Keteneylidenetriphenylphosphorane as a 'C_2O building block' in the synthesis of highly functionalised tetramic and tetronic acids.

Vorgelegt von

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Abstract

Naturally occurring 4-hydroxy-pyrrol-2(5*H*)-ones and 4-hydroxy-furan-2(5*H*)-ones are known to possess a wide range of biological activities such as anti-viral and tumour inhibition. For this reason, the synthesis of a number of these compounds was attempted, namely Tenuazonic Acid, Reutericyclin and Carlosic acid.

A general synthesis of 4-hydroxy-pyrrol-2-ones was established by reaction of a phosphorus ylide (Ph_3PCCO) with a variety of amino esters. A number of derivatives were prepared with varying substituents at the 3- and 5-positions of the nitrogen heterocycle. A general method for the preparation of highly functionalised furan-2-ones from simple α-hydroxy esters was also developed.

Progress has been made in the synthesis of N-substituted pyrrol-2-ones where simple amide esters were reacted with a phosphorus ylide (Ph_3PCCO) in the construction of highly functionalised nitrogen heterocycles.

A new acylation procedure was developed in order to selectively introduce an acetyl residue to pyrrolidine-2-ones and furan-2-ones. A phosphorus ylide (Ph_3PCCO) and its solid supported variant were used as acylating agents under relatively mild, basic conditions.

Complex heterocycles were prepared using the Diels-Alder methodology and from reaction of Ph_3PCCO with relatively simple molecules.

Abstrakt

Natürlich vorkommende 4-Hydroxy-pyrrol-2(5*H*)-one und 4-Hydroxy-furan-2(5*H*)-one besitzen hohe biologische Aktivität. So zeigen sie unter Anderem anti-virale als auch anti-tumour Eigenschaften. Auf Grund dessen wurde versucht einen synthetischen Zugang zu Tenuazonsäure, Reutericyclin und Carlosischer Säure, zu finden.

Ein allgemeiner Syntheseweg zur Herstellung von 4-Hydroxy-pyrrol-2-onen wurde durch die Reaktion von Phosphor Ylid Ph_3PCCO mit verschiedenen Aminosäureestern etabliert. Durch die Einführung von verschiedenen Substituenten der 3- und 5-Positionen des Stickstoff-Heterocyclus wurde eine Vielzahl von Derivaten synthetisiert. Zusätzlich wurde auch eine allgemeine Syntheseroute zur Herstelllung von hochfunktionalisierten Furan-2-onen ausgehend von α-Hydroxyestern.

Deutliche Fortschritte in Bezug auf die Synthese von N-substituierten Pyrrol-2-onen wurden verzeichnet. Durch Umsatz von einfachen α-Amidoestern mit Phosphor Ylid Ph_3PCCO wurden hochfunktionalisierten wurden Stickstoff-Heterocyclen erhalten.

Ein neuen Acylierungsmethode zur selektiven Einführung von einem Acetylrest in Pyrrol-2-one und Furan-2-one konnte gefunden und etabliert werden. Phosphor Ylid (Ph_3PCCO) und dessen festphasengebundene Variante wurden als Acylierungmittel verwendet. Diese Reaktion wurde unter milden und basischen Bedingungen durchgeführt.

Komplexe Heterocycle wurden mittels der Diels-Alder Methode als auch der Reaktion von Ph_3PCCO mit relativ einfachen Molekülen hergestellt.

Objectives

The aim of this project was to synthesise a number of biologically active 3-acyl-4-hydroxy-5-alkyl-pyrrol-2-ones and 3-acyl-4-hydroxy-5-functionalised-furan-2-ones using a phosphorus ylide (Ph_3PCCO) as a C_2O (carbon-oxygen) source to construct the heterocyclic nucleus. Using this approach, the objectives of this project were:

- Development of a general procedure for the preparation of 5-alkyl-pyrrolidine-2,4-diones, starting from amino acids.
- Investigation of common acylation procedures to selectively introduce a 3-acyl substituent to the sensitive pyrrolidine-2,4-dione nucleus.
- Reaction of amide esters with Ph_3PCCO to generate highly functionalised nitrogen heterocycles.
- Preparation of complex furan-2-ones using Ph_3PCCO and simple α-hydroxy esters.
- Development of a mild and selective acylation procedure for pyrrol-2-ones and furan-2-ones using Ph_3PCCO.
- Development of a stereoselective synthesis of highly substituted furan-2-ones.
- Construction of complex heterocycles using the Diels Alder methodology.
- Reaction of cyclic ketols with phosphorus ylide Ph_3PCCO to generate highly substituted oligocycles.

Table of Contents

Abbreviations

approx.	approximately
arom.	aromatic
Bn	benzyl
b.p.	boiling point
cat.	catalytic
C^q	quartenary carbon atom
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
decomp.	decomposition
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMSO	Dimethylsulfoxide
equiv.	equivalent
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
gp.	group
h	hour
HMDS	Hexamethyldisilazane
Hz	Hertz
***i*-Bu**	*iso*-butyl (-$CH_2CH(CH_3)_2$)
IMDA	Intramolecular Diels-Alder reaction
IMWO	Intramolecular Wittig olefination
***i*-Pr**	iso-propyl (-$CH(CH_3)_2$)
IR	infrared
J	coupling constant
m	multiplet
***m*-C**	*meta*-carbon atom
Me	methyl
MeOH	Methanol
MF	molecular formula
min	minute
mL	millilitre
mmol	millimole
mol	mole
m.p.	melting point
MS	Mass spectrometry
MW	molecular weight/mass
***n*-Bu**	butyl (-$(CH_2)_3CH_3$)
NMR	Nuclear Magnetic Resonance
***o*-C**	*ortho*-carbon atom
***p*-C**	*para*-carbon atom
PCC	Pyridinium chlorochromate
Pd/C	Palladium on charcoal
PEG-MME	Polyethyleneglycol-monomethyl ether
PEG-DCT	Polyethyleneglycol-dichlorotriazine
pet.ether	petroleum ether
PMB	4-Methoxybenzene
PO	Triphenylphosphine oxide
Ph	phenyl
PhLi	Phenyllithium
ppm	parts per million
PTSA	4-Toluene sulfonic acid
PTSCl	4-Toluene sulfonyl chloride
py	Pyridine
q	quartet
r.t.	room temperature
***sec*-Bu**	-$CH(CH_3)CH_2CH_3$
T	time
TCT	Trichlorotriazine
Temp.	temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatograpy
TMS	Tetramethylsilane
unsat.	unsaturated
↑	an increase in

1. General Section

1.1 General Introduction

Naturally occurring compounds isolated from flowers, plants and insects are used for their taste, colour, odour and medical application. Hence, with such a range of applications, it is worthwhile to develop chemical pathways to synthesise these natural products on a large scale.

Natural product chemistry deals with the extraction of naturally occurring compounds, their structure elucidation, function in their natural environment and biosynthesis. A combination of these factors provides a better understanding of the molecule for its total synthesis in the laboratory. The development of general procedures to prepare these naturally occurring compounds not only allows larger scale production, but also facilitates the synthesis of analogues which may not be present in nature.

Analogues of compounds are useful especially in drug development, for comparisons of their structure-activity relationships. A small modification in the structure of a molecule can have a huge impact on its activity. Therefore, by testing analogues of compounds, it is possible to find the most biologically active and potential drug candidate.

The role of the chemist is to search for cost-effective, efficient and versatile syntheses of biologically active compounds, where the overall yield and purity of the final product are not only of immense importance but also the chemical concepts behind each individual step in the synthesis.

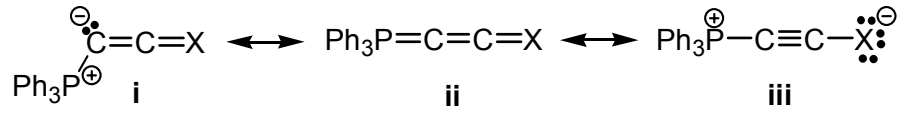
Due to the extensive use of keteneylidenetriphenylphosphorane **1a** both as a 'CCO' building block in construction of highly functionalised 4-hydroxy-pyrrol-2-ones and 4-hydroxy-furan-2-ones and as an acylating agent, it's structure, properties and characteristic reactions are discussed below.

1.2 Keteneylidenetriphenylphosphorane: Structure and Properties

The electronic structure and distribution of phosphorus $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^3$ allows the formation of tri-, tetra-, penta- and hexa-coordinate derivatives where the ligands can be

organic or inorganic. The importance and widespread use of organophosphorus compounds stems from the range of possible coordination numbers it can possess, from $P^{(III)}$ through to $P^{(VI)}$. The strong bonds phosphorus forms with O, S, N and C, and its capability to stabilise adjacent anions are also important when dealing with reactions of organophosphorus reagents such as ylides (or ylids).

An ylide is defined as *'a substance in which a carbanion is directly attached to a heteroatom carrying a substantial degree of positive charge, and in which the positive charge is created by sigma bonding of the substituents to the heteroatom'*[1]. Phosphacumulene ylides[2] are described by $R_3P{=}C{=}C{=}X$ where R represents a variety of aliphatic and aromatic groups (usually alkyl or phenyl groups) and generally X = O **1a**, S **1b** or NPh **1c**. The resonance structures for phosphacumulene ylides are shown below[3]:



1a: X = O
1b: X = S
1c: X = NPh

Fig.1

Resonance structures **i - iii** differ in their geometry and electron distribution depending on the nature of X. As the electron accepting character of X increases, there is less of a tendency of C^{β}=X to participate in the double bond and so the electronic structure leans towards that of **iii**. Therefore, from X=NPh **1c** to X=O **1a** to X=S **1b**, the $PC^{\alpha}C^{\beta}$ bond angle increases from approximately 120° to 180° and the $C^{\alpha}{=}C^{\beta}$ bond length shortens[4]. This has been proven by X-ray structure analysis of compounds **1a**[5], **1b**[6] and **1c**[7], as shown in **Table 1**:

	P-C^{α} bond length (Å)	**C^{α}-C^{β} bond length (Å)**	**$PC^{\alpha}C^{\beta}$ angle (°)**
1a, X = O	1.648	1.210	145.5
1b, X = S	1.677	1.204	168.0
1c, X = NPh	1.677	1.248	134.0

Table 1: Bond lengths and bond angles of phosphacumulene ylides **1a-c**.

The differences in the $PC^{\alpha}C^{\beta}$ bond angles can be attributed to the variation in hybridisation of C^{α}. **1c**, which is largely represented by structure **i** (**Fig.1**), contains a more sp^2-hybridised ylide carbon and a bond angle close to 120° which produces a triangular shape, while **1b** exhibits more sp-hybridisation with structure **iii** (**Fig.1**)

carrying more weight, resulting in a shape close to linear. In general, the $C^{\alpha}=C^{\beta}$ bonds are considerably short in comparison to the normal allene length of 1.31 Å and more in line with the length of alkyne bonds (1.21 Å)[8], see **Table 1**. This indicates a substantial contribution from the triple bonded resonance structure **iii,** especially in **1a** and **1b**.

The P-C bond lengths quoted in **Table 1** are distinctly shorter than an average single P-C bond (1.85 Å). For many years, this was explained by back-bonding from the ylide carbon (C^{α}) into the vacant d-orbitals of phosphorus[9,10], but more recently it is thought that the back-bonding occurs into the phosphorus sp^3-hybrid orbitals, with little or no contribution from the d-orbitals.

The stability and reactivity of phosphorus ylides depends largely on the substituents attached to the ylidic carbon atom and somewhat on the phosphorus substituents. Electron donating groups on the phosphorus atom increase the dipole moment of the P-C^{α} bond, leading to a greater charge separation and a slightly enhanced reactivity. While electron withdrawing groups lower the charge separation, leading to an increase in the participation of resonance structure **ii** (**Fig.1**), resulting in a reduction of the ylide reactivity.

In general, electron withdrawing groups e.g. CO_2Et and CN attached to the carbon end of the dipole, delocalise the carbanionic charge which reduces the nucleophilicity (i.e. decreasing the ylidic character) of the ylide and hence stabilise it. In contrast, electron donating groups such as alkyl residues, decrease ylide stability by increasing its overall reactivity e.g. $Me_3P=CH_2$ **2a**, $Ph_3P=CH_2$ **2b** and $Ph_3P=CHMe$ **2c** are customarily prepared *in situ* due their extreme reactivity. Keteneylidenetriphenylphosphorane **1a** is incorporated into many syntheses as a 'C_2O'-building block because of its intermediate stability and reactivity when activated with catalytic quantities of benzoic acid.

Ylides containing alkoxy residues at C^{α} are rather reactive and even react with sterically hindered ketones, while silyl groups stabilise the negative charge on C^{α} of an ylide, reducing its reactivity. Ylides with main group metal substituents attached to the ylidic carbon have also been prepared and possess significant nucleophilicity e.g. lithiated derivatives have the potential to react with even weak electrophiles which are unreactive towards the non-lithiated parent ylide. Finally, ylides with a transition metal substituent at C^{α} have also been synthesised but are not commonly used due to their lack of consistency and unproductive reaction procedures.

Phosphacumulene ylides such as **1a** contain four electrons in each orthogonal π-system (**Fig.2**) i.e. 4 electrons in the $2p_x$ orbital system and 4 electrons in the $2p_y$ orbital system. Unlike ketenes with their nucleophilic π^4- and electrophilic π^2-systems, both ylide π^4-systems are nucleophilic and the lack of electrophilic (and dipolar) character prevents the ylide from dimerising i.e. reacting with a second molecule of itself. Therefore, neutral ylides can only behave as nucleophiles with electrophiles adding across their P-C^α or C^α=C^β bonds.

