Keteneylidenetriphenylphosphorane as a Versatile C-2 Building Block Leading to Tetronic Acids with Potential Herbicidal and anti-HIV Activity

by

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Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel verwendet habe.

Ich habe nicht versucht (mit oder ohne Erfolg), eine Dissertation einzureichen oder mich der Doktorprufung zu unterziehen.

Bayreuth, den 19. Januar, 2004

Gary Gordon

The following work was completed from February 2000 until September 2001 at The Queen's University of Belfast (U.K.) and from October 2001 until January 2004 at the University of Bayreuth (Germany). This work was completed under the supervision of Prof. Schobert.

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This work is dedicated to
my Mother,
Donna, Debbie
and Aimée

Table of Contents

Abbreviations

Ac	acetyl
aq	aqueous
br	broad
bp	boiling point
d	doublet
DCM	dichloromethane
DHU	Dicyclohexylurea
DIAD	Diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DME	Dimethoxyethane
DIBAL-H	Diisobutylaluminium hydride
EDC	N-(3-Dimethylaminopropyl)-N'-ethyl carbodiimide
h	hour
GC	Gas Chromatography
Hz	Hertz
HMDS	hexamethyldisilazane
HOMO	Highest Occupied Molecular Orbital
LUMO	Lowest Unoccupied Molecular Orbital
LDA	lithium diisopropylamide
MTBSTFA	N-tert-butyldimethylsilyl-N-methyltrifluroacetamide
min	minute (s)
NaHMDS	sodium hexamethyldisilazainide
q	quartet
quin.	quintet
ΔT	heating
TBDMSCl	tert-butyldimethylchlorosilane
TMSOTf	Trimethylsilyl triflate
TLC	Thin Layer Chromatography
ppm	parts per million
R_f	Retention factor
r.t.	room temperature
s	singlet
t	triplet

1.0 General section

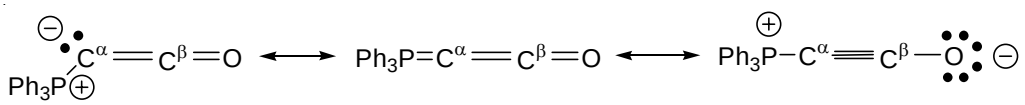
1.1 Introduction and objectives

Mankind has long been fascinated with the extraction of chemical compounds from natural plant and animal sources for the betterment of everyday life. From the Romans who dyed their emperors clothes with extracts from Mediterranean molluscs to the Jesuits who treated malaria patients with the alkaloid quinine extracted from the bark of the South American cinchona tree, organic chemistry has played a profound and dramatic role in the lives and history of all peoples, long before chemistry was recognised as a science.

Due to their ease of availability, plants have in the past been the most common source of natural compounds. Today pharmaceutical research has found that many varieties of microorganisms and fungi also provide a diverse and rich source of natural compounds.[1] No doubt as new species of plant and animal life are discovered in the oceans and rainforests many interesting and useful natural compounds await discovery.

Chemists are not only interested in the structure of biologically active natural products but also on the mechanism of action of the compound and its metabolites in the body. Structural modifications can have a profound impact on the activity of a compound; as a result chemists are especially interested in synthetic procedures which allow the construction of libraries of molecules. Efficient and economic synthetic concepts can save pharmaceutical companies millions of Euros and are therefore highly prized and sought after. Domino reactions offer substantial advantages over traditional multistep-processes and meet the demands of the modern pharmaceutical industry. Domino reactions consist of two or more bondforming transformations which take place under the same reaction conditions without additional reagents or catalysts.[2,3] The subsequent reactions proceed in a well ordered manner with the formation of a functional group which is transformed in the following step. The protection of functionalities is therefore not necessary, nor is the isolation of reaction intermediates.

The cumulated ylide keteneylidenetriphenylphosphorane **1**[4,5] meets all these requirements for use as a donor-acceptor C2-building block in domino reactions. The appeal of **1** is further enhanced due to its low toxicity, easy accessibility and simple handling.



1a **1b** **1c**

This work is principally concerned with the utilisation of **1** to quickly construct biologically interesting heterocycles with the expansion of the synthetic concept to a domino process. The synthetic concepts within should be applied to the synthesis of natural products and biologically active compounds.

Recently our group has made use of a domino cascade where **1** has been reacted to form tetronic acids. These naturally occurring derivatives often pose a significant challenge to chemists due to their high degree of functionalisation and polarity. 3,5-Disubstiuted derivatives are especially important due to their many properties such as antibiotic, antiviral and antitumour activities. Driven by the need to develop an effective treatment for patients with AIDS, the focus of pharmaceutical research within this field has shifted to derivatives with pronounced HIV-protease inhibitor activity, such as the 5-spiro-3-(cyclopropyl) benzyltetronic acids. Starting from α-hydroxy esters and **1** our group has reached the immediate precursers of 5-spiro-3-(cyclopropyl) benzyltetronic acids, the 5-spiro-3-allyl derivatives.

One of the objectives of this work is to investigate the cyclopropanation of 5-spiro-3-allyl tetronic acids with the aim to develop anti-HIV active spirotetronic acids (Section 2.2.1). Cyclopropanation of these 5-spiro-3-allyl tetronic acids requires a protocol which is compatible with a free acidic hydroxy group. Recent work with Simmons Smith reagents have failed to produce the desired 5-spiro-3-(cyclopropyl) benzyltetronic acids and further work in this area will focus on more reactive Simmons-Smith reagents.

On route to the 5-spiro-3-(cyclopropyl) benzyltetronic acids our group discovered that 3-(spirocyclopropyl)-dihydrofuran-4,12-diones are readily formed. Some work has already been conducted on the mechanism of formation of these compounds and this work will focus further on the mechanism and on the optimisation of this interesting reaction (Section 2.1.3 and 2.1.4). Cyclopropanes are electrophilic and as such we expect that 3-(spirocyclopropyl)-dihydrofuran-4,12-diones are amenable to attack from various nucleophiles which would lead to 3,5-(disubstituted) tetronic acids which have a high probability of biological activity (Section 2.1.7).

Once optimisation of the conditions has been achieved the cascade will be extended to investigate the feasibility of introducing polar groups to the phenyl ring (Section 2.1.5) The aim is to build up a small library of 3,5-(alkyl) tetronic acids for biological testing as herbicides (Section 2.1.7). Polar groups present on the phenyl ring are known to enhance the anti-HIV activity of 5-spiro-3-(cyclopropyl) benzyltetronic acids and we expect this to be also the case for the 3,5-(disubstituted)tetronic acids.

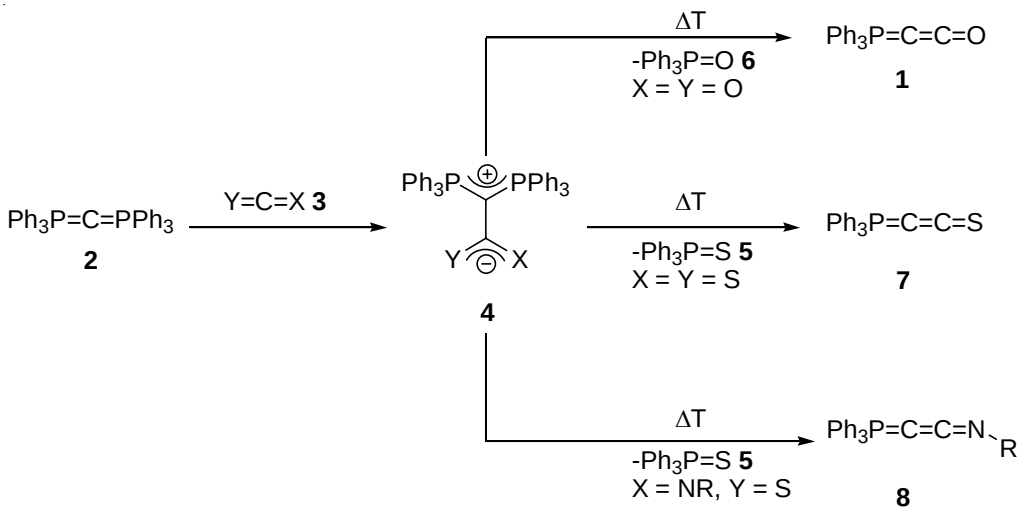
Interestingly 3-(spirocyclopropyl)-dihydrofuran-4,12-diones are only formed when the allyl group is bonded to a phenyl group. When phenyl is replaced with an alkyl group only products arising from an abnormal Claisen rearrangement are identified. It is likely that such abnormal Claisen rearrangement products are produced via 3-(spirocyclopropyl)-dihydrofuran-4,12-diones intermediates. This work will investigate in greater detail the mechanistic aspects of abnormal Cliasen rearrangements with the desire to prove that all abnormal Claisen rearrangements reported in literature actually proceed through elusive 3-(spirocyclopropyl)-dihydrofuran-4,12-diones (Section 2.3)

Multi-component and domino reactions are interesting to the chemical industry and this project not only uses and develops these techniques but also allows the preparation of anti-HIV, antiviral and potential herbicidal targets from the various interceptable intermediates of one particular cascade.

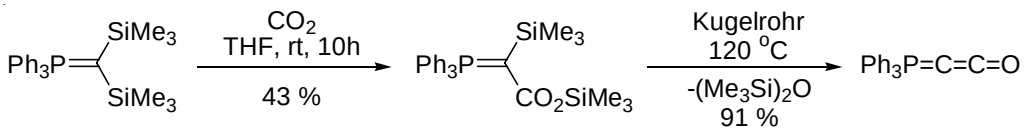
1.2 Synthesis, structure and properties of keteneylidenetriphenylphosphorane

1.2.1 Synthesis of keteneylidenetriphenylphosphorane

Hexaphenylcarbodiphosphorane **2** was first synthesised in 1961 by Ramirez.[5] A few years later Birum and Matthews successfully converted this ylide with CO_2, CS_2 and RNCS to give the betaines **4**. Pyrolysis of the betaines led to elimination of either triphenylphosphane oxide **6** or triphenylphosphane sulfide **5** to give keteneylidenetriphenylphosphorane **1**[4], the analogous thio compound **7**[4] and the imino derivative **8**.[6]



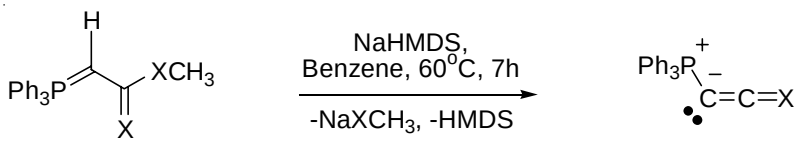
Bissilyated phosphonium ylides such as **9**[7, 8] insert carbon dioxide to give α-silylated silylester ylides such as **10** which upon pyrolysis decompose with formation of disiloxanes and the cumulated ylide **1** in excellent ylides.[9]



9 **10** **1**

Both these methods suffer from serious drawbacks, mainly due to the expense of starting materials and the overall low yield of the product. Another serious problem is the difficulty of scale up of the thermolysis step. A review by Matthews in 1969 covers the early work in the synthesis and investigation of **1**.[10]

Bestmann developed a new synthetic method[11 - 13] for the molar scale production of cumulated ylides and went on to investigate in detail their many unusual properties and reactions.

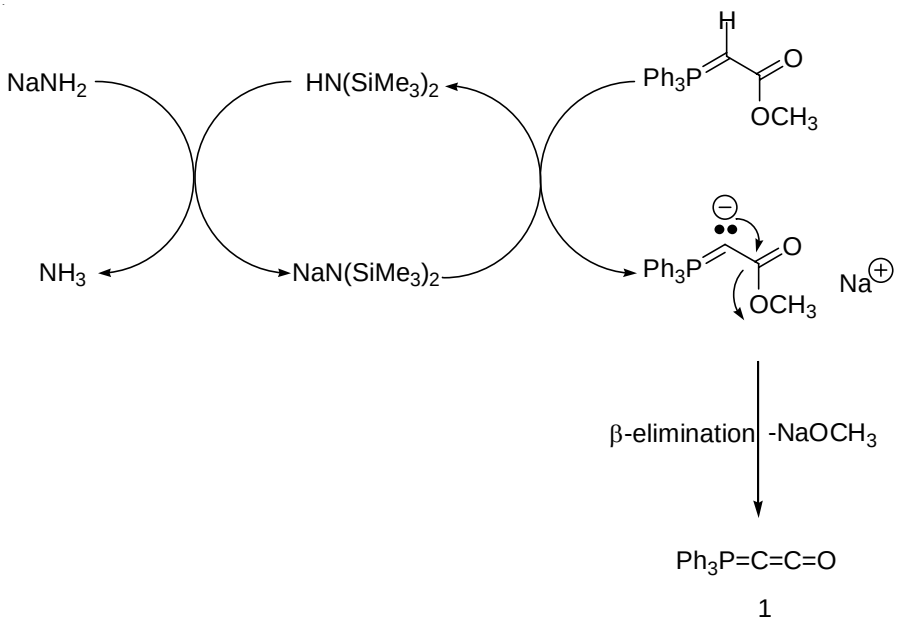


X = O, **11**
X = S, **12**

X = O; 80%, **1**
X = S; 76%, **7**

Methoxycarbonylmethylenetriphenylphosphorane **11** is easily accessible from bromoacetic acid methyl ester and triphenylphosphine followed by deprotonation of the phosphonium salt with sodium hydroxide.[14]

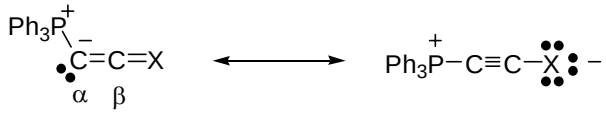
When a solution of methoxycarbonylmethylenetriphenylphosphorane **11**[14] in benzene or toluene is mixed with an equimolar quantity of a strong base such as sodium hexamethyldisilazanide (NaHMDS) or crystalline sodium amide, deprotonation occurs at the ylidic carbon atom C^{α}. After the immediate loss of methanolate (β-elimination) the cumulated ylide **1** is released [15]. If the cheaper sodium amide is used as the base, drastic conditions (refluxing in benzene for several days) are required.[16] The crude product in this case must be repeatedly recrystallised for purification. Addition of catalytic quantities of hexamethyldisilazane (HMDS) to the suspension of sodium amide in benzene or toluene distinctly improved the reaction time (24 h at 60°C) and the product purity.[17] Pure ylide **1** is obtained in good yields after separation of the by-product, sodium methoxide. During the course of this work it was discovered that formation of NaHMDS in situ followed by addition of **11** to the solution led to an overall reduction in the time of synthesis, coupled with better yields and higher product purity (Section 3.1). Analogously, triphenylphosphoranylidenethioketene **7** was prepared from methyldithiocarbonylmethylene-triphenylphosphorane **12** and KHMDS.[15]



Scheme 1: Catalytic cycle in the synthesis of **1**.

1.2.2 Structure and properties of keteneylidenetriphenylphosphorane

Phospha(hetero)cumulene ylides **1**, **7** and **8** feature unique electronic and structural properties and exhibit a chemistry which is quite distinct from that of ylides bearing three substituents on the ylidic carbon atom C^{α}.[11] The molecular structures as obtained by X-ray diffraction analysis of a single crystal of **7**,[18] **1**,[19], **8**,[20] suggest electronic structures best described by resonance forms **13A** and **13B** and by a hybridization of C^{α} ranging from sp^2 to sp depending on the nature of the substituents.



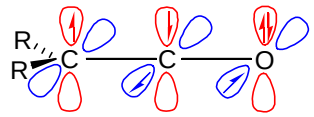
13A **8**: X = NPh **13B**
1: X = O
7: X = S

As the electron-accepting character of the heteroatom increases, electron density around the heteroatom increases and the population of structure **13B** increases.Therefore it can be expected that the angle P-C^{α}-C^{β} will increase and the C^{α}-C-$^{\beta}$ bond length will decrease in the order **8**, **1**, **7** and this is confirmed by X-ray analysis (Table 1).

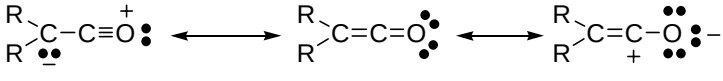
Table 1: Properties of phosphacumulene ylides of type **13**

Compound	Distance C^{α} - C^{β} [A^{o}]	Angle P-C^{α}-C^{β} [^{o}]	^{31}P: δ (ppm)	mp ^{o}C
8, X = NPh	1.248	134.0	2.39	151 - 153
1, X = O	1.210	145.5	6.00	172
7, X = S	1.209	168.0	-8.02	224 - 226

Keteneylidenetriphenylphosphorane **1** has a “ketene-like” structure however **1** reacts in a different manner from ketenes. Ketenes have two orthogonal π-electron systems, one system contains four electrons and the other has two electrons. The electron-donor nature of oxygen makes the π^4-electron system nucleophilic, with a partial negative charge at C^{β} and induces a partial positive charge at C^{α} in the π^2-system. Ketenes as a result have dipolar character (**14a** <–> **14b** <–> **14c**).

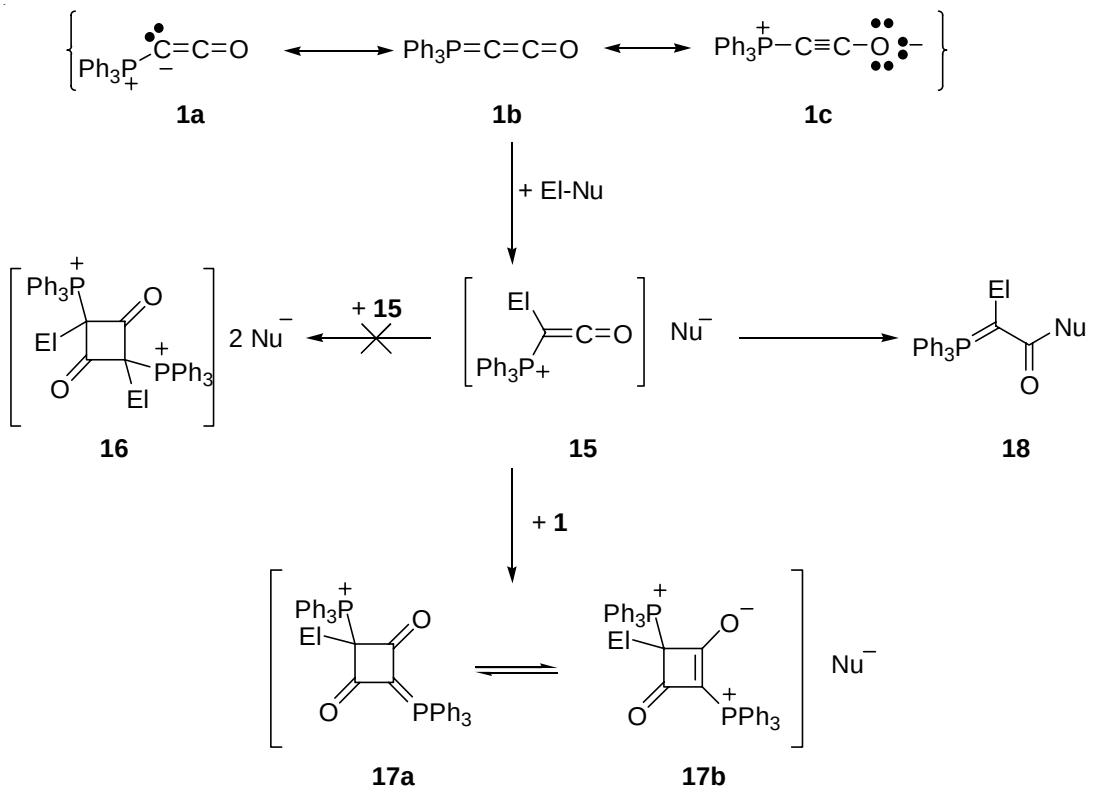


$\pi^4 \perp \pi^2$
14

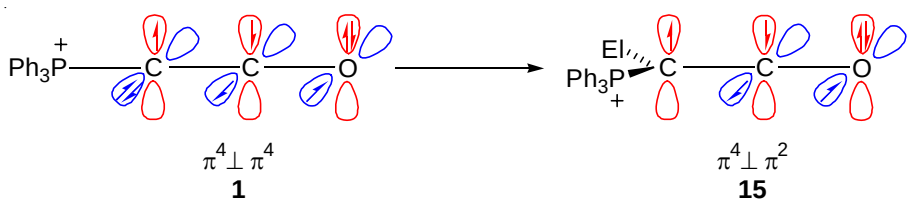


14a **14b** **14c**

The phosphacumulene ylides do not undergo any electrophilic reactions typical of dipolar ketenes and keteneimines including dimerisation and are thus much more stable (eg. solid samples of **1** and **8** can be stored for months and handled under ambient conditions without decomposition). This is due to the presence of an additional electron pair on C^{α} leading to an orthogonal set of two π^4-electron systems spread over three atoms. These compounds are isoelectronic with carbon dioxide, isocyanate and carbodiimides and so lack the electrophilicity of ketenes featuring a dipolar $\pi^4 \perp \pi^2$ system.



Reaction of **1** with El-Nu compounds results in the initial formation of phosphonium salt **15**. The electrophile is now bound to the free electron pair on C^{α}. This changes the nucleophilic $\pi^4 \perp \pi^4$-electron system into a dipolar ketene like $\pi^4 \perp \pi^2$-electron system. **15** can now react in a ketene like fashion.



The phosphonium salt **15** does not dimerise to **16** and cannot be isolated. However **15** will react with a second molecule of **1** to form the [2+2]-cycloaddition product **17**, if **1** is more nucleophilic than Nu^-. However if Nu^- is more nucleophilic than **1**, the Wittig active acylylide **18** is normally formed instead.

Wittig alkenation which is so characteristic of common trivalent ylides is rarely observed and sluggish with phosphaheterocumulene ylides. The difference in basicity is quite apparent for the cumulated ylides **1**, **7** and **8**. While **1** and **8** easily react with alcohols, thiols, primary and some secondary amines, **7** will only react well with acidic phenols.

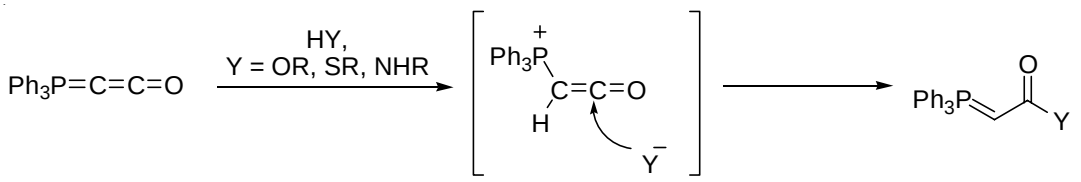
1.2.3 Applications of keteneylidenetriphenylphosphorane

1.2.3.1 Reaction with halogen compounds

1 reacts with hydrogen halides[21] (and alkyl halides[10, 22 - 24]) to form highly reactive phosphoniumketene salts, which undergo an immediate [2+2] cycloaddition with a second equivalent of the starting ylide to give "dimer salts" of type **17**. The nucleophilic character of the halides is not sufficient for an attack on the carbonyl carbon of **15**.

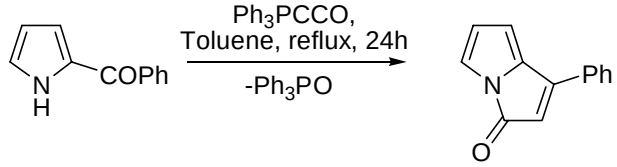
1.2.3.2 Reaction with acidic compounds

Upon reaction of alcohols, amines and thiols with **1** the intermediate ketene cation **19** gets intercepted by the more strongly nucleophilic counter anion (alkoxide, amide, thiolate) yielding monomer "acyl" ylides **20**. Since acyl ylides enter into Wittig alkenation reactions far more quickly than the starting ylide, multi-component or domino reactions between the latter, an acidic component (alcohol, amine, thiol) and a carbonyl compound becomes possible leading to α, β-unsaturated carbonyl derivatives.



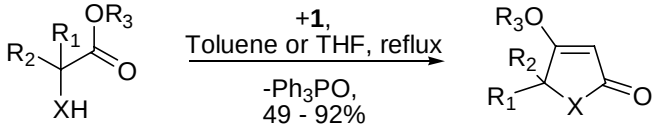
1 **19** **20**

α and β -hydroxy, or -aminoaldehydes and -ketones can enter into a domino addition-intra Wittig alkenation reaction with cumulated ylides to furnish five and six membered oxacycles or azacycles, respectively.[25]



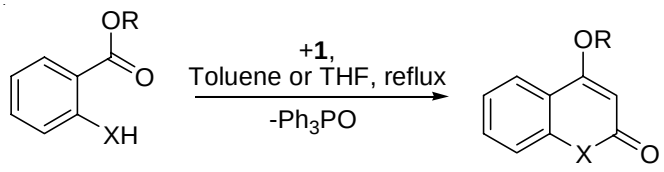
21 **22**

Esters of α-hydroxy, α-amino, or α-sulfonylcarboxylic acids react with **1** in refluxing THF to yield the corresponding tetronates, tetramates or thiotetronates.[26]



23 **24**

Six membered heterocycles can be obtained from **1** and β-functionalised esters. Salicyates, anthranilates and thiosalicylates lead to the respective coumarins, quinolones and thiocoumarins. Common functionalities (further than 5 bonds from X-H) such as acetals, esters, aldehydes etc are not affected.[26, 27]

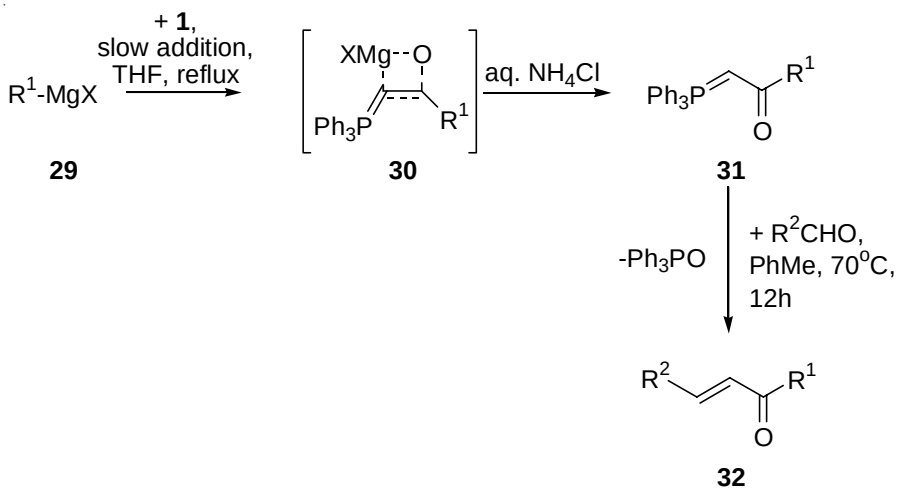


25

26: X = O, R = Me, (75%)
27: X = NH, R = Et, (52%)
28: X = S, R = Et, (45%)

1.2.3.3 Reaction with Grignard compounds

It has been shown that **1** easily opens access to ester ylides (1.2.3.2) but it is also possible to generate acyl ylides from **1** by addition of Grignard reagents. Heating a mixture of **1** with a prepared Grignard solution **29** gives a metalated intermediate **30** which can be immediately used to alkenate carbonyl compounds to give E-2-enones. Alternatively they can be hydrolysed to the corresponding acyl ylides **31** which can then be subjected to the Wittig alkenation reaction. Highly functionalised, long chained acyl ylides[16] can be easily synthesised by this method and have been used for the construction of many natural products.[28, 29]

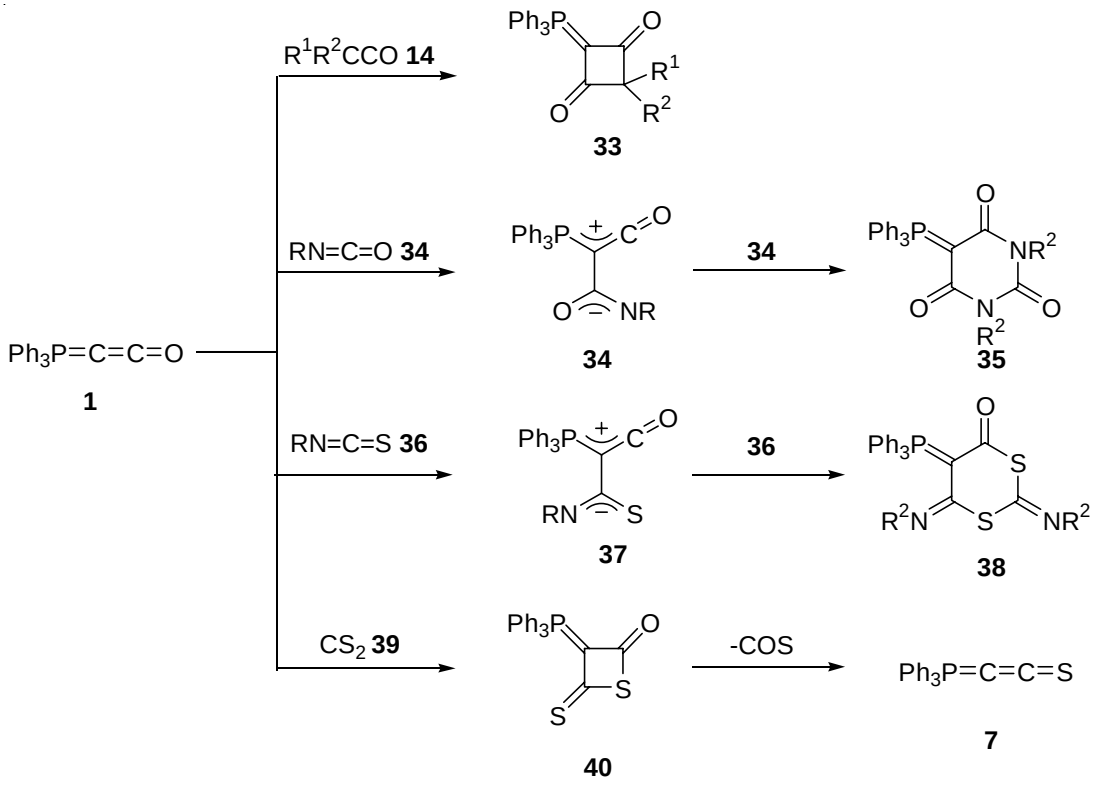


29 **30** **31** **32**

1.2.3.4 Cycloadditions of keteneylidenetriphenylphosphorane

Cumulated ylides have been reported[11] to undergo [2+2] and [2+4]-cycloaddition reactions with multiple-bond systems such as the ketenes, ketenimines, alkynes, isocyanates, isothiocyanates, CO_2, COS, CS_2 etc. Addition will occur across either the P-C^{α} or the C^{α}-C^{β} bond in the starting ylides resulting in various types of four and six membered carbocycles and heterocycles.

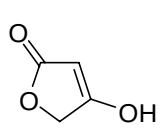
The reaction depends strongly on the combination and stoichiometry of the starting materials. When addition occurs across the C^{α}-C^{β} bond it normally proceeds in such a manner so that the most nucleophilic atom of the multiple bond system adds onto C^{β}. The reaction of keteneylidenetriphenylphosphorane **1** with ketenes results in the formation of 1,3-cyclobutandiones,[30] while the reaction with isocyanates and isothiocyanates leads to six-membered ring systems. An interesting outcome is experienced with the reaction of **1** and CS_2; initially a 4-membered thietane is produced which spontaneously expels a molecule of COS to give the cumulated ylide triphenylphosphoranylidenethioketene **7**.[30] The stabilization of the positive charge on the C^{α} atom of the intermediate betaines governs whether four or six membered systems are formed in these reactions.



1.3 Synthesis and properties of tetronic acids

1.3.1 Properties of tetronic acids

Heterocycles constitute one of the most versatile and important branches of chemistry. They are found throughout the plant and animal kingdoms and have very diverse structures, reactivities and biological effects. An important class of heterocycles are the tetronic acids. Tetronic acid **41** and its simple derivatives are moisture and air stable solids, the vast majority exist in the enol form; pK_a values of approximately three have been calculated for simple 5-alkylsubstituted tetronic acids. Thus the name of tetronic acid is employed for this class of heterocycles as they are stonger acids than acetic and formic acids. By far the most well known of the tetronic acids is vitamin C (ascorbic acid) **42** an essential component in the diet of all primates, guinea-pigs and fruit bats. Vitamin C is essential for the production of collagen in these animals, it is also recognised as a scavenger of toxins in the human body by the action of hydride ion transfer to oxidants such as dangerously reactive peroxides or Fe(III).



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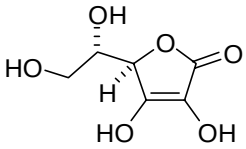

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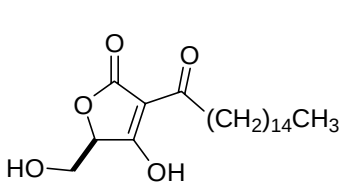
Tetronic acids and their metabolites exhibit a large array of biological properties[31, 32] such as antibiotic,[33-36] anticoagulant,[37-39] antiepileptic,[40] antifungal,[34,41] insecticidal,[42] analgesic,[43,44] antiinflammatory,[45] antitumour,[46,47] and skin-whitening[48] effects. In recent years tetronic acid derivatives have been found to be important HIV-1 protease inhibitors.[49,50] Some tetronic acids such as RK-682 **43** are known to be selective inhibitors of protein tyrosine phosphatases (PTPs). PTPs represent a diverse family of enzymes that exist as integral membrane and non receptor forms. Disorders in the normal function of PTPs are suspected to be involved in a number of serious diseases including cancers, autoimmune diseases and diabetes.[51]

Common natural sources of tetronic acids are the marine sponges an example of which is (-)-ircinianin **44**[52] isolated from the *Ireinia* species. Other important sources include mushrooms, lichens and a wide range of fungal metabolites, for example (S)-carlosic acid **45**[53] a mould metabolite. Further tetronic acids with interesting structures which are found in nature,[51, 54,55] include chlorothricin[56], (-)-vertinolide[57], and hippospongin[58].



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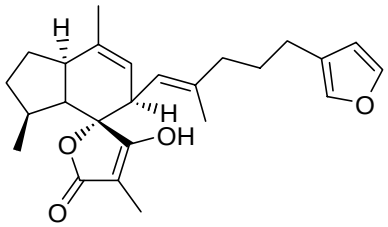

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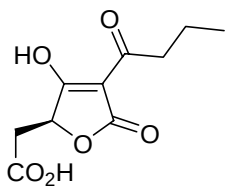
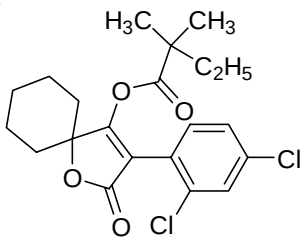


45

Recent years have seen an increase in the number of natural products which contain a spirotetronic acid unit.[59] **44** is an example along with spirodiclofen **46** which has recently been synthesised by Bayer CropScience.[60] Spirodiclofen has undergone numerous greenhouse and field trials and has been selected as a candidate for further development due to its acaricidal and herbicidal properties and also its tolerability of common plants such as grapevines, apple trees, stone fruits and household plants.



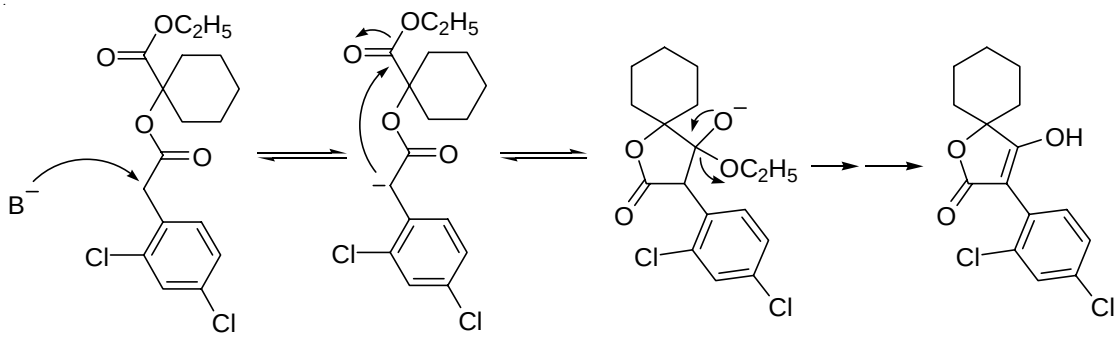
46

1.3.2 Synthesis of tetronic acids

Since the first synthesis of 2-methyltetronic acid in 1879 by Demarcay[61] followed by pulvinone in 1895 by Claisen and Ewan,[62] a host of synthetic methods of varying complexity have been employed in the synthesis of tetronic acids. Cyclisation reactions play an important role in the construction of heterocycles and are especially important for tetronic acid synthesis. Tetronic acid cyclisations have traditionally made use of γ-hydroxy-β-ketoesters[65-67] (generated by Claisen or Blaise conditions), γ-halogen-β-ketoesters,[68, 69] α-acetoxy-β-ketoesters[70,71], α-oxybenzylesters,[72,73] and γ-trimethylsilyloxy-β-ketoesters[74]; a high degree of functionality, substitution and stereochemistry can be tolerated by each of these methods.

1.3.2.1 By Dieckmann condensation

Carboxylic esters which contain an α-hydrogen undergo a condensation reaction to give a β-keto ester under the action of strong bases. This reaction is known as a Claisen condensation however when two ester groups are present in the same molecule the reaction is called a Dieckmann condensation.[63] The Dieckmann condensation normally proceeds with high yields when the internal condensation results in a five-, six- or seven-membered ring. Larger ring systems give poorer results with intermolecular as opposed to intramolecular condensation becoming dominant. High dilution factors result in an ester enolate being formed at one end of the molecule which has a higher probability of intramolecular condensation. This is because the low concentration of substrate makes it unlikely for the ester enolate to encounter another ester molecule. High dilution can therefore partially overcome this drawback, however in most cases the Dieckmann condensation is limited to heterocyclic ketones with a five-, six- or seven ring. The synthesis of **49**[60] (an intermediate in the formation of spirodiclofen) from **47** illustrates the mechanism which simply consists of one molecule of the ester being converted to an ester enolate under basic conditions. The second ester acts as a substrate and nucleophilic addition of the enolate to the substrate gives an unstable intermediate **48** which can eliminate RO^-. It should be noted that tetronic acids exist in the enol form and not the keto form.

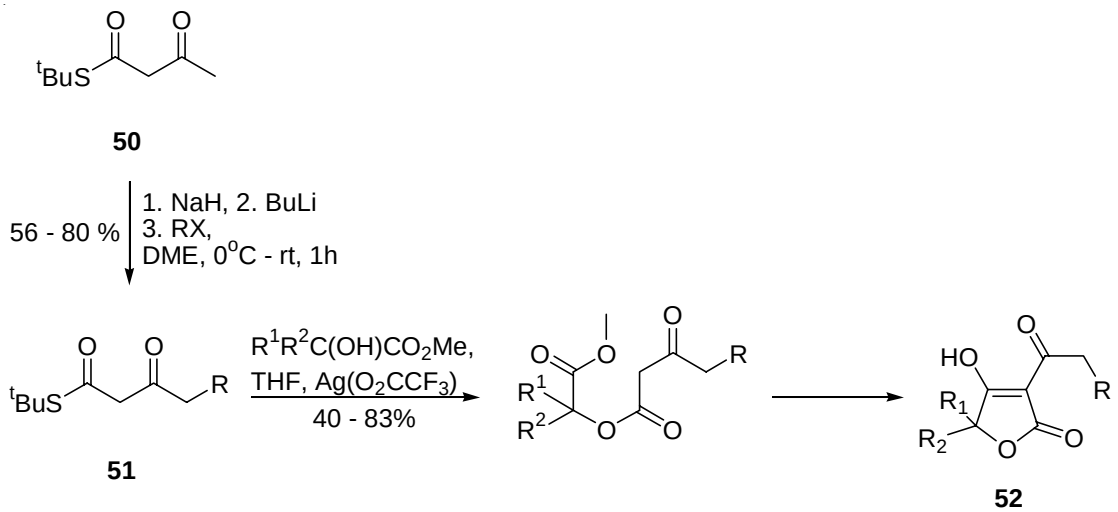


47 **48** **49**

Numerous methods exist in the literature for the synthesis of suitable diesters for tetronic acid construction. Perhaps the simplest method is to react an α-hydroxy acid with a simple alcohol to form an α-hydroxy ester. The α-hydroxy group can be converted to an ester with a suitable acid chloride to form a diester which will undergo Dieckmann condensation.[60,64]

Another versatile method involves the use of S-t-butyl acetothioacetate **50** which can be alkylated by numerous electrophiles at the γ-carbon.[53] These alkylated thio ester derivatives **51** underwent rapid transesterification with a series of α-hydroxy esters in the presence of silver (I) salts to give acetoacetate products. These acetoacetates can undergo a normal Dieckmann condensation to generate 3-acyl-tetronic acids; R can tolerate a high degree of complexity. Various bases can be used for the Dieckmann condensation and traditionally NaOEt was the agent of choice. In many cases much stronger bases are required such as sodium hydride, potassium t-butoxide and potassium carbonate.

Ley[53] has shown that in difficult cases where cyclisation did not proceed under forcing conditions with strong bases, then the use of tetrabutylammonium fluoride in THF gave excellent yields even at room temperature. Later work by Sodeoka[50,51] has shown that tetrabutylammonium fluoride also leads to Dieckmann condensation with retention of configuration of the C-5 stereocentre again with excellent yields.

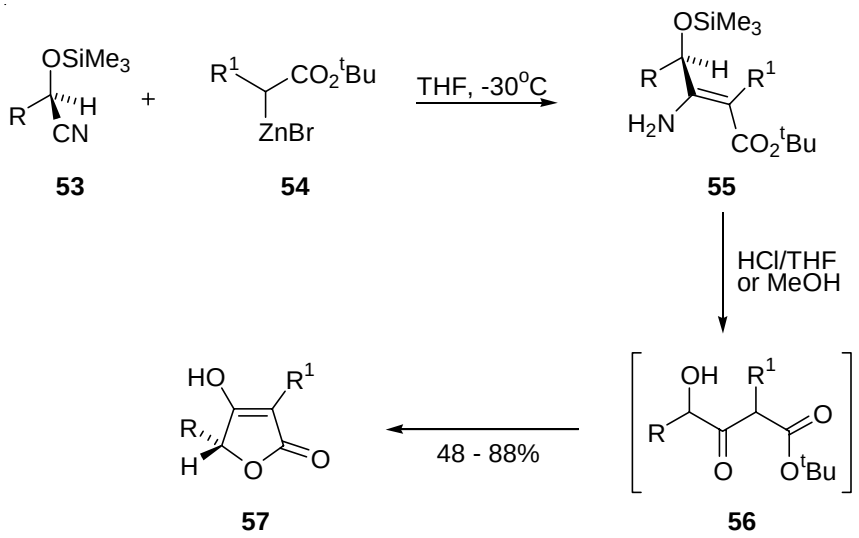


50

51 **52**

1.3.2.2 By Blaise reaction

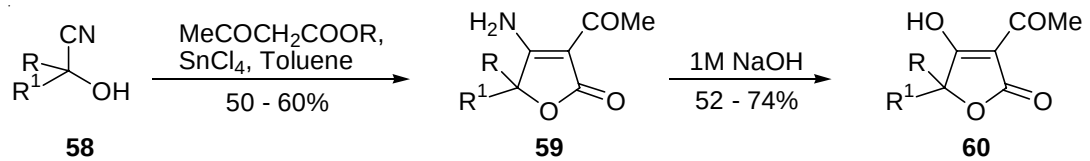
The addition of Reformatsky reagents **54**, by the Blaise reaction, to O-trimethylsilylated cyanohydrins **53** constitutes a facile route to tetronic acids. An excess of an α-bromoester added to a mixture of O-trimethylsilylated cyanohydrin and zinc dust in THF leads to enaminoesters **55** which can be hydrolysed to γ-hydroxy-β-keto-esters **56** which cannot be isolated, rearranging immediately to tetronic acids **57**.[31,67,75] This reaction is limited by steric constraints with cyanohydrins derived from ketones resulting in very low yields of the product. However this method has considerable advantages such as the ease of work-up and the ready availability of starting materials.



53 **54** **55** **57** **56**

1.3.2.3 By tin chloride mediated cyclisation of α-hydroxy nitriles with β-dicarbonyl compounds

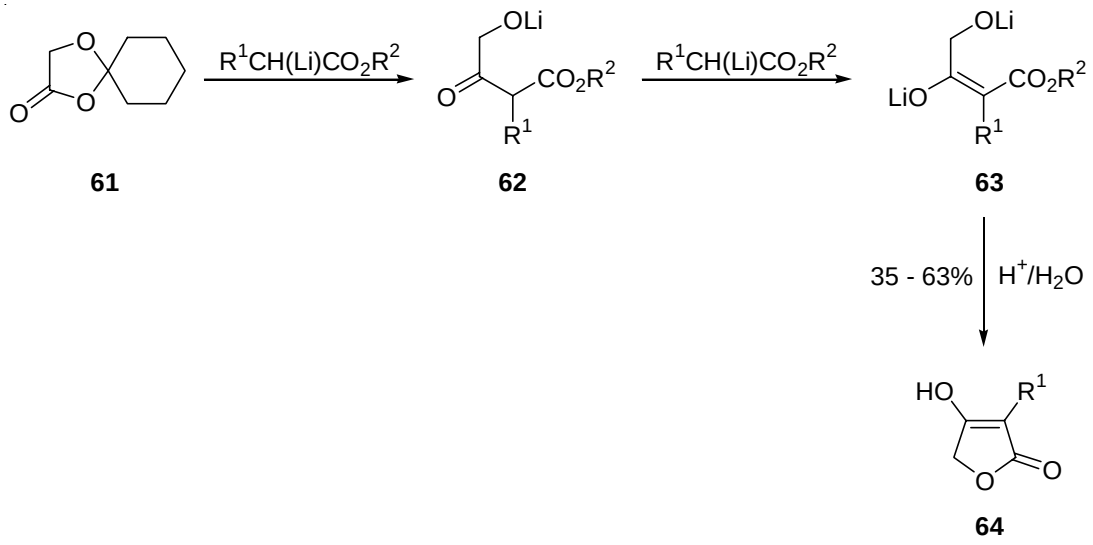
α-Hydroxy nitriles react intermolecularly with methyl or ethyl acetoacetates in the presence of stoichiometric amounts of tin (IV) chloride to yield 3-acyl-4-amino-2(5H)-furanones **59**.[76] The same α-hydroxy nitriles react in a similar manner with ethyl malonate to give the ethyl 4-amino-2,5-dihydro-2-oxo-3-furancarboxylates. The mechanism is thought to proceed through coordination of the tin chloride to both the β-dicarbonyl oxygen atoms and also to the nitrile atom. This is theorised to enhance the nucleophilic character of the dicarbonyl compound and at the same time to enhance the electrophilic character of the nitrile. The tin chloride cyclisation of nitriles which contain either a β-keto ester/malonate does not proceed, probably due to the tin chloride being unable to coordinate to three atoms due to steric or perhaps geometric constraints. The 4-aminofuranones can be easily converted to the corresponding tetronic acids simply by refluxing in sodium hydroxide solutions.



58 **59** **60**

1.3.2.4 Tetronic acids from dioxolanones and α-lithioacetic acids

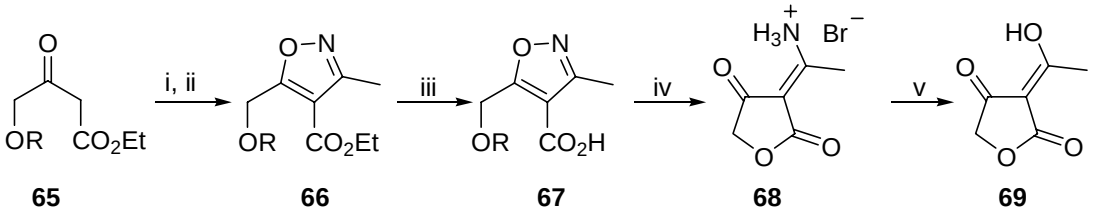
Tetronic acids can be synthesised from readily available dioxolanones such as **61**.[77] Dioxolanones undergo nucleophilic attack from α-lithioacetic esters which are themselves generated from LDA and an appropriate ester. Initial attack of the lithium enolate is thought to proceed with expulsion of cyclohexanone, with a second equivalent of the lithium enolate necessary to produce the intermediate dianion **63**. Normal acidic workup of the lithium intermediates leads to 3-substituted tetronic acids. This method has also been extended to the synthesis of pulvinones by use of the appropriate dioxolanone.



61 **62** **63** **64**

1.3.2.5 Tetronic acids from other cyclisation methods

A relatively recent procedure involves the use of isoxazoles which act as masked 1,3-dicarbonyl compounds, the advantage being that tetronic acids can be formed via non-polar intermediates. Starting with β-keto ester **65** an isoxazole **66** was generated by the action of pyrrolidine, nitroethane and phosphorous oxychloride.[78] The next task is the formation of the furan ring which is accomplished firstly by basic hydrolysis of the ester function to liberate the free acid, followed by removal of the hydroxy protecting group with HBr-AcOH, the furan is formed spontaneously at this stage with simultaneous reduction of the N-O bond by the HBr to yield the salt **68**. Liberation of the free 3-actyltetronic acid **69** was achieved with NaOH solution.

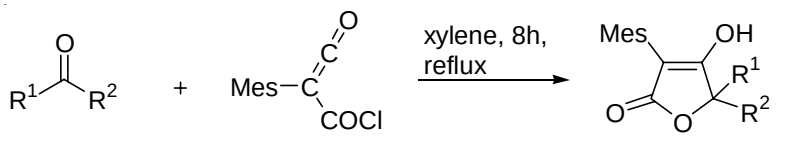


65 **66** **67** **68** **69**

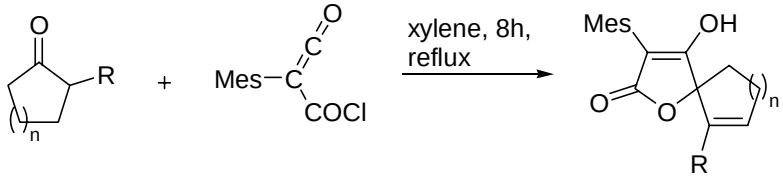
R = ^{t}Bu, CH_2Ph

Reagents and Conditions: i, pyrrolidine, toluene, reflux; ii, $EtNO_2$, Et_3N, $POCl_3$, 0-5°C; iii, 2M NaOH aq., reflux; iv, HBr-AcOH (2 mol equiv.); v, 2M NaOH aq., 25°C.

Diacylchlorides and phenylmalonic acid derivatives have long been utilised in the construction of various heterocycles.[79] (Chlorocarbonyl)mesitylketene **71** has been used as a synthetic equivalent to phenylmalonic acid derivatives. When **71** was reacted with various acyclic α-substituted ketones in stoichiometric quantities the reaction yielded 4-hydroxy-3-mesityl tetronic acids **73** and not the expected 4-hydroxy-3-mesityl pyrones. The reaction with **71** could also be extended to the formation of spirotetronic acids **75** through reaction with α-substituted cycloalkanones **74**.

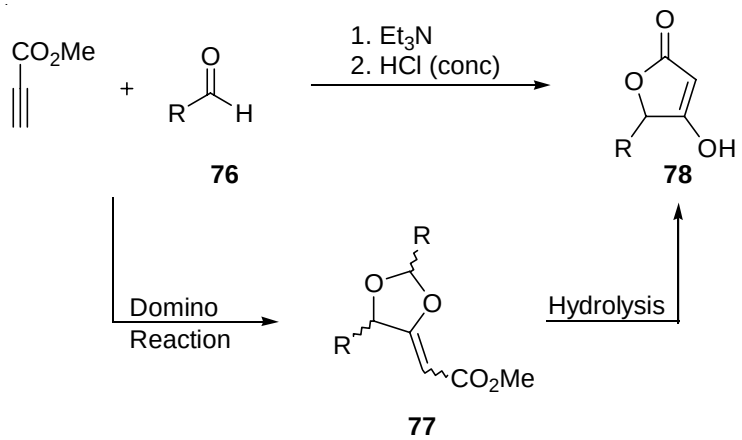


70 **71** **73**



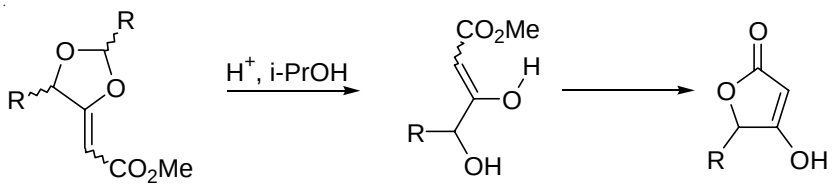
74 **71** **75**

The domino reaction of simple alkyl aldehydes **76** together with ester alkynes constitutes another novel method in the synthesis of tetronic acids.[80] The reaction proceeds by the Michael addition of triethylamine to the terminal conjugated alkynoate resulting in an ammonium acetylide which can undergo reaction with the aldehyde present in solution to form 1,3-dioxolanes in excellent yields.



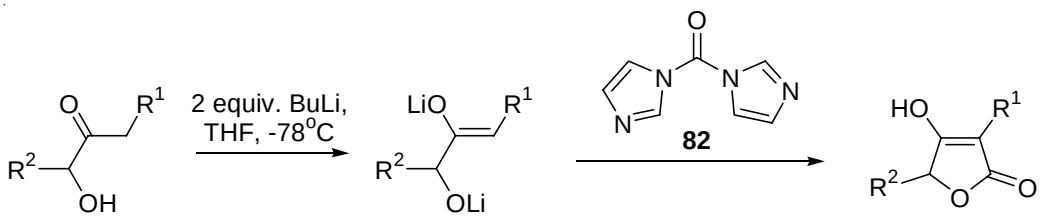
76 **78** **77**

Tetronic acids can react readily with aldehydes to form dilactones, fortunately however it is possible to control the hydrolysis of **77** without significant formation of dilactone.[80] **77** thus reacts under acid hydrolysis by a *trans*-acetalisation reaction to give the required γ-hydroxy β-ketoester intermediates **79** which rapidly lactonise to the desired tetronic acids **78**. R can tolerate allyl and oxybenzyl groups and sterically bulky alkyl chains.



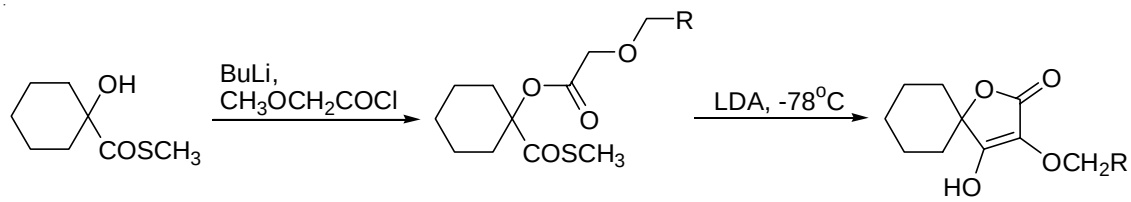
77 **79** **78**

From a retrosynthetic point of view it should be possible to condense a suitable carbonyl compound with a dianion derived from α-hydroxyketones to form tetronic acids. Smith[81] has successfully achieved this by the use of 1,1'-carbonyldiimidazole as a carbonyl equivalent with the formation of a number of tetronic and pulvinone acids.



80 **81** **83**

Another cyclisation route to tetronic acids utilises hydroxy thiomethyl ester **84** which can be prepared from cycloalkanoates in higher yield than the corresponding hydroxy esters. Deprotonation of the hydroxy group with BuLi followed by reaction with methoxyacetyl chloride gave compounds **85**. Reaction of **85** with strong bases leads to spiroannulated tetronic acids of type **86**.[82]



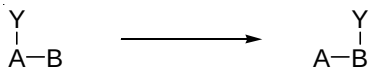
84 **85** **86**

The various methods shown display a number of disadvantages, in particular the majority of cyclisation reactions leading to tetronic acids requires the use of either strong acid or basic conditions. Therefore the use of protecting groups is required for acid/base sensitive functionalities. Other cyclisations proceed with low yields or only with simple alkyl groups present. Therefore we were driven to investigate new routes to the biologically important tetronic acids through the use of keteneylidenetriphenylphosphorane **1**.

1.4 Rearrangements in organic synthesis

1.4.1 Definition of rearrangement reactions

Rearrangement reactions play a vital role in modern synthetic chemistry. A simple definition would describe a rearrangement reaction as the migration of a group from one atom to another atom within the same molecule.[83] Rearrangements have long been known, with many important examples having been discovered in the 19th century long before the introduction of modern organic theory, such as the Benzil-Benzilic Acid rearrangement first observed by Liebig in 1838.[84] The departing segment moves from what is named the migration origin **87** (atom A) and after rearrangement is bonded to the migration terminus **88** (atom B).



87 **88**

In any rearrangement there are two possible modes of reaction, one possiblility involves the complete removal of **Y** from the atom **A** with **Y** becoming attached to atom **B** of another molecule. Normally intermolecular rearrangements are considered along with intramolecular rearrangements even though they do not strictly fall under the above definition. The second mode of reaction involves the movement of **Y** from **A** to **B** within the same molecule, an intramolecular rearrangement. Migrations are almost always from one atom to an adjacent atom (1,2-migrations) however longer movements can be achieved through a series of [1,2]-migrations. Rearrangements can be classified broadly as nucleophilic, electrophilic, pericyclic or free radical. In a nucleophilic rearrangement, the migrating group **Y** moves with its electron pair. In an electrophilic rearrangement, the migrating group **Y** moves without its electron pair and finally in a free radical rearrangement, the migrating group moves with a single electron. Nucleophilic rearrangements are by far the most common type and the reason for this can be seen from consideration of the transition states **89** involved.

89 **Nucleophilic** **Free radical** **Electrophilic**

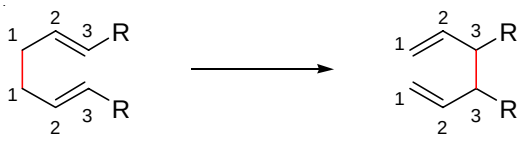
The transition state (or intermediate) for all three cases is represented by **89** with the two electron A-Y bond overlapping with an orbital on atom B, which contains zero, one or two electrons, in the case of nucleophilic, free radical and electrophilic respectively. With a nucleophilic rearrangement only two electrons are involved with both occupying a bonding orbital which translates to a low energy transition state. However with a free radical or electrophilic rearrangement there are three or four electrons respectively which must be occupied in antibonding orbitals thus raising the energy of the transition state **89**. When these rearrangements are observed, the migrating group is normally aromatic, the aryl group being able to accomodate the extra electron. Pericyclic rearrangements proceed through cyclic transition states and are classified by a system based on migration of a sigma bond. Either end of the sigma bond which rearranges is numbered unity and each carbon atom is then numbered sequentially. The final location of the sigma bond determines the classification of the reaction e.g. these include [1,5]-, [2,3]-, and [3,3]-sigmatropic rearrangements among others.

1.4.2 Sigmatropic rearrangements

Sigmatropic rearrangements have been defined as:[85]

"The migration, in an uncatalysed intramolecular process of a σ bond, adjacent to one or more π systems, to a new position in a molecule, with the π systems becoming reorganised in the process."

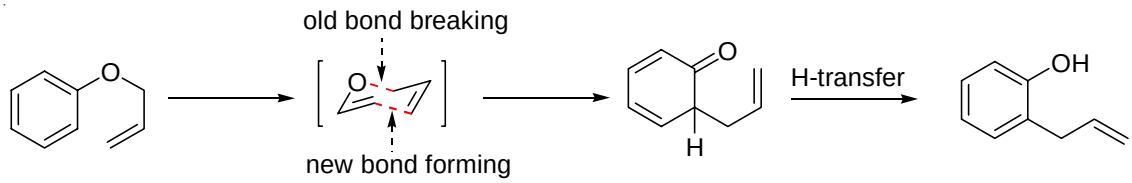
These reactions are called sigmatropic because a σ-bond appears to move from one place to another throughout the course of the reaction. A numbering system has been developed to identify the order of sigmatropic reactions. The rearrangement of **90** into **91** is known as a [3,3]-sigmatropic rearrangement, each terminus of the sigma bond drawn in red for **90** is numbered **1**, simply counting to the ends of the new sigma bond in **91** gives the order of the reaction.



90 **91**

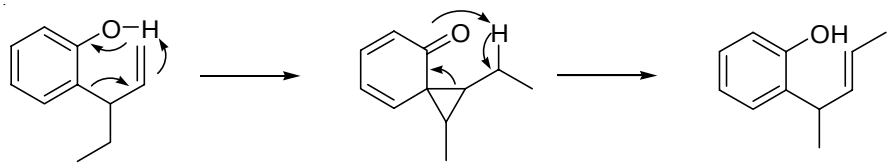
1.4.2.1 The Claisen rearrangement

The first sigmatropic rearrangement was reported by Claisen in 1913[86] when an aryl allyl ether **92** was heated without solvent to give an ortho-allyl phenol **94**. Aryl allyl ethers which bear substituents in both ortho positions undergo allyl migration to the para position. The mechanism is a concerted pericyclic [3,3] sigmatropic rearrangement requiring no catalyst. If the α-carbon next to the oxygen atom bears a non-hydrogen substituent then stereoisomers will be generated. In the majority of cases the resulting double bond will be *trans* since the Claisen rearrangement proceeds through a cyclic chairlike transition state **93**,[87,88] and any substituent R will adopt an equatorial position which is retained in the final product.



92 **93** **94**

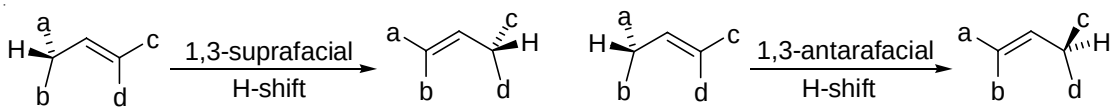
Ethers which contain an alkyl group in the γ-position sometimes rearrange to give so-called abnormal products such as **97**.[89] These are postulated to arise from the initial formation of the normal rearranged products such as **95** which subsequently rearrange to cyclopropane intermediates like **96**[90] which can undergo a [1,5]- sigmatropic hydrogen shift to form the "abnormal" products such as **97**.



95 **96** **97**

The mechanism of the Claisen rearrangement does not involve ions and theoretically it should not be dependent to a great extent on the presence or absence of electron donating/withdrawing substituents. Electron donating substituents have been found to increase the rate whereas electron withdrawing substituents have been found to decrease it.[91-93] However the effect is small and solvent effects have been shown to be much more important[94,95] with highly polar solvents like trifluoroacetic acid being especially effective even at room temperature.[96] Normally Claisen rearrangements are performed without catalysts but recent research has focused on the use of catalysts such as BF_3 and $AlCl_3$ to effect rearrangement at lower reaction temperatures.[97] The presence of an aromatic ring is not necessary for the Claisen rearrangement with the same reaction also proceeding with aliphatic ethers. The reaction is then either known as an aliphatic Claisen rearrangement or as a Claisen-Cope rearrangement. [3,3]-Sigmatropic rearrangements which only contain carbon atoms in the intermediate chair transition state ring are known as Cope rearrangments.[98]

A discussion of the stereochemistry of sigmatropic rearrangements normally includes consideration of the frontier orbitals involved. It should be recognised that a sigmatropic migration can occur by two distinct routes. When the migrating group remains associated with the same face of the conjugated π system **99** during the course of the rearrangement then the migration is termed suprafacial. Alternatively the term antarafacial is employed when the migrating group moves to the opposite face of the π system **101** during the course of the migration.



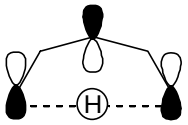
98 **99** **100** **101**

In order to determine whether a rearrangement will proceed by suprafacial or antarafacial migration, a detailed examination is conducted of the orbital symmetry requirements between the π system and the orbitals from the migrating fragment. A frontier orbital analysis of the simple 1,3-H shift can be thought of as a hydrogen atom interacting with an allyl radical. The HOMO for an allyl radical is the only frontier orbital we need consider for the rearrangement. The hydrogen atom has only a 1s orbital which has only one lobe. Sigmatropic rearrangements of hydrogen follow a rule stating that the hydrogen atom must move from a plus to a plus or from a minus to a minus lobe, of the HOMO; it cannot move to a lobe of opposite sign. This follows from the rule that bonds form from the overlap of orbitals of the same sign. Since this is a concerted reaction, the hydrogen orbital in the transition state must overlap simultaneously with one lobe from the migration origin and one from the terminus. Clearly these orbitals must have the same sign.

antarafacial suprafacial

The 1,3-suprafacial hydrogen shift is forbidden by orbital symmetry considerations. Therefore for a 1,3-H migration only the antarafacial is allowed, however because the transition state contained a rigid three carbon chain the 1,3-antarafacial rearrangement is not observed in practice which is convenient otherwise double bonds would easily migrate around organic molecules.

A similar analysis of the 1,5-sigmatropic rearrangement of hydrogen leads to the opposite conclusion. In this case the suprafacial process is allowed whereas the antarafacial process is now forbidden.

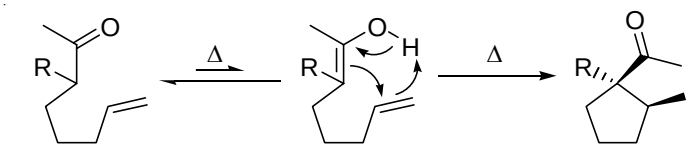


Thermally allowed 1,5-suprafacial hydrogen shift in 1,3-pentadiene

Photochemistry changes all these observations due to the promotion of an electron into the former LUMO. Thus thermal 1,3-H shifts by the antarafacial route are unknown however the photochemical 1,3-H suprafacial shift contains a few examples in the literature.[99] The situation is reversed for 1,5-H shifts. Thermal suprafacial shifts are very common with photochemical antarafacial shifts being much less common.[100]

1.4.3 The Conia rearrangement

The thermal cyclisation of unsaturated carbonyl compounds as a method for the formation of carbon-carbon σ-bonds is sometimes called the Conia rearrangement. The rearrangement can be thought of as an intramolecular variant of the "Ene" reaction[101] where an alkene can add to another alkene, with the formal addition of RH to a double bond. This is a useful method for the construction of cyclic systems α to an aldehyde or ketone. Conceptually the ene reaction can be classified by six different cyclisations; Mikami[102] provides a short discussion on ene nomenclature. The intramolecular thermal reaction of unsaturated carbonyl compounds leads to considerable changes in structure without the need for expensive catalysts or additives, with the formation of cycloalkyl ketones, cycloalkanones and bridged bicycloalkanes having been prepared by this method.[103] The mechanism of the Conia rearrangement implies an enol tautomer **103** which is formed in catalytic amounts by a [1,3]-hydrogen displacement at elevated temperatures. The hydrogen from the enol can then be transfered to the terminus of the double bond with formation of a new carbon-carbon sigma bond.



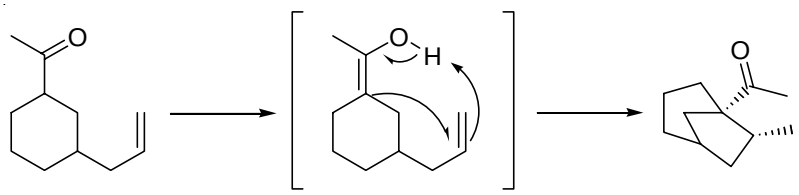
R = H, alkyl, aryl

102 **103** **104**

A single non-epimerisable product **104** is formed when R = CH_3 with the methyl group that is formed in the cyclisation step having a *cis* relationship with the acyl group. The formation of a five ring always proceeds with a *cis* relationship between the newly formed alkyl group and the acyl group.[104] The presence or absence of substituents in the compound has no effect on this outcome. In certain cases observation of products containing the *trans* relationship between the new alkyl group and the acyl group can be detected. Formation of the *trans* isomer has been explained by assuming that the *cis* isomer is formed initially which under the elevated reaction temperatures is able to re-enolise in the direction of the newly formed ring. Reformation of the

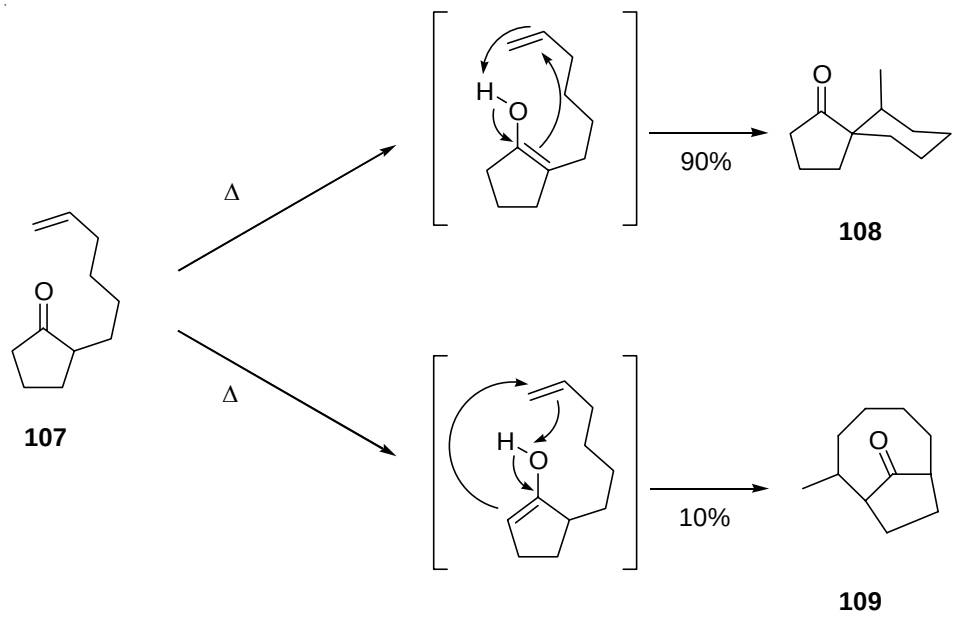
keto group leads to the thermodynamically more stable *trans* isomer being formed. This explanation does not hold for all observations of the *trans* product, with examples known that result from the different orientations of the two allyl groups in the transition state.

Bridged carbonyl compounds can be formed in good yields by a Conia rearrangement of 3-alkyl acetylcyclohexane **105** to give the corresponding 1-acetylbicyclo[3.2.1] alkane **106**. Only one stereoisomer, with the methyl group *cis* with respect to the acetyl group, appears to be formed in this reaction.[105]



105 **106**

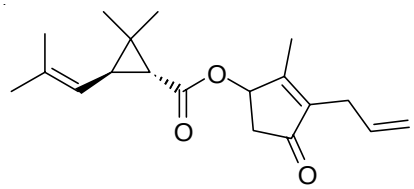
By a similar mode of action spiro compounds of type **108** can be synthesised from substituted 2-alkenylcycloalkanones such as **107**. The ring size of the starting ketone is not important with both cyclopentane and cyclohexane rings having been used; the nature of the side chain is more important. Hex-ω-enyl ketones of type **107** lead to two products, *cis*-6-methyl-spiroketones **108** and compound **109. 109** is formed as a result of the cyclic ketone enolising to the α'-carbon followed by ring closure to give a [5.2.1]-bicycle **109**.[106] Numerous examples exist of so-called α'-cyclisations where the enol intermediate is orientated or forced to the opposite side followed by the cyclisation step.[104] When the side chain contains a terminal alkyne as opposed to an alkene the formation of spiro systems containing an exo double bond is observed and represents an excellent method for the generation of spirodiketones.



1.5 Cyclopropanes in organic synthesis

1.5.1 Properties of cyclopropanes

The cyclopropane subunit exists in numerous natural products, having been isolated from a wide range of plants, fungi and microorganisms. A great number of these natural cyclopropanes exhibit biological activity and present themselves as possible drug leads. Important examples include the pyrethrins which are very powerful natural insecticides. **110** is derived from the East African pyrethrum daisy and a synthetic analogue (decamethrin) is one of the most important insecticides in agriculture. Other examples include the volatile dictyopterene **111**, produced by female brown algae to attract male gametes and is the compound which gives the sea its distinct smell. Hypoglycin **112** an extract from the ackee tree is an important blood sugar lowering agent and the source of Jamaican vomiting sickness.



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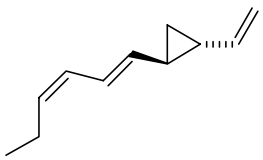

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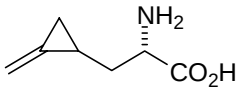


112

The cyclopropane unit can interact with biological systems in a variety of ways.[107] In compounds where the cyclopropane is a stable unit they may simply act as a space filling element, the orientation, position or lipophilicity differing from similar open-chained moieties. More important is their ability to form rigid structural units with locked angles that deviate from the normal tetrahedron angle. The cyclopropane serves as a source of energy due to the highly strained ring system, not surprisingly cyclopropanes act as high-energy intermediates in metabolism.[107] The cyclopropane subunit is electrophilic they are therefore susceptible to nucleophilic attack with many examples reported in the literature.[107] In natural systems, amino groups from DNA or thiol groups from enzymes can act as the nucleophile. This is an extremely important reaction in biological systems with many examples of enzymes reacting by nucleophilic addition to cyclopropanes, the reaction is irreversible thus leading to irreversible inhibition of the protein. Many important cyclopropanes exist such as mitromycin, duocarmycin and CC-1065 which are known to be potent anti-tumour and antibiotic compounds.[107]

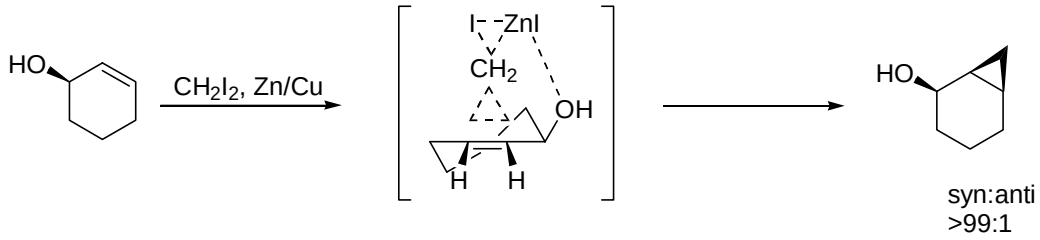
1.5.2 Synthesis of cyclopropanes

Various synthetic routes have been employed for the generation of cyclopropane systems. An excellent review by Charette[109] covers the most important methods which have been published in recent years including halomethylmetal mediated cyclopropanation reactions, transition metal catalysed decomposition of diazoalkanes, Michael initiated ring closure and enzymatic methods.

1.5.2.1 By halomethylmetals

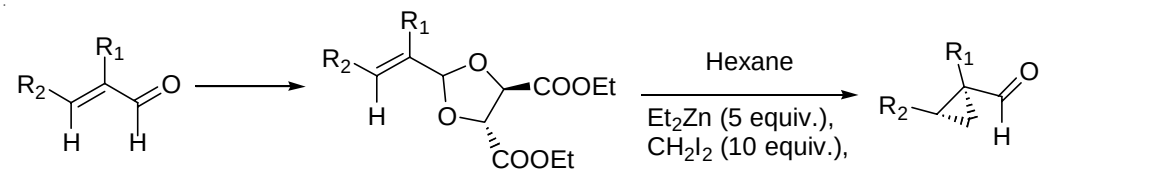
One of the most common and versatile methods of cyclopropane generation is by the action of an iodomethylzinc species with an alkene, the Simmons-Smith reaction.[108] These reagents have

high chemoselectivity tolerating a wide range of functionality such as esters, enamines, ketones etc. Many different halomethylmetals are now known with varying reactivities, structures, stereoselectivity and chemoselectivity.[109] In general the classic Simmons-Smith reagent ($IZnCH_2I$) in ether has been used in over 90% of all zinc-mediated cyclopropanations.[109] A very powerful feature of these organozinc reagents is their ability to coordinate to hydroxy groups. When an allylic alcohol **113** is cyclopropanated, the new methylene group adds stereoselectively to the same face of the double bond as the alcohol group **115**. Allylic alcohols have also been found to accelerate the cyclopropanation reaction. Allylic alcohols are known to react over one hundred times faster than their unfunctionalised counterparts.[109] In the absence of a directing group, the cyclopropanation of cyclic alkenes is generally subject to steric effects. The rate acceleration is thought to proceed due to coordination of the metal to the alcohol group, this interaction brings the carbene into close proximity to the alkene leading to reaction.



113 **114** **115**

The use of directing groups is the focus of much new research, in particular the use of chiral auxiliaries,[110-112] chiral ligands[113,114] and more recently the use of chiral catalysts.[109] Chiral auxiliaries work by reaction of the substrate with a suitable chiral molecule; alcohols have been reacted with carbohydrates. The cyclopropanating reagent is then directed to the alkene by the chiral auxiliary in a stereoselective manner. Whereas α,β-unsaturated aldehydes **116** can be converted to a chiral acetal **117** followed by cyclopropanation. Once the reaction is complete the chiral auxiliary can be removed easily; high diastereoselectivities have been reported.[109] Stoichiometric chiral ligands work in a slightly different manner with dioxaborolanes being the most widely used chiral ligands. The mechanism is thought to proceed in the case of allylic alcohols by an initial deprotonation of the alcohol by the zinc reagent. This is followed by a reaction between the zinc alkoxide and the dioxaborolane ligand in an irreversible manner to generate a tetracoordinated boron intermediate. The final step is an amide directed cyclopropanation on the most stable conformation of the allylic ether chain.



Starting Material — Chiral Auxilliary — Product after cleavage
50 - 95%
(93 - 97% diastereoselectivity)

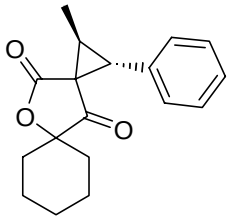
116 **117** **118**

2.0 Discussion

2.1 Synthesis of 3,5-dispirodihydrofuran-4,12-diones

2.1.1 Synthesis of 3,5-dispirodihydrofuran-4,12-dione

3,5-Dispirodihydrofuran-4,12-dione **119** has recently been synthesised by our working group, however to date little work has been conducted on the mechanism of formation, follow-up reactions, biological activity and the possibility of synthesis of functionalised derivatives.[115] Initial work was concentrated on the synthesis of 5-spiro-3-(α-cyclopropylbenzyl) tetronic acids **120.** On the basis of X-ray structural analyses of respective HIV-protease-drug complexes, a rationale was developed for the observed structural-activity dependencies of **120** and of analogous 4-hydroxy(benzo)pyran-2-ones.



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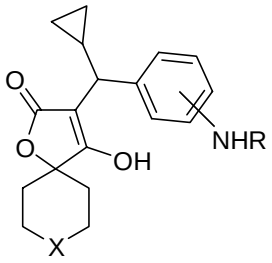
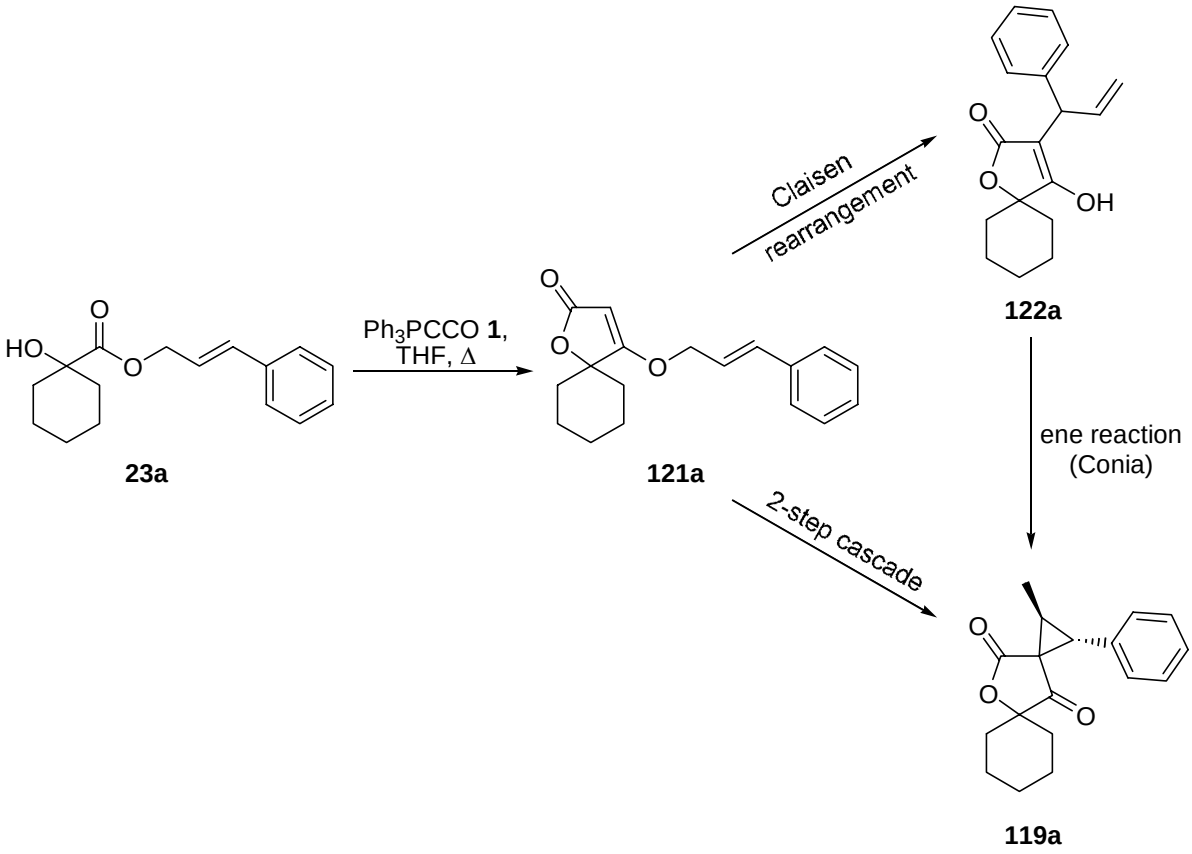


120

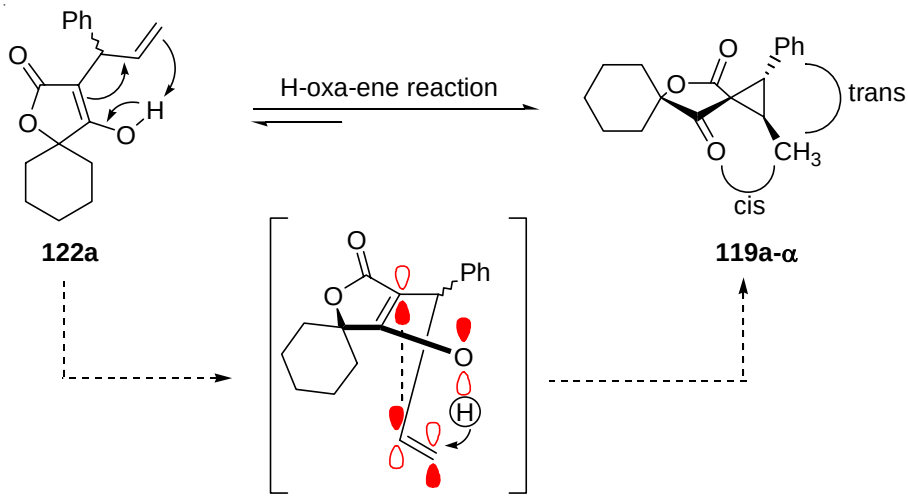
The initial plan was to synthesise **120** by our established domino Wittig olefination-Claisen rearrangement approach[116] by preparing the immediate precursor compounds 5-spiro-3-allyl derivatives **122,** which should be easily amenable to cyclopropanation. Allyl esters **23** from α-hydroxycycloalkanoic acids can be readily prepared by either direct acid catalysed esterification between the corresponding allyl alcohol and the carboxylic acid, or by treatment of the latter with an allyl isourea. Simply refluxing THF solutions of **23a** with keteneylidentriphenylphosphorane **1** [117] gave the corresponding 5-spirotetronates **121a**. The reaction proceeds by initial deprotonation of the hydroxy functionality by **1** to generate an ion pair, which is followed by a nucleophilic addition of O^- to the C=C double bond of **1** to give a stable acyl ylide. Under the reaction conditions this acyl ylide undergoes an intramolecular Wittig olefination reaction to yield **121a**. Under the relatively mild conditions of refluxing THF no follow-up rearrangement was observed. Under more harsh conditions (refluxing toluene/ toluene solutions heated to 200°C in a sealed glass tube) follow-up cascades have been observed for 4-allyloxycoumarins and 4-allyloxyquinolones to give the corresponding 3-allyl-4-hydroxy derivatives after a simple [3,3]-sigmatropic rearrangement. In a deviation from this rule, **121a** when kept in a sealed glass tube for 48h was not converted into the expected Claisen rearranged 5-spiro-3-allyltetronic acid **122a** but exclusively into the dispirolactone **119a**. A reasonable mechanistic explanation would be that the first reaction step should still be a Claisen rearrangement to give **122a**, but that 5-spiroannulation would then enable compounds **122a** to undergo a subsequent, quick oxa-ene reaction of the Conia type[103, 104] to close the 3-spirocyclopropyl ring. As well as the 5-substituents on the tetronic acid **122a**, other factors influencing the progress of the domino Claisen-Conia sequence

include the nature of the allyl chain, the reaction temperature and the polarity of the solvent. It proved possible to find conditions suitable for producing selectively either the pure dispirolactone **119a** or the tetronic acid **122a**.[115]

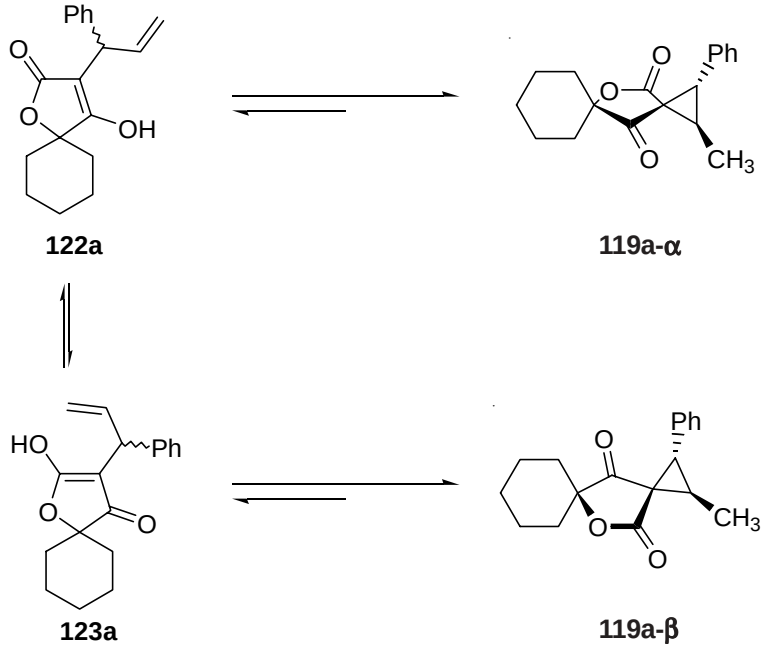


2.1.2 Investigations into the mechanism of 3,5-dispirodihydrofuran-4,12-dione formation

Starting from **121a** which is achiral, it was assumed that the initial Claisen rearrangement would lead to a racemic mixture. The Conia rearrangement is known to proceed with *cis*-selectivity which should have led to a racemic mixture of a single diastereoisomer **119a-α**. A formal frontier orbital description of the transition state using the HOMO of the enol radical and the LUMO of the alkene, provides a rationale for the observed stereochemistry of this particular Conia reaction. The product isomer with a *cis* constellation of the newly created methyl group and the oxo group that participated (as the enol tautomer) in the reaction should be formed exclusively.



However, after reaction NMR spectroscopy revealed a 1:1 mixture of two diasteroisomers **119a-α** and **119a-β**, this mixture could be separated by crystallisation with **119a-β** readily forming crystals. X-ray structural analysis of **119a-β** indicated a *trans* relationship not only between the phenyl residue and the methyl group but also between the phenyl residue and the carbonyl moiety at C-2.[115] Since the carbon atoms adjacent to the newly formed keto group do not contain any hydrogen atoms, enolisation is no longer possible which means that the *trans*-isomer could not be formed by the normal route of enolisation and equilibrium. Instead the mechanism must proceed by reaction of the terminal alkene with the enol of the ester carbonyl group. At the high reaction temperatures it can be assumed that both the keto and ester enols exist in solution. We initially assumed that the diastereoisomers of **119a** once formed were stable. However when a solution of a single isomer (Figure 1: **β** diastereoisomer) of **119a** was heated in toluene at 160°C in a sealed glass tube for 12h, they surprisingly re-equilibrated back to a 1:1 mixture of **α** and **β** diastereoisomers (Figure 2). One explanation for these findings is the assumption that both enol forms **122a** and **123a** are present as an equilibrium mixture under the applied high temperature conditions and independently undergo reversible Conia rearrangements to produce the respective diastereoisomers. The Conia equilibria apparently lie far to the product side, since no residual starting materials could be detected by TLC or by NMR. A solution of **119a** in chloroform was used to grow pure crystals of **119a-β**.



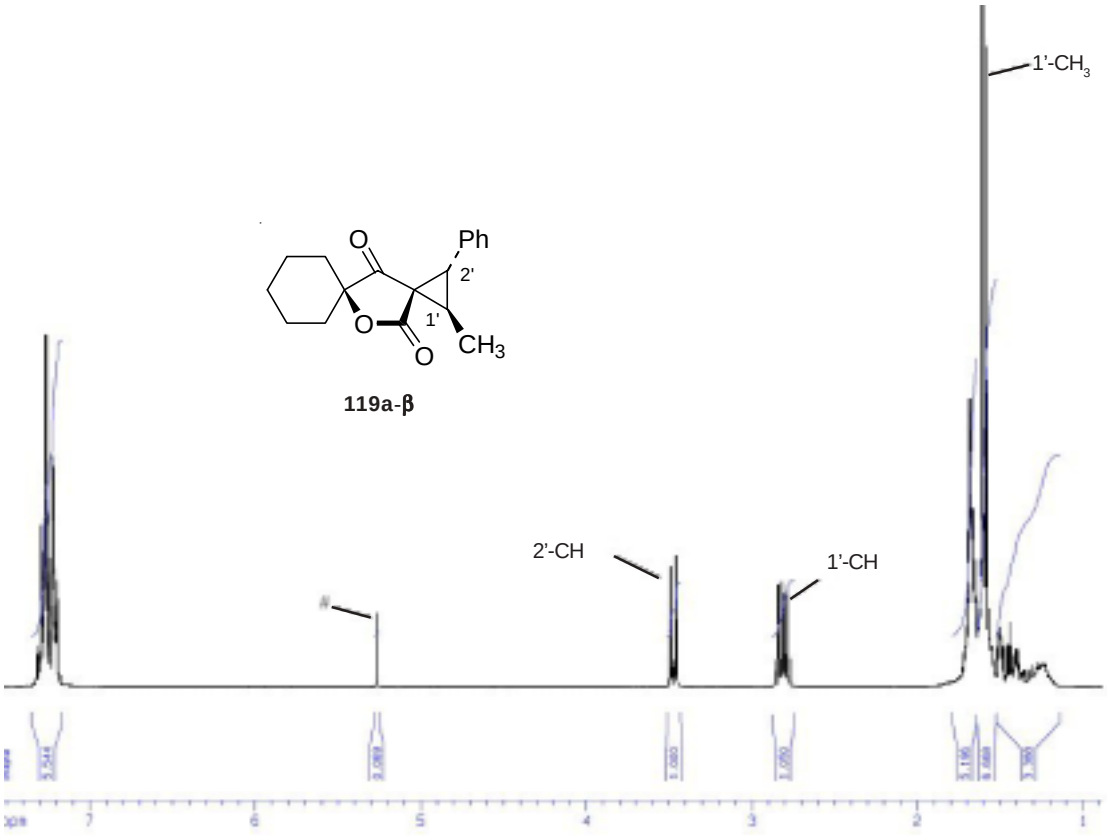


Figure 1: β-diastereoisomer of **119a-β**: # = DCM solvent.

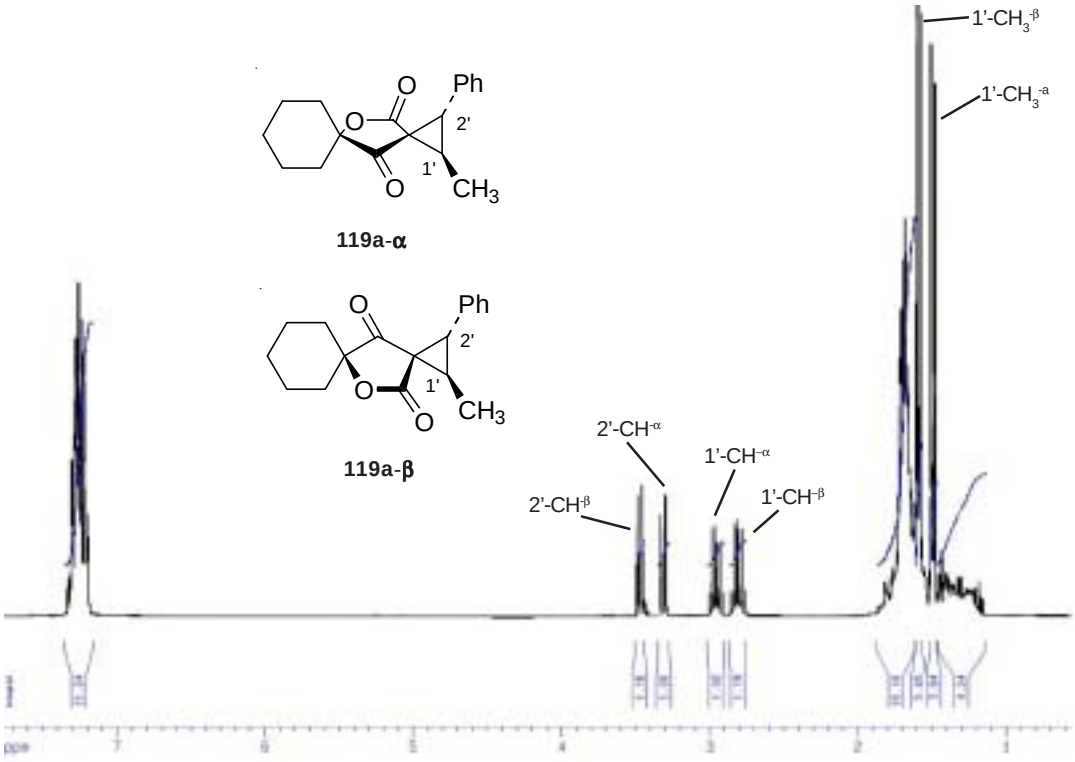


Figure 2: Mixture of **119a-α and 119a-β**.

2.1.3 Optimisation of 3,5-dispirodihydrofuran-4,12-dione formation

All previous experiments leading to formation of **119a** made use of reaction temperatures of 200°C, with the use of toluene being the most favourable solvent for **119a** formation.[115] A series of experiments were performed to investigate if **119a** could be formed using lower reaction temperatures without significant degradation of the yield. Also it was thought that perhaps the diastereoselectivity of the reaction could be controlled by using lower temperatures which as a consequence would favour the formation of either compound **122a** or compound **123a**.

Table 2: Conditions and yields of **119a** resulting from rearrangement of **121a**

Experiment No.	Reaction Conditions[a]	122a yield, [%]	119a yield, [%]
1	Toluene, 48h, 200°C, sealed glass tube	-	67
2	Toluene, 24h, 200°C, sealed glass tube	-	64
3	Toluene, 24h, 170°C, sealed glass tube	-	69
4	Toluene, 24h, 165°C, sealed glass tube	-	68
5	Toluene, 24h, 160°C, sealed glass tube	-	68
6	Toluene, 16h, 160°C, sealed glass tube	-	65
7	Toluene, 10h, 160°C, sealed glass tube	-	41
8	Toluene, 24h, 150°C, sealed glass tube	8	54
9	Toluene, 24h, 130°C, sealed glass tube	41	27
10	Toluene, 24h, 100°C, sealed glass tube	16	9
11	Toluene, 24h, 80°C, sealed glass tube	-	-
12	Acetonitrile, 24h, 85°C,	-	-
13	Acetonitrile, 24h, 125°C,	62	6
14	Acetonitrile, 24h, 125°C, 10% benzoic acid	75	-
15	TFA, 24h, rt	Decomposition	
16	BF_3-ethyl etherate, 24, rt	-	-
17	THF, 1 equiv. Et_2AlCl, 24h, rt	-	-

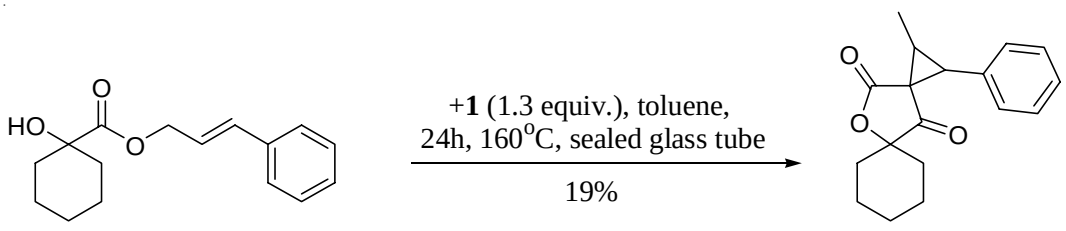
a All temperatures recorded are indicative of the oil bath temperature

From Table 2 it is clear that reaction temperatures of between 160 - 170°C are sufficient to effect the Conia rearrangement without a reduction in yield. Indeed raising the temperature to 200°C gives a very small reduction in yield perhaps due to decomposition of the product over time. Furthermore it is shown that reaction times can also be reduced to around 16 - 24h with no

significant reduction in the overall yield. Below temperatures of 150°C the yield of **119a** begins to fall significantly with production stopping altogether at temperatures of 80°C, which is not surprising as the Conia rearrangement is known as a thermal reaction. In each of the experiments reported in Table 2 product **119a** was examined by NMR to determine the ratio of α to β diastereoisomers present in each reaction product. In all the cases examined the ratio of α to β was found to be almost unity which leads to the conclusion that stereoselective control cannot be achieved by thermal manipulation in this case.

Acetonitrile has a boiling point of 81°C and solutions of **121a** in acetonitrile have previously been reported to undergo a normal Claisen rearrangement under a gentle reflux.[115] During the course of this work the Claisen rearrangement could not be reproduced under such conditions. Gently refluxing acetonitrile solutions where the oil bath is maintained between 85 - 100°C usually give no rearrangement at all or in a few cases a small amount of product can be detected by TLC. This work has revealed that oil bath temperatures of approximately 120°C are required, effecting a vigorously refluxing solution which leads to good yields of Claisen rearranged tetronic acids **122a** (Table 1: Entry 13). The use of a simple acid catalyst led to a slight increase in the yield of **122a** however more common catalysts for Claisen rearrangement such as trifluoroacetic acid,[118] BF_3-ethyl etherate[119] and diethyl aluminium chloride, which normally affect rearrangements at room temperature failed in this case to give any satisfactory results. The use of THF as a solvent has already been mentioned as effecting no rearrangement, however it should be noted that if the reaction of **23a** with **1** is maintained for several days it is possible to observe **119a** by TLC however it is usually impossible to isolate **119a** after column chromatography of the mixture.

A separate two step synthesis of **119a** is not neccessary and it is possible for **23a** to undergo an addition, intramolecular Wittig, Claisen, Conia domino sequence with **1** in toluene.[115] The information obtained from Table 1 would suggest that by using gentler reaction conditions the outcome of this four step domino sequence could be improved. After 24h at 160°C the yield was increased to 19% from the previously reported 17%,[115] however it was also possible to recover 43% of **23a** from the reaction mixture after column chromatography. Numerous side products were generated in the reaction but **122a** was not recovered from the mixture. It is possible that **1** is unstable under these reaction conditions and undergoes slow decomposition which would account for the relatively large amount of starting material that was recovered.



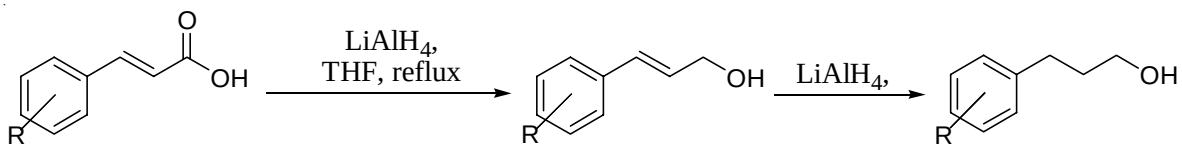
23a **119a**

2.1.4 Synthesis of functionalised 3,5-dispirodihydrofuran-4,12-diones

Initial biological screening of **119a** showed an intriguing herbicidal activity. Namely **119a** caused a form of chlorosis, the discolouration of foliage due to a reduction in the number of chloroplasts or from the lack of nutrients such as iron or manganese, with the effect more pronunced in grasses and weeds.[120] Theoretically available from two simple steps, coupled with herbicidal activity, **119a** shows great potential to the chemical industry as a future commercial lead compound acting either as a photosynthetic inhibitor, with the vital process of photosynthesis disrupted, or as a pigment inhibitor with disruption of chlorophyll production. It therefore became necessary to investigate if a library of functionalised derivatives, hopefully possessing a greater biological effect could be synthesised by our sequence. It was envisaged that a library could be quickly constructed and tested from functionalised cinnamyl alcohols, and to this end strongly electron withdrawing and electron donating substituents were selected.

2.1.4.1 Synthesis of functionalised cinnamyl alcohols

Functionalised cinnamyl alcohols are not available for purchase from any of the major chemical suppliers (except for 4-nitrocinnamyl alcohol[121]) however the corresponding chloro/nitro cinnamic acids are readily available. The reduction of carboxylic acids to alcohols is a well known and operationally simple chemical reaction, however problems were immediately encountered with the reduction of cinnamic acids.



124 **125** **126**

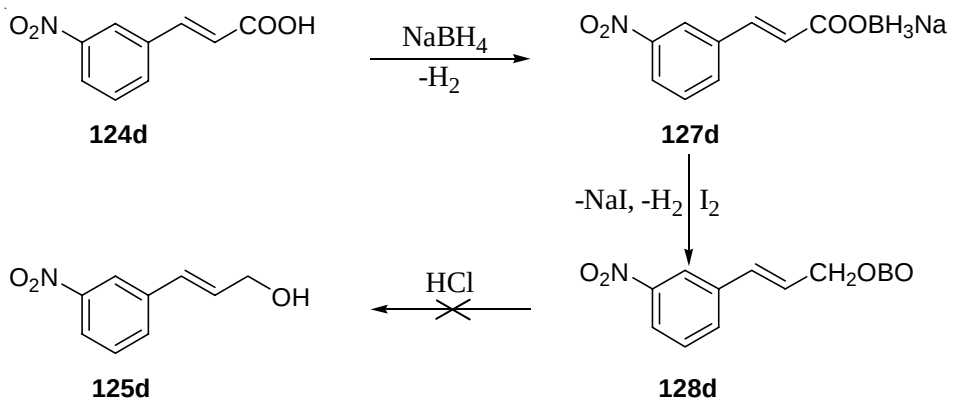
Table 3: $LiAlH_4$ reduction of functionalised cinnamic acids

126	**R**	**yield, [%]**
a	ortho-Cl	78
b	meta-Cl	81
c	para-Cl	67
d	meta-NO_2	29

In each attempt an over-reduction was encountered leading to the saturated alcohols (Table 3). To overcome this problem the reaction was repeated several times using lower temperatures and by changing the solvent to ether, however in each case the saturated alcohol was always obtained

albeit with lower yields, and in many cases as complicated mixtures of acid, unsaturated alcohol and saturated alcohol.

Kanth[122] recently published a new method for the reduction of cinnamic acid to cinnamyl alcohol by use of $NaBH_4$ and iodine in THF. The initially formed organoborane **127** is thought to react with iodine with expulsion of hydrogen and sodium iodide to give **128** which undergoes hydrolysis to give **125**.

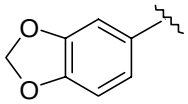
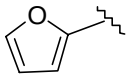


124d **127d** **128d** **125d**

Despite repeated attempts with **124d** and **124b** using different stoichiometries of $NaBH_4$ and iodine, alteration of reaction temperature and reaction times, the corresponding cinnamyl alcohol was never obtained. In each case the starting acid could be completely recovered. Reduction of the carboxylic acids was also attempted with the excellent reducing agent DIBAL-H. While the unsaturated alcohols were recovered, the yields of the products never exceeded 30% with numerous side products making workup difficult. Attempts were made to convert the acid to the acyl chloride followed by reduction of the acyl chloride with sodium borohydride, again this method of reduction repeatedly failed.To overcome this problem the functionalised cinnamic acids were converted to the corresponding methyl esters. This was accomplished by refluxing the acids in a mixture of chloroform and methanol in a Dean-Stark apparatus using *p*-toluenesulphonic acid as an acid catalyst. Yields ranged from 90 - 98%. Again the literature contains many examples of ester to alcohol reduction with $LiAlH_4$ being the preferred reagent.[123 - 128] Once again $LiAlH_4$ failed as a suitable choice for ester reduction with the saturated alcohol being the main product recovered even with careful control of the stoichiometry and reaction temperature. 3,4-(Methoxyenedioxy)-cinnamyl acid methyl ester for example was reduced to the corresponding saturated alcohol in 77% yield. Other reagents which were attempted include $NaBH_4$, BF_3-THF and sodium bis(2-methoxyethoxy)-aluminium hydride, in each case the starting material was completely recovered. The esters were finally converted to the corresponding α,β-unsaturated alcohols by the action of DIBAL-H in a solution of dichloromethane. Excellent yields (Table 4) were obtained in all cases except when a nitro group was present in the molecule probably due to partial reduction of the nitro functionality. It should be noted that in the recent literature DIBAL-H is replacing lithium aluminium hydride as the reducing agent for many cinnamic acid esters, probably due to the problem of over-reduction.

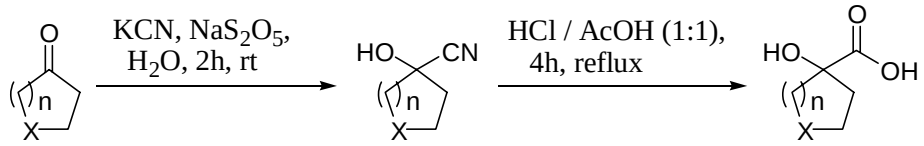
129 **130**

Table 4: Formation of functionalised cinnamyl alcohols **130** by DIBAL-H reduction of methyl cinnamyl esters **129**

130	**R**	**yield, [%]**
a	ortho-Cl-Ph	84
b	meta-Cl-Ph	93
c	para-Cl-Ph	96
d	meta-NO_2-Ph	51
e	ortho-NO_2-Ph	69
f	$PhCH_2$	92
g		89
h		78

2.1.4.2 Synthesis of α-hydroxycarboxylic acids

α-Hydroxycarboxylic acids can be easily prepared by a procedure developed by Carr[129,130]. Starting from the corresponding ketone, attack by potassium cyanide in the presence of sodium pyrosulfite leads directly to the cyanohydrins which are then simply hydrolysed by glacial acetic acid and hydrochloric acid mixtures.



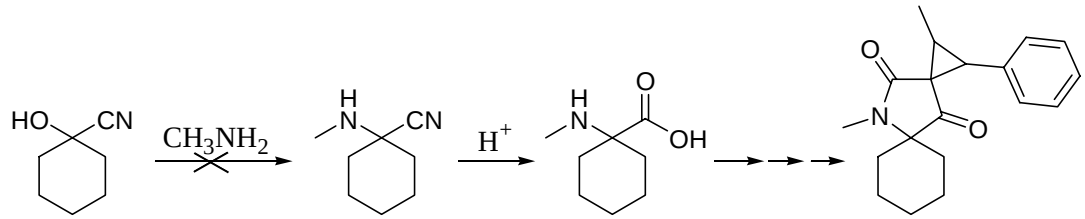
131 **132** **133**

133a (X = CH_2, n = 2, 74%)
133b (X = O , n = 2, 55%)
133c (X = S , n = 1, 0%)

Substituents located in the C-5 position of tetronic acids play an important role in the chemistry of tetronic acids. For this reason it was decided to synthesise 3,5-Dispirodihydrofuran-4,12-diones with variable substituents in the C-5 position; this also enables us to prove that our synthesis is versatile not only at C-3 but also at C-5. To this end when X = O the product was obtained in reasonable yield, the product was unamenable to recrystallisation but the crude product was of sufficient purity for characterisation and for follow-up chemistry. Replacement with sulphur unfortunately lead only to unspecified decomposition during the hydrolysis step, even when milder hydrolysis conditions were employed. The initial cyanohydrin step was also sluggish and gave poor yields.

2.1.4.3 Attempted synthesis of α-aminocyclohexane carboxylic acid

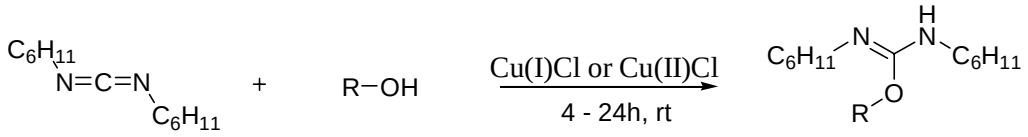
With the knowledge that tetronates containing a cyclohexane moiety at C-5 lead to 3,5-Dispirodihydrofuran-4,12-diones an attempt was made to synthesise the 1,11-dimethyl-2-phenyl-11-azadispiro[2.1.5.2]dodecane-4,12-dione **136** starting from **135**. **135** was considered a suitable candidate due to the presence of the cyclohexane ring which is known to facilitate Claisen rearrangents more readily than mono-substituted homologues. The use of a primary amine would after reaction with **1** have given a secondary amine which are difficult to separate from phosphine oxide, the byproduct from intramolecular Wittig olefination.[131] Starting from a secondary amine would give a tertiary amine which should circumvent this potential problem. A slightly modified procedure by Kurtz[132] was used, however formation of **134** was not observed. Other commericially available amino acids have not to date been examined due to the potential problems already mentioned.



132a **134** **135** **136**

2.1.4.4 Esterification of α-hydroxycarboxylic acids using isoureas

Isoureas represent a powerful class of compound for esterification reactions in organic synthesis. This operationally simple, relatively non-toxic route is under-utilised in modern chemistry. Simple addition of an alcohol **138** in the presence of a copper catalyst to DCC **137** leads to the isourea **139** in excellent yields with the added advantage that solvents are not required, making this method extremely attractive from an environmental point of view.[137] Isoureas can be purified by filtration over a small plug of neutral alumina. It should be noted that normal column chromatography leads to severe decomposition. Distillation can be employed when R is small, however distillation of isoureas with bulky/long chain residues once again leads to decomposition. Table 5 shows new examples of α,β-unsaturated isoureas.



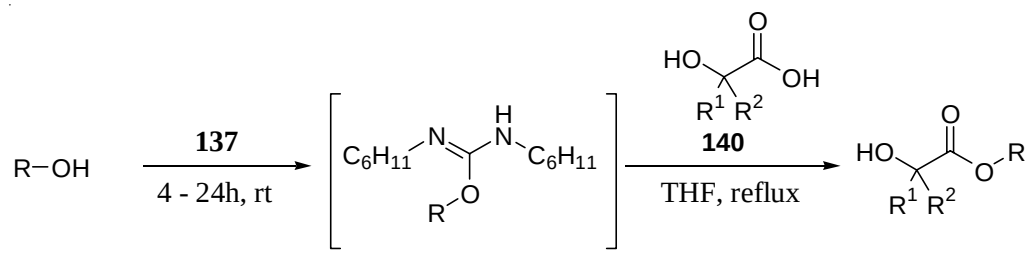
137 **138** **139**

Table 5: Examples of new unsaturated iosureas **139**

139	**Alcohol**	**yield, [%]**
a	$(CH_3)ClC^{q}=CHCH_2OH$	92
b	$CH_3CH=CHCH=CHCH_2OH$	87
c	meta-Cl-ArCH=$CHCH_2OH$	73
d	$CH_3CH_2CH_2CH=CHCH_2OH$	96
e	$CH_3CH_2CH_2CH(OH)CH=CH_2$	81

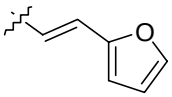
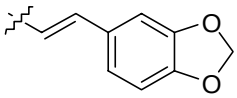
The main disadvantage of using isoureas as esterification agents is their inherent instability. Some isoureas can be stored for months at a time under an inert atmosphere, however for many examples decomposition occurs after several days. Once the isourea has been synthesised, the ester may be formed by simple addition of a suitable solvent (eg. THF) followed by the acid. Gentle heating of the solution for a few hours gives a solution of the ester plus a precipitate of DHU which can simply be filtered off.

Since we have undertaken a synthetic route of several steps we were interested in maximising yields at every possible stage. Examination of the IR profile is normally used to determine the end point of isourea formation, DCC has a distinct peak at ~2100 cm^{-1} and once this peak completely disappears the reaction is judged to be complete. If the entire peak disappears it is reasonable to surmise that complete addition has occurred. This would suggest that significant amounts of isourea are lost on workup, a problem inherent to most forms of purification. Unreacted DCC, alcohol and the copper catalyst are unlikely to interfere with the second step of the reaction, so the logical conclusion would be to perform the second step of the esterification on unpurified isourea. All three components cannot be added together as competing reactions between an acid and an alcohol with DCC would lead to complicated mixtures and probably poor yields. Taking the standard system using cinnamyl alcohol which forms the isourea in 79% with the second step with α-hydroxycyclohexane carboxylic acid resulting in a 72% yield. As a two step reaction this gives an overall yield of 57% which is quite poor compared to many esterification methods. It was found however that preformation of the isourea followed by immediate (indicated by disapperence of DCC peak at 2100 cm^{-1}) addition of dry THF followed by addition of the acid led to the desired ester in a much improved yield of 75%. Not only are yields greatly improved by this simple modification but reaction times are considerably shortened and careful purification techniques are no longer required. In all cases investigated where an isourea could be formed from the alcohol, immediate reaction without purification led to significant improvements in yield as shown in Table 6. For purposes of clarity the older method using pure isoureas has been named route A, whereas use of the crude isourea mixture is named route B. Yields in Table 6 are based on the starting alcohol.



138 **139** **23**

Table 6: Synthesis of **23** by route A a) and route B b)

23	**R**	**R^1**	**R^2**	**Route A yield, [%]**	**Route B, yield, [%]**
a	$CH_2CH=CHPh$	$-(CH_2)_5-$		57[115]	75
b	$CH_2CH=CHAr$-ortho-Cl	$-(CH_2)_5-$		-	98
c	$CH_2CH=CHAr$-meta-Cl	$-(CH_2)_5-$		53	76
d	$CH_2CH=CHAr$-para-Cl	$-(CH_2)_5-$		-	70
e, f, g	$CH_2CH=CHAr-NO_2$ (m,o,p)	$-(CH_2)_5-$		Isourea not formed	
h	$CH_2CH=CHPh$	$-(CH_2)_2O(CH_2)_2-$		48	69
i	$CH_2CH=CHPh$	Ph	H	-	83
j		$-(CH_2)_5-$		Isourea not formed	
k		$-(CH_2)_5-$		Isourea not formed	
l	$CH_2CH=CHAr$-para-CH_3	$-(CH_2)_5-$		Isourea not formed	
m	$CH_2CH=C(CH_3)_2$	$-(CH_2)_5-$		54[115]	73
n	$CH_2CH=C(CH_3)Cl$	$-(CH_2)_5-$		76	91
o	$CH_2CH=CHCH_2CH_3$	$-(CH_2)_5-$		-	86
p	$CH_2CH=CHCH_2CH_2CH_3$	$-(CH_2)_5-$		79	90
q	$CH_2CH=CHCH_2CH_2CH_3$	Ph	H	-	86
r	$CH_2CH=CHCH_2Ph$	$-(CH_2)_5-$		-	76
s	$CH_2CH=CHCH=CHCH_3$	$-(CH_2)_5-$		41	50
t	$CH_2CH=CHCH=CHPh$	$-(CH_2)_5-$		Isourea not formed	
u	$CH_2CH=CH_2$	$-(CH_2)_5-$		65	82
v	CH_2C^qCH	$-(CH_2)_5-$		Isourea not formed	

a) **139** prepared then purified before reaction with **140**
b) **139** prepared and reacted with **140** without purification

Clearly not all alcohols can be esterified by the isourea method. It was found that the presence of electron donating groups on the phenyl ring of cinnamyl alcohols, and also strongly electron-withdrawing groups for example the nitro functionality, lead to complete failure. Experiments with these alcohols were conducted at temperatures ranging from 0°C - 60°C in the presence (dry THF, dry hexane) and absence of solvents. Isourea formation was never observed.

