Fused and spiro furanones from tetronic acid synthons: Oxa and azacycles featuring the butenolide ring

Vorgelegt von

Juan-Manuel URBINA-GONZALEZ

Dissertation

zur Erlangung des Doktorgrades

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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 25. April, 2006

Juan Manuel Urbina González

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And heartfelt thanks to each of my family members who support me through the distance and have always been there for me. Since I know this part of the thesis will be read by everybody, I want to apologize in advance if I forgot your name – Do not worry, sure you are in some part of my mind.

"…..We must consider another element which can almost be considered the most essential part of chemistry itself, which chemists boastfully, no doubt with reason, prefer above all others, and because of which they triumphantly celebrate, and to which they attribute above all others the marvelous effects of their science. And this they call the solvent."

Hermannus Boerhaave (1668-1738); De menstruis dictis in chemia in Elementa Chemiae (1733)

"Chemical synthesis always has some element of planning in it. But, the planning should never be too rigid. Because, in fact, the specific objective which the synthetic chemist uses as the excuse for his activity is often not of special importance in the general sense; rather, the important things are those that he finds out in the course of attempting to reach his objective"

Robert Burns Woodward (1917-1979)

This research was carried out from December 2001 to September 2005 in the Department of Organic Chemistry I, University of Bayreuth (Germany), under the supervision of Prof. Dr. Rainer Schobert.

Vollständiger Abdruck der von der Fakultät Biologie, Chemie und Geowissenschaften der Universität Bayreuth zur Erlangung des akademischen Grades eines Doktors der Naturwissenschaften genehmigten Dissertation.

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Abbreviations

δ	NMR chemical shift (in ppm)
$\bar{\nu}$	IR absorption frequency band (in cm^{-1})
ν	Tension vibration absorption (in IR)

Abund.	Abundance
AcOEt	Ethyl acetate
ADMET	acyclic diene metathesis polymerisation
ATR	Attenuated Total Refraction (IR)
Bn	benzyl
br	broad
br. s.	broad singlet (NMR multiplicity)
d	doublet (NMR multiplicity)
CM	cross-metathesis
CMS	Conventional Microwave Synthesis
DBU	1,8-Diazabicyclo[5.4.0]undec-3-ene
DCC	N,N'-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DIAD	diisopropyldiazadicarboxylate
DMAP	dimethylaminopyridine
DMF	N,N-dimethylformamide
EMS	Enhanced Microwave Synthesis
GC	Gas Chromatography
h	hours
HSQC	Heteronuclear Single Quantum Correlation (NMR experiment)
IR	Infrared spectroscopy
^{n}J	coupling constant (in Hertz) through n bonds (NMR)
m	multiplet (NMR multiplicity)
M	Medium (intensity in IR spectra)
MS	Mass Spectrometry
MW	Microwave
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Enhancement Spectroscopy

Ph	phenyl
q	quadruplet (NMR multiplicity)
qu	quintet (NMR multiplicity)
R_f	ratio of fronts (TLC)
RCM	Ring Closing olefin Metathesis
ROM	ring-opening metathesis
ROMP	ring-opening metathesis polymerisation
RT	room temperature
s	singlet (NMR multiplicity)
S	Strong (intensity in IR spectra)
t	triplet (NMR multiplicity)
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
Ts	tosyl
VS	Very strong (intensity in IR spectra)
VW	Very weak (intensity in IR spectra)
W	Weak (intensity in IR spectra)
W	Watt

Table of Contents

Chapter 1
General Section

1.1 Introduction and objectives

The synthesis of natural products is a challenge and chemists have acquired the power through new synthetic methods, reagents, conditions, synthetic strategies to recreate exciting molecules from the natural world. Natural products isolated from diverse sources have shown vast utility in pharmaceutical chemistry, showing great benefit as biological tools and playing an important role in general industry.

The molecules produced by living systems have always fascinated and inspired synthetic organic chemists. Particularly bioactive natural products, which show enormous value in pharmaceutical as well as general chemistry and play an important role in biology, have stimulated their ambition. As the chemists' skills and equipment have advanced - for example regarding new synthetic methods and strategies, reagents and/or conditions - the compounds chosen for synthesis have become ever more challenging. So it is no surprise that today's targets are found among the most "diabolically complex" natural substances ever discovered - the various secondary metabolites produced by plants and micro organisms for self-defense.

Among the different chemical methodologies applied during the evolution of this thesis, the ring closing olefin metathesis must be mentioned as one of the most important. Robert Grubbs, Richard Schrock and Yves Chauvin were awarded the 2005 Nobel Prize in Chemistry for their contribution to the metathesis catalysts technology and the consequent enrichment in diverse chemistry areas of drug discovery, flavour / fragrances and polymers, which help scientists to discover new disconnections-connections and paths in synthetic organic chemistry. The use of RCM in the construction of new oxa (aza) heterocycles is discussed in sections 2.8 and 2.9.

This work is principally concerned with the use of allyl tetronic acids as synthons for diverse natural products featuring a γ-lactone. The synthetic paths developed should be used for the synthesis of diverse biologically active compounds.

The objectives of this work were:

♣ Application of the domino addition – Wittig reaction between α-hydroxy esters and cumulated ylides for preparation of complex tetronates.

♣ Claisen rearrangement based synthesis of 3-allyl tetronic acids and explotation of the domino Claisen – Conia concept for the synthesis of spiro furandiones.

♣ Application of the reaction of keteneylidenetriphenylphosphorane with tetronic acids for the synthesis of 3-acetyl tetronic acid derivatives.

♣ Application of high pressure hydrogenation on tetronic acids in the synthesis of chiral γ-lactone derivatives.

♣ Preparation of 3,3-diallyl furandiones following the palladium assisted allylation reaction concept, and investigations into reactions of the allylic double bonds under ring closing olefin metathesis conditions. The results were to be applied later to the synthesis of selected natural products.

♣ Investigation into derivatising the allylic double bond in 3-allyl tetronic acids via ozone and Jones' reagent for the preparation of synthons of natural products.

1.2 Microwave irradiation in organic synthesis

In the electromagnetic spectrum, the microwave radiation region is located between infrared radiation and radio waves. Microwaves have wavelengths of 1mm – 1m, corresponding to frequencies between 0.3 and 300 GHz. Telecomunication and microwave radar equipment occupy many of the band frequencies in this region. In general, in order to avoid interference, the wavelength at which industrial and domestic microwave apparatus intended for heating operates is regulated to 12.2 cm, corresponding to a frequency of 2.450 (±0.050) GHz, but other frequency allocations do exist.

It has been known for a long time that microwaves can be used to heat materials. In fact, the development of microwave ovens for the heating of food has a history of more than a 50 year. In the 1970s, the construction of the microwave generator, the magnetron, was both improved and simplified. In inorganic chemistry, microwave technology has been used since the late 1970s, however it has only been implemented in organic chemistry since the mid 1980s.

The development of the technology for organic chemistry has been rather slow compared to combinatorial chemistry and computational chemistry. This slow uptake of the technology has been principally attributed to its lack of controllability and reproducibility, safety aspects and a generally low degree of understanding of the basics of microwave dielectric heating. Since the 1990s however, the number of publications has increased significantly, mainly because the availability of commercial microwave equipment intended for organic chemistry and to an increased interest in shorter reaction times.[1]

Microwaves (MW`s) are electromagnetic waves of a relatively low energy per photon (0.12 J/mol to 0.12 kJ/mol) compared with the energy required to cleave molecular bonds (~350 kJ/mol). Thus MW`s do not affect the structure of a molecule but stimulate molecular rotations and vibrations.

1.2.1 Microwave heating process

In comparison with traditional heating methods, MW heating does not depend on the thermal conductivity of the vessel materials but on a direct coupling with the molecules leading to a rapid increase in temperature ("molecular heating"). The result is an instantaneous localized superheating as a consequence of either dipole rotation or ionic conduction. In the first case polar molecules try to align themselves with the rapidly changing electromagnetic field of the MW, and that is why the rotational motion results in a transfer of energy. In the second case the electric field generates ionic motion as the molecules try to orient themselves in the changing field causing the so called instantaneous superheating (T_I) that is greater than the bulk temperature (T_B).

It is important to note that MW`s do not influence the activation energy of a reaction, but accelerate an overcoming of the activation barrier and thus lead to higher reaction rates because of the superheating. Using microwave energy causes a non equilibrium state of the molecules, because energy transfer takes place every 10^{-9} s whereas relaxation of excited molecules needs 10^{-5} s. This results in a high instantaneous temperatures (T_I) that increases the reaction rate k according to Arrhenius law ($k = A \, exp \, [-E_a/RT]$) in comparison to a lower T_B.[2]

In pressurized systems, it is possible to rapidly increase the temperature far above the conventional boiling point of the utilized solvent. But also at atmospheric pressure, the boiling points of the used solvents can be raised by up to 26°C above their usual values. This phenomenon is called the superheating effect and is widely believed to be responsible for many of the rate increases, which often accompany solution phase microwave-assisted organic reactions at atmospheric pressure.

1.2.2 Enhanced Microwave Synthesis

Recently, an alternative method for performing microwave-assisted organic reactions, termed "*Enhanced Microwave Synthesis*" (EMS), has been examined.[3] By externally cooling the reaction vessel with compressed air, while simultaneously administering microwave irradiation, more energy can be directly applied to the reaction mixture. In "Conventional Microwave Synthesis" (CMS), the initial microwave power is high, increasing the bulk temperature to the desired set point very quickly. However, upon reaching this temperature, the microwave power decreases or shuts off completely in order to maintain the desired bulk temperature without exceeding it. When microwave irradiation is off, classical thermal chemistry takes over, losing the full advantage of microwave-accelerated synthesis. With CMS, microwave irradiation is predominantly used to reach the bulk temperature faster. Microwave enhancement of chemical reactions will only take place during application of microwave energy.[4] This source of energy will directly activate the molecules in a chemical reaction; therefore, it is not desirable to suppress its application. EMS ensures that a high, constant level of microwave energy is applied.

Simultaneous cooling enables a greater amount of microwave energy to be introduced into a reaction, while keeping the reaction temperature low. This results in significantly greater yields and cleaner chemistries.[5]

1.3 Palladium assisted allylic alkylation – The Tsuji-Trost reaction[6,7]

Today it is widely recognized that Pd has very significantly changed and improved the art of organic synthesis over the last three decades. It seems reasonable to state that Pd is already one of the most versatile, useful, and hence significant metals in organic synthesis along with Li, Mg, B, Cu, Ru and a few others and its significance is increasing still. It has been reported that Wollaston in London discovered and isolated Pd in 1803 and named it after the asteroid Pallas, which was discovered a year before.

The use of Pd in organic synthesis was initially reported in 1873 by Saytzeff on the reduction of benzophenone and related carbonyl compounds with H_2. By 1912 the use of Pd in catalytic reduction including that of alkenes and alkynes had been reported by various chemists (Paal, Amberger and Wieland), as well as the autoclave technology which let to high-pressure catalytic hydrogenation (Ipatieff).

The invention of the Wacker process in 1959 and its subsequent development represent one of the most important milestones in the history of organopalladium chemistry. The catalytic

hydrogenation and the Wacker oxidation firmly established that Pd and its compounds can serve as catalysts for both reduction and oxidation.

The discovery of the carbon-carbon bond forming reaction of the 1,5-cyclooctadiene – Pd π-complex with ethyl malonate in the presence of Na_2CO_3 was reported by Tsuji in 1965. It is noteworthy that this reaction remained only stoichiometric in Pd for several years. Once its catalytic version was developed, this reaction has been extensively studied by Tsuji, Trost, and many others. Today, it is widely referred to as the Tsuji-Trost reaction, and it represents one of the most widely investigated areas of the organopalladium chemistry.
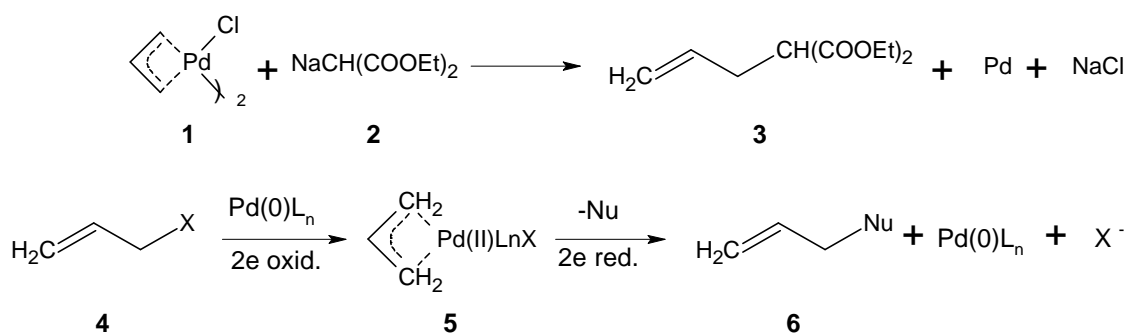
Figure 1.
Original stoichiometric version (top) and the catalytic version (bottom) of the Tsuji-Trost reaction.

Allylic compounds with good leaving groups are excellent allylating agents but they suffer from stereochemical ambiguity and loss of regiochemistry due to competition between the direct S_N2 and S_N2' reactions. In contrast, π-allyl cation complexes of palladium allow both the stereochemistry and regiochemistry of nucleophilic displacement reactions to be controlled. A number of allylic leaving groups with different reactivities are used for Pd-catalyzed reactions. Although allylation with allylic chlorides proceeds without a Pd catalyst, their reactions accelerate in the presence of a Pd catalyst. Allylic alcohols are rather poor substrates. Instead, their esters, typically allylic acetates, are used for smooth allylation. In addition to allylic esters, even allylic nitro compounds and sulfones are used for allylation. Reactions of the allylic esters are usually carried out in the presence of a stoichiometric amount of base, although allylic acetates react also with soft carbon nucleophiles, except malonate, under neutral conditions.

The mechanism of the Tsuji-Trost reaction involves nucleophilic attack of the conjugated bases of the proton-active substrates on a cationic (p-allyl)-palladium complex formed *in situ* from an allylic derivate and a zerovalent palladium stabilized by ligands, generally phosphines.

The reaction starts with the oxidative addition of the allylic substrate to the Pd(0)-catalyst and leads (under inversion) to a η^1-allyl complex. The latter is in a state of equilibrium

with the corresponding η^3-allyl complex. In the presence of surplus ligands, cationic η^3-allyl complexes that have high reactivity towards nucleophiles are formed.
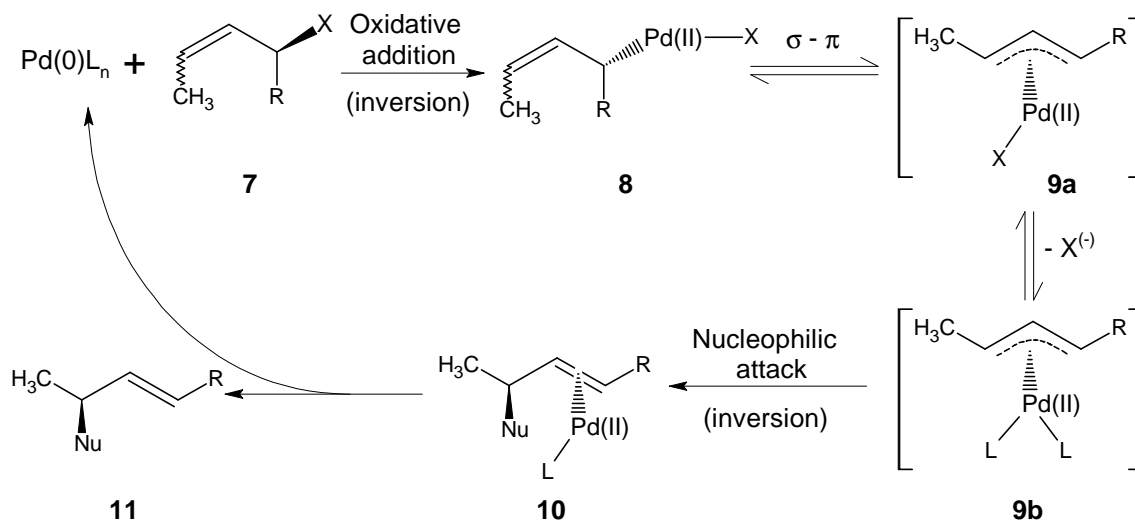
Figure 2.
The palladium (0) catalyst reactions with nucleophiles.

p-allylpalladium cations can be regarded as 'soft' electrophiles, and react most smoothly with 'soft' nucleophiles[8] having electron withdrawing groups. The attack of the nucleophile occurs always at the opposite site of the metal (inversion) and gives the allylated nucleophile under regeneration of Pd(0), which rejoins the catalytic-cycle again. Because of the two inversions, the allylic substitution always proceeds under stereoselective retention of the configuration. In principle, the nucleophile can attack either of the two termini of the η^3-allyl complex. In practice it is found that the less hindered terminus is attacked.[9]

In some cases the regioselectivity depends on ligands and leaving groups. For example, regioselectivity in the allylation of malonate with allyl sulfones is changed by ligands as depicted below.

Pd(Ph$_3$P)$_4$	88% yield		23 : 77
Pd(dppe)$_2$	92% yield		67 : 33
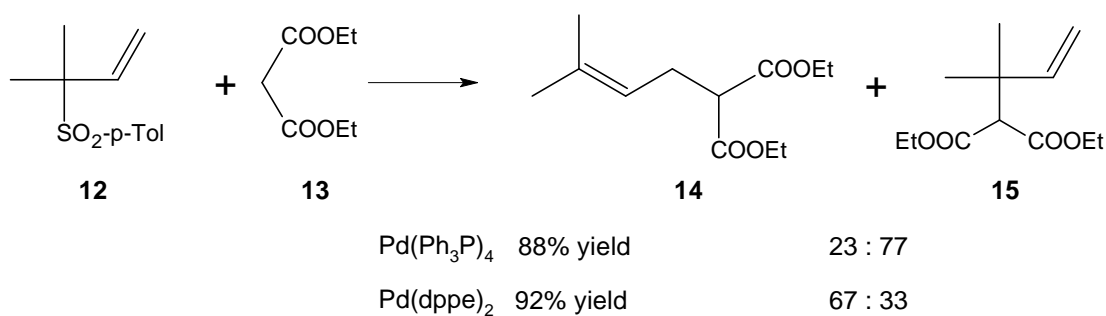
Figure 3.
Regioselectivity of the Tsuji-Trost reaction.

A strong memory effect in the reaction of the methyl allylic acetate depicted below (**Figure 4** - bottom) to give the corresponding addition products was found when using bulky aliphatic phosphines, typically PCy$_3$. No memory effect was observed in the reaction of the butenyl acetate (**Figure 4** - top). In these reactions, P(t-Bu)$_3$ is a more effective ligand than PCy$_3$.
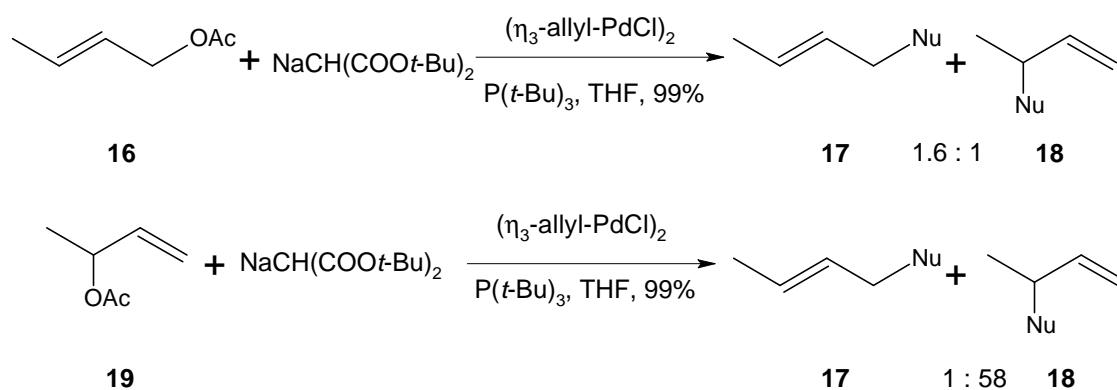
Figure 4.
Memory effect in the Tsuji-Trost reaction. The configuration of the double bond remains *trans-* due to a "twist" of the allyl group during the π-complex.

Interestingly, allylation of stabilized carbon nucleophiles has been found to be reversible. Complete transfer or rearrangement of dimethyl methylmalonate moiety from the secondary carbon to the primary carbon, involving C-C cleavage, was observed by treatment of the allylated malonate with Pd catalyst after 24 h, showing that the C-C bond cleavage of the monoallylic system proceeds slowly.

Figure 5.
Reversibility of the Tsuji-Trost reaction.

The potential of the allylation reaction continues to grow with the development of new ligands, nucleophiles and processes. It is noteworthy that the asymmetric allylation was not discussed here. The research around the Tsuji-Trost reaction is very extensive and will continue developing; it will result in new efficiencies mainly in total synthesis of natural products.

1.4   Ring Closing Olefin Metathesis using Grubbs' first and second generation catalysts

Olefin metathesis is an efficient and powerful reaction for the formation of carbon-carbon bonds, *via* a net exchange of olefin substituents.[10] The reaction between substrate and an active catalyst proceeds through the reversible formation of a metallacyclobutane intermediate. A significant evolution in the development of olefin metathesis catalysts involves the utilization of ruthenium-based catalysts discovered in the Grubbs' research group at Caltech.

The broad synthetic utility of ruthenium-based catalysts is derived from their capacity to orchestrate key metathetical transformations (**Figure 6**), including Ring-Opening Metathesis Polymerization (ROMP), Ring-closing Metathesis (RCM), and Acyclic Diene Metathesis Polymerization (ADMET). These transformations enable the production of novel compounds, often of pharmacological importance, or highly valuable science products.
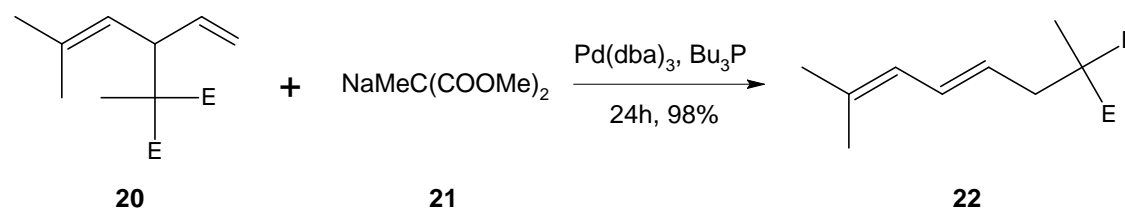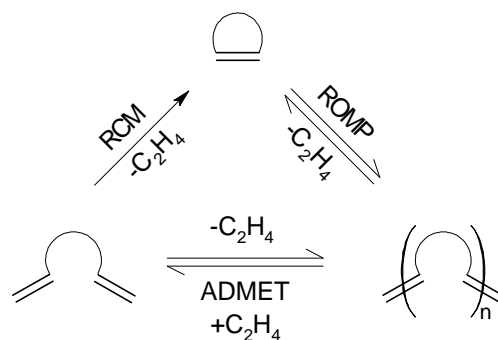

Figure 6.
Olefin metathesis reactions in organic synthesis.

It is interesting to recall the history of olefin metathesis and the origins of ruthenium-based catalysts. The basic mechanistic picture of olefin metathesis, a carbon-carbon-bond-forming reaction, which was first observed by chemists working at petrochemical companies in the 1950s, was worked out with contributions from the groups of *Calderon*, *Mol*, *Pettit*, *Chauvin*, *Casey*, *Katz*, *Schrock*, *Grubbs*, and others. *Chauvin* and his student *Hérisson* were the first who recognized that olefin metathesis is initiated by a metal carbene. As they proposed, the metal carbene reacts with an olefin to form a metallacyclobutane intermediate that breaks apart to form a new olefin and a new metal carbene, which propagates the reaction.[11]

The most responsible chemists for developing the metal carbene catalysts were *R. R. Schrock* and *R. H. Grubbs*. The first of Grubbs' ruthenium catalysts $(PCy_3)_2Cl_2Ru=CHCH=CPh_2$ was prepared in 1992. Further refinements of Grubbs' first catalyst led in 1996 to the more reactive catalyst $(PCy_3)_2Cl_2Ru=CHPh$, known as "Grubbs' first-generation catalyst", which pushed metathesis to the organic synthetic community due to its air

and moisture stability and functional group tolerance.[12] In 1999 the so-called "second-generation Grubbs' catalyst" was born, in which one of the tricyclohexylphosphines was replaced by a N,N-disubstituted imidazolyl ligand.[13] The new catalyst showed more reactivity than the highly active Schrock catalyst (a tungsten carbene) in many cases.[14] Further synthesis of ruthenium carbene complexes has been and will be reported due mainly to their remarkable stability toward functional groups and protic media, and their ease of handling.[15]
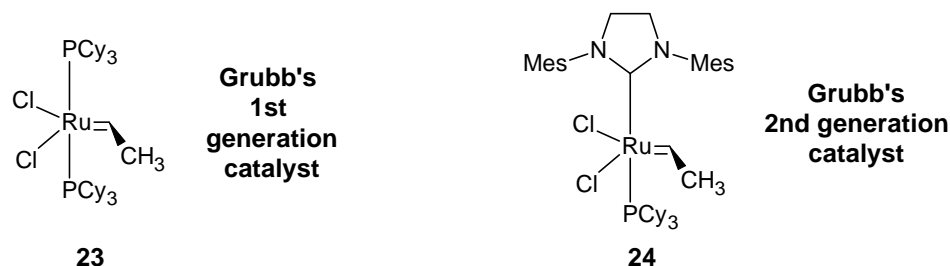
Figure 7.
First and second generation Grubbs' catalysts.

Catalyst initiation involves the formation of a metathesis-active ruthenium species from the starting precatalyst and its entry into the catalytic cycle. For Grubb's first and second-generation catalysts, the initiation event consists of phosphine (PCy_3) dissociation to produce the 14-electron intermediate [(L)(Cl$_2$)Ru=CHR'], where L = PCy_3 for Grubbs' first-generation catalyst and L = IMes for Grubbs' second-generation catalyst. Consistent with a dissociative mechanism, catalytic turnover is inhibited by the addition of free phosphine, and enhanced by the addition of phosphine scavengers.
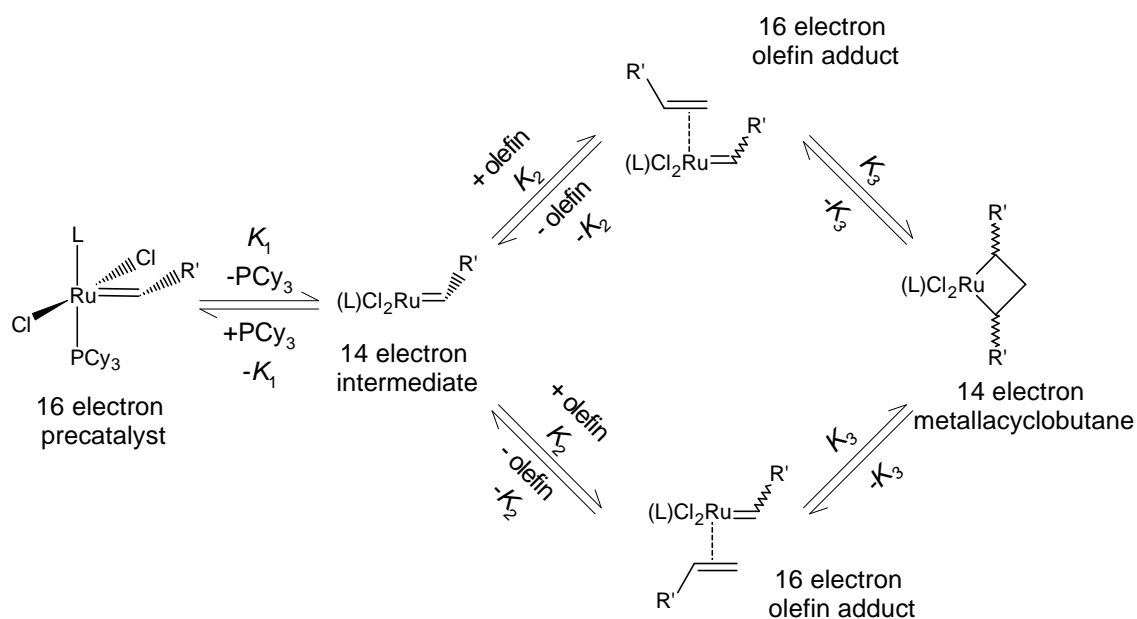
Figure 8.
Olefin metathesis catalyzed by (L)(PCy₃)(Cl)₂Ru=CHR' complexes (L = PCy_3 for Grubb's first-generation catalyst, IMes for Grubb's second generation catalyst).

The rate of catalyst initiation -and thus the concentration of the catalytically active 14-electron species in solution- is determined by the lability of the ligand that must dissociate from the ruthenium centre. In turn, the lability of this ligand is directly related to the strength of the ruthenium-ligand bond, a function of the stereoelectronic characteristics of both the ligand and the entire ruthenium-carbene moiety. Grubbs's second generation catalyst has a slower initiation rate constant (k_1), two orders of magnitude slower compared to that of Grubbs' first generation catalyst: the strong electron-donating power of the IMes ligand increases the electron density of the ruthenium centre and thus the strength of the Ru-PCy$_3$ interaction.

Once the [(L)(Cl)$_2$Ru=CHR'] intermediate forms, it has the potential to enter the catalytic cycle by coordinating with an olefinic substrate. Then, the resulting 16-electron olefin adduct can undergo [2+2] cycloaddition to form a 14-electron metallacyclobutane species. Subsequent metallacycle cleavage regenerates an olefin adduct, and productive propagation is completed by liberation of the coordinated olefin and regeneration of the 14-electron intermediate.

Grubbs's second generation catalyst exhibits overall superior activity and improved substrate scope relative to the first generation catalyst. Whereas the first generation catalyst is unactive towards sterically congested or electronically deactivated substrates, the second generation catalyst successfully mediates the formation of tetra-substituted olefins in five- and six-membered ring systems. These differences in activity depend of the N-heterocyclic carbene coodinated species [(IMes)(Cl$_2$)Ru=CHR'], which is far more active for olefin metathesis than the corresponding phosphine coordinated derivative [(PCy$_3$)(Cl)$_2$Ru=CHR']. The N-heterocyclic carbene ligands stabilize the two critical electron-deficient coordinatevely-unsaturated intermediates {[(L)(Cl)$_2$Ru=CHR'] and the metallacyclobutane species} through steric and electronic influences.[10]

Olefin metathesis, which is mainly *E*-selective and does not racemize stereogenic centres, has found considerable application in industry as it promises cleaner, cheaper, and more efficient processes. The ruthenium compound has a high preference for carbon-carbon double bonds and is indifferent to alcohols, amides, aldehydes, or carboxylic acids. For this reason, these catalysts can be used for olefin metathesis with starting materials bearing a variety of heteroatom-containing functional groups, which had poisoned earlier catalysts.[16]

The olefin metathesis catalysts are mainly used in polymerisation processes (e.g. polydicyclopentadiene) and the production of pheromones.[13] The catalysts are also used in organic synthesis. For example, several recent syntheses of a variety of natural and non-natural products use RCM to accomplish difficult macrocyclizations[16]. Grubb's second-generation catalyst, (IMes)(PCy$_3$)Cl$_2$Ru=CHPh, has been shown to facilitate "one pot" tandem catalytic metathesis-hydrogenation processes.[17] After the RCM reaction is complete by NMR, the

reaction container can be pressurized with hydrogen and then heated to 70°C. The Grubbs research team performed this "one-pot" tandem protocol to obtain (*R*)-(-)-Muscone **27** in an expeditious fashion and in good (56% overall) yield. This methodology has also been extended to include the cross metathesis of vinylketones with aryl olefins, followed by subsequent regiospecific hydrogenation.
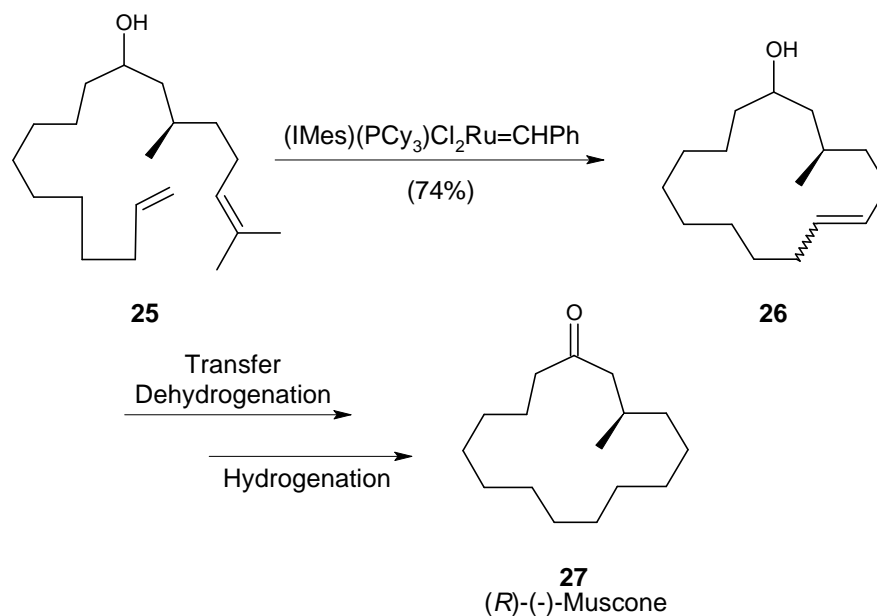
Figure 9.
Synthesis of (R)-(-)-Muscone *via* olefin metathesis.

It is evident that there is a virtual explosion of research in the area of RCM. There are an increasing number of applications of RCM to the synthesis of complex and highly functionalized organic molecules of importance in natural product chemistry, chemical biology and material science. Improved catalysts for specific applications, including enantioselective synthesis, continue to be developed, and it seems likely this area of research will remain fruitful for some time to come. Tandem reactions involving olefin metathesis are becoming more popular, as such processes enable the rapid construction of complex skeletal frameworks. It seems fair to predict that the future holds considerable promise for more advances and applications of RCM not only in heterocyclic chemistry but in other arenas as well.[18]

Chapter 2
Original Work – Results and Discussion

As part of our group's synthetic efforts towards the structural cores of diverse natural oxacycles, the present thesis explored the feasibility of using allyl tetronic acid derivatives as synthons for the different natural products depicted below. The synthetic steps mainly include the use of a cumulated ylide, allyl rearrangements, hydrogenations and / or double allylation-ring closing metathesis sequences.

28b
Pesthetoxin

29-epi
(-)-3-*epi*-Blastmycinolactone

30
(+)-Bakkenolide A

31
Canadensolide
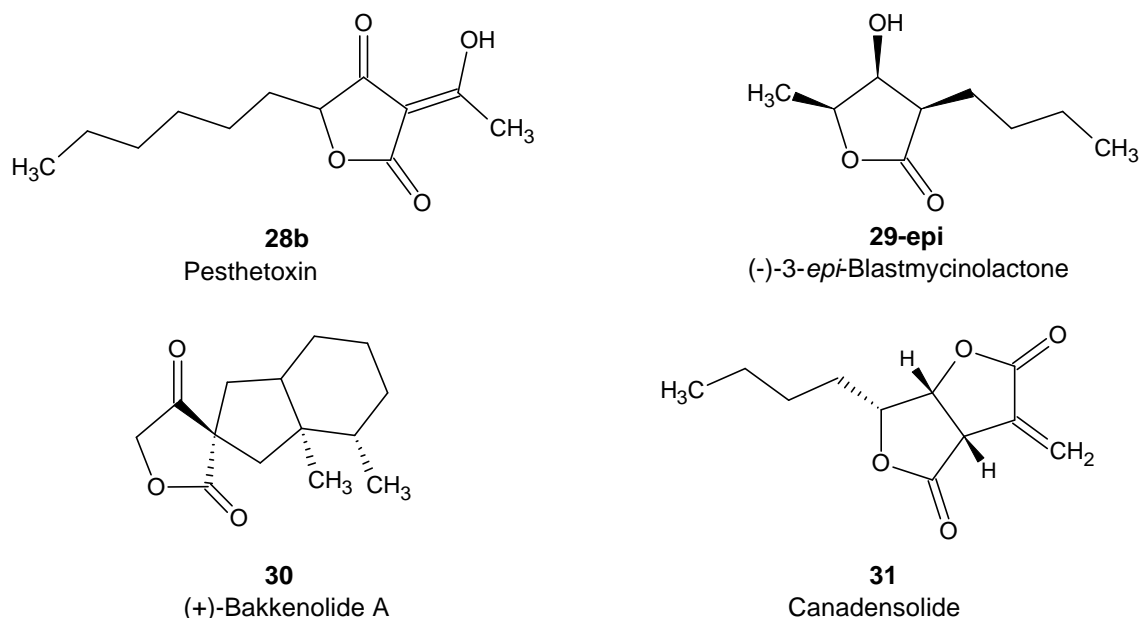
Figure 10.
Diverse natural products containing the γ-lactone ring.

Whereas 3,3-diallyldihydrofurane-2,4-diones with identical allyl residues have been obtained by allylation of tetronic acids with allyl halides under basic conditions followed by the thermal Claisen rearrangement of the intermediate 3,4-diallyl tetronates,[19] the preparation of congeners with two different allyl residues which are not accessible likewise is described here. Also, despite the recent report of a ring closing metathesis of the unsubstituted parent 3,3-diallyldihydrofuran-2,4-dione to give 3-spirocyclopentenylfuran-2,4-dione,[20] nothing was known about the generality of the approach presented, nor about allylation-metathesis routes towards 4-spiro-annulated or 3,4-fused butanolides as occurring in natural products.

This work expands the previous initials efforts of our research group towards the synthesis of 4-*O*-allyl tetronates and 3-allyl tetronic acid derivatives and their chemistry, and it is focused on the synthesis of natural products or synthons for them. The spectral data (IR, 1D and 2D NMR, MS-DI and / or GC-MS) for the substances prepared in this thesis is available following the instructions given in the Experimental Section.

2.1 Synthesis of **a**-hydroxy acids and **a**-hydroxy esters: a comparison between Fischer and Steglich esterification

Esterification of carboxylic acids is a fundamental transformation in organic chemistry and several methods exist for that purpose.[21] Mild high yielding procedures for the formation of carboxylic acid esters are desirable and necessary for the synthesis of many highly functionalised and sensitive compounds of current chemical interest. In the field of peptide synthesis, for example, the nature of the N-terminus and side chain protecting groups precludes the use of many normal esterification procedures. With other complex organic compounds, degradation and side reactions with common procedures may reduce the yield and purity of the desired esters. Some reagents or procedures, have inherent undesirable characteristics (e.g., the danger of explosion with diazomethane) or form difficult-to-remove impurities (e.g., the N-acylureas formed in the carbodiimide method).

The esterification of α-hydroxy carboxylic acids is a particular case due to the dual existence of reactive groups in the molecule. For this particular process potassium and caesium salts have proved useful. The CsF promoted esterification of carboxylic acids described by *Otera et al.* is a good way to gain esters using alkyl bromides. The reaction is usually carried out under mild conditions and shows less racemization than the Mitsunobu esterification.[22] Correspondingly TCNE (tetracyanoethylene) can be used as a catalyst for the selective synthesis of α-hydroxy esters according to a procedure first described by *Masaki* et al.[23]

The synthesis of α-hydroxyesters was initially achieved through a transesterification reaction from the α-hydroxyacid self-condensed product (a linear oligomer **33** consisting of about 3 units formed initially) and allyl alcohol, according to previous reports in the literature.[24,25]
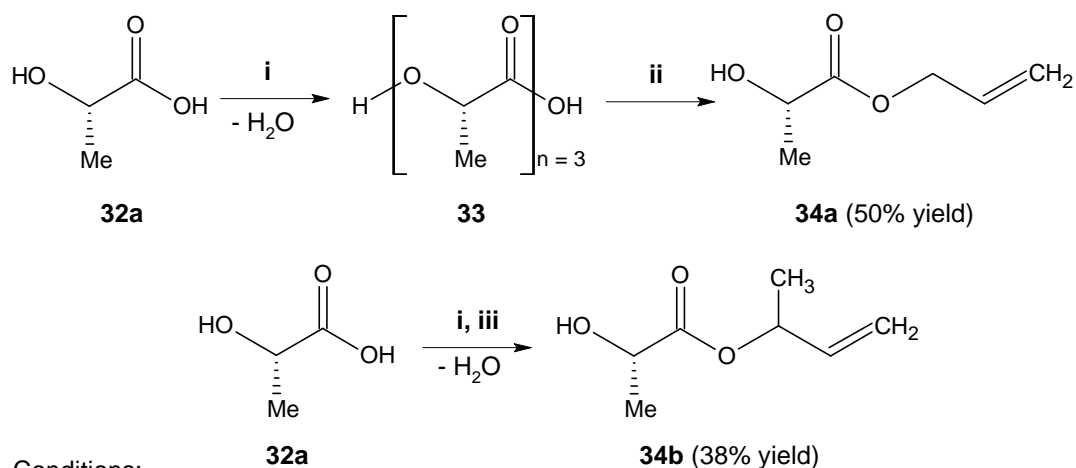
Conditions:
i. Benzene, H_2SO_4 cat, reflux, 4-6 h. **ii**. Allyl alcohol, 60°C, 20 h. **iii**. Methallyl alcohol, 60°C, 20 h.

Figure 11.
Synthesis of allyl lactate **34a** and methallyl lactate **34b** by reaction of the oligomer **33**.

This route was considered since previous reports were not reproducible.[26] These experiments described by members of our research group consider the formation of the α-hydroxy carboxylic acid esters via Fischer esterification, which does not apply in all cases. The products obtained from this methodology were only analyzed via NMR. The formation of secondary compounds can only be observed when the progress of the reaction is followed by GC.

It was found that Fischer esterification always forms a secondary compound in considerable yield. This derivative has NMR spectra similar to the expected molecule; this difference is only obviously noticeable by gas chromatography. To avoid the formation of this second product, and in order to obtain the pure allyl ester of an α-hydroxy acid, a modified Fischer esterification was used.[25] In this way it was possible to form (*S*)-allyl lactate **34a** in relatively good yields. Unfortunately under these conditions ester interchange occurs and polylactic acid (linear polyester) was also formed. A small amount of the dimer of lactic acid allyl ester was also found in the NMR spectra.

Preparation of methallyl lactate was not wholly satisfactory because the acid catalyzes the rearrangement of methallyl alcohol to isobutyraldehyde.[25] To try to avoid this problem, boric acid was used as catalyst, but unfortunately the reaction works very well only when a high amount of allyl alcohol is used.[27]

Conditions:
i. Allyl alcohol (solvent), H_3BO_3 (10% mol), reflux, 18 h
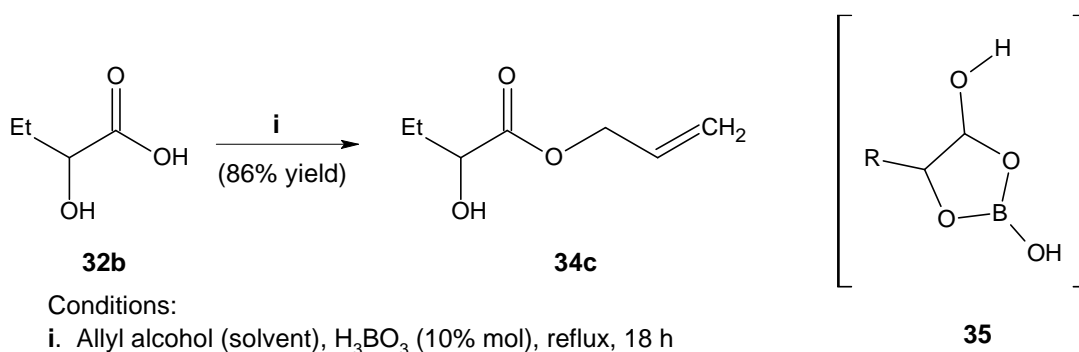
Figure 12.
Synthesis of allyl 2-hydroxy butyrate **34c** using boric acid as catalyst. The proposed intermediate is a boron complex **35** between the carboxylic and the hydroxy function. Under these conditions the allyl alcohol can attack the complex formed and the formation of a dimer is not possible.

Another common way to esterify hydroxy carboxylic acids is to treat them with an alcohol in the presence of a dehydrating agent. One of these is DCC (dicyclohexylcarbodiimide) **37**, which has over the past years, proven to be an exceptionally useful reagent. The carbodiimide is converted in the process to an isourea and eventually to dicyclohexylurea (DHU): the urea is the more thermodynamically stable of the two isomers and its formation provides the driving force for the ready conversion of the isourea to the urea *via* loss of the oxygen substituent. It is this driving force the basis for the synthetic applications of isoureas.

Given the relatively low yields (and formation of secondary products) of the modified Fischer and the boron mediated esterification, the synthesis of α-hydroxy carboxylic acid allyl (and benzyl) esters **34** was achieved mainly by the carbodiimide method. Work in this field of chemistry has been restarted since it facilitates the convenient preparation and use of polymer supported *O*-allyl (benzyl) isoureas.[28]

According to *Faure et al*. when using *Steglich* conditions[29] for the synthesis of allyl lactate (DCC + DMAP+ allyl alcohol + lactic acid), the dimer was also formed but to a minor degree.[30] It is also worth mentioning that with this normal method, the thermally unstable *O*-alkylisourea is the intermediate in the reaction. Rearrangement of this species to the *N*-alkylurea decreases the overall yield and more importantly, this side product is often difficult to remove from the desired material. Thus, the need for careful temperature control, and the formation of impurities somewhat limits the application of the normal method. Furthermore, rigorous exclusion of water is necessary to prevent hydrolysis of the intermediate **36**.

Consequently the reactions were carried out by initially preparing the isoureas and reacting them with the diverse α-hydroxy acids. The diverse *O*-alkyl isoureas employed as mild esterification reagents were prepared following the initial survey by *Vowinkel*.[31] Only the *O*-but-2-enyl isourea **36d** derived from crotyl alcohol was not purified, but used directly without

further separation (it decomposes during the SiO$_2$ column chromatography). Thus, *in situ* isourea generation was a viable alternative for the isolation of the reactive isourea intermediate.
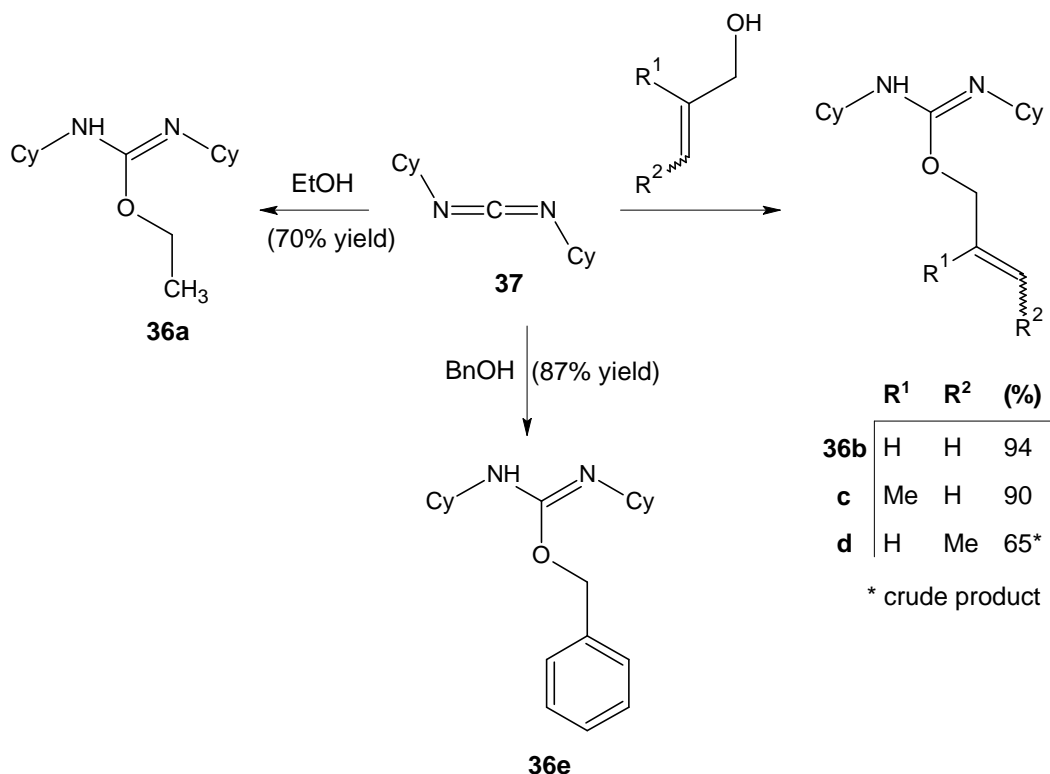
Figure 13.
Synthesis of diverse *N,N'*-dicyclohexyl-*O*-alkyl isoureas **36** as mild esterification reagents. Conditions: THF, CuCl (cat.), reflux, 16 h.

With the isourea method, the individual steps in the process were carried out separately. Thus, the isourea was isolated before conversion to the ester. This offers two advantages over the normal procedure: the isourea may be purified prior to use, and, more importantly, they may be stored for extended periods of time. In the absence of moisture, typical isoureas may be stored in the cold or on the shelf for several months with little or no change in quality. Moisture causes gradual hydrolysis to the alcohol and the urea, although it was found that complete drying of solvents was not necessary for high yields.

Ester formation *via* the isourea is mild and proceeds in excellent yields. The carbodiimide esterification was used preferentially because of the simple work up, the high purity of the final products and because no large excess of alcohol was necessary.[32] The isourea method only failed in the case of the synthesis of (*S*)-allyl lactate. This was because of the high amount of water inside the (*S*)-lactic acid (20%) which hydrolyzes the isourea formed.
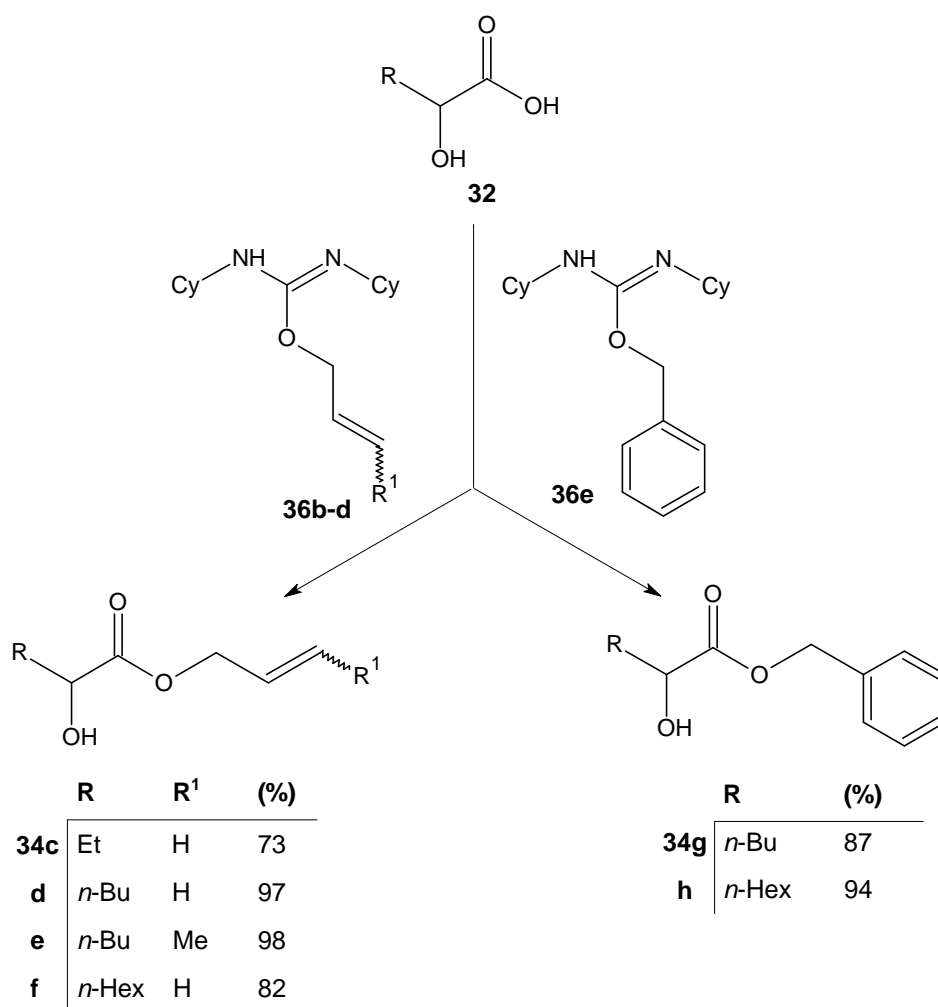
Figure 14.
Synthesis of diverse α-hydroxy esters **34** using *O*-alkyl isoureas as mild esterification reagents. Conditions: THF, reflux, 16 h.

To facilitate purification, THF was used as solvent because the urea side-product is insoluble. All the compounds were obtained as colourless oils in high yields and were pure according to GC; their structures were determined by NMR experiments.

2.2   Synthesis of tetronic acids

Several strategies have been used for the preparation of 5-substituted tetronic acids. Most of them utilize either a Dieckmann reaction or the cyclization of a suitable β-ketoester derivative bearing a γ-halogen atom or a γ-oxygenated function. Other methods utilize ketenes to generate the γ-lactone ring. Also, 1,3-dioxolan-4-ones, 2-dioxolanones, and substituted 3-furanones have also been used as templates for the synthesis of these molecules. A remarkable

review of the synthetic preparations and chemistry of tetronic acids has been reported by *Tejedor and Garcia-Tellado*.[33]
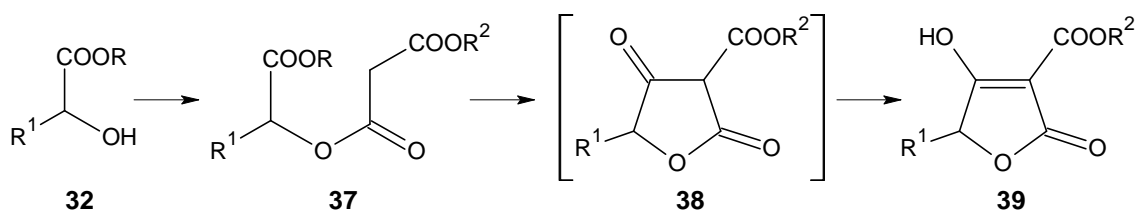
Figure 15.
Preparation of 3-acyloxy tetronic acid derivatives **39** using a base promoted Dieckmann cyclization of acetoacetates derivative **37**.

It is important to mention that most of the methods reported the preparation of 3-acyl (mainly acetyl) tetronic acid derivatives. A significant short-step synthesis of chiral derivatives of 3-acyl tetronic acid **28** was reported by *Markopoulou et al.* [34]

Conditions:
i. NaH, DCC, THF anhyd. **ii**. MeOH, 10% HCl, rt
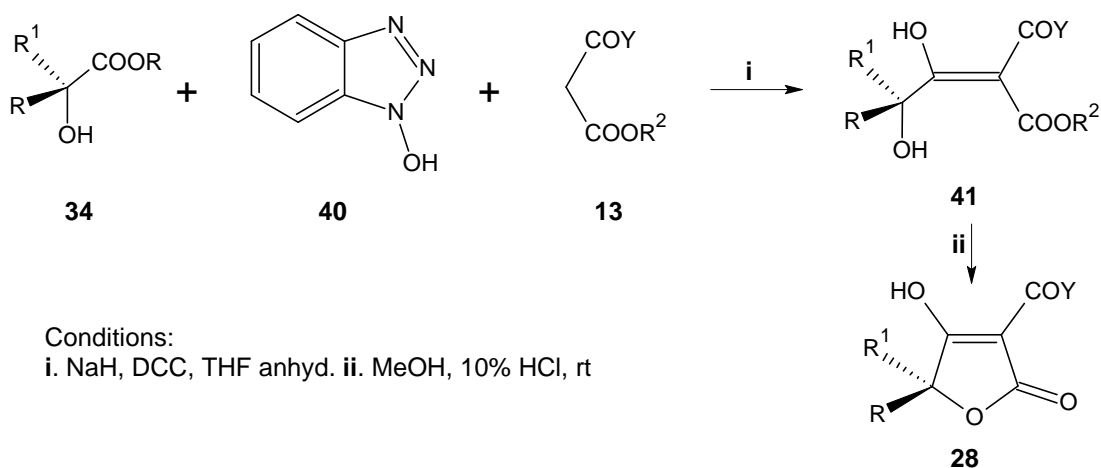
Figure 16.
Short-step synthesis of chiral 3-substituted tetronic acids **28** *via* a *C*-acylation reaction between the *N*-hydroxy benzotriazole ester of an appropriate *O*-protected α-hydroxy acid **34** and an active methylene compound **13**.

There are two different methodologies for the effective one-pot synthesis of 5-substituted tetronic acids. *Tejedor et al.* reported a one-pot synthesis of 5-substituted tetronic acids using a catalytic domino reaction to build the 1,3-dioxolane scaffold **45a** and a two-step acid-catalyzed trans-acetalization-lactonization reaction to furnish the tetronic acid derivative **47**. [35,36]
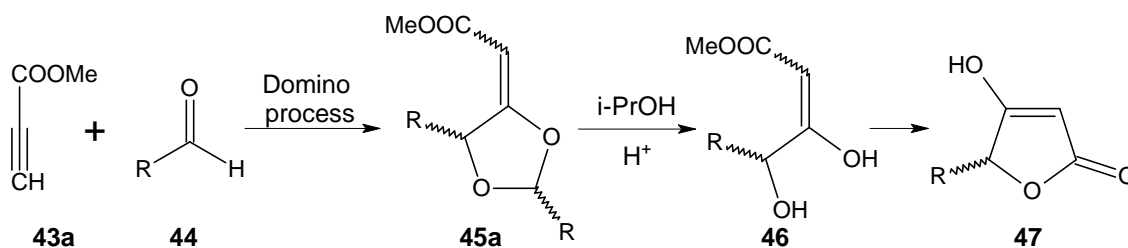
Figure 17.
One-pot synthesis of 5-substituted tetronic acids **47** *via* a catalytic domino reaction. The 1,3-dioxolane **45a** initially prepared by a domino process is converted through an acid-catalyzed transacetalization-lactonization into the tetronic acid **47**.

This procedure works quite well for aliphatic aldehydes and it is an excellent reaction for the synthesis of 5-alkyl substituted tetronic acids.
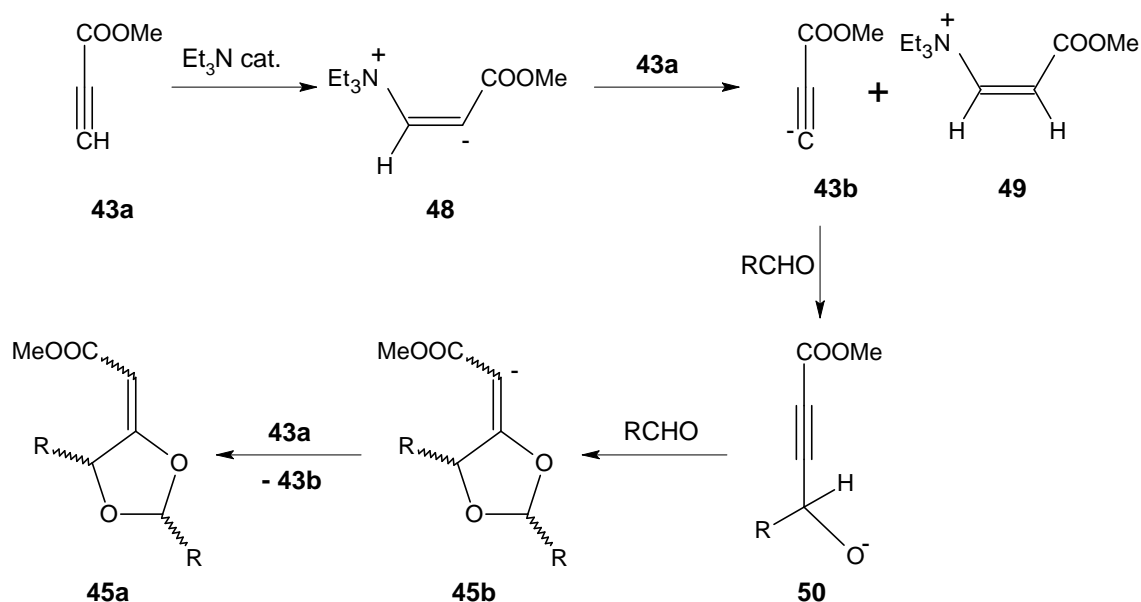
Figure 18.
Mechanism proposed for the domino process in the synthesis of 1,3-dioxolane **45a**.

On the other hand *Schobert et al*. reported the use of keteneylidenetriphenylphosphorane (Ph$_3$PCCO) **52** as an effective C$_2$O-building block in the synthesis of 5-substituted tetronic acids *via* addition - Wittig - ring closure cascade reaction with α-hydroxy ester derivatives. This last methodology was employed in the preparation of diverse tetronic acid derivatives and is discussed in section 2.2.2.

2.2.1 Synthesis of 4-*O*-allyl (propargyl) tetronate by direct alkylation of tetronic acid

Simple and convenient methods for the preparation of alkyl ethers of tetronic acid have lately become of interest and a sizeable literature exists on the synthesis of these compounds.

Virtually all such reports, however, are restricted to methyl and ethyl ethers of tetronic acid, produced using different alkylating agents.

The most often used procedure for the 4-*O*-allylation of tetronic acid mainly involves allyl bromide and eventually expensive caesium salts and has been the chosen route for several investigations.[19,37,38] *Gordon* prepared the 4-*O*-allyl tetronic acid directly from the tetronic acid and allyl alcohol under refluxing benzene[39] according to a proposed method reported by *Zimmer et al.*[40] The effectiveness of this procedure is directly related to the tetronic acid concentration in the solution mixture (see experimental section for details of the procedure). It is important to mention that the reaction also worked well when using propargyl alcohol in the synthesis of 4-prop-2-ynyloxy-*5H*-furan-2-one **51b**.

Unfortunately this reaction is limited to the alkyl or non-substituted allyl derivatives. When using 2-methylallyl alcohol, this methodology was unsatisfactory: the synthesis of β-methallyl tetronate failed because the strong mineral acid catalyzes the rearrangement of methallyl alcohol to isobutyraldehyde as observed in methallyl esterification processes.[25] This particular esterification reaction could not be successfully carried out even using the carbodiimide method, heating the tetronic acid with the corresponding *O*-methylallyl isourea in THF, nor when using DMAP and DMAP-HCl as a proton transfer catalyst.[41]

Conditions : benzene, H_2SO_4 cat., reflux, 20 h, $-H_2O$
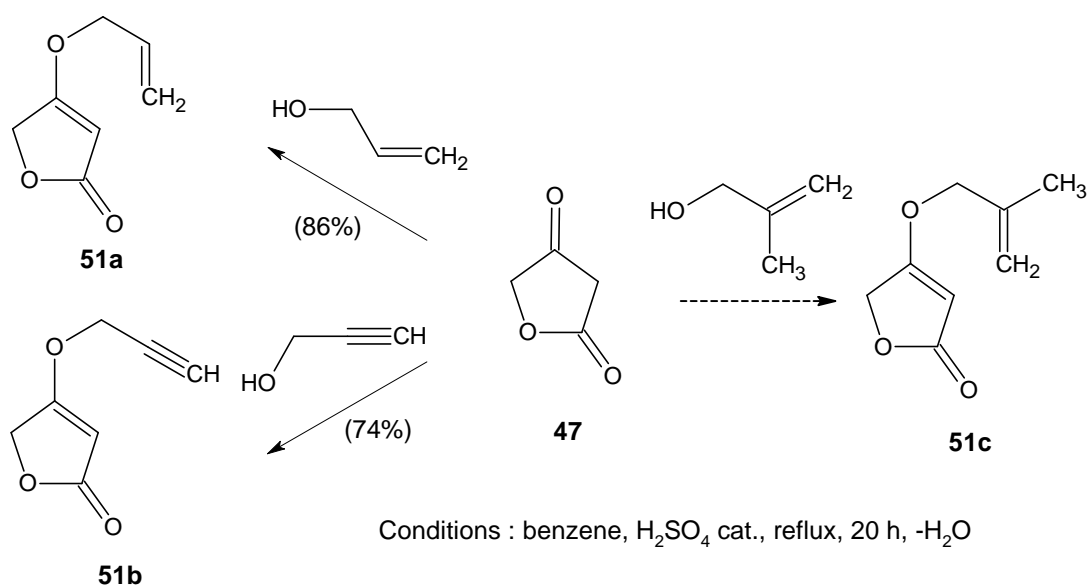
Figure 19.
Synthesis of 4-*O*-allyl (propargyl) tetronic acid **51a-b** via Fischer esterification using tetronic acid and allyl (propargyl) alcohol. Due to the acidic conditions, the reaction could not be carried out when methallyl alcohol was used because of the rearrangement of methallyl alcohol to isobutyraldehyde.

2.2.2 Synthesis of 4-*O*-allyl (benzyl) tetronates using keteneylidenetriphenylphosphorane: the addition – Wittig domino reaction

Keteneylidenetriphenylphosphorane (Ph₃PCCO) **52** is an example of a multipurpose reagent that can be used to introduce a carbon-carbonyl building block during the synthesis of diverse compounds.[42] This is accomplished by a cascade reaction comprising an addition and a Wittig olefination reaction. The reaction can result in a variety of different heterocycles[43] or α,β-unsaturated amides or esters.[44] The reaction conditions are in general mild and regioselective. Keteneylidenetriphenylphosphorane **52** appeared in the literature as a reagent for the first time in 1966.[45] It can be easily obtained from methyl bromoacetate and triphenylphosphine in a three-step synthesis,[46] and today its preparation is a general method in organic chemistry.[47]
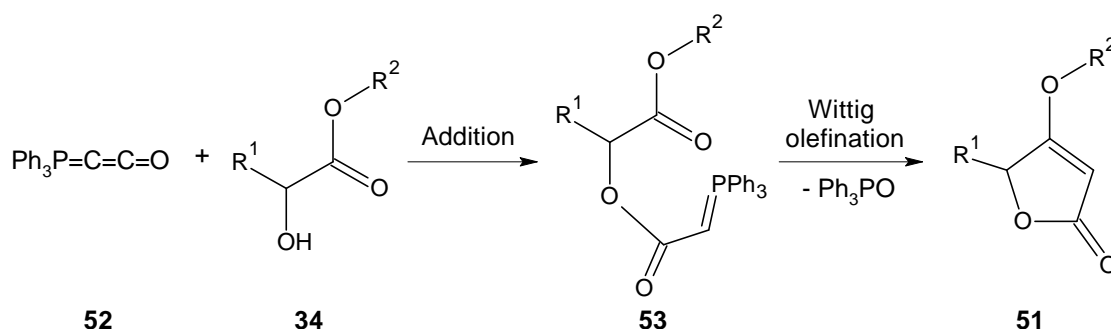
Figure 20.
Cascade synthesis of 4-*O*-allyl tetronates **51** using keteneylidenetriphenylphosphorane (Ph₃PCCO). The residual Ph₃PO was easily separated out from the reaction mixture by filtration through silica gel using DCM as eluent (see details in experimental part).

During the preparation of Ph₃PCCO it was found that working on a 0.1 mol scale gave a high quality cumulated ylide.[48] Although the yields obtained were about 60%, recrystallization of Ph₃PCCO is a critical step for the removal of the residual base (mainly sodium methoxide) and benefits the subsequent reactions. Pure Ph₃PCCO appears as white crystals and its solution in THF – water (1:1) has a pH value of 7. This criteria can be applied prior to the use of Ph₃PCCO in the synthesis of chiral compounds although this part of the chemistry is not totally clear considering that previous reports show complete racemization when using definitely base-free Ph₃PCCO and even using labelling experiments with *O*-deuterated L-lactic acid and L-mandelic acid ethyl esters.[49,50] (During the synthesis of 5-(*S*)-methyl tetronic acid derivative **51c** it was found that no racemization occurred when a good batch of Ph₃PCCO was used – this particular fact has been also reported in the synthesis of pyrrolenones[51]).
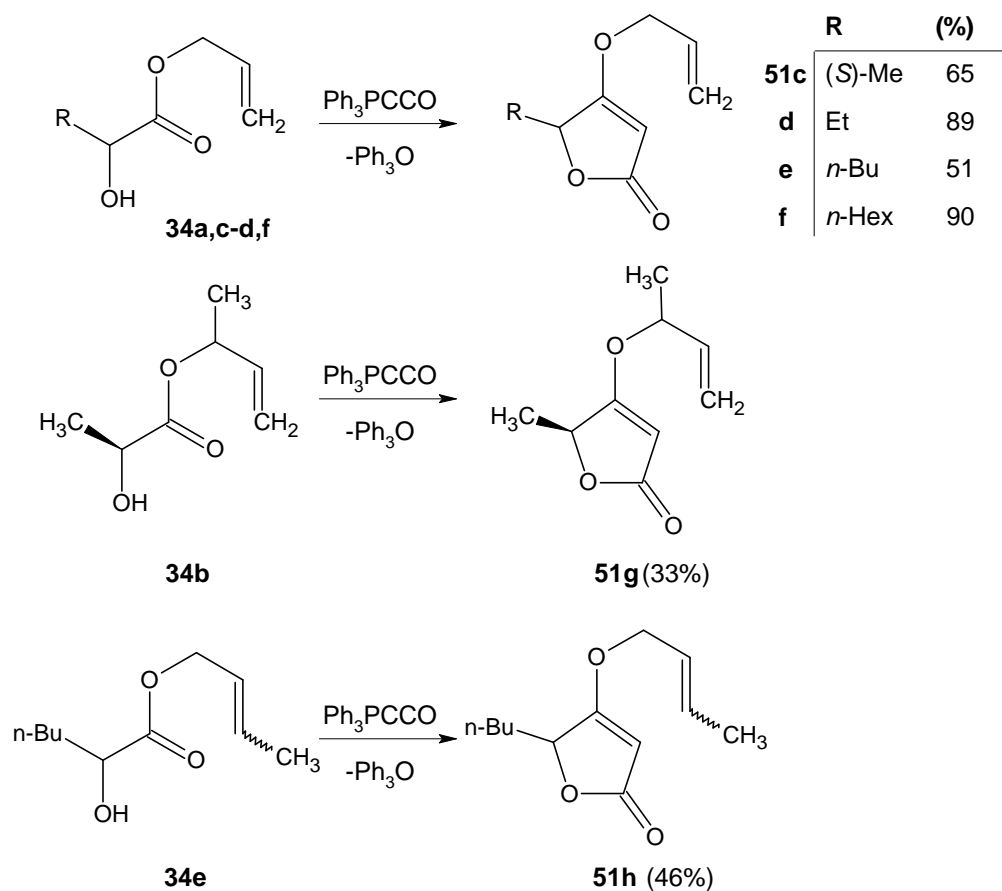
Figure 21.
Synthesis of diverse 4-*O*-allyl tetronic acids **51** *via* Ph₃PCCO in a domino reaction according the procedure described by *Schobert et. al.*

Compounds **51c-h** were obtained from the corresponding allyl α-hydroxy esters **34a-f** and Ph₃PCCO, using THF as solvent. The residual Ph₃PO was totally removed by filtration on silica gel chromatography column using DCM as solvent.[43b] Subsequent purification of the product by column chromatography gives **51c-h** in good to excellent yields. GC-MS showed the compounds were pure and their fragmentation pattern was according with the expected.[52]
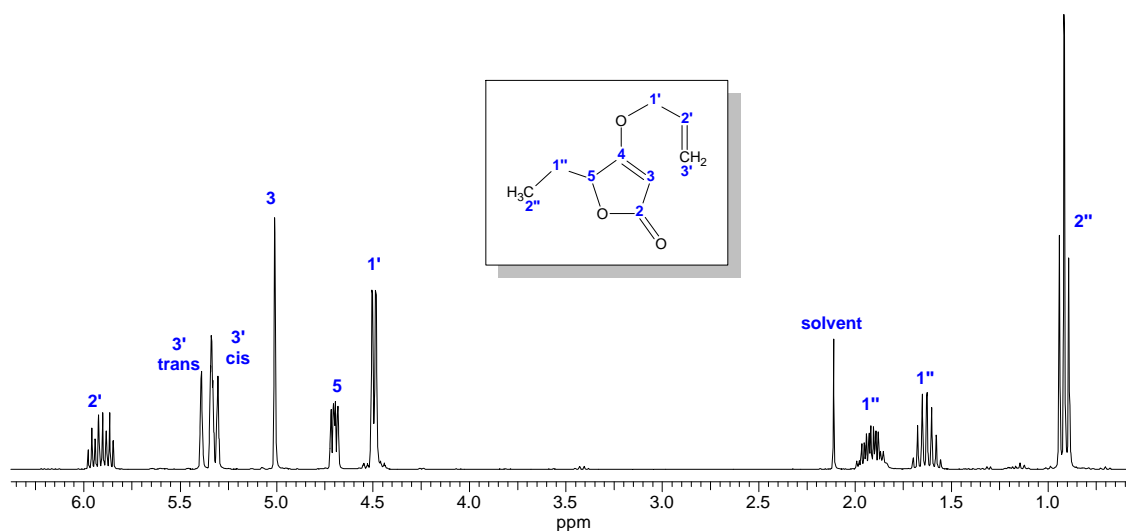
Figure 22.
300 MHz ^{1}H-NMR spectrum of compound **51d** in CDCl$_3$.

Two more examples bearing a benzyl moiety as a protecting group on the ester function were prepared. These derivatives having an alkyl residue in position C-5 were obtained in a higher yield than the corresponding allyl tetronates so long as recrystallized Ph$_3$PCCO was used for the experiments. The 5-alkyl-4-*O*-benzyl tetronates **51i-j** are synthons of pestethoxin and its *n*-butyl analogue.

	R	(%)
51i	*n*-Bu	66
j	*n*-Hex	75
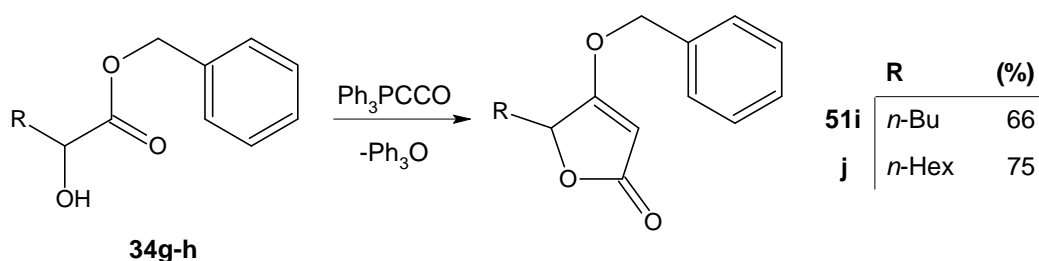
Figure 23.
Synthesis of *n*-butyl and *n*-hexyl 4-O-benzyl tetronates *via* Ph$_3$PCCO in a domino reaction. Derivatives **51i-j** were used as building blocks for the synthesis of 3-acetyl tetronic acids (see section 2.3).

The high regioselectivity of the intramolecular Wittig olefination step was once more demonstrated when using the dimer **34i** in the tandem "addition-Wittig olefination" reaction. The furan-2-one derivative **51k** was the only product isolated from the reaction mixture. No formation of the dioxocine derivative **54** was detected.
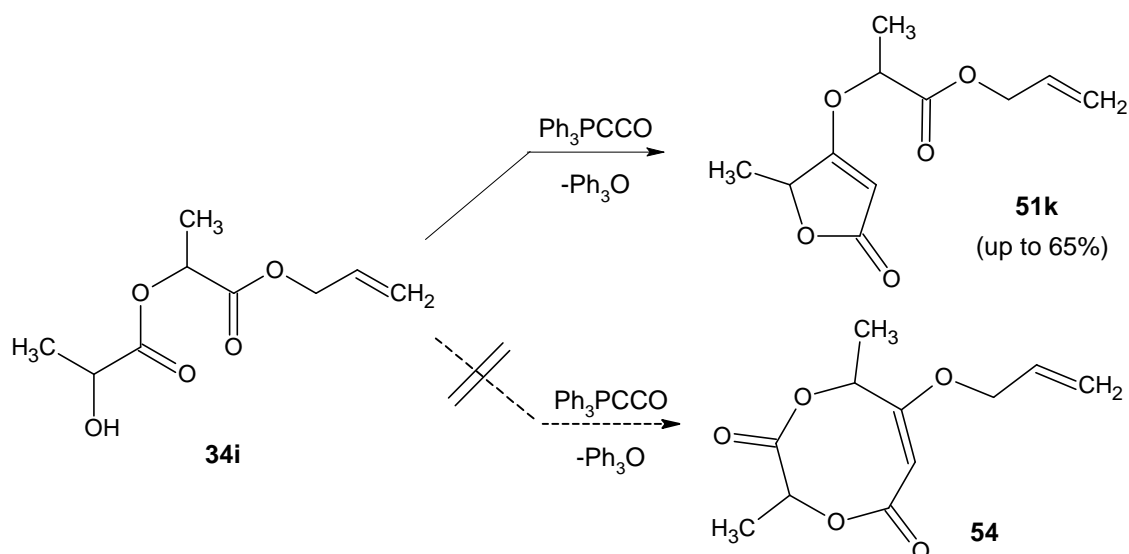
Figure 24.
Derivative **51k** was found during the purification of derivative **51c**. The amount of **51k** isolated was dependent on the amount of dimer **34i** in the starting material when the hydroxy ester **34a** was prepared *via* Fischer esterification.

Although the addition - Wittig domino reaction has been previously reported to work well under microwave conditions,[53] the formation of **51c-h** from α-hydroxy esters **34a-f** and Ph₃PCCO gave considerably low yields. During the conventional heating higher yields were obtained in comparison with the microwave assisted experiments. In addition, when using conventional heating, the amount of product for every single reaction could be scaled up to multi-gram scale (the volume of the microwave reactor with a pressure control is only 7 mL).

2.3 Preparation of 3-acetyl tetronic acid using Ph₃PCCO as acetyl source: synthesis of pesthetoxin.

A significant number of naturally occurring or biologically relevant tetronates feature 3-acyl residues. Among them, the 3-acetyl-5-*n*-butyl-tetronic acid **28a** appears as an important derivative with promise for use as hematopoietic agent.[54] The derivative **28a** was prepared by direct acetylation of 5-*n*-butyl-tetronic acid **47a** following a Steglich procedure.[54,55] The analogous substance bearing a *n*-hexyl chain is known as pesthetoxin **28b**, and causes leaf-necrosis in tea plants. It was isolated from the fungus *Pestalotiopsis theae*,[56] and was previously prepared from the alkaline treatment of the ester **55** in 80% yield.[57]
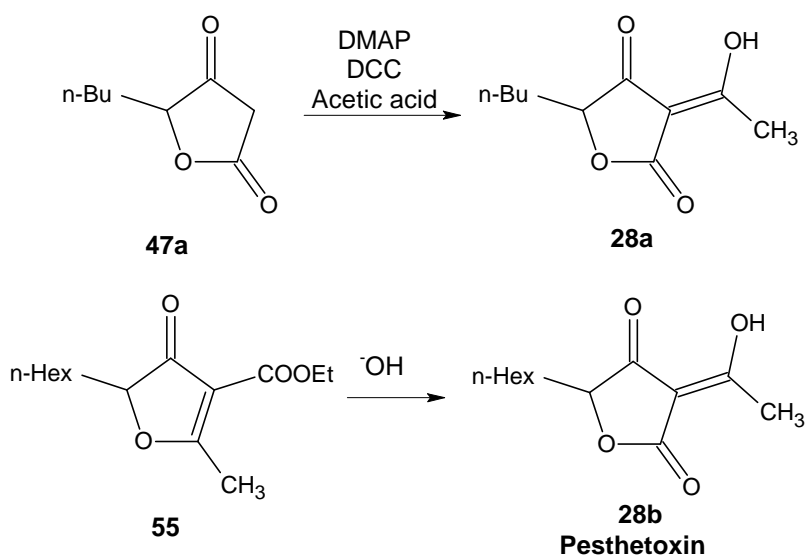
Figure 25.
3-Acetyl-5-*n*-butyl tetronic acid **28a** and 3-acetyl-5-*n*-hexyl tetronic acid **28b** have previously been prepared from the corresponding synthons **47a** and **55**. Derivative **28b** is the natural product Pesthetoxin, isolated from the fungus *Pestalotiopsis theae*.

The simplest approach to these systems is clearly the direct acetylation of the heterocyclic parent compound **47**.[58] Only one example for the use of Ph₃PCCO as an acetyl source has to-date been reported towards the synthesis of 3-acetyl tetronic acid derivatives.[59] Using Ph₃PCCO in the synthesis of the starting 5-alkyl tetronic acid, as well as the acetyl source for the side chain shows the versatility of Ph₃PCCO as a C_2O building block in the easy synthesis of 3-acetyl-5-alkyl tetronic acids.

Formation of **47a** (R = *n*-Bu) was previously described *via* a Ph₃PCCO addition – Wittig reaction from the corresponding α-hydroxy benzyl ester **34g**[26]; the resulting 4-*O*-benzyl tetronate **51i** was effectively deprotected under normal hydrogenolysis conditions. This protocol was used in the synthesis of derivative **47b** (R = *n*-Hex) with excellent results.

34g-h					**R**	**(%)**				**R**	**(%)**
				51i	*n*-Bu	66		**47a**	*n*-Bu	83
				j	*n*-Hex	75		**b**	*n*-Hex	99*
										* crude compound
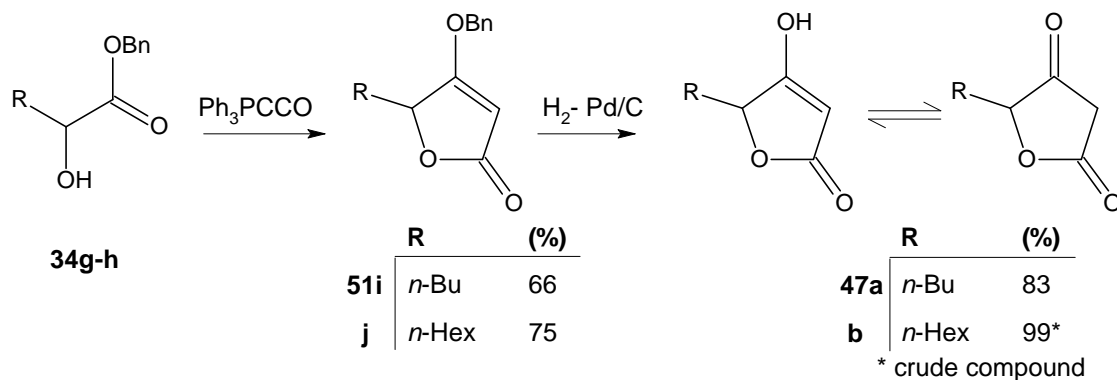
Figure 26.
Synthesis of 5-*n*-butyl (*n*-hexyl) tetronic acid **47a-b**. The easy debenzylation step gave excellent yields. In the particular case of derivative **47b**, the corresponding tetronic acid was not purified by column chromatography and it was directly used in the subsequent reaction.

Derivatives **47a-b** were found as white-yellow solids. When using CDCl₃ as solvent, their ¹H-NMR spectra show the *enol* form in a ratio of 3 : 2 to the *keto* form. **Figure 27** clearly show the tautomers found in the spectra of 5-*n*-butyl tetronic acid **47a**.

Figure 27.
300MHz ¹H-NMR spectrum of derivative **47a** in CDCl₃. The different signals for the *keto* and the *enol* tautomers are shown in colours. The doublet of doublets corresponding to each proton 5-H is shown in detail as well as the integral value for the signal of each tautomer.

The 5-alkyl tetronic acid **47** is an enolized 1,3-dicarbonyl moiety and reacts readily with Ph₃PCCO upon heating in THF to produce the corresponding 3-(triphenylphosphoranylideneoxoethyl) derivative **56**.[43d,60] Derivatives **56a-b** were not isolated from the reaction mixture since the formation of **28a-b** was carried out as a one-pot reaction.

	R	(%)
28a	*n*-Bu	85*
b	*n*-Hex	83*

* after sublimation
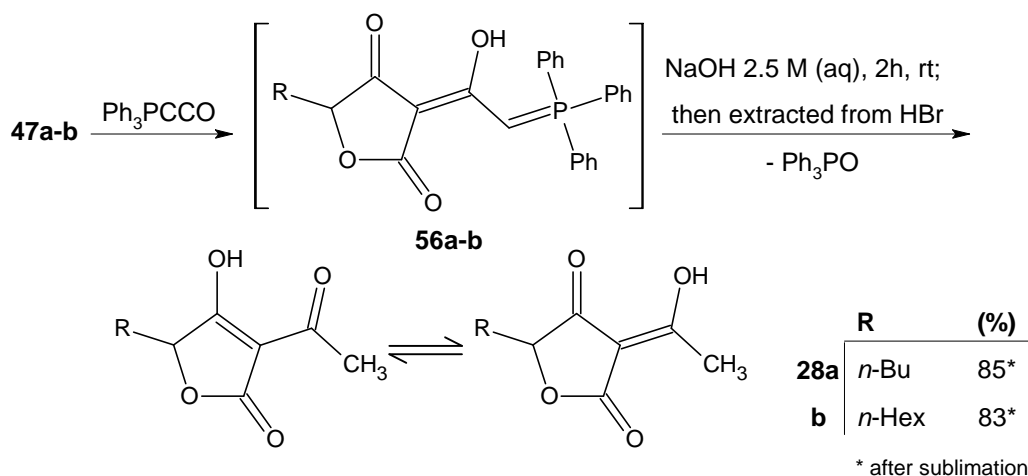
Figure 28.
The preparation of **56a** has already been reported by our research group,[26,59] and can be easily followed by IR-spectroscopy: the formation of **56** is complete when the IR signal corresponding to the cumulated ylide (Ph₃PCCO) disappears (2090 cm⁻¹). The resulting mixture was then hydrolysed to obtain the 3-acetyl tetronic acid **28a-b**.

Although hydrolysis of the phosphorus ylides can be performed in alkaline, acidic or neutral media, depending on the medium the hydrolysis can proceed in different directions; under neutral or basic conditions hydrolysis of acetylmethylides proceeds with cleavage of the P=C bond producing a triphenylphosphine oxide and a hydrocarbon, probably via a hydroxyphosphorane which readily eliminates one of the groups connected to the phosphorus.[60]

According to a previous report,[59] hydrolysis of the phosphorus ylide **56a-b** using sodium hydroxide resulted in cleavage of the carbon-phosphorus multiple bond. The ylidic carbon atom was converted to a methyl group, producing the 3-acetyl tetronic acid **28a-b**, whereas the phosphorus becomes a P=O group. In this particular case, the triphenylphosphine oxide was effectively eliminated during an acid extraction. The purification of the 3-acetyl tetronic acids **28a-b** from the phosphine oxide was done via complexation of the phosphine oxide with hydrobromic acid, a stronger acid than the 3-acetyl tetronic acid. This method of purification was based on the fact shown by *Etter and Baures* that triphenylphosphine oxide is a good hydrogen-bond acceptor and forms large high-quality crystals when cocrystallized with a variety of hydrogen-bond donors. It is also known that this procedure has been used as a crystallization aid for compounds that do not crystallize well on their own.[61] Thus, the 3-acetyl tetronic acid **28** was easily separated out by an extraction with diethyl ether from an acid solution of the reaction mixture (about 20% HBr inside the water phase) [CAUTION!!! – The pressure inside the funnel can increase during the extraction – the presence of concentrated HBr during the extraction process obliges extra caution].

The ^{1}H-NMR and ^{13}C-NMR spectra data obtained agreed with the structure assigned to the major tautomeric structures showed in **Figure 29** (α form - internal tautomers *ab*); it is well known that the 3-acyl tetronic acids **28** exists in four tautomeric forms in solution.[62] All four enol tautomers are stabilized through hydrogen bonding of the enol to the adjacent carbonyl group. Interconversions *a* to *b* and *c* to *d* involving displacement of the enolic proton along the hydrogen bond are presumed to be too fast on the NMR time scale to be observed.[63] On the contrary, interconversion *ab* to *cd* (or α to β form) is expected to be slow enough to give discrete sets of signals in the NMR spectra.
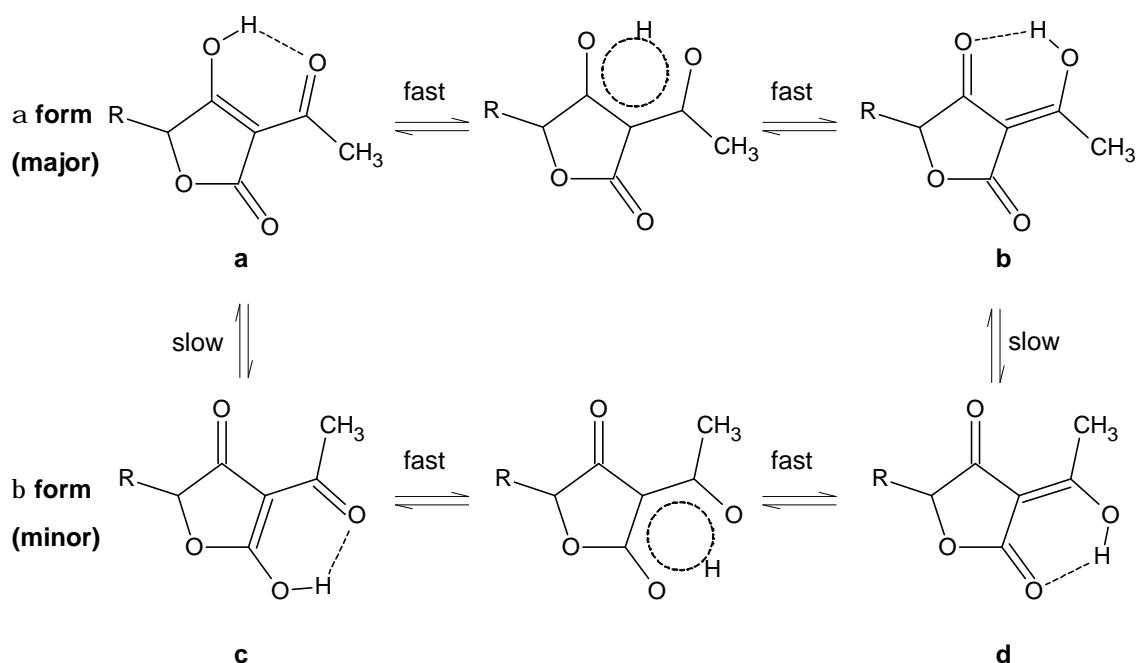
Figure 29.
The reported studies of the tautomeric structures of acyl tetronic acids has shown the pair ***ab*** (α form-top) as the major tautomer in chloroform during ^{1}H-NMR experiments.[62,63]

In accordance with these considerations, two sets of signals were observed in the NMR spectra of derivatives **28a-b**. The α form ***ab*** was assigned as the dominant tautomeric form, in agreement with previous spectroscopic and ab initio studies.[64]
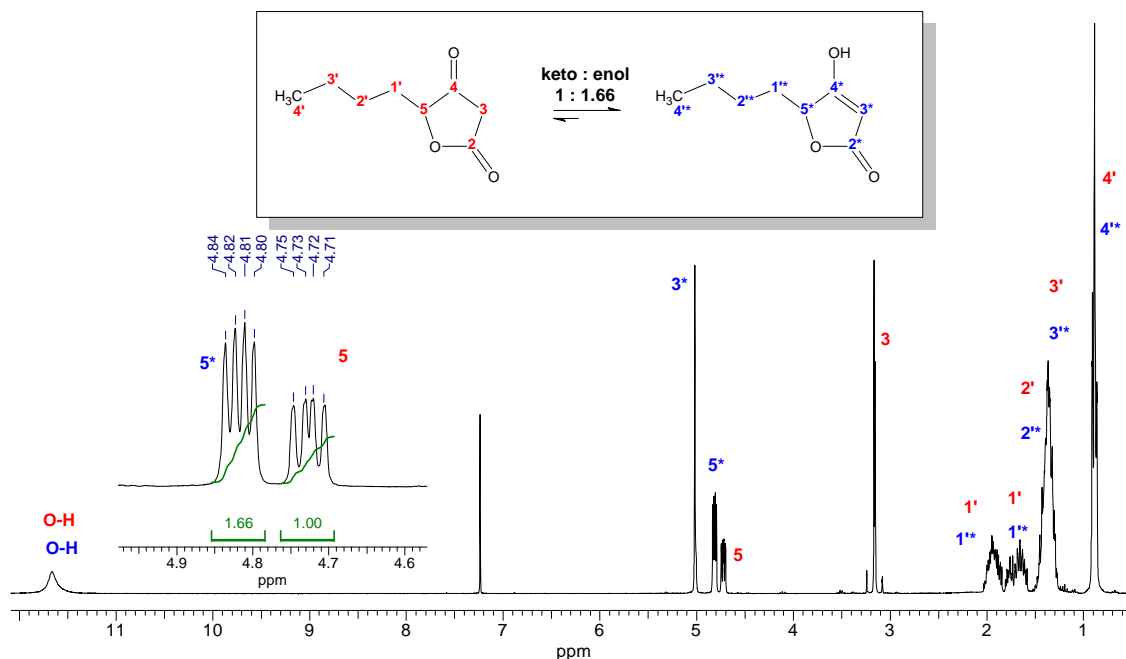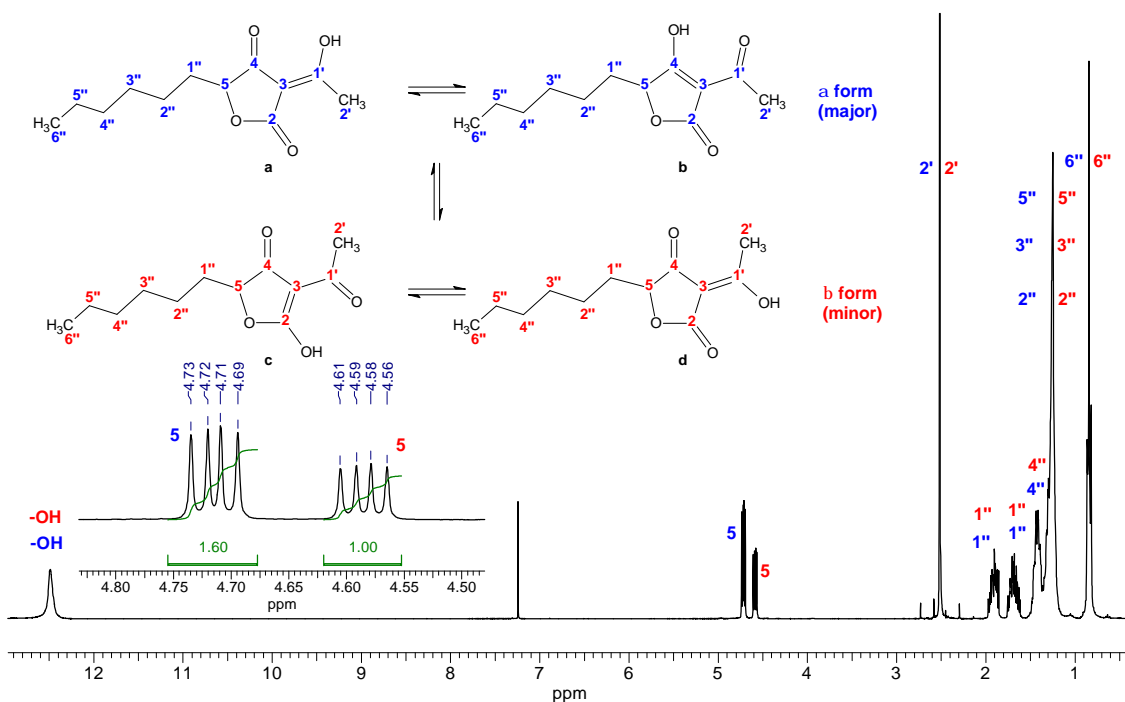

Figure 30.
300 MHz ^{1}H-NMR spectrum of Pesthetoxin **28b** in CDCl$_3$. The different signals for the *keto* and the *enol* tautomers are shown in colour. The doublet of doublets corresponding to each proton 5-H is shown in detail as well as the integral value for the signal of each tautomer. The 2D-NMR correlated spectra (COSY and HSQC) showed the signal corresponding to protons 4''-H at higher frequencies than the alkyl chain protons 5''-H, 3''-H and 2''-H.

A second purification was carried out with derivatives **28a-b**. By serendipity during the preparation of the samples for NMR it was found the solid sublimates under high vacuum. Thus, pure 5-*n*-butyl-3-acetyl-tetronic acid **28a** and pure pesthetoxine **28b** were obtained by sublimation of the corresponding raw compounds without large differences in their yields. The pure compounds appear as white – yellowish crystals. **28a** and **28b** exist as a racemic mixture because the starting α-hydroxy benzyl ester derivatives **34g-h** were not chiral compounds.
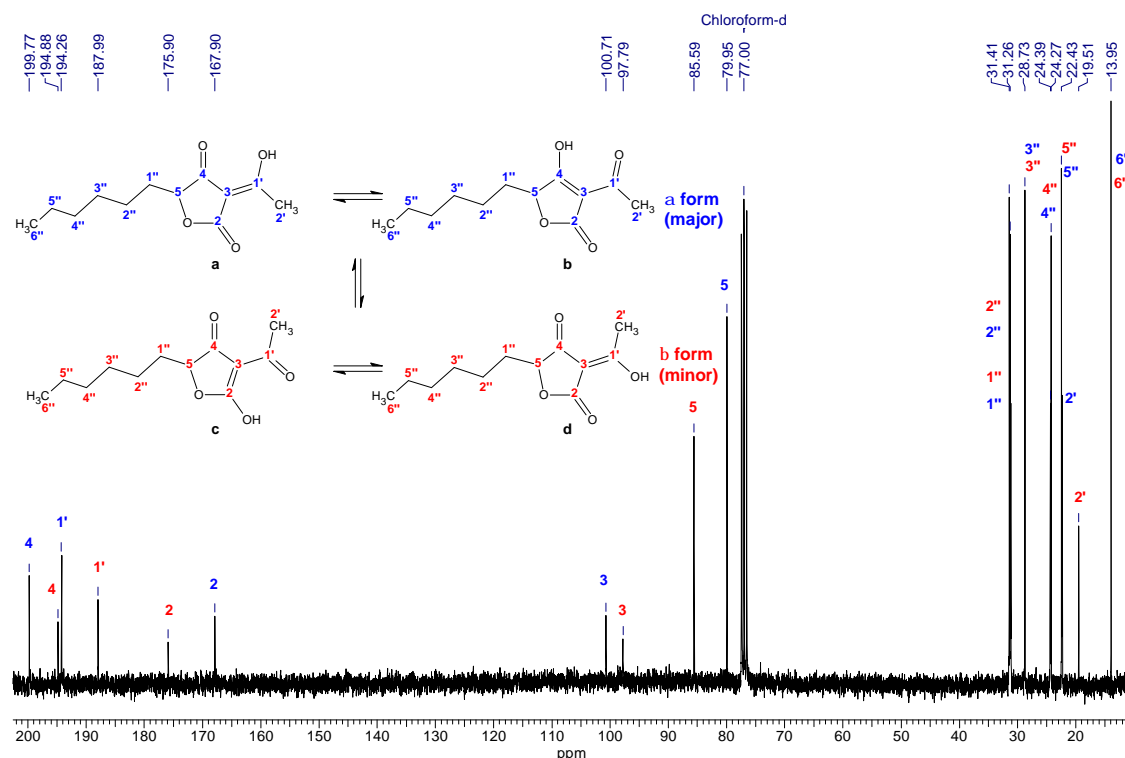
Figure 31.
75 MHz ^{13}C-NMR spectrum of Pesthetoxin **28b** in CDCl₃. The different signals for the *keto* and *enol* tautomers are shown in colour.

2.4 Microwave assisted pericyclic rearrangement: synthesis of 3-allyl tetronic acids and spiro cyclopropane furandiones

According to previous reports, when the formation of 4-*O*-allyl tetronates is carried out in THF at temperatures below 80°C, no subsequent Claisen – Conia products are formed. [26] However, when the synthesis of **51d** was carefully followed via TLC, GC and GC-MS the extended Claisen product **57c** and Claisen-Conia product **58c** were also found; the ratio of the compounds **51d**: **57c**: **58c** was 17 : 7 : 1 calculated by integration of peaks in the gas chromatogram.
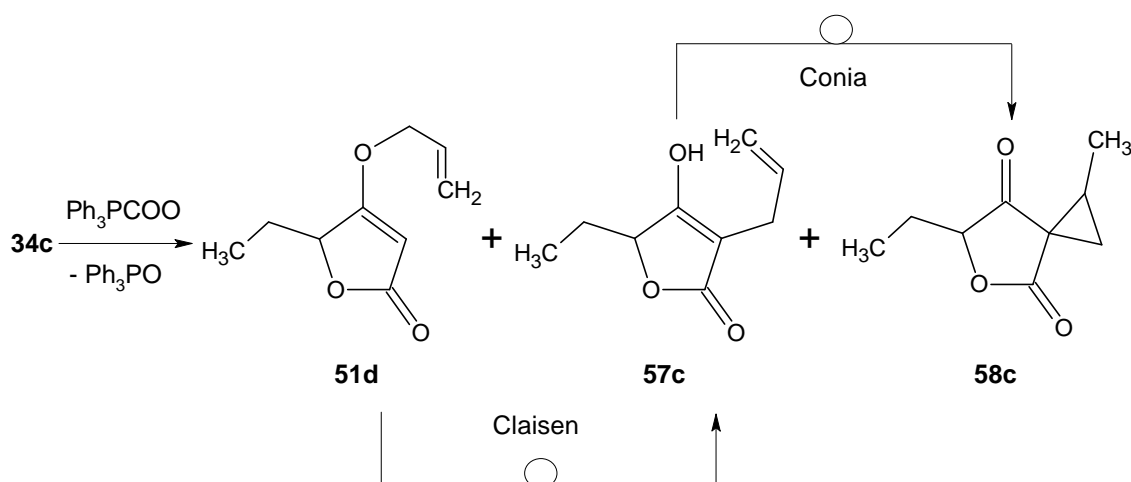
Figure 32.
Formation of 4-*O*-allyl tetronate **51d**, Claisen product **57c** and Conia product **58c** as consequence of a not thermally controllable domino reaction. The yield of **51d** depends of the extended formation of derivatives **57c** and **58c**. For that reason, the synthesis and purification of **57** and **58** was preferentially done from **51**, once derivatives **51** were totally identified.

It has been found that the domino sequence gives higher yields once the Ph$_3$PO is removed after the first 2 steps (addition – Wittig olefination).[26] When the reaction also involves the Claisen rearrangement (where the 3-allyl tetronic acid **57** is formed) the residual Ph$_3$PO interacts forming a bond with the acidic proton of the tetronic acid and their separation is not always complete from the reaction mixture; this particular behaviour is well known since Ph$_3$PO is often used as a co-crystallization agent: the favourable formation of aggregates between Ph$_3$PO and acid interchangable proton containing derivates is a key procedure in the preparation of monocrystals for X-ray spectroscopy [61].
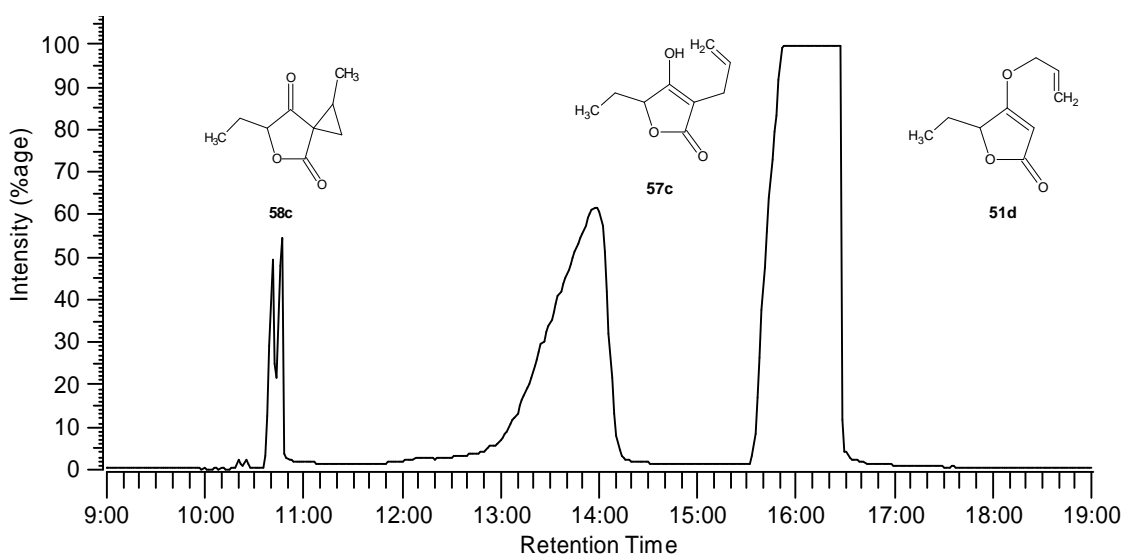
Figure 33.
The gas chromatogram of product **51d** also showed formation of compounds **57c** and **58c**. Different temperatures in the injection port were tested in order to prove **57c** and **58c** were not formed during the analysis.

Although the domino reaction addition – Wittig – Claisen – Conia has been previously reported to work under thermal conditions, the formation under microwave conditions of **57** (and **58**) from α-hydroxy esters **34** and Ph$_3$PCCO gave considerably low yields in contrast with the reported by *Westman and Orrling*.[53] The highly polar Ph$_3$PO formed in a major quantity after the first two stages of the reaction cascade interacts effectively with the microwave field heating the solvent and increasing the pressure of the reaction system (generating in all cases overpressure which causes the microwave reactor to stop automatically before the tube explodes). Thus the classical formation of derivatives **51** by conventional heating was used preferentially.

Previous experiments made by our group were focused on the Claisen and Claisen-Conia rearrangement of 4-*O*-cinnamyl tetronates by both thermal[65] and microwave assisted heating[39,66] as well as the formation of **57** from a Claisen rearrangement of derivatives bearing an unsubstituted allyl group.[26,39] Until now no description has been made of Conia derivatives prepared from 4-*O*-allyl-5-alkyl tetronates when an unsubstituted allyl group was rearranged at 190°C by microwave irradiation.
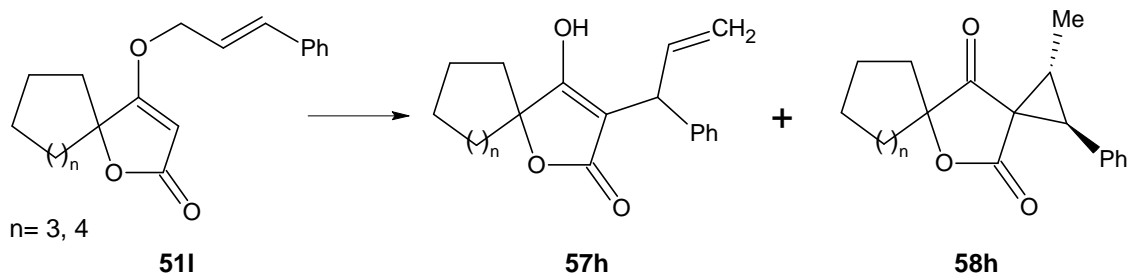
Figure 34.
Claisen product **57h** and Conia product **58h** formed from the rearrangement of 4-*O*-cinnamyl tetronates, previously reported and extensively studied by *Schobert et. al*. (See reference 67 for a complete review).

The experiments were performed using dry toluene as the solvent on a 500 mg scale. The reaction time was optimized after following the progress of the reaction via GC to 190°C for 10 minutes (240 Watt, 8 Bar = 110 PSI – **Figure 35**). When small amounts of 4-*O*-allyl tetronate were used, the amount of substance in a non polar solvent (toluene or xylene) was not enough to interact with the microwave field and the solution never reached 190°C (CMS conditions); 350 mg of sample was determined as the minimum amount to be loaded inside the microwave reactor.
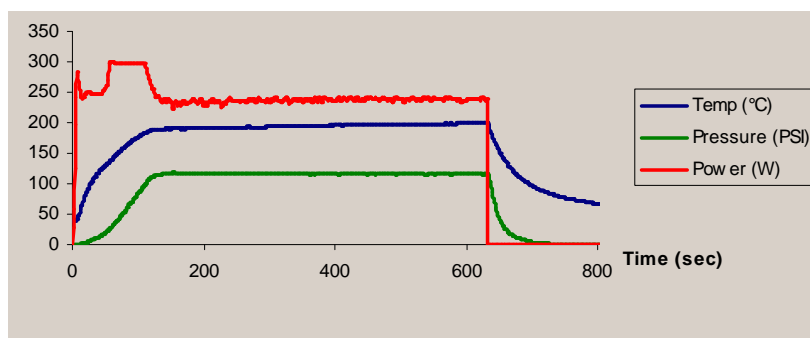
Figure 35.
Profile of a Conventional Microwave Synthesis (CMS) of Claisen product **57** using a mono-mode reactor (CEM – Discovery).

Previous attempts to form spiro cyclopropane furandiones **58a-f** from 4-*O*-allyl tetronates **51** reported only the exclusive formation of the Claisen product in contrast to the formation of the spiro cyclopropane cinnamyl analogue **58i**.[26] Another important fact observed previously when studying the cinnamyl derivative **58i**, was how the cyclopropane ring was opened spontaneously via nucleophilic addition of water during purification by column chromatography generating the corresponding 3-hydroxypropyl tetronic acid derivative **59a**.[26,70]
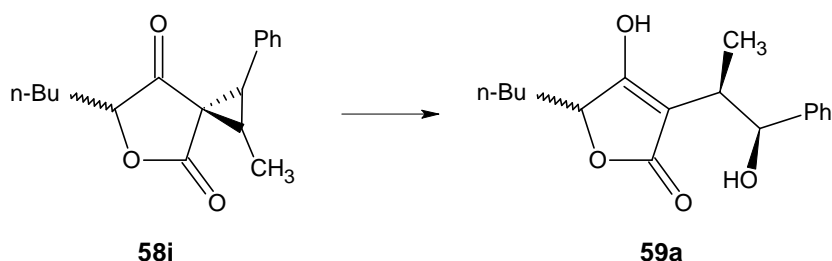
Figure 36.
Nucleophilic ring opening of previously reported derivate **58i** in presence of wet SiO_2.

