

Synthesis of γ-Lactones from Epoxides and Ketenes

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School of Chemical Sciences

Under the supervision of Dr. Nessan Kerrigan

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Declaration

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List of Publications and Presentations

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Abbreviations:

AIBN	Azobisisobutyronitrile
app	Apparent (in NMR)
app sept	Apparent septet
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
$CDCl_3$	Deuterated chloroform
δ	Chemical Shifts in parts per million
CH_2Cl_2	Dichloromethane
$CuCl_2$	Copper (II) chloride
d	Doublet (in NMR)
ddd	Doublet of doublet of doublets
DIPEA	N,N-Diisopropylethylamine
dig	Diagonal
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl Acetate
Equiv.	Equivalent
$FcPf_6$	Ferrocenium hexafluorophosphate
GC-MS	Gas Chromatography – Mass Spectroscopy
qd	Quartet of doublets
qt	Quartet of triplets
h	Hour/hours
HMPA	Hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
HRMS	High-resolution mass spectrum
Hz	Hertz
IR	Infrared
J	Coupling constant (in NMR)
K_2CO_3	Potassium Carbonate
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LiI	Lithium Iodide
LUMO	Lowest Unoccupied Molecular Orbital
M	Moles per litre
m	Multiplet (in NMR)
*m*CPBA	*meta*-chloroperoxybenzoic acid
MHz	Megahertz
Min	Minute/minutes
mL	millilitre
MS	Mass Spectrometry
$NaBH_4$	Sodium borohydride
NaHMDS	Sodium bis(trimethylsilyl)amide
Na_2SO_4	Sodium Sulfate
n-BuLi	n-Butyllithium
NMR	Nuclear Magnetic Resonance(spectroscopy)

Nu	Nucleophile
o/n	overnight
ppm	Parts per million (NMR spectra)
q	Quartet (in NMR)
rt	Room temperature
s	Singlet (in NMR)
SET	Single Electron Transfer
SL	Sesquiterpene Lactone
$SnBu_3H$	Tributyltin hydride
S_N2	Biomolecular nucleophilic substitution
t	Triplet (in NMR)
TBSCl	Tert-Butyldimethylsilyl chloride
t-BuOk	Potassium tert-butoxide
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
tet	Tetrahedral
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Tetramethylsilane
TMSCl	Trimethylsilyl chloride
TMSOI	Trimethysulfoxonium Iodide
TMSI	Trimethylsulfonium Iodide
trig	Trigonal
µL	microlitre

Abstract

Synthesis of γ-lactones from epoxides and ketenes

By Zarah McGeever

This project was focused on the synthesis of an important five-membered ring named a γ-lactone. γ-Lactone formation involved an intermolecular cycloaddition. The targeted reaction was a LiI -promoted [3 + 2]-cycloaddition of epoxides with ketenes to form γ-lactones. The conditions of the reaction were studied, including catalyst loading, catalyst type, reactant equivalents, light, temperature and reaction time. This project involved synthesising a range of epoxides and three different ketenes.

Chapter 2 and 3 describes the attempted cycloaddition reactions carried out to form the desired cyclic product or the undesired acyclic ester product. These studies revealed that γ-lactones were formed through the formal [3 + 2]-cycloaddition of diarylketenes with certain epoxides. Twelve γ-lactones (**4a**-**4m**) were prepared, purified and fully characterised. The γ-lactones were formed in low to good yields of 12-72%. These twelve γ-lactones were formed with the 3,4-γ-regioisomers as the major isomer. The remainder of examples described in the thesis project were formed as the undesired acyclic ester product (**5a**-**5e**: yields of 18-57% and **5f-o**: crude yields of 47->99%). In this thesis, a proposed explanation for why some epoxides (aryl, vinyl, and ester-substituted) and diphenylketene react to form the γ-lactone was presented and compared to reaction of diphenylketene, ethylphenylketene, methylphenylketene and methylketene with certain epoxides that favour formation of the undesired acyclic ester product.

Exploration of the substrate scope indicated what combinations of epoxides and ketenes favoured the formation of the γ-lactone and what combinations of epoxides and ketenes favoured formation of an enolate intermediate-derived acyclic ester product.

To interrogate the reaction mechanism a number of mechanistic and control reaction experiments were implemented in Chapter 5 and Chapter 6. These studies suggested that the reaction may involve a single electron transfer step (SET step), although further well designed experiments will be required to provide strong evidence for a radical intermediate.

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Chapter 1: Introduction

1.1 General project overview:

The goal of this project was to prepare γ-lactones through a catalytic formal [3 + 2]-cycloaddition reaction of epoxides and ketenes. The formation of γ-lactones through this cycloaddition approach represents a direct and conceptually simple approach. The importance of γ-lactones stems from their prevalence in 10% of all natural products and their use as intermediates in natural product and pharmaceutical synthesis.[1,2] The formation of both the desired γ-lactone and an acyclic ester product was observed during these studies. The two starting materials that were used in this project are epoxides and ketenes. The epoxide is a three - membered cyclic ether, and the ketene is a heterocumulene compound shown in Figure 1.

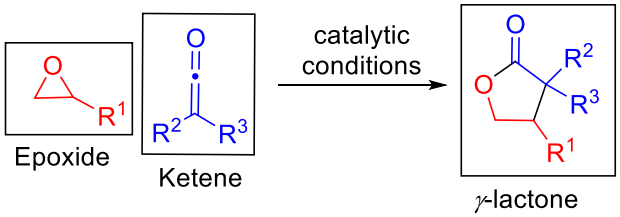


Figure 1: Formal cycloaddition of epoxide and ketene to form γ-lactone.

The proposed formal [3+2] cycloaddition reaction involves an intramolecular cyclisation as a key step.[3] According to the literature, ring-opening reactions of epoxides, such as cyclohexene oxide, are very slow, and a catalyst is often required to accelerate the reaction.[4] Group 1 metals can be employed as Lewis acids in the ring-opening of epoxides to increase the rate of the reaction. There has been a wide study of the use of Lewis acids in epoxide ring-opening reactions.[5]

Epoxides are highly strained but require reagents or nucleophiles to initiate ring-opening.[5] The nucleophiles commonly used to ring-open the epoxide include halides, hydride reagents, C-nucleophiles, and O-nucleophiles.[6] The nature of the reaction has a large influence on the regioselectivity of the ring-opening of non-symmetrical epoxides. The regioselectivity of the ring-opening depends on the reaction conditions, whether acidic or basic. It has been reported that, under basic

conditions, the nucleophile attacks the least hindered/least substituted side of the epoxide, as shown in Figure 2. In comparison, when the reaction is carried out under acidic conditions, the more substituted/more hindered carbon is attacked by the nucleophile. The oxygen in the epoxide is protonated under acidic conditions. This makes the C-O bond weaker and more polarised. The more substituted the carbon in the epoxide is, the better it stabilises the partial positive charge on that carbon, and hence the more polarised the specific C-O bond is. This then causes the electron-rich nucleophile to attack the more substituted carbon.[6,7] The epoxide ring-opening under acidic conditions follows a 'loose' or quasi-S_N2 mechanism, with significant S_N1 character. In the ring-opening of the epoxide under basic conditions, there is no proton available to polarise the C-O bond. The reaction occurs through a pure S_N2 mechanism. In an S_N2, the nucleophile attacks the carbon from the backside, and therefore, more space is needed for the backside attack. Nucleophilic attack on a less sterically hindered carbon is favoured under basic conditions.

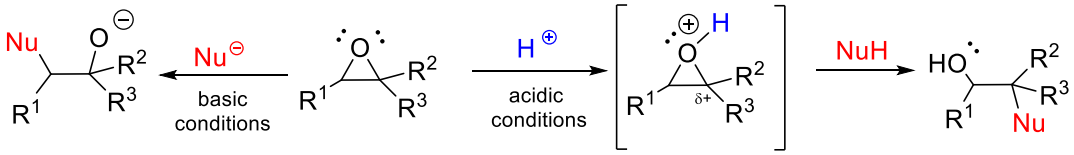


Figure 2: Regioselectivity in the attack of the nucleophile on the epoxide under acidic and basic conditions.

1.2 Ketenes

There are a number of different methods available to prepare ketenes. Ketenes are very reactive intermediates and are important in organic chemistry.[8] Ketenes are classified as heterocumulene compounds, as they have an sp-hybridised carbon atom in the centre connected via two double bonds to oxygen and to carbon on either side. The ketene molecule is also referred to as a heteroallenic molecule as it has an allene structure with a heteroatom. This plays a role in the molecule's reactivity.[9,10] The ketene molecule is shown in Figure 3. The ketene moiety has an electrophilic carbon (represented as a dot in Figure 3).[11,12] The central electrophilic carbon is the position in ketenes that nucleophiles typically attack due to its electropositive nature. Ketenes are commonly used in cycloaddition reactions.[13]

Ketenes are generally kinetically unstable molecules, but it has been reported that ketenes can be stabilised by an electropositive or bulky substituent and can be destabilised with an electronegative substituent.[14] This lack of stability was observed during the project, with a relatively short shelf-life of 1-2 weeks observed for the prepared ketenes (e.g., ethylphenylketene). The more bulky ketenes have a longer shelf-life. The carbonyl carbon in the ketene moiety is electron deficient and is susceptible to attack by a nucleophile by nucleophilic addition. Therefore, ketenes degrade to carboxylic acids in the presence of water during storage. The water molecule acts as the nucleophile, attacking the electrophilic carbon in the ketene. The ketene forms an ene-diol, which then tautomerizes to form the carboxylic acid.[15] Ketenes have been utilised in many reactions including S_N2 nucleophilic substitutions, [2 + 2], [3 + 2] and [4 + 2] cycloadditions, and nucleophilic and electrophilic additions.[9]

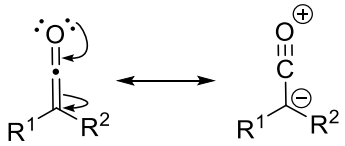


Figure 3: Ketene structure and its resonance form.

1.2.1 Staudinger synthesis of ketenes

The first scientist credited with ketene synthesis is Hermann Staudinger. Staudinger reported ketene synthesis in 1905.[16] The first ketene synthesised was diphenylketene, and this was synthesised from subjecting 2-chloro-2-diphenylacetyl chloride to reaction with zinc as shown in Figure 4.[17] The formation of the ketene was unexpected, but was later identified as diphenylketene.[9] The reaction scheme is shown in Figure 4. Zinc is a reducing metal, and in this reaction, it is used to promote dehalogenation to form the ketene product.[18] The zinc inserts into the carbon-chlorine bond at the α-carbon forming an organozinc intermediate. The organozinc intermediate undergoes an elimination step, forming the desired ketene and a zinc dichloride by-product. It was reported that ketenes are reactive intermediates and are known to form four-membered rings through a [2 + 2]-dimerization reaction.[19] Staudinger also reported a cycloaddition reaction, known as the Staudinger reaction, forming a β-lactam from diphenylketene and an imine.[20]

This was the beginning of research into cycloaddition reactions using ketenes and a variety of other organic starting materials to form new cyclic products.

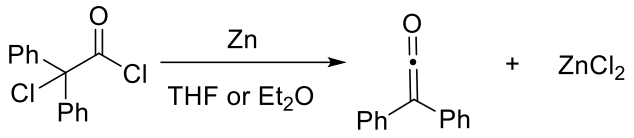


Figure 4: Staudinger reaction forming diphenylketene.

There are many ways to form ketene. Many ketenes are generated in situ as they are not readily isolable. Ketene synthesis can be carried out by Zn-mediated dehalogenation of the precursor halo-acyl halide, as shown by Staudinger. There are many other methods to synthesise ketenes, and the various important methods, besides the Staudinger method, are described in sections 1.2.2 and 1.2.3.

1.2.2 Wolff rearrangement

The Wolff rearrangement, as shown in Figure 5, is a method for the synthesis of ketenes from α-diazocarbonyls. In this reaction, visible light or heat is used to generate the ketene.[9] Dilute solutions of ketene can be synthesised by the Wolff rearrangement, which limits ketene dimerisation. Ketene dimerisation is an example of a side reaction that often occurs during ketene synthesis.

The Wolff rearrangement is the conversion of an α-diazocarbonyl compound into a ketene by a 1,2-shift with the loss of nitrogen.[21] The ketene product is usually not isolated in pure form. Therefore, it is used in crude form in solution for cycloaddition and nucleophilic addition reactions.[21] This method for ketene synthesis has broadened the scope of ketene synthesis by enabling the synthesis of unstable ketenes, such as alkylketenes. The first report of using the Wolff rearrangement was in 1902.[22]

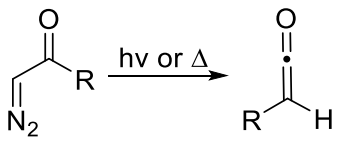


Figure 5: Wolff rearrangement for the preparation of ketenes.

The Wolff rearrangement was primarily used for many years for the one-carbon homologation of carboxylic acids as part of the Arndt-Eistert homologation.[23] In Wolff's carboxylic acid synthesis method, water was used in the reaction. The function of water in this reaction was initially undetermined.[22] However, Schröter suggested that ketenes were an intermediate in the carboxylic acid formation using the Wolff rearrangement.[24] Wolff originally synthesised carboxylic acids from the α-diazo ketones. The function of the water was to convert the ketene intermediate into the carboxylic acid.[25] As described above, ketene is an intermediate in this reaction, and this method is now well-known for ketene synthesis when water is excluded.

In the case above, the Wolff rearrangement may be activated by photolysis, metal catalysis, or thermolysis.[26] Thermolysis required temperatures up to 180 °C, and hence, this method is not commonly used to promote ketene formation. Horner reported the irradiation of an α-diazocompound to enhance ketene synthesis through nitrogen extrusion/elimination from the diazocompound.[27] However, photolysis generally enables the formation of carbene intermediates, leading to byproducts and lowering the yield of the Wolff rearrangement product.[25] The photo-Wolff rearrangement product (ketene) is formed as a result of light exciting the diazocompound and generally involves the formation of a singlet carbene intermediate, which can quickly rearrange to the ketene. Alternatively, the ketene may be formed in a concerted fashion, without a discrete carbene intermediate being involved.

Metal catalysts can promote the Wolff rearrangement reaction and allow it to proceed at lower temperatures. The success of the metal catalyst on the reaction depends on the type of interaction the metal has with the substrate. The use of certain metals can lead to the formation of a new product compared to when photolysis or thermolysis is used.[26] Metal salts used in the Wolff rearrangement include silver, copper, mercury, and platinum salts. Silver salts have been recorded to be used in many α-diazoketones reactions to form carboxylic acids. The silver salts promote the Wolff rearrangement. The reduction of silver oxide promotes the extrusion of nitrogen from the α-diazoketone, leading to the formation of the carboxylic acid product in the presence of water. This reaction forms the carboxylic

acid in good yields (86-97%). [26,28,29] As seen in Figure 6, when a high temperature was used, the α-diazoketone was converted into an alcohol. In comparison, when silver oxide was used, the carboxylic acid was formed.

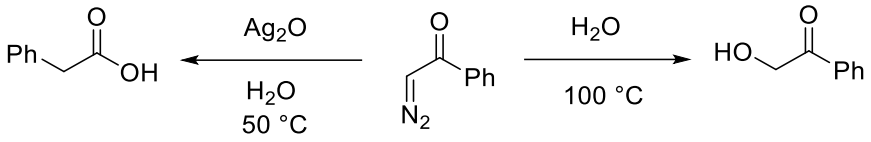


Figure 6: Effect of reaction conditions on the product formed in the presence of water.

1.2.3 Dehydrohalogenation of acyl chlorides (Wedekind's method)

A third important synthesis method of ketenes is the dehydrohalogenation of acyl chlorides with tertiary amines, popularised by Wedekind's group.[30,31] This is the most common and easiest method to form ketenes.[30] This method is used by the Kerrigan research group and many others to synthesise the more stable disubstituted ketenes, including diphenylketene, ethylphenylketene and methylphenylketene.[32–36] This method of ketene synthesis is reported in the literature to work for disubstituted ketenes that are kinetically stable and distillable.[9] Monosubstituted ketenes are more unstable, and using acid chlorides for the synthesis of monosubstituted ketenes has been reported to be more variable in success due to the reactivity of the generated ketenes. In the case of monosubstituted ketenes, their high reactivity means that they must be generated in situ at low temperatures and subjected to reaction as they are formed. The reaction scheme for the amine-mediated dehydrohalogenation route is shown in Figure 7.

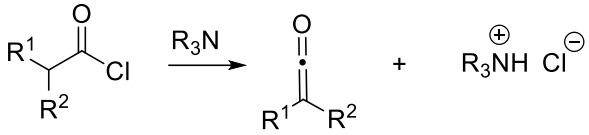


Figure 7: Wedekind's synthesis of ketenes.

The Lectka group used a resin-bound phosphazene base known as BEMP to eliminate ammonium salt by-products, which often affect the stability and purity of the ketene, especially when monosubstituted ketenes are being prepared.[9] This method facilitated the in situ formation of ketene, and in parallel, an imino ester was

added, and the desired β-lactam was formed under nucleophilic catalysis conditions.[37] This method demonstrates the use of an alternative base for the in situ formation of ketenes from acid chlorides.

1.3 Ketene cycloadditions

There are three main types of cycloadditions that ketenes engage in: the [2 + 2], [3 + 2], and the [4 + 2]-cycloaddition. The [2 + 2]-cycloaddition reaction is the most studied and most widely reported cycloaddition reaction involving ketenes. In 1907, Staudinger was the first to study and report the [2 + 2] cycloaddition reaction employing a ketene.[19] The [2 + 2]-cycloaddition of a ketene and an imine to prepare a *β*-lactam is one of the simplest, and yet most important, methods for the synthesis of *β*-lactams. The [2 + 2]-cycloaddition, in this case, is not a concerted pericyclic reaction but occurs in a stepwise fashion, forming a zwitterionic intermediate before it cyclises, through a $\pi 4_a$ electrocyclisation, to form the cyclic *β*-lactam. The reaction scheme for the *β*-lactam synthesis is shown in Figure 8.

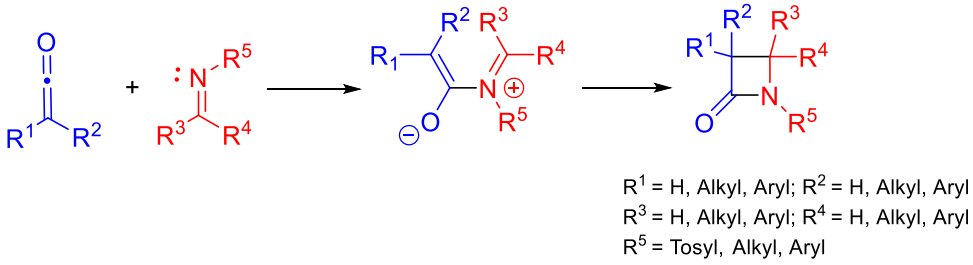


Figure 8: [2 + 2] cycloaddition of ketene and imine to form the β-lactam. [19,38]

The formal [2 + 2]-cycloaddition reaction between ketenes and a variety of starting materials has been widely studied. An example of a product formed is a β-lactone, prepared from a ketene and an aldehyde.[10] The *β*-lactone synthesised through this method requires a nucleophilic or Lewis acid catalyst to promote the desired formal cycloaddition. An example of a catalyst used is TMS-quinidine.[10] Another example of a [2 + 2]-cycloaddition reaction is the reaction of ketene with an alkene or alkyne.[10]

Brown et al. studied the Lewis acid-promoted [2 + 2]-cycloaddition of ketenes and alkenes.[39] The reaction of ketenes with alkenes is limited to activated alkenes, for example, styrene's, vinyl ethers and dienes to form cyclobutanone products.

However, a Lewis acid was reported to be very effective at promoting the desired [2 + 2]-cycloadditions even with unactivated alkenes (Figure 9). The Lewis acid is used in excess to facilitate the formation of cyclobutanones in high yields of up to 91%. The Lewis acid studied by Brown et al. was ethyl aluminium dichloride ($EtAlCl_2$).[40] The $EtAlCl_2$-promoted methodology is shown in Figure 9.

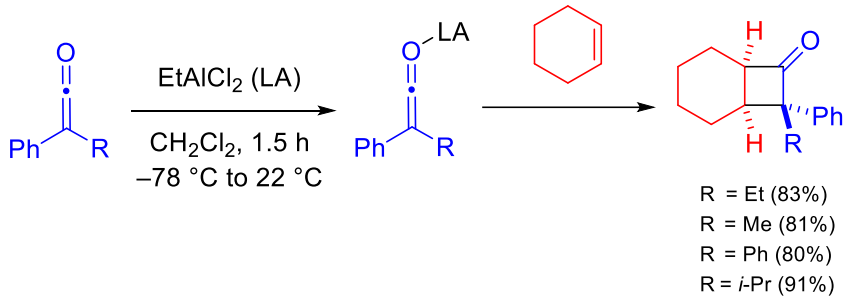


Figure 9: Lewis acid-promoted alkene-ketene [2 + 2]-cycloaddition.

Although [4 + 2]-cycloadditions involving ketenes are less studied in comparison with [2 + 2]-cycloadditions.[10] Singleton et al. reported the formation of a cycloadduct from the [4 + 2]-cycloaddition of diphenylketene and cyclopentadiene.[10,41] This paper indicates that the [4 + 2] product is formed initially and then the [2 + 2] product is formed due to rearrangement of the [4 + 2] product. This reaction was first described by Yamabe et al., and it was predicted that the [4 + 2] product would be formed although, as described above, the [4 + 2] product can undergo isomerisation via [3,3]-sigmatropic rearrangement and form the [2 + 2] product.[42] Yamabe et al. studied the two products activation energies. The activation energy to form the [4 + 2] adduct product was lower compared to the [2 + 2] adduct. Therefore, the [4 + 2] adduct is formed first, and over time the [4 + 2] adduct isomerises to form the [2 + 2] adduct. Singleton et al. reported that when the reaction was carried out at -20 °C in CD_2Cl_2, the concentration of the [4 + 2] product was at its maximum concentration at approximately 2 h and then, over time, the concentration of this adduct decreased gradually, forming the [2 + 2] adduct. The [4 + 2] and the [2 + 2] product are shown in Figure 10.

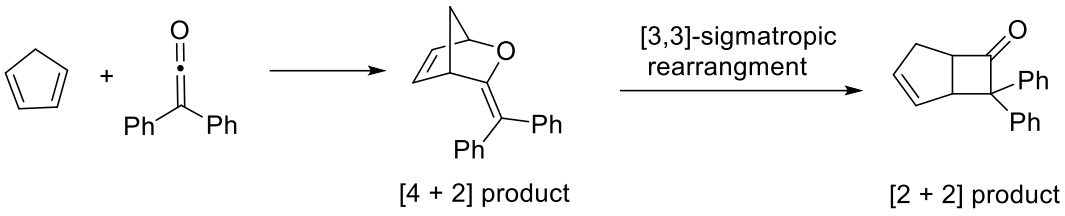


Figure 10: Cycloaddition products from the reaction of diphenylketene with cyclopentadiene.

The last cycloaddition to be discussed, the [3 + 2]-cycloaddition involving ketenes, has been the least explored. Recently, some advances have been made, including cycloadditions with bicyclo[1.1.0]butanes (BCBs) and donor-acceptor cyclopropanes.[43] Both reactions are Lewis acid-catalysed [3 + 2]-cycloadditions. The Kerrigan group studied cyclopentanone synthesis by dual Lewis acid-catalysed [3 + 2]-cycloaddition of ketenes and donor-acceptor cyclopropanes.[44] The cyclopentanones were formed with yields of up to 99%, and the reaction methodology is shown in Figure 11. Good to excellent diastereoselectivity was observed with monosubstituted ketenes (dr up to 37:1), but only moderate diastereoselectivity (dr up to 3:1) was obtained with disubstituted ketenes.

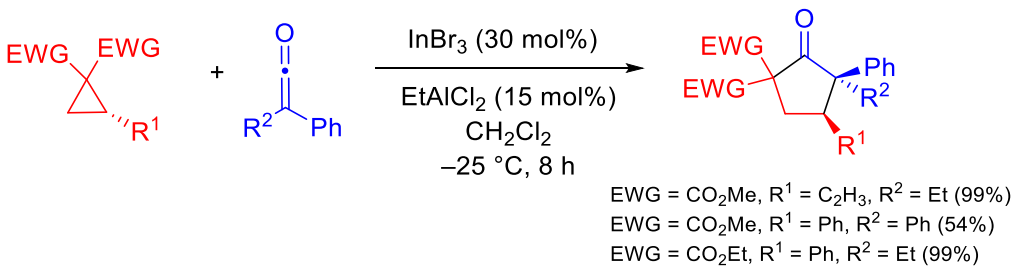


Figure 11: Lewis acid-catalysed [3 + 2]-cycloadditions of donor-acceptor cyclopropanes and ketenes to form cyclopentanone products.

1.4 Baldwin's Rules:

Baldwin's Rules are a set of rules which are used to predict if a cyclisation will be favoured or disfavoured. Jack E. Baldwin developed these rules in 1976 and in the years after. These are empirical reported rules used in organic synthesis to predict the ability of a reaction substrate to undergo ring closure, and the rules are based on the stereoelectronic properties of the reaction substrate or reactive intermediate.[45]

Baldwin outlined the rules for cyclisation reactions with three terms. The first term is ring size, the number of atoms in the formed ring. The second term is the bond position of the bond being broken to form the ring-closed product. Baldwin used two prefixes to describe the bond-breaking position. The first is endo, where the bond broken for ring closure is inside the ring being formed, and exo describes when the bond broken is outside the ring being formed. The last term describes the hybridisation of the carbon that is being attacked to form the cyclised product. The terms used to describe the carbon's geometry are tet for sp^3, trig for sp^2, and dig for sp. Cyclisation involving nucleophilic attack for exo-tet cyclisations is described using the mechanistic theory of an S_N2 reaction, i.e. there is a preferred nucleophilic attack angle of 180˚ with respect to the leaving group.

According to Baldwin's rules, a favoured ring closure depends on the geometry of the transition-state. Therefore, the orbital overlap and the bond angles of the HOMO of the nucleophile and the LUMO of the electrophile governs if the ring closure is favoured or disfavoured. A favoured reaction is dependent on multiple factors, including the length and structure of the molecule, and is also dependent upon the terminal atoms reaching the correct geometry for effective orbital overlap. A disfavoured reaction is disfavoured for ring closure. This can be caused by bond-angle strain and insufficient chain length, and in these cases, the correct geometry cannot be reached. If the ring closure is not favourable, the substrate/intermediate may still undergo cyclisation, but it is more difficult for it to occur, and it may occur more slowly. [45,46]

The geometry of the electrophile (e.g. trigonal or tetrahedral) is used to determine whether cyclisation would be favoured based on the preferred angle of enolate nucleophile attacking the electrophile.[47]

Table 1: Baldwin's Rules for ring closure.[45]

Ring size	3		4		5		6		7	
	endo	exo	endo	exo	endo	exo	endo	exo	endo	exo
tet										
trig										
dig										

Favoured
Disfavoured

It is also reported that the reaction conditions for ring closure can affect the reaction outcome. According to Baldwin's rules, as shown in Table 1, 5-endo-trig is disfavoured for ring closure. However, Baldwin's rules can be affected by the solution's acidity and basicity. An example, involving 5-endo-trig cyclisation, showed that a ketol starting material failed to cyclise under basic conditions; however, when the reaction is performed under acidic conditions, the ketol successfully underwent ring closure to form the ring-closed product, as shown in Figure 12.[47] The ring closure in this example is explained by the reaction involving a ketone, which allows for good orbital overlap, and hence, the ring closure occurs.[48] The angle between the atoms that are involved in the ring closure reaction is maintained in the product.[45]

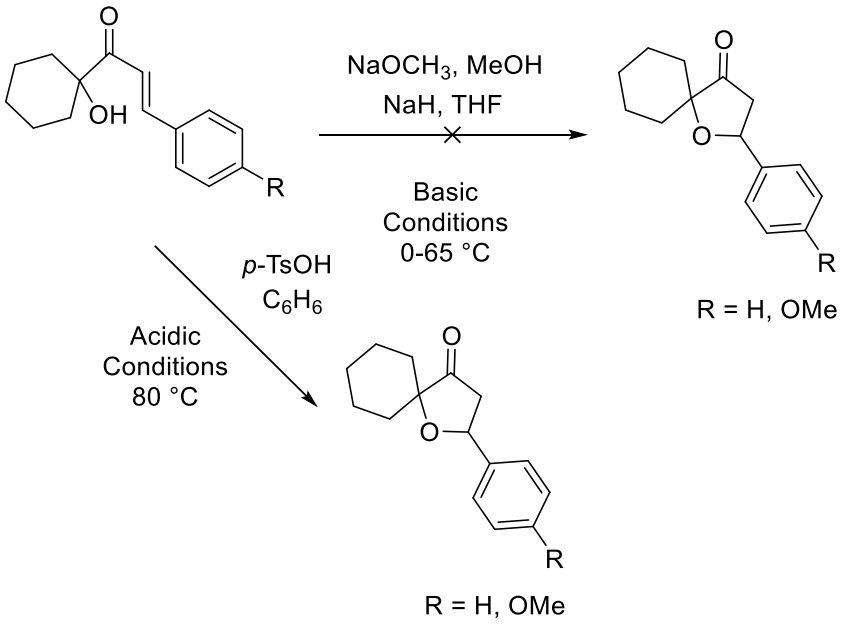


Figure 12: Effect of reaction conditions on the ring-closure of a ketol starting material to form furanone product.

In 1977, Baldwin et al reported a change in the rules when an enolate is involved in the ring-closing reaction. Table 2 indicates the favoured and disfavoured conditions. They reported that the reaction is controlled by the nucleophile's electronic interactions. Successful carbon or oxygen alkylation required the electrophile to be located in different positions. In oxygen alkylation, the enolate O-atom approaches the electrophile in the plane of the C-X bond, and in carbon alkylation, the enolate C=C approaches the electrophile perpendicular to the plane of the C-X bond.[49]

Table 2: Baldwin's Rules for enolate cyclisations. [50]

	exo-tet					exo-trig				
	3	4	5	6	7	3	4	5	6	7
enolendo										
enolexo										

favoured
disfavoured

At the outset of our studies, two possibilities for cyclisation were considered, as shown in Figure 13. One possible approach would involve nucleophilic attack of a ketene-derived enolate on the epoxide, followed by lactonisation (5-exo-trig) to

afford the γ-lactone. This pathway, the ketene-first pathway (**1**), is shown in Figure 13.

Another possible approach called the epoxide-first pathway (**2**), would involve lactone formation through a 5-enolendo-exotet cyclisation. This is shown in Figure 13. According to Baldwin's rules γ-lactone formation from a 5-enolendo-exotet cyclisation is disfavoured. However, there are known exceptions to Baldwin's rules, especially where a non-second row element is involved as nucleophile or leaving group.[49]

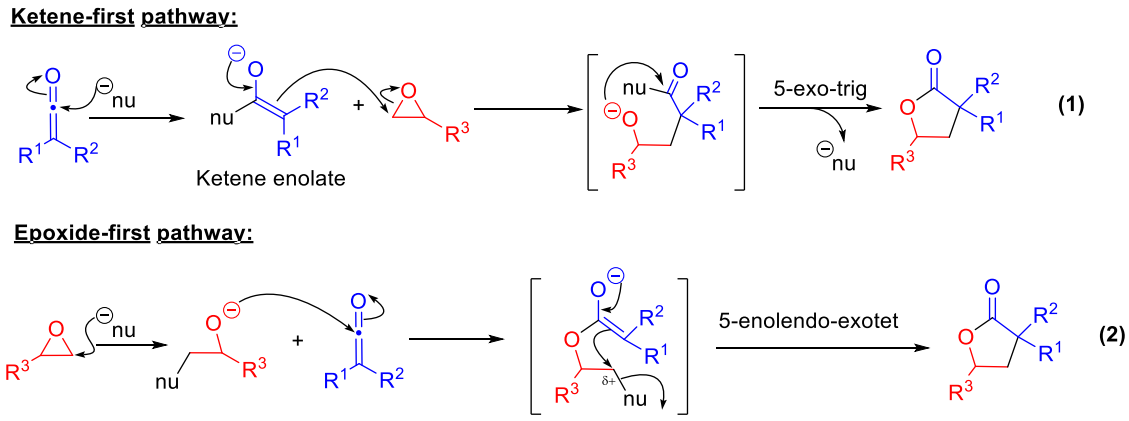


Figure 13: Two approaches to form the γ-lactone product from epoxide and ketene.

1.5 Epoxides:

An epoxide is a three-membered heterocyclic ring. Specifically, it is a three-membered cyclic ether. The heterocyclic ring contains an oxygen atom. Epoxides are reactive molecules due to the ring strain of the three-membered ring.[5] Benson et al. reported the ring strain of an oxirane to be 26.8 kcal mol^{-1}.[51] As a result, epoxides are highly reactive toward nucleophilic attack, allowing for epoxides to undergo a wide range of ring-opening reactions. The epoxide acts as an electrophile in these ring-opening reactions. Ring-opening reactions of epoxides can proceed under both basic and acidic conditions, generally yielding different regioselective outcomes.[6,7] Under acidic conditions, the epoxide generally undergoes ring-opening through nucleophilic attack on the more substituted carbon atom (a quasi-S_N2 type reaction, with significant $S_N1$character); under basic conditions, the

reaction tends to favour ring-opening at the less substituted carbon atom (in a pure S_N2 reaction). The two approaches are seen in Figure 14.

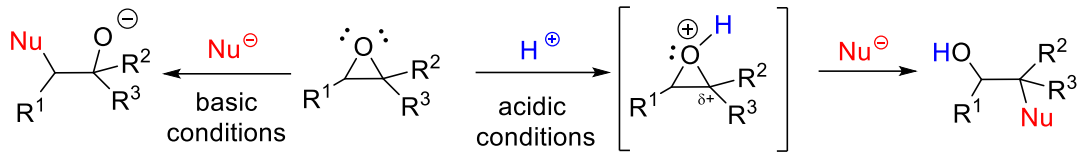


Figure 14: Two approaches for epoxide ring opening with a nucleophile under acidic and basic conditions.

Epoxides are widely used as starting materials for the synthesis of various compounds, including terpenoids, alkaloids, steroids and other natural products.[5] An example of the use of an epoxide to prepare a *γ*-lactone was the synthesis of (-)-(4*R*,5*R*)-Muricatacin. This product is synthesised using a vinyl epoxide as the starting material to access the product with high regioselectivity and stereospecificity, as shown in Figure 15.[52]

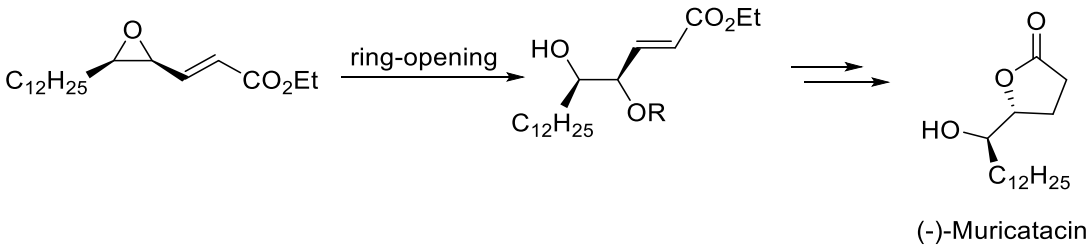


Figure 15: Synthesis of (-)-Muricatacin from vinyl epoxide.

There are many methods that are used to prepare epoxides. The most widely used methods to synthesise epoxides include the Johnson-Corey Chaykovsky reaction, Prilezhaev epoxidation of alkenes, Sharpless epoxidation and Darzens reaction.

1.5.1 Johnson Corey-Chaykovsky reaction

One of the most important epoxide synthesis methods is the Johnson-Corey-Chaykovsky reaction. In this reaction, a sulfur ylide reacts with an aldehyde to form an epoxide. The sulfur ylide was discovered by Jessop and Ingold in the 1930s.[53] Johnson initially reported the methylene transfer of a sulfonium ylide to an aldehyde.[54] Corey and Chaykovsky then reported the use of sulfoxonium and sulfonium ylides in reaction with ketones and aldehydes to form epoxides.[55]

The sulfur ylides are divided into two categories based on their stability, reactivity, and the sulfur atom's valence/bonding. The oxidation number of the sulfur atom and

the relative stability of the sulfur ylide have a large effect on the reaction.[56] The sulfonium ylide is a better nucleophile due to its lower oxidation number (IV) and relatively lower stability, in comparison to the sulfoxonium ylide. The sulfoxonium ylide has a higher oxidation number (VI), is a more stabilised ylide, and hence is a less reactive nucleophile. The sulfoxonium ylide is more stable due to a combination of electrostatic attraction (between positively charged sulfur and negatively charged carbanion) and negative hyperconjugation (between the filled lone pair orbital (n) and the σ^* orbital of the carbon–sulfur bond).[57] The two sulfur ylides dimethylsulfoxonium methylide and dimethylsulfoxonium methylide are shown in Figure 16. The dimethylsulfoxonium iodide methylide is formed by base-mediated deprotonation of a methyl proton from the sulfoxonium salt, and the dimethylsulfonium methylide is generated by deprotonation of one of the methyl protons in the sulfonium salt.

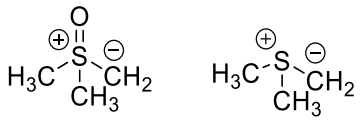


Figure 16: Dimethylsulfonium methylide and dimethylsulfoxonium methylide.[58]

This method of forming a three-membered heterocyclic ring is effective. The sulfur ylide is prepared as described above by deprotonation of an α-proton from the sulfoxonium or sulfonium salt. The sulfur ylides are easily synthesised due to the positively charged sulfur atoms. The positive charge polarises the C-H bond in the methyl substituent, making it more acidic and more susceptible to deprotonation. This forms a carbanion adjacent to the positively charged sulfur atom, forming a zwitterionic intermediate.[59] The negatively charged carbon attacks the electrophile via nucleophilic addition, forming a new bond to access a betaine intermediate (Figure 17). The alkoxide in the betaine intermediate attacks the adjacent electrophilic carbon, inducing an intramolecular cyclisation (3-exo-tet) resulting in the formation of the epoxide, and producing dimethyl sulfide (DMS) or dimethyl sulfoxide (DMSO) as a side product.

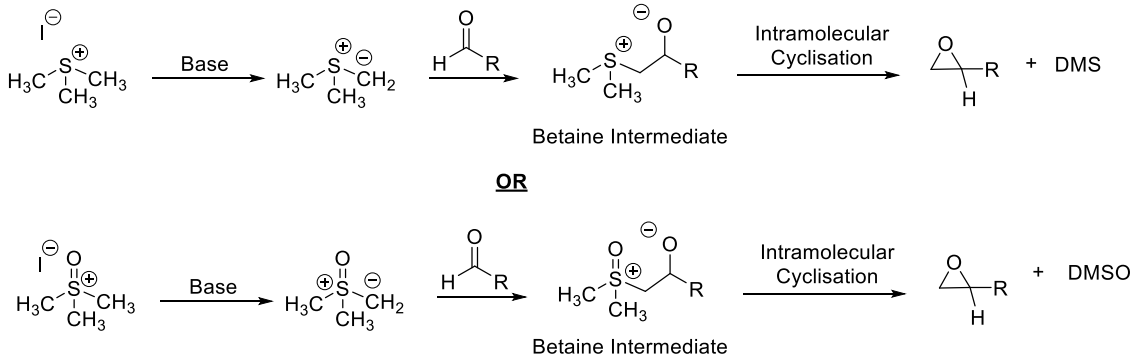


Figure 17: Johnson Corey-Chaykovsky reaction scheme.

The Johnson-Corey-Chaykovsky reaction is a versatile reaction used to convert aldehydes/ketones, α,β-unsaturated aldehydes/ketones and imines respectively into epoxides, cyclopropanes and aziridines.[59] Enantioselective variants employing chiral sulfides have been reported by Aggarwal's group.[60]

1.5.2 Epoxidation of alkenes

The conversion of an alkene to an epoxide is achieved through the oxidation of an alkene. An oxygen atom is added across the alkene double bond to form the epoxide in the oxidation reaction. Peroxycarboxylic acids, alkyl hydroperoxides, and hydrogen peroxides are examples of oxidizing agents that allow for the addition of oxygen across the alkene's double bond.[61] The most commonly employed oxidation method for epoxidation of an alkene is the Prilezhaev method. Bartlett proposed a mechanism for the epoxidation of the alkene (Figure 18).[61] The carbon-carbon double bond acts as the nucleophile in this reaction due to its high electron density. In a concerted mechanism, the carbon-carbon double bond attacks the electrophilic oxygen atom (in the O-O bond) attached to the terminal hydrogen atom of the peroxyacid. The O-O bond breaks and, at the same time, the lone pair on the carbonyl oxygen interacts with the peroxyacid proton, causing the proton to transfer intramolecularly, leading to the formation of the epoxide and the acid byproduct. This mechanism is shown in Figure 18 and is often referred to in literature as the 'butterfly mechanism'.[61,62]

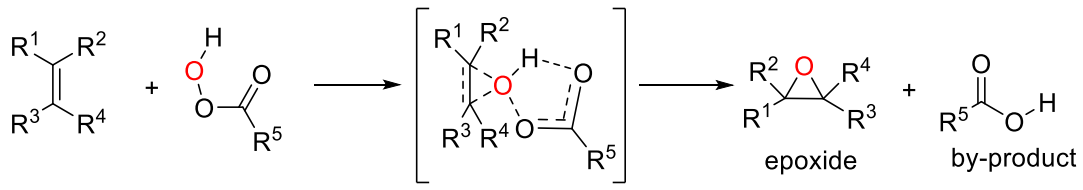


Figure 18: Bartlett mechanism for the epoxidation of alkenes to afford epoxides.

1.5.3 Sharpless epoxidation

The Sharpless epoxidation is a method used to synthesise epoxides enantioselectively from allylic alcohols.[63] It has been reported that epoxides can be synthesised from primary and secondary homoallylic alcohols and allylic alcohols. This epoxidation method was first discovered in 1980.[64] In 1980, the Sharpless group reported the asymmetric synthesis of epoxides from allylic alcohols through a titanium tartrate complex-catalysed oxidation reaction. The catalytic system was generated from Ti(O-*i*-Pr)$_4$ and the chiral ligand, diethyl tartrate (DET), with *tert*-butyl hydroperoxide (TBHP) acting as the oxidant.[65] The reaction scheme is shown in Figure 19.[65]

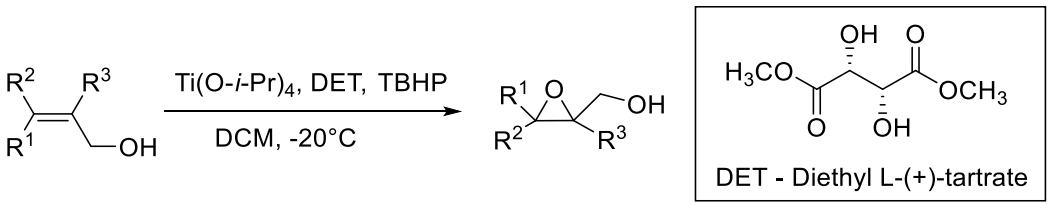


Figure 19: Sharpless epoxidation.

The enantioselectivity of this epoxidation reaction is high due to the oxidising agent's steric bulk, which promotes attack on one enantioface over the other. The chiral titanium tartrate complex [Ti(DET)(O-i-Pr)$_2$] is formed by exchange of two O-*i*-Pr ligands with the DET ligand.[63] The Sharpless epoxidation forms chiral epoxides in high enantiomeric excess from prochiral allylic alcohols.

Sharpless epoxidation method is a readily used method to form a chiral epoxide from prochiral allylic alcohols.[63] The starting material of the Sharpless epoxidation method is an alcohol. Therefore, the presence of the hydroxyl group is retained in the epoxide product. This method is a good route for epoxide synthesis if a hydroxyl substituent is required in the epoxide structure.

1.6 γ-lactone:

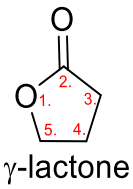


Figure 20: γ-lactone moiety.

A γ-lactone is a five-membered cyclic ester, and the numbering convention of the γ-lactone is as shown in Figure 20. It can be formed intermolecularly or intramolecularly. γ-Lactones are found in 10% of all natural products.[1] The γ-lactone moiety is found in a range of biological compounds.[2] γ-Lactone moieties are extracted from oak wood, and are also found in a variety of alcoholic beverages, including whiskey and brandy, and are responsible for their distinctive odours.[66,67] The moiety is also found in microorganisms; for example, mupirocin H is a very good antibiotic, and it contains the γ-lactone moiety.[68] Additionally, the γ-lactone motif is present in many natural compounds that are found in fruit, including peaches, pears, and apricots.[69] The γ-lactones in fruit are responsible for the aroma associated with these fruits. Moreover, the γ-lactone motif is very important because it constitutes a chiral building block that can be used to synthesise many biologically active compounds, thus providing the compounds with chirality.[2]

1.7 γ-lactone synthesis:

The γ-lactone moiety is used as a building block for pharmaceutical products.[70] There are many synthetic pathways to synthesise the γ-lactone due to its biological activity. The γ-lactone moiety can be present in mono-, di-, and tri- cyclic lactone products. Mono-cyclic products include γ-butyrolactones, α-methylene-γ-lactones, and butenolides. Two methods used to form the γ-lactones are C-C and C-O bond forming cyclisations.

1.7.1 C-C bond forming cyclisation

1.7.1.1 Synthesis of γ-lactones from ketenes and epoxides using tetraphenylstibonium

In 1988, Baba and co-workers investigated the synthesis of five and six-membered rings from oxiranes/oxetanes and ketenes (Figure 21).[71] The two ketenes used in the study were diphenylketene and ethylphenylketene, and the catalyst studied was tetraphenylstibonium (Ph_4SbI). The epoxide substituent affected the resulting product: it formed either the desired γ-lactone or a cyclic ketene acetal. Three solvents were studied in this paper; benzene was found to be the optimum solvent for γ-lactone formation. In all, just four γ-lactones were accessed using this method. When the reaction was carried out under the same conditions, but changing the solvent to acetonitrile or HMPA, the cyclic ketene acetal product was favoured. The reaction was proposed to proceed by an *α*-cleavage of the oxirane through a nucleophilic ring-opening caused by the iodide-based catalyst. The reaction mechanism initially proceeds via catalyst-mediated alkoxide formation. The alkoxide attacks the electrophilic carbon of the ketene molecule through nucleophilic addition. The enolate intermediate then presumably undergoes S_N2 cyclisation (5-enolendo-exo-tet) to form the desired γ-lactone. However, no study of stereospecificity was carried out, and so the exact details of the reaction mechanism are open to question. In addition, no diastereoselectivity study was conducted. Finally, tetraphenylstibonium iodide is regarded as having high toxicity, due to the known significant toxicity of organoantimony compounds, and this has limited its widespread use. This contrasts with the low toxicity exhibited by simple lithium salts.

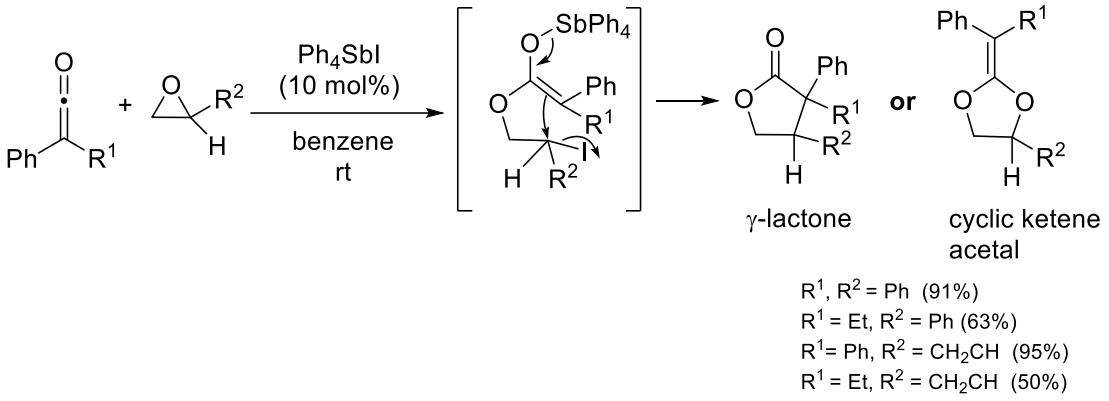


Figure 21: Ph_4SbI-catalysed synthesis of γ-lactones from epoxides and ketenes.

1.7.2 C-O bond forming cyclisation

1.7.2.1 Synthesis of γ-lactones via reductive coupling of an α, β-unsaturated ester with a carbonyl compound using samarium (II) di-iodide.

In 1988, Fukuzawa et al reported the reductive coupling of an *α,β*-unsaturated ester with carbonyl compounds using SmI_2 to synthesise *γ*-lactone products (Figure 22).[72] The reaction proceeded under mild conditions, yielding the desired product in good yield in some cases. The *γ*-lactones were prepared from crotonates or methacrylate. The carbonyl compound is reduced by SmI_2 and forms a ketyl radical anion. (Alternatively, one electron is transferred from the metal to the α,β-unsaturated ester). The ketyl radical anion attacks the *β*-position of the α,β-unsaturated ester, forming a new C-C bond. The resulting radical/enolate intermediate is then quenched by an alcohol and undergoes cyclisation to form the *γ*-lactone. The reaction was studied with a range of aldehydes and ketones, as well as with different *α,β*-unsaturated esters. The *γ*-lactones were formed in moderate to good yields (40-76%). The reaction conditions were different when an aldehyde was used in comparison to the reaction conditions when a ketone was used as the starting material. Hence, the two different carbonyl compounds required different reaction conditions. The reaction was carried out at room temperature when the less reactive ketones were used, but at a temperature below 0 °C when aldehydes were used in order to reduce side-product formation.

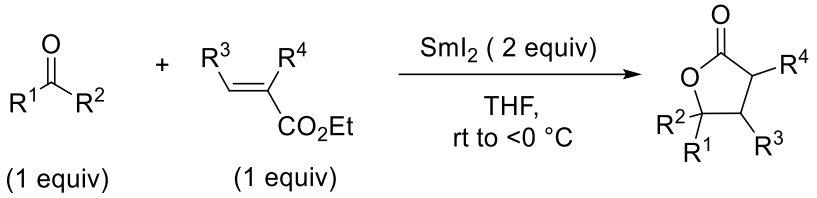


Figure 22: SmI_2-mediated coupling of carbonyl compounds with α,β-unsaturated esters.

Later, the Fukuzawa group further developed the reductive coupling of α,β-unsaturated esters with ketones and aldehydes to form enantioenriched chiral γ-butyrolactones (Figure 23).[73] They used the chiral auxiliary (1*R*,2*S*)-N-methylephedrine with the acrylate compound, which was determined to be the optimal chiral auxiliary for the reaction. The acrylates and crotonates derived from (1*R*,2*S*)-N-methylephedrine facilitated the formation of γ-lactones in moderate to high yields (43-88%), with good to excellent enantiomeric excess in many cases (43->99% ee).

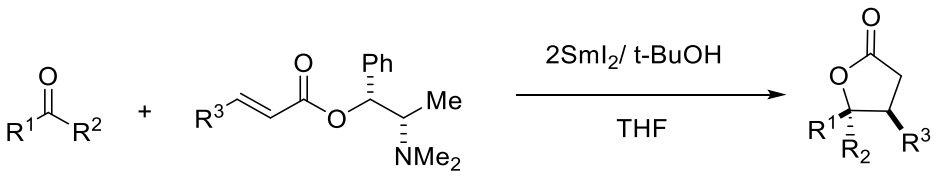


Figure 23: SmI_2 -mediated reductive coupling of carbonyl compounds with chiral ephedrinyl α,β-unsaturated esters.

1.7.2.2 Ephedrine chiral linker enabling a solid phase 'asymmetric catch-release' synthesis of γ-butyrolactones

Procter's group applied Fukuzawa's method to form γ-butyrolactones through a solid-phase system, enabling a catch-and-release approach (Figure 24).[74] Acrylates and crotonates linked to the polystyrene resin via ephedrine were used. The resin-bound acrylate trapped the ketyl radical anion intermediate, and, following cyclisation, yielded the enantiomerically enriched γ-butyrolactone. The purification of the reaction was simplified as the ephedrine auxiliary was immobilised onto the resin. The reaction produced the γ-butyrolactone product with high enantiomeric excess (up to 96% ee).

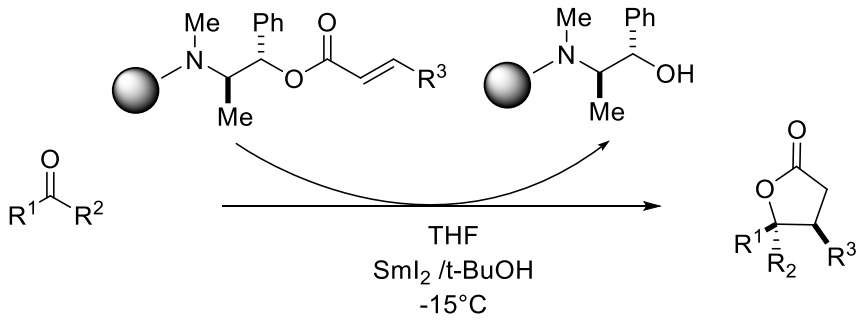


Figure 24: γ-Butyrolactone formation through an asymmetric catch and release approach.

Vaccaro et al. reported the synthesis of γ-lactones from epoxides and silyl ketene acetals.[75] The silyl ketene acetal initially acts as the nucleophile, and the epoxide as the electrophile in the reaction. This is the opposite of the 'epoxide-first' mechanism previously proposed by Baba and co-workers for epoxide-ketene cycloadditions; under Ph_4SbI catalysis, the opened epoxide acts as a nucleophile, and the ketene acts as the electrophile. In this method, the silyl ketene acetal is activated by a fluoride catalyst, causing desilylation to form an enolate. The enolate attacks the epoxide at the less hindered side, forming an alkoxide intermediate. This is then converted into a γ-lactone product by the alkoxide attacking the carbonyl carbon, followed by methoxy group elimination to form the ring-closed product. The reaction scheme is shown in Figure 25. This reaction is interesting because it was carried out under solvent-free conditions. A number of fluoride catalysts were investigated. The free tetrabutylammonium fluoride catalyst was the optimal catalyst for this reaction when the epoxide phenyl glycidyl ether and silyl ketene acetal were used. The reaction formed the γ-lactone product in high yields when numerous alkyl- and aryl-substituted epoxides were used, in combination with generally alkyl-substituted silylketene acetals. However, generally the 3,5-regioisomer of the lactone was favoured and poor diastereoselectivity was observed with unsymmetrical silyl ketene acetals.

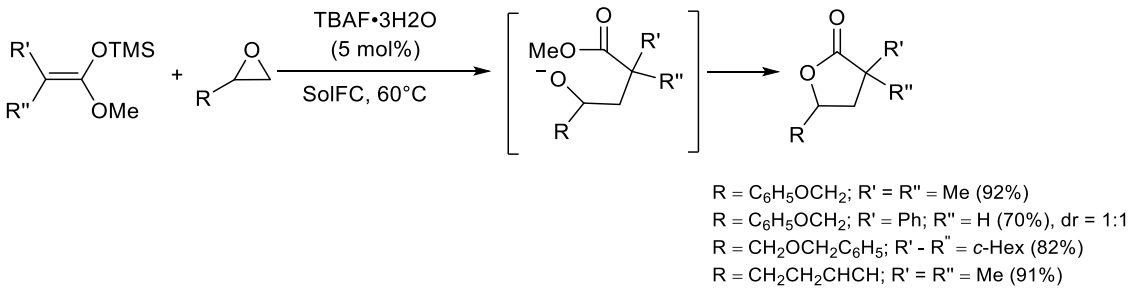


Figure 25: TBAF-catalysed synthesis of γ-lactones from silyl ketene acetals and epoxides.

1.7.2.3 Diastereoselective synthesis of γ-lactones from sulfoxonium ylides, aldehydes, and ketenes

Work has previously been carried out in the Kerrigan group on the synthesis of γ-lactones. The group studied the synthesis of γ-lactones through the reaction of sulfoxonium ylides, aldehydes, and ketenes.[76] The sulfoxonium ylide (**2**) is formed by treating the sulfoxonium salt with base. The reaction scheme is shown in Figure 26. This sulfoxonium ylide was reported to be the best zwitterionic intermediate for γ-lactone formation. The reaction was carried out at −78 °C to slow the reaction rate. They reported that at room temperature, the γ-lactone yield was lower; this could be due to many reasons. The Johnson-Corey-Chaykovsky reaction forms epoxides through the reaction of aldehydes with sulfoxonium ylides. Therefore, at room temperature, the epoxide may form; hence, the reaction was carried out at lower temperatures to prevent this. At lower temperatures, it allowed for the betaine (**4**) to react with the ketene to form an intermediate (**5**). The enolate (**5**) could then potentially cyclise via a 5-enolendoexo-tet cyclisation (although disfavoured according to Baldwin's rules) to form the γ-lactone product.

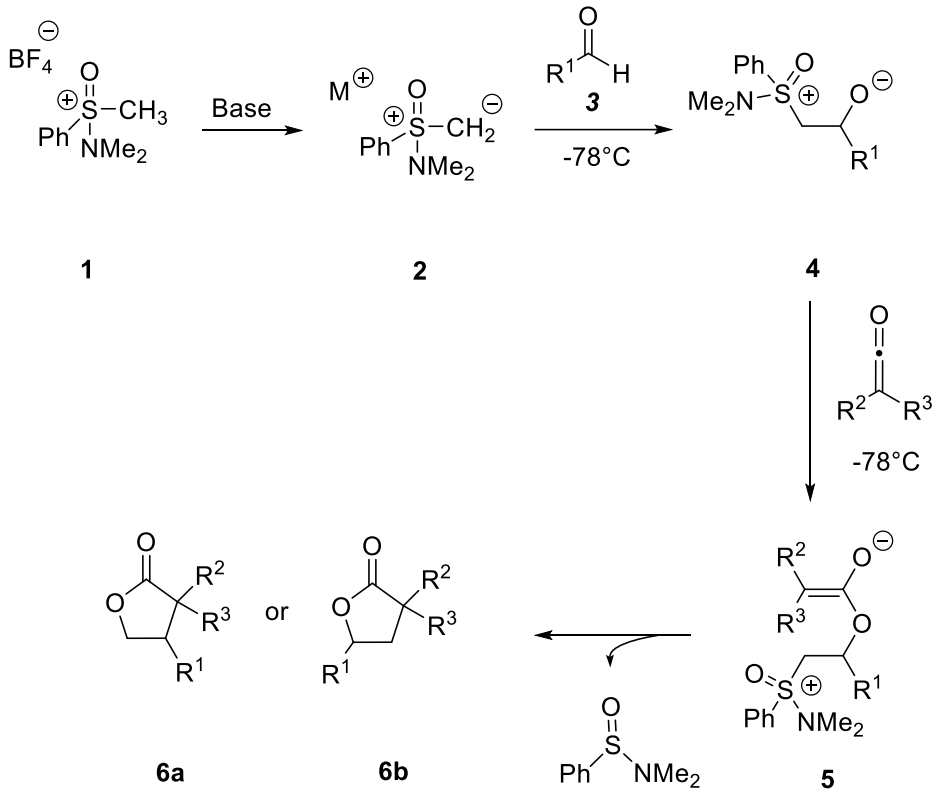


Figure 26: Diastereoselective synthesis of γ-lactones from aldehydes, sulfoxonium ylide and ketenes

The scope of this reaction was studied by varying the substituents on the ketene and the aldehyde. A variety of aromatic, heterocyclic, and aliphatic substituents on the aldehyde were studied against disubstituted ketenes that had an aryl on one side and a differing second substituent. The second non-aryl substituent on the ketene included isobutyl, ethyl, and methyl. The diastereoselectivity of the reaction was high with a dr of up to 92:8 and yields of up to 93%. They also studied the base used for sulfoxonium ylide generation, with *n*-BuLi being optimal, and the best additive ($MgCl_2$) for forming the γ-lactone with the highest yield. The aromatic aldehydes, in general, gave better yields.

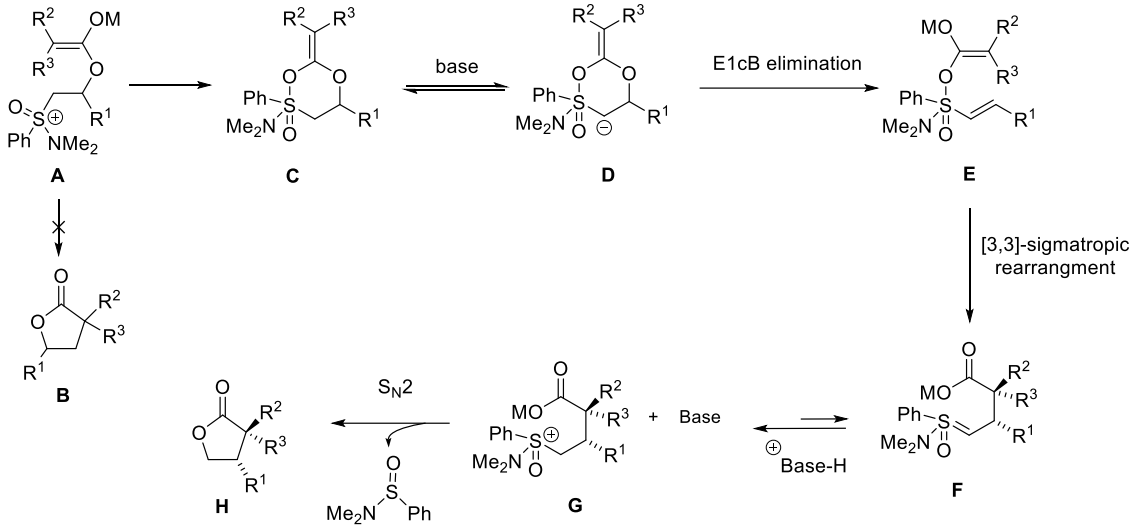


Figure 27: Mechanism of the diastereoselective synthesis of γ-lactones from aldehydes, sulfoxonium ylide and ketenes.

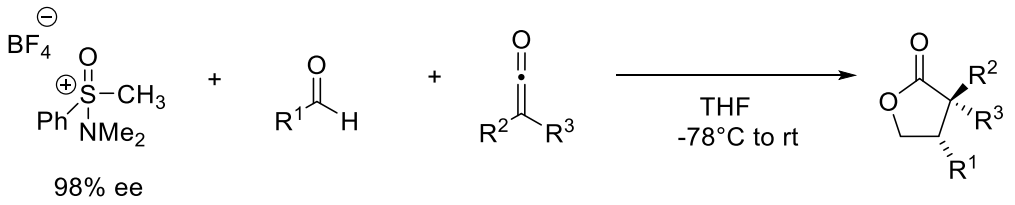
The mechanism of the reaction was studied and is shown above in Figure 27.[76] It was reported that the enolate **5/A** shown in Figure 26 and Figure 27 does not undergo direct cyclisation to **B**; instead, the enolate cyclises to form a six-membered intermediate called a sulfurane oxide (**C**). It is deprotonated by a base to form a sulfurane oxide anion (**D**). The sulfurane oxide anion undergoes E1cB elimination, to form alkene intermediate **E**. [3,3]-Sigmatropic rearrangement of the alkene/enolate intermediate **E** then occurs to form a carboxylate (**F**). Protonation leads to the formation of the next intermediate (**G**). This then cyclises via an intramolecular S_N2 reaction to form the γ-lactone (**H**).

1.7.2.4 Asymmetric synthesis of γ-lactones from aldehydes, ketenes and sulfoxonium ylides

The group later studied the asymmetric synthesis of γ-lactones from aldehydes, ketenes, and enantioenriched aminosulfoxonium ylide. They reported again that the aromatic aldehydes generated γ-lactones with the highest yields.[77] This could be due to the α,β-unsaturated sulfurane oxide intermediate **E**, formed before the [3,3]-sigmatropic rearrangement occurs, being more reactive when an aromatic group is present. The yield is higher when an aromatic group is present because it is more reactive and undergoes the [3,3] sigmatropic rearrangement faster, leaving less time for competing side reactions. In contrast, when an aliphatic group is on the aldehyde, the γ-lactone yield is lower as the α,β-unsaturated sulfurane oxide

intermediate **E** is less reactive and the [3,3]-sigmatropic rearrangement is slower, leading to competing side reactions. This is shown in Table 3. γ-Lactones were formed with enantiomeric excess of up to 79% from aminosulfoxonium salt of 98% ee.

Table 3: Effect of the substituents on the yield of the asymmetric aminosulfoxonium ylide reaction.



Entry	R^1	R^2	R^3	Yield (%)	%ee
1	*i*-Pr	*i*-Bu	Ph	41	76
2	2-NO_2Ph	*i*-Bu	Ph	65	6

1.7.2.5 Diastereoselective synthesis of γ-lactones from α,β-Unsaturated sulfoxonium salts and enediolates

Aggarwal's group reported the formation of monocyclic and bicyclic products from the reaction of vinyl sulfonium salts with various nucleophiles.[78–81] The Kerrigan group also studied the formation of γ-lactones from lithium enediolates and vinyl sulfoxonium salts, a new synthesis route to the desired product. The Kerrigan group built on this and reported the formation of γ-lactones with high diastereoselectivity. The reaction scheme is shown in Figure 28. The enediolate was generated by treating the carboxylic acid with *n*-BuLi at -78 °C in THF. This enediolate was then subjected to reaction with vinyl sulfoxonium salts, that were prepared according to Johnson et al.[82] The yields of the γ-lactone were high, with yields up to >99% and high diastereoselectivity (dr >90:10 for 10 examples) achieved. Substitution patterns on the carboxylic acid and the vinylsulfoxonium salt were investigated. The carboxylic acid α-aryl substituents, including electron-withdrawing and electron-donating, did not affect the yield. In comparison, when *t*-Bu was the α-substituent on the carboxylic acid, the yield decreased significantly to 33%. Lithium enediolates from α,α-disubstituted acetic acids were also studied, and they provided access to γ-lactones with an α-quaternary centre. The yield (52-62%) and diastereoselectivity (dr 73:27 to 80:20) of the formed γ-lactones decreased when they were

disubstituted at the α-position. In conclusion, this is an efficient method to form γ-lactones with high diastereoselectivity, albeit with some substrate scope deficiencies noted.

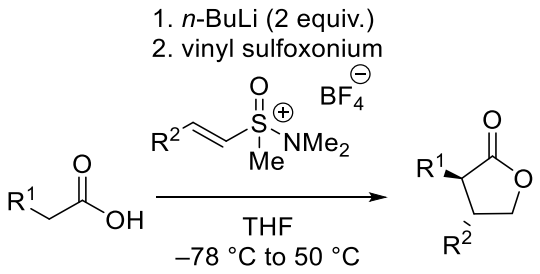


Figure 28:Reaction of vinyl sulfoxonium salts with lithium enediolates, generated from carboxylic acids, to form γ-lactones.

1.8 Applications:

The γ-lactone motif has been used in many drugs, for example, in anticancer agents, contraceptive drugs, anti-inflammation agents, immunosuppressive agents, and treatments for many other types of diseases/ailments.[83] The FDA has approved many γ-lactone-containing drugs for the treatment of diseases. Some of these include pilocarpine, which reduces intraocular pressure in the eye and treats xerostomia; and spironolactone and eplerenone for high blood pressure and heart failure.[83]

1.8.1 Antifungal:

Sesquiterpene lactones (SL) contain a five-membered lactone ring, as part of a bicyclic or tricyclic structure.[84] SLs display antifungal and antibacterial activity. This area has been widely investigated due to the common occurrence of fungal and bacterial infections, and, more importantly, the resistance of these pathogens to medication. A common feature of SL is the α-methylene-γ-lactone ring, which is shown in Figure 29. Part of the SL is a γ-lactone.

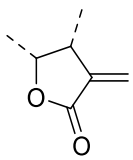


Figure 29: α-methylene-γ-lactone ring structure.

The compound shown in Figure 30 displayed antifungal activity against a number of fungi, for example, botrytis cinerea, colletotrichum lagenarium, *and erysiphe graminis*.[85]

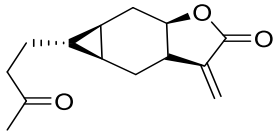


Figure 30: Compound obtained from Carpesium macrocephalum.

Food and health safety are growing concerns as pest-resistant strains emerge; therefore, finding natural crop protection methods against these strains is increasingly important in the agrochemical industry. Compounds containing the α-methylene-γ-lactone ring, particularly sesquiterpene natural products, play a significant role in the agrochemical industry for crop protection.[86] In particular, carabrol and carabrone are important natural SLs that have antifungal activity against *C. Lagenarium*.

1.8.2 Antibacterial:

Lactivicin is an antibacterial antibiotic that contains a γ-lactone structure. It is derived from two Gram-negative bacteria, YK- 258 and YK-422.[87, 88] It was one of the first antibiotics, that is not a β-lactam, that bound to penicillin-binding proteins. It was reported to have a wide range of activity against a broad range of bacteria. A study of clarithromycin γ-lactone ketolides showed that heteroaromatic groups on the γ-lactone molecule improved the antibiotic's antibacterial activity when tested against antibiotic-resistant bacterial strains.[89] In particular, one of the clarithromycin γ-lactone ketolides has displayed strong antibacterial activity against common Gram-positive pathogens and also against pathogens resistant to Macrolide, Lacosamide, *and Streptogramin B* antibiotics.[90] γ-Lactone ketolides are effective macrolide antibiotics.

1.8.3 Anticancer:

Naturally occurring products have been widely used as chemotherapeutic agents; among these are sesquiterpene lactones.[91] SLs are natural products, and they are

found in a large number of flowering plants.[92] Many SLs have been used to arrest cell cycle progression. Cell differentiation is very important because it regulates cell proliferation. In cancer, this does not occur, and therefore, it has been reported that costunolide can differentiate leukaemia cells. Therefore, costunolide and other anticancer drugs, when combined with chemotherapeutic drugs, promote the differentiation of leukaemia cells. Costunolide and dehydrocostus lactones have a variety of pharmacological activities, including anti-cancer, anti-inflammatory and anti-cancer. These two compound structures are shown in Figure 31. These SLs contain an α-methylene-γ-lactone moiety, which is credited with inducing cell death and cell cycle arrest. This occurs when the α-methylene moiety in the SL drug interacts with cancer cell proteins via nucleophilic cysteine residues.

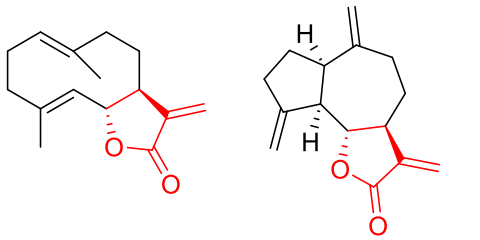


Figure 31: SL Costunolide and Dehydrocostus.

However, costunolide and dehydrocostus have limitations, including water solubility and non-selective cytotoxicity. Therefore, research has focused on investigating structural modifications of them to resolve some of the limitations. Another anticancer chemotherapy drug is gemicitabine. The drug molecule itself is not a γ-lactone, but the key intermediate in its synthesis is a γ-lactone. The MacMillan group synthesised an α,β-dioxyaldehyde and subjected it to reaction with a silylketene acetal.[93] This reaction is a Mukaiyama aldol reaction; the Lewis acid, dichlorotitanium diisopropoxide ($TiCl_2(O^iPr)_2$), activated the aldehyde. The silyl ketene acetal (**1**) hence, acted as the nucleophile to attack the aldehyde (**2**) to form the β-hydroxyester (**3**). The O-TMP of the β-hydroxy ester was cleaved (through Zn-mediated N-O bond cleavage), and then in situ cyclisation, prompted by aqueous trifluoracetic acid, provided the γ-lactone (**4**). The lactone was then converted into a C-nucleoside through a two-step process. An aryllithium reduced the lactone to a

lactol, while also forming a new C-Ar bond. The resulting lactol was deoxygenated (reduced) diastereoselectively (under two different sets of reducing conditions) to form the C-nucleoside selectively as the α or β-anomer, as shown in Figure 32.

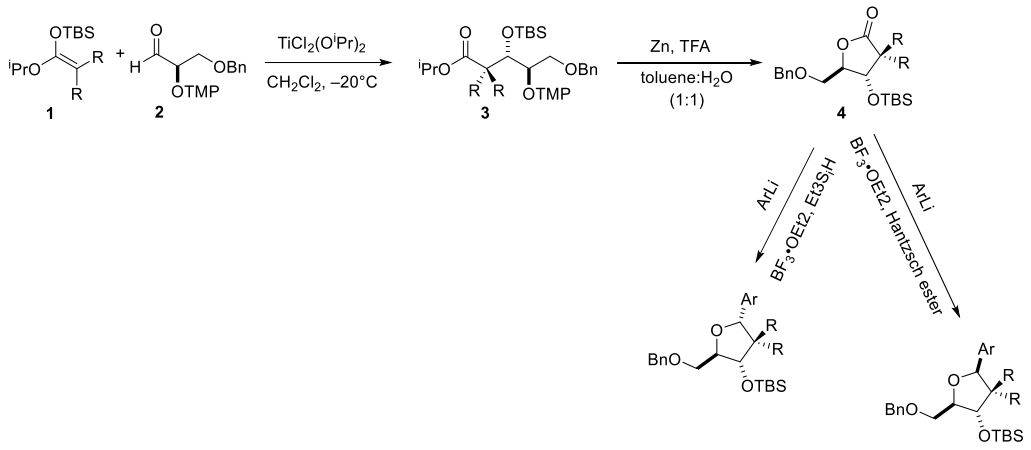


Figure 32: Formation of C-nucleosides from an α,β-dioxyaldehyde and a silyl ketene acetal.