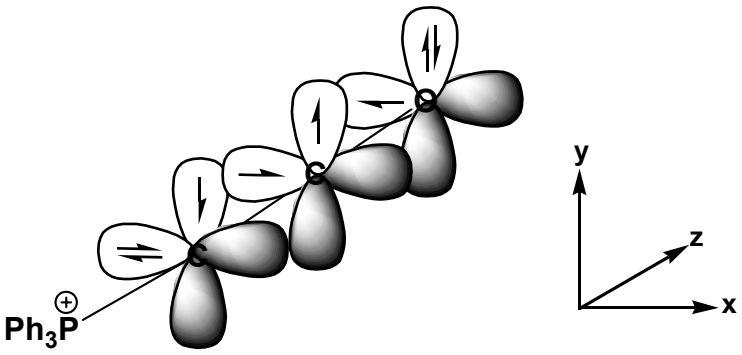
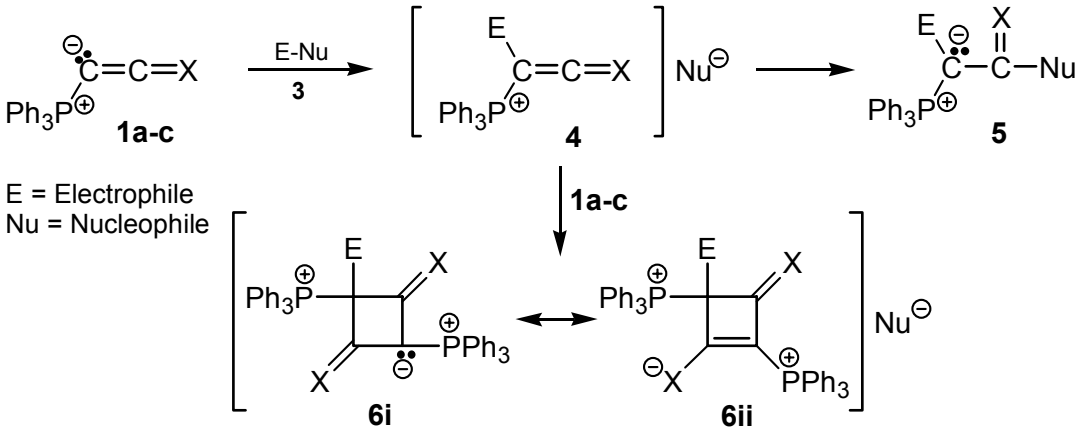


Fig.2 π-system of the zwitterionic structure of ylide **1a**.

The $\pi^4 \perp \pi^4$-electron system of cumulated ylides is transformed into the ketene $\pi^4 \perp \pi^2$-system by addition of an electrophile ($\mathbf{E}^+$) to the ylidic carbon producing phosphonium ion **4** (see **Scheme 1**[4]). This activates the ylide for reaction.

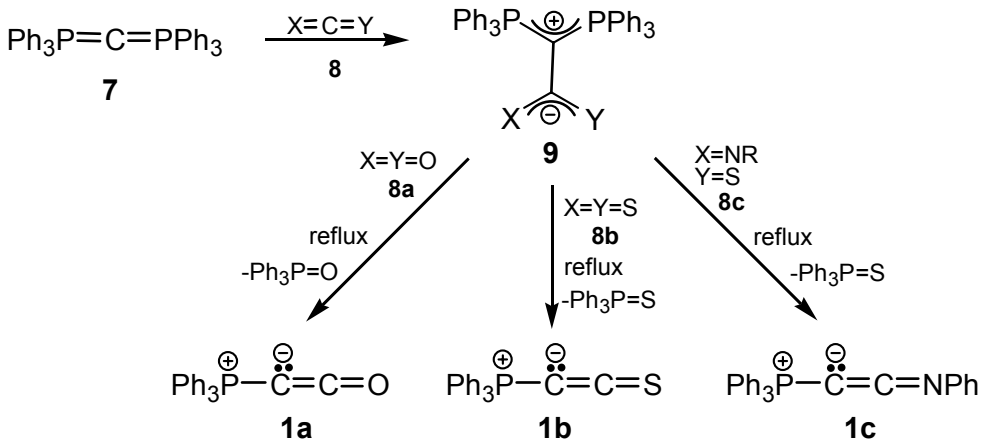
If the starting ylide **1a-c** is a stronger nucleophile than $\mathbf{Nu}^-$ (**E-Nu**), it will react with **4** via a [2+2]-cycloaddition to form the four-membered ring system **6**, of which resonance structures **6i** and **6ii** are shown (**Scheme 1**). But if $\mathbf{Nu}^-$ is the stronger nucleophile, it will attack C^β of **4** generating compound **5**, which can undergo Wittig reactions depending on the nature of $\mathbf{E}^+$ and $\mathbf{Nu}^-$. The latter reaction is the basis for the use of keteneylidenetriphenylphosphorane **1a** throughout this project, allowing the construction of complex organic molecules.



Scheme 1

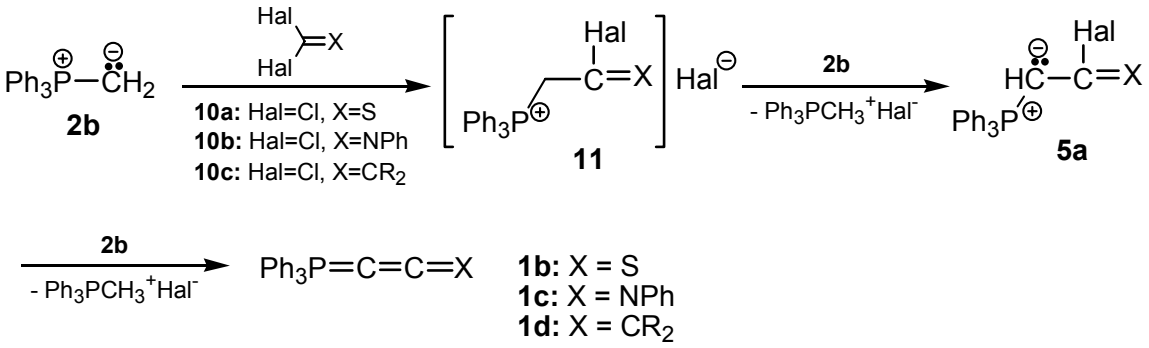
1.3 Synthesis of $Ph_3P{=}C{=}C{=}X$

Keteneylidenetriphenylphosphorane **1a** was first synthesised by *Birum and Matthews* in 1961[11] by the electrophilic addition of CO_2 **8a** to hexaphenylcarbodiphosphorane **7**[12] in diglyme. The thermolytic conditions used, promoted eviction of the triphenylphosphine oxide furnishing ylide **1a**. The thio **1b** and imino **1c** derivatives were also synthesised[6,13] by reacting **8b** and **8c** respectively, with **7**.



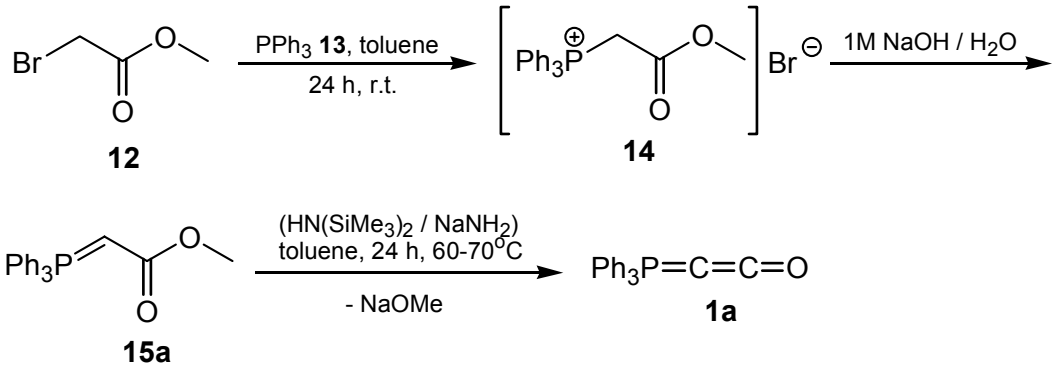
Scheme 2

Some years later, *Bestmann*[14] reacted methylene triphenylphosphorane **2b** with dihalo compounds **10** yielding the corresponding phosphacumulene ylides **1b**, **1c** and **1d**:



Scheme 3

Three equivalents of ylide **2b** were needed: to initially react with dihalo compound **10** forming phosphonium salt **11**, to dehydrohalogenate **11** to ylide **5a** and finally to dehydrohalogenate compound **5a** to generate the corresponding cumulated phosphonium ylide **1**. This method was highly inefficient due to the large excess of starting ylide **2b** needed. An improved synthesis of **1a** is described below:



Scheme 4

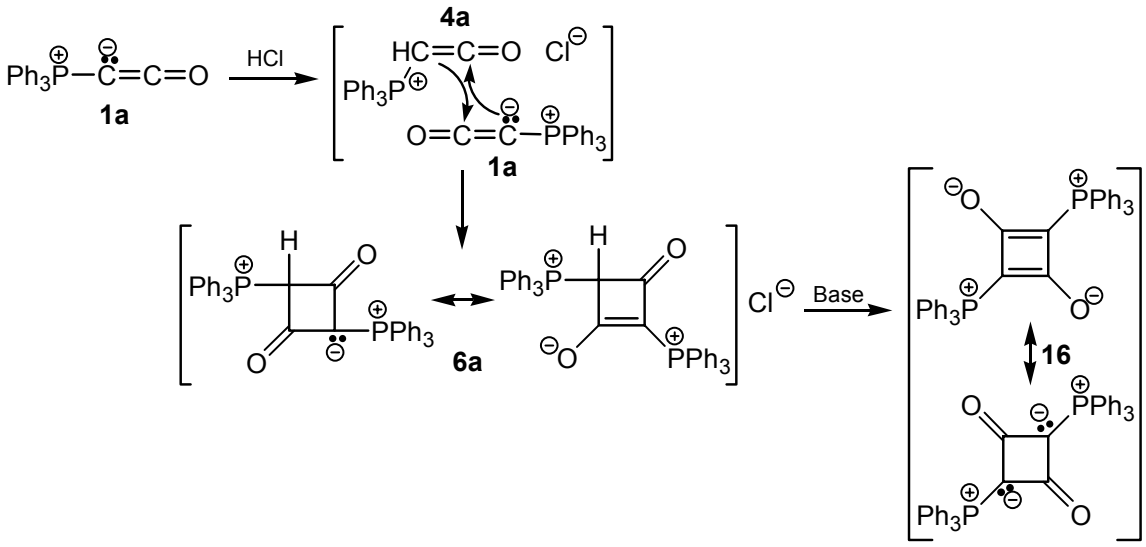
Triphenylphosphane **13** and methyl α-bromo-ethanoate **12** react together to form the air-stable, quartenary phosphonium bromide **14**, which precipitates from the reaction mixture. The precipitate is treated with a 1M sodium hydroxide solution causing dehydrohalogenation to ester ylide **15a**. The ester ylide is treated with $NaN(SiMe_3)_2$ which deprotonates C^{α} and with the elimination of sodium methoxide, keteneylidenetriphenylphosphorane **1a** is produced. $NaN(Si(CH_3)_3)_2$ can be generated *in situ*.

When a catalytic amount of hexamethyldisilazane is added to sodium amide in benzene (or toluene) followed by addition of the ester ylide, the reaction conditions needed are milder and the yields notably improve[15] in comparison to the reaction without $(SiMe_3)_2NH$. The use of molar quantities of both HMDS and $NaNH_2$ was even more effective. Simple filtration of the reaction mixture removes the sodium methoxide by-product, followed by evaporation of the volatile hexamethyldisilazane and ammonia by-products leaving ylide **1a** in solution. This procedure has also been adapted for the synthesis of the analogous compound **1b**[14a,16].

1.4 Reactions of Keteneylidenetriphenylphosphorane

1.4.1 Dimerisation reactions

The dimerisation of neutral phosphacumulene ylides does not occur due to their $\pi^4 \perp \pi^4$-electron system but when protonated at C^{α}, the ylide possesses a $\pi^4 \perp \pi^2$-system enabling it to react immediately with a molecule of **1a**:

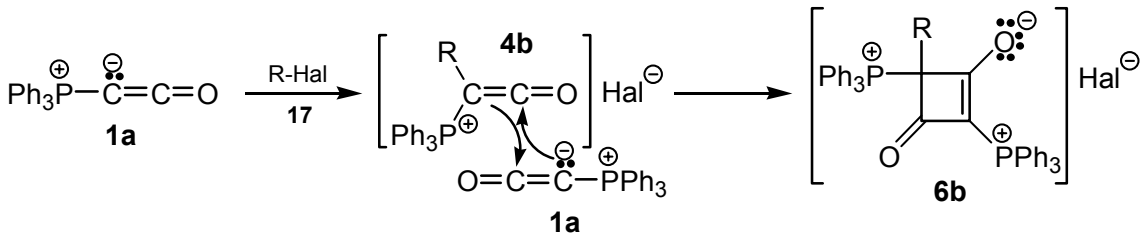


Scheme 5

4a and **1a** react via a [2+2]-cycloaddition reaction to generate carbocycle **6a**, which forms the stable cyclobutadiene **16** on treatment with base such as $NaN(SiMe_3)_2$.

1.4.2 Reactions with Halogen compounds

Phosphacumulene ylides such as **1a** readily react with alkyl halides[17,18] **17** via a nucleophilic substitution reaction to yield highly reactive phosphonium salts **6b**:



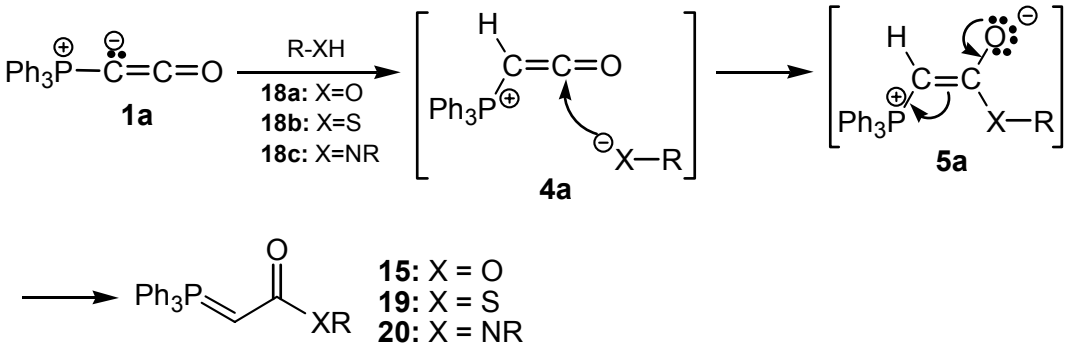
Scheme 6

The $\pi^4 \perp \pi^2$-electron system of **4b** allows an immediate reaction with a molecule of **1a** forming cyclic phosphonium salt **6b**, which ring-opens on treatment with sodium methoxide[18].

1.4.3 Reactions with Acidic compounds

1.4.3.1 Synthesis of Carboxylic acid derivatives

Ylide **1a** reacts with H-X acidic compounds such as alcohols **18a**, thiols **18b** and amines **18c** forming ion pair **4a**, which in turn generates acyl ylides **15, 19** and **20**.