This evidence shows that the spiro derivatives were in fact formed, but in those experiments they were not isolated because of their conversion into the more polar 2-hydroxypropyl tetronic acids **59**. These derivatives probably remained in the chromatography columns during the purification due to the formation of a strong hydrogen bridge with SiO_2. Once the formation of these new cyclopropane spiro furandiones were detected via GC, compounds **58a-f** were isolated as secondary compounds during the formation of the Claisen products **57**. The use of column chromatography using dry silica gel and dry solvents (*n*-hexane / ether were used as eluant mixture) prevented nucleophilic ring opening during the purification process.
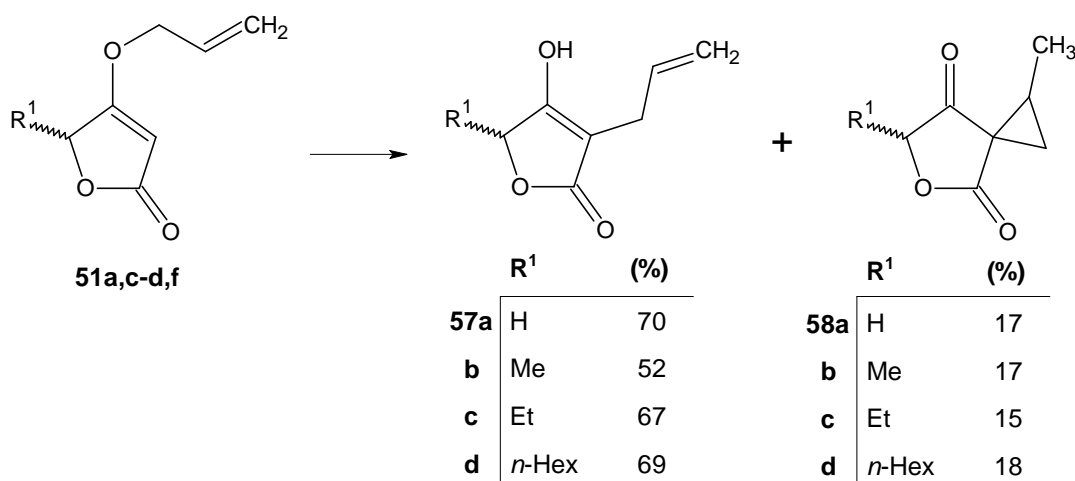
Figure 37.
Reagents and conditions: allyl tetronate (500 mg), 7 mL dry toluene, mw irradiation (CMS, 190°C, 10 min., 8 Bar, 120 Watt). Appendix A contains a graphical description in relation to the different isomers **58** can form.

After separation of **57f** it was found that the Claisen product, expected to be formed as the main product, was isolated in low yield (11%) with respect to the favoured Conia product **58f** (50%). This was presumably a result of the stabilizing effect of the secondary methyl group and a substantial increase in the pressure during the reaction (12 Bar). The increasing in the pressure was observed in the computed reported log file after the experiment was finished. This pressure increment was an accidental consequence of letting a small volumen in the vapour head of the reactor.
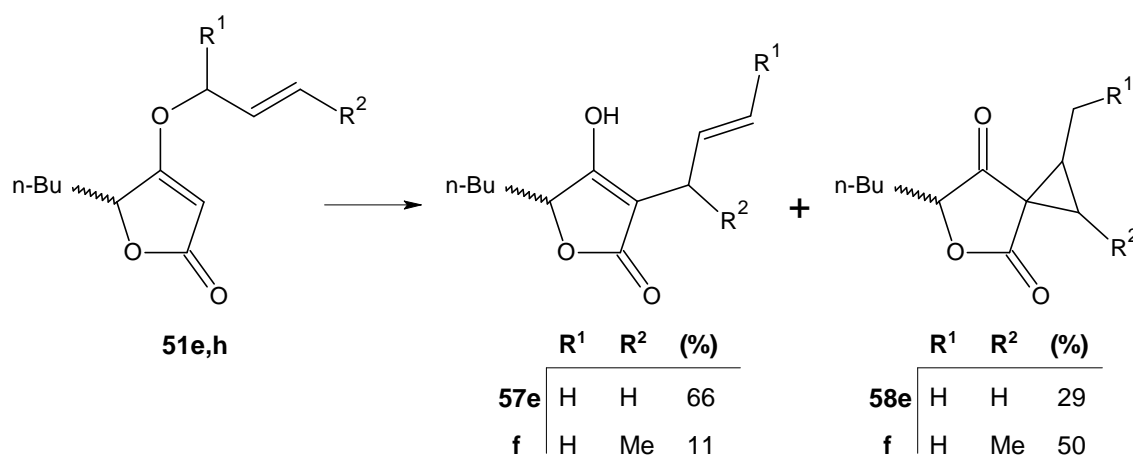
Figure 38.
The increment in the pressure during the microwave assisted Claisen rearrangement presumably favours the formation of the Conia product. Reagents and conditions: allyl tetronate (500 mg), 7 mL dry toluene, mw irradiation (CMS, 190°C, 120 W, 10 min). For formation of **57e-58e** pressure was 8 Bar. For **57f-58f** pressure was 12 Bar.

On the other hand, when **51g** was heated under microwave conditions, the buten-3-yl residue rearranged giving the but-2-enyl derivate **57g** in 87% yield; the expected cyclopropane

spiro furandione **58g** bearing the ethyl group was not effectively isolated from the reaction mixture.
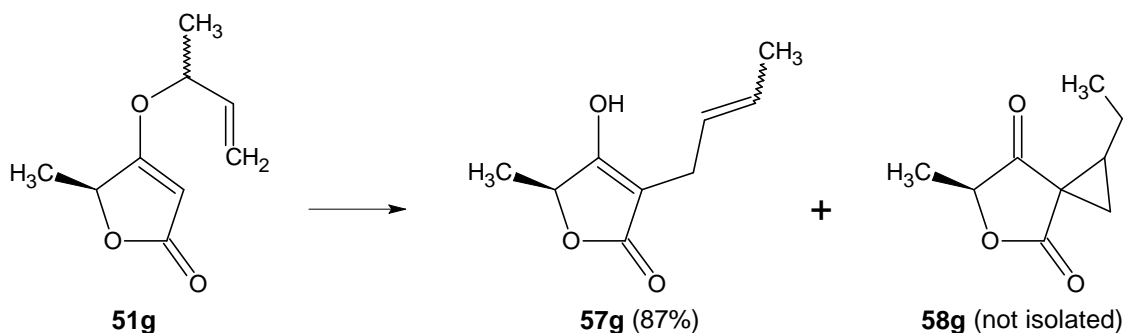
Figure 39.
During the microwave assisted Claisen rearrangement of derivate **51g**, the corresponding Conia product **58g** was observed in GC-MS spectra but was not possible to isolate. Reagents and conditions: allyl tetronate (500 mg), 7 mL dry toluene, microwave irradiation (CMS, 190°C, 8 bar, 120 W, 10 min)

The different oxa-spiro[2.4]heptane-4,7-diones **58** were found as mixture of diastereoisomers. The formation of two diastereoisomers was explained in terms of an equilibrium between the two possible enol forms of **57** under high temperatures[65]; each diastereoisomer is generated as a mixture of enantiomers (Appendix A). Analysis of MS spectra for either diastereoisomer (previously separated via GC) showed no difference between their fragmentation patterns. This suggests that initial dissociation occurs at the furan-2,4-dione (ring opening), and from this first step there is no notable difference in the registered mass spectra for each isomer because subsequent fragmentations are equal in all cases. Thus, unfortunately ionization via electron impact (70 eV) did not let distinct the individual isomers via mass spectrometry.

An approximation was done to assign the NMR signals from the new methyl group formed during the Conia reaction. Thus, the α diastereoisomers were determined as the derivatives bearing the methyl group next to the ketone, while the compounds bearing the methyl group next to the lactone group were assigned as β. This assignment was based on previous studies of Claisen-Conia rearrangements of cinnamyl residues.[68] The assignment was done based on the computed 3D models and two factors: firstly, a small distance difference exists between the carbon atoms from the methyl - keto group (3.18Å) respective to the methyl - lactone group (3.23Å);[69] and secondly, there is a slight difference in the magnetic environment around the methyl group as a consequence of the different diamagnetic field between the ketone and the lactone groups.
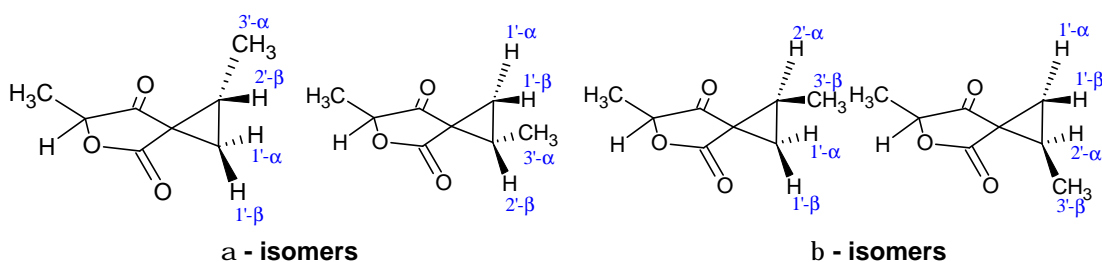
Figure 40.
Description of the characterized protons for the diverse diastereoisomers **58b** formed after the Conia rearrangement. The assignment was done in order to have a comprehensible ¹H-NMR signal assignment for the spectrum. The mixture of diastereoisomers was not separable into the single compounds using conventional column chromatography.

The formation of a preferential isomer was not detected via GC nor by NMR experiments as in the case of derivatives **58h**.[68] The ratio between isomers was maintained to some extent in the order α = β except in the case of the 5(*S*)-methyl derivate **58b**. **Figure 42** shows the ¹³C-NMR-spectra of compound **58c**. The "zoom in" regions clearly show the existence of isomers α and β with the corresponding enantiomers (considering the chiral centre in carbon C-5, four different diastereomers were observed).

R	a	b
H	1	1.2
(*S*)-Me	1.4	1
Et	1	1
n-Bu	1	1.2
n-Hex	1	1.3
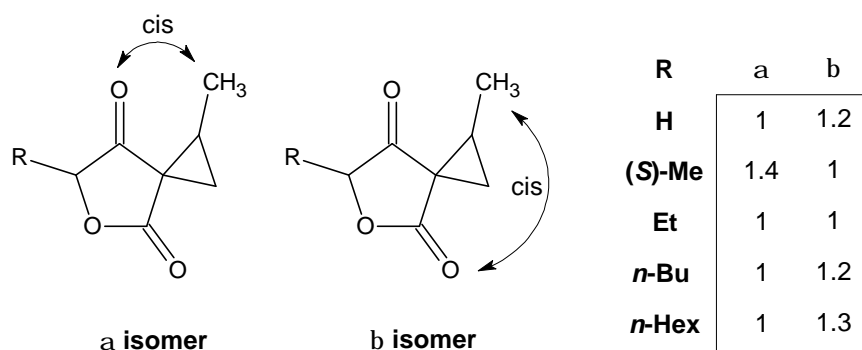
Figure 41.
Description of the relative amount of α / β isomer in cyclopropane spiro furandiones **58**. No formal explanation was found for the inverse value in the case of (*S*)-methyl derivate **58b** (second entry).
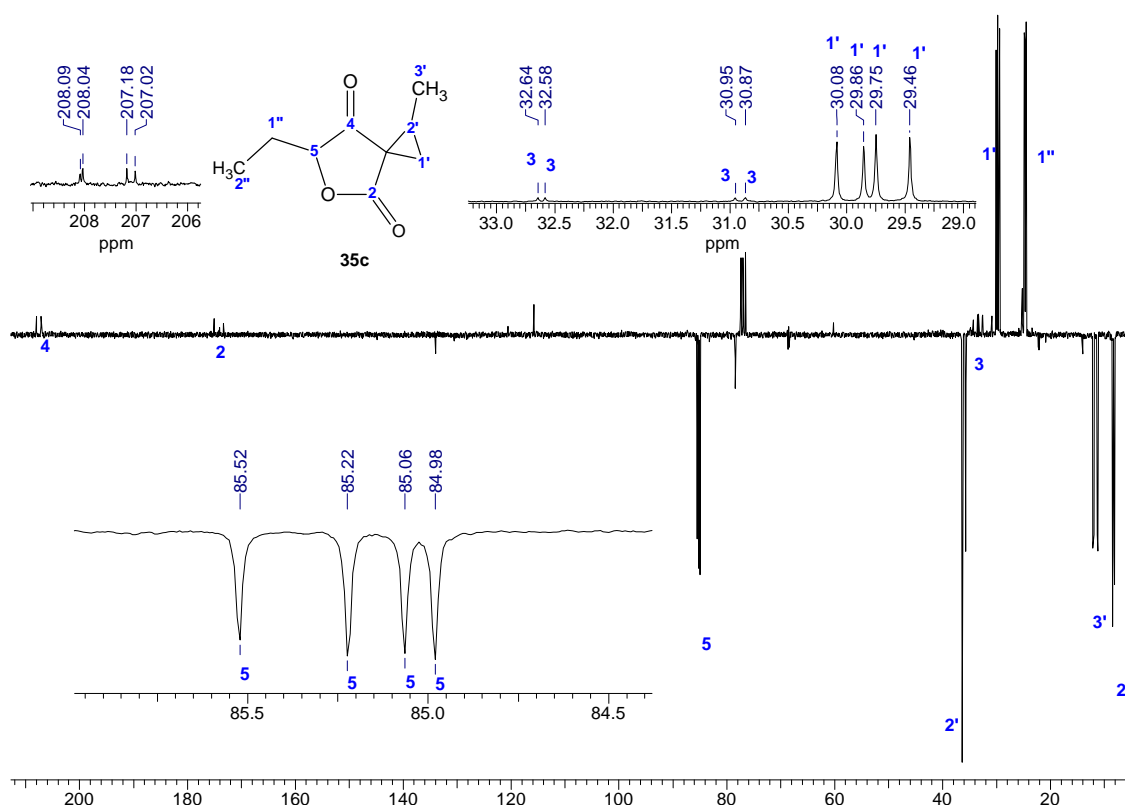
Figure 42.
75 MHz ^{13}C-APT-NMR spectrum of compound **58c** in CDCl$_3$. The "zoom in" regions show clearly four signals corresponding to four different diastereoisomers.

When optimising the reaction it was found that the Conia product **58** can be easily synthesised from the Claisen derivative **57** in two different ways: a) by increasing temperature (and pressure) and eventually the time during the reaction or b) using enhanced microwave synthesis (EMS). – The last procedure was used when studying the derivatisation via nucleophilic ring opening of spiro cyclopropane furandiones and is described in section 2.5.

2.5   Functionalisation of spiro cyclopropane furandiones. The cascade Conia – ring opening reaction

2.5.1   Nucleophilic ring opening of cyclopropane spiro furandiones

Once the diverse cyclopropane spiro furandiones **58** were isolated they were used as starting material for a nucleophilic ring opening with alcohols in accordance with previous experiments with spirocyclopropane chemistry.[39] It is important to mention that the formation of spiro cyclopropane furandiones and the ring opening of the resulting spirocyclopropane

system have been reported previously by our research group[70], although no derivatives bearing a single methylcyclopropane nor an alkyl chain in position C-5 have been described.

The strained cyclopropane ring of the Conia product was opened via nucleophilic attack by methanol and allyl alcohol (**Figure 43**). By simply refluxing the spiro-compounds in a mixture of chloroform and the respective alcohol, the corresponding 3-(β-alkoxy)alkyltetronic acids **60** were obtained in excellent yields. As in previous research, chloroform was added to improve the solubility of the Conia compound.[39]

	R	R^1	(%)
60a	H	Me	95
b	Me	Me	83
c	*n*-Hex	Me	95
d	H	Allyl	91
e	Me	Allyl	94
f	Et	Allyl	89
g	*n*-Hex	Allyl	89
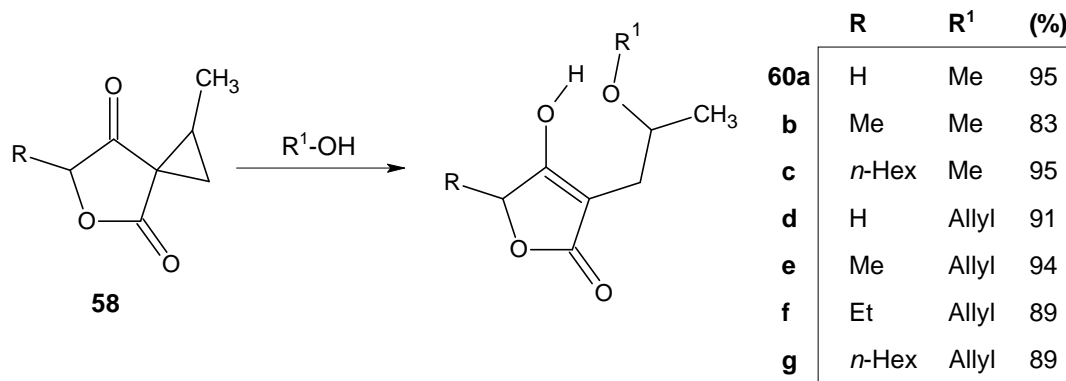
Figure 43.
Thermally assisted spirocyclopropane ring opening using methyl and allyl alcohol in excess as nucleophile. No catalyst was used. Conditions and reagents: R'-OH (10 eq), CHCl₃, 16 to 22h, 70°C, argon.

The cyclopropanes **58** were found to be highly reactive. In the presence of alcohols in refluxing chloroform, the ring was opened without the aid of a Lewis acid catalyst contrary to previous suggestions.[71]

The ^{1}H-NMR spectra of compounds **60** show identical patterns. For example, compound **60d** (**Figure 44**) displays two clearly separated double doublets for the methylene group adjacent to the oxygen atom of the 1-propenyl rest. This phenomenon can be explained by the existence of a strong hydrogen bond between the tetronic acid hydroxy group and the alkoxy oxygen atom. The resulting pseudo seven ring would restrict rotation about the O-CH$_2$ bond, so that the two geminal hydrogens of the methylene group experience different chemical environments ($\delta_{H4'a} = 4.01$ ppm; $\delta_{H4'b} = 4.16$ ppm) and would consequently undergo geminal coupling.[39] That means that each double doublet belongs to one of the magnetically non equivalent 4'-hydrogen atoms. The observed splitting can be explained by a coupling between the 5'-hydrogen atom and one of the 4'-hydrogen atoms leading to a doublet ($^3J_{H4'a-H5'} = 6.17$ Hz; $^3J_{H4'b-H5'} = 5.63$ Hz) and a geminal coupling between the 4'-hydrogen atoms ($^2J_{HH} = 12.21$ Hz) leading to the double doublet. The fine splitting correspond to a coupling through 4 bonds with the olefin protons ($^4J_{HH} = 1.24$ Hz and $^4J_{HH} = 1.37$ Hz).
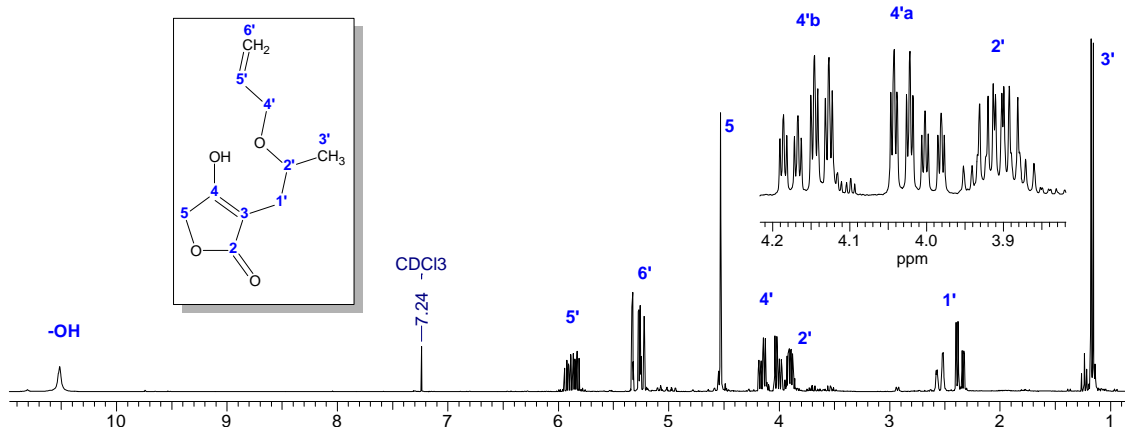
Figure 44.
300 MHz ^{1}H-NMR spectrum of compound **60d** in CDCl$_3$. The zoom region clearly shows the similar pattern of couplings for protons labelled as 4'-H with a different chemical shift in a ABMX$_2$ system; note the "roof effect" for the AB protons.

2.5.2 One-pot nucleophilic ring opening of spiro cyclopropane furandiones under microwave conditions

This ring opening reaction can also be done with different nucleophiles, generating various functionalised molecules using common starting compounds and mild conditions. The process gave no side products and good yields.

Ring opening with benzyl alcohol was also carried out with pure 1,6-dimethyl-5-oxa-spiro[2,4]heptane-4,7-dione **58b** in chloroform under reflux at 80°C for 9 hrs and using ytterbium-(III)-trifluoromethanesulfonate hydrate as catalyst (54% yield after purification via column chromatography). The use of the catalyst was essential because no reaction was detected via GC without its use – the more sterically demanding alcohol does not react as well as methanol or allyl alcohol under thermal heating.
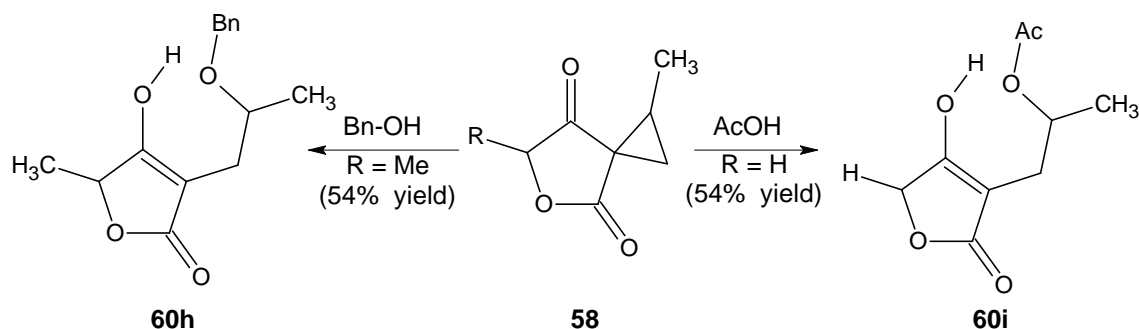
Figure 45.
Nucleophilic attack of benzyl alcohol and acetic acid on the cyclopropane ring using conventional heating and Lewis acid as catalyst. Reagents and conditions: Nucleophile (10 eq), Yb(OTf)$_3$ (10 mol-%), CHCl$_3$, 80°C, 16h.

The same behaviour was observed when acetic acid was used as the nucleophile: only in presence of the Lewis acid was a change observed during the reaction control.

In order to increase the yield of the reaction based on the amount of 3-allyl tetronic acid used as starting material, microwave assisted synthesis was performed. Thus, to obtain compound **60j,** the 3-allyl tetronic acid **57a** was initially heated under CMS conditions (190°C, 4.2 bar, 120 W, 1h) to convert it into the cyclopropane spiro derivative **58a**. The extension of the reaction was followed via GC and the comparison was possible once the cyclopropane spiro furandione was totally characterized. When the Conia (and highly reactive) product **58a** was formed, the cyclopropane ring was opened with benzyl alcohol (in excess) under EMS conditions (185°C, 0.9 bar, 205 W, 8h). This second part of the reaction was carefully followed via GC. These conditions were chosen in order to guarantee a microwave effect and to insure the Conia product was always present inside the reactor. The starting material and intermediate were no longer detected after 8 hours of irradiation.
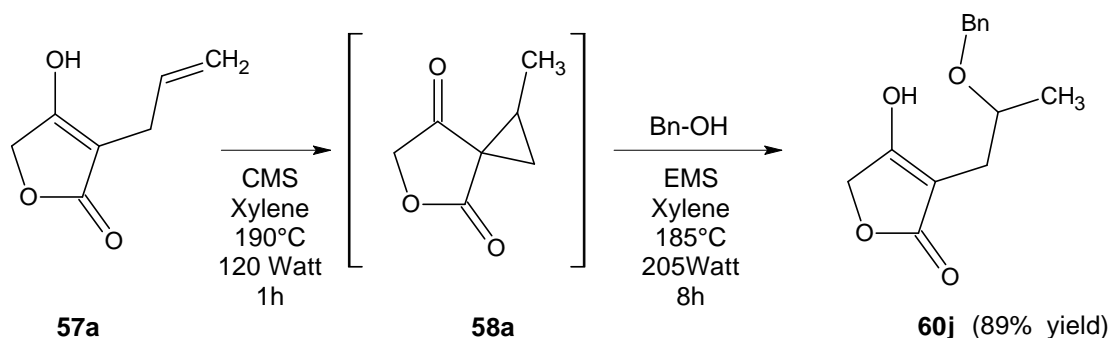
Figure 46.
One-pot nucleophilic attack of benzylic alcohol on the cyclopropane ring using microwave conditions. The reaction was followed via GC.

Comparing the formation of **60h** and **60j** it could be seen, that the use of microwave irradiation (EMS) leads to higher yields (89%) and makes a one pot reaction possible. An important fact has to be mentioned about the scope of the reaction: under the established conditions it is limited only to alcohols with a boiling point of at least 160°C considering a microwave super-heating effect[1,72] (b.p. of benzyl alcohol is 205°C). This was observed once the reaction was tried with methanol as the nucleophile; the reaction could not be carried out because under the reaction conditions the alcohol existed as vapour, substantially increasing the pressure inside the reactor. The overpressure generated causes the microwave reactor to stop automatically on exceeding the maximum pressure value allowed.

When extending the reaction to acetic acid as the nucleophile, the reaction did not go to completion. After irradiatiating the reactor under microwave conditions and on being sure all the allyl tetronic acid **57e** was converted into the spiro cyclopropane **58e** (controlling the reaction via GC), the acetic acid was added. The presence of the acetic acid made the retro-

Conia a competing reaction (**Figure 47** – top, dotted line). After 8 h of irradiation, the starting product was isolated as the main compound after the purification of the reaction mixture via column chromatography. None of the expected product was observed. Instead the formation of the diacyl derivative **60l** was observed in a moderate yield (16%) and the 4-*O*-acyl tetronate **60k** was also isolated in a similar amount (23% yield) (**Figure 47** – bottom).
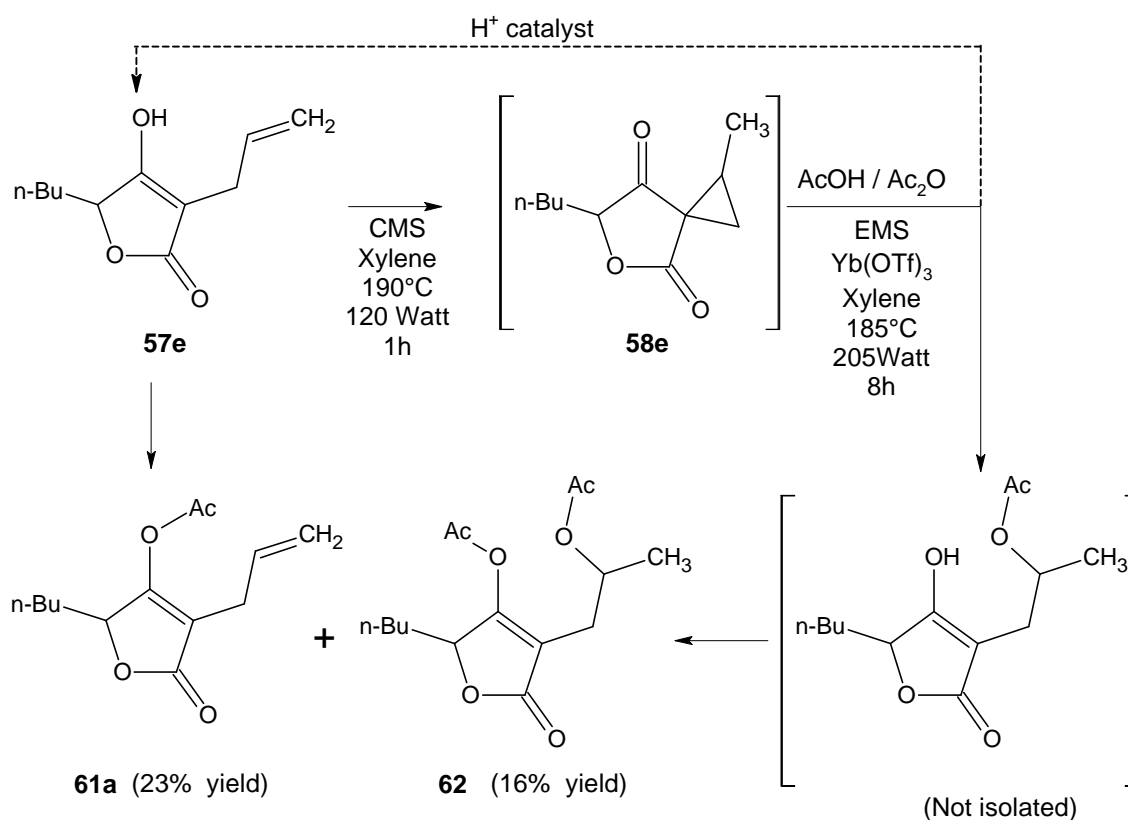
Figure 47.
One-pot nucleophilic ring opening microwave reaction using acetic acid to attack the cyclopropane derivative **58e**. The dotted arrows show the competing reaction occurring during the reaction. The stability of compound **62** was tested in a separate experiment. GC showed no reactivity of **62** when heating it in toluene at 150°C for 1h.

These observations imply a 4-*O*-acylation as the predominant reaction due to the presence of the acid in the reaction. Nevertheless, it was of interest to explore the direct reaction of tetronic acid **57e** in presence of acetic acid under microwave conditions. As was expected and also previously reported by *Boll et al.*[73], the regioselective 4-*O*-acetylated derivative was the main product formed. Compound **61a** was isolated from the reaction mixture in good yields (71%). The diacetyl derivative **62** was produced in a minimum amount (10% yield) as consequence of the Conia – ring opening sequence, corroborating the previous scheme where the retro-Conia process and the direct 4-*O*-acylation were predominant.
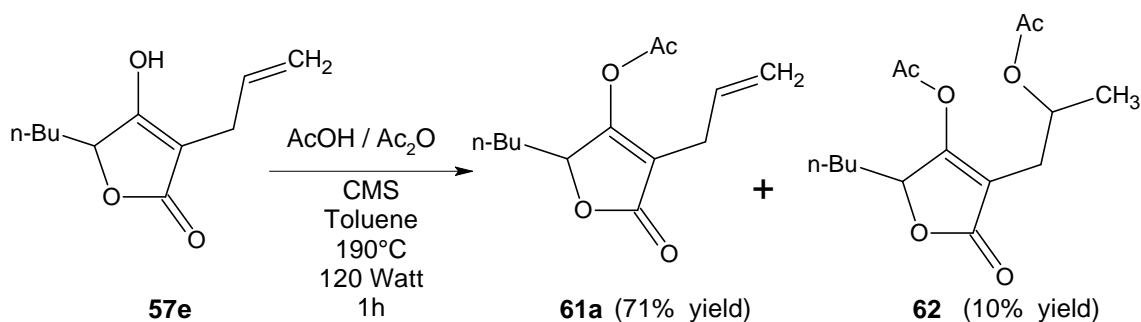
Figure 48.
Microwave reaction using acetic acid to acylate regioselectively the 4-*O*-position in tetronic acid **57e**. Compound **62** was formed as a secondary product from a Conia – Ring opening reaction (see **Figure 38**). Derivative **62** is not formed from **61a**. In a separate experiment using the 4-*O*-tosyl tetronic acid **116**, the GC showed no reactivity when using the same reaction conditions.

It is significant to declare that the 4-*O*-acylated tetronic acid **62** is a stable derivative under the reaction conditions. Once isolated, the doubly *O*-acylated derivative **62** was irradiated under microwave using toluene as solvent (1h, 150°C, 150 Watt). No difference was noted in the gas chromatogram controls. The potential elimination of the acetyl group of **62** was not attempted in presence of AcOH.

On the other hand, derivative **62** is not formed from direct addition of AcOH to the double bond of **61a**. The reactivity of the double bond was examined using a tosyl protected tetronic acid. When the 4-*O*-tosyl tetronic acid **61b** was irradiated under the same reaction conditions, no difference was noted in the gas chromatogram controls.

2.6 4-*O*-Alkylation of 3-allyl tetronic acid: isoureas for the 4-*O*-benzyl protection and Mitsunobu esterification

Enol ethers (vinylogous esters) of tetronic acids are versatile building blocks in the syntheses of natural products, a good deal of which exhibit interesting biological activities of various sorts. As the regioselective 4-*O*-alkylation of the corresponding tetronic acids is the most direct approach to these vinylogous esters, the practical implications of this process have been the focus of many investigations. However, many of the published protocols have major disadvantages. In alkylations with diazomethane and trialkyloxonium tetrafluoroborates for example, the product is a mixture of isomeric alkylated tetronic acid derivates. This fact can be explained by the tautomeric equilibrium, which can exist between the 4-hydroxy-, the 2-hydroxy- and the diketo form of the tetronic acid.[74]
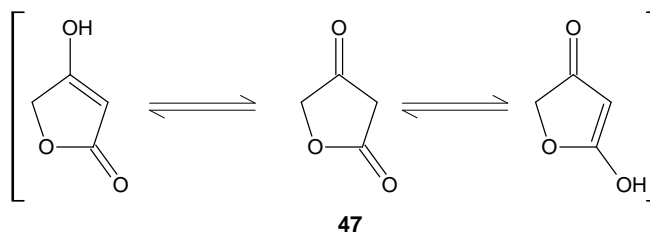
Figure 49.
Tautomeric equilibrium between the 4-hydroxy-, the diketo- and the 2-hydroxy-form of the tetronic acid. This equilibrium is responsible for the different reactivity of tetronic acid derivatives under different conditions.

Another drawback of many protocols is that they often only work well for 3-unsubstituted tetronic acids.[74,75] Two further literature protocols for the direct 4-*O*-alkylation of tetronic acids deserve mentioning due to their high specificity, high yield and broad scope. *Otera et al.* published the CsF-promoted 4-*O*-alkylation of free tetronic acids by primary and secondary alkyl halides in DMF[37] and *Bajwa and Anderson* described the alkylation of tetronic acids with stoichiometric amounts of primary and secondary alcohols under Mitsunobu conditions.[76] The latter method was also adapted to the regio- and chemoselective alkylation of L-ascorbic acid to synthesize medicinally important 3-*O*-alkyl analogues.[77] Even higher yields and better regioselectivities for the 4-*O*-alkylation of tetronic acids were achieved in a synthesis involving the phosphonium trifluoromethanesulfonate **63a** (**Figure 50**) as key intermediates instead of the oxyphosphonium hydrazide **63b**, which occur under Mitsunobu conditions and which are less stable because their nucleophilic counter ion competes with the alcohol for the reaction with the tetronic acid.[75]
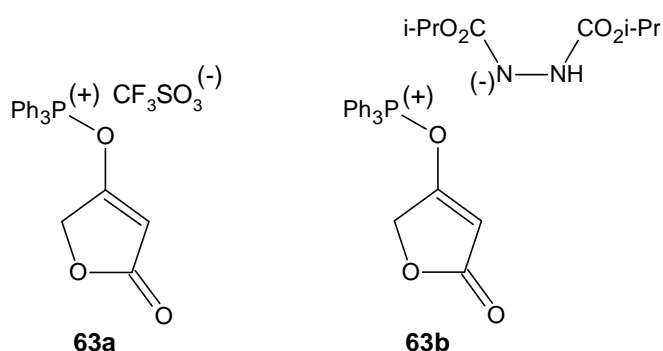
Figure 50.
Oxyphosphonium trifluoromethanesulfonate **63a** and oxyphosphonium hydrazide **63b** as selective intermediates in the synthesis of 4-*O*-alkyl tetronic acids.

2.6.1 C-3 as another nucleophilic centre in the 4-*O*-benzyl protection of tetronic acid derivatives *via O*-benzyl isourea

Schobert and Siegfried reported that the regiospecific 4-*O*-alkylation of various types of 3-substituted tetronic acids and 3,5-disubstituted tetronic acids worked well by reaction with

stoichiometric amounts of isoureas of the respective primary or secondary alcohols.[74] However when the same described protocol[26,74] was used to selectively protect the tetronic acids **57a-e** with a benzyl group, the corresponding 4-*O*-benzyl derivatives **64a-e**, as well as the 3-C-benzyl derivatives **65a-e**, were found. The attack from the more nucleophilic oxygen atom generates the 4-*O*-benzyl derivatives **64** preferentially in good yields. The 3-C-benzyl derivatives **65** were formed in a minor amount as consequence of the 3-C atom attack to the isourea, showing clearly its behaviour as a nucleophile. None of the 3-benzyl derivatives **65** have been described before.

	R	(%)		R	(%)
64a	H	52	**65a**	H	15
b	Me	43	**b**	Me	13
c	Et	48	**c**	Et	15
d	*n*-Bu	36	**d**	*n*-Bu	14
e	*n*-Hex	40	**e**	*n*-Hex	10
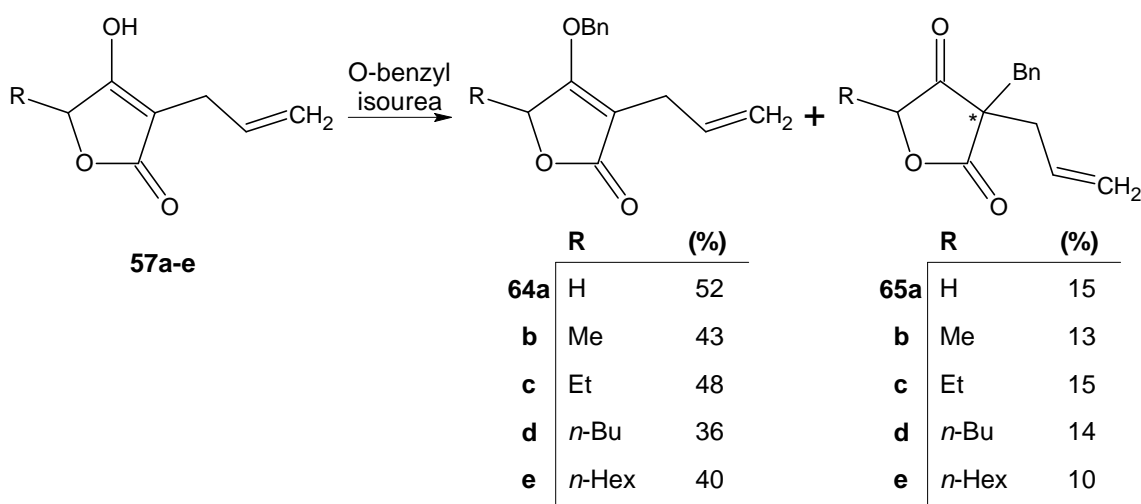
Figure 51.
Synthesis of 4-*O*-benzyl tetronates **64** and 3-benzyl-furan-2,4-diones **65** *via* isoureas. The *O*-benzyl isourea was prepared from DCC and benzyl alcohol according to section 2.1. The *O*-benzyl isourea was purified before the reaction in order to eliminate the possibility that remaining DCC could react with the tetronic acid. Although derivative **64d** was prepared as part of previous research[26] none of the derivatives **65** were observed.

Derivatives **64** were totally characterized as well as the secondary compounds **65**. The formation of 3-benzyl furan-2,4-diones **65** clearly show that a nucleophilic attack of C-3 to the benzylic carbon is very likely following the indicated equation showed in **Figure 52**.
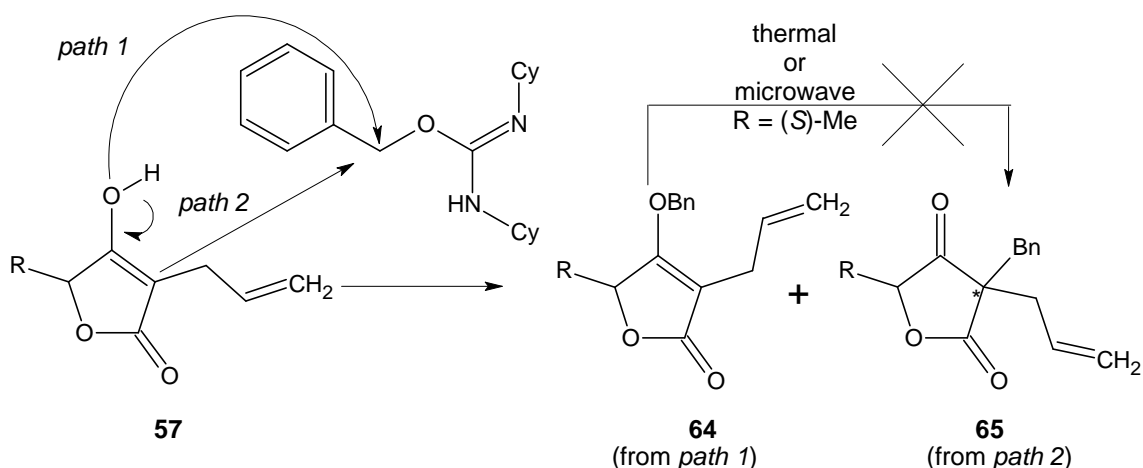
Figure 52.
Illustration of the 2 paths giving derivatives **64** and **65**: 4-*O*-alkylation vs. 3-C-alkylation. In a separate experiment the rearrangement of **64b** to **65b** was tried. It was not possible to rearrange the compound thermally or under microwave irradiation.

A tandem process involving the conversion of **64** to **65** was considered but the addition of the benzyl group to position C-3 cannot be explained with an anionic [1,3] rearrangement[70] because neither a base nor a proton was present at position C-3. A thermal rearrangement from **64b** to **65b** could be ruled out since the treatment under microwave in a sealed tube (CMS conditions, 7 Bar, 80°C, 2.5 h) resulted exclusively in the starting compound.

It was determined derivatives **65** exist as a mixture of diastereoisomers α and β. The diastereoisomeric ratio in all cases was not 1 : 1 because the formation of one of the isomers was slightly favoured (the major formed isomer was labelled as α).

The configuration of the major isomer of **65** was deduced from the COSY, HSQC and NOESY NMR spectral data. All protons were assigned by COSY and HSQC experiments. As can be seen in **Figure 53**, the ^{13}C-NMR spectra of the purified compound **65b** proved the existence of two diastereoisomers (α and β) in different amounts.
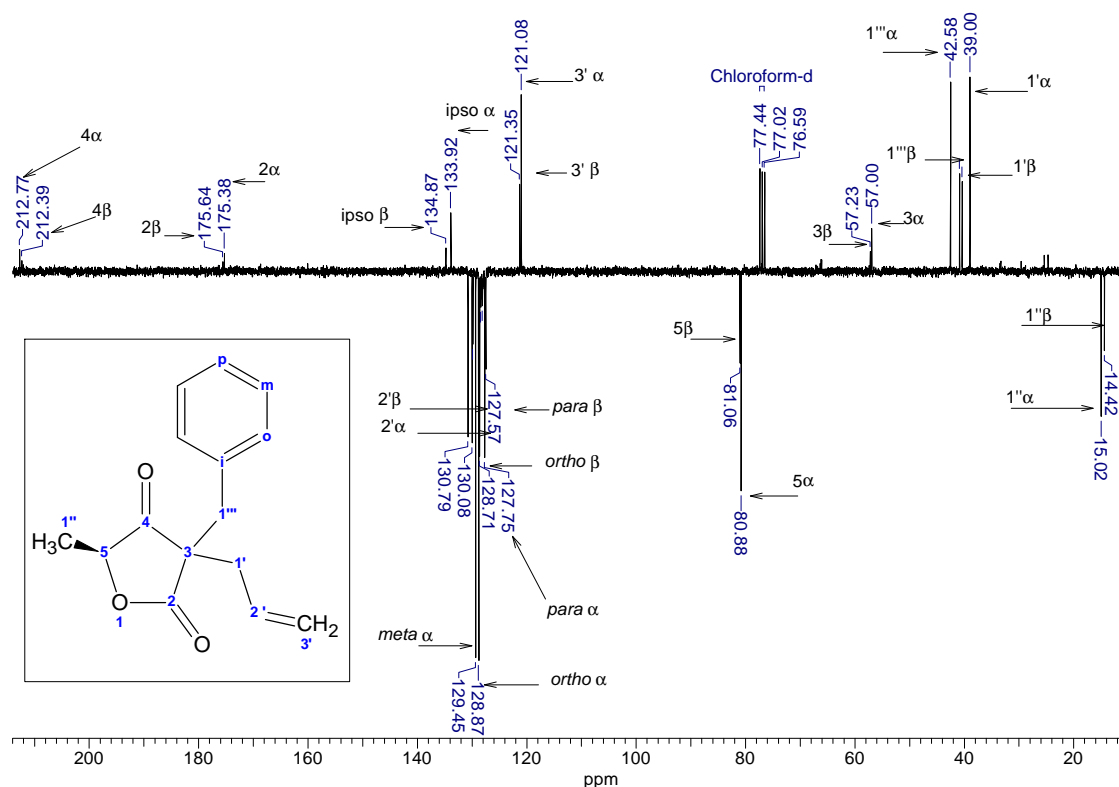
Figure 53.
75 MHz ^{13}C-APT-NMR spectrum of the diastereoisomers mixture of 3-allyl-3-benzyl-5-(*S*)-methyl-furan-2,4-dione **65b** in CDCl$_3$. The major and minor isomers can be distinguished according their signal intensities. **a** - Major isomer, **b** - Minor isomer.

In order to distinguish between the diastereoisomers α and β formed, derivative **65b** was chosen and its chiral centre C-5 used as base in a NOESY NMR experiment. The spectra showed a NOE signal for the correlation peak between the (*S*)-methyl group indicated in **Figure 54** as 1''-H and the allyl protons indicated as 3'-H*cis*, 3'-H*trans* and 2'-H. The NOESY spectra also show the relation between the proton 5-H with the aromatic ring (only *ortho-* and *meta-* protons gave a signal). No NOE signals were noticed for the minor isomer (the signals were overlapped with COSY signals). This data suggests a relatively favourable *"Si"* attack (corresponding to the formation of the α product) from the voluminous *O*-benzyl isourea. The diastereomeric ratio determined was not equal (d.r.= 10 : 1), a direct consequence of the sterically hindering influence of the (*S*)-methyl group in position C-5.
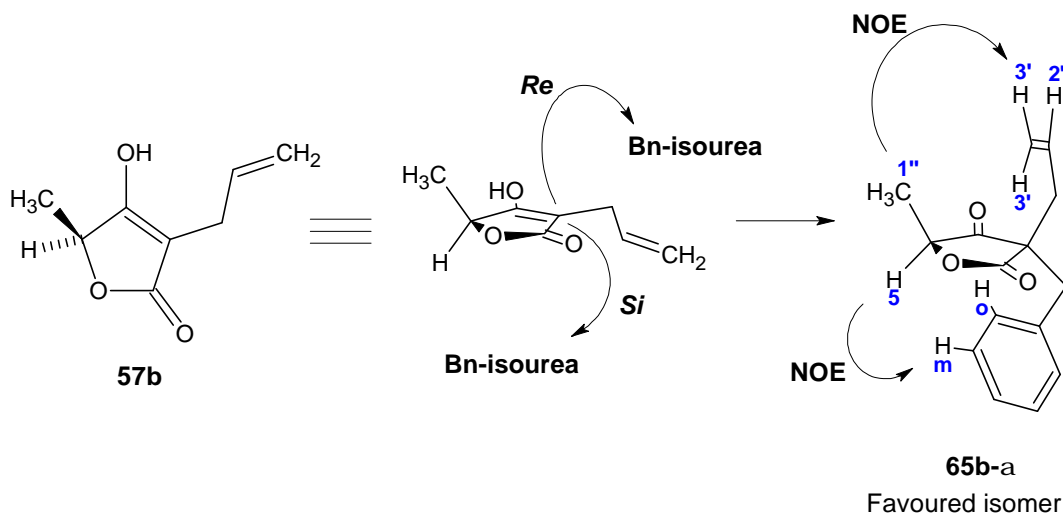
Figure 54.
The formation of the favoured diastereoisomer **65b-a** from the C-3 *Si*-attack of the *O*-benzyl isourea on the chiral tetronic acid **57b**.

The diastereomeric ratio for α and β in derivatives **65** was calculated from the integration values for the discernible signals in their ^{1}H-NMR spectra. The ratios of diastereoisomers α and β for the different 5-alkyl substituted derivatives **65** are summarized in **Table 1**.

Table 1. Diastereomeric ratio of 3-allyl-3-benzyl-furan-2,4-diones **65** for different alkyl substituents at C-5.

Derivative	R	Ratio **a** : **b**
65b	(*S*)-Me	10 : 1[*]
65c	Et	14 : 1**
65d	*n*-Bu	5 : 1**
65e	*n*-Hex	10 : 1**

* from ^{1}H-NMR integration
** from HSQC integration; each diastereoisomer exists as a racemic mixture.

The formation of the α–diastereoisomer was preferencial in all cases. This shows that a favourable attack occurred from the less sterically hindered side of the tetronic acid ring to the isourea (the benzyl rest is then *trans-* to the alkyl rest). No formal explanation was found for the higher ratio of **65d** respect to **65e**.

In a particular case, when working with enough material of derivative **57c** and using the same reaction protocol, a third fraction was also separated from the column chromatography purification. Thus, the formation of the 2-*O*-benzyl derivative **66a** was also determined. This fact can be described by the tautomeric equilibrium which exists between the 4-hydroxy-, the 2-hydroxy- and the diketo-form of the tetronic acid (**Figure 49**).
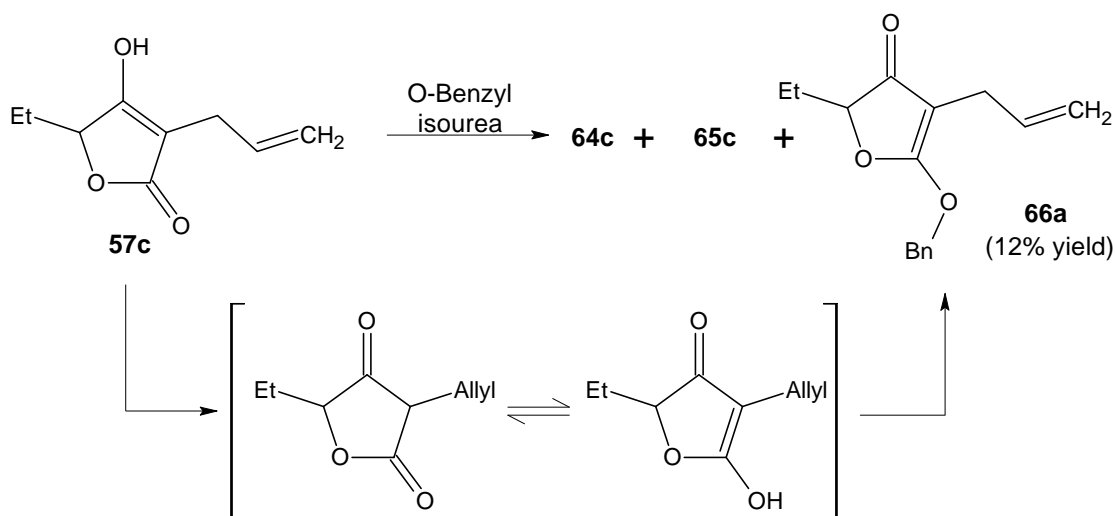
Figure 55.
The tautomeric equilibrium between the 4-hydroxy-, the diketo- and the 2-hydroxy-form of the diverse tetronic acid derivatives **57** is responsible for the different products formed during the alkylation via *O*-benzyl isourea. The 2-*O*-benzyl derivative **66a** was also isolated and completely characterized from the reaction mixture (despite a previous report made by our research group).

Consequently this last example **66a** as well as the formation of five new 3-benzyl derivatives **65** contradict the reported regio-selectivity of this process.[74]

2.6.2 4-*O*-Allyllation of 3-allyl tetronic acid under Mitsunobu conditions

An alternative high-yielding route to 4-*O*-allyl tetronic acids comprises the esterification of 3-allyltetronic acids such as **57** with different allylic alcohols. The esterification of **57a** with allyl (methallyl and cinnamyl) alcohol to give **67a-c** was only possible under modified Mitsunobu conditions[77] while both the Steglich-Hassner as well as our own isourea method[74] failed completely.

To synthesize 3-allyl-4-allyloxy-5*H*-furan-2-one **67a**, 3-allyl-4-(2-methyl-allyloxy)-5*H*-furan-2-one **67b** and 3-allyl-4-(3-phenylallyloxy)-5*H*-furan-2-one **67c** (**Figure 56**)**,** a protocol was carried out similar to that described by *Tahir and Hindsgaul*[77]. Although several methods are known to effect this transformation[74-77] the conditions used were sufficient to deliver the desired substrates. The relatively high acidity of 3-allyl tetronic acid **57** allows its use as the acidic component under Mitsunobu conditions. This property was exploited by *Bach et al.* who prepared mono allyl derivatives analogues as synthons for inter- and intramolecular [2+2]-photocycloaddition of tetronates.[78,79]
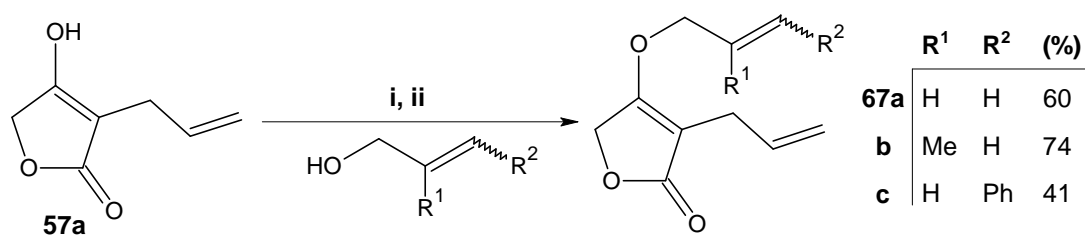
Figure 56. Synthesis of 4-*O*-allyl tetronates **67** *via* Mitsunobu reaction. Reagents and conditions: **i**.Ph₃P (1.3 eq), DIAD (1.3 eq), THF, -78°C. **ii**. R-OH (1.5 eq); -78°C to rt.

The compounds were identified by ¹H-NMR, ¹³C-NMR, GC, GC-MS, and IR. As an example, **Figure 57** shows the ¹³C-APT-NMR spectrum of compound **67a**.
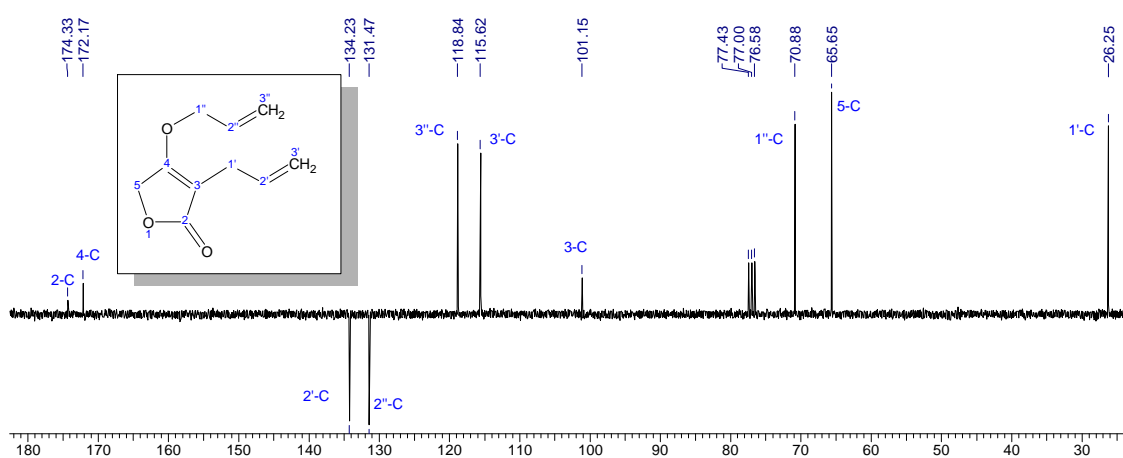
Figure 57.
75 MHz ¹³C-APT-NMR spectrum of compound **67a** in CDCl₃. This compound was previously prepared by *Kotha et al.* as part of a mixture in 55% yield from tetronic acid and allyl bromide[80] using a modified procedure which originally reported 12% yield [38].

One particular aspect of the Mitsunobu reaction was that under the chosen reaction conditions the cinnamyl alcohol did not react completely (a considerable amount of cinnamyl alcohol was recovered after chromatographic purification). It is well known that in reactions with sterically demanding alcohols the phosphonium intermediate reacts faster with the hydrazide than with the alcohol, and even with unhindered alcohols this reaction occurs to some extent. Another difficulty commonly encountered with the alkylation under Mitsunobu conditions was the separation of the products from the dialkyl 1,2-hydrazinedicarboxylates formed during the reaction.[75]

On the other hand, the Mitsunobu reaction has many advantages. Firstly, the reaction proceeds under mild, essentially neutral conditions. This means that little or no elimination - normally competing with S_N2 substitutions at secondary sp³-hybridized carbons - occurs in the Mitsunobu reaction. Secondly, it is very specific and has high yields as well as a broad scope: in the 3-*O*-alkylating Mitsunobu reaction with L-ascorbic acid it is not required to protect the

hydroxyl groups OH-5 and OH-6. And finally, the procedure employs readily available alcohols as alkylating agents. By contrast, alkyl halides for instance may not be commercially available.[74,77]

2.6.3 Sigmatropic rearrangement of 5-alkyl-4-*O*-allyl-furan-2-ones

Synchronous [3,3]-sigmatropic rearrangements like the experimentally easy Claisen rearrangement have become more and more important over the past decades because of the high demands for the uniform stereochemical course of syntheses, leading to natural or pharmaceutical products.[81] The Claisen rearrangement of allyl-vinyl ethers is a symmetry-allowed and concerted pericyclic reaction involving a suprafacial pathway which proceeds with high preference through a chairlike transition state, since in this conformation the 1,1-diaxial interactions are minimal.[82,83].

	R^1	R^2	(%)
68a	H	H	92
b	Me	H	99
c	H	Ph	91
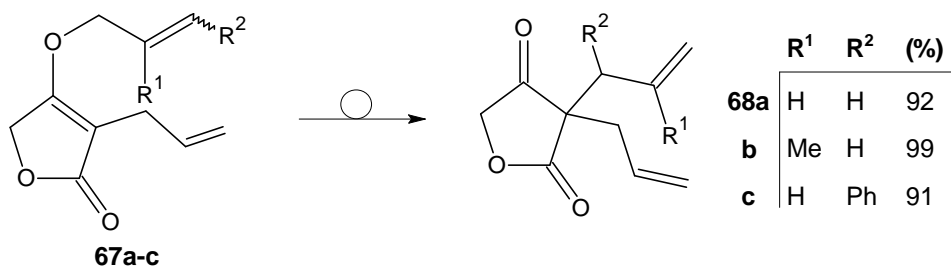
Figure 58.
Reagents and conditions: allyl tetronate (500 mg), 7 mL dry toluene, mw irradiation (CMS, 190°C, 20 min., 8 Bar, 120 Watt). Compound **68a** was prepared previously by *Kotha et al. via* microwave assisted Claisen rearrangement with SiO$_2$ as support from **67a** in 75% yield.[20]

A thermally induced Claisen rearrangement was carried out to synthesize compounds **68a-c** starting from compounds **67a-c** in good to excellent yields (91 to 99 %) by heating in toluene at 190°C for 20 min under microwave irradiation (mono-mode *CEM Discover*). Once compound **68a** was prepared as reference, synthesis of derivative **68b** was followed via GC: chromatograms show that when carried out under microwave irradiation the Claisen step proceeded quantitatively and without allyl scrambling and formation of product mixtures. For compound **68c**, which has two chiral centres (one at carbon atom C-3 and one at the benzylic carbon atom C-1'), a mixture of two diastereomers in a ratio of 5 : 9 was isolated; in the ^{1}H-NMR spectra, the hydrogen atoms 1', 5, 1'' and 2'' showed different chemical shifts for both isomers. Furthermore, ^{13}C-NMR showed two peaks for several carbon atoms (see details in experimental part) which means that these atoms are in different magnetic environments in the two isomers. Last but not least, gas chromatography displayed two peaks, whose integration reveals the isomer-ratio of 5 : 9.
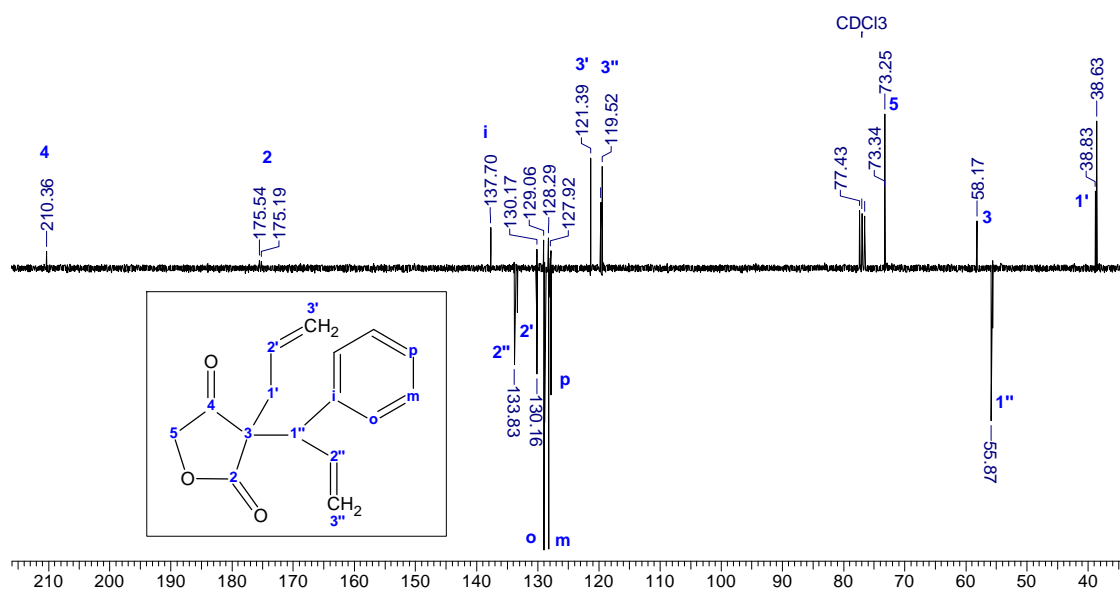
Figure 59.
75 MHz ^{13}C-APT-NMR spectrum of compound **68c** in CDCl$_3$. The presence of two chiral centres generates two diastereoisomers with slight differences in their NMR signals. Note the double signal pattern for some carbon atoms in the peaks values, as consequence of the mixture of isomers.

This significant difference in the ratio of diastereomers can be explained in the following way: the major diastereoisomer is likely to be formed directly from the starting material, in which the double bond has *E*-configuration. It is then the result of a *like* addition, which is energetically favoured because the bulky phenyl group prefers the equatorial position in the six membered "chair like" transition state. The minor diastereoisomer could be formed in two different plausible ways. Firstly, it could be the product of an *unlike* addition, whose transition state (a twist boat) is not energetically favoured. Secondly, a constitutional change from *E* to *Z* in the double bond of the reactant - as a consequence of either an isomerization or a retro-Claisen reaction occurred during the evolution of the reaction under the microwave conditions – this could lead to a new *cis*-olefin, which could then rearrange to form the minor diastereoisomer. A detailed analysis of the starting material via GC demonstrated the existence of the *Z* isomer in the compound, solving easily the discussion about the difference in ratio of the isomers.
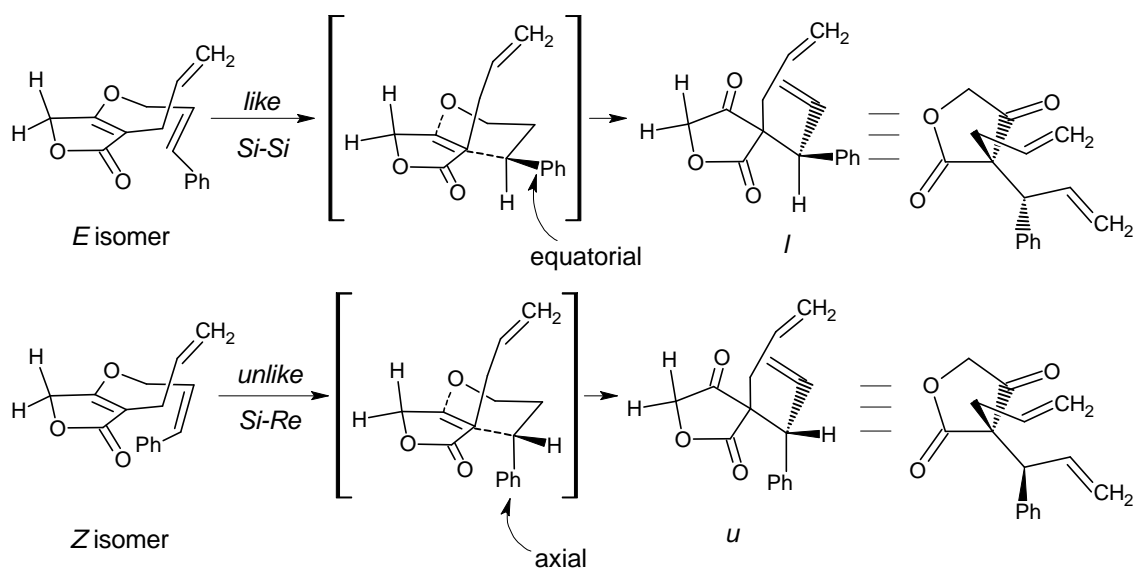
Figure 60. The *like* and *unlike* products **68c** formed from the Claisen rearrangement of 4-*O*-cinnamyl tetramates **67c**. Each diastereoisomer also forms the corresponding enantiomer.

2.7 Chemistry of 3-allyl tetronic acid derivatives

2.7.1 Synthesis of (-)-3-*epi*-Blastmycinolactol *via* a Rhodium catalyzed hydrogenation

Many different syntheses have been and continue to be published to produce fully functionalized γ-lactones having three contiguous asymmetric centres on α-, β- and γ-positions.[84] The biological activities of many of these naturally occurring compounds are attributed to their butyrolactone cores.[84d]

(3*R*,4*R*,5*S*)-3-butyl-4-hydroxy-5-methyldihydrofuran-2(3*H*)-one also known as (-)-3-*epi*-blastmycinolactol **29-*epi*** (**Figure 64.**) was prepared starting from (5*S*)-3-[(2*E,Z*)-but-2-en-1-yl]-4-hydroxy-5-methylfuran-2(5*H*)-one **57g**. (-)-Blastmycinolactol **29**, the epimer of the compound prepared and reported in this section, was first synthesized in 1973 and is, like the more famous polyketide (+)-blastmycinone **70**, a hydrolysis product of antimycin A₃ **69**. The latter is a secondary metabolite isolated from *Streptomyces* with antibiotic activity against phytotoxic fungi, yeasts, mites, flies, moths, meal beattles and others by inhibiting the respiratory chain.[84]
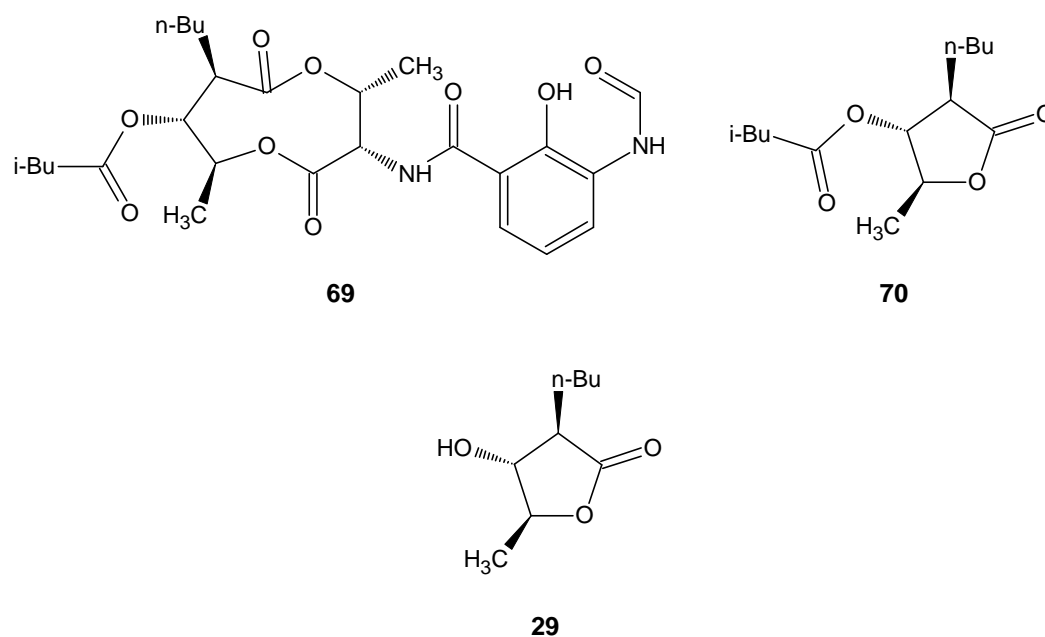
Figure 61.
Structural formulas of antimycin A₃ **69**, (+)-blastmycinone **70** and (-)-blastmycinolactol **29**.

A practical methodology to form trisubstituted γ-lactones is constructing first the corresponding substituted tetronic acids (with the skeletal structure 4-hydroxy-2(5*H*)-furanone), which are then subsequently reduced. Several reduction methodologies report the use of Raney nickel as catalyst; 3,5-disubstituted tetronic acids have been reduced under high pressure using different reaction conditions (132 bar, 70°C, 29h[85] or 69 bar, 70°C, 24h[86] or 90 bar, 70°C, 72h[87]). These studies concluded that the hydrogen molecule attacks the double bond in the tetronic ring from the opposite side of the 5-substituent and consequently one diastereisomer is always formed predominantly.[85-87]
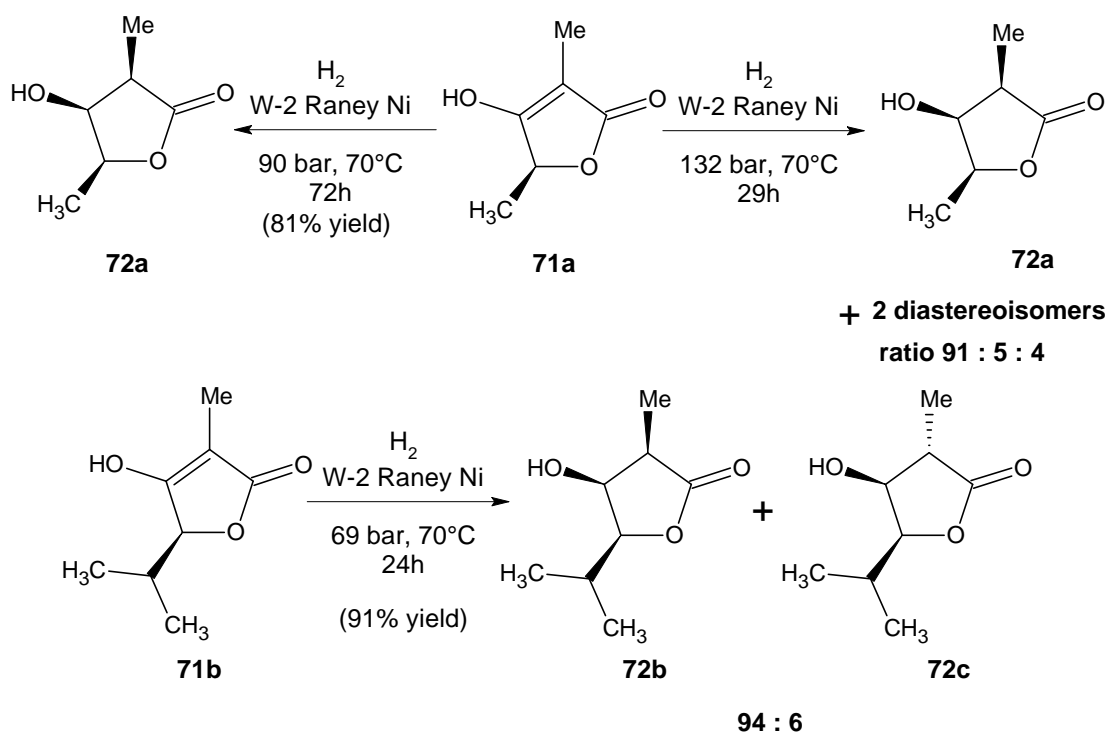
Figure 62.
Catalytical reduction of the tetronic acid core using Raney Nickel. According literature reports the formation of the trisubstituted γ-lactone **72** is enantioselective.

Excellent yields of mixtures of the *cis*- and *trans*-hydroxy lactones were obtained on reduction of 5-methyl tetronic acid **57i** with ammonia-borane or on catalytic hydrogenation over rhodium. The former reagent gave a high proportion of the thermodynamically more stable *trans*- product **49-epi**, while the latter gave the *cis*- and *trans*-compounds in a ratio of 86:14.[88] A further possibility for the asymmetrical hydrogenation of tetramic or tetronic acid derivates is the use of catalytic, optically active rhodium-, ruthenium- or iridium-complexes bearing chiral diphosphines as ligands.[89]
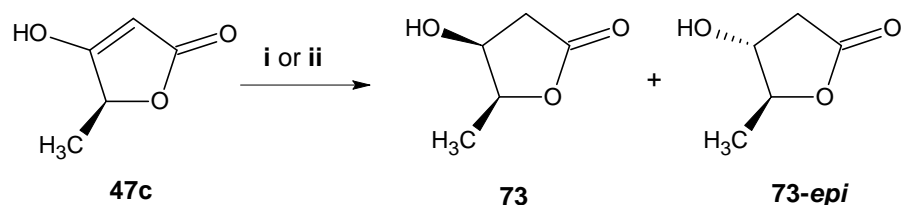
Conditions:
i. NH$_3$.BH$_3$, MeOH / H$_2$O. Ratio **73** : **73-epi** = 25 : 75
ii. H$_2$, Rh / C (5%), 5 bar, 22°C, 60h, AcOEt. Ratio **73** : **73-epi** = 86 : 14

Figure 63.
Catalytical reduction of the tetronic acid core using ammonia – borane and catalytic hydrogenation over rhodium.

The hydrogenation of (5*S*)-3-butyl-4-hydroxy-5-methyl-5*H*-furan-2-one **57i** with 5% rhodium-alumina under a hydrogen pressure of 5 bar to give optically pure (-)-3-*epi*-blastmycinolactol **29-epi** shall also be mentioned. As in the previous examples, NMR analysis using chiral shift reagents showed **29-epi** was formed optically pure.[84a]
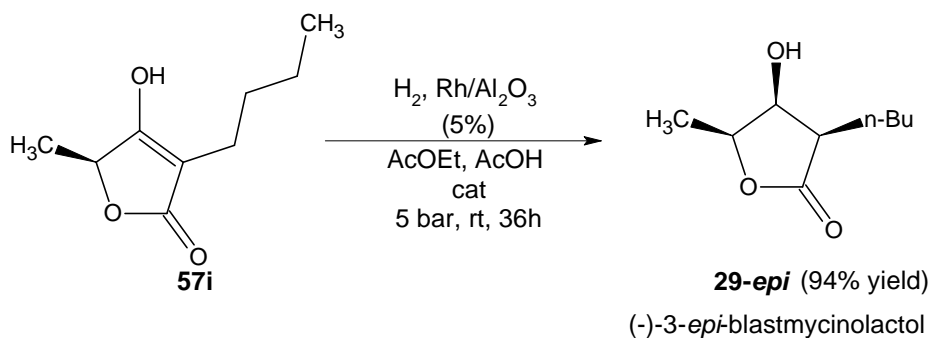
Figure 64.
Enantioselective synthesis of (-)-3-*epi*-blastmycinolactol by *Nishide et al.*[84a] from the hydrogenation of tetronic acid derivative **57i** using rhodium as catalyst.

Derivative **57i** was previously prepared in our research group for the synthesis of blastmycinolactol **29** starting fom α-methallyl lactate and Ph₃PCCO. After the separation of Ph₃PO, tetronate *rac*-**51g** was then heated to facilitate a Claisen rearrangement to the tetronic acid *rac*-**57g**. Formation of 3-*n*-butyl derivative **57i** was completed by hydrogenation of the exocyclic double bond. The synthesis of blastmycinolactol **29** was completed by selective *trans*-hydrogenation of the endocyclic C=C bond *via* chloro compounds **74** and **75**. The racemic blastmycinolactol **29** could then be synthesized over 7 steps in 25% overall yield.[50]
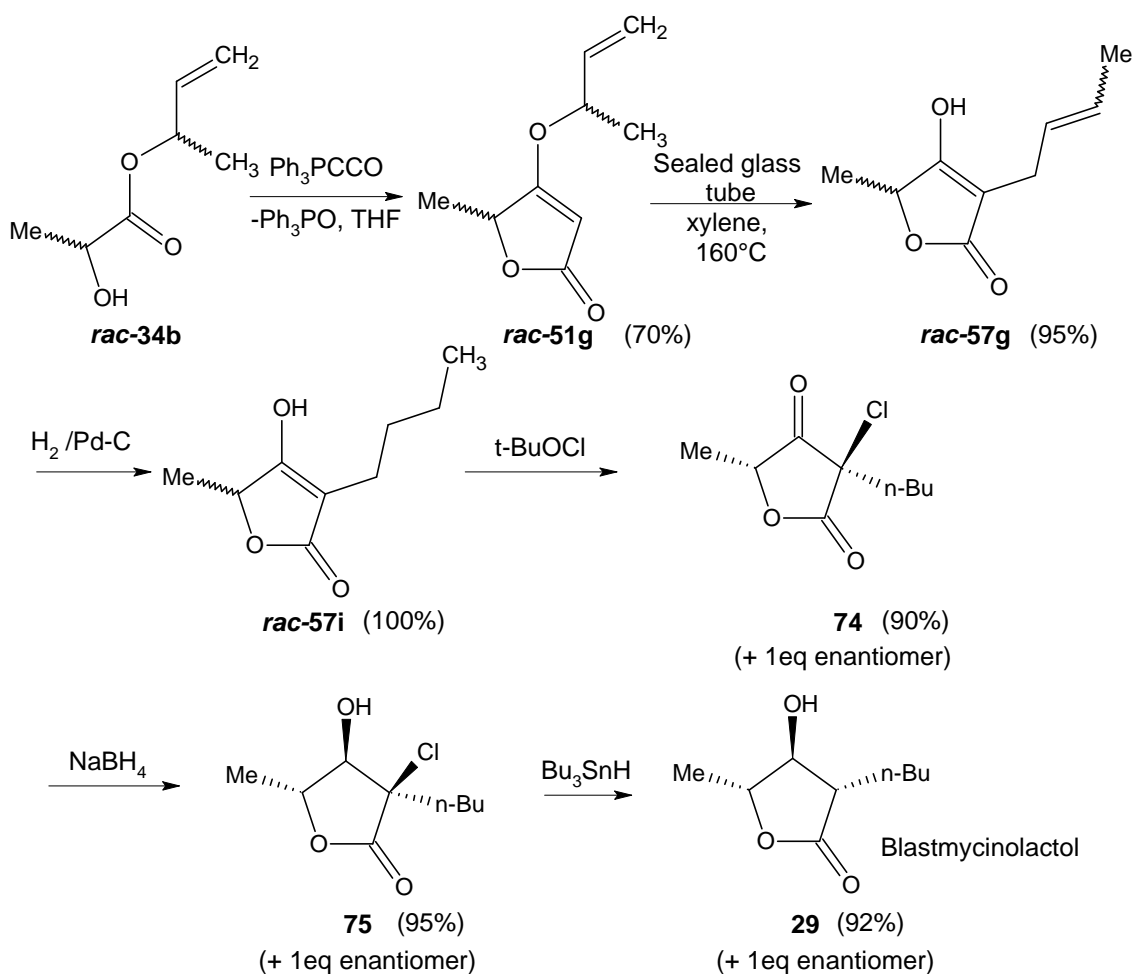
Figure 65.
Racemic synthesis of (-)-3-blastmycinolactol **29** by *Löffler and Schobert*.[50] The racemic product was formed because (R,S)-α-methallyl lactate *rac-***34b** was used.

For the synthesis of (-)-3-*epi*-blastmycinolactol (**Figure 67.**), a mixed protocol was followed. An initial test performed on 3-allyl tetronic acid **57a** under the conditions described by *Nishide et al.*[84a] showed no reaction. When the pressure and temperature were increased, only the exocyclic double bond was hydrogenated.
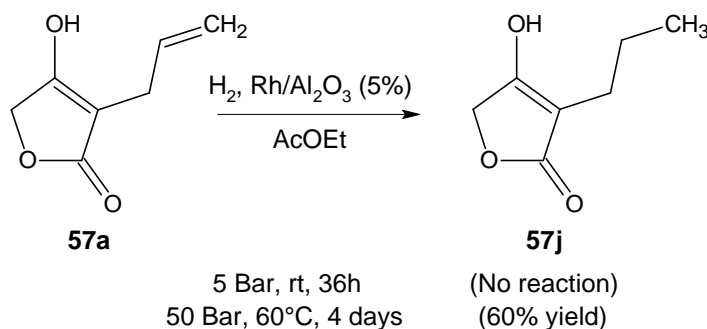
Figure 66.
Hydrogenation of 3-allyl tetronic acid using rhodium over alumina as catalyst. When using the similar reaction conditions described by *Nishide et al.*[84a] only the exocyclic double bond was reduced.

In order to reduce the exocyclic and the endocyclic double bonds, a 1:1-mixture of ethyl acetate and acetic acid was used as solvent and the hydrogenation was performed at 50 bars and 60°C for five days. When using equivalent masses of the catalyst Rh/Al$_2$O$_3$ and the starting material **57g**, (-)-3-*epi*-blastmycinolactol **29-epi** was obtained only in 16% yield. When increasing the amount of catalyst inside the reaction mixture to the amounts described by *Nishide et al.*[84a], the (-)-3-*epi*-blastmycinolactol **29-epi** was obtained {[α]$_D^{25}$ –57.05° (0.638 g/100mL, MeOH), [Ref 84a [α]$_D^{25}$ -84.8° (0.66, MeOH); Ref 84g [α]$_D^{17}$ -96° (0.34, MeOH)]} in 42% yield.
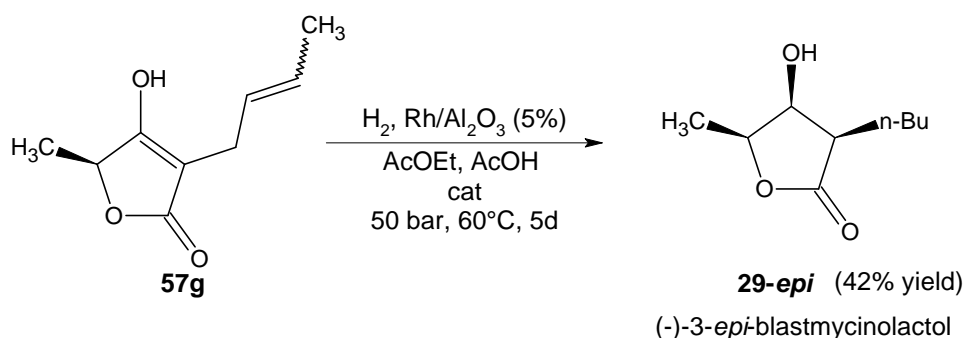
Figure 67.
Synthesis of (-)-3-*epi*-blastmycinolactol **29-epi** *via* double hydrogenation of 3-but-2-enyl tetronic acid derivative **57g** using rhodium on alumina as catalyst. The synthetic sequence starting from α-methallyl lactate was carried out in 3 steps with an overall yield of 12%.

Configurational assignment of compound **29-epi** was based on the ^{1}H-NMR. The spectrum showed that the (-)-3-*epi*-blastmycinolactol **29-epi** prepared was diastereomerically pure.

^{1}H-NMR displays that both the reduction of the butenyl residue and the hydrogenation of the internal double bond of the tetronic acid were successful. The mere existence of signals for the hydrogen atoms 3-H and 4-H already proves that the endocyclic double bond was hydrogenated. The signal splitting for the hydrogen atoms 4'-H into a triplet (δ = 0.89 ppm; ^3J = 6.86 Hz) can only be explained by their coupling with two neighbouring hydrogen atoms, which exist only in the reduced form. The signals multiplicity for the hydrogen atoms 3-H, 4-H and 5-H deliver the proof for the diastereoselective reduction of the tetronic acid.
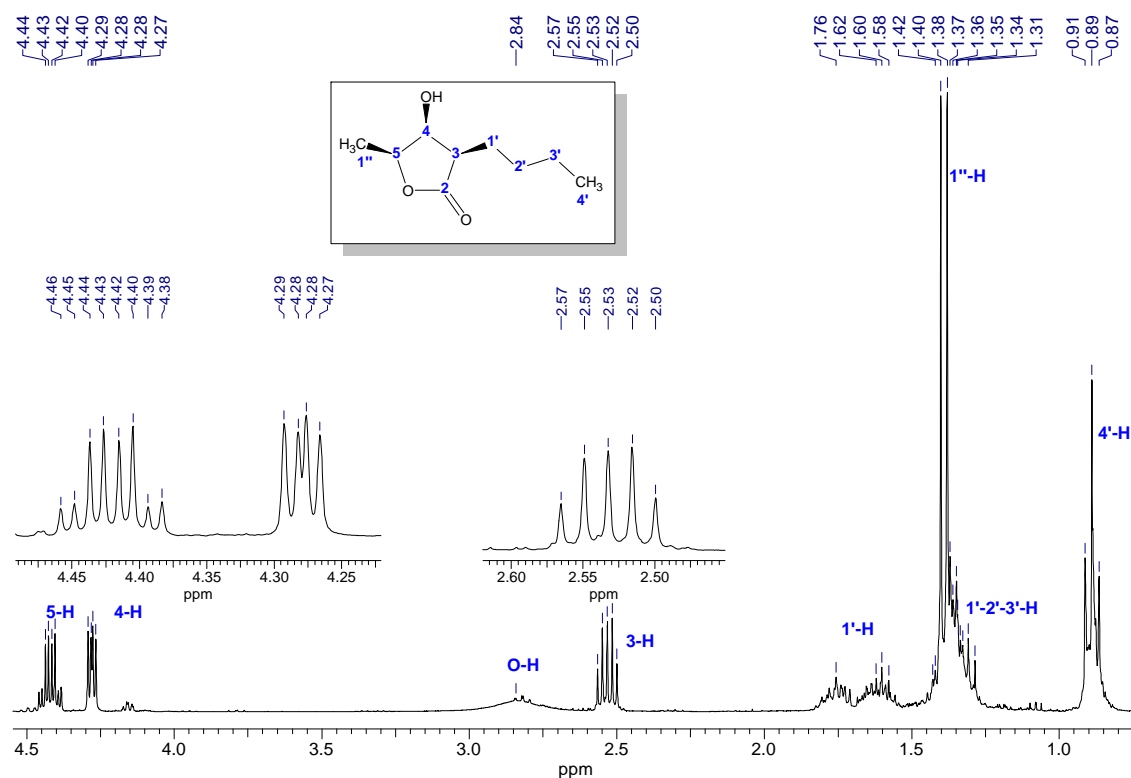
Figure 68.
300 MHz ^{1}H-NMR spectrum (-)-3-*epi*-blastmycinolactol **29-*epi*** in CDCl$_3$.

For 3-H, a doublet of triplets (δ = 2.53 ppm; ^3J = 4.94 Hz; ^2J = 10.02 Hz) is observed resulting from coupling with 4-H and the two diastereotopic hydrogen atoms 1'-H. The doublet of doublets of 4-H (δ = 4.28 ppm; ^3J = 3.02 Hz; 4.94 Hz) can be explained by its coupling with hydrogen atoms 3-H and 5-H. The signal for 5-H shows the expected doublet of quartets (δ = 4.43 ppm; ^3J = 3.02 Hz; 6.45 Hz), as it is neighboured by the methyl-group 1'' and by the hydrogen atom 4-H. According to the coupling constants measured for the hydrogen atoms 3-H, 4-H and 5-H, the stereochemistry of the product was identified to be that shown in **Figure 68.** The relatively low value for the coupling constants for 4-H agrees with the existence of neighbouring protons in the same side of the molecule.

In the ^{13}C-NMR-APT spectrum, single signals for each carbon atom are shown. This is also a preliminary conclusion that only 1 diastereoisomer was formed during the reaction. Thus five signals for C-atoms with an odd number of H-atoms (carbon atoms 4'-C, 1''-C, 3-C, 4-C and 5-C) and four signals for C-atoms with an even number of C-atoms (carbon atoms 3'-C, 1'-C, 2'-C and 2-C) appear. This again can only agree with the proposed structure of (-)-3-*epi*-blastmycinolactol **29-*epi***.
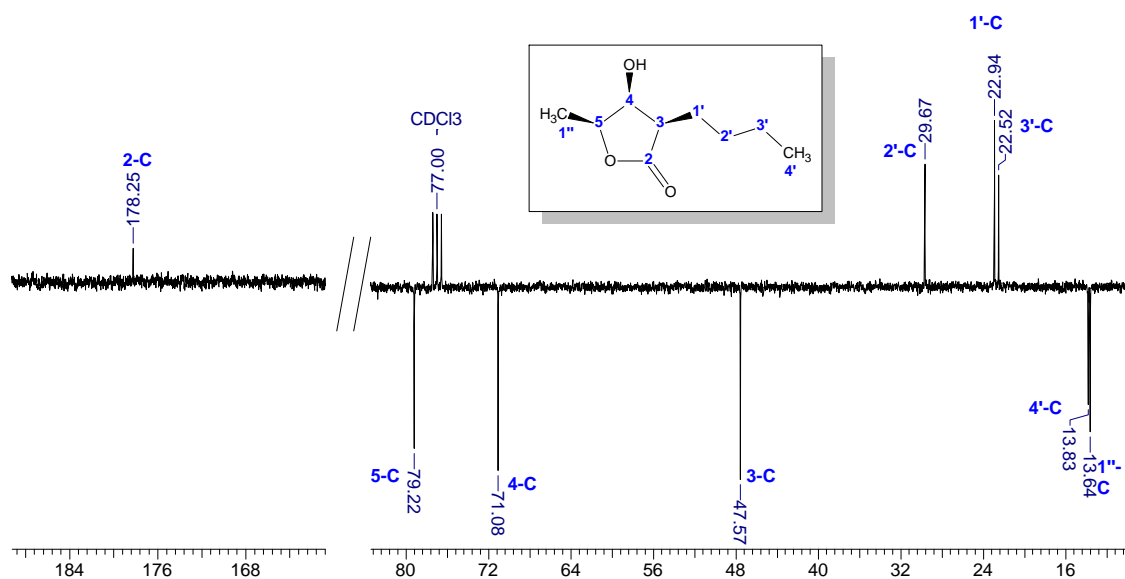
Figure 69.
75 MHz ^{13}C-NMR spectrum of (-)-3-*epi*-blastmycinolactol **29-epi** in CDCl$_3$.

GC-MS analysis showed only one substance in the chromatogram with a molecular mass and fragmentation pattern corresponding to product **29-epi**. Chiral gas chromatography confirmed that the hydrogenation proceeded enantioselectively to a large extends: the chromatogram shows four signals (peaks 3 to 6) - one for each of the four different diastereoisomers that occur because of the formation of two new chiral centres during the hydrogenation - but only one main peak (Conc. = 88%).

Peak Number	Retention Time (min)	Area	Concentration (%)
1*	71.56	895	0.526
2*	72.35	1287	0.757
3	75.32	8080	4.751
4	76.27	149667	88.003
5	76.99	4049	2.381
6	77.97	6092	3.582

* Signals 1 and 2 are probably impurities.
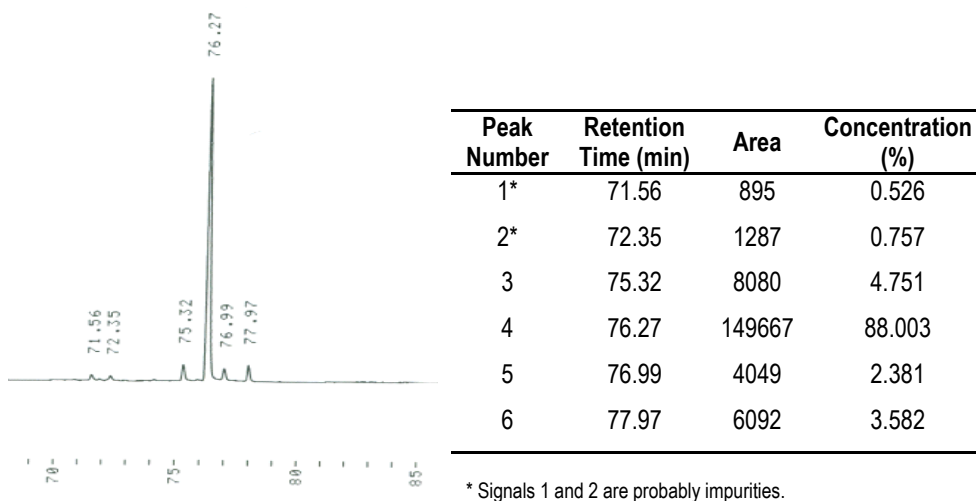
Figure 70.
Chiral GC spectrum of compound **3**. Note that only 1 main signal appears. The expected attack to the endocyclic double bond during the hydrogenation generates 4 different isomers. Experimental conditions: The temperature program was the following: 15 min at 50°C, 15 min at 100°C, 20 min at 200°C, and 15 min at 220°C. The thermal response was 3°C/min - A capillary column with cyclodextrine LIPODEX-E 50m x 0.25mm *Macherey-Nagel* was used -

Based on these results, the starting product obtained from the addition-Wittig olefination and subsequent Claisen rearrangement should be enantiomerically rich and no racemization occured during that reaction sequence. Since the starting material was obtained from the (*S*)-methallyl lactate **34b** (section 2.1), the absolute stereochemistry of **29-*epi*** agrees with the structure of (-)-3-*epi*-blastmycinolactol.

Once again the data found do not agree with previous reports of our research group. The enantioselective synthesis of (-)-3-*epi*-blastmycinolactol **29-*epi*** showed once more that the cascade reaction addition – Wittig olefination occurred without racemization of position C-5. It is clear that the quality of the cumulated ylide plays an important role in the racemization of the tetronate. When scaling up the synthesis of (-)-3-*epi*-blastmycinolactol, non-recrystallized Ph$_3$PCCO was used and consequently the hydrogenation reaction showed the formation of 2 diastereoisomers according to ^{1}H-NMR and ^{13}C-NMR. During the study of the reaction products of enantioselective / diastereoselective reactions, the use of GC with DB-5 capillary columns as well as capillary columns with cyclodextrines for the chromatography analysis was essential.

2.7.2 Palladium catalyzed allylation of (5-alkyl) tetronic acids: synthesis of 3,3-diallyl furan-2,4-diones *via* Tsuji-Trost reaction

Although substituted tetronic acids have received much attention as starting materials for several classes of natural products, the selective C-alkylation essential for the modification of the system has been reported only to a small extent as a synthetic strategy.[38] The effective C-allylation of tetronic acids was therefore examined.
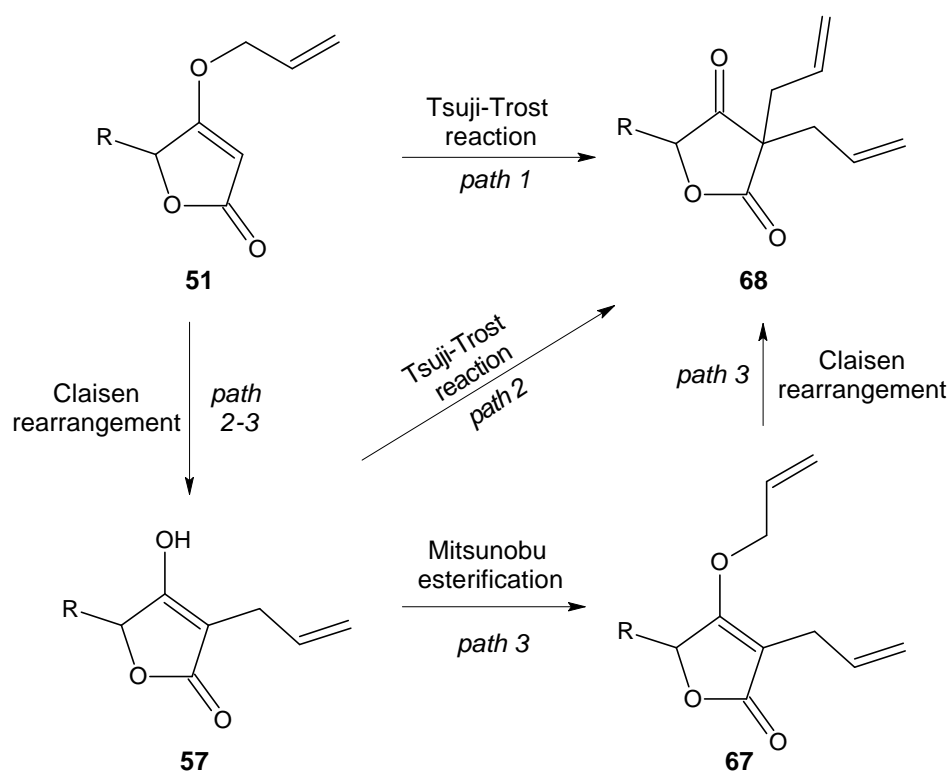
Figure 71.
Possible pathways to *gem*-diallyl compound **68**. *Paths 1* and *2* use allyl acetate as the external source for the second allyl function.

As described above, there are three possible ways to prepare the 3,3-diallyl furan-2,4-dione **68** starting from allyl tetronates **51**. The first possibility (*path 1*) is the direct palladium-catalyzed transformation of the *O*-allylated tetronic-acid **51** with an allyl donor.

A second possibility for the synthesis of derivatives **68** (*path 2*) involves a two step procedure: initially a Claisen rearrangement of **51** to the 3-allyl tetronic acid **57**, as described in section 2.4. The second step, the palladium assisted allylation using an allyl donor in order to obtain compound **68**.

A three step sequence (*path 3*) to reach derivatives **68** involves a Mitsunobu esterification of the allyl tetronic acid **57** (section 2.6.2) to the corresponding 4-*O*-allyl tetronate **67**, which is then converted effectively to **68** using a Claisen rearrangement (section 2.6.3). Although *path 3* is a sequence involving three reactions, the purity of the resulting compounds and their yields in each individual step make this path also attractive for the easy synthesis of 3,3-diallyl furan-2,4-diones **68**.

There are many β-dicarbonyl heterocyclic compounds having pK_a values around 5 or even less which frequently exist predominantly as the enol form, and which are particularly difficult to alkylate at the central carbon atom; it is well known that compounds such as tetronic acid have a great propensity to get alkylated at the oxygen atom of the enol form.
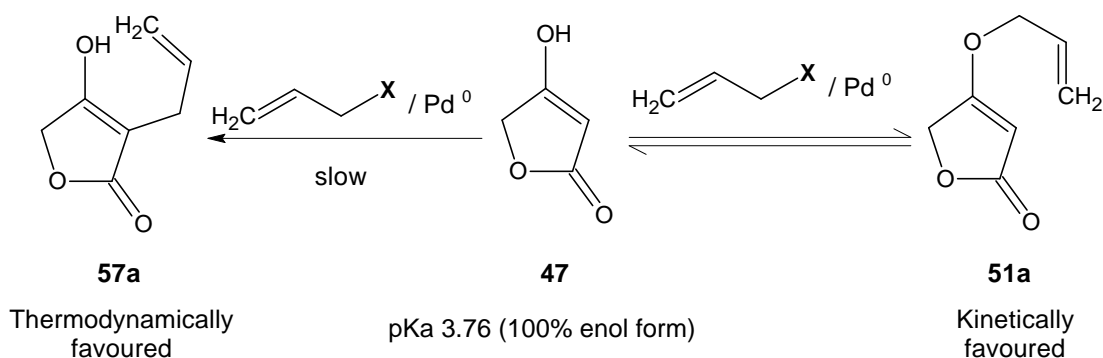
Figure 72.
β-Dicarbonyl compounds react under palladium assisted allylation conditions. Tetronic acid forms the 3-allyl tetronic acid **57a** and / or the *O*-allylated product **51a**.

The palladium-catalyzed alkylation of proton active substrates with allylic systems is a useful method of carbon – carbon bond formation.[8] The acidity of the most frequently used proton active substrates range in between pK_a 10 – 24. However, more acidic substrates ($pK_a <$ 8) have received much less attention.

Moreno-Mañas et al. carried out an extensive study on the chemistry of the Tsuji-Trost reaction on acidic substrates, among them the triacetic acid lactone and the tetronic acid.[90,91] The chemistry reported was extended to the different 5-alkyl tetronic acid derivatives prepared as described in previous sections.
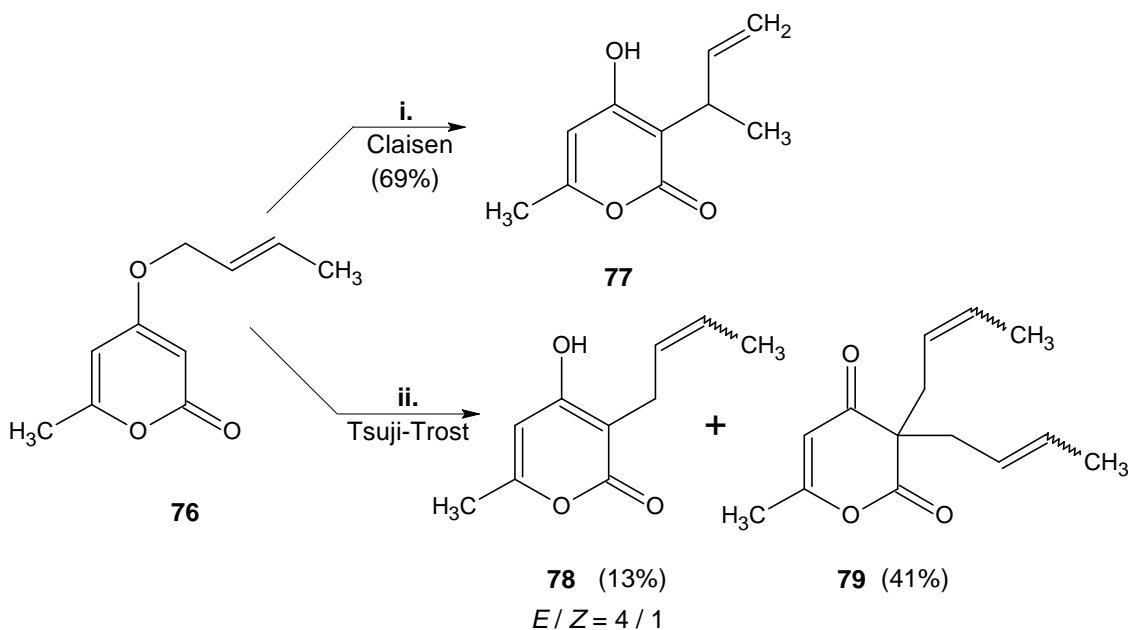
Conditions:
i. Toluene, reflux, 19h **ii.** Toluene, Pd(acac)$_2$ (5% molar), Ph$_3$P (20% molar), 85°C, 1h

Figure 73.
Initial experiments described by *Moreno-Mañas et al.* using allyl derivates of triacetic acid lactone. The palladium assisted allylation gave a mixture of mono and dialkylated products. Similar experiments were described for the tetronic acid.

It is known that the Tsuji-Trost reaction mechanism involves a nucleophilic attack of the conjugated base of a proton-active substrate on a cationic (p-allyl)-palladium complex formed *in situ* from an allylic derivate and a zerovalent palladium stabilized by ligands, generally phosphines.[8] A great variety of leaving groups has been used for the formation of the palladium complex, although acetates and alkoxy carbonates have met with the most general acceptance.[90b]

The double C-allylation of tetronic acid was attempted following previous literature reports using allyl acetate as the allyl source and tetrakistriphenylphosphine palladium (0) as the catalyst.[92] Similar procedures have been reported in the synthesis of 2,2-diallyl 1,3-cyclopentadienone and related diketones.[93,94] Diallyl tetronic acid **68a** has been previously prepared in a two steps synthesis by direct allylation using allyl bromide and a Claisen rearrangement.[38,80]

When the reaction was carried out in toluene or THF, no products were observed and the starting material was recovered almost quantitatively. The high acidity and low solubility of the tetronic acid do not allow the allyl group to be added to the tetronic ring. The direct C-3 diallyl product could be formed from the tetronic acid in low yield, only when a base such as DBU was present in the reaction media.[91]
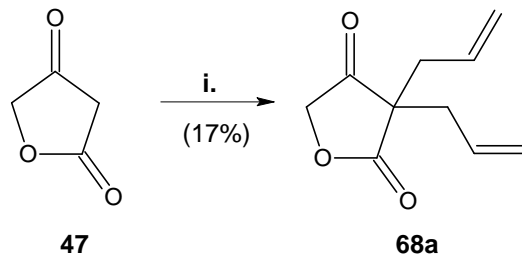
Conditions:
i. AcOAllyl (2 eq), DBU (1 eq), Pd(Ph$_3$P)$_4$ (5% mol), toluene, 3h, reflux, argon, no light

Figure 74.
Synthesis of 3,3-diallyl tetronic acid **68a** from tetronic acid and allyl acetate using a palladium assisted allylation.

From this result two facts are clear: firstly, the C-alkylation of the tetronic acid is achieved when the kinetically preferred *O*-alkylation is performed under reversible conditions thus permitting the slower C-alkylation to predominate under thermodynamic control.
And secondly, during the palladium catalyzed allylic alkylation the enol ether initially formed under kinetic control acts itself as an alkylating agent: the enolate anion, being the conjugate base of a relative strong acid, is itself an efficient leaving group. In other words, the *O*-alkylation is reversible.[90a]

These two are important considerations, because when using the 4-*O*-allyl tetronate **51** this compound serves as an allyl-donor itself, hence the allyl migration is possible. Thus, the

palladium assisted allylation reaction was extended to allylate **51** at its central carbon atom to get the 3,3-diallyl derivatives **68**.
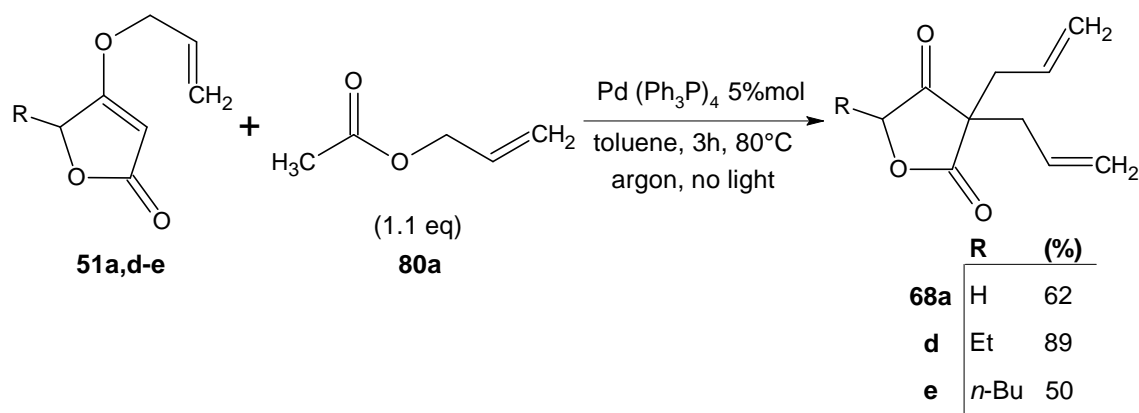
Figure 75.
Palladium assisted allylation reaction of *O*-allyl tetronates **51a,d-e** in the synthesis of *gem*-diallyl compounds **68a,d-e**.

The reaction of the *O*-allyltetronic acid **51** with allyl acetate in presence of tetrakis(triphenylphosphine)-palladium(0)[95] as catalyst produces the desired 3,3-diallyl tetronic acids derivatives **68a,d-e** in good to excellent yields. The reaction worked well presumably because the 4-*O*-allyl substituted tetronic acids **51** are non acidic substances. The reaction was carried out using toluene as solvent and heating the reaction mixture at 80°C for 3-5 hours. Similar yields were observed when the reaction mixture was irradiated under microwave for 10 min. It is worth mentioning that the reaction product was easy to purify. No secondary products were formed and the only impurities separated out were Ph₃P and Ph₃PO both of which were part of the catalyst.
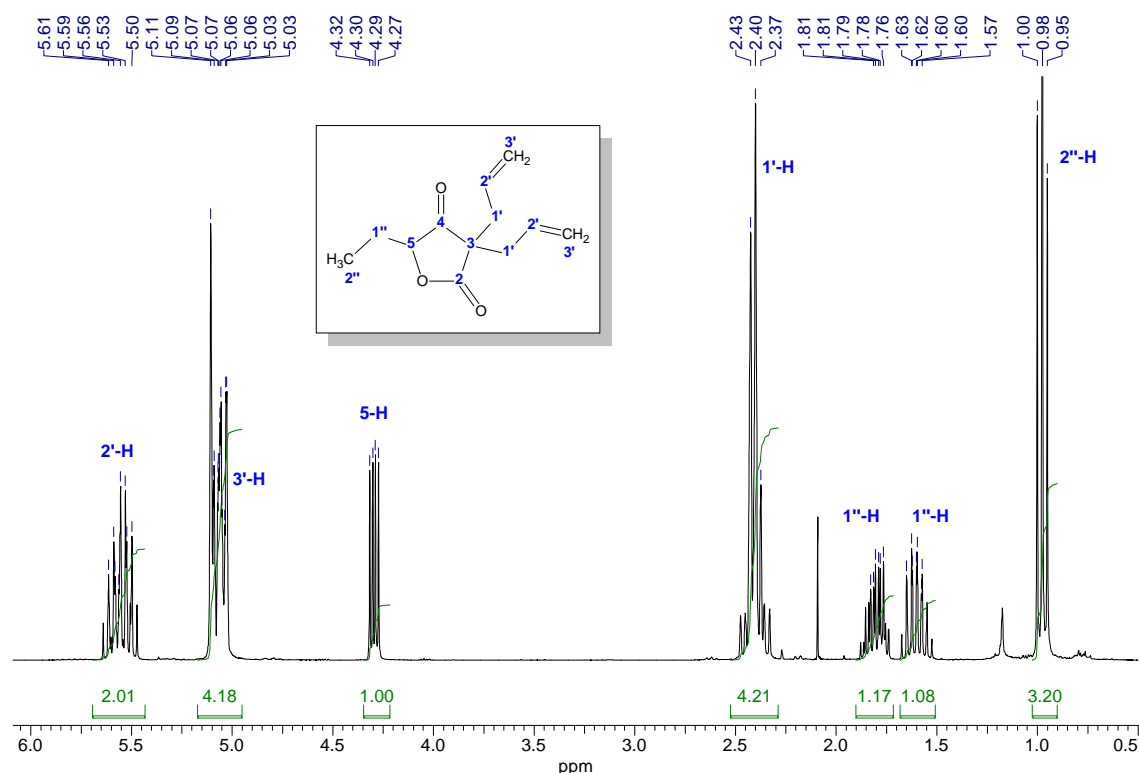
Figure 76.
300 MHz ^{1}H-NMR spectrum of *gem*-diallyl derivative **68d** in CDCl$_3$.