Gemcitabine is a fluorinated nucleoside analogue, and these molecules are receiving increased attention in the pharmaceutical industry as research into fluorinated compounds continues. For the synthesis of monofluorinated nucleosides, the γ-lactone intermediate would be fluorinated first and then reduced to form the lactol, as shown in Figure 33.

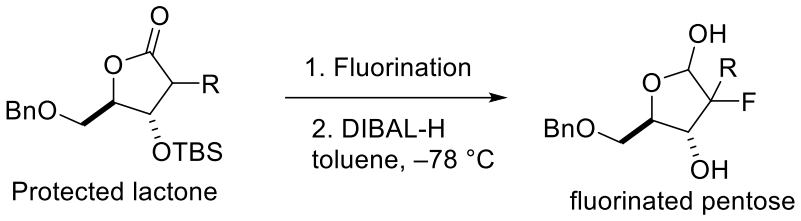


Figure 33: Fluorination and reduction of a γ-lactone to a fluorinated pentose.

A specific difluorinated pentose is further elaborated in four additional steps to yield the anticancer drug gemcitabine. This anti-cancer drug is synthesised in nine steps from the α,β-dioxyaldehyde (see Figure 32) with an overall yield of 23%, as shown in Figure 34.

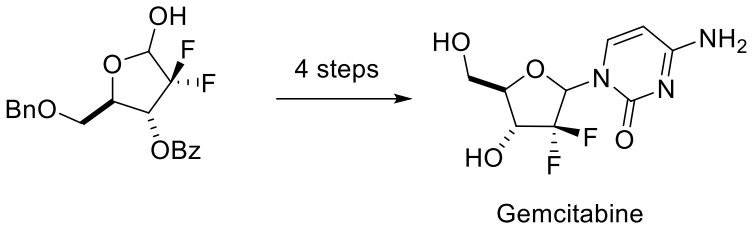


Figure 34: Synthesis of Gemcitabine from difluorinated lactol.

1.9 Epoxide and Ketene Reaction Pathway

The dominant reaction pathway in formal [3 + 2]-cycloadditions of epoxides and ketenes previously investigated in the literature has been predicated on the ketene acting as the electrophile, and the ring-opened epoxide acting as the nucleophile ('Epoxide-first pathway', shown in Figure 35). The epoxide is a strained three-membered ring and a good electrophile. This reaction requires a catalyst/reagent to open the epoxide to generate the nucleophile. The opened epoxide forms an alkoxide intermediate, which can act as a nucleophile in a reaction with a ketene. The nucleophilic catalyst attacking the ring-strained epoxide would, under purely basic/nucleophilic conditions, be expected to open the epoxide at the less-substituted carbon (in a pure S_N2 fashion), although regioselectivity will be examined throughout the project. The involvement of a Lewis acidic counterion (associated with the nucleophile) could activate the epoxide and alter the regioselectivity of ring-opening, providing similar regioselectivity to acid-catalysed epoxide ring-opening, where a quasi-S_N2 reaction with significant S_N1 character is operative.

A second possible pathway ('Ketene-first pathway'), which could be investigated, arises because ketenes have an electrophilic and a nucleophilic carbon, as shown in Figure 35. The terminal carbon of the ketene can be rendered nucleophilic under appropriate nucleophile-catalytic conditions and can attack the electrophilic epoxide to form an alkoxide intermediate in this reaction (Figure 35). The epoxide as described above is a good electrophile due to its ring strain. In theory, a ketene-derived enolate could attack the epoxide at its less-substituted carbon atom and, upon lactonisation, form the γ-lactone. Generally, ketenes acting directly as a nucleophile have not been widely reported, although silyl ketenes, acting as

nucleophiles in reactions, have been described. The reaction of silyl ketenes and chelating carbonyl substrates has been studied in an enantioselective Lewis acid-catalysed [2 + 2]-cycloaddition to access β-lactones.[94] However, the silyl ketene is reported to be a poor nucleophile. A second class of nucleophilic ketene analogues are silyl ketene imines.[95]

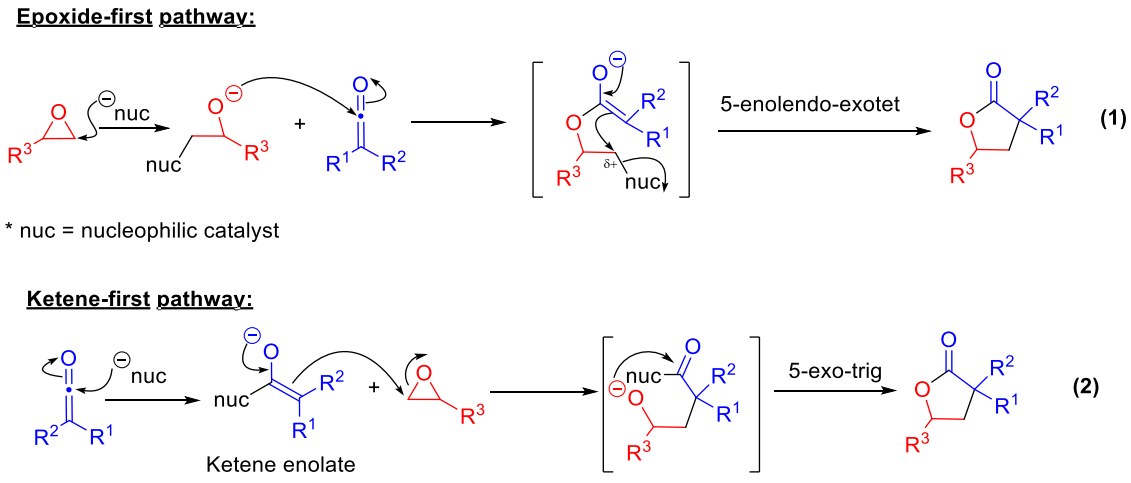


Figure 35: Epoxide-first and ketene-first pathways.

This introduction to the thesis shows that γ-lactones are important compounds. There are many ways that they can be synthesised as previously described, although each method frequently has limitations (e.g., substrate scope, stereoselectivity). In this thesis, a new method for the catalytic synthesis of γ-lactones from epoxides and ketenes will be described. The reaction scope will be explored to determine which substitution patterns on substrates allow the reaction to proceed and which hinder product formation. The reaction mechanism will also be explored.

1.10 Aims of Research

The γ-lactone structure has a wide range of applications as seen in the introduction, including anti-cancer, anti-viral, and treatments for other diseases and ailments. There are many methods by which the γ-lactone can be synthesised.

This research project aimed to synthesise γ-lactones via a [3 + 2]-cycloaddition reaction. The [3 + 2]-cycloaddition reaction of epoxides and ketenes was studied. The scope of epoxides and ketenes that resulted in the formation of the desired γ-

lactone product was evaluated. The desired γ-lactone product was anticipated to be formed as the 3,5-γ-lactone regioisomer based on the expected regioselectivity in ring-opening of the epoxide. The scope of the reaction of epoxides with diphenylketene was analysed to determine if the predicted 3,5-γ-lactone was formed or the unexpected 3,4-γ-lactone regioisomer.[71]

The conditions of the reaction were investigated to determine if the reaction method had an effect on the product. The conditions that were studied included solvent, light, temperature, mole equivalents of starting materials, and starting material addition order.

Mechanistic studies of the reaction were carried out and the results analysed to determine the reaction mechanism. There were two proposed reaction mechanisms, and these two mechanisms were studied via ring-opening experiments of the epoxide, quenching reactions, enolate trapping experiments, and experiments using radical scavengers and radical trapping agents.

Chapter 2: Optimisation and Scope of the [3 + 2]-cycloaddition reaction: Experimental

2.1 Introduction:

The preparation of starting materials and final products are documented in this chapter. The procedures developed and followed for each reaction are documented, and the characterisation data for each compound synthesised in this project are presented.

2.2 Experimental:

2.2.1 Instruments used in the project:

Type of analysis	**Instrument model**
NMR	Bruker Avance III Ultrashield NMR Spectrometer
IR	Thermoscientific Nicolet I.S5 ATR.IR Spectrometer
GC-MS	GC-MS Hewlett Packard HP 6890 GC instrument with a 5973 mass selective detector
UV lamp	UVP UVG-11
Balance	Mettler Toledo AG245
Heating mantle	Barnstead/electrothermal heating mantle EM0100CE
Magnetic Stirrer Heating Plate	IKA Yellow Line MST Basic C Magnetic Stirrer heating Plate
Rota Evaporator	IKA RC 10 digital Dry Ice Condenser
Rota Evaporator pump	MVP 10 basic vacuum pump
Pump in fume hood	Edwards E-LAB 2 vacuum pump

2.2.2 General Information:

Unless otherwise specified, all glassware used was flame-dried under vacuum and subsequently placed under a nitrogen atmosphere using standard inert-atmosphere techniques. A distillation still was used to dry THF over sodium/benzophenone. A purple/ blue colour was observed when the THF was dry and ready for use. CH_2Cl_2 and hexane were dried over calcium hydride in a still. *N*,*N*-Dimethylethylamine was distilled from KOH and was distilled at an oil bath temperature of 50 °C under N_2. Diphenylacetyl chloride was purchased from Fisher Scientific Ireland Ltd but other acetyl chlorides were prepared and 2-Phenylpropanoyl chloride was prepared by S. Ayidi of our group. TLC plates (Machery-Nagel SIL G-25 /UV_{254} Glass Plates) were used unless otherwise stated. Propionyl chloride was distilled under N_2. *N*,*N*-diisopropylethylamine (DIPEA) was distilled under reduced pressure from KOH. All commercially available starting materials were purchased from Fisher Scientific Ireland, Sigma-Aldrich (Merck) and Fluorochem. NMR spectra were recorded using the Bruker Avance III 600 spectrometer (600 MHz) for the generation of ^{1}H NMR, ^{13}C NMR and DEPT spectra. NMR chemical shifts were calibrated relative to TMS (0 ppm) or $CDCl_3$ (7.26 ppm) for ^{1}H and to $CDCl_3$ (77.23 ppm) for ^{13}C NMR spectra. The purified compounds were purified by column chromatography using Iatro beads (neutral silica) or acidic silica. The products were eluted from the column using EtOAc and Hexane mixture.

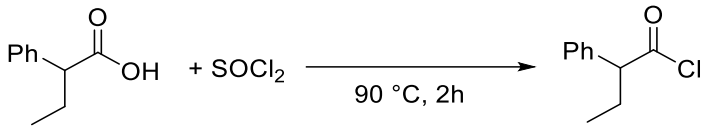
2.2.2.1 Sample analysis

GC-MS analysis was performed on both the purified and crude product samples. The samples were dissolved in CH_2Cl_2 or EtOAc (at 5 mg/mL concentration), and they were then injected on the GC-MS. After GC-MS analysis the remaining sample was added back to the reaction mixture, and the excess solvent was removed by rotary evaporation. The purity of the sample as determined by GC-MS analysis was further corroborated through parallel NMR analysis. The % peak area in the GC-MS spectra was used to determine the amount of the desired product in the sample and was corroborated by NMR analysis. The NMR spectra for purified products are present in the appendix, and four examples of the GC-MS traces with the % peak areas and fragmentation patterns are shown in Spectrum 1-Spectrum 10. The crude

acyclic ester proposed products **5f-5p** were partially characterised by using both NMR and GC-MS analysis together. These products were formed in poor yield or there was a low % peak area of the desired product according to GC-MS. Hence, these crude products were not subjected to purification. The products that were formed from ethylphenylketene had very complex NMR spectra due to side products in the samples as well as a mixture of diastereoisomers from the reaction. Therefore, the GC-MS fragmentation pattern of these samples was compared to characterised samples to ensure they contained some of the common acyclic ester fragmentation patterns and contained fragmentation patterns that correspond to that acyclic ester product. The ^{13}C NMR spectrum was also analysed in parallel to the GC-MS spectrum to ensure that there were peaks in the regions expected. The acyclic esters that have characteristic peaks listed contain peaks that were used to confirm the formation of the acyclic product; these included the carbonyl peak and some alkyl peaks that were characteristic of the acyclic ester product. These samples were reported via MS data and characteristic peaks from NMR analysis. Eleven examples of acyclic ester products (**5f**-**5p**) were not purified beyond the crude stage, due to low product formation as judged by GC-MS analysis of crudes.

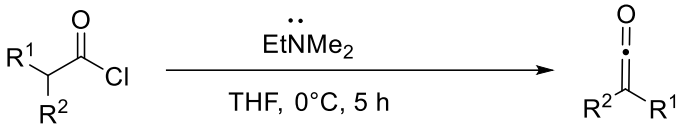
2.3 Preparation of Acetyl chlorides and Ketenes

2.3.1 2-Phenylbutyryl chloride (**1a**)



2-Phenylbutyric acid (10.95 g, 66.7 mmol) was suspended in $SOCl_2$ (14.5 mL, 198.7 mmol) and then refluxed at 90 °C for 2 h. The reaction mixture was cooled to room temperature, and the reaction mixture was placed under reduced pressure to remove excess $SOCl_2$. The acyl chloride was distilled under reduced pressure to afford the product as a colourless liquid (10.8g, 89%), ^1H NMR (600 MHz, $CDCl_3$) δ 7.42-7.31 (m, 5H), 3.92 (*app* t, *J* = 7.5 Hz, 1H), 2.27-2.22 (m, 1H), 1.92-1.88 (m,1H), 0.96 (*app* t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.1, 136.0, 129.2, 128.6, 128.4, 65.3, 26.8,11.9 ppm.

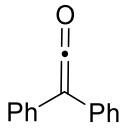
2.3.2 General ketene synthesis:



R^1 = Ph
R^2 = Ph, Me. Et

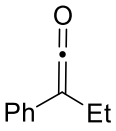
Acyl chloride (1 equiv.) (yellow/white powder or colourless liquid) was added to a 100 mL round-bottom flask that had been previously flame-dried under vacuum and placed under an inert atmosphere. Still-dried THF was added, and a colourless/faint yellow reaction mixture was observed. The reaction was then cooled in an ice bath using a Dewar vessel and stirred for 5–10 min to bring the reaction to 0 °C. *N*,*N*-dimethylethylamine (4 equiv.), freshly distilled, was added dropwise over 5-10 min. The reaction mixture turned canary yellow in colour after two drops of *N*,*N*-dimethylethylamine. The reaction was stirred at 0 °C for a total of 5 h, and in some cases stored at –35 °C overnight. The reaction mixture was transferred to a Schlenk filter funnel under N_2 atmosphere, then filtered through a sintered disc under vacuum into a Schlenk round-bottom flask to remove ammonium hydrochloride salt. THF (10 mL) was added to the reaction flask to remove any remaining ketene and to wash excess ketene adhering to the ammonium salts in the Schlenk filter funnel into the Schlenk round-bottom flask. The filtrate was evaporated under reduced pressure to yield a yellow/orange oil. It was transferred via syringe into a short path distillation apparatus (including a 5 mL round-bottom boiling flask with magnetic stirrer) and was distilled under vacuum. The distilled ketene was orange/yellow in colour and was stored under a nitrogen atmosphere at -35 °C. The purity was determined by NMR and GC-MS analysis.

2.3.2.1 Diphenylketene (**2a**)



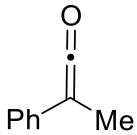
Diphenylacetyl chloride (2.9 g, 12.6 mmol) was added to a 100 mL round-bottom flask, and then THF (42 mL) was added. The reaction mixture was cooled to 0 °C, and $EtNMe_2$ (5.45 mL, 52 mmol) was added over 5 min. The reaction was stirred at 0 °C for 5 h and then distilled, using a heat gun to aid distillation, to afford a yellow oil (1.7 g, 69%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.33 (m, 4H), 7.22-7.21 (m, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.3, 131.0, 129.4, 127.9, 126.4, 47.1 ppm. The spectral data corresponds to reported literature. [96]

2.3.2.2 Ethylphenylketene (**2b**)



2-Phenylbutyryl chloride (1.8 g, 9.9 mmol) was added to a 100 mL round-bottom flask, and then THF (32 mL) was added. The reaction was brought to 0 °C, and $EtNMe_2$ (3.23 mL, 30.6 mmol) was added dropwise over 6 min. The reaction was stirred at 0 °C for 5h and then distilled at 110 °C (oil bath temperature) to afford a yellow oil (1.07 g, 74%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.32 (m, 2H), 7.10-7.05 (m, 3H), 2.46 (q, *J* = 7.4 Hz, 2H), 1.25 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 205.5, 133.0, 129.2, 124.4, 124.2, 42.1, 17.2, 13.1 ppm. The spectral data corresponds to reported literature.[43,96,97]

2.3.2.3 Methylphenylketene (**2c**)



2-Phenylpropanoyl chloride (3.27 g, 19.5 mmol) was added to a 100 mL round-bottom flask and then THF (54 mL) was added. The reaction mixture was cooled to 0 °C, and $EtNMe_2$ (4.78 g, 65.4 mmol) was added dropwise over 6 min. The reaction was stirred at 0 °C for 5 h and then distilled at 110 °C (oil bath temperature) to yield

a yellow oil (1.69 g, 66%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.32 (m, 2H), 7.10-7.07 (m, 1H), 7.05-7.03 (m, 2H), 2.02 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.7, 133.6, 129.1, 124.3, 123.8, 33.9, 8.8 ppm. The spectral data corresponds to reported literature.[43,97]

2.4 Preparation of epoxides

2.4.1 General Procedure A (Reduction of α-Bromoketone) :

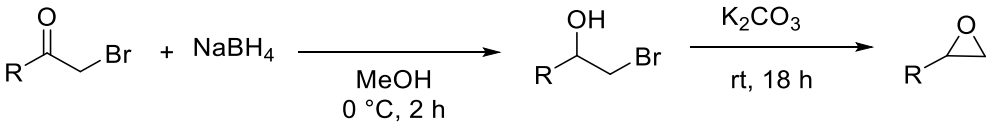


Figure 36: Procedure A for the synthesis of epoxides.

The general procedure for this method was adapted from the procedure by Campbell and Durón.[98] α-Bromoketone (4.39-9.43 mmol, 1 equiv.) was added to a two-necked round-bottom flask, which was placed under vacuum, and then under a N_2 atmosphere. Anhydrous MeOH/THF (10-20 mL, 0.44-0.47 M) was added to the round-bottom flask, and the reaction mixture was cooled to 0 °C in an ice bath. $NaBH_4$ (4.89-19.92 mmol, 1.1-2.1 equiv.) was added in small portions to the reaction at 0 °C. The reaction was stirred at 0 °C for 2 h. K_2CO_3 or *t*-BuOK (4.42-20.42 mmol, 1.0-2.4 equiv.) was added slowly via one of the side-arms to the round-bottom flask at 0 °C. The reaction flask was removed from the ice bath and allowed to warm to room temperature. The reaction was then stirred for 18 h at room temperature. An aqueous work-up was carried out using brine (15 mL), the organic layer was extracted with diethyl ether (15 mL), and the combined organic layer was dried over Na_2SO_4. The crude product was generally purified via flash column chromatography using Iatrobeads (neutral silica).

2.4.2 General Procedure B (Johnson-Corey-Chaykovsky Reaction):

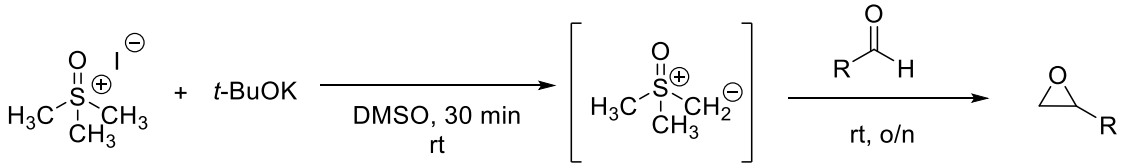


Figure 37: Procedure B for the synthesis of epoxides.

The procedure was modified from the procedures of Prapurna et al., Cruz-Almanza et al. Ma et al and Furstoss et al.[99–102] Potassium *tert*-butoxide *(t*-BuOK) (8.67-10.85 mmol, 1.2-1.4 equiv) was added to a pre-flame dried two-necked round-bottom flask under N_2 with a stir bar. After addition the reaction flask was placed under vacuum for 10 min, followed by N_2. Dry DMSO (13-25 mL, 0.35-0.69 M) was added to the round-bottom flask under inert conditions. The DMSO was dried over molecular sieves for 3 days before use in the reaction. Trimethylsulfoxonium iodide (TMSOI) (8.29-11.87 mmol, 1.3-1.4 equiv.) was weighed and added to the round-bottom flask; the N_2 flow was increased upon addition. The reaction was stirred at room temperature for 30 min. The aldehyde (7.32-9.13 mmol, 1 equiv.) was added. A colour change was observed upon addition of the aldehyde to the reaction mixture. The reaction was stirred overnight at room temperature under inert conditions. An aqueous work-up was performed using deionised water (30 mL) and extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine (3 × 70 mL) and dried over Na_2SO_4. The crude product was generally purified by flash column chromatography using neutral silica.

2.4.3 General Procedure C (Johnson-Corey-Chaykovsky Reaction):

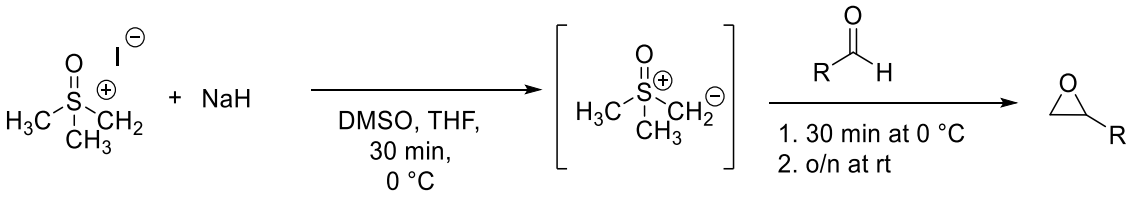


Figure 38: Procedure C for the synthesis of epoxides.

The general method for this reaction was adapted from that of Xu et al.[103] NaH (18.82-76.21 mmol, 1.5-7.38 equiv. (60% dispersion in oil)) was added to a pre-flame-dried two-necked round-bottom flask under N_2. After the addition of the base to the round-bottom flask, the flask was placed under vacuum for 10 min, and then under N_2. Dry hexane was added to the flask to remove the oil from the NaH. It was washed three times using dry hexane. Dry hexane was added to the round-bottom flask and stirred for 10 min. The hexane containing the oil was then removed via syringe. When the hexane used to wash the NaH went colourless, this indicated the absence of oil. The round-bottom flask was subsequently placed under vacuum to

remove excess hexane, and then under N_2. The solvents used for this reaction were DMSO (9.5-30 mL) and THF (7.5-25 mL) (0.18-0.44 M). After the addition of the solvents, the round-bottom flask was placed in an ice bath to bring the temperature of the reaction to 0 °C. Trimethylsulfoxonium iodide (TMSOI)(9.0-30.07 mmol, 1.2-2.9 equiv.) was added via one of the two-necked round-bottom flask's side necks. It was then stirred for 30 min at 0 °C. The aldehyde (7.49-10.33 mmol, 1.0 equiv.) was added neat over 2 min. The reaction was stirred at 0 °C for 30 min, and then left to stir at room temperature overnight. A colour change was observed upon addition of the aldehyde to the reaction mixture. An aqueous work-up was carried out using deionised water (6 mL) and extracted with EtOAc (4 × 7 mL). The combined organic layers were washed with brine (3 × 40 mL) and dried over Na_2SO_4. In most cases, the crude product was purified by flash column chromatography using Iatrobeads

2.4.4 General Procedure D (Prilezhaev method):

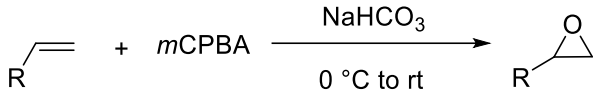
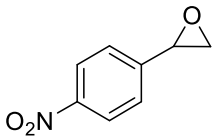


Figure 39: Procedure D for the synthesis of epoxides.

The general method was adapted from the method described by Punniyamurthy et al.[104] A two-necked round-bottom flask was flame-dried under vacuum, and then placed under a N_2 atmosphere. The alkene (3.73-3.8 mmol, 1 equiv.) was added under inert conditions. CH_2Cl_2 (8 mL) was added to the round-bottom flask. Sodium bicarbonate (6.02-8.14 mmol, 1.6-2.1 equiv.) was added via one of the round-bottom flask side necks. The round-bottom flask was then placed in an ice bath to cool the reaction to 0 °C. A second round-bottom flask was flame-dried under vacuum and, when cooled, placed under N_2. *m*CPBA (≤77%) (4.44-8.02 mmol, 1.2-2.1 equiv.) was added to the round-bottom flask, then placed under vacuum for 10 min, followed by N_2. CH_2Cl_2 (20 mL) was added to the *m*CPBA. The *m*CPBA and CH_2Cl_2 mixture was added via syringe over 15 min to the cooled base and alkene reaction mixture. The reaction was allowed to warm to room temperature and was stirred overnight. It was worked up through successive washes with saturated sodium thiosulfate solution (10 mL) and saturated sodium carbonate solution (10 mL). Following the separation of layers, the organic layer was dried over Na_2SO_4.

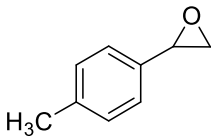
2.4.5 Epoxide Scope:

2.4.5.1 4-Nitrophenyloxirane ***(3a)***



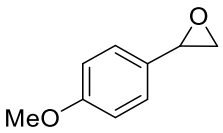
The reaction was carried out following general procedure A. 2-Bromo-4'-nitroacetophenone (2.09 g, 8.55 mmol) was dissolved in MeOH (20 mL). $NaBH_4$ (0.63 g, 16.59 mmol) and K_2CO_3 (2.82 g, 20.4 mmol) were added. Without further purification by column chromatography, the product was isolated as a yellow solid (1.34 g, 95% (crude)), with 94% purity as determined by GC-MS analysis. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22-8.20 (m, 2H), 7.46-7.44 (m, 2H), 3.96 (dd, *J* = 4.0, 2.5 Hz, 1H), 3.23 (dd, *J* = 5.5, 4.1 Hz, 1H), 2.78 (dd, *J* = 5.5, 2.5 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.9, 145.4, 126.3, 123.8, 51.7, 51.5 ppm. NMR data corresponds to literature.[105] MS (EI 70 eV): 165 (M^+), 118, 89, 77, 45 m/z.

2.4.5.2 2-(4-Methylphenyl)oxirane ***(3b)***



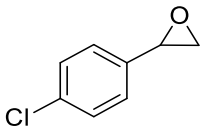
The reaction was carried out following general procedure A. 2-Bromo-4'-methylacetophenone (2.01 g, 9.43 mmol) was dissolved in THF (20 mL). $NaBH_4$ (0.76 g, 19.92 mmol) and *t*-BuOK (1.06 g, 9.43 mmol) were added. The crude product was purified by plug column using Iatrobeads, eluting with 3% EtOAc/Hexane, and **3b** was isolated as a yellow oil (517 mg, 41%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22-7.18 (m, 4H), 3.85 (dd, *J* = 4 .0, 2.6 Hz, 1H), 3.14 (dd, *J* = 5.4, 4.1 Hz, 1H), 2.82 (dd, *J* = 5.4, 2.6 Hz, 1H), 2.38(s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 138.0, 134.7, 129.3, 125.6, 52.4, 51.1, 21.2 ppm. The spectral data corresponds to reported literature.[103] MS (EI 70 eV): 134 (M^+), 119, 105, 91 m/z.

2.4.5.3 2-(4-Methoxyphenyl)oxirane ***(3c)***



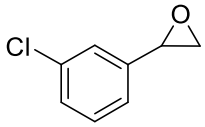
The reaction was carried out following general procedure A. 2-bromo-4'-methoxyacetophenone (1.0 g, 4.39 mmol) was dissolved in MeOH (10 mL). $NaBH_4$ (0.18 g, 4.89 mmol) and *t*-BuOK (0.50 g, 4.41 mmol) were added. Without further purification by column chromatography, the product **3c** was isolated as a brown oil (601.2 mg, 91 % (crude)), with 68% purity as determined by GC-MS analysis. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23-7.18 (m, 2H), 6.89-6.85 (m, 2H), 3.80 (dd, *J* = 4.0, 2.6 Hz, 1H), 3.78 (s, 3H), 3.10 (dd, *J* = 5.3, 4.1 Hz, 1H), 2.79 (dd, *J* = 5.3, 2.6 Hz, 1H) ppm ; ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 159.8, 129.5, 126.9, 114.1, 55.3, 52.3, 51.0 ppm. The spectral data corresponds to reported literature.[103] MS (EI 70 eV): 150 (M^+), 121, 91, 77 m/z.

2.4.5.4 2-(4-chlorophenyl) oxirane ***(3d)***



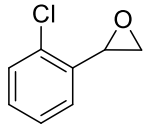
The reaction was carried out following general procedure A. 2-bromo-4'-chloroacetophenone (1.94 g, 8.32 mmol) was dissolved in MeOH (20 mL). $NaBH_4$ (0.35 g, 9.17 mmol) and K_2CO_3 (0.14 g, 8.28 mmol) were added. The crude product mixture contained a combination of the ketone starting material, the alcohol intermediate, and a small amount of epoxide. The crude product was resubjected to the reaction conditions. The crude product (1.83 g, 7.81 mmol) was added to a round-bottom flask and dissolved in MeOH (20 mL). $NaBH_4$ (0.35 g, 9.08 mmol) and *t*-BuOK (0.88 g, 7.84 mmol) were added. Without further purification by column chromatography, the product **3d** was isolated as a pale yellow oil (1.19 g, 93% (crude)) with 93% purity as determined by GC-MS analysis. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32-7.29 (m, 2H), 7.20-7.18 (m, 2H), 3.82 (dd, *J* = 4.0, 2.6 Hz, 1H), 3.13 (dd, *J* = 5.3, 4.1 Hz, 1H), 2.74 (dd, *J* = 5.5, 2.5 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 136.3, 134.0, 128.8, 127.0, 51.9, 51.4 ppm. The spectral data corresponds to reported literature.[103] MS (EI 70 eV): 154 (M^+), 139, 119, 89 m/z.

2.4.5.5 2-(3-Chlorophenyl)oxirane ***(3e)***



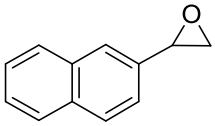
Following general procedure B, TMSOI (2.09 g, 9.49 mmol) and *t*-BuOK (0.97 g, 8.67 mmol) were dissolved in DMSO (20 mL). 3-Chlorobenzaldehyde (0.83 mL, 7.32 mmol) in DMSO (3 mL) was added to the reaction over 2 min. The crude product was purified by plug column using Iatrobeads, eluting with 3% EtOAc/Hexane, and **3e** was isolated as a colourless oil (397 mg, 35%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27-7.25 (m, 3H), 7.17-7.15 (m, 1H), 3.82 (dd, *J* = 4.0, 2.5 Hz, 1H), 3.12 (dd, *J* = 5.6, 4.1 Hz, 1H), 2.74 (dd, *J* = 5.6, 2.6 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.0, 134.7, 129.9, 128.4, 125.6, 123.9, 51.8, 51.3 ppm. The NMR data corresponds to literature.[106] MS (EI 70 eV): 154 (M^+), 119, 89 m/z.

2.4.5.6 2-Chlorophenyloxirane ***(3f)***



Following general procedure B, TMSOI (2.60 g, 11.84 mmol) and *t*-BuOK (1.22 g, 10.85 mmol) were dissolved in DMSO (20 mL). 2-Chlorobenzaldehyde (1.00 mL, 8.88 mmol) in DMSO (5 mL) was added to the reaction over 2 min. The crude product was purified through a plug column of Iatrobeads, eluting with 5% EtOAc/Hexane, and **3f** was isolated as a colourless oil (435 mg, 32%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.33 (m, 1H), 7.24-7.20 (m, 3H), 4.20 (dd, *J* = 4.1, 2.6 Hz, 1H), 3.17 (dd, *J* = 5.8, 4.1 Hz, 1H), 2.65 (dd, *J* = 5.7, 2.6 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.7, 133.4, 129.2, 129.0, 127.1, 125.8, 50.7, 50.1 ppm. The spectral data corresponds to literature data.[107] MS (EI 70 eV): 153 (M-1),119, 89 m/z.

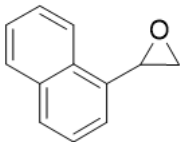
2.4.5.7 2-(Naphthalen-2-yl)oxirane ***(3g)***



Following general procedure B, TMSOI (1.84 g, 8.29 mmol) and *t*-BuOK (0.92 g, 8.25 mmol) were dissolved in DMSO (9 mL). 2-Naphthaldehyde (0.95 g, 6.08 mmol) in

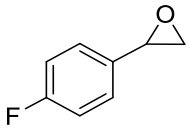
DMSO (4 mL) was added to the reaction. The crude product was purified through a plug column of Iatrobeads, eluting with 3% EtOAc/Hexane, and **3g** was isolated as a white solid (372 mg, 35%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86-7.82 (m, 4H), 7.53–7.50 (m, 2H), 7.36 (dd, *J* = 8.5, 1.7 Hz, 1H), 4.04 (dd, *J* = 4.0, 2.7 Hz, 1H), 3.23 (dd, *J* = 5.3, 4.1 Hz, 1H), 2.93 (dd, *J* = 5.3, 2.6 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 135.2, 133.5, 133.3, 128.5, 127.9, 126.5, 126.2, 125.3, 122.8, 52.7, 51.4 ppm. The spectral data corresponds to literature.[103] MS (EI 70 eV): 170 (M^+), 141, 115, 89 m/z.

2.4.5.8 2-(Naphthalen-1-yl)oxirane ***(3h)***



Following general procedure B, TMSOI (2.12 g, 9.65 mmol) and *t*-BuOK (0.99 g, 8.83 mmol) were dissolved in DMSO (14 mL). 1-Naphthaldehyde (1.00 mL, 7.36 mmol) in DMSO (7 mL) was added to the reaction. The crude product was purified through a plug column of Iatrobeads, eluting with 3% EtOAc/Hexane, and **3h** was isolated as a pale yellow oil (333 mg, 27%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19-8.18 (m, 1H), 7.94-7.93 (m, 1H), 7.86-7.84 (m, 1H), 7.62-7.49 (m, 4H), 4.53 (*app* t, *J* = 3.4 Hz, 1H), 3.32 (dd, *J* = 5.7, 4.1 Hz, 1H), 2.85 (dd, *J* = 5.7, 2.7 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 133.8, 133.4, 131.6, 128.8, 128.3, 126.5, 126.0, 125.6, 123.0, 122.4, 50.8, 50.2 ppm. The spectral data corresponds to literature.[108,109] MS (EI 70 eV): 170 (M^+), 155, 141, 115, 89 m/z.

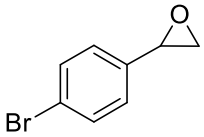
2.4.5.9 4-Fluorophenyloxirane ***(3i)***



Following general procedure B, TMSOI (2.61 g, 11.87 mmol) and *t*-BuOK (1.22 g, 10.86 mmol) were dissolved in DMSO (22 mL). 4-Fluorobenzaldehyde (0.97 mL, 9.04 mmol) with DMSO (3 mL) was added to the reaction. The crude product was purified through a plug column of Iatrobeads, eluting with 5% EtOAc/Hexane, and **3i** was isolated as a colourless oil (379 mg, 30%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24-7.21 (m, 2H), 7.03 – 6.99 (m,2H), 3.82 (dd, *J* = 4.0, 2.6 Hz, 1H), 3.11 (dd, *J* = 5.4, 4.0 Hz, 1H),

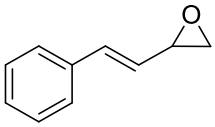
2.74 (dd, *J* = 5.4, 2.6 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.7 (d, *J* = 244.8 Hz) 133.5 (d, *J* = 2.7 Hz), 127.3 (d, *J* = 7.9 Hz), 115.6 (d, *J* = 21.8 Hz), 51.9, 51.2 ppm. The spectral data correspond to literature data.[106] MS (EI 70 eV): 137 (M-1), 109, 95 m/z.

2.4.5.10 2-(4-Bromophenyl)oxirane ***(3j)***



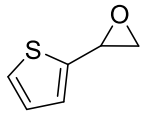
Following general procedure B, TMSOI (2.59 g, 11.77 mmol) and *t*-BuOK (1.22 g, 10.85 mmol) were dissolved in DMSO (25 mL). 4-Bromobenzaldehyde (1.69 g, 9.13 mmol) was added to the reaction mixture. The crude product was purified through a plug of Iatrobeads, eluting with 3% EtOAc/Hexane, and **3j** was isolated as a colourless oil (694 mg, 38 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46-7.44 (m, *J* = 8.5 Hz, 2H), 7.14-7.12 (m, *J* = 8.4 Hz, 2H), 3.81 (dd, *J* = 4.0, 2.6 Hz, 1H), 3.13 (dd, *J* = 5.4, 4.1 Hz, 1H), 2.73 (dd, *J* = 5.5, 2.5 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.9, 131.7, 127.3, 122.1, 51.9, 51.3 ppm. The spectral data corresponds to literature data.[103] MS (EI 70 eV): 198 (M^+), 169, 119, 89 m/z.

2.4.5.11 2-Styryloxirane ***(3k)***



Following general procedure C, NaH in 60% oil (1.83 g, 76.21 mmol) was dissolved in THF (25 mL) and DMSO (30 mL). Trimethylsulfonium iodide (TMSI) (6.14 g, 30.07 mmol) was added. Cinnamaldehyde (1.3 mL, 10.34 mmol) and DMSO (4 mL) were added to the reaction mixture. The product **3k** was isolated as a yellow-orange oil (1.50 g, 99% (crude)), with 89% purity as determined by GC-MS analysis. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41-7.39 (m, 2H). 7.36-7.33 (m, 2H), 7.30-7.28 (m, 1H), 6.83 (d, *J* = 16.0 Hz, 1H), 5.91 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.53-3.52 (m, 1H), 3.06 (dd, *J* = 5.2, 4.1 Hz, 1H), 2.78 (dd, *J* = 5.2, 2.6 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.2, 134.6, 128.7, 128.2, 127.1, 126.5, 52.7, 49.3 ppm. The NMR peaks corresponds to the literature values.[103] MS (EI 70 eV): 146 (M^+), 117, 91, 77 m/z.

2.4.5.12 2-Thienyloxirane (**3l**)



Following general procedure C, NaH in 60% oil (0.45 g, 18.82 mmol) was dissolved in THF (7.5 mL) and DMSO (9.5 mL). TMSI (1.84 g, 9.0 mmol) and 2-thiophenecarboxaldehyde (0.70 mL, 7.49 mmol) were added. The product **3l** was isolated as a yellow/orange oil (881 mg, 93% (crude)), with 67% purity as determined by GC-MS analysis. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 4.8, 1.0 Hz, 1H), 7.13-7.12 (m, 1H), 6.98 (dd, *J* = 5.0, 3.5 Hz, 1H), 4.10 (dd, *J* = 3.5, 2.8 Hz, 1H), 3.19 (dd, *J* = 5.0, 4.0 Hz, 1H), 2.99 (dd, *J* = 5.2, 2.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 141.6, 127.2, 126.4, 125.3, 51.7, 49.4 ppm. The NMR data corresponds to literature.[103] MS (EI 70 eV): 128 (M+2), 111, 97, 91, 84, 69 m/z.

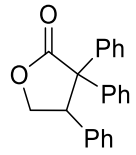
2.5 [3 + 2] cycloaddition reaction of epoxides with ketenes

2.5.1 General procedure for synthesis of γ-lactones or acyclic esters:

The reaction was carried out using two round-bottom flasks. The two round-bottom flasks were flame-dried, and then both were placed under a nitrogen atmosphere. Ketene (0.22-0.43 mmol, 1.0-2.0 equiv.) was added via syringe to the first pre-weighed round-bottom flask. The volume of CH_2Cl_2 was split between the two round-bottom flasks. CH_2Cl_2 (1.3 mL) was added to the round-bottom flask containing the ketene, and the epoxide (0.22 mmol, 1.0 equiv.) was then added via microsyringe. LiI or other catalyst (0.20-0.37 mmol, 0.9-1.6 equiv.) was added to the second round-bottom flask. The round-bottom flask containing the catalyst was placed under vacuum for 1-2 min to remove any moisture/air before being back-filled with nitrogen. CH_2Cl_2 (1.3 mL) was added to the round-bottom flask containing LiI (or other catalyst), and the mixture was stirred. The ketene-epoxide solution was added to the lithium iodide/catalyst suspension over one minute (or in one portion). The reaction flask was covered with aluminium foil, and allowed to stir overnight (total reaction time = 18 h in most cases). The reaction was quenched with cold-deionised water (10 mL) and then extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4. The crude product was purified using column

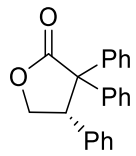
chromatography (50-100 times × crude weight) on a silica or Iatrobeads (neutral silica) column, eluting with an EtOAc/Hexane solvent system.

*2.5.1.1 3,3,4-triphenyldihydrofuran-2(3H)-one (racemic) (**4a**)*



The reaction followed the general procedure for synthesis of γ-lactones. Diphenylketene (84.1 mg, 0.43 mmol) was dissolved in CH_2Cl_2 (1.3 mL). Racemic styrene oxide (25 μL, 0.22 mmol) was added to the reaction mixture. LiI (31.0 mg, 0.23 mmol, 1 equiv.) was suspended in CH_2Cl_2 (1.3 mL). The crude product was purified by passing it through a silica column (6.9 g), eluting with 3% EtOAc/Hexane, and **4a** was isolated as a colourless-peach coloured oil (39.5 mg, 58%). R_f = 0.15 (10% EtOAc/Hexane); HPLC analysis: 1% ee [Daicel Chiralcel OD-H column; 1.0 mL/min; solvent system: 10% isopropanol in hexane; retention times: 13.4 min (major), 24.3 min (minor)]; IR (thin film): 1769, 1146, 706 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.62-7.60 (m, 2H), 7.40-7.32 (m, 3H), 7.16-7.07 (m, 6 H), 6.83-6.78 (m, 4H), 4.66 (dd, *J* = 8.7, 6.5 Hz, 1H), 4.62 (*app* t, *J* = 6.4 Hz, 1H), 4.52 (dd, *J* = 8.6, 6.2 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.5, 139.9, 138.6, 136.7, 129.7, 129.1, 128.8, 128.6, 128.5, 128.1, 127.9, 127.7, 127.3, 70.0, 62.3, 50.7 ppm. The NMR data corresponded to literature.[110] MS (EI 70 eV): 314(M^+), 194, 165, 104, 77, 51 m/z; $(M+Na)^+$ HRMS m/z calcd for $(C_{22}H_{18}O_2Na)^+$: 337.1204; found: 337.1199.

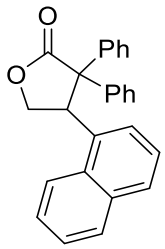
2.5.1.2 (S)-3,3,4-triphenyldihydrofuran-2(3H)-one (**4b**)



The reaction followed the general procedure for synthesis of γ-lactones. Diphenylketene (132.9 mg, 0.68 mmol) was dissolved in CH_2Cl_2 (2.5 mL). (*R*)-(+) styrene oxide (39 μl, 0.34 mmol) of >95% ee was added to the reaction mixture. LiI (56.4 mg, 0.42 mmol, 1.2 equiv.) was suspended in CH_2Cl_2 (2.5 mL). The crude product was purified by passing it through a silica column (15.2 g), eluting with 3% EtOAc/Hexane, and **4b** was isolated as a colourless-peach coloured oil (56.5 mg,

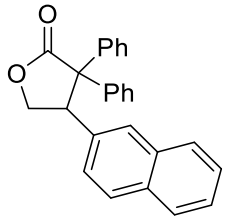
53%). R_f = 0.19 (10% EtOAc/Hexane); HPLC analysis: 84% ee [Daicel Chiralcel OD-H column; 1.0 mL/min; solvent system: 10% isopropanol in hexane; retention times: 13.8 min (major), 25.4 min minor)]; $[\alpha]_D^{26} = -11.88$ (c = 0.542 g/100mL, CH_2Cl_2); IR (thin film): 1766, 1147, 695 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.63-7.61 (m, 2H), 7.41-7.32 (m, 3H), 7.16-7.07 (m, 6H), 6.83-6.79 (m, 4H), 4.67 (dd, *J* = 8.3, 6.5 Hz, 1H), 4.64 (dd, *J* = 6.2 Hz, 1H), 4.52 (dd, *J* = 8.3, 5.9 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.5, 139.9, 138.6, 136.7, 129.7, 129.1, 128.8, 128.6, 128.5, 128.1, 127.9, 127.8 127.3, 70.0, 62.3, 50.7 ppm; MS (EI 70 eV): 314(M^+), 194, 165, 104, 77, 51 m/z; $(M + Na)^+$ HRMS m/z calcd for $(C_{22}H_{18}O_2Na)^+$: 337.1204; found: 337.1191.

2.5.1.3 4-(naphthalen-1-yl)-3,3-diphenyldihydrofuran-2(3H)-one (**4c**)



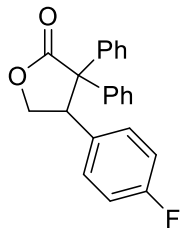
The reaction followed the general procedure for the synthesis of γ-lactones. Diphenylketene (80.4 mg, 0.41 mmol) was dissolved in CH_2Cl_2 (1.6 mL). 2-Naphthalen-1-yl)oxirane (70.5 mg, 0.41mmol) was added to the reaction mixture. LiI (64.9 mg, 0.49 mmol, 1.2 equiv.) was suspended in CH_2Cl_2 (1.6 mL). The crude product was purified by passing it through a silica column (18.9 g), eluting with 3% EtOAc/Hexane, and **4c** was isolated as a white solid (80.8 mg, 51%). R_f = 0.34 (10% EtOAc/Hexane); mp: 164-166 °C; IR (thin film): 1758, 1147, 697 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.80-7.67 (m, 5H), 7.48-7.29 (m, 7H), 6.79-6.75 (m, 5H), 5.41 (dd, *J* = 5.8, 2.0 Hz, 1H), 4.79 (dd, *J* = 9.5, 5.9 Hz, 1H), 4.72 (dd, *J* = 9.4, 2.1 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.8, 139.3, 138.7, 134.9, 133.7, 131.8, 129.8, 129.3, 128.9, 128.4, 128.4, 128.1, 127.0, 126.6, 126.0, 125.6, 125.4, 125.3, 123.0, 71.4, 62.8, 45.5 ppm; MS (EI 70 eV): 364 (M^+), 194, 154, 77 m/z; $(M + Na)^+$ HRMS m/z calcd for $(C_{26}H_{20}NaO_2)^+$: 387.1361 found: 387.1345.

2.5.1.4 4-(naphthalen-2-yl)-3,3-diphenyldihydrofuran-2(3H)-one (**4d**)



The reaction followed the general procedure for synthesis of γ-lactones. Diphenylketene (74.3 mg, 0.38 mmol) was dissolved in CH_2Cl_2 (1.5 mL). 2-Naphthalen-2-yl)oxirane (65.2 mg, 0.38 mmol) was added to the reaction mixture. LiI (78.7 mg, 0.59 mmol, 1.5 equiv.) was suspended in CH_2Cl_2 (1.5 mL). The crude product was purified by passing it through a silica column (18.9 g), eluting with 5% EtOAc/Hexane, and **4d** was isolated as a peach/white coloured solid (73.9 mg, 53%). R_f = 0.3 (10% EtOAc/Hexane); mp: 159-163 °C; IR (thin film): 1762, 1141, 694 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.74-7.56 (m, 5H), 7.45-7.32 (m, 6H), 7.13-7.03 (m, 3H), 6.86-6.83 (m, 3H) 4.80 (*app* t, *J* = 6.8 Hz, 1H), 4.72 (dd, *J* = 9.2, 6.6 Hz, 1H), 4.61 (dd, *J* = 9.2, 7.0 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.6, 139.9, 138.5, 133.9, 133.1, 132.7, 129.7, 128.7, 128.6, 128.3, 128.1, 128.0, 128.0, 127.9, 127.6, 127.3, 126.9, 126.4, 126.3, 70.0, 62.2, 50.9 ppm; MS (EI 70 eV): 364 (M^+), 194, 154, 77 m/z; ($(M + Na)^+$ HRMS m/z calcd for $(C_{26}H_{20}NaO_2)^+$: 387.1361 found: 387.1351.

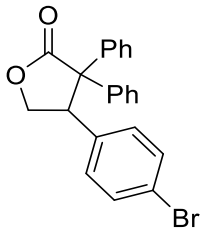
2.5.1.5 4-(4-fluorophenyl)-3,3-diphenyldihydrofuran-2(3H)-one (**4e**)



The reaction followed the general procedure for the synthesis of γ-lactones. Diphenylketene (105.1 mg, 0.54 mmol) was dissolved in CH_2Cl_2 (2.0 mL). 4-Fluorophenyloxirane (0.04 mL, 0.34 mmol) was added to the reaction mixture. LiI (41.0 mg, 0.31 mmol, 1.1 equiv.) was suspended in CH_2Cl_2 (2.0 mL). The crude product was purified by passing it through a neutral silica column (5.4 g), eluting with 3% EtOAc/Hexane, and **4e** was isolated as a pale yellow/colourless wax (50.1 mg, 45%). R_f = 0.3 (10% EtOAc/Hexane); IR (thin film): 1762, 1141, 695 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.60-7.58 (m, 2H), 7.4-7.34 (m, 3H), 7.14 -7.09 (m, 3H), 6.82-

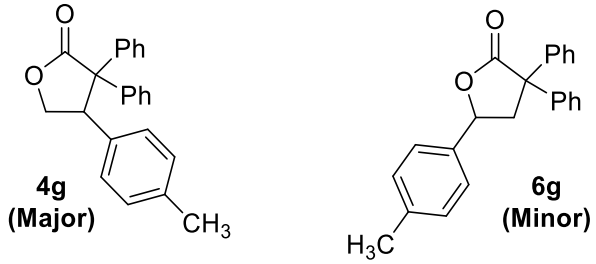
6.76 (m, 6H), 4.66 (dd, *J* = 8.8, 6.7 Hz, 1H), 4.61 (*app* t, *J* = 6.4 Hz, 1H), 4.47 (dd, *J* = 8.8, 6.2 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.3, 162.3 (d, *J* = 246 .0 Hz), 139.6. 138.5, 132.4 (d, *J* = 3.5 Hz) 130.6 (d, *J* = 8.0Hz), 129.6, 128.8, 128.5, 128.2, 128.1, 127.4, 115.4 (d, *J* = 22.0 Hz), 69.9, 62.2, 49.9 ppm; MS (EI 70 eV): 332 (M^+), 194, 165, 122, 96, 77 m/z; $(M + Na)^+$ HRMS m/z calcd for $(C_{22}H_{17}FNaO_2)^+$: 355.1110; found: 355.1095.

2.5.1.6 4-(4-bromophenyl)-3,3-diphenyldihydrofuran-2(3H)-one (**4f**)



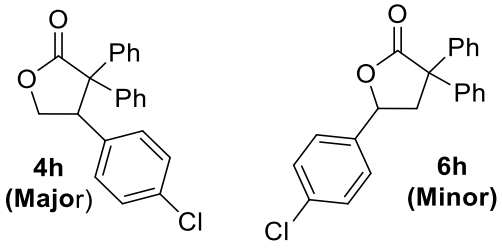
The reaction followed the general procedure for the synthesis of γ-lactones. Diphenylketene (115.9 mg, 0.60 mmol) was dissolved in CH_2Cl_2 (2.4 mL). 4-Bromophenyloxirane (0.12 mL, 0.60 mmol) was added to the reaction mixture. LiI (88.7 mg, 0.66 mmol, 1.1 equiv.) was suspended in CH_2Cl_2 (2.4 mL). The crude product was purified by passing it through a neutral silica column (23 g), eluting with 3% EtOAc/Hexane, and **4f** was isolated as a pale yellow/white coloured gum (25.7 mg, 21%), with 85% purity as determined by GC-MS analysis. R_f = 0.26 (10% EtOAc/Hexane); IR (thin film): 1769, 1145, 695 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59-7.57 (m, 2H), 7.40-7.32 (m, 3H), 7.26-7.22 (m, 2H), 7.17-7.08 (m, 3H), 6.83-6.68 (m, 4H), 4.66 (dd, *J* = 9.0, 6.5 Hz, 1H), 4.58 (*app* t, *J* = 6.4 Hz, 1H), 4.44 (dd, *J* = 9.0, 6.5 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.2, 139.5, 138.3, 135.7, 131.6, 130.7, 129.6, 128.8, 128.5, 128.2, 128.1, 127.5, 121.8, 69.7, 62.0, 50.2 ppm; MS (EI 70 eV): 394 (M^+), 194, 165, 77 m/z; $(M + Na)^+$ HRMS m/z calcd for $(C_{22}H_{17}BrNaO_2)^+$: 415.0310; found: 415.0291.

2.5.1.7 3,3-diphenyl-4-(p-tolyl)dihydrofuran-2(3H)-one (**4g**)



The reaction followed the general procedure for synthesis of γ-lactones. Diphenylketene (87.7 mg, 0.45 mmol) was dissolved in CH_2Cl_2 (1.7 mL). 4-Methylphenyloxirane (0.06 mL, 0.43 mmol) was added to the reaction mixture. LiI (71.5 mg, 0.53 mmol, 1.2 equiv.) was suspended in CH_2Cl_2 (1.7 mL). The crude product was purified by passing it through a neutral silica column (15 g), eluting with 2% EtOAc/Hexane, and **4g** was isolated as a yellow coloured oil (18.4 mg, 12%), composed of an inseparable mixture of regioisomers (**4g**:**6g** = 19:1), as determined by GC-MS and NMR analysis R_f = 0.32 (10% EtOAc/Hexane); IR (thin film): 1767, 1147, 695 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$), major isomer) δ 7.61-7.59 (m, 2H), 7.39-7.30 (m, 3H), 7.15-7.09 (m, 3H), 6.92-6.67 (m, 6H) 4.63-4.59 (m, 2H), 4.45 (dd, *J* = 7.7. 6.2 Hz, 1H), 2.24 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, major isomer) δ 177.7, 140.1, 138.6, 137.5, 133.2, 129.8, 129.1, 129.1, 128.7, 128.0, 128.0, 127.3, 70.0, 62.1, 50.4, 29.9, 21.2 ppm; MS (EI 70 eV): 328 (M^+), 194, 165, 118, 77 m/z; $(M + Na)^+$ HRMS m/z calcd for $(C_{23}H_{20}NaO_2)^+$: 351.1361; found: 351.1350.

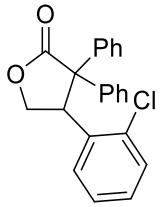
2.5.1.8 4-(4-chlorophenyl)-3,3-diphenyldihydrofuran-2(3H)-one (**4h**)



The reaction followed the general procedure for the synthesis of γ-lactones. Diphenylketene (88.6 mg, 0.46 mmol) was dissolved in CH_2Cl_2 (1.8 mL). 4-Chlorophenyloxirane (0.07 mL, 0.46 mmol) was added to the reaction mixture. LiI (67.4 mg, 0.50 mmol, 1.1 equiv.) was suspended in CH_2Cl_2 (1.8 mL). The crude product was purified by passing it through a neutral silica column (19 g), eluting with

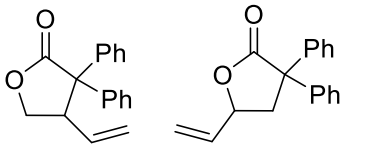
3% EtOAc/Hexane, and **4h** was isolated as a yellow coloured oil (70.4 mg, 45%), composed of an inseparable mixture of regioisomers (**4h**:**6h** = 3:1), as determined by NMR analysis. R_f = 0.10 (20% EtOAc/Hexane); IR (thin film): 1769, 1145, 694 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major) δ 7.59-7.57 (m, 2H), 7.40-7.32 (m, 3H), 7.26-7.23 (m, 2H), 7.16-7.08 (m, 3H), 6.80-6.74 (m, 4H), 4.65 (dd, *J* = 8.9, 6.6 Hz, 1H), 4.60 (*app* t, *J* = 6.4 Hz, 1H), 4.45 (dd, *J* = 8.9, 6.4 Hz, 1H) ppm; (select minor isomer signals) δ 4.81 (dd, *J* = 8.5, 3.7 Hz, 1H), 3.47 (dd, *J* = 10.3, 3.8 Hz, 1H), 3.38-3.35 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, major) δ 177.2, 139.5, 138.4, 135.2, 133.7, 130.4, 129.6, 129.0, 128.8, 128.6, 128.5, 128.1, 127.5, 69.7, 62.1, 50.1 ppm; (minor isomer signals) δ 177.2, 139.8, 138.5, 138.4, 133.8, 130.4, 129.6, 129.0, 128.8, 128.6, 128.5, 128.2, 127.4, 73.5, 29.9, 15.2 ppm; MS (EI 70 eV): 348 (M^+), 194, 165, 77 m/z; $(M + Na)^+$ HRMS m/z calcd for $(C_{22}H_{17}ClNaO_2)^+$: 371.0815; found: 371.0809.

2.5.1.9 4-(2-chlorophenyl)-3,3-diphenyldihydrofuran-2(3H)-one (**4j**)



The reaction followed the general procedure for synthesis of γ-lactones. Diphenylketene (101.1 mg, 0.52 mmol) was dissolved in CH_2Cl_2 (1.9 mL). 2-Chlorophenyloxirane (0.04 mL, 0.26 mmol) was added to the reaction mixture. LiI (41.5 mg, 0.31 mmol, 1.2 equiv.) was suspended in CH_2Cl_2 (1.9 mL). The crude product was purified by passing it through a neutral silica column (23 g), eluting with 3% EtOAc/Hexane, and **4j** was isolated as a white/colourless waxy solid (64.8 mg, 72%), with 91% purity as determined by GC-MS analysis. R_f = 0.18 (10% EtOAc/Hexane); IR (thin film): 1758, 1145, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.72-7.71 (m, 2H), 7.46-7.27 (m, 4H), 7.18-6.88 (m, 8H), 5.21 (dd, *J* = 5.9, 1.5 Hz, 1H), 4.66 (dd, *J* = 9.6, 6.0 Hz, 1H), 4.56 (dd, *J* = 9.5, 1.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 177.4, 138.8, 138.6, 137.1, 134.6, 129.8, 129.7, 129.2, 128.9, 128.7, 128.4, 128.0, 127.4, 127.3, 126.9, 70.9, 62.2, 47.2 ppm; MS (EI 70 eV): 348 (M^+), 194, 165, 77 m/z; $(M + Na)^+$ HRMS m/z calcd for $(C_{22}H_{17}ClNaO_2)^+$: 371.0815; found: 371.0799.

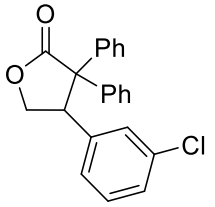
2.5.1.10 3,3-diphenyl-4-vinyldihydrofuran-2(3H)-one (**4k***)*



Major (4k) **Minor (6k)**

The reaction followed the general procedure for synthesis of γ-lactones. Diphenylketene (72.2 mg, 0.37 mmol) was dissolved in CH_2Cl_2 (1.5 mL). Butadiene monoxide (30 μL, 0.37 mmol) was added to the reaction solution. LiI (57.1 mg, 0.43 mmol, 1.2 equiv.) was suspended in CH_2Cl_2 (1.5 mL). The crude product was purified by passing it through a neutral silica column (10.3 g), eluting with 3% EtOAc/Hexane, and **4k** was isolated as a pale yellow gum (31 mg, 32%), composed of an inseparable mixture of regioisomers (**4k**[111]:**6k**[112] = 4.5:1), as determined by GC-MS and NMR analysis. R_f = 0.10 (10% EtOAc/Hexane); IR (thin film): 1768, 1018, 700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major) δ 7.54-7.53 (m, 2H), 7.39-7.27 (m, 6H), 7.03-7.02 (m, 2H), 5.35-5.33 (m, 2H), 5.19-5.18 (m, 1H), 4.43 (dd, *J* = 11.1, 6.9 Hz, 1H) 4.08-4.05 (m, 1H), 4.03-4.00 (m, 1H); (minor isomer) δ 7.54-7.53 (m, 2H), 7.39-7.27 (m, 6H), 7.03-7.02 (m, 2H), 5.96-5.90 (m, 1H), 5.43-5.37 (m, 1H), 5.31-5.29 (m, 1H), 4.78 (ddd, *J* = 10.7, 5.9, 5.3 Hz, 1H), 3.11 (dd, *J* = 13.0, 10.5 Hz, 1H), 2.76 (dd, *J* = 13.0, 10.5 Hz, 1H) ppm ; ^{13}C NMR (150 MHz, $CDCl_3$, major isomer) δ 177.7, 140.3, 138.3, 133.2, 129.1, 128.6, 128.4, 128.4, 127.8, 128.6, 119.8, 68.4, 59.8, 48.6; (minor isomer) δ 177.0. 141.9, 139.8, 135.1, 128.8, 128.6, 128.0, 127.9, 127.5, 127.5, 119.0, 77.7, 58.2, 44.0 ppm. The NMR data corresponded to the literature. MS (EI 70 eV): 264 (M^+), 219, 165, 91, 77 m/z; $(M + Na)^+$ HRMS m/z calcd for $(C_{18}H_{16}NaO_2)^+$: 287.1048; found 287.1040.

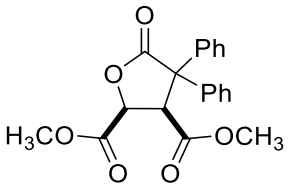
2.5.1.114-(3-chlorophenyl)-3,3-diphenyldihydrofuran-2(3H)-one (**4i**)



The reaction followed the general procedure for synthesis of γ-lactones. Diphenylketene (132.3 mg, 0.68 mmol) was dissolved in CH_2Cl_2 (2.5 mL). 3-Chlorophenyloxirane (0.04 mL, 0.32 mmol) was added to the reaction mixture. LiI

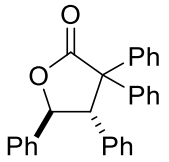
(52.5 mg, 0.39 mmol, 1.2 equiv) was suspended in CH_2Cl_2 (2.5 mL). The crude product was purified by passing it through a neutral silica column (6 g), eluting with 3% EtOAc/Hexane, and **4i** was isolated as a white/colourless waxy solid (49 mg, 44%). R_f = 0.28 (10% EtOAc/Hexane); IR (thin film): 1761, 1154, 698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$,) δ 7.60-7.33 (m, 5H), 7.17-7.03 (m, 5H), 6.81-6.74 (m, 4H), 4.66 (dd, *J* = 9.1, 6.5 Hz, 1H), 4.58 (*app* t, *J* = 6.3 Hz, 1H), 4.48 (dd, *J* = 9.1, 6.2 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.1, 139.4, 138.9, 138.4, 134.3, 129.7, 129.6, 129.3, 128.9, 128.5, 128.2, 128.1, 127.9, 127.5, 127.2, 69.6, 62.2, 50.3 ppm; MS (EI 70 eV): 348 (M^+), 194, 165, 77 m/z; $(M + Na)^+$ HRMS m/z calcd for $(C_{22}H_{17}ClNaO_2)^+$: 371.0815; found: 371.0801.

2.5.1.12 Dimethyl 5-oxo-4,4-diphenyltetrahydrofuran-2,3-dicarboxylate (**4l**)



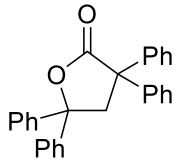
The reaction followed the general procedure for synthesis of γ-lactones. Diphenylketene (113.2 mg, 0.58 mmol) was dissolved in CH_2Cl_2 (2.2 mL). (2*R*,3*S*)-Dimethyloxirane-2,3-dicarboxylate (37 μL, 0.29 mmol) was added to the reaction mixture. LiI (41.8 mg, 0.31 mmol, 1.1 equiv.) was suspended in CH_2Cl_2 (2.2 mL). The crude product was purified by passing it through a neutral silica column (15 g), eluting with 3% EtOAc/Hexane, and **4l** was isolated as a white/orange waxy solid (61 mg, 59%) and as a single diastereomer. R_f = 0.32 (10% EtOAc/Hexane); mp 157-158 °C; IR (thin film): 1734, 1140, 695 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.53-7.52 (m, 2H), 7.42-7.32 (m, 4H), 7.25-7.25 (m, 4H), 5.05 (d, *J* = 5.9 Hz, 1H), 4.54 (d, *J* = 5.9 Hz, 1H), 3.81 (s, 3H), 3.23 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.5, 169.7, 168.0, 138.5, 136.8, 129.5, 128.9, 128.8, 128.3, 127.9, 127.3, 73.9, 60.6, 54.7, 53.1, 52.4 ppm; MS (EI 70 eV): 354 (M^+), 191, 165, 77 m/z, $(M + Na)^+$ HRMS m/z calcd for $(C_{20}H_{18}NaO_6)^+$: 337.1001; found: 337.0996. NOESY analysis indicated the *cis*-relative stereochemistry of the ester groups at C-4 and C-5 of the lactone.

2.5.1.13 Attempted synthesis of 3,3,4,5-tetraphenyldihydrofuran-2(3H)-one (**4m**)



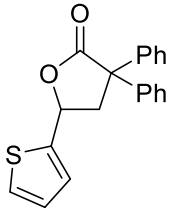
The reaction followed the general procedure for synthesis of γ-lactones. Diphenylketene (31.1 mg, 0.16 mmol) and *trans*-stilbene oxide (34.3 mg, 0.17 mmol) were dissolved in CH_2Cl_2 (2.1 mL). LiI (24.4 mg, 0.18 mmol, 1.1 equiv.) was suspended in CH_2Cl_2 (2.1 mL). The crude product was isolated as a bright yellow oil (93 mg, >99% (crude)) (crude)) and analysed by ^{13}C NMR. However, there were no carbonyl peaks identified, and the peaks in the aliphatic region did not match the predicted signals for the product.

2.5.1.14 Attempted synthesis of 3,3,5,5-tetraphenyldihydrofuran-2(3H)-one (**4n**)



The reaction followed the general procedure for synthesis of γ-lactones. Diphenylketene (56.7 mg, 0.29 mmol) was dissolved in CH_2Cl_2 (1.1 mL). 1,1-Diphenylethylene oxide (29.2 mg, 0.14 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (0.4 mL) and then added to the reaction mixture. LiI (21.3 mg, 0.16 mmol, 1.1 equiv.) was suspended in CH_2Cl_2 (0.6 mL). The crude product was isolated as a bright yellow oil (72 mg, 57%(crude)) and analysed by ^{13}C NMR. However, expected characteristic ^{13}C NMR peaks were not present.

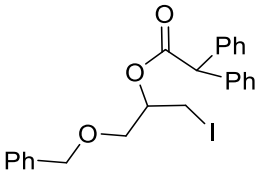
2.5.1.15 Attempted synthesis of 3,3-diphenyl-5-(thiophen-2-yl)dihydrofuran-2(3H)-one (**4o**)



The reaction followed the general procedure for synthesis of γ-lactones. Diphenylketene (105.5 mg, 0.54 mmol) and 2-thienyloxirane (crude) (96 mg, 0.76

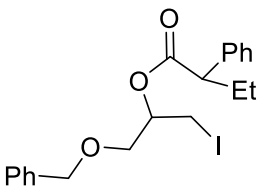
mmol, 1.4 equiv.) were dissolved in CH_2Cl_2 (2.2 mL). LiI (76.1 mg, 0.57 mmol, 1.1 equiv.) was suspended in CH_2Cl_2 (2.2 mL). The crude product was isolated as a brown foam (185 mg, 76% (crude)), and analysed by ^{13}C NMR and GC-MS. However, expected characteristic ^{13}C NMR peaks were not present. The GC-MS spectrum was complex and did not show the presence of the desired product.

2.5.1.16 1-(benzyloxy)-3-iodopropan-2-yl 2,2-diphenylacetate (**5a**)



The reaction followed the general procedure for the synthesis of γ-lactones. Diphenylketene (79.3 mg, 0.41mmol) was dissolved in CH_2Cl_2 (1.7 mL). Benzyl glycidyl ether (99%)(31 µL, 0.20 mmol) was added to the reaction mixture. LiI (27.3 mg, 0.20 mmol, 1.0 equiv.) was suspended in CH_2Cl_2 (1.7 mL). The crude product was purified by passing it through a silica column (8.3 g), eluting with 3% EtOAc/Hexane, and **5a** was isolated as a colourless oil (21 mg, 30%). R_f = 0.29 (10% EtOAc/Hexane); IR (thin film) 1741,1451, 1107, 726 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34-7.27 (m, 13H), 7.26-7.24 (m, 2H), 5,08 (s, 1H), 5.04 (*app* quintet, *J* = 5.4 Hz, 1H), 4.48 (*app* q, *J* = 11.8 Hz, 2H), 3.68 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.60 (dd, *J* = 10.4, 4.7 Hz, 1H), 4.41 (dd, *J* = 10.5, 5.8 Hz, 1H), 3.32 (dd, *J* = 10.5, 5.6 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 138.5, 138.4, 137.8, 129.0, 128.9, 128.8, 128.8, 128.6, 128.0, 127.8, 127.6, 127.5, 73.6, 72.5, 70.4, 57.3, 3.4 ppm; MS (EI 70 eV): 358,165, 105, 91, 77 m/z; $(M + Na)^+$ HRMS m/z calcd for $(C_{24}H_{23}INaO_3)^+$: 509.0590; found: 509.0593.

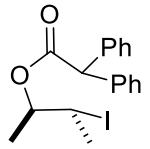
2.5.1.17 1-(benzyloxy)-3-iodopropan-2-yl 2-phenylbutanoate (**5b**)



The reaction followed the general procedure for the synthesis of γ-lactones. Ethylphenylketene (54.5 mg, 0.37 mmol) was dissolved in CH_2Cl_2 (1.3 mL). Benzyl glycidyl ether (99%)(28 µL, 0.19 mmol) was added to the reaction mixture. LiI (26.6

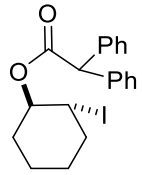
mg, 0.19 mmol, 1.0 equiv.) was suspended in CH_2Cl_2 (1.3 mL). The crude product was purified by passing it through a neutral silica column (2.4 g), eluting with 3% EtOAc/Hexane, and **5b** was isolated as a colourless oil (47 mg, 57%), and as an inseparable mixture of diastereomers (dr 1:1, as determined by NMR analysis). R_f = 0.25 (10% EtOAc/Hexane); IR (thin film) 1732, 1160 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, for both isomers)) δ 7.37-7.20 (m, 20H)**,** 4.93 (*app* sept, *J* = 5.3 Hz, 2H), 4.52 (dd, *J* = 17.0, 12.0 Hz, 2H), 4.40 (dd, *J* = 22.0, 11.9 Hz, 2H), 3.68 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.60-3.58 (m, 2H), 3.53-3.47 (m, 3H), 3.44 (dd, *J* = 10.6, 5.4 Hz, 1H), 3.35-3.31 (m, 2H), 3.26 (dd, *J* = 10.5, 5.4 Hz, 1H), 2.18-2.09 (m, 2H), 1.87-1.79 (m, 2H), 0.94-0.90 (m, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, for both isomers) δ 173.3, 173.3, 138.9, 138.9, 137.9, 137.9, 128.8, 128.8, 128.6, 128.6, 128.3, 128.3, 128.0, 127.9, 127.9, 127.8, 127.5, 127.5, 73.6, 73.6, 71.9, 71.6, 70.4, 70.3, 53.8, 53.6, 26.9, 26.7, 12.4, 12.4, 4.1, 3.6 ppm; MS (EI 70 eV): 310,164, 119, 91, 77 m/z; $(M + Na)^+$ HRMS m/z calcd for $(C_{20}H_{23}INaO_3)^+$: 461.0590; found: 461.0588.

2.5.1.18 3-Iodobutan-2-yl 2,2-diphenylacetate (**5c**)



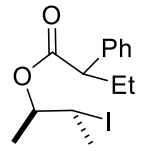
The reaction followed the general procedure for the synthesis of γ-lactones. Diphenylketene (94.8 mg, 0.49 mmol) was dissolved in CH_2Cl_2 (1.8 mL). *cis*-2,3-Epoxybutane (22 μL, 0.25 mmol) was added to the reaction mixture. LiI (40.2 mg, 0.3 mmol, 1.2 equiv.) was suspended in CH_2Cl_2 (1.8 mL). The crude product was purified by passing it through a neutral silica column (7 g), eluting with 3% EtOAc/Hexane, and **5c** was isolated as a colourless oil (46 mg, 47%), and as a single diastereomer (as determined by NMR analysis). R_f = 0.39 (10% EtOAc/Hexane); IR (thin film) 1732, 1127, 695 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36-7.26 (m, 10H), 5.06 (s,1H), 4.75 (dq, *J* = 6.2, 4.2 Hz, 1H), 4.18 (dq, *J* = 7.2, 4.1 Hz, 1H), 1.72 (d, *J* = 7.1 Hz, 3H), 1.33 (d, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 138.6, 138.5, 128.9, 128.9, 128.8, 128.8, 127.5, 127.5, 74.6, 57.4, 29.4, 23.9, 18.7 ppm; MS (EI 70 eV): 394 (M^+),266, 167, 55 m/z; $(M + Na)^+$ HRMS m/z calcd for $(C_{18}H_{19}INaO_2)^+$: 417.0327; found: 417.0325.

