, R. L.; Beitz, D. C.; Johnson, D. C. *Comp. Biochem. Physiol. [B]* **1985**, *81*, 667.

(115) Ranganathan, S.; Ranganathan, D.; Bhattacharyya, D. *Chem. Commun.* **1987**, 1085.

(116) Chan, C.-O.; Crich, D.; Natarajan, S. *Tetrahedron Lett.* **1992**, *33*, 3405.

(117) Klein, H.; Steinmetz, A. *Tetrahedron Lett.* **1975**, 4249.

(118) Tius, M. A.; Reddy, N. K. *Synth. Comm.* **1994**, *24*, 859.

(119) Arenz, C.; Giannis, A. *Eur. J. Org. Chem.* **2001**, *1*, 137.

(120) Haseltine, J. N.; Cabal, M. P.; Mantlo, J.; Schulte, G. K. *J. Am. Chem. Soc.* **1991**, *113*, 3850.

(121) Cabal, M. P.; Coleman, R. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 3253.

(122) Cacioli, P.; Reiss, J. A. *37* **1984**, *12*.

(123) Gesson, J.; Mondon, M.; Pokrovska, N. *Synlett* **1997**, 1395.

(124) Adam, W.; Ahrweiler, M.; Sauter, M. *Chem. Ber.* **1994**, *127*, 941.

(125) Adam, W.; Hauer, H.; Mossandl, T.; Saha-Moller, C. R.; Wagner, W.; Wild, D. *Liebigs Ann. Chem.* **1990**, 1227.

(126) Basselier, J.; Cherton, J.; Caille, J.; Normant, M. H. *C. R. Acad. Sc. Paris, Serie C* **1971**, *273*, 514.

(127) Adam, W.; Ahrweiler, M.; Reinhardt, D. *J. Am. Chem. Soc.* **1994**, *116*, 6713.

(128) Awad, W. I.; Salih, Z. S.; Aiube, Z. H. *J. Chem. Soc. Perkin Trans. I* **1977**, 1280.

(129) Awad, W. I.; Taha, A. A.; Wasef, W. N.; Shindy, S. M. *Eygpt. J. Chem* **1983**, *26*, 65.

(130) Awad, W. I.; Al-Sabti, R. R. *J. Prakt. Chem.* **1978**, *320*, 986.

(131) Davies, A. G. *Organic Peroxides Volume II*; Butterworths: London, 1961.

(132) Miller, B. *J. Am. Chem. Soc.* **1965**, *87*, 5515.

(133) Carnduff, J.; Leppard, D. G. *Chem. Commun.* **1967**, 829.

(134) Carnduff, J.; Leppard, D. G. *J. Chem. Soc. Perkin Trans. I* **1976**, 2570.

(135) Brady, P. A.; Carnduff, J. *Chem. Commun.* **1974**, 816.

(136) Greenland, H.; Pinhey, J. T.; Sternhell, S. *Aust. J. Chem.* **1987**, *40*, 325.

(137) Engelhardt, L. M.; Hewgill, F. R.; Stewart, J. M.; White, A. H. *J. Chem. Soc. Perkin Trans. I* **1988**, *7*, 1845.

(138) Becker, H. D.; Elebring, T. *J. Org. Chem.* **1985**, *50*, 1319.

(139) Carnduff, J.; Leppard, D. G. *Chem. Commun.* **1971**, 975.

(140) Carnduff, J.; Leppard, D. G. *J. Chem. Soc. Perkin Trans. I* **1977**, 1329.

(141) Spinzak, Y. *J. Am. Chem. Soc.* **1958**, *80*, 5449.

(142) Santamaria, J.; Jroundi, R.; Rigaudy, J. *Tetrahedron Lett.* **1989**, *30*, 4677.

(143) Glover, S. A.; Goosen, A.; McCleland, C. W.; Taljaard, B.; Vogel, F. R. *J. Chem. Soc. Perkin Trans. II* **1985**, 1205.

(144) Glover, S. A.; Goosen, A.; McCleland, C. W.; Taljaard, B.; Vogel, F. R. *S. African J. Chem.* **1985**, *38*, 203.

(145) Quannes, C.; Wilson, T. *J. Am. Chem. Soc.* **1968**, *90*, 6527.

(146) Nishinaga, A.; Iwasaki, H.; Shimizu, T.; Toyoda, Y.; Matsuura, T. *J. Org. Chem.* **1986**, *51*, 2257.

(147) Nishinaga, A.; Iwasaki, H.; Kondo, K.; Matsuura, T. *Chem. Lett.* **1985**, *1*, 5.

(148) Nishinaga, A.; Nishizawa, K.; Tomita, H.; Matsuura, T. *Synthesis* **1977**, *4*, 270.

(149) Hart, H.; Lavrik, P. B. *J. Org. Chem.* **1974**, *39*, 1793.

(150) Al Jazzaa, A.; Clark, J. H.; Miller, J. M. *Chem. Lett.* **1983**, 89.

(151) Santiago, A. N.; Iyer, V. S.; Adcock, W.; Rossi, R. A. *J. Org. Chem.* **1988**, *53*, 3016.

(152) Perrin, D. D.; Armego, W. L. F. *Purification of Laboratory Chemicals*; Permagon Press: Oxford, 1988.

(153) Badone, D.; Cecchi, R.; Guzzi, U. *J. Org. Chem.* **1992**, *57*, 6321.

(154) Tzeng, Y. L.; Yang, P. F.; Mei, N. W.; Juan, T. M.; Yu, C. C.; Lu, T. Y. *J. Org. Chem.* **1991**, *56*, 5289.

(155) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1993**, *58*, 7421.

(156) Satoh, T.; Hanaki, N.; Yamada, N.; Asano, T. *Tetrahedron* **2000**, *56*, 6223.

(157) Jevric, M.; Taylor, D. K.; Tiekink, E. R. T. *Z. Krist.* **2001**, *216*, 545.

(158) Archer, W. J.; Taylor, R.; Gore, P. H.; Kamounah, F. S. *J. Chem. Soc. Perkin Trans. II* **1980**, 1828.

(159) Rosini, C.; Scamuzzi, S.; Uccello-Barretta, G.; Salvadori, P. *J. Org. Chem.* **1994**, *59*, 7395.

(160) Yasuda, M.; Kojima, R.; Ohira, R.; Shiragami, T.; Shima, K. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1655.

(161) Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265.

(162) Van Hijfte, L.; Little, R. D.; Petersen, J. L.; Moeller, K. D. *J. Org. Chem.* **1987**, *52*, 4647.

(163) Sangaiah, R.; Gold, A. *J. Org. Chem.* **1987**, *52*, 3205.

(164) Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1947**, *69*, 1197.

(165) Tsukayama, M.; Fujimoto, K.; Horie, T.; Masamura, M.; Nakayama, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 136.

(166) Koenigkramer, R. E.; Zimmer, H. *J. Org. Chem.* **1980**, *45*, 3994.

(167) Seemuth, P. D.; Zimmer, H. *J. Org. Chem.* **1978**, *43*, 3063.