2.1.4.5 Esterification of α-hydroxycarboxylic acids by other methods

The most simple method of ester formation is the reaction of a carboxylic acid or an alcohol in the presence of an acid catalyst. Previous work claimed that the product could not be purified from the excess cinnamyl alcohol.[115] However the use of stoichiometric quantities of alcohol and α-hydroxyacid, coupled with p-toluenesulphonic acid (10 mole%) catalyst in chloroform proved to be effective. Good to excellent yields were obtained for phenyl bearing a nitro residue as well as for the normal cinnamyl alcohol. Propargyl alcohol was also coupled with mandelic acid by this method. Alkynes cannot form isoureas as the amine reacts in a nucleophilic manner with the triple bond.

The Mitsunobu esterification is a widely used and increasingly popular esterification method.[138-141] The major disadvantage of this method is that the DIAD reagent is relatively expensive. The Mitsunobu reaction represented a very useful addition to our synthesis in the cases where the esterification of α-hydroxyacids proved impossible by all other means. Yields were however disappointing (Table 7), the reason for which could be explained by competing dimerisation of the α-hydroxyacids.

Methylenedioxycinnamyl alcohol **23k** proved incredibly stubborn to all attempts to form an α-hydroxy ester. This problem was solved by a procedure by Hanessian[142] which made use of EDC and DMAP. The yield from this reaction was disappointing (47%) as Hanessian had reported a 95% yield with acrylic acid. Another disadvantage to this procedure was the use of a six-fold excess of acid. No attempts were made to optimise this reaction.

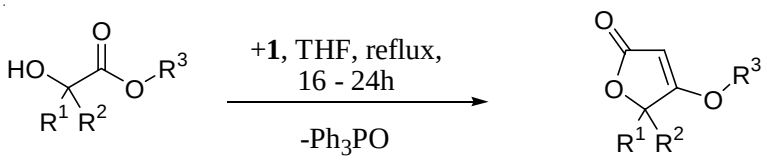
It should be noted that for compounds **23s** and **23t** the starting alcohols contained all *trans* double bonds. The NMR data for these compounds contains only multiplets for the double bond signals but it is highly unlikely that esterification would alter these bonds.

Table 7: Synthesis of **23** by other methods

23	Reaction Conditions	yield, [%]
e	$CHCl_3$, p-toluenesulphonic acid, reflux, 24h	74
f	$CHCl_3$, p-toluenesulphonic acid, reflux, 16h	54
g	$CHCl_3$, p-toluenesulphonic acid, reflux, 48h	79
h	DIAD, Ph_3P, THF, -10°C	29
j	DIAD, Ph_3P, THF, -10°C	47
k	EDC, DMAP, DCM, 0°C	47
t	DIAD, Ph_3P, THF, -10°C	48
v	$CHCl_3$, p-toluenesulphonic acid, reflux, 24h	91

2.1.4.6 Synthesis of 4-allyl-5-spirotetronates

The domino addition-intramolecular Wittig reaction of keteneylideneylidenetriphenylphosphorane **1** with α-hydroxyesters **23** proceeded in yields ranging from 23 - 93% (Table 8). The low yield (23%) of **121s** can be attributed to the inherent instability of the product which slowly decomposes over time. A low yield is also recorded for **121n**, this can be accounted for due to difficulties in the workup. **121n** is inactive to all common methods of TLC analysis, column chromatography without TLC analysis inevitably led to significant reduction in the yield.



23 **121**

Table 8: Synthesis of 4-allyltetronates **121** from α-hydroxycarboxylic esters **23**

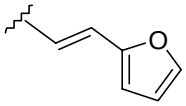
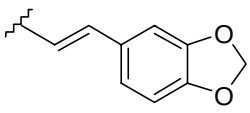
121	R	R^1	R^2	Yield (%)
a	$CH_2CH=CHPh$	$-(CH_2)_5-$		78
b	$CH_2CH=CHAr$-ortho-Cl	$-(CH_2)_5-$		66
c	$CH_2CH=CHAr$-meta-Cl	$-(CH_2)_5-$		70
d	$CH_2CH=CHAr$-para-Cl	$-(CH_2)_5-$		50
e	$CH_2CH=CHAr$-meta-NO_2	$-(CH_2)_5-$		93
f	$CH_2CH=CHAr$-ortho-NO_2	$-(CH_2)_5-$		41
g	$CH_2CH=CHAr$-para-NO_2	$-(CH_2)_5-$		78
h	$CH_2CH=CHPh$	$-(CH_2)_2O(CH_2)_2-$		69
i	$CH_2CH=CHPh$	Ph	H	58
j		$-(CH_2)_5-$		77
k		$-(CH_2)_5-$		72
m	$CH_2CH=C(CH_3)_2$	$-(CH_2)_5-$		64
n	$CH_2CH=C(CH_3)Cl$	$-(CH_2)_5-$		44
o	$CH_2CH=CHCH_2CH_3$	$-(CH_2)_5-$		93
p	$CH_2CH=CHCH_2CH_2CH_3$	$-(CH_2)_5-$		84

Table 8: Synthesis of 4-allyltetronates **121** from α-hydroxycarboxylic esters **23**

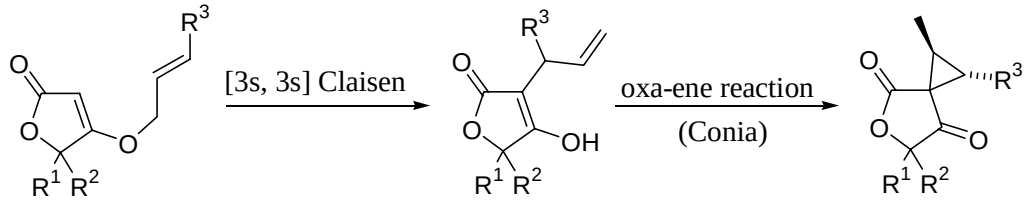
121	R	R^1	R^2	Yield (%)
q	$CH_2CH=CHCH_2CH_2CH_3$	Ph	H	90
r	$CH_2CH=CHCH_2Ph$	$-(CH_2)_5-$		75
s	$CH_2CH=CHCH=CHCH_3$	$-(CH_2)_5-$		23
t	$CH_2CH=CHCH=CHPh$	$-(CH_2)_5-$		76
v	CH_2C^qCH	Ph	H	74

2.1.4.7 Controllable synthesis of functionalised 3,5-dispirodihydrofuran-4,12-diones and 3-phenylallyl-5-spiro-tetronic acids. A comparison between thermal and microwave synthesis

By proper choice of conditions either the Claisen product **122a** or the oxa-ene (Conia) rearranged product, 3-(spirocyclopropyl)dihydrofuran-4,12-dione **119a**, was formed as main product where the allyl tetronate **122a** bore a phenyl residue R^3. The use of microwave irradiation dramatically decreases the reaction times required for the formation of **119**. Microwave irradiation also facilitates the synthesis of Claisen rearranged products from allyl tetronates bearing chloroaryl residues R^3 which has proved to be impossible under classical thermal conditions.

The conventional thermal synthesis of **122a** (alongside some follow-up Conia product **119a**) from the tetronate **121a** in refluxing acetonitrile normally requires long reaction times, typically 24-48h. A selective synthesis of **119a** could be achieved by heating solutions of **121a** in toluene in a sealed glass tube at 160-190 °C for 24-48h. (see Section 2.1.3)

While tetronates **121b-d** with an *o*-, *m*-, or *p*-chlorophenyl substituent R^3 could be converted into the corresponding 1-(chlorophenyl)-2-methyl-11-oxadispiro[2.1.5.2]dodeca-4,12-diones **119** under these conditions, the corresponding tetronic acids **122** were not accessible by refluxing in acetonitrile. Even prolonged reaction times (up to 84 h) still resulted in 100% of the starting tetronate being recovered from the reaction mixture. However, heating of acetonitrile solutions of these tetronates in a sealed vessel placed in a 300 W focussed single-mode microwave reactor (CEM GmbH, Germany) at 150 °C for 1 h gave easily separable mixtures of compounds **122** and **119** in almost quantitative yields (Table 9). Although allyl tetronates containing a nitrophenyl group can be rearranged to tetronic acids **122** by conventional heating in acetonitrile, we found that microwave irradiation gave similar yields in a much shorter time with less solvent being required. Only when pure tetronic acid **122g** is to be prepared is the thermal process superior to the microwave protocol. Difficulties were encountered with the *o*-nitrophenyl **122f** and furan **122j** derivatives both under conventional thermal and microwave conditions which led to complicated mixtures of inseparable products. In general though, microwave irradiation represents a highly efficient means for the Claisen rearrangement of differently substituted allyl tetronates. It reduces reaction times from days to a single hour while at the same time increasing the overall yields considerably. It should also be noted that compound **122b** only formed the α-diastereoisomer; it is probable that the β-diasteroisomer is not formed as this would lead to too great an interaction between the o-chloro group and the ester group in the lactone ring.



121 **122** **119**

	R^3	R^1 R^2
121, 122, 119 b	Ar-ortho-Cl	$-(CH_2)_5-$
c	Ar-meta-Cl	$-(CH_2)_5-$
d	Ar-para-Cl	$-(CH_2)_5-$
e	Ar-meta-NO_2	$-(CH_2)_5-$
f	Ar-ortho-NO_2	$-(CH_2)_5-$
g	Ar-para-NO_2	$-(CH_2)_5-$
h	Ph	$-(CH_2)_2O(CH_2)_2-$
i	Ph	Ph H
j	Furan	$-(CH_2)_5-$
k	Ar-meta-OCH_2-o-para	$-(CH_2)_5-$

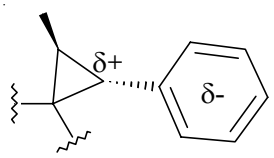
Table 9: Thermal *vs* microwave syntheses of tetronic acids **122** and spirocyclopropylfurandiones **119**

Starting Compound	Yields **122**:**119** (%) thermal reaction in CH_3CN	Yields of **122**:**119** (%) MW reaction in CH_3CN	Yields **122**:**119** (%) thermal reaction in toluene/sealed tube
121a	62:6	12:19[b]	0:69[c]
b	0:0[a]	42:58[b]	0:64[c]
c	0:0[a]	55:45[b]	0:63[c]
d	0:0[a]	43:52[b]	0:89[c]
e	56:8[d]	44:16[b]	0:68[e]
f	0:0[a]	0:0[a]	0:0[a]
g	32:0[d]	26:37[b]	0:42[f]
h	88:0[d]	–	0:57[e]
i	42:12[d]	61:16[h]	0:70
j	57:0[d]	–	i
k	0:0[a]	–	0:67[c]

[a] CH_3CN, refl., 84h.
[b] CH_3CN, 300W microwave, 150°C, 1h.
[c] toluene, 160°C, 48h, sealed tube.
[d] CH_3CN, refl., 48h.
[e] toluene, 170°C, 35h, sealed tube.
[f] toluene, 180°C, 48h, sealed tube.
[g] CH_3CN, 300W microwave, 130°C, 1h.
[h] CH_3CN, 300W microwave, 150°C, 1h.
[i] Decomposition

2.1.5 Ring opening of 3,5-dispirodihydrofuran-4,12-diones with nucleophiles

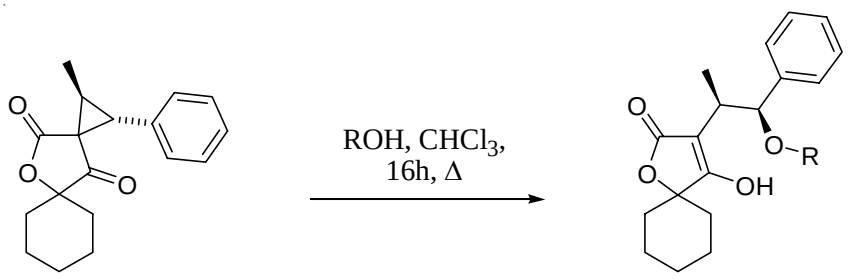
Having successfully optimised the conditions for 3,5-Dispirodihydrofuran-4,12-dione **119a** formation and successfully obtained a small library of functionalised derivatives, we became more interested in the reactivity of **119**. Since this molecule contains a phenyl substituted cyclopropane ring, we suspected that the electron-withdrawing properties of the phenyl moiety would leave the α-carbon susceptible to nucleophilic attack. Nucleophilic attack of the cyclopropane ring could be expected to lead to 3,5-substituted tetronic acids. 3-5-Disubstituted tetronic acids are of medicinal interest as potential antibiotic, antiviral and antineoplastic agents.[55,143-145] We therefore designed a series of experiments with suitable nucleophiles to investigate the reactivity of **119a** which was taken as a stereochemical simple standard system.



119a

2.1.5.1 Ring opening reactions with oxygen nucleophiles

Alcohols are nucleophilic and were expected to react readily with **119a**. Indeed simply by refluxing **119a** in a mixture of chloroform and the respective alcohols led to the corresponding 3-(β-alkoxy)alkyltetronic acids **141** in good to excellent yields.[146,147,148] Chloroform is generally added to improve the solubility of **119a**. From earlier single-crystal X-ray structural analyses[115] of tetronic acids bearing similar residues we knew that vicinal coupling constants ^3J(1'-H/2'-H) of ~2 - 4Hz are indicative of a syn configuration of the stereocentres in the side chain at C-3. All examples prepared from ring opening with alcohols showed exclusively the syn configuration. This can be explained in terms of a selective attack of the nucleophile on the benzylic carbon atom in the intact three membered ring from the same face as the adjacent methyl group.

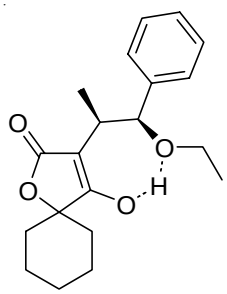


119a **141**

Table 10: Ring opening with O-nucleophiles

141	R	Conditions	Yield (%)
a	CH_3	chloroform, reflux, 16h	70
b	CH_2CH_3	chloroform, reflux, 16h	76
c	$CH_2CH_2CH_3$	p-toluene sulphonic acid, propanol, 80°C, 16h	72
d	$CH_2CH{=}CH_2$	chloroform, reflux, 16h	50
e	$CH_2CH{=}C^q(CH_3)_2$	DCM, reflux, 16h	53

3-(β-alkoxy)alkyltetronic acids **141b-e** which contain a methylene group adjacent to the oxygen atom display interesting NMR spectra (Figure 3). The NMR signal for this methylene group does not for **141b** display the simple expected quartet. Instead two clearly separated double quartets are visible. We believe that a strong hydrogen bond exists between the tetronic acid hydroxy group and the alkoxy oxygen atom; this would result in a pseudo seven ring **142b** which is likely to restrict rotation about the O-CH_2 bond, leading to the two geminal hydrogens in different chemical environments and able to undergo geminal coupling. To investigate the relative strength of this internal hydrogen bond an NMR sample in chloroform was measured at different temperatures from room temperature to 60°C. It was expected that at increased temperatures the internal bond would weaken and allow rotation about the O-CH_2 axis, however even at temperatures of 60°C this was not observed, suggesting a very strong hydrogen bond interaction. It is also possible that steric congestion simply restricts rotation.



142b

When **119a** is heated under reflux in solutions of chloroform and propanol no reaction is observed.[148] Even refluxing solutions of propanol do not effect any reaction at all. However when a solution of **119a**, propanol and HBF_4 are heated to 80°C for 16h good yields are obtained. Propanol is not an especially good nucleophile and this reaction provides some insight into the reaction mechanism. By using an acid catalyst it is likely that a proton interacts with the ketone oxygen atom leading to a weakened cyclopropane bond which would be amenable to nucleophilic attack by the propanol. It is unlikely that the bond completly breaks as this would lead to a product with an anti configuration. Indeed this reaction leads to a 72% yield of product **141c**, higher than previous yields obtained for uncatalysed alcohols. This would suggest that the yields of **141** could be increased by an acid catalyst.

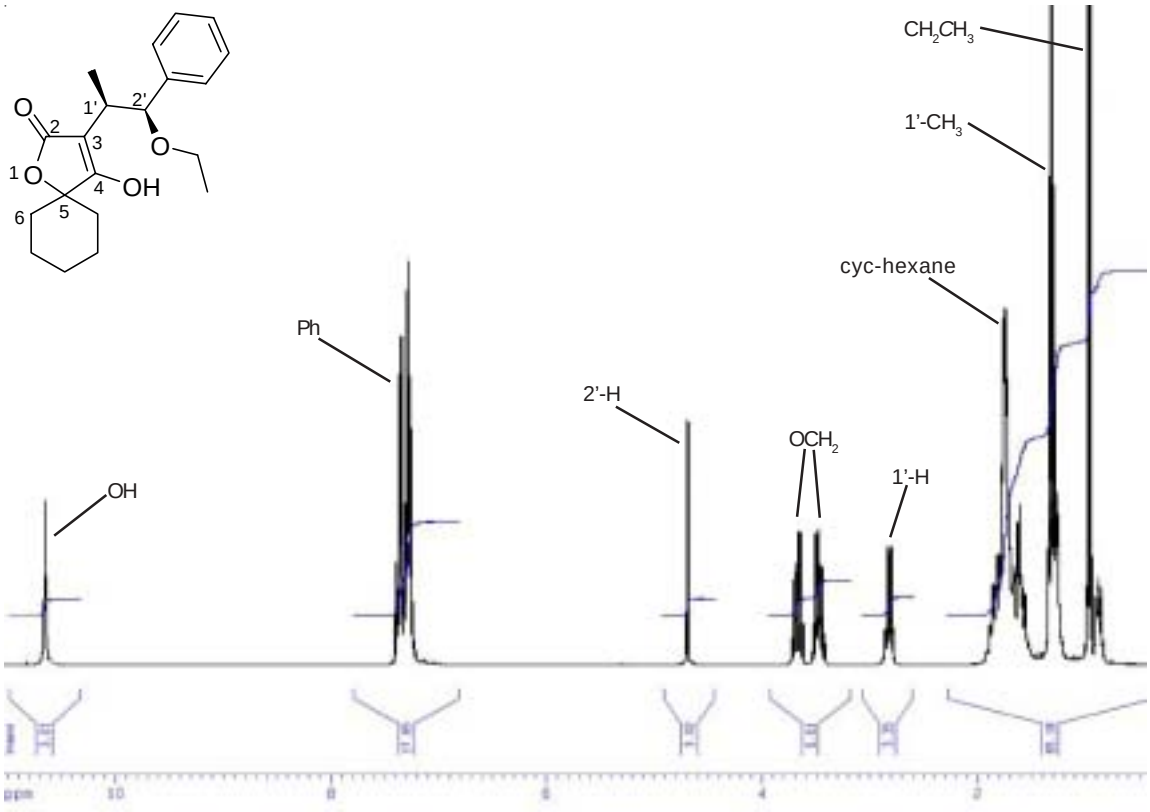


Figure 3a: [1]H-NMR of compound **141b**:

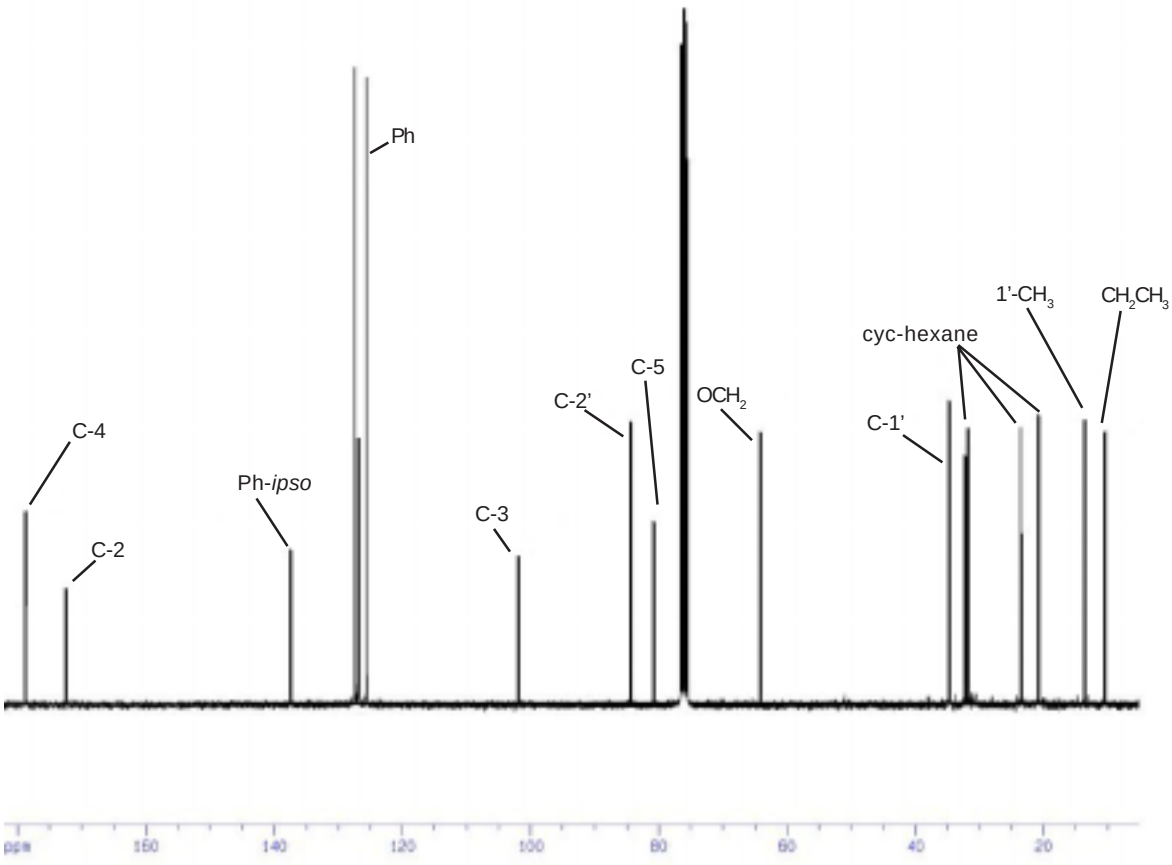
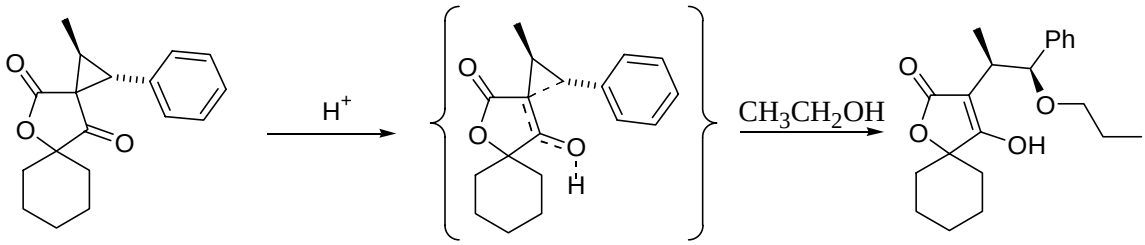


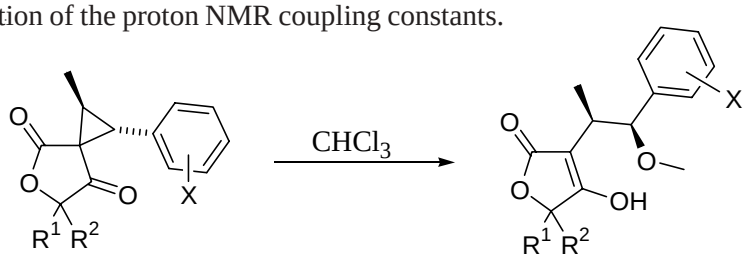
Figure 3b: [13]C-NMR of compound **141b**:



119a **143** **141c**

Initial biological screening[120] of the 3-5-Disubstituted tetronic acids **141a-e** showed that these tetronic acids exhibited positive results as potential herbicides. The number of compounds which exhibited activity in the initial screening was above average. These compounds did not contain any extra functionality on the phenyl ring; the presence of functionality is likely to increase activity. Therefore we were requested to provide additional samples for biological tests with functionality on the phenyl ring. Initially we had to investigate if these ring opening reactions could be extended to derivatives containing extra functionality.

This proved once again to be possible for most derivatives by simply using refluxing solutions of methanol and chloroform. However derivatives which bore a strongly electron withdrawing nitro group proved to be totally inert to refluxing methanol/chloroform mixtures. Protonation of the ketone oxygen leads to a benzyl cation which is so well delocalised throughout the phenyl ring and by the nitro group that there is no discernable positive charge for the nucleophilic methanol to react with. This problem was overcome by simply dissolving the starting material in dry chloroform and by the slow addtion of one equivalent of HBF_4-ethyl etherate solution. This solution was stirred for 1 hour at room temperature before methanol was introduced. The resulting solution was refluxed gently for 16 hours to yield the corresponding 3-(β-methoxy)alkyltetronic acids in good yield. The syn configuration for each of these compounds was again determined by the examination of the proton NMR coupling constants.



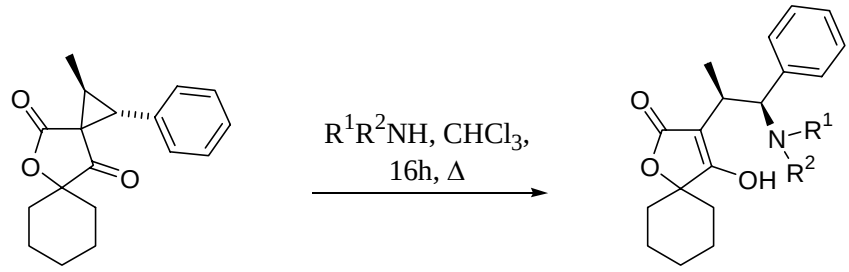
119 **141**

Table 11: Ring opening of functionalised 3,5-dispirodihydrofuran-4,12-diones with **119** methanol

Compound	X	R^1	R^2	Conditions	Yield (%)
141 f	o-Cl	$-(CH_2)_5-$		methanol, reflux, 24h	63
g	m-Cl	$-(CH_2)_5-$		methanol, reflux, 16h	56
h	p-Cl	$-(CH_2)_5-$		methanol, reflux, 16h	89
i	m-NO_2	$-(CH_2)_5-$		HBF_4, methanol, reflux, 16h	92
j	p-NO_2	$-(CH_2)_5-$		HBF_4, methanol, reflux, 16h	80
k	H	$-(CH_2)_2O(CH_2)_2-$		methanol, reflux, 24h	81
l	H	Ph	H	methanol, reflux, 24h	64

2.1.5.2 Ring opening reactions with nitrogen nucleophiles

Amines are also excellent nucleophiles and we expected them to react readily with **119a**. Both primary and secondary amines were found to react readily.[149] While investigating ring opening of **119a** with amines it was found that high temperatures are not required. Simply stirring the amine and **119a** in chloroform at room temperature is sufficient to form the ring opened systems **144** (Figure 4:^{1}H- and ^{13}C-NMR of **144d**). The syn geometry was determined by coupling constants which were similar to those observed for compounds **141**. (eg **141d** ^{3}J(1'-H/2'-H) = 2.04 Hz and **144d** ^{3}J(1'-H/2'-H) = 2.10 Hz).



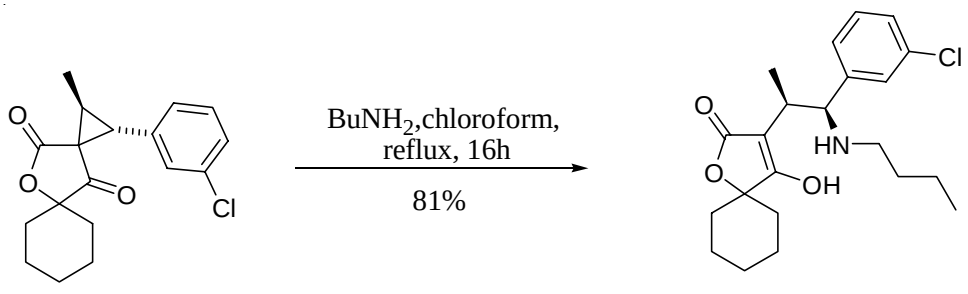
119a **144**

Table 11: Ring opening of **119a** with amine nucleophiles

144	R^1	R^2	Conditions	Yield (%)
a	H	Et	chloroform, reflux, 18h	78
b	H	Bu	chloroform, reflux, 16h	67
c	H	Bn	chloroform, reflux, 24h	79
d	H	$CH_2CH{=}CH_2$	chloroform, r.t., 18h	92
e	Et	Et	chloroform, reflux, 18h	64

Attempts to open the cyclopropane ring using diisopropyl amine failed, even when the solution was heated to 120^{O}C in a sealed tube, with the starting material being completely recovered. This is an unsurprising result as diisopropyl amine is a highly sterically hindered molecule.

119c was reacted with butyl amine with the expected ring opened tetronic acid **144f** being readily formed in high yield. This provides further proof that any reaction of **119a** can be extended easily to fuctionalised systems.



119c **144f**

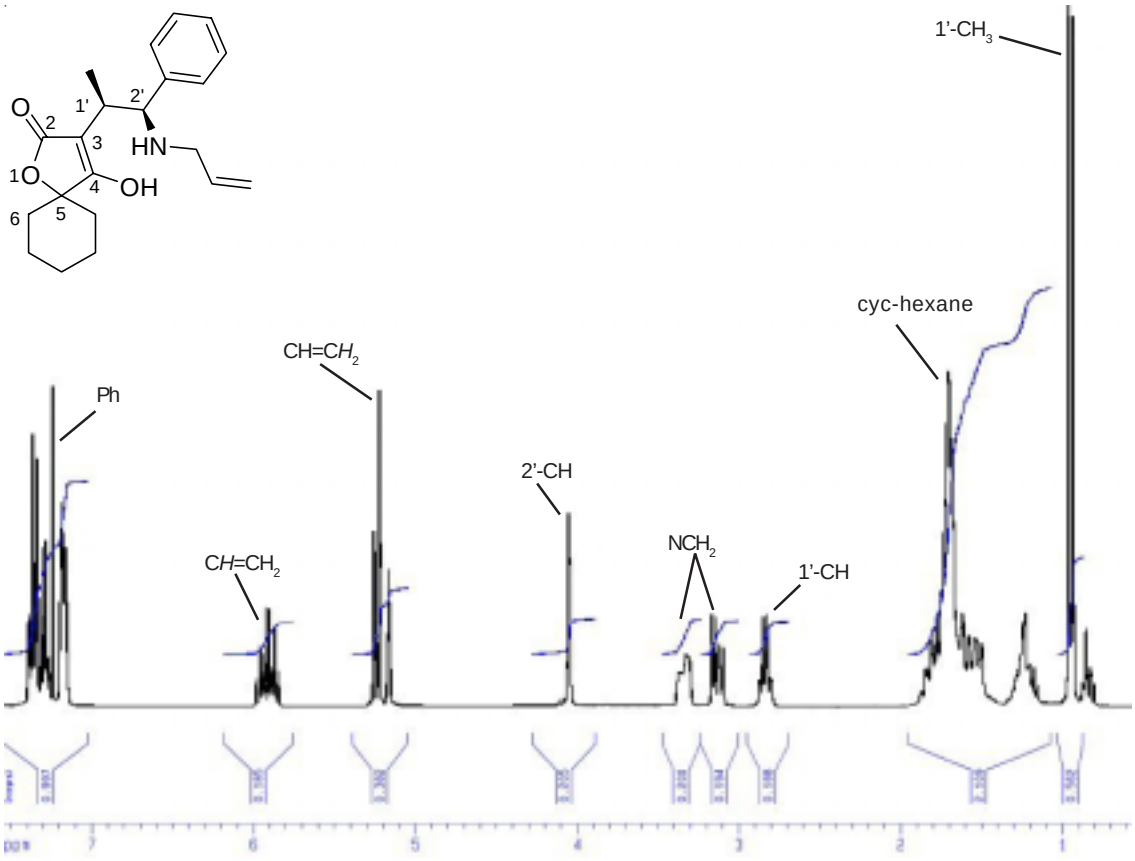


Figure 4a: ^{1}H-NMR of compound **144d**:

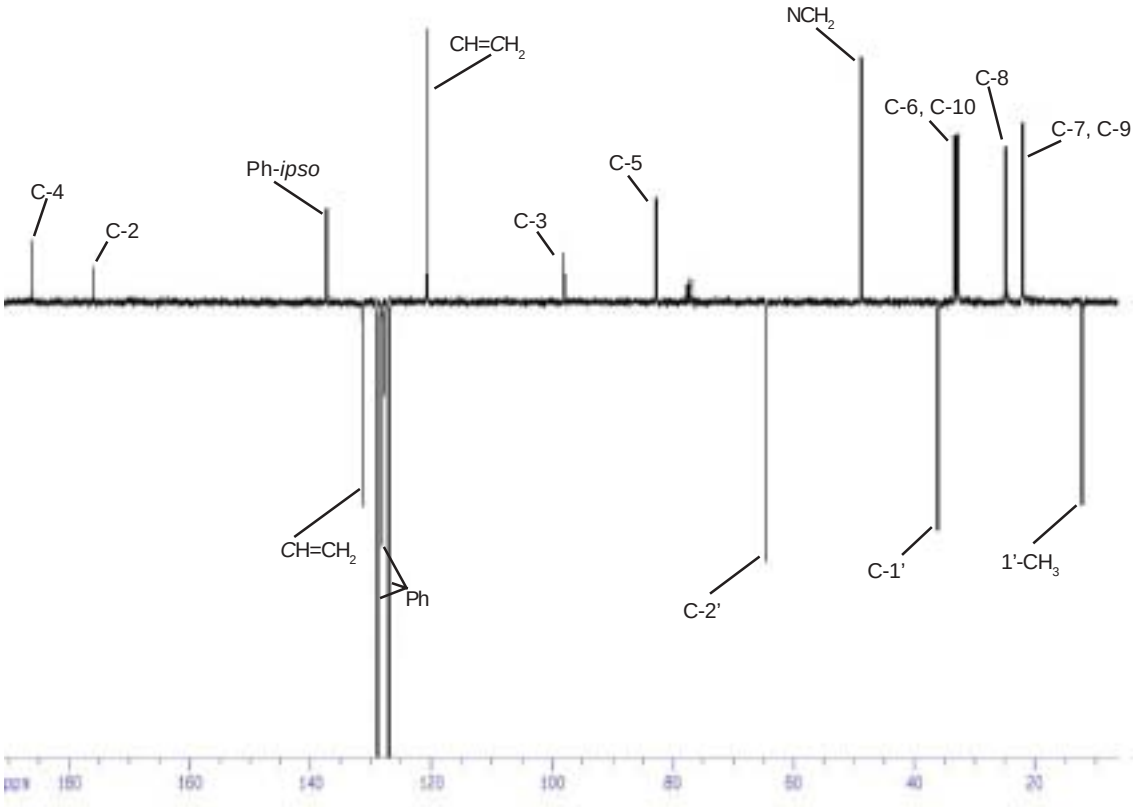
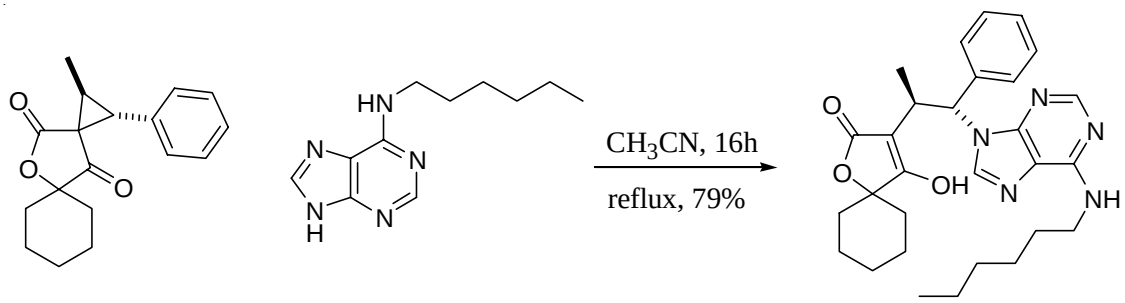


Figure 4b: ^{13}C-NMR of compound **144d**:

Purines arouse considerable interest for a number of reasons; their most important and well known role, together with pyrimidine bases, is as a constituent of nucleotides which are monomers of DNA and RNA. Nucleotides and nucleosides act as neurotransmitters and hormones and are present in certain enzymes. They are present in numerous natural products, e.g. caffeine and theobromine, a constituent of chocolate. In modern medicinal chemistry purines because of their importance to biological systems are finding uses as anti-viral, anti-cancer and recently anti-impotence drugs. With this in mind we set out to couple a purine base with **119a**, the product of which should have considerably increased aqueous solubility, a pre-requisite for drugs; we could also reasonably expect the product to be biologically active. Initially we attempted to react **119a** with adenine using DMSO as a solvent. The choice of solvent proved to be unfortunate as solubility problems of the adenine were encountered together with the difficulty of DMSO removal after reaction. Several hours of heating lead to a brown solution and TLC analysis showed that **119a** had been consumed in the reaction. After purification however, the only detectable product was **122a**. It is likely that the basic nature of the purine base over time lead to the reverse oxa-ene reaction. Undeterred we repeated the reaction replacing adenine with **145**. **145** is a more suitable choice to begin investigations with since the alkyl chain blocks the secondary amine group from reacting with **119a** due to steric considerations. Reaction with the secondary amine could have led to a competing ring opening reaction, futhermore the alkyl chain was expected to improve the solubility of the purine base (**119a** is very unpolar and polar protic solvents may not be used (Section 2.1.5.1). By changing to acetonitrile as the solvent medium we observed excellent solubility for both starting materials. **146** was obtained in excellent yields (79%) as determined by GC-MS. An anti configuration was observed for **146** $^3J(1'\text{-H}/2'\text{-H}) = 11.81$ Hz. No explanation has of yet explained why an anti configuration should be observed in this case.

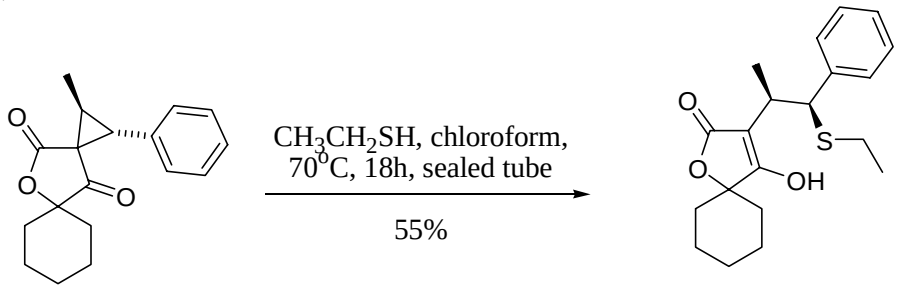


119a **145** **146**

Having successfully synthesised **146**, this opens the possiblity of coupling **119a** with the other purine bases leading to not only interesting structures but potentially medicinally useful compounds as well.

2.1.5.3 Ring opening with thiols

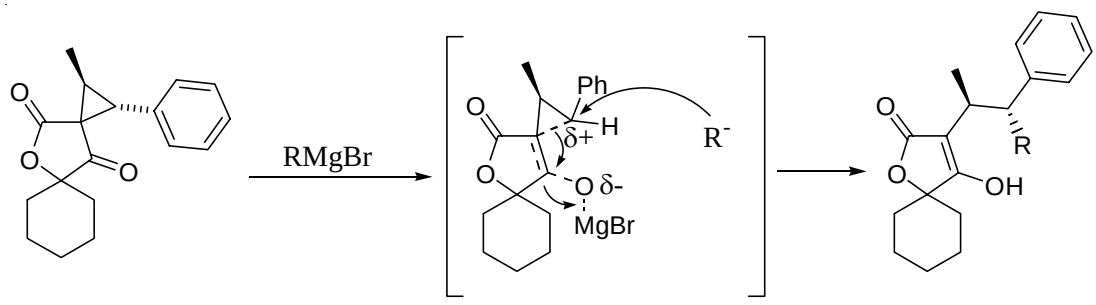
119a reacts readily with ethane thiol. It should be noted that because **119a** is capable of conjugate addition reactions it is probably a carcinogenic substance. Since **119a** reacts with simple thiols it is likely that it will also react with glutathione in the body, a tripeptide which is an important carcinogen scavenger.



119a **147**

2.1.5.4 Reaction with other carbon nucleophiles

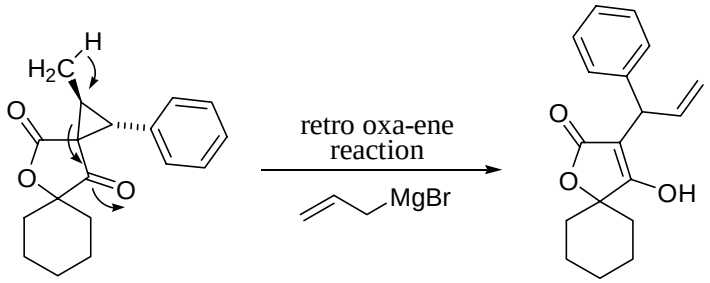
The formation of C-C bonds is one of the most important objectives in organic chemistry. Organometallic reagents such as the Grignard reagent are nucleophilic due to the polarisation of the metal carbon bond. Grignard reagents are often reacted with aldehydes and ketones to form secondary and tertiary alcohols. An examination of **119a** shows that a Grignard reagent could react at three possible sites, at the cyclopropane ring, the ketone group and the ester functionality. Simple alkyl Grignard reagents, butyl and ethyl, react only at the cyclopropane ring. No products from reaction with the ketone or the ester functionality were recovered. Treatment of **119a** with ethyl magnesium bromide led to a single diastereoisomer which was assigned the anti configuration, due to $^{3}J(1'\text{-}H/2'\text{-}H) > 10Hz$. This finding can be explained by assuming that the cyclopropane ring undergoes partial opening followed by attack from the hard nucleophilic Grignard reagent onto a carbenium ionic transition state **148** from underneath.



119a **148** **149**

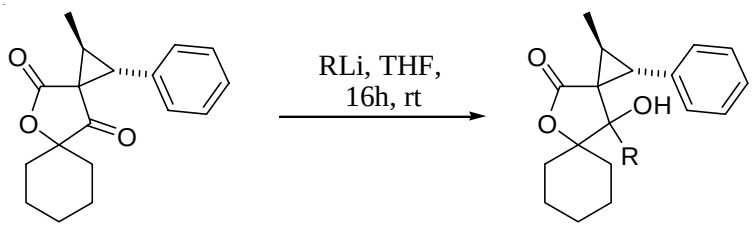
149a R = Et, 61% yield
149b R = Bu, 42% yield

Experiments were undertaken with more complicated Grignard reagents, however each attempt was met with failure.[150] Attempts with benzyl magnesium bromide, cyclopropane magnesium bromide and isopropyl magnesium bromide gave no reaction at all. In each case the starting material could be recovered and no products arising from attack on the ketone or ester functionality could be detected. The use of allyl magnesium bromide however led to **122a**. Grignard reagents are basic compounds and we suspect that in the case of allyl magnesium bromide the Grignard reagent has deprotonated **119a** leading to a retro oxa-ene reaction back to **122a**.[151]



119a **122a**

Organolithium reagents are highly reactive hard nucleophiles and it was suspected that organolithium compounds would react at the hard electrophilic ketone group. The reaction of methyl and butyl lithium with a sample of **119a-β** led to **150** in high yields. Only one diastereoisomer was observed suggesting that the phenyl ring prevents addition of the alkyl lithium reagent from one face of the molecule. No products arising from attack on the cyclopropane ring or the ester functionality were detected. The reaction of **119a-β** with phenyl lithium led to an incomplete reaction. NMR spectroscopy of the mixture showed the presence of the desired product mixed with the starting material. These two compounds proved impossible to separate by normal chromatography. Despite the expected change in polarity these compounds exhibit almost identical R_f values in a range of solvent mixtures. An attempt was also made to react **119c** with organolithium reagents; the result was a complicated mixture of products, probably arising from a lithium chlorine exchange which subsequently led to undefined reactions.

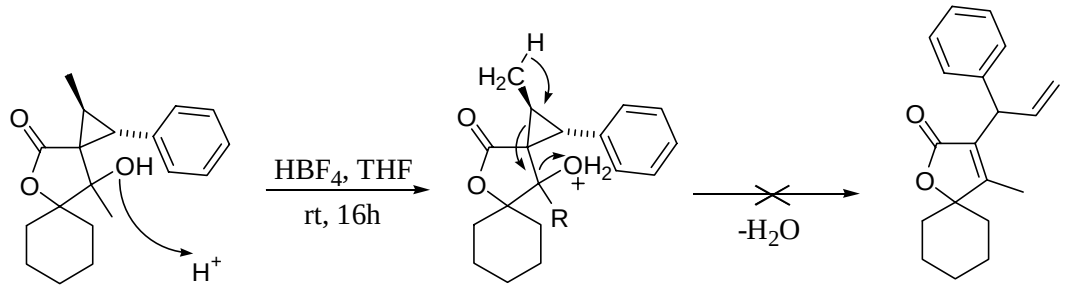


119a **150**

150a R = Me, 83% yield
150b R = n-Bu, 65% yield

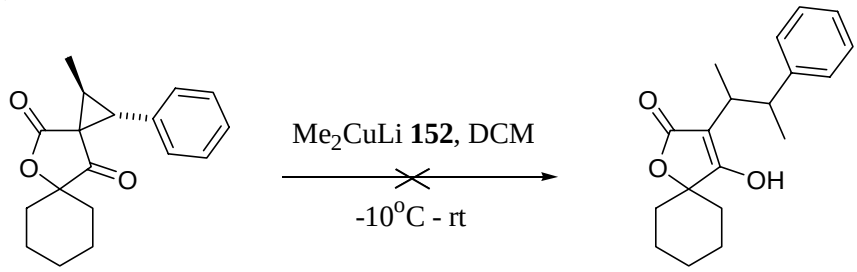
150 is a stable molecule and can be handled with ease under ambient conditions. Theoretically it should be possible to react **150** with an acidic compound; protonation of the hydroxy group, a rearrangement and elimination of water should lead to 4-alkyl-α,β-butenolides of type **151**. This reaction was attempted with HBF_4 in THF which led to complete decomposition, probably as a result of using such a strong acid. The use of HBF_4 with more suitable solvents such as DCM,

or toluene, and the use of milder acids or dehydrating agents have not yet been attempted. Another possiblity would be the conversion of the alcohol functionality to a tosylate group (an excellent leaving group); such systems should be amenable to ring opening reactions to generate butenolides.



150a **151**

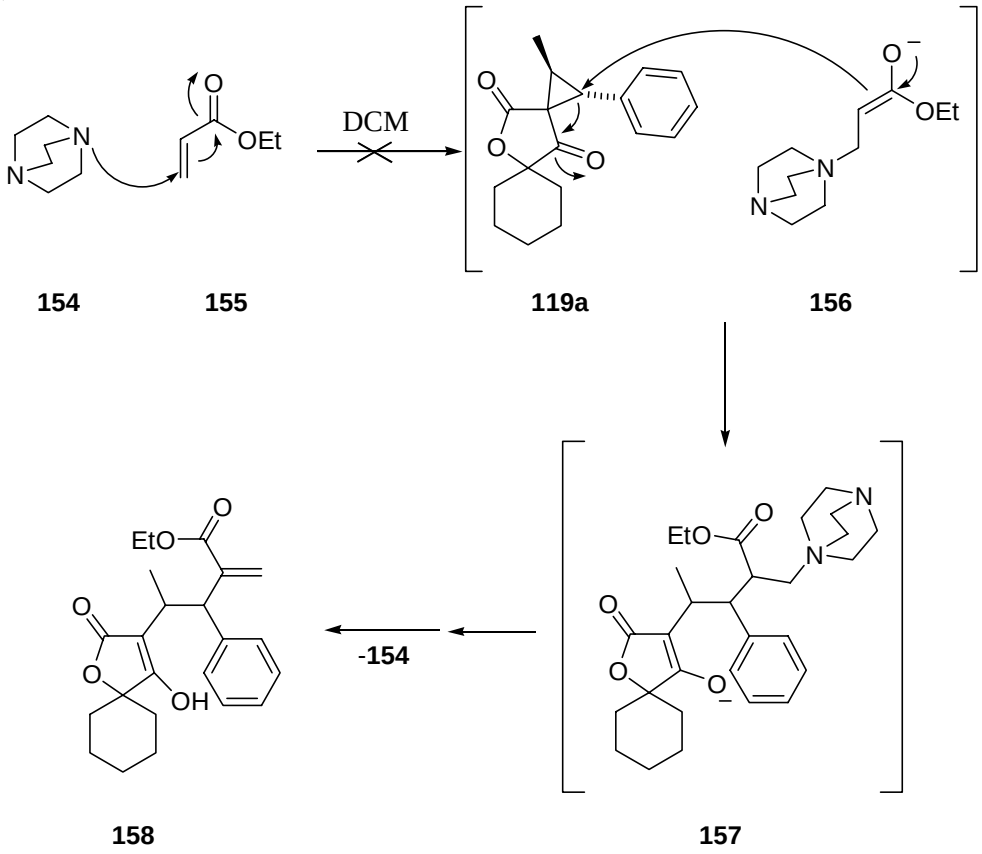
Organocopper compounds are well known to undergo nucleophilic displacements with halides and sulfonates. They also react with epoxides, add to alkynes and undergo conjugate additions to α,β-unsaturated systems.[152-155] Organocuprates were therefore suitable candidates for reaction with **119a**. The simple dimethyl lithium cuprate **152** was formed from copper bromide and methyl lithium. Solutions of **152** were formed at -10°C upon which a solution of **119a** was introduced. Unfortunately no reaction was observed even when temperatures were raised to 0°C and later raising the solution to room temperature gave no reaction. Addition to the cyclopropane probably requires higher reaction temperatures however unfortunately simple organocuprates are not normally stable above room temperature. More stable mixed cuprates obtained from alkyllithium compounds and copper cyanide were not tested as these mixed cuprates are often not as reactive. It should be noted that compounds of type **153** have been synthesised by other members of our working group starting from **119a** by using Knochel and Normant type cuprates.[147,197]



119a **153**

The Baylis-Hillman reaction continues to be an interesting carbon-carbon bond forming reaction, with the reaction between α,β-unsaturated esters and aldehydes, utilising tertiary amines or phosphines as catalysts, leading to densely functionalised molecules.[156-158] Examination of the Baylis-Hillman mechanism leads to the possibility of an interesting analogous reaction with **119a**. The first step of the Baylis-Hillman reaction normally involves the conjugate addition of the nucleophilic reagent DABCO **154** to an α,β-unsaturated ester e.g. ethyl acrylate **155**. This results in an enolate **156** which is normally reacted with an aldehyde. We proposed to replace the aldehyde with **119a** which we expected to react by a similar mechanism resulting in **157**

which should subsequently eliminate DABCO **154** leading to interesting compounds of type **158**.

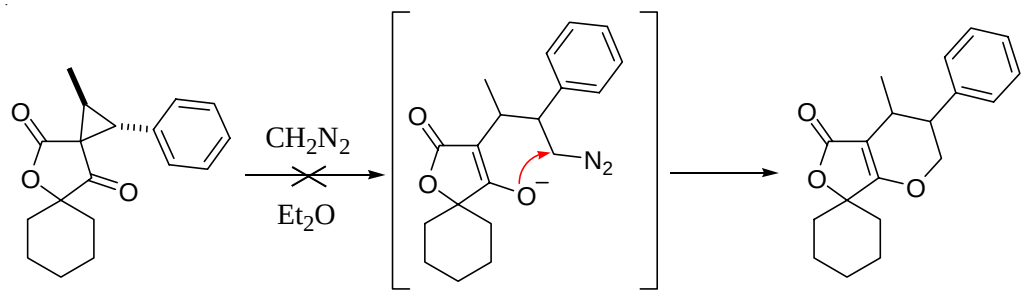


154 **155** **119a** **156** **157** **158**

One of the main disadvantages of the Baylis-Hillman reaction is that it normally requires several days of reaction time. Many examples exist in the literature for acceleration of this reaction. We therefore performed this reaction under ultrasound conditions in DCM. The temperature was kept between 35 - 40°C for 72h with no reaction having taken place.The reaction was once again performed this time utilising microwave conditions which in recent years has been shown to vastly accelerate the reaction. Heating of DCM solutions in a sealed vessel placed in a 300 W focussed single-mode microwave reactor (CEM) at 100 °C for 1 h led to recovery after column chromatography of 55% of **119a** with ~15% of compound **122a** also recovered. No products corresponding to **158** were recovered. **122a** was probably produced due to the basic nature of the DABCO catalyst leading to a reverse oxa-ene rearrangement already discussed on Page 48.

2.1.5.5 Attempted ring opening with diazomethane

Before we recognised that the mechanism for ring opening reactions of **119a** involved an initial protonation of the keto oxygen, we attempted to react compound **119a** with diazomethane. Diazomethane is a nucleophile and we expected it to react with **119a** in a similar manner to previous examples. The alkoxide ion would likely attack the diazo-functionality with subsequent expulsion of nitrogen, resulting in interesting compounds **163** with a new annulated six ring.

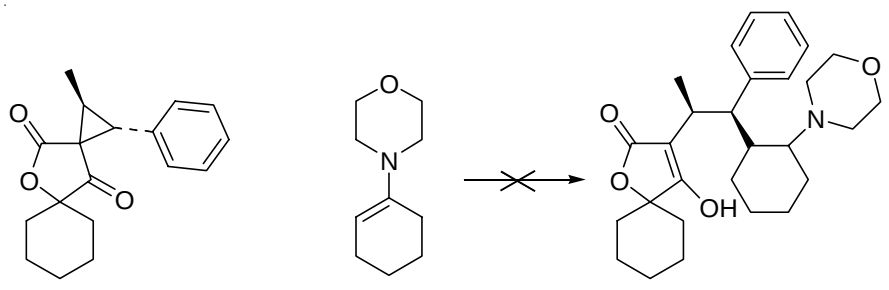


119 **162** **163**

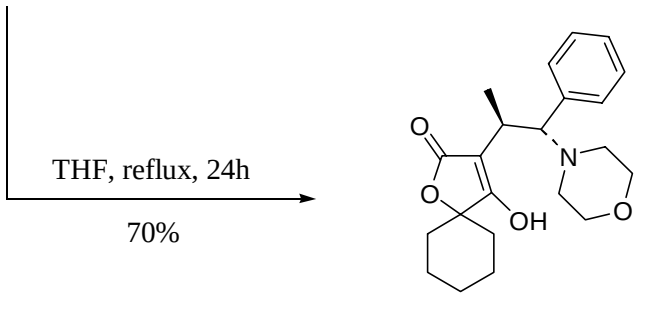
An ethereal solution of **119a** was stirred with an excess of diazomethane for several hours at room temperature; no reaction was observed with TLC analysis. Diazomethane is a very reactive molecule so it was therefore reasonable to assume that protonation of keto oxygen is a pre-requisite for ring opening reactions of **119a**. To this effect we added a Lewis Acid catalyst, zinc bromide, with the hope that it would co-ordinate to the keto oxygen thus allowing the diazomethane to react in the desired manner. Unfortunately the addition of the zinc bromide led to immediate decomposition of the diazomethane.

2.1.5.6 Attempted ring opening with enamines

The nucleophilicity of their β-carbon atoms permits enamines to be used in synthetically useful alkylation reactions. Enamines were therefore expected to readily C-alkylate compound **119a** with the product being amenable to acidic hydrolysis forming a ketone. Enamines derived from cyclohexanone are commonly used in synthetic applications. We therefore prepared **164**, a relatively stable enamine and refluxed it for 24h in a solution with **119a** in THF. The expected ring opened product **165** was not formed, however **166** was recovered in 70% yield.



119a **164** **165**

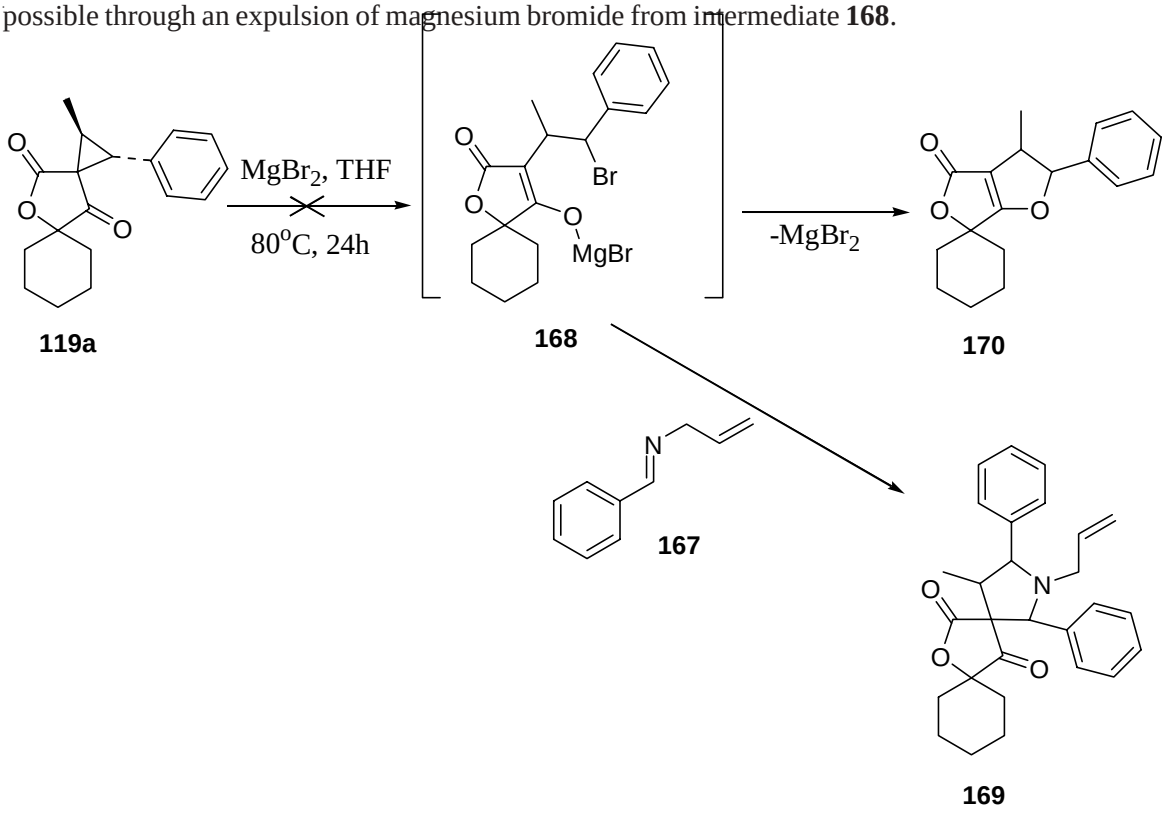


166

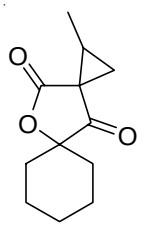
A major problem with enamines is their ability to react with less reactive alkylating agents at the nitrogen atom as opposed to the usual carbon alkylation. For example simple alkyl halides react with enamines to give a quaternary ammonium salt. Hydrolysis of the ammonium salt leads to alkylation at the nitrogen atom together with the starting ketone. This would appear to be a reasonable explanation for the formation of **166**. Compound **119a** is an electrophile however it not as reactive as acyl chlorides, benzyl halides or allyic halides, the normal alkylating agents for enamines. Therefore it can be assumed that **164** underoges N-alkylation with **119a** to give a quaternary ammonium salt which is hydrolysed under the workup conditions to give **166**. **166** was formed with 1'-H/2'-H located in an anti configuration ($^3J_{HH}$ = 7.44 Hz) as with compound **146**. The large enamine molecule can explain why attack occurs from the backside of **119a** to give exclusively the anti product. This method means that both the syn and anti 1'-methyl-2'-amino tetronic acids can be easily synthesised. Reaction with 1-Cyclopent-1-en-1-ylpyrrolidine, a less sterically hindered enamine was also attempted again with the ring opened compound of type **166** being formed in high yield.

2.1.5.7 Attempted ring opening with imines

Recently Carreira[159] has reported a ring expansion of a series of spirocyclopropan-1,3'-oxindoles with a range of simple imines to generate spiro[pyrrolidin-3,3'-oxindoles]. These systems are structurally similar to **119a** and we believed that this reaction could be easily extended to our system. The reaction is reported to be highly diastereoselective and makes use of an initial ring opening with magnesium iodide. We therefore synthesised *N*-[(1*E*)-phenylmethylene]prop-2-en-1-amine **167** in excellent yields from benzaldehyde and allyl amine using magnesium sulphate monohydrate as the dehydrating agent. A solution of **119a** and **167** in the presence of 1 equivalent of magnesium bromide was heated to 80°C in THF for 24h. From this reaction **119a** could be completely recovered without any detection of **169** or **170**. Formation of **170** was thought possible through an expulsion of magnesium bromide from intermediate **168**.



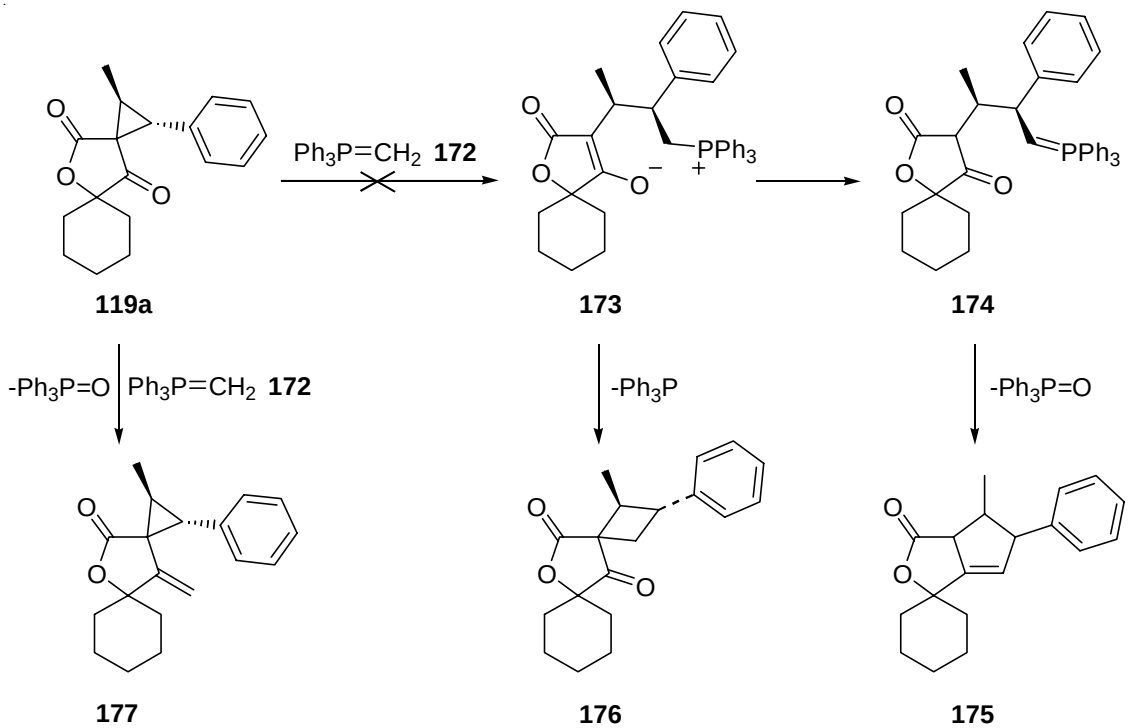
The choice of **119a** may have been the reason for failure. This system contains a bulky phenyl group which presents a huge steric challenge to an approaching imine molecule. Compound **171** has been previously synthesised[115] and represents a less sterically hindered molecule that should be amenable to the Carreira[159] reaction. Another possibility for failure was the choice of magnesium bromide, the use of the much more reactive magnesium iodide should lead to greater success.



171

2.1.5.8 Attempted ring opening with phosphorus ylides

Phosphorus ylides are nucleophilic species and we expected them to enter into the reaction with **119a**. Making use of methyleneylidenetriphenylphosphorane **172**, we postulated three possible modes of reaction. The first possibility would be a reaction of **172** with the carbonyl group of the ester. This was considered highly unlikely as an ester is less reactive than a keto group, nonetheless reaction at this site is a distinct possibility. Secondly **172** could attack the cyclopropyl ring this would give an internal phosphonium salt **173** which theoretically could be deprotonated to give an ylide **174** which would lead to an internal Wittig olefination leading to **175**. The third possibility is the expulsion of triphenylphosphine from **173** to give **176**. The final possibility was normal Wittig reaction with the keto functionality of **119a**. This in fact proved to be the case and **177** (Figure 5) was formed in excellent yields from a sample of **119a-β**. **177** is in itself an interesting structure since it contains an exocyclic double bond. Numerous pathways become possible such as the Heck reaction, Michael additions, Cope rearrangement and addition of organometallics to name but a few possible follow up reactions.



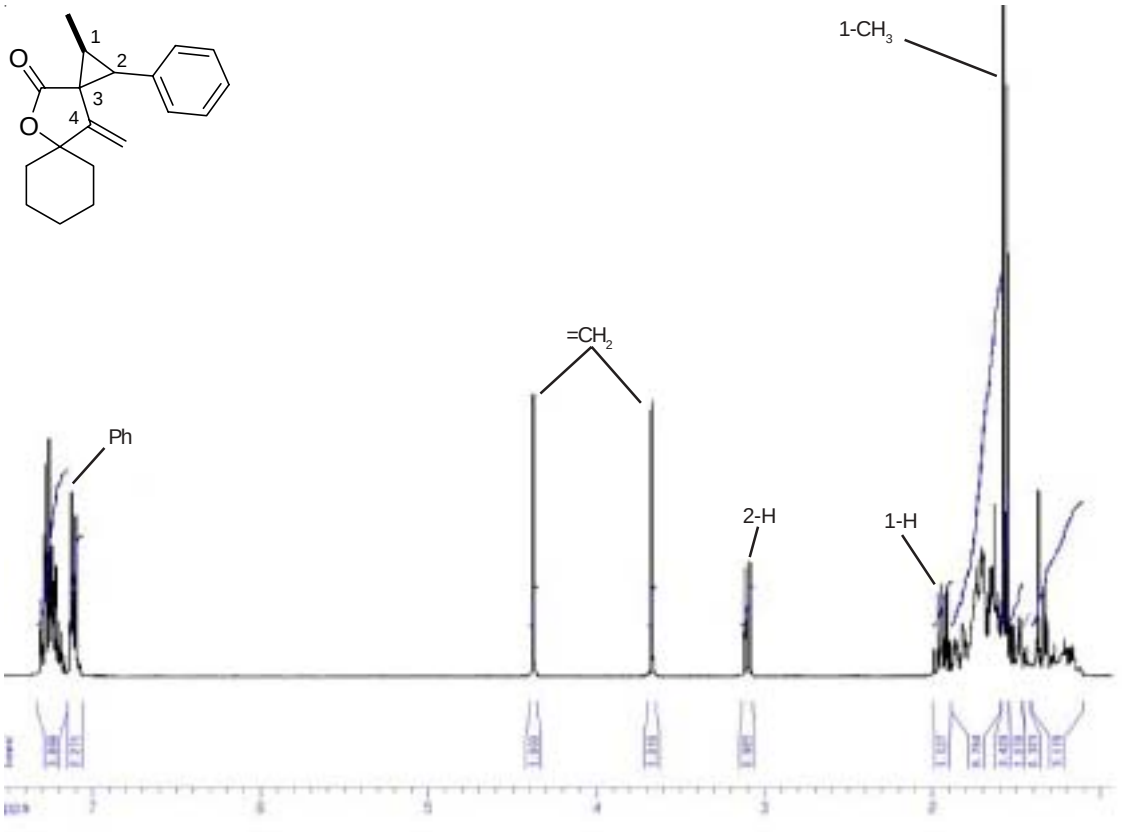


Figure 5a: [1]H-NMR spectra of compound **177**:

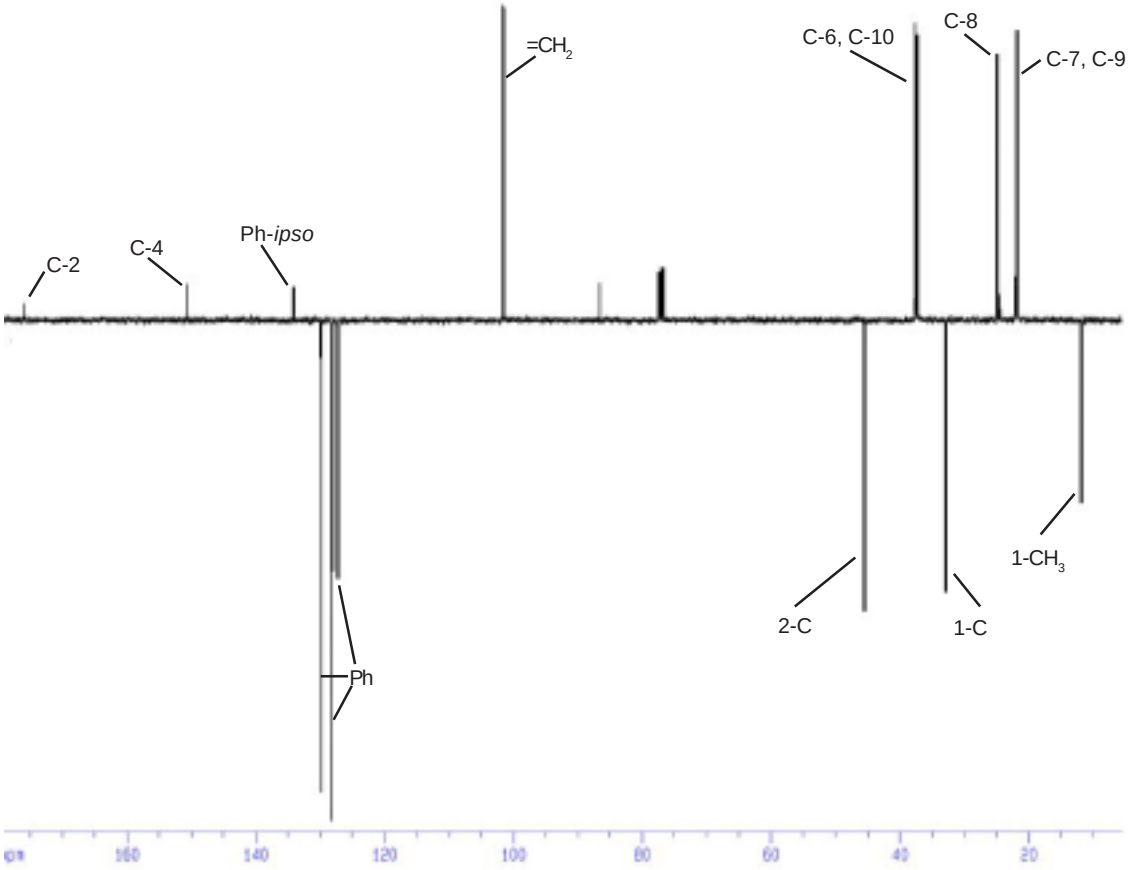
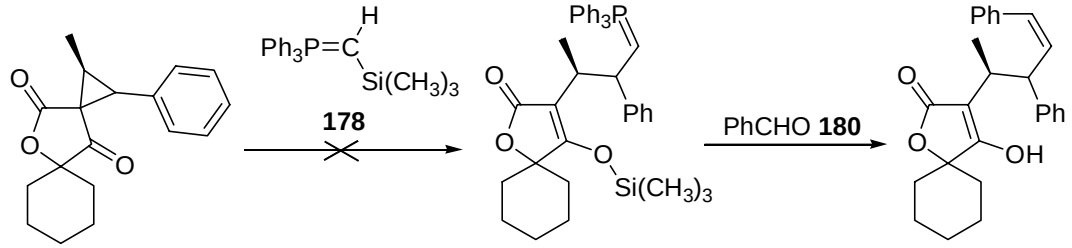


Figure 5b: [13]C-NMR spectra of compound **177**:

It is not difficult to imagine that this reaction could be easily extended to include other unstabilised phosphorus ylides. We decided to extend this reaction to include the silyl phosphorous ylides **178** which do not always undergo "normal" ylide reactions[13]. We envisaged a reaction at the cyclopropane group with the mobile silyl group becoming attached to the keto oxygen **179**. Such an intermediate should react easily with aldehydes leading to interesting molecules of type **181**.

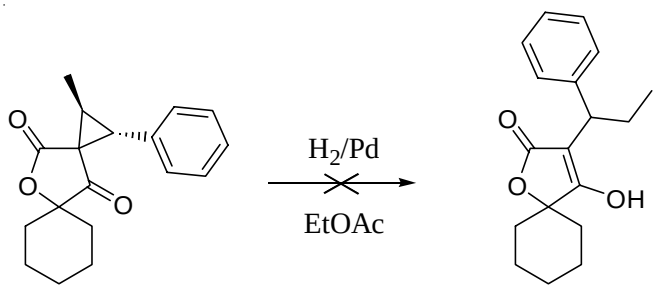


119a **179** **181**

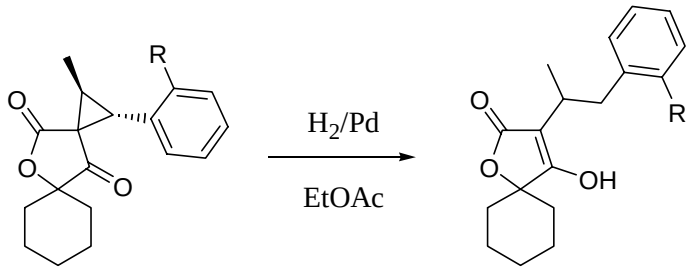
178 is not a very reactive ylide perhaps explaining why the reaction did not proceed; it was possible to recover about 90% of **119a** from the reaction mixture. This would suggest that unstabilised and semi-stabilised ylides may not be amenable to reaction with **119a**. No attempt has been made to react **119a** with keteneylidenetriphenylphosphorane **1** since **119a** was recovered in a relatively high yield after reaction with **23a** and **1** as a domino process (see Section 2.1.3).

2.1.5.9 Hydrogenation of 3,5-dispirodihydrofuran-4,12-diones

It has long been known that cyclopropanes can be hydrogenated under mild conditions with a variety of metal catalysts.[160,161] The mechanism of hydrogenation is still not fully understood. The addition of hydrogen could occur at either C-1' or C-2' of **119a**. The addition of a hydrogen atom to the carbon adjacent to the methyl group would lead to tetronic acids of type **183**. Homologues of **183** containing a pyrone as opposed to a furan subunit are known to be HIV inhibitors.[162] Each of these inhibitors contain a 3-(1'-phenylpropane) unit which seems to be very important for activity. The synthesis of **183** would therefore be highly interesting as they are likely to be HIV inhibitors as well. The second possibility was addition of hydrogen to the carbon atom next to the phenyl group; this has been exclusively observed for all other ring opening reactions and was considered the most likely outcome. The resulting tetronates **184** are constitutional isomers of **183** and potentially possess activity as HIV inhibitors as well.



119a **183**



119a,b **184**

184a : R = H, yield = 94%

184b : R = Cl, yield = 87%

184 was formed as expected, with the excellent yields that are normally expected with hydrogenation reactions recorded. These tetronic acids readily form crystals and the structure was confirmed by X-ray single crystal structure analysis (Figure 6).

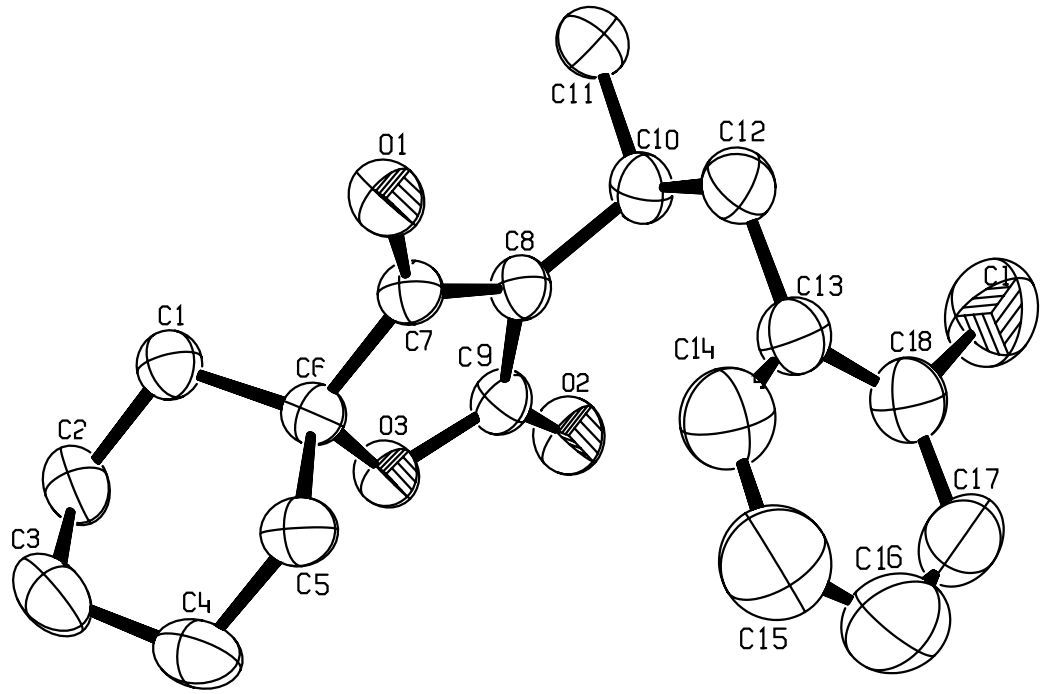
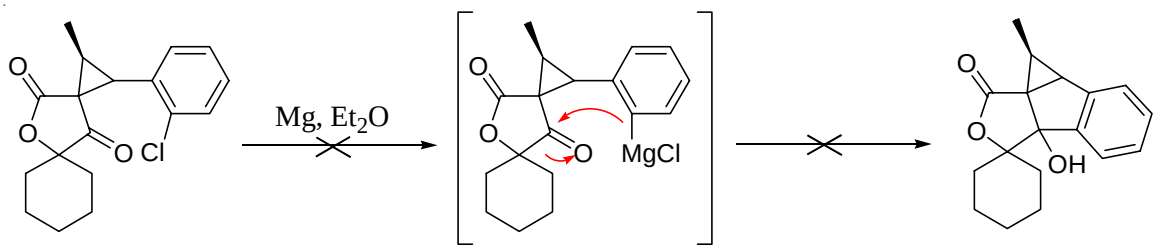


Figure 6: X-Ray structure for compound **184b**. Hydrogen atoms are omitted.

2.1.6 Attempted reaction of 1-(2-chlorophenyl)-2-methyl-11oxadispiro [2.1.5.2]dodecane-4,12-dione with magnesium

Compound **119b** is an interesting molecule and the presence of the chlorine group represents a pathway to new functionality. **119b** should react readily to form a Grignard reagent **185** which we suspected could then undergo an internal Grignard reaction with the keto functionality. The

product **186** from such a reaction should have an interesting bridged ring system**.**



119b **185** **186**

Unfortunately it proved impossible to react **119b** with magnesium metal. Despite the use of fresh magnesium turnings, the use of iodine and dibromoethane initiators, boiling solutions of both diethyl ether and THF, sonication and microwave irradiation the metal insertion reaction could not be initiated. Replacement of chlorine with iodine or transmetalation with i-PrMgX could possibly solve the problem.

2.1.7 Preliminary results from biological tests

As mentioned in earlier sections our 3,5-dispirodihydrofuran-4,12-diones along with the new ring opened systems were suspected to be biologically active molecules. Many of the substances already discussed in the preceeding sections have been synthesised on the gram scale and have been submitted for biological testing.[120] Preliminary results have proved our compounds exhibiting a form of chlorosis; of the first ten compounds that we have received results for only three compounds showed no activity at all. While activity was descriped as being weak we are nonetheless encouraged as these compounds were in most cases unfunctionalised and we expect the fuctionalised derivatives to display a much greater activity.

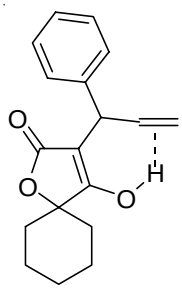
Table 12: Preliminary herbicidal results for furandiones

Compound	Herbicide Activity Microtest	Additional Tests
119a	Active	-
121a	Active	Active, but effect weak
121n	Active	Inactive
122a	Active	Active, but effect weak
141b	Inactive	-
141d	Active	Active, but effect weak
141j	Active	Inactive
144a	Inactive	-
144b	Inactive	-
144e	Active	Inactive

2.2 Derivatives of 3-allyl-tetronic acids

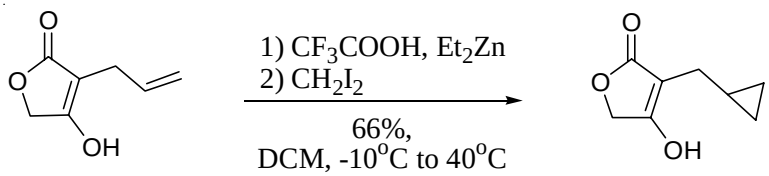
2.2.1 Cyclopropanation of 5-spiro-(3-α-phenylallyl)-tetronic acids

One of the initial objectives of this work was the synthesis of the 5-spiro-3-(α-cyclopropylbenzyl) tetronic acids **120**. These cyclopropyl tetronic acids should be easily prepared from the allyl precursors **122**. Surprisingly we could find no examples in the literature where an allyl group located in the 3-position of a tetronic acid was cyclopropanated. Most methods in the literature make use of the addition of a cyclopropyl moiety while introducing an alkyl chain into the 3-position. An initial reaction of **122a** with diiodomethane and a zinc/copper couple, the classic Simmons Smith reagent[163], failed to give any of the corresponding cyclopropane. Following this failure the more reactive reagent prepared from diiodomethane and diethyl zinc was attempted with no cyclopropane product detected. This was a surprising result as allylic alcohols are well known (Section 1.5.2.1) to accelerate the cyclopropanation reaction by bonding of the oxygen to the cyclopropanating species which results in the carbanion **114** being directed towards the alkene. We expected this to be the case for **122a**, however repeated experiments using various solvents, temperatures and even a large excess of the cyclopropanating agent failed each time, with **122a** recovered each time in stoichiometric amounts. Clearly there is something unusual about our system which prevents cyclopropanation; normally a fast, efficient, high yielding reaction. We postulate that the hydroxy group of the tetronic acid forms a strong hydrogen bond interaction with the allyl group **187**, this hydrogen bond interaction would have to be quite strong to prevent reaction with such a reactive species as the Simmons-Smith reagent. However we have already observed from the NMR data that compounds **141b-e** exhibit an interaction (Figure 3) between the hydroxy group and the alkoxy oxygen atom. In order to counter this observed effect our initial plan was to protect the hydroxy group thus breaking any hydrogen bond interaction, then cyclopropanate the double bond, followed by hydrolysis of the protecting group. The silyl protection of 3-allyl tetronic acids with TBDMSCl using 2,6-lutidine as a base is already known[115] and was thought to be the most suitable starting point. The reaction was followed for several hours with no formation of the protected tetronic acid. Heating solutions of the silylating reagent and **122a** in solutions of DCM, acetonitrile and DMF to 60°C and even sonication of the respective solutions[164] failed to give any of the expected product, with **122a** being recovered in quantitative yields. TBDMSCl has been largely replaced with the more reactive MTBSTFA[165], the silylating potential of which can be increased by the addition of 1% of TBDMSCl[166-168]. Once again despite numerous experiments from the analytical scale to the gram scale no reaction was observed; MSTFA was also attempted without success. Clearly the presence of the phenyl group is somehow having an influence on the protection step; probably due to steric constraints. Therefore it was obvious that another method would have to be found in order to introduce the cyclopropane moiety. We therefore decided to investigate different methods using the simple 3-allyl tetronic acid **188**, which has never been converted to a cyclopropane which was surprising due to the interest in tetronic acids of type **120**. **188** was formed from the Claisen rearrangement of **121x**.The rationale was to use **188** as a simple substrate while we investigated the use of more reactive cyclopropanating agents. Further attempts began with two procedures by Charette[169] which are reported to lead to high conversions



187

with alkenes containing hydroxy groups. Both procedures utilise diethyl zinc and diiodomethane, with one procedure using a catalytic amount of oxygen which supposedly is required for carbenoid formation. The other procedure involved the use of a Lewis acid catalyst and we made use of diethyl aluminium chloride which was reported to give good results. Once again however both methods failed to give any of the desired product despite numerous attempts. Recently Evans[170]has reported the cyclopropanation of a vinyl chloride which proved difficult to react under Furukawa[171] and Denmark[172] reaction conditions. The use of Shi[173] conditions involving the addition of trifluoroacetic acid to the diethyl zinc solution followed by additon of diiodomethane resulted in a highly reactive cyclopropanating species which lead to high yields. The use of this reagent proved successful with **188**, however it was found that reaction temperatures from 0°C gave no product and the reaction was very sluggish at room temperature. Good yields were obtained only when the solution was heated to 40°C. The structure of **189** was confirmed by X-ray single crystal structure analysis (Figure 7).



188 **189**

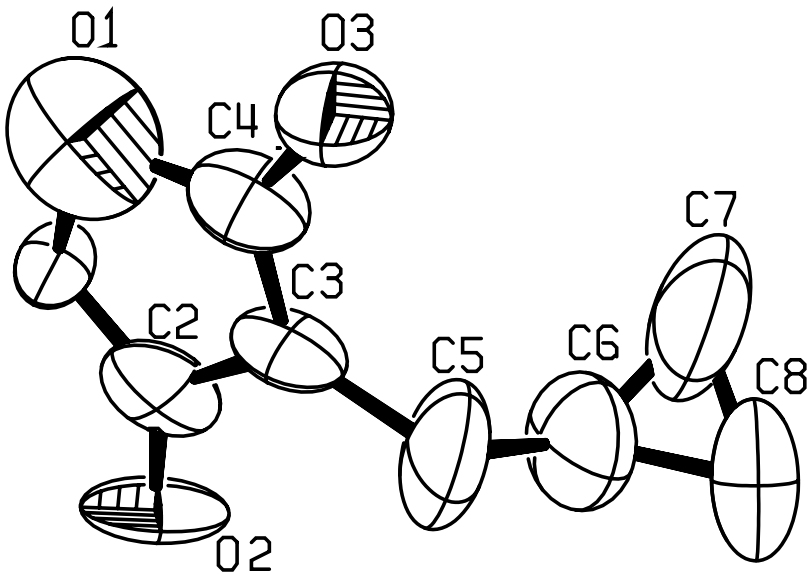
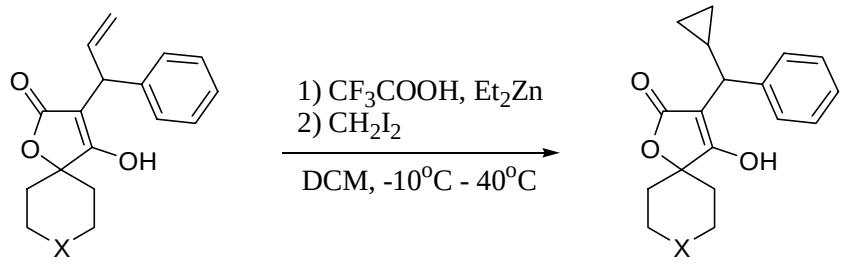


Figure 7: X-Ray structure for compound **189**. Hydrogen atoms are omitted.

We subsequently found that this method could be easily extended to the more complicated 5-spiro-3-phenylallyl-tetronic acids leading to **190** in good to excellent yields. These examples demonstrate a fast general method for the construction of our original target molecules **120**. No cyclopropanation reaction has ever been observed with the electron-poor sterically hindered endocyclic double bond.

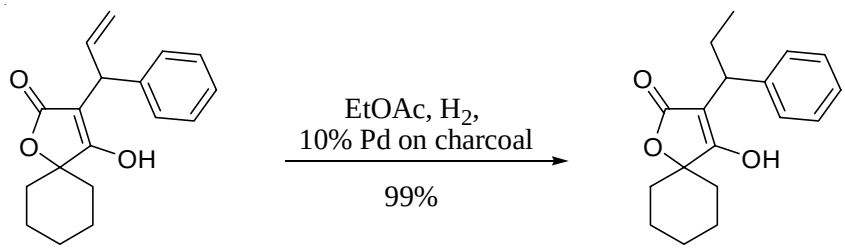


122a X = CH_2
122h X = O

190a X = CH_2, 84% yield
190b X = O, 65% yield

2.2.2 Hydrogenation of 5-spiro-3-phenylallyl tetronic acid

Having successfully synthesised our original target molecules **190**, we returned our interest to the 3-(phenylpropane) tetronic acids **183**, which are expected to act as HIV protease inhibitors. Earlier we attempted the synthesis of **183** through an hydrogenation of **119a** (Section 2.1.5.9). Clearly tetronic acid **183** should be easily amenable by a simple hydrogenation of **122a**. We are happy to report that **183** was obtained through the use of a palladium on charcoal catalyst in excellent yield, thus opening a route to a potentially useful subclass of molecule.

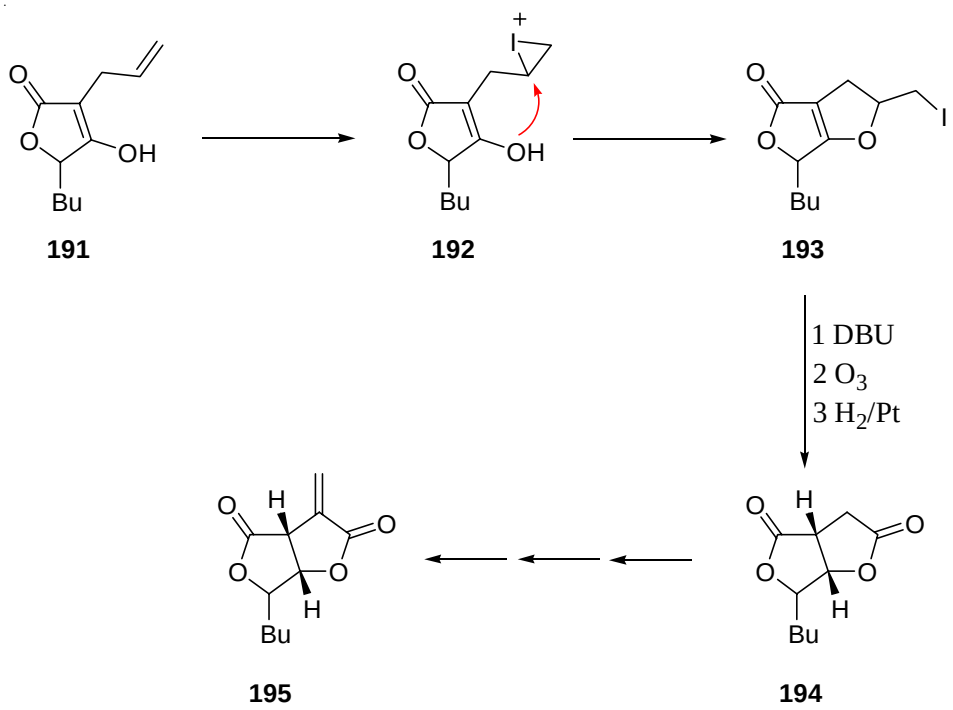


122a **183**

2.2.3 Iodocyclisation of 3-allyl tetronic acids

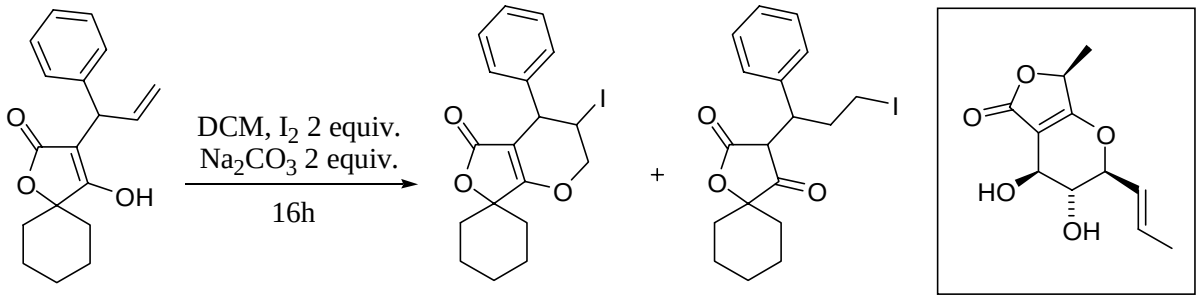
Iodine is an excellent electrophile for effecting intramolecular nucleophilic addition reactions; an especially important reaction is the iodolactonisation reaction.[174] The reaction of iodine with carboxylic acids bearing a closely located alkene results in the formation of iodolactones.[175] Recently Antonioletti[176,177] has reported the iodine induced cyclisation of 2-alkenyl-1,3-dicarbonyl compounds which are very similar to compound **122a**. Application of this reaction to our systems should lead to the formation of the furan **193** from **191**. **193** could in principle be reacted over a number of steps to form **194** a known molecule which has been converted[178-180] to the

metabolite Canadensolide **195** isolated from Penicillium canadense.



191 **192** **193** **194** **195**

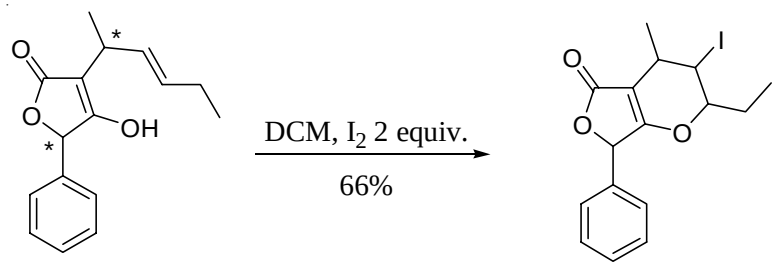
The reaction of **122a** following conditions described by Antonioletti[177] led not to the expected five ring furan but to the six ring pyrone **196** and to **197**. Although the yield of **196** was disappointedly low (17%) it is the first example of utilising the tetronic acid OH to close a second annulated ring. Coupled with the fact that the new pyrone ring contains the highly useful iodine functionality this represents an important new reaction. This substucture is present in many natural products[181,182] including Massarilactione B **198** which has antibacterial properties.[183] The fact that **197**, the product from a formal addition of HI, exists in the keto form and not the enol form is difficult to explain but could arise due to the reaction proceeding in a basic solution which may encourage rearrangement to the keto form. Although **196** and **197** account for only 45% of the yield, no products arising from the formation of a five ring furan were detectable. Five ring furans are almost always formed from iodocyclisation reactions with an anti configuration. We suspect that **196** also has an anti configuration between 1'-H and 2'-H, since a syn configuration would require bulky iodine and phenyl groups to be close together in space. ^{1}H-NMR spectra of **196** gave only multiplet signals for 1'-H and 2'-H and we were therefore unable to prove the anti configuration.



122a **196** 17% **197** 28% **198**

Knight[184] has reported the use of large silyl protecting groups in the iodocyclisation of allylic alcohols as it prevents iodine oxidation of the alcohol. The iodonium ion is still attacked by the oxygen functionality with expulsion of the silyl group. This method could not be used in conjunction with **122a** due to the problems encountered previously with silyl protection (Section 2.2.1). Iodine monobromide was also used in replacement of iodine with no change in results.

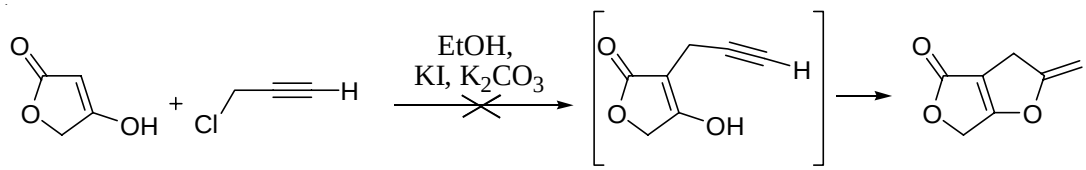
A second iodocyclisation reaction was attempted using a 3-[(2'*E*)-1-methylpent-2'-enyl] tetronic acid **212d**. Once again no five ring furan product was detected, however the six ring pyrone was isolated in an overall yield of 66% **199**. The higher yield could perhaps be attributed to the absence of base. Unfortunately this reaction did not proceed in a stereoselective manner and four different isomers were recovered, with tentative structures proposed from NOESY, HMQC and COSY spectra (Section 3). The four isomers can be explained from the mixture of enantiomers present on the C-1' of the substrate, and from which face the hydroxy group attacks the iodonium ion. Unfortunately the choice of substrate was perhaps unwise as it was in itself a mixture of diastereoisomers, however the purpose of the experiment was to demonstrate that the reaction was general. Iodocyclisation reactions are well known and proceed stereoselectively with a great deal of literature devoted to the mechanism of addition. The use of enantiomerically pure 3-(2E)-1-methylalkyl-2-enyl] tetronic acids should lead to a stereoselective reaction.



212d **199**

2.2.4 Reaction of tetronic acid with 3-chlorobutyne

Chenevert[185] has prepared a number of furocoumarins by the reaction of 4-hydroxycoumarin with 3-chloro-3-methyl-butyne. We wished to extend this reaction to the tetronic acids which would be expected to react in a similar manner. The resulting product would be a bislactone **201** thus opening another possible route to Canadensolide **195**. Commercially available tetronic acid was used, however reaction according to the conditions used by Chenevert for the structurally similar coumarins led only to complete decomposition.



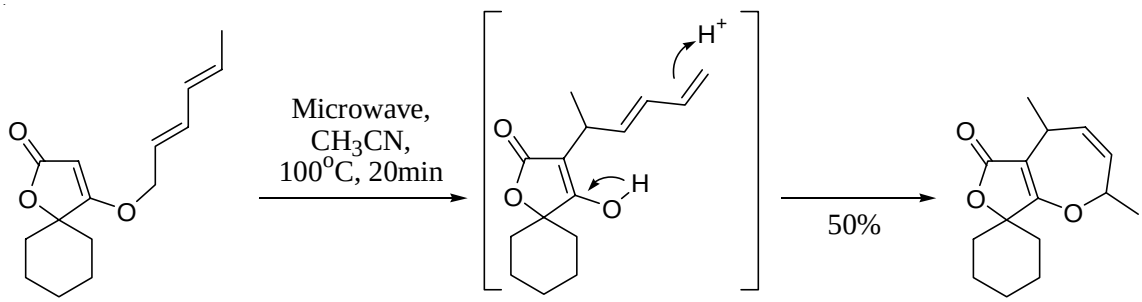
41 **200** **201**

2.3 Rearrangements of tetronates without a cinnamyl residue and spirocyclopropane trapping reactions

Up to this point all rearrangements of tetronates have involved tetronates that bear a cinnamyl residue in the 4 position. It would be interesting to investigate if other residues will also generate 3,5-dispirodihydrofuran-4,12-diones.

2.4.1 Cyclisation of a pentadienyl tetronate

3-(Penta-2',4'-dienyl)tetronic acids are the vinylogues of 3-allyltetronic acids; in principle they could undergo the same thermally induced Conia rearrangement to form 3,5-dispirodihydrofuran-4,12-diones, a (3,6) oxa-ene reaction to give 3-(spirocyclopentenyl)dihydrofuran-4,12-diones, a [2+4] cycloaddition, or finally an addition of the hydroxy group to either of the double bonds. The reaction was found to proceed when a solution of hexadienyl tetronate **121s** was heated in acetonitrile to 100°C for 20 min under microwave conditions (300W) with the 2H,5H-furano[4,3-*b*]oxepin-6-one **203** formed in 50% yield. Heating of **121s**, however, in a bomb tube resulted in uncontrolled decomposition.[147,150]



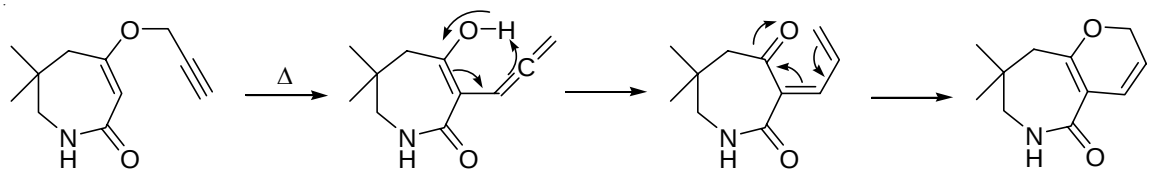
121s **202** **203**

A reasonable mechanistic explanation would hypothesise that an initial [3,5] or a [2,3] sigmatropic rearrangement of **121s** would result in the intermediate **202**. This intermediate would then be expected to undergo a Markovnikov-type addition of the OH group across the terminal C=C bond. The use of acetonitrile as the solvent seemed to be crucial for both the rearrangement step and the cyclisation sequence which was formally comprised of protonation/allyl cation formation/ charge-controlled tetronate attack. Unfortunately this reaction does not appear to be general, **121t** (replacement of terminal methyl group with a phenyl group) rearranged to give numerous products none of which could be identified.

3-Allyltetronic acids (e.g. **188**) will rearrange under prolonged heating in acetonitrile or toluene and undergo an orbital controlled Conia rearrangement to give the corresponding cyclopropane. No charge controlled addition of the OH group onto the C=C bond in **188** and similar systems has ever been observed, probably due to the instability of an intermediate carbenium ion in relation to the allyl cation in **202**. It should be noted that 3-allyl-4-hydroxycoumarins and 3-allyl-4-hydroxyquinolones do not form isolatable Conia-type spirocyclopropanaes but rather addition of the OH group onto the C=C to give furano derivatives at high temperatures, despite the involvement of a relatively unstabilised cation.[147,186] However recent findings suggest that spirocyclopropanes of 3-allyl-4-hydroxycoumarins do exist as intermediates (Section 2.3.7.2).[238].

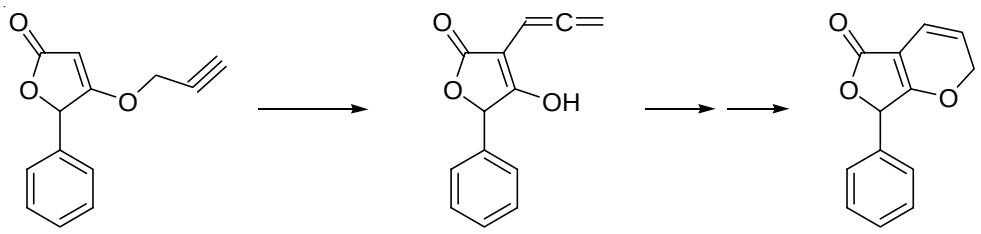
2.3.2 Attempted rearrangement of a 4-O-alkynyl tetronate

The propargyl ether of a hexahydroazepin-2-one **204** was found by Mooney to rearrange to an unsaturated six ring pyrone **207** and not to the expected acetylene.[187] The reaction was investigated under various pyrolysis conditions but in each case neither the acetylene nor the intermediate allene **205** could be identified.



204 **205** **206** **207**

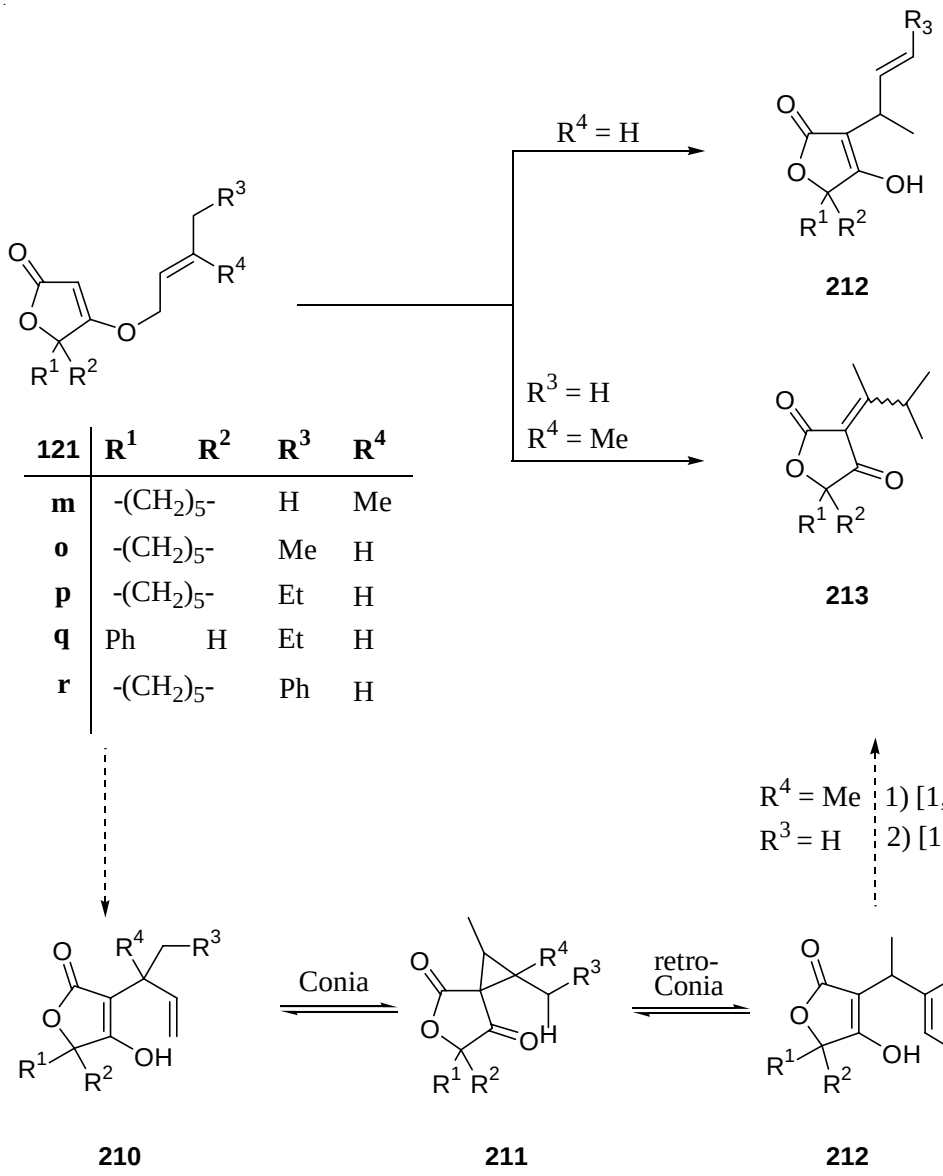
We had hoped to extend this reaction to our tetronates. To this effect we synthesised **121v** (Section 2.1.4.6) and attempted to rearrange it in various media. We had hoped to form the annulated six ring; the acetylene would however also have been welcome. However despite numerous attempts we could not force **121v** to undergo rearrangement. 5-Mono-substituted tetronates are known to be more difficult to rearrange than their 5-disubstituted analogues, however this is not normally an obstacle and it is extremely unlikely that this was the reason for a lack of reactivity. Heating acetonitrile and toluene solutions of **121v** to reflux for several days led to no reaction. The use of sealed bomb tubes where higher temperatures of 160°C and 200°C respectively were used also gave no result. Even the use of diethylaniline, a high boiling polar solvent, when heated to 200°C for 24h gave no rearranged products (**208** or **209**) and the starting material **121v** was recovered in 90% after Kugelrohr distillation of the solvent and column chromatography of the residue. Heating of **121v** in a sealed tube using water as a solvent unsurprisingly gave complete decomposition. This fact alone suggests that the alkyne had rearranged to the allene where it underwent hydrolysis of the intermediate followed by subsequent elimination/rearrangement reactions, thus proving that the rearrangement of the alkyne is at least feasible. Investigations using acetonitrile solutions irradiated with microwaves led to complete decomposition. The use of vacuum pyrolysis to effect reaction has not yet been attempted.



121v **208** **209**

2.3.3 Abnormal claisen rearrangements of tetronates

From a mechanistic point of view we were interested in the possibility of extending our Domino-Claisen-Conia rearrangement to simple systems bearing two or three alkyl substituents on the alkene group. We were interested in forming either the normal Claisen products, the products from a Claisen-Conia rearrangement or indeed the "abnormal" Claisen rearranged system. Ethers which contain an alkyl group in the γ-position sometimes rearrange to give so-called abnormal products **97**.[89] Compounds **121o-r** which contain an alkyl group attached to the alkene were found to rearrange exclusively to the abnormally [2,3]-rearranged 3-alkylidenetetronic acids **212** upon reaction in a sealed tube heated to 160°C using toluene as solvent (Table 13). Exchanging the conditions for refluxing solutions of either toluene or acetonitrile also led exclusively to the abnormal products. No products arising from either normal Claisen rearrangement **210** or from Claisen-Conia rearrangement **211** were recovered or detected.



121	R^1	R^2	R^3	R^4
m	-$(CH_2)_5$-		H	Me
o	-$(CH_2)_5$-		Me	H
p	-$(CH_2)_5$-		Et	H
q	Ph	H	Et	H
r	-$(CH_2)_5$-		Ph	H

Table 13: 3-Allyltetronic acids **212** from allyl tetronates **121**

212	R^1 R^2	R^3	R^4	M.p. [°C]	Yield (%)
a	$-(CH_2)_5-$	H	Me	Not isolated rearranged to **213**	
b	$-(CH_2)_5-$	Me	H	135	98
c	$-(CH_2)_5-$	Et	H	112	70
d	Ph H	Et	H	-	52
e	$-(CH_2)_5-$	Ph	H	159	84

A plausible mechanistic pathway would first begin with a normal Claisen rearrangement to give the 3-allyl tetronic acids **210**. These are not isolatable and quickly rearrange in solution by a Conia-type oxa-ene reaction to give the spirocyclopropanes **211**. These new spirocyclopropanes unlike the cinnamyl derivatives bear hydrogen atoms instead of a phenyl ring. The possibility now exists for the cyclopropane ring to open in two different directions. Opening the ring from a hydrogen atom of the newly created methyl group simply leads back to the "normal" Claisen products **210**. Opening of the ring through a hydrogen from the CH_2-R group gives the "abnormal" retro-Conia products **212**. These latter products are thermodynamically favoured therefore the equilibria lies far to the right under thermal conditions. Alternatively, it is possible that **212** could be formed from **211** by a polar E1-type elimination pathway involving zwitterionic carbenium tetronate conditions. The structure of **212c** was confirmed by X-ray single crystal structure analysis (Figure 8). The *trans*-configuration of the double bond was determined by the X-ray structural analysis of **212c** and from the coupling constant obtained for **212e** (16.29 Hz).

Compound **121m** when heated in a sealed bomb tube with dry toluene to 180°C rearranges quickly and quantitatively to the 3-(1',2'-dimethylpropylidene)-5-spirodihydrofuran-2,4-dione **213** (Yield 60%, m.p. 149°C) through two consecutive H-shifts. The driving force for these H-shifts is the formation firstly of a tetrasubstituted alkene, followed by the formation of an alkene in conjunction with both carbonyl groups. Compounds **212o-r** do not undergo additional H-shifts, as this would involve the formation of a less thermodynamically stable trisubstituted alkene.

Surprisingly compound **121n,** where a methyl group from **121m** has been replaced with a chlorine atom, could not be forced to undergo even the Claisen rearrangement step. While electron withdrawing groups are known to decrease the rate of Claisen rearrangement the effect is small and solvent effects are much more important.[91-93] Nonetheless heating solutions of **121n** in a sealed tube to 200°C for several days led to no reaction. The use of well known rearrangement catalysts such as BF_3-ethyl etherate and trifluoroacetic acid also failed to rearrange **121n**.

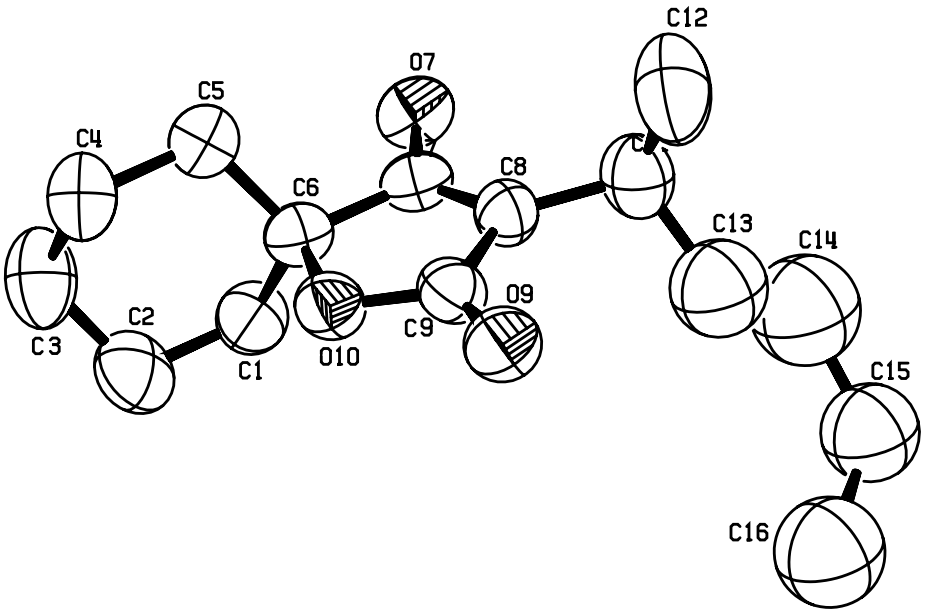
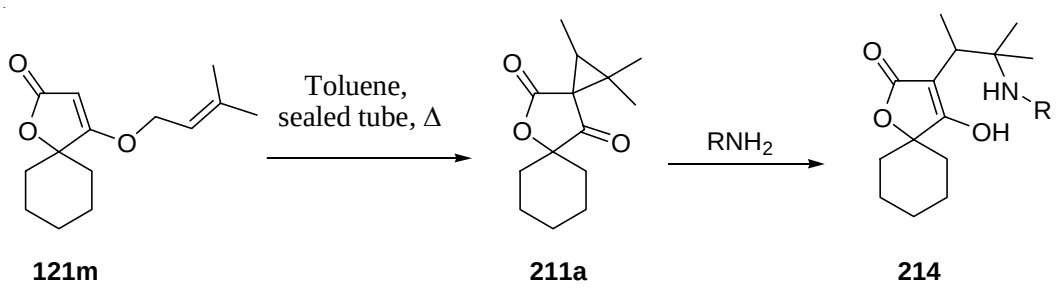


Figure 8: X-Ray structure for compound **212c**. Hydrogen atoms are omitted.

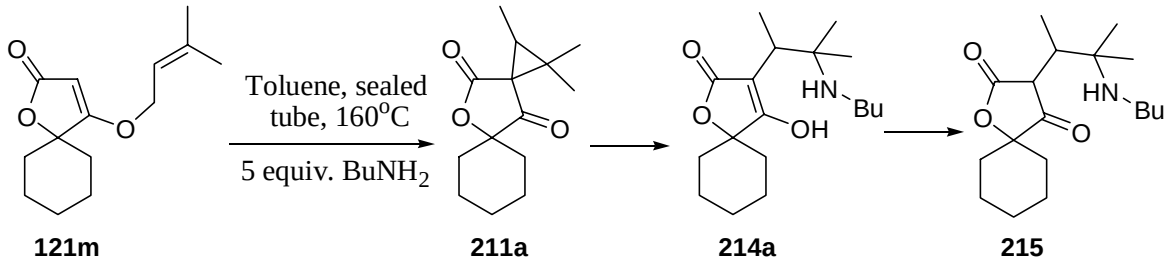
2.3.4 Trapping of spirocyclopropane intermediates

Despite numerous attempts with various solvents and reaction temperatures the elusive spirocyclopropanes **211** could not be isolated. Spirocyclopropanes have been proposed as intermediates for abnormal Claisen rearrangements before[90,188-191], however to our knowledge no conclusive proof has ever been documented. Since we have already reacted stable spirocyclopropanes before with amines (Section 2.1.5.2) we speculated that it should be possible to trap the spirocyclopropane intermediate generated from **121m**. If, as we believed the spirocyclopropane was the intermediate generated on route to the abnormal product, then a large excess of an amine could possibly react with the intermediate **211** before it rearranged to **213**. Not only would such a reaction prove the intermediacy of [2,3]-sigmatropic rearrangements but would also open synthetic routes to functionalised 3-alkyltetronic acids **214** with alkyl instead of aryl residues at C^{β} on the side chain.