*2.5.1.19 2-iodocyclohexyl 2,2-diphenylacetate (**5d**)*



The reaction followed the general procedure for the synthesis of γ-lactones. Diphenylketene (87.7 mg, 0.45 mmol) was dissolved in CH_2Cl_2 (1.3 mL). Cyclohexene oxide (23 μL, 0.23 mmol) was added to the reaction mixture. LiI (56.3 mg, 0.23 mmol, 1.0 equiv) was suspended in CH_2Cl_2 (1.3 mL). The crude product was purified by passing it through a neutral silica column (9 g), eluting with 3% EtOAc/Hexane, and **5d** was isolated as a colourless oil (52 mg, 49%), and as a single diastereomer (as determined by NMR analysis). R_f = 0.34 (10% EtOAc/Hexane); IR (thin film) 1734, 1147, 698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36-7.27 (m, 10H), 5.07 (s, 1H), 4.99 (td, *J* = 9.2, 4.2 Hz, 1H), 4.07 (td, *J* = 9.8, 4.1 Hz, 1H), 2.35-2.33 (m, 1H), 2.14-2.11 (m, 1H), 2.02-1.96 (m, 1H), 1.77-1.73 (m, 1H), 1.57-1.54 (m, 2H), 1.48-1.41 (m, 1H), 1.38-1.34 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 138.7, 138.6, 129.1, 128.9, 128.8, 128.7, 127.4, 127.4, 77.5, 57.4, 37.6, 31.2, 31.0, 26.9, 23.5 ppm; MS (EI 70 eV): 420 (M^+), 292, 194, 165, 105, 81 m/z; $(M + Na)^+$ HRMS m/z calcd for $(C_{20}H_{21}INaO_2)^+$: 443.0484; found: 443.0476.

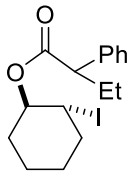
2.5.1.20 3-Iodobutan-2-yl 2-phenylbutanoate (**5e**)



The reaction followed the general procedure for the synthesis of γ-lactones. Ethylphenylketene (62.6 mg, 0.43 mmol) and *cis*-2,3-epoxybutane (37 μL, 0.43 mmol) in CH_2Cl_2 (1.3 mL) were added to LiI (90 mg, 0.67 mmol) in CH_2Cl_2 (1.3 mL). The crude product was purified by passing it through a silica column (3 g), eluting with 1% EtOAc/Hexane, and **5e** was isolated as a brown oil (28 mg, 18%), and as an inseparable mixture of diastereomers (dr 1:1 as determined by NMR analysis). R_f = 0.38 (10% EtOAc/Hexane); IR (thin film) 1732, 1064, 697 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$ for both isomers) δ 7.34-7.26 (m, 9H), 7.25-7.23 (m, 1H), 4.64 (qd, *J* = 4.3, 2.0 Hz, 1H), 4.60 (qd, *J* = 3.8, 2.5 Hz, 1H), 4.17 (qd, *J* = 4.2, 2.9 Hz, 1H), 4.10 (q d, *J* = 3.8,

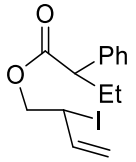
3.3 Hz, 1H), 3.49-3.45 (m, 2H), 2.18-2.09 (m, 2H), 1.87-1.81 (m, 2H), 1.80 (d, *J* = 7.1 Hz, 3H), 1.61 (d, *J* = 7.1 Hz, 3H), 1.30 (d, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 7.1 Hz, 3H), 0.94-0.90 (m, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, for both isomers) δ 173.3, 173.2, 139.1, 139.0, 128.8, 128.7, 128.3, 128.3, 127.5, 127.4, 74.0, 73.7, 54.0, 53.9, 29.9, 29.9, 26.6, 26.4, 24.2, 23.8, 19.0, 18.8, 12.4, 12.3 ppm; MS (EI 70 eV): 346 (M^+), 219, 183, 119, 91, 77 m/z.

2.5.1.21 2-iodocyclohexyl 2-phenylbutanoate (**5f**)



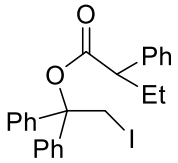
The reaction followed the general procedure for the synthesis of γ-lactones. Ethylphenylketene (54.1 mg, 0.37 mmol) and cyclohexene oxide (38 μL, 0.38 mmol) in CH_2Cl_2 (1.3 mL) were added to LiI (52.4 mg, 0.39 mmol, 1.1 equiv.) in CH_2Cl_2 (1.3 mL). The crude product **5f** was isolated as a pale brown oil (75 mg, 54% (crude)), with 60% purity as determined by GC-MS analysis. MS (EI 70 eV): 372 (M^+), 208, 119, 91 m/z.

2.5.1.22 2-iodobut-3-en-1-yl 2-phenylbutanoate (**5g**)



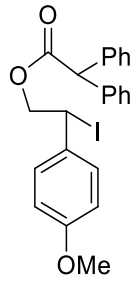
The reaction followed the general procedure for the synthesis of γ-lactones. Ethylphenylketene (51.7 mg, 0.35 mmol) and 2-vinyloxirane (29 μL, 0.36 mmol) in CH_2Cl_2 (1.3 mL) were added to LiI (50.7 mg, 0.38 mmol, 1.1 equiv.) in CH_2Cl_2 (1.3 mL). The crude product **5g** was isolated as a brown oil (57 mg, 47% (crude)), with 60% purity as determined by GC-MS analysis. MS (EI 70 eV): 344 (M^+), 217, 181, 91, 77 m/z.

2.5.1.23 2-iodo-1,1-diphenylethyl 2-phenylbutanoate (**5h**)



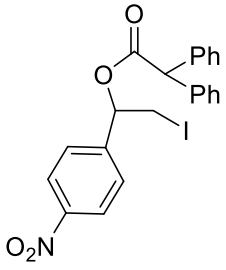
The reaction followed the general procedure for the synthesis of γ-lactones. Ethylphenylketene (61.4 mg, 0.42 mmol) was dissolved in CH_2Cl_2 (1.5 mL), and 1,1-diphenyl oxirane (88.7 mg, 0.45 mmol) was dissolved in CH_2Cl_2 (0.3 mL). LiI (62.7 mg, 0.47 mmol, 1.1 equiv.) was suspended in CH_2Cl_2 (1.5 mL). The crude product **5h** was isolated as a yellow oil (131 mg, 66% (crude)), with 59% purity as determined by GC-MS analysis. MS (EI 70 eV): 342, 196, 165, 119, 91, 77 m/z.

2.5.1.24 2-iodo-2-(4-methoxyphenyl)ethyl 2,2-diphenylacetate (**5i**)



The reaction followed the general procedure for the synthesis of γ-lactones. Diphenylketene (68.9 mg, 0.36 mmol) and 4-methoxyphenyl oxirane (crude) (105.6 mg, 0.70 mmol, 2.0 equiv.) were dissolved in CH_2Cl_2 (2.8 mL). LiI (50.2 mg, 0.37 mmol, 1.0 equiv.) was suspended in CH_2Cl_2 (2.8 mL). The crude product **5i** was isolated as a brown oil (84 mg, 50% (crude)) with a purity of 20% as determined by GC-MS analysis. ^{13}C NMR (150 MHz, $CDCl_3$, characteristic peaks) δ 171.4, 114.6, 68.5, 58.0, 21.2 ppm; MS (EI 70 eV): 346, 150, 135, 91, 77 m/z. The ^{13}C NMR contained carbonyl and alkyl peaks corresponding to the acyclic product.

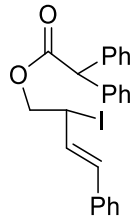
2.5.1.25 2-iodo-1-(4-nitrophenyl)ethyl 2,2-diphenylacetate (**5j**)



The reaction followed the general procedure for the synthesis of γ-lactones. Diphenylketene (122.1 mg, 0.63 mmol) and 4-nitrophenyl oxirane (29 mg, 0.18 mmol) were dissolved in CH_2Cl_2 (2.4 mL). LiI (42 mg, 0.34 mmol, 1.1 equiv.) was suspended in CH_2Cl_2 (2.4 mL). The crude product **5j** was isolated as a yellow oil (144

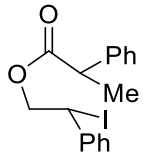
mg, >99% (crude)) with a purity of 35%, as determined by GC-MS analysis. ^{13}C NMR (150 MHz, $CDCl_3$, characteristic peaks) δ 171.2, 75.0, 57.2, 30.0 ppm; MS (EI 70 eV): 359, 194, 165, 152, 133, 77 m/z. The ^{13}C NMR contained carbonyl and alkyl peaks corresponding to the acyclic product.

2.5.1.26 (E)-2-iodo-4-phenylbut-3-en-1-yl 2,2-diphenylacetate (**5k**)



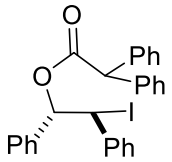
The reaction followed the general procedure for the synthesis of γ-lactones. Diphenylketene (142 mg, 0.73 mmol) and 2-styryloxirane (107 mg, 0.73 mmol) were dissolved in CH_2Cl_2 (2.9 mL). LiI (101.1 mg, 0.76 mmol, 1.0 equiv.) was suspended in CH_2Cl_2 (2.9 mL). The crude product **5k** was isolated as a yellow oil/foam (254 mg, 74% (crude)), with 33% purity as determined by GC-MS analysis. ^{13}C NMR (150 MHz, $CDCl_3$, characteristic peaks) δ 171.8, 68.9, 57.2, 28.6 ppm; MS (EI 70 eV): 340, 194, 146, 130, 77 m/z. The ^{13}C NMR contained carbonyl and alkyl peaks corresponding to the acyclic product.

2.5.1.27 2-iodo-2-phenylethyl 2-phenylpropanoate (**5l**)



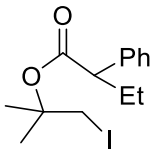
The reaction followed the general procedure for the synthesis of γ-lactones. Methylphenylketene (69.7 mg, 0.53 mmol) and racemic styrene oxide (30 μL, 0.26 mmol) were dissolved in CH_2Cl_2 (1.5 mL). LiI (44.8 mg, 0.35 mmol, 1.3 equiv.) was suspended in CH_2Cl_2 (1.5 mL). The crude product **5l** was isolated as a yellow oil (87 mg, 87% (crude)), with 31% purity as determined by GC-MS analysis. ^{13}C NMR (150 MHz, $CDCl_3$, characteristic peaks, two isomers) δ 173.7, 75.5, 69.0, 46.6, 27.2, 18.5, 8.0 ppm; MS (EI 70 eV): 253, 231, 132, 105, 77 m/z. The ^{13}C NMR contained carbonyl and alkyl peaks corresponding to the acyclic product.

2.5.1.28 2-iodo-1,2-diphenylethyl 2,2-diphenylacetate (**5m***)*



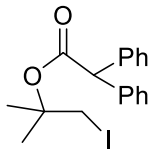
The reaction followed the general procedure for the synthesis of γ-lactones. Diphenylketene (76.9 mg, 0.40 mmol) was dissolved in CH_2Cl_2 (1.0 mL). *Cis*–stilbene oxide (77.7 mg, 0.40 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and then added to the ketene round-bottom flask. LiI (55.6 mg, 0.42 mmol, 1.1 equiv.) was suspended in CH_2Cl_2 (1.0 mL). The crude product **5m** was isolated as a yellow oil (157 mg, 77% (crude)), with 23% purity as determined by GC-MS analysis. ^{13}C NMR (150 MHz, $CDCl_3$, characteristic peaks) δ 171.1, 80.3, 57.4, 35.6 ppm; MS (EI 70 eV): 390, 194, 180, 91, 77 m/z. The ^{13}C NMR contained carbonyl and alkyl peaks corresponding to the acyclic product.

2.5.1.29 1-iodo-2-methylpropan-2-yl 2-phenylbutanoate (**5n**)



The reaction followed the general procedure for the synthesis of γ-lactones. Ethylphenylketene (65.7 mg, 0.45 mmol) and 1,1-dimethyl oxirane (40 μL, 0.45 mmol) were dissolved in CH_2Cl_2 (3.3 mL). LiI (70.2 mg, 0.52 mmol, 1.2 equiv.) was suspended in CH_2Cl_2 (3.3 mL). The crude product **5n** was isolated as a pale yellow/colourless oil (37 mg, 24% (crude)), with 22% purity as determined by GC-MS analysis. MS (EI 70 eV): 346 (M^+), 218, 119, 91, 77 m/z.

2.5.1.30 2-iodo-2-methylpropyl 2,2-diphenylacetate (**5o**)



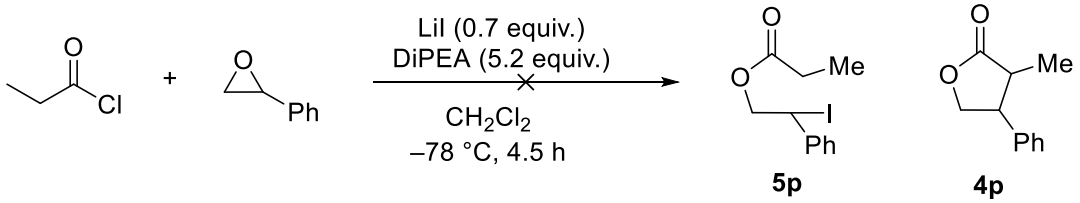
The reaction followed the general procedure for the synthesis of γ-lactones. Diphenylketene (87.2 mg, 0.45 mmol) and isobutylene oxide (31 mg, 0.45 mmol) were dissolved in CH_2Cl_2 (1.8 mL). LiI (70.5 mg, 0.53 mmol, 1.2 equiv.) was

suspended in CH_2Cl_2 (1.8 mL). The crude product **5o** was isolated as a pale yellow oil (95 mg, 61%), with 62% purity as determined by GC-MS analysis. ^{13}C NMR (150 MHz, $CDCl_3$, characteristic peaks) δ 171.8, 81.1, 58.0, 25.0, 24.9, 15.9 ppm; MS (EI 70 eV): 266, 194, 91, 77 m/z. The ^{13}C NMR contained carbonyl and alkyl peaks corresponding to the acyclic product.

2.5.1.31 Attempted synthesis of 2-iodo-2-phenylethyl propionate (**5p**) from in situ-generated methylketene and racemic styrene oxide

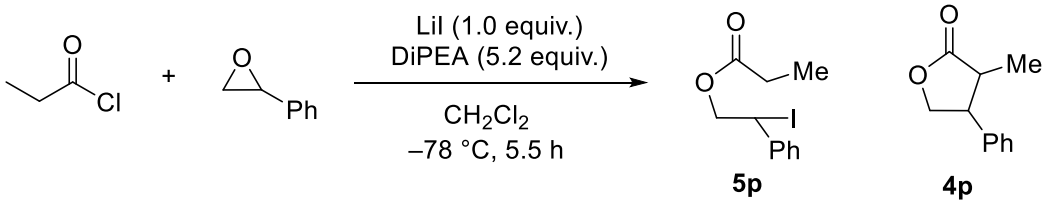
Three methods were used to synthesise methyl ketene in situ. The three procedures involved the addition of the starting materials in a different order or employing different addition times.

2.5.1.31.1 Procedure 1:



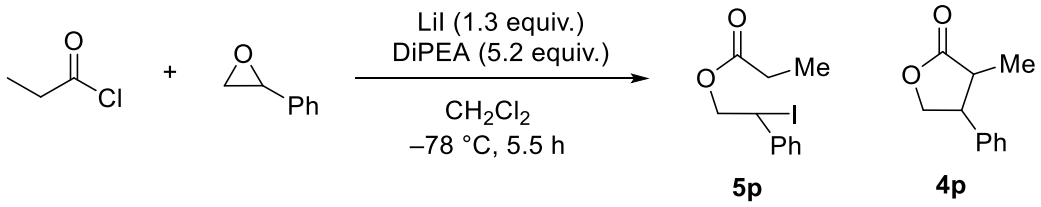
This procedure was modified from the method by Kerrigan et al.[113] LiI (45.2 mg, 0.34 mmol) was added to a pre-flame dried round-bottom flask, and dry CH_2Cl_2 (7.0 mL) was added. Freshly distilled propionyl chloride (0.22 mL, 2.50 mmol, 5 equiv.) was added to the LiI-CH_2Cl_2 suspension in one portion. The reaction mixture was cooled to –78 °C. Freshly distilled *N*,*N*-diisopropylethylamine (DIPEA) (0.45 mL, 2.58 mmol, 5.2 equiv.) was added dropwise using a syringe pump over 30 min. Racemic styrene oxide (57 μL, 0.50 mmol) was dissolved in CH_2Cl_2 (2.0 mL) and was added in one portion to the reaction. This reaction was stirred at –78 °C for 4 h. It was allowed to warm to room temperature overnight (18 h). The reaction was quenched with cold deionised water (10 mL) and CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4. The crude product was initially isolated as a white powder and passed through a silica plug column, eluting with CH_2Cl_2. The product was then isolated as a yellow oil (103 mg (crude)) and analysed by GC-MS. However, no peak in the GC-MS spectrum corresponded to the γ-lactone (176 m/z) or acyclic ester product **5p** (304 m/z).

2.5.1.31.2 Procedure 2:



This procedure was modified from the method by Kerrigan et al.[113] LiI (117.8 mg, 0.83 mmol) was added to a pre-flame dried round-bottom flask, and dry CH_2Cl_2 (7 mL) was added. Freshly distilled propionyl chloride (0.36 mL, 4.2 mmol, 4.7 equiv.) was added to the LiI-CH_2Cl_2 in one portion. The reaction mixture was cooled to –78 °C. Freshly distilled DIPEA (0.75 mL, 4.3 mmol, 5.2 equiv.) was added dropwise over 30 min using a syringe pump. Racemic styrene oxide (95 μL, 0.83 mmol) was dissolved in CH_2Cl_2 (2 mL). It was added over 1 h via syringe pump. The reaction was stirred at –78 °C for 4 h. It was allowed to warm to room temperature and stirred for 2 days. The reaction was quenched with methanol-triethylamine (2:1, 1.0 mL). The reaction mixture was poured into ice cold 10% HCl solution (20 mL). It was then extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with cold deionised water (30 mL) and brine (30 mL), and then dried over Na_2SO_4. The crude product was isolated as a yellow oil (211 mg, 84% (crude)). ^{13}C NMR analysis of the crude product showed a carbonyl signal at δ 172.7 ppm along with some aliphatic carbon signals. However, some expected characteristic carbons were not present in the NMR spectrum. GC-MS analysis indicated a peak with a 22% peak area and a m/z of 231, 177. MS (EI 70 eV): 231, 177, 121, 103, 77, 57 m/z.

2.5.1.31.3 Procedure 3:

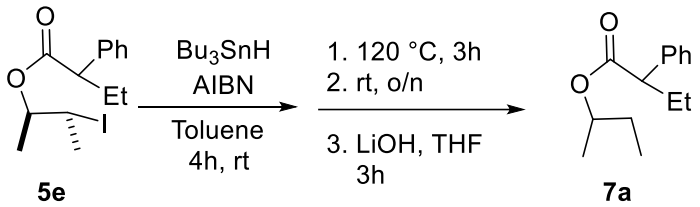


5p **4p**

This procedure was modified from the method by Kerrigan et al.[113] LiI (87.3 mg, 0.65 mmol) was added to a pre-flame dried round-bottom flask and dry CH_2Cl_2 (7 mL) was added. Freshly distilled DIPEA (0.45 mL, 2.58 mmol, 5.2 equiv.) was added to the reaction mixture in one portion. Freshly distilled propionyl chloride (0.22 mL, 2.45 mmol, 5.0 equiv.) was added dropwise using a syringe pump over 30 min. Racemic styrene oxide (57 μL, 0.50 mmol) was dissolved in CH_2Cl_2 and added via syringe over 1 h using a syringe pump. The reaction was stirred for 4 h at –78 °C, and then allowed to warm to room temperature overnight. The reaction was split into two portions before quenching. 4.8 mL of the crude product solution was removed

and added to cold deionised water (10 mL) and extracted with CH_2Cl_2 (4 × 6 mL). The combined organic layers were dried over Na_2SO_4. The crude product was isolated as a yellow oil (63.7 mg, 84% (crude)). The other half of the crude product solution (4.8 mL) was quenched with methanol-triethylamine (2:1, 0.5 mL). The reaction mixture was poured into ice cold 10% HCl solution (10 mL). It was extracted with CH_2Cl_2 (3 × 12 mL). The combined organic layers were washed with cold deionised water (15 mL) and brine (15 mL), and then dried over Na_2SO_4. The product was isolated as a yellow oil (116 mg, >99% (crude)). ^{13}C NMR analysis of the crude product showed a carbonyl signal at δ 172.8 ppm along with some aliphatic carbon signals. However, some expected characteristic carbon signals were not present in the NMR spectrum. GC-MS analysis indicated a peak with 12% peak area and a m/z of 231, 177 for the first portion and 6% peak area for the second portion. MS (EI 70 eV): 231, 177, 121, 77, 57 m/z.

2.6 Cleaving C-I bond to afford sec-butyl 2-phenylbutanoate(**7a**)



5e **7a**

The reaction procedure was modified from the procedure by Wang et al.[114] 3-Iodobutan-2-yl 2-phenylbutanoate (**5e**) was previously prepared from epoxide and acyl chloride. A 25 mL round-bottom flask was flame-dried and placed under an inert atmosphere. AIBN (0.2 M in toluene, 0.17 mL, 0.03 mmol) and Bu_3SnH (0.19 mL, 0.57 mmol) were dissolved in toluene (2.6 mL), and the solution was stirred. 3-Iodobutan-2-yl 2-phenylbutanoate (80.2 mg, 0.23 mmol) was dissolved in toluene (1.1 mL). The 3-Iodobutan-2-yl 2-phenylbutanoate solution was added to the AIBN-Bu_3SnH-toluene solution over 4 h using a syringe pump. The reaction was then refluxed for 3 h at 120 °C under inert conditions in an oil bath. The reaction was removed from the oil bath and left stirring overnight under inert conditions to bring it to room temperature. The toluene was removed under reduced pressure the next day. A LiOH solution (1 M, 4.56 mL) prepared in deionised water (100 mL) and THF (4.56 mL) was added the next day. The reaction was left stirring for 3 h. The reaction

was quenched with saturated sodium bicarbonate solution (20 mL) and then extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (3 × 20 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on a silica plug column, eluting with hexane. The product (**7a)** was isolated as a colourless oil (35 mg, 69%), and as a mixture of diastereomers (dr 1:1). ^{1}H NMR (600 MHz, $CDCl_3$ for both diastereomers) δ 7.31-7.29 (m, 8H), 7.25-7.22 (m,2H), 4.87-4.80 (m, 2H), 3.48-3.41 (m, 2H), 2.15-2.07 (m, 2H), 1.83-1.76 (m, 2H), 1.62-1.44 (m, 4H), 1.10 (d, *J* = 6.3 Hz, 6H), 0.94-0.85 (m, 12H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$ for both diastereomers) δ 173.9, 173.9, 139.7, 139.6, 128.7, 128.6, 128.2, 128.1, 127.3, 127.2, 72.6, 72.6, 54.1, 53.6, 29.0, 28.9, 26.9, 26.7, 19.7, 19.4, 12.4, 12.3, 9.9, 9.6 ppm; MS (EI 70 eV): 220 (M^+) 119, 91, 77 m/z.

Chapter 3: Optimisation and Scope of Catalytic [3 + 2]-Cycloaddition of Epoxides with Ketenes: Discussion

3.1 Introduction:

In this chapter, the results of the catalytic [3 + 2]-cycloaddition of epoxides and ketenes will be discussed. The epoxide results, including examples of different methods used to synthesise epoxides, purification techniques, and the effects of purification on some of the examples, will be discussed. The optimisation of the reaction, including reaction time, equivalents of starting materials, catalyst equivalents, and light, will be analysed. The scope of products formed from the catalytic formal [3 + 2]-cycloaddition of epoxides and ketenes will be discussed.

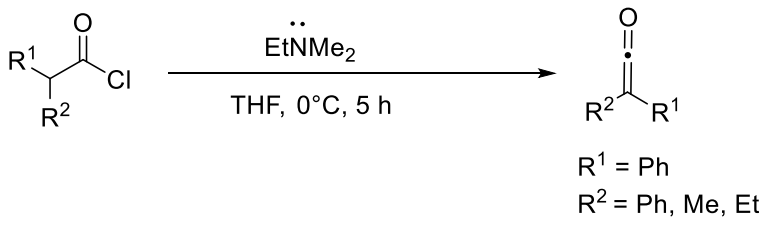
3.2 Preparation of Acyl Chlorides and Ketenes

As described in the introduction, several methods can be used to synthesise ketenes. The Kerrigan group have mainly used the dehydrohalogenation of acyl chlorides method. This method is commonly known as Wedekind's method. This method was used to synthesise the three isolated ketenes in this project. 2,2-Diphenylacetyl chloride was commercially available and can be synthesised using the same procedure used for the preparation of 2-phenylbutyl chloride. 2-Phenylbutyryl chloride was a colourless liquid following distillation, whereas crude 2-phenylpropanoyl chloride (prepared by S. Ayidi) was a yellow/orange liquid. The yellow/orange colour of the 2-phenylpropanoyl chloride was due to its crude/non-distilled form, which was found to be important for the success of subsequent methylphenylketene generation. 2,2-Diphenylacetyl chloride can also be synthesised according to the procedure detailed in section 2.3.1 and was formed as a green solid (not purified).

The three ketenes, diphenylketene, ethylphenylketene, and methylphenylketene, were synthesised using Wedekind's method. Ketenes are important reactive intermediates in organic chemistry.[115] Diphenylketene was the most commonly used ketene throughout this project, as the reactions with other ketenes generally

resulted in poor yield or no formation of the desired γ-lactone product. As shown in Table 4, the ketenes were obtained in relatively high yields. The three ketenes are not stable to air/moisture and must be stored under a nitrogen atmosphere at low temperature (e.g., at - 35 °C) and handled with care to prolong the ketenes shelf life. Diphenylketene was the most stable of the three due to the presence of the two phenyl substituents, which provided steric hindrance and additional stabilisation through resonance of the aromatic π-system. Ethylphenylketene has one fewer phenyl substituent and is less stable than diphenylketene but more stable than methyphenylketene. This is due to the ethyl substituent in the ketene being bigger and more sterically bulky than a methyl group, which makes it more resistant to attack by nucleophiles (like H_2O) and hence is more stable. The stability of ketenes is evident in their shelf life. Diphenylketene is the most stable and can be stored in the freezer at −35 °C for 3-4 weeks, ethylphenylketene lasts up to two weeks, and methylphenylketene is the least stable and polymerises within 1-2 weeks.

Table 4: Synthesis of ketenes using dehydrohalogenation of acyl chlorides (Wedekind's method).

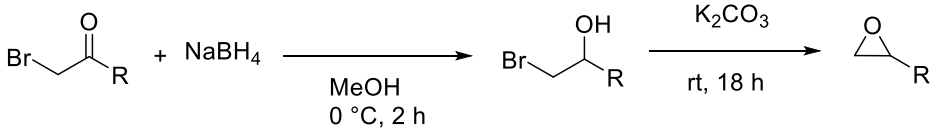


Ketene	Yield (%)
Diphenylketene	69
Ethylphenylketene	74
Methylphenylketene	66

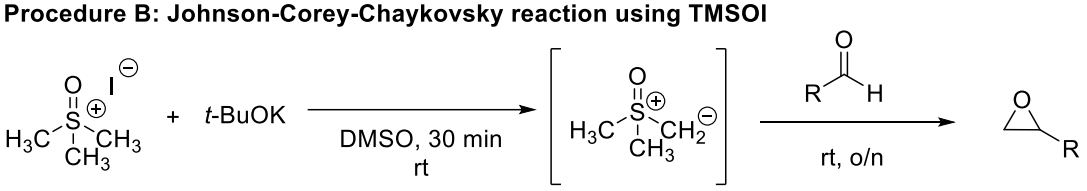
3.3 Preparation of Epoxides:

There were twelve epoxides synthesised in this project. The two main starting materials for the synthesis of epoxides were ketones (α-bromoketones) and aldehydes. As described above in the experimental section, three main methods (Procedures A-C) were used for the synthesis of epoxide compounds from ketones and aldehydes. There was also a fourth method for epoxide synthesis that was used for two examples to determine whether the epoxide could be formed with greater purity (Figure 40).

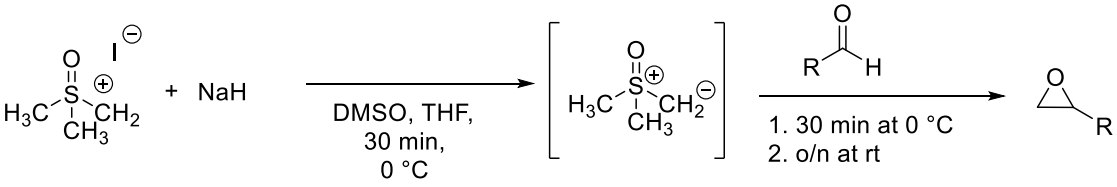
Procedure A: Reduction of α-bromoketone



Procedure B: Johnson-Corey-Chaykovsky reaction using TMSOI



Procedure C: Johnson-Corey-Chaykovsky reaction using TMSOI or TMSI



Procedure D: Prilezhaev method

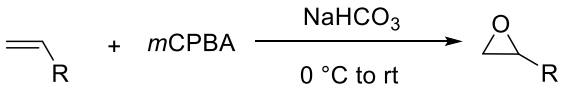


Figure 40: Four different procedures for the synthesis of the epoxides.

The two main methods are method A and method B/C shown in Figure 40. In methods B and C, the procedures differ slightly, but the reaction chemistry remains the same. The first method for the synthesis of epoxides is shown in Figure 41. The α-bromoketone is reduced by $NaBH_4$ to the alcohol intermediate (**1**). The base K_2CO_3 aids deprotonation of the hydroxy group during the transition state for the formation of the epoxide (**3**).

Methods B and C follow the Johnson-Corey-Chaykovsky reaction scheme as shown in Figure 42. The reaction begins with the formation of a sulfur ylide **4** from trimethylsulfoxonium/ trimethylsulfonium iodide). The base deprotonates the sulfur salt, deprotonating one of the methyl groups attached to sulfur. This forms the sulfur ylide (**4**). The ylide carbanion then attacks the carbonyl carbon of the aldehyde, forming a betaine intermediate (**5**). The negatively charged oxygen attacks the carbon adjacent to sulfur, displacing DMSO or DMS (when TMSI is used) and forming the epoxide (**3**). Therefore, when a bromoketone is used as the starting material, it undergoes reduction-cyclisation to form the epoxide; when an aldehyde

is used as the starting material, the Johnson-Corey-Chaykovsky reaction is applied to form the epoxide.

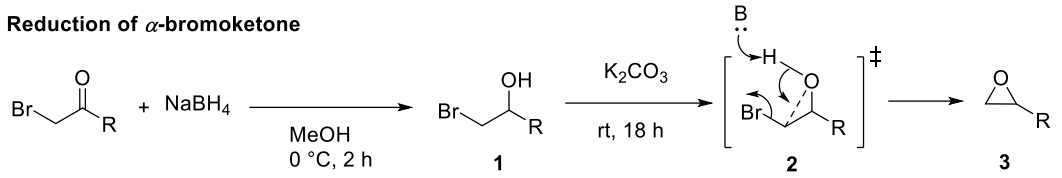


Figure 41: Reduction of α-bromoketone synthetic route.

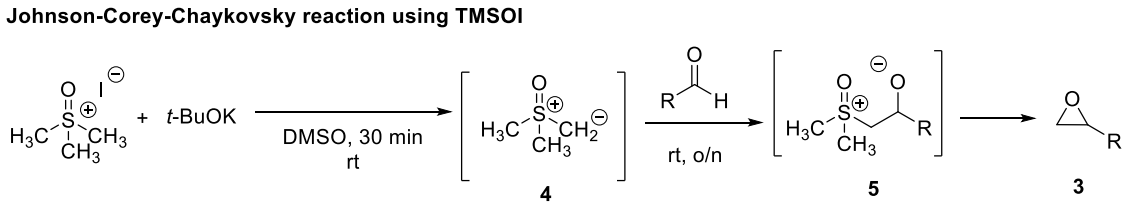
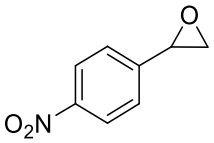
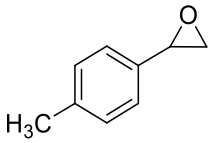
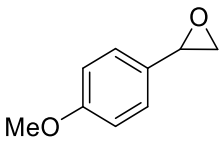
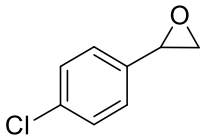
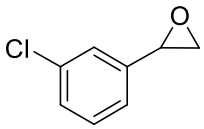
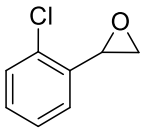
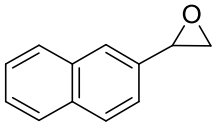
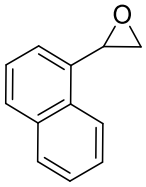
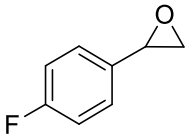
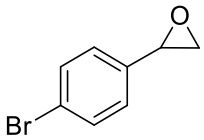
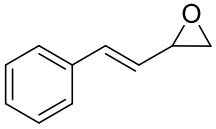
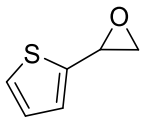


Figure 42: Johnson-Corey-Chaykovsky reaction with TMSOI synthetic route.

The epoxides synthesised in the project are shown in Table 5. The purified products were generally isolated in low yields, although GC-MS analysis indicated that the epoxide products formed were typically of high purity. There were four exceptions where further purification was not carried out. The four epoxides were 2-(4-nitrophenyl)oxirane (**3a**), 2-(4-methoxyphenyl)oxirane (**3c**), 2-styryloxirane (**3k**) and 2-thienyloxirane (**3l**). These epoxides were not purified because they decomposed during attempted column chromatography or were already highly pure, as determined by GC-MS analysis. The other epoxides were purified via a neutral silica plug column and were found to be of high purity, as determined by GC-MS and NMR analysis. The epoxides formed were mainly aryl-substituted. Most epoxides prepared have a substituent at the *para*-position of the phenyl ring. The substituents on the phenyl ring were a mixture of electron-withdrawing (fluoro-, chloro-, bromo-) and electron-donating groups (methyl-).

Table 5: Epoxide scope.

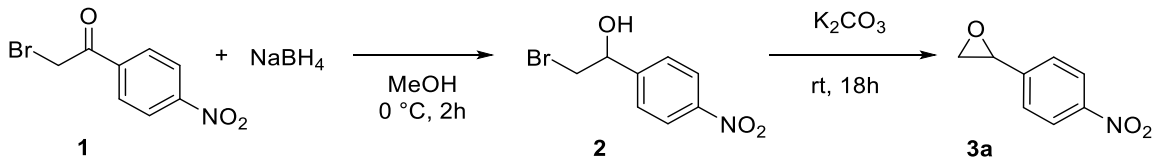
Entry	Experimental reference	Procedure[a]	Compound	Yield (%)	GC-MS peak area/purity (%)
1	**3a**	A		95[b]	94
2	**3b**	A		41	85
3	**3c**	A		91[b]	68
4	**3d**	A		93[b]	93
5	**3e**	B		35	94
6	**3f**	B		32	98
7	**3g**	B		35	73[c]
8	**3h**	B		27	97
9	**3i**	B		30	94
10	**3j**	B		38	99
11	**3k**	C		99[b]	89

12	**3l**	C		93[b]	67

[a] Procedure A: α-bromoketone and $NaBH_4$ stirred at 0 °C for 2h in MeOH, base added in and warmed up to rt over 18h; Procedure B: trimethylsulfoxonium iodide and t-BuOK stirred for 30 min at rt in DMSO, aldehyde added in and stirred o/n; Procedure C: trimethylsulfoxonium/trimethylsulfonium iodide and NaH stirred for 30 min at 0 °C in DMSO and THF, aldehyde added in and stirred o/n at rt. [b] crude product. [c] contains an isomer of the desired product (26%).

The literature procedure for converting the α-bromoketone to epoxide was followed for the 2-(4-nitrophenyl)oxirane **3a** example.[98] In this procedure, α-bromoketone (1 equiv.), $NaBH_4$ (1.1 equiv.) and K_2CO_3 (1 equiv.) were used. The successful formation of the epoxide using this method resulted in the stoichiometry of the reaction being further investigated. As shown in Table 6, reaction 2 showed that increasing the equivalents of the reducing agent and the base caused an increase in the epoxide % peak area (as determined by GC-MS), with reduced by-product formation and improved overall reaction selectivity.

*Table 6: Effect of the starting materials equivalents on the formation of epoxide (**3a**).*



Reaction	Mol. Equiv. of ketone	Mol. Equiv. of $NaBH_4$	Mol. Equiv. of K_2CO_3	GC-MS peak area (%)[a]
1	1	1.1	1	61
2	1	1.9	2.4	94

[a] % peak area determined by GC-MS analysis.

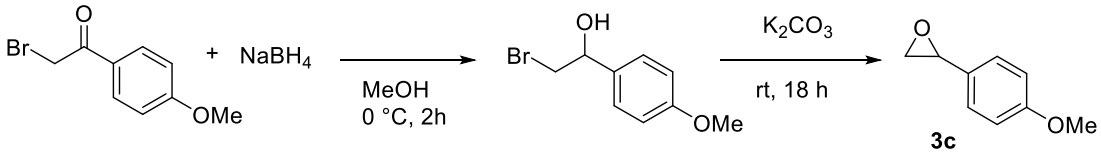
The 2-(4-methoxyphenyl)oxirane product (**3c**) was found to be unstable. Attempts were made to purify the crude 2-(4-methoxyphenyl)oxirane using neutral silica, normal silica, and aluminium oxide, but all were unsuccessful. When the epoxide was loaded onto purification columns and eluted, GC-MS analysis indicated that the compound had degraded. Connon's group also reported the epoxide's

instability.[116] Their group stated that the epoxide decomposes during column chromatography and Kugelrohr distillation.

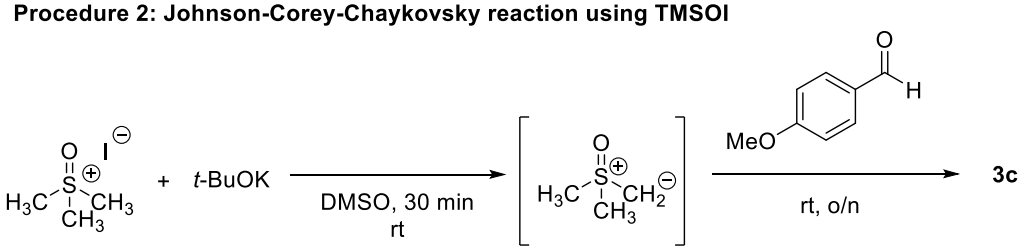
Therefore, since the epoxide could not be purified, alternative synthetic methods were investigated and are summarised in Table 7. The most effective approach to synthesising the epoxide involved starting with the 2-bromo-4'-methyoxyacetophenone, reducing it, and then performing base-promoted cyclisation. In contrast, the other two routes, starting from alkene or aldehyde, resulted in significantly lower epoxide formation, with GC-MS peak areas of 16% and 36%, respectively. For comparisons, the ketone method produced the epoxide with a higher % peak area (purity) of 68%.

*Table 7: Different methods to prepare 2-(4-methoxyphenyl)oxirane (**3c**).*

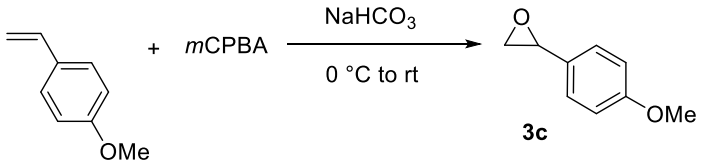
Procedure 1: Reduction of an α-bromoketone



Procedure 2: Johnson-Corey-Chaykovsky reaction using TMSOI



Procedure 3: Prilezhaev reaction



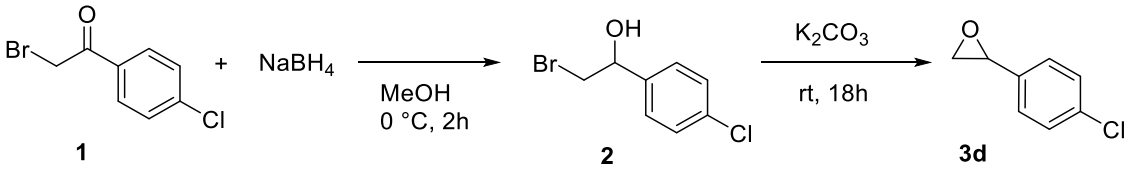
Entry	Starting material	Procedure	Conditions	Crude GC-MS peak area (%)[a]
1	2-bromo-4'-methoxyacetophenone	1	$NaBH_4$, K_2CO_3	68

2	4-methoxybenzaldehyde	2	Trimethylsulfoxonium iodide, KOH, CH_3CN. The aldehyde was dissolved in CH_3CN and added over 4 min.[117]	36
3	4-methoxystyrene	3	*m*CPBA, sodium bicarbonate	16

[a] % peak area determined by GC-MS analysis.

The epoxide 2-(4-chlorophenyl)oxirane (**3d**) was not purified because both the NMR and GC-MS spectra indicated it was already present in high purity at the crude stage when the crude product from the first reaction was re-subjected to the reaction conditions. As described in the experimental section 2.4.5.4., this epoxide was prepared via two synthetic routes, changing only the base in the reaction. In the first method, 1 equivalent of the α-bromoketone was subjected to reaction with 1.1 equivalents of $NaBH_4$ and 1 equivalent of K_2CO_3. GC-MS and NMR analysis confirmed that the reaction did not go to completion. The crude mixture contained unreacted α-bromoketone starting material (**1**), the intermediate alcohol (**2**), and a small amount of the desired epoxide product (**3**). The peak area of the crude products are shown in Table 8. The crude product from this reaction was resubjected to the reaction again using 1 equivalent of the crude product, 1.2 equivalents of $NaBH_4$, and 1 equivalent of *t*-BuOK. The reaction proceeded successfully this time, and the desired product **3d** was formed. GC-MS analysis showed that the epoxide was formed with a purity of 93%, and **3d** was isolated in a yield of 93%. Therefore, this reaction was not purified, and the crude product was used directly in subsequent [3 + 2]-cycloaddition reactions

*Table 8: GC-MS peak area of the 2-(4-chlorophenyl)oxirane (**3d**).*



Compound	Reference	GC-MS peak area (%)[a]
α-bromoketone (unreacted starting material) **1**	1	40
Alcohol (intermediate) **2**	2	50
Epoxide **3d**	3	3

[a] % peak area determined by GC-MS analysis.

The 2-Naphthyloxirane **3g** displayed two peaks in the GC-MS spectrum. Both peaks had identical mass spectral fragmentation patterns MS (EI 70 eV): 170 (M^+), 141, 115 m/z. The carbon bearing the naphthyl substituent is chiral, and the 2-naphthyloxirane is therefore a mixture of enantiomers. However, because the GC column used was achiral, enantiomers would not be separated. Therefore, the presence of two peaks suggests either the formation of a closely related by-product with similar retention times or partial decomposition of the epoxide during GC-MS analysis. The decomposition of the epoxide would be reasonable due to the ring strain of the epoxide and the temperature that the sample is exposed to during GC-MS analyses.[118]

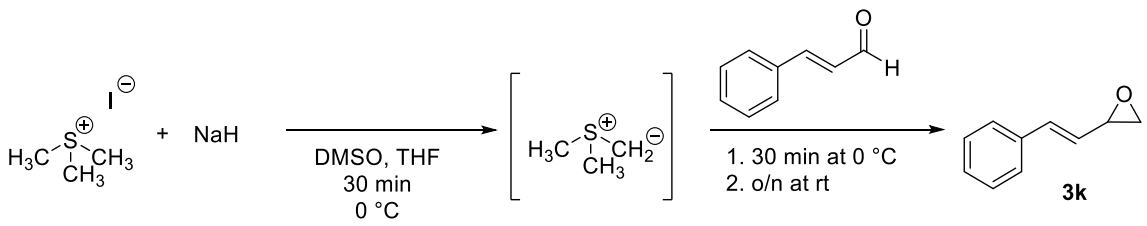
The stability of 2-styryloxirane **3k**, prepared through Procedure C, was examined as summarised in

. The purification of 2-styryloxirane was studied using both (acidic) silica and neutral silica. The crude product was analysed by GC-MS analysis, and this showed a purity of 89%. After attempted purification by column chromatography on acidic silica, the epoxide peak area was reduced to 66%. The effect of attempted purification using neutral silica on the peak area was also analysed. A similar decrease in the epoxide peak area was noted. This decrease in the product peak area observed by GC-MS can be explained by epoxide decomposition on the column. The epoxide degraded

on the column, generating the aldehyde starting material. Therefore, the crude product has a higher purity than the epoxide product batches subjected to column chromatography. As a result of the instability of 2-styryloxirane **3k** on silica, the crude epoxide was used in subsequent reactions with ketenes.

*Table 9: 2-styryloxirane **3k** purity following purification by different methods.*

Procedure C: Johnson-Corey-Chaykovsky reaction using TMSI



Compound	Purified or crude	GC-MS peak area (%)[a]
2-styryloxirane	Crude	89
2-styryloxirane	Purified by silica plug column	66
2-styryloxirane	Purified by a neutral silica plug column	73

[a] Purity (%) determined by GC-MS analysis.

Significant effort went into developing the synthesis of 2-thienyloxirane **3l**. A summary of the synthetic methods employed is shown in Table 10. GC-MS analysis of entries 3 and 4 in Table 10 indicated that no epoxide was present. Instead, it indicated that diol product was formed. This diol product formed when the reaction was quenched with cold deionised water, and the reaction mixture was stirred for 10 minutes. The quenching method, as shown in entries 1 and 2 in Table 10, yielded a lower epoxide peak area than with other methods. In entries 1 and 2 in Table 10, a small amount of the desired epoxide was present, but the diol was also detected in the sample by GC-MS.

When the quenching procedure was changed to the addition of ice-cold deionised water, and the organic layer was extracted immediately, the peak area at 126 m/z was recorded, and the desired epoxide was detected. The 2-thienyl oxirane epoxide **3l** has a molecular weight of 126 g/mol, and the peak corresponding to the epoxide

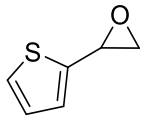
has a molecular ion present (126 m/z). This was present at higher levels in the GC-MS samples when the immediate work-up was the quenching method used.

However, attempts to purify the epoxide were unsuccessful. Therefore, various synthetic methods were studied to identify conditions that would yield the epoxide in high purity, and thus avoid the need for purification by column chromatography. The first method involved changing the organosulfur salt from trimethylsulfoxonium iodide to trimethylsulfonium iodide as shown in Table 10, entry 7. In theory, trimethylsulfonium iodide forms a less stable ylide and reacts faster with the aldehyde, leading to the formation of fewer side products. In comparison, trimethylsulfoxonium iodide forms a more stabilised ylide and reacts more slowly (and more reversibly) with the aldehyde, which can lead to the formation of more by-products. The aldehyde used in the reaction was 2-thiophenecarboxaldehyde. The carbonyl group in this aldehyde is less electrophilic due to the electron-donating properties of the thiophene group. This makes the aldehyde more prone to side reactions. Therefore, trimethylsulfonium iodide is a better sulfur salt in this case because it reacts faster with the aldehyde. This modification is evident in entries 7 and 8 in Table 10. The peak area corresponding to the epoxide increased to 71%, and fewer side products were observed.

For entry 8 in Table 10, the crude mixture was split into two portions. One portion was concentrated by rotary evaporation and analysed by GC-MS. The epoxide peak area in the sample was 71%. The second portion was worked up according to literature procedures.[103] The crude product was passed through a neutral silica plug eluting with 4% EtOAc/Hexane. The GC-MS spectrum of the second portion was complex, and all of the epoxide was spread across multiple collected fractions. Therefore, this column chromatography method is not an efficient way to purify epoxide **3l**.

The final synthetic method investigated with the goal of avoiding column chromatographic purification was the Prilezhaev method, which used an alkene and *m*CPBA shown as entry 9 in Table 10. However, this method produced only a very small amount of the epoxide as determined by GC-MS analysis. The epoxide peak area in this crude sample was <1%.

*Table 10: Optimisation of synthesis methods for the preparation of 2-thienyloxirane (**3l**).*



Reaction	Starting materials	GC-MS peak area (%)[a]	Conditions
1	Aldehyde (5.14 mmol, 1 equiv.), TMSOI[b] (10.02 mmol, 1.95 equiv.), *t*-BuOK (10.02 mmol, 1.95 equiv.) in DMSO (20 mL, 0.26 M)	24	Aldehyde was added in neat. Quenched and left stirring for 10 min.
2	Aldehyde (5.13 mmol, 1 equiv.), TMSOI (5.54, 1.1 equiv.), *t*-BuOK (5.03 mmol, 1 equiv.) in DMSO (8 mL, 0.64 M)	24	Aldehyde was added with DMSO over 2 min. Quenched and left stirring for 10 min.
3	Aldehyde (10.06 mmol, 1 equiv.), TMSOI (11.0 mmol, 1.09 equiv.), *t*-BuOK (10.87 mmol, 1.06 equiv.) in DMSO (30 mL, 0.34 M)	No epoxide formed	Reaction at 50 ˚C . Aldehyde was added in neat over 10 min. Quenched and left stirring for 10 min.
4	Aldehyde (7.5 mmol, 1 equiv.), TMSOI (9.03 mmol, 1.2 equiv.), NaH (11.31 mmol, 1.5 equiv.) in DMSO (10 mL) and THF (7.5 mL)(0.43 M)	No epoxide	Aldehyde was added in neat. Quenched and left stirring for 10 min.
5	Aldehyde (4.06 mmol, 1 equiv.), TMSOI (4.45 mmol, 1.1 equiv.), *t*-BuOK (4.02 mmol, 1 equiv.) in DMSO (9 mL, 0.45 M))	53 (two isomers)	When the reaction was quenched, it was worked up straight after. Less diol formed.
6	Aldehyde (3.96 mmol, 1 equiv.), TMSOI (4.41 mmol, 1.1 equiv.), *t*-BuOK (3.99 mmol, 1 equiv.) in DMSO (9 mL, 0.44 M)	65 (two isomers)	Aldehyde added in over 3 minutes with DMSO. Quenched and worked-up straight away.
7	Aldehyde (14.98 mmol, 1 equiv.), TMSI[c] (18.36 mmol, 1.2 equiv.), NaH (15 mmol, 1 equiv.) in DMSO (19 mL) and THF (15 mL)(0.44 M)	67 (one isomer)	Aldehyde added in neat. Quenched and worked-up straight away.

8	Aldehyde (11.25 mmol, 1 equiv.), TMSI (13.52 mmol, 1.2 equiv.), NaH (11.29 mmol, 1 equiv.) in DMSO (12 mL) and THF (11 mL)(0.49 M)	Method 1: 71 Method 2: complex mixture	**Method 1**: Rotary-evaporated in fume hood: 71% by GC-MS **Method 2**: Passed through a silica plug column according to the literature. Epoxide spread over multiple fractions
9	Alkene (3.81 mmol, 1 equiv.), *m*CPBA (8.02 mmol, 2.1 equiv.), $NaHCO_3$ (8.14 mmol, 2.1 equiv.) in CH_2Cl_2 (28 mL, 0.14 M)	~1	Prilezhaev epoxidation method.

[a] Purity (%) determined by GC-MS analysis.[b] TMSOI: trimethylsulfoxonium iodide; [c] TMSI: trimethylsulfonium iodide

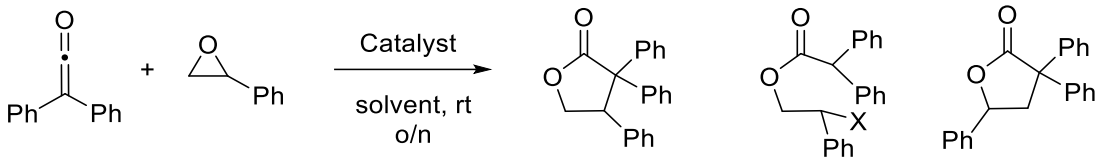
3.4 [3 + 2]-cycloaddition of epoxides with ketenes

3.4.1 Optimisation:

The optimisation studies shown in this section were carried out to optimise the reaction. The conditions of the reaction were studied, including catalyst loading, catalyst type, mole equivalents of starting materials, light, temperature and reaction time. All these studies were carried out to find optimum reaction conditions for the [3 + 2]-cycloaddition of epoxides and ketenes.

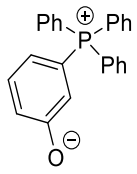
3.4.1.1 Catalyst Study:

*Table 11: Effect of the catalyst on the formation of the γ-lactone **4a** from diphenylketene and racemic styrene oxide.*



2a **3n** **4a** **5aa** **6a**

X = I or Br

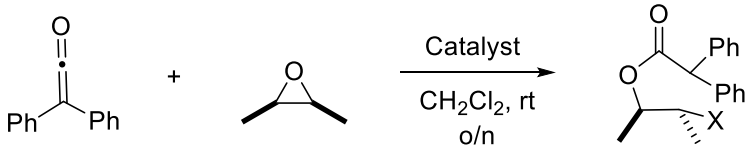
Entry	Catalyst Equiv	Ketene Equiv	Solvent	4a (%)[a]	5aa + 6a (%)[a]
1	LiI (1 equiv.)	2	CH_2Cl_2	64	18
2	KI (1 equiv.)	1	CH_2Cl_2	0	0
3	Ph_4PBr (0.5 equiv.)	2	CH_2Cl_2	0	0
4	LiBr (1 equiv.)	2	Toluene	1[b]	21[b]
5	MgI_2 (1 equiv.)	2	Toluene	1[b]	16[b]
6	PBu_3 (0.3 equiv.)/LiI (1 equiv.)	1	THF	3[c]	27[c]
7	 (1 equiv.)	2	CH_2Cl_2	1[b]	19[b]

[a] % conversion determined by GC-MS analysis; [b] performed by Dr. Nessan Kerrigan; [c] performed by Samuel Maisonneuve.

The influence of the catalyst on the formation of the γ-lactone from racemic styrene oxide and diphenylketene was studied. The main solvent used in this study was CH_2Cl_2. As shown above in Table 11, LiI was found to be the optimum catalyst for the reaction. The major product was determined to be the 3,3,4-isomer (also termed 3,4-isomer elsewhere) of the γ-lactone (**4a**), rather than the 3,3,5-isomer (**6a**). When other catalysts, for example, KI, LiBr and Ph_4PBr were used in the

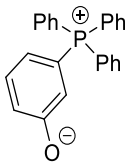
reaction, the desired product **4a** was not formed, or only a trace amount was observed.

*Table 12: Effect of the catalyst on the formation of the acyclic ester product **5c** from diphenylketene and cis-2,3-epoxybutane.*



2a **3o** **5**

X = I, Br, Cl

Entry	Catalyst	Ketene Equiv.	5 (%)[a]
1	LiI (1 equiv.)	1	75
2	$InBr_3$ (1 equiv.)	1	47
3	LiCl (1 equiv.)	1	0
4	 (1 equiv.)	1	0

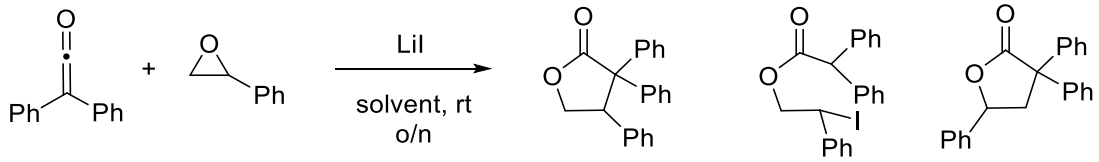
[a] % conversion determined by GC-MS analysis.

The effect of different catalysts on the reaction of diphenylketene and *cis*-2,3-epoxybutane was also examined (Table 12). LiI was found to be the optimal catalyst for this reaction, giving the highest peak area for the acyclic ester product (75%). It was notable that no γ-lactone was produced in this reaction. In contrast, $InBr_3$, led to a decrease in the acyclic ester product peak area, whereas LiCl and the phosphonium aryl oxide organocatalyst (Table 12, entry 4) yielded no desired lactone or acyclic ester product (0%).

Therefore, based on the two studies shown in Table 11 and Table 12, LiI was identified as the optimal catalyst for the reactions involving diphenylketene with both racemic styrene oxide and *cis*-2,3-epoxybutane, and was investigated as the catalyst of choice for all other studies.

3.4.1.2 Solvent Study:

*Table 13: Effect of solvent on γ-lactone **4a** synthesis from diphenylketene and racemic styrene oxide.*



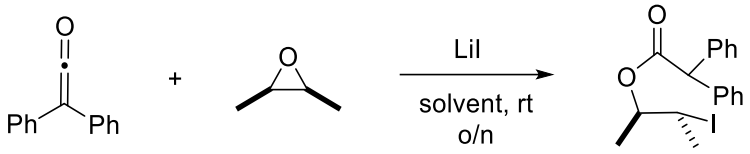
2a **3n** **4a** **5q** **6a**

Entry	LiI Equiv	Ketene Equiv	Solvent	4a (%)[a]	5q + 6a (%)[a]
1	1	2	CH_2Cl_2	64	18
2	1	2	Hexane	28	7
3	1	2	Toluene	33	51
4	1	2	THF	29	64[b]
5	1	1	CH_3CN	8	73[b]

[a] % conversion by GC-MS, [b] reaction performed by Samuel Maisonneuve

As shown in Table 13, CH_2Cl_2 was the best solvent for the formation of the 3,4-γ-lactone **4a**. The other solvents formed the 3,5-γ-lactone **6a** or the acyclic ester product **5q** in greater quantities compared to when CH_2Cl_2 was used for the reaction. Hexane was the least polar solvent examined, and the peak area of the desired 3,4-γ-lactone decreased relative to CH_2Cl_2, according to the GC-MS peak area. Equally, the peak area for **4a** when using acetonitrile, a more polar solvent, was much lower than that observed with CH_2Cl_2, while **5q** and **6a** were formed as the major products. The change in regioselectivity with CH_3CN is presumably due to the Li^+ ion (of LiI) being solvated by CH_3CN and not available to activate styrene oxide, and therefore a pure S_N2 attack of iodide at the less substituted carbon of the epoxide is favoured, leading to **6a** dominating. The use of a more polar solvent may also cause a change in cyclisation mechanism.

Table 14: Effect of solvent on the formation of the acyclic ester product ***5c*** *from diphenylketene and cis-2,3-epoxybutane.*



2a **3o** **5c**

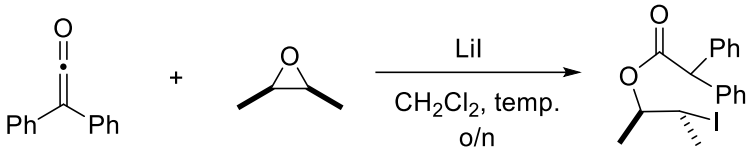
Entry	LiI Equiv.	Ketene Equiv.	Solvent	5c (%)[a]
1	1	1	CH_2Cl_2	61
2	1	1	THF	6
3	1	1	THF: CH_2Cl_2 (1:1)	2
4	1	1	Hexane	46

[a] % conversion by GC-MS analysis.

The effect of different solvents on the reaction between diphenylketene and *cis*-2,3-epoxybutane was also studied (Table 14). It was observed that the peak area of the acyclic ester product was highest when CH_2Cl_2 was used as the solvent (Table 14, entry 1). When a less polar solvent than CH_2Cl_2 was used, the peak area of the acyclic ester product decreased (Table 14, entry 4). The effect of a more polar solvent than hexane, THF, was also examined. It yielded a significantly lower peak area. A 50:50 mixture of CH_2Cl_2 and THF had a negative effect on the formation of the acyclic ester product, with the peak area of the desired product dropping to 2%, which was much lower than the peak area when CH_2Cl_2 was used alone. As with the reaction of styrene oxide, the solvating ability of the solvent had a dramatic impact on the outcome of the reaction, with the reaction being almost completely stopped when carried out in THF, the most polar of the solvents tested (Table 14, entries 2 and 3).

3.4.1.3 Temperature

Table 15: Effect of temperature on the formation of the acyclic ester product ***5c*** *from diphenylketene and cis-2,3-epoxybutane.*



2a **3o** **5c**

Entry	LiI Equiv.	Ketene Equiv.	Temp (°C)	5c (%)[a]
1	1	1	rt	61
2	1	1	40 °C	64
3	1	1	−78 °C	64

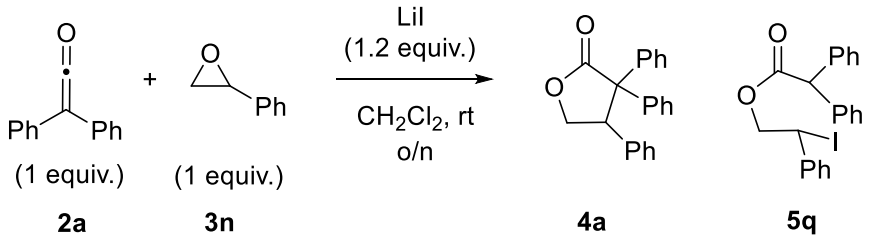
[a] % peak area determined by GC-MS analysis.

The effect of temperature on the reaction between diphenylketene and *cis*-2,3-epoxybutane was investigated. Three temperature conditions were studied: room temperature (rt), 40 °C and −78 °C. The reactions at room temperature and 40 °C were maintained throughout the entire reaction period. For the experiment at −78 °C, the starting materials were added at −78 °C, after which the reaction mixture was left overnight in a dry ice/acetone bath, and gradually warmed to room temperature overnight. The GC-MS peak areas of the crude products formed at each temperature were compared, and it was concluded that temperature did not have a significant effect on the reaction outcome, as there was minimal variation in the peak areas.

3.4.1.4 Time Study

The impact of reaction time on the LiI-catalysed reaction of diphenylketene with racemic styrene oxide was studied. An aliquot was removed from the reaction mixture 30 min after the initiation of the reaction, then after 1 h, and subsequently at hourly intervals for 10 h and then after 24 h. Each aliquot underwent the same workup. The method of analysis for this reaction was GC-MS analysis. The peak area of the desired γ-lactone was determined after each time interval in the time study.

*Table 16: Effect of time on the LiI-catalysed synthesis of γ-lactone **4a** from diphenylketene and racemic styrene oxide.*



Time (h)	Peak area of the γ-lactone (4a) (%)[a]	Peak area of acyclic product (5q)(%)[a]
0.5	35	15
1	64	25
2	78	0
3	56	28
4	75	1
5	56	32
6	85	5
7	75	4
8	74	0
9	75	25
10	54	25
24	55	32

[a] % peak area determined by GC-MS analysis.

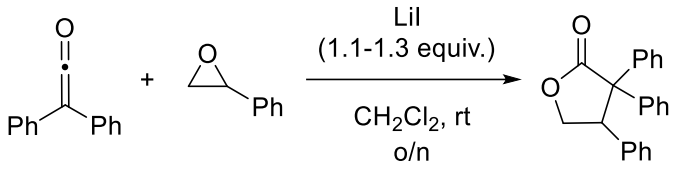
According to GC-MS analysis results, the peak area corresponding to the γ-lactone increased gradually between 0.5 h. and 1 h. The epoxide starting material was still present in the spectra between 0.5 h and 1 h, but was completely consumed by 2 h. The γ-lactone reached its maximum peak area at approximately 6 h (85%). From 6-10 h the peak areas corresponding to the γ-lactone decreased gradually to 54%. This drop may be explained as follows: the epoxide and ketene in the presence of LiI can cyclise to form the γ-lactone product, which may subsequently reopen to form the acyclic ester/ester enolate product. In support of this, the GC-MS spectra of the aliquots that showed a decrease in the peak area of the γ-lactone **4a**

displayed an increase in the peak area of the acyclic ester product **5q**. By 24 h, the γ-lactone conversion appeared to remain constant with a peak area of 55%.

3.4.1.5 Light Study:

The light study was carried out to determine if the presence of light in the reaction had an effect on the product formed. In particular, light was examined to determine if it had an effect on the organic intermediates e.g the C-I bond or LiI present in the reaction.

*Table 17: Effect of light on LiI-catalysed formation of γ-lactone **4a** from diphenylketene and racemic styrene oxide.*



2a **3n** **4a**

Entry	Reaction conditions	Ketene equiv.	Racemic styrene oxide equiv.	LiI equiv.	Peak area according to GC-MS (%)
1	Darkness	2	1	1	69
2	Light and then covered in aluminium foil overnight	2	1	1	69
3	Light left on in fumehood	2	1	1	68

[a] % peak area determined by GC-MS analysis of crude product.

The reaction was carried out under three different sets of conditions. The first was that the reaction was carried out in darkness; all the round-bottomed flasks used in the reaction were covered with aluminium foil to ensure that the reaction was in darkness. In the second case, the reaction was carried out exposed to light, and then the reaction was covered with aluminium foil overnight. The third reaction was exposed to light throughout the reaction by not wrapping it in aluminium foil and leaving the light on in the fume hood overnight. The reactions were carried out simultaneously using the same reagents. GC-MS analysis was used to compare the reaction solutions peak areas, with a focus on that of the γ-lactone. There was only

a very slight change in peak areas when comparing the GC-MS spectra. Therefore, light does not appear to effect this reaction. Light had no effect on the reaction and therefore did not increase the amount of the desired γ-lactone product formed in the reaction.

3.4.1.6 Addition order:

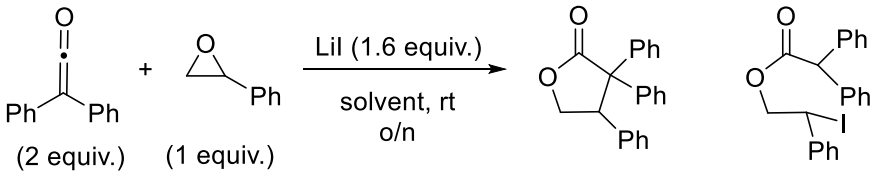
The order of addition of the reactants has a significant effect on γ-lactone **4a** formation. The ^{13}C NMR spectra of entries 1 and 2 were overlaid with the 3,3,4-triphenyldihydrofuran-2(3H)-one (**4a**) spectrum, as shown in Figure 43. In entry 1, the characteristic peaks of the 3,4-γ-lactone are clearly observed. The procedure for entry 1 involved adding the epoxide to the diphenylketene dissolved in CH_2Cl_2, and the resulting solution was added to the LiI catalyst suspension in CH_2Cl_2, leading to the formation of the 3,4-γ-lactone **4a**. The 3,4-γ-lactone peak area for entry 1 was 62%. A summary of the two reactions is shown in Table 18.

In contrast, for entry 2, as shown in Table 18, the catalyst (LiI) and epoxide (racemic styrene oxide) were suspended in CH_2Cl_2 and stirred at room temperature under inert atmosphere conditions for 30 min before the addition of diphenylketene. The ^{13}C NMR spectrum of this reaction showed signals at δ 177.4 and 58.0 ppm, and these peaks are characteristic of a carboxylic acid derived from diphenylketene (Figure 44). The carboxylic acid peak area in the GC-MS spectrum was 18%. There was no peak area corresponding to the 3,4-γ-lactone **4a** when the reaction was carried out using this procedure.

The control in Figure 43 is the purified spectrum of compound **4a**. Compound 4a was overlaid on the spectrum to compare entries 1 and 2. The desired product for entries 1 and 2 was the 3,4-γ-lactone (**4a**). Both entries 1 and 2 display the peaks corresponding to the carbonyl carbon of the acyclic ester product **5q** (δ171.4 and 171.8 ppm). The peaks at δ 76.3, 57.3 and 29.9 ppm are characteristic of the alkyl carbons of the acyclic ester product . Overall, the ^{13}C NMR data indicate that entry 1 mainly forms the 3,4-γ-lactone **4a** with a small amount of acyclic ester product **5q**. In contrast, entry 2 main products are the carboxylic acid derived from diphenylketene (diphenylacetic acid), shown in Figure 44 and acyclic ester product

5q. There is no evidence for 3,4-γ-lactone formation in entry 2, as the characteristic aliphatic carbon peaks of the 3,4-γ-lactone control compound (**4a**) were not present.

*Table 18: Effect of the order of addition of reactants on the formation of γ-lactone product **4a**.*



Entry	Reagents in flask 1	Reagents in flask 2	Peak area of γ-lactone 4a (%)[a]	Peak area of acyclic ester product 5q (%)[a]
1	Diphenylketene, CH_2Cl_2, racemic styrene oxide	LiI, CH_2Cl_2	62	30
2	Diphenylketene, CH_2Cl_2	LiI, CH_2Cl_2, racemic styrene oxide	0	25

[a] % peak area determined by GC-MS analysis of crude product.

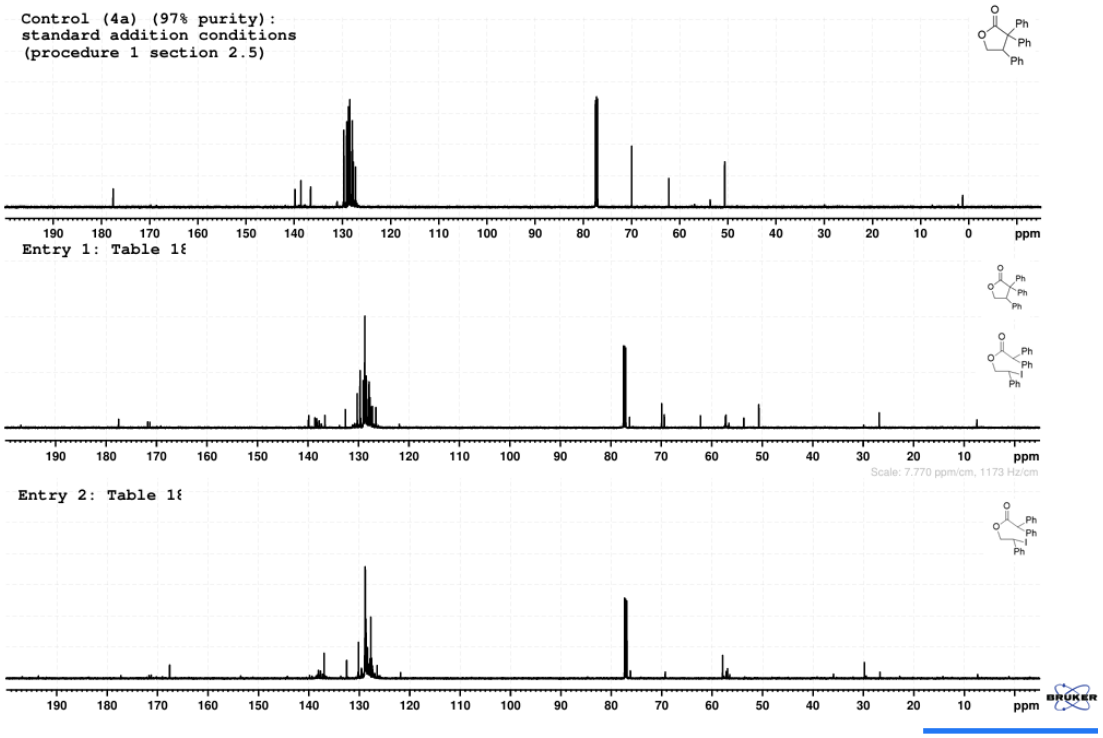
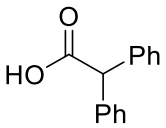


Figure 43: Overlayed spectra of the control and the two spectra from the two reactions of adding reactants in a different order



diphenylacetic acid

Figure 44: Carboxylic acid derived from diphenylketene.

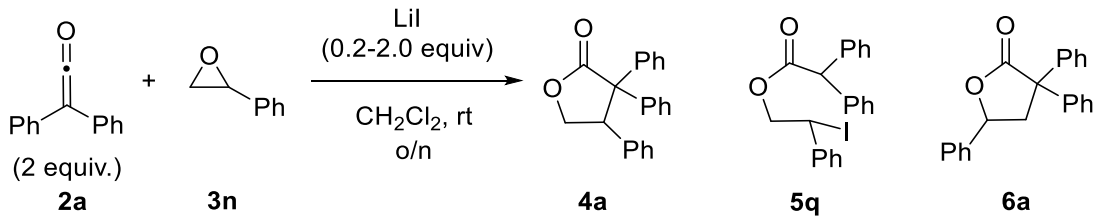
3.4.1.7 LiI equivalents:

The effect of varying the equivalents of LiI on the reaction was explored. The effect of five different equivalents of the catalyst on the GC-MS peak area of the 3,4-γ-lactone **4a** and other products is summarised in Table 19. The results indicate that when 2 equivalents of LiI were used, the peak area of the 3,4-γ-lactone was at its maximum level (55%). As the catalyst loading decreased, the corresponding peak area of **4a** decreased. When the catalyst loading was reduced to 0.5 and 0.2 equivalents, there was no 3,4-γ-lactone **4a** formed. These results indicate that a higher catalyst loading in the reaction facilitates the formation of the 3,4-γ-lactone and more complete consumption of epoxide starting material. LiI causes epoxide

ring-opening. The ring-opened epoxide acts as a nucleophile and reacts with the ketene to form the desired product. The higher concentration of the catalyst in the reaction results in a higher yield of the ring-opened epoxide and leads to increased product formation.

As the catalyst (LiI) should, in theory, be regenerated at the end of each cycle of the reaction, there may be undetermined pathways causing catalyst decomposition, leading to the requirement for a minimum of 1 mole equivalent of LiI to facilitate a productive reaction.

*Table 19: Effect of varying the number of equivalents of LiI on the formation of 3,4-γ-lactone **4a**.*



Entry	Equiv. of LiI	Peak area of 4a (%)[a]	Peak area of the 5q + 6a (%)[a]
1	2	55	3
2	1.5	38	8
3	1	25	13
4	0.5	0[,b]	6[b]
5	0.2	0[b]	0[b]

[a] % peak area determined by GC-MS analysis of crude product. [b] reactions carried out by Dr. Nessan Kerrigan.

