THE UNIVERSITY
of LIVERPOOL

SYNTHESIS AND TRANSFORMATIONS OF SUBSTITUTED FURANS

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy

by

Valerie Ross

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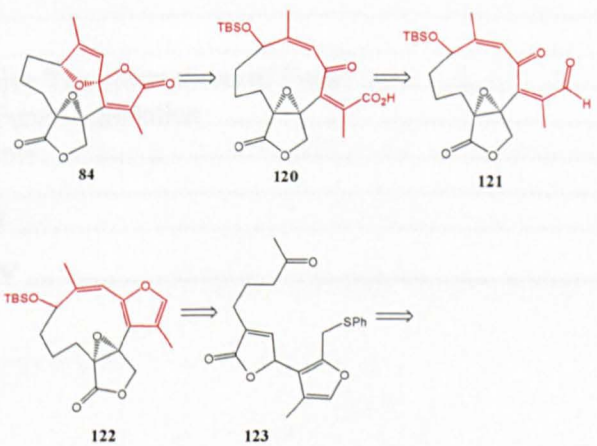
ABSTRACT

Synthesis and Transformations of Substituted Furans

Valerie Ross

The furan unit is predominant in a wide range of biologically active compounds. Owing to the versatility of the types of reactions possible at the electron-rich double bonds, it is possible to use these compounds as synthons for the synthesis of terpenoid natural products. Relevant applications toward the oxidation, functionalization, and annelation of these compounds are described herein.

Model systems based on neoliacine **84**, a germacranolide sesquiterpene, which exhibits antitumour properties *in vitro* in the form of its oxidized metabolite, neoliacinic acid; were synthesized utilizing furan chemistry. The synthetic strategy involved the preparation of the most labile spiroketal portion of structure to determine the feasibility of a final ring-closing cascade sequence to generate the highlighted portion of neoliacine. Concurrently, a second model system was examined to determine the appropriate route for the carbocyclic ring-closing step, which would involve a sulfoxide condensation, thereby furnishing **122** from **123**.



84 120 121

122 123

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GLOSSARY

ATP. Adenosine Triphosphate

Bu_3SnH. Tributyltin Hydride

CaH_2. Calcium Hydride

CHN. Carbon Nitrogen, Hydrogen, Microanalysis

CH_2Cl_2. Dichloromethane

C.I. Chemical Ionisation

DBU. Diazabicyclo[5.4.0]undecene

DIBAL. Diisobutylaluminum Hydride

DMA. *N,N*-dimethylacetamide

DMAP. 4-Dimethylamino Pyridine

DMAPP. Dimethylallyl Pyrophosphate

MSO. Dimethyl Sulfoxide

DPPE. Bisdiphenylphosphinoethane

ee. Enantiomeric Excess

E.I. Electron Impact

Et_2O. Diethyl Ether

EtOH. Ethanol

EtOAc. Ethyl Acetate

Et_3N. Triethylamine

GC. Gas Chromatography

IPP. Isopentyl Pyrophosphate

LDA. Lithium Diisopropylamide

$LiAlH_4$. Lithium Aluminum Hydride

***m*-CPBA.** *m*-Chloroperbenzoic Acid

MeI. Methyl Iodide

MOM. Methoxymethyl

$NaBH_4$. Sodium Borohydride

NBS. N-Bromosuccinimide

NIS. N-Iodosuccinimide

NMR. Nuclear Magnetic Resonance

PAF. Platelet Activating Factor

PCC. Pyridinium Chlorochromate

PDC. Pyridinium Dichromate

TBS. *t*-Butyldimethylsilyl

TFA. Trifluoroacetic Acid

THF. Tetrahydrofuran

TIPS. Triisopropylsilane

TMS. Trimethylsilyl

TLC. Thin Layer Chromatography

Chapter 1

INTRODUCTION

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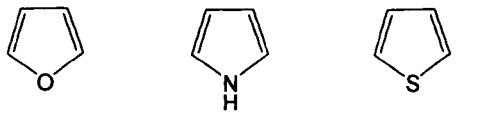
1.1 Furans as Synthetic Intermediates

Furans are volatile and generally fairly stable compounds with pleasant odours. Furan is mainly of commercial importance due to its role as the precursor of the widely used solvent tetrahydrofuran. It is a readily available compound and is produced by the gas phase decarbonylation of furfural, which is in turn produced in large quantities by the action of acids on vegetable residues. Furfural has been produced in this way since 1831, and its name is derived from *furfur*, the latin word for bran. Conversely, in 1870, the word furan was derived from the same root.[1]

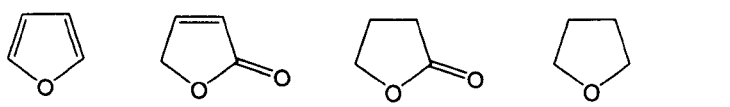
Furan is an aromatic oxygen heterocycle, being more reactive than benzene and thiophene, and possessing less reactivity than that of pyrrole. Although reactive, it is the least aromatic of the aforementioned heterocycles, and as such has the greatest tendency to react to give addition products. The aromaticity of furan and similar heterocycles is due to the electron donating ability of the heteroatom lone pair electrons into the carbon π-electron system. The combination of the four carbon π-electrons and the two lone electrons of the oxygen satisfy Huckel's 4n + 2 rule of aromaticity[2].



furan pyrrole thiophene

Figure 1.1 Aromatic heterocycles

Furans are common building blocks of many naturally occurring compounds, which contain a variety of important commercial properties, such as insect antifeedant,[3] antileukaemic,[4] and fish antifeedant;[5] therefore they are desirable candidates as synthetic intermediates. This ring system, though not found in animal metabolism, occurs widely in secondary plant metabolites, and is particularly predominant in germacranolide sesquiterpene lactones and furanocembranolides (diterpene cembranoids), which have various furan types (furan, butenolide, butyrolactone, and tetrahydrofuran) incorporated into their basic structure.[6] The furan types are interrelated since furan heterocycles can exist in a range of oxidation states; thus various oxidation, reduction, etc. transformations are possible at the electron rich double bond sites, which lead to interconversion between the types (Figure 1.2).

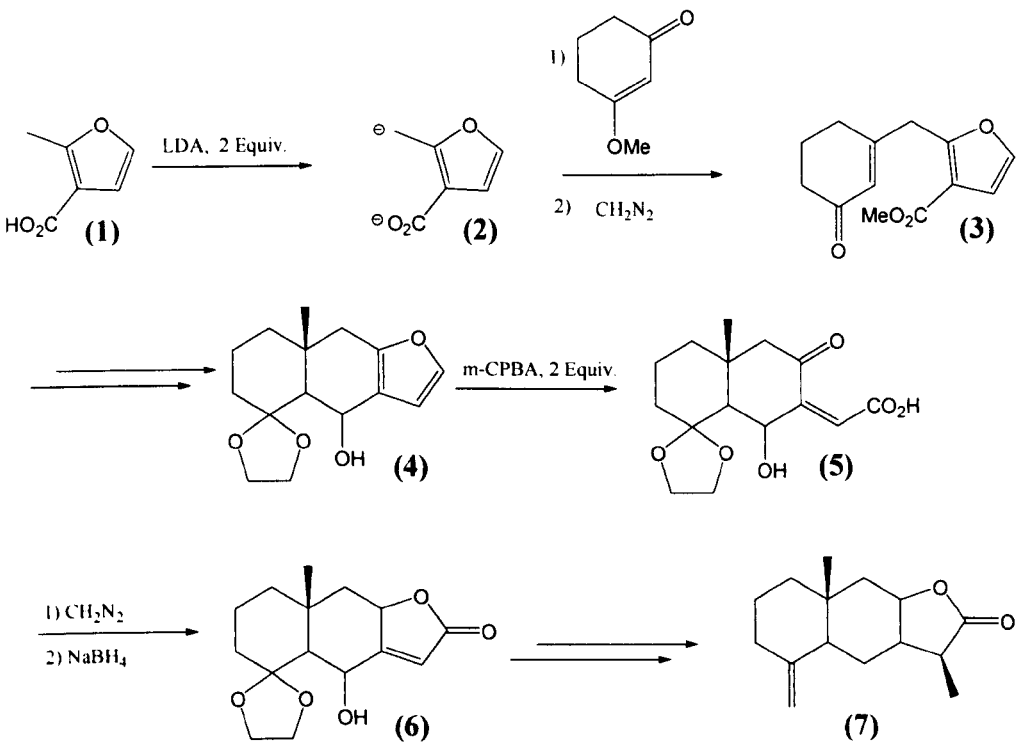


furan butenolide butyrolactone tetrahydrofuran

Figure 1.2 Furan oxidation states.

Tada[7] utilized these transformations using a reaction sequence that originates with 2-methyl-3-furoic acid (**1**) for the total synthesis of (±)-isoalantolactone and (±)-dihydrocallitrisin (scheme 1.1). Reactive dianion (**2**) reacted with the α,β-unsaturated carbonyl *via* 1,2-addition-hydrolysis and gave the substituted furan (**3**). The furan was oxidized using 2 equivalents of *m*-CPBA. Although Tada did not provide a mechanism for this transformation, the mechanism for this reaction could involve an epoxide intermediate. The first equivalent could provide an unsaturated

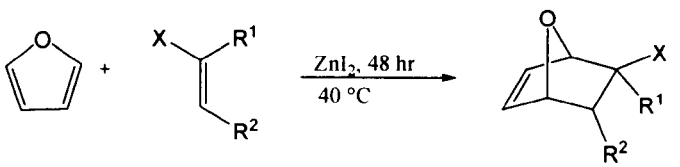
aldehyde *via* an epoxide intermediate. The hydrate form of the aldehyde could subsequently be oxidized by the second equivalent of *m*-CPBA to the corresponding acid (**5**). The dicarbonyl species was subsequently reduced to the butenolide functionality (**6**) following methylation using diazomethane/Et_2O, and with further steps, the target compound, (±)-dihydrocallitrisin (7) was synthesized. Scheme 1.1 nicely represents the range of oxidations utilizing the oxidative/reductive transformations from furan to butyrolactone in the synthesis of (±)-dihydrocallitrisin.



Scheme 1.1 Synthesis of (±) Dihydrocallitrisin

In comparison to other heteroaromatic systems, the furan ring is the most commonly synthesised heterocycle in organic synthesis. The electron rich nature of the furan double bonds is exploited for its ability to undergo Diels-Alder

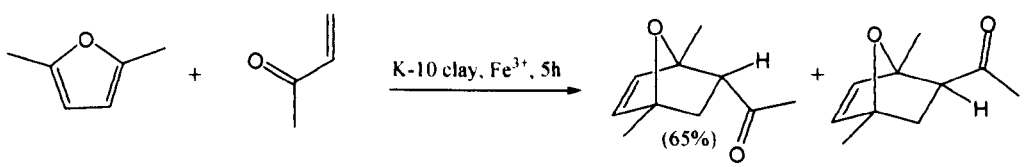
cycloadditions.[8] This intermolecular process is commonly used for carbon-carbon bond formation, which generates a large variety of target compounds in a single-step process. Campbell and Sainsbury[8, 9] have reported the zinc iodide catalysed cycloadditions, which were originally described by Brion,[10] of furan with acrylate (scheme 1.2).



X = H, Cl
R^1 = $COOCH_3$, CN
R^2 = $COOCH_3$, H

Scheme 1.2 ZnI_2 catalysed cycloadditions

Lewis acids, such as the aforementioned ZnI_2, are commonly used to enhance the rate of these reactions. Moreover, Kotzuki demonstrated that $BF_3{\cdot}OEt_2$ promotes the additions of acrolyl chloride and methyl acrylate to furan in high yields.[8, 11] When K-10 bentonite clay is doped with ferric salts or $AlCl_3$, 2,5-dimethyl furan and furan each add to acrolein at – 43 °C to give a mixture of the *endo:exo* adducts with the major product being the *endo* due to the transition state as shown in figure 1.3.[8, 12]



Scheme 1.3 2,5-Dimethylfuran cycloaddition to acrolein

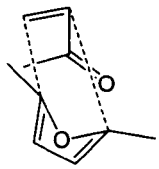
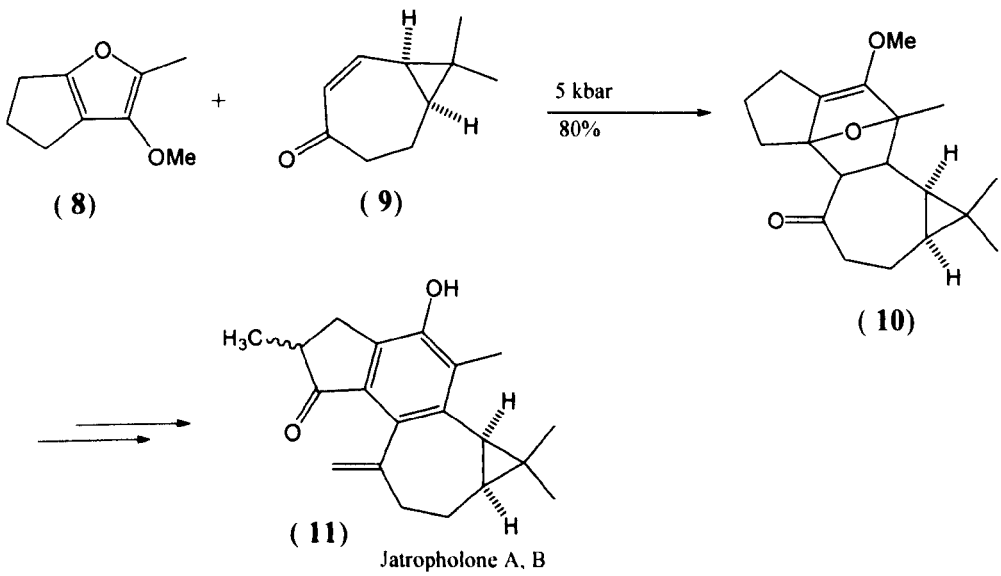


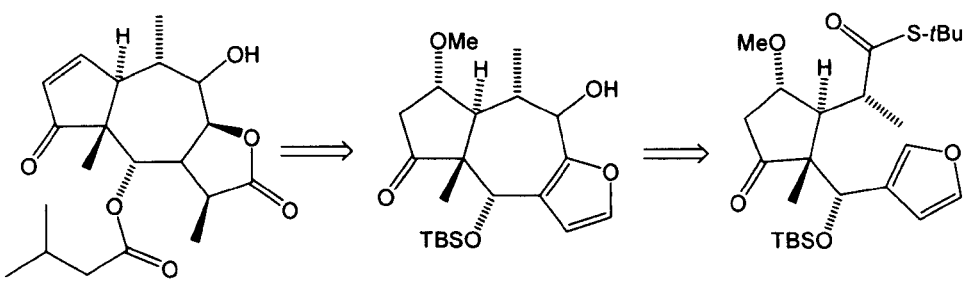
Figure 1.3 Transition state for the cycloaddition of 2,5-dimethylfuran and acrolein

Alternatively, high-pressure conditions (1-20 kbar) can be applied to accelerate cycloadditions with less activated dienophiles. At these pressures, these otherwise sluggish reactions can occur at both reasonable rates and at lower temperatures with otherwise inert substrates. Total syntheses of (+)-jatropholone A and B have been performed using high pressure Diels-Alder additions of methoxyfuran (**8**) to chiral enone (**9**).[8, 13] Intermediate (**10**) was converted into (+)-jatropholone A,B following several short steps.



Scheme 1.4 Synthesis of (+)-jatropholone A, B

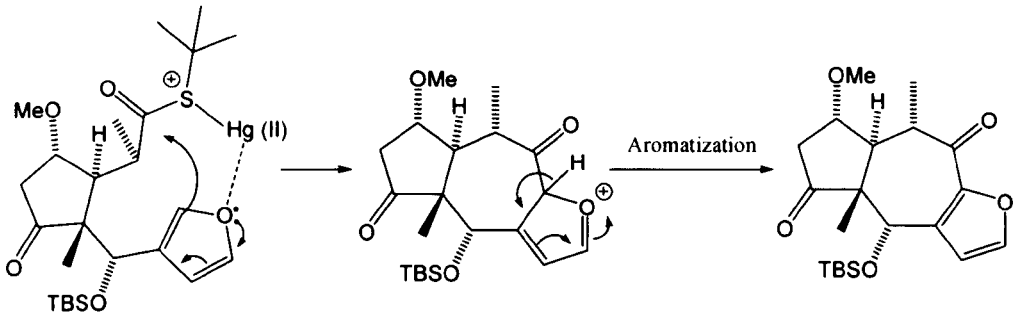
Furan terminated cyclization strategies constitute another approach for the synthesis of biologically active products. Fastigilin-C (**12**), a complex helenanolide, which exhibits cytotoxic and antineoplastic activity *in vivo*, has been synthesized by Tanis.[14] It represents an interesting target among the helenanes for synthesis because it is substituted at every position along its seven-membered ring. Tanis and co-workers investigated the furan terminated cationic cyclization strategy (conversion of structure **14** to **13**) as a key step for the construction of linearly fused, bridged, spirocyclic-alkaloid, and terpenoid ring systems.



12 **13** **14**

Equation 1.1 Retrosynthetic approach to (–)-fastigilin C synthesis

The synthesis of the bicyclo [5.3.0] decane nucleus began with cyclopentenone (**15**). After several steps, a cyclization initiator in the form of a stabilized cation promoted the cyclization step, which terminated with the furan (Equation 1.2).

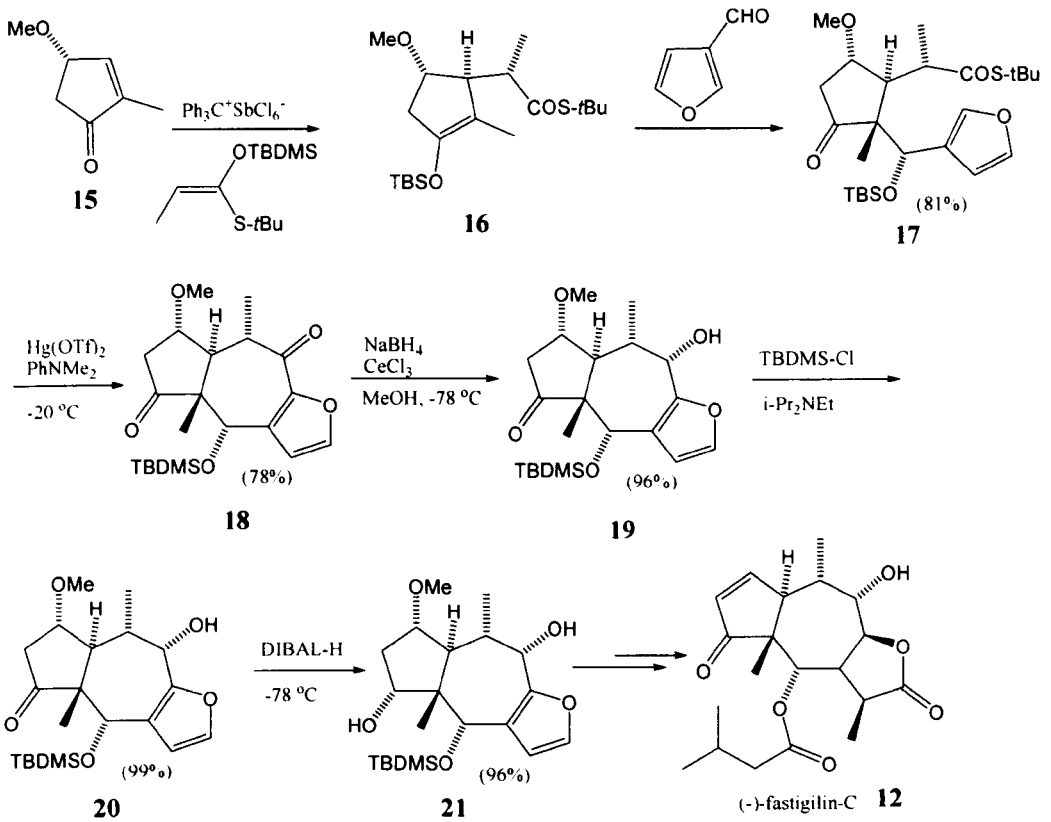


Equation 1.2 Proposed mechanism for furan terminating cyclization

The incorporation of the furan functionality was also intended to locally control the regiochemistry and stereochemistry for the introduction of the carbocyclic nucleus because the normally rigid 7-membered ring would be firmly held in place by the furan anchor.

The synthesis of cyclopentenone (**15**) was a challenge to be overcome, as a method to synthesise the (*S*)-(+)-4-methoxy-2-methyl-2-cyclopentenone in high yield and with a high degree of purity was necessary. In order to isolate the *S*-isomer of the compound, the method chosen by Tanis *et al.* was enzymatic resolution using porcine pancreatic lipase (PPL), which essentially is a lipase-catalysed acylative resolution technique using β,-β,-β-trifluoroethyl butyrate dissolved in ether as the acylating agent. The enantiomer was further enriched through conversion of the generated (*R*)-butyrate ester by cleaving it to the (*R*)-alcohol, then inverting the stereocenter using Mitsunobu conditions to give the (*S*)-alcohol. The batches of the

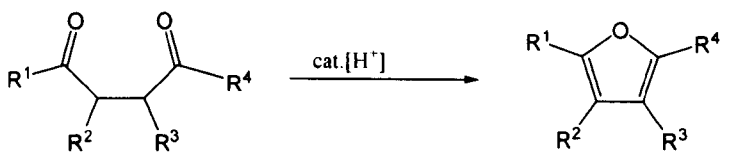
S-enantiomer alcohol were mixed and subjected again to the lipase catalytic resolution giving a final 52% isolated yield and ≥ 98% ee at 41% conversion.



Scheme 1.5 Synthesis of (-)-Fastigilin-C

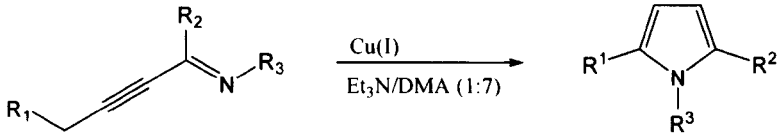
1.2 Furan Construction and Functionalization

The predominance of the furan moiety in natural product synthesis has also spawned a range of strategies towards the synthesis of furans. These methods consist of the condensation of β-ketoesters with α-hydroxycarbonyl compounds,[15] the Feist-Benary method,[16] which is the base-promoted condensation of β-dicarbonyl compounds with α-haloketones, and the Paal-Knorr acid-catalysed cyclocondensation of 1,4-dicarbonyl compounds. Each of these classical methods presents limitations due to lack of availability of starting materials or toxicity of the reagents. The Paal-Knorr synthesis of furans from 1,4-diketones has been the most widely used classical method (scheme 1.6).[17] The main limitation of this method is its incompatibility with acid sensitive substrates.



Scheme 1.6 Paal-Knorr synthesis of furan

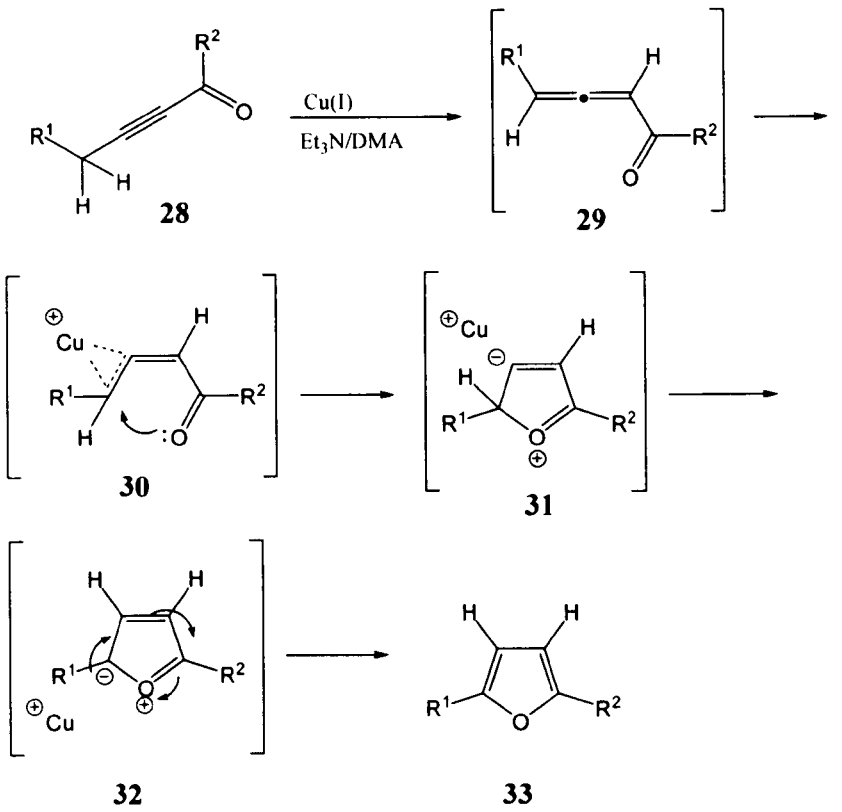
Alternatively, Kel'in *et al.* have described a method involving the efficient synthesis of 2-mono and 2,5-disubstituted furans which is carried out by the CuI-catalysed cycloisomerization of alkynyl ketones.[18] The authors initially carried out this transformation on alkynyl imines in a Et_3N-DMA system in the presence of Cu(I) salts (scheme 1.7).



Scheme 1.7 Alkynyl imine conversion to pyrroles

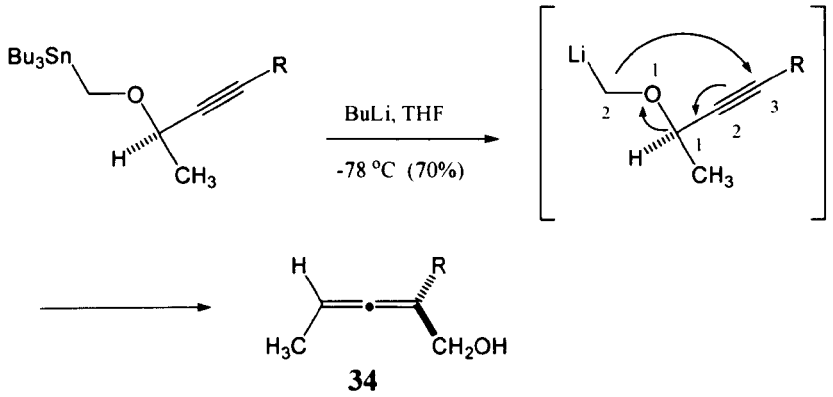
As this method was found to work successfully for the transformation to pyrroles, the authors were hopeful that the same success would be possible for furan. In fact, they found that this reaction generally performed better for the synthesis of furans than for the synthesis of pyrroles. The reactions involving pyrrole synthesis required 30-50 mol% of copper iodide, whereas those involving furans required only 5 mol% of the catalyst were generated in high yield (63%-94%). This method also proved to be quite versatile in allowing a number of functional groups, such as alkenyl and hydroxyl groups, to be introduced into the furan ring.

The mechanism for this reaction is proposed to occur as represented in scheme 1.8. First, the triethylamine-Cu(I) catalysed isomerization of the alkynyl ketone (**28**) gave allenyl ketone (**29**). Then, coordination of copper to the terminal double bond of the allene (**30**), which made it more electrophilic, led to intramolecular nucleophilic attack on the allene by the oxygen lone pair, producing zwitterionic intermediate (**31**). This intermediate isomerised *via* deprotonation-protonation leading to the more stable isomer (**32**), which gave the furan product (**33**).



Scheme 1.8 Proposed mechanism for the Cu(I) catalysed formation of furan

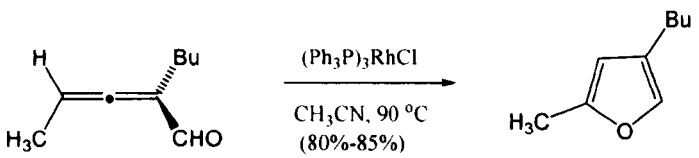
Allenals and allenones have also been utilized for the synthesis of disubstituted furans[19]. Marshall *et al.* previously synthesized optically active allenes through the [2,3]-Wittig rearrangement of nonracemic propargylic ethers (scheme 1.9). The Wittig rearrangement falls within the class of sigmatropic reactions, which involves the unimolecular isomerization in which a σ-bond moves from one position to another with a concomitant movement of the conjugated π-bond system to accommodate the forming σ-bond and to fill in the vacancy which was left behind. A [2,3] Wittig rearrangement entails the formation of the σ-bond at the 2,3-position (scheme 1.9); whereas a [1,2] rearrangement is the formation at the 1,2-position.



34

Scheme 1.9 Wittig rearrangement of propargylic ethers

These planar chiral allenes were formed in high (86-93%) ee.[20] In the course of their efforts to determine the absolute stereochemistry of (**34**), the formyl derivative (**35**) was synthesised, which was believed to decarbonylate under the given reaction conditions (scheme 1.10) to a disubsubstituted allene, but surprisingly furan product (**36**) was the only isolated product.



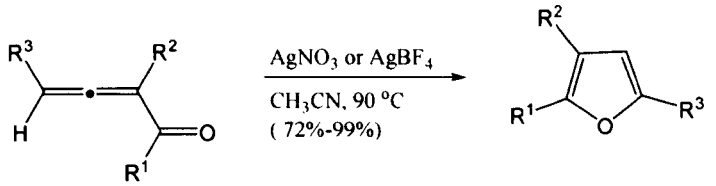
35 **36**

Scheme 1.10 Allenal derived synthesis of furan

Under the assumption that the cyclization was initiated by the Rh(I) coordination with the double bond, Marshall decided to examine other π-coordinating Lewis acids, and found that $AgNO_3$ and $AgBF_4$ also proved to be highly effective catalysts for this reaction. Aldehyde (**35**) and similar derivatives were converted to their

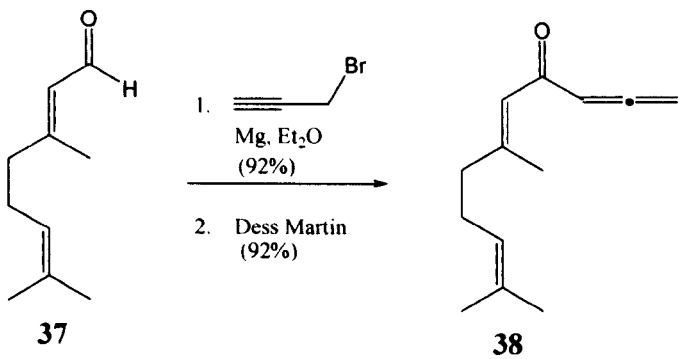
ketone counterparts and the corresponding allenyl ketones afforded furans in high yield (scheme 1.11) when treated with the $AgNO_3$ and $AgBF_4$ catalysts.

The successful preparation of ketone (**38**) by the addition of propargylmagnesium bromide to geranial (**37**), followed by Dess-Martin periodinane oxidation of the alcohol to ketone, suggested an application of this novel method to the construction of furan-bridged cembranoids such as lophotoxin, pukalide, and their congeners. A model system was employed towards the synthesis of the 2,5-bridged furanocembranoid products.



R^1 = H, CH_3, C_9H_{15}
R^2 = H, *n*-C_7H_{15}
R^3 = H, CH_3

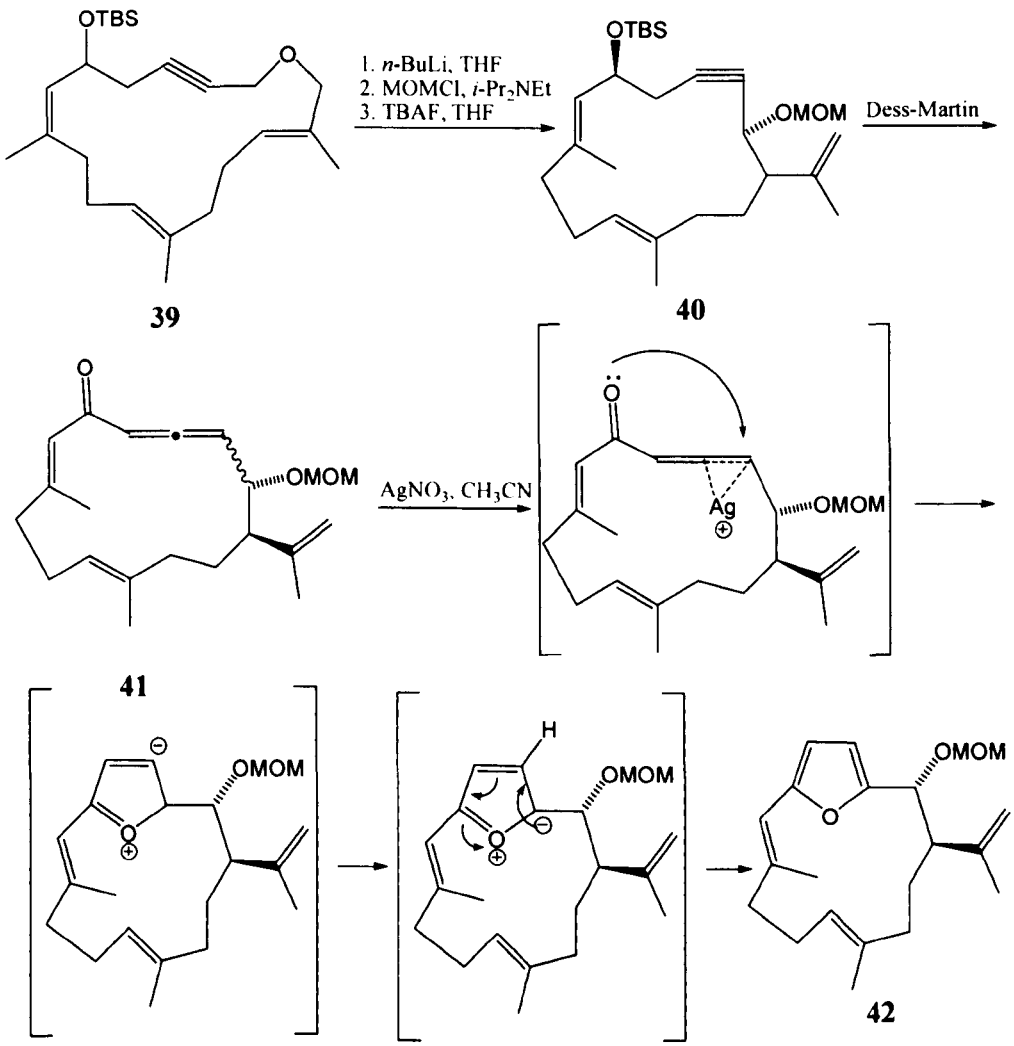
Scheme 1.11 Lewis acid catalysed cyclisation of allenyl ketones



37 **38**

Scheme 1.12 Propargylic ketone synthesis

The reaction sequence shown in scheme 1.13 gives (**41**) as the model macrocycle that verified this experimental approach to these systems. Marshall initially attempted this synthesis by generating the furan functionality prior to the [2,3]-Wittig ring contraction, but only succeeded in generating a 16-membered [1,2]-Wittig rearrangement product.



Scheme 1.13 $AgNO_3$ catalysed macrocyclic ether synthesis

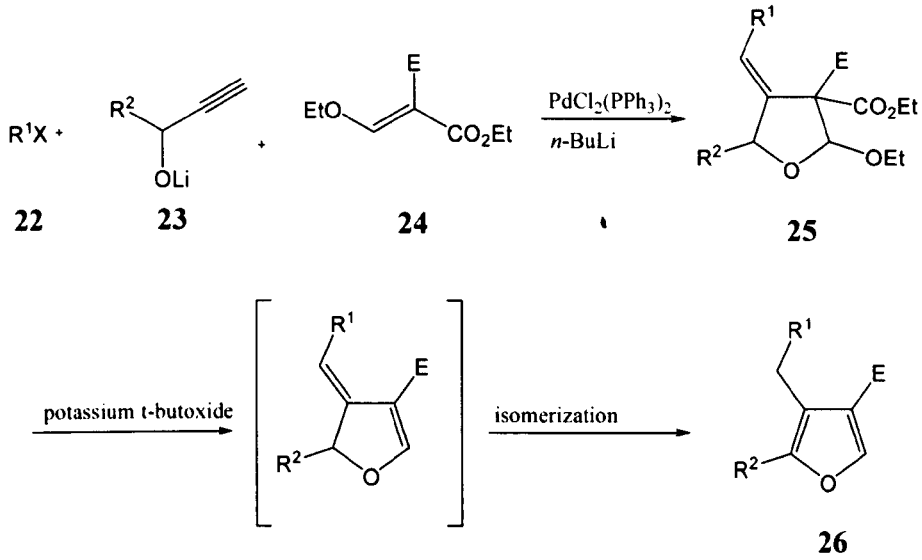
Figure 1.4 Movement of electrons for [2,3] versus [1,2] rearrangements

Therefore, the [2,3]-Wittig rearrangement was accordingly performed prior to the formation of furan. Thus, **39** was treated with *n*-butyllithium, which promoted the rearrangement, followed by protection of the resulting alcohol and TBS cleavage gave the desired macrocycle (**40**) in 80% yield. Dess-Martin periodinane oxidation of this mixture gave **41** as a 15:85 mixture of propargylic ketone and diastereomeric allenones. Treatment of the major allenone with $AgNO_3$ afforded the furan containing macrocycle **42** in 50% isolated yield.

These results demonstrated the potential application of this novel furan synthesis toward the generation of furanocembranoids and related natural products. Whereas previous approaches to this synthesis have encountered complications during the ring closure step due to the chemical reactivity and the stereochemical constraints inherent in the incorporation of a preformed furan moiety, this method successfully incorporated the labile furan portion at the end to overcome these difficulties.

Balme[21] originated a novel synthetic method consisting of a three-component system that permitted the preparation of functionalized 3-benzylfurans as precursors of dibenzyltetrahydrofuran lignans for the total synthesis of lignan antitumour agent, (±)-burseran.