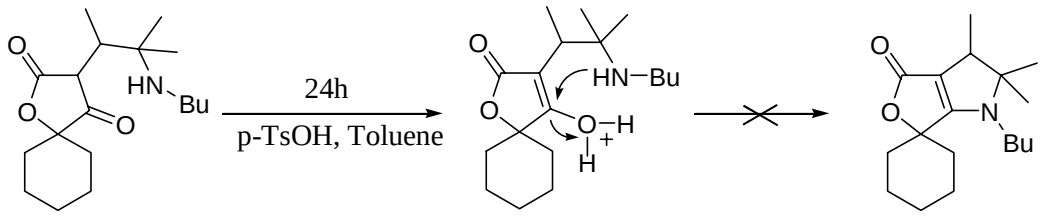
121m **211a** **214**

From Section 2.1.5.2 we knew that butyl amine reacted with **119a** to give **144b** in 67% yield. When a mixture of **121m** was heated in a sealed tube to 160°C with 5 equivalents of butyl amine for 16h the expected tetronic acid **214a** was not obtained. Instead a single compound was isolated with a molecular mass ion that corresponded to **121m** plus butyl amine. This told us that butyl amine had indeed reacted with **121m**. Initially we proposed stucture **215** and all experimental data seemed to confirm such a structure.



121m **211a** **214a** **215**

Tetronic acids almost always exist in the enol form, however we suspected that since the reaction had been performed using a large excess of basic amine that the basic nature of the solution had converted the enol to the keto form. Another explanation that we had proposed was that the amino group existed as a H-bridge with the keto oxygen, which lead to greater thermodynamic stability than the enol form. 3-Alkyl tetronic acids have been converted as a bimolecular reaction with amines into butenolides[192]. Compound **215** should be amenable to such a reaction by acid catalyst azeotropic heating in a suitable solvent to give **217**. However refluxing **215** for 24h in a Dean-Stark apparatus using toluene as a solvent gave only the quantitative amounts of starting material.



215 **216** **217**

Attempts to induce the enol form, thus generating **214**, by refluxing **215** in first methanol followed by chloroform solutions containg p-toluenesulphonic acid gave no result. Clearly there was a problem with the proposed structure **215**. Reaction of **121a** with allyl amine furtuitously gave a white crystalline solid; from which it was possible to grow suitable crystals for X-ray analysis. X-ray single crystal structure analysis (Figure 9) shows that we had rather synthesised a 3,4,5-trisubstituted butyrolactam. The NMR spectra of these 3,4,5-trisubstituted butyrolactams would be almost identical to that of structure **215**, thus explaining the initial confusion in the identity of compounds **218**. The all-*trans* configuration of the residues at C-3, C-4 and C-5 fits with the vicinal coupling constants of ^{3}J(3-H/4-H) = 10.04 Hz and ^{3}J(4-H/5-H) = 8.45 Hz. Similar values were found for other derivatives. Figure 10 shows the proton and carbon NMR spectra of **218a**. Obviously, at elevated temperatures an excess of the polar amine opens the intermediate cyclopropane ring with a considerably weakened, if not entirely broken, C-C bond and a good deal of carbenium ion character of the more highly substituted atom C-2'. A fascinating

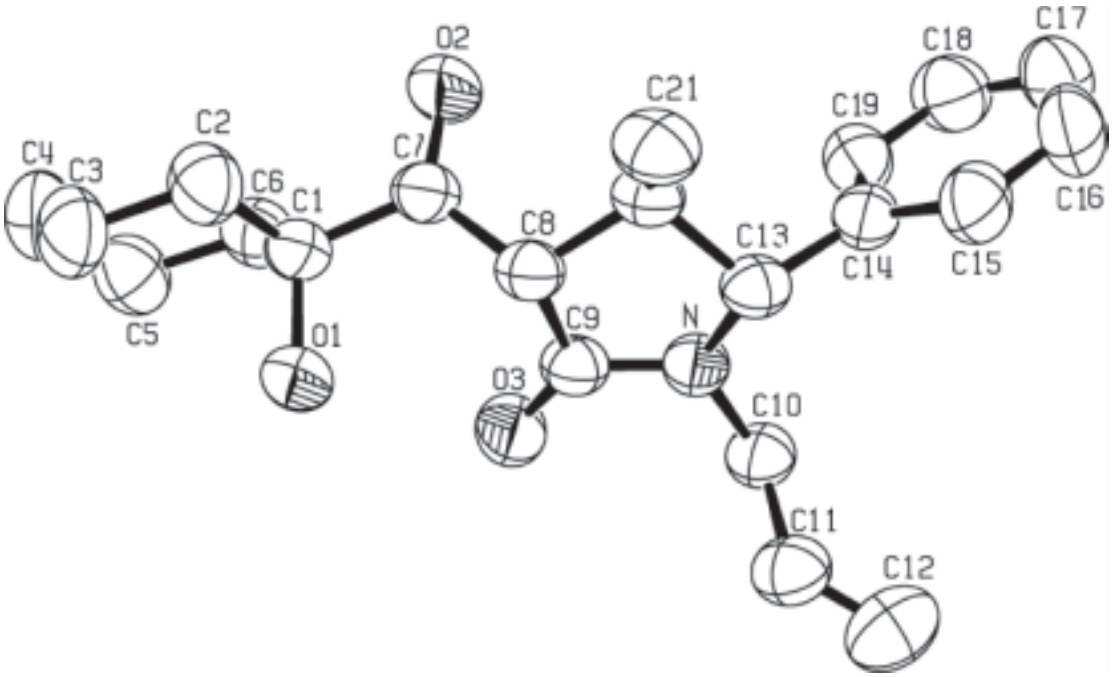


Figure 9: X-Ray structure for compound **218a-α**. Hydrogen atoms are omitted.

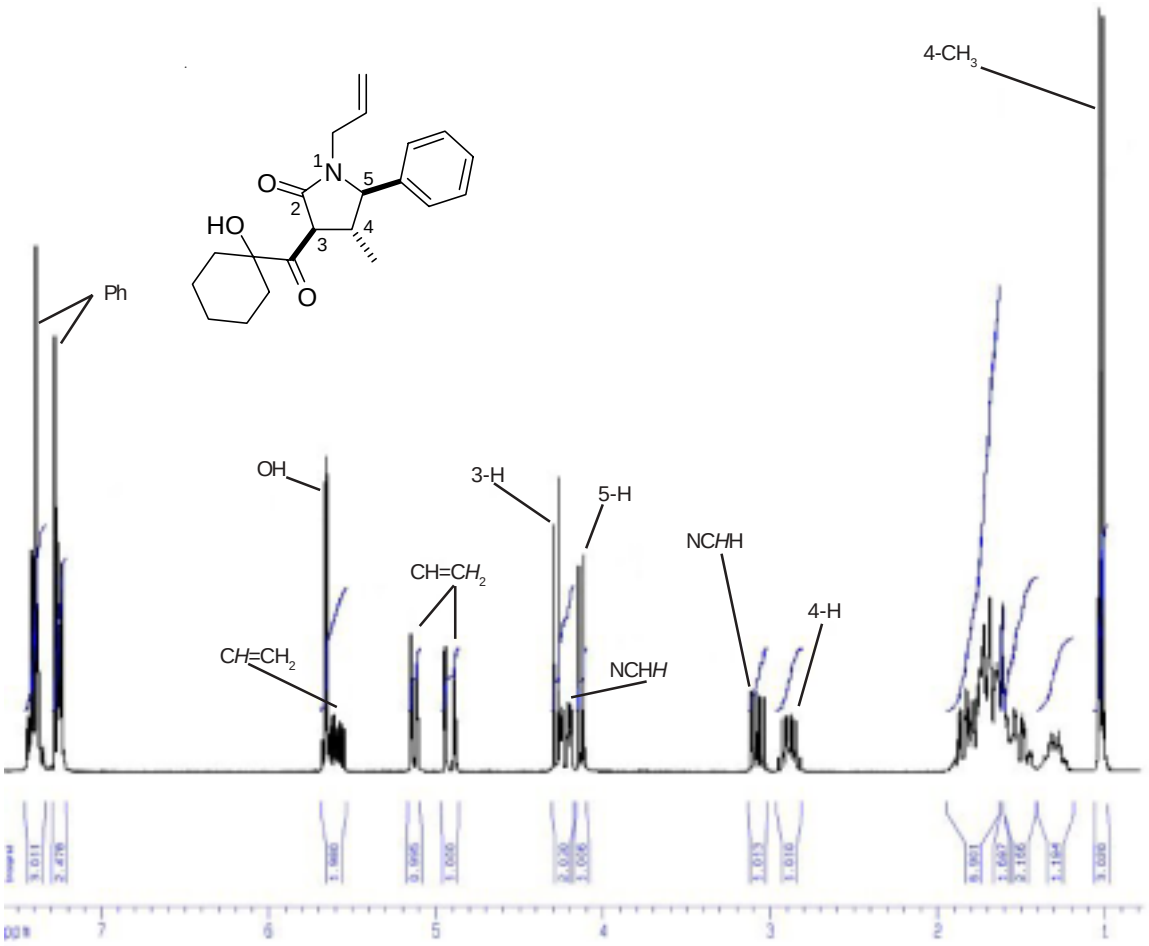


Figure 10a : ^{1}H NMR for **218a-α**:

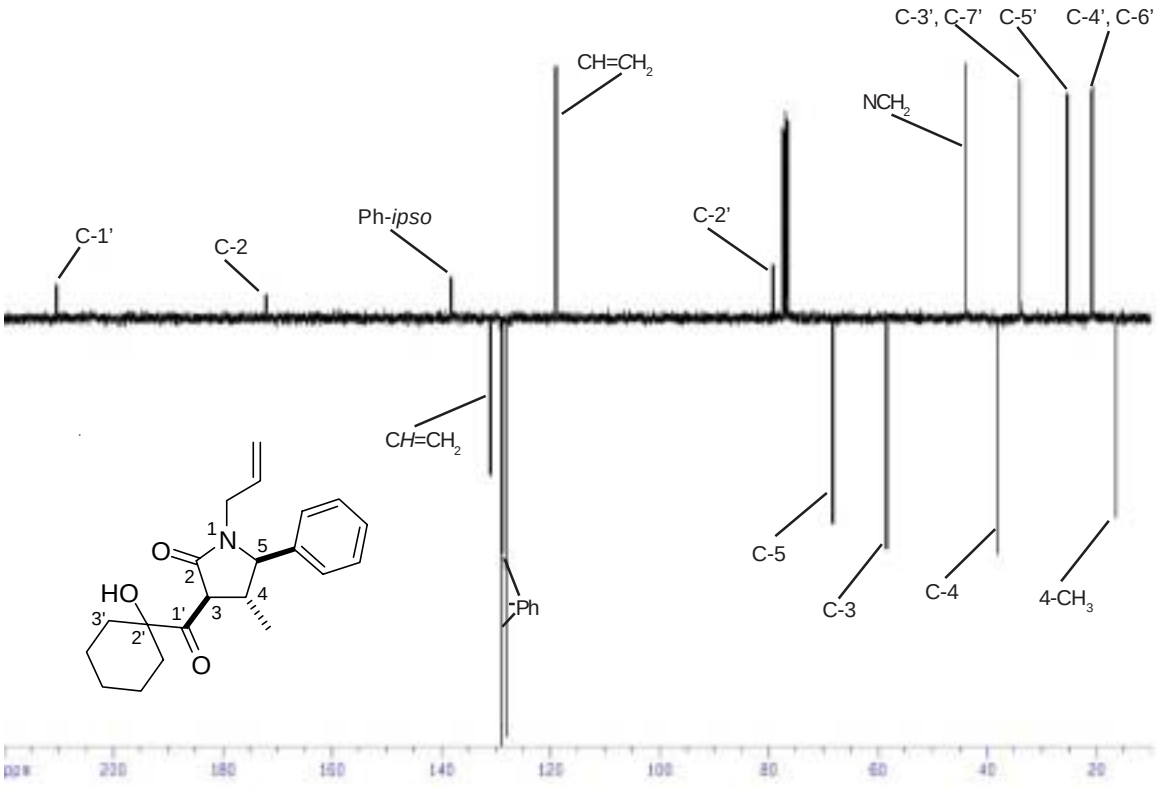


Figure 10b: ^{13}C-NMR for compound **218a**:

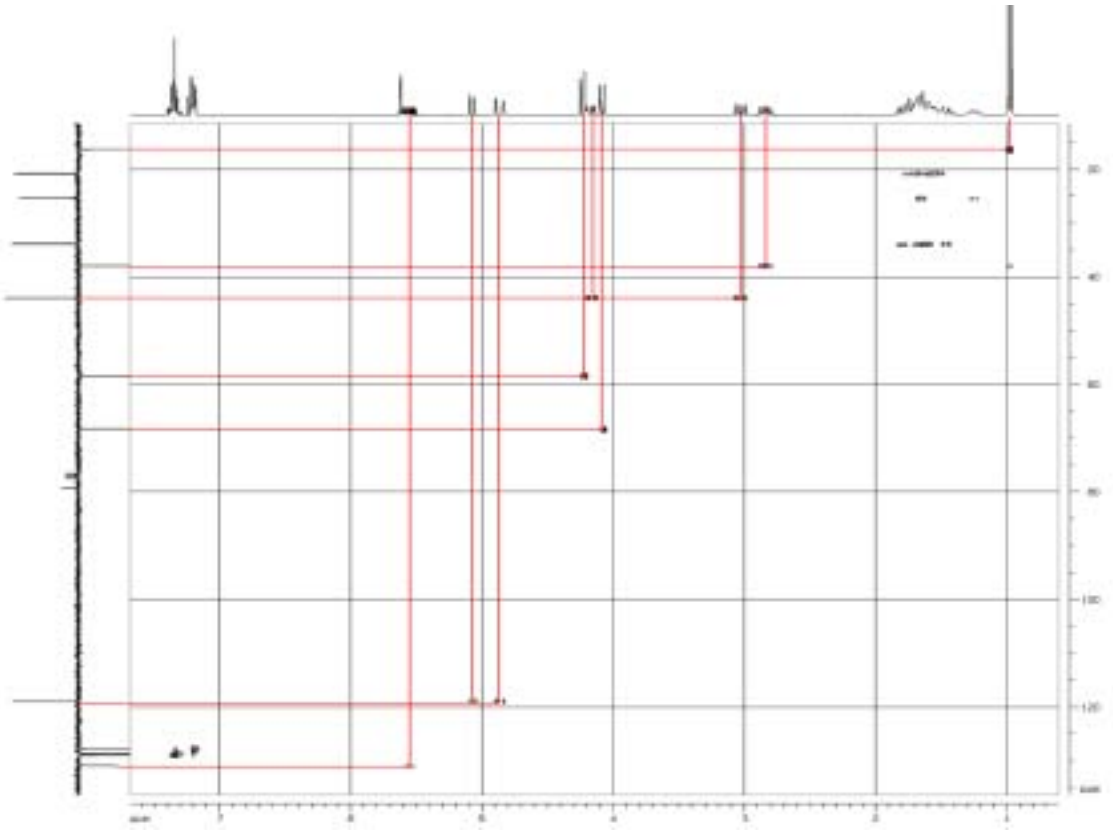


Figure 10c HMQC NMR for compound **218a**.

intramolecular lactone to lactam reaction then proceeds. The breaking of the C-C bond could explain why a *trans-cis* **218β** configuration was observed in some cases. For example the "all *trans*" isomer for **218α** was recovered in 73% yield with a further 23% recovered which contained an approximate 1:1 mixture of isomers. One isomer contained the all *trans* configuration **218a-α** with the other isomer **218a-β** having a *cis* relationship between C-3 and C-4 ($^3J_{HH}$ = 8.01 Hz) with a *trans* configuration between C-4 and C-5 ($^3J_{HH}$ = 9.51 Hz) **218a-β**. This is in contrast to the *syn*-selective ring opening of **119** with amines in DCM or chloroform at ambient temperatures or slightly above to give **149**.

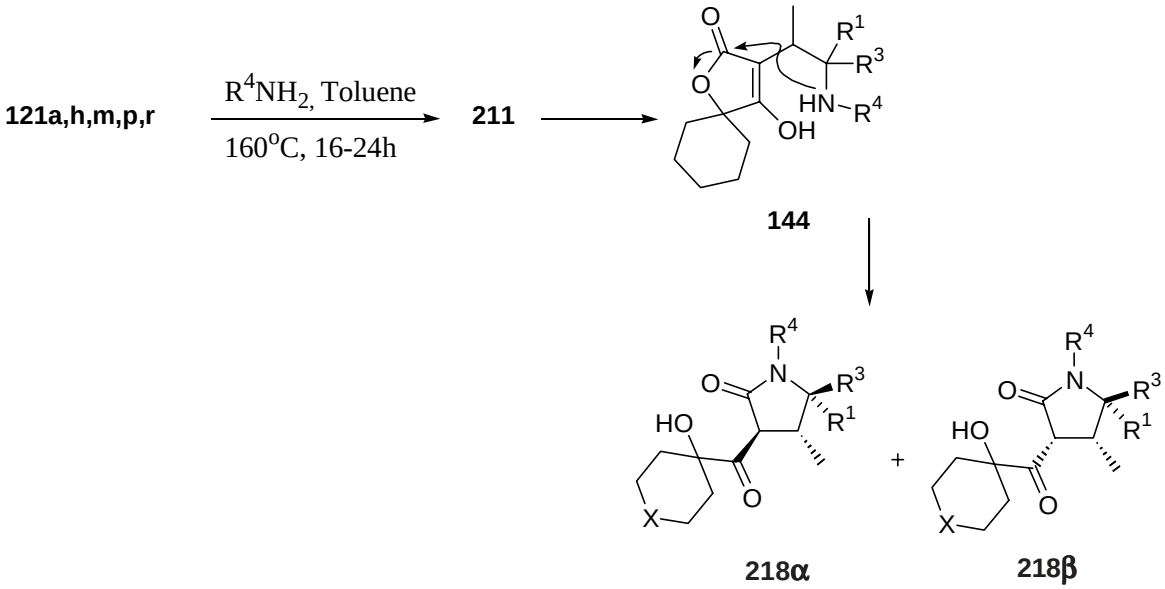


Table 14: Formation of butyrolactams **218** from **121** and a primary amine

218	X	R^1	R^3	R^4	Yield[a]
a	CH_2	H	Ph	$-CH_2CH=CH_2$	94[b]
b	CH_2	H	Ph	$(CH_3)_2CHCH_2-$	67[c]
c	CH_2	H	Ph	Bu	84[d]
d	CH_2	H	Ph	$(CH_3)_2CHCH_2CH-CO_2CH_3$	97[e]
e	O	H	Ph	$-CH_2CH=CH_2$	66[d]
f	CH_2	H	Pr	Bu	54[f]
g	CH_2	H	CH_2Ph	Bu	67[h]
h	CH_2	Me	H	Bu	67[d]
i	CH_2	Me	H	$CH_3CH_2OC_3H_6-$	84[d]

[a] Combined yield of all isomers

[b] 73% α recovered pure, 23% impure mixture of α and β

[c] Ratio of α:β; 3:1

[d] Isomer α recovered only

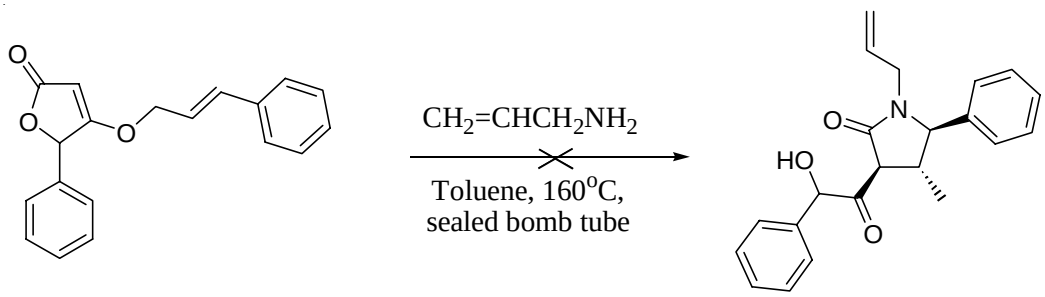
[e] 36% α, 46% two unassigned isomers, 15% β

[f] Ratio of α:β; 4:1

[h] Isomer β recovered only

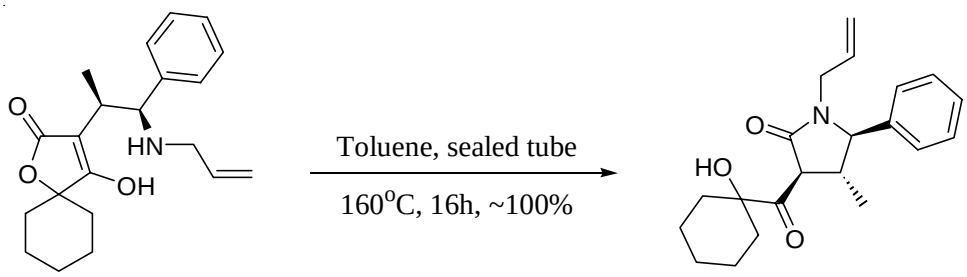
Although two diastereoisomers were identified for **218a**, the predominant isomer, as with all other examples, is the all-*trans* configuration **218a-α**. The overall yield for **218a** was 94% which is truly remarkable for a Domino two step rearrangement-nucleophilic addition, internal trans-esterification reaction. Considering that the highest yield obtained for the single step conversion of **121a** to **119** was only 73% under the reaction conditions used to synthesis **218**. Clearly this is a highly efficient reaction, it is reasonable to assume that **119a** and the more elusive cyclopropanes **211** react immediately with the large excess of amine before side products or decomposition can occur. The yields for compounds **218h-i** were much higher than we originally expected with 84% obtained for **218i**. In hindsight this is unsurprising as compounds **210**, **211** and **212** are all expected to exist as an equilibrium mixture under the reaction conditions; therefore as **211** reacts with the amine more of **211** is generated from the reservoirs of **210** and **212**.

This reaction appears to tolerate a wide variety of amines with even the complex methyl (2*R*)-2-amino-4-methylpentanoate giving very high yields, albeit with a mixture of up to 4 diastereoisomers. Unfortunately when **121q** was reacted in toluene with allyl amine or butyl amine the result was complete decomposition. This could be possible through an attack of the carbenium ion at the C-5 position with expulsion of the phenyl group followed by uncontrolled rearrangements.



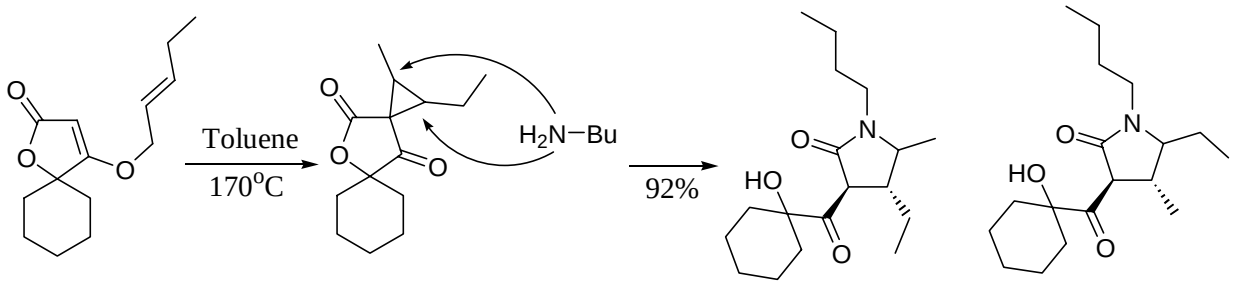
121q **219**

As a final proof for the reaction sequence we have proposed, a solution of **144d** was heated in a sealed tube to 160°C for 16h using toluene as a solvent. TLC and GC analysis of the reaction mixture showed only the presence of compound **218a**. No other compounds could be detected in the reaction mixture.

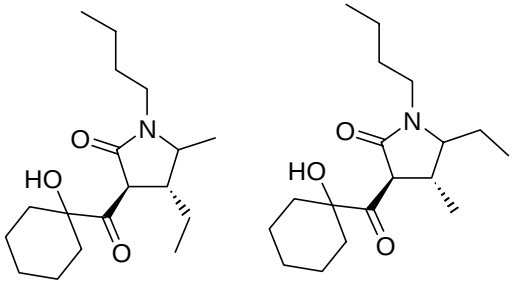


144d **218a**

Compound **121o** gave a more complicated set of results when heated with an excess of butyl amine. This time the elusive spirocyclopropane contains a methyl and ethyl group attached to the cyclopropane ring. Clearly C-1' and C-2' occupy almost identical chemical enviroments and unsurprisingly the nucleophilic butyl amine attacked both positions. A total of four isomers were recovered, the two *trans* (3-H and 4-H) structures were present as a mixture as were the two *cis* (3-H and 4-H) diastereoisomers. No information could be determined for the stereochemistry between 4-H and 5-H due to the complexity of the NMR signals. No attempt was made to further purify these compounds by chiral HPLC. The structures and stereochemistry was determined by ^{1}H coupling constants and confirmed by COSY, HMQC and NOESY

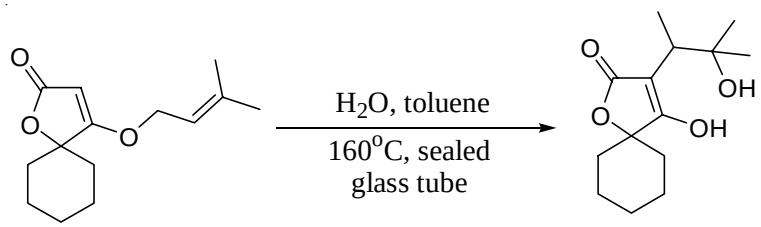


121o **220α** **220β**



221α **221β**

The reaction of **121m** with N,N-dimethylamine using the same reaction conditions as before for spirocyclopropane trapping reactions, led to **222**. The structure was confirmed by X-ray single crystal structure analysis (Figure 11). **222** must have arisen due to the presence of water in the toluene solvent. The water therefore attacked the intermediate cyclopropane much faster than the secondary amine.



121m **222**

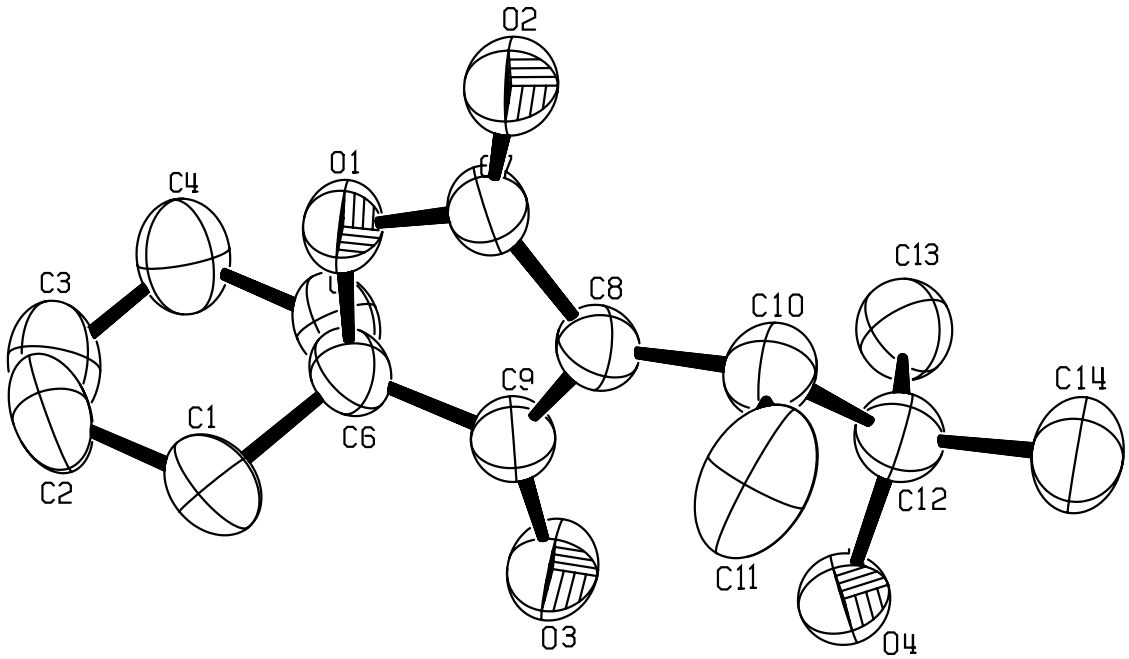
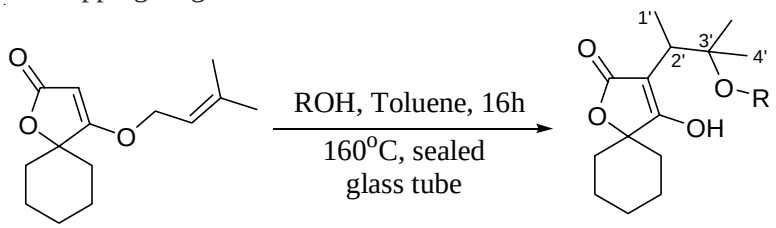


Figure 11: X-Ray structure for compound **222**. Hydrogen atoms are omitted.

The formation of **222** from **121m** with water would suggest that the elusive spirocyclopropanes could theoretically also be trapped using alcohols, without the subsequent lactone to lactam conversion step.When a mixture of **121m** and five equivalents of ethanol were heated together in a sealed glass tube under nitrogen, to 165°C for 16h, the corresponding (3'-ethoxybut-2'-yl)-tetronic acid **223b** was obtained in an excellent 92% yield (Figure 12). The use of methanol also gave an excellent yield of 88%. It should be mentioned that reaction of **121q** under these conditions with methanol led to complete decomposition as with reaction with the amines.

From these results we can be certain that abnormal Claisen rearrangements of allyl tetronates proceed through cyclopropane intermediates. It is therefore reasonable to assume that all abnormal Claisen rearrangements proceed through spirocyclopropane intermediates and can in theory be trapped using suitable trapping reagents.



121m **223**

223	**R**	**Yield**
a	Me	88%
b	Et	92%

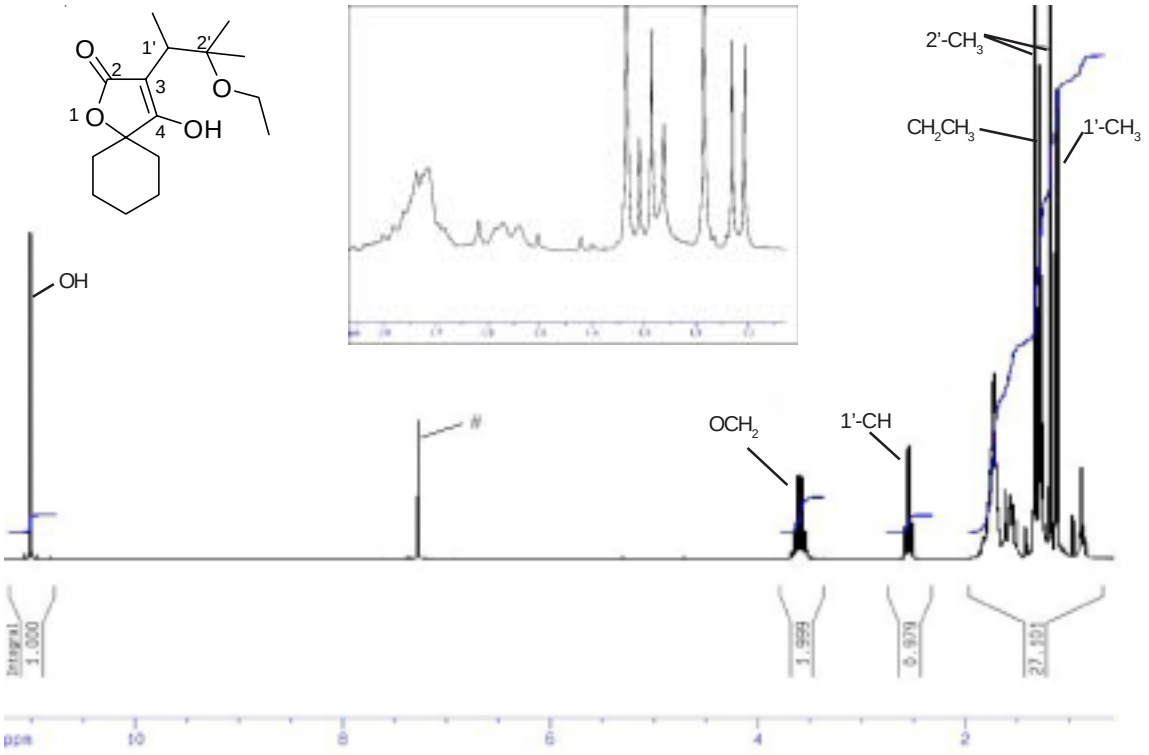


Figure 12a:[1]H-NMR of compound **223b**:, # = $CDCl_3$.

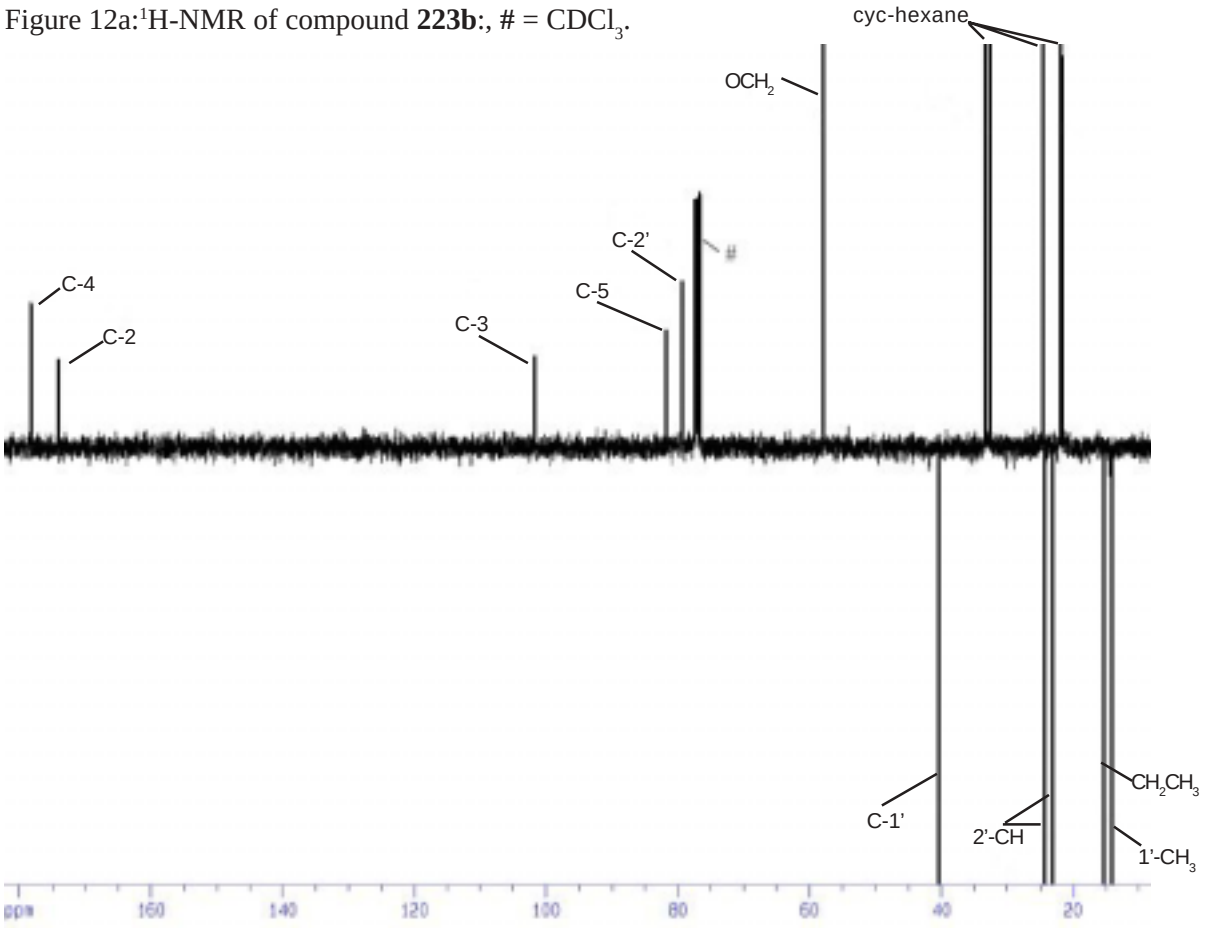
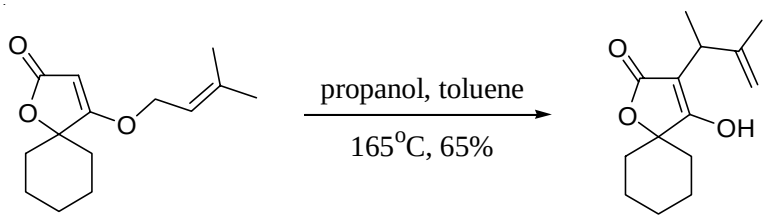


Figure 12b:[13]C-NMR of compound **223b**: # = $CDCl_3$.

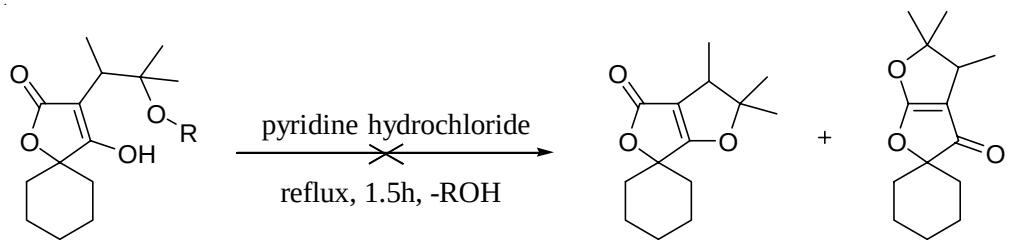
Reaction of **121m** with propanol did not lead to **223**. Instead we were surprised to find **212a**. Even if propanol was too weak of a nucleophile to react with the intermediate spirocyclopropane we would have expected it to rearrange through the full sequence to compound **213**. One possible explanation for this observation is that propanol interacts through hydrogen bonding with the hydroxy group in **212a** thus confering stability to **212a** and making the [1,3], [1,5]-H-shifts thermodynamically unfavourable. **212a** has also recently been prepared in our group using microwave irradiation.[241]



121m **212a**

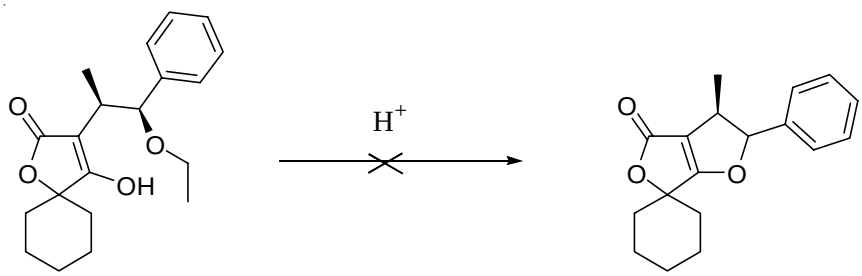
2.3.5 Attempts to dehydrate 3-(2'-alkoxy)tetronic acids

Several examples are known in the literature where 4-hydroxycoumarins[193] and benzofuroquinolines[194] with a similar structure as compounds **223** have under acidic conditions reacted to give an annulated five ring. 4-Hydroxy tetronic acids are the five ring analogues of the 4-hydroxycoumarins and should be amenable to similar reactions. Compounds **223a** and **223b** were vigorously refluxed using anhydrous pyridine hydrochloride as solvent following a procedure by Yamaguchi[194]. After removal of the solvent we found that the expected product **224** or **225** was not formed; instead the starting material had undergone decomposition.



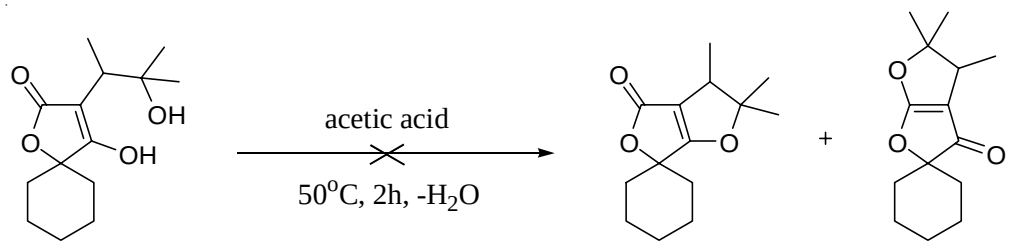
223 **224** **225**

141b was then subjected to milder conditions using firstly a refluxing solution of BF_3-diethyletherate in a THF solution. Later **141b** with p-toluenesulphonic acid in refluxing chloroform was also attempted. In both cases it was possible to completely recover **141b**.



141b **226**

Finally **222** as synthesised in Section 2.3.4 was gently heated to 50°C with acetic acid for 2 hours. This resulted in complete decomposition of our starting compound and once again neither compound **224** nor **225** could be recovered.

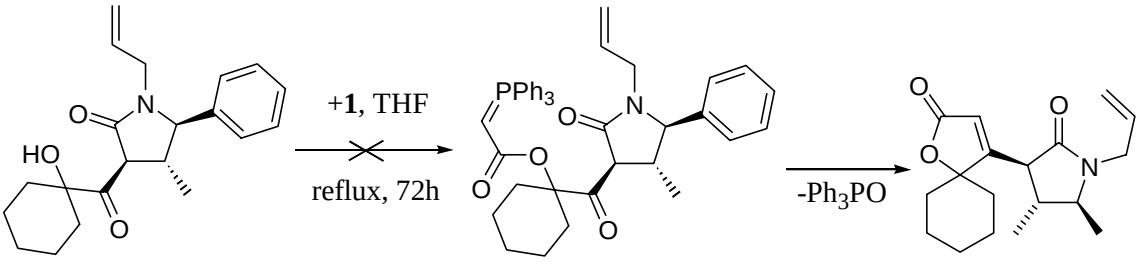


222 **224** **225**

The examples from literature[193,194] all involve the expulsion of an alkoxy or a hydroxy group from a benzene ring, our examples have an hydroxy/alkoxy group conneced to an alkyl chain. The mechanism could be expected to follow a S_N2 pathway with expulsion of the alkoxy/hydroxy group from the benzene ring, which would lead to a relatively stable benzylium ion which could then be attacked by the remaining hydroxy group leading to a new ring system attached to the benzene ring. Clearly with our systems a benzylium ion cannot be generated as the alkoxy/ hydroxy group is attached to an alkyl residue. The formation of a carbocation after alkoxy/ hydroxy expulsion therefore leads to uncontrolled rearrangements and ultimately decomposition.

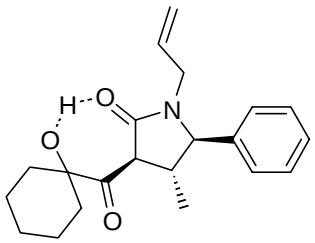
2.3.6 Attempts to react 3,4,5-trisubstituted butyrolactams with 1

3,4,5-Trisubstituted butyrolactams **218** all contain an α-hydroxy ketone. Ketones are much more amenable to Wittig olefination reactions than esters[13], so we therefore expected compounds **218** to react readily with keteneylidenetriphenylphosphorane **1**. The result of such a reaction would be the formation of a new tetronate **227**; therefore our synthesis would have extended to two formal additions of **1** to a simple α-hydroxyacid. Another possiblity would be the reaction of **1** at the acidic 3-H of the lactam ring, resulting in an acyl ylide connected at C-3. Such a reaction was considered unlikely however due to steric considerations. To our surprise when **218a** was stirred in THF with **1** no reaction was observed and **218a** could be quantitatively recovered. The reaction was repeated using longer reaction times (72h), with toluene as a solvent under normal reflux conditions and in a bomb tube heated to 160°C. Finally the reaction was repeated with THF solutions heated to 90°C under microwave irradiation (300W) for 1h. In each case the starting material could be recovered in yields of over 85%. Minor side products were in these cases isolated; the structures of which could not be determined. These side products appeared to be products from various elimination reactions and were certainly not the expected tetronate **227** nor the acyl ylide **226**.

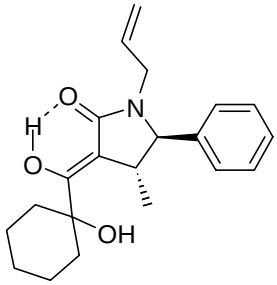


218a **226** **227**

Since **1** was present in the reaction solution and no acyl ylide has been detected from these reactions, it is clear that the stumbling block must be the initial OH addition to **1**. It is inconceivable that compounds of type **226** would not immediately eliminate Ph_3PO **6**, in fact such a reaction would be expected to proceed in THF solutions at room temperature. X-ray structural analysis of **218a** (Figure 9) shows that the lactam carbonyl group and the hydroxy group are oriented towards one another. A hydrogen bridge between these two groups would lead to a stable seven ring **228**. We assume therefore that the stability of the hydrogen bridge is sufficient to prevent addition to the ylide. Another possibly is that in solution compounds **218** exist as the more stable 6-ring chelates, similar in structure to β-keto esters previously prepared in our group. These β-keto esters undergo nucleophilic attack on **1** to give stable acyl ylides.[115] Clearly this cannot happen for compounds **229** as the enol is sterically hindered.



228a



229a

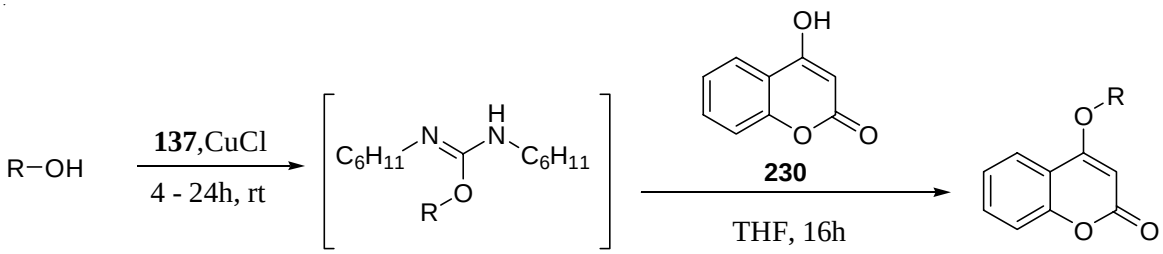
In order to circumvent this problem we attempted to protonate the ylide **1**. Normally all reactions of **1** are performed with a catalytic amount of benzoic acid which acts an initiator leading to improved yields. We attempted the reaction of **218a** with 1 equivalent of benzoic acid in order to ensure that the ylide in solution was completely protonated which should assist the addition of COH to the ylide. The conjugate base of benzoic acid is a very weak nucleophile and this reaction can therefore be performed without fear of benzoic acid addition to **1**. Once again only starting material could be recovered; the ylide over time underwent [2+2]-cycloaddition to give the corresponding dimer **17**. This idea was extended to the stronger acid HBF_4. To a THF solution of **218i** and **1** at 60°C was slowly added a diluted solution of HBF_4. Immediately a dark orange solution which is characteristic of all successful reactions of **1** was produced. After complete addition of the HBF_4 and continued stirring of the solution it was apparent that the solution had unfortunatley started to polymerise. Further attempts with either catalytic quantities of HBF_4 or with weaker acids have not yet been performed.

2.3.7 Attempts to trap coumarin spirocyclopropanes

Coumarins are distributed widely throughout the natural world,[195,196] often they possess high biological activities and as such have been widely investigated. We were therefore interested in extending our investigations from the tetronic acids to the coumarins.

2.3.7.1 O-Alkylation of 4-hydroxycoumarins

4-Alkoxycoumarins are normally prepared from the alkylation of 4-hydroxycoumarins with alkyl halides under basic conditions.[137] Recently our working group discovered that 4-hydroxycoumarins could be alkylated with isoureas.[115] So far only simple O-alkyl isoureas have been investigated for 4-hydroxycoumarin alkylation. Herein we would like to report the extension of this method to more interesting α,β-unsaturated alcohols. Although yields are poor they are comparable to literature results using alkyl bromides. The reaction failed with cinnamyl alcohol, however for simple α,β-unsaturated alcohols this appears to be a useful alternative to alkyl bromide alkylation.



138 **139** **231**

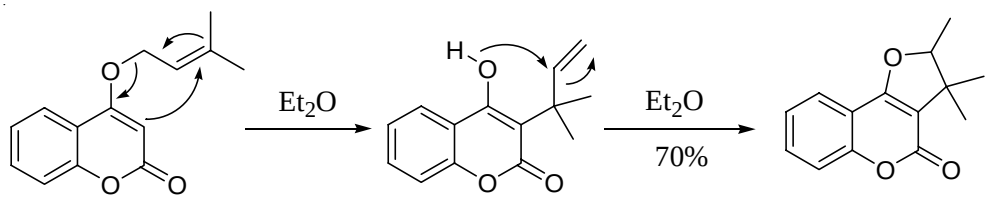
231a R = $CH_2CH{=}CH_2$, yield = 44%

231b R = $CH_2CH{=}C(CH_3)_2$ = 43%

231c R = $CH_2CH{=}CHCH_2CH_2CH_3$, 73%

2.3.7.2 Rearrangements of 4-alkoxycoumarins

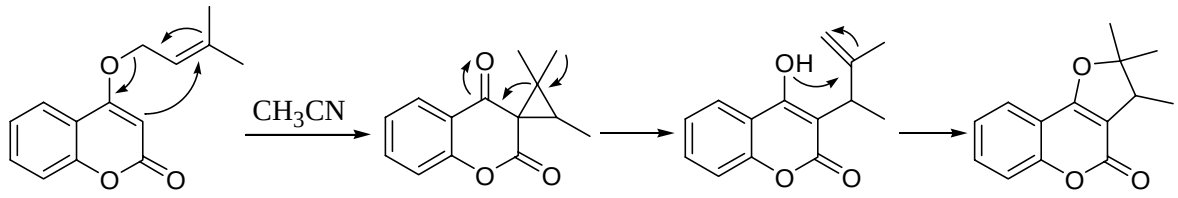
3-Allyl-4-hydroxycoumarins (formed from 4-Allyloxycoumarins) are known to undergo addition of the hydroxy group to the C=C bond to give furano derivatives.[242] **231b** is reported to undergo rearrangement in refluxing diethyl ether to the furano derivative **233**.[198]



231b **232** **233**

However when we repeated this rearrangement in refluxing acetonitrile the furano constitutional isomer **236** was formed in 78% yield. The only mechanistic explanation which could explain

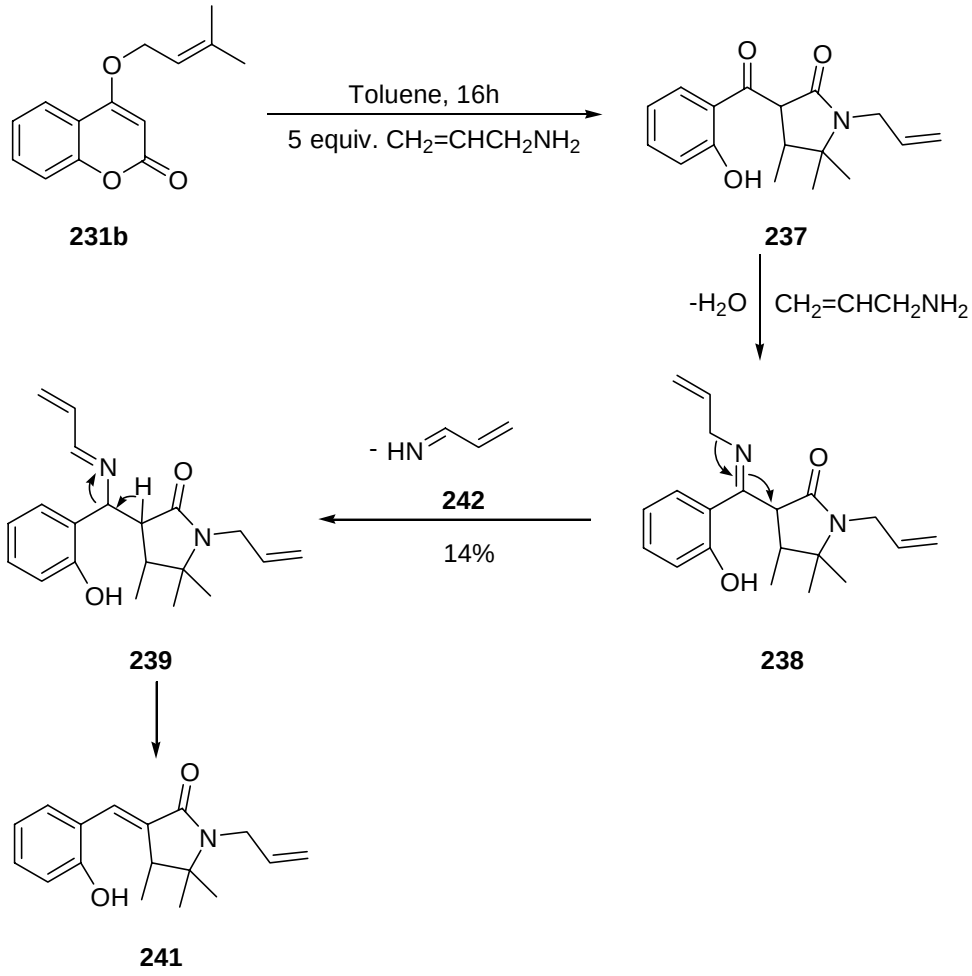
such a transformation is an abnormal Claisen rearrangement passing through a cyclopropane intermediate **234**, with a final addition of the OH to the terminal C=C bond. **233** could not be detected from the reaction mixture.



231b **234** **235** **236**

2.3.7.3 Ring Trapping of coumarin cyclopropanes

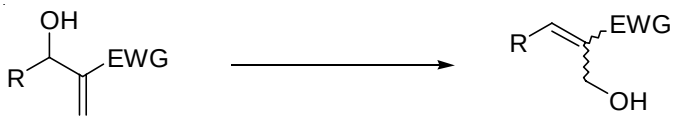
Having identified in the previous section that cyclopropanes **234** form in coumarin systems we were eager to discover if it was possible to trap the cyclopropane using an amine. Furthermore it would be interesting to learn if a similar lactone to lactam trans-esterification reaction would result (Section 2.4.4). When a solution of **231b** was heated in a sealed tube with toluene and 5 equivalents of allyl amine we found through NMR analysis that compound **241** had formed. We propose the following mechanism to explain this finding. Initially we believe that in this example the phenyl ring withdraws electron density from the carbonyl group, thus making the carbonyl carbon more electronpositive and therefore more amenable to attack from the excess of allyl amine present. The imine formed undergoes a [1,3]-H-shift followed by elimination of **240** to give **241** in 14% yield.[243]



231b **237** **238** **239** **241**

2.4 Investigations into the Baylis-Hillman alcohols

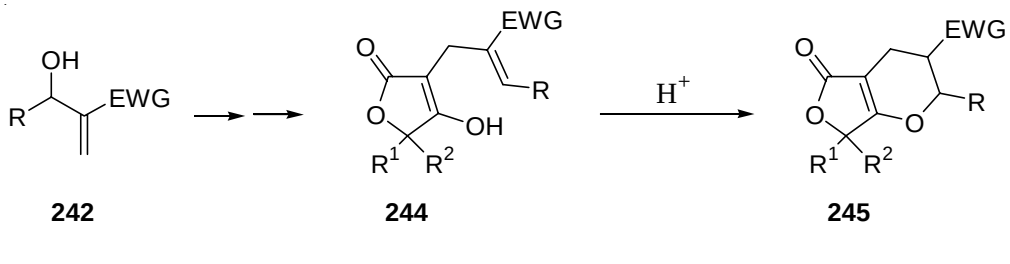
The Baylis-Hillman reaction is a very important method for the formation of C-C bonds. The Baylis-Hillman compounds can be constructed easily and they represent a very powerful method for the introduction of functionality to organic systems. They are formed from the conjugate addition of esters or amide to aldehydes using bases such as DABCO or trialkylphosphines.[199-202] These compounds all contain a secondary allylic alcohol functionality **242**; many examples exist where **242** has been converted to the more thermodynamically stable primary alcohols **243**.[203-207]



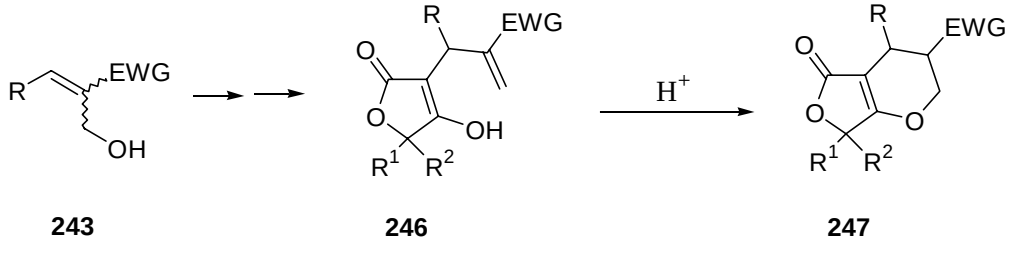
242 **243**

R = alkyl, aryl
EWG = Ester, nitrile

Both **242** and **243** could in theory enter our domino addition-Wittig olefination-Claisen rearrangement sequence. The products of such a sequence due to the presence of the ester/ nitrile groups are Michael systems. In theory they should be amenable to hydroxy addition to the double bond to give annulated six ring systems **245** and **247**. Furthermore compounds **244** and **246** could also participate in all our chemistry mentioned in previous sections, i.e. cyclopropanation, formation of spirocyclopropane systems, ring trapping/ring opening reactions of spirocyclopropanes. By careful control of the reaction conditions it should be possible to convert the Baylis-Hillman alcohols quickly and efficiently into highly functionalised, interesting molecules.



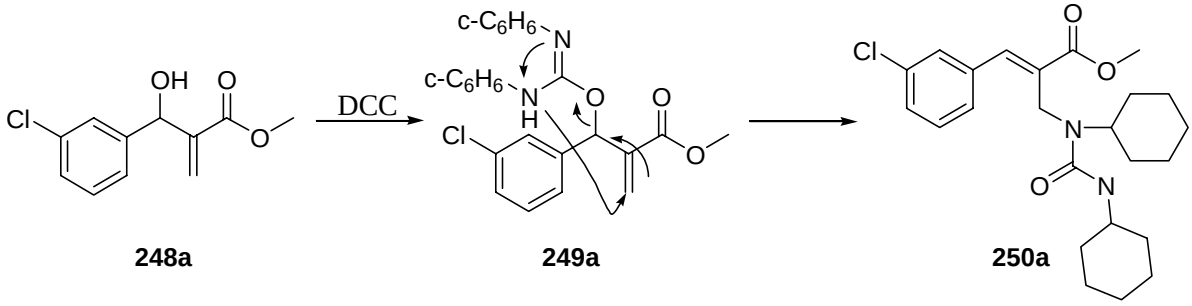
242 **244** **245**



243 **246** **247**

2.4.1 Attempts to synthesise Baylis-Hillman isoureas

Previously in Section 2.1.4.4 we investigated the synthesis of isoureas as an excellent method for esterification of α-hydroxyacids. To date there are few reports of Baylis-Hillman alcohols **242** entering into esterification reactions. Examples are limited to reaction with simple acetic anhydrides and simple acyl chlorides. We assumed that the alcohols **242** would be amenable to isourea formation. When **248a** was stirred with DCC in the presence of a copper catalyst the normal green solution developed and DCC was clearly consumed (evident from the disappearance of diimide peak at 2100 cm^{-1}). Reaction of this solution with a variety of α-hydroxyacids failed to give any esters. Attempts to purify the "isourea" resulted in the discovery that the isourea **249a** had undergone an intramolecular rearrangent to give a highly stable 1,3-dicyclohexyl-1-(2-acrylate-3-phenylallyl)urea **250a** (Figure 13). This reaction appears to be dependent on the ester functionality. When a nitrile group replaces the ester the result is a mixture of decomposition products and starting materials. Compounds of type **249** and **250** cannot be recovered.



248a **249a** **250a**

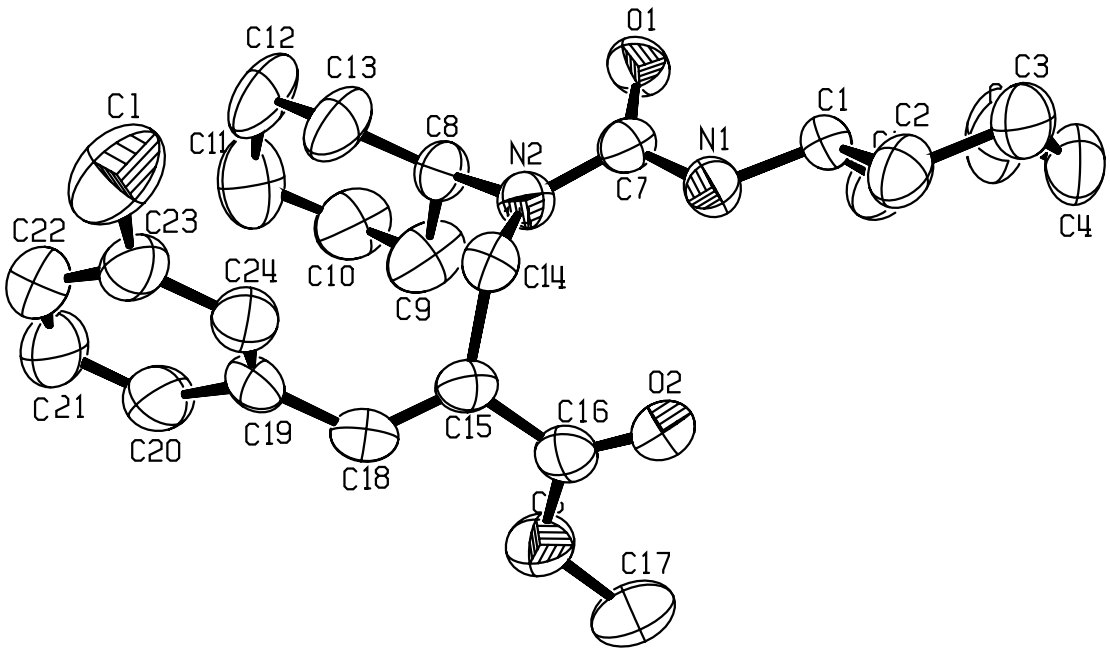
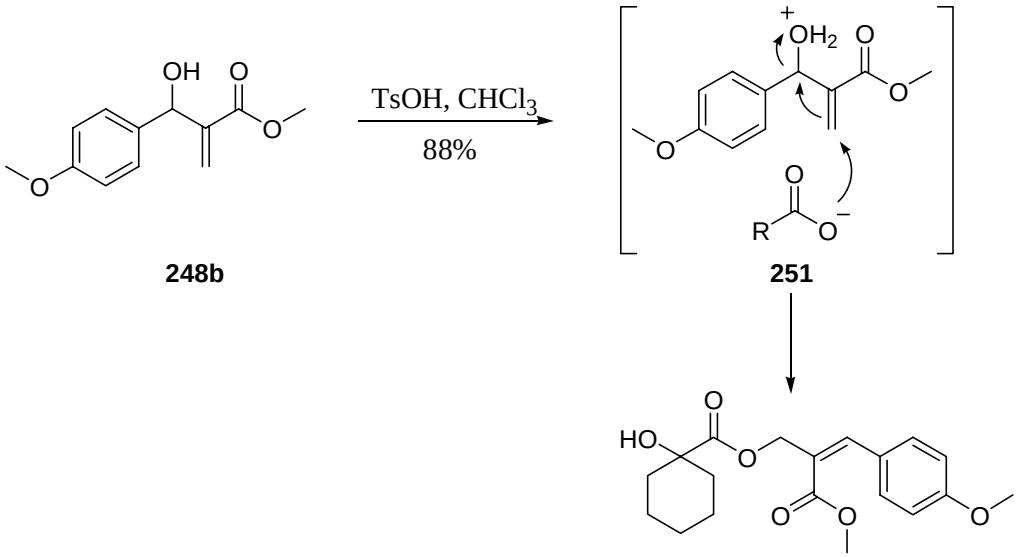


Figure 13: X-ray structure for compound **250a**. Hydrogen atoms omitted.

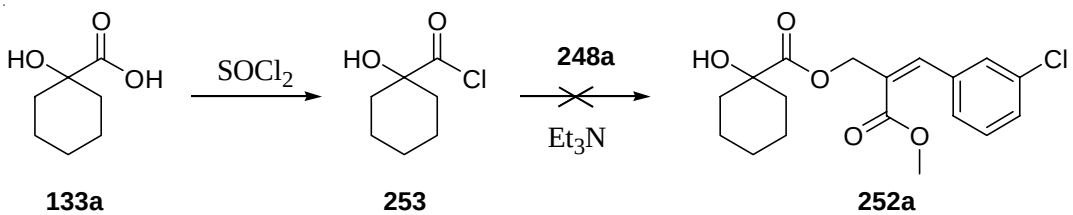
2.4.2 Other attempts to esterify Baylis-Hillman alcohols with α-hydroxyacids

Attempts to effect esterification of Baylis-Hillman alcohols by acid catalysed methods using a Dean-Stark apparatus also failed. When the phenyl ring contained a chlorine, the alcohol could in every case be recovered quantitatively. Both *p*-toluenesulphonic acid and sulphuric acid failed to effect any reaction using chloroform, DCM and toluene as solvents. However when the phenyl ring contained an electron donating group as in **248b** (methoxy) esterification did take place with high yields, however the carboxylic group had attacked the double bond and not the hydroxy group to give the undesired rearranged ester **252b**.



248b **251** **252b**

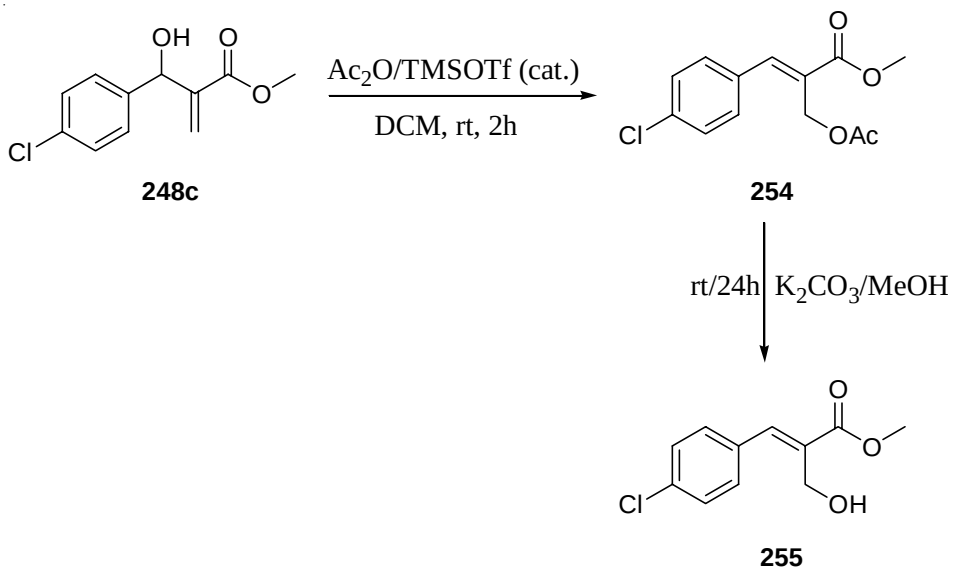
Several dehydrating agents have also been attempted including silica gel,[212] magnesium hydrate monohydrate, DCC with an aminopyridine[213-215], N,N'carbonyldiimidazole[216,217] and Castro's reagent.[218]In each case the starting material was completely recovered from the various reaction mixtures. Various attempts were also made using microwave esterification using both acids and dehydrating agents again with no success. Mason[219] has reported the esterification of a Baylis-Hillman alcohol with a reactive acid using DCC in DCM. In this case the carboxylic acid is likely to react with the DCC with the subsequent carboxylic isourea being susceptible to attack from the alcohol. Unfortunately we could not repeat this reaction with our α-hydroxyacids or even with simple benzoic acid. As mentioned earlier Baylis-Hillman alcohols react readily with acyl chlorides[210,211]. We therefore attempted to convert α-hydroxycyclohexanecarboxylic acid to the corresponding acyl chloride **253**. The pure acyl chloride was added to a solution of the alcohol containing triethylamine. No reaction was observed even after 48h and the alcohol was recovered unchanged.



133a **253** **252a**

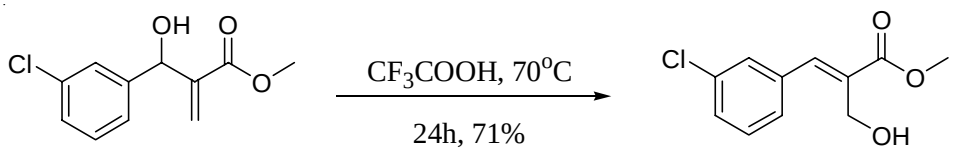
2.4.3 Formation of rearranged Baylis-Hillman α-hydroxy esters

Baylis-Hilman alcohols can easily rearrange to the thermodynamically more stable primary alcohols **243** which contain a cinnamyl alcohol moiety. Basavaiah[205] has reported the transformation of compounds of type **242** to type **243** by formation of the rearranged acetate which is subsequently hydrolised. When Basavaiah's procedure was repeated we found that in our hands the second hydrolysis step required longer times than reported. After reaction of **248c** for the reported time of one hour we recovered **253** in 82% yield. We found that formation of **255** required much longer methanol/K_2CO_3 hydrolysis times. After 24h we isolated **255** in 72% yield.



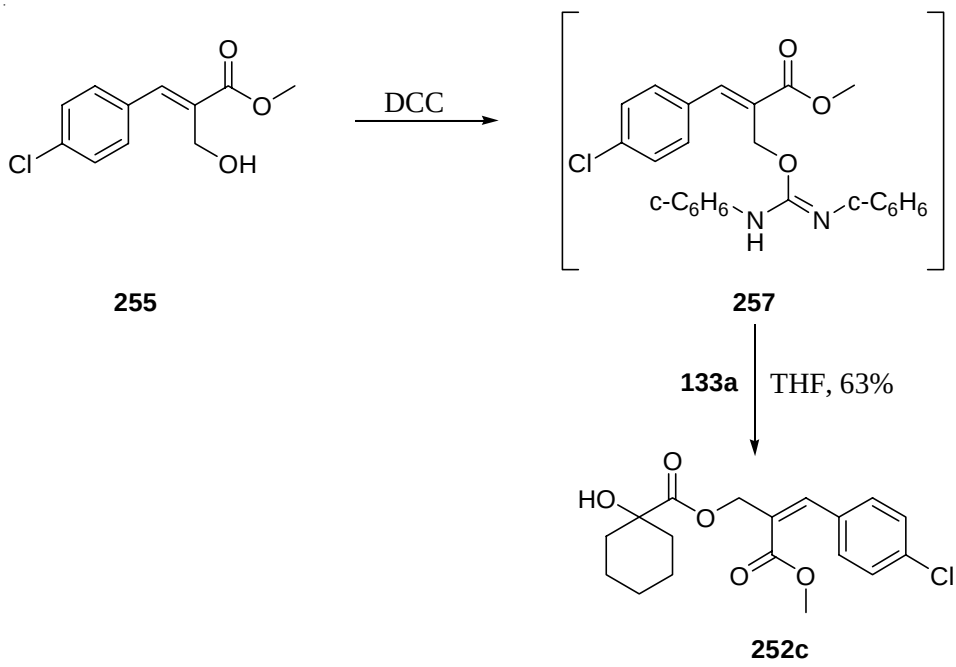
248c **254** **255**

Another method by Kim[203] initiates the rearrangement simply by heating the alcohol in trifluoroacetic acid. We found this to be a useful method with yields comparable with the previous method, however this reaction is operationally more simple and the trifluoroacetic acid method is also more economical. Trifluoroacetic acid may also be used in cases were the ester group is replaced with a nitrile, however yields are much lower; sulphuric acid has been found to be a much better reagent in these cases.[206]



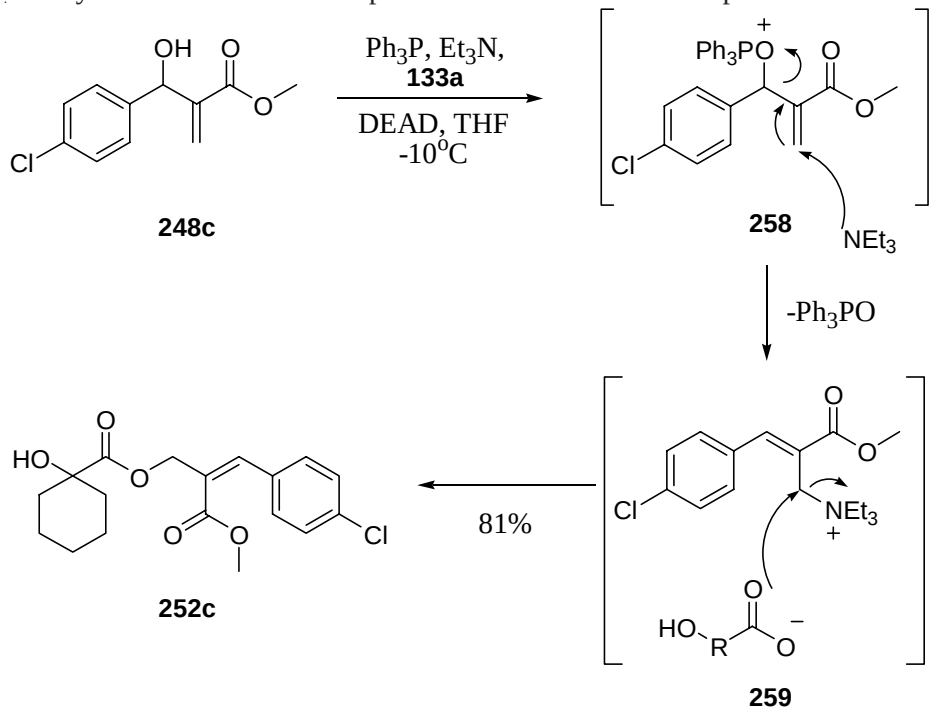
248a **256**

We have found that compounds of type **243** readily form isoureas which can then be converted in situ to esters. This was unsurprising since compounds of type **243** are structurally similar to cinnamyl alcohols. **252c** was obtained in an overall yield of 63% from **248c**, intermediate isoureas were not isolated.



255 **257** **252c**

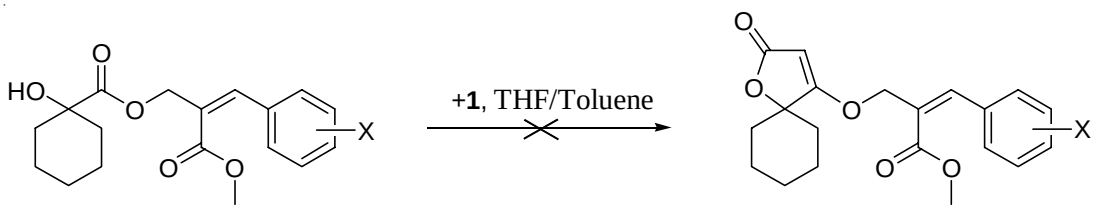
Charette[220] has reported an alternative method for the construction of esters derived from rearranged Baylis-Hillman alcohols. This method is based on the Mitsunobu esterification procedure. The initial step involves addition of triphenylphosphine to the Baylis-Hillman alcohol **242**, followed by an S_N2 attack by triethylamine on the alkene, with expulsion of triphenylphosphine oxide **6,** leading to the rearranged system **259**. A further S_N2 attack by the carboxylate ion expels the triethylamine to directly give the ester. Charette has only investigated this reaction with simple benzoic and acetic acids, however we are happy to report that this reaction can be extended to the α-hydroxyacids with excellent yields observed. Overall yields are considerably higher than those obtained when a two step rearrangement-isourea esterification is performed. Furthermore the Charette procedure is operationally simple and is complete after a few hours. Unfortunately the reaction would not proceed when the ester was replaced with a nitrile.



248c **258** **259** **252c**

2.4.4 Attempts to react rearranged Baylis-Hillman esters with 1

Esters of type **252** generated in the previous section should react readily with **1** to give the corresponding tetronates. Refluxing solutions of **252** with **1** in THF and toluene were reacted under normal conditions (Section 2.1.4.5) and in sealed glass tubes heated for several days to temperatures of 200°C. Experiments were also performed using microwave irradiation in THF and toluene solutions. In every case the starting ester could be quantitatively recovered from the reaction solution. The reason for reaction failure is not completely apparent, it is possible that a similar H-bonding system is in operation as in the case of the butyrolactams **228**. This would mean an intramolecular eight ring hydrogen bridge which is unlikely to be strong enough to prevent reaction with **1**. More likely the reaction would not proceed due to steric constraints arising from the bulky ester group.



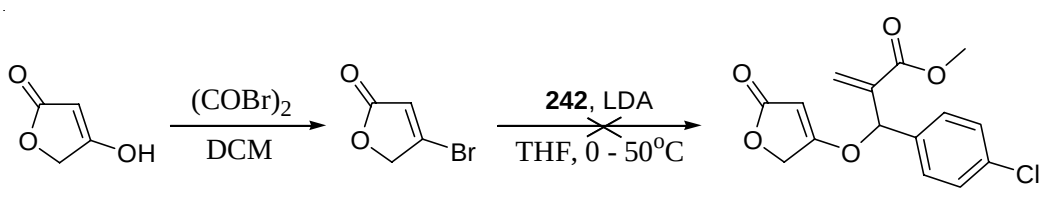
252 **260**

X = p-Cl, m-Cl, p-OCH_3

2.4.5 Attempts to alkylate tetronic acids with Baylis-Hillman alcohols

Tetronic Acids are in many regards similar to carboxylic acids. With this in mind we attempted direct reaction between the alcohol and tetronic acid, in order to circumvent the problem described in the previous section. With the simple free tetronic acid **41** we attempted direct alkylation using azeotropic distillation. Various acid catalysts were used as were both the Baylis-Hillman alcohols **242** and their rearranged constitutional isomers **243**. Alkylation of the tetronic acid was not observed.

To increase the reactivity of tetronic acid **41** we decided to convert it to 4-bromofuran-2(5H)-one **261**. **261** should be analogous to an acyl bromide and subsequently be much more reactive than tetronic acid **41**. Many examples exist in the literature where an acyl chloride has been reacted with Baylis-Hillman alcohols in the presence of base to give the corresponding esters. In theory **261** should react in a similar manner. Once again no reaction was observed when **261** was reacted with alcohols of type **242** and **243**. Even when the conjugate base of **248c** was generated using LDA, no reaction with **261** was observed.

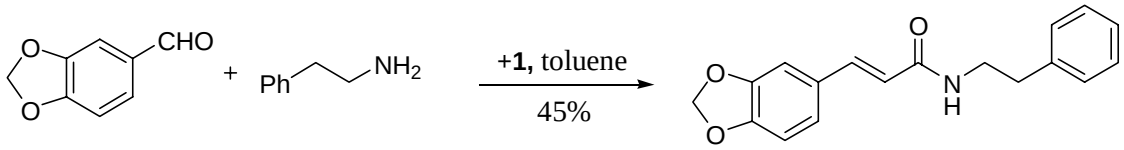


41 **261** **262**

2.5 Three component synthesis of (E)-α,β-unsaturated Amides

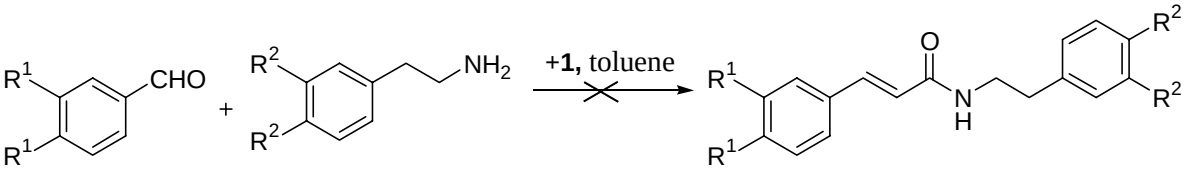
Previously our working group had investigated the synthesis of (E)-α,β-unsaturated amides by a three-component reaction between the corresponding amine, aldehyde and **1**.[115] Yields were typically good; possible byproducts arising from the Wittig olefination of **1** with an aldehyde or imine formation were not observed. (E)-α,β-unsaturated amides are distributed widely in the natural world.[222-227] The reaction proceeds by an initial fast reaction between the amine and **1** to give an acyl ylide which subsequently reacts with the aldehyde to produce α,β-unsaturated amides. We wished to extend this synthetic method to other α,β-unsaturated amides which have not been developed using this efficient three component reaction.

Compound **265** was synthesised in 45% yield from **1**, 2-phenylethylamine and piperonal.[228] A congener of **265** lacking acetalisation of the diol moiety was isolated from *annona cherimola Mill,*[229,230] and was found to inhibit arachidonate 5-lipoxygenase and PG synthetase.[231]



263 **264** **265**

When this reaction was however extended to other α,β-unsaturated amides which would have led to interesting natural products, we failed to isolate the expected products. Instead complicated mixtures were obtained.



266 **267** **268**

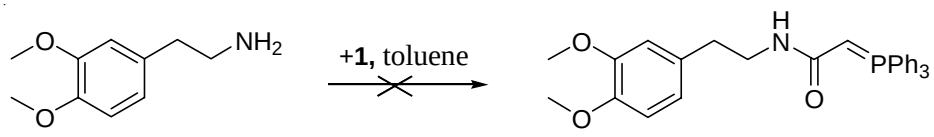
$R^1 = OCH_2O$, $R^2 = OCH_2O$

$R^1 = OCH_3$, $R_2 = OCH_2O$

$R^1 = OCH_3$, $R_2 = OCH_3$

R^1 OCH_2O, $R^2 = OCH_3$

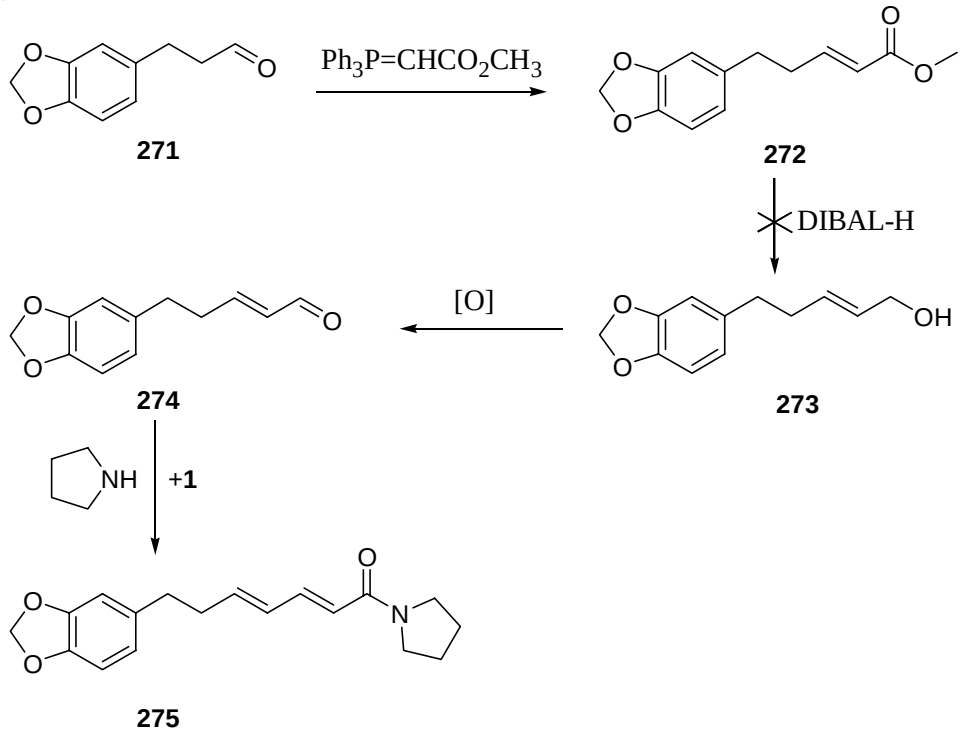
Reaction failure was found to originate during the first reaction step, addition of **1** to the primary amine. This was discovered by heating the primary amines with **1** in solutions of toluene to temperatures ranging from room temperature to 160°C (sealed glass tube). In all of the above cases the acyl ylides of type **270** could not be recovered.



269 **270**

The common feature of each of these amines is that they all contain electron donating groups on the benzene ring. Previous examples made use of simple alkyl amines only.[115] It is possible that the initial deprotonation of the amine is unfavourable because the electron-donating effect raises the pKa values of these amines, so that **1** cannot deprotonate the amine.

We also attempted to synthesise "Piper amalago"[232] **275** starting from 3-(1,3-benzodioxol-5-yl)propanal **271**. The use of DIBAL-H as a reducing agent for **272** failed. A complicated mixture was obtained, even when the reaction was performed at -78°C, of both the unsaturated product and the undesired saturated product. This mixture could not be separated by normal column chromatography or by distillation.



271 **272** **273** **274** **275**

3.0 Experimental section

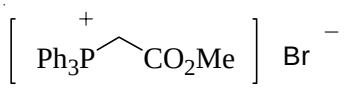
3.1 General

Melting points were recorded using a Gallenkamp or a Wagner & Munz apparatus and are uncorrected. IR spectra were recorded on a Bruker FT-IR Vector 22, a Perkin-Elmer Model 983G instrument coupled to a Perkin-Elmer 3700 Data Station and a Perkin-Elmer 1605 FT-IR as either postassium bromide (KBr) disks or films (film). Nuclear magnetic resonance (NMR) spectra were recorded under conditions as indicated using Bruker DPX 300, DRX 500 and Jeol JMM EX 400 spectrometers. Chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane (internal, ^{1}H- and ^{13}C-NMR) or H_3PO_4 (85%, external, ^{31}P-NMR) and coupling constants (J) are recorded in Hz. Mass spectra were recorded using a Double Focusing Triple Sector VG Auto Spec (EI) and a Double Focusing Finnigan MAT 95 (70 eV) with inversed Nier-Johnson geometries and combined EI/CI Ion spring. GC-MS were recorded on the Finnigan MAT 95 coupled with a Hewlett Packard 5890 Series II machine using a fused silica column DB-5 from J&W Scientific (Mainz-Kastel). Microanalyses were obtained using a Perkin-Elmer 2400 CHN and a Heraeus C-H-N Mikromonar elemental analyser. Analytical GC were recorded using a United Technologies Packard Model 438S with a fused silica column DB-5 (J&W Scientific, Mainz-Kastel) (column length 30m, diameter 0.32 mm, injector temperature 270°C, detector temperature 290°C, start temperature 80°C raising 3°C per minute until 280°C is reached) spectra were recorded using a Shimadzu C-R3A integrator. Microwave reactions were performed using a CEM Discover Microwave connected to a IBM PC. Analytical TLC was carried out on Merck Kieselgel 60 254 plates. Column chromatography was performed using Merck Kieselgel 60 (230 - 400 mesh). Visualisation of analytical TLC was performed using a UV-lamp, stained with iodine absorbed on silica gel or stained with a developing solution of conc. H_2SO_4 (6 ml), $Ce(SO_4)_2$ (1.0 g) and $12MoO_3.H_3PO_4$ (2.5 g) in water (94 ml). Dry solvents were obtained by standard procedures[233] and were stored under a nitrogen atmosphere. Ethyl acetate was dried over anhydrous $MgSO_4$ for 4h followed by either distillation or filtration of the solution under a nitrogen atmosphere.

3.2 Synthesis of keteneylidenetriphenylphosphorane 1[234-236]

Carbomethoxymethyl-triphenylphosphonium bromide[14]

To a solution of triphenylphosphane (262 g, 1.0 mole) in toluene (1500 ml), methyl bromoacetate (152 g, 1.0 mole) was added dropwise over a period of 30 min and after complete addition the reaction mixture was stirred for an additional 24 hr at room temperature. The white precipitate was collected on a Buchner funnel, washed with toluene (500 ml) and then with diethyl ether (1000 ml). The remaining solid was dried under reduced pressure yielding carbomethoxymethyl-triphenylphosphonium bromide **11a** (404 g, 0.97 mole, 97 %) as a white solid, mp 162 °C (lit.: mp 163 °C[14]).



IR (KBr); ν(cm^{-1}) = 3053 (w), 2794 (w), 2729 (w), 1721 (s), 1439 (m), 1317 (s), 1197 (s), 1109 (s), 996 (m), 890 (m), 876 (s), 747 (s), 727 (m).

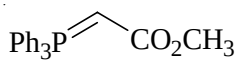
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 3.59 (s, 3H, OCH_3), 5.56 (d, $^{2}J_{PH}$ = 13.43 Hz, 2H, Ph_3P^{+}-CH_2), 7.67 - 7.92 (m, 15H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 32.92 (d, $^1J_{PC}$ = 58.09 Hz, P-CH_2), 53.39 (CH_3, OCH_3), 117.90 (d, $^1J_{PC}$ = 83.67 Hz, C-*ipso*, P-phenyl), 130.32 (d, $^3J_{PC}$ = 12.93 Hz, CH-*meta*, P-phenyl), 133.93 (d, $^2J_{PC}$ = 10.79 Hz, CH-*ortho*, P-phenyl), 135.20 (CH, CH-*para*, P-phenyl), 165.15 (C^q, *C*O_2CH_3)

^{31}P-NMR (161.7 MHz, H_3PO_{4ext}, $CDCl_3$); δ(ppm) = 21.8

Carbomethoxymethylene-triphenylphosphorane 11[14]

Carbomethoxymethyl-triphenylphosphonium bromide (208 g, 0.5 mole) was dissolved in water (3000 ml). The resulting solution was filtered to remove any insoluble impurities. The aqueous layer was then layered with hot toluene (1500 ml). Under vigorous stirring of this two phase system a dilute solution of NaOH (100 ml, 5M) was added dropwise over a period of 30 min. A heating basket should be employed to maintain a temperature of approximetly 60°C in the toluene layer. The pH of the aqueous layer was checked to ensure that the solution was slightly basic. The two layers were separated and the aqueous layer was further washed with two portions of toluene (500 ml). The combined organic layers were dried over magnesium sulphate and the toluene was removed by rotary evaporation to yield carbomethoxymethylene-triphenylphosphorane **11** (160 g, 0.48 mole, 95%) as a white solid, Molecular formula $C_{21}H_{19}O_2P$, mp 163°C (lit.: mp 163°C[14]).



IR (KBr); ν(cm^{-1}) = 3058 (w), 2956 (w), 2941 (w), 1616 (s), 1482 (m), 1434 (m), 1346 (s), 1180 (w), 1120 (s), 1101 (s), 922 (w), 883 (s), 746 (s), 710 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 2.92 (s, broad, 1H, Ph_3P=C*H*), 3.53 (s, 3H, OCH_3), 7.42 - 7.67 (m, 15H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 29.60 (d,$^1J_{PC}$ = 129.30 Hz, P=CH), 49.93 (CH_3, OCH_3), 127.69 (d, $^1J_{PC}$ = 91.88 Hz, C-*ipso*, P-phenyl), 128.75 (d, $^3J_{PC}$= 12.14 Hz, CH-*meta*, P-phenyl), 131.94 (CH, CH-*para*, P-phenyl), 132.97 (d, $^2J_{PC}$ = 10.10 Hz, CH-*ortho*, P-phenyl), 171.86 (d, $^2J_{PC}$ = 14.78 Hz, C^q, CO_2CH_3).

^{31}P-NMR (161.7 MHz, H_3PO_4ext, $CDCl_3$); δ(ppm) = 17.69 and 19.60 (rotamers).

MS (EI, 70 eV): m/z = 334 (21) [M^+], 333 (100) [M^+-H], 304 (17), 303 (25) [M^+-OCH_3], 301 (9) [M^+-H_2O-CH_3], 275 (37) [*303* - CO], 261 (9) [*275* - CH_2], 185 (40) [$(C_6H_5)_2P^+$], 183 (34), 165 (14), 108 (4) [$C_6H_5P^+$], 107 (5), 77 (16) [Ph^+], 51 (8).

Keteneylidenetriphenylphosphorane 1[234-236] (new procedure)

To a suspension of sodium amide (19.5 g, 0.5 mole) in dry toluene (1200 ml) was added under a nitrogen atmosphere bis(trimethylsilyl)amine (HMDS, 80.5 g, ~100 ml, 0.5 mole). The solution was heated to 70°C and after 5h the sodium amide had dissolved to give a clear solution. The solution was cooled to room temperature and carbomethoxymethylenetriphenylphosphorane **11** (167 g, 0.5 mole) was slowly added. The solution turned bright yellow when **11** was added and the solution was immediately reheated to 70°C and maintained for a further 24 - 48h. During this time nitrogen was bubbled regularly through the apparatus to remove generated ammonia. Once ammonia production has ceased the solution was cooled to ~40°C and transfered to a Schlenck-type filter funnel (fritt) to remove the sodium methoxide byproduct. During filtration the solution was maintained at a temperature between 50 - 60°C to prevent premature crystallisation. To

facilitate fast filtration a slight underpressure was generated in the receiving flask while a slight overpressure of nitrogen was maintained in the top part of the fritt. After filtration the sodium methoxide was washed with a further portion of hot dry toluene (500 ml). After filtration the toluene solution can be transfered under inert atmosphere to a rotary evaporator, toluene was removed to the point where crystals began to form on the flask surface. Evaporation of toluene was stopped immediately at this stage and the sealed flask was placed in a freezer at -10°C for 24 - 48h. The yellow crystals were collected in a fritt, washed twice with dry diethyl ether (500 ml) and dried under reduced pressure to yield keteneylidenetriphenylphosphorane **1** (107g, 0.35 mole, 70%) as a bright yellow crystalline solid, molecular formula $C_{20}H_{15}O_2P$, mp 173°C (lit.:mp 173°C[234]).

$Ph_3P{=}C{=}C{=}O$

IR (KBr); ν(cm^{-1}) = 3063 (w), 2865 (w), 2089 (s), 1481 (w), 1434 (m), 1307 (w), 1108 (m), 996 (w), 741 (m), 715 (m), 689 (m).

^{1}H-NMR (500 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 7.17 - 7.74 (m, 15H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = -10.58 (d, $^1J_{PC}$ = 186.97 Hz, C^q, P=C), 128.74 (d, $^3J_{PC}$ = 12.90 Hz, CH-*meta*, P-phenyl), 129.40 (d, $^1J_{PC}$ = 98.96 Hz, CH-*ipso*, P-phenyl), 132.09 (CH, CH-*para*, P-phenyl), 132.10 (d, $^2J_{PC}$ = 10.71 Hz, CH-*ortho*, P-phenyl), 145.56 (d, $^2J_{PC}$ = 43.02 Hz, C^q, C=O).

^{31}P-NMR (161.7 MHz, $H_3PO_{4\ ext}$, $CDCl_3$); δ (ppm) = 5.97.

MS (EI, 70 eV): m/z = 302 (51) [M+], 301 (100), 183 (22), 165 (24), 152 (7), 107 (7), 77 (18), 51 (30).

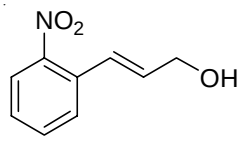
3.3 Synthesis of 3, 5-dispirodihydrofuran-2,4-diones and tetronic acids

3.3.1 Synthesis of functionalised cinnamyl alcohols

General Experimental Procedure: The cinnamic acid (0.05 mole) was weighed into a clean round bottom flask along with p-toluenesulphonic acid (5 mmole, 0.86 g). Chloroform (100 ml) and methanol (50 ml) were added to the flask and a Dean-Stark apparatus (water seperator) was attached. The solution was refluxed strongly for 6h after which time the Dean Stark was removed and the solvent was evaporated on a rotary evaporator. Column chromatography of the residue gave a pure methyl cinnamyl ester (yields are normally 90 - 100%). The ester (0.04 mole) was weighed into a three-necked round bottomed flask attached with a reflux condenser connected to a mercury bubbler, a nitrogen inlet and a dropping funnel. The flask was evacuated and filled with nitrogen gas. Dry chloroform (200 ml) was added and the resulting solution was cooled to 0°C. DIBAL-H[244] (0.08 mole, 80 ml) was slowly dropped into the solution over a period of 1h. After this time the solution was allowed to warm to room temperature were it was stirred overnight to ensure complete reaction. After complete reaction a saturated aqueous solution of ammonium chloride (~10 ml) was slowly dropped into the solution. The resulting precipitate was allowed to stand for several hours after which time it was filtered on a Buchner funnel. The dried precipitate was extracted on a Soxhlet extractor using DCM as a solvent. The DCM and chloroform filtrates were combined and the organic solvent was removed by rotary evaporation. The resulting residue was purified by column chromatography (silica gel; solvent as indicated).

(2*E*)-3-(2-Nitrophenyl)prop-2-en-1-ol 130e

Brown solid (4.94 g, 27.6 mmol, 69%) from methyl (2*E*)-3-(2-nitrophenyl)acrylate (8.28 g, 0.04 mole) dissolved in dry chloroform (200 ml), to which was added DIBAL-H[244] (80 ml, 0.08 mole). The solution was stirred for 16h at rt. Molecular formula $C_9H_9NO_3$. M.p. 59°C (lit.: mp 60-61 °C[237].



IR (KBr); ν(cm^{-1}) = 3501 (s) [ν (OH)], 3096 (w), 2867 (w), 1653 (m), 1597 (s) [ν (Ar)], 1505 (s) [ν (NO_2)], 1456 (m), 1335 (s) [ν (NO_2)], 1230 (w), 1183 (w), 1101 (s) [ν (C-O)], 971 (m), 858 (m), 735 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 2.19 (s, 1H, OH), 4.34 (dd, $^3J_{HH}$ = 5.30 Hz, $^4J_{HH}$ = 1.71 Hz, 2H, CH_2O), 6.31 (dt, $^3J_{HH}$ = 15.74, 5.30 Hz, 1H, CH=C*H*), 7.04 (dt, $^3J_{HH}$ = 15.74 Hz, $^4J_{HH}$ = 1.71 Hz, 1H, C*H*=CH), 7.24 - 7.38 and 7.52 - 7.56 (m, 3H, Ar), 7.87 (dd, $^3J_{HH}$ = 8.18 Hz, $^4J_{HH}$ = 0.94 Hz, 1H, Ar-6).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 63.2 (CH_2, OCH_2), 124.4 (CH, CH=C*H*), 125.7, 128.1, 128.7 (CH, Ph), 132.5 (C^q, Ar-*ipso*), 133.0 (CH, C*H*=CH), 134.2 (CH, Ph), 147.5 (C^q, Ar-NO_2).

MS (EI, 70 eV): m/z = 179 (2) [M^+], 162 (5) [M^+-H_2O], 132 (39) [M^+-HNO_3^+], 104 (61), 92 (57), 77 (100) [Ar], 65 (12), 55 (7).

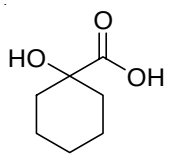
*NB: Experimental data for **130e** has been included as an example. Satisfactory data were obtained for the other cinnamyl alcohols, however experimental data has not been included as these compounds are well known with structural data previously reported.*[245-247]

3.3.2 Synthesis of α-hydroxy-carboxylic acids

General experimental procedure for the synthesis of α-hydroxy-carboxylic acids 133:[130]
Sodium metabisulphite (11.6 g, 61.0 mmol) was dissolved in distilled water (50 ml). This solution was dropped slowly over a period of 30 min. to a stirred solution of ketone **131** (0.1 mol) and potassium cyanide (7.81 g, 0.12 mol) in distilled water (50 ml). After complete addition of all components the reaction mixture was stirred for an additional 2h at room temperature. The solution was extracted with diethyl ether and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave the crude cyanohydrins **132**.

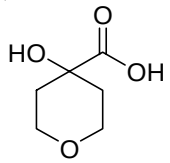
The carbonitrile was then refluxed with glacial acetic acid (200 ml) and concentrated HCl (200 ml) for 3h. After which time, the solution was cooled to room temperature and concentrated in vacuo. The residue (**133a**: white solid; **133b**: brown oil) was dissolved in chloroform, washed twice with small portions of water and dried over $MgSO_4$. This was followed by filtration of the drying agent and evaporation of the chloroform. The crude **133a** was recrystallised from hexane. The crude **133b** was used as such since recrystallisation was not possible. Distillation was not attempted as it was thought that the high temperatures neccessary may lead to decomposition. Column chromatography was not attempted as **133b** is very polar and have been difficult to remove from the column.

1-Hydroxy-cycloheptanecarboxylic acid 133a[130].
White needles (10.48 g, 74 mmol, 74 %) from cyclohexanone **131a** (9.81 g 0.1 mole), sodium metabisulphite (11.6 g, 61.0 mmol), potassium cyanide (7.81 g, 0.12 mole) dissolved in water (100 ml). Molecular formula $C_7H_{12}O_3$. Mp 106 °C (lit.: mp 106 - 107 °C [239]).



IR (KBr); ν(cm^{-1}) = 3415 (s, broad) [ν (OH)], 2852 (s) [ν (COOH)], 2629 (m), 1732 (s), 1453 (m), 1320 (m), 1278 (m), 1235 (s), 1150 (s), 1039 (m), 991 (s), 745 (s).
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.31 - 1.99 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 6.41 (s, broad, 2H, O*H*, CO_2*H*).
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 20.6 (CH_2; C-3, C-5), 24.6 (CH_2; C-4), 33.8 (CH_2; C-2, C-6), 73.2 (C^q; C-1), 177.3 (C^q; CO_2*H*).
MS (EI, 70 eV): m/z = 145 (7) [MH^+], 127 (15) [MH^+ - H_2O], 117 (7) [MH^+ - CO], 109 (11), 99 (100) [M^+ - CO_2H], 81 (95) [127 - $CH_2O_2^+$], 68 (27), 55 (93), 43 (95).
$C_7H_{12}O_3$ (144.17): Calculated C = 58.32%, H = 8.39%; found C = 58.27%, H = 8.40%.

4-hydroxytetrahydro-2*H*-pyran-4-carboxylic acid 133b.
Crude product could not be purified and was isolated as a brown oil (4.2 g, 28 mmol, 55%) from tetrahydro-4*H*-pyran-4-one **131b** (5.20 g, 52 mmol), potassium cyanide (4.06 g, 62 mmol) and sodium metabisulphite (5.93 g, 31 mmol). Molecular formula $C_6H_{10}O_3$.



IR (film, KBr); ν(cm^{-1}) = 3389 (br) [ν (OH)], 2963 (s), 2872 (s), 2635 (m), 1733 (s), 1436 (m), 1387 (m), 1243 (s), 1149 (s), 1097 (s), 1064 (s), 1018 (s), 932 (m), 840 (m), 748 (m).
^{1}H-NMR (500 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.51 - 1.58 and 2.12 - 2.19 (m, 4H, 2-H and 6-H), 3.78 - 3.88 (m, 4H, 3-H and 5-H), 5.28 (s, 1H, OH).
^{13}C-JMOD NMR (125 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 34.3, 34.4 (CH_2, C-2 and C-6), 63.1, 63.2 (CH_2, C-3 and C-5), 70.8 (C^q, C-1), 179.3 (C^q, CO_2).
MS (EI, 70 eV): m/z = 146 (2) [M^+], 128 (2) [M+-H_2O], 116 (3), 101 (100) [M+-COOH], 83 (19) [*101* - H_2O], 71 (54), 56 (9), 53 (22), 43 (13).

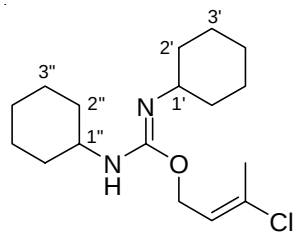
3.3.3 Synthesis of O-allyl-isoureas

General experimental procedure for the synthesis of O-Allyl-Isoureas: The respective alcohol **138** (10 mmol) was added to a mixture of copper(II)chloride (~1%) and N,N'-dicyclohexylcarbodiimide (DCC) **137** (2.06 g, 10 mmol). The resulting brown liquid quickly turned green and was stirred at room temperature until the reaction was complete. Completion of reaction was determined by IR by the disappearance of the diimide band (2100 cm^{-1}) and

from the appearance of the very strong isourea band (1660 cm^{-1}). Reaction times vary from 6-24h. Once the reaction was determined complete, hexane (30 ml) was added and the solution stirred for 15 min. The solution was then transferred to a short plug of neutral alumina, in order to remove the copper salt. The product was eluted with a further volume of 100 ml of hexane. The solvent was then evaporated on a rotary evaporator to give a pure product. Vacuum distillation was used in cases were the isourea was not pure at this stage.

O-[(2*E*)-3-Chlorobut-2-enyl]-*N,N*'-dicyclohexylimidocarbamate 139a.

Clear oil (3.84 g, 12.23 mmol, 92%) from 3-chloro-2-but-1-ol (1.35 g, 12.74 mmol), DCC **137** (2.61 g, 12.67 mmol) and copper(I)chloride (catalytic amount). The mixture was stirred for 12h and then filtered over a short plug of neutral alumina and washed with hexane. The crude product was then Kugelrohr distilled. Molecular formula $C_{17}H_{29}ClN_2O$. Bp 152 °C at 1bar.



IR (film, KBr); ν(cm^{-1}) = 3440 (w) and 3324 (w) [ν (NH)], 2928 (s), 2853 (s), 1666 (s), 1536 (w), 1448 (m), 1384 (s), 1321 (s), 1242 (m), 1189 (m), 1126 (s), 1042 (s), 928 (w), 890 (s), 83 (w), 799 (w), 711 (w).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.88 - 1.89 (m, 20H, 2'-H, 2''-H, 3'-H, 3''-H, 4'-H, 4''-H, CH_2), 2.12 (s, 3H, CH_3), 2.78 - 2.80 (m, 1H, 1''-H), 3.35 - 3.48 (m, 2H, 1'-H, NH), 4.69 (d, $^{3}J_{HH}$ = 6.09 Hz, 2H, OCH_2), 5.69 - 5.74 (m, 1H, CH=C^q).

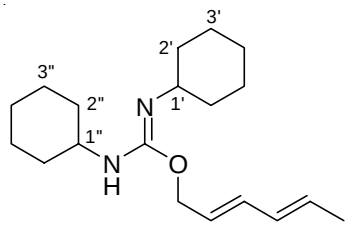
^{13}C-NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 24.8, 25.0 (CH_2, C-3', C-3''), 25.7 (CH_2, C-4' or C-4''), 26.0 (CH_3, C^qCH_3), 26.3 (CH_2, C-4' or C-4''), 34.5 (CH_2, C-2' and C-2''), 50.4 (CH, C-1''), 54.7 (CH, CH, C-1'), 62.0 (CH_2, OCH_2), 122.6 (CH, CH=C^q), 132.4 (C^q, C-Cl), 150.80 (C^q, NH-C=N).

MS (EI, 70 eV): m/z = 314 (7) [M^+, ^{37}Cl], 312 (23) [M^+, ^{35}Cl], 278 (4), 2977 (27) [M^+-Cl], 224 (6) [M^+-C_4H_5Cl], 167 (100), 143 (4), 124 (3), 98 (63) [$C_6H_{10}NH_2^+$], 89 (38), 83 (23) [$C_6H_{11}^+$], 70 (12), 56 (49), 53 (36), 43 (24), 28 (42).

Accurate Mass:- Calculated Mass = 312.196842; found = 312.196838

O-[(**2*E*,4*E*)-Hexa-2,4-dienyl]-*N,N*'-dicyclohexylisourea 139b.**

Colourless oil (20.18 g, 66.4 mmol, 87%) from DCC **137** (15.70 g, 76.5 mmol) and (2*E*,4*E*)-hexa-2,4-dien-1-ol (7.50g, 76.5 mmol). Molecular formula $C_{19}H_{32}N_2O$.



IR (film, KBr); ν(cm^{-1}) = 3439 (m) and 3327 (m) [ν (NH)], 2927 (s), 2849 (s), 1664 (s), 1448 (s), 1384 (s), 1320 (s), 1244 (m), 1123 (s), 1037 (s), 988 (s), 927 (w), 890 (m).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.83 - 1.79 (m, 25H, 2'-H, 2''-H, 3'-H, 3''-H, 4'-H, 4''-H, CH_3), 2.77 - 2.79 (m, 1H, 1'-H), 3.62 - 3.69 (m, 1H, 1''-H), 3.94 (s, broad, 1H, NH), 4.26 (d, $^3J_{HH}$ = 4.87 Hz, 2H, OCH_2), 5.06 - 5.21 (m, 1H, 5-H), 5.41 - 6.29 (m, 3H, 2-H, 3-H, 4-H).

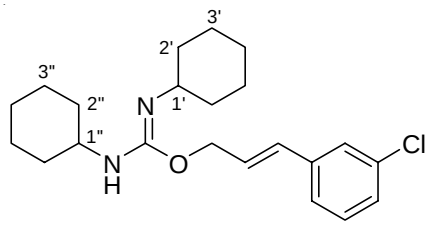
^{13}C-JMOD NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 14.1 (CH_3, C-6), 24.6, 24.7 (CH_2, C-3', C-3''), 25.6, 26.0 (CH_2, C-4', C-4''), 33.6, 33.7 (CH_2, C-2', C-2''), 49.0 (CH; C-1''), 55.4 (CH, C-1'), 70.3 (CH_2, OCH_2), 128.1, 130.3, 131.7, 137.8 (CH, CH-*alkene*), 156.6 (C^q, N=*C*NH).

MS (EI, 70 eV): m/z = 305 (9) [M^++1], 304 (79) [M^+], 289 (2) [M^+-CH_3], 275 (1) [M+-C_2H_5], 261 (3) [M^+-C_3H_7], 249 (11) [M^+-C_4H_7], 223 (8) [M^+-C_6H_9], 207 (2) [M^+-$C_6H_9O^+$] 206 (1) [M^+-C_6H_9OH], 179 (22), 164 (16), 150 (6), 136 (17), 125 (14), 110 (3), 98 (48) [$C_6H_{11}NH^+$], 96 (98) [$C_6H_{10}N^+$], 83 (17) [$C_6H_{11}^+$], 81 (100), 55 (52), 41 (29).

$C_{19}H_{32}N_2O$ (304.47): Calculated C = 74.95%, H = 10.59%, N = 9.20%; found C = 74.86%, H = 10.64%, N = 9.16%.

O-(E-3-Metachlorophenyl-allyl)-N,N'-dicyclohexylisourea 139c.

Colourless oil (650 mg, 1.74 mmol, 73%) from DCC **137** (490 mg, 2.38 mmol), (2*E*)-3-(3-chlorophenyl)prop-2-en-1-ol **130b** (400 mg, 2.38 mmol) and copper (I) chloride (catalytic amount). Green mixture was stirred for 36h after which the DCC signal at ~2100 cm^{-1} (IR spectrum) had vanished. Filtration of the mixture over a short plug of neutral alumina, followed by repeated washing with hexane gave a pure product. Molecular formula $C_{22}H_{31}ClN_2O$. R_f 0.28 (diethyl ether: hexane, 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3441 (m) [ν (NH)], 2929 (s), 2853 (s), 1668 (s), 1594 (m), 1566 (m), 1450 (s), 1387 (s), 1319 (s), 1243 (m), 1127 (s), 1045 (s), 962 (s) [δ (CH=CH)-*trans*], 890 (m), 739 (s) [ν (C-Cl)].

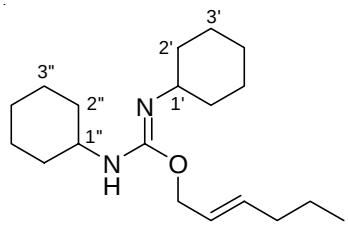
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.06 - 1.94 (m, 20H, 2'-H, 2''-H, 3'-H, 3''-H, 4-H, 4''-H, 5'-H, 5''-H, 6'-H, 6''-H), 2.72 - 2.84 (m, 1H, 1''-H), 3.38 - 3.52 (m, 2H, 1'-H, NH), 4.70 (dd, $^3J_{HH}$ = 5.63 Hz, $^4J_{HH}$ = 1.38 Hz, 2H, OCH_2), 6.34 (dt, $^3J_{HH}$ = 15.97, 5.63 Hz, 1H, C*H*=CH), 6.54 (dd, $^3J_{HH}$ = 15.97 Hz, $^4J_{HH}$ = 1.38 Hz, 1H, CH=C*H*), 7.15 - 7.24 (m, 3H, Ar), 7.35 (d, $^4J_{HH}$ = 1.50 Hz, 1H, C^qC*H*CCl).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 24.7, 25.0, 25.2, 25.4 (CH_2, C-3', C-3''), 25.7, 25.9 (CH_2, C-4', C-4''), 34.5 (CH_2, C-2', C-2''), 50.4 (d, $^1J_{CN}$ = 6.87 Hz, CH, C-1''), 54.8 (CH, C-1'), 65.0 (CH_2, OCH_2), 124.7 (CH, *C*H=CH), 126.3, 127.6, 129.5, 129.7, (CH, Ar), 130.1 (CH, CH=*C*H), 134.5 (C^q, Ar-Cl), 138.9 (C^q, Ar-*ipso*), 150.8 (C^q, N=C(O)-N).

MS (EI, 70 eV): m/z = 376 (3) [M^+1, ^{37}Cl], 375 (2) [M^++1, ^{35}Cl], 374 (11) [M^+, ^{35}Cl], 224 (4) [M^+-C_9H_8Cl], 223 (3), 222 (4), 167 (100) [$C_{12}H_{23}^+$], 153 (12) [Cl-$C_6H_4C_3H_4^+$, ^{37}Cl], 151 (26) [Cl-$C_6H_4C_3H_4^+$, ^{35}Cl], 116 (25) [*153* - ^{37}Cl, *151* - ^{35}Cl], 115 (39) [*153* - H^{37}Cl, *151* - H^{35}Cl], 98 (79) [$C_6H_{11}NH_2^+$], 83 (27) [$C_6H_{11}^+$], 56 (37), 55 (71), 43 (32), 41 (83).

O-[(2E)-Hex-2-enyl]-N,N'-dicyclohexylisourea 139d.

Colourless oil (1.47 g, 4.8 mmol, 96%) from trans-2-hexen-1-ol (0.50 g, 5 mmol), DCC **137** (1.03 g, 5 mmol) and copper (I) chloride (catalytic amount). Reaction mixture was stirred for 6h and then filtered over a short plug of neutral alumina. Molecular formula $C_{19}H_{34}N_2O$.



IR (film, KBr); ν(cm^{-1}) = 3443 (w) and 3324 (w) [ν (NH)], 2928 (s), 2853 (s), 1664 (s), 1449 (m), 1389 (m), 1319 (s) 1259 (w), 1242 (m), 1153 (w), 1125 (m), 1094 (w), 1043 (m), 969 (m), 890 (m).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.90 (t, $^3J_{HH}$ = 7.25 Hz, 3H, CH_3), 1.05 - 2.18 (m, 24H, 2'-H, 2''-H, 3'-H, 3''-H, 4'-H, 4''-H, 4-H, 5-H, CH_2), 2.76 (m, 1H, 1''-H), 3.40 (m, 1H, 1'-H), 3.48 (br., 1H, NH), 4.48 (d, $^3J_{HH}$ = 5.04 Hz, 2H, OCH_2), 5.64 (m, 2H, CH=CH).

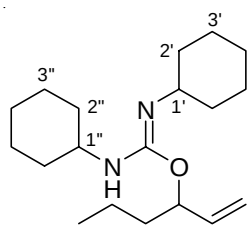
^{13}C-NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 13.7 (CH_3, C-6), 22.3 (CH_2, C-5), 25.3, 25.8 (CH_2, C-3', C-3''), 25.9, 26.0 (CH_2, C-2', C-2''), 30.9 (CH_2, C-4), 34.4, 34.6 (CH_2, C-4', C-4''), 50.3 (CH, C-1''), 54.9 (CH, C-1'), 65.7 (CH_2, OCH_2), 125.8 (CH, C-2), 133.7 (CH, C-3), 151.3 (C^q, N=C-N).

MS (EI, 70 eV): m/z = 307 (8) [M^++1], 306 (13) [M^+], 278 (7), 277 (31) [M^+-C_2H_4], 225 (10), 224 (16), 223 (11) [M^+-$C_6H_{11}^+$], 222 (7), 195 (17) [M^+-$C_7H_{11}O$], 182 (28), 181 (13), 168 (7), 167 (53), 143 (16), 138 (19), 125 (7), 110 (5), 98 (100), 83 (41), 70 (13), 67 (16), 55 (95), 41 (43).

Accurate Mass:- Calculated Mass = 306.267114 Found = 306.265594

O-(2-Hex-1-ene)-N,N'-dicyclohexylisourea 139e.