^{1}H-NMR spectrum clearly showed the existence of two magnetically equivalent allyl groups in the molecule, although in the ^{13}C-NMR spectrum, the signals corresponding to the carbon atoms of the two allyl groups have a slight difference in their chemical shift (attributed to the influence of keto vs. ester in a space interaction as was noticed in the case of spiro cyclopropane furandiones **58** – section 2.4).

Thus, the possibility to obtain **68** by *path 1* dominates over the two other potential pathways described above in **Figure 71**. The target molecule was reached after just one step and no side products were found (*paths 2-3* use a Claisen-rearrangement protocol and as described in section 2.4, the Claisen-Conia product was also found after the rearrangement).

Once the formation of 3,3-diallyl furan-2,4-diones **68a,d-e** was effectively carried out (when the same "allyl migrating residue" and "allyl added residue" were used), the formation of 3,3-diallyl furan-2,4-diones with different allyl residues on C-3 was investigated.

When the *O*-allyl tetronic acid **51a** was reacted with cinnamyl acetate[96] in the presence of the palladium catalyst, a mixture of three different products was found by GC-MS analysis.
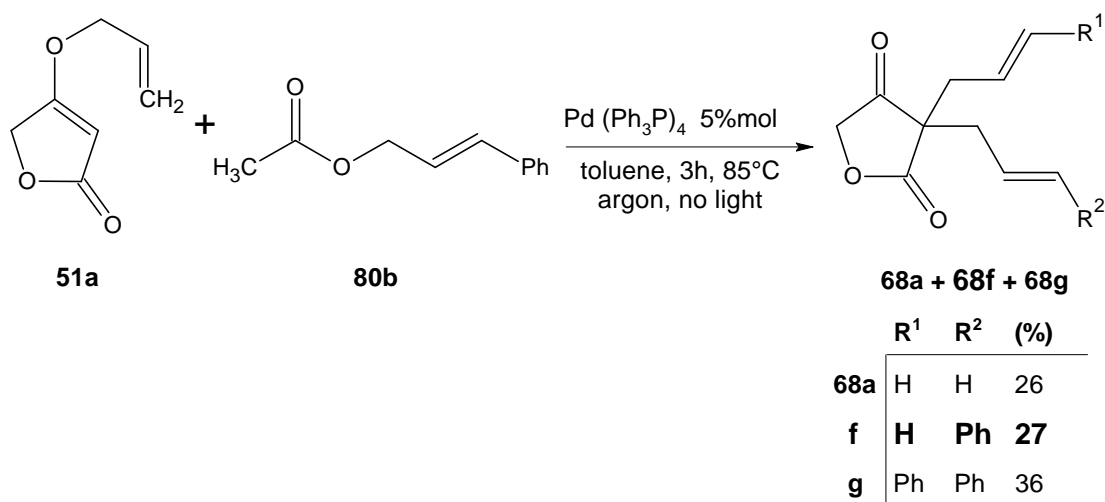
Figure 77.
The synthesis of 3,3-diallyl furan-2,4-dione **68f** also generated derivatives **68a** and **68g**. The formation of three different products during the reaction in a similar ratio proved the reversibility of the reaction.

The existence of the voluminous phenyl group enabled the separation of the mixture of products into individual compounds by column chromatography. The formation of equivalent amounts for each of the different products is evidence of an initial attack of the "external" allyl moiety before the migration occurs. The reaction is then going through the equilibrium state when the allyl group is attacking the C-3 position and also attacking the *O*-4 position (kinetically favoured).

Spectroscopic analysis of the individual derivatives **68f-g** showed that the cinnamyl group remains intact and no isomerization of the double bond occurred. The GC spectrum for **68f** (and **68g**) showed that only one main compound was formed. ^{1}H-NMR proved the *trans*-configuration of the double bond since the coupling constant for proton 3-H was in the order of 16 Hz. It is known that the attack of the nucleophile to the palladium η^3-allyl complex always occurs on the opposite side to the metal (inversion) and gives the allylated nucleophile under regeneration of Pd (0), which rejoins the catalytic-cycle again. Because of the two inversions (see section 1.2), the allylic substitution always proceeds under stereoselective retention of the configuration. In principle, the nucleophile can attack either of the two termini of the η^3-allyl complex. In practice it was found that the less hindered terminus is attacked.[9]

In order to obtain the non symmetric C-3 diallyl compound **68** the Tsuji-Trost reaction was also studied in 3-allyl tetronic acids **57**. Derivatives **57** were prepared previously as described in section 2.4. Thus, the second allyl group can be introduced through a second Claisen rearrangement (section 2.6.3) or by a Tsuji-Trost reaction; this involves one step more in the reaction sequence depicted in **Figure 71**, but reduces the possibility to obtain a mixture of compounds.

As described in section 2.6.3, the formation of the C-3 diallyl compound **68b** was carried out initially through a Claisen rearrangement of the corresponding 3-allyl-4-*O*-methallyl derivative **67b** under microwave irradiation (**Figure 58**). The yield in that case was almost quantitative and the product was pure enough to be used in the next reaction without further purification. No scrambling of the allyl residue was detected during the Claisen rearrangement. Derivative **68b** was used as a control for the chromatographic analysis.

When the 3-allyl tetronic acid **57a** reacted with methallyl acetate in the presence of DBU and palladium (0), the formation of a mixture of the three possible compounds **68a-b,h** was detected by GC-MS; in this case the chromatographic separation of the product mixture into the individual components was not possible because of their similar polarities.

Conditions:
i. DBU (1 eq), Pd (Ph$_3$P)$_4$ 5%mol, THF, reflux, 3h, argon, no light.

* Yields according to integration in the GC spectra

	R^1	R^2	(%)*
68a	H	H	34
b	**H**	**Me**	**56**
h	Me	Me	10
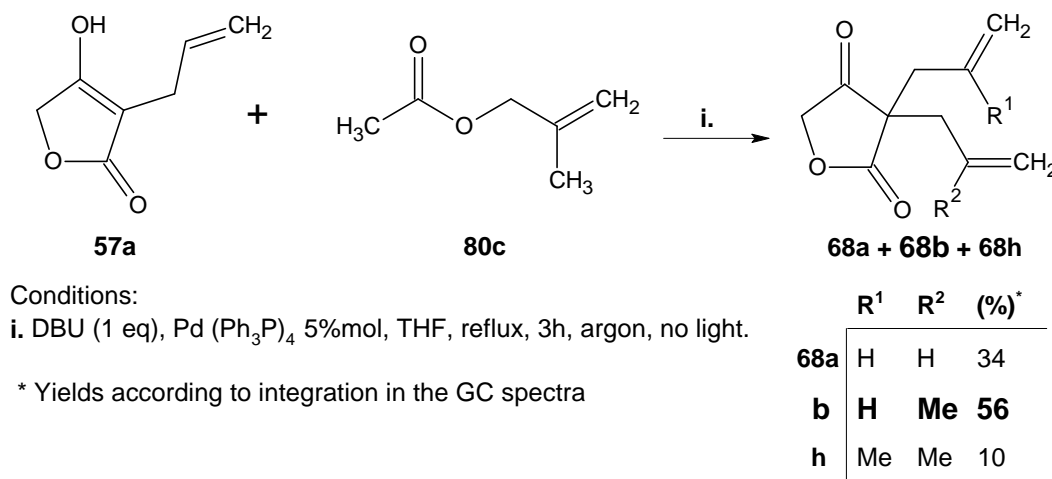
Figure 78.
The palladium assisted allylation of 3-allyl tetronic acid **57a** generated three different derivatives **68a-b,h**. THF was used as solvent because **57a** is not totally soluble in toluene. Compound **68b** was previously prepared from a Claisen rearrangement and was used as a standard for controlling the progress of the reaction by GC.

This fact can be explained considering the formation of two allyl-palladium species in the reaction media, the η^3-methallyl- and η^3-allyl-palladium complexes[97]; the first is formed from the methallyl acetate, and the second is formed once the reaction mixture is heated through a palladium insertion in the C-3 position (and then "de-allylating" the compound); this mixture in the reaction media can attack the C-3 position in another molecule and then produce the corresponding mixture of compounds. The formation of the dimethallyl derivative **68h** (10% GC-yield) showed that the "cascading" organopalladium reaction is reversible in all points.

Bearing in mind that good to excellent yields were obtained in the case of the palladium assisted allylation of non acidic derivatives **51a,d,e**, the use of neutral conditions for the Tsuji-Trost reaction[98] of 3-allyl tetronic acids **57** was studied. The neutral condition was obtained using the sodium tetronate **57k** as starting material. As depicted above, using DBU was not adequate to reach the ideal conditions for the Tsuji-Trost reaction.

Formation of the sodium tetronate **57k** was easily achieved using sodium methanolate in methanol.[99] The salt appeared as a white solid. Is worth mentioning that the salt is a highly hygroscopic substance, but can be characterized by IR and ^{1}H-NMR in deuterated methanol.

	R^1	R^2	(%)
68a	H	H	8
f	**H**	**Ph**	**70**
g	Ph	Ph	5
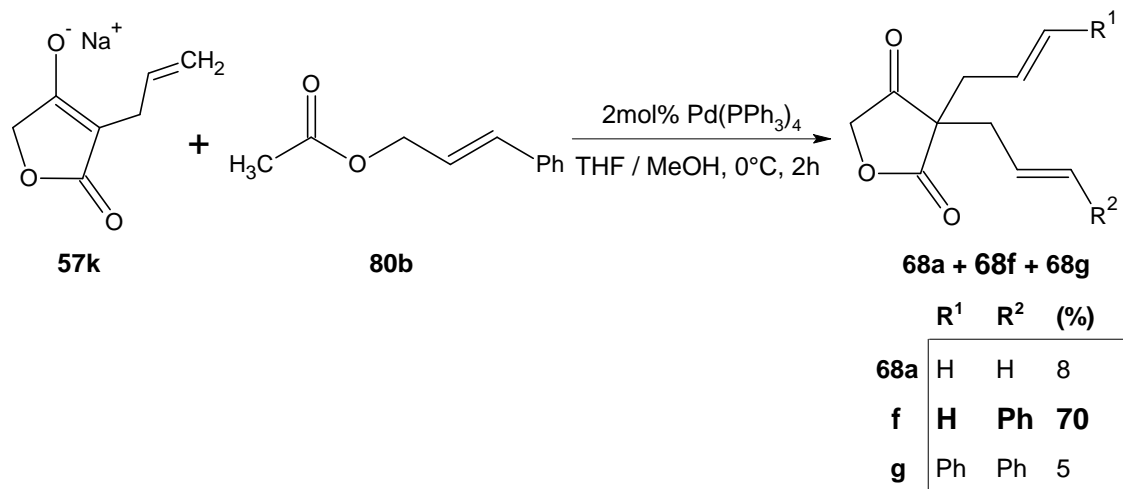
Figure 79.
Synthesis of non symmetric 3,3-diallyl furan-2,4-dione **68f**. The selective synthesis was improved when using the sodium tetronate **57k** instead of the 4-*O*-allyl tetronate **51a** as was previously depicted in **Figure 77**.

After separation of the reaction mixture into the individual compounds formed, it was observed that the formation of the desired derivative **68f** was favourable under the new reaction conditions. It was noticed that the scrambling of the allyl residues occurred to a low degree. Thus, the efficient synthesis of 3,3-diallyl-furan-2,4-diones **68** with different allyl residues was afforded by Pd-catalysed Tsuji-Trost allylation of the sodium salt of the 3-allyltetronic acid **57k**.[100]

2.8 Synthesis of novel oxa heterocycles via Ring Closing Olefin Metathesis

Ruthenium-based olefin metathesis technology has found a privileged status as the driving force behind the manufacture of countless pharmaceutical intermediates and natural products. The ring closing olefin metathesis reaction is used to transform acyclic dienes under cleavage of ethylene or other volatile olefines into carbo- or heterocycles. As the catalyst is less reactive against substituted olefines as against normal double bonds the back reaction, ring opening metathesis does not occur. Therefore due to kinetical reasons the desired metathesis product is formed.[14]

As discussed in section 1.4, the olefin metathesis is a catalytic process. The key step consists of a reaction between an olefin and a transition metal alkylidene complex. A [2+2]-

reaction gives an unstable intermediate. All reaction steps are reversible and in competition with one another, so the overall result depends heavily on relative rates.

2.8.1 Synthesis of furo[3,4-*b*]oxepines *via* Ring Closing Metathesis

Oxepines are important structural elements present in numerous biologically active molecules. The preparation of fused oxepines via RCM has been previously reported on a β-naphtol core in the synthesis of naphthoxepin and related derivatives.[101] No derivatives fused to a butanolide core have been prepared *via* RCM.

The effective formation of 3-allyl-4-*O*-allyl tetronates **67** via Mitsunobu esterification (section 2.6.2) yield substrates for RCM. In this context, the formation of novel furo[3,4-*b*]oxepines **81** involving ring closing metathesis reaction using Grubbs' catalyst for the key C-C bond formation is described.
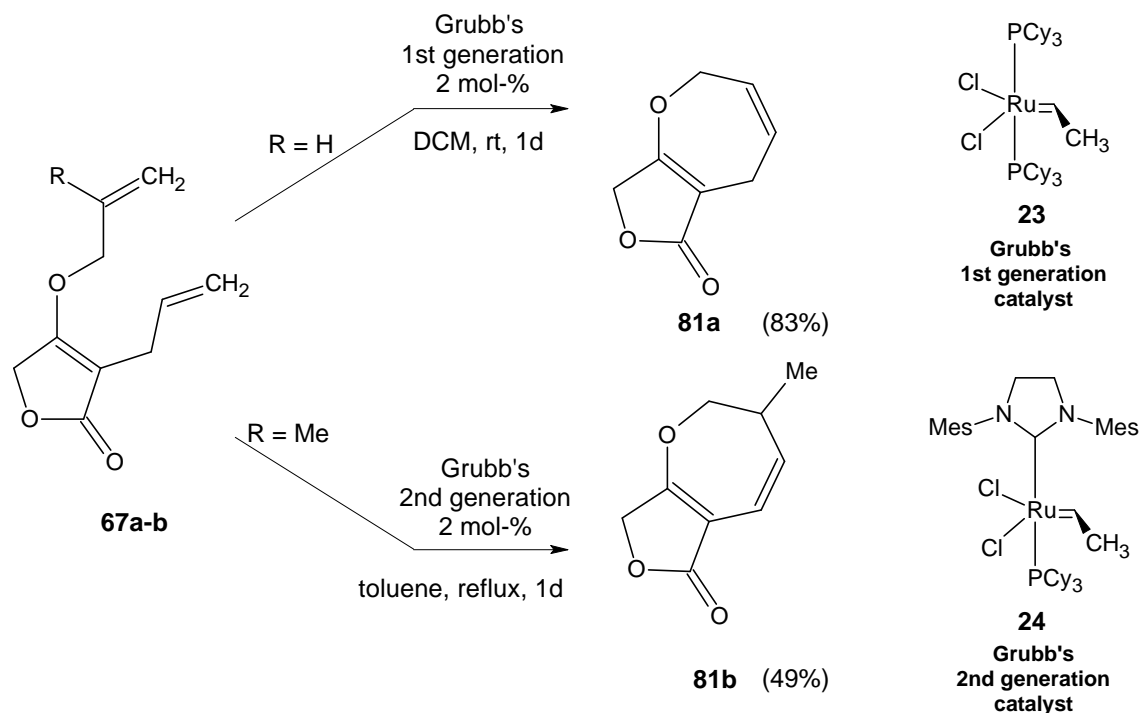
Figure 80.
Ring-closing olefin metathesis to synthesize furo[3,4-*b*]oxepines **81**. Derivative **81b** was formed only under forcing conditions. It was determined the double bond migrated to the conjugated position.

Initially the reaction was performed under microwave irradiation, using a CEM-Discover monomode system and closed vessels in presence of dichloromethane as solvent. The temperature was fixed at 50°C, evaluated by infrared detection, and it was maintained constant all along the reaction by modulation of emitted MW power according to the procedure described by *Thanh and Loupy*.[102] Although the reaction worked according the expectations, the use of 10 mol-% of Grubbs' first-generation catalyst, $Cl_2(PCy_3)_2Ru=CHPh$, for the

microwave reaction was considered an excess. Thus, the reactions were carried out under conventional procedures using only 2 mol-% of catalyst.

The furo[3,4-*b*]oxepine **81a** was initially obtained in high purity according GC. No secondary products were detected. The drawback of the reaction was the formation of greyish to black crude products. The removal of the residual ruthenium compounds which are responsible for the black hue of the crude products was effectively done after the treatment of the reaction mixture with 5 mol-% of lead tetraacetate according a procedure described by *Paquette et al.*[103] After the effective removal of the ruthenium compounds, derivative **81a** was obtained as a white solid in 83% yield.

The RCM was extended to build the seven-membered ring of 3-methyl-3,8-dihydro-2*H*-furo[3,4-*b*]oxepin-6-one **81b**. When the RCM was performed with compound **67b**, the product was not the expected compound **81c**. The allyl-methallyl derivative **67b** required the more reactive second generation Grubbs' catalyst and forcing conditions to be formed, which caused a concomitant shift of the double bond into a conjugated position furnishing **81b**. The reaction was carried out in refluxing toluene using 2 mol-% of the catalyst.

This result was supported by the ^{1}H-NMR spectrum, whose signals and multiplicities can be explained only by the structure of compound **81b**.
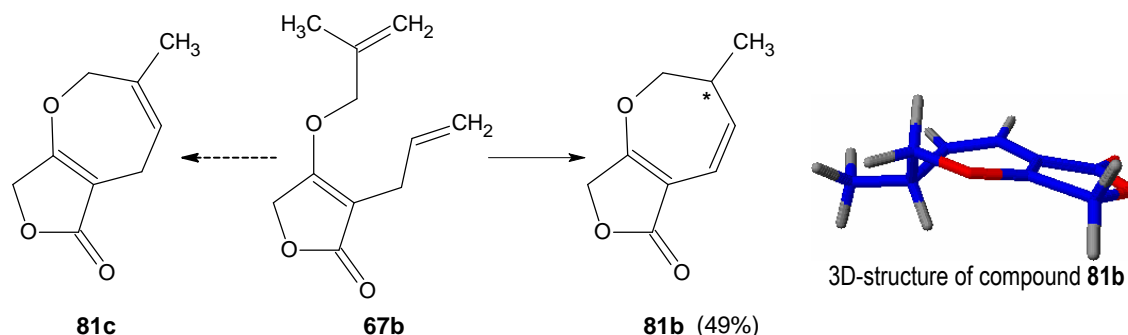
Figure 81.
Ring closing olefin metathesis reaction of 3-allyl-4-*O*-methallyl tetronate **67b**. The expected derivative **81c** was converted into **81b** during the reaction. The minimized energy structure of **81b** show the equatorial preference for the methyl group.[69]

The doublet for the methyl group results from the coupling with 3-H (δ = 1.10 ppm; ^3J = 7.41 Hz) and the doublet of doublets for 4-H (δ = 5.85 ppm; ^3J = 5.08 Hz; 10.57 Hz) derives from the coupling with the 3-H and 5-H hydrogen atoms. A multiplet was observed at δ = 2.77 ppm for the 3-H atom and a doublet of doublets for each of the 2-H atoms (zoom region).

Considering the more stable equatorial disposition of the methyl group in the "bed like" dihydroxepine ring (**Figure 81**), the hydrogen atoms of carbon atom 2-C were identified as 2ax (δ = 4.14 ppm; $^3J_{aa}$ = 5.90 Hz; ^2J = 10.98 Hz) and 2eq (δ = 4.26 ppm; $^3J_{ea}$ = 1.09 Hz; ^2J = 10.98 Hz) according to the different values in their coupling constants.
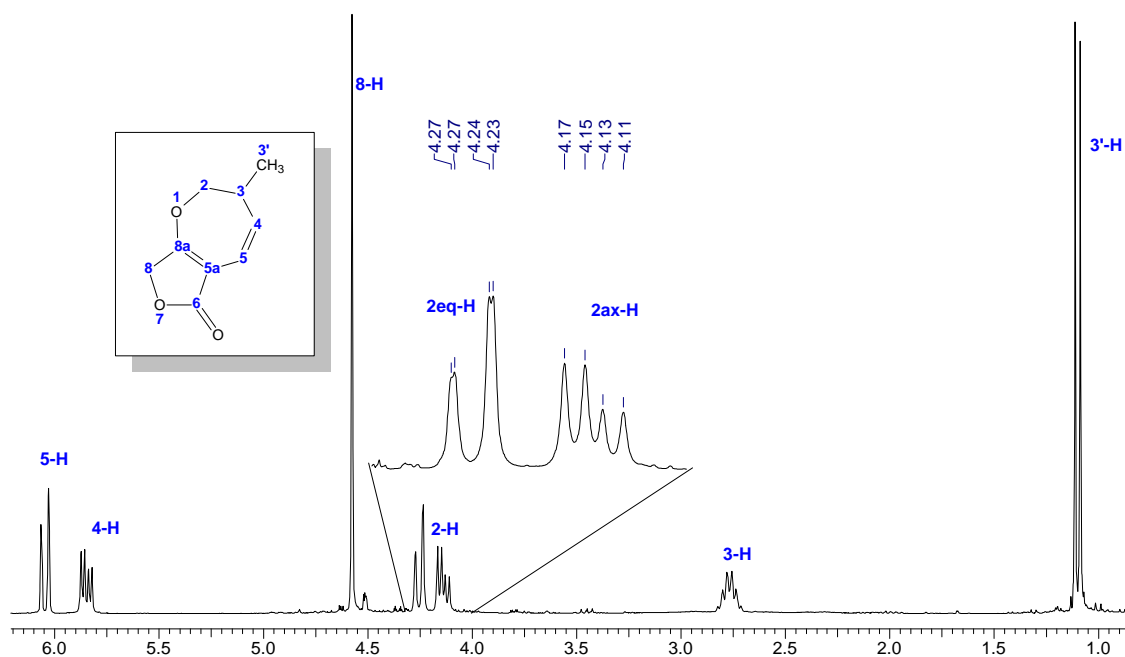
Figure 82.
300 MHz ^{1}H-NMR spectrum of fused furanone **81b** in CDCl$_3$. Axial vs. equatorial conformations for protons 2-H were assigned according to their coupling constants.

The ^{13}C-APT-NMR spectrum showed four signals for C-atoms with an odd number of H-atoms and five signals for C-atoms with an even number of H-atoms. This fact can only be brought into agreement with the structure of compound **81b**. Further evidence delivered by chiral gas chromatography showed an enantiomer mixture in ratio 1:1. Whereas in compound **81b** the carbon atom 3-C is a chiral centre, compound **81c** has not chiral centres. These results indicate that once compound **81c** was formed under the used reaction conditions (toluene, 110°C) a 1,3-H shift took place and the double bond moved in order to form the more stable conjugated system **81b**. No traces of compound **81c** were detected. Alkene isomerisation as a side or a follow-up reaction to metathesis processes initiated with Grubbs' catalysts has been frequently reported, especially for allylic alcohols and allyl ethers.[104]
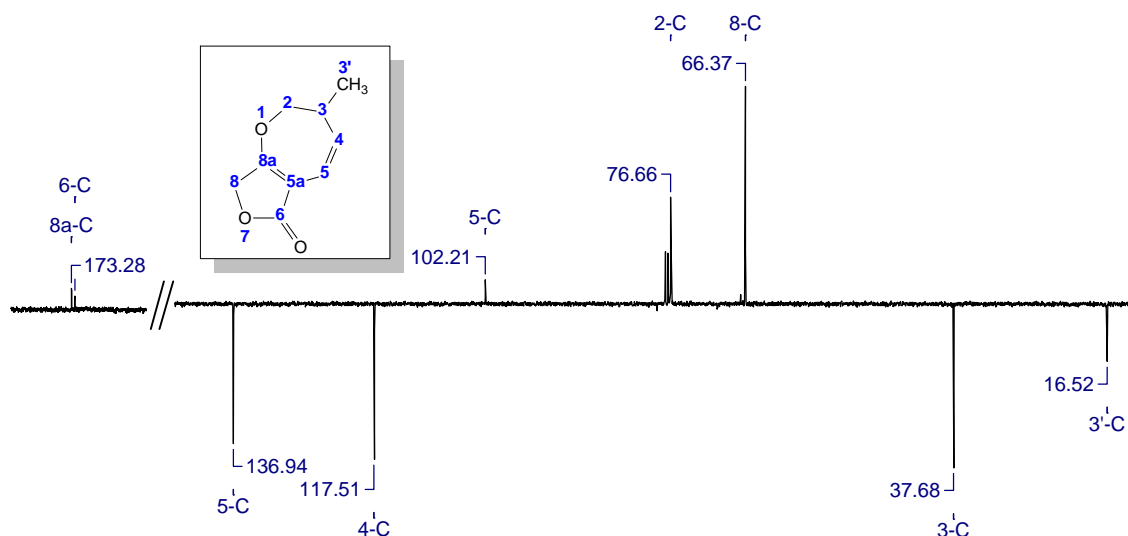
Figure 83.
75 MHz ^{13}C-APT-NMR spectrum of the fused furo[3,4-*b*]oxepine **81b** in CDCl$_3$.

Thus, while first generation catalyst Cl$_2$(PCy$_3$)$_2$Ru=CHPh was efficacious in the RCM of derivative **67a** with two allyl residues, Grubb's second-generation catalyst, (IMes)(PCy$_3$)Cl$_2$Ru=CHPh, and harsh conditions were required for the ring closure of **67b**, most likely due to sterical hinderance.

2.8.2 Synthesis of 3-spirocyclopentenylfuran-2,4-diones *via* Ring Closing Metathesis

Ring closing olefin metathesis has recently emerged as a powerful tool for the formation of a variety of ring systems including spiro-annulation.[93,105] Spiro-annulation has considerable synthetic value because the spiro-linkage is present in many natural products such as in the cytotoxic Fredericamycin **82**. Furthermore, it is of industrial interest as some heterospirenes act as photochromic systems, which find their utility in silver-free imaging systems and as memories in data display devices.[93]

Spirolactones are important structural units because of their unique molecular geometry and interesting biological activity. This type of spiro system is present as key framework of numerous steroids like drospirenone and spironolactone.[106] It is also present in diverse natural products like in the structural core of the bakkanes **83**[107], for example bakkenolide A.[108]

Related 2,2-diallyl 1,3-cyclopentadienones has been effectively converted in their spiro-cyclic derivatives previously.[93,94] Spirocyclic enones has been also prepared via RCM.[101] A single ring closing metathesis, namely of symmetrical 3,3-diallyl furan-2,4-dione **84a** has been reported.[20]
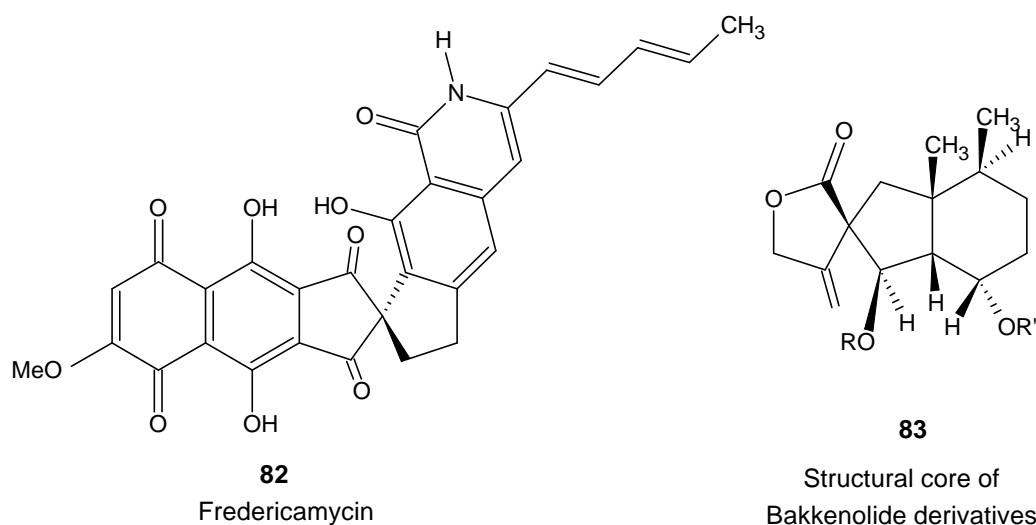
Figure 84.
Fredericamycin **82** and bakkenolides (structural core **83**) are examples of natural products containing a spiro-annulated linkage.

Ring closing metathesis reactions were then carried out with bis-allyl tetronates of types **68** to build up the structural target motifs of butanolides with 3,3-spirocyclopentenyl annulation **84**.

As described in the previous section, the reaction was carried out under dry conditions using Grubb's first-generation catalyst, $Cl_2(PCy_3)_2Ru=CHPh$, an argon atmosphere and dry DCM as solvent. Residual ruthenium compounds responsible for a greyish to black hue of the crude products were effectively removed by treatment with 5 mol-% of lead tetraacetate according to *Paquette et al.*[103]

	R	(%)
84a	H	90
b	Et	85
c	*n*-Bu	91
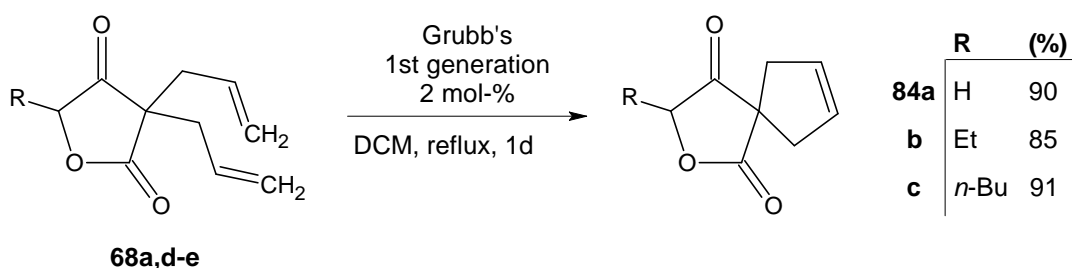
Figure 85.
The metathesis reaction of various 3,3-diallylfurandiones **68** with Grubbs 1st generation catalysts gave 3,3-spirocyclopentenyldihydrofuran-2,4-diones **84a-c** in excellent yields.

The high yields and easy purification showed that, in addition to the reaction efficiency and simplicity, the present approach may find application in natural product synthesis.

In the ^{1}H-NMR spectrum of compound **84b**, the four methylene protons ($H_\alpha - H_\beta$) next to the furandione-ring have different magnetic properties. In the ^{13}C-NMR spectra the corresponding signals for these methylene carbons appeared at $\delta = 42.07$ ppm and $\delta = 43.24$

ppm, showing that they are also non magnetically equivalent. The correct assignment of the signals was done by a HSQC-NMR experiment. The spectrum revealed the corresponding signal in the ^{1}H-NMR dimension for each proton.
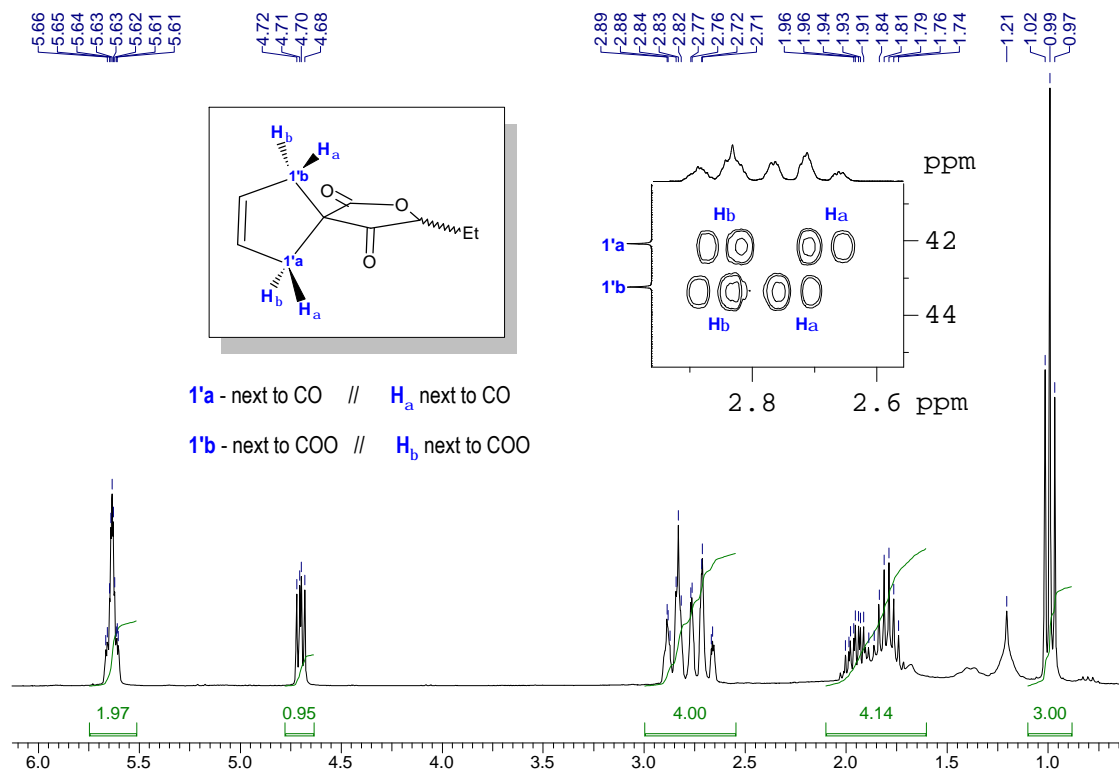
Figure 86.
300 MHz ^{1}H-NMR spectrum of derivative **84b** in CDCl$_3$. Assignation of the H$_\alpha$ and H$_\beta$ signals was done from the HSQC spectra.

The RCM of 3,3-diallyl furandiones was extended to the case of non symmetric allyl groups. As it was found in the previous section, the 3-allyl-3-methallyl derivative **68b** only formed the methylcyclopentenyl ring when hard conditions were used.
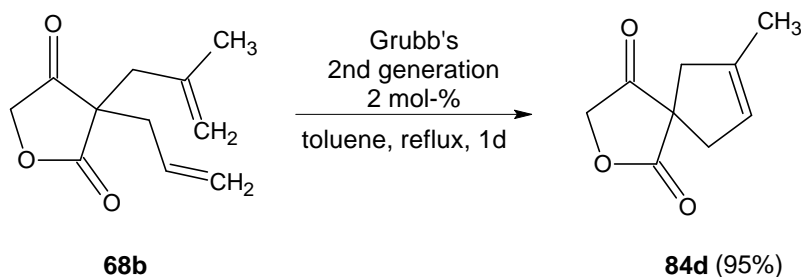
Figure 87.
Ring-closing olefin metathesis to synthesize 7-methyl-2-oxa-spiro[4.4]non-7-ene-1,4-dione **84d**. Derivative **84d** was formed only under harsh conditions.

The five-membered ring of the spiro-compound 7-methyl-2-oxa-spiro[4.4]non-7-ene-1,4-dione **84d** was formed effectively. The compound was obtained as a colourless oil in 95% yield after the treatment with lead tetraacetate to remove the ruthenium impurities.[103]

While Grubb's 1st generation catalyst was efficacious in the RCM of derivatives with two allyl residues, a Grubb's second-generation catalyst, (IMes)(PCy$_3$)Cl$_2$Ru=CHPh, and harsh conditions were required for the ring closure of **84d**. A similar observation has been reported recently for the RCM of 2,3-bisalkenylcyclopentanones to give [5.7]bicycles.[109] No isomerization of the new double bond was observed although isomerization in cyclopentenyl derivatives has been previously reported.[101] An alternative method for removing ruthenium by-products generated during olefin metathesis reactions using Ph$_3$PO was described by *Ahn et al*.[110] The use of polymer-bound phosphines has been also reported,[111] although a more convenient alternative is the use of immobilized Ru catalysts for olefin metathesis because their ability to be recycled and reused without loss of activity.[112]

It is worth mentioning that an increment in the reaction yield was obtained when the solution of the compound to react was previously degassed under sonic bath / slight vacuum.

2.9 The aza analogue case - from 4-aminobutenolides to fused furoazepines

2.9.1 Synthesis of 4-aminobutenolides

Although there are only few 4-aminofuran-2(5*H*)-one-derivatives in nature, their synthetic analogues are widely used in chemical, pharmaceutical and agrochemical research. Some of them also are used as intermediates in the synthesis of natural products and many of these derivatives have been patented as herbicides or insecticides as well as pro-drugs.[113]
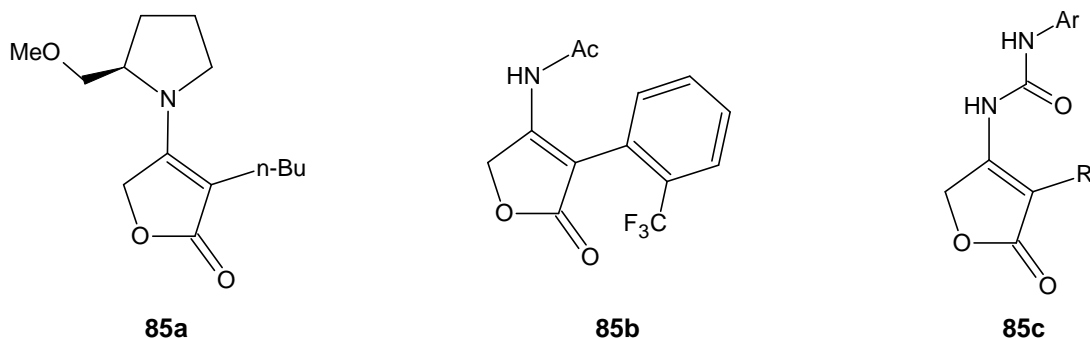
Figure 88.
Some of the 3-substituted aminobutenolides used as herbicides.

Many methods have been developed for the preparation of 4-aminofuran-2(5*H*)-one derivatives, which are mainly obtained through enamine formation from a suitable tetronic acid precursor[114] or by direct synthesis.[33] Although 4-halo or 4-hydroxy-furan-2(5*H*)-ones can be aminated to provide the corresponding unsubstituted, primary and secondary 4-aminofuran-2(5*H*)-ones conveniently, there are only few procedures for direct synthesis of 4-aminofuran-2(5*H*)-ones.

One route uses 2-substituted 4-hydroxy-3-amino-cyclobutenones; in the presence of TFA in refluxing *p*-xylene for 0.5 to 4 hours, the butanone ring expands to form 3-alkyl-4-aminofuran-2(5*H*)-ones in good yields.[115]
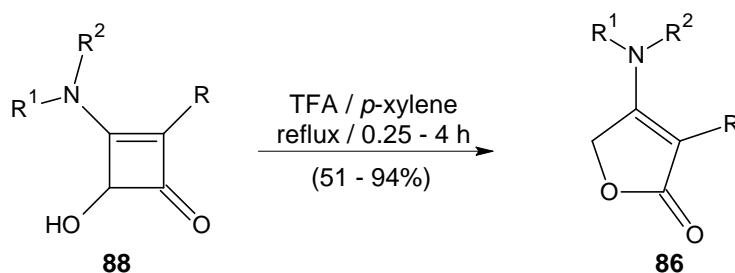
Figure 89.
The thermal electrocyclic ring opening of α-hydroxybutenones forms not only 3-substituted aminobutenolides; with the appropriate unsaturated substituent on C-4 the ring expansion products include highly substituted phenols, quinones and heteroaromatic compounds.

Another direct method is the one-pot preparation of 4-dialkylamino-furan-2(5*H*)-ones starting from simple building blocks: alk-2-yn-1-ols and dialkylamines. The reaction is carried out using the secondary alkylamine as a nucleophile catalyzed by PdI_2 in dioxane at 100 °C under 20 atm of a 4/1 mixture of CO / air.[116]
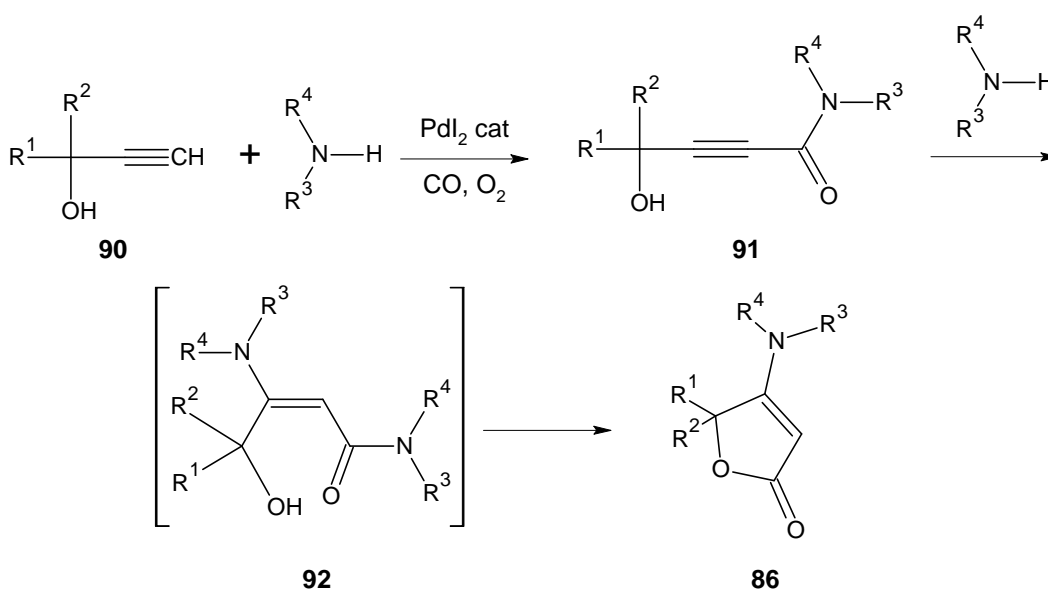
Figure 90.
Pd-catalyzed monoaminocarbonylation of terminal alkynes and intramolecular alcoholysis of the amide function give the corresponding 4-aminofuranones.

Tetronic acids can be converted to the corresponding 4-aminobutenolide derivatives by a direct amination: having the corresponding substituted or unsubstituted 4-hydroxy-dihydrofuran-2-ones **57**, the condensation with a primary amine gives direct access to 3- and / or 5-substituted 4-allylamino-2-dihydrofuran-2(5*H*)-ones **86** also using simple building blocks and rather mild conditions.[114]

The procedure uses acetic acid as solvent; under this condition, the primary amine initialises a nucleophilic substitution over the hydroxy function, generating a molecule of water during the process. The final product is obtained after azeotropic distillation of the reaction mixture.
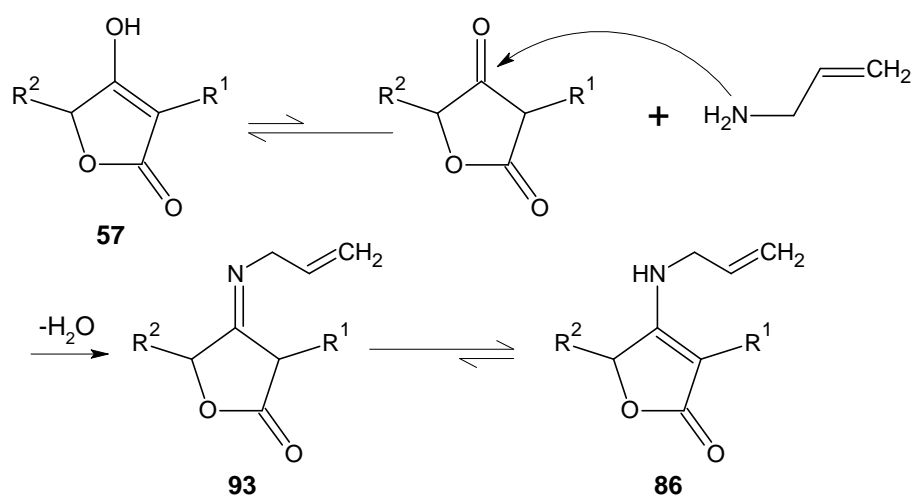
Figure 91.
Formation of the tetronamide **86** by direct condensation between a tetronic acid **57** and a primary amine.

Using diverse 5-substituted 4-hydroxy-3-allyl-furan-2-ones **57** in the condensation reaction with allylamine and aniline, the corresponding 5-alkyl-3-allyl-4-allyl(phenyl)amino-furan2-ones **86** were obtained in good to excellent yields.

86e (Yield: 40%)   **57**
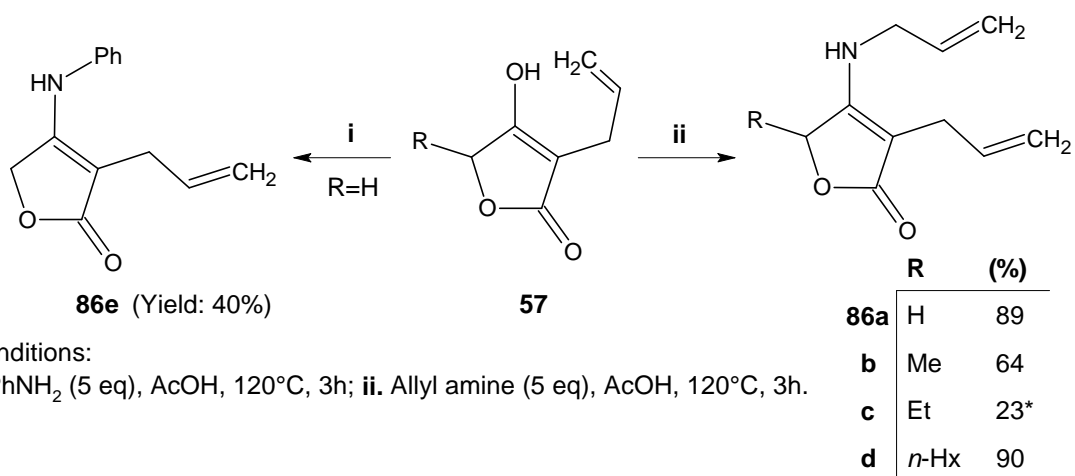
Conditions:
i. PhNH$_2$ (5 eq), AcOH, 120°C, 3h; **ii.** Allyl amine (5 eq), AcOH, 120°C, 3h.

	R	(%)
86a	H	89
b	Me	64
c	Et	23*
d	*n*-Hx	90

Figure 92.
Reactions were carried out heating only for 3 hours. (*) **86c** was obtained after refluxing for 1 day and a second compound was also formed.

The N-phenylamino butenolide **86e** was difficult to isolate from the acetanilide formed during the reaction, consequently giving a moderate yield. 4-N-allylamino butenolide **86c** was separated out from the reaction mixture after heating under reflux for 24 hours.
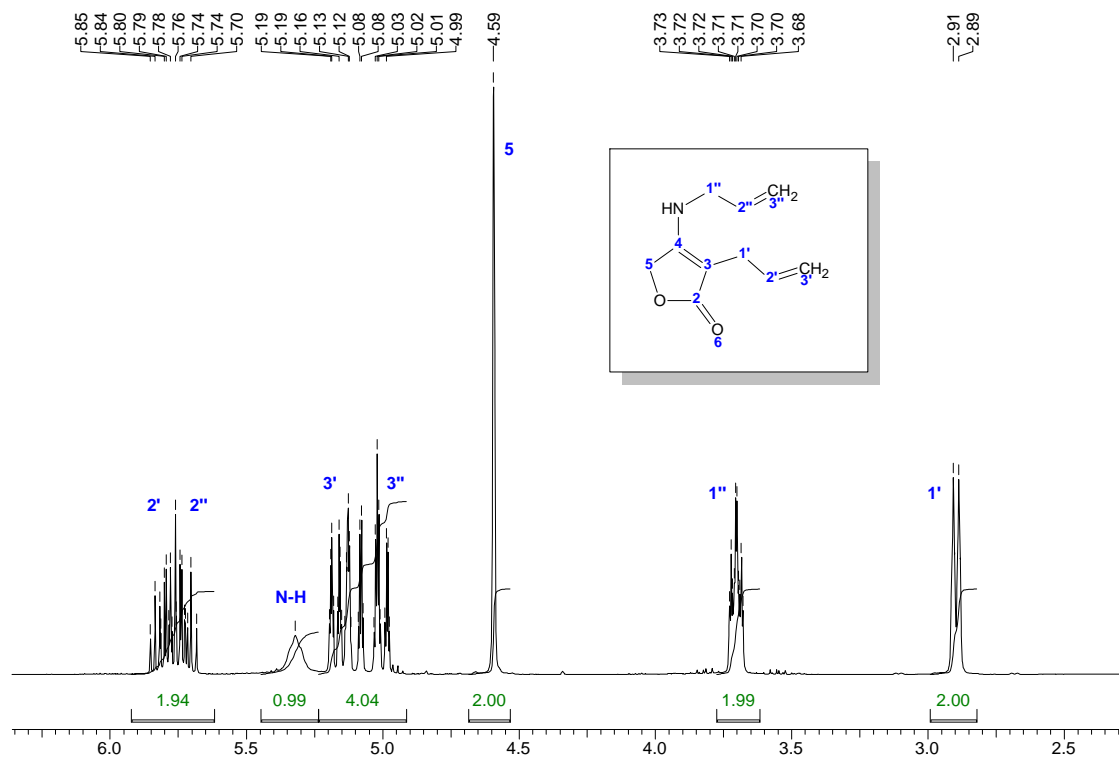
Figure 93.
300 MHz ^{1}H-NMR spectrum of aminobutenolide derivative **86a** in CDCl$_3$. Some derivatives show NMR signals for protons 1'-H and 1''-H as diastereomeric signals in a AB system with a ^{2}J coupling constant of -16Hz! (this high value can be explained due to the existence of highly electronic density groups next to the methylene group).

When the reaction time was increased from 3 hours to 1 day, a secondary compound was formed; its structure was identified by a series of NMR experiments and MS spectrometry. This new N-allylamine butenolide derivative **95** bears an acetyl residue, and was isolated in 21 % yield. The formation of **95** is presumably the result of a tandem reaction (aza-ene reaction – ring opening) due to the high reactivity involving the allyl group in C-3 and the butenolide ring under the conditions employed:
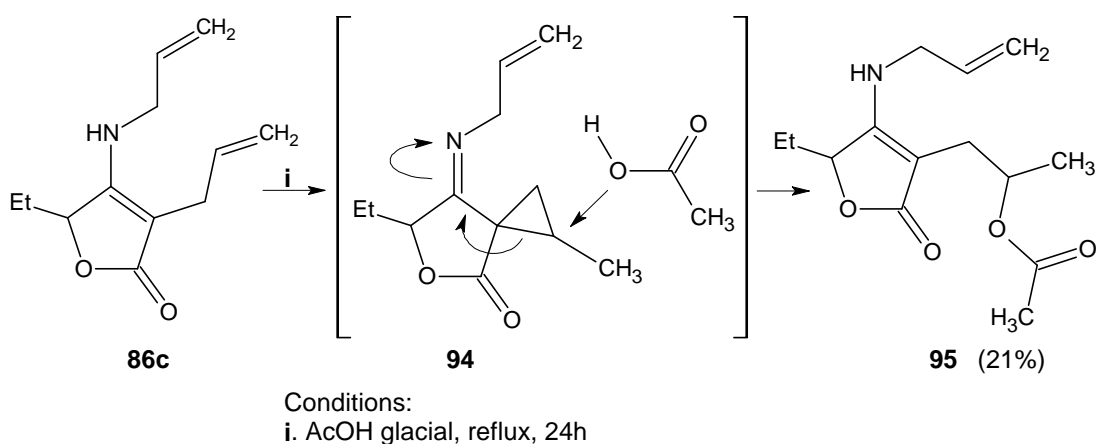
Figure 94.
Product **95** was formed in 21% yield from aminobutenolide **86c** as a result of a subsequent aza-ene rearrangement followed by a spirocyclopropyl ring opening with the acetic acid used as solvent.

As a result the yield of **86c** decreased noticeably, since the formed product is taking part in another reaction involving the solvent (glacial acetic acid) and forming the second product **95**.

Compound **95** was revealed when examining TLC after the reaction. Two spots with slightly different retention factors were evidenced indicating the existence of a second reaction product [R_f (**86c**) = 0.42; R_f (**95**) = 0.29; SiO$_2$, Et$_2$O]. The TLC controls of products **86a-b** and **86d** also incorporated a second and weaker spot with different retention factor than the main product. Unfortunately the amounts were minimal and the compounds were not isolated during the purification by column chromatography. As an early conclusion, molecules similar to **95** were formed from the 4-allylamino butenolides and glacial acetic acid, but when keeping the heating time at 3 h, the amount of these second products was kept at low level.
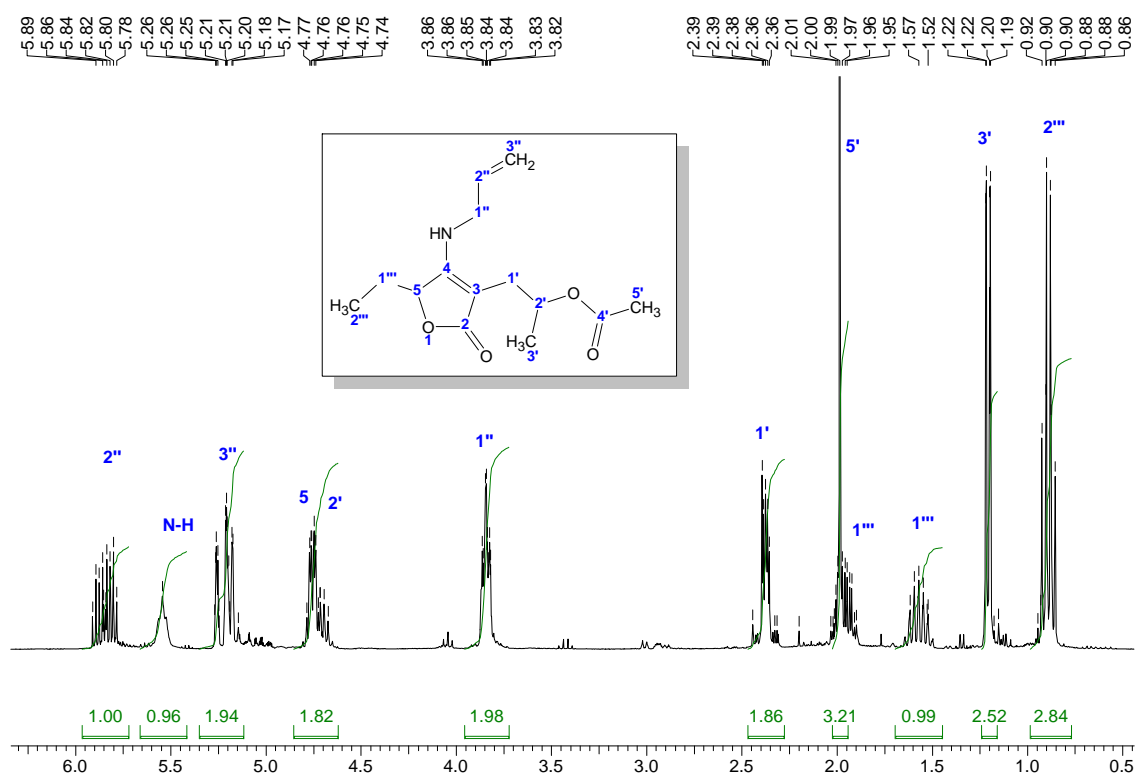
Figure 95.
300 MHz ^{1}H NMR spectrum of derivate **95** - mixture of isomers- in CDCl$_3$. The compound was isolated as a secondary product formed during the reaction after heating for 24 h.

It is interesting to note that ring opening was done with acetic acid but not with allyl amine because the latter exists as a salt –the amine is protonated by the excess of acetic acid in the media-. The low yield can be explained in terms of the low nucleophilicity of the reagents (acetate anion is more a base than a nucleophile).

2.9.2 Synthesis of furo[3,4-*b*]azepines *via* Ring Closing Metathesis

One way for obtaining compounds containing azacycles is using the "Grubbs´ complex" as catalyst, a ruthenium carbene originally obtained from the decomposition of phenyldiazomethane in the presence of a ruthenium (II) complex. Several examples have been reported using this strategy in the synthesis of diverse heterocycles.[117]

Using the obtained compounds **86** carrying two allylic systems, the next step was to merge the double bonds via RCM in order to obtain molecules with seven-membered azepine ring structure fused to the furan-2-one-skeleton **96**. These highly functionalised heterocyclic systems are versatile and can either be used as building blocks in drug or natural product synthesis as well as conformationally restricted β-amino acid analogues.[118]

When first using 3-allyl-4-allylamino-5-hexyl-5*H*-furan-2-one **86d** as an unprotected secondary amine for metathesis following the general procedure, no reaction took place and **86d** was recovered completely.
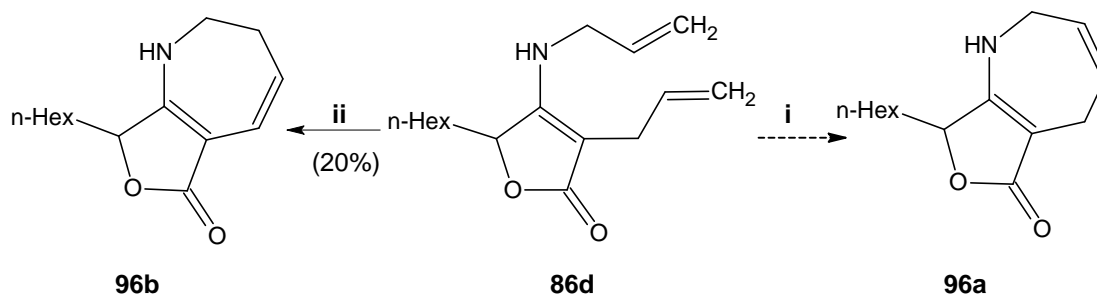
Conditions :
i. Grubbs 1st generation (2 mol%), DCM, 24 h
ii. Grubbs 2nd generation (2 mol%), toluene, reflux, 48 h

Figure 96.
RCM reaction of derivate **86d**. Compound **96b** was formed after a double bond shifting which is presumably induced by remaining catalyst metal.

Literature reports also show zero to very low yields when using Grubb's first-generation catalyst, $Cl_2(PCy_3)_2Ru=CHPh$, on secondary amines. This negative result is supported by observations showing that a chelating substituent in close proximity to one of the double bonds (in this case the nitrogen atom) shuts down the catalytic cycle.[119] For metathetic synthesis of cyclic unsaturated amines, which can hardly be prepared by alternative methods, the use of a chiral Mo complex prepared in situ has been developed.[120]

When the RCM reaction of **86d** was followed via GC using the more reactive Grubb's second-generation catalyst $(IMes)(PCy_3)Cl_2Ru=CHPh$, (**Figure 96** – left), the starting material was converted only when the reaction mixture was heated in toluene under reflux for 48. After several purifications in order to remove the black colour from the sample via $Pb(OAc)_4$ complexation,[103] the fused furo[3,4-*b*]azepine **96b** was isolated in 20% yield.

The low reactivity of **86d** can be explained in the same way as when using the 1st generation Grubb's catalyst (chelating effect derived from the nitrogen next to the double bond).

A detailed examination of the NMR data shows a double bond isomerization in the azepine-ring: the final product contains the olefin bond shifted one position, compared to the expected structure, forming the more stable conjugated system **96b**. This "double bond shifting" has been reported as a result from the reaction between the ring closing product and remaining ruthenium metal from the catalyst.[104]
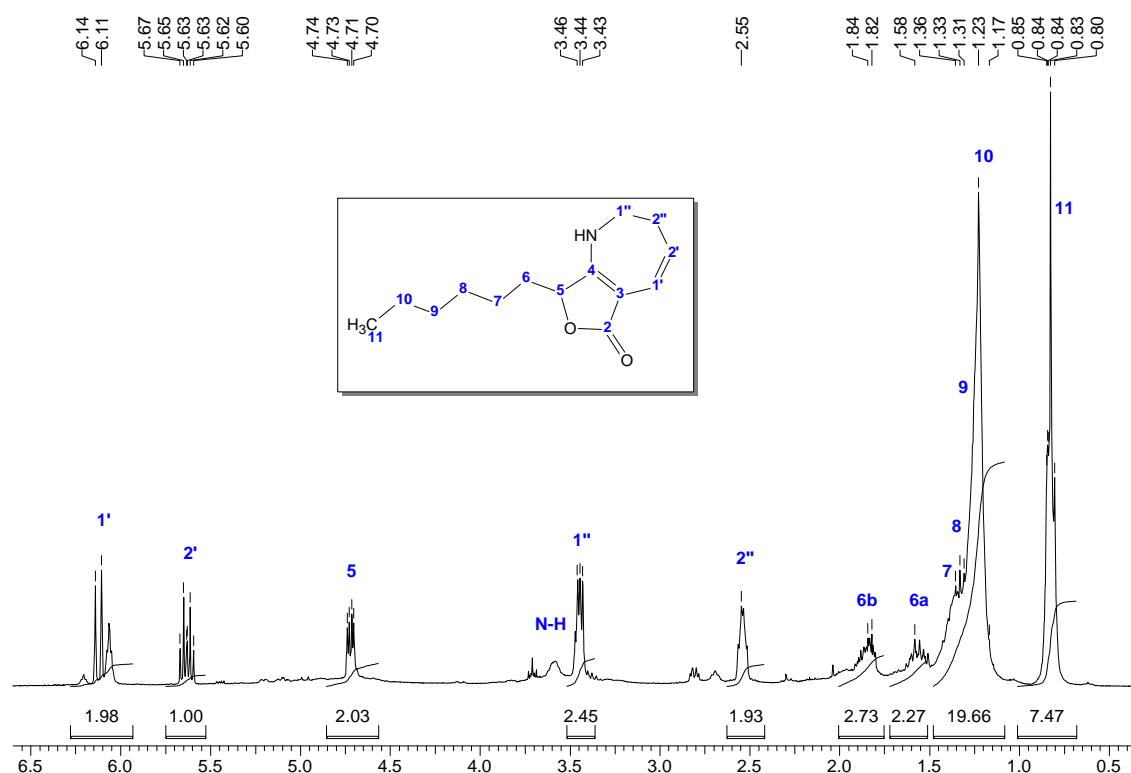
Figure 97.
300 MHz ^{1}H NMR spectrum of derivate **96b** in CDCl$_3$.

Since the RCM is an effective process that usually gives conversions in nearly quantitative yields in derivatives bearing tertiary amines and amides (especially when using protective groups for later elimination or substitution), compounds **86a**-**b** were N-acylated in order to try the Grubb´s metathesis on the corresponding new N-protected system.

The protection of 3-allyl-4-allylamino-5-methyl-5*H*-furan-2-one **86b** using BOC anhydride was obtained only when the reaction mixture was refluxed under toluene for 3 days, due to the extremely low reactivity of the tetronamide system. The separation of **97a** from the reaction mixture gave massive problems because a secondary product was also formed. This new product was identified by NMR and GC-MS and the structure agrees with the derivate **97b**. The new ethoxycarbonyl derivate was formed probably as consequence of an elimination of the *t*-butyl rest – replacing it for an ethyl rest from the triethylamine due to the harsh conditions used during the reaction.

86b   **97a**   **97b**

Conditions:

i. BOC anhydride (200 mol%), Et$_3$N (1000 mol %), toluene, reflux, 3 d.
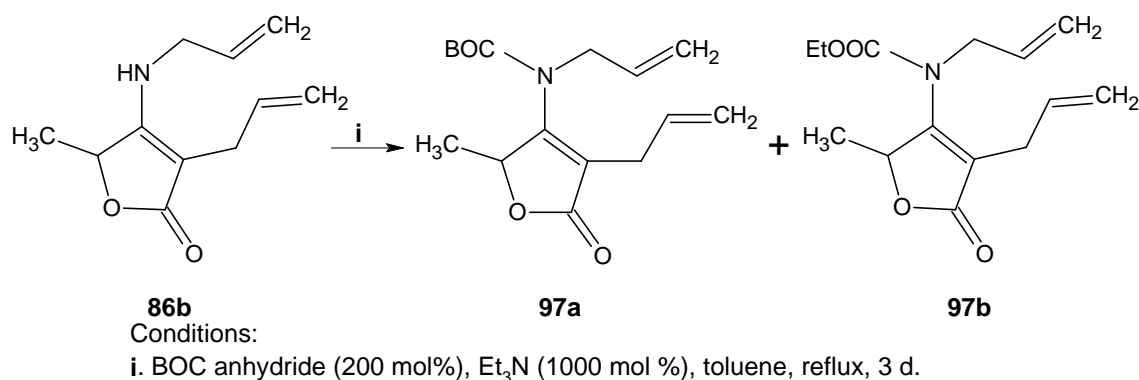
Figure 98.

Formation of protected aminobutenolide **73a** via BOC anhydride (yield: 21%). New derivate **73b** (EtOOC = Ethoxycarbonyl) was isolated in 15% yield. In the ^{1}H-MNR spectra the signals corresponding to the protons in 1" show an amazing coupling constant ^2J of about -16Hz due to the existence of high electron density groups neighbours (the amide and the double bond) next to the methylene protons (see details in experimental part).

Another procedure for the N-BOC protection of 3-allyl-4-allylamino-5*H*-furan-2-one **86a** was tried using NaHCO$_3$ as base, refluxing the reaction mixture in THF for 1 day. These hard conditions employed led to by product formation, and several chromatography columns were required in order to recover the final product.

86a   **97c**
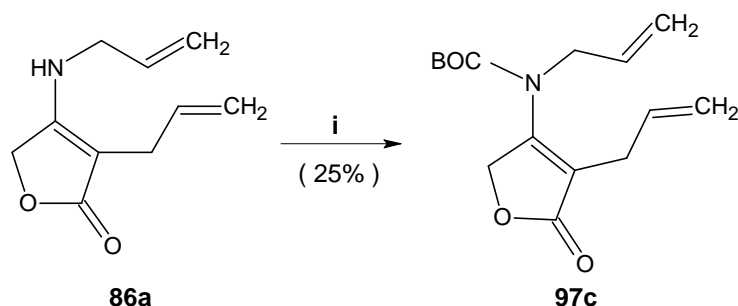
Conditions:

i. BOC anhydride (1000 mol%), NaHCO$_3$ (200 mol %), THF, reflux, 1d.

Figure 99.

Formation of protected aminobutenolide **97c** *via* BOC anhydride using NaHCO$_3$ as base.

This low accessibility of amides *via* acetylation of amino butenolides (and the corresponding small yields) for the same class of reaction were also reported in similar systems and proves the difficulty of the N-protection attempts. [Note 1]

Note [1]:
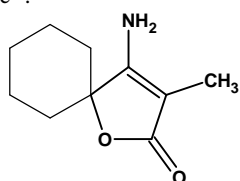
Tetronamide is hardly acetylable – After 4 days under reflux, the compound depicted, in the presence of an excess of acetic anhydride formed only 30% of the diacetyl derivative. The remaining 70% was starting material.

Payard, M.; Paris, J.; Tronche, P. Synthèse et tautomérie d'amino-3 et d'hydroxy-3 buténolide. *J. Heterocyclic Chem.* **1978**, *15*, 1493-1496.
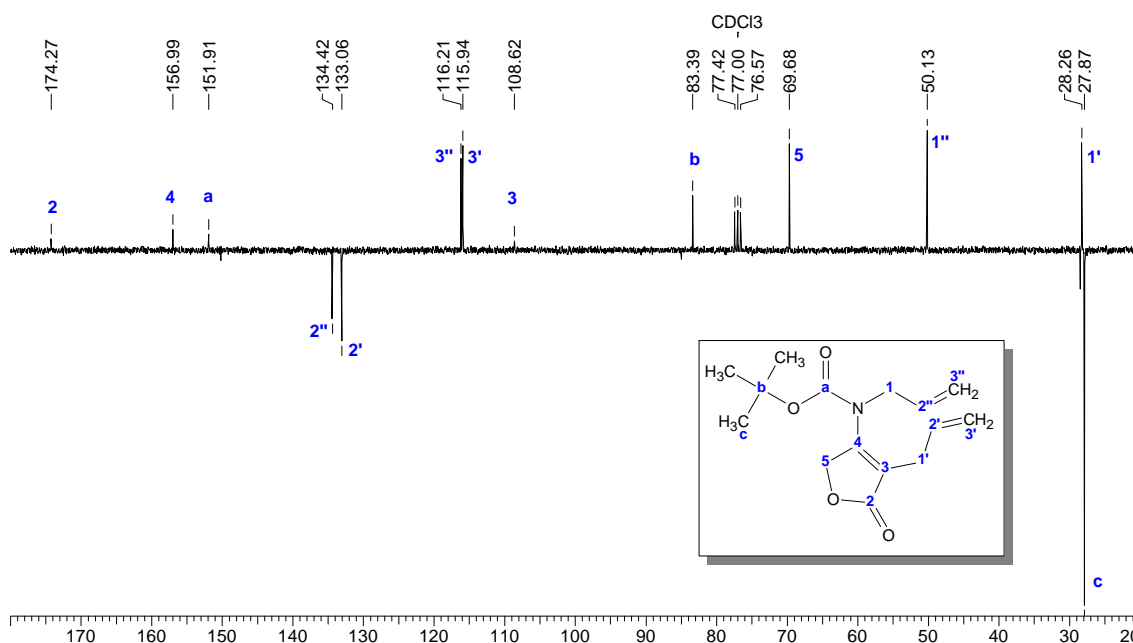
Figure 100.
75 MHz ^{13}C-APT NMR spectrum of *t*-butoxycarbonyl butenolide **97c** in CDCl$_3$. It is interesting to note that in the ^{13}C-NMR spectra of derivates **97**, C-3 moves from ~88 ppm to ~110 ppm when the amino butenolide is converted into the alkoxycarbonylamino butenolide derivate.

Once the N-BOC protected aminobutenolides were isolated, the RCM was performed under standard conditions (2 mol % catalyst, DCM, rt). The new fused furo[3,4-*b*]azepines were formed as well as considerable unidentified by products, a surprising behaviour not noticeable in the case of the oxa analogues.[100]

The new furo[3,4-*b*]azepines **98** formed contain the double bond in the expected position and no isomerization products were observed. The more reactive Grubb's 2nd generation catalyst appears to have an "alternate isomerization effect" over the substrate when the ring closing metathesis was done in comparison with the Grubb's first-generation catalyst, Cl$_2$(PCy$_3$)$_2$Ru=CHPh.[104] This effect was dependent on the temperature used during the process.

	R^1	R^2	(%)
98a	H	BOC	22
b	Me	EtOOC*	37

*EtOOC = Ethoxycarbonyl
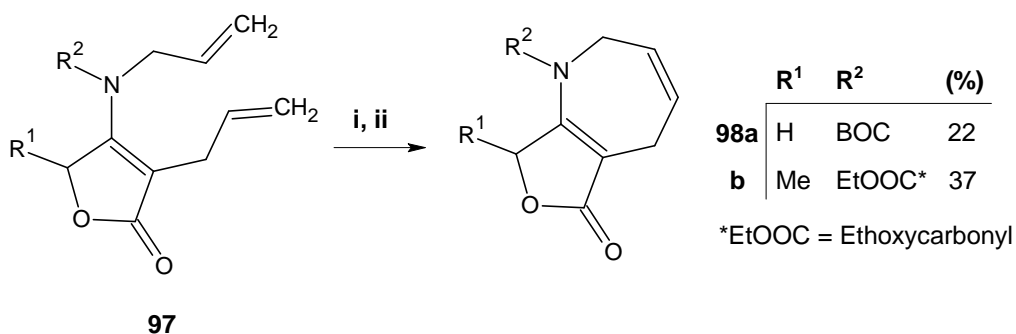
Conditions:
i. Grubb's 1st generation (2 mol-%), DCM, rt, 1d. Then Pb (OAc)$_4$ to complex the residual metal

Figure 101.
Synthesis of furo[3,4-*b*]azepines **98** by ring closing olefin metathesis.
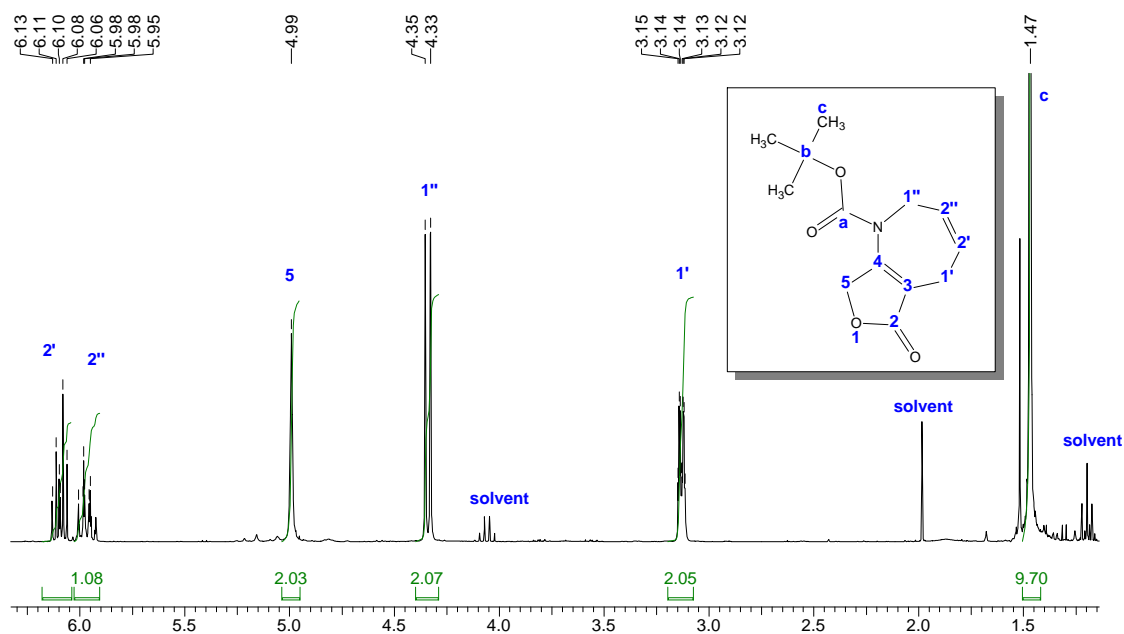
Figure 102.
300 MHz ^{1}H-NMR spectrum of furo[3,4-*b*]azepine derivate **98a** in CDCl₃. The methyl group signal is truncated to zoom-in the rest of the signals – Ethyl acetate is giving the marked solvent signals in the spectra.

The effective formation of fused furo[3,4-*b*]azepines **98** was not totally accomplished mainly due to their low reactivity under ring closing metathesis conditions. Firstly, it is believed the free nitrogen atom is able to complex the ruthenium metal[119]. Secondly, the formation of a tertiary amino group was not effectively done because of the highly conjugated system in the tetronamide as described above. The use of a different RCM catalyst should be tried in order to increase the efficiency of the reaction.

2.10 Contribution to the synthesis of Bakkenolide synthons

One interesting family of natural compounds is the large Bakkenolide family. Also known as bakkanes, they incorporate sesquiterpenes that have in common a hydrine skeleton and a spiro fused γ-butyrolactone that generally bears an otherwise rare ß-methylene function. The archetype of this family, Bakkenolide A (fukinanolide), was first isolated in 1968 from the flower stalks of the wild butterbur *Petasites japonicus* by two Japanese groups working independently.[121] More complex bakkanes like Homogynolide B possess significant antifeedant activity against a number of feed and grain pests.[122]
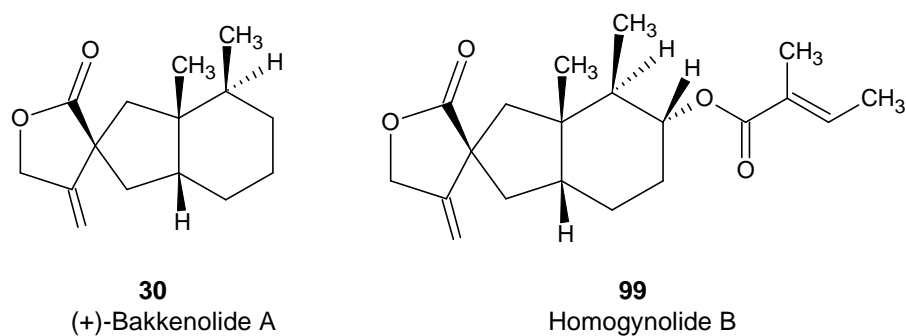
Figure 103.
Structures of (+)-Bakkenolide A and (±)-Homogynolide B.

The use of Claisen rearrangement (section 2.6.3) and/or palladium catalyzed substitution (section 2.7.2) followed by ring closing olefin metathesis (section 2.8.2) offers the ability to prepare the synthon **84d**, a basic core of Bakkenolide A.
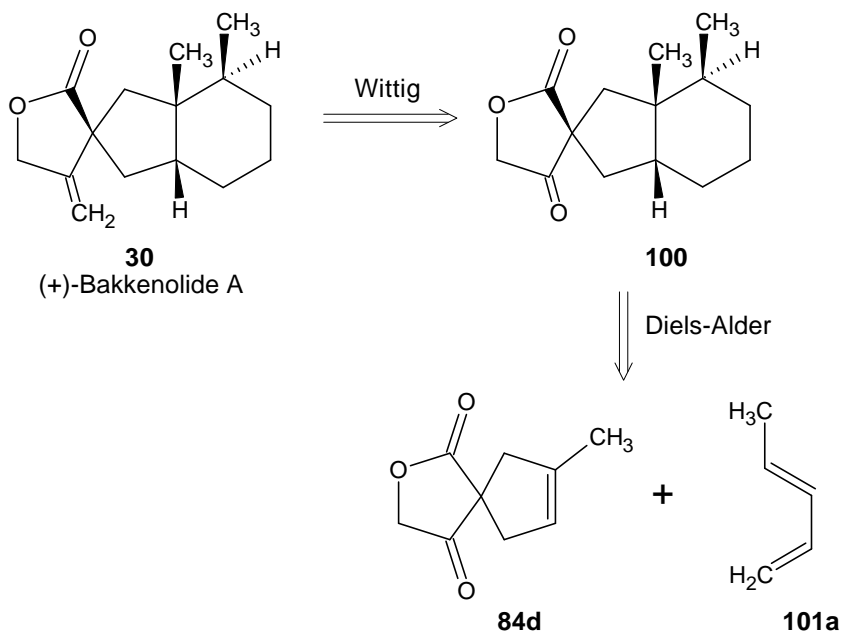
Figure 104.
Retrosynthetical scheme for (+)-Bakkenolide A. Compound **84d** was prepared *via* ring closing olefin metathesis according section 2.8.2.

The presence of the double bond in the spiro system **84** allows further functionalization. In our particular case, the study of the Diels-Alder addition of this double bond with Danishefsky's diene **101b**, ethyl sorbinate **101c** and benzylidenaniline **101d** was performed.

When compound **84a** was heated with Danishefsky's diene **101b** in a sealed tube in toluene[123] in order to complete the bakkane framework via a Diels-Alder reaction with the cyclopentene, the corresponding hetero-Diels Alder 3,4-dispiro adduct **103** was obtained instead.[100]
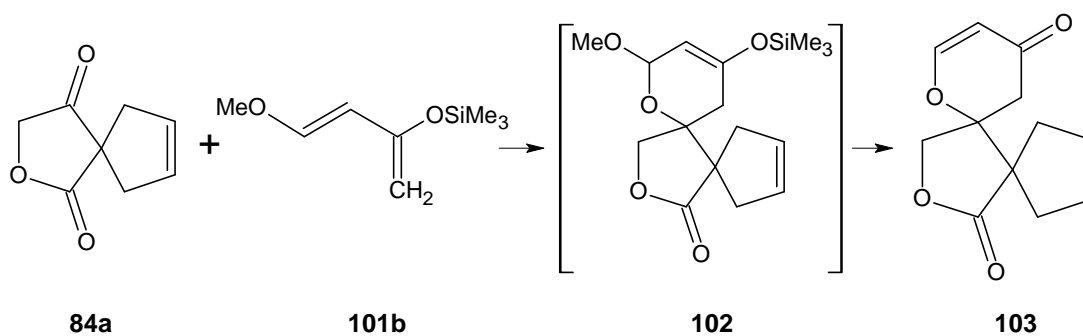
Figure 105.
Synthesis of 3,4-dispirobutanolide **103**. The cycloadduct **102** was not isolated and was converted directly into **103** after acid work-up.

The dispiro derivative **103** appeared as a white solid in 44% yield after purification through column chromatography and recrystallization.
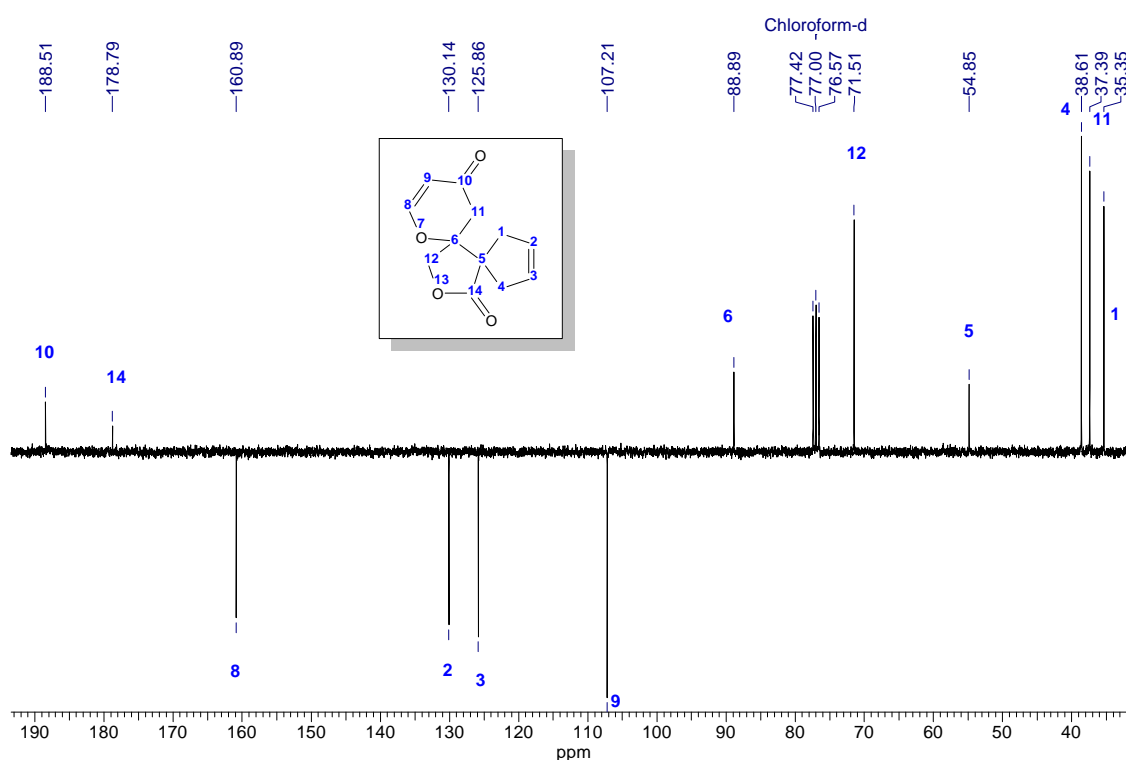
Figure 106.
300 MHz ^{1}H-NMR spectrum of 3,4-dispiro derivative **103** in CDCl$_3$.

The hetero Diels-Alder cycloaddition reaction of aldehydes and ketones with 1,3-dienes is a well established synthetic procedure for the preparation of dihydropyrans, which are attractive substrates for the synthesis of carbohydrates and other natural products.[124] It is worth to mention that carbonyl compounds are in general of limited reactivity in hetero Diels-Alder reactions with dienes since only electron-deficient carbonyl groups as in glyoxylates, chloral,

ketomalonate, 1,2,3-triketones, and related types of compounds, react with dienes having electron-donating groups.[125]

Initial analyses of the obtained spectra were not conclusive. For that reason and in order to make an unequivocal assignment of the spectrum signals (^{1}H and ^{13}C), a [1]H-detected 2D-INEPT-INADEQUATE-NMR experiment was used. This experiment detects carbon-carbon connectivities. It is estimated to be about a factor of 13 times more sensitive than the standard 2D INADEQUATE but in contrast, the method lacks the generality of the normal experiment since connectivities between two quaternary carbon atoms C^q-C^q cannot be detected. However, it is possible to see a C^q-CH_n moiety.[126]
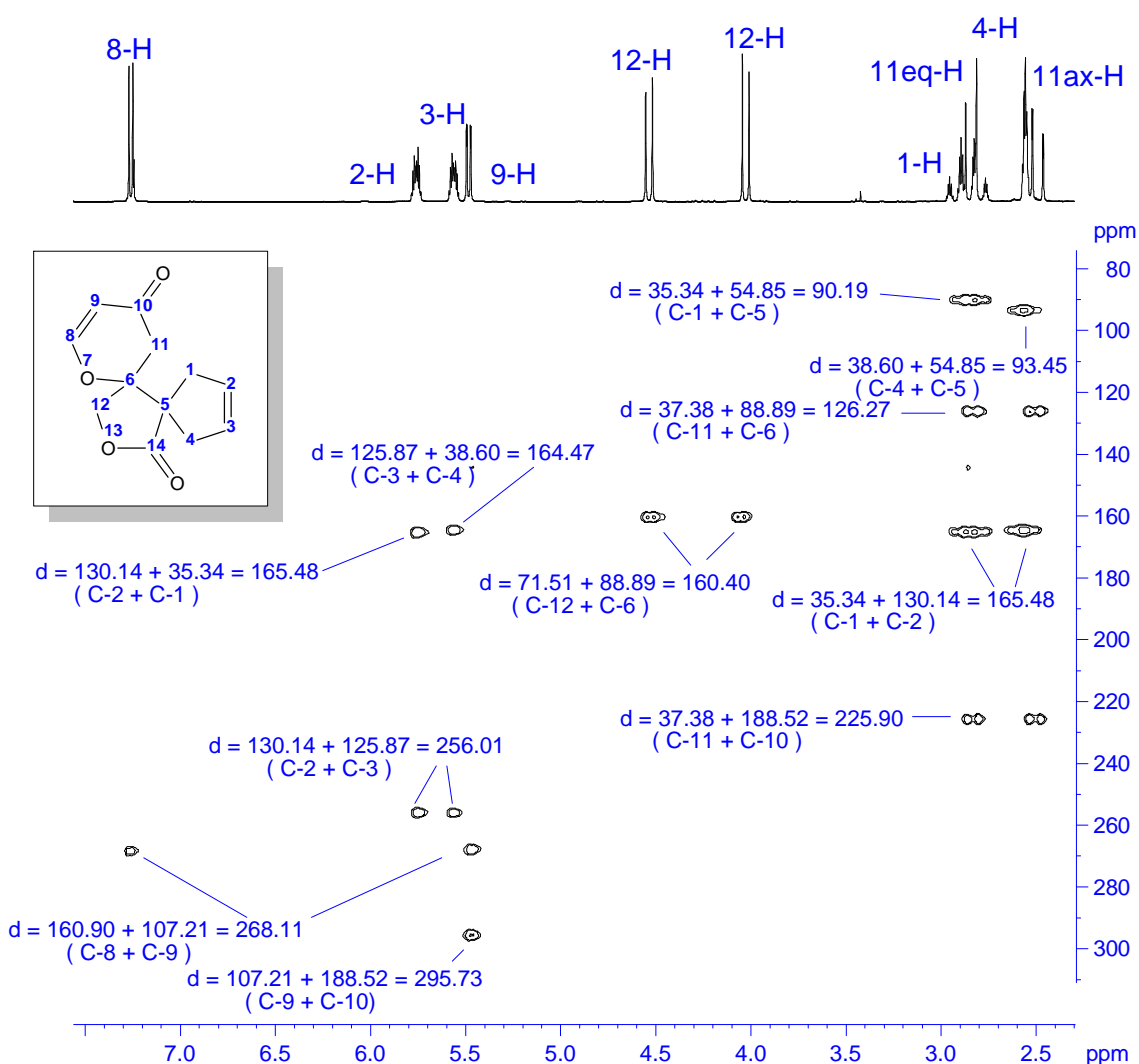
Figure 107.
[1]H-Detected INEPT-INADEQUATE spectrum of 3,4-dispiro derivative **103** in CDCl$_3$.

The figure shows the ^{1}H detected INEPT-INADEQUATE spectrum obtained on an AM-300 spectrometer. 9-H displays a double quantum signal (DQ) at δ_{DQ} = 295.73 ppm which corresponds to δ_{C-9} = 107.21 ppm + δ_{C-10} = 188.52 ppm and another DQ signal at δ_{DQ} = 268.11

ppm ($\delta_{C-9} + \delta_{C-8}$). This connectivity is also seen in the proton dimension for the signal of 8-H. 2-H shows the next DQ signal at $\delta_{DQ} = 256.01$ ppm ($\delta_{C-2} + \delta_{C-3}$) leading to 3-H which displays at $\delta_{DQ} = 164.47$ ppm the connectivity C-3 – C-4. 2-H also shows a DQ signal at $\delta_{DQ} = 165.48$ ppm ($\delta_{C-2} + \delta_{C-1}$) and this connectivity is also seen in the proton dimension for the signals of 1-H. The DQ signal of 12-H appears at $\delta_{DQ} = 160.40$ ppm ($\delta_{C-12} + \delta_{C-6}$) and stands alone since C-12 has no further connectivities and C-6 is a quaternary carbon atom. In the same way, a first DQ signal of 11-H appears at 126.27 ppm ($\delta_{C-11} + \delta_{C-6}$) and stands connected to a second DQ signal at 225.90 ppm ($\delta_{C-11} + \delta_{C-10}$). 1-H shows a DQ signal at $\delta = 90.19$ ppm ($\delta_{C-1} + \delta_{C-5}$) and 4-H shows a DQ signal at $\delta = 93.45$ ppm ($\delta_{C-4} + \delta_{C-5}$). Following the connectivities, it was possible the unequivocal assignment of the ^{1}H and ^{13}C-NMR signals.

The chemistry of the spiro furan-2,4-dione with different dienes was also attempted. Dispirofuranone **84a** was also treated with ethyl sorbinate **101c** in order to form the bakkane core through a Diels-Alder reaction. The progress of the reaction was followed by GC but unfortunately no product was observed under classical thermal or Lewis acid catalysed conditions. The starting material was recovered quantitatively.
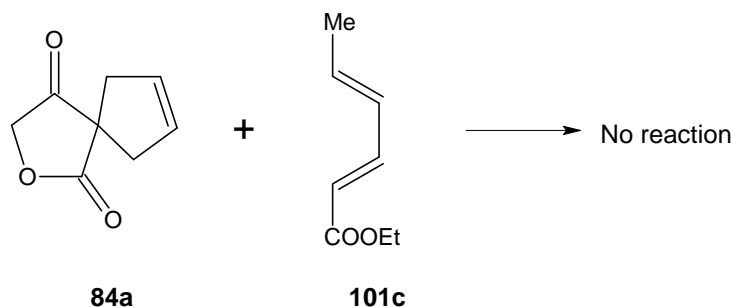
Figure 108.
Attempted reaction of **84a** with ethyl sorbinate **101c** in order to complete the bakkane framework via a Diels-Alder reaction with the cyclopentene. Conditions tried: **i**. Toluene, sealed tube, 180°C, 18h; **ii**. Toluene, Yb(OTf)$_3$ 2 mol-%, sealed tube, 180°C, 24h; **iii**. Toluene, EtAlCl$_2$, sealed tube, 180°C, 15h.

In a separate test, an aza Diels-Alder reaction was attempted. It is well known that the [4+2] Diels-Alder reaction between N-arylamines and electron-rich dienophiles is probably one of the most powerful synthetic tools for constructing N-containing six-membered heterocyclic compounds [127].

In order to functionalise the spiro-compound **84a** previously formed, a [4+2] Diels-Alder cycloaddition between **84a** and N-benzylideneaniline **101d** catalyzed by ytterbium-triflate under normal heating[127] and under microwave irradiation conditions[128] was attempted. Compound **101d** was prepared according to standard procedures.[129] The progress of the reaction was followed by GC but unfortunately no addition product was detected. Under microwave irradiation no reaction occurred in spite of heating up to 190°C for 20 min.
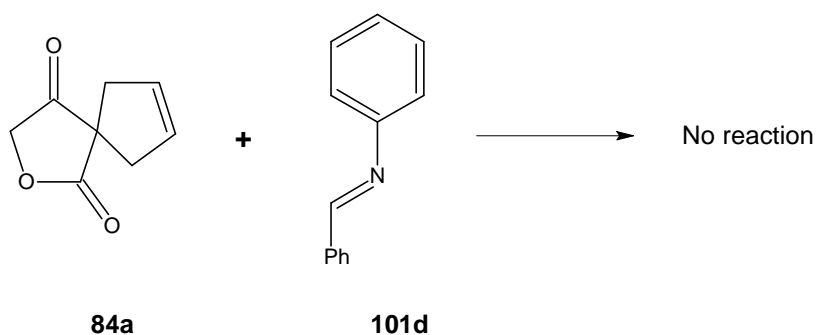
Figure 109.
Attempted reaction of **84a** with benzylidenaniline **101d** in order to obtain a quinoline derivative cycloadduct. Conditions tried: **i**. Acetonitrile, Yb(OTf)₃, 80°C, 60h; **ii**. Acetonitrile, MW irratidiation, 190°C, 20min.

The Diels-Alder reaction is facilitated by the presence of electron-donating groups on the diene component and by the presence of electron-attracting groups on the monoene component.[130] The spiro derivative **84** as monoene does not carry electron-attracting groups next to the double bond, and it was determined to be non reactive when using the electron deficient diene **101c**, in spite of using Yb(OTf)₃ as catalyst and extended heating, to undergo the reaction. The oxa Diels-Alder reaction when using the electron rich diene **101b** was preferential. A possibility to induce the aza Diels-Alder reaction with benzylidenaniline as well as the Diels-Alder reaction with ethyl sorbinate could be under high-pressure.[121b,131]

2.11 Contribution to the synthesis of furo[3,4-*b*]furan-2,4-diones. A potential access to (±)-Canadensolide and related natural compounds

Tetrahydro[3,4-*b*]furan derivatives show anti-ulcer activity and are useful in the treatment of gastric or duodenal ulcers.[132] It is worth observing that the furo[3,4-*b*]furan-2,4-dione structure has four potential asymmetric centres, namely those at the 3, 3a, 6 and 6a positions, for that reason and according to the synthetic procedure, the compound may therefore exist in one or more racemic or optically active forms of varying stereochemistry that is, varying epimeric forms.

It is further to be understood that the two furan rings will always be *cis*- fused, that is, the hydrogen atom at the 3a- position and the radical R² at the 6a- position must always be on the same side of the furo[3,4-*b*]furan nucleus. Throughout this specification the position of the hydrogen at the 3a- position and the radical R² at the 6a- position of the furo[3,4-*b*]furan will be

designated as α-, and the stereochemical arrangement of the other substituents designated α- or β- correspondingly.

Canadensolide **31** is a mold metabolite produced by *Penicillium canadense* and has an antigerminative activity against fungi, e.g., *Botrytis alii*. It was isolated from the culture filtrate, along with another closely related compound, dihydrocanadensolide **104**, and their isolation and first molecular structure were assigned by *McCorkindale et al.*[133] Although the relative stereochemistry of canadensolide was initially not well determined on the basis of NMR evidence, stereoselective synthesis of the compound and its epimer was initially done by *Yoshikoshi et al.*[134]. *Anderson and Fraser-Reid* finally reported that the absolute stereochemistry of naturally occurring (-)-Canadensolide **31** as 2*S*,3*R*,4*R*.[135]

31
Alternative
nomenclature for
Canadensolide

104

Nomenclature of
furo[3,4-b]furan-2,4-diones
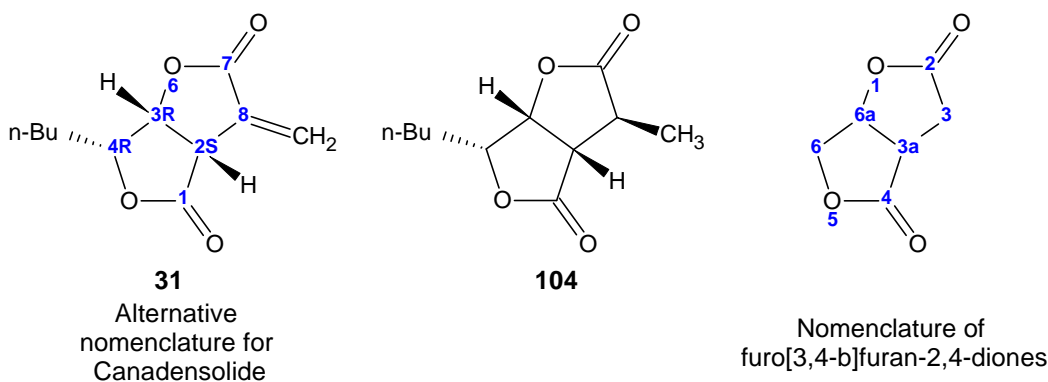
Figure 110.
Molecular structure of Canadensolide **31** and dihydrocanadensolide **104**. The nomenclature used in literature for the furo[3,4-*b*]furanones is different to the one used for the canadensolide.

Using the nomenclature mentioned above, the known optically active compound dihydrocanadensolide is the epimer named 6β-*n*-butyl-3,3aα,6,6aα-tetrahydro-3α-methylfuro[3,4-*b*]furan-2,4-dione. This configuration for the epimer has been confirmed by *Kato et al.*[136]

A remarkable number of reports describe the synthesis of Canadensolide and related bis lactones. Some of them most be cited: the stereoselective bislactone ring formation made from *cis*-ethylenic esters[134,136], the unexpected double lactone synthesis of furofuran derivatives reported by *Mukaiyama et. al.*[137], the addition of the itaconic acid trianion to α-hydroxyvaleraldehyde protected as ethoxyethyl ether[138] and similar reactions[139], the use of photochemical reactions to construct the *cis*- fused bicycle[140], the use of glucose[135,,141,142], mannose[143], xylose[144] or arabinose[145,146] derivatives as chiral synthons for di-γ-lactones, the lactonization of halo esters[147] or halo alkynes[148], the use of modified pyranones[149], the use of intramolecular cyclopropanation[150], the use of tungsten π-allyl complexes[151] and other related cyclisations[152,153].

R = Et   Xylobovide (Ethisolide)

R = *n*-Bu   Canadensolide

R = *n*-Hex   Sporothriolide

R = *n*-Oct   Avenociolide
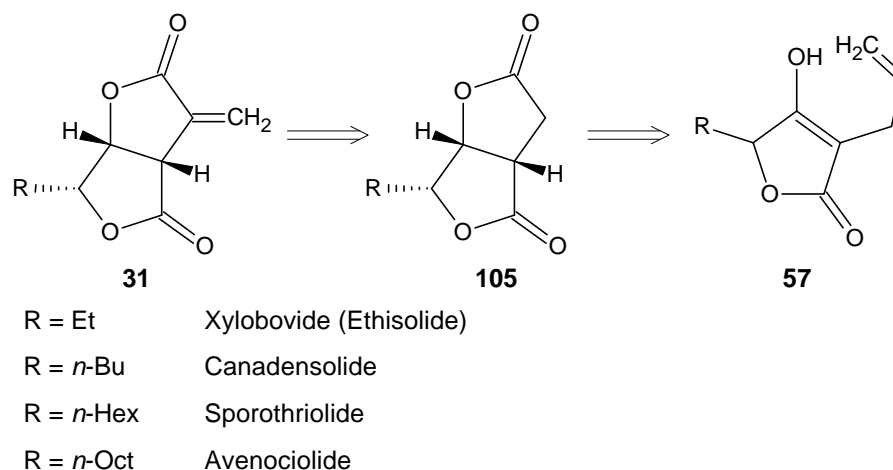
Figure 111.
Retrosynthetical scheme of natural bis-lactones **31**. The core of the system is a γ-lactone derivative and can be formed from the tetronic acid **57**.

There are no reports about the use of tetronic acids in the synthesis of bis-lactones. The formation of bislactones is usually carried out after converting the tetronic acid into the corresponding hydroxybutenolide. A remarkable example was reported by *Strawson et al*. in the preparation of (±)-3,3aα,6,6aα-tetrahydrofuro[3,4-*b*]furan-2,4-dione **105a** through a Rhodium catalyzed hydrogenation.[132]
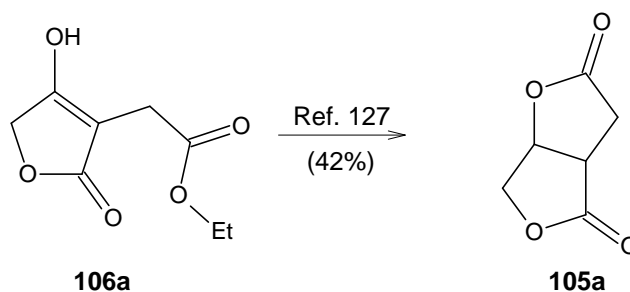
Figure 112.
The use of rhodium on alumina catalyst convert the 3-ethoxycarbonylmethyltetronic acid **106a** into the corresponding hydroxylactone. After acid treatment (HCl gas, 0°C), the second lactone ring is formed.

Thus, the formation of the ethoxycarbonylmethyl tetronic acid **106** was investigated from the tetronic acid derivatives **57** through an oxidation – protection sequence as the chosen path.

The oxidation of the 4-*O*-benzyl tetronic acid derivatives **64** using ozone was previously described by *Siegfried*.[26] This part of the research was followed according to those preliminary results. Initially, the ozonolysis of the allylic double bond efficiently converted the 4-*O*-benzyl tetronic acid **64** into the aldehyde **107**.[154] During the study it was found the use of dimethyl sulphide as an ozonide reductor, was better than Ph₃P. The reduction is carried out under neutral

conditions and any excess of dimethyl sulphide is readily removed by evaporation (b.p. = 37°C) and the by-product, dimethyl sulfoxide, causes no purification problems.[155] It is worth mentioning that the purity of the reagents and solvents plays an important role during the ozonolysis. When working with crude products a considerable increase in the amount of by-products was observed.
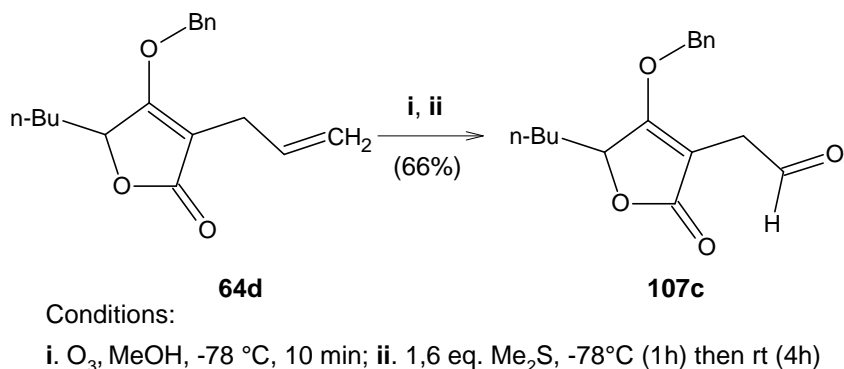
Figure 113.
Allyl cleavage using ozone. Aldehyde **107c** was difficult to handle due to the easy formation of polymeric substances.

Aldehyde **107c** showed a slight decomposition with time. For that reason, derivatives **107** were converted directly to the dimethyl acetal **108** or to the carboxylic acid derivatives **111** using a Jones' oxidation.

The acetal formation proceded smoothly giving good to nearly quantitative yields of **108**. Compound **108** is a double protected tetronic acid which can be used as a synthon for the fused furofuranone **105**.

Conditions:
i. O₃, MeOH, -78 °C, 10 min; **ii**. 1,6 eq. Me₂S, -78°C (1h) to rt (4h);
iii. MeOH / HCl, 80 °C, 1h

	R	(%)
108a	Me	74
b	Et	93
c	*n*-Bu	98
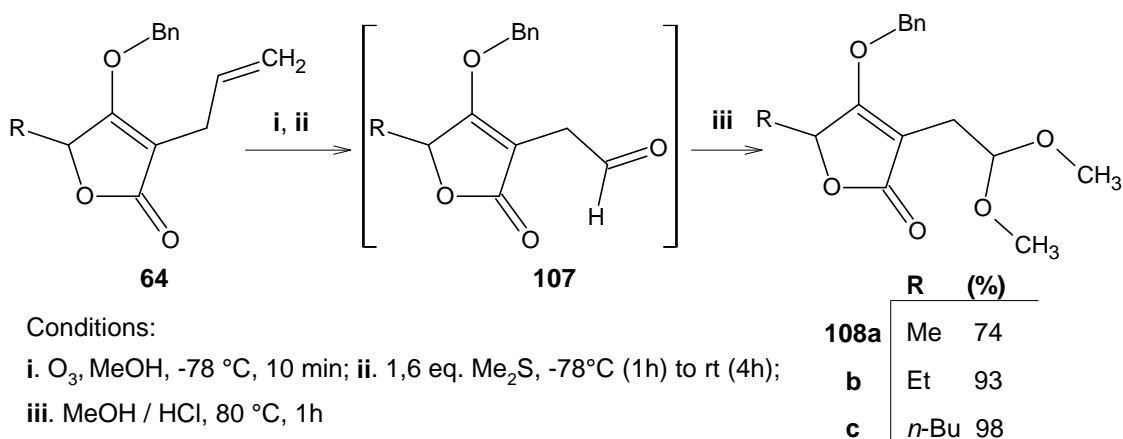
Figure 114.
One-pot oxidation – dimethyl acetal protection of 4-*O*-benzyl tetronic acid **64**.

Dimethyl acetal derivatives **108** were purified via column chromatography in silica gel. The dimethyl acetal function makes these derivatives considerably stable and they can be stored without loss of purity. A typical ¹³C-NMR spectrum is shown. Note that the methyl groups in

the dimethyl acetal function have slightly difference in their chemical shift and its intensity appears to be smaller than the normal carbons, possibly due to the strong influence or the neighbour oxygen atom.
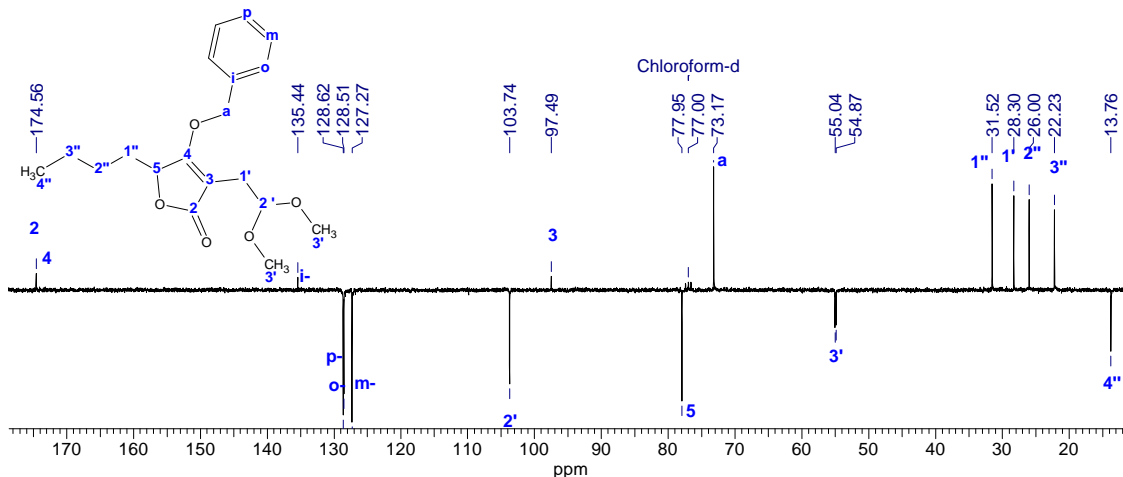
Figure 115.
75 MHz ^{13}C-APT-NMR spectrum of derivative **108c** in CDCl$_3$.

The benzyl protected dimethyl acetal derivatives **108a-b** were effectively converted into the tetronic acid dimethyl acetal **109**, using Pd over charcoal and anhydrous methanol during the debenzylation.

Conditions:
i. H$_2$, Pd/C, MeOH, rt, 3h

	R	(%)
109a	Et	77
b	*n*-Bu	98
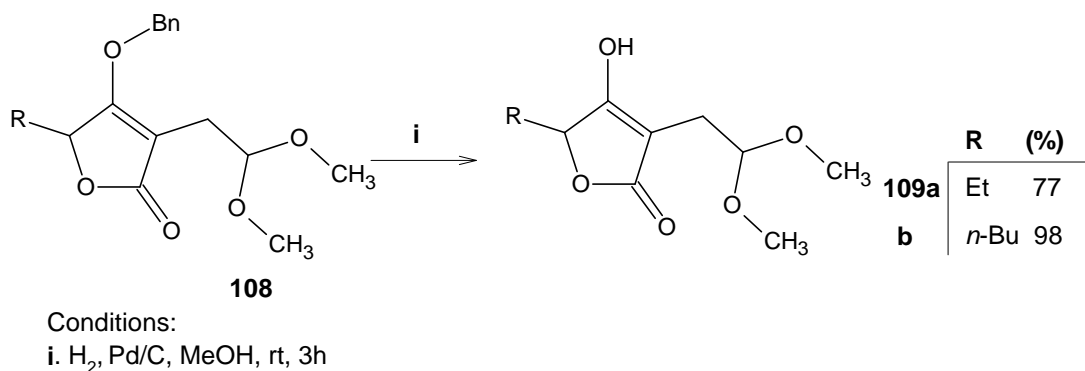
Figure 116.
Catalytical debenzylation of derivative **108a-b** using Pd on charcoal.

It was intended to use the acetal derivatives **108** and **109** as starting material in the formation of bislactones derivated from tetronic acid. The construction of the new lactone ring was tried using several known methods for the construction of lactones.[156] No product could be detected in spite of numerous attempts, possibly due to the existence of the internal double bond in the tetronic acid moiety and the consequent keto – enol tautomerization effect, which prevents the cyclisation.
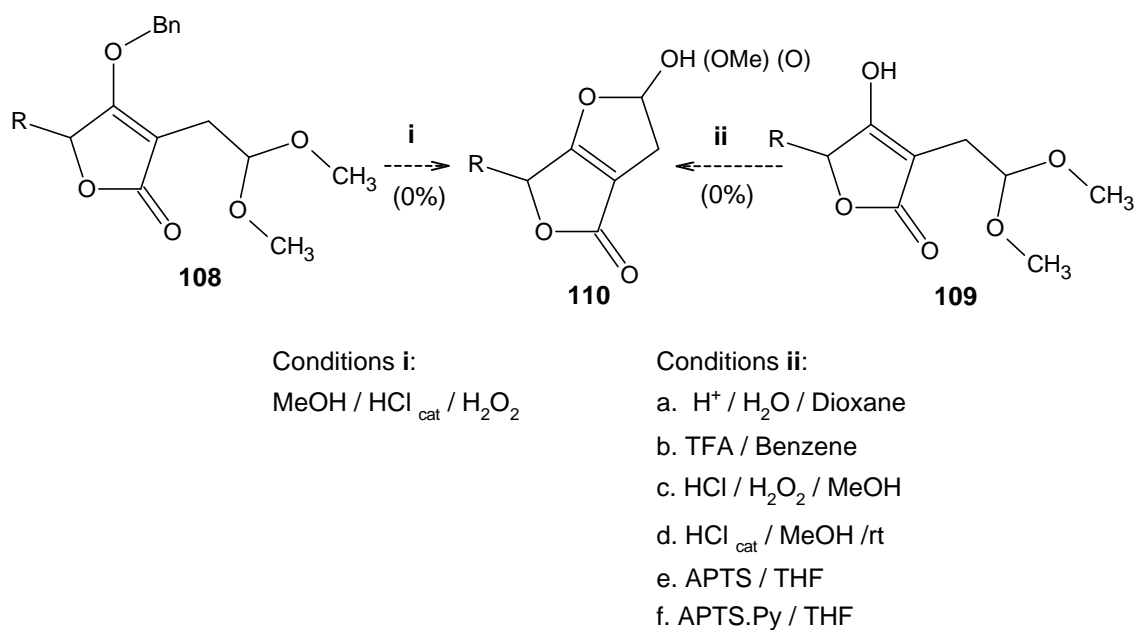
Figure 117.
Tried experiments to close the second lactone ring in tetronic acid derivatives **108** and **109**.