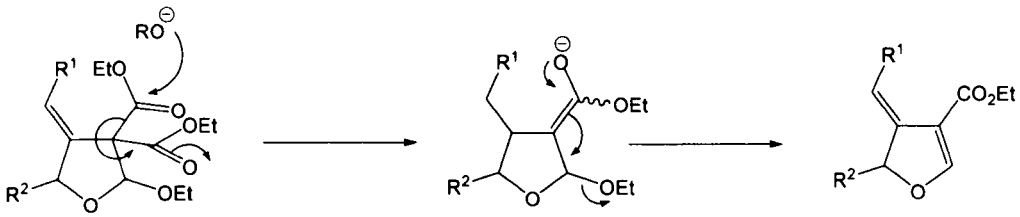
Mechanistically, this strategy was based on a domino type reaction (scheme 1.14) involving the enolate resulting from the 1,4 addition of propargylic alkoxide (**23**) to conjugate acceptor (**24**). The adduct then underwent a palladium catalysed cyclization with an unsaturated halide (or triflate) (**22**).



R^1 = aryl, vinyl, R^2 = aryl, alkyl
E = electron withdrawing group

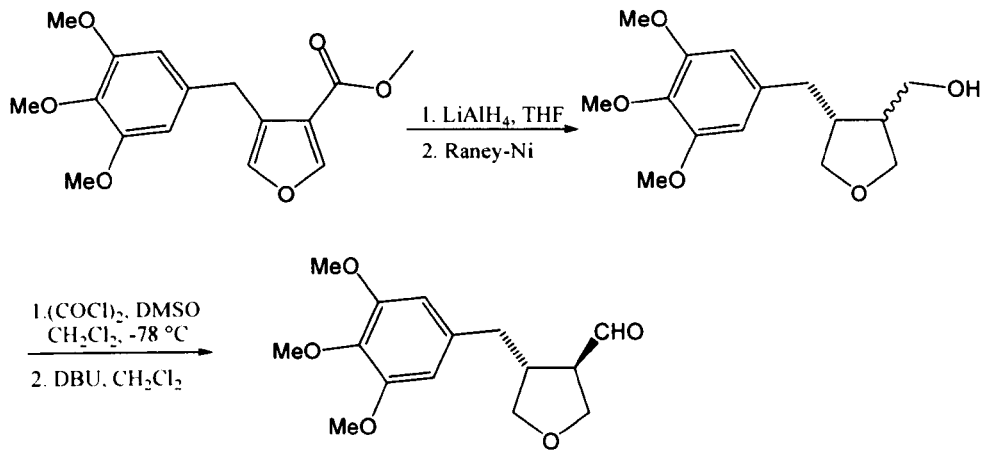
Scheme 1.14 Palladium catalysed 3-component synthesis of 3-benzyl (or allyl-) furans

This methodology, which Balme originally applied towards the synthesis of dibenzyltetrahydrofurans,[22] was utilized to synthesise tetrasubstituted tetrahydrofuran (**25**). The generation of the intermediate species was promoted by the decarboxylative elimination following the addition of potassium *tert*-butoxide to **25**. This occurred after the nucleophilic addition of the *tert*-butoxide into the carbonyl group of the ester functionality. This elimination followed an E1cb mechanism as indicated in the mechanistic sequence in scheme 1.15.

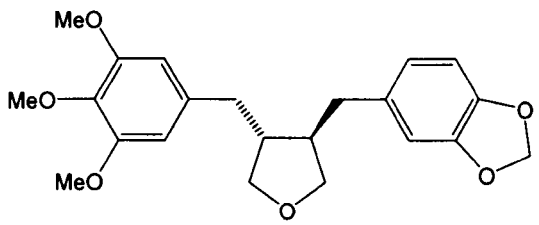


Scheme 1.15 Decarboxylation/elimination mechanism

Application of this methodology towards the synthesis of burseran applied the previous work of Hanessian,[23] which involved the transformation of racemic benzyltetrahydrofuran aldehydes into dibenzyltetrahydrofurans using a 3-step sequence that allowed the production of both (+) and (−) enantiomers. Balme utilized the novel, single-step procedure to synthesize the corresponding benzyltetrahydrofuran aldehydes using the following sequence: reduction of the ester to the corresponding alcohol, Raney-Ni hydrogenation of the furan double bonds, followed by Swern oxidation of the primary alcohol to the aldehyde (scheme 1.16). Following Hanessian's findings, the given aldehyde was diastereomerically enriched as its *trans* isomer (20:1) by equilibration with DBU. The desired target (**27**) was thus obtained within four synthetic steps in 47% overall yield from a combination of three building blocks.



Scheme 1.16 Synthesis of benzyltetrahydrofuran aldehyde

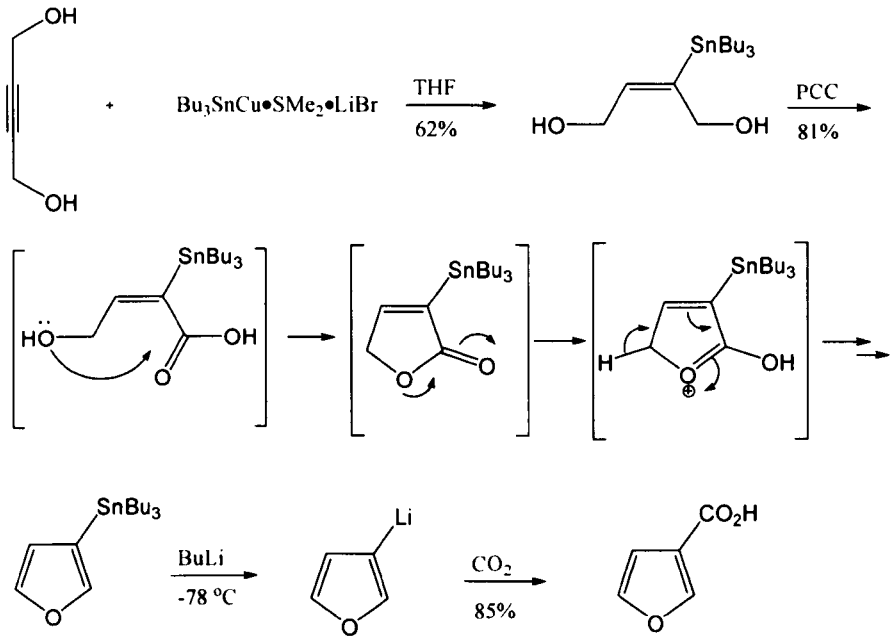


27

Figure 1.5 Burseran target compound

The construction of 3-substituted furans from acyclic precursors is possible using stannanes.[24] A simple, two-step reaction using the inexpensive compound butyne-1,4-diol as starting material was used. Scheme 1.17 shows the reaction sequence utilized for the formation of the substituted furan-3-carboxylic acid. PCC oxidation of the (*E*)-stannylbutanediol, which was proposed to undergo a mechanism involving a lactone intermediate as shown in scheme 1.17, which following the elimination of water, gave the 3-*tri*-*n*-butylstannylfuran. Following transmetalation, the 3-lithiated furan nucleophile was generated. This reactive

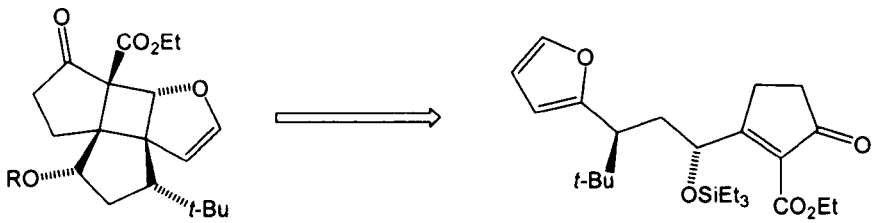
nucleophile serves as a very important building block for the synthesis of 3-substituted furans.



Scheme 1.17 Stannane mediated formation of 3-substituted furan

Substituted furan rings used as starting materials can also be manipulated to give a diverse range of products. The natural product extract of the ginkgo biloba tree has been used as an herbal medicine for over 5000 years for treatment of such conditions as coughs, asthma, and circulatory disorders. The ginkgolide B extract, a PAF antagonist, is the most potent among the ginkgo biloba extracts. Ginkgolide B possesses a highly complex molecular structure that includes six rings, eleven stereogenic centers, ten oxygenated carbons, and four contiguous fully substituted carbons.[25] The ginkgolides were first characterized in 1967, and the first syntheses were reported by Corey and co-workers in 1988.[26, 27] The Crimmins synthesis utilized zinc-copper homoenolate[28] and double diastereoselective intramolecular

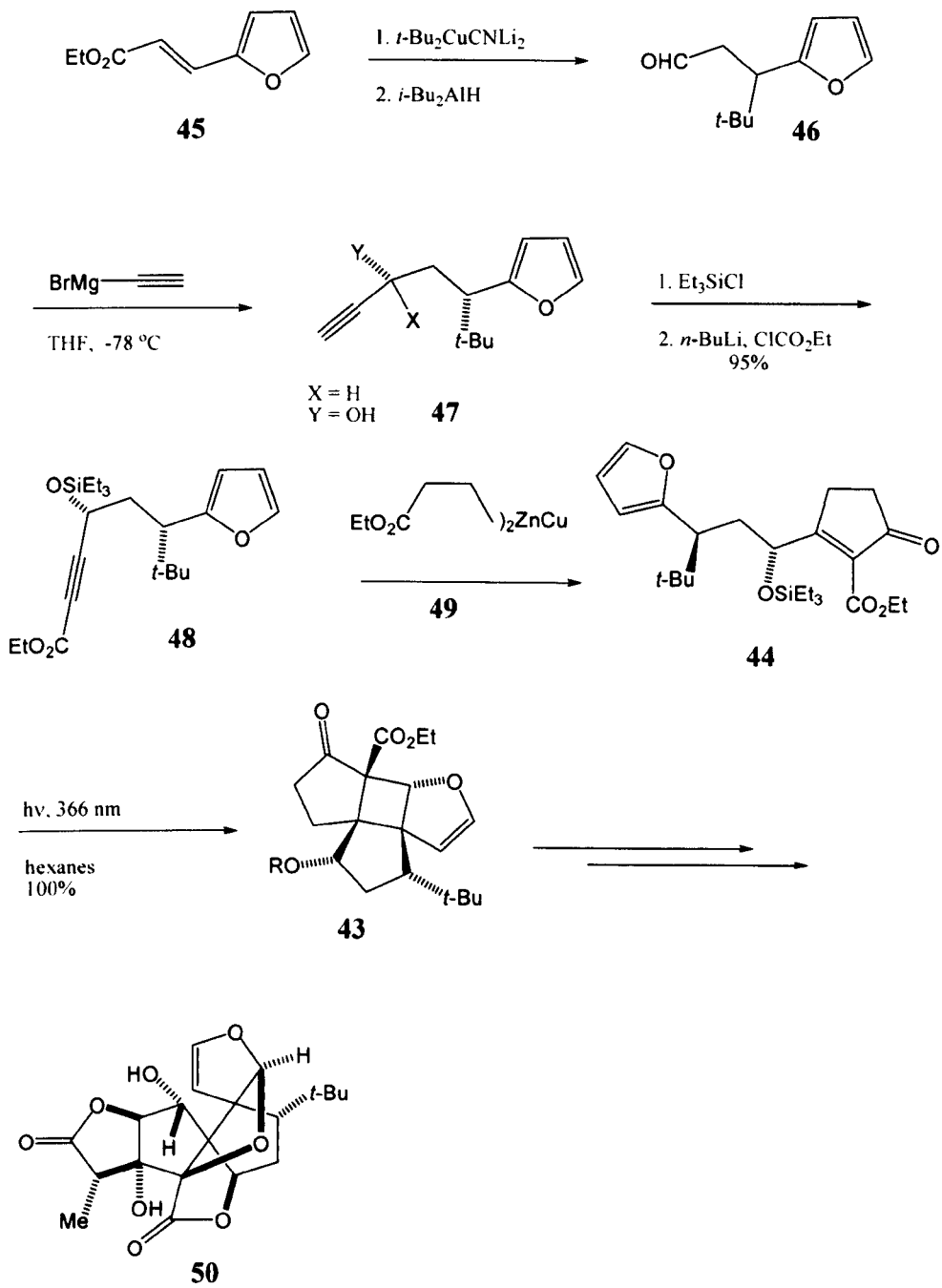
(the double diastereoselectivity was due to the presence of stereocenters at both of the reactive sites, which confer chirality to the product) [2+2] photocycloaddition[29] methodologies (**43**) for the total synthesis of ginkgolide B (**50**).



43 **44**

Scheme 1.18 Retrosynthetic view of enone-furan cycloaddition producing [2+2] adduct

The stereoselective intramolecular photocycloaddition was expected to provide the remote stereocontrol necessary to construct the complex core of the compound. The synthesis of the photocycloaddition adduct was accomplished by intramolecular [2+2] cycloaddition of the cyclopentenone and furan moieties of substrate **44**. The synthesis of **43** was initiated with the alkylation of **45** using a higher order cuprate to incorporate a *t*-butyl group into the furan sidechain (scheme 1.19). The resulting ester was then reduced with *i*-Bu_2AlH giving aldehyde **46** in 95% overall yield.



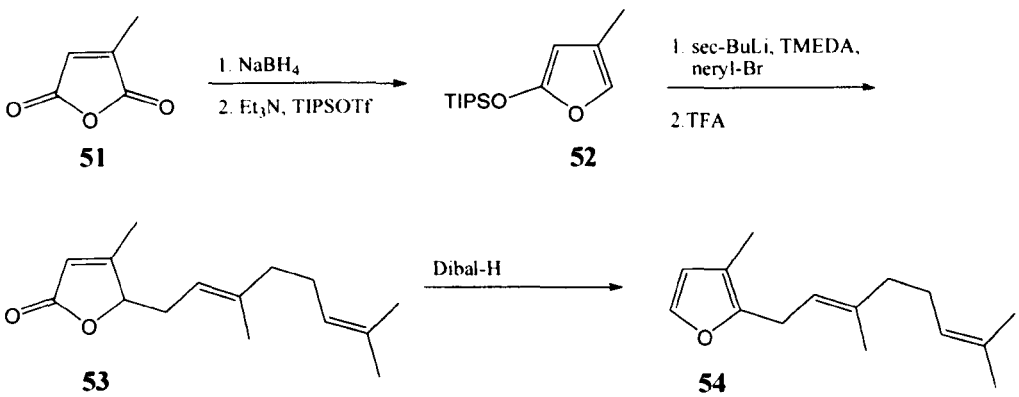
Scheme 1.19 Synthesis of Ginkgolide B

The addition of ethynylmagnesium bromide gave a 1.2:1 *syn/anti* isomeric ratio of acetylenic alcohol **47**. Following separation of the isomers, the undesired *anti* alcohol was converted to the *syn* isomer by Mitsunobu conversion. The alcohol was protected as its triethylsilyl ether , then the acetylene was carboxylated to produce acetylenic ester **48** in 95% yield. Addition of this compound to the homoenolate (**49**) produced an intermediate ketene acetal, which underwent intramolecular acylation to produce photosubstrate **44** in 82% yield. Irradiation of this enone in hexanes at 366 nm produced photocycloadduct **43** in quantitative yield and greater than 98:2 diastereoselectivity, thus establishing the two contiguous quaternary centres of the core skeleton of the compound. These conditions using furan as a partner in an intramolecular enone-olefin photocycloaddition provided the first reaction of its kind.[29] Following a further sequence of steps, the ginkgolide B (**50**) was generated in 52% yield.

Other established procedures stemming from readily available furan precursors include a method introduced by Vassilikogiannakis *et al.*[30] In 2001, the first synthesis of the newly isolated sesquiterpenes, the litseaverticillols, was published by Zhang and co-workers.[31] This family of natural products are potent and selective anti-HIV compounds. The litseaverticillols are isolated from the leaves and twigs of a perennial shrub, *Litsea verticillata* Hance, which grows in the Ninh Binh province of Vietnam.

It is known in phytochemistry that the three components in plant matter necessary for the promotion of singlet oxygen are air containing molecular dioxygen (20%), proliferation of photosensitizers such as chlorophyll, and high levels of visible spectrum light, which together promote the excitation of molecular

dioxygen to singlet oxygen. Once promoted, this highly reactive singlet oxygen can react with available double-bonded species, such as furan, resulting in the oxidative ring opening of furan. Vassilikogiannakis and co-workers proposed that litseaverticillols are the products of a cascade initiated with the aforementioned photochemical sequence. Thus, naturally occurring furans were expected to undergo a [4+2] cycloaddition with singlet oxygen initiating a cascade, affording the respective labile (*Z*)-1,4-enedione. This enedione could then undergo an intramolecular aldol reaction resulting in a mixture of geometric isomers, the first-generation litseaverticillols. The second-generation litseaverticillols could be synthesised through a second singlet oxygen addition *via* an ene reaction.

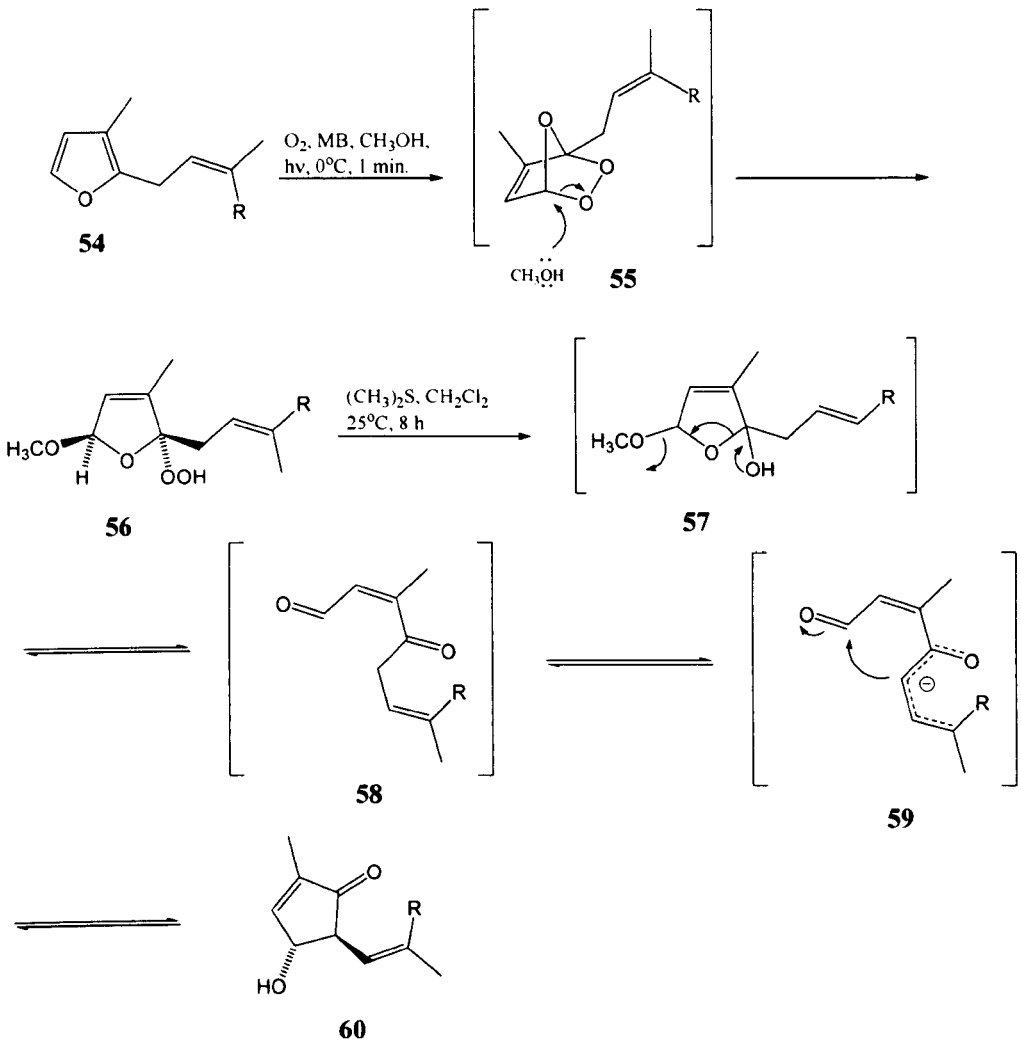


51 **52** **53** **54**

Scheme 1.20 Preparation of furan

Furan **54** was the precursor for this reaction. The synthesis began with the cheap, readily available citraconic anhydride **51**. The anhydride was converted into furan **52** by a two-step procedure, which begins with the sodium borohydride reduction to the corresponding diol, loss of water, and subsequent aromatisation, which, following TIPS-triflate protection, gave **52**. *Ortho*-metalation of **52** with

sec-butyllithium, quench of the resultant anion with neryl bromide, and *in-situ* hydrolysis of the TIPS ether assisted by TFA, produced lactone **53**. Reduction of the lactone with Dibal furnished the furan **54** in high yield.



Scheme 1.21 Singlet oxygen transformation of furan **54** into litseaverticillol B

Once furan **54** was generated, the synthesis of litseaverticillol B (**60**) was predicted to occur in a biomimetic fashion, as shown in scheme 1.21. Thus, furan **54** readily participated in a [4+2] cycloaddition with singlet oxygen by methylene

blue assisted photoexcitation of molecular dioxygen. Using methanol as solvent, this reaction proceeds through intermediate endoperoxide **55**, which was cleaved by the solvent to give hydroperoxide **56** quantitatively. The hydroperoxide was then reduced using excess dimethyl sulfide to a mixture of unstable diastereomeric hemiacetals (**57**), which ring opened with the elimination of methanol to give (*Z*)-1,4-enedione **58**. Base-induced intramolecular aldol reaction gave litseaverticillol B (**60**) directly accompanied by trace amounts (5%) of its diastereoisomer. It was determined that it was vital at this point not to leave the mixture for an excess period of time (>12 h) in the presence of Hünig's base because substantial amounts (15%) of the geometrical isomer are isolated from the mixture (figure 1.6). The other members of this family can thus be generated by the extension of the furan side chain, making this a valuable entry into an entire family of natural products.

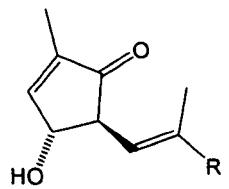
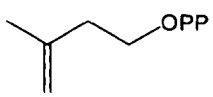


Figure 1.6 Unwanted geometrical isomer

1.3 Furan Predominance in Terpene Morphology

Terpenoids are a unique and versatile creation of nature. They possess a plethora of carbocyclic frameworks with unusual arrays of rings and functionalities. Owing to this immense structural diversity, they present a solid framework for developing and testing new synthetic methodologies. Furans are major constituents within the framework of these natural products.

Terpenoids constitute one of the largest groups of natural products as there are over 30,000 known compounds within this group. They are secondary metabolites that are non-nutritional, yet control biological activities within organisms. Some of these activities include animal metabolism, hormone production, and vitamin production. These can be found in most parts of all higher plants and animal species. They are biosynthesized from IPP (**61**) and DMAPP (**62**), which are pyrophosphate-containing isomers of one another, in organisms.[32]



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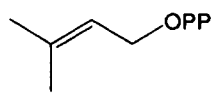

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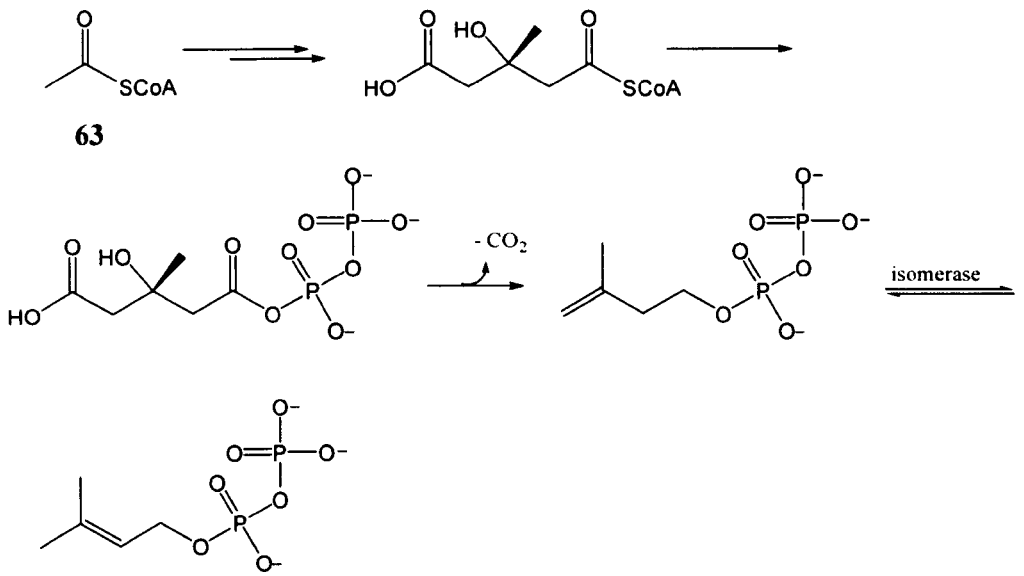
Figure 1.7 Structures of IPP and DMAPP respectively

IPP and DMAPP precursors are generated through the mevalonate pathway in animals, fungi, and archaea. Plants predominantly use the mevalonate pathway, but some plants and eubacteria have been found to utilize the deoxyxylulose-5-phosphate pathway. IPP and DMAPP are derived from acetyl-CoA (**63**) through the mevalonate pathway. The mechanism occurs *via* three acetate units, affording the five carbon atoms of IPP with the loss of one acetate carboxylic group as CO_2,

following ATP phosphorylation. Finally, DMAPP is generated from IPP by an isomerase (Scheme 1.22).



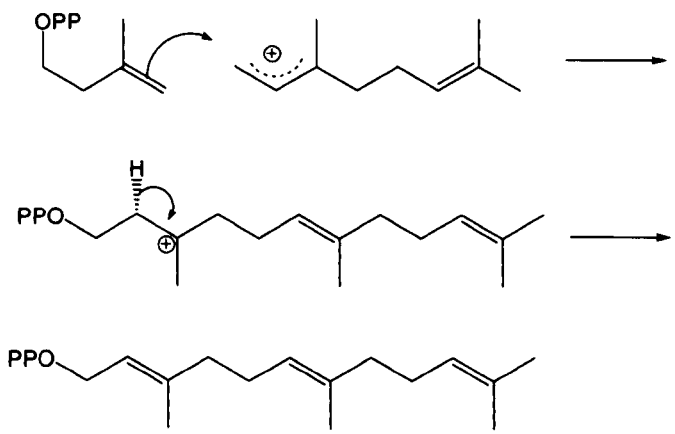
Scheme 1.22 Biosynthesis of DMAPP

Terpenes can be generally classified into seven different classifications based on their number of constituent carbons. They are classified as shown in table 1.1. The different groups are formed *via* different key intermediate precursors. Farnesyl pyrophosphate is the key intermediate in the biosynthesis of many sesquiterpenes.[33] Farnesyl pyrophosphate is formed by a condensation of isopentyl pyrophosphate with a geranyl carbocation in a head-to-tail fashion, ultimately leading to farnesyl pyrophosphate (**64**) as shown in scheme 1.23. The farnesyl pyrophosphate undergoes facile loss of the labile leaving group, pyrophosphate. The resulting farnesyl cation cyclizes by intramolecular nucleophilic attack on the cation, and

given the possibility of a range of rearrangements, the generation of the various sesquiterpenes is spawned.

Table 1.1 Classsification of terpenes

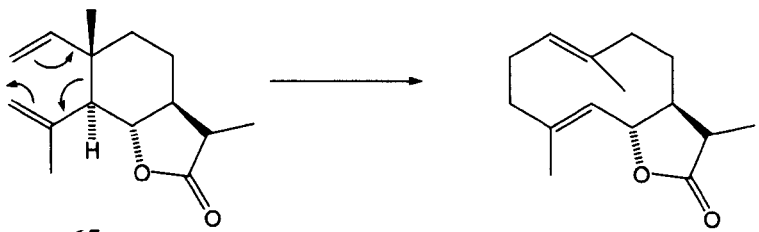
Carbon Units	CATEGORY
C-5	Hemiterpenes
C-10	Monoterpenes
C-15	Sesquiterpenes
C-20	Diterpenes
C-25	Sesterterpenes
C-30	Triterpenes (2 x C-15)
C-40	Tetraterpenes (2 x C-20)



64

Scheme 1.23 Biosynthesis of farnesyl pyrophosphate

Terpenes are interrelated within their respective families by allylic transpositions, oxidations, Wagner-Meerwein rearrangements, etc. Grieco[34] utilized the [3,3]-Cope rearrangement of dehydrosaussurea lactone (**65**) to generate germacranolide (+)-dihydrocostunolide (**66**) as shown in scheme 1.24.



65 **66**

Scheme 1.24 Synthesis of (+)-dihydrocostunolide

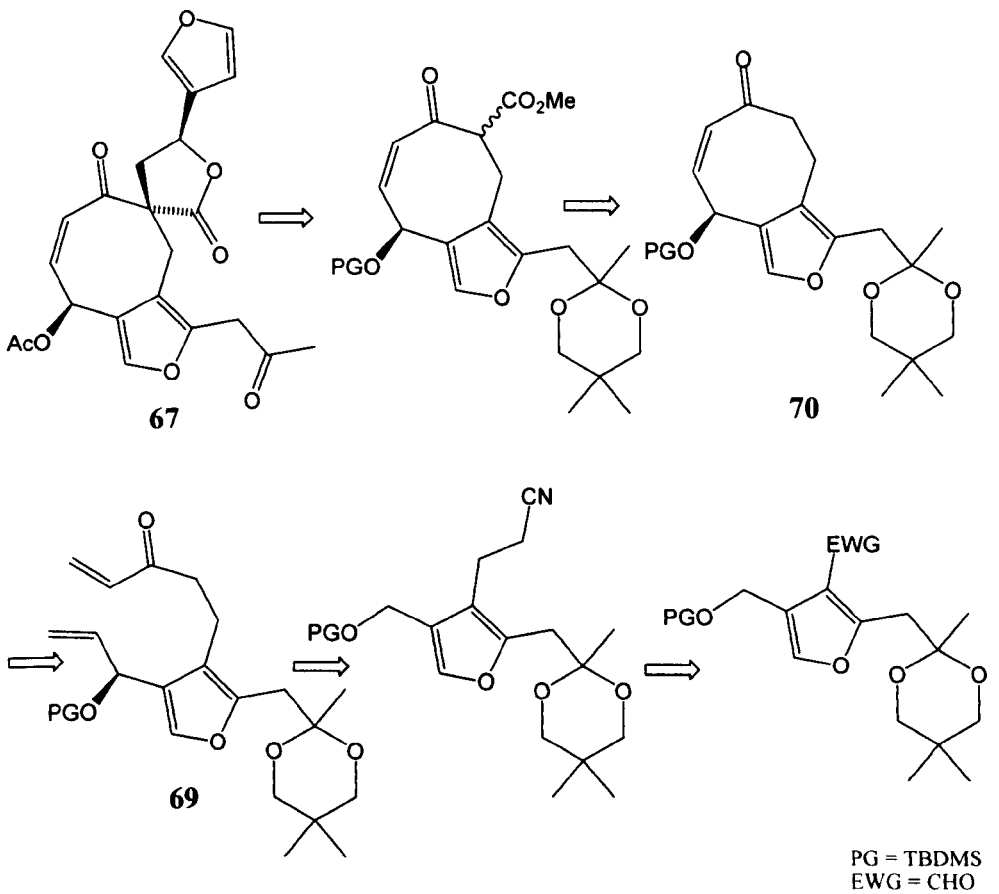
Dihydrocostunolide is of interest due to its 10-membered carbocyclic unit. The structure represents a possible biogenetic link between farnesol and other polycyclic sesquiterpenes, especially the guaianolide and eudesmanolide types.[35]

Novel approaches for the synthesis of the terpenes are necessary which rely on local, as well as remote, asymmetric induction for the assembly of these highly functionalised systems. Paquette and co-workers published the first total syntheses of *neo*-clerodanes, teubrevin G and teubrevin H.[36] The reported synthetic strategy relied on a highly stereoselective approach, and the synthesis of teubrevin G (**67**) is described below (see scheme 1.25).

Teubrevin G is a member of a small group of natural products, diterpenoid in structure, of the clerodane and *neo*-clerodane families, which were isolated by Rodriguez and co-workers[37] in 1995 from the aerial parts of the *Teucrium*

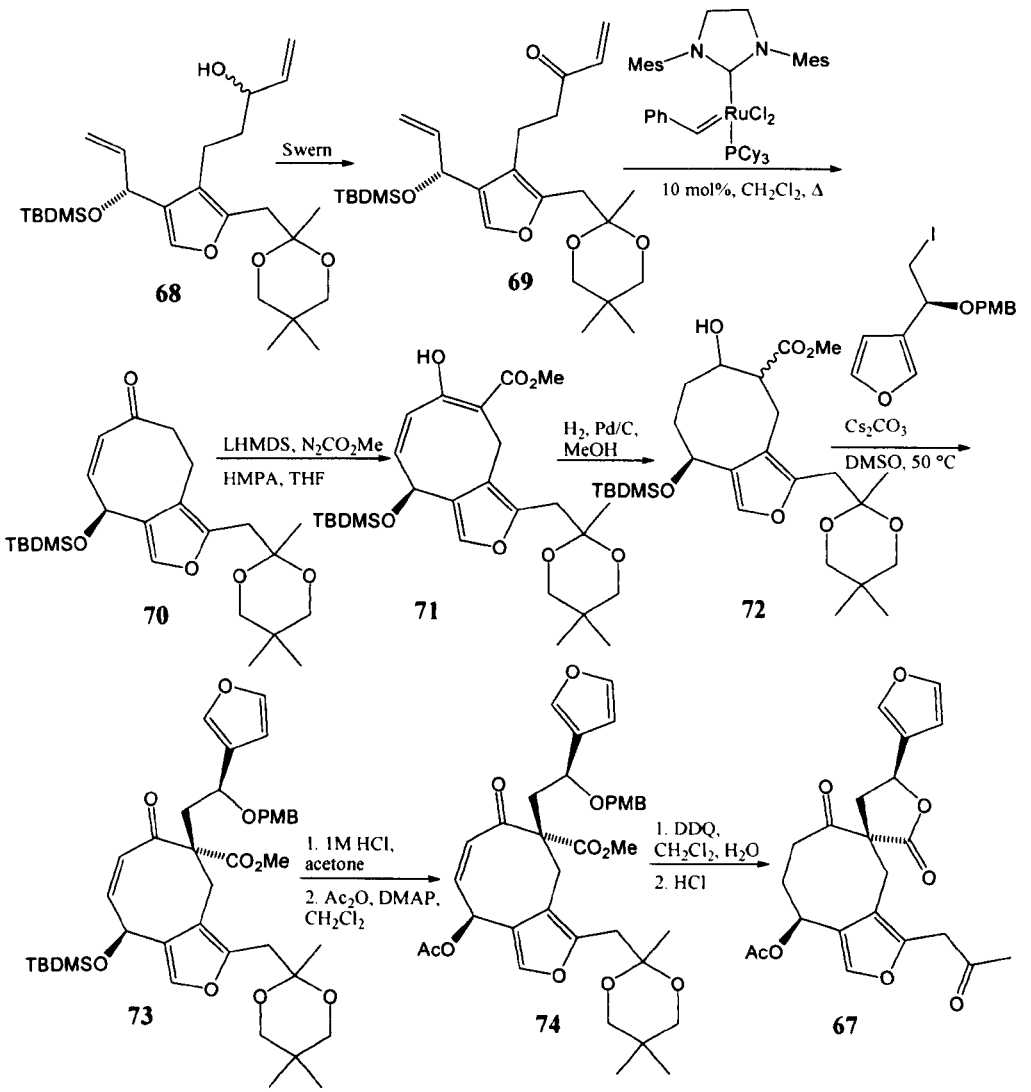
brevifolium plant. The teubrevins were of particular interest because they possessed a cyclooctanone core, fused and spiroannelated to smaller oxygen containing rings, rather than the conventional decalin framework of most of the members of this family.

A successful synthesis relied upon a synthetic route that would involve the difficult construction of the various rings, which would render the desired stereochemistry. The retrosynthesis entailed a pathway, which involved the synthesis of the spirolactone moiety concurrently with the formation of the desired stereocenters. The major steps included sterocontrolled alkylation, ring-closing metathesis, and synthesis of the trisubstituted furan.



Scheme 1.25 Retrosynthesis of teubrevin G

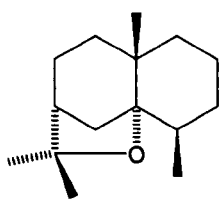
The synthesis of **67** was initiated with the generation of a chiral furan. Once this was subjected to Swern oxidation giving allylic ketone (**69**), the ring-closing olefin metathesis was performed. This was first attempted using the traditional Grubb's benzylidene catalyst, but as this catalyst only provided the carbocycle in very modest yield, greater success was realized using dimesitylimidazole substituted, ruthenium catalyst.



Scheme 1.26 Synthesis of teubrevin G

This gave the product in greater than 90% yield. C-acylation was achieved following deprotonation of the carboxyl α-proton and reaction of the resulting lithium enolate with methylcyanoformate giving **71**. After hydrogenation and stereocontrolled alkylation, the furan substituted **73** was generated. Acetylation and alcohol deprotection furnished teubrevin G (**67**).

Hydroxylated sesquiterpene ester synthesis provides an entry into the polyhydroxylated agarofurans based on the dihydroagarofuran skeleton (**75**). These polyols originate from plants of the *Celastraceae* family and are an essential source of hydroxylated sesquiterpene esters.[38] These compounds have generated a good deal of interest based on their cytotoxic, antitumour, immunosuppressive, and insect antifeedant activities. Esters of 3,4-dideoxymaytol are some of the most commonly encountered derivatives of **75** among the Celastraceous sesquiterpenes These substances are isolated from the leaves and twigs of the shrub *Catha edulis* and are present in the drug, khat, which is widely used in East Africa for its appetite-suppressant and euphoriant properties.