Colourless oil (272 mg, 0.89 mmol, 89%) from DCC **137** (2.06 g, 10 mmol), 1-hexen-3-ol (1.0 g, 10 mmol) and copper (I) chloride (catalytic amount). Mixture was stirred for 16h at 40°C and filtered over a small plug of neutral alumina followed by removal of the hexane. Molecular formula $C_{19}H_{34}N_2O$. Bp 184°C at 1x10^{-2} Torr.



IR (film, KBr); ν(cm^{-1}) = 3439 (w) and 3363 (w) [ν (NH)], 3083 (w), 2928 (s), 2854 (s), 1668 (s), 1509 (m), 1450 (m), 1363 (m), 1341 (m), 1309 (m), 1258 (w), 1242 (m), 1190 (w), 1153 (w), 1125 (w), 1027 (m), 988 (w), 921 (m), 891 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.89 - 0.96 (m, 3H, CH_3), 1.05 - 1.94 (m, 24H, 4-CH_2, 5-CH_2, 2'-H, 2''-H, 3'-H, 3''-H, 4'-H, 4''-H, 5'-H, 5''-H, 6'-H, 6''-H), 2.73 - 2.85 (m, 1H, 1''-H), 3.39 - 3.45 (m, 1H, 1'-H), 3.62 (d, $^{3}J_{HH}$ = 3.95 Hz, 1H, NH), 5.07 (dt, $^{3}J_{HH}$ = 10.58 Hz, $^{2}J_{HH}$ = 1.56 Hz, 1H, CH=CH*H-cis*), 5.19 (dt, $^{3}J_{HH}$ = 17.30 Hz, $^{2}J_{HH}$ =1.56 Hz, 1H, CH=C*H*H-*trans*), 5.36 - 5.38 (m, 1H, OCH), 5.81 (ddd, $^{3}J_{HH}$ = 17.30, 10.58, 5.74 Hz, 1H, C*H*=CH_2).

^{13}C-NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 14.1 (CH_3, C-6), 18.2 (CH_2, C-5), 24.8, 25.1 (CH_2, C-3', C-3''), 25.9, 26.1 (CH_2, C-2', C-2''), 34.3, 34.4 (CH_2, C-4', C-4''), 44.1 (CH_2, C-4), 50.2 (CH, C-1'), 54.6 (CH, C-1''), 73.2 (CH, OCH), 114.7 (CH, *C*H=CH_2), 138.4 (CH_2, CH=*C*H_2), 150.1 (C^{q}, N=C-N).

MS (EI, 70 eV): m/z = 306 (7) [M^+], 277 (5) [M^+-C_2H_5], 263 (2) [M^+-C_3H_7], 225 (16), 224 (14), 223 (19) [M^+-C_6H_{11}], 209 (47), 181 (8), 152 (10), 143 (18), 138 (15), 125 (9), 98 (100) [$C_6H_{10}NH_2^+$], 83 (70) [$C_6H_{11}^+$], 70 (19), 56 (52), 55 (100), 43 (33), 41 (63), 28 (20).

$C_{19}H_{34}N_2O$ (306.49): Calculated C = 74.46%, H = 11.18%, N = 9.14%; found C = 73.81%, H = 11.04%, N = 9.36%.

3.3.4 Synthesis of α-hydroxy-esters

General experimental procedure for the synthesis of α-hydroxy-esters:
Route A: To the respective O-allyl-N,N'-dicyclohexylisourea **139** (10.0 mmol) was added dry THF (75 ml) and the α-hydroxy acid **133** (10.0 mmol). The solution was stirred under reflux for 16h after which time the solution was cooled and the urea precipitate was filtered. The THF solvent was removed by rotary evaporation and the residue was purified by column chromatography (silica gel; solvent as indicated).

Route B: The respective alcohol (10 mmol) was added under a nitrogen atmosphere to a mixture of copper(I)chloride (~1%) and N,N'-dicyclohexylcarbodiimide **137** (2.06 g, 10 mmol). The resulting brown liquid quickly turned green and was stirred at room temperature until the reaction was complete. Completion of reaction was determined by the disappearance of the diimide band (2100 cm^{-1}) and from the appearance of the very strong isourea band (1660 cm^{-1}). Reaction times varied from 6-24h. To this solution was added dry THF (75 ml) and the α-hydroxy acid **133**, the solution was stirred under reflux for 16h after which time the solution was cooled and the urea precipitate was filtered. The THF solvent was removed by rotary evaporation and the residue was purified by column chromatography (silica gel; solvent as indicated).

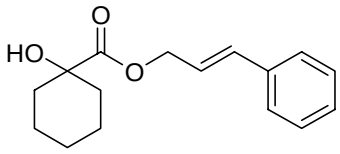
Route C: The respective alcohol (12.0 mmol), α-hydroxycyclohexane carboxylic acid **133a** (12.0 mmol) and p-toluenesulphonic acid (1.20 mmol) were weighed into a 250 ml round bottomed flask. Dry chloroform (150 ml) was added to the flask and a Dean-Stark apparatus was fitted to the flask. The solution was refluxed for approximately 16h after which time the solvent was removed by rotary evaporation. The residue was then purified by column chromatography to give a pure product.

Route D: The respective alcohol (14.5 mmol), α-hydroxyacid (21.75 mmol) and triphenylphosphine (5.68 g, 21.75 mmol) were weighed into a nitrogen filled round bottomed flask. To the flask was added dry THF (50 ml) under an inert atmosphere of nitrogen. After all the components had dissolved, the solution was then cooled in an ice-salt bath to -10°C. To this solution was added DIAD (4.2 ml, 21.75 mmol) over a period of 10 min. The solution was left to stir for 6h after which time DCM (50 ml) was added and the solution was extracted with sodium hydrogen carbonate solution and washed twice with water. The solution was dried with magnesium sulphate and the solvent removed by rotary evaporation. Column chromatography of the residue gave a pure product.

(E)-(3-Phenyl-allyl)-1-hydroxy-cyclohexane-1-carboxylate 23a.

Route A: Prepared in 72% yield from the corresponding isourea and in 57% yield from the corresponding alcohol.[115]

Route B: White solid (16.46 g, 63.3 mmol, 74.7%), from a mixture of cinnamyl alcohol (10.0 g, 84.75 mmol), DCC (17.45 g, 84.75 mmol) and copper (I) chloride (82 mg, 0.85 mmol) stirred for 16h under an inert atmosphere. To the dark green solution was added dry THF (250 ml) followed by α-hydroxy-cyclohexanecarboxylic acid **133a** (12.20 g, 84.75 mmol). The solution was refluxed under nitrogen for 24h. Molecular formula $C_{16}H_{20}O_3$. R_f 0.61 (diethyl ether: hexane, 1:1, v:v), mp 44°C (lit.: 43°C[115]).



IR (KBr); ν(cm^{-1}) = 3494 (br) [ν (OH)], 3054 (w), 2941 (s), 2856 (m), 1718 (s) [ν (C=O)], 1578 (s), 1495 (m), 1447 (m), 1297 (m), 1276 (m), 1240 (s), 1177 (m), 1160 (m), 1136 (m), 1057 (m), 745 (m), 690 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.30 - 1.86 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 2.88 (s, 1H, OH), 4.81 (dd, $^3J_{HH}$ = 6.48 Hz, $^4J_{HH}$ = 1.24 Hz, 2H, OCH_2), 6.29 (dt, $^3J_{HH}$ = 15.90, 6.48 Hz, 1H, C*H*=CH), 6.65 (dd, $^3J_{HH}$ = 15.90 Hz, $^4J_{HH}$ = 1.24 Hz, 1H, CH=CH), 7.23 - 7.42 (m, 5H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 22.1 (CH_2, C-3 and C-5), 25.3 (CH_2, C-4), 37.5 (CH_2, C-2 and C-6), 66.1 (CH_2, OCH_2), 73.7 (C^q, C-1), 122.5 (CH, *C*H=CH), 128.2, 129.1, 129.1 (CH, Ph), 135.0 (CH, CH=*C*H), 136.1 (C^q, Ph-*ipso*), 177.1 (C^q, CO_2).

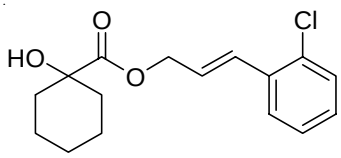
MS (EI, 70 eV): m/z = 260 (35) [M^+], 242 (17) [M^+-H_2O], 134 (22) [$C_9H_{10}O^+$], 117 (100) [$C_9H_9^+$], 115 (80), 110 (81) [M^+-$C_9H_{10}O_2$, *242* - $C_9H_8O^+$], 91 (64), 81 (92) [$C_6H_9^+$], 65 (14), 55 (58), 41 (38).

$C_{16}H_{20}O_3$ (260.33): Calculated C = 73.82%, H = 7.74%; found C = 73.88%, H = 7.77%.

(2*E*)-3-(2-Chlorophenyl)prop-2-enyl 1-hydroxycyclohexanecarboxylate 23b.

Route B: Colourless oil (3.19 g, 10.85 mmol, 98%) from 2-chloro-cinnamyl alcohol **130a** (2.0 g, 11.90 mmol) and DCC **137** (2.46 g, 11.9 mmol) stirred for 24 hrs, followed by addition of THF (60 ml) and α-hydroxycyclohexane carboxylic acid **133a** (1.71 g, 11.90 mmol) with additional heating under reflux for 16h. Filtration of the urea and column chromatography. Molecular

formula $C_{16}H_{19}ClO_3$.R_f 0.59 (diethyl ether: hexane 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3509 (m) [ν (OH)], 2935 (s), 2859 (m), 1729 (s), 1445 (m), 1267 (w), 1232 (m), 1154 (m), 1047 (m), 991 (s), 966 (m), 750 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.17 - 1.87 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.82 (s, 1H, OH), 4.84 (dd, $^3J_{HH}$ = 6.14 Hz, $^4J_{HH}$ = 1.42 Hz, 2H, OCH_2), 6.25 (dt, $^3J_{HH}$ = 15.90 Hz, 6.14 Hz, 1H, $CH_2C\mathit{H}$=CH), 7.04 (d, $^3J_{HH}$ = 15.90 Hz, 1H, CH=C*H*), 7.17 - 7.53 (m, 4H, Ar).

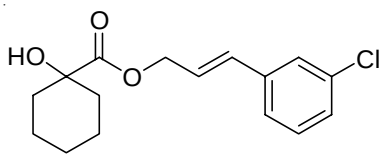
^{13}C-NMR-JMOD (500 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.2 (CH_2, C-3 and C-5), 25.2 (CH_2, C-4), 34.8 (CH_2, C-2 and C-6), 65.7 (CH_2, OCH_2), 73.7 (C^q, C-1), 125.4 (CH, $CH_2\mathit{C}$H=CH), 126.9 (CH, CH=*C*H), 129.2, 129.7, 130.1, 130.2 (CH, Ar), 132.1 (C^q, Ar-Cl), 134.2 (C^q, Ar-*ipso*), 177.0 (C^q, CO_2).

MS (EI, 70 eV): m/z = 296 (0.2) [M^+, ^{37}Cl], 294 (0.6) [M^+, ^{35}Cl], 278 (0.3) [M^+-H_2O, ^{37}Cl], 276 (1) [M^+-H_2O, ^{35}Cl], 251 (2), 170 (6), 151 (9), 114 (13), 113 (24), 99 (100) [$C_6H_{11}O^+$], 81 (78) [$C_6H_{11}O^+$ - H_2O], 67 (3), 55 (13), 41 (7).

(2*E*)-3-(3-Chlorophenyl)prop-2-enyl-1-hydroxycyclohexanecarboxylate 23c.

Route A: Colourless oil (371 mg, 1.26 mmol, 73%) from O-(E-3-chlorophenyl-allyl)-N,N'-dicyclohexylisourea **138c** (650 mg, 1.74 mmol) and α-hydroxycyclohexane carboxylic acid **133a** (250 mg, 1.74 mmol) dissolved in dry THF and heated to reflux for 16h. Filtration of the urea byproduct followed by column chromatography gave a pure product. Overall yield calculated from the alcohol 53%.

Route B: Colourless oil (1.34 g, 4.56 mmol, 76%) from 3-chlorocinnamyl alcohol **130b** (1.00g, 5.95 mmol), DCC **137** (1.20 g, 5.85 mmol) and copper(I) chloride (10 mg). After 16h of stirring THF (50 ml) and α-hydroxycyclohexane carboxylic acid **133a** (0.98 g, 6.80 mmol) were added. The mixture was heated under reflux for 16 hr followed by column chromatography. R_f 0.68 (diethyl ether: hexane, 1:1, v:v). Formula $C_{16}H_{19}ClO_3$.



IR (film, KBr); ν(cm^{-1}) = 3506 (s) [ν (OH)], 2934 (s), 2858 (s), 1727 (s) [ν (C=O)], 1629 (w), 1594 (m), 1567 (m), 1448 (m), 1273 (s), 1232 (s), 1154 (s) [ν (C-O-C)], 1051 (m), 965 (s) , 884 (w), 776 (m), 685 (m) [ν (C-Cl)].

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.24 - 1.81 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 2.81 (s, 1H, OH), 4.80 (d, $^3J_{HH}$ = 6.32 Hz, 2H, OCH_2), 6.27 (dt, $^3J_{HH}$ = 15.72 Hz, 6.32 Hz, 1H, C*H*=CH), 6.59 (d, $^3J_{HH}$ = 15.72 Hz, 1H, CH=C*H*), 7.24 - 7.37 (m, 4H, Ar).

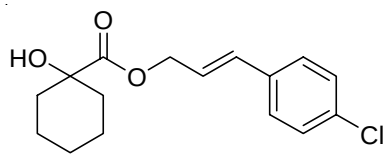
^{13}C-JMOD NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.6 (CH_2; C-3 and C-5), 25.0 (CH_2;

C-4), 35.2 (CH_2, C-2 and C-6), 65.8 (CH_2; OCH_2), 77.8 (C^q; C-1), 121.5 (CH; *C*H=CH), 125.7, 126.6, 128.8, 130.0 (CH, Ar), 134.7 (CH; CH=*C*H), 135.0 (C^q; Ar-Cl), 137.8 (C^q, Ar-*ipso*), 171.6 (C^q, CO_2).

MS (EI, 70 eV): m/z = 296 (1) [M^+, ^{37}Cl], 294 (3) [M^+, ^{35}Cl], 278 (1) [M^+-H_2O, ^{37}Cl], 276 (3) [M^+-H_2O, ^{35}Cl], 251 (1), 170 (4), 151 (17), 114 (15), 113 (17), 110 (19), 99 (100) [$C_6H_{11}O^+$], 81 (47) [$C_6H_{11}O^+$ - H_2O], 67 (3), 55 (6), 41 (4).

(2E)-3-(4-Chlorophenyl)prop-2-enyl 1-hydroxycyclohexanecarboxylate 23d

Route B: Clear oil (3.98 g, 13.51 mmol, 70%), from 4-chlorocinnamyl alcohol **130c** (3.24 g, 19.29 mmol), DCC **137** (3.97 g, 19.27 mmol) stirred overnight with copper (I) chloride (catalytic amount). Addition of dry THF (75 ml) followed by α-hydroxycyclohexane carboxylic acid **133a** (2.78 g, 19.30 mmol). Solution refluxed for 16h followed by filtration of urea and column chromatography of the residue. Molecular formular $C_{16}H_{19}ClO_3$. R_f 0.66 (diethyl ether:hexane. 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3445 (s) [ν (OH)], 2935 (s), 2859 (m), 1726 (s) and 1632 (s) [ν (C=O)], 1492 (m), 1523 (m), 1492 (s), 1450 (s), 1404 (m), 1232 (s), 1154 (m), 1089 (m), 967 (m), 847 (m), 804 (m) [ν (C-Cl)], 741 (w).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.84 - 1.92 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 2.81 (s, 1H, OH), 4.78 (d, $^3J_{HH}$ = 6.33 Hz, 2H, OCH_2), 6.24 (dq, $^3J_{HH}$ = 15.87 Hz, 6.33 Hz, 1H, C*H*=CH), 6.60 (d, $^3J_{HH}$ = 15.87 Hz, 1H, CH=C*H*), 7.25 - 7.33 (m, 4H, Ar).

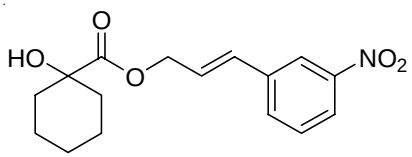
^{13}C-JMOD NMR (65 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.2, 21.3 (CH_2, C-3 and C-5), 25.3 (CH_2, C-4), 34.8, 34.9 (CH_2, C-2 and C-6), 65.9 (CH_2, OCH_2), 73.8 (C^q, COH), 123.4 (CH, *C*H=CH), 127.9, 127.9, 128.7, 128.9 (CH, Ar), 133.3 (CH, CH=*C*H), 134.0 and 134.6 (C^q, Ar-*ipso* and Ar-Cl), 177.1 (C^q, CO_2).

MS (EI, 70 eV): m/z = 295 (1) [M^+, ^{37}Cl], 293 (M^+, ^{35}Cl), 278 (2) [M^+-H_2O, ^{37}Cl], 276 (4) [M^+-H_2O, ^{35}Cl], 251 (1.5) [M^+-CO_2, ^{37}Cl], 249 (3) [M^+-CO_2, ^{35}Cl], 225 (0.75), 223 (2.25), 197 (3), 168 (3), 166 (9), 153 ($C_9H_8Cl^+$, ^{37}Cl], 151 (100) [$C_9H_8Cl^+$, ^{35}Cl], 116 (77), 115 (100) [$C_6H_{11}O_2^+$], 110 (57), 99 (97) [$C_6H_{11}O^+$], 81 (76) [*99* - H_2O], 67 (8) [*81* - CH_2], 55 (45) [*81* - C_2H_2], 41 (18) [*55* - CH_2].

$C_{16}H_{19}ClO_3$ (294.77): Calculated C = 65.19%, H = 6.50%; found C = 65.25%, H = 6.63%.

(2*E*)-3-(3-Nitrophenyl)prop-2-enyl-1-hydroxycyclohexanecarboxylate 23e.

Yellow oil (2.64 g, 8.65 mmol, 74%) from 3-nitrocinnamyl alcohol **130d** (2.10 g, 11.73 mmol), α-hydroxycyclohexanecarboxylic acid **133a** (1.69 g, 11.73 mmol) p-toluenesulphonic acid (200 mg, 1.16 mmol) in chloroform (150 ml) heated under reflux for 16 h. Molecular formula $C_{10}H_{19}NO_5$. R_f 0.70 (ethyl acetate:hexane, 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3517 (m) [ν (OH)], 3086 (w), 2935 (s), 2859 (s), 1728 (s), 1529 (s), 1449 (m), 1351 (s) [ν (NO_2)], 1276 (m), 1231 (s), 1155 (s), 1054 (s), 1039 (s), 994 (s), 966 (s) [δ (CH=CH)-*trans*], 902 (w) , 818 (m), 732 (s), 675 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.18 - 1.82 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 2.78 (s, 1H, OH), 4.84 (d, $^3J_{HH}$ = 6.08 Hz, 2H, OCH_2), 6.41 (dt, $^3J_{HH}$ = 15.94 Hz, 6.07 Hz, 1H, C*H*=CH), 6.69 (d, $^3J_{HH}$ = 15.94 Hz, 1H, CH=C*H*), 7.46 - 7.68 (m, 2H, Ar-2H and Ar-4H), 8.08 - 8.23 (m, 2H, Ar-5H and Ar-6H).

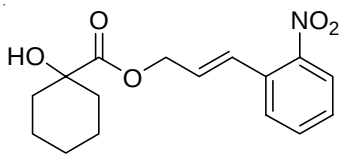
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.1, 21.2 (CH_2, C-3 and C-5), 25.2 (CH_2, C-4), 34.7, 34.8 (CH_2, C-2 and C-6), 65.3 (CH_2, OCH_2), 73.7 (C^q, C-1), 121.2 (CH, *C*H=CH), 122.7, 128.1, 129.6, 131.6 (CH, Ar), 132.4 (CH, CH=*C*H), 137.8 (C^q, Ar-*ipso*), 147.9 (C^q, Ar-NO_2), 177.0 (C^q, CO_2).

MS (EI, 70 eV): m/z = 305 (1) [M^+], 289 (2) [M^+-O], 272 (2.5) [M^+-H_2O-CH_3], 253 (1), 243 (4) [M^+-NO_2-O], 226 (3), 210 (1), 162 (24), 145 (3), 127 (2), 116 (56), 115 (71), 99 (100) [$C_6H_{11}O^+$], 81 (24) [$C_6H_9^+$], 77 (1).

$C_{10}H_{19}NO_5$ (305.33): Calculated C = 62.94%, H = 6.27%, N = 4.59%; found C = 62.59%, H = 6.17%, N = 4.48%.

(2E)-3-(2-Nitrophenyl)prop-2-enyl-1-hydroxycyclohexanecarboxylate 23f.

Brown oil (2.48 g, 8.13 mmol, 54%) from α-hydroxycyclohexane carboxylic acid **133a** (2.17 g, 15.08 mmol), 2-nitrocinnamyl alcohol **130e** (2.70 g, 15.08 mmol) and p-toluenesulphonic acid (0.26 g, 1.50 mmol) dissolved in dry toluene (100 ml) and refluxed for 24h on a Dean Stark apparatus. Molecular formula $C_{16}H_{19}NO_5$. R_f 0.31 (diethyl ether:hexane, 1:1, v:v). Note that when the reaction was carried out with dry chloroform as solvent only 1.5% of the product could be recovered.



IR (film, KBr); ν(cm-^{1}) = 3449 (s) [ν (OH)], 2936 (s), 2859 (m), 1725 (s) [ν (C=O)], 1607 (w), 1571 (w), 1525 (s), 1449 (m), 1347 (s), 1233 (s), 1155 (s), 1040 (m), 993 (m), 965 (m), 859 (w), 785 (w), 738 (m), 673 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.20 - 1.87 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 2.85 (s, 1H, OH), 4.83 (dd, $^3J_{HH}$ = 5.86 Hz, $^4J_{HH}$ = 1.56 Hz, 1H, OCH_2), 6.23 (dt, $^3J_{HH}$ = 15.77, 5.86 Hz, 1H, C*H*=CH), 7.13 (dt, $^3J_{HH}$ = 15.77 Hz, $^4J_{HH}$ = 1.52 Hz, 1H, CH=C*H*), 7.37 - 7.44 (m, 1H, Ar), 7.52 - 7.58 (m, 2H, Ar), 7.91 - 7.94 (m, 1H, Ar-3-H).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.2 (CH_2, C-3 and C-5), 25.2 (CH_2, C-4), 34.8 (CH_2, C-2 and C-6), 65.2 (CH_2, OCH_2), 73.7 (C^q, C-1), 124.7 (CH, *C*H=CH), 128.1, 128.7, 128.8, 129.0 (CH, Ar), 131.9 (C^q, Ar-*ipso*), 133.2 (CH,

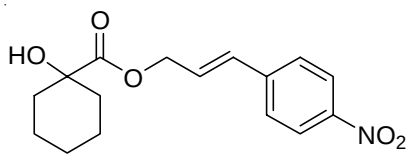
CH=*C*H), 147.8 (C^q, Ar-NO_2), 176.9 (C^q, CO_2).

MS (EI, 70 eV): m/z = 306 (0.6) [M^++1], 305 (2.1) [M^+], 242 (0.7), 196 (0.7) [*242* - NO_2], 179 (1.5) [*196* - OH], 163 (24), 162 (23), 146 (22), 134 (33), 116 (21), 99 (100) [$C_6H_{10}OH^+$], 81 (61) [*99* - H_2O], 77 (7), 55 (9), 41 (5).

Accurate Mass:- Calculated Mass = 305.12632 Found = 305.12628

(2*E*)-3-(4-Nitrophenyl)prop-2-enyl 1-hydroxycyclohexanecarboxylate 23g.

Colourless oil (1.2 g, 3.93 mmol, 79%) from α-hydroxycyclohexanecarboxylic acid **133a** (0.81 g, 5.59 mmol), 4-nitrocinnamyl alcohol (1.0 g, 5.59 mmol) and p-toluenesulphonic acid (100 mg, 0.58 mmol) dissolved in dry chloroform (30 ml). Reaction heated in a Dean Stark apparatus for 48 hr. R_f 0.62 (ethyl acetate / hexane, 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3515 (br) [ν (OH)], 2935 (m), 2860 (w), 1728 (s) [ν (C=O)], 1597 (m), 1517 (s), 1343 (s), 1231 (m), 1154 (m), 1056 (w), 966 (m), 863 (m), 740 (w).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.18 - 1.97 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 2.78 (s, 1H, OH), 4.79 (dd, $^3J_{HH}$ = 5.95 Hz, $^4J_{HH}$ = 1.31 Hz, 2H, OCH_2), 6.39 (dt, $^3J_{HH}$ = 15.96 Hz, 5.97 Hz, 1H, C*H*=CH), 6.65 (d, $^3J_{HH}$ = 15.96, 1H, CH=C*H*), 7.45 (d, $^3J_{HH}$ = 8.78 Hz, 2H, Ar-*meta*), 8.12 (d, $^3J_{HH}$ = 8.78 Hz, 2H, Ar-*ortho*).

^{13}C-NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.1 (CH_2, C-3 and C-5), 25.1 (CH_2, C-4), 34.7 (CH_2, C-2 and C-6), 65.2 (CH_2, OCH_2), 73.4 (C^q, C-1), 123.9 (CH, *C*H=CH), 127.3 and 127.9 (CH, Ar), 131.7 (CH, CH=*C*H), 142.4 (C^q, Ar-*ipso*), 147.3 (C^q, Ar-NO_2), 176.9 (C^q, CO_2).

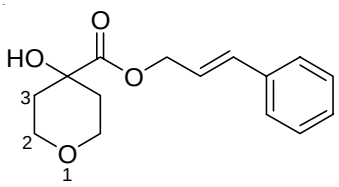
MS (EI, 70 eV): m/z = 306 (1) [M^++1], 305 (3) [M^+], 287 (1) [M^+-H_2O], 221 (1), 179 (17) [$C_9H_9NO_3^+$], 163 (15), 146 (4), 116 (37), 110 (14), 99 (100) [$C_6H_{11}O^+$], 82 (2), 81 (56), 55 (3), 43 (3).

(2*E*)-3-Phenylprop-2-enyl-4-hydroxytetrahydro-2*H*-pyran-4-carboxylate 23h.

Route B: Colourless oil (2.94 g, 11.22 mmol, 69%) from cinnamyl alcohol (2.20 g, 16.41 mmol), DCC **137** (3.38 g, 16.41 mmol) and copper (I) chloride (catalytic amount). Solution was stirred for 36h followed by addition of THF (100 ml) and 4-hydroxytetrahydro-2*H*-pyran-4-carboxylic acid **133b** (2.40 g, 16.44 mmol) followed by heating to reflux for 16h.

Route D: Colourless oil (1.23 g, 4.69 mmol, 29%) from 4-hydroxytetrahydro-2*H*-pyran-4-carboxylic acid **133b** (2.35 g, 16.10 mmol) and triphenylphosphine (4.22 g, 16.10 mmol) dissolved in dry THF (60 ml). Solution cooled to -10°C and DIAD (3.20 ml, 16.27 mmol) was added slowly followed by the slow addition of cinnamyl alcohol (2.16g, 16.10 mmol).

Molecular formula $C_{15}H_{18}O_4$. R_f 0.26 (diethyl ether:hexane, 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3402 (s) [ν (OH)], 3027 (w), 2960 (s), 2869 (s), 1732 (s), 1495 (m), 1449 (s), 1386 (s), 1242 (s), 1147 (s), 1098 (s), 1064 (s), 967 (s), 844 (s), 747 (s), 693 (s).

1H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.95 - 1.29 and 2.10 - 2.21 (m, 4H, 2-H), 3.08 (s, 1H, OH), 3.75 - 4.22 (m, 4H, 3-H), 4.82 (dd, $^3J_{HH}$ = 6.51 Hz, $^4J_{HH}$ = 1.30 Hz, 2H, OCH_2), 6.26 (dt, $^3J_{HH}$ = 6.51 Hz, 15.86 Hz, 1H, C*H*=CH), 6.67 (d, $^3J_{HH}$ = 15.86 Hz, 1H, CH=C*H*), 7.24 - 7.39 (m, 5H, Ph).

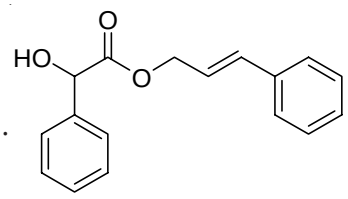
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 34.9 (CH_2, 2xC-3), 63.2, 63.3 (CH_2, 2xC-2), 66.5 (CH_2, OCH_2), 71.1 (C^q, C-4), 122.1 (CH, *C*H=CH), 126.7, 128.3, 128.7 (CH, Ph), 135.1 (CH, CH=*C*H), 135.9 (C^q, Ph-*ipso*), 175.7 (C^q, CO_2).

MS (EI, 70 eV): m/z = 263 (1) [M^++1], 262 (9) [M^+], 244 (3) [M^+-H_2O], 234 (1) [M^+-CO], 134 (7) [$C_9H_9OH^+$], 133 (5), 118 (21), 117 (100) [$C_9H_9^+$], 115 (27), 114 (21) [$C_6H_8O_2^+$], 101 (81) [$C_5H_9O_2^+$], 77 (4) [$C_6H_5^+$], 71 (70), 53 (19), 43 (11).

Accurate Mass:- Calculated Mass = 262.12051 Found = 262.12052

(2*E*)-3-Phenylprop-2-enyl mandelate 23i.

Route B: Colourless oil (8.27 g, 30.9 mmol, 83%) from cinnamyl alcohol (5.0 g, 37.3 mmol) and DCC **137** (7.68 g, 37.3 mmol) and copper (II) chloride (catalyic amount) stirred together for 12h. To this was added dry THF (100 ml) and mandelic acid **140h** (5.67 g, 37.3 mmol) solution heated under reflux for 12h. Molecular formula $C_{17}H_{16}O_3$. R_f 0.78 (ethyl acetate:hexane, 3:7, v:v), mp 62 °C. Note that **23i** exists for several days as an oil before very slowly solidifying.



IR (film, KBr); ν(cm^{-1}) = 3437 (s) [ν (OH)], 3031 (m), 2931 (m), 1732 (s), 1631 (w), 1494 (w), 1451 (m), 1397 (w), 1268 (m), 1180 (s), 1088 (m), 1064 (s), 961 (s), 745 (s), 692 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 3.47 (d, $^3J_{HH}$ = 5.75 Hz, 1H, C*H*(OH)), 4.80 (m, 2H, OCH_2), 5.21 (d, $^3J_{HH}$ = 5.75 Hz, 1H, OH), 6.17 (dt, $^3J_{HH}$ = 15.90 Hz, 6.24 Hz, 1H, C*H*=CH), 6.49 (dt, $^3J_{HH}$ = 15.90 Hz, $^4J_{HH}$ = 1.33 Hz, 1H, CH=C*H*), 7.24 - 7.43 (m, 10 H, Ph).

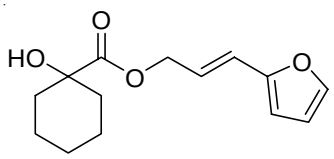
^{13}C-JMOD NMR (75.47 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 66.42 (CH_2, OCH_2), 72.97 (CH, CH(OH)), 118.48 (CH, *C*H=CH), 126.18, 128.33, 128.50, 128.54, 128.58 (CH, Ph), 134.55 (CH, CH=*C*H), 136.52 (C^q, C'-*ipso*), 140.06 (C^q, C-*ipso*), 173.43 (Cq, CO_2)

MS (EI, 70 eV): m/z = 269 (2) [M^++1], 268 (4) [M^+], 250 (11) [M^+-H_2O], 232 (11) [*250* - H_2O], 215 (5), 206 (13) [M^+-H_2O-CO_2], 191 (7), 178 (14) [M^+-C_6H_6CH], 165 (8) [M^+-$C_6H_6C_2H_2$], 152 (3) [M^+-C_9H_8], 132 (2) [*152* - H_2O], 118 (36) [C_9H_{10}], 117 (100) [$C_9H_9^+$], 116 (64), 107 (78), 105 (24), 91 (36), 90 (14), 79 (46), 77 (43) [$C_6H_6^+$], 63 (14), 51 (21).

$C_{17}H_{16}O_3$ (268.31): Calculated C = 76.10%, H = 6.01%; found C = 76.08%, H = 5.97%.

(2*E*)-3-(2'-Furyl)prop-2-enyl-1-hydroxycyclohexanecarboxylate 23j.

Route D: Yellow oil (1.71 g, 6.84 mmol, 47%) from (2*E*)-3-(2-furyl)prop-2-en-1-ol **130h** (1.80 g, 14.52 mmol), α-hydroxycyclohexanecarboxylic acid **133a** (3.13 g, 21.75 mmol), triphenylphosphine (5.68 g, 21.75 mmol) and DIAD (4.2 ml, 21.75 mmol) dissolved in THF (50 ml). Molecular formula $C_{14}H_{18}O_4$. R_f 0.56 (diethyl ether:hexane, 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3512 (s) [ν (OH)], 3115 (w), 3049 (w), 2949 (s), 2856 (m), 1731 (s), 1693 (m), 1531 (w), 1442 (m), 1384 (w), 1335 (w), 1234 (s), 1154 (s), 1063 (m), 994 (m), 956 (m), 737 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.23 - 1.85 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 2.82 (br., 1H, OH), 4.75 (dd, $^3J_{HH}$ = 6.46 Hz, $^4J_{HH}$ = 1.21 Hz, 2H, OCH_2), 6.13 - 6.48 (m, 4H, C*H*=C*H*, C^qCH-C*H*), 7.34 (d, $^3J_{HH}$ = 1.54 Hz, 1H, OCH).

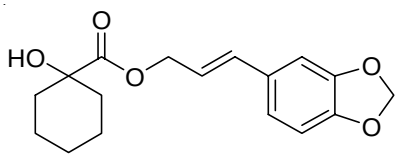
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.1 (CH_2, C-3 and C-5), 25.2 (CH_2, C-4), 34.7, 34.8 (CH_2, C-2 and C-6), 65.7 (CH_2, OCH_2), 73.7 (C^q, C-1), 109.2, 111.4 (OC^qCH-*C*H), 121.0 (CH, *C*H=CH), 122.6 (CH, CH=*C*H), 142.5 (CH, O*C*H), 151.7 (C^q, OC^q), 177.1 (C^q, COO).

MS (EI, 70 eV): m/z = 251 (4) [M^++1], 250 (29) [M^+], 233 (2) [M^+-OH], 232 (11) [M^+-H_2O], 124 (40) [$C_7H_8O_2^+$], 110 (52), 107 (100) [$C_7H_7O^+$], 99 (77) [$C_6H_{11}O^+$], 81 (74) [*99* - H_2O], 79 (31), 77 (26), 55 (12), 41 (9).

Accurate Mass:- Calculated Mass = 250.12051 Found = 250.12052

(2*E*)-3-(Methylenedioxy)prop-2-enyl-1-hydroxycyclohexanecarboxylate 23k.[142]

To a solution of methylenedioxycinnamyl alcohol (2.59 g, 14.55 mmol) and α-hydroxycyclohexane carboxylic acid (12.57 g, 87.29 mmol) in dry DCM (80 ml) was added at 0°C, EDC (6.77 g, 43.7 mmol) and DMAP (180 mg). The reaction mixture was stirred at rt for 24 h and then poured into a separatory funnel containing diethyl ether (250 ml) and HCl (30 ml of a 10% solution). The organic phase was washed three times with the HCl solution (30 ml) followed by four washings with a saturated sodium bicarbonate (30 ml) solution followed by an additional wash with a brine solution (30 ml). The organic phase was dried with sodium sulphate and concentrated in vacuo. The residue was purified by column chromatography (diethyl ether: hexane, 1:1, v:v). Colourless oil (1.63 g, 5.36 mmole, 47 %) Molecular formula $C_{17}H_{20}O_6$. R_f 0.46 (diethyl ether: hexane, 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3502 (s) [ν (OH)], 2934 (s), 2858 (s), 1729 (s), 1652 (m), 1504 (s), 1492 (s), 1448 (s), 1237 (s), 1156 (s), 1133 (s), 1039 (s), 995 (m), 966 (m), 933 (m), 855 (w), 794 (m), 741 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.22 - 1.81 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 2.87 (s, 1H, OH), 4.74 (dd, $^{3}J_{HH}$ = 6.60 Hz, $^{4}J_{HH}$ = 1.26 Hz, 2H, OCH_2), 5.93 (s, 2H, OCH_2O), 6.07 (dt, $^{3}J_{HH}$ = 15.79, 6.60 Hz, 1H, C*H*=CH), 6.54 (d, $^{3}J_{HH}$ = 15.79 Hz, 1H, CH=C*H*), 6.71 - 6.90 (m, 3H, Ar).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.3 (CH_2, C-3 and C-5), 25.4 (CH_2, C-4), 35.0, 35.0 (CH_2, C-2 and C-6), 66.3 (CH_2, OCH_2), 81.5 (C^q, COH), 101.3 (CH_2, OCH_2O), 105.8, 108.2, 120.6 (CH, Ar), 121.5 (*C*H, CH=CH), 130.4 (C^q, Ar-*ipso*), 134.5 (CH, CH=*C*H), 147.7, 148.0 (C^q, Ar-3 and Ar-4), 171.4 (C^q, CO_2).

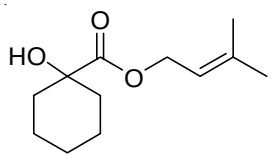
MS (EI, 70 eV): m/z = 305 (7) [M^++1], 304 (37) [M^+], 178 (49) [$C_{10}H_9O_2OH^+$], 176 (15), 162 (17), 161 (82) [*178* - H_2O], 142 (9) [$C_6H_{10}O_3^+$], 131 (100) [*161* - CH_2O], 103 (36) [*131* - CO, *131* - C_2H_2], 99 (67) [$C_6H_{10}OH^+$], 81 (55) [*99* - H_2O], 87 (17), 55 (12), 41 (9).

Accurate Mass:- Calculated Mass = 304.13108 Found = 304.13105

3-Methylbut-2-enyl-1-hydroxycyclohexanecarboxylate 23m.

Route A: Colourless oil (1.38 g, 6.51 mmol, 65%) from α-hydroxy-cyclohexanecarboxylic acid **133a** (1.44 g, 10.0 mmol) and O-(3-methyl-but-2-enyl)-N,N'-dicyclohexylisourea (3.5 g, 12.0 mmol). Yield calculated from alcohol is 54%

Route B: Colourless oil (3.89 g, 18.34 mmol, 73%) from a mixture of DCC **137** (5.15 g, 25 mmol), 3-methyl-2-but-en-1-ol (2.15 g, 25 mmol) and copper (I) chloride (catalytic amount) stirred for 16h. α-Hydroxycyclohexane carboxylic acid **133a** (3.60 g, 25 mmol) was then added along with dry THF (100 ml) and the resulting blue solution was refluxed for 16 h. Molecular formula $C_{12}H_{20}O_3$. R_f 0.72 (diethyl ether: hexane, 1:1, v:v), bp 145 °C at 0.15 Torr (Kugelrohr distillation) (lit.: bp 137°C at 0.10 Torr[115]).



IR (KBr); ν(cm^{-1}) = 3520 (s) [ν (OH], 2934 (s), 2858 (s), 1724 (s), 1449 (s), 1380 (s), 1336 (m), 1234 (s), 1156 (s), 1040 (s), 994 (s), 913 (m), 836 (w), 767 (w), 742 (w), 688 (w).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.18 - 1.75 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 1.72 and 1.77 (s, 6H, $C(CH_3)_2$), 2.86 (s, 1H, OH), 4.64 (d, $^{3}J_{HH}$ = 7.13 Hz, 2H, OCH_2), 5.31 - 5.36 (m, 1H, $CH=C^q$).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 18.5 (CH_3, $C(CH_3)_2$-*cis*), 21.6 (CH_2, C-3 and C-5), 25.6 (CH_3, $C(CH_3)_2$-*trans*), 26.2 (CH_2, C-4), 35.1 (CH_2, C-2 and C-6), 62.9 (CH_2, OCH_2), 74.0 (C^q, C-1), 118.5 (CH, *C*H=C^q), 140.1 (C^q, CH=*C*^{q}), 177.8 (C^q, CO_2).

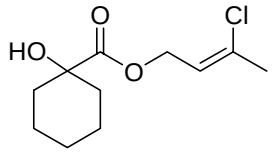
MS (EI, 70 eV): m/z = 212 (2) [M^+], 144 (16) [M^+-C_5H_8], 128 (13) [M^+-C_5H_8OH], 110 (23), 99 (100) [$C_6H_{10}OH^+$], 81 (36) [$C_6H_9^+$], 69 (29), 55 (19).

$C_{12}H_{20}O_3$ (212.29): Calculated C = 68.89%, H = 9.50%; found C = 68.94%, H = 9.56%.

(2*Z*)-3-Chlorobut-2-enyl-1-hydroxycyclohexanecarboxylate 23n.

Route A: Colourless oil (83%) from O-(3-chlorobut-2-enyl)-N,N'-dicyclohexylisourea **139a** (3.0 g, 9.62 mmol) and α-hydroxycyclohexane carboxylic acid **133a** (1.38 g, 9.62 mmol) refluxed together for 16h in dry THF (100 ml). Yield calculated from starting alcohol 76%

Route B: Colourless oil (4.22 g, 18.15 mmol, 91%) from a mixture of DCC **137** (5.15 g, 25 mmol), 3-chlor-2-but-en-1-ol (2.66 g, 25 mmol) and copper (I) chloride (catalytic amount) stirred for 60h. Followed by addition of α-hydroxycyclohexane carboxylic acid **133a** (2.88 g, 25 mmol) and dry THF (100 ml) and heated to reflux for 16 h. Molecular formula $C_{11}H_{17}ClO_3$.



IR (film, KBr); ν(cm^{-1}) = 3512 (br) [ν (OH)], 2936 (s), 2859 (m), 1729 (s) [ν (C=O)], 1671 (w), 1448 (m), 1381 (w), 1275 (m), 1231 (s), 1156 (s), 1095 (w), 1054 (m), 995 (m), 742 (m) [ν (C-Cl)], 690 (w), 632 (w)

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.08 - 1.82 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 2.16 (s, 3H, CH_3), 2.81 (s, 1H, OH), 4.84 (d, $^3J_{HH}$ = 6.81 Hz, 2H, OCH_2), 5.66 (m, 1H, $CH=C^q$),

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.5, 21.8 (CH_2, C-3 and C-5), 25.5 (CH_2, C-4), 26.7 (CH_3, C^qCH_3), 62.8 (CH_2, OCH_2), 74.0 (C^q, C-1), 120.2 (C^q, C^qCl), 136.2 (CH, *C*H=C^q), 177.5 (C^q, CO_2).

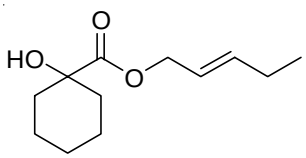
MS (EI, 70 eV): m/z = 145 (17) [M^+-C_4H_4Cl], 127 (9) [*145* - H_2O], 110 (29) [*127* - OH], 99 (80), 91 (33) [C_4H_6Cl, *37*Cl], 89 (63) [C_4H_6Cl, ^{35}Cl], 81 (100) [C_6H_9+], 79 (34), 69 (19), 57 (48), 55 (59).

Note M^+ ion was not observed by EI-MS. FAB was unavailable at time of measurement. All other data is consistent with proposed structure.

$C_{11}H_{17}ClO_3$ (232.70): Calculated C = 56.78%, H = 7.36%; found C = 56.61%, H = 7.50%.

(2*E*)-Pent-2-enyl-1-hydroxycyclohexanecarboxylate 23o.

Route B: Clear oil (4.21 g, 19.8 mmol, 86%) from *trans*-2-penten-1-ol (2.0 g, 23.0 mmol) and DCC **137** (4.8 g, 23.0 mmol) and a catalytic amount of copper (I) chloride. After stirring at rt for 16 hr, dry THF (50 ml) and α-hydroxycyclohexanecarboxylic acid (3.31 g, 23.0 mmol) were added, followed by heating under reflux for 16h. Filtration of urea and further purification by column chromatography. Molecular formula $C_{12}H_{20}O_3$. R_f 0.27 (100% hexane).



IR film (KBr); ν(cm^{-1}) = 3517 (s) [ν (OH)], 2934 (s), 2859 (s), 1726 (s) [ν (C=O)], 1630 (w), 1517 (w), 1450 (m), 1381 (w), 1269 (m), 1233 (s), 1155 (s), 1048 (m), 969 (m), 743 (w).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.99 (t, $^3J_{HH}$ = 7.40 Hz, 3H, CH_3), 1.20 - 1.78 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 2.01 - 2.12 (p, $^3J_{HH}$ = 6.96 Hz, 3H, C*H*$_2$$CH_3$),

2.84 (s, 1H, OH), 4.58 (d, $^3J_{HH}$ = 6.43 Hz, 2H, OCH_2), 5.53 (dt, $^3J_{HH}$ = 15.24 Hz, 6.43 Hz, 1H, C*H*=CH), 5.82 (dt, $^3J_{HH}$ = 15.24 Hz, 6.96 Hz, 1H, CH=C*H*).

^{13}C-NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 13.2 (CH_3, CH_2CH_3), 20.8 (CH_2, CH_2CH_3), 21.2 (CH_2, C-3 and C-5), 25.3 (CH_2, C-4), 34.8 (CH_2, C-2 and C-6), 66.4 (CH_2, OCH_2), 73.6 (C^q, C-1), 122.4 (CH, *C*H=CH), 138.5 (CH, CH=*C*H), 177.2 (C^q, CO_2).

MS (EI, 70 eV): m/z = 212 (1) [M^+], 125 (2) [M^+- $C_5H_9^+$-H_2O], 109 (58) [M^+-$C_5H_9O^+$-H_2O], 100 (65) [$C_6H_{12}O^+$], 99 (100) [$C_6H_{11}O^+$], 97 (25), 82 (36), 81 (95) [$C_6H_{11}O^+$ - H_2O], 69 (77), 67 (63), 57 (42), 55 (84), 53 (44), 43 (39).

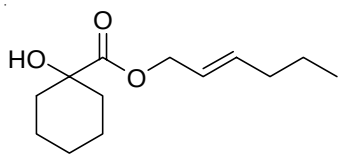
GC:retention time = 20.6 min

(2E)-Hex-2-enyl-1-hydroxycyclohexanecarboxylate 23p.

Route A: Colourless viscous liquid (604 mg, 2.67 mmol, 82%) from O-[(2E)-hex-2-enyl]-N,N'-dicyclohexylisourea **139d** (1.0 g, 3.26 mmol) and α-hydroxycyclohexanecarboxylic acid **133a** (0.47 g, 3.26 mmol) refluxed together in dry THF (50 ml) for 16h. Overall yield calculated from the alcohol 79%

Route B: Colourless viscous liquid (4.05 g, 17.9 mmol, 90%) from *trans*-2-hexan-1-ol (2.5 g, 25 mmol), DCC **137** (5.15 g, 25 mmol), copper (I) chloride (catalytic amount) and α-hydroxycyclohexanecarboxylic acid **133a** (4.52 g, 20 mmol).

Molecular formula $C_{13}H_{22}O_3$. R_f 0.72 (diethylether / hexane, 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3520 (m) [ν (OH)], 2932 (s), 2858 (s), 1726 (s), 1450 (s), 1232 (s), 1156 (s), 1041 (s), 971 (m), 743 (w).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm)= 0.90 (t, $^3J_{HH}$ = 7.41 Hz, 3H, CH_3), 1.41 (sex, $^3J_{HH}$ = 7.41 Hz, 2H, 5'-CH_2), 1.30 - 1.79 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.02 - 2.05 (m, 2H, 4'-CH_2), 2.88 (s, 1H, OH), 4.60 (dt, $^3J_{HH}$ = 6.36 Hz, $^4J_{HH}$ = 0.78 Hz, 2H, OCH_2), 5.56 (dtt, $^3J_{HH}$ = 15.40 Hz, 6.36 Hz, $^4J_{HH}$ = 1.34 Hz, 1H, C*H*=CH), 5.78 (dtt, $^3J_{HH}$ = 15.40 Hz, 6.70 Hz, $^4J_{HH}$ = 0.78 Hz, 1H, CH=C*H*).

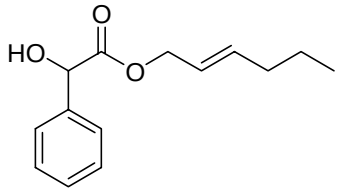
^{13}C-NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 13.6 (CH_3), 21.2 (CH_2, C-3 and C-5), 22.1 (CH_2, C-6), 25.2 (CH_2, 5'-C), 34.3 (CH_2, C-2 and C-6), 34.8 (CH_2, 4'-C), 66.3 (CH_2, OCH_2), 73.6 (C^q, COH), 123.4 (CH, *C*H=CH), 136.9 (CH, CH=C*H*), 177.2 (C^q, CO_2).

MS (EI, 70 eV): m/z = 226 (4) [M^+], 225 (11) [M^+-1], 208 (6) [M^+-H_2O], 195 (7), 181 (10), 164 (4), 152 (8), 144 (16), 143 (28), 138 (68), 100 (24) [$C_6H_{12}O^+$], 99 (38), 98 (61), 85 (91), 79 (17), 67 (24), 61 (16), 56 (100).

$C_{13}H_{22}O_3$ (226.31): Calculated C = 67.25%, H = 10.35%; found C = 67.18%, H = 10.39%.

(±)-(2*E*)-Hex-2-enyl (2*R, 2S*)-hydroxy(phenyl)acetate 23q.

Route B: Colourless oil (5.04 g, 21.54 mmol, 86%) from (2*E*)-hex-2-en-1-ol (2.50 g, 25 mmol), DCC **137** (5.15 g, 25 mmol) and copper (I) chloride (catalytic amount). After stirring at rt for 24 hr mandelic acid **140h** (3.80 g, 25 mmol) was added and the solution was refluxed for 16 h. Molecular formula $C_{14}H_{18}O_3$. R_f 0.55 (diethyl ether:hexane, 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3484 (s) [ν (OH)], 3032 (w), 2958 (s), 2871 (m), 1737 (s) [ν (C=O)], 1621 (w), 1495 (w), 1454 (m), 1380 (w), 1261 (s), 1181 (s), 1095 (s), 1067 (m), 971 (s), 733 (m), 697 (m).

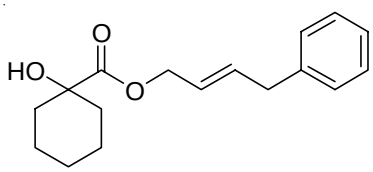
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.84 (t, $^3J_{HH}$ = 7.37 Hz, 3H, 6-H), 1.34 (sex, $^3J_{HH}$ = 7.37 Hz, 2H, 5-H), 1.97 (tdd, $^3J_{HH}$ = 7.37 Hz, 6.76 Hz, $^4J_{HH}$ = 1.38 Hz, 2H, 4-H), 3.43 (d, $^3J_{HH}$ = 5.71 Hz, 1H, C*H*(OH), 4.50 - 4.66 (m, 2H, OCH_2), 5.15 (d, $^3J_{HH}$ = 5.71 Hz, 1H, CH(O*H*), 5.46 (dtt, $^3J_{HH}$ = 15.41 Hz, 6.34 Hz, $^4J_{HH}$ = 1.38 Hz, 1H, 2-H), 5.67 (dtt, $^3J_{HH}$ = 15.41 Hz, 6.76 Hz, $^4J_{HH}$ = 1.03 Hz, 1H, 3-H), 7.24 - 7.42 (m, 5H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 13.7 (CH_3, 6-CH_3), 21.9 (CH_2, 5-CH_2), 34.2 (CH_2, 4-CH_2), 66.8 (CH_2, OCH_2), 72.9 (CH, CHOH), 122.9 (CH, 2-CH), 126.5, 128.4, 128.5 (CH, Ph), 137.2 (CH, 3-CH), 138.4 (C^q, Ph-*ipso*), 173.5 (C^q, CO_2).

MS (EI, 70 eV): m/z =234 (0.02) [M^+], 216 (0.04) [M^+-H_2O], 189 (0.02), 178 (0.9), 165 (0.8) [M^+-C_5H_9], 151 (5) [$C_8H_7O_3^+$], 136 (9) [*151* - O], 118 (37) [*136* -H_2O], 108 (76), 107 (100) [$C_7H_7O^+$], 106 (51), 105 (77), 91 (31), 83 (68) [$C_6H_{11}^+$], 82 (61), 79 (100), 78 (44), 77 (97) [$C_6H_5^+$], 67 (88), 55 (88), 51 (60), 42 (16).

(2*E*)-4-Phenylbut-2-enyl 1-hydroxycyclohexanecarboxylate 23r.

Route C: Colourless oil (2.88 g, 10.5 mmol, 76%) from (2*E*)-4-phenylbut-2-en-1-ol **130f** (2.05 g, 13.85 mmol), α-hydroxycyclohexane carboxylic acid **133a** (1.99 g, 13.85 mmol) and p-toluenesulphonic acid (247 mg, 1.38 mmol) in dry chloroform (100 ml). Refluxed for 24h in a Dean-Stark apparatus. Compound purified by column chromatography. Molecular formula $C_{17}H_{22}O_3$. R_f 0.25 (diethylether:hexane, 1:1, v:v)



IR (film, KBr); ν(cm^{-1}) = 3504 (m) [ν (OH)], 2935 (s), 2858 (w), 1726 (s) [ν (C=O)], 1601 (w), 1495 (w), 1450 (m), 1376 (w), 1276 (m), 1234 (s) [ν (OH)], 1155 (s) [ν (CO)], 1048 (m), 991 (m), 744 (w), 698 (m).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.18 - 1.82 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 3.28 (s, broad, 1H, OH), 3.40 (d, $^{3}J_{HH}$ = 6.65 Hz, 2H, CH_2Ph), 4.62 (d, $^{3}J_{HH}$ = 6.22 Hz, 2H, OCH_2), 5.62 (dt, $^{3}J_{HH}$ = 15.22 Hz, 6.22 Hz, 1H, C*H*=CH), 5.94 (dt, $^{3}J_{HH}$ =15.22 Hz, 6.65 Hz, 1H, CH=C*H*), 7.15 - 7.29 (m, 5H, Ph).

^{13}C-JMOD NMR (125.7 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.1, 21.4 (CH_2, C-7 and C-9), 25.2 (CH_2, C-8), 34.7, 35.0 (CH_2, C-6 and C-10), 38.6 (CH_2, CH_2Ph), 65.8 (CH_2, OCH_2), 73.6 (C^q, COH), 125.2 (CH, CH=*C*H), 126.3, 126.7, 128.3, 128.5, 128.9 (CH, C-*arom*), 135.1 (CH, *C*H=CH), 139.4 (C^q, C-*ipso*), 177.1 (C^q, CO_2).

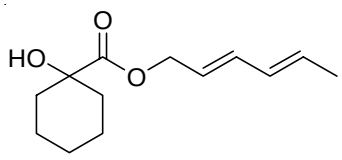
MS (EI, 70 eV): m/z = 197 (0.5) [M^+-C_6H_5], 179 (1) [*197* - H_2O], 131 (7) [$C_{10}H_{11}^+$], 130 (38) [$C_{10}H_{10}^+$], 116 (4), 115 (7), 103 (13) [$C_8H_8^+$], 99 (100) [$C_6H_{11}O^+$], 91 (29) [$C_6H_5CH_2$], 81 (75) [*99* - H_2O], 77 (6),69 (1), 65 (4), 55 (9), 41 (8), 29 (2).

(2*E*,4*E*)-Hexa-2,4-dienyl 1-hydroxycyclohexanecarboxylate 23s.

Route A: Clear oil (6.57 g, 29.3 mmol, 47%) from O-[(2*E*,4*E*)-hexa-2,4-dienyl]-*N*,*N*'-dicyclohexylisourea **139b** (19.0 g, 62.5 mmol) and α-hydroxycyclohexane carboxylic acid **133a** (9.0 g, 62.5 mmol) refluxed together in dry THF (200 ml) for 5h. Overall yield calculated from the alcohol: 41%.

Route B: Clear oil (1.71 g, 7.63 mmol, 50%). From *trans*, *trans*-2,4-hexadien-1-ol (1.49 g, 15.2 mmol), DCC **137** (3.13 g, 15.2 mmol) and copper(I) chloride (catalytic amount) stirred under a nitrogen atmosphere for 16h. Dry THF (75 ml) followed by α-hydroxycyclohexane carboxylic acid **133a** (2.19 g, 15.2 mmol) were added under a nitrogen atmosphere. Reaction mixture was stirred under reflux for 5h. Filtration of urea followed by column chromatography gave **141r**. Molecular formula $C_{13}H_{20}O_3$. R_f 0.69 (ethyl acetate:hexane, 1:1, v:v.) bp (1 Torr) 110°C.

Note that the alkene bonds show only multiplets in the ^{1}H-NMR spectra, however we know that in the product ester the stereochemistry must be trans, trans since we started with a trans, trans alcohol.



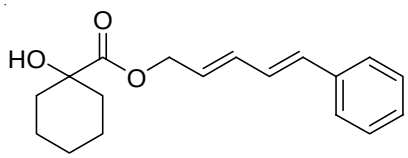
IR (film, KBr); ν(cm^{-1}) = 3443 (s) [ν (OH)], 3088 (w), 2934 (s), 2857 (m), 1724 (s) [ν (C=O)], 1629 (m), 1525 (w), 1449 (m), 1378 (w), 1275 (s), 1236 (s), 1157 (s), 1039 (s), 993 (s) [ν (*trans*-CH=CH)], 952 (w), 912 (m), 856 (m), 806 (w), 742 (w), 688 (w).

^{1}H-NMR (500 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.33 (d, $^{3}J_{HH}$ = 6.50 Hz, 3H, 6'-CH_3), 1.55 - 1.77 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 2.87 (s, 1H, OH), 4.62 (d, $^{3}J_{HH}$ = 6.66 Hz, 2H, OCH_2), 5.11 - 5.25 (m, 1H, 2'-CH), 5.37 - 5.46 (m, 1H, 5'-CH), 5.59 - 5.81 (m, 1H, 4'-CH), 6.19 - 6.29 (m, 1H, 3'-CH).

^{13}C-JMOD NMR (125.7 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 20.0 (CH_3, 6'-CH_3), 21.1 (CH_2, C-3 and C-5), 25.2 (CH_2, C-4), 34.6, 34.7 (CH_2, C-2 and C-6), 66.0 (CH_2, OCH_2), 73.5 (C^q, COH), 132.1 (CH, 2'-CH), 132.5 (CH, 5'-CH), 135.4 (CH, 4'-CH), 135.9 (CH, 3'-CH), 176.6 (C^q, CO_2).

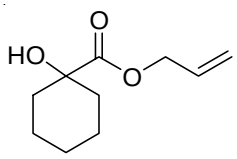
MS (EI, 70 eV): m/z = 224 (24) [M^+], 207 (5) [M^+-OH], 206 (20) [M^+-H_2O], 110 (14) [*207* - $C_6H_9O^+$], 99 (92) [$C_6H_{11}O^+$], 81 (100) [*99* - H_2O], 55 (11), 41 (16).
$C_{13}H_{20}O_3$ (224.30): Calculated C = 69.61%, H = 8.99%; found C = 69.71%, H = 9.03%.

(2*E*',4'*E*)-5'-Phenylpenta-2',4'-dienyl-1-hydroxycyclohexanecarboxylate 23t.
Route D: Clear oil (1.36 g, 4.76 mmol, 48%) from (2*E*,4*E*)-5-phenylpenta-2,4-dien-1-ol (2.39 g, 14.94 mmol), α-hydroxycyclohexane carboxylic acid **133a** (1.44 g, 1.0 mmol), DIAD (3 ml) and triphenylphosphine (3.91 g, 14.92 mmol) in THF (20 ml) stirred overnight. Molecular formula $C_{18}H_{22}O_3$. R_f 0.54 (diethyl ether: hexane, 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3512 (s) [ν (OH)], 3028 (w), 2935 (s), 2859 (m), 1829 (m), 1728 (s), 1494 (w), 1449 (s), 1374 (m), 1233 (s), 1153 (s), 1103 (w), 1053 (m), 992 (s), 912 (m), 746 (m), 697 (m).
^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.16 - 1.82 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 2.83 (s, 1H, OH), 4.70 (d, $^3J_{HH}$ = 5.36 Hz, 2H, OCH_2), 5.80 - 5.94 (m, 1H, 2'-H), 6.18 - 6.85 (m, 3H, 3'-H, 4'-H, 5'-H), 7.20 - 7.40 (m, 5H, Ph).
^{13}C-JMOD NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.1, 21.2 (CH_2, C-3 and C-5), 25.3 (CH_2, C-4), 34.7, 34.8 (CH_2, C-2 and C-6), 67.3 (CH_2, OCH_2), 73.7 (C^q, C-1), 126.6, 127.3, 128.4, 128.7, 129.0 (CH, Ph), 130.3, 131.7, 134.2, 135.1 (CH, C-2', C-3', C-4', C-5'), 135.6 (Cq, Ph-*ipso*), 177.1 (C^q, CO_2).
MS (EI, 70 eV): m/z = 287 (0.9) [M^++1], 286 (5) [M^+], 268 (1.4) [M^+-H_2O], 226 (2), 198 (2), 160 (6) [M^+-$C_7H_{10}O_2$], 156 (4), 143 (21) [$C_{11}H_{11}^+$], 128 (11) [*143* - CH_3], 99 (100) [$C_6H_{10}OH^+$], 91 (21), 81 (59) [*99* - H_2O], 65 (6), 55 (9), 43 (14).
Accurate Mass:- Calculated Mass = 286.15689 Found = 286.15698

Allyl 1-hydroxycyclohexanecarboxylate 23u.
Route A: Colourless oil (2.26 g, 12.31 mmol, 62%) from α-hydroxycyclohexanecarboxylic acid **133a** (2.86 g, 19.83 mmol) and O-allyl-N,N'-dicyclohexylisourea (5.24 g, 19.86 mmol) refluxed together in dry THF (75 ml) for 16h. Overall yield from the alcohol 65%.
Route B: Colourless oil (5.21 g, 28.3 mmol, 81%) from allyl alcohol (2.0 g, 34.5 mmol), DCC **137** (7.10 g, 34.5 mmol) and copper (I) chloride (catalytic amount) stirred together for 12h. Addition of dry THF (75 ml) and α-hydroxycyclohexanecarboxylic acid **133a** (4.97 g, 34.5 mmol) followed by heating to reflux for 16h.
Route C: Colourless oil (1.46 g, 7.93 mmol, 79%) from α-hydroxycyclohexanecarboxylic acid **133a** (1.44, 10.0 mmol) and allyl alcohol (2.90 g, 50.0 mmol).[115]
Molecular formula $C_{10}H_{16}O_3$. R_f 0.81 (diethyl ether: hexane, 1:1, v:v).



IR (film, KBr); ν(cm-^{1}) = 3517 (br) [ν (OH)], 2936 (s), 2859 (m), 1730 (s), 1648 (w), 1449 (m), 1274 (s), 1233 (s), 1155 (s), 1054 (m), 993 (s), 932 (m).

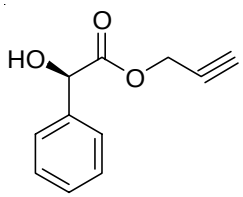
1H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.52 - 1.81 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 4.65 (d, $^{3}J_{HH}$ = 5.66 Hz, 2H, OCH_2), 5.28 (dd, $^{3}J_{HH}$ = 10.21 Hz, $^{2}J_{HH}$ = 2.20 Hz, 1H, CH=CH*H-cis*), 5.35 (dd, $^{3}J_{HH}$ = 17.24 Hz, $^{2}J_{HH}$ = 2.20 Hz, 1H, CH=C*H*H-*trans*), 5.93 (ddd, $^{3}J_{HH}$ = 17.24, 10.21, 5.66 Hz, 1H, C*H*=CH_2).

^{13}C-NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.1 (CH_2, C-3 and C-5), 25.2 (CH_2, C-4), 34.7, 34.8 (CH_2, C-2 and C-6), 66.0 (CH_2, OCH_2), 73.6 (C^{q}, C-1), 118.6 (CH, CH=*C*H_2), 131.6 (CH_2, CH=CH_2), 177.0 (C^{q}, CO_2).

MS (EI, 70 eV): m/z = 184 (14) [M^{+}], 166 (48) [M^{+}-H_2O], 155 (29), 139 (9), 127 (26) [M^{+}-C_3H_5O], 121 (44), 109 (60) [*167* - $C_3H_6O^{+}$], 99 (93) [M^{+}-$C_4H_5O_2$], 81 (79) [*99* - H_2O^{+}], 69 (39), 55 (100), 43 (70).

Prop-2-ynyl-(2*R*)-mandelate 23v.

Route C: White solid (3.40 g, 17.89 mmol, 91%) from R-mandelic acid (3.00 g, 19.74 mmol), propargyl alcohol (1.04 g, 19.62 mmol) and p-toluenesulphonic acid (337 mg, 1.96 mmol) dissolved in dry chloroform (75 ml). Solution refluxed for 24 hr in a Dean-Stark apparatus. Molecular formula $C_{11}H_{10}O_3$. R_f 0.74 (ethyl acetate:hexane, 1:1, v:v), mp 49^{o}C.



IR (KBr); ν(cm^{-1}) = 3437 (s) [ν (OH)], 3293 (s) [ν (CH)], 3048 (w), 2952 (2), 2129 (w), 1746 (s) [ν (C=O)], 1495 (w), 1455 (w), 1368 (w), 1368 (w), 1266 (m), 1179 (s), 1093 (m), 1068 (s), 989 (w), 737 (m), 697 (m) [δ (CH)].

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 2.45 (t, $^{4}J_{HH}$ = 2.49 Hz, 1H, C^{q}CH), 3.61 (s, 1H, OH), 4.62 (dd, $^{2}J_{HH}$ = 15.52 Hz, $^{4}J_{HH}$ = 2.49 Hz, 1H, OC*H*H), 4.77 (dd, $^{2}J_{HH}$ = 15.52 Hz, $^{4}J_{HH}$ = 2.49 Hz, 1H, OCH*H*), 5.20 (s, 1H, C*H*OH), 7.33 - 7.49 (m, 5H, Ph).

^{13}C NMR (75.4 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 52.2 (CH_2, OCH_2), 72.4 (CH, C^{q}*C*H), 75.3 (CH, CHOH), 77.0 (C^{q}, CH_2*C*), 126.5, 128.5, 128.6 (CH, Ph), 138.4 (C^{q}, C-*ipso*), 171.8 (C^{q}, CO_2).

MS (EI, 70 eV): m/z = 191 (7) [M^{+}+1], 190 (22) [M^{+}], 174 (21) [M^{+}+1-OH], 173 (3) [M^{+}-OH], 135 (10) [M^{+}-C_3H_3O], 129 (11) [M^{+}-CO_2-OH], 118 (19) [M^{+}-C_3H_3O - OH], 115 (12), 108 (40), 107 (100) [$C_7H_7O^{+}$], 105 (34), 90 (11), 79 (93), 77 (90) [$C_6H_5^{+}$], 63 (11), 53 (16), 51 (42), 39 (67), 32 (13), 28 (37).

Accurate Mass:- Calculated Mass = 190.062994 Found = 190.062439

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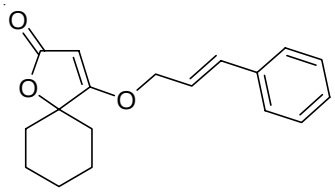
3.3.5 Synthesis of tetronates using keteneylidenetriphenylphosphorane 1

General experimental procedure for the formation of tetronates from α-hydroxy carboxylic acids and keteneylidentriphenylphosphorane 1: A solution of the respective α-hydroxy carboxylic acid (5.0 mmol), keteneylidenetriphenylphosphorane **1** (7.5 mmol) and benzoic acid (catalytic amount) were refluxed together under the exclusion of air and moisture in dry THF (50 ml). Reaction times vary from 12 - 16h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography (silica gel; solvent as indicated).

(E)-4-(3-Phenyl-allyloxy)-1-oxa-spiro[4.5]dec-3-en-2-one 121a.

White solid (4.81 g, 16.92 mmol, 78%) from (E)-(3'-phenyl-allyl)-1-hydroxy-cyclohexane-1-carboxylate **23a** (5.64 g, 21.69 mmol) and keteneylidenetriphenylphosphorane **1** (9.83 g, 32.54 mmol) refluxed for 24h in dry THF (250 ml). Molecular formula $C_{18}H_{20}O_3$. R_f 0.36 (diethyl ether:hexane, 1:1, v:v), mp 104°C (lit.: mp 105°C[115]).



IR (KBr); ν(cm^{-1}) = 2931 (s), 2844 (m), 1738 (s), 1624 (s), 1599 (m), 1447 (m), 1340 (m), 1270 (m), 1246 (m), 1187 (s), 984 (m), 937 (m), 780 (s), 746 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.20 - 1.74 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.59 (dd, $^3J_{HH}$ = 6.36 Hz, $^4J_{HH}$ = 1.14 Hz, 2H, OCH_2), 4.93 (s, 1H, 3-H), 6.23 (dt, $^3J_{HH}$ = 15.91, 6.36 Hz, 1H, *C*H=CH), 6.64 (d, $^3J_{HH}$ = 15.91Hz, 1H, CH=C*H*), 7.19 - 7.35 (m, 5H, Ph).

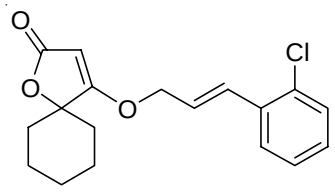
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 22.1 (CH_2, C-7 and C-9), 24.8 (CH_2, C-8), 33.5 (CH_2, C-6 and C-10), 73.4 (CH_2, OCH_2), 84.5 (C^q, C-5-*spiro*), 88.1 (CH, C-3), 121.5 (CH, *C*H=CH), 127.2, 129.0, 129.1 (CH, Ph), 135.7 (CH, CH=*C*H), 136.0 (C^q, Ph-*ipso*), 172.6 (C^q, C-2), 185.4 (C^q, C-4).

MS (EI, 70 eV): m/z = 285 (10) [M^++1], 284 (43) [M^+], 266 (4) [M^+-H_2O], 240 (19) [M^+-CO_2], 206 (16) [M^+-C_6H_6], 175 (20), 157 (17), 117 (100) [$C_9H_9^+$], 116 (14), 91 (28), 69 (12), 55 (9), 39 (12).

Accurate Mass:- Calculated Mass = 284.14124 Found = 284.14128

4-{[(2'E)-3'-(2''-Chlorophenyl)prop-2'-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one 121b

Clear oil (1.18 g, 3.71 mmol, 66%) from (2E)-3-(2-chlorophenyl)prop-2-enyl 1-hydroxycyclohexanecarboxylate **23b** (2.5 g, 8.50 mmol), keteneylidenetriphenylphosphorane **1** (3.50 g, 11.59 mmol) and benzoic acid (catalytic amount) in THF (50 ml) for 15 hr. Molecular formula $C_{18}H_{19}ClO_3$. R_f 0.17 (diethyl ether: hexane, 1:1, v:v).



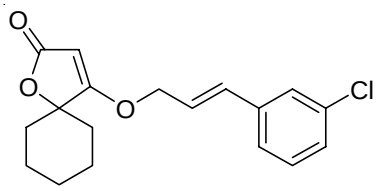
IR (film, KBr); ν(cm^{-1}) = 2937 (s), 2860 (m), 1748 (s) [ν (C=O)], 1625 (s), 1445 (m), 1337 (s), 1268 (w), 1192 (s), 1133 (w), 1037 (w), 978 (m), 807 (w), 753 (s) [ν (C-Cl)].

^{1}H-NMR (500 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.17 - 1.22 and 1.58 - 1.76 (m, 10 H, 6-H, 7-H,8-H, 9-H, 10-H), 4.65 (dd, $^3J_{HH}$ = 6.06 Hz, $^4J_{HH}$ = 1.4 Hz, 2H, OCH_2), 4.94 (s, 1H, 3-H), 6.21 (dt, $^3J_{HH}$ = 15.94 Hz, 6.06 Hz, 1H, C*H*=CH), 7.04 (d, $^3J_{HH}$ = 15.94 Hz, 1H, CH=C*H*), 7.15 - 7.21 (m, 1H, Ar), 7.30 - 7.32 (m, 2H, Ar), 7.46 - 7.48 (m, 1H, Ar).

^{13}C-NMR-JMOD (125.7 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.7 (CH_2, C-7 and C-9), 24.4 (CH_2, C-8), 33.1 (CH_2, C-6 and C-10), 72.6 (CH_2, OCH_2), 84.0 (C^q, C-5-*spiro*), 87.8 (CH, C-3), 123.9, 127.0, 129.5, 131.2 (CH, Ar), 133.4 (C^q, Ar-Cl), 133.7 (C^q, Ar-*ipso*), 172.1 (C^q, C-2), 184.8 (C^q, C-4).

MS (EI, 70 eV): m/z = 320 (17) [M^+, ^{37}Cl], 318 (76) [M^+, ^{35}Cl], 302 (3) [M^+ - H_2O, ^{37}Cl], 300 (9) [M^+ - H_2O, ^{35}Cl], 283 (100) [M^+ - Cl], 274 (7), 265 (1), 246 (1), 239 (2), 220 (3).

4-{[(2'*E*)-3'-(3''-Chlorophenyl)prop-2'-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one 121c. Colourless oil (1.67 g, 5.25 mmol, 70%) from (2E)-3-(3-chlorophenyl)prop-2-enyl 1-hydroxycyclohexanecarboxylate **23c** (2.23 g, 7.57 mmol) and keteneylidenetriphenylphosphorane **1** (2.74 g, 9.10 mmol) in THF (50 ml). Product purified by column chromatography. R_f 0.40 (diethyl ether: hexane, 1:1, v:v). Formula $C_{18}H_{19}ClO_3$.



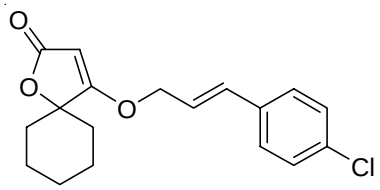
IR (film, KBr); ν(cm^{-1}) = 2937 (s), 2860 (m), 1749 (s) [ν (C=O stretch], 1626 (s), 1449 (w), 1337 (m), 1268 (w), 1241 (w), 1193 (s), 1135 (w), 1093 (w), 979 (m), 807 (m), 777 (w), 686 (s).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.25 - 1.85 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10H), 4.64 (d, $^3J_{HH}$ = 5.99 Hz, 2H, OCH_2), 4.98 (s, 1H, 3-H), 6.28 (dt, $^3J_{HH}$ = 15.87 Hz, 5.99 Hz, 1H, C*H*=CH), 6.62 (d, $^3J_{HH}$ = 15.87 Hz, 1H, CH=C*H*), 7.26 - 7.38 (m, 4H, Ar).

^{13}C-JMOD NMR (126 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.7 (CH_2, C-7 and C-9), 24.4 (CH_2, C-8), 33.1 (CH_2, C-6 and C-10), 72.5 (CH_2, OCH_2), 84.0 (C^q, C-5), 87.8 (CH, C-3), 122.7 (CH, *C*H=CH), 125.0, 126.6, 128.5, 130.0 (CH, Ar), 133.9 (CH;CH=*C*H), 134.7 (C^q, Ar-Cl), 137.3 (C^q, Ar-*ipso*), 172.0 (C^q; C-2), 184.8 (C^q; C-4).

MS (EI, 70 eV):m/z = 321 (1) [M^++1, ^{37}Cl], 320 (3) [M^+, ^{37}Cl], 319 (2) [M^++1, ^{35}Cl], 318 (6) [M^+, ^{35}Cl], 302 (1) [M^+-H_2O, ^{37}Cl], 300 (3) [M^+-H_2O, ^{35}Cl], 279 (1), 277 (2), 249 (2), 220 (1), 209 (3), 153 (40) [$C_9H_8{}^{37}Cl$], 151 (100) [$C_9H_8{}^{35}Cl$], 127 (2), 125 (7), 116(18), 115 (43), 81 (2), 69 (3), 55 (2), 41 (2).

4-{[(2'*E*)-3'-(4''-Chlorophenyl)prop-2'-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one 121d. White solid (1.15 g, 3.62 mmol, 50%) from (2E,4E)-hexa-2,4-dienyl 1-hydroxy cyclohexanecarboxylate **23d** (2.11 g, 7.18 mmol), keteneylidenetriphenylphosphorane **1** (2.81 g, 9.30 mmol) and benzoic acid (catalytic amount) dissolved in dry THF (100 ml) under a nitrogen atmosphere. Solution refluxed for 16h. Molecular formula $C_{18}H_{19}ClO_3$. R_f 0.24 (diethyl ether:hexane, 1:1, v:v), mp 111 - 112°C.



IR (KBr); ν(cm^{-1}) = 3112 (w), 2934 (s), 2847 (w), 1753 (s) and 1624 (s) [ν (C=O)], 1488 (m), 1443 (m), 1401 (w), 1334 (s), 1268 (m), 1234 (m), 1189 (s), 1131 (w), 1087 (s), 960 (s), 932 (s), 849 (s), 818 (s), 692 (m), 617 (w), 500 (m).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.81 - 1.89 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.64 (d, $^{3}J_{HH}$ = 6.32 Hz, 2H, OCH_2), 4.98 (s, 1H, OH), 6.27 (dq, $^{3}J_{HH}$ = 15.87 Hz, 1H, C*H*=CH), 6.64 (d, $^{3}J_{HH}$ = 15.87 Hz, 1H, CH=C*H*), 7.24 - 7.59 (m, 4H, Ar).

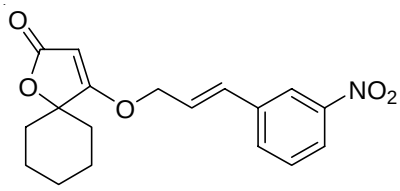
^{13}C-JMOD NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.7 (CH_2, C-7 and C-9), 24.4 (CH_2, C-8), 33.1 (CH_2, C-6 and C-10), 72.7 (CH_2, OCH_2), 121.8 (CH, *C*H=CH), 127.9 128.9 (CH, Ar), 134.0 (C^q, Ar-Cl), 134.2 (CH, CH=*C*H), 134.3 (C^q, Ar-*ipso*), 172.0 (C^q, C-2), 184.8 (C^q, C-4).

MS (EI, 70 eV): m/z = 320 (0.3) [M^+, ^{37}Cl], 318 (0.9) [M^+, ^{35}Cl], 302 (0.1) [M^+-H_2O, ^{37}Cl], 300 (0.3) [M^+-H_2O, ^{35}Cl], 276 (0.3) [M^+-CO_2, ^{37}Cl], 274 (0.9) [M^+-CO_2], 210 (0.1), 208 (0.3), 153 (32) [$C_9H_8Cl^+$, $_{37}$Cl], 151 (100) [$C_9H_8Cl^+$, ^{35}Cl], 116 (44), 115 (63) [$C_6H_{11}O_2^+$], 99 (1) [*115* - H_2O], 89 (3), 69 (5), 55 (3), 41 (2).

$C_{18}H_{19}ClO_3$ (318.79): Calculated C = 67.82%, H = 6.01%; found C = 67.49%, H = 5.87%.

4-{[(2*E*)-3-(3-Nitrophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one 121e.

Yellow solid (2.38 g, 7.23 mmol, 93%) from (2E)-3-(3-nitrophenyl)prop-2-enyl 1-hydroxycyclohexanecarboxylate **23e** (2.38 g, 7.80 mmol) and keteneylidene triphenylphosphorane **1** (3.53 g, 11.70 mmol) in dry THF (100 ml) refluxed for 24 hours. Molecular formula $C_{18}H_{19}NO_5$. R_f 0.29 (diethyl ether:hexane, 1:1, v:v) mp 117 - 119 °C.



IR (KBr); ν(cm^{-1}) = 3087 (w), 3039 (w), 2937 (m), 2870 (w), 1745 (s) [ν (C=O)], 1627 (s), 1530 (s) [ν (NO_2)], 1441 (w), 1352 (s) [ν (NO_2)], 1292 (m), 1243 (m), 1200 (m), 1079 (w), 1057 (m), 970 (m), 949 (w), 911 (w), 806 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.21 - 1.83 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.70 (dd, $^{3}J_{HH}$ = 5.93 Hz, $^{4}J_{HH}$ = 1.42, 2H, OCH_2), 4.99 (s, 1H, 3-H), 6.43 (dt, $^{3}J_{HH}$ = 15.99 Hz, 5.93 Hz, 1H, C*H*=CH), 6.75 (d, $^{3}J_{HH}$ = 15.99 Hz, 1H, CH=C*H*), 7.24 - 7.71 (m, 2H, Ar), 8.11 - 8.26 (m, 2H, Ar).

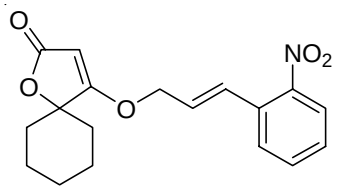
^{13}C-NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.7 (CH_2, C-7 and C-9), 24.4 (CH_2, C-8), 33.1, 33.2 (CH_2, C-6 and C-10), 72.1 (CH_2, OCH_2), 84.0 (C^q, C-5), 88.0 (CH, C-3), 121.3 (CH, *C*H=CH), 123.0, 124.7, 129.6, 129.8 (CH, Ph), 132.5 (CH, CH=*C*H), 137.3 (C^q, Ar-*ipso*), 148.3 (C^q, Ar-NO_2), 171.9 (C^q, C-2), 184.7 (C^q, C-4).

MS (EI, 70 eV): m/z = 330 (0.25) [M^++1], 329 (0.5) [M^+], 313 (0.5) [M^+-O], 299 (0.75) [M^+-NO], 277 (0.5), 225 (0.3), 203 (2), 162 (86) [$C_9H_8NO_2^+$], 116 (100), 115 (72), 110 (8),

99 (3) [$C_6H_{11}O^+$], 81 (4) [$C_6H_9^+$], 69 (6), 55 (4), 41 (2).

$C_{18}H_{19}NO_5$ (329.35): Calculated C = 65.64%, H = 5.81%, N = 4.25%; found C = 65.59%, H = 5.79%, N = 4.11%.

4-{[(2'*E*)-3'-(2''-Nitrophenyl)prop-2'-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one 121f. Brown oil (1.44 g, 4.38 mmol, 44%) from (2E)-3-(2-nitrophenyl)prop-2-enyl 1-hydroxy cyclohexanecarboxylate **23f** (3.00 g, 9.84 mmol) keteneylidenetriphenylphosphorane **1** (4.48 g, 14.76 mmol) and benzoic acid (catalytic amount) refluxed for 18h in dry THF (80 ml). Molecular formula $C_{18}H_{19}NO_5$. R_f 0.18 (diethylether: hexane, 1:1, v:v).



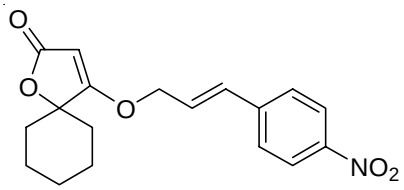
IR (film, KBr); ν(cm-^{1}) = 3114 (w), 3067 (w), 2938 (s), 2861 (s), 1750 (s) and 1627 (s) [ν (C=O)], 1572 (w), 1524 (s), 1447 (m), 1343 (s), 1267 (m), 1194 (m), 1036 (w), 982 (s), 857 (m), 808 (m), 734 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.20 - 1.80 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.70 (dd, $^3J_{HH}$ = 5.76 Hz, $^4J_{HH}$ = 1.54 Hz, 2H, OCH_2), 4.99 (s, 1H, 3-H), 6.23 (dt, $^3J_{HH}$ = 15.81 Hz, 5.76 Hz, 1H, C*H*=CH), 7.21 (dt, $^3J_{HH}$ = 15.81 Hz, $^4J_{HH}$ = 1.54 Hz, 1H, CH=CH), 7.43 - 7.47 (m, 1H, Ar), 7.57 - 7.60 (m, 2H, Ar), 7.95 - 7.98 (m, 1H, Ar).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.7 (CH_2, C-7 and C-9), 24.3 (CH_2, C-8), 33.0, 33.1 (CH_2, C-6 and C-10), 72.0 (CH_2, OCH_2), 84.0 (C^q, C-5), 87.9 (CH, C-3), 124.7 (CH, *C*H=CH), 126.6, 128.9, 129.1, 130.0 (CH, Ar), 131.3 (C^q, Ar-*ipso*), 133.5 (CH, CH=*C*H), 147.7 (C^q, Ar-NO_2), 172.0 (C^q, C-2), 184.8 (C^q, C-4).

MS (EI, 70 eV): m/z = 329 (0.2) [M^+], 303 (1.2), 277 (5), 262 (8), 163 (21), 162 (58), 117 (34), 116 (100), 115 (25), 105 (8), 99 (4) [$C_6H_{10}OH^+$], 77 (7), 55 (9).

4-{[(2'*E*)-3'-(4''-Nitrophenyl)prop-2'-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one 121g. White solid (840 mg, 2.55 mmol, 78%) from (2E)-3-(4-nitrophenyl)prop-2-enyl 1-hydroxy cyclohexanecarboxylate **23g** (1.0 g, 3.27 mmol), keteneylidenetriphenylphosphorane **1** (1.48 g, 5.0 mmol) and benzoic acid (catalytic amount) dissolved in THF (60 ml). Solution refluxed for 16 hours. R_f 0.34 (ethyl acetate: hexane, 1:1, v:v), mp 156 °C.



IR (KBr); ν(cm^{-1}) = 2927 (m), 2853 (w), 1732 (s) and 1621 (s) [ν (C=O)], 1513 (m) [ν (NO_2)], 1336 (s) [ν (NO_2)], 1201 (m), 1105 (w), 970 (w), 858 (w).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.23 - 1.80 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.70 (dd, $^3J_{HH}$ = 5.85 Hz, $^4J_{HH}$ = 1.37 Hz, 2H, OCH_2), 4.99 (s, 1H, CH-3), 6.46 (dt, $^3J_{HH}$ = 16.00 Hz, 5.85 Hz, 1H, C*H*=CH), 6.75 (d, $^3J_{HH}$ = 6.75 Hz, 1H, CH=C*H*),

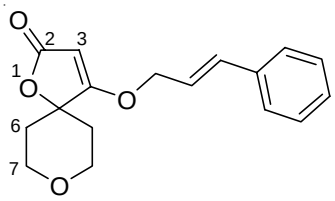
7.53 (d, $^{3}J_{HH}$ = 8.83 Hz, 2H, Ar-*meta*-H), 8.19 (d, $^{3}J_{HH}$ = 8.83 Hz, 2H, Ar-*ortho*-H).

^{13}C-NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.7 (CH_2, C-7 and C-9), 24.4 (CH_2, C-8), 33.1 (CH_2, C-6 and C-10), 72.1 (CH_2, OCH_2), 84.0 (CH, C-3), 88.0 (C^q, C-5-*spiro*), 124.1 (2xCH, Ar-*meta*), 126.1 (CH, *C*H=CH), 127.3 (2xCH, Ar-*ortho*), 132.5 (C^q, C-*ipso*), 147.5 (C^q, C-NO_2), 171.8 (C^q, C-2), 184.6 (C^q, C-4).

MS (EI, 70 eV): m/z = 330 (1) [M^++1], 329 (2) [M^+], 311 (1) [M^+-H_2O], 163 (3), 162 (40), 117 (28), 116 (100), 115 (25), 110 (16), 69 (2).

4-{[(2'*E*)-3'-Phenylprop-2'-enyl]oxy}-1,8-dioxaspiro[4.5]dec-3-en-2-one 121h.

White solid (2.88 g, 10.07 mmol, 69%) from (2E)-3-phenylprop-2-enyl 4-hydroxytetrahydro-2H-pyran-4-carboxylate **141g** (3.85 g, 14.69 mmol), keteneylidenetriphenylphosphorane **1** (6.00 g, 19.87 mmol) and benzoic acid (catalytic amount) dissolved in THF (125 ml) and refluxed for 72h. Molecular formula $C_{17}H_{18}O_4$. R_f 0.16 (ethyl acetate: hexane, 1:3, v:v), mp 74 - 75 °C.



IR (KBr); ν(cm^{-1}) = 3106 (m), 3028 (w), 2954 (m), 2923 (w), 2871 (m), 1747 (s), 1628 (s), 1453 (w), 1433 (w), 1343 (s), 1301 (m), 1247 (m), 1202 (s), 1153 (m), 1120 (s), 1100 (s), 1060 (w), 1020 (w), 978 (s), 933 (s), 827 (s), 783 (w), 732 (m), 692 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.42 - 1.51 and 2.03 - 2.19 (m, 4H, 6-H and 10-H), 3.73 - 3.94 (m, 4H, 7-H and 9-H), 4.67 (dd, $^{3}J_{HH}$ = 6.34 Hz, $^{4}J_{HH}$ = 1.32 Hz, 2H, OCH_2), 5.04 (s, 1H, 3-H), 6.27 (dt, $^{3}J_{HH}$ = 15.92, 6.34 Hz, 1H, C*H*=CH), 6.69 (d, $^{3}J_{HH}$ = 15.92 Hz, 1H, CH=C*H*), 7.24 - 7.39 (m, 5H, Ar).

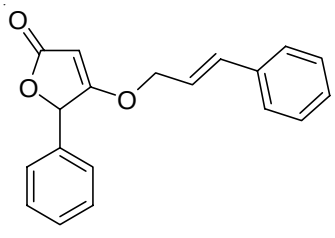
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 32.9, 33.0 (CH_2, C-6 and C-10), 63.5 (CH_2, C-7 and C-9), 73.2 (CH_2, OCH_2), 81.0 (C^q, C-5), 88.2 (CH, C-3), 120.7 (CH, *C*H=CH), 126.7, 128.6, 128.7 (CH, Ar), 135.3 (C^q, Ar-*ipso*), 135.8 (CH, CH=*C*H), 171.3 (C^q, C-2), 183.1 (C^q, C-4).

MS (EI, 70 eV):m/z = 287 (0.4) [M^++1], 286 (2.6) [M^+], 268 (0.5) [M^+-H_2O], 242 (1.4) [M^+-CO_2], 198 (2.4), 174 (2.6), 157 (4.6), 154 (5), 140 (1.6), 118 (19), 117 (100) [$C_9H_9^+$], 116 (11), 115 (37), 91 (19) 69 (17), 39 (8).

Accurate Mass:- Calculated Mass = 286.12051 Found = 286.12052

5-Phenyl-4-{[(2'*E*)-3'-phenylprop-2'-enyl]oxy}furan-2(5*H*)-one 121i.

White solid (3.52 g, 12.05 mmol, 58%) from (2E)-3-phenylprop-2-enyl hydroxy(phenyl)acetate **23i** (5.56 g, 20.75 mmol) and keteneylidenetriphenylphosphorane **1** (8.14 g, 26.95 mmol) refluxed in dry THF (150 ml) overnight. Molecular formula $C_{19}H_{16}O_3$. R_f 0.29 (diethyl ether:hexane, 1:1, v:v) mp 116°C.



IR (KBr); ν(cm^{-1}) = 3025 (w), 2928 (w), 1740 (s) [ν (C=O)], 1618 (s), 1449 (m), 1327 (m), 1283 (w), 1229 (m), 1158 (m), 1046 (m), 971 (m), 936 (m), 899 (w), 750 (s), 691 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 4.64 - 4.68 (m, 2H, OCH_2), 5.19 (d, $^4J_{HH}$ = 1.08 Hz, 1H, 5-H), 5.70 (d, $^4J_{HH}$ = 1.08 Hz, 1H, 3-H), 6.19 (dt, $^3J_{HH}$ = 15.92 Hz, 6.29 Hz, 1H, C*H*=CH), 6.59 (dt, $^3J_{HH}$ = 15.92 Hz, $^4J_{HH}$ = 1.33 Hz, 1H, CH=C*H*), 7.24 - 7.40 (m, 10H, Ar).

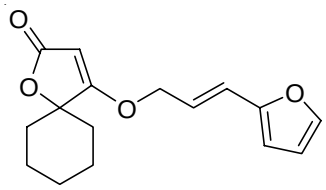
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 73.3 (CH_2, OCH_2), 80.4 (CH, C-3), 88.9 (CH, C-5), 120.7 (CH, *C*H=CH), 126.6, 126.7, 128.6, 128.7, 128.8, 129.3 (CH, Ar), 134.1 (C^q, C-6), 135.4 (C^q, Ar-*ipso*), 135.7 (CH, CH=*C*H), 172.6 (C^q, C-2), 180.2 (C^q, C-4).

MS (EI, 70 eV): m/z = 293 (1) [M^++1], 292 (5) [M^+], 274 (5) [M^+-H_2O], 248 (2) [M^+-CO_2], 230 (1) [M^+-H_2O-CO_2], 217 (1) [*230* - CH], 157 (6), 129 (12), 118 (37), 117 (100) [$C_9H_9^+$], 116 (8), 115 (24), 105 (17) [$C_8H_9^+$], 91 (19) [$C_7H_7^+$], 77 (6) [$C_6H_6^+$], 51 (3), 39 (2).

Accurate Mass:- Calculated Mass = 292.10990 Found = 292.10994

4-{[(2*E*)-3-(2-Furyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one 121j.

Brown oil (1.27 g, 5.08 mmol, 77%), from (2E)-3-(2-furyl)prop-2-enyl 1-hydroxy cyclohexanecarboxylate **23j** (1.51 g, 6.04 mmol) and keteneylidenetriphenylphosphorane **1** (2.74 g, 9.06 mmol) refluxed in THF (50 ml) for 27 h. Molecular formula $C_{16}H_{18}O_4$. R_f 0.30 (diethyl ether:hexane, 1:1, v:v).



IR (KBr); ν(cm^{-1}) = 3118 (w), 2937 (s), 2861 (m), 1748 (s), 1625 (s), 1488 (w), 1449 (m), 1336 (s), 1266 (m), 1193 (s), 1138 (m), 1013 (m), 979 (s), 806 (m), 741 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.20 - 1.75 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.61 (dd, $^3J_{HH}$ = 6.35 Hz, $^4J_{HH}$ = 1.22 Hz, 2H, OCH_2), 4.95 (s, 1H, 3-H), 6.20 (dt, $^3J_{HH}$ = 15.82, 6.35 Hz, 1H, C*H*=CH), 6.32 (d, $^3J_{HH}$ = 3.32 Hz, 1H, OCCH), 6.38 (dd, $^3J_{HH}$ = 3.32, 1.73 Hz, 1H, OCCHC*H*), 6.47 (dt, $^3J_{HH}$ = 15.82 Hz, $^4J_{HH}$ = 1.22 Hz, 1H, CH=C*H*), 7.37 (d, $^3J_{HH}$ = 1.73 Hz, OCH).

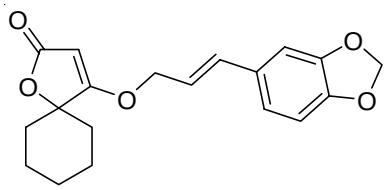
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.3 (CH_2, C-7 and C-9), 24.4 (CH_2, C-8), 33.0, 33.2 (CH_2, C-6 and C-10), 72.6 (CH_2, OCH_2), 84.1 (C^q, C-5), 87.8 (CH, C-3), 109.9 (CH, OC^qCH), 111.6 (CH, OC^qCHCH), 119.5 (CH, *C*H=CH), 123.4 (CH, CH=*C*H), 142.9 (CH, O*C*H), 151.2 (C^q, OC^q), 172.2 (C^q, C-2), 184.9 (C^q, C-4).

MS (EI, 70 eV): m/z = 275 (2) [M^++1], 274 (8) [M^+], 256 (1) [M^+-H_2O], 169 (8), 164 (16), 107 (100) [$C_7H_7O^+$], 79 (15), 77 (13), 69 (6), 43 (9).

Accurate Mass:- Calculated Mass = 274.12051 Found = 274.12052

4-{[(2'*E*)-3'-(1'',3''-Benzodioxol-5''-yl)prop-2'-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one 121k.

Colourless oil (1.48 g, 4.51 mmol, 72%) from (2E)-3-(1,3-benzodioxol-5-yl)prop-2-enyl 1-hydroxycyclohexanecarboxylate **23k** (1.90 g, 6.25 mmol), keteneylidenetriphenylphosphorane **1** (2.83 g, 9.37 mmol), benzoic acid (catalytic amount) dissolved in dry THF (60 ml) and heated to reflux for 24 h). Molecular formula $C_{19}H_{20}O_5$. R_f 0.46 (diethyl ether: hexane, 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 2938 (s), 2860 (m), 1745 (s), 1628 (s), 1490 (s), 1446 (s), 1336 (s), 1249 (s), 1197 (s), 1135 (m), 1037 (s), 981 (s), 941 (s), 852 (m), 804 (m), 766 (m), 682 (w).

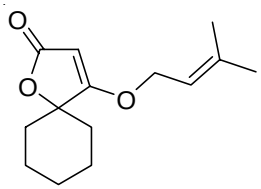
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.20 - 1.74 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.60 (dd, $^3J_{HH}$ = 6.50 Hz, $^4J_{HH}$ = 1.25 Hz, 2H, OCH_2), 4.94 (d, J_{HH} = 10.25 Hz, 1H, 3-H), 5.94 (s, 2H, OCH_2O), 6.09 (dt, $^3J_{HH}$ = 15.81 Hz, 6.50 Hz, 1H, C*H*=CH), 6.58 (d, $^3J_{HH}$ = 15.81 Hz, 1H, CH=C*H*), 6.73 - 6.91 (m, 3H, Ar).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.7 (CH_2, C-7 and C-9), 24.4 (CH_2, C-8), 33.1, 33.2 (CH_2, C-6 and C-10), 73.1 (CH_2, OCH_2), 86.9, 87.6 (CH, C-3), 101.2 (CH_2, OCH_2O), 105.8, 108.3, 121.8 (CH, Ar), 119.2 (CH, C*H*=CH), 129.9 (C^q, Ar-*ipso*), 135.5 (CH, CH=C*H*), 148.0, 148.2 (C^q, Ar-3 and Ar-4), 172.2 (C^q, C-2), 184.9 (C^q, C-4).

MS (EI, 70 eV): m/z = 329 (3) [M^++1], 328 (12) [M^+], 310 (2) [M^+-H_2O], 161 (78) [$CH_2OC_6H_3C_3H_4O^+$], 131 (100) [*161* - OCH_2], 103 (40) [*131* - CO], 79 (8), 77 (17), 55 (7), 41 (8).

4-[(3'-Methylbut-2'-enyl)oxy]-1-oxaspiro[4.5]dec-3-en-2-one 121m.[115]

White solid (1.28 g, 5.42 mmol, 64%) from 3-methylbut-2-en-1-yl 1-hydroxycyclo hexanecarboxylate **23m** (1.80 g, 8.49 mmol), keteneylidenetriphenylphosphorane **1** (3.20 g, 10.59 mmol) and benzoic acid (catalytic amount) dissolved in dry THF (60 ml) and refluxed for 16h. Molecular formula $C_{14}H_{20}O_3$. R_f 0.49 (diethyl ether: hexane, 1:1, v:v), mp 37°C.



IR (KBr); ν(cm^{-1}) = 2939 (s), 2860 (m), 1753 (s), 1624 (s), 1445 (m), 1382 (s), 1345 (m), 1326 (m), 1264 (m), 1191 (s), 1136 (s), 985 (s), 937 (s), 805 (w).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.26 - 1.80 (m, 16H, 6-H, 7-H, 8-H, 9-H, 10-H, $C^q(CH_3)_2$), 4.50 (d, $^3J_{HH}$ = 6.97 Hz, 2H, OCH_2), 4.91 (s, 1H, 3-H), 5.39 (t, $^3J_{HH}$ = 6.97 Hz, 1H, $CH=C^q$).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 18.7 (CH_3, $C^q(CH_3)$-*cis*), 22.1 (CH_2, C-7 and C-9), 24.8 (CH_2, C-8), 26.2 (CH_3, $C^q(CH_3)$-*trans*), 33.3 (CH_2, C-6 and

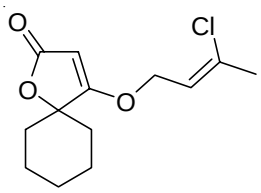
C-10), 69.6 (CH_2, OCH_2), 84.5 (C^q, C-5), 87.6 (CH, C-3), 117.6 (CH, *C*H=C^q), 141.4 (C^q, *C*$^q(CH_3)_2$), 172.9 (C^q, C-2), 185.7 (C^q, C-4).

MS (EI, 70 eV): m/z = 237 (1) [M^++1], 236 (10) [M^+], 218 (34) [M^+-H_2O], 169 (45) [M^+-C_5H_7], 150 (7), 127 (5), 109 (38), 110 (17) [$C_6H_{10}CO^+$], 91 (10), 81 (24) [$C_6H_9^+$], 69 (100) [$C_5H_9^+$].

$C_{14}H_{20}O_3$ (236.14): Calculated C = 71.16%, H = 8.53%, found C = 71.20%, H = 8.63%.

4-{[(2*Z*)-3-Chlorobut-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one 121n.

White solid (1.55 g, 5.69 mmol, 44%) from (2Z)-3-chlorobut-2-enyl 1-hydroxycyclo hexanecarboxylate **23n** (3.00 g, 12.90 mmol), keteneylidenetriphenylphosphorane (4.68 g, 15.50 mmol) and benzioc acid (catalytic amount) dissolved in dry THF (75 ml) and refluxed for 48h. Molecular formula $C_{13}H_{17}ClO_3$. Mp 64ºC. *Note that this compound was not TLC active to UV, iodine, or molybdenum developing solution which could explain why a low yield was recovered after column chromatography.*



IR (KBr); ν(cm^{-1}) = 3042 (w), 2932 (s), 2859 (m), 1747 (s), 1673 (m), 1626 (s), 1452 (m), 1394 (m), 1341 (m), 1261 (m), 1226 (w), 1097 (w), 1020 (w), 986 (s), 964 (m), 940 (m), 848 (w), 794 (s), 764 (w), 692 (w), 663 (w), 634 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.19 - 1.76 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.19 (t, $^4J_{HH}$ = 1.14 Hz, 3H, CH_3), 4.67 (dt, $^3J_{HH}$ = 6.30 Hz, $^4J_{HH}$ = 1.14 Hz, 2H, OCH_2), 4.98 (s, 1H, 3-H), 5.68 (dt, $^3J_{HH}$ = 6.30, $^4J_{HH}$ = 1.14 Hz, 1H, CH=C^q).

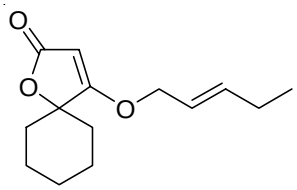
^{13}C- NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 22.1 (CH_2, C-7 and C-9), 24.8 (CH_2, C-8), 26.7 (CH_3, C-3'), 33.5 (CH_2, C-6 and C-10), 69.5 (CH_2, OCH_2), 84.3 (CH, C-3), 88.2 (C^q, C-5), 119.3 (CH, *C*H=C^q), 137.2 (C^q, CH=*C*^{q}), 172.5 (C^q, C-2), 185.1 (C^q, C-4).

MS (EI, 70 eV): m/z = 259 (13) [M^++1, ^{37}Cl], 258 (6) [M^+, ^{37}Cl], 257 (34) [M^++1, ^{35}Cl], 256 (4) [M^+, ^{35}Cl], 221 (31) [M^+-Cl], 169 (59), 168 (83) [$C_9H_{11}O_2OH^+$], 150 (31) [*168* - H_2O], 110 (67) [$C_6H_{10}CO^+$], 91 (78), 81 (47) [$C_6H_9^+$], 69 (81) [$C_5H_9^+$], 55 (100) [$C_4H_7^+$], 39 (87), 27 (96).

$C_{13}H_{17}ClO_3$ (256.72): Calculated C = 60.82%, H = 6.67%; found C = 60.80%, H = 6.62%.

4-[(2E)-Pent-2-enyloxy]-1-oxaspiro[4.5]dec-3-en-2-one 121o

Colourless oil (1.45 g, 6.14 mmol, 93%) from (2E)-pent-2-enyl 1-hydroxycyclohexanecarboxylate **23o** (1.4 g, 6.60 mmol) and keteneylidenetriphenylphosphorane **1** (2.59 g, 8.60 mmol) and benzoic acid (catalytic amount) in dry THF (100 ml). Solution was refluxed for 48 hr. Evaporation of solvent and column chromatography. Molecular formula $C_{14}H_{20}O_3$. R_f 0.79 (ethyl acetate:hexane, 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3115 (m), 2936 (s), 2861 (m), 1833 (w), 1752 (s) [ν (C=O)], 1627 (s), 1450 (m), 1340 (s), 1268 (m), 1240 (m), 1193 (s), 1136 (m), 1095 (w), 1069 (w), 1034 (w), 983 (m) [δ (CH=CH)-*trans*], 941 (m), 890 (w), 851 (w), 804 (m), 764 (w), 692 (w).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.00 (t, $^{3}J_{HH}$ = 7.43 Hz, 3H, CH_3), 1.15 - 1.73 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.09 (qddt, $^{3}J_{HH}$ = 7.43 Hz, $^{3}J_{HH}$ = 6.25 Hz, $^{4}J_{HH}$ = 1.60 Hz, $^{5}J_{HH}$ = 1.06 Hz, 2H, 4'-CH_2), 4.43 (ddt, $^{3}J_{HH}$ = 6.39 Hz, $^{4}J_{HH}$ = 1.19 Hz, $^{5}J_{HH}$ = 1.06 Hz, 2H, OCH_2), 4.89 (s, 1H, 3-H), 5.56 (dtt, $^{3}J_{HH}$ = 15.43 Hz, $^{3}J_{HH}$ = 6.39 Hz, $^{4}J_{HH}$ = 1.60 Hz, 1H, 2'-CH), 5.87 (dtt, $^{3}J_{HH}$ = 15.43 Hz, $^{3}J_{HH}$ = 6.25 Hz, $^{4}J_{HH}$ = 1.19 Hz, 1H, 3'-CH).

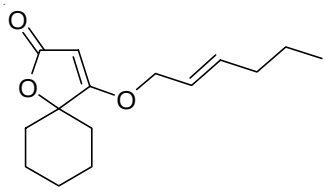
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 13.0 (CH_3, C-5'), 21.7 (CH_2, C-7 and C-9), 24.4 (CH_2, C-8), 25.3 (CH_2, C-4'), 33.1 (CH_2, C-6 and C-10), 73.1 (CH_2, OCH_2), 84.0 (C^q, C-5), 87.9 (CH, C-3), 121.2 (CH, CH-2'), 139.7 (CH, CH-3'), 172.4 (C^q, C-2), 185.0 (C^q, C-4).

MS (EI, 70 eV): m/z = 237 (1) [M^++1], 236 (3) [M^+], 208 (1) [M^+-CO], 195 (1) [M^+-C_3H_5], 169 (48), 151 (3) [M^+-C_5H_9O], 125 (1), 112 (3), 81 (3), 69 (100) [$C_5H_9^+$], 55 (9) [$C_4H_7^+$], 41 (67) [$C_3H_5^+$].

$C_{14}H_{20}O_3$ (236.31): Calculated C = 71.16%, H = 8.53%; found C = 70.98%, H = 8.62%.

4-[(2'E)-Hex-2'-enyloxy]-1-oxaspiro[4.5] dec-3-en-2-one 121p.

Colourless viscous oil (900 mg, 3.6 mmol, 90%) from (2E)-hex-2-enyl α-hydroxycyclo hexanecarboxylate **23p** (900 mg, 3.98 mmol), keteneylidenetriphenylphosphorane **1** (1.66 g 5.50 mmol) in dry THF (40 ml) and a catalytic amount of benzoic acid. Molecular formula $C_{15}H_{22}O_3$. R_f 0.46 (diethylether: hexane, 1:1, v/v).



IR (film, KBr); ν(cm^{-1}) = 2935 (s), 2863 (s), 1753 (s) [ν (C=O)], 1628 (s) [ν (C=C)], 1540 (w), 1453 (m), 1338 (s), 1267 (m), 1240 (m), 1192 (s), 1136 (m), 983 (m), 930 (m), 851 (w), 804 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.92 (t, $^{3}J_{HH}$ = 7.41 Hz, 3H, CH_3), 1.41 (sex, $^{3}J_{HH}$ = 7.41 Hz, 2H, 5'-CH_2), 1.25 - 1.76 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H, CH_2), 2.04 - 2.11 (m, 2H, 4'-CH_2), 4.46 (dt, $^{3}J_{HH}$ = 6.36 Hz, $^{4}J_{HH}$ = 1.06 Hz, 2H, OCH_2), 4.92 (s, 1H, 3-CH), 5.60 (dtt, $^{3}J_{HH}$ = 15.40 Hz, 6.36 Hz, $^{4}J_{HH}$ = 1.06 Hz, 1H, CH=C*H*), 5.84 (dt, $^{2}J_{HH}$ = 15.40 Hz, 6.36 Hz, 1H, C*H*=CH).

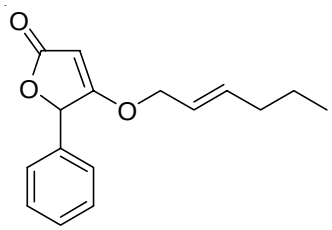
^{13}C-NMR (75.4 MHz, TMS_{int}, $CDCl_3$): δ(ppm) = 13.6 (CH_3, C-6'), 21.7, 21.9 (CH_2, C-7 and C-9), 23.5 (CH_2, C-8), 24.5 (CH_2, C-5'), 33.1 (CH_2, C-6 and C-10), 34.3 (CH_2, C-4'), 73.1 (CH_2, OCH_2), 84.0 (C^q, C-5-*spiro*), 87.4 (C^q, C-3), 122.3 (CH, *C*H=CH), 138.2 (CH, CH=*C*H), 172.4 (C^q, C-2), 185.1 (C^q, C-4).

MS (EI, 70 eV): m/z = 251 (6) [M^++1], 203 (11), 170 (24) 169 (74) [$C_9H_{13}O_3^+$], 168 (19), 151 (17) [M^+ - $C_6H_{11}O$], 150 (16), 125 (6), 124 (21), 122 (24), 113 (14), 105 (37), 99 (16), 86 (68), 83 (100) [$C_6H_{11}^+$], 77 (24), 69 (63), 55 (97), 51 (52), 49 (82), 47 (36), 41 (83), 29 (51), 28 (57), 27 (44).

Accurate Mass:- Calculated Mass = 250.156895 Found = 250.156193

(±)-**4-[(2'*E*)-Hex-2'-enyloxy]-5-phenylfuran-2(5*H*)-one 121q.**

Clear oil (4.29 g, 16.6 mmol, 84%) from (±)-(2E)-hexenyl mandalate **23q** (4.69 g, 20.00 mmol), keteneylidenetriphenylphosphorane **1** (9.10 g, 30.10 mmol) and benzoic acid (20 mg) dissolved in dry THF (150 ml) and refluxed for 18h. Molecular formula $C_{16}H_{18}O_3$. R_f 0.41 (diethyl ether:hexane, 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3034 (w), 2931 (s), 2871 (m), 1754 (s), 1628 (s), 1497 (w), 1457 (m), 1334 (s), 1273 (s), 1236 (s), 1154 (s), 1022 (m), 972 (m), 924 (m), 895 (m), 805 (m), 765 (m), 700 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.86 (t, $^3J_{HH}$ = 7.35 Hz, 3H, 6'-H), 1.36 (sex, $^3J_{HH}$ = 7.35 Hz, 2H, 5'-H), 1.99 - 2.07 (m, 2H, 4'-H), 4.38 - 4.50 (m, 2H, OCH_2), 5.11 (d, $^4J_{HH}$ = 1.07 Hz, 1H, 3-H), 5.48 (dtt, $^3J_{HH}$ = 15.41 Hz, 6.35 Hz, $^4J_{HH}$ = 1.45 Hz, 1H, 3'-CH), 5.64 (d, $^4J_{HH}$ = 1.07 Hz, 1H, 5-H), 5.75 (dtt, $^3J_{HH}$ = 15.41 Hz, 6.72 Hz, $^4J_{HH}$ = 1.12 Hz, 1H, 2'-CH), 7.28 - 7.37 (m, 5H, Ph).

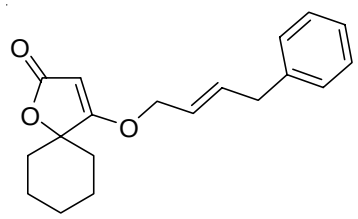
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 13.5 (CH_3, C-6'), 21.8 (CH_2, C-5'), 34.2 (CH_2, C-4'), 73.6 (CH_2, OCH_2), 80.4 (CH, C-3), 88.6 (CH, C-5), 121.9 (CH, *C*H=CH), 126.6, 128.7, 129.2 (CH, Ph), 138.5 (CH, CH=*C*H), 172.8 (C^q, C-2), 180.3 (C^q, C-4).

MS (EI, 70 eV): m/z = 259 (3) [M^++1], 258 (17) [M^+], 240 (6) [M^+-H_2O], 2'25 (4) [M^+- H_2O - CH_3], 211 (18) [*225* - CH_2], 203 (23), 177 (82), 167 (11),157 (8) 149 (11), 124 (22), 118 (67), 109 (22), 107 (42) [$C_7H_7O^+$], 105 (22), 96 (29), 95 (45), 82 (100), 81 (40), 67 (37), 55 (44).

Accurate Mass:- Calculated Mass = 258.12559 Found = 258.12558

4-{[(2'*E*)-4'-Phenylbuten-1'-yl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one 121r.

Colourless oil (717 mg, 2.41 mmol, 75%) from (2E)-4-phenylbut-2-enyl 1-hydroxycyclo hexanecarboxylate **23r** (880 mg, 3.21 mmol) and keteneylidene triphenylphosphorane **1** (1.26 g, 4.18 mmol) in dry THF (75 ml) for 16 h. Molecular formula $C_{19}H_{22}O_3$. R_f 0.21 (diethyl ether:hexane, 1:1, v:v).



IR (KBr); ν(cm^{-1}) = 3038 (m), 2936 (s), 2860 (m), 1746 (s) [C=O stretch], 1623 (s), 1449 (m), 1338 (s), 1268 (m), 1240 (m), 1192 (s), 1135 (m), 978 (m), 926 (m), 807 (m), 739 (m), 698 (m).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.19 - 1.71 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 3.42 (d, $^3J_{HH}$ = 6.65 Hz, 2H, CH_2Ph), 4.46 (d, $^3J_{HH}$ = 6.22 Hz, 2H, OCH_2), 5.66 (dt, $^3J_{HH}$ = 15.29 Hz, 6.22 Hz, 1H, C*H*=CH), 5.99 (dt, $^3J_{HH}$ = 15.29 Hz, 6.65 Hz, 1H, CH=C*H*), 7.15 - 7.37 (m, 5H, Ph).

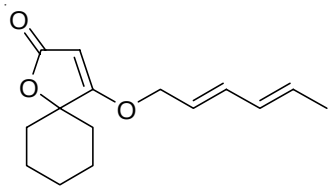
^{13}C- JMOD NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.7 (CH_2, C-7 and C-9), 24.4 (CH_2, C-8), 33.1 (CH_2, C-6 and C-10), 38.6 (CH_2, CH_2Ph), 72.7 (CH_2, OCH_2), 84.1 (C^q, C-5), 87.5 (CH, C-3), 123.5 (CH, CH=*C*H), 127.0 (CH, *C*H=CH), 126.4, 128.6, 128.7, 128.8 (CH, Ph), 136.3 (C^q, C-*ipso*), 172.3 (C^q, C-2), 185.0 (C^q, C-4).

MS (EI, 70 eV): m/z = 299 (0.2) [M^++1], 298 (0.1) [M^+], 280 (0.1) [M^+-H_2O], 273 (1), 272 (5), 258 (0.2), 217 (1), 132 (41) [$C_{10}H_{12}^+$], 131 (100) [$C_{10}H_{11}^+$], 130 (83), 116 (16) [$C_9H_9^+$], 105 (99) [$C_8H_9^+$], 104 (83), 91 (93) [$C_6H_5CH_2^+$], 77 (8) [$C_6H_5^+$], 69 (14), 55 (6), 41 (3).

$C_{19}H_{22}O_3$ (298.38): Calculated C = 76.48%, H = 7.43%; found C = 76.24%, H = 7.38%.

4-[(2*E*,4*E*)-Hexa-2,4-dienyloxy]-1-oxaspiro[4.5]dec-3-en-2-one 121s.