The conversion of the aldehyde function into the carboxylic acid was easily done using Jones' oxidation. Thus, derivatives **107b-c** were converted to the corresponding carboxylic acids **111a-b**. The drawback of this procedure was the removal of the residual chromium salts in the reaction mixture. The effective purification of the product was done through a basic – acid double extraction followed of recrystallization from *n*-hexane : ether. The presence of chromium compounds contaminating the product can be observed in the ^{1}H-NMR spectrum when the expected sharp proton signals appear as broad shaped shoulders.
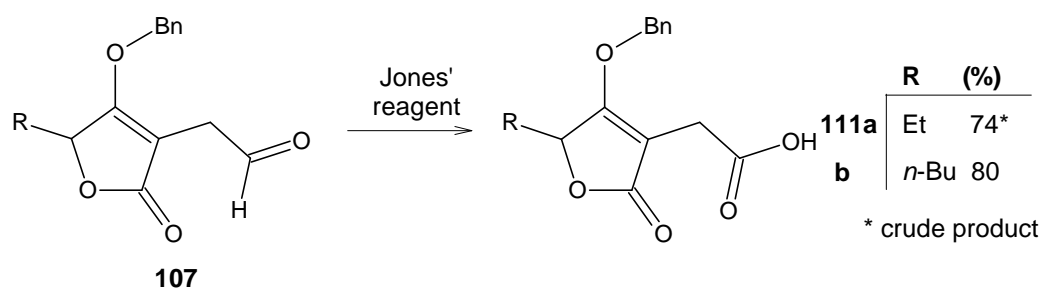
Figure 118.
Jones' oxidations of aldehyde derivatives **107**. The synthesis of the compounds was not possible to follow by gas chromatography since the carboxylic acid derivatives **111** are thermally decomposed.

It is worth mentioning the high stability of the tetronic acid derivatives **107** under the highly acidic conditions for the Jones' oxidation. The benzyl protecting group remains in the 4-*O*-position in spite of the presence of sulphuric acid and chromium oxide in the reaction

mixture. It is also important to mention that the time and the temperature also play an important role in the stability of derivative **107** during the oxidation.
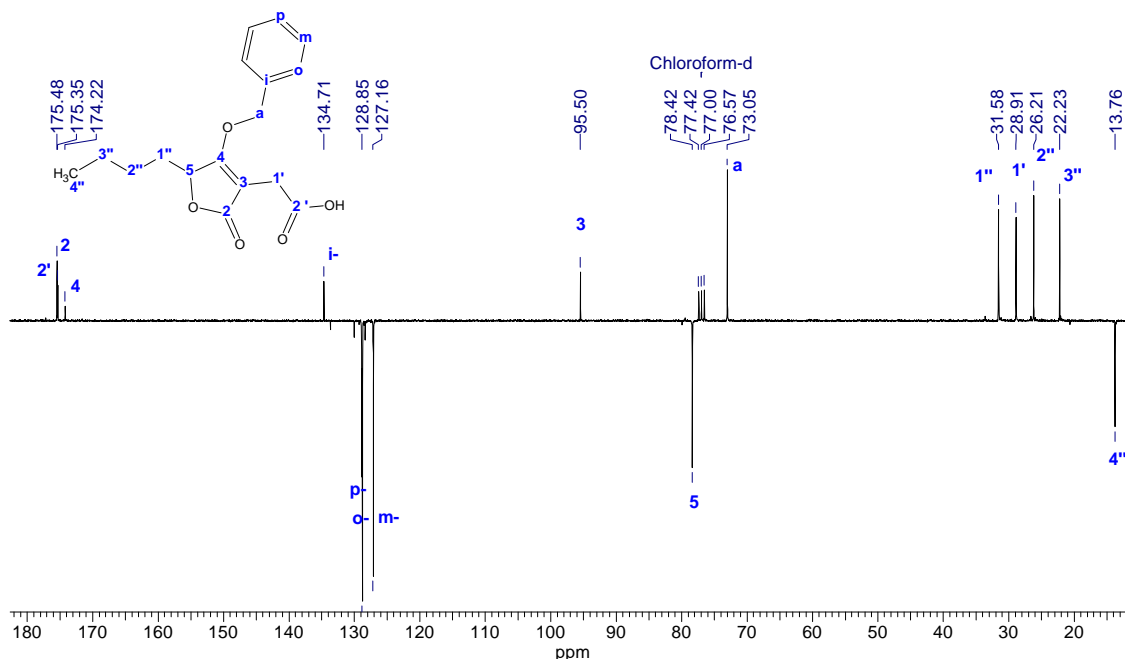
Figure 119.
75 MHz ^{13}C-NMR spectrum of Jones' oxidation product **111b** in CDCl$_3$. Derivative **111a** was a more polar compound and it was dissolved in deuterated acetone for the NMR experiments.

The existence of the carboxylic function into the molecule converts derivative **111** into a more reactive starting material for the lactonization reaction. When debenzylating **111** under normal hydrogenation conditions, the expected ring closure or free tetronic acid bearing the carboxylic moiety were not detected or at least the spectral information from the products formed was not totally determined. The reaction formed two different compounds with similar NMR spectra. Their structures were not determined due to ambiguities in the signal assignment.

The formation of the second lactone ring was attempted in the carboxyl tetronic acids **111b**. For this lactonization between a carboxylic acid and a benzyl protected "alcohol" the methodology reported by *Jacobi et al*. was tried.[84f,157] Although the cleavage of benzyl ethers with P$_4$S$_{10}$ does not appear to be a general reaction, this reagent works well with carboxylic acids where intramolecular participation is possible. Unfortunately no products were detected despite several attempts at the reaction.
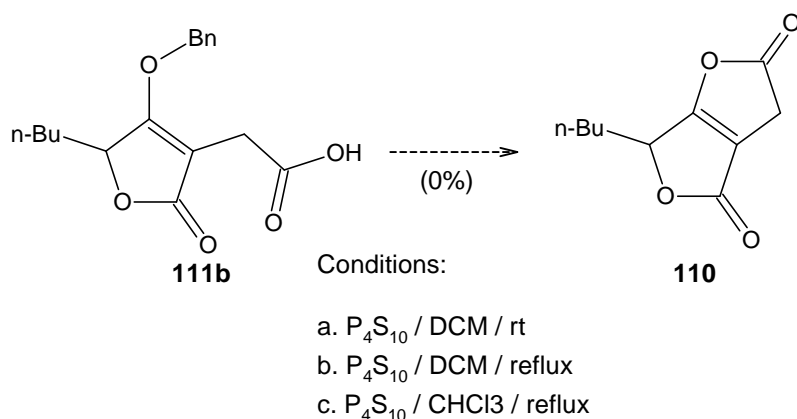
Figure 120.
The P_4S_{10} reaction of benzyl ethers with carboxylic acids is a method for the synthesis of lactones. The reaction depicted did not give the desired product probably because the 4-*O*-benzyl protected tetronic acid is not an ether but a pseudo-ester.

In order to form the bislactone system, the attention was focussed on the hydrogenation of the double bond in the tetronic acid derivative **111b** and the posterior cyclisation according to the information reported by *Strawson et al.*[132]. Benzyl tetronic acid **111b** was reacted with *O*-ethyl isourea in order to form the corresponding ethyl ester of the carboxylic acid **112**. After debenzylation of **112** with hydrogen in presence of palladium (5%) on charcoal, the tetronic acid **106b** was recovered almost quantitatively. Unfortunately loss of material occurred during the purification.
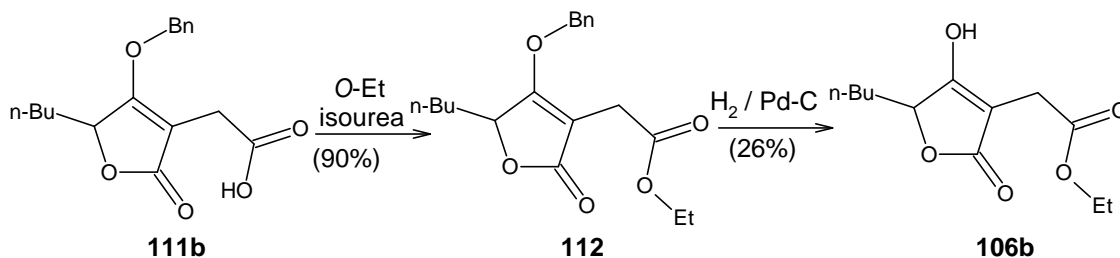
Figure 121.
The *O*-Ethyl isourea was used to form the ethyl ester **112**. Posterior debenzylation afforded the tetronic acid **106b**.

The methyl ester analogue to **106b** was previously prepared by *Schlessinger et al.*[158] who mentioned its use as potential synthon of canadensolide. The use of reductive conditions as reported by *Strawson et al.*[132] turn the tetronic acid moiety into the corresponding hydroxybutenolide derivative. The ring closure is then possible since no potential problems exist. The acidity of the system decreases as well since there is no keto-enol tautomeric equilibrium. The use of hydroxybutenolides in the synthesis of bisfuranones is one of the accesses reported in the synthesis of canadensolide and related natural products. [152,153]
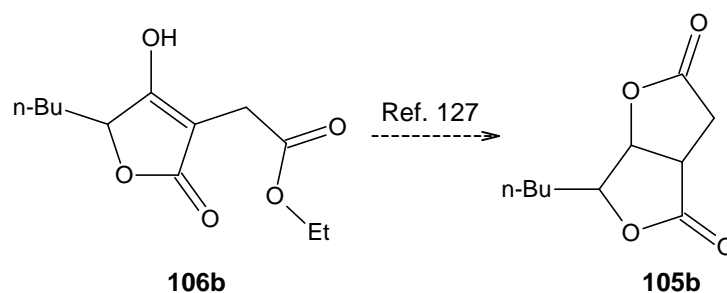
Figure 122.
The reductive conditions reported the formation of the correspondent hydroxybutenolide as reaction intermediate. This also helps with the stretching-bond problem during the formation of the bisfuranone **105**.

This can be considered as a potential formal synthesis of the bisfuranone **105b**. During the attempted synthesis of this system, it was found the tetronic acid did not form the unsaturated bis-furanone in spite of all the attempts tried. The easy access to the bisfuranone **105** is through a direct lactonization from the 4-hydroxybutanolide product.

Chapter 3
Experimental Section

NMR – spectra were recorded on a *Bruker AM – 300* (300.13 MHz for ^{1}H-NMR and 75.48 MHz for ^{13}C – NMR) spectrometer with solutions in $CDCl_3$ or acetone-d6 with TMS as internal standard (0 ppm). Peak assignments were aided by DQF-COSY ^{1}H-^{1}H and GS-HSQC ^{1}H-^{13}C correlation experiments. All coupling constants are quoted in Hertz (Hz).

IR – Spectra were recorded on a *Perkin – Elmer Spectrum One* spectrometer with an additional *ATR cell*. Intensities were automatically determined using ACD/SpecViewer v.4.53 (Advanced Chemistry Development Inc.) with relative intensity intervals (% of maximum height) as Very Weak (VW) 0% - 10%, Weak (W) 10% - 30%, Medium (M) 30% - 60%, Strong (S) 60% - 90% and Very Strong (VS) 90% - 100%.

Mass – spectra were recorded under EI conditions (70 eV) with previous gas chromatographic analysis on a *Finnigan MAT – 8500* spectrometer coupled with a *Hewlett Packard 5890 Series II* GC unit.

Microwave experiments were performed using a mono – mode *CEM Discover Microwave* (ν = 2450 MHz, 0 = P = 300 Watt) controlled by an IBM computer. The temperature of the reagents was measured by infrared pyrometry and the power of the magnetron was automatically controlled to maintain the set temperature. The reactor (borosilicate glass) had the following dimensions: inside diameter 15 mm; glass thickness 1.2 mm; maximum content 7 mL.

Ozonolysis was done employing a Fischer OZON *Generator 500.*

Melting points were recorded using an *Electrothermal 9100* apparatus and are uncorrected.

Analytical gas chromatography was performed using a *Packard United Technologies Gas Chromatograph* Model 438S with DB – 5 silica column (30 m length and 0.32 mm diameter - J&W Scientific) 80°C injection port, 3°C / min to 280°C coupled to a Shimadzu C-R3A as integrator.

Optical rotation values were detemined using a 10 cm cell (volume 1 mL) in a *Perkin Elmer Polarimeter model 341*.

Column chromatography was realized using Merck silica gel 60, particle size 0.063 – 0.2 mm (70 – 230 mesh).

Preparative TLC was performed on 20cm x 20cm glass plates previously covered with Merck Silica Gel 60 F 254.

Thin layer chromatography (TLC in SiO_2 plates: POLYGRAM® SIL G/UV$_{254}$) was visualized with UV light (254 nm) and by heating after spraying with an aqueous developing solution (100 mL) of 1 g $CeSO_4$, 6 mL conc. H_2SO_4 and 2.5 g $12MoO_3$-H_3PO_4-H_2O.

The solvents THF, toluene, benzene and diethyl ether were purified by distillation after refluxing them over sodium under an argon atmosphere; for methylenchloride CaH_2 was used. For methanol and ethanol, Mg turnings (2.5 g in 500 mL) were used. Ethyl acetate was dried over P_2O_5.

Annotation:

The numbering of the atoms DOES NOT correspond to the numbers given by the CAS nomenclature in order to have an unequivocal assignment and easier comparison of the ^{13}C NMR signals.

Original spectral data files obtained during the development of this dissertation are property of the University of Bayreuth – Chair of Organic Chemistry.

Most of the data contained in the experimental part was obtained with spectrometers coupled to a computer belonging to the University of Bayreuth. The opportunity of having access to the original spectral data files will be of use to future chemists.

For access to *.dx copies of ^{1}H, ^{13}C, IR spectra and *.ms2 copies of MS and /or GC-MS spectra, as well as for the names of the original files, please contact me at jmurbina@gmail.com. Once you know the name of the original file please contact Frau Kerstin Hannemann for original NMR-Bruker fid, acqu, acqus and ser files (1D and 2D). For original *.dat MS and / or GC-MS files, please contact our Central Analytics at the University of Bayreuth.

3.1 Synthesis of **a**-hydroxy acids

a-Hydroxybutanoic acid (32b)

General experimental procedure:

30 g (19.45 mL, 179 mmol) of α-bromobutyric acid were added dropwise to a magnetically stirred cold solution (ice-bath, <5°C) of $NaHCO_3$ 1M (prepared from 50.8g $NaHCO_3$ dissolved in 605 mL of water). When the addition of the bromoacid was completed, the mixture was heated under reflux for 6 hours. Afterwards the reaction mixture was cooled with an ice bath. Then 16.1 mL of H_2SO_4 conc. was added to the stirred mixture until a pH = 1 was reached. The reaction mixture was exhaustively extracted with CH_2Cl_2 (100 mL x 6). The organic layers were

dried over Na_2SO_4 overnight. The organic layer was then being filtered and rotary evaporated until all the solvent was removed. The product then initially appears as oil and it was crystallized shaking it in cold *n*-hexane; the white crystals formed (hygroscopic) were stored in a dessicator.

Yield: 82% (15.28 g, 147 mmol). R_f (SiO_2) = 0.13 (*n*-hexane : ethyl acetate + acetic acid 5%, 4 : 1, v : v). m.p. = 52°C.

Molecular Formula = $C_4H_8O_3$

Formula Weight = 104.105
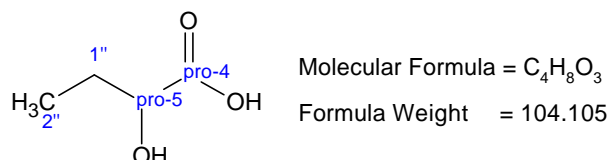
IR (ATR) $\bar{v}$ (cm^{-1}) = 3182 (M) [v (O-H)], 2973 (S) [v (-CH$_2$-)], 2940 (M) [v (-CH$_2$-)], 2883 (M) [v (-CH$_2$-)], 2642 (W) [v (O-H) intermolecular bridge], 1715 (VS) [v (C=O)], 1211 (M) [v (C-O-C)], 1124 (S) [v (C-O)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) $\mathbf{d}$ (ppm) = 0.91 (t, $^3J_{HH}$ = 7.48 Hz, 3H, 2''-H), 1.58 – 1.76 (m, 1H, 1''-H), 1.73 – 1.89 (m, 1H, 1''-H), 4.18 (dd, $^3J_{HH}$ = 7.00 Hz, $^3J_{HH}$ = 4.53 Hz, 1H, pro-5-H), 7.70 (br. s., 1H, O-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) $\mathbf{d}$ (ppm) = 8.74 (CH$_3$, 2''-C), 26.86 (CH$_2$, 1''-C), 71.25 (CH, pro-5-C), 178.36 (C^q, pro-4-C).

$\mathbf{a}$-Hydroxyhexanoic acid (32c)

White crystals (6.1 g, 46 mmol, 95%) from 10 g (7.3 mL, 51.2 mmol) of α-bromocaproic acid dissolved in a NaHCO$_3$ 1M solution (14.5 g of NaHCO$_3$ in 173 mL of water) initially refluxed for 6 hours and posterior treatment with 4.6 mL of H_2SO_4 to reach pH = 1.

R_f (SiO_2) = 0.13 (*n*-hexane : ethyl acetate + acetic acid 5%, 4 : 1, v : v). m.p. = 61°C.

Molecular formula = $C_6H_{12}O_3$

Molecular Weight = 132.158
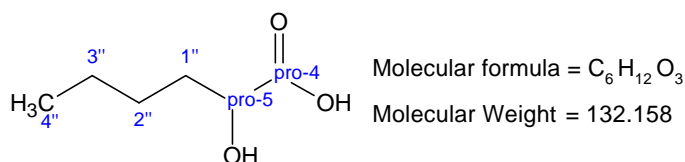
IR (ATR) $\bar{v}$ (cm^{-1}) = 3450 (M) [v (O-H) acid], 3395 (M) [v (O-H) alcohol], 2958 (M) [v (-CH$_2$-)], 2625 (W) and 2570 (W) [v (O-H) intermolecular bridge], 1708 (VS) [v (C=O)], 1206 (S) [v (C-O-C)], 1082 (VS) [v (C-O)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) $\mathbf{d}$ (ppm) = 0.88 (t, $^3J_{HH}$ = 7.11 Hz, 3H, 4''-H), 1.23 – 1.48 (m, 4H, 3''-H and 2''-H), 1.58 – 1.74 (m, 1H, 1''-H), 1.74 – 1.89 (m, 1H, 1''-H), 4.25 (dd, $^3J_{HH}$ = 7.58 Hz, $^3J_{HH}$ = 4.30 Hz, 1H, pro-5-H), 7.40 (br. s., 1H, O-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.78 (CH$_3$, 4''-C), 22.27 (CH$_2$, 3''-C), 26.80 (CH$_2$, 2''-C), 33.71 (CH$_2$, 1''-C), 70.29 (CH, pro-5-C), 179.58 (C^q, pro-4-C).

MS (direct inlet, EI, 70 eV) m/z (%) = 132 (1) [M$^+$], 114 (1) [M-H$_2$O]$^+$, 87 (45) [M-CO$_2$]$^+$, 76 (16) [M-C$_4$H$_9$]$^+$, 69 (100) [M$_{87}$-H$_2$O]$^+$, 57 (25) [C$_4$H$_9$$^+$], 45 (33) [M$_{114}$-69]$^+$, 39 (34) [M$_{114}$-76]$^+$.

a-Hydroxyoctanoic acid (32d)

White crystals (21.85 g, 136.4 mmol, 98%) from 31.06 g (19.45 mL, 0.139 mol) of α-brom octanoic acid dissolved in a NaHCO$_3$ 1M solution (23 g of NaHCO$_3$ in 274 mL of water) initially refluxed for 6 hours and posterior treatment with 7.46 mL of H$_2$SO$_4$ to reach pH = 1. R_f (SiO$_2$) = 0.83 (ethyl acetate + acetic acid 5%). m.p. = 70°C.

Molecular formula = C$_8$H$_{16}$O$_3$
Molecular Weight = 160.211

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3449 (M) [ν (O-H) acid], 3390 (M) [ν (O-H) alcohol], 2958 (M) [ν (-CH$_2$-)], 2919 (M) [ν (-CH$_2$-)], 2562 (W) [ν (O-H) intermolecular bridge], 1706 (VS) [ν (C=O)], 1085 (S) [ν (C-O-C)], 915 (S) [ν (C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.86 (t, $^3J_{HH}$ = 7.00 Hz, 3H, 6''-H), 1.21 – 1.35 (m, 6H, 5''-H and 4''-H and 3''-H), 1.36 – 1.47 (m, 2H, 2''-H), 1.60 – 1.74 (m, 1H, 1''-H), 1.76 – 1.89 (m, 1H, 1''-H), 4.26 (dd, $^3J_{HH}$ = 7.55 Hz, $^3J_{HH}$ = 4.26 Hz, 1H, pro-5-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 14.02 (CH$_3$, 6''-C), 22.54 (CH$_2$, 5''-C), 24.67 (CH$_2$, 4''-C), 28.89 (CH$_2$, 3''-C), 31.59 (CH$_2$, 2''-C), 34.16 (CH$_2$, 1''-C), 70.29 (CH, pro-5-C), 180.08 (C^q, pro-4-C).

MS (direct inlet, EI, 70 eV) m/z (%) = 161 (1) [M+H]$^+$, 142 (1) [M-H$_2$O]$^+$, 115 (31) [(M-H)-CO$_2$]$^+$, 97 (52) [M$_{115}$-H$_2$O]$^+$, 76 (19) [(M-H)-C$_6$H$_{13}$]$^+$, 55 (100) [C$_4$H$_7$$^+$], 43 (40) [C$_3H_7$$^+$], 41 (33) [C$_3H_5$$^+$].

3.2 Synthesis of a-hydroxy esters

(S)-Allyl lactate (34a) [25]

General experimental procedure:

In a 250 mL round bottom flask, 5.0 g (55 mmol) of (*S*)-lactic acid (acid contains about 20% water inside) were dissolved in 200 mL of benzene and 5 drops of concentrated sulphuric acid

were added to the remaining solution as catalyst. A Dean – Stark apparatus was connected to trap the water by azeotropic distillation (5 hours). After the water was collected, 150 mL of benzene were distilled. The reaction mixture was cooled down to room temperature and 10.65 g (12.5 mL, 183 mmol) of allyl alcohol were added. Then the mixture was heated under reflux for 20 hours. The reaction flask was cooled to room temperature and the reaction mixture was extracted with diethyl ether from a sodium bicarbonate solution (pH = 10) (4 x 50 mL) and the combined organic layers were dried over sodium sulphate. The solvent was removed by rotary evaporation and the resulting residue was purified by distillation under reduced pressure. The pure product appeared as a colourless oil.

Yield: 50% (3.58 g, 27.5 mmol). R_f (SiO$_2$) = 0.46 (*n*-hexane : diethyl ether, 2 : 3, v : v). b.p. = 60°C / 8 mmHg – Kugelrohr.
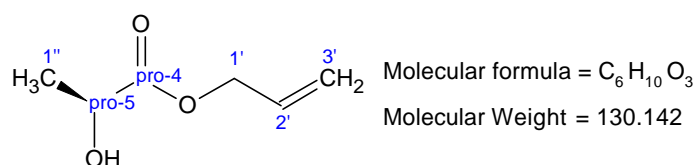
Molecular formula = $C_6H_{10}O_3$
Molecular Weight = 130.142

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3440 (W) [ν (O-H)], 2987 (W) [ν (-CH$_2$-)], 2942 (W) [ν (-CH$_2$-)], 1735 (S) [ν (C=O)], 1201 (S), 1123 (VS) [ν (C-O)], 1043 (M) [ν (C-O-C)], 924 (S) [ν (C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 1.34 (dd, $^3J_{HH}$ = 6.86 Hz, 3H, 1''-H), 4.23 (q, $^3J_{HH}$ = 6.86 Hz, 1H, pro-5-H), 4.57 (dt, $^3J_{HH}$ = 5.77 Hz, $^4J_{HH}$ = 1.24 Hz, 2H, 1'-H), 5.17 (dq, $^3J_{HH}$ = 10.56 Hz, $^4J_{HH}$ = 1.24 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 5.24 (dq, $^3J_{HH}$ = 17.16 Hz, $^4J_{HH}$ = 1.24 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{trans}$), 5.85 (ddt, $^3J_{HH}$ = 5.77 Hz, $^3J_{HH}$ = 10.56 Hz, $^3J_{HH}$ = 17.16 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 20.16 (CH$_3$, 1''-C), 65.79 (CH$_2$, 1'-C), 66.62 (CH, pro-5-C), 118.60 (CH$_2$, 3'-C), 131.39 (CH, 2'-C), 175.17 (C^q, pro-4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 131 (2) [M+H]$^+$, 130 (2) [M]$^+$, 115 (29) [M-CH$_3$]$^+$, 112 (13) [M-H$_2$O]$^+$, 86 (20) [M-C$_2$H$_5$O]$^+$, 57 (46) [C$_3$H$_5$O$^+$], 45 (100) [C$_2$H$_5$O$^+$], 43 (39) [C$_3$H$_7^+$].

2-(*S*)-Hydroxypropionic acid 1-methyl allyl ester (34b)

Colourless oil (1.50 g, 10.4 mmol, 38%) from 3.15 g (27.7 mmol) of (*S*)-lactic acid and 3.9 g (110 mmol) of methyl allyl carbinol dissolved in 150 mL of benzene using 0.31 g (1.8 mmol) of APTS as catalyst, refluxing for 1 day.

R_f (SiO$_2$) = 0.52 (*n*-hexane : diethyl ether, 2 : 3, v : v). b.p. = 55°C/8 mmHg.
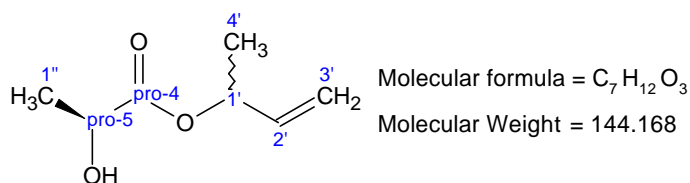
Mixture of diastereoisomers α *and* β. *Ratio* α: β = 1 : 1.

IR (ATR) $\bar{v}$ **(cm^{-1})** = 3465 (W) [ν (O-H)], 2985 (W) [ν (-CH$_2$-)], 1730 (S) [ν (C=O)], 1207 (S) [ν (C-O)], 1126 (VS) [ν (C-O)], 1041 (S) [ν (C-O)], 990 (M) [ν (=C-H)], 936 (S) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 1.302 (d, $^3J_{HH}$ = 6.45 Hz, 3H, 4'-H$^\alpha$), 1.305 (d, $^3J_{HH}$ = 6.58 Hz, 3H, 4'-H$^\beta$), 1.37 (d, 6H, 1''-H), 2.96 (br. s., 2H, O-H), 4.217 (q, $^3J_{HH}$ = 6.86 Hz, 1H, pro-5-H$^\alpha$), 4.222 (q, $^3J_{HH}$ = 6.86 Hz, 1H, pro-5-H$^\beta$), 5.125 (qu, $^3J_{HH}$ = 10.57 Hz, $^4J_{HH}$ = 1.10 Hz, $^2J_{HH}$ = 1.24 Hz, 2H, 3'-H$_{cis}$), 5.220 (qu, $^3J_{HH}$ = 17.29 Hz, $^4J_{HH}$ = 1.10 Hz, $^2J_{HH}$ = 1.24 Hz, 2H, 3'-H$_{trans}$), 5.37 (dq, $^3J_{HH}$ = 6.45 Hz, $^3J_{HH}$ = 6.58 Hz, $^3J_{HH}$ = 3.98 Hz, $^3J_{HH}$ = 7.96 Hz, 2H, 1'-H), 5.797 (ddd, $^3J_{HH}$ = 3.98 Hz, $^3J_{HH}$ = 10.57 Hz, $^3J_{HH}$ = 17.29 Hz, 1H, 2'-H$^\alpha$), 5.799 (ddd, $^3J_{HH}$ = 7.96 Hz, $^3J_{HH}$ = 10.57 Hz, $^3J_{HH}$ = 17.29 Hz, 1H, 2'-H$^\beta$).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = (*NB: **a** and **b** isomers assignation was tentative due to a low resolution in the HSQC spectra*) 19.76 (CH$_3$, 4'-C$^\alpha$), 19.82 (CH$_3$, 4'-C$^\beta$), 20.28 (CH$_3$, 1''-C$^\alpha$), 20.33 (CH$_3$, 1''-C$^\beta$), 66.73 (CH, pro-5-C), 72.27 (CH, 1'-C$^\alpha$), 72.45 (CH, 1'-C$^\beta$), 116.25 (CH$_2$, 3'-C$^\alpha$), 116.47 (CH$_2$, 3'-C$^\beta$), 136.86 (CH, 2'-C$^\alpha$), 136.93 (CH, 2'-C$^\beta$), 174.95 (C^q, pro-4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 144 (1) [M$^+$], 129 (3) [M-CH$_3$]$^+$, 126 (3) [M-H$_2$O]$^+$, 111 (8) [M$_{126}$-CH$_3$]$^+$, 99 (29) [M-C$_2$H$_5$O]$^+$, 89 (17) [M-C$_4$H$_7$]$^+$, 55 (98) [C$_4$H$_7$$^+$], 45 (100) [C$_2H_5O^+$].

2-Hydroxybutanoic acid allyl ester (34c)

General experimental procedure:

A solution of of 2-hydroxybutanoic acid **32b** (10.66 g, 101.3 mmol) and *O*-allyl isourea **36b** (26.79 g, 101.3 mmol) in 400 mL dry THF was stirred for 16 hours at 60°C under argon atmosphere. The N,N'-dicyclohexylurea formed during the reaction was separated out by filtration and the product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (9/1) as eluent. Afterwards the product was distilled at 80°C and 7 mmHg. The product appeared as a colourless oil.

Yield: 73% (10.22 g, 70.9 mmol). R_f (SiO$_2$) = 0.46 (*n*-hexane : diethyl ether, 2 : 3, v : v). b.p. = 80°C / 7 mmHg – Kugelrohr.

Molecular formula = $C_7H_{12}O_3$
Molecular Weight = 144.168

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3474 (W) [ν (O-H)], 2969 (W) [ν (-CH$_2$-)], 2939 (W) [ν (-CH$_2$-)], 1732 (VS) [ν (C=O)], 1198 (S) [ν (C-O-C)], 1128 (VS) [ν (C-O)], 991 (S) [ν (=C-H)], 932 (S) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.91 (t, $^3J_{HH}$ = 7.48 Hz, 3H, 2''-H), 1.56 - 1.74 (m, 1H, 1''-H), 1.70 - 1.88 (m, 1H, 1''-H), 2.96 (br. s., 1H, O-H), 4.13 (dd, $^3J_{HH}$ = 6.68 Hz, $^3J_{HH}$ = 4.60 Hz, 1H, pro-5-H), 4.62 (d, $^3J_{HH}$ = 5.77 Hz, 2H, 1'-H), 5.21 (dt, $^3J_{HH}$ = 10.43 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 5.28 (dd, $^3J_{HH}$ = 17.25 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{trans}$), 5.87 (ddt, $^3J_{HH}$ = 5.77 Hz, $^3J_{HH}$ = 10.43 Hz, $^3J_{HH}$ = 17.15 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 8.82 (CH$_3$, 2''-C), 27.39 (CH$_2$, 1''-C), 65.90 (CH$_2$, 1'-C), 71.35 (CH, pro-5-C), 118.85 (CH$_2$, 3'-C), 131.42 (CH, 2'-C), 174.78 (C^q, pro-4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 145 (5) [M+H]$^+$, 126 (2) [M-H$_2$O]$^+$, 115 (8) [M-C$_2$H$_5$]$^+$, 86 (3) [M-C$_3$H$_7$O]$^+$, 70 (21) [M$_{126}$-C$_3$H$_5$O]$^+$, 59 (100) [C$_3$H$_7$O$^+$], 57 (41) [C$_3$H$_5$O$^+$], 41 (95) [C$_3$H$_7^+$].

2-Hydroxyhexanonic acid allyl ester (34d)

Colourless oil (6.95 g, 40.4 mmol, 97%) from 5.50 g (41.6 mmol) of 2-hydroxyhexanoic acid **32c** and 11.00 g (41.6 mmol) of *O*-allyl isourea **36b** dissolved in 250 mL of dry THF, stirring and refluxing for 16 h under argon atmosphere. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (95/5) mixture as eluent.

R_f (SiO$_2$) = 0.77 (*n*-hexane : diethyl ether, 2 : 3, v : v). b.p. = 80°C / 7 mmHg – Kugelrohr.

Molecular formula = $C_9H_{16}O_3$
Molecular Weight = 172.222

IR (KBr) $\bar{\nu}$ **(cm^{-1})** = 3471 (M) [ν (O-H)], 2958 (S) [ν (-CH$_2$-)], 2869 (S) [ν (-CH$_2$-)], 1743 (VS) [ν (C=O)], 1133 (S) [ν (C-O-C)], 1084 (S) [ν (C-O)], 988 (S) [ν (=C-H)], 932 (M) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.89 (t, $^3J_{HH}$ = 7.08 Hz, 3H, 4''-H), 1.25 - 1.50 (m, 4H, 2''-H and 3''-H), 1.55 - 1.70 (m, 1H, 1''-H), 1.70 - 1.87 (m, 1H, 1''-H), 2.62 (br. s., 1H, O-H), 4.19 (dd, $^3J_{HH}$ = 5.08 Hz, $^3J_{HH}$ = 4.25 Hz, 1H, pro-5-H), 4.67 (d, $^3J_{HH}$ = 5.81 Hz,

2H, 1'-H), 5.28 (dt, $^3J_{HH}$ = 10.39 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 5.35 (dd, $^3J_{HH}$ = 17.25 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{trans}$), 5.93 (ddt, $^3J_{HH}$ = 5.81 Hz, $^3J_{HH}$ = 10.39 Hz, $^3J_{HH}$ = 17.25 Hz, 1H, 2'-H).
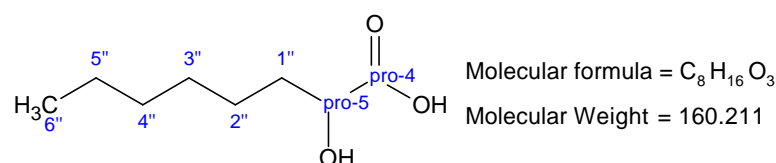
^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.89 (CH$_3$, 4''-C), 22.37 (CH$_2$, 3''-C), 26.84 (CH$_2$, 2''-C), 34.11 (CH$_2$, 1''-C), 66.08 (CH$_2$, 1'-C), 70.46 (CH, pro-5-C), 119.01 (CH$_2$, 3'-C), 131.47 (CH, 2'-C), 175.13 (C^q, pro-4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 173 (8) [M+H]$^+$, 154 (3) [M-H$_2$O]$^+$, 127 (14) [M-C$_2$H$_3$]$^+$, 115 (3) [M-C$_4$H$_9$]$^+$, 87 (88) [M$_{115}$-CO]$^+$, 69 (100) [M$_{127}$-C$_4$H$_9$]$^+$, 57 (28) [C$_4$H$_9^+$], 43 (34) [C$_3$H$_7^+$].

(2*E,Z*)-But-2-enyl 2-hydroxyhexanoate (34e)

Colourless oil (16.70 g, 89.6 mmol, 98%) from 11.89 g (90 mmol) of 2-hydroxyhexanoic acid **32c** and 25.00 g (90 mmol) of *O*-(2-butenyl) isourea **36d** dissolved in 250 mL of dry THF, stirring and refluxing for 16 h under argon atmosphere. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (gradient from mixture 95/5 to only diethyl ether) as eluent.

R_f (SiO$_2$) = 0.76 (*n*-hexane : diethyl ether, 2 : 3, v : v).

Molecular formula = C$_{10}$H$_{18}$O$_3$
Molecular Weight = 186.248

IR (KBr) $\bar{\nu}$ (cm^{-1}) = 3484 (M) [ν (O-H)], 2954 (S) [ν (-CH$_2$-)], 2865 (S) [ν (-CH$_2$-)], 1735 (VS) [ν (C=O)], 1454 (M), 1202 (S), 1134 (M) [ν (C-O-C)], 1083 (S) [ν (C-O)], 968 (S) [ν (=C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.79 (t, $^3J_{HH}$ = 7.14 Hz, 3H, 4''-H), 1.15 - 1.38 (m, 4H, 2''-H and 3''-H), 1.45 - 1.75 (m, 2H, 1''-H), 1.65 (d, $^3J_{HH}$ = 6.48 Hz, 3H, 4'-H), 3.11 (br. s., 1H, O-H), 4.07 (dd, $^3J_{HH}$ = 6.70 Hz, $^3J_{HH}$ = 4.39 Hz, 1H, pro-5-H), 4.49 (d, $^3J_{HH}$ = 6.55 Hz, 2H, 1'-H), 5.41 – 5.53 (m, 1H, 2'-H), 5.63 – 5.77 (m, 1H, 3'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.63 (CH$_3$, 4''-C), 17.43 (CH$_3$, 4'-C), 22.15 (CH$_2$, 3''-C), 26.68 (CH$_2$, 2''-C), 33.84 (CH$_2$, 1''-C), 65.77 (CH$_2$, 1'-C), 70.29 (CH, pro-5-C), 124.38 (CH, 2'-C), 131.79 (CH, 3'-C), 174.93 (C^q, pro-4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 186 (4) [M]$^+$, 168 (3) [M-H$_2$O]$^+$, 114 (9) [M-C$_4$H$_7$O]$^+$, 87 (77) [C$_5$H$_7$O$^+$], 69 (100) [M$_{87}$-H$_2$O]$^+$, 57 (34) [C$_4$H$_9^+$], 55 (81) [C$_4$H$_7^+$], 43 (37) [C$_3$H$_7^+$].

2-Hydroxyoctanoic acid allyl ester (34f)

Colourless oil (5.10 g, 25.4 mmol, 82%) from 5.00 g (31.2 mmol) of 2-hydroxyoctanoic acid **32d** and 8.25 g (31.2 mmol) of *O*-allyl isourea **36b** dissolved in 200 mL of dry THF, stirring and refluxing for 16 h under argon atmosphere. The product was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (4 / 1) mixture as eluent.

R_f (SiO_2) = 0.30 (*n*-hexane : diethyl ether, 4 : 1, v : v).

Molecular formula = $C_{11}H_{20}O_3$

Molecular Weight = 200.275

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3482 (W) [ν (O-H)], 2955 (M) [ν (-CH$_2$-)], 2927 (M) [ν (-CH$_2$-)], 2859 (M) [ν (-CH$_2$-)], 1734 (VS) [ν (C=O)], 1457 (M), 1130 (S) [ν (C-O-C)], 1088 (S) [ν (C-O)], 985 (S) [ν (=C-H)], 932 (S) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.82 (t, $^3J_{HH}$ = 7.00 Hz, 3H, 6''-H), 1.15 - 1.30 (m, 6H, 3''-H and 4''-H and 5''-H), 1.25 - 1.50 (m, 2H, 2''-H), 1.51 - 1.66 (m, 1H, 1''-H), 1.66 - 1.81 (m, 1H, 1''-H), 2.92 (d, $^3J_{HH}$ = 5.90 Hz, 1H, O-H), 4.16 (ddd, 1H, pro-5-H), 4.61 (ddt, $^3J_{HH}$ = 5.76 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.51 Hz, 2H, 1'-H), 5.21 (dt, $^3J_{HH}$ = 10.43 Hz, $^4J_{HH}$ = 1.51 Hz, $^2J_{HH}$ = 1.23 Hz, 1H, 3'-H$_{cis}$), 5.28 (dt, $^3J_{HH}$ = 17.29 Hz, $^4J_{HH}$ = 1.51 Hz, $^2J_{HH}$ = 1.23 Hz, 1H, 3'-H$_{trans}$), 5.87 (ddt, 1H, $^3J_{HH}$ = 5.76 Hz, $^3J_{HH}$ = 10.43 Hz, $^3J_{HH}$ = 17.29 Hz, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.91 (CH$_3$, 6''-C), 22.43 (CH$_2$, 5''-C), 24.59 (CH$_2$, 4''-C), 28.86 (CH$_2$, 3''-C), 31.54 (CH$_2$, 2''-C), 34.32 (CH$_2$, 1''-C), 65.88 (CH$_2$, 1'-C), 70.41 (CH, pro-5-C), 118.79 (CH$_2$, 3'-C), 131.45 (CH, 2'-C), 174.99 (C^q, pro-4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 200 (2) [M+H]$^+$, 182 (1) [M-H$_2$O]$^+$, 171 (7) [M-C$_2$H$_5$]$^+$, 115 (30) [M-C$_2$H$_5$O$_2$]$^+$, 97 (86) [M$_{115}$-H$_2$O]$^+$, 69 (25) [M$_{97}$-C$_2$H$_4$]$^+$, 55 (100) [C$_4$H$_7$]$^+$, 43 (40) [C$_3$H$_7^+$].

2-Hydroxyhexanoic acid benzyl ester (34g)[26,159]

Colourless oil (1.38 g, 6.2 mmol, 87%) from 0.94 g (7.1 mmol) of 2-hydroxyhexanoic acid **32c** and 2.24 g (7.1 mmol) of *O*-benzyl isourea **36e** dissolved in 50 mL of dry THF, stirring and refluxing for 19 h under argon atmosphere. The product was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (1 / 1) mixture as eluent.

R_f (SiO_2) = 0.56 (*n*-hexane : diethyl ether, 1 : 1, v : v).

Molecular formula = $C_{13}H_{18}O_3$
Molecular Weight = 222.280

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3478 (W) [ν (O-H)], 2957 (M) [ν (-CH$_2$-)], 1731 (S) [ν (C=O)], 1193 (S) [ν (C-O-C)], 1129 (S) [ν (C-O)], 1083 (S) [ν (C-O)], 749 (S) and 696 (VS) [ν (C-H arom. monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.87 (t, $^3J_{HH}$ = 7.35 Hz, 3H, 4''-H), 1.20 - 1.49 (m, 4H, 3''-H and 2''-H), 1.57 - 1.72 (m, 1H, 1''-H), 1.73 - 1.86 (m, 1H, 1''-H), 2.95 (d, $^3J_{HH}$ = 5.90 Hz, 1H, O-H), 4.21 (ddd, $^3J_{HH}$ = 7.27 Hz, $^3J_{HH}$ = 5.90 Hz, $^3J_{HH}$ = 4.25 Hz, 1H, pro-5-H), 5.17 (d, $^2J_{HH}$ = 12.21 Hz, 1H, 1'-H), 5.22 (d, $^2J_{HH}$ = 12.21 Hz, 1H, 1'-H), 7.30 – 7.37 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.79 (CH$_3$, 4''-C), 22.28 (CH$_2$, 3''-C), 26.71 (CH$_2$, 2''-C), 33.98 (CH$_2$, 1''-C), 67.09 (CH$_2$, 1'-C), 70.44 (CH, pro-5-C), 128.52 (CH, *ortho*-C), 128.22 (CH, *para*-C), 128.41 (CH, *meta*-C), 135.21 (C^q, *ipso*-C), 175.16 (C^q, pro-4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 223 (2) [M+H]$^+$, 204 (1) [M-H$_2$O]$^+$, 91 (100) [C$_7$H$_7^+$], 87 (38) [C$_5$H$_{11}$O$^+$], 77 (6) [C$_6$H$_5^+$], 69 (87) [C$_5$H$_9^+$], 65 (13) [C$_5$H$_5^+$], 41 (29) [C$_3$H$_5^+$].

2-Hydroxyoctanoic acid benzyl ester (34h)

Colourless oil (3.76 g, 15.0 mmol, 94%) from 2.55 g (15.9 mmol) of 2-hydroxyoctanoic acid **32d** and 5.00 g (15.9 mmol) of *O*-benzyl isourea **36e** dissolved in 150 mL of dry THF, stirring and refluxing for 19 h under argon atmosphere. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (2 / 3) mixture as eluent.

R_f (SiO$_2$) = 0.56 (*n*-hexane : diethyl ether, 1 : 1, v : v).

Molecular formula = $C_{15}H_{22}O_3$
Molecular Weight = 250.333

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3483 (W) [ν (O-H)], 2927 (M) [ν (-CH$_2$-)], 2958 (W) [ν (-CH$_2$-)], 1732 (S) [ν (C=O)], 1187 (S) [ν (C-O)], 1130 (S) [ν (C-O)], 749 (S) and 696 (VS) [ν (C-H arom. monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.86 (t, $^3J_{HH}$ = 7.13 Hz, 3H, 6''-H), 1.15 - 1.50 (m, 8H, 5''-4''-3'' and 2''-H), 1.56 - 1.71 (m, 1H, 1''-H), 1.71 - 1.86 (m, 1H, 1''-H), 2.86

(d, $^3J_{HH}$ = 5.76 Hz, 1H, O-H), 4.21 (ddd, $^3J_{HH}$ = 7.13 Hz, $^3J_{HH}$ = 5.76 Hz, $^3J_{HH}$ = 4.40 Hz, 1H, pro-5-H), 5.17 (d, $^2J_{HH}$ = 12.21 Hz, 1H, 1'-H), 5.22 (d, $^2J_{HH}$ = 12.21 Hz, 1H, 1'-H), 7.32 – 7.37 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.97 (CH$_3$, 6''-C), 22.45 (CH$_2$, 5''-C), 24.55 (CH$_2$, 4''-C), 28.88 (CH$_2$, 3''-C), 31.57 (CH$_2$, 2''-C), 34.33 (CH$_2$, 1''-C), 67.15 (CH$_2$, 1'-C), 70.48 (CH, pro-5-C), 128.27 (CH, *meta*-C), 128.46 (CH, *ortho*-C), 128.57 (CH, *para*-C), 135.22 (C^q, *ipso*-C), 175.21 (C^q, pro-4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 250 (2) [M$^+$], 115 (22) [C$_7$H$_{15}$O$^+$], 97 (59) [C$_7$H$_{13}^+$], 91 (100) [C$_7$H$_7^+$], 77 (4) [C$_6$H$_5^+$], 55 (90) [C$_4$H$_7^+$], 43 (20) [C$_3$H$_7^+$].

2-Mercaptopropionic acid benzyl ester (34i)

In a 250 mL round bottom flask 2.00 (18.8 mmol) of thiolactic acid were dissolved in 150 mL of dry dichloroethane; to the resulting solution were added 2.04 g (18.8 mmol) of benzyl alcohol dissolved in dry dichloroethane and 0.20 g (1.16 mmol) of APTS as catalyst. The reaction mixture was heated under reflux for 18 h collecting the water formed in a Dean-Stark apparatus. The reaction mixture was extracted from a NaHCO$_3$ solution (pH = 10) with ethyl acetate (3 x 100 mL). The organic layer was dried over Na$_2$SO$_4$ and the product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (4/1) as eluent. Afterwards the product was distilled under reduced pressure. The product appeared as a colourless oil.

Yield: 71% (2.63 g, 13.4 mmol). R_f (SiO$_2$) = 0.57 (*n*-hexane : diethyl ether, 4 : 1, v : v). b.p. = 110°C / 8 mmHg.

Molecular formula = C$_{10}$H$_{12}$O$_2$S
Molecular Weight = 196.267

IR (ATR) $\bar{v}$ (cm^{-1}) = 3034 (VW) [ν (=C-H)], 2979 (VW) [ν (-CH$_2$-)], 2567 (VW) [ν (S-H)], 1731 (VS) [ν (C=O)], 1162 (VS) [ν (C-O-C)], 1060 (M) [ν (C-O)], 736 (S) and 695 (VS) [ν (C-H) aromatic monosubstituted].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 1.53 (d, $^3J_{HH}$ = 7.04 Hz, 3H, 1''-H), 2.16 (d, $^3J_{HH}$ = 8.36 Hz, 1H, S-H), 3.54 (dq, $^3J_{HH}$ = 7.04 Hz, $^3J_{HH}$ = 8.36 Hz, 1H, pro-5-H), 5.16 (d, $^4J_{HH}$ = 1.00 Hz, 2H, 1'-H), 7.25 - 7.40 (m, 5H, aromatic protons).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 20.99 (CH$_3$, 1''-C), 35.64 (CH, pro-5-C), 67.00 (CH$_2$, 1'-C), 128.07 (CH, *ortho*-C), 128.29 (CH, *meta*-C), 128.53 (CH, *para*-C), 135.48 (C^q, ipso-C), 173.37 (C^q, pro-4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 196 (4) [M$^+$], 164 (6) [M-S]$^+$, 123 (53), 108 (20) [$C_7H_7O^+$], 91 (100) [$C_7H_7^+$], 77 (9) [$C_6H_5^+$], 65 (18) [$C_5H_5^+$], 61 (22) [$C_2H_5S^+$].

3.3 Synthesis of *O*-Alkyl-N,N'-dicyclohexylisoureas

O-Ethyl-N,N'-dicyclohexylisourea (36a) [160]

General experimental procedure:

In a round bottom flask 2.23 g (48.4 mmol) of dry ethyl alcohol are added to 10.00 g (48.5 mmol) of DCC under argon; 0.04 g of CuCl$_2$ are added as a catalyst. The mixture was stirred at 40°C until the imide band ($\bar{v}$ = 2119 cm^{-1}) disappeared in IR (after 24 h). The crude product was previously purified from the cupper salts and secondary compounds in an Al$_2$O$_3$ wet column using *n*-hexane / diethyl ether (9/1) as eluent. The separation of the pure product was made using Kugelrohr distillation. The pure product appears as colourless oil. Yield: 70% (8.55 g, 33.9 mmol). R_f (SiO$_2$) = 0.72 (*n*-hexane : diethyl ether, v : v, 9 : 1). b.p. = 120 °C / 7 mmHg.

Molecular Formula = C$_{15}$H$_{28}$N$_2$O
Formula Weight = 252.396

IR (ATR) $\bar{v}$ **(cm^{-1})** = 3444 (VW) [ν (N-H)], 2976 (W) [ν (-CH$_2$-)], 2925 (S) [ν (-CH$_2$-)], 2852 (M) [ν (-CH$_2$-)], 1661 (VS) [ν (C=N)], 1314 (S) [ν (C-O-C)], 1063 (S) [ν (C-O)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.90 – 1.20 (m, 4H, 2-H$_{ax}$, 2'-H$_{ax}$), 1.10 – 1.40 (m, 6H, 3-H$_{ax}$, 3'-H$_{ax}$, 4-H$_{ax}$, 4'-H$_{ax}$), 1.17 (t, $^3J_{HH}$ = 7.08 Hz, 3H, 2''-H), 1.55 (m, 2H, 2'-H$_{eq}$), 1.60 – 1.80 (m, 6H, 3-H$_{eq}$, 3'-H$_{eq}$, 4-H$_{eq}$, 4'-H$_{eq}$), 1.86 (m, 2H, 2-H$_{eq}$), 2.71 (br. s., 1H, 1'-H$_{ax}$), 3.33 (m, 1H, 1-H$_{eq}$), 4.01 (q, $^3J_{HH}$ = 7.08 Hz, 2H, 1''-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 14.30 (CH$_3$, 2''-C), 24.93 (CH$_2$, 3'-C), 25.22 (CH$_2$, 3-C), 25.64 (CH$_2$, 4'-C), 25.91 (CH$_2$, 4-C), 34.29 (CH$_2$, 2-C), 34.46 (CH$_2$, 2'-C), 50.10 (CH, 1-C), 54.75 (CH, 1'-C), 60.45 (CH$_2$, 1''-C), 151.36 (C^q, 5-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 252 (20) [M$^+$], 237 (2) [M-CH$_3$]$^+$, 223 (14) [M-C$_2$H$_5$]$^+$, 209 (49) [M-C$_3$H$_7$]$^+$, 98 (100) [$C_6H_{10}NH_2^+$], 83 (54) [$C_6H_{11}^+$], 55 (65) [$C_4H_7^+$].

O-Allyl-N,N'-dicyclohexylisourea (36b)

Colourless oil (42.7 g, 161 mmol, 94%) from 10.0 g (172 mmol) of allyl alcohol and 35.0 g (172 mmol) of DCC; 0.04 g (0.29 mmol)of $CuCl_2$ were added as catalyst. The resulting mixture was heated at 60°C for 2d (controlled via IR). The product was purified by column chromatography on SiO_2 [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (10/1) to (5/1) gradient mixture as eluent.

R_f (SiO_2) = 0.42 (*n*-hexane : diethyl ether, 1 : 1, v : v).

Molecular Formula = $C_{16}H_{28}N_2O$
Formula Weight = 264.406

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3447 (VW) [ν (N-H)], 2924 (S) [ν (-CH_2-)], 1662 (VS) [ν (C=N)], 1311 (S) [ν (C-O-C)], 1055 (M) [ν (C-O)], 919 (M) [ν (=C-H allyl)], 887 (M) [ν (=CH_2)], 710 (W) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.95 – 1.38 (m, 10H, 2-H_{ax}, 2'-H_{ax}, 3-H_{ax}, 3'-H_{ax}, 4-H_{ax}, 4'-H_{ax}), 1.50 – 1.78 (m, 8H, 2'-H_{eq}, 3-H_{eq}, 3'-H_{eq}, 4-H_{eq}, 4'-H_{eq}), 1.83 – 1.97 (m, 2H, 2-H_{eq}), 2.70 (m, 1H, 1'-H_{ax}), 3.35 (m, 1H, 1-H_{ax}), 4.51 (dt, $^3J_{HH}$ = 5.35 Hz, $^4J_{HH}$ = 1.51 Hz, 2H, 1''-H), 5.11 (dq, $^3J_{HH}$ = 10.43 Hz, $^2J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.51 Hz, 1H, 3''-H_{cis}), 5.25 (dq, $^3J_{HH}$ = 17.29 Hz, $^2J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.51 Hz, 1H, 3''-H_{trans}), 5.91 (m, $^3J_{HH}$ = 5.35 Hz, $^3J_{HH}$ = 10.43 Hz, $^3J_{HH}$ = 17.29 Hz, 1H, 2''-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 25.67 (CH_2, 3'-C), 25.91 (CH_2, 3-C), 26.36 (CH_2, 4'-C), 26.65 (CH_2, 4-C), 34.37 (CH_2, 2-C), 34.43 (CH_2, 2'-C), 50.24 (CH, 1-C), 54.77 (CH, 1'-C), 65.51 (CH_2, 1''-C), 115.81 (CH_2, 3''-H), 134.11 (CH, 2''-C), 150.97 (C^q, 5-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 264 (7) [M^+], 221 (8) [M-C_3H_7]$^+$, 182 (27) [M-C_6H_{11}]$^+$, 167 (100) [M-$C_6H_{12}N$]$^+$, 139 (11) [M_{167}-CO]$^+$, 124 (11) [M_{182}-C_3H_5]$^+$, 98 (89) [$C_6H_{12}N^+$], 83 (37) [$C_6H_{11}^+$].

1,3-Dicyclohexyl-2-(2-methyl-allyl)-isourea (36c) [161]

Colourless oil (4.86 g, 17.4 mmol, 90%) from 1.40 g (19.4 mmol) of 2-methyl-2-propen-1-ol and 4.0 g (19.4 mmol) of DCC; 0.04 g (0.29 mmol) of $CuCl_2$ were added as catalyst. The

resulting mixture was stirred at rt for 1d (controlled via IR). The product was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (10/1) to (5/1) gradient mixture as eluent.

R_f (SiO$_2$) = 0.55 (*n*-hexane : diethyl ether, 2 : 3, v : v).

Molecular Formula = $C_{17}H_{30}N_2O$
Formula Weight = 278.432

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3443 (VW) [ν (N-H)], 3079 (VW) [ν (=C-H)], 2925 (S) [ν (-CH$_2$-)], 2852 (S) [ν (-CH$_2$-)], 1665 (VS) [ν (C=N)], 1449 (M) [ν (C-H)], 1316 (S) [ν (C-O-C)], 889 (S) [ν (=C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.05 (m, 2H, 2-H$_{ax}$), 1.24 (m, 2H, 2'-H$_{ax}$), 1.10 – 1.35 (m, 6H, 3-H$_{ax}$, 3'-H$_{ax}$, 4-H$_{ax}$, 4'-H$_{ax}$), 1.70 (m, 2H, 2'-H$_{eq}$), 1.50 – 1.75 (m, 6H, 3-H$_{eq}$, 3'-H$_{eq}$, 4-H$_{eq}$, 4'-H$_{eq}$), 1.74 (s, 3H, 4''-H), 1.91 (m, 2H, 2-H$_{eq}$), 2.74 (br. s., 1H, 1'-H$_{ax}$), 3.41 (m, 1H, 1-H$_{ax}$), 3.47 (br.s., 1H, N-H), 4.42 (s, 2H, 1''-H), 4.82 (s, 1H, 3''-H$_{cis}$), 4.94 (s, 1H, 3''-H$_{trans}$).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 19.72 (CH$_3$, 4''-C), 25.01 (CH$_2$, 3'-C), 25.25 (CH$_2$, 3-C), 25.67 (CH$_2$, 4'-C), 25.95 (CH$_2$, 4-C), 34.44 (CH$_2$, 2'-C, 2-C), 50.43 (CH, 1'-C), 54.85 (CH, 1-C), 68.09 (CH$_2$, 1''-C), 110.83 (CH$_2$, 3''-C), 141.70 (C^q, 2''-C), 151.09 (C^q, 5-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 278 (4) [M$^+$], 263 (1) [M-CH$_3$]$^+$, 181 (88) [M-C$_6$H$_{12}$N]$^+$, 110 (39) [M$_{181}$-C$_4$H$_7$O]$^+$, 98 (100) [C$_6$H$_{10}$NH$_2$$^{2+}$], 83 (54) [C$_6H_{11}$$^+$], 55 (92) [C$_4H_7$$^+$], 41 (48) [C$_3H_5$$^+$].

2-But-2-enyl-1,3-dicyclohexyl-isourea (36d)

Yellowish oil (25.16 g, 90.3 mmol, 65%) from 10.0 g (139 mmol) of crotyl alcohol and 28.0 g (136 mmol) of DCC; 0.04 g (0.29 mmol)of CuCl$_2$ were added as catalyst. The resulting mixture was stirred at 40°C for 2d (controlled via IR). The product was purified filtering the mixture in a small pad of Al$_2$O$_3$ using *n*-hexane / diethyl ether (2/3) mixture as eluent. The compound was unstable to be purified by column chromatography on SiO$_2$ as support.

IR (ATR) $\bar{v}$ **(cm^{-1})** = 3441 (W) [ν (N-H)], 2827 (S) [ν (-CH$_2$-)], 2853 (S) [ν (-CH$_2$-)], 1664 (VS) [ν (C=N)], 1448 (M) [ν (C-H)], 1318 (S) [ν (C-O-C)], 1034 (M) [ν (C-O)], 966 (W) [ν (=C-H)].

O-Benzyl-N,N'-dicyclohexylisourea (36e) [160]

Colourless oil (10.39 g, 33 mmol, 87%) from 4.10 g (38 mmol) of benzyl alcohol and 7.82 g (38 mmol) of DCC; 0.04 g (0.29 mmol)of CuCl$_2$ were added as catalyst. The resulting mixture was stirred at 60°C for 1d (controlled via IR). The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (10/1) to (5/1) gradient mixture as eluent.

R_f (SiO$_2$) = 0.30 (*n*-hexane : diethyl ether, 10 : 1, v : v).

IR (ATR) $\bar{v}$ **(cm^{-1})** = 3440 (VW) [ν (N-H)], 3032 (VW) [ν (=C-H)], 2928 (S) [ν (-CH$_2$-)], 2853 (M) [ν (-CH$_2$-)], 1665 (VS) [ν (C=N)], 1055 (M) [ν (C-O-C)], 734 (M) and 698 (S) [ν (C-H arom. monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.00 – 1.35 (m, 6H, 3-H$_{ax}$, 3'-H$_{ax}$, 4-H$_{ax}$, 4'-H$_{ax}$), 1.10 (m, 2H, 2-H$_{ax}$), 1.35 (m, 2H, 2'-H$_{ax}$), 1.80 (m, 2H, 2'-H$_{eq}$), 1.50 – 1.85 (m, 6H, 3-H$_{eq}$, 3'-H$_{eq}$, 4-H$_{eq}$, 4'-H$_{eq}$), 1.95 (m, 2H, 2-H$_{eq}$), 2.87 (br. s., 1H, 1'-H$_{ax}$), 3.47 (m, 1H, 1-H$_{ax}$), 3.58 (br. s., 1H, N-H), 5.16 (s, 2H, a-H), 7.20 – 7.35 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) $\mathbf{d}$ (ppm) = 25.05 (CH$_2$, 3'-C), 25.28 (CH$_2$, 3-C), 25.78 (CH$_2$, 4'-C), 26.15 (CH$_2$, 4-C), 34.53 (CH$_2$, 2-C), 34.60 (CH$_2$, 2'-C), 50.43 (CH, 1-C), 54.91 (CH, 1'-C), 66.54 (CH$_2$, 1''-C), 127.28 (CH, *para*-C), 127.52 (CH, *ortho*-C), 128.21 (CH, *meta*-C), 138.29 (C^q, *ipso*-C), 151.15 (C^q, 5-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 314 (11) [M$^+$], 223 (9) [M-C$_7$H$_7$]$^+$, 98 (100) [C$_6$H$_{10}$NH$_2^{+\cdot}$], 91 (94) [C$_7$H$_7^+$], 83 (21) [C$_6$H$_{11}^+$], 55 (29) [C$_4$H$_7^+$].

3.4 Synthesis of 4-*O*-Allyl tetronates

4-Allyloxy-5*H*-furan-2-one (51a) [26,39]

In a 250 mL round bottom flask were added 4.50 g (45 mmol) of tetronic acid and 5.22 g (90 mmol) of allyl alcohol to 150 mL of benzene. 5 drops of concentrated sulphuric acid were added to the remaining solution as catalyst. A Dean – Stark apparatus was connected and the water was separated out by azeotropic distillation after 15 hours (*NB: because of the low solubility of the tetronic acid, good to excellen yields were obtained when the tetronic acid was used as a fine powder in diluted benzene solutions – about 5 g in 100 mL – and the reaction mixture was effectively stirred during the experiment*). The reaction flask was cooled down to room temperature and the solvent was removed by rotary evaporation; the resulting residue was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent. The pure product appeared as a colourless oil.

Yield: 86% (5.42 g, 38.6 mmol). R_f (SiO$_2$) = 0.57 (diethyl ether).

Molecular formula = C$_7$H$_8$O$_3$

Molecular Weight = 140.137

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 1774 (S) [ν (C=C)], 1740 (S) and 1619 (VS) [ν (Tetronate ring)], 1315 (S) [ν (C-O)], 1047 (S) [ν (C-O-C)], 970 (S) [ν (=CH$_2$)], 880 (S) [ν (C-H allyl)], 800 (S) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) $\mathbf{d}$ (ppm) = 4.51 (dt, $^3J_{HH}$ = 5.70 Hz, $^4J_{HH}$ = 1.20 Hz, 2H, 1'-H), 4.58 (d, $^4J_{HH}$ = 1.20 Hz, 2H, 5-H), 5.04 (t, $^4J_{HH}$ = 1.20 Hz, 1H, 3-H), 5.31 (ddt, $^3J_{HH}$ = 10.50 Hz, $^4J_{HH}$ = 1.20 Hz, $^2J_{HH}$ = 1.50 Hz, 1H, 3'-H$_{cis}$), 5.36 (ddt, $^3J_{HH}$ = 17.40 Hz, $^4J_{HH}$ = 1.20 Hz, $^2J_{HH}$ = 1.50 Hz, 1H, 3'-H$_{trans}$), 5.91 (ddt, $^3J_{HH}$ = 5.70 Hz, $^3J_{HH}$ = 10.50 Hz, $^3J_{HH}$ = 17.40 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 67.70 (CH$_2$, 5-C), 73.06 (CH$_2$, 1'-C), 89.25 (CH, 3-C), 120.04 (CH$_2$, 3'-C), 130.13 (CH, 2'-C), 173.28 (C^q, 4-C), 178.80 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 140 (15) [M$^+$], 122 (42) [M-H$_2$O]$^+$, 112 (8) [M-CO]$^+$, 97 (14) [M-CO$_2$]$^+$, 82 (82) [M-C$_3$H$_6$O]$^+$, 66 (23) [M$_{122}$-C$_3$H$_5$O]$^+$, 54 (100) [M$_{112}$-C$_2$H$_6$O]$^+$, 39 (68) [M$_{97}$-C$_3$H$_6$O]$^+$.

4-Prop-2-ynyloxy-5*H*-furan-2-one (51b)

White solid (1.64 g, 11.8 mmol, 74%) obtained via Fisher esterification from tetronic acid (1.59 g, 16 mmol), propargyl alcohol (1.78 g, 32 mmol) and 5 drops of H$_2$SO$_4$, in a 100 mL round bottom flask connected to a Dean – Stark apparatus, using benzene as solvent. The solvent was removed and the residual oil was purified by chromatography column in SiO$_2$ [length 40 cm, ⌀ 2 cm] using diethyl ether as eluent.

R_f (SiO$_2$) = 0.69 (diethyl ether).

Molecular Formula = C$_7$H$_6$O$_3$
Formula Weight   = 138.121

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3212 (M) [ν (C≡C)], 3114 (M) [ν (=C-H)], 2128 (W) [ν (≡C-H)], 1731 (S) and 1609 (S) [ν (Tetronate ring)], 1162 (S) [ν (C-O)], 820 (S) [ν (C-H)], 716 (VS) [ν (C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 2.68 (t, $^4J_{HH}$ = 2.46 Hz, 1H, 3'-H), 4.65 (d, $^4J_{HH}$ = 1.22 Hz, 2H, 5-H), 4.72 (d, $^4J_{HH}$ = 2.46 Hz, 2H, 1'-H), 5.25 (t, $^4J_{HH}$ = 1.22 Hz, 1H, 3-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 59.71 (CH$_2$, 1'-C), 67.65 (CH$_2$, 5-C), 75.18 (C^q, 2'-C), 78.07 (CH, 3'-C), 90.60 (CH, 3-C), 172.76 (C^q, 2-C), 177.63 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 139 (1) [M+H]$^+$, 138 (9) [M$^+$], 110 (7) [M-CO]$^+$, 94 (20) [M-CO$_2$]$^+$, 80 (30) [M-C$_2$H$_2$O$_2$]$^+$, 69 (67) [M^{++}], 39 (100) [C$_3$H$_3$$^+$]
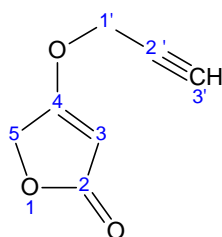
4-Allyloxy-5(*S*)-methyl-5*H*-furan-2-one (51c)

General experimental procedure:

In a 250 mL round bottom flask, a mixture of Ph$_3$CCO (6.38 g, 21.1 mmol), (*S*)-allyl lactate **34a** (2.74 g, 21.1 mmol) and benzoic acid (0.52 g, 4.25 mmol) in 150 mL of THF was heated under reflux in argon atmosphere for 18 hours. After cooling down the reaction mixture, the remaining

solution was filtered in a column over a small plug of SiO_2 [length 2 cm, $\varnothing$ 2 cm]. The THF was removed by rotary evaporation and the residue was dissolved in a small amount of DCM and filtered again in a wet SiO_2 column [length 40 cm, $\varnothing$ 2 cm] using DCM as eluent with the purpose of remove the triphenylphosphin oxide. The DCM was removed by rotary evaporation and the residual oil was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (4/1) as eluent. The pure product appeared as a colourless oil. Yield: 65% (2.11 g, 13.7 mmol). R_f (SiO_2) = 0.77 (diethyl ether).

Molecular formula = $C_8H_{10}O_3$
Molecular Weight = 154.163
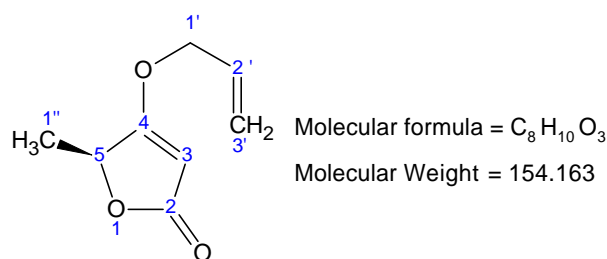
IR (ATR) $\bar{v}$ **(cm^{-1})** = 3119 (VW) [v (=C-H)], 2987 (VW) [v (-CH2-)], 2938 (VW) [v (-CH2)], 1747 (S) and 1624 (VS) [v (Tetronate ring)], 1294 (S) [v (C-O)], 945 (S) [v (=CH$_2$)], 804 (S) [v (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 1.31 (d, $^3J_{HH}$ = 6.73 Hz, 3H, 1''-H), 4.43 (dt, $^3J_{HH}$ = 5.63 Hz, $^4J_{HH}$ = 1.37 Hz, $^4J_{HH}$ = 1.24 Hz, 2H, 1'-H), 4.69 (q, $^3J_{HH}$ = 6.73 Hz, 1H, 5-H), 4.90 (s, 1H, 3-H), 5.21 (ddd, $^3J_{HH}$ = 10.43 Hz, $^4J_{HH}$ = 1.24 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 5.27 (ddd, $^3J_{HH}$ = 17.29 Hz, $^4J_{HH}$ = 1.37 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{trans}$), 5.83 (ddt, $^3J_{HH}$ = 5.63 Hz, $^3J_{HH}$ = 10.43 Hz, $^3J_{HH}$ = 17.29 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 17.69 (CH$_3$, 1''-C), 73.00 (CH$_2$, 1'-C), 75.26 (CH, 5-C), 88.54 (CH, 3-C), 119.88 (CH$_2$, 3'-C), 130.23 (CH, 2'-C), 172.36 (C^q, 4-C), 181.87 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 154 (3) [M$^+$], 136 (4) [M-H$_2$O]$^+$, 126 (2) [M-CO]$^+$, 110 (5) [M-CO$_2$]$^+$, 82 (100) [M$_{110}$-C$_2$H$_4$]$^+$, 69 (92) [M$_{110}$-C$_3$H$_5$]$^+$, 54 (26) [M$_{82}$-C$_2$H$_4$]$^+$, 43 (31) [C$_2$H$_3$O$^+$].

4-Allyloxy-5-ethyl-5*H*-furan-2-one (51d)

Colourless oil (2.35 g, 13.9 mmol, 89%) from 2.26 g (15.7 mmol) of 2-hydroxybutanoic acid allyl ester **34c**, 6.17 g (20.4 mmol) of Ph$_3$PCCO and 0.10 g (0.8 mmol) of benzoic acid dissolved in 100 mL of dry THF, stirring and refluxing for 18 h under argon atmosphere. The product was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (4/1) mixture as eluent.

R_f (SiO_2) = 0.66 (diethyl ether).

Molecular formula = $C_9H_{12}O_3$

Molecular Weight = 168.190
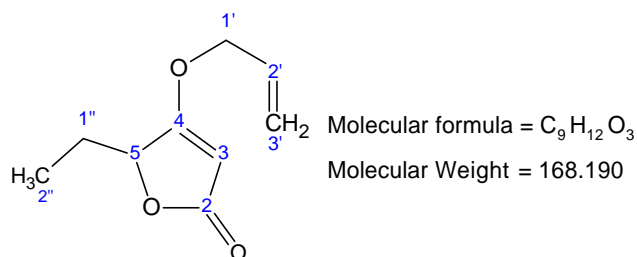
IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 2974 (W) [ν (-CH$_2$-)], 2939 (W) [ν (-CH$_2$-)], 1741 (S) and 1621 (VS) [ν (Tetronate ring)], 1307 (S) [ν (C-O-C)], 1157 (S) [ν (C-O)], 993 (S) and 803 (S) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.92 (t, $^3J_{HH}$ = 7.27 Hz, 3H, 2''-H), 1.54 - 1.71 (m, 1H, 1''-H), 1.82 - 2.01 (m, 1H, 1''-H), 4.49 (d, $^3J_{HH}$ = 5.77 Hz, 2H, 1'-H), 4.70 (dd, $^3J_{HH}$ = 6.59 Hz, $^3J_{HH}$ = 4.12 Hz, 1H, 5-H), 5.01 (s, 1H, 3-H), 5.32 (d, $^3J_{HH}$ = 10.43 Hz, 1H, 3'-H$_{cis}$), 5.36 (d, $^3J_{HH}$ = 15.65 Hz, 1H, 3'-H$_{trans}$), 5.91 (ddt, $^3J_{HH}$ = 15.65 Hz, $^3J_{HH}$ = 10.43 Hz, $^3J_{HH}$ = 5.77 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 7.70 (CH$_3$, 2''-C), 24.39 (CH$_2$, 1''-C), 72.69 (CH$_2$, 1'-C), 79.31 (CH, 5-C), 89.04 (CH, 3-C), 119.46 (CH$_2$, 3'-C), 130.08 (CH, 2'-C), 172.39 (C^q, 2-C), 180.36 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 168 (3) [M$^+$], 139 (56) [M-C$_2$H$_5$]$^+$, 99 (18) [M$_{139}$-C$_3$H$_5$]$^+$, 82 (95) [M$_{139}$-C$_3$H$_5$O]$^+$, 69 (83) [C$_3$HO$_2^+$], 57 (20) [C$_3$H$_5$O$^+$], 41 (100) [C$_3$H$_5^+$], 39 (61) [C$_3$H$_3^+$].

4-Allyloxy-5-butyl-5*H*-furan-2-one (51e)

Colourless oil (1.89 g, 9.6 mmol, 51%) from 3.26 g (18.9 mmol) of 2-hydroxyhexanoic acid allyl ester **34d**, 6.30 g (20.8 mmol) of Ph$_3$PCCO and 0.63 g (5.2 mmol) of benzoic acid dissolved in 100 mL of dry THF, stirring and refluxing for 18 h under argon atmosphere. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (4/1) mixture as eluent.

The tetronate can also be formed under microwave conditions from 0.10 g (0.58 mmol) of 2-hydroxyhexanoic acid allyl ester **34d**, 0.228 g (0.75 mmol) of Ph$_3$PCCO, using benzoic acid as catalyst, in 7 mL of dry THF, and heated the sealed tube under pressure at 100°C for 10 min. The yield obtained was similar than under thermal conditions.

R_f (SiO$_2$) = 0.37 (*n*-hexane : diethyl ether, v : v, 2 : 3).

Molecular formula = $C_{11}H_{16}O_3$

Molecular Weight = 196.243
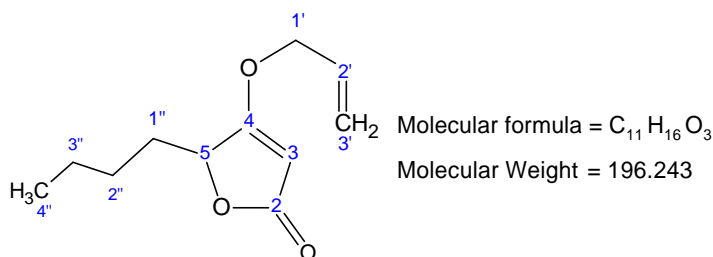
IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3118 (W) [ν (=C-H)], 2958 (W) [ν (-CH$_2$-)], 2932 (W) [ν (-CH$_2$-)], 1747 (S) and 1623 (VS) [ν (Tetronate ring)], 1309 (M) [ν (C-O-C)], 1156 (M) [ν (C-O)], 1014 (M) [ν (C-O)], 927 (S) and 803 (S) [ν (C-H allyl)].

^{1}H-NMR (250 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.85 (t, $^3J_{HH}$ = 7.20 Hz, 3H, 4''-H), 1.25 - 1.40 (m, 4H, 3''-H and 2'' H), 1.55 (m, 1H, 1''-H), 1.85 (m, 1H, 1''-H), 4.50 (d, $^3J_{HH}$ = 5.70 Hz, 2H, 1'-H), 4.72 (dd, $^3J_{HH}$ = 7.50 Hz, $^3J_{HH}$ = 3.70 Hz, 1H, 5-H), 4.98 (s, 1H, 3-H), 5.32 (d, $^3J_{HH}$ = 10.50 Hz, 1H, 3'-H$_{cis}$), 5.36 (d, $^3J_{HH}$ = 17.10 Hz, 1H, 3'-H$_{trans}$), 5.90 (m, 1H, 2'-H).

^{13}C-NMR (62.9 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 13.65 (CH$_3$, 4''-C), 22.14 (CH$_2$, 3''-C), 26.14 (CH$_2$, 2''-C), 31.33 (CH$_2$, 1''-C), 72.92 (CH$_2$, 1'-C), 78.85 (CH, 5-C), 89.07 (CH, 3-C), 119.84 (CH$_2$, 3'-C), 130.22 (CH, 2'-C), 172.64 (C^q, 2-C), 180.92 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 196 (8) [M$^+$], 168 (1) [M-CO]$^+$, 155 (16) [M-C$_3$H$_5$]$^+$, 140 (89) [M-C$_3$H$_5$O]$^+$, 139 (60) [M-C$_4$H$_9$]$^+$, 112 (23) [M$_{168}$-C$_3$H$_5$O]$^+$, 82 (100), 69 (71).

4-Allyloxy-5-hexyl-5*H*-furan-2-one (51f)

Colourless oil (3.43 g, 15.3 mmol, 90%) from 3.41 g (17.0 mmol) of 2-hydroxyoctanoic acid allyl ester **34f**, 5.14 g (17.0 mmol) of Ph$_3$PCCO and 0.63 g (5.2 mmol) of benzoic acid dissolved in 100 mL of dry THF, stirring and refluxing for 16 h under argon atmosphere. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / ether (3/2) mixture as eluent.

R_f (SiO$_2$) = 0.41 (*n*-hexane : ether, v : v, 2 : 3).

Molecular formula = $C_{13}H_{20}O_3$

Molecular Weight = 224.296
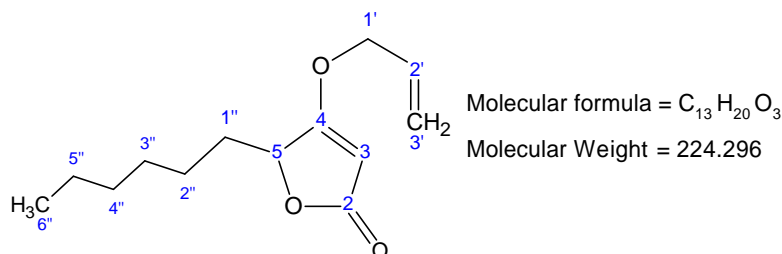
IR (ATR) $\bar{\nu}$ (cm^{-1}) = 2928 (M) [ν (-CH$_2$-)], 2859 (W) [ν (-CH$_2$-)], 1748 (S) and 1624 (VS) [ν (Tetronate ring)], 1303 (M) [ν (C-O-C)], 1154 (M) [ν (C-O)], 956 (M) and 815 (S) [ν (=C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.83 (t, $^3J_{HH}$ = 6.79 Hz, 3H, 6''-H), 1.15 - 1.45 (m, 8H, 5'', 4'', 3''-H, 2''-H), 1.49 – 1.64 (ddd, $^3J_{HH}$ = 7.55 Hz, $^3J_{HH}$ = 7.69 Hz, $^2J_{HH}$ = 14.00 Hz, 1H, 1''-H), 1.79 – 1.93 (ddd, $^3J_{HH}$ = 3.80 Hz, $^3J_{HH}$ = 7.55 Hz, $^2J_{HH}$ = 14.00 Hz, 1H, 1''-H), 4.50 (dd, $^3J_{HH}$ = 5.77 Hz, $^4J_{HH}$ = 1.24 Hz, 2H, 1'-H), 4.72 (ddd, $^3J_{HH}$ = 3.80 Hz, $^3J_{HH}$ = 7.69 Hz, $^4J_{HH}$ = 0.69 Hz, 1H, 5-H), 5.00 (d, $^4J_{HH}$ = 0.69 Hz, 1H, 3-H), 5.34 (ddd, $^3J_{HH}$ = 10.43 Hz, $^4J_{HH}$ = 1.24 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 5.37 (ddd, $^3J_{HH}$ = 17.15 Hz, $^4J_{HH}$ = 1.24 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{trans}$), 5.92 (ddt, $^3J_{HH}$ = 17.15 Hz, $^3J_{HH}$ = 10.43 Hz, $^3J_{HH}$ = 5.77 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 13.92 (CH$_3$, 6''-C), 22.41 (CH$_2$, 5'-C), 24.09 (CH$_2$, 4''-C), 28.78 (CH$_2$, 3''-C), 31.45 (CH$_2$, 2''-C), 31.76 (CH$_2$, 1''-C), 72.99 (CH$_2$, 1'-C), 78.98 (CH, 5-C), 89.19 (CH, 3-C), 119.97 (CH$_2$, 3'-C), 130.29 (CH, 2'-C), 172.70 (C^q, 2-C), 180.99 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 224 (3) [M$^+$], 206 (1) [M-H$_2$O]$^+$, 183 (7) [M-C$_3$H$_5$]$^+$, 153 (8) [M-C$_5$H$_{11}$]$^+$, 140 (30) [M-C$_6$H$_{13}$]$^+$, 113 (21) [M$_{183}$-C$_5$H$_{11}$]$^+$, 82 (47) [M-C$_8$H$_{14}$O$_2$]$^+$, 41 (100) [C$_3$H$_5^+$].

5(*S*)-Methyl-4-(1-methyl-allyloxy)-5*H*-furan-2-one (51g)

Colourless oil (0.94 g, 5.6 mmol, 33%) from 2.41 g (16.7 mmol) of 2-hydroxypropionoic acid 1-methyl allyl ester **34b**, 5.59 g (18.5 mmol) of Ph$_3$PCCO and 0.10 g (0.8 mmol) of benzoic acid dissolved in 100 mL of dry THF, stirring and refluxing for 16 h under argon atmosphere. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (1/1) mixture as eluent.

R_f (SiO$_2$) = 0.35 (*n*-hexane : diethyl ether, 1 : 1, v : v). R_f (SiO$_2$) = 0.59 (diethyl ether).

Molecular formula = C$_9$H$_{12}$O$_3$
Molecular Weight = 168.190
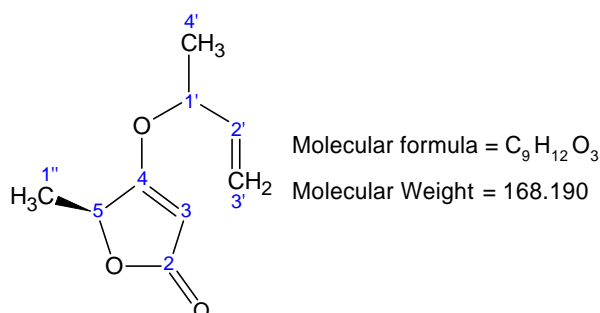
Mixture of diastereoisomers α *and* β*. Ratio* α: β = 1 : 1.

IR (ATR) $\bar{v}$ (cm^{-1}) = 2986 (S) [v (-CH$_2$-)], 1753 (S) and 1617 (VS) [v (Tetronate ring)], 1292 (S) [v (C-O)], 1083 (S) [v (C-O)], 954 (S) [v (C=C)], 905 (S) [v (C-H allyl)], 803 (S) [v (C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.39 (d, $^3J_{HH}$ = 6.79 Hz, 6H, 1''-H$^{\alpha+\beta}$), 1.40 (d, $^3J_{HH}$ = 6.41 Hz, 3H, 4'-H$^{\alpha \text{ or } \beta}$), 1.41 (d, $^3J_{HH}$ = 6.42 Hz, 3H, 4'-H$^{\alpha \text{ or } \beta}$), 4.55-4.65 (m, 2H,

1'-H$^{\alpha+\beta}$), 4.71 (dq, $^3J_{HH}$ = 6.79 Hz, $^4J_{HH}$ = 0.96 Hz, 1H, 5-H$^{\alpha \text{ or } \beta}$), 4.73 (dq, $^3J_{HH}$ = 6.79 Hz, $^4J_{HH}$ = 0.96 Hz, 1H, 5-H$^{\alpha \text{ or } \beta}$), 4.91 (d, $^4J_{HH}$ = 0.96 Hz, 1H, 3-H$^{\alpha \text{ or } \beta}$), 4.92 (d, $^4J_{HH}$ = 0.96 Hz, 1H, 3-H$^{\alpha \text{ or } \beta}$), 5.197 (ddd, $^3J_{HH}$ = 10.43 Hz, $^2J_{HH}$ = 1.10 Hz, $^4J_{HH}$ = 0.96 Hz, 1H, 3'-H$_{cis}^{\alpha \text{ or } \beta}$), 5.206 (ddd, $^3J_{HH}$ = 10.43 Hz, $^2J_{HH}$ = 1.10 Hz, $^4J_{HH}$ = 0.96 Hz, 1H, 3'-H$_{cis}^{\alpha \text{ or } \beta}$), 5.21 (ddd, $^3J_{HH}$ = 17.42 Hz, $^2J_{HH}$ = 1.10 Hz, $^4J_{HH}$ = 1.10 Hz, 1H, 3'-H$_{trans}^{\alpha \text{ or } \beta}$), 5.233 (ddd, $^3J_{HH}$ = 17.42 Hz, $^2J_{HH}$ = 1.10 Hz, $^4J_{HH}$ = 1.10 Hz, 1H, 3'-H$_{trans}^{\alpha \text{ or } \beta}$), 5.734 (ddd, $^3J_{HH}$ = 17.42 Hz, $^3J_{HH}$ = 10.43 Hz, $^3J_{HH}$ = 6.49 Hz, 1H, 2'-H$^{\alpha \text{ or } \beta}$), 5.75 (ddd, $^3J_{HH}$ = 17.42 Hz, $^3J_{HH}$ = 10.43 Hz, $^3J_{HH}$ = 6.56 Hz, 1H, 2'-H$^{\alpha \text{ or } \beta}$).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 17.67 (CH$_3$, 1''-C), 20.14 and 20.26 (CH$_3$, 4-C), 75.44 (CH, 5-C), 80.03 and 80.21 (CH, 1'-C), 88.71 and 88.75 (CH, 3-C), 117.57 and 117.83 (CH$_2$, 3'-C), 135.87 (CH, 2'-C), 172.74 (C^q, 2-C), 181.00 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 168 (14) [M$^+$], 150 (25) [M-H$_2$O]$^+$, 135 (7) [M$_{150}$-CH$_3$]$^+$, 127 (13) [M-C$_4$H$_7$]$^+$, 114 (33) [M-C$_4$H$_7$]$^+$, 95 (31) [M$_{150}$-C$_4$H$_7$]$^+$, 81 (53) [M$_{153}$-C$_3$H$_4$O$_2$]$^+$, 55 (100) [M-114]$^+$.

4-But-2-enyloxy-5-butyl-5*H*-furan-2-one (51h)

Colourless oil (0.83 g, 3.9 mmol, 46%) from 1.60 g (8.6 mmol) of 2-hydroxyhexanoic acid but-2-enyl ester **34e**, 3.10 g (10.2 mmol) of Ph$_3$PCCO and 0.31 g (2.5 mmol) of benzoic acid dissolved in 100 mL of dry THF, stirring and refluxing for 16 h under argon atmosphere. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluent.

R_f (SiO$_2$) = 0.40 (*n*-hexane : diethyl ether, v : v, 2 : 3).

Molecular formula = C$_{12}$H$_{18}$O$_3$
Molecular Weight = 210.269
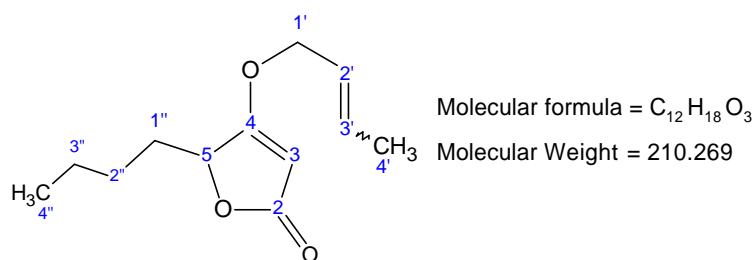
IR (KBr) $\overline{\nu}$ (cm^{-1}) = 3118 (W) [ν (=C-H)], 2931 (S) [ν (-CH$_2$-)], 2864 (M) [ν (-CH$_2$-)], 1755 (VS) and 1628 (VS) [ν (Tetronate ring)], 1312 (M) [ν (C-O-C)], 1159 (M) [ν (C-O)], 815 (S) [ν (=C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.81 (t, $^3J_{HH}$ = 7.16 Hz, 3H, 4''-H), 1.15 - 1.37 (m, 4H, 3''-H and 2'' H), 1.40 – 1.60 (m, 1H, 1''-H), 1.67 (d, $^3J_{HH}$ = 6.50 Hz, 3H, 4'-H), 1.70 – 1.90 (m, 1H, 1''-H), 4.38 (d, $^3J_{HH}$ = 6.44 Hz, 2H, 1'-H), 4.65 (dd, $^3J_{HH}$ = 7.66 Hz, $^3J_{HH}$ = 3.72 Hz, 1H, 5-H), 4.94 (s, 1H, 3-H), 5.56 (m, 1H, 2'-H), 5.82 (m, 1H, 3'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.61 (CH$_3$, 4''-C), 17.58 (CH$_3$, 4'-C), 22.10 (CH$_2$, 3''-C), 26.11 (CH$_2$, 2''-C), 31.28 (CH$_2$, 1''-C), 73.01 (CH$_2$, 1'-C), 78.88 (CH, 5-C), 88.75 (CH, 3-C), 123.21 (CH, 2'-C), 133.29 (CH, 3'-C), 172.79 (C^q, 2-C), 181.03 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 210 (8) [M$^+$], 167 (22) [M-C$_3$H$_7$]$^+$, 154 (100) [M-C$_4$H$_9$]$^+$, 136 (8) [M$_{154}$-H$_2$O]$^+$, 108 (8) [M$_{136}$-CO]$^+$, 96 (49) [M$_{167}$-C$_4$H$_7$O]$^+$, 81 (32) [M$_{96}$-CH$_3$]$^+$, 68 (75) [M$_{96}$-CO]$^+$, 56 (44) [C$_4$H$_9^+$].

4-Benzyloxy-5-butyl-5*H*-furan-2-one (51i)

Colourless oil (1.01 g, 4.1 mmol, 66%) from 1.38 g (6.2 mmol) of 2-hydroxyhexanoic acid benzyl ester **34g**, 1.88 g (6.2 mmol) of Ph$_3$PCCO and 0.20 g (1.6 mmol) of benzoic acid dissolved in 100 mL of dry THF, stirring and refluxing for 17 h under argon atmosphere. The product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluent.

R_f (SiO$_2$) = 0.35 (*n*-hexane : diethyl ether, v : v, 2 : 3).

Molecular formula = C$_{15}$H$_{18}$O$_3$
Molecular Weight = 246.301
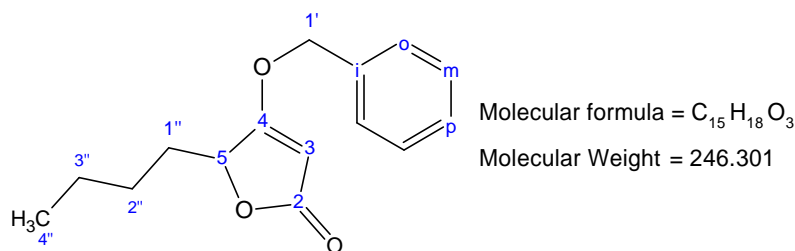
IR (ATR) $\bar{\nu}$ (cm^{-1}) = 2957 (W) [ν (-CH$_2$-)], 1750 (S) and 1623 (VS) [ν (Tetronate ring)], 1156 (S) [ν (C-O)], 1014 (M) [ν (C-O)], 802 (S) [ν (=C-H)] , 738 (S) and 696 (S) [ν (C-H arom. monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.86 (t, $^3J_{HH}$ = 7.21 Hz, 3H, 4''-H), 1.24 - 1.44 (m, 4H, 3''-H and 2''-H), 1.52 – 1.68 (m, 1H, 1''-H), 1.83 – 1.97 (m, 1H, 1''-H), 4.76 (ddd, $^3J_{HH}$ = 7.55 Hz, $^3J_{HH}$ = 3.70 Hz, $^4J_{HH}$ = 0.83 Hz, 1H, 5-H), 5.02 (d, $^2J_{HH}$ = 14.27 Hz, 2H, 1'-H), 5.09 (d, $^4J_{HH}$ = 0.83 Hz, 1H, 3-H), 7.31 - 7.43 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.74 (CH$_3$, 4''-C), 22.22 (CH$_2$, 3''-C), 26.21 (CH$_2$, 2''-C), 31.40 (CH$_2$, 1''-C), 74.26 (CH$_2$, 1'-C), 78.99 (CH, 5-C), 89.56 (CH, 3-C), 127.82 (CH, *meta*-C), 128.77 (CH, *ortho*-C), 128.97 (CH, *para*-C), 133.91 (C^q, *ipso*-C), 172.63 (C^q, 2-C), 181.00 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 246 (1) [M$^+$], 228 (1) [M-H$_2$O]$^+$, 218 (1) [M-CO]$^+$, 190 (3) [M-C$_4$H$_7$]$^+$, 155 (1) [M-C$_7$H$_7$]$^+$, 91 (100) [C$_7$H$_7^+$], 77 (2) [C$_6$H$_5^+$], 65 (7) [C$_5$H$_5^+$].

4-Benzyloxy-5-hexyl-5*H*-furan-2-one (51j)

Colourless oil (3.50 g, 12.7 mmol, 75%) from 4.27 g (17.1 mmol) of 2-hydroxyoctanoic acid benzyl ester **34h**, 5.42 g (17.9 mmol) of Ph$_3$PCCO and 0.20 g (1.6 mmol) of benzoic acid dissolved in 150 mL of dry THF, stirring and refluxing for 24 h under argon atmosphere. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluent.

R_f (SiO$_2$) = 0.42 (*n*-hexane : diethyl ether, v : v, 2 : 3).

Molecular formula = C$_{17}$H$_{22}$O$_3$
Molecular Weight = 274.355
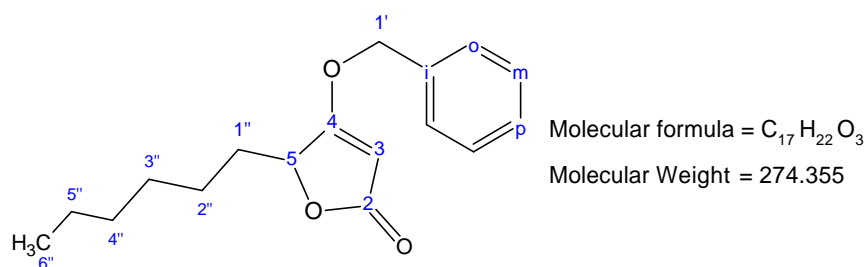
IR (ATR) $\bar{\nu}$ (cm^{-1}) = 2928 (W) [ν (-CH$_2$-)], 1752 (S) and 1625 (VS) [ν (Tetronate ring)], 1300 (M) [ν (C-O)], 1155 (S) [ν (C-O)], 802 (S) [ν (=C-H)] , 740 (M) and 696 (S) [ν (C-H arom. monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.86 (t, $^3J_{HH}$ = 6.79 Hz, 3H, 6''-H), 1.15 - 1.45 (m, 8H, 5''-4''-3''- and 2''-H), 1.51 – 1.66 (m, 1H, 1''-H), 1.80 – 1.96 (m, 1H, 1''-H), 4.76 (ddd, $^3J_{HH}$ = 7.68 Hz, $^3J_{HH}$ = 3.71 Hz, $^4J_{HH}$ = 0.96 Hz, 1H, 5-H), 4.99 (d, $^2J_{HH}$ = 11.58 Hz, 1H, 1'-H), 5.04 (d, $^2J_{HH}$ = 11.58 Hz, 1H, 1'-H), 5.09 (d, $^4J_{HH}$ = 0.96 Hz, 1H, 3-H), 7.30 - 7.42 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 13.89 (CH$_3$, 6''-C), 22.37 (CH$_2$, 5''-C), 24.04 (CH$_2$, 4''-C), 28.75 (CH$_2$, 3''-C), 31.43 (CH$_2$, 2''-C), 31.71 (CH$_2$, 1''-C), 74.24 (CH$_2$, 1'-C), 78.98 (CH, 5-C), 89.52 (CH, 3-C), 127.81 (CH, *meta*-C), 128.75 (CH, *ortho*-C), 128.95 (CH, *para*-C), 133.89 (C^q, ipso-C), 172.61 (C^q, 2-C), 181.00 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 274 (2) [M$^+$], 256 (1) [M-H$_2$O]$^+$, 190 (5) [M-C$_6$H$_{12}$]$^+$, 183 (5) [M-C$_7$H$_7$]$^+$, 165 (1) [M$_{183}$-H$_2$O]$^+$, 91 (100) [C$_7$H$_7$$^+$], 77 (1) [C$_6H_5$$^+$], 65 (10) [C$_5H_5$$^+$].

2(*S*)-(2(*S*)-Methyl-5-oxo-2,5-dihydrofuran-3-yloxy)-propionic acid allyl ester (51k)

Colourless oil (up to 65% according the conditions used forming the corresponding lactic acid dimer allyl ester). *NB: The compound is a secondary compound formed from the non isolated dimer and Ph$_3$PCCO; the product was separated out after the Claisen rearrangement experiment by column chromatography on SiO$_2$ [length 40 cm, Æ 2 cm] using n-hexane / diethyl ether (4/1) as eluent. Chiral GC show only 1 signal.*

R_f (SiO$_2$) = 0.29 (*n*-hexane : diethyl ether, 2 : 3, v : v); R_f (SiO$_2$) = 0.47 (*n*-hexane : diethyl ether, 1 : 4, v : v).

Molecular formula = C$_{11}$H$_{14}$O$_5$

Molecular Weight = 226.226

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 1749 (VS) and 1628 (VS) [ν (Tetronate ring)], 1294 (S) [ν (C-O)], 1199 (S) [ν (C-O-C)], 1079 (S) [ν (C-O)], 954 (S), 920 (S) [ν (=C-H allyl)], 807 (S) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.46 (d, $^3J_{HH}$ = 6.72 Hz, 3H, 1''-H), 1.60 (d, $^3J_{HH}$ = 6.86 Hz, 3H, 1''*-H), 4.62 (dt, $^3J_{HH}$ = 5.90 Hz, $^4J_{HH}$ = 1.10 Hz, 2H, 1'-H), 4.63 (q, $^3J_{HH}$ = 6.86 Hz, 1H, 5*-H), 4.81 (qd, $^3J_{HH}$ = 6.72 Hz, $^4J_{HH}$ = 0.96 Hz, 1H, 5-H), 4.89 (s, 1H, 3-H), 5.25 (ddt, $^3J_{HH}$ = 10.29 Hz, $^4J_{HH}$ = 1.10 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 5.30 (ddt, $^3J_{HH}$ = 17.15 Hz, $^4J_{HH}$ = 1.10 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{trans}$), 5.84 (ddt, $^3J_{HH}$ = 5.90 Hz, $^3J_{HH}$ = 10.29 Hz, $^3J_{HH}$ = 17.15 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 17.58 (CH$_3$, 1''-C), 17.76 (CH$_3$, 1''*-C), 66.31 (CH$_2$, 1'-C), 75.29 (CH, 5-C), 76.19 (CH, 5*-C), 89.28 (CH, 3-C), 119.67 (CH$_2$, 3'-C), 130.82 (CH, 2'-C), 168.85 (C^q, 4-C), 172.03 (C^q, 2-C), 181.06 (C^q, 2*-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 227 (5) [M+H]$^+$, 226 (5) [M$^+$], 211 (5) [M-CH$_3$]$^+$, 185 (20) [M-C$_3$H$_5$]$^+$, 154 (65) [M-C$_3$H$_5$O$_2$]$^+$, 141 (43) [M$_{185}$-CO$_2$]$^+$, 113 (21) [M^{++}], 69 (100) [C$_4$H$_5$O$^+$], 43 (48) [C$_2$H$_3$O$^+$].

4-Benzyloxy-5-methyl-5*H*-thiophen-2-one (51l)

Colourless oil (0.29 g, 1.3 mmol, 10%) from 2.63 g (13.4 mmol) of thiolactic acid benzyl ester **34i**, 4.23 g (14.0 mmol) of Ph$_3$PCCO and 0.16 g (0.1 mmol) of benzoic acid dissolved in 100 mL of dry THF, stirring and refluxing for 17 h under argon atmosphere. The product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluent. – 1.63 g (62%) of the starting material was recovered.

R_f (SiO$_2$) = 0.56 (*n*-hexane : diethyl ether, v : v, 2 : 3).

Molecular formula = $C_{12}H_{12}O_2S$

Molecular Weight = 220.287

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 1670 (S) and 1599 (VS) [ν (Tetronate ring)], 1323 (S) [ν (C-O-C)], 1193 (S) [ν (C-O)], 1128 (S), 962 (M) [ν (=C-H allyl)], 739 (S) and 696 (S) [ν (C-H arom. monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 1.60 (d, $^3J_{HH}$ = 7.11 Hz, 3H, 1''-H), 4.26 (q, $^3J_{HH}$ = 7.11 Hz, 1H, 5-H), 4.99 (s, 1H, 1'-H), 5.00 (s, 1H, 1'-H), 5.46 (s, 1H, 3-H), 7.25 – 7.50 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 19.03 (CH$_3$, 1''-C), 44.91 (CH, 5-C), 74.25 (CH$_2$, 1'-C), 102.60 (CH, 3-C), 127.70 (CH, *meta*-C), 128.79 (CH, *ortho*-C), 128.88 (CH, *para*-C), 134.25 (C^q, *ipso*-C), 184.23 (C^q, 4-C), 194.42 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 220 (11) [M$^+$], 201 (5), 160 (7) [M-C$_2$H$_4$S]$^+$, 132 (13) [M-C$_3$H$_4$OS]$^+$, 98 (59), 91 (100) [C$_7$H$_7^+$], 77 (5) [C$_6$H$_5^+$], 65 (39) [C$_5$H$_5^+$].

3.5 Synthesis of 5-Alkyl tetronic acid derivatives

5-Butyl-furan-2,4-dione (47a)[26,59]

A Schlenk 100 mL round – bottom flask, condenser, magnetic stirrer were previously dried over vacuum. Then hydrogen was filled in a balloon and connected to the reactor through a stopper-key. The flask was first flushed with argon for 2 min using the Schlenk inlet and then ventilated through a syringe needle inserted in a septum in the condenser. Under slight argon positive pressure, the flask was charged with Pd / C (10%), the solvent (absolute ethanol / methanol or ethyl acetate) and the compound. Argon was ventilated 2 min more. The argon was removed using the vacuum line in the manifold and then the connection between the flask and the H$_2$ in the balloon was open. The reaction mixture was stirred at room temperature for 24 hours. Filtration in Celite and SiO$_2$ chromatography column were done and the product was recovered from the mixture formed.

From 2.61 g (10.8 mmol) of 4-benzyloxy-5-butyl-5*H*-furan-2-one **51i** using 260 mg of Pd / C (10%) and ethanol as solvent. The reaction mixture was purified via chromatography column in SiO$_2$ [length 40 cm, $\varnothing$ 1 cm] using diethyl ether as eluent. The compound was obtained as white solid (1.38 g, 83 % yield).

R_f (SiO$_2$) = 0.65 (diethyl ether). m.p. = 103 °C.[Ref 58 m.p. = 101-103°C (AcOH or Et$_2$O)]

Molecular Formula = C$_8$H$_{12}$O$_3$
Formula Weight   = 156.179

IR (ATR) $\bar{v}$ (cm^{-1}) = 2691 (M) and 2530 (W) [ν (O-H intramolecular bridge)], 1692 (S) [ν (C=O)], 1627 (S) [ν (C=O)], 1567 (VS) [ν (C=O)O], 1275 (VS) [ν (C-O)], 805 (VS) [ν (C-H)], 733 (S) [ν (=C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = *KETO Form:* 0.89 (t, $^3J_{HH}$ = 7.07 Hz, 3H, 4'-H), 1.26 – 1.48 (m, 4H, 3'-2'-H), 1.71 – 1.83 (m, 1H, 1'a-H), 1.83 – 1.93 (m, 1H, 1'b-H), 3.16 (s, virt. $^4J_{HH}$ = 0.55 Hz, 2H, 3-H), 4.72 (ddd, $^3J_{HH}$ = 4.67 Hz, $^3J_{HH}$ = 7.14 Hz, 1H, 5-H).

ENOL Form: 0.89 (t, $^3J_{HH}$ = 7.07 Hz, 3H, 4'*-H), 1.26 – 1.48 (m, 4H, 3'*- 2'*-H), 1.56 – 1.73 (m, 1H, 1'*a-H), 1.90 – 2.05 (m, 1H, 1'*b-H), 4.82 (dd, $^3J_{HH}$ = 3.84 Hz, $^3J_{HH}$ = 7.54 Hz, 1H, 5*-H), 5.02 (s, 1H, 3*-H), 11.66 (br. s., 1H, -OH*-H). Ratio keto : enol = 1 : 1.7 from the integrated signal of 5-H and 5*-H.

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = *KETO Form:* 13.68 (CH$_3$, 4'-C), 22.14 (CH$_2$, 3'-C), 26.50 (CH$_2$, 2'-C), 31.01 (CH$_2$, 1'-C), 37.53 (CH$_2$, 3-C), 86.46 (CH, 5-C), 169.94 (C^q, 2-C), 205.64 (C^q, 4-C).

ENOL Form: 13.77 (CH$_3$, 4'*-C), 22.27 (CH$_2$, 3'*-C), 26.24 (CH$_2$, 2'*-C), 31.07 (CH$_2$, 1'*-C), 80.45 (CH, 5*-C), 88.87 (CH, 3*-C), 178.01 (C^q, 2*-C), 183.98 (C^q, 4*-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 156 (1) [M$^+$], 128 (4) [M-CO]$^+$, 100 (72) [C$_4$H$_4$O$_3^{+}$], 99 (11) [M-C$_4$H$_9$]$^+$, 86 (41) [C$_5$H$_{10}$O]$^+$, 72 (17) [M$_{100}$-CO]$^+$, 57 (35) [C$_4$H$_9^+$], 43 (100) [C$_3$H$_7^+$].

5-Hexyl-furan-2,4-dione (47b)

From 3.48 g (12.7 mmol) of 4-benzyloxy-5-hexyl-5*H*-furan-2-one **51j** using 348 mg of Pd / C (10%) and methanol as solvent. The reaction mixture was filtered over a chromatography column in SiO$_2$ [length 5 cm, ∅ 1 cm] using diethyl ether as eluent. The compound was obtained as white solid (2.38 g of crude product, 99 % yield).

Molecular Formula = $C_{10}H_{16}O_3$
Formula Weight = 184.232

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3129 (W) [ν (O-H)], 2926 (M) [ν (-CH$_2$-)], 2690 (M) and 2529 (W) [ν (O-H intramolecular bridge)], 1692 (S) [ν (C=O)], 1567 (VS) [ν (C=O)O], 1277 (VS) [ν (C-O)], 803 (VS) [ν (C-H)].

MS (GC inlet, EI, 70 eV) m/z (%) = 184 (6) [M$^+$], 156 (1) [M-CO]$^+$, 142 (2) [M-C$_2$H$_2$O]$^+$, 114 (12) [M$_{142}$-CO]$^+$, 100 (100) [C$_4$H$_4$O$_3^+$], 96 (9) [M$_{114}$-H$_2$O]$^+$, 86 (24) [M$_{156}$-C$_3$H$_2$O$_2^+$], 43 (72) [C$_3$H$_7^+$].

3.6 Synthesis of 3-acetyl-5-alkyl tetronic acids

3-Acetyl-5-butyl-4-hydroxy-5*H*-furan-2-one (28a)[59]

In a 100 mL round bottom flask, a mixture of 0.97 g (3.2 mmol) of Ph$_3$PCCO and 0.46 g (2.9 mmol) of 5-butyl-furan-2,4-dione **47a** dissolved in dry THF (50 mL) were heated under reflux in argon atmosphere for 60 hours. The reaction mixture was allowd to cool and to the THF solution was slowly dropped an aqueous NaOH solution (2.5 M, 20 mL). The resulting mixture was stirred for 2h at r.t. Then HBr (47%) was added carefully to the reaction mixture until the volume was twice the original [CAUTION!!! HBr is extreme corrosive – personal protecting measures should be taken]. This aqueous solution was extracted with diethyl ether (3 x 20 mL) [CAUTION!!! exist an overpressure inside the funnel during the extraction], the combined organic fractions were washed with water (2 x 10 mL), dried over Na$_2$SO$_4$ and the solvent was removed using a rotary evaporator. The resulting solid was sublimated under pressure (membrane pump) at 80°C. The sublimated solid appear as white crystalls of pure 3-acetyl tetronic acid (495mg, 85% yield).