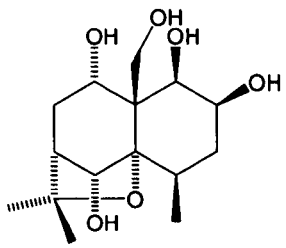


75

Figure 1.8 Dihydroagarofuran skeleton

White and co-workers performed the synthesis of (±)-3,4-dideoxymaytol and

(±)-euonyminol, the sesquiterpenoid core of several cathedulins, using a strategy based on a cascade cyclization to establish the dihydroagarofuran core of these cathedulin compounds. (±)-3,4-Dideoxmaytol and (±)-euonyminol were of synthetic interest as these compounds contain five and nine hydroxyl groups, respectively, and represent the two extreme degrees of hydroxylation within this class of compounds.



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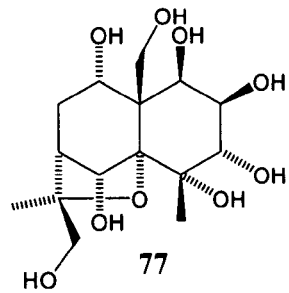
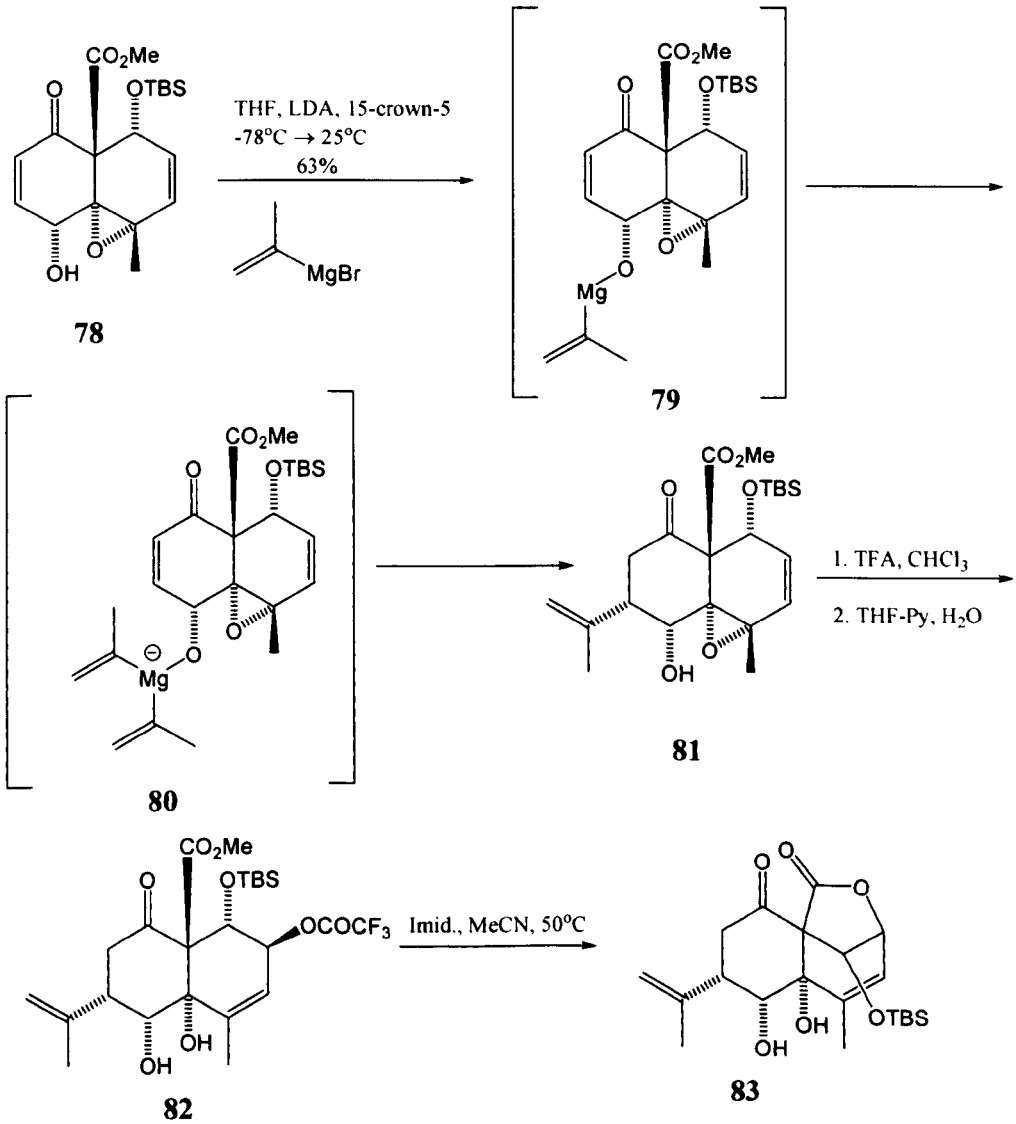


77

Figure 1.9 (±)-3,4-Dideoxymaytol (**76**) and (±)-euonyminol (**77**)

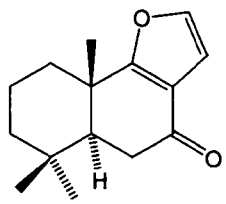
Therefore, the structures of the other members of this group could be synthesized, in principal, by modifications of the pathways leading to these two compounds. The synthetic approach is based on the initial construction of the tetrahydrofuran portion of these compounds. Compound **78** was synthesized following a sequence of steps *en route* to (±)-dideoxymaytol. Compound **81** was formed in good yield following treatment of **78** with lithium diisopropylamide, then with 15-crown-5, and finally with isopropenylmagnesium bromide. This reaction sequence was undertaken to ensure that an equilibrium would be established in which the binary complex **79** would be forced towards the more reactive ternary ate complex **80**. This latter species is believed to be responsible for the stereoselective intramolecular transfer

of the isoprenyl group to the β carbon for the conjugate addition. Treatment of **81** with trifluoroacetic acid generated the hydroxy trifluoroacetate **82** from an *anti* S_N2' opening of the allylic epoxide. The trifluoroacetate was then hydrolysed to the hydroxy ester, which underwent facile lactonization to **83** under imidazole catalysis. Further transformations led to the target (±)-3,4-dideoxymaytol (**76**).



.Scheme 1.27 Synthetic route to (±)-dideoxymaytol

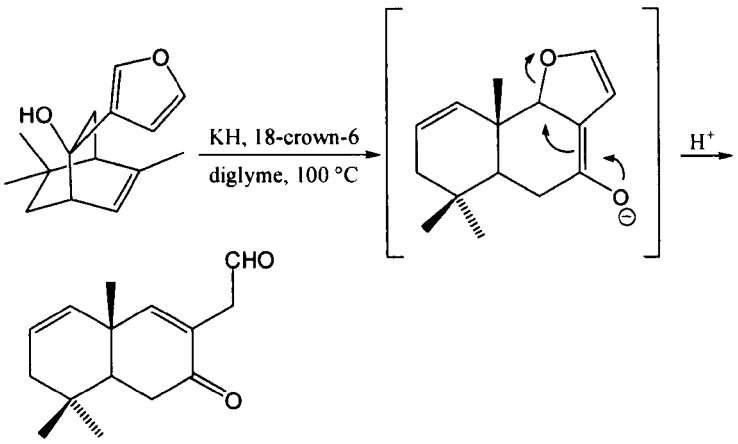
Furanosesquiterpenes of unusual skeletal types are also of interest as they may provide further insight into the biosynthesis of terpenes. (+)-Pallescencin A (**84**) is an example of a sesquiterpene that is constituted of a new skeletal type, because it is not of mono-cyclofarnesane origin as are the usual sesquiterpenes. Pallescensin A is a marine metabolite and was first isolated in 1975 from the sponge *Disidera pallescens* by Cimino and co-workers.[39] It was synthesised by Paquette and co-workers using regioselective and stereoselective pathways.[40]



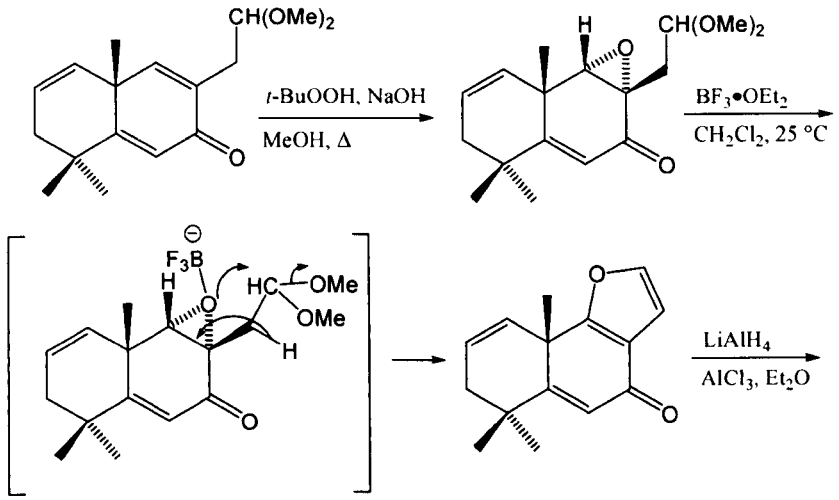
84

Figure 1.10 (+)-Pallescensin A

The enantioselective route chosen by Paquette involved an anionic oxy-Cope rearrangement promoted by 18-crown-6 and potassium hydride, which provided the desired intermediate bicyclo-dicarbonyl species (scheme 1.28). Following a short sequence of transformations, the reaction sequence of scheme 1.29 was undertaken. Regioselective *t*-butyl hydroperoxide epoxidation was followed by boron trifluoride etherate catalysed formation of furan, which was expected to occur by the suggested mechanism in scheme 1.29. Once the carbonyl group was reduced with lithium aluminium hydride, catalytic hydrogenation in the presence of diethylamine gave the title compound (**84**).



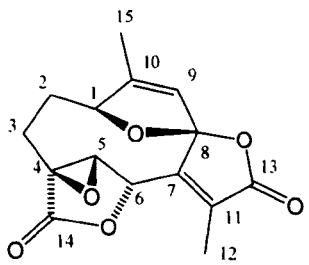
Scheme 1.28 Synthesis of dicarbonyl intermediate



Scheme 1.29 Synthesis of (+)-pallescensin A

1.4 Neoliacine Background

Neoliacine **84**, a germacranolide dilactone sesquiterpene, was isolated from the *Neolitsea acciculata* Koidz leaves of the Lauraceae plant family in 1983 by Takaoka and co-workers in Japan. It has been generated as an oxidation product from the sesquiterpene, zeylanidine (figure 1.12)[41], of the *Neolitsea zeylanica* plant, as the furan ring of furanogermacranolide sesquiterpenes are very susceptible to oxidation if dissolved in solvents such as chloroform, but to date, there is no total synthesis of this compound.



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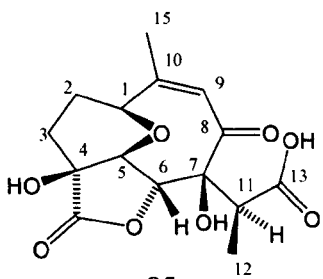

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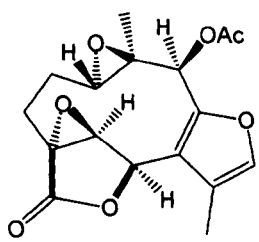
Figure 1.11 Structures and numbering of neoliacine and neoliacinic acid



Zeylanidine

Figure 1.12 Zeylanidine structure

Its biological metabolite, neoliacinic acid[42] **85** has been found to exhibit moderate cytotoxicity in the HeLa cell culture[43] *in vitro*. X-ray crystal structure, spectral, and chemical transformation analysis were used to elucidate the structures in figure 1.11.[44]

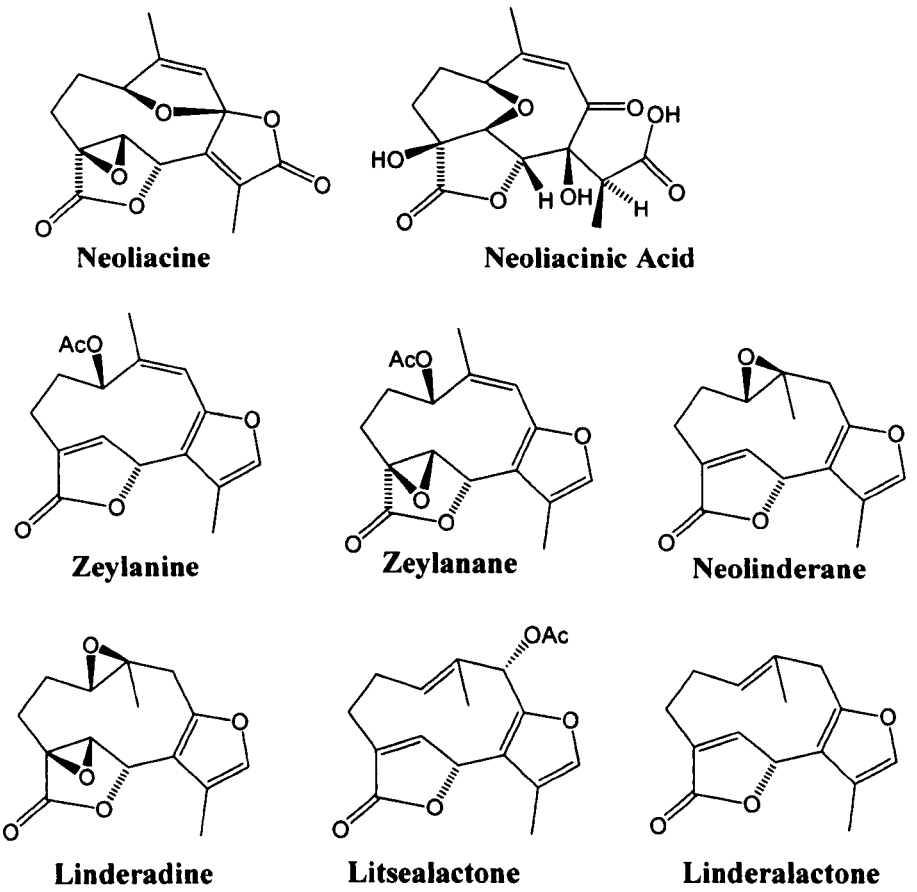


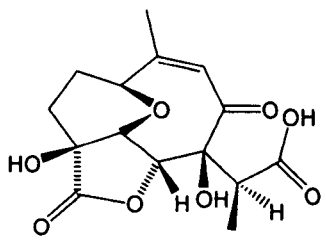
Figure 1.13 Members of the *Neolitsea acciculata* Koidz plant family

The various members of the *N. acciculata* plant family (see figure 1.13) are interrelated by Wagner-Meerwein rearrangements, allylic transpositions, acetylations, Cope rearrangements, etc. Therefore, it is possible to approach the synthesis of the neoliacine compound by going through one of its corresponding

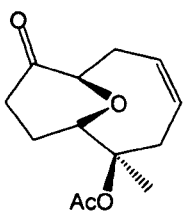
family members in a biomimetic synthetic approach.

Moreover, Clark and co-workers[45] have approached the synthesis of the 10-membered carbocyclic core of neoliacinic acid using stereoselective metal carbenoid methodology to generate structure **86**. The overall approach involved oxonium ylide formation and [2,3]-sigmatropic ring-expansion utilizing a metal carbenoid catalytically generated from an α-diazo ketone **90**, then to construct the tetrahydrofuran nucleus present in the α-diazo ketone **90** by intramolecular C-H insertion of the generated metal carbenoid from the acyclic α-diazo ketone.

The synthesis of model system **86** was initiated with starting material (*R*)-isopropylideneglyceraldehyde. The aldehyde **87** was treated with a Grignard reagent prepared from 3-bromopropanol *p*-methoxybenzyl ether giving a diastereomeric mixture of alcohols (4:1 ratio) which was converted into the allyl ether **88**. The acetonide protecting group was hydrolysed to the 1,2-diol, then cleaved with sodium periodate affording aldehyde **89** in high yield.



85

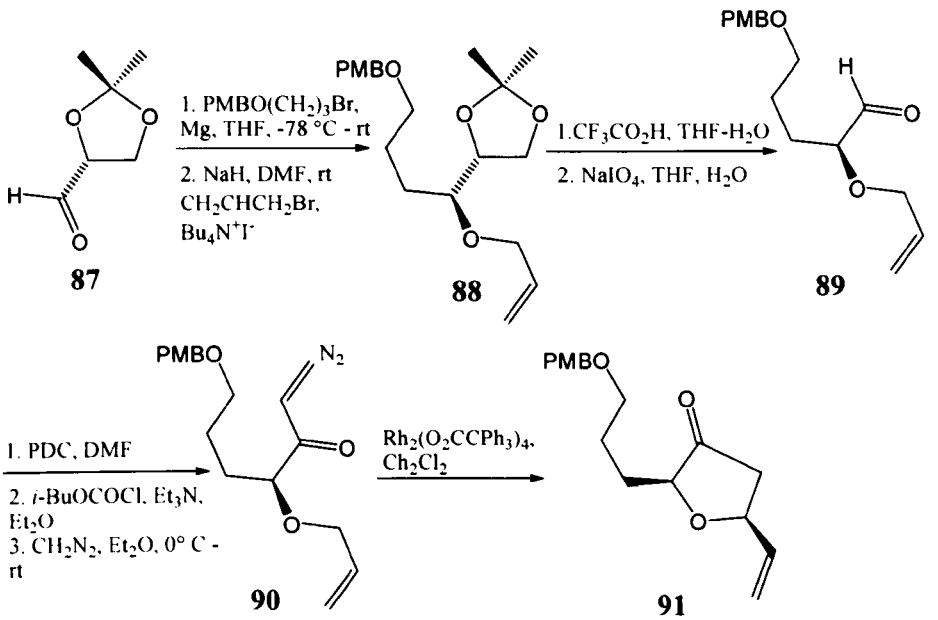


86

Figure 1.14 Neoliacinic acid and its bicyclic core model respectively

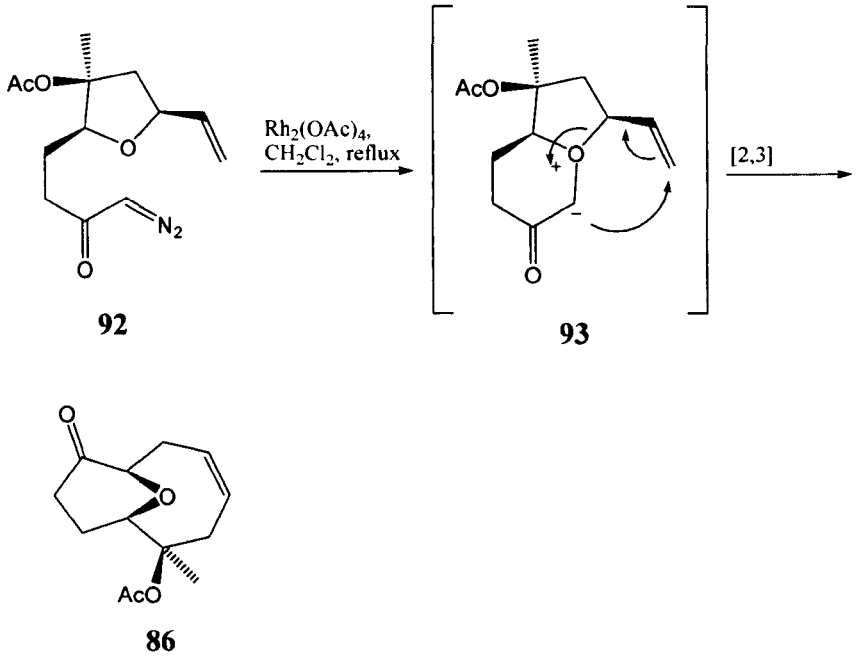
This aldehyde was oxidized to the carboxylic acid using PDC. Converting the carboxylic acid into the mixed anhydride by reaction with isobutyl chloroformate

generated the α-diazo ketone **90**. This was followed by treatment of the anhydride with excess diazomethane to give the diazo ketone. The furanone **91** was then constructed by intramolecular C-H insertion of the carbenoid derived from **90**.



Scheme 1.30 Construction of furanone **91**

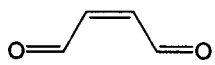
The diazo ketone was treated with a rhodium (II) complex, $Rh_2(TPA)_4$, in dichloromethane to give **91** in 65% yield. Following a sequence of steps, a second α-diazo ketone was generated giving **92**. The final step of the synthesis involved the metal catalysed tandem oxonium ylide formation and rearrangement of the diazo ketone **92**, giving the cyclization product with concomitant ring-expansion of the vinyl tetrahydrofuran (scheme 1.31).



Scheme 1.31 Synthesis of carbocyclic model **86**

1.5 Latent 1,4 Dicarbonyl Species

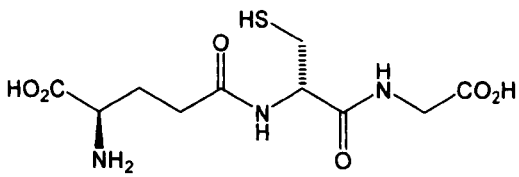
Cis-2-butene-1,4-dial (**94**) is an active metabolite of furan. This compound has important commercial uses in food and is also found in cigarette smoke.[46] This unsaturated aldehyde readily reacts with nucleophilic sites in proteins and nuclear bases such as glutathione within the body, thus causing DNA damage. Glutathione[47] is a tripeptide present in all tissues which consists of glutamic acid, cysteine, and glycine.



94

Figure 1.15 Butenedial

Its role is to protect the body against oxidizing agents and foreign chemicals, and it is also a cofactor for many dehydrogenases. It can react through Michael addition to the oxidant, which results in the formation of the corresponding conjugate addition product. Conversely, it can behave as a carbonyl group reducing agent, thereby giving the corresponding diol of substrate **94** and its corresponding glutathione disulfide (figure 1.17). When dial **94** works as an electrophile scavenger within the body, it reacts by electrophilic addition to the thiol group of the glutathione cysteine functionality by 1,4-addition.



Glutathione

Figure 1.16 Glutathione structure

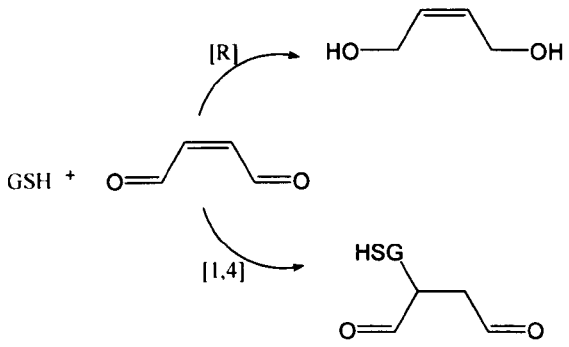


Figure 1.17 Alternate glutathione reaction pathways

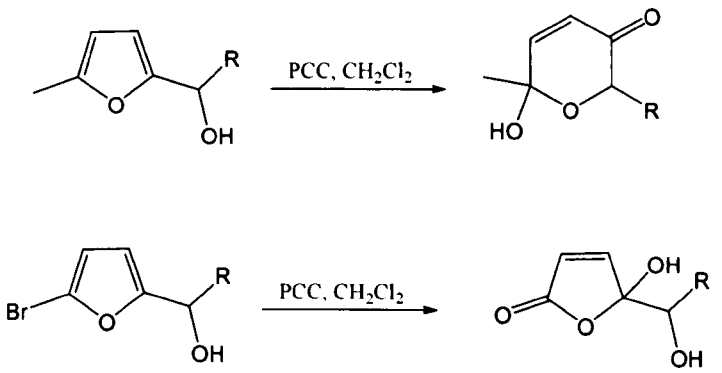
Thus, substituted dicarbonyl analogs can also serve as useful selective cytotoxic agents for pharmaceutical purposes.

Due to the reactivity of 1,4-dicarbonyl species, they also play a role as key precursors to important natural products and other pharmacologically active materials.[48] Furan ring opening is a popular synthetic route to these compounds.

Furan ring opening can be effected by a large variety of methods. These methods involve either acid catalysed or oxidative ring opening. The unmasking of the enedicarbonyl functionality can open the pathway to a range of targets for the synthesis of complex products. Furan compounds are rather sensitive to acids and oxidants due to their electronic properties and their intermediates can be metamorphosed into such structures as butenolides, cyclopentenones, butyrolactones, pyrans, etc.[49] Scheme 1.32 illustrates the transformations of furylcarbinols and bromofurylcarbinols to pyranones and butenolides.

Furans are sensitive to acidic conditions because they are weakly aromatic compounds; therefore, the oxygen heteroatom increases the electron density of the carbon atoms on the ring and makes these compounds sensitive to electrophiles. Furans containing electron-donating substituents are unstable to protic acids, with

protonation occurring readily at the *ortho*-position. Alkyl furans in particular are quite sensitive to mineral acids, therefore care must be taken with the conditions employed, otherwise extensive ring cleavage or polymerization is possible. Furans containing electron-withdrawing substituents are more resistant to these conditions and are less prone to unwanted by-products.



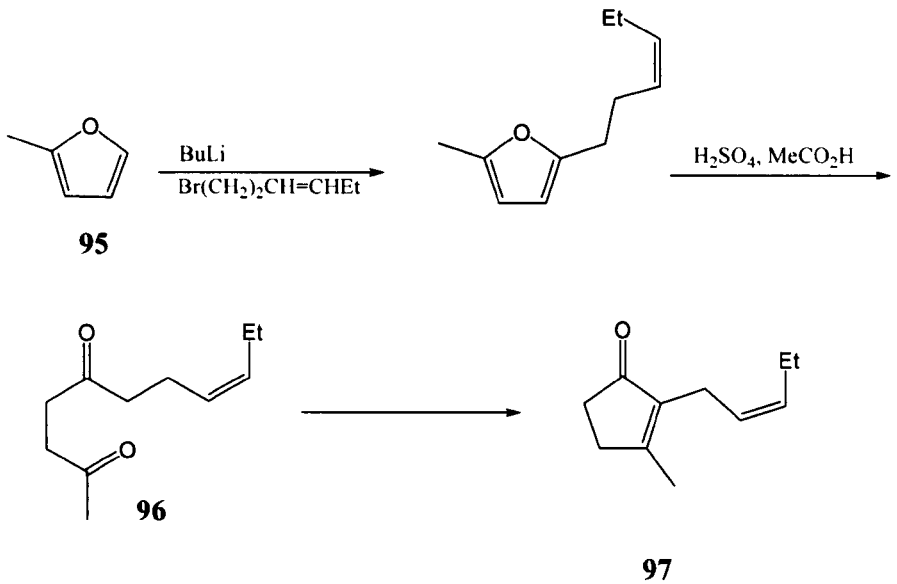
R = $-CH_3$, $-CH_2CH{=}CH_2$, $-CH_2(CH_2)_4CH_3$

Scheme 1.32 Transformation of furylcarbinols to pyranones and butenolides

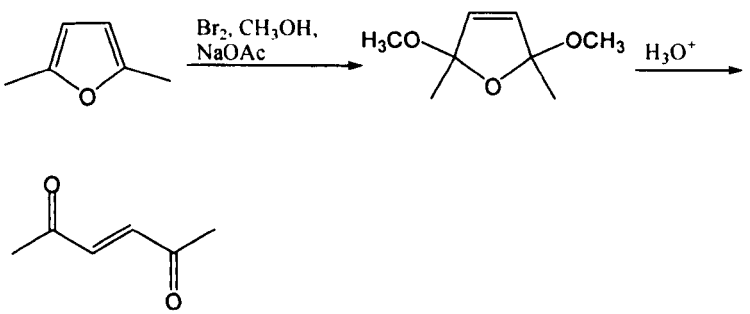
Acidic hydrolysis of furans has been applied towards the synthesis of jasmanoids and prostanoids by Crombie and co-workers.[50] Scheme 1.33 details the Crombie synthesis of *cis*-jasmone **97** from 2-methyl furan **95**. This procedure was initiated with furan *ortho*-lithiation using *n*-butyllithium followed by electrophilic addition. Hydrolysis of the substituted furan gave the 1,4-dicarbonyl species. After further steps, the cyclopentenone, *cis*-jasmone was generated.

Furan rings are also very sensitive to oxidants due to their electron rich character. Methods successfully used for the cleavage include the classical bromine induced oxidation (scheme 1.34),[51] electrochemical oxidation,[52] photosensitised

oxygenation,[53] hydrogen peroxide oxidation,[54] pyridinium chlorochromate oxidation,[49] sodium hypochlorite oxidation,[55] and *tert*-butylhydroperoxide oxidation.[56] There are many methods, but many of them suffer from disadvantages such as contamination with undesired *trans*-isomers, requirement of further steps following oxidation, non-regioselectivity, or requirement for special equipment.

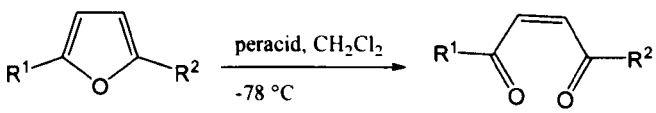


Scheme 1.33 Synthesis of *cis*-jasmone



Scheme 1.34 Oxidative bromination of furan giving enedione

Peracid oxidation of furans is one of the most common methods used for oxidative ring opening as it is a relatively mild method. Sato and co-workers[57] used *meta*-chloroperoxybenzoic acid and peracetic acid to oxidatively cleave 2,5-disubstituted furans to *cis*-1,2-diacylethylenes, a reaction applied to the synthesis of prostaglandins and rethrolones (scheme 1.35). This method was found to oxidize the substituted furans, even in the presence of labile groups, such as the trimethylsilyl group, at the C-3 position.

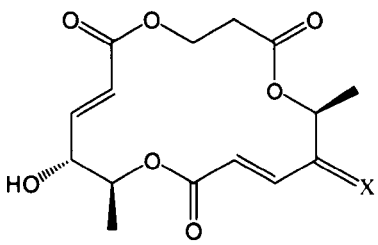


R^1 = CH_3, *n*-C_4H_9, *n*-C_3H_7
R^2 = Ph, *n*-C_4H_9, *n*-C_6H_{13}, *i*-C_3H_7, C_2H_5

Scheme 1.35 Peracid oxidation of furan

Kobayashi and co-workers[58] have reported a furan ring oxidation strategy applied towards the synthesis of macrosphelides A and B. Their protocol called for the conversion of 2-substituted furans into 4-oxo-2-alkenoic acids using N-bromosuccinimide (scheme 1.36) to oxidize the furan to the corresponding dicarbonyl compound followed by a second oxidation using sodium chlorite to oxidize the aldehyde functionality to carboxylic acid. This oxidative conversion reportedly proceeded under mild conditions and is compatible with functional groups such as carbonyl groups, acid labile protecting groups, and free hydroxyl groups at distal positions. As such, this method provided a relevant pathway for biologically active molecules containing 4-hydroxy-2-alkenoic acid moieties,

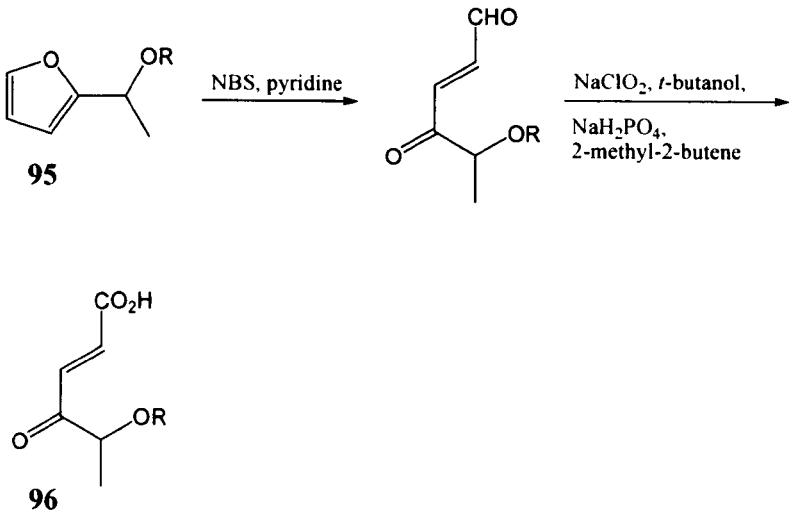
which constitute the major part of the lactone backbones (see figure 1.18). These macrosphelide natural products strongly inhibit the adhesion of human leukaemia HL-60 cells to human-umbilical-vein endothelial cells.



Macrosphelide A: X=H,OH
Macrosphelide B: X=O

Figure 1.18 Macrosphelides A and B

Furan **95** was used as the major intermediate for the macrosphelide synthesis. The distal alcohol was protected with a range of protecting groups (R = THP, MOM, PMB). Then, the furan ring was oxidatively cleaved to its corresponding enedial using N-bromosuccinimide. The aldehyde oxidation step resulting in the γ-keto acid **96** was performed using sodium chlorite giving overall yields of 52-60%.



Scheme 1.36 NBS oxidation of furan

1.6 Dicarbonyl Oxidation

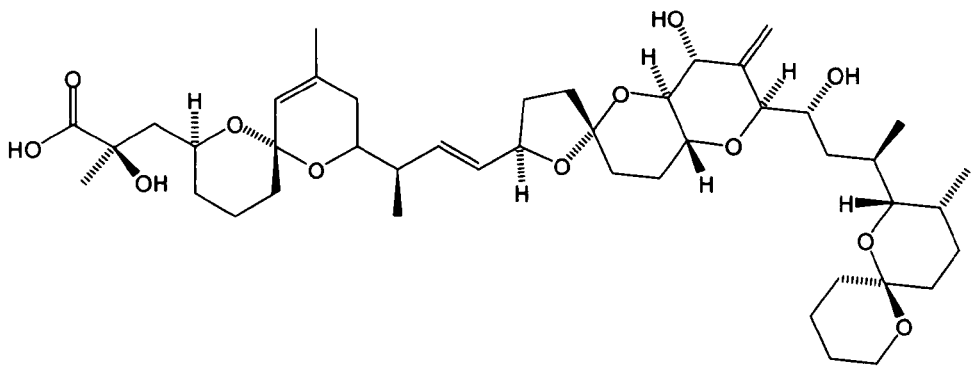
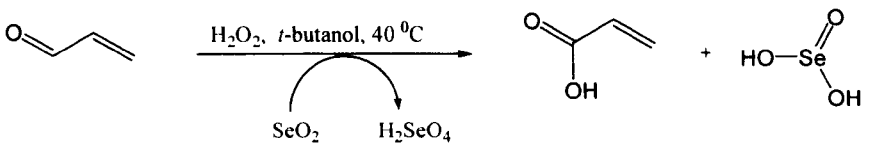


Figure 1.18 Okadaic acid

The spiroketal moiety is type of acetal which is found in many natural products ranging from insect pheromones to chemically complex systems such as monensin, okadaic acid (figure 1.18),[59] and the avermectin family of antibiotics. This moiety is also found in the natural product of interest, neoliacine. A common approach towards the structure of these structures involves furan oxidation methodology.[60] The sequence would involve the reaction of the 1,4-enedicarbonyl species generated from the furan precursor. Applied functional group interconversion could convert the aldehyde functionality to its corresponding acid, and subsequent ring-closing cascade could transform the dicarbonyl to the desired spiroketal lactone species.

A variety of methods exist for the conversion of α,β-unsaturated aldehydes to their corresponding acids. Oxidizing agents such as Jones reagent, potassium permanganate, silver oxide, and sodium hypochlorite are used among other reagents for this conversion. Unfortunately, many classical methods incorporate conditions that are too harsh for the transformations of sensitive compounds.[61] For

example, the traditional method applied to convert aldehyde to acid utilizing alkaline silver(I) oxide is not appropriate for α,β-unsaturated aldehydes because a high degree of *cis-trans* isomerization and other base-catalysed side reactions can occur in the process.

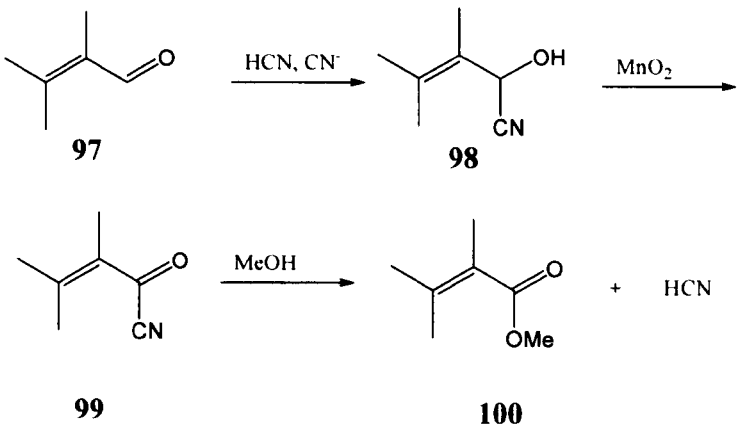


Scheme 1.37 Selenium dioxide oxidation of α,β-unsaturated aldehyde

Smith and co-workers implemented a novel method using selenium dioxide as catalyst in conjunction with hydrogen peroxide as a system for oxidation of acrolein and methacrolein to their corresponding acrylic and methacrylic acids.[62] Under the conditions used for the conversion of acrolein to acrylic acid, selenium is used in catalytic quantities (4.5 mol%) with hydrogen peroxide, and the active oxidation species, selenic acid, was generated by the oxidation of selenium dioxide by hydrogen peroxide. The selenium dioxide was mixed with the aldehyde substrate in 1:1 molar ratio, giving the corresponding acid product in 90% yield. They also found that it was necessary to use tertiary alcohol (*tert*-butanol or *tert*-amyl alcohols) in order to avoid the conversion of the acid to its corresponding ester. The conditions and the results for the methyacrylate were found to be analogous giving a yield of 93% for the acid conversion.

Corey and co-workers[63] devised a method for the stereospecific conversion of unsaturated alcohols to their respective esters under mild conditions *en route* to the synthesis of an insect juvenile hormone using manganese dioxide. They found that

this method only proceeded to the aldehyde oxidation level. Therefore, in the process of preparing these compounds, they also experimented with the idea of converting unsaturated aldehydes to their corresponding acids in the presence of cyanide/sodium cyanide following the sequence in scheme 1.38.