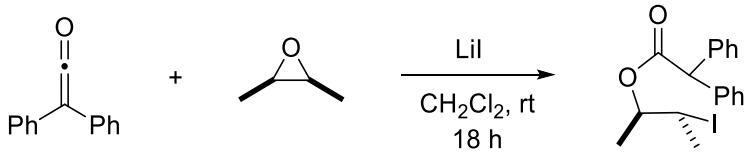
3.4.1.8 Equivalents of starting materials:

The effect of varying the equivalents of starting materials on the reaction was investigated using diphenylketene (ketene), *cis*-2,3-epoxybutane (epoxide), LiI (catalyst) and CH_2Cl_2 (solvent). The results are summarised in Table 20. In entry 1, the reaction employed 2 equivalents of ketene and 1 equivalent of both the epoxide and catalyst. Although the crude yield was higher under these conditions, the GC-MS peak area of the acyclic ester **5c** was only 53%. As seen before (see Table 12 & Table 14), no γ-lactone was produced by either reaction.

In comparison, entry 2 used 2 equivalents of both the epoxide and the catalyst, and 1 equivalent of ketene. Initial analysis suggested that this entry yielded a higher peak area (purity) for the acyclic ester **3c**. Hence, employing excess epoxide and

catalyst may be optimal reaction conditions. However, the isolated yield of this reaction was significantly lower (40%), but it had a larger peak area (88%), which can be rationalised by considering the reaction work-up and analysis conditions. Firstly, LiI, which was present in excess, this would not appear in the GC-MS spectrum and yield as a byproduct as it would be removed due to its high solubility in water during aqueous work-up. Also, *cis*-2,3-epoxybutane is a small, volatile molecule, and the crude product was subjected to vacuum for 3 hours before analysis. As a result, excess epoxide would likely have been removed, leaving the acyclic ester **5c** as the major component of the sample analysed. Therefore, the results from entry 1 are considered to be better than entry 2 and provide a better overall result (about 46% of **5c**).

*Table 20: Investigation of the variation of equivalents of starting materials for the formation of **5c**.*



2a **3o** **5c**

Entry	Equiv. of ketene	Equiv. of epoxide	Equiv. of LiI	Yield (%)	GC-MS peak area of 5c (%)[a]
1	2	1	1.1	86	53
2	1	2	2.3	40	88

[a] % peak area determined by GC-MS analysis of crude product.

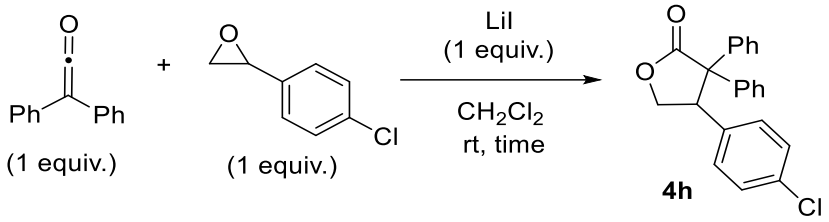
3.4.1.9 Optimisation studies investigating formation of 3,4-γ-lactone products from diphenylketene and different epoxides

3.4.1.9.1 Effect of reaction time on the formation of 4-(4-chlorophenyl)-3,3-diphenyldihydrofuran-2(3H)-one **4h**

The effect of time on the formation of 4-(4-chlorophenyl)-3,3-diphenyldihydrofuran-2(3H)-one **4h** was investigated. The optimal reaction time for this reaction was determined to be 18 h. After 18 h, the GC-MS peak area for the desired product **4h** was at its highest (50%). In comparison, when the reaction time was increased to 4 days the peak area decreased, and the decrease in the peak area of the desired product **4h** was also observed when the time was decreased to just 2 h. Only 14%

of the desired product was detected in the crude sample by GC-MS analysis after 2 h.

*Table 21: Effect of the variation of reaction time on formation of 4-(4-chlorophenyl)-3,3-diphenyldihydrofuran-2(3H)-one (**4h**).*



Entry	Reaction time	GC-MS peak area of 4h (%)[a]
1	2 h	14
2	18 h	50
3	4 days	36

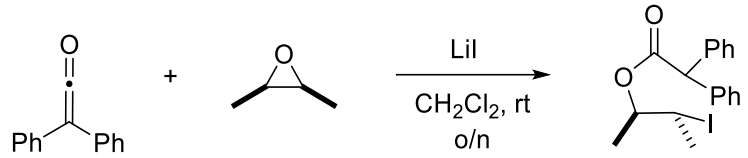
[a] % peak area determined by GC-MS analysis of crude product.

3.4.1.9.2 Effect of changing the equivalents of the epoxide in the reaction on the formation of **4a, 4d, 4e** and **5c.**

In Tables 22-25, the effect of changing the ketene equivalent on the formation of various 3,4-γ-lactone and the acyclic ester products was investigated. For the reaction of *cis*-2,3-epoxybutane (Table 22) and racemic styrene oxide (Table 23, changing the number of equivalents of ketene did not significantly affect the peak area of the desired product.

However, variation in the ketene equivalents had a larger impact on the peak areas of reactions involving 2-naphthyloxirane (Table 24) and 4-fluorophenyloxirane (Table 25. In particular, for the reaction with 4-fluorophenyloxirane, increasing the ketene to 2 equivalents led to an increase in the peak area of the 3,4-γ-lactone to 79% compared to 18% when just 1 equivalent of the ketene was used.

Table 22: Effect of the number of equivalents of ketene on the formation of the desired acyclic ester product 5c formed from diphenylketene and cis-2,3-epoxybutane.

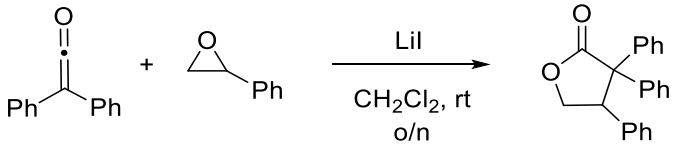


2a **3o** **5c**

Diphenylketene Equiv.	*cis*-2,3-epoxybutane Equiv.	LiI Equiv.	GC-MS peak area of 5c (%)[a]
2	1	1	73
1	1	1	69

[a] % peak area determined by GC-MS analysis of crude product.

Table 23: Effect of the number of equivalents of ketene on the formation of the desired γ-lactone product 4a from diphenylketene and racemic styrene oxide.

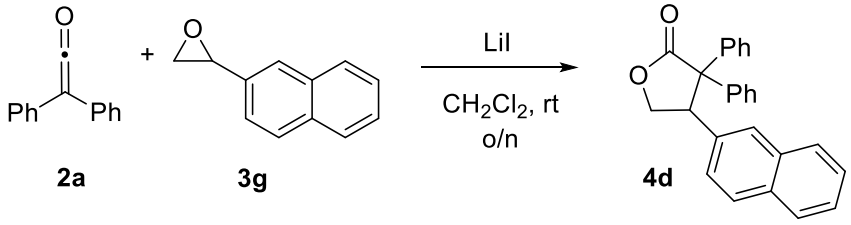


2a **3n** **4a**

Diphenylketene (Equiv.)	Racemic styrene oxide (Equiv.)	LiI (Equiv.)	GC-MS peak area of 4a (%)[a]
2	1	1	64
1	1	1	62

[a] % peak area determined by GC-MS analysis of crude product.

*Table 24: Effect of the number of equivalents of ketene on the formation of the desired γ-lactone product **4d** from diphenylketene and 2-naphthyloxirane.*



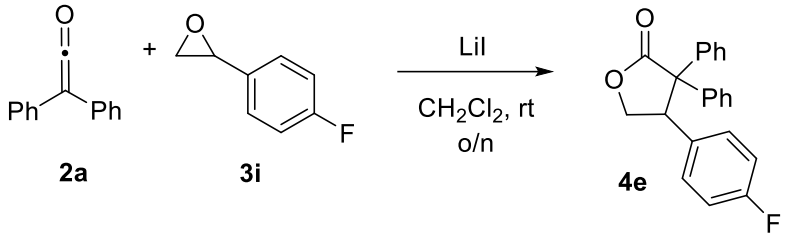
2a **3g** **4d**

Diphenylketene (Equiv.)	2-naphthyloxirane (Equiv.)	LiI (Equiv.)	GC-MS peak area of 4d (%)[a]
2	1	1	50
1	1	1.5	62

[a] % peak area determined by GC-MS analysis of crude product.

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*Table 25: Effect of the number of equivalents of ketene on the formation of the desired γ-lactone product **4e** from diphenylketene and racemic 4-fluorophenyloxirane.*



Diphenylketene (Equiv.)	4-fluorophenyloxirane (Equiv.)	LiI (Equiv.)	GC-MS peak area of 4e (%)[a]
2	1	1	79
1	1	1	18

[a] % peak area determined by GC-MS analysis of crude product.

3.5 Predicted 3,5-γ-lactone vs the 3,4-γ-lactone formed in the reaction

The product **4a** (3,3,4-triphenyldihydrofuran-2(3H)-one) is a 3,4-γ-lactone. However, this product was not the initially expected regioisomer. As discussed in the introduction, the predicted ring-opening is at the less substituted carbon under purely S_N2 reaction conditions (basic conditions or with a charged nucleophile). If the anticipated pathway was followed, the ring opened nucleophilic species, after attack on the ketene, would result in the formation of the 3,5-γ-lactone **6a** as illustrated in Figure 45 labelled 'Predicted regioselectivity'. Ring-opening at the less substituted position is generally favoured under neutral or basic conditions.[7] Since this reaction proceeds under overall neutral conditions, the formation of the 3,5-γ-lactone **6a** would be expected. Both the predicted pathway mechanism and the mechanism to the 3,4-γ-lactone **4a** are shown in Figure 45. The ring-opening of the epoxide at the more substituted carbon was not anticipated under the reaction conditions to which the reactions were subjected in this project. However, the 3,4-γ-lactone was observed as the major product across all examples studied in this project. An explanation for the opening of the racemic styrene oxide at the more substituted carbon could be due to the ability of the phenyl group to stabilise a partial positive charge on the benzylic carbon, in combination with the ability of the

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lithium ion to bind to the epoxide oxygen and therefore further polarise the C-O bonds. The scope of the 3,4-γ-lactone formation is presented in Table 26.

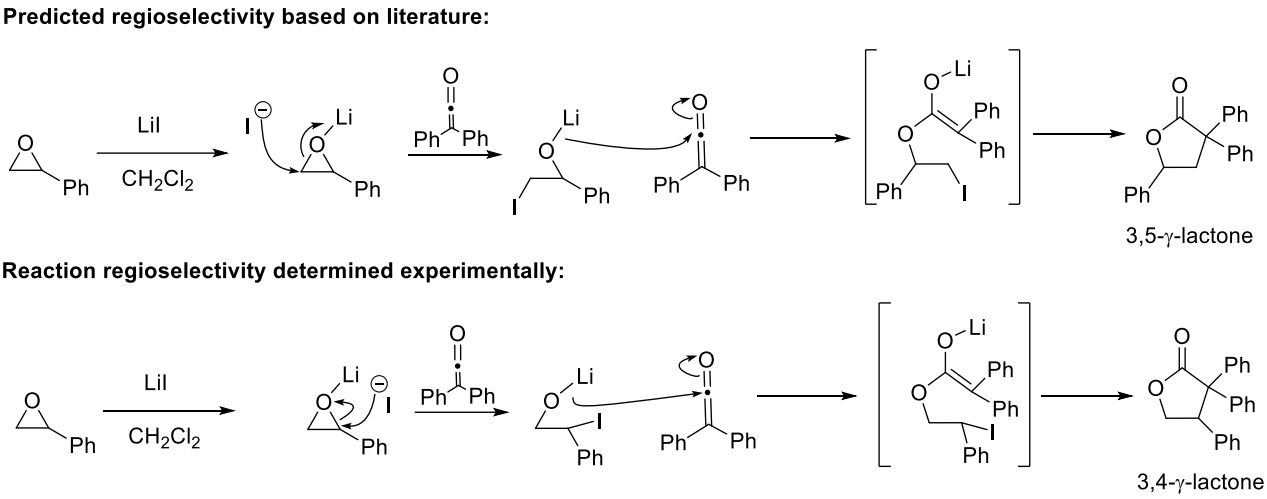


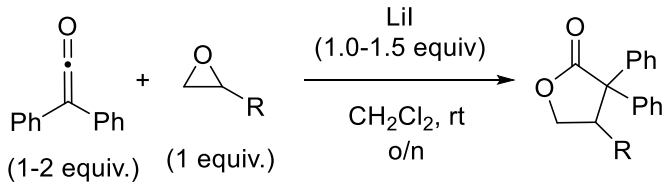
Figure 45: Expected regioselectivity in γ-lactone formation from racemic styrene oxide and diphenylketene.

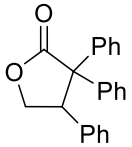
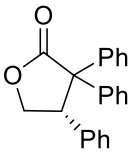
3.6 Reaction scope of the [3 + 2] cycloaddition reaction of epoxides with ketene

3.6.1.1 Scope of 3,4-γ-lactone formation

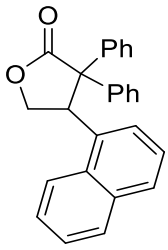
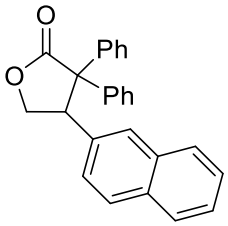
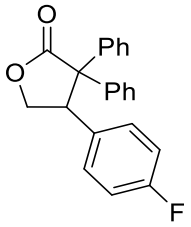
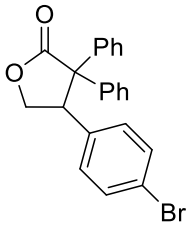
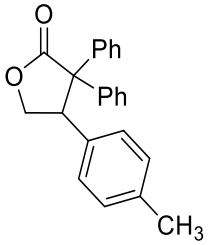
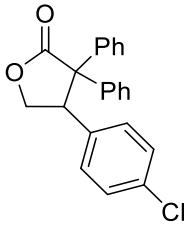
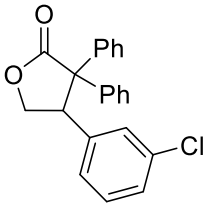
The scope of the reaction is shown in Table 26. The table shows the γ-lactone formed from the [3 + 2] cycloaddition of diphenylketene with a range of different epoxides.

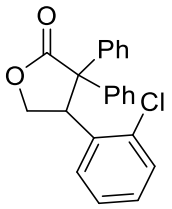
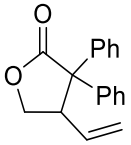
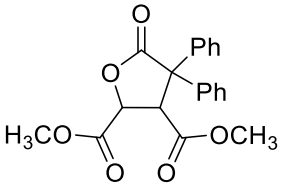
Table 26: Scope of the LiI-catalysed formation of 3,4-γ-lactone products from epoxides and diphenylketene.



Entry	Compound	Experimental reference	Yield (%)	Purity of 4 (%)[a]
1		**4a**	58	97
2		**4b**	53 (84% ee)	96

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	(from enantioenriched styrene oxide)			
3		**4c**	51	93
4		**4d**	53	95
5		**4e**	45	97
6		**4f**	21	85
7		**4g**	12	93
8		**4h**	45	87
9		**4i**	49	91

10		**4j**	72	91
11		**4k**	32	98
12		**4l**	59	98

[a] % purity determined by GC-MS analysis of purified product.

The reaction scope of the 3,4-γ-lactone's synthesised in this project are shown in Table 26. The purified yields of the formed 3,4-γ-lactones were low to good (12-72%). As shown, the formal [3 + 2]-cycloaddition between diphenylketene and aryl/vinyl or ester-substituted epoxides consistently formed 3,4-γ-lactone products. The substituents in these products are mainly aromatic groups. In all the examples (entries 1-12), the epoxide ring opens at the more substituted carbon. This is contradictory to the expected regioselectivity for ring-opening of the epoxide. The ring-opening under neutral conditions is generally expected to occur at the less substituted carbon.[7] This regioselectivity can be explained by the substituent's ability to stabilise the partial positive charge at the electrophilic carbon being attacked. The coordination of the lithium ion (acting as a Lewis acid) to the oxygen atom in the epoxide during ring-opening increases the polarisation of the C-O bond. This increases the partial positive charge on the more substituted carbon atom. Substituents that stabilise this charge favour attack at the more substituted position. Aryl substituents stabilise the positive charge through resonance, while vinyl groups stabilise through conjugation. The epoxides examined in this project mainly possess aromatic substituents, and hence the regioselectivity of epoxide ring-opening is consistent with the stabilisation of the transition state via resonance and conjugation.

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In entries 1 and 2, the epoxide was changed from racemic styrene oxide to an enantioenriched styrene oxide ((*R*)-Styrene oxide, 95% ee). The purified yields of these two products are similar; the yield of the 3,4-γ-lactone **4a** synthesised from racemic styrene oxide was 58% and the 3,4-γ-lactone **4b** prepared from enantioenriched styrene oxide was 53%. These two reactions were analysed by chiral HPLC to determine the enantiomeric excess of the products and **4b** was determined to have an ee of 84%. This decrease in % ee suggests that the reaction mechanism does not proceed completely through S_N2 reactions.

Entries 3 and 4 both represent naphthyl-substituted 3,4-γ-lactones (**4c** and **4d**). The difference between these two lactones is the position at which the naphthyl is attached to the lactone structure. The yields of both these naphthyl-substituted lactones were quite similar, with yields of 51 and 53%, respectively, and indicated that the position on the naphthyl (1- or 2-) had little impact on the success of the reaction.

There were four γ-lactone products that had a *para*-substituted aryl substituent. The four substituents in the *para*-position of the aryl ring were fluoro- (**4e**), bromo- (**4f**), chloro- (**4h**), and methyl- (**4g**). Hence, three electron-withdrawing and one electron-donating group at the *para*-position. The γ-lactone with a fluoro group on the phenyl ring was formed with a moderate yield (45%). However, the purity of this product was high, with the peak area of the GC-MS spectrum corresponding to 97%. According to NMR, the 3.4-γ-lactone was formed. In the ^{13}C NMR, there were extra peaks. The carbons bonded to fluorine on the phenyl ring of **4e** all appear as doublets due to spin-spin coupling. This accounts for the extra four peaks found in the ^{13}C NMR. Entries 6 and 8 both have electron-withdrawing groups attached to the phenyl ring. When these products were purified, byproducts were formed, as determined by GC-MS analysis. The two products had carbonyl peaks in the ^{13}C NMR around δ 190 ppm. These by-products were inseparable from the desired product and lowered the overall purity of the desired products to *ca*. 85-87%. The identity of the contaminant byproduct was not unambiguously determined, but is suspected to be an aldehyde derived from the epoxide.

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The last *para*-substituted group examined was the methyl group, and this formed the 3,4-γ-lactone product **4g**, albeit in a poor isolated yield (12%). The low yield of the desired product was also observed at the crude stage by GC-MS analysis. The low yield could result from a relatively inefficient cyclisation step. NMR spectroscopic analysis showed that the product (entry 7) was formed as an inseparable mixture of two isomers of the product. The ratio of the isomers was 19:1, favouring the 3,4-isomer **4g** over the 3,5-isomer **6g**.

The effect of changing the position of the chloro-substituent on the phenyl ring (*ortho*-, *meta*- and *para*-) of the epoxide on the overall formation of the 3,4-γ-lactone was studied. The effect of variation of the chloro-position on the phenyl ring is shown in entries 8-10. The results of these three entries are not as expected. The 3,4-γ-lactone **4h** with a chloro- substituent at the *para*-position would be expected to form with the highest yield due to the substituent being away from the reaction site, minimising steric hindrance. However, in these experiments, placing the chloro-substituent at the *ortho*-position of the phenyl ring led to the formation of the desired lactone product **4j** in the highest yield (72%). There was also a slight increase in the yield of the 3,4-γ-lactone formed when the chloro-group was changed from the *para*-position (entry 8) to the *meta*-position of the phenyl ring. The yield of the 3,4-γ-lactone increased from 45% to 49%.

The γ-lactone formed from the vinyl epoxide substrate consisted of two isomers (3,4- and 3,5-isomers). The major and minor isomers can be seen in the NMR spectra. The isomers were formed in a 4.5:1 ratio, favouring the 3,4-substituted γ-lactone **4k** over the 3,5-isomer **6k**.

The dimethyl 5-oxo-4,4-diphenyltetrahydrofuran-2,3-dicarboxylate product was formed in a reasonable isolated yield (59%) and with a high purity based on the GC-MS peak area (98%). The synthesis of dimethyl 5-oxo-4,4-diphenyltetrahydrofuran-2,3-dicarboxylate **4l** is from a meso-starting material (2*R*,3*S*)-dimethyloxirane-2,3-dicarboxylate. The relative stereochemistry of the product, with its two ester groups at contiguous chiral centres, was examined using NOSEY. NOESY is a 2D NMR technique which is used to determine the stereochemistry of the compound by

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detecting proton interactions through-space. The two protons at C-4 and C-5 in this compound were investigated to determine whether the ester substituents on C-4 and C-5 are close in space and, hence, on the same side of the molecule, indicating *cis*-relative stereochemistry. Two protons that are close in space appear as cross-peaks on the NOESY spectrum. In this spectrum, the two relevant protons have significant cross-peaks between them, as shown in Figure 46. Therefore, the two ester groups are *cis* to each other, and the compound's structure is shown in Figure 47.

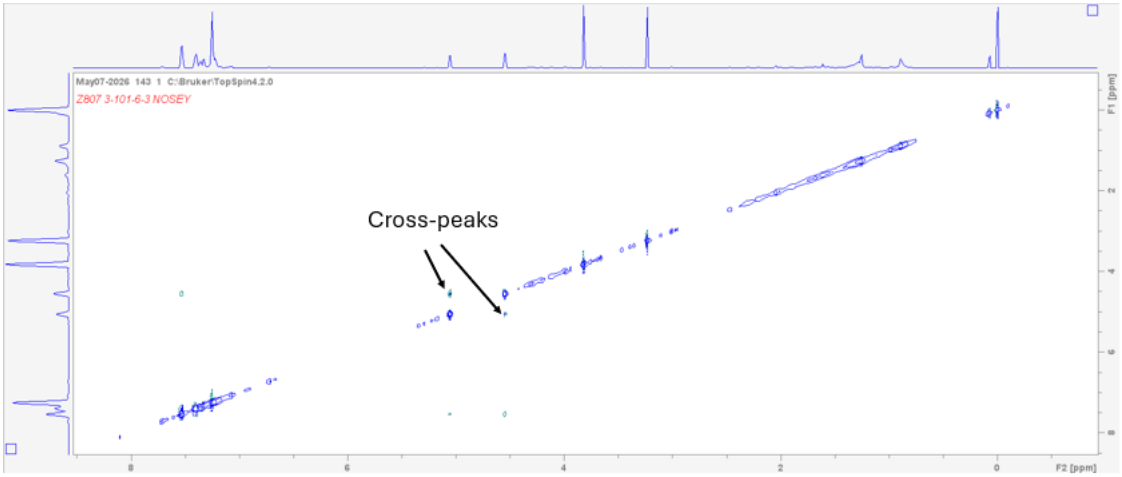


Figure 46: NOESY of 5-oxo-4,4-diphenyltetrahydrofuran-2,3-dicarboxylate.

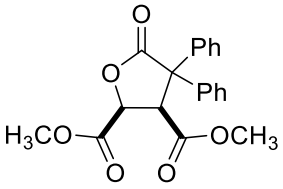


Figure 47: Relative stereochemistry of dimethyl 5-oxo-4,4-diphenyltetrahydrofuran-2,3-dicarboxylate ***4l****.*

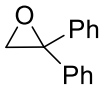
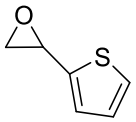
3.6.1.2 Other attempted [3+2] cycloaddition of epoxides and ketenes

The synthesis of three γ-lactones was attempted but, according to a combination of GC-MS and NMR analysis, it was concluded that these did not form the 3,4-γ-lactone nor the acyclic ester product. The epoxides studied in reaction with diphenylketene were *trans*-stilbene oxide (**4m**), 1,1-diphenylethylene oxide (**4n**) and 2-thienyloxirane (**4o**). The reason these reactions did not proceed could be as a result of steric hindrance. In the case of *trans*-stilbene oxide, the presence of the

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phenyl substituent on both faces of the epoxide results in a bulky system. If the epoxide ring-opening proceeds through an S_N2 mechanism, nucleophilic backside attack would be sterically hindered, preventing efficient epoxide ring-opening and subsequent intramolecular cyclisation to form the γ-lactone or the acyclic ester product. The reaction with 2-thienyloxirane produced a complex GC-MS spectrum, while the ^{13}C NMR showed no carbonyl peaks. The absence of characteristic carbonyl peaks is diagnostic of the absence of the γ-lactone or acyclic ester product.

Table 27: Epoxides that did not form the desired γ-lactone 4 or the acyclic ester product 5.

Entry	Experimental reference	Epoxide	γ-lactone or acyclic ester peak area (%)[a]
1	**4m**		0
2	**4n**		0
3	**4o**		0

[a] % peak area determined by GC-MS analysis

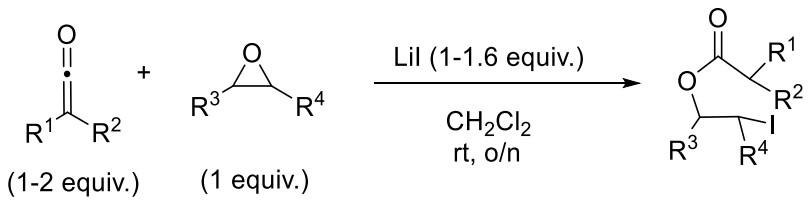
3.6.1.3 Scope of acyclic ester product formation

The sixteen entries show the acyclic ester products that did not cyclise to form the desired γ-lactone products (Table 28). Eight of these products were synthesised through the reaction of diphenylketene with various epoxides, while six entries employed ethylphenylketene, one used methylphenylketene, and the last entry used in situ-generated methylketene. The epoxides used in these reactions had aliphatic substituents (e.g. methyl and cyclohexyl) or a (glycidyl benzyl) ether substituent. For the reaction of both diphenylketene and ethylphenylketene with benzyl glycidyl ether, the epoxide underwent ring-opening at the less substituted carbon to form the acyclic ester products **5a** and **5b**. This contrasts with the other examples in the project that led to 3,4-substituted γ-lactones, where the opening occurred at the more substituted carbon. The difference can be explained by the substituent's ability to stabilise partial positive charge at the electrophilic carbon

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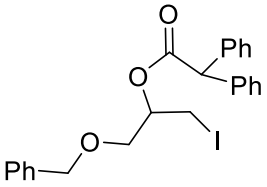
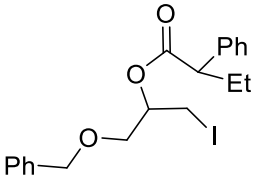
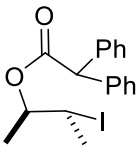
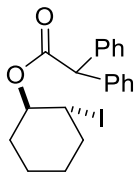
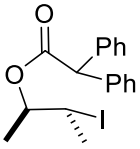
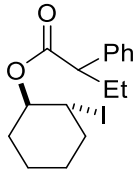
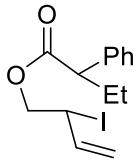
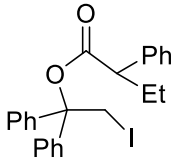
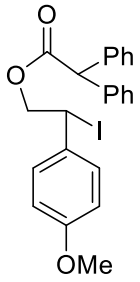
on the epoxide during nucleophilic attack. The benzyl ether substituent in benzyl glycidyl ether is electron-donating but does not have the same ability to stabilise the partial positive charge of the electrophilic carbon through resonance or conjugation, unlike the aryl substituents present in other substrates studied. As a result, there is little stabilisation of the transition state involving attack at the more substituted carbon and no S_N1-like character to the dominant transition state. Instead, ring-opening of the epoxide by iodide proceeds via pure S_N2 attack at the less substituted carbon, leading to the formation of the acyclic ester product. As described in section 2.5.1.17, there is a 1:1 dr. This can be explained by the starting material having one chiral centre, and the new product forms a second chiral centre. This reaction is not diastereoselective leading to a mix of diastereoisomers. Similarly, epoxides bearing aliphatic substituents also yielded acyclic ester products (**5c**-**5f**). This may be due to the increased steric hindrance provided by alkyl substitution, without the benefit of resonance stabilisation provided by aryl-substitution, which overall hinders intramolecular S_N2 cyclisation by slowing nucleophilic attack of the enolate intermediate at this position. Alternatively, if cyclisation requires a preceding single electron transfer (SET) step, where the C-I bond (of enolate intermediate, Figure 45) is broken to give a radical intermediate, then that would be favoured by aryl/vinyl or ester substitution at C-I but not so much by alkyl group-substitution. These mechanistic possibilities, and experiments developed to probe them, will be discussed further in Chapter 5.

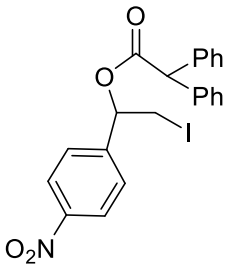
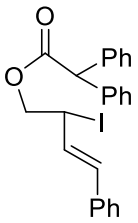
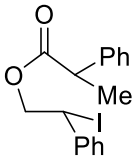
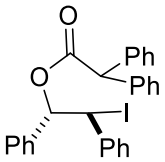
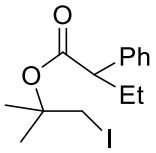
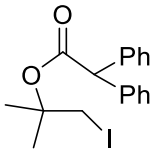
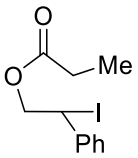
Table 28: Acyclic ester products formed from ketenes and epoxides.



Entry	Compound number	Compound	Yield (%)	Purity (%)[b]

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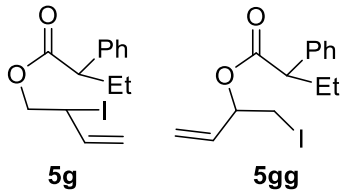
1	**5a**		30[a]	100
2	**5b**		57[a]	97
3	**5c**		47[a]	97
4	**5d**		49[a]	96
5	**5e**		18[a]	>99 (dr 54:46)
6	**5f**		54[c]	60
7	**5g**		47[c]	60
8	**5h**		66[c]	59
9	**5i**		50[c]	20

10	**5j**		>100[c]	35
11	**5k**		74[c]	33
12	**5l**		87[c]	31
13	**5m**		77[c]	23
14	**5n**		24[c]	22
15	**5o**		61[c]	71
16	**5p**		84->100[c]	6-22

[a] Isolated yield of purified product. [b] % purity determined by GC-MS analysis of purified or crude product. [c] crude yield.

In several examples, the epoxide was ring-opened at the more substituted carbon, whereas in other examples, the epoxide was ring-opened at the less substituted carbon. Butadiene monoxide was opened at the more substituted carbon, and this was facilitated by allylic conjugation. Allylic conjugation stabilises the developing partial positive charge on the more substituted carbon. The ^{13}C NMR indicated that the majority of the product formed due to opening at the more substituted carbon

of the vinyl epoxide to afford **5g,** as shown in Figure 48. The minor product **5gg** resulted from the epoxide ring-opening at the less substituted carbon.



5g **5gg**

Figure 48: The two acyclic ester product regioisomers are formed from the ring-opening of the epoxide at different carbons.

The acyclic ester products synthesised from the reactions of ethylphenylketene with 1,2-diphenylethylene oxide (**5h**) and isobutylene oxide (**5n**) were both formed through ring-opening of the epoxide at the less substituted side of the epoxide, as indicated by the crude ^{13}C NMR spectra.

The reaction between 2-(4-methoxyphenyl)oxirane and diphenylketene formed the product **5i** (Table 28, entry 9). This epoxide opened at the more sterically hindered carbon. The methoxy-substituent is electron-donating and increases electron density on the aromatic ring through resonance. This increases stabilisation of the developing partial positive charge at the benzylic carbon of the epoxide and can account for the preferential attack at the more substituted carbon, despite the substituent being sterically bulky.

In contrast, when the *para*-substituent on the phenyl ring was changed to a nitro-group, the regioselectivity was reversed, and the acyclic ester product formed corresponded to that expected from ring-opening occurring at the less substituted carbon. The nitro group is an electron-withdrawing group and destabilises the partial positive charge formation at the benzylic carbon of the epoxide, and therefore, opening at the less substituted side is favoured. This regioselectivity was observed experimentally in the reaction between 2-(4-nitrophenyl)oxirane and diphenylketene to afford **5j** (Table 28, entry 10).

The reaction between diphenylketene and 2-styryloxirane to form **5k** was also investigated (Table 28, entry 11). Interpretation of the spectral data proved difficult. The ^{13}C NMR spectrum contained a single set of aliphatic peaks and a carbonyl peak

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that was characteristic of the desired product. However, the GC-MS spectrum displayed two peaks with identical fragmentation patterns. The product contains a chiral centre, and so the possibility of peaks arising from enantiomers was considered. However, an achiral GC column was used, and enantiomers would have identical retention times due to a lack of separation. Nevertheless, both GC-MS and ^{13}C NMR data suggest the formation of an acyclic ester product; further analysis is required to determine the exact structure of the acyclic ester product(s) formed.

As shown in Table 27, *trans*-stilbene oxide did not react to form any product. In contrast, *cis*-stilbene oxide was observed to form the acyclic ester product **5m** (Table 28, entry 13). In the *cis*-epoxide, the two phenyl substituents are on the same side of the molecule. This potentially reduces steric hindrance during the reaction of the iodoalkoxide intermediate with ketene substrate, ultimately leading to the formation of the acyclic ester product, albeit in modest yield.

The final epoxide subjected to reaction with diphenylketene was isobutylene oxide and this reaction led to the formation of **5o** (entry 15). According to ^{13}C NMR, ring-opening of the epoxide occurred at the less substituted side, forming an acyclic ester product in which the dimethyl-substitution was adjacent to the oxygen atom.

The reaction between methylphenylketene and racemic styrene oxide underwent opening at the benzylic carbon, resulting in the acyclic ester product with the phenyl substituent on the terminal carbon. As described previously in section 3.5, this regioselectivity can be attributed to resonance stabilisation by the phenyl substituent. The reaction of in situ generated methylketene with racemic styrene oxide was explored; the reaction was carried out three times, varying the order of addition of the base and acyl chloride to investigate the effect on product formation as described in section 2.5.1.31.1 to 2.5.1.31.3. In the first experiment, the desired product was not formed; this could be a result of the epoxide being added too rapidly. In the other reactions, the epoxide solution in CH_2Cl_2 was added dropwise over one hour. In the second reaction, the base was added slowly to the acyl chloride. The GC-MS indicated the possible formation of the acyclic ester **5p** with a

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product peak area of 22% by GC-MS. The GC-MS fragmentation pattern had a peak at 231 and 177 m/z. The 177 m/z indicates that the atoms are present to form the γ-lactone although the cyclisation does not *occur*. In the final experiment, the acyl chloride was added slowly to the base. This reaction was split into two portions, and different work-up procedures were carried out. The GC-MS results demonstrated that when the acyl chloride was added slowly to the base, the peak area decreased to 6% compared to 22% under identical work-up conditions. The other work-up technique, in which the acyl chloride was added slowly to the base, showed a slightly higher peak area of 12%. Further studies will be required as the ^{13}C NMR spectra of the products were complex but showed a peak in the carbonyl region indicative of the formation of the acyclic ester product.

In conclusion, twelve 3,4-γ-lactones were prepared from diphenylketene and various epoxides under LiI catalysis. When the substituent on the epoxide was changed from aryl, vinyl or ester, the acyclic ester product was formed. Five acyclic ester products were isolated in pure form and characterised, with another eleven acyclic esters formed that were not purified further due to instability or low yield at the crude stage.

3.7 Cleaving C-I bond to afford *sec*-butyl 2-phenylbutanoate(**7a**)

Cleaving the C-I bond to afford *sec*-butyl 2-phenylbutonate was carried out to determine if the cleavage of the C-I bond was possible. This reaction, according to GC-MS analysis, had a peak corresponding to the desired molecular ion at m/z 220. As described in section 2.6 a LiOH solution, prepared in deionised water was employed, and this could promote the hydrolysis of the desired ester. However, according to both the NMR and the GC-MS analysis of the crude product hydrolysis did not occur. Instead, the data suggests that the C-I bond was cleaved, forming a new C-H bond, and that the ester moiety intermediate remained intact. One reason that the hydrolysis may not have occurred was that the addition of LiOH was at room temperature, and a higher temperature may have been required to promote hydrolysis. As seen in previous literature, an increase in temperature in organic reactions promotes the hydrolysis reaction [119]

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Chapter 4: Mechanistic studies of the catalytic formal [3 + 2]- cycloaddition reaction: Experimental:

4.1 Introduction:

In this chapter, the experimental of the different reactions that were carried out to study the mechanism of the lithium iodide-catalysed formal [3 + 2] -cycloaddition of epoxides with ketenes are presented. This chapter details, the opening of the racemic styrene epoxide with the optimal catalyst, the attempted synthesis of acyclic esters from epoxides and acyl chlorides, attempts at trapping intermediates in the reaction, and further mechanistic studies involving radical trapping agents and control reactions.

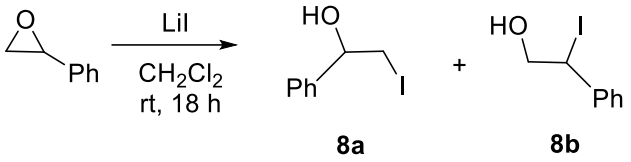
4.2 General Information:

In this section, the reactions were brought to a crude stage and not purified, as the crude reactions provided enough information without extra purification required. As seen in section 2.2.2 GC-MS analysis was used to determine the amount of a certain product in the crude sample. . The samples were dissolved in CH_2Cl_2 or EtOAc (at 5 mg/mL concentration), and they were then injected on the GC-MS. The GC-MS was used as it gave a peak area % report, which was used to determine the amount of the certain product present in the sample. In certain examples, characteristic peaks were provided, including carbonyl peaks and other distinguishable peaks that confirmed the formation of the desired product. Compounds **5c** and **5e** in section 4.3.2 synthesised from acyl chlorides and epoxides had previously been synthesised with ketene and epoxide. The characteristic peaks reported for these matched with the peaks reported in section 2.5. The other compounds synthesised in section 4.3.2 contained characteristic carbonyl and alkyl peaks, and the GC-MS fragmentation patterns for the desired product were as predicted. The other sections contained a mixture of GC-MS analysis and characterised ^{13}C NMR peaks. GC-MS analysis was corroborated

through parallel with ^{13}C NMR analysis to confirm the presence of the predicted compounds.

4.3 Experimental:

4.3.1 Ring-opening of racemic styrene oxide with LiI to form 2-iodo-2-phenylethan-1-ol and 2-iodo-1-phenylethan-1-ol (**8a/8b**)

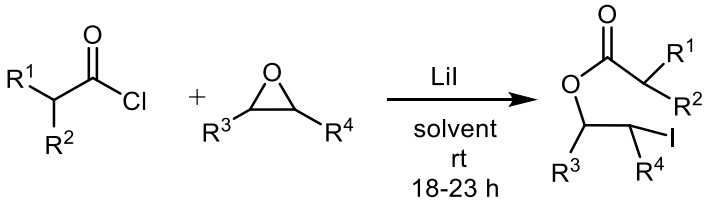


8a **8b**

The reaction was carried out using a 10 mL round-bottom flask with a magnetic stirring bar. The round-bottom flask was flame-dried and then placed under a nitrogen atmosphere. LiI (42.1 mg, 0.31 mmol, 1 equiv.) was added to the round-bottom flask and placed under vacuum for 10 min. It was then placed under an inert atmosphere. Dry CH_2Cl_2 (4.6 mL) was added to the LiI. The reaction was stirred, and then racemic styrene oxide (36 μL, 0.31 mmol, 1 equiv.) was added to the reaction solution. The reaction flask was covered with aluminium foil, and allowed to stir overnight (total reaction time = 18 h). The reaction was quenched with cold-deionised water (10 mL) and then extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4. The product **8** was not purified further; it was a colourless oil (43 mg, 55% (crude)), with a purity of 27%. ^{13}C NMR (150 MHz, $CDCl_3$, characteristic peaks of **8**) δ 141.4, 74.3, 15.5 ppm; Open-epoxide **8**: MS (EI 70 eV): 248 (M^+), 121, 107, 91 m/z; Unknown: MS (EI 70 eV): 222, 103, 91, 77. The characteristic peaks included distinguishable alkyl peaks.

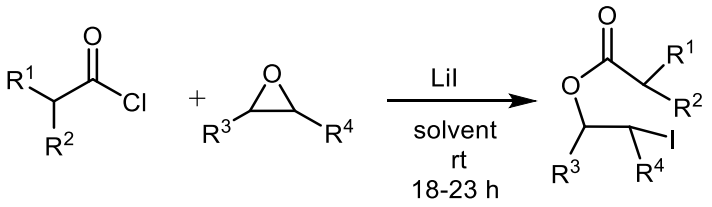
4.3.2 LiI-promoted reaction of epoxides with acyl chlorides:

4.3.2.1 Procedure 1 – for the synthesis of acyclic esters from epoxides and acyl chlorides



The reaction was carried out in two round-bottom flasks (5 mL and 10 mL) with a magnetic stirring bar in the 10 mL flask. The two round-bottom flasks were flame-dried and then placed under a nitrogen atmosphere. In the first flask (5 ml), the acyl chloride (0.27 mmol, 2 equiv.) was added, then the flask was placed under vacuum before being placed under a N_2 atmosphere. The volume of dry solvent was split between the two round-bottom flasks. Solvent (1 mL) was added to the 5 mL round-bottom flask using a syringe, and then epoxide (0.14 mmol, 1 equiv.) was added. In the 10 mL round-bottom flask, LiI (0.15 mmol, 1.1 equiv.) was added, and it was placed under vacuum, followed by N_2. The remaining solvent volume (1 mL) was added to the LiI, and the reaction mixture was stirred. The acyl chloride-epoxide mixture was added to the LiI suspension over a minute. The reaction flask was covered with aluminium foil, and allowed to stir overnight (total reaction time = 19 h). The reaction was quenched with cold-deionised water (10 mL) and then extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4. The purity of the crude product was determined by GC-MS analysis.

4.3.2.2 Procedure 2 – for the synthesis of acyclic esters from epoxides and acyl chlorides

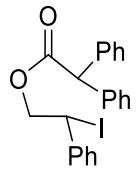


The reaction was carried out in two round-bottom flasks (5 mL and 10 mL) with a magnetic stirring bar in the 10 mL flask. The two round-bottom flasks were flame-dried and then placed under a nitrogen atmosphere. In the first flask (5 mL), the acyl chloride (0.33-4.65 mmol, 1 equiv.) was added, the flask was placed under vacuum, and the contents were then placed under a N_2 atmosphere. Dry solvent was added to the round-bottom flask via syringe. In the second round-bottom flask (10 mL), LiI (0.36-4.88 mmol, 0.9-1.5 equiv.) was added, and it was placed under vacuum followed by N_2. The remaining solvent volume was added to the LiI, and the reaction mixture was stirred. Epoxide (0.33-4.65 mmol, 1.0-1.2 equiv.) was added to the LiI-solvent mixture and stirred for 5 min. The acetyl chloride-solvent mixture was added

to the lithium iodide-epoxide suspension over a minute. The reaction flask was covered with aluminium foil and stirred overnight (total reaction time = 19-23 h). The reaction was quenched with cold-deionised water (10 mL) and then extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4. The purity of the crude product was determined by GC-MS analysis.

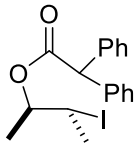
4.3.2.3 Scope of LiI-promoted reaction of epoxides with acyl chlorides:

4.3.2.3.1 2-iodo-2-phenylethyl 2,2-diphenylacetate(**5q**):



The reaction followed procedure 1 for the synthesis of acyclic esters from acyl chlorides. Diphenylacetyl chloride (62.1 mg, 0.27 mmol) was dissolved in CH_2Cl_2 (1 mL). Racemic styrene oxide (16 μL, 0.14 mmol) was added to the diphenylacetyl chloride-CH_2Cl_2 solution. LiI (19.6 mg, 0.15 mmol, 1.1 equiv.) and CH_2Cl_2 (1 mL) was added. The crude product **5q** was isolated as an orange/brown oil (89 mg, 99% (crude)), composed of 43% acyclic ester product **5q** and a trace amount of γ-lactone **4a** based on GC-MS analysis. ^{13}C NMR (150 MHz, $CDCl_3$, characteristic peaks) δ 171.8, 69.4, 57.2, 26.8 ppm; MS (EI 70 eV): 314, 194, 167, 91, 77 m/z. The ^{13}C NMR peaks were carbonyl and alkyl peaks that corresponded to the acyclic product.

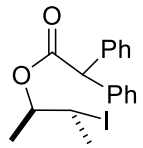
4.3.2.3.2 3-Iodobutan-2-yl 2,2-diphenylacetate (**5c**)



The reaction followed procedure 2 for the synthesis of acyclic esters from acyl chlorides. Diphenylacetyl chloride (75.5 mg, 0.33 mmol) was dissolved in CH_2Cl_2 (1.3 mL). LiI (48.7 mg, 0.36 mmol, 1.1 equiv.) was suspended in CH_2Cl_2 (1.3 mL). *Cis*-2,3-epoxybutane (29 μL, 0.33 mmol) was added to the LiI-CH_2Cl_2 solution. The product **5c** was isolated as a brown oil (105 mg, 81% (crude)), as a mixture of diastereomers, with 72% purity as determined by GC-MS analysis. ^{13}C NMR (150 MHz, $CDCl_3$, characteristic peaks) δ 171.9, 171.7, 74.8, 74.6, 57.4, 57.0, 30.2, 29.4,

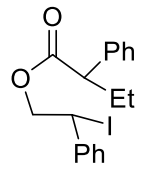
24.0, 23.9, 18.7, 18.5 ppm; MS (EI 70 eV): 266, 165, 105, 77 m/z. The ^{13}C NMR peaks were carbonyl and alkyl peaks that corresponded to the acyclic product.

4.3.2.3.3 3-Iodobutan-2-yl 2,2-diphenylacetate (**5c**)



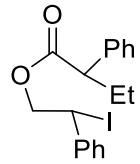
The reaction followed procedure 2 for the synthesis of acyclic esters from acyl chlorides. Diphenylacetyl chloride (85.0 mg, 0.37 mmol) was dissolved in THF (1.3 mL). LiI (60.2 mg, 0.45 mmol, 1.2 equiv.) was dissolved in THF (1.3 mL). *Cis*-2,3-epoxybutane (32 μL, 0.37 mmol) was added to the LiI-THF solution. The product was isolated as a brown oil (98 mg, 67% (crude)), as a mixture of diastereomers, with 41% purity as determined by GC-MS analysis. ^{13}C NMR (150 MHz, $CDCl_3$, characteristic peaks) δ 172.7, 171.7, 72.5, 58.0, 57.3, 30.0, 29.6, 25.8, 25.2, 23.0, 22.3 ppm; MS (EI 70 eV): 394 (M^+), 267, 167, 91, 77 m/z. The ^{13}C NMR peaks were carbonyl and alkyl peaks that corresponded to the acyclic product.

4.3.2.3.4 2-iodo-2-phenylethyl 2-phenylbutanoate (**5r**)



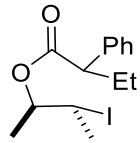
The reaction followed procedure 2 for the synthesis of acyclic esters from acyl chlorides. 2-Phenylbutyryl chloride (83.2 mg, 0.46 mmol) was dissolved in CH_2Cl_2 (2.3 mL). LiI (85 mg, 0.63 mmol, 1.4 equiv.) was suspended in CH_2Cl_2 (2.3 mL). Racemic styrene oxide (65 μL, 0.57 mmol, 1.2 equiv.) was added to the LiI-CH_2Cl_2 mixture. The product was isolated as an orange/brown oil (152 mg, 84% (crude)), as a mixture of diastereomers, with 62% purity as determined by GC-MS analysis. ^{13}C NMR (150 MHz, $CDCl_3$, characteristic peaks) δ 173.3, 172.8, 68.9, 68.9, 53.5, 53.5, 27.2, 27.1, 26.5, 26.5, 12.3, 12.2 ppm; MS (EI 70 eV): 231,146, 119, 91, 77 m/z. The ^{13}C NMR peaks were carbonyl and alkyl peaks that corresponded to the acyclic product.

4.3.2.3.5 2-iodo-2-phenylethyl 2-phenylbutanoate (**5r**)



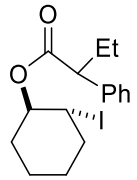
The reaction followed procedure 2 for the synthesis of acyclic esters. 2-Phenylbutyryl chloride (217 mg, 1.48 mmol) was dissolved in toluene (6 mL). LiI (215 mg, 1.61 mmol, 1.1 equiv.) was suspended in toluene (2.3 mL). Racemic styrene oxide (169 μL, 1.48 mmol) was added to the LiI-toluene$_2$ mixture. The product was isolated as an orange/brown oil (491 mg, 99% (crude)), as a mixture of diastereomers, with 48% purity as determined by GC-MS analysis. ^{13}C NMR (150 MHz, $CDCl_3$, characteristic peaks) δ 173.3, 172.8, 68.9, 68.9, 53.5, 53.5, 27.3, 27.1, 26.5, 26.5, 12.3, 12.2 ppm; MS (EI 70 eV): 267, 146, 119, 91, 77 m/z. The ^{13}C NMR peaks were carbonyl and alkyl peaks that corresponded to the acyclic product. The ^{13}C NMR peaks were carbonyl and alkyl peaks that corresponded to the acyclic product.

4.3.2.3.6 3-Iodobutan-2-yl 2-phenylbutanoate (**5e**)



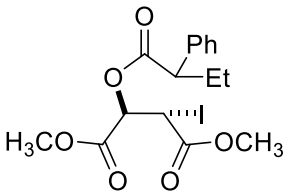
The reaction followed procedure 2 for the synthesis of acyclic esters. 2-Phenylbutyryl chloride (132.3 mg, 0.73 mmol) was dissolved in CH_2Cl_2 (3 mL). LiI (99.8 mg, 0.75 mmol, 1 equiv.) was suspended in CH_2Cl_2 (3 mL). *Cis*-2,3-epoxybutane (63 μL, 0.72 mmol) was added to the LiI-CH_2Cl_2 mixture. The product was isolated as a brown oil (216 mg, 86% (crude)), as a mixture of diastereomers, with 86% purity as determined by GC-MS analysis. ^{13}C NMR (150 MHz, $CDCl_3$, characteristic peaks) δ 173.2, 173.1, 73.9, 73.6, 53.9, 53.8, 30.0, 29.9, 26.6, 26.3, 24.2, 23.8, 19.0, 18.7, 12.4, 12.3 ppm; MS (EI 70 eV): 346 (M^+), 219, 119, 91, 77 m/z. The ^{13}C NMR peaks were carbonyl and alkyl peaks that corresponded to the acyclic product.

4.3.2.3.7 2-iodocyclohexyl 2-phenylbutanoate (**5f**)



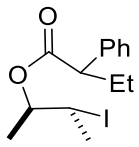
The reaction followed procedure 2 for the synthesis of acyclic esters. 2-Phenylbutyryl chloride (63.8 mg, 0.35 mmol) was dissolved in CH_2Cl_2 (1.3 mL). LiI (69.7 mg, 0.52 mmol) was suspended in CH_2Cl_2 (1.3mL). *Cis*-2,3-epoxybutane (34 μL, 0.35 mmol) was added to the LiI-CH_2Cl_2 mixture. The product was isolated as a brown oil (97 mg, 74% (crude)), as a mixture of diastereomers, with 60% purity as determined by GC-MS analysis. MS (EI 70 eV): 372 (M^+), 245, 119, 91 m/z.

4.3.2.3.8 Dimethyl 2-iodo-3-((2-phenylbutanoyl)oxy)succinate (**5s**)



The reaction followed procedure 2 for the synthesis of acyclic esters. 2-Phenylbutyryl chloride (65.9 mg, 0.36 mmol) was dissolved in CH_2Cl_2 (1.5 mL). LiI (56.1 mg, 0.42 mmol, 1.2 equiv.) was suspended in CH_2Cl_2 (1.5 mL). (2*R*,3*S*)-Dimethyloxirane-2,3-dicarboxylate (46 μL, 0.36 mmol) was added to the LiI-CH_2Cl_2 mixture. The product was isolated as a brown oil (139 mg, 89% (crude)), as a mixture of diastereomers, with 74% purity as determined by GC-MS analysis. MS (EI 70 eV): 434 (M^+), 307, 146, 91 m/z.

4.3.2.3.9 Large scale synthesis of 3-iodobutan-2-yl 2-phenylbutanoate (**5e**)



The reaction followed procedure 2 for the synthesis of acyclic esters. 2-Phenylbutyryl chloride (478.8 mg, 2.62 mmol) was dissolved in CH_2Cl_2 (10 mL). LiI (351.4 mg, 2.62 mmol, 1 equiv.) was suspended in CH_2Cl_2 (10 mL). *Cis*-2,3-epoxybutane (229 μL, 2.62 mmol) was added to the LiI-CH_2Cl_2 mixture. The product was isolated as a brown oil (877.9 mg, 97% (crude)), as a mixture of diastereomers,

with 83% purity as determined by GC-MS analysis. ^{13}C NMR ($CDCl_3$, 150 MHz, characteristic peaks) δ 173.2, 173.2, 74.0, 73.9, 53.9, 53.8, 30.0, 29.8, 26.6, 26.5, 24.2, 24.0, 19.0, 18.7, 12.4, 12.3 ppm; (MS (EI 70 eV): 346 (M^+), 219, 119, 91, 77 m/z. The ^{13}C NMR peaks were carbonyl and alkyl peaks that corresponded to the acyclic product.

4.3.3 Quenching of reactions:

4.3.3.1 Formation of **5c** through ice cold deionised water quench

The reaction followed the general procedure for the synthesis of γ-lactones. Diphenylketene (95.7 mg, 0.49 mmol) was dissolved in dry CH_2Cl_2 (2 mL). *Cis*-2,3-epoxybutane (43 μL, 0.49 mmol) was added to the ketene-CH_2Cl_2 reaction solution. LiI (68.5 mg, 0.49 mmol, 1 equiv.) was suspended in CH_2Cl_2 (2 mL), and the epoxide-ketene solution was added. The reaction was quenched with cold-deionised water (10 mL) and then extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried over Na_2SO_4. The product **5c** was isolated as a yellow oil (92 mg, 47% (crude)), with 75% purity as determined by GC-MS analysis. MS (EI 70 eV): 394 (M^+), 266, 194, 77 m/z.

4.3.3.2 Formation of **5c** through quench with deuterated water

The reaction followed the general procedure for the synthesis of γ-lactones. Diphenylketene (84.6mg, 0.44 mmol) was dissolved in dry CH_2Cl_2 (1.8 mL). *Cis*-2,3-epoxybutane (38 μL, 0.44 mmol) was added to the ketene-CH_2Cl_2 reaction solution. LiI (62.7 mg, 0.47 mmol, 1.1 equiv.) was suspended in CH_2Cl_2 (1.8 mL), and the epoxide-ketene solution was added. The reaction was quenched with D_2O (3 mL) and then extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4. The product **5c** was isolated as an orange oil (85 mg, 49% (crude)), with 69% purity as determined by GC-MS analysis. MS (EI 70 eV): 394 (M^+), 266, 194, 77 m/z. No evidence for the incorporation of deuterium in **5c** was observed.

4.3.4 Type of CH_2Cl_2 used in the reaction

4.3.4.1 Formation of **5c** using dry CH_2Cl_2 as solvent

The reaction followed the general procedure for the synthesis of γ-lactones. Diphenylketene (94.8 mg, 0.49 mmol) was dissolved in dry CH_2Cl_2 (1.8 mL). *Cis*-2,3-epoxybutane (22 μL, 0.25 mmol) was added to the ketene-CH_2Cl_2 reaction solution.

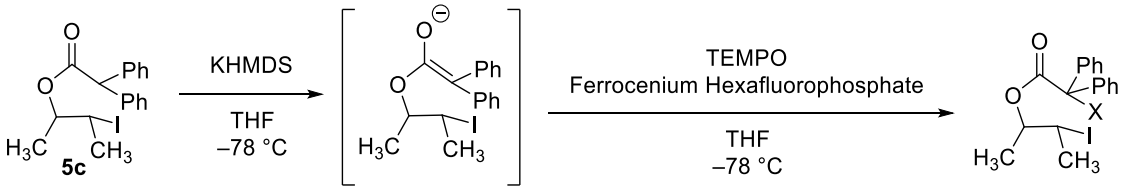
LiI (40.2 mg, 0.30 mmol, 1.2 equiv.) was suspended in CH_2Cl_2 (1.8 mL), and the epoxide-ketene solution was added. The reaction was quenched with deionised water (10 mL) and then extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4. The product **5c** was isolated as a yellow oil (85 mg, 87% (crude)), with 73% purity as determined by GC-MS analysis. MS (EI 70 eV): 394 (M^+), 266, 194, 77 m/z.

4.3.4.2 Formation of **5c** using dry CD_2Cl_2 as solvent

The reaction followed the general procedure for the synthesis of γ-lactones, with the exception of using CD_2Cl_2 as the solvent. Diphenylketene (53.7 mg, 0.28 mmol) was dissolved in CD_2Cl_2 (1 mL). *Cis*-2,3-epoxybutane (12 μL, 0.14 mmol) was added to the ketene-CD_2Cl_2 reaction solution. LiI (19.2 mg, 0.14 mmol, 1 equiv.) was suspended in CD_2Cl_2 (1 mL) and the epoxide-ketene solution was added. The reaction was quenched with deionised water (10 mL) and then extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4. The product **5c** was isolated as a yellow/orange oil (32 mg, 58% (crude)), with 15% purity as determined by GC-MS analysis. MS (EI 70 eV): 394 (M^+), 266, 194, 77 m/z. No evidence for the incorporation of deuterium in **5c** was observed.

4.3.5 Attempted formation of enolate/radical intermediate from acyclic esters

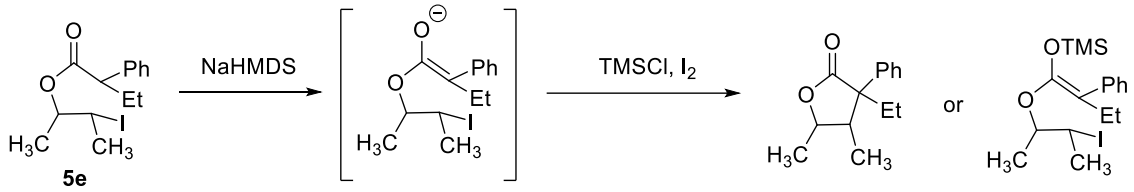
4.3.5.1 Employing KHMDS, TEMPO, and ferrocenium hexafluorophosphate to attempt to form a TEMPO-trapped radical intermediate.



The procedure was modified from Jahn et al.[120] KHMDS (42 mg, 0.20 mmol) was added to a pre-flame dried round-bottom flask under inert atmosphere conditions. The reaction mixture was cooled to –78 °C using a dry ice-acetone bath. 3-Iodobutan-2-yl 2,2-diphenylacetate **5c** (60 mg, 0.15 mmol) was dissolved in THF (1 mL) and added to the base. TEMPO (27 mg, 0.17 mmol) was dissolved in THF (1 mL) and added to the reaction mixture. Ferrocenium hexafluorophosphate (76.5 mg,

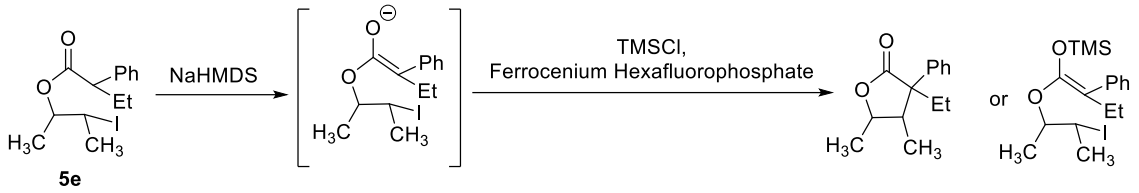
0.23 mmol) was dissolved in THF (2 mL) and added to the reaction mixture. The reaction was stirred for 2.5 h at −78 °C. The reaction was then warmed to room temperature over 30 min to 1 h, and then 5 drops of deionised water and diethyl ether (3 mL) were added. The crude product was passed through a plug column of silica eluting with diethyl ether. The product was isolated as a colourless oil (135 mg (crude)). NMR analysis showed no evidence for the desired product. ^{13}C NMR (150 MHz, $CDCl_{3,}$, acyclic ester characteristic peaks) δ 171.2, 74.1, 56.9, 28.8, 25.3, 18.2 ppm.

4.3.5.2 Employing NaHMDS, I_2, and TMSCl to form a TMS-trapped enolate intermediate or lactone



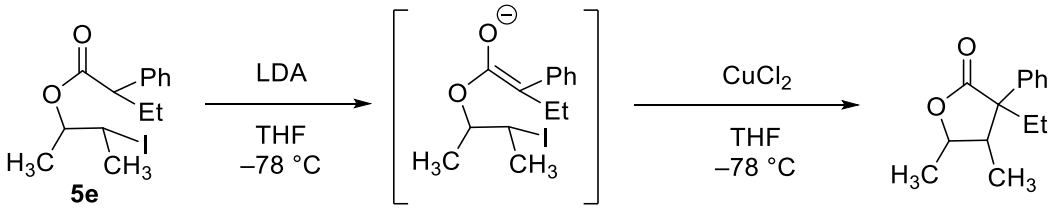
The procedure was modified from the method by Studer et al.[121] NaHMDS (1 M solution in THF, 0.61 mL, 0.61 mmol) was added to a pre-flame dried round-bottom flask under a nitrogen atmosphere. The subsequent reaction was carried out at rt. 3-Iodobutan-2-yl 2,2-diphenylacetate **5e** (105 mg, 0.30 mmol) was dissolved in THF (1 mL) and added to the NaHMDS solution at rt. The reaction was stirred for 1 h. The reaction mixture was then added via syringe to a second round-bottom flask containing I_2 (170 mg, 0.68 mmol) dissolved in THF (1 mL). TMSCl (77 μL, 0.61 mmol) was added to the reaction mixture, and it was left to stir overnight. The next day, aqueous saturated sodium sulfite solution (4.5 mL) and EtOAc (6 mL) were added to the reaction, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 6 mL). The combined organic layers were dried over $MgSO_4$ The crude product was isolated as a brown oil (93.3 mg (crude)). NMR and GC-MS analysis showed no evidence for the desired product. ^{13}C NMR spectrum was complex but had a weak carbonyl and alkyl peaks corresponding to the acyclic ester **5e**.

4.3.5.3 Employing NaHMDS, ferrocenium hexafluorophosphate, and TMSCl to form a TMS-trapped enolate intermediate or lactone.



The procedure was modified from the method by Studer et al.[121] NaHMDS (1M solution in THF, 0.51 mL, 0.51 mmol) was added to a pre-flame dried round-bottom flask under a nitrogen atmosphere. The subsequent reaction was carried out at rt. 3-Iodobutan-2-yl 2,2-diphenylacetate **5e** (88.5 mg, 0.22 mmol) was dissolved in THF (1 mL) and was added to the NaHMDS solution at rt. The reaction was stirred for 1 h. Ferrocenium hexafluorophosphate (0.20 g, 0.61 mmol) was dissolved in THF (1 mL) and added to the reaction mixture. TMSCl (49 μL, 0.39 mmol) was added to the reaction, and the reaction was left to stir overnight. The next day, aqueous saturated sodium sulfite solution (6 mL) and EtOAc (6 mL) were added to the reaction, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 6 mL). The combined organic layers were dried over $MgSO_4$. The crude product was isolated as a brown oil (174 mg (crude)). NMR analysis showed no evidence for the desired product. The characteristic peaks for the acyclic ester **5e** or the desired product were not present in the ^{13}C NMR spectrum.

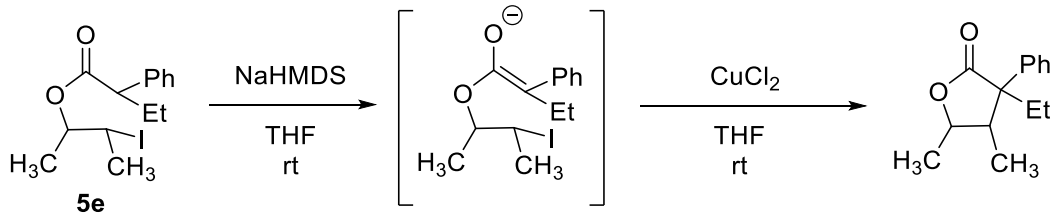
4.3.5.4 Attempted synthesis of lactone through use of LDA and $CuCl_2$



The procedure was modified from the method by Studer et al.[121] The LDA was prepared from diisopropylamine (0.06 mL, 46 mmol) in THF (1.6 mL) was added to a round-bottom and it was brought down at –78 °C. *n*-BuLi (2.5 M in hexane, 0.18 mL, 0.45 mmol) was added dropwise to the amine solution, and the mixture was stirred at –78 °C for 0.5 h. 3-Iodobutan-2-yl 2-phenylbutanoate **5e** (70.7 mg, 0.20 mmol, 1 equiv.) was dissolved in THF (2 mL) and added to the LDA solution (0.45

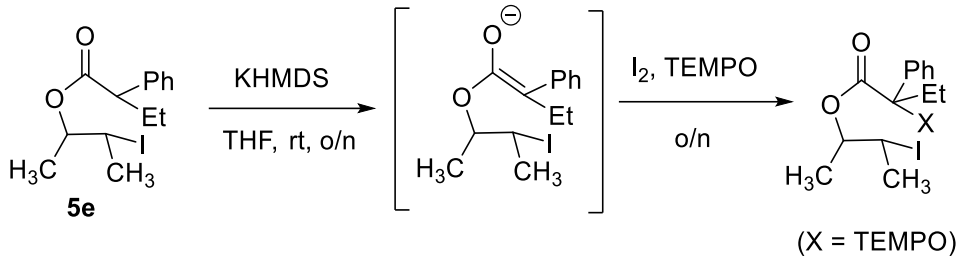
mmol, 2.2 equiv.). $CuCl_2$ (39.9 mg, 0.30 mmol) was dissolved in THF (2.5 mL) and added to the reaction mixture. The reaction was stirred for 2 h at −78 °C. The reaction was warmed to room temperature overnight, and the next day, aqueous saturated sodium sulfite solution (14 mL) and EtOAc (6 mL) were added; the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 6 mL). The combined organic layers were dried over $MgSO_4$. The crude product was isolated as a red-brown oil (42 mg (crude)). NMR showed no evidence for the desired product. ^{13}C NMR (150 MHz, $CDCl_3$, acyclic ester characteristic peaks) δ 173.3, 173.2, 74.0, 73.7, 53.9, 53.8, 30.0, 29.9, 26.6, 26.3, 24.2, 23.8, 19.0, 18.8, 12.4, 12.3 ppm.

4.3.5.5 Employing NaHMDS and $CuCl_2$ to form a lactone



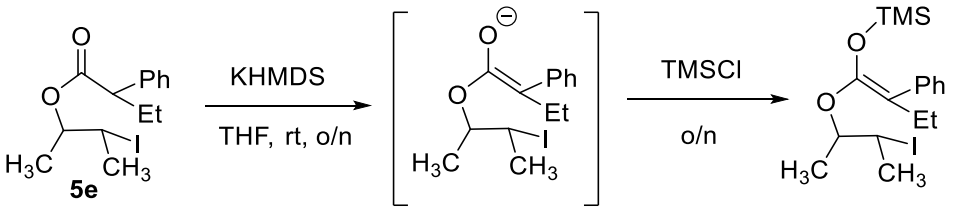
The procedure was modified from the method by Studer et al.[121] NaHMDS (1 M in THF, 0.13 mL, 0.06 mmol) was added to a pre-flame dried flask under a nitrogen atmosphere. 3-Iodobutan-2-yl 2-phenylbutanoate **5e** (22 mg, 0.064 mmol) was dissolved in THF (1 mL) and added to the NaHMDS solution at rt. $CuCl_2$ (8 mg, 0.064 mmol) was dissolved in THF (1 mL) and added to the reaction mixture. The reaction was stirred overnight at rt. The next day, aqueous saturated sodium sulfite (14 mL) and EtOAc (6 mL) were added, the layers separated, and the aqueous layer was extracted with EtOAc (3 × 6 mL). The combined organic layers were dried over $MgSO_4$. The crude product was passed through a plug column of silica eluting with ethyl acetate. The product was isolated as a yellow oil (7.6 mg (crude)). NMR analysis of the oil showed no evidence for the desired product.

4.3.5.6 Employing KHMDS, I_2, and TEMPO to form a TEMPO-trapped radical intermediate



The procedure was modified from the method by Studer et al.[121] KHMDS (0.5M in toluene, 0.49 mL, 0.24 mmol) was added to a pre-flame dried round-bottom flask under a N_2 atmosphere. The reaction was carried out at rt. 3-Iodobutan-2-yl 2,2-diphenylacetate **5e** (84.8 mg, 0.24 mmol) was dissolved in THF (1 mL). The reaction was stirred for 1h. Iodine (I_2) (137 mg, 0.54 mmol) was dissolved in THF (1 mL) and added to the reaction. TEMPO (38 mg, 0.25 mmol) was then added to the reaction. The reaction was stirred overnight. The next day, aqueous saturated sodium sulfite solution (14 mL) and EtOAc (6 mL) were added to the reaction, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 6 mL). The combined organic layers were dried over $MgSO_4$. The crude product was isolated as a yellow oil (105 mg (crude)). The ^{13}C NMR spectrum was complex but had the carbonyl and aliphatic peaks corresponding to the acyclic ester. ^{13}C NMR (150 MHz, $CDCl_3$, acyclic ester characteristic peaks) δ 173.3, 173.2, 74.0, 73.7, 54.0, 53.9, 30.0, 29.9, 26.6, 26.4, 24.2, 23.8, 19.1, 18.8, 12.5, 12.4 ppm.

4.3.5.7 Employing KHMDS and TMSCl to form a TMS-trapped enolate intermediate

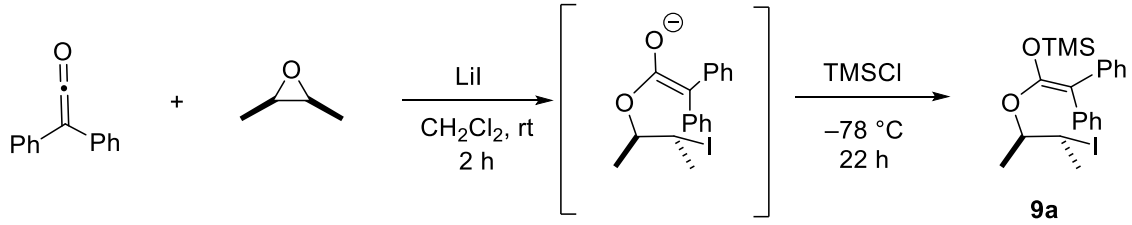


The procedure was modified from the method by Studer et al.[121] 3-Iodobutan-2-yl 2-phenylbutanoate **5e** (73.8 mg, 0.21 mmol) was dissolved in THF (1 mL). KHMDS (0.5M in toluene, 0.42 mL, 0.21 mmol) was added to the ester solution at rt. The reaction was stirred overnight. TMSCl (27.3 μL, 0.21 mmol) was added the next day. The reaction was stirred overnight. The next day aqueous saturated sodium sulfite

solution (14 mL) and EtOAc (6 mL) was added to the reaction, the organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (3 x 6 mL). The combined organic layers were dried over $MgSO_4$. The crude product was passed through a plug column of silica eluting with ethyl acetate. The product was isolated as a pale yellow oil (75.4 mg (crude)). NMR analysis showed no evidence for the desired product. ^{13}C NMR (150 MHz, $CDCl_3$, acyclic ester characteristic peaks) δ 173.3, 173.2, 73.9, 73.7, 53.9, 53.8, 30.0, 29.8, 26.7, 26.5, 24.2,23.8, 19.0, 18.8, 12.4, 12.3 ppm.

4.3.6 TMSCl/TBSCl enolate trapping experiments from reaction of ketenes and epoxides

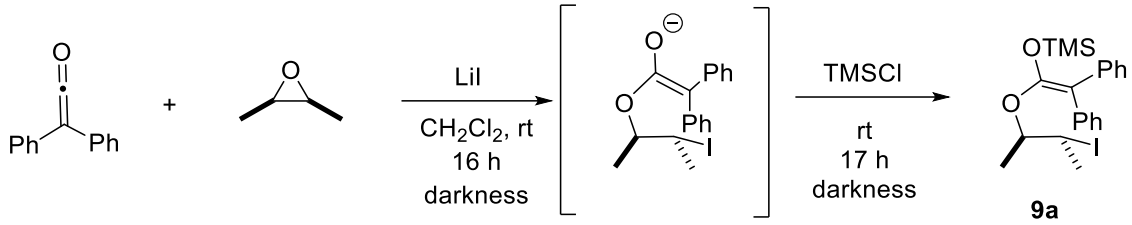
4.3.6.1 Attempted synthesis of **9a** (TMSCl added after 2 h, reaction at −78 °C)



9a

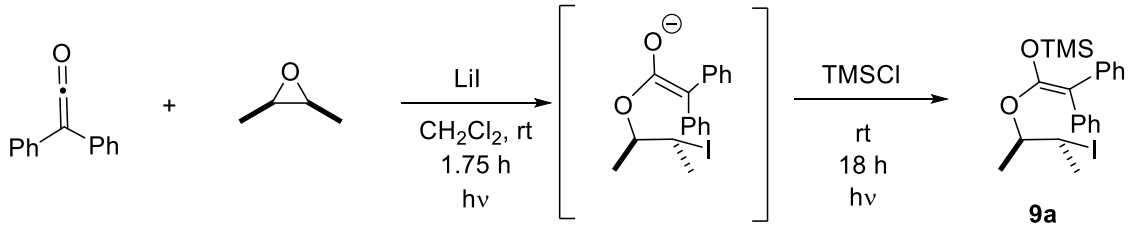
The reaction was carried out according to the general procedure for the synthesis of γ-lactone (Chapter 2) and TMSCl was added to attempt to trap the enolate intermediate this was a modified method from Willard et al.[122] Diphenylketene (69.3 mg, 0.36 mmol) was dissolved in CH_2Cl_2 (1.3 mL). *Cis*-2,3-epoxybutane (31 μL, 0.36 mmol) was added to the ketene solution. LiI (47.8 mg, 0.36 mmol, 1 equiv.) was suspended in CH_2Cl_2 (1.3 mL). The ketene-epoxide reaction solution was added to the LiI mixture. The reaction was stirred for 2h. The reaction was then cooled to −78 °C using a dry ice-acetone bath. TMSCl (67 μL, 0.53 mmol, 1.5 equiv.) was added to the reaction. The reaction was left stirring overnight and allowed to warm up to room temperature. Following standard workup, the crude product was isolated as a brown oil (97 mg, 69% (crude). NMR and GC-MS analysis showed no evidence for the desired product. Acyclic ester **5c** (63%) and carboxylic acid (24%) were observed by GC-MS analysis of the crude. Acyclic ester **5c**: MS (EI 70 eV): 394 (M^+), 266, 194, 77 m/z; Ketene-derived carboxylic acid: 212 (M^+), 194, 167 m/z.