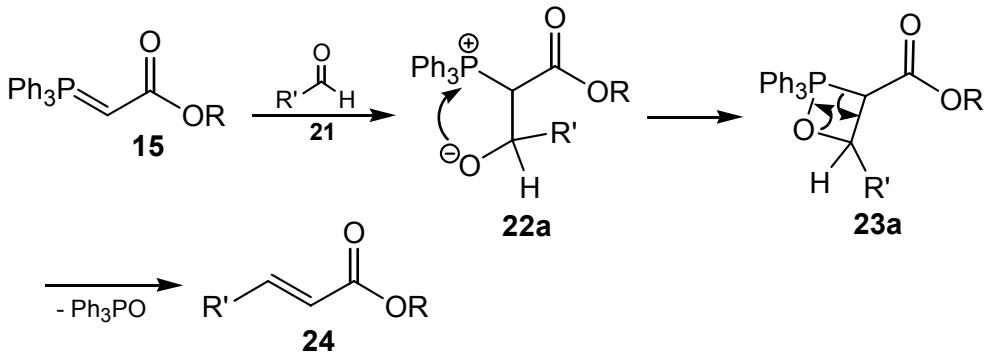


Scheme 7

The activated, protonated ylide does not react with a second equivalent of **1a** because of the higher nucleophilicity of $\mathbf{RX}^-$.

Ylides **1a** and **1c** ($Ph_3PCCNPh$) react readily with alcohols, thiols and acidic N-H compounds, however **1b** (Ph_3PCCS) reacts with thiols and phenols, less rapidly with aliphatic alcohols and not at all with N-H acids[4].

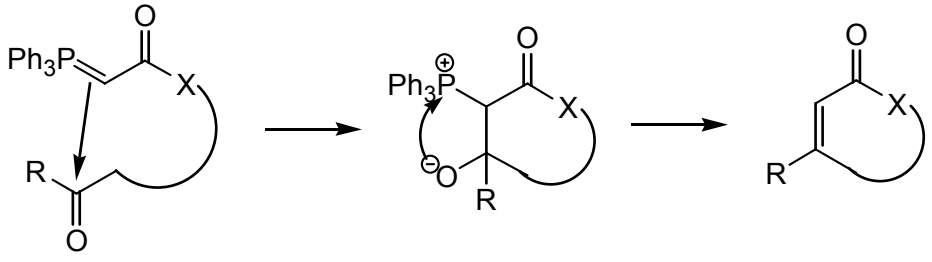
Ester ylides **15** react with aldehydes **21** via a Wittig-olefination reaction yielding α,β-unsaturated esters **24**[4].



Scheme 8

This is a valuable reaction because ester ylides **15** can be subjected to reactions while the alkene function is masked as an ylide and at the end of the synthesis, the phosphorus group is expelled furnishing a new P-free compound.

If the ester ylide and carbonyl functionalities are part of the same molecule, they react via an intramolecular Wittig-olefination resulting in ring closure, and with eviction of triphenylphosphine oxide, a cyclic compound containing a double bond is generated:



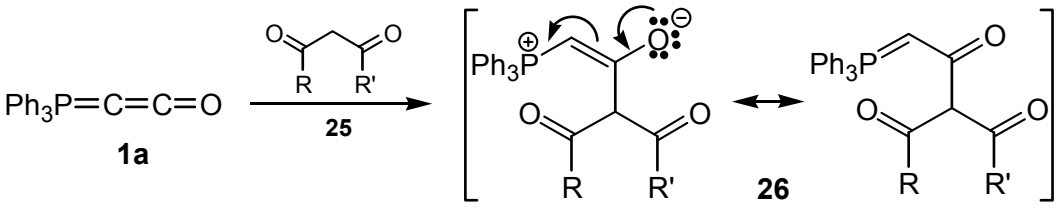
Scheme 9

The addition of amines and alcohols to keteneylidenetriphenylphosphorane **1a**, followed by an intramolecular Wittig reaction (**Scheme 9**) is a particularly useful sequence of reactions in this project as it generates 5-membered oxygen and nitrogen containing heterocycles.

This type of reaction is rather flexible in terms of linkage possibilities between the ylide and carbonyl functionalities, as well as the nature of other functional groups present in the molecule which do not take part in the Wittig reaction. This opens doors for interesting and versatile syntheses of heterocycles of various sizes and containing different heteroatoms.

1.4.3.2 Addition of C-H acids

Keteneylidenetriphenylphosphorane **1a** reacts with compounds of type CH_2RR', where R and R' are electron-withdrawing groups e.g. 1,3-dicarbonyl compounds **25**, generating products such as **26**.



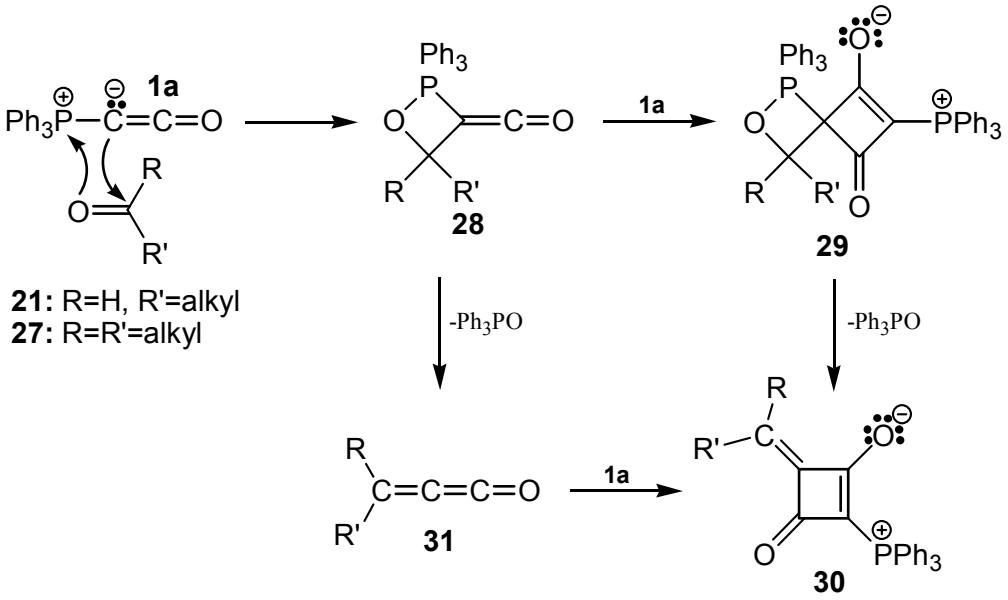
Scheme 10

Due to extensive delocalisation of electrons across 'the former ylide portion' of **26**, it exists as the tautomeric forms shown above and cannot undergo further Wittig reactions[4].

1.4.4 Reaction with Aldehydes and Ketones

Generally, **1a** undergoes addition reactions across its $C^{\alpha}=C^{\beta}$ bond. The only exception is found in its reaction with aldehydes **21** or ketones **27**, where the carbonyl group of the aldehyde/ketone adds across the ylidic P-C^{α} bond of **1a**, as shown in **Scheme 11**[19].

27 adds to **1a** in a [2+2]-cycloaddition reaction, forming the unstable, four-membered cyclic intermediate **28**, which reacts in either of two ways; with a second equivalent of **1a** followed by elimination of Ph_3PO to form **30** or by breaking down, evicting triphenylphosphine oxide and the ketene product reacts with ylide **1a** generating the four-membered carbocycle **30**.

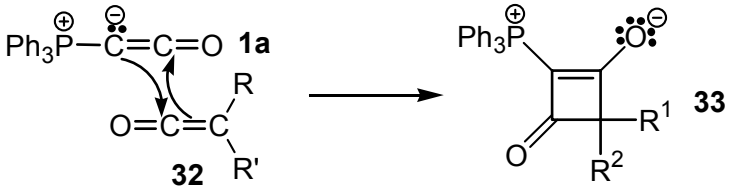


Scheme 11

1.4.5 Cycloaddition reactions to other double bonds

1.4.5.1 Reactions with Ketenes

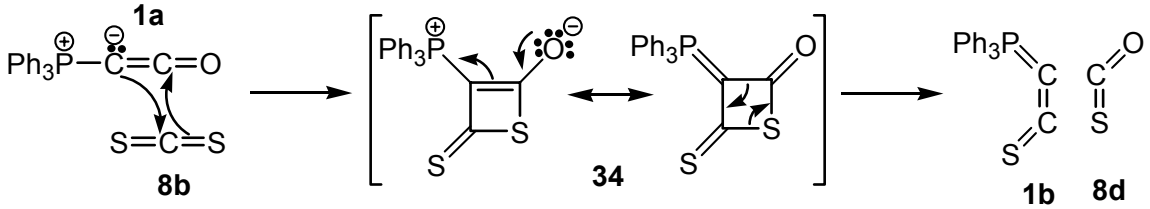
Ketenes **32** add across the $C^{\alpha}=C^{\beta}$ of keteneylidenetriphenylphosphorane **1a** in a [2+2]-cycloaddition fashion to produce 1,3-cyclobutadienones **33**[4]:



Scheme 12

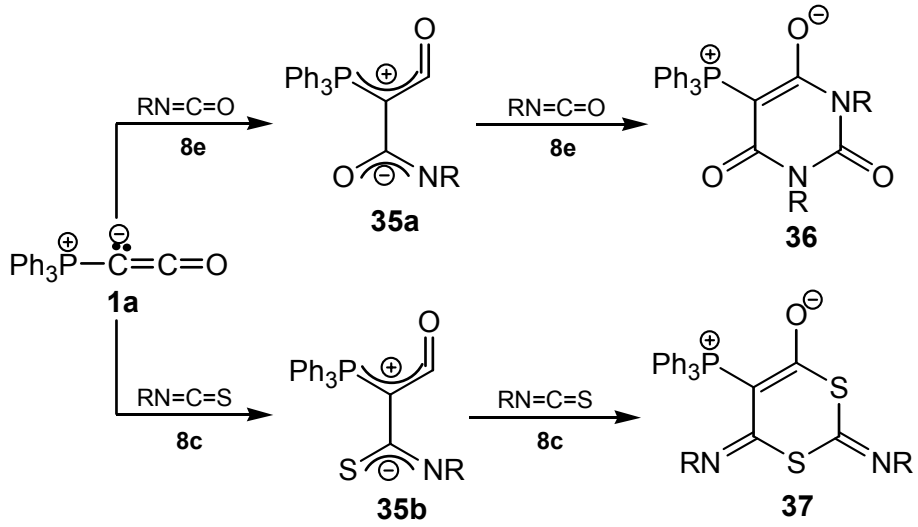
1.4.5.2 Reactions with isocyanates and isothiocyanates

Addition of carbon disulfide **8b** across the $C^{\alpha}=C^{\beta}$ bond of **1a** forms the four-membered heterocycle **34**, which decomposes via a cycloreversion to give thioketeneylidenetriphenylphosphorane **1b** and COS **8d**[20]:



Scheme 13

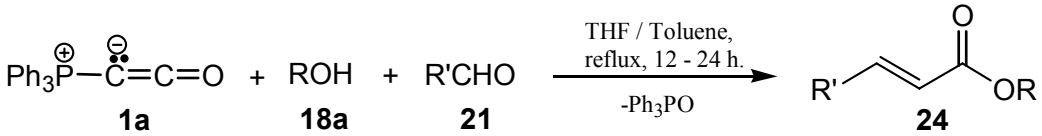
But isocyanate **8e** and ylide **1a** react in a 2:1 molar ratio to generate the neutral, 6-membered heterocyclic phosphorane, barbituric acid derivative **36**[20,21]. Isothiocyanates **8c** also react with keteneylidenetriphenylphosphorane **1a** in a 2:1 molar ratio, but because of the higher nucleophilicity of the sulphur atom (over the nitrogen), the 6-membered dithiane **37** is formed.



Scheme 14

1.4.6 Multi-component reactions

The multi-component reaction is a method of conveniently preparing the backbone of complex organic structures that may be otherwise difficult using conventional multistep syntheses. The three component, 'one-pot' reaction of a cumulated ylide **1a**, an alcohol **18a** and an aldehyde **21** generates α,β-unsaturated esters **24**:



Scheme 15

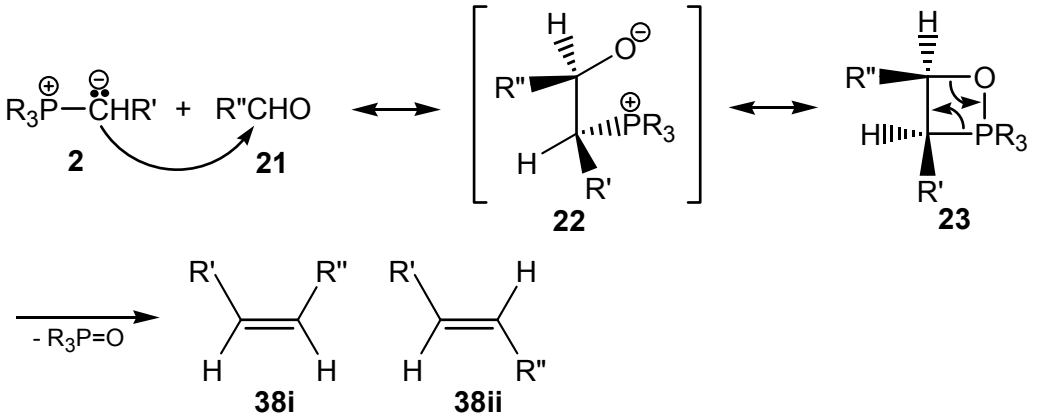
Ylide **1a** deprotonates the alcohol, leaving **RO**$^-$ to react with the carbonyl group of the ketenylidium cation producing an ester ylide intermediate (compound **15**, **Scheme 7**). The aldehyde **21** reacts with this ester ylide via a Wittig olefination reaction* to give the α,β-unsaturated ester **24**. This reaction also works well for the synthesis of the corresponding thioesters and amides[22].

*The mechanism of which is discussed in **Section 1.5**.

1.5 The Wittig Reaction

1.5.1 General

The Wittig reaction, although first discovered in the 1920's by *Staudinger* and students[23,24], was developed and made known by *Georg Wittig* and co-workers[25] in the early 1950's. *Wittig* reacted aldehydes **21** and ketones **27** with phosphorus ylides **2** producing alkenes **38**, with no ambiguity about the position of the double bond:



Scheme 16

The Wittig reaction has become a cornerstone in organic synthesis because it is:

- ✓ regiospecific with respect to the double bond
- ✓ effective using relatively mild reaction conditions
- ✓ often carried out in the presence of other functional groups
- ✓ efficient as a 'one-pot' reaction where the phosphorus group is also removed as the corresponding oxide
- ✓ often stereoselective depending on the nature of the ylide, the carbonyl components and the experimental conditions used.

The discovery of the Wittig reaction[25] prompted the widespread use of triphenylphosphonium ylides (over other ylides) due to the easy accessibility of Ph_3P and the chemoselectivity of deprotonation in the final step of ylide synthesis.

The nature of the carbanion substituents of the ylide has a major influence on the Wittig activity of the ylide. Those ylides with strong carbanion-stabilising groups, e.g. triphenylphosphine cyclopentadieneylide, are of insufficient nucleophilicity to react with aldehydes or ketones[26], while ylides with electron-donating groups such as alkyl or vinyl residues readily react with aldehydes, but more sluggishly with ketones[27,28].