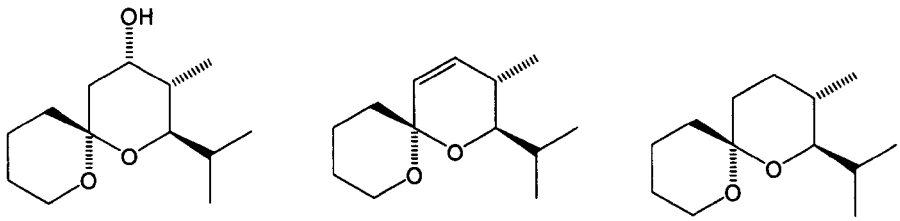


Scheme 1.38 Cyanohydrin intermediate based aldehyde oxidation to acid

Aldehyde **97** represents a range of aldehydes used for the conversion to their corresponding methyl esters. The aldehydes and representative yields involved are given as follows: benzaldehyde (>95%), cinnamaldehyde (>95%), furfural (>95%), geranial (85-95%), and farnesal (95%). Each of these compounds were mixed in a methanolic solution of sodium cyanide, acetic acid, and manganese dioxide. The reaction was predicted to proceed through initial formation of the cyanohydrin following nucleophilic attack on the aldehyde by the cyanide giving intermediate **98**. Subsequent oxidation of the complex gave intermediate **99**. Methanolysis of **99** gave the methyl ester product **100** in high yield in all cases using α,β-unsaturated aldehydes.

1.7 Spiroketalization

DeShong and co-workers devised a stereoselective approach towards spiroketals *en route* to the avermectin / milbemycin family of antibiotics[60]. The avermectins and milbemcyins are broad-spectrum antiparasitic and insecticidal agents. They consist of a 16-membered lactone system consisting of a mono or bicyclic portion and a functionalized 6,6-spiroketal (figure 1.20).



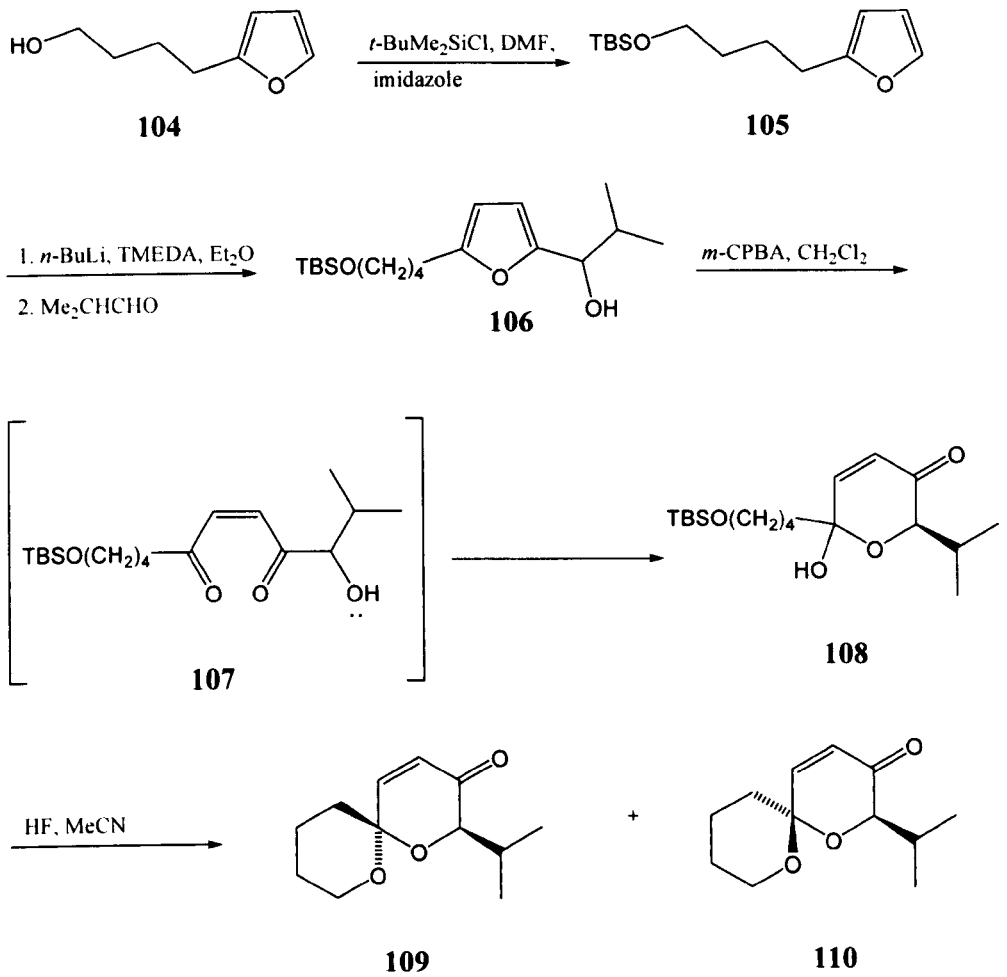
101 **102** **103**

Figure 1.20 Model systems for spiroketal moieties of avermectins / milbemycins

The synthesis of the spiroketal lactone moiety began with the TBS silylation of furylbutanol **104** (scheme 1.39). The furan was *ortho*-metallated followed by condensation with isobutyraldehyde, affording furylalcohol **106**. Oxidation of the furan moiety with *m*-CPBA gave the 1,4-dicarbonyl intermediate **107**, which underwent an intramolecular, nucleophilic ring closure providing pyranone **108** in 90% yield. ^{1}H NMR spectroscopy of the pyranone indicated that this compound existed as a single diastereoisomer, however, the stereochemistry at the anomeric center was not determined.

Pyranone **108** was treated with hydrofluoric acid to de-protect the TBS alcohol. Alcohol de-protection initiated a ring-closing cascade (scheme 1.40). This cascade

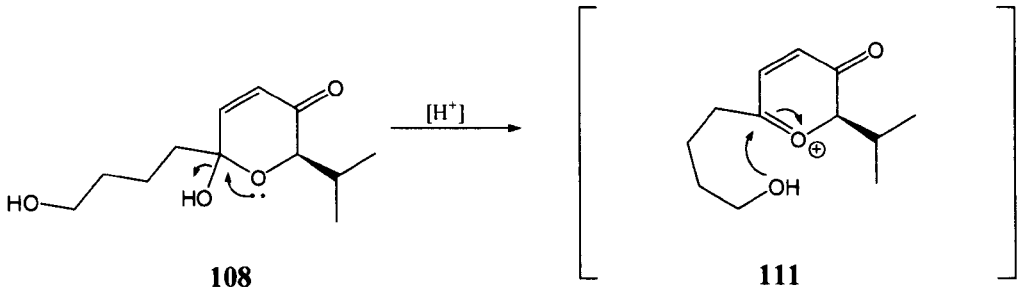
afforded the spiroketals **109** and **110** in a combined yield of 96%. The ratio of **109:110** was 95:5. The stereochemical assignment of these compounds was confirmed by subsequent transformations of the spiroketals.



Scheme 1.39 Synthesis of 6,6-spiroketal lactones

Spiroketalization can also be achieved following reaction of furyllithiums with lactones. Albizati and co-workers[64] developed this method, which involved a convergent, two-step process to generate the spiroketal (scheme 1.35). This

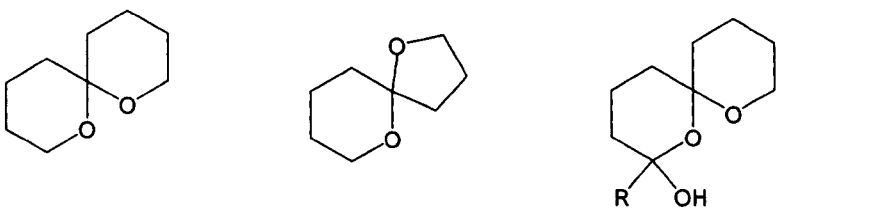
synthetic route provided entry into the synthesis of three spiroketal types (figure 1.21).



108 **111**

Scheme 1.40 Spiroketal ring-closing cascade

Spiroketal **114**, which was oxidized at the C2-position, was the representative target of this methodology. Important natural products containing this functional arrangement are the aplysiatoxin-oscillatoxin metabolites of marine blue-green algae and the trioxadispiroketal-containing polyethers salinomycin, narasin, and their analogues.

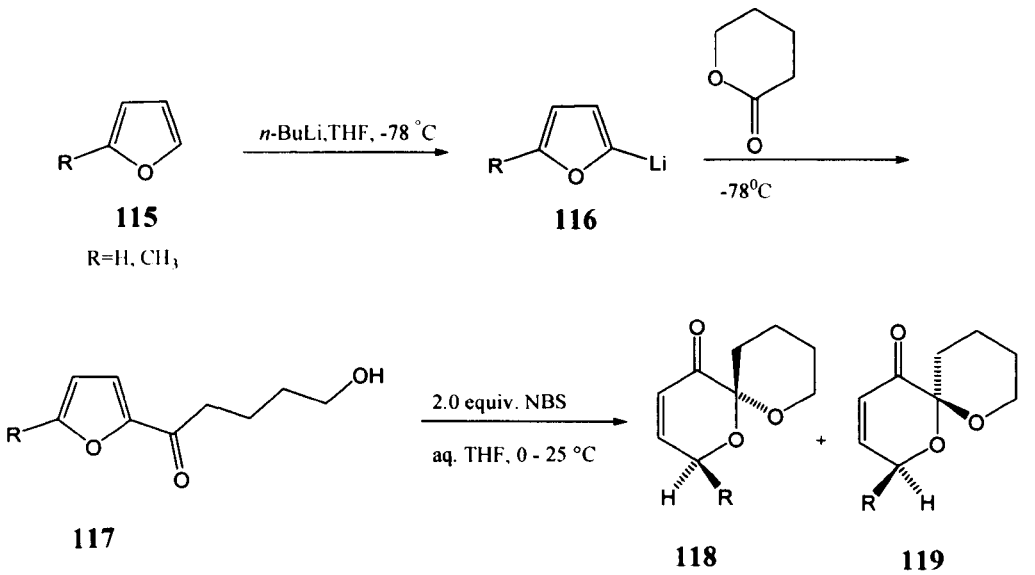


R=remainder of natural product

112 **113** **114**

Figure 1.21 Representation of 6,6 and 6,5 spiroketal types

The spiroketal synthesis began with the *n*-butyllithium lithiation of furan **115**. The furyllithium was treated with δ-valerolactone producing monoaddition product **117** in 50% and 62% yield for R-substituents –CH_3 and –H respectively.



Scheme 1.41 6,6-Spiroketal synthesis

Various amounts of the double addition by-product were observed with no trace of the ring-closed spiroketal form of the hydroxy ketone. When mono-addition product **117** was subjected to two equivalents of N-bromosuccinimide in aqueous THF, spiroketals **118** and **119** (diastereomeric ratio 5:1) were generated in good yield (51% and 60% for –CH_3 and –H substituents respectively).

Chapter 2

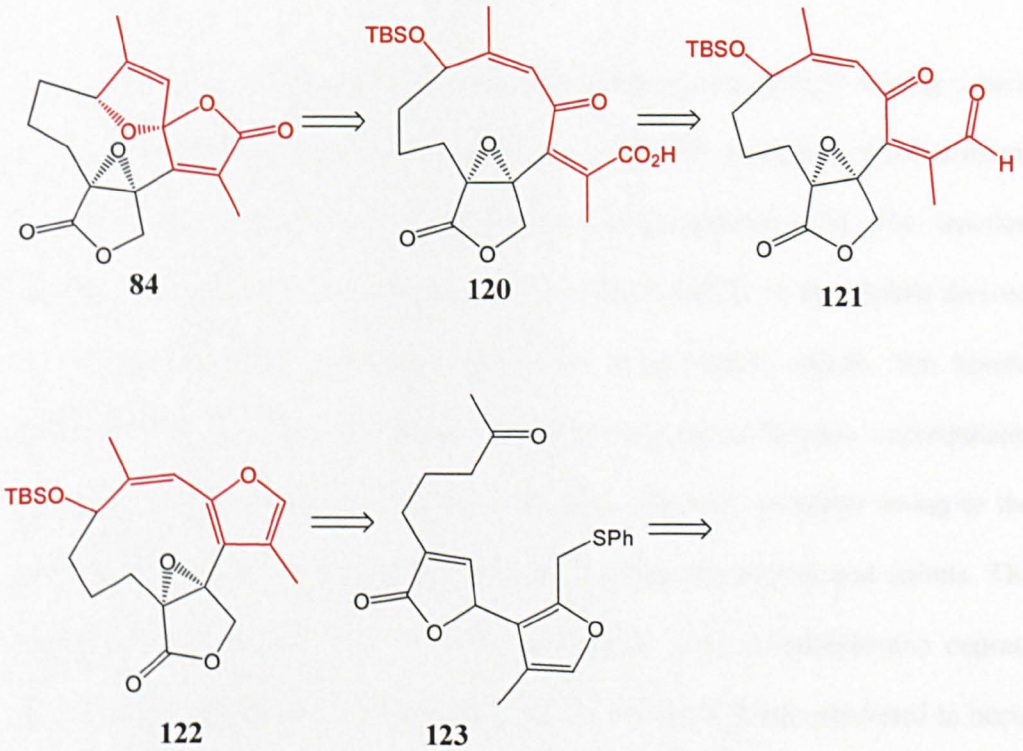
SYNTHETIC APPROACHES TO SPIROKETAL MODEL

Chapter 2

SYNTHETIC APPROACHES TO SPIROKETAL MODEL

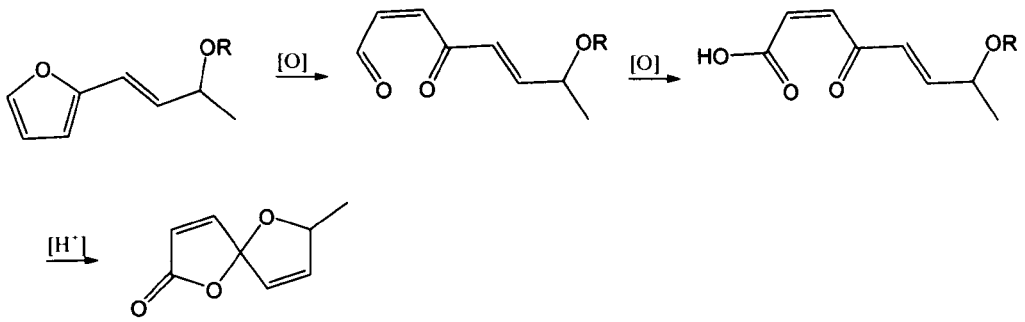
2.1 Retrosynthetic Analysis of Neoliacine

A major objective of our work was the synthesis of portions of the neoliacine **84** skeleton. The chemistry involved the employment of furan transformations to generate the various segments (scheme 2.1). The overall proposed retrosynthetic scheme involved the preparation of the most labile spiroketal portion of structure **84** - the highlighted portion of the compound - through a series of reactions involving oxidative ring opening of furan, and a final ring-closing cascade sequence to give the title compound.



Scheme 2.1 Retrosynthesis of neoliacine

The purpose of this was to determine the feasibility of the final step of the retrosynthetic sequence, giving compound **84** from **120**. As stated in chapter 1, furans are sources of 1,4-enedicarbonyl compounds and as such, this concept could be applied to our synthesis using these reactive intermediates *en route* to the desired spiroketal lactone (scheme 2.2).

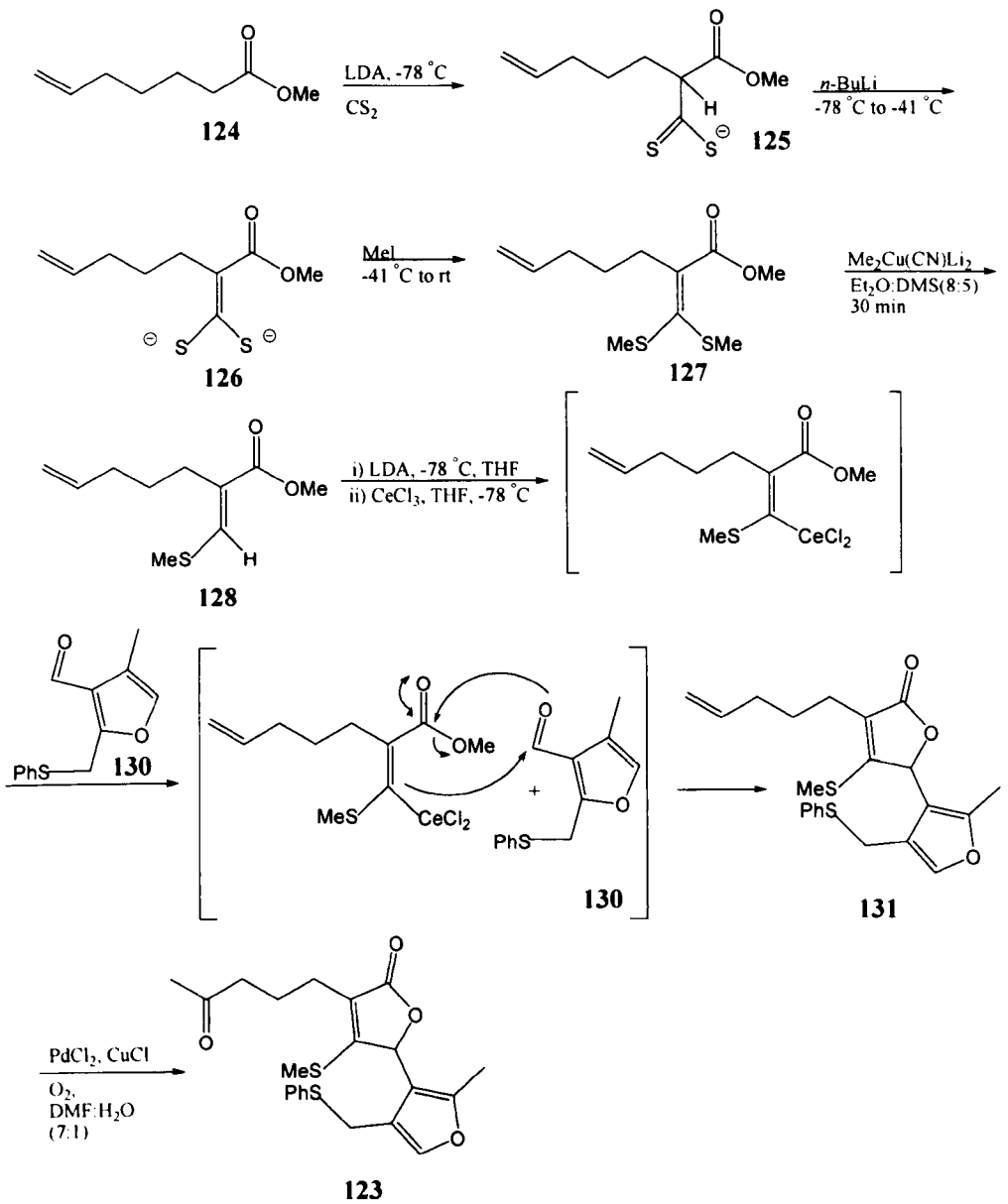


Scheme 2.2 Proposed synthetic sequence for spiroketal lactone

This synthesis was built on past work performed in the group[65] during which segment **123** of the skeleton was constructed by Wacker oxidation of the terminal alkene portion of **131** to its corresponding ketone (scheme 2.3). The reaction sequence was initiated with the addition of carbon disulfide to the enolate derived from heptenoate **124**. Following alkylation using methyl iodide, the ketene thioacetal **127** was generated. Ketene thioacetals are useful reactive intermediates because they can possess both normal and umpulong type reactivity owing to the stabilizing influence of the sulfur atom on neighbouring cations and anions. The reduction of the ketene thioacetal was undertaken using a methylcyano cuprate species. Although the mechanism of this step is unknown, it was predicted to occur by 1,4-addition of the methylcyanocuprate nucleophile to the enone system

followed by the elimination of the methylthio group giving **128**. This species was deprotonated with LDA, then metallated with cerium, producing an active nucleophilic intermediate which was cyclized with furan **130** giving the desired furan – butenolide species **131**.

With the synthesis of compound **123** at hand, the other major steps that would need to be completed for this synthesis would be the synthesis of the spiroketal portion of neoliacine and a ring-closing step to go from **123** to **122**. The focus of this chapter is the former step.

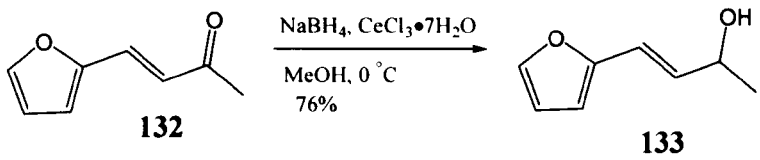


Scheme 2.3 Synthesis of furan / butenolide fragment of neoliacine

2.2 Reduction of Furyl ketone

The initial step involved the reduction of the readily available starting material, furfurylidene acetone **(132),** to its corresponding alcohol. A regioselective reduction of the allylic ketone was necessary to obtain the 1,2-addition product.

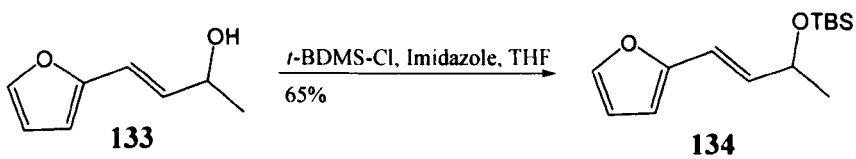
Therefore, this reaction was performed under Luche[66] conditions using the lanthanide species, cerium (III) chloride heptahydrate in combination with sodium



Scheme 2.4 1,2 reduction of allylic ketone

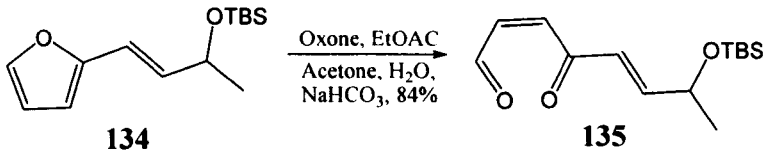
borohydride. Cerium (III) formed a complex with the oxygen of the carbonyl, thereby increasing the electrophilicity of the carbonyl making it more susceptible to attack at the 1,2-position rather than at the conjugated 1,4-double bond site.

The hydrolysis of the intermediate borohydride species called for the acidification to pH 4 using 1N HCl, but as some decomposition product was observed under these conditions, milder hydrolysis conditions using dilute ammonium chloride were chosen to generate the secondary alcohol. The furyl alcohol **133** was subsequently protected with *t*-butyldimethylsilyl chloride so that it could withstand the conditions of the upcoming oxidations.



Scheme 2.5 *t*-Butyldimethylsilyl protection

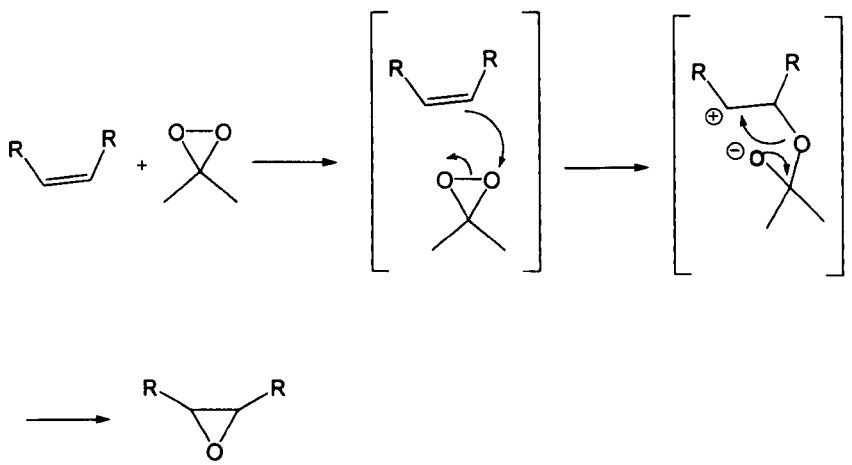
2.3 Oxidative Ring Opening of Furan



134 **135**

Scheme 2.6 Furan oxidation

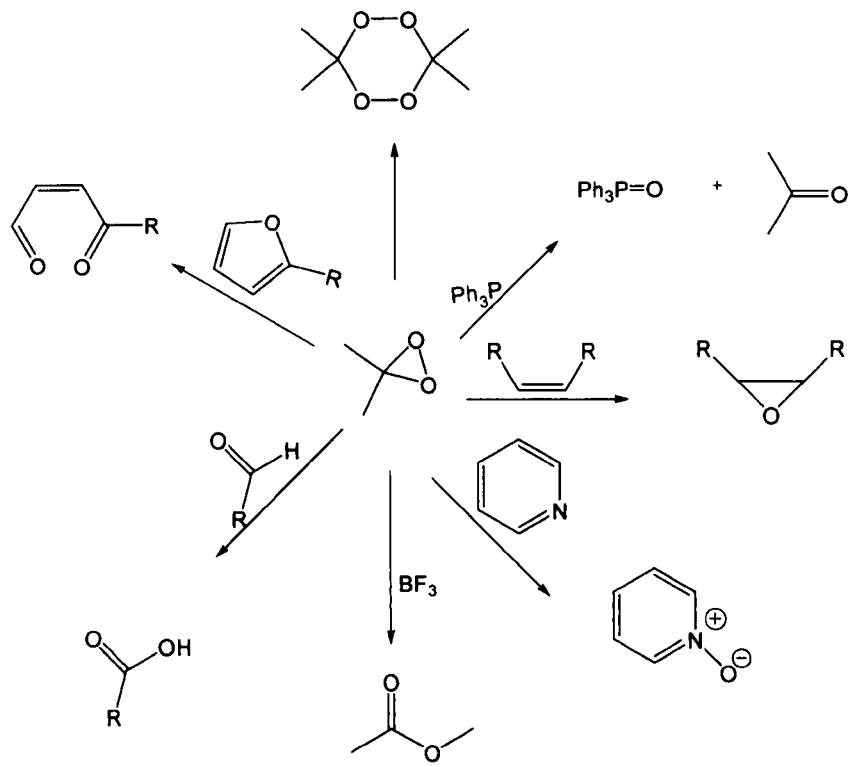
The next step in the reaction sequence involved the the oxidative ring opening of **134** to generate the desired carbonyl **135**. The oxidizing species employed was dimethyldioxirane, a cyclic peroxide system, which undergoes O-atom transfer of its peroxide oxygen giving epoxide intermediates (scheme 2.7).[67] Dimethyldioxirane and methyl(trifluoromethyl)dioxirane are the most common dioxirane species, with the latter being more reactive and giving higher conversion percentage.[68, 69]



Scheme 2.7 DMDO oxidation mechanism

This particular oxidizing agent was chosen due to the fact that it is reportedly easy to generate and due to the only by-product being acetone. Dimethyldioxirane

is an efficient oxidizing agent for a wide range of functional groups. Electron rich double bonds, such as silyl enol ethers are smoothly oxidized, among the wide range of oxidations possible with this reagent (see scheme 2.8), and dimethyldioxirane is reported to oxidize furans cleanly and rapidly at room temperature in acetone.[70]



Scheme 2.8 DMDO chemical transformations

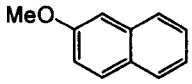
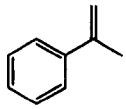
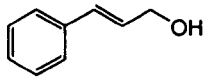
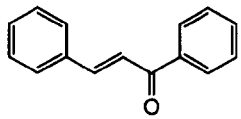
Conventional methods[71] were used to setup a dioxirane generator apparatus, i.e., a low pressure and temperature distillation apparatus, which enabled the dioxirane/acetone mixture to co-distill from a solution of water, acetone, sodium bicarbonate, and potassium hydrogen monoperoxy sulfate ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, Oxone® triple salt). The drawbacks of using this

preparation method were the time-consuming apparatus set-up, short shelf life of DMDO (3-4 days, −78°C), and low yield of product. Literature values of 0.1M[72] have been reported for the isolated product, but the highest concentration that we were able to generate was 0.04M (iodometric titration).

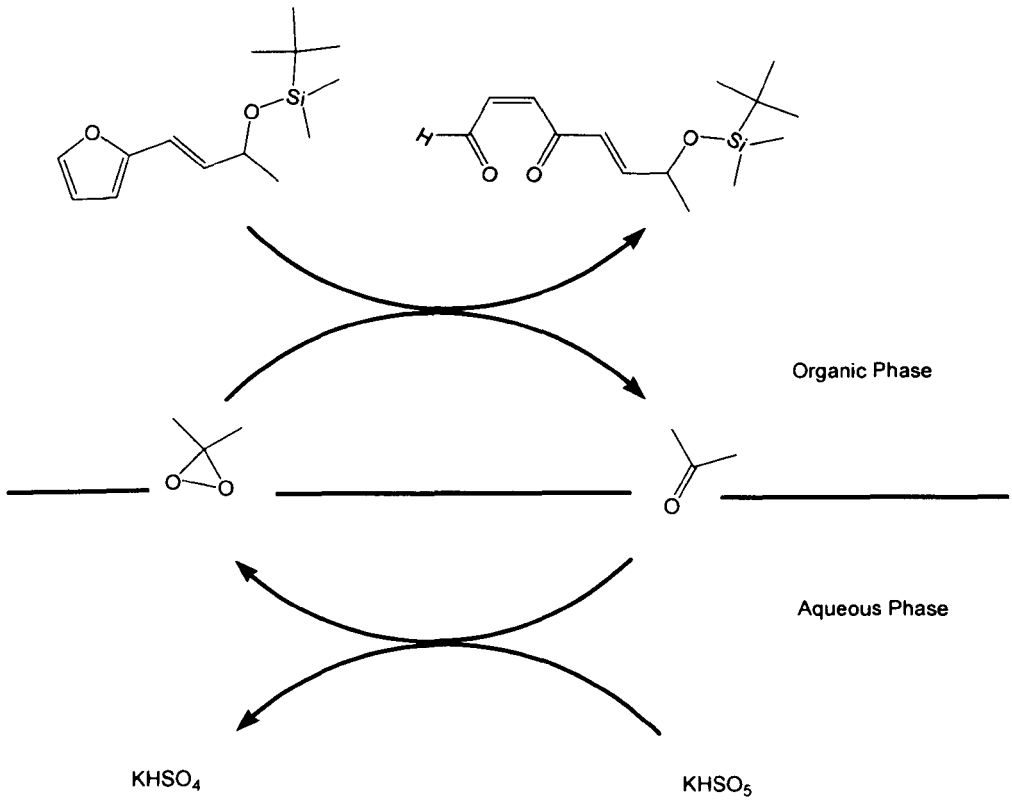
The limitation of using a reagent that could only be generated at 0.04M concentrations was that this precluded the possibility of working on a large scale. Therefore we decided to apply a method to generate the DMDO *in situ* by Hashimoto,[73] which he originally used for the catalytic epoxidation of olefins (table 2.1), to our furan oxidation strategy.

We decided to apply these reaction conditions as a novel means of oxidizing our furans, as prior methods only used isolated DMDO for this process. Using this procedure, the DMDO could be generated *in-situ* using a bi-phasic solvent system (water / ethyl acetate) in which an aqueous solution of Oxone® was slowly added over a 1h period *via* syringe pump and reacted with acetone in the aqueous phase to generate the DMDO (scheme 2.9). DMDO was transported to the organic phase without the need for a phase transfer catalyst (commonly tetrabutylammonium sulfate), which would require the strict control of the solution pH to avoid oxidation of the phase-transfer catalyst, and requires removal through purification.

Table 2.1: DMDO oxidation of olefins[73]

Substrate	Equiv. of $NaHCO_3$	Yield
	5	81
	5	94
	5	83
	5	5

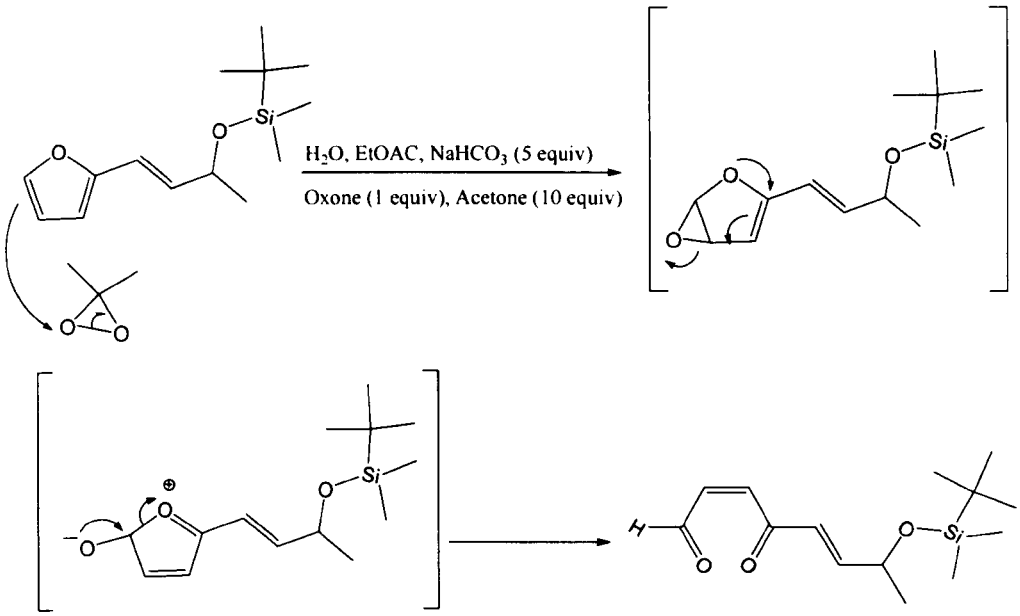
Hashimoto and co-workers determined that the concentration of acetone in the aqueous phase of a bi-phasic solution of water / ethyl acetate at 20 °C was 62% as opposed to values such as 32% and 33% for dichloromethane and dichloromethane/ phase transfer catalyst respectively. As the DMDO was generated initially in the aqueous phase, this was an important detail in terms of the limitations to the concentration of available DMDO that could be transported to the organic phase. Furthermore, the DMDO is more lipophilic than acetone and has a high affinity for ethyl acetate and this factor precluded the need to use a phase transfer catalyst under these conditions.



Scheme 2.9 DMDO *in-situ* mechanism

The proposed mechanism for this reaction is as shown in scheme 2.10. The reaction initiated with the nucleophilic attack of the furan double bonds on the peroxide and subsequent O-transfer gave the transient epoxide, which collapsed giving the 1,4-enedicarbonyl species **135**.

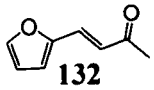
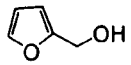
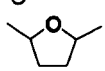
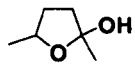
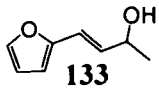
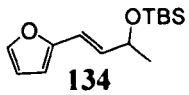
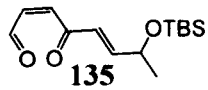
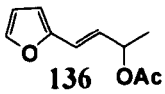
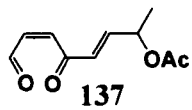
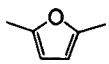
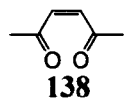
The next step was to determine the feasibility of this method with a range of furan substrates (see table 2.2). In a bi-phasic system, the lipophility was crucial for successful transformation to product. Thus, the greater the lipophilicity of the substrate, the greater was the percentage conversion to product.



Scheme 2.10 Proposed mechanism for DMDO oxidation of furan

After examining various substrates, we determined that substrates with a CLog P (estimated using ChemDraw® Ultra) less than 1.14 were not appreciably oxidized under the reaction conditions (< 5%). Using the *in situ* method, 1 equivalent of oxone could be added per hour, and it was possible to add a second equivalent after 2 hours, but any addition beyond this resulted in a saturation of the monoperoxysulfate solution in the aqueous layer precluding a proportional transfer of DMDO to the aqueous layer. Based on the findings in table 2.2, we found it reasonable to conclude that there was a direct relationship based on substrate affinity for the organic solvent.

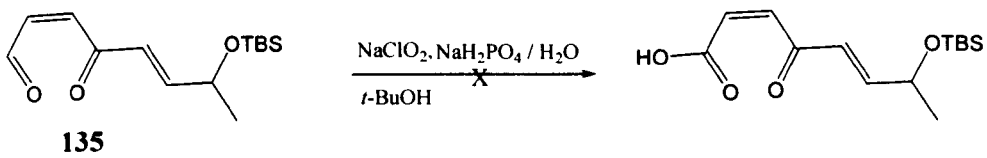
Table 2.2 Range of furans subjected to DMDO oxidation

Substrate	CLog P	Oxone Equiv.	Product	Yield (%)	*Cis/Trans*
 **132**	0.4	2	-	0	-
	0.08	2	-	0	-
	1.04	2		<5	-
 **133**	1.13	2	-	0	-
 **134**	-	1	 **135**	84	4:1
 **136**	1.14	2	 **137**	13	4:1
	1.27	1	 **138**	10	10:1

Our results showed that furans containing a conjugated ketone functionality are not oxidixed to an appreciable extent by the DMDO. This finding concurred with the results of Hashimoto (table 2.1), which showed that all of the olefins were oxidized in at least 80% yield, except for the ketone containing substrate which was only oxidized in 5% yield. This is likely due to reaction of the DMDO with the ketone, as well as the alkene functionality, in addition to electron withdrawing properties of the conjugated carbonyl group, which pulls electron density away from the electron rich furan double bonds. Results also demonstrated that DMDO reactions are stereospecific for production of *cis* olefins giving at least 4:1 *cis/trans* ratios for the oxidized products.

2.4 Sodium chlorite oxidation

Subsequent to the DMDO oxidation to give the enedicarbonyl, the next step of the synthesis involved the oxidation of the aldehyde to the carboxylic acid.