4.3.6.2 Attempted synthesis of **9a** (TMSCl added the following day, reaction carried out in darkness)



The reaction was carried out according to the general procedure for synthesis of γ-lactones (Chapter 2) and TMSCl was added to attempt to trap the enolate intermediate this was a modified method from Willard et al.[122] Diphenylketene (86.9 mg, 0.45 mmol) was dissolved in CH_2Cl_2 (2.5 mL). The reaction was carried out in darkness. *Cis*-2,3-epoxybutane (39 μL, 0.45 mmol) was added. LiI (59.9 mg, 0.45 mmol, 1 equiv.) was suspended in CH_2Cl_2 (2.5 mL). The ketene-epoxide solution was added to the LiI suspension. The reaction was stirred for 16 h. TMSCl (86 μL, 0.68 mmol, 1.5 equiv.) was added at rt. The reaction was left stirring overnight (18 h). The product was isolated as a brown/dark purple oil (113 mg, 64% (crude)). NMR and GC-MS analysis showed no evidence for the desired product. Acyclic ester **5c** (74%) was observed by GC-MS analysis of the crude. Acyclic ester **5c**: MS (EI 70 eV): 394 (M^+), 266, 194, 77 m/z.

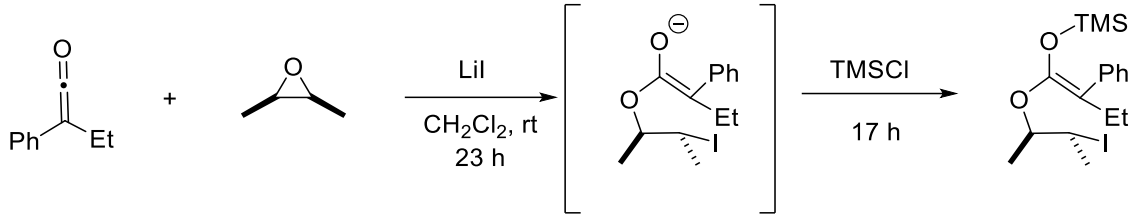
4.3.6.3 Attempted synthesis of **9a** (TMSCl added after 1.75 h, reaction carried out with fume hood light left on overnight)



The reaction was carried out according to the general procedure for synthesis of γ-lactones (Chapter 2) and TMSCl was added to attempt to trap the enolate intermediate this was a modified method from Willard et al.[122] The reaction was carried out and left in a fume hood with the light left on for the duration of the reaction. Diphenylketene (119.2 mg, 0.61 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (2.5 mL). *Cis*-2,3-epoxybutane (54 μL, 0.61mmol, 1 equiv.) was added. LiI (82.1 mg, 0.61 mmol, 1 equiv.) was suspended in CH_2Cl_2 (2.5 mL). The ketene-epoxide

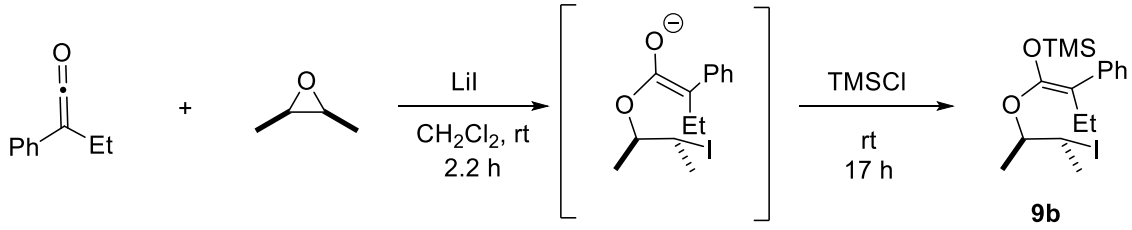
solution was added to the LiI suspension. The reaction was stirred for 1.75 h. TMSCl (117 μL, 0.92 mmol, 1.5 equiv.) was added at rt. The reaction was left stirring overnight (18 h). The crude product was isolated as a brown oil (91 mg, 38% (crude)). NMR and GC-MS analysis showed no evidence for the desired product. Acyclic ester **5c** (44%) was observed by GC-MS analysis of the crude. Acyclic ester **5c**: MS (EI 70 eV): 266, 194, 77 m/z.

4.3.6.4 Attempted synthesis of **9b** (TMSCl added the next day)



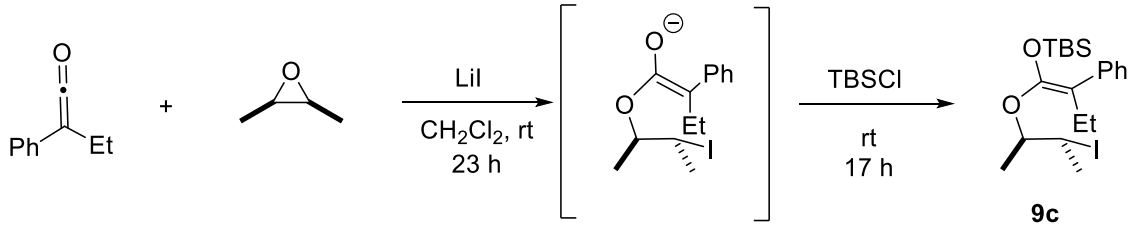
The reaction was carried out according to the general procedure for the synthesis of γ-lactones (Chapter 2) and TMSCl was added to attempt to trap the enolate intermediate this was a modified method from Willard et al.[122] Ethylphenylketene (77.2 mg, 0.53 mmol, 2 equiv.) was added to a pre-flame dried and pre-weighed round-bottom flask under a nitrogen atmosphere. Half the CH_2Cl_2 (2.0 mL) was added to the flask containing the ketene. *Cis*-2,3-epoxybutane (23 μL, 0.26 mmol, 1 equiv.) was added. LiI (45.8 mg, 0.34 mmol, 1.3 equiv.) was added to a second round-bottom flask and suspended in CH_2Cl_2 (2.0 mL). The ketene-epoxide solution was added to the LiI suspension. The reaction flask was covered with aluminium foil and stirred overnight (total reaction time = 23 h). TMSCl (81 μL, 0.64 mmol, 2.2 equiv.) was added to the reaction mixture over 2 min at rt. It was then stirred for 18 h. The reaction was worked up according to the standard work-up. The crude product was isolated as a brown oil (95 mg, >99% (crude)). NMR and GC-MS analysis showed no evidence for the desired product. Acyclic ester **5e** (42%) was observed by GC-MS analysis of the crude. Acyclic ester **5e**: MS (EI 70 eV): 346 (M^+), 219, 183, 119, 91, 77 m/z.

*4.3.6.5 Attempted synthesis of **9b** (TMSCl added after 2.2 h)*



The reaction was carried out according to the general procedure for the synthesis of γ-lactones (Chapter 2) and TMSCl was added to attempt to trap the enolate intermediate this was a modified method from Willard et al.[122] Ethylphenylketene (66.4 mg, 0.46 mmol, 2.0 equiv.) was added to a pre-flame dried and pre-weighed round-bottom flask under a nitrogen atmosphere. Half of the CH_2Cl_2 (1.7 mL) was added to the flask containing the ketene. *Cis*-2,3-epoxybutane (19 μL, 0.22 mmol, 1.0 equiv.) was added to the ketene solution. LiI (38.9 mg, 0.29 mmol, 1.3 equiv.) was added to a second round-bottom flask and suspended in CH_2Cl_2 (1.7 mL). The ketene-epoxide solution was added to the LiI suspension. The reaction flask was covered with aluminium foil and stirred for 2.2 h. TMSCl (70 μL, 0.55 mmol, 2.2 equiv.) was then added to the reaction mixture over 2 min. The reaction was then stirred for 18 h. The reaction was worked up according to the standard work-up. The crude product was isolated as an orange/yellow oil (83.9 mg, >99% (crude)). NMR and GC-MS analysis showed no evidence for the desired product. Acyclic ester **5e** (36%) was observed by GC-MS analysis of the crude. Acyclic ester **5e**: MS (EI 70 eV): 346 (M^+), 219, 183, 119, 91, 77 m/z.

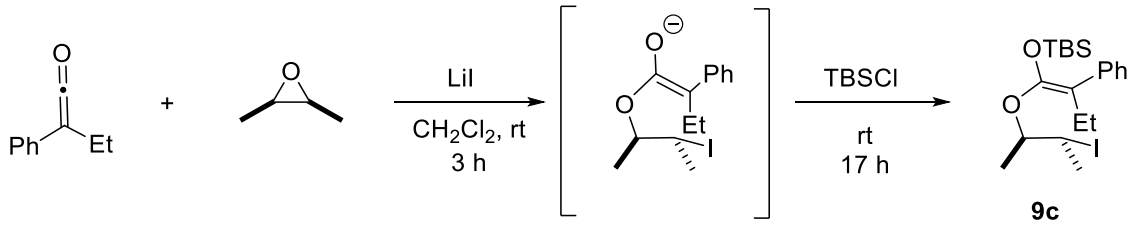
4.3.6.6 Attempted synthesis of **9c** (TBSCl added the following day after reaction began)



The reaction was carried out according to the general procedure for the synthesis of γ-lactones (Chapter 2) and TBSCl was added to attempt to trap the enolate intermediate this was a modified method from Willard et al.[122] Ethylphenylketene (70.9 mg, 0.49 mmol, 2 equiv.) was added to a pre-flame dried and pre-weighed

round-bottom flask under a nitrogen atmosphere. Half of the CH_2Cl_2 (1.8 mL) was added to the flask containing the ketene. *Cis*-2,3-epoxybutane (21 μL, 0.24 mmol, 1.0 equiv.) was added to the ketene solution. LiI (34.9 mg, 0.26 mmol, 1.1 equiv.) was added to a second round-bottom flask and suspended in CH_2Cl_2 (1.8 mL). The ketene-epoxide solution was added to the LiI suspension. The reaction flask was covered with aluminium foil and stirred overnight (total reaction time = 23 h). TBSCl (87.8 mg, 0.64 mmol, 2.2 equiv.) was then dissolved in CH_2Cl_2 (0.5 mL) and added to the reaction mixture over 2 min. The reaction was then stirred for 17 h. The reaction was worked up according to the standard work-up. The crude product was isolated as a brown oil (72 mg, 87% (crude)). NMR and GC-MS analysis showed no evidence for the desired product. Acyclic ester **5e** (56%) was observed by GC-MS analysis of the crude. Acyclic ester **5e**: MS (EI 70 eV): 346 (M^+), 219, 183, 119, 91, 77 m/z.

4.3.6.7 Attempted synthesis of **9c** (TBSCl added in after 3 h)



9c

The reaction was carried out according to the general procedure for the synthesis of γ-lactones (Chapter 2) and TBSCl was added to attempt to trap the enolate intermediate this was a modified method from Willard et al.[122] Ethylphenylketene (72.7 mg, 0.50 mmol, 2 equiv.) was added to a pre-flame dried and pre-weighed round-bottom flask under a nitrogen atmosphere. Half of the CH_2Cl_2 (2.0 mL) was added to the flask containing the ketene. *Cis*-2,3-epoxybutane (23 μL, 0.26 mmol, 1.1 equiv.) was added to the ketene solution. LiI (38.0 mg, 0.28 mmol, 1.1 equiv.) was added to a second round-bottom flask and suspended in CH_2Cl_2 (2.0 mL). The ketene-epoxide solution was added to the LiI suspension. The reaction was stirred for 3 h. TBSCl (96.6 mg, 0.64 mmol, 2.3 equiv.) was then dissolved in CH_2Cl_2 (0.5 mL) and added to the reaction mixture over 2 min. The reaction was then stirred for 17 h. The reaction was worked up according to the standard work-up. The crude product was isolated as a yellow oil (80 mg, 87% (crude)). NMR and GC-MS analysis

showed no evidence for the desired product. Acyclic ester **5e** (50%) was observed by GC-MS analysis of the crude. Acyclic ester **5e**: MS (EI 70 eV): 346 (M^+), 219, 183, 119, 91, 77 m/z.

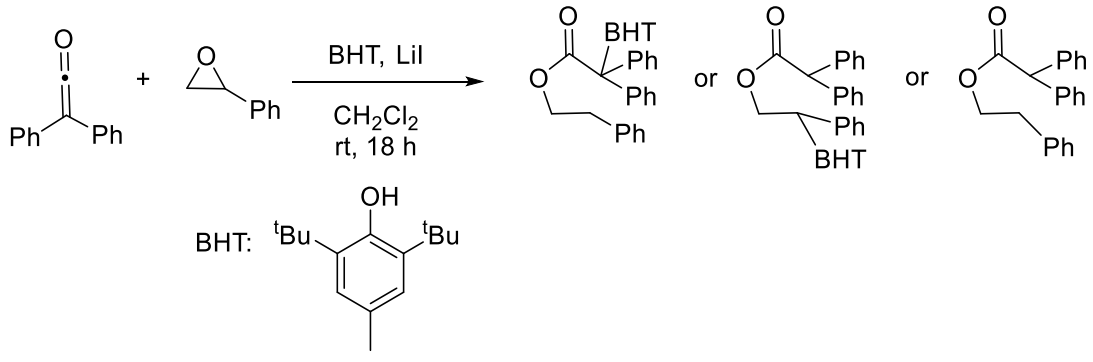
4.3.7 Radical trapping experiments:

4.3.7.1 Attempted radical trapping experiments:

4.3.7.1.1 General reaction conditions for attempting to trap radical intermediate:

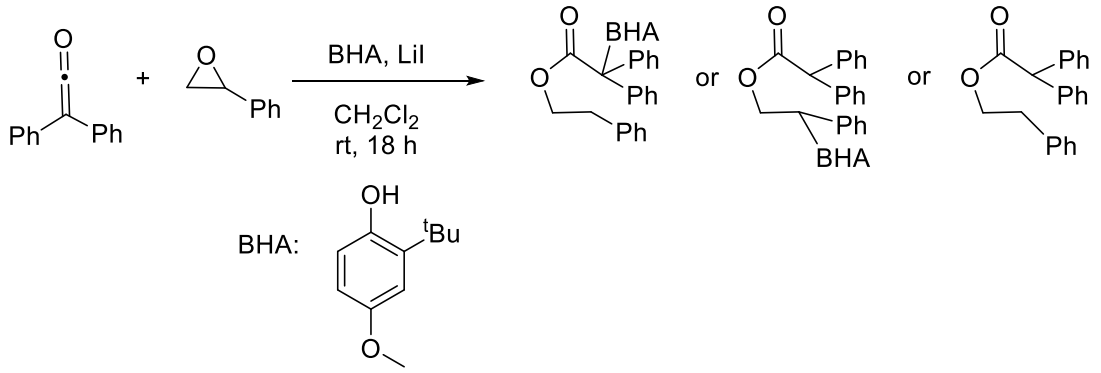
The reaction was carried out according to the general procedure for the synthesis of γ-lactone (Chapter 2), and the radical trapping component was a modified procedure by Argyropoulos et al.[123] Diphenylketene (0.34-0.45 mmol, 2 equiv.) was added to a pre-flame dried, pre-weighed round-bottom flask under inert atmosphere conditions. Half of the volume of dry CH_2Cl_2 (1.4-2.5 mL) was added to the flask containing the ketene. Racemic styrene oxide (0.18-0.22 mmol, 1 equiv.) was added to the ketene-CH_2Cl_2 reaction solution. The radical scavenger/trapping agent (0.54-0.68 mmol, 3.0-3.1 equiv) and LiI (0.19-0.23 mmol, 1-1.1 equiv.) were added to a second pre-flame dried round-bottom flask with a stirring bar. It was placed under vacuum followed by N_2 atmosphere. The remaining volume of CH_2Cl_2 (1.4-2.5 mL) was added to the radical trap-LiI. The ketene-epoxide solution was added to the radical trap-LiI mixture. The reaction flask was covered with aluminium foil and stirred overnight (total reaction time = 18-19 h). The reaction was quenched with cold-deionised water (10 mL) and then extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4. Following filtration of the drying agent, the solvent was removed in vacuo to afford crude product for GC-MS analysis.

4.3.7.1.1.1 Reaction with BHT



The reaction was carried out according to the general method to trap radicals. Diphenylketene (79.4 mg, 0.41 mmol) was dissolved in CH_2Cl_2 (1.5 mL). Racemic styrene oxide (24 μL, 0.21 mmol) was added to the ketene-CH_2Cl_2 solution. BHT (140.3 mg, 0.64 mmol) and LiI (27.5 mg, 0.21 mmol, 1 equiv.) were suspended in CH_2Cl_2 (1.5 mL), and the epoxide-ketene solution was added and stirred for 18h. The crude product was isolated as a white solid (214.8 mg (crude)), and found to be composed of BHT (40%), acyclic ester (9%), γ-lactone (1%) and unknown (49%) by GC-MS analysis. ^{13}C NMR ($CDCl_3$, 150 MHz, acyclic ester characteristic peaks) δ 171.8, 69.4, 57.2, 26.8 ppm; ^{13}C NMR ($CDCl_3$, 150 MHz, BHT) δ 151.7, 34.4, 31.5, 21.4 ppm; BHT: MS (EI 70 eV): 220 (M^+), 205, 177, 57; unknown: MS (EI 70 eV): 220, 194, 91, 77 m/z. .

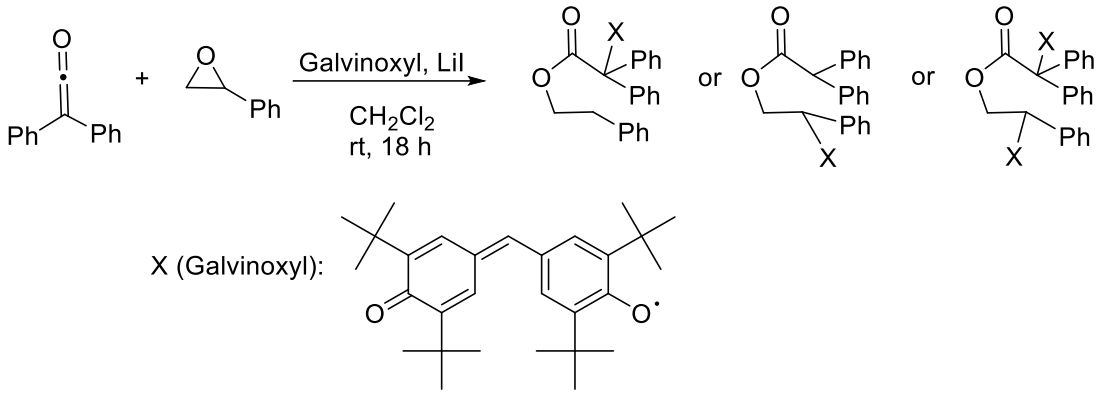
4.3.7.1.1.2 Reaction with BHA



The reaction was carried out according to the general method to trap radicals. Diphenylketene (87.7 mg, 0.45 mmol) was dissolved in CH_2Cl_2 (1.7 mL). Racemic styrene oxide (25 μL, 0.22 mmol) was added to the ketene-CH_2Cl_2 solution. BHA (122.1 mg, 0.68 mmol) and LiI (30.3 mg, 0.23 mmol, 1 equiv.) were suspended in CH_2Cl_2 (1.7 mL). The ketene-epoxide solution was added to the BHT-LiI suspension and stirred for 18 h. The crude product was isolated as a yellow oil (204.5 mg (crude)), and was found to be composed of BHA (31%), unknown (41%), γ-lactone (0.3%) and acyclic ester (8%) by GC-MS analysis.^{13}C NMR ($CDCl_3$, 150 MHz, acyclic ester characteristic peaks) δ 171.8, 69.4, 57.8, 26.7 ppm; ^{13}C NMR ($CDCl_3$, 150 MHz, BHA characteristic peaks) δ 153.4. 148.6, 117.0, 114.3, 110.7, 55.9, 34.9, 29.7 ppm

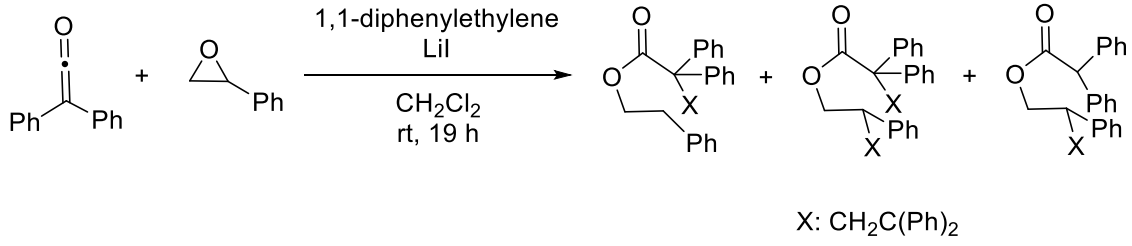
;BHA: MS (EI 70 eV): 180 (M^+), 165, 137 m/z; unknown: MS (EI 70 eV): 315, 180, 91 m/z. ^{13}C NMR analysis confirmed that unknown is not γ-lactone **4a**.

4.3.7.1.1.3 Reaction with Galvinoxyl



The reaction was carried out according to the general method to trap radicals. Diphenylketene (74 mg, 0.38 mmol) was dissolved in CH_2Cl_2 (1.4 mL). Racemic styrene oxide (22 μL, 0.19 mmol) was added to the ketene-CH_2Cl_2 solution. Galvinoxyl (241.4 mg, 0.57 mmol) and LiI (25.7 mg, 0.19 mmol, 1 equiv.) were suspended in CH_2Cl_2 (1.4 mL), and the ketene-epoxide solution was added and the reaction mixture was stirred for 18 h. The crude product was isolated as an orange foam (351 mg (crude)), and was found to be composed of galvinoxyl (61%), unknown (3%), γ-lactone (1%) and acyclic ester (13%) by GC-MS analysis. ^{13}C NMR ($CDCl_3$, 150 MHz, acyclic ester characteristic peaks) δ 171.8, 69.4, 57.2, 26.8 ppm; ^{13}C NMR ($CDCl_3$, 150 MHz, free galvinoxyl characteristic peaks) δ 186.6, 155.7, 149.0, 34.6, 30.5 ppm; free galvinoxyl: MS (EI 70 eV): 422 (M^+), 365, 216 m/z.

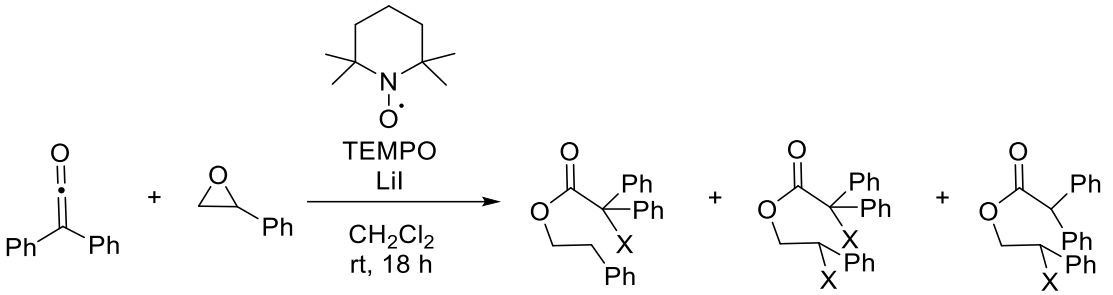
4.3.7.1.1.4 Reaction with 1,1-diphenylethylene



Diphenylketene (83.4 mg, 0.43 mmol) was dissolved in CH_2Cl_2 (1.6 mL). Racemic styrene oxide (25 μL, 0.22 mmol) was added to the ketene-CH_2Cl_2 solution. LiI (30.9 mg, 0.23 mmol) was suspended in CH_2Cl_2 (1.6 mL). 1,1-Diphenylethylene (0.11 mL, 0.64 mmol) was added to the LiI suspension, and finally, the ketene-epoxide

solution was added. The reaction mixture was stirred for 19 h. The crude product was isolated as a yellow oil (244 mg (crude)), and was found to be composed of 1,1-diphenylethylene (60%), γ-lactone (18%) and acyclic ester (4%) by GC-MS analysis. ^{13}C NMR ($CDCl_3$, 150 MHz, γ-lactone characteristic peaks) δ 177.5, 69.9, 62.2, 50.7 ppm; ^{13}C NMR ($CDCl_3$, 150 MHz, 1,1-diphenylethylene characteristic peaks) δ 150.3, 141.7, 114.4 ppm; 1,1-Diphenylethylene: MS (EI 70 eV): 180 (M^+), 165, 152, 89. 77, 51 m/z; γ-lactone: MS (EI 70 eV): 314, 194, 165, 77 m/z.

4.3.7.1.1.5 Reaction with TEMPO



Diphenylketene (66.7 mg, 0.35 mmol) was dissolved in CH_2Cl_2 (2.5 mL). Racemic styrene oxide (20 μL, 0.18 mmol) was added to the ketene-CH_2Cl_2 solution. TEMPO (83.8 mg, 0.54 mmol) and LiI (26.3 mg, 0.20 mmol) were suspended in CH_2Cl_2 (2.5 mL), and the ketene-epoxide solution was added. The reaction mixture was stirred for 18 h. The crude product was isolated as an orange oil (155 mg (crude)), and was found to be composed of TEMPO (39%), Iodohydrin **8a** (23%) as shown in Figure 49 and unknown (32%) by GC-MS analysis.^{13}C NMR ($CDCl_3$, 150 MHz, TEMPO characteristic peaks) δ 60.8, 40.0, 21.0, 17.5 ppm; TEMPO: MS (EI 70 eV): 156 (M^+), 141, 81 m/z; Iodohydrin **8a/8b**: (EI 70 eV): 248 (M^+), 121, 91 m/z.

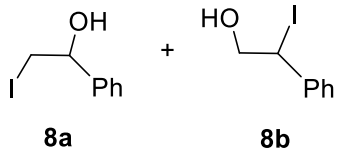
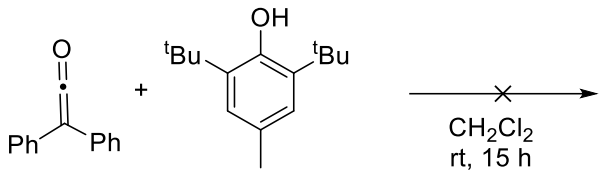


*Figure 49: Structure of Iodohydrin **8a/8b***

4.3.7.2 Control reactions for radical scavengers/ trapping experiments

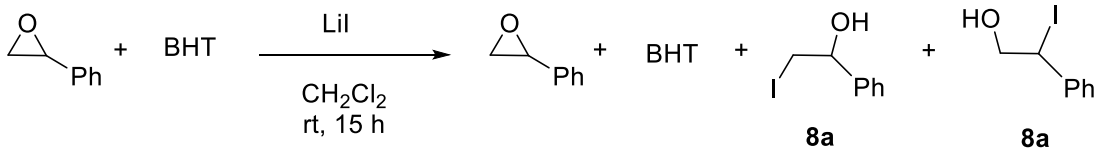
4.3.7.2.1 BHT and diphenylketene:



BHT

Diphenylketene (66.3 mg, 0.34 mmol, 2 equiv.) was added to a pre-flame dried, pre-weighed round-bottom flask under inert atmosphere conditions. Half the volume of dry CH_2Cl_2 (1.3 mL) was added to the ketene. BHT (122.6 mg, 0.56 mmol, 3.3 equiv.) was added to a second pre-flame dried round-bottom flask with a stirring bar. It was placed under vacuum followed by N_2. The remaining volume of CH_2Cl_2 (1.3 mL) was added to the BHT. The ketene-CH_2Cl_2 solution was added to the BHT-CH_2Cl_2 reaction solution. The reaction flask was covered with aluminium foil, and allowed to stir overnight (total reaction time = 15 h). The reaction was quenched with cold-deionised water (10 mL) and then extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4. The crude product was isolated as a yellow gel and was found to be composed of diphenylketene (28%) and BHT (72%) by GC-MS analysis. Diphenylketene: MS (EI 70 eV): 194 (M^+), 165 m/z; BHT: MS (EI 70 eV): 220 (M^+) , 205, 177, 57.

4.3.7.2.2 BHT, LiI and racemic styrene oxide

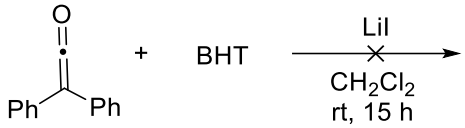


8a **8a**

BHT (292.5 mg, 1.33 mmol, 3.0 equiv.) and LiI (62.8 mg, 0.47 mmol, 1.1 equiv.) were added to a pre-flame dried round-bottom flask with a stirring bar. It was placed under vacuum followed by N_2 atmosphere. Dry CH_2Cl_2 (6.4 mL) was added to the BHT-LiI mixture. The mixture was stirred. Racemic styrene oxide (50 μL, 0.44 mmol, 1 equiv.) was added to the BHT-LiI reaction mixture. The reaction flask was covered with aluminium foil, and allowed to stir overnight (total reaction time = 15 h). The reaction was quenched with cold-deionised water (10 mL) and then extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4. The crude

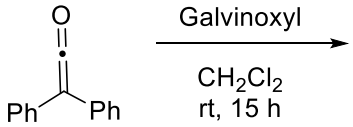
product was isolated as a white solid and was found to be composed of BHT (86%), styrene oxide (2%) and iodohydrin **8a** (4%) by GC-MS analysis. BHT: MS (EI 70 eV): 220 (M^+), 205, 177, 57 m/z; styrene oxide MS (EI 70 eV): 120 (M^+), 91; iodohydrin **8a**: (EI 70 eV): 248 (M^+), 121, 91 m/z.

4.3.7.2.3 BHT, LiI and diphenylketene



Diphenylketene (95.8 mg, 0.49 mmol, 2 equiv.) was added to a pre-flame dried, pre-weighed round-bottom flask under inert atmosphere conditions. Half of the volume of dry CH_2Cl_2 (1.8 mL) was added to the flask containing the ketene. In a second round-bottom flask, BHT (188.4 mg, 0.86 mmol, 3.2 equiv.) and LiI (35.8 mg, 0.27 mmol, 1.1 equiv.) were added to a second pre-flame dried round-bottom flask with a stirring bar. It was placed under vacuum followed by N_2 atmosphere. The remaining volume of CH_2Cl_2 (1.8 mL) was added to the BHT-LiI mixture. The ketene-CH_2Cl_2 solution was added to the BHT-LiI mixture. The reaction flask was covered with aluminium foil, and allowed to stir overnight (total reaction time = 15 h). The reaction was quenched with cold-deionised water (10 mL) and then extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4. The crude product was isolated as a yellow gel and was found to be composed of BHT (70%) and diphenylketene (30%) by GC-MS analysis. Diphenylketene: MS (EI 70 eV): 194 (M^+),165 m/z; BHT: MS (EI 70 eV): 220 (M^+), 205, 177, 57 m/z.

4.3.7.2.4 Galvinoxyl and diphenylketene control



Diphenylketene (75 mg, 0.39 mmol, 2 equiv.) was added to a pre-flame dried, pre-weighed round-bottom flask under inert atmosphere conditions. Half the volume of dry CH_2Cl_2 (1.4 mL) was added to the flask containing the ketene. In a second round-bottom flask, free galvinoxyl (247.6 mg, 0.59 mmol, 3.0 equiv) was added to a second pre-flame dried round-bottom flask with a stirring bar. It was placed under vacuum followed by a N_2 atmosphere. The remaining volume of CH_2Cl_2 (1.4 mL) was

added to the galvinoxyl. The ketene solution was added to the galvinoxyl solution. The reaction flask was covered with aluminium foil and stirred overnight (total reaction time = 15 h). The reaction was quenched with cold-deionised water (10 mL) and then extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4. The crude product was isolated as an orange foam (342 mg (crude)) and was found to be composed of galvinoxyl (44%), ketene (11%) and an unknown (26%) by GC-MS analysis. Galvinoxyl: MS (EI 70 eV): 422 (M^+), 365, 216 m/z; unknown: 348, 194, 165, 91, 77 m/z.

Chapter 5: Mechanistic studies of the catalytic formal [3 + 2] cycloaddition reaction: Results and Discussion

5.1 Introduction:

In this chapter mechanistic studies of the formal [3 + 2]-cycloaddition of epoxides with ketenes were studied. The mechanistic studies were conducted by introducing radical-trapping and radical scavenger agents into the reaction to determine whether the reaction proceeded via a typical S_N2 mechanism for the cyclisation step or involved a single electron transfer (SET) step preceding cyclisation. The most likely mechanism is discussed based on the outcome of these radical trapping/scavenging experiments and other observations.

A second objective of this chapter was to investigate the feasibility of generating an α-radical-TEMPO derivative or lactone from acyclic ester products.

5.2 Mechanism studies:

5.2.1 Mechanisms of the [3 + 2] cycloaddition reaction of epoxides and ketenes.

An S_N2 reaction that occurs on a primary alkyl iodide generally proceeds more quickly than on a secondary alkyl iodide.[124] The reason a primary carbon centre is better for an S_N2 reaction is that an S_N2 reaction occurs by backside attack, and there is less steric hindrance compared to when the electrophilic carbon is disubstituted. Two products whose structure can be compared to gain mechanistic insight are **4a** and **5a**, formed from the reaction of diphenylketene with racemic styrene oxide and with benzyl glycidyl ether respectively. The 3,4-regioselectivity in lactone formation suggests that the racemic styrene oxide is opened at the more substituted carbon, forming a secondary benzylic iodide as shown in Figure 50. In comparison, when benzyl glycidyl ether is used in the reaction, the epoxide opens at the less sterically hindered side, forming a primary alkyl iodide at the terminal carbon. If the cyclisation step involved a true S_N2 reaction, it would be predicted that the enolate intermediate derived from the benzyl glycidyl ether substrate would

be more likely to cyclise to form the desired lactone product (Figure 50). This does not occur; instead, the γ-lactone is formed when the terminal carbon is a secondary benzylic iodide. These results raise the question of whether the cyclisation step proceeds via a pure S_N2 mechanism or via a SET mechanism.

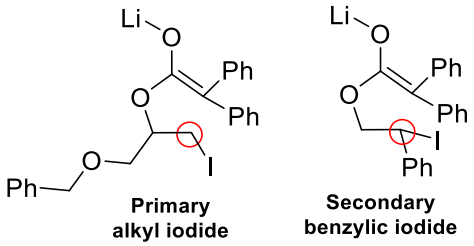


Figure 50: Structures of the primary alkyl iodide and the secondary benzylic iodide intermediates.

As detailed in Chapter 2 Experimental, the enantiomeric excess of the γ-lactone product **4b** derived from enantioenriched styrene oxide (95% ee) and diphenylketene was significantly decreased (to 84% ee). This indicates that the cyclisation step is not a true S_N2 reaction, as the enantiomeric excess of the epoxide should be translated to the product if it proceeded via a pure S_N2 cyclisation mechanism. This suggests that another reaction mechanism may be operative. In a SET reaction step, racemisation can occur due to planarisation of the sp^2 hybridised radical carbon centre. The erosion of enantiomeric excess of the product may be a result of a SET mechanistic step occurring prior to cyclisation. Alternatively, loss of stereochemical integrity may occur at the epoxide ring-opening stage if the benzylic iodide (of the iodoalkoxide) that results undergoes racemisation (e.g., via reversible carbocation/radical formation). However, further studies need to be carried out to determine if enantiopurity is lost in the very first step (epoxide ring-opening) or in a later step.

5.2.2 Proposed mechanism for the [3 + 2] cycloaddition of epoxides and ketenes.

There are two proposed reaction mechanisms, one involving an S_N2 cyclisation step and another involving a SET step prior to cyclisation. Both pathways follow the same reaction mechanism until the cyclisation step. Intermediate **A** (an iodoalkoxide) is formed by the attack of the catalyst LiI on the epoxide. The lithium cation in the catalyst coordinates to the oxygen atom of the epoxide, as the oxygen is electron-

rich. Li^+, which coordinates to the oxygen, polarises the C-O bond, making the carbon end of the bond more electrophilic. This makes the epoxide more susceptible to nucleophilic attack. The iodide in the catalyst acts as the nucleophile and attacks the epoxide at the carbon adjacent to the oxygen. The resulting lithium iodoalkoxide **A** then acts as a nucleophile, attacking the electrophilic carbonyl carbon of the ketene to form an enolate intermediate **B**. If the ketene is unsymmetrical, it is expected that the iodoalkoxide would add to the ketene from the less sterically hindered side (not an issue with diphenylketene) to generate the ester enolate **B** stereoselectively.[125] As mentioned previously, where the epoxide has an aryl or vinyl substituent, regioselectivity in epoxide ring-opening, involving iodide attack on the more substituted epoxide carbon, leads to formation of the 3,4-substituted lactone product **4**. The scheme is shown in Figure 51.

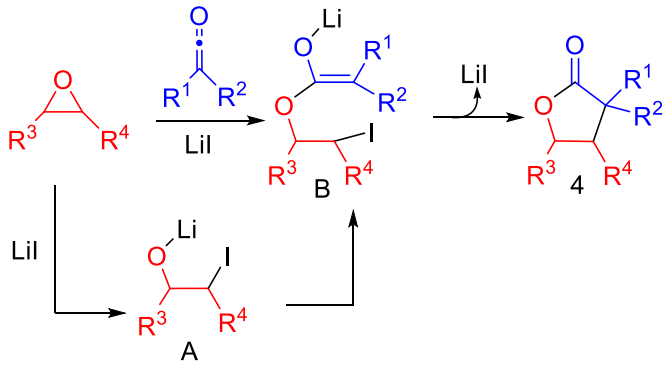


Figure 51: Proposed reaction mechanism of epoxide and ketene

5.2.2.1 [3 + 2] cycloaddition involving an S_N2 cyclisation step

For an S_N2 reaction to occur, there must be a nucleophile and a good leaving group. The nucleophile attacks the electrophilic carbon bearing the leaving group from the backside. This results in the formation of the cyclised product in a single concerted step. An S_N2 reaction involves inversion of stereochemistry at the carbon bearing the halide leaving group, but the enantiopurity of the starting material is retained and faithfully translated to the product. This is a very important feature in helping to determine if a reaction occurs via an S_N2 ring-closing mechanism or not. The proposed S_N2 mechanism for the cyclisation of the enolate intermediate **B** in Figure 52 is described. The iodo alkoxide cyclises via an S_N2 intramolecular cyclisation, forming the five-membered ring, the γ-lactone **4**. This involves an 5-enolendo-exotet

cyclisation, a cyclisation that is notably disfavoured by Baldwin's rules.[49] In this intramolecular cyclisation, the carbon of the enolate acts as the nucleophile attacking the carbon-iodide bond. The polarisation of the carbon-iodide bond makes the carbon electrophilic and hence susceptible to nucleophilic attack. In the mechanism, the enolate attacks the carbon of the C-I bond, forming a new C-C bond and displacing the iodide, forming the product shown as **4** (mainly observed as the 3,4-isomer in these studies). Alternatively, if cyclisation does not proceed effectively, the enolate **B** can potentially abstract a proton from solvent, reactants or quenching agent, producing the acyclic ester product labelled **5** in Figure 52.

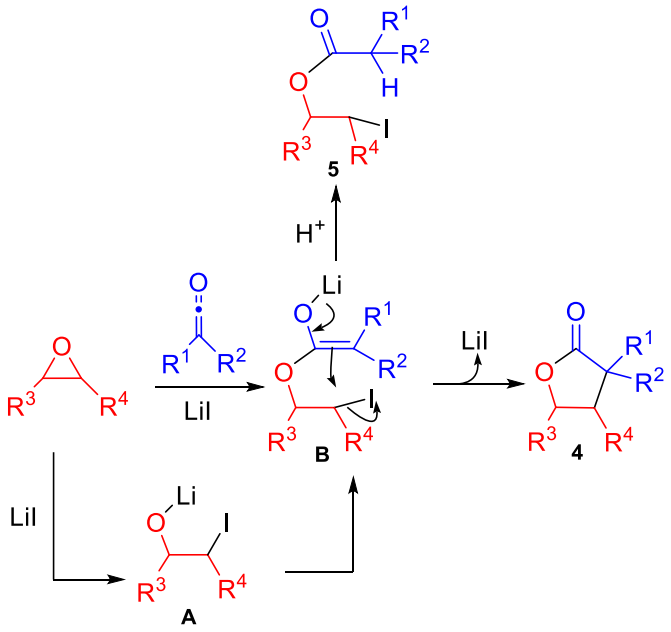


Figure 52: Proposed reaction mechanism 1, with S_N2 for the cyclisation step.

5.2.2.2 [3 + 2] cycloaddition involving a SET step

The alternative pathway involves a SET step, which refers to a single-electron transfer rather than a two-electron process, ultimately leading to the cyclised product. There is precedent in the work of Ashby et al. for the reaction of alkyl iodides with ketone lithium enolates via SET rather than S_N2.[123] The SET pathway generates radical intermediates that can potentially undergo racemisation if long-lived, leading to a loss of enantiopurity. Therefore, reduced enantiopurity is expected to be characteristic of a SET-involved mechanism. The SET-involved reaction mechanism is the second proposed pathway for the cyclisation of the enolate intermediate to form the γ-lactone, as shown in Figure 53. The electron-rich

enolate undergoes SET to the C-I bond in **B**. The donation of an electron causes homolytic cleavage of the C-I bond, generating iodide and a diradical intermediate **C**. Intramolecular radical cyclisation (radical recombination) between the benzylic carbon radical and the radical on the α-carbon in **C** forms the new C-C bond, as part of the cyclised product **4**.

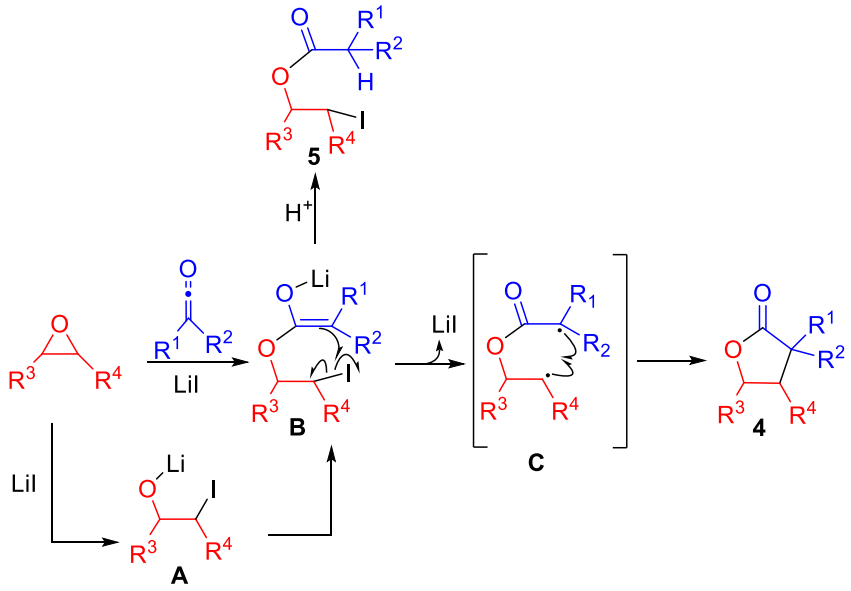


Figure 53: Proposed reaction mechanism 2, with SET step preceding cyclisation.

As seen previously in Table 26 (Chapter 3), the γ-lactone product is formed when the substituents are aromatic. The aromatic substituent (R^4 in **C**) on the benzylic carbon stabilises the radical generated following homolytic cleavage of the C-I bond in **B**. Vinyl and ester substituents at this position can also stabilise the radical. In addition, in these examples, diphenylketene is used; the α-carbon of the enolate bears two phenyl substituents (R^1 = R^2 = Ph in **C**). These phenyl groups further stabilise the radical formed by SET oxidation of the enolate, and make the parent enolate particularly prone to oxidation (giving up an electron). The diradical intermediate **C** is resonance-stabilised, but the close proximity of the two radical centres enables intramolecular radical-radical coupling to form the γ-lactone product **4**.

In contrast, the acyclic ester products shown in Table 28 are often formed from ethylphenylketene, where there is one fewer phenyl substituent on the α-carbon (R^1 = Ph, R^2 = Et in **B**). This reduced stabilisation stops SET from occurring, making

intramolecular cyclisation less favourable and promoting the formation of the acyclic ester product (from protonation of **B**) instead. Furthermore, when the R^4 substituent (in **B**) is a methyl group, the potentially formed alkyl radical is significantly less stable than a benzylic radical, and therefore, there is a higher energy barrier to its formation through SET.

5.3 Ring opening of epoxide

The first step in the proposed reaction mechanism for lactone formation was explored as detailed. In the γ-lactone forming reaction, lithium iodide (LiI) is the catalyst used to promote the reaction. Li^+ can act as a Lewis acid, and therefore, an electron acceptor. The oxygen in the epoxide has two lone pairs and acts as a Lewis base, attracting the Lewis acid. The lithium ion coordinates to the oxygen via its lone pairs, making the C-O bonds in the epoxide more polarised by pulling electron density from the oxygen atom. This increases the electrophilicity of the carbons in the epoxide ring, increasing the partial positive charge on those carbons, and hence the ring carbons are more susceptible to nucleophilic attack. The iodide in the LiI catalyst acts as the nucleophile in the reaction and attacks the epoxide, and the epoxide ring opens as shown in Figure 54.

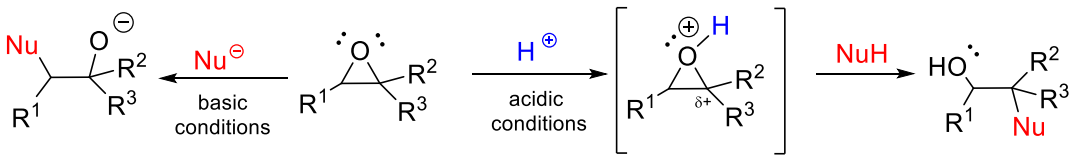


Figure 54: Regioselectivity in the attack of the nucleophile on the epoxide under acidic and basic conditions.

As shown above, the predicted ring opening of the epoxide is on the less substituted carbon of the epoxide.[6,7] The conditions of this reaction are overall neutral, and in the absence of a Lewis acid, it would be expected to follow the regioselectivity of basic conditions shown in Figure 54. However, the involvement of Li ion as a Lewis acid in combination with an aryl substituent on the epoxide can alter regioselectivity due to the transition state having some S_N1 character.

According to GC-MS of the crude sample of the opening of racemic styrene oxide with LiI, the peak area of the ring-opened epoxide was 27% of the crude product, and there was 52% of another unknown compound present in the sample. The NMR

data suggest that the major product **8a** results from epoxide opening at the less-substituted side, as shown in Figure 55. However, a carbonyl peak is present in the ^{13}C NMR spectrum. The 2-iodo-ring opened epoxide is not very stable and can undergo further reactions or decomposition, forming a carbonyl byproduct, as observed in the crude ^{13}C NMR spectrum. The byproduct shown in the GC-MS spectrum, accounting for 52% of the crude product's peak area, could be an aldehyde decomposition product of the ring-opened epoxide. Regioselectivity for ring-opening at the less-substituted end of styrene oxide was observed. However, formation of a significant unknown byproduct, which we surmise could arise from ring-opening occurring at the more sterically hindered end of the epoxide, hinders the accurate determination of regioselectivity in ring-opening. Further studies would be needed to quantitatively measure this.

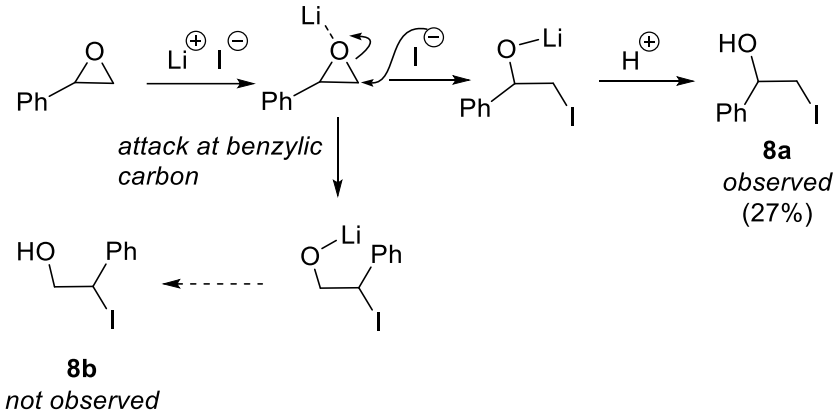


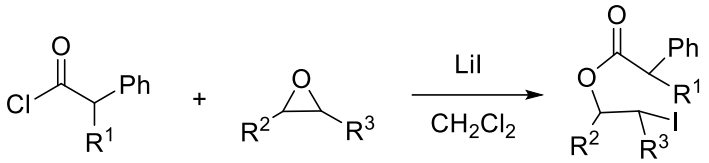
*Figure 55: 2-iodo-1-phenylethan-1-ol product **8a** formed from the ring-opening of racemic styrene oxide with LiI.*

5.4 Substrate scope of LiI-promoted reaction of epoxides with acyl chlorides

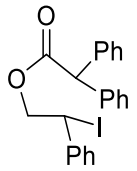
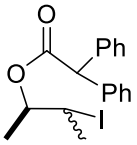
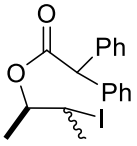
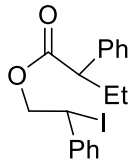
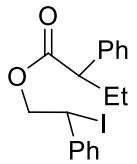
A series of acyclic ester products were prepared through the LiI-promoted reaction of various epoxides with diphenylacetyl chloride and 2-phenylbutyryl chloride. The acyclic esters were needed as starting materials to test cyclisation reaction strategies involving enolate and radical intermediates. The scope of the study is shown in Table 29. In general, the acyclic ester product was formed as the major product in these reactions (Tables 29-32). The products in this section were analysed via GC-MS and ^{13}C NMR. These products were not purified as the crude product provided the information required. In this section a range of epoxides that

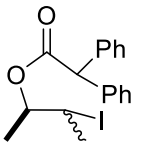
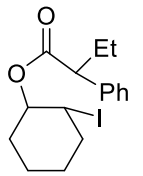
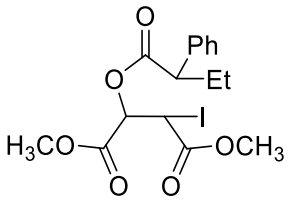
were previously reacted with ketene in section 2.5.1 were instead reacted with diphenylacetyl chloride or 2-phenylbutyryl chloride. Two of the products **5c** and **5e** formed the same product as section 2.5.1 . Therefore, the data in section 2.5.1 were used to confirm the formation of these products. The other products formed in this section were characterised by GC-MS analysis using the MS fragmentation pattern and further collaborated by ^{13}C NMR analysis. ^{13}C NMR was used to identify the carbonyl and alkyl peaks in the acyclic ester product. These peaks, along with GC-MS were used to confirm the formation of the acyclic ester product.

Table 29: Scope of the LiI-promoted reaction of acyl chlorides with epoxides.



R^1 = Ph, Et

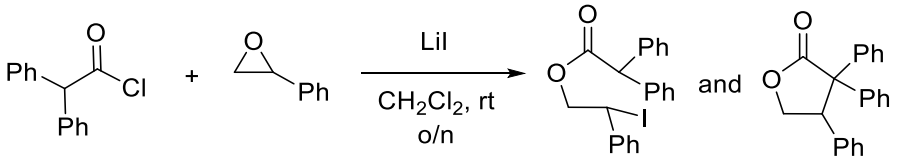
Reference compound number	Compound structure	Solvent	Crude GC-MS peak area (%)
5q		CH_2Cl_2	43
5c + 5cc		CH_2Cl_2	72
5c + 5cc		THF	41
5r		CH_2Cl_2	62
5r		Toluene	48

5e		CH_2Cl_2	86
5f		CH_2Cl_2	60
5s		CH_2Cl_2	74

[a] % peak area determined by GC-MS analysis of crude product.

The product profile of the styrene oxide-diphenylacetyl chloride reaction is shown in Table 30.

Table 30: Products formed from from LiI-promoted reaction of diphenylacteyl chloride with racemic styrene oxide.



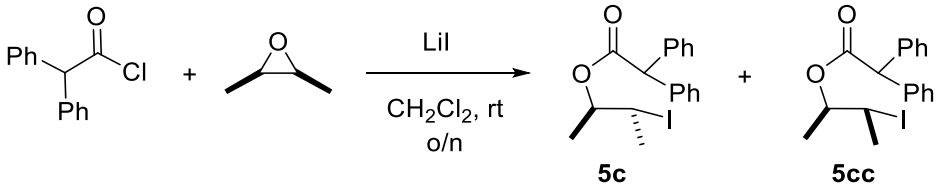
Compound	Peak area (%)[a]
Diphenylketene	8
Diphenylacetyl chloride	29
γ-lactone	2
Acyclic ester product	43

[a] % peak area determined by GC-MS analysis of crude product.

2-Iodo-2-phenylethyl 2,2-diphenylacetate **5q** was formed as the major product through the reaction of diphenylacetyl chloride with styrene oxide. The peak area corresponding to the acyclic ester product **5q** was 43% of the total peak area of the crude product. According to GC-MS analysis, a peak with 314 m/z and a peak area of 2% was observed, which corresponds to lactone **4a**, but the characteristic peaks of the lactone were not present in the NMR spectrum. However, the peaks not showing in the ^{13}C NMR could be due to the low concentration of the sample. The peaks reported in the experimental section correspond to the carbonul and alkyl peaks of the acyclic ester product **5q**. Diphenylketene (8%) was also present in the

crude GC-MS sample. This indicated that there must be a base present that is deprotonating the α-proton of the acyclic ester product and the α-proton of the acetyl chloride. The deprotonation of these two products potentially forms the ketene and the γ-lactone products. Ring-opening of the epoxide with LiI forms an alkoxide intermediate, which then generally attacks the electrophilic carbon of the acetyl chloride. The alkoxide intermediate can also act as a base, causing deprotonation of the α-positions in the acyl chloride and acyclic ester product.

Table 31: Effect of the solvent on the formation of 3-iodobutan-2-yl 2,2-diphenylacetate ***5c***.



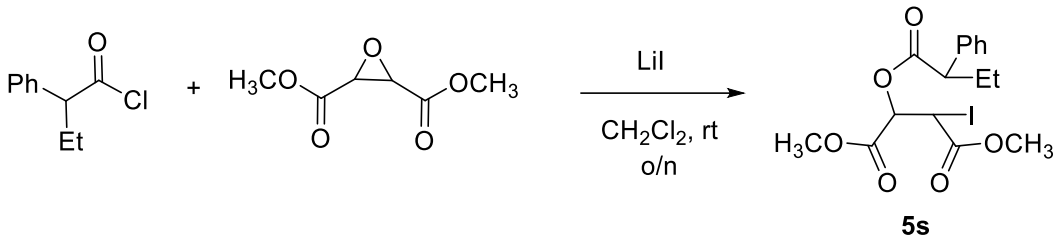
5c **5cc**

Compound	Solvent	Peak area of one diastereomer (%)	Peak area of second diastereomer (%)[a]
5c/5cc	CH_2Cl_2	32	39
5c/5cc	THF	26	15

[a] % peak area determined by GC-MS analysis of crude product.

The compounds synthesised from diphenylacetyl chloride and *cis*-2,3-epoxybutane, using two different solvents, were investigated. The 3-iodobutan-2-yl 2,2-diphenylacetate compounds formed as major products, and the GC-MS and NMR of each compound were analysed. The NMR peaks of these compounds corresponded to ^{13}C NMR peaks of the acyclic ester product synthesised from diphenylketene and *cis*-2,3-epoxybutane (section 2.5.1.18). The GC-MS analysis showed that in each solvent, the major product **5**, consisted of diastereomers. Using CH_2Cl_2 as solvent in one reaction, the ratio of diastereomers was 1:1.2; using THF as solvent in another reaction, the ratio of the diastereomers was 1.7:1. The overall peak area of **5c**/**5cc**, synthesised using CH_2Cl_2 as the solvent, was 72% in comparison to 41% with THF. Therefore, CH_2Cl_2 is a better solvent for the formation of this product.

*Table 32: Effect of time on the formation of the acyclic ester product **5s** from 2-phenylbutyryl chloride and (2R,3S)-dimethyl oxirane-2,3-dicarboxylate.*



5s

Entry	Reaction time	Peak area of acyclic ester product 5s (%)[a]
1	1 day	61
2	2 days	69
3	1 week	74

[a] % peak area determined by GC-MS analysis of crude product.

As shown above, when the reaction was left on for a week, the peak area of the two diastereomers together was slightly more than when the reaction was left on for 1 or 2 days.

The product **5e** was also prepared on a larger scale. When the scale of the reaction was increased to 2.62 mmol of the 2-phenylbutryl chloride from 0.72 mmol, the product **5e** was formed with a peak area of 83%. The structure of the compound is shown in Figure 56. This indicated that scaling up the reaction had no significant detrimental effect. In the smaller-scale reaction, the peak area corresponding to the acyclic product (**5e**) was 86% in comparison to 83% when the scale of the reaction was increased.

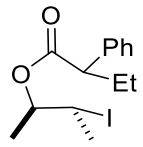


Figure 56: Structure of compound 5e.

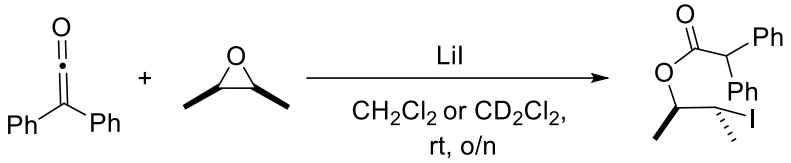
5.5 Quenching reaction results

The impact of the type of water used to quench the reaction during aqueous work-up was investigated. Deionised water was used for the quenching of one experiment, while deuterated water (D_2O) was used for quenching another. The yields of the product **5c** were similar regardless of quenching solvent, 47% with H_2O quench and 49% with D_2O quench. The peak areas of the two crude products were found to differ by 10%. The peak area of **5c** for H_2O-quench crude was 75%, while the peak area of **5c** for D_2O-quench crude was 65%. Most significantly, GC-MS and NMR analysis revealed that there was no evidence for incorporation of deuterium in **5c**. Therefore, the acyclic ester product **5c** is formed through protonation of an enolate intermediate or H-atom transfer from a source other than the solvents used for quenching the reaction and during the aqueous work-up. Attempted enolate trapping experiments with TMSCl/TBSCl, to be discussed later, further corroborated this observation.

5.6 Effect of the CH_2Cl_2 used in the reaction

Changing the solvent used in the formation of **5c** from CH_2Cl_2 dried over calcium hydride to CD_2Cl_2 affected the reaction. While the other reaction conditions were kept constant, the only aspect that was varied in the reaction was the solvent. As shown in Table 33, the peak area of the acyclic ester product decreased when CH_2Cl_2 was replaced with CD_2Cl_2. This suggests that the formation of the acyclic ester product **5c** could depend on the solvent. If the proton on the α-carbon of **5c** was from the solvent (CH_2Cl_2), then when deuterated solvent (CD_2Cl_2) was used, a deuterium would be expected to be transferred to the α-carbon. However, the α-proton was still observed as a singlet in the ^{1}H NMR spectrum of **5c** formed in CD_2Cl_2. The relative integration of the singlet also remained the same even when the solvent was changed to CD_2Cl_2. Therefore, formation of the acyclic ester product may be affected by the solvent (as seen before in Chapter 3), but there is likely a hydrogen atom/H^+ source other than the solvent.

*Table 33: Effect of the solvent on the peak area of the acyclic ester **5c** formed in the reaction.*



Solvent	Acyclic ester product 5c (%)[a]
CH_2Cl_2	73
CD_2Cl_2	14

[a] % peak area determined by GC-MS analysis of crude product.

5.7 Attempted formation of enolate/radical intermediate from acyclic esters

The results of these reactions are shown in Table 34 . For entry 1, the base was KHMDS (potassium bis(trimethylsilyl)amide). The base was added to deprotonate the α-proton and generate the enolate intermediate. TEMPO was added before the oxidising agent (ferrocenium hexafluorophosphate), to trap any radicals formed that may be generated with the addition of the oxidising agent. The oxidising agent was added to promote the formation of a radical at the α-carbon. If the radical was formed and TEMPO was present to trap the radical, an absence of the original carbonyl group would be expected in the ^{13}C NMR spectrum of the crude product. However, in this reaction, the carbonyl peak characteristic of the acyclic ester product was present. This implies that no radical was trapped. One explanation is that the base did not effectively deprotonate the α-proton, preventing enolate formation or causing elimination of the iodide. However, TEMPO may have been sterically bulky enough to prevent trapping the radical at the α-carbon. The radical generated in the reaction may instead have abstracted a hydrogen atom from a reactant (or become further oxidised) to ultimately reform the acyclic ester starting material. The α-proton signal present in the ^{1}H NMR spectrum of the crude provides evidence that the trapped enolate was not formed, and either the proton was never abstracted, or the acyclic ester was regenerated. The characteristic peaks of the acyclic ester products were also observed in the ^{13}C NMR spectrum.

In entry 2, The base was changed to NaHMDS, the oxidising agent to I_2, and TMSCl was added at the end of the reaction to trap any enolate that may be formed. The

^{13}C NMR spectrum was complex, and the peaks were quite broad. A weak carbonyl peak was detected, corresponding to the acyclic ester. This indicated that the enolate was not trapped. In another reaction (entry 3), the oxidising agent was changed to ferrocenium hexafluorophosphate, but all other conditions remained the same. The ^{13}C NMR spectrum of the crude product displayed weak aromatic signals and a signal at 68.6 ppm. The absence of characteristic aliphatic peaks suggests that the reaction did not occur, or decomposition of the desired product may have occurred. The signals expected for the trapped enolate, acyclic ester or γ-lactone were not present.

In entry 4, LDA was used as the base to deprotonate 3-Iodobutan-2-yl 2-phenylbutanoate **5e**, and $CuCl_2$ was employed as the oxidising agent to generate the radical at the α-carbon. The predicted carbonyl signal for the γ-lactone was not present in the ^{13}C NMR spectrum of the crude, but the peaks characteristic of the acyclic ester starting material **5e** were present. This indicated that no significant reaction had occurred.

For entry 5, the base was changed back to NaHMDS, but the oxidising reagent ($CuCl_2$) was kept the same as entry 4. For this reaction, the work-up involved the crude being passed through a plug column of silica. The crude product may have degraded on the column as the carbonyl peak in the acyclic ester (**5e**) was not present, and there was no evidence of the cyclic product that should have formed in this reaction.

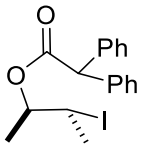
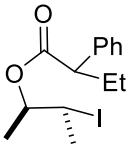
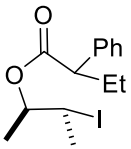
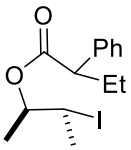
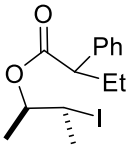
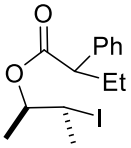
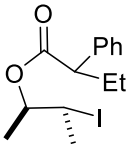
In entry 6, the reaction did not form the desired TEMPO-trapped α-carbon radical product. The ^{13}C NMR spectrum of the crude product was complex. After the crude product was purified, only the acyclic ester **5e** was obtained. This method was not effective at trapping the expected radical.

The final entry (entry 7) in Table 34, the base (KHMDS) was added as described above, but no oxidising agent was added. TMSCl was added to trap the enolate intermediate. Therefore, in the ^{13}C NMR spectrum of the crude product, the absence of the carbonyl signal would be expected. However, the carbonyl peak of the acyclic

ester **5e** was detected, and so the enolate was not successfully generated or was not successfully trapped under these conditions.

Therefore, in conclusion, enolate trapping and radical trapping under a variety of reaction conditions were unsuccessful.

Table 34: Attempted formation of enolate and trapping of the enolate or α-radical.

Entry	Acyclic ester starting material	Base	Oxidising agent	Other	Comment
1		KHMDS	$FcPF_6$ [a]	TEMPO	No trapping of the radical.
2		NaHMDS	I_2	TMSCl	Acyclic ester carbonyl present.
3		NaHMDS	$FcPF_6$ [a]	TMSCl	No product formed.
4		LDA	$CuCl_2$	-	Acyclic ester carbonyl present – no carbonyl corresponding to γ-lactone.
5		NaHMDS	$CuCl_2$		Carbonyl and aliphatic peaks corresponding to acyclic ester not present
6		KHMDS	I_2	TEMPO	Acyclic ester present- the radical was not trapped
7		KHMDS	-	TMSCl	Acyclic ester present- enolate not trapped

[a] $FcPF_6$ = ferrocenium hexafluorophosphate

5.8 TMSCl/ TBSCl enolate trapping experiments

A series of experiments were carried out to attempt to trap an in situ-generated acyclic ester enolate intermediate with a silylating agent (TMSCl or TBSCl). It was planned that the resulting silyl ketene acetals would be studied under various conditions to explore cyclisation.

A summary of the results of the attempts at trapping the enolate intermediate from the LiI-catalysed epoxide-ketene reactions is illustrated in Table 35. The first attempt to trap the ester enolate was using TMSCl in the reaction between diphenylketene and *cis*-2,3-epoxybutane at −78 °C. TMSCl was added after 2 h, and the reaction was allowed to stir at rt overnight, but it did not trap the enolate (entry 1). The ^{13}C NMR spectrum of this reaction was compared to the acyclic ester product **5c** formed from diphenylketene and *cis*-2,3-epoxybutane. The characteristic signals of the acyclic ester product were present in the crude product's ^{13}C NMR spectrum. The characteristic signals of the acyclic ester product included the δ 171.7 ppm carbonyl peak and the 74.6, 57.4, 29.4, 23.9, 18.7 ppm alkyl peaks. This indicated that the enolate was not trapped.

In the next attempt (entry 2), using the same ketene and epoxide, but the reaction was carried out in the dark at rt, and stirred overnight. TMSCl was added the following day to the reaction mixture, which was then stirred overnight at rt. The ^{13}C NMR spectrum of the crude product indicated that the trapped enolate did not form, as the peaks in the ^{13}C NMR spectrum were the same as for the acyclic ester product (**5c**).

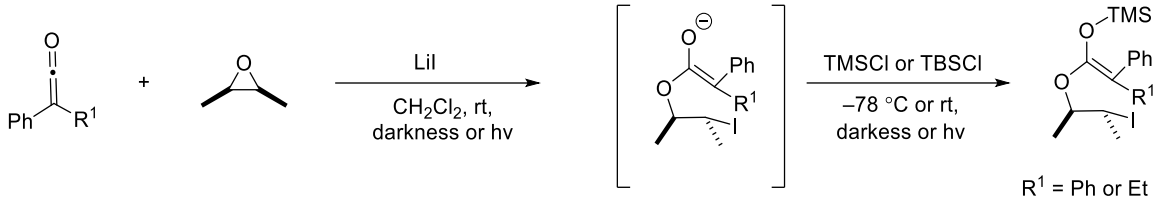
The third reaction was not covered in aluminium foil and was left with the fume hood light on for the duration of the reaction. TMSCl was added to this reaction after 1.75 h, and the reaction was left stirring overnight, exposed to light. The crude ^{13}C NMR of this reaction was overlaid with that of the acyclic ester product **5c**, and the signals in the spectra were found to be identical. This indicated that the acyclic ester product was present and that no TMS-trapped product was formed. Another indication that TMSCl did not trap the enolate was the absence of TMS signals in the

^{13}C NMR spectrum. An aqueous work-up destroys unreacted TMSCl, and the absence of TMS peaks in the ^{13}C NMR spectrum indicated that the TMSCl remained unreacted and was destroyed in the aqueous work-up.

In the next four reactions, the effect of two trapping agents (TMSCl and TBSCl) on the reaction between ethylphenylketene and *cis*-2,3-epoxybutane was explored. The effect of the specific trapping agent, and also the effect of adding the trapping agent after 2-3 h or the following day was studied. In the first reaction of these experiments, TMSCl was added the next day to the reaction that was covered in aluminium foil (entry 4). No trapped enolate product was formed, but the acyclic ester product (**5e**) was present. There were no TMS-derived peaks in the ^{13}C NMR spectrum, and this again indicated that the TMSCl did not undergo reaction and was removed during aqueous work-up. The effect of addition time of TMSCl addition on the reaction was investigated, and a second reaction was carried out simultaneously. In this reaction, TMSCl was added after 2.2 h and the reaction flask was covered with aluminium foil (entry 5), stirred overnight and worked-up the following day. The signals in the ^{13}C NMR spectrum of the crude product corresponded to the acyclic ester product **5e**, and there were no TMS-derived peaks observed, confirming that the enolate was not trapped.

In the remaining two reactions, the trapping agent was changed to TBSCl. In the first of these two reactions, the reaction was stirred overnight before TBSCl was added. The reaction was then stirred overnight and worked up the following day (entry 6). The ^{13}C NMR spectrum of the crude product once again corresponded to the acyclic ester product **5e**. If TBSCl had trapped the enolate, the carbonyl peak would not be present. However, the carbonyl signal was present, confirming the enolate was not trapped. In the final experiment, TBSCl was added after 3 h. The reaction was covered with aluminium foil and worked up the following day (entry 7). As seen in all the other examples, the acyclic ester product (**5e**) was present, and there was no significant evidence that the enolate was trapped.

Table 35: Attempt at trapping the enolate intermediate using TMSCl or TBSCl.



R^1 = Ph or Et

Entry	Ketene (R^1)	TMSCl or TBSCl	Addition time	Darkness or light	Comment[a]
1	Ph	TMSCl	After 2h	Darkness	No trapped enolate, acyclic product **5c** (63%)[a] was formed.
2	Ph	TMSCl	Next day (After 16h)	Darkness	No trapped enolate, acyclic ester product **5c** (74%) formed.
3	Ph	TMSCl.	After 1.75 h	Light	No trapped enolate, acyclic ester product **5c (**44%) formed.
4	Et	TMSCl	Next day	Darkness	No trapped enolate, acyclic ester product **5e** (42%) formed.
5	Et	TMSCl	2.2 h	Darkness	No trapped enolate, acyclic ester product **5e** (36%) formed.
6	Et	TBSCl	Next day	Darkness	No trapped enolate, acyclic ester product **5e** (56%) formed.
7	Et	TBSCl	3 h	Darkness	No trapped enolate, acyclic ester product **5e** (50%) formed.

[a] % peak area determined by GC-MS analysis of crude product.

5.9 Mechanistic studies using radical scavenger/trapping agents

As previously discussed, two mechanistic scenarios could be predicted for the cyclisation step(s) to access γ-lactone **4a**. Therefore, a number of radical trapping agents were added into the reaction from the beginning to determine if a radical intermediate was formed during the reaction these results are tabulated in Table 36.

BHT (butylated hydroxytoluene) was added to the reaction, and formation of a new peak was reported in the GC-MS spectrum (49%) along with an acyclic ester (9%) and trace γ-lactone **4a** (1%). The ^{13}C NMR spectrum of the crude product was complex, but peaks corresponding to the acyclic ester product were observed. BHT

is a good hydrogen atom donor, and the acyclic ester product was formed rather than the usual γ-lactone when the only variation in the reaction was the addition of BHT. This suggests that the reaction may proceed through a single-electron transfer (SET) mechanism, forming a radical at the α-carbon. The α-carbon radical can abstract the phenolic hydrogen atom from BHT, forming a new C-H bond at the α-carbon. There were also signals present in the crude ^{13}C NMR corresponding to BHT. Purification of the crude product to isolate the unknown compound present (49% peak area in GC-MS) was attempted. After purification, the BHT peaks still remained in the ^{13}C NMR spectrum of the unknown compound. However, BHT does not seem to form an adduct with the radical at either the α-carbon or at the terminal benzylic carbon, as there are no peaks in the ^{13}C NMR corresponding to the BHT adduct. In the MS fragmentation pattern of the new GC-MS peak (49% of total area) in the crude product, there are fragments at 220 and 57 m/z, and these correspond to BHT. The results of this trapping experiment were inconclusive and further studies would be required to support the conclusion that BHT formed an adduct with a radical intermediate. It may be that the acyclic ester product arises from two hydrogen atoms being transferred from BHT molecules to the proposed diradical intermediate (see Mechanism involving SET, Figure 53).

Employment of a second radical-trapping agent, BHA (butylated hydroxyanisole), indicated by the ^{13}C NMR spectrum also formed an acyclic ester product. Similarly to BHT, BHA is a hydrogen atom donor, and the formation of the new peak in the GC-MS spectra and the signals in ^{13}C NMR corresponding to the acyclic product could be due to the BHA donating a hydrogen atom through hydrogen atom transfer in trapping the radical intermediate. Although, as reported with BHT, the new peak in the crude GC-MS (41%) contained fragments that correspond to BHA, but there were no peaks that indicated that BHA formed an adduct with the acyclic ester. Again, it may be that the acyclic ester product is formed due to two molecules of BHA transferring hydrogen atoms to the diradical intermediate, and therefore, no adduct with BHA would be formed.