The nature of the carbonyl reactant also affects the feasibility of the Wittig reaction. Clearly the reactivity of the carbonyl group is determined by its electrophilicity, with aldehydes more prone to attack by nucleophiles than ketones. Therefore, almost any variation of aldehyde, even sterically hindered ones, can participate in the Wittig reaction but only certain ketones can be used.

1.5.2. Mechanism of the Wittig Reaction

The Wittig reaction occurs by nucleophilic attack of an ylide carbanion **2** at the carbonyl carbon of an aldehyde **21** (or ketone) to form what was assumed to be 'betaine' **22**. This intermediate cyclises to the unstable oxaphosphetane system (or OPT) **23** and subsequently breaks down to the corresponding olefin **38** and phosphane oxide (see **Scheme 16**). However, there has been much debate whether the betaine or oxaphosphetane intermediates actually exist and if so, how they influence the stereochemical course of the reaction.

In the 1960's, just after the discovery of the Wittig reaction, it was believed that both betaines[25,29] and OPT's[25a] were likely intermediates. Although some 10 years later, more emphasis was placed on the dipolar betaine intermediate due to experimental data attempting to prove its existence[25,30]. Oxaphosphetanes (OPT's) were not considered 'true' intermediates but simply transition states from the betaine 'en route' to the final products. But in the late 70's, betaines were abandoned as likely intermediates because they could not be isolated but only trapped as salts[25,30] and the emphasis was redirected towards OPT's, which were isolatable. The 'betaine' proposal could not justify the stereoselectivity of various Wittig reactions.

Therefore, the general mechanism in **Scheme 16** is not an up-to-date description of the Wittig mechanism, but modern chemists rely more on a proposal put forward by *Vedejs*[31]. This consists of a four-centred transition state, the geometry of which is believed to govern the geometry of the subsequently formed OPT, in turn determining the stereochemistry of the Wittig products.

Non-stabilised, reactive ylides form 'early' transition states with non-planar or 'puckered' geometries and a close to tetrahedral phosphorus, see **39i**. The aldehyde molecule takes up a pseudo-equitorial orientation in relation to the ylide and the alkyl group attached to the ylidic carbon assumes a pseudoaxial position. As a result of this geometry, there is maximum separation between the aldehyde and ylide (both the

phosphorus and C^{α}) substituents. 1,3-interactions dominate in this structure favouring a *cis*-selective reaction; the intermediate is more stable as the *cis*-oxaphosphetane **39i** and the *Z*-alkene product is favoured. Formation of an intermediate with planar geometry **39ii** is not favoured due to severe methyl-alkyl interactions. The *Z*-selectivity of this reaction is reduced by using unbranched aldehydes.

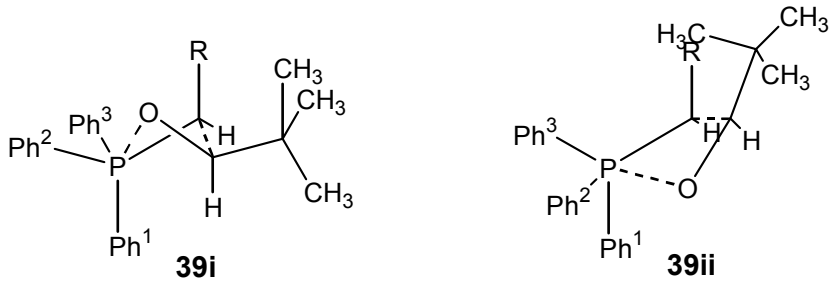


Fig.3 39i: non-planar geometry of *cis*-arranged 'early' transition state
39ii: unfavourable planar *cis* geometry.

On the contrary, stabilised ylides form late, product-like, planar transition states with an almost trigonal bipyramidal phosphorus atom (**39iii**):

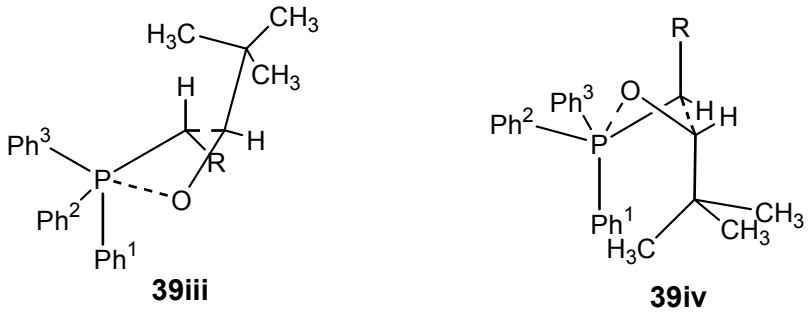


Fig.4 39iii: planar geometry of *E*-arranged 'late' transition state, **39iv:** unfavourable non-planar *trans* geometry.

Here, 1,2-interactions dominate, promoting a *trans*-selective reaction and favouring formation of the *E*-alkene. 1,3-interactions which destabilise **39iii** depend on the aldehyde substituents e.g. an aldehyde bearing an α-hydrogen could orientate itself so the hydrogen points towards the PPh_3 group, reducing these 1,3-interactions and stabilising the structure. The alternative *trans*-selective geometry **39iv** is not favoured due to steric repulsion between Ph^1 and an α-methyl group of the aldehyde.

In conclusion, the 1,2- and 1,3-interactions which greatly influence the *cis*/*trans*-selectivity of the Wittig reaction can be enhanced or reduced by careful choice of both the ylide and aldehyde substituents[30, 32].

Factors affecting the stereochemistry of the Wittig reaction

In general, stabilised ylides[33] such as ester ylides promote a *E*-selective Wittig reaction, semi-stabilised ylides show no preference, while non-stable, reactive ylides[34] e.g. alkyl ylides, favour production of the thermodynamically less stable *Z*-olefins. However, there are exceptions to this rule.

The ylide phosphorus substituents affect the reactivity of the ylide and have little or no influence on the stereochemical outcome of the Wittig reaction. However, replacement of one or more phenyl ligands of a triphenylphosphonium ylide with a 2-methoxy-phenyl group enhances the stereoselectivity of the reaction[35]. Trialkyl phosphorus ylides have also been known to promote high *E*-stereoselectivity[36].

The carbonyl compound used in the Wittig reaction greatly affects the rate of the reaction and can also improve the stereoselectivity of the reaction[37] e.g. non-stabilised ylides react with bulky, aliphatic aldehydes such as $(CH_3)_3CCHO$, exhibiting improved *Z*-alkene stereoselectivity in comparison to less bulky, unbranched aldehydes.

Lithium salts are known to exert a profound effect on the stereochemistry of the Wittig reaction e.g. reactive ylides promote *E*-selectivity in the presence of lithium salts in comparison to the 'normal' *Z*-selectivity[38]. Dilution of the reaction mixture, use of solvents which solvate the lithium cation or other complexation possibilities for the lithium cation e.g. addition of alcohols or crown ethers[39], can significantly reduce this effect.

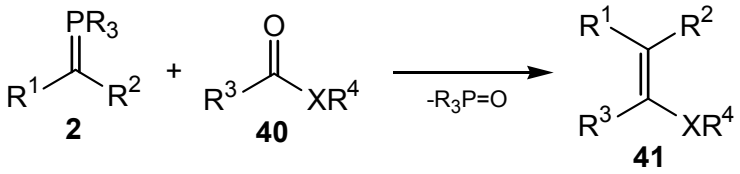
Wittig reactions of unstable ylides, without organolithium bases, produce high ratios of *Z*:*E*-isomer products e.g. the reaction of triphenyl-propylylide and hexanal produced a *Z*:*E* olefin ratio of 96:4 in the presence of $NaN(SiMe_3)_3$ and only a 50:50 ratio when *n*-BuLi was used[40]. Therefore, the preparation of ylides using 'salt-free' methods i.e. the use of a base which is not an organolithium one, are highly beneficial and have attracted much interest.

The choice of solvent used in Wittig reactions can also affect the stereoselectivity of the reaction. The reaction of unstable ylides in aprotic solvents such as THF, are *Z*-selective[30,41], while use of polar aprotic solvents such as DMF, give a 50:50 mixture of the olefinic products[39,42].

In summation, the stereoselectivity of the Wittig reaction may be optimised by careful choice of the ylide, carbonyl compound and reaction conditions.

1.5.3 'Non-classical' Wittig Reactions

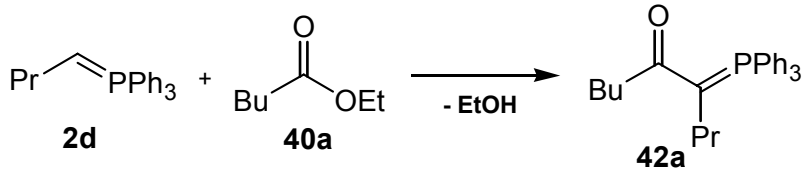
The reaction between a phosphorane **2** and a carboxylate derivative **40** such as a carboxylic ester, an amide etc, generates a heterosubstituted alkene **41** and is known as a 'non-classical' Wittig reaction[43]:



Scheme 17

1.5.3.1 Wittig Reactions with carboxylic esters

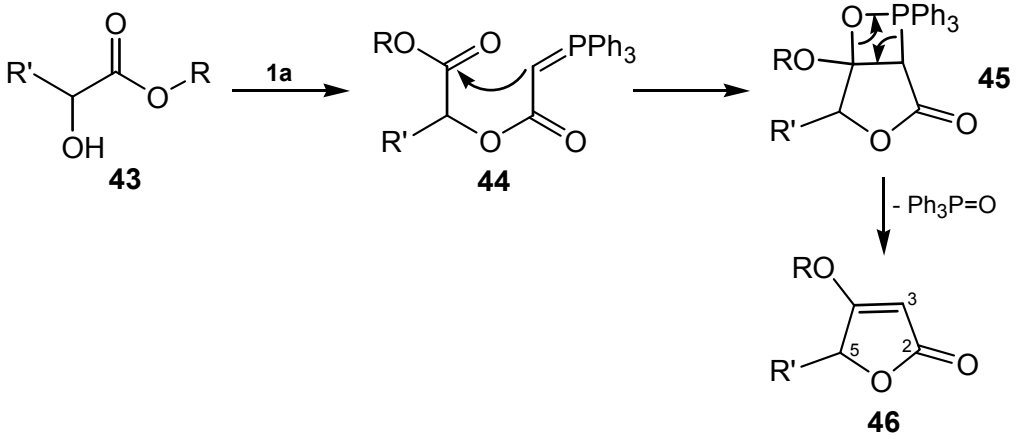
Carboxylic esters and phosphoranes undergo intermolecular or intramolecular Wittig reactions generating acyclic, carbocyclic or heterocyclic products e.g. the reaction of **2d** with a simple ester **40a** yields β-ketophosphorane **42a**[43a,44]:



Scheme 18

But when the propyl residue of **2d** is substituted with a strong electron-withdrawing group, Wittig products i.e. the phosphorus-free alkene and phosphine oxide are produced. However, this concept is not clear-cut. It has been shown that variation of the temperature or the presence of alkali salts can produce a mixture of both the β-ketophosphorane and olefin products[44].

Reaction of keteneylidenetriphenylphosphorane **1a** and α-hydroxy ester **43** generates ester ylide **44**, which undergoes an intramolecular Wittig cyclisation to the corresponding tetronate **46**[45] and phosphane oxide:



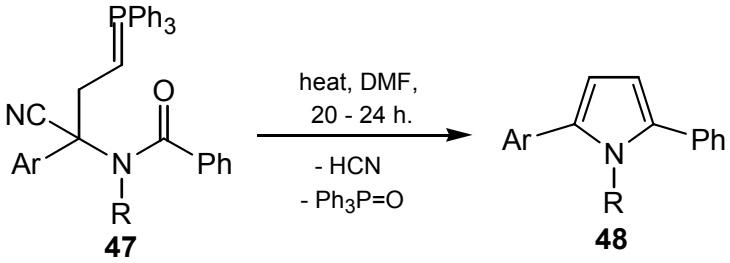
Scheme 19

The reaction described above is generally not stereoselective, although there are some exceptions[45]. This reaction has also been applied to the synthesis of thiotetronates and tetramates[46], benzofurans and chromenes[47], dihydrofurans[48] and bicyclic heterocycles[49].

When R = allyl, a Claisen rearrangement to C-3 of **46** takes place yielding the α,γ-disubstituted tetronic acid[45]. This reaction is temperature dependent.

1.5.3.2 Wittig Reactions with amides

Amides are much less susceptible to nucleophilic attack than esters and only the more reactive ylides can alkenate them, typically in an intramolecular process. Pyrroles **48** were synthesised by an intramolecular Wittig condensation of **47**[43]:

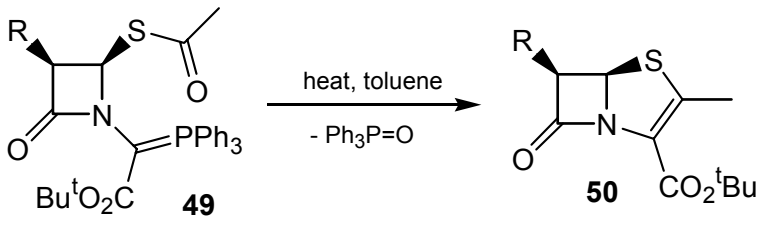


Scheme 20

The cyanide residue adjacent to the amide functionality of **47** influences the conjugation of the nitrogen lone pair across the amide, thus increasing amide reactivity for reaction with the ylide residue. There are no reports of intramolecular Wittig reactions with simple, less substituted amides.

1.5.3.3 Wittig Reactions with thiol esters

The 'non-classical' intermolecular Wittig reaction of thiol esters is of limited use as β-ketophosphoranes are generally formed over the olefinic products[50]. But the intramolecular reaction has attracted some interest, especially in the synthesis of penem and carbapenem antibiotics[51] e.g.:

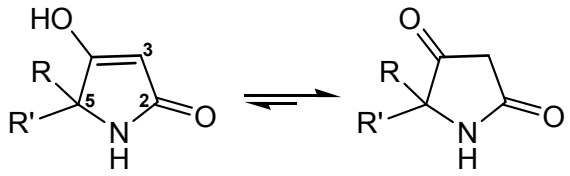


Scheme 21

2. Original work: Tetramic Acids

2.1 Introduction

Tetramic acids possess a common pyrrolidine-2,4-dione nucleus (**Fig.5**) with the possibility of diversity at C-3 and C-5 of the heterocycle. A number of biologically active tetramic acids possess a 3-acyl substituent which contributes to their antibiotic, antiviral and antifungal activity[52,53].