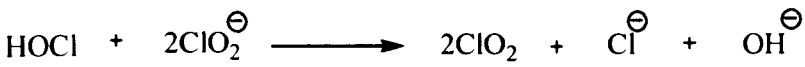
135

Scheme 2.11 Sodium chlorite oxidation conditions

The oxidant chosen for this step was sodium chlorite. Sodium chlorite is a mild oxidant,[61] which has the ability to tolerate a wide range of substrates. Additionally, it regioselectively converts α,β-unsaturated aldehydes to their corresponding acids whereas other agents may not be effective. α,β-Unsaturated aldehydes are often overly sensitive to Jones oxidation,[74] and potassium permanganate oxidizes both aliphatic and aromatic aldehydes to acids, but attacks the double bond of α,β-unsaturated aldehydes.[75]

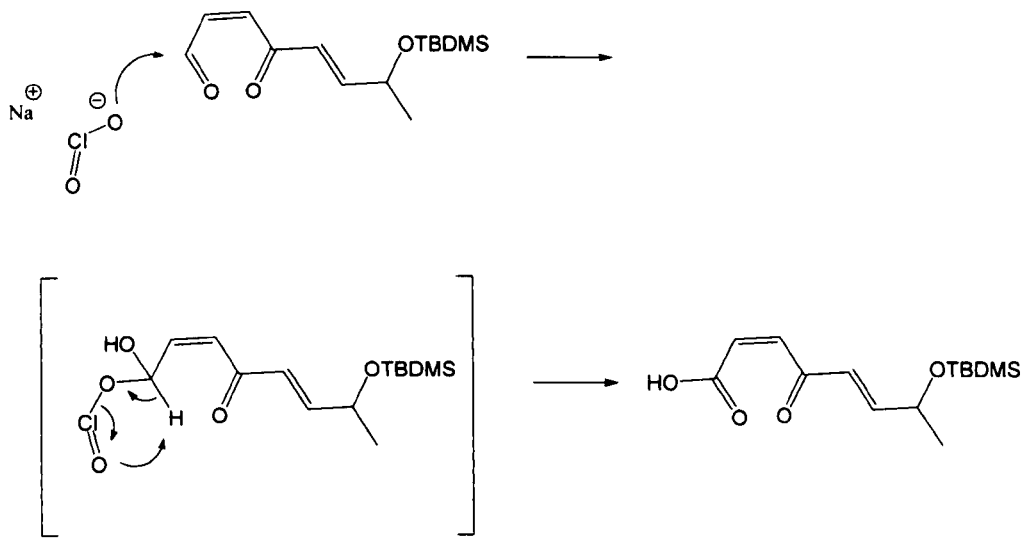
The sensitive functionality incorporated in our substrate was the TBS alcohol-protecting group; therefore we needed an oxidant, which required only mild acidic conditions. This method utilized 2-methyl-2-butene as a hypochlorite scavenger so as to prevent unwanted side reactions produced in the course of this reaction (see equation 2.1). The pH was maintained at 4.0 with sodium dihydrogenphosphate buffer. The mechanism of this reaction is suggested to proceed as shown in scheme 2.12.[55] Firstly, the nucleophilic chlorite ion attacks the

carbonyl, then the tetrahedral intermediate is predicted to break down in a concerted manner. Following the loss of $HOCl^-$, the carboxylic acid is produced.



Equation 2.1 Sodium chlorite oxidation by-products

Unfortunately, we encountered difficulties generating the acid species. Proton NMR spectroscopy revealed a loss of the *trans* alkene functionality indicating that alkene addition was also occurring. Many variations of the oxidant were investigated.



Scheme 2.12 Sodium chlorite oxidation mechanism

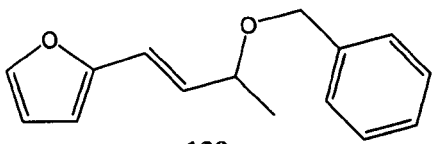
This included varying the number of equivalents of sodium chlorite between 9 equivalents and 1.2 equivalents. Also, the 2-methyl-2-butene scavenger concentration was adjusted between 10 equivalents, and in excess of 100

equivalents. None of these variations resulted in the formation of the acid. In an attempt to determine if the product was trapped in the aqueous phase of the solution, continuous extractions of the aqueous layer were performed under reflux in ethyl acetate for 24 hours. NMR spectroscopic analysis of the extractions indicated the absence of organic material in the aqueous layer.

The next strategy was to determine if the TBS protecting group might not be robust enough to survive the conditions of this oxidation. Therefore, we decided to vary the protecting group on the furan and subjected these compounds to the DMDO and sodium chlorite oxidations. The various substituted furans are shown in Table 2.3.

Table 2.3 Oxidation yields for furyl alcohol protections

Protecting Group	Substrate	DMDO Oxidation Yield %	Sodium Chlorite Oxidation Yield (%)
-OAc	**136**	13	0
-OBn	**139**	40	0
-OTBDPS	**140**	49	0
-TIPS	**148**	70	0



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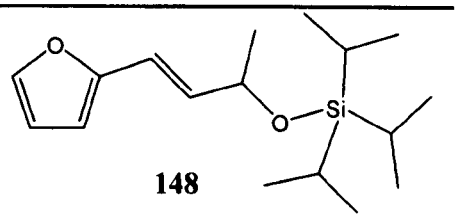
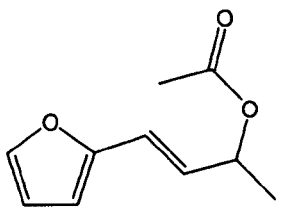
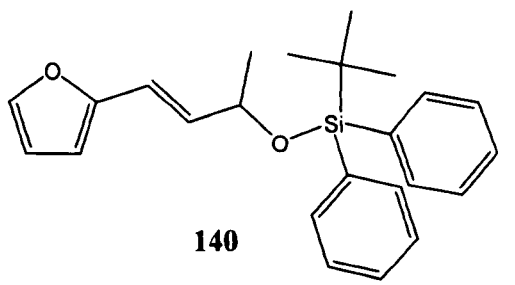


148



136

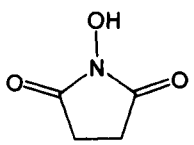


140

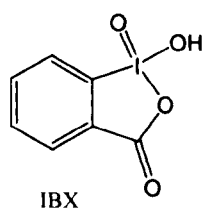
Figure 2.2 Range of alcohol protections

The *t*-butyldiphenylsilyl, acetyl, and benzyl protected alcohols were generated and oxidized to produce their corresponding enedicarbonyl compounds (table 2.3). Unfortunately, when these dicarbonyls were subjected to the sodium chlorite oxidation, using 1 equivalent of the sodium chlorite, the proton NMR spectra revealed a loss of the aldehyde, but a disappearance of the *trans*-alkene, apparent displacement of the protecting groups, and an overall complex spectrum with the appearance of by-products probably due to the addition of chlorite to the substrate.

The next course of action was to determine if another mild oxidation would be a suitable alternative to overcome these problems. A hypervalent iodine reagent, *o*-iodoxybenzoic acid (**141**) was chosen as the first alternative method. IBX has been utilized for numerous synthetically useful oxidative transformations, such as the benzylic oxidation of aromatic compounds,[76] and the oxidation of alcohols and 1,2-diols to aldehydes or ketones, and α-ketols to α-diketones,[77] respectively. More recently, it has been used as an oxidant for the transformation of primary alcohols and aldehydes to form carboxylic acids by Giannis and co-workers.[78] They reported the oxidation of aldehydes using IBX and oxygen nucleophiles (N-hydroxysuccinimide) at ambient temperatures.



N-hydroxysuccinimide

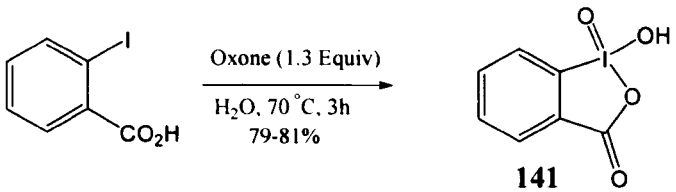


IBX

Figure 2.3 Hydroxysuccinimide and IBX structures

This reaction was predicted to proceed through the formation of a hemiacetal following the attack of the O-nucleophile. IBX oxidized the hemiacetal to its corresponding ester, and hydrolysis gave the desired acid.

IBX is not a readily available compound, and it is also unstable, therefore it was best for us to prepare the compound. It was prepared using a procedure introduced by Santagostino and co-workers,[79] which involves the preparation of IBX from Oxone® under aqueous conditions (see scheme 2.13).



141

Scheme 2.13 Synthesis of IBX

When we performed this synthesis, elemental analysis revealed that the IBX compound was mainly 2-iodosobenzoic acid (figure 2.4), but very little of the desired 2-iodoxybenzoic acid. Therefore, we used a much purer sample of IBX generated by Stylacats Labs hoping that this would give our carboxylic acid. Using this IBX, we only recovered starting material. In spite of the promising potential of this route, it appeared to pose problematic issues at this introductory step, therefore we decided that a more feasible procedure was called for.

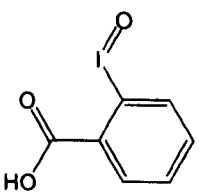
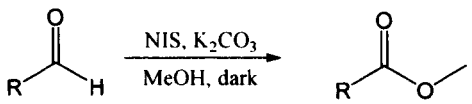
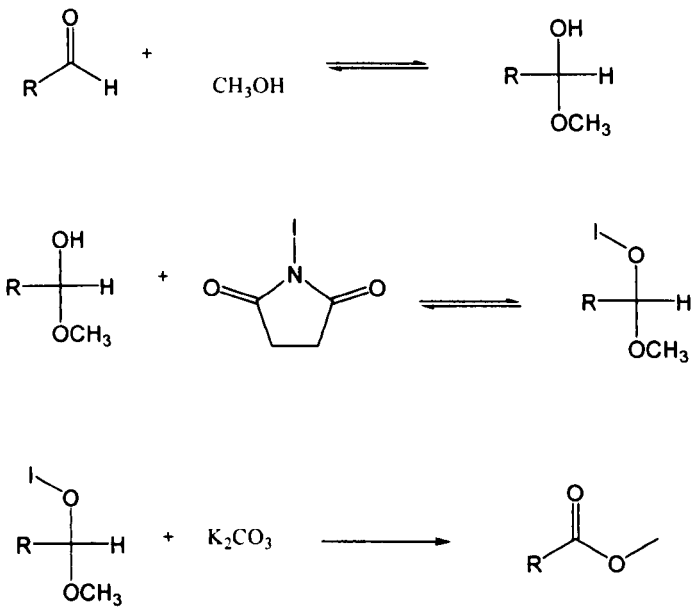


Figure 2.4 2-Iodosobenzoic acid contaminant

A classical method for the preparation of methyl esters from aldehydes[80] was chosen as the next route (scheme 2.14). The proposed mechanism (scheme 2.15) for this reaction initiated with the nucleophilic addition of methanol to the aldehyde. The methyl hemiacetal formed at this step was oxidized by the N-iodosuccinimide giving the corresponding hemiacetal hypoiodite species. Subsequent elimination of hydrogen iodide gave the desired methyl ester.



Scheme 2.14 NIS oxidation to methyl ester



Scheme 2.13 Mechanism of NIS oxidation of Aldehyde

Unfortunately, using the reaction conditions for this transformation, the desired methyl ester was not generated. There was no trace of the $-CO_2CH_3$ protons in the 3-4 ppm region in the proton NMR spectrum of this product. Futhermore, the aldehyde peak was still present at 10 ppm. It is possible that the first step of the reaction sequence may not have led to a favourable equilibrium for the initial formation of the hemiacetal. Another possible obstacle, which could have deterred the success of this reaction, concerned the dependence of the progress of the reaction upon the selective oxidation of the hemiacetal in the presence of a much higher concentration of methanol.

A variety of oxidations to the carboxylic acid and methyl ester functionalities were attemped to no avail. Each attempt resulted in nucleophilic addition to the alkene double bonds, or no reaction at all. We then attempted vanadium pentoxide[81] oxidation of aldehydes to methyl esters, Oxone,[82] and TEMPO / BAIB[83] oxidations of the aldehyde to its corresponding acid without success (table 2.4). Therefore, we determined that a new approach was necessary.

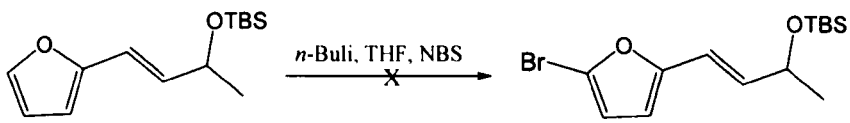
Table 2.4 Range of attempted aldehyde oxidations

Substrate	Method	Result
135	V_2O_5 / H_2O_2	Complex mixture of by-products
135	Oxone	Complex mixture of by-products
135	TEMPO / BAIB	No reaction

2.5 Wittig Olefination

We decided that it would be desirable to attempt to generate a furan, which contained a leaving group at the 5-position in order to eliminate the need to oxidize

our reactive enedicarbonyl species (scheme 2.14). Initially we attempted N-bromosuccinimide based bromination[84] using *ortho*-lithiation techniques. Unfortunately, we found that we only recovered the starting material; therefore, it was reasonable to conclude that the lithiation was not occurring. Variation of the reaction conditions, increasing the temperature from –78 °C to 0 °C, and varying the equivalents of *n*-butyllithium from 1.2 equiv. – 2 equiv. did not prove effective. In order to determine if the problem was due to the lithiation step; we then performed the lithiation and quenched using the reactive reagent trimethylchlorosilane, which is a well precendented reaction for furan compounds.[85,86]



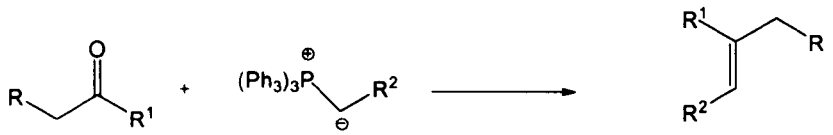
134

Scheme 2.14 Attempted bromination of furan

Based on NMR findings – disappearance of furan 5H proton at 7.2 ppm - we determined that this reaction was occurring in 50% yield. This led us to conclude that the problem was due to methodology using N-bromosuccinimide.

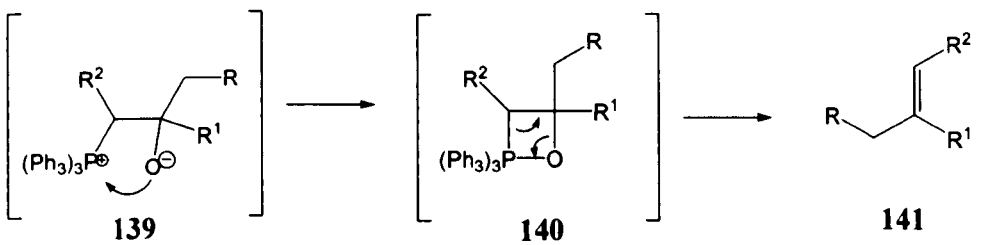
We decided to examine a different route to a substituted furan containing a bromine leaving group at the 5-position on the furan. The material chosen for this pathway was 5-bromofuraldehyde. The bromine was already present at the 5-position, therefore a functional group interconversion was necessary for the conversion of the aldehyde to an alkene. The Wittig reaction[87] (scheme 2.15)

which is commonly utilized as the method of choice for this type of transformation, as this method selectively converts aldehydes and ketones to alkenes, was chosen as a synthetic route to the alkene.



Scheme 2.15 General Wittig reaction

The Wittig reaction mechanistically involves the condensation of a phosphonium ylide with the carbonyl functionality of an aldehyde or ketone.

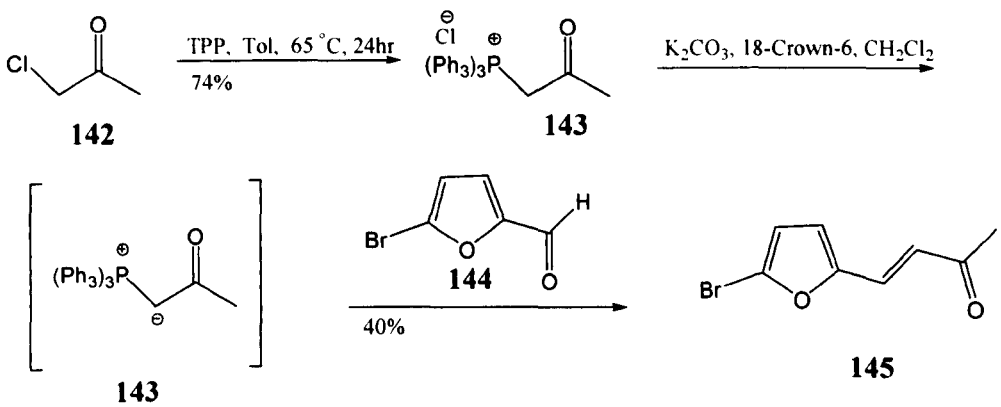


Scheme 2.16 Mechanism of olefin formation

The mechanism is as shown in scheme 2.16. The phosphonium ylide nucleophile attacks the carbonyl giving zwitterionic betaine intermediate **139**. The cyclization of **139** gives the cyclic oxaphosphetane intermediate **140**. Following the elimination of triphenylphosphine oxide, the driving force of the reaction, the alkene **141** is generated. The stereochemical outcome of the reaction is dependent upon various factors (solvent, reactant excess, reaction times, etc.).[88] It has been determined that the reaction stereochemistry of non-resonance stabilized ylides generally varies

from resonance stabilized ylides. Non-stabilized ylides selectively yield *cis* olefins, whereas, stabilized ylides give the *trans* olefins. Non-stabilized ylides react rapidly, subsequently leading to a rapid ring opening, which gives the kinetic product *cis* alkene. A stabilized ylide is not as reactive, and with an extended reaction time, the thermodynamic product, the more stable *trans* alkene is generated.

The reaction, following the conditions of Boden and co-workers,[89] used to generate our *trans* olefin is as shown in scheme 2.17. This method involved the generation of the olefin steroselectively, exclusively *trans*, without the use of halogen salts, which can suffer from the production of difficult to remove contaminants.

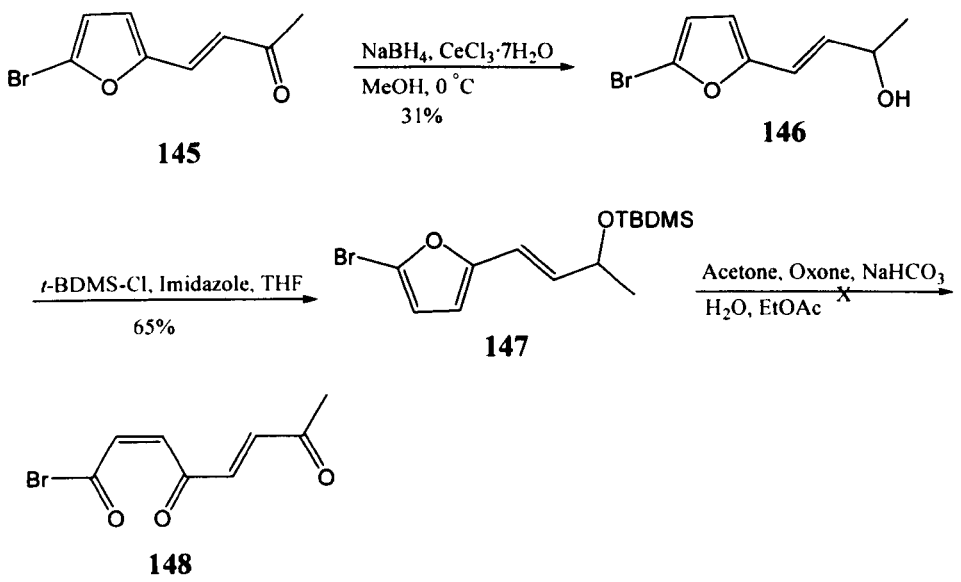


Scheme 2.17 Wittig olefination of bromofuraldehyde

The crown ether, 18-crown-6, complexed with the potassium carbonate base, which was used for phosphorane formation, catalysed this method. In the presence of these types of complexes, it has been observed that, for non-stabilized ylides, a salt-free product distribution in tetrahydrofuran was noted, whereas in dichloromethane solution, a reversal in the product distribution was obtained. In the

case of stabilized phosphoranes, either solvent resulted in the formation of *trans* alkenes as the major product. In the absence of the crown ether, little or no product formation was observed.

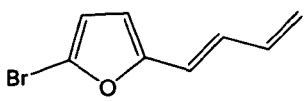
Chloroacetone **142** was chosen as the starting material *en route* to the stabilized phosphonium ylide **144**. The ylide was generated following deprotonation of the phosphorane **143**. Condensation of bromofuraldehyde **144** with the phosphorane gave the target *trans* olefin **145** in 40% yield. The yield of this reaction was lower than expected due to the difficulties in the removal of the triphenylphosphine oxide that was generated. Before chromatographic separation of this elimination product was performed, the bulk of the triphenylphosphine was removed from the solution by crystallization overnight in cold ether. It is advantageous to remove as much as the triphenylphosphine as possible due to the fact that it streaks in the silica column upon separation and tends to co-elute with the product. In spite of this, it was still possible to obtain pure product, and scale up of the reaction allowed for larger scale preparation of the target olefin.



Scheme 2.18 DMDO oxidation of bromofuran

Following the synthesis of the bromofuran **145**, the aim was to generate the acyl bromide **148** by dimethyldioxirane oxidation of the furan. The first step was to reduce the ketone to its corresponding alcohol using the same conditions as those for alcohol **133**, followed by TBS silylation of the alcohol giving **147**. Oddly, the furyl alcohol, **146**, ^{13}C NMR values did not correspond to the structure of the target furan. Based on the ^{13}C values, we expected to see a $-CH_3$ carbon shift in the 20 ppm range and a quaternary carbon shift on the 65 ppm range, and neither was detected. Furthermore, the ^{13}C values of this product contained all of the carbon in the 108 ppm – 152 ppm range. This correlated closer to the dehydration product **149**. To the contrary, the mass spectrum indicated that the desired alcohol **146** had in fact been generated as shown by the 1:1 ratio of molecular ion mass values of 215 and 217 at 100% intensity. This led us to conclude that we had the product, but

due to the acidity of the deuterated chloroform, the reactive furan underwent an elimination of water in the NMR tube upon sitting for several days.



149

Figure 2.4 Bromofuran elimination product

After performing the sequence of reactions, we found that the desired acyl bromide **148** was not the end product expected from the DMDO oxidation. The proposed structure of the product obtained is that shown in figure 2.5. This hypothesis was based upon mass spectrometry data indicating a 1:1 ratio of molecular ion mass values of 364 and 366 at 4% intensity and a mass fragmentation of 234 at 97% intensity indicating the loss of –OTBS.

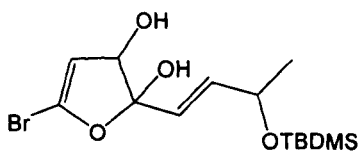
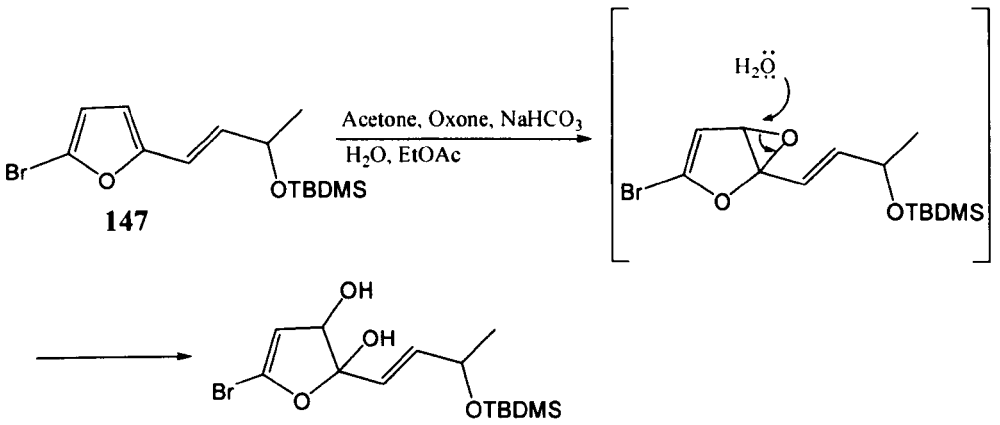


Figure 2.5 Proposed DMDO oxidation product

In order to obtain this proposed oxidation product, the DMDO oxidation mechanism would have to have undergone a transition state involving the formation of a transient epoxide species as shown in scheme 2.19. Therefore, we deduced that this reaction sequence was not working at the DMDO oxidation step due to the reactivity difference of the halogenated furan as compared to the previous furan,

which had been successfully subjected to this oxidation.



Scheme 2.19 Proposed mechanism for formation of oxidation by-product

2.6 Furan Alkylations

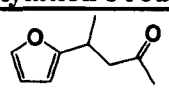
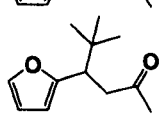
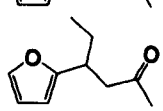
At this point, we decided to generate a library of furans to determine the scope of these oxidations and to generally expand the horizon of this project. This sequence of reactions was comprised of alkyllithium additions to the furfurylidene acetone starting material.

Alkylation of carbonyl compounds to generate substituted alcohols is one of the most fundamental and versatile reactions in organic chemistry and has a wide range of synthetic applications. Two common methods utilized towards this end are Grignard reactions and alkyllithium additions. We initially prepared Grignard reagents *in situ*, followed by the use of purchased reagents (MeMgBr, PhMgr, etc.), but found that we suffered in terms of yield with these reagents. As these reagents are relatively softer than lithium reagents due to their larger, more diffuse orbitals, they react with the corresponding softer sites on the substrates. α,β-Unsaturated ketones have two reactive sites for nucleophilic attack from these reagents. When

1,2-addition occurs, attack happens at the carbonyl. Alternatively, with 1,4-addition, nucleophilic attack occurs on the double bond, which is the softer site for attack. We found that the Grignard reactions were suffering from quite poor yields, < 10%, as the major products generated were the 1,4-addition products occurring with double bond addition (table 2.5) as determined by ^{1}H NMR spectroscopy. These 1,2-addition products generated using methyl magnesium bromide, *t*-butyl magnesium bromide, and ethyl magnesium bromide, contained peaks in their NMR spectra in the 2.1 – 2.2 ppm region for the $-COCH_3$ protons, indicating the presence of ketone. Additionally, this was accompanied by a reduction of the *trans* double bond signal in the 6 – 7 ppm region and the appearance of complex multiplets in the 2 – 4 ppm region for the saturated carbon protons.

Therefore, we decided to carry on using the alkyllithium reagents, as these are more selective for carbonyl addition, and give only minor 1,4-addition products. The range of alkylations performed are given in table 2.6.

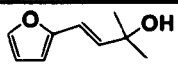
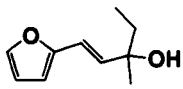
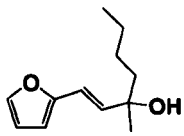
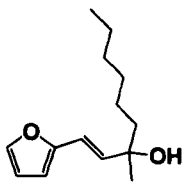
Table 2.5 Range of 1,2-addition products

Substrate	Grignard	Alkylation Product	Yield (%)
132	CH_3MgBr		30
132	*t*-BuMgBr		27
132	CH_3CH_2MgBr		25

These products represented a pathway into a range of new unsaturated dicarbonyls, which would provide useful synthetic intermediates, and are also quite

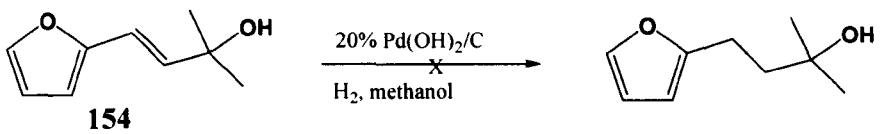
easy to prepare. Alkylation at –78 °C, followed by ammonium chloride quench gave the target alcohols in one step. The DMDO oxidation sequence was followed to generate the 1,4 carbonyls shown in table 2.7. We found that these substituted ene dicarbonyls were not able to withstand the conditions of the sodium chlorite oxidations, therefore we decided that it would be useful to lower the level of conjugation of the corresponding oxidized enedicarbonyl derivatives by catalytic hydrogenation of the substituted furan *trans* double-bond.

Table 2.6 Furan alkylation products

Substrate	Alkyllithium	Alkylation Product	Yield (%)
132	CH_3Li	 **154**	20
132	CH_3CH_2Li	 **155**	24
132	$CH_3(CH_2)_3Li$	 **156**	31
132	$CH_3(CH_2)_5Li$	 **157**	31

The method that we utilized for catalytic hydrogenation was 20% palladium hydroxide on carbon.[90] We attempted this procedure with furan **154** (scheme 2.20) unsuccessfully. TLC, and the ^1H NMR spectrum of the material exhibiting the *trans*

double bond shifts in the 6.3 – 6.4 ppm region, indicated the recovery of the starting material using 5% of the 20% palladium hydroxide/carbon catalyst. Unfortunately, the palladium hydroxide catalyst was unreactive toward our substituted furan **154** for reaction times between 2h – 48 hr. On the other hand, when we performed the hydrogenation on species **156**, we were able to generate the desired reduced species in high yield (scheme 2.21).



154

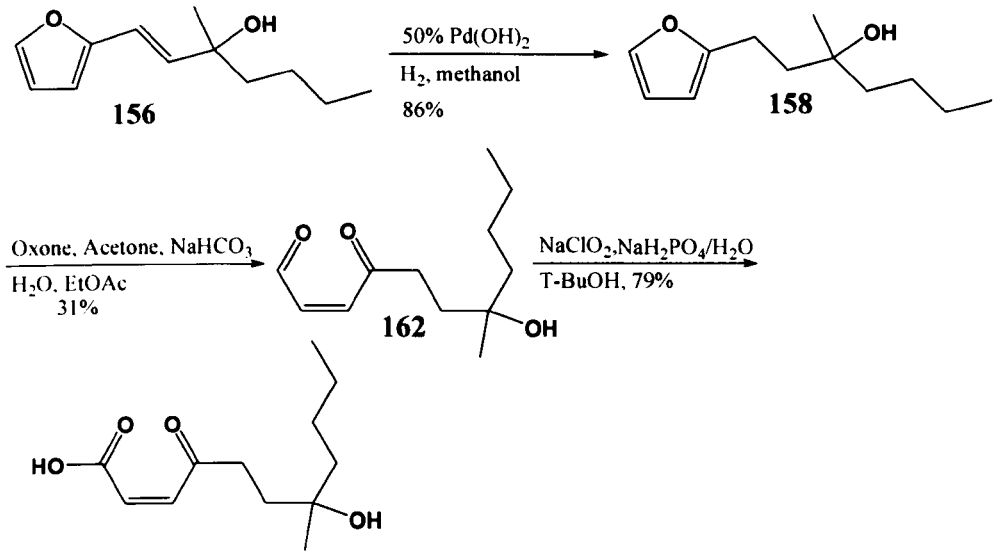
Scheme 2.20 Attempted reduction of *trans* double bond

We attributed this to the likelihood that the longer alkyl chain of **156** helped to offset the effects of the conjugation of the *trans* double bond to the furan double bonds, which are less reactive towards reduction than isolated *trans* double bonds.

When we subjected **158** to the DMDO and subsequent sodium chlorite oxidation of the aldehyde to its corresponding acid, we found that this less conjugated derivative was successfully converted to the desired enedicarbonyl species (scheme 2.21). In the absence *trans* double bond, there was no possibility for chlorite addition at this position, which minimized the possibility of double bond addition by-products.

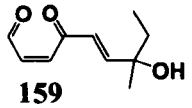
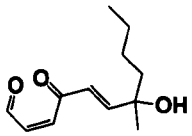
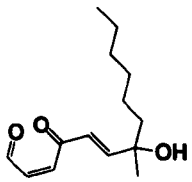
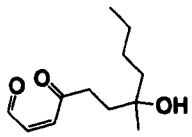
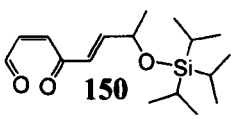
The conjugated ene dicarbonyls are highly reactive species and proved to be too reactive for our oxidative conversions. Moreover, there are no precedents of these oxidations performed on such species. Thus, once we determined that oxidation of the lesser functionalized ene dicarbonyls was possible, we decided that we should

next perform a readily reversible conversion of our *trans* double bond prior to the sodium chlorite oxidation step.



Scheme 2.21 Oxidation of furan **156**

Table 2.7 DMDO oxidations of alkylated furans

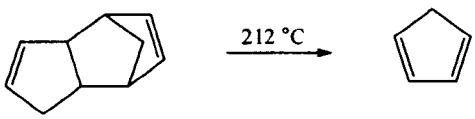
Substrate	*DMDO* Oxidation Product	Yield (%)	*Cis / Trans*
155	 **159**	40	8:1
156	 **160**	60	4:1
157	 **161**	60	5:1
158	 **162**	31	4:1
148	 **150**	84	4:1

2.7 Diels-Alder Cycloadditions

In light of the discovery that the sodium chlorite oxidation of the aldehyde to the carboxylic acid was possible with species **162**, and because we could not find literature examples of this oxidation using substrates with as much local conjugation as our compounds, we decided that the next practical course of action would be the further functionalization of the enedicarbonyl in order to stabilize the

compound so that it would be robust enough to survive the conditions of the oxidation. In order to lower the level of conjugation, thereby lowering the reactivity of our compounds, we decided to functionalise the double bond of the enedicarbonyl by performing a Diels-Alder cycloaddition. It was predicted that the more stable cycloadduct would be robust enough to survive the conditions of the oxidation, and a reverse Diels-Alder cycloaddition could be performed following spiroketalization to deprotect the double bond.

The Diels-Alder reaction falls within the category of pericyclic cycloaddition reactions that occur as a result of –intra or –intermolecular interaction between overlapping frontier molecular π-orbitals. The particular reaction chosen consisted of the cycloaddition of cyclopentadiene, which had been freshly generated *via* the cracking of dicyclopentadiene[91] (scheme 2.21), with a selection of our enedicarbonyl compounds as shown in table 2.8.

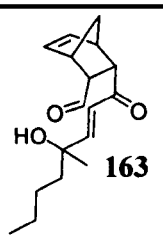
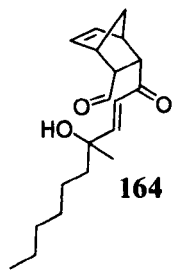
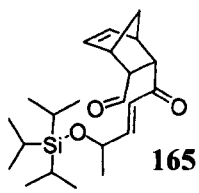


Scheme 2.21 Cracking of dicyclopentadiene

This reaction readily occurred at room temperature in all cases and it was deduced that the stereochemistry of the major product was *cis-endo* based on literature findings[92] for similar types of compounds and structural estimations generated by the CHARGE molecular modelling program and ^{1}H proton shift estimations generated by the complementary PCModel program (Table 2.9). These programs generate proton shift estimations for both *endo* and *exo* cycloadducts.

The *endo* shift approximations appeared to match our product shifts more accurately. In particular, it was a closer match with the *endo* shifts, which varied most greatly from the *exo* shifts for protons #5 and #8.

Table 2.8 Diels-Alder cycloaddition products

Substrate	Cycloaddition Product	Yield (%)
160	 **163**	40
161	 **164**	60
162	 **165**	60

The ^{1}H NMR spectral representation of bicycloadduct **165** is shown in figures 2.7 – 2.10. This spectral data is representative of the various regions of interest and demonstrates the level of complexity of the coupling between the various protons. Protons # 3 and # 4, which are expected to have a coupling frequency between 0 – 3 Hz both appeared as broad singlets in the 3.0 – 3.2 ppm region (figure 2.10). Also, the coupling of the bridge protons # 7 and # 8 is an indicator of

stereochemistry as the more highly coupled proton #7 indicated that the stereochemistry of this proton was *endo* with respect to protons #4 and #6. The signal was split into a double triplet and its coupling constant of 1.9 indicated that it was coupling to bridgehead proton #4 (figure 2.11).

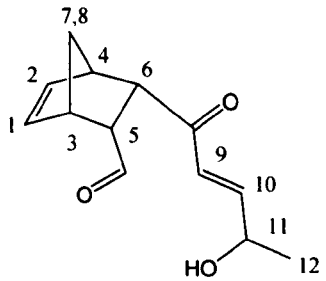


Figure 2.6 Numbered structure of bicycloadduct

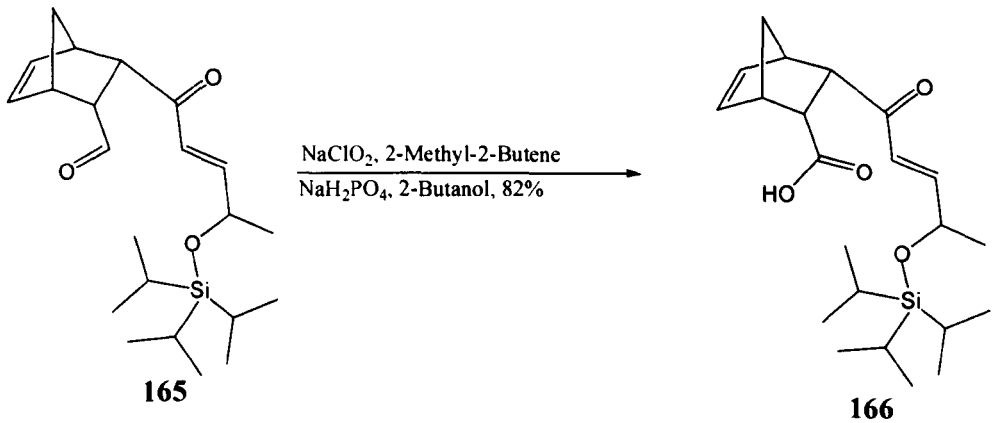
Table 2.9 Estimated and Product ^{1}H NMR shifts of Bicycloadduct **165**

Proton	Endo-Shift (ppm)	Exo-Shift (ppm)	Product-Shift (ppm)
1	6.094	6.069	6.0 – 6.1
2	6.208	6.070	6.3 – 6.4
3	3.690	3.475	3.4
4	3.554	3.427	3.2
5	3.136	2.698	3.1
6	3.311	3.765	3.8
7	1.796	1.579	1.4
8	1.587	2.462	1.26 – 1.29

Protons #5 and #6 coupled to each other with a frequency of 9.6 Hertz indicating that these protons both assume an equatorial conformation (figures 2.9, 2.10). The proton-proton coupling partners were assigned based on 2D COSY NMR spectroscopy (figure 2.12). The assignment of proton #5 was immediately obvious as this proton was the only coupling partner of the aldehyde proton with a coupling frequency of 3.5 Hertz. At this point the vicinal proton, #6, which was shown to be

the coupling partner of #5 was assigned. The combination of the various data sets permitted the determination of the bicycloadducts.