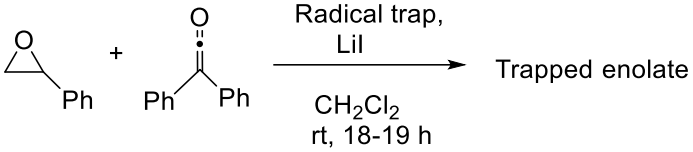
Free galvinoxyl was also analysed in the reaction to determine if it trapped the radical and formed an adduct. The ^{13}C NMR and GC-MS spectra were complex, but

in the ^{13}C NMR, the aliphatic and carbonyl peaks matched the acyclic ester product. Therefore, this indicates that the radical was not trapped.

1,1-Diphenylethylene is known as a good radical trapping agent. Therefore, this reaction was analysed. The crude product formed was compared to the ^{13}C NMR spectrum of the γ-lactone **4a**. The peaks observed in the crude product were the same as the peaks in the γ-lactone spectrum. The GC-MS also confirmed the formation of the γ-lactone product. This indicated that the radical trapping agent did not successfully trap the radical. This could be due to the α-carbon having two phenyl rings that are sterically bulky. The steric bulk may have prevented the trapping agent from effectively trapping the radical at the α-carbon, enabling the reaction to proceed to form the γ-lactone product instead.

The final radical-trapping agent studied was TEMPO. TEMPO has been found by other groups to react with ketene to form a ketene-TEMPO adduct.[126,127] The ^{13}C NMR spectrum of the crude product was complex, as TEMPO caused the peaks to broaden. The GC-MS of the crude product indicated that there was ring-opened epoxide **8a** (23%), TEMPO (39%), and two unknown peaks (32%). The two unknown GC-MS peaks could be the ketene-TEMPO adduct as there was no ketene detected in the NMR spectrum. Moreover, ring-opened epoxide was observed, which indicated that the epoxide had not fully reacted, presumably because the ketene and TEMPO had reacted together before the epoxide could react with the ketene.

Table 36: Outcome of radical trapping experiments.



Radical scavenger/trapping agent	Comment
No radical trapping agent	γ-lactone formed (30%)
Butylated hydroxytoluene (BHT)	New peak in GC-MS with BHT m/z in fragmentation pattern (49%). Very small amount of γ-lactone (1%) and acyclic ester (9%).
Butylated hydroxyanisole (BHA)	New peak in GC-MS with BHA m/z in fragmentation pattern (41%). Very small amount of γ-lactone (<1%).
Galvinoxyl free radical	Many peaks in crude GC-MS. No significant γ-lactone peak (1%). Acyclic ester (13%) also formed.
1,1-diphenylethylene	γ-lactone formed based on GC-MS (18%).
TEMPO	TEMPO reacts with ketene. Iodohydrin **8a** (23%) formed.

[a] % peak area determined by GC-MS analysis of crude product.

A number of control experiments were carried out to ensure that the radical-trapping/scavenger agents do not react with the starting materials to form the new peaks observed in the GC-MS traces. The control reactions are shown in The control experiments indicate that without the radical scavenger BHT, the desired lactone product is formed. When the radical scavenger was exposed to the starting materials individually or one of the starting materials was excluded, no new product was formed. The GC-MS of these reactions only showed the starting materials, and there were no additional peaks corresponding to the starting materials and BHT reacting together. This confirmed that BHT does not react with the starting materials. However, importantly, when BHT was added in a reaction with all the starting materials, the crude GC-MS peak for the γ-lactone was much reduced, and a new peak was formed. This indicated that something significant had happened in the reaction. . The control experiments indicate that without the radical scavenger BHT, the desired lactone product is formed. When the radical scavenger was exposed to the starting materials individually or one of the starting materials was

excluded, no new product was formed. The GC-MS of these reactions only showed the starting materials, and there were no additional peaks corresponding to the starting materials and BHT reacting together. This confirmed that BHT does not react with the starting materials. However, importantly, when BHT was added in a reaction with all the starting materials, the crude GC-MS peak for the γ-lactone was much reduced, and a new peak was formed. This indicated that something significant had happened in the reaction.

Table 37: Controls performed for the BHT radical trapping reactions

Diphenylketene	Epoxide	LiI	BHT	Comment[b]
				γ-lactone (30%) formed based on GC-MS analysis.
				New peak (49% peak area) in GC-MS with BHT m/z in fragmentation pattern. Very small amount of γ-lactone (1%). Acyclic ester (9%) also formed.
				BHT (72%) and Ketene (28%) only observed in GC-MS trace.
				BHT (69%) and Ketene (31%) only observed in GC-MS trace.
				BHT (86%) and ring-opened epoxide **8a** (4%)observed in GC-MS trace.

Green = present; red = absent. [b] % peak area determined by GC-MS analysis of crude product.

A control reaction was run between diphenylketene and free galvinoxyl in CH_2Cl_2, and a new peak appeared in the GC-MS spectrum. The fragmentation pattern of this peak had a fragment at 194 m/z. This fragment corresponded to the ketene. An intact ketene-galvinoxyl adduct itself would have a larger m/z than the GC-MS could detect. However, the presence of the 194 m/z fragment indicated that the ketene and galvinoxyl could react together. This was compared to the control reaction between diphenylketene and BHT, which showed no evidence that they had reacted together.

Table 38: Control experiments between radical trapping agents and diphenylketene to determine if they react together.

Entry	Ketene	Radical trapping agent	Comment[a]
1	Diphenylketene	BHT	No adduct formed, two separate peaks appear, corresponding to the ketene (28%) and BHT (72%).
2	Diphenylketene	Free galvinoxyl	A new peak (% area) on the GC-MS not corresponding to galvinoxyl (26%) or ketene (44%), but could be derived from the ketene-galvinoxyl adduct.

[a] % peak area determined by GC-MS analysis of crude product.

To summarise, while there does appear to be some evidence for the formation of a radical/diradical intermediate, particularly in the radical scavenging experiments involving BHT and BHA, further experiments with more sophisticated radical traps need to be designed and carried out.

The SET mechanism is a plausible reaction mechanism, but more specific experiments would need to be carried out to prove or disprove the mechanism. More experiments are required to determine if the radical-forming step in the proposed SET mechanism occurs, for example, by employing a cyclopropane radical clock trap.[128]

Chapter 6: Conclusion and Future work

6.1 Conclusion:

There were twelve γ-lactones synthesised, and they all had the 3,4-γ-lactone regioisomer as the major isomer. This indicated that all the epoxides were opened at the more substituted carbon. The isolated yields of the formed 3,4-γ-lactone ranged from low to good (12-72%), with good to excellent purity based on GC-MS peak area analysis (85-98%). When changing the ketene from diphenylketene or when epoxides containing alkyl substituents were employed, the acyclic ester product was formed as the major product. Five acyclic ester products were fully characterised, confirming their structure. Eleven more acyclic esters were synthesised, but they were not isolated in pure form due to instability during purification or low yields in the crude product mixture, as determined by GC-MS analysis.

Earlier in our studies, the reaction mechanism for the Li-catalysed [3 + 2]-cycloaddition of epoxides and ketenes was thought to involve a concerted S_N2 cyclisation step, albeit a disfavoured 5-enolendo exo-tet cyclisation by Baldwin's Rules. However, the reaction between diphenylketene and enantioenriched styrene oxide (95% ee) raised questions about the proposed S_N2 mechanism. In a true S_N2 mechanism the enantiopurity of the starting materials should be transferred to the product, as inversion of configuration should occur but without erosion of enantiomeric excess. In this example, the enantiomeric excess of the product decreased from 95% ee at the epoxide stage to 84% ee at the γ-lactone stage. This suggests that a SET mechanism may be at work in this reaction. Therefore, now an S_N2 cyclisation step is the simplest explanation for the [3 + 2]-cycloaddition reaction between the epoxide and ketene, but the observed loss of enantiomeric excess makes the SET mechanism a plausible alternative.

Mechanistic studies employing radical-trapping agents and radical scavenger agents for the Li-catalysed reaction of diphenylketene with racemic styrene oxide were carried out. In the absence of the radical-trapping/radical scavenger agent,

the desired 3,4-γ-lactone was formed. The addition of the radical scavenger agents BHA and BHT, which are hydrogen atom donors, resulted in inhibition of γ-lactone formation. In each case, a new peak was formed in the GC-MS spectrum of the crude product. The inhibition of γ-lactone formation when the radical scavenger agents were used suggests that a SET step may be involved in the reaction mechanism, but more extensive studies will have to be carried out to confirm this theory

6.2 Future work

There are a lot of routes that this project may take in the future. This thesis details the current scope of the LiI-catalysed [3 + 2]-cycloaddition reaction of epoxides with ketenes. The examples studied in this project were mainly alkyl- and aromatic-substituted epoxides. An attempt to synthesise a heteroaromatic epoxide and subject it to reaction with a ketene, but purification issues were encountered, as seen in the results and discussion. Therefore, in the future, heteroaromatic/heterocyclic-substituted examples of epoxides should be studied to determine whether lactone formation is favoured when these epoxides are used in pure form.

As seen in this thesis, the main ketene used was diphenylketene, which was the most successful ketene in forming the desired γ-lactone product. When the ketene was changed away from diphenylketene, it was found that the desired γ-lactone was not formed, but instead an acyclic ester product was formed. Therefore, further research is needed to develop a method that allows the desired γ-lactone product to be formed in those cases. The ketenes that have been tested so far are ketenes with at least one phenyl substituent, while the second substituent was changed from a phenyl to an alkyl substituent. Another substrate that should be studied is a diaromatic ketene (other than simple Ph-substituted), as aromatic substrates appear to be very effective at forming the γ-lactone product. One method of in situ ketene synthesis was investigated in this project; in the future, other methods of in situ ketene generation such as blue LED-irradiation of diazocarbonyls will be studied.

The reaction mechanism was originally thought to have involved a true S_N2 cyclisation step; however, throughout this project, evidence has been gathered that suggests a SET reaction step may be involved, rather than a simple S_N2 cyclisation step. Indeed, as described above, racemisation occurs during the reaction, which can occur where radical intermediates are formed as a result of SET. Radical-trapping experiments were begun in this project, but further research is needed to provide clear experimental data demonstrating radical formation and supporting the SET reaction mechanism.

This project focused on a LiI promoted [3 + 2]-cycloaddition of epoxides and ketenes to synthesise a 5-membered cyclic product, the γ-lactone. Further research in the group will focus on generating larger ring-sized products. These reactions will include catalytic formal [4 + 2]- and [5 + 2]-cycloadditions. These new cycloaddition reactions will potentially generate larger ring-sized lactones, including δ-lactones, from oxetanes and ketenes, and 7-membered rings (ε-lactones) from oxolanes and ketenes. All of these cyclic esters will be investigated as monomers for polymerisations to access interesting materials.

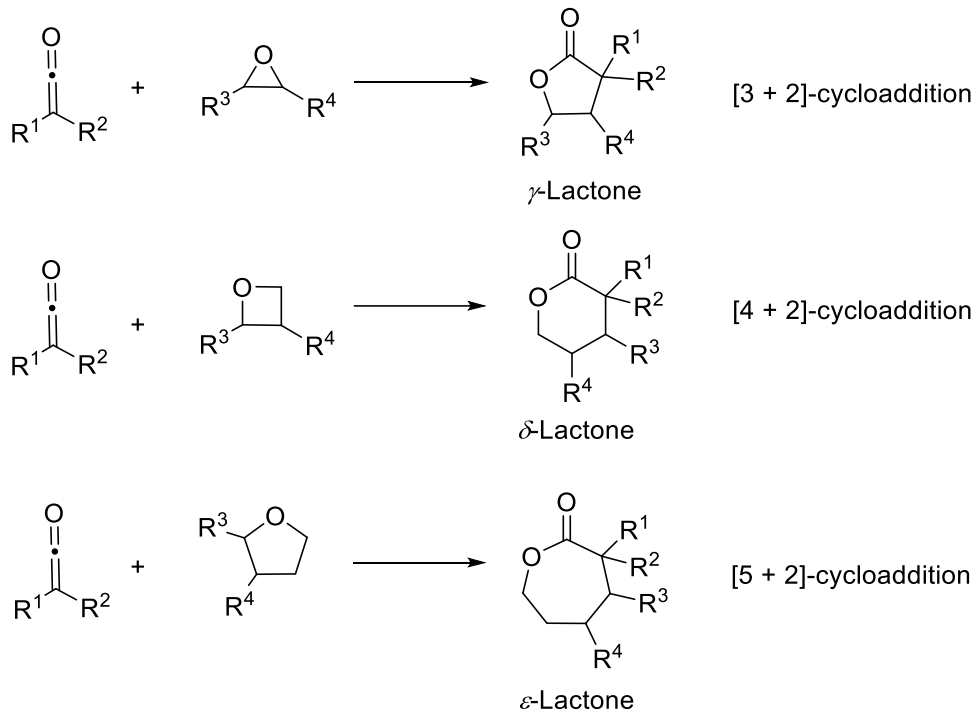


Figure 57: catalytic cycloadditions of ketenes with a variety of cyclic ethers to form different ring-sized lactones.

The enantioselectivity of the reaction is another major area of interest. The use of chiral ligands for organolithium intermediates will be studied. Examples of chiral ligands that will be studied in this reaction include sparteine and koga amine.[129,130] These chiral ligands could associate with the lithium counterion to potentially create a chiral environment around reactive intermediates and ultimately control which enantiomer of lactone is formed.

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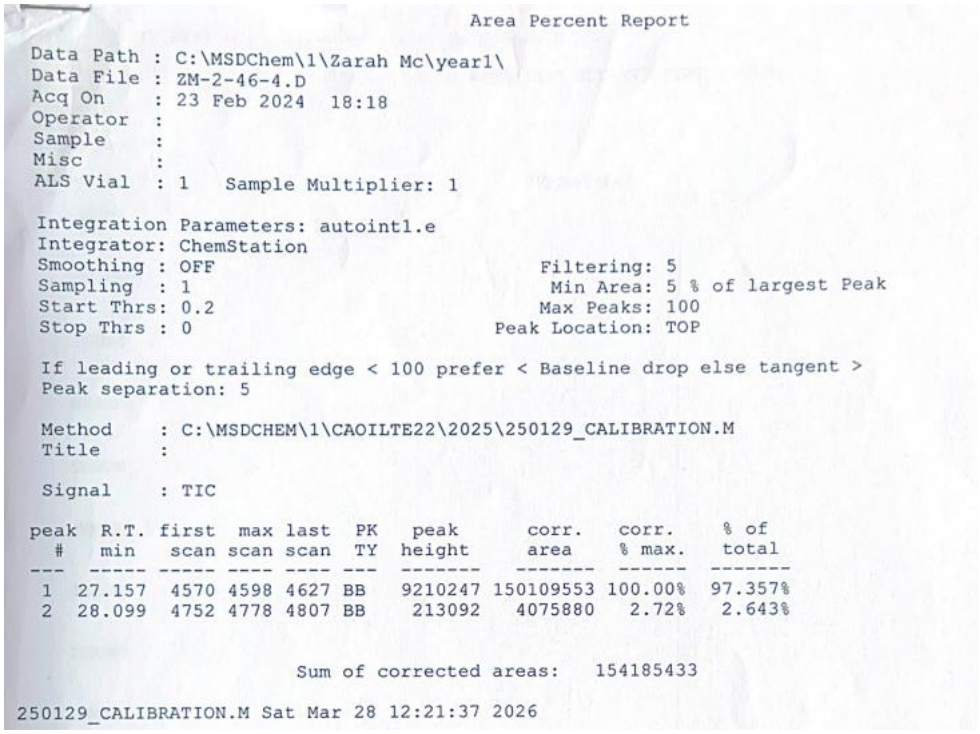
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Chapter 8: Appendix:



Area Percent Report

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Data File : ZM-2-46-4.D
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Operator :
Sample :
Misc :
ALS Vial : 1 Sample Multiplier: 1

Integration Parameters: autoint1.e
Integrator: ChemStation
Smoothing : OFF Filtering: 5
Sampling : 1 Min Area: 5 % of largest Peak
Start Thrs: 0.2 Max Peaks: 100
Stop Thrs : 0 Peak Location: TOP

If leading or trailing edge < 100 prefer < Baseline drop else tangent >
Peak separation: 5

Method : C:\MSDCHEM\1\CAOILTE22\2025\250129_CALIBRATION.M
Title :

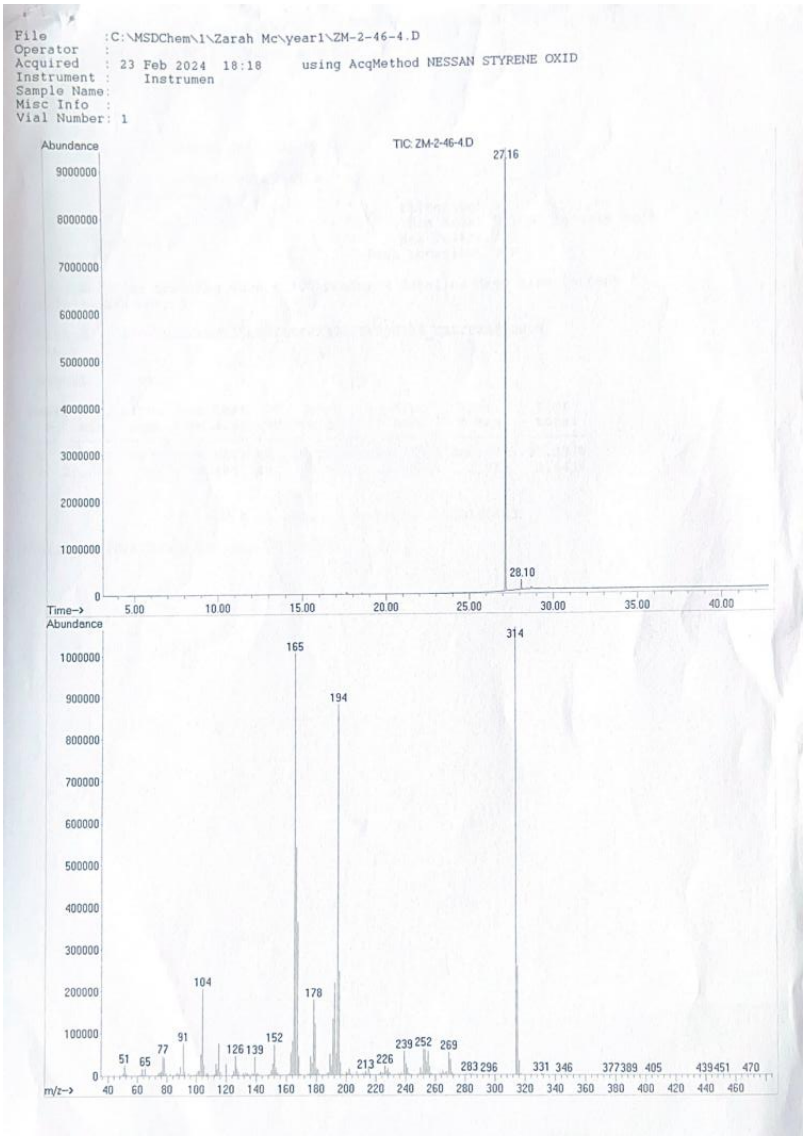
Signal : TIC

peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	27.157	4570	4598	4627	BB	9210247	150109553	100.00%	97.357%
2	28.099	4752	4778	4807	BB	213092	4075880	2.72%	2.643%

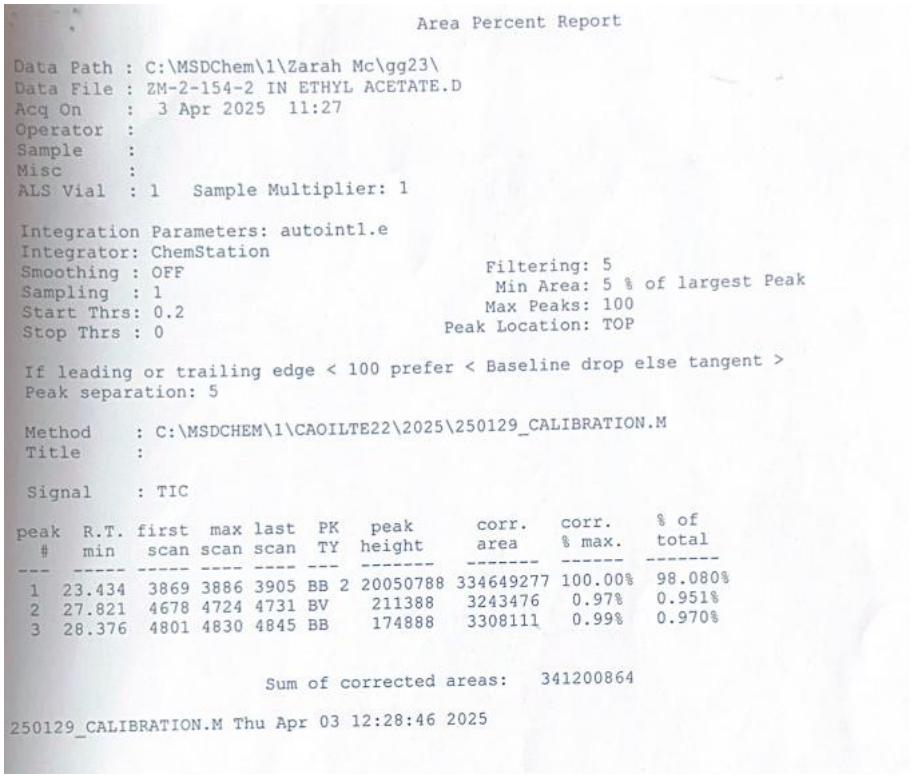
Sum of corrected areas: 154185433

250129_CALIBRATION.M Sat Mar 28 12:21:37 2026

*Spectrum 1: GC-MS trace of 3,3,4-triphenyldihydrofuran-2(3H)-one (**4a**)*



*Spectrum 2: GC-MS spectrum and fragmentation pattern of 3,3,4-triphenyldihydrofuran-2(3H)-one(**4a**)*



Area Percent Report

Data Path : C:\MSDChem\1\Zarah Mc\gg23\
Data File : ZM-2-154-2 IN ETHYL ACETATE.D
Acq On : 3 Apr 2025 11:27
Operator :
Sample :
Misc :
ALS Vial : 1 Sample Multiplier: 1

Integration Parameters: autoint1.e
Integrator: ChemStation
Smoothing : OFF Filtering: 5
Sampling : 1 Min Area: 5 % of largest Peak
Start Thrs: 0.2 Max Peaks: 100
Stop Thrs : 0 Peak Location: TOP

If leading or trailing edge < 100 prefer < Baseline drop else tangent >
Peak separation: 5

Method : C:\MSDCHEM\1\CAOILTE22\2025\250129_CALIBRATION.M
Title :

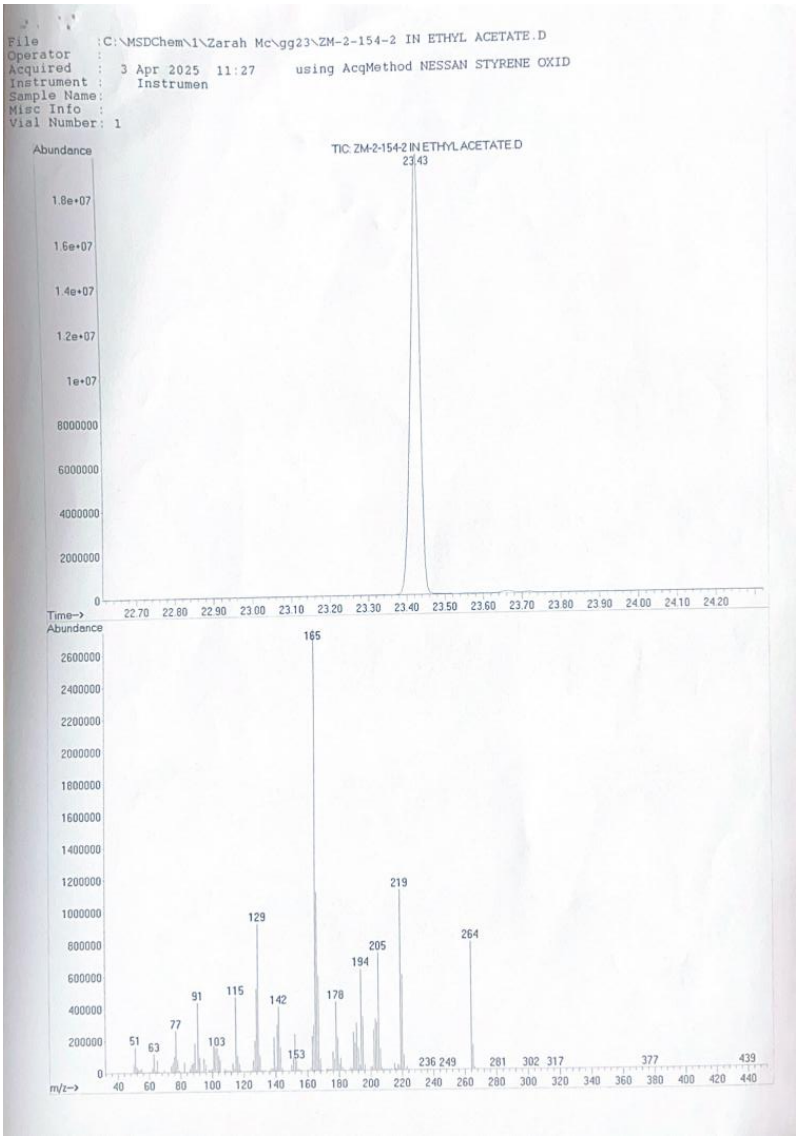
Signal : TIC

peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	23.434	3869	3886	3905	BB 2	20050788	334649277	100.00%	98.080%
2	27.821	4678	4724	4731	BV	211388	3243476	0.97%	0.951%
3	28.376	4801	4830	4845	BB	174888	3308111	0.99%	0.970%

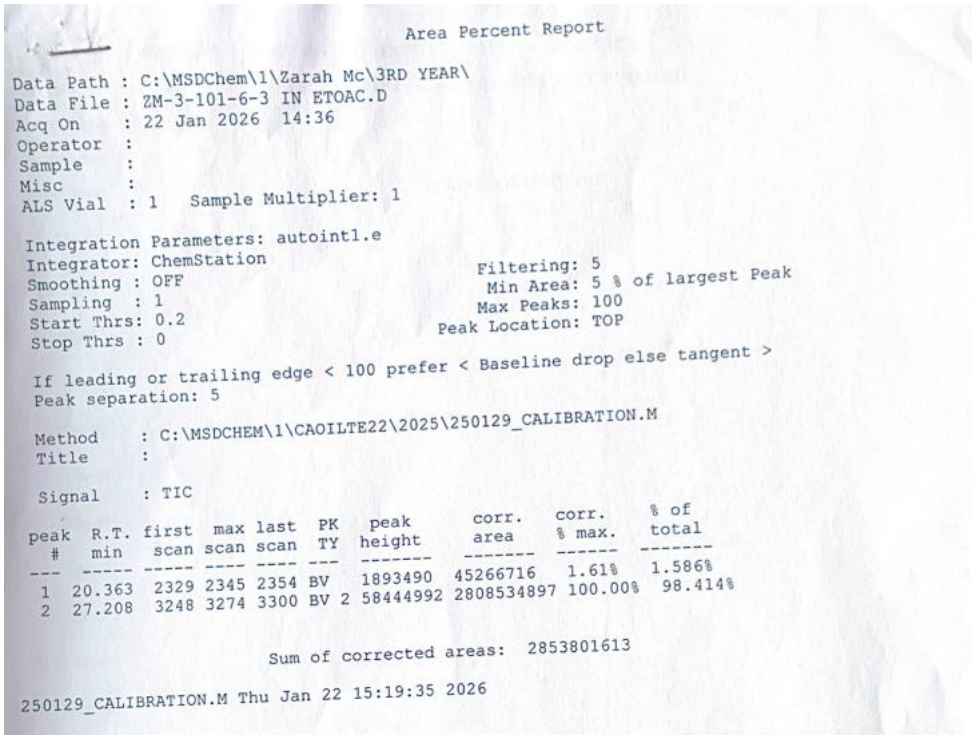
Sum of corrected areas: 341200864

250129_CALIBRATION.M Thu Apr 03 12:28:46 2025

*Spectrum 3: GC-MS trace of 3,3-diphenyl-4-vinyldihydrofuran-2(3H)-one (**4k**)*



*Spectrum 4: GC-MS spectrum and fragmentation pattern of 3,3-diphenyl-4-vinyldihydrofuran-2(3H)-one (**4k**)*



Area Percent Report

Data Path : C:\MSDChem\1\Zarah Mc\3RD YEAR\
Data File : ZM-3-101-6-3 IN ETOAC.D
Acq On : 22 Jan 2026 14:36
Operator :
Sample :
Misc :
ALS Vial : 1 Sample Multiplier: 1

Integration Parameters: autoint1.e
Integrator: ChemStation
Smoothing : OFF
Sampling : 1
Start Thrs: 0.2
Stop Thrs : 0

Filtering: 5
Min Area: 5 % of largest Peak
Max Peaks: 100
Peak Location: TOP

If leading or trailing edge < 100 prefer < Baseline drop else tangent >
Peak separation: 5

Method : C:\MSDCHEM\1\CAOILTE22\2025\250129_CALIBRATION.M
Title :

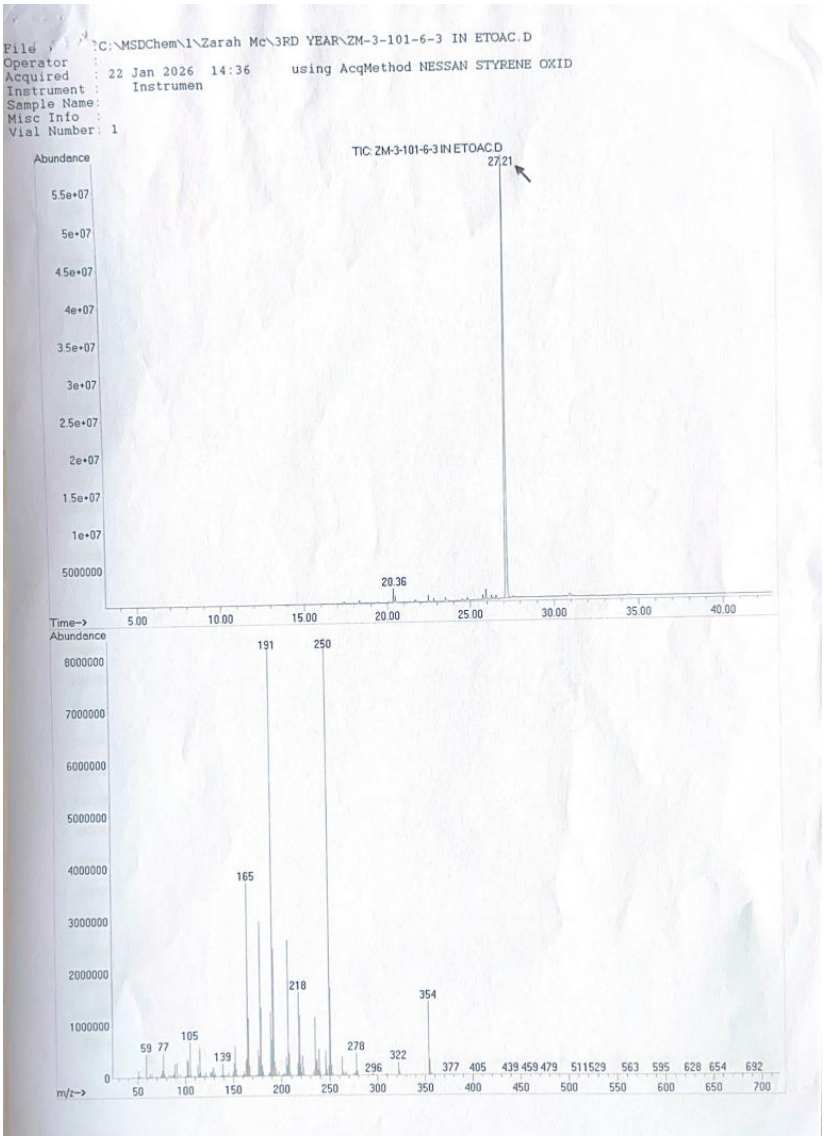
Signal : TIC

peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	20.363	2329	2345	2354	BV	1893490	45266716	1.61%	1.586%
2	27.208	3248	3274	3300	BV 2	58444992	2808534897	100.00%	98.414%

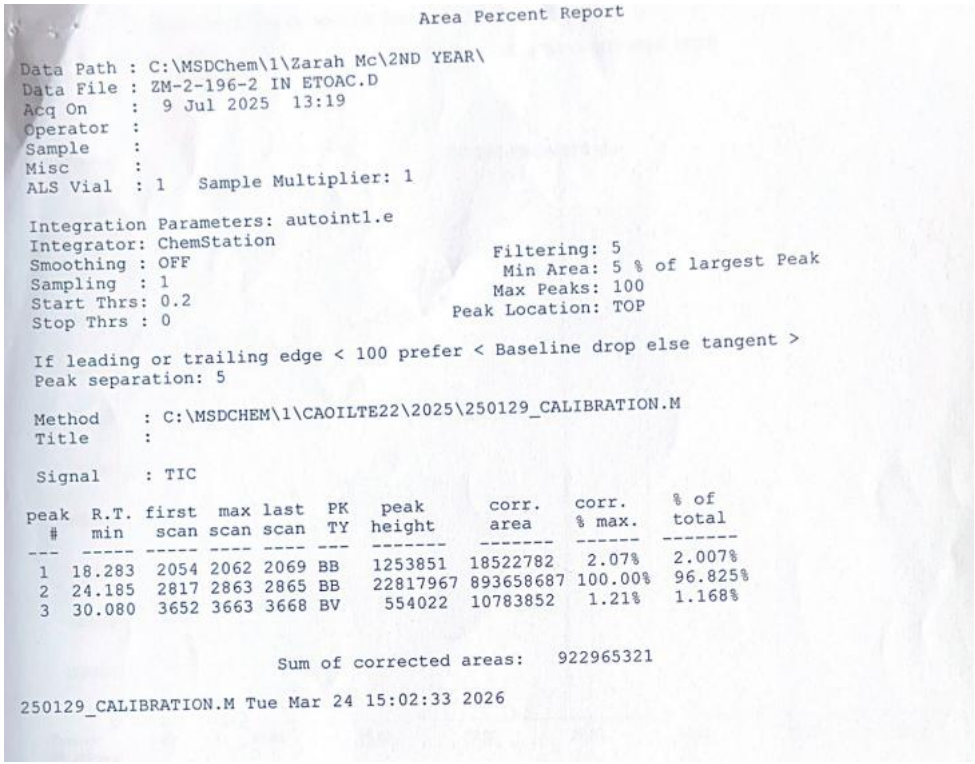
Sum of corrected areas: 2853801613

250129_CALIBRATION.M Thu Jan 22 15:19:35 2026

*Spectrum 5: GC-MS traces of dimethyl 5-oxo-4,4-diphenyltetrahydrofuran-2,3-dicarboxylate (**4l**)*



*Spectrum 6: GC-MS spectrum and fragmentation pattern of dimethyl 5-oxo-4,4-diphenyltetrahydrofuran-2,3-dicarboxylate (**4l**)*



Area Percent Report

Data Path : C:\MSDChem\1\Zarah Mc\2ND YEAR\
Data File : ZM-2-196-2 IN ETOAC.D
Acq On : 9 Jul 2025 13:19
Operator :
Sample :
Misc :
ALS Vial : 1 Sample Multiplier: 1

Integration Parameters: autoint1.e
Integrator: ChemStation
Smoothing : OFF
Sampling : 1
Start Thrs: 0.2
Stop Thrs : 0
Filtering: 5
Min Area: 5 % of largest Peak
Max Peaks: 100
Peak Location: TOP

If leading or trailing edge < 100 prefer < Baseline drop else tangent >
Peak separation: 5

Method : C:\MSDCHEM\1\CAOILTE22\2025\250129_CALIBRATION.M
Title :

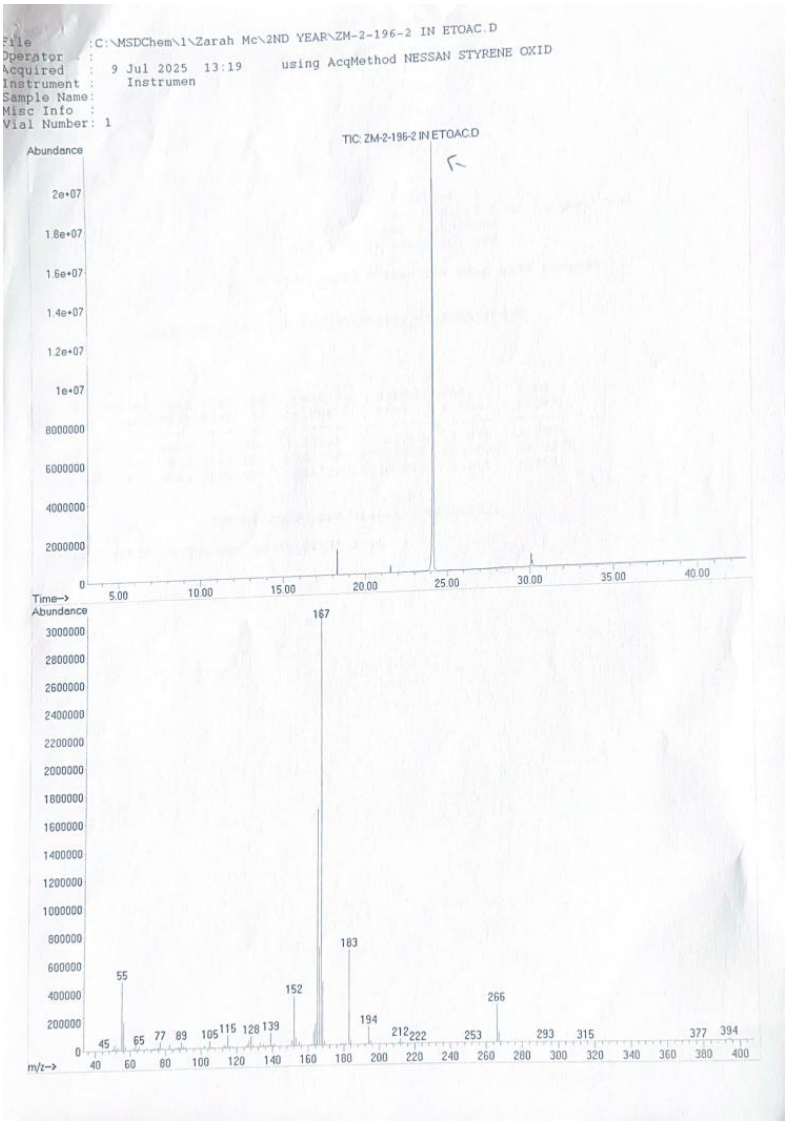
Signal : TIC

peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	18.283	2054	2062	2069	BB	1253851	18522782	2.07%	2.007%
2	24.185	2817	2863	2865	BB	22817967	893658687	100.00%	96.825%
3	30.080	3652	3663	3668	BV	554022	10783852	1.21%	1.168%

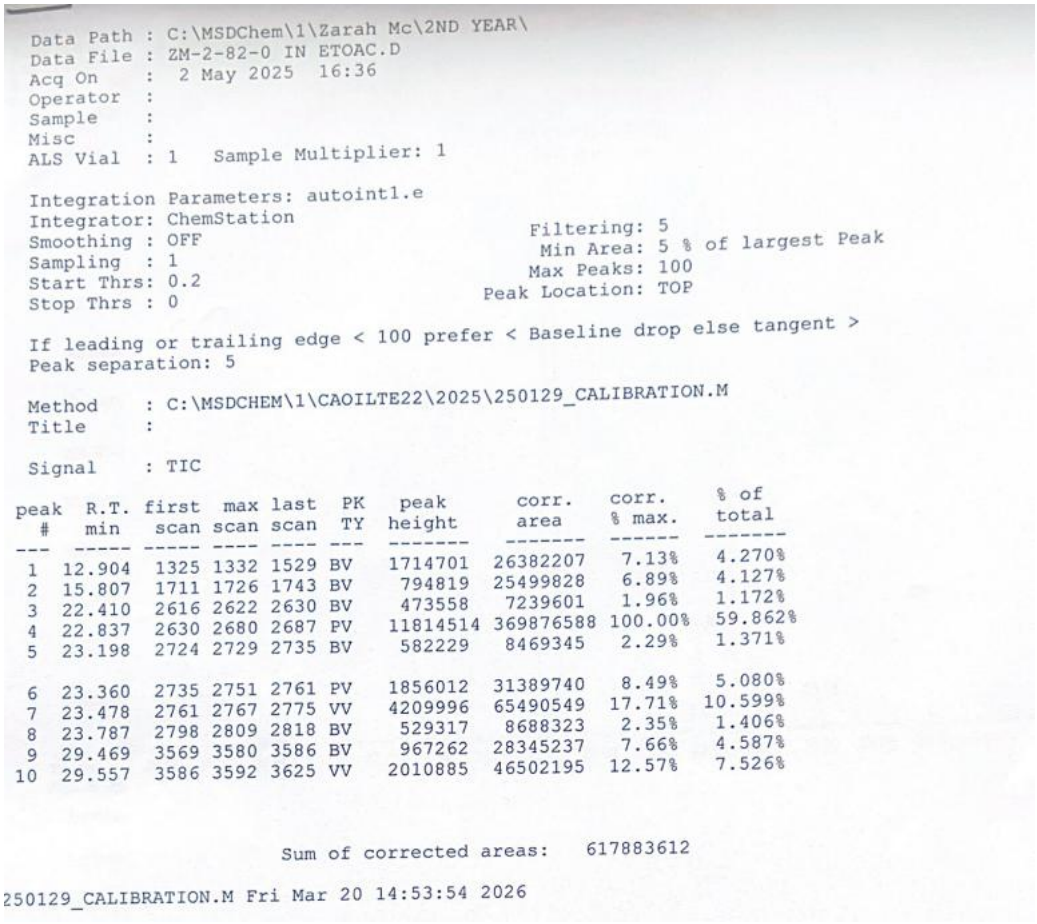
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250129_CALIBRATION.M Tue Mar 24 15:02:33 2026