White solid (412 mg, 1.66 mmol, 23%) from (2*E*,4*E*)-hexa-2,4-dienyl α-hydroxy cyclohexanecarboxylate **23s** (1.62 g, 7.23 mmol) and keteneylidenetriphenylphosphorane **1** (2.90 g, 9.60 mmol) in dry THF (60 ml) refluxed for 16h, workup by column chromatography. Molecular formula $C_{15}H_{20}O_3$. R_f 0.35 (ethyl acetate:hexane, 1:1, v:v).



IR (KBr); ν(cm^{-1}) = 2938 (s), 2847 (w), 1697 (s), 1628 (m), 1447 (m), 1299 (m), 1150 (s), 1106 (m), 971 (m), 913 (w).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.38 (d, $^{3}J_{HH}$ = 6.40 Hz, 3H, CH_3), 1.11 - 1.72 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.82 (d, $^{3}J_{HH}$ = 4.33 Hz, 2H, OCH_2), 5.16 (s, 1H, 3-CH), 5.50 - 5.59 (m, 1H, 5'-CH), 5.86 - 5.96 (m, 1H, 2'CH), 6.13 - 6.26 (m, 2H, 3'CH and 4'-CH).

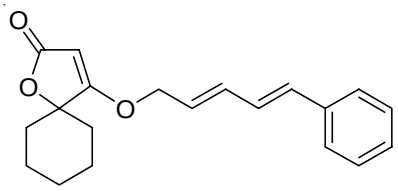
^{13}C-NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 17.8 (CH_3, C-6'), 24.4, 24.6 (CH_2, C-7 and C-9), 25.7 (CH_2, C-8), 33.1, 33.6 (CH_2, C-6 and C-10), 71.9 (CH_2, OCH_2), 79.3 (C^q, C-5), 88.0 (CH, C-3), 128.1 (CH, C-5'), 130.8 (CH, C-4'), 131.3 (CH, C-3'), 135.4 (CH, C-2'), 172.8 (C^q, C-2), 185.8 (C^q, C-4).

MS (EI, 70 eV): m/z = 248 (87) [M^+], 233 (9) [M^+-CH_3], 230 (43) [M^+-H_2O], 215 (30) [*230*-CH_3], 202 (15) [M^+-H_2O-CO], 187 (13), 175 (11), 149 (13) [M^+-H_2O-C_6H_9], 139 (12), 122 (100) [M^+-CO-C_6H_9OH], 109 (28), 94 (16), 82 (24) [$C_6H_{10}^+$], 79 (30), 67 (18), 55 (9), 41 (12).

$C_{15}H_{20}O_3$ (248.32): Calculated C = 72.55%, H = 8.12%; found C = 72.64%, H = 8.26%.

4-{[(2'*E*,4'*E*)-5-Phenylpentadie-1-nyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one 121t.

Clear oil (1.06 g, 3.42 mmol, 76%) from (2E,4E)-5-phenylpenta-2,4-dienyl 1-hydroxycyclo hexanecarboxylate **23t** (1.29 g, 4.51 mmol), ketenylidenetriphenylphosphorane **1** (2.04 g, 6.77 mmol) and benzoic acid (catalytic amount) dissolved in THF (60 ml) and refluxed for 11 h. Molecular formula $C_{20}H_{22}O_3$. R_f 0.23 (diethyl ether: hexane, 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3115 (w), 3027 (w), 2937 (s), 2860 (m), 1751 (s), 1626 (s), 1493 (w), 1449 (m), 1336 (m), 1267 (m), 1238 (m), 1191 (s), 1135 (m), 1095 (w), 1031 (w), 982 (s), 808 (m), 746 (m), 697 (m).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.16 - 1.80 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.56 (d, $^{3}J_{HH}$ = 5.57 Hz, 2H, OCH_2), 5.02 (s, 1H, 3-H), 5.83 - 5.96 (m, 1H, 2'-H), 6.22 - 6.86 (m, 3H, 3'-H, 4'-H, 5'-H), 7.24 - 7.41 (m, 5H, Ph).

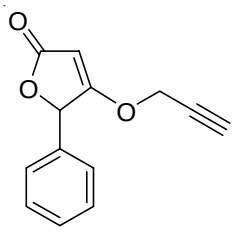
^{13}C-JMOD NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.8 (CH_2, C-7 and C-9), 24.5 (CH_2, C-8), 33.2, 33.2 (CH_2, C-6 and C-10), 74.2 (CH_2, OCH_2), 84.1 (C^q, C-5), 87.7 (CH, C-3), 126.6, 127.8, 128.4, 129.0, 129.1 (CH, Ph), 131.3, 132.7, 135.2, 136.0 (CH, C-2', C-3', C-4', C-5'), 134.3 (C^q, Ph-*ipso*), 172.1 (C^q, C-2), 184.9 (C^q, C-4).

MS (EI, 70 eV):m/z = 310 (4) [M^+], 292 (1) [M^+-H_2O], 266 (1.5) [M^+-CO2], 200 (6), 169 (6), 143 (100) [$C_{11}H_{11}^+$], 128 (38) [*143* - CH_3], 115 (10) [*128* - CH], 91 (6), 65 (6), 55 (4), 44 (3).

Accurate Mass:- Calculated Mass = 310.15689 Found = 310.15688

(±)-5-phenyl-4-(prop-2-ynyloxy)furan-2(5*H*)-one 121v.

White solid (2.50 g, 11.68 mmol, 74%) from prop-2-ynyl (2R)-hydroxy(phenyl)acetate **23v** (3.0 g, 16 mmol), keteneylidenetriphenylphosphorane **1** (6.0 g, 19.87 mmol) and benzoic acid (catalytic amount) dissolved in dry THF (75 ml). Solution was refluxed for 16 hr. Molecular formula $C_{13}H_{10}O_3$. R_f 0.17 (diethyl ether:hexane, 1:1, v:v), mp 87 °C.



IR (KBr); ν(cm^{-1}) = 3231 (s), 3115 (m), 3035 (w), 2943 (w), 2123 (m), 1738 (s) and 1618 (s) [C=O stretch], 1456 (w), 1374 (w), 1332 (m), 1296 (m), 1264 (m), 1239 (w), 1210 (w), 1167 (m), 1020 (s), 988 (m), 947 (m), 912 (m), 824 (m), 768 (m), 694 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 2.65 (t, $^4J_{HH}$ = 2.43 Hz, 1H, C^qCH), 4.65 (d, $^4J_{HH}$ = 2.43 Hz, 2H, OCH_2), 5.33 (s, 1H, 3-H), 5.70 (s, 1H, 5-H), 7.27 - 7.43 (m, 5H, Ph).

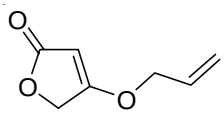
^{13}C NMR (75.4 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 60.30 (CH_2, OCH_2), 75.56 (CH, C^qCH), 78.60 (C^q, CH_2C), 80.73 (CH, C-5), 90.72 (CH, C-3), 127.20, 129.28, 129.90 (CH, Ph), 134.05 (C^q, Ph-*ipso*), 172.50 (C^q, C-2), 179.27 (C^q, C-4).

MS (EI, 70 eV): m/z = 215 (13) [M^++1], 214 (27) [M^+], 175 (14) [M^+-C_3H_3], 170 (77) [M^+-CO_2], 147 (11), 141 (14), 139 (6), 119 (17), 118 (96), 109 (63) [M^+- C_7H_5O], 105 (94) [$C_7H_5O^+$], 91 (20), 89 (12), 80 (84), 77 (100) [$C_6H_5^+$], 69 (94), 67 (50), 63 (23), 53 (42), 51 (84), 41 (24), 39 (95) [$C_3H_3^+$], 37 (10), 27 (14).

$C_{13}H_{10}O_3$ (214.22): Calculated C = 72.83%, H = 4.71%; found C = 71.83%, H = 4.55%.

4-(Allyloxy)furan-2(5*H*)-one 121x.

Colourless oil (4.70 g, 33.57 mmol, 59%) from tetronic acid **41** (5.70 g, 57.0 mmol), allyl alcohol (3.31g, 57.0 mmol) and p-toluenesulphonic acid (0.96 g, 5.70 mmol) in benzene (130 ml). Solution was refluxed in a Dean-Stark apparatus for 15h. Removal of solvent on a rotary evaporator followed by column chromatography of the residue gave a pure product. Molecular formula $C_7H_8O_3$. R_f 0.48 (ethyl acetate:hexane, 1:1, v:v). Note reaction failed completely when chloroform was used as a solvent.



IR (film, KBr); ν(cm^{-1}) = 3125 (m), 3060 (w), 2941 (s), 2877 (m), 1778 (s),1744 (s), 1628 (s), 1451 (s), 1390 (s), 1359 (m), 1320 (s), 1272 (m), 1235 (m), 1151 (s), 1051 (s), 978 (s), 885 (s) 805 (s), 725 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 4.51 (dt, $^3J_{HH}$ = 5.74 Hz, $^4J_{HH}$ = 1.38 Hz, 2H, $OCH_2CH=CH_2$), 4.58 (d, $^4J_{HH}$ = 1.18 Hz, 1H, 5-H), 5.04 (t, $^4J_{HH}$ = 1.18 Hz, 1H, 3-H),

5.31 (ddt, $^{2}J_{HH}$ = 1.20 Hz, $^{3}J_{HH}$ = 10.47 Hz, $^{4}J_{HH}$ = 1.38 Hz, 1H, CH=CH-*cis*), 5.35 (ddt, $^{2}J_{HH}$ = 1.20 Hz, $^{3}J_{HH}$ = 17.44 Hz, $^{4}J_{HH}$ = 1.38 Hz, 1H, CH=CH-*trans*), 5.90 (ddt, $^{3}J_{HH}$ = 17.44, 10.47, 5.74 Hz, 1H, C*H*=CH_2).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 67.7 (CH_2, C-5), 73.1 (CH_2, O*C*H_2CH=CH_2), 89.2 (CH, C-3), 120.0 (CH_2, CH=*C*H_2), 130.1 (CH, *C*H=CH_2), 173.3 (C^q, C-4), 178.8 (C^q, C-2).

MS (EI, 70 eV): m/z = 140 (18) [M^+], 122 (64) [M^+-H_2O], 94 (13), 82 (45) [$C_4H_2O_2^+$], 81 (31) [$C_4H_1O_2^+$], 69 (12), 66 (27) [*82* - O], 54 (100), 53 (24), 42 (21).

3.3.6 Synthesis of Claisen Rearranged 3-Allyl Tetronic Acids

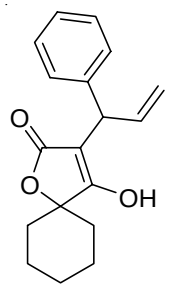
Method A: The respective tetronates **142** (5 mmol) were placed in a clean dry nitrogen flushed round bottomed flask. Dry acetonitrile (50 ml) was added and the solution was heated to an oil bath temperature of 120°C for 16h. After cooling the solvent was removed by rotary evaporation and the residue was purified by column chromatography.

Method B: The respective tetronate **142** (1 mmol) was placed in a glass tube and dry acetonitrile (5 ml) was added. The glass tube was sealed with a teflon cap and placed inside a CEM Discovery microwave oven (300W). The sample was irradiated with microwaves (300W) until a temperature of 150°C was obtained. Internal pressure was recorded as being ~ 3.8 mbar. External cooling was then applied and the sample was irradiated for a 60 minutes. After cooling the cap was removed and the solvent was evaporated on a rotary evaporator. The residue was purified by column chromatography.

Method C: A solution of the respective tetronate **142** (5 mmol) in dry toluene (15 ml) was prepared under the exclusion of air and moisture. The solution was transfered to a sealable glass tube and sealed. The tube was heated to 160°C for 16 - 24h. After cooling, the solution was removed by rotary evaporation and the residue was purified by column chromatography (silica gel, eluent as indicated).

4-Hydroxy-3-(1'-phenylprop-2'-enyl)-1-oxaspiro[4.5]dec-3-en-2-one 121a.

White solid (493 mg, 1.74 mmol, 62%) from (E)-4-(3-Phenyl-allyloxy)-1-oxa-spiro[4.5]dec-3-en-2-one **12a** (800 mg, 2.82 mmol) dissolved in dry acetonitrile (20 ml) and refluxed strongly for 24 h. Molecular formula $C_{18}H_{20}O_3$. R_f 0.15 (diethyl ether: hexane, 1:1, v:v), mp 148°C (lit.: mp 149°C[115]).



IR (KBr); ν(cm^{-1}) = 3387 (br) [ν (OH)], 3032 (w), 2940 (s), 2859 (s), 1700 (s), 1618 (s), 1493 (w), 1449 (m), 1292 (m), 1265 (s), 1231 (s), 1151 (m), 1106 (m), 980 (m), 907 (m), 805 (w), 740 (w), 695 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.09 - 1.78 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.46 (d, $^{3}J_{HH}$ = 6.33 Hz, 1H, 1'-H), 5.00 (d, $^{3}J_{HH}$ = 17.23 Hz, 1H, CH=C*H*H-*trans*), 5.21 (d, $^{3}J_{HH}$ = 10.23 Hz, 1H, CH=CH*H-cis*), 6.22 (ddd, $^{3}J_{HH}$ = 17.23 Hz, 10.23 Hz, 6.33 Hz, 1H, C*H*=CH_2), 7.15 - 7.34 (m, 5H, Ph), 8.64 (br., 1H, OH).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 20.8 (CH_2, C-7 and C-9), 23.3 (CH_2, C-8), 31.8 (CH_2, C-6 and C-10), 41.8 (CH, 1'-CH), 81.6 (C^q, C-5-*spiro*), 99.7 (C^q, C-3), 116.6 (CH_2, CH=*C*H_2), 126.3, 126.9, 128.1 (CH, Ph), 136.4 (CH, C*H*=CH_2), 138.6 (C^q, Ph-*ipso*), 171.9 (C^q, C-2), 177.7 (C^q, C-4).

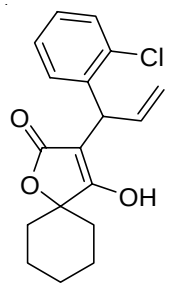
MS (EI, 70 eV): m/z = 285 (10) [M^++1], 284 (37) [M^+], 266 (12) [M^+-H_2O], 240 (16) [M^+-CO_2], 223 (1), 206 (24) [M^+-C_6H_6], 175 (16), 157 (14), 117 (100) [$C_9H_9^+$], 116 (17), 115 (47), 91 (31), 69 (14), 55 (7), 39 (10).

$C_{18}H_{20}O_3$ (284.35): Calculated C = 76.03%, H = 7.09%; found C = 75.89%, H = 6.98%.

3-[1-(2-Chlorophenyl)prop-2-enyl]-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one 122b.

Method A: No reaction observed.

Method B: White solid (227 mg, 0.72 mmol, 42%) from 4-{[(2E)-3-(2-chlorophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121b** (550 mg, 1.73 mmol) dissolved in dry acetonitrile (5 ml) and heated to 150°C and 3.8 bar with microwaves in a sealed glass tube. Molecular formula $C_{18}H_{19}ClO_3$. R_f 0.19 (diethyl ether:hexane, 1:1, v:v), mp 158 - 159°C. *Note that **119b-α** (322 mg, 1.02 mmol, 58%) was also recovered from this reaction.*



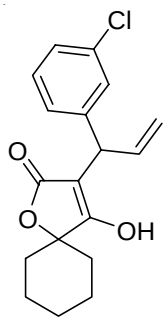
IR (KBr); ν(cm^{-1}) = 3415 (m) [ν (OH)], 2943 (s), 2862 (m), 1750 (s), 1697 (m), 1625 (s), 1472 (w), 1442 (m), 1385 (m), 1339 (m), 1263 (m), 1230 (m), 1192 (m), 1151 (m), 1098 (m), 1033 (w), 977 (s), 803 (s), 743 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.16 - 1.77 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10H), 4.65 (dd, $^{3}J_{HH}$ = 6.07 Hz, $^{4}J_{HH}$ = 1.47 Hz, 1H, 1'-CH), 5.00 (dt, $^{3}J_{HH}$ = 17.30 Hz, $^{4}J_{HH}$ = 1.47 Hz, 1H, CH=C*H*H-*trans*), 5.27 (dt, $^{3}J_{HH}$ = 10.20 Hz, $^{4}J_{HH}$ = 1.47 Hz, 1H, CH=CH*H-cis*), 6.14 - 6.26 (m, 1H, C*H*=CH2), 7.02 - 7.49 (m, 4H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.7 (CH_2, C-7 and C-9), 24.4 (CH_2, C-8), 32.8, 32.9 (CH_2, C-6 and C-10), 40.1 (CH, C-1'), 82.5 (C^q, C-5), 99.1 (C^q, C-3), 117.8 (CH_2, CH=*C*H_2), 128.5, 129.6, 129.9, 130.1 (CH, Ar), 134.1 (C^q, Ar-Cl), 136.3 (CH, *C*H=CH_2), 137.3 (C^q, Ar-*ipso*), 179.0 (C^q, C-2), 185.0 (C^q, C-4).

MS (EI, 70 eV): m/z = 321 (0.4) [M^++1, ^{37}Cl], 320 (0.8) [M^+, ^{37}Cl), 319 (0.7) (M^++1, ^{35}Cl], 318 (1.6) [M^+, ^{35}Cl], 302 (0.1) [M^+-H_2O, ^{37}Cl], 301 (0.2) [M^++1 - H_2O, ^{35}Cl], 300 (0.3) [M^+-H_2O, ^{35}Cl], 283 (78), 194 (4), 193 (3), 192 (8), 191 (6), 153 (44) [$C_9H_8{}^{37}Cl^+$], 152 (14), 151 (100) [$C_9H_8{}^{35}Cl$], 129 (22), 128 (12), 116 (53), 115 (68), 110 (5) [$C_7H_{10}O^+$], 81 (8), 69 (9), 55 (8), 41 (7).

3-[1'-(3''-Chlorophenyl)prop-2'-enyl]-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one 122c.
Method A: No reaction observed.
Method B: White solid (290 mg, 0.91 mmol, 55%) from 4-{[(2E)-3-(3-chlorophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **142b** (530 mg, 1.67 mmol) in dry acetonitrile (5 ml) with microwave irradiation at 150 °C and 3.8 bar for 80 min. Product purified by column chromatography. Molecular formula $C_{18}H_{19}ClO_3$. R_f 0.1 (diethyl ether : hexane, 1:1, v:v), mp 134 - 135 °C. *Not that **119c** (240 mg, 0.75 mmol, 45.3%) was also recovered from this reaction.*



IR (KBr); ν(cm^{-1}) = 3418 (m) [ν (OH)], 2938 (s), 2860 (m), 1745 (m) [ν (C=O)], 1702 (m), 1624 (s), 1469 (w), 1444 (m), 1388 (w), 1338 (w), 1294 (m), 1265 (s), 1228 (s), 1147 (m), 1096 (m), 978 (s), 914 (m), 779 (w), 724 (s) [ν (C-Cl)], 686 (w).

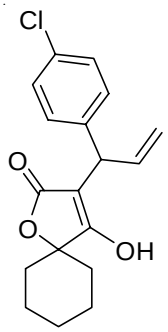
^{1}H-NMR (500 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.16 - 1.82 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.47 (d, $^3J_{HH}$ = 6.97 Hz, 1H, 1'-H), 5.05 (d, $^3J_{HH}$ = 17.20 Hz, 1H, CH=C*H*H-*trans*), 5.22 (d, $^3J_{HH}$ = 10.11 Hz, 1H, CH=CH*H-cis*), 6.27 (ddd, $^3J_{HH}$ = 17.20 Hz, 10.11 Hz, 6.97 Hz, 1H, C*H*=CH_2), 7.10 - 7.26 (m, 4H, Ar).

^{13}C-JMOD NMR (125 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.0 (CH_2; C-7 and C-9), 24.3 (CH_2; C-8), 33.0 (CH_2; C-6 and C-10), 44.2 (CH; C-1'), 83.2 (C^q; C-5-*spiro*), 100.2 (C^q; C-3), 117.5 (CH_2; CH=*C*H_2), 126.7, 127.7, 128.8, 129.7 (CH; Ar), 134.4 (C^q; Ar-Cl), 136.98 (CH; *C*H=CH_2), 142.64 (C^q; C-*ipso*), 173.66 (C^q; C-2), 179.79 (C^q; C-4).

MS (EI, 70 eV): m/z = 320 (3) [M^+, ^{37}Cl], 318 (10) [M^+, ^{35}Cl], 302 (1) [M^+-H_2O, ^{37}Cl], 300 (4) [M^+-H_2O, ^{35}Cl], 274 (3) [M^+-CO_2, ^{35}Cl], 218 (2), 209 (4), 169 (3), 157 (48), 153 (44) [$C_9H_8{}^{37}Cl^+$], 152 (41), 151 (100) [$C_9H_8{}^{35}Cl^+$], 129 (68), 116 (42), 115 (64), 110 (61), 99 (8) [$C_6H_{11}O^+$], 89 (4), 81 (8), 69 (7), 55 (9), 41 (8).

Accurate Mass:- Calculated Mass = 318.1023 Found = 318.1022

3-[1'-(4''-Chlorophenyl)prop-2'-enyl]-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one 122d.
Method A: No reaction observed.
Method B: White solid (133 mg, 0.42 mmol, 43%) from 4-{[(2E)-3-(4-chlorophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121d** (310 mg, 0.97 mmol) dissolved in dry acetonitrile (6 ml) and heated in sealed tube by microwaves to 142°C with a pressure of 3.6 bar for 1h. Molecular formula $C_{18}H_{19}ClO_3$. R_f 0.13 (diethyl ether: hexane, 1:1, v:v), mp 164 - 165°C. *Note that **119d** (160 mg, 0.50 mmol, 52%) was also recovered from the reaction.*



IR (KBr); ν(cm^{-1}) = 3420 (m) [ν (OH)], 3021 (w), 2937 (s), 2859 (m), 1689 (s), 1638 (s), 1564 (s), 1450 (m), 1404 (w), 1328 (s), 1287 (s), 1230 (m), 1154 (m), 1088 (m), 1047 (m), 1012 (w), 965 (m), 921 (m), 830 (m) [Ph-para], 762 (s) [ν (C-Cl)], 702 (m), 609 (w), 578 (w), 528 (m).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.81 - 1.86 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.47 (d, $^{3}J_{HH}$ = 7.08 Hz, 1H, 1'-H), 5.04 (d, $^{3}J_{HH}$ = 17.15 Hz, 1H, CH=CH-*trans*), 5.12 (d, $^{3}J_{HH}$ = 10.29 Hz, 1H, CH=CH-*cis*), 6.27 (ddd, $^{3}J_{HH}$ = 17.15 Hz, 10.29 Hz, 7.08 Hz, 1H, 2'-H), 7.11 - 7.36 (m, 4H, Ar), 11.26 (s, 1H, OH).

^{13}C-JMOD NMR (65 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.7, 21.8 (CH_2, C-7 and C-10), 24.3 (CH_2, C-8), 32.7, 33.2 (CH_2, C-6 and C-10), 42.3 (CH, CH-1'), 83.4 (C^q, C-5), 100.5 (C^q, C-3), 117.2 (CH_2, CH=*C*H_2), 128.0, 128.7, 129.0, 129.3 (CH, Ar), 132.6 (C^q, Ar-Cl), 137.3 (CH, *C*H=CH_2), 139.3 (C^q, Ar-*ipso*), 174.2 (C^q, C-2), 180.1 (C^q, C-4).

MS (EI, 70 eV): m/z = 321 (1) [M^++1, ^{37}Cl], 320 (6) [M^+, ^{37}Cl), 319 (3) (M^++1, ^{35}Cl], 318 (18) [M^+, ^{35}Cl], 302 (6) [M^+-H_2O, ^{37}Cl], 301 (2) [M^++1 - H_2O, ^{35}Cl], 300 (18) M^+-H_2O, ^{35}Cl], 211 (4), 209 (12), 194 (8), 193 (7), 192 (20), 191 (11), 153 (33) [$C_9H_8{}^{37}Cl^+$], 152 (32), 151 (100) [$C_9H_8{}^{35}Cl$], 129 (29), 128 (14), 116 (24), 115 (31), 110 (38) [$C_7H_{10}O^+$], 99 (4), 81 (7), 67 (5), 55 (3), 46 (4).

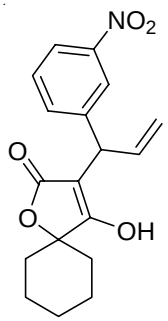
Accurate Mass:- Calculated Mass = 318.10227 Found = 318.10224

4-Hydroxy-3-[1'-(3''-nitrophenyl)prop-2'-enyl]-1-oxaspiro[4.5]dec-3-en-2-one 122e.

Method A: Brown paste (415 mg, 1.26 mmol, 56%) from 4-{[(2E)-3-(3-nitrophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121e** (740 mg, 2.25 mmol) in dry acetonitrile (40 ml) refluxed strongly for 48 hr. *Note that **119e** (59 mg, 0.18 mmol, 8%) was also recovered from the reaction.*

Method B: Brown paste (145 mg, 0.44 mmol, 44%) from 4-{[(2E)-3-(3-nitrophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121e** (330 mg, 1.00 mmol) in dry acetonitrile (5 ml) and heated in sealed tube by microwaves to 150°C with a pressure of 3.7 bar for 1h. *Note that **119e** (53 mg, 0.16 mmole, 16%) was also recovered from the reaction.*

Molecular formula $C_{18}H_{19}NO_5$ .R_f 0.79 (DCM: methanol, 9:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3423 (m) [ν (OH)], 3079 (w), 2936 (s), 2860 (w), 1729 (s), 1638 (s), 1529 (s) [ν (NO_2)], 1446 (w), 1350 (ν (NO_2)], 1259 (m), 1152 (m), 1091 (m), 969 (m), 919 (w), 781 (w), 733 (m), 689 (w).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.43 - 1.88 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.55 (d, $^3J_{HH}$ = 7.95 Hz, 1H, 1'-H), 5.14 - 5.19 (m, 2H, CH=C*H*$_2$), 6.33 - 6.44 (m, 1H, C*H*=CH_2), 7.47 - 8.19 (m, 4H, Ar).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, CD_3OD): δ (ppm) = 23.3 (CH_2, C-7 and C-9), 25.8 (CH_2, C-8), 33.9 and 34.0 (CH_2, C-6 and C-10), 44.2 (C^q, C-1'), 84.8 (C^q, C-5-*spiro*), 98.2 (C^q, C-3), 116.9 (CH_2, CH=*C*H$_2$), 122.3 (CH, Ar-2''), 123.7 (CH, Ar-4''), 130.4 (CH, Ar-5''), 135.5 (CH, Ar''-6), 138.7 (CH, *C*H=CH_2), 146.5 (C^q, Ph-*ipso*), 149.2 (C^q, Ar-NO_2), 177.1 (C^q, C-2), 187.0 (C^q, C-4).

MS (EI, 70 eV): m/z = 330 (4) [M^++1], 329 (26) [M^+], 312 (17) [M^+-OH], 294 (7), 283 (3) [M^+-NO_2], 268 (6), 248 (3), 230 (10), 203 (100) [M^+-C_6H_{10}-CO_2], 186 (69) [*203* - OH], 163 (19), 162 (62), 128 (46), 116 (51), 115 (53), 110 (22), 109 (24), 99 (24) [$C_6H_{10}O^+$], 81 (34) [*99* - H_2O], 55 (25), 41 (18).

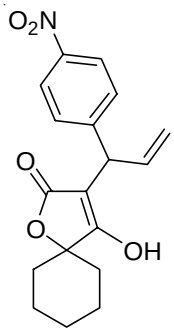
Accurate Mass:- Calculated Mass = 329.12632 Found = 329.12632

4-Hydroxy-3-[1'-(4''-nitrophenyl)prop-2'-enyl]-1-oxaspiro[4.5]dec-3-en-2-one 122g.

Method A: Red oil (128 mg, 0.39 mmol, 32%) from 4-{[(2E)-3-(4-nitrophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121g** (400 mg, 1.22 mmol) dissolved in dry acetonitrile (20 ml). Solution refluxed for 24h.

Method B: Red oil (52 mg, 0.16 mmol, 26%) from 4-{[(2E)-3-(4-nitrophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121g** (200 mg, 0.61 mmol) dissolved in dry acetonitrile (5 ml) and heated in sealed tube by microwaves to 150°C with a pressure of 3.8 bar for 1h. *Note that **119g** (74 mg, 0.22 mmol) was also recovered from the reaction.*

Molecular formula $C_{18}H_{19}NO_5$. R_f 0.41 (ethyl acetate, 100%).



IR (film, KBr); ν(cm^{-1}) = 3077 (br) [ν (OH)], 2939 (s), 2862 (m), 1706 (s), 1638 (s) [ν (CH=CH)], 1520 (s) [ν (NO_2)], 1392 (m) [ν (NO_2)], 1447 (w), 1346 (s), 1151 (w), 1106 (m), 968 (w), 910 (m), 856 (w), 733 (s).

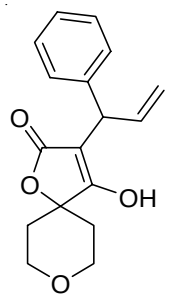
^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.10 - 1.88 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10H), 4.57 (d, $^3J_{HH}$ = 7.39 Hz, 1H, 1'-H), 5.05 (d, $^3J_{HH}$ = 17.12 Hz, 1H, CH=C*H*H-*trans*), 5.12 (d, $^3J_{HH}$ = 10.13 Hz, 1H, CH=CH*H-cis*), 6.24 (ddd, $^3J_{HH}$ = 17.12 Hz, 10.13 Hz, 7.39 Hz), 7.35 (d, $^3J_{HH}$ = 8.71 Hz, 2H, Ar-2''), 8.02 (d, $^3J_{HH}$ = 8.71 Hz, Ar-3'').

^{13}C-NMR-JMOD (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.7 (CH_2, C-7 and C-9), 24.1 (CH_2, C-8), 32.5 (CH_2, C-6 and C-10), 42.5 (CH, C-1'), 84.1 (C^q, C-5-*spiro*), 99.3 (C^q, C-3), 117.8 (CH_2, CH=*C*H_2), 123.5 (2xCH, Ar-2''), 128.6 (2xCH, Ar-3''), 136.0 (CH, *C*H=CH_2), 146.5 (C^q, Ar-*ipso*), 149.0 (C^q, Ar-NO_2), 174.9 (C^q, C-2), 181.8 (C^q, C-4).

MS (EI, 70 eV): m/z = 330 (8), [M^++1], 329 (43) [M^+], 311 (5), [M^+-H_2O], 285 (3) [M^+-CO], 204 (7), 203 (100), 186 (21), 163 (13), 162 (22), 156 (9), 128 (44), 116 (81), 115 (24), 110 (26), 99 (7), 81 (14), 69 (7), 55 (13), 41 (9).

4-Hydroxy-3-(1'-phenylprop-2''-enyl)-1,8-dioxaspiro[4.5]dec-3-en-2-one 122h.

Method B: White solid (1.08 g, 3.78 mmol, 88%) from 4-{[(2E)-3-phenylprop-2-enyl]oxy}-1,8-dioxaspiro[4.5]dec-3-en-2-one **121h** (1.23 g, 4.30 mmol) dissolved in dry acetonitrile (40 ml) and strongly refluxed for 36h. Molecular formula $C_{17}H_{18}O_4$. R_f 0.24 (ethyl acetate, 100%), mp 177°C.



IR (KBr); ν(cm^{-1}) = 3384 (br) [ν (OH)], 3024 (w), 2929 (m), 2855 (m), 1702 (s), 1622 (s), 1362 (w), 1271 (m), 1241 (s), 1151 (m), 1103 (s), 990 (w), 971 (m), 922 (m), 695 (m).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.38 - 1.48 and 2.00 - 2.20 (m, 4H, 6-H and 10-H), 3.70 - 3.94 (m, 4H, 7-H and 9-H), 4.52 (d, $^3J_{HH}$ = 6.72 Hz, 1H, 1'-CH), 5.06 (d, $^3J_{HH}$ = 17.19 Hz, 1H, CH=CH*H-trans*), 5.24 (d, $^3J_{HH}$ = 10.20 Hz, 1H, CH=C*H*H-*cis*), 6.28 (ddd, $^3J_{HH}$ = 17.19 Hz, 10.20 Hz, 6.72 Hz, 1H, C*H*=CH_2), 7.21 - 7.32 (m, 5H, Ar).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 32.7, 32.8 (CH_2, C-6 and C-10), 42.8 (CH, C-1'), 63.5, 63.6 (CH_2, C-7 and C-9), 79.6 (C^q, C-5-*spiro*), 101.5 (C^q, C-3), 117.2 (CH_2, CH=*C*H_2), 127.1, 127.7, 128.9 (CH, Ar), 137.1 (CH, *C*H=CH_2), 139.9 (C^q, Ar-*ipso*), 172.3 (C^q, C-2), 176.8 (C^q, C-4).

MS (EI, 70 eV): m/z = 286 (7) [M^+], 269 (3) [M^+-OH], 268 (6) [M^+-H_2O], 225 (6), 175 (9), 157 (21) [*175* - H_2O], 129 (39) [*157* - CO], 117 (100) [$C_6H_5C_3H_4^+$], 115 (48), 103 (11) [*117* - CH_2], 91 (24) [$C_6H_5CH_2^+$], 77 (12) [$C_6H_5^+$], 69 (8), 53 (13), 39 (10).

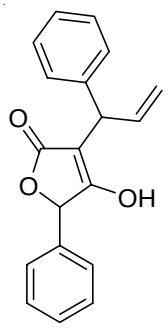
Accurate Mass:- Calculated Mass = 286.12051 Found = 286.12062

4-Hydroxy-5-phenyl-3-(1'-phenylprop-2'-enyl)furan-2(5*H*)-one 122i.

Method A: White solid (548 mg, 1.88 mmol, 42%) from 5-phenyl-4-{[(2E)-3-phenylprop-2-enyl]oxy}furan-2(5H)-one **121i** (1.30 g, 4.45 mmol) dissolved in dry acetonitrile (30 ml) and strongly refluxed for 48h. *Note that **119i** (156 mg, 0.53 mmol, 12%) was recovered from the reaction.*

Method B: White solid (183 mg, 0.63 mmol, 61%) from 5-phenyl-4-{[(2E)-3-phenylprop-2-enyl]oxy}furan-2(5H)-one **142h** (300 mg, 1.03 mmol) dissolved in dry acetonitrile (5 ml) heated in a microwave reactor to 124ºC and 3.8 bar for 60 min. *Note that **119i** (48 mg, 0.16 mmol, 16%) was also recovered from the reaction.*

Molecular formula $C_{19}H_{16}O_3$. R_f 0.63 (ethyl acetate:hexane, 1:1, v:v), mp 202ºC.



IR (KBr); ν(cm^{-1}) = 3327 (s) [ν (OH)], 3034 (m), 2930 (s), 2853 (m), 1733 (s) and 1630 (s) [ν (C=O)], 1581 (s), 1495 (m), 1451 (m), 1390 (s), 1270 (s), 1087 (m), 1008 (m), 918 (w), 847 (w), 729 (w), 698 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 4.51 - 4.55 (m, 1H, 1'-H), 5.48 (s, 1H, 5-H), 5.08 (ddd, $^3J_{HH}$ = 17.17 Hz, $^4J_{HH}$ = 2.85 Hz, $^2J_{HH}$ = 1.42 Hz, 1H, CH=CH*H-trans*), 5.22 (dd, $^3J_{HH}$ = 10.14 Hz, $^2J_{HH}$ = 1.42 Hz, 1H, CH=C*H*H-*cis*), 6.29 (ddd, $^3J_{HH}$ = 17.17 Hz, 10.14 Hz, 7.02 Hz, 1H, C*H*=CH_2), 7.13 - 7.44 (m, 5H, Ph).

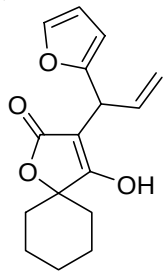
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 43.1, 43.2 (CH, C-1'), 79.7, 79.9 (CH, C-5), 102.7, 102.9 (C^q, C-3), 117.1, 117.2 (CH_2, CH=*C*H_2), 125.6, 126.4, 127.0, 127.1, 127.3, 127.8, 128.3, 128.9, 129.5, 130.1 (CH, Ph), 133.6 (C^q, Ph-*ipso*), 136.7, 137.0 (CH, *C*H=CH_2), 140.0, 140.2 (C^q, Ph-5-*ipso*), 174.2 (C^q, C-2), 174.7 (C^q, C-4).

MS (EI, 70 eV): m/z = 293 (7) [M^++1], 292 (28) [M^+], 275 (7) [M^++1-H_2O], 276 (35) [M^+-H_2O], 246 (12) [*276* - C_2H_4], 224 (50), 201 (11), 183 (12), 158 (15), 157 (21), 143 (32), 130 (27), 121 (29), 117 (82) [$C_9H_9^+$], 115 (36), 99 (41), 98 (24), 90 (19) [$C_7H_6^+$], 77 (17) [$C_6H_5^+$], 70 (17), 61 (28), 56 (100) [$C_4H_8^+$], 55 (21) [$C_4H_7^+$], 41 (12) [$C_3H_5^+$].

Accurate Mass:- Calculated Mass = 292.1099 Found = 292.1098

3-[1'-(2''-Furyl)prop-2'-enyl]-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one 122j.

Method B: Brown oil (41 mg, 0.15 mmol, 51%) from 4-{[(2E)-3-(2-furyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121j** (80 mg, 0.29 mmol) dissolved in dry acetonitrile (6 ml) and heated in sealed tube by microwaves to 142ºC with a pressure of 3.6 bar for 1h. Molecular formula $C_{16}H_{18}O_4$. R_f 0.17 (diethyl ether, hexane, 1:1, v:v).



IR (KBr); ν(cm^{-1}) = 3394 (br) [ν (OH)], 2962 (s), 2861 (m), 1746 (s), 1655 (s), 1449 (m), 1399 (m), 1261 (s), 1095 (s), 1021 (s), 861 (w), 800 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.23 - 1.79 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.57 (dt, $^{3}J_{HH}$ = 5.15 Hz, $^{4}J_{HH}$ = 1.78 Hz, 1H, 1'-H), 5.04 (ddd, $^{3}J_{HH}$ = 17.14 Hz, $^{4}J_{HH}$ = 1.87 Hz, $^{2}J_{HH}$ = 0.95 Hz, 1H, CH=CH*H-trans*), 5.18 (ddd, $^{3}J_{HH}$ = 10.15 Hz, $^{4}J_{HH}$ = 1.87 Hz, $^{2}J_{HH}$ = 0.95 Hz, 1H, CH=C*H*H-*cis*), 5.97 (ddd, $^{3}J_{HH}$ = 17.14, 10.15, 5.15 Hz, 1H, C*H*=CH_2), 6.18 - 6.20 (m, 1H, OCH=C*H*), 6.34 - 6.36 (m, 1H, OC^{q}=C*H*), 7.39 (dd, $^{3}J_{HH}$ = 1.92 Hz, $^{4}J_{HH}$ = 0.92 Hz, 1H, OCH), 7.65 (s, 1H, OH).

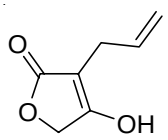
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.7 (CH_2, C-7 and C-9), 24.5 (CH_2, C-8), 32.8, 33.1 (CH_2, C-6 and C-10), 36.5 (CH_2, C-1'), 82.6 (C^{q}, C-5), 98.6 (C^{q}, C-3), 107.3, 111.0 (CH, OCH*C*H*C*H), 116.4 (CH_2, CH=*C*H_2), 134.9 (CH, C-2'), 142.2 (CH, OCH), 153.2 (C^{q}, furan-*ipso*), 172.2 (C^{q}, C-2), 178.6 (C^{q}, C-4).

MS (EI, 70 eV): m/z = 275 (12) [M^{+}+1], 274 (54) [M^{+}], 256 (100) [M^{+}-H_2O], 241 (57) [*256* - CH_3], 228 (22), 227 (21), 214 (19), 174 (34), 147 (55), 107 (100) [$C_7H_7O^{+}$], 91 (41), 55 (16), 41 (23).

Accurate Mass:- Calculated Mass = 274.12051 Found = 274.12050

3-Allyl-4-hydroxyfuran-2(5*H*)-one 188.

White solid (984 mg, 7.03 mmol, 24%) from 4-(allyloxy)furan-2(5H)-one **121x** (4.09 g, 29.21 mmol) dissolved in dry acetonitrile (50 ml) and refluxed very strongly for 48h. Molecular formula $C_7H_8O_3$. R_f 0.59 (diethyl ether, 100%), mp 105°C.



IR (KBr); ν(cm^{-1}) = 3419 (m) [ν (OH)], 2984 (s), 1749 (s), 1645 (s), 1562 (s), 1448 (s), 1270 (m), 1187 (m), 1109 (m), 1059 (m), 1033 (s), 990 (m), 921 (m), 825 (m), 791 (m), 699 (m), 650 (w).

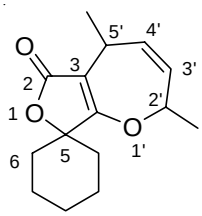
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 2.94 (d, $^{3}J_{HH}$ = 6.23 Hz, 2H, 1'-H), 4.66 (s, 2H, 5-H), 5.04 (d, $^{3}J_{HH}$ = 10.42 Hz, 1H, CH=C*H*H-*cis*), 5.07 (d, $^{3}J_{HH}$ = 17.05 Hz, 1H, CH=CH*H-trans*), 5.78 - 5.88 (m, 1H, CH=CH_2), 10.70 (s, 1H, OH).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 25.1 (CH_2, C-3), 67.91 (CH_2, C-5), 99.06 (C^{q}, C-3), 115.81 (CH_2, CH=*C*H_2), 133.71 (CH, *C*H=CH_2), 175.02 (C^{q}, C-2), 178.50 (C^{q}, C-4).

MS (EI, 70 eV): m/z = 141 (6) [M^++1], 140 (51) [M^+], 122 (100) [M^+-H_2O], 99 (14) [M^+-C_3H_5], 82 (79) [M^+-C_3H_5OH], 81 (66), 69 (22), 66 (47), 54 (87), 43 (24), 41 (57) [$C_3H_5^+$], 39 (75).

Accurate Mass:- Calculated Mass = 140.04735 Found = 140.09139

2',5'-Dimethyl-2',5'-dihydro-6'*H*-spiro[cyclohexane-1,8'-furo[3,4-*b*]oxepin]-6'-one 203.
Method B: Colourless oil (15 mg, 0.06 mmol, 50%) from 4-[(2E,4E)-hexa-2,4-dienyloxy]-1-oxaspiro[4.5]dec-3-en-2-one **142s** (30 mg, 0.012 mmol) dissolved in dry acetonitrile (5 ml) and irradiated in a 300W microwave at 100°C for 20min. Molecular formula $C_{15}H_{20}O_3$. R_f 0.72 (ethyl acetate:hexane, 1:2, v:v).



IR (KBr); ν(cm^{-1}) = 2935 (s), 2842 (m), 1748 (s) [ν (C=O)], 1663 (s), 1448 (m), 1266 (m), 1223 (m), 1118 (s), 1028 (s), 974 (m), 856 (m).

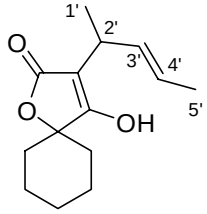
^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.31 (d, $^3J_{HH}$ = 7.13 Hz, 3H, OCHC*H*$_3$), 1.45 (d, $^3J_{HH}$ = 6.25 Hz, 3H, CCHC*H*$_3$), 1.55 - 1.74 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 3.09 (quin, $^3J_{HH}$ = 6.25 Hz, 1H, 5'-H), 5.05 (quin, $^3J_{HH}$ = 7.13 Hz, 1H, 2'-H), 5.56 (dd, $^3J_{HH}$ = 10.62 Hz, 6.25 Hz, 1H, 3'-H), 6.12 (dd, $^3J_{HH}$ = 10.62 Hz, 5.89 Hz, 1H, 4'-H).

^{13}C-JMOD NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 20.9 (CH_3, C-2'), 21.1 (CH_3, C-5'), 21.7, 21.9 (CH_2, C-7 and C-9), 24.1 (CH_2, C-8), 29.2 (CH, C-5'), 75.2 (CH, C-2'), 82.7 (C^q, C-5), 102.7 (C^q, C-3), 130.0 (CH, C-4'), 140.1 (CH, C-3'), 173.4 (C^q, C-2), 179.0 (C^q, C-4).

MS (EI, 70 eV): m/z = 248 (43) [M^+], 233 (9) [M^+-CH_3], 230 (34) [M^+-H_2O], 215 (34) [*230* - CH_3], 202 (15) [M^+-H_2O-CO], 187 (12), 175 (11), 149 (13) [M^+-H_2O-C_6H_9], 139 (11), 122 (100) [M^+-CO_2-C_6H_{10}], 109 (36), 94 (24), 82 (33) [$C_6H_{10}^+$], 79 (47), 67 (32), 55 (17), 41 (23).

$C_{15}H_{20}O_3$ (248.32): Calculated C = 72.55%, H = 8.12%; found C = 72.49%, H = 8.05%.

4-Hydroxy-3-[(3'*E*)-penten-2-yl]-1-oxaspiro[4.5]dec-3-en-2-one 212b.
Method A: White solid (638 mg, 2.70 mmol, 98%) from 4-[(2*E*)-pent-2-enyloxy]-1-oxaspiro[4.5]dec-3-en-2-one **121o** (650 mg, 2.75 mmol) in dry toluene (10 ml) heated for 24 hrs at 160 °C. Evaporation of solvent and recrystallised from hexane. Molecular formula $C_{14}H_{20}O_3$. R_f 0.29 (ethyl acetate: hexane, 1:1, v:v), mp 135°C.



IR (KBr); ν(cm^{-1}) = 3406 (m) [ν (OH)], 2937 (s), 2855 (m), 2644 (m), 1700 (s), 1652 (s), 1448 (w), 1389 (s), 1337 (m), 1271 (m), 1252 (w), 1234(w), 1151 (w), 1082 (w), 1032 (w), 1005 (w), 961 (s) [ν (CH=CH)-*trans*], 857 (w), 776 (w), 622 (w).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.23 (d, $^{3}J_{HH}$ = 7.08 Hz, 3H, 1'-H), 1.52 - 1.75 (m, 13H, 6-H, 7-H, 8-H, 9-H, 10-H, 5'-H), 3.19 - 3.25 (m, 1H, 2'-H), 5.70 - 5.75 (m, 2H, CH=CH), 10.21 (s, 1H, OH).

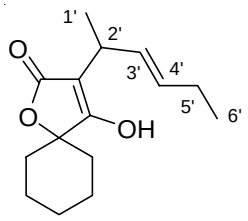
^{13}C-NMR J-MOD (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 18.4 (CH_3, C-5'), 19.6 (CH_3, C-1'), 21.7, 21.8 (CH_2, C-7 and C-9), 24.4 (CH_2, C-8), 30.7 (CH, C-2'), 32.9, 33.0 (CH_2, C-6 and C-10), 82.0 (C^q, C-5-*spiro*), 102.9 (C^q, C-3), 127.23 (CH, C-4'), 132.7 (CH, C-3'), 172.0 (C^q, C-2), 177.3 (C^q, C-4).

MS (EI, 70 eV): m/z = 237 (1) [M^++1], 236 (5) [M^+], 221 (1) [M^+-CH_3], 218 (3) [M^+-H_2O], 203 (6) [221 - H_2O or 218 - CH_3], 195 (2) [M^+ - $C_3H_5^+$], 189 (3) [203 - CH_2], 169 (46), 151 (2), 136 (3), 121 (2), 110 (78) [$C_7H_{10}O^+$], 109 (56), 96 (4), 95 (100) $C_7H_{11}^+$], 82 (100) [$C_6H_{10}^+$], 69 (46) [$C_5H_9^+$], 67 (42), 55 (18), 53 (11), 41 (64), 39 (9), 29 (5).

$C_{14}H_{20}O_3$(236.31): Calculated C = 71.16%, H = 8.53%; found C = 71.32%, H = 8.49%.

4-Hydroxy-3-[(3'E)-hexen-2-yl]-1-oxa spiro[4.5]dec-3-en-2-one 212c.

Method A: White crystalline solid (375 mg, 1.50 mmol, 70%) from 4-[(2*E*)-hex-2-enyloxy]-1-oxaspiro[4.5]dec-3-en-2-one **121c** (540 mg, 2.16 mmol) in dry Toluene (15 ml). Molecular formula $C_{15}H_{22}O_3$. R_f 0.16 (diethyl ether/ hexane, 1:1, v/v), mp 112°C.



IR (KBr); ν(cm^{-1}) = 3421 (w) [ν (OH)], 2936 (m), 2862 (m), 2635 (w), 1699 (s) [ν (C=O)], 1636 (s) [ν (C=C)], 1451 (m), 1388 (s), 1330 (s), 1270 (s), 1151 (w), 1097 (w), 1030 (w), 960 (s), 819 (w).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.98 (t, $^{3}J_{HH}$ = 7.49 Hz, 3H, 6'-H), 1.26 (d, $^{3}J_{HH}$ = 7.06 Hz, 3H, 1'-H), 1.55 - 1.89 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.05 (dt, $^{3}J_{HH}$ = 7.49, 5.67 Hz, 2H, 5'-H), 3.32 (m, 1H, 2'-H), 5.62 (dd, $^{3}J_{HH}$ = 5.67 Hz, $^{3}J_{HH}$ = 15.87 Hz, 1H, 3'-H), 5.71 (dt, $^{3}J_{HH}$ = 5.67 Hz, $^{2}J_{HH}$ = 15.87 Hz, 1H, 4'-H), 9.07 (s, 1H, OH).

^{13}C-NMR (75.4 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 14.1 (CH_3, C-6'), 18.8 (CH_3, C-1'), 21.4, 22.2 (CH_2, C-7 and C-9), 24.7 (CH, C-8), 25.7 (CH_2, C-5'), 30.9 (CH_2, C-6 and C-10), 33.1 (CH_2, C-2'), 83.1 (C^q, C-5-*spiro*), 103.3 (C^q, C-3), 131.0 (CH, C-4'), 133.1 (CH, C-3'), 174.8 (C^q, C-2), 178.8 (C^q, C-4).

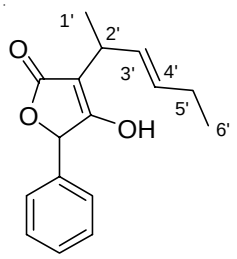
MS (EI, 70 eV): m/z = 251 (14) [M^+1], 250 (25) [M^+], 235 (10) [M-CH_3], 232 (14) [M^+-H_2O], 221 (5) [M^+-C_2H_5], 217 (47) [M^+-H_2O-CH_3], 203 (13), 195 (19) [M^+-C_4H_7], 177 (19) [M^+-H_2O-C_4H_7], 170 (20), 169 (82), 124 (29), 123 (42), 110 (53) [$C_7H_{10}O^+$], 109 (47), 96 (43), 95 (61), 82 (100) [$C_6H_{10}^+$], 69 (29) [$C_5H_9^+$], 67 (48), 55 (73), 53 (24), 41 (32), 39 (30), 28 (24).

Accurate Mass Calculated Mass:- 250.156895 Found:- 250.156479

$C_{15}H_{22}O_3$ (250.33): Calculated C = 71.97%, H = 8.75%; found C = 71.86%, H = 8.75%.

4-Hydroxy-3-[(3'*E*)-hexen-2-yl]-5-phenylfuran-2(5*H*)-one 212d.

Method C: Clear oil (763 mg, 2.96 mmol, 52%) from 4-[(2E)-hex-2-enyloxy]-5-phenylfuran-2(5H)-one **121q** (1.48 g, 5.74 mmol) dissolved in dry toluene (15 ml) and heated to 165 °C for 48h. Molecular formula $C_{16}H_{18}O_3$. R_f 0.28 (diethyl ether:hexane, 1:1, v:v).



IR (film, KBr); ν(cm^{-1}) = 3065 (m), 2937 (s), 2860 (m), 2645 (br), 1700 (s) and 1644 (s), 1447 (m), 1386 (s), 1335 (s), 1270 (s), 1151 (m), 1111 (m), 1048 (s), 961 (m), 886 (m), 824 (m), 795 (m), 741 (m), 622 (m), 537 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.93 - 0.98 (m, 3H, 6'-H), 1.25 (td, $^3J_{HH}$ = 6.06 Hz, $^4J_{HH}$ = 1.48 Hz, 3H, 1'-H), 1.98 - 2.07 (m, 2H, 5'-CH_2), 3.25 - 3.34 (m, 1H, 2'-H), 5.51 (s, 1H, 5-H), 5.53 (s, 1H, OH), 5.57 - 5.72 (m, 2H, CH=CH), 7.23 - 7.35 (m, 5H, Ph).

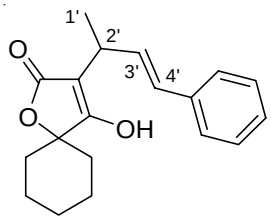
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 13.6 (CH_3, C-6'), 17.9 (CH_3, C-1'), 25.4 (CH_2, C-5'), 30.8 (CH, C-2'), 78.8 (CH, C-5), 104.6 (C^q, C-3), 126.9, 128.6, 129.4, (CH, Ph), 130.0 (CH, CH=*C*H), 134.1 (C^q, Ph-*ipso*), 134.4 (CH, *C*H=CH), 172.1 (C^q, C-2), 173.6 (C^q, C-4).

MS (EI, 70 eV): m/z = 259 (3) [M^++1], 258 (11) [M^+], 260 (4) [M^+-H_2O], 225 (3) [M^+-CH_3-OH], 211 (13) [*225* - CH_2], 203 (14) [M^+-$C_4H_7^+$], 178 (12), 177 (100) [M^+-C_6H_9], 167 (8), 149 (8), 129 (6), 118 (55), 109 (17), 107 (14), 105 (15), 96 (23), 95 (38), 90 (4), 82 (77), 77 (16) [$C_6H_5^+$], 55 (27), 41 (23), 29 (6).

Accurate Mass:- Calculated Mass = 258.1256 Found = 258.1255

4-Hydroxy-3-[(3'*E*)-4'-phenyl-buten-2-yl]-1-oxaspiro[4.5]dec-3-en-2-one 212e.

Method C: White crystalline solid (318 mg, 1.07 mmol, 84%) from 4-{[(2E)-4-phenylbut-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **122r** (380 mg, 1.28 mmol) in a bomb tube dissolved in dry toluene (5 ml). Reaction vessel heated to 160 °C for 16 h. Molecular formula $C_{19}H_{22}O_3$. R_f 0.13 (diethyl ether:hexane, 1:1, v:v), mp 158 - 159°C.



IR (KBr); ν(cm^{-1}) = 3417 (br) [ν (OH)], 3025 (m), 2933 (s), 2861 (m), 2642 (m), 1698 (s), 1639 (s), 1446 (m), 1389 (s), 1335 (m), 1270 (m), 1146 (w), 1096 (w), 962 (s), 813 (w), 784 (w), 747 (m), 690 (m).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.38 (d, $^{3}J_{HH}$ = 7.05 Hz, 3H, 1'-H), 1.17 - 1.88 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 3.54 (dq, $^{3}J_{HH}$ = 7.05 Hz, 5.13 Hz, 1H, 2'-H), 6.49 (dd, $^{3}J_{HH}$ = 16.29 Hz, 5.13 Hz, 1H, 3'-H), 6.60 (d, $^{3}J_{HH}$ = 16.29, 1H, 4'-H), 7.21 - 7.42 (m, 5H, Ph).

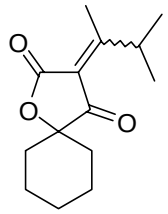
^{13}C-JMOD NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 18.5 (CH_3, C-1'), 21.9 (CH_2, C-7 and C-9), 24.4 (CH_2, C-8), 31.2 (CH, C-2'), 32.8 (CH_2, C-6 and C-10), 83.2 (C^q, C-5-*spiro*), 126.3, 126.4 (CH, Ph-*ortho*), 127.4 (CH, Ph-*para*), 128.6, 128.7 (CH, Ph-*meta*), 129.9 (CH, C-4'), 131.7 (CH, C-2'), 137.0 (C^q, Ph-*ipso*), 174.8 (C^q, C-2), 179.2 (C^q, C-4).

MS (EI, 70 eV): m/z = 299 (3) [M^++1], 298 (24) [M^+], 280 (21) [M^+-H_2O], 265 (2) [M^+-H_2O-CH_3], 254 (9) [M^+-CO_2], 224 (2), 198 (3), 188 (19) [M^+-$C_7H_{10}O^+$], 171 (89) [*188* - OH], 157 (12) [171 - CH_2], 143 (78) [157 - CH_2], 131 (100) [$C_{10}H_{11}^+$], 129 (57), 128 (44), 110 (57) [$C_7H_{10}O^+$], 105 (20), 91 (58) [$C_7H_7^+$], 67 (6), 55 (4), 41 (6).

$C_{19}H_{22}O_3$ (298.38): Calculated C = 76.48%, H = 7.43%; found C = 76.42%, H = 7.39%.

(3*E*+*Z*)-3-(1,2-Dimethylpropylidene)-1-oxaspiro[4.5]decane-2,4-dione 213.

Method C: White solid (0.345 g, 2.01 mmol, 60%) from 4-(3-methyl-but-2-enyloxy)-1-oxa-spiro[4.5]dec-3-en-2-one (0.80 g, 3.39 mmol) in Toluene (20 ml) heated to 180°C for 48h. Molecular formula $C_{14}H_{20}O_3$. R_f 0.43 (diethyl ether: hexane, 1:8, v:v), mp 141°C (decomp).[115]



IR (KBr); ν(cm-^{1}) = 2940 (s), 2869 (m), 1760 (s), 1713 (s), 1605 (s), 1448 (m), 1366 (w), 1347 (w), 1219 (m), 1087 (m), 962 (m).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.09 and 1.13 (d, $^{3}J_{HH}$ = 6.86 Hz, 6H, CH(CH_3)$_2$), 1.37 - 1.89 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.47 (s, 3H, 1'-CH_3), 4.41 (quin., $^{3}J_{HH}$ = 6.86 Hz, 1H, 2'-H), 4.47 (quin., $^{3}J_{HH}$ = 6.86 Hz, 1H, 2'-H).

^{13}C-JMOD NMR (64 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 15.88, 15.94, 19.98, 20.15 (CH_3, C-2'), 20.79, 21.01 (CH_2, C-7 and C-9), 23.93, 24.36 (CH_2, C-8), 29.67 (CH, C-2'), 31.81, 32.21 (CH_2, C-6 and C-10), 85.21, 85.27 (C^q, C-5-*spiro*), 112.57, 112.87 (C^q, C-3), 164.45, 165.40 (C^q, 1'-C), 189.31, 189.89 (C^q, C-2), 199.93, 200.21 (C^q, C-4).

MS (EI, 70 eV): m/z = 236 (18) [M^+], 218 (9) [M^+-H_2O], 203 (25) [*218* - CH_3], 190 (21) [*218* - CO], 175 (19), 153 (6), 136 (14), 110 (7) [*190* - C_6H_7], 95 (100) [*175* - C_6H_7], 67 (24).

3.3.7 Synthesis of 3,5-dispirodihydrofuran-4,12-diones from 5-spiro-allyl tetronates 121.

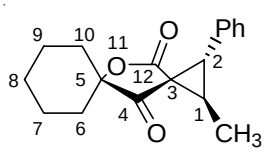
*General experimental procedure for the domino Claisen-Conia rearrangement of 5-spiro-allyl tetronates **121**:*

Method A: A solution of the respective tetronate **121** (5 mmol) in dry toluene (15 ml) was prepared under the exclusion of air and moisture. The solution was transfered to a sealable glass tube and sealed. The tube was heated to 160°C for 16 - 24h. After cooling, the solvent was removed and the residue was purified by column chromatography (silica gel, solvent as indicated).

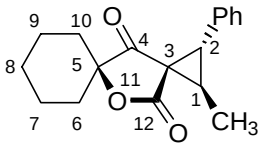
Method B: The respective tetronate **142** (1 mmol) was placed in a glass tube and dry acetonitrile (5 ml) were added. The glass tube was sealed with a teflon cap and placed inside a CEM Discovery microwave oven (300W). The sample was irradiated with microwaves (300W) until a temperature of 150°C was obtained. Internal pressure was recorded as being ~ 3.8 bar. External cooling was applied for a further 60 minutes to ensure that a constant streanm of microwave energy was applied to the sample. After cooling the cap was removed and the solvent was evaporated on a rotary evaporator. The residue was purified by column chromatography (silica gel, solvent as indicated).

1-Methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione 119a.

Method A: White solid (1.24 g, 4.36 mmol, 76%) from (E)-4-(3-Phenyl-allyloxy)-1-oxa-spiro[4.5]dec-3-en-2-one **122** (1.65 g, 5.81 mmol) in dry toluene (20 ml). Solution was heated to 160°C for 24h. Molecular formula $C_{18}H_{20}O_3$. R_f 0.78 and 0.75 (diethyl ether: hexane: 1:1, v:v), mp 150°C.



119a-α



119a-β

Mixture of diastereoisomers **(±)-119a-α** and **(±)-119a-β**: Ratio α:β = 1:1.

IR (KBr); ν(cm-[1]) = 3060 (w), 2938 (s), 2865 (m), 1772 (s), 1733 (s), 1448 (m), 1311 (s), 1278 (m), 1210 (m), 1170 (m), 1117 (s), 978 (m), 968 (m), 945 (w), 762 (m), 728 (m), 670 (s).

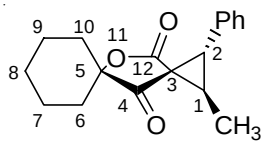
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.31 - 1.83 (m, 13H, 6-H$^{α–β}$, 7-H$^{α–β}$, 8-H$^{α–β}$, 9-H$^{α–β}$, 10-H$^{α–β}$, including two doublets at 1.50 ppm, $^3J_{HH}$ = 6.16 Hz, from 1-$CH_3^β$ and 1.60 ppm, $^3J_{HH}$ = 6.24 Hz, from 1-$CH_3^α$), 2.82 (dq, $^3J_{HH}$ = 9.25, 6.16 Hz, 1H, 1-H^β), 2.96 (dq, $^3J_{HH}$ = 9.27, 6.24 Hz, 1H, 1-H^α), 3.32 (d, $^3J_{HH}$ = 9.27 Hz, 1H, 2-H^α), 3.48 (d, $^3J_{HH}$ = 9.25 Hz, 1H, 2-H^β), 7.20 - 7.31 (m, 5H, Ph$^{α–β}$).

^{13}C-JMOD NMR (74.5 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 11.35 (CH_3, 1-$CH_3^β$), 11.84 (CH_3, 1-$CH_3^α$), 20.76, 20.88, (CH_2, C-7^α and C-9^α), 20.95, 21.01 (CH_2, C-7^β and C-9^β), 24.39 (CH_2, C-8^α), 24.43 (CH_3, C-8^β), 31.74, 31.86 (CH_2, C-6^α and C-10^α), 32.32, 32.71 (CH_2, C-6^β and C-10^β), 35.67 (CH, C-1^α), 37.34 (CH, C-1^β), 38.73 (C^q, C-3^α-*spiro*), 38.88 (C^q, C-3^β-*spiro*), 51.29 (CH, C-2^β), 51.77 (CH, C-2^α), 88.57 (C^q, C-5^β-*spiro*), 88.72 (C^q, C-5^α-*spiro*), 128.15, 128.16, 128.19, 128.29, 128.82, 128.97 (CH, Ph$^{α-β}$),

132.25 (C^q, Ph-*ipso*$^\alpha$), 132.56 (C^q, Ph-*ipso*$^\beta$), 171.04 (C^q, C-12$^\alpha$), 172.48 (C^q, C-12$^\beta$), 206.09 (C^q, C-4$^\alpha$), 208.53 (C^q, C-4$^\beta$).

MS (EI, 70 eV): m/z = 284 (90) [M^+], 266 (39) [M^+-H_2O], 251 (26) [*266* - CH_3], 238 (9) [*266* - C_2H_4; *266* - CO], 223 (10) [*251* - CO], 205 (26), 198 (9), 175 (14) [*266* - C_7H_7; *251* - C_6H_4], 158 (75), 150 (5), 118 (100) [$C_9H_{10}^+$], 115 (77), 109 (29), 91 (41) [$C_7H_7^+$], 81 (23) [$C_6H_9^+$], 55 (22), 41 (30).

(±)–α-diastereoisomer 119a-α (purified by column chromatography) R_f 0.78 (diethyl ether: hexane, 1:1, v:v).

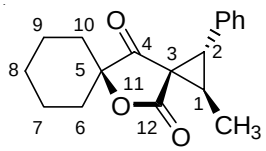


119a-α

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.31 - 1.83 (m, 13H, 6-H, 7-H, 8-H, 9-H, 10-H, including a doublet at 1.60 ppm, $^3J_{HH}$ = 6.24 Hz, from 1-CH_3), 2.96 (dq, $^3J_{HH}$ = 9.27, 6.24 Hz, 1H, 1-H), 3.32 (d, $^3J_{HH}$ = 9.27 Hz, 1H, 2-H), 7.20 - 7.31 (m, 5H, Ph).

^{13}C-JMOD NMR (74.5 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 11.84 (CH_3, C-1), 20.76, 20.88, (CH_2, C-7 and C-9) 24.39 (CH_2, C-8), 31.74, 31.86 (CH_2, C-6 and C-10), 35.67 (CH, C-1), 38.73 (C^q, C-3-*spiro*), 51.77 (CH, C-2), 88.72 (C^q, C-5-*spiro*), 128.15, 128.16, 128.19 (CH, Ph), 132.25 (C^q, Ph-*ipso*), 71.04 (C^q, C-12), 206.09 (C^q, C-4)

(±)–β-diastereoisomer 119a-β (purified by column chromatography followed by crystallisation from DCM), R_f 0.75 (diethyl ether: hexane, 1:1, v:v).



119a-β

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.31 - 1.83 (m, 13H, 6-H, 7-H, 8-H, 9-H, 10-H, including a doublet at 1.50 ppm, $^3J_{HH}$ = 6.16 Hz, from 1-CH_3), 2.82 (dq, $^3J_{HH}$ = 9.25, 6.16 Hz, 1H, 1-H), 3.48 (d, $^3J_{HH}$ = 9.25 Hz, 1H, 2-H), 7.20 - 7.31 (m, 5H, Ph).

^{13}C-JMOD NMR (74.5 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 11.35 (CH_3, C-1), 20.95, 21.01 (CH_2, C-7 and C-9), 24.43 (CH_3, C-8), 32.32, 32.71(CH_2, C-6 and C-10), 37.34 (CH, C-1), 38.88 (C^q, C-3-*spiro*), 51.29 (CH, C-2), 88.57 (C^q, C-5-*spiro*), 128.29, 128.82, 128.97 (CH, Ph), 132.56 (C^q, Ph-*ipso*), 172.48 (C^q, C-12), 208.53 (C^q, C-4).

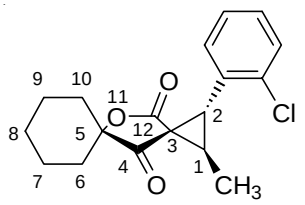
1-Methyl-2-(2-Chlorophenyl)-11-oxadispiro[2.1.5.2]dodecane-4,12-dione (±)-119b.

Method A: White solid (507 mg, 1.59 mmol, 64%) from 4-{[(2E)-3-(2-chlorophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121b** (801 mg, 2.52 mmol) dissolved in dry toluene (15 ml). Solution was heated to 160^{o}C inside a sealed glass tube for 48hr.

Method B: White crystals (319 mg, 1.00 mmol, 58%) from 4-{[(2E)-3-(2-chlorophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **119b** (550 mg, 1.73 mmol) dissolved in dry acetonitrile (6 ml) and heated to 160 °C and 3.9 bar in a sealed tube for 60 min under 300W microwave conditions.

Molecular formula $C_{18}H_{19}ClO_3$. R_f 0.84 (diethyl ether:hexane, 1:1, v:v), mp 175 °C.

NB By both methods of preparation only ***(±)-119b-α*** *was identified, the corresponding β-diastereoisomer was never observed by TLC or GC. The most likely explanation would be that steric crowding between the chloro atom and the ester group prevents the formation of* ***119b-β****. The α-diasteroisomer was identified as such by the comparision of the chemical shifts with those obtained for* ***119a****.*



119b-α

IR (KBr); ν(cm^{-1}) = 3054 (w), 2939 (s), 2863 (m), 1773 (s), 1732 (s), 1439 (m), 1385 (w), 1309 (s), 1276 (m), 1210 (m), 1175 (m), 1120 (s), 1089 (m), 1041 (m), 966 (m), 944 (m), 855 (w), 806 (w), 762 (m), 737 (m).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.16 - 1.89 (m, 13H, 6-H, 7-H, 8-H, 9-H, 10-H, including a doublet at 1.50 ppm, $^3J_{HH}$ = 6.21 Hz, from 1-CH_3), 2.90 (dq, $^3J_{HH}$ = 9.21 Hz, 6.21 Hz, 1H, 1-H), 3.27 (d, $^3J_{HH}$ = 9.21 Hz, 1H, 2-H), 7.24 - 7.40 (m, 4H, Ar).

^{13}C-JMOD NMR (125.7 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.36 (CH_3, C-1), 20.98, 21.12 (CH_2, C-7 and C-9), 24.52 (CH_2, C-8), 32.16, 32.36 (CH_2, C-6 and C-10), 37.75 (C^q, C-3-*spiro*), 37.99 (CH, C-1), 47.28 (CH, C-2), 89.18 (C^q, C-5-*spiro*), 126.79, 129.30, 129.61, 130.61 (CH, Ar), 131.37 (C^q, Ar-Cl), 135.43 (C^q, Ar-*ipso*), 171.27 (C^q, C-2), 208.39 (C^q, C-4).

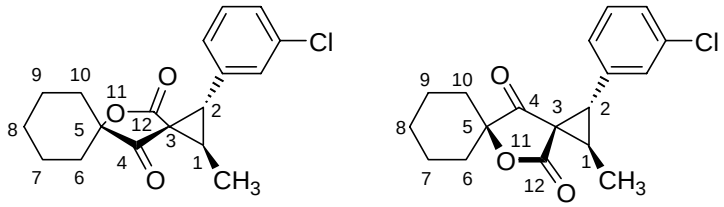
MS (EI, 70 eV): m/z = 321 (4) [M^++1, ^{37}Cl], 320 (38) [M^+, ^{37}Cl], 319 (14) [M^++1, ^{35}Cl], 318 (91) [M^+, ^{35}Cl], 305 (6) [M^+-CH_3, ^{37}Cl], 303 (32) [M^+-CH_3, ^{35}Cl], 302 (6) [M^+-H_2O, ^{37}Cl], 300 (19) [M^+-H_2O, ^{35}Cl], 287 (6) [*302* - CH_3], 285 (18) [*300* - CH_3], 283 (66) [M+-Cl, ^{35}Cl], 265 (23) [*300* - ^{35}Cl], 237 (5), 219 (18), 193 (8), 192 (7) [M^+-C_6H_{10}-CO_2, ^{35}Cl], 178 (17), 175 (13),164 (14) [*192* - CO], 157 (48), 154 (17), 152 (85) [*164* - C], 129 (100), 128 (64), 117 (77) [$C_9H_9^+$], 115 (42), 109 (18), 91 (3), 81 (9) [$C_6H_9^+$], 67 (7), 55 (13), 41 (14).

1-Methyl-2-(3'-chlorophenyl)-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione-(±)-119c.

Method A: White solid (380 mg, 1.19 mmol, 63%) from 4-{[(2E)-3-(3-chlorophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121c** (600 mg, 1.89 mmol) dissolved in dry toluene (15 ml) and heated to 170 °C for 48h in a sealed bomb tube.

Method B: White solid (240 mg, 0.75 mmol, 45%) from 4-{[(2E)-3-(3-chlorophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121c** (530 mg, 1.67 mmol) dissolved in dry acetonitrile (5 ml) and heated to 150 °C and 3.7 bar in a sealed tube for 60 min under 300W microwave conditions.

Molecular formula $C_{18}H_{19}ClO_3$. R_f 0.75 (diethyl ether:hexane, 1:1, v:v), mp 106 - 111°C. *NB It is possible to separate the diastereoisomers by column chromatography and repeated recrystallisation as with **119a**. The α, β diasteroisomers were identified as such by the comparision of the chemical shifts with those obtained for **119a**.*



119c-α **119c-β**

Mixture of diasteroisomers **(±)-119c-α** and **(±)-119c-β**. Ratio of α to β; 2:1.

IR (KBr); ν(cm^{-1}) = 3059 (w), 2936 (m), 2858 (w), 1778 (s), 1734 (s), 1646 (w), 1585 (w), 1549 (w), 1500 (m), 1314 (m), 1265 (m), 1213 (w), 1169 (m), 1090 (m), 1031 (m), 974 (w), 799 (s) [C-Cl], 732 (w), 690 (m).

^{1}H-NMR (250 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.21 - 1.83 (m, 13H, 6-H$^{α-β}$, 7-H$^{α-β}$, 8-H$^{α-β}$, 9-H$^{α-β}$, 10-H$^{α-β}$, including two doublets at 1.48 ppm, $^3J_{HH}$ = 6.47 Hz, from 1-$CH_3^β$ and 1.59 ppm, $^3J_{HH}$ = 6.16 Hz, from 1-$CH_3^α$), 2.75 (dq, $^3J_{HH}$ = 9.15 Hz, 6.16 Hz, 1H, 1-H^β), 2.90 (dq, $^3J_{HH}$ = 9.18 Hz, 6.16 Hz, 1H, 1-H^α), 3.24 (d, $^3J_{HH}$ = 9.18 Hz, 1H, 2-H^α), 3.40 (d, $^3J_{HH}$ = 9.15 Hz, 1H, 2-H^β), 7.21 - 7.25 (m, 4H, Ar-$^{α–β}$).

^{13}C-JMOD NMR (62.9 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.32 (CH_3, C-1^α), 11.83 (CH_3, C-1^β), 20.80, 20.91 (CH_2, C-7^α and C-9^α), 20.97, 21.04 (CH_2, C-7^β and C-9^β), 24.45 (CH_2, C-8^α), 24.52 (CH_2, C-8^β), 31.86, 31.97 (CH_2, C-6^α and C-10^α), 32.25, 32.99 (CH_2, C-6^β and C-10^β), 35.97 (CH, C-1^β), 37.45 (CH, C-1^α), 38.41 (C^q, C-3^α-*spiro*), 38.57 (C^q, C-3^β-*spiro*), 49.50 (CH, C-2^α), 50.16 (CH, C-2^β), 88.91 (C^q, C-5^α-*spiro*), 127.06, 127.15, 128.07, 128.18, 129.06, 129.27, 129.55, 129.68 (CH, Ph$^{α–β}$), 134.23 (C^q, Ar-Cl^α), 134.66 (C^q, Ar-*ipso*^{α}), 170.98 (C^q, C-12^α), 208.30 (C^q, C-4^α). *Quarternary carbons for the β isomer were not visible due to insufficient NMR time.*

MS (EI, 70 eV): m/z = 321 (2) [M^++1, ^{37}Cl], 320 (8) [M^+, ^{37}Cl], 319 (4) [M^++1, ^{35}Cl], 318 (24) [M^+, ^{35}Cl], 305 (1) [M^+-CH_3, ^{37}Cl], 303 (4) [M^+-CH_3, ^{35}Cl], 302 (3) [M^+-H_2O, ^{37}Cl], 300 (8) [M^+-H_2O, ^{35}Cl], 287 (2) [*302* - CH_3], 285 (7) [*300* - CH_3], 265 (6) [*300* - ^{35}Cl], 237 (3), 219 (10), 193 (3), 192 (10), 192 (8) [M^+-C_6H_{10}-CO_2, ^{35}Cl], 175 (7), 166 (3), 164 (14) [*192* - CO], 154 (8), 152 (38) [*164* - C], 129 (100), 117 (83) [$C_9H_9^+$], 115 (22), 109 (15), 91 (6), 81 (10) [$C_6H_9^+$], 67 (8), 55 (15), 41 (15).

Accurate Mass:- Calculated Mass = 318.1022 Found = 318.1043

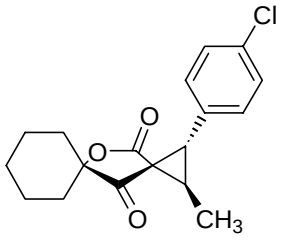
1-Methyl-2-(4'-chlorophenyl)-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione-(±)-119d.

Method A: White solid (530 mg, 1.67 mmol, 89%) from 4-{[(2E)-3-(4-chlorophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121d** (600 mg, 1.89 mmol) dissolved in dry toluene (10 ml) and heated to 170 °C in a sealed tube for 48h.

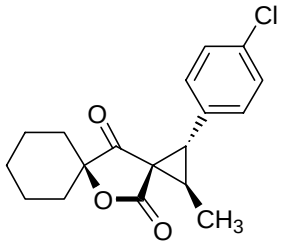
Method B: White solid (160 mg, 0.50 mmol, 52%) from 4-{[(2E)-3-(4-chlorophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121d** (310 mg, 0.97 mmol) dissolved in dry acetonitrile (6 ml) and heated to 150 °C and 3.7 bar in a sealed tube for 60 min under 300W microwave conditions.

Molecular formula $C_{18}H_{19}ClO_3$. R_f 0.69 (diethyl ether:hexane, 1:1, v:v), mp 107 - 109°C.

*NB It is possible to separate the diastereoisomers by column chromatography and repeated recrystallisation as with **119a**. The α, β diasteroisomers were identified as such by the comparision of the chemical shifts with those obtained for **119a**.*



119d-α



119d-β

Mixture of diastereoisomers **119d-α** *and* **119d-β**. Ratio α:β = 1:1.

IR (KBr); ν(cm^{-1}) = 3071 (w), 2936 (s), 2859 (m), 1775 (s), 1734 (s), 1496 (m), 1450 (m), 1402 (w), 1313 (s), 1276 (m), 1210 (m), 1175 (m), 1119 (m), 1088 (m), 1015 (w), 973 (m), 849 (w), 804 (m).

^{1}H-NMR (500 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.29 - 1.83 (m, 13H, 6-$H^{\alpha-\beta}$, 7-$H^{\alpha-\beta}$, 8-$H^{\alpha-\beta}$, 9-$H^{\alpha-\beta}$, 10-$H^{\alpha-\beta}$, including two doublets at 1.48 ppm, $^{3}J_{HH}$ = 6.15 Hz, from 1-CH_3^{β} and 1.59 ppm, $^{3}J_{HH}$ = 6.24 Hz, from 1-CH_3^{α}), 2.76 (dq, $^{3}J_{HH}$ = 9.17 Hz, 6.15 Hz, 1H, 1-H^{β}), 2.90 (dq, $^{3}J_{HH}$ = 9.20 Hz, 6.24 Hz, 1H, 1-H^{α}), 3.25 (d, $^{3}J_{HH}$ = 9.20 Hz, 1H, 2-H^{α}), 3.41 (d, $^{3}J_{HH}$ = 9.17 Hz, 1H, 2-H^{β}), 7.14 - 7.18 (m, 4H, Ar^{α}), 7.25 - 7.30 (m, 4H, Ar^{β}).

^{13}C-JMOD NMR (125.7 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.36 (CH_3, C-1^{β}), 11.86 (CH_3, C-$1'^{\alpha}$), 20.82, 20.93 (CH_2, C-7^{α}, C-9^{α}), 21.00, 21.06 (CH_2, C-7^{β} and C-9^{β}), 24.43 (CH_2, C-8^{α}), 24.47 (CH_2, C-8^{β}), 31.85, 31.96 (CH_2, C-6^{α} and C-10^{α}), 32.18, 32.74 (CH_2, C-6^{β} and C-10^{β}), 35.87 (CH, C-1^{α}), 37.44 (C^{q}, C-3^{α}-*spiro*), 37.45 (CH, C-1^{β}), 38.81 (C^{q}, C-3^{β}-*spiro*), 50.02 (CH, C-2^{β}), 50.62 (CH, C-2^{α}), 88.86 (C^{q}, C-5^{β}-*spiro*), 88.95 (C^{q}, C-5^{α}-*spiro*), 128.53, 128.60, 128.72, 128.76, 130.16, 130.34, 131.37, 131.39 (CH, $Ar^{\alpha-\beta}$), 130.84 (C^{q}, Ar-Cl^{α}), 131.11 (C^{q}, Ar-Cl^{β}), 133.93 (C^{q}, Ar^{α}-*ipso*), 134.18 (C^{q}, Ar^{β}-*ipso*), 171.07 (C^{q}, C-12^{β}), 171.51 (C^{q}, C-12^{α}), 207.86 (C^{q}, C-4^{α}), 208.34 (C^{q}, C-4^{β}).

MS (EI, 70 eV): m/z = 321 (2) [M^{+}+1, ^{37}Cl], 320 (14) [M^{+}, ^{37}Cl], 319 (8) [M^{+}+1, ^{35}Cl], 318 (69) [M^{+}, ^{35}Cl], 305 (4) [M^{+}-CH_3, ^{37}Cl], 303 (12) [M^{+}-CH_3, ^{35}Cl], 302 (7) [M^{+}-H_2O, ^{37}Cl], 300 (21) [M^{+}-H_2O, ^{35}Cl], 287 (4) [*302* - CH_3], 285 (12) [*300* - CH_3], 265 (18) [*300* - ^{35}Cl], 237 (5), 219 (17), 193 (13), 192 (11), 192 (72) [M^{+}-C_6H_{10}-CO_2, ^{35}Cl], 175 (7), 166 (13), 164 (76) [*192* - CO], 154 (18), 152 (84) [*164* - C], 129 (100), 117 (68) [$C_9H_9^{+}$], 115 (16), 109 (21), 91 (6), 81 (13) [$C_6H_9^{+}$], 55 (8), 41 (9).

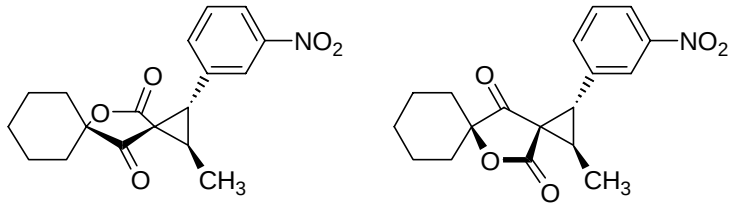
1-Methyl-2-(3-nitrophenyl)-11-oxadispiro[2.1.5.2]dodecane-4,12-dione-(±)-119e.

Method 1:White solid (338 mg, 1.03 mmol, 68%) from 4-{[(2E)-3-(3-nitrophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121e** (498 mg, 1.51 mmol) dissolved in dry toluene (8 ml) heated to 170°C for 35h.

Method 2: White solid (78 mg, 0.24 mmol, 16%) from 4-{[(2E)-3-(3-nitrophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121e** (501 mg, 1.51 mmol) dissolved in dry acetonitrile (6 ml) and heated to 142 °C and 3.6 bar in a sealed tube for 60 min under 300W microwave conditions.

Molecular formula $C_{18}H_{19}NO_5$. R_f 0.31 (diethyl ether:hexane, 1:1, v:v), mp 132 - 134 °C.

*NB It is possible to separate the diastereoisomers by column chromatography and repeated recrystallisation as with **119a**. The α, β diasteroisomers were identified as such by the comparision of the chemical shifts with those obtained for **119a**.*



119e-α **119e-β**

Mixture of diastereoisomers (±)-**119e-α** and (±)-**119e-β.**: Ratio α:β = 2:3.

IR (KBr); ν(cm^{-1}) = 3092 (w), 2939 (s), 2856 (m), 1772 (s), 1732 (s), 1531 (s) [ν (NO_2)], 1450 (m), 1352 (s) [ν (NO_2)], 1314 (s), 1278 (m), 1241 (m), 1214 (m), 1179 (m), 1126 (m), 1109 (m), 976 (m), 888 (w), 815 (w), 730 (m), 687 (m), 600 (w), 560 (w).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.22 - 1.88 (m, 13H, 6-H$^{α-β}$, 7-H$^{α-β}$, 8-H$^{α-β}$, 9-H$^{α-β}$, 10-H$^{α-β}$, including two doublets at 1.51 ppm, $^3J_{HH}$ = 6.20 Hz, from 1-$CH_3^β$ and 1.62 ppm, $^3J_{HH}$ = 6.17 Hz, from 1-$CH_3^α$), 2.81 (dq, $^3J_{HH}$ = 9.14 Hz, 6.20 Hz, 1H, 1-H^β), 2.96 (dq, $^3J_{HH}$ = 9.10 Hz, 6.24 Hz, 1H, 1-H^α), 3.33 (d, $^3J_{HH}$ = 9.10 Hz, 1H, 2-H^α), 3.48 (d, $^3J_{HH}$ = 9.14 Hz, 1H, 2-H^β), 7.38 - 7.56 and 8.10 - 8.14 (m, 4H, Ar$^{α–β}$).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.23 (CH_3, C-1^β), 11.78 (CH_3, C-1^α), 20.78, 20.90 (CH_2, C-7^α, C-9^α), 21.07, 21.14 (CH_2, C-7^β and C-9^β), 24.37 (CH_2, C-8^α), 24.42 (CH_2, C-8^β), 31.97, 32.06 (CH_2, C-6^α and C-10^α), 32.16, 32.61 (CH_2, C-6^β and C-10^β), 36.31 (CH, C-1^α), 37.47 (CH, C-1^β), 38.25 (C^q, C-3^α-*spiro*), 38.35 (C^q, C-3^β-*spiro*), 47.90 (CH, C-2^β), 48.79 (CH, C-2^α), 89.20 (C^q, C-5^β-*spiro*), 88.78 (C^q, C-5^α-*spiro*), 122.90, 122.99, 123.92, 124.22, 129.29, 129.48, 134.93, 135.01 (CH, Ar$^{α–β}$), 134.62 (C^q, Ar-Cl^α), 134.85 (C^q, Ar-Cl^β), 148.08 (C^q, Ar^α-*ipso*), 148.14 (C^q, Ar^β-*ipso*), 170.87 (C^q, C-12^β), 171.70 (C^q, C-12^α), 206.41 (C^q, C-4^α), 207.78 (C^q, C-4^β).

MS (EI, 70 eV): m/z = 330 (13) [M$^+$+1], 329 (100) [M$^+$], 315 (8) [M$^+$-CH_3], 312 (9) [M$^+$-OH], 311 (18) [M$^+$-H_2O], 297 (11) [*312* - CH_3], 294 (14) [*311* - OH], 283 (6) [M$^+$-NO_2], 248 (11), 230 (18), 203 (3), 193 (9), 175 (21), 163 (76) [$C_9H_9NO_2^+$], 128 (46), 115 (22), 109 (16), 99 (8) [$C_6H_{10}O^+$], 91 (9), 81 (11), 55 (11).

Accurate Mass:- Calculated Mass = 329.1263 Found = 329.1263

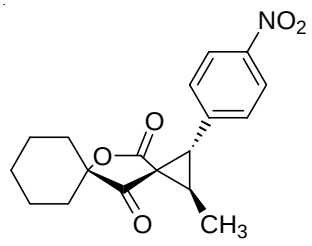
1-Methyl-2-(4'-nitrophenyl)-11-oxadispiro[2.1.5.2]dodecane-4,12-dione-(±)-119g.

Method A: White solid (340 mg, 1.03 mmol, 42%) from 4-hydroxy-3-[1-(4-nitrophenyl)prop-2-enyl]-1-oxaspiro[4.5]dec-3-en-2-one **121g** (810 mg, 2.46 mmol) and dry toluene (20 ml) in a sealed bomb tube at 180 °C for 48h.

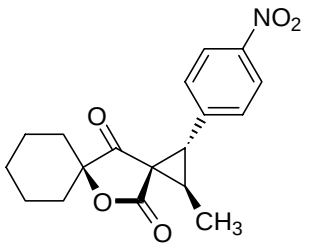
Method B: White solid (93 mg, 0.28 mmol, 37%) from 4-hydroxy-3-[1-(4-nitrophenyl)prop-2-enyl]-1-oxaspiro[4.5]dec-3-en-2-one **121g** (250 mg, 0.76 mmol) dissolved in dry acetonitrile (6 ml) and heated to 150 °C and 3.7 bar in a sealed tube for 60 min under 300W microwave conditions.

Molecular formula $C_{18}H_{19}NO_5$. R_f 0.72 (ethyl acetate:hexane, 1:1, v:v), mp 107 - 109°C.

*NB It is possible to separate the diastereoisomers by column chromatography and repeated recrystallisation as with **119a**. The α, β diasteroisomers were identified as such by the comparision of the chemical shifts with those obtained for **119a**.*



119f-α



119f-β

Mixture of diasteroisomers (±)-**144f-α** *and* (±)-**144f-β**. Ratio of α:β = 1:1.

IR (KBr); ν(cm^{-1}) = 2940 (m), 2861 (w), 1769 (m), 1735 (s), 1603 (w), 1519 (s), 1447 (w), 1345 (s), 1316 (s), 1273 (w), 1174 (m), 1113 (m), 972 (m), 856 (w)

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.22 - 1.79 (m, 13H, 6-$H^{\alpha\beta}$, 7-$H^{\alpha\beta}$, 8-$H^{\alpha\beta}$, 9-$H^{\alpha\beta}$, 10-$H^{\alpha\beta}$; including two doublets at 1.51 ppm, $^{3}J_{HH}$ = 6.21 Hz from 1-CH_3^{β} and 1.62 ppm, $^{3}J_{HH}$ = 6.14 Hz from 1-CH_3^{α}), 2.81 (dq, $^{3}J_{HH}$ = 9.21 Hz, 6.21 Hz, 1H, 1-H^{β}), 2.95 (dq, $^{3}J_{HH}$ = 9.17 Hz, 6.14 Hz, 1H, 1-H^{α}), 3.31 (d, $^{3}J_{HH}$ = 9.17 Hz, 1H, 2-H^{α}), 3.46 (d, $^{3}J_{HH}$ = 9.21, 1H, 2-H^{β}), 7.39 - 7.44 and 8.15 - 8.12 (m, 5H, Ar).

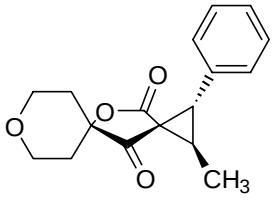
^{13}C-NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.26 (CH_3; C-1^{β}), 11.41 (CH_3; C-1^{α}), 20.76, 20.88 (CH_2; C-7^{α} and C-9^{α}), 20.94, 21.01 (CH_2; C-7^{β} and C-9^{β}), 24.36 (CH_2; C-8^{α}), 24.41 (CH_2; C-8^{β}), 31.94, 32.04 (CH_2; C-6^{α} and C-10^{α}), 32.59, 32.65 (CH_2; C-6^{β} and C-10^{β}), 36.23 (CH; C-1^{α}), 37.54 (CH; C-1^{β}), 38.57 (C^{q}; C-3^{α}-*spiro*), 38.67 (C^{q}; C-3^{β}-*spiro*), 48.18 (CH; C-2^{β}), 49.00 (CH; C-2^{α}), 89.27 (C^{q}; C-5^{β}-*spiro*), 89.42 (C^{q}; C-5^{α}-*spiro*), 123.51, 123.55, 129.82, 130.02 (CH; $CH^{\alpha,\beta}$-Ph), 139.80 (C^{q}; C^{α}-*ipso*), 140.04 (C^{q}; C^{β}-*ipso*), 147.59 (C^{q}; C-NO_2^{α}), 147.63 (C^{q}; C-NO_2^{β}), 170.79 (C^{q}; C-12^{β}), 171.66 (C^{q}; C-12^{α}), 207.80 (C^{q}, C-4a), 210.24 (C^{q}, C-4^{β}).

MS (EI, 70 eV): m/z = 330 (8) [M^{+}+1], 329 (100) [M^{+}], 311 (11) [M^{+}-H_2O], 296 (6) [M^{+}-H_2O-CH_3], 283 (4) [311 - C_2H_4], 248 (6), 230 (7), 193 (5), 175 (13), 163 (24), 150 (4), 129 (10), 128 (13), 115 (4), 109 (12), 91 (6) [$C_7H_7^{+}$], 81 (4), 55 (6) [$C_3H_3O^{+}$].

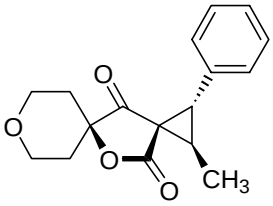
Accurate Mass:- Calculated Mass = 329.12632 Found = 329.12630

1-Methyl-2-phenyl-8,11-dioxadispiro[2.1.5.2]dodecane-4,12-dione-(±)-119h.

White solid (343 mg, 1.20 mmol, 57%) from 4-{[(2E)-3-phenylprop-2-enyl]oxy}-1,8-dioxaspiro[4.5]dec-3-en-2-one **121h** (600 mg, 2.10 mmol) dissolved in dry toluene (10 ml) and heated in a sealed tube to 170 °C for 16 h. Molecular formula $C_{17}H_{18}O_4$. R_f 0.35 (diethyl ether: hexane, 1:1, v:v), mp 65°C. *NB It is possible to separate the diastereoisomers by column chromatography and repeated recrystallisation as with **119a**. The α, β diasteroisomers were identified as such by the comparision of the chemical shifts with those obtained for **119a**.*



119h-α



119h-β

Mixture of diastereoisomers (±)-**119h-α**:and (±)-**119h-β**; Ratio α:β = 1:1.

IR (KBr); ν(cm^{-1}) = 2960 (m), 2922 (w), 2865 (m), 1781 (s), 1735 (s), 1500 (w), 1432 (m), 1385 (w), 1302 (s), 1212 (s), 1169 (s), 1102 (s), 1020 (w), 990 (m), 855 (w), 766 (w), 741 (w), 695 (s), 600 (w), 564 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.49 (d, $^3J_{HH}$ = 6.18 Hz, 3H, 1-CH_3^{α}), 1.58 (d, $^3J_{HH}$ = 6.17 Hz, 3H, 1-CH_3^{β}), 1.62 - 1.73 and 1.93 - 2.15 (m, 4H, 6-$H^{\alpha-\beta}$ and 10-$H^{\alpha-\beta}$), 2.76 - 2.89 (m, 1H, 1-H^{β}), 2.94 (m, 1H, 1-H^{α}), 3.35 (d, $^3J_{HH}$ = 9.34Hz, 1H, 2-H^{α}), 3.50 (d, $^3J_{HH}$ = 9.31Hz, 1H, 2-H^{β}), 3.66 - 3.94 (m, 4H, 7-$H^{\alpha-\beta}$ and 9-$H^{\alpha-\beta}$), 7.17 - 7.28 (m, 5H, $Ar^{\alpha-\beta}$).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.23 (CH_3, C-1^{α}), 11.69 (CH_3, C-1^{b}), 31.59, 31.70, 32.48, 32.81 (CH_2, C-$6^{\alpha-\beta}$ and C-$10^{\alpha-\beta}$), 35.90 (CH, 1-C^{β}), 38.09 (CH, 1-C^{α}), 51.80 (CH, 2-C^{α}), 52.24 (CH, 2-C^{β}), 62.62, 62.78 (CH_2, C-$7^{\alpha-\beta}$ and C-$9^{\alpha-\beta}$), 85.14 (C^{q}, C-5^{α}), 85.25 (C^{q}, C-5^{β}), 128.27, 128.64, 129.14, 129.75, 129.81, 129.90 (CH, $Ar^{\alpha-\beta}$), 131.82 (C^{q}, Ar-*ipso*$^{\beta}$), 132.10 (C^{q}, Ar-*ipso*$^{\alpha}$), 170.28 (C^{q}, C-2^{α}), 171.71 (C^{q}, C-2^{β}), 204.21 (C^{q}, C-4^{β}), 206.58 (C^{q}, C-4^{α}).

MS (EI, 70 eV): m/z = 287 (15) [M^++1], 286 (66) [M^+], 268 (31) [M^+-H_2O], 253 [*268* - CH_3], 241 (44), 223 (14), 185 (53), 158 (42), 130 (76), 129 (56), 118 (100), 117 (74), 115 (73), 110 (19), 91 (31), 77 (13), 51 (11), 39 (14).

Accurate Mass:- Calculated Mass = 286.12051 Found = 286.12052

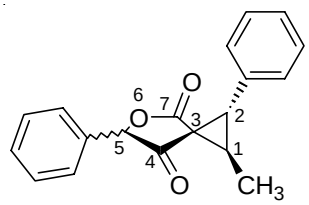
1-Methyl-2,6-diphenyl-5-oxaspiro[2.4]heptane-4,7-dione-(±)-119i.

Method A: Yellow crystalline solid (461 mg, 1.58 mmol, 77%) from 5-phenyl-4-{[(2E)-3-phenylprop-2-enyl]oxy}furan-2(5H)-one **121i** (600 mg, 2.05 mmol) dissolved in dry toluene and heated to 165°C in a sealed tube for 36h.

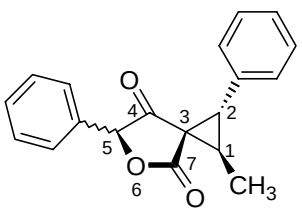
Method B: Yellow crystalline solid (43 mg, 0.15 mmol, 16%) from 5-phenyl-4-{[(2E)-3-phenylprop-2-enyl]oxy}furan-2(5H)-one **121i** (270 mg, 0.92 mmol) dissolved in dry acetonitrile (6 ml) and heated to 142 °C and 3.6 bar in a sealed tube for 60 min under 300W microwave conditions.

Molecular formula $C_{19}H_{16}O_3$. R_f 0.52 (diethyl ether:hexane, 1:1, v:v), mp 169°C.

*NB It is possible to separate the diastereoisomers by column chromatography and repeated recrystallisation as with **119a**. The α, β diasteroisomers were identified as such by the comparision of the chemical shifts with those obtained for **119a**.*



119i-α



119i-β

Mixture of diastereomers **(±)-119i-α**:and **119i-β**. Ratio α:β = 8:5.

IR (KBr); ν(cm^{-1}) = 3048 (w), 2928 (w), 1786 (s) [lactone], 1736 (s), 1452 (m), 1311 (M), 1206 (m), 1158 (m), 1118 (w), 1010 (m), 748 (w), 703 (m), 546 (w).

^{1}H-NMR (500 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.39 (d, $^3J_{HH}$ = 6.17 Hz, 3H, 1-CH_3^{α}), 1.61 (d, $^3J_{HH}$ = 6.19 Hz, 1-CH_3^{β}), 2.85 (dq, $^3J_{HH}$ = 9.38 Hz, 6.19 Hz, 1H, 1-H^{β}), 3.09 (dq, $^3J_{HH}$ = 9.34 Hz, 6.17 Hz, 1H, 1-H^{α}), 3.49 (d, $^3J_{HH}$ = 9.34 Hz, 1H, 2-H^{α}), 3.61 (d, $^3J_{HH}$ = 9.38 Hz, 1H, 2-H^{β}), 5.27 (s, 1H, 5-H^{β}), 5.65 (s, 1H, 5-H^{α}), 7.14 - 7.47 (m, 10H, $Ph^{\alpha-\beta}$).

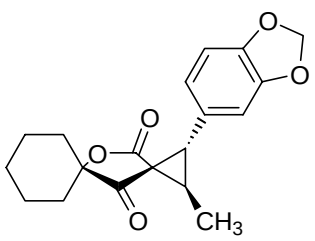
^{13}C-JMOD NMR (125.7 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.36 (CH_3, C-1$^{\alpha}$), 12.12 (CH_3, C-1$^{\beta}$), 37.97 (CH, C-1$^{\alpha}$), 38.69 (CH, C-1$^{\beta}$), 39.03 (C^{q}, C-3$^{\alpha-\beta}$-*spiro*), 51.13 (CH, C-2$^{\alpha}$), 52.39 (CH, C-2$^{\beta}$), 83.98, 84.39 (CH, C-5$^{\alpha-\beta}$), 125.29, 125.67, 128.02, 128.12, 128.44, 128.52, 128.80, 129.144, 129.88 (CH, Ph^{a-b}), 131.98, 132.09 (C^{q}, C-6-Ph$^{\alpha-\beta}$-*ipso*), 133.40 (C^{q}, Ph$^{\alpha-\beta}$-*ipso*), 171.38 (C^{q}, C-7$^{\alpha-\beta}$), 203.26 (C^{q}, C-4$^{\alpha-\beta}$).

MS (EI, 70 eV): m/z = 293 (1) [M^++1], 292 (13) [M^+], 277 (6) [M^+-CH_3], 247 (4) [M^+-COOH], 224 (3), 201 (1), 186 (5), 158 (2), 129 (11), 118 (100) [$C_8H_6O^+$], 117 (19), 115 (16), 105 (6) [$C_7H_5O^+$], 91 (8), 77 (3) [$C_6H_6^+$], 43 (2).

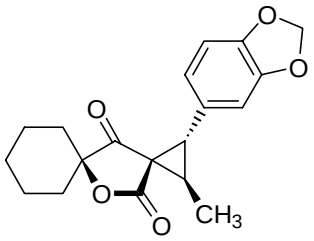
Accurate Mass:- Calculated Mass = 292.10994 Found = 292.10998

1-Methyl-2-(1',3'-benzodioxol-5-yl)-11-oxadispiro[2.1.5.2]dodecane-4,12-dione-(±)-119k-α.

Yellow solid (374 mg, 1.14 mmol, 67%) from 4-{[(2E)-3-(1,3-benzodioxol-5-yl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121k** (560 mg, 1.71 mmol) dissolved in dry toluene (10 ml) and heated to 160^{O}C for 48 h. Molecular formula $C_{19}H_{20}O_5$. *NB It is possible to separate the diastereoisomers by column chromatography and repeated recrystallisation as with **119a**. The α, β diasteroisomers were identified as such by the comparision of the chemical shifts with those obtained for **119a**.*



119k-α



119k-β

Mixture of diastereoisomers **121k-α** and **121k-β.**: Ratio α:β = 2:5.

IR (KBr); ν(cm^{-1}) = 3060 (s), 2936 (s), 2862 (m), 1772 (s), 1730 (s), 1654 (w), 1506 (s), 1490 (m), 1448 (s), 1318 (m), 1241 (s), 1197 (m), 1175 (m), 1128 (m), 1109 (m), 1034 (s), 977 (m), 931 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.23 - 1.80 (m, 13H, 6-H$^{\alpha-\beta}$, 7-H$^{\alpha-\beta}$, 8-H$^{\alpha-\beta}$, 9-H$^{\alpha-\beta}$, 10-H$^{\alpha-\beta}$, including two doublets at 1.51 ppm, $^{3}J_{HH}$ = 6.10 Hz, from 1-CH_3^{α} and 1.60 ppm, $^{3}J_{HH}$ = 6.21 Hz, from 1-CH_3^{β}), 2.77 (m, 1H, 1-H$^{\beta}$), 2.92 (m, 6.24 Hz, 1H, 1-H$^{\alpha}$), 3.29 (d, $^{3}J_{HH}$ = 9.24 Hz, 1H, 2-H$^{\alpha}$), 3.44 (d, $^{3}J_{HH}$ = 9.23 Hz, 1H, 2-H$^{\beta}$), 5.91 and 5.92 (s, 2H, $OCH_2O^{\alpha-\beta}$), 6.67 - 6.72 (m, 4H, Ar$^{\alpha-\beta}$).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.41 (CH_3, C-1$^{\alpha}$), 11.91 (CH_3, C-1$^{\beta}$), 20.68, 20.86 (CH_2, C-7$^{\alpha}$, C-9$^{\alpha}$), 21.03, 21.10 (CH_2, C-7$^{\beta}$ and C-9$^{\beta}$), 24.35 (CH_2, C-8$^{\alpha}$), 24.49 (CH_2, C-8$^{\beta}$), 31.95, 32.05 (CH_2, C-6$^{\alpha}$ and C-10$^{\alpha}$), 32.15, 32.35 (CH_2, C-6$^{\beta}$ and C-10$^{\beta}$), 36.17 (CH, C-1$^{\beta}$), 37.66 (CH, C-1$^{\alpha}$), 39.05 (C^{q}, C-3$^{\beta}$-*spiro*), 39.17 (C^{q}, C-3$^{\alpha}$-*spiro*), 51.66 (CH, C-2$^{\beta}$), 51.83 (CH, C-2$^{\alpha}$), 88.71 (C^{q}, C-5$^{\beta}$-*spiro*), 88.86 (C^{q}, C-5$^{\alpha}$-*spiro*), 101.09 (CH_2, OCH_2O^{α}), 101.26 (CH_2, OCH_2O^{β}), 108.44, 108.61, 109.72, 109.90, 122.46, 122.79 (CH, Ar$^{\alpha-\beta}$), 126.03 (C^{q}, Ar-*ipso*$^{\beta}$), 126.31 (C^{q}, Ar-*ipso*$^{\alpha}$), 147.55, 147.61 (C^{q}, Ar$^{\beta}$-*meta* and Ar$^{\beta}$-*para*), 172.62 (C^{q}, C-12$^{\beta}$), 206.28 (C^{q}, C-4$^{\beta}$). *Note that Ph$^{\alpha}$-meta, Ph$^{\alpha}$-para, C-2$^{\alpha}$ and C-4$^{\alpha}$ were too weak to be observed due to insufficient measuring time.*

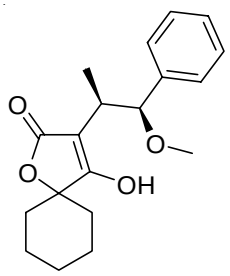
MS (EI, 70 eV): m/z = 329 (7) [M^++1], 328 (32) [M^+], 310 (1.5) [M^+-H_2O], 218 (9) [M^+-$C_6H_{10}CO$], 202 (41) [*218* - O], 174 (100) [*202* - CO], 162 (49) [*174* - C], 149 (26) [*162* - CH], 135 (37) [*149* - CH_2], 115 (50), 103 (29), 77 (26), 55 (23), 41 (41).
Accurate Mass:- Calculated Mass = 328.13108 Found = 328.13076

3.4 Ring opening of spirocyclopropyldihydrofuran-4,12-diones 119 with nucleophiles

3.4.1 Ring opening of spirocyclopropyldihydrofuran-4,12-diones 119 with oxygen nucleophiles

*General Experimental Procedure for reaction of spirocyclopropyldihydrofuran-4,12-diones **119** with alcohols*: The respective spirocyclopropyl compound **119** (580 mg, 2.04 mmol) was dissolved in a mixture of dry chloroform (15 ml) and methanol (10 ml). The solution was refluxed for 16 hours after which time the solvent was removed by rotary evaporation and the residue was purified by column chromatography (silica gel: solvent as indicated). *NB The syn configuration was established by comparison of the coupling constants with those obtained from a previously prepared analogue whose structure was determined by X-ray crystallography.*[115]

(±)syn-4-Hydroxy-3-[(syn)-2'-methoxy-1'-methyl-2'-phenylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 141a.
White crystalline solid (431 mg, 1.4 mmol, 70%) from 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119a** (580 mg, 2.04 mmol) dissolved in dry chloroform (15 ml) and methanol (10 ml). Solution was refluxed for 16 hours. Molecular formula $C_{19}H_{24}O_4$. R_f 0.72 (ethyl acetate:hexane, 1:1, v:v), mp 154 °C.



IR (KBr); ν(cm^{-1}) = 3430 (br) [ν (OH)], 2938 (s), 2829 (m), 1702 (s), 1659 (s), 1607 (s), 1492 (w), 1450 (m), 1370 (m), 1366 (m), 1320 (s), 1276 (m), 1232 (m), 1162 (m), 1129 (m), 1090 (s), 999 (w), 963 (m), 787 (w), 760 (m), 702 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.96 (d, $^3J_{HH}$ = 7.33 Hz, 3H, 1'-CH_3), 1.55 - 1.85 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.82 (dq, $^3J_{HH}$ = 7.33 Hz, 2.13 Hz, 1'-H), 3.42 (s, 3H, OCH_3), 4.60 (d, $^3J_{HH}$ = 2.13, 1H, 2'-H), 7.26 - 7.41 (m, 5H, Ph), 10.48 (s, 1H, OH).

^{13}C-NMR (75.4 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.4 (CH_3, C-1'), 21.8, 21.9 (CH_2, C-7 and C-9), 24.6 (CH_2, C-8), 32.8, 33.3 (CH_2, C-6 and C-10), 35.8 (CH, C-1'), 57.2 (OCH_3), 81.5 (C^q, C-5-spiro), 87.5 (CH, C-2'), 102.8 (C^q, C-3), 126.7, 128.0, 128.4 (CH, Ph), 137.8 (C^q, Ph-*ipso*), 173.3 (C^q, C-2), 179.6 (C^q, C-4).

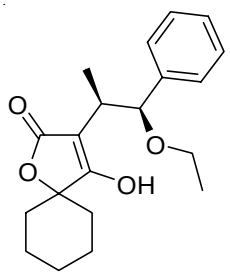
MS (EI, 70 eV): m/z = 316 (1) [M^+], 301 (9) [M^+-CH_3], 285 (1) [M^+-OCH_3], 284 (2) [M^+-CH_3OH], 279 (3), 266 (3) [M+-CH_3OH - H_2O], 258 (2), 240 (1), 223 (1), 149 (15), 148 (12), 122 (35), 121 (100) [$C_8H_9O^+$], 105 (11), 91 (17), 77 (23), 69 (10), 55 (10), 41 (14), 32 (6) 28 (24).

$C_{19}H_{24}O_4$ (316.39): Calculated C = 72.13%, H = 7.65%; found C = 72.19%, H = 7.66%.

GC retention time = 65 min

(±)syn-4-Hydroxy-3-[-2'-ethoxy-1'-methyl-2'-phenylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 141b.

White crystalline solid (250 mg, 0.76 mmol, 76%), from 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119a** (284 mg, 1.0 mmol) and ethanol (5 ml) dissolved in dry chloroform (25 ml). The mixture was refluxed for 16h. Molecular formula $C_{20}H_{26}O_4$. R_f 0.78 (ethyl acetate: hexane, 1:1, v:v), mp 145 ^oC.



IR (KBr); ν(cm^{-1}) = 3434 (br) [ν (OH)], 2936 (s), 2864 (s), 1704 (m) and 1659 (s) [ν (C=O)], 1603 (s), 1448 (w), 1321 (s), 1277 (m), 1232 (m), 1164 (m), 1096 (s), 996 (w), 961 (w), 762 (w), 704 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.97 (d, $^3J_{HH}$ = 7.36 Hz, 3H, 1'-CH_3), 1.32 (t, $^3J_{HH}$ = 7.07 Hz, 3H, OCH_2CH_3), 1.56 - 1.86 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.82 (dq, $^3J_{HH}$ = 7.36, 2.13 Hz, 1H, 1'-H), 3.48 (dq, $^2J_{HH}$ = 9.60 Hz, $^3J_{HH}$ = 7.07 Hz, 1H, OC*H*H), 3.67 (dq, $^2J_{HH}$ = 9.60 Hz, $^3J_{HH}$ = 7.07 Hz, 1H, OC*H*H), 4.69 (d, $^3J_{HH}$ = 2.13 Hz, 1H, 2'-H), 7.12 - 7.40 (m, 5H, Ph), 10.65 (s, 1H, OH).

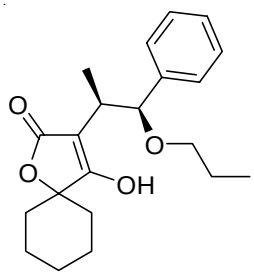
^{13}C-NMR (75.4 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 10.4 (CH_3, C-1'), 13.6 (CH_3, OCH_2CH_3), 20.0, 20.7 (CH_2, C-7 and C-9), 23.5 (CH_2, C-8), 31.7, 32.3 (CH_2, C-6 and C-10), 34.7 (CH, C-1'), 64.2 (CH_2, OCH_2), 80.8 (C^q, C-5-*spiro*), 84.4 (CH, C-2'), 101.9 (C^q, C-3), 125.6, 126.9, 127.3 (CH, CH-*arom*), 137.5 (C^q, C-*ipso*), 172.3 (C^q, C-4), 178.7 (C^q, C-2)

MS (EI, 70 eV): m/z = 330 (8) [M^+], 302 (3) [M^+-$C_2H_4^+$], 301(24) [M^+-C_2H_5], 284 (12) [M^+-C_2H_5OH], 266 (10) [M_+-C_2H_5OH - H_2O], 251 (5), 185 (7), 162 (7), 158 (15), 136 (36), 135 (100) [$C_6H_{11}O_+$], 130 (20), 118 (25), 107 (74), 91 (15), 79 (49), 69 (7), 55 (11), 44 (5), 41 (19), 32 (94), 28 (74).

$C_{20}H_{26}O_4$ (330.42): Calculated C = 72.70%, H = 7.93%; found C = 72.86%, H = 7.96%.

(±)syn-4-Hydroxy-3-[-2'-propoxy-1'-methyl-2'-phenylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 141c.

To a solution of 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119a** (870 mg, 3.06 mmol) in propanol (60 ml) was slowly added HBF_4 in diethyl ether (1.53 mmol). After stirring of the solution for 30 min at room temperature the temperature was raised to 80°C and kept constant for 16h. After cooling, DCM (100 ml) was added and the solution was washed with sodium carbonate solution and water. The organic layers were dried with magnesium sulphate and the solvent was removed in vacuo. Column chromatography of the residue gave a pure product. White crystalline solid (760 mg, 2.21 mmol, 72%). Molecular formula $C_{21}H_{28}O_4$. R_f 0.24 (100 % dichloromethane), mp 149 - 151 °C.



IR (KBr); ν(cm^{-1}) = 3430 (br) [ν (OH)], 2937 (s), 2867 (s), 1701 (s), 1657 (s), 1604 (s), 1451 (m), 1322 (m), 1278 (m), 1231 (m), 1162 (m), 1088 (m), 999 (w), 962 (w), 758 (w), 701 (m).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.93 (t, $^3J_{HH}$ = 7.48 Hz, 3H, CH_2CH_3), 0.93 (d, $^3J_{HH}$ = 7.39 Hz, 1'-CH_3), 1.15 - 1.92 (m, 12H, 6-H, 7-H, 8-H, 9-H, 10H, CH_2CH_3), 2.80 (dq, $^3J_{HH}$ = 7.39 Hz, 2.11 Hz, 1H, 1'-H), 3.37 (ddd, $^2J_{HH}$ = 9.45 Hz, $^3J_{HH}$ = 7.48, 5.74 Hz, 1H, OCHH), 3.51 (dt, $^2J_{HH}$ = 9.45 Hz, $^3J_{HH}$ = 7.48 Hz, 1H, OCHH), 4.66 (d, $^3J_{HH}$ = 2.11 Hz, 1H, 2'-H), 7.25 - 7.40 (m, 5H, Ph), 10.29 (s, 1H, OH).

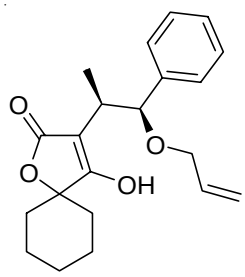
^{13}C-NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 10.6 (CH_2, CH_2CH_3), 18.3 (CH_3, C-1'), 21.8, 21.9 (CH_2, C-7 and C-9), 22.7 (CH_2, CH_2CH_3), 24.6 (CH_2, C-8), 32.7, 33.2 (CH_2, C-6 and C-10), 35.8 (CH, C-1'), 71.3 (CH_2, OCH_2), 81.9 (C^q, C-5-*spiro*), 85.6 (CH, C-2'), 102.8 (C^q, C-3), 126.7, 127.9, 128.0, 128.3, 128.5 (CH, Ph), 138.7 (C^q, Ph-*ipso*), 173.4 (C^q, C-2), 179.7 (C^q, C-4).

MS (EI, 70 eV): m/z = 345 (1) [M^++1], 344 (2) [M^+], 301 (3) [M^+-$C_3H_7^+$], 285 (3) [M^+-$C_3H_7O^+$], 266 (3) [M^+-C_3H_7 - H_2O], 258 (4), 251 (2), 233 (1), 149 (100), 107 (66), 79 (8).

$C_{21}H_{28}O_4$ (344.44):Calculated C = 73.23%, H = 8.19%; Found C = 73.19%, H = 8.07%.

(±)syn-4-Hydroxy-3-[-2'-allyloxy-1'-methyl-2'-phenylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 141d.