Once the cycloaddition was performed, this permitted the sodium chlorite oxidation of our aldehyde **166** (scheme 2.22).



165 **166**

Scheme 2.22 Sodium chlorite oxidation of aldehyde **165**

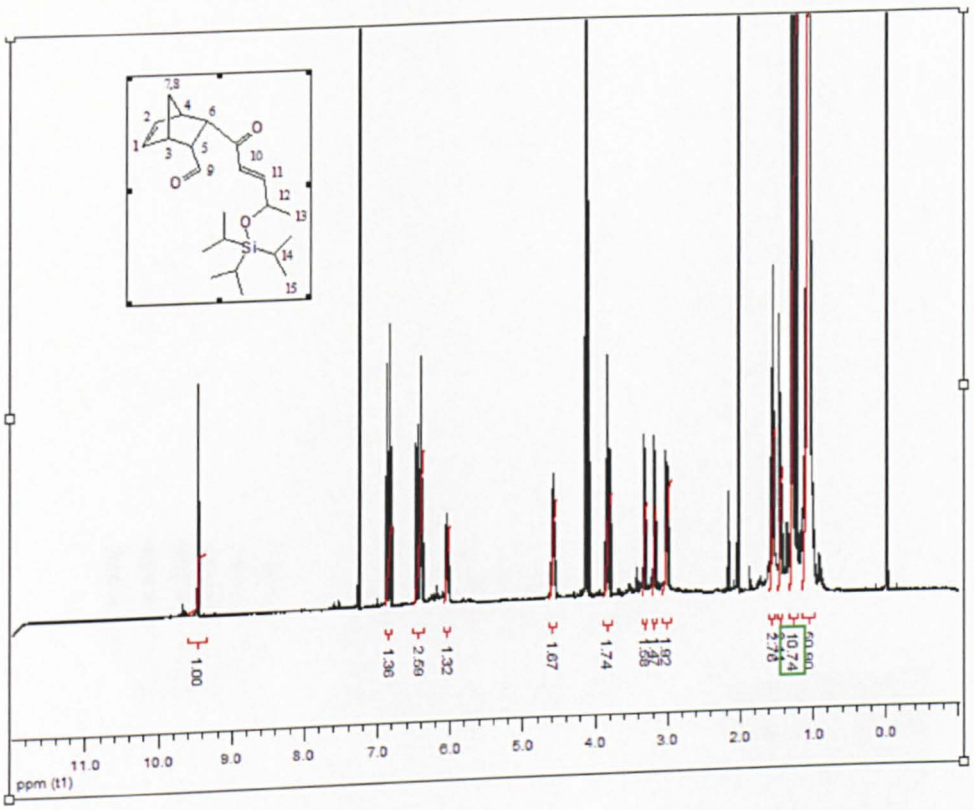


Figure 2.7 ^{1}H NMR spectra of bicycloadduct **162**

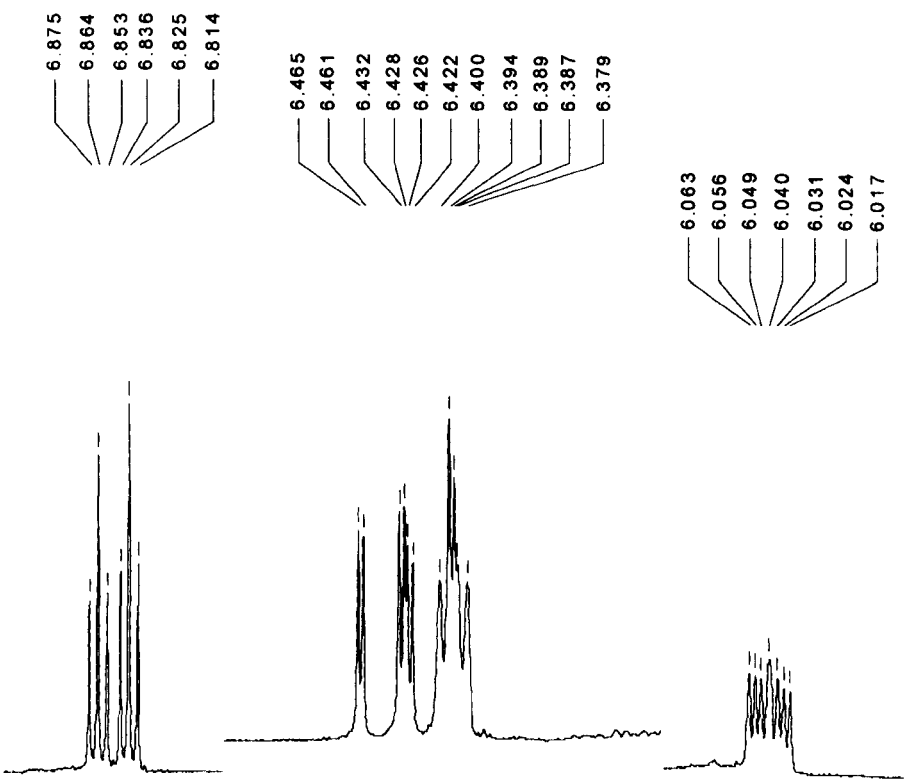


Figure 2.8 Proton H1, H2, H9, and H10 spectra

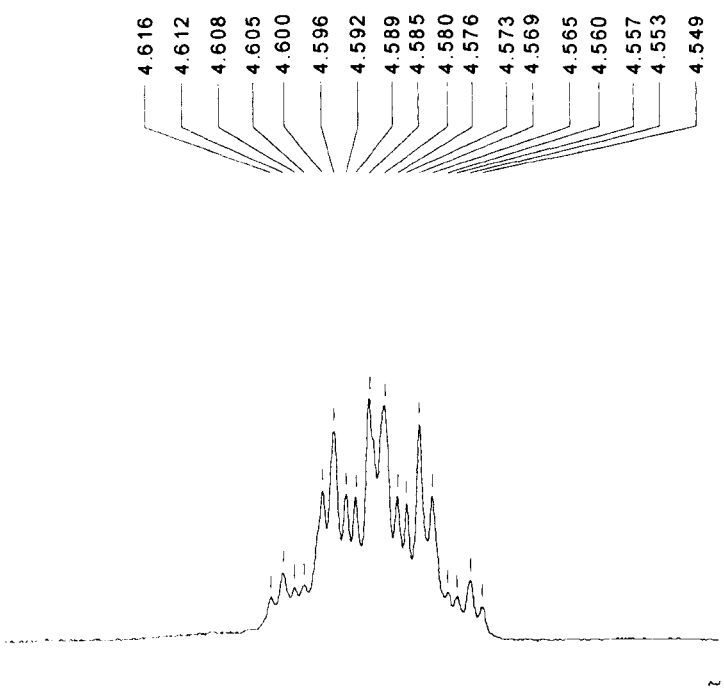


Figure 2.9 Proton H6 and H11 spectra

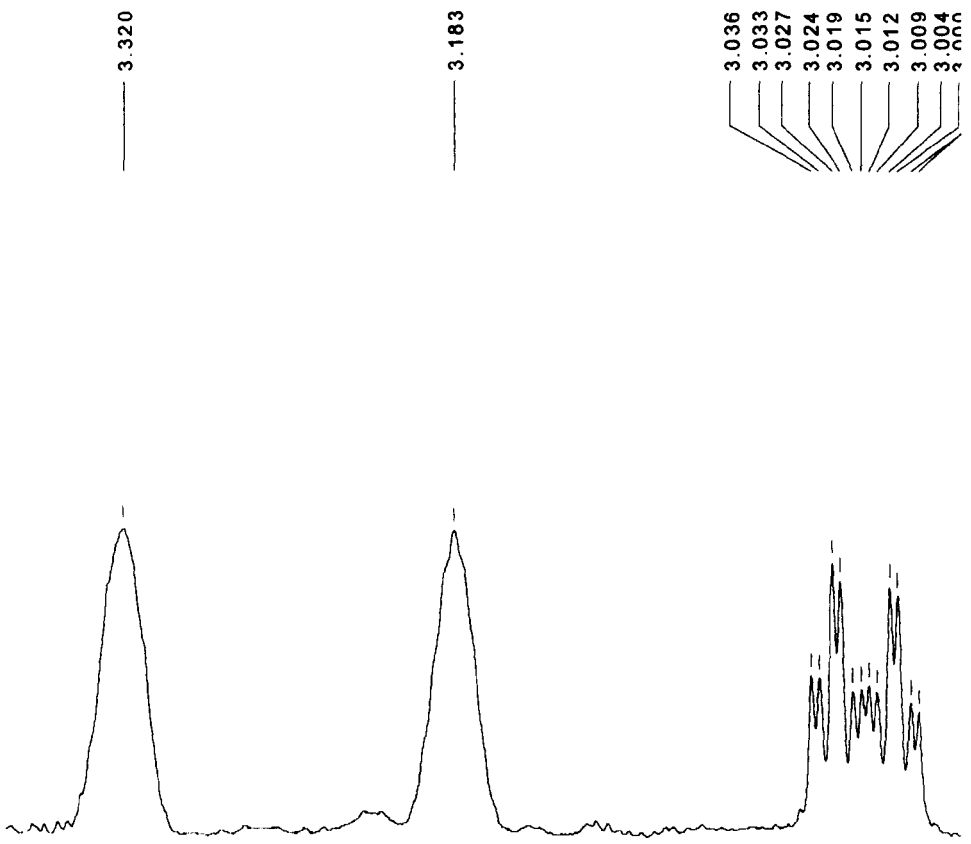


Figure 2.10 Proton H3, H4 and H5 spectra

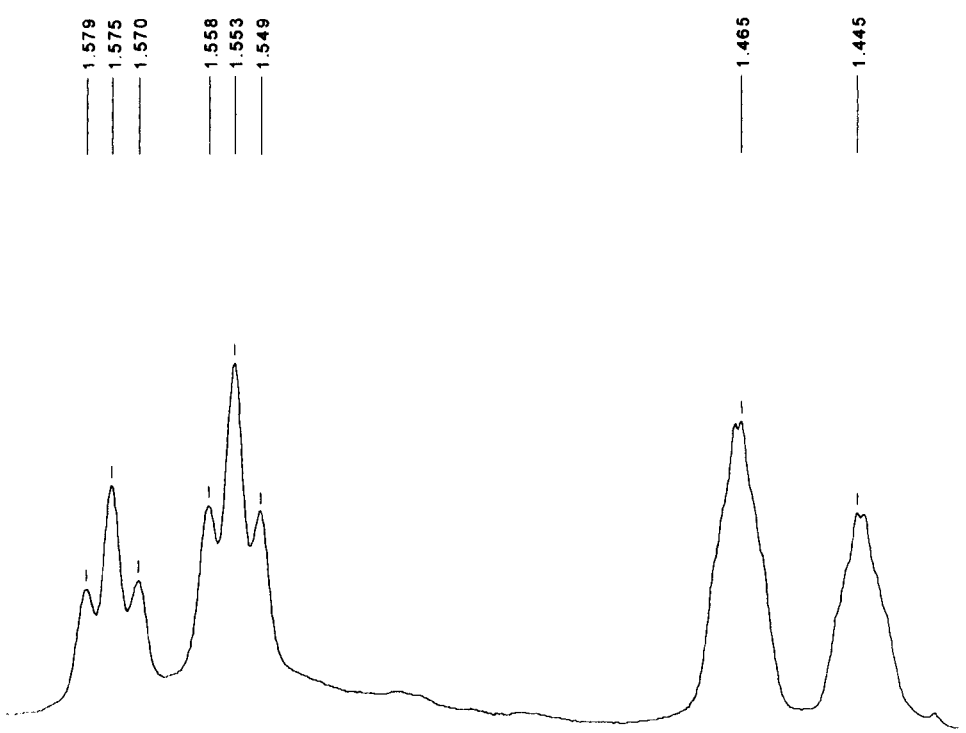


Figure 2.11 Proton H7 and H8 spectra

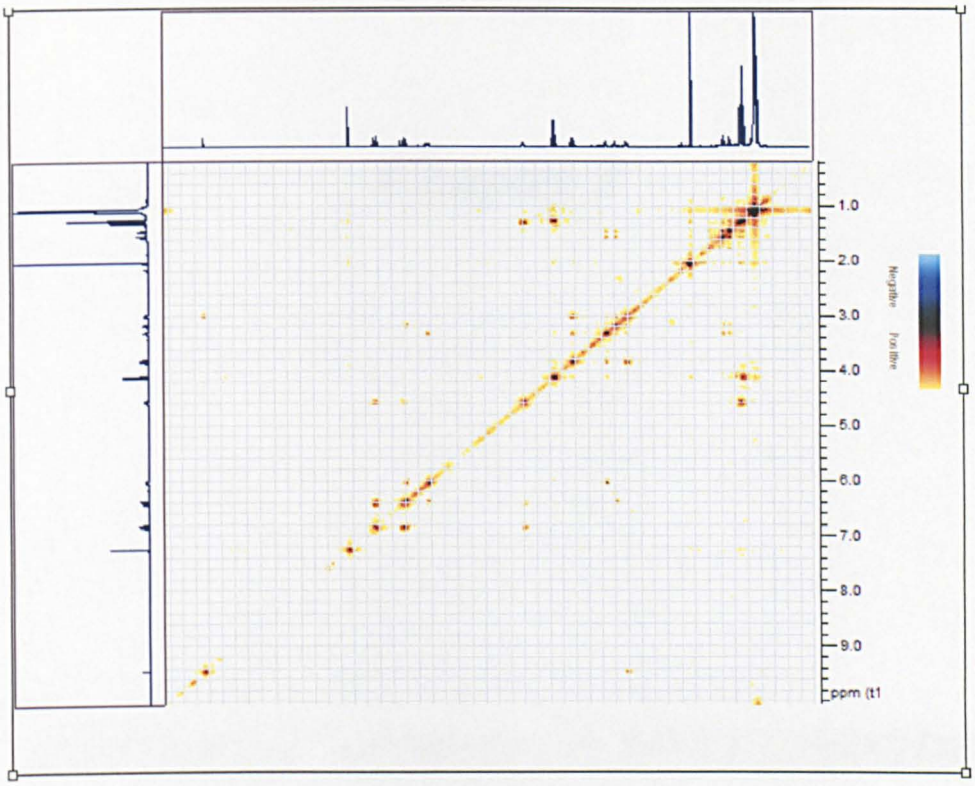


Figure 2.12 COSY spectrum of bicycloadduct

Chapter 3

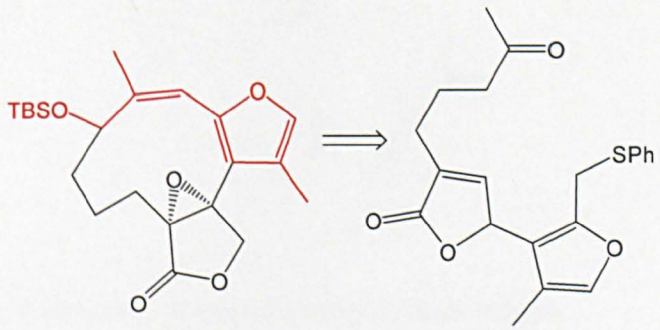
SYNTHETIC APPROACH TO SULFOXIDE MODEL

Chapter 3

SYNTHETIC APPROACH TO SULFOXIDE MODEL

3.1 Synthetic Aims

A second model *en route* to the desired 10-carbon carbocyclic portion of Neoliacine had been examined concurrently with the spiroketal model, which was a model to be used for the ring-closing step of neoliacine (scheme 3.1).



122 **123**

Scheme 3.1 Neoliacine carbocyclic ring-closing step

The reaction sequence for this compound (scheme 3.3) consisted of the synthesis of the model furan **167**, followed by its proposed condensation with a ketone giving compound **168**. Elimination of water from **168** was to give the allylic sulfoxide **169**, which was envisaged to undergo 2,3-Wittig rearrangement of the allylic sulfoxide, and, following hydrolysis, the desired product **170** was expected. This model sequence for the conversion of **167** to **168** could be applied to the ring-closing step intended to provide **122** *via* intramolecular condensation of the sulfoxide with the ketone functionality. Earlier work performed in our group was

aimed at undergoing this sequence,[93] but difficulties were encountered at the step involving the deprotonation of the sulfoxide α-proton. Neither LDA nor *n*-butyllithium were effective bases for this reaction. A feasible resolution for this problem would be to lengthen the alkyl side chain of the furan (figure 3.1), which would increase the distance of the α-proton from the electron-rich furan, thus increasing the acidity of this proton.

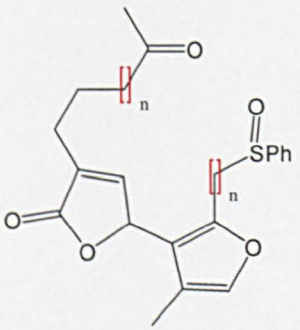
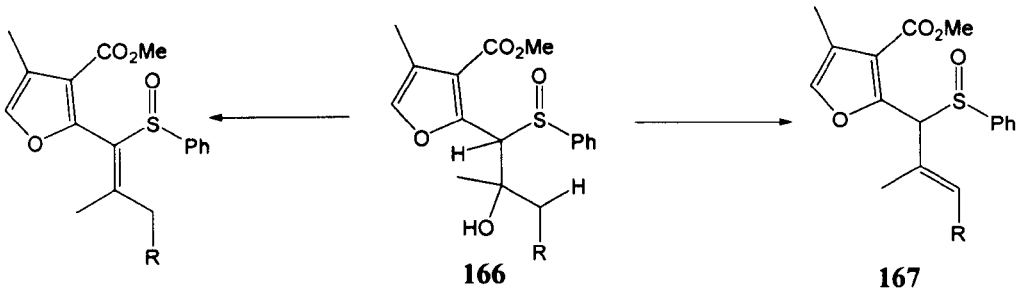
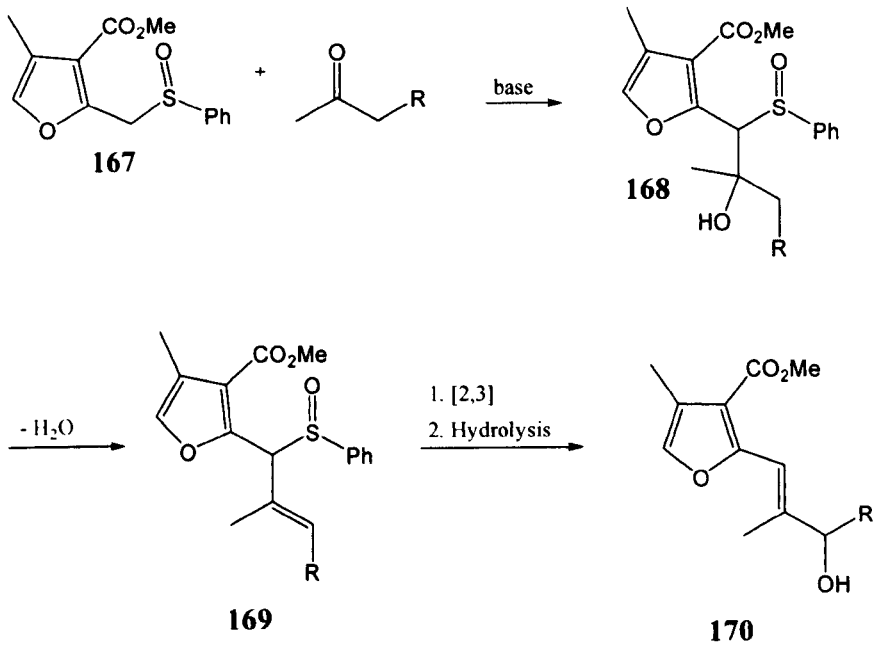


Figure 3.1 Representation of variation of alkyl chain lengths

Another foreseeable issue with this synthetic approach concerned the presence of two acidic sites for the conversion of **168** to **169**. At this E1cb elimination step, deprotonation at the R-group carbon would give the desired **167**. However, deprotonation of the sulfoxide α-proton would result in an undesired vinyllic sulfoxide species (scheme 3.2). The solution to this concern would be to condense the sulfoxide with a ketone containing an electron withdrawing R-group, such as an ester, to promote regioselective E1cb elimination at this site.



Scheme 3.2 Alternative paths for dehydration of **166**

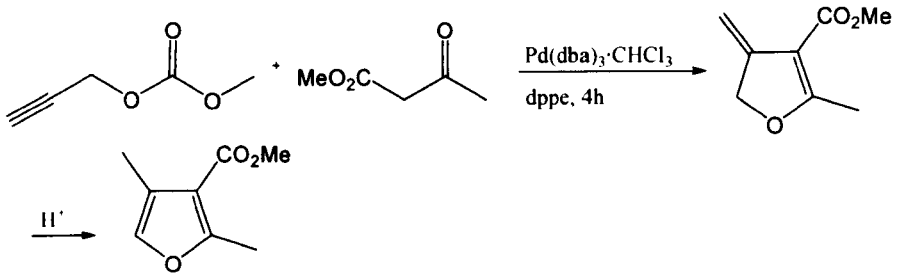


Scheme 3.3 Proposed model for ring-closing step

3.2 Synthesis of Furan Sulfide

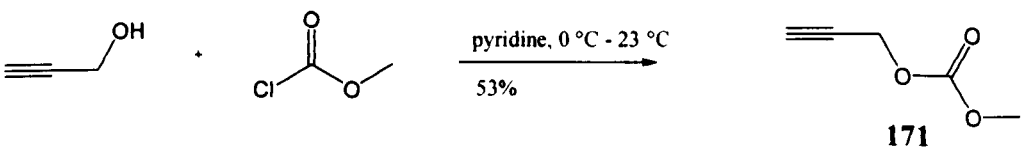
Tsuji and co-workers[94] developed a palladium(0) catalysed method using propynyl carbonate with soft carbonucleophiles, β-keto esters, under mild neutral conditions to prepare alkylidene-2,3-dihydrofurans. These unstable dihydrofurans were found to readily aromatise to their corresponding furans under slightly acidic

conditions (scheme 3.4). Our model furan was synthesized using this palladium chemistry which involved a palladium(0) catalysed ring closing step in which Pd(II) was the active catalytic species in the cycle. This procedure was a variation of the Tsuji palladium(0) catalysed ring annelation method in which we used carbonate (**171**) and a β-keto ester (**172**) as substrates for the conversion to **173**. (scheme 3.5 and scheme 3.6).



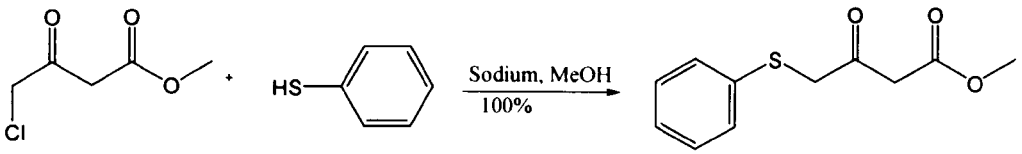
Scheme 3.4 Tsuji's Pd(0) furan ring annelation

Additionally, we used palladium acetate instead of palladium dibenzylideneacetone as the catalyst, thereby reducing the $Pd(OAc)_2$ (5 mol%) using bidentate diphenylphosphinoethane (10 mol%) as the ligand, as Tsuji had done previously, thus generating $Pd(dppe)_2$ using a more cost effective alternative to the conventional method used for the annelation. The catalytic cycle (scheme 3.8) began with the oxidative Pd(0) coordination to the propynyl carbonate species which displaced CO_2 and generated our methoxide base *in-situ*.



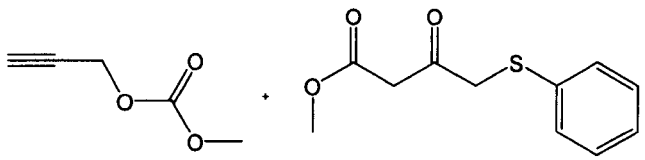
171

Scheme 3.5 Synthesis of propynyl carbonate

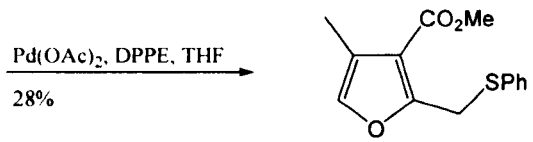


172

Scheme 3.6 Synthesis of phenylthioacetoacetate



171 **172**

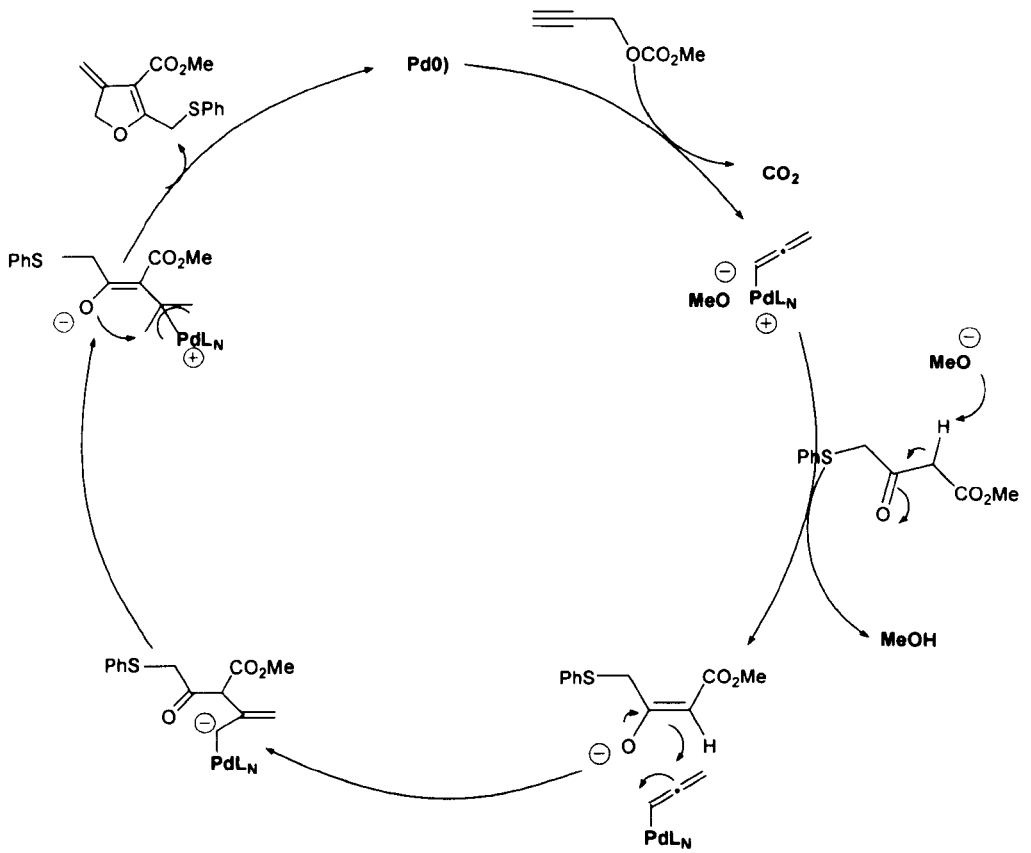


173

Scheme 3.7 Palladium(0) catalysed furan ring annelation

The methoxide base then deprotonated an acidic α-carbonyl proton of the methyl pheylthioacetoacetate, thus generating a reactive enolate, which performed a nucleophilic attack on the palladium complex. Following a second deprotonation, which gave a second enolate, an intramolecular ring closing reaction occurs with the β-elimination of the Pd(0) catalyst giving an oxygen heterocycle with an exocyclic double bond. Following aromatization with dilute HCl, our furan target (**173**) was generated. The methylfuroate can be oxidized with a variety of oxidants, such as sodium periodate,[95] to its sulfoxide.

Once prepared, the sulfoxide was to be subjected to the conditions as described above. The first step involved oxidation of the sulfide moiety to its corresponding sulfoxide.

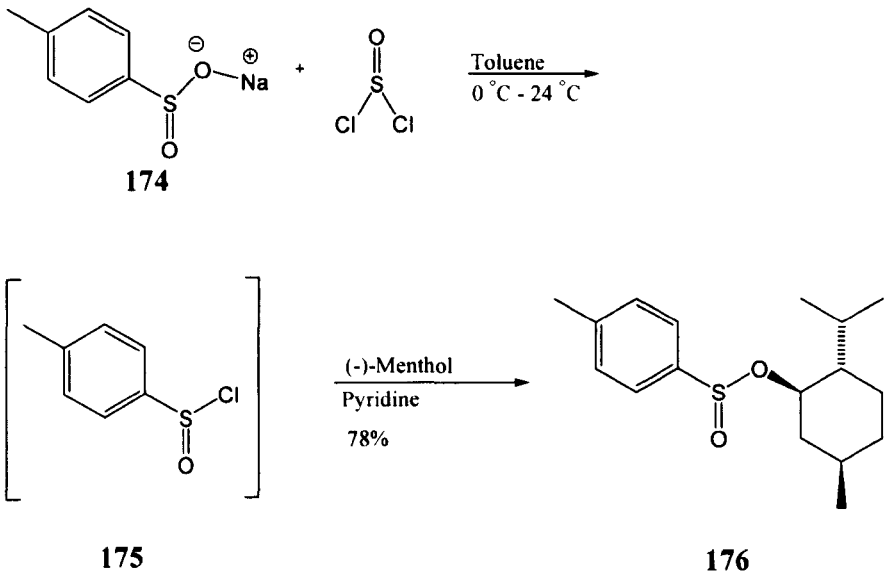


Scheme 3.8 Mechanism of Pd(0) catalysed furan annelation

3.3 Sulfide Oxidation

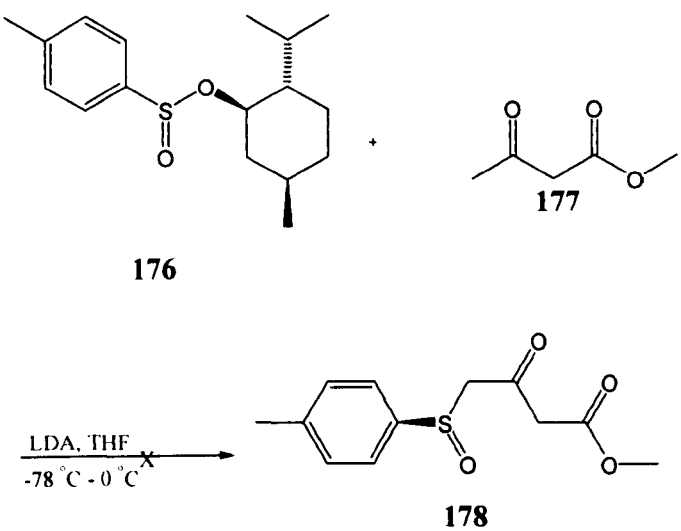
The sulfide oxidation of **173** was attempted using sodium periodate. Unfortunately, after varied attempts, this only resulted in the recovery of starting material. At this point, we decided that it could be useful to oxidize the sulfide prior to the furan annelation reaction as this could have proven to be a useful alternative to the aforementioned sulfide oxidation. We decided to utilize a synthetic route that would involve the generation of a chiral sulfoxide species using (−)-menthol as a

chiral auxiliary for this process (scheme 3.9).[96] It was hoped that the (–)-menthol would confer its chirality to the sulfoxide when structure **178** was generated.



174 **175** **176**

Scheme 3.9 Synthesis of menthyl sulfinate



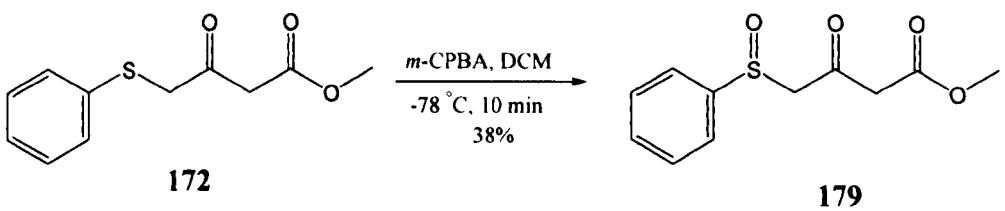
176 **177**

178

Scheme 3.10 Attempted synthesis of oxobutyric ester

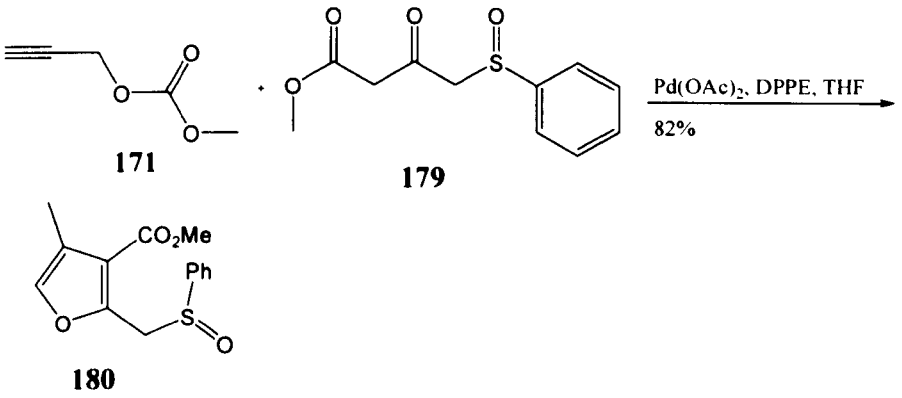
We succeeded in generating the menthyl sulfinate (**176**) in high yield, but at the next step of the synthesis, we encountered difficulties (scheme 3.10). This was probably due to the possibility that the LDA had not been generated *in-situ* as expected, or the possible presence of minor quantities of water in the reaction.

At this point, we decided that as it was not necessary to explore the chiral analog of our desired compound, therefore we proceeded with our previous phenylthioacetoacetate **172**. The Pd(0) had not been previously attempted using a sulfoxide species. Therefore, we decided to generate the sulfoxide from **172** prior to the annelation to determine how the sulfoxide would respond to the annelation. We first attempted the oxidation using Oxone[97] due to our previous successes with this reagent. The use of Oxone only resulted in the generation of the corresponding sulfone, a result of over-oxidation, which was apparent due to the ^{1}H NMR shift of the $-SOCH_2$ protons from the 3.7 ppm range for the sulfoxide to 4.2 ppm range for the corresponding sulfone. Therefore, *meta*-chloroperoxybenzoic acid[98] was next utilized as the oxidant for this conversion. This oxidant had been reported to successfully oxidize sulfides selectively to sulfoxides at low temperatures (-78 °C). Using these reaction conditions, we successfully synthesised our sulfoxide **179** (scheme 3.11).



172 **179**

Scheme 3.11 *m*-CPBA oxidation of sulfide



Scheme 3.12 Synthesis of furan sulfoxide

Once generated, sulfoxide **179** was subjected to the Pd(0) furan annelation reaction (scheme 3.12). The goal was to determine if the sulfoxide would react favourably to the annelation conditions. We also decided to optimise reaction conditions by adjusting the catalyst ratio from 5% - 30% to obtain a higher yield for this reaction. Using 30 mol% of $Pd(OAc)_2$ / 60 mol% DPPE, the desired sulfoxide was generated in 82% yield. We determined that we had generated the furan based on elemental analysis of the product (Theory C: 60.42%, H: 5.07%, Found C: 60.20%, H: 5.12%).

Chapter 4

CONCLUSION

Chapter 4

CONCLUSION

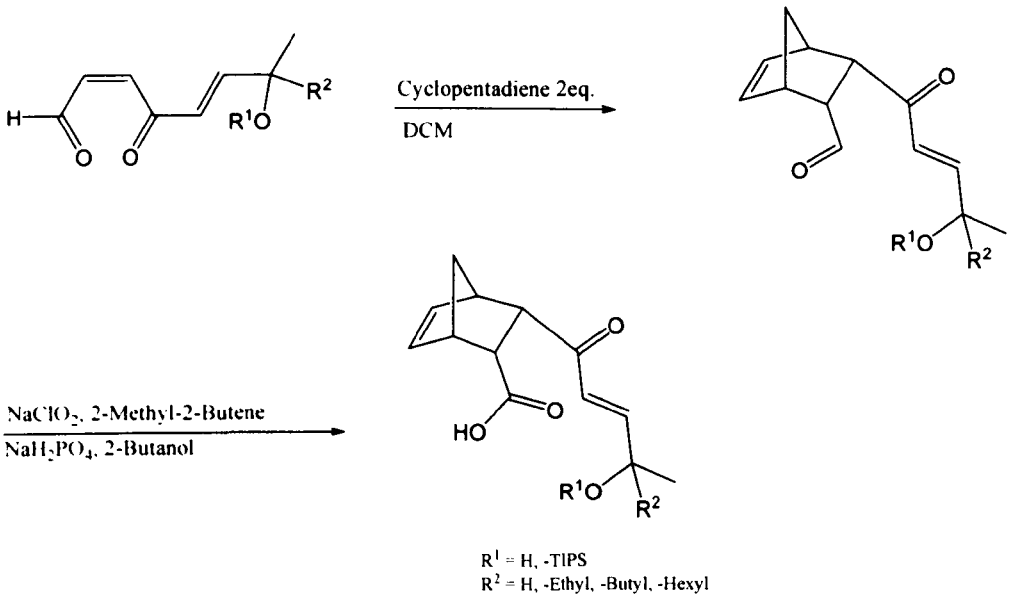
4.1 Oxidative Transformations of Furan

We have generated useful methods for the preparation of our substituted furyl alcohols and the oxidation of the respective furans to produce the 1,4-dicarbonyl species. These furans were fairly reactive, thus readily decomposed, polymerised, etc., even under inert atmospheres. Therefore, it was necessary to purify these compounds and carry on to further steps within a fairly reasonable amount of time (2-3 days) in order to ensure the integrity of this chemistry. The oxidative transformations were performed using catalytic quantities of DMDO, which was formed *in situ*. We devised this novel alternative in order to overcome the scale-up limitations of using isolated DMDO as the isolated DMDO could only be synthesised in 0.04 Molar concentration. Additionally, we found that the success of the *in-situ* oxidation of furans was dependent upon the lipophilicity of the furan substrates (table 2.2). Thus, furans with a CLogP less than 1.14 were not sufficiently oxidized under these conditions. Following these results, we concluded that bulky, lipophilic furans, such as those containing TBS sidechains were oxidized under the biphasic conditions of the *in-situ* DMDO oxidation.