51α **51β**

Fig.5

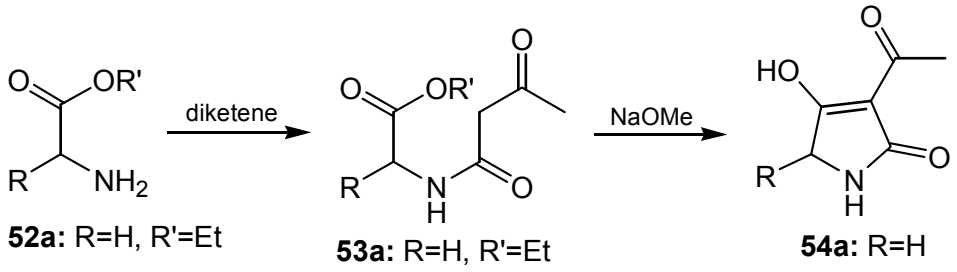
The pyrrolidine-2,4-dione system **51** is a useful intermediate in a total synthesis because of the variety of reactions it can undergo[54]:

- Reactions with electrophiles at C-3 e.g. acyl halides, bromine
- Reactions of organometallic bases such as BuLi at 3-H
- Acylation of 4-OH and possibly 1-H
- Nucleophilic attack at C-4

1-H tetramic acids are generally represented by the keto tautomer pyrrolidine-2,4-dione **51β**, with the corresponding enol variant **51α** present only as the minor isomer[55]. Tetronic acids (4-hydroxy-furan-2-ones) exist mainly as the enol tautomer. When tetronic acid (4-hydroxy-furan-2(5*H*)-one) was first prepared in 1896[56], experimental data proved the major tautomer to be the 3,4-enol form and so it was automatically expected that tetramic acid, due to its similarity in structure, would also exist mainly as the 3,4-enol tautomer. But contrary to this proposal, in 1972 the first synthesis of **51a** (R=R'=H)[55] revealed it to be a much weaker acid than its oxygen analogue and not highly enolised. Experimental data has since backed up this theory and as a result, tetramic acid **51a** is now generally accepted as existing predominantly in the 2,4-diketo form **β**.

In the mid 1950's, *Lacey*[57] synthesised α-acetyl-tetramic acids **54** from N-acetoacetyl amino esters **53** via an intramolecular Claisen condensation reaction

(**Scheme 22**). This method was also applied to the synthesis of 3-polyenoyl tetramic acids[58].

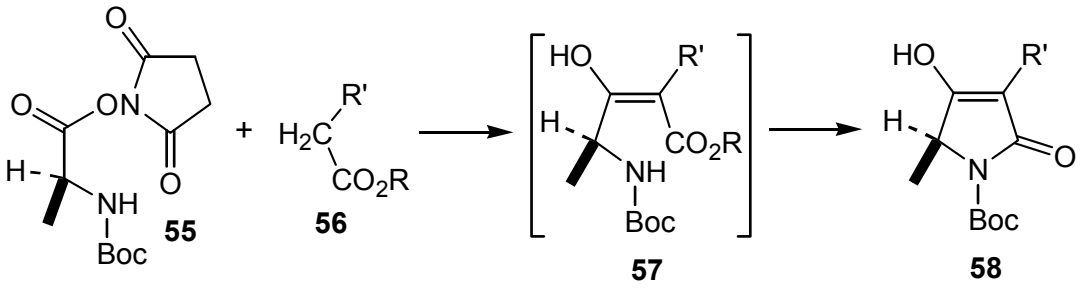


52a: R=H, R'=Et **53a:** R=H, R'=Et **54a:** R=H

Scheme 22

The use of various amino acids as starting materials introduces flexibility at the 5-position of the pyrrolidine ring, but the basic conditions used for ring closure limits the applicability of the reaction with unstable molecules and may induce racemisation at C-5 of an optically pure starting compound. Other syntheses of 3-substituted tetramic acids include:

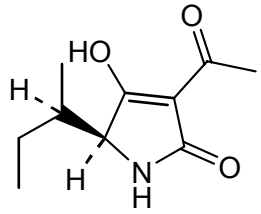
- Reaction of active methylene compounds **56** with N-hydroxysuccinimide esters of N-Boc amino acids **55**, followed by an intramolecular condensation to the corresponding N-alkoxy 3-substituted tetramic acid **58**[59]:



Scheme 23

- Dieckmann cyclisation of N-acyl α-amino esters followed by hydrolysis and subsequent acylation[60].
- Solid-phase synthesis from a resin-bound α-amino acid, which is functionalised to the corresponding amide, followed by a base-induced cyclisation[61].

One of the more simplistic tetramic acids is **Tenuazonic acid**, the structure of which was elucidated by *Stickings*[53] in 1959 as 3-acetyl-5-*sec*-butyl-4-hydroxy-Δ^3-pyrrolin-2-one **54b**:



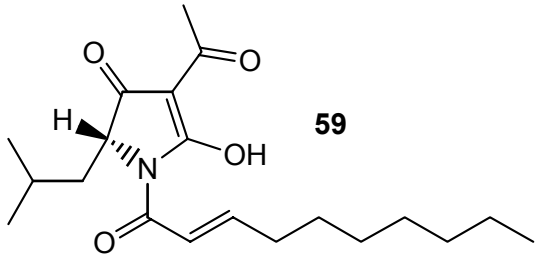
54b

Tenuazonic acid was first isolated in 1957 from culture filtrates of the *Alternaria tenuis* organism by *Rosett et al*[62] and a couple of years later, *Stickings*[53] showed that it was biosynthetically derived from *L*-isoleucine and identified the absolute configuration of the chiral centres to be *5S*,*6S*. Interestingly, the biosynthetic pathway was found to proceed by reaction of 2 equivalents of acetate with *L*-isoleucine via N-acetoacetyl-*L*-isoleucine, rather than ring closure followed by 3-acylation by the second acetate molecule.

Tenuazonic acid **54b** is known to possess a low level of antibacterial activity[63] and has an inhibitory effect on many viruses[64]. It has been shown to inhibit adenocarcinoma growing in the human embryo by inhibiting the incorporation of amino acids into the microsomal protein[65]. The activity of **54b** is believed to result from a combination of the pyrrolidine-2,4-dione ring, the chirality at C-5, the 3-acyl functionality and its ability to form complexes with metal ions[66]. Although, tenuazonic acid **54b** has the potential to be useful in medicine, its toxicity has impeded its clinical application to date.

The aim of the project was to synthesise tenuazonic acid **54b** by using keteneylidenetriphenylphosphorane **1a** in construction of the pyrrolidine-2,4-dione framework. The synthesis should be sufficiently flexible in order to prepare a number of derivatives.

A more complex member of the family of tetramic acids is the N-functionalised **Reutericyclin 59** which is thought to possess a wide range of biological activity including antiulcerative properties, inhibition of tumours and fungicidal activity[67]. But because of its particularly recent isolation and characterisation, the true medicinal potential of reutericyclin **59** has not yet been realised.



59

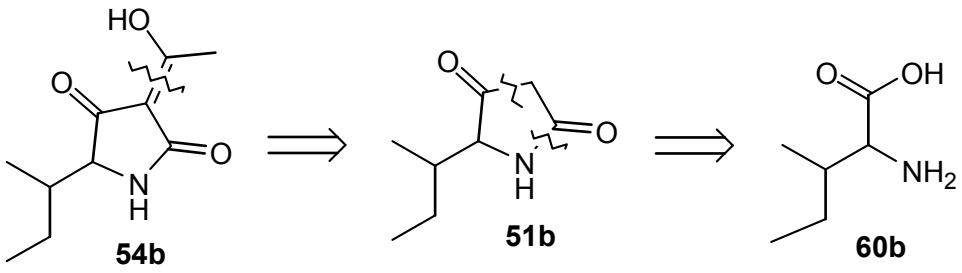
At the end of the 20th century, reutericyclin **59** was isolated from *Lactobacillus reuteri* LTH2854, a strain of lactic acid bacteria present in wheat and rye sourdoughs used in the production of commercial baking aids[68]. It has also been described as a stable constituent of the intestinal microflora of humans and animals[69]. To date, many metabolites originating from meat or milk fermentations have been isolated and characterised, but there is somewhat less data available on compounds such as **59** produced by cereal fermentations. Reutericyclin **59** has been characterised as (*5R*)-3-acyl-1-(dec-2'-enoyl)-2-hydroxy-5-*iso*butyl-Δ^2-pyrroline-4-one by *Jung et al*[70] and the same group successfully prepared **59**[71] by cyclisation of N-acyl amino acids followed by 3-acylation, but poor yields were obtained.

The aim of this part of the project was to develop a general, high yielding synthesis for the preparation of **59**, with the opportunity to vary the substituents at positions 1, 3 and 5 of the heterocycle in order to prepare analogues.

2.2 Synthesis of Tenuazonic Acid

2.2.1 Aim of Project

The aim of this project was to prepare tenuazonic acid **54b** using a short and efficient pathway, incorporating keteneylidenetriphenylphosphorane **1a** as a 'C_2O' source in construction of the tetramic acid core **51**. A short synthesis increases the opportunity to obtain good yields and is generally more economical and less time consuming. This is especially advantageous in large scale syntheses. The individual steps should be flexible towards the introduction of a variety of substituents giving rise to tetramic acid analogues. A retrosynthetic approach to tenuazonic acid **54b** is described below:



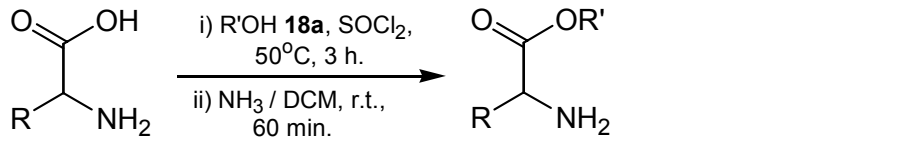
Scheme 24

Reaction of an amino acid with a 'C_2O' source such as keteneylidenetriphenylphosphorane **1a**, builds up the tetramic acid skeleton in a way that a range of amino acids could furnish a variety of 5-substituted pyrrolidine-2,4-diones. The final step should involve a general and simple 3-acylation procedure in order to introduce a number of different acyl groups.

Past research has highlighted the problems associated with this highly polar molecule **54b** and so a synthetic approach was needed in which the polar functionalities are masked until late in the total synthesis[72].

2.2.2 Synthesis of Amino Esters

The first step in the synthesis of **54b** involves the nucleophilic attack of ylide **1a** by the amine group of **60b**. For this to occur exclusively, the acid function of **60b** must be protected to prevent competing reactions. Amino acids **60** were easily esterified using an alcohol **18a** and thionyl chloride[73], followed by treatment with an ammonia solution:



60a: R=Me
60b: R=CH(Me)Et

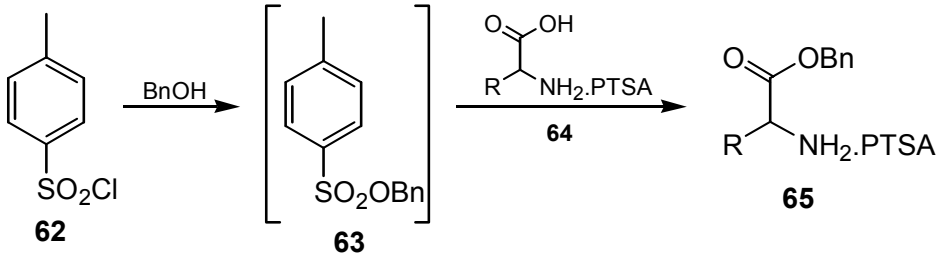
	Individual yields (%)
52b: R=R'=Me	85
52c: R=CH(Me)Et, R'=Et	83

Scheme 25

Good yields of (±)-methyl-2-amino-propanoate **52b** and (*2S*,*3S*)-ethyl-2-amino-3-methyl-pentanoate **52c** were obtained, but the preparation of benzyl protected amino acids was not so productive using this method due to the insolubility of the amino acid in benzyl alcohol, even when heated. The reaction was carried out using an excess of benzyl alcohol as the reaction solvent or stiochiometric amounts of benzyl alcohol with

various solvents (DCM, Et_2O, EtOAc and THF), but neither were successful, even when heat was applied. Therefore, other esterification procedures were investigated.

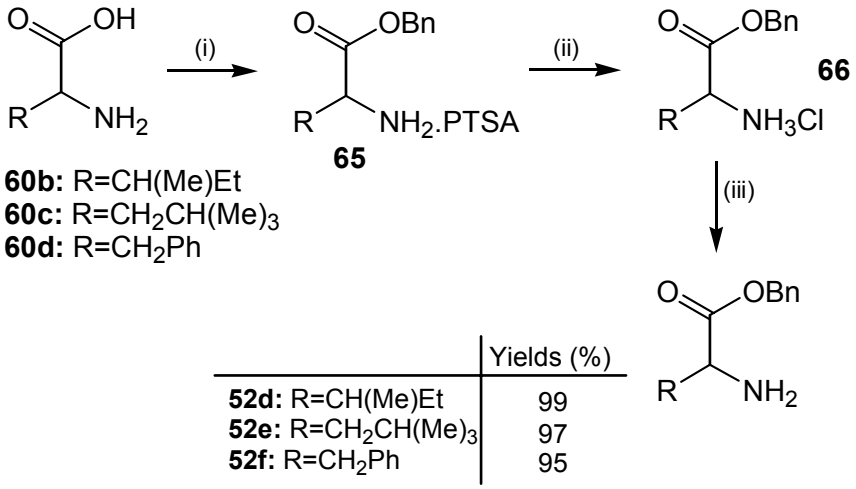
Benzyl esterification was successfully accomplished using *p*-toluenesulfonic acid **61**, *p*-toluenesulfonyl chloride **62** and benzyl alcohol as the reaction medium[74]:



Scheme 26

p-Toluenesulfonyl chloride (PTSCl) **62** and benzyl alcohol form a *p*-toluenesulfonyl ether **63**, while *p*-toluenesulfonic acid (PTSA) **61** protects the amine function of the amino acid. The *p*-toluenesulfonate portion of ether **63** is an exceptionally good leaving group and is easily displaced by the carboxylate of **64**[75] generating benzyl ester salt **65**. This esterification procedure is highly effective because formation of **64**, which has an increased solubility over its amino acid precursor in benzyl alcohol, deals with the solubility problem encountered with other esterification procedures. The *p*-toluenesulfonyl salts **65** were easily purified with excellent yields of 97-99%.

Direct treatment of the *p*-toluenesulfonate (PTS) salts **65** with ammonia to furnish amino esters **52** was not successful with yields of only 9%. A method using a saturated aqueous Na_2CO_3 solution could also have been used but only moderate yields are possible[76]. The PTS-salt **65** was then converted to the corresponding hydrochloride salt **66** which was effectively transformed to 'free' amino esters **52d-f** on treatment with ammonia (**Scheme 27**). The total synthesis of amino esters **52d-f** produced almost quantitative yields and the work-up of the intermediate salts was simple and easily reproducible on a large scale.