White crystalline solid (210 mg, 0.61 mmol, 50%) from 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119a** (350 mg, 1.23 mmol) and allyl alcohol (0.30 g, 5 mmol) in dry chloroform (20 ml). The solution was refluxed for 16h. Compound was purified by the removal of solvent and recrystallisation from hexane, column chromatography was not required. Molecular formula $C_{21}H_{26}O_4$. R_f 0.4 (diethyl ether / hexane, 1:1, v:v), mp 147 °C.



IR (KBr); ν(cm^{-1}) = 3434 (br) [ν (OH)], 2936 (s), 2862 (m), 1775 (s), 1775 (s) and 1659 (s) [ν (C=O)], 1602 (m), 1448 (m), 1316 (s), 1279 (w), 1233 (m), 1212 (w), 1165 (m), 1085 (s), 978 (m), 812 (w), 762 (w), 695 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.92 (d, $^{3}J_{HH}$ = 7.35 Hz, 3H, 1'-CH_3), 1.19 - 1.78 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.77 (dq, $^{3}J_{HH}$ = 7.35, 2.04 Hz, 1'-H), 3.81 (dd, $^{2}J_{HH}$ = 12.36 Hz, $^{3}J_{HH}$ = 6.83 Hz, 1H, OCH*H*), 4.12 (dd, $^{2}J_{HH}$ = 12.36, $^{3}J_{HH}$ = 4.99 Hz, 1H, OC*H*H), 4.67 (d, $^{3}J_{HH}$ = 2.04 Hz, 1H, 2'-H), 5.24 (dd, $^{3}J_{HH}$ = 10.54 Hz, $^{4}J_{HH}$ = 1.34 Hz, 1H, CH=CH*H-cis*), 5.28 (dd, $^{3}J_{HH}$ = 17.15 Hz, $^{4}J_{HH}$ = 1.32 Hz, 1H, CH=CH*H-trans*), 5.87 (dddd, $^{3}J_{HH}$ = 17.15, 10.54, 6.83, 4.99 Hz, 1H, $CH_2CH=CH_2$), 7.17 - 8.03 (m, 5H, Ph), 10.24 (s, 1H, OH).

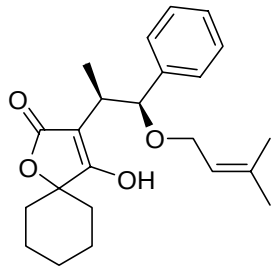
^{13}C-NMR (75.4 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.4 (CH_3, C-1'), 21.7, 21.9 (CH_2, C-7 and C-9), 24.7 (CH_2, C-8), 32.8, 33.3 (CH_2, C-6 and C-10), 35.7 (CH, C-1'), 70.1 (CH_2, OCH_2), 81.8 (C^q, C-5-*spiro*), 84.8 (CH, C-2'), 102.9 (C^q, C-3), 119.6 (CH_2, C=*C*H_2), 126.6, 128.0, 128.3 (CH, Ph), 132.2 (CH, *C*H=CH_2), 138.1 (C^q, Ph-*ipso*), 173.3 (C^q, C-4), 179.5 (C^q, C-2).

MS (EI, 70 eV): m/z = 343 (13) [M^++1], 284 (9) [M^+-C_3H_6O], 266 (5) [M^+-C_3H_6O - H_2O], 245 (5), 232 (8), 214 (5), 185 (4), 159 (8), 148 (87), 131 (6), 130 (14), 118 (100), 105 (48), 91 (28), 86 (50), 81 (8), 74 (23), 69 (13).

$C_{21}H_{26}O_4$ (342.43): Calculated C = 73.66% H = 7.65% Found C = 73.76% , H = 7.66%.

(±)syn-4-Hydroxy-3-[1-methyl-2-[(3-methylbut-2-nyl)oxy]-2-phenylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 141e.

White crystalline solid (204 mg, 0.5 mmol, 53%) from 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119a** (300 mg, 1.05 mmol) and 3-methylbut-2-en-1-ol (500 mg, 5.8 mmol) dissolved in dry DCM (25 ml). Solution refluxed for 16h, purification of product by column chromatography and recrystallisation from hexane. Molecular formula $C_{22}H_{30}O_4$. R_f 0.52 (ethyl acetate / hexane, 1:1, v:v), mp 131°C.



IR (KBr); ν(cm^{-1}) = 3419 (br) [ν (OH)], 2936 (s), 2863 (m), 1700 (s) and 1659 (s) [ν (C=O)], 1604 (s), 1455 (w), 1372 (w), 1324 (s), 1277 (w), 1233 (w), 1164 (w), 1050 (w), 1002 (w), 961 (w), 762 (w), 705 (m).

^{1}H-NMR (500 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.96 (d, $^3J_{HH}$ = 7.35, 3H, 1'-CH_3); 1.55 - 1.85 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 1.57 (s, 3H, C^qCH_3-*cis*), 1.78 (s, 3H, C^qCH_3-*trans*), 2.82 (dq, $^3J_{HH}$ = 7.35 Hz, 2.17 Hz, 1H, 1'-H), 3.91 (dd, $^2J_{HH}$ = 11.40 Hz, $^3J_{HH}$ = 8.39 Hz, 1H, OCH_a), 4.08 (dd, $^2J_{HH}$ = 11.40 Hz, $^3J_{HH}$ = 6.64 Hz, 1H, OCH_b), 4.71 (d, $^3J_{HH}$ = 2.17 Hz, 1H, 2'-H), 5.36 (m, 1H, C*H*=$C(CH_3)_2$), 7.26 - 7.39 (m, 5H, Ph), 10.54 (br, 1H, OH).

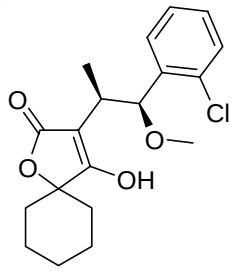
^{13}C-NMR (75.4 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.4 (CH_3, C-1'), 18.0 (CH_3, CCH_3-*cis*), 21.8, 22.0 (CH_2, C-7 and C-9), 24.5 (CH_2, C-8), 25.9 (CH_3, CCH_3-*trans*), 32.7, 33.3 (CH_2, C-6 and C-10), 35.7 (CH, C-1'), 65.8 (OCH_2), 81.8 (C^q, C-5-*spiro*), 84.5 (CH, C-2'), 102.9 (C^q, C-3), 118.3 (CH, *C*H=C^q), 126.8, 127.8, 128.4 (CH, Ph), 138.0 (C^q, C-*ipso*), 140.6 (C^q, *C*$(CH_3)_2$), 173.5 (C^q, C-4), 179.8 (C^q, C-2).

MS (EI, 70 eV): m/z =369 (3) [M^+-1], 301 (9) [M^+-C_5H_9], 285 (8) [M^+-C_5H_9O], 264 (9) [M^+-C_7H_6O], 197 (16), 196 (94) [M^+-$C_{12}H_{14}O$], 195 (64), 178 (29) [M^+-$C_{12}H_{14}O$ - H_2O], 177 (56), 169 (16), 159 (9), 149 (5), 129 (6), 118 (28), 109 (55), 107 (58), 96 (10), 91 (15), 81 (24), 85 (20), 69 (100) [$C_5H_9^+$], 55(17), 41 (66), 28 (30).

Accurate Mass:- Calculated Mass = 370.214410 Found = 370.215317

(±)syn-4-Hydroxy-3-[-2'-(2"-chlorophenyl)-2'-methoxy-1'-methylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 141f.

White solid (279 mg, 0.80 mmol, 63%) from 1-(2-chlorophenyl)-2-methyl-11-oxadispiro[2.1.5.2]dodecane-4,12-dione **119b** (400 mg, 1.26 mmol) dissolved in dry chloroform (20 ml) and methanol (5 ml) and refluxed for 24 h. Molecular formula $C_{19}H_{23}ClO_4$. Mp 180°C.



IR (KBr); ν(cm^{-1}) = 3416 (s), 3051 (w), 2936 (s), 2868 (w), 1705 (s), 1632 (s), 1446 (m), 1314 (s), 1228 (m), 1160 (m), 1118 (s), 1086 (s), 1005 (m), 962 (m), 753 (s), 614 (w).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.92 (d, $^3J_{HH}$ = 7.29 Hz, 3H, 1'-CH_3), 1.16 - 1.84 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.98 (dq, $^3J_{HH}$ = 7.29 Hz, 1.93 Hz, 1H, 1'-H), 3.39 (s, 3H, OCH_3), 4.93 (d, $^3J_{HH}$ = 1.93 Hz, 1H, 2'-H), 7.23 - 7.40 (m, 4H, Ar), 10.25 (s, 1H, OH).

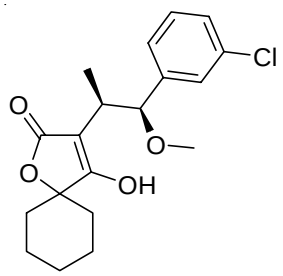
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.6 (CH_3, C-1'), 21.8, 22.0 (CH_2, C-7 and C-9), 24.6 (CH_2, C-8), 32.7 (CH, C-1'), 32.9, 33.3 (CH_2, C-6 and C-10), 57.4 (CH_3, OCH_3), 81.9 (C^q, C-5-*spiro*), 84.3 (CH, C-2'), 102.8 (C^q, C-3), 126.6, 127.8, 129.2, 130.2 (CH, Ar), 133.3 (C^q, Ar-Cl), 135.1 (C^q, Ar-*ipso*), 173.0 (C^q, Ar-2), 179.3 (C^q, C-4).

MS (EI, 70 eV): m/z = 352 (0.2) [M^+, ^{37}Cl], 351 (0.1) [M^++1, ^{35}Cl], 350 (0.9) [M^+, ^{35}Cl], 320 (0.1) [M^+ - CH_3OH, ^{37}Cl], 318 (0.7) [M+ - CH_3OH, ^{35}Cl], 302 (0.1) [*320* - H_2O], 300 (0.3) [*318* - H_2O], 287 (0.1) [*302* - CH_3], 285 (0.3) [*300* - CH_3], 265 (0.7), 221 (0.2), 219 (0.9), 157 (39) [$C_8H_8ClO^+$, ^{37}Cl], 155 (100) [$C_8H_8ClO^+$, ^{35}Cl], 139 (2), 109 (1), 91 (4), 69 (3), 55 (2), 41 (6).

Accurate Mass:- Calculated Mass = 350.128549 Found = 350.128487

(±)syn-4-Hydroxy-3-[-2'-(3''-chlorophenyl)-2'-methoxy-1'-methylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 141g.

White solid (214 mg, 0.61 mmol, 56%) from 1-methyl-2-(3-chlorophenyl)-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119c** (350 mg, 1.10) dissolved in dry chloroform (20 ml) and methanol (5 ml). The solution was refluxed overnight. Molecular formula $C_{19}H_{23}ClO_4$. R_f 0.15 (diethyl ether:hexane, 1:1, v:v), mp 176°C.



IR (KBr); ν(cm^{-1}) = 3456 (m) [ν (OH)], 3011 (w), 2938 (m), 2865 (w), 1703 (s), 1658 (s), 1602 (s), 1448 (m), 1316 (s), 1231 (m), 1161 (m), 1078 (m), 1000 (m), 964 (m), 879 (w), 785 (m), 698 (m) [C-Cl].

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.94 (d, $^3J_{HH}$ = 7.29 Hz, 3H, 1'-CH_3), 1.16 - 1.89 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.76 - 2.83 (m, 1H, 1'-H), 3.42 (s, 3H, OCH_3), 4.54 (br, 1H, 2'-H), 7.13 - 7.34 (m, 4H, Ar), 10.20 (s, 1H, OH).

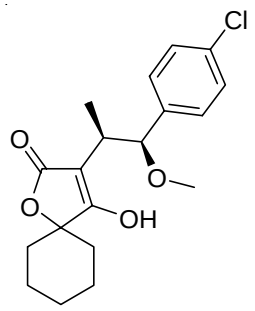
^{13}C-JMOD NMR (75 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.4 (CH_3, C-1'), 21.8, 22.0 (CH_2, C-7 and C-10), 24.6 (CH_2, C-8), 32.9, 33.3 (CH_2, C-6 and C-10), 35.7 (CH, C-1'), 57.5 (CH_3, OCH_3), 82.0 (C^q, C-5-*spiro*), 87.0 (CH, C-2'), 102.6 (C^q, C-3), 125.0, 126.8, 128.3, 129.9 (CH, Ar), 134.7 (C^q, Ar-Cl), 140.2 (C^q, Ar-*ipso*), 173.2 (C^q, C-2), 179.7 (C^q, C-4).

MS (EI, 70 eV): m/z = 353 (0.1) [M^++1, ^{37}Cl], 352 (0.5) [M^+, ^{37}Cl], 351 (0.4) [M^++1, ^{35}Cl], 350 (15) [M^+, ^{35}Cl], 337 (0.1) [*352* - CH_3], 335 (0.5) [*350* - CH_3], 320 (0.2) [*337* - OH], 318 (0.7) [*335* - OH], 302 (0.2) [*320* - H_2O], 300 (0.6) [*318* - H_2O], 287 (0.2) [*302* - CH_3], 285 (0.6) [*300* - CH_3], 265 (0.7), 221 (0.3), 219 (0.9), 157 (42) [$C_8H_8ClO^+$, ^{37}Cl], 155 (100) [$C_8H_8ClO^+$, ^{35}Cl], 139 (3), 109 (2), 99 (2), 91 (10), 69 (3), 55 (3), 41 (4).

Accurate Mass:- Calculated Mass = 350.1285 Found = 350.1285.

(±)syn-4-Hydroxy-3-[-2'-(4''-chlorophenyl)-2'-methoxy-1'-methylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 141h.

White solid (511mg, 1.46 mmol, 89%) from 1-(4-chlorophenyl)-2-methyl-11-oxadispiro[2.1.5.2]dodecane-4,12-dione **119b** (520 mg, 1.64 mmol) and methanol (5 ml) dissolved in dry chloroform (20 ml) and heated to reflux for 16h. Molecular formula $C_{19}H_{23}ClO_4$. R_f 0.33 (diethyl ether:hexane, 1:1, v:v), mp 177°C (decomp.).



IR (KBr); ν(cm^{-1}) = 3458 (s) [ν (OH)], 3115 (w), 2938 (m), 2861 (w), 1706 (m), 1656 (s), 1490 (w), 1453 (w), 1388 (s), 1346 (m), 1264 (m), 1202 (w), 1087 (s), 996 (m), 961 (m), 825 (m), 779 (m), 626 (m).

^{1}H-NMR (250 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.92 (d, $^3J_{HH}$ = 7.36 Hz, 3H, 1'-CH_3), 1.15 - 1.82 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.76 (dq, $^3J_{HH}$ = 7.36 Hz, 2.11 Hz, 1H, 1'-H), 3.38 (s, 3H, OCH_3), 4.54 (d, $^3J_{HH}$ = 2.11 Hz, 1H, 2'-H), 7.19 (m, 2H, Ar-*ortho*), 7.31 - 7.36 (m, 2H, Ar-*meta*), 10.29 (s, 1H, OH).

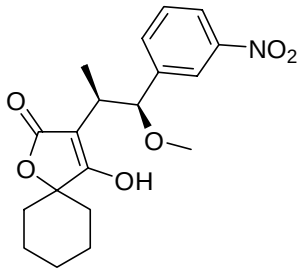
^{13}C-JMOD NMR (62.9 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.3 (CH_3, C-1'), 21.7, 21.9 (CH_2, C-7 and C-9), 24.5 (CH_2, C-8), 32.7, 33.2 (CH_2, C-6 and C-10), 35.7 (CH, 1'-C), 57.2 (CH_3, OCH_3), 81.9 (C^q, C-5-*spiro*), 86.9 (CH, C-2'), 102.5 (C^q, C-3), 128.0 (CH, Ar-*meta*), 128.7 (CH, Ar-*ortho*), 133.8 (C^q, Ar-Cl), 136.3 (C^q, Ar-*ipso*), 170.8 (C^q, C-2), 179.6 (C^q, C-4).

MS (EI, 70 eV): m/z = 352 (0.2) [M^+, ^{37}Cl], 351 (0.2) [M^++1, ^{35}Cl], 350 (0.8) [M^+, ^{35}Cl], 337 (0.3) [M^+-CH^3, ^{37}Cl], 335 (0.7) [M^+-CH^3, ^{35}Cl], 320 (0.3) [M^+-CH_3OH, ^{37}Cl], 318 (1) [M^+-CH^3OH, ^{35}Cl], 302 (0.2) [*320* - H_2O], 300 (1.1) [*318* - H_2O], 287 (0.2), 285 (0.9), 265 (1), 257 (0.2), 221 (0.2), 219 (1), 157 (74) [$C_8H_8O^{37}Cl^+$], 156 (16), 155 (100) [$C_8H_8O^{35}Cl^+$], 139 (4), 109 (5), 91 (12), 69 (3), 55 (4), 41 (5).

$C_{19}H_{23}ClO_4$ (350.84): Calculated C = 65.05%, H = 6.61%; found C = 64.99%, H = 6.62%.

(±)syn-4-Hydroxy-3-[-2'-(3''-nitrophenyl)-2'-methoxy-1'-methylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 141i.

To a solution of 4-{[(2E)-3-(3-nitrophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **119e** (520 mg, 1.58 mmol) in dry chloroform (20 ml) was slowly added HBF_4 in diethyl ether (0.2 ml). After stirring of the solution for 1h at room temperature, methanol (10 ml) was added and the combined solution was then heated to reflux for 16h. After cooling DCM (100 ml) was added the solution was washed twice with sodium carbonate solution (20 ml) and with water (20 ml). The organic layer was then dried with magnesium sulphate and the solvent was removed in vacuo. The residue was purified by column chromatography to give a white solid of **141i** (526 mg, 1.46 mmol, 92%). Molecular formula $C_{19}H_{23}NO_6$. R_f 0.65 (100% DCM), mp 163°C.



IR (KBr); ν(cm^{-1}) = 3433 (m) [ν (OH)], 3049 (w), 2937 (s), 1701 (s), 1660 (s) [ν (C=O)], 1602 (s), 1570 (m), 1536 (s) [ν (NO_2)], 1447 (w), 1353 (s) [ν (NO_2)], 1319 (s), 1276 (m), 1233 (m), 1164 (m), 1093 (s), 1074 (m), 1001 (w), 964 (w), 910 (w), 813 (w), 786 (m), 738 (m), 681 (w).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.96 (d, $^3J_{HH}$ = 7.33 Hz, 3H, 1'-CH_3), 1.13 - 1.84 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.83 (dq, $^3J_{HH}$ = 7.33 Hz, 2.81 Hz, 1H, 1'-H), 3.40 (s, 3H, OCH_3), 4.66 (d, $^3J_{HH}$ = 2.81 Hz, 1H, 2'-H), 7.43 - 7.61 and 8.10 - 8.17 (m, 4H, Ar), 10.00 (s, 1H, OH).

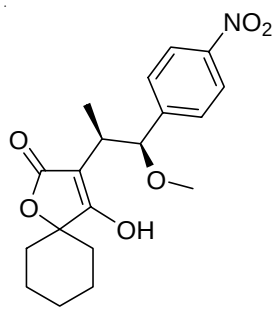
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 14.6 (CH_3, C-1'), 21.6, 21.8 (CH_2, C-7 and C-9), 24.4 (CH_2, C-8), 32.6, 33.1 (CH_2, C-6 and C-10), 35.5 (CH, C-1'), 57.6 (CH_3, OCH_3), 82.1 (C^q, C-5-*spiro*), 86.4 (CH, C-2'), 102.0 (C^q, C-3), 121.4 (CH, Ar-3), 123.0 (CH, Ar-4), 129.6 (CH, Ar-5), 132.9 (CH, Ar-6), 140.6 (C^q, Ar-*ipso*), 148.4 (C^q, Ar-NO_2), 173.0 (C^q, C-2), 179.67 (C^q, C-4).

MS (EI, 70 eV): m/z = 361 (0.5) [M^+], 344 (1) [M^+-OH], 331 (2) [M^+-NO], 329 (17) [M^+-CH_3OH], 311 (3) [*329* - OH], 299 (8), 281 (3), 253 (2), 230 (4), 193 (3), 167 (47) [$C_9H_{11}O_3^+$], 166 (100) [$C_9H_{10}O_3^+$], 150 (37) [*167* - OH, *166* - O], 136 (14), 120 (22), 109 (6), 99 (5) [$C_6H_{11}O^+$], 81 (4), 69 (7), 41 (4).

Accurate Mass:- Calculated Mass = 361.1525 Found = 361.1525

(±)syn-4-Hydroxy-3-[-2'-(4''-nitrophenyl)-2'-methoxy-1'-methylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 141j.

To a solution of 4-{[(2E)-3-(3-nitrophenyl)prop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **119g** (370 mg, 1.12 mmol) in dry chloroform (20 ml) was slowly added HBF_4 in diethyl ether (0.1 ml, 0.56 mmol). After stirring of the solution for 1h at room temperature, methanol (10 ml) was added and the combined solution was then heated to reflux for 16h. After cooling DCM (100 ml) was added the solution was washed twice with sodium carbonate solution (20 ml) and with water (20 ml). The organic layer was then dried with magnesium sulphate and the solvent was removed in vacuo. The residue was purified by column chromatography to give a white crystalline solid of **141j** (323 mg, 0.9 mmol, 80%). Molecular formula $C_{19}H_{23}NO_6$. R_f 0.66 (ethyl acetate:hexane, 1:1, v:v), mp 198°C (decomp.).



IR (KBr); ν(cm^{-1}) = 3431 (m) [ν (OH)], 2934 (s), 2924 (w), 1688 (w), 1655 (s), 1601 (s), 1522 (s) [ν (NO_2)], 1453 (m), 1346 (s) [ν (NO_2)], 1283 (w), 1233 (w), 1164 (w), 1083 (s), 1003 (w), 964 (m), 851 (w).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.93 (d, $^3J_{HH}$ = 7.36 Hz, 3H, 1'-CH_3), 1.52 - 1.88 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.83 (dq, $^3J_{HH}$ = 7.36 Hz, 2.22 Hz, 1H, 1'-H), 3.43 (s, 3H, OCH_3), 4.66 (d, $^3J_{HH}$ = 2.22 Hz, 1H, 2'-H), 7.46 (d, $^3J_{HH}$ = 8.71 Hz, 2H, Ar-*meta*), 8.25 (d, $^3J_{HH}$ = 8.71 Hz, 2H, Ar-*ortho*), 9.98 (s, 1H, OH).

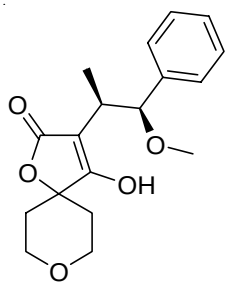
^{13}C-NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.3 (CH_3, C-1'), 21.7 and 21.8 (CH_2, C-7 and C-9), 24.5 (CH_2, C-8), 32.7 and 33.2 (CH_2, C-6 and C-10), 35.5 (CH, C-1'), 57.7 (CH_3, OCH_3), 82.1 (C^q, C-5-*spiro*), 86.9 (CH, C-2'), 102.3 (C^q, C-3), 123.8 (2xCH, Ar-*meta*), 127.5 (2xCH, Ar-*ortho*), 145.4 (C^q, Ar-NO_2), 147.7 (C^q, Ar-*ipso*), 172.9 (C^q, C-2), 179.7 (C^q, C-4).

MS (EI, 70 eV): m/z = 362 (1) [M^++1], 361 (3) [M^+], 346 (1) [M^+ - CH_3], 329 (1) [M^+ - CH_3OH], 303 (2), 193 (7), 167 (100) [$C_9H_{11}O_3^+$], 166 (93) [$C_9H_{10}O_3^+$], 150 (60) [$C_9H_{10}O_2^+$], 136 (2), 120 (16), 91 (3), 69 (4), 55 (2), 41 (3).

Accurate Mass:- Calculated Mass = 361.3938 Found = 361.3940

(±)-syn-4-Hydroxy-3-[-2'-methoxy-1'-methyl-2'-phenylethyl]-1,8-dioxaspiro[4.5]dec-3-en-2-one 141k.

White solid (268 mg, 0.91 mmol, 81%) from 1-methyl-2-phenyl-11-oxadispiro[2.1.5.2]dodecane-4,12-dione **119h** (300 mg, 1.05 mmol), methanol (5 ml) and chloroform (20 ml) heated to reflux for 24h. Molecular formula $C_{19}H_{24}O_4$. R_f 0.42 (ethyl acetate:hexane, 1:3, v:v), m.p. >217°C (decomp.)



IR (KBr); ν(cm-^{1}) = 3446 (br) [ν (OH)], 2970 (m), 2862 (w), 1720 (s), 1654 (s), 1559 (m), 1455 (m), 1397 (m), 1310 (m), 1244 (m), 1154 (m), 1099 (m), 1022 (m), 991 (m), 928 (w), 829 (m), 783 (m), 762 (m), 703 (m), 620 (w), 559 (w).

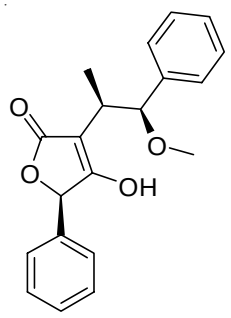
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.94 (d, $^3J_{HH}$ = 7.32 Hz, 3H, 1'-CH_3), 1.36 - 1.51 and 2.08 - 2.20 (m, 4H, 6-H and 10-H), 2.79 (qd, $^3J_{HH}$ = 7.32 Hz, 2.23 Hz, 1H, 1'-H), 3.39 (s, 3H, OCH_3), 3.73 - 3.97 (m, 4H, 7-H and 9-H), 4.57 (d, $^3J_{HH}$ = 2.23 Hz, 1H, 2'-H), 7.21 - 7.36 (m, 5H, Ph), 10.59 (s, 1H, OH).

^{13}C-NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.5 (CH_3, C-1'), 32.6, 33.0 (CH_2, C-6 and C-10), 35.7 (CH, C-1'), 57.1 (CH_3, OCH_3), 63.6, 63.7 (CH_2, C-7 and C-9), 78.9 (C^q, C-5-*spiro*), 87.2 (CH, C-2'), 103.3 (C^q, C-3), 126.6, 128.0, 128.4, 128.4 (CH, Ph), 137.6 (C^q, Ph-*ipso*), 172.6 (C^q, C-2), 177.8 (C^q, C-4).

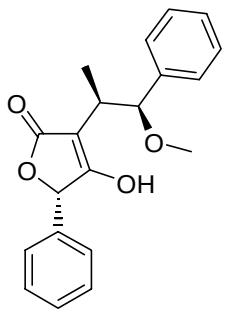
MS (EI, 70 eV): m/z = 319 (0.2) [M^++1], 318 (1.2) [M^+], 287 (0.8) [M^+-CH_3O], 286 (3.6) [M^+-CH_3OH], 271 (1) [*286* - CH_3], 268 (2) [*286* - H_2O], 241 (5) [M^+-C_6H_5], 167 (6), 158 (7), 121 (100) [$C_6H_5C_2H_4O^+$], 105 (19) [$C_6H_5C_2H_4^+$], 91 (54) [$C_6H_5CH_2^+$], 77 (32) [$C_6H_5^+$], 69 (15), 43 (22) [$C_3H_7^+$], 41 (27) [$C_3H_5^+$].

(±)-syn-(5 R/S)-4-Hydroxy-3-[-2'-methoxy-1'-methyl-2'-phenylethyl]-5-phenylfuran-2(5*H*)-one 141l.

White solid (85 mg, 0.23 mmol, 64%) from 1-methyl-2,6-diphenyl-5-oxaspiro[2.4]heptane-4,7-dione **119i** (120 mg, 0.41 mmol) and methanol (2 ml) dissolved in dry chloroform (15 ml). Solution was heated to reflux for 16h. Molecular formula $C_{20}H_{20}O_4$. R_f 0.21 (diethyl ether:hexane, 1:1, v:v), mp 59°C. Note that α/β have been arbitrarily assigned in order to distinguish the NMR signals. *Also note that integretion of ^{1}H-NMR signals refers to a hypothetical 1:1 mixture of diastereoisomers.*



141l-α



119l-β

*Mixture of diasteroisomers **141l-α**, **141l-β**: 5:3*

IR (KBr); ν(cm^{-1}) = 3576 (s) [ν (OH)], 3042 (w), 2982 (w), 2933 (w), 1748 (s) [ν (lactone)], 1656 (s), 1454 (m), 1395 (m), 1312 (m), 1194 (s), 1086 (m), 1011 (m), 924 (w), 761 (m), 700 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.00 (d, $^3J_{HH}$ = 7.27 Hz, 3H, 1'-CH_3^{α}), 1.03 (d, $^3J_{HH}$ = 5.91 Hz, 3H, 1'-CH_3^{β}), 2.90 (dt, $^3J_{HH}$ = 7.27 Hz, 1.66 Hz, 1H, 1'-H^{α}), 2.97 - 3.02 (m, 1H, 1'-H^{β}), 3.32 (s, 3H, OCH_3^{β}), 3.40 (s, 3H, OCH_3^{α}), 4.60 (d, $^3J_{HH}$ = 1.70 Hz, 1H, 2'-H^{β}), 4.66 (d, $^3J_{HH}$ = 1.66 Hz, 1H, 2'-H^{α}), 5.64 (s, 2H, 5-$H^{\alpha-\beta}$), 7.23 - 7.40 (m, 10 H, $Ph^{\alpha-\beta}$), 10.62 (s, 1H, OH^{β}), 10.68 (s, 1H, OH^{α}).

^{13}C-JMOD NMR (65.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.6 (CH_3, C-1'$^{\alpha-\beta}$), 36.1, 36.2 (CH, C-1'$^{\alpha-\beta}$), 57.2, 58.3 (CH_3, $OCH_3^{\alpha-\beta}$), 78.7, 78.8 (CH, CH-2'$^{\alpha-\beta}$), 87.3, 89.4 (CH, C-5$^{\alpha-\beta}$), 104.3 (C^q, C-3$^{\alpha-\beta}$), 126.7, 126.8, 128.2, 128.9, 129.2, 129.3 (CH, $Ph^{\alpha-\beta}$), 134.5, 134.0 (C^q, C-6-Ph-*ipso*$^{\alpha-\beta}$), 137.6 (C^q, C-3'-Ph-*ipso*$^{\alpha-\beta}$), 173.9 (C^q, C-2$^{\alpha-\beta}$), 174.8 (C^q, C-4$^{\alpha-\beta}$).

MS (EI, 70 eV): m/z = 325 (0.75) [M^++1], 324 (3) [M^+], 309 (1) [M^+-CH_3], 292 (3) [M^+-CH_3OH], 247 (2) [M^+-C_6H_5], 148 (4), 122 (10), 121 (100) [$C_8H_9O^+$], 118 (14) [$C_9H_{10}^+$], 105 (6), 91 (5) [$C_7H_7^+$], 77 (6) [$C_6H_6^+$], 59 (1), 51 (2), 41 (1).

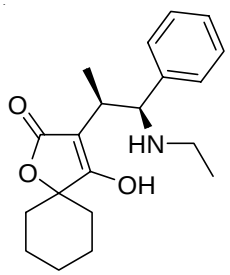
$C_{20}H_{20}O_4$ (324.37): Calculated C = 74.06&, H = 6.21%; found C = 74.26%, H = 6.19%.

3.4.2 Ring opening of spirocyclopropyldihydrofuran-4,12-diones 119 with nitrogen nucleophiles

*General experimental procedure for ring opening of spirocyclopropyldihydrofuran-4,12-diones **119** with amines:* The respective spirocyclopropyl compound **119** (356 mg, 1.30 mmol) was weighed in a clean dry flask and dissolved in dry chloroform (10 ml). The respective amine (1.30 mmol) was added and the resulting solution was stirred for 18h at room temperature. The solvent was then removed by rotary evaporation and the resulting residue was purified by column chromatography (silica gel: solvent as indicated). *NB It should be noted that for compounds **144** it is often not possible to identify the OH and NH signals. The signals are extremely broad which makes identification extremely difficult, however all other data are consistent with proposed structures.*

(±)-syn-4-hydroxy-3-[-1'-methyl-2'-(ethylamino)-2'-phenylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 144a.

White crystalline solid (323 mg, 1.0 mmol, 78%) from 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119a** (356 mg, 1.3 mmol) and ethylamine (56 mg, 1.3 mmol) dissolved in dry chloroform (10 ml). The solution was stirred under an argon atmosphere for 18h at room temperature. Molecular formula $C_{20}H_{27}NO_3$.R_f 0.27 (ethyl acetate, 100%), mp 112°C.



IR (KBr); ν(cm^{-1}) = 3429 (br) [ν (OH, NH)], 2934 (s), 2857 (m), 1682 (s), 1563 (s), 1452 (m), 1259 (w), 1224 (w), 1024 (m), 962 (m), 755 (m).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.99 (d, $^3J_{HH}$ = 7.08 Hz, 3H, 1'-CH_3), 1.18 (t, $^3J_{HH}$ = 7.29 Hz, 3H, CCH_3), 1.39 - 1.83 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.56 - 2.69 (m, $^3J_{HH}$ = 7.08 Hz, 1H, 1'-H), 2.75 - 2.94 (m, $^3J_{HH}$ = 7.29 Hz, 2H, NCH_2), 4.04 (s, 1H, 2'-H), 7.19 - 7.38 (m, 5H, Ph).

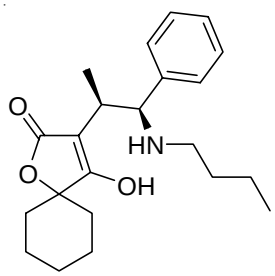
^{13}C-NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 18.4 (CH_3; C-1'), 20.0 (CH_2; C-7 and C-9), 28.4 (CH_2; C-8), 28.5 (CH_3; C*C*H_3), 31.1 (CH_2; C-6 and C-10), 39.3 (CH; C-1'), 42.7 (CH_2; NCH_2), 71.0 (CH_2; C-2'), 88.8 (C^q; C-5-*spiro*), 105.5 (C^q; C-3), 133.1, 134.3, 135.3 (CH; Ph), 144.2 (C^q; Ph-*ipso*), 181.5 (C^q; C-2), 190.5 (C^q; C-4).

MS (EI, 70 eV): m/z = 330 (5) [M^++1], 329 (29) [M^+], 328 (3) [M^+-1], 300 (1) [M^+-C_2H_5], 266 (1), 251 (1), 229 (1), 203 (1), 185 (2), 158 (2), 136 (4), 135 (64) [$C_9H_{13}N^+$], 134 (100) [$C_9H_{12}N^+$], 118 (5), 106 (88), 91 (4), 79 (8).

$C_{20}H_{27}NO_3$ (329.43): Calculated C = 72.92%, H = 8.26%, N = 4.25%; found C = 72.88%, H = 8.33%, N = 4.21%.

(±)-syn-4-Hydroxy-3-[1'-methyl-2'-(butylamino)-2'-phenylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 144b.

White Solid (287 mg, 0.8 mmol, 67 %), from 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119a** (0.35 g, 1.2 mmol) and *n*-butylamine (0.1 g, 1.4 mmol) in chloroform (20 ml). Solution was heated to reflux for 16h. Molecular formula $C_{22}H_{31}NO_3$. R_f 0.48 (ethyl acetate 100%), m.p. 124°C.



IR (KBr); ν(cm^{-1}) = 3448 (br) [ν (OH, NH)], 2934 (s), 2866 (w), 1738 (w), 1681 (s), 1582 (s), 1429 (m), 1243 (w), 1050 (m), 963 (w).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.89 (t, $^3J_{HH}$ = 7.50 Hz, 3H, CH_2CH_3), 0.95 (d, $^3J_{HH}$ = 7.29 Hz, 3H, 1'-CH_3), 1.32 (m, 2H, CH_2CH_3), 1.41 - 1.88 (m, 12H, 6-H, 7-H, 8-H, 9-H, 10-H, $NCCH_2$), 2.50 - 2.73 (m, 2H, NCH_2), 2.83 (dq, $^3J_{HH}$ = 7.29 Hz, 2.19 Hz, 1H, 1'-H), 4.03 (d, $^3J_{HH}$ = 2.19 Hz, 1H, 2'-H), 7.17 - 7.37 (m, 5H, Ph).

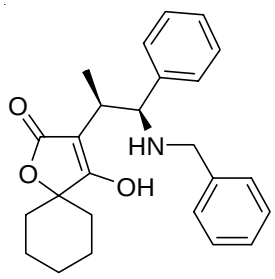
^{13}C-NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 12.0 (CH_3; CH_2CH_3), 13.7 (CH_3; C-1'), 20.2 (CH_2; CH_2CH_3), 21.9 (CH_2; C-7 and C-9), 24.6 (CH_2; C-8), 30.0 (CH_2; $NCCH_2$), 32.7 (CH_2; C-6 and C-10), 36.1 (CH; C-1'), 46.4 (CH_2; NCH_2), 65.3 (CH; C-2'), 82.6 (C^q; C-5-*spiro*), 97.6 (C^q; C-3), 126.8, 127.9, 128.8 (CH; Ph), 137.3 (C^q; C-*ipso*), 175.7 (C^q; C-2), 186.2 (C^q; C-4).

MS (EI, 70 eV): m/z = 358 (1.5) [M^++1], 357 (4) [M^+], 323 (1), 314 (1) [M^+-C_3H_7], 300 (2) [M^+-C_4H_9], 285 (1.5) [M^+-C_4H_9NH], 267 (2) [M^+-C_4H_9NH -H_2O], 163 (47) [$C_{11}H_{17}N^+$] 162 (100) [$C_{11}H_{16}N^+$], 129 (2), 107 (5), 106 (90), 79 (3).

$C_{22}H_{31}NO_3$ (357.49): Calculated C = 73.91, H = 8.74, N = 3.92; found C = 74.06, H = 8.72, N= 4.03.

(±)-syn-4-Hydroxy-3-[-2'-(benzylamino)-1'-methyl-2'-phenylethyl]-1-oxa-spiro[4.5]dec-3-en-2-one 144c.

White Crystalline solid (230 mg, 0.59 mmol, 79%) from 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119a** (210 mg, 0.73 mmol) and benzyl amine (160 mg, 1.5 mmol) in dry DCM (25 ml). The solution was refluxed for 24 h. This compound was purified by filtration over a short plug of nuetral alumina because it is unstable when applied to normal silica columns. Mp 63°C.



IR (KBr); ν(cm^{-1}) = 3422 (br), 3063 (w), 3031 (w), 2932 (s), 2855 (s), 1735 (s), 1684 (s), 1655 (s), 1602 (m), 1558 (s), 1498 (w), 1456 (m), 1354 (w), 1261 (m), 1150 (w), 1113 (w), 1026 (s), 962 (s), 802 (w), 749 (s), 699 (s), 609 (w).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.96 (d, $^3J_{HH}$ = 7.29 Hz, 3H, 1'-CH_3), 1.28 - 1.86 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.83 (dq, $^3J_{HH}$ = 7.29 Hz, 2.19 Hz, 1H, 1'-H), 3.58 (d, $^2J_{HH}$ = 12.65 Hz, 1H, NC*H*H), 3.83 (d, $^2J_{HH}$ = 12.65 Hz, 1H, NCH*H*), 4.07 (d, $^3J_{HH}$ = 2.19 Hz, 1H, 2'-H), 7.24 - 7.45 (m, 10 H, Ph), 15.98 (s, 1H, OH).

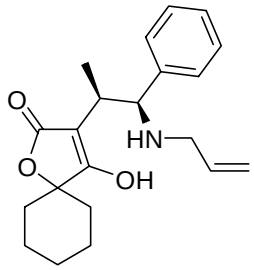
^{13}C-NMR (75.4 MHz, TMS_{int}, $CDCl_3$): δ = 11.1 (CH_3, C-1'), 21.0, 21.1 (CH_2, C-7 and C-9), 23.7 (CH_2, C-8), 31.7, 32.1 (CH_2, C-6 and C-10), 34.8 (CH, 1'-C), 49.1 (CH_2, $NHCH_2$), 63.5 (CH, C-2'), 81.5 (C^q, C-5-*spiro*), 96.8 (C^q, C-3), 125.9, 126.1, 127.1, 127.2, 127.9, 128.4, 133.2 (CH, Ph), 136.3 (Cq, Ph-*ipso*), 174.7 (C^q, C-2), 185.4 (C^q, C-4).

MS (EI, 70 eV): m/z = 392 (2) [M^++1], 391 (4) [M^+], 372 (1) [M^+-H_2O], 266 (8) [M_+-H_3O^+-C_7H_7-CH_3], 265 (16), 257 (4), 197 (17), 196 (67) [$C_{14}H_{14}N^+$], 158 (6), 130 (11), 118 (14), 107 (22), 106 (62) [$C_7H_6O^+$], 91 (61), 84 (16), 75 (16), 65 (18), 55 (77), 51 (82), 47 (58), 39 (54), 32 (72), 28 (100).

Accurate Mass:- Calculated Mass = 391.214744 Found = 391.213303

(±)-syn-4-Hydroxy-3-[-1'-methyl-2'-(allylamino)-2'-phenylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 144d.

White solid (386 mg, 1.13 mmol, 92%) from 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119a** (350 mg, 1.23 mmol) and allylamine (86 mg, 1.51 mmol) dissolved in dry DCM (25 ml) and stirred at room temperature for 18h. Molecular formula $C_{21}H_{27}NO_3$. R_f 0.39 (ethylacetate:hexane, 3:1, v:v), mp 151°C.



IR (KBr); ν(cm^{-1}) = 3422 (m), 3064 (m), 2971 (m), 2929 (s), 2856 (s), 1679 (s), 1579 (s), 1420 (m), 1257 (w), 1226 (w), 1148 (m), 1050 (m), 957 (s), 938 (m), 907 (m), 852 (w), 734 (s), 706 (m), 613 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.01 (d, $^3J_{HH}$ = 7.31 Hz, 3H, 1'-CH_3), 1.48 - 1.84 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.83 (qd, $^3J_{HH}$ = 7.31, 2.10 Hz, 1H, 1'-H), 3.14 (dd, $^2J_{HH}$ = 13.61 Hz, $^3J_{HH}$ = 7.33 Hz, 1H, NCH*H*), 3.47 (dd, $^2J_{HH}$ = 13.61 Hz, $^3J_{HH}$ = 5.86 Hz, 1H, NC*H*H), 4.12 (d, $^3J_{HH}$ = 2.19 Hz, 1H, 2'-H), 5.18 (dd, $^3J_{HH}$ = 17.10 Hz, $^2J_{HH}$ = 1.06 Hz, 1H, CH=CH*H-trans)*, 5.24 (dd, $^3J_{HH}$ = 10.30 Hz, $^2J_{HH}$ = 1.06 Hz, 1H, CH=C*H*H-*cis*), 5.86 - 5.99 (m, 1H, C*H*=CH_2), 7.26 - 7.38 (m, 5H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 12.0 (CH_3, C-1'), 21.9, 22.0 (CH_2, C-7 and C-9), 24.6 (CH_2, C-8) 32.7, 33.1 (CH_2, C-6 and C-10), 36.0 (CH, C-1'), 48.7 (CH_2, NCH_2), 64.2 (CH, C-2'), 82.4 (C^q, C-5-*spiro*), 98.6 (C^q, C-3), 120.2 (CH_2, CH=*C*H_2), 126.8, 126.8, 127.8, 128.7 (CH, Ph), 131.6 (CH, *C*H=CH_2), 137.3 (C^q, Ph-*ipso*), 175.2 (C^q, C-2), 184.7 (C^q, C-4).

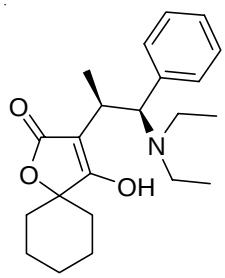
MS (EI, 70 eV): m/z = 341 (2.4) [M^+], 326 (1) [M^+-CH_3], 300 (2) [M^+-C_3H_5], 284 (1) [M^+-

$C_3H_5NH_2$], 215 (17), 200 (6), 147 (11), 146 (100) [$C_{10}H_{12}N$], 106 (74), 91 (7), 41 (13) [$C_3H_5^+$].

Accurate Mass:- Calculated Mass = 341.19909 Found = 341.19908

(±)-syn-4-Hydroxy-3-[1'-methyl-2'-(diethylamino)-2'-phenylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 144e.

White crystalline solid (228 mg, 0.64 mmol, 64%) from 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119a** (284 mg, 1.0 mmol) and *N*,*N*-Diethylamine (73 mg, 1.0 mmol) in dry chloroform (10 ml). The mixture was stirred for 18 hr at room temperature under an argon atmosphere. R_f 0.46 (acetonitrile), mp 116°C.



IR (KBr); ν(cm^{-1}) = 3442 (br) [ν (OH)], 2980 (m), 2938 (s), 2860 (m), 1709 (s), 1605 (s), 1495 (w), 1453 (m), 1403 (s), 1279 (w), 1210 (w), 1030 (m), 766 (s).

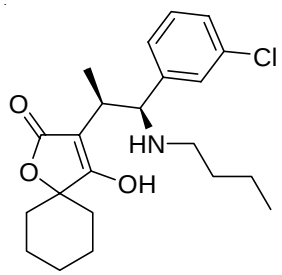
^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.05 (d, $^3J_{HH}$ = 6.86 Hz, 3H, 1'-CH_3), 1.14 - 1.32 (s, broad, 6H, CH_2CH_3), 1.51 - 1.89 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.45 - 2.63 (s, broad, 1H, NCH_2), 2.81 - 3.02 (s, broad, 1H, NCH_2), 3.27 (q, $^3J_{HH}$ = 6.86 Hz, 2.19 Hz, 1'-H), 3.87 (d, $^3J_{HH}$ = 6.86, 1H, 2'-H), 7.25 - 7.42 (m, 5H, Ph).

^{13}C-NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 16.7 (CH_3; C-1'), 22.0 (CH_3; CH_2CH_3), 22.2 (CH_3; CH_2CH_3), 24.8 (CH_2; C-7 and C-9), 31.6 (CH_2; C-8); 33.0 (CH_2; C-6 and C-10), 33.2 (CH; C-1'), 42.8 (CH_2; NCH_2), 71.1 (CH; C-2'), 82.0 (C^q; C-*spiro*), 91.5 (C^q; C-3), 128.8, 129.2, 130.1 (CH; Ph), 134.0 (C^q; Ph-*ipso*), 176.0 (C^q; C-2), 187.9 (C^q; C-4).

MS (EI, 70 eV): m/z = 358 (2) [M^++1], 357 (3) [M^+], 356 (1) [M^+-1], 284 (8) [M^+-C_4H_9NH], 266 (6) [M^+-C_4H_9NH - H_2O], 238 (1), 198 (1), 185 (3), 163 (53), 162 (100), 158 (7), 134 (92), 118 (6), 91 (5), 58 (4).

(±)-syn-3-[-2'-(3''-chlorophenyl)-1'-methyl-2'-(butylamino)ethyl]-4-hydroxy-1-oxaspiro [4.5]dec-3-en-2-one 144f.

Yellow solid (328 mg, 1.03 mmol, 81%) from 1-methyl-2-(3-chlorophenyl)-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119c** (360 mg, 1.13 mmol) and n-butyl amine (165 mg, 2.26 mmol) dissolved in dry chloroform (20 ml) and refluxed for 18h. Molecular formula $C_{22}H_{30}ClNO_3$. R_f 0.34 (diethyl ether:hexane, 1:1, v:v), mp 74 - 78°C.



IR (KBr); ν(cm^{-1}) = 3314 (br) [ν (OH and NH)], 3058 (w), 2934 (s), 2860 (m), 1680 (br), 1561 (s), 1437 (s), 1258 (m), 1154 (m), 1084 (m), 1028 (m), 964 (m), 909 (w), 784 (m), 730 (s), 608 (m).

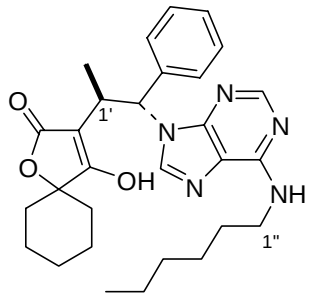
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.89 (m, 3H, CH_2CH_3), 1.03 (d, $^3J_{HH}$ = 7.20 Hz, 3H, 1'-CH_3), 1.21 - 1.83 (m, 14H, 6-H, 7-H, 8-H, 9-H, 10-H, $NCCH_2$, CH_2CH_3), 2.55 - 2.83 (m, 2H, NCH_2), 3.18 - 3.32 (m, 1H, 1'-CH), 3.44 (br, 2H, OH and NH), 4.10 - 4.12 (br, 1H, 2'-CH), 7.04 - 7.58 (m, 4H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 12.4 (CH_3, CH_2CH_3), 13.5 (CH_3, C-1'), 20.5 (CH_2, C-7 and C-9), 22.0 (CH_2, CH_2CH_3), 24.6 (CH_2, C-8), 29.1 (CH_2, $NCCH_2$), 31.4, 31.6 (CH_2, C-6 and C-10), 35.9 (CH, C-1'), 46.7 (CH_2, NCH_2), 65.9 (CH, C-2'), 83.2 (C^q, C-5-*spiro*), 95.4 (C^q, C-3), 125.4, 127.5, 128.2, 129.6 (CH, Ph), 134.8 (C^q, Ar-Cl), 139.0 (C^q, Ar-*ipso*), 176.7 (C^q, C-2), 188.6 (C^q, C-4).

MS (EI, 70 eV): m/z = 393 (4) [M^+, ^{37}Cl], 391 (11) [M^+, ^{35}Cl], 375 (1.5) [M^+-H_2O, ^{37}Cl], 373 (4.5) [M^+-H_2O, ^{35}Cl], 360 (1) [*375* - CH_3], 358 (3) [*373* -CH_3], 336 (1.5) [M^+-C_4H_9, ^{37}Cl], 334 (5) [M^+-C_4H_9, ^{35}Cl], 320 (6) [M^+-$C_4H_9NH_2$, ^{37}Cl], 318 (18) [M^+-$C_4H_9NH_2$, ^{35}Cl], 283 (7), 281 (21), 267 (12), 265 (36), 252 (8), 250 (26), 198 (32), 196 (100), 142 (24), 140 (76), 129 (6), 109 (6), 81 (5), 69 (6), 81 (6), 41 (9).

(±)-anti-4-Hydroxy-3-[-1-methyl-2-(N-hexyl-9H-purine-6-amine)-2-phenylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 165.

The purine base N-hexyl-9H-purine-6-amine **145** (230 mg, 1.05 mmol) was dissolved in dry acetonitrile (20 ml) and placed in a clean dry flask previously flushed with nitrogen. Under an inert atmosphere of nitrogen dry acetonitrile (20 ml) was added followed by 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119a** (300 mg, 1.06 mmol). The mixture was heated with stirring to a temperature of 60°C for 5h. After cooling, the solvent was removed and the residue filtered over a small plug of silica using DCM as eluent. The solvent was removed and the white solid **146** (417 mg, 0.83 mmol, 79%) was dried in vacuo. Molecular formula $C_{29}H_{37}N_5O_3$.



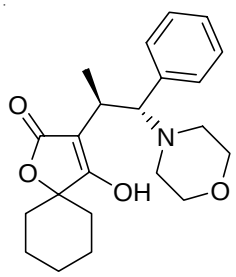
^{1}H-NMR (300 MHz, TMS_{int}, CD_3CN); δ (ppm) = 0.79 - 0.83 (m, 3H, $(CH_2)_5CH_3$), 0.90 - 1.91 (m, 21H, 6-H, 7-H, 8-H, 9-H, 10-H, 1'-CH_3, 2''-H, 3''-H, 4''-H, 5''-H), 3.44 - 3.52 (m, 2H, 1''-H_2), 4.03 - 4.18 (m, 1'-H), 6.02 (d, $^3J_{HH}$ = 11.81 Hz, 1H, 2'-H), 7.14 - 9.05 (m, 8H, Ph, 2xNCHN, NH).

MS (EI, 70 eV):m/z = 503 (1.4) [M^+], 488 (0.6) [M^+-CH_3], 336 (15), 309 (44), 284 (27), 266 (21), 251 (12), 219 (21), 162 (29), 148 (100), 135 (62), 118 (35), 91 (12), 41 (14).

Accurate Mass:- Calculated Mass = 503.28964 Found = 503.29011

(±)-anti-4-Hydroxy-3-[(1*R*,2*R*)-1-methyl-2-morpholin-4-yl-2-phenylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 166.

A solution of 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119a** (351 mg, 1.24 mmol) and 4-cyclohex-1-en-1-ylmorpholine **164** (823 mg, 4.92 mmol) dissolved in dry THF (30 ml) was heated to reflux for 24h. After cooling the solvent was removed by rotary evaporation, column chromatography of the residue gave **166** as a white solid (319 mg, 0.86 mmol, 70%). Molecular formula $C_{22}H_{29}NO_4$. R_f 0.35 (100% ethyl acetate) mp 172 - 174 °C. *NB Although **164** is an enamine the product is the formal result of a ring opening reaction of **119a** by an amine (Section 2.2.5.8). The anti configuration was determined by the coupling constant ^3J(1'-H/2'-H) = 7.44 Hz, which is much higher than that observed for syn compounds.*



IR (KBr); ν(cm^{-1}) = 3422 (s) [ν (OH)], 2933 (s), 2858 (m), 1654 (s), 1559 (s), 1449 (s), 1365 (w), 1259 (m), 1235 (w), 1115 (m), 1070 (m), 1020 (w), 961 (m), 781 (w), 706 (m), 598 (m), 550 (m).

^{1}H-NMR (300 MHz, TMS_{int}, d-DMSO); δ (ppm) = 1.16 (d, $^3J_{HH}$ = 6.92 Hz, 3H, 1'-CH_3), 1.28 - 1.78 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.82 - 2.97 (m, 4H, NCH_2), 3.30 - 3.82 (m, 5H, OCH_2, 1'-H), 4.18 (d, $^3J_{HH}$ = 7.44 Hz, 1H, 2'-H), 7.31 - 7.51 (m, 5H, Ph), 8.05 (s, 1H, OH).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, δ-DMSO): δ (ppm) = 16.9 (CH_3, C-1'], 23.3, 23.5 (CH_2, C-7 and C-9], 26.0 (CH_2, C-8), 28.9 (CH, C-1'), 33.9, 34.1 (CH_2, C-6 and C-10), 51.5 (CH_2, 2xNCH_2), 66.4 (CH_2, 2xOCH_2), 75.7 (CH, C-2'), 84.1 (C^q, C-5-*spiro*), 94.4 (C^q, C-3), 129.7, 130.0, 131.5 (CH, Ph), 134.9 (C^q, Ph-*ipso*), 178.7 (C^q, C-2), 190.3 (C^q, C-4).

MS (EI, 70 eV): m/z = 372 (1) [M^++1], 371 (7) [M^+], 343 (3) [M^+-CO], 284 (12) [M^+-C_4H_9NO], 266 (12) [*284* - H_2O], 251 (5) [*266* - CH_3], 238 (4) [*251* - CH], 177 (38), 176 (100) [$C_{11}H_{12}O_2^+$], 148 (2), 131 (16) [*176* - CO_2H], 119 (10), 105 (6), 91 (8), 57 (3), 43 (2), 32 (5).

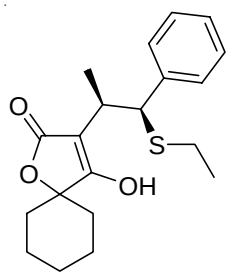
Accurate Mass:- Calculated Mass = 371.20966 Found = 371.2679.

3.4.3 Ring opening of spirocyclopropyldihydrofuran-4,12-diones 119 with thiols

(±)-syn-3-[2'-(ethylthio)-1'-methyl-2'-phenylethyl]-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one 147.

1-Methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119** (300 mg, 1.05 mmol) was dissolved in dry chloroform (5 ml) and transfered to a sealable glass tube. The glass tube was evacuated and filled with nitrogen gas. Under a nitrogen atmosphere ethanethiol (1 ml) was added and the tube was sealed and heated to 70°C for 18h. Solution was evaporated on a

transfered to the glass tube which was then sealed. The tube was placed in an oil bath and heated to a temperature of 70°C for 18h. After cooling the solution was very quickly transfered to a round bottomed flask containing an gas inlet/outlet adaptor. The glass tube was also very quickly rinsed with chloroform (~ 20ml) and the combined washings transfered to the round bottomed flask. A continuous stream of nitrogen was bubbled through the solution for several hours. The outlet stream of gas was passed through a solution of commerical bleach to remove the excess ethanethiol. After all the ethanethiol was removed the reamaning solvent was distilled on a rotary evaporator. The residue was then purified by column chromatography (silica gel; ethyl acetate:hexane, 1:1, v:v) to give a white crystalline solid (190 mg, 0.55 mmol, 55%). Molecular formula $C_{20}H_{26}SO_3$. R_f 0.32 (ethyl acetate / hexane, 1:1,v:v), mp 189 °C. *NB Ethanethiol has an extremely unpleasent odour which is detectable by humans in very small concentrations. Extreme care should be used when handling this substance.*



IR (KBr); ν(cm^{-1}) = 3419 (w) [ν (OH)], 2937 (s), 2855 (w), 1701 (s) and 1661 (s) [ν (C=O)], 1635 (s), 1455 (m), 1304 (m), 1264 (m), 1222 (m), 1156 (m), 1091 (w), 988 (w), 951 (w), 741 (w), 697 (w).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.19 (t, $^3J_{HH}$ = 7.38 Hz, 3H, SCH_2CH_3), 1.29 (d, $^3J_{HH}$ = 7.08 Hz, 3H, 1'-CH_3), 1.30 - 1.80 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.42 (q, $^3J_{HH}$ = 7.38 Hz, 2H, SCH_2CH_3), 3.10 (dq, $^3J_{HH}$ = 7.08 Hz, 4.92 Hz, 1H, 1'-H), 4.19 (d, $^3J_{HH}$ = 4.92 Hz, 1H, 2'-H), 7.20 - 7.43 (m, 5 H, Ph), 10.01 (s, 1H, OH).

^{13}C-NMR (75.4 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 14.7 (CH_3, C-1'), 15.5 (CH_3, SCH_2CH_3), 22.2, 22.3 (CH_2, C-7 and C-9), 24.8 (CH_2, C-8), 26.2 (CH_2, SCH_2), 33.0, 33.1 (CH_2, C-6 and C-10), 36.4 (CH, C-1), 54.6 (CH, 2'-C), 82.9 (C^q, C-5-*spiro*), 103.3 (C^q, C-3), 128.0, 128.4, 128.8 (CH, Ph), 142.0 (C^q, Ph-*ipso*), 174.6 (C^q, C-2), 178.6 (C^q, C-4).

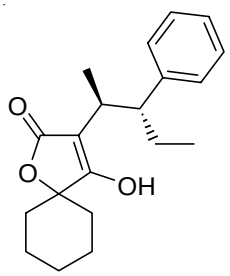
MS (EI, 70 eV): m/z = 346 (16) [M^+], 318 (11) [M^+-CO], 290 (16), 284 (5) [M^+-CH_3CH_2SH], 262 (6), 231 (8), 178 (39) [$C_{11}H_{14}S^+$], 177 (85), 152 (21) [$C_9H_{12}S^+$], 151 (100) [$C_9H_{11}S^+$], 130 (11), 118 (16), 117 (18), 103 (10), 91 (21), 79 (11), 69 (11), 55 (20).

Accurate Mass:- Calculated Mass = 346.160267 Found = 346.159836.

3.4.4 Ring opening of spirocyclopropyldihydrofuran-4,12-diones 119 with Grignard reagents

*General experimental procedure for the reaction of Grignard reagents with spirocyclopropyl dihydrofuran-4,12-diones **119***: Magnesium turnings (73 mg, 3.0 mmol) were weighed into a clean flask under a nitrogen atmposhere. Dry diethyl ether (20 ml) was added to the flask followed by a catalytic amount of iodine to etch the surface of the metal. After all the iodine had vanished the alkyl bromide (3 mmol) was added as a solution in ether (5 ml). The resulting solution was heated until all the magnesium had vanished (~1h). The solution was then cooled and 1-Methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119** (568 mg, 2.0 mmol) was added as a solution in diethyl ether (5 ml). The solution was allowed to stir at room temperature for 30 mins followed by heating to reflux for a further 2 hours. Ammonium chloride solution was then added to the cooled solution. Once a clear solution had formed the solution was washed with diethyl ether and DCM. Removal of the solvent on a rotary evaporator followed by column chromatography (silica gel; solvent as indicated) gave a pure product.

(±)-anti-4-Hydroxy-3-[-1'-methyl-2'-phenylbutyl]-1-oxaspiro[4.5]dec-3-en-2-one 149a. White solid (150 mg, 0.48 mmol, 42%) from ethylmagnesium bromide (1.64 g, 1.24 mmol) in dry diethyl ether (10 ml) and 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119a** (320 mg, 1.13 mmol) in dry THF (10 ml) heated under reflux with the exclusion of air and moisture for 24 h. Molecular formula $C_{20}H_{26}O_3$. R_f 0.62 (ethyl acetate : hexane, 1:1, v:v), mp 125 °C. NB The anti configuration was determined from a coupling constant of ^3J(1'-H/2'-H) = 10.60 Hz.



IR (KBr); ν(cm^{-1}) = 3486 (br) [ν (OH)], 3056 (w), 3015 (w), 2936 (s), 2872 (w), 1712 (s), 1646 (s), 1496 (w), 1450 (m), 1394 (m), 1309 (s), 1311 (m), 1254 (m), 1156 (m), 978 (m), 965 (m), 739 (m), 701 (m).

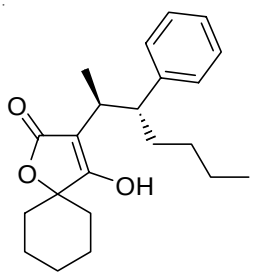
^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.85 (d, $^3J_{HH}$ = 7.50 Hz, 3H, 1'-CH_3), 1.17 - 1.98 (m, 15H, 6-H, 7-H, 8-H, 9-H, 10-H, C*H*$_2$CH$_3$, CH$_2$C*H*$_3$), 2.72 - 2.90 (m, 1H, 2'-H), 3.45 (dq, $^3J_{HH}$ = 10.60, 7.50 Hz, 1H, 1'-H), 7.13 - 7.28 (m, 5H, Ph), 8.44 (s, 1H, OH).

^{13}C-JMOD-NMR (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 12.3 (CH_3, C-4'), 16.9 (CH_3, C-1'), 21.9 (CH_2, C-7 and C-9), 24.5 (CH_2, C-8), 26.7 (CH_2, C-3'), 32.2, 32.3 (CH_2, C-6 and C-10), 33.5 (CH, C-1'), 51.0 (CH, C-2'), 82.58 (C^q, C-5-*spiro*), 104.0 (C^q, C-3), 125.9, 127.6, 129.1 (CH, Ph), 144.8 (C^q, C-*ipso*), 175.0 (C^q, C-2), 178.4 (C^q, C-4).

MS (EI, 70 eV): m/z = 314 (2) [M^+], 296 (3) [M^+-H_2O], 286 (10) [M^+- C_2H_4], 268 (2) [M^+-H_2O - C_2H_4], 257 (3), 197 (5), 196 (44) [M^+- C_6H_6 - C_3H_5], 178 (8), 169 (70), 147 (10), 146 (100), 120 (7), 119 (62), 109 (10), 91 (90), 81 (7), 69 (19), 55 (5), 41 (12).

$C_{20}H_{26}O_3$ (314.42): Calculated C = 76.40%, H = 8.33%; found C = 76.47%, H = 8.54%.

(±)-anti-4-Hydroxy-3-(1'-methyl-2'-phenylhexyl)-1-oxaspiro [4.5] dec-3-en-2-one 149b. White crystalline solid (420 mg, 1.23 mmol, 61%) from 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119a** (568 mg, 2.00 mmol), n-butylamine (411 mg, 0.32 ml, 3 mmol), magnesium turnings (73 mg, 3 mmol), in diethyl ether (~20 ml). Molecular formula $C_{22}H_{30}O_3$. R_f 0.75 (ethyl acetate:hexane, 1:1, v:v), mp 148°C. *NB The anti configuration was based on the result obtained for **149a**.*



IR (KBr); ν(cm^{-1}) = 3414 (m) and 3184 (br) [ν (OH)], 2931 (s), 2856 (m), 1712 (s), 1629 (s), 1452 (w), 1379 (w), 1302 (m), 1267 (m), 1215 (m), 1154 (m), 1112 (w), 982 (w), 750 (w), 700 (m), 617 (w).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.76 (t, $^3J_{HH}$ = 7.33 Hz, 3H, 6'-CH_3), 1.23 (d, $^3J_{HH}$ = 6.45 Hz, 3H, 1'-CH_3), 0.84 - 1.72 (m, 16H, 6-H, 7-H, 8-H, 9-H, 10-H, 3'-H, 4'-H, 5'-H), 2.76 - 2.78 (m, 2H, 1'-H, 2'-H), 6.99 - 7.30 (m, 5H, Ph), 11.00 (s, 1H, OH).

^{13}C-NMR-JMOD (68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 13.9 (CH_3, C-6'), 16.6 (CH_3, C-1'), 21.4, 21.5 (CH_2, C-7 and C-9), 22.1 (CH_2, C-5'), 23.9 (CH_2, C-4'), 25.7 (CH_2, C-8), 31.8, 31.9 (CH_2, C-6 and C-10), 32.6 (CH, C-1'), 32.9 (CH_2, C-3'), 48.3 (CH, 2'-C-2'), 80.2 (C^q, C-5-*spiro*), 102.3 (C^q, C-3), 125.5, 127.8, 128.0 (CH, Ph), 144.8 (C^q, Ph-*ipso*), 171.7 (C^q, C-2), 176.8 (C^q, C-4).

MS (EI, 70 eV): m/z = 342 (1) [M^+], 289 (1) [M^+-C_4H_9], 267 (1), [M+-C_4H_9 - H_2O], 196 (64), 174 (65), 169 (45), 147 (18), 132 (79), 91 (100), 69 (17).

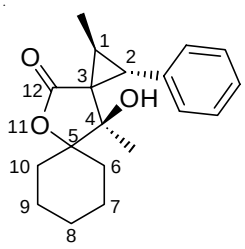
Accurate Mass:- Calculated Mass = 342.2195 Found = 342.2195

3.4.5. Other reactions of carbon nucleophiles with spirocyclopropyldihydrofuran-4,12-diones 119

*General Procedure for the reaction of alkyl lithium reagents with spirocyclopropyldihydrofuran-2,13-diones **119**:* A pure sample of 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione-β diastereoisomer **119a-β** (300 mg, 1.06 mmole) was dissolved in dry THF (20 ml) under an inert atmosphere of nitrogen. To this solution was dropped slowly over 15 min the respective alkyllithium (1.20 mmole). The solution was stirred for a further 16h after which time the THF solution was filtered over a small plug of silica and washed with THF. The solvent was evaporated and the residue purified by column chromatography (silica gel: solvent as indicated).

(±)-4-Hydroxy-1,4-dimethyl-2-phenyl-11-oxadispiro[2.1.5.2]dodecan-12-one 150a. White solid (263 mg, 0.88 mmol, 83%) from 1-Methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione-β diastereoisomer **119a-β** (300 mg, 1.06 mmol) and methyl

lithium 1.6M in diethyl ether (0.75 ml, 1.20 mmol) dissolved in dry THF (20 m). Solution stirred for 16h at r.t. Molecular formula $C_{19}H_{24}O_3$. R_f 0.42 (diethyl ether: hexane, 1:1, v:v), mp 189°C.



IR (KBr); ν(cm^{-1}) = 3423 (m), 2938 (m), 2849 (w), 1724 (s), 1429 (w), 1386 (m), 1371 (m), 1325 (m), 1291 (m), 1243 (m), 1194 (m), 1138 (m), 1118 (m), 1067 (w), 1029 (w), 950 (s), 887 (m), 854 (w), 830 (w), 757 (m), 718 (m), 690 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.79 (s, 3H, 4-CH_3), 1.34 (d, $^3J_{HH}$ = 6.19 Hz, 3H, 1-CH_3), 1.38 - 1.78 (m, 11H, 6-H, 7-H, 8-H, 9-H, 10-H, OH), 2.09 - 2.16 (m, 1H, 1-CH), 2.89 (d, $^3J_{HH}$ = 7.76 Hz, 1H, 2-CH), 7.23 - 7.34 (m, 5H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.8 (CH_3, C-1), 20.5 (CH_3, C-4), 21.2, 21.5 (CH_2, C-7 and C-9), 25.0 (CH, C-1), 25.3 (CH_2, C-8), 27.2 (CH_2, C-6), 33.3 (CH_2, C-10), 34.8 (CH, C-2), 42.0 (C^q, C-3), 80.0 (C^q, C-5-*spiro*), 89.2 (C^q, C-4), 127.1, 127.6, 128.1, 128.6 (CH, Ph), 134.6 (C^q, Ph-*ipso*), 175.2 (C^q, C-12).

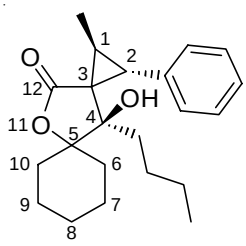
MS (EI, 70 eV): m/z = 301 (1) [M^++1], 300 (6) [M^+], 283 (13), 282 (44) [M^+-H_2O], 267 (3) [*282* - CH_3], 257 (16) [M_+-CH_3-C_2H_4], 239 (4) [257 - H_2O], 237 (22) [*282* - CO_2H], 223 (9) [*237* - CH_2], 195 (11), 194 (27) [*237* - C_3H_6], 176 (11), 159 (11), 147 (7), 129 (16), 118 (53) [$PhCHCHCH_3^+$], 117 (51), 105 (31) [*118* - CH], 91 (33) [*105* - CH_2], 81 (13) [$C_6H_9^+$], 77 (8) [Ph^+], 69 (11), 55 (12), 43 (100) [$C_3H_7^+$].

Accurate Mass:- Calculated Mass = 300.17255 Found = 300.17308

GC retention time = 54.02 min.

(±)-4-Butyl-4-hydroxy-1-methyl-2-phenyl-11-oxadispiro[2.1.5.2]dodecan-12-one 150b.

White solid (197 mg, 0.58 mmol, 65%) from 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione-β diastereoisomer **119β** (250 mg, 0.88 mmol) and butyl lithium 1.6M in diethyl ether (0.66 ml, 1.06 mmol) dissolved in dry THF (25 ml). Solution stirred for 16h at r.t. Molecular formula $C_{22}H_{30}O_3$.



IR (KBr); ν(cm^{-1}) = 3428 (m), 2932 (m), 2867 (m), 1732 (vs), 1449 (m), 1368 (m), 1336 (m), 1297 (m), 1276 (m), 1241 (m), 1187 (w), 1122 (m), 1068 (m), 1020 (m), 961 (s), 934 (m), 894 (m), 730 (m), 696 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.66 (t, $^{3}J_{HH}$ = 6.97 Hz, 3H, 4'-H), 0.89 - 1.79 (m, 19H, 6-H, 7-H, 8-H, 9-H, 10-H, 1'-H, 2'-H, 3'-H, including a doublet at 1.33 ppm, $^{3}J_{HH}$ = 6.18 Hz, 3H, 1-CH_3), 2.08 - 2.21 (m, 2H, 1-H, OH), 2.89 (d, $^{3}J_{HH}$ = 7.92 Hz, 1H, 2-H), 7.16 - 7.33 (m, 5H, Ph).

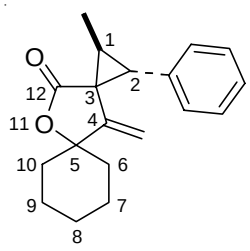
^{13}C-JMOD + HSQC-TOCSY NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.8 (CH_3, C-1), 13.4 (CH_3, C-4'), 21.6, 22.1 (CH_2, C-7 and C-9), 23.2 (CH_2, C-3'), 24.1 (CH, C-1), 24.7 (CH_2, C-2'), 25.3 (CH_2, C-8), 29.7 (CH_2, C-6), 32.8 (CH_2, C-10), 34.3 (CH_2, C-1'), 35.01 (CH, C-2), 81.0 (C^q, C-5-*spiro*), 89.0 (C^q, C-4), 127.1, 128.7, 129.5 (CH, Ph), 134.5 (C^q, Ph-*ipso*), 175.1 (C^q, C-12).

MS (EI, 70 eV): m/z = 343 (5) [M^++1], 342 (6) [M^+], 325 (12) [M^+-OH], 324 (34) [M^+-H_2O], 285 (11) [M^+-C_4H_9], 267 (7) [*285* - H_2O], 257 (16) [*285* - C_2H_5], 236 (9), 223 (12), 185 (5), 181 (6), 153 (15), 129 (11), 118 (49), 117 (31), 91 (33), 81 (22) [$C_6H_9^+$], 57 (51), 43 (38), 41 (100).

Accurate Mass:- Calculated Mass = 342.21950 Found = 342.21944

(±)-1-methyl-4-methylene-2-phenyl-11-oxadispiro[2.1.5.2]dodecan-12-one 177.

To a slurry of methanetriphenylphosphonium bromide (750 mg, 2.11 mmol) in dry THF (30 ml) was slowly added under an inert atmosphere a solution of butyl lithium (1.3 ml). The dark red solution was allowed to stir at room temperature for 30 min. To this solution was added a solution of 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione-β diastereomer **119a-β** (500 mg, 1.76 mmol) in THF (10 ml). The resulting solution was allowed to stir for 5 hours at room temperature. After this time the solution was filtered over a small plug of silica (~1 cm) to remove the lithium salts. The silica was then washed with diethyl ether (~50 ml). The combined organic solution was removed by rotary evaporation and the residue was purified by column chromatography, to give a pure white solid (407 mg, 1.44 mmol, 82%). Molecular formula $C_{19}H_{22}O_2$. R_f 0.47 (diethyl ether: hexane, 1:1, v:v).



IR (KBr); ν(cm^{-1}) = 3058 (w), 3010 (w), 2933 (s), 2856 (m), 1757 (s), 1662 (m), 1602 (w), 1497 (w), 1450 (m), 1378 (w), 1320 (m), 1269 (m), 1236 (m), 1215 (m), 1176 (m), 1129 (s), 1033 (m), 968 (s), 950 (w), 943 (m), 868 (s), 763 (s), 702 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.31 - 1.96 (14H, m, including a doublet at 1.56 ppm $^{3}J_{HH}$ = 6.21 Hz, 1-CH_3, 6-H, 7-H, 8-H, 9-H, 10-H, 1-H), 3.10 (d, $^{3}J_{HH}$ = 8.45 Hz, 1H, 2-H), 3.67 (d, $^{2}J_{HH}$ = 1.09 Hz, 1H, C^q=C*H*H), 4.37 (d, $^{2}J_{HH}$ = 1.09 Hz, 1H, C^q=CH*H*), 7.09 - 7.30 (m, 5H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 11.2 (CH_3, C-1), 21.8, 22.0 (CH_2, C-7 and C-9), 24.9 (CH_2, C-8), 31.9 (CH, 1-C), 34.6 (C^q, C-3-*spiro*), 37.2, 37.6 (CH_2, C-6 and C-10), 45.5 (CH, C-2), 86.6 (C^q, C-5-*spiro*), 101.5 (CH_2, =CH_2), 127.3, 128.3, 129.8 (CH, Ph), 134.0 (C^q, Ph-*ipso*), 150.5 (C^q, C-4), 175.8 (C^q, C-12).

MS (EI, 70 eV):m/z = 283 (17) [M^++1], 282 (100) [M^+], 267 (11) [M^+-CH_3], 237 (34) [M^+-COOH], 223 (11) [*237* - CH_2], 195 (25), 191 (14), 181 (14), 178 (14), 165 (10), 155 (15), 141 (19), 117 (17), 115 (23), 105 (46) [$C_8H_9^+$], 91 (59) [$C_7H_7^+$], 77 (14) [Ph], 55 (19), 41 (64).

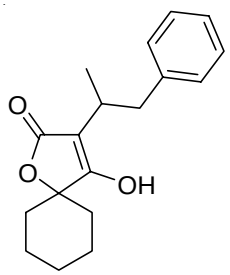
Accurate Mass:- Calculated Mass = 282.16198 Found = 282.16203

3.3.6 Ring opening of spirocyclopropyldihydrofuran-4,12-diones 119 with hydrogen and hydrogenation of compound 122a

Typical experimental procedure: Dry ethyl acetate (30 ml) was transfered under an inert atmosphere to a round bottomed flask which contained 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119a** (473 mg, 1.62 mmol). A catalytic amount of palladium absorbed onto charcoal was added to the solution. An empty balloon was connected to the open neck of the flask and secured, the balloon was filled with hydrogen gas via the side arm. The solution was then allowed to stir at room temperature for 16 h. After this time the solution was filtered over a plug of celite and washed well with ethyl acetate. Evaporation of the solvent gave a relatively pure product which could be further purified if required by column chromatography or recyrstallisation from DCM.

(±)-4-Hydroxy-3-(1'-methyl-2'-phenylethyl)-1-oxaspiro[4.5]dec-3-en-2-one 184a.

White crystalline solid (473 mg, 1.62 mmol, 94%) from 1-ethyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119** (500 mg, 1.76 mmol), palladium absorbed on charcoal (catalytic amount) dissolved in dry ethyl acetate (30 ml). The pure compound was obtained by column chromatography and recrystallisation of the residue from DCM. Molecular formula $C_{18}H_{22}O_3$.R_f 0.33 (diethyl ether:hexane, 1:1, v:v) mp 149°C.



IR (KBr); v(cm-[1]) = 3399 (br), 3023 (m), 2931 (s), 2860 (s), 1700 (s), 1670 (s), 1616 (s), 1445 (s), 1373 (m), 1328 (s), 1276 (s), 1237 (s), 1193 (w), 1157 (s), 1120 (m), 1089 (w), 1056 (w), 994 (s), 960 (s), 742 (s) and 697 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.26 (d, $^3J_{HH}$ = 6.61 Hz, 3H, 1'-CH_3), 1.20 - 1.92 (m, 11H, 6-H, 7-H, 8-H, 9-H, 10-H, 1'-H), 2.87 - 3.05 (m, 2H, 2'-H_2), 7.11 - 7.36 (m, 5H, Ph), 10.16 (s, 1H, OH).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 18.2 (CH_3, C-1'), 21.8 (CH_2, C-7 and C-9), 24.4 (CH_2, C-8), 29.7 (CH, C-1'), 32.4 (CH_2, C-6 and C-10), 40.3 (CH_2, C-2'), 83.2 (C^q, C-5-*spiro*), 102.7 (C^q, C-3), 125.8 (CH, Ph-*para*), 128.2, 128.6, 129.1, 129.1 (CH, Ph-*ortho*, Ph-*meta*), 140.8 (C^q, Ph-*ipso*), 175.9 (C^q, C-2), 180.1 (C^q, C-4).

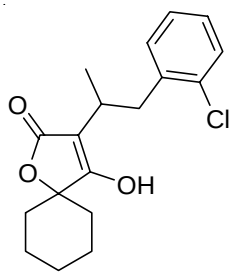
MS (EI, 70 eV): m/z = 287 (0.3) [M^++1], 286 (1) [M^+], 196 (4), 195 (15) [M^+-$C_6H_5CH_2$], 177 (12) [*195* - H_2O], 170 (6), 169 (69) [*195* - C_2H_4], 119 (11), 118 (100) [$C_6H_5C_3H_5^+$], 117 (34), 91 (17) [$C_6H_5CH_2^+$], 69 (26), 41 (21).

Accurate Mass:- Calculated Mass = 286.15689 Found = 286.15687

GC retention time = 48 min.

(±)-4-Hydroxy-3-[2'-(2''-chlorophenyl)-1'-methylethyl]-1-oxaspiro[4.5]dec-3-en-2-one 184b.

White crystalline solid (439mg, 1.31 mmol, 87%) from from 1-methyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecane-4,12-dione **119b** (500 mg, 1.76 mmol) and palladium absorbed on charcoal (catalytic amount) dissolved in dry ethyl acetate (30 ml). The solution was stirred for 16h under a hydrogen atmosphere. The pure compound obtained by column chromatography and recrystallisation of the residue from DCM. Molecular formula $C_{18}H_{21}ClO_3$. R_f 0.73 (ethyl acetate: hexane, 1:1. v:v), mp 180 ^oC.



IR (KBr); ν(cm^{-1}) = 3072 (br), 2932 (m), 2861 (m), 1699 (s), 1638 (s), 1443 (w), 1400 (s), 1374 (m), 1329 (s), 1273 (m), 1245 (w), 1189 (m), 1098 (m), 1083 (m), 1036 (m), 989 (m), 956 (m), 849 (w), 810 (m).

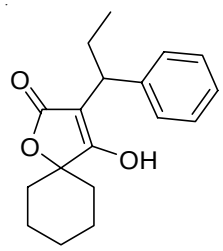
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.26 (d, $^3J_{HH}$ = 6.72 Hz, 3H, 1'-CH_3), 1.20 - 1.74 (m, 11H, 6-H, 7-H, 8-H, 9-H, 10-H, 1'-H), 2.90 - 3.04 (m, 2H, 2'-H), 7.06 - 7.27 (m, 4H, Ph), 8.73 (s, 1H, OH).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 18.4 (CH_3, C-1'), 21.3, 21.6 (CH_2, C-7 and C-9), 25.0 (CH_2, C-8), 28.0 (CH, C-1'), 32.6, 32.7 (CH_2, C-6 and C-10), 37.9 (CH_2, C-2'), 82.1 (C^q, C-5-*spiro*), 102.3 (C^q, C-3), 126.5, 127.5, 129.2, 131.6 (CH, Ph), 133.8 (C^q, Ph-Cl), 138.4 (C^q, Ph-*ipso*), 173.7 (C^q, C-2), 178.3 (C^q, C-4).

MS (EI, 70 eV): m/z = 322 (0.1) [M^+, ^{37}Cl], 321 (0.1) [M^++1, ^{35}Cl], 320 (0.2) [M^+, ^{35}Cl], 285 (0.4) [M^+-Cl], 195 (4) [M^+-$ClC_6H_4CH_2$], 177 (5) [*195* - H_2O], 170 (3), 169 (21) [*195* - C_2H_4], 152 (22) [*169* - OH], 127 (4) [$ClC_6H_4CH_2^+$, ^{37}Cl], 125 (13) [$ClC_6H_4CH_2^+$, ^{35}Cl], 118 (12), 91 (11), 69 (100), 55 (13), 41 (77), 39 (23).

(±)-4-Hydroxy-3-(1-phenylpropyl)-1-oxaspiro[4.5]dec-3-en-2-one 183.

White solid (496 mg, 1.73 mmole, 99%), from 4-hydroxy-3-(1-phenylprop-2-enyl)-1-oxaspiro[4.5]dec-3-en-2-one **122a** (500 mg, 1.76 mmol) and palladium absorbed on carcoal (~5 mole%) and dissolved in dry ethyl acetate (30 ml). The solution was stirred at room temperature for 24h under a slight overpressure of hydrogen gas. Filtration of solution over celite and rotary evaporation of solvent gave a pure product. Molecular formula $C_{18}H_{22}O_3$. R_f, mp 223^{o}C.



IR (KBr); ν(cm^{-1}) = 3424 (br), 3027 (w), 2933 (s), 2862 (m), 1700 (m), 1616 (s), 1494 (w), 1158 (m), 1406 (m), 1300 (m), 1249 (m), 1230 (m), 1154 (m), 1113 (m), 1057 (m), 1019 (m), 977 (s), 909 (w), 757 (m), 697 (s), 590 (w), 527 (m).

^{1}H-NMR (300 MHz, TMS$_{int}$, CD_3OD); δ (ppm) = 0.89 (t, $^{3}J_{HH}$ = 7.35 Hz, 3H, 3'-H), 1.26 - 2.21 (m, 12H, 6-H, 7-H, 8-H, 9-H, 10-H, 2'-H), 3.52 - 3.58 (m, 1H, 1'-H), 7.11 - 7.36 (m, 5H, Ph).

^{13}C- NMR (75.5 MHz, TMS$_{int}$, CD_3OD): δ (ppm) = 13.3 (CH_3, C-3'), 23.2, 23.2 (CH_2, C-7 and C-9), 25.7 (CH_2, C-8), 26.9 (CH_2, C-2'), 33.9, 34.2 (CH_2, C-6 and C-10), 42.8 (CH, C-1'), 83.8 (C^q, C-5-*spiro*), 102.1 (C^q, C-3), 127.2, 128.9, 129.3 (CH, Ph), 145.8 (C^q, Ph-*ipso*), 176.5 (C^q, C-2), 182.7 (C^q, C-4).

MS (EI, 70 eV): m/z = 287 (0.8) [M^++1], 286 (1.8) [M^+], 268 (0.6) [M^+-H_2O], 257 (3.6) [M^+-C_2H_7], 240 (1) [*257* - OH], 211 (1.4), 170 (6), 169 (17), 155 (8) [$C_8H_{11}O_3^+$], 154 (13), 132 (27), 131 (81) [$PhC_4H_6^+$], 118 (47) [*131* - CH], 110 (12) [*154* - CO_2], 103 (24) [*118* - CH_3], 91 (56), 77 (30), 67 (21), 55 (24), 41 (100).

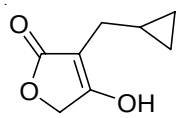
Accurate Mass:- Calculated Mass = 286.15689 Found = 286.15682.

3.3.7 Cyclopropanation of 3-allyl-tetronic acids

General experimental procedure for cyclopropanation of tetronic acids:[173] To a cooled (-10^{o}C) solution of Et_2Zn (2ml, 2.0 mmol) in DCM (5 ml) was added very slowly trifluroacetic acid (0.15 ml, 2.0 mmol) under an inert atmosphere. The solution was stirred for 20 mins after which time diiodomethane (0.16 ml, 2.0 mmol) was added and the solution was stirred for a further 20 min. To this solution was added the respective tetronic acid (1 mmol) dissolved in DCM (2 ml). After addition of all components the solution was heated to room temperature and stirred at room temperature for a further 20 mins after which time the solution was heated to 40^{o}C for 16h. The solution was then cooled, DCM (20 ml) was added to the reaction mixture and the organic layer was washed with NH_4Cl (10 ml) solution, brine (10 ml) and finally water (10 ml). The organic layer was dried with magnesium sulphate and the solvent removed by rotary evaporation. The residue was purified by column chromatography (silica gel; solvent as indicated).

3-(Cyclopropylmethyl)-4-hydroxyfuran-2(5*H*)-one 189.

White solid (288 mg, 1.87 mmol, 66%) from 3-allyl-4-hydroxyfuran-2(5*H*)-one **188** (400 mg, 2.86 mmol), diethyl zinc (6 ml), trifluoroacetic acid (0.46 ml) and diiodomethane (0.48 ml) dissolved in DCM(6 ml). The reaction was set at -10^{o}C and heated to 40^{o}C for 24h. Purified by column chromatography and finally by recrystallisation from DCM. Molecular formula $C_8H_{10}O_3$. R_f 0.52 (ethyl acetate: hexane, 3:1, v:v), mp. 145^{o}C.



IR (KBr); ν(cm^{-1}) = 3087 (m), 3001 (s), 2938 (w), 2701 (s), 1718 (s), 1642 (s), 1453 (s), 1394 (s), 1277 (m), 1220 (m), 1135 (m),1101 (s), 1041 (s), 1020 (s), 826 (s), 794 (m), 775 (m), 754 (m), 691 (m), 634 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.16 - 0.23 and 0.47 - 0.51 (m, 4H, 3'-H and 4'-H), 0.92 - 0.99 (m, 1H, 2'-H), 2.14 (d, $^{3}J_{HH}$ = 6.91 Hz, 2H, 1'-H), 4.65 (s, 2H, 5-H), 9.32 (s, broad, 1H, OH).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 5.00 (CH_2, C-3' and C-4'), 9.4 (CH, C-2'), 26.6 (CH_2, C-1'), 67.6 (C^q, C-5), 101.5 (C^q, C-3), 173.5 (C^q, C-2), 177.6 (C^q, C-4).

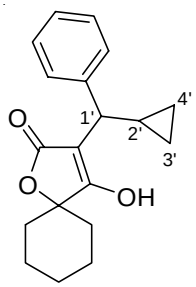
MS (EI, 70 eV): m/z = 154 (1.2) [M^+], 139 (4) [M^+-CH_3], 136 (10) [M^+-H_2O], 121 (9) [*136* - CH_3], 113 (22) [M^+-C_3H_5], 101 (8), 100 (31), 85 (6), 81 (12), 68 (27), 55 (44), 54 (100), 41 (33) [$C_3H_5^+$], 39 (61) [$C_3H_3^+$].

Accurate Mass:- Calculated Mass = 154.06300 Found = 154.06293

GC retention time = 19 min.

4-Hydroxy-3-[α-cyclopropylbenzyl]-1-oxaspiro[4.5]dec-3-en-2-one 190a.

White solid (407 mg, 1.37 mmol, 84%) from 4-hydroxy-3-(1-phenylprop-2-enyl)-1-oxaspiro[4.5]dec-3-en-2-one **122a** (460 mg, 1.62 mmol), diethyl zinc (5 ml, 5 mmol), trifluroacetic acid (0.39 ml, 5 mmol) and diiodomethane (0.40 ml, 5 mmole) dissolved in DCM (12.5 ml). The reaction was set at -10°C and stirred for 1h at this temperature before slow heating to room temperature followed by gentle heating to 40°C for 16h. Molecular formula $C_{19}H_{22}O_3$. R_f 0.14 (diethyl ether: hexane, 1:1, v:v), mp 185°C.



IR (KBr); ν(cm^{-1}) = 3446 (s), 2938 (s), 2861 (m), 1751 (s), 1696 (m), 1653 (s), 1636 (s), 1559 (m), 1448 (m), 1384 (m), 1262 (m), 1100 (s), 1022 (s), 799 (m), 698 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.14 - 0.30 (m, 2H, 4'-H), 0.46 - 0.53 and 0.57 - 0.67 (m, 2H, 3'-H), 1.18 - 1.95 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.04 - 2.08 (m, 1H, 2'-H), 2.96 (d, $^{3}J_{HH}$ = 10.16 Hz, 1H, 1'-H), 7.17 - 7.46 (m, 5H, Ph).

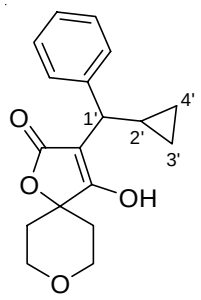
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 5.3 (CH_2, C-4'), 7.0 (CH_2, C-3'), 15.3 (CH, C-2'), 23.1, 23.2 (CH_2, C-7 and C-9), 25.7 (CH_2, C-8), 34.2, 34.3 (CH_2, C-6 and C-10), 45.6 (CH, C-1'), 82.4 (C^q, C-5-*spiro*), 104.3 (C^q, C-3), 127.4, 129.1, 129.4 (CH, Ph), 144.9 (C^q, Ph-*ipso*), 173.1 (C^q, C-2), 178.5 (C^q, C-4).

MS (EI, 70 eV): m/z = 299 (1) [M^++1], 298 (3) [M^+], 280 (2) [M^+-H_2O], 131 (100) [$PhC_4H_6^+$],115 (14), 110 (2) [$C_6H_{10}CO^+$], 103 (8), 91 (27), 81 (8) [$C_6H_9^+$], 77 (9) [$C_6H_5^+$], 53 (6), 41 (11).

Accurate Mass:- Calculated Mass = 298.15689 Found = 298.15682.

4-Hydroxy-3-[a-cyclopropyl(phenyl)methyl]-1,8-dioxaspiro[4.5]dec-3-en-2-one 190b.

White solid (68 mg, 0.23 mmol, 65%) from 4-hydroxy-3-(1-phenylprop-2-enyl)-1,8-dioxaspiro[4.5]dec-3-en-2-one **122h** (100 mg, 0.35 mmol), diethyl zinc (2 ml, 2.0 mmol), trifluroacetic acid (0.15 ml, 2.0 mmol) and diiodomethane (0.16 ml, 2.0 mmol) dissolved in dry DCM (5 ml). The reaction was set at -10°C and stirred for 30 mins before being heated to 40°C for 16h. Molecular formula $C_{18}H_{20}O_4$. R_f 0.13 (ethyl acetate:hexane, 1:3, v:v), mp 158 - 160°C.



IR (KBr); ν(cm^{-1}) = 3445 (s) [ν (OH)], 3067 (w), 3031 (w), 2955 (m), 2858 (s), 1745 (m), 1701 (s), 1626 (s), 1494 (w), 1453 (w), 1387 (m), 1298 (m), 1243 (s), 1137 (s), 1103 (s), 1021 (m), 975 (m), 825 (m), 738 (m), 699 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.16 - 0.23 and 0.30 - 0.39 (m, 2H, 4'-H), 0.53 - 0.62 (m, 2H, 3'-H), 1.39 - 1.57 and 2.05 - 2.19 (m, 5H, 2'-H, 6-H, 10-H), 3.16 (d, $^3J_{HH}$ = 9.06 Hz, 1H, 1'-H), 3.60 - 3.94 (m, 4H, 7-H and 9-H), 7.15 - 7.38 (m, 5H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CD_3C(O)CD_3$): δ (ppm) = 4.9 (CH_2, C-4'), 5.9 (CH_2, C-3'), 13.7 (CH, C-2'), 32.5, 32.7 (CH_2, C-6 and C-10), 43.3 (CH, C-1'), 63.6, 63.7 (CH_2, C-7 and C-9), 79.4 (C^q, C-5-*spiro*), 103.7 (C^q, C-3), 127.0, 127.7, 128.8 (CH, Ph), 141.2 (C^q, Ph-*ipso*), 172.8 (C^q, C-2), 176.2 (C^q, C-4).

MS (EI, 70 eV): m/z = 300 (6) [M^+], 282 (8) [M^+-H_2O], 272 (8) [M^+-C_2H_4], 261 (3), 243 (6), 223 (4) [M^+-Ph], 211 (5), 198 (7), 184 (10), 166 (7), 144 (28), 131 (100) [$PhC_4H_6^+$], 130 (53), 116 (36), 115 (69), 103 (36), 91 (100) [$PhCH_2^+$], 77 (56) [Ph^+], 69 (46), 51 (47), 41 (89).

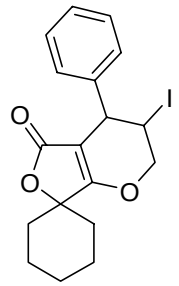
$C_{18}H_{20}O_4$ (300.35): Calculated C = 71.98, H = 6.71; found C = 72.05, H = 6.73.

3.3.8 Iodocyclisation Reactions

3'-Iodo-4'-phenyl-3',4'-dihydro-2'*H*,5'*H*-spiro[cyclohexane-1,7'-furo[3,4-*b*]pyran]-5'-one 196.

Iodine (1.02 g, 4.0 mmol) was weighed into a clean round bottomed flask with a side arm. Under an inert atmosphere of nitrogen freshly dried DCM (40 ml) was added. To this solution was added sodium carbonate (0.42 g, 2 mmol) followed by a solution of 4-hydroxy-3-(1-phenylprop-2-enyl)-1-oxaspiro[4.5]dec-3-en-2-one **122a** (580 mg, 2.11 mmol) in DCM (5 ml). The resulting

solution was stirred for 6h after which time the solution was washed with twice with sodium thiosulphate solution (10 ml) to remove the excess iodine. The organic layer was washed twice more with distilled water (10 ml). The organic layer was dried with sodium sulphate and the solvent removed by rotary evaporation. The resulting residue was purified by column chromatography to give a white solid **196** (143 mg, 0.35 mmole, 17%). Molecular formula $C_{18}H_{19}IO_3$. R_f 0.45 (diethyl ether:hexane, 1:1, v:v), mp/decomp 162 °C. *NB 3-(3-iodo-1-phenylpropyl)-1-oxaspiro[4.5]decane-2,4-dione **197** was recovered from this reaction in 28% yeild. The stereochemistry of **196** is assumed to be anti between C-1' and C-2'. However this cannot be proved due to the presence of complicated multiplets which resulted from long range ($^4J_{HH}$) coupling.*



IR (KBr); ν(cm^{-1}) = 3035 (w), 2934 (s), 2849 (w), 1744 (m), 1700 (s), 1595 (s), 1478 (s), 1441 (s), 1268 (m), 1197 (w), 1115 (m), 1063 (w), 993 (w), 910 (m), 853 (w), 824 (w), 749 (m), 694 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.23 - 1.82 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.17 (d, $^3J_{HH}$ = 3.71 Hz, 1H, CHPh), 4.30 - 4.34 (m, 2H, CHI), 4.38 - 4.41 (m, 2H, OCH_2), 7.15 - 7.30 (m, 5H, Ph).

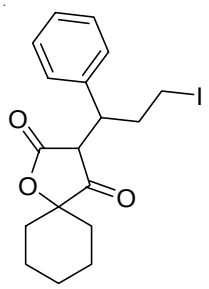
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.6, 21.7 (CH_2, C-7 and C-9), 23.2 (CH, CHI), 24.2 (CH_2, C-8), 31.5, 31.6 (CH_2, C-6 and C-10), 45.1 (CH, CHPh), 72.3 (CH_2, OCH_2), 86.6 (C^q, C-5-*spiro*), 93.1 (C^q, C-3), 128.6, 128.9 (CH, Ph), 140.2 (C^q, Ph-ipso), 179.0 (C^q, C-2), 198.1 (C^q, C-4).

MS (EI, 70 eV): m/z = 410 (100) [M^+], 369 (5), 355 (10), 329 (6) [M^+-C_6H_9], 311 (6), 283 (16) [M^+-I], 265 (24) [*283* - H_2O], 237 (9) [*265* - C_2H_2], 197 (7), 185 (19), 158 (15), 157 (56) [M^+-I-CO_2-C_6H_{10}], 128 (62) [*157* - CHO], 117 (53), 115 (36), 110 (24) [$C_7H_{10}O^+$], 91 (26), 81 (19), 55 (16), 41 (18).

Accurate Mass:- Calculated Mass = 410.03789 Found = 410.03786.

3-(3'-Iodo-1'-phenylpropyl)-1-oxaspiro[4.5]decane-2,4-dione 197.

White solid which turns yellow over time (238 mg, 0.58 mmol, 28%) from 4-hydroxy-3-(1-phenyl-allyl)-1-oxa-spiro[4.5]dec-3-en-2-one **122a** (580 mg, 2.11 mmol), sodium carbonate (424 mg, 4.0 mmol) and iodine (1.02 g, 4.0 mmol) dissolved in dry CH_2Cl_2 (45 ml) for six h. Molecular formula $C_{18}H_{21}IO_3$. R_f 0.68 (diethyl ether:hexane, 1:1, v:v), mp 140 - 142°C. *See procedure for compound **196**. NB 3'-Iodo-4'-phenyl-3',4'-dihydro-2'H,5'H-spiro[cyclohexane-1,7'-furo[3,4-b]pyran]-5'-one **196** was also recovered in 17% from this reaction.*



Mixture of diastereoisomers α and β, ratio 1:1.

IR (KBr); ν(cm^{-1}) = 3026 (w), 2929 (s), 2854 (m), 1775 (m), 1737 (s), 1496 (w), 1445 (s), 1308 (s), 1212 (m), 1166 (m), 1105 (m), 1030 (w), 974 (w), 949 (m), 814 (m), 757 (m), 737 (m), 694 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.84 - 1.83 (m, 12H, C*H*$_2$CH_2I, 6-H, 7-H, 8-H, 9-H, 10-H$^{α–β}$), 3.22 (dt, $^{3}J_{HH}$ = 8.67 Hz, 7.12 Hz, 1H, 1'-H^{α}), 3.37 (dt, $^{3}J_{HH}$ = 8.72 Hz, 6.20 Hz, 1H, 1'-H^{β}), 3.49 (d, $^{3}J_{HH}$ = 8.72 Hz, 1H, 3-H^{β}), 3.55 (d, $^{3}J_{HH}$ = 8.67 Hz, 1H, 3-H^{α}), 3.56 - 3.86 (m, 2H, $CH_2I^{α–β}$), 7.02 - 7.33 (m, 5H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = -1.2, -0.4 (CH_2, $CH_2I^{α–β}$), 20.8, 20.9, 20.9, 21.0 (CH_2, C-7$^{α–β}$ and C-9$^{α–β}$), 24.3, 24.4 (CH_2, C-8$^{α–β}$), 29.3, 29.6 (CH_2, 2'-CH_2), 31.9, 32.2, 32.3, 32.5 (CH_2, C-6$^{α–β}$ and C-10$^{α–β}$), 43.1 (CH, 1'-CH^{α}), 44.2 (CH, 1'-CH^{β}), 52.8 (CH, C-3^{β}), 53.1 (CH, C-3^{α}), 89.4, 89.7 (C^{q}, C-5-*spiro*$^{α–β}$), 128.2, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 129.0, 129.7 (CH, Ph$^{α–β}$), 131.3, 131.5 (C^{q}, Ph-*ipso*$^{α–β}$), 169.7, 171.5 (C^{q}, C-2$^{α–β}$), 204.8, 208.1 (C^{q}, C-4$^{α–β}$).

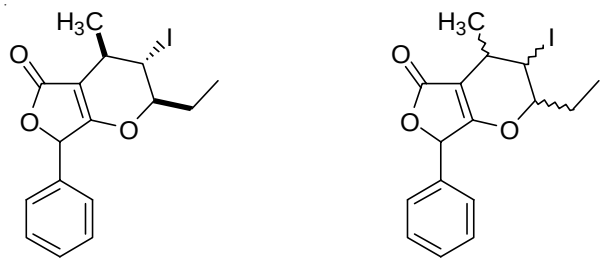
MS (EI, 70 eV): m/z = 410 (0.5) [M^{+}-H_2], 284 (4) 283 (14) [*410* - I], 266 (8) [*283* - OH], 265 (10) [*283* - H_2O], 239 (3), [*265* - C_2H_2], 158 (37), 157 (100), 129 (64), 128 (56), 117 (38), 115 (21), 91 (13) [$C_7H_7^{+}$], 55 (9), 41 (6).

2-ethyl-3-iodo-4-methyl-7-phenyl-2,3,4,7-tetrahydro-5*H*-furo[3,4-*b*]pyran-5-one 199.

Iodine (1.02 g, 4.0 mmol) was weighed into a clean round bottomed flask. Under an inert atmosphere of nitrogen freshly dried DCM (40 ml) was added. To this was added 4-hydroxy-3-[(2*E*)-1-methylpent-2-enyl]-5-phenylfuran-2(5*H*)-one **212d** (600 mg, 2.33 mmol) and the solution was stirred for 16h at room temperature, after which time the solution was washed twice with sodium thiosulphate solution (10 ml) to remove the excess iodine. The organic layer was washed twice more with distilled water (10 ml). The organic layer was dried with sodium sulphate and the solvent removed by rotary evaporation. The resulting residue was purified by column chromatography to give 2-ethyl-3-iodo-4-methyl-7-phenyl-2,3,4,7-tetrahydro-5H-furo[3,4-b]pyran-5-one **199**. Four isomers were identified combined yield 66% (581 mg, 1.51 mmol).

First and Second distereoisomers are present as an inseperable mixture. Ratio α:β = 2:1.

Brown solid **199a** (282 mg, 0.73 mmol, 32%) from 4-hydroxy-3-[(2*E*)-1-methylpent-2-enyl]-5-phenylfuran-2(5*H*)-one **212d** (600 mg, 2.33 mmol) and iodine (1.19 g, 4.65 mmol) dissolved in dry DCM (20 ml) and stirred overnight. Molecular formula $C_{16}H_{17}IO_3$. R_f 0.69 (diethyl ether: hexane, 1:1, v:v). *NB The diastereoisomer labelled **199a-β** could not be assigned due to the fact that β was present in a low concentration. Integretions are calculated as a hypothetical 1:1 mixture of diasteroisomers..*



α **β**

Isomer β was not strong enough for stuctural determination. Ratio α:β, 2:1.

IR (KBr); ν(cm^{-1}) = 3065 (w), 3034 (w), 2971 (m), 2932 (m), 1749 (s), 1668 (s), 1456 (m), 1409 (s), 1340 (w), 1308 (w), 1276 (m), 1153 (m), 1116 (m), 1036 (m), 985 (s), 926 (m), 900 (m), 837 (w), 770 (m), 733 (w), 702 (s),

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.86 (t, $^{3}J_{HH}$ = 7.11 Hz, 3H, $CH_2CH_3^{\alpha}$), 0.93 (t, $^{3}J_{HH}$ = 7.38 Hz, 3H, $CH_2CH_3^{\beta}$), 1.48 (d, $^{3}J_{HH}$ = 6.86 Hz, 3H, 4'-CH_3^{α}), 1.50 (d, $^{3}J_{HH}$ = 6.87 Hz, 3H, 4'-CH_3^{β}), 1.79 - 2.00 (m, 2H, $CH_2CH_3^{\alpha}$), 2.18 - 2.38 (m, 2H, $CH_2CH_3^{\beta}$), 2.92 (m, 1H, 4'-$CH^{\alpha-\beta}$), 3.69 - 3.89 (m, 1H, 3'-$H^{\alpha-\beta}$), 4.16 - 4.23 (dt, $^{3}J_{HH}$ = 7.03 Hz, 7.23 Hz, 1H, 2'-H^{α}), 4.33 - 4.43 (m, 1H, 2'-H^{β}), 5.65, 5.66 (s, 1H, C-$5^{\alpha-\beta}$), 7.29 - 7.39 (m, 5H, $Ph^{\alpha-\beta}$).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 7.99, 8.04 (CH_3, $CH_2CH_3^{\alpha-\beta}$), 17.17, 17.57 (CH_3, 4'-$CH_3^{\alpha-\beta}$), 27.77, 28.00 (CH_2, $CH_2CH_3^{\alpha-\beta}$), 33.85, 33.89 (CH, CH-$I^{\alpha-\beta}$), 36.45, 36.49 (CH, CH-$I^{\alpha-\beta}$), 77.81, 77.95 (CH, 2'-$CH^{\alpha-\beta}$), 84.82, 84.92 (CH, 5-$CH^{\alpha-\beta}$), 101.14, 101.29 (C^{q}, C-$3^{\alpha-\beta}$), 126.31, 126.40, 128.81, 128.84, 129.21, 129.23 (CH, $Ph^{\alpha-\beta}$), 133.80, 133.96 (Cq, Ph-*ipso*$^{\alpha-\beta}$), 170.14 (C^{q}, C-2), 174.36, 174.39 (C^{q}, C-$4^{\alpha-\beta}$).

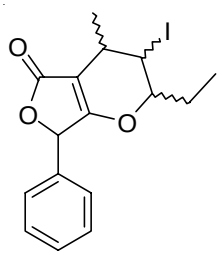
^{1}H-NOESY (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 2'-H showed crosspeaks with CH_2CH_2 and CH_2CH_3. No crosspeak with 3'-H therfore indicating a *trans* configuration between 2'-H and 3'-H. 3'-H had no crosspeaks with any other group. 4'-H had no crosspeaks with any other group. Therefore there must be a *trans* configuration between 4'-H and 3'-H.

MS (EI, 70 eV): m/z = 385 (5) [M^{+}+1], 384 (34) [M^{+}], 258 (21) [M^{+}+1-I], 257 (100) [M^{+}-I], 240 (11), 239 (59) [*257* - H_2O], 211 (8), 183 (5), 171 (33), 143 (11), 123 (19), 105 (24) [$C_6H_5CO^{+}$], 95 (21), 91 (19), 83 (37), 79 (12), 77 (16) [$C_6H_5^{+}$], 55 (29), 41 (13).

Accurate Mass:- Calculated Mass = 384.02224 Found = 384.02226.

Third Diastereoisomer:

Brown solid **199b** (125 mg, 0.33 mmol, 14%) from 4-hydroxy-3-[(2*E*)-1-methylpent-2-enyl]-5-phenylfuran-2(5*H*)-one **212d** (600 mg, 2.33 mmol) and iodine (1.19 g, 4.65 mmol) dissolved in dry DCM (20 ml) and stirred overnight. Molecular formula $C_{16}H_{17}IO_3$. R_f 0.54 (diethyl ether: hexane, 1:1, v:v).



IR (KBr); ν(cm^{-1}) = 3065 (w), 3034 (w), 2971 (m), 2932 (m), 1749 (s), 1668 (s), 1456 (m), 1409 (s), 1340 (w), 1308 (w), 1276 (m), 1153 (m), 1116 (m), 1036 (m), 985 (s), 926 (m), 900 (m), 837 (w), 770 (m), 733 (w), 702 (s),

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.71 (t, $^3J_{HH}$ = 7.34 Hz, 3H, CH_2CH_3), 1.38 (dd, $^3J_{HH}$ = 6.74 Hz, $^4J_{HH}$ = 1.33 Hz, 3H, 4'-CH_3), 1.55 - 1.77 (m, 2H, CH_2CH_3), 2.42 - 2.51 (m, 1H, 4'-H), 4.29 - 4.33 (m, 1H, 3'-H), 4.54 (td, $^3J_{HH}$ = 8.74, 4.62 Hz, 1H, 2'-H), 5.27 (s, 1H, 5-H), 7.31 - 7.41 (m, 5H, Ph).

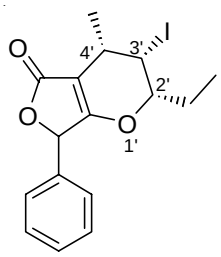
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 8.83 (CH_3, CH_2CH_3), 19.83 (CH_3, 4'-CH_3), 26.55 (CH_2, CH_2CH_3), 28.07 (CH, 4'-CH), 33.50 (CH, 3'-CH), 78.15 (CH, C-5), 85.11 (CH, 2'-CH), 100.43 (C_q, C-3), 126.24, 127.20, 128.77 (CH, Ph), 134.03 (C^q, Ph-*ipso*), 170.94 (C^q, C-2), 172.97 (C^q, C-4).

MS (EI, 70 eV): m/z = 385 (7) [M^++1], 384 (40) [M^+], 295 (19), 257 (100) [M^+-I], 239 (60) [*257* - H_2O], 171 (54), 143 (28), 129 (17), 105 (59) [$C_6H_5CO^+$], 95 (69), 91 (36), 83 (59), 79 (37), 77 (47) [$C_6H_5^+$], 67 (21), 55 (73) [$C_4H_7^+$], 41 (33).

Accurate Mass:- Calculated Mass = 384.02224 Found = 384.02226.

Fourth Diastereoisomer:

Brown solid **199c** (174 mg, 0.45 mmol, 20%) from 4-hydroxy-3-[(2*E*)-1-methylpent-2-enyl]-5-phenylfuran-2(5*H*)-one (600 mg, 2.33 mmol) and iodine (1.19 g, 4.65 mmol) dissolved in dry DCM (20 ml) and stirred overnight. Molecular formula $C_{16}H_{17}IO_3$. R_f 0.41 (diethyl ether: hexane, 1:1, v:v). *NB. The all syn configuration was based on coupling constants between 2'-H, 3'-H and 4'-H = 4.76 Hz.*



IR (KBr); ν(cm^{-1}) = 3065 (w), 3034 (w), 2972 (s), 2934 (s), 2878 (m), 1755 (s), 1666 (s), 1496 (w), 1456 (m), 1413 (m), 1380 (w), 1340 (m), 1307 (m), 1276 (s), 1160 (m), 1119 (m), 988 (s), 929 (m), 902 (m), 834 (w), 765 (m), 732 (w), 699 (s), 501 (s) [C-I].

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.97 (t, $^3J_{HH}$ = 7.41 Hz, 3H, CH_2CH_3), 1.37 (d, $^3J_{HH}$ = 6.74 Hz, 3H, 1'-H_3), 1.83 (pent., $^3J_{HH}$ = 7.41 Hz, 2H, CH_2CH_3), 2.46 (qdd, $^3J_{HH}$ = 6.74, 4.76 Hz, $^4J_{HH}$ = 1.95 Hz, 1H, 4'-H), 4.36 (dd, $^3J_{HH}$ = 4.76, 4.76 Hz, 1H, CH-I), 4.47 - 4.53 (m, 1H, 2'-H), 5.61 (d, $^4J_{HH}$ = 1.95 Hz, 1H, 5-H), 7.29 - 7.40 (m, 5H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 9.3 (CH_3, CH_2CH_3), 20.1 (CH_3, C-4'), 26.99 (CH_2, CH_2CH_3), 27.99 (CH, C-4'), 33.48 (CH, C-3'), 78.6 (CH, C-5), 85.34 (CH, C-2'), 101.31 (C_q, C-3), 127.29, 128.80, 129.50 (CH, Ph), 133.46 (C^q, Ph-*ipso*), 170.82 (C^q, C-2), 172.44 (C^q, C-4).

MS (EI, 70 eV): m/z = 385 (8) [M^++1], 384 (38) [M^+], 295 (14), 257 (100) [M^+-I], 239 (67) [*257* - H_2O], 171 (62), 143 (26), 129 (20), 123 (34), 105 (53) [$C_6H_5CO^+$], 95 (46), 91 (40), 83 (56), 79 (35), 77 (51) [$C_6H_5^+$], 67 (23), 55 (73) [$C_4H_7^+$], 41 (33).

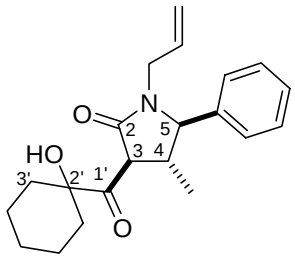
Accurate Mass:- Calculated Mass = 384.02224 Found = 384.02226

3.5 Ring Trapping of 3-(spirocyclopropyl)-dihydrofuran-4,12-diones 212 leading to Butyrolactams 218

A solution of the respective tetronate (1.0 mmol) was dissolved, under a inert atmosphere of nitrogen, in dry toluene (5 ml) and transfered to a sealable glass tube. The respective amine/ alcohol (5 - 10 mmol) was dissolved in dry toluene (1 ml) and then added to the glass tube, which was then sealed. The glass tube was heated in a normal oil bath to 160°C for 16h. After cooling the solvent was removed by rotary evaporation and the residue was purified by column chromatography (silica gel: solvent as indicated).

***trans,trans*-1-Allyl-3-[(2'-hydroxycyclohexyl)carbonyl]-4-methyl-5-phenylpyrrolidin-2-one 218a-A.**

White crystalline solid (368 mg, 1.08 mmol; 73%) from (E)-4-(3-Phenyl-allyloxy)-1-oxa-spiro[4.5]dec-3-en-2-one **121a** (284 mg, 1.00 mmol) and allylamine (290 mg, 5.10 mmol) dissolved in toluene (6 ml) and heated to 170°C for 16h. Molecular formula $C_{21}H_{27}NO_3$. R_f 0.57 (diethyl ether / hexane, 1:1, v/v), mp 107°C.



IR (KBr); ν(cm^{-1}) = 3455 (s) [ν (OH)], 3045 (w), 2939 (m), 2852 (w), 1708 (m), 1667 (s), 1456 (m), 1427 (m), 1412 (m), 1366 (m), 1224 (m), 1038 (m), 990 (s), 926 (m), 768 (m), 699 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.96 (d, $^3J_{HH}$ = 6.71 Hz, 3H, 4-CH_3), 1.16 - 1.80 (m, 10H, 3'-H, 4'-H, 5'-H, 6'-H, 7'-H), 2.82 (ddq, $^3J_{HH}$ = 10.04, 8.45, 6.71 Hz, 1H, 4-H), 3.01 (dd, $^2J_{HH}$ = 15.04 Hz, $^3J_{HH}$ = 7.58 Hz, 1H, NCH*H*), 4.07 (d, $^3J_{HH}$ = 8.45 Hz, 1H, 5-H), 4.16 (ddt, $^2J_{HH}$ = 15.04 Hz, $^3J_{HH}$ = 4.89 Hz, $^4J_{HH}$ = 1.57 Hz, 1H, NC*H*H), 4.22 (d, $^3J_{HH}$ = 10.04 Hz, 1H, 3-H), 4.84 (d, $^3J_{HH}$ = 17.06 Hz, 1H, CH=CH*H*-*trans*), 5.05 (d, $^3J_{HH}$ = 10.15 Hz, 1H, CH=CHH-*cis*), 5.48 - 5.58 (m, 1H, C*H*=CH_2), 5.60 (d, $^4J_{HH}$ = 2.04 Hz, 1H, OH), 7.18 - 7.35 (m, 5H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 16.3 (CH_3, 4-Me), 20.6, 20.8 (CH_2, C-4' and C-6'), 25.4 (CH_2, C-5'), 33.9, 34.0 (CH_2, C-3' and C-7'), 38.0 (CH, C-4), 43.9 (CH_2, NCH_2), 58.4 (CH, C-3), 68.3 (CH, C-5), 79.1 (C^q, C-2'), 118.9 (CH_2, CH=*C*H_2), 127.9, 128.7, 128.9, 130.9 (CH, Ph), 138.0 (C^q, Ph-*ipso*), 172.0 (C^q, C-2), 210.28 (C^q, 1'-C).