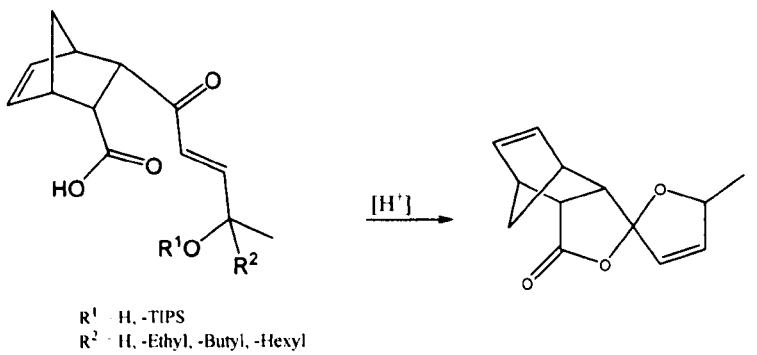
The subsequent oxidation of the aldehyde to its corresponding carboxylic acid also posed a sizable challenge. These oxidations initially resulted in the mixture of complex by-products due to the fact that the 1,4-dicarbonyls are highly reactive species, and due to the high degree of conjugation of these particular compounds, they often reacted in unpredictable ways. Optimization of the aldehyde oxidation to

generate carboxylic acid required a great deal of method variation using a range of equivalents of sodium chlorite oxidant and 2-methyl-2-butene hypochlorite scavenger. Eventually, we determined a strategy that allowed us to overcome this problem. We resolved this by lowering of the conjugation level at the *cis* double bond *via* Diels-Alder cycloaddition at this position. The functionality increase thus lowered the reactivity of these compounds and presented us with a suitable template for the aldehyde oxidation to the corresponding acid. We successfully oxidized out TIPS protected **165** to its corresponding acid, and this would be followed by the oxidation of the alkylated furans (scheme 4.1).

The next step within the model synthesis would entail the synthesis of the spiroketal lactone (scheme 4.2), which would be the last step within the envisaged total synthesis of neoliacine. The ring-closing cascade, which would initiate the sequence, would be triggered by the deprotection of the alcohol as described in chapter 2. This would involve an acid catalysed spiroketalization, for which our TIPS protected compound **165** would be suitable for, as deprotection would involve acid catalysed conditions. On the other hand, alcohols **163** and **164** require basic conditions for removal of the alcohol proton, therefore would require different conditions to effect spiroketalization.



Scheme 4.1 General scheme representing synthesis of carboxylic acid

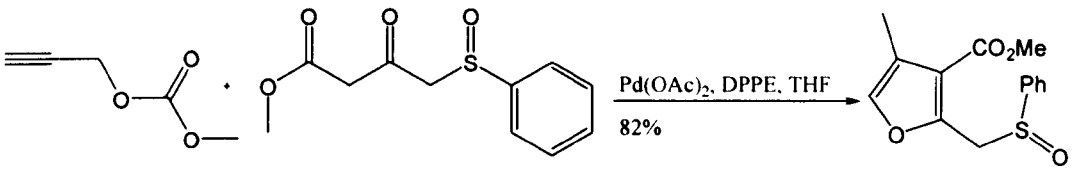


Scheme 4.2 Envisaged synthesis of spiroketal

4.2 Pd(0) Furan Annelation

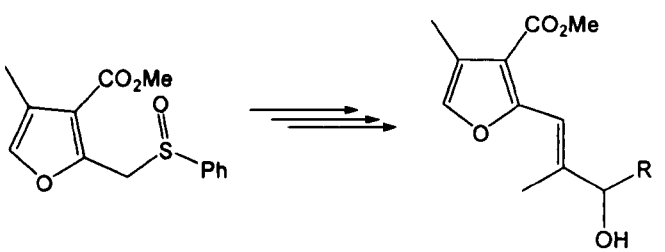
Our second model system, the thiofuran generated by the Pd(0) ring annelation reaction also required method optimization. We developed a reaction sequence that allowed us to generate our sulfinylfuran at the furan annelation step. This was desirable as we encountered difficulties when we attempted to oxidize the thiofuran. Therefore, the phenylthioacetoacetate was oxidized to its corresponding

sulfoxide, then subjected to the annelation. This outcome of this was uncertain as the sulfoxide functionality had not been previously been utilized under the reaction conditions of the furan. We were pleased to find that the reaction worked very well in high yield (scheme 4.3).



Scheme 4.3 Generation of sulfinylfuran

With this accomplished, future work would involve the condensation of the sulfinylfuran with various ketones to create model systems to be applied toward the final ring closing step of the neoliacine product as described in chapter 3 (see scheme 4.4).

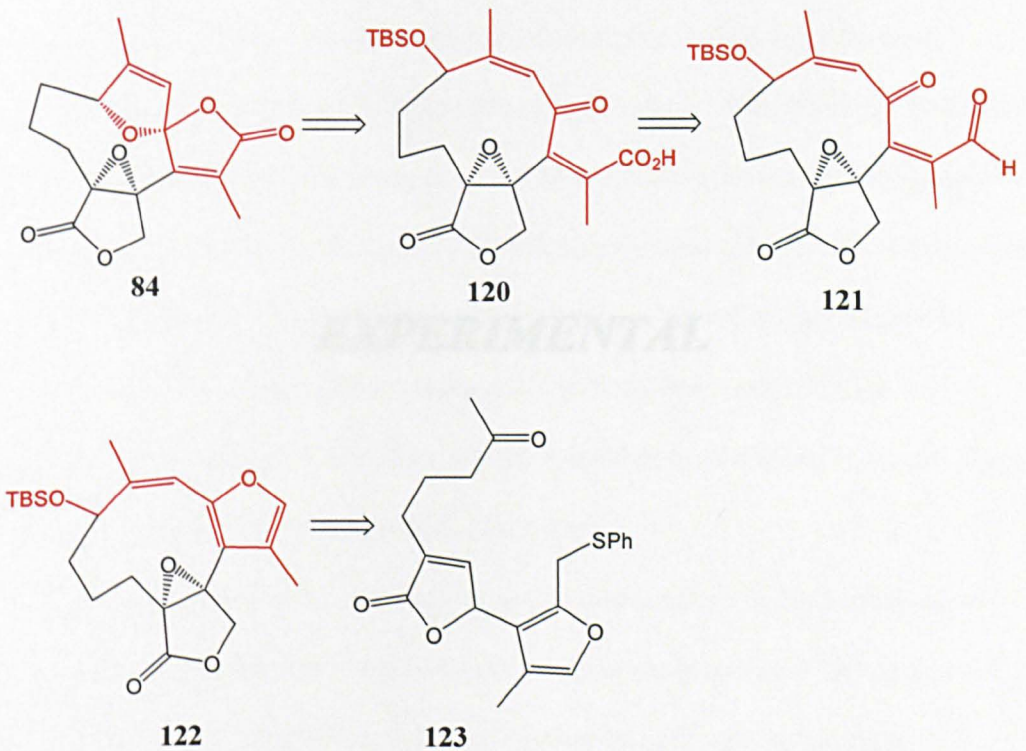


Scheme 4.4 Synthesis of allylic alcohol

4.3 Overview

In summary, the 1,4-dicarbonyls generated from these furans, can be applied to the total synthesis of neoliacine as model systems (scheme 4.5) as stated previously.

The model systems could be applied as an extension of the sequence of transformations that initiated with the highlighted portion of **122**, which incorporated the furan species, and terminate with the highlighted spiroketal portion of **84** following the series of furan oxidations. On a more general basis, these compounds could be utilized for the synthesis of a range of natural products, from the structurally simple *cis*-jasmone to the complex spirocycle-containing okadaic acid (section 1.5). Thus, the synthetic scope of furans applies to a wide range of natural products.



84 **120** **121**

122 **123**

Scheme 4.5 Retrosynthesis of neoliacine

Chapter 5

EXPERIMENTAL

Chapter 5

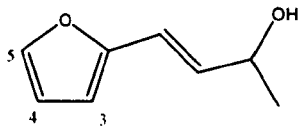
EXPERIMENTAL

Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected. Unless otherwise specified, THF, dioxane, and Et_2O were distilled under nitrogen atmosphere, in dried glassware, over sodium and benzophenone prior to use. Toluene and dichloromethane were freshly distilled over powdered CaH_2 prior to use. Microanalyses were determined using a Carlo Elba elemental analyser instrument. Nominal and accurate mass spectra were recorded on a VG7070E, CIPOS, Kratos Profile HV3 and TRIO1000 instruments. Infrared spectra were recorded on a Perkin Elmer 881 infrared spectrophotometer, over the range 4000-800 cm^{-1}. ^{1}H-NMR spectra were recorded on a Bruker AC200 (200 MHz), or a Bruker 400 Avance (400 MHz) instrument. ^{13}C-NMR spectra were recorded on a Bruker 400 Avance (100 MHz) instrument. All chemical shifts are quoted in ppm relative to tetramethylsilane (TMS). The following abbreviations were used to define the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The coupling constants (*J*) are measured in Hertz (Hz).

Reactions were monitored by thin layer chromatography (TLC), performed on glass backed silica gel Merk 60F-254 plates in a variety of solvents.The plates were visualised by U.V. light (254 nm) and by application of cerium ammonium molybdate (CAM), p-anisaldehyde, potassium permanganate or 2,4-dinitrophenyl hydrazine and baked with a heat gun. Column chromatography was conducted with Merck Kieselgel 60: 230-400 mesh for flash chromatography.

Neolicine Spiroketal Synthesis

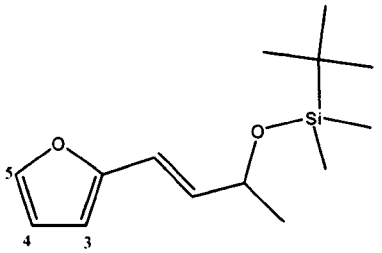
4-Furan-2-yl-but-3-en-2-ol (133)



Furfurylideneacetone (6.86 g, 50.4 mmol) was added to methanol (75 mL) followed by the addition of $CeCl_3 \cdot 7H_2O$ (18.84 g, 50.2 mmol). The solution was stirred for 10 minutes, then submerged in a 0 °C ice bath. $NaBH_4$ (1.48g, 39.0 mmol) was added in portions over a period of 45 minutes with stirring. The mixture was quenched with water (50 mL) and the mixture was subsequently acidified to pH 4 using dilute hydrochloric acid (1N). Following extraction of the aqueous layer with ether (3 x 50 mL), the combined organic layers were dried over magnesium sulfate. The solvent was then removed under reduced pressure to afford a dark brown oil. The crude material was purified by flash column chromatography (EtOAc / *n*-hexane, 1:2) to give the title compound as a pale orange oil (5.3 g, 76%).

δ_H (400 MHz, $CDCl_3$) 7.32 (1H, b.s., furyl-5), 6.37 (1H, d, J = 15.7, C<u>H</u>=CH), 6.34 (1H, dd, J = 3.3, 1.4, furyl-4), 6.20 (1H, d, J = 3.1, furyl-3), 6.19 (1H, dd, J = 15.7, 5.0), 4.41 (1H, qd, J = 6.4, 5.0, -CH), δ 2.1 (1H, b.s, OH), 1.3 (3H, d, J = 6.4, -CH_3); MS (C.I. +ve) (%) 138(M+, 9.29%), 121(M-OH, 100%); CHN Required for $C_8H_{10}O_2$: C, 69.54%, H, 7.30% Found: C, 69.39%, H, 7.27%. δ_C (100 MHz, $CDCl_3$) 152.7, 142.36, 132.6, 118.1, 111.7, 108.4, 68.9, 23.8; IR ν_{max}/cm^{-1}(neat) 3347 (s, OH), 2974 (m, CH), 1457 (w, alkene), 1049 (s, COC).

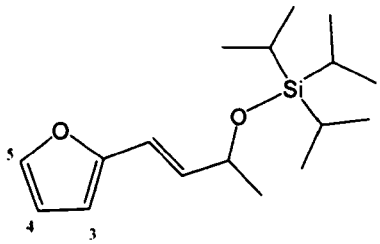
((*E*)-(4-Furan-2-yl-1)but-3-en-2-yloxy(*t*-butyl)dimethylsilane (134)



Dry THF (50 mL) was syringed into a flask containing alcohol (133) (4.75 g, 0.03 mol) under nitrogen. Imidazole (10.52 g, 0.16mol) and *t*-butyldimethylsilyl chloride (11.61 g, 0.08 mol) were added to the mixture. The mixture was left stirring overnight under nitrogen. The following day, all volatiles were removed by rotary evaporation and deionized water (75 mL) was added to the resulting sludge, which was extracted with dichloromethane (3 x 35 mL). The combined organic layers were dried over magnesium sulfate and vacuum filtered over celite. Rotary evaporation of the volatiles under reduced pressure gave a clear, orange oil. The crude material was purified by flash column chromatography (EtOAc / hexane, 1 : 5). The title product was recovered as a yellow oil (8.2 g, 94%).

δ_H (400 MHz, $CDCl_3$) 7.23 (1H, b.s., furyl-5), 6.27 (1H, d, J = 15.3, C<u>H</u>=CH), 6.26 (1H, dd, J = 2.4, 1.3, furyl-4), 6.11 (1H, d, J = 2.4, furyl-3), 6.09 (1H, dd, J = 15.7, 5.1, CH=C<u>H</u>), 4.36 (1H, dq, J = 6.4, 5.1, -CH), 1.18 (3H, d, J = 6.4, $-CH_3$), 0.84 (9H, s, *t*-butyl), 0.82 (3H, s, CH_3), 0.80 (3H, s, CH_3); (C.I. +ve) (%) 253(M+, 6.86%), 159(M-C_6H_7O,100%); δ_C(400 MHz, $CDCl_3$) 151.9, 140.4, 132.3, 115.3, 110.0, 106.0, 67.6, 24.8, 23.4, 17.2, -5.7; ν_{max}/cm^{-1} (neat) 2953 (s, CH), 1471 (s, alkene), 1255 (s, Si-CH), 1082 (s, COC), 886 (s, Si-O), 774 (s, *t*-butyl).

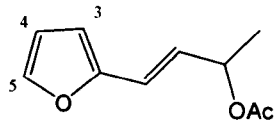
((*E*)-(4-Furan-2-yl-1)but-3-en-2-yloxytriisopropylsilane (148)



Alcohol (133) (0.07 g, 0.5 mmol) was dissolved in dry THF (20 mL) under nitrogen. Imidazole (0.07 g, 1.1 mmol) and triisopropylsilyl chloride (0.13 mL, 0.5 mmol) were added to the mixture. The solution was left stirring overnight under nitrogen. The following day, the mixture was diluted with deionized water (25 mL) and extracted with diethyl ether (3 x 35 mL). The combined organic layers were washed with deionized water (3 x 30 mL), dried over magnesium sulfate, and vacuum filtered over celite. Rotary evaporation of the volatiles under reduced pressure gave a clear, orange oil. The crude material was purified by flash column chromatography (EtOAC / light petroleum ether, 1 : 5). The title product was recovered as a yellow oil (1.1 g, 70%).

δ_H (400 MHz, $CDCl_3$) 7.15 (1H, b.s., furyl-5), 6.37 (1H, d, J = 15.7, C<u>H</u>=CH), 6.35 (1H, dd, J = 3.16, 1.44, furyl-4), 6.19 (1H, d, J = 3.16, furyl-3), 6.18 (1H, d, J = 15.7, CH=C<u>H</u>), 4.36 (1H, dq, J = 6.36, 5.0, -CH), 1.31 (3H, d, J = 6.36, CH_3), 1.23 – 1.27 (1H, m, -SiCH), 1.06 (18H, d, J = 7.16, -SiCHC<u>H</u>$_3$); HRMS (C.I. +ve) (%) ([M-H_2O+H]$^+$, Required: 295.07015, Found: 295.07026); δ_C (100 MHz, $CDCl_3$) 141.9, 134.2, 116.7, 111.5, 107.5, 69.2, 25.3, 18.6, 12.8; IR ν_{max}/cm^{-1} (neat) 2944 (s, CH), 1462 (s, alkene), 1251 (s, Si-CH), 881 (s, Si-O).

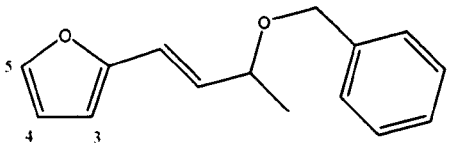
(E)-4-(Furan-2-yl)but-3-en-2-yl acetate (136)



Alcohol (133) (0.78 g, 5.68 mmol) was weighed into a flask and dissolved in acetic anhydride (15 mL, 0.16 mol) and pyridine (20 mL, 0.25 mol) under nitrogen. N,N-4-dimethylaminopyridine (0.25 g, 5.68 mmol) was added to the mixture. The mixture was left stirring overnight under nitrogen. The following day, all volatiles were removed by rotary evaporation with heating (37 °C) and the resulting mixture was extracted with dichloromethane (3 x 35 mL), then washed with deionized water (5 x 35 mL). The combined organic layers were dried over magnesium sulfate and vacuum filtered over celite. Rotary evaporation of the volatiles under reduced pressure gave a brown oil. The crude material was purified by flash column chromatography (EtOAc / light petroleum, 1 : 5). The title product was recovered as a yellow oil (0.8 g, 82%).

δ_H (400 MHz, $CDCl_3$) 7.33 (1H, b.s., furyl-5), 6.41 (1H, d, J = 15.9, C<u>H</u>=CH), 6.36 (1H, dd, J = 1.9, 3.3, furyl-4), 6.3 (1H, d, J = 3.3, furyl-3), 6.1 (1H, dd, J = 15.9, 6.7, CH=C<u>H</u>), 5.5 (1H, dq, J = 6.5, 6.7, -CH), 2.1 (3H, s, CH_3CO), 1.38 (3H, d, J = 6.5, -C<u>H</u>$_3$CH); (C.I.+ve) (%) 198($M+NH_4$, 7.21%), 180($[M]^+$, 2.78%), 121($[M - OAc]^+$, 100%); δ_C(400 MHz, $CDCl_3$) 170.3, 152.0, 142.2, 127.5, 119.8, 111.4, 108.7, 70.6, 21.3, 20.3; ν_{max}/cm^{-1} (neat) 2980 (m, CH_3), 1740 (s, C=O), 1660 (w, alkene).

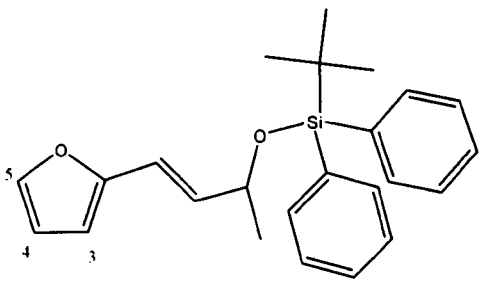
2-((*E*)-3-(Benzyloxy)but-1-enyl)furan (139)



Alcohol (133) (0.61 g, 4.0 mmol) was weighed into a dry, 3-neck flask and placed under nitrogen and dissolved in dry THF (25 mL) followed by the addition of sodium hydride (0.19 g, 8.0 mmol). Tetrabutyl ammonium bromide (1.48 g, 4.0 mmol) and benzyl bromide (0.48 mL, 4.1 mmol) were added to the stirred solution. The mixture was left stirring overnight at room temperature. The following day, the reaction was quenched with saturated ammonium chloride (10 mL). Following extraction of the aqueous layer with diethyl ether (3 x 20 mL), the combined organic layers were dried over magnesium sulfate and vacuum filtered over celite. The solvent was then removed under reduced pressure to afford a dark brown oil. The crude material was purified by flash column chromatography (EtOAc / light petroleum, 1 : 3). The title product was recovered as a clear, yellow oil (0.5 g, 58%).

δ_H (400 MHz, $CDCl_3$) 7.4 – 7.3 (6H, m, phenyl-H, furyl-5), 6.4 (1H, d, J = 15.9, -C<u>H</u>=CH), 6.3 (1H, dd, J = 3.2, 1.8, furyl-4), 6.2 (1H, d, J = 3.2, furyl-3), 6.1 (1H, dd, J = 15.9, 7.3, CH=C<u>H</u>), 4.6 (1H, d, J = 12.0, C<u>H</u>$_2$), 4.4 (1H, d, J = 12.1, C<u>H</u>$_2$) 4.1 (1H, dq, J = 6.5, 7.3, -C<u>H</u>), 1.4 (3H, d, J = 6.5, CH_3); (C.I.+ve) (%) 229($[M+H]^+$, 0.16%), 137($[M-Bn]^+$, 3.35%), 108($[OBn+H]^+$,100%) ; δ_C(400 MHz, $CDCl_3$) 152.8, 142.4, 138.2, 130.9, 128.8, 127.8, 127.4, 120.0, 108.3, 111.2, 75.8, 70.5, 22.1.

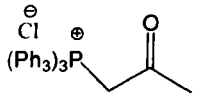
((*E*)-4-(Furan-2-yl)but-3-en-2-yloxy)(*tert*-butyl)diphenylsilane (140)



Dry dichloromethane (30 mL) was syringed into a flask containing alcohol (133) (0.69 g, 4.99 mmol) under nitrogen. Imidazole (0.68 g, 0.01 mol) and *t*-butyldiphenylsilyl chloride (1.43 mL, 5.20 mmol) were added to the mixture. The mixture was left stirring overnight under nitrogen. The following day, the solution was diluted with deionized water (30 mL) and extracted with dichloromethane (3 x 35 mL). The combined organic layers were dried over magnesium sulfate and vacuum filtered over celite. Rotary evaporation of the volatiles under reduced pressure gave a clear, orange oil. The crude material was purified by flash column chromatography (EtOAc / light petroleum, 1 : 5). The title product was recovered as a yellow oil (1.2 g, 66%).

δ_H (400 MHz, $CDCl_3$) 7.7 – 7.6 (4H, m, phenyl-H), 7.4 – 7.3 (7H, m, phenyl-H, furyl-5), 6.3 (1H, dd, J = 3.3, 1.9, furyl-4), 6.2 (1H, d, J = 15.9, -C<u>H</u>=CH), 6.2 (1H, dd, J = 15.7, 5.4, -CH=C<u>H</u>), 6.1 (1H, d, J = 3.3, furyl-3), 4.5 (1H, dq, J = 6.2, 5.3), 1.2 (3H, d, J = 6.2, $-CH_3$), 1.08 (9H, s, *t*-butyl); HRMS (C.I. +ve) (%) ([M-H_2O+H]$^+$, Required: 377.13666, Found: 377.19222), 376([M]$^+$, 13.26%), 319([M-*t*-butyl]$^+$, 15.88%), 121([M-OTBDPS]$^+$, 100%); δ_C(400 MHz, $CDCl_3$) 153.3, 142.0, 134.9, 133.3, 129.9, 129.9, 128.1, 117.2, 111.5, 107.7, 70.2, 27.4, 24.7, 19.7.

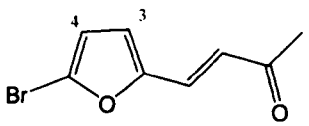
(2-Oxo-propyl)-triphenyl-phosphonium chloride (143)



Triphenylphosphine (10 g, 38.1 mmol) was weighed into a dry flask, flushed with nitrogen, and dissolved in dry toluene (70 mL). Chloroacetone (3.04 mL, 38.1 mmol) was added to the stirred mixture and the mixture was warmed to 65 °C and left overnight. After 24 h, the majority of the toluene was removed under reduced pressure and the solid product was filtered and washed with cold diethyl ether (3 x 10 mL), then dried under reduced pressure to give the desired product as a light brown solid (m.p. 235 238 °C, 9.6 g, 72%).

CHN $C_{21}H_{20}ClOP$ requires C 71.09; H 5.68: Found C 71.27; H 5.63. δ_H (400MHz, $CDCl_3$) 7.5 – 8.1 (15H, m, Ph-H), 6.13 (2H, d, J = 11.7 Hz, $-CH_2$), 2.57 (3H, s, CH_3), δ_C 201.9, 135.1, 130.6, 119.7, 40.1, 32.8.

(*E*)-4-(5-Bromofuran-2-yl)but-3-en-2-one (145)

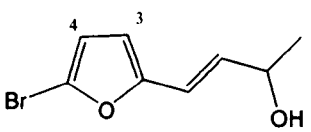


Triphenylphosphonium chloride (143) (1.48 g, 4.2 mmol) was weighed into a dry flask, flushed with nitrogen, and dissolved in dry DCM (25 mL). Potassium carbonate (0.59 g, 4.2 mmol) and 18-crown-6 (0.01 g, 0.04 mmol) were added to

the solution and the mixture was refluxed overnight. The following day, 5-bromo-2-furaldehyde (0.74 g, 4.2 mmol) was weighed into a dry flask, flushed with nitrogen, and dissolved in dry DCM (7 mL). This solution was added to the reaction flask and the mixture was allowed to stir for a further 0.5 h under reflux. The solvent was removed under reduced pressure and the resulting slurry was diluted with deionized water (10 mL) and diethyl ether (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over magnesium sulfate and filtered. The solution was left in the refrigerator overnight to precipitate triphenylphosphine oxide, then filtered. The solvent was removed under reduced pressure to give a brown oil. Column chromatography on silica gel (EtOAc / light petroleum, 1 : 3) gave the product as a yellow solid (m.p. 186-188 °C, 0.3 g, 37% yield).

CHN $C_8H_7BrO_2$ requires C 44.68; H 3.28: Found C 44.67; H 3.28. NMR (400MHz) δ_H ($CDCl_3$) 7.2 (1H, d, J = 15.8 Hz, -C<u>H</u>=CH), 6.7 (1H, d, J = 15.8 Hz, -CH=C<u>H</u>), 6.6 (1H, d, J = 3.4 Hz, furyl-4), 6.4 (1H, d, J = 3.4 Hz, furyl-3), 2.3 (1H, s, COC<u>H</u>$_3$). δ_C 197.7, 153.3, 128.3, 124.8, 117.9, 114.8, 28.6; *m/z* (C.I.) 233 (7%, $[M+(NH_4)]^+$), 231 (7%, $[M+(NH_4)]^+$), 215 (76%, $[M-(Br)]^+$), 137 (100%, $[M]^+$); IR ν_{max}/cm^{-1}(neat) 2917 (m, CH_3), 1685 (m, C=O), 1608 (s, C=C), 963 (m, C=C-H).

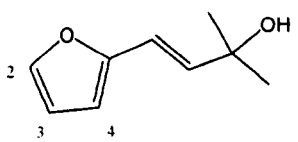
(*E*)-4-(5-Bromofuran-2-yl)but-3-en-2-ol (146)



Bromofuran (145) (1.88 g, 8.8 mmol) was added to methanol (50 ml) followed by the addition of $CeCl_3 \cdot 7H_2O$ (3.26 g, 8.8 mmol). The solution was stirred for 10 min, then submerged in a 0 °C ice bath. $NaBH_4$ (0.27g, 0.80 mmol) was added in portions over a period of 15 minutes with stirring. The mixture was quenched with water (25 ml) and the mixture was subsequently acidified to pH 4 using dilute hydrochloric acid (1N). Following extraction of the aqueous layer with diethyl ether (3 x 25 mL), the combined organic layers were dried over magnesium sulfate. The solvent was then removed under reduced pressure to afford a dark brown oil. The crude material was purified by flash column chromatography (EtOAc / *n*-hexane, 1: 2) to give the title compound as a pale yellow oil (0.6 g, 31%).

δ_H (400MHz, $CDCl_3$) 6.9 (1H, d, J = 15.8 Hz, -C<u>H</u>=CH), 6.4 (1H, dd, J = 15.8, 5.1, -CH=C<u>H</u>), 6.3 (1H, d, J = 3.1 Hz, furyl-4), 6.2 (1H, d, J = 3.1 Hz, furyl-3), 4.43 (1H, qd, J = 6.2, 5.1), 2.0 (1H, b.s., -OH), 1.3 (3H, d, J = 6.2);. *m/z* (C.I.) 235 (3%, $[M+(NH_4)]^+$), 233 (3%, $[M+(NH_4)]^+$), 217 (100%, $[M]^+$), 215 (100%, $[M]^+$) 137 (49%, $[M-(Br)]^+$); IR ν_{max}/cm^{-1}(neat) 3360 (s, OH), 2920 (m, CH_3), 1610 (s, C=C), 963 (m, C=C-H).

(*E*)-4-(Furan-2-yl)-2-methylbut-3-en-2-ol (154)

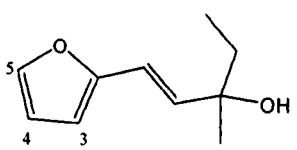


Furfurylidene acetone (1.09 g, 8.0 mmol) was weighed into a dry, 3-neck flask and placed under nitrogen. Dry THF (20 mL) was syringed into the flask, then methyllithium (7.5 mL, 1.6 M solution in hexane) was slowly syringed into the

mixture under nitrogen at −78 °C. The mixture was left stirring overnight at room temperature. The following day, the reaction was quenched with saturated ammonium chloride (15 mL). Following extraction of the aqueous layer with ether (3 x 25 mL), the combined organic layers were dried over magnesium sulfate and vacuum filtered over celite. The solvent was then removed under reduced pressure to afford a dark brown oil. The crude material was purified by flash column chromatography (light petroleum / EtOAc, 1 : 2). The title product was recovered as a clear, yellow oil (0.6 g, 49%).

δ_H (400 MHz, $CDCl_3$) 7.31(1H, b.s., furyl-5), 6.43 (1H, d, J = 15.8, -C<u>H</u>=CH), 6.37 (1H, dd, J = 3.1, 1.7, furyl-4), 6.30 (1H, d, J = 15.8, -CH=C<u>H</u>), 6.22 (1H, d, J = 3.1, furyl-3), 2.33(1H, b.s., -OH), 1.40(6H, s); HRMS (C.I. +ve) (%) ($[M-H_2O+H]^+$, Required: 135.08099, Found: 135.08103), 170($[M+NH_4]^+$, 1%), 153($[M+H]^+$, 9%), 137($[M-CH_3]^+$, 100%) δ_C (100 MHz, $CDCl_3$) 152.6, 145.0, 129.4, 115.7, 112.6, 111.3, 70.9, 29.9; IR ν_{max}/cm^{-1} (neat) 3411 (s, OH), 2917 (s, CH_3), 1622 (m, C=C), 972 (w, C=C-H).

(*E*)-1-(Furan-2-yl)-3-methylpent-1-en-3-ol (155)

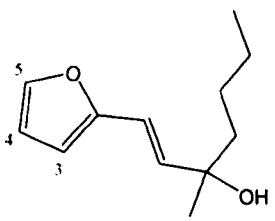


According to the above procedure, furfurylidene acetone (1.09 g, 8.0 mmol) was weighed into a dry, 3-neck flask and placed under nitrogen. Dry THF (20 mL) was

syringed into the flask, then ethyllithium (24 mL, 0.5 M solution in hexane) was slowly syringed into the mixture. The crude brown oil was purified by flash column chromatography (light petroleum / EtOAc, 1:2). The title product was recovered as a clear, yellow oil (0.3 g, 24%).

δ_H (400 MHz, $CDCl_3$) 7.28(1H, b.s., furyl-5), 6.38 (1H, d, J = 15.8, -CH=CH), 6.31 (1H, dd, J = 2.8, 2.1, furyl-4), 6.17 (1H, d, J = 15.8, -CH=CH), 6.16 (1H, d, J = 2.8, furyl-3), 1.99 (1H, b.s., -OH), 1.58 (2H, q, J = 7.6, $-CH_2$), 1.29 (3H, s, $-CH_3$), δ0.88 (3H, t, J = 7.6, $-CH_3$); HRMS (C.I. +ve) (%) ($[M-H_2O+H]^+$, Required: 149.09665, Found: 149.09659), 184 ($[M+NH_4]^+$, 2.51%), 151 ($[M-CH_3]^+$, 8.42%), 149 ($[M-OH]^+$, 100%); δ_C (100 MHz, $CDCl_3$) 153.1, 142.1, 135.6, 116.4, 114.0, 111.9, 73.7, 35.7, 28.1, 8.7; IR ν_{max}/cm^{-1}(neat) 3420 (s, OH), 2926 (s, CH_3), 1626 (m, C=C).

(*E*)-1-(Furan-2-yl)-3-methylhept-1-en-3-ol (156)

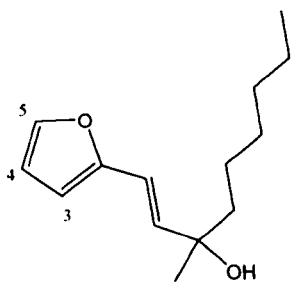


According to the above procedure, furfurylidene acetone (1.09 g, 8.0 mmol) was weighed into a dry, 3-neck flask and placed under nitrogen. Dry THF (20 mL) was syringed into the flask, then butyllithium (4.8 mL, 2.5 M solution in hexane) was slowly syringed into the mixture. The crude brown oil was purified by flash column

chromatography (light petroleum / EtOAc, 1:2). The title product was recovered as a clear, yellow oil (1.2 g, 79%).

δ_H (400 MHz, $CDCl_3$) 7.33 (1H, b.s., furyl-5), 6.42 (1H, d, J = 15.9, -C<u>H</u>=CH), 6.36 (1H, dd, J = 3.3, 1.9, furyl-4), 6.23 (1H, d, J = 15.9, -CH=C<u>H</u>), 6.21 (1H, d, J = 3.3, furyl-3), 2.07 (1H, b.s., -OH), 1.46 (2H, t, J = 3.6, aliphatic-CH_2), 1.35 (3H, s, -CH_3), 1.30 - 1.33 (4H, m, aliphatic-CH_2), 0.91 (3H, t, J = 6.9, -CH_3); MS (C.I. +ve) (%) 212 ($[M+NH_4]^+$, 23%), 195 ($[M+H]^+$, 100%), 177 ($[M-OH]^+$, 84%); δ_C 100 MHz, $CDCl_3$) 153.6, 142.5, 136.4, 116.6, 112.1, 108.4, 73.9, 43.5, 27.1, 24.0, 23.4, 14.8.

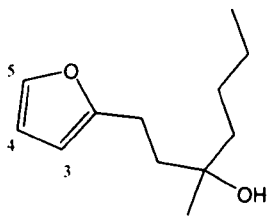
(*E*)-1-(Furan-2-yl)-3-methylnon-1-en-3-ol (157)



According to the above procedure, furfurylidene acetone (1.09 g, 8.0 mmol) was weighed into a dry, 3-neck flask and placed under nitrogen. Dry THF (20 mL) was syringed into the flask, then hexyllithium (4.2 mL, 2.3 M solution in hexane) was slowly syringed into the mixture. The crude brown oil was purified by flash column chromatography (light petroleum / EtOAc, 1:2). The title product was recovered as a clear, yellow oil (1.1 g, 61%).

δ_H (400 MHz, $CDCl_3$) 7.33 (1H, d, J = 1.44, furyl-5), 6.42 (1H, d, *J* = 16.0, -C<u>H</u>=CH), 6.37 (1H, dd, *J* = 3.2, 1.4, furyl-4), 6.23 (1H, d, *J* = 16.0, -CH=C<u>H</u>), 5.99 (1H, d, *J* = 3.2, furyl-3), 2.32 (1H, b.s., -OH), 1.35 (3H, s, $-CH_3$), 1.30 - 1.34 (10H, m, aliphatic-CH_2), 0.88 (3H, t, *J* = 6.9, $-CH_3$); HRMS (C.I. +ve) (%) ($[M-H_2O+H]^+$, Required: 223.16980, Found: 223.17008), 240 ($[M+NH_4]^+$, 3%), 205 ($[M-H_2O+H]^+$, 100%); δ_C (100 MHz, $CDCl_3$) 153.2, 142.0, 136.0, 116.2, 111.6, 107.9, 73.4, 43.1, 34.9, 29.7, 28.6, 26.6, 23.5, 14.3; IR ν_{max}/cm^{-1}(neat) 3420 (s, OH), 2917 (s, CH), 1626 (m, C=C), 968 (m, C=C-H).

1-(Furan-2-yl)-3-methylheptan-3-ol (158)



Furan (156) (0.4 g, 2.06 mmol) was weighed into a flask, dissolved in EtOAc (20 mL), and degassed under inert atmosphere. Palladium hydroxide, Pd 20% on carbon, (0.05 g) was added to the stirred solution, then the solution was placed under hydrogen atmosphere for 3 h. The catalyst was filtered off followed by rotary evaporation of the solution to remove all volatiles. The crude yellow oil was purified by flash column chromatography (light petroleum / EtOAc, 1:2). The title product was recovered as a clear oil (0.3 g, 84% yield).