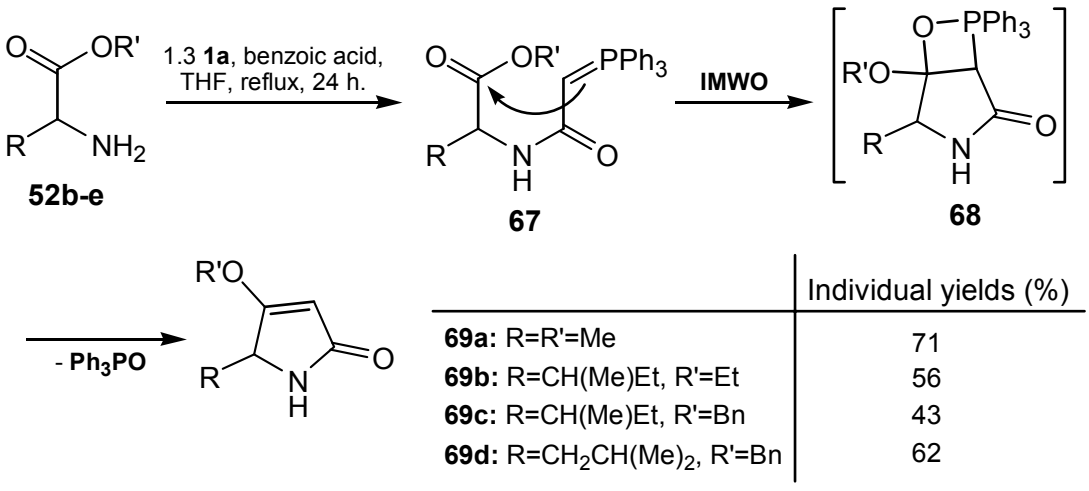


Scheme 27 Reagents and conditions: (i) BnOH, PTSA **61**, PTSCl **62**, 80°C, 2 h. (ii) 2M HCl/Et_2O, $CHCl_3$, 0°C, 30 min. (iii) NH_3/DCM, $CHCl_3$, r.t., 60 min.

Benzyl esters were prepared because the general deprotection of the benzyl group requires relatively mild reagents and conditions in comparison to other ester groups. The benzyl esters were used in construction of the pyrrolidine-2,4-diones, after which the benzyl protecting group must be removed. A mild deprotection step reduces the likelihood of unwanted side-reactions occurring.

2.2.3 Synthesis of Tetramates

Amino esters **52b-e** were reacted with keteneylidenetriphenylphosphorane **1a** to generate pyrrol-2-one derivatives, tetramates **69a-d**:



Scheme 28

This reaction can be referred to as a domino reaction[77] where a) the amine group of **52** adds across the $C^{\alpha}=C^{\beta}$ of **1a** forming acyl ylide **67** and b) the ylide and ester

functionalities of **67** react via an intramolecular Wittig olefination (IMWO) generating an unstable 4-membered oxaphosphetane intermediate **68**, which decomposes to the stable tetramate **69** and triphenylphosphine oxide. Reaction of the amino ester and ylide is initiated by the addition of a catalytic amount of benzoic acid which protonates ylide **1a** at C^{α}, rendering C^{β} more reactive towards nucleophiles, while the intramolecular Wittig reaction is promoted by heating. Both steps occur as part of a 'one-pot' reaction under the conditions shown (**Scheme 28**). Formation of the 5-membered heterocycle was clearly indicated by the disappearance of the ester peak of **52** at around 1740cm^{-1} in the IR spectrum and the appearance of a peak around 1680cm^{-1}, characteristic of tetramates **69**.

Derivatives of *L*-isoleucine **52c** and **52d** reacted with ylide **1a** generating the corresponding tetramates as mixtures of diastereoisomers. Taking advantage of the presence of a second chiral centre at the 5-*sec*-butyl group of **69b** and **69c**, ^{1}H-NMR spectroscopy was used to measure the extent of epimerisation at C-5. The ^{1}H-NMR spectrum of **69b** showed two multiplet signals for 5-H at 4.0 and 4.1 ppm, the integrations for which revealed the diastereoisomeric ratio to be 1:4.25. The presence of two clear singlet signals at 5.35 and 5.39 ppm for N-H further consolidated this ratio.

The ^{1}H-NMR of **69c** (**Fig.6**) shows two clear doublet signals at 4.08 and 4.15 ppm for 5-H of the diastereoisomers, in a 1:1 ratio. This ratio is also supported by the integrations of the two clear signals at 6.48 and 6.57 ppm for N-H.

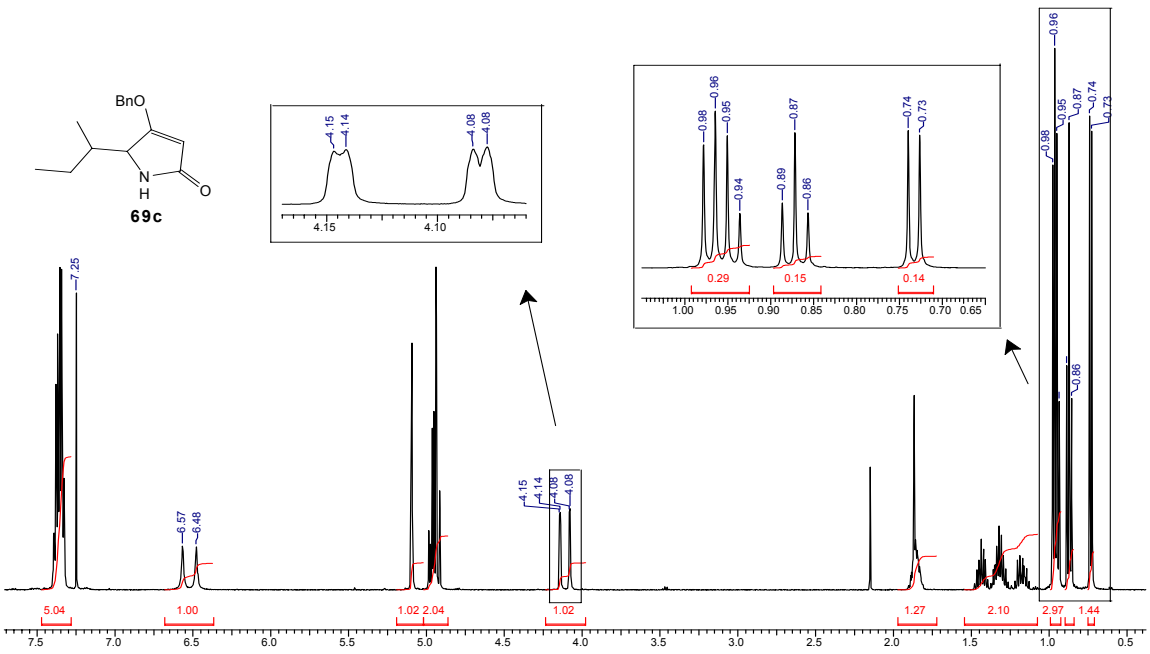


Fig.6 ^{1}H-NMR spectrum of tetramate **69c**

The absence of a second chiral centre in tetramates **69a** and **69d** prevented the detection of racemisation using ^{1}H-NMR spectroscopy.

Problems were encountered in the purification of tetramate **69c** from the triphenylphosphine oxide side product, this is a well-documented setback when dealing with reactions of ylides[78]. When applied to TLC plates, the crude mixture was difficult to separate, even with a variety of solvent systems. Both **69c** and phosphine oxide travelled up the plate together appearing as an inseparable streak (**Fig.7**), even when well diluted.

Solvent system	Tetramate 69c R_f values	Ph_3PO R_f values
1) Et_2O	0.11	0.17
2) EtOAc	0.22	0.64
3) 1:1 Hex, EtOAc	0.08	0.1
4) 1:1 Et_2O, EtOAc	0.35	0.42
5) 1:19 MeOH, EtOAc	0.62	0.68
6) 3:1:1 EtOAc, Et_2O, Hex	0.26	0.28

Table 2 R_f values of **69c** and **Ph_3PO** with a variety of solvent systems

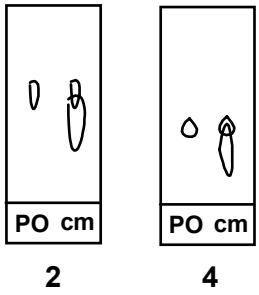


Fig.7 TLC plates for solvent systems 2 and 4 (**Table 2**); PO = pure Ph_3PO, cm = crude **69c** and PO mixture

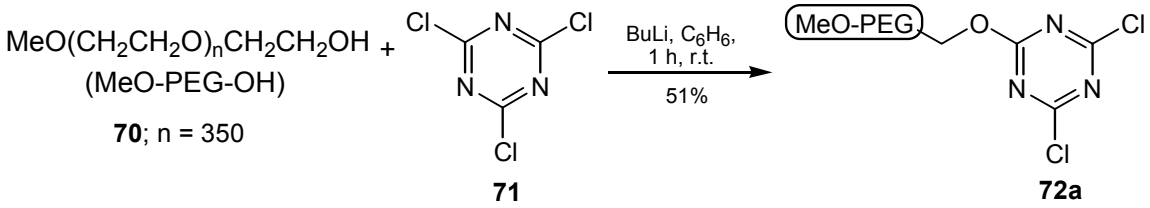
The best separation was achieved with ethyl acetate as the developing solution, but when applied to column chromatography, the phosphine oxide was not completely removed. The size of the glass column, the length of the silica plug and the method of application were all varied, but to no avail. The tetramate-phosphine oxide mixture was also applied to a preparative TLC plate and developed using ethyl acetate, but this failed to remove all of the phosphine oxide**.**

Extraction of either the desired product **69c** or the phosphine oxide was attempted with various solvents, both cold and warm, but separation was not achieved due to the 'sticky' unmanageable consistency of the crude product. However, repetitive washing with a hexane-ethyl acetate mixture, followed by numerous recrystallisations, yielded pure **69c**. Poor yields were obtained using this method of purification and it would not be suitable for larger scale preparations of tetramates.

An 'acid-base' work-up was also tested in the hope that protonation of the tetramate nitrogen of **69c** would allow easy extraction of the phosphine oxide. This was tested using a homogeneous system with various solvents, 2M solution of HCl in Et_2O and a non-aqueous base, but the salt of **69c** did not precipitate out of solution. A heterogeneous system was also tested, but again the consistency of the **69c**-Ph_3PO crude mixture proved problematic. Ph_3PO is soluble in DCM but this solvent could not be used due to the slight solubility of the tetramate ammonium salt.

Hot extraction of the oxide from the crude mixture using a 'soxhlet apparatus' was also considered but the tetramate proved partially soluble in all hot solvents tested.

Attention was then turned to a polymer supported scavenger which is believed to completely remove alcohols, thiols, phosphines and phosphine oxide from reaction mixtures[79,80]. The scavenger is Poly(ethylene glycol) derivative **72a** and is synthesised by the nucleophilic substitution of Poly(ethylene glycol)-monomethylether 350 (PEG-MME 350) **70** on 2,4,6-trichloro[1,3,5]triazine (cyanuric chloride or TCT) **71**. The reaction was carried out in benzene with butyl lithium[80] as the base to activate **70** for reaction:



Scheme 29

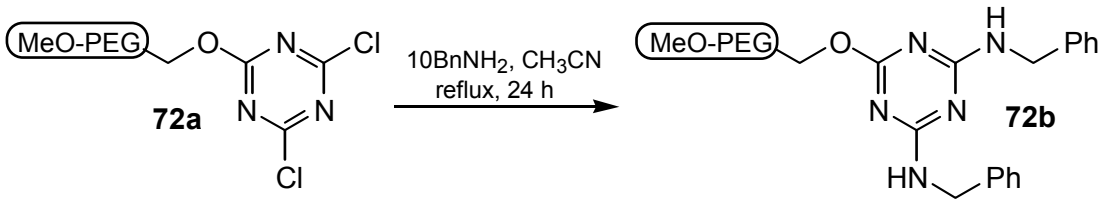
The reaction was also carried out in chloroform in the presence of DIPEA (diisopropylethyl amine or Hünigs base; $(i\text{-Pr})_2NEt$), as described by Taddei and Falchi[79], but was difficult to optimise, even when the quantities of TCT **71** and DIPEA were varied:

Expt. no.	PEG-MME 70 equiv.	TCT 71 equiv.	DIPEA equiv.	Time (h)	Reaction ?
1	1	1	cat.	12	X
2	1	1	cat.	48	X
3	1	5	cat.	24	☺
4	1	5	1	24	X
5	1	5	2	48	X

Table 3 Conditions applied to reaction in **Scheme 29**. All reactions were carried out at r.t. See abbreviations for details.

No more than a 20% yield was achieved using the quantities and conditions in experiment 3. Although, when DIPEA was substituted with butyl lithium[80] and used in approx. equimolar amounts with a large excess of TCT **71** in pre-dried solvents, the reaction was much more successful (51%). It was crucial to the success of the reaction that the solvents used during the reaction and subsequent work-up were pre-distilled over drying agents directly before use and cyanuric chloride **71** was recrystallised a number of times, also directly before use.

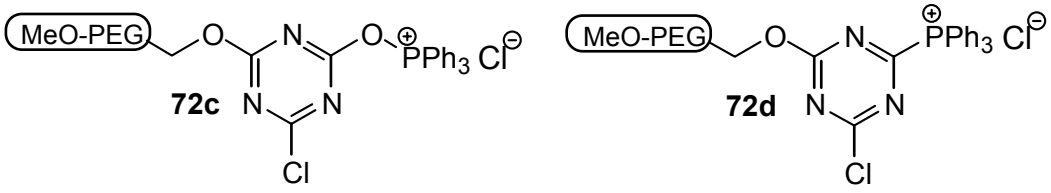
The monosubstitution of PEG-DCT **72a** was only confirmed when derivatised with excess benzylamine, producing the trisubstituted derivative **72b**[79]:



Scheme 30

It was possible to record a ^{1}H-NMR spectrum of **72b** and the relative integrations of the signals for the methylene groups of the benzylamine residues and the terminal methoxy peak revealed a 4:3 ratio, which proved the substitution of only one chlorine atom of **71**.