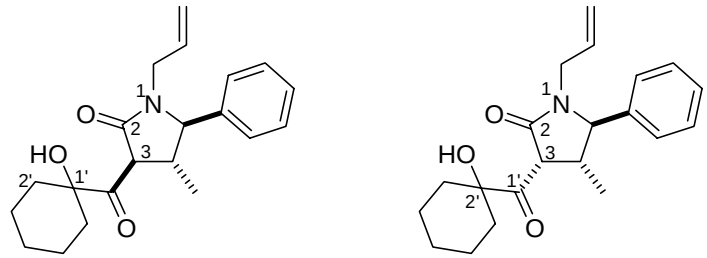
MS (EI, 70 eV): m/z = 341 (0.1) [M^+], 313 (1.2) [M^+-CO], 297 (0.4) [M^+-CO_2], 215 (100) [M^+-$C_6H_{10}COO$], 201 (7), 200 (51) [*215* - CH_3], 174 (8) [$C_5H_7NOPh^+$], 106 (6), 99 (3), 81 (4), 69 (6), 41 (6).

$C_{21}H_{27}NO_3$ (341.44): Calculated C = 73.86%, H = 7.97%, N = 4.10%; found C = 73.98%, H = 8.12%, N = 3.96%.

X-ray crystal structure analysis of **218a-A**: Clear, colourless crystals were obtained from diethyl ether :hexane solution allowed to evaporate at room temperature. Cambridge database registration no CCDC 213176.

1-Allyl-3-[(2'-hydroxycyclohexyl)carbonyl]-4-methyl-5-phenylpyrrolidin-2-one 218a-α and 218a-β.

White crystalline solid (107 mg, 0.31 mmol; 21%) from (E)-4-(3-Phenyl-allyloxy)-1-oxa-spiro[4.5]dec-3-en-2-one **121a** (284 mg, 1.00 mmol) and allylamine (290 mg, 5.10 mmol) dissolved in toluene (6 ml) and heated to 170°C for 16h. Molecular formula $C_{21}H_{27}NO_3$. R_f 0.60 (diethyl ether / hexane, 1:1, v/v). *NB 73% of **218a-A** was obtained in a pure form from this reaction(see previous page 218a-A).*



Mixture of two diasteroisomers: Ratio α:β = 1:1.

IR (KBr); ν(cm^{-1}) = 3455 (s) [ν (OH)], 3045 (w), 2939 (m), 2852 (w), 1708 (m), 1667 (s), 1456 (m), 1427 (m), 1412 (m), 1366 (m), 1224 (m), 1038 (m), 990 (s), 926 (m), 768 (m), 699 (s).

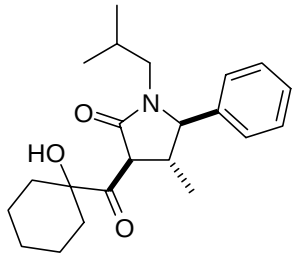
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.96 (d, $^3J_{HH}$ = 6.71 Hz, 3H, 4-CH_3^{α}), 1.16 - 1.80 (m, 10H, 3'-H$^{\alpha-\beta}$, 4'-H$^{\alpha-\beta}$, 5'-H$^{\alpha-\beta}$, 6'-H$^{\alpha-\beta}$, 7'-H$^{\alpha-\beta}$ including a doublet at 1.22 ppm, $^3J_{HH}$ = 6.14 Hz, 3H, 4-CH_3^{β}), 2.82 (ddq, $^3J_{HH}$ = 10.04, 8.45, 6.71 Hz, 1H, 4-H$^{\alpha}$), 3.01 (dd, $^2J_{HH}$ = 15.04 Hz, $^3J_{HH}$ = 7.58 Hz, 1H, NCH*H*$^{\alpha}$), 3.58 (m, 2H, NCH_2^{β}), 3.69 (dq, $^3J_{HH}$ = 8.01 Hz, 6.14 Hz, 1H, 4-CH$^{\beta}$), 4.07 (d, $^3J_{HH}$ = 8.45 Hz, 1H, 5-H$^{\alpha}$), 4.12 - 4.26 (m, 3H, NCH*H*$^{\alpha}$, 3-H$^{\alpha}$, 3-H$^{\beta}$), 4.64 (d, $^3J_{HH}$ = 9.51 Hz, 1H, 5-H$^{\beta}$), 4.84 (d, $^3J_{HH}$ = 17.06 Hz, 1H, CH=CH*H-trans*$^{\alpha}$), 5.05 (d, $^3J_{HH}$ = 10.15 Hz, 1H, CH=CHH-*cis*$^{\alpha}$), 5.16 - 5.22 (m, 2H, $CH=CH_2^{\beta}$), 5.48 - 5.77 (m, 4H, C*H*=$CH_2^{\alpha-\beta}$, OH$^{\alpha-\beta}$), 7.16 - 7.35 (m, 5H, Ph$^{\alpha-\beta}$).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 16.29 (CH_3, 4-CH_3^{α}),18.09 (CH_3, 4-CH_3^{β}), 20.44, 20.60, 20.67, 20.71 (CH_2, C-4'$^{\alpha-\beta}$ and C-6'$^{\alpha-\beta}$), 25.20, 25.27 (CH_2, C-5'$^{\alpha-\beta}$), 33.49, 33.76, 33.83, 33.91 (CH_2, C-3'$^{\alpha-\beta}$ and C-7'$^{\alpha-\beta}$), 37.88 (CH, C-4$^{\alpha}$), 43.47, 43.78 (CH_2, $NCH_2^{\alpha-\beta}$), 47.02 (CH, C-4$^{\beta}$), 58.31, 58.82 (CH, C-3$^{\alpha-\beta}$), 59.44 (CH, C-5$^{\beta}$), 68.28 (CH, C-5$^{\alpha}$), 78.91, 79.02 (C^{q}, C-2'$^{\alpha-\beta}$), 118.48, 118.82 (CH_2, CH=$CH_2^{\alpha-\beta}$), 127.33, 127.58, 128.55, 130.79, 131.56 (CH, Ph$^{\alpha-\beta}$), 137.90 (C^{q}, Ph-*ipso*$^{\alpha}$), 139.64 (C^{q}, Ph-*ipso*$^{\beta}$), 170.40 (C^{q}, C-2$^{\beta}$), 171.83 (C^{q}, C-2$^{\alpha}$), 209.62, 210.16 (C^{q}, 1'-C$^{\alpha-\beta}$).

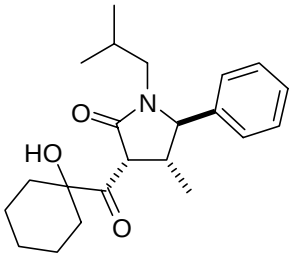
MS (EI, 70 eV): m/z = 341 (0.1) [M$^+$], 313 (1.2) [M$^+$-CO], 297 (0.4) [M$^+$-CO_2], 215 (100) [M$^+$-$C_6H_{10}COO$], 201 (7), 200 (51) [*215* - CH_3], 174 (8) [$C_5H_7NOPh^+$], 106 (6), 99 (3), 81 (4), 69 (6), 41 (6).

1-Isobutyl-3-[(2'-hydroxycyclohexyl)carbonyl]-4-methyl-5-phenylpyrrolidin-2-one 218b-α and 218b-β.

Colourless liquid (304 mg, 0.85 mmol, 67%), from (E)-4-(3-Phenyl-allyloxy)-1-oxa-spiro[4.5]dec-3-en-2-one **121a** (360 mg, 1.27 mmol) and isobutyl amine (0.67 g, 9.15 mmol) dissolved in toluene (6 ml) and heated in a sealed tube for 25h. Molecular formula $C_{22}H_{31}NO_3$. R_f 0.33 (diethyl ether:hexane: 1:1, v:v).



α



β

Mixture of diastereoisomers. Ratio of α:β; 2.7:1

IR (KBr); v(cm^{-1}) = 3324 (s) [OH], 3065 (w), 3031 (w), 2930 (s), 2872 (s), 1715 (s) [5-ring lactam], 1661 (s), 1424 (s), 1340 (m), 1280 (m), 1230 (m), 1170 (m), 1124 (m), 992 (s), 957 (w), 768 (m), 735 (m), 701 (s).

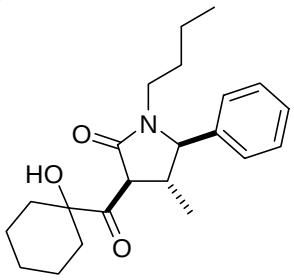
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.70 (d, $^3J_{HH}$ = 6.67 Hz, 3H, CH(CH_3)CH_3^{α}), 0.76 (d, $^3J_{HH}$ = 6.66 Hz, CH(CH_3)CH_3^{α}), 0.88 (d, $^3J_{HH}$ = 6.99 Hz, 3H, CH(CH_3)CH_3^{β}), 0.90 (d, $^3J_{HH}$ = 7.11 Hz, 3H, CH(CH_3)CH_3^{β}), 0.97 (d, $^3J_{HH}$ = 6.70 Hz, 3H, 4-CH_3^{α}), 1.23 (d, $^3J_{HH}$ = 6.14 Hz, 3H, 4-CH_3^{β}), 1.15 - 1.84 (m, 11H, 3'-H$^{\alpha-\beta}$, 4'-H$^{\alpha-\beta}$, 5'-H$^{\alpha-\beta}$, 6-H$^{\alpha-\beta}$, 7'-H$^{\alpha-\beta}$, C*H*(CH_3)$_2^{\alpha-\beta}$), 2.35 (dd, $^2J_{HH}$ = 13.62 Hz, $^3J_{HH}$ = 5.63 Hz, 1H, NCH*H*$^{\alpha}$), 2.74 - 2.88 (m, 2H, 4-CH$^{\alpha}$, NCH*H*$^{\beta}$), 3.29 (dd, $^2J_{HH}$ = 13.62 Hz, $^3J_{HH}$ = 9.57 Hz, 1H, NC*H*H$^{\alpha}$), 3.36 (dd, $^2J_{HH}$ = 13.76 Hz, $^3J_{HH}$ = 9.56 Hz, 1H, NC*H*H$^{\beta}$), 3.58 (d, $^3J_{HH}$ = 8.11 Hz, 1H, 5-H$^{\beta}$), 3.68 (ddt, $^3J_{HH}$ = 9.63, 8.11, 6.14 Hz, 1H, 4-H$^{\beta}$), 4.08 (d, $^3J_{HH}$ = 8.33 Hz, 1H, 5-H$^{\alpha}$), 4.26 (d, $^3J_{HH}$ = 10.06 Hz, 1H, 3-H$^{\alpha}$), 4.68 (d, $^3J_{HH}$ = 9.63 Hz, 1H, 3-H$^{\beta}$), 5.75 (d, $^4J_{HH}$ = 2.04 Hz, 1H, OH$^{\beta}$), 5.78 (d, $^4J_{HH}$ = 2.00 Hz, 1H, OH$^{\alpha}$), 7.18 - 7.35 (m, 5H, Ph$^{\alpha-\beta}$).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 16.46 (CH_3, 4-CH_3^{α}), 18.23 (CH_3, 4-CH_3^{β}), 19.76 (CH_3, CH(*C*H_3)CH_3^{α}), 19.98 (CH_3, CH(CH_3)*C*H_3^{β}), 20.29 (CH_3, CH(CH_3)*C*H_3^{α}), 20.42 (CH_3, CH(C*H*$_3$)CH_3^{β}), 20.77, 20.87 (CH_2, 4'-C$^{\alpha-\beta}$ and 6'-C$^{\alpha-\beta}$), 25.39, 25.45 (CH_2, 5'-C$^{\alpha-\beta}$), 26.09 (CH, CH(CH_3)$_2^{\alpha}$), 26.59 (CH, CH(CH_3)$_2^{\beta}$), 33.69, 33.87, 33.96, 34.04 (CH_2, 3'-C$^{\alpha-\beta}$, 7'-C$^{\alpha-\beta}$), 38.25 (CH, C-4$^{\alpha}$), 47.25 (CH, C-3$^{\beta}$), 48.12 (CH_2, NCH_2^{β}), 48.46 (CH_2, NCH_2^{α}), 58.41 (CH, C-3$^{\alpha}$), 58.86 (CH, C-5$^{\beta}$), 59.86 (CH, C-4$^{\beta}$), 69.10 (CH, C-5$^{\alpha}$), 78.99, 79.12 (C^{q}, 2'-C$^{\alpha-\beta}$), 127.48, 127.77, 128.40, 128.89, 128.94, 128.99 (CH, Ph$^{\alpha-\beta}$), 138.16 (C^{q}, Ph-*ipso*$^{\alpha}$), 139.86 (C^{q}, Ph-*ipso*$^{\beta}$), 170.90 (C^{q}, C-2b), 172.30 (C^{q}, C-2$^{\alpha}$), 209.88 (C^{q}, 1'-C$^{\beta}$), 210.45 (C^{q}, 1'-C$^{\alpha}$).

MS (EI, 70 eV): m/z = 357 (0.1) [M^+], 339 (4) [M^+-H_2O], 314 (2) [M^+-C_3H_7], 296 (2.5) [*314* - H_2O], 280 (2) [M^+-C_6H_5], 258 (2), 231 (100) [M^+-$C_6H_{10}CO_2$], 216 (43) [*231* - CH_3], 188 (37) [*216* - CO], 174 (3), 154 (5), 131 (5), 109 (3), 91 (7), 69 (3), 55 (2).

(3*S*,4*R*,5*R*)-3-[(2'-Hydroxycyclohexyl)carbonyl]-1-butyl-4-methyl-5-phenylpyrrolidin-2-one 218c-α.

Colourless oil (1.18 g, 3.31 mmol, 84%) from (E)-4-(3-Phenyl-allyloxy)-1-oxa-spiro[4.5]dec-3-en-2-one **121a** (1.12 g, 3.94 mmol) and n-butyl amine (1.44 g, 19.72 mmol) dissolved in dry toluene (7 ml) and heated in a sealed tube to 175 °C for 12 h. Molecular formula $C_{22}H_{31}NO_3$. R_f 0.64 (diethyl ether, 1:1, v:v). *NB Note that **218c-B** was not recovered from this reaction.*



IR (KBr); ν(cm^{-1}) = 3324 (m) [ν (OH)], 3064 (w), 3031 (w), 2932 (s), 2861 (m), 1714 (m), 1664 (s), 1494 (m), 1424 (s), 1378 (m), 1317 (m), 1266 (m), 1228 (m), 1171 (m), 1123 (m), 1036 (m), 992 (m), 957 (m), 701 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.84 (t, $^3J_{HH}$ = 7.25 Hz, 3H, $N(CH_2)_3CH_3$), 1.02 (d, $^3J_{HH}$ = 6.68 Hz, 3H, 4-CH_3), 1.14 - 1.87 (m, 10H, 3'-H, 4'-H, 5'-H, 6'-H, 7'-H), 2.56 (dt, $^2J_{HH}$ = 13.70 Hz, $^3J_{HH}$ = 6.78 Hz, 1H, NC*H*H), 2.78 - 2.91 (m, 1H, 4-H), 3.56 (dt, $^2J_{HH}$ = 13.70 Hz, $^3J_{HH}$ = 7.88 Hz, 1H, NCH*H*), 4.11 (d, $^3J_{HH}$ = 8.43 Hz, 1H, 5-H), 4.26 (d, $^3J_{HH}$ = 10.07 Hz, 1H, 3-H), 5.81 (d, $^4J_{HH}$ = 1.89 Hz, 1H, OH), 7.25 - 8.00 (m, 5H, Ph).

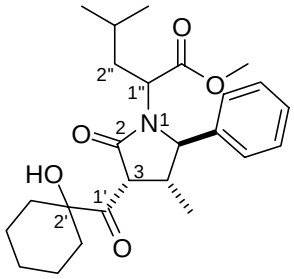
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 13.6 (CH_3, $N(CH_2)_3CH_3$), 16.3 (CH_3, 4-CH_3), 19.9 (CH_2, *C*H_2CH_3), 20.7, 20.8 (CH_2, C-4' and C-6'), 25.3 (CH_2, C-5'), 28.7 (CH_2, NC*C*H_2), 33.9, 34.0 (CH_2, C-3', C-7'), 38.1 (CH, C-4), 41.0 (CH_2, NCH_2), 58.5 (CH, C-3), 68.7 (CH, C-5), 79.1 (C^q, C-2'), 127.7, 128.6, 128.8,128.9, 128.9 (CH, Ph), 138.2 (C^q, Ph-*ipso*), 172.0 (C^q, C-2), 210.5 (C^q, C-1').

MS (EI, 70 eV): m/z = 358 (1) [M^++1], 357 (0.15) [M^+], 329 (1.25) [M^+-CO], 314 (1) [*329* - CH_3], 258 (1.3) [*314* - C_4H_9], 231 (100) [M^+-C_6H_{10} -CO_2], 216 (78) [*231* -CH_3], 188 (6), 154 (3), 91 (6), 81 (4), 69 (5).

(3R, 4R, 5R)-3-[(2'-hydroxycyclohexyl)carbonyl]-1-[methyl-4''-methylpentanoate]-4-methyl-5-phenylpyrrolidin-2-one 218d-β.

Four diastereoisomers were recovered, overall yield 97%.

1st diastereoisomer: Clear colourless oil (170 mg, 0.40 mmol, 15%) from 4-{[(2*E*)-3-phenylprop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121a** (750 mg, 2.64 mmole) and methyl (2*R*)-2-amino-4-methylpentanoate (1.40 g, 9.66 mmol) dissolved in dry toluene (20 ml) and heated in a sealed tube to 170°C for 26h. Purified by column chromatography. Molecular formula $C_{25}H_{35}NO_5$. R_f 0.53 (diethyl ether: hexane, 1:1, v:v). *NB Stereochemistry was determined from coupling constants.*



β

IR (film, KBr); ν(cm^{-1}) = 3356 (s) [ν (OH)], 3065 (w), 3032 (m), 2932 (s), 2868 (s), 1744 (s) [ν (C=O)], 1716 (s), 1666 (s), 1434 (s), 1370 (m), 1328 (s), 1242 (s), 1173 (s), 1126 (m), 1037 (m), 992 (s), 914 (w), 762 (m), 702 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.47 (d, $^3J_{HH}$ = 6.31 Hz, 3H, 3''-CH_3), 0.48 (d, $^3J_{HH}$ = 6.94 Hz, 3H, 3''-CH_3), 0.76 - 1.80 (m, 16H, 4-CH_3, 3'-CH_2, 4'-CH_2, 5'-CH_2, 6'-CH_2, 7'-CH_2, 2''-CH_2, 3''-CH), 3.29 - 3.40 (m, 1H, 4-H), 3.67 (s, 3H, $COOCH_3$), 4.35 (d, $^3J_{HH}$ = 11.40Hz, 1H, 5-H), 4.47 (m, 1H, 1''-H), 4.75 (d, $^3J_{HH}$ = 8.51 Hz, 1H, 3-H), 5.29 (d, $^4J_{HH}$ = 2.15 Hz, 1H, OH), 7.15 - 7.31 (m, 5H, Ph).

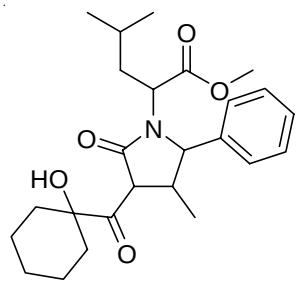
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 14.0 (CH_3, C-4), 20.6, 20.7 (CH_2, C-4' and C-6'), 21.5 (CH_3, C-3''), 22.1 (CH_3, C-3''), 24.6 (CH, C-3''), 25.2 (CH_2, C-5'), 33.7, 33.9 (CH_2, C-3', C-4'), 34.1 (CH, C-4), 38.2 (CH_2, C-2''), 52.2 (CH_3, $COOCH_3$), 52.2 (CH, C-3''), 54.4 (CH, C-5), 65.4 (CH, C-3), 79.1 (C^q, C-2'), 128.3, 128.6, 128.9 (CH, Ph), 137.5 (C^q, Ph-*ipso*), 171.0 (C^q, CO_2), 173.3 (C^q, C-2), 209.9 (C^q, C-1').

MS (EI, 70 eV): m/z = 430 (1.2) [M^++1], 429 (0.2) [M^+], 414 (0.5) [M^+-CH_3], 398 (0.6) [M^+-OCH_3], 370 (5) [M^+-CO_2-CH_3], 304 (31), 303 (100) [M^+-$C_6H_{10}COO$], 288 (36) [*303* - CH_3], 244 (16) [*288* - CO_2], 234 (44) [*288* - C_4H_8], 228 (14) [*244* - H_2O], 174 (38) [$C_5H_7NOPh^+$], 131 (12), 106 (22), 86 (33), 84 (55), 54 (24), 43 (56).

3-[(2'-hydroxycyclohexyl)carbonyl]-1-[methyl-4''-methylpentanoate]-4-methyl-5-phenylpyrrolidin-2-one 218d.

Second and third diastereoisomers

Clear colourless oil (520 mg, 1.21 mmol, 46%) from 4-{[(2*E*)-3-phenylprop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121a** (750 mg, 2.64 mmol) and methyl (2*R*)-2-amino-4-methylpentanoate (1.40 g, 9.66 mmol) dissolved in dry toluene (20 ml) and heated in a sealed tube to 170ºC for 26h. Molecular formula $C_{25}H_{35}NO_5$. R_f 0.48 (diethyl ether: hexane, 1:1, v:v).



Mixture of at least two diasteroisomers. Not possible to intepret NMR spectra.

IR (film, KBr); ν(cm^{-1}) = 3356 (s) [ν (OH)], 3065 (w), 3032 (m), 2932 (s), 2868 (s), 1744 (s) [ν (C=O)], 1716 (s), 1666 (s), 1434 (s), 1370 (m), 1328 (s), 1242 (s), 1173 (s), 1126 (m), 1037 (m), 992 (s), 914 (w), 762 (m), 702 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) =

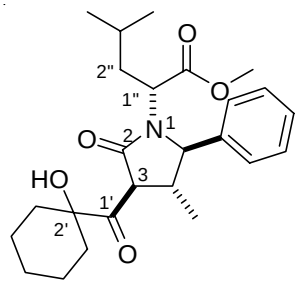
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) =

MS (EI, 70 eV): m/z = 430 (0.3) [M^++1], 429 (0.1) [M^+], 414 (0.9) [M^+-CH_3], 398 (0.8) [M^+-OCH_3], 370 (2.5) [M^+-CO_2-CH_3], 304 (29), 303 (100) [M^+-$C_6H_{10}COO$], 288 (28) [*303* - CH_3], 244 (11) [*288* - CO_2], 234 (7) [*288* - C_4H_8], 228 (13) [*244* - H_2O], 174 (7) [$C_5H_7NOPh^+$], 131 (3), 106 (3), 91 (6), (55), 54 (2), 43 (3).

(3S, 4R, 5R)-3-[(2'-Hydroxycyclohexyl)carbonyl]-1-[methyl-4''-methylpentanoate]-4-methyl-5-phenylpyrrolidin-2-one 218d-α.

Fourth diastereoisomer:

Clear colourless oil (410 mg, 0.96 mmol, 36%) from 4-{[(2*E*)-3-phenylprop-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121a** (750 mg, 2.64 mmol) and methyl (2*R*)-2-amino-4-methylpentanoate (1.40 g, 9.66 mmol) dissolved in dry toluene (20 ml) and heated in a sealed tube to 170°C for 26h. Molecular formula $C_{25}H_{35}NO_5$. R_f 0.42 (diethyl ether: hexane, 1:1, v:v).



α

IR (film, KBr); ν(cm^{-1}) = 3356 (s) [ν (OH)], 3065 (w), 3032 (m), 2932 (s), 2868 (s), 1744 (s) [ν (C=O)], 1716 (s), 1666 (s), 1434 (s), 1370 (m), 1328 (s), 1242 (s), 1173 (s), 1126 (m), 1037 (m), 992 (s), 914 (w), 762 (m), 702 (s).

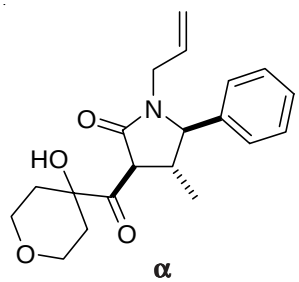
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.56 (d, $^3J_{HH}$ = 6.54 Hz, 3H, 3''-CH_3), 0.62 (d, $^3J_{HH}$ = 6.65 Hz, 3H, 3''-CH_3), 0.76 - 1.80 (m, 16H, 3'-CH_2, 4'-CH_2, 5'-CH_2, 6'-CH_2, 7'-CH_2, 2''-CH_2, 3''-CH, including a doublet at 0.92 ppm, $^3J_{HH}$ = 6.67 Hz, 4-CH_3), 2.95 (ddq, $^3J_{HH}$ = 10.31 Hz, 8.92 Hz, 6.67Hz, 1H, 4'-H), 3.54 (s, 3H, $COOCH_3$), 3.72 - 3.77 (m, 1H, 1''-H), 4.08 (d, $^3J_{HH}$ = 8.92 Hz, 1H, 5-H), 4.22 (d, $^3J_{HH}$ = 10.31 Hz, 1H, 3-H), 5.42 (d, $^4J_{HH}$ = 1.95 Hz, 1H, OH), 7.15 - 7.31 (m, 5H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 16.0 (CH_3, C-4), 20.6, 20.7 (CH_2, C-4' and C-6'), 21.7 (CH_3, C-3''), 22.2 (CH_3, C-3''), 24.7 (CH, C-3''), 25.2 (CH_2, C-5'), 33.7, 33.8 (CH_2, C-3', C-4'), 37.4 (CH, C-4), 37.8 (CH_2, C-2''), 52.1 (CH_3, $COOCH_3$), 54.5 (CH, C-1''), 58.3 (CH, C-3), 70.1 (CH, C-5), 79.1 (C^q, C-2'), 128.4, 128.8, 128.9, 129.0 (CH, Ph), 137.2 (C^q, Ph-*ipso*), 170.6 (C^q, CO_2), 173.3 (C^q, C-2), 210.1 (C^q, C-1').

MS (EI, 70 eV): m/z = 430 (0.4) [M^++1], 429 (0.2) [M^+], 414 (0.6) [M^+-CH_3], 398 (0.5) [M^+-OCH_3], 370 (5) [M^+-CO_2-CH_3], 304 (34), 303 (100) [M^+-$C_6H_{10}COO$], 288 (59) [*303* - CH_3], 244 (26) [*288* - CO_2], 234 (21) [*288* - C_4H_8], 228 (34) [*244* - H_2O], 174 (15) [$C_5H_7NOPh^+$], 159 (24), 131 (8), 106 (10), 91 (17), 86 (12), 54 (5), 41 (10).

(3*S*,4*R*,5*R*)-1-allyl-3-[(4-hydroxytetrahydro-2*H*-pyran-4-yl)carbonyl]-4-methyl-5-phenylpyrrolidin-2-one 218e-α.

White solid (317 mg, 0.92 mmol, 66%) from 4-{[(2E)-3-phenylprop-2-enyl]oxy}-1,8-dioxaspiro[4.5]dec-3-en-2-one **121h** (400 mg, 1.40 mmol) and allyl amine (800 mg, 14.03 mmol) dissolved in dry toluene (10 ml) and heated in a sealed tube to 170 °C for 16 h. Molecular formula $C_{20}H_{25}NO_4$. R_f 0.28 (ethyl acetate: hexane, 1:3, v:v), mp 81 - 85 °C.



α

IR (KBr); ν(cm^{-1}) = 3402 (br) [ν (OH)], 2961 (m), 2869 (m), 1717 (m), 1661 (s), 1415 (m), 1277 (m), 1240 (m), 1102 (m), 1026 (m), 934 (m).

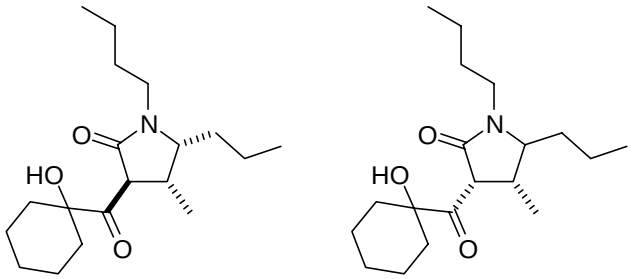
^{1}H-NMR (300 MHz, TMS$_{int}$, CDCl$_3$); δ (ppm) = 1.00 (d, $^{3}J_{HH}$ = 6.70 Hz, 3H, 4-CH$_3$), 1.45 - 1.59 and 2.12 - 2.24 (m, 4H, 3'-H and 7'-H), 2.86 (ddq, $^{3}J_{HH}$ = 10.06, 8.44, 6.74 Hz, 1H, 4-H), 3.05 (dd, $^{2}J_{HH}$ = 15.01 Hz, $^{3}J_{HH}$ = 7.57 Hz, 1H, NCH*H*), 3.76 - 3.92 (m, 4H, 4'-H and 6'-H), 4.11 (d, $^{3}J_{HH}$ = 8.44 Hz, 1H, 5-H), 4.18 (ddt, $^{2}J_{HH}$ = 15.01 Hz, $^{3}J_{HH}$ = 4.91 Hz, $^{4}J_{HH}$ = 1.55 Hz, 1H, NC*H*H), 4.21 (d, $^{3}J_{HH}$ = 10.04 Hz, 1H, 3-H), 4.89 (d, $^{3}J_{HH}$ = 17.07 Hz, 1H, CH=CH*H-trans*), 5.10 (d, $^{3}J_{HH}$ = 10.14 Hz, 1H, CH=C*H*H-*cis*), 5.51 - 5.64 (m, 1H, C*H*=CH$_2$), 6.00 (d, $^{4}J_{HH}$ = 2.31 Hz, OH), 7.18 - 7.38 (m, 5H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS$_{int}$, CDCl$_3$): δ (ppm) = 16.2 (CH$_3$, C-4), 34.0, 34.3 (CH$_2$, C-3' and C-7'), 37.8 (CH, C-4), 43.9 (CH$_2$, NCH$_2$), 58.6 (CH, C-3), 62.5, 62.9 (CH$_2$, C-4' and C-6'), 68.3 (CH, C-5), 76.5 (C^{q}, C-2'), 119.1 (CH$_2$, CH=*C*H$_2$), 127.5, 127.8, 128.0 (CH, Ph), 130.7 (CH, *C*H=CH), 137.7 (C^{q}, Ph-*ipso*), 171.7 (C^{q}, C-2), 208.5 (C^{q}, C-1').

MS (EI, 70 eV): m/z = 344 (4.2) [M^{+}+1], 343 (0.8) [M^{+}], 325 (0.6) [M^{+}-H$_2$O], 315 (4) [M^{+}-CO], 299 (2.2) [M^{+}-CO$_2$], 242 (6) [M^{+}-C$_5$H$_9$O$_2$], 216 (24), 215 (100) [M^{+}-C$_5$H$_8$OCOO], 201 (12), 200 (88) [*215* - CH$_3$], 174 (21), 131 (19), 117 (24), 106 (31), 91 (38), 71 (23), 69 (47), 53 (35), 41 (84).

5-Propyl-3-[(2'-hydroxycyclohexyl)carbonyl]-4-methyl-1-butylpyrrolidin-2-one 218f.

Clear oil (337 mg, 1.04 mmol, 54%) from 4-[(2E)-hex-2-enyloxy]-1-oxaspiro[4.5]dec-3-en-2-one **121p** (480 mg, 1.92 mmol) and butylamine (700 mg, 9.60 mmol) dissolved in dry toluene (6 m) heated to 165ºC for 16 h. Molecular formula C$_{19}$H$_{33}$NO$_3$. R$_f$ 0.64 (diethyl ether:hexane, 1:1, v:v).



α **β**

Mixture of diastereoisomers: Ratio α:β = 4:1.

IR (film, KBr); ν(cm^{-1}) = 3317 (m) [ν (OH)], 2931 (s), 2865 (m), 1713 (m), 1659 (s), 1443 (s), 1379 (m), 1319 (w), 1238 (m), 1111 (w), 1039 (w), 994 (m).

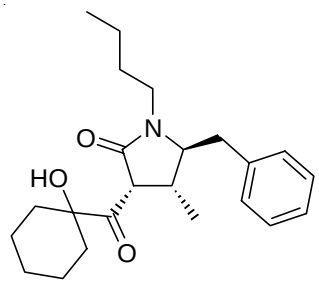
^{1}H-NMR (500 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.78 - 0.94 (m, 6H, 8-$H^{\alpha-\beta}$, N$(CH_2)_3CH_3^{\alpha-\beta}$), 1.00 (d, $^{3}J_{HH}$ = 6.86 Hz, 3H, 4-CH_3^{β}), 1.22 (d, $^{3}J_{HH}$ = 6.39 Hz, 3H, 4-CH_3^{α}), 1.04 - 1.85 (m, 18H, 3'-$H^{\alpha-\beta}$, 4'-$H^{\alpha-\beta}$, 5'-$H^{\alpha-\beta}$, 6'-$H^{\alpha-\beta}$, 7'-$H^{\alpha-\beta}$, 6-$H^{\alpha-\beta}$, 7$H^{\alpha-\beta}$, 2''-$H^{\alpha-\beta}$, 3''-$H^{\alpha-\beta}$), 2.43 - 2.47 (m, 1H, 4-H^{α}), 2.60 - 2.64 (s, 1H, 4-H^{β}), 2.79 - 2.85 (m, 1H, NC*H*H^{β}), 2.86 - 2.91 (m, 1H, NC*H*H^{α}), 3.07 - 3.12 (m, 1H, 5-H^{β}), 3.21 - 3.25 (p, $^{3}J_{HH}$ = 6.39 Hz, 1H, 5-H^{α}), 3.41 - 3.55 (m, 1H, NCH*H*$^{\alpha-\beta}$), 4.07 (d, $^{3}J_{HH}$ = 7.32 Hz, 1H, 3-H^{β}), 4.21 (d, $^{3}J_{HH}$ = 8.11 Hz, 1H, 3-H^{α}), 5.94 (s, 1H, OH^{α}), 5.97 (s, 1H, OH^{β}).

^{13}C-JMOD NMR (125.7 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 13.60 (CH_3, C-4''$^{\alpha-\beta}$), 14.02 (CH_3, C-8^{α}), 14.16 (C-8^{β}), 19.13 (CH_3, C-4^{α}), 19.39 (CH_3, 4-C-4^{β}), 20.02 (CH_2, C-3''$^{\alpha-\beta}$), 20.54 (CH_2, C-$7^{\alpha-\beta}$), 20.74, 20.76 (CH_2, C-4'$^{\alpha-\beta}$ and C-6'$^{\alpha-\beta}$), 25.34 (CH_2, C-5'$^{\alpha-\beta}$), 31.71 (CH, C-4^{β}), 33.87 (CH_2, C-2''$^{\alpha-\beta}$), 34.25, 34.33 (CH_2, C-3'$^{\alpha-\beta}$ and C-7'$^{\alpha-\beta}$), 36.08 (CH_2, C-$6^{\alpha-\beta}$), 39.68 (CH, C-4^{α}), 40.33 (NCH_2^{α}), 40.52 (NCH_2^{β}), 58.32 (CH, C-3^{α}), 59.44 (CH, C-5^{α}), 63.59 (CH, C-3^{β}), 65.78 (CH, C-5^{β}), 79.14 (C^{q}, C-2'$^{\beta}$), 79.24 (C^{q}, C-2^{α}), 170.90 (C^{q}, C-$2^{\alpha-\beta}$), 210.81 (C^{q}, C-1'$^{\alpha-\beta}$).

MS (EI, 70 eV): m/z *Isomer 1* = 324 (0.5) [M^{+}+1], 323 (1) [M^{+}], 305 (0.2) [M^{+}-H_2O], 295 (1), 294 (3) [M^{+}-CO], 281 (2), 280 (5) [*294* - CH_3], 262 (1) [*280* - H_2O], 254 (3) [*280* - C_2H_2], 198 (7), 197 (74) [M^{+}-$C_7H_{10}O_2$], 182 (8) [*197* - CH_3], 155 (17), 154 (100) [*197* - C_3H_7], 113 (2), 99 (3) [$C_6H_{11}O^{+}$], 81 (3), 69 (2), 55 (7), 41 (3).
Isomer 2 = 324 (3) [M^{+}+1], 323 (1) [M^{+}], 296 (1), 295 (3) [M^{+}-CO], 280 (4) [*295* - CH_3], 198 (23), 197 (100) [M^{+}-$C_7H_{10}O_2$], 182 (54) [*197* - CH_3], 155 (81), 154 (100) [*197* - C_3H_7], 140 (3), 110 (8), 99 (7) [$C_6H_{11}O^{+}$], 98 (12), 81 (17), 69 (6), 55 (24), 41 (10), 29 (4).

$C_{19}H_{33}NO_3$ (323.47): Calculated C = 70.55%, H = 10.28%, N = 4.33%; found C = 70.58%, H = 10.23%, N = 4.29%.

5-Benzyl-3-[(1-hydroxycyclohexyl)carbonyl]-4-methyl-1-butylpyrrolidin-2-one 218g-β. Clear crystalline solid (249 mg, 0.67 mmol, 67%) from 4-{[(2E)-4-phenylbut-2-enyl]oxy}-1-oxaspiro[4.5]dec-3-en-2-one **121r** (290 mg, 0.97 mmol) and butylamine (360 mg, 4.93 mmol) in dry toluene (7 ml). Molecular formula $C_{23}H_{33}NO_3$. R_f 0.29 (diethyl ether:hexane, 1:1, v:v) mp 148 °C. *NB Stereochemistry between 3-H and 4-H was identified using the coupling constants. The trans relationship between 4-H and 5-H is an assumption based on the observation that in most examples a trans relationship exists.*



β

IR (KBr); ν(cm^{-1}) = 3418 (m) [ν (OH)], 3025 (w), 2934 (s), 2864 (m), 1697 (s), 1639 (s), 1493 (w), 1446 (m), 1387 (s), 1338 (m), 1262 (s), 1232 (m), 1098 (m), 1031 (w), 994 (w), 854 (w), 807 (w), 786 (m), 749 (m), 718 (w), 692 (m), 619 (m).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.86 (t, $^{3}J_{HH}$ = 7.29 Hz, 3H, 4''-CH_3), 0.93 - 1.63 (m, 14H, 3'-H, 4'-H, 5'-H, 6'-H, 7'-H, 6'-H, 3''-H), 1.11 (d, $^{3}J_{HH}$ = 6.27 Hz,

3H, 4-CH_3), 2.46 - 2.54 (m, 1H, 6-C*H*H), 2.74 - 2.90 (m, 3H, 6-CH*H*, NC*H*H, 1'-CH), 3.30 - 3.48 (m, 2H, NCH*H*, 5-CH), 4.24 (d, $^3J_{HH}$ = 7.55 Hz, 1H, 3-H), 5.79 (d, $^4J_{HH}$ = 2.11 Hz, 1H, OH), 7.05 - 7.22 (m, 5H, Ph).

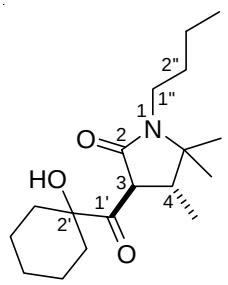
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 13.6 (CH_3, C-4''), 19.1 (CH_3, C-4), 20.0 (CH_2, C-3''), 20.7, 20.8 (CH_2, C-4' and C-6'), 25.26 (CH_2, C-5'), 29.1 (CH_2, C-2''), 33.6, 34.3 (CH_2, C-3' and C-7'), 39.5 (CH_2, C-6), 40.4 (CH_2, $NHCH_2$), 41.2 (CH, C-4), 56.7 (CH, C-3), 57.9 (CH, C-5), 79.1 (C^q, C-2'), 126.6 (CH, Ph-*para*), 128.6 (CH, Ph-*meta*), 129.1 (CH, Ph-*ortho*), 138.1 (C^q, C-*ipso*), 170.5 (C^q, C-2), 210.2 (C^q, C-1').

MS (EI, 70 eV): m/z = 371 (0.2) [M^+], 353 (0.5) [M^+-H_2O], 343 (1) [M^+-CO], 328 (2) [M^+-C_3H_7], 245 (64) [M^+-$C_7H_{10}O_2$], 155 (46), 154 (100) [*245* - C_7H_7], 110 (9) [$C_7H_{10}O^+$], 99 (14) [$C_6H_{11}O^{+]}$, 91 (17), 55 (8), 41 (3).

$C_{23}H_{33}NO_3$ (371.51): Calculated C = 74.36%, H = 8.95%, N = 3.77; found C = 74.38% , H = 9.02%, N = 3.74%.

1-Butyl-3-[(2'-hydroxycyclohexyl)carbonyl]-4,5,5-trimethylpyrrolidin-2-one 218h.

White crystalline solid (257 mg, 0.92 mmol, 67%) from 4-(3-Methyl-but-2-enyloxy)-1-oxa-spiro[4.5]dec-3-en-2-one **121m** (280 mg, 1.19 mmol) and n-butylamine (480 mg, 6.58 mmol) dissolved in dry toluene (30 ml). The mixture was heated to150 °C for 24 hr under an Argon atmosphere in a sealed bomb tube. Molecular formula $C_{18}H_{31}NO_3$. R_f 0.42 (ethyl acetate), mp 77 °C.



IR (KBr); ν(cm^{-1}) = 3423 (m) [ν (OH)], 2937 (s), 2861 (m), 1713 (w), 1644, 1422 (m), 1378 (w), 1263 (w), 1097 (w), 1026 (w), 806 (w).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.88 (d, $^3J_{HH}$ = 6.87 Hz, 3H, 4-CH_3), 0.89 (t, $^3J_{HH}$ = 7.23 Hz, 3H, 4''-CH_3), 1.03 (s, 3H, $C(CH_3)_2$), 1.26 (s, 3H, $C(CH_3)_2$), 1.19 - 1.81 (m, 14H, 3'-H, 4'-H, 5'-H, 6'-H, 7'-H, 2''-H, 3''-H), 2.57 (dq, $^3J_{HH}$ = 11.45 Hz, 6.87 Hz, 1H, 4-H), 2.92 (ddd, $^2J_{HH}$ = 13.76 Hz, $^3J_{HH}$ = 9.96 Hz, 5.75 Hz, 1H, NC*H*H), 3.22 (ddd, $^2J_{HH}$ = 13.76 Hz, $^3J_{HH}$ = 9.96 Hz, 5.85 Hz, 1H, NCH*H*), 4.05 (d, $^3J_{HH}$ = 11.45, 1H, 3-H), 5.84 (d, J_{HH} = 2.12 Hz, 1H, OH).

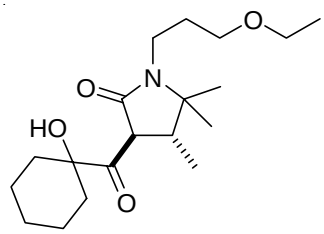
^{13}C-NMR-JMOD(68 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 12.5 (CH_3, C-3''), 13.7 (CH_3, C-4), 20.5, 20.7, 20.8 (CH_2, C-4' and C-6', C-3''), 21.1 (CH_3, C-5(CH_3)$_2$), 25.4 (CH_2, C-5'), 26.1 (CH_3, C-5(CH_3)$_2$), 31.6 (CH_2, C-2''), 33.8, 33.9 (CH_2, C-3' and C-7'), 39.3 (CH, C-4), 40.4 (CH_2, NCH_2), 56.7 (CH, C-3), 62.6 (C^q, $C(CH_3)_2$), 79.0 (C^q, C-2'), 171.1 (C^q, C-2), 211.09 (C^q, C-1').

MS (EI, 70 eV): m/z = 310 (1) [M^++1], 309 (1) [M^+], 294 (1) [M^+-CH_3], 281 (4) [M^+-CHO], 266 (2) [M^+-CO_2], 238 (1) [M^+-$C_4H_{10}N$], 184 (20), 183 (100) [M^+- $C_8H_{17}N$], 169 (18), 168 (99) [M^+-$C_9H_{20}N$], 140 (8), 111 (5), 81 (4), 69 (9), 55 (8), 41 (4).

$C_{18}H_{31}NO_3$ (309.44): Calculated C = 69.86%, H = 10.10%, N = 4.53%; found C = 70.02%, H = 10.06%, N = 4.50%.

(3*S*,4*R*)-1-(3-ethoxypropyl)-3-[(2'-hydroxycyclohexyl)carbonyl]-4,5,5-trimethylpyrrolidin-2-one 218i.

Colourless oil (1.21 g, 3.57 mmol, 84%) from 4-[(3-methylbut-2-enyl)oxy]-1-oxaspiro[4.5]dec-3-en-2-one **121m** (1.00 g, 4.24 mmol) and 3-ethoxypropan-1-amine (2.18 g, 21.2 mmol) dissolved in dry Toluene (15 ml) and heated to 170°C for 24h. Molecular formula $C_{19}H_{33}NO_4$. R_f 0.27 (diethyl ether: hexane, 1:1, v:v), mp 54°C



IR (KBr); ν(cm^{-1}) = 3307 (s) [ν (OH)], 2932 (s), 2859 (s), 1714 (s), 1445 (s), 1418 (s), 1374 (s), 1267 (s), 1194 (s), 1117 (s), 1038 (m), 1013 (m), 993 (s), 956 (w), 866 (w), 808 (w), 686 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.88 (d, $^3J_{HH}$ = 6.88 Hz, 3H, 4-CH_3), 1.02 (s, 3H, 5-CH_3), 1.14 (t, $^3J_{HH}$ = 7.02 Hz, 3H, OCH_2CH_3), 1.26 (s, 3H, 5-CH_3), 1.36 - 1.82 (m, 10H, 3'-H, 4'-H, 5'-H, 6'-H, 7'-H), 2.56 (dq, $^3J_{HH}$ = 11.44, 6.88 Hz, 1H, 4-H), 3.01 - 3.11 (m, 1H, NC*H*H), 3.24 - 3.34 (m, 1H, NCH*H*), 3.35 - 3.44 (m, 4H, CH_2OCH_2), 4.04 (d, $^3J_{HH}$ = 11.43 Hz, 1H, 3-H), 5.80 (d, $^4J_{HH}$ = 2.13 Hz, 1H, OH).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 12.74 (CH_3, C-4), 15.3 (CH_3, OCH_2CH_3), 20.9, 21.0 (CH_2, C-4' and C-6'), 21.1 (CH_3, C-5), 25.6 (CH_2, C-5'), 26.2 (CH_3, C-5), 29.7 (CH_2, $NCCH_2$), 34.0, 34.1 (CH_2, C-3' and C-7'), 38.3 (CH_2, NCH_2), 39.5 (CH, C-4), 56.9 (CH, C-3), 63.0 (C^q, C-5), 66.4 (CH_2, OCH_2), 68.2 (CH_2, OCH_2), 79.2 (C^q, C-2'), 171.55 (C^q, C-1), 211.18 (C^q, C-1').

MS (EI, 70 eV): m/z = 340 (2.4) [M^++1], 339 (0.05) [M^+], 324 (1) [M^+-CH_3], 310 (1) [M^+-CH_2CH_3], 294 (4.4) [M^+-OCH_2CH_3], 276 (0.7) [*294* - H_2O], 267 (1), 266 (1.1), 250 (2) [*294* - CO_2], 248 (1.2), 214 (32), 213 (100) [M^+-C_6H_{10} - CO_2], 199 (17), 198 (67) [*213* - CH_3], 152 (44) [*198* - OCH_2CH_3], 144 (5), 140 (4), 124 (21), 111 (11), 96 (3), 81 (16), 69 (13), 55 (18), 41 (25).

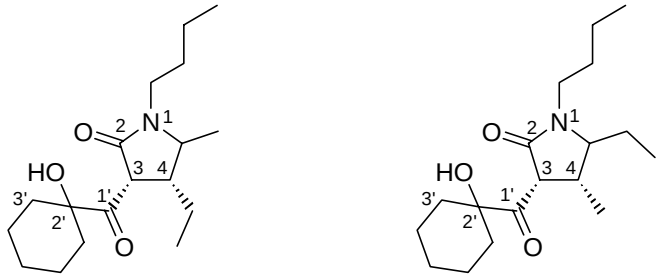
$C_{19}H_{33}NO_4$ (339.47): Calculated C = 67.22%, H = 9.80%, N = 4.13%; found C = 67.26%, H = 9.89%, N = 4.17%.

GC retention time = 51.9 min

5-Ethyl-3-[(1-hydroxycyclohexyl)carbonyl]-4-methyl-1-butylpyrrolidin-2-one and 4-ethyl-3-[(1-hydroxycyclohexyl)carbonyl]-5-methyl-1-butylpyrrolidin-2-one 221.

Diasteroisomer mixture 1:

Colourless oil (522 mg, 0.52 mmol, 52%) from 4-[(2*E*)-pent-2-enyloxy]-1-oxaspiro[4.5]dec-3-en-2-one (770 mg, 3.26 mmol) and n-butylamine (1.19 g, 16.31 mmol) dissolved in dry Toluene (7 ml) and heated to 170°C for 24 h. R_f 0.73 (diethyl ether:hexane, 1:1, v:v).



α β

Diasteroisomer 1:Mixture of diastereoisomers: Ratio α:β = 2.3:1

IR (film, KBr); ν(cm^{-1}) = 3306 (s) ν (OH)], 2932 (s), 2860 (s), 1715 (s), 1660 (s), 1446 (s), 1380 (m), 1310 (w), 1264 (m), 1236 (s), 1173 (w), 1135 (w), 1111 (w), 1039 (m), 993 (s), 918 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.80 (t, $^{3}J_{HH}$ = 7.43 Hz, 3H, 4-$CH_2C\mathit{H}_3^{\alpha}$), 0.86 - 0.93 (m, 6H, 5-$CH_2C\mathit{H}_3^{\beta}$, $N(CH_2)_3C\mathit{H}_3^{\alpha-\beta}$), 1.02 (d, $^{3}J_{HH}$ = 6.87 Hz, 3H, 4-CH_3^{β}), 1.25 (d, $^{3}J_{HH}$ = 6.26 Hz, 3H, 5-CH_3^{α}), 1.20 - 1.74 (m, 16H, 3'-$H^{\alpha-\beta}$, 4'-$H^{\alpha-\beta}$, 5'-$H^{\alpha-\beta}$, 6-$H^{\alpha-\beta}$, 7-$H^{\alpha-\beta}$, 4-CH_2^{α}, 5-CH_2^{β}, $NCC\mathit{H}_2C\mathit{H}_2^{\alpha-\beta}$), 2.37 - 2.46 (m, 1H, 4-H^{α}), 2.62 - 2.69 (m, 1H, 4-H^{β}), 2.78 - 2.95 (m, 1H, $NCH\mathit{H}^{\alpha-\beta}$), 3.08 - 3.14 (m, 1H, 5-H^{β}), 3.22 - 3.31 (m, 1H, 5-H^{α}), 3.43 - 3.61 (m, 1H, $NC\mathit{H}H^{\alpha-\beta}$), 4.10 (d, $^{3}J_{HH}$ = 7.59 Hz, 1H, 3-H^{β}-*cis*), 4.23 (d, $^{3}J_{HH}$ = 8.14 Hz, 1H, 3-H^{α}-*cis*), 5.95 (s-broad, 1H, $OH^{\alpha-\beta}$).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 8.48 (CH_3, 5-$CH_2C\mathit{H}_3^{\beta}$), 11.73 ($CH_3$, 4-$CH_2C\mathit{H}_3^{\alpha}$), 13.65 ($CH_3$, $N(CH_2)_3CH_3^{\alpha-\beta}$), 19.23, 19.28 ($CH_3$, 5-$CH_3^{\alpha}$, 4-$CH_3^{\beta}$), 20.05 ($CH_2$, $NCC\mathit{H}_2^{\alpha-\beta}$), 20.71, 20.75 ($CH_2$, 4'-$CH_2^{\alpha-\beta}$ and 6'-$CH_2^{\alpha-\beta}$), 24.28 (CH_2, 5-CH_2^{β}), 25.36 (CH_2, C-5'$^{\alpha-\beta}$), 26.39 (CH_2, C-4$^{\alpha}$), 29.02, 29.13 (CH_2, $NC\mathit{H}_2^{\alpha-\beta}$), 30.93 (CH, C-4$^{\beta}$), 33.90, 34.26, 34.29, 34.39 (CH_2, C-3'$^{\alpha-\beta}$ and C-7'$^{\alpha-\beta}$), 40.36, 40.52 (CH_2, $NCH_2^{\alpha-\beta}$), 41.40 (CH, C-4$^{\alpha}$), 56.96 (CH, C-3$^{\alpha}$), 58.03 (CH, C-5$^{\alpha}$), 59.37 (CH, C-3$^{\beta}$), 64.48 (CH, C-5$^{\beta}$), 79.15, 79.28 (C^{q}, C-2'$^{\alpha-\beta}$), 170.90, 171.04 (C^{q}, C-2$^{\alpha-\beta}$), 210.60, 210.90 (C^{q}, C-1'$^{\alpha-\beta}$).

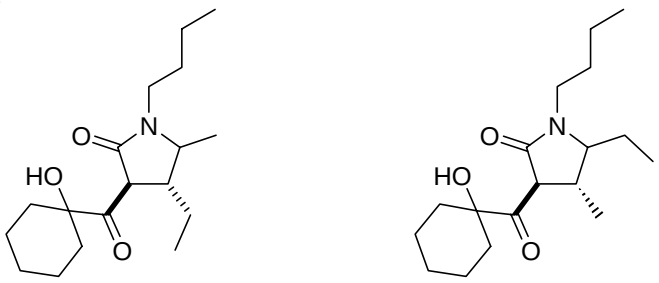
MS (EI, 70 eV): m/z = 310 (0.4) [M^{+}+1], 309 (0.05) [M^{+}], 281 (12) [M^{+}-CO], 266 (11) [M^{+}-C_3H_7], 210 (2), 183 (68) [M^{+}-$C_6H_{10}COO$], 168 (16) [*183* - CH_3], 154 (100) [*183* - C_2H_5], 98 (3), 81 (4), 69 (3), 55 (5), 41 (4), 32 (8).

Accurate Mass:- Calculated Mass = 309.23039 Found = 309.23031

5-ethyl-3-[(1-hydroxycyclohexyl)carbonyl]-4-methyl-1-butylpyrrolidin-2-one and 4-ethyl-3-[(1-hydroxycyclohexyl)carbonyl]-5-methyl-1-butylpyrrolidin-2-one 220.

Diasteroisomer mixture 2:

Colourless oil (407 mg, 1.32 mmol, 40%) from 4-[(2*E*)-pent-2-enyloxy]-1-oxaspiro[4.5]dec-3-en-2-one (770 mg, 3.26 mmol) and n-butylamine (1.19 g, 16.31 mmol) dissolved in dry Toluene (7 ml) and heated to 170^{o}C for 24 h. Molecular formula $C_{18}H_{31}NO_3$. R_f 0.67 and 0.64 (diethyl ether:hexane, 1:1, v:v).



α β

Diasteroisomer 2:Mixture of diastereoisomers: Ratio α:β = 2.4:1.

IR (film, KBr); ν(cm^{-1}) = 3311 (br) [ν (OH)], 2932 (s), 2861 (m), 1715 (s), 1660 (s), 1448 (s), 1381 (w), 1354 (w), 1264 (m), 1172 (w), 1134 (w), 1109 (w), 1038 (w), 992 (m), 971 (w).

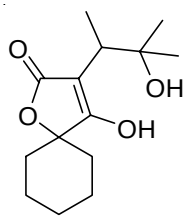
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.83 (t, $^{3}J_{HH}$ = 7.43 Hz, 3H, 4-CH_2CH3^{α}), 0.87 - 0.90 (m, 6H, 5-$CH_2CH_3^{\beta}$, $N(CH_2)_3CH_3^{\alpha-\beta}$), 0.94 (d, $^{3}J_{HH}$ = 7.14 Hz, 3H, 4-CH_3^{β}), 1.07 (d, $^{3}J_{HH}$ = 6.57 Hz, 3H, 5-CH_3^{α}), 1.23 - 1.67 (m, 16H, 3'-$H^{\alpha-\beta}$, 4'-$H^{\alpha-\beta}$, 5'-$H^{\alpha-\beta}$, 6-$H^{\alpha-\beta}$, 7-$H^{\alpha-\beta}$, 4-CH_2^{α}, 5-CH_2^{β}, 4-CH_2^{α}, $NCCH_2CH_2^{\alpha-\beta}$), 2.78 - 2.90 (m, 2H, 4-H^{α} 4-H^{β}), 2.91 - 3.00 (m, 1H, NCH_2^{β}), 3.19 - 3.30 (m, 1H, 5-H^{β}), 3.49 - 3.61 (m, 1H, NCH_2^{α}), 3.68 - 3.75 (m, 1H, 5-H^{α}), 4.11 (d, $^{3}J_{HH}$ = 9.37 Hz, 1H, 3-H^{β}-*trans*), 4.19 (d, $^{3}J_{HH}$ = 10.51 Hz, 1H, 3-H^{α}-*trans*), 5.72 (d, $^{4}J_{HH}$ = 2.15 Hz, 1H, OH^{α}), 5.76 (d, $^{4}J_{HH}$ = 2.06 Hz, 1H, OH^{β}).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 9.86 (CH_3, 5-$CH_2CH_3^{\beta}$), 12.28 (CH_3, 4-$CH_2CH_3^{\alpha}$), 13.66, 13.88 (CH_3, $N(CH_2)_3CH_3^{\alpha-\beta}$), 19.24, 19.28 ($CH_3$, 5-$CH_3^{\alpha}$, 4-$CH_3^{\beta}$), 20.03 ($CH_2$, $NCCCH_2^{\alpha-\beta}$), 20.73, 20.81 (CH_2, C-4'$^{\alpha-\beta}$ and C-6'$^{\alpha-\beta}$), 21.90 (CH_2, C-5$^{\beta}$), 25.29 (CH_2, C-5'$^{\alpha-\beta}$), 26.40 (CH_2, C-4$^{\alpha}$), 29.24, 29.38 (CH_2, $NCCH_2^{\alpha-\beta}$), 31.42 (CH, C-4H$^{\beta}$), 33.83, 33.99, 34.18, 34.27 (CH_2, C-3'$^{\alpha-\beta}$ and C-7'$^{\alpha-\beta}$), 38.31 (CH, C-4$^{\alpha}$), 40.74, 41.00 (CH_2, $NCH_2^{\alpha-\beta}$), 54.96 (CH, C-3$^{\alpha}$), 55.19 (CH, C-5$^{\alpha}$), 58.27 (CH, CH-3$^{\beta}$), 60.33 (CH, CH-5$^{\beta}$), 79.12, 79.28 (C^{q}, C-2'$^{\alpha-\beta}$), 171.09, 171.44 (C^{q}, C-2$^{\alpha-\beta}$), 210.87, 211.08 (C^{q}, C-1'$^{\alpha-\beta}$).

MS (EI, 70 eV): m/z = 310 (2) [M^{+}+1], 309 (0.2) [M^{+}], 281 (1) [M^{+}-CO], 266 (3) [M^{+}-C_3H_7], 210 (1), 184 (16), 183 (100) [M^{+}-$C_6H_{10}COO$], 168 (27) [*183* - CH_3], 154 (100) [*183* - C_2H_5], 140 (11), 110 (8), 98 (8), 81 (17), 69 (4), 55 (21), 41 (18).

4-Hydroxy-3-(2-hydroxy-1,2-dimethylpropyl)-1-oxaspiro[4.5]dec-3-en-2-one 222.

White crystalline solid (378 mg, 1.37 mmol, 82%) from 4-[(3-methylbut-2-enyl)oxy]-1-oxaspiro[4.5]dec-3-en-2-one **121m** (430 mg, 1.82 mmol) and *N*,*N*-dimethylamine (0.81 g, 18.4 mmol) dissolved in toluene (8 ml) and heated to 175ºC for 28h. Molecular formula $C_{14}H_{22}O_4$. R_f 0.27 (diethyl ether: hexane, 1:1, v:v), mp 160 ºC.



IR (KBr); ν(cm^{-1}) = 3229 (s) [ν (OH)], 2979 (s), 2943 (s), 2864 (w), 2600 (br) [ν (OH-H)], 1709 (s), 1655 (s), 1502 (w), 1451 (m), 1386 (s), 1323 (m), 1271 (m), 1232 (m), 1196 (w), 1078 (m), 1030 (s), 972 (s), 912 (m), 856 (m), 787 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.12 (d, $^{3}J_{HH}$ = 7.02 Hz, 3H, 1'-CH_3), 1.43 (s, 3H, $C^{q}(CH_3)_2$), 1.51 (s, 3H, $C^{q}(CH_3)_2$), 1.34 - 1.80 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.91 (q, $^{3}J_{HH}$ = 7.02 Hz, 1H, 1'-H), 11.00 (s, 2H, 2xOH).

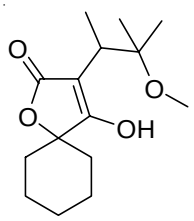
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 14.5 (CH_3, C-1'), 21.7, 21.9 (CH_2, C-7 and C-9), 24.5 (CH_2, C-8), 27.7, 28.7 (CH_3, $C^{q}(CH_3)_2$), 32.6, 33.2 (CH_2, C-6 and C-10), 39.1 (CH, C-1'), 74.7 (C^{q}, 1'-C^{q}), 82.5 (C^{q}, C-5-*spiro*), 101.3 (C^{q}, C-3), 175.4 (C^{q}, C-2), 178.8 (C^{q}, C-4).

MS (EI, 70 eV): m/z = 254 (1.2) [M^{+}], 239 (3) [M^{+}-CH_3], 236 (23) [M^{+}-H_2O), 221 (26) [*236* - CH_3], 218 (34) [*236* - H_2O], 203 (56) [*218* - CH_3], 196 (100) [M^{+}-C_3H_6O], 178 (37) [*196* - H_2O], 175 (39) [*203* - C_2H_4], 163 (17), 153 (19), 136 (27), 128 (50), 110 (57) [*128* - H_2O, $C_7H_{10}O^{+}$], 109 (52), 99 (24) [$C_6H_{10}OH^{+}$], 95 (97), 81 (36), 70 (40), 67 (36), 59 (41), 55 (34), 43 (19)

$C_{14}H_{22}O_4$ (254.32): Calculated C = 66.12%, H = 8.72%; found C = 66.09%, H = 8.74%.

4-Hydroxy-3-(2'-methoxy-1',2'-dimethylpropyl)-1-oxaspiro[4.5]dec-3-en-2-one 223a.

White solid (349 mg, 1.30 mmol, 88%) from 4-[(3-methylbut-2-enyl)oxy]-1-oxaspiro[4.5]dec-3-en-2-one **121m** (350 mg, 1.48 mmol) and methanol (474 mg, 14.8 mmol) dissolved in dry toluene (6 ml) and heated to 170°C for 16 hr. Molecular formular $C_{15}H_{24}O_4$. R_f 0.24 (diethyl ether:hexane, 1:1, v:v), mp 82 °C.



IR (KBr); ν(cm^{-1}) = 2937 (s), 2861 (w), 2708 (w) [ν (OH-O)], 1745 (s) [ν (C=O)], and 1661 (s), 1493 (w), 1454 (m), 1372 (s), 1316 (m), 1271 (m), 1226 (m), 1158 (w), 1081 (w), 1047 (s), 1019 (s), 965 (m), 838 (m), 781 (w), 725 (w).

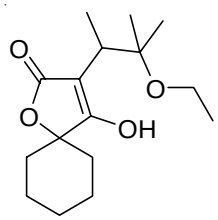
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.83 - 1.75 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 1.11 (d, $^{3}J_{HH}$ = 7.16 Hz, 3H, 1'-CH_3), 1.17 (s, 3H, 2'-CH_3), 1.33 (s, 3H, 2'-CH_3), 2.56 (q, $^{3}J_{HH}$ = 7.16 Hz, 1H, 1'-H), 3.36 (s, 3H, OCH_3).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 14.1 (CH_3, C-1'), 21.8, 21.9 (CH_2, C-7 and C-9), 22.4 (CH_3, C-2'), 23.4 (CH_3, C-2'), 24.6 (CH_2, C-8), 33.3, 34.7 (CH_2, C-6 and C-10), 40.2 (CH, C-1'), 49.5 (CH_3, OCH_3), 79.6 (C^{q}, C-2'), 81.7 (C^{q}, C-5-*spiro*), 101.6 (C^{q}, C-3), 173.6 (C^{q}, C-2), 178.3 (C^{q}, C-4).

MS (EI, 70 eV): m/z = 269 (3) [M^{+}+1], 268 (10) [M^{+}], 253 (2) [M^{+}-CH_3], 236 (11) [M^{+}-CH_3OH], 221 (21) [*236* - CH_3], 219 (18), 203 (57) [*221* - H_2O], 196 (34), 190 (4), 175 (28), 153 (11), 137 (18), 109 (3), 95 (5), 73 (100), 41 (3).

Accurate Mass:- Calculated Mass = 268.16746 Found = 268.16742

4-Hydroxy-3-[-2'-ethoxy-1',2'-dimethylpropyl]-1-oxaspiro[4.5]dec-3-en-2-one 223b.
White solid (385 mg, 1.36 mmol, 92%) from 4-[(3-methylbut-2-enyl)oxy]-1-oxaspiro[4.5]dec-3-en-2-one **121m** (350 mg, 1.48 mmol) and ethanol (680 mg, 14.8 mmol) dissolved in toluene (10 ml). Molecular formula $C_{14}H_{20}O_3$. R_f 0.46 (diethyl ether:hexane, 1:1, v:v) mp 73 - 74°C.



IR (KBr); ν(cm^{-1}) = 3476 (w) [ν (OH)], 2980 (m), 2938 (s), 2864 (w), 2711 (w) [ν (OH-O)], 1752 (s) [ν (C=O)], 1662 (s), 1450 (m), 1373 (m), 1320 (m), 1269 (m), 1223 (m), 1168 (m), 1114 (w), 1050 (m), 1014 (m), 976 (m), 865 (m), 835 (m), 778 (w), 739 (w).

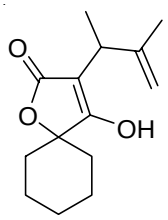
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.12 (d, $^3J_{HH}$ = 7.15 Hz, 3H, 1'-CH_3), 1.18 (s, 3H, 2'-CH_3), 1.29 (t, $^3J_{HH}$ = 7.02 Hz, 3H, CH_2CH_3), 1.33 (s, 3H, 2'-CH_3), 1.71 - 2.56 (m, 10H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.55 (q, $^3J_{HH}$ = 7.15 Hz, 1H, 1'-H), 3.51 - 3.68 (m, 2H, CH_2CH_3), 11.01 (s, 1H, OH).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 14.1 (CH_3, C-1'), 15.3 (CH_3, CH_2CH_3), 21.8, 21.9 (CH_2, C-7 and C-9), 23.2 (CH_3, 2'-CH_3) , 24.2 (CH_3, 2'-CH_3), 24.6 (CH_2, C-8), 32.6, 33.3 (CH_2, C-6 and C-10), 40.4 (CH, C-1'), 57.8 (CH_2, OCH_2), 79.3 (C^q, C-2'), 81.7 (C^q, C-5-*spiro*), 101.6 (C^q, C-3), 174.2 (C^q, C-2), 178.3 (C^q, C-4).

MS (EI, 70 eV): m/z = 283 (1) [M^++1], 282 (4) [M^+], 237 (2) [M^+-C_2H_5O], 219 (2), 218 (6), 203 (19), 175 (11), 137 (6), 109 (5), 99 (2) [$C_6H_{11}O^+$], 87 (100) [$C_5H_{11}O^+$], 81 (4), 59 (29), 41 (4).

Accurate Mass:- Calculated Mass = 282.18311 Found = 282.18312.

3-(1,2-dimethylprop-2-enyl)-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one 212a.
White solid (217 mg, 0.92 mmol, 62%) from 4-[(3-methylbut-2-enyl)oxy]-1-oxaspiro[4.5]dec-3-en-2-one **121m** (350 mg, 1.48 mmol) and propanol (0.89 g, 14.8 mmol) dissolved in dry toluene (6 ml). Solution heated to 165°C for 12h. Molecular formula $C_{14}H_{20}O_3$. R_f 0.25 (diethyl ether:hexane, 1:1, v:v), mp 132°C.



IR (KBr); ν(cm^{-1}) = 3413 (m) [ν (OH)], 3076 (m), 2937 (s), 2861 (w), 1703 (s), 1643 (s), 1447 (m), 1388 (s), 1335 (s), 1270 (s), 1150 (m), 1111 (w), 1048 (m), 960 (m), 886 (m), 823 (w), 794 (w), 735 (w), 621 (w), 536 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.26 (d, $^3J_{HH}$ = 7.14 Hz, 3H, 1'-CH_3), 1.20 - 1.81 (m, 13H, 6-H, 7-H, 8-H, 9-H, 10-H, including a singlet at 1.72, 3'-CH_3), 3.12

(q, $^3J_{HH}$ = 7.14 Hz, 1H, 1'-CH), 4.94 (s, 1H, C^q=C*H*H), 4.96 (s, 1H, C^q=CH*H*), 8.44 (s, 1H, OH).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 16.76 (CH_3, C^qCH_3), 21.7 (CH_2, C-7 and C-9), 22.1 (CH_3, 1'-CH_3), 24.3 (CH_2, C-8), 32.4 (CH_2, C-6 and C-10), 34.4 (CH, C-1'), 82.4 (C^q, C-5-*spiro*), 101.6 (C^q, C-3), 110.7 (CH_2, C^q=*C*H_2), 148.1 (C^q, *C*^{q}=CH_2), 174.0 (C^q, C-2), 178.5 (C^q, C-4).

MS (EI, 70 eV): m/z = 237 (17) [M^++1], 236 (79) [M^+], 221 (39) [M^+-CH_3], 219 (62) [M^+-OH], 203 (83) [M^+-H_2O-CH_3], 190 (20), 175 (36), 137 (32), 136 (26), 110 (100) [$C_7H_{10}O^+$], 95 (100) [*110* - CH_3], 81 (43) [*95* - CH_2], 69 (40), 67 (31), 41 (59).

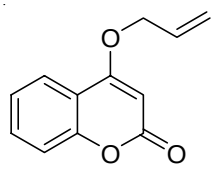
Accurate Mass:- Calculated Mass = 236.14125 Found = 236.14124.

3.6 O-Alkylation of 4-hydroxycoumarins

General experimental procedure for the O-alkylation of 4-hydroxycoumarins: The respective alcohol (10 mmol) was added to a mixture of copper (II) chloride (~1%) and N,N'-dicyclohexylcarbodiimide **137** (2.06 g, 10 mmol). The resulting brown liquid quickly turned green and was stirred at room temperature until the reaction was complete. Completion of reaction was determined by the disappearance of the diimide band (2100 cm^{-1}) and from the appearance of the very strong isourea band (1660 cm^{-1}) in the IR spectra. Reaction times vary from 6-24h. To the isourea was added a solution of 4-hydroxycoumarin (1.62 g, 10 mmol) in dry THF (100 ml). The resulting solution was stirred for 16h after which time the solution was filtered to remove the urea byproduct. The solvent was removed by rotary evaporation and the residue was transfered to a short plug of silica (~5 cm) and washed through with hexane (~200 ml) to remove excess urea and 4-hydroxycoumarin. The hexane was evaporated and the residue purified by column chromatography. Normally washing of the residue with hexane is required to obtain a completly pure product.[134-137]

4-(allyloxy)-2*H*-chromen-2-one 231a.

White solid (179 mg, 0.89 mmol, 44%) from 4-hydroxycoumarin **230** (324 mg, 2.0 mmol) and O-allyl-N,N'-dicyclohexylisourea (524 mg, 4.0 mmol) dissolved in dry THF (30 ml) and refluxed for 16h. Molecular formula $C_{12}H_{10}O_3$. R_f 0.25 (ethyl acetate: hexane, v:v, 1:1) mp 115°C (lit. 115°C[196].



IR (KBr); ν(cm^{-1}) = 3064 (w), 2927 (s), 2853 (m), 1740 (s), 1626 (m), 1565 (m), 1493 (w), 1452 (w), 1423 (m), 1406 (m), 1369 (m), 1328 (w), 1274 (w), 1240 (s), 1180 (m), 1144 (m), 1112 (m), 1093 (m), 1020 (w), 974 (m), 924 (s), 874 (w), 824 (m), 764 (m), 749 (m).

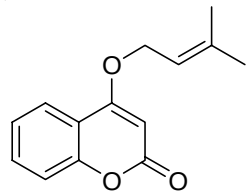
^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 4.70 (d, $^3J_{HH}$ = 5.44 Hz, 2H, OCH_2), 5.43 (d, $^3J_{HH}$ = 10.52 Hz, 1H, CH=CH*H-cis*), 5.52 (d, $^3J_{HH}$ = 17.26 Hz, 1H, CH=C*H*H-*trans*), 5.70 (s, 1H, 3-H), 6.03 - 6.16 (m, 1H, C*H*=CH_2), 7.26 - 7.33, 7.53 - 7.59 and 7.84 - 7.87 (m, 4H, Ph).

^{13}C-NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 69.8 (CH_2, OCH_2), 91.0 (CH, C-3), 115.7 (C^q, C-5), 116.8 (CH, C-9), 119.6 (CH_2, CH=*C*H_2), 123.1 (CH, C-6), 123.9 (CH, C-7), 130.7 (CH, C-8), 132.4 (CH, *C*H=CH_2), 153.4 (C^q, C-10), 162.8 (C^q, C-2), 165.2 (C^q, C-4).

MS (EI, 70 eV): m/z = 203 (5) [M^++1], 202 (75) [M^+], 187 (41) [M^+-CH_3], 139 (54), 121 (93) [*139* - H_2O], 120 (53), 98 (61), 96 (96), 83 (73), 82 (44), 55 (59), 41 (100), 39 (42), 28 (88).

4-[(3-methylbut-2-enyl)oxy]-2*H*-chromen-2-one 231b.

White needles (247 mg, 1.07 mmol, 43%) from 4-hydroxycoumarin **230** (405 mg, 2.50 mmol) added to O-(3,3-Dimethyl-allyl)-N,N'-dicyclohexylisourea (730 mg, 2.50 mmol) dissolved in dry THF (20 ml) and stirred for 5h at 50°C. Molecular formula $C_{14}H_{14}O_3$. R_f 0.52 (diethyl ether:hexane, 1:1, v:v), mp 74°C.



IR (KBr); ν(cm^{-1}) = 3081 (w), 2937 (m), 1725 (s), 1621 (s), 1563 (s), 1492 (m), 1460 (m), 1413 (m), 1401 (m), 1367 (m), 1273 (w), 1243 (s), 1188 (m), 1140 (m), 1104 (m), 926 (s), 764 (m), 752 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.78 (s, 3H, C(CH_3)-*cis*), 1.84 (s, 3H, C(CH_3)-*trans*), 4.68 (s, $^2J_{HH}$ = 6.81 Hz, 2H, OCH_2), 5.48 - 5.54 (m, 1H, CH=C^q), 5.68 (s, 1H, 3-H), 7.23 - 7.29 (m, 2H, 7-H, 9-H), 7.51 - 7.57 (m, 1H, 8-H), 7.84 (dd, $^3J_{HH}$ = 6.39 Hz, $^4J_{HH}$ = 1.51 Hz, 1H, 6-H).

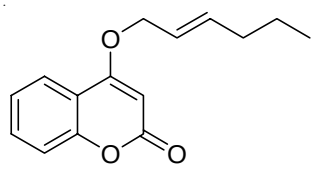
^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 18.4 (CH_3, C(CH_3)-*cis*), 25.8 (CH_3, C(CH_3)-*trans*), 66.2 (CH_2, OCH_2), 90.6 (C^q, C-3), 116.7 (CH, C-9), 117.4 (CH, C-7), 123.2 (CH, C-6), 123.8 (CH, C-8), 132.3 (CH, *C*H=C^q), 140.5 (CH_3, CH=*C*^{q}), 153.4 (C^q, C-10), 163.0 (C^q, C-2), 165.6 (C^q, C-4).

MS (EI, 70 eV): m/z = 231 (4) [MH^+], 230 (33) [M^+], 215 (100) [M^+-CH_3], 213 (21) [M^+-OH], 203 (4), 189 (4), 187 (13) [M^+-C_3H_7], 175 (12) [M^+-C_4H_7], 163 (13), 128 (12), 121 (74) [$C_8H_9O^+$], 77 (19) [$C_6H_5^+$], 71 (31), 69 (50), 67 (37), 65 (24), 53 (30), 41 (90).

$C_{14}H_{14}O_3$ (230.26): Calculated C = 73.03%, H = 6.13%; found C = 72.98%, H = 6.09%.

4-[(2*E*)-hex-2-enyloxy]-2*H*-chromen-2-one 231c.

White crystalline solid (0.54 g, 2.21 mmol, 73%) from 4-hydroxycoumarin **230** (0.49 g, 3 mmol) added to a solution of O-[(2E)-Hex-2-enyl]-N,N'-dicyclohexylisourea **139d** (1.53 g, 5.0 mmol) in dry THF (50 ml) and refluxed for 16 h. The urea was filtered and a column was made to remove the least polar compound. Evaporation of the solvent followed by washing with a very small amount of hexane followed by recrystallisation from hexane gave a pure product. R_f 0.95 (ethyl acetate: hexane, 1:1, v:v), mp 72 - 73°C.



IR (KBr); ν(cm^{-1}) = 3081 (w) [ν (CH=CH)], 2930 (s), 2870 (m), 1721 (s), 1625 (m), 1565 (m), 1492 (w), 1460 (m), 1415 (m), 1363 (m), 1329 (m), 1273 (m), 1248 (m), 1189 (m), 1140 (m), 1106 (m), 1029 (w), 973 (m), 930 (s), 846 (m), 766 (s), 751 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.94 (t, $^{3}J_{HH}$ = 7.35 Hz, 3H, CH_3), 1.47 (hex., $^{3}J_{HH}$ = 7.35 Hz, 2H, C*H*$_2$CH$_3$), 2.10 (quin., $^{3}J_{HH}$ = 7.35 Hz, 3H, CHC*H*$_2$), 4.63 (dd, $^{3}J_{HH}$ = 6.21 Hz, $^{4}J_{HH}$ = 0.60 Hz, 2H, OCH_2), 5.69 (s, 1H, 3-H), 5.70 - 5.77 (m, 1H, CH=C*H*), 5.94 (dt, $^{3}J_{HH}$ = 15.32 Hz, 6.21 Hz, 1H, C*H*=CH), 7.24 - 7.32 and 7.52 - 7.57 and 7.83 - 7.86 (m, 4H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 14.0 (CH_3, CH_2*C*H$_3$), 22.3 (CH_2, C*H*$_2$CH$_3$), 34.7 (CH_2, CH*C*H$_2$), 70.5 (CH_2, O*C*H$_2$), 91.1 (CH, C-3), 116.2 (C^{q}, C-5), 117.1 (CH, C-9), 122.9 (CH, *C*H=CH), 123.5 (CH, C-6), 124.2 (CH, C-7), 132.7 (CH, CH=*C*H), 153.7 (C^{q}, C-10), 163.4 (C^{q}, C-2), 165.8 (C^{q}, C-4).

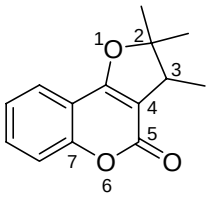
MS (EI, 70 eV): m/z = 244 (11) [M^{+}], 215 (6) [M^{+}-C_2H_5], 202 (24), 201 (24) [M^{+}-C_3H_7], 175 (12) [M^{+}-C_5H_9], 163 (81) [M^{+}-C_6H_9], 162 (21), 138 (4), 121 (26), 120 (44), 92 (19), 83 (42), 67 (22), 55 (100), 41 (69), 29 (22).

Accurate Mass:- Calculated Mass = 244.109945 Found = 244.10952.

3.7 Rearrangement of O-alkylated coumarins

2,2,3-Trimethyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one 233.

4-[(3-methylbut-2-enyl)oxy]-2H-chromen-2-one **231b** (100 mg, 0.43 mmol) was dissolved in dry acetonitrile (15 ml) and refluxed for 64h. The acetonitrile was removed by rotary evaporation and the residue was purified by column chromatography to give **233** as a white solid (78 mg, 0.34 mmol, 78%). Molecular formula $C_{14}H_{14}O_3$. *(See General Procedure for Claisen Rearrangements Section 3.3.6: **Method A**).*



IR (KBr); ν(cm^{-1}) = 2976 (m), 2928 (s), 1714 (s), 1612 (s), 1555 (s), 1443 (s), 1374 (m), 1260 (m), 1170 (w), 1102 (m), 953 (w), 890 (w), 801 (w), 758 (w), 703 (w).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.35 (d, $^{3}J_{HH}$ = 6.99 Hz, 3H, 3-CH_3), 1.50 and 1.56 (s, 6H, C^{q}(CH_3)$_2$), 3.32 (q, $^{3}J_{HH}$ = 6.99 Hz, 1H, 3-H), 7.27 - 7.44 and 8.20 - 8.50 (m, 4H, Ph).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 14.8 (CH_3, C-3), 23.0 and 29.1 (CH_3, 2-(CH_3)$_2$), 43.0 (CH, 3-CH), 94.4 (C^{q}, 2-C), 100.0 (C^{q}, C-4), 117.7 (C^{q}, C-8), 124.6 (C^{q}, C-12), 125.7 (CH, C-10), 126.1 (CH, C-11), 132.6 (CH, C-9), 153.7 (C^{q}, C-7), 167.7 (C^{q}, C-5), 175.8 (C^{q}, C-13).

MS (EI, 70 eV): m/z = 231 (13) [M^++1], 230 (74) [M^+], 216 (18), 215 (100) [M^+-CH_3], 187 (21) [M^+-C_2H_4], 175 (12), 158 (24), 156 (67), 141 (23), 139 (64), 136 (48), 121 (66), 111 (42), 92 (14), 75 (28), 65 (18), 50 (21), 39 (24), 28 (28).

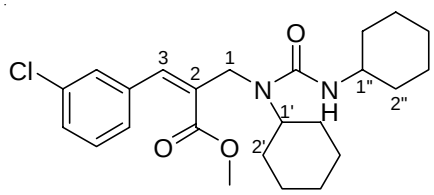
$C_{14}H_{14}O_3$ (230.26): Calculated C = 73.03%, H = 6.13%; found C = 72.99%, H = 6.08%.

3.8 Formation of rearranged Baylis-Hillman isoureas

See general experimental procedure for the O-alkylation of 4-hydroxycoumarins (Section 3.6).

Methyl(2*Z*)-3-(3-chlorophenyl)-2-({cyclohexyl[(cyclohexylamino) carbonyl]amino}methyl)acrylate 250a.

Clear crystalline solid (1.37 g, 3.58 mmol, 92%) from DCC (0.71 g, 3.44 mmol), methyl 2-[(3-chlorophenyl)(hydroxy)methyl]acrylate **248a** (0.81 g, 3.58 mmol) and copper (I) chloride (catalytic amount). The mixture was stirred for 17h followed by filtration over neutral alumina. The alumina was washed with hexane (100 ml). Molecular formula $C_{24}H_{33}ClN_2O_3$. R_f 0.42 (diethyl ether: hexane, 1:1, v:v), mp 106°C.



IR (KBr); ν(cm^{-1}) = 3339 (s) [ν (NH)], 3062 (w), 2930 (s), 2852 (s), 1703 (s), 1638 (s), 1534 (s), 1453 (m), 1360 (w), 1279 (m), 1249 (m), 1088 (m), 892 (m), 796 (m), 660 (w).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.69 - 1.88 (m, 20H, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 3.30 (tt, $^3J_{HH}$ = 11.76, 3.62 Hz, 1H, 1'-H), 3.42 - 3.54 (m, 1H, 1''-H), 3.76 (s, 3H, OCH_3), 4.18 (d, $^4J_{HH}$ = 0.60 Hz, 1H, 1-H), 5.50 (d, $^3J_{HH}$ = 7.14 Hz, 1H, NH), 7.07 - 7.47 (m, Ar, CH=C^q).

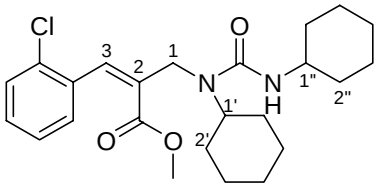
^{13}C-NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 24.9 (CH_2, C-3'' and C-5''), 25.5, 25.7 (CH_2, C-4' and C-4''), 26.2 (CH_2, C-3' and C-5'), 30.23 (CH_2, C-2' and C-6'), 33.6 (CH_2, C-2'' and C-6''), 41.4 (CH_2, C-1), 49.2 (CH_3, OCH_3), 52.3 (CH, C-1''), 56.6 (CH, C-1'), 127.0, 128.7, 128.9, 129.8 (CH, Ar), 134.0 (C^q, Ar-Cl), 134.5 (C^q, C-2), 136.3 (C^q, Ar-*ipso*), 138.0 (CH, C-3), 158.7 (C^q, NC(O)N), 168.5 (C^q, CO_2).

MS (EI, 70 eV): m/z = 435 (3) [M^++1, ^{37}Cl], 434 (14) [M^+, ^{37}Cl], 433 (9) [M^++1, ^{35}Cl], 432 (49) [M+, ^{35}Cl], 373 (18) [*432* - $COOCH_3$], 308 (52), 307 (47), 306 (100) [*432* - $C_6H_{11}NHCO$], 264 (41), 226 (27), 224 (84) [*306* - C_6H_{10}], 209 (7), 151 (8), 149 (17), 115 (12), 98 (34), 83 (8), 55 (34).

$C_{24}H_{33}ClN_2O_3$ (432.98): Calculated C = 66.57%, H = 7.68%, N = 6.47%; found C = 66.59%, H = 7.74%, N = 6.51%.

Methyl(2Z)-3-(2-chlorophenyl)-2-({cyclohexyl[(cyclohexylamino) carbonyl]amino}methyl)acrylate 250b.

Clear crystalline solid (1.34 g, 3.10 mmol, 70%) from DCC (0.91g, 4.42 mmole), methyl 2-[(2-chlorophenyl)(hydroxy)methyl]acrylate (1.00 g, 4.42 mmol) and copper (I) chloride (catalytic amount). The mixture was stirred for 17h followed by filtration over neutral alumina. The alumina was then washed with hexane (100 ml). Molecular formula $C_{24}H_{33}ClN_2O_3$. R_f 0.15 (diethyl ether: hexane, 1:3, v:v), mp 107°C.



IR (KBr); ν(cm^{-1}) = 3353 (w) [ν (NH)], 2931 (m), 2853 (m), 1703 (s), 1638 (s), 1588 (w), 1529 (s), 11451 (m), 1433 (m), 1371 (m), 1260 (m), 1157 (w), 1096 (w), 1055 (w), 944 (w), 894 (m), 761 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 0.79 - 1.87 (m, 20H, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 3.12 - 3.35 (m, 1H, 1'-H), 3.41 - 3.58 (m, 1H, 1''-H), 3.82 (s, 3H, OCH_3), 4.13 (d, $^4J_{HH}$ = 0.75, 1H, 1-H), 5.73 (d, $^3J_{HH}$ = 7.11 Hz, 1H, NH), 7.14 - 7.65 (m, Ph, CH=C^q).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 25.0 (CH_2, C-3'' and C-5''), 25.5, 25.8 (CH_2, C-4' and C-4''), 26.2 (CH_2, C-3' and C-5'), 30.2 (CH_2, C-2' and C-6'), 33.6 (CH_2, C-2'' and C-6''), 41.7 (CH_2, C-1), 49.3 (CH_3, OCH_3), 52.4 (CH, C-1''), 56.4 (CH, C-1'), 126.5, 129.7, 130.1, 130.7 (CH, Ar), 133.1 (C^q, Ar-Cl), 133.7 (C^q, C-2), 133.8 (C^q, Ar-*ipso*), 137.6 (CH, C-3), 158.8 (C^q, NC(O)N), 168.6 (C^q, CO_2).

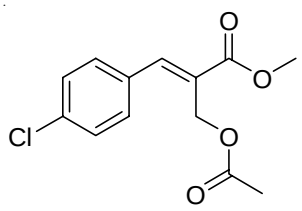
MS (EI, 70 eV): m/z = 435 (2) [M^++1, ^{37}Cl], 434 (6) [M^+, ^{37}Cl], 433 (3) [M^++1, ^{35}Cl], 432 (17) [M+, ^{35}Cl], 373 (17) [*432* - $COOCH_3$], 308 (38), 307 (34), 306 (100) [*432* - $C_6H_{11}NHCO$], 266 (20), 264 (57), 226 (27), 224 (82) [*306* - C_6H_{10}], 209 (18), 151 (13), 149 (27), 115 (26), 98 (55), 83 (13), 55 (49), 41 (31).

3.9 Investigations into the Baylis-Hillman alcohols

3.9.1 Rearrangement of methyl 2-[hydroxy(phenyl)methyl]acrylates 242 to methyl (2*E*)-2-(hydroxymethyl)-3-phenylacrylate 243

Methyl (2*E*)-2-[(acetyloxy)methyl]-3-(4-chlorophenyl)acrylate 254.[205]

To a stirred solution of the Baylis Hillman alcohol (0.226 g, 1 mmol) and acetic anhydride (0.113 ml, 1.2 mmol) in DCM (2 ml) was added TMSOTf (0.02 ml, 11 mole%) at room temperature. After 2h of stirring DCM was removed on a rotary evaporator. Methanol (2 ml) and potassium carbonate (0.414 g, 3.0 mmol) were added and the reaction mixture was stirred for a further 2h at room temperature. The solvent was removed by rotary evaporation, the residue dissolved in water and extracted with diethyl ether (3x 5ml). The combined organic layers were dried with sodium sulphate. The solvent was evaporated to give a crude mixture which was purified by column chromatography to give **254** as a colourless oil (219 mg, 0.82 mmol, 82%). Molecular formula $C_{13}H_{13}ClO_4$. R_f 0.26 (ethyl acetate: hexane, 1:3, v:v).

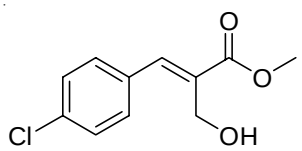


^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 2.08 (s, 3H, C(O)CH_3), 3.83 (s, 3H, $COOCH_3$), 4.90 (s, 2H, OCH_2), 7.20 - 7.39 (m, 4H, Ar), 7.89 (s, 1H, CH=C^{q}).

^{13}C-NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.0 (CH_3, *C*H_3C=O), 52.4 (CH_3, COO*C*H_3), 59.1 (CH_2, OCH_2), 127.2 (C^{q}, CH=*C*^{q}), 129.1, 130.7 (CH, Ar), 132.6 (C^{q}, Ar-Cl), 135.8 (C^{q}, Ar-*ipso*), 144.1 (CH, *C*H=C^{q}), 167.1 (C^{q}, *C*$OOCH_3$), 170.6 (C^{q}, CH_3*C*=O).

Methyl (2*E*)-2-[(acetyloxy)methyl]-3-phenylacrylate 255.

To a stirred solution of Methyl (2*E*)-2-[(acetyloxy)methyl]-3-(4-chlorophenyl)acrylate **254** (2.26 g, 10 mmol) and acetic anhydride (1.13 ml, 12 mmol) in DCM (20 ml) under a nitrogen atmosphere was slowly added TMSOTf (0.2 ml, 11 mole%) at room temperature. After stirring for 2h at room temperature the DCM solvent was removed on a rotary evaporator. Methanol (20 ml) and potassium carbonate (4.14 g, 30 mmol) were added and the reaction mixture was stirred for 24h at room temperature. The solvent was then removed by rotary evaporation and the residue was dissolved in water (30 ml) and extracted with diethyl ether (4x50ml). The combined organic layers were dried with sodium sulphate. Rotary evaporation of the etheral solvent followed by column chromatography of the residue gave a colourless oil **255** (1.62 g, 7.17 mmol, 72%). Molecular formula $C_{11}H_{11}ClO_3$. R_f 0.50 (ethyl acetate: hexane, 1:3, v:v).

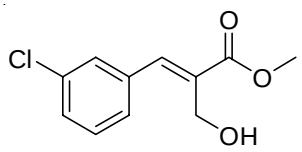


^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 2.56 (s, br., 1H, OH), 3.84 (s, 3H, $COOCH_3$), 4.42 (s, 2H, CH_2OH), 7.34 - 7.41 (m, 4H, Ar), 7.75 (s, 1H, CH=C^{q}).

^{13}C-NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 52.3 (CH_3, COO*C*H_3), 57.7 (CH_2, CH_2OH), 128.9, 129.1, 130.7, 130.9 (CH, Ar), 131.3 (C^{q}, CH=*C*^{q}), 132.9 (C^{q}, C-Cl), 135.4 (C^{q}, Ar-*ipso*), 141.4 (CH, CH=C^{q}), 168.2 (C^{q}, CO_2).

Methyl (2*E*)-3-(3-chlorophenyl)-2-(hydroxymethyl)acrylate 256.[203]

Methyl 2-[(3-chlorophenyl)(hydroxy)methyl]acrylate **248a** (2.26 g, 10.0 mmol) was dissolved in trifluoroacatic acid (10 ml) and refluxed for 24 h. The reaction mixture was poured into cold water and extracted with ether. The organic layers were washed with sodium carbonate solution followed by distilled water, dried with magnesium sulphate and evaporated to dryness. Column chromatography of the residue gave methyl (2E)-3-(3-chlorophenyl)-2-(hydroxymethyl)acrylate **256** as a colourless oil (1.60 g, 7.08 mmol, 71%). Molecular formula $C_{11}H_{11}ClO_3$. R_f 0.37 (ethyl acetate: hexane 1:9, v:v).



IR (film, KBr); ν(cm^{-1}) = 3510 (br) [ν (OH)], 3060 (w), 3002 (w), 2957 (m), 1789 (s), 1719 (s), 1638 (w), 1594 (w), 1565 (m), 1439 (m), 1364 (m), 1335 (m), 1290 (m), 1221 (s), 1149 (s), 1014 (m), 939 (m), 888 (w), 832 (w), 791 (s), 729 (w), 687 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.56 (br) [OH], 3.85 (s, 3H, OCH_3), 5.15 (s, 2H, C*H*$_2$OH), 7.24 - 7.39 (m, 4H, CH=C^{q}, Ar-4-H, Ar-5-H, Ar-6-H), 8.01 (s, 1H, Ar-2-H).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 52.7 (CH_3, OCH_3), 62.1 (CH_2, CH_2OH), 126.1 (C^{q}, CH=*C*^{q}), 127.1, 129.2, 130.1, 130.3 (CH, Ar), 135.1 (C^{q}, Ar-Cl), 135.4 (C^{q}, Ar-*ipso*), 145.9 (CH, *C*H=C^{q}), 166.0 (C^{q}, CO_2).

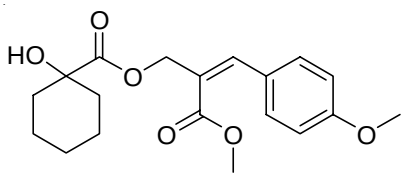
MS (EI, 70 eV): m/z = 228 (9) [M^{+}, ^{37}Cl], 226 (26) [M^{+}, ^{35}Cl], 212 (8) [*228* - H_2O], 210 (26) [*226* - H_2O], 197 (44), 193 (53), 167 (62), 165 (100), 159 (61), 151 (34), 149 (100), 140 (29), 138 (37), 131 (78), 115 (71), 103 (44), 75 (28), 59 (34).

$C_{11}H_{11}ClO_3$ (226.66): Calculated C = 58.29%, H = 4.89%; found C = 58.18%, H = 4.86%.

3.9.2 Esterification of methyl 2-[hydroxy(phenyl)methyl]acrylates 242 with α-hydroxycyclohexane carboxylic acid 133a.

(2*Z*)-2-(Methoxycarbonyl)-3-(4-methoxyphenyl)prop-2-enyl-1-hydroxycyclohexanecarboxylate 252b.

To a solution of methyl 2-[hydroxy(4-methoxyphenyl)methyl]acrylate **148b** (1.00 g, 4.5 mmol) and p-toluene sulfonic acid (80 mg, 0.45 mmol) dissolved in dry $CHCl_3$ was added α-hydroxycyclohexane carboxylic acid **133a** (0.65 g, 4.5 mmol). The round bottomed flask was connected to a Dean-Stark apparatus and refluxed for 16h. After cooling of the solution the solvent was removed and the residue was purified by column chromatography to give **252b** as a colourless liquid (1.38 g, 3.97 mmol, 88%). Molecular formula $C_{19}H_{24}O_6$. R_f 0.4 (ethyl acetate: hexane, 1:5, v:v).



IR (KBr); ν(cm^{-1}) = 3517 (m) [ν (OH)], 2937 (s), 2863 (m), 1715 (s), 1604 (s), 1512 (s), 1442 (s), 1383 (w), 1240 (s), 1179 (s), 1094 (s), 1034 (m), 840 (m), 753 (w).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.18 - 1.26 and 1.48 - 1.78 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H), 2.80 (s, 1H, OH), 3.76 and 3.78 (2xs, 6H, $COOCH_3$ and Ar-OCH_3), 4.23 (s, 2H, OCH_2), 6.87 (d, $^{3}J_{HH}$ = 8.85 Hz, 2H, Ar-*meta*), 7.47 (d, $^{3}J_{HH}$ = 8.85 Hz, 2H, Ar-*ortho*), 7.82 (s, 1H, C^{q}=CH).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.2 (CH_2, C-3 and C-5), 25.2 (CH_2, C-4), 34.7 (CH_2, C-2 and C-6), 52.1 (CH_3, COO*C*H_3), 55.3 (CH_3, PhOCH_3), 65.9 (CH_2, OCH_2), 73.4 (C^q, C-1), 114.0 (CH, Ar-*meta*), 126.5 (C^q, Ar-*ipso*), 127.4 (C^q, *C*^{q}=CH), 131.9 (CH, Ar-*ortho*), 144.6 (CH, C^q=*C*H), 160.7 (C^q, Ar-O), 168.5 (C^q, *C*OOCH$_3$), 177.4 (C^q, *C*OOCH$_2$).

MS (EI, 70 eV): m/z = 348 (0.5) [M^+], 222 (4), 221 (76) [M^+-$C_6H_{11}CO_2^+$], 205 (59) (M^+-$C_6H_{11}CO_3^+$], 189 (100), 173 (3), 161 (7), 145 (22), 131 (3), 103 (3), 81 (4).

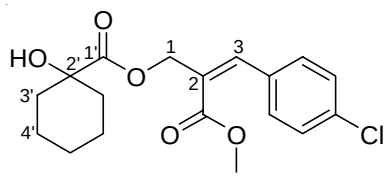
$C_{19}H_{24}O_6$ (348.39): Calculated C = 65.50%, H = 6.94%; found C = 65.47%, H = 6.90%.

(2*Z*)-3-(4-Chlorophenyl)-2-(methoxycarbonyl)prop-2-enyl-1-hydroxycyclohexanecarboxylate 252c.

Method A: Colourless oil (590 mg, 1.67 mmol, 81%) from from α-hydroxycyclohexane carboxylic acid **133a** (0.45 g, 3.12 mmol), triphenylphosphine (0.82 g, 3.12 mmol) and triethylamine (0.43 ml, 3.12 mmol) stirred in THF (20 ml) at -10°C, followed by the slow addition of DIAD (0.60 ml, 3.12 mmol). After 15 min, methyl 2-[(4-chlorophenyl)(hydroxy)methyl]acrylate **248c** (0.47 g, 2.08 mmol) was added slowly and the solution was allowed to warm to room temperature overnight. The THF solvent was removed on a rotary evaporator and the residue was purified by column chromatography.

Method B: DCC (1.23 g, 5.97 mmol) and copper (I) chloride (catalytic amount) was slowly added under a nitrogen atmosphere to methyl (2E)-2-[(acetyloxy)methyl]-3-phenylacrylate **248c** (1.35 g, 5.97 mmol) under a nitrogen atmosphere. The reaction was followed by IR. After 16h the isourea peak at 2100cm^{-1} had vanished indicating that the isourea had formed. To the green solution was added dry THF (75 ml) and α-hydroxycyclohexane carboxylic acid **133a** (0.86 g, 5.97 mmol). The resulting azure blue solution was gently refluxed for 16h. The white urea precipitate was filtered and the THF solution removed on a rotary evaporator. The residue was purified by column chromatography to give (2Z)-3-(4-chlorophenyl)-2-(methoxycarbonyl)prop-2-enyl-1-hydroxycyclo hexanecarboxylate **252c** (1.33g, 3.77 mmole, 63%).

Molecular formula $C_{18}H_{21}ClO_5$. R_f 0.28 (ethyl acetate:hexane, v:v, 1:5).



IR (film, KBr); ν(cm^{-1}) = 3505 (s) [ν (OH)], 2937 (s), 2858 (m), 1723 (s), 1637 (w), 1592 (w), 1490 (m), 1441 (m), 1281 (s), 1238 (s), 1152 (s), 1121 (s), 1051 (m), 994 (m), 840 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.19 - 1.78 (m, 10H, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H), 2.80 (s, 1H, OH), 3.83 (s, 3H, $COOCH_3$), 4.98 (CH_2, OCH_2), 7.22 - 7.39 (m, 4H, Ar), 7.93 (1H, 3-H).

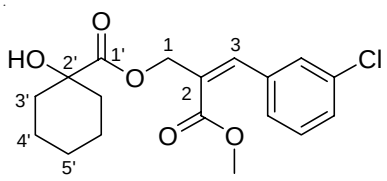
^{13}C-NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.1 (CH_2, C-4' and C-6'), 25.1 (CH_2, C-5'), 34.6 (CH_2, C-3' and C-7'), 52.4 (CH_3, COO*C*H_3), 60.1 (CH_2, OCH_2), 73.7 (C^q, C-2'), 126.8 (C^q, C-2), 129.1, 130.6 (CH, Ar), 132.44 (C^q, Ar-*ipso*), 144.5 (CH, C-3), 166.8 (C^q, CO_2CH_3), 176.9 (C^q, C-1').

MS (EI, 70 eV): m/z = 354 (0.2) [M^+, ^{37}Cl), 353 (0.1) [M^++1, ^{35}Cl), 352 (2) [M^+, ^{35}Cl), 323 (0.5) [M^+-OCH_3, ^{37}Cl], 321 (0.5) [M^+-OCH_3, ^{35}Cl], 310 (0.1) [M^+-CO_2, ^{37}Cl], 308 (0.1) [M^+-CO_2, ^{35}Cl], 293 (0.2) [M^+-CO_2CH_3, ^{35}Cl], 226 (6), 212 (18), 210 (67), 195 (6), 178 (4), 150 (13), 149 (8), 115 (13), 109 (11), 99 (100) [$C_6H_{11}O^+$], 81 (73) [$C_6H_9^+$], 55 (9), 43 (11).

Accurate Mass:- Calculated Mass = 352.10775 Found = 352.10770

(2*Z*)-3-(3-Chlorophenyl)-2-(methoxycarbonyl)prop-2-enyl-1-hydroxycyclohexanecarboxylate 252a.

Colourless oil (2.13 g, 6.05 mmol, 91%) from α-hydroxycyclohexane carboxylic acid **133a** (1.43 g, 9.93 mmol), triphenylphosphine (2.61 g, 9.96 mmol) and triethylamine (1.38 ml, 10 mmol) stirred in THF (40 ml) at 0°C, followed by the slow addition of DIAD (1.92 ml, 10 mmol). After 15 min, methyl 2-[(3-chlorophenyl)(hydroxy)methyl]acrylate **248a** (1.50 g, 6.64 mmol) was added slowly and the solution was allowed to warm to room temperature overnight. Molecular formula $C_{18}H_{21}ClO_5$.R_f 0.41 (ethyl acetate:hexane, v:v, 1:3).



IR (film, KBr); ν(cm^{-1}) = 3448 (s), 3067 (w), 2935 (m), 2858 (m), 1720 (s), 1638 (m), 1594 (w), 1565 (w), 1438 (m), 1346 (w), 1231 (m), 1153 (s), 1053 (m), 995 (m), 890 (m), 789 (m), 738 (m), 687 (s).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 1.55 - 1.75 (m, 10H, 3'-H, 4'-H, 5'-H, 6'-H, 7'-H), 2.81 (s, 1H, OH), 3.82 (s, 3H, OCH_3), 4.96 (s, 2H, OCH_2), 7.20 - 7.34 (m, 4H, Ph), 7.91 (s, 1H, 3-H).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 21.1 (CH_2, C-4' and C-6'), 25.1 (CH_2, C-5'), 34.7 (CH_2, C-3' and C-7'), 52.4 (CH_3, OCH_3), 60.0 (CH_2, C-1), 73.7 (C^q, C-2'), 127.4, 129.2, 129.7, 130.1 (CH, Ar), 127.6 (C^q, C-2), 134.8 (C^q, Ar-Cl), 135.8 (C^q, Ar-*ipso*), 144.2 (CH, C-3), 166.7 (C^q, CO_2CH_3), 176.9 (C^q, C-1').

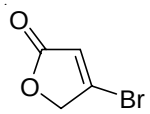
MS (EI, 70 eV): m/z = 355 (0.7) [M^++1, ^{37}Cl], 354 (1) [M^+, ^{37}Cl), 353 (1.4) [M^++1, ^{35}Cl), 352 (2.2) [M^+, ^{35}Cl), 323 (2.4) [M^+-OCH_3, ^{37}Cl], 321 (3.6) [M^+-OCH_3, ^{35}Cl], 310 (5.7) [M^+-CO_2, ^{37}Cl], 308 (13) [M^+-CO_2, ^{35}Cl], 295 (2) [M^+-CO_2CH_3, ^{37}Cl], 293 (5) [M^+-CO_2CH_3, ^{35}Cl], 217 (6), 215 (18), 212 (11), 210 (29), 197 (2), 195 (5), 180 (4), 178 (13), 150 (12), 149 (8), 115 (19), 99 (100) [$C_6H_{11}O^+$], 81 (43) [$C_6H_9^+$], 55 (7).

Accurate Mass:- Calculated Mass = 352.10775 Found = 352.10770.

4-bromofuran-2(5*H*)-one 261.

To a suspension of tetronic acid **41** (9.0 g, 90 mmol) in dry CH_2Cl_2 (200 ml) was added dry DMF (9 ml, 117 mmol). The solution was cooled to -10°C in an ice-NaCl bath and to the cooled solution was added dropwise Oxalyl bromide (23.30 g, 10 ml, 108 mmol) over a period of approximately 60 min. The internal temperature was controlled by thermometer to ensure the temperature did not exceed 0°C. The solution was stirred for a further hour in the ice bath solution and then for a further 4h at room temperature. During this time the solution changed from a

yellow colour to a dark green. Water (250 ml) was added to the solution and the phases separated. The aqueous phase was washed four times with diethyl ether (100 ml) and the combined organic phases were then washed with water, saturated $NaHCO_3$ (100 ml) and saturated NaCl (100 ml). The organic phase was dried with magnesium sulphate and then filtered over a very short plug of silica gel. Evaporation of the solvent gave a red/yellow solid which was recrystallised from diethyl ether to give white needles (11.75g, 72.98 mmol, 81%), R_f 0.51 (diethyl ether:hexane, 1:1, v:v), mp 77°C, (lit 77°C). Molecular formula $C_4H_3BrO_2$.



IR (KBr); ν(cm^{-1}) = 3097 (w), 1805 (w), 1781 (s), 1742 (s), 1598 (s), 1439 (s), 1410 (m), 1342 (m), 1264 (s), 1151 (s), 1013 (s), 864 (s), 842 (s), 696 (s).

^{1}H-NMR (270 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 4.83 (d, $^4J_{HH}$ = 1.91 Hz, 1H, 5-H), 6.32 (t, $^4J_{HH}$ = 1.91 Hz, 2H, 3-H).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 74.8 (CH_2, C-5), 121.7 (CH, C-3), 146.1 (C^q, C-4), 170.7 (C^q, C-2).

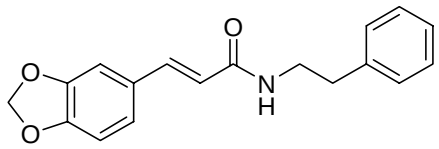
MS (EI, 70 eV): m/z = 164 (46) [M^+, ^{81}Br], 162 (46) [M^+, ^{79}Br], 135 (39) [M^+-CHO, ^{81}Br], 133 (43) [M^+-CHO, ^{79}Br], 107 (18) [*135* - CH_2O], 106 (19) [*135* - OCH_3], 105 (21) [*133* - CHO], 104 (20) [*133* - OCH_3], 83 (100) [M^+-Br], 55 (16), 53 (24), 39 (34).

Accurate Mass:- Calculated Mass = 161.93164 Found = 161.93159.

3.10 Synthesis of (E)-α,β-unsaturated amides

(E)-N-Phenethyl-3',4'-(methylenedioxy)cinnamamide 265.

A solution of 2-phenylethylamine **264** (0.61 g, 5.0 mmol), piperonal **263** (0.75 g, 5.0 mmol), keteneylidenetriphenylphosphorane **1** (2.27 g, 7.5 mmol) and benzoic acid (catalytic amount) were dissolved in toluene (10 ml) and transferred to a sealable glass tube. The glass tube was sealed and heated to 140°C for 24 h. After cooling the solvent was removed on a rotary evaporator and the residue was purified by column chromatography to give **265** as a white solid (0.63 g, 2.29 mmole, 45%). Molecular formula $C_{18}H_{17}NO_3$. R_f 0.83 (ethyl acetate, 100%), mp 117°C.



IR (KBr); ν(cm^{-1}) = 3434 (br) and 3291 (s) [ν (NH)], 3048 (w), 2922 (w), 2855 (w), 1650 (s), 1617 (s), 1544 (m), 1501 (m), 1443 (m), 1249 (s), 1193 (w), 1101 (w), 1040 (m), 968 (m), 930 (m), 813 (w), 748 (w), 698 (w).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 2.79 (t, $^3J_{HH}$ = 6.62 Hz, 2H, $NCCH_2$), 3.64 (dt, 2H, NCH_2), 5.86 (s, 2H, OCH_2O), 5.94 (s, 1H, NH), 6.17 (d, $^3J_{HH}$ = 15.49 Hz, 1H, CH=C*H*), 6.66 (d, $^3J_{HH}$ = 8.46 Hz, 1H, 5'-H), 6.85 (d, $^3J_{HH}$ = 8.46 Hz, 1H, 6'-H), 7.10 - 7.25 (m, 6H, Ph, 2'-H), 7.44 (d, $^3J_{HH}$ = 15.49 Hz, 1H, C*H*=CH).

^{13}C-JMOD NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 34.7 (CH_2, NC*C*H_2), 39.8 (CH_2,

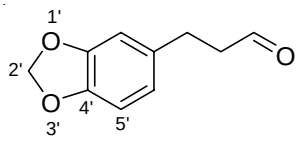
NCH_2), 100.4 (CH_2, OCH_2O), 105.3, 107.1 (CH, C-2', C-5'), 117.8 (CH, CH=*C*H), 122.8 (CH, C-6'), 125.8 (CH, C-1'), 127.3, 127.6, 129.0 (CH, Ar), 137.9 (C^q, Ar-*ipso*), 139.6 (CH, *C*H=CH), 147.0 (C^q, C-3'), 148.0 (C^q, C-4'),
165.1 (C^q, C-1).

MS (EI, 70 eV): m/z = 296 (9) [M^++1], 295 (38) [M^+], 190 (42) [M^+-C_8H_9], 175 (100) [M^+-$C_8H_{10}N$], 145 (21), 117 (13), 91 (14), 89 (26), 63 (9).

$C_{18}H_{17}NO_3$ (295.33): Calculated C = 73.20%, H = 5.80%; found C = 73.34%, H =5.84%.

3-(1,3-benzodioxol-5-yl)propanal 271.

Colourless oil (1.72 g, 9.66 mmol, 59%) from 3-(1,3-benzodioxol-5-yl)propan-1-ol (2.96 g, 16.4 mmol) dissolved in dry DCM (20 ml) and dropped slowly into a solution of pyridine chlorochromate (4.26 g, 19.7 mmol) and silica gel (1.0 g) in dry dichloromethane (50 ml). After 4 hours of stirring at room temperature the solution was filtered and the solvent removed. The residue was purified by Kugelrohr distillation. Molecular formula $C_{10}H_{10}O_3$. Bp 125°C at 0.1 Torr.



IR (KBr); ν(cm^{-1}) = 3070 (w), 2897 (m), 2727 (w) [ν (CHO)], 1724 (s) [ν (CHO)], 1608 (w), 1490 (s), 1445 (s), 1247 (s), 1189 (m), 1100 (m), 1038 (s), 930 (m), 869 (w), 810 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 2.71 - 2.76 (m, 2H, C*H*$_2$CHO), 2.88 (t, $^3J_{HH}$ = 7.11 Hz, 2H, $ArCH_2$), 5.93 (s, 2H, OCH_2O), 6.62 - 6.76 (m, 3H, Ar), 9.75 (d, $^3J_{HH}$ = 6.09 Hz, 1H, CHO).

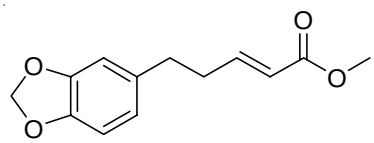
^{13}C NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 27.9 (CH_2, $PhCH_2$), 45.6 (CH_2, *C*H_2CHO), 100.9 (CH_2, OCH_2O), 108.3, 108.8 (CH, C-5' and C-8'), 121.1 (CH, C-6'), 134.1 (C^q, C-3), 146.0, 147.8 (C^q, C-4', C-9'), 201.54 (C^q, C-1).

MS (EI, 70 eV): m/z = 179 (20) [M^++1], 178 (100) [M^+], 150 (20) [M^+-CO], 147 (12) [M^+-CH_3O], 136 (28) [M^+-C_3H_6], 135 (94) [M^+-CH_3CO], 122 (74) [M^+-C_3H_4O], 121 (23), 119 (20), 105 (25), 91 (51) [$C_7H_7^+$], 89 (20), 79 (18), 77 (62) [$C_6H_5^+$], 65 (43), 63 (37), 53 (14), 51 (52), 39 (42).

$C_{10}H_{10}O_3$ (178.18): Calculated C = 67.41%, H = 5.66%; found C = 67.43%, H = 5.71%.

Methyl (2*E*)-5-(1,3-benzodioxol-5-yl)pent-2-enoate 272.

To a solution of 3-(1,3-benzodioxol-5-yl)propanal **271** (540mg, 3.03 mmol) dissolved in dry benzene (20 ml) was added methoxycarbonylmethylenetriphenylphosphorane **11** (1.01g, 3.03 mmol). The solution was refluxed with exclusion of air and moisture for 24 h. After cooling to room temperature, the solvent was evaporated on a rotary evaporator and the crude product was purified by column chromatograpy to yield methyl (2*E*)-5-(1,3-benzodioxol-5-yl)pent-2-enoate **272** (620mg, 2.65 mmol, 87.4%) as a clear viscious oil, R_f 0.61 (diethyl ether:hexane, 50:50, v:v). Molecular formula $C_{13}H_{14}O_4$.



IR (film, KBr); ν(cm^{-1}) = 2949 (m), 1722 (s), 1656 (m), 1490 (s), 1441 (m), 1246 (s), 1099 (w), 1039 (s), 935 (m), 857 (w), 810 (m).