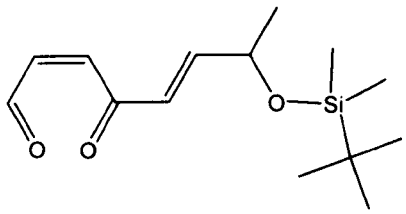
δ_H (400 MHz, $CDCl_3$) 7.29(1H, b.s., furyl-5), 6.27 (1H, dd, J = 3.0, 1.9, furyl-4), 5.99 (1H, d, J = 3.0, furyl-4), 2.71 (2H, t, J = 7.8, furan-$C\underline{H_2}$-CH_2), 2.06(1H, b.s., -OH), 1.48 (2H, t, J = 7.8, furan-CH_2-$C\underline{H_2}$), 1.30 - 1.34 (6H, m, aliphatic-CH_2), 1.29 (3H, s, -CH_3), 0.90 (3H, t, J = 6.8, -CH_3); HRMS (C.I. +ve) (%) ([M+H], Required: 197.15414, Found: 197.15459), 197 ($[M+H]^+$, 56. %), 196 ($[M]^+$, 8%), 179 ($[M-H_2O+H]^+$, 100%); δ_C (100 MHz, $CDCl_3$) 156.3, 140.8, 110.2, 104.5, 67.7, 42.7, 41.1, 27.1, 26.8, 23.3, 23.3, 14.1; IR ν_{max}/cm^{-1}(neat) 3417 (s, OH), 2932 (s, CH).

3,3-Dimethyldioxirane (129)

Utilizing an apparatus according to literature,[99] a vacuum distillation (room temp, 251 mbar) was performed. Sodium bicarbonate (12.03 g, 0.14 mol) and deionized water (20 mL), followed by acetone (13 mL, 0.18 mol) were added to the reaction flask. Then, Oxone® (25.09 g, 0.04 mol) was slowly added to the solution *via* a solid addition tube with vigorous stirring. Following the addition of Oxone®, the apparatus was placed under vacuum and the dimethyldioxirane / acetone mixture was collected at –78 °C. Iodometric titration (REF) indicated a solution molarity of 0.04 M. The solution was stored at –20 °C in deep freeze.

δ_H (400 MHz, $CDCl_3$) 1.35(6H, s, CH_3) (Lit., 1.65 ppm).[68]

7-(*tert*-Butyl-dimethyl-silanyloxy)-4-oxo-octa-2,5-dienal (135)

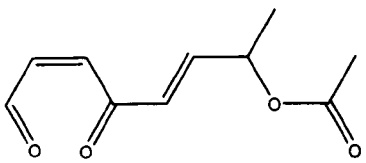


Sodium bicarbonate (3.55g, 42.26mmol) and deionized water (40ml) were added to a flask with vigorous stirring. Furan (134) (1.09 g, 4.31 mmol) and ethyl acetate were added to the mixture, followed by the addition of acetone (3.11 ml, 42.30 mmol). Then, Oxone® (2.69 g, 4.38 mmol) in deionized water (18 ml) was slowly added to the stirred solution over one hour using a syringe pump. Following the addition of Oxone®, the solution was left to stir for an additional two hours. The aqueous layer was extracted with ethyl acetate (3 x 30 ml), and then the organic layer was washed with aqueous sodium chloride (20% w/v). The organic layers were dried over magnesium sulphate and vacuum filtered over celite. Rotary evaporation gave the product as a clear, yellow oil (1.0g, 84% yield).

Required for $C_{14}H_{24}O_3Si$ C, 62.64%, H, 9.01% Found: C, 62.49%, H, 9.02%; δ_H (400 MHz, $CDCl_3$) 10.08 (1H, d, J = 7.5, aldehyde-H), 7.11(1H, d, J = 11.9, *cis*-CH=C<u>H</u>), 6.85 (1H, dd, J = 15.7, 6.9, *trans*-CH=C<u>H</u>), 6.39 (1H, d, J= 15.7, *trans*-C<u>H</u>=CH), 6.19 (1H, dd, J = 11.9, 7.5, *cis*-C<u>H</u>=CH), 4.45 (1H, dq, J = 6.9, 6.6, -CH), 1.21 (3H, d, J = 6.6, $-CH_3$), 0.84 (9H, s, *t*-butyl), 0.82 (3H, s, Si-methyl), 0.80 (3H, s, Si-methyl); (C.I. +ve) (%) 269($[M+NH_4]^+$, 20%), 159($[M-C_6H_6O_2]^+$, 100%); ^{13}C NMR δ_C ($CDCl_3$) 192.4, 189.9, 152.5, 151.4, 140.4, 133.9, 68.6, 25.9, 23.5,

18.3, -4.8; ν_{max}/cm^{-1} (neat) 2928 (s, CH), 1682 (s, C=O), 1626 (m, C=C), 1253 (s, Si-CH), 1094 (s, Si-O), 776 (s, *t*-butyl).

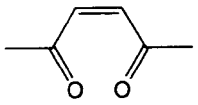
(3*E*, 6*Z*)-7-Formyl-5-oxohepta-3,6-dien-2-yl acetate (137)



According to the above procedure, sodium bicarbonate (1.16 g, 13.85 mmol) and deionized water (20 ml) were added to a flask with vigorous stirring. Furan (136) (0.5 g, 2.77 mmol) and ethyl acetate were added to the mixture, followed by the addition of acetone (2.04 mL, 27.70 mmol). Then, Oxone® (3.4 g, 5.54 mmol) in deionized water (40 ml) was slowly added to the stirred solution. Rotary evaporation gave the product as a clear, yellow oil (0.2g, 37% yield).

δ_H (400 MHz, $CDCl_3$) 9.65 (1H, d, J = 7.4, aldehyde-H), 7.37 (1H, d, J = 11.0, *cis*-CH=C<u>H</u>), 6.88 (1H, d, J = 15.7, 7.0, *trans*-CH=C<u>H</u>), 6.62 (1H, d, J= 15.7, *trans*-C<u>H</u>=CH), 6.35 (1H, dd, J = 11.0, 7.4, *cis*-C<u>H</u>=CH), 5.50 (1H, dq, J = 7.0, 6.5, -CH), 1.41 (3H, d, J = 6.5, $-CH_3$); (C.I. +ve) (%) 214 ($[M+NH_4]^+$, 10%), 153 ($[M-COCH_3]^+$, 100%), 137 ($[M-OAc]^+$, 19%); ν_{max}/cm^{-1} (neat) 2944 (m, CH), 1731(s, CO-O), 1692 (m, CHO), 1667 (m, C=O), 1644 (w, alkene), 690 (m, C=C-H)

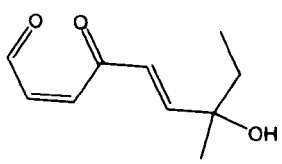
(*Z*)-Hex-3-ene-2,5-dione (138)



According to the above procedure, sodium bicarbonate (2.18 g, 26.0 mmol) and deionized water (20 ml) were added to a flask with vigorous stirring. 2,5-Dimethylfuran (0.5 g, 5.20 mmol) and ethyl acetate were added to the mixture, followed by the addition of acetone (3.82 mL, 52.0 mmol). Then, Oxone® (4.80 g, 7.80 mmol) in deionized water (25 mL) was slowly added to the stirred solution. Rotary evaporation gave the product as a clear, yellow oil (0.1 g, 10% yield).

δ_H (400 MHz, $CDCl_3$) 6.79 (2H, s, -C<u>H</u>=C<u>H</u>), 2.38 (6H, s, $-CH_3$), (Lit. 6.79, 2.31 ppm)[100]; Required for $C_6H_8O_2$ C, 64.27%, H, 7.19% Found: C, 64.64%, H, 7.34%; ^{13}C NMR δ_C ($CDCl_3$) 198.8, 138.2, 28.3.

(2*Z*,5*E*)-7-Hydroxy-7-methyl-4-oxonona-2,5-dienal (159)

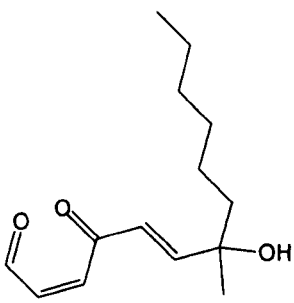


According to the above procedure, sodium bicarbonate (0.81 g, 9.65 mmol) and deionized water (20 ml) were added to a flask with vigorous stirring. Furan (155) (0.32 g, 1.93 mmol) and ethyl acetate were added to the mixture, followed by the addition of acetone (1.12 ml, 19.3 mmol). Then, Oxone® (1.19 g, 1.93 mmol) in

deionized water (15 mL) was slowly added to the stirred solution. Rotary evaporation gave the product as a clear, yellow oil (0.2 g, 68% yield).

δ_H (400 MHz, $CDCl_3$) 9.82 (1H, d, J = 7.5, aldehyde-H), 7.2 (1H, d, J = 12.0, *cis*-CH=C<u>H</u>), 7.0 (1H, d, J = 15.8, *trans*-CH=C<u>H</u>), 6.5 (1H, d, J = 15.8, *trans*-C<u>H</u>=CH), 6.3 (1H, dd, J = 12.0, 7.5, *cis*-C<u>H</u>=CH), 2.1 (1H, b.s., -OH), 1.68 (2H, q, J = 7.2, $-CH_2$), 1.25 (3H, s, $-CH_3$), 0.92 (3H, t, J = 7.2, $-CH_3$); HRMS (C.I. +ve) (%) ($[M-H_2O+H]^+$, Required: 200.12866, Found: 200.12901), 200 ($[M+NH_4]^+$, 25%), 167 ($[M-CH_3]^+$, 100%), 165 ($[M-OH]^+$, 58%); δ_C (100 MHz, $CDCl_3$) 197.4, 19.0, 157.5, 141.5, 140.7, 129.3, 73.7, 38.6, 29.0, 4.9.0; IR ν_{max}/cm^{-1}(neat) 3390 (s, OH), 2952 (m, CH), 1764 (m, CHO), 1665 (m, C=O), 1626 (C=C).

(2*Z*,5*E*)-7-Hydroxy-7-methyl-4-oxotrideca-2,5-dienal (161)

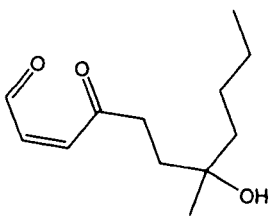


According to the above procedure, sodium bicarbonate (3.55g, 42.26mmol) and deionized water (40ml) were added to a flask with vigorous stirring. Furan (157) (1.09g, 4.31mmol) and ethyl acetate were added to the mixture, followed by the addition of acetone (3.11ml, 42.30mmol). Then, Oxone® (2.69g, 4.38mmol) in

deionized water (18ml) was slowly added to the stirred solution. Rotary evaporation gave the product as a clear, yellow oil (1.0 g, 84%).

δ_H (400 MHz, $CDCl_3$) 10.2 (1H, d, J = 7.3, aldehyde-H), 7.2 (1H, d, J = 11.9, *cis*-CH=C<u>H</u>), 7.0 (1H, d, J = 15.9, *trans*-CH=C<u>H</u>), 6.5 (1H, d, J = 15.9, *trans*-C<u>H</u>=CH), 6.3 (1H, dd, J = 11.9, 7.3, *cis*-C<u>H</u>=CH), 2.0 (1H, b.s., -OH), 1.63-1.60 (10H, m, -CH_2), 1.27 (3H, s, -CH_3), 0.88 (3H, t, J = 7.0, -CH_3); HRMS (C.I. +ve) (%) ([M-H_2O+H]$^+$, Required: 239.05103, Found: 239.05122), 256 ([M+NH_4]$^+$, 13%), 223 ([M-CH_3]$^+$, 43%), 221 ([M-OH]$^+$, 100%); ^{13}C NMR δ_C ($CDCl_3$) 197.0, 192.8, 156.8, 141.3, 140.7, 127.1, 73.7, 42.6, 31.5, 30.0, 29.6, 22.9, 21.4, 14.4; IR ν_{max}/cm^{-1}(neat) 3420 (s, OH), 2926 (m, CH), 1703 (m, CHO), 1668 (m, C=O), 1626 (C=C).

(*Z*)-7-Hydroxy-7-methyl-4-oxoundec-2-enal (162)

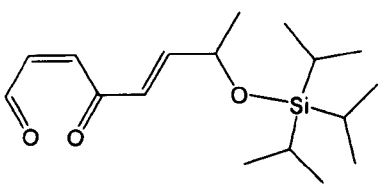


According to the above procedure, sodium bicarbonate (0.53 g, 6.35 mmol) and deionized water (20 mL) were added to a flask with vigorous stirring. Furan (158) (0.25 g, 1.27 mmol) and ethyl acetate were added to the mixture, followed by the addition of acetone (0.86 mL, 12.7 mmol). Then, Oxone® (0.78 g, 1.27 mmol) in

deionized water (10 mL) was slowly added to the stirred solution. Rotary evaporation gave the product as a clear, yellow oil (0.1 g, 31%).

Required for $C_{12}H_{20}O_3$ C, 67.89%, H, 9.5% Found: C, 68.26%, H, 9.58%; δ_H (400 MHz, $CDCl_3$) 9.9 (1H, d, J = 7.2, aldehyde-H), 7.2 (1H, d, J = 11.5, *cis*-CH=C<u>H</u>), 6.7 (1H, dd, J = 11.5, 7.2, *cis*-C<u>H</u>=CH), 2.93 (2H, t, J = 7.4, -CH=CHCOC<u>H</u>$_2$), 2.01(1H, b.s., -OH), 1.50 (2H, t, J = 7.4, CH=CHCOCH$_2$C<u>H</u>$_2$), 1.30 - 1.34 (6H, m, aliphatic-CH_2), 1.29 (3H, s, -CH_3), 0.88 (3H, t, J = 6.7, -CH_3); HRMS (C.I. +ve) (%) $[M+H]^+$ Required: 213.14906, Found: 213.14946, 213 ($[M+H]^+$, 14%), 197 ($[M-CH_3]^+$, 100%); ^{13}C NMR δ_C ($CDCl_3$) 201.0, 193.2, 152.5, 143.7, 73.0, 43.0, 35.6, 28.1, 27.1, 23.6, 23.5, 14.4. IR ν_{max}/cm^{-1}(neat) 3429 (s, OH), 2952 (s, CH), 1703 (m, CHO), 1680 (m, C=O), 729 (w, C=C-H).

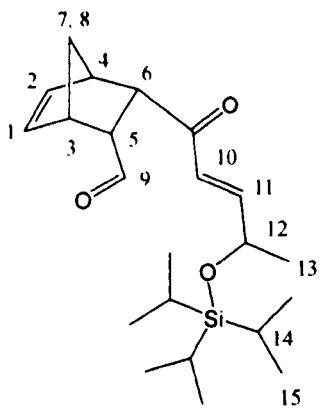
7-(*Tri*-isopropyl-silanyloxy)-4-oxo-octa-2,5-dienal (150)



According to the above procedure, sodium bicarbonate (3.55g, 42.26mmol) and deionized water (40ml) were added to a flask with vigorous stirring. Furan (148) (1.09g, 4.31mmol) and ethyl acetate were added to the mixture, followed by the addition of acetone (3.11ml, 42.30mmol). Then, Oxone® (2.69g, 4.38mmol) in deionized water (18ml) was slowly added to the stirred solution. Rotary evaporation gave the product as a clear, yellow oil (1.0 g, 84%).

δ_H (400 MHz, $CDCl_3$) 10.2 (1H, d, J = 7.3, aldehyde-H), 7.17 (1H, d, J = 11.9, *cis*-CH=C<u>H</u>), 6.9 (1H, dd, J = 15.9, 4.3, *trans*-CH=C<u>H</u>), 6.5 (1H, d, J = 15.9, *trans*-C<u>H</u>=CH), 6.28 (1H, dd, J = 11.9, 7.3, *cis*-C<u>H</u>=CH), 4.5 – 4.7 (1H, m, -CH), 1.3 (3H, d, J = 6.5, CH_3), 1.2 – 1.3 (3H, m, Si-CH), 1.1 (18H, d, J = 6.8, $-CH_3$); (C.I. +ve) (%) 328 ($[M+NH_4]^+$, 15%), 311 ($[M+H]^+$, 30%), 154 ($[M+H]$-TIPS$]^+$, 100%), ^{13}C NMR δ_C ($CDCl_3$) 192.3, 189.1, 157.7, 156.3, 142.5, 136.8, 68.0, 24.9, 18.0, 12.3; IR ν_{max}/cm^{-1}(neat) 2930 (w, CH_3), 1710 (m, CHO), 1670 (m, C=O), 967 (m, C=C-H), 880 (s, SiO).

(2*E*)-4-(*Tri*-isopropyl-silanyl)-1-(3-al-bicyclo[2.2.1]hept-5-en-2-yl)pent-2-en-1-one (165)

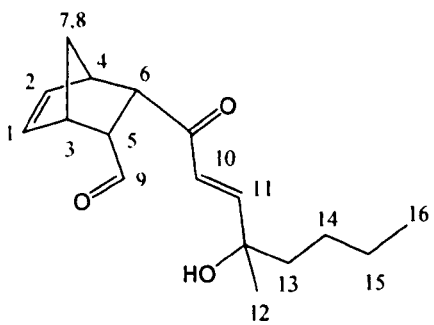


Dicarbonyl (150) (1.16 g, 3.74 mmol) was weighed into a flask and dissolved in dry dichloromethane under nitrogen atmosphere. Freshly cracked cyclopentadiene (0.5 mL, 7.48 mmol) was added to the stirred solution and the mixture was left stirring for 3 h. The volatiles were removed under reduced pressure and the crude yellow

oil was purified by flash column chromatography (light petroleum / EtOAc, 3 : 1). The title product was recovered as a light yellow oil (1.3 g, 92%).

δ_H (400 MHz, $CDCl_3$) 9.5 (1H, d, J = 3.5, H-9), 6.8 (1H, dt, J = 15.5, 4.4, H-11), 6.4 (1H, dd, J = 15.5, 1.8, H-10), 6.38 (1H, q, J = 2.8, H-1), 6.04 (1H, ddd, J = 9.2, 6.5, 2.8, H-2), 4.57 – 4.60 (1H, m, H-12), 3.8 (1H, ddd, J = 9.6, 6.4, 3.5, H-6), 3.3 (1H, b.s., H-3), 3.18 (1H, b.s., H-4), 3.02 (1H, dtd, J = 9.6, 3.5, 1.28, H-5), 1.6 (1H, dt, J = 8.4, 1.9, H-8), 1.5 (1H, d, J = 8.4, H-7), 1.3 – 1.2 (3H, m, H-14), 1.3 (1H, d, J = 7.2, H-13), 1.1 (18H, d, J = 6.8, H-15); HRMS (C.I. +ve) (%) $[M+H]^+$ Required: 377.25119, Found: 377.25090, 377 ($[M+H]^+$, 84%), 203 ($[M-OTIPS]^+$, 100%); ^{13}C NMR δ_C ($CDCl_3$) 202.9, 199.0, 151.2, 136.1, 134.1, 125.1, 68.1, 49.3, 47.6, 47.5, 45.9, 23.9, 18.1, 12.3; IR ν_{max}/cm^{-1}(neat) 2960 (m, CH), 1725 (w, CHO), 1670 (w, C=O), 1610 (w, C=C), 968 (m, C=C-H), 743 (s, SiO).

(2*E*)- 4-Hydroxy-4-methyl -1-(3-al-bicyclo[2.2.1]hept-5-en-2-yl)-oct-2-en-1-one (163)

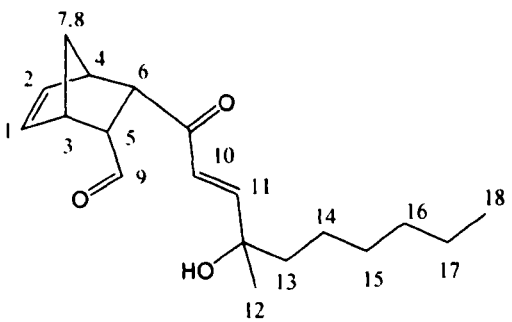


According to the above procedure, dicarbonyl (160) (0.42 g, 2.0 mmol) was dissolved in dry dichloromethane (20 mL). Cyclopentadiene was added to the

stirred solution (0.27 mL, 3.99 mmol). The title product was recovered as a yellow oil (0.5 g, 91%).

δ_H (400 MHz, $CDCl_3$) 9.3 (1H, d, J = 3.4, H-9), 6.9 (1H, d, J = 15.5, H-11), 6.4 (1H, d, J = 15.5, H-10), 6.3 (1H, q, J = 3.1, H-1), 6.0 (1H, ddd, J = 9.5, 6.4, 3.1, H-2), 3.8 (1H, td, J = 9.3, 6.4, 3.5, H-6), 3.3 (1H, b.s., H-3), 3.2 (1H, b.s., H-4), 2.9 (1H, dtd, J = 9.3, 3.4, 1.2, H-5), 2.1 (1H, b.s.,-OH), 1.6 (1H, d, J = 8.4, 1.7, H-8), 1.5 (1H, d, J = 8.4, H-7), 1.4 – 1.2 (6H, m, H-13, H-14, H-15), 1.2 (3H, s, H-12), 0.9 (3H, t, J = 6.9, H-16); HRMS (C.I. +ve) (%) $[M+H]^+$ Required: 277.18039, Found: 277.18065, 277 ($[M+H]^+$, 100%), 259 ($[M-OH]^+$, 75%); ^{13}C NMR δ_C ($CDCl_3$) 204.6, 201.3, 145.6, 136.2, 133.1, 126.5, 73.2, 47.0, 45.7, 44.8, 44.5, 43.9, 28.0, 23.2, 23.1, 14.3; IR ν_{max}/cm^{-1}(neat) 2926 (s, CH), 1723 (m, CHO), 1665 (w, C=O), 1626 (w, C=C).

(2*E*)- 4-Hydroxy-4-methyl -1-(3-al-bicyclo[2.2.1]hept-5-en-2-yl)-dec-2-en-1-one (164)

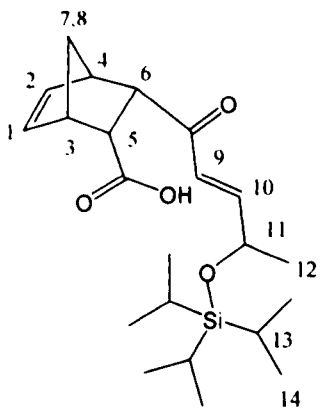


According to the above procedure, dicarbonyl (163) (0.42 g, 2.0 mmol) was dissolved in dry dichloromethane (20 mL). Cyclopentadiene was added to the

stirred solution (0.27 mL, 3.99 mmol). The title product was recovered as a yellow oil (0.5 g, 84%).

δ_H (400 MHz, $CDCl_3$) 9.7 (1H, d, J = 3.3, H-9), 6.8 (1H, d, J = 16.0, H-11), 6.4 (1H, d, J = 16.0, H-10), 6.3 (1H, q, J = 3.0, H-1), 6.1 (1H, ddd, J = 8.7, 6.6, 3.0, H-2), 3.8 (1H, ddd, J = 9.1, 6.6, 3.1, H-6), 3.3 (1H, b.s, H-3.), 3.2 (1H, b.s., H-4), 3.0 – 2.9 (1H[5], dtd, J = 9.1, 6.4, 3.3), 2.1 (1H, b.s.,-OH), 1.8 (1H, d, J = 8.9, H-8), 1.6 (1H, d, J = 8.9, H-7), 1.6 – 1.3 (10H, m, H-13, H-14, H-15, H-16, H-17), 1.3 (3H, s, H-12), 0.9 (3H, t, J = 6.1, H-18); HRMS (C.I. +ve) (%) $[M+H]^+$ Required: 305.21167, Found: 305.21220, 305 ($[M+H]^+$, 100%), 287 ($[M-OH]^+$, 69%); ^{13}C NMR δ_C ($CDCl_3$) 204.1, 201.3, 145.3, 136.1, 131.4, 126.3, 73.0, 47.0, 45.7, 44.8, 44.2, 44.0, 32.0, 30.5, 28.3, 23.0, 22.4, 14.3; IR ν_{max}/cm^{-1}(neat) 2945 (s, CH), 1730 (m, CHO), 1665 (w, C=O), 1628 (w, C=C).

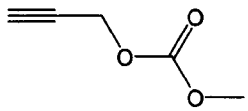
(2*E*)-4-(*Tri*-isopropyl-silanyl)-1-(bicyclo[2.2.1]hept-5-en-2-yl)pent-2-enoic acid (166)



Aldehyde (165) (0.20 g, 0.5 mmol) was dissolved in *t*-butanol (10 mL). 2-methyl-2-butene (0.85 mL, 5 mmol) and sodium dihydrogen phosphate (2.5 mL) were added to the stirred solution. Sodium chlorite (0.05 g, 0.5 mmol) in deionized water (2 mL) was added dropwise to the flask with stirring. After 0.5 h, the volatile components were evaporated under reduced pressure. Following extraction of the aqueous layer with ether (3 x 25 mL), the combined organic layers were dried over magnesium sulfate and vacuum filtered over celite. The solvent was then evaporated to afford a dark yellow oil. The crude material was purified by flash column chromatography (light petroleum / EtOAc, 1 : 2). The title product was recovered as a clear, yellow oil (0.10 g, 54%).

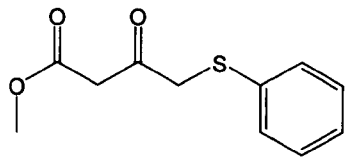
δ_H (400 MHz, $CDCl_3$) 6.8 (1H, dd, J = 15.7, 4.6, H-10), 6.3 (1H, dd, J = 15.7, 1.4, H-9), 6.29 (1H, q, J = 3.0, H-1), 6.06 (1H, ddd, J = 8.6, 6.3, 3.0, H-2), 4.58 – 4.54 (1H, m, H-11), 3.7 (1H, dtd, J = 9.7, 6.3, 3.4, H-6), 3.24 (1H, dd, J = 9.7, 2.5, H-5), 3.19 (2H, b.s., H-3, H-4), 1.5 (1H, dt, J = 8.4, 2.6, H-8), 1.4 (1H, d, J = 8.4, H-7), 1.3 – 1.2 (3H, m, H-13), 1.3 (3H, d, J = 6.6, H-12), 1.1 (18H, d, J = 6.8, H-14); HRMS (C.I. +ve) (%) $[M+H]^+$ Required: 393.24609 Found: 393.24682, 410 ($[M+NH_4]^+$, 12%), 393 ($[M+H]^+$, 100%), 219 ($[M\text{-}OTIPS]^+$, 83%); ^{13}C NMR δ_C ($CDCl_3$) 202. 9, 199.0, 151.2, 136.1, 134.1, 127.1, 68.1, 49.3, 47.6, 47.1, 45.9, 23.9, 18.1, 12.3; IR ν_{max}/cm^{-1}(neat) 2960 (m, CH), 1725 (w, CHO), 1670 (w, C=O), 1610 (w, C=C), 968 (m, C=C-H), 743 (s, SiO).

Methyl-2-Propynyl Carbonate (171)



Dry diethyl ether (83 mL) was added to a flask submerged in a 0 °C ice bath under nitrogen atmosphere. Anhydrous pyridine (21 mL, 0.26 mol) was syringed into the flask followed by the addition of propargyl alcohol (10 mL, 0.17 mol). Methyl chloroformate (13 mL, 0.17 mol) was added dropwise *via* a pressure-equalized addition funnel in a solution of dry diethyl ether (37 mL). Following the addition, the flask was removed from the ice bath and allowed to proceed at room temperature for three hours with stirring. Dilute hydrochloric acid (80 mL, 1N) was added to the flask to quench the reaction. Then, the aqueous layer was extracted with ether (3 x 40 mL). The combined organic layers were washed with $CuSO_4$ (40 mL, 0.1M), then brine (40 mL), and the organic layer was dried over magnesium sulfate and vacuum filtered over celite. Rotary evaporation of the volatiles under reduced pressure gave a clear, yellow oil. The crude material was purified by distillation (10.1 g, 53%) as a colorless oil, b.p.34 °C / 8 Torr. δ_H (400 MHz, $CDCl_3$) 4.7(2H, dd, J = 2.2, 1.5, $-CH_2$), 3.8 (3H, d, J = 1.5, $-CH_3$), 2.6 (1H, t, J = 2.2, -CH); (C.I. +ve) (%) 132 ($[M+NH_4]^+$, 100%), 55($[M-C_2H_3O_2]^+$, 58 %); Required for $C_5H_6O_3$ C, 52.63%, H, 5.30% Found: C, 52.63%, H, 5.30%.; δ_C (400 MHz, $CDCl_3$) 155.5, 77.7, 75.9, 55.5, 55.1.

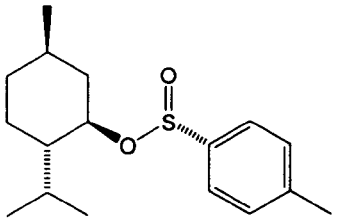
3-oxo-4-phenylsulfanyl-butyric acid methyl ester (172)



Dry methanol (50ml) was added to a flask and flushed with nitrogen. Sodium cuttings (0.80 g, 0.03 mol) were slowly added to the flask and the flask was submerged in a 0 °C ice bath. Then, methyl-4-chloroacetoacetate (4 mL, 0.03 mol) and thiophenol (3.6 mL, 0.03 mol) were syringed into the flask. The solution was left stirring overnight under nitrogen. The following day, all volatiles were evaporated under reduced pressure in the fume hood with gentle heating (33 °C, 15mbar). Diethyl ether (20 mL) and ammonium chloride (20 mL) were added to the mixture and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were dried over magnesium sulphate and filtered under reduced pressure over celite. Rotary evaporation gave the product as a clear, yellow oil (7.0 g, 100%).

δ_H(400 MHz, $CDCl_3$) 7.4-7.2 (6H, m, Ph-H), 3.8 (2H, s, $-COCH_2$), 3.7 (2H, s, $-SCH_2$), 3.6 (3H, s, $-CH_3$); (C.I. +ve) (%) 242 ($[M+NH_4]^+$, 100%), 123 ($[M-C_4H_5O_3]^+$, 34%); Required for $C_{11}H_{12}O_3S$ C, 58.91%, H, 5.39% Found: C, 59.00%, H, 5.40%; δ_C(400 MHz, $CDCl_3$) 198.1, 167.8, 135.4, 130.3, 129.6, 127.6, 52.8, 46.6, 44.4.

(1R,2S,5R)-(-)-menthyl-*p*-toluenesulfinate (176)

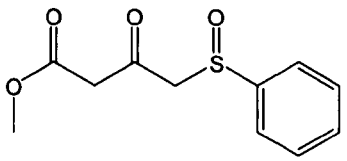


According to literature,[101] azeotropically dried sodium salt of *p*-toluenesulfinic acid (2.0 g, 0.01 mol) was added in portions to thionyl chloride (3.64 mL, 0.05 mol) in dry toluene (20 mL) at 0 °C under inert atmosphere. The mixture was left stirring overnight. The following day, the volatiles were evaporated from the reaction flask using a CO_2 / acetone ice bath (-78 °C) using moderate heating (35 °C) until the solution was approximately one quarter its original volume. Anhydrous ether (20 mL) was added to the solution under inert atmosphere with stirring. A solution of (-)-menthol (1.73 g, 0.01 mol) in pyridine (5 mL) was added dropwise to the solution at 0 °C. The solution was allowed to warm to room temperature and the mixture was hydrolyzed within 0.25 h with deionized water (15 mL). Following extraction of the aqueous layer with EtOAc (3 x 35 mL), the combined organic layers were washed consecutively with 10% HCl (8 mL) followed by brine (8 mL), then dried over magnesium sulfate and vacuum filtered over celite. The solvent was then removed under reduced pressure with moderate heating (30 °C). The title compound was recrystallized from EtOAc (2.3 g, 78.1%).

δ_H(400 MHz, $CDCl_3$) 7.6 (2H, d, J = 8.2, Ph-H), 7.3 (2H, d, J = 8.2, Ph-H), 4.3 – 4.1 (1H, m, -CH), 2.41 (3H, s, $-CH_3$), 1.7 – 1.6 (1H, m, isopropyl-CH), 1.5 – 1.4 (2H, m, -CH, $-CH_2$), 1.4 – 1.3 (3H, m, -CH, $-CH_2$), δ1.3 – 1.2 (3H, m, $-CH_2$), 1.0

(3H, d, J = 6.5, -CH_3), 0.7 (6H, d, J = 6.8, -CH_3); Required for $C_{17}H_{26}O_2S$ C, 69.34%, H, 8.90% Found: C, 69.14%, H, 9.18%; δ_C(400 MHz, $CDCl_3$) 142.8, 130.0, 125.4, 124.9, 82.4, 48.7, 43.4, 34.4, 31.3, 23.6, 22.3, 21.3, 21.2. m.p. 105 – 108 °C (Lit. m.p. 107 °C)[101]

Methyl-3-oxo-4-(phenylsulfinyl)butanoate (179)

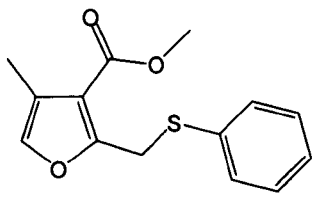


Phenylthioacetoacetate (172) (1.0 g, 4.46 mmol) was dissolved in dry dichloromethane (5 mL) in a flask and placed under nitrogen, then cooled to –78 °C. A solution of *m*-CPBA (0.88 g, 5.13 mmol) in dry dichloromethane (2 mL) was added to the cooled solution. After 10 min, the flask was removed from the ice bath and allowed to warm to room temperature. The reaction was then quenched with saturated sodium hydrogen sulfite (4 mL). The aqueous layer was extracted with dichloromethane (3 x 25 mL) and the combined organic layers were washed with saturated sodium bicarbonate. The organic layer was dried over magnesium sulfate and vacuum filtered over celite. Rotary evaporation of the volatiles gave a clear, yellow oil. The title compound was recrystallized from diethyl ether giving a white solid (0.4 g, 38%)

δ_H(400 MHz, $CDCl_3$) 7.67-7.64 (3H, m, phenyl-H), 7.56-7.53 (2H, m, phenyl-H), 3.9 (2H, s, -SO_2CH_2), 3.7 (3H, s, -CO_2CH_3), 3.47 (2H, s, -CO_2CH_2); (C.I. +ve) (%)

258 ($[M+NH_4]^+$, 100%), 241($[M+H]^+$, 27%), 240($[M]^+$, 1%); δ_C(400 MHz, $CDCl_3$) 196.0, 168.8, 144.5, 133.6, 131.3, 126.0, 65.4, 54.4, 52.6.

Methyl-4-methyl-2-[(phenylthio)methyl]-3-furoate (173)

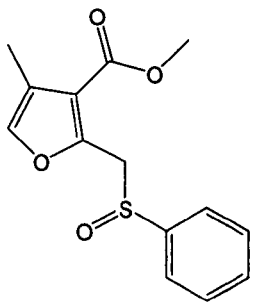


$Pd(OAc)_2$ (0.06g, 0.26mmol) and diphenylphosphinoethane (0.20g, 0.50mmol) were added to a flask followed by the addition of dry THF (5ml), flushed with nitrogen, and stirred for fifteen minutes. Then, carbonate (171) (0.57 g, 5.02 mmol) and β-keto ester (172) (1.12 g, 5.01 mmol) were added *via* syringe in a solution of THF (5 mL). The solution was refluxed at 75°C for 4 h, cooled to room temperature, followed by dilute hydrochloric acid (20 ml, 2N). The solution was left stirring for an additional ten minutes, then vacuum filtered. The aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were dried over magnesium sulfate and vacuum filtered over celite. Rotary evaporation gave a brown oil. The crude material was purified by flash column chromatography (light petroleum / ether, 5 : 1). The title product was recovered as a yellow oil (0.37g, 28%).

δ_H (400 MHz, $CDCl_3$) 7.4-7.2 (6H, m, Ph-H), 7.13 (1H, s, furyl-H), 4.43 (2H, s, -SCH_2), 3.71 (3H, s, -CO_2CH_3), 2.12 (3H, s, -CH_3); (E.I. +ve) (%) 262 ($[M]^+$, 18%), 153 ($[M-C_6H_5S]^+$, 100%); Required for $C_{14}H_{14}O_3S$ C, 64.10%, H, 5.38% Found: C,

63.98%, H, 5.42%; δ_C (400 MHz, $CDCl_3$) 170.6, 164.7, 139.5, 135.4, 131.9, 129.6, 127.7, 121.8, 115.1, 51.6, 31.8, 7.0.

Methyl 4-methyl-2-((phenylsulfinyl)methyl)furan-3-carboxylate (180)



$Pd(OAc)_2$ (0.09 g, 0.20mmol) and Diphenylphosphinoethane (0.18 g, 0.39 mmol) were added to a flask followed by the addition of dry THF (5ml), flushed with nitrogen, and stirred for fifteen minutes. Then, carbonate (171) (0.08g, 0.67mmol) and β-keto ester (179) (0.16g, 0.67mmol) were added *via* syringe in a solution of THF (5ml). The solution was refluxed at 75 °C for 4 hr, cooled to room temperature, followed by dilute hydrochoric acid (10ml, 2N). The solution was left stirring for an additional ten minutes, then vacuum filtered. The aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were dried over magnesium sulfate and vacuum filtered over celite followed by rotary evaporation under reduced pressure. The crude material was purified by flash column chromatography (100% diethyl ether). The title product was recovered as a white solid (0.2g, 82%).

δ_H (400 MHz, $CDCl_3$) 7.51-7.47 (6H, m, Ph-H), 7.12 (1H, s, furyl-5), 4.46 (2H, s,

-$SOCH_2$), 3.74 (3H, s, -CO_2CH_3), 2.09 (3H, s, -CH_3); (C.I. +ve) (%) 279 ($[M+H]^+$, 100%), 155([M-CH_2SPH, 37%); Required for $C_{14}H_{14}O_4S$: C, 60.42%, H, 5.07% Found: C, 60.20%, H, 5.12%; δ_C (400 MHz, $CDCl_3$) 171.0, 163.8, 147.8, 139.5, 131.2, 129.2, 127.7, 121.8, 114.8, 52.0, 46.3, 7.0. m.p. 72 – 74 °C.

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