R_f (SiO$_2$) = 0.29 (diethyl ether : ethyl acetate – AcOH 5%, 1:1). m.p. = 54°C. [Ref 59 m.p. = 54-54.5°C]

Molecular Formula = $C_{10}H_{14}O_4$
Formula Weight = 198.216

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3079 (W) [ν (O-H)], 2958 (M) [ν (-CH$_2$-)], 2923 (M) [ν (-CH$_2$-)], 1746 (VS) [ν (C=O)O], 1666 (VS) [ν (C=O)], 1597 (S) [ν (C=C)], 1156 (S) [ν (C-O)], 1012 (S) [ν (C-O)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.84 (t, $^3J_{HH}$ = 7.28 Hz, 4''-H$^\beta$), and 0.85 (t, $^3J_{HH}$ = 7.13 Hz, 4''-H$^\alpha$) (Total integral = 3H, ratio α / β = 1.67), 1.20 – 1.45 (m, 4H, 3''-4''-H), 1.57 – 1.74 (m, 1H, 1''a-H), 1.82 – 1.96 (m, 1H, 1''b-H), 2.48 (s, 3H, 2'-H), 4.55 (dd, $^3J_{HH}$ = 4.26 Hz, $^3J_{HH}$ = 7.96 Hz, 5-H$^\beta$) and 4.68 (dd, $^3J_{HH}$ = 4.39 Hz, $^3J_{HH}$ = 7.69 Hz, 5-H$^\alpha$) (Total integral = 1H, ratio α / β = 1.67), 10.91 (br. s., 1H, O-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 13.72 (CH$_3$, 4''-C$^{\alpha+\beta}$), 19.53 (CH$_3$, 2'-C$^\beta$), 22.22 (CH$_2$, 3''-C$^\alpha$), 22.23 (CH$_2$, 3''-C$^\beta$), 22.37 (CH$_3$, 2'-C$^\alpha$), 26.39 (CH$_2$, 2''-C$^\alpha$), 26.52 (CH$_2$, 2''-C$^\beta$), 30.89 (CH$_2$, 1''-C$^\beta$), 30.97 (CH$_2$, 1''-C$^\alpha$), 79.96 (CH, 5-C$^\alpha$), 85.60 (CH, 5-C$^\beta$), 97.82 (C^q, 3-C$^\beta$), 100.74 (C^q, 3-C$^\alpha$), 167.94 (C^q, 2-C$^\alpha$), 175.93 (C^q, 2-C$^\beta$), 188.05 (C^q, 1'-C$^\beta$), 194.30 (C^q, 1'-C$^\alpha$), 194.92 (C^q, 4-C$^\beta$), 199.81 (C^q, 4-C$^\alpha$).

MS (GC inlet, EI, 70 eV) m/z (%) = 199 (1) [M+H]$^+$, 198 (8) [M$^+$], 180 (1) [M-H$_2$O]$^+$, 155 (14) [M-C$_2$H$_3$O]$^+$, 142 (100) [M$_{199}$-C$_4$H$_9$]$^+$, 99 (4) [M^{++}], 84 (57) [C$_4$H$_4$O$_2^+$], 43 (39) [C$_2$H$_3$O$^+$].

3-Acetyl-5-hexyl-4-hydroxy-5*H*-furan-2-one (28b)[56]

From 625 mg (2.07 mmol) of Ph$_3$PCCO and 346 mg (1.8 mmol) of 5-hexyl-furan-2,4-dione **47b** dissolved in dry THF (50 mL) and heated under reflux in argon atmosphere for 20 hours. After extraction the yellowish solid obtained was sublimated. The sublimated solid appear as yellowish crystals of pure pesthetoxine (351 mg, 83% yield).

R_f (SiO$_2$) = 0.30 (diethyl ether : ethyl acetate – AcOH 5%, 1:1). m.p. = 58°C.

Molecular Formula = $C_{12}H_{18}O_4$

Formula Weight = 226.269

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3078 (W) [ν (O-H)], 1747 (S) [ν (C=O)], 1665 (VS) [ν (C=O)O], 1601 (S) [ν (C=O)O], 1581 (S) [ν (C=C)], 1166 (S) [ν (C-O)], 1078 (S) [ν (C-O)], 1019 (S) [ν (C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.84 (t, $^3J_{HH}$ = 6.72 Hz, 3H, 4''-H$^{\alpha+\beta}$), 1.17 – 1.36 (m, 6H, 5''-3''-2''-H), 1.36 – 1.52 (m, 2H, 4''-H), 1.61 – 1.77 (m, 1H, 1''a-H), 1.83 – 1.98 (m, 1H, 1''b-H), 2.52 (s, 3H, 2'-H), 4.59 (dd, $^3J_{HH}$ = 4.26 Hz, $^3J_{HH}$ = 7.96 Hz, 5-H$^\beta$) and 4.71 (dd, $^3J_{HH}$ = 4.45 Hz, $^3J_{HH}$ = 7.73 Hz, 5-H$^\alpha$) (Total integral = 1H, ratio α / β = 1.60), 12.49 (br. s., 1H, O-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 13.95 (CH$_3$, 6''-C$^{\alpha+\beta}$), 19.51 (CH$_3$, 2'-C$^\beta$), 22.36 (CH$_3$, 2'-C$^\alpha$), 22.43 (CH$_2$, 5''-C$^{\alpha+\beta}$), 24.27 (CH$_2$, 4''-C$^\alpha$), 24.39 (CH$_2$, 4''-C$^\beta$), 28.73 (CH$_2$, 3''-C$^\alpha$), 28.75 (CH$_2$, 3''-C$^\beta$), 31.18 (CH$_2$, 2''-C$^\beta$), 31.26 (CH$_2$, 2''-C$^\alpha$), 31.41 (CH$_2$, 1''-C$^{\alpha+\beta}$), 79.95 (CH, 5-C$^\alpha$), 85.59 (CH, 5-C$^\beta$), 97.79 (C^q, 3-C$^\beta$), 100.71 (C^q, 3-C$^\alpha$), 167.90 (C^q, 2-C$^\alpha$), 175.90 (C^q, 2-C$^\beta$), 187.99 (C^q, 1'-C$^\beta$), 194.26 (C^q, 1'-C$^\alpha$), 194.88 (C^q, 4-C$^\beta$), 199.77 (C^q, 4-C$^\alpha$).

MS (GC inlet, EI, 70 eV) m/z (%) = 227 (2) [M+H]$^+$, 226 (9) [M$^+$], 208 (1) [M-H$_2$O]$^+$, 183 (1) [M-C$_2$H$_3$O]$^+$, 165 (1) [M$_{183}$-H$_2$O]$^+$, 155 (23) [M$_{183}$-CO]$^+$, 142 (100) [M$_{227}$-C$_6$H$_{13}$]$^+$, 85 (20) [C$_6$H$_{13}$$^+$], 43 (26) [C$_2H_3O^+$].
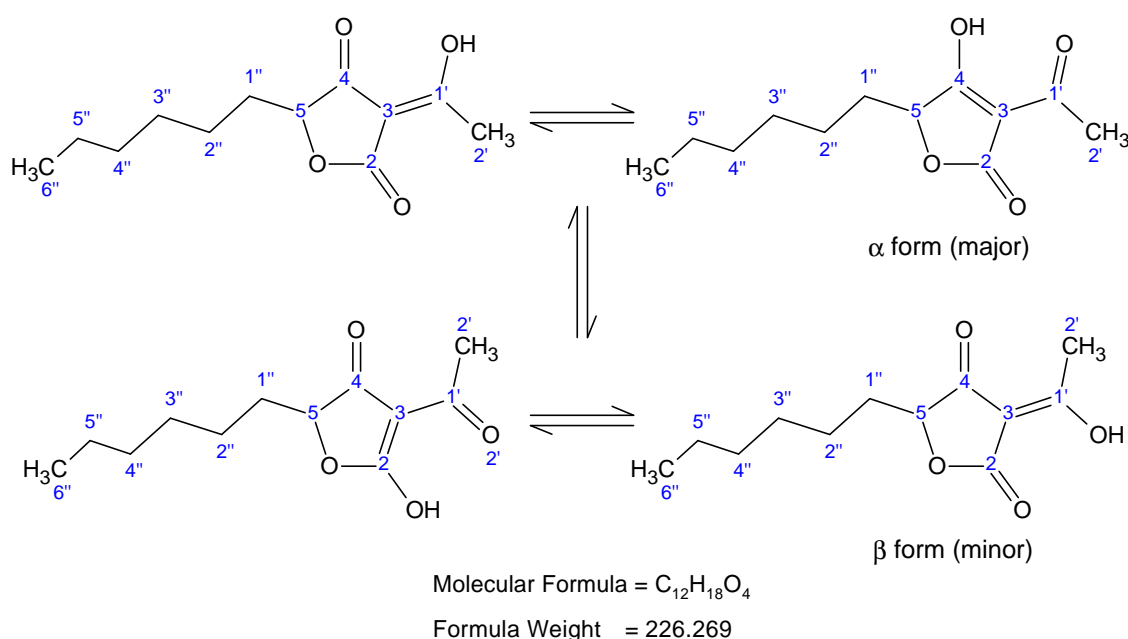
3.7 Synthesis of 3-Allyl tetronic acids

3-Allyl-4-hydroxy-5*H*-furan-2-one (57a)

General experimental procedure:

0.5 g of 4-allyloxy-5*H*-furan-2-one **51a** were dissolved in 7 mL of dry toluene and the resulting mixture was irradiated under mw (*CEM Discover*) in a closed vessel (mw needs at least 350 mg of sample in 7 mL toluene). The conditions were programmed with temperature control giving 3 minutes to obtain 190°C (ramp time) and keeping this temperature for 10 min (hold time). After the reaction flask was cooled down to room temperature, the solvent was removed by rotary evaporation; the resulting residue was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent. The pure product appears as white crystals.

Yield: 70% (0.35 g, 2.5 mmol). R_f (SiO_2) = 0.59 (diethyl ether). m.p. = 105 °C. [Ref 39 m.p. = 105°C]
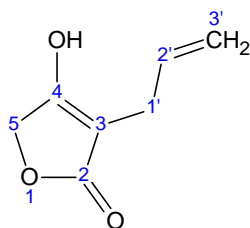
Molecular formula = $C_7 H_8 O_3$

Molecular Weight = 140.137

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3084 (W) [ν (C=C-H)], 2983 (M) [ν (-CH$_2$-)], 2701 (M) [ν (O-H) intramolecular bridge], 1718 (M) and 1644 (S) [ν (Tetronic ring)], 1574 (S), 1389 (VS) [ν (C-O-C)], 1033 (VS) [ν (C-O-C)], 922 (S) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 2.96 (d, $^3J_{HH}$ = 6.31 Hz, 2H, 1'-H), 4.68 (s, 2H, 5-H), 5.03 (dd, $^3J_{HH}$ = 10.03 Hz, $^2J_{HH}$ = 1.38 Hz, 1H, 3'-H$_{cis}$), 5.09 (dd, $^3J_{HH}$ = 17.12 Hz, $^4J_{HH}$ = 1.65 Hz, 1H, 3'-H$_{trans}$), 5.83 (ddt, $^3J_{HH}$ = 6.31 Hz, $^3J_{HH}$ = 10.03 Hz, $^3J_{HH}$ = 17.12 Hz, 1H, 2'-H), 10.50 (br. s., 1H, -OH).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 25.28 (CH$_2$, 1'-C), 67.92 (CH, 5-C), 99.12 (C^q, 3-C), 116.20 (CH$_2$, 3'-C), 133.74 (CH, 2'-C), 175.01 (C^q, 2-C), 178.42 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 140 (15) [M$^+$], 122 (45) [M-H$_2$O]$^+$, 111 (8) [M-CO]$^+$, 94 (14) [M$_{122}$-CO]$^+$, 82 (85) [M-C$_2$H$_2$O]$^+$, 54 (100) [M$_{82}$-CO]$^+$, 41 (30) [C$_3$H$_5^+$], 39 (66) [C$_3$H$_3^+$].

3-Allyl-4-hydroxy-5(*S*)-methyl-5*H*-furan-2-one (57b) [158]

Colourless oil – white solid with a melting point < 30°C (725 mg, 4.71 mmol, 52%) from 1.40 g (9.08 mmol) of 4-allyloxy-5(*S*)-methyl-5*H*-furan-2-one **51c**. The reaction was done in 3

separate reactors, each containing 0.46 g of reactant in 7 mL of toluene. The product was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (1/4) mixture as eluent.

R_f (SiO_2) = 0.35 (*n*-hexane : diethyl ether, 1 : 4, v : v). $[\alpha]_D^{30}$ +2.53° (0.1576 g/100mL, MeOH)
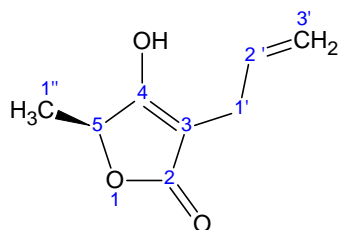
Molecular formula = $C_8H_{10}O_3$

Molecular Weight = 154.163

IR (ATR) $\bar{v}$ **(cm^{-1})** = 3079 (W) [v (=C-H)], 2984 (M) [v (-CH$_2$-)], 2617 (W) [v (-OH bridge)], 1713 (M) and 1613 (S) [v (Tetronic ring)], 1254 (S) [v (C-O)], 1074 (VS) [v (C-O)], 909 (S) [v (=CH$_2$)], 789 (S) [v (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.48 (d, $^3J_{HH}$ = 6.73 Hz, 3H, 1''-H), 2.95 (d, $^3J_{HH}$ = 6.18 Hz, 2H, 1'-H), 4.82 (q, $^3J_{HH}$ = 6.73 Hz, 1H, 5-H), 5.03 (dq, $^3J_{HH}$ = 10.02 Hz, $^4J_{HH}$ = 1.37 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 5.09 (dq, $^3J_{HH}$ = 17.15 Hz, $^4J_{HH}$ = 1.65 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{trans}$), 5.83 (ddt, $^3J_{HH}$ = 6.18 Hz, $^3J_{HH}$ = 10.02 Hz, $^3J_{HH}$ = 17.15 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 17.72 (CH$_3$, 1''-C), 25.24 (CH$_2$, 1'-C), 75.37 (CH, 5-C), 98.38 (C^q, 3-C), 116.15 (CH$_2$, 3'-C), 133.97 (CH, 2'-C), 176.87 (C^q, 2-C), 177.83 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 154 (14) [M$^+$], 139 (2) [M-CH$_3$]$^+$, 136 (33) [M-H$_2$O]$^+$, 121 (3) [M$_{139}$-H$_2$O]$^+$, 108 (8) [M$_{136}$-CO]$^+$, 82 (96) [M-C$_3$H$_4$O$_2$]$^+$, 54 (100) [M$_{136}$-C$_5$H$_6$O]$^+$, 43 (28) [C$_2$H$_3$O$^+$].

3-Allyl-5-ethyl-4-hydroxy-5*H*-furan-2-one (57c)

Colourless oil (0.34 g, 2.0 mmol, 67%) from 0.50 g (3.0 mmol) of 4-allyloxy-5-ethyl-5*H*-furan-2-one **51d**. The product was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (4/1) mixture as eluent.

R_f (SiO_2) = 0.39 (*n*-hexane : diethyl ether, 4 : 1, v : v).
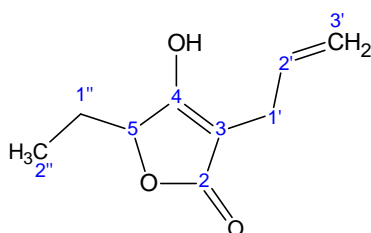
Molecular formula = $C_9H_{12}O_3$

Molecular Weight = 168.190

IR (ATR) $\bar{\nu}$ **(cm⁻¹)** = 3080 (M) [ν (C=CH)], 2974 (M) [ν (-CH₂-)], 2939 (M) [ν (-CH₂-)], 2701 (W) [ν (-OH bridge)], 1717 (M) and 1638 (VS) [ν (Tetronic ring)], 1397 (S) [ν (C-O-C)], 1251 (S) [ν (C-O)], 914 (M) [ν (C-H allyl)].

¹H-NMR (300 MHz, CDCl₃, TMS$_{int}$) d (ppm) = 0.88 (t, $^3J_{HH}$ = 7.41 Hz, 3H, 2''-H), 1.55 - 1.75 (m, 1H, 1''-H), 1.89 - 2.07 (m, 1H, 1''-H), 2.90 (d, $^3J_{HH}$ = 6.03 Hz, 2H, 1'-H), 4.71 (dd, $^3J_{HH}$ = 6.59 Hz, $^3J_{HH}$ = 3.85 Hz, 1H, 5-H), 4.91 (dd, $^3J_{HH}$ = 10.08 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 4.98 (dd, $^3J_{HH}$ = 17.14 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3'-H$_{trans}$), 5.74 (ddt, $^3J_{HH}$ = 17.14 Hz, $^3J_{HH}$ = 10.08 Hz, $^3J_{HH}$ = 6.03 Hz, 1H, 2'-H), 10.29 (br. s., 1H, -OH).

¹³C-NMR (75 MHz, CDCl₃, TMS$_{int}$) d (ppm) = 7.91 (CH₃, 2''-C), 24.42 (CH₂, 1'-C), 24.88 (CH₂, 1''-C), 79.69 (CH, 5-C), 99.16 (C^q, 3-C), 115.31 (CH₂, 3'-C), 133.86 (CH, 2'-C), 176.59 (C^q, 2-C), 177.49 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 168 (9) [M⁺], 153 (4) [M-CH₃]⁺, 140 (8) [M-CO]⁺, 122 (8) [M$_{140}$-H₂O]⁺, 82 (100) [M$_{140}$-C₄H₈]⁺, 54 (69) [M$_{82}$-CO]⁺, 41 (15) [C₃H₅⁺], 39 (27) [C₃H₃⁺].

3-Allyl-5-hexyl-4-hydroxy-5*H*-furan-2-one (57d)

Colourless oil (0.45 g, 2.0 mmol, 90%) from 0.50 g (2.2 mmol) of 4-allyloxy-5-hexyl-5*H*-furan-2-one **51f**. The product was purified by column chromatography on SiO₂ [length 40 cm, ∅ 2 cm] using diethyl ether as eluent.

R_f (SiO₂) = 0.41 (diethyl ether).
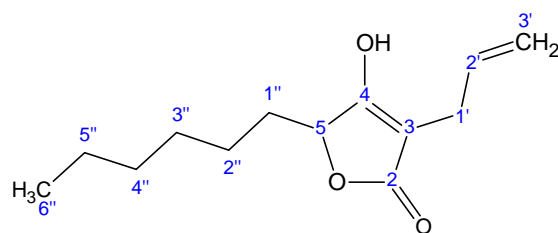
Molecular formula = C₁₃H₂₀O₃
Molecular Weight = 224.296

IR (ATR) $\bar{\nu}$ **(cm⁻¹)** = 3080 (W) [ν (-OH)], 2927 (M) [ν (-CH₂-)], 2694 (W) [ν (-OH bridge)], 1717 (S) and 1631 (VS) [ν (Tetronic ring)], 1397 (S) [ν (C-O-C)], 1254 (S) [ν (C-O)], 1063 (S) [ν (C-O)], 913 (M) [ν (=C-H allyl)].

¹H-NMR (300 MHz, CDCl₃, TMS$_{int}$) d (ppm) = 0.84 (t, $^3J_{HH}$ = 6.80 Hz, 3H, 6''-H), 1.15 - 1.45 (m, 8H, 5''-4''-3''-H and 2''-H), 1.52 – 1.67 (m, 1H, 1''-H), 1.90 – 2.05 (m, 1H, 1''-H), 2.95 (ddd, $^3J_{HH}$ = 6.18 Hz, $^4J_{HH}$ = 1.37 Hz, $^4J_{HH}$ = 1.51 Hz, 2H, 1'-H), 4.75 (dd, $^3J_{HH}$ = 3.36 Hz, $^3J_{HH}$ = 7.62 Hz, 1H, 5-H), 4.99 (dt, $^3J_{HH}$ = 10.15 Hz, $^4J_{HH}$ = 1.37 Hz, $^4J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 5.06 (dt, $^3J_{HH}$ = 17.02 Hz, $^4J_{HH}$ = 1.51 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{trans}$), 5.81 (ddt, $^3J_{HH}$ = 17.02 Hz, $^3J_{HH}$ = 10.15 Hz, $^3J_{HH}$ = 6.18 Hz, 1H, 2'-H), 10.40 (br. s., 1H, -OH).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.98 (CH$_3$, 6''-C), 22.49 (CH$_2$, 5''-C), 24.18 (CH$_2$, 4''-C), 25.17 (CH$_2$, 1'-C), 28.87 (CH$_2$, 3''-C), 31.54 (CH$_2$, 2''-C), 31.59 (CH$_2$, 1''-C), 79.05 (CH, 5-C), 98.96 (C^q, 3-C), 115.86 (CH$_2$, 3'-C), 133.99 (CH, 2'-C), 176.98 (C^q, 2-C), 177.36 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 224 (9) [M$^+$], 206 (1) [M-H$_2$O]$^+$, 183 (7) [M-C$_3$H$_5$]$^+$, 153 (22) [M-C$_5$H$_{11}$]$^+$, 140 (91) [M-C$_6$H$_{13}$]$^+$, 112 (8) [M$_{140}$-CO]$^+$, 82 (100) [M-C$_8$H$_{14}$O$_2$]$^+$, 54 (62) [M$_{82}$-CO]$^+$, 41 (9) [C$_3$H$_5$$^+$].

3-Allyl-5-butyl-4-hydroxy-5*H*-furan-2-one (57e) [26,162]

Colourless oil (0.45 g, 2.3 mmol, 90%) from 0.50 g (2.5 mmol) of 4-allyloxy-5-butyl-5*H*-furan-2-one **51e**. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluent.

R_f (SiO$_2$) = 0.29 (*n*-hexane : diethyl ether, 2 : 3, v : v).

Molecular formula = C$_{11}$H$_{16}$O$_3$
Molecular Weight = 196.243

IR (KBr) $\bar{\nu}$ (cm^{-1}) = 1719 (S) and 1644 (VS) [ν (Tetronic ring)], 1402 (S), 1110 (M) [ν (C-O-C)], 1062 (M) [ν (C-O)], 1011 (M) [ν (C-O)], 915 (M) [ν (C-H allyl)].

^{1}H-NMR (270 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.87 (t, ^{3}J$_{HH}$ = 6.90 Hz, 3H, 4''-H), 1.18 - 1.46 (m, 4H, 3''-H and 2''-H), 1.60 (m, 1H, 1''-H), 1.95 (m, 1H, 1''-H), 2.96 (d, ^{3}J$_{HH}$ = 6.10 Hz, 2H, 1'-H), 4.75 (dd, ^{3}J$_{HH}$ = 7.50 Hz, ^{3}J$_{HH}$ = 3.43 Hz, 1H, 5-H), 5.03 (d, ^{3}J$_{HH}$ = 11.50 Hz, 1H, 3'-H$_{cis}$), 5.09 (d, ^{3}J$_{HH}$ = 18.70 Hz, 1H, 3'-H$_{trans}$), 5.83 (m, 1H, 2'-H), 9.95 (br. s., 1H, -OH).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.79 (CH$_3$, 4''-C), 22.29 (CH$_2$, 3''-C), 25.28 (CH$_2$, 1'-C), 26.29 (CH$_2$, 2''-C), 31.28 (CH$_2$, 1''-C), 78.92 (CH, 5-C), 99.01 (C^q, 3-C), 116.17 (CH$_2$, 3'-C), 134.01 (CH, 2'-C), 176.66 (C^q, 2-C), 176.96 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 196 (52) [M$^+$], 153 (12) [M-C$_3$H$_7$]$^+$, 140 (59) [M-C$_4$H$_8$]$^+$, 122 (8) [M$_{140}$-H$_2$O]$^+$, 112 (11) [M$_{140}$-CO]$^+$, 82 (100), 54 (48), 41 (11) [C$_3$H$_5$$^+$].
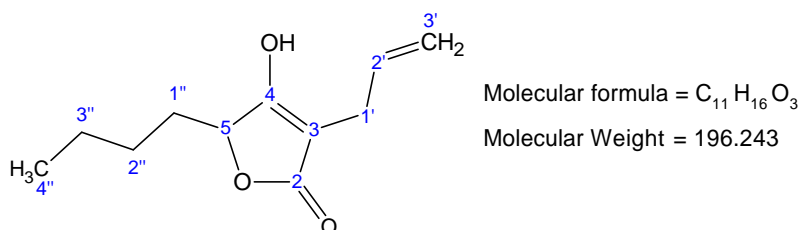
5-Butyl-4-hydroxy-3-(1-methyl-allyl)-5*H*-furan-2-one (57f)

Colourless oil (0.06 g, 0.26 mmol, 11%) from 0.50 g (2.4 mmol) of 4-but-2-enyloxy-5-butyl-5*H*-furan-2-one **51h**. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluent.

R_f (SiO$_2$) = 0.30 (*n*-hexane : diethyl ether, 2 : 3, v : v).

Molecular formula = C$_{12}$H$_{18}$O$_3$
Molecular Weight = 210.269
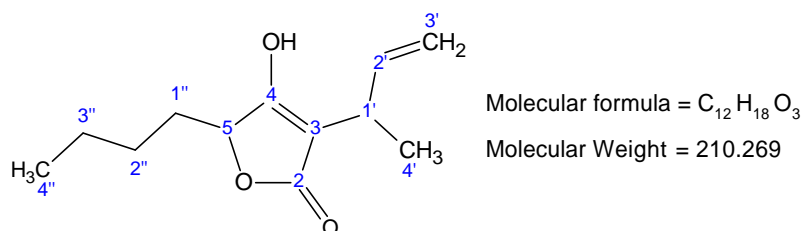
Mixture of diastereoisomers

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3079 (W) [ν (-OH)], 2960 (M) [ν (-CH$_2$-)], 2932 (M) [ν (-CH$_2$-)], 1716 (S) and 1636 (VS) [ν (Tetronic ring)], 1399 (VS), 1013 (S) [ν (C-O)], 912 (S) [ν (=CH$_2$)], 731 (S) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.82 (t, $^3J_{HH}$ = 5.90 Hz, 3H, 4''-H), 1.21 (d, $^3J_{HH}$ = 7.11 Hz, 3H, 4'-H), 0.99 - 1.45 (m, 4H, 3''-H, 2'' H), 1.50 – 1.75 (m, 1H, 1''-H), 1.75 – 2.05 (m, 1H, 1''-H), 3.20 – 3.42 (m, 1H, 1'-H), 4.69 (dd, $^3J_{HH}$ = 7.40 Hz, $^3J_{HH}$ = 3.20 Hz, 1H, 5-H), 4.90 – 5.11 (m, 2H, 3'-H), 5.90 - 6.08 (m, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.74 (CH$_3$, 4''-C), 17.75 (CH$_3$, 4'-C), 17.84 (CH$_3$, 4'-C *2nd diastereomer*), 22.27 (CH$_2$, 3''-C), 26.17 (CH$_2$, 2''-C), 26.21 (CH$_2$, 2''-C *2nd diastereomer*), 31.29 (CH$_2$, 1''-C), 31.32 (CH$_2$, 1''-C *2nd diastereomer*), 31.61 (CH, 1'-C), 31.63 (CH, 1'-C *2nd diastereomer*), 78.42 (CH, 5-C), 103.79 (C^q, 3-C), 113.79 (CH$_2$, 3'-C), 139.98 (CH, 2'-C), 140.02 (CH, 2'-C *2nd diastereomer*), 175.75 (C^q, 2-C), 176.22 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 210 (8) [M$^+$], 195 (4) [M-CH$_3$]$^+$, 177 (3) [M-H$_2$O]$^+$, 167 (27) [M$_{195}$-CO]$^+$, 154 (100) [M-C$_4$H$_7$]$^+$, 96 (80) [M$_{167}$-C$_3$H$_5$]$^+$, 81 (58) [M$_{96}$-CH$_3$]$^+$, 68 (73) [M$_{96}$-CO]$^+$, 55 (45) [C$_4$H$_7^+$], 41 (64) [C$_3$H$_5^+$].

3-But-2-enyl-4-hydroxy-5(S)-methyl-5*H*-furan-2-one (57g)

Colourless oil (0.44 g, 2.6 mmol, 87%) from 0.50 g (3.0 mmol) of 5(*S*)-methyl-4-(1-methyl-allyloxy)-5*H*-furan-2-one **51g**. The product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using diethyl ether as eluent.

R_f (SiO$_2$) = 0.54 (diethyl ether).

Molecular formula = C$_9$H$_{12}$O$_3$
Molecular Weight = 168.190
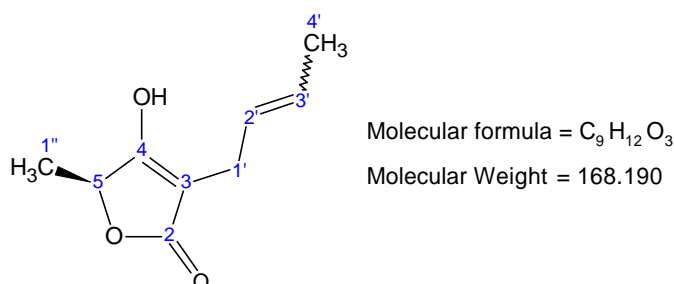
Mixture of diastereoisomers Z and E. Ratio Z : E = 1 : 2.3.

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3191 (W) [ν (-OH)], 2985 (M) [ν (-CH$_2$-)], 2709 (W) [ν (-OH bridge)], 1719 (S) and 1631 (VS) [ν (Tetronic ring)], 1057 (VS) [ν (C-O)], 964 (S) [ν (C=C-H)], 732 (S) [ν (=C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 1.46 (d, $^3J_{HH}$ = 6.72 Hz, 1''-H^E) and 1.47 (d, $^3J_{HH}$ = 6.72, 1''-H^Z) (integral 2H), 1.60 (d, $^3J_{HH}$ = 4.80 Hz, 4'-H^Z) and 1.66 (d, $^3J_{HH}$ = 6.42 Hz, 4'-H^E) (integral 3H), 2.86 (d, $^3J_{HH}$ = 4.94 Hz, 1'-H^Z) and 2.94 (d, $^3J_{HH}$ = 6.72 Hz, 1'-H^E) (integral 2H – ratio 1 : 2.3), 4.80 (q, $^3J_{HH}$ = 6.72 Hz, 1H, 5-H), 5.30 – 5.60 (m, 2H, 3'-H and 2'-H), 10.33 (br. s., 1H, -OH).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 12.74 (CH$_3$, 4'-C^Z), 17.65 (CH$_3$, 4'-C^E), 17.69 (CH$_3$, 1''-C^E), 17.70 (CH$_3$, 1''-C^Z), 19.15 (CH$_2$, 1'-C^Z), 24.02 (CH$_2$, 1'-C^E), 75.31 (CH, 5-C), 99.17 (C^q, 3-C^E), 99.44 (C^q, 3-C^Z), 125.81 (CH, 3'-C^E), 126.21 (CH, 3'-C^Z), 126.44 (CH, 2'-C^E), 126.59 (CH, 2'-C^Z), 176.98 (C^q, 2-C^Z), 177.11 (C^q, 2-C^E), 177.17 (C^q, 4-C^Z), 177.52 (C^q, 4-C^E).

MS (GC inlet, EI, 70 eV) m/z (%) = 168 (24) [M$^+$], 150 (39) [M-H$_2$O]$^+$, 140 (2) [M-CO]$^+$, 135 (11) [M$_{150}$-CH$_3$]$^+$, 127 (25) [M-C$_3$H$_5$]$^+$, 114 (53) [M-C$_4$H$_7$]$^+$, 95 (61) [M$_{150}$-C$_4$H$_7$]$^+$, 81 (100) [M$_{153}$-C$_3$H$_4$O$_2$]$^+$, 55 (63) [C$_4$H$_7^+$].

Sodium 4-Allyl-5-oxo-2,5-dihydrofuran-3-olate (57k)

Hygroscopic white solid (231 mg, 100%) from 200 mg (1.43 mmol) of 3-allyl-4-hydroxy-5*H*-furan-2-one **57a** dissolved in dry methanol and 79.5 mg (1.43 mmol) of sodium methoxide, stirred under argon atmosphere for 2 h. The solvent was removed under vacuum to give quantitatively the salt.

m.p. = 180°C (dec.)
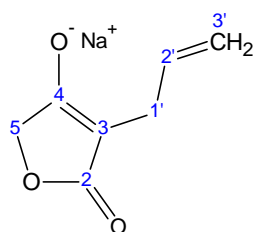
Molecular Formula = C$_7$H$_7$NaO$_3$
Formula Weight = 162.118

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 1735 (M) and 1638 (S) [ν (Tetronate ring)], 1549 (VS) [ν (C-O$^{(-)}$)], 1351 (S) [ν (C-H)], 1032 (S) [ν (C-O)] , 992 (S) [ν (=C-H)], 911 (S) [ν (C-H allyl)], 703 (S) [ν (C-H)].

^{1}H-NMR (300 MHz, MeOH-d$_4$, TMS$_{int}$) d (ppm) = 2.81 (ddd, $^3J_{HH}$ = 6.04 Hz, $^4J_{HH}$ = 1.51 Hz, $^4J_{HH}$ = 1.79 Hz, 2H, 1'-H), 4.34 (s, 2H, 5-H), 4.86 (dq, $^3J_{HH}$ = 10.01 Hz, $^4J_{HH}$ = 1.51 Hz, $^2J_{HH}$ = 2.20 Hz, 1H, 3'-H$_{cis}$), 4.98 (dq, $^3J_{HH}$ = 17.15 Hz, $^4J_{HH}$ = 1.79 Hz, $^2J_{HH}$ = 2.20 Hz, 1H, 3'-H$_{trans}$), 5.81 (ddt, $^3J_{HH}$ = 17.15 Hz, $^3J_{HH}$ = 10.01 Hz, $^3J_{HH}$ = 6.04 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, MeOH-d$_4$, TMS$_{int}$) d (ppm) = 26.32 (CH$_2$, 1'-C), 70.84 (CH$_2$, 5-C), 93.28 (C^q, 3-C), 114.33 (CH$_2$, 3'-C), 137.57 (CH, 2'-C), 182.70 (C^q, 2-C), 187.43 (C^q, 4-C).

MS (Direct inlet, EI, 70 eV) m/z (%) = 140 (9) [M$^+$], 122 (19) [M-H$_2$O]$^+$, 112 (5) [M-CO]$^+$, 95 (10) [M-CO$_2$]$^+$, 82 (61) [M-C$_2$H$_2$O$_2$]$^+$, 66 (31), 54 (100) [C$_4$H$_6^+$], 39 (98).

3.8 Synthesis of 5-Oxa-spiro[2.4]heptane-4,7-diones

General experimental procedure:

The oxa-spiro[2.4]heptane diones were a secondary product formed during the Claisen rearrangement experiment. The new spiro derivatives were separated out by column chromatography on previously dehydrated SiO$_2$. The reaction mixture was loaded into the column once the supported material was deactivated with dry solvents (the sample was eluted using dry solvents because the resulting product was water sensitive).

1-Methyl-5-oxa-spiro[2.4]heptane-4,7-dione (58a)

Colourless oil from 0.5 g (3.6 mmol) of 4-allyloxy-5*H*-furan-2-one **51a**. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (1/4) mixture as eluent.

Yield: 17% (0.09 g, 0.6 mmol). R_f (SiO$_2$) = 0.83 (diethyl ether).

Molecular formula = C$_7$H$_8$O$_3$
Molecular Weight = 140.137

Mixture of two diastereoisomers α *and* β. Ratio α : β = 1 : 1.2. (β isomer has the methyl group next to the lactone group)

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 2973 (VW) [ν (-CH$_2$-)], 2939 (VW) [ν (-CH$_2$-)], 1789 (M) [ν (C=O)], 1733 (VS) [ν (C=O)], 1341 (S) [ν (C-O-C)], 1163 (S) [ν (C-O-C)], 1032 (S) [ν (cyclopropane)], 857 (M) [ν (C-H cyclopropane)].

a - diastereomer   **b - diastereomer**

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.30 (d, $^3J_{HH}$ = 6.17 Hz, 3H, 3'-H$^\alpha$), 1.37 (d, $^3J_{HH}$ = 6.17 Hz, 3H, 3'-H$^\beta$), 1.72 (dd, $^3J_{HH}$ = 8.64 Hz, $^4J_{HH}$ = 3.71 Hz, 1H, 1'α-H$^\alpha$), 1.75 (dd, $^3J_{HH}$ = 8.78 Hz, $^4J_{HH}$ = 3.71 Hz, 1H, 1'α-H$^\beta$), 2.02 (dd, $^3J_{HH}$ = 8.78 Hz, $^4J_{HH}$ = 3.57 Hz, 1H, 1'β-H$^\beta$), 2.05 (dd, $^3J_{HH}$ = 8.64 Hz, $^4J_{HH}$ = 3.71 Hz, 1H, 1'β-H$^\alpha$), 2.20 (qt, $^3J_{HH}$ = 6.17 Hz, $^3J_{HH}$ = 8.78 Hz, 1H, 2'α-H$^\beta$), 2.36 (qt, $^3J_{HH}$ = 6.17 Hz, $^3J_{HH}$ = 8.64 Hz, 1H, 2'β-H$^\alpha$), 4.61 (s, 5-H$^\beta$), 4.64 (s, 2H, 5-H$^\alpha$) (Total integral = 2H, ratio α / β : 1 / 1.2).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = (signals are not totally α or β assigned because of the low resolution in the HSQC spectra) 11.33 (CH$_3$, 3'-C$^\alpha$), 11.96 (CH$_3$, 3'-C$^\beta$), 30.21 (CH$_2$, 1'-C$^\alpha$), 30.43 (CH$_2$, 1'-C$^\beta$), 32.42 (C^q, 3-C), 33.16 (C^q, 3-C), 36.23 (CH, 2'-C$^\beta$), 36.77 (CH, 2'-C$^\alpha$), 72.87 (CH$_2$, 5-C$^\alpha$), 73.28 (CH$_2$, 5-C$^\beta$), 173.56 (C^q, 2-C), 175.43 (C^q, 2-C), 204.49 (C^q, 4-C), 205.50 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = (α and β isomers were separated in the GC column and contain the same fragmentation pattern) 140 (21) [M$^+$], 122 (89) [M-H$_2$O]$^+$, 111 (5) [M-CO]$^+$, 94 (23) [M$_{122}$-CO]$^+$, 82 (38) [M$_{111}$-C$_2$H$_2$O]$^+$, 54 (100) [M$_{82}$-CO]$^+$, 42 (39) [C$_3$H$_6^+$], 39 (52) [C$_3$H$_3^+$].

1,6(S)-Dimethyl-5-oxa-spiro[2.4]heptane-4,7-dione (58b)

Colourless oil from 0.5 g (3.2 mmol) of 4-allyloxy-5(*S*)-methyl-5*H*-furan-2-one **51c**. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (1/4) mixture as eluent.

Yield: 17% (0.09 g, 0.6 mmol). R_f (SiO$_2$) = 0.58 (diethyl ether).
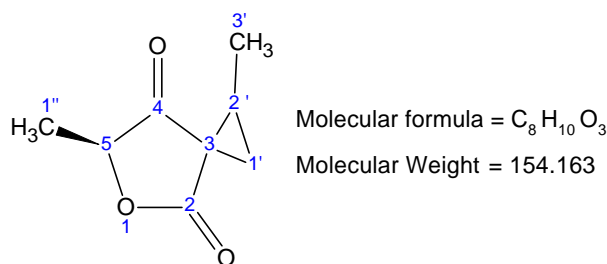
Molecular formula = C$_8$H$_{10}$O$_3$
Molecular Weight = 154.163

Mixture of four diastereoisomers α, α∗ and β, β∗. Ratio α : β = 1.4 : 1 (β isomer has the methyl group next to the lactone group)

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 2937 (VW) [ν (-CH$_2$-)], 1786 (M) [ν (C=O)], 1737 (VS) [ν (C=O)], 1334 (S) [ν (C-O-C)], 1168 (S) [ν (C-O-C)], 1064 (S) [ν (C-O)], 983 (S) [ν (cyclopropane)], 855 (M) [ν (C-H cyclopropane)].

a - isomers   **b - isomers**

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 1.24 (d, $^3J_{HH}$ = 6.17 Hz, 3H, 3'-H$^\alpha$), 1.26 (d, $^3J_{HH}$ = 6.04 Hz, 3H, 3'-H$^{\alpha*}$), 1.34 (d, $^3J_{HH}$ = 6.17 Hz, 3H, 3'-H$^\beta$), 1.35 (d, $^3J_{HH}$ = 6.17 Hz, 3H, 3'-H$^{\beta*}$), 1.41 (d, $^3J_{HH}$ = 7.14 Hz, 3H, 1''-H$^\alpha$), 1.43 (d, $^3J_{HH}$ = 7.14 Hz, 3H, 1''-H$^\beta$), 1.43 (d, $^3J_{HH}$ = 7.14 Hz, 3H, 1''-H$^{\beta*}$), 1.44 (d, $^3J_{HH}$ = 7.14 Hz, 3H, 1''-H$^{\alpha*}$), 1.64 (dd, $^3J_{HHtrans}$ = 6.04 Hz, $^2J_{HH}$ = 3.71 Hz, 1H, 1'α-H$^{\alpha*}$), 1.67 (dd, $^3J_{HHtrans}$ = 6.04 Hz, $^2J_{HH}$ = 3.71 Hz, 1H, 1'α-H$^\alpha$), 1.69 (dd, $^3J_{HHtrans}$ = 6.04 Hz, $^2J_{HH}$ = 3.71 Hz, 1H, 1'β-H$^{\beta*}$), 1.72 (dd, $^3J_{HHtrans}$ = 6.04 Hz, $^2J_{HH}$ = 3.56 Hz, 1H, 1'β-H$^\beta$), 1.94 (dd, $^3J_{HHcis}$ = 8.78 Hz, $^2J_{HH}$ = 3.56 Hz, 1H, 1'α-H$^\beta$), 1.96 (dd, $^3J_{HHcis}$ = 8.64 Hz, $^2J_{HH}$ = 3.71 Hz, 1H, 1'α-H$^{\beta*}$), 2.01 (dd, $^3J_{HHcis}$ = 8.65 Hz, $^2J_{HH}$ = 3.71 Hz, 1H, 1'β-H$^\alpha$), 2.02 (dd, $^3J_{HHcis}$ = 8.64 Hz, $^2J_{HH}$ = 3.71 Hz, 1H, 1'β-H$^{\alpha*}$), 2.13 (ddq, $^3J_{HHtrans}$ = 6.04 Hz, $^3J_{HHcis}$ = 8.78 Hz, $^3J_{HH}$ = 6.17 Hz, 1H, 2'α-H$^\beta$), 2.14 (ddq, $^3J_{HHtrans}$ = 6.04 Hz, $^3J_{HHcis}$ = 8.64 Hz, $^3J_{HH}$ = 6.17 Hz, 1H, 2'α-H$^{\beta*}$), 2.30 (ddq, $^3J_{HHtrans}$ = 6.04 Hz, $^3J_{HHcis}$ = 8.65 Hz, $^3J_{HH}$ = 6.17 Hz, 1H, 2'β-H$^\alpha$), 2.30 (ddq, $^3J_{HHtrans}$ = 6.04 Hz, $^3J_{HHcis}$ = 8.64 Hz, $^3J_{HH}$ = 6.04 Hz, 1H, 2'β-H$^{\alpha*}$), 4.72 (q, $^3J_{HH}$ = 7.14 Hz, 1H, 5-H$^{\alpha*}$), 4.73 (q, $^3J_{HH}$ = 7.14 Hz, 1H, 5-H$^\alpha$), 4.77 (q, $^3J_{HH}$ = 7.14 Hz, 1H, 5-H$^{\beta*}$), 4.77 (q, $^3J_{HH}$ = 7.14 Hz, 1H, 5-H$^\beta$). Integral determined via 2D COSY (manual integration) on single signals; ratio α/β : 1.4/1.

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = (signals are not totally α, α∗ and / or β, β∗ assigned because of the low resolution in the HSQC spectra – Carbon atoms with same magnetic environment have the same chemical shift in more than one isomer and are not listed repeated$^\#$) 11.29 (CH$_3$, 3'-C$^\alpha$), 11.33 (CH$_3$, 3'-C$^\alpha$), 11.94 (CH$_3$, 3'-C$^\beta$), 11.96 (CH$_3$, 3'-C$^\beta$), 16.69 (CH$_3$, 1''-C), 16.73 (CH$_3$, 1''-C), 16.81 (CH$_3$, 1''-C), 17.06 (CH$_3$, 1''-C), 29.49 (CH$_2$, 1'-C$^\alpha$), 29.73 (CH$_2$, 1'-C$^\alpha$), 29.73 (CH$_2$, 1'-C$^\beta$), 29.97 (CH$_2$, 1'-C$^\beta$), 31.78 (C^q, 3-C), 31.97 (C^q, 3-C), 32.43 (C^q, 3-C), 32.60 (C^q, 3-C), 35.90 (CH, 2'-C$^\beta$), 35.99 (CH, 2'-C$^\beta$), 36.31 (CH, 2'-C$^\alpha$),

36.44 (CH, 2'-C$^\alpha$), 80.38 (CH, 5-C$^\beta$), 80.43 (CH, 5-C$^\beta$), 80.65 (CH, 5-C$^\alpha$), 80.91 (CH, 5-C$^\alpha$), 172.89 (C^q, 2-C), 173.22 (C^q, 2-C), 174.71$^\#$ (C^q, 2-C), 207.18 (C^q, 4-C), 207.21 (C^q, 4-C), 208.23 (C^q, 4-C), 208.33 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = (α, $\alpha*$, β and $\beta*$ isomers were separated in the GC column and contain the same fragmentation pattern) 154 (46) [M$^+$], 139 (8) [M-CH$_3$]$^+$, 136 (64) [M-H$_2$O]$^+$, 108 (17) [M$_{136}$-CO]$^+$, 82 (76) [M-C$_3$H$_4$O$_2$]$^+$, 68 (31) [M$_{82}$-CH$_3$]$^+$, 54 (100) [C$_4$H$_6^+$], 42 (50) [C$_3$H$_6^+$].

6-Ethyl-1-methyl-5-oxa-spiro[2.4]heptane-4,7-dione (58c)

Colourless oil from 0.5 g (2.97 mmol) of 4-allyloxy-5-ethyl-5*H*-furan-2-one **51d**. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluent.

Yield: 15% (0.08 g, 0.4 mmol). R_f (SiO$_2$) = 0.81 (*n*-hexane : diethyl ether, v : v, 2 : 3).

Molecular formula = C$_9$H$_{12}$O$_3$
Molecular Weight = 168.190
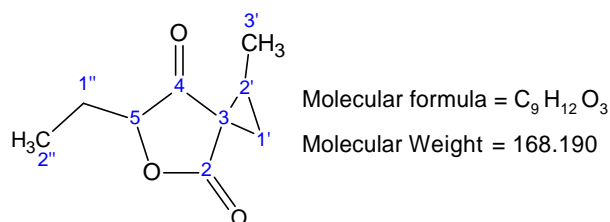
Mixture of four diastereoisomers α, $\alpha*$ *and* β, $\beta*$. Ratio α : β = 1 : 1 (β isomer has the methyl group next to the lactone group)
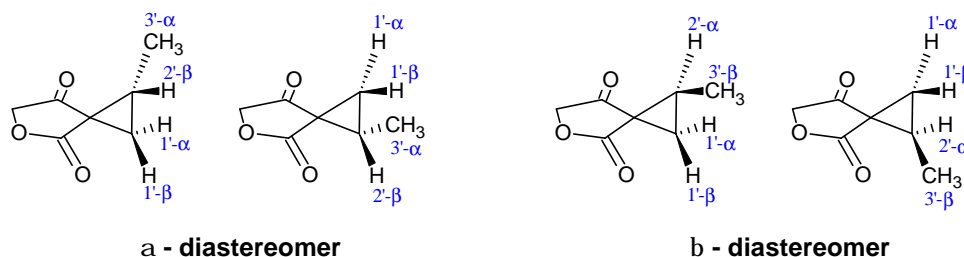
IR (ATR) $\bar{\nu}$ (cm^{-1}) = 2973 (M) [ν (-CH$_2$-)], 2938 (W) [ν (-CH$_2$-)], 1786 (M) [ν (C=O)], 1737 (VS) [ν (C=O)], 1659 (S), 1335 (S) [ν (C-O-C)], 1167 (S) [ν (C-O)], 976 (S) [ν (cyclopropane)].

a - isomers   **b - isomers**
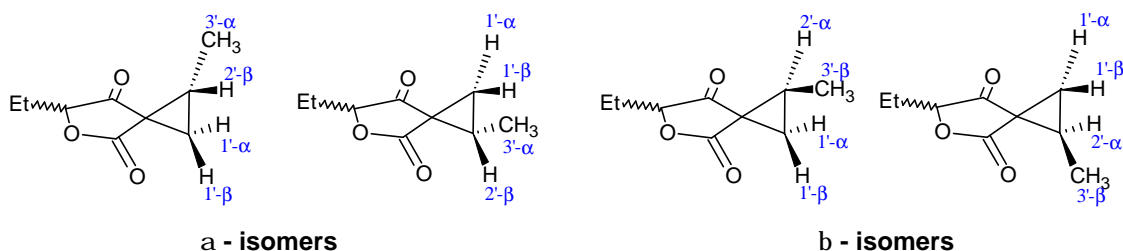
^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.93 (t, $^3J_{HH}$ = 7.41 Hz, 3H, 2''-H), 0.93 (t, $^3J_{HH}$ = 7.41 Hz, 3H, 2''-H), 0.94 (t, $^3J_{HH}$ = 7.41 Hz, 3H, 2''-H), 0.95 (t, $^3J_{HH}$ = 7.41 Hz, 3H, 2''-H), 1.26 (d, $^3J_{HH}$ = 6.18 Hz, 3H, 3'-H$^\alpha$), 1.27 (d, $^3J_{HH}$ = 6.03 Hz, 3H, 3'-H$^{\alpha*}$), 1.35 (d, $^3J_{HH}$ = 6.03 Hz, 3H, 3'-H$^\beta$), 1.36 (d, $^3J_{HH}$ = 6.17 Hz, 3H, 3'-H$^{\beta*}$), 1.60 - 1.72 (m, 2H, 1'α-H$^{\alpha+\alpha*}$), 1.63 - 1.85 (m, 4H, 1''-H), 1.68 - 1.77 (m, 2H, 1'α-H$^{\beta+\beta*}$), 1.85 - 2.02 (m, 4H, 1''-H), 1.90 - 2.02 (m,

2H, 1'β-H$^{β+β*}$), 1.97 - 2.06 (m, 2H, 1'β-H$^{α+α*}$), 2.04 – 2.24 (m, 2H, 2'α-H$^{β+β*}$), 2.25 – 2.40 (m, 2H, 2'β-H$^{α+α*}$), 4.64 (dd, $^3J_{HH}$ = 4.66 Hz, $^3J_{HH}$ = 6.45 Hz, 1H, 5-H), 4.65 (dd, $^3J_{HH}$ = 4.60 Hz, $^3J_{HH}$ = 6.79 Hz, 1H, 5-H), 4.68 (dd, $^3J_{HH}$ = 5.07 Hz, $^3J_{HH}$ = 6.31 Hz, 1H, 5-H), 4.68 (dd, $^3J_{HH}$ = 4.66 Hz, $^3J_{HH}$ = 6.73 Hz, 1H, 5-H). Integral determined via 2D COSY (manual integration) on single signals; ratio α/β : 1/1.

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = (signals are not totally α, α∗ and / or β, β∗ assigned because of the low resolution in the HSQC spectra – Carbon atoms with same magnetic environment have the same chemical shift in more than one isomer and are not listed repeated$^{\#}$) 8.11 (CH$_3$, 2''-C), 8.18 (CH$_3$, 2''-C), 8.43$^{\#}$ (CH$_3$, 2''-C), 11.23 (CH$_3$, 3'-C^{α}), 11.33 (CH$_3$, 3'-C^{α*}), 11.96 (CH$_3$, 3'-C^{β}), 12.16 (CH$_3$, 3'-C^{β*}), 24.55 (CH$_2$, 1''-C), 24.59 (CH$_2$, 1''-C), 24.74 (CH$_2$, 1''-C), 24.84 (CH$_2$, 1''-C), 29.46 (CH$_2$, 1'-C^{α}), 29.75 (CH$_2$, 1'-C^{α*}), 29.86 (CH$_2$, 1'-C^{β}), 30.09 (CH$_2$, 1'-C^{β*}), 32.58 (C^q, 3-C), 32.64 (C^q, 3-C), 33.35 (C^q, 3-C), 33.56 (C^q, 3-C), 35.74 (CH, 2'-C^{β}), 36.29 (CH, 2'-C^{β*}), 36.41 (CH, 2'-C$^{α+α*}$), 84.98 (CH, 5-C), 85.06 (CH, 5-C), 85.22 (CH, 5-C), 85.52 (CH, 5-C), 173.27 (C^q, 2-C), 173.34 (C^q, 2-C), 174.05 (C^q, 2-C), 175.12 (C^q, 2-C), 207.02 (C^q, 4-C), 207.18 (C^q, 4-C), 208.04 (C^q, 4-C), 208.09 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = (α, α∗, β and β∗ isomers were separated in the GC column and contain the same fragmentation pattern) 168 (16) [M$^+$], 153 (17) [M-CH$_3$]$^+$, 150 (8) [M-H$_2$O]$^+$, 140 (29) [M-CO]$^+$, 122 (13) [M$_{140}$-H$_2$O]$^+$, 82 (43) [M$_{140}$-C$_4$H$_8$]$^+$, 54 (100) [M$_{82}$-CO]$^+$, 42 (27) [C$_3$H$_6$$^+$].

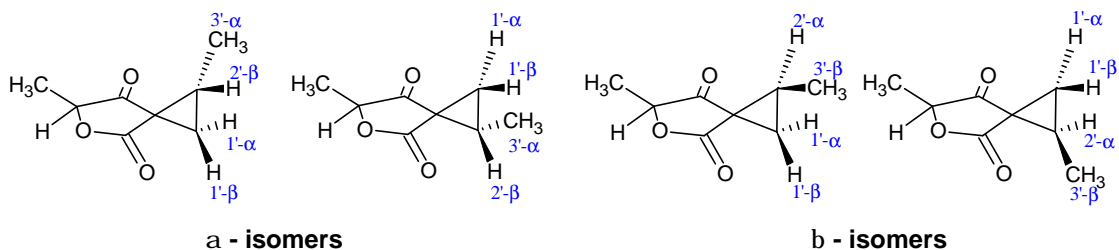## 6-Hexyl-1-methyl-5-oxa-spiro[2.4]heptane-4,7-dione (58d)

Colourless oil (0.09 g, 0.4 mmol, 18%) from 0.50 g (2.2 mmol) of 4-allyloxy-5-hexyl-5*H*-furan-2-one **51f**. The product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (2/3) as eluent.

R_f (SiO$_2$) = 0.68 (*n*-hexane : diethyl ether, v : v, 2 : 3).

Molecular formula = C$_{13}$H$_{20}$O$_3$
Molecular Weight = 224.296
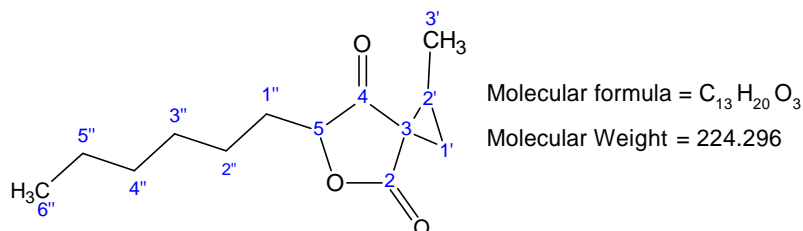
Mixture of four diastereoisomers α, α∗ and β, β∗. Ratio α : β = 1 : 1.3 (β isomer has the methyl group next to the lactone group)

IR (ATR) $\bar{ν}$ (cm^{-1}) = 2956 (W) [ν (-CH$_2$-)], 2929 (W) [ν (-CH$_2$-)], 2860 (W) [ν (-CH$_2$-)], 1787 (M) [ν (C=O)], 1738 (VS) [ν (C=O)], 1336 (M) [ν (C-O-C)], 1167 (S) [ν (C-O)], 1035 (M) [ν (cyclopropane)].

a - isomers **b - isomers**
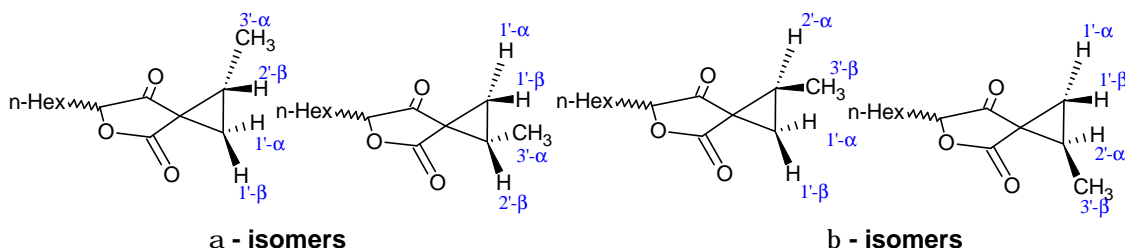
^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.82 (t, $^3J_{HH}$ = 6.65 Hz, 6H, 6''-H), 1.12 - 1.33 (m, 4H, 2''-H), 1.13 - 1.56 (m, 4H, 4''-H), 1.16 - 1.30 (m, 4H, 5''-H), 1.18 - 1.47 (m, 4H, 3''-H), 1.26 (d, $^3J_{HH}$ = 6.18 Hz, 3'-H$^\alpha$) and 1.29 (d, $^3J_{HH}$ = 6.18 Hz, 3'-H$^{\alpha*}$) (integral 3H), 1.37 (d, $^3J_{HH}$ = 6.04 Hz, 3H, 3'-H$^{\beta+\beta*}$), 1.61 – 1.78 (m, 2H, 1''-H), 1.62 – 1.72 (m, 1H, 1'α-H$^{\alpha+\alpha*}$), 1.71 – 1.77 (m, 1H, 1'α-H$^{\beta+\beta*}$), 1.78 – 1.97 (m, 2H, 1''-H), 1.92 – 2.00 (m, 1H, 1'β-H$^{\beta+\beta*}$), 2.00 – 2.06 (m, 1H, 1'β-H$^{\alpha+\alpha*}$), 2.07 – 2.23 (m, 1H, 2'α-H$^{\beta+\beta*}$), 2.26 – 2.41 (m, 1H, 2'β-H$^{\alpha+\alpha*}$), 4.61 – 4.72 (m, 2H, 5-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = (signals have a temptative α, $\alpha*$ and / or β, $\beta*$ assignation because of the low resolution in the HSQC spectra) 11.30 (CH$_3$, 3'-C$^\alpha$), 11.37 (CH$_3$, 3'-C$^{\alpha*}$), 11.99 (CH$_3$, 3'-C$^\beta$), 12.14 (CH$_3$, 3'-C$^{\beta*}$), 13.88 (CH$_3$, 6''-C$^{\alpha+\alpha*,\ \beta+\beta*}$), 22.36 (CH$_2$, 5''-C$^{\alpha+\alpha*,\ \beta+\beta*}$), 24.01 (CH$_2$, 4''-C$^{\alpha+\alpha*}$), 24.22 (CH$_2$, 4''-C$^\beta$), 24.24 (CH$_2$, 4''-C$^{\beta*}$), 28.65 (CH$_2$, 3''-C$^{\alpha+\alpha*,\ \beta+\beta*}$), 29.47 (CH$_2$, 1'-C$^\alpha$), 29.81 (CH$_2$, 1'-C$^{\alpha*}$), 29.86 (CH$_2$, 1'-C$^\beta$), 30.10 (CH$_2$, 1'-C$^{\beta*}$), 31.30 (CH$_2$, 1''-C$^\alpha$), 31.36 (CH$_2$, 2''-C$^{\alpha+\alpha*,\ \beta+\beta*}$ and CH$_2$, 1''-C$^{\alpha*}$), 31.48 (CH$_2$, 1''-C$^\beta$), 31.62 (CH$_2$, 1''-C$^{\beta*}$), 32.45 (C^q, 3-C$^\alpha$), 32.52 (C^q, 3-C$^{\alpha*}$), 33.23 (C^q, 3-C$^\beta$), 33.35 (C^q, 3-C$^{\beta*}$), 35.79 (CH, 2'-C$^\beta$), 36.31 (CH, 2'-C$^{\beta*}$), 36.35 (CH, 2'-C$^\alpha$), 36.41 (CH, 2'-C$^{\alpha*}$), 84.25 (CH, 5-C$^\alpha$), 84.27 (CH, 5-C$^{\alpha*}$), 84.50 (CH, 5-C$^\beta$), 84.73 (CH, 5-C$^{\beta*}$), 173.23 (C^q, 2-C$^\alpha$), 173.28 (C^q, 2-C$^{\alpha*}$), 175.07 (C^q, 2-C$^\beta$), 175.09 (C^q, 2-C$^{\beta*}$), 207.18 (C^q, 4-C$^\alpha$), 207.25 (C^q, 4-C$^{\alpha*}$), 208.20 (C^q, 4-C$^\beta$), 208.24 (C^q, 4-C$^{\beta*}$).

MS (GC inlet, EI, 70 eV) m/z (%) = (α and β isomers were separated in the GC column and contain the same fragmentation pattern) 224 (9) [M$^+$], 153 (32) [M-C$_5$H$_{11}$]$^+$, 140 (100) [M-C$_6$H$_{12}$]$^+$, 122 (3) [M$_{140}$-H$_2$O]$^+$, 111 (10) [M-C$_7$H$_{14}$O]$^+$, 82 (29) [M-C$_8$H$_{14}$O$_2$]$^+$, 54 (64) [C$_4$H$_6^+$], 41 (27) [C$_3$H$_5^+$].

6-Butyl-1-methyl-5-oxa-spiro[2.4]heptane-4,7-dione (58e)

Colourless oil from 0.5 g (2.97 mmol) of 4-allyloxy-5-butyl-5*H*-furan-2-one **51e**. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluent.

Yield: 29% (0.08 g, 0.4 mmol). R_f (SiO$_2$) = 0.63 (*n*-hexane : diethyl ether, v : v, 2 : 3).
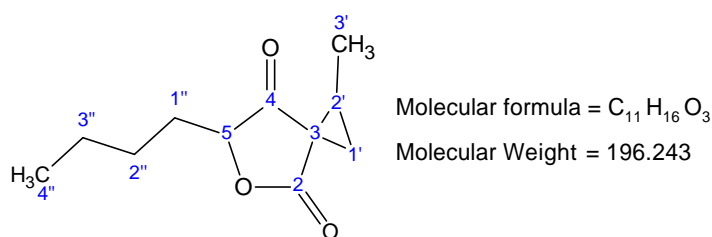
Molecular formula = $C_{11}H_{16}O_3$

Molecular Weight = 196.243

Mixture of four diastereoisomers α, α∗ and β, β∗. Ratio α : β = 1 : 1.2 (β isomer has the methyl group next to the lactone group)

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 2959 (W) [ν (-CH$_2$-)], 2934 (W) [ν (-CH$_2$-)], 1786 (M) [ν (C=O)], 1737 (VS) [ν (C=O)], 1337 (M) [ν (C-O-C)], 1168 (S) [ν (C-O)], 1007 (M) [ν (cyclopropane)], 755 (M) [ν (C-H cyclopropane)].

a - isomers   **b - isomers**
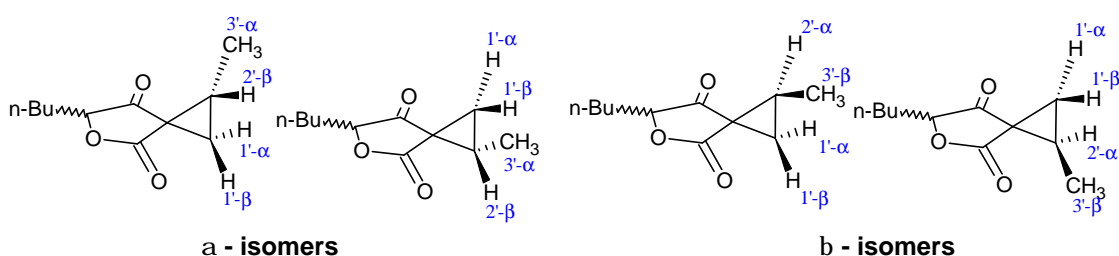
^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.83 (t, $^3J_{HH}$ = 7.00 Hz, 6H, 4''-H), 1.15 - 1.43 (m, 8H, 3''-H, 2''-H), 1.24 (d, $^3J_{HH}$ = 6.16 Hz, 3'-H$^\alpha$) and 1.27 (d, $^3J_{HH}$ = 6.16 Hz, 3'-H$^{\alpha*}$) (integral 3H), 1.34 (d, $^3J_{HH}$ = 6.11 Hz, 3H, 3'-H$^{\beta+\beta*}$), 1.60 – 1.70 (m, 1H, 1'α-H$^{\alpha+\alpha*}$), 1.60 – 1.76 (m, 2H, 1''-H), 1.69 – 1.75 (m, 1H, 1'α-H$^{\beta+\beta*}$), 1.76 – 1.92 (m, 2H, 1''-H), 1.90 – 1.98 (m, 1H, 1'β-H$^{\beta+\beta*}$), 1.97 – 2.05 (m, 1H, 1'β-H$^{\alpha+\alpha*}$), 2.05 – 2.22 (m, 1H, 2'α-H$^{\beta+\beta*}$), 2.25 – 2.37 (m, 1H, 2'β-H$^{\alpha+\alpha*}$), 4.68 (m, 2H, 5-H). Integral determined via 2D COSY (manual integration) on single signals; ratio α/β : 1/1.2.

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = (signals are not totally α, α∗ and / or β, β∗ assigned because of the low resolution in the HSQC spectra) 11.20 (CH$_3$, 3'-C$^\alpha$), 11.25 (CH$_3$, 3'-C$^{\alpha*}$), 11.89 (CH$_3$, 3'-C$^\beta$), 12.05 (CH$_3$, 3'-C$^{\beta*}$), 13.53 (CH$_3$, 4''-C$^{\alpha+\alpha*}$), 13.63 (CH$_3$, 4''-C$^{\beta+\beta*}$), 22.00$^\#$ (CH$_2$, 3''-C$^{\alpha+\alpha*}$), 22.14 (CH$_2$, 3''-C$^\beta$), 22.16 (CH$_2$, 3''-C$^{\beta*}$), 26.01 (CH$_2$, 2''-C$^{\alpha+\alpha*}$), 26.22 (CH$_2$, 2''-C$^\beta$), 26.25 (CH$_2$, 2''-C$^{\beta*}$), 29.47 (CH$_2$, 1'-C$^\alpha$), 29.83 (CH$_2$, 1'-C$^{\alpha*}$), 29.87 (CH$_2$, 1'-C$^\beta$), 30.12 (CH$_2$, 1'-C$^{\beta*}$), 30.85 (CH$_2$, 1''-C$^\alpha$), 30.90 (CH$_2$, 1''-C$^{\alpha*}$), 31.03 (CH$_2$, 1''-C$^\beta$), 31.17 (CH$_2$, 1''-C$^{\beta*}$), 32.45 (C^q, 3-C$^\alpha$), 32.52 (C^q, 3-C$^{\alpha*}$), 33.24 (C^q, 3-C$^\beta$), 33.36 (C^q, 3-C$^{\beta*}$), 35.90 (CH, 2'-C$^\beta$), 36.41 (CH, 2'-C$^{\beta*}$), 36.47 (CH, 2'-C$^\alpha$), 36.51 (CH, 2'-C$^{\alpha*}$), 84.24 (CH, 5-C$^\alpha$), 84.26 (CH, 5-C$^{\alpha*}$), 84.49 (CH, 5-C$^\beta$), 84.74 (CH, 5-C$^{\beta*}$), 173.46 (C^q, 2-C$^\alpha$), 175.36 (C^q, 2-

C$^{\alpha *}$), 176.61 (C^q, 2-C$^{\beta+\beta *}$), 207.08 (C^q, 4-C$^\alpha$), 207.15 (C^q, 4-C$^{\alpha *}$), 208.16 (C^q, 4-C$^\beta$), 208.20 (C^q, 4-C$^{\beta *}$).

MS (GC inlet, EI, 70 eV) m/z (%) = (α, $\alpha *$, β and $\beta *$ isomers were separated in the GC column and contain the same fragmentation pattern) 196 (4) [M$^+$], 167 (1) [M-CO]$^+$, 153 (16) [M-CO$_2$]$^+$, 140 (100) [M-C$_4$H$_9$]$^+$, 82 (27), 54 (61) [M$_{82}$-CO]$^+$, 41 (17) [C$_3$H$_5^+$].

## 6-Butyl-1,2-dimethyl-5-oxa-spiro[2.4]heptane-4,7-dione (58f)

Colourless oil (0.25 g, 1.2 mmol, 50%) from 0.50 g (2.4 mmol) of 4-but-2-enyloxy-5-butyl-5*H*-furan-2-one **51h**. The product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluent.

R_f (SiO$_2$) = 0.73 (*n*-hexane : diethyl ether, 2 : 3, v : v).

Molecular formula = C$_{12}$H$_{18}$O$_3$
Molecular Weight = 210.269
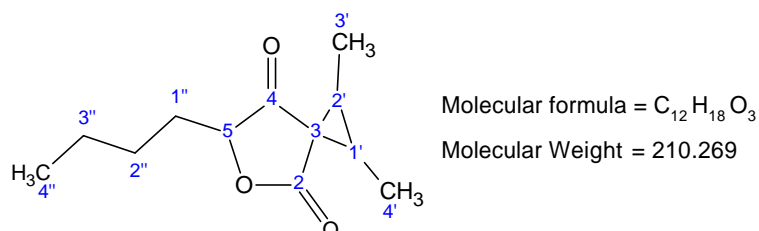
Mixture of four diastereoisomers (not distinction nor quantification was possible between them)

IR (ATR) $\overline{\nu}$ **(cm^{-1})** = 2933 (W) [ν (-CH$_2$-)], 2874 (W) [ν (-CH$_2$-)], 1782 (M) [ν (C=O)], 1733 (VS) [ν (C=O)], 1334 (M) [ν (C-O-C)], 1186 (S) [ν (C-O)], 1082 (M), 1011 (M) [ν (cyclopropane)].
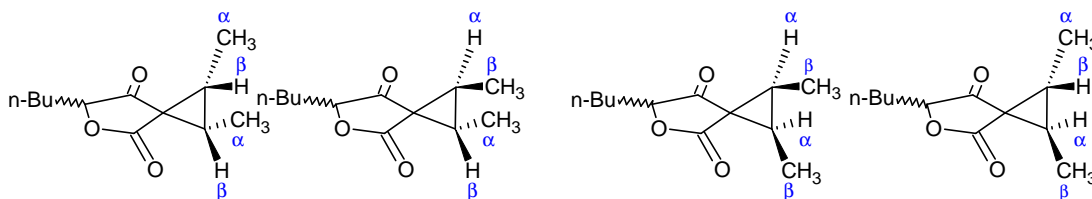
^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.80 (t, ^{3}J$_{HH}$ = 7.07 Hz, 3H, 4''-H), 1.09 – 1.41 (m, 4H, 3''-H and 2''-H), 1.21 (d, ^{3}J$_{HH}$ = 6.02 Hz, 3'H) and 1.24 (d, ^{3}J$_{HH}$ = 5.97 Hz, 3'H) and 1.28 (d, ^{3}J$_{HH}$ = 6.14 Hz, 3'H) and 1.29 (d, ^{3}J$_{HH}$ = 6.14 Hz, 3'H) (Integral 3H), 1.25 (d, ^{3}J$_{HH}$ = 6.08 Hz, 4'H) and 1.28 (d, ^{3}J$_{HH}$ = 6.12 Hz, 4'H) and 1.34 (d, ^{3}J$_{HH}$ = 6.15 Hz, 4'H) and 1.35 (d, ^{3}J$_{HH}$ = 6.09 Hz, 4'H) (Integral 3H), 1.60 – 1.77 (m, 1H, 1''-H), 1.77– 1.95 (m, 1H, 1''-H), 2.01 – 2.19 (m, 1H, 1'-H), 2.20 – 2.55 (m, 1H, 2'-H), 4.54 – 4.66 (m, 1H, 5-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = (Carbon atoms with same magnetic environment have the same chemical shift in more than one isomer and are not listed repeated[#]) 5.94[#] (CH$_3$, 3'-C), 6.55 (CH$_3$, 3'-C), 6.76 (CH$_3$, 3'-C), 11.07 (CH$_3$, 4'-C), 11.15 (CH$_3$, 4'-C), 11.75 (CH$_3$, 4'-C), 11.95 (CH$_3$, 4'-C), 13.54[#] (CH$_3$, 4''-C), 22.02[#] (CH$_2$, 3''-C), 22.04[#] (CH$_2$,

3''-C), 26.03# (CH$_2$, 2''-C), 26.08# (CH$_2$, 2''-C), 30.99 (CH$_2$, 1''-C), 31.07 (CH$_2$, 1''-C), 31.10 (CH$_2$, 1''-C), 31.19 (CH$_2$, 1''-C), 37.12# (C^q, 3-C), 37.28# (C^q, 3-C), 38.53 (CH, 1'-C), 38.93 (CH, 1'-C), 39.20 (CH, 1'-C), 39.34 (CH, 1'-C), 42.07 (CH, 2'-C), 42.97 (CH, 2'-C), 43.20 (CH, 2'-C), 43.49 (CH, 2'-C), 83.27 (CH, 5-C), 83.61 (CH, 5-C), 83.83 (CH, 5-C), 84.02 (CH, 5-C), 172.04 (C^q, 2-C), 173.56 (C^q, 2-C), 173.61 (C^q, 2-C), 175.67 (C^q, 2-C), 206.65 (C^q, 4-C), 207.35 (C^q, 4-C), 207.38 (C^q, 4-C), 208.48 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = (3 of 4 isomers were separated in the GC column and contain the same fragmentation pattern) 210 (8) [M$^+$], 195 (2) [M-CH$_3$]$^+$, 167 (20) [M$_{195}$-CO]$^+$, 154 (100) [M-C$_4$H$_7$]$^+$, 136 (7) [M$_{154}$-H$_2$O]$^+$, 125 (8) [M$_{154}$-CO]$^+$, 96 (28) [M$_{125}$-CO]$^+$, 68 (52) [M$_{96}$-CO]$^+$.

3.9   Synthesis of 4-Hydroxy-3-(2-alkyloxypropyl)-5*H*-furan-2-ones

3-Allyl-4-hydroxy-5*H*-furan-2-one (60a)

General experimental procedure:

In a dry 100 mL two-necked flask 0.35 g (2.5 mmol) of 1-methyl-5-oxa-spiro[2.4]heptane-4,7-dione **58a** were dissolved in 15 mL dry chloroform and 10 mL methanol. The solution was refluxed under stirring for 22 h at 70°C. The solvent was removed under reduced pressure at 38°C and the product appeared as a colourless oil.

Yield: 95% (0.41 g, 2.37 mmol). R_f (SiO$_2$) = 0.39 (diethyl ether).
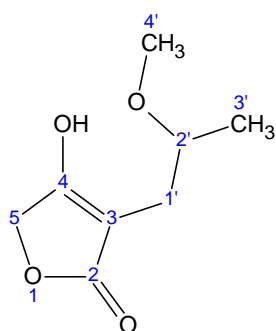
Molecular formula = C$_8$H$_{12}$O$_4$
Molecular Weight = 172.178

IR (ATR) $\bar{v}$ (cm^{-1}) = 2974 (W) [ν (-CH$_2$-)], 2728 (W) [ν (O-H) intramolecular bridge], 1748 (M) and 1647 (S) [ν (Tetronic ring)], 1081 (S) [ν (C-O-C)], 1042 (VS) [ν (C-O)], 984 (S) [ν (C-H)], 693 (S) [ν (C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 1.15 (d, $^3J_{HH}$ = 6.17 Hz, 3H, 3'-H), 2.32 (ddt, $^3J_{HH}$ = 5.76 Hz, $^2J_{HH}$ = 16.47 Hz, $^5J_{HH}$ = 1.10 Hz, 1H, 1'-H$_{pseudo\ axial}$), 2.53 (d, $^3J_{HH}$ = 3.25 Hz, $^2J_{HH}$ = 16.47 Hz, $^5J_{HH}$ = 1.37 Hz, 1H, 1'-H$_{pseudo\ equatorial}$), 3.42 (s, 3H, 4'-H), 3.73 (ddt, $^3J_{HH}$ =

3.25 Hz, $^3J_{HH}$ = 5.76 Hz, $^3J_{HH}$ = 6.17 Hz, 1H, 2'-H$_{pseudo\ axial}$), 4.52 (t, $^5J_{HH}$ = 1.10 Hz, $^5J_{HH}$ = 1.37 Hz, 2H, 5-H), 9.70 (br. s., 1H, O-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 17.51 (CH$_3$, 3'-C), 28.80 (CH$_2$, 1'-C), 55.90 (CH$_3$, 4'-C), 66.59 (CH$_2$, 5-C), 77.42 (CH, 2'-C), 96.84 (C^q, 3-C), 173.58 (C^q, 2-C), 175.44 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 172 (3) [M$^+$], 157 (6) [M-CH$_3$]$^+$, 139 (2) [M$_{157}$-H$_2$O]$^+$, 122 (4), 114 (11) [M-C$_2$H$_2$O$_2$]$^+$, 96 (4) [M$_{114}$-H$_2$O]$^+$, 82 (5), 59 (100) [C$_3$H$_7$O$^+$].

4-Hydroxy-3-(2-methoxypropyl)-5-methyl-5*H*-furan-2-one (60b)

Colourless oil (181 mg, 0.97 mmol, 83%) from 180 mg (1.17 mmol) of 1,6-dimethyl-5-oxa-spiro[2.4]heptane-4,7-dione **58b** and 10 mL of methanol in 20 mL of chloroform, heated under reflux for 24 h. The product was purified by column chromatography on SiO$_2$ [length 20 cm, $\varnothing$ 1 cm] using diethyl ether as eluent.

R_f (SiO$_2$) = 0.59 (diethyl ether).

Molecular Formula = C$_9$H$_{14}$O$_4$
Formula Weight   = 186.205
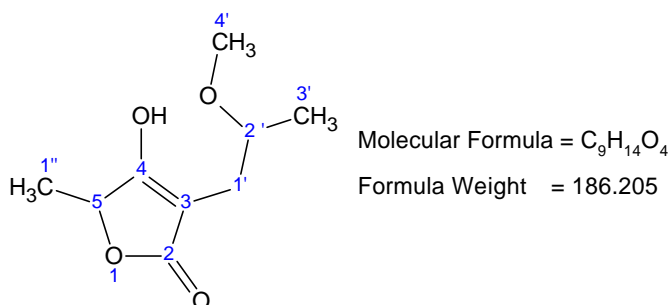
*Mixture of diastereoisomers **a** and **b**.* Ratio α : β = 1 : 1.

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3000 (W) [ν (O-H)], 2978 (M) [ν (-CH$_2$-)], 2709 (W) [ν (-OH bridge)], 1747 (S) and 1657 (VS) [ν (Tetronic ring)], 1088 (S) [ν (C-O)] , 1053 (VS) [ν (C-O)], 1029 (S) [ν (C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.12 (d, $^3J_{HH}$ = 6.17 Hz, 3'-H*a isomer*), 1.15 (d, $^3J_{HH}$ = 6.17 Hz, 3'-H*b isomer*) (Total integral = 3H; ratio 1 : 1), 1.40 (d, $^3J_{HH}$ = 6.72 Hz, 3H, 1''-H), 2.32 (dddd, $^3J_{HH}$ = 5.63 Hz, $^2J_{HH}$ = 16.46 Hz, $^5J_{HH}$ = 0.69 Hz, $^5J_{HH}$ = 0.97 Hz, 1H, 1'-H$_{pseudo\ axial}$), 2.52 (d, $^2J_{HH}$ = 16.46 Hz, 1H, 1'-H$_{pseudo\ equatorial}$), 3.42 (s, 3H, 4'-H), 3.68 – 3.80 (m, 1H, 2'-H), 4.71 (m, 1H, 5-H), 10.42 (br. s., 1H, O-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = (signals are not totally α and / or β assigned because of the low resolution in the HSQC spectra) 17.42 (CH$_3$, 3'-C$^\alpha$), 17.48 (CH$_3$, 3'-C$^\beta$), 17.64 (CH$_3$, 1''-C$^\alpha$), 17.74 (CH$_3$, 1''-C$^\beta$), 28.64 (CH$_2$, 1'-C$^\alpha$), 28.68 (CH$_2$, 1'-C$^\beta$), 55.92 (CH$_3$, 4'-C$^\alpha$), 55.94 (CH$_3$, 4'-C$^\beta$), 73.90 (CH, 5-C$^{\alpha+\beta}$), 77.44 (CH, 2'-C$^{\alpha+\beta}$), 96.05 (C^q, 3-C$^\alpha$), 96.08 (C^q, 3-C$^\beta$), 174.47 (C^q, 2-C$^{\alpha+\beta}$), 176.66 (C^q, 4-C$^\alpha$), 176.77 (C^q, 4-C$^\beta$).

MS (GC inlet, EI, 70 eV) m/z (%) = 186 (4) $[M^+]$, 171 (10) $[M-CH_3]^+$, 153 (2) $[M_{171}$-$H_2O]^+$, 138 (1) $[M_{153}-CH_3]^+$, 128 (25) $[M-C_3H_7O]^+$, 110 (11) $[M_{128}-H_2O]^+$, 82 (8) $[M_{110}-CO]^+$, 59 (100) $[C_3H_7O^+]$.

5-Hexyl-4-hydroxy-3-(2-methoxypropyl)-5*H*-furan-2-one (60c)

Colourless oil (540 mg, 2.11 mmol, 95%) from 500 mg (2.22 mmol) of 6-hexyl-1-methyl-5-oxa-spiro[2.4]heptane-4,7-dione **58d** and 10 mL of methanol in 20 mL of chloroform, heated under reflux for 24 h. The product was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent.

R_f (SiO_2) = 0.59 (diethyl ether).

Molecular Formula = $C_{14}H_{24}O_4$
Formula Weight = 256.338
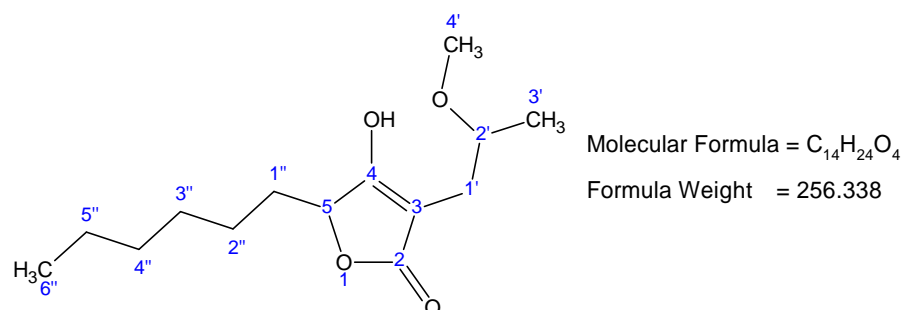
*Mixture of diastereoisomers **a** and **b**. Ratio* $\alpha : \beta$ = 1 : 1.3

IR (ATR) $\bar{v}$ **(cm^{-1})** = 3000 (W) [v (-OH)], 2928 (M) [v (-CH_2-)], 2735 (W) [v (-OH intramolecular bridge)], 1751 (S) and 1655 (VS) [v (Tetronic ring)], 1458 (M), 1055 (VS) [v (C-O)], 760 (M) [v (C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.81 (t, $^3J_{HH}$ = 6.79 Hz, 3H, 6''-H), 1.12 (d, $^3J_{HH}$ = 6.18, 3'-H*a isomer*) and 1.15 (d, $^3J_{HH}$ = 6.18 Hz, 3'-H*b isomer*) (Total integral = 3H, ratio 1 : 1), 1.16 – 1.31 (m, 6H, 5''-3''-2''-H), 1.31 – 1.43 (m, 2H, 4''-H), 1.45 – 1.61 (m, 1H, 1''-H), 1.78 – 1.94 (m, 1H, 1''-H), 2.32 (dddd, $^3J_{HH}$ = 5.63 Hz, $^2J_{HH}$ = 16.47 Hz, $^5J_{HH}$ = 0.82 Hz, $^5J_{HH}$ = 0.97 Hz, 1H, 1'-H$_{pseudo\ axial}$), 2.52 (d, $^2J_{HH}$ = 16.47 Hz, 1H, 1'-H$_{pseudo\ equatorial}$), 3.41 (s, 3H, 4'-H), 3.66 – 3.79 (m, 1H, 2'-H), 4.63 (m, 1H, 5-H), 10.47 (br. s., 1H, O-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = (signals are not totally α and / or β assigned because of the low resolution in the HSQC spectra) 13.90 (CH_3, 6''-C$^{\alpha+\beta}$), 17.41 (CH_3, 3'-C$^{\alpha}$), 17.44 (CH_3, 3'-C$^{\beta}$), 22.38 (CH_2, 5''-C$^{\alpha+\beta}$), 24.00 (CH_2, 4''-C$^{\alpha}$), 24.09 (CH_2, 4''-C$^{\beta}$), 28.63 (CH_2, 1'-C$^{\alpha}$), 28.68 (CH_2, 1'-C$^{\beta}$), 28.81 (CH_2, 3''-C$^{\alpha+\beta}$), 31.46 (CH_2, 2''-C$^{\alpha+\beta}$), 31.61 (CH_2, 1''-C$^{\alpha}$), 31.63 (CH_2, 1''-C$^{\beta}$), 55.89 (CH_3, 4'-C$^{\alpha}$), 55.92 (CH_3, 4'-C$^{\beta}$), 77.40 (CH, 2'-C$^{\alpha}$), 77.49 (CH, 2'-C$^{\beta}$), 77.55 (CH, 5-C$^{\alpha+\beta}$), 96.68 (C^q, 3-C$^{\alpha}$), .96.70 (C^q, 3-C$^{\beta}$), 174.82 (C^q, 2-C$^{\alpha+\beta}$), 175.75 (C^q, 4-C$^{\alpha}$), 175.80 (C^q, 4-C$^{\beta}$).

MS (GC inlet, EI, 70 eV) m/z (%) = 257 (1) $[M+H]^+$, 256 (4) $[M^+]$, 241 (4) $[M-CH_3]^+$, 224 (5) $[M_{257}-CH_3O]^+$, 198 (3) $[M_{257}-C_3H_7O]^+$, 172 (6) $[M_{257}-C_6H_{13}]^+$, 140 (11) $[M_{224}-C_6H_{13}]^+$, 127 (4) $[M_{241}-C_7H_{14}O]^+$, 109 (7) $[M_{127}-H_2O]^+$, 59 (100) $[C_3H_7O^+]$.

3-(2-Allyloxypropyl)-4-hydroxy-5*H*-furan-2-one (60d)

Colourless oil (440 mg, 2.22 mmol, 91%) from 350 mg (2.44 mmol) of 1-methyl-5-oxa-spiro[2.4]heptane-4,7-dione **58a** and 10 mL of allyl alcohol in 20 mL of chloroform, heated under reflux for 24 h. The product was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent.

R_f (SiO_2) = 0.42 (diethyl ether).

Molecular Formula = $C_{10}H_{14}O_4$
Formula Weight = 198.216
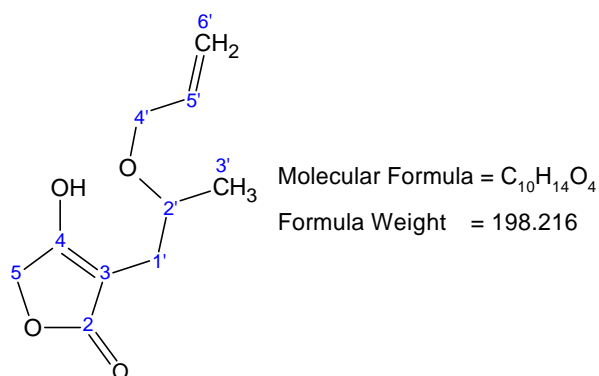
IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3300 (W) [ν (-OH)], 2976 (W) [ν (-CH$_2$-)], 2731 (W) [ν (-OH bridge)], 1749 (S) and 1647 (VS) [ν (Tetronic ring)], 1040 (VS) [ν (C-O-C)], 989 (S) [ν (=C-H)], 921 (S) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 1.17 (dd, $^3J_{HH}$ = 6.31 Hz, $^4J_{HH}$ = 0.41 Hz, 3H, 3'-H), 2.36 (ddt, $^3J_{HH}$ = 5.35 Hz, $^2J_{HH}$ = 16.33 Hz, $^5J_{HH}$ = 1.10 Hz, 1H, 1'-H), 2.55 (ddt, $^3J_{HH}$ = 3.30 Hz, $^2J_{HH}$ = 16.33 Hz, $^4J_{HH}$ = 0.41 Hz, 1H, 1'-H), 3.90 (ddq, $^3J_{HH}$ = 3.30 Hz, $^3J_{HH}$ = 5.35 Hz, $^3J_{HH}$ = 6.31 Hz, 1H, 2'-H), 4.01 (dd, $^3J_{HH}$ = 6.17 Hz, $^2J_{HH}$ = 12.21 Hz, $^4J_{HH}$ = 1.24 Hz, $^4J_{HH}$ = 1.37 Hz, 1H, 4'-H), 4.16 (dd, $^3J_{HH}$ = 5.63 Hz, $^2J_{HH}$ = 12.21 Hz, $^4J_{HH}$ = 1.24 Hz, $^4J_{HH}$ = 1.37 Hz, 1H, 4'-H), 4.53 (dd, $^5J_{HH}$ = 1.10 Hz, $^5J_{HH}$ = 0.82 Hz, 2H, 5-H), 5.24 (ddd, $^3J_{HH}$ = 10.29 Hz, $^2J_{HH}$ = 1.30 Hz, $^4J_{HH}$ = 1.24 Hz, 1H, 6'-H$_{cis}$), 5.31 (ddd, $^3J_{HH}$ = 17.15 Hz, $^2J_{HH}$ = 1.30 Hz, $^4J_{HH}$ = 1.37 Hz, 1H, 6'-H$_{trans}$), 5.87 (dddd, $^3J_{HH}$ = 5.63 Hz, $^3J_{HH}$ = 6.17 Hz, $^3J_{HH}$ = 10.29 Hz, $^3J_{HH}$ = 17.15 Hz, 1H, 5'-H), 10.52 (br. s., 1H, O-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 18.00 (CH$_3$, 3'-C), 29.08 (CH$_2$, 1'-C), 66.64 (CH$_2$, 5-C), 69.64 (CH$_2$, 4'-C), 75.26 (CH, 2'-C), 96.87 (C^q, 3-C), 119.16 (CH$_2$, 6'-C), 132.64 (CH, 5'-C), 173.49 (C^q, 2-C), 175.58 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 198 (2) $[M^+]$, 180 (1) $[M-H_2O]^+$, 157 (11) $[M-C_3H_5]^+$, 141 (25) $[M-C_3H_5O_2]^+$, 122 (22), 113 (57) $[M-C_5H_9O]^+$, 85 (98) $[C_5H_9O^+]$, 43 (100) $[C_3H_7^+]$.

3-(2-Allyloxypropyl)-4-hydroxy-5-methyl-5*H*-furan-2-one (60e)

Colourless oil (390 mg, 1.84 mmol, 94%) from 300 mg (1.95 mmol) of 1,6-dimethyl-5-oxa-spiro[2.4]heptane-4,7-dione **58b** and 10 mL of allyl alcohol in 20 mL of chloroform, heated under reflux for 24 h. The product was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent.

R_f (SiO_2) = 0.94 (diethyl ether).

Molecular Formula = $C_{11}H_{16}O_4$
Formula Weight = 212.242
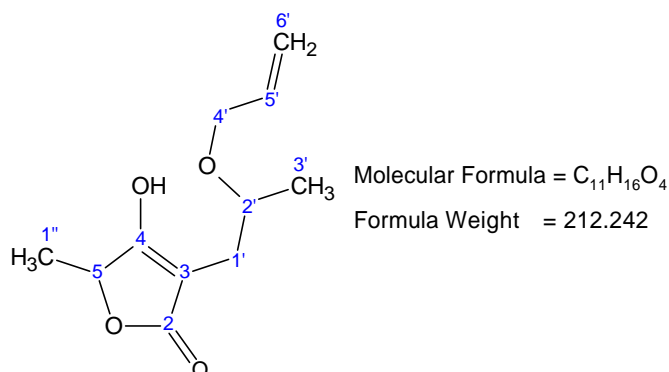
*Mixture of diastereoisomers **a** and **b**. Ratio* $\alpha : \beta = 1 : 1$.

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3000 (W) [ν (O-H)], 2724 (W) [ν (O-H bridge)], 1748 (S) and 1655 (VS) [ν (Tetronic ring)], 1329 (S) [ν (C-O)], 1089 (S) [ν (C-O)], 1032 (VS) [ν (C-O)], 924 (S) [ν (=C-H)], 779 (M) [ν (C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.14 (d, $^3J_{HH}$ = 6.32 Hz, 3H, 3'-H), 1.38 (d, $^3J_{HH}$ = 6.72 Hz, 1''-H*a isomer*) and 1.39 (d, $^3J_{HH}$ = 6.72 Hz, 1''-H*b isomer*) (Total integral = 3H), 2.33 (ddd, $^3J_{HH}$ = 5.21 Hz, $^2J_{HH}$ = 16.33 Hz, $^4J_{HH}$ = 0.96 Hz, 1H, 1'-H$_{pseudo\ axial}$), 2.52 (d, $^2J_{HH}$ = 16.33 Hz, 1H, 1'-H$_{pseudo\ equatorial}$), 3.85 – 3.96 (m, 1H, 2'-H), 3.99 (dddd, $^3J_{HH}$ = 6.18 Hz, $^2J_{HH}$ = 12.21 Hz, $^4J_{HH}$ = 1.10 Hz, $^4J_{HH}$ = 1.37 Hz, 1H, 4'-H), 4.14 (dddd, $^3J_{HH}$ = 5.62 Hz, $^2J_{HH}$ = 12.21 Hz, $^4J_{HH}$ = 1.10 Hz, $^4J_{HH}$ = 1.37 Hz, 1H, 4'-H), 4.66 – 4.79 (m, 1H, 5-H), 5.22 (dddd, $^3J_{HH}$ = 10.43 Hz, $^2J_{HH}$ = 1.51 Hz, $^4J_{HH}$ = 1.10 Hz, $^4J_{HH}$ = 1.37 Hz, 1H, 6'-H$_{cis}$), 5.28 (dddd, $^3J_{HH}$ = 17.15 Hz, $^2J_{HH}$ = 1.51 Hz, $^4J_{HH}$ = 1.10 Hz, $^4J_{HH}$ = 1.37 Hz, 1H, 6'-H$_{trans}$), 5.80 – 5.97 (m, 1H, 5'-H), 10.43 (br. s., 1H, O-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = (signals are not totally α and / or β assigned because of the low resolution in the HSQC spectra) 17.57 (CH$_3$, 3'-C$^\alpha$), 17.70 (CH$_3$, 3'-C$^\beta$), 17.88 (CH$_3$, 1''-C$^{\alpha+\beta}$), 28.81 (CH$_2$, 1'-C$^\alpha$), 28.87 (CH$_2$, 1'-C$^\beta$), 69.58 (CH$_2$, 4'-C$^{\alpha+\beta}$), 73.92 (CH, 5-C$^\alpha$), 73.94 (CH, 5-C$^\beta$), 75.20 (C^q, 2-C$^\alpha$), 75.25 (C^q, 2-C$^\beta$), 96.02 (C^q, 3-C$^{\alpha+\beta}$), 119.03 (CH$_2$, 6'-C$^{\alpha+\beta}$), .132.63 (CH, 5'-C$^\alpha$), 132.65 (CH, 5'-C$^\beta$), 174.58 (C^q, 2-C$^{\alpha+\beta}$), 176.64 (C^q, 4-C$^\alpha$), 176.70 (C^q, 4-C$^\beta$).

MS (GC inlet, EI, 70 eV) m/z (%) = 212 (2) [M$^+$], 197 (1) [M-CH$_3$]$^+$, 171 (12) [M-C$_3$H$_5$]$^+$, 155 (24) [M-C$_3$H$_5$O]$^+$, 127 (29) [M-C$_5$H$_9$O]$^+$, 109 (23) [M$_{127}$-H$_2$O]$^+$, 85 (48) [C$_5$H$_9$O$^+$], 41 (100) [C$_3$H$_5^+$].

3-(2-Allyloxypropyl)-5-ethyl-4-hydroxy-5*H*-furan-2-one (60f)

Colourless oil (0.34 g, 1.5 mmol, 89%) from 0.28 g (1.69 mmol) of 6-ethyl-1-methyl-5-oxa-spiro[2.4]heptane-4,7-dione **58c**. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent.

R_f (SiO$_2$) = 0.73 (diethyl ether).

Molecular Formula = C$_{12}$H$_{18}$O$_4$
Formula Weight = 226.269
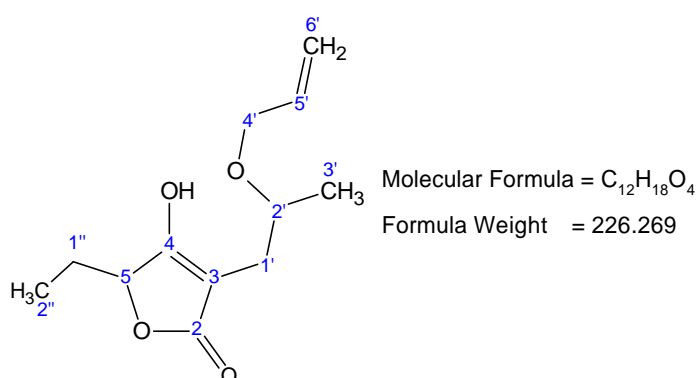
*Mixture of diastereoisomers **a** and **b**.* Ratio α : β = 1 : 1.

IR (ATR) $\overline{\nu}$ **(cm^{-1})** = 3080 (W) [ν (-OH)], 2974 (M) [ν (-CH$_2$-)], 1749 (S) and 1655 (VS) [ν (Tetronic ring)], 1299 (S) [ν (C-O)], 1038 (S) [ν (C-O-C)], 979 (VS) [ν (=C-H)], 922 (S) [ν (=C-H)], 770 (M) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.92 (t, $^3J_{HH}$ = 7.41 Hz, 2''-H$^\alpha$) and 0.93 (t, $^3J_{HH}$ = 7.41 Hz, 2''-H$^\beta$) (Total integral : 3H), 1.16 (d, $^3J_{HH}$ = 6.18 Hz, 3'-H$^\alpha$) and 1.17 (d, $^3J_{HH}$ = 6.31 Hz, 3'-H$^\beta$) (Total integral : 3H), 1.55 – 1.73 (m, 1''-H) and 1.86 – 2.04 (m, 1''-H) (Total integral : 2H), 2.37 (dddd, $^3J_{HH}$ = 5.21 Hz, $^2J_{HH}$ = 16.46 Hz, $^4J_{HH}$ = 1.51 Hz, $^4J_{HH}$ = 0.68 Hz, 1H, 1'-H), 2.56 (ddt, $^3J_{HH}$ = 3.30 Hz, $^2J_{HH}$ = 16.46 Hz, $^4J_{HH}$ = 0.41 Hz, 1H, 1'-H), 3.85 - 3.96 (m, 1H, 2'-H), 3.96 – 4.07(m, $^3J_{HH}$ = 5.77 Hz, $^2J_{HH}$ = 12.21 Hz, $^4J_{HH}$ = 1.24 Hz, $^4J_{HH}$ = 1.37 Hz, 1H, 4'-H), 4.11 – 4.21 (ddt, $^3J_{HH}$ = 5.62 Hz, $^2J_{HH}$ = 12.21 Hz, $^4J_{HH}$ = 1.24 Hz, $^4J_{HH}$ = 1.37 Hz, 1H, 4'-H), 4.61 – 4.68 (m, 1H, 5-H), 5.25 (ddt, $^3J_{HH}$ = 10.43 Hz, $^2J_{HH}$ = 1.51 Hz, $^4J_{HH}$ = 1.24 Hz, 1H, 6'-H$_{cis}$), 5.31 (ddt, $^3J_{HH}$ = 17.29 Hz, $^2J_{HH}$ = 1.51 Hz, $^4J_{HH}$ = 1.37 Hz, 1H, 6'-H$_{trans}$), 5.81 – 5.96 (dddd, $^3J_{HH}$ = 5.62 Hz, $^3J_{HH}$ = 5.77 Hz, $^3J_{HH}$ = 10.43 Hz, $^3J_{HH}$ = 17.29 Hz, 1H, 5'-H), 10.39 (s, O-H$^\alpha$), 10.43 (s, O-H$^\beta$) (Total integral : 1H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = (signals are not totally α and / or β assigned because of the low resolution in the HSQC spectra) 7.99 (CH$_3$, 2''-C$^\alpha$), 8.18 (CH$_3$, 2''-C$^\beta$), 17.95 (CH$_3$, 3'-C$^\alpha$), 17.98 (CH$_3$, 3'-C$^\beta$), 24.59 (CH$_2$, 1''-C$^\alpha$), 24.68 (CH$_2$, 1''-C$^\beta$), 28.92

(CH$_2$, 1'-C$^\alpha$), 28.98 (CH$_2$, 1'-C$^\beta$), 69.65 (CH$_2$, 4'-C$^\alpha$), 69.70 (CH$_2$, 4'-C$^\beta$), 75.36 (CH, 2'-C$^\alpha$), 75.44 (CH, 2'-C$^\beta$), 78.31 (CH, 5-C$^\alpha$), 78.37 (CH, 5-C$^\beta$), 97.07 (C^q, 3-C$^{\alpha+\beta}$), 119.13 (CH$_2$, 6'-C$^\alpha$), 119.19 (CH$_2$, 6'-C$^\beta$), 132.69 (CH, 5'-C$^{\alpha+\beta}$), 174.90 (C^q, 2-C$^\alpha$), 174.94 (C^q, 2-C$^\beta$), 175.25 (C^q, 4-C$^\alpha$), 175.39 (C^q, 4-C$^\beta$).

MS (GC inlet, EI, 70 eV) m/z (%) = 226 (2) [M$^+$], 211 (1) [M-CH$_3$]$^+$, 197 (2) [M-C$_2$H$_5$]$^+$, 185 (13) [M-C$_3$H$_5$]$^+$, 169 (25) [M$_{197}$-CO]$^+$, 141 (17) [M-C$_5$H$_9$O]$^+$, 123 (27) [M$_{141}$-H$_2$O]$^+$, 85 (51) [C$_5$H$_9$O$^+$], 41 (100) [C$_3$H$_5^+$].

3-(2-Allyloxypropyl)-5-hexyl-4-hydroxy-5*H*-furan-2-one (60g)

Colourless oil (0.56 g, 1.98 mmol, 89%) from 0.50 g (2.23 mmol) of 6-hexyl-1-methyl-5-oxa-spiro[2.4]heptane-4,7-dione **58d**. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (2/3) as eluent.

R_f (SiO$_2$) = 0.41 (*n*-hexane : diethyl ether, v : v, 2 : 3).

Molecular Formula = C$_{16}$H$_{26}$O$_4$

Formula Weight = 282.375
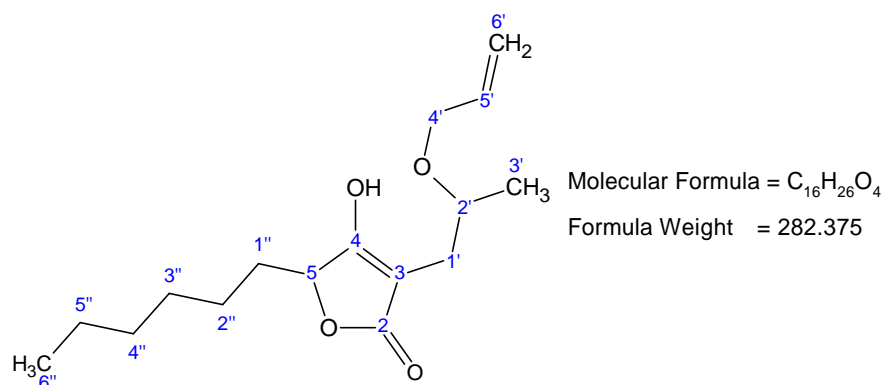
*Mixture of diastereoisomers **a** and **b**.* Ratio α : β = 1 : 1.

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3081 (W) [ν (-OH)], 2927 (M) [ν (-CH$_2$-)], 2859 (M) [ν (-CH$_2$-)], 2738 (W) [ν (-OH bridge)], 1751 (S) and 1665 (VS) [ν (Tetronic ring)], 1338 (M) [ν (C-O)], 1031 (VS) [ν (C-O)], 922 (M) [ν (=C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.83 (t, $^3J_{HH}$ = 6.60 Hz, 3H, 6''-H), 1.15 (d, $^3J_{HH}$ = 6.18 Hz, 3'-H$^\alpha$) and 1.17 (d, $^3J_{HH}$ = 6.04 Hz, 3'-H$^\beta$) (Total integral : 3H), 1.19 - 1.31 (m, 6H, 5'', 3'', 2''-H), 1.31 – 1.45 (m, 2H, 4''-H), 1.47 – 1.63 (m, 1H, 1''-H), 1.80 – 1.95 (m, 1H, 1''-H), 2.36 (m, 1H, 1'-H$_{pseudo\ axial}$), 2.55 (m, 1H, 1'-H$_{pseudo\ equatorial}$), 3.85 – 3.95 (m, 1H, 2'-H), 3.96 – 4.06 (m, 1H, 4'-H), 4.10 – 4.20 (m, 1H, 4'-H), 4.65 (m, 1H, 5-H), 5.25 (ddt, $^3J_{HH}$ = 10.29 Hz, $^4J_{HH}$ = 1.09 Hz, $^2J_{HH}$ = 1.24 Hz, 1H, 6'-H$_{cis}$), 5.32 (ddt, $^3J_{HH}$ = 17.29 Hz, $^4J_{HH}$ = 1.37 Hz, $^2J_{HH}$ = 1.24 Hz, 1H, 6'-H$_{trans}$), 5.88 (m, 1H, 5'-H), 10.39 (s, O-H) and 10.42 (s, O-H) (Total integral : 1H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = (signals are not totally α and / or β assigned because of the low resolution in the HSQC spectra) 13.95 (CH$_3$, 6''-C$^{\alpha+\beta}$), 17.93 (CH$_3$, 3'-C$^{\alpha}$), 17.97 (CH$_3$, 3'-C$^{\beta}$), 22.43 (CH$_2$, 5''-C$^{\alpha+\beta}$), 24.05 (CH$_2$, 4''-C$^{\alpha}$), 24.15 (CH$_2$, 4''-C$^{\beta}$), 28.85 (CH$_2$, 3''-C$^{\alpha+\beta}$), 28.91 (CH$_2$, 1'-C$^{\alpha}$), 28.97 (CH$_2$, 1'-C$^{\beta}$), 31.51 (CH$_2$, 2''-C$^{\alpha+\beta}$), 31.66 (CH$_2$, 1''-C$^{\alpha+\beta}$), 69.63 (CH$_2$, 4'-C$^{\alpha}$), 69.67 (CH$_2$, 4'-C$^{\beta}$), 75.36 (CH, 2'-C$^{\alpha}$), 75.39 (CH, 2'-C$^{\beta}$), 77.56 (CH, 5-C$^{\alpha}$), 76.57 (CH, 5-C$^{\beta}$), 96.73 (C^q, 3-C$^{\alpha+\beta}$), 119.09 (CH$_2$, 6'-C$^{\alpha}$), 119.15 (CH$_2$, 6'-C$^{\beta}$), 132.68 (CH, 5'-C$^{\alpha}$), 132.69 (CH, 5'-C$^{\beta}$), 174.79 (C^q, 2-C$^{\alpha}$), 174.81 (C^q, 2-C$^{\beta}$), 175.59 (C^q, 4-C$^{\alpha}$), 175.70 (C^q, 4-C$^{\beta}$).

MS (GC inlet, EI, 70 eV) m/z (%) = 282 (10) [M$^+$], 267 (1) [M-CH$_3$]$^+$, 241 (21) [M-C$_3$H$_5$]$^+$, 225 (21) [M$_{267}$-C$_3$H$_5$]$^+$, 198 (19) [M-C$_5$H$_9$O]$^+$, 140 (27) [M$_{225}$-C$_5$H$_9$O]$^+$, 125 (24) [M$_{140}$-CH$_3$]$^+$, 85 (84) [C$_5$H$_9$O$^+$], 43 (89) [C$_3$H$_7^+$], 41 (100) [C$_3$H$_5^+$].

3-(2-Benzyloxypropyl)-4-hydroxy-5-methyl-5*H*-furan-2-one (60h)

Colourless oil (175 mg, 0.67 mmol, 54%) from 190 mg (1.23 mmol) of 1,6-dimethyl-5-oxa-spiro[2.4]heptane-4,7-dione **58b**, 133 mg (1.23 mmol) of benzyl alcohol in 20 mL of chloroform and 20 mg of ytterbium-(III)-trifluormethansulfonathydrate (hygroscopic) as catalyst, heated under reflux for 9 h. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent.

R_f (SiO$_2$) = 0.55 (diethyl ether).
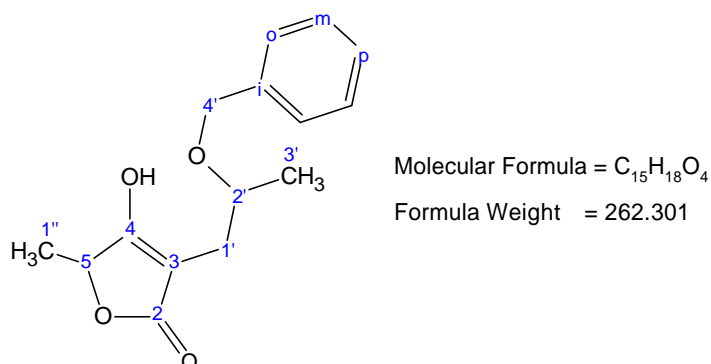
Molecular Formula = C$_{15}$H$_{18}$O$_4$
Formula Weight = 262.301

*Mixture of diastereoisomers **a** and **b**. Ratio α : β = 1 : 1.*

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3170 (W) [ν (-OH)], 2978 (W) [ν (-CH$_2$-)], 2738 (W) [ν (-OH bridge)], 1746 (S) and 1662 (VS) [ν (Tetronic ring)], 1292 (S) [ν (C-O-C)], 1089 (S) [ν (C-O)], 1026 (VS) [ν (C-O)], 734 (S) and 697 (VS) [ν (C-H arom. monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.18 (d, $^3J_{HH}$ = 6.31 Hz, 3H, 3'-H), 1.34 (d, $^3J_{HH}$ = 6.72 Hz, 1''-H$^{\alpha}$) and 1.35 (d, $^3J_{HH}$ = 6.72 Hz, 1''-H$^{\beta}$) (Total integral : 3H), 2.35 (ddd, $^3J_{HH}$ = 5.22 Hz, $^2J_{HH}$ = 16.33 Hz, $^5J_{HH}$ = 1.10 Hz, 1H, 1'-H), 2.53 (dtd, $^3J_{HH}$ = 3.70 Hz, $^2J_{HH}$ = 16.33 Hz, $^5J_{HH}$ = 0.82 Hz, 1H, 1'-H), 3.93 (m, 1H, 2'-H), 4.47 (d, $^2J_{HH}$ = 11.25 Hz, 1H, 4'-H),

4.63 (d, $^2J_{HH}$ = 11.25 Hz, 1H, 4'-H), 4.65 (q, $^3J_{HH}$ = 6.72 Hz, 1H, 5-H), 7.22 – 7.35 (m, 5H, arom-H), 10.28 (br. s., 1H, -OH).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = (signals are not totally α and / or β assigned because of the low resolution in the HSQC spectra) 17.56 (CH$_3$, 1''-C$^\alpha$), 17.73 (CH$_3$, 1''-C$^\beta$), 17.86 (CH$_3$, 3'-C$^{\alpha+\beta}$), 28.79 (CH$_2$, 1'-C$^\alpha$), 28.89 (CH$_2$, 1'-C$^\beta$), 70.89 (CH$_2$, 4'-C$^\alpha$), 70.95 (CH$_2$, 4'-C$^\beta$), 73.82 (CH, 5-C$^\alpha$), 73.85 (CH, 5-C$^\beta$), 75.25 (CH, 2'-C$^\alpha$), 75.26 (CH, 2'-C$^\beta$), 95.94 (C^q, 3-C$^\beta$), 96.05 (C^q, 3-C$^\alpha$), 128.07 (CH, *meta*-C$^\alpha$), 128.12 (CH, *meta*-C$^\beta$), 128.44 (CH, *para*-C$^{\alpha+\beta}$), 128.66 (CH, *ortho*-C$^{\alpha+\beta}$), 135.93 (C^q, *ipso*-C$^\alpha$), 135.95 (C^q, *ipso*-C$^\beta$), 174.42 (C^q, 2-C$^{\alpha+\beta}$), 176.51 (C^q, 4-C$^{\alpha+\beta}$).