^{1}H-NMR (300 MHz, TMS_{int}, $CDCl_3$); δ (ppm) = 2.44 - 2.51 (m, 2H, C*H*$_2$CH), 2.67 (t, $^{3}J_{HH}$ = 7.11 Hz, 2H, ArCH_2), 3.72 (s, 3H, OCH_3), 5.83 (d, $^{3}J_{HH}$ = 15.67 Hz, 1H, CH=C*H*), 5.93 (s, 2H, OCH_2O), 6.60 - 6.67 (m, 3H, Ar), 6.98 (dt, $^{3}J_{HH}$ = 15.67, 6.84 Hz, 1H, C*H*=CH),

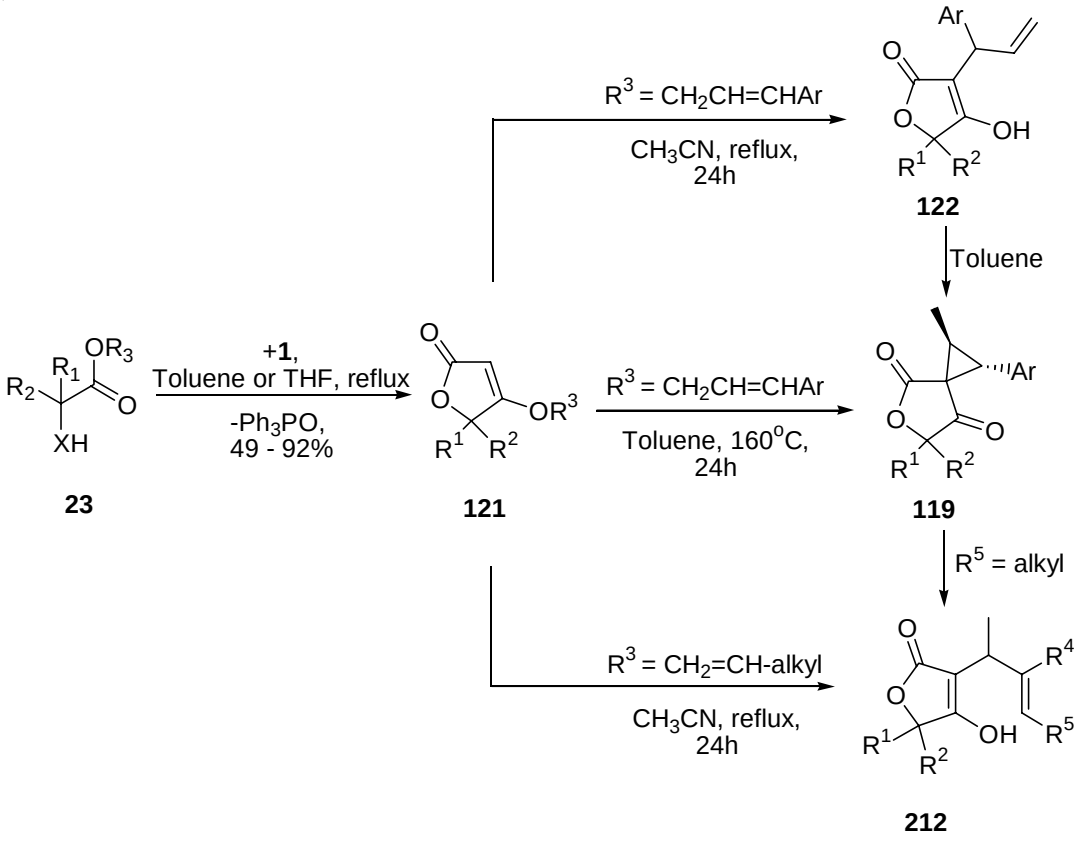
^{13}C NMR (75.5 MHz, TMS_{int}, $CDCl_3$): δ (ppm) = 32.3 (CH_2, *C*H_2CH), 34.1 (CH_2, ArCH_2), 51.5 (CH_3, OCH_3), 100.9 (CH_2, OCH_2O), 108.2, 108.8 (CH, C-5' and C-8'), 121.1 (CH, CH=*C*H), 134.6 (C^q, C-7'), 145.9 (CH, CH=CH), 147.7, 148.2 (C^q, C-4' and C-9'), 167.0 (C^q, CO_2).

MS (EI, 70 eV): m/z = 234 (26) [M^+], 206 (10) [M^+-CO], 203 (5) [M^+-CH_3O], 175 (6) [M^+-$C_2H_3O_2$], 136 (20) [M^+-$C_5H_6O_2$], 135 (100) [M^+-$C_5H_7O_2$], 115 (5), 86 (27), 84 (40), 77 (26) [C_6H_5], 51 (42), 49 (64), 47 (15).

$C_{13}H_{14}O_4$ (234.25): Calculated C = 66.66%, H = 6.02%; found C = 66.48%, H = 5.94%.

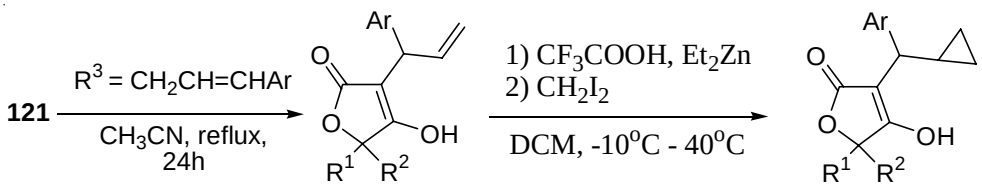
4.0 Summary

Keteneylidenetriphenylphosphorane **1** reacts with XH acidic compounds **23** (where X = O, NH, S) to give an acyl ylide which immediately undergoes an intramolecular Wittig oelfination to give compounds **121**. When X = O and R^3 contains an allyl residue we can convert the tetronates into either the 3-allyl derivatives **122**, the 3-(spirocyclopropyl)-dihydrofuran-4,12-diones **119** or the abnormally [2,3]-rearranged 3-alkylidenetetronic acids **212**, depending on the nature of the residue R^3 and by careful control of the reaction conditions.



5-spiro-3-allyl derivatives **122** are generated as a result of a simple Claisen rearrangement of the starting tetronates. By changing the solvent to toluene and through the use of higher reaction temperatures it is possible to synthesise the 3-(spirocyclopropyl)-dihydrofuran-4,12-diones **119** from either **121**or from **122**. Compounds of **122** are in fact intermediates when starting from **121** and they undergo a thermal Conia rearrangement to compounds **119**. When the starting tetronate has a cinnamyl residue the end-product of the sequence under these conditions is always compound **119**, however when an alkyl residue is used the exclusive product is always **212**. Compounds of type **212** are formed from a retro-Conia rearrangement of **119**. When **119** contains a phenyl residue the retro-Conia rearrangement cannot proceed due to the absence of a CH_2 or CH_3 adjacent to the cyclopropane ring. In those cases were the tetronate contains an alkyl group the corresponding 3-allyl tetronic acids **122** and the 3-(spirocyclopropyl)-dihydrofuran-4,12-diones **119** cannot be isolated. Under the reaction conditions they form the thermodynamically more stable [2,3]-rearranged 3-alkylidenetetronic acids **212** in high yield.[143, 146, 147]

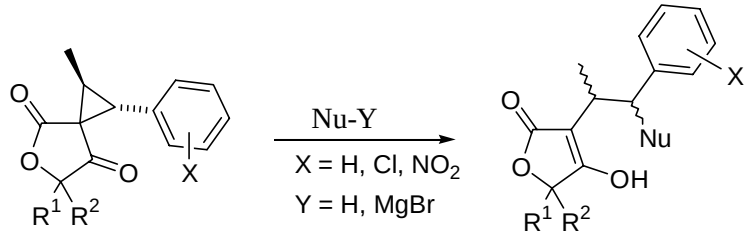
One of the initial objectives of this work was to construct 5-spiro-(3-α-cyclopropylbenzyl)-tetronic acids **120** from the corresponding 5-spiro-3-allyl derivatives **122**. This proved to be much more difficult than originally planned with the 5-spiro-3-allyl derivatives proving to be very stubborn towards traditional and more modern cyclopropanation methods.[163,169] The use of the highly reactive "Shi" reagent[173] also failed under the reported conditions; however we found that it was necessary to heat the solution above room temperature before cyclopropanation would take place. By solving this problem we have completed our initial synthetic plan to construct the anti-HIV 5-spiro-(3-α-cyclopropylbenzyl)-tetronic acids **120**. These useful molecules can now be constructed in high yield by a three step synthesis staring from an α-hydroxy-allyl-ester reacted with **1**.



122 **120**

Another objective of this work has been the synthesis of 3,5-Dispirodihydrofuran-4,12-dione **119a** (R^1 and R^2 = -$(CH_2)_5$-, X = H). During this work we have optimised the conditions necessary for the construction of this molecule (Section 2.1.3). It was also possible to synthesise a series of functionalised derivatives of **119** with various substituents on the phenyl ring. When a substituent was present on the phenyl ring we found that it was preferable to perform the synthesis in a microwave oven (CEM GmbH, Germany). Yields were in many cases greatly improved and the duration of reaction was reduced to 1 hour or less. Our overall reaction scheme has therefore been proved to be general and we can in theory place great variety of functionality on the phenyl ring or on the spiro-5-position. We were however unable to generate the corresponding 3-(spirocyclopropyl)-dihydrofuran-4,12-diones when the phenyl ring was replaced with a furan ring (Section 2.1.4.7).

3-(spirocyclopropyl)-dihydrofuran-4,12-diones **119** contain a cyclopropane ring and it was suspected that this would be amenable to ring opening reactions with nucleophilic reagents. We successfully reacted compound **119** with alcohols, amines, thiols, Grignard reagents, purine bases and with hydrogen.



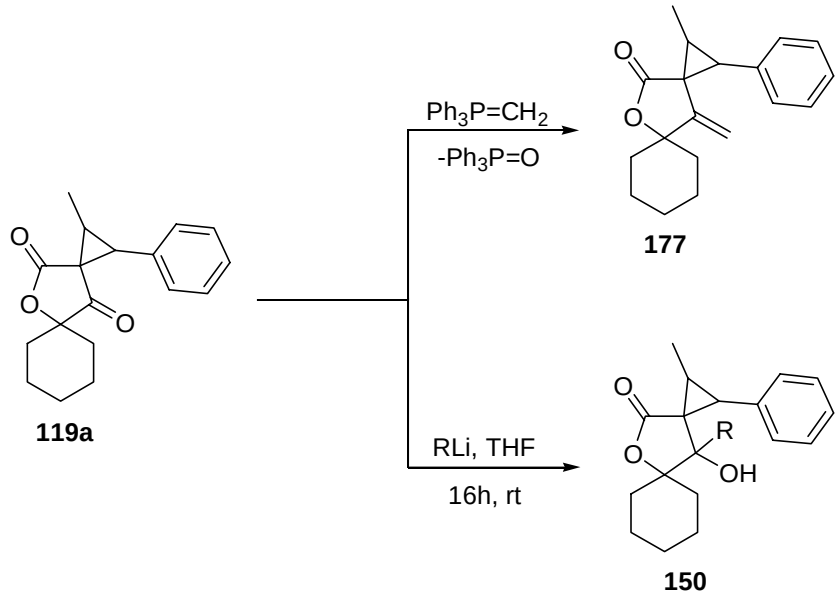
119

	R^1	R^2
a	-$(CH_2)_5$-	
b	H	Ph
c	-$(CH_2)_2O(CH_2)_2$-	

	Nu	Config.
141	OR^3	syn
144	NR^3R^4	syn
147	SR^3	syn
149	R^3	anti
184	H	-

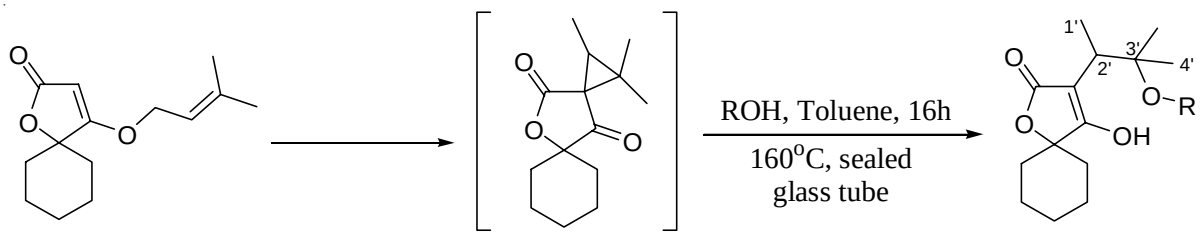
The 3,5-disubstituted-tetronic acids formed are interesting compounds and the simple unsubstituted derviatives show promise as potential herbicidal compounds. Furthermore we have been able to extend this sequence to functionalised derivatives. However we were unsuccessful in extending the cascade through the use of Baylis-Hillman esters. In these examples we could either not form the desired ester or in some cases reaction with **1** did not proceed (Section 2.4).

Other nucleophilic reagents have been found to react preferentially at the ketone, with no reaction observed at the cyclopropane ring. These include the alkyl lithium reagents (Section 2.1.5.4) and the phosphorus ylides (Section 2.1.5.8) Both reactions give interesting structures which are amenable to possible follow-up chemistry.



119a **177** **150**

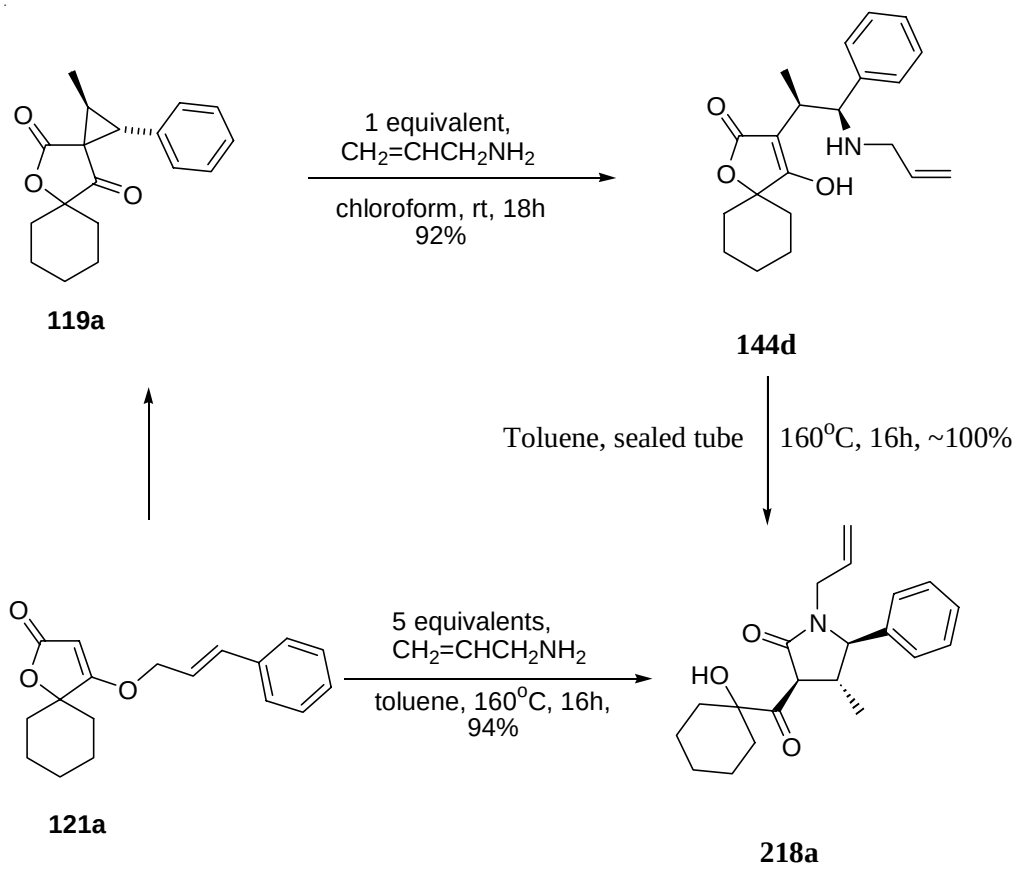
As already mentioned replacement of the phenyl group with an alkyl chain has been shown to lead not to the expected, 3,5-dispirodihydrofuran-2,4-diones **119** but to the abnormally Claisen rearranged products **212**. The mechanism was proposed to proceed through a cyclopropane intermediate **211a** and this was proved by the interception of these elusive spirocyclopropanes using an excess of either an alcohol or an amine nucleophile. While cyclopropanes have been proposed before as mechanistic intermediates in the abnormal Claisen rearrangement reaction we have demonstrated the first conclusive proof of their existence (Section 2.3.4).



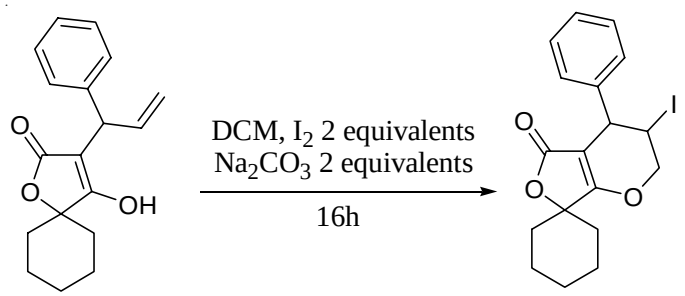
121m **211a** **223**

223	R	Yield
a	Me	88%
b	Et	92%

When these elusive cyclopropanes were intercepted using amine nucleophiles we found that the process did not stop at the ring opening step, it was found to be preceded by an unexpected lactone to lactam *trans*-esterification reaction. The products were γ-lactams which were formed in excellent yields despite the fact that a domino process of four steps takes place. We have also been able to demonstrate that the trapping of spirocyclopropanes can be extended to the more biologically active coumarin systems, albeit with lower yields. Normally these systems undergo an addition of the OH group across the double bond to give furano derivatives (Section 2.3.4).



Finally we have had some success with the reaction of compounds of type **122** and type **212** with iodine to initiate formation of a second annulated six ring system. We had expected the formation of furofuranones as iodine normally leads to a five ring, however the formation of a six ring **196** was also welcome in our attempts to synthesise compounds of interest to the pharmaceutical industry. Unfortunately yields were much lower than expected, however this reaction has potential for development and could represent an important method for the synthesis of new natural products (Section 2.2.3).

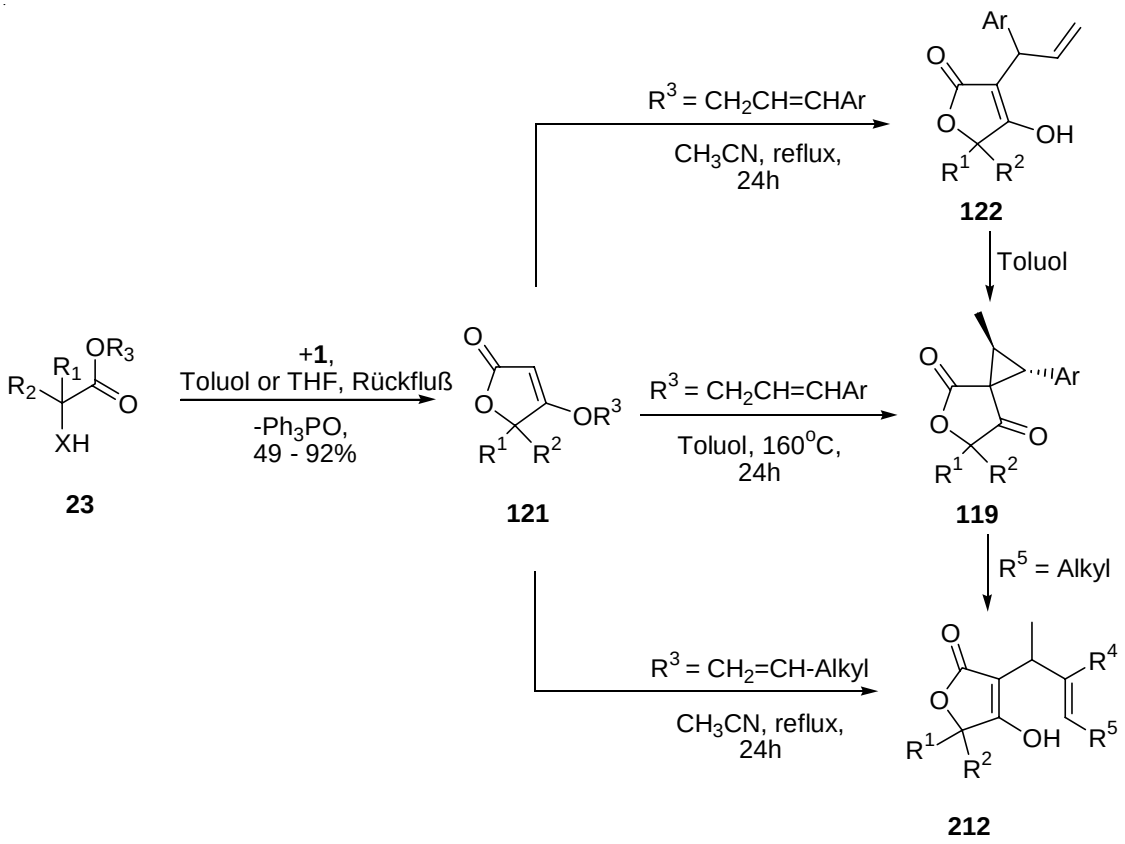


122a **196**

This work has principally been concerned with the construction of new 3-(spirocyclopropyl)-dihydrofuran-4,12-diones **119**, the anti-HIV active 5-spiro-(3-α-phenylallyl)-tetronic acids **120** and the [2,3]-rearranged 3-alkylidenetetronic acids **212**. Not only has this work contributed to the chemistry of tetronic acids, with many new molecules with interesting and useful functionality having been synthesised, but we have provided new insights into rearrangement chemistry. Claisen rearrangements are one of the most used and well known of the rearrangement reactions and we have contributed not only to the mechanism of abnormal Claisen rearrangements but have also investigated the acceleration of this reaction through the use of microwaves. It is hoped that this work will be of use to future chemists in the fields of tetronic acid research, rearrangement chemistry and general natural product synthesis.

4.1 Zusammenfassung

Ketenylidentriphenylphosphoran **1** reagiert mit XH-aciden Verbindungen **23** (mit X = O, NH, S) zu einem Acylylid, das sofort eine intramolekularen Wittig-Olefinierung zu **121** eingeht. Abhängig von der Art des Restes R und durch genaue Kontrolle der Reaktionsbedingungen können 3-(Spirocyclopropyl)-dihydrofuran-4,12-dione **119** oder anomal [2,3]-umgelagerte 3-Alkylidentetronsäuren **212** umgesetzt werden, sofern X = O und R^3 ein Allylrest ist.

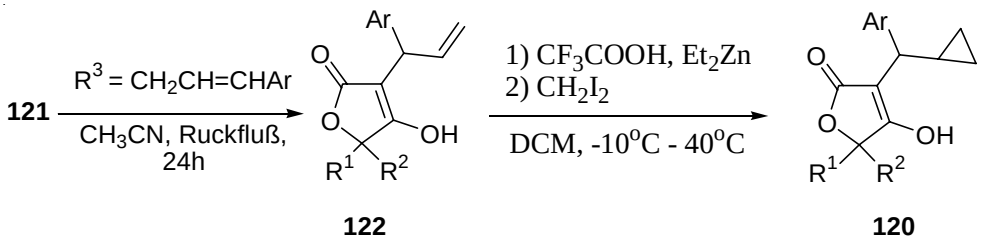


5-Spiro-3-allyl-Derivate **122** werden als Folge einer einfachen Claisen-Umlagerung aus den Ausgangstetronaten erhalten. Durch Verwendung von Toluol als Lösungsmittel und höhere Reaktionstemperaturen ist es möglich 3-(Spirocyclopropyl)-dihydrofuran-4,12-dione **119** aus **121** oder **122** zu synthetisieren. Ausgehend von **121** sind Verbindungen vom Typ **122** tatsächlich Intermediate, die eine thermische Conia-Umlagerung zu **119** eingehen.

119 wird durch eine thermische Conia-Umlagerung aus **121** erhalten, wobei Verbindungen des Typs **122** tatsächlich als Intermediate auftreten.Wenn das Ausgangstetronat einen Cinnamyl-Rest hat, befindet sich **119** unter dieser Reaktionssequenz, während bei einem Alkylrest stets **212** das ausschließlich gebildete Reakionsprodukt ist. Verbindungen des Typs **212** entstehen durch eine retro-Conia-Umlagerung aus **119**. Enthält **119** eine Phenylgruppe X kann keine retro-Conia- Umlagerung ablaufen. Dies ist auf das Fehlen einer zum Cyclopropanring benachbarten CH2- oder CH_3-Gruppe zurückzuführen. Falls das Tetronat eine Alkylgruppe enthält, können die entsprechenden 3-Allyltetronsäuren **122** und die 3-(Spirocyclopropyl)-dihydrofuran-4,12-dione

119 nicht isoliert werden. Unter diesen Reaktionsbedingungen bilden sich die thermodynamisch stabileren [2,3]-umgelagerten 3-Alkylidentetronsäuren **212** in hohen Ausbeuten. [143,146,147]

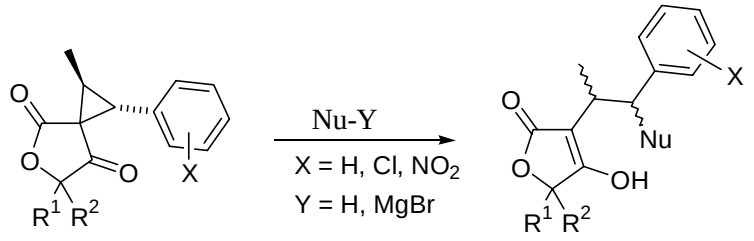
Eines der Ziele dieser Arbeit war die Synthese von 5-Spiro-(3-α-cyclopropylbenzyl)-tetronsäuren **120** aus den entsprechenden 5-Spiro-3-allyl-Derivaten **122**, was sich jedoch als viel schwieriger herausstellte als ursprünglich geplant, weil 5-Spiro-3-allyl-Derivate sich als sehr resistent gegenüber herkömmlichen und modernen Cyclopropanierungen herausstellten.[163,169] Auch die Verwendung des hochreaktiven "Shi"-Reagenz[173] brachte unter den angegebenen Bedingungen nicht den erwünschten Erfolg. Jedoch stellte sich heraus, dass für den Ablauf der Cyclopropanierung eine höhere Temperatur erforderlich war. Nach Beseitigung dieses Problems konnte die Synthese von anti-HIV aktiven 5-Spiro-(3-α-cyclopropylbenzyl)-tetronsäuren **120** durchgeführt werden. Diese wertvollen Zielmolekule sind nun in einer 3-stufigen Synthese ausgehend von a-Hydroxyallylestern durch Umsetzung mit **1** in hohen Ausbeuten erhältlich.



122 **120**

Ein anderes Ziel dieser Arbeit bestand in der Synthese von 3,5-Dispirodihydrofuran-4,12-dionen **119a** (R^1 und R^2 = -$(CH_2)_5$-, X = H). Im Verlauf der Arbeit wurden die zur Herstellung dieser Moleküle nötigen Reaktionsbedingungen optimiert. Es ist auch gelungen eine Reihe funktionalisierter Derivate von **119** herzustellen, die am Phenylring verschiedene Substituenten besitzen. Ist der Phenylring substituiert, stellte es sich als günstig heraus die Synthese in der Mikrowelle (CEM Gmblt, Deutschland) durchzuführen. In diesem Fall konnten Ausbeuten enorm gesteigert und Reaktionszeiten auf eine Stunde oder weniger verkürzt werden. Dadurch zeigte sich, dass unsere Reaktionssequenz allgemein anwendbar ist und theoretisch eine große Vielfalt unterschiedlicher Funktionalitäten am Phenylring oder an der Spiro-5-Position möglich sind. Es war jedoch nicht möglich entsprechende 3-(Spirocyclopropyl)-dihydrofuran-4,12-dione zu generieren, wenn der Phenylring durch einen Furanring ersetzt wurde (Abschnitt 2.1.4.7).

Da 3-(Spirocyclopropyl)-dihydrofuran-4,12-dione **119** einen Cyclopropanring besitzen, wurde vermutet dass dieser für Ringöffnungsreaktionen durch Nukleophile zugänglich sein müsste. Wir konnten Verbindung **119** erfolgreich mit Alkoholen, Aminen, Thiolen, Grignard-Reagenzien, Purinbasen und Wasserstoff umsetzen.

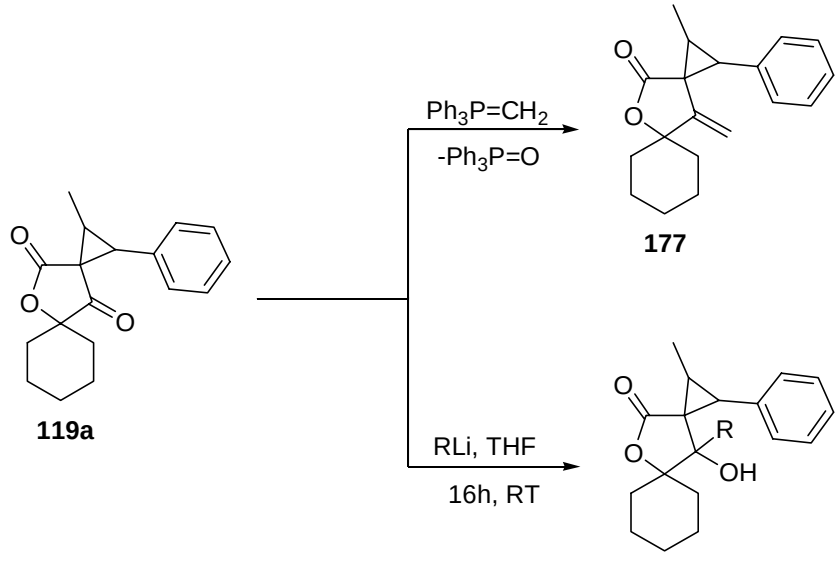


119

	R^1	R^2
a	$-(CH_2)_5-$	
b	H	Ph
c	$-(CH_2)_2O(CH_2)_2-$	

	Nu	Konfig.
141	OR^3	syn
144	NR^3R^4	syn
147	SR^3	syn
149	R^3	anti
184	H	-

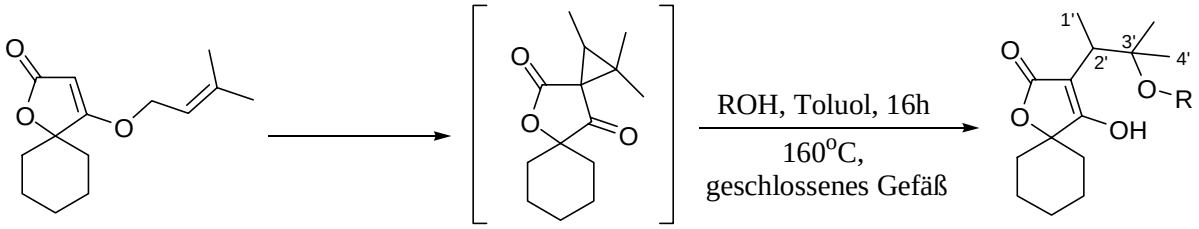
Die daraus erhaltenen 3,5-Disubstituierten Tetronsäuren sind interessante Moleküle, da selbst die einfachen unsubstituierten Derivate als mögliche Herbizide vielversprechend sind. Darüberhinaus waren wir in der Lage die Reaktionssequenz auf funkionalisierte Derivate zu übertragen. Nicht gelungen ist uns die Reaktionskaskade auf Baylis-Hillmannester auszudehnen. In diesen Fällen konnten wir entweder den gewünschten Ester nicht synthetisieren oder die Ester zeigten keine Reaktion mit **1** (Abschnitt 2.4). Bei einigen Nukleophilen stellte sich heraus, dass sie bevorzugt mit der Ketogruppe reagieren und den Cyclopropanring nicht angreifen. Dies schliesst sowohl Alkyllithium-Reagenzien (Abschnitt 2.1.5.4) als auch Phosphorylide (Abschnitt 2.1.5.8) ein. Beide Reaktionen führen zu Strukturen, deren Folgechemie von Interesse sein könnte.



119a **177** **150**

Wie bereits erwähnt, führt die Substitution der Phenylgruppe durch eine Alkylkette nicht wie erwartet zu den 3,5-Dispirodihydrofuran-4,12-dionen **119** sondern zu den anomalen Claisen-Produkten **212**.

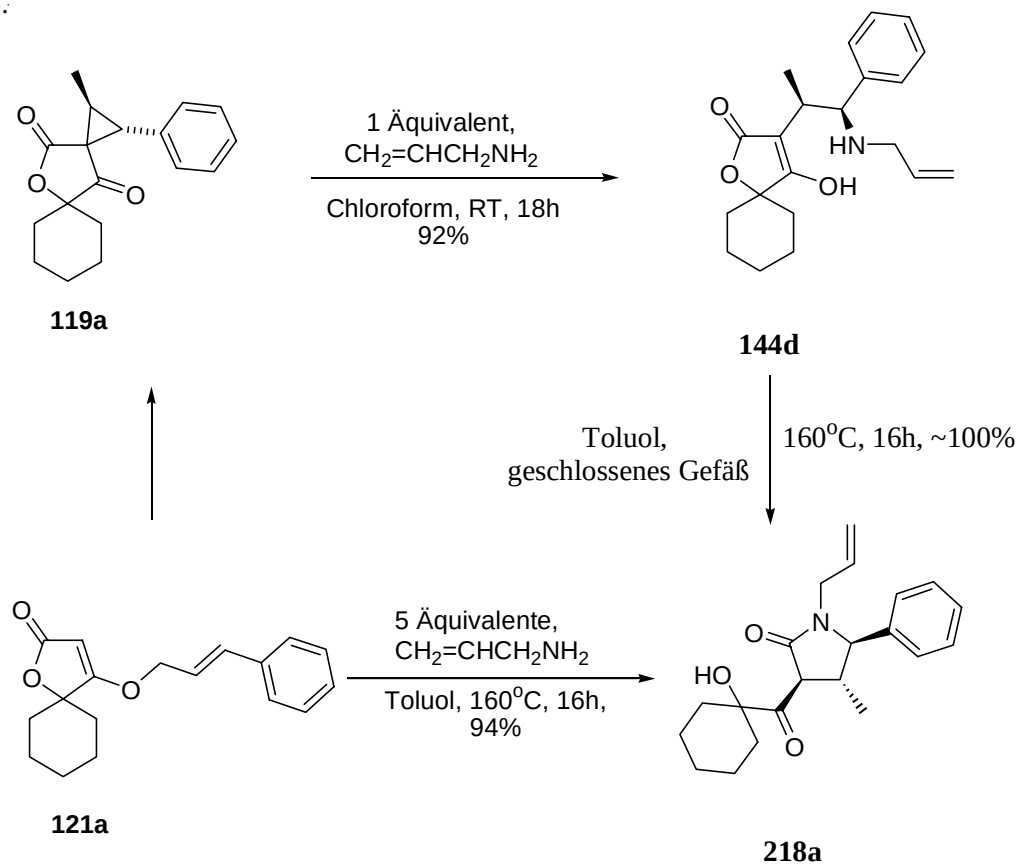
Der vorgeschlagene Reaktionsmechanismus verläuft über ein schwer fassbares Cyclopropan-Zwischenprodukt **211a**. Dies wurde durch nukleophile Ringöffnung des Cyclopropanrings mit einem Überschuß an Alkohol oder Amin bewiesen. Während Cyclopropane seit Längerem als Zwischenprodukte im Mechanismus der abnormalen Claisen-Umlagerung diskutiert werden, konnten wir als Erste einen schlüssigen Beweis für deren Existenz erbringen (Abschnitt 2.3.4).



121m **211a** **223**

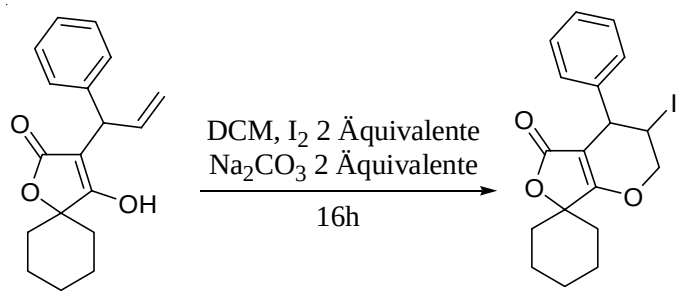
223	R	Yield
a	Me	88%
b	Et	92%

Wenn diese schwer fassbaren Cyclopropane durch nukleophile Amine abgefangen wurden, blieb die Reaktion nicht auf der Stufe der Ringöffnung stehen, sondern führte zu einer unerwarteten Lacton-Lactam-Umesterung. Trotz der Tatsache, dass eine Dominoreaktion in vier Schritten stattfindet, werden die resultierenden γ-Lactame in sehr hohen Ausbeuten gebildet. Wir konnten auch zeigen, dass das Abfangen des Spirocylopropanes mit dem biologisch aktiveren Coumarin-System möglich ist, auch wenn die Ausbeuten niedriger ausfielen. Doppelbindung und bilden Furan-Derivate. (Übersetzung nicht gesichert! Rücksprache mit den Übersetzern.) (Abbildung 2.3.4).



119a **144d** **121a** **218a**

Schliesslich gelang es uns Verbindungen des Typs **122** und **212** durch eine Jod-induzierte Bildung eines zweiten annulierten Sechsrings umzusetzen. Ursprünglich hatten wir den Aufbau eines Furofuranones erwartet, weil Jod normalerweise zu einer Fünfringbildung führt. Jedoch war die Bildung des Sechsrings **196** für unsere Zwecke zur Synthese von Verbindungen mit hohem Potential für die pharmazeutische Industrie durchaus von Interesse. Obwohl die Ausbeuten viel niedriger als erwartet waren, eröffnet diese Reaktion neue Möglichkeiten und könnte eine wichtige Methode zur Darstellung neuer Naturstoffe werden (Abschnitt 2.2.3).



122a **196**

Diese Arbeit hat sich hauptsächlich mit der Synthese von neuen 3-(Spirocyclopropyl)-dihydrofuran-4,12-dionen **119**, anti-HIV aktiven 5-spiro-(3-α-cyclopropylbenzyl)-tetronsäuren **120** und [2,3]-umgelagerten 3-Alkylidenetetronsäuren **212** befaßt. Sie hat nicht nur durch die Synthese vieler neuer Moleküle mit interessanten und nützlichen funktionellen Gruppen einen Beitrag zur Chemie der Tetronsäuren geleistet, sondern auch neue Einblicke in die Chemie der Umlagerungen eröffnet. Claisen-Umlagerungen gehören mit zu den meistverwendeten und am besten bekannten Umlagerungsreaktionen. Wir haben nicht nur zur Klärung des Mechanismus der abnormalen Claisen-Umlagerung beigetragen, sondern auch die Beschleunigung der Reaktion durch Einsatz von Mikrowellen untersucht. Es bleibt zu hoffen, dass diese Arbeit für Chemiker auf dem Gebiet der Tetronsäurechemie, der Umlagerungschemie und der Naturstoffsynthese von Nutzen ist.

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Appendix A

Table A 1: Crystal data for the structural determination of compound 184b

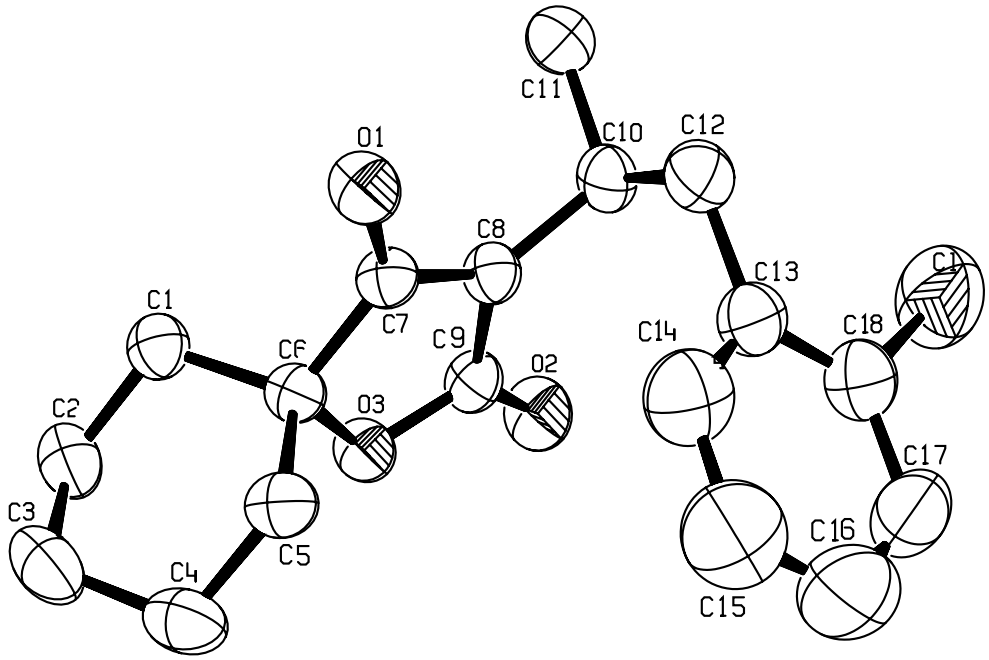


Table 1. Crystal data and structure refinement for **184b**.

Empirical formula	$C_{18} H_{21} Cl O_3$	
Formula weight	320.80	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 6.7568(14) Å	α= 90°.
	b = 21.780(4) Å	β= 105.86(3)°.
	c = 11.628(2) Å	γ = 90°.
Volume	1646.1(6) $Å^3$	
Z	4	
Density (calculated)	1.294 Mg/m^3	
Absorption coefficient	0.242 mm^{-1}	
F(000)	680	
Crystal size	0.28 x 0.18 x 0.08 mm^3	
Theta range for data collection	1.87 to 25.98°.	
Index ranges	-7<=h<=7, -26<=k<=26, -14<=l<=14	
Reflections collected	11304	
Independent reflections	3015 [R(int) = 0.0400]	
Completeness to theta = 25.98°	92.9 %	
Absorption correction	Numerical	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3015 / 0 / 199	

Goodness-of-fit on F^2	1.047
Final R indices [I>2sigma(I)]	R1 = 0.0759, wR2 = 0.2323
R indices (all data)	R1 = 0.0994, wR2 = 0.2561
Largest diff. peak and hole	0.447 and -0.810 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for **184b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl	2088(2)	6787(1)	3396(2)	105(1)
O(1)	11062(3)	6970(1)	6490(2)	48(1)
O(2)	4868(4)	6535(1)	7414(2)	55(1)
O(3)	8076(3)	6213(1)	8196(2)	43(1)
C(1)	11492(5)	6582(1)	9165(3)	43(1)
C(2)	11958(6)	6129(2)	10195(3)	54(1)
C(3)	12858(6)	5535(2)	9849(3)	62(1)
C(4)	11397(6)	5250(2)	8751(4)	59(1)
C(5)	10903(5)	5695(1)	7704(3)	45(1)
C(6)	10091(4)	6314(1)	8013(2)	37(1)
C(7)	9634(4)	6756(1)	6987(2)	37(1)
C(8)	7626(5)	6902(1)	6636(2)	37(1)
C(9)	6665(5)	6556(1)	7401(3)	40(1)
C(10)	6469(5)	7323(1)	5654(3)	45(1)
C(11)	7154(6)	7987(2)	5898(3)	57(1)
C(12)	6653(6)	7114(2)	4422(3)	55(1)
C(13)	6023(6)	6452(2)	4117(3)	57(1)
C(14)	7507(8)	5996(2)	4270(4)	75(1)
C(15)	7040(11)	5392(3)	4005(5)	99(2)
C(16)	5013(12)	5218(3)	3553(5)	101(2)
C(17)	3492(9)	5651(3)	3372(4)	89(2)
C(18)	4021(7)	6268(2)	3667(3)	69(1)

Table 3. Bond lengths [Å] and angles [°] for **184b**.

Cl-C(18)	1.690(5)	O(1)-C(7)	1.337(3)
O(2)-C(9)	1.220(4)	O(3)-C(9)	1.356(4)
O(3)-C(6)	1.451(4)	C(1)-C(2)	1.518(4)
C(1)-C(6)	1.529(4)	C(2)-C(3)	1.529(5)
C(3)-C(4)	1.516(6)	C(4)-C(5)	1.519(5)
C(5)-C(6)	1.535(4)	C(6)-C(7)	1.498(4)
C(7)-C(8)	1.344(4)	C(8)-C(9)	1.447(4)
C(8)-C(10)	1.506(4)	C(10)-C(11)	1.522(5)
C(10)-C(12)	1.540(5)	C(12)-C(13)	1.520(5)

C(13)-C(18)	1.370(6)	C(13)-C(14)	1.387(6)
C(14)-C(15)	1.369(7)	C(15)-C(16)	1.379(9)
C(16)-C(17)	1.368(9)	C(17)-C(18)	1.409(7)
C(9)-O(3)-C(6)	109.3(2)	C(2)-C(1)-C(6)	112.8(3)
C(1)-C(2)-C(3)	110.8(3)	C(4)-C(3)-C(2)	110.7(3)
C(3)-C(4)-C(5)	111.3(3)	C(4)-C(5)-C(6)	112.7(3)
O(3)-C(6)-C(7)	102.5(2)	O(3)-C(6)-C(1)	108.1(2)
C(7)-C(6)-C(1)	113.3(2)	O(3)-C(6)-C(5)	108.1(2)
C(7)-C(6)-C(5)	112.8(2)	C(1)-C(6)-C(5)	111.5(3)
O(1)-C(7)-C(8)	125.0(3)	O(1)-C(7)-C(6)	123.5(2)
C(8)-C(7)-C(6)	111.4(2)	C(7)-C(8)-C(9)	106.0(3)
C(7)-C(8)-C(10)	130.3(3)	C(9)-C(8)-C(10)	123.8(3)
O(2)-C(9)-O(3)	119.1(3)	O(2)-C(9)-C(8)	130.0(3)
O(3)-C(9)-C(8)	110.8(3)	C(8)-C(10)-C(11)	111.6(3)
C(8)-C(10)-C(12)	111.7(3)	C(11)-C(10)-C(12)	110.9(3)
C(13)-C(12)-C(10)	114.1(3)	C(18)-C(13)-C(14)	116.4(4)
C(18)-C(13)-C(12)	123.4(4)	C(14)-C(13)-C(12)	120.2(4)
C(15)-C(14)-C(13)	123.0(5)	C(14)-C(15)-C(16)	119.6(5)
C(17)-C(16)-C(15)	119.7(5)	C(16)-C(17)-C(18)	119.3(5)
C(13)-C(18)-C(17)	122.0(5)	C(13)-C(18)-Cl	120.6(3)
C(17)-C(18)-Cl	117.4(4)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **184b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl	78(1)	101(1)	119(1)	-7(1)	-5(1)	11(1)
O(1)	29(1)	61(1)	59(1)	14(1)	19(1)	4(1)
O(2)	27(2)	72(2)	70(2)	8(1)	19(1)	3(1)
O(3)	29(1)	51(1)	50(1)	10(1)	15(1)	0(1)
C(1)	37(2)	47(2)	46(2)	0(1)	12(1)	1(1)
C(2)	48(2)	64(2)	46(2)	9(2)	8(1)	6(2)
C(3)	54(2)	64(2)	66(2)	21(2)	13(2)	17(2)
C(4)	58(2)	42(2)	78(2)	10(2)	24(2)	9(2)
C(5)	39(2)	42(2)	57(2)	1(1)	19(1)	1(1)
C(6)	31(2)	38(1)	43(1)	4(1)	14(1)	2(1)
C(7)	32(2)	39(1)	41(1)	0(1)	14(1)	0(1)
C(8)	31(2)	42(2)	39(1)	0(1)	10(1)	1(1)
C(9)	29(2)	45(2)	45(2)	-1(1)	11(1)	0(1)
C(10)	34(2)	50(2)	49(2)	4(1)	6(1)	5(1)
C(11)	55(2)	49(2)	61(2)	7(2)	7(2)	3(2)

C(12)	55(2)	60(2)	48(2)	7(2)	12(1)	-6(2)
C(13)	73(3)	59(2)	37(2)	0(1)	12(2)	-13(2)
C(14)	82(3)	80(3)	65(2)	-10(2)	25(2)	4(2)
C(15)	129(5)	85(3)	84(3)	-22(3)	29(3)	24(3)
C(16)	145(6)	72(3)	82(3)	-19(3)	25(3)	1(3)
C(17)	104(4)	89(3)	65(3)	-4(2)	6(2)	-39(3)
C(18)	81(3)	71(2)	50(2)	1(2)	8(2)	-10(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **118b**.

	x	y	z	U(eq)
H(1C)	11954	6709	6536	58
H(1A)	12774	6712	9018	51
H(1B)	10838	6943	9388	51
H(2A)	10704	6037	10414	64
H(2B)	12929	6310	10883	64
H(3A)	14163	5622	9686	74
H(3B)	13107	5247	10509	74
H(4A)	10133	5133	8936	70
H(4B)	12015	4882	8531	70
H(5A)	9880	5511	7042	54
H(5B)	12135	5764	7448	54
H(10A)	5011	7302	5633	54
H(11A)	7012	8109	6665	85
H(11B)	6315	8247	5290	85
H(11C)	8567	8025	5894	85
H(12A)	5802	7379	3813	66
H(12B)	8068	7167	4399	66
H(14A)	8883	6106	4567	89
H(15A)	8083	5100	4128	119
H(16A)	4682	4809	3371	121
H(17A)	2122	5539	3057	107

Table 6. Torsion angles [°] for **184b**.

C(6)-C(1)-C(2)-C(3)	54.9(4)	C(1)-C(2)-C(3)-C(4)	-57.5(4)
C(2)-C(3)-C(4)-C(5)	57.2(4)	C(3)-C(4)-C(5)-C(6)	-54.0(4)
C(9)-O(3)-C(6)-C(7)	-0.8(3)	C(9)-O(3)-C(6)-C(1)	119.0(3)
C(9)-O(3)-C(6)-C(5)	-120.2(2)	C(2)-C(1)-C(6)-O(3)	67.7(3)
C(2)-C(1)-C(6)-C(7)	-179.5(3)	C(2)-C(1)-C(6)-C(5)	-51.1(4)
C(4)-C(5)-C(6)-O(3)	-68.3(3)	C(4)-C(5)-C(6)-C(7)	179.1(3)
C(4)-C(5)-C(6)-C(1)	50.4(4)	O(3)-C(6)-C(7)-O(1)	-178.5(2)
C(1)-C(6)-C(7)-O(1)	65.3(4)	C(5)-C(6)-C(7)-O(1)	-62.5(4)
O(3)-C(6)-C(7)-C(8)	1.1(3)	C(1)-C(6)-C(7)-C(8)	-115.1(3)
C(5)-C(6)-C(7)-C(8)	117.1(3)	O(1)-C(7)-C(8)-C(9)	178.7(3)
C(6)-C(7)-C(8)-C(9)	-0.9(3)	O(1)-C(7)-C(8)-C(10)	-0.3(5)
C(6)-C(7)-C(8)-C(10)	-180.0(3)	C(6)-O(3)-C(9)-O(2)	-179.9(3)
C(6)-O(3)-C(9)-C(8)	0.4(3)	C(7)-C(8)-C(9)-O(2)	-179.4(3)
C(10)-C(8)-C(9)-O(2)	-0.2(5)	C(7)-C(8)-C(9)-O(3)	0.3(3)
C(10)-C(8)-C(9)-O(3)	179.5(3)	C(7)-C(8)-C(10)-C(11)	-65.0(4)
C(9)-C(8)-C(10)-C(11)	116.1(3)	C(7)-C(8)-C(10)-C(12)	59.8(4)
C(9)-C(8)-C(10)-C(12)	-119.2(3)	C(8)-C(10)-C(12)-C(13)	54.1(4)
C(11)-C(10)-C(12)-C(13)	179.2(3)	C(10)-C(12)-C(13)-C(18)	82.0(4)
C(10)-C(12)-C(13)-C(14)	-99.2(4)	C(18)-C(13)-C(14)-C(15)	-0.6(6)
C(12)-C(13)-C(14)-C(15)	-179.5(4)	C(13)-C(14)-C(15)-C(16)	0.6(8)
C(14)-C(15)-C(16)-C(17)	0.1(9)	C(15)-C(16)-C(17)-C(18)	-0.9(8)
C(14)-C(13)-C(18)-C(17)	-0.2(6)	C(12)-C(13)-C(18)-C(17)	178.7(4)
C(14)-C(13)-C(18)-Cl	-177.8(3)	C(12)-C(13)-C(18)-Cl	1.1(5)
C(16)-C(17)-C(18)-C(13)	0.9(7)	C(16)-C(17)-C(18)-Cl	178.6(4)

Symmetry transformations used to generate equivalent atoms:

Table A 2: Crystal data for the structural determination of compound 189

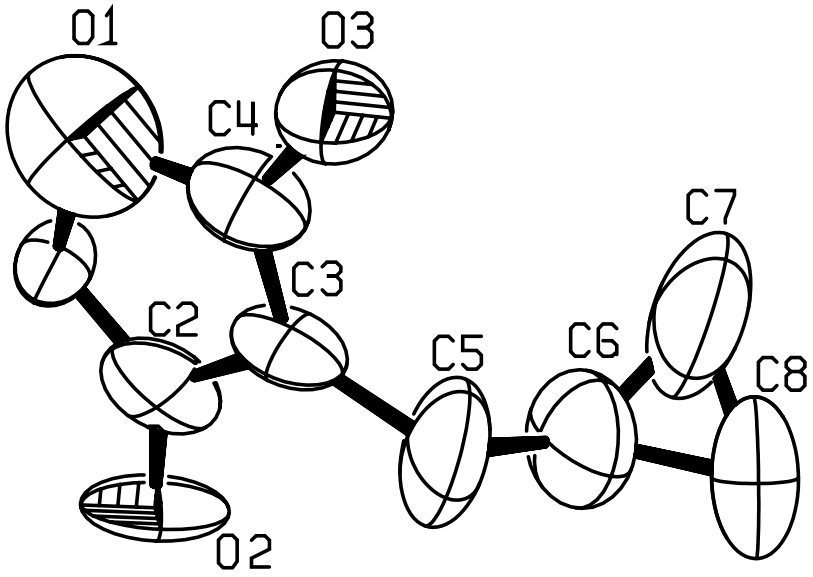


Table 1. Crystal data and structure refinement for **189.**

Empirical formula	$C_8 H_{10} O_3$	
Formula weight	154.16	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pca2(1)	
Unit cell dimensions	a = 7.9689(16) Å	α= 90°.
	b = 6.3941(13) Å	β= 90°.
	c = 31.734(6) Å	γ = 90°.
Volume	1617.0(6) $Å^3$	
Z	8	
Density (calculated)	1.267 Mg/m^3	
Absorption coefficient	0.097 mm^{-1}	
F(000)	656	
Crystal size	0.22 x 0.18 x 0.14 mm^3	
Theta range for data collection	2.57 to 26.47°.	
Index ranges	-9<=h<=9, -7<=k<=7, -38<=l<=38	
Reflections collected	4971	
Independent reflections	2141 [R(int) = 0.2330]	
Completeness to theta = 26.47°	79.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2141 / 1 / 209	
Goodness-of-fit on F^2	1.241	
Final R indices [I>2sigma(I)]	R1 = 0.1435, wR2 = 0.3411	
R indices (all data)	R1 = 0.2164, wR2 = 0.4093	

Absolute structure parameter	9(6)
Extinction coefficient	0.004(6)
Largest diff. peak and hole	0.351 and -0.420 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3)for **189**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	3684(17)	5290(30)	1214(6)	140(6)
O(2)	3894(12)	-31(14)	995(4)	87(3)
O(3)	5112(13)	6897(18)	589(3)	83(3)
C(1)	3265(17)	3104(17)	1285(3)	53(3)
C(2)	3989(14)	1920(30)	992(5)	75(4)
C(3)	4746(14)	3240(20)	667(5)	60(3)
C(4)	4480(17)	5140(20)	788(6)	72(4)
C(5)	5550(50)	2520(40)	263(6)	213(19)
C(6)	4420(30)	1920(30)	-79(7)	116(7)
C(7)	3820(40)	3380(50)	-349(6)	158(11)
C(8)	4940(40)	1950(60)	-512(5)	151(12)
O(4)	6507(10)	1831(15)	1869(3)	64(3)
O(5)	4723(15)	-1908(16)	2588(4)	90(4)
O(6)	5893(18)	4956(16)	2156(3)	101(4)
C(9)	6090(20)	-300(19)	1966(3)	72(4)
C(10)	5187(13)	-197(19)	2380(4)	51(3)
C(11)	4972(15)	1830(30)	2508(4)	62(4)
C(12)	5707(16)	3060(20)	2199(4)	60(3)
C(13)	4226(17)	2650(20)	2883(5)	66(3)
C(14)	5120(30)	3390(40)	3198(10)	133(8)
C(15)	4720(40)	3310(40)	3660(8)	142(11)
C(16)	6120(110)	1950(80)	3445(12)	210(40)
C(16')	5790(170)	2000(200)	3640(40)	540(30)

Table 3. Bond lengths [Å] and angles [°] for **189**.

O(1)-C(1)	1.458(19)	O(1)-C(4)	1.49(3)
O(2)-C(2)	1.251(18)	O(3)-C(4)	1.384(18)
C(1)-C(2)	1.33(2)	C(2)-C(3)	1.46(2)
C(3)-C(4)	1.29(2)	C(3)-C(5)	1.50(3)
C(5)-C(6)	1.46(4)	C(6)-C(7)	1.36(3)
C(6)-C(8)	1.43(3)	C(7)-C(8)	1.38(4)
O(4)-C(12)	1.453(15)	O(4)-C(9)	1.435(16)
O(5)-C(10)	1.331(16)	O(6)-C(12)	1.232(15)
C(9)-C(10)	1.500(18)	C(10)-C(11)	1.368(18)
C(11)-C(12)	1.39(2)	C(11)-C(13)	1.431(19)
C(13)-C(14)	1.32(3)	C(14)-C(16)	1.44(5)
C(14)-C(15)	1.50(4)	C(14)-C(16')	1.75(6)
C(15)-C(16')	1.20(19)	C(15)-C(16)	1.57(5)
C(16)-C(16')	0.68(16)	C(1)-O(1)-C(4)	100.0(13)
C(2)-C(1)-O(1)	109.7(12)	O(2)-C(2)-C(1)	122.4(14)
O(2)-C(2)-C(3)	127.2(16)	C(1)-C(2)-C(3)	110.2(14)
C(4)-C(3)-C(2)	105.3(14)	C(4)-C(3)-C(5)	127.8(17)
C(2)-C(3)-C(5)	126.9(18)	C(3)-C(4)-O(3)	124.5(16)
C(3)-C(4)-O(1)	113.7(14)	O(3)-C(4)-O(1)	120.9(15)
C(6)-C(5)-C(3)	117(3)	C(7)-C(6)-C(8)	59.2(17)
C(7)-C(6)-C(5)	121(2)	C(8)-C(6)-C(5)	122(3)
C(6)-C(7)-C(8)	63.2(19)	C(7)-C(8)-C(6)	57.7(16)
C(12)-O(4)-C(9)	104.9(10)	O(4)-C(9)-C(10)	104.8(9)
O(5)-C(10)-C(11)	126.6(13)	O(5)-C(10)-C(9)	122.1(11)
C(11)-C(10)-C(9)	111.2(11)	C(10)-C(11)-C(12)	105.8(11)
C(10)-C(11)-C(13)	130.3(14)	C(12)-C(11)-C(13)	123.8(14)
O(6)-C(12)-C(11)	133.5(13)	O(6)-C(12)-O(4)	113.5(12)
C(11)-C(12)-O(4)	112.9(12)	C(14)-C(13)-C(11)	122.5(16)
C(13)-C(14)-C(16)	119(4)	C(13)-C(14)-C(15)	128(2)
C(16)-C(14)-C(15)	64(2)	C(13)-C(14)-C(16')	126(4)
C(16)-C(14)-C(16')	22(7)	C(15)-C(14)-C(16')	42(7)
C(16')-C(15)-C(14)	80(5)	C(16')-C(15)-C(16)	24(5)
C(14)-C(15)-C(16)	56.1(19)	C(16')-C(16)-C(14)	105(10)
C(16')-C(16)-C(15)	46(10)	C(14)-C(16)-C(15)	60(2)
C(16)-C(16')-C(15)	110(10)	C(16)-C(16')-C(14)	53(7)
C(15)-C(16')-C(14)	57(3)		

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for g3. The anisotropicdisplacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	104(9)	151(15)	166(13)	7(12)	-29(11)	-37(9)
O(2)	77(6)	25(7)	159(10)	9(6)	14(7)	11(4)
O(3)	110(8)	55(8)	84(6)	-1(6)	4(5)	3(5)
C(1)	96(8)	20(6)	43(5)	4(5)	16(5)	-15(6)
C(2)	28(5)	94(13)	102(9)	26(10)	1(6)	15(6)
C(3)	61(7)	25(8)	92(9)	8(6)	-18(7)	-11(5)
C(4)	66(7)	50(11)	100(10)	14(8)	-9(8)	-14(6)
C(5)	460(60)	130(20)	49(8)	-23(11)	-3(17)	90(20)
C(6)	155(17)	116(17)	79(10)	-18(12)	-35(11)	-3(13)
C(7)	180(20)	230(30)	63(10)	-40(16)	-1(13)	30(20)
C(8)	220(30)	190(30)	50(8)	11(13)	-1(13)	20(20)
O(4)	59(4)	43(6)	92(6)	-5(5)	4(4)	2(3)
O(5)	122(8)	37(7)	110(8)	13(7)	11(7)	-23(6)
O(6)	180(11)	41(8)	82(6)	3(5)	11(8)	-28(7)
C(9)	131(12)	27(8)	58(6)	-8(5)	1(8)	33(7)
C(10)	55(6)	40(8)	58(5)	-6(5)	-8(5)	7(4)
C(11)	71(7)	62(11)	54(6)	-11(6)	-5(6)	12(6)
C(12)	78(8)	45(9)	56(6)	-9(6)	-3(6)	5(7)
C(13)	64(8)	57(10)	77(8)	-5(7)	7(7)	-1(6)
C(14)	170(20)	93(17)	131(19)	9(14)	21(17)	21(14)
C(15)	210(30)	98(18)	112(16)	-51(14)	27(17)	20(16)
C(16)	430(100)	120(40)	90(20)	30(20)	40(40)	210(60)
C(16')	560(80)	640(90)	420(80)	460(70)	-440(60)	-538

Table A 3: Crystal data for the structural determination of compound 212c

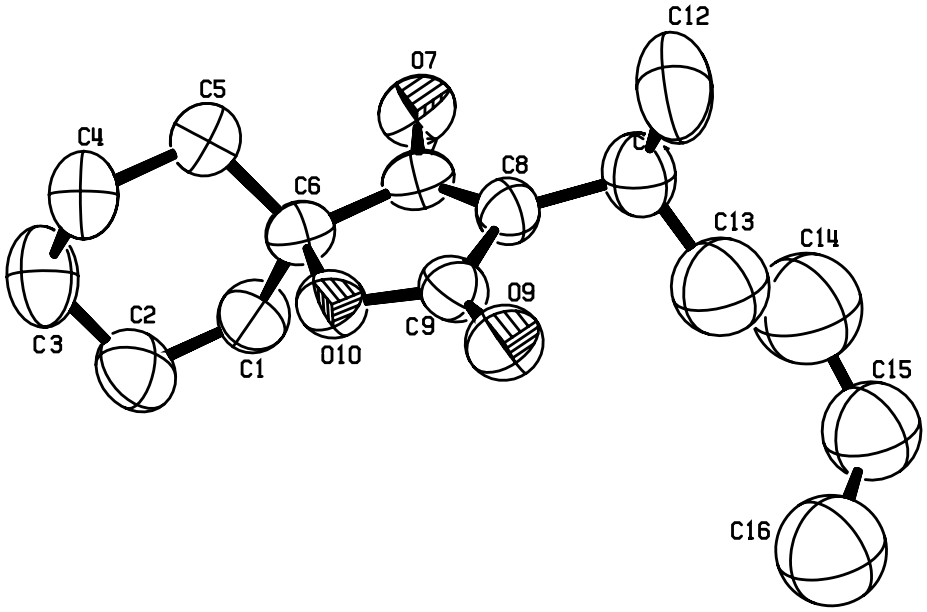


Table 1. Crystal data and structure refinement for **212c**.

Crystal data	
Chemical formula	$C_{15}H_{22}O_3$
M_r	250.33
Cell setting, space group	Tetragonal, *I*4(1)/*a*
a, *c* (Å)	17.3260 (15), 19.597 (2)
V (Å^3)	5882.7 (10)
Z	16
D_x (Mg m^{-3})	1.126
Radiation type	Mo *K*α
No. of reflections for cell parameters	?
θ range (°)	?–?
μ (mm^{-1})	0.08
Temperature (K)	153 (2)
Crystal form, colour	Block, colourless
Crystal size (mm)	MISSING × MISSING × MISSING
Data collection	
Diffractometer	CCD area detector
Data collection method	phi and ω scans
Absorption correction	None
T_{min}	–
T_{max}	–
No. of measured, independent and observed parameters	15708, 3028, 1031
Criterion for observed reflections	$I > 2\sigma(I)$
R_{int}	0.114
θ_{max} (°)	26.4

Range of *h, k, l*	$-21 \rightarrow h \rightarrow 21$ $-16 \rightarrow k \rightarrow 21$ $-19 \rightarrow l \rightarrow 24$
Refinement	
Refinement on	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.084, 0.274, 1.10
No. of relections	3028 reflections
No. of parameters	159
H-atom treatment	Mixture of independent and constrained re-
finement	
Weighting scheme	Calculated $w = 1/[\sigma^2(F_o^2) + (0.105P)^2]$
where $P = (F_o^2 + 2F_c^2)/3$	
$(\Delta/\sigma)_{max}$	2.182
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.43, –0.36

Table 2 - Final Coordinates and Equivalent Isotropic DisplacementParameters of the non-Hydrogen atoms for: **212c**

Atom	x	y	z	U(eq) [Ang^2]
O7	0.63988(17)	0.64682(17)	0.07179(16)	0.0667(12)
O9	0.86712(18)	0.58953(18)	0.19420(15)	0.0690(12)
O10	0.74485(16)	0.61108(16)	0.22436(15)	0.0597(11)
C1	0.6138(3)	0.5665(3)	0.2066(3)	0.0693(19)
C2	0.5910(3)	0.5658(3)	0.2804(3)	0.087(3)
C3	0.5621(3)	0.6440(4)	0.3038(3)	0.095(3)
C4	0.6224(3)	0.7058(3)	0.2905(3)	0.074(2)
C5	0.6450(2)	0.7072(3)	0.2165(2)	0.0603(17)
C6	0.6718(2)	0.6293(2)	0.1904(2)	0.0533(17)
C7	0.6952(3)	0.6300(2)	0.1171(2)	0.0553(17)
C8	0.7702(3)	0.6150(2)	0.1091(2)	0.0557(17)
C9	0.8003(3)	0.6041(2)	0.1766(2)	0.0577(17)
C11	0.8190(3)	0.6133(3)	0.0461(3)	0.078(2)
C12	0.8740(4)	0.6810(4)	0.0423(3)	0.113(3)
*C13	0.8585(4)	0.5348(4)	0.0384(4)	0.123(3)
*C14	0.8702(9)	0.4930(9)	-0.0087(9)	0.162(7)

*C15	0.9133(8)	0.4155(8)	-0.0012(7)	0.127(5)
*C16	0.9442(10)	0.3791(9)	0.0703(8)	0.154(7)
*C13'	0.8585(4)	0.5348(4)	0.0384(4)	0.123(3)
*C14'	0.873(3)	0.4675(16)	0.044(3)	0.45(4)
*C15'	0.9113(19)	0.3844(16)	0.038(2)	0.207(12)
*C16'	0.909(3)	0.2933(18)	0.031(2)	0.48(3)

U(eq) = 1/3 of the trace of the orthogonalized U Tensor
Starred Atom sites have a S.O.F less than 1.0

Table 3 - Hydrogen Atom Positions and Isotropic DisplacementParameters for: **212c**

Atom	x	y	z	U(iso) [Ang^2]
H1B	0.63630	0.51580	0.19450	0.0830
H2A	0.63610	0.55060	0.30850	0.1050
H1A	0.56720	0.57420	0.17820	0.0830
H3A	0.55030	0.64210	0.35320	0.1140
H3B	0.51400	0.65710	0.27910	0.1140
H2B	0.55000	0.52690	0.28750	0.1050
H4B	0.66860	0.69560	0.31880	0.0880
H5A	0.68700	0.74530	0.21010	0.0720
H5B	0.60020	0.72440	0.18910	0.0720
H11	0.78290	0.61850	0.00650	0.0940
H12A	0.88440	0.69340	-0.00560	0.1700
H12B	0.92250	0.66760	0.06520	0.1700
H12C	0.85080	0.72580	0.06480	0.1700
*H13	0.87780	0.51520	0.08040	0.1470
*H14	0.85240	0.50800	-0.05260	0.1940
*H15A	0.95890	0.41900	-0.03140	0.1520
*H15B	0.87910	0.37590	-0.02160	0.1520
*H16A	0.99010	0.40730	0.08530	0.2310
*H16B	0.95720	0.32460	0.06350	0.2310
*H16C	0.90370	0.38350	0.10500	0.2310
H4A	0.60150	0.75690	0.30370	0.0880
*H14'	0.83210	0.45400	0.07370	0.5400
*H15C	0.94620	0.38790	0.07760	0.2490
*H15D	0.94560	0.39520	-0.00160	0.2490
*H16D	0.96030	0.27230	0.04230	0.7130
*H16E	0.89570	0.27900	-0.01580	0.7130

Table 4 - (An)isotropic Displacement Parameters for: **212c**

Atom	U(1,1) or	U U(2,2)	U(3,3)	U(2,3)	U(1,3)	U(1,2)
O7	0.061(2)	0.070(2)	0.069(2)-	0.0058(16)	-0.0207(17)	0.0037(15)
O9	0.055(2)	0.081(2)	0.071(2)	0.0090(17)	-0.0065(17)	0.0093(17)
O10	0.0542(19)	0.068(2)	0.057(2)	0.0076(15)	-0.0045(16)	0.0048(15)
C1	0.061(3)	0.062(3)	0.085(4)	-0.002(3)	0.008(3)	-0.010(2)
C2	0.078(4)	0.090(4)	0.094(5)	0.010(3)	0.017(3)	-0.019(3)
C3	0.071(4)	0.121(5)	0.092(4)	-0.019(4)	0.020(3)	-0.013(4)
C4	0.064(3)	0.087(4)	0.070(4)	-0.015(3)	0.006(3)	-0.006(3)
C5	0.053(3)	0.064(3)	0.064(3)	-0.005(2)	-0.005(2)	-0.002(2)
C6	0.045(3)	0.053(3)	0.062(3)	0.001(2)	-0.007(2)	-0.001(2)
C7	0.058(3)	0.045(3)	0.063(3)	0.000(2)	-0.010(3)	0.000(2)
C8	0.056(3)	0.060(3)	0.051(3)	0.000(2)	0.001(2)	0.003(2)
C9	0.055(3)	0.059(3)	0.059(3)	0.008(2)	0.002(3)	-0.002(2)
C11	0.078(4)	0.095(4)	0.061(4)	-0.005(3)	-0.001(3)	0.001(3)
C12	0.099(5)	0.130(6)	0.110(5)	-0.022(4)	0.037(4)	-0.019(4)

Table 5 - Bond Distances (Angstrom) for: **212c**

O7	-C7	1.339(6)	C3	-H3B	0.9901
O9	-C9	1.234(6)	C4	-H4A	0.9909
O10	-C6	1.464(5)	C4	-H4B	0.9897
O10	-C9	1.347(5)	C5	-H5A	0.9905
C1	-C2	1.499(8)	C5	-H5B	0.9898
C1	-C6	1.515(6)	C11	-H11	1.0008
C2	-C3	1.516(9)	C12	-H12A	0.9797
C3	-C4	1.519(8)	C12	-H12B	0.9805
C4	-C5	1.502(7)	C12	-H12C	0.9790
C5	-C6	1.516(6)	C13	-H13	0.9511
C6	-C7	1.493(6)	C14	-H14	0.9501
C7	-C8	1.334(7)	C15	-H15A	0.9890
C8	-C9	1.434(6)	C15	-H15B	0.9908
C8	-C11	1.497(7)	C16	-H16A	0.9786
C11	-C12	1.513(9)	C16	-H16B	0.9799
C11	-C13	1.530(9)	C16	-H16C	0.9801
C11	-C13'	1.530(9)	C14'	-C15'	1.59(4)
C13	-C14	1.191(18)	C15'	-C16'	1.58(4)
C14	-C15	1.54(2)	C14'	-H14'	0.9464
C15	-C16	1.63(2)	C15'	-H15C	0.9857
C1	-H1A	0.9897	C15'	-H15D	0.9952

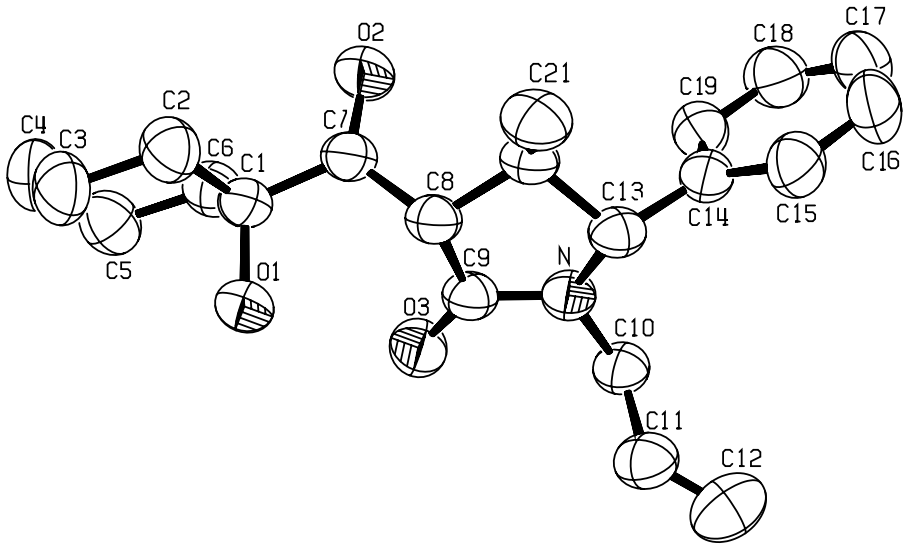
C1	-H1B	0.9899	C16'	-H16D	0.9856
C2	-H2A	0.9916	C16'	-H16E	0.9776
C2	-H2B	0.9891	C16'	-H16F	0.9779
C3	-H3A	0.9900			

Table 6 - Bond Angles (Degrees) for: **212c**

C6-O10-C9	108.7(3)	C1-C15-C16	125.3(12)
C2-C1-C6	112.5(4)	C2-C1-H1A	109.18
C1-C2 -C3	111.8(5)	C2-C1-H1B	109.13
C2-C3-C4	110.6(4)	C6-C1-H1A	109.06
C3-C4-C5	110.9(4)	C6-C1-H1B	109.02
C4-C5-C6	113.0(4)	H1A-C1-H1B	107.83
O10-C6-C1	108.9(3)	C1-C2-H2A	109.28
O10-C6-C5	107.7(3)	C1-C2-H2B	109.30
O10-C6-C7	101.8(3)	C3-C2-H2A	109.26
C1-C6-C5	111.4(3)	C3-C2-H2B	109.23
C1-C6-C7	112.8(4)	H2A-C2-H2B	107.87
C5-C6-C7	113.6(3)	C2-C3-H3A	109.54
O7-C7-C6	116.5(4)	C2-C3-H3B	109.58
O7-C7-C8	131.4(4)	C4-C3-H3A	109.47
C6-C7-C8	112.1(4)	C4-C3-H3B	109.48
C7-C8-C9	105.7(4)	H3A-C3-H3B	108.17
C7-C8-C11	130.6(4)	C3-C4-H4A	109.50
C9-C8-C11	123.6(5)	C3-C4-H4B	109.53
O9-C9-O10	119.6(4)	C5-C4-H4A	109.44
O9-C9-C8	128.7(4)	C5-C4-H4B	109.45
O10-C9-C8	111.7(4)	H4A-C4-H4B	107.99
C8-C11-C12	112.4(4)	C4-C5-H5A	108.93
C8-C11-C13	110.6(5)	C4-C5-H5B	108.91
C8-C11-C13'	110.6(5)	C6-C5-H5A	109.00
C12-C11-C13	113.7(5)	C6-C5-H5B	108.98
C12-C11-C13'	113.7(5)	H5A-C5-H5B	107.87
C11-C13-C14	133.9(10)	C8-C11-H11	106.55
C13-C14-C15	122.5(14)	C12-C11-H11	106.60
C13-C11-H11	106.45	C15-C16-H16B	109.39
C13'-C1-H11	106.45	C15-C16-H16C	109.37
C11-C12-H12A	109.45	H16A-C16-H16B	109.58
C11-C12-H12B	109.49	H16A-C16-H16C	109.55
C11-C12-H12C	109.50	H16B-C16-H16C	109.50
H12A-C12-H12B	109.44	C14'-C15'-C16'	154(3)
H12A-C12-H12C	109.46	C15'-C14'-H14'	97.71
H12B-C12-H12C	109.48	C14'-C15'-H15C	98.17
C11-C13-H13	112.91	C14'-C15'-H15D	97.85

C14-C13-H13	113.19	C16'-C15'-H15C	98.33
C13-C14-H14	118.71	C16'-C15'-H15D	97.75
C15-C14-H14	118.77	H15C-C15'-H15D	103.65
C14-C15-H15A	106.03	C15'-C16'-H16D	109.00
C14-C15-H15B	105.94	C15'-C16'-H16E	109.85
C16-C15-H15A	106.04	C15'-C16'-H16F	109.43
C16-C15-H15B	106.01	H16D-C16'-H16E	109.26
H15A-C15-H15B	106.19	H16D-C16'-H16F	109.28
C15-C16-H16A	109.42	H16E-C16'-H16F	110.01

Table A 4: Crystal data for the structural determination of compound 218a



Empirical formula	$C_{21}H_{27}NO_3$	
Formula weight	341.44	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 5.9991(12) Å	α= 91.28(3)°.
	b = 11.495(2) Å	β= 95.95(3)°.
	c = 14.318(3) Å	γ = 100.10(3)°.
Volume	966.0(3) $Å^3$	
Z	2	
Density (calculated)	1.174 Mg/m^3	
Absorption coefficient	0.078 mm^{-1}	
F(000)	368	
Crystal size	0.22 x 0.17 x 0.09 mm^3	
Theta range for data collection	2.25 to 26.01°.	
Index ranges	-6<=h<=6, -14<=k<=13, -17<=l<=17	
Reflections collected	6781	
Independent reflections	3499 [R(int) = 0.0270]	
Completeness to theta = 26.01°	91.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3499 / 0 / 226	
Goodness-of-fit on F^2	0.911	
Final R indices [I>2sigma(I)]	R1 = 0.0440, wR2 = 0.1055	
R indices (all data)	R1 = 0.0718, wR2 = 0.1183	
Largest diff. peak and hole	0.141 and -0.136 $e.Å^{-3}$	

Table 1: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **219a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	2908(2)	1591(1)	6425(1)	73(1)
O(2)	758(3)	3378(1)	8055(1)	89(1)
O(3)	4370(2)	3872(1)	5952(1)	73(1)
N	6303(2)	5288(1)	7021(1)	55(1)
C(1)	1198(3)	1849(1)	6973(1)	57(1)
C(2)	677(4)	799(2)	7602(1)	73(1)
C(3)	-326(4)	-328(2)	7023(2)	85(1)
C(4)	-2449(4)	-184(2)	6400(2)	91(1)
C(5)	-1999(4)	855(2)	5778(2)	80(1)
C(6)	-950(3)	1985(2)	6346(1)	68(1)
C(7)	2043(3)	2968(1)	7600(1)	58(1)
C(8)	4543(3)	3552(1)	7645(1)	53(1)
C(9)	5026(3)	4233(2)	6766(1)	55(1)
C(10)	7327(3)	6067(2)	6326(1)	60(1)
C(11)	9610(4)	5849(2)	6127(1)	72(1)
C(12)	11322(4)	6652(2)	6025(2)	96(1)
C(13)	7073(3)	5432(1)	8030(1)	54(1)
C(14)	7058(3)	6651(2)	8443(1)	56(1)
C(15)	8826(4)	7192(2)	9092(1)	75(1)
C(16)	8740(5)	8263(2)	9532(2)	98(1)
C(17)	6923(6)	8815(2)	9324(2)	100(1)
C(18)	5176(5)	8299(2)	8674(2)	86(1)
C(19)	5226(4)	7220(2)	8241(1)	67(1)
C(20)	5385(3)	4462(1)	8452(1)	54(1)
C(21)	6419(4)	3967(2)	9340(1)	72(1)

Table 2: Bond lengths [Å] and angles [°] for **219a.**

O(1)-C(1)	1.421(2)	O(2)-C(7)	1.208(2)
O(3)-C(9)	1.2300(19)	N-C(9)	1.338(2)
N-C(10)	1.464(2)	N-C(13)	1.468(2)
C(1)-C(6)	1.526(3)	C(1)-C(2)	1.530(2)
C(1)-C(7)	1.530(2)	C(2)-C(3)	1.517(3)
C(3)-C(4)	1.513(3)	C(4)-C(5)	1.509(3)#
C(5)-C(6)	1.517(3)	C(7)-C(8)	1.526(3)
C(8)-C(9)	1.523(2)	C(8)-C(20)	1.525(2)
C(10)-C(11)	1.489(3)	C(11)-C(12)	1.277(3)
C(13)-C(14)	1.511(2)	C(13)-C(20)	1.547(2)

C(14)-C(19)	1.383(3)	C(14)-C(15)	1.384(3)
C(15)-C(16)	1.381(3)	C(16)-C(17)	1.366(4)
C(17)-C(18)	1.368(4)	C(18)-C(19)	1.381(3)
C(20)-C(21)	1.522(2)	C(9)-N-C(10)	121.33(13)
C(9)-N-C(13)	113.67(13)	C(10)-N-C(13)	122.91(14)
O(1)-C(1)-C(6)	110.83(14)	O(1)-C(1)-C(2)	106.17(14)
C(6)-C(1)-C(2)	109.92(16)	O(1)-C(1)-C(7)	111.44(14)
C(6)-C(1)-C(7)	109.81(14)	C(2)-C(1)-C(7)	108.58(13)
C(3)-C(2)-C(1)	111.18(15)	C(4)-C(3)-C(2)	111.23(18)
C(5)-C(4)-C(3)	111.60(18)	C(4)-C(5)-C(6)	111.60(17)
C(5)-C(6)-C(1)	112.11(15)	O(2)-C(7)-C(8)	120.53(16)
O(2)-C(7)-C(1)	120.63(17)	C(8)-C(7)-C(1)	118.84(14)
C(9)-C(8)-C(20)	104.26(13)	C(9)-C(8)-C(7)	111.47(14)
C(20)-C(8)-C(7)	115.42(13)	O(3)-C(9)-N	125.20(15)
O(3)-C(9)-C(8)	125.82(16)	N-C(9)-C(8)	108.98(13)
N-C(10)-C(11)	113.55(15)	C(12)-C(11)-C(10)	125.2(2)
N-C(13)-C(14)	113.77(13)	N-C(13)-C(20)	102.66(13)
C(14)-C(13)-C(20)	112.37(13)	C(19)-C(14)-C(15)	118.09(18)
C(19)-C(14)-C(13)	121.56(15)	C(15)-C(14)-C(13)	120.19(18)
C(16)-C(15)-C(14)	120.7(2)	C(17)-C(16)-C(15)	120.6(2)
C(16)-C(17)-C(18)	119.4(2)	C(17)-C(18)-C(19)	120.5(2)
C(18)-C(19)-C(14)	120.69(19)	C(21)-C(20)-C(8)	114.69(14)
C(21)-C(20)-C(13)	113.20(15)	C(8)-C(20)-C(13)	104.48(12)

Symmetry transformations used to generate equivalent atoms:

Table 3. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **219a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	70(1)	66(1)	86(1)	-15(1)	27(1)	11(1)
O(2)	74(1)	83(1)	109(1)	-31(1)	39(1)	4(1)
O(3)	89(1)	78(1)	45(1)	-2(1)	8(1)	-3(1)
N	62(1)	60(1)	40(1)	4(1)	9(1)	5(1)
C(1)	61(1)	53(1)	60(1)	-1(1)	18(1)	12(1)
C(2)	89(2)	61(1)	68(1)	6(1)	8(1)	12(1)
C(3)	112(2)	53(1)	86(1)	9(1)	11(1)	5(1)
C(4)	93(2)	73(1)	99(2)	-10(1)	8(1)	-8(1)
C(5)	77(2)	81(1)	80(1)	-9(1)	-2(1)	18(1)
C(6)	71(1)	67(1)	70(1)	3(1)	11(1)	22(1)
C(7)	67(1)	54(1)	58(1)	2(1)	21(1)	14(1)
C(8)	60(1)	54(1)	48(1)	4(1)	14(1)	14(1)
C(9)	58(1)	63(1)	45(1)	1(1)	10(1)	11(1)
C(10)	65(1)	66(1)	47(1)	8(1)	10(1)	8(1)

C(11)	79(2)	73(1)	68(1)	14(1)	22(1)	15(1)
C(12)	69(2)	119(2)	100(2)	23(1)	11(1)	17(1)
C(13)	54(1)	64(1)	44(1)	5(1)	6(1)	12(1)
C(14)	60(1)	60(1)	44(1)	4(1)	6(1)	4(1)
C(15)	72(1)	83(1)	62(1)	-1(1)	-2(1)	-2(1)
C(16)	110(2)	89(2)	79(1)	-21(1)	3(1)	-23(2)
C(17)	128(2)	65(1)	102(2)	-19(1)	36(2)	-6(2)
C(18)	101(2)	65(1)	99(2)	3(1)	30(1)	19(1)
C(19)	72(1)	64(1)	63(1)	0(1)	6(1)	11(1)
C(20)	62(1)	60(1)	44(1)	4(1)	13(1)	15(1)
C(21)	90(2)	79(1)	49(1)	11(1)	11(1)	20(1)

Table 4. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **219a**.

	x	y	z	U(eq)
H(1A)	3552	2204	6217	109
H(2A)	2067	691	7973	87
H(2B)	-391	962	8031	87
H(3A)	796	-531	6635	101
H(3B)	-698	-970	7439	101
H(4A)	-2996	-899	6011	109
H(4B)	-3630	-71	6790	109
H(5A)	-3419	961	5430	96
H(5B)	-977	693	5329	96
H(6A)	-2056	2204	6734	81
H(6B)	-576	2617	5920	81
H(8A)	5478	2933	7694	64
H(10A)	7468	6882	6550	71
H(10B)	6315	5961	5744	71
H(11A)	9806	5066	6073	86
H(12A)	11195	7445	6074	115
H(12B)	12695	6443	5902	115
H(13A)	8615	5253	8142	64
H(15A)	10085	6832	9234	90
H(16A)	9931	8610	9974	118
H(17A)	6874	9537	9621	120
H(18A)	3945	8677	8523	104
H(19A)	4016	6872	7808	80
H(20A)	4089	4811	8612	65
H(21A)	5298	3373	9570	107
H(21B)	6912	4594	9811	107
H(21C)	7700	3624	9201	107

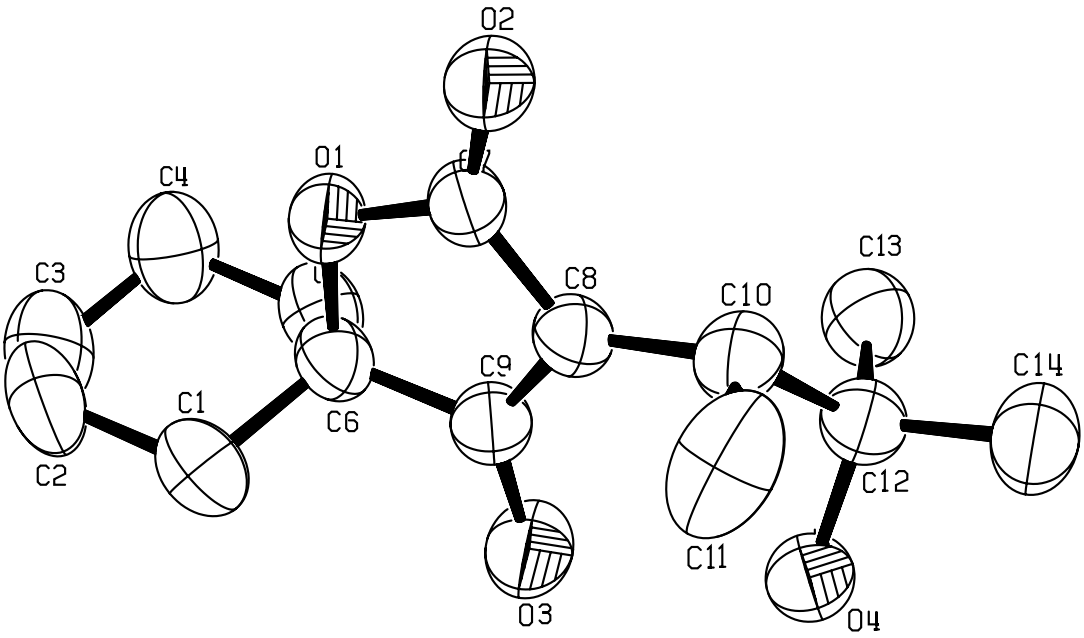
H(21B)	6912	4594	9811	107
H(21C)	7700	3624	9201	107

Table 5. Torsion angles [°] for **219a**.

O(1)-C(1)-C(2)-C(3)	-64.0(2)	C(6)-C(1)-C(2)-C(3)	55.9(2)
C(7)-C(1)-C(2)-C(3)	176.09(17)	C(1)-C(2)-C(3)-C(4)	-56.7(2)
C(2)-C(3)-C(4)-C(5)	55.5(2)	C(3)-C(4)-C(5)-C(6)	-54.2(2)
C(4)-C(5)-C(6)-C(1)	54.4(2)	O(1)-C(1)-C(6)-C(5)	62.1(2)
C(2)-C(1)-C(6)-C(5)	-54.9(2)	C(7)-C(1)-C(6)-C(5)	-174.32(15)
O(1)-C(1)-C(7)-O(2)	173.68(17)	C(6)-C(1)-C(7)-O(2)	50.5(2)
C(2)-C(1)-C(7)-O(2)	-69.7(2)	O(1)-C(1)-C(7)-C(8)	-6.8(2)
C(6)-C(1)-C(7)-C(8)	-129.96(16)	C(2)-C(1)-C(7)-C(8)	109.84(18)
O(2)-C(7)-C(8)-C(9)	-104.50(19)	C(1)-C(7)-C(8)-C(9)	75.94(18)
O(2)-C(7)-C(8)-C(20)	14.2(2)	C(1)-C(7)-C(8)-C(20)	-165.38(14)
C(10)-N-C(9)-O(3)	-8.9(3)	C(13)-N-C(9)-O(3)	-172.88(17)
C(10)-N-C(9)-C(8)	170.61(15)	C(13)-N-C(9)-C(8)	6.59(19)
C(20)-C(8)-C(9)-O(3)	-170.87(17)	C(7)-C(8)-C(9)-O(3)	-45.7(2)
C(20)-C(8)-C(9)-N	9.67(18)	C(7)-C(8)-C(9)-N	134.82(15)
C(9)-N-C(10)-C(11)	-88.2(2)	C(13)-N-C(10)-C(11)	74.3(2)
N-C(10)-C(11)-C(12)	-138.5(2)	C(9)-N-C(13)-C(14)	-141.30(15)
C(10)-N-C(13)-C(14)	55.0(2)	C(9)-N-C(13)-C(20)	-19.62(18)
C(10)-N-C(13)-C(20)	176.65(14)	N-C(13)-C(14)-C(19)	45.4(2)
C(20)-C(13)-C(14)-C(19)	-70.68(19)	N-C(13)-C(14)-C(15)	-139.20(17)
C(20)-C(13)-C(14)-C(15)	104.68(18)	C(19)-C(14)-C(15)-C(16)	0.9(3)
C(13)-C(14)-C(15)-C(16)	-174.64(18)	C(14)-C(15)-C(16)-C(17)	-1.0(3)
C(15)-C(16)-C(17)-C(18)	0.1(4)	C(16)-C(17)-C(18)-C(19)	0.9(3)
C(17)-C(18)-C(19)-C(14)	-1.0(3)	C(15)-C(14)-C(19)-C(18)	0.1(3)
C(13)-C(14)-C(19)-C(18)	175.59(16)	C(9)-C(8)-C(20)-C(21)	-145.28(16)
C(7)-C(8)-C(20)-C(21)	92.12(19)	C(9)-C(8)-C(20)-C(13)	-20.76(17)
C(7)-C(8)-C(20)-C(13)	-143.36(15)	N-C(13)-C(20)-C(21)	149.48(14)
C(14)-C(13)-C(20)-C(21)	-87.89(18)	N-C(13)-C(20)-C(8)	24.01(16)
C(14)-C(13)-C(20)-C(8)	146.64(14)		

Symmetry transformations used to generate equivalent atoms:

Table A 5: Crystal data for the structural determination of compound 222



Crystal data	
Chemical formula	$C_{14}H_{22}O_4$
M_r	254.32
Cell setting, space group	Monoclinic, *P*2(1)/*c*
a, *b*, *c* (Å)	11.176 (2), 11.418 (2), 11.456 (2)
β (°)	95.39 (3)
V (Å^3)	1455.5 (5)
Z	4
D_x (Mg m^{-3})	1.161
Radiation type	Mo *K*α
No. of reflections for cell parameters	?
θ range (°)	?–?
μ (mm^{-1})	0.08
Temperature (K)	293 (2)
Crystal form, colour	Plate, colourless
Crystal size (mm)	0.28 × 0.22 × 0.10
Data collection	
Diffractometer	STOE IPDS I
Data collection method	phi scans
Absorption correction	None
T_{min}	–
T_{max}	–
No. of measured, independent and observed parameters	
9865, 2717, 1253	
Criterion for observed reflections	$I > 2\sigma(I)$

R_{int}	0.087
θ_{max} (°)	26.0
Range of *h, k, l*	$-13 \rightarrow h \rightarrow 13$ $-14 \rightarrow k \rightarrow 13$ $-13 \rightarrow l \rightarrow 13$
Refinement on	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.057, 0.131, 0.83
No. of relections	2717 reflections
No. of parameters	163
H-atom treatment	Mixture of independent and constrained refinement
Weighting scheme where $P = (F_o^2 + 2F_c^2)/3$	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0664P)^2]$
$(\Delta/\sigma)_{max}$	<0.0001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.28, –0.18

Table 2 - Final Coordinates and Equivalent Isotropic Displacement Parameters of the non-Hydrogen atoms for: **222**

Atom	x	y	z	U(eq) [Ang^2]
O1	0.70624(15)	1.57443(13)	-0.48174(14)	0.0594(7)
O2	0.77625(17)	1.47004(14)	-0.62537(17)	0.0684(8)
O3	0.76268(19)	1.40809(16)	-0.22067(16)	0.0835(8)
O4	0.85653(17)	1.20789(14)	-0.25399(15)	0.0687(7)
C1	0.7692(3)	1.6622(2)	-0.2942(3)	0.0716(11)
C2	0.7122(3)	1.7806(2)	-0.3223(3)	0.0858(15)
C3	0.5813(3)	1.7829(3)	-0.2986(3)	0.0961(16)
C4	0.5119(3)	1.6858(3)	-0.3631(3)	0.0855(14)
C5	0.5667(2)	1.5674(2)	-0.3333(3)	0.0700(11)
C6	0.6985(2)	1.5629(2)	-0.3565(2)	0.0564(9)
C7	0.7599(2)	1.4774(2)	-0.5219(2)	0.0525(9)
C8	0.7907(2)	1.3951(2)	-0.4278(2)	0.0534(9)
C9	0.7555(2)	1.4454(2)	-0.3312(2)	0.0581(10)
C10	0.8609(2)	1.2849(2)	-0.4475(2)	0.0604(10)
C11	0.9963(3)	1.3127(3)	-0.4309(3)	0.0972(14)
C12	0.8265(2)	1.1783(2)	-0.3773(2)	0.0600(10)
C13	0.6925(2)	1.1531(2)	-0.4004(3)	0.0727(11)
C14	0.8991(3)	1.0701(2)	-0.4041(3)	0.0780(11)

U(eq) = 1/3 of the trace of the orthogonalized U Tensor

Table 3 - Hydrogen Atom Positions and Isotropic Displacement Parameters for: **222**

Atom	x	y	z	U(iso) [Ang^2]
H1A	0.77390	1.64920	-0.21030	0.0860
H1B	0.85040	1.66200	-0.31750	0.0860
H2A	0.75560	1.84020	-0.27510	0.1030
H2B	0.71860	1.79890	-0.40410	0.1030
H3A	0.57530	1.77460	-0.21510	0.1150
H3B	0.54650	1.85770	-0.32320	0.1150
H3C	0.78760	1.34050	-0.21750	0.1250
H4A	0.84160	1.15190	-0.21300	0.1030
H4B	0.51050	1.69890	-0.44690	0.1030
H4C	0.42950	1.68670	-0.34280	0.1030
H5A	0.52270	1.50770	-0.37980	0.0840
H5B	0.55970	1.55040	-0.25130	0.0840
H10A	0.84280	1.26450	-0.53040	0.0730
H11A	1.01270	1.38020	-0.47680	0.1460
H11B	1.04090	1.24690	-0.45590	0.1460
H11C	1.01970	1.32830	-0.34960	0.1460
H13A	0.67240	1.08600	-0.35570	0.1090
H13B	0.67300	1.13780	-0.48240	0.1090
H13C	0.64760	1.21970	-0.37760	0.1090
H14A	0.87490	1.00520	-0.35850	0.1170
H14B	0.98310	1.08540	-0.38470	0.1170
H14C	0.88500	1.05160	-0.48600	0.1170

The Temperature Factor has the Form of Exp(-T) Where T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms

Table 4 - (An)isotropic Displacement Parameters for: **222**

Atom	U(1,1) or U	U(2,2)	U(3,3)	U(2,3)	U(1,3)	U(1,2)
O1	0.0811(12)	0.0450(10)	0.0528(12)	0.0010(7)	0.0105(8)	0.0056(8)
O2	0.1048(15)	0.0564(11)	0.0457(13)	0.0033(8)	0.0162(9)	0.0077(10)
O3	0.1414(18)	0.0668(12)	0.0439(13)	0.0029(9)	0.0177(10)	0.0197(11)
O4	0.1032(14)	0.0583(11)	0.0442(12)	0.0073(8)	0.0051(9)	0.0021(9)
C1	0.0789(19)	0.0684(17)	0.068(2)-	0.0182(14)	0.0095(14)	-0.0050(14)
C2	0.108(3)	0.0522(16)	0.098(3)	-0.0208(15)	0.0142(18)	-0.0122(16)
O3	0.1414(18)	0.0668(12)	0.0439(13)	0.0029(9)	0.0177(10)	0.0197(11)
C4	0.077(2)	0.073(2)	0.109(3)	-0.0101(18)	0.0217(18)	0.0109(16)

C5	0.0751(19)	0.0636(17)	0.074(2)	-0.0092(14)	0.0205(14)	-0.0077(14)
C6	0.0731(17)	0.0502(14)	0.0472(17)	-0.0055(11)	0.0118(12)	-0.0035(12)
C7	0.0652(16)	0.0441(13)	0.0487(18)	-0.0022(11)	0.0080(12)	-0.0017(11)
C8	0.0698(16)	0.0484(14)	0.0425(15)	-0.0017(11)	0.0078(11)	-0.0008(12)
C9	0.0796(18)	0.0519(15)	0.0432(17)	0.0013(12)	0.0077(12)	0.0008(12)
C10	0.0799(19)	0.0575(16)	0.0457(17)	0.0061(12)	0.0153(12)	0.0071(13)
C11	0.072(2)	0.084(2)	0.140(3)	0.035(2)	0.0328(19)	0.0086(16)
C12	0.0783(19)	0.0586(15)	0.0441(17)	-0.0008(11)	0.0105(12)	0.0068(13)
C13	0.0760(19)	0.0657(17)	0.077(2)	0.0024(14)	0.0100(15)	-0.0068(14)
C14	0.107(2)	0.0593(17)	0.070(2)	0.0047(14)	0.0207(16)	0.0176(15)

The Temperature Factor has the Form of Exp(-T) Where T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms T = 2*(Pi**2)*Sumij(h(i)*h(j)*U(i,j)*Astar(i)*Astar(j)), for Anisotropic Atoms. Astar(i) are Reciprocal Axial Lengths and h(i) are the Reflection Indices.

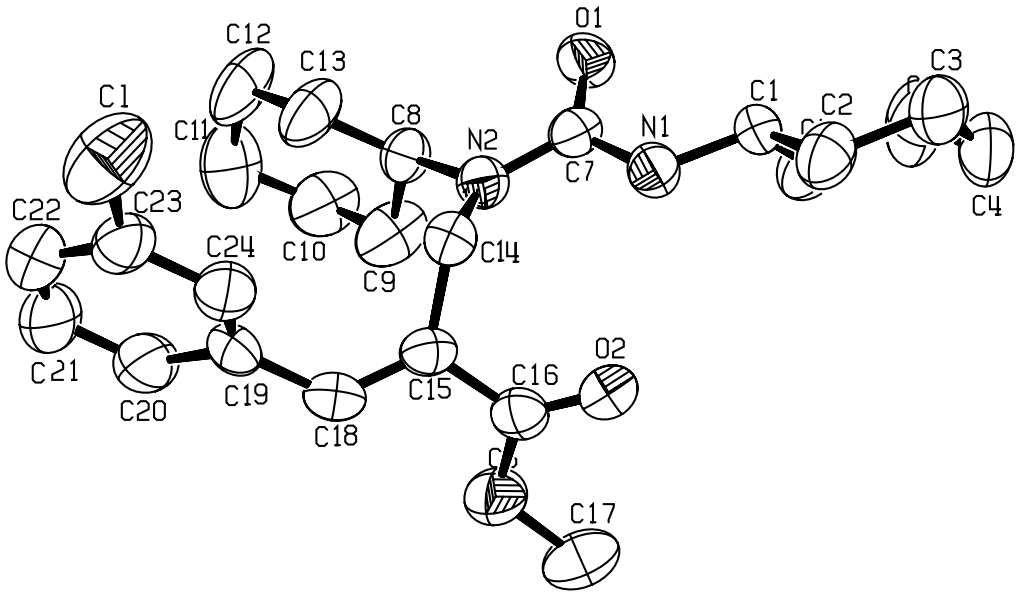
Table 5 - Bond Distances (Angstrom) for: **222**

O1-C6	1.451(3)	C1	-H1A	0.9691
O1-C7	1.360(3)	C1	-H1B	0.9697
O2-C7	1.219(3)	C2	-H2A	0.9703
O3-C9	1.331(3)	C2	-H2B	0.9693
O4-C12	1.461(3)	C3	-H3A	0.9698
O3-H3C	0.8201	C3	-H3B	0.9693
O4-H4A	0.8196	C4	-H4B	0.9703
C1-C2	1.516(4)	C4	-H4C	0.9708
C1-C6	1.521(4)	C5	-H5A	0.9701
C2-C3	1.513(5)	C5	-H5B	0.9696
C3-C4	1.506(5)	C10	-H10A	0.9803
C4-C5	1.510(4)	C11	-H11A	0.9603
C5-C6	1.522(3)	C11	-H11B	0.9601
C6-C9	1.502(3)	C11	-H11C	0.9601
C7-C8	1.447(3)	C13	-H13A	0.9598
C8-C10	1.511(3)	C13	-H13B	0.9602
C8-C9	1.338(3)	C13	-H13C	0.9607
C10-C11	1.540(4)	C14	-H14A	0.9601
C10-C12	1.528(3)	C14	-H14B	0.9602
C12-C14	1.525(4)	C14	-H14C	0.9602
C12-C13	1.524(3)			

Table 6 - Bond Angles (Degrees) for: **222**

C6-O1-C7	109.24(17)	C10-C12-C14	112.0(2)
C9-O3-H3C	109.46	C13-C12-C14	110.2(2)
C12-O4-H4A	109.45	C10-C12-C13	110.5(2)
C2-C1-C6	112.1(3)	O4-C12-C10	106.17(18)
C1-C2-C3	111.8(3)	C2-C1-H1A	109.25
C2-C3-C4	111.2(3)	C2-C1-H1B	109.21
C3-C4-C5	111.6(3)	C6-C1-H1A	109.18
C4-C5-C6	111.7(2)	C6-C1-H1B	109.11
O1-C6-C5	108.5(2)	H1A-C1-H1B	107.92
O1-C6-C1	108.6(2)	C1C2 -H2A	109.21
C1-C6-C9	112.5(2)	C1-C2-H2B	109.26
C5-C6-C9	113.35(19)	C3-C2-H2A	109.21
O1-C6-C9	102.02(18)	C3-C2-H2B	109.28
C1-C6-C5	111.2(2)	H2A-C2-H2B	108.01
O2-C7-C8	129.2(2)	C2-C3-H3A	109.45
O1-C7-O2	119.7(2)	C2-C3-H3B	109.36
O1-C7-C8	111.01(19)	C4-C3-H3A	109.38
C9-C8-C10	132.7(2)	C4-C3-H3B	109.38
C7-C8-C10	121.3(2)	H3A-C3-H3B	108.05
C7-C8-C9	105.6(2)	C3-C4-H4B	109.37
O3-C9-C8	130.8(2)	C3-C4-H4C	109.33
O3-C9-C6	117.1(2)	C5-C4-H4B	109.28
C6-C9-C8	112.1(2)	C5-C4-H4C	109.21
C8-C10-C12	115.15(19)	H4B-C4-H4C	107.93
C8-C10-C11	109.1(2)	C4-C5-H5A	109.33
C11-C10-C12	113.1(2)	C4-C5-H5B	109.29
O4-C12-C13	110.2(2)	C6-C5-H5A	109.23
O4-C12-C14	107.7(2)	C6-C5-H5B	109.26
H5A-C5-H5B	107.97	C12-C13-H13B	109.47
C8-C10-H10A	106.25	C12-C13-H13C	109.47
C11-C10-H10A	106.23	H13A-C13-H13B	109.50
C12-C10-H10A	106.35	H13A-C13-H13C	109.41
C10-C11-H11A	109.49	H13B-C13-H13C	109.49
C10-C11-H11B	109.48	C12-C14-H14A	109.47
C10-C11-H11C	109.44	C12 -C14-H14B	109.46
H11A-C11-H11B	109.48	C12 -C14-H14C	109.47
H11A-C11-H11C	109.49	H14A-C14-H14B	109.50
H11B-C11-H11C	109.44	H14A-C14-H14C	109.46
C12-C13-H13A	109.49	H14B-C14-H14C	109.47

Table A 5: Crystal data for the structural determination of compound 250a



Empirical formula	C24 H33 Cl N2 O3	
Formula weight	432.97	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.7195(14) Å	α= 90°.
	b = 11.8875(16) Å	β= 90°.
	c = 20.510(3) Å	γ = 90°.
Volume	2369.7(6) $Å^3$	
Z	4	
Density (calculated)	1.214 Mg/m^3	
Absorption coefficient	0.188 mm^{-1}	
F(000)	928	
Crystal size	0.24 x 0.18 x 0.10 mm^3	
Theta range for data collection	1.98 to 25.00°.	
Index ranges	-11<=h<=1, -14<=k<=1, -1<=l<=24	
Reflections collected	3068	
Independent reflections	2873 [R(int) = 0.0263]	
Completeness to theta = 25.00°	98.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2873 / 0 / 267	
Goodness-of-fit on F^2	1.033	
Final R indices [I>2sigma(I)]	R1 = 0.0592, wR2 = 0.1190	
R indices (all data)	R1 = 0.1161, wR2 = 0.1443	

Absolute structure parameter	-0.23(16)
Extinction coefficient	0.0029(12)
Largest diff. peak and hole	0.247 and -0.240 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3)
for **250a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl	3069(2)	8015(2)	7453(1)	104(1)
O(1)	1910(4)	8344(3)	11301(2)	61(1)
O(2)	6578(4)	8053(3)	10783(2)	68(1)
O(3)	7571(4)	9650(3)	10466(2)	71(1)
N(1)	3805(4)	7288(3)	11137(2)	55(1)
N(2)	3409(4)	8856(3)	10494(2)	50(1)
C(1)	3536(5)	6545(4)	11684(2)	50(1)
C(2)	4253(7)	5428(4)	11576(3)	67(2)
C(3)	3957(7)	4611(5)	12126(4)	90(2)
C(4)	4388(8)	5101(6)	12776(3)	93(2)
C(5)	3654(8)	6228(6)	12885(3)	106(3)
C(6)	3957(7)	7036(5)	12327(3)	73(2)
C(7)	2974(5)	8167(4)	11001(2)	49(1)
C(8)	2673(5)	9932(4)	10401(3)	56(1)
C(9)	3519(7)	10909(5)	10590(3)	82(2)
C(10)	2734(7)	12012(5)	10551(4)	86(2)
C(11)	2046(9)	12155(5)	9906(4)	103(2)
C(12)	1197(8)	11194(5)	9728(4)	99(2)
C(13)	1960(7)	10072(5)	9770(3)	81(2)
C(14)	4259(5)	8426(4)	9955(2)	51(1)
C(15)	5617(5)	9020(4)	9879(3)	50(1)
C(16)	6605(6)	8857(5)	10424(3)	53(1)
C(17)	8600(6)	9493(6)	10981(3)	90(2)
C(18)	5974(6)	9633(4)	9362(3)	57(2)
C(19)	5186(5)	9808(5)	8757(3)	57(2)
C(20)	5039(7)	10894(5)	8506(3)	80(2)
C(21)	4284(8)	11081(7)	7949(4)	99(2)
C(22)	3676(7)	10210(7)	7626(3)	88(2)
C(23)	3845(6)	9135(6)	7861(3)	65(2)
C(24)	4606(5)	8911(5)	8422(3)	60(2)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **250a**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl	104(1)	120(2)	88(1)	-32(1)	-24(1)	27(1)
O(1)	51(2)	60(2)	72(2)	8(2)	17(2)	10(2)
O(2)	50(2)	79(3)	74(2)	14(2)	-9(2)	-1(2)
O(3)	61(2)	71(3)	82(3)	4(2)	-13(2)	-12(2)
N(1)	48(3)	53(3)	64(3)	12(2)	13(2)	14(2)
C(1)	45(3)	48(3)	57(3)	15(3)	0(3)	-2(3)
C(2)	72(4)	54(3)	75(4)	1(3)	-15(4)	6(4)
C(3)	81(5)	59(4)	129(6)	33(5)	-19(5)	0(4)
C(4)	87(5)	108(6)	85(5)	44(5)	7(4)	19(5)
C(5)	125(7)	129(6)	63(4)	29(4)	3(5)	32(6)
C(6)	75(4)	71(4)	73(4)	-8(4)	-9(3)	15(4)
C(7)	45(3)	45(3)	56(3)	-3(3)	-5(3)	1(3)
C(8)	52(3)	43(3)	72(4)	12(3)	-2(3)	13(3)
C(9)	81(4)	51(3)	114(5)	-21(3)	-23(4)	11(4)
C(10)	87(5)	53(4)	118(6)	-12(4)	-12(4)	6(4)
C(11)	143(7)	53(4)	112(6)	16(4)	0(6)	31(5)
C(12)	102(6)	66(4)	127(6)	10(4)	-52(5)	30(4)
C(13)	78(4)	62(4)	103(5)	5(4)	-35(4)	15(4)
C(14)	50(3)	53(3)	51(3)	4(3)	-2(3)	2(3)
C(15)	39(3)	52(3)	58(3)	-2(3)	2(3)	2(3)
C(16)	47(3)	58(4)	56(3)	-1(3)	10(3)	6(3)
C(17)	62(4)	107(5)	101(5)	-14(4)	-25(4)	-9(4)
C(18)	42(3)	63(4)	64(4)	-2(3)	8(3)	-3(3)
C(19)	48(3)	70(4)	52(3)	13(3)	14(3)	0(3)
C(20)	64(4)	70(4)	107(5)	25(4)	-7(4)	-7(4)
C(21)	85(5)	84(5)	127(6)	55(5)	-24(5)	-6(5)
C(22)	68(5)	111(6)	85(5)	37(5)	-15(4)	-2(5)
C(23)	50(4)	89(5)	57(4)	-1(4)	1(3)	12(4)
C(24)	51(4)	73(4)	57(3)	2(3)	9(3)	13(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **250a**.

	x	y	z	U(eq)
H(1A)	4510	7165	10894	66
H(1B)	2544	6404	11700	60
H(2A)	5237	5551	11545	80
H(2B)	3944	5106	11167	80
H(3A)	2981	4441	12135	108
H(3B)	4452	3914	12050	108
H(4A)	5376	5214	12781	112
H(4B)	4153	4583	13123	112
H(5A)	2670	6103	12915	127
H(5B)	3961	6556	13293	127
H(6A)	3465	7736	12398	88
H(6B)	4934	7204	12319	88
H(8A)	1931	9914	10724	67
H(9A)	4315	10950	10306	98
H(9B)	3847	10803	11032	98
H(10A)	2046	12032	10894	103
H(10B)	3365	12632	10623	103
H(11A)	1475	12824	9919	123
H(11B)	2742	12266	9574	123
H(12A)	866	11297	9286	118
H(12B)	402	11168	10013	118
H(13A)	1309	9462	9713	97
H(13B)	2629	10029	9420	97
H(14A)	3746	8497	9551	62
H(14B)	4432	7631	10026	62
H(17A)	9235	10111	10975	135
H(17B)	9089	8803	10907	135
H(17C)	8149	9463	11397	135
H(18A)	6822	9993	9386	68
H(20A)	5456	11496	8717	96
H(21A)	4188	11810	7791	118
H(22A)	3155	10342	7254	105
H(24A)	4723	8177	8569	73

Table 6. Torsion angles [°] for **250a**.

C(7)-N(1)-C(1)-C(6)	-78.0(6)
C(7)-N(1)-C(1)-C(2)	158.5(5)
N(1)-C(1)-C(2)-C(3)	-178.0(5)
C(6)-C(1)-C(2)-C(3)	56.8(6)
C(1)-C(2)-C(3)-C(4)	-57.4(7)
C(2)-C(3)-C(4)-C(5)	56.8(8)
C(3)-C(4)-C(5)-C(6)	-56.8(8)
N(1)-C(1)-C(6)-C(5)	180.0(5)
C(2)-C(1)-C(6)-C(5)	-56.8(7)
C(4)-C(5)-C(6)-C(1)	57.5(8)
C(1)-N(1)-C(7)-O(1)	-4.8(7)
C(1)-N(1)-C(7)-N(2)	175.4(4)
C(14)-N(2)-C(7)-O(1)	-151.6(5)
C(8)-N(2)-C(7)-O(1)	10.6(7)
C(14)-N(2)-C(7)-N(1)	28.2(6)
C(8)-N(2)-C(7)-N(1)	-169.6(4)
C(7)-N(2)-C(8)-C(9)	108.7(5)
C(14)-N(2)-C(8)-C(9)	-88.5(6)
C(7)-N(2)-C(8)-C(13)	-118.2(5)
C(14)-N(2)-C(8)-C(13)	44.6(6)
C(13)-C(8)-C(9)-C(10)	50.8(8)
N(2)-C(8)-C(9)-C(10)	-175.1(5)
C(8)-C(9)-C(10)-C(11)	-51.3(8)
C(9)-C(10)-C(11)-C(12)	52.4(9)
C(10)-C(11)-C(12)-C(13)	-52.1(9)
C(9)-C(8)-C(13)-C(12)	-49.3(8)
N(2)-C(8)-C(13)-C(12)	178.3(5)
C(11)-C(12)-C(13)-C(8)	50.1(8)
C(7)-N(2)-C(14)-C(15)	-121.6(5)
C(8)-N(2)-C(14)-C(15)	76.4(5)
N(2)-C(14)-C(15)-C(18)	-115.4(6)
N(2)-C(14)-C(15)-C(16)	66.4(5)
C(17)-O(3)-C(16)-O(2)	-0.5(7)
C(17)-O(3)-C(16)-C(15)	-177.5(5)
C(14)-C(15)-C(18)-C(19)	-3.6(9)
C(15)-C(18)-C(19)-C(24)	-48.2(8)
C(15)-C(18)-C(19)-C(20)	133.1(6)
C(24)-C(19)-C(20)-C(21)	2.7(9)
C(18)-C(19)-C(20)-C(21)	-178.6(6)
C(19)-C(20)-C(21)-C(22)	-0.7(11)
C(20)-C(21)-C(22)-C(23)	-0.9(11)
C(21)-C(22)-C(23)-C(24)	0.7(10)

C(21)-C(22)-C(23)-Cl	179.8(6)
C(20)-C(19)-C(24)-C(23)	-2.8(8)
C(18)-C(19)-C(24)-C(23)	178.5(5)
C(22)-C(23)-C(24)-C(19)	1.2(8)
Cl-C(23)-C(24)-C(19)	-178.0(4)

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