*Spectrum 7: GC-MS trace of 3-iodobutan-2-yl 2,2-diphenylacetate (**5c**)*



*Spectrum 8: GC-MS spectrum and fragmentation pattern of 3-iodobutan-2-yl 2,2-diphenylacetate (**5c**)*



```
Data Path : C:\MSDChem\1\Zarah Mc\2ND YEAR\
Data File : ZM-2-82-0 IN ETOAC.D
Acq On    :  2 May 2025  16:36
Operator  :
Sample    :
Misc      :
ALS Vial  : 1   Sample Multiplier: 1

Integration Parameters: autoint1.e
Integrator: ChemStation                          Filtering: 5
Smoothing : OFF                                   Min Area: 5 % of largest Peak
Sampling  : 1                                    Max Peaks: 100
Start Thrs: 0.2                                Peak Location: TOP
Stop Thrs : 0

If leading or trailing edge < 100 prefer < Baseline drop else tangent >
Peak separation: 5

Method    : C:\MSDCHEM\1\CAOILTE22\2025\250129_CALIBRATION.M
Title     :

Signal    : TIC

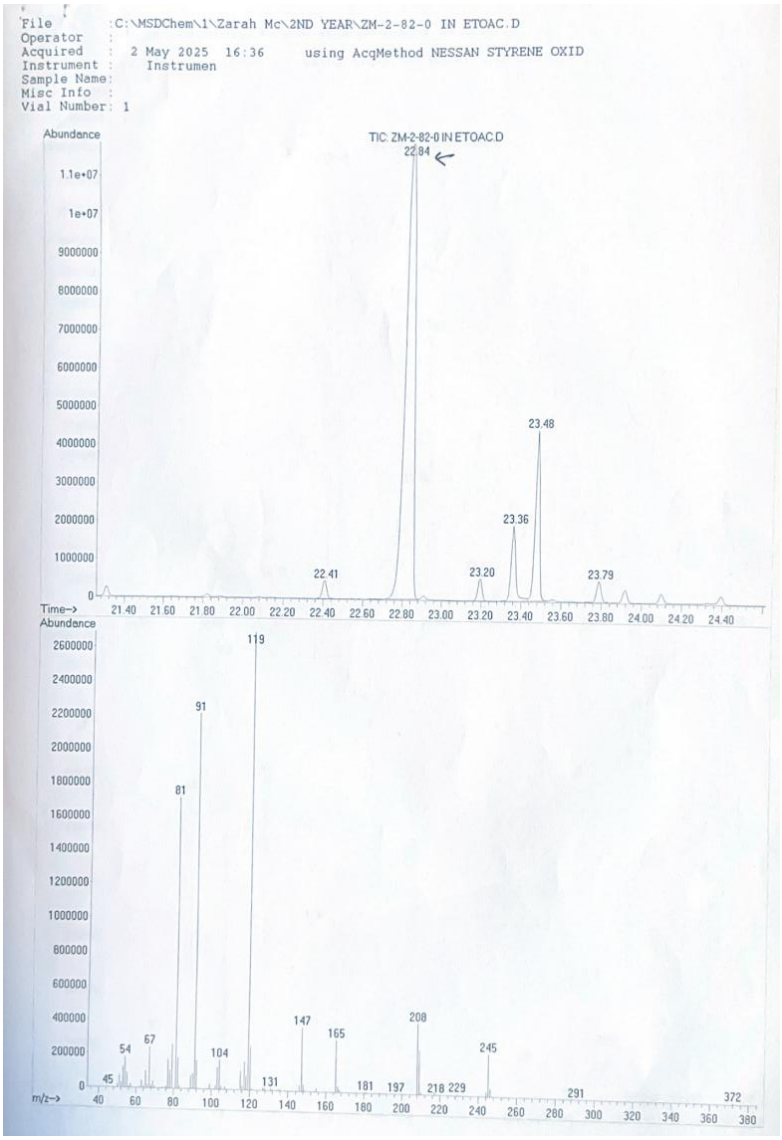
peak  R.T. first  max last  PK   peak      corr.     corr.    % of
  #   min  scan scan scan  TY  height      area     % max.   total
---  ----- ----- ---- ---- --- -------   -------   ------   -------
 1  12.904  1325 1332 1529 BV   1714701  26382207   7.13%    4.270%
 2  15.807  1711 1726 1743 BV    794819  25499828   6.89%    4.127%
 3  22.410  2616 2622 2630 BV    473558   7239601   1.96%    1.172%
 4  22.837  2630 2680 2687 PV  11814514 369876588 100.00%   59.862%
 5  23.198  2724 2729 2735 BV    582229   8469345   2.29%    1.371%

 6  23.360  2735 2751 2761 PV   1856012  31389740   8.49%    5.080%
 7  23.478  2761 2767 2775 VV   4209996  65490549  17.71%   10.599%
 8  23.787  2798 2809 2818 BV    529317   8688323   2.35%    1.406%
 9  29.469  3569 3580 3586 BV    967262  28345237   7.66%    4.587%
10  29.557  3586 3592 3625 VV   2010885  46502195  12.57%    7.526%

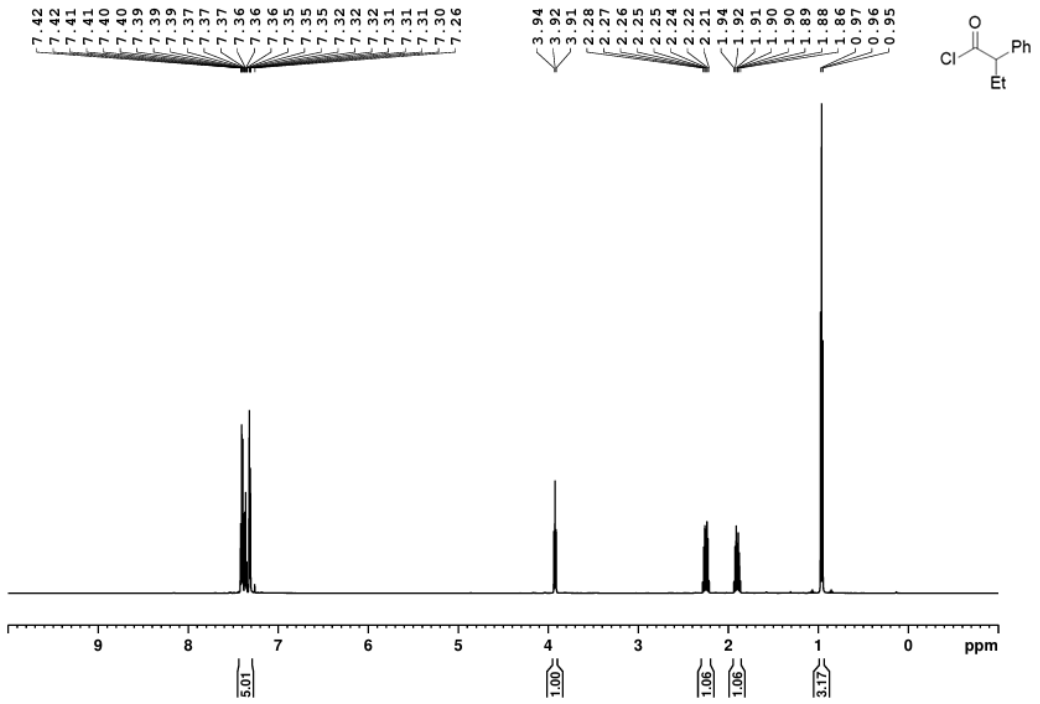

                        Sum of corrected areas:   617883612

250129_CALIBRATION.M Fri Mar 20 14:53:54 2026
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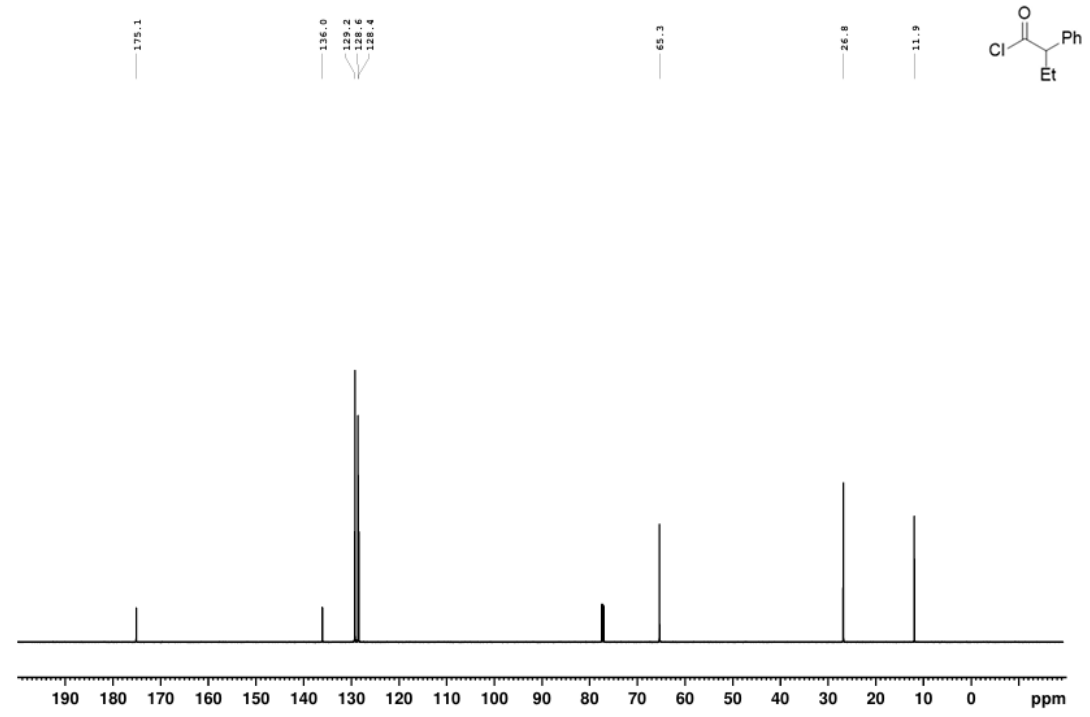
*Spectrum 9: GC-MS trace of 2-iodocyclohexyl 2-phenylbutanoate (**5f**)*



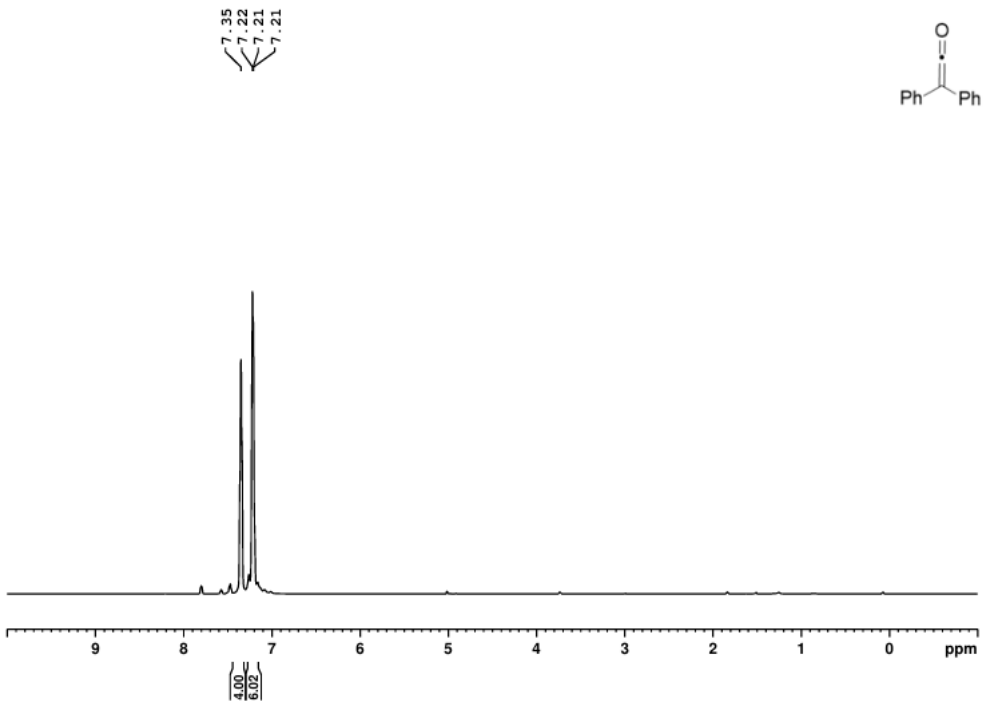
*Spectrum 10: GC-MS spectrum and fragmentation pattern of 2-iodocyclohexyl 2-phenylbutanoate (**5f**)*



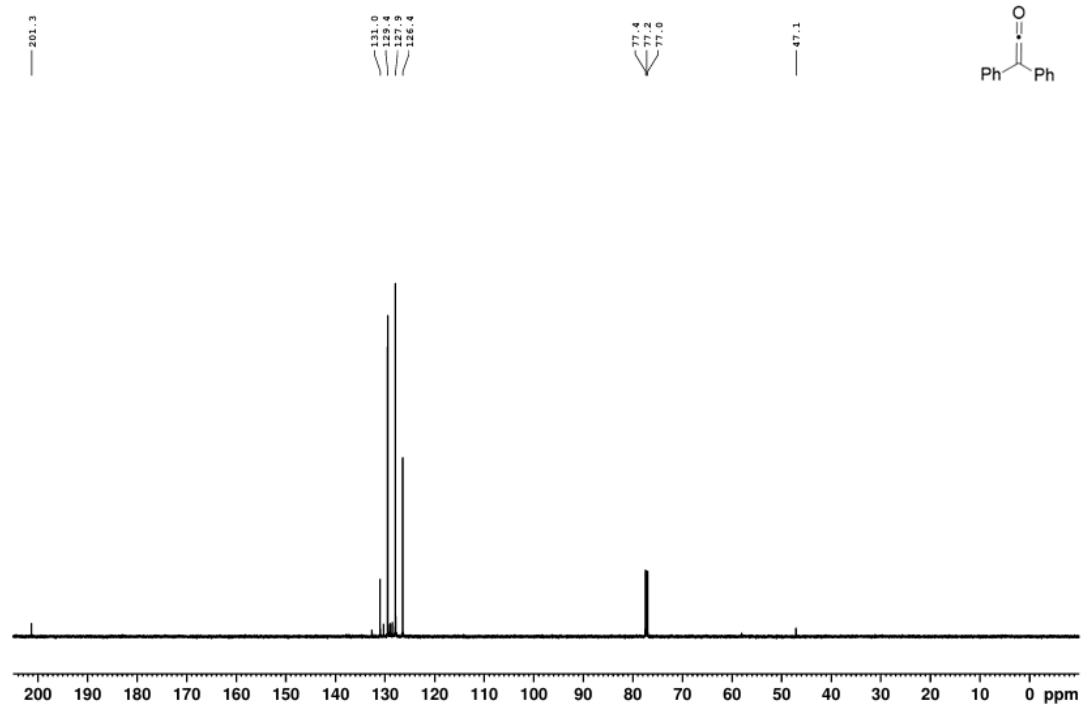
*Spectrum 11: [1]H NMR of 2-Phenybutyryl chloride (**1a**)*



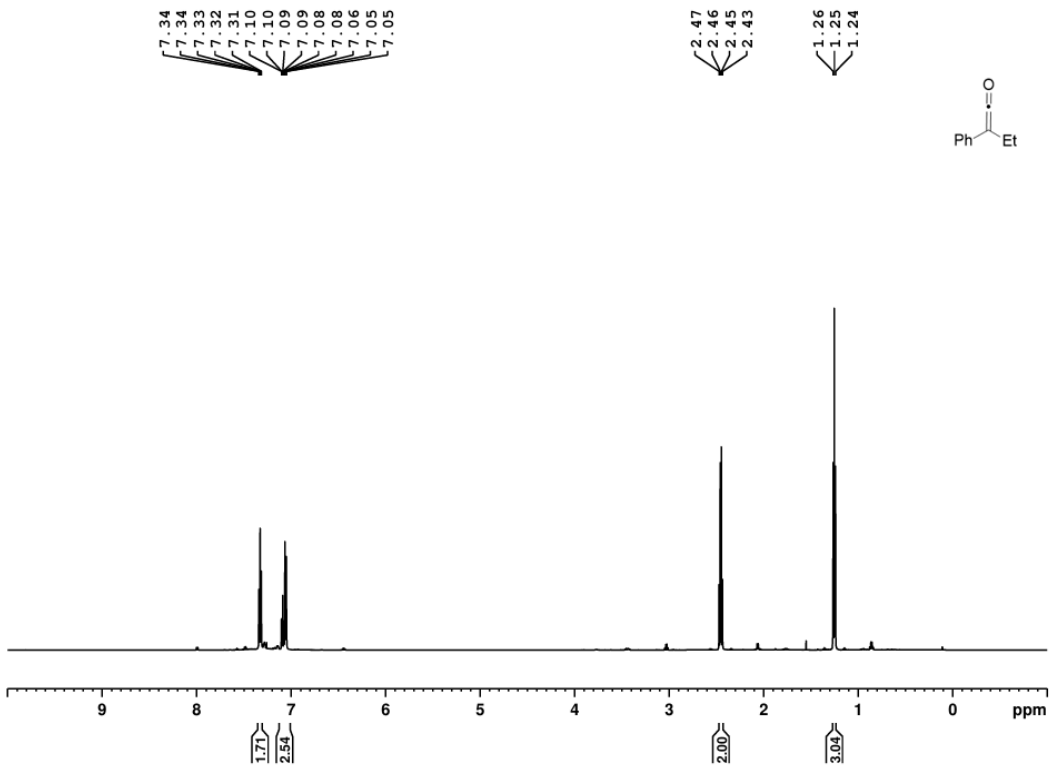
*Spectrum 12: [13] C NMR of 2-Phenybutyryl chloride (**1a**)*



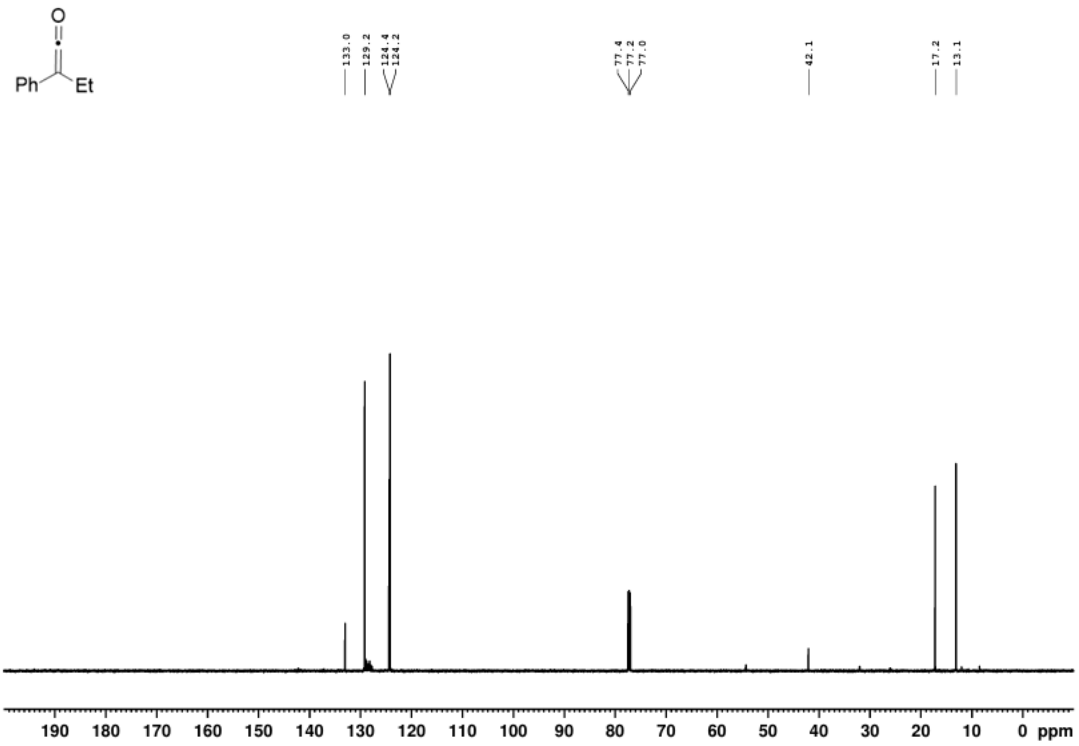
*Spectrum 13: [1]H NMR of diphenylketene (**2a**)*



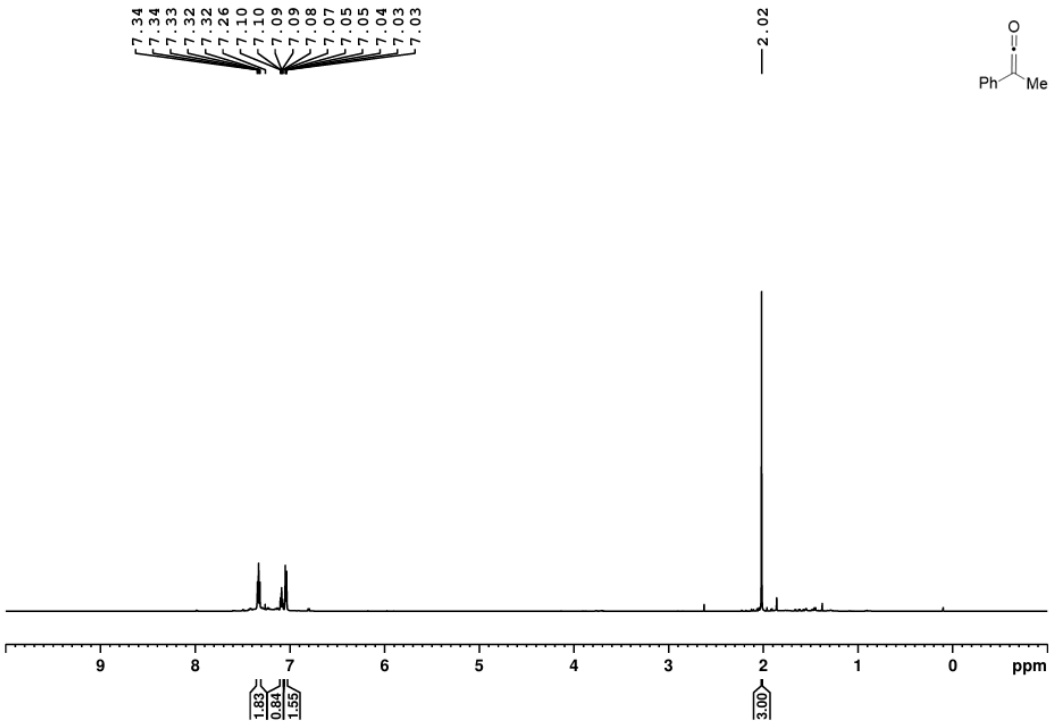
*Spectrum 14: [13]C NMR of diphenylketene (**2a**)*



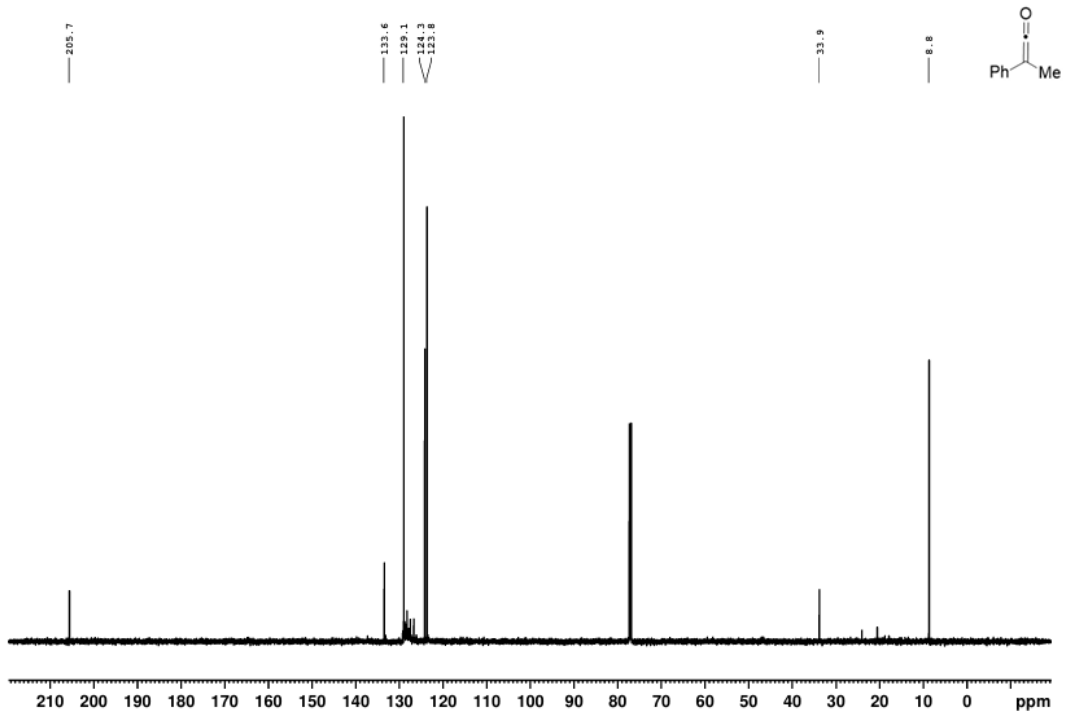
*Spectrum 15: [1]H NMR ethylphenylketene(**2b**)*



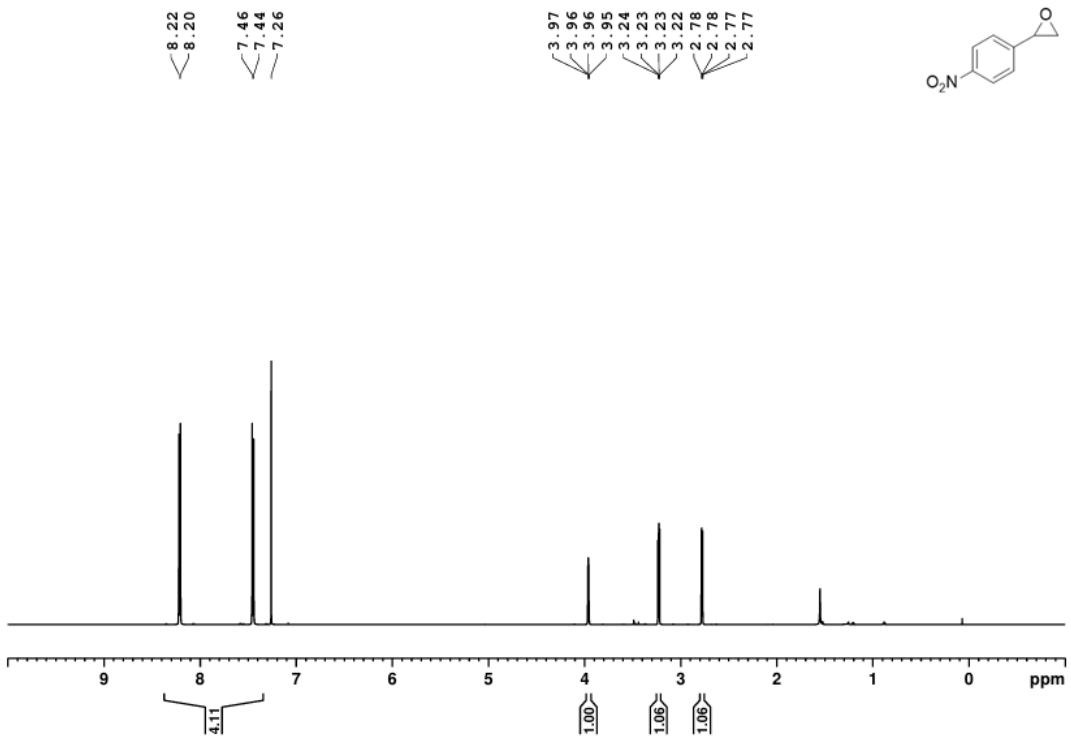
*Spectrum 16: [13]C NMR ethylphenylketene (**2b**)*



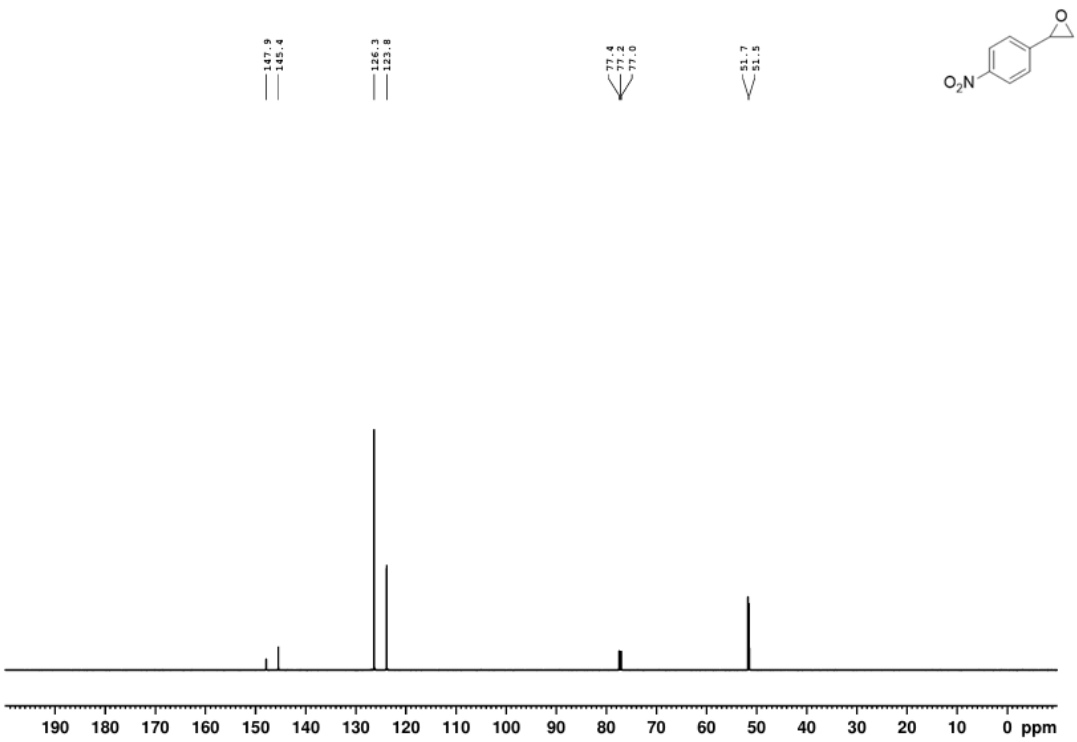
*Spectrum 17: [1]H NMR of methylphenylketene (**2c**)*



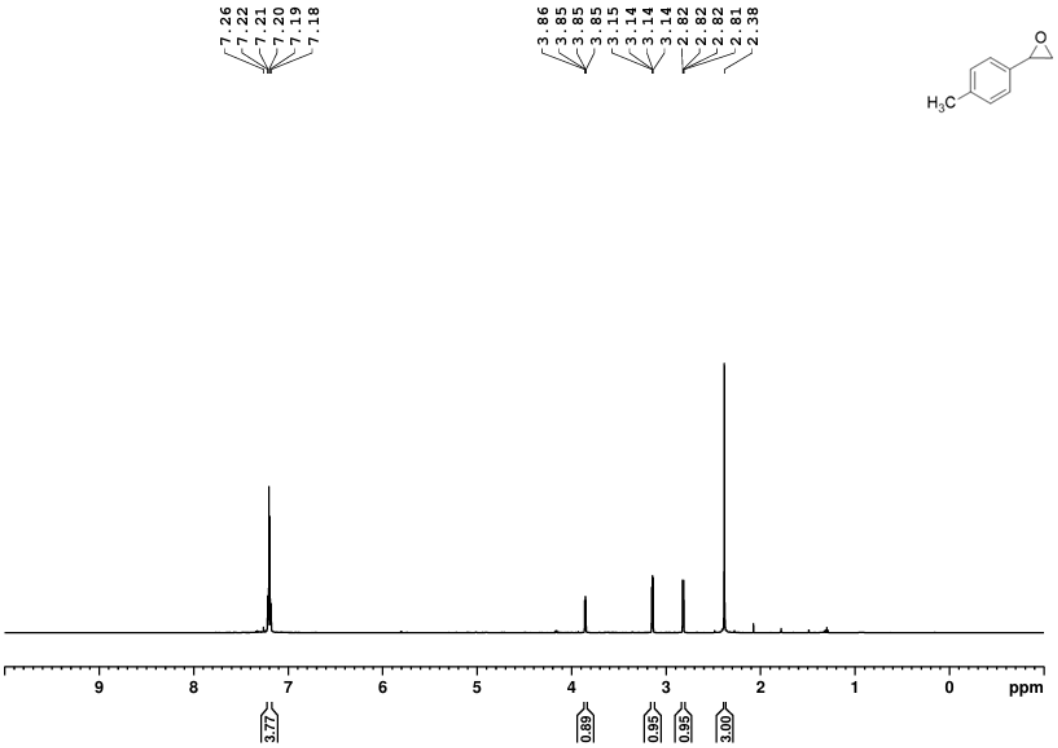
*Spectrum 18: [13]C NMR of methyphenylketene (**2c**)*



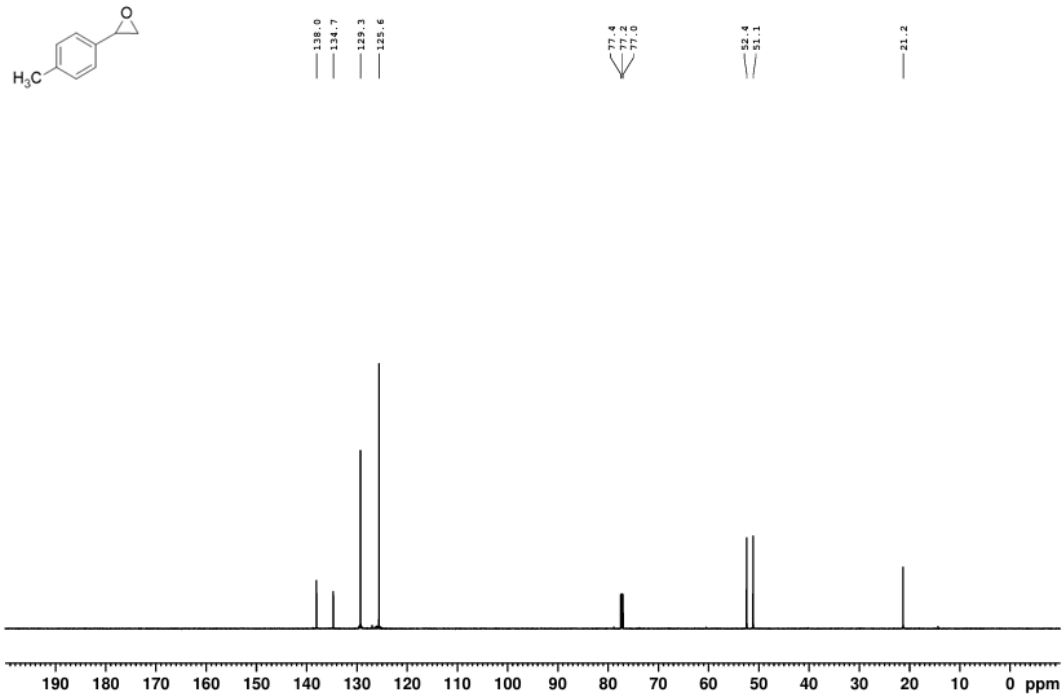
*Spectrum 19: [1]H NMR of 2-(4-nitrophenyl)oxirane (**3a**)*



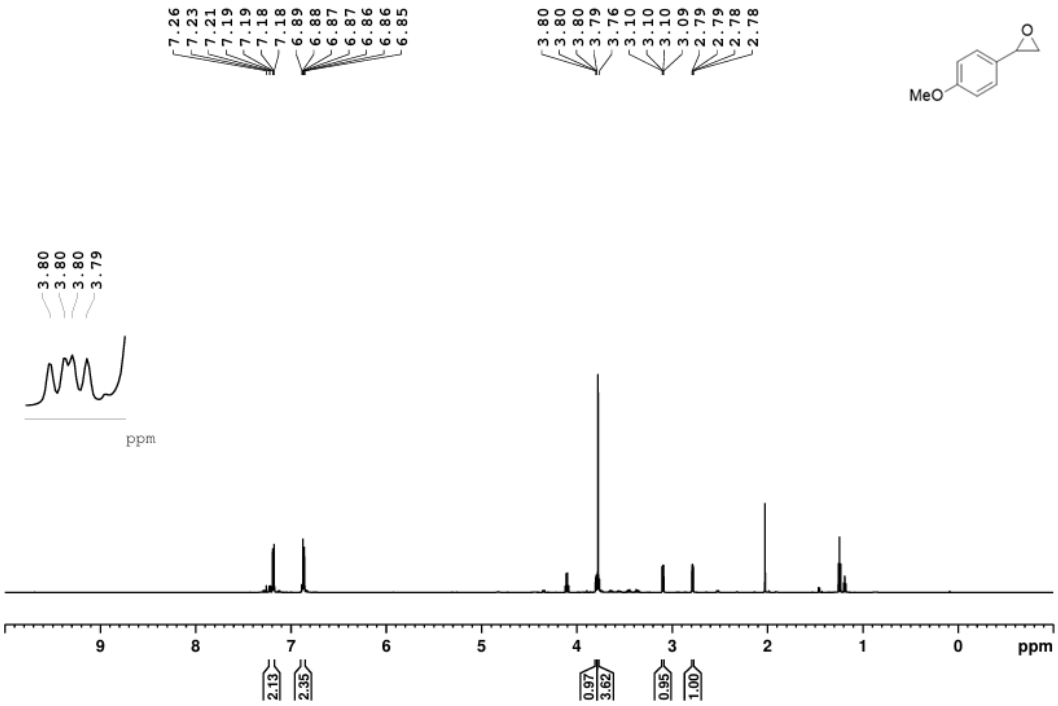
*Spectrum 20: [13]C NMR of 2-(4-nitrophenyl)oxirane (**3a**)*



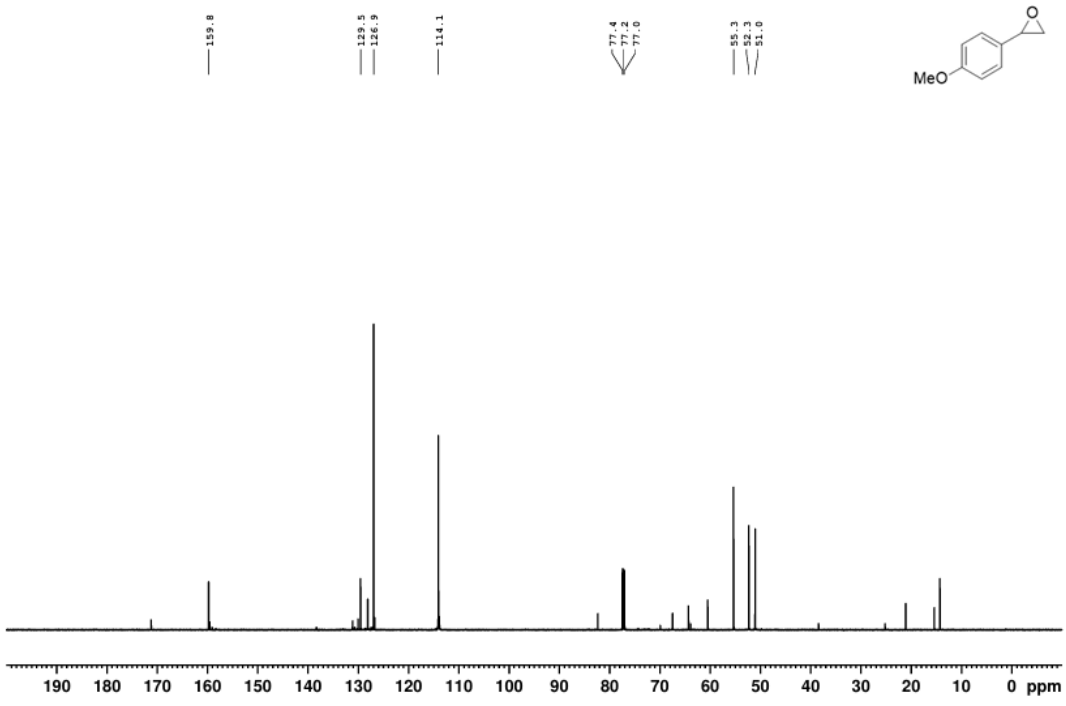
*Spectrum 21: ^{1}H NMR of 2-(4-methylphenyl)oxirane (**3b**)*



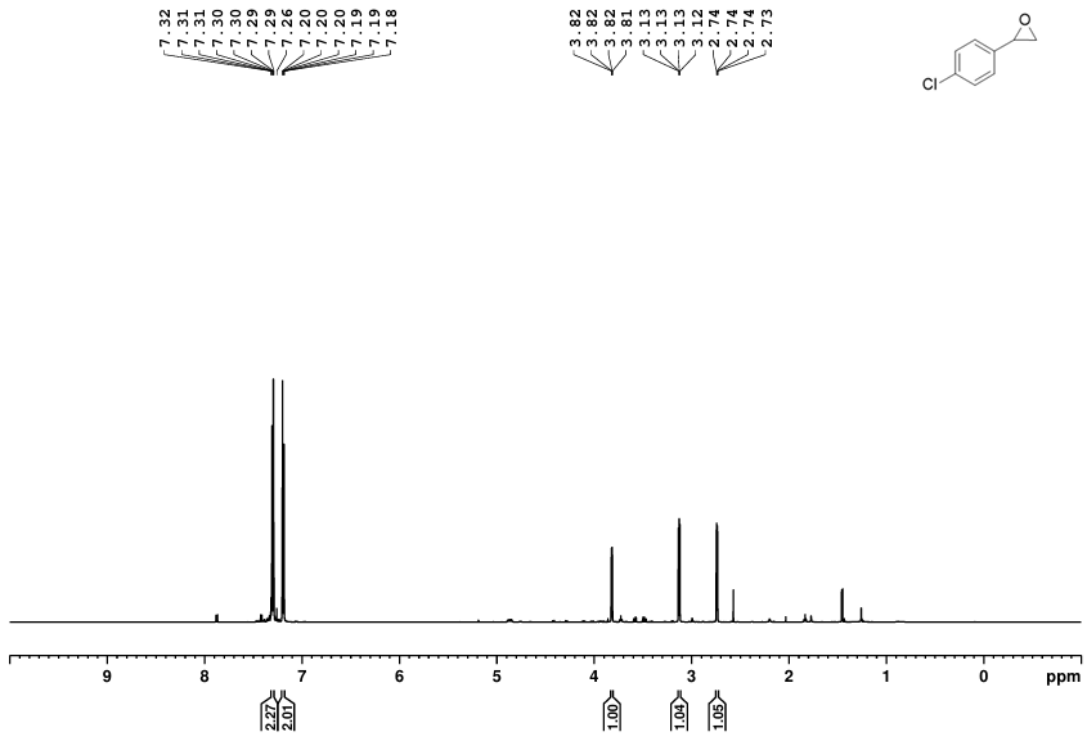
*Spectrum 22: ^{13}C NMR of 2-(4-methylphenyl)oxirane (**3b**)*



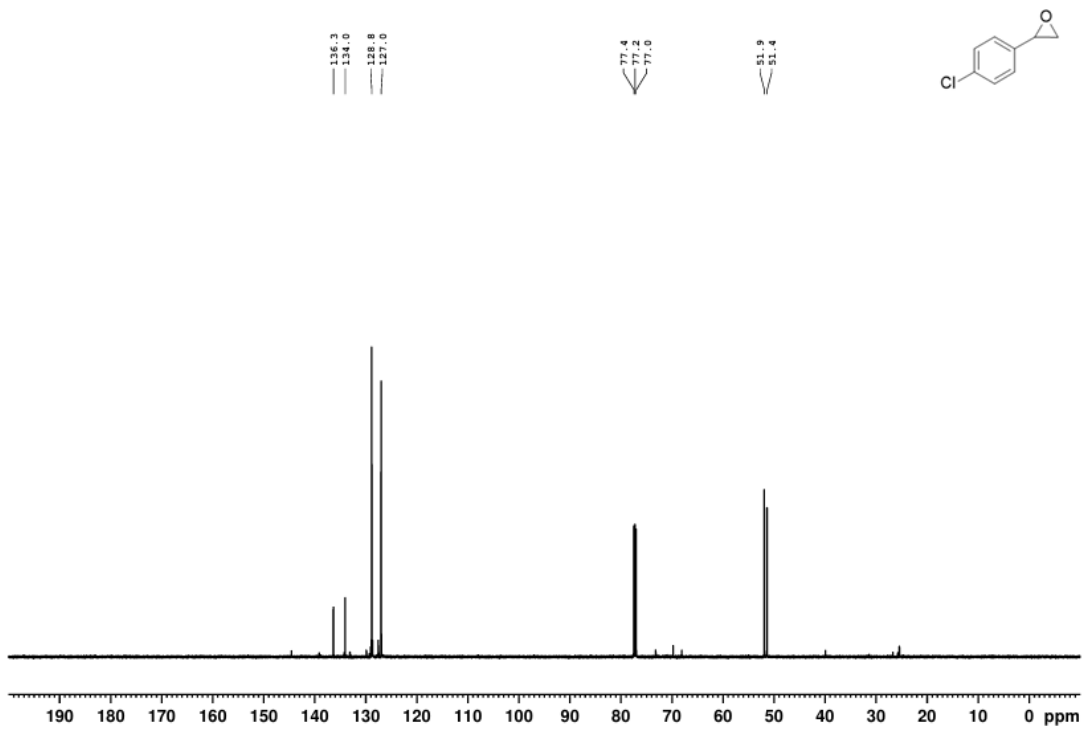
*Spectrum 23: [1]H NMR of 2-(4-methoxyphenyl)oxirane (**3c**)*



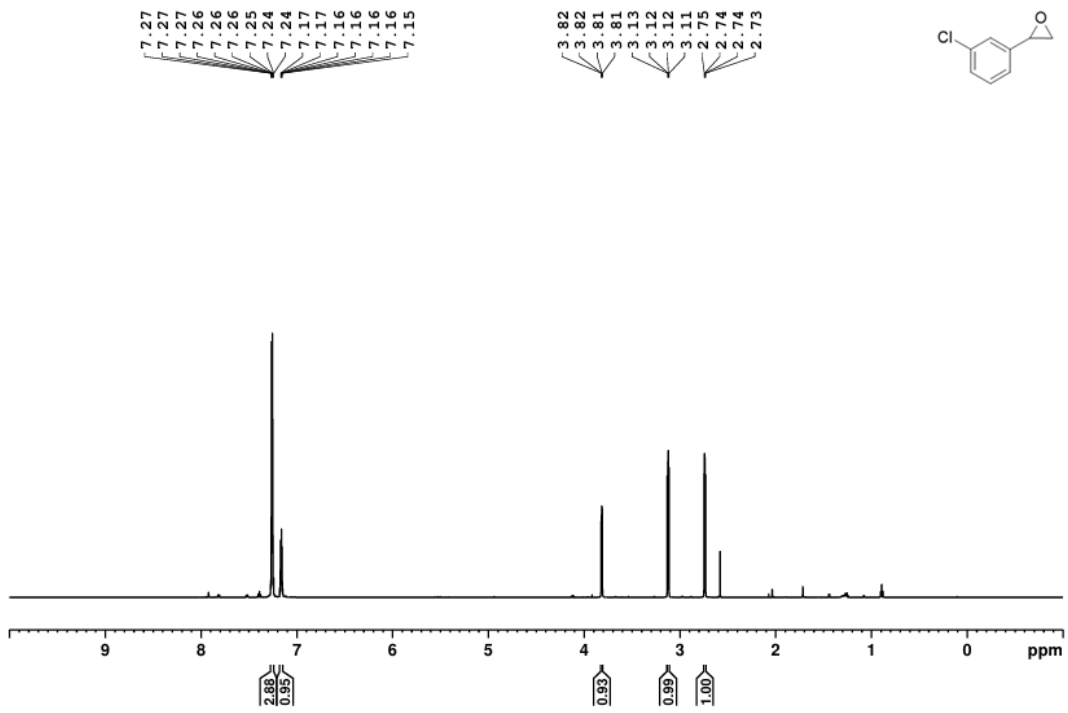
*Spectrum 24: [13]C NMR of 2-(4-methoxyphenyl)oxirane (**3c**)*



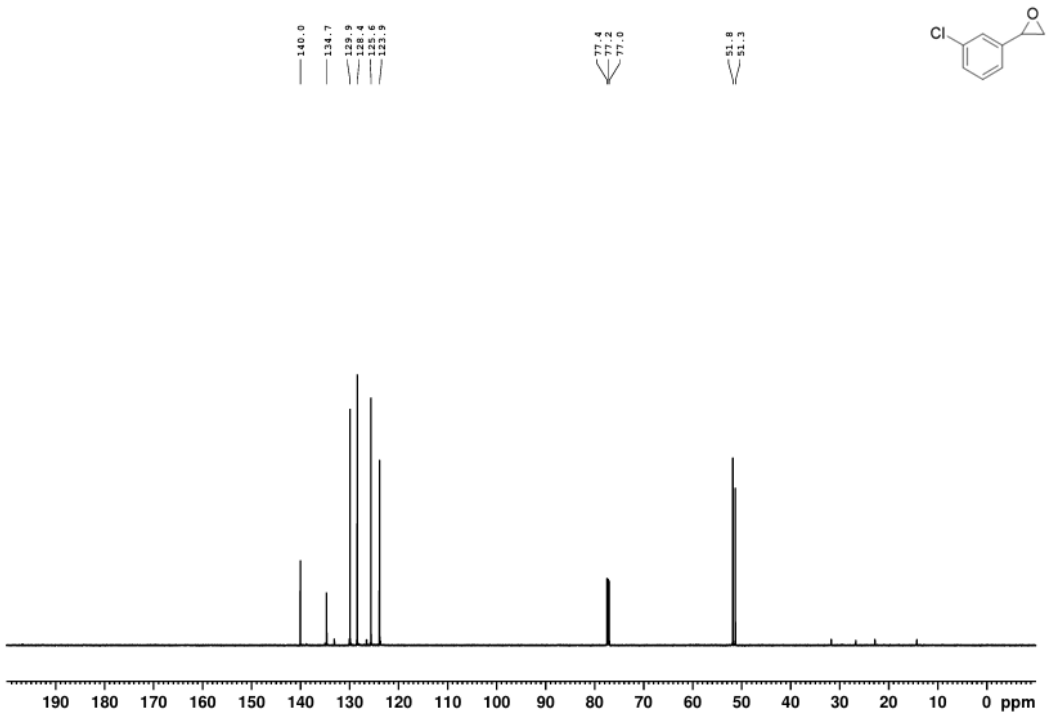
*Spectrum 25: [1]H NMR of 2-(4-chlorophenyl)oxirane (**3d**)*



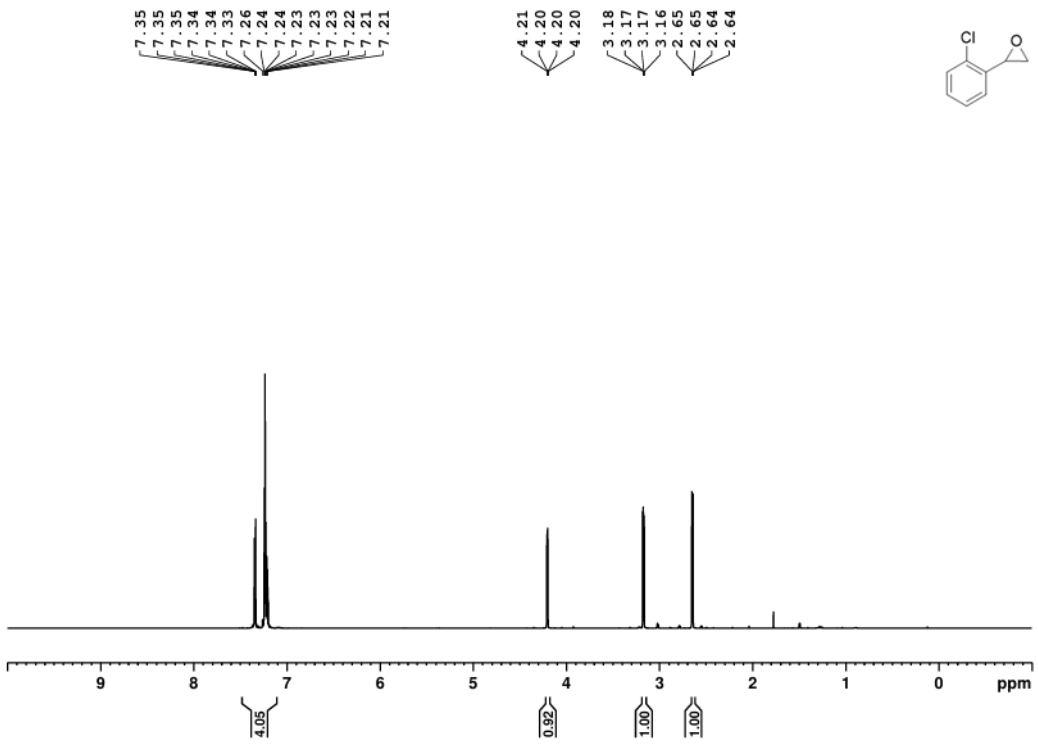
*Spectrum 26: [13]C NMR of 2-(4-chlorophenyl)oxirane (**3d**)*



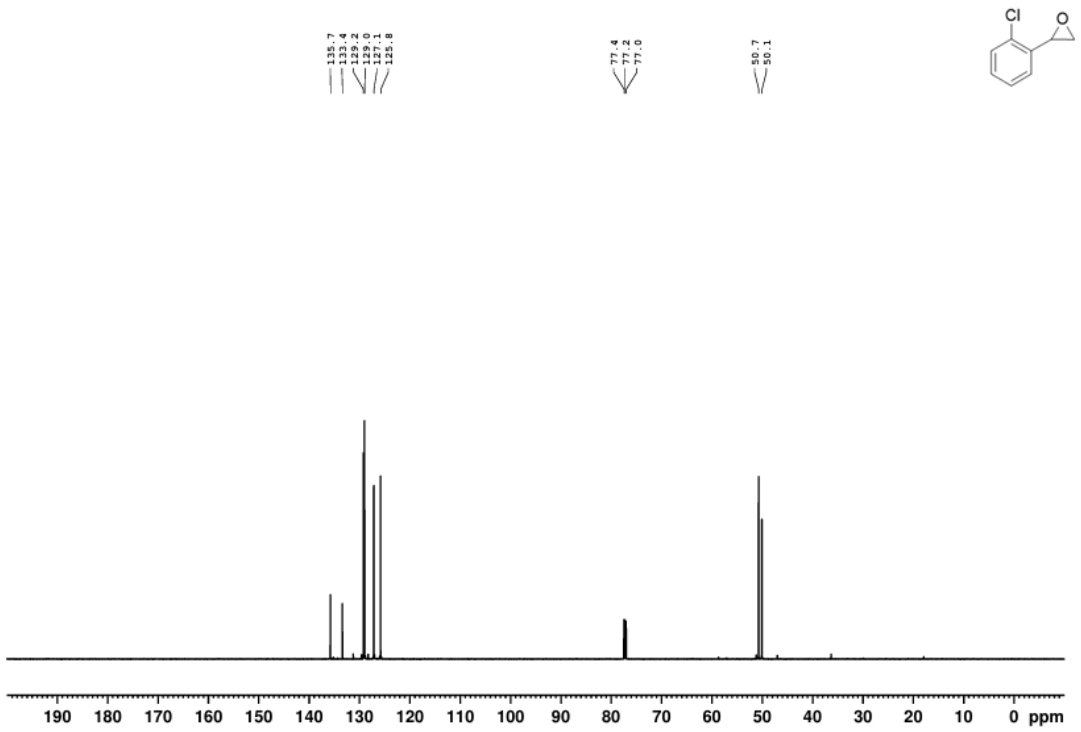
*Spectrum 27: [1]H NMR of 2-(3-chlorophenyl)oxirane (**3e**)*



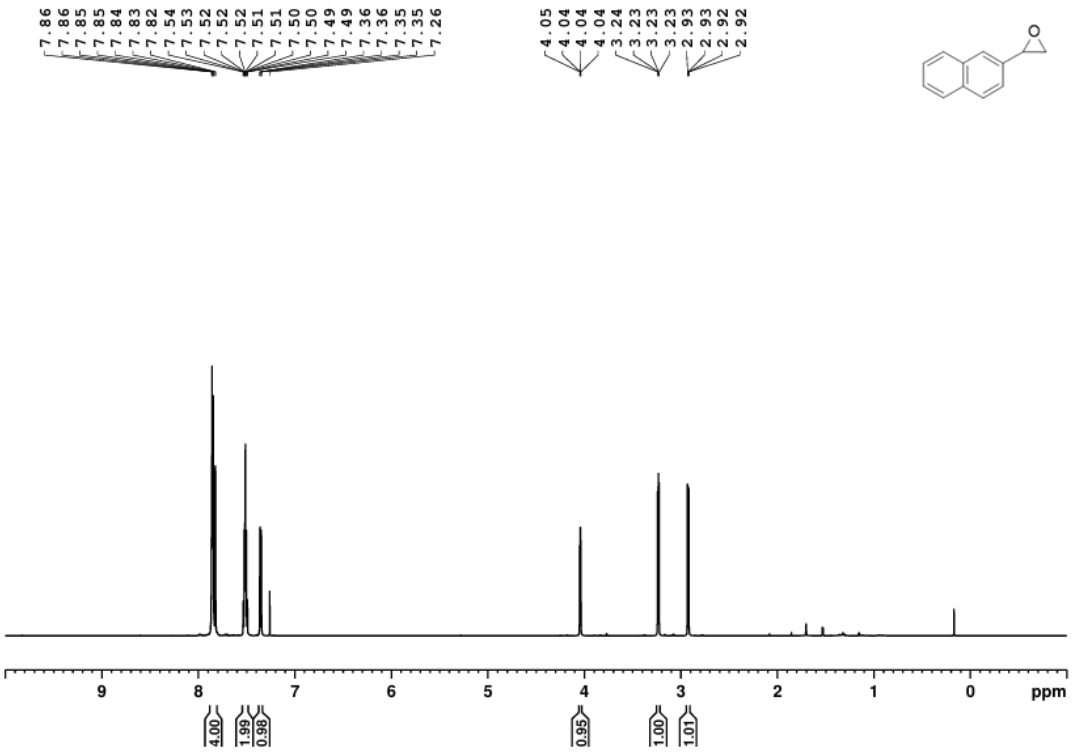
*Spectrum 28: [13]C NMR of 2-(3-chlorophenyl)oxirane (**3e**)*



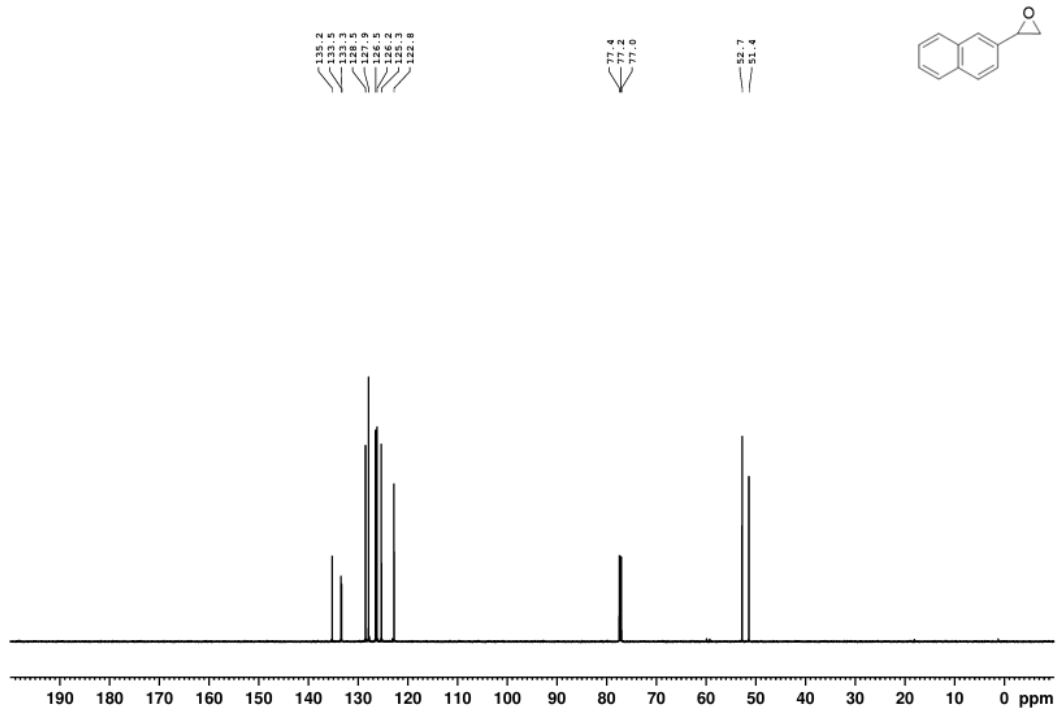
*Spectrum 29: [1]H NMR of 2-(2-chlorophenyl)oxirane (**3f**)*



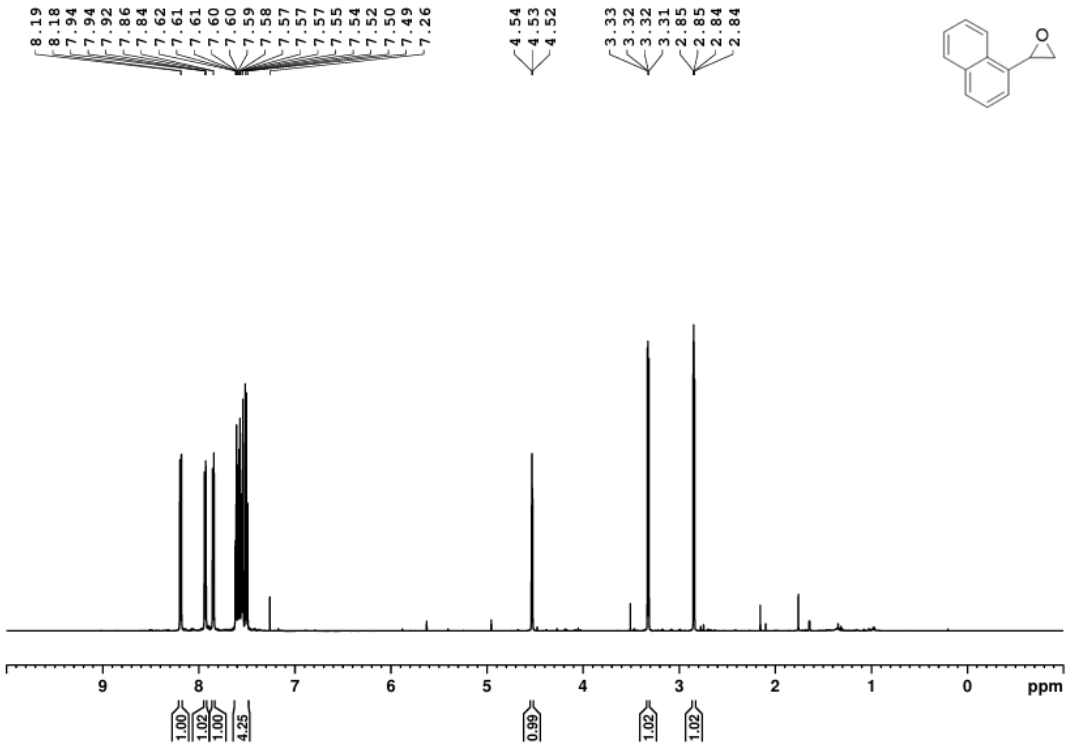
*Spectrum 30: [13]C NMR of 2-(2-chlorophenyl)oxirane (**3f**)*



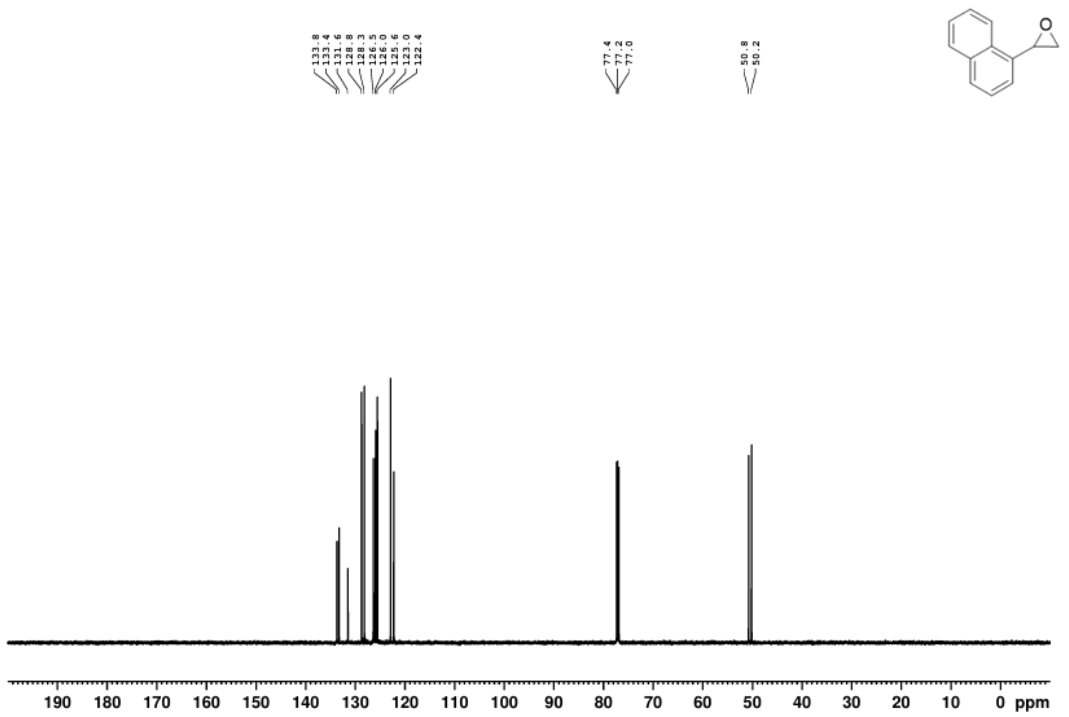
*Spectrum 31: [1]H NMR of 2-(naphthalen-2-yl)oxirane (**3g**)*



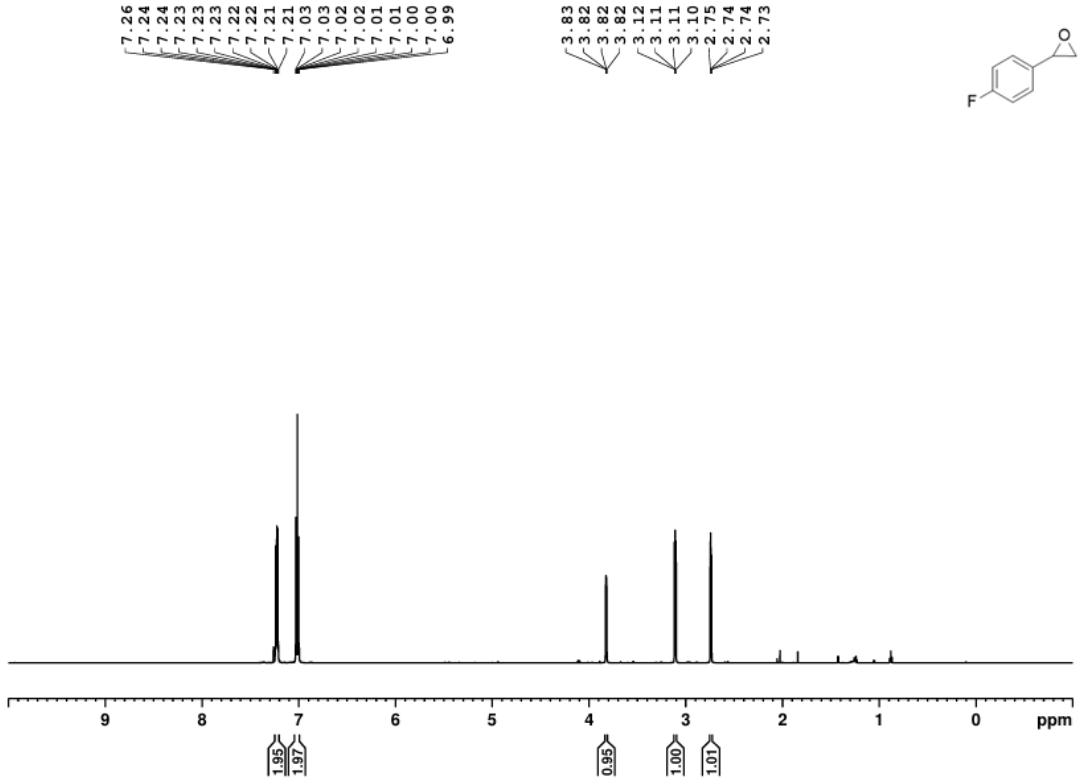
*Spectrum 32: [13]C NMR of 2-(naphthalen-2-yl)oxirane (**3g**)*



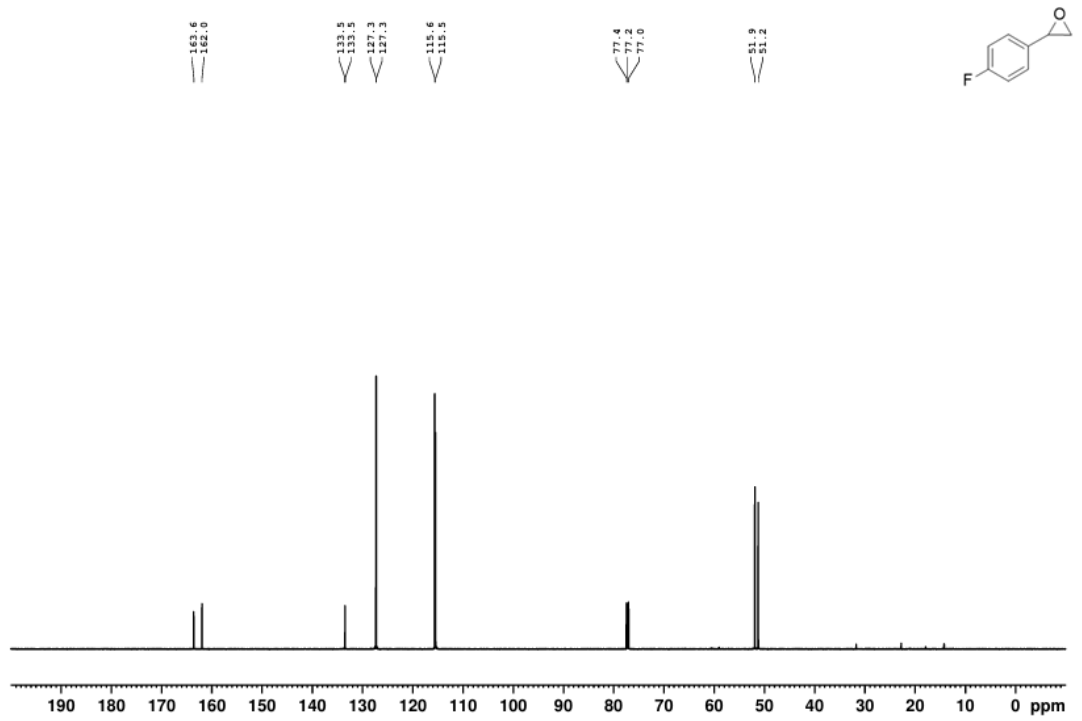
*Spectrum 33: [1]H NMR of 2-(naphthalen-1-yl)oxirane (**3h**)*



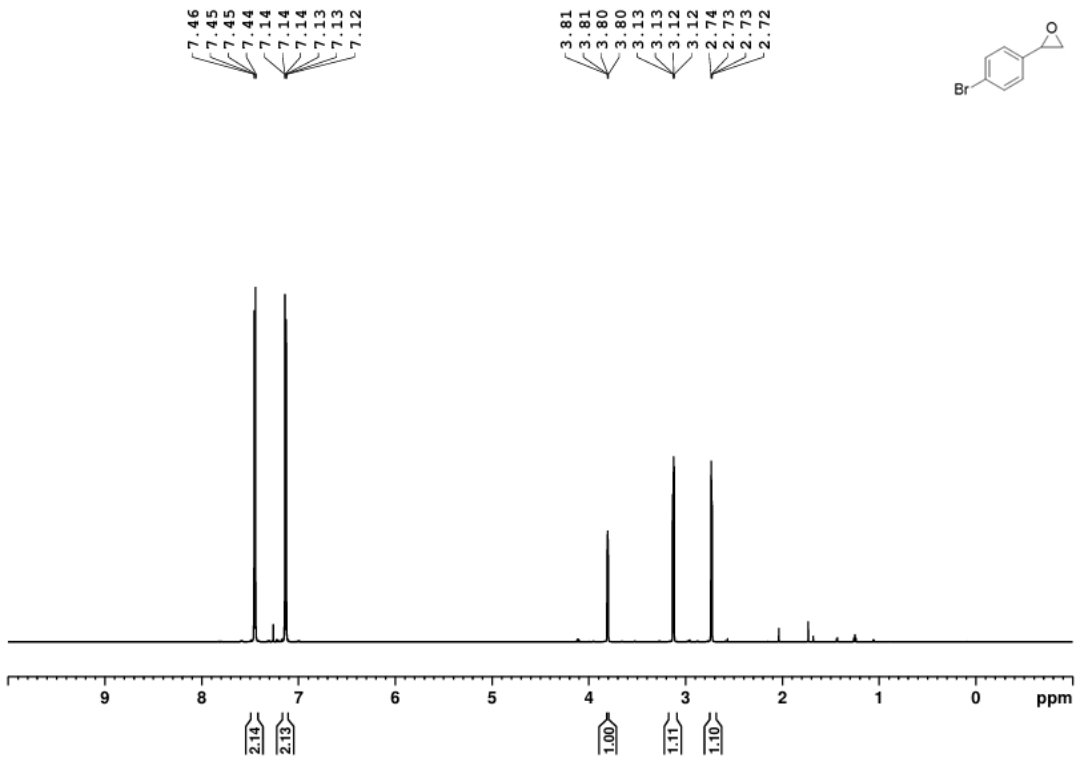
*Spectrum 34: [13]C NMR of 2-(naphthalen-1-yl)oxirane (**3h**)*



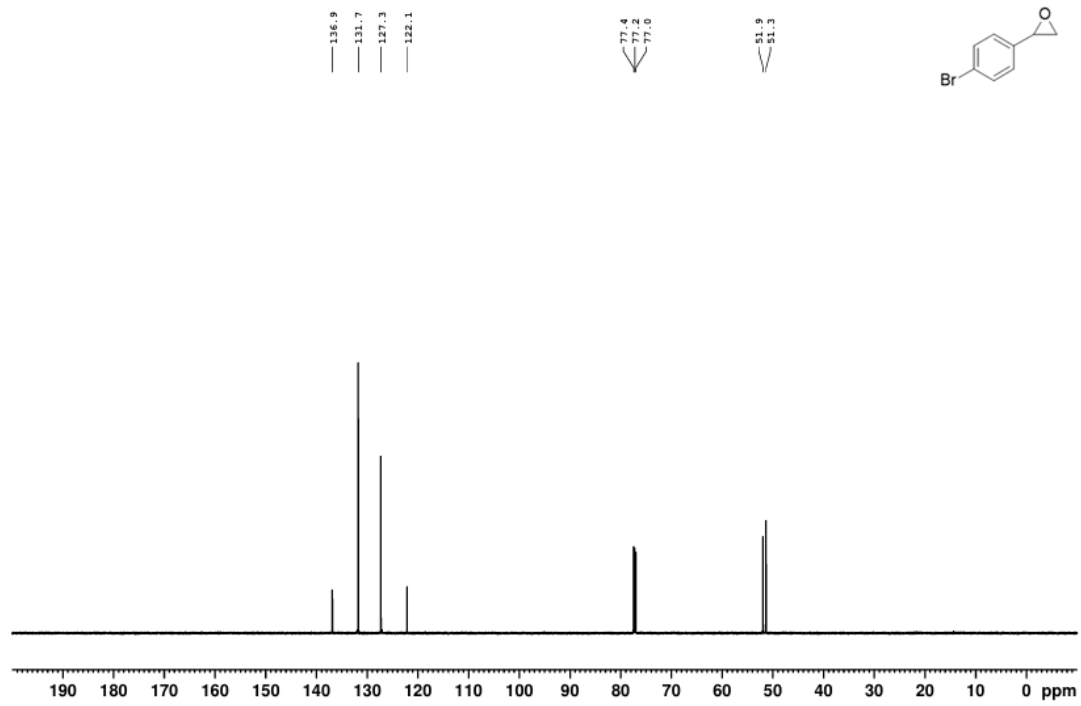
*Spectrum 35: ^{1}H NMR of 2-(4-fluorophenyl)oxirane (**3i**)*



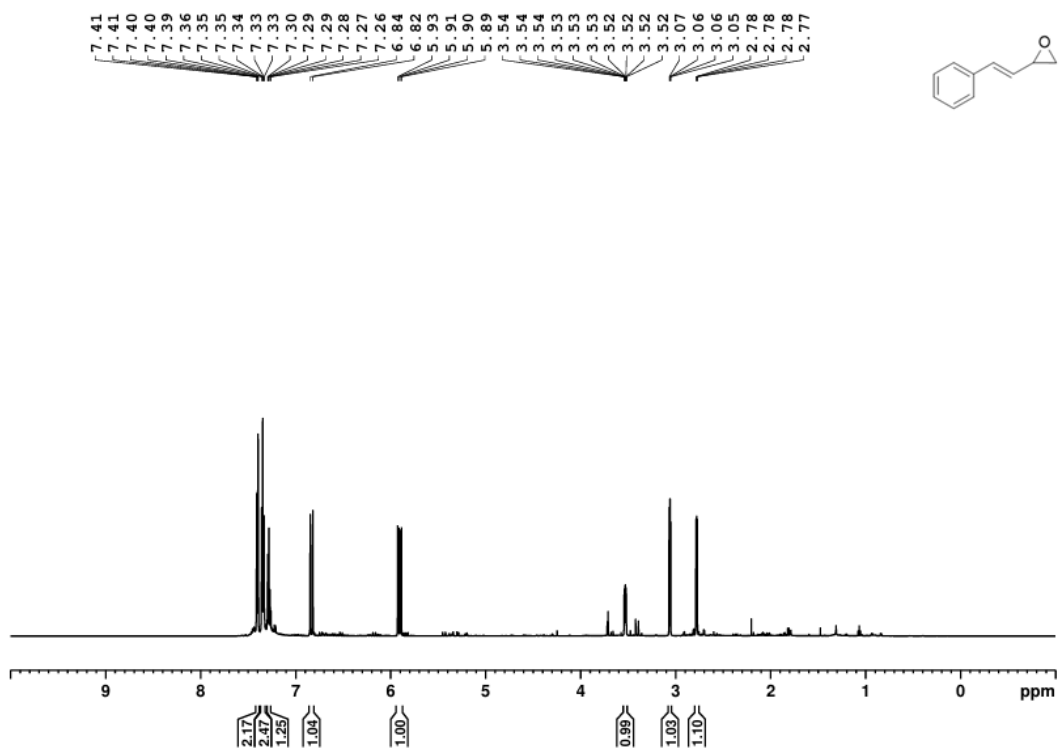
*Spectrum 36: ^{13}C NMR of 2-(4-fluorophenyl)oxirane (**3i**)*