PEG-DCT **72a** is valuable as a phosphine oxide scavenger because of its solubility, unlike many polymer supports, in many organic solvents such as acetonitrile, benzene and toluene, and it removes nucleophilic reagents or by-products simply by precipitation from the reaction mixture. It is not known how exactly this scavenger system works but it has been suggested that it forms species such as **72c** or **72d**[80]:



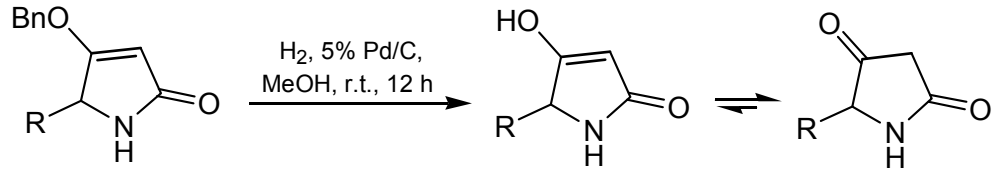
After column chromatography, which removed unreacted ylide **1a** and some phosphine oxide from the tetramate **69c**-Ph_3PO mixture, subsequent treatment with PEG-DCT **72a** removed residual traces of phosphine oxide (monitored by TLC). A simple filtration removed the new phosphine oxide compound, leaving pure **69c** in solution.

This method of tetramate purification was effective when dealing with the removal of small quantities of triphenylphosphine oxide on a preparative scale, but is not suitable for larger scale reactions. Preparation of scavenger **72a** proved costly and laborious to generate due to the quantity of dry solvents needed and the experimental protocol used gave inconsistent results.

It was surprising that the purification of tetramate **69c** proved so tedious, as other similar tetramates were prepared using ylide **1a** and triphenylphosphine oxide was effectively removed using column chromatography.

2.2.4 Synthesis of 3-Acyl Tetramic Acids

4-Benzyloxy-5-substituted-pyrrolidine-2-ones **69c** and **69d** were transformed to 4-hydroxy-pyrrol-2-ones **51b** and **51c** by hydrogenolysis using palladium on charcoal:



69c: R=CH(Me)Et
69d: R=$CH_2CH(Me)_2$

	Individual yields (%)
51b: R=CH(Me)Et	98
51c: R=$CH_2CH(Me)_2$	96

Scheme 31

Excellent yields were obtained and the double bond of the heterocycle remained intact. A methanolic solution of **51c** produced a tautomeric mixture i.e. a combination of 3-enol (**α**) and 2,4-diketo (**β**) tautomers, in a 1:2.3 ratio respectively. While tetramic acid **51b** in *d*-MeOH produced an **α**:**β** ratio of 1:2.8, with each tautomer consisting of a 50:50 mixture of diastereoisomers. The diastereoisomers present are (*5S,1'S*)- and (*5R,1'S*)-4-

hydroxy-5-*sec*-butyl-pyrrol-2(*5H*)-one and (*5S*,*1'S*)- and (*5R*,*1'S*)-5-*sec*-butyl-pyrrolidine-2,4-dione.

The tautomers of **51b** were easily separated due to their differences in solubility; the 2,4-diketo tautomer (**β**) was readily soluble in ethyl acetate while the enol tautomer (**α**) was only sparingly soluble in methanol. The ^{13}C-NMR spectrum of the diketo (**β**) tautomer of **51b** in **Fig.8** clearly shows two signals for each carbon atom which are characteristic of the diastereoisomers present. The further away the carbon atom is from the chiral centres, the closer the signals of the diastereoisomers e.g. the signals for C-2 downfield in the spectrum are relatively close, almost merging as one signal, in comparison to the pair of signals for C-1':

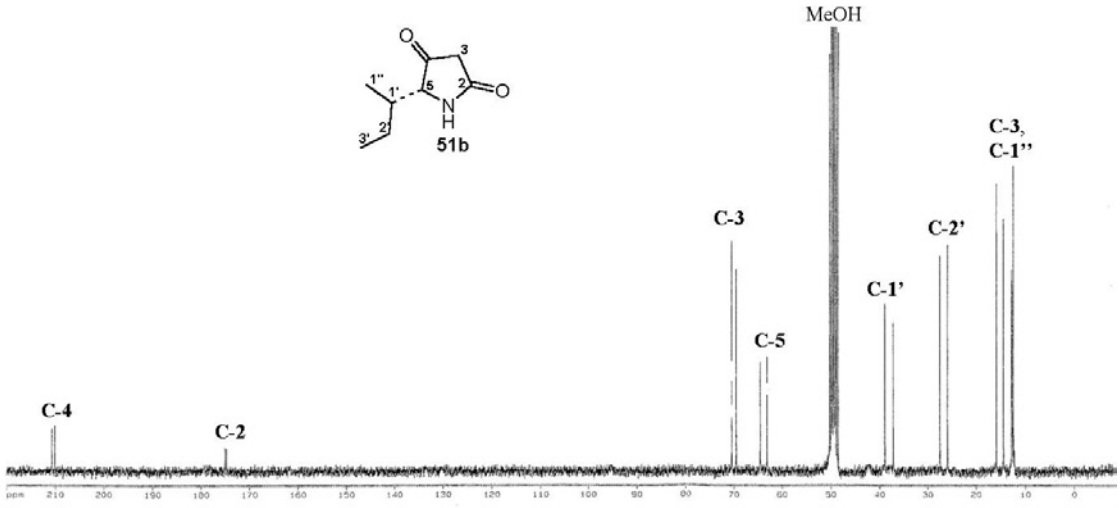


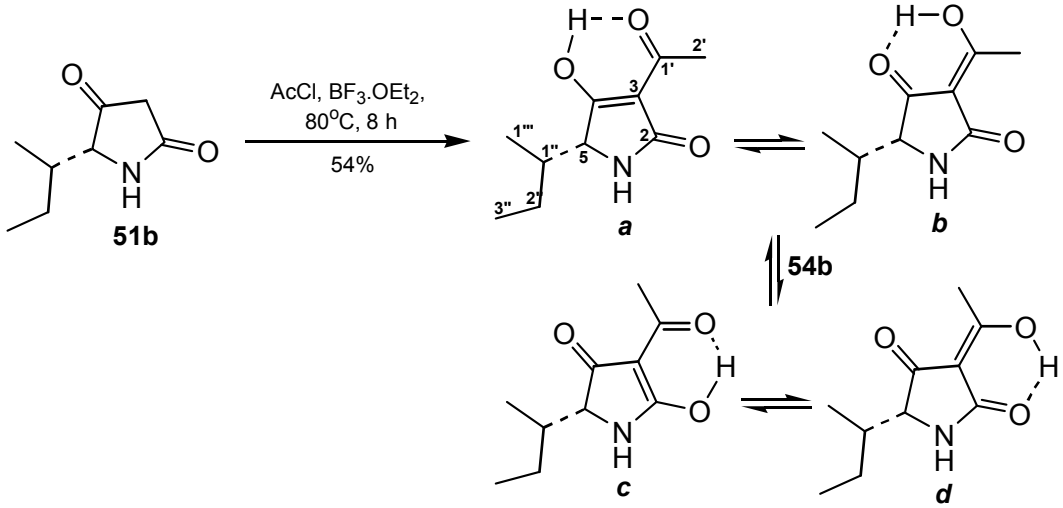
Fig.8 ^{13}C-NMR spectrum of the tautomer mixture of **51b**

The final step of the total synthesis of **54b** involves 3-acylation of **51b**. It was not possible to 3-acylate benzyl tetramate **69c** because the 4-O protecting group 'ties up' the electrons of the 3-double bond, hindering reactivity at the 3-position. Therefore, removal of the protecting group induces keto-enol tautomerisation, rendering C-3 available for reaction with electrophiles.

A number of acylation procedures available involve the use of a strong base, usually BuLi, and the corresponding acyl chloride. This is not suitable for use with tetramic acids such as **51b** because of the possibility of competing reactions at 1-H and 4-OH. If the preparation of **51b** was stereoselective, this acylation procedure would also induce racemisation at position-5 of the heterocycle. Attempts by other groups to acylate pyrrolidine-2,4-diones using these base-mediated procedures led predominantly to

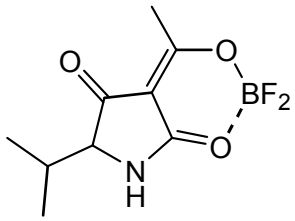
formation of the 4-O acylated product or exceptionally low yields of the desired 3-acyl tetramic acid. Such procedures include the use of various metal enolate derivatives and the corresponding chloride/fluoride[81] or triethylamine and an active ester[82]. Therefore, only acid-mediated acylation procedures were considered here.

Acylation was achieved in reasonable yields (54%) by treating 5-*sec*-butyl-pyrrolidine-2,4-dione **51b** with $BF_3.OEt_2$ and acetyl chloride in the absence of solvent[83], while acylation using titanium tetrachloride in nitrobenzene (50°C, 2.5 h) also generated product **54b** but lower yields (41%) were obtained[60].



Scheme 32

The BF_3-etherate method, a Lewis acid-mediated acylation, generates a neutral boron difluoride complex similar to **73**[83]:



73

73 has been isolated as a neutral compound and characterised[83], but generally an aqueous work-up or immediate treatment with methanol directly generates the 3-acyl tetramic acid.

3-Acetyl-5-*sec*-butyl-pyrrolidine-2,4-dione **54b** possesses a β-tricarbonyl system and exists in several tautomeric forms, namely two pairs of 'internal' tautomers ***a*↔*b*** and ***c*↔*d***, and 'external' tautomers ***ab*↔*cd***. Rapid interconversion occurs between the internal tautomers by an intramolecular proton transfer along the hydrogen bond, while external tautomers interchange much more slowly due to necessary rotation of the C-3 acyl residue[84]. Therefore, on an NMR-timescale, internal tautomers are not detected

separately but as one signal, whereas the comparatively slower external tautomerisation can be measured by NMR spectroscopy with a separate signal for each tautomer pair (***ab*** and ***cd***) and the ***ab***:***cd*** ratio determined.

Proton	δ	Multiplicity	Intensity Ratio	J/Hz
1-H	6.44, 6.25	2 x s	3:1	
5-H	3.76, 3.95	2 x d	2.86:1	3.7, 4.21
2'-H	2.43, 2.48	2 x s	3.55:1	
1"-H	1.9	m		
2"-H	1.23	m		
3"-H, 1'"-H	0.9-1.0	m		
		Average ratio =	3.1:1	

Table 4 ^{1}H-NMR data of **54b** in $CDCl_3$. See **Scheme 32** for numbering key

NB *for simplicity, the chemical shifts and multiplicity patterns quoted in* **Table 4** *are averages of the diastereomers present. For precise values, see P.91.*

The ^{1}H-NMR spectrum of 3-acetyl-5-*sec*-butyl-pyrrolidine-2,4-dione **54b** was recorded in deuteriochloroform and only some protons gave two clear sets of peaks: N-H, 5-H and 2'-H corresponding to the two sets of external tautomers. Comparison of the integrations of these signals revealed an average ratio of 3.1:1, which is largely concentration independent. The more intense peaks are thought to arise from the ***cd*** external tautomer pair while the smaller signals result from the ***ab*** pair i.e. ***ab***:***cd*** 1:3.1. This has been proven in literature[85] and is also based on the fact that diamagnetic anisotropy of the carbonyl groups causes deshielding of the neighbouring protons positioned in the same plane as the double bond and shields protons out of that plane[84,85]. Therefore, the 5-H peak of the ***cd*** tautomers appears higher field (3.76 ppm) in relation to 5-H of the ***ab*** tautomers (3.95 ppm). This significant difference in chemical shift, coupled with the two sets of peaks corresponding to N-H and 2'-H, allows calculation of the ratios of external tautomers from the intensities of the individual peaks.

The individual diastereoisomers were also identified in the ^{1}H-NMR spectrum of **54b** in a 1:1 ratio, from the 1-H and 5-H signals. The peaks corresponding to the diastereoisomers appeared within 0.02 ppm of each other in the spectrum e.g. 5-H of the ***ab*** tautomer pair displayed two doublet signals at 3.94 and 3.96 ppm and so it is safe to assume that these signals do not result from tautomers. Signals arising from the two

external tautomer pairs have a larger separation, see **Table 4**. Comparison of the ^{1}H-NMR spectrum of **54b** with that of the non-acylated precursor **51b** also allows assignment of the peaks corresponding to the diastereomers.

^{13}C-NMR spectroscopy was more advantageous for the study of tautomerisation, as the chemical shift of the carbon atom is hugely dependant on the hybridisation of the carbon atom itself and is hardly affected by the anisotropy of nearby substituents. Again, a $CDCl_3$ solution of **54b** produced a double set of signals for some carbons in the ^{13}C-NMR spectrum:

Carbon	2	3	4	5	1'	2'	1''	2''	3'',1'''
δ	171.2	100.3	194.7*	64.8	184.2*	19.5	36.9	26.6	13.2
	175.0*		194.8*	65.2	188.7	20.3	37.4	27.0	13.4
			199.4	67.1*			37.9		15.9
			199.5	67.6*			38.2		16.3

Table 5 ^{13}C-NMR data of 3-acetyl-5-*sec*-butyl-pyrrolidine-2,4-dione **54b** in $CDCl_3$
* more intense signal for specified carbon atom

The external tautomers, ***ab*** and ***cd***, are clearly represented by two peaks for each of C-2 and C-4. The difference in chemical shifts of the two signals for each carbon atom is attributed to the enol-keto tautomerisation of that carbon atom and hydrogen-bonding with the 3-acetyl residue. Hydrogen-bonded carbonyls are thought to resonate lower field in comparison to the corresponding free carbonyl[84], therefore C-2 of the ***cd*** tautomer pair should resonate at a higher frequency than in ***ab*** while the C-4 signal of ***cd*** should occur higher field than ***ab***.

Four signals are observed for C-4, C-5 and C-1''' which correspond to the diastereoisomers present; two diastereomers for each external tautomer pair. Assignment of the diastereoisomers and tautomers was based on theory outlined above, comparisons with ^{1}H-NMR and ^{13}C-NMR spectra of the non-acylated precursor **51b** and experimental data from previous research in this area[85]. It was deduced that the more intense peaks in the ^{13}C-NMR spectrum (*, **Table 5**) of **54b** result from the ***cd*** tautomeric forms.