MS (GC inlet, EI, 70 eV) m/z (%) = 262 (1) [M$^+$], 247 (1) [M-CH$_3$]$^+$, 218 (16) [M-CO$_2$]$^+$, 200 (2) [M$_{218}$-H$_2$O]$^+$, 171 (11) [M-C$_7$H$_7$]$^+$, 156 (29) [M$_{171}$-CH$_3$]$^+$, 127 (17) [M-C$_9$H$_{11}$O]$^+$, 107 (32) [C$_7$H$_7$O$^+$], 91 (100) [C$_7$H$_7$$^+$], 65 (21) [C$_5H_5$$^+$].

Acetic acid 2-(4-hydroxy-2-oxo-2,5-dihydro-furan-3-yl)-1-methyl-ethyl ester (60i)

Colourless oil (170 mg, 0.84 mmol, 54%) from 330 mg (2.35 mmol) of 1-methyl-5-oxa-spiro[2.4]heptane-4,7-dione **58a**, 3 mL of acetic acid in 20 mL of chloroform heated under reflux for 16 h. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent. *NB: via retro-Conia, a considerable amount of the Claisen product 57a was also formed.*

R_f (SiO$_2$) = 0.34 (diethyl ether).
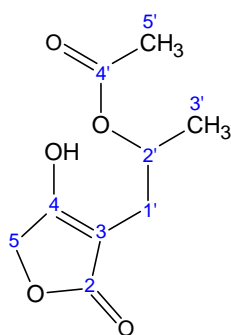
Molecular Formula = C$_9$H$_{12}$O$_5$

Formula Weight = 200.189

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3195 (W) [ν (O-H)], 2983 (W) [ν (-CH$_2$-)], 2939 (W) [ν (-CH$_2$-)], 2710 (W) [ν O-H bridge)], 1733 (S) [ν (C=O Tetronate ring)], 1646 (S) [ν (C=O acyl)], 1239 (VS) [ν (C-O)], 1040 (VS) [ν (C-O)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.20 (d, $^3J_{HH}$ = 6.32 Hz, 3H, 3'-H), 1.99 (s, 3H, 5'-H), 2.44 (d, $^3J_{HH}$ = 5.90 Hz, 2H, 1'-H), 4.63 (s, 2H, 5-H), 4.95 (sext, $^3J_{HH}$ = 6.32 Hz, $^3J_{HH}$ = 5.90 Hz, 1H, 2'-H), 9.58 (br. s., 1H, O-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 19.46 (CH$_3$, 3'-C), 21.26 (CH$_3$, 5'-C), 27.64 (CH$_2$, 1'-C), 67.52 (CH$_2$, 5-C), 70.19 (CH, 2'-C), 97.32 (C^q, 3-C), 171.56 (C^q, 4'-C), 175.63 (C^q, 2-C), 177.44 (C^q, 4-C).

MS (Direct inlet, EI, 70 eV) m/z (%) = 200 (1) [M$^+$], 157 (4) [M-CH$_3$CO]$^+$, 143 (4) [M$_{157}$-CH$_3$]$^+$, 140 (27) [M$_{157}$-H$_2$O]$^+$, 122 (24) [M$_{140}$-H$_2$O]$^+$, 114 (24) [M$_{157}$-C$_2$H$_3$O]$^+$, 96 (11) [M$_{114}$-H$_2$O]$^+$, 43 (100) [CH$_3$CO$^+$].

3-(2-Benzyloxy-propyl)-4-hydroxy-5*H*-furan-2-one (60j)

0.25 g (1.78 mmol) of 3-allyl-4-hydroxy-5*H*-furan-2-one **57a** were heated under stirring with 5 mL xylene without any catalyst in a sealed glass bomb tube under CMS conditions (190°C, 4.2 bar, 120 Watt, 60 min). When the Conia product **58a** had been formed (controlled via GC), 1 mL of benzyl alcohol was added. The reaction mixture was heated under EMS conditions (185 °C, 0.9 bar, 205 Watt, 8 h) to make **58a** react completely (controlled via GC). The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent. Yellowish oil (394 mg, 1.58 mmol, 89%)

R_f (SiO$_2$) = 0.52 (diethyl ether).
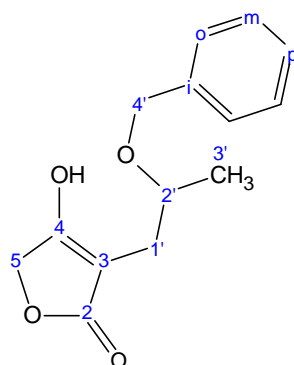
Molecular Formula = C$_{14}$H$_{16}$O$_4$
Formula Weight   = 248.274

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3263 (W) [ν (O-H)], 2933 (W) [ν (-CH$_2$-)], 2731 (W) [ν (O-H bridge)], 1749 (S) and 1647 (S) [ν (Tetronate ring)], 1080 (S) [ν (C-O)], 1041 (VS) [ν (C-O)], 740 (S) and 697 (VS) [ν (C-H aromatic monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 1.20 (d, $^3J_{HH}$ = 6.31 Hz, 3H, 3'-H), 2.36 (dd, $^3J_{HH}$ = 5.21 Hz, $^2J_{HH}$ = 16.33 Hz, 1H, 1'-H), 2.55 (d, $^2J_{HH}$ = 16.33 Hz, 1H, 1'-H), 3.95 (m, 1H, 2'-H), 4.47 (s, 2H, 5-H), 4.49 (d, $^2J_{HH}$ = 11.12 Hz, 1H, 4'-H), 4.65 (d, $^2J_{HH}$ = 11.12 Hz, 1H, 4'-H), 7.22 – 7.35 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 17.99 (CH$_3$, 3'-C), 29.10 (CH$_2$, 1'-C), 66.64 (CH$_2$, 5-C), 71.03 (CH$_2$, 4'-C), 75.33 (CH, 2'-C), 96.83 (C^q, 3-C), 128.18 (CH, *meta*-C), 128.56 (CH, *para*-C), 128.73 (CH, *ortho*-C), 135.89 (C^q, *ipso*-C), 173.47 (C^q, 2-C), 175.66 (C^q, 4-C).

MS (Direct inlet, EI, 70 eV) m/z (%) = 248 (3) [M$^+$], 230 (2) [M-H$_2$O]$^+$, 204 (19) [M-CO$_2$]$^+$, 171 (2) [M-C$_6$H$_5$]$^+$, 157 (8) [M-C$_7$H$_7$]$^+$, 142 (32) [M-C$_7$H$_7$O]$^+$, 113 (13) [M$_{157}$-CO$_2$]$^+$, 107 (40) [C$_7$H$_7$O$^+$], 91 (100) [C$_7$H$_7^+$].

4-Allyl-2-butyl-5-oxo-2,5-dihydrofuran-3-yl acetate (61a)

Method 1:

Yellowish oil (434 mg, 1.82 mmol, 71%) from 500 mg (2.55 mol) of 3-allyl-5-butyl-4-hydroxy-5*H*-furan-2-one **57e**, acetic acid (153 mg, 2.55 mol) and acetic anhydride (260 mg, 2.55 mmol), heated as a toluene solution under microwave at 190°C for 1h (CMS, 7 Bar, 170 Watt). Then the reaction mixture was extracted with ether (pH = 10, NaHCO$_3$ solution). The organic layer was dried over Na$_2$SO$_4$, the solvent was evaporated and the residual oil was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / ether (3/2) as eluent.

Method 2:

Yellowish oil (118 mg, 0.49 mmol, 23%) from 422 mg (2.15 mmol) of 6-butyl-1-methyl-5-oxa-spiro[2.4]heptane-4,7-dione **58e**, Yb(OTf)$_3$ 2mol-% (26 mg, 0.043 mmol), acetic acid (129 mg, 2,15 mmol) and acetic anhydride (219 mg, 2.15 mmol), heated under microwave at 150°C for 1 h. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / ether (3/2) as eluent. *NB: Via Retro-Conia, a considerable amount of the Claisen product **57e** was also formed.*

R$_f$ (SiO$_2$) = 0.36 (n-hexane : ether, 3 : 2, v : v).

Molecular Formula = C$_{13}$H$_{18}$O$_4$

Formula Weight = 238.279
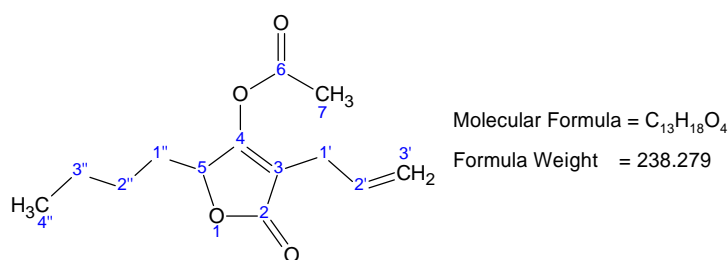
IR (ATR) $\bar{\nu}$ (cm^{-1}) = 2958 (W) [ν (-CH$_2$-)], 1783 (M) [ν (C=O furanone)], 1758 (VS) [ν (C=O acyl)], 1691 (M) [ν (C=C furan)], 1163 (VS) [ν (C-O)], 1046 (M) [ν (C-O)], 1012 (S) [ν (C-O)], 917 (M) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.86 (t, ^{3}J$_{HH}$ = 6.86 Hz, 3H, 4''-H), 1.20-1.43 (m, 4H, 3''-2''-H), 1.41-1.55 (m, 1H, 1''-H), 1.74-1.88 (m, 1H, 1''-H), 2.24 (d, ^{space}J$_{HH}$ = 0.55 Hz, 3H, 7-H), 2.94 (d, ^{3}J$_{HH}$ = 6.31 Hz, ^{4}J$_{HH}$ = 1.37 Hz, ^{4}J$_{HH}$ = 1.51 Hz, 2H, 1'-H), 5.05 (ddd, ^{3}J$_{HH}$ = 10.16 Hz, ^{4}J$_{HH}$ = 1.51 Hz, ^{2}J$_{HH}$ = 1.65 Hz, 1H, 3'-H$_{cis}$), 5.10 (ddd, ^{3}J$_{HH}$ = 17.57 Hz, ^{4}J$_{HH}$ = 1.37 Hz, ^{2}J$_{HH}$ = 1.65 Hz, 1H, 3'-H$_{trans}$), 5.10 (m, 1H, 5-H), 5.76 (dddd, ^{3}J$_{HH}$ = 6.31 Hz, ^{3}J$_{HH}$ = 6.31 Hz, ^{3}J$_{HH}$ = 10.16 Hz, ^{3}J$_{HH}$ = 17.57 Hz, ^{space}J$_{HH}$ = 0.55 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.71 (CH$_3$, 4''-C), 20.48 (CH$_3$, 7-C), 22.21 (CH$_2$, 3''-C), 26.46 (CH$_2$, 2''-C), 26.88 (CH, 1'-C), 31.24 (CH$_2$, 1''-C), 78.25 (CH, 5-C), 114.28 (C^q, 3-C), 116.79 (CH$_2$, 3'-C), 132.29 (CH, 2'-C), 165.76 (C^q, 6-C), 166.81 (C^q, 4-C), 171.64 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 238 (2) [M$^+$], 220 (1) [M-H$_2$O]$^+$, 196 (27) [M-CH$_3$CO]$^+$, 178 (2) [M$_{196}$-H$_2$O]$^+$, 153 (12) [M$_{197}$-CO$_2$]$^+$, 140 (32) [M$_{197}$-C$_4$H$_9$]$^+$, 43 (100) [CH$_3$CO$^+$], 41 (91) [C$_3$H$_5^+$].

2-[4-(Acetyloxy)-5-butyl-2-oxo-2,5-dihydrofuran-3-yl]-1-methylethyl acetate (62)

Yellowish oil (103 mg, 0.34 mmol, 16%) from 422 mg (2.15 mmol) of 6-butyl-1-methyl-5-oxa-spiro[2.4]heptane-4,7-dione **58e**, Yb(OTf)$_3$ 2mol-% (26 mg, 0.043 mmol), acetic acid (129 mg, 2,15 mmol) and acetic anhydride (219 mg, 2.15 mmol), heated under microwave at 150°C for 1 h. The product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / ether (3/2) as eluant. *NB: this compound was the second fraction collected from the previous experiment (Method B) – Via retro-Conia, a considerable amount of the Claisen product **57e** was also formed.*

R$_f$ (SiO$_2$) = 0.13 (n-hexane : ether, 3 : 2, v : v).
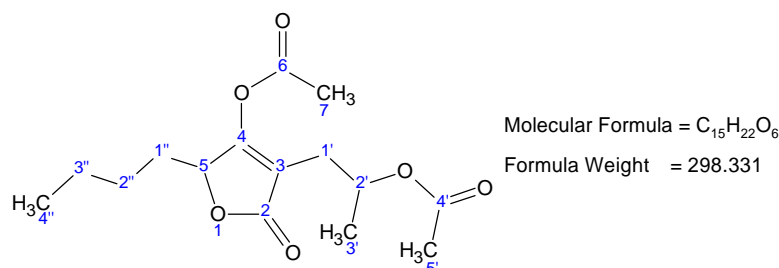
Molecular Formula = C$_{15}$H$_{22}$O$_6$
Formula Weight = 298.331

Mixture of two diastereoisomers α *and* β. *Ratio* α : β = 1 : 1.

IR (ATR) v̄ (cm^{-1}) = 2959 (W) [ν (-CH$_2$-)], 1783 (M) [ν (C=O furanone)], 1760 (S) [ν (C=O 4-O-acyl)], 1735 (S) [ν (C=O acyl)], 1692 (M) [ν (C=C furan)], 1237 (S) [ν (C-O)], 1167 (VS) [ν (C-O)], 1011 (S) [ν (C-O)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.84 (t, $^3J_{HH}$ = 7.00 Hz, 3H, 4''-H), 1.19 (d, $^3J_{HH}$ = 6.31 Hz, 3H, 3'-H), 1.23-1.37 (m, 4H, 3''-2''-H), 1.37-1.52 (m, 1H, 1''-H), 1.70-1.84 (m, 1H, 1''-H), 1.93 (s, 5'-H) and 1.94 (s, 5'-H) (Total integral : 3H), 2.27 (s, 3H, 7-H), 2.44 (d, $^3J_{HH}$ = 6.45 Hz, 2H, 1'-H), 4.99 (sext, $^3J_{HH}$ = 6.31 Hz, $^3J_{HH}$ = 6.45 Hz, $^3J_{HH}$ = 6.45 Hz, 2'-H) and 5.06 (sext, $^3J_{HH}$ = 6.31 Hz, $^3J_{HH}$ = 6.45 Hz, $^3J_{HH}$ = 6.45 Hz, 2'-H) (Total integral : 1H), 5.17 (dd, $^3J_{HH}$ = 3.70 Hz, $^3J_{HH}$ = 7.82 Hz, 5-H) and 5.20 (dd, $^3J_{HH}$ = 3.57 Hz, $^3J_{HH}$ = 7.55 Hz, 5-H) (Total integral : 1H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 13.66 (CH$_3$, 4''-C), 19.68 (CH$_3$, 3'-C), 20.47 and 20.51 (CH$_3$, 7-C), 21.05 (CH$_3$, 5'-C), 22.11 (CH$_2$, 3''-C), 26.22 and 26.32 (CH$_2$, 2''-C), 28.63 and 28.82 (CH$_2$, 1'-C), 31.00 and 31.08 (CH$_2$, 1''-C), 68.16 and 68.36 (CH, 2'-C), 78.18 and 78.21 (CH, 5-C), 112.38 and 112.56 (C^q, 3-C), 165.82 and 165.97 (C^q, 6-C), 168.02 and 168.18 (C^q, 4-C), 170.20 and 170.24 (C^q, 4'-C), 171.61 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 299 (1) [M+H]$^+$, 256 (1) [M-CH$_3$CO]$^+$, 238 (2) [M$_{256}$-H$_2$O]$^+$, 213 (9) [M$_{256}$-CH$_3$CO]$^+$, 196 (68) [M$_{238}$-CH$_3$CO]$^+$, 178 (15) [M$_{196}$-H$_2$O]$^+$, 153 (18) [M$_{197}$-CO$_2$]$^+$, 140 (33) [M$_{197}$-C$_4$H$_9$]$^+$, 43 (100) [CH$_3$CO$^+$].

3.10 Synthesis of 3-Allyl-4-benzyloxy-5*H*-furan-2-ones

3-Allyl-4-benzyloxy-5*H*-furan-2-one (64a)

General experimental procedure:

500 mg (3.57 mmol) of 3-allyl-4-hydroxy-5*H*-furan-2-one **57a** and 1 equivalent of *O*-benzyl-N,N'-dicyclohexylisourea **36e** (1.12 g) dissolved in 40 mL of THF and under argon atmosphere were heated under reflux for 16 hours. After cooling down to room temperature the solution was filtered over a small plug of SiO$_2$ to separate out the crystalline urea using a mixture of *n*-hexane / diethyl ether (3/2) as eluent. Solvents were evaporated in vacuum and the crude material was dissolved in acetone, mixed with 5 gr. of SiO$_2$ and the solvent was removed under a very low vacuum at rt. The product was separated out after column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane/ diethyl ether (3/2) mixture as eluant. The pure product appears as colourless oil. Yield: 52% (427 mg, 1.86 mmol). R_f (SiO$_2$) = 0.59 (diethyl ether).
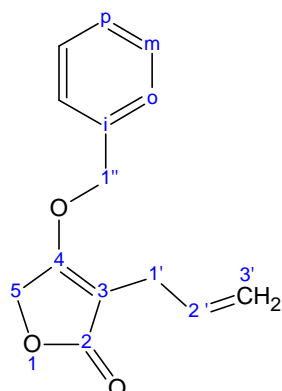
Molecular Formula = C$_{14}$H$_{14}$O$_3$
Formula Weight   = 230.259

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3065 (W) [ν (=C-H)], 2979 (VW) [ν (-CH$_2$-)], 1745 (S) and 1660 (VS) [ν (Tetronate ring)], 1047 (S) [ν (C-O-C)], 912 (S) [ν (C-H allyl)], 738 (S) and 696 (VS) [ν (C-H aromatic monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 3.03 (dt, $^3J_{HH}$ = 6.04 Hz, $^4J_{HH}$ = 0.82 Hz, $^4J_{HH}$ = 0.96 Hz, 2H, 1'-H), 4.64 (dd, $^4J_{HH}$ = 0.82 Hz, $^4J_{HH}$ = 0.96 Hz, 2H, 5-H), 5.04 (dq, $^3J_{HH}$ = 10.02 Hz, $^4J_{HH}$ = 1.65 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 5.06 (dq, $^3J_{HH}$ = 17.02 Hz, $^4J_{HH}$ = 1.65 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{trans}$), 5.18 (s, 2H, 1''-H), 5.87 (ddt, $^3J_{HH}$ = 6.04 Hz, $^3J_{HH}$ = 10.02 Hz, $^3J_{HH}$ = 17.02 Hz, 1H, 2'-H), 7.29 – 7.43 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 26.34 (CH$_2$, 1'-C), 65.81 (CH$_2$, 5-C), 72.15 (CH$_2$, 1''-C), 101.47 (C^q, 3-C), 115.69 (CH$_2$, 3'-C), 127.11 (CH, *ortho*-C), 128.83 (CH, *meta*-C, *para*-C), 134.29 (CH, 2'-C), 134.82 (C^q, *ipso*-C), 172.24 (C^q, 2-C), 175.30 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 230 (1) [M$^+$], 212 (1) [M-H$_2$O]$^+$, 197 (1) [M$_{212}$-CH$_3$]$^+$, 184 (1) [M$_{212}$-CO]$^+$, 139 (1) [M-C$_7$H$_7$]$^+$, 117 (2), 91 (100) [C$_7$H$_7^+$], 65 (8) [C$_5$H$_5^+$].

3-Allyl-4-benzyloxy-5(*S*)-methyl-5*H*-furan-2-one (64b)

Yellowish oil (486 mg, 1.96 mmol, 43%) from 721 mg (4.67 mmol) of 3-allyl-4-hydroxy-5(*S*)-methyl-5*H*-furan-2-one **57b** and 1472 mg (4.67 mmol) of *O*-benzyl-N,N'-dicyclohexylisourea **36e** refluxed in 40 mL of dry THF for 23 h. The product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluent.

R_f (SiO$_2$) = 0.45 (*n*-hexane : diethyl ether, 2 : 3, v : v).
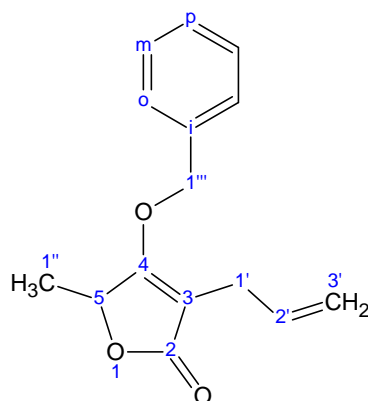
Molecular Formula = C$_{15}$H$_{16}$O$_3$
Formula Weight = 244.286

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 2982 (VS) [ν (-CH$_2$-)], 1745 (S) and 1655 (VS) [ν (Tetronate ring)], 1038 (S) [ν (C-O)], 911 (M) [ν (=CH$_2$)], 714 (M) [ν (C-H allyl)], 735 (S) and 695 (S) [ν (C-H aromatic monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 1.46 (d, $^3J_{HH}$ = 6.72 Hz, 3H, 1''-H), 3.12 (dt, $^3J_{HH}$ = 5.62 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.78 Hz, 1H, 1'-H), 3.13 (dt, $^3J_{HH}$ = 5.62 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.78 Hz, 1H, 1'-H), 4.76 (q, $^3J_{HH}$ = 6.72 Hz, 1H, 5-H), 5.04 (dq, $^3J_{HH}$ = 17.15 Hz, $^2J_{HH}$ = 1.51 Hz, $^4J_{HH}$ = 1.78 Hz, 1H, 3'-H$_{trans}$), 5.09 (dq, $^3J_{HH}$ = 10.15 Hz, $^2J_{HH}$ = 1.51 Hz,

$^4J_{HH}$ = 1.65 Hz, 1H, 3'-H_{cis}), 5.31 (s, 2H, 1'''-H), 5.91 (ddt, $^3J_{HH}$ = 5.62 Hz, $^3J_{HH}$ = 10.15 Hz, $^3J_{HH}$ = 17.15 Hz, 1H, 2'-H), 7.28 – 7.43 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 18.27 (CH$_3$, 1''-C), 27.01 (CH$_2$, 1'-C), 72.71 (CH$_2$, 1'''-C), 74.15 (CH, 5-C), 99.27 (C^q, 3-C), 115.55 (CH$_2$, 3'-C), 127.13 (CH, *meta*-C), 128.75 (CH, *ortho*-C), 128.79 (CH, *para*-C), .135.17 (C^q, *ipso*-C), 135.54 (CH, 2'-C), 173.92 (C^q, 2-C), 175.01 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 244 (5) [M$^+$], 226 (2) [M-H$_2$O]$^+$, 198 (1) [M$_{226}$-CO]$^+$, 171 (1) [M-C$_3$H$_4$O$_2$]$^+$, 153 (5) [M-C$_7$H$_7$]$^+$, 130 (8) [M$_{171}$-C$_3$H$_5$]$^+$, 91 (100) [C$_7$H$_7^+$], 65 (30) [C$_5$H$_5^+$].

3-Allyl-4-benzyloxy-5-ethyl-5*H*-furan-2-one (64c)

Colourless oil (2.23 g, 8.6 mmol, 48%) from 2.99 g (18 mmol) of 3-allyl-5-ethyl-4-hydroxy-5*H*-furan-2-one **57c** and 5.60 g (18 mmol) of *O*-benzyl-N,N'-dicyclohexylisourea **36e** refluxed in 100 mL of dry THF for 16 h. The product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (3/2) mixture as eluent.

R_f (SiO$_2$) = 0.54 (*n*-hexane : diethyl ether, 2 : 3, v : v).
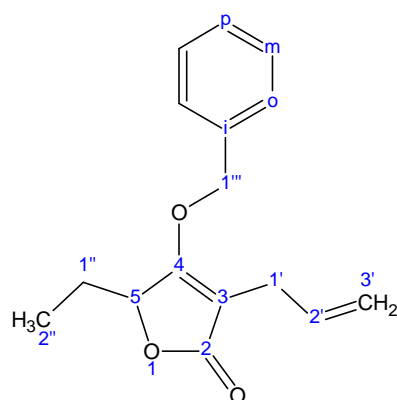
Molecular Formula = C$_{16}$H$_{18}$O$_3$
Formula Weight = 258.312

IR (ATR) ν̄ (cm^{-1}) = 2972 (W) [ν (-CH$_2$-)], 2937 (W) [ν (-CH$_2$-)], 1746 (S) and 1655 (VS) [ν (Tetronate ring)], 991 (S), 911 (M) [ν (=C-H allyl)], 737 (S) and 695 (S) [ν (C-H aromatic monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.96 (t, $^3J_{HH}$ = 7.41 Hz, 3H, 2''-H), 1.64 (ddq, $^3J_{HH}$ = 7.41 Hz, $^3J_{HH}$ = 6.87 Hz, $^2J_{HH}$ = 14.50 Hz, 1H, 1''-H), 1.94 (ddq, $^3J_{HH}$ = 7.41 Hz, $^3J_{HH}$ = 3.71 Hz, $^2J_{HH}$ = 14.50 Hz, 1H, 1''-H), 3.13 (dt, $^3J_{HH}$ = 5.49 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.78 Hz, 2H, 1'-H), 4.67 (dd, $^3J_{HH}$ = 3.71 Hz, $^3J_{HH}$ = 6.87 Hz, 1H, 5-H), 5.04 (dq, $^3J_{HH}$ = 17.04 Hz, $^4J_{HH}$ = 1.78 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3'-H_{trans}), 5.09 (dq, $^3J_{HH}$ = 10.16 Hz, $^4J_{HH}$ = 1.65 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3'-H_{cis}), 5.31 (d, $^4J_{HH}$ = 1.92 Hz, 2H, 1'''-H), 5.91 (ddt, $^3J_{HH}$ = 5.49 Hz, $^3J_{HH}$ = 10.16 Hz, $^3J_{HH}$ = 17.04 Hz, 1H, 2'-H), 7.28 – 7.42 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 8.23 (CH$_3$, 2''-C), 25.04 (CH$_2$, 1''-C), 27.08 (CH$_2$, 1'-C), 72.69 (CH$_2$, 1'''-C), 78.52 (CH, 5-C), 100.06 (C^q, 3-C), 115.51 (CH$_2$, 3'-C), 127.13 (CH, *ortho*-C), 128.71 (CH, *meta*-C), 128.74 (CH, *para*-C), 135.15 (C^q, *ipso*-C), 135.57 (CH, 2'-C), 173.57 (C^q, 2-C), 174.21 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 258 (3) [M$^+$], 240 (1) [M-H$_2$O]$^+$, 212 (1) [M$_{240}$-CO]$^+$, 167 (2) [M-C$_7$H$_7$]$^+$, 130 (4), 118 (3), 91 (100) [C$_7$H$_7^+$], 65 (21) [C$_5$H$_5^+$].

3-Allyl-4-benzyloxy-5-butyl-5*H*-furan-2-one (64d)

Colourless oil (1.23 g, 4.3 mmol, 36%) from 2.35 g (12 mmol) of 3-allyl-5-butyl-4-hydroxy-5*H*-furan-2-one **57e** and 3.92 g (12.5 mmol) of *O*-benzyl-N,N'-dicyclohexylisourea **36e** stirred at 40°C in 100 mL of dry THF for 16 h. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (3/2) mixture as eluent.
R_f (SiO$_2$) = 0.63 (*n*-hexane : diethyl ether, 2 : 3, v : v).
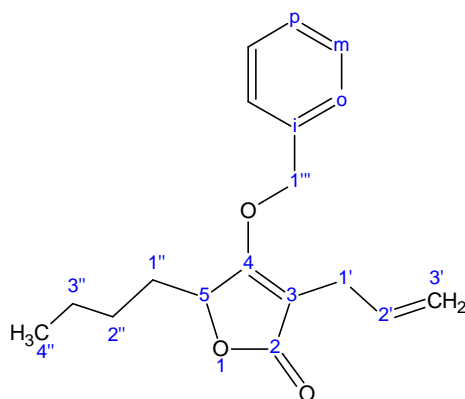
Molecular Formula = C$_{18}$H$_{22}$O$_3$
Formula Weight = 286.365

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 2955 (M) [ν (-CH$_2$-)], 2867 (W) [ν (-CH$_2$-)], 1745 (S) and 1653 (VS) [ν (Tetronate ring)], 1329 (S), 1027 (S) [ν (C-O-C)], 912 (M) [ν (C-H allyl)], 738 (S) and 696 (VS) [ν (C-H aromatic monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.88 (t, $^3J_{HH}$ = 7.17 Hz, 3H, 4''-H), 1.24 – 1.35 (m, 2H, 3''-H), 1.37 – 1.43 (m, 2H, 2''-H), 1.54 - 1.61 (m, 1H, 1''-H), 1.90 - 1.96 (m, 1H, 1''-H), 3.13 (d, $^3J_{HH}$ = 5.43 Hz, 2H, 1'-H), 4.69 (dd, $^3J_{HH}$ = 7.53 Hz, $^3J_{HH}$ = 3.20 Hz, 1H, 5-H), 5.05 (d, $^3J_{HH}$ = 17.14 Hz, 1H, 3'-H$_{trans}$), 5.09 (d, $^3J_{HH}$ = 10.13 Hz, 1H, 3'-H$_{cis}$), 5.30 (d, $^2J_{HH}$ = 15.76 Hz, 1H, 1'''-H), 5.32 (d, $^2J_{HH}$ = 15.76 Hz, 1H, 1'''-H), 5.92 (ddt, $^3J_{HH}$ = 5.43 Hz, $^3J_{HH}$ = 10.13 Hz, $^3J_{HH}$ = 17.14 Hz, 1H, 2'-H), 7.30 – 7.40 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 13.82 (CH$_3$, 4''-C), 22.33 (CH$_2$, 3''-C), 26.44 (CH$_2$, 2''-C), 27.15 (CH$_2$, 1'-C), 31.82 (CH$_2$, 1''-C), 72.74 (CH$_2$, 1'''-C), 77.86 (CH, 5-C), 99.83 (C^q, 3-C), 115.59 (CH$_2$, 3'-C), 127.20 (CH, *ortho*-C), 127.56 (CH, *para*-C), 128.82 (CH, *meta*-C), 135.22 (C^q, ipso-C), 135.64 (CH, 2'-C), 174.05 (C^q, 2-C), 174.33 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 286 (14) [M$^+$], 268 (9) [M-H$_2$O]$^+$, 230 (12) [M-C$_4$H$_9$]$^+$, 195 (27) [M-C$_7$H$_7$]$^+$, 140 (12) [M$_{230}$-C$_7$H$_7$]$^+$, 130 (27), 117 (27), 91 (100) [C$_7$H$_7^+$].

3-Allyl-4-benzyloxy-5-hexyl-5*H*-furan-2-one (64e)

Colourless oil (378 mg, 1.22 mmol, 40%) from 702 mg (3.13 mmol) of 3-allyl-5-hexyl-4-hydroxy-5*H*-furan-2-one **57d** and 980 mg (3.13 mmol) of *O*-benzyl-N,N'-dicyclohexylisourea **36e** in 100 mL of dry THF stirred under reflux for 14 h. The product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (1/1) mixture as eluent.

R_f (SiO$_2$) = 0.56 (*n*-hexane : diethyl ether, 1 : 1, v : v).

Molecular Formula = C$_{20}$H$_{26}$O$_3$
Formula Weight = 314.419
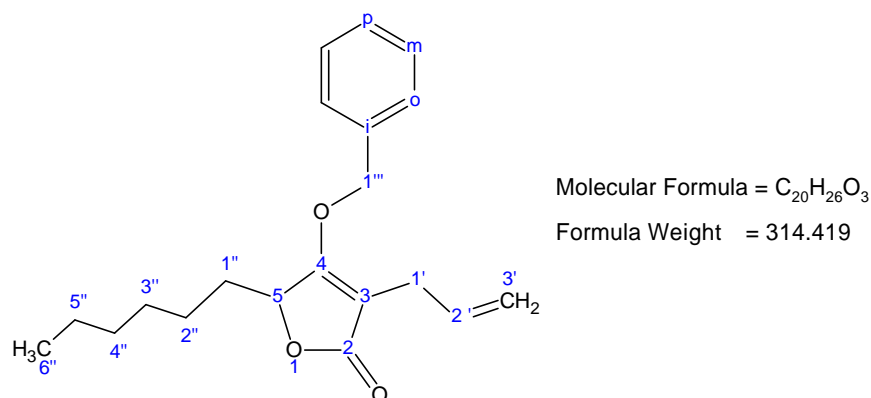
IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3035 (VW) [ν (=C-H)], 2927 (M) [ν (-CH$_2$-)], 1748 (VS) and 1656 (VS) [ν (Tetronate ring)], 1038 (S) [ν (C-O)], 911 (M) [ν (=C-H)], 735 (S) and 695 (S) [ν (C-H aromatic monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.85 (t, $^3J_{HH}$ = 6.86 Hz, 3H, 6''-H), 1.17 – 1.35 (m, 6H, 2''-H – 3''-H – 5''-H), 1.35 - 1.47 (m, 2H, 4''-H), 1.51 – 1.65 (m, 1H, 1''-H), 1.86 – 1.99 (m, 1H, 1''-H), 3.12 (dt, $^3J_{HH}$ = 5.62 Hz, $^4J_{HH}$ = 1.78 Hz, 1H, 1'-H), 3.13 (dt, $^3J_{HH}$ = 5.49 Hz, $^4J_{HH}$ = 1.78 Hz, 1H, 1'-H), 4.68 (dd, $^3J_{HH}$ = 3.51 Hz, $^3J_{HH}$ = 7.62 Hz, 1H, 5-H), 5.04 (dq, $^3J_{HH}$ = 17.02 Hz, $^4J_{HH}$ = 1.78 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{trans}$), 5.09 (dq, $^3J_{HH}$ = 10.16 Hz, $^4J_{HH}$ = 1.65 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 5.29 (d, $^2J_{HH}$ = 11.53 Hz, 1H, 1'''-H), 5.33 (d, $^2J_{HH}$ = 11.53 Hz, 1H, 1'''-H), 5.91 (ddt, $^3J_{HH}$ = 5.49 Hz, $^3J_{HH}$ = 10.16 Hz, $^3J_{HH}$ = 17.02 Hz, 1H, 2'-H), 7.28 – 7.43 (m, 5H, arom-H).

**^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm)** = 13.95 (CH$_3$, 6''-C), 22.43 (CH$_2$, 5''-C), 24.27 (CH$_2$, 4''-C), 27.13 (CH$_2$, 1'-C), 28.86 (CH$_2$, 3''-C), 31.52 (CH$_2$, 2''-C), 32.14 (CH$_2$, 1''-C), 72.73 (CH$_2$, 1'''-C), 77.82 (CH, 5-C), 99.85 (C^q, 3-C), 115.55 (CH$_2$, 3'-C), 127.18 (CH, *meta*-C), 128.76 (CH, *para*-C), 128.79 (CH, *ortho*-C), 135.22 (C^q, *ipso*-C), 135.62 (CH, 2'-C), 174.01 (C^q, 2-C), 174.24 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 314 (1) $[M^+]$, 296 (1) $[M-H_2O]^+$, 273 (1) $[M-C_3H_5]^+$, 223 (7) $[M-C_7H_7]^+$, 91 (100) $[C_7H_7^+]$, 65 (7) $[C_5H_5^+]$, 41 (7) $[C_3H_5^+]$.

4-Benzyloxy-5-butyl-3-(1-methylallyl)-5*H*-furan-2-one (64f)

Colourless oil (170 mg, 0.56 mmol, 35%) from 0.34 g (1.62 mmol) of 5-butyl-4-hydroxy-3-(1-methyl-allyl)-5*H*-furan-2-one **57f** and 0.51 g (1.62 mmol) of *O*-benzyl-N,N'-dicyclohexylisourea **36e** stirred at 40°C in 100 mL of dry THF for 16 h. The product was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (3/2) mixture as eluent.

R_f (SiO_2) = 0.44 (*n*-hexane : diethyl ether, 3 : 2, v : v).

Molecular Formula = $C_{19}H_{24}O_3$
Formula Weight = 300.392
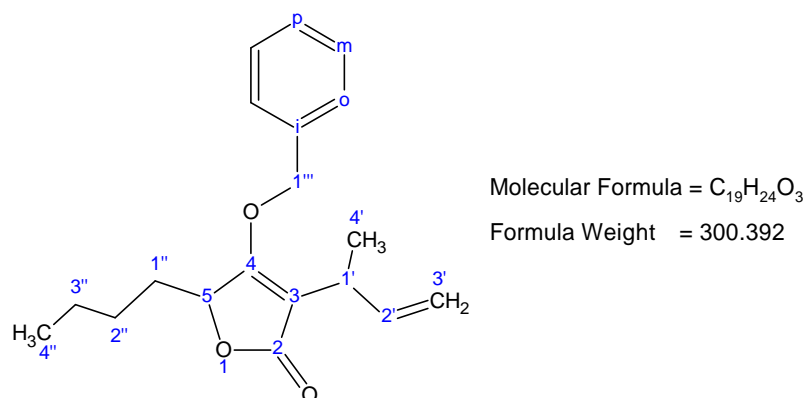
Mixture of diastereoisomers

IR (ATR) $\bar{v}$ **(cm^{-1})** = 3068 (VW) [v (=C-H)], 2958 (W) [v (-CH$_2$-)], 1743 (VS) and 1654 (S) [v (Tetronate ring)], 1003 (S) [v (C-O-C)], 910 (M) [v (C-H allyl)], 736 (S) and 697 (VS) [v (C-H aromatic monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.87 (t, $^3J_{HH}$ = 7.14 Hz, 3H, 4''-H), 1.28 (d, $^3J_{HH}$ = 7.14 Hz, 3H, 4'-H), 1.22 – 1.45 (m, 4H, 3''-H and 2''-H), 1.47 – 1.67 (m, 1H, 1''-H), 1.86 – 2.03 (m, 1H, 1''-H), 3.44 (m, 1H, 1'-H), 4.73 (dd, $^3J_{HH}$ = 3.15 Hz, $^3J_{HH}$ = 7.40 Hz, 1H, 5-H), 4.96 (d, $^3J_{HH}$ = 9.70 Hz, 1H, 3-H$_{cis}$), 4.97 (d, $^3J_{HH}$ = 17.53 Hz, 1H, 3'-H$_{trans}$), 5.11 (d, $^2J_{HH}$ = 11.67 Hz, 1'''-H) and 5.14 (d, $^2J_{HH}$ = 11.67 Hz, 1'''-H) and 5.21 (d, $^2J_{HH}$ = 11.67 Hz, 1'''-H) and 5.24 (d, $^2J_{HH}$ = 11.67 Hz, 1'''-H) (Total integral : 2H), 6.04 (m, 1H, 2'-H), 7.27 – 7.42 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 13.72 (CH$_3$, 4''-C), 18.27 (CH$_3$, 4'-C), 18.43 (CH$_3$, 4'-C$_{2nd\ diastereomer}$), 22.21 (CH$_2$, 3''-C), 26.19 (CH$_2$, 2''-C), 26.22 (CH$_2$, 2''-C$_{2nd\ diastereomer}$), 31.99 (CH$_2$, 1''-C), 32.01 (CH$_2$, 1''-C$_{2nd\ diastereomer}$), 32.91 (CH, 1'-C), 32.97 (CH, 1'-C$_{2nd\ diastereomer}$), 73.11 (CH$_2$, 1'''-C), 73.14 (CH$_2$, 1'''-C$_{2nd\ diastereomer}$), 76.71 (CH, 5-C), 76.73 (CH, 5-C$_{2nd\ diastereomer}$), 108.23 (C^q, 3-C), 113.64 (CH$_2$, 3'-C), 127.13 (CH, *meta-*

C), 128.69 (CH, *ortho*-C), 128.71 (CH, *para*-C), 135.10 (Cq, *ipso*-C), 140.09 (CH, 2'-C), 140.13 (CH, 2'-C$_{2nd\ diastereomer}$), 172.66 (C^q, 2-C), 172.85 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 300 (2) [M$^+$], 282 (1) [M-H$_2$O]$^+$, 244 (2) [M-C$_4$H$_9$]$^+$, 209 (5) [M-C$_7$H$_7$]$^+$, 144 (4), 118 (2), 91 (100) [C$_7$H$_7$$^+$], 65 (8) [C$_5H_5$$^+$].

4-Allyl-3-benzyloxy-2-ethyl-2*H*-furan-3-one (66a)

Colourless oil (0.56 g, 2.16 mmol, 12%) from 2.99 g (18 mmol) of 3-allyl-5-ethyl-4-hydroxy-5*H*-furan-2-one **57c** and 5.60 g (18 mmol) of *O*-benzyl-N,N'-dicyclohexylisourea **36e** refluxed in 100 mL of dry THF for 16 h. The product was a secondary fraction collected when the main crude product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (3/2) mixture as eluent.

R_f (SiO$_2$) = 0.53 (diethyl ether).
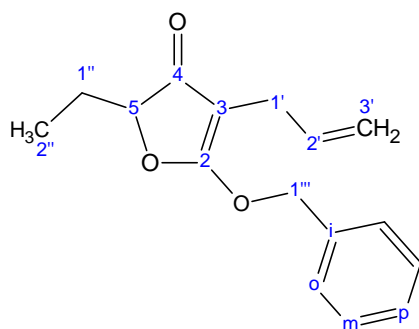
Molecular Formula = C$_{16}$H$_{18}$O$_3$
Formula Weight = 258.312

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 2972 (W) [ν (-CH$_2$-)], 2938 (W) [ν (-CH$_2$-)], 1750 (W) [ν (C=C-O)], 1696 (M) [ν (C=C)], 1594 (VS) [ν (C=O)], 1431 (S), 737 (S) and 696 (S) [ν (C-H aromatic monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.85 (t, $^3J_{HH}$ = 7.41 Hz, 3H, 2''-H), 1.67 (ddq, $^3J_{HH}$ = 7.14 Hz, $^3J_{HH}$ = 7.41 Hz, $^2J_{HH}$ = 14.50 Hz, 1H, 1''-H), 1.93 (ddq, $^3J_{HH}$ = 4.26 Hz, $^3J_{HH}$ = 7.41 Hz, $^2J_{HH}$ = 14.50 Hz, 1H, 1''-H), 2.78 (dt, $^3J_{HH}$ = 6.17 Hz, $^4J_{HH}$ = 1.51 Hz, $^4J_{HH}$ = 1.65 Hz, 2H, 1'-H), 4.49 (dd, $^3J_{HH}$ = 4.26 Hz, $^3J_{HH}$ = 7.14 Hz, 1H, 2-H), 4.89 (dq, $^3J_{HH}$ = 10.02 Hz, $^4J_{HH}$ = 1.51 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3'-H$_{cis}$), 4.94 (dq, $^3J_{HH}$ = 17.02 Hz, $^4J_{HH}$ = 1.78 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3-H$_{trans}$), 5.32 (s, 2H, 1'''-H), 5.75 (ddt, $^3J_{HH}$ = 6.17 Hz, $^3J_{HH}$ = 10.02 Hz, $^3J_{HH}$ = 17.02 Hz, 1H, 2'-H), 7.27 – 7.35 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 8.22 (CH$_3$, 2''-C), 23.48 (CH$_2$, 1'-C), 23.96 (CH$_2$, 1''-C), 70.57 (CH$_2$, 1'''-C), 87.68 (C^q, 2-C), 91.70 (C^q, 4-C), 114.42 (CH$_2$, 3'-C), 127.69 (CH, *meta*-C), 128.47 (CH, *ortho*-C), 128.63 (CH, *para*-C), 134.34 (C^q, *ipso*-C), 134.81 (CH, 2'-C), 180.13 (CH, 5-C), 197.45 (C^q, 3-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 258 (14) [M$^+$], 240 (2) [M-H$_2$O]$^+$, 179 (4), 167 (9) [M-C$_7$H$_7$]$^+$, 130 (11), 117 (13), 91 (100) [C$_7$H$_7$$^+$], 65 (39) [C$_5H_5$$^+$].

3.11 Synthesis of 3-Allyl-3-benzyl-furan-2,4-diones

The diverse 3-allyl-3-benzyl-furan-2,4-diones **65** were isolated as secondary products from the synthesis of 3-allyl-4-benzyloxy-5*H*-furan-2-ones **64** during the chromatography purification.

3-Allyl-4-benzyloxy-5*H*-furan-2-one (65a)

Colourless oil (123 mg, 0.53 mmol, 15%) from 500 mg (3.57 mmol) of 3-allyl-4-hydroxy-5*H*-furan-2-one **57a** and 1 equivalent of *O*-benzyl-N,N'-dicyclohexylisourea **36e** (1.12 g) refluxed in 40 mL of dry THF for 16 h. The product was a secondary fraction collected when the main crude product was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (3/2) mixture as eluent.

R_f (SiO_2) = 0.59 (*n*-hexane : diethyl ether, 3 : 2, v : v).
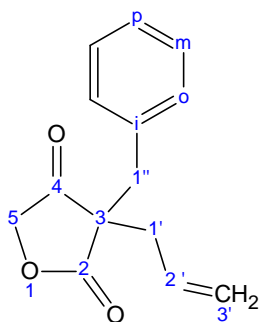
Molecular Formula = $C_{14}H_{14}O_3$
Formula Weight = 230.259

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3033 (VW) [ν (=C-H)], 2928 (VW) [ν (-CH$_2$-)], 1799 (S) and 1753 (VS) [ν (furan-2,4-dione ring)], 1226 (M), 1052 (S) [ν (C-O-C)], 747 (M) and 700 (S) [ν (C-H aromatic monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 2.60 (d, $^3J_{HH}$ = 7.41 Hz, 2H, 1'-H), 3.01 (d, $^2J_{HH}$ = 12.90 Hz, 1H, 1''-H), 3.09 (d, $^2J_{HH}$ = 12.90 Hz, 1H, 1''-H), 3.58 (d, $^2J_{HH}$ = 17.16 Hz, 1H, 5-H), 4.14 (d, $^2J_{HH}$ = 17.16 Hz, 1H, 5-H), 5.12 (dq, $^3J_{HH}$ = 10.02 Hz, $^4J_{HH}$ = 0.69 Hz, $^4J_{HH}$ = 0.84 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3'-H$_{cis}$), 5.16 (dq$_u$, $^3J_{HH}$ = 17.01 Hz, $^4J_{HH}$ = 1.23 Hz, $^4J_{HH}$ = 1.51 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3'-H$_{trans}$), 5.62 (ddt, $^3J_{HH}$ = 7.41 Hz, $^3J_{HH}$ = 10.02 Hz, $^3J_{HH}$ = 17.01 Hz, 1H, 2'-H), 7.06 – 7.24 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 39.48 (CH$_2$, 1'-C), 41.47 (CH$_2$, 1''-C), 56.28 (C^q, 3-C), 73.22 (CH$_2$, 5-C), 121.27 (CH$_2$, 3'-C), 127.69 (CH, *para*-C), 128.80 (CH, *ortho*-C), 129.48 (CH, *meta*-C), 130.00 (CH, 2'-C), 133.98 (C^q, *ipso*-C), 175.78 (C^q, 2-C), 210.42 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 230 (2) [M$^+$], 212 (8) [M-H$_2$O]$^+$, 189 (5) [M-C$_3$H$_5$]$^+$, 171 (3) [M$_{212}$-C$_3$H$_5$]$^+$, 139 (20) [M-C$_7$H$_7$]$^+$, 117 (7), 91 (100) [C$_7$H$_7^+$], 65 (8) [C$_5$H$_5^+$].

3-Allyl-3-benzyl-5(*S*)-methyl-furan-2,4-dione (65b)

Colourless oil (148 mg, 0.6 mmol, 13%) from 721 mg (4.67 mmol) of 3-allyl-4-hydroxy-5(*S*)-methyl-5*H*-furan-2-one **57b** and 1472 mg (4.67 mmol) of *O*-benzyl-N,N'-dicyclohexylisourea **36e** refluxed in 40 mL of dry THF for 23 h. The product was a secondary fraction collected when the main crude product was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (3/2) mixture as eluent.

R_f (SiO_2) = 0.34 (*n*-hexane : diethyl ether, 2 : 3, v : v). $[\alpha]_D^{25}$ -12.07° (4.1345 g/100 mL, MeOH)
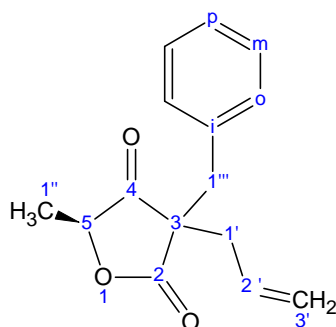
Molecular Formula = $C_{15}H_{16}O_3$
Formula Weight = 244.286

Mixture of two diastereoisomers α *and* β. *Ratio* $\alpha : \beta$ = 2.2 : 1 (β isomer has the methyl group *cis* to the aromatic ring – determined via NOESY)

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3033 (VW) [ν (=C-H)], 2923 (W) [ν (-CH$_2$-)], 1797 (M) and 1751 (VS) [ν (furan-2,4-dione ring)], 1076 (S) [ν (C-O)], 924 (M) [ν (=C-H allyl)], 744 (M) and 700 (S) [ν (C-H aromatic monosubstituted)].
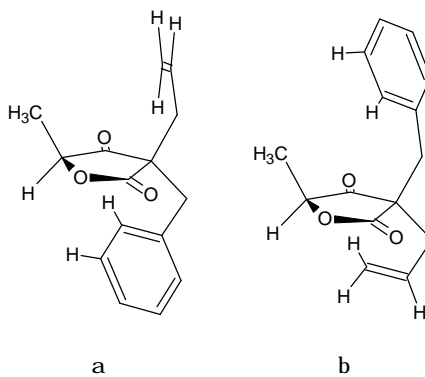
Favoured isomer

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.51 (d, $^3J_{HH}$ = 7.14 Hz, 1''-H$^\beta$) and 1.20 (d, $^3J_{HH}$ = 7.14 Hz, 1''-H$^\alpha$) (Total integral : 3H; ratio α / β : 2.2 / 1), 2.45 – 2.65 (m, 2H, 1'-H$^{\alpha+\beta}$), 2.92 (d, $^2J_{HH}$ = 13.04 Hz, 1'''-H$^\beta$), 2.93 (d, $^2J_{HH}$ = 12.76 Hz, 1'''-H$^\alpha$), 3.05 (d, $^2J_{HH}$ = 12.76 Hz, 1'''-H$^\alpha$), 3.07 (d, $^2J_{HH}$ = 13.04 Hz, 1'''-H$^\beta$) (Integral : 2H), 3.56 (q, $^3J_{HH}$ = 7.14 Hz, 5-H$^\alpha$), 4.31 (q, $^3J_{HH}$ = 7.14 Hz, 5-H$^\beta$) (Total integral : 3H; ratio α / β : 2.2 / 1), 5.07 – 5.20 (m, 2H, 3'-H$^{\alpha+\beta}_{cis/trans}$), 5.49 – 5.66 (m, 2'-H$^\alpha$), 5.54 – 5.69 (m, 2'-H$^\beta$) (Integral : 2H), 7.04 – 7.10 (m, 2H, *meta*-H$^{\alpha+\beta}$), 7.17 – 7.25 (m, 3H, *ortho*- and *para*-H$^{\alpha+\beta}$).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 14.39 (CH$_3$, 1''-C$^\beta$), 15.00 (CH$_3$, 1''-C$^\alpha$), 38.98 (CH$_2$, 1'-C$^\alpha$), 40.43 (CH$_2$, 1'''-C$^\beta$), 40.88 (CH$_2$, 1'-C$^\beta$), 42.56 (CH$_2$, 1'''-C$^\alpha$), 56.98 (C^q, 3-C$^\alpha$), 57.20 (C^q, 3-C$^\beta$), 80.86 (CH, 5-C$^\alpha$), 81.05 (CH, 5-C$^\beta$), 121.07 (CH$_2$, 3'-C$^\alpha$), 121.34 (CH$_2$, 3'-C$^\beta$), 127.57 (CH, *para*-C$^\beta$), 127.75 (CH, *ortho*-C$^\beta$), 128.70 (CH, *para*-C$^\alpha$), 128.86 (CH, *ortho*-C$^\alpha$), 129.45 (CH, *meta*-C$^\alpha$), 129.93 (CH, 2'-C$^\beta$), 130.08 (CH, *meta*-C$^\beta$), 130.79 (CH, 2'-C$^\alpha$), 133.91 (C^q, *ipso*-C$^\alpha$), 134.87 (C^q, *ipso*-C$^\beta$), 175.38 (C^q, 2-C$^\alpha$), 175.64 (C^q, 2-C$^\beta$), 212.38 (C^q, 4-C$^\beta$), 212.77 (C^q, 4-C$^\alpha$).

MS (GC inlet, EI, 70 eV) m/z (%) = 244 (1) [M$^+$], 226 (6) [M-H$_2$O]$^+$, 216 (1) [M-CO]$^+$, 203 (4) [M-C$_3$H$_5$]$^+$, 153 (26) [M-C$_7$H$_7$]$^+$, 91 (100) [C$_7$H$_7$$^+$], 77 (5) [C$_6H_5$$^+$], 65 (30) [C$_5H_5$$^+$].

3-Allyl-3-benzyl-5-ethyl-furan-2,4-dione (65c)

Colourless oil (0.69 g, 2.7 mmol, 15%) from 2.99 g (18 mmol) of 3-allyl-5-ethyl-4-hydroxy-5*H*-furan-2-one **57c** and 5.60 g (18 mmol) of *O*-benzyl-N,N'-dicyclohexylisourea **36e** refluxed in 100 mL of dry THF for 16 h. The product was a secondary fraction collected when the main crude product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (3/2) mixture as eluent.

R_f (SiO$_2$) = 0.79 (*n*-hexane : diethyl ether, 3 : 2, v : v).

Molecular Formula = C$_{16}$H$_{18}$O$_3$
Formula Weight = 258.312

Mixture of two diastereoisomers α *and* β. *Ratio* α : β = 3.6 : 1 (β isomer has the methyl group *cis* to the aromatic ring)

IR (ATR) $\bar{v}$ (cm^{-1}) = 3033 (VW) [ν (=C-H)], 2977 (VW) [ν (-CH$_2$-)], 2928 (W) [ν (-CH$_2$-)], 1796 (M) and 1751 (VS) [ν (furan-2,4-dione ring)], 1223 (M) [ν (C-O)], 742 (M) and 700 (VS) [ν (C-H aromatic monosubstituted)].

a   **b**

Favoured enantiomers

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.58 (t, $^3J_{HH}$ = 7.41 Hz, 2''-H$^\beta$) and 0.80 (t, $^3J_{HH}$ = 7.48 Hz, 2''-H$^\alpha$) (Total integral : 3H; ratio α / β : 3.6 / 1), 0.30 – 0.45 (m, 1''-H$^\beta$), 0.94 – 1.11 (m, 1''-H$^\beta$), 1.36 – 1.52 (m, 1''-H$^\alpha$), 1.54 – 1.71 (m, 1''-H$^\alpha$) (Total integral : 2H), 2.51 (d, $^3J_{HH}$ = 7.55 Hz, 2H, 1'-H$^{\alpha+\beta}$), 2.90 (d, $^2J_{HH}$ = 12.76 Hz, 1'''-H$^\alpha$) and 2.90 (d, $^2J_{HH}$ = 13.17 Hz, 1'''-H$^\beta$) and 3.02 (d, $^2J_{HH}$ = 12.76 Hz, 1'''-H$^\alpha$) and 3.05 (d, $^2J_{HH}$ = 13.17 Hz, 1'''-H$^\beta$) (Integral : 2H), 3.31 (dd, $^3J_{HH}$ = 4.67 Hz, $^3J_{HH}$ = 8.65 Hz, 5-H$^\alpha$) and 4.05 (dd, $^3J_{HH}$ = 4.87 Hz, $^3J_{HH}$ = 8.97 Hz, 5-H$^\beta$) (Total integral : 1H; ratio α / β : 3.6 / 1), 5.04 (dm, $^3J_{HH}$ = 10.35 Hz, 1H, 3'-H$_{cis}$ $^{\alpha+\beta}$), 5.08 (dm, $^3J_{HH}$ = 16.30 Hz, 1H, 3'-H$_{trans}$ $^{\alpha+\beta}$), 5.48 – 5.65 (m, 1H, 2'-H$^{\alpha+\beta}$), 6.98 – 7.04 (m, 2H, *ortho*-H$^{\alpha+\beta}$), 7.10 – 7.37 (m, 3H, *meta-* and *para*-H$^{\alpha+\beta}$).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 9.19 (CH$_3$, 2''-C$^\beta$), 9.44 (CH$_3$, 2''-C$^\alpha$), 22.78 (CH$_2$, 1''-C$^\beta$), 23.38 (CH$_2$, 1''-C$^\alpha$), 38.73 (CH$_2$, 1'-C$^\alpha$), 40.01 (CH$_2$, 1'''-C$^\beta$), 41.05 (CH$_2$, 1'-C$^\beta$), 42.51 (CH$_2$, 1'''-C$^\alpha$), 56.69 (C^q, 3-C$^\alpha$), 57.09 (C^q, 3-C$^\beta$), 85.58 (CH, 5-C$^\alpha$), 85.81 (CH, 5-C$^\beta$), 120.81 (CH$_2$, 3'-C$^\alpha$), 121.19 (CH$_2$, 3'-C$^\beta$), 127.63 (CH, *meta*-C$^\alpha$), 127.41 (CH, *meta*-C$^\beta$), 128.73 (CH, *para*-C$^\alpha$), 128.51 (CH, *para*-C$^\beta$), 129.36 (CH, *ortho*-C$^\alpha$), 129.51 (CH, *ortho*-C$^\beta$), 129.99 (CH, 2'-C$^\beta$), 130.70 (CH, 2'-C$^\alpha$), 133.84 (C^q, *ipso*-C$^\alpha$), 134.81 (C^q, *ipso*-C$^\beta$), 175.37 (C^q, 2-C$^{\alpha+\beta}$), 211.64 (C^q, 4-C$^\beta$), 212.17 (C^q, 4-C$^\alpha$).

MS (GC inlet, EI, 70 eV) m/z (%) = 258 (1) [M$^+$], 240 (3) [M-H$_2$O]$^+$, 213 (8) [M$_{240}$-C$_2$H$_3$]$^+$, 188 (8), 167 (17) [M-C$_7$H$_7$]$^+$, 129 (13) [M^{++}], 91 (100) [C$_7$H$_7^+$], 65 (6) [C$_5$H$_5^+$].

3-Allyl-3-benzyl-5-butyl-furan-2,4-dione (65d)

Colourless oil (280 mg, 0.98 mmol, 14%) from 1.40 g (7.13 mmol) of 3-allyl-5-butyl-4-hydroxy-5*H*-furan-2-one **57e** and 2.24 g (7.13 mmol) of *O*-benzyl-N,N'-dicyclohexylisourea **36e** in 150 mL of dry THF stirred under reflux during 14 h. The product was a secondary fraction collected when the main crude product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using n-hexane / diethyl ether (3/2) mixture as eluent.

R_f (SiO$_2$) = 0.79 (n-hexane : ether, 3 : 2, v : v).

Molecular Formula = C$_{18}$H$_{22}$O$_3$

Formula Weight = 286.365

Mixture of two diastereoisomers α *and* β. *Ratio* α : β = 5.6 : 1 (β *isomer has the butyl group* cis *to the aromatic ring*)

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3086 (VW) [ν (=C-H)], 2958 (W) [ν (-CH$_2$-)], 1798 (M) and 1751 (VS) [ν (Furan-2,4-dione ring)], 1225 (M) [ν (C-O)], 1030 (M) [ν (C-O)], 743 (M) and 701 (S) [ν (C-H aromatic monosubstituted)].

a

b

Favoured enantiomers

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.65 (t, $^3J_{HH}$ = 6.86 Hz, 4''-H^β) and 0.76 (t, $^3J_{HH}$ = 6.72 Hz, 4''-H^α) (Total integral : 3H; ratio α / β : 5.6 / 1), 1.09 – 1.29 (m, 4H, 2''-H – 3''-H$^{α+β}$), 1.31 - 1.46 (m, 1H, 1''-H$^{α+β}$), 1.53 – 1.68 (m, 1H, 1''-H$^{α+β}$), 2.53 (d, $^3J_{HH}$ = 7.14 Hz, 2H, 1'-H$^{α+β}$), 2.91 (d, $^2J_{HH}$ = 13.04 Hz, 1'''-H^β) and 2.92 (d, $^2J_{HH}$ = 12.90 Hz, 1'''-H^α) and 3.04 (d, $^2J_{HH}$ = 12.90 Hz, 1'''-H^α) and 3.08 (d, $^2J_{HH}$ = 13.04 Hz, 1'''-H^β) (Total integral : 2H), 3.37 (m, 5-H^α) and 4.12 (m, 5-H^β) (Total integral : 1H; ratio α / β : 5.6 / 1), 5.04 – 5.15 (m, 2H, 3'-H$_{cis/trans}$$^{α+β}$), 5.51 – 5.66 (m, 1H, 2'-H$^{α+β}$), 6.99 – 7.05 (m, 1H, *ortho*-H$^{α+β}$), 7.13 – 7.21 (m, 5H, *meta*- and *para*-H$^{α+β}$).
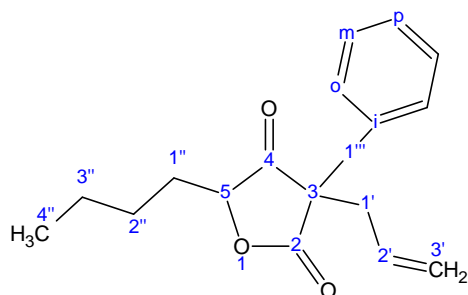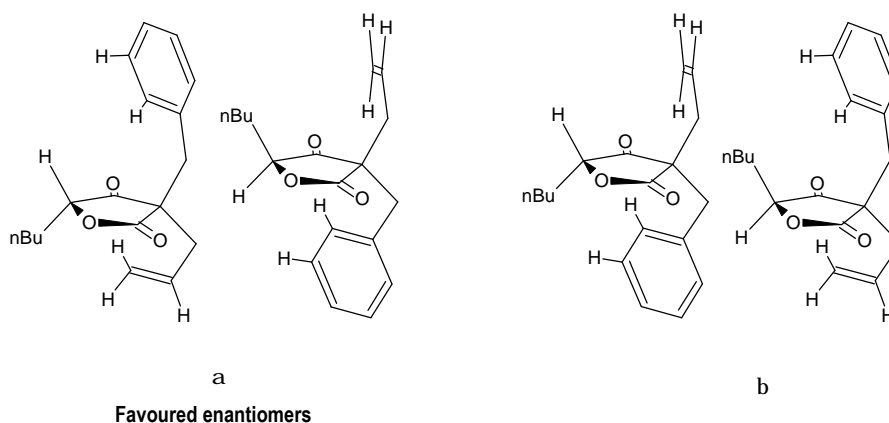
^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.45 (4''-C^β), 13.58 (4''-C^α), 21.88 (3''-C^β), 21.99 (3''-C^α), 26.73 (1''-C^β), 27.20 (1''-C^α), 29.03 (2''-C^β), 29.74 (2''-C^α), 38.89 (1'-C^α), 40.29 (4'-C^β), 41.07 (1'-C^β), 42.57 (4'-C^α), 56.79 (3-C$^{α+β}$), 84.73 (5-C^α), 84.85 (5-C^β), 120.92 (3'-C^α), 121.28 (3'-C^β), 127.51 (*para*-C^β), 127.71 (*para*-C^α), 128.63 (*ortho*-C^β), 128.81 (*ortho*-C^α), 129.44 (*meta*-C^α), 129.93 (*meta*-C^β), 130.11 (2'-C^β), 130.77 (2'-C^α), 133.91 (*ipso*-C$^{α+β}$), 175.50 (2-C$^{α+β}$), 212.45 (4-C$^{α+β}$).

MS (GC inlet, EI, 70 eV) m/z (%) = 286 (2) [M$^+$], 268 (3) [M-H$_2$O]$^+$, 245 (6) [M-C$_3$H$_5$]$^+$, 227 (3) [M$_{245}$-H$_2$O]$^+$, 195 (27) [M-C$_7$H$_7$]$^+$, 188 (17) [M$_{245}$-C$_4$H$_9$]$^+$, 177 (13) [M$_{195}$-H$_2$O]$^+$, 143 (11) [M^{++}], 91 (100) [C$_7$H$_7^+$], 65 (8) [C$_5$H$_5^+$].

3-Allyl-3-benzyl-5-hexyl-furan-2,4-dione (65e)

Colourless oil (98 mg, 0.31 mmol, 10%) from 702 mg (3.13 mmol) of 3-allyl-5-hexyl-4-hydroxy-5*H*-furan-2-one **57d** and 980 mg (3.13 mmol) of *O*-benzyl-N,N'-dicyclohexylisourea **36e** in 100 mL of dry THF stirred under reflux for 14 h. The product was a secondary fraction collected when the main crude product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (1/1) mixture as eluent.

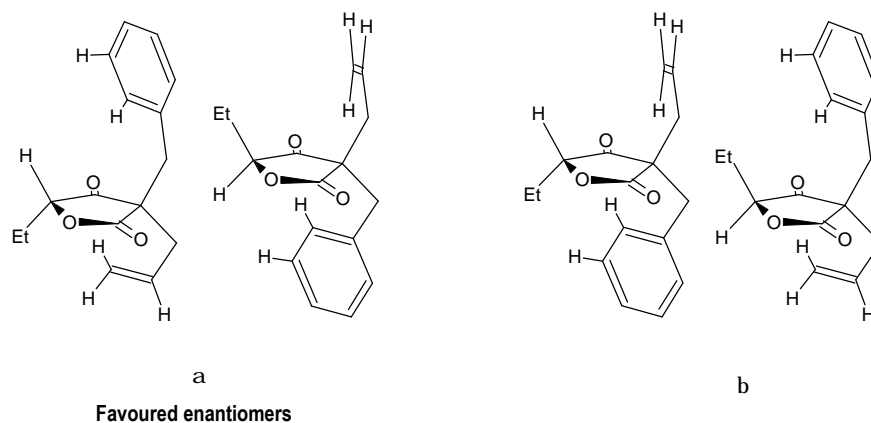R_f (SiO$_2$) = 0.84 (*n*-hexane : diethyl ether, 1 : 1, v : v).
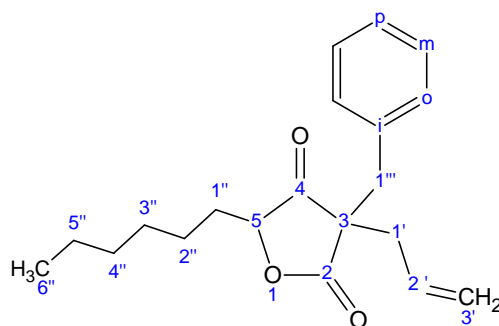
Molecular Formula = C$_{20}$H$_{26}$O$_3$
Formula Weight = 314.419

Mixture of two diastereoisomers α *and* β. *Ratio* α : β = 2.4 : 1 (β *isomer has the methyl group* cis *to the aromatic ring*)

IR (ATR) $\bar{v}$ **(cm^{-1})** = 3033 (VW) [ν (=C-H)], 2926 (M) [ν (-CH$_2$-)], 2858 (W) [ν (-CH$_2$-)], 1797 (M) and 1752 (VS) [ν (furan-2,4-dione ring)], 1032 (M) [ν (C-O)], 927 (M) [ν (=C-H)], 743 (M) and 700 (S) [ν (C-H aromatic monosubstituted)].

a

Favoured enantiomers

b

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.81 (t, $^3J_{HH}$ = 7.28 Hz, 3H, 6''-H$^{\alpha+\beta}$), 0.95 – 1.34 (m, 8H, 2''-H, 3''-H, 4''-H, 5''-H$^{\alpha+\beta}$), 1.34 - 1.52 (m, 1H, 1''-H$^{\alpha+\beta}$), 1.53 – 1.72 (m, 1H, 1''-H$^{\alpha+\beta}$), 2.58 (d, $^3J_{HH}$ = 7.13 Hz, 2H, 1'-H$^{\alpha+\beta}$), 2.96 (d, $^2J_{HH}$ = 13.04 Hz, 1'''-H$^{\beta}$) and 2.97

(d, $^2J_{HH}$ = 12.90 Hz, 1'''-H$^\alpha$) and 3.08 (d, $^2J_{HH}$ = 12.90 Hz, 1'''-H$^\alpha$) and 3.12 (d, $^2J_{HH}$ = 13.04 Hz, 1'''-H$^\beta$) (Total integral : 2H), 3.42 (m, 5-H$^\alpha$) and 4.17 (m, 5-H$^\beta$) (Total integral : 1H; ratio α / β : 2.4 / 1), 5.08 – 5.20 (m, 1H, 3'-H$_{cis/trans}$$^{\alpha+\beta}$), 5.55 – 5.73 (m, 1H, 2'-H$^{\alpha+\beta}$), 7.04 – 7.10 (m, 1H, *meta*-H$^{\alpha+\beta}$), 7.16 – 7.26 (m, 5H, *ortho*- and *para*-H$^{\alpha+\beta}$).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 13.91 (CH$_3$, 6''-C$^{\alpha+\beta}$), 22.35 (CH$_2$, 5''-C$^\alpha$), 22.41 (CH$_2$, 5''-C$^\beta$), 24.87 (CH$_2$, 4''-C$^\beta$), 25.09 (CH$_2$, 4''-C$^\alpha$), 28.56 (CH$_2$, 3''-C$^\alpha$), 28.74 (CH$_2$, 3''-C$^\beta$), 29.35 (CH$_2$, 1''-C$^\beta$), 30.08 (CH$_2$, 1''-C$^\alpha$), 31.14 (CH$_2$, 2''-C$^\beta$), 31.32 (CH$_2$, 2''-C$^\alpha$), 38.93 (CH$_2$, 1'-C$^\alpha$), 40.34 (CH$_2$, 1'''-C$^\beta$), 41.09 (CH$_2$, 1'-C$^\beta$), 42.62 (CH$_2$, 1'''-C$^\alpha$), 56.83 (C^q, 3-C$^\alpha$), 57.26 (C^q, 3-C$^\alpha$), 84.82 (CH, 5-C$^\alpha$), 84.92 (CH, 5-C$^\beta$), 120.96 (CH$_2$, 3'-C$^\alpha$), 121.33 (CH$_2$, 3'-C$^\beta$), 127.55 (CH, *para*-C$^\beta$), 127.75 (CH, *para*-C$^\alpha$), 128.67 (CH, *ortho*-C$^\beta$), 128.85 (CH, *ortho*-C$^\alpha$), 129.49 (CH, *meta*-C$^\alpha$), 129.96 (CH, 2'-C$^\beta$), 130.14 (CH, *meta*-C$^\beta$), 130.81 (CH, 2'-C$^\alpha$), 133.96 (C^q, *ipso*-C$^\alpha$), 134.95 (C^q, *ipso*-C$^\beta$), 175.57 (C^q, 2-C$^\alpha$), 175.83 (C^q, 2-C$^\beta$), 212.05 (C^q, 4-C$^\beta$), 212.51 (C^q, 4-C$^\alpha$).

MS (GC inlet, EI, 70 eV) m/z (%) = 314 (3) [M$^+$], 296 (5) [M-H$_2$O]$^+$, 273 (10) [M-C$_3$H$_5$]$^+$, 223 (34) [M-C$_7$H$_7$]$^+$, 205 (16) [M$_{223}$-H$_2$O]$^+$, 188 (28) [M$_{273}$-C$_6$H$_{13}$]$^+$, 91 (100) [C$_7$H$_7$$^+$], 65 (9) [C$_5H_5$$^+$].

3.12 Synthesis of 3-Allyl-4-*O*-allyl tetronates

3-Allyl-4-allyloxy-5*H*-furan-2-one (67a)

General experimental procedure:

To a stirred solution of triphenylphosphine (2.43 g, 9.28 mmol) in dry THF under argon atmosphere and at -78°C was added dropwise DIAD (1.88 g, 9.27 mmol) as a THF solution. After ~15 min at -78°C, a white solid (Mitsunobu betaine) was formed. Stirring was continued at -78°C for an additional 10 min. Then 1.00 g (7.14 mmol) of 3-allyl-4-hydroxy-5*H*-furan-2-one **57a** was added as a THF solution (*via* cannula under argon flux) to the above mixture at -78°C. The cooling bath was removed. After the entire solid had dissolved (~5 min), allyl alcohol (0.62 g, 10.7 mmol) was added as THF solution *via* cannula. The mixture was allowed to warm to room temperature and stirred for 2 hours. Then the sample was poured into water and extracted at pH = 10 (NaHCO$_3$) with diethyl ether. The organic layer was dried over Na$_2$SO$_4$. The solvent was removed by rotary evaporation and the product purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane : diethyl ether (2:3, v : v) as eluent.

The pure product was oily and colourless.

Yield: 60% (0.77 g, 4.27 mmol). R_f (SiO$_2$) = 0.60 (diethyl ether).

Molecular Formula = $C_{10}H_{12}O_3$
Formula Weight = 180.200

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3083 (VW) [ν (C=C-H)], 2981 (VW) [ν (-CH$_2$-)], 2939 (VW) [ν (-CH$_2$-)], 1745 (S) and 1663 (VS) [ν (Tetronate ring)], 1391 (S) [ν (C-O-C)], 1046 (S) [ν (C-O-C)], 914 (S) and 786 (M) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 2.97 (dddd, $^3J_{HH}$ = 6.18 Hz, $^4J_{HH}$ = 1.51 Hz, $^5J_{HH}$ = 0.82 Hz, $^5J_{HH}$ = 0.96 Hz, 2H, 1'-H), 4.62 (dt, $^3J_{HH}$ = 5.22 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.51 Hz, 2H, 1''-H), 4.63 (t, $^5J_{HH}$ = 0.96 Hz, $^5J_{HH}$ = 0.82 Hz, 2H, 5-H), 4.99 (dq, $^3J_{HH}$ = 10.15 Hz, $^4J_{HH}$ = 1.51 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3'-H$_{cis}$), 5.02 (dq, $^3J_{HH}$ = 17.02 Hz, $^4J_{HH}$ = 1.78 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3'-H$_{trans}$), 5.29 (dq, $^3J_{HH}$ = 10.57 Hz, $^4J_{HH}$ = 1.37 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3''-H$_{cis}$), 5.34 (dq, $^3J_{HH}$ = 17.15 Hz, $^4J_{HH}$ = 1.51 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3''-H$_{trans}$), 5.83 (ddt, $^3J_{HH}$ = 6.18 Hz, $^3J_{HH}$ = 10.15 Hz, $^3J_{HH}$ = 17.02 Hz, 1H, 2'-H), 5.91 (ddt, $^3J_{HH}$ = 5.22 Hz, $^3J_{HH}$ = 10.57 Hz, $^3J_{HH}$ = 17.15 Hz, 1H, 2''-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 26.25 (CH$_2$, 1'-C), 65.65 (CH$_2$, 5-C), 70.88 (CH$_2$, 1''-C), 101.15 (C^q, 3-C), 115.62 (CH$_2$, , 3'-C), 118.84 (CH$_2$, 3''-C), 131.47 (CH, 2''-C), 134.23 (CH, 2'-C), 172.17 (C^q, 2-C), 174.33 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 180 (15) [M$^+$], 162 (5) [M-H$_2$O]$^+$, 147 (4) [M$_{162}$-CH$_3$]$^+$, 139 (83) [M-C$_3$H$_5$]$^+$, 122 (10) [M-C$_2$H$_2$O$_2$]$^+$, 113 (23) [M$_{139}$-C$_2$H$_3$]$^+$, 79 (18), 41 (100) [C$_3$H$_5$$^+$].
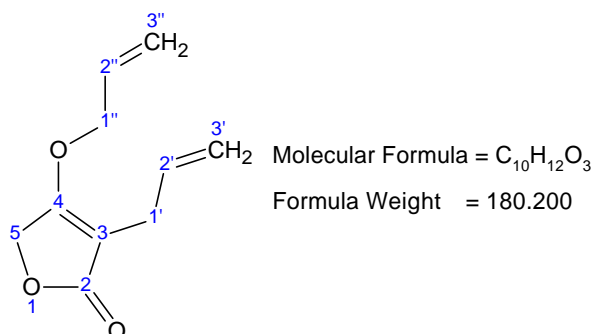
3-Allyl-4-(2-methyl-allyloxy)-5*H*-furan-2-one (67b)

Colourless oil (0.51 g, 2.6 mmol, 74%) from 1.22 g (4.65 mmol) of triphenylphosphine, 0.94 g (4.65 mmol) DIAD, 0.50 g (3.57 mmol) 3-allyl-4-hydroxy-5*H*-furan-2-one **57a** and 0.39 g (5.41 mmol) of methallyl alcohol. The product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluent.

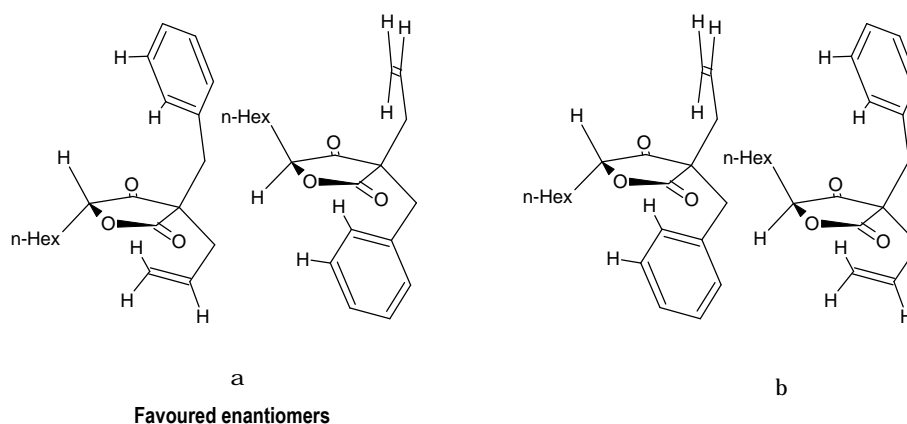R_f (SiO$_2$) = 0.57 (*n*-hexane : diethyl ether, 2 : 3, v : v); R_f (SiO$_2$) = 0.67 (diethyl ether)
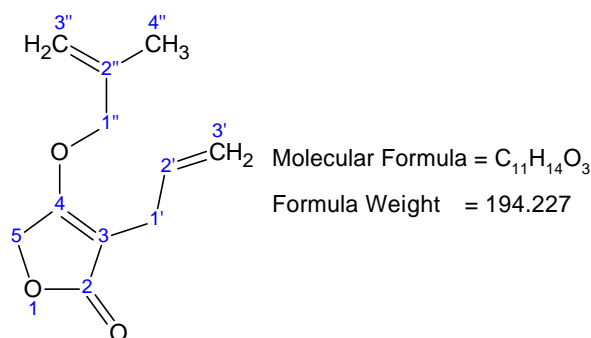
IR (ATR) $\overline{\nu}$ **(cm^{-1})** = 3082 (W) [ν (C=C-H)], 2980 (VW) [ν (-CH$_2$-)], 2942 (VW) [ν (-CH$_2$-)], 1746 (S) and 1667 (VS) [ν (Tetronate ring)], 1389 (S) [ν (C-O-C)], 1045 (S) [ν (C-O-C)], 910 (S) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.72 (s, 3H, 4''-H), 2.94 (d, $^3J_{HH}$ = 6.17 Hz, 2H, 1'-H), 4.49 (s, 2H, 1''-H), 4.64 (s, 2H, 5-H), 4.96 (m, 2H, 3'-H), 4.95 (m, 2H, 3''-H), 5.81 (ddt, $^3J_{HH}$ = 6.17 Hz, $^3J_{HH}$ = 10.02 Hz, $^3J_{HH}$ = 17.02 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 18.73 (CH$_3$, 4''-C), 26.15 (CH$_2$, 1'-C), 65.48 (CH$_2$, 5-C), 73.64 (CH$_2$, 1''-C), 101.17 (C^q, 3-C), 113.79 (CH$_2$, 3''-C), 115.54 (CH$_2$, 3'-C), 134.17 (CH, 2'-C), 139.24 (C^q, 2''-C), 172.38 (C^q, 2-C), 174.26 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 194 (10) [M$^+$], 176 (16) [M-H$_2$O]$^+$, 161 (27) [M$_{176}$-CH$_3$]$^+$, 139 (60) [M-C$_4$H$_7$]$^+$, 113 (15) [M-C$_5$H$_5$O]$^+$, 93 (11), 81 (30) [M$_{139}$-C$_2$H$_2$O$_2$]$^+$, 55 (100) [C$_4$H$_7^+$].

3-Allyl-4-(3-phenylallyloxy)-5*H*-furan-2-one (67c)

Yellowish oil (0.43 g, 1.68 mmol, 41%) from 1.93 g (7.35 mmol) of triphenylphosphine, 1.49 g (7.37 mmol) DIAD, 0.57 g (4.06 mmol) of 3-allyl-4-hydroxy-5*H*-furan-2-one **57a** and 1.14 g (8.49 mmol) of cinnamyl alcohol. The product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (1/1) mixture as eluent. – The low yield was due to the difficult removal of the residual diisopropyl hydrazine-1,2-dicarboxylate from the product.

R_f (SiO$_2$) = 0.19 (*n*-hexane : diethyl ether, 1 : 1, v : v); R_f (SiO$_2$) = 0.67 (diethyl ether)

Molecular Formula = $C_{16}H_{16}O_3$

Formula Weight = 256.296
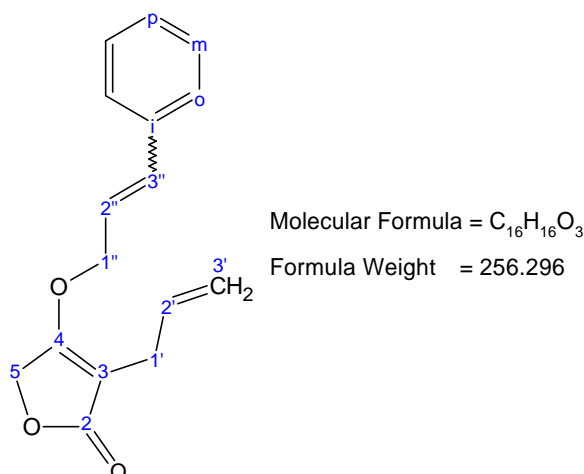
Mixture of diastereoisomers Z and E. Ratio Z : E = 2 : 1 *only distinguishable via GC.*

IR (ATR) $\bar{\nu}$ **(cm⁻¹)** = 3082 (VW) [ν (C=C-H)], 2981 (VW) [ν (-CH₂-)], 1749 (VS) and 1665 (VS) [ν (Tetronate ring)], 1373 (S) [ν (C=C)], 1337 (S) [ν (C-O-C)], 1261 (S) [ν (C-O)], 1047 (VS) [ν (C-O)], 916 (S) [ν (=C-H)].

¹H-NMR (300 MHz, CDCl₃, TMS_int) d (ppm) = 2.99 (dd, ³J_{HH} = 6.04 Hz, ⁵J_{HH} = 0.82 Hz, ⁵J_{HH} = 0.96 Hz, 2H, 1'-H), 4.64 (dd, ⁵J_{HH} = 0.82 Hz, ⁵J_{HH} = 0.96 Hz, 2H, 5-H), 4.76 (dd, ³J_{HH} = 6.04 Hz, ⁴J_{HH} = 1.37 Hz, 1H, 1''-H), 4.76 (dd, ³J_{HH} = 5.90 Hz, ⁴J_{HH} = 1.37 Hz, 1H, 1''-H), 5.02 (ddd, ³J_{HH} = 17.02 Hz, ⁴J_{HH} = 1.51 Hz, ²J_{HH} = 1.65 Hz, 1H, 3'-H_trans), 5.04 (ddd, ³J_{HH} = 10.02 Hz, ⁴J_{HH} = 1.79 Hz, ²J_{HH} = 1.65 Hz, 1H, 3'-H_cis), 5.84 (ddt, ³J_{HH} = 6.04 Hz, ³J_{HH} = 10.02 Hz, ³J_{HH} = 17.02 Hz, 1H, 2'-H), 6.22 (ddd, ³J_{HH} = 5.90 Hz, ³J_{HH} = 6.04 Hz, ³J_{HH} = 15.92 Hz, 1H, 2''-H), 6.62 (dt, ³J_{HH} = 15.92 Hz, ⁴J_{HH} = 1.37 Hz, 1H, 3''-H), 7.17 – 7-35 (m, 5H, arom-H).

¹³C-NMR (75 MHz, CDCl₃, TMS_int) d (ppm) = 26.45 (CH₂, 1'-C), 65.84 (CH₂, 5-C), 71.06 (CH₂, 1''-C), 101.36 (Cq, 3-C), 115.79 (CH₂, 3'-C), 122.12 (CH, 2''-C), 126.69 (CH, *meta*-C), 128.73 (CH, *para*-C), 128.91 (CH, *ortho*-C), 134.39 (CH, 2'-C), 134.79 (CH, 3''-C), 135.42 (Cq, *ipso*-C), 172.13 (Cq, 2-C), 174.40 (Cq, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = (E and Z isomers were separated in the GC column and contain the same fragmentation pattern) 256 (5) [M⁺], 238 (6) [M-H₂O]⁺, 214 (4), 143 (7), 117 (100) [C₉H₉⁺], 91 (11) [C₇H₇⁺], 77 (3) [C₆H₅⁺], 65 (2) [C₅H₅⁺].

3.13 Synthesis of 3,3-Diallyl-furan-2,4-diones

The diverse 3,3-diallyl-furan-2,4-diones were both prepared via Tsuji-Trost reaction (*Method 1*) and/or by Claisen rearrangement from the corresponding 3-allyl-4-O-allyl tetronates (*Method 2*).

3,3-Diallyl-furan-2,4-dione (68a) [38]

Method 1 – Tsuji-Trost reaction. General experimental procedure:

In a 50 mL Schlenk round bottom flask protected from the light, a mixture of 0.39 g (3.9 mmol) of allyl acetate, 0.50 g (3.6 mmol) of 4-allyloxy-5*H*-furan-2-one **51a** and 0.20 g (5% mol) of tetrakistriphenylphosphine palladium (0) dissolved in toluene (25 mL) were heated at 80°C in argon atmosphere for 3 hours. After cool down the reaction mixture, the solution was filtered over Celite and washed with toluene. The solvent was removed by rotary evaporation and the product was separated out by column chromatography on SiO_2 [length 20 cm, $\varnothing$ 1 cm] using DCM as eluent.

Method 2 – via Claisen rearrangement. General experimental procedure:

0.5 g of 3-allyl-4-allyloxy-5*H*-furan-2-one **67a** were dissolved in 7 mL of dry toluene and the resulting mixture was irradiated under microwave (*CEM Discover*) in a closed vessel (mw needs at least 350 mg of sample in 7 mL toluene). The conditions were programmed with temperature control giving 3 minutes to obtain 190°C (ramp time) and keeping this temperature for 20 min (hold time). After the reaction flask was cooled down to room temperature, the solvent was removed by rotary evaporation; the resulting residue was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent.

The pure product appears as a colourless oil. R_f (SiO_2) = 0.78 (*n*-hexane : diethyl ether, v : v, 2 : 3).

Method 1 - Yield: 52% (0.34 g, 1.87 mmol).

Method 2 - Yield: 92% (0.34 g, 1.89 mmol).

The compound can also be prepared via Tsuji-Trost reaction (*Method 1*) from 3-allyl-4-hydroxy-5*H*-furan-2-one **57a** and allyl acetate (Yield: 28%), from 4-allyloxy-5*H*-furan-2-one **51a** and allyl acetate under microwave irradiation for 10 min (Yield : 62 %), or from commercial tetronic acid – neutralized with 1 equivalent of DBU – and allyl acetate in a THF solution under microwave irradiation for 10 min (Yield: 17%).
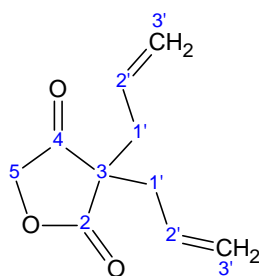
Molecular Formula = $C_{10}H_{12}O_3$
Formula Weight = 180.200

IR (ATR) $\overline{v}$ **(cm^{-1})** = 3084 (VW) [v (C=C-H)], 2983 (VW) [v (-CH$_2$-)], 2937 (VW) [v (-CH$_2$-)], 1802 (M) and 1752 (VS) [v (furan-2,4-dione ring)], 1214 (M) [v (C-O-C)], 1049 (S) [v (C-O)], 926 (S) [v (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 2.44 (d, $^3J_{HH}$ = 7.27 Hz, 4H, 1'-H), 4.35 (s, 2H, 5-H), 5.08 (d, $^3J_{HH}$ = 9.74 Hz, 2H, 3'-H$_{cis}$), 5.09 (d, $^3J_{HH}$ = 17.29 Hz, 2H, 3'-H$_{trans}$), 5.57 (ddt, $^3J_{HH}$ = 7.27 Hz, $^3J_{HH}$ = 9.74 Hz, $^3J_{HH}$ = 17.29 Hz, 2H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 38.95 (CH$_2$, 1'-C), 53.92 (C^q, 3-C), 73.23 (CH$_2$, 5-C), 121.15 (CH$_2$, 3'-C), 129.95 (CH, 2'-C), 175.61 (C^q, 2-C), 209.85 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 180 (2) [M$^+$], 162 (50) [M-H$_2$O]$^+$, 152 (9) [M-CO]$^+$, 139 (64) [M-C$_3$H$_5$]$^+$, 113 (67) [M$_{166}$-C$_2$H$_3$]$^+$, 79 (95), 68 (57) [C$_5$H$_8^+$], 41 (100) [C$_3$H$_5^+$].

3-Allyl-3-(2-methyl-allyl)-furan-2,4-dione (68b)

Colourless oil (*Method 2* : 0.46 g, 2.4 mmol, 99%) from 0.47 g (2.42 mmol) of 3-allyl-4-(2-methyl-allyloxy)-5*H*-furan-2-one **67b**. The product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (3/2) mixture as eluent.

R_f (SiO$_2$) = 0.76 (*n*-hexane : diethyl ether, 2 : 3, v : v), R_f (SiO$_2$) = 0.67 (*n*-hexane : diethyl ether, 3 : 2, v : v).

Molecular Formula = C$_{11}$H$_{14}$O$_3$
Formula Weight = 194.227
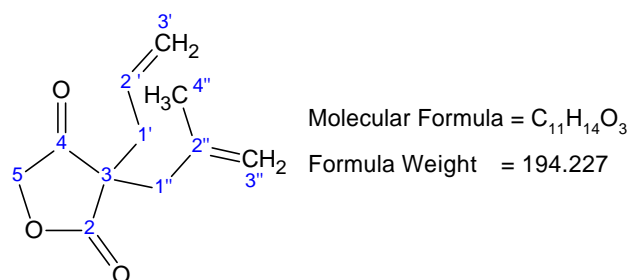
IR (ATR) $\bar{ν}$ (cm^{-1}) = 3084 (VW) [ν (=C-H)], 2981 (VW) [ν (-CH$_2$-)], 1804 (W) and 1754 (VS) [ν (furan-2,4-dione ring)], 1438 (M), 1219 (M) [ν (C-O)] , 1044 (S) [ν (C-O)], 928 (M) [ν (=CH$_2$)], 907 (M) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.65 (dd, $^4J_{HH}$ = 0.96 Hz, $^4J_{HH}$ = 1.37 Hz, 3H, 4''-H), 2.47 (dd, $^3J_{HH}$ = 7.28 Hz, $^4J_{HH}$ = 1.37 Hz, $^4J_{HH}$ = 1.23 Hz, 2H, 1'-H), 2.50 (s, 2H, 1''-H), 4.38 (d, $^2J_{HH}$ = 17.16 Hz, 1H, 5-H), 4.39 (d, $^2J_{HH}$ = 17.16 Hz, 1H, 5-H), 4.68 (m, $^4J_{HH}$ = 1.37 Hz, $^4J_{HH}$ = 0.96 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3''-H$_{cis}$), 4.83 (qu, $^4J_{HH}$ = 1.37 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3''-H$_{trans}$), 5.12 (m, $^3J_{HH}$ = 9.74 Hz, $^4J_{HH}$ = 1.37 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 5.12 (m, $^3J_{HH}$ = 17.29 Hz, $^4J_{HH}$ = 1.23 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{trans}$), 5.60 (ddt, $^3J_{HH}$ = 7.28 Hz, $^3J_{HH}$ = 9.74 Hz, $^3J_{HH}$ = 17.29 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 23.77 (CH$_3$, 4''-C), 40.33 (CH$_2$, 1'-C), 42.57 (CH$_2$, 1''-C), 54.19 (C^q, 3-C), 73.58 (CH$_2$, 5-C), 116.07 (CH$_2$, 3''-C), 121.43 (CH$_2$, 3'-C), 129.83 (CH, 2'-C), 139.40 (C^q, 2''-C), 176.19 (C^q, 2-C), 210.17 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 194 (2) [M$^+$], 179 (15) [M-CH$_3$]$^+$, 176 (50) [M-H$_2$O]$^+$, 166 (17) [M-CO]$^+$, 150 (14) [M-CO$_2$]$^+$, 139 (88) [M-C$_4$H$_7$]$^+$, 121 (27) [M$_{176}$-C$_4$H$_7$]$^+$, 55 (100) [C$_4$H$_7^+$].

3-Allyl-3-(1-phenyl-allyl)-furan-2,4-dione (68c)

Colourless oil (*Method 2* : 135 mg, 0.53 mmol, 91%) from 148 mg (0.58 mmol) of 3-allyl-4-(3-phenylallyloxy)-5*H*-furan-2-one **67c**. The product was purified by column chromatography on SiO$_2$ [length 20 cm, ∅ 1 cm] using *n*-hexane / diethyl ether (3/2) mixture as eluent.

R_f (SiO$_2$) = 0.65 (*n*-hexane : diethyl ether, 3 : 2, v : v).

Molecular Formula = C$_{16}$H$_{16}$O$_3$
Formula Weight = 256.296
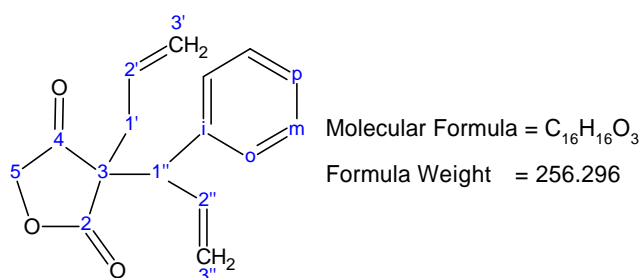
Mixture of two diastereoisomers α *and* β*. Ratio* α *:* β *= 1 : 1.8.*

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3083 (VW) [ν (=C-H)], 1800 (W) and 1752 (VS) [ν (furan-2,4-dione ring)], 1213 (S) [ν (C-O)], 1051 (S) [ν (C-O)], 996 (M) [ν (C=C-H)], 927 (S) [ν (=C-H)], 701 (S) and 665 (M) [ν (C-H aromatic monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 2.34 (dd, $^3J_{HH}$ = 7.96 Hz, $^3J_{HH}$ = 13.31 Hz, 1'-H$^\beta$) and 2.36 (dd, $^3J_{HH}$ = 8.10 Hz, $^3J_{HH}$ = 13.31 Hz, 1'-H$^\alpha$) and 2.57 (dd, $^3J_{HH}$ = 7.13 Hz, $^3J_{HH}$ = 13.31 Hz, 1'-H$^\beta$) and 2.65 (dd, $^3J_{HH}$ = 7.00 Hz, $^3J_{HH}$ = 13.31 Hz, 1'-H$^\alpha$) (Total Integral 2H – ratio α / β : 1 / 1.8), 3.39 (d, $^2J_{HH}$ = 17.15 Hz, 5-H$^\alpha$) and 3.68 (d, $^2J_{HH}$ = 17.15 Hz, 5-H$^\beta$) and 4.03 (d, $^2J_{HH}$ = 17.15 Hz, 5-H$^\alpha$) and 4.06 (d, $^2J_{HH}$ = 17.15 Hz, 5-H$^\beta$) (Total Integral 2H – ratio α / β : 1 / 1.8), 3.55 (d, $^2J_{HH}$ = 10.15 Hz, 1''-H$^\alpha$) and 3.62 (d, $^2J_{HH}$ = 10.29 Hz, 1''-H$^\beta$) (Total Integral 1H – ratio α / β : 1 / 1.8), 5.03 (ddt, $^3J_{HH}$ = 10.02 Hz, $^4J_{HH}$ = 0.82 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 5.07 (ddt, $^3J_{HH}$ = 17.02 Hz, $^4J_{HH}$ = 1.37 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{trans}$), 5.17 (ddd, $^3J_{HH}$ = 16.88 Hz, $^4J_{HH}$ = 0.82 Hz, $^2J_{HH}$ = 1.37 Hz, 1H, 3''-H$_{trans}$), 5.23 (ddd, $^3J_{HH}$ = 10.15 Hz, $^4J_{HH}$ = 0.96 Hz, $^2J_{HH}$ = 1.37 Hz, 1H, 3''-H$_{cis}$), 5.49 (dddd, $^3J_{HH}$ = 7.00 Hz, $^3J_{HH}$ = 8.10 Hz, $^3J_{HH}$ = 10.02 Hz, $^3J_{HH}$ = 17.02 Hz, 1H, 2'-H), 6.34 (dt, $^3J_{HH}$ = 10.15 Hz, $^3J_{HH}$ = 16.88 Hz, 2''-H) and 6.42 (dt, $^3J_{HH}$ = 10.15 Hz, $^3J_{HH}$ = 16.88 Hz, 2''-H) (Integral 1H), 7.07 – 7.26 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = (Carbon atoms with same magnetic environment have the same chemical shift in more than one isomer and are not listed repeated[#]) 38.63 (CH$_2$, 1'-C$^\alpha$), 38.83 (CH$_2$, 1'-C$^\beta$), 55.59 (CH, 1''-C$^\beta$), 55.87 (CH, 1''-C$^\alpha$), 58.17[#] (C^q, 3-

C), 73.25 (CH_2, 5-C^α), 73.34 (CH_2, 5-C^β), 119.52 (CH_2, 3''-C^α), 119.72 (CH_2, 3''-C^β), 121.39$^\#$ (CH_2, 3'-C), 127.91 (CH, *para*-C^α), 127.97 (CH, *para*-C^β), 128.26 (CH, *meta*-C^α), 128.29 (CH, *meta*-C^β), 128.91 (CH, *ortho*-C^β), 129.05 (CH, *ortho*-C^α), 130.16 (CH, 2'-C^α), 130.20 (CH, 2'-C^β), 133.38 (CH, 2''-C^β), 133.84 (CH, 2''-C^α), 137.71$^\#$ (C^q, *ipso*-C), 175.19 (C^q, 2-C^α), 175.54 (C^q, 2-C^β), 210.37$^\#$ (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 256 (5) [M$^+$], 238 (5) [M-H_2O]$^+$, 215 (2) [M-C_3H_5]$^+$, 169 (2) [M-$C_3H_2O_3$]$^+$, 117 (100) [$C_9H_9^+$], 91 (14) [$C_7H_7^+$], 77 (2) [$C_6H_5^+$], 65 (2) [$C_5H_5^+$].

3,3-Diallyl-5-ethyl-furan-2,4-(3*H*,5*H*)-dione (68d)

Reddish oil (*Method 1* : 0.55 g, 2.64 mmol, 89%) from 0.50 g (2.97 mmol) of 4-allyloxy-5-ethyl-5*H*-furan-2-one **51d**, 0.29 g (2.97 mmol) of allyl acetate and 172 mg (10 mol%) of tetrakistriphenilphosphine palladium (0). The product was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (3/2) mixture as eluent.

R_f (SiO_2) = 0.73 (*n*-hexane : diethyl ether, 3 : 2, v : v).

Molecular Formula = $C_{12}H_{16}O_3$
Formula Weight = 208.253
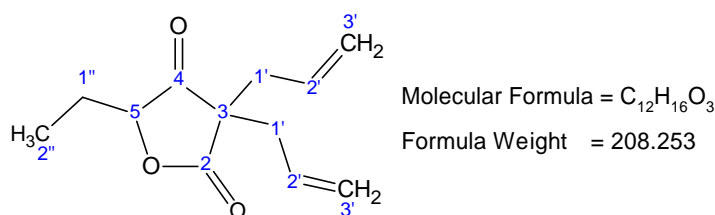
IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3084 (VW) [ν (=C-H)], 2979 (W) [ν (-CH_2-)], 2941 (VW) [ν (-CH_2-)], 1797 (M) and 1751 (VS) [ν (furan-2,4-dione ring)], 1211 (M) [ν (C-O-C)], 977 (M) and 926 (M) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.98 (t, $^3J_{HH}$ = 7.48 Hz, 3H, 2''-H), 1.51 – 1.69 (m, 1H, 1''-H), 1.72 - 1.89 (m, 1H, 1'' H), 2.41 (d, $^3J_{HH}$ = 7.69 Hz, 4H, 1'-H), 4.29 (dd, $^3J_{HH}$ = 4.52 Hz, $^3J_{HH}$ = 8.64 Hz, 1H, 5-H), 5.01 – 5.12 (m, 4H, 3'-H$_{cis}$ and 3'-H$_{trans}$), 5.46 – 5.65 (m, 2H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 9.64 (CH_3, 2''-C), 23.80 (CH_2, 1''-C), 37.95 (CH, 1'-C), 40.28 (CH, 1'-C$_{2nd\ allyl\ group}$), 54.48 (C^q, 3-C), 85.69 (CH, 5-C), 120.76 (CH_2, 3'-C), 121.19 (CH_2, 3'-C$_{2nd\ allyl\ group}$), 129.88 (CH, 2'-C), 130.77 (CH, 2'-C$_{2nd\ allyl\ group}$), 175.31 (C^q, 2-C), 211.66 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 208 (5) [M$^+$], 190 (17) [M-H_2O]$^+$, 180 (16) [M-CO]$^+$, 166 (33) [M-C_3H_5]$^+$, 122 (42) [M$_{166}$-CO]$^+$, 93 (48) [M$_{122}$-CO]$^+$, 79 (100), 41 (79) [$C_3H_5^+$].

3,3-Diallyl-5-butyl-furan-2,4-dione (68e)

Colourless oil (from modified *Method 1* : 255 mg, 1.0 mmol, 50%) from 500 mg (2.55 mmol) of 4-allyloxy-5-butyl-5*H*-furan-2-one **51e** and 147 mg (5 mol%) of tetrakistriphenylphosphine palladium (0) stirring at 80°C for 3h under argon and protected from light. The product was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent.

R_f (SiO_2) = 0.83 (*n*-hexane : diethyl ether, v : v, 3 : 2).

Molecular Formula = $C_{14}H_{20}O_3$
Formula Weight   = 236.307
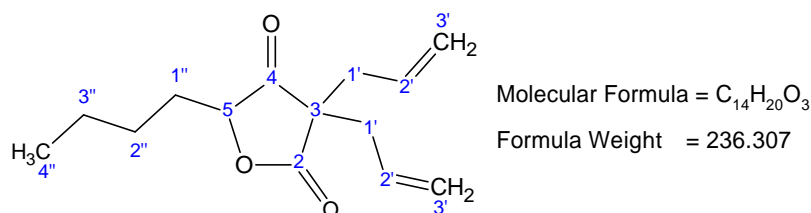
IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3082 (W) [ν (=C-H)], 2957 (S) [ν (-CH$_2$-)], 2869 (M) [ν (-CH$_2$-)], 1798 (S) and 1755 (VS) [ν (furan-2,4-dione ring)], 1214 (S) [ν (C-O-C)], 1031 (M) [ν (C-O)], 929 (M) [ν (=C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.83 (t, $^3J_{HH}$ = 7.15 Hz, 3H, 4''-H), 1.10 - 1.40 (m, 4H, 3''-H and 2''-H), 1.40 – 1.60 (m, 1H, 1''-H), 1.65 – 1.87 (m, 1H, 1''-H), 2.41 (d, $^3J_{HH}$ = 7.46 Hz, 4H, 1'-H), 4.34 (dd, $^3J_{HH}$ = 4.25 Hz, $^3J_{HH}$ = 9.12 Hz, 1H, 5-H), 5.05 (m, 2H, 3'-H$_{cis}$), 5.11 (m, 2H, 3'-H$_{trans}$), 5.45 – 5.70 (m, 2H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 13.60 (CH$_3$, 4''-C), 22.00 (CH$_2$, 3''-C), 27.29 (CH$_2$, 2''-C), 30.08 (CH$_2$, 1''-C), 38.08 (CH, 1'-C), 40.25 (CH, 1'-C), 54.45 (C^q, 3-C), 84.67 (CH, 5-C), 120.78 (CH$_2$, 3'-C), 121.18 (CH$_2$, 3'-C), 129.93 (CH, 2'-C), 130.81 (CH, 2'-C), 175.35 (C^q, 2-C), 211.85 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 236 (5) [M$^+$], 218 (4) [M-H$_2$O]$^+$, 208 (2) [M-CO]$^+$, 195 (6) [M-C$_3$H$_5$]$^+$, 180 (20) [M-C$_4$H$_9$]$^+$, 139 (23) [M$_{180}$-C$_3$H$_5$]$^+$, 79 (100), 41 (29) [C$_3$H$_5$$^+$].

3-Allyl-3[(2E)-3-phenylprop-2-en-1-yl]furan-2,4-(3*H*,5*H*)-dione (68f)

Colourless oil (from modified *Method 1*: 255 mg, 1.0 mmol, 70%) from 231 mg (1.42 mmol) of sodium 4-allyl-5-oxo-2,5-dihydrofuran-3-olate **57k**, 276 mg (1.57 mmol) of cinnamyl acetate and 164 mg (10 mol%) of tetrakistriphenylphosphine palladium (0), using THF as solvent (MeOH was added to dissolve the salt) stirring at 0°C for 2h under argon and protecting from light. The product was purified by column chromatography on SiO_2 [length 20 cm, $\varnothing$ 1 cm] using diethyl ether as eluent.

R_f (SiO_2) = 0.72 (*n*-hexane : diethyl ether, v : v, 2 : 3), R_f (SiO_2) = 0.52 (toluene).

Molecular Formula = $C_{16}H_{16}O_3$
Formula Weight = 256.296

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3028 (W) [ν (=C-H)], 1801 (W) and 1753 (VS) [ν (furan-2,4-dione ring)], 1435 (M) [ν (C=C)], 1218 (M) [ν (C-O)], 1049 (S) [ν (=C-H)], 969 (M) [ν (=C-H)], 745 (S) and 692 (S) [ν (=C-H aromatic monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 2.48 (d, $^3J_{HH}$ = 7.27 Hz, 2H, 1'-H), 2.59 (dd, $^3J_{HH}$ = 7.41 Hz, $^5J_{HH}$ = 1.09 Hz, 2H, 1''-H), 4.30 (d, $^5J_{HH}$ = 1.09 Hz, 2H, 5-H), 5.10 (dd, $^3J_{HH}$ = 10.15 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 5.10 (dd, $^3J_{HH}$ = 17.02 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{trans}$), 5.56 (ddt, $^3J_{HH}$ = 7.27 Hz, $^3J_{HH}$ = 10.15 Hz, $^3J_{HH}$ = 17.02 Hz, 1H, 2'-H), 5.93 (qu, $^3J_{HH}$ = 7.41 Hz, $^3J_{HH}$ = 15.78 Hz, 1H, 2''-H), 6.40 (d, $^3J_{HH}$ = 15.78 Hz, 1H, 3''-H), 7.12 – 7.24 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 38.31 (CH$_2$, 1''-C), 39.05 (CH$_2$, 1'-C), 54.31 (C^q, 3-C), 73.26 (CH$_2$, 5-C), 120.75 (CH, 2''-C), 121.29 (CH$_2$, 3'-C), 126.42 (CH, *meta*-C), 127.98 (CH, *para*-C), 128.33 (CH, *ortho*-C), 129.99 (CH, 2'-C), 136.00 (CH, 3''-C), 136.10 (C^q, *ipso*-C), 175.78 (C^q, 2-C), 210.08 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 256 (4) [M$^+$], 215 (6) [M-C$_3$H$_5$]$^+$, 143 (19) [C$_{11}$H$_{11}^+$], 117 (100) [C$_9$H$_9^+$], 104 (35) [C$_8$H$_8$]$^+$, 91 (18) [C$_7$H$_7^+$], 77 (4) [C$_6$H$_5^+$], 65 (3) [C$_5$H$_5^+$].

Bis-3[(2E)-3-phenylprop-2-en-1-yl]furan-2,4-(3*H*,5*H*)-dione (68g)

Colourless crystals (from modified *Method 1* : 42 mg, 0.13 mmol, 5%) separated out as secondary compound from the Tsuji-Trost reaction from 0.50 g (2.5 mmol) of 4-allyloxy-5-butyl-5*H*-furan-2-one **51e**, 276 mg (1.57 mmol) of cinnamyl acetate and 164 mg (10 mol%) of tetrakistriphenylphosphine palladium (0) stirring at rt for 3h under argon and protected from light. The product was purified by column chromatography on SiO$_2$ [length 20 cm, ∅ 1 cm] using toluene as eluent.

R_f (SiO$_2$) = 0.62 (toluene). m.p. = 93°C.