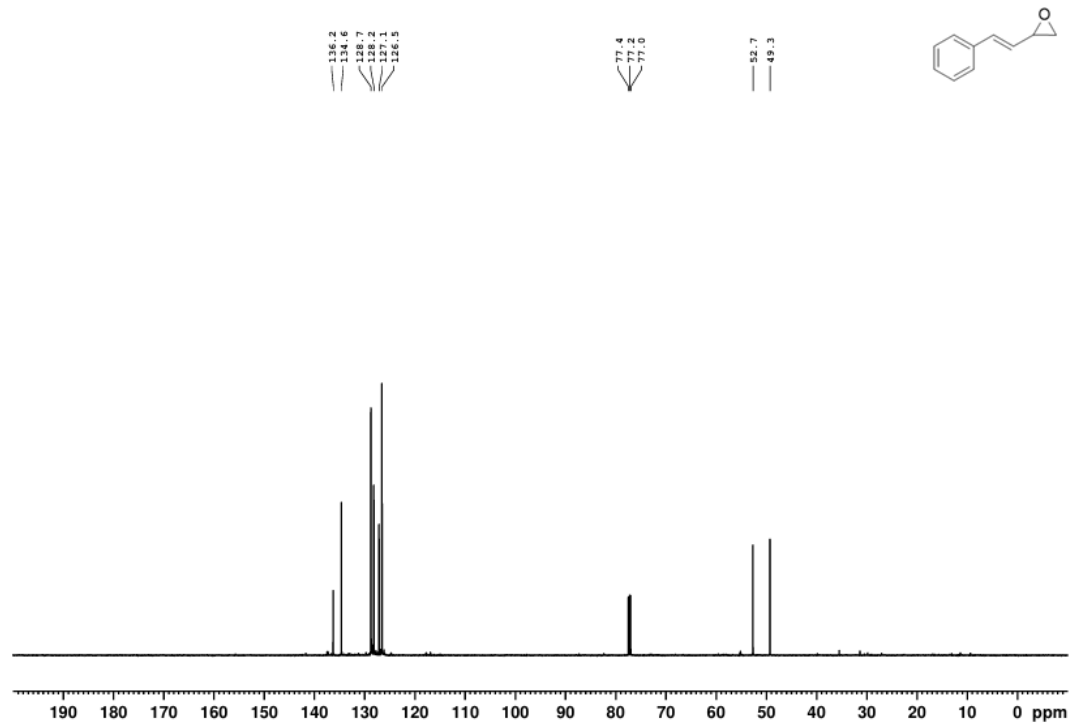
*Spectrum 37: [1]H NMR of 2-(4-bromophenyl)oxirane (**3j**)*



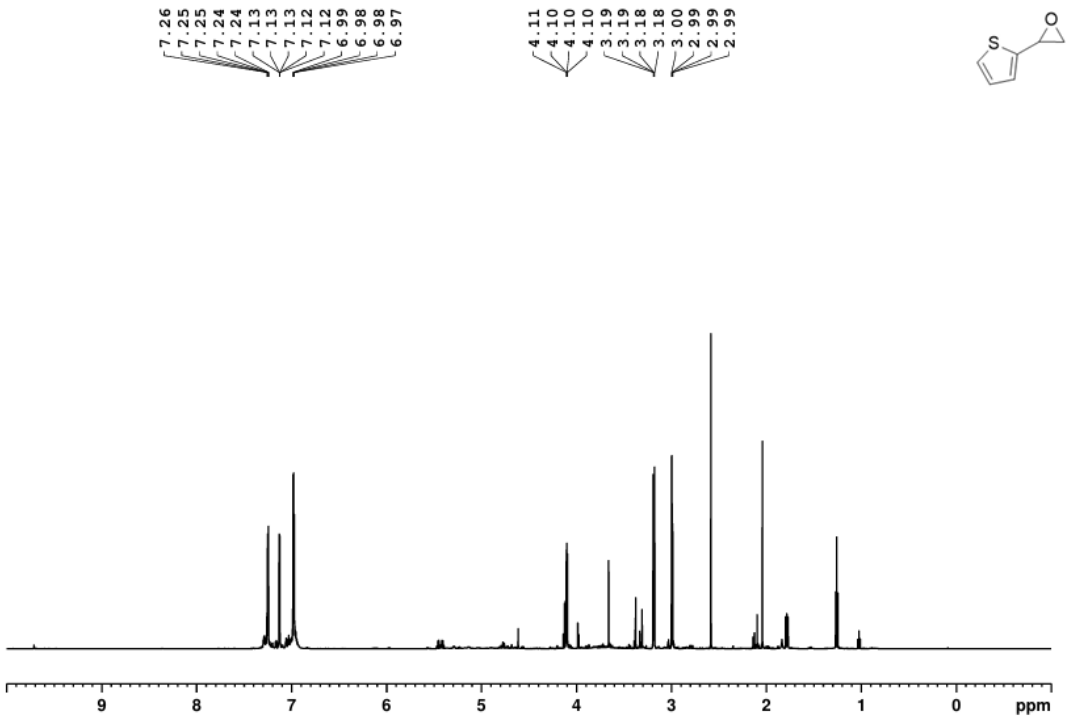
*Spectrum 38: [13]C NMR of 2-(4-bromophenyl)oxirane (**3j**)*



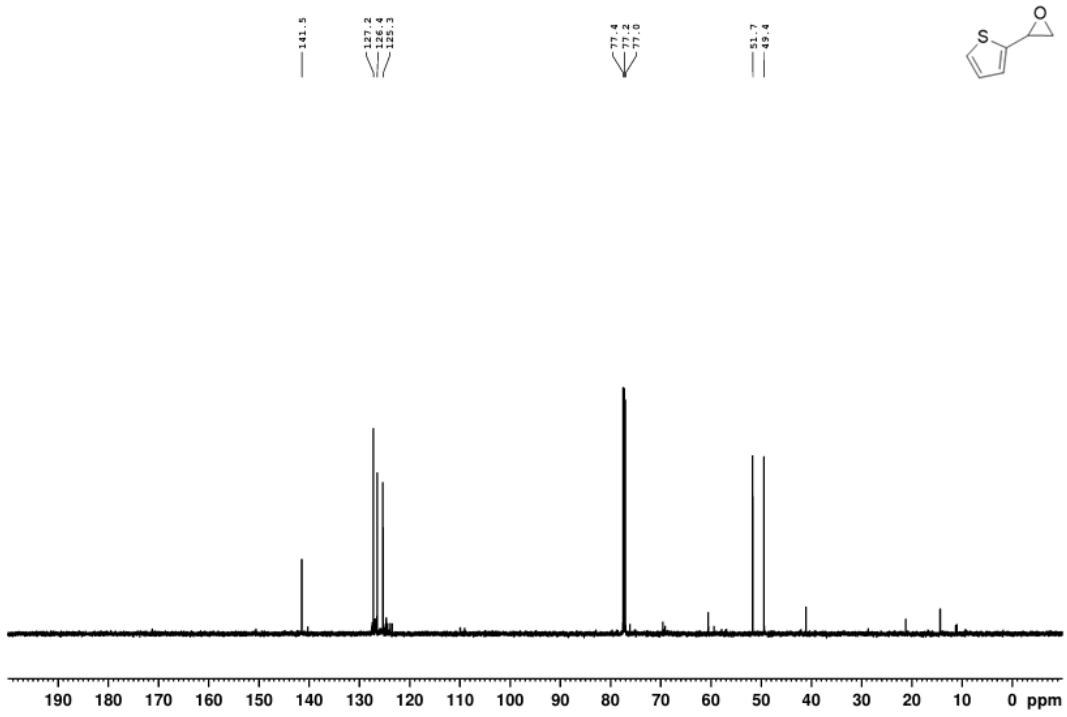
*Spectrum 39: [1]H NMR of 2-styryloxirane (**3k**)*



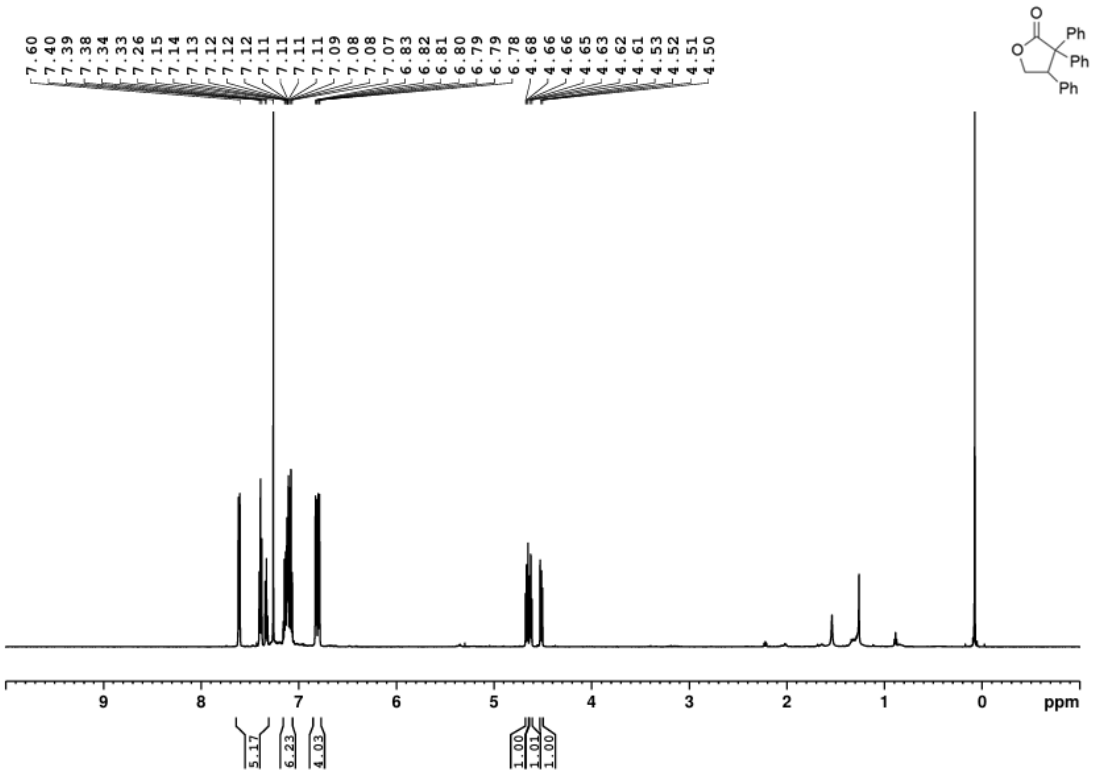
*Spectrum 40: [13]C NMR of 2-styryloxirane (**3k**)*



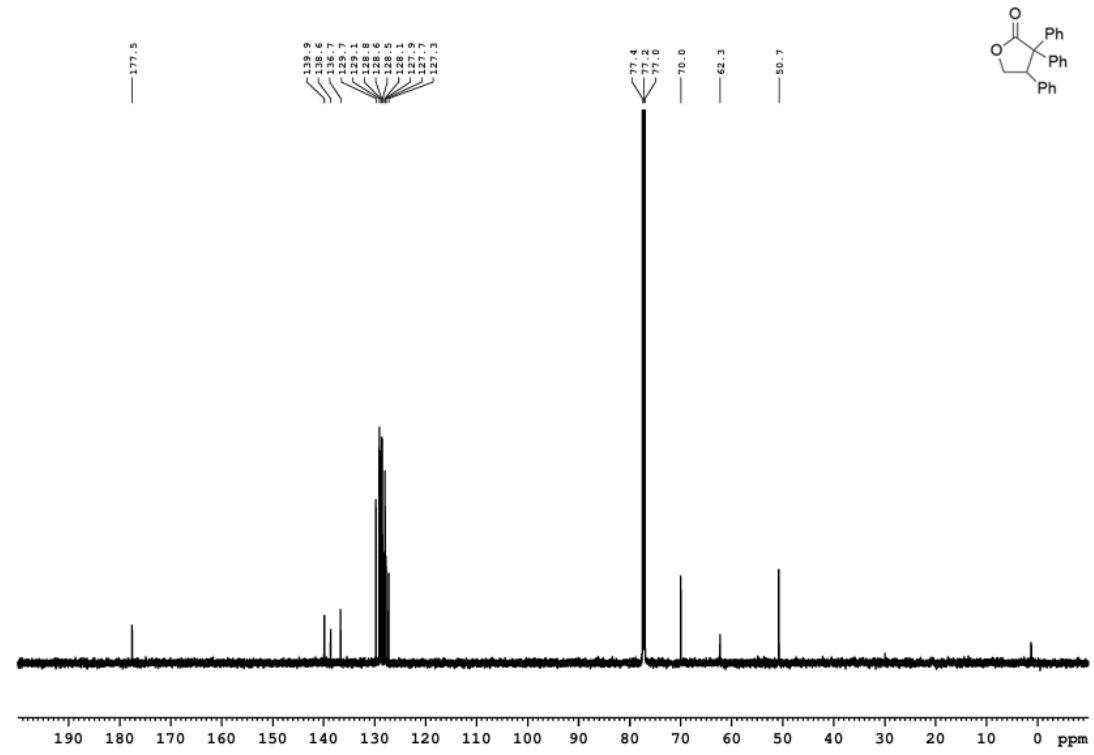
*Spectrum 41: [1]H NMR of 2-(thiophen-2-yl)oxirane (**3l**)*



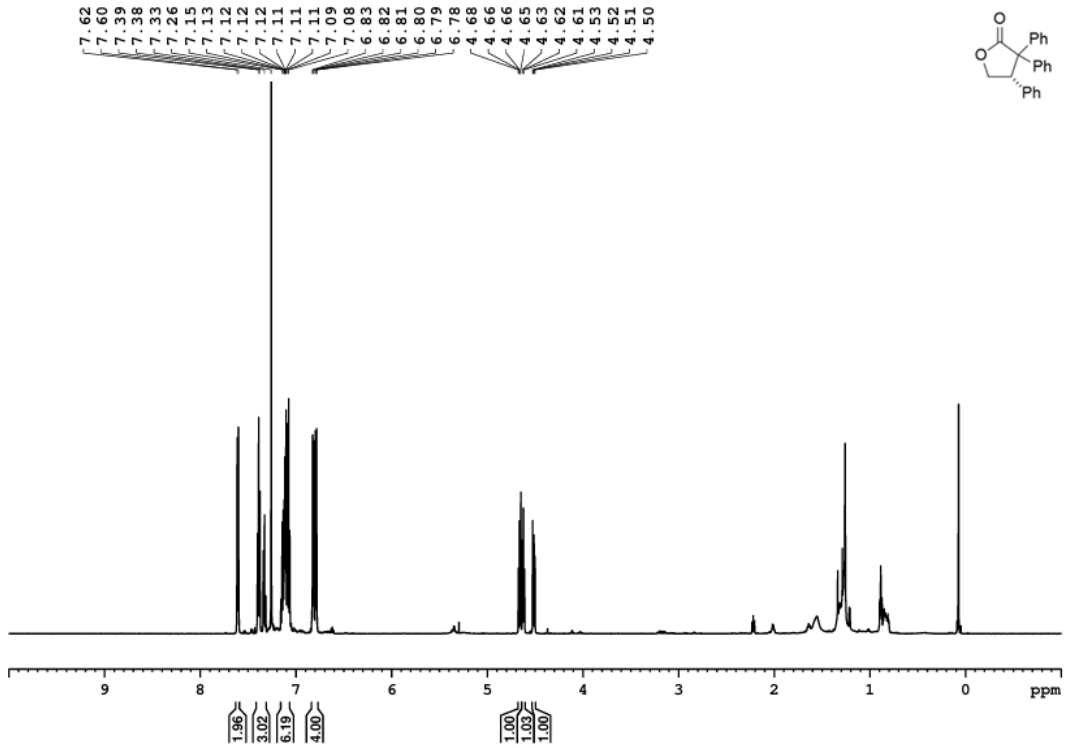
*Spectrum 42: [13]C NMR of 2-(thiophen-2-yl)oxirane (**3l**)*



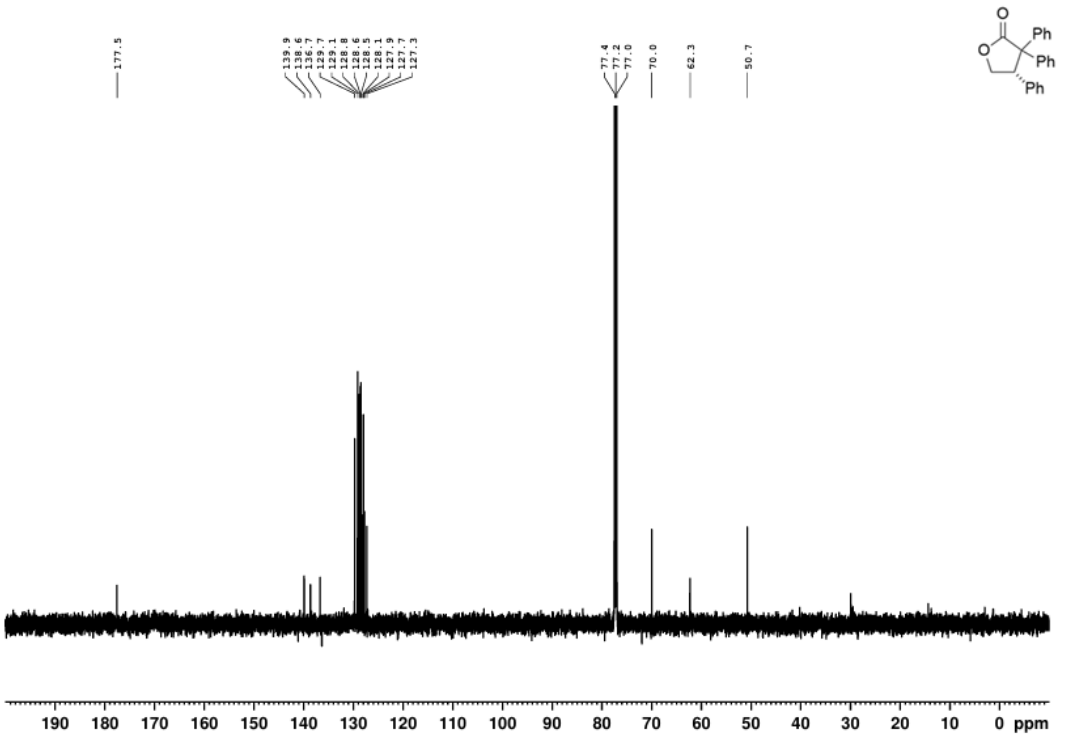
*Spectrum 43: [1]H NMR of 3,3,4-triphenyldihydrofuran-2(3H)-one(**4a**)*



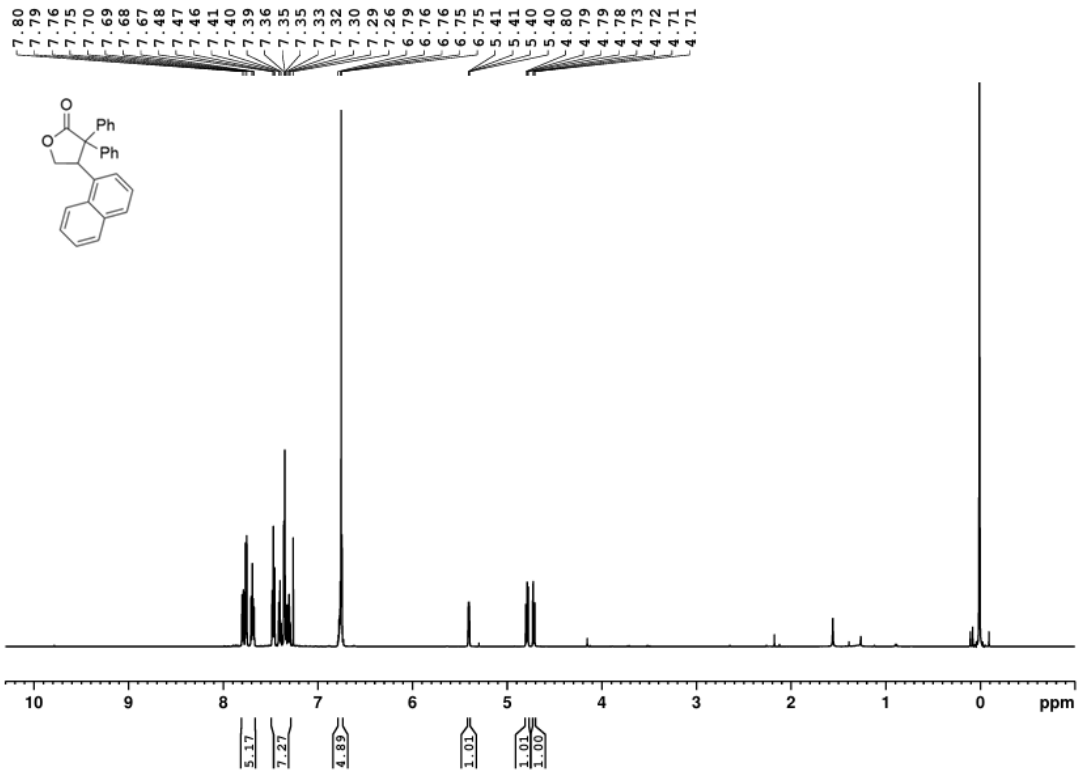
*Spectrum 44: [13]C NMR of 3,3,4-triphenyldihydrofuran-2(3H)-one(**4a**)*



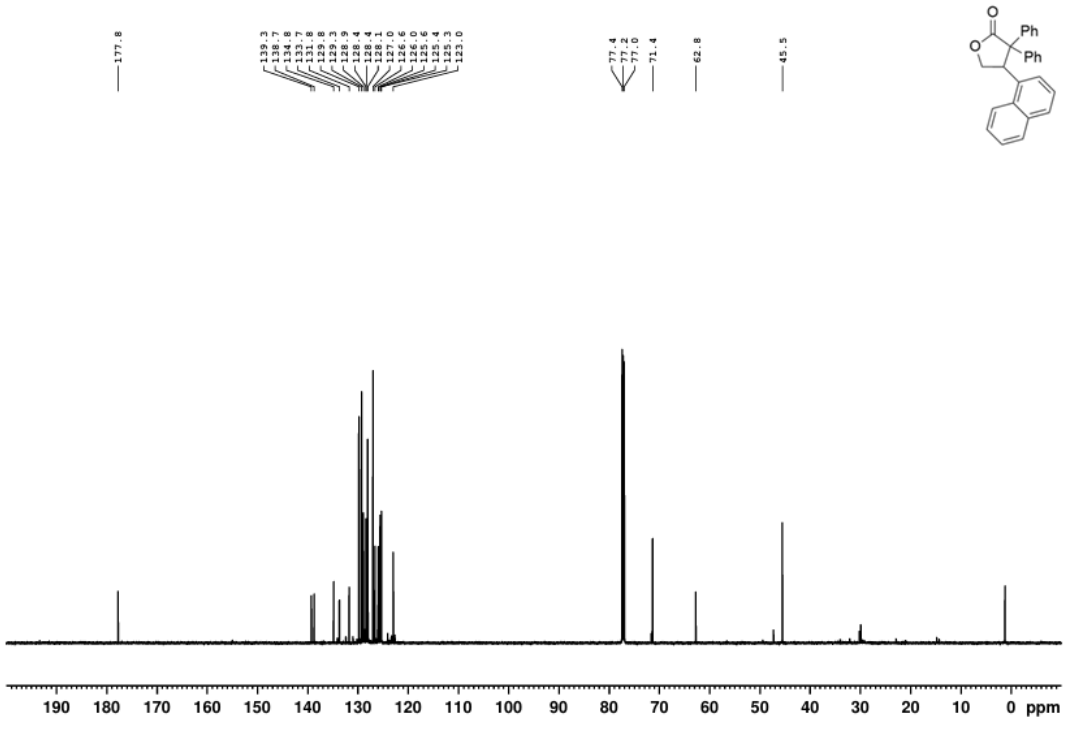
*Spectrum 45: [1]H NMR of 3,3,4-triphenyldihydrofuran-2(3H)-one (**4b**)*



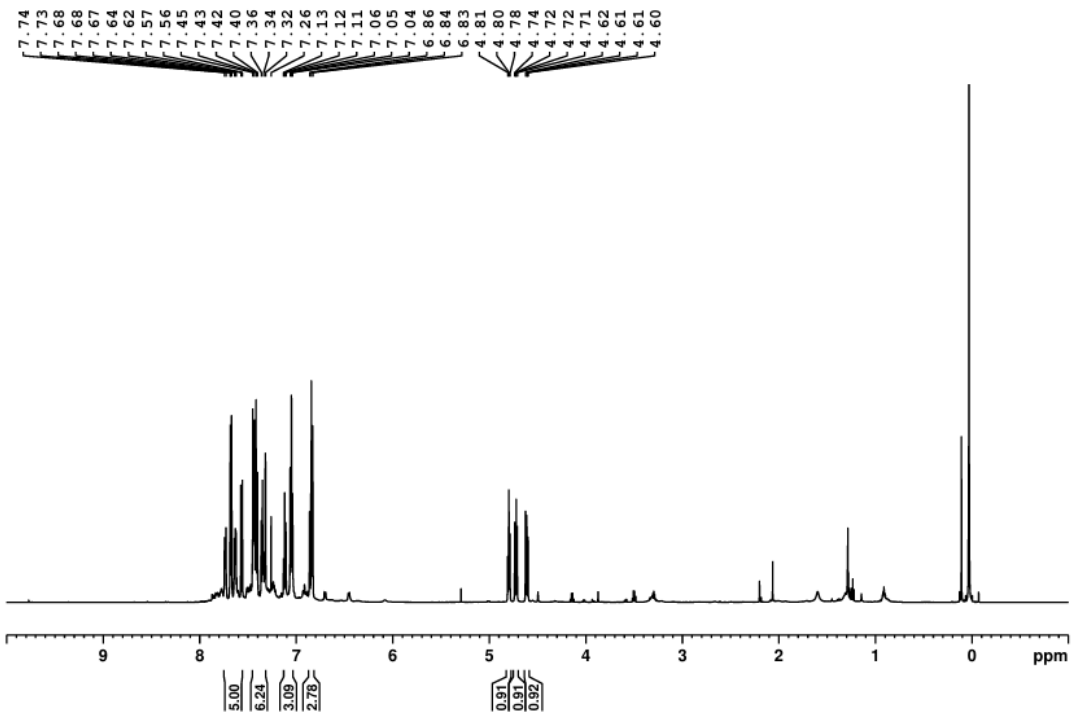
*Spectrum 46: [13]C NMR of 3,3,4-triphenyldihydrofuran-2(3H)-one (**4b**)*



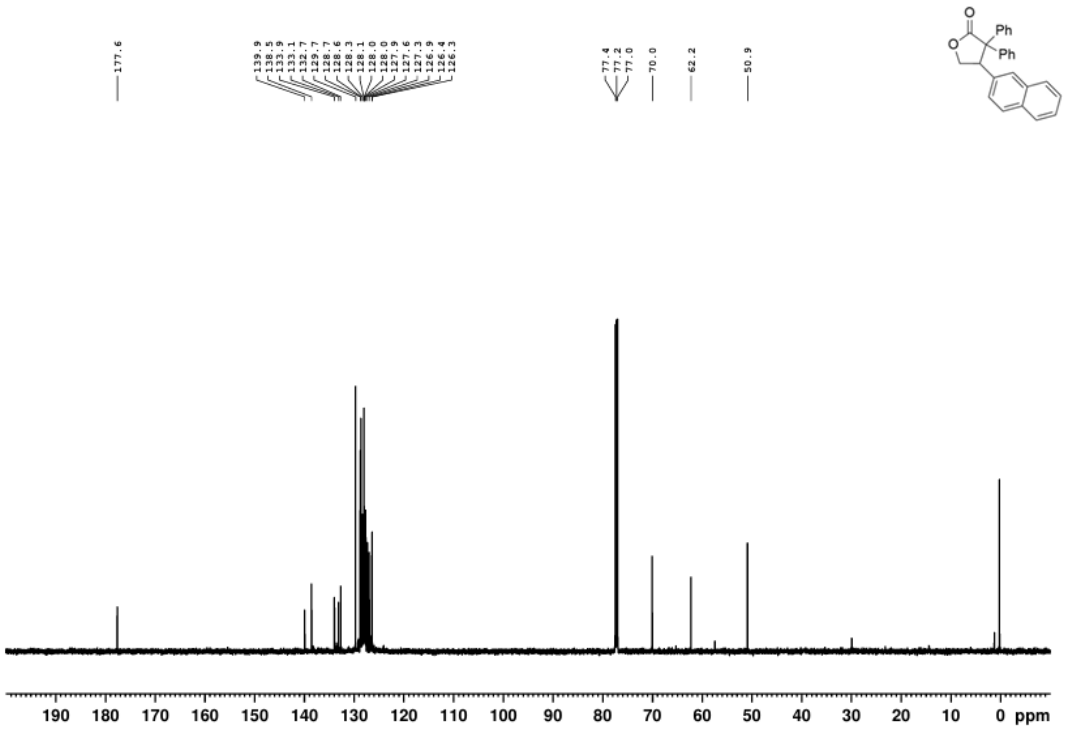
*Spectrum 47: [1]H NMR of 4-(naphthalen-1-yl)-3,3-diphenyldihydrofuran-2(3H)-one(**4c**)*



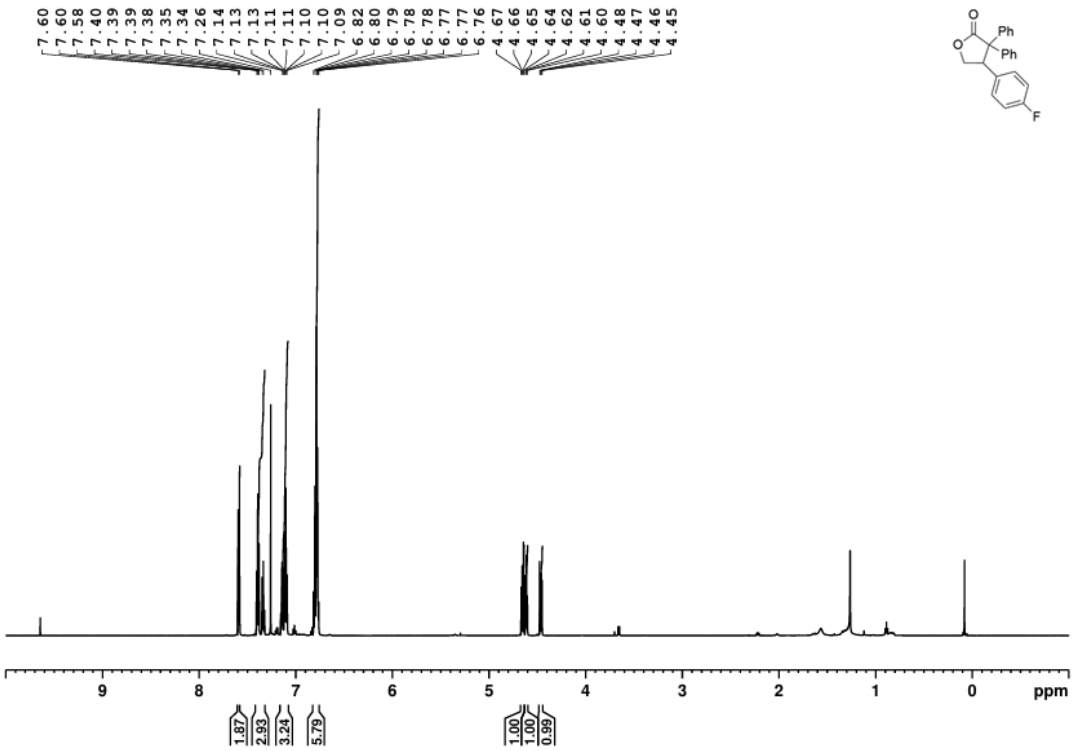
*Spectrum 48: [13]C NMR of 4-(naphthalen-1-yl)-3,3-diphenyldihydrofuran-2(3H)-one(**4c**)*



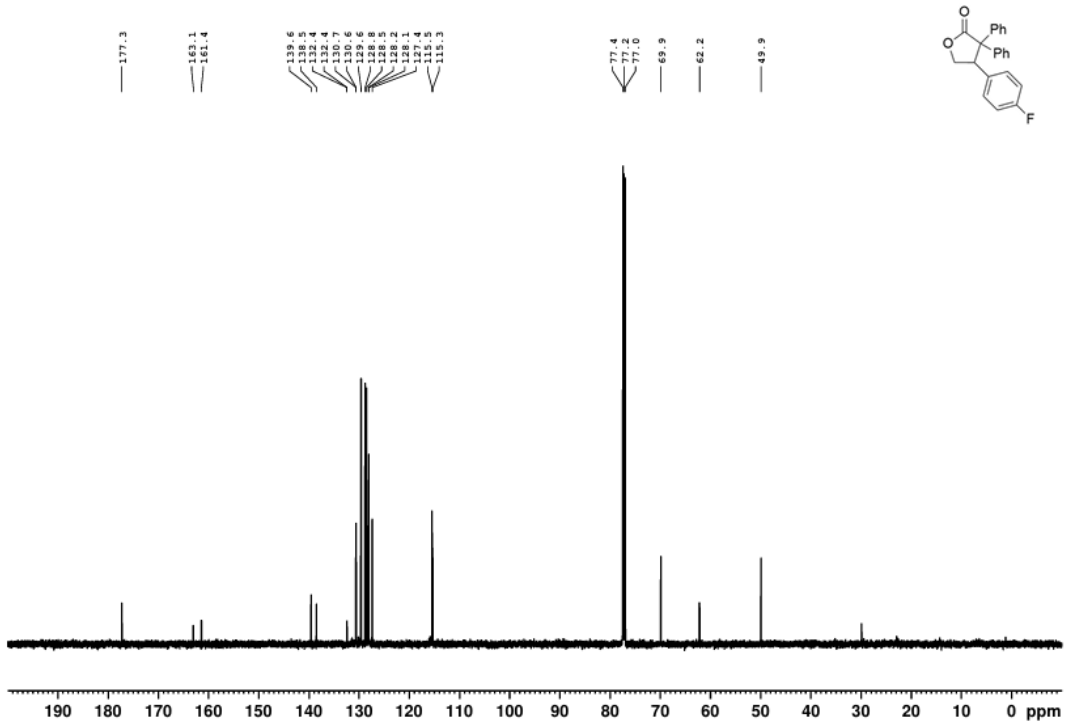
*Spectrum 49: [1]H NMR of 4-(naphthalen-2-yl)-3,3-diphenyldihydrofuran-2(3H)-one(**4d**)*



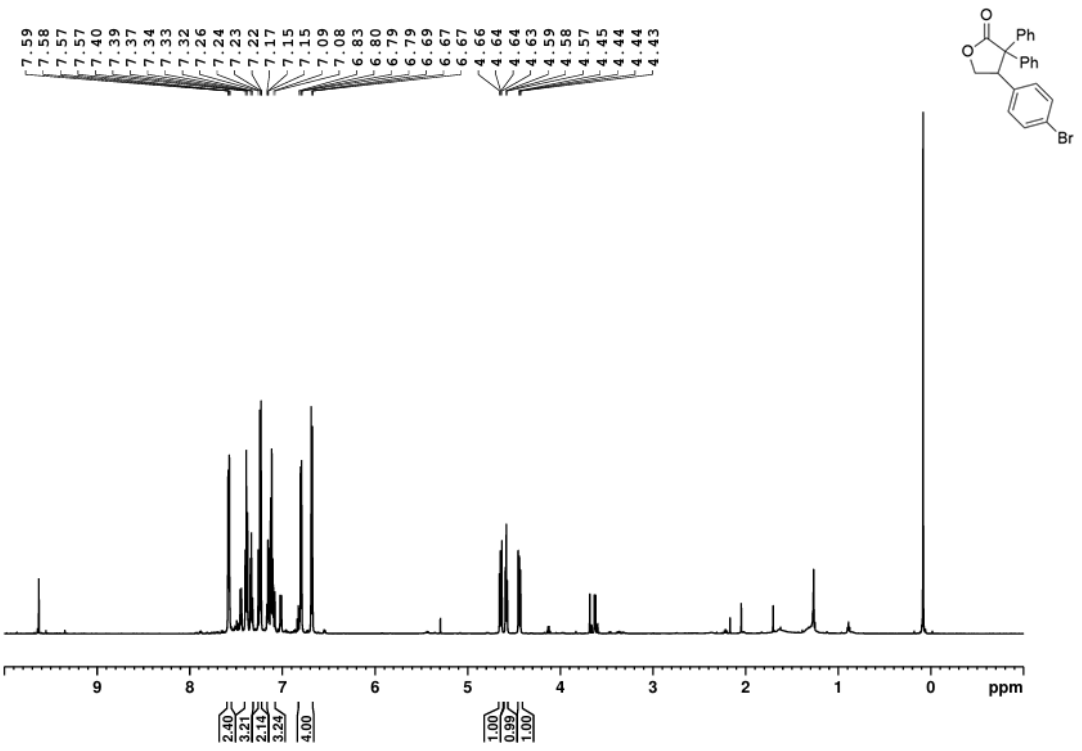
*Spectrum 50: [13] C NMR of 4-(naphthalen-2-yl)-3,3-diphenyldihydrofuran-2(3H)-one(**4d**)*



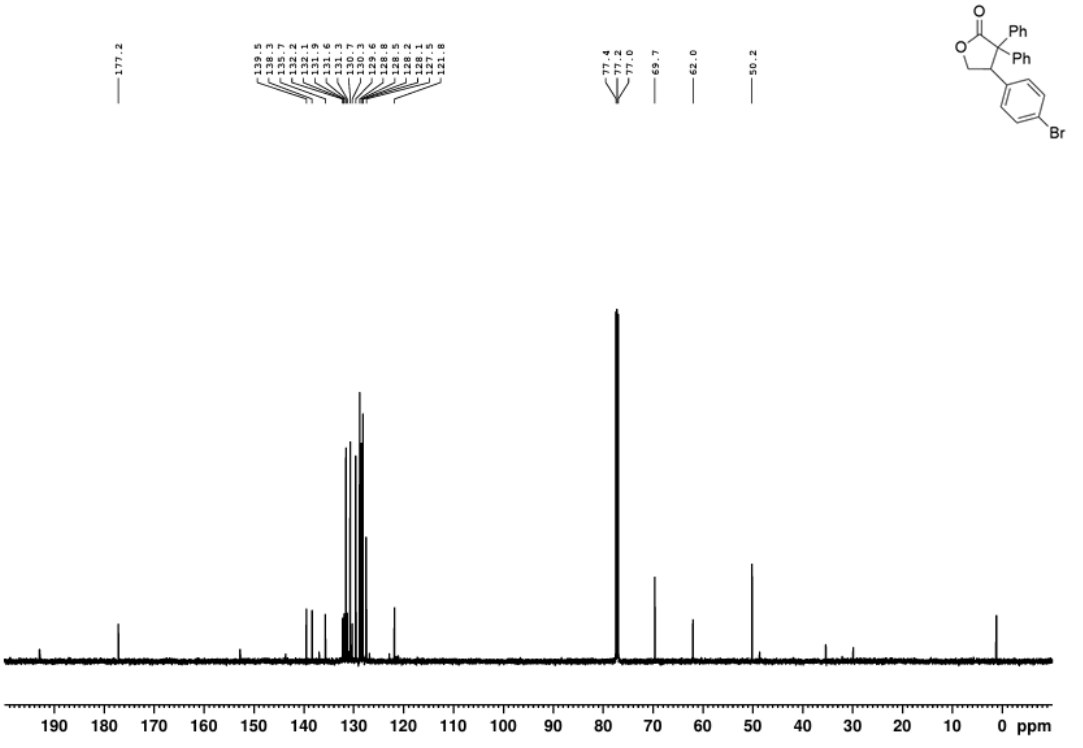
*Spectrum 51: [1]H NMR of 4-(4-fluorophenyl)-3,3-diphenyldihydrofuran-2(3H)-one(**4e**)*



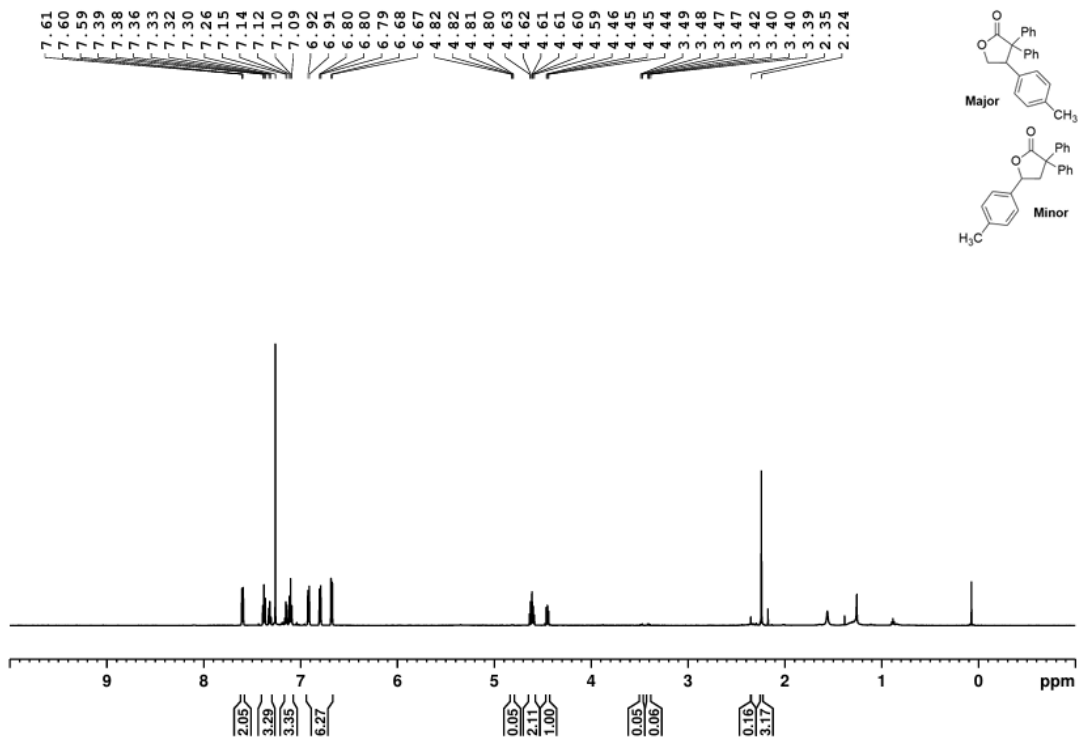
*Spectrum 52: [13]C NMR of 4-(4-fluorophenyl)-3,3-diphenyldihydrofuran-2(3H)-one(**4e**)*



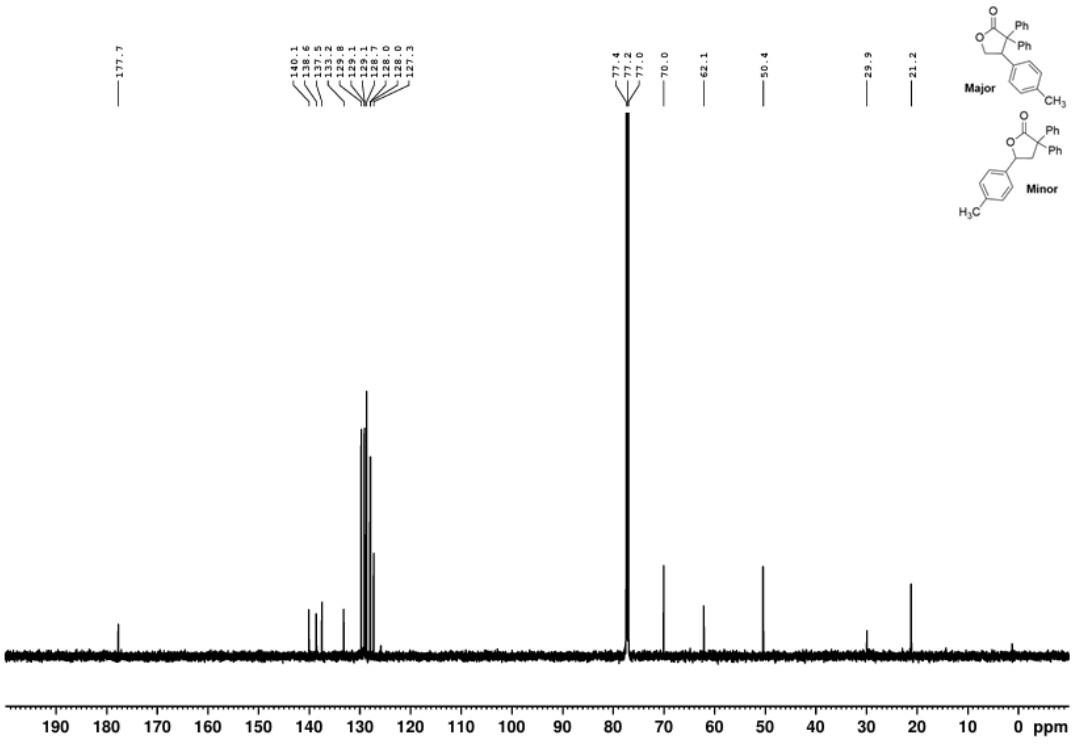
*Spectrum 53: [1]H NMR of 4-(4-bromophenyl)-3,3-diphenyldihydrofuran-2(3H)-one(**4f**)*



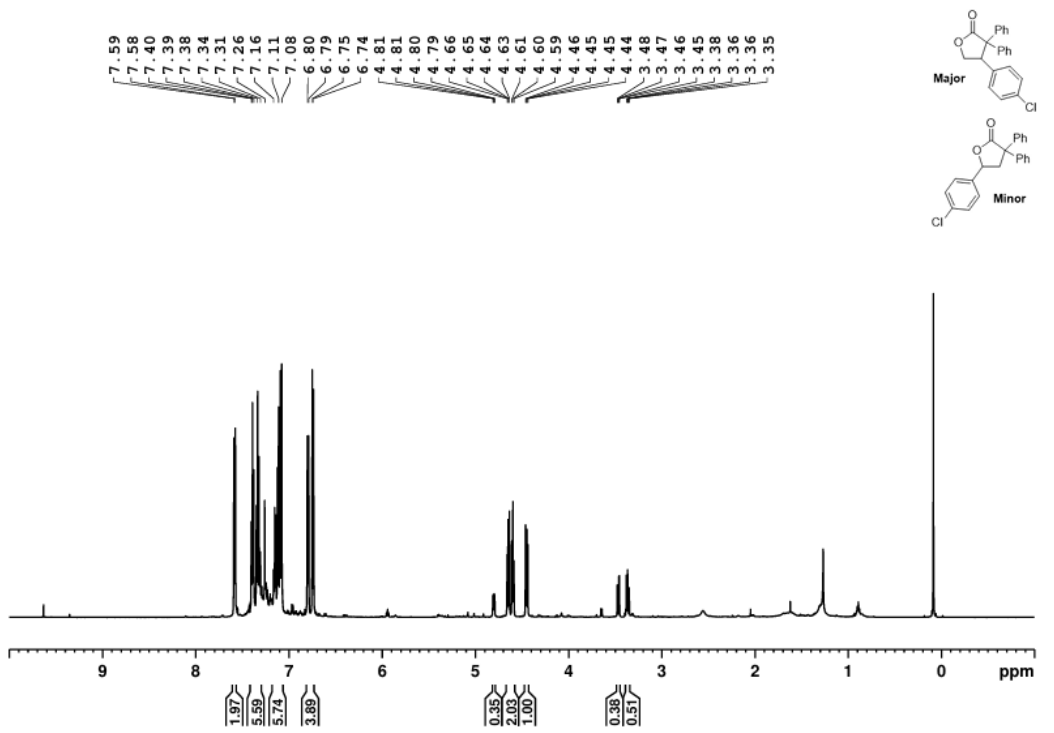
*Spectrum 54: [13]C NMR of 4-(4-bromophenyl)-3,3-diphenyldihydrofuran-2(3H)-one(**4f**)*



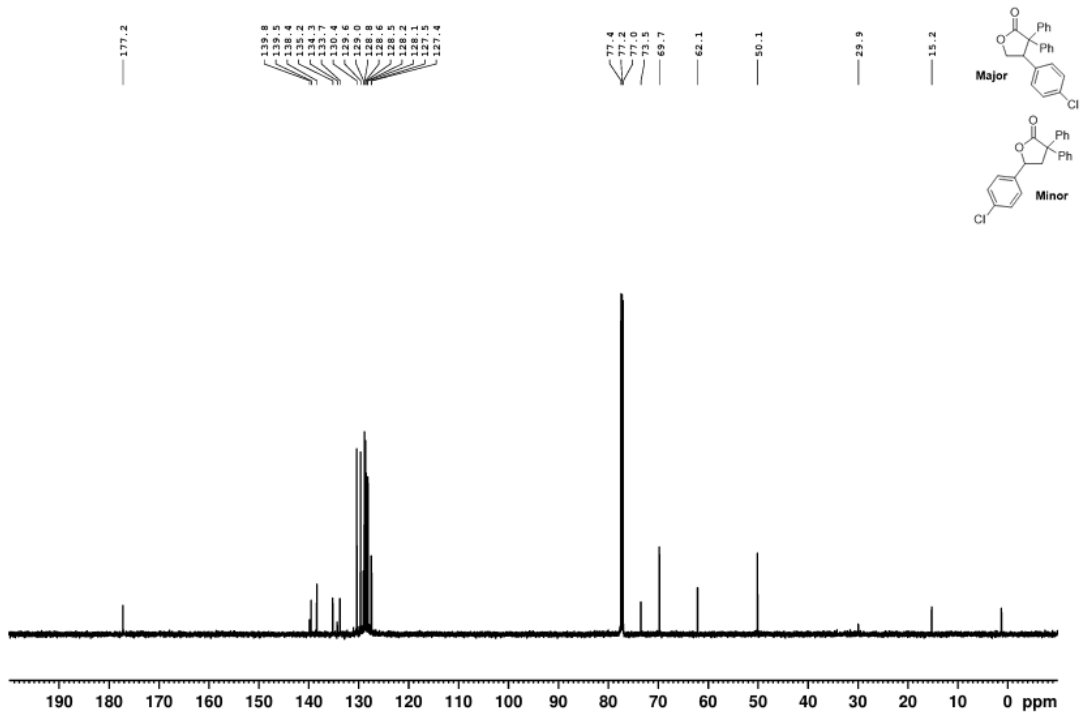
*Spectrum 55: [1]H NMR of 3,3-diphenyl-4-(p-tolyl)dihydrofuran-2(3H)-one(**4g**)*



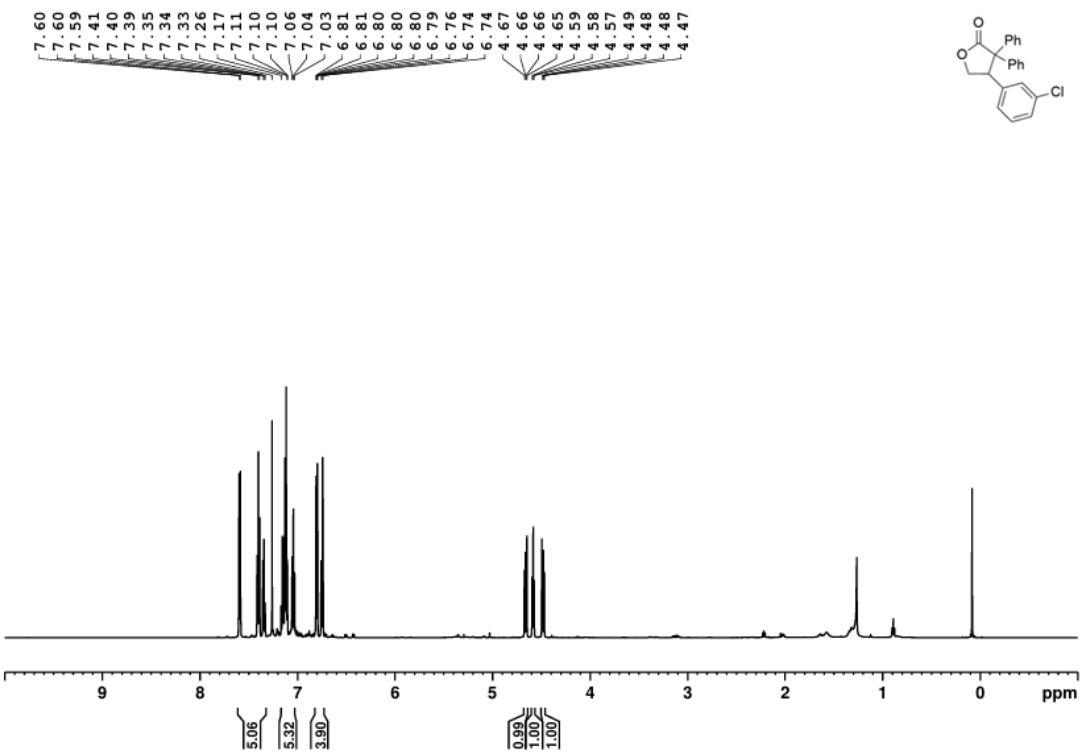
*Spectrum 56: [13]C NMR of 3,3-diphenyl-4-(p-tolyl)dihydrofuran-2(3H)-one (**4g**)*



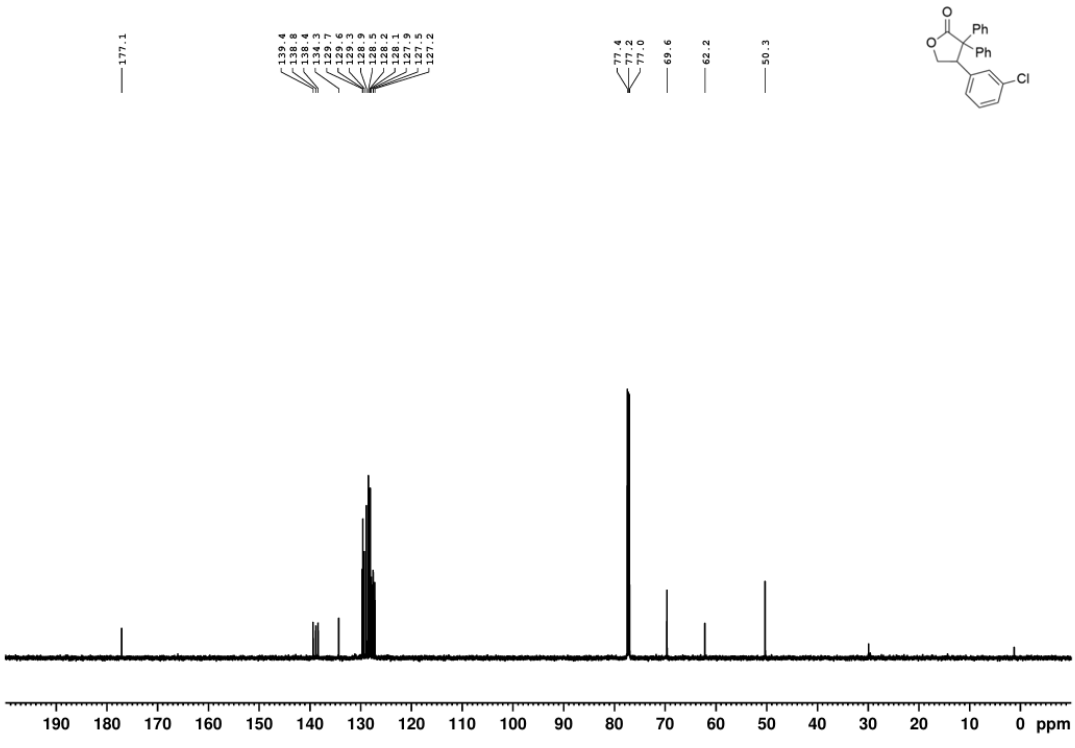
*Spectrum 57: [1]H NMR of 4-(4-chlorophenyl)-3,3-diphenyldihydrofuran-2(3H)-one (**4h**)*



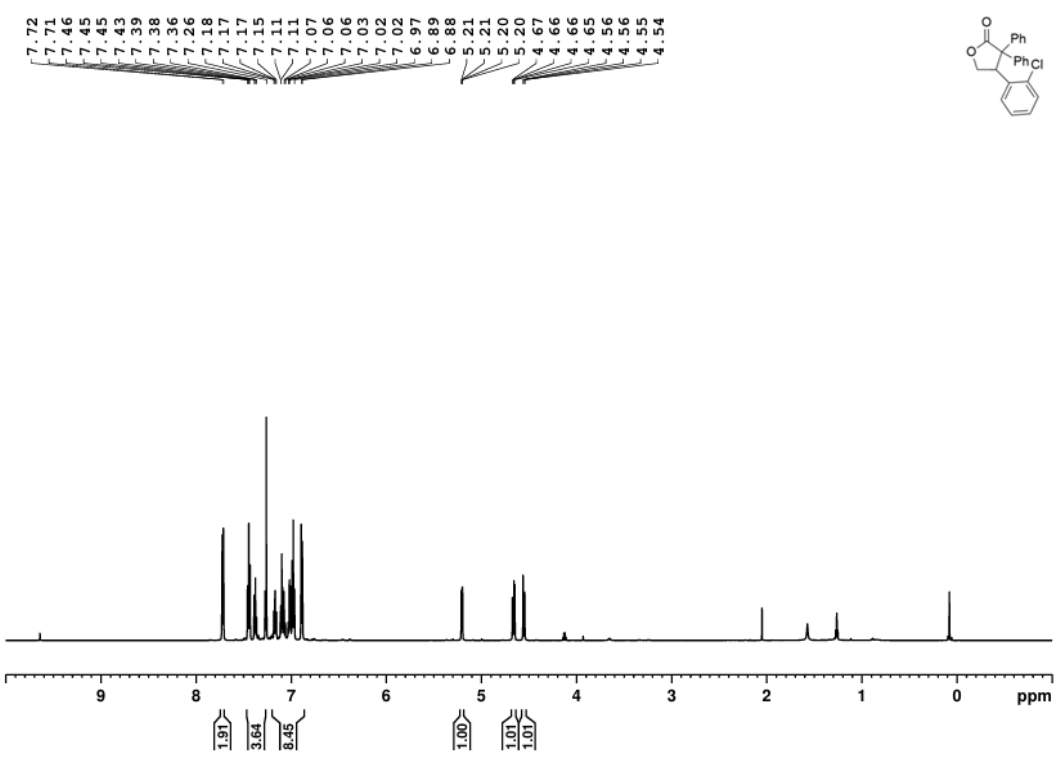
*Spectrum 58: [13]C NMR of 4-(4-chlorophenyl)-3,3-diphenyldihydrofuran-2(3H)-one (**4h**)*



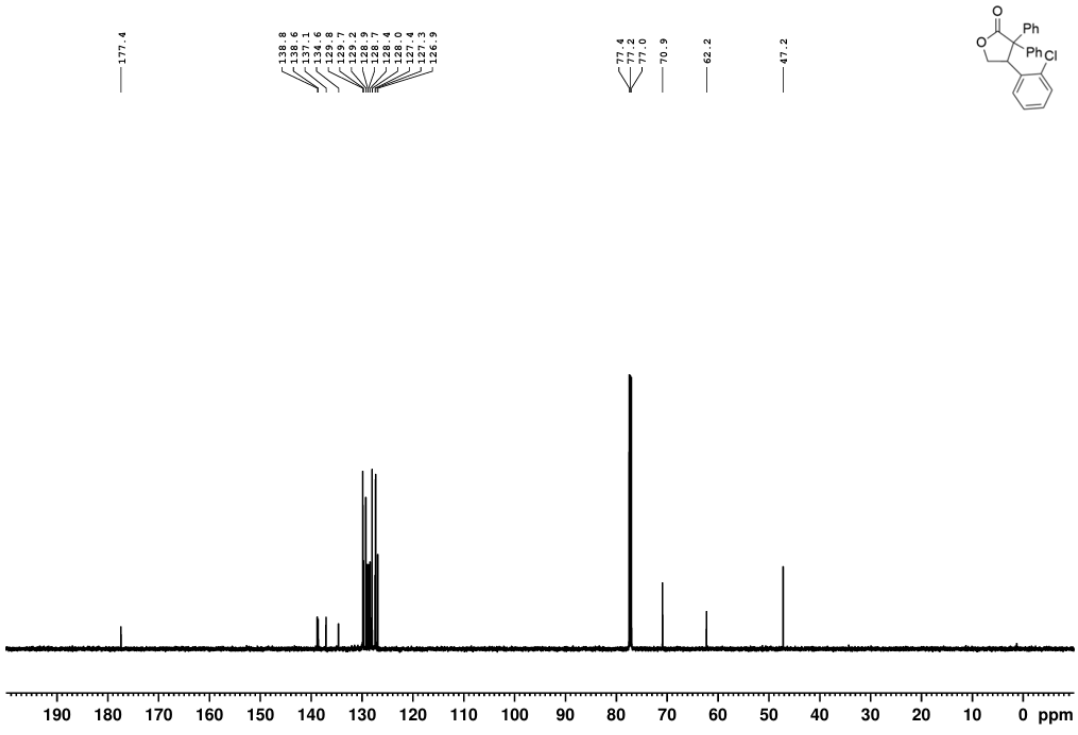
*Spectrum 59: [1]H NMR of 4-(3-chlorophenyl)-3,3-diphenyldihydrofuran-2(3H)-one(**4i**)*



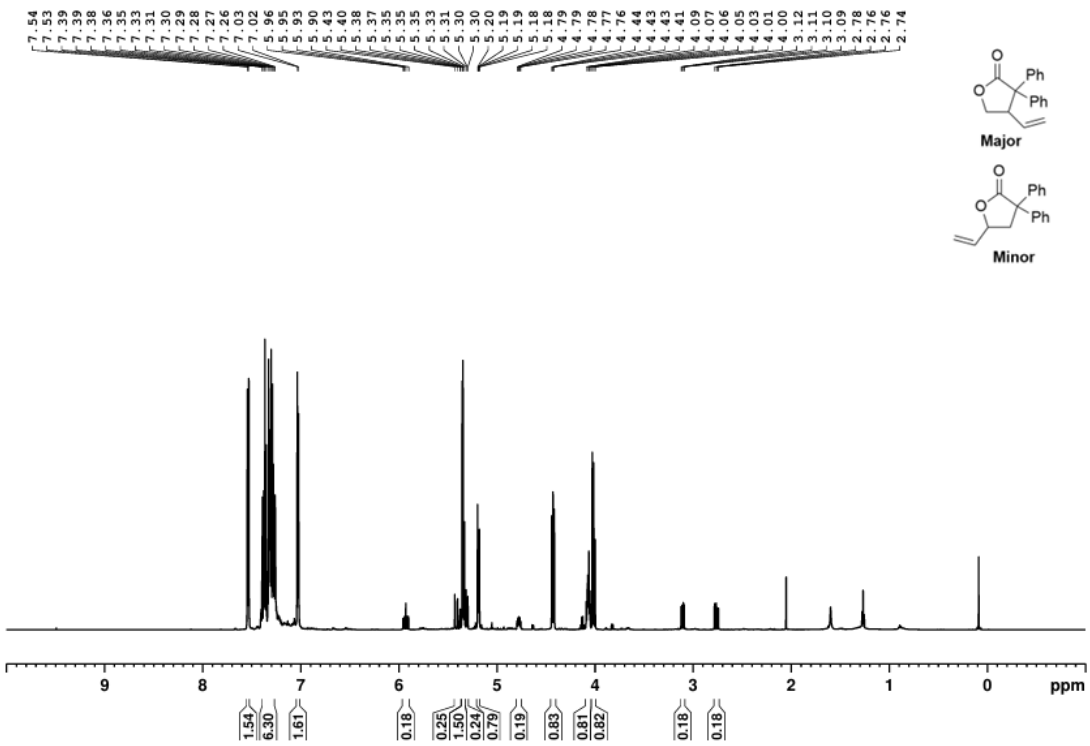
*Spectrum 60: [13]C NMR of 4-(3-chlorophenyl)-3,3-diphenyldihydrofuran-2(3H)-one(**4i**)*



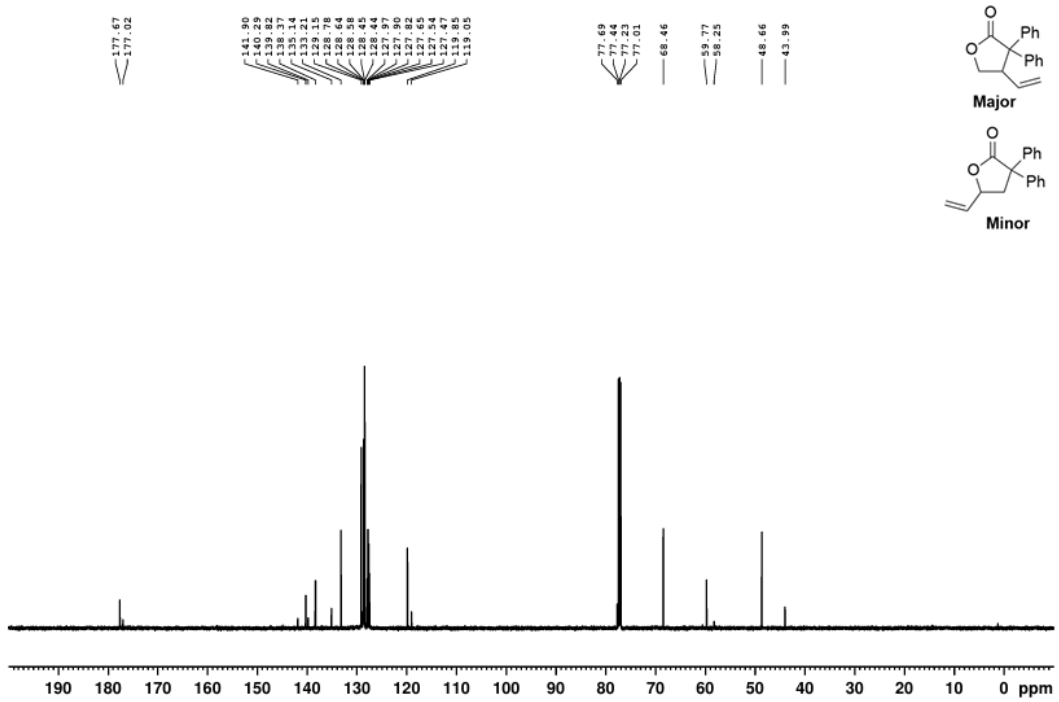
*Spectrum 61: [1]H NMR of 4-(2-chlorophenyl)-3,3-diphenyldihydrofuran-2(3H)-one (**4j**)*



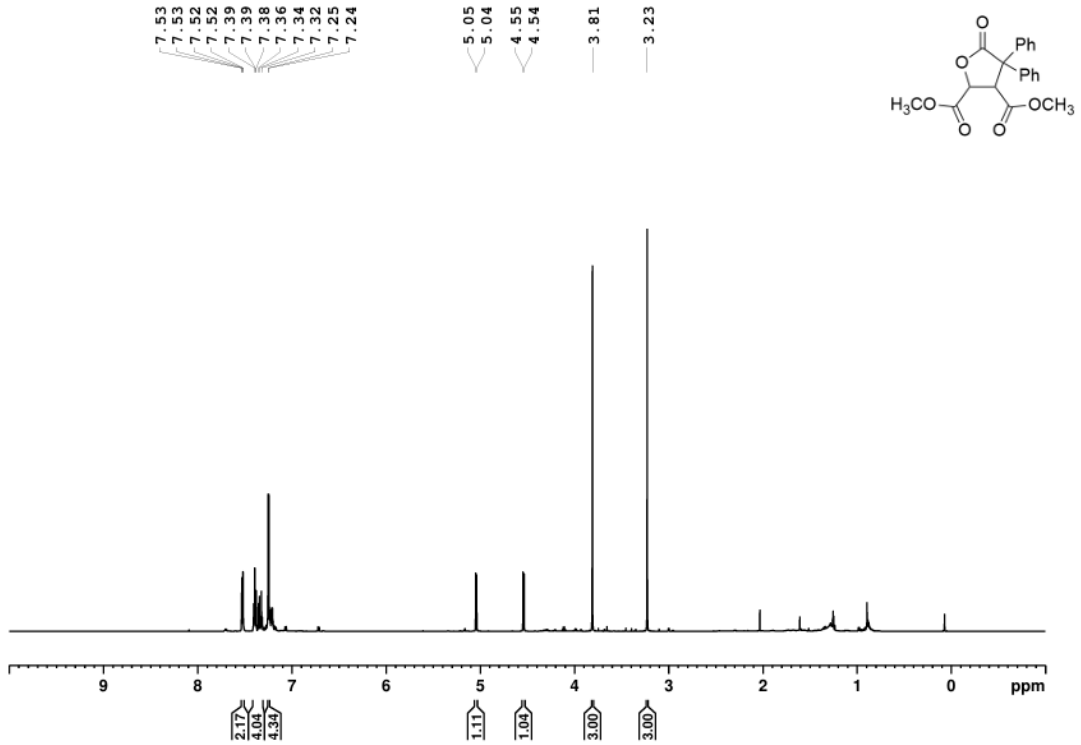
*Spectrum 62: [13]C NMR of 4-(2-chlorophenyl)-3,3-diphenyldihydrofuran-2(3H)-one(**4j**)*



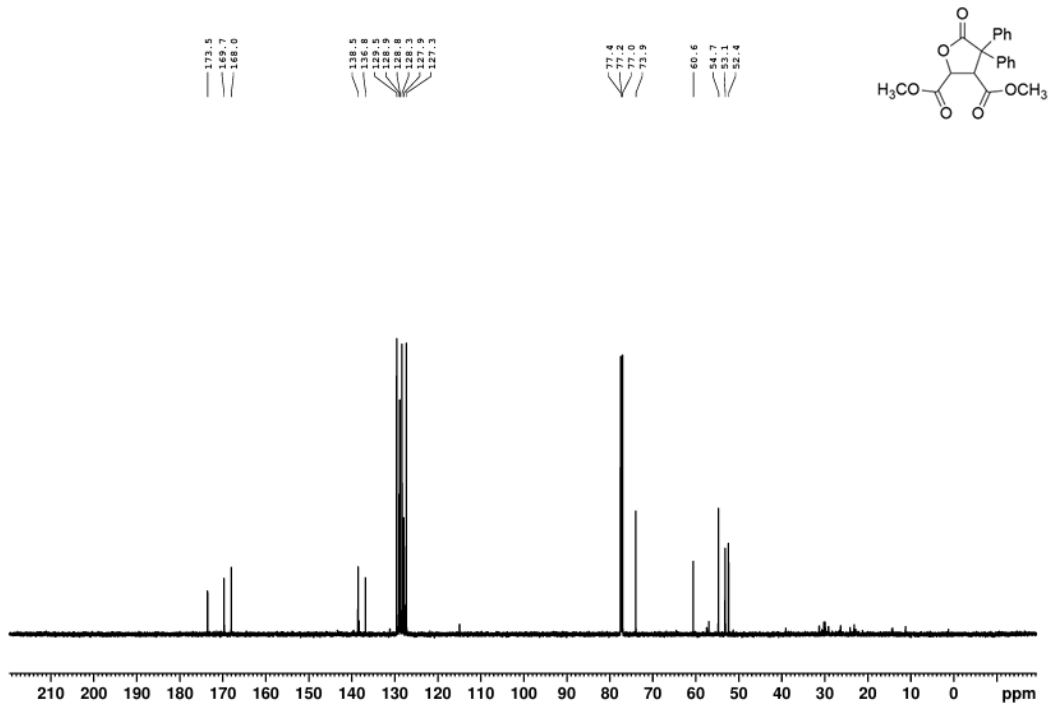
*Spectrum 63: [1]H NMR of 3,3-diphenyl-4-vinyldihydrofuran-2(3H)-one(**4k**)*



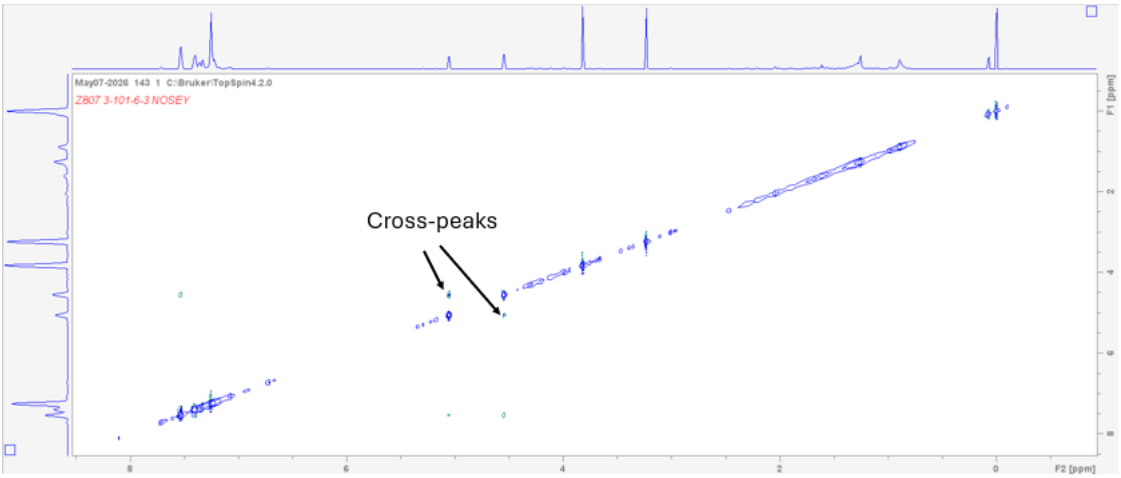
*Spectrum 64: [13]C NMR of 3,3-diphenyl-4-vinyldihydrofuran-2(3H)-one(**4k**)*



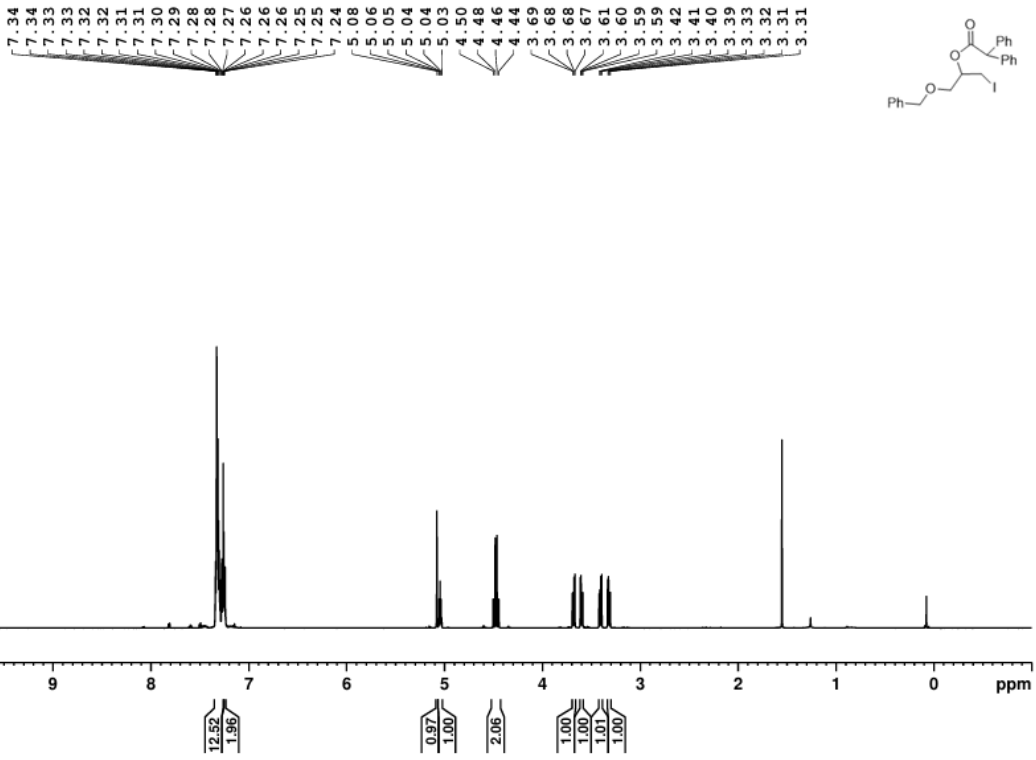
*Spectrum 65: [1]H NMR of dimethyl 5-oxo-4,4-diphenyltetrahydrofuran-2,3-dicarboxylate(**4l**)*



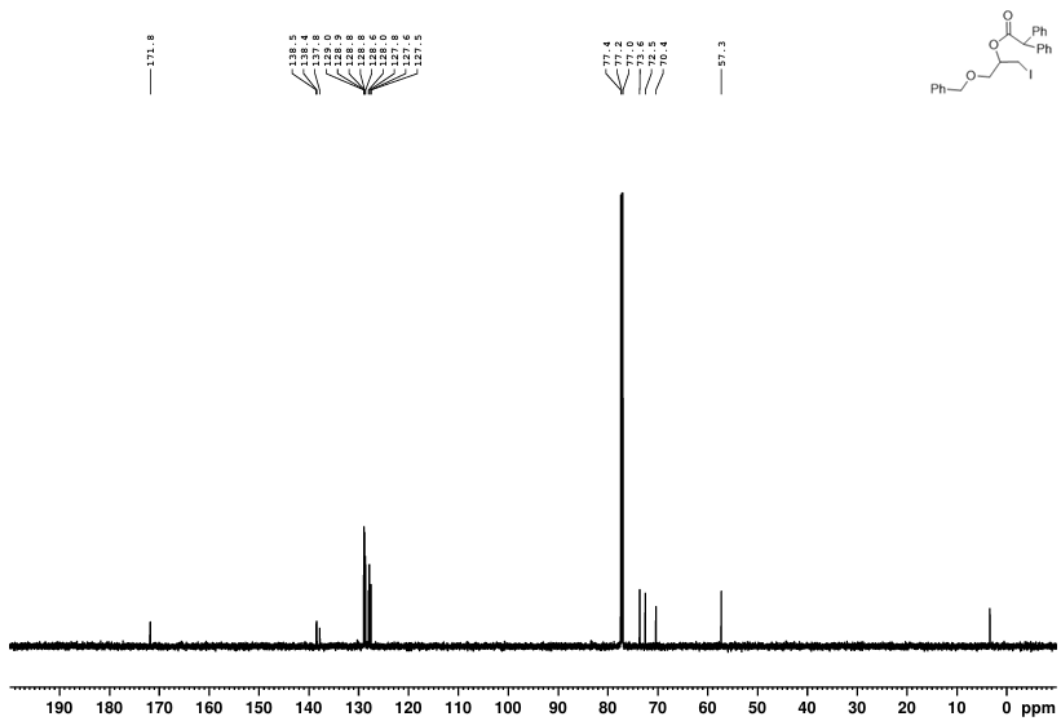
*Spectrum 66: [13]C NMR of dimethyl 5-oxo-4,4-diphenyltetrahydrofuran-2,3-dicarboxylate(**4l**)*



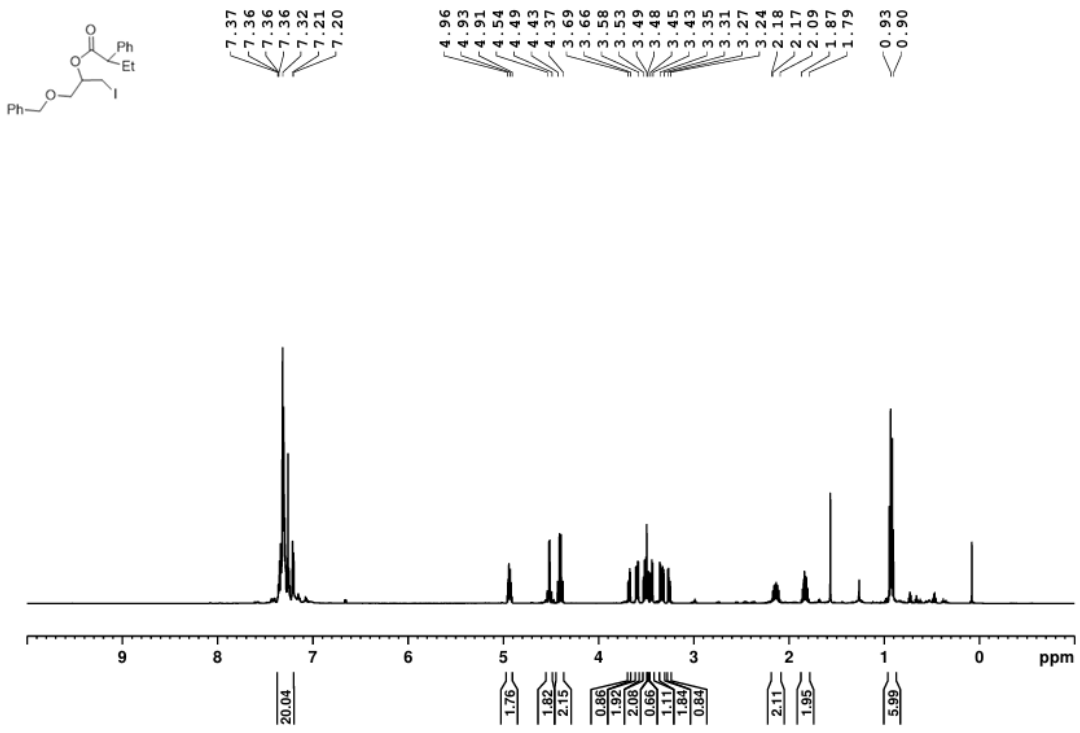
*Spectrum 67: NOESY of dimethyl 5-oxo-4,4-diphenyltetrahydrofuran-2,3-dicarboxylate(**4l**)*



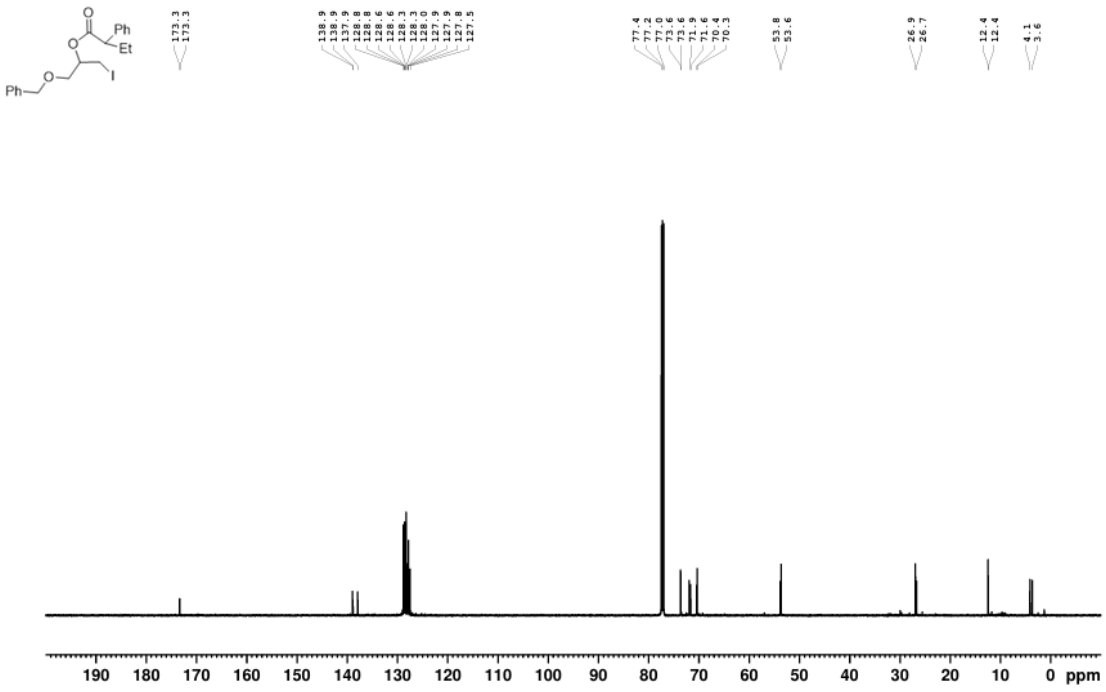
*Spectrum 68: ^{1}H NMR of 1-(benzyloxy)-3-iodopropan-2-yl 2,2-diphenylacetate (**5a**)*



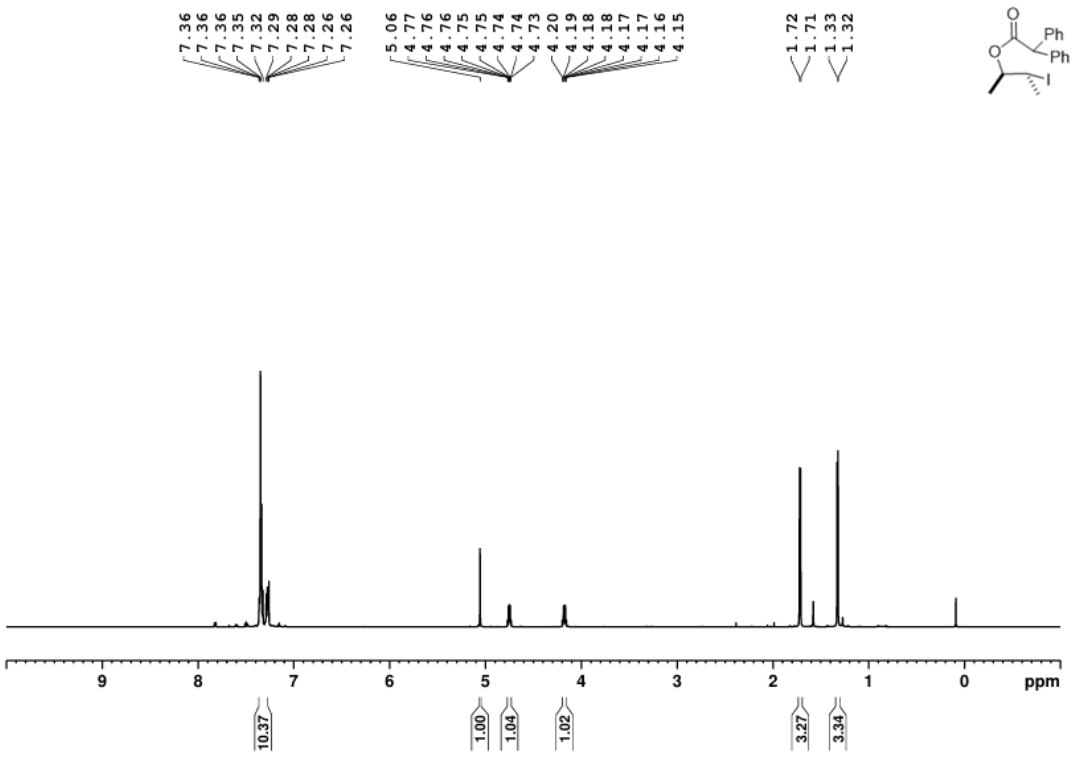
*Spectrum 69: [13]C NMR of 1-(benzyloxy)-3-iodopropan-2-yl 2,2-diphenylacetate (**5a**)*



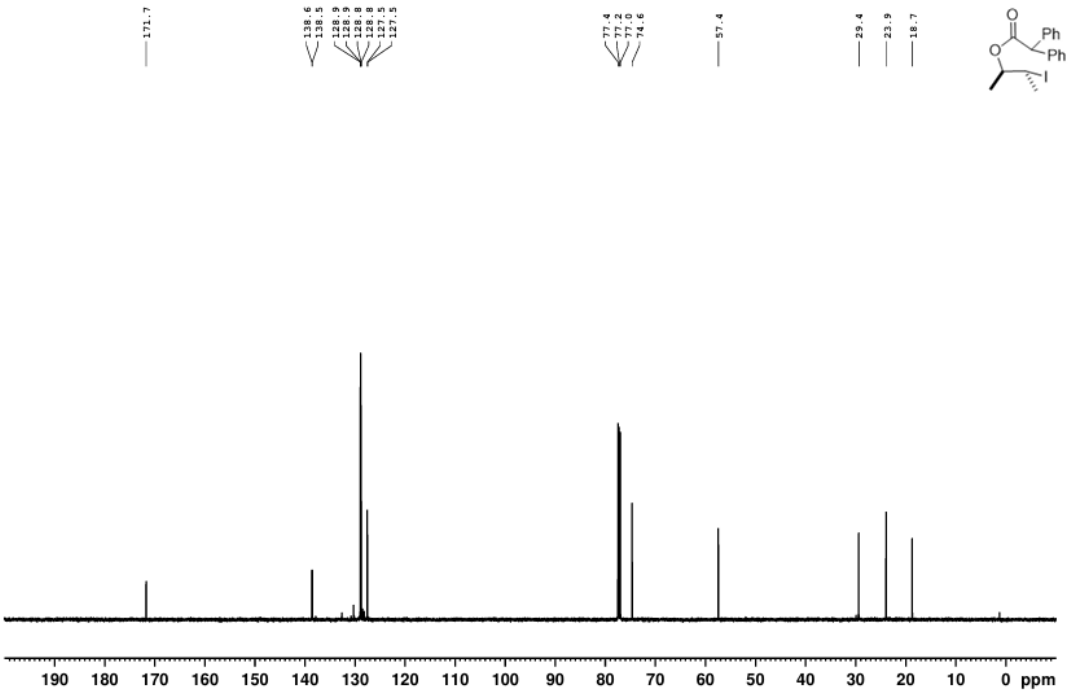
*Spectrum 70: [1]H NMR of 1-(benzyloxy)-3-iodopropan-2-yl 2-phenylbutanoate (**5b**)*



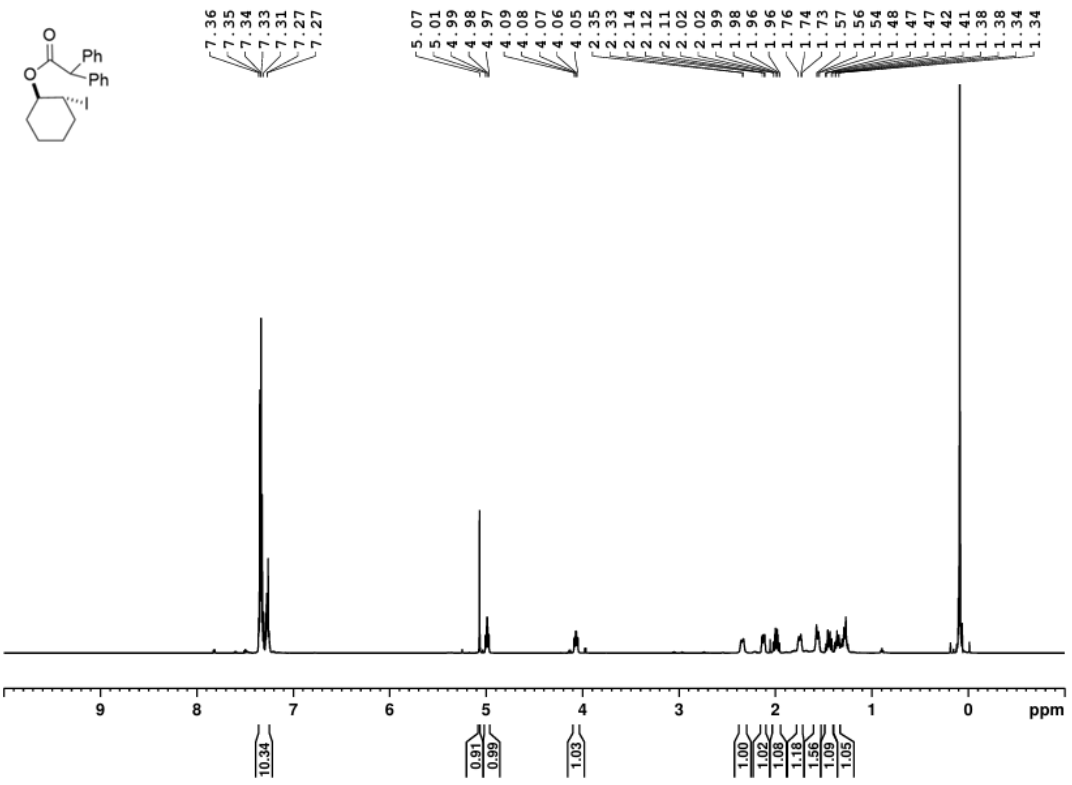
*Spectrum 71: [13]C NMR of 1-(benzyloxy)-3-iodopropan-2-yl 2-phenylbutanoate (**5b**)*



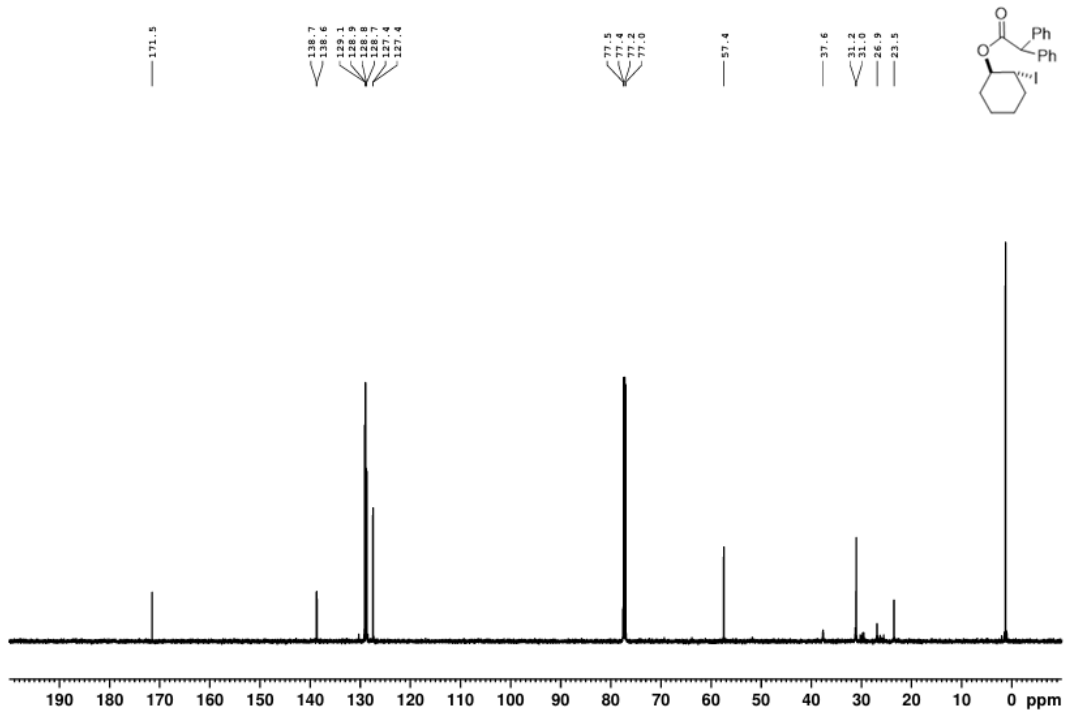
*Spectrum 72: [1]H NMR of 3-iodobutan-2-yl 2,2-diphenylacetate (**5c**)*



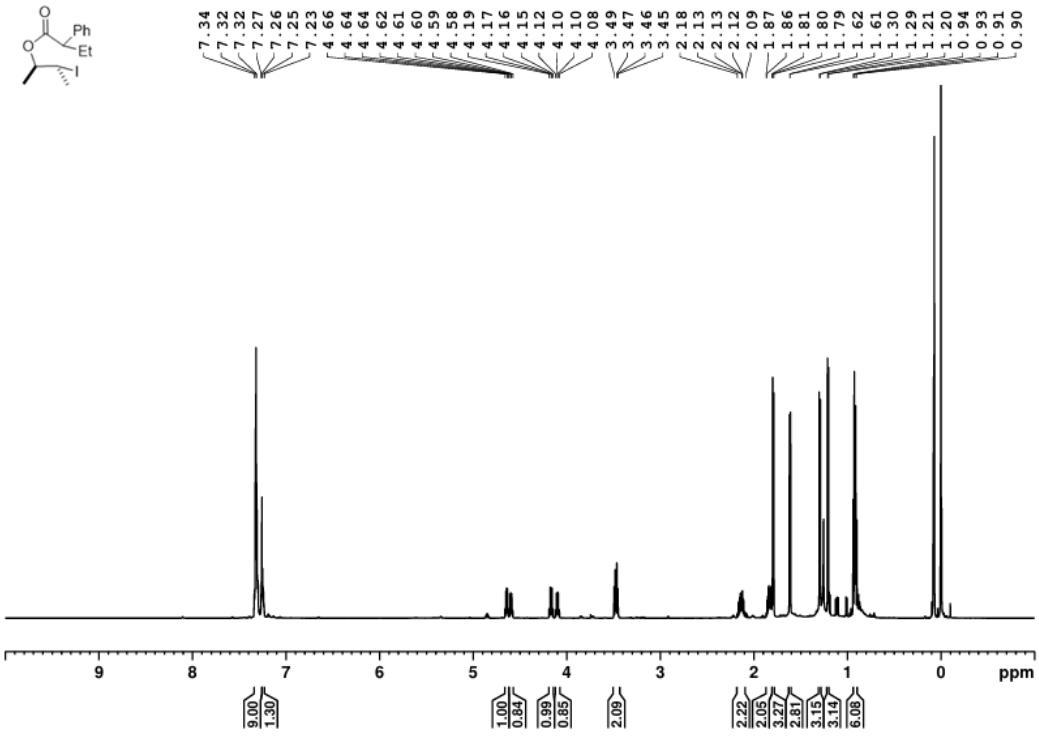
*Spectrum 73: ^{13}C NMR of 3-iodobutan-2-yl 2,2-diphenylacetate (**5c**)*



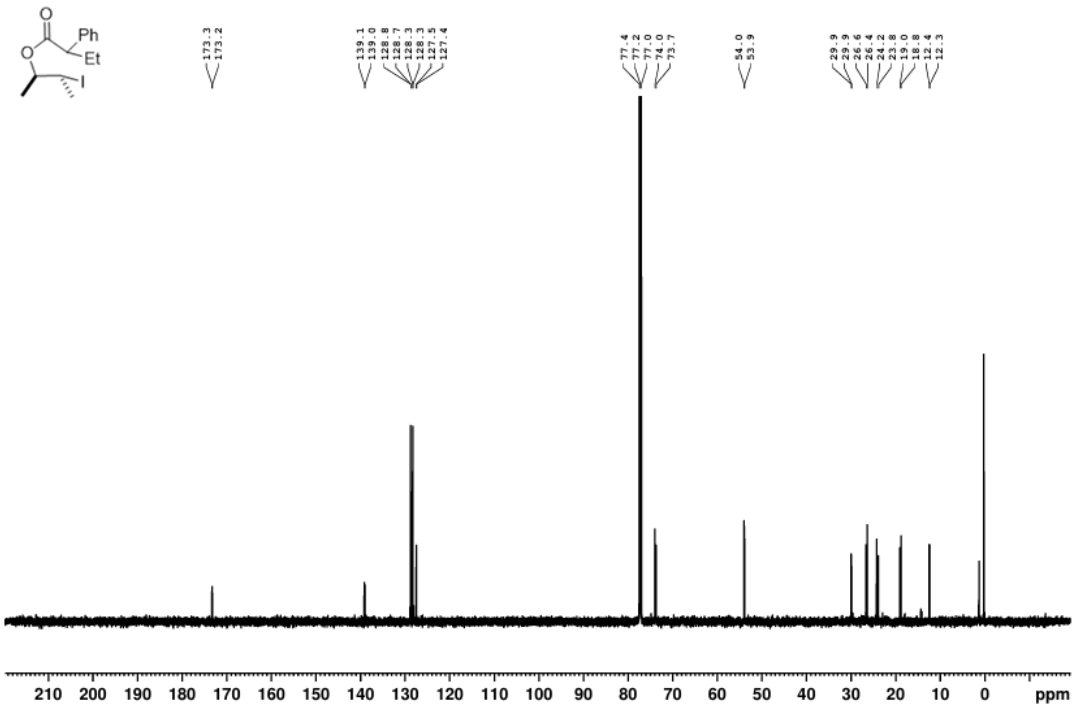
*Spectrum 74: ^{1}H NMR of 2-iodocyclohexyl 2,2-diphenylacetate (**5d**)*



*Spectrum 75: ^{13}C NMR of 2-iodocyclohexyl 2,2-diphenylacetate (**5d**)*



*Spectrum 76: ^{1}H NMR 3-iodobutan-2-yl 2-phenylbutanoate (**5e**)*



*Spectrum 77: ^{13}C NMR 3-iodobutan-2-yl 2-phenylbutanoate (**5e**)*