Molecular Formula = $C_{22}H_{20}O_3$

Formula Weight = 332.392

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3082 (VW) [ν (=C-H)], 1805 (M) and 1755 (VS) [ν (furan-2,4-dione ring)], 1431 (M) [ν (C=C)], 1215 (M) [ν (C-O)], 1057 (M) [ν (C-O)], 972 (S) [ν (=C-H)], 746 (S) and 691 (VS) [ν (C-H aromatic monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 2.65 (d, $^3J_{HH}$ = 7.28 Hz, 4H, 1'-H), 4.30 (s, 2H, 5-H), 5.96 (qu, $^3J_{HH}$ = 7.28 Hz, $^3J_{HH}$ = 15.64 Hz, 2H, 2'-H), 6.44 (d, $^3J_{HH}$ = 15.64 Hz, 2H, 3'-H), 7.15 – 7.27 (m, 10H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 38.39 (CH$_2$, 1'-C), 54.64 (C^q, 3-C), 73.29 (CH$_2$, 5-C), 120.77 (CH, 2'-C), 126.41 (CH, *meta*-C), 128.05 (CH, *para*-C), 128.62 (CH, *ortho*-C), 136.10 (CH, 3'-C), 136.14 (C^q, *ipso*-C), 175.92 (C^q, 2-C), 210.29 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 332 (20) [M$^+$], 286 (2) [M-H$_2$O]$^+$, 241 (11) [M-C$_7$H$_7$]$^+$, 219 (54), 117 (100) [C$_9$H$_9^+$], 91 (35) [C$_7$H$_7^+$], 77 (5) [C$_6$H$_5^+$], 65 (4) [C$_5$H$_5^+$].

3.14 Synthesis of 3-Alkyl-furan-2-ones *via* catalytic hydrogenation

4-Hydroxy-3-propyl-5*H*-furan-2-one (57j)

Method A:

300 mg of the catalyst Rh/Al$_2$O$_3$ (5 %) were placed in an autoclave under argon. 15 mL ethyl acetate were added and then 300 mg (2.14 mmol) of 3-allyl-4-hydroxy-5*H*-furan-2-one **57a** dissolved in 5 mL ethyl acetate. The tetronic acid was hydrogenated under a hydrogen pressure of 50 Bar at 60°C for 4 days. After the catalyst had been filtered off by the use of a Büchner funnel (solvent: ethyl acetate), the reaction mixture was filtered through Celite (2 cm, solvent: ethyl acetate). The solvent was removed at 38°C under reduced pressure and the brownish, oily residue was purified via a wet SiO$_2$ chromatography column with diethyl ether as eluent to give the product as white crystals in 60% yield (180 mg, 1.27 mmol).

Method B:

40 mg of Pd/C (10 w%) were placed in a 100 mL three neck bottle flask and covered with 3 mL dry methanol while slightly flushing the flask with argon. Then 390 mg (1.57 mmol) of 3-(2-benzyloxy-propyl)-4-hydroxy-5*H*-furan-2-one **60j** dissolved in methanol were added and all air was taken out using an argon stream for 1 minute. After closing all necks pure hydrogen was flushed into the flask six times to take out the argon. Working with a slight overpressure (filled balloon) the reaction ran for 2 hours (control via GC). After filtering the red solution over SiO_2 (or Celite) one did not find any starting material in the GC plot. After some time a crystalline material precipitated, that was not soluble in diethyl ether but better in ethyl acetate. About 5 g of SiO_2 were added and the solvents were evaporated under a very slight vacuum at room temperature. Column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] was carried out with ethyl acetate. The yield was only 10% (20 mg; 0.13 mmol) of the theoretical amount. The desired deprotected component 4-hydroxy-3-(2-hydroxy-propyl)-5*H*-furan-2-one could not be isolated.

R_f (SiO$_2$) = 0.52 (diethyl ether – AcOH 5%). m.p. = 102°C.

Molecular Formula = $C_7H_{10}O_3$
Formula Weight = 142.152

IR (ATR) $\overline{v}$ **(cm^{-1})** = 3426 (W) [v (O-H)], 2926 (M) [v (-CH$_2$-)], 2936 (M) [v (-CH$_2$-)], 2708 (W) [v (O-H bridge)], 1747 (S) and 1654 (S) [v (Tetronic ring)], 1394 (S) [v (C-O)], 1041 (VS) [v (C-O)].

^{1}H-NMR (300 MHz, Acetone-D$_6$, TMS$_{int}$) δ (ppm) = 0.75 (t, $^3J_{HH}$ = 7.41 Hz, 3H, 3'-H), 1.35 (sext, $^3J_{HH}$ = 7.41 Hz, $^3J_{HH}$ = 6.73 Hz, 2H, 2'-H), 2.00 (t, $^3J_{HH}$ = 6.73 Hz, $^5J_{HH}$ = 0.82 Hz, 2H, 1'-H), 4.45 (t, 2H, $^5J_{HH}$ = 0.82 Hz, 5-H), 10.00 (br. s., 1H, O-H).

^{13}C-NMR (75 MHz, Acetone-D$_6$, TMS$_{int}$) δ (ppm) = 14.06 (CH$_3$, 3'-C), 21.91 (CH$_2$, 2'-C), 23.96 (CH$_2$, 1'-C), 67.14 (CH$_2$, 5-C), 101.51 (C^q, 3-C), 172.91 (C^q, 2-C), 175.48 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 142 (5) [M$^+$], 127 (3) [M-CH$_3$]$^+$, 113 (12) [M-C$_2$H$_5$]$^+$, 101 (77) [M-C$_3$H$_5$]$^+$, 84 (12) [M$_{127}$-CO$_2$]$^+$, 69 (9) [M$_{113}$-CO$_2$]$^+$, 55 (100) [C$_4$H$_7^+$], 41 (27) [C$_3$H$_5^+$].

(*3R,4S,5S*)-3-Butyl-4-hydroxy-5-methyltetrahydrofuran-2-one [(-)-3-*epi*-Blastmycinolactol)] (29-*epi*)

Colourless crystals (40 mg, 0.23 mmol, 16%) from *Method A* using 252 mg (1.5 mmol) of 3-but-2-enyl-4-hydroxy-5(*S*)-methyl-5*H*-furan-2-one **57g**, 252 mg of the catalyst Rh/Al$_2$O$_3$ (5%),

20 mL ethyl acetate and 10 mL AcOH. The resulting mixture was stirred at 60°C for 5d under hydrogen pressure (50 Bar). The reaction mixture was filtered through Celite and the product was purified by column chromatography on SiO_2 [length 20 cm, $\varnothing$ 1 cm] using diethyl ether as eluent. When using excess of catalyst (20 mol-%), the yield was improved up to 42%.

R_f (SiO_2) = 0.76 (diethyl ether). m.p. = 93°C. [Ref 84a m.p. = 101-102°C (AcOEt - hexane); Ref 84g m.p. = 99.5-100°C]

$[\alpha]_D^{25}$ –57.05° (0.638 g/100mL, MeOH), [Ref 84a $[\alpha]_D^{25}$ -84.8° (0.66, MeOH); Ref 84g $[\alpha]_D^{17}$ -96° (0.34, MeOH)]

Molecular Formula = $C_9H_{16}O_3$
Formula Weight   = 172.221

IR (ATR) $\overline{\nu}$ **(cm^{-1})** = 3427 (W) [ν (O-H)], 2959 (M) [ν (-CH_2-)], 2936 (M) [ν (-CH_2-)], 2875 (W), 1741 (VS) [ν (C=O)], 1457 (M) [ν (C-O)], 1187 (S) [ν (C-O)], 1063 (S) [ν (C-H)].

^{1}H-NMR (300 MHz, $CDCl_3$, TMS_{int}) d (ppm) = 0.89 (t, $^3J_{HH}$ = 6.86 Hz, 3H, 4'-H), 1.30 – 1.41 (m, 2H, 3'-H), 1.39 (d, $^3J_{HH}$ = 6.45 Hz, 3H, 1''-H), 1.35 – 1.44 (m, 2H, 2'-H), 1.53 – 1.69 (m, 1H, 1'-H), 1.69 – 1.84 (m, 1H, 1'-H), 2.53 (dt, $^3J_{HH}$ = 4.94 Hz, $^3J_{HH}$ = 10.02 Hz, 1H, 3-H), 2.84 (br. s., 1H, O-H), 4.28 (dd, $^3J_{HH}$ = 3.02 Hz, $^3J_{HH}$ = 4.94 Hz, 1H, 4-H), 4.43 (dq, $^3J_{HH}$ = 3.02 Hz, $^3J_{HH}$ = 6.45 Hz, 1H, 5-H).

^{13}C-NMR (75 MHz, $CDCl_3$, TMS_{int}) d (ppm) = 13.63 (CH_3, 1''-C), 13.83 (CH_3, 4'-C), 22.51 (CH_2, 3'-C), 22.94 (CH_2, 1'-C), 29.67 (CH_2, 2'-C), 47.57 (CH, 3-C), 71.08 (CH, 4-C), 79.23 (CH, 5-C), 178.26 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 172 (2) [M^+], 155 (8), 129 (10) [$M-C_3H_7$]$^+$, 116 (87), 99 (69), 85 (37) [$M_{129}-CO_2$]$^+$, 57 (100) [$C_4H_9^+$], 43 (37) [$C_3H_7^+$].

3.15 Synthesis of dihydro-2*H*-furo[3,4-*b*]oxepin-6-ones and oxa-spiro[4.4]non-7-ene-1,4-diones

5,8-Dihydro-2*H*-furo[3,4-*b*]oxepin-6-one (81a)

General experimental procedure:

In a Schlenk round bottom flask previously dried 37mg (0.02 mmol, 2% mol) of Grubbs' catalyst (1st generation) were dissolved in 25 mL of dry DCM under a flux of argon; then 0.40 g (2.22 mmol) of 3-allyl-4-allyloxy-5*H*-furan-2-one **67a** were added, the system was closed and

the reaction mixture was stirred at room temperature for 1 day. Then lead tetra acetate (0.11 g, 0.25 mmol) was added in order to remove the ruthenium by complexation. The mixture was filtered in Celite and washed with DCM, the solvent was evaporated and the residual black phosphine and ruthenium complex were removed by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] eluting the sample with DCM.

The product was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluant.

White crystals (0.28 g, 1.84 mmol, 83%). R_f (SiO_2) = 0.32 (*n*-hexane : diethyl ether, v : v, 2 : 3). m.p. = 85°C.

Molecular Formula = $C_8H_8O_3$
Formula Weight   = 152.147

IR (ATR) $\overline{\nu}$ (cm^{-1}) = 3043 (W) [ν (=C-H)], 2940 (W) [ν (-CH$_2$-)], 1734 (S) and 1662 (S) [ν (tetronate ring)], 1291 (S) [ν (C-O)], 1019 (VS) [ν (C-O)], 921 (VS) [ν (C=C)], 715 (VS) [ν (=C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 3.08 (ddd, $^3J_{HH}$ = 5.63 Hz, $^5J_{HH}$ = 1.51 Hz, $^5J_{HH}$ = 1.64 Hz, 2H, 1'-H), 4.46 (dd, $^5J_{HH}$ = 1.51 Hz, $^5J_{HH}$ = 1.64 Hz, 2H, 5-H), 4.73 (d, $^3J_{HH}$ = 7.00 Hz, 2H, 1''-H), 5.96 (dtt, $^3J_{HH}$ = 7.00 Hz, $^3J_{HH}$ = 10.43 Hz, $^4J_{HH}$ = 1.51 Hz, 1H, 2''-H), 6.25 (ddt, $^3J_{HH}$ = 5.63 Hz, $^3J_{HH}$ = 10.43 Hz, $^4J_{HH}$ = 0.42 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 22.06 (CH$_2$, 1'-C), 66.74 (CH$_2$, 5-C), 67.63 (CH$_2$, 1''-C), 99.62 (C^q, 3-C), 125.44 (CH, 2''-C), 137.19 (CH, 2'-C), 174.17 (C^q, 2-C), 174.23 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 152 (70) [M$^+$], 137 (17) [M-CH$_3$]$^+$, 123 (9) [M-C$_2$H$_5$]$^+$, 110 (38) [M-C$_2$H$_2$O]$^+$, 94 (39) [M-C$_2$H$_2$O$_2$]$^+$, 66 (100) [M$_{110}$-CO$_2$]$^+$, 54 (49) [M$_{94}$-C$_3$H$_4$]$^+$, 39 (59) [C$_3$H$_3$$^+$].
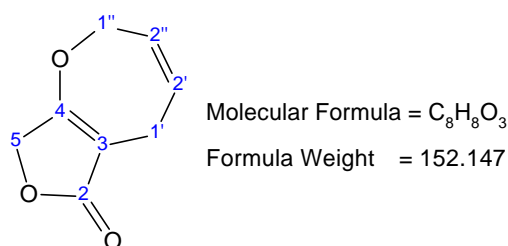
3-Methyl-3,8-dihydro-2*H*-furo[3,4-*b*]oxepin-6-one (81b)

Colourless oil (80 mg, 0.48 mmol, 49%) from 191 mg (0.98 mmol) of 3-allyl-4-(2-methyl-allyloxy)-5*H*-furan-2-one **67b** and 16 mg (2 mol%) of Grubbs' catalyst (2nd generation) dissolved in toluene, stirring under reflux for 24 h at 110°C. 17 mg (0.04 mmol) of lead tetraacetate were used to remove the ruthenium. After the filtration over Celite, the product was purified by column chromatography on SiO_2 [length 30 cm, $\varnothing$ 2 cm] using diethyl ether as eluant.

R_f (SiO$_2$) = 0.77 (diethyl ether).

Molecular Formula = C$_9$H$_{10}$O$_3$

Formula Weight = 166.174
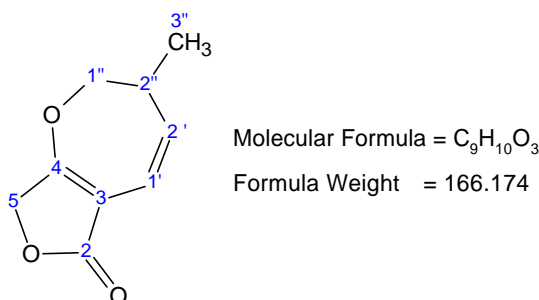
Mixture of two enantiomers. Ratio according chiral GC = 1 : 1.

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 1747 (VS) and 1647 (VS) [ν (Tetronate ring)], 1423 (S) [ν (C-C)], 1305 (S) [ν (C-O)] , 1050 (S) [ν (C-O)], 1009 (VS) [ν (C-H)], 909 (S) [ν (=C-H)], 729 (S) [ν (C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 1.10 (d, $^3J_{HH}$ = 7.41 Hz, 3H, 3''-H), 2.77 (m, 1H, 2''-H), 4.14 (dd, $^3J_{HH}$ = 5.90 Hz, $^3J_{HH}$ = 10.98 Hz, 1H, 1''-H), 4.26 (dd, $^3J_{HH}$ = 1.09 Hz, $^3J_{HH}$ = 10.98 Hz, 1H, 1''-H), 4.58 (s, 2H, 5-H), 5.85 (dd, $^3J_{HH}$ = 5.08 Hz, $^3J_{HH}$ = 10.57 Hz, 1H, 2'-H), 6.05 (d, $^3J_{HH}$ = 10.57 Hz, 1H, 1'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 16.60 (CH$_3$, 3''-C), 37.77 (CH, 2''-C), 66.45 (CH$_2$, 5-C), 76.75 (CH$_2$, 1''-C), 102.29 (C^q, 3-C), 117.59 (CH, 2'-C), 137.03 (CH, 1'-C), 173.01 (C^q, 2-C), 173.37 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 166 (100) [M$^+$], 151 (59) [M-CH$_3$]$^+$, 137 (27) [M-C$_2$H$_5$]$^+$, 124 (42) [M$_{151}$-C$_2$H$_5$]$^+$, 107 (24) [M$_{151}$-CO$_2$]$^+$, 91 (23), 79 (74) [M$_{124}$-C$_2$H$_5$O]$^+$, 65 (27).

2-Oxa-spiro[4.4]non-7-ene-1,4-dione (84a)

Colourless oil (246 mg, 1.64 mmol, 90%) from 330 mg (1.83 mmol) of 3,3-diallyl-furan-2,4-dione **68a** and 80 mg (2 mol%) of Grubbs' catalyst (1st generation) dissolved in DCM, stirring for 24 h at rt. 17 mg (0.04 mmol) of lead tetraacetate were used to remove the ruthenium. After the filtration over Celite, the product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using diethyl ether as eluant.

R_f (SiO$_2$) = 0.77 (diethyl ether).

Molecular Formula = C$_8$H$_8$O$_3$

Formula Weight = 152.147
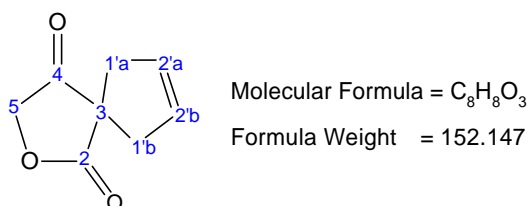
IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3073 (VW) [ν (=C-H)], 2936 (W) [ν (-CH$_2$-)], 2853 (VW) [ν (-CH$_2$-)], 1781 (M) and 1745 (VS) [ν (furan-2,4-dione ring)], 1246 (S) [ν (C-O-C)], 1047 (VS) [ν (C-O)], 677 (VS) [ν (=C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 2.70 – 2.74 (m) and 2.75 – 2.81 (m) (Integral 1H, 1'a-H$_\alpha$), 2.81 – 2.86 (m) and 2.87 – 2.92 (m) (Integral 1H, 1'a-H$_\beta$), 2.70 – 2.74 (m) and 2.75 – 2.81 (m) (Integral 1H, 1'b-H$_\alpha$), 2.81 – 2.86 (m) and 2.87 – 2.92 (m) (Integral 1H, 1'b-H$_\beta$), 4.65 (d, ^{5}J$_{HH}$ = 0.69 Hz, 2H, 5-H), 5.65 (s, 2H, 2'a-H and 2'b-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = (The compound has a "pseudo" C$_2$ axis giving carbon atoms with same magnetic environment and the same chemical shift; these signals are not listed repeated$^#$) 42.41$^#$ (CH$_2$, 1'a-C) and (CH$_2$, 1'b-C), 50.77 (C^q, 3-C), 72.14 (CH$_2$, 5-C), 127.36$^#$ (CH, 2'a-C) and (CH, 2'b-C), 177.58 (C^q, 2-C), 209.33 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 152 (80) [M$^+$], 137 (7) [M-CH$_3$]$^+$, 124 (5) [M-CO]$^+$, 110 (41) [M$_{137}$-CH$_2$O]$^+$, 94 (33) [M-C$_2$H$_2$O$_2$]$^+$, 82 (13) [M$_{110}$-CO]$^+$, 66 (100) [M$_{124}$-C$_2$H$_2$O$_2$]$^+$, 39 (30) [C$_3$H$_3$$^+$].

3-Ethyl-2-oxa-spiro[4.4]non-7-ene-1,4-dione (84b)

Colourless oil (110 mg, 0.61 mmol, 85%) from 150 mg (0.72 mmol) of 3,3-diallyl-5-ethyl-furan-2,4-(3*H*,5*H*)-dione **68d** and 12 mg (2 mol%) of Grubbs' catalyst (1st generation) dissolved in DCM, stirring for 24 h at rt. After the filtration over Celite, the product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (2/3) as eluant.

R$_f$ (SiO$_2$) = 0.63 (*n*-hexane : diethyl ether, v : v, 2 : 3).

Molecular Formula = C$_{10}$H$_{12}$O$_3$
Formula Weight   = 180.200

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3066 (VW) [ν (=C-H)], 2975 (W) [ν (-CH$_2$-)], 2938 (W) [ν (-CH$_2$-)], 1796 (M) and 1747 (VS) [ν (furan-2,4-dione ring)], 1333 (M) [ν (C-O-C)], 1242 (S) [ν (C-O)], 1046 (S) [ν (C-C)], 976 (S) [ν (=C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.99 (t, $^3J_{HH}$ = 7.41 Hz, 3H, 2''-H), 1.70 – 1.88 (m, 1H, 1''-H), 1.88 – 2.05 (m, 1H, 1''-H), 2.68 (dm, $^2J_{HH}$ = 16.48 Hz, 1H, 1'a-H$^\alpha$), 2.74 (dm, $^2J_{HH}$ = 16.23 Hz, 1H, 1'b-H$^\alpha$), 2.86 (dm, $^2J_{HH}$ = 16.48 Hz, 1H, 1'a-H$^\beta$), 2.86 (dm, $^2J_{HH}$ = 16.23 Hz, 1H, 1'b-H$^\beta$), 4.70 (dd, $^3J_{HH}$ = 4.80 Hz, $^3J_{HH}$ = 7.00 Hz, 1H, 5-H), 5.63 (s, 1H, 2'a-H), 5.63 (s, 1H, 2'b-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 8.81 (CH$_3$, 2''-C), 24.67 (CH$_2$, 1''-C), 42.07 (CH$_2$, 1'a-C), 43.24 (CH$_2$, 1'b-C), 50.96 (C^q, 3-C), 84.73 (CH, 5-C), 126.94 (CH, 2'a-C), 127.57 (CH, 2'b-C), 177.42 (C^q, 2-C), 211.72 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 180 (73) [M$^+$], 162 (4) [M-H$_2$O]$^+$, 151 (5) [M-C$_2$H$_5$]$^+$, 138 (5) [C$_7$H$_6$O$_3$$^+$], 123 (5) [M$_{151}$-CO]$^+$, 110 (13) [M$_{138}$-CO]$^+$, 94 (95) [M$_{138}$-CO$_2$]$^+$, 66 (100) [M$_{94}$-CO]$^+$.
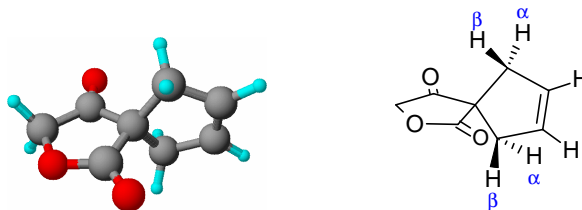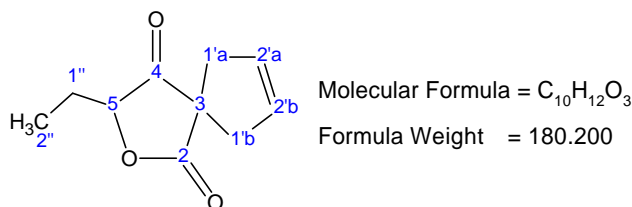
3-Butyl-2-oxa-spiro[4.4]non-7-ene-1,4-dione (84c)

Colourless oil (120 mg, 0.58 mmol, 91%) from 150 mg (0.63 mmol) of 3,3-diallyl-5-butyl-furan-2,4-dione **68e** and 10 mg (2 mol%) of Grubbs' catalyst (1st generation) dissolved in DCM, stirring for 24 h at rt. After the filtration over Celite, the product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (2/3) as eluant. R_f (SiO$_2$) = 0.59 (*n*-hexane : diethyl ether, v : v, 2 : 3).

Molecular Formula = C$_{12}$H$_{16}$O$_3$
Formula Weight = 208.253
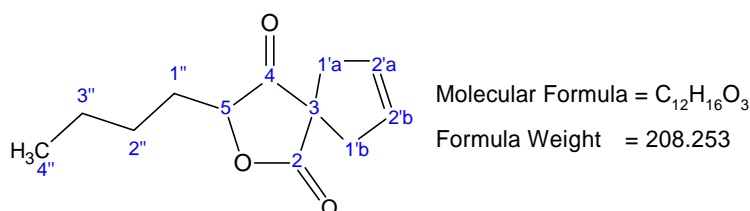
IR (ATR) $\bar{\nu}$ (cm^{-1}) = 2957 (W) [ν (-CH$_2$-)], 2930 (W) [ν (-CH$_2$-)], 2862 (W) [ν (-CH$_2$-)], 1798 (S) and 1749 (VS) [ν (furan-2,4-dione ring)], 1250 (M) [ν (C-O-C)], 1052 (M) [ν (C-O)], 1011 (M) [ν (=C-H)].
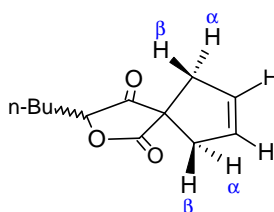
^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.84 (t, $^3J_{HH}$ = 6.93 Hz, 3H, 4''-H), 1.22 - 1.45 (m, 4H, 3''-H and 2''-H), 1.60 – 1.76 (m, 1H, 1''-H), 1.77 – 1.95 (m, 1H, 1''-H), 2.65 (dm, $^2J_{HH}$ = 15.65 Hz, 1H, 1'a-H$^\alpha$), 2.70 (dm, $^2J_{HH}$ = 15.52 Hz, 1H, 1'b-H$^\alpha$), 2.82 (dm, $^2J_{HH}$ = 15.65 Hz, 1H, 1'a-H$^\beta$), 2.83 (dm, $^2J_{HH}$ = 15.52 Hz, 1H, 1'b-H$^\beta$), 4.71 (dd, $^3J_{HH}$ = 4.53 Hz, $^3J_{HH}$ = 7.95 Hz, 1H, 5-H), 5.60 (s, 1H, 2'a-H), 5.60 (s, 1H, 2'b-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 13.47 (CH$_3$, 4''-C), 21.92 (CH$_2$, 3''-C), 26.59 (CH$_2$, 2''-C), 30.98 (CH$_2$, 1''-C), 42.15 (CH$_2$, 1'a-C), 43.07 (CH$_2$, 1'b-C), 50.81 (C^q, 3-C), 83.72 (CH, 5-C), 126.94 (CH, 2'a-C), 127.46 (CH, 2'b-C), 177.31 (C^q, 2-C), 211.68 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 208 (21) [M$^+$], 189 (2) [M-H$_2$O]$^+$, 152 (3) [M-C$_4$H$_9$]$^+$, 138 (2) [C$_7$H$_6$O$_3$$^+$], 110 (5) [M$_{138}$-CO]$^+$, 98 (5) [C$_6H_{10}O^+$], 94 (100) [M$_{138}$-CO$_2$]$^+$, 66 (84) [M$_{94}$-CO]$^+$.
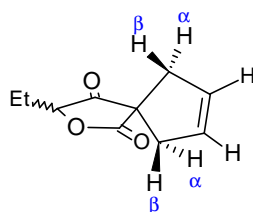
7-Methyl-2-oxa-spiro[4.4]non-7-ene-1,4-dione (84d)

Colourless oil (284 mg, 1.71 mmol, 95%) from 250 mg (1.8 mmol) of 3-allyl-3-(2-methyl-allyl)-furan-2,4-dione **68b** and 44 mg (2 mol%) of Grubbs' catalyst (2nd generation) dissolved in toluene, stirring under reflux for 24 h at 110°C. 110 mg (0.25 mmol) of lead tetraacetate were used to remove the ruthenium. After the filtration over Celite, the product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using diethyl ether as eluant.

R_f (SiO$_2$) = 0.46 (diethyl ether).

Molecular Formula = C$_9$H$_{10}$O$_3$
Formula Weight   = 166.174

Mixture of two enantiomers. Ratio according chiral GC = 1 : 1.

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 2915 (W) [ν (-CH$_2$-)], 1807 (W) – 1791 (W) and 1750 (VS) [ν (furan-2,4-dione ring)], 1433 (M), 1339 (M), 1242 (S) [ν (C-O-C)], 1042 (S) [ν (C-O)], 1005 (M), 685 (M) [ν (C=C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 1.72 (m, 3H, 3'-H), 2.60 (dm, $^2J_{HH}$ = 15.32 Hz, 1'a-H$_\alpha$), 2.69 (dm, $^2J_{HH}$ = 17 Hz, 1'b-H$_\alpha$), 2.73 (dm, $^2J_{HH}$ = 15.32 Hz, 1H, 1'a-H$_\beta$), 2.81 (dm, $^2J_{HH}$ = 17 Hz, 1H, 1'b-H$_\beta$), 4.63 (d, $^5J_{HH}$ = 1.65 Hz, 2H, 5-H), 5.22 (m, 1H, 2'b-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 15.56 (CH$_3$, 3'-C), 42.59 (CH$_2$, 1'a-C), 45.38 (CH$_2$, 1'b-C), 51.50 (C^q, 3-C), 72.07 (CH$_2$, 5-C), 120.74 (CH, 2'b-C), 137.39 (CH, 2'b-C), 177.74 (C^q, 2-C), 209.15 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 166 (64) [M$^+$], 151 (20) [M-CH$_3$]$^+$, 138 (3) [M-CO]$^+$, 124 (41) [M$_{167}$-C$_3$H$_7$]$^+$, 107 (28) [M$_{151}$-CO$_2$]$^+$, 93 (36) [M$_{151}$-C$_2$H$_2$O$_2$]$^+$, 79 (100) [C$_6$H$_7^+$], 65 (24) [C$_5$H$_5^+$].

3.16 Synthesis of 4-Allyl(phenyl)amino-5*H*-furan-2-ones

3-Allyl-4-allylamino-5*H*-furan-2-one (86a)

General experimental procedure: [114]

970 mg (17.0 mmol) of allyl amine were added to a solution of 476 mg (3.4 mmol) of 3-allyl-4-hydroxy-5*H*-furan-2-one **57a** in glacial acetic acid (8.5 mL) and the resulting mixture was heated at 115 – 120 °C for 3 h, followed by azeotropic distillation after adding dry toluene dropwise to the reaction mixture at 115 – 120 °C (Caution!). After additional heating for 2 h, the reaction mixture was evaporated under reduced pressure. The residue was dissolved in chloroform (170 mL), and anhydrous sodium carbonate (8.5 g) was added to the solution. The resulting suspension was stirred until the acid was completely consumed. On filtration of the suspension and subsequent evaporation of the filtrate, the aminobutenolide was obtained and was purified *via* chromatography column in SiO$_2$ [length 40 cm, ∅ 2 cm] using diethyl diethyl ether / ethyl acetate (4/1) mixture as eluent. The compound was obtained as pale yellow oil that solidified with time to a pale yellow powder.

Yield: 89 % (540 mg, 3.01 mmol). R_f (SiO$_2$) = 0.67 (diethyl ether : ethyl acetate, 4 : 1, v : v). m.p. = 59 – 60 °C.

Molecular Formula = C$_{10}$H$_{13}$NO$_2$
Formula Weight   = 179.216

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3299 (W) [ν (N-H)], 3083 (W) [ν (=C-H)], 2978 (VW) [ν (-CH$_2$-)], 1719 (M) and 1607 (VS) [ν (Tetramide ring)], 1333 (M) [ν (C-O)], 1047 (S) [ν (C-O-C)], 913 (S) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ **(ppm)** = 2.90 (dtt, $^3J_{HH}$ = 6.17 Hz, $^4J_{HH}$ = 1.51 Hz, $^4J_{HH}$ = 1.79 Hz, 2H, 1'-H), 3.70 (ddd, $^3J_{HH}$ = 6.45 Hz, $^4J_{HH}$ = 1.51 Hz, $^4J_{HH}$ = 1.78 Hz, 1H, 1''-H), 3.70 (ddd, $^3J_{HH}$ = 6.45 Hz, $^4J_{HH}$ = 1.51 Hz, $^4J_{HH}$ = 1.78 Hz, 1H, 1''-H), 4.59 (s, 2H, 5-H), 5.00 (ddd, $^3J_{HH}$ = 10.02 Hz, $^4J_{HH}$ = 1.51 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3'-H$_{cis}$), 5.05 (ddd, $^3J_{HH}$ = 17.15 Hz, $^4J_{HH}$ = 1.79 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3'-H$_{trans}$), 5.13 (ddd, $^3J_{HH}$ = 10.29 Hz, $^4J_{HH}$ = 1.65 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3''-H$_{cis}$), 5.17 (ddd, $^3J_{HH}$ = 17.15 Hz, $^4J_{HH}$ = 1.78 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3''-H$_{trans}$), 5.32 (br. s., 1H, N-H), 5.75 (ddt, $^3J_{HH}$ = 6.17 Hz, $^3J_{HH}$ = 10.02 Hz, $^3J_{HH}$ = 17.15 Hz, 1H, 2'-H), 5.79 (ddt, $^3J_{HH}$ = 4.81 Hz, $^3J_{HH}$ = 10.29 Hz, $^3J_{HH}$ = 17.15 Hz, 1H, 2''-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ **(ppm)** = 26.37 (CH$_2$, 1'-C), 46.03 (CH$_2$, 1''-C), 65.18 (CH$_2$, 5-C), 91.00 (C^q, 3-C), 115.49 (CH$_2$, 3'-C), 116.61 (CH$_2$, 3''-C), 133.83 (CH, 2''-C), 134.76 (CH, 2'-C), 163.82 (C^q, 4-C), 175.71 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 180 (11) [M+H]$^+$, 179 (81) [M]$^+$, 160 (20) [M$_{180}$-H$_2$O]$^+$, 152 (15) [M-C$_2$H$_3$]$^+$, 134 (59) [M$_{152}$-H$_2$O]$^+$, 120 (27) [M$_{180}$-C$_3$H$_5$]$^+$, 106 (24) [M$_{120}$-NH$_2$]$^+$, 93 (26) [M$_{120}$-C$_2$H$_3$]$^+$, 53 (35) [M$_{80}$-C$_2$H$_3$]$^+$, 41 (100) [C$_3$H$_5$$^+$].
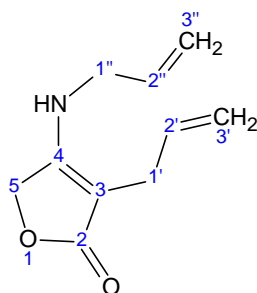
3-Allyl-4-allylamino-5-methyl-5*H*-furan-2-one (86b)

Pale yellow oil (400 mg, 2.04 mmol, 64%) from 930 mg (16.2 mmol) of allylamine and 500 mg (3.2 mmol) of 3-allyl-4-hydroxy-5(*S*)-methyl-5*H*-furan-2-one **57b**. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / ethyl acetate (1/3) mixture as eluent.

R$_f$ (SiO$_2$) = 0.46 (*n*-hexane : ethyl acetate, 1 : 3, v : v).

Molecular Formula = C$_{11}$H$_{15}$NO$_2$
Formula Weight = 193.242
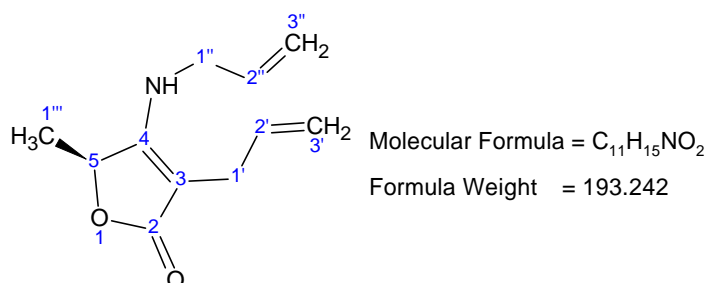
IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3295 (W) [ν (N-H)], 3085 (W) [ν (=C-H)], 1712 (M) and 1613 (VS) and 1555 (S) [ν (Tetramide ring)], 1331 (M) [ν (C-O)], 1038 (S) [ν (C-O)], 911 (S) [ν (=C-H)], 783 (S) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ **(ppm)** = 1.43 (d, $^3J_{HH}$ = 6.58 Hz, 3H, 1'''-H), 2.91 (ddd, $^3J_{HH}$ = 5.63 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.78 Hz, 2H, 1'-H), 3.82 (ddd, $^3J_{HH}$ = 4.94 Hz, $^4J_{HH}$

= 1.65 Hz, $^4J_{HH}$ = 1.78 Hz, 2H, 1''-H), 4.77 (q, $^3J_{HH}$ = 6.58 Hz, 1H, 5-H), 4.98 (ddd, $^3J_{HH}$ = 16.94 Hz, $^4J_{HH}$ = 1.78 Hz, $^2J_{HH}$ = 1.78 Hz, 1H, 3'-H$_{trans}$), 4.99 (ddd, $^3J_{HH}$ = 10.40 Hz, $^4J_{HH}$ = 1.65 Hz, $^2J_{HH}$ = 1.78 Hz, 1H, 3'-H$_{cis}$), 5.14 (ddd, $^3J_{HH}$ = 10.02 Hz, $^4J_{HH}$ = 1.65 Hz, $^2J_{HH}$ = 1.23 Hz, 1H, 3''-H$_{cis}$), 5.15 (ddd, $^3J_{HH}$ = 17.37 Hz, $^4J_{HH}$ = 1.78 Hz, $^2J_{HH}$ = 1.23 Hz, 1H, 3''-H$_{trans}$), 5.23 (br. s., 1H, N-H), 5.79 (ddt, $^3J_{HH}$ = 5.63 Hz, $^3J_{HH}$ = 10.40 Hz, $^3J_{HH}$ = 16.94 Hz, 1H, 2'-H), 5.81 (ddt, $^3J_{HH}$ = 4.94 Hz, $^3J_{HH}$ = 10.02 Hz, $^3J_{HH}$ = 17.37 Hz, 1H, 2''-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 19.73 (CH$_3$, 1'''-C), 26.49 (CH$_2$, 1'-C), 46.09 (CH$_2$, 1''-C), 73.03 (CH, 5-C), 90.69 (C^q, 3-C), 115.02 (CH$_2$, 3'-C), 116.44 (CH$_2$, 3''-C), 134.33 (CH, 2''-C), 135.88 (CH, 2'-C), 166.80 (C^q, 4-C), 175.07 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 194 (9) [M+H]$^+$, 193 (69) [M$^+$], 178 (38) [M-CH$_3$]$^+$, 160 (25) [M$_{178}$-H$_2$O]$^+$, 150 (73) [M$_{178}$-CO]$^+$, 134 (26) [M$_{178}$-CO$_2$]$^+$, 93 (23) [M$_{150}$-C$_3$H$_7$N]$^+$, 41 (100) [C$_3$H$_5$$^+$].

3-Allyl-4-allylamino-5-ethyl-5*H*-furan-2-one (86c)

Pale yellow oil (144 mg, 0.69 mmol, 23 %) from 849 mg (14.9 mmol) of allylamine and 500 mg (3.2 mmol) of 3-allyl-5-ethyl-4-hydroxy-dihydrofuran-2(5*H*)-one **57c**, after heating for 24 h. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent.

R_f (SiO$_2$) = 0.42 (diethyl ether).

Molecular Formula = C$_{12}$H$_{17}$NO$_2$
Formula Weight = 207.269

IR (ATR) $\bar{v}$ (cm^{-1}) = 3292 (W) [ν (N-H)], 3084 (W) [ν (=C-H)], 1711 (S) and 1613 (VS) and 1553 (S) [ν (Tetramide ring)], 1338 (M) [ν (C-O)], 1047 (M) [ν (C-O)], 911 (S) [ν (C=C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.90 (t, $^3J_{HH}$ = 7.41 Hz, 3H, 2'''-H), 1.57 (septuplet, $^3J_{HH}$ = 6.86, $^3J_{HH}$ = 7.41 Hz, $^2J_{HH}$ = 14.41 Hz, 1H, 1'''-H), 1.95 (d. sext., $^3J_{HH}$ = 3.30, $^3J_{HH}$ = 7.41 Hz, $^2J_{HH}$ = 14.41 Hz, 1H, 1'''-H), 2.93 (dq, $^3J_{HH}$ = 5.63 Hz, $^4J_{HH}$ = 1.78 Hz, 2H, 1''-H), 3.82 (ddd, $^3J_{HH}$ = 6.45 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.78 Hz, 1H, 1'-H), 3.83 (ddd, $^3J_{HH}$ = 6.45 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.78 Hz, 1H, 1'-H), 4.69 (dd, $^3J_{HH}$ = 3.30 Hz, $^3J_{HH}$ = 6.86 Hz, 1H, 5-H), 4.97 (d, $^3J_{HH}$ = 16.47 Hz; $^4J_{HH}$ = 1.78 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3''-H$_{trans}$), 4.98 (d, $^3J_{HH}$ = 11.39 Hz; $^4J_{HH}$ = 1.78 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3''-H$_{cis}$), 5.14 (d, $^3J_{HH}$ = 10.29 Hz; $^4J_{HH}$ = 1.65 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 5.16 (d, $^3J_{HH}$ = 17.15 Hz; $^4J_{HH}$ = 1.78 Hz, $^2J_{HH}$ = 1.51 Hz, 1H,

3'-H$_{trans}$), 5.79 (ddt, $^3J_{HH}$ = 5.63 Hz, $^3J_{HH}$ = 11.39 Hz, $^3J_{HH}$ = 16.47 Hz, 1H, 2''-H), 5.81 (ddt, $^3J_{HH}$ = 6.45 Hz, $^3J_{HH}$ = 10.29 Hz, $^3J_{HH}$ = 17.15 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 8.04 (CH$_3$, 2'''-C), 26.17 (CH$_2$, 1'''-C), 26.61 (CH$_2$, 1''-C), 46.19 (CH$_2$, 1-C), 77.43 (CH, 5-C), 91.85 (C^q, 3-C), 115.01 (CH$_2$, 3''-C), 116.48 (CH$_2$, 3'-C), 134.39 (CH, 2''-C), 135.99 (CH, 2'-C), 164.81 (C^q, 4-C), 175.44 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 208 (7) [M+H]$^+$, 207 (48) [M$^+$], 192 (23) [M-CH$_3$]$^+$, 178 (37) [M-C$_2$H$_5$]$^+$, 164 (66) [M$_{192}$-CO]$^+$, 150 (20) [M$_{178}$-CO]$^+$, 148 (23) [M$_{192}$-CO$_2$]$^+$, 134 (25) [M$_{178}$-CO$_2$]$^+$, 120 (25) [M$_{178}$-C$_3$H$_6$O]$^+$, 41 (100) [C$_3$H$_5$$^+$].
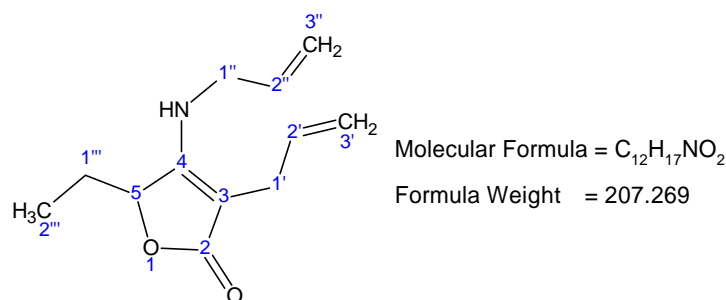
3-Allyl-4-allylamino-5-hexyl-dihydrofuran-2-one (86d)

Pale yellow oil (520 mg, 1.98 mmol, 90%) from 628 mg (11.0 mmol) of allyl amine and 500 mg (2.2 mmol) of 3-allyl-5-hexyl-4-hydroxy-dihydrofuran-2(5*H*)-one **57d**. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using diethyl ether / ethyl acetate (4/1) mixture as eluent.

R_f (SiO$_2$) = 0.64 (diethyl ether).

Molecular Formula = C$_{16}$H$_{25}$NO$_2$
Formula Weight = 263.375
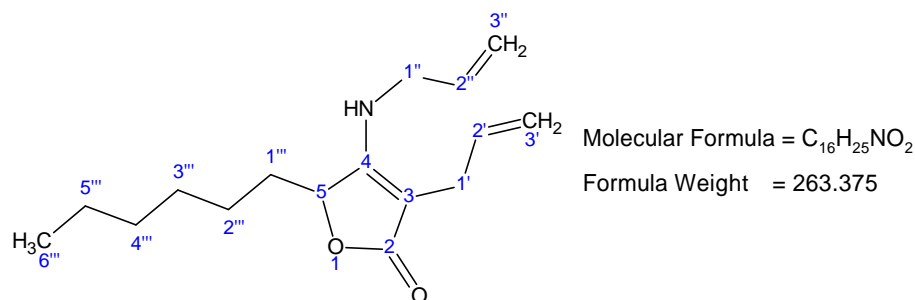
IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3291 (W) [ν (N-H)], 3084 (W) [ν (=C-H)], 2928 (M) [ν (-CH$_2$-)], 1712 (M) and 1617 (VS) and 1556 (M) [ν (Tetronamide ring)], 1338 (S) [ν (C-O-C)], 1036 (M) [ν (C-O)], 912 (M) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.83 (t, $^3J_{HH}$ = 6.79 Hz, 3H, 6'''-H), 1.16 – 1.33 (m, 6H, 2''', 3''', 5'''-H), 1.33 – 1.43 (m, 2H, 4'''-H), 1.43 – 1.57 (m, 1H, 1'''-H), 1.79 – 1.94 (m, 1H, 1'''-H), 2.93 (ddd, $^3J_{HH}$ = 5.17 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1. 78 Hz, 2H, 1'-H), 3.82 (dddd, $^3J_{HH}$ = 4.94 Hz, $^3J_{HH}$ = 6.59 Hz (N-H), $^4J_{HH}$ = 1.78 Hz, $^4J_{HH}$ = 1.65 Hz, 2H, 1''-H), 4.70 (dd, $^3J_{HH}$ = 7.55 Hz, $^3J_{HH}$ = 2.86 Hz, 1H, 5-H), 4.96 (br. s., 1H, N-H), 4.98 (ddd, $^3J_{HH}$ = 17.02 Hz, $^4J_{HH}$ = 1.65 Hz, $^2J_{HH}$ = 1.78 Hz, 1H, 3'-H$_{trans}$), 5.01 (ddd, $^3J_{HH}$ = 10.43 Hz, $^4J_{HH}$ = 1.65 Hz, $^2J_{HH}$ = 1.78 Hz, 1H, 3'-H$_{cis}$), 5.17 (ddd, $^3J_{HH}$ = 10.43 Hz, $^4J_{HH}$ = 1.65 Hz, $^2J_{HH}$ = 1.78 Hz, 1H, 3''-H$_{cis}$), 5.19 (ddd, $^3J_{HH}$ = 17.02 Hz, $^4J_{HH}$ = 1.65 Hz, $^2J_{HH}$ = 1.78 Hz, 1H, 3''-H$_{trans}$), 5.79 (ddt, $^3J_{HH}$ = 17.02 Hz, $^3J_{HH}$ = 10.43 Hz, $^3J_{HH}$ = 5.71 Hz, 1H, 2'-H), 5.82 (ddt, $^3J_{HH}$ = 17.02 Hz, $^3J_{HH}$ = 10.43 Hz, $^3J_{HH}$ = 4.94 Hz, 1H, 2''-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.93 (CH$_3$, 6'''-C), 22.44 (CH$_2$, 5'''-C), 24.16 (CH$_2$, 4'''-C), 26.63 (CH$_2$, 1'-C), 28.87 (CH$_2$, 3'''-C), 31.54 (CH$_2$, 2'''-C), 33.46 (CH$_2$, 1'''-C), 46.29 (CH$_2$, 1''-C), 76.61 (CH, 5-C), 91.93 (C^q, 3-C), 115.11 (CH$_2$, 3'-C), 116.63 (CH$_2$, 3''-C), 134.33 (CH, 2''-C), 135.87 (CH, 2'-C), 165.23 (C^q, 4-C), 175.18 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 264 (9) [M+H]$^+$, 263 (49) [M$^+$], 222 (51) [M-C$_3$H$_5$]$^+$, 220 (85) [M-C$_3$H$_7$]$^+$, 192 (65) [M$_{220}$-CO]$^+$, 179 (70) [M$_{220}$-C$_3$H$_5$]$^+$, 164 (36) [M$_{220}$-C$_3$H$_6$N]$^+$, 134 (29) [M$_{192}$-C$_3$H$_7$N]$^+$, 122 (36) [M$_{179}$-C$_3$H$_7$N]$^+$, 41 (100) [C$_3$H$_5$]$^+$.

3-Allyl-4-phenylamino-5*H*-furan-2-one (86e)

Pale brown powder (300 mg, 1.39 mmol, 39%) from 1660 mg (17.8 mmol) of aniline and 500 mg (3.57 mmol) of 3-allyl-4-hydroxy-dihydrofuran-2(5*H*)-one **57a**. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent. The low yield was consequence of the difficult separation from the acetanilide formed.

R_f (SiO$_2$) = 0.46 (diethyl ether). m.p. = 122°C.

Molecular Formula = C$_{13}$H$_{13}$NO$_2$
Formula Weight = 215.248
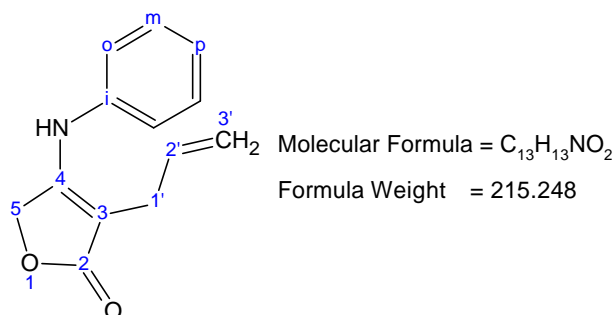
IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3308 (M) [ν (N-H)], 1721 (S) and 1629 (VS) and 1587 (VS) [ν (Tetronamide ring)], 1501 (S) [ν (C=C)], 1317 (S) [ν (C-O-C)], 1189 (S) [ν (C-O)], 1034 (S) [ν (C-O)], 906 (M) [ν (C-H allyl)], 749 (VS) and 690 (VS) [ν (C-H aromatic monosubstituted)].

^{1}H-NMR (270 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 3.05 (d; $^3J_{HH}$ = 6.32 Hz, $^4J_{HH}$ = 1.51 Hz, $^5J_{HH}$ = 0.83 Hz, 2H, 1'-H), 4.81 (d, $^5J_{HH}$ = 0.83 Hz, 2H, 5-H), 5.13 (dq, $^3J_{HH}$ = 10.02 Hz, $^4J_{HH}$ = 1.51 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3'-H$_{cis}$), 5.19 (dq; $^3J_{HH}$ = 17.15 Hz, $^4J_{HH}$ = 1.79 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3'-H$_{trans}$), 5.84 (ddt, $^3J_{HH}$ = 6.32 Hz, $^3J_{HH}$ = 10.02 Hz, $^3J_{HH}$ = 17.15 Hz, 1H, 2'-H), 6.83 (br.s., 1H, N-H), 6.96 (d, $^3J_{HH}$ = 7.41 Hz, 2H, *ortho*-H), 7.14 (tt, $^3J_{HH}$ = 7.41 Hz; $^4J_{HH}$ = 1.09 Hz, 1H, *para*-H), 7.83 (t; $^3J_{HH}$ = 7.41 Hz, 2H, *meta*-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 26.81 (CH$_2$, 1'-C), 66.27 (CH$_2$, 5-C), 95.29 (C^q, 3-C), 116.37 (CH$_2$, 3'-C), 121.13 (CH, *ortho*-C), 125.09 (CH, *para*-C), 129.76 (CH, *meta*-C), 134.37 (CH, 2'-C), 138.54 (C^q, *ipso*-C), 160.36 (C^q, 4-C), 174.72 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 216 (15) [M+H]$^+$, 215 (100) [M$^+$]$^+$, 214 (54) [M-H]$^+$, 196 (68) [M$_{214}$-H$_2$O]$^+$, 170 (55) [M$_{214}$-CO$_2$]$^+$, 168 (50) [M$_{196}$-CO]$^+$, 156 (21) [M$_{214}$-C$_2$H$_2$O$_2$]$^+$, 77 (54) [C$_6$H$_5$$^+$]$^+$.

Acetic acid 2-(4-allylamino-5-ethyl-2-oxo-2,5-dihydro-furan-3-yl)-1-methylethyl ester (95)

Colourless oil that turns with time to a pale yellow semi-solid (130 mg, 0.67 mmol, 21%) from 849 mg (14.9 mmol) of allyl amine and 500 mg (3.2 mmol) of 3-allyl-5-ethyl-4-hydroxy-dihydrofuran-2(5*H*)-one **57c**, after heating for 24 h. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent.

R_f (SiO$_2$) = 0.29 (diethyl ether).

Molecular Formula = C$_{14}$H$_{21}$NO$_4$
Formula Weight = 267.321

Mixture of two diastereoisomers α *and* β*. Ratio* α : β = 1 : 1

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3301 (W) [ν (N-H)], 3089 (VW) [ν (=C-H)], 1715 (S) and 1619 (VS) and 1555 (M) [ν (Tetronamide ring)], 1239 (S) [ν (C-O-C)], 1049 (S) [ν (C-O)], 917 (M) [ν (C-H allyl)].

^{1}H-NMR (270 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.88 (t, $^3J_{HH}$ = 7.28 Hz, 2'''-H$^\alpha$) and 0.90 (t, $^3J_{HH}$ = 7.27 Hz, 2'''-H$^\beta$) (Total integral : 3H), 1.20 (d, $^3J_{HH}$ = 6.32 Hz, 3'-H$^\alpha$) and 1.21 (d, $^3J_{HH}$ = 6.31 Hz, 3'-H$^\beta$) (Total integral : 3H), 1.49 – 1.65 (m, 1H, 1'''-H$^{\alpha+\beta}$) and 1.88 – 2.04 (m, 1H, 1'''-H$^{\alpha+\beta}$), 1.99 (s, 3H, 5'-H$^{\alpha+\beta}$), 2.34 – 2.41 (m, 2H, 1'-H$^{\alpha+\beta}$), 3.81 – 3.88 (m, 2H, 1''-H$^{\alpha+\beta}$), 4.65 – 4.81 (m, 1H, 2'-H$^{\alpha+\beta}$), 4.76 (dd, $^3J_{HH}$ = 2.74 Hz, $^3J_{HH}$ = 6.72 Hz, 1H, 5-H$^{\alpha+\beta}$), 5.20 (dm, $^3J_{HH}$ = 10.29 Hz, 1H, 3''-H$_{cis}$$^{\alpha+\beta}$), 5.23 (dm, $^3J_{HH}$ = 17.15 Hz, 1H, 3''-H$_{trans}$$^{\alpha+\beta}$), 5.54 (br. s., 1H, N-H$^{\alpha+\beta}$), 5.85 (ddt, $^3J_{HH}$ = 17.15 Hz, $^3J_{HH}$ = 10.29 Hz, $^3J_{HH}$ = 5.22 Hz, 1H, 2''-H$^{\alpha+\beta}$).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = (signals are not totally α and / or β assigned because of the low resolution in the HSQC spectra) 7.79 (7-C$^\alpha$), 8.05 (7-C$^\beta$), 19.29 (3'-C$^\alpha$), 19.35 (3'-C$^\beta$), 21.34 (5'-C$^\alpha$), 21.36 (5'-C$^\beta$), 25.99 (6-C$^\alpha$), 26.10 (6-C$^\beta$), 28.85 (1'-C$^\alpha$), 29.06 (1'-C$^\beta$), 46.57 (1''-C$^{\alpha+\beta}$), 70.92 (2'-C$^\alpha$), 70.98 (2'-C$^\beta$), 76.89 (5-C$^{\alpha+\beta}$), 91.41 (3-C$^\alpha$), 91.94 (3-C$^\beta$), 117.01 (3''-C$^\alpha$), 117.10 (3''-C$^\beta$), 133.94 (2''-C$^{\alpha+\beta}$), 165.99 (4-C$^\alpha$), 166.03 (4-C$^\beta$), 171.15 (4'-C$^{\alpha+\beta}$), 174.78 (2-C$^\alpha$), 174.90 (2-C$^\beta$).

MS (GC inlet, EI, 70 eV) m/z (%) = 267 (4) [M$^+$], 224 (12) [M-C$_2$H$_3$O]$^+$, 207 (82) [M-C$_2$H$_4$O$_2$]$^+$, 192 (57) [M$_{207}$-CH$_3$]$^+$, 180 (100) [M$_{224}$-CO$_2$]$^+$, 178 (62) [M$_{207}$-C$_2$H$_5$]$^+$, 166 (39) [M$_{207}$-C$_3$H$_5$]$^+$, 126 (87) [M-CH$_3$]$^{++}$, 43 (82) [C$_2$H$_3$O$^+$].

3.17 Synthesis of N-BOC (EtOOC) 4-allylamino furan-2-ones

Allyl-(4-allyl-5-oxo-2,5-dihydro-furan-3-yl)-carbamic acid *tert*-butyl ester (97c)

Procedure [163]**:**

3-Allyl-4-allylamino-5*H*-furan-2-one (1270 mg, 7.09 mmol) **86a** was dissolved in THF (45 mL). Then BOC$_2$O (3090 mg, 1000 mol-%) and NaHCO$_3$ (560 mg, 200 mol-%) were added and the mixture was refluxed for 24 h, followed by evaporation of the solvent. The reaction mixture was purified via chromatography column in SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / Et$_2$O (2/3) mixture as eluent. The compound was obtained as pale yellow oil.

Yield: 25 % (500 mg). R_f (SiO$_2$) = 0.40 (*n*-hexane : Et$_2$O, 2 : 3, v : v).

Molecular Formula = C$_{15}$H$_{21}$NO$_4$
Formula Weight   = 279.33

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 2978 (W) [ν (-CH$_2$-)], 1749 (S) and 1719 (S) [ν (Tetramide ring)], 1630 (M) [ν (C=O BOC)], 1369 (S), 1237 (S) [ν (C-O-C)], 1142 (VS) [ν (C-O-C)], 914 (M) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.42 (s, 9H, 8-H), 3.03 (dtt, $^3J_{HH}$ = 5.63 Hz, $^4J_{HH}$ = 1.79 Hz, $^4J_{HH}$ = 1.51 Hz, 2H, 1'-H), 4.20 (dt, $^3J_{HH}$ = 3.53 Hz, $^3J_{HH}$ = 6.45, $^4J_{HH}$ = 1.78 Hz, $^4J_{HH}$ = 1.51 Hz, $^2J_{HH}$ = 12.00 Hz, 2H, 1''-H), 4.94 (ddd, $^3J_{HH}$ = 17.16 Hz, $^4J_{HH}$ = 1.79 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3'-H$_{trans}$), 5.00 (ddd, $^3J_{HH}$ = 10.43 Hz, $^4J_{HH}$ = 1.51 Hz, $^2J_{HH}$ = 1.65 Hz, 1H, 3'-H$_{cis}$), 5.03 (s, 2H, 5-H), 5.05 (ddd, $^3J_{HH}$ = 17.15 Hz, $^4J_{HH}$ = 1.78 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3''-H$_{trans}$), 5.16 (ddd, $^3J_{HH}$ = 10.43 Hz, $^4J_{HH}$ = 1.65 Hz, $^2J_{HH}$ = 1.51 Hz, 1H, 3''-H$_{cis}$), 5.79 (ddt, $^3J_{HH}$ = 17.15 Hz, $^3J_{HH}$ = 10.43 Hz, $^3J_{HH}$ = 4.67 Hz, 1H, 2''-H), 5.79 (ddt, $^3J_{HH}$ = 17.16 Hz, $^3J_{HH}$ = 10.43 Hz, $^3J_{HH}$ = 5.63 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 27.87 (CH$_3$, 8-C), 28.25 (CH$_2$, 1'-C), 50.12 (CH$_2$, 1''-C), 69.68 (CH$_2$, 5-C), 83.39 (C^q, 7-C), 108.62 (C^q, 3-C), 115.95 (CH$_2$, 3'-C), 116.22 (CH$_2$, 3''-C), 133.07 (CH, 2'-C), 134.43 (CH, 2''-C), 151.29 (C^q, 6-C), 156.99 (C^q, 4-C), 174.28 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 279 (1) [M$^+$], 223 (6) [M-C$_4$H$_8$]$^+$, 206 (2) [M$_{223}$-H$_2$O]$^+$, 194 (1) [M$_{223}$-CO]$^+$, 178 (4) [M-C$_5$H$_9$O$_2$]$^+$, 164 (3) [M$_{223}$-C$_2$H$_2$O$_2$]$^+$, 134 (8) [M$_{178}$-CO$_2$]$^+$, 57 (100) [C$_4$H$_9^+$], 41 (31) [C$_3$H$_5^+$].

Allyl-(4-allyl-2-methyl-5-oxo-2,5-dihydro-furan-3-yl)-carbamic acid *tert*-butyl ester (97a)

Pale yellow oil (130 mg, 0.43 mmol, 21%) from 400 mg (2.07 mmol) of 3-allyl-4-allylamino-5-methyl-5*H*-furan-2-one **86b** dissolved in toluene (45 mL). Then triethylamine (210 mg, 1000 mol-%) and BOC$_2$O (904 mg, 200 mol-%) were added and the mixture was refluxing the mixture for 3 d at 130 °C. After cooling down the reaction mixture, water was added and the mixture was extracted with ethyl acetate, dried with Na$_2$SO$_4$ and filtrated. The product was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluent.

R_f (SiO$_2$) = 0.63 (*n*-hexane : diethyl ether, 2 : 3, v : v).

Molecular Formula = C$_{16}$H$_{23}$NO$_4$
Formula Weight = 293.358

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 2981 (W) [ν (–CH$_3$)], 1754 (S) [ν (C=O)], 1711 (S) [ν (C=O)], 1369 (S) [ν (C-O)], 1237 (S) [ν (C-O)], 1144 (VS) [ν (C-O)], 928 (M) [ν (=C-H)], 914 (S) [ν (C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 1.34 (d, ^{3}J$_{HH}$ = 6.72 Hz, 3H, 1'''-H), 1.45 (s, 9H, 8-H), 2.96 (ddq, ^{3}J$_{HH}$ = 5.76 Hz, ^{2}J$_{HH}$ = 16.13 Hz, ^{4}J$_{HH}$ = 1.78 x2 Hz, ^{5}J$_{HH}$ = 1.65 Hz, 1H, 1'-H), 3.08 (ddtd, ^{3}J$_{HH}$ = 6.17 Hz, ^{2}J$_{HH}$ = 16.13 Hz, ^{4}J$_{HH}$ = 1.64 x2 Hz, ^{5}J$_{HH}$ = 0.55 Hz, 1H, 1'-H), 4.00 (ddt, ^{3}J$_{HH}$ = 6.31 Hz, ^{2}J$_{HH}$ = 16.05 Hz, ^{4}J$_{HH}$ = 1.37 x2 Hz, 1H, 1''-H), 4.20 (ddt, ^{3}J$_{HH}$ = 5.07 Hz, ^{2}J$_{HH}$ = 16.05 Hz, ^{4}J$_{HH}$ = 1.65 Hz, ^{4}J$_{HH}$ = 1.51 Hz, 1H, 1''-H), 5.02 (dddd, ^{3}J$_{HH}$ = 17.02 Hz, ^{2}J$_{HH}$ = 1.64 Hz, ^{4}J$_{HH}$ = 1.78 Hz, ^{4}J$_{HH}$ = 1.64 Hz, 1H, 3'-H$_{trans}$), 5.05 (dddd, ^{3}J$_{HH}$ = 10.29 Hz,

$^2J_{HH}$ = 1.64 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 0.55 Hz, 1H, 3'-H$_{cis}$), 5.13 (dddd, $^3J_{HH}$ = 17.15 Hz, $^2J_{HH}$ = 1.64 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.37 Hz, 1H, 3''-H$_{trans}$), 5.16 (dddd, $^3J_{HH}$ = 10.43 Hz, $^2J_{HH}$ = 1.64 Hz, $^4J_{HH}$ = 1.51 Hz, $^4J_{HH}$ = 1.37 Hz, 1H, 3''-H$_{cis}$), 5.40 (q, $^3J_{HH}$ = 6.72 Hz, $^5J_{HH}$ = 1.65 Hz, 1H, 5-H), 5.80 (dddd, $^3J_{HH}$ = 17.02 Hz, $^3J_{HH}$ = 10.29 Hz, $^3J_{HH}$ = 6.17 Hz, $^3J_{HH}$ = 5.76 Hz, 1H, 2'-H), 5.80 (dddd, $^3J_{HH}$ = 17.15 Hz, $^3J_{HH}$ = 10.43 Hz, $^3J_{HH}$ = 6.31 Hz, $^3J_{HH}$ = 5.07 Hz, 1H, 2''-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 18.58 (CH$_3$, 1'''-C), 28.04 (CH$_3$, 8-C), 28.21 (CH$_2$, 1'-C), 51.44 (CH$_2$, 1''-C), 76.37 (CH, 5-C), 82.88 (C^q, 7-C), 108.40 (C^q, 3-C), 116.47 (CH$_2$, 3'-C), 117.76 (CH$_2$, 3''-C), 133.12 (CH, 2'-C), 133.27 (CH, 2''-C), 152.07 (C^q, 6-C), 161.62 (C^q, 4-C), 172.86 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 293 (1) [M$^+$], 237 (6) [M-C$_4$H$_8$]$^+$, 220 (2) [M-C$_4$H$_9$O]$^+$, 192 (3) [M$_{220}$-CO]$^+$, 178 (5) [M$_{220}$-42]$^+$, 148 (6) [M$_{220}$-C$_3$H$_4$O$_2$]$^+$, 57 (100) [C$_4$H$_9^+$], 41 (22) [C$_3$H$_5^+$].

Allyl-(4-allyl-2-methyl-5-oxo-2,5-dihydro-furan-3-yl)-carbamic acid ethyl ester (97b)

Pale yellow oil (90 mg, 0.31 mmol, 15 %) from 400 mg (2.07 mmol) of 3-allyl-4-allylamino-5-methyl-5*H*-furan-2-one **86b** dissolved in toluene (45 mL). Then triethylamine (210 mg, 1000 mol-%) and BOC$_2$O (904 mg, 200 mol-%) were added and the mixture was refluxing the mixture for 3 d at 130 °C. After cooling down the reaction mixture, water was added and the mixture was extracted with ethyl acetate, dried with Na$_2$SO$_4$ and filtrated. The product was a secondary fraction collected when the main crude product was purified by column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / ethyl acetate (2/3) mixture as eluent.

R_f (SiO$_2$) = 0.55 (*n*-hexane : ethyl acetate, 2 : 3, v : v).

Molecular Formula = C$_{14}$H$_{19}$NO$_4$
Formula Weight = 265.305

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3083 (VW) [ν (=C-H)], 1754 (S) [ν (C=O)], 1714 (VS) [ν (C=O)], 1656 (M) [ν (C=C)], 1375 (S) [ν (C-O)], 1227 (VS) [ν (C-O)], 928 (S) [ν (=C-H allyl)], 768 (S) [ν (=C-H allyl)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.26 (t, $^3J_{HH}$ = 7.13 Hz, 3H, 8-H), 1.33 (d, $^3J_{HH}$ = 6.59 Hz, 3H, 1'''-H), 2.94 (ddm, $^3J_{HH}$ = 6.04 Hz, $^2J_{HH}$ = 16.33 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.51 Hz, 1H, 1'-H), 3.07 (ddm, $^3J_{HH}$ = 6.04 Hz, $^2J_{HH}$ = 16.33 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.51 Hz, 1H, 1'-H), 4.00 (ddm, $^3J_{HH}$ = 6.59 Hz, $^2J_{HH}$ = 16.05 Hz, $^4J_{HH}$ = 1.35 Hz, $^4J_{HH}$ = 1.26 Hz, 1H, 1''-H), 4.20 (q, $^3J_{HH}$ = 7.13 Hz, 2H, 7-H), 4.27 (ddm, $^3J_{HH}$ = 5.21 Hz, $^2J_{HH}$ = 16.05 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.51 Hz, 1H, 1''-H), 5.03 (dm, $^3J_{HH}$ = 17.02 Hz, $^2J_{HH}$ = 1.64 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{trans}$), 5.05 (dm, $^3J_{HH}$ = 10.29 Hz, $^2J_{HH}$ = 1.64 Hz, $^4J_{HH}$ = 1.65 Hz, $^4J_{HH}$ = 1.51 Hz, 1H, 3'-H$_{cis}$), 5.15 (dm, $^3J_{HH}$ = 17.15 Hz, $^2J_{HH}$ = 1.64 Hz, $^4J_{HH}$ = 1.35 Hz, $^4J_{HH}$ = 1.26 Hz, 1H, 3''-H$_{trans}$), 5.17 (dm, $^3J_{HH}$ = 10.43 Hz, $^2J_{HH}$ = 1.64 Hz, $^4J_{HH}$ = 1.35 Hz, $^4J_{HH}$ = 1.26 Hz, 1H, 3''-H$_{cis}$), 5.36 (q, $^3J_{HH}$ = 6.59 Hz, 1H, 5-H), 5.79 (m, 1H, 2'-H), 5.79 (m, 1H, 2''-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 14.29 (CH$_3$, 8-C), 18.54 (CH$_3$, 1'''-C), 28.27 (CH$_2$, 1'-C), 51.32 (CH$_2$, 1''-C), 62.96 (CH$_2$, 7-C), 76.19 (CH, 5-C), 116.67 (CH$_2$, 3'-C), 118.29 (CH$_2$, 3''-C), 132.83 (CH, 2'-C), 132.88 (CH, 2''-C), 153.34 (C^q, 6-C), 160.84 (C^q, 4-C), 172.64 (C^q, 2-C), (C-3 was not observed in the spectra).

MS (GC inlet, EI, 70 eV) m/z (%) = 266 (4) [M+H]$^+$, 265 (35) [M$^+$], 250 (6) [M-CH$_3$]$^+$, 236 (17) [M-C$_2$H$_5$]$^+$, 224 (62) [M-C$_3$H$_5$]$^+$, 192 (74) [M$_{236}$-CO$_2$]$^+$, 178 (66), 150 (52) [M$_{178}$-CO]$^+$, 41 (100) [C$_3$H$_5$$^+$].
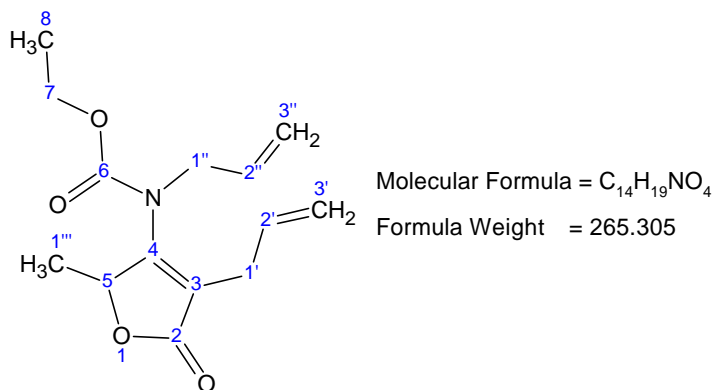
3.18 Synthesis of tetrahydrofuro[3,4-*b*]azepin-6-ones

8-Hexyl-1,2,3,8-tetrahydro-furo[3,4-*b*]azepin-6-one (96a)

To a degassed solution of 3-allyl-4-allylamino-5-hexyl-dihydrofuran-2-one **86d** (580 mg, 2.20 mmol) in dry toluene (freshly distilled from Na) and after excluding any moisture or air, 2 mol-% of 2nd generation Grubbs' catalyst was added under argon atmosphere. The mixture was stirred under reflux for 48 h, the reaction mixture was cooled to rt and 4 mol-% Pb(AcO)$_4$ was added for removal of the ruthenium [103]. The reaction mixture was stirred for 18 h and the ruthenium-Pb(OAc)$_4$-complex was removed by filtration over SiO$_2$ [length 2 cm, $\varnothing$ 2 cm]; the solvent was evaporated and the residual oil was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent. The product was obtained as pale brown oil that solidified with the time (100 mg, 19%).

R_f (SiO$_2$) = 0. 63 (diethyl ether). m.p. = 70°C.

Molecular Formula = $C_{14}H_{21}NO_2$
Formula Weight = 235.322
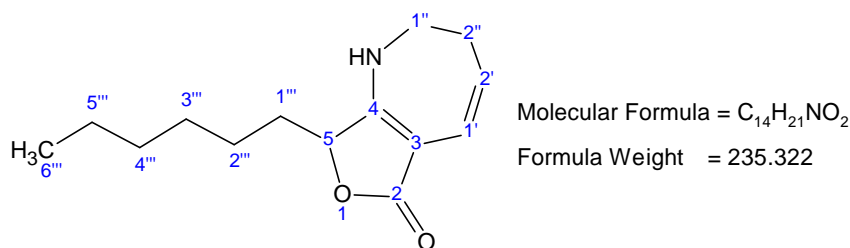
IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3243 (M) [ν (N-H)], 3095 (W) [ν (=C-H)], 2926 (M) [ν (-CH$_2$-)], 1702 (S) and 1610 (VS) [ν (Tetramide system)], 1329 (S) [ν (C-O)], 1046 (S) [ν (C-O)], 727 (S) [ν (=C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.83 (t, $^3J_{HH}$ = 6.86 Hz, 3H, 6'''-H), 1.15 – 1.45 (m, 8H, 2''', 3''', 4''', 5'''-H), 1.49 – 1.65 (m, 1H, 1'''-H), 1.79 – 1.93 (m, 1H, 1'''-H), 2.55 (m, 2H, 2''-H), 3.44 (m, 2H, 1''-H), 3.60 (br. s., 1H, N-H), 4.72 (dd, $^3J_{HH}$ = 3.30 Hz, $^3J_{HH}$ = 7.55 Hz, 1H, 5-H), 5.63 (dt, $^3J_{HH}$ = 5.90 Hz, $^3J_{HH}$ = 10.71 Hz, 1H, 2'-H), 6.13 (d, $^3J_{HH}$ = 10.71 Hz, 1H, 1'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.97 (CH$_3$, 6'''-C), 22.47 (CH$_2$, 5'''-C), 24.00 (CH$_2$, 4'''-C), 28.94 (CH$_2$, 3'''-C), 31.55 (CH$_2$, 2'''-C), 32.55 (CH$_2$, 2''-C), 33.26 (CH$_2$, 1'''-C), 45.32 (CH$_2$, 1''-C), 77.02 (CH, 5-C), 95.27 (C^q, 3-C), 120.79 (CH, 1'-C), 126.09 (CH, 2'-C), 165.14 (C^q, 4-C), 174.39 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 236 (10) [M+H]$^+$, 235 (63) [M$^+$], 220 (3) [M-CH$_3$]$^+$, 206 (4) [M-C$_2$H$_5$]$^+$, 164 (23) [M-C$_5$H$_{11}$]$^+$, 150 (28) [M-C$_6$H$_{13}$]$^+$, 122 (100) [M$_{150}$-CO]$^+$, 94 (16) [M$_{164}$-C$_4$H$_6$NH$_2$]$^+$, 65 (14) [M$_{94}$-C$_2$H$_5$]$^+$.

6-Oxo-2,5,6,8-tetrahydro-furo[3,4-*b*]azepine-1-carboxylic acid *tert*-butyl ester (98a)

To a degassed solution of allyl-(4-allyl-5-oxo-2,5-dihydro-furan-3-yl)-carbamic acid *tert*-butyl ester **97c** (500 mg, 1.79 mmol) in DCM (freshly distilled from CaH$_2$) and under argon atmosphere, 2 mol % of Grubb's 1st generation catalyst were added (moisture and / or air must be avoided). The mixture was stirred for 24 h at rt. Then Pb(AcO)$_4$ (4 mol-%) was added for complexing the ruthenium[103]. After stirring for 18 h, the ruthenium-catalyst-Pb(AcO)$_4$-complex was removed by filtration over Celite washing with DCM. Evaporation of the solvent gave a brown oil that was purified via chromatography column in SiO$_2$ [length 40 cm, ∅ 2 cm] using diethyl ether as eluent. The compound was obtained as pale yellow oil.

Yield: 22 % (100 mg). R_f (SiO$_2$) = 0.63 (diethyl ether).

Molecular Formula = $C_{13}H_{17}NO_4$

Formula Weight = 251.278
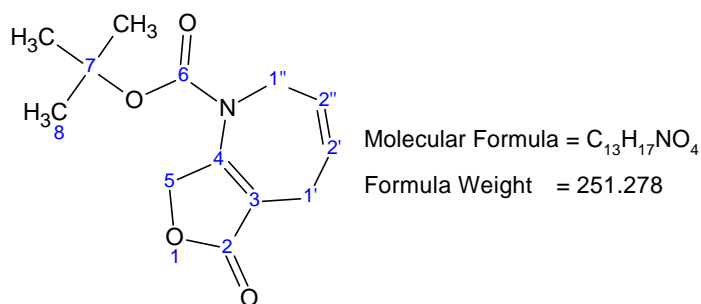
IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3040 (VW) [ν (=C-H)], 2979 (W) [ν (–CH$_3$)], 1747 (S) and 1712 (S) [ν (Tetramide system)], 1629 (S) [ν (C=O BOC)], 1369 (S) [ν (C-O-C)], 1148 (VS) [ν (C-O-C)], 1133 (VS) [ν (C-O-C)], 1033 (S) [ν (C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.47 (s, 9H, 8-H), 3.13 (dq, $^3J_{HH}$ = 5.63 Hz, $^4J_{HH}$ =1.09 Hz, $^5J_{HH}$ =1.37 Hz, $^5J_{HH}$ =1.65 Hz, 1H, 1'-H), 3.13 (dq, $^3J_{HH}$ = 5.77 Hz, $^4J_{HH}$ =1.24 Hz, $^5J_{HH}$ =1.37 Hz, $^5J_{HH}$ =1.65 Hz, 1H, 1'-H), 4.34 (d, $^3J_{HH}$ = 7.41 Hz, 1H, 1''-H), 4.34 (d, $^3J_{HH}$ = 7.55 Hz, 1H, 1''-H), 4.99 (dd, $^5J_{HH}$ = 1.37 Hz, $^5J_{HH}$ = 1.65 Hz, 2H, 5-H), 5.96 (dtt, $^3J_{HH}$ = 7.41 Hz, $^3J_{HH}$ = 7.55 Hz, $^3J_{HH}$ = 9.74 Hz, $^4J_{HH}$ = 1.09 Hz, $^4J_{HH}$ =1.24 Hz, 1H, 2''-H), 6.10 (ddd, $^3J_{HH}$ = 5.63 Hz, $^3J_{HH}$ = 5.77 Hz, $^3J_{HH}$ = 9.74 Hz, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 22.44 (CH$_2$, 1'-C), 27.92 (CH$_3$, 8-C), 44.14 (CH$_2$, 1''-C), 69.69 (CH$_2$, 5-C), 83.88 (C^q, 7-C), 104.59 (C^q, 3-C), 126.19 (CH, 2''-C), 134.32 (CH, 2'-C), 151.35 (C^q, 6-C), 157.88 (C^q, 4-C), 173.88 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 251 (2) [M$^+$], 207 (1) [M-CO$_2$]$^+$, 195 (16) [M-C$_4$H$_8$]$^+$, 178 (7) [M-C$_4$H$_9$O]$^+$, 151 (35) [M$_{195}$-CO$_2$]$^+$, 150 (18) [M-C$_5$H$_9$O$_2$]$^+$, 122 (6) [M$_{150}$-CO]$^+$, 106 (16) [M$_{150}$-CO$_2$]$^+$, 57 (100) [C$_4$H$_9$$^+$], 41 (42) [C$_3H_5$$^+$].

8-Methyl-6-oxo-2,5,6,8-tetrahydro-furo[3,4-*b*]azepine-1-carboxylic acid ethyl ester (98b)

Pale yellow oil (30 mg, 0.12 mmol, 37%) from 91 mg (0.34 mmol) of allyl-(4-allyl-2-methyl-5-oxo-2,5-dihydro-furan-3-yl)-carbamic acid ethyl ester **97b** dissolved in DCM (freshly distilled, 25 mL) and 2 mol-% of Grubbs' 1st generation catalyst, stirred for 1d under argon atmosphere. Then 12 mg (8 mol-%) of Pb(OAc)$_4$ were added and the reaction mixture was stirred for 10 h. After filtering over Celite, the reaction mixture was purified via column chromatography on SiO$_2$ [length 40 cm, ⌀ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluent.

R_f (SiO$_2$) = 0. 39 (*n*-hexane : diethyl ether, 2 : 3, v : v).

Molecular Formula = $C_{12}H_{15}NO_4$

Formula Weight = 237.252
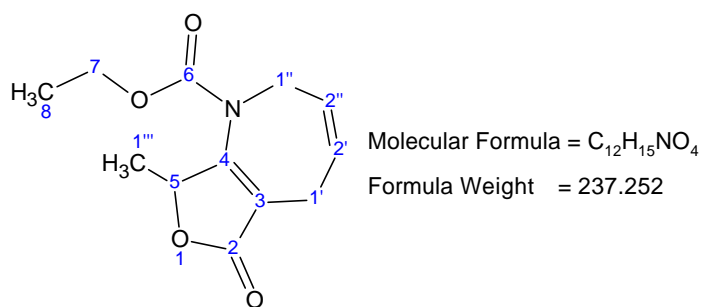
IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3040 (VW) [ν (=C-H)], 2984 (W) [ν (-CH$_3$)], 1749 (S) and 1713 (VS) [ν (Tetramide system)], 1647 (S) [ν (C=O EOC)], 1377 (S) [ν (C-O)], 1203 (VS) [ν (C-O)], 767 (S) [ν (=C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.30 (t, $^3J_{HH}$ = 7.14 Hz, 3H, 8-H), 1.37 (d, $^3J_{HH}$ = 6.45 Hz, 3H, 1'''-H), 3.05 (ddm, $^3J_{HH}$ = 5.63 Hz, $^2J_{HH}$ = 20.86 Hz, 1H, 1'-H), 3.30 (dm, $^2J_{HH}$ = 20.86 Hz, 1H, 1'-H), 4.00 (ddm, $^3J_{HH}$ = 5.19 Hz, $^2J_{HH}$ = 14.41 Hz, 1H, 1''-H), 4.21 (q, $^3J_{HH}$ = 7.14 Hz, 1H, 7-H), 4.22 (q, $^3J_{HH}$ = 7.14, 1H, 7-H), 4.57 (dm, $^3J_{HH}$ = 5.49 Hz, $^2J_{HH}$ = 14.41 Hz, 1H, 1''-H), 5.52 (q, $^3J_{HH}$ = 6.45 Hz, 1H, 5-H), 6.00 (m, 1H, 2'-H), 6.01 (m, 1H, 2''-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 14.26 (CH$_3$, 8-C), 18.82 (CH$_3$, 1'''-C), 23.92 (CH$_2$, 1'-C), 45.83 (CH$_2$, 1''-C), 63.22 (CH$_2$, 7-C), 76.87 (CH, 5-C), 108.47 (C^q, 3-C), 126.99 (CH, 2'-C), 132.47 (CH, 2''-C), 152.62 (C^q, 6-C), 162.28 (C^q, 4-C), 172.61 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 237 (76) [M$^+$], 208 (18) [M-C$_2$H$_5$]$^+$, 194 (100) [M-C$_2$H$_3$O]$^+$, 166 (29) [M$_{194}$-CO]$^+$, 164 (48) [M$_{208}$-CO$_2$]$^+$, 150 (16) [M$_{194}$-CO$_2$]$^+$, 136 (15) [M$_{164}$-CO]$^+$, 120 (41) [M$_{164}$-CO$_2$]$^+$, 93 (23) [M$_{166}$-C$_3$H$_5$O$_2$]$^+$.

3.19 Synthesis of a dispiro furan-2-one derivative

7,13-Dioxa-dispiro[4.0.5.3]tetradeca-2,8-diene-10,14-dione (103)

White solid (0.14 g, 0.64 mmol, 44%) obtained via hetero Diels Alder reaction from 0.22 g (1.45 mmol) of 2-oxa-spiro[4.4]non-7-ene-1,4-dione **84a** and 0.49 g (2.84 mmol) of Danishefsky's diene, dissolved in toluene and heated at 180°C for 3 days into a sealed tube. The Diels-Alder adduct was then treated with a previously prepared mixture of 35 mL THF and 15 mL HCl (0.1 N), which was poured by portions (5 mL x 3) to the reaction mixture. The remaining solution (35mL) was added and the resulting mixture was extracted with ethyl acetate (20 mL x 4). The organic layer was separated and dried over Na$_2$SO$_4$. The solvent was removed and the residual oil was purified by column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent.

R_f (SiO$_2$) = 0.53 (diethyl ether).

Molecular Formula = $C_{12}H_{12}O_4$

Formula Weight = 220.221
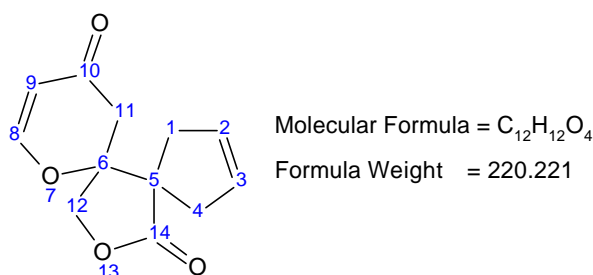
IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 1767 (VS) [ν ((C=O)O)], 1675 (S) [ν ((C=O)C=)], 1601 (S) [ν (C=C)], 1399 (S)) [ν (C=C + C=O)], 1267 (S) [ν (C-O)], 1215 (S) [ν (C-O)], 1039 (VS) [ν (C-O)], 1005 (VS) [ν (=C-H)], 795 (S) [ν (C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 2.46 (dd, $^2J_{HH}$ = 17.15 Hz, $^4J_{HH}$ = 1.10 Hz, 1H, 11-H$_{pseudo\ axial}$), 2.53 (m, 2H, 4-H), 2.81 (d, $^2J_{HH}$ = 17.15 Hz, 1H, 11-H$_{pseudo\ equatorial}$), 2.71 - 2.82 (m, 1H, 1-H), 2.84 - 2.95 (m, 1H, 1-H), 4.00 (d, $^2J_{HH}$ = 10.56 Hz, 1H, 12-H), 4.51 (d, $^2J_{HH}$ = 10.56 Hz, 1H, 12-H), 5.46 (dd, $^3J_{HH}$ = 6.18 Hz, $^4J_{HH}$ = 1.10 Hz, 1H, 9-H), 5.50 – 5.57 (m, 1H, 3-H), 5.70 – 5.77 (m, 1H, 2-H), 7.23 (d, $^3J_{HH}$ = 6.18 Hz, 1H, 8-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 35.34 (CH$_2$, 1-C), 37.38 (CH$_2$, 11-C), 38.60 (CH$_2$, 4-C), 54.85 (C^q, 5-C), 71.51 (CH$_2$, 12-C), 88.89 (C^q, 6-C), 107.21 (CH, 9-C), 125.87 (CH, 3-C), 130.14 (CH, 2-C), 160.90 (CH, 8-C), 178.80 (C^q, 14-C), 188.52 (C^q, 10-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 220 (46) [M$^+$], 202 (4) [M-H$_2$O]$^+$, 192 (8) [M-CO]$^+$, 176 (21) [M-CO$_2$]$^+$, 110 (97), 91 (100), 71 (91) [C$_3$H$_2$O$_2^+$]$^+$, 66 (55) [M$_{100}$-CO$_2$]$^+$.

3.20 Synthesis of (4-benzyloxy-2,5-dihydrofuran-3-yl)-acetaldehyde and dimethyl acetal derivatives

(4-Benzyloxy-5-butyl-2-oxo-2,5-dihydrofuran-3-yl)-acetaldehyde (107c)

In a round bottom flask (previously dried) a magnetically stirred solution of 3-allyl-4-benzyloxy-5-butyl-5*H*-furan-2-one **64d** (500 mg, 1.75 mmol) dissolved in dry methanol (freshly distilled from Mg) was cooled to -78°C using isopropanol and dry ice. Then a stream of O$_3$ / O$_2$ was bubbled through the reaction mixture until the blue colour of O$_3$ appeared (usually after 10 min). Then a small flux of argon was streamed in order to remove the O$_3$ in excess. The reductive work up was done with dimethyl sulphide (DMS) (1.6 mol per mol reactant), dropping the DMS previously dissolved in methanol at -78°C and then, wait to reach room temperature (approximately 4 h). The solvent was removed by rotary evaporation as well as the DMS in excess. The resulting oily residue was purified using SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] (dry column – adsorbed sample) with *n*-hexane / ethyl acetate (3:1) as eluent. Alternatively FPLC

can be used with *n*-hexane / ethyl acetate as a solvent mixture. The pure product appears as a colourless oil.

Yield: 66% (333 mg). R_f (SiO$_2$) = 0.72 (*n*-hexane : ethyl acetate, 3 : 1, v : v).

Molecular Formula = $C_{17}H_{20}O_4$

Formula Weight = 288.338
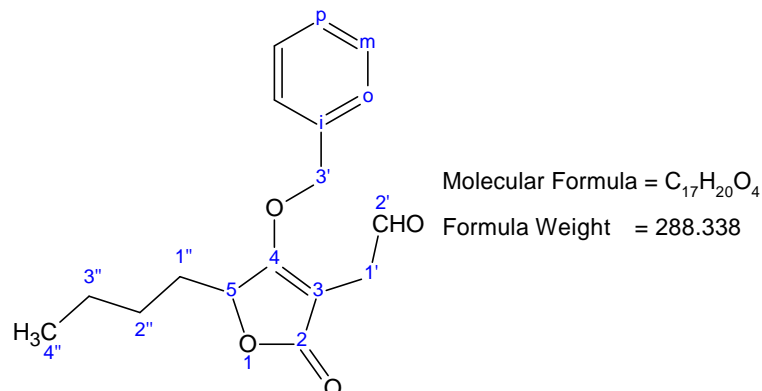
IR (ATR) $\bar{v}$ **(cm^{-1})** = 2955 (M) [ν (-CH$_2$-)], 2866 (M) [ν (-CH$_2$-)], 1748 (S) and 1661 (VS) [ν (Tetronate ring)], 1336 (S) [ν (C-O)], 1071 (VS) [ν (C-O-C)], 743 (S) and 699 (VS) [ν (C-H arom. monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.89 (t, ^{3}J = 7.07 Hz, 3H, 4''-H), 1.38 (m, 4H, 3'', 2''-H), 1.63 (m, 1H, 1''-H), 1.95 (m, 1H, 1''-H), 3.49 (s, 2H, 1'-H), 4.79 (dd, ^{3}J = 3.39 Hz, ^{3}J = 7.72 Hz, 1H, 5-H), 5.18 (d, ^{2}J = 13.94 Hz, 1H, 3'-H), 5.21 (d, ^{2}J = 13.94 Hz, 1H, 3'-H), 7.26 – 7.33 (m, 2H, *meta*-H), 7.33 – 7.45 (m, 3H, *ortho*-H and *para*-H), 9.66 (s, 1H, 2'-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.89 (CH$_3$, 4''-C), 22.39 (CH$_2$, 3''-C), 26.42 (CH$_2$, 2''-C), 31.85 (CH$_2$, 1''-C), 38.51 (CH$_2$, 1'-C), 73.20 (CH$_2$, 3'-C), 78.60 (CH, 5-C), 94.19 (C^q, 3-C), 127.29 (CH, *ortho*-C), 128.59 (CH, *para*-C), 129.09 (CH, *meta*-C), 134.76 (C^q, *ipso*-C), 174.00 (C^q, 4-C), 176.18 (C^q, 2-C), 197.59 (C^q, 2'-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 289 (1) [M+H]$^+$, 288 (5) [M$^+$], 270 (2) [M-CO]$^+$, 260 (5) [M-H$_2$O]$^+$, 245 (1) [M$_{289}$-CO$_2$]$^+$, 197 (3) [M-C$_7$H$_7^+$], 169 (23) [M$_{260}$-C$_7$H$_7^+$], 91 (100) [C$_7$H$_7^+$], 65 (10) [C$_5$H$_5^+$].

4-Benzyloxy-3-(2,2-dimethoxy-ethyl)-5-(*S*)-methyl-5*H*-furan-2-one (108a)

General procedure:

In a round bottom flask a magnetically stirred solution of 3-allyl-4-benzyloxy-5(*S*)-methyl-5*H*-furan-2-one **64b** (486 mg; 1.99 mmol) in dry methanol was cooled to -78°C using isopropanol and CO$_2$ (solid). Then a stream of O$_3$/O$_2$ was bubbled through the reaction mixture until the blue colour of O$_3$ appeared (11 min). Then a gentle flux of argon was used to remove the excess of O$_3$. The reductive work up to the intermediate aldehyde was done with 1.6 eq. of Me$_2$S (3.18 mmol; 198 mg; 0.233 mL) that was dropped over septum slowly. After reaching room temperature (4 h) 0.15 mL concentrated HCl solution was added and the mixture was heated 60

min at 80°C. Having neutralized the mixture with a concentrated $NaHCO_3$ solution, the organic layer was extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. Evaporation of the solvent gave a yellow oil that was purified via chromatography column in SiO_2 [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent. The compound was obtained as pale yellow oil.

Yield: 74% (430 mg). R_f (SiO_2) = 0.77 (diethyl ether).

Molecular Formula = $C_{16}H_{20}O_5$
Formula Weight = 292.327
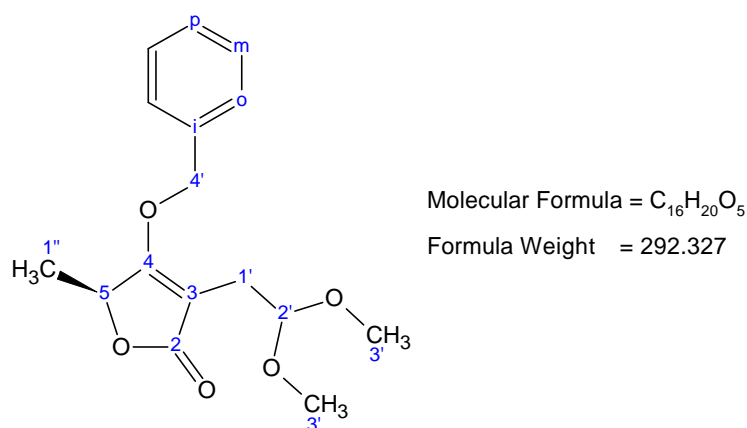
IR (ATR) $\bar{v}$ **(cm^{-1})** = 2985 (W) [v (-CH$_2$-)], 2936 (W) [v (-CH$_2$-)], 1747 (S) and 1658 (VS) [v (Tetronate ring)], 1342 (S) [v (C-O)], 1065 (VS) [v (C-O-C)], 735 (S) and 697 (VS) [v (C-H arom. monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 1.43 (d, ^3J = 6.73 Hz, 3H, 1''-H), 2.64 (d, ^3J = 5.62 Hz, 2H, 1'-H), 3.37 (s, 3H, 3'-H), 3.38 (s, 3H, 3'-H), 4.43 (t, ^3J = 5.62 Hz, 1H, 2'-H), 4.73 (q, ^3J = 6.73 Hz, 1H, 5-H), 5.40 (d, ^2J = 11.46 Hz, 1H, 4'-H), 5.46 (d, ^2J = 11.46 Hz, 1H, 4'-H), 7.28 - 7.42 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 18.15 (CH$_3$, 1''-C), 28.21 (CH$_2$, 1'-C), 54.95 and 54.98 (CH$_3$, 3'-C), 73.15 (CH$_2$, 4'-C), 74.39 (CH, 5-C), 96.76 (C^q, 3-C), 103.68 (CH, 2'-C), 127.25 (CH, *meta*-C), 128.53 (CH, *para*-C), 128.66 (CH, *ortho*-C), 135.39 (C^q, *ipso*-C), 174.29 (C^q, 4-C), 175.73 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 292 (1) [M$^+$], 277 (1) [M-CH$_3$]$^+$, 261 (3) [M-CH$_3$O]$^+$, 183 (1) [M-C$_7$H$_9$O]$^+$, 170 (2) [M$_{261}$-C$_7$H$_7$]$^+$, 109 (2) [C$_7$H$_9$O$^+$], 91 (97) [C$_7$H$_7^+$], 75 (100) [C$_3$H$_7$O$_2^+$], 65 (11) [C$_5$H$_5^+$].

4-Benzyloxy-3-(2,2-dimethoxy-ethyl)-5-ethyl-5*H*-furan-2-one (108b)

Pale yellow oil (30 mg, 0.12 mmol, 93%) from 500 mg (1.75 mmol) of 3-allyl-4-benzyloxy-5-ethyl-5*H*-furan-2-one **64c** and 174 mg (0.20 mL, 2.80 mmol) of Me$_2$S. The compound was purified by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent.

R_f (SiO_2) = 0. 79 (diethyl ether).
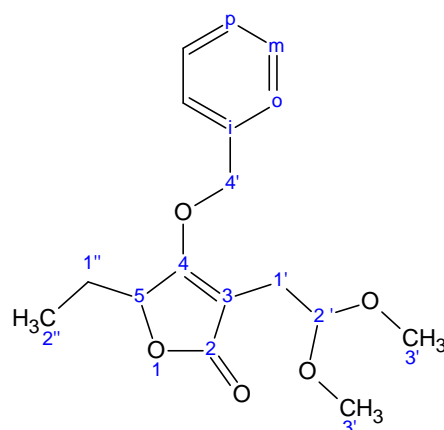
Molecular Formula = $C_{17}H_{22}O_5$

Formula Weight = 306.354

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 2970 (W) [ν (-CH$_2$-)], 2937 (W) [ν (-CH$_2$-)], 1747 (S) and 1659 (VS) [ν (Tetronate ring)], 1327 (S) [ν (C-O)], 1050 (VS) [ν (C-O-C)], 739 (S) and 697 (S) [ν (C-H arom. monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.90 (t, $^3J_{HH}$ = 7.41 Hz, 3H, 2''), 1.63 (ddq, $^3J_{HH}$ = 7.41 Hz; $^3J_{HH}$ = 6.44 Hz; $^2J_{HH}$ = 14.25 Hz, 1H, 1''), 1.95 (ddq, $^3J_{HH}$ = 7.41 Hz; $^3J_{HH}$ = 3.70 Hz; $^2J_{HH}$ = 14.25 Hz, 1H, 1''), 2.65 (d, $^3J_{HH}$ = 5.63 Hz, 2H, 1'), 3.36 (s, 6H, 3'), 4.42 (t, $^3J_{HH}$ = 5.63 Hz, 1H, 2'), 4.65 (dd, $^3J_{HH}$ = 3.70 Hz, $^3J_{HH}$ = 6.44 Hz, 1H, 5), 5.42 (s, 2H, 4'-H), 7.27 – 7.39 (m, 5H, arom.-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 7.75 (CH$_3$, 2''-C), 24.78 (CH$_2$, 1''-C), 28.24 (CH$_2$, 1'-C), 54.80 (CH$_3$, 3'-C), 55.01 (CH$_3$, 3'-C), 73.14 (CH$_2$, 4'-C), 78.62 (CH, 5-C), 97.71 (C^q, 3-C), 103.69 (CH, 2'-C), 127.26 (CH, *meta*-C), 128.48 (CH, *para*-C), 128.58 (CH, *ortho*-C), 135.38 (C^q, *ipso*-C), 174.14 (C^q, 4-C), 174.53 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 306 (4) [M$^+$], 291 (9) [M-CH$_3$]$^+$, 274 (4) [M-CH$_3$O]$^+$, 242 (2) [M-C$_2$H$_6$O$_2$]$^+$, 155 (3), 127 (2) [155-CO]$^+$, 91 (100) [C$_7$H$_7^+$], 75 (68) [C$_3$H$_7$O$_2^+$].

4-Benzyloxy-5-butyl-3-(2,2-dimethoxy-ethyl)- 5*H*-furan-2-one (108c)

Pale yellow oil (686 mg, 2.05 mmol, 98%) from 600 mg (2.09 mmol) of 3-allyl-4-benzyloxy-5-butyl-5*H*-furan-2-one **64d** and 174 mg (0.20 mL, 2.80 mmol) of Me$_2$S. The compound was purified *via* column chromatography on SiO$_2$ [length 40 cm, ∅ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluent.

R_f (SiO$_2$) = 0. 53 (*n*-hexane : diethyl ether, 2 : 3, v : v).
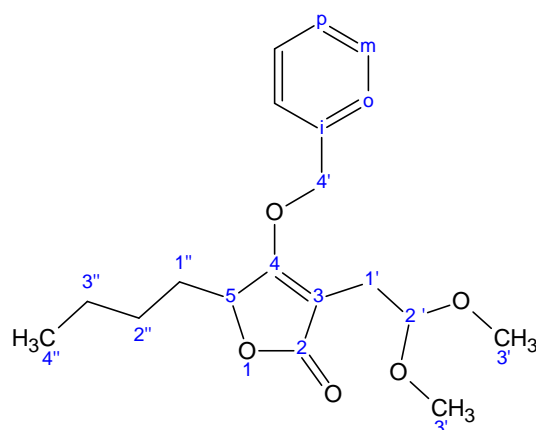
Molecular Formula = $C_{19}H_{26}O_5$

Formula Weight   = 334.407

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3034 (W) [ν (-CH$_2$-)], 2955 (W) [ν (-CH$_2$-)], 2872 (W) [ν (-CH$_2$-)], 1750 (S) and 1664 (VS) [ν (Tetronate ring)], 1330 (S) [ν (C-O)], 1120 (VS) [ν (C-O-C)], 739 (S) and 698 (S) [ν (C-H arom. monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 0.85 (t, $^3J_{HH}$ = 7.11 Hz, 3H, 4''-H), 1.20 - 1.45 (m, 4H, 3'', 2''-H), 1.50 - 1.65 (m, 1H, 1''-H), 1.82 - 1.95 (m, 1H, 1''-H), 2.65 (d, $^3J_{HH}$ = 5.65 Hz, 2H, 1'-H), 3.37 (s, 6H, 3'-H), 4.42 (t, $^3J_{HH}$ = 5.65 Hz, 1H, 2'-H), 4.68 (dd, $^3J_{HH}$ = 3.54 Hz; $^3J_{HH}$ = 7.32 Hz, 1H, 5-H), 5.42 (s, 2H, 4'-H), 7.23 - 7.42 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 13.76 (CH$_3$, 4''-C), 22.22 (CH$_2$, 3''-C), 25.99 (CH$_2$, 2''-C), 28.29 (CH$_2$, 1'-C), 31.52 (CH$_2$, 1''-C), 54.87 (CH$_3$, 3'-C), 55.04 (CH$_3$, 3'-C), 73.17 (CH$_2$, 4'-C), 77.95 (CH, 5-C), 97.49 (C^q, 3-C), 103.74 (CH, 2'-C), 127.28 (CH, *meta*-C), 128.29 (CH, *para*-C), 128.63 (CH, *ortho*-C), 135.44 (C^q, *ipso*-C), 174.57 (C^q, 4-C and 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 334 (1) [M$^+$], 319 (2) [M-CH$_3$]$^+$, 303 (5) [M-CH$_3$O]$^+$, 183 (5), 151 (4) [M-M$_{183}$]$^+$, 91 (82) [C$_7$H$_7$$^+$], 75 (100), [C$_3H_7O_2$$^+$], 65 (4) [C$_5H_5$$^+$].

3.21 Synthesis of 3-(2,2-Dimethoxy-ethyl)-4-hydroxy-5*H*-furan-2-ones

3-(2,2-Dimethoxy-ethyl)-5-ethyl-4-hydroxy-5*H*-furan-2-one (109a)

General procedure:

A Schlenk 100 mL round – bottom flask, condenser, magnetic stirrer were previously dried over vacuum. Then H$_2$ was filled in a balloon and connected to the reactor through a stopper-key. The flask was first flushed with argon for 2 min using the Schlenk inlet and then ventilated through a syringe needle inserted in a septum in the condenser. Under slight argon positive pressure, the flask was charged with Pd / C (10%), the solvent (absolute ethanol or ethyl acetate) and the compound. Argon was ventilated 2 min more. The argon was removed using

the vacuum line in the manifold and then the connection between the flask and the H_2 in the balloon was open. The reaction mixture was stirred at room temperature for 2 – 6 hours. Filtration in Celite and SiO_2 chromatography column were done and the product was recovered from the mixture formed.

Pale yellow oil (0.30 g, 1.38 mmol, 77%) from 0.55 g (1.79 mmol) of 4-benzyloxy-3-(2,2-dimethoxy-ethyl)-5-ethyl-5*H*-furan-2-one **108b** using 10 mg of Pd / C and dry ethyl acetate as solvent working under 30 Bar of H_2 for 4 days. The reaction mixture was purified by column chromatography in SiO_2 [length 20 cm, $\varnothing$ 1 cm] using ethyl acetate as eluent. The compound was obtained as pale yellow oil.

R_f (SiO_2) = 0. 44 (diethyl ether).

Molecular Formula = $C_{10}H_{16}O_5$
Formula Weight   = 216.231

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3000 (W) [ν (-OH)], 2972 (W) [ν (-CH$_2$-)], 1749 (M) and 1653 (S) [ν (Tetronic ring)], 1340 (M) [ν (C-O-C)], 1181 (M) [ν (C-O-C)], 1046 (VS) [ν (C-O-C)], 981 (S) [ν (C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.88 (t, ^3J = 7.41 Hz, 3H, 2''-H), 1.60 (ddq, ^3J = 7.41 Hz, ^3J = 6.58; ^2J = 14.40 Hz, 1H, 1''-H), 1.90 (ddq, ^3J = 7.41 Hz, ^3J = 4.11; ^2J = 14.40 Hz, 1H, 1''-H), 2.53 (dd, ^3J = 4.26 Hz, ^5J = 0.83 Hz, 2H, 1'-H), 3.385 (s, 3H, 3'-H), 3.391 (s, 3H, 3'-H), 4.52 (t, ^3J = 4.26 Hz, 1H, 2'-H), 4.61 (dd, ^3J = 4.11 Hz, ^3J = 6.58 Hz, 1H, 5-H), 9.60 (br. s., 1H, -O-H),

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 7.89 (CH$_3$, 2''-C), 24.47 (CH$_2$, 1''-C), 26.30 (CH$_2$, 1'-C), 54.53 (CH$_3$, 3'-C), 54.63 (CH$_3$, 3'-C), 78.49 (CH, 5-C), 95.14 (C^q, 3-C), 104.27 (CH, 2'-C), 174.78 (C^q, 4-C), 175.43 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 216 (4) [M$^+$], 201 (2) [M-CH$_3$]$^+$, 184 (100) [M-CH$_3$O]$^+$, 166 (33) [M$_{184}$-H$_2$O]$^+$, 142 (36) [M-C$_3$H$_8$O$_2$]$^+$, 127 (68) [M$_{142}$-CH$_3$]$^+$, 99 (74) [M$_{127}$-CO]$^+$, 75 (79) [C$_3$H$_7$O$_2$$^+$], 58 (81) [C$_3H_6O^+$].
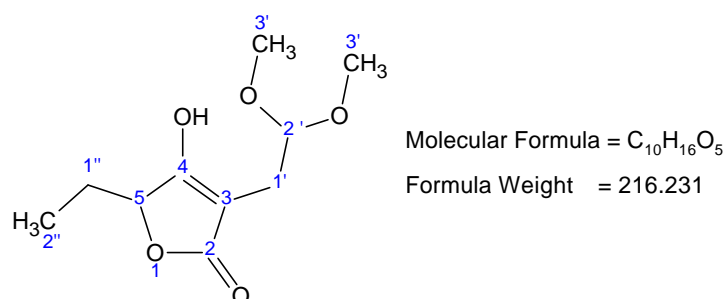
5-Butyl-3-(2,2-dimethoxy-ethyl)-4-hydroxy-5*H*-furan-2-one (109b)

Pale yellow oil (0.36 g, 1.46 mmol, 98%) from 500 mg (1.49 mmol) of 4-benzyloxy-5-butyl-3-(2,2-dimethoxy-ethyl)-5*H*-furan-2-one **108c** and 50 mg of Pd / C (10%) and dry methanol as

solvent. The compound was purified *via* column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent.

R_f (SiO_2) = 0. 57 (diethyl ether).

Molecular Formula = $C_{12}H_{20}O_5$

Formula Weight   = 244.284
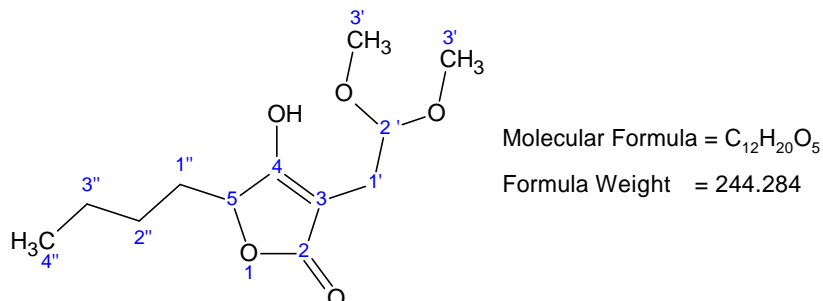
IR (KBr) $\bar{\nu}$ **(cm^{-1})** = 3425 (M) [ν (-OH)], 2957 (S) [ν (-CH$_2$-)], 2873 (S) [ν (-CH$_2$-)], 1751 (S) and 1664 (VS) [ν (Tetronic ring)], 1121 (S) [ν (C-O)], 1054 (S) [ν (C-O-C)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.87 (t, $^3J_{HH}$ = 7.13 Hz, 3H, 4''-H), 1.20 - 1.40 (m, 4H, 3'', 2''-H), 1.58 (m, 1H, 1''-H), 1.88 (m, 1H, 1''-H), 2.58 (d, $^3J_{HH}$ = 4.22 Hz, 2H, 1'-H), 3.44 (s, 6H, 3'-H), 4.55 (t, $^3J_{HH}$ = 4.22 Hz, 1H, 2'-H), 4.67 (dd, $^3J_{HH}$ = 3.80 Hz, $^3J_{HH}$ = 7.50 Hz, 1H, 5-H), 9.83 (br. s., 1H, -O-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 13.82 (CH$_3$, 4''-C), 22.33 (CH$_2$, 3''-C), 26.28 (CH$_2$, 2''-C), 26.51 (CH$_2$, 1'-C), 31.35 (CH$_2$, 1''-C), 54.63 (CH$_3$, 3'-C), 54.74 (CH$_3$, 3'-C), 77.71 (CH, 5-C), 94.88 (C^q, 3-C), 104.52 (CH, 2'-C), 174.44 (C^q, 2-C), 175.65 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 244 (1) [M$^+$], 212 (77) [M-OMe]$^+$, 194 (10) [M$_{212}$-H$_2$O]$^+$, 169 (16) [M-C$_3$H$_7$O$_2$]$^+$, 156 (45) [M$_{213}$-C$_4$H$_9$]$^+$, 127 (100) [M-C$_4$H$_9$O$_2$]$^+$, 124 (15) [M$_{212}$-C$_4$H$_9$O$_2$]$^+$, 99 (69) [M$_{127}$-CO]$^+$, 75 (86) [C$_3$H$_7$O$_2$$^+$].

3.22 Synthesis of (4-benzyloxy-2,5-dihydrofuran-3-yl)-acetic acid derivatives

(4-Benzyloxy-5-ethyl-2-oxo-2,5-dihydro-furan-3-yl)-acetic acid (111a)

General procedure:

JONES' REAGENT: A suspension of 25 g of chromic anhydride (CrO$_3$) in 25 mL of H$_2$SO$_4$ was poured slowly with stirring into 75 mL of water. The deep orange-red solution was cooled to room temperature before use. A good grade of acetone should be used. Some samples of acetone may become cloudy in appearance in 20 sec.; this does not interfere, providing the test solution becomes yellow. If the acetone gives a positive test, it should be purified by adding a small amount of KMnO$_4$ and distilling.

1.62 mL of Jones' reagent were added (drop by drop) to a solution of 0.32 g (1.23 mmol) of (4-benzyloxy-5-ethyl-2-oxo-2,5-dihydrofuran-3-yl)-acetaldehyde **107b** (in 60 mL of acetone), at 0°C. The mixture was stirred 1h at low temperature. Then a saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The mixture was filtered. Then the mixture was diluted with 80 mL ethyl acetate, washed with HCl 1% and brine. In this step, beaker and 2 extractions were used: 1st extraction at pH > 9-10 and 2nd extraction at pH ~2 that contains the desired compound. The organic layer was dried over Na_2SO_4 anhydrous and concentrated. The solid residue was re-crystallized from *n*-hexane / diethyl ether. Yield: 74% (of crude product).

R_f (SiO$_2$) = 0. 58 (diethyl ether + AcOH 5%).

Molecular Formula = $C_{15}H_{16}O_5$
Formula Weight   = 276.285

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3474 (VW) [ν (-OH)], 1731 (S) and 1659 (VS) [ν (Tetronate ring)], 1331 (S) [ν (C-O)], 1261 (S) [ν (C-O-C)], 1054 (S) [ν (C-O-C)], 737 (S) and 698 (S) [ν (C-H arom. monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) **δ (ppm)** = 0.94 (t, ^3J = 7.41 Hz, 3H, 2''-H), 1.57-1.78 (m, 1H, 1''-H), 1.93-2.14 (m, 1H, 1''-H), 3.46 (d, ^4J = 1.78 Hz, 1H, 1'-H), 3.47 (d, ^4J = 1.92 Hz, 1H, 1'-H), 4.87 (dd, ^3J = 6.32 Hz, ^3J = 3.85 Hz, 1H, 5-H), 5.52 (s, 2H, 3'-H), 7.35-7.49 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) **δ (ppm)** = 8.29 (CH$_3$, 2''-C), 25.78 (CH$_2$, 1''-C), 29.29 (CH$_2$, 1'-C), 73.81 (CH$_2$, 3'-C), 79.15 (CH, 5-C), 97.68 (C^q, 3-C), 128.55 (CH, *meta*-C), 129.49 (CH, *para*-C), 129.61 (CH, *ortho*-C), 136.85 (C^q, *ipso*-C), 172.10 (C^q, 2-C), 174.09 (C^q, 2'-C), 175.32 (C^q, 4-C).

MS (Direct inlet, EI, 70 eV) m/z (%) = 277 (1) [M+H]$^+$, 276 (2) [M$^+$], 259 (1) [M$_{277}$-H$_2$O]$^+$, 232 (7) [M-CO$_2$]$^+$, 185 (1) [M-C$_7$H$_7$]$^+$, 141 (5) [M$_{185}$-CO$_2$]$^+$, 99 (23) [M-C$_4$H$_6$O$_2$]$^+$, 91 (100) [C$_7$H$_7$$^+$], 65 (77) [C$_5H_5$$^+$].

(4-Benzyloxy-5-butyl-2-oxo-2,5-dihydro-furan-3-yl)-acetic acid (111b)

White solid (30 mg, 0.12 mmol, 80%) from 700 mg (2.3 mmol) of (4-benzyloxy-5-butyl-2-oxo-2,5-dihydrofuran-3-yl)-acetaldehyde **107c** and 3.17 mL of Jones' reagent. The compound was purified by crystallization.

R_f (SiO$_2$) = 0. 38 (*n*-hexane : diethyl ether; 2 : 3; v : v). R_f (SiO$_2$) = 0. 77 (diethyl ether + AcOH 5%). m.p. = 83°C.

Molecular Formula = $C_{17}H_{20}O_5$

Formula Weight = 304.338

IR (KBr) $\bar{\nu}$ (cm^{-1}) = 3200 (W) [ν (-OH)], 2958 (W) [ν (-CH$_2$-)], 1748 (S) and 1674 (VS) [ν (Tetronate ring)], 1703 (S) [ν (C=O acid)], 1355 (S) [ν (C-O)], 1057 (VS) [ν (C-O-C)], 732 (S) and 694 (S) [ν (C-H arom. monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.81 (t, $^3J_{HH}$ = 7.10 Hz, 3H, 4''-H), 1.15 – 1.41 (m, 4H, 3'', 2''-H), 1.45 – 1.65 (m, 1H, 1''-H), 1.82 – 1.97 (m, 1H, 1''-H), 3.37 (s, 2H, 1'-H), 4.70 (dd, $^3J_{HH}$ = 7.60 Hz, $^3J_{HH}$ = 7.70 Hz, 1H, 5-H), 5.26 (d, $^2J_{HH}$ = 13.59 Hz, 2H, 3'-H), 7.22 – 7.37 (m, 5H, arom-H), 9.20 (br. s., 1H, -OH).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 13.76 (CH$_3$, 4''-C), 22.24 (CH$_2$, 3''-C), 26.21 (CH$_2$, 2''-C), 28.90 (CH$_2$, 1'-C), 31.58 (CH$_2$, 1''-C), 73.05 (CH$_2$, 3'-C), 78.42 (CH, 5-C), 95.50 (C^q, 3-C), 127.16 (CH, *meta*-C), 128.85 (CH, *ortho*-C), 128.90 (CH, *para*-C), 134.71 (C^q, *ipso*-C), 174.22 (C^q, 4-C), 175.35 (C^q, 2-C), 175.47 (C^q, 2'-C).

MS (Direct inlet, EI, 70 eV) m/z (%) = 304 (11) [M$^+$], 286 (4) [M-H$_2$O]$^+$, 260 (5) [M-CO$_2$]$^+$, 248 (16) [M-C$_4$H$_9$CHO]$^+$, 213 (33) [M-C$_7$H$_7$]$^+$, 168 (20) [M$_{260}$-C$_7$H$_7$]$^+$, 158 (22) [M$_{248}$-C$_7$H$_7$]$^+$, 140 (17) [M$_{158}$-H$_2$O]$^+$, 112 (25) [M$_{140}$-CO]$^+$, 91 (100) [C$_7$H$_7^+$].

(4-Benzyloxy-5-butyl-2-oxo-2,5-dihydro-furan-3-yl)- acetic acid ethyl ester (112)

A solution of (4-benzyloxy-5-butyl-2-oxo-2,5-dihydro-furan-3-yl)-acetic acid **111a** (2.35 g, 12 mmol) and *O*-ethyl isourea **36a** (3.92 g, 12.5 mmol) in dry THF (100 mL) were stirred at 40°C for 16 hours. When the reaction was completed, the reaction mixture was filtrated in order to

remove the precipitated urea. The solvent was removed by rotary evaporation and the compound was purified in SiO_2 [length 40 cm, $\varnothing$ 2 cm] using polarity gradient – with *n*-hexane / diethyl ether mixture as eluant. The sample appears as a colourless oil.

R_f (SiO_2) = 0. 46 (*n*-hexane : diethyl ether; 2 : 3; v : v).

Molecular Formula = $C_{19}H_{24}O_5$
Formula Weight = 332.391

IR (KBr) $\bar{v}$ **(cm^{-1})** = 3067 (VW) [v (=C-H)], 2958 (VW) [v (-CH_2-)], 2873 (W) [v (-CH_2-)], 1734 (VS) and 1662 (VS) [v (Tetronate ring)], 1192 (S) [v (C-O)], 1026 (S) [v (C-O)], 737 (S) and 697 (S) [v (C-H arom. monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.82 (t, $^3J_{HH}$ = 7.13 Hz, 3H, 4''-H), 1.19 (t, $^3J_{HH}$ = 7.14 Hz, 3H, 4'-H), 1.20 – 1.44 (m, 4H, 3'', 2''-H), 1.48 – 1.67 (m, 1H, 1''-H), 1.81 – 1.99 (m, 1H, 1''-H), 3.33 (s, 2H, 1'-H), 4.09 (q, $^3J_{HH}$ = 7.14 Hz, 2H, 3'-H), 4.69 (dd, $^3J_{HH}$ = 3.50 Hz, $^3J_{HH}$ = 7.48 Hz, 1H, 5-H), 5.27 (s, 2H, 5'-H), 7.24 - 7.38 (m, 5H, arom-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 13.76 (CH$_3$, 4'-C), 14.05 (CH$_3$, 4''-C), 22.26 (CH$_2$, 3''-C), 26.12 (CH$_2$, 2''-C), 29.13 (CH$_2$, 1'-C), 31.58 (CH$_2$, 1''-C), 61.34 (CH$_2$, 3'-C), 72.89 (CH$_2$, 5'-C), 78.13 (CH, 5-C), 95.99 (C^q, 3-C), 127.22 (CH, *meta*-C), 128.83 (CH, *ortho*-C), 128.87 (CH, *para*-C), 134.92 (C^q, *ipso*-C), 170.49 (C^q, 2'-C), 173.85 (C^q, 4-C), 174.96 (C^q, 2-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 332 (3) [M$^+$], 314 (1) [M-H$_2$O]$^+$, 287 (14) [M-C$_2$H$_5$O]$^+$, 276 (16) [M-C$_4$H$_9$]$^+$, 258 (4) [M-C$_3$H$_5$O$_2$]$^+$, 241 (29) [M-C$_7$H$_7$]$^+$, 186 (9) [M$_{276}$-C$_7$H$_7$]$^+$, 91 (100) [C$_7$H$_7^+$].

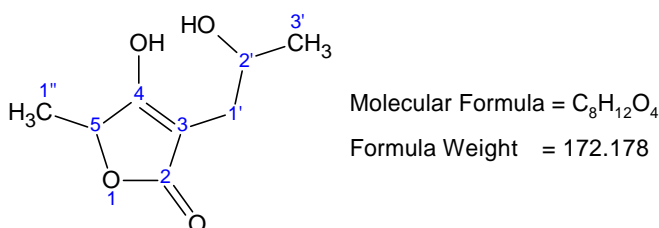## 3.23 Synthesis of diverse tetronic acid derivatives

4-Hydroxy-3-(2-hydroxy-propyl)-5-methyl-5*H*-furan-2-one (113)

To a magnetically stirred solution of 3-(2-allyloxypropyl)-4-hydroxy-5-methyl-5*H*-furan-2-one **60e** (390 mg; 1.84 mmol) in dry THF was added N,N'-dimethyl barbituric acid (0.86 g, 5.5 mmol) by portions at room temperature. The reaction was stirred for 2 h protecting it from the

light. Evaporation of the solvent gave a solid that was purified via chromatography column in SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (4/1) mixture as eluent. The compound was obtained as a colourless solid.

Yield: 32% (430 mg). R_f (SiO$_2$) = 0.65 (Et$_2$O / AcOH 5%). m.p. = 101 - 103°C.

Alternatively the compound was also formed from debenzylation under hydrogen from 3-(2-benzyloxypropyl)-4-hydroxy-5-methyl-5*H*-furan-2-one **60h** (135 mg, 0.51 mmol) using Pd-C 10% (13 mg) as catalyst using dry methanol as solvent [Yield: 34% (30 mg)].

Molecular Formula = C$_8$H$_{12}$O$_4$
Formula Weight = 172.178

*Mixture of diastereoisomers **a** and **b**. Ratio α : β = 1 : 1.*

IR (ATR) $\bar{v}$ (cm^{-1}) = 3222 (W) [v (-OH)], 2972 (W) [v (-CH$_2$-)], 2515 (W) [v (-OH intramolecular bridge)], 1715 (M) and 1657 (VS) [v (Tetronate ring)], 1417 (S), 1281 (S) [v (C-O)], 1039 (S) [v (C-O-C)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.268 (d, ^3J = 6.31 Hz, 3'-H$^\alpha$) and 1.271 (d, ^3J = 6.31 Hz, 3'-H$^\beta$) (Total integral : 3H; ratio 1 : 1), 1.433 (d, ^3J = 6.73 Hz, 1''-H$^\alpha$) and 1.435 (d, ^3J = 6.73 Hz, 1''-H$^\beta$) (Total integral : 3H), 2.299 (ddd, ^3J = 7.27 Hz, ^2J = 16.33 Hz, ^5J = 1.24 Hz, 1'a-H$^\alpha$) and 2.303 (ddd, ^3J = 7.41 Hz, ^2J = 16.33 Hz, ^5J = 1.10 Hz, 1'a-H$^\beta$) (Total integral : 2H), 2.50 (ddd, ^3J = 2.74 Hz, ^2J = 16.33 Hz, ^5J = 0.95 Hz, 2H, 1'b-H), 4.22 (ddq, ^3J = 2.74 Hz, ^3J = 6.31 Hz,; ^3J = 7.27 Hz, 2'-H$^\alpha$) and 4.22 (ddq, ^3J = 2.74 Hz, ^3J = 6.31 Hz,; ^3J = 7.41 Hz, 2'-H$^\beta$) (Total integral : 1H), 4.75 (qdd, ^3J = 6.73 Hz, ^5J = 1.10 Hz, ^5J = 0.96 Hz, 1H, 5-H), 11.18 (br. s., 1H, O-H), (second –O-H not observed).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = (signals are not totally α and / or β assigned because of the low resolution in the HSQC spectra) 17.70 (CH$_3$, 1''-C$^{\alpha+\beta}$), 22.42 (CH$_3$, 3'-C$^\alpha$), 22.46 (CH$_3$, 3'-C$^\beta$), 30.97 (CH$_2$, 1'-C$^\alpha$), 30.98 (CH$_2$, 1'-C$^\beta$), 68.81 (CH, 5-C$^\alpha$), 68.83 (CH, 5-C$^\beta$), 74.44 (CH, 2'-C$^\alpha$), 74.46 (CH, 2'-C$^\beta$), 96.49 (C^q, 3-C$^\alpha$), 96.51 (C^q, 3-C$^\beta$), 175.57 (C^q, 4-C$^{\alpha+\beta}$), 177.46 (C^q, 2-C$^\alpha$), 177.51 (C^q, 2-C$^\beta$).

MS (GC inlet, EI, 70 eV) m/z (%) = 172 (4) [M$^+$], 154 (4) [M-H$_2$O]$^+$, 128 (64) [M-C$_2$H$_4$O]$^+$, 110 (51) [M$_{128}$-H$_2$O]$^+$, 100 (100) [M-C$_3$H$_4$O$_2$]$^+$, 82 (43) [M$_{100}$-H$_2$O]$^+$, 55 (45) [M$_{110}$$^{++}$], 43 (58).

5-Ethyl-4-hydroxy-3-(2-hydroxy-propyl)-5*H*-furan-2-one (114)

White semi solid (83 mg, 4.4 mmol, 99%) from 75 mg (4.5 mmol) of 6-ethyl-1-methyl-5-oxa-spiro[2.4]heptane-4,7-dione **58c** after storage in the presence of moisture for 3 months. The compound was purified *via* column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] using *n*-hexane / diethyl ether (2/3) mixture as eluent.

R_f (SiO_2) = 0. 33 (*n*-hexane : diethyl ether, v : v, 2 : 3).

Molecular Formula = $C_9H_{14}O_4$

Formula Weight = 186.205
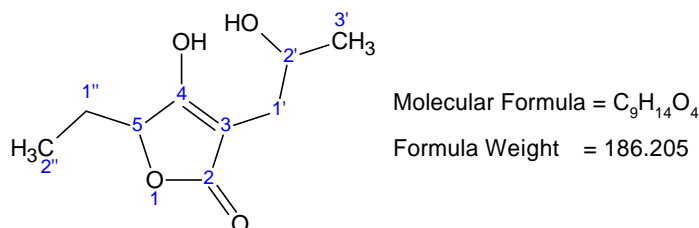
*Mixture of diastereoisomers **a** and **b**.* Ratio $\alpha : \beta$ = 1 : 1.

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3319 (W) [ν (-OH)], 2973 (M) [ν (-CH$_2$-)], 2937 (W) [ν (-CH$_2$-)], 2550 (W) [ν (-OH intramolecular bridge)], 1744 (S) and 1652 (VS) [ν (Tetronate ring)], 1084 (VS) [ν (C-O)], 1048 (VS) [ν (C-O)], 978 (S) [ν (C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.94 (t, $^3J_{HH}$ = 7.41 Hz, 3H, 2''-H), 1.26 (d, $^3J_{HH}$ = 6.17 Hz, 3H, 3'-H$_{pseudo\ equatorial}$), 1.68 – 1.74 (m, 1H, 1''-H), 1.89 – 2.04 (m, 1H, 1''-H), 2.31 (ddd, $^4J_{HH}$ = 0.96 Hz, $^3J_{HH}$ = 7.00 Hz, $^2J_{HH}$ = 16.33 Hz, 1H, 1'-H$_{pseudo\ axial}$), 2.51 (ddd, $^4J_{HH}$ = 1.65 Hz, $^3J_{HH}$ = 2.33 Hz, $^2J_{HH}$ = 16.33 Hz, 1H, 1'-H$_{pseudo\ equatorial}$), 3.80 (br. s., 1H, 2'-O-H), 4.24 (ddq, $^3J_{HH}$ = 2.33 Hz, $^3J_{HH}$ = 6.17 Hz, $^3J_{HH}$ = 7.00 Hz, 1H, 2'-H$_{pseudo\ axial}$), 4.67 (dd, $^3J_{HH}$ = 4.12 Hz, $^3J_{HH}$ = 6.59 Hz, 1H, 5-H), 11.24 (br. s., 1H, 4-O-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = (signals are not totally α and / or β assigned because of the low resolution in the HSQC spectra) 8.11 (CH$_3$, 2''-C$^\alpha$), 8.19 (CH$_3$, 2''-C$^\beta$), 22.35 (CH$_3$, 3'-C$^\alpha$), 22.47 (CH$_3$, 3'-C$^\beta$), 24.64 (CH$_2$, 1''-C$^\alpha$), 24.75 (CH$_2$, 1''-C$^\beta$), 31.94 (CH$_2$, 1'-C$^\alpha$), 31.02 (CH$_2$, 1'-C$^\beta$), 68.69 (CH, 2'-C$^\alpha$), 68.80 (CH, 2'-C$^\beta$), 78.79 (CH, 5-C$^{\alpha+\beta}$), 97.38 (C^q, 3-C$^{\alpha+\beta}$), 175.85 (C^q, 4-C$^{\alpha+\beta}$), 176.11 (C^q, 2-C$^{\alpha+\beta}$).

MS (GC inlet, EI, 70 eV) m/z (%) = 186 (2) [M$^+$], 171 (2) [M-CH$_3$]$^+$, 168 (4) [M-H$_2$O]$^+$, 142 (28) [M$_{171}$-C$_2$H$_5$]$^+$, 124 (40) [M$_{142}$-H$_2$O]$^+$, 100 (100) [M$_{171}$-C$_3$H$_4$O$_2$]$^+$, 82 (55) [M$_{100}$-H$_2$O]$^+$, 55 (88) [C$_2$H$_5$O$^+$].

5-Butyl-4-hydroxy-3-(2-hydroxy-propyl)-5*H*-furan-2-one (115)

In a round bottom flask equipped with a mechanical stirrer, 1.75 g (5.5 mmol) of mercury (II) acetate were dissolved with 5.5 mL of water; then, 2.5 mL of diethyl ether were added. While this suspension was stirred vigorously, 1.08 g (5.5 mmol) of 3-allyl-5-butyl-4-hydroxy-5*H*-

furan-2-one **57e** in 2.5 mL of diethyl ether were added, and the stirring was continued for 24 hours at room temperature. Then a solution of 2.8 mL of 6N sodium hydroxide was added followed by 5.5 mL of 0.5M sodium borohydride in 3N sodium hydroxide. The sodium borohydride was added at a rate that the reaction mixture was maintained at or below 25°C with an ice bath. The reaction mixture was stirred at room temperature for 2 hours, after which time the mercury was found as a shiny liquid. The supernatant liquid was separated from the mercury, the diethyl ether layer was separated and the aqueous solution was extracted with 3 portions of diethyl ether. The combined diethyl ether solutions were dried over sodium sulphate. The product was separated out (as a white semi solid) by column chromatography on SiO_2 [length 40 cm, $\varnothing$ 2 cm] eluting it with *n*-hexane / diethyl ether mixture (a gradient was used) and finally by preparative TLC with diethyl ether as eluent.

Yield: 30% (353 mg, 1.65 mmol). R_f (SiO_2) = 0. 50 (diethyl ether).

Molecular Formula = $C_{11}H_{18}O_4$
Formula Weight = 214.258
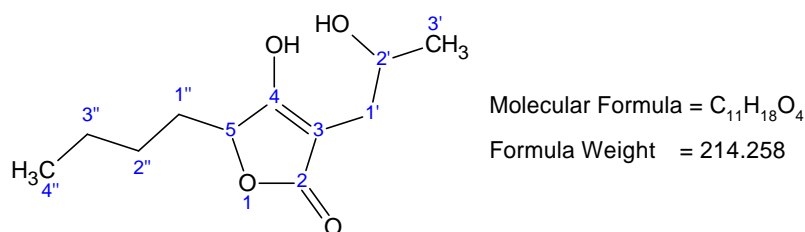
*Mixture of diastereoisomers **a** and **b**. Ratio* $\alpha : \beta$ = 1 : 1.

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3201 (W) [ν (-OH)], 2953 (M) [ν (-CH$_2$-)], 2870 (W) [ν (-CH$_2$-)], 2547 (W) [ν (-OH intramolecular bridge)], 1710 (S) and 1656 (VS) [ν (Tetronate ring)], 1363 (M) [ν (C-O)], 1066 (M) [ν (C-O)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.88 (t, $^3J_{HH}$ = 7.10 Hz, 3H, 4''-H), 1.28 (dd, $^3J_{HH}$ = 2.91 Hz, $^3J_{HH}$ = 6.24 Hz, 3H, 3'-H$_{pseudo\ equatorial}$), 1.30 – 1.48 (m, 4H, 3'', 2''-H), 1.50 – 1.67 (m, 1H, 1''-H), 1.82 – 2.20 (m, 1H, 1''-H), 2.32 (dd, $^3J_{HH}$ = 7.33 Hz, $^2J_{HH}$ = 16.29 Hz, 1H, 1'-H$_{pseudo\ axial}$), 2.52 (dd, $^3J_{HH}$ = 2.52 Hz, $^2J_{HH}$ = 16.29 Hz, 1H, 1'-H$_{pseudo\ equatorial}$), 3.55 (br. s., 1H, 2'-O-H), 4.15 – 4.32 (m, 1H, 2'-H$_{pseudo\ axial}$), 4.68 (dd, $^3J_{HH}$ = 3.7 Hz, $^3J_{HH}$ = 7.5 Hz, 1H, 5-H), 10.90 (br. s., 1H, 4-OH).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = (signals are not totally α and / or β assigned because of the low resolution in the HSQC spectra) 13.84 (CH$_3$, 4''-C$^{\alpha+\beta}$), 22.36 (CH$_2$, 3''-C$^{\alpha+\beta}$), 22.54 (CH$_3$, 3'-C$^{\alpha}$), 22.61 (CH$_3$, 3'-C$^{\beta}$), 26.33 (CH$_2$, 2''-C$^{\alpha}$), 26.37 (CH$_2$, 2''-C$^{\beta}$), 30.93 (CH$_2$, 1'-C$^{\alpha}$), 30.99 (CH$_2$, 1'-C$^{\beta}$), 31.38 (CH$_2$, 1''-C$^{\alpha}$), 31.47 (CH$_2$, 1''-C$^{\beta}$), 69.11 (CH, 2'-C$^{\alpha}$), 69.22 (CH, 2'-C$^{\beta}$), 77.99 (CH, 5-C$^{\alpha}$), 78.00 (CH, 5-C$^{\beta}$), 97.16 (C^q, 3-C$^{\alpha}$), 97.19 (C^q, 3-C$^{\beta}$), 175.60 (C^q, 4-C$^{\alpha+\beta}$), 176.31 (C^q, 2-C$^{\alpha+\beta}$).

MS (GC inlet, EI, 70 eV) m/z (%) = 214 (13) [M^+], 196 (11) [$M-H_2O$]$^+$, 170 (52) [$M-CO_2$]$^+$, 152 (98) [$M_{196}-CO_2$]$^+$, 127 (63) [$M_{170}-C_3H_7$]$^+$, 109 (94) [$M_{152}-CO$]$^+$, 100 (100) [$M_{127}-CO$]$^+$, 82 (63) [$M_{100}-H_2O$]$^+$.
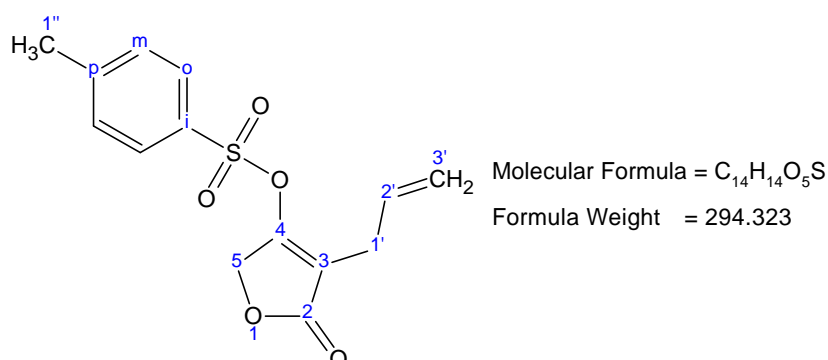
Toluene-4-sulfonic acid 4-allyl-5-oxo-2,5-dihydro-furan-3-yl ester (116)

General procedure:

To a solution of tetronic acid (0.5 g, 3.6 mmol) and *p*-toluenesulfonyl chloride (0.75 g, 4 mmol) in dry dichloromethane (50 mL) was added triethylamine (0.43 g, 4.3 mmol) under argon at room temperature. The reaction mixture was stirred at room temperature for 2 hours, following completion of the reaction as monitored by TLC. The reaction mixture was concentrated to a residue that was purified by chromatography.

White solid (0.30 g, 1.38 mmol, 95%) from 0.5 g (3.6 mmol) of 3-allyl-4-hydroxy-5*H*-furan-2-one **57a** and 0.75 g (4 mmol) of *p*-toluenesulfonyl chloride using 0.43 g (4.3 mmol) of triethylamine. The reaction mixture was purified via chromatography column in SiO$_2$ [length 20 cm, ∅ 1 cm] using *n*-hexane / diethyl ether (2 / 3) mixture as eluent.

R_f (SiO$_2$) = 0. 61 (*n*-hexane : diethyl ether; v : v; 2 : 3). m.p. = 90°C (dec.).

Molecular Formula = $C_{14}H_{14}O_5S$
Formula Weight = 294.323

IR (ATR) $\bar{\nu}$ **(cm^{-1})** = 3095 (W) [ν (=C-H)], 2986 (W) [ν (-CH$_2$-)], 1766 (S) and 1689 (M) [ν (Tetronate ring)], 1391 (S) [ν (C-O-C)], 1178 (VS) [ν (C-O-C)], 757 (VS) [ν (C-H)], 674 (S) [ν (C-H)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 2.47 (s, ^{4}J = 1.51 Hz, 3H, 1''-H), 2.78 (dd, ^{3}J = 6.45 Hz, ^{4}J = 1.37 Hz, 2H, 1'-H), 4.87 (t, ^{5}J = 1.23 Hz, ^{5}J = 1.38 Hz, 2H, 5-H), 4.92 (dq, ^{3}J = 17.31 Hz, ^{4}J = 1.51 Hz, ^{2}J = 1.65 Hz, 1H, 3'-H$_{cis}$), 4.93 (dq, ^{3}J = 9.90 Hz, ^{4}J = 1.37 Hz, ^{2}J = 1.65 Hz, 1H, 3'-H$_{trans}$), 5.60 (ddt, ^{3}J = 6.45 Hz, ^{3}J = 9.90 Hz, ^{3}J = 17.31 Hz, 1H, 2'-H), 7.40 (d, ^{3}J = 8.64 Hz, 2H, *meta*-H), 7.82 (d, ^{3}J = 8.64 Hz, 2H, *ortho*-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 21.80 (CH$_3$, 1''-C), 26.21 (CH$_2$, 1'-C), 67.21 (CH$_2$, 5-C), 115.53 (C^q, 3-C), 117.24 (CH$_2$, 3'-C), 128.21 (CH, *ortho*-C), 130.46 (CH,
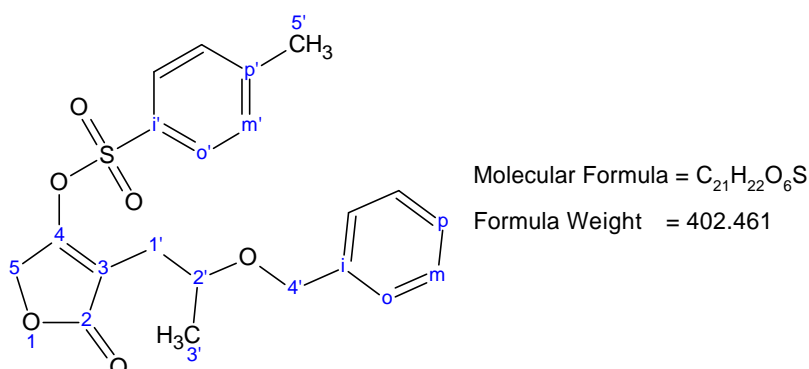
meta-C), 131.43 (C^q, *ipso*-C), 131.56 (CH, 2'-C), 147.10 (C^q, *para*-C), 162.29 (C^q, 2-C), 171.10 (C^q, 4-C).

MS (GC inlet, EI, 70 eV) m/z (%) = 294 (6) [M$^+$], 278 (1) [M-O]$^+$, 262 (1) [M-2xO]$^+$, 172 (1) [M- C$_7$H$_7$SO$_3$]$^+$, 155 (94) [M-C$_7$H$_7$SO$_2$]$^+$, 139 (21) [M-C$_7$H$_7$]$^+$, 91 (100) [C$_7$H$_7^+$], 65 (11) [C$_5$H$_5^+$].

Toluene 4-sulfonic acid 4-(2-benzyloxy-propyl)-5-oxo-2,5-dihydro-furan-3-yl ester (117)

Pale white solid (380 mg, 0.94 mmol, 81%) from 290 mg (1.17 mmol) of 3-(2-benzyloxy-propyl)-4-hydroxy-5*H*-furan-2-one **60j**, toluene-4-sulfonic acid chloride (1.28 mmol; 245 mg) and triethylamine (1.40 mmol; 142 mg), stirred in 50 mL dry CH$_2$Cl$_2$ over night. The compound was purified *via* column chromatography on SiO$_2$ [length 40 cm, $\varnothing$ 2 cm] using diethyl ether as eluent.

R_f (SiO$_2$) = 0. 34 (diethyl ether).

Molecular Formula = C$_{21}$H$_{22}$O$_6$S
Formula Weight = 402.461

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 2973 (VW) [ν (-CH$_2$-)], 1762 (S) and 1688 (M) [ν (Tetronate ring)], 1176 (S) [ν (C-O)], 1088 (S) [ν (C-O-C)], 1042 (S) [ν (C-O-C)], 742 (VS) and 695 (S) [ν (C-H aromatic)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 1.02 (d, $^3J_{HH}$ = 6.17 Hz, 3H, 3'-H), 2.11 (ddt, $^3J_{HH}$ = 5.77 Hz, $^2J_{HH}$ = 14.00 Hz, $^5J_{HH}$ = 1.10 Hz, 1H, 1'a-H), 2.30 (ddt, $^3J_{HH}$ = 6.86 Hz, $^2J_{HH}$ = 14.00 Hz, $^5J_{HH}$ = 1.10 Hz, 1H, 1'b-H), 2.39 (s, 3H, 5'-H), 3.65 (sext., $^3J_{HH}$ = 6.17 Hz, $^3J_{HH}$ = 5.77 Hz, $^3J_{HH}$ = 6.86 Hz, 1H, 2'-H), 4.31 (d, $^2J_{HH}$ = 11.80 Hz, 1H, 4'a-H), 4.41 (d, $^2J_{HH}$ = 11.80 Hz, 1H, 4'b-H), 4.81 (d, $^5J_{HH}$ = 1.10 Hz, 2H, 5-H), 7.14-7.25 (m, 5H, arom-H), 7.29 (d, $^3J_{HH}$ = 8.37 Hz, 2H, *meta'*-H), 7.73 (d, $^3J_{HH}$ = 8.37 Hz, 2H, *ortho'*-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 19.72 (CH$_3$, 3'-C), 21.79 (CH$_3$, 5'-C), 29.17 (CH$_2$, 1'-C), 67.13 (CH$_2$, 5-C), 70.54 (CH$_2$, 4'-C), 72.18 (CH, 2'-C), 114.14 (C^q, 3-C), 127.46 (CH, *ortho'*-C), 127.51 (CH, *meta*-C), 128.18 (CH, *ortho*-C), 128.28 (CH, *para*-C),

130.41 (CH, *meta'*-C), 131.56 (C^q, *para'*-C), 138.56 (C^q, *ipso*-C), 146.99 (C^q, *ipso'*-C), 163.34 (C^q, 4-C), 171.49 (C^q, 2-C).
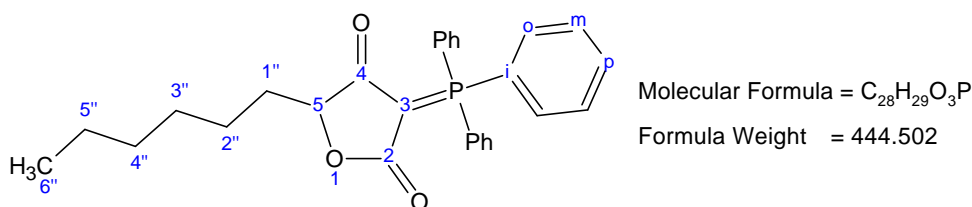
MS (GC inlet, EI, 70 eV) m/z (%) = 358 (2) $[M-CO_2]^+$, 311 (2) $[M-C_7H_7]^+$, 296 (10) $[M_{311}-CH_3]^+$, 247 (2) $[M-C_7H_7SO_2]^+$, 203 (42) $[M_{358}-C_7H_7SO_2]^+$, 155 (46) $[C_7H_7SO_2]^+$, 141 (34) $[M_{296}-C_7H_7SO_2]^+$, 91 (100) $[C_7H_7^+]$, 65 (18) $[C_5H_5^+]$, (molecular ion not observed).

5-Hexyl-3-(triphenyl-λ^5-phosphanyliden)-furan-2,4-dione (118) [164]

In a 250 mL round bottom flask, a mixture of 6.00 g (19.8 mmol) of Ph$_3$PCCO, 3.61 g (22.5 mmol) of α-hydroxyoctanoic acid **32d** and 0.63 g (10% w/w) of benzoic acid dissolved in dry THF (150 mL) were heated under reflux in argon atmosphere for 16 hours. After cooling down the reaction mixture the solution was filtered on a small plug of SiO$_2$ [length 2 cm, ⌀ 2 cm]. The solvent was removed and the residual oil was purified by column chromatography on SiO$_2$ [length 40 cm, ⌀ 2 cm] (dry column – adsorbed sample) using *n*-hexane / diethyl ether (3 /2) as eluent.

The product appeared as a colourless oil that solidify to a white powder with time (4.90 g, 11.0 mmol, 49%). m. p. = 80°C (the solid was obtained from a *n*-hexane : ethyl acetate mixture at low temperature – ice bath).

R_f (SiO$_2$) = 0.37 (diethyl ether).

Molecular Formula = $C_{28}H_{29}O_3P$

Formula Weight = 444.502

IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3059 (VW) [ν (=CH-)], 2925 (W) [ν (-CH$_2$-)], 1717 (M) and 1632 (VS) [ν (Tetronic ring)], 1343 (S) [ν (C-O)], 1107 (S) [ν (C-O)], 998 (S) [ν (=C-H)], 748 (S) and 688 (VS) [ν (C-H arom. monosubstituted)].

^{1}H-NMR (300 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 0.83 (t, $^3J_{HH}$ = 6.65 Hz, 3H, 6''-H), 1.16 – 1.35 (m, 6H, 5''-3''-2''-H), 1.40 – 1.54 (m, 2H, 4''-H), 1.62 – 1.72 (m, 1H, 1''a-H), 1.84 – 1.98 (dd, $^3J_{HH}$ = 3.77 Hz, $^3J_{HH}$ = 7.48 Hz, 1H, 1''b-H), 4.52 (m, 1H, 5-H), 7.44 – 7.53 (m, 6H, *meta*-H), 7.56 – 7.67 (m, 9H, *ortho*-, *para*-H).

^{13}C-NMR (75 MHz, CDCl$_3$, TMS$_{int}$) δ (ppm) = 13.90 (CH$_3$, 6''-C), 22.35 (CH$_2$, 5''-C), 24.45 (CH$_2$, 4''-C), 28.85 (CH$_2$, 3''-C), 31.51 (CH$_2$, 2''-C), 31.81 (CH$_2$, 1''-C), 61.19 (C^q, d, $^1J_{CP}$ = 121.89 Hz, 3-C), 83.31 (CH, d, $^3J_{CP}$ = 13.74 Hz, 5-C), 121.63 (C^q, d, $^1J_{CP}$ = 93.67 Hz, *ipso*-C), 128.90 (CH, d, $^2J_{CP}$ = 13.06 Hz, *ortho*-C), 133.25 (CH, d, $^4J_{CP}$ = 2.94 Hz, *para*-C),

133.88 (CH, d, $^3J_{CP}$ = 10.94 Hz, *meta*-C), 175.06 (C^q, d, $^2J_{CP}$ = 19.39 Hz, 2-C), 197.38 (C^q, d, $^2J_{CP}$ = 8.53 Hz, 4-C).

^{31}P-NMR (121.5 MHz, CDCl$_3$, TMS$_{int}$) d (ppm) = 11.56.

MS (GC inlet, EI, 70 eV) m/z (%) = 445 (12) [M+H]$^+$, 444 (38) [M$^+$], 373 (16) [M-C$_5$H$_{11}$]$^+$, 360 (100) [M$_{445}$-C$_6$H$_{13}$]$^+$, 301 (40) [M$_{445}$-C$_8$H$_{14}$O$_2$]$^+$, 262 (51) [PPh$_3$$^+$], 183 (34) [M$_{445}$-PPh$_3$]$^+$, 165 (16) [M$_{183}$-H$_2$O]$^+$, 108 (18) [PhP$^+$]$^+$, 77 (8) [C$_5H_5$$^+$]$^+$.

Chapter 4
Summary

Diverse 4-*O*-allyl tetronates **51** were obtained by reaction of α-hydroxy allyl esters **34** with keteneylidenetriphenylphosphorane in a domino reaction (addition – Wittig olefination).

Derivative **51a** (R^1=R^2=R^3=H) was prepared by direct allylation from tetronic **47** acid *via* Fischer esterification.

34   **51**
7 Derivatives
(33-90% yield)
      47
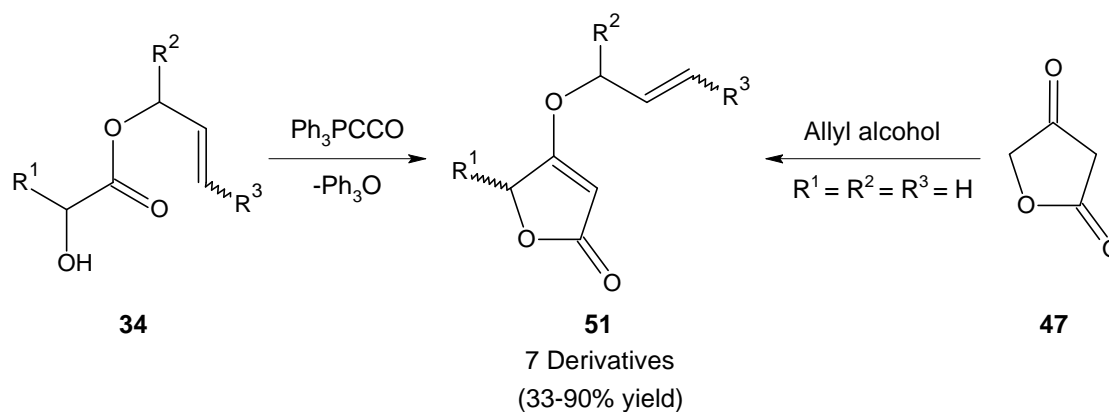
3-Allyl tetronic acid derivatives **57** were then generated as a result of a Claisen rearrangement of the starting tetronates **51**. A following Conia reaction produced the corresponding spiro cyclopropane furandiones **58** as secondary product.

51   **57**   **58**
7 Derivatives   6 Derivatives
(11-87% yield)   (15-50% yield)
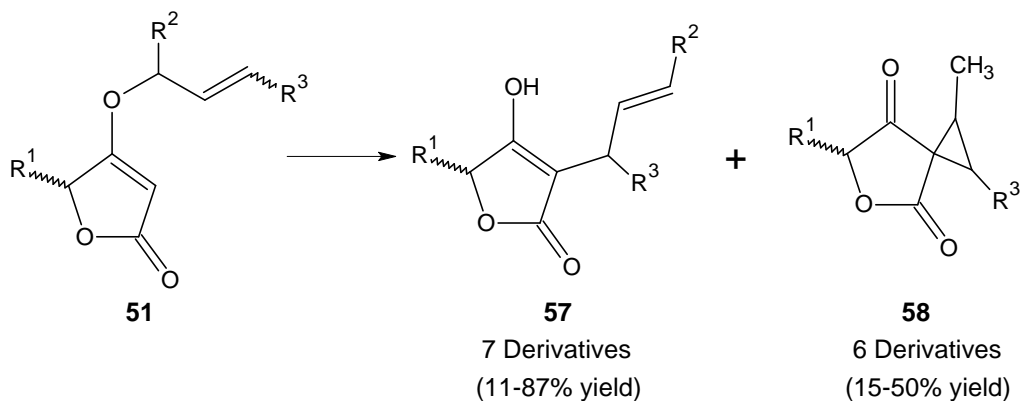
The cyclopropane ring of **58** was opened with diverse alcohols as nucleophiles to generate derivatives **60**. Nucleophilic attack of benzylic alcohol on the cyclopropane ring was effectively achieved under microwave conditions (EMS) from 3-allyl tetronic acid **57a**.

R^4 = Me, Allyl, Bn, Ac

10 Derivatives

(54-95% yield)
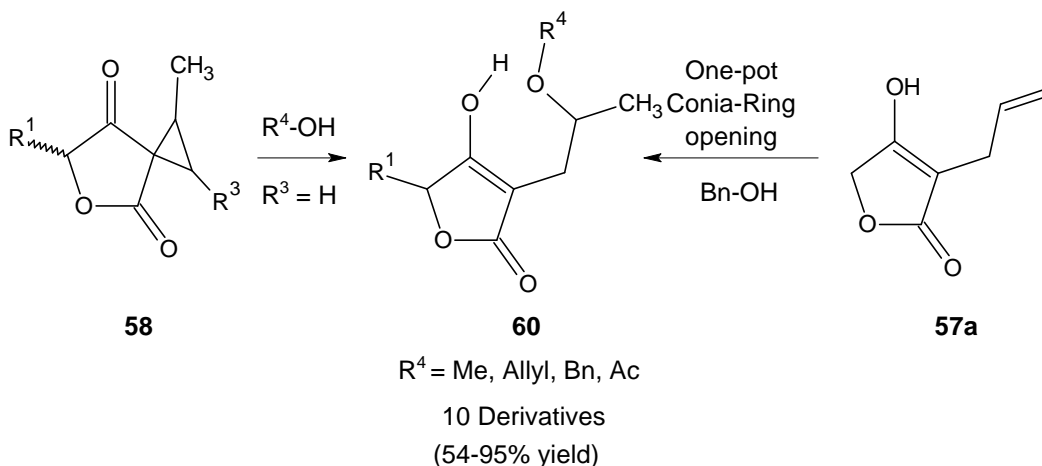
The isourea method for the 4-*O*-alkylation of tetronic acids reported by *Siegfried* [26,74] was not regioselective in the 4-*O*-benzyl protection of 3-allyl tetronic acid derivatives **57**. Five 3-allyl-3-benzylfurandiones **65** were isolated from the non regioselective benzyl alkylation. The reaction of tetronic acid **57e** (R = *n*-Bu) and acetic acid generated the 4-*O*-acetyl derivative **61a** preferentially. When reacting **57c** (R = Et) with *O*-benzyl isourea, the 5-ethyl-2-*O*-benzyl furanone **66a** was also formed – all tautomeric forms were benzylated.
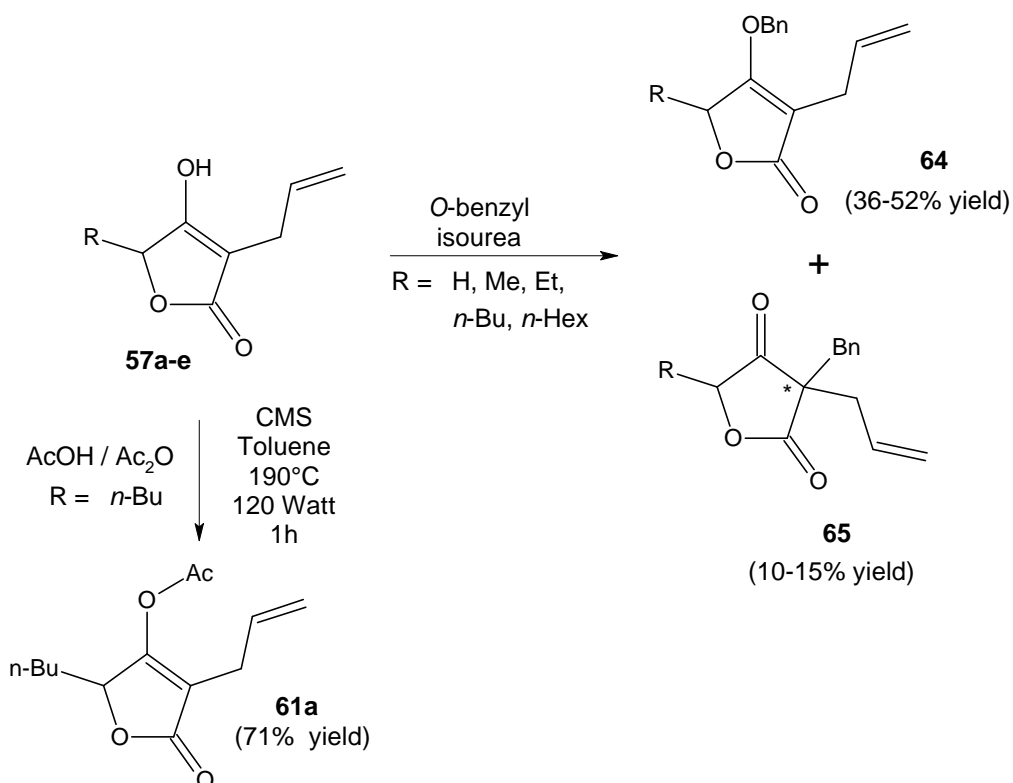
The Mitsunobu reaction proved to be a better way for the 4-*O*-alkylation of 3-allyl tetronic acid **57**. The 4-*O*-allyl derivatives **67a-c** were converted into the corresponding 3,3-diallyl furandiones **68a-c** *via* Claisen rearrangement in excellent yields.

57a

67
(41-72% yield)

68
(91-99% yield)
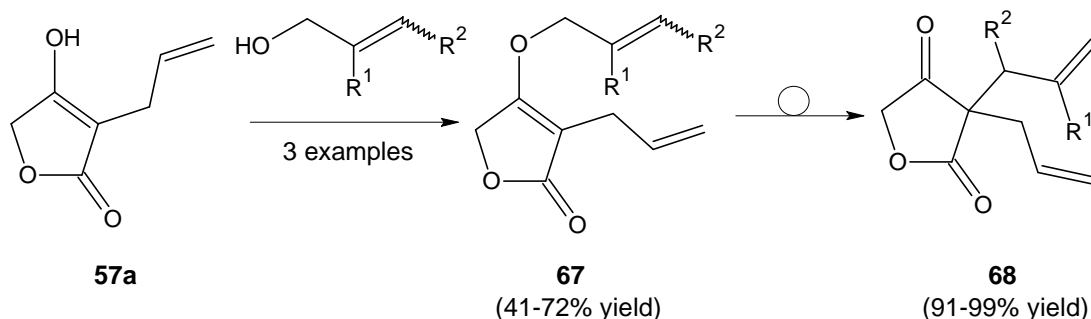
In addition, the Mitsunobu alkylation followed by RCM presents an easy way of synthesising fused furo[3,4-*b*]oxepines **81**. This procedure can be used in the synthesis of diverse building blocks of similar natural products; because of the presence of the double bond, the system offers a possibility for further functionalisation.

81a
(83% yield)

67a (R = H)

67b (R = Me)

81b
(49% yield)
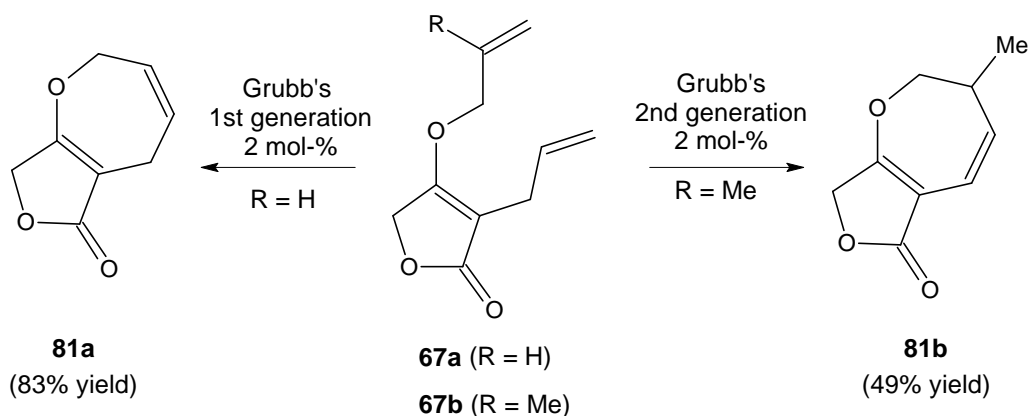
3,3-Diallyldihydrofuran-2,4-diones **68a,d-e** with two identical allyl residues were obtained by Tsuji-Trost-type Pd-catalysed allylation of 4-*O*-allyl tetronates **51**.

51a,d-e

80a
(1.1 eq)

Pd (Ph₃P)₄ 5%mol
toluene, 3h, 80°C
argon, no light

	R	(%)
68a	H	62
d	Et	89
e	*n*-Bu	50
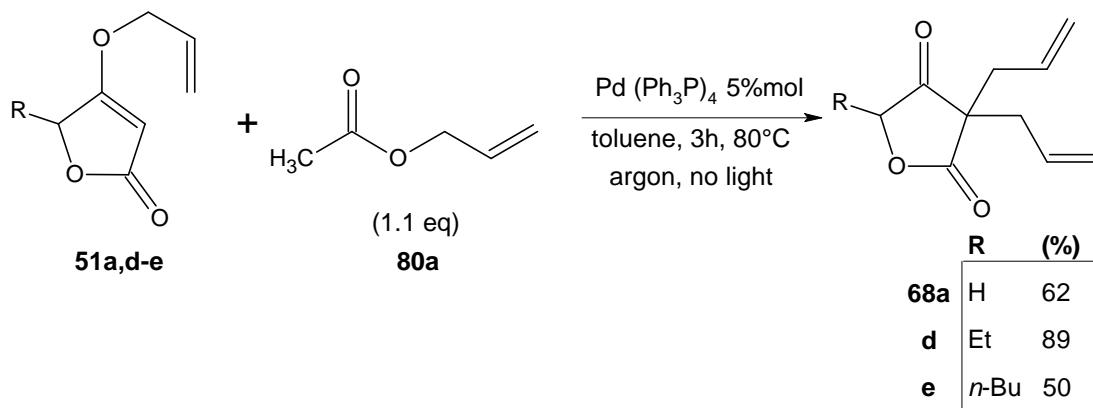
Pd assisted allylation of sodium 3-allyltetronate **57k** with cinnamyl acetate gave a preferential derivative **68f**. The reaction is comparable to the Claisen rearrangement of 3-allyl-4-allyloxy-furanones **67** under microwave conditions.

	R^1	R^2	(%)
68a	H	H	8
f	**H**	**Ph**	**70**
g	Ph	Ph	5
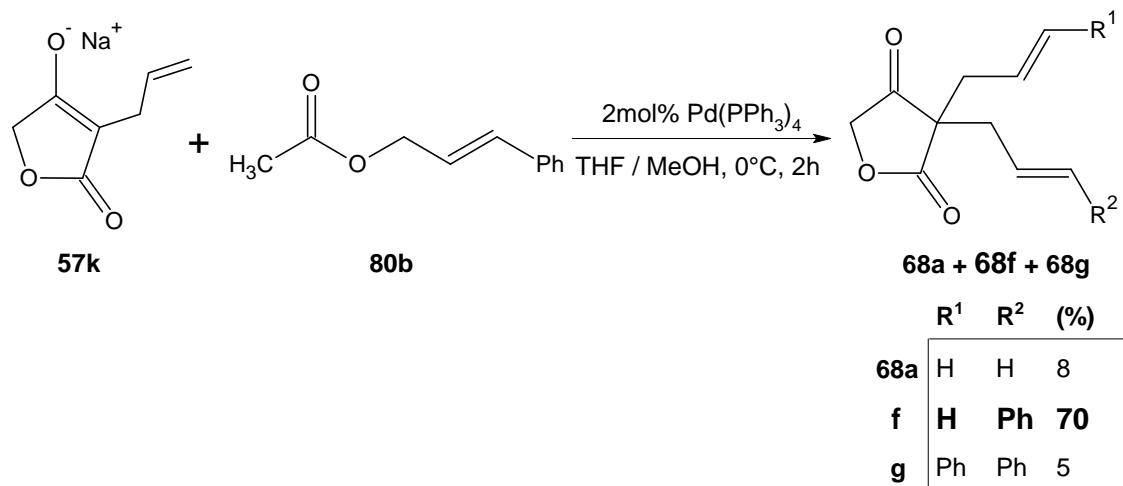
Compounds **68** were converted to butanolides with 3,3-spirocyclopentenyl annulation by ring closing metathesis with Grubbs' catalysts. The general procedure can serve as a base in the synthesis of the building block of Bakkenolide A and similar natural products.

	R	R^1	(%)
84a	H	H	90
b	Et	H	85
c	*n*-Bu	H	91
d	H	Me	95
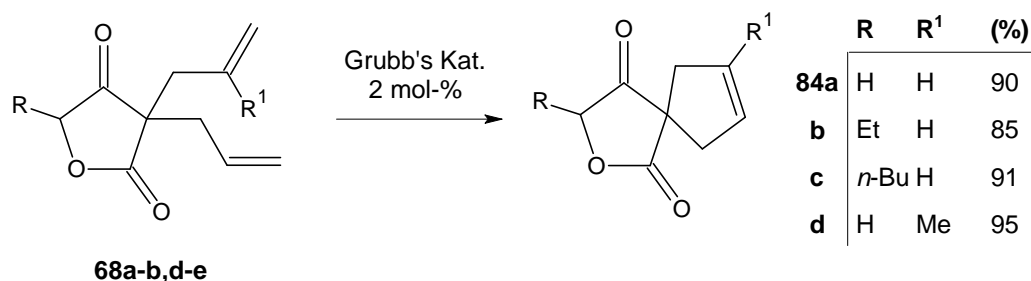
The same chemistry was attempted in the case of 4-amino butenolide derivatives **86**. Formation of derivatives **86** was effectively done by condensation of **57** with allyl amine.

86e
(40% yield)

57

86a-d
(23-90% yield)
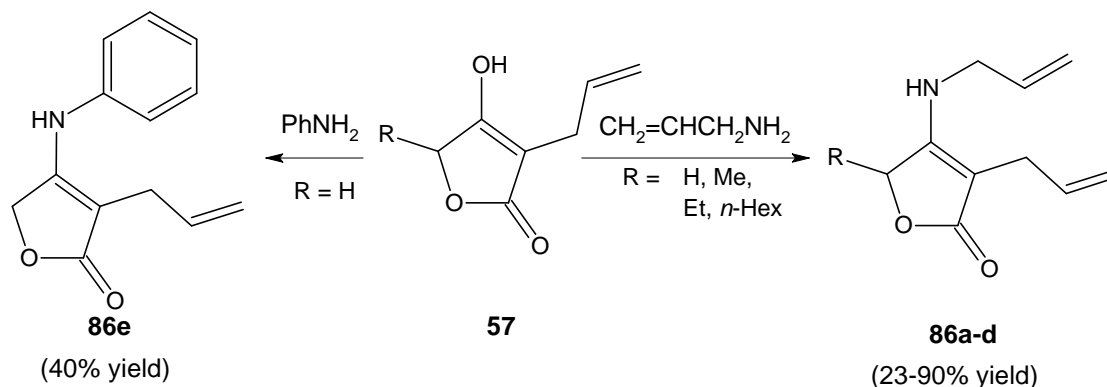
The RCM reaction showed a lower efficiency with **86** due probably to the chelating properties of the nitrogen atom. BOC-protection of the amino group was difficult due to the conjugation in the aminobutenolide system **86** (also known as tetramide).

86a-b,d

N -Protection

96b
(20% yield)

97a-c
3 Derivatives
(15-25% yield)

98a-b
2 Derivatives
(22-90% yield)
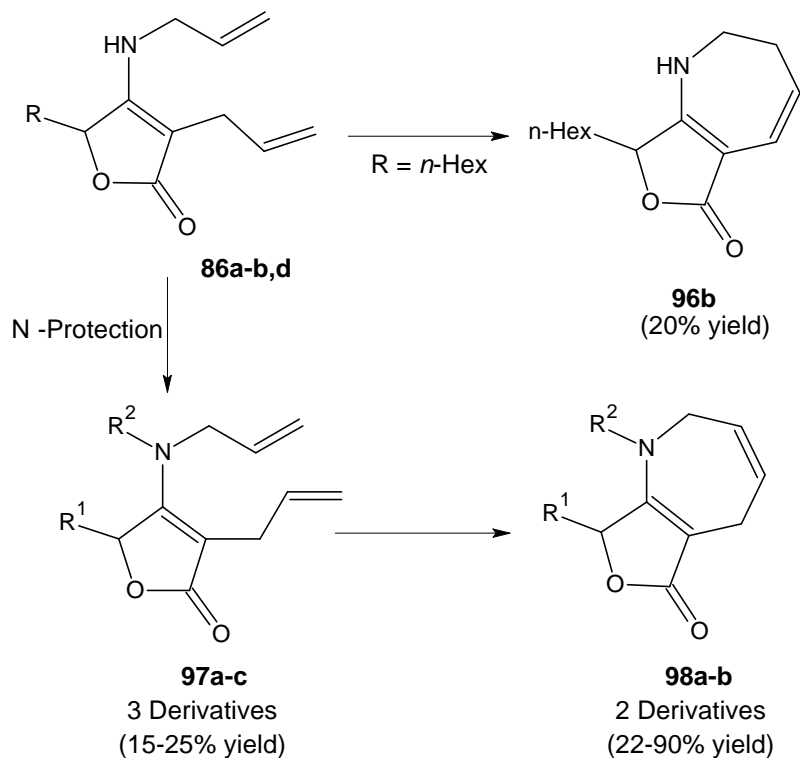
Hetero Diels-Alder reaction of derivative **84a** generates the corresponding 3,4-dispirobutanolide **103**. The cycloadduct **102** was not isolated and was converted directly to **103** after acidic work-up of the reaction.

84a   **101b**   **102**   **103**
(50% yield)
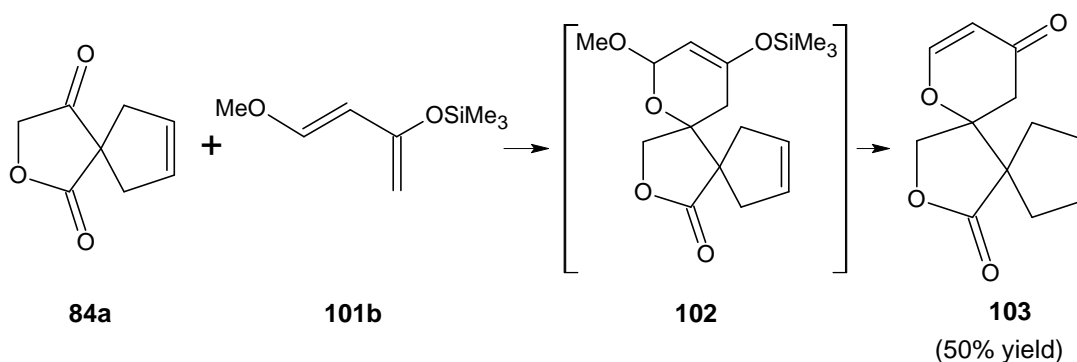
The allyl functionalisation of 4-*O*-benzyl tetronates **64** was done using ozone. Aldehyde **107** was difficult to handle due to the formation of polymeric substances. To solve this problem, aldehydes **107** were converted into the dimethyl acetal **108** by a one-pot oxidation – protection. Debenzylation of **108** generated the corresponding tetronic acid derivatives **109**. Carboxylic acid derivatives **111** were obtained after a Jones' oxidation of aldehyde derivatives **107**. *O*-Ethyl isourea was used to form the ethyl ester **112**. Subsequent debenzylation afforded the tetronic acid **106b**, a synthon in the preparation of bisfuranones.

64

107

108
R = Me, Et, *n*-Bu
(74-98% yield)

O$_3$
MeOH

H$^+$
MeOH

Jones'
reagent

H$_2$ / Pd-C

O-Et
isourea
(90%)

112

111
R = Et, *n*-Bu
(74*-80% yield)
* crude product

109
R = Et, *n*-Bu
(77-98% yield)

H$_2$ / Pd-C

106b
(26% yield)
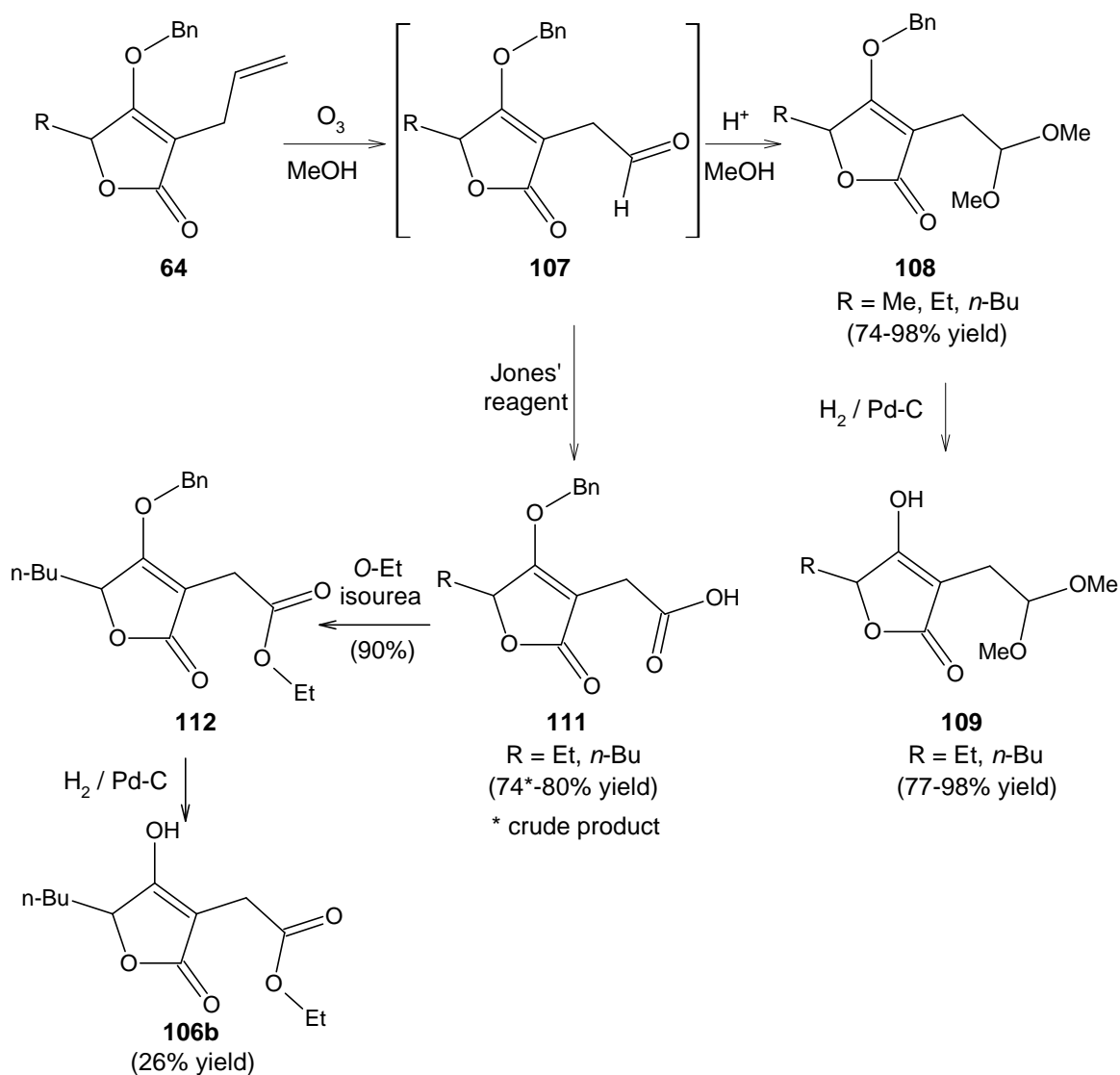
3-Acetyl tetronic acids **28a-b** were prepared *via* a double Ph$_3$PCCO addition to α-hydroxy benzyl ester **34g-h**, thus demonstrating the utility of keteneylidenetriphenylphosphorane as a versatile C$_2$O building block. Initially formed tetronates **51j-i** were debenzylated in excellent yields to give the tetronic acids **47a-b**. A second addition of Ph$_3$PCCO converted **47** into 3-acylidenetetronic acid betaine **56a-b**. The basic hydrolysis of **56** gave the 3-acetyl tetronic acids **28a-b**. **28b** is the natural product pesthetoxine. Only one previous example from our research group employed Ph$_3$PCCO as an acetyl source in the 3-acetylation of tetronic acids.

34g (R = *n*-Bu)			R	(%)				R	(%)
34h (R = *n*-Hex)		**51i**	*n*-Bu	66		**47a**		*n*-Bu	83
		j	*n*-Hex	75		**b**		*n*-Hex	99*

* crude compound

	R	(%)
28a	*n*-Bu	85
b	*n*-Hex	83

56a-b
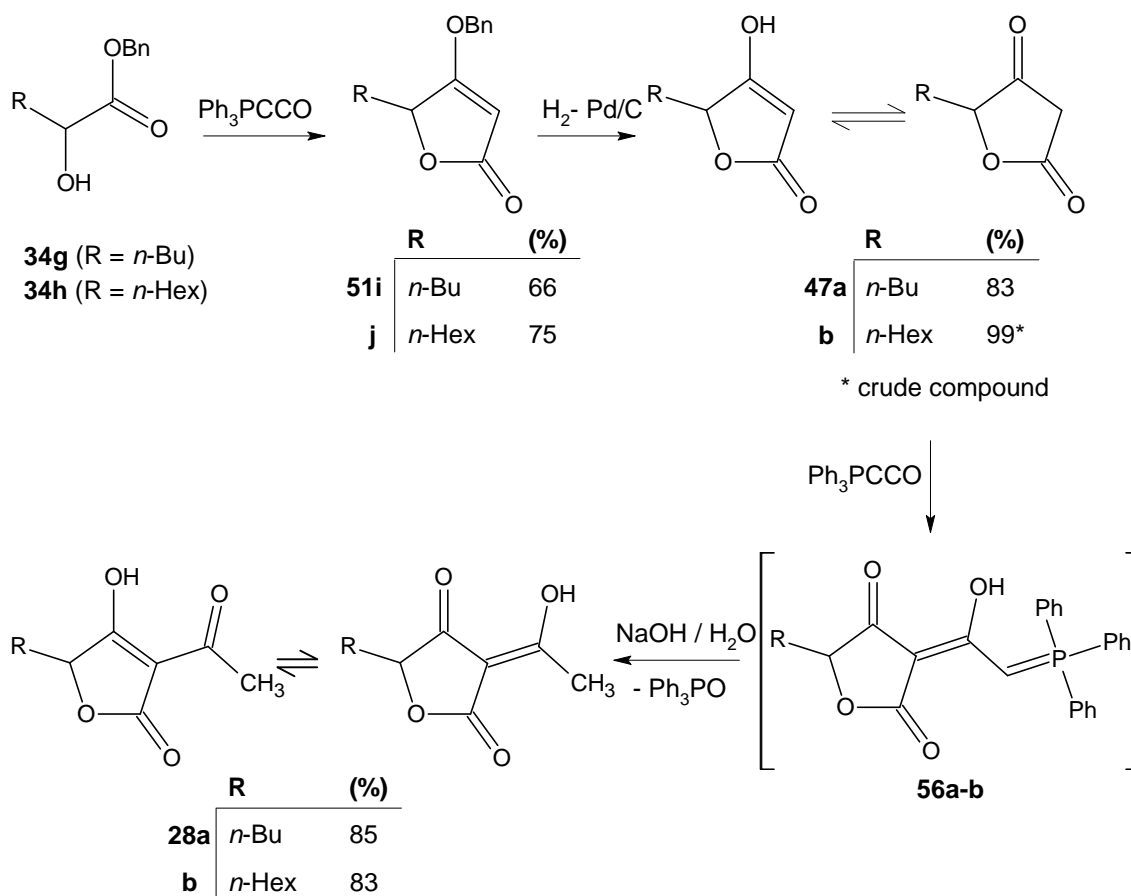
Finally, the natural product (-)-3-*epi*-blastmycinolactol **29-*epi*** was prepared diastereoselectively *via* double hydrogenation of 3-but-2-enyl tetronic acid **57g**. Only the enantiomer **29-epi** was obtained.

57g   H$_2$, Rh/Al$_2$O$_3$ (5%) / AcOEt, AcOH cat / 50 bar, 60°C, 5d   **29-*epi*** (42% yield)

(-)-3-*epi*-blastmycinolactol
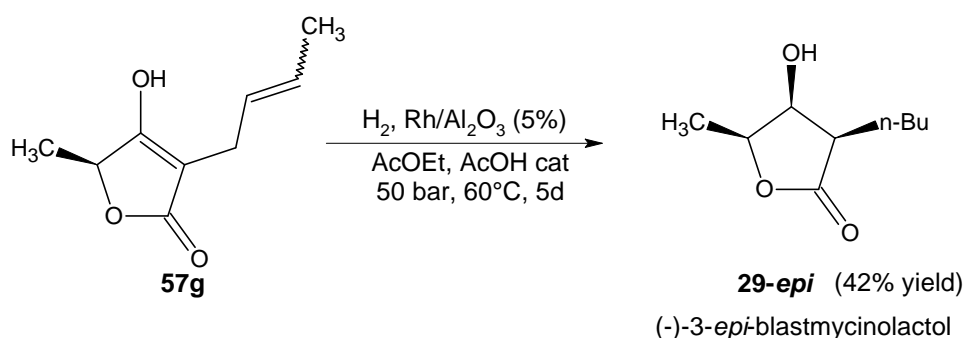
Chapter 4b

Zusammenfassung

Im Rahmen dieser Arbeit wurden verschiedene 4-O-Allyltetronate **51** synthetisiert. Die Darstellung gelang durch eine so genannte Dominoreaktion, bei der Ketenylidentriphenylphosphoran mit a-Hydroxyallylestern **34** umgesetzt wurde.

Die Verbindung **51a** ($R^1=R^2=R^3=H$) wurde durch direkte Allylierung von Tetronsäure **47** *via* Fischer-Veresterung hergestellt.

34 **51** **47**
7 Derivate
(33-90%)
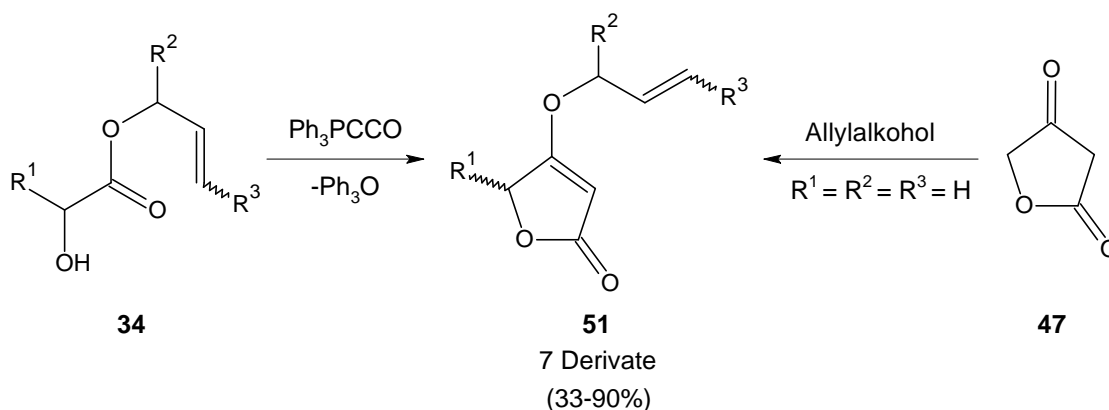
Die 3-Allyltetronsäurederivate **57** wurden durch Claisen-Umlagerung aus den 4-*O*-Allyltetronaten **51** erhalten. Mittels einer sich anschließenden Conia-Reaktion wurden die entsprechenden Spirocyclopropanfurandione **58** als Nebenprodukt erzeugt.

51 **57** **58**
7 Derivate 6 Derivate
(11-87%) (15-50%)
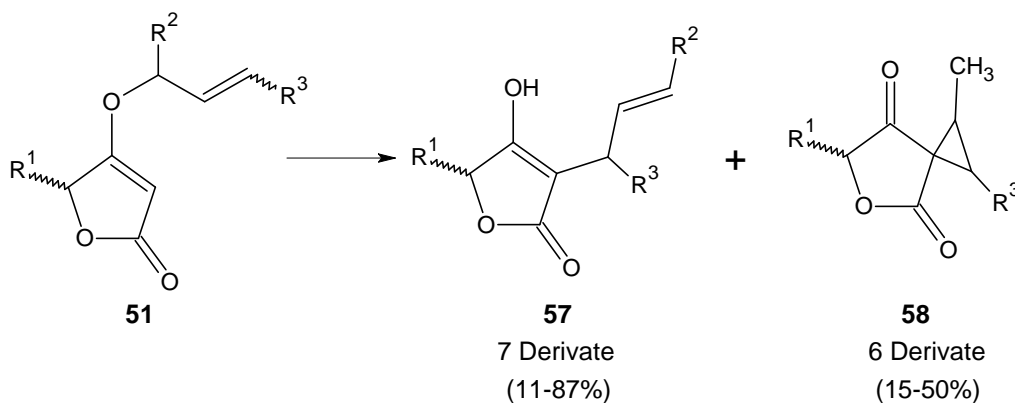
Um Derivate von **60** herzustellen, wurde der Cyclopropanring mit verschiedenen Alkoholen nukleophil geöffnet. Ausgehend von 3-Allyltetronsäure **57a** wurde im Zuge einer Eintopf-Reaktion unter Mikrowellenbedingungen der nukleophile Angriff von Benzylalkohol an den Cyclopropanring ermöglicht.

58   **60**   **57a**

R^4 = Me, Allyl, Bn, Ac

10 Derivate

(54-95%)
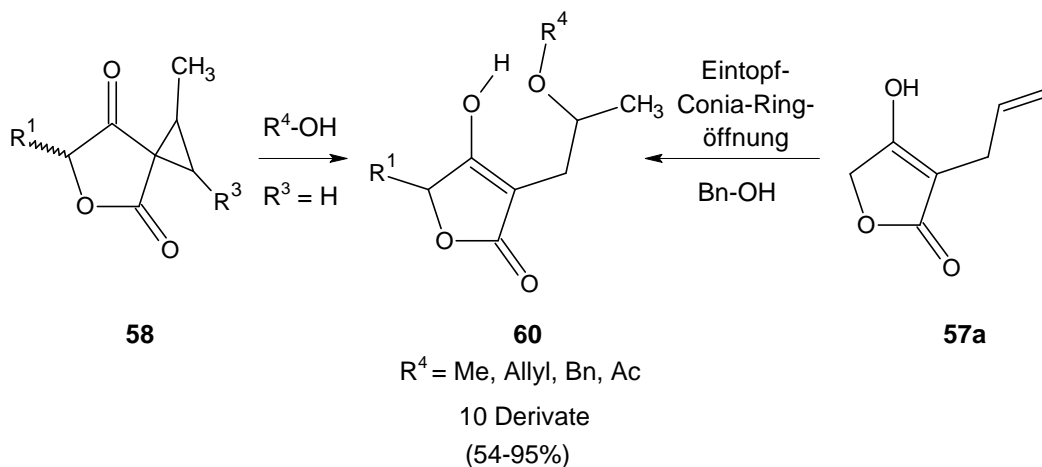
Die 4-*O*-Alkylierung der Tetronsäuren durch die Isoharnstoff-Methode von *Siegfried*[26,74] war in diesem Fall nicht regioselektiv. Bei allen fünf durchgeführten Versuchen entstand neben dem gewünschten Produkt **64** auch noch **65**. Lässt man **57e** (R = *n*-Bu) mit Essigsäure reagieren, bildet sich das 4-*O*-Acetyl Derivat **61a**. Interessanterweise entstand beim Umsatz von **57c** (R = Et) mit *O*-Benzyl-Isoharnstoff 2-*O*-Benzyl-5-ethyl-furanon **66a**.

64

(36-52%)

+

65

(10-15%)

57a-e

O-Benzyl Isoharnstoff

R = H, Me, Et, *n*-Bu, *n*-Hex

AcOH / Ac$_2$O
R = *n*-Bu

CMS
Toluol
190°C
120 Watt
1h

61a

(71%)
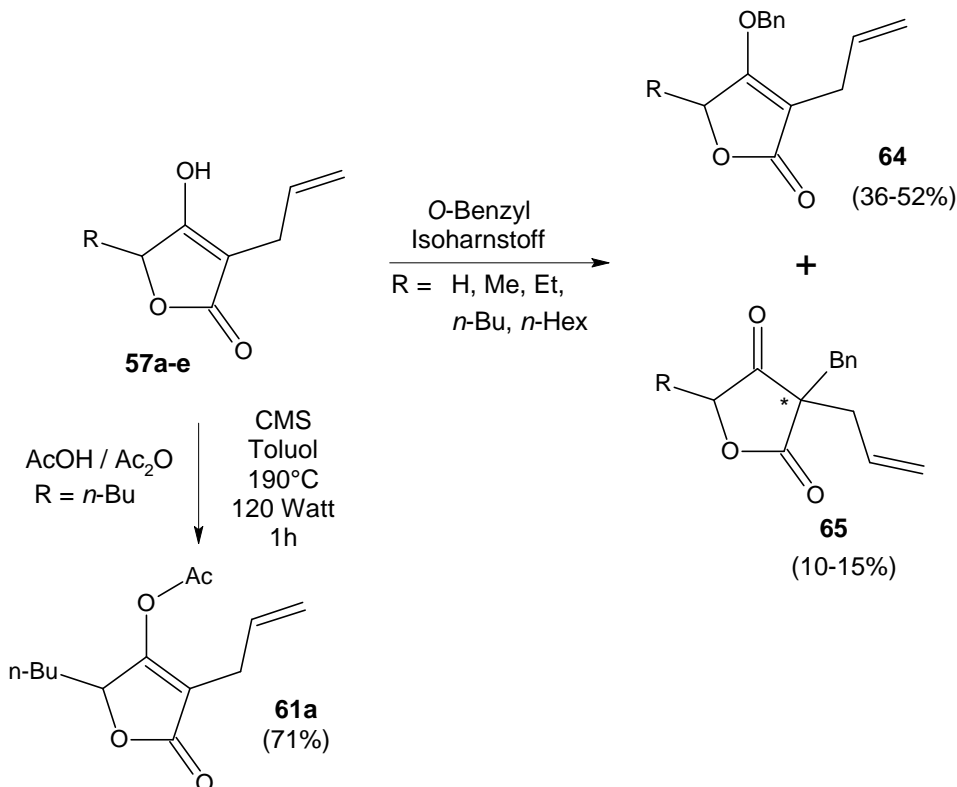
Die Mitsunobu Reaktion erwies sich als besserer Weg für die 4-*O*-Alkylierung der 3-Allyl-tetronsäuren **57**. Die 4-*O*-Allylderivate **67a-c** wurden über die Claisen-Umlagerung zu den jeweiligen 3,3-Diallylfurandionen **68a-c** in hervorragenden Ausbeuten umgesetzt.

57a   **67a-c**   **68a-c**
                            (41-72%)   (91-99%)
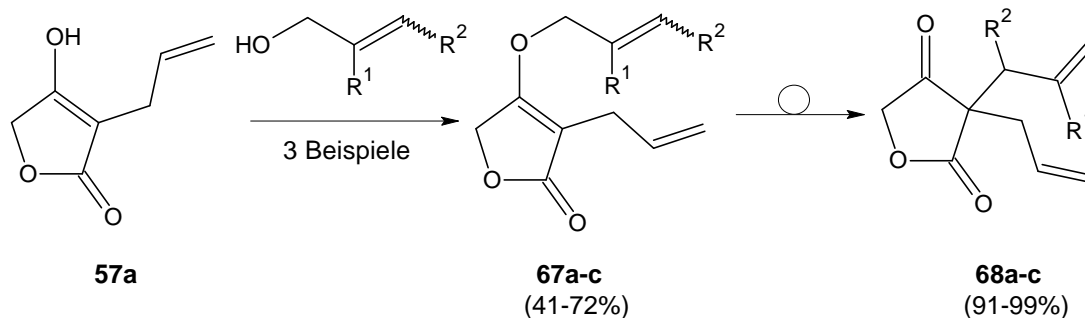
Gefolgt von RCM stellt die Mitsunobu-Reaktion einen zusätzlichen einfachen Weg dar "fusionierte" Furo[3,4-*b*]oxepine **81** zu synthetisieren. Die allgemeine Vorschrift kann als Basis dienen, um verschiedene Bausteine ähnlicher Naturstoffe zu synthetisieren. Durch die vorhandenen Doppelbindungen bietet das System die Möglichkeit weiterer Funktionalisierungen.

81a   **67a** (R = H)   **81b**
(83%)   **67b** (R = Me)   (49%)
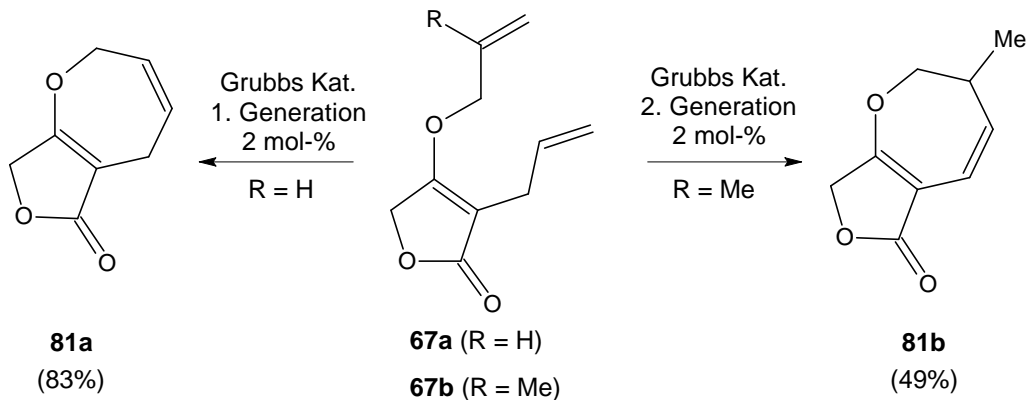
3,3-Diallyldihydrofuran-2,4-dione **68a,d-e** mit zwei identischen Allylresten wurden durch die Paladium-katalisierte Tsuji-Trost-Reaktion mit 4-*O*-Allyltetronaten **51** erhalten.

Pd (Ph$_3$P)$_4$ 5%mol
Toluol, 3h, 80°C
Argon, kein Licht

51a,d-e   **80a**
                            (1.1 eq)

	R	(%)
68a	H	62
d	Et	89
e	*n*-Bu	50
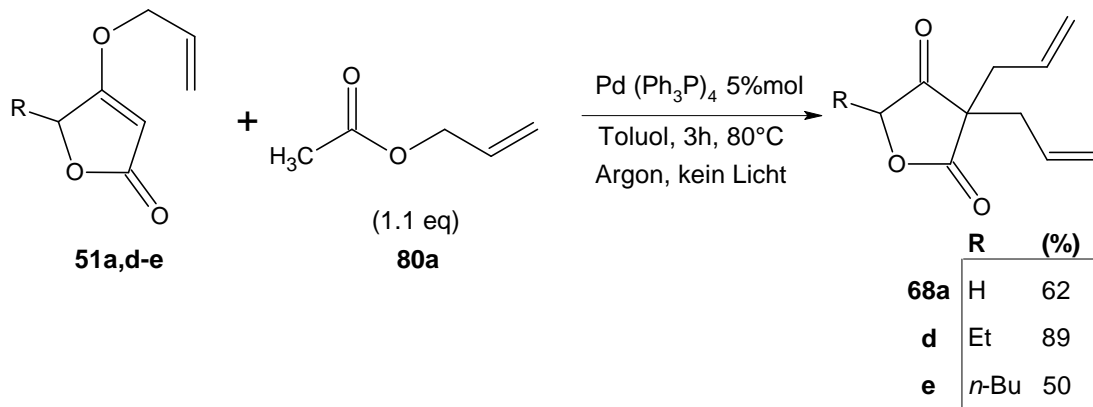
Tsuji-Trost Reaktion von Natrium 3-Allyltetronat **57k** mit Zimtacetat ergab Verbindung **68f** in sehr guten Ausbeuten. Die Reaktion ist vergleichbar mit der Claisen-Umlagerung der 3-Allyl-4-allyloxyfuranon **67** unter Mikrowellen-Bedingungen.

	R^1	R^2	(%)
68a	H	H	8
f	**H**	**Ph**	**70**
g	Ph	Ph	5
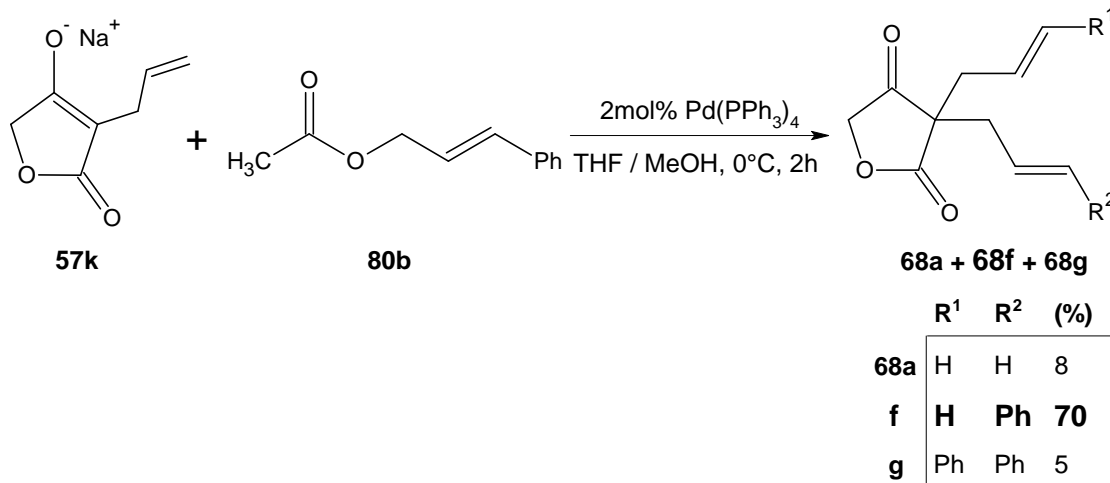
Die Verbindungen **68a-b,d-e** wurde mit Grubbs-Katalysator zu Butanoliden mit 3,3-Spirocyclopentenyl-Annullierung umgesetzt. Diese allgemeine Vorschrift kann als Basis für die Synthese weiterer Bausteine von Bakkenolid A und ähnlichen Naturstoffen dienen.

	R	R^1	(%)
84a	H	H	90
b	Et	H	85
c	*n*-Bu	H	91
d	H	Me	95
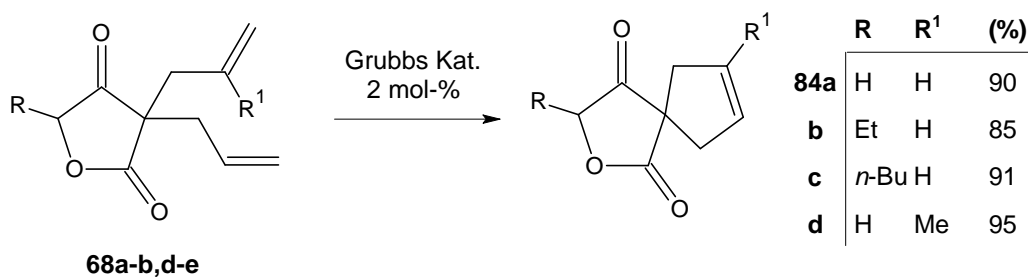
Der gleiche Syntheseweg wurde bei 4-Aminobutenolid-Derivaten **86** angewendet. Die Bildung der Verbindungen **86a-d** wurde erfolgreich durch Kondensation von **57** mit Allylamin durchgeführt.

86e   **57**   **86a-d**

(40%)   (23-90%)
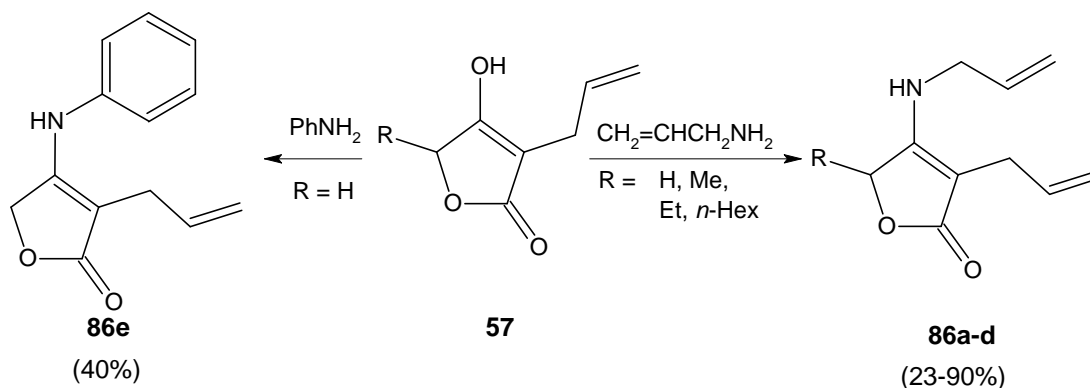
Die RCM Reaktion mit **86** zeigte, wahrscheinlich infolge der chelatisierenden Eigenschaften des Stickstoffatoms, eine geringere Effizienz. Die Einführung einer BOC-Schutzgrupe an der Aminofunktion war aufgrund der Konjugation im Aminobutenolid-System (auch bekant als Tetramid) schwierig.

86a-b,d

N -Schützung

97a-c
3 Derivate
(15-25%)

R = *n*-Hex

96b
(20%)

98a-b
2 Derivate
(22-90%)
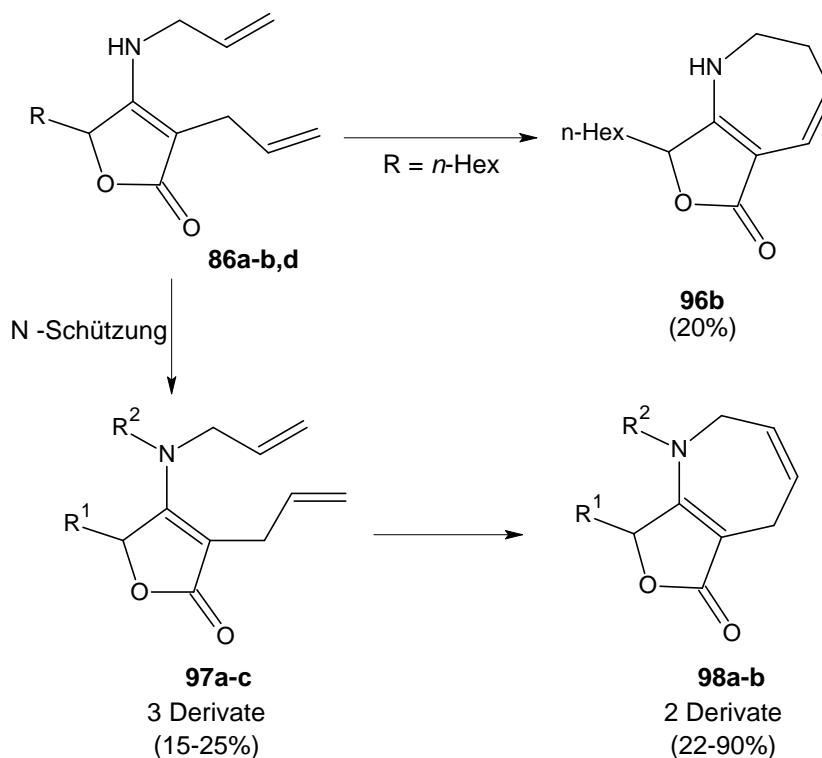
Die Hetero Diels-Alder Reaktion der Verbindung **84a** führte zum entsprechenden 3,4-Dispirobutanolid **103**. Das Cycloaddukt **102** wurde nicht isoliert, sondern direkt durch saure Aufarbeitung der Reaktionsmischung zum Produkt **103** umgesetzt.

84a   **101b**   **102**   **103**
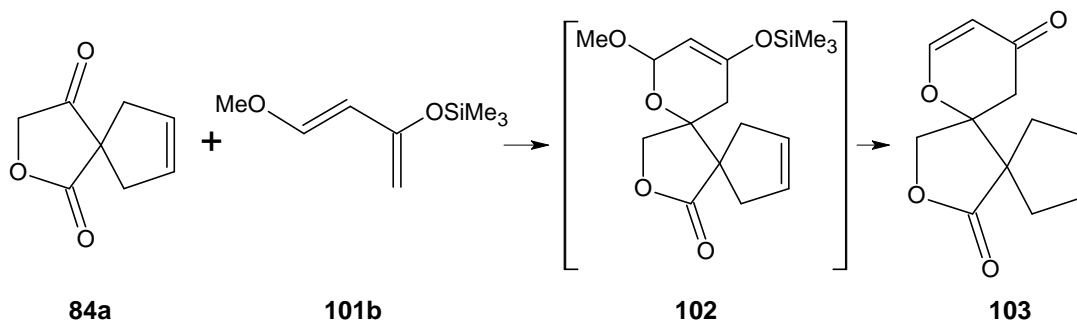
Die Allylspaltung der 4-*O*-Benzyltetronate **64** wurde mit Ozon durchgeführt. Infolge der einfachen Bildung von Polymeren der Aldehyde **107** waren diese schwierig zu handhaben. Um dieses Problem zu lösen, wurden die Aldehyde **107** in Dimethylacetale **108** überführt. Die Debenzylierung von **108** ergab die jeweiligen Tetronsäurederivate **109**. Mit Hilfe des Jones-Reagenz' konnten die Aldehydderivate **107** zu Carboxylsäurederivaten **111** oxidiert werden. Die Carboxysäuren wurden mit *O*-Ethyl-Isoharnstoff zu Ethylester **112** verestert. Die anschließende Debenzylierung führte zur Tetronsäure **106b**, einem Synthon in der Herstellung der Bisfuranone.
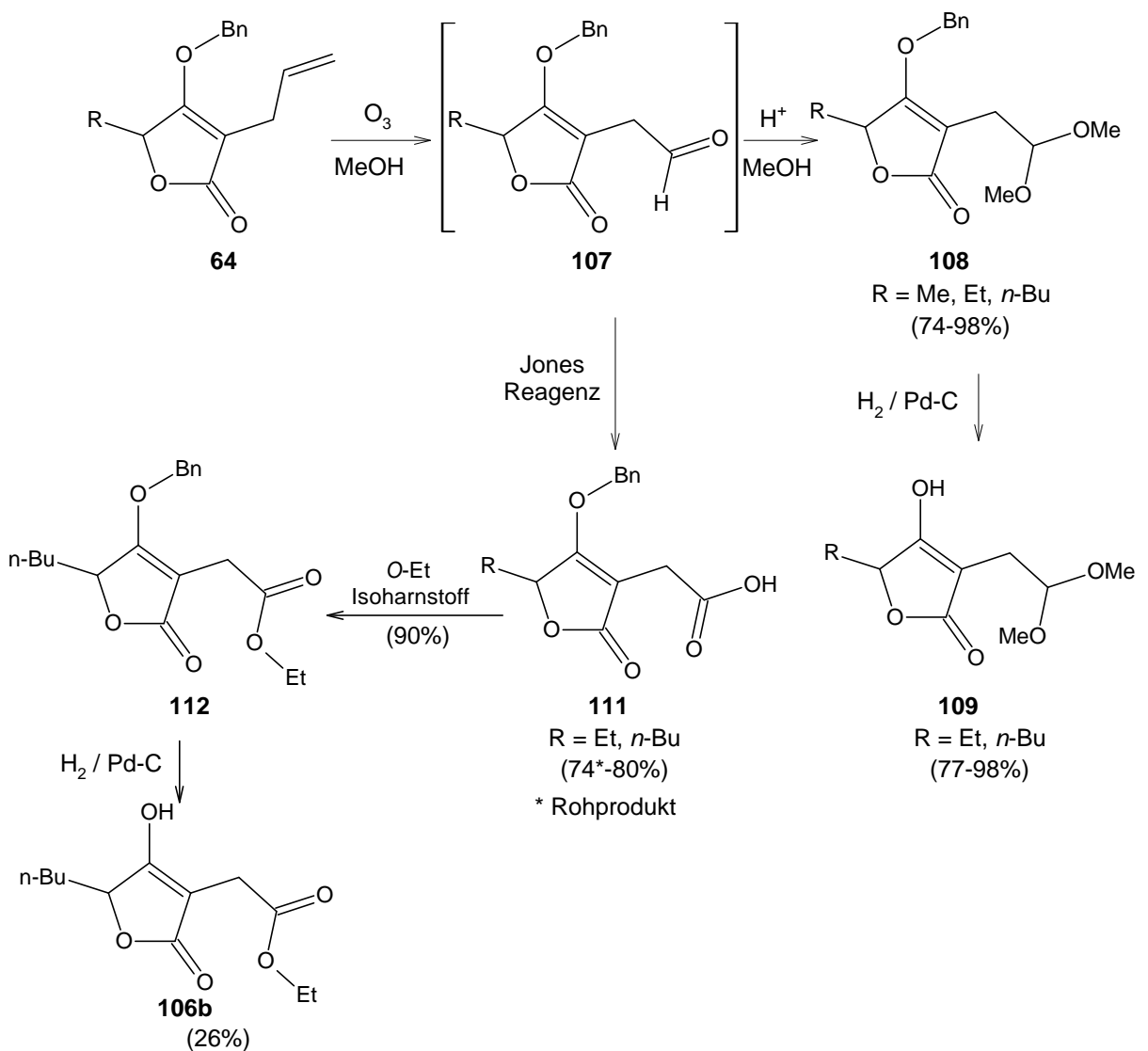
Die 3-Acetyltetronsäuren **28a-b** wurden über zweifache Ph₃PCCO Addition ausgehend von α-Hydroxybenzylestern **34g-h** synthetisiert. Dies demonstriert das hohe Potenzial von Ketenylidentriphenylphosphoran als vielfältigen C_2O-Baustein. Zunächst gebildete Tetronate **51i-j** wurden mit hervorragenden Ausbeuten zu Tetronsäuren **47a-b** debenzyliert. Eine zweite Addition von Ph₃PCCO setzte **47a-b** in 3-Acylidentetronsäurebetaine **56a-b** um. Die basische Hydrolyse von **56** ergab die 3-Acetyltetronsäuren **28a-b**. Bei **28b** handelt es sich um den Naturstoff Pesthetoxin. Die von unserem Arbeitskreis nicht vollständig entwickelten Reaktionschritte wurden zu einer Eintopf-Reaktion mit ausgezeichneten Ausbeuten entwickelt.

34g (R = *n*-Bu)
34h (R = *n*-Hex)

	R	(%)
51i	*n*-Bu	66
j	*n*-Hex	75

	R	(%)
47a	*n*-Bu	83
b	*n*-Hex	99*

* Rohprodukt

Ph₃PCCO

	R	(%)
28a	*n*-Bu	85
b	*n*-Hex	83

56a-b
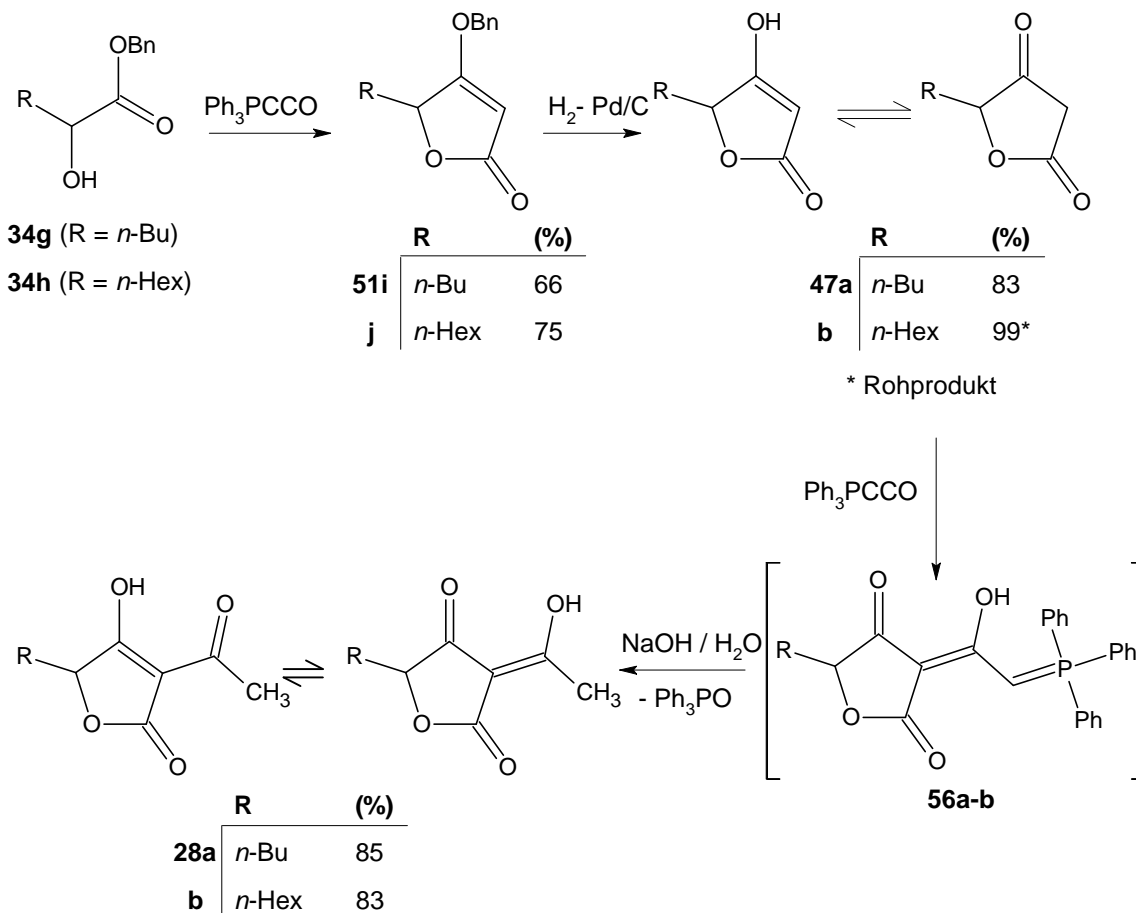
Der Naturstoff (-)-3-*epi*-Blastmycinolactol **29-*epi*** wurde enantioselektiv durch doppelte Hydrierung aus dem 3-but-2-enyl Tetrosäurederivat **57g** synthetisiert.

57g

H_2, Rh/Al₂O₃ (5%)
AcOEt, AcOH Kat.
50 bar, 60°C, 5d

29-*epi* (42%)

(-)-3-*epi*-Blastmycinolactol
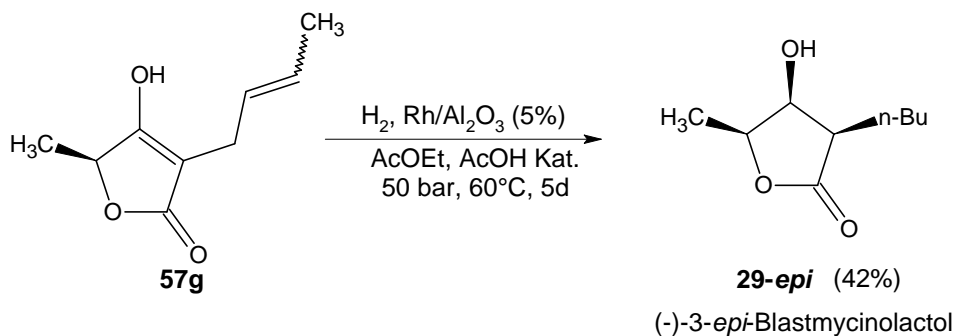
Chapter 5

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Appendix A

The formation of diastereoisomers of cyclopropane spiro furandiones from the oxa – ene reaction.
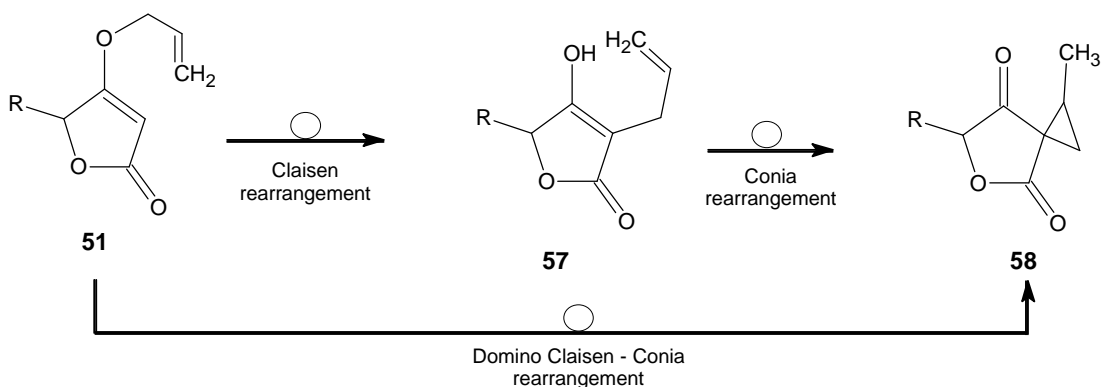

Figure A-123. Claisen and Claisen Conia rearrangements of tetronates **51**.

A plausible mechanistic explanation for the formation of compounds **58** is that the primary step (Claisen rearrangement) forming the 3-allyltetronic acids **57** is followed by an oxa-ene reaction giving the 3-spiro ring closure product **58** (Conia rearrangement).

- The Conia rearrangement can be described as

a thermal intramolecular hetero - ene reaction between an enol (oxa-ene component) and an electrophile (enophile component).[165]

In the ene – reaction certain electrophilic carbon–carbon (or carbon–oxygen / carbon-nitrogen) double bond can undergo an addition reaction with alkenes in which an allylic hydrogen is transferred to the the electrophile ([1,5] shift).[166]
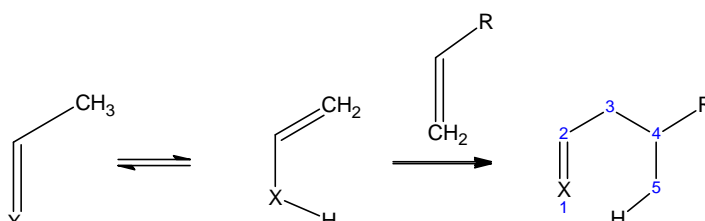

Figure A-124. The concerted intermolecular ene reaction (for x = CH_2) or hetero–ene reaction (for x = O: oxa–ene; x = N: aza-ene). A bond between the ene component and the enophile is formed with the concomitant [1,5]-hydrogen shift and the migration of the double bond.

The particular stereochemistry of the oxa-ene reaction for the formation of derivatives **8** can be explained with a formal frontier orbital description of the transition state, using the HOMO of

the enol radical and the LUMO of the alkene. The product isomer with a *cis* constellation of the created methyl group and the oxo group form the isomer α.
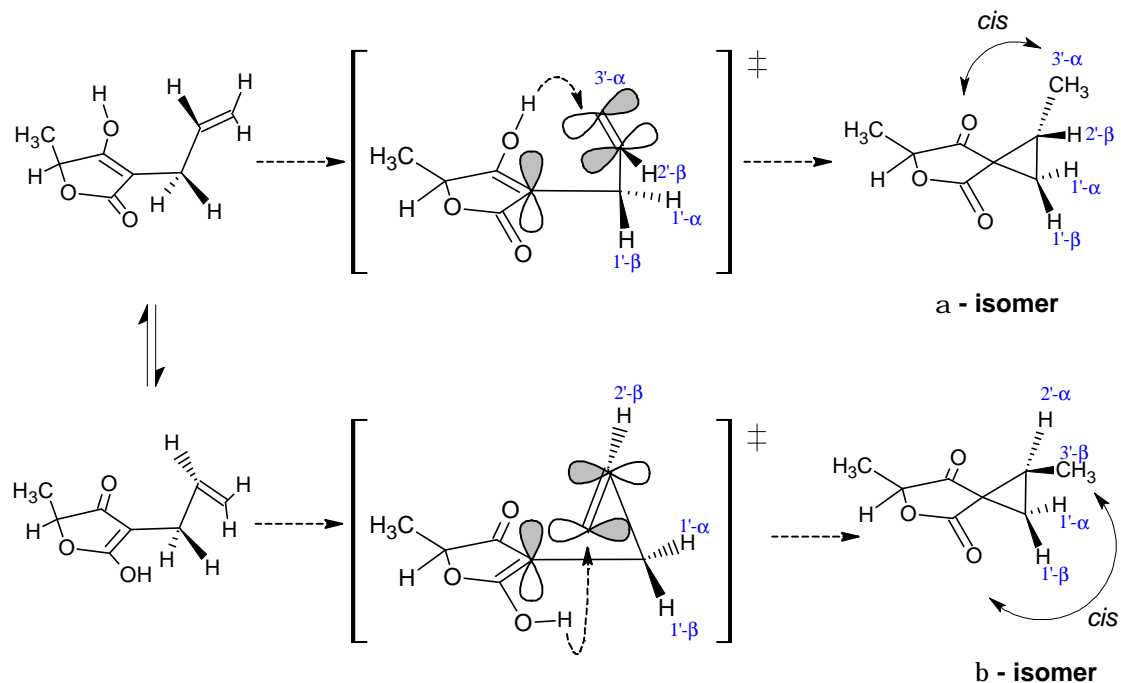

Figure A-125.
The concerted oxa – ene reaction: interaction of a hydrogen atom with the HOMO of the enol radical and the LUMO of the alkene. The formation of α and β diastereoisomers depends of the tautomers formed.