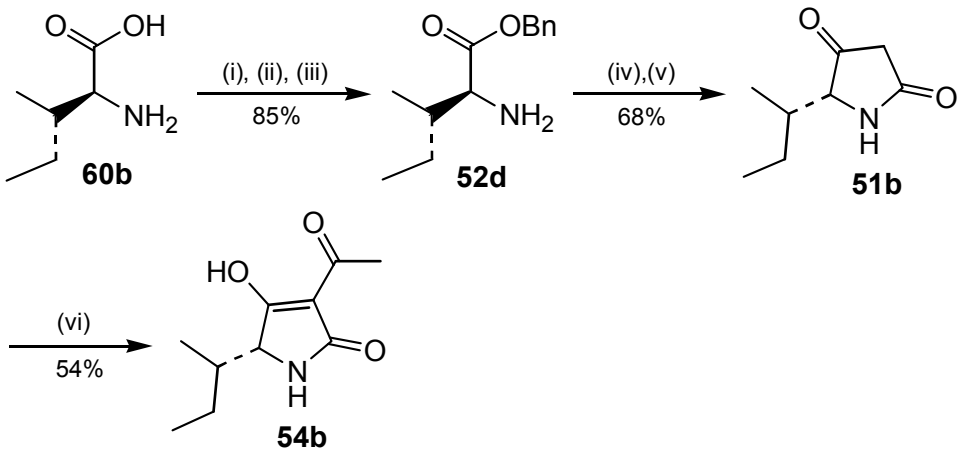
Carbon	δ *ab*^{lit}	δ *cd*^{lit}	δ^{expt}
2	169.9	175.6	175.0
3	105.7	102.5	100.3
4	201.0	195.5	194.8
1'	188.4	184.0	184.2

Table 6 Lit.[85] and current experimental values for the ^{13}C-NMR chemical shifts of **54b** in a $CHCl_3$ solution

Enolic carbon atoms resonate at a lower frequency than their keto carbon counterparts[84], therefore from the more intense, lower frequency signal for an enolic C-1' atom and with the predominance of the higher frequency, hydrogen-bonded C-2 (**Table 6**), it appears that, with respect to **54b**, tautomer ***d*** is the main tautomeric form. *Steyn and Wessels*[85] have supported this theory with the X-ray crystallographic structure determination.

The predominance of the ***d*** tautomer of **54b** over its geometric isomer ***b*** and internal isomer ***c*** is due to the greater ability of the C-2 carbonyl, over the 4-oxo function, to form an intramolecular hydrogen bond with the 3-acetyl residue. Nitrogen, as part of an amide structure, donates electrons to the C-2 carbonyl moiety, thereby enhancing its proton accepting ability. Research has shown that when the nitrogen atom is acylated, the major external tautomer pair is ***ab*** because the nitrogen lone pair can no longer enhance the proton-accepting ability of the C-2 carbonyl, which in turn increases the possibility of hydrogen-bonding at C-4[86].

In conclusion, the total synthesis of 3-acetyl-4-hydroxy-5-*s*-butyl-pyrrol-2(5*H*)-one **54b** was established with few intermediate steps and reasonable yields. The versatility of the individual steps introduces flexibility to the synthesis, enabling a number of amino acids to be used as starting materials, generating a range of tetramic acids. These intermediate compounds are further functionalised by a simple 3-acylation.



Scheme 33 Total synthesis of **54b**: Reagents and conditions (i) BnOH, PTSA **61**, PTSCl **62**, 80°C, 2 h. (ii) 2M HCl in Et_2O, $CHCl_3$, 0°C, 30 min. (iii) NH_3/DCM, $CHCl_3$, r.t., 60 min. (iv) 1.3 **1a**, benzoic acid, THF, reflux, 24 h. (v) H_2, 5% Pd/C, MeOH, r.t., 12 h. (vi) AcCl, $BF_3{\cdot}OEt_2$, 80°C, 8 h.

Further work:

- Investigation of inorganic reagents to complex phosphine oxide, aiding its removal from crude tetramate mixtures.
- Synthesis of derivatives of **54b** with a range of substituents at C-5 and C-3.

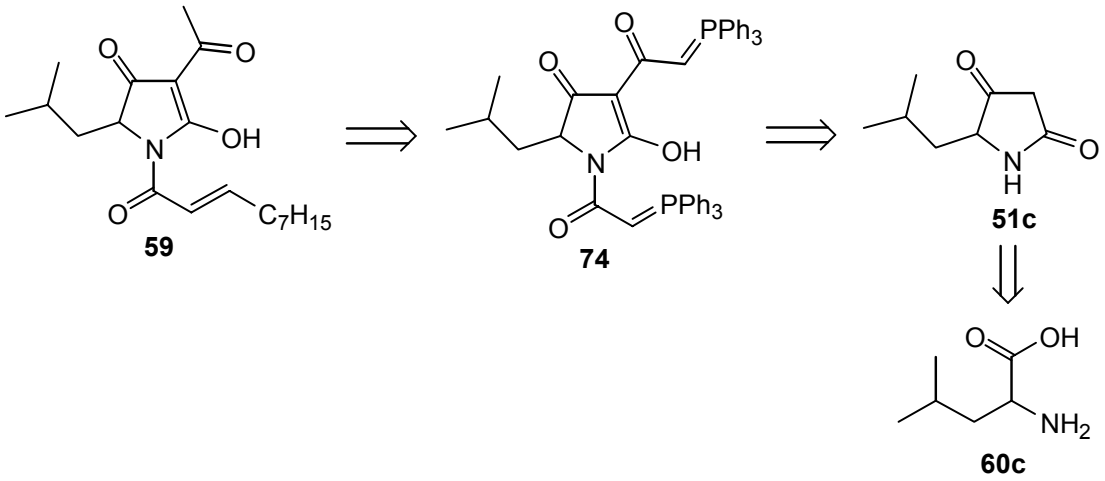
2.3 Synthesis of Reutericyclin

2.3.1 Aim of project

The aim of this part of the project was to synthesise the novel tetramic acid derivative **Reutericyclin 59**[67,70] adapting the knowledge gained from development of the synthesis of tenuazonic acid **54b**. The total synthesis of **59** must contain individual steps which are flexible with regard to the substituents at N-1, C-3 and C-5 of the pyrrolidine-2,4-dione nucleus, allowing the preparation of analogues. The synthesis was also designed to incorporate keteneylidenetriphenylphosphorane **1a** as the 'C_2O' source in construction of the nitrogen heterocycle.

2.3.2 Attempted synthesis 1 of reutericyclin

The first retrosynthetic approach to reutericyclin **59** involves formation of the 5-alkyl nitrogen heterocycle followed by further functionalisation at the 1- and 3-positions:

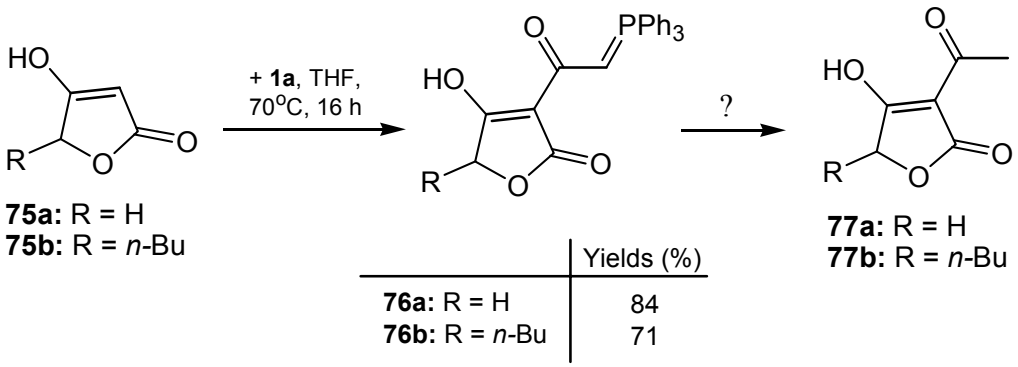


Scheme 34

Multiple use of ylide **1a** should facilitate in the construction of pyrrolidine-2,4-dione nucleus **51c** and act as an acylating agent to introduce two new acyl groups to it. The latter use of the ylide relies on an adequately reactive nitrogen within **51c** and expected differences in the reactivity of both the 1- and 3-acylylidene functions of **74**. The 3-acylidene function of **74** should be non-Wittig active permitting selective olefination of the amide ylide. A mild saponification procedure should liberate the phosphane oxide from the 3-acylylidene moiety of **74**, generating **59**.

5-*iso*-Butyl-pyrrolidine-2,4-dione **51c** was prepared using the procedure described in **Scheme 33** from leucine benzylester **52e** and keteneylidenetriphenylphosphorane **1a**, followed by a simple hydrogenation.

Before the preparation of **74** was attempted, new methods to liberate Ph_3PO from 3-acylylidene tetramic or tetronic acids (4-hydroxy-furan-2-ones) were tested. This general reaction has been attempted before within our research group but did meet with success. The test experiments were carried out using the readily available tetronic acid 4-hydroxy-furan-2-one **75a**, which reacted with ylide **1a** generating **76a**[87]:



Scheme 35

The 3-acylylidene-5-*n*-butyl tetronic acid **76b** was also prepared using this method. The progress of this reaction was monitored using IR-spectroscopy; disappearance of a peak at 2100cm-1 characteristic of the cumulated ylide **1a** at 2100cm^{-1} and appearance of a peak around 1730cm^{-1} for the 3-acylylidene products **76**.

The ^{1}H- and ^{13}C-NMR spectra of both **76a** and **76b** contained more signals than expected due to the presence of two species of the same compound; an ylide species **α** and a phosphonium-betaine compound **β** (**Fig.9**). Past research in this area has highlighted the spectroscopic differences between both forms[88].

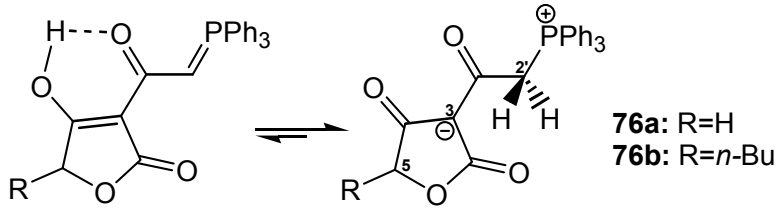
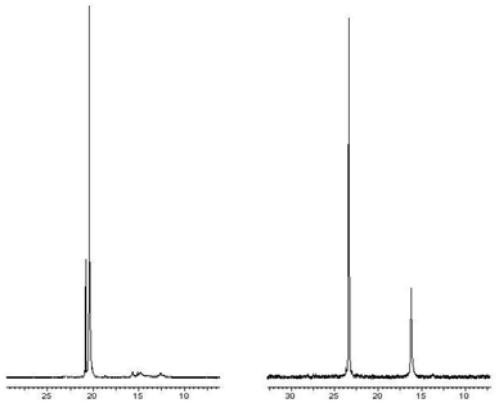


Fig.9

A $CDCl_3$ solution of **76a** produced peaks in the ^{1}H-NMR spectrum which are characteristic of both the **α** and **β** species, with two singlet signals for 5-H and two distinct signals for 2'-H (a singlet signal and a doublet peak displaying P-H coupling). Peaks typical of the phosphonium-betaine compound **β** were found in the ^{13}C-NMR spectrum and signals attributable to C-5 and C-2' of species **α** were also present. The ^{31}P-NMR spectrum of **76a** in $CDCl_3$ confirmed the presence of the **α** and **β** forms of **76a**, with a signal for the **α** compound at 16.0 ppm and a signal for the **β** isomer arising at 23.2 ppm. A more concentrated $CDCl_3$ solution of **76a** produced an additional signal for phosphonium-betaine **β** at 22.21ppm, but this was only a minor signal (3.2% of the total signals detected).

A ^{31}P-NMR experiment of **76a** in d^{6}-DMSO revealed two signals for isomer **β** around 20 ppm and a negligible signal for isomer **α**:



(i) **(ii)**

Fig.10 ^{31}P-NMR spectra of **76a** in i) DMSO and ii) $CDCl_3$

The two peaks for phosphonium-betaine **β** in **Fig.10(i)** are thought to arise from two possible tautomers, where 2'-H forms an intramolecular hydrogen-bond with either of the C-2 or C-4 carbonyl groups of the tetronic acid nucleus[88]. Similar trends were observed for the 3-acylylidene-5-*n*-butyl tetronic acid **76b**.

With the successful preparation of **76a** and **76b**, a method for the cleavage of the triphenylphosphine group was needed in order to liberate the 'free' 3-acetyl tetronic acid **77**. A simple hydrolysis should oxidise the triphenylphosphine group to triphenylphosphine oxide but the conditions must be mild enough to prevent ring-opening of the furan-2-one ring.

A number of relatively mild reaction conditions were tested; stirring in methanol, the use of a range of concentrations of aqueous $NaHCO_3$ solution with a variation in temperature, but cleavage of the triphenylphosphine group could not be achieved. Only, the starting **76a** was detected in the reaction mixture.

Experiment	Solvent system	Temp. (^{o}C)	T (h)	Reaction?
1	MeOH	r.t.	12	X
2	"	90	12	X
3	THF / $NaHCO_3$ / H_2O	r.t.	12	X
4	"	30	12	X
5	"	60	48	X
6	"	90 - 100	12	X
7	THF / NaOH / H_2O	r.t	2	84% yield

Table 7 Conditions for hydrolysis of **76a** to **77a** (**Scheme 35**); range of aqueous NaOH and $NaHCO_3$ solutions were used, from 0.01M – 2M.

Finally, 2M aqueous NaOH solution was added dropwise to **76a** in THF at room temperature and the 3-acyl tetronic acid **77a** was formed with ease within a 2 h period. The triphenylphosphine oxide was effortlessly removed from the dried crude products by washing with methylene chloride. This method was also gentle enough to prevent cleavage of the oxygen heterocycle. **77b** was also prepared using this procedure.

3-Acyl-4-hydroxy-furan-2-one **77a** exists as a mixture of four tautomeric forms:

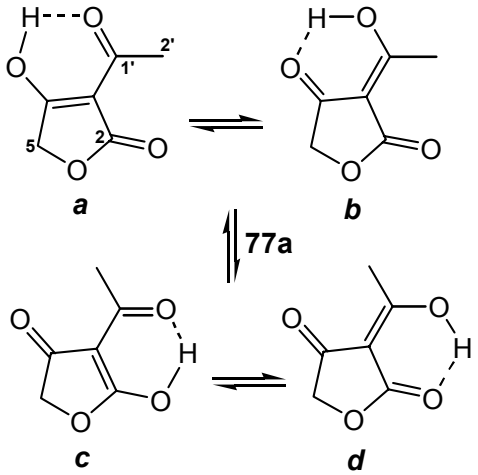


Fig. 11

As is the case for 3-acetyl tetramic acid **54b**, the equilibria between the internal tautomer forms (***a*↔*b*** and ***c*↔*d***) of **77a** are fast while the equilibria between the external tautomer species (***a*,*b*↔*c*,*d***) are relatively slow, allowing the latter to be detected on an NMR timescale. The ^{1}H-NMR of **77a** clearly illustrates this (**Fig.12**); the 5-H signal for each external tautomer pair shows the most visible separation with a clear indication of the ***ab*:*cd*** ratio. The 5-H next to the 4-carbonyl function e.g. tautomer form ***d***, resonates at a

higher field than the corresponding proton next to a double bond[89] (internal tautomer ***a***). Using this principle, the signal at 4.51 ppm was attributed to the ***cd*** tautomers while the singlet signal at 4.62 ppm was assigned to the ***ab*** external tautomer pair, in a ***ab***:***cd*** ratio of 1.61:1. The separation of the two peaks for 2'-H of **77a** was not as apparent but the aforementioned ratio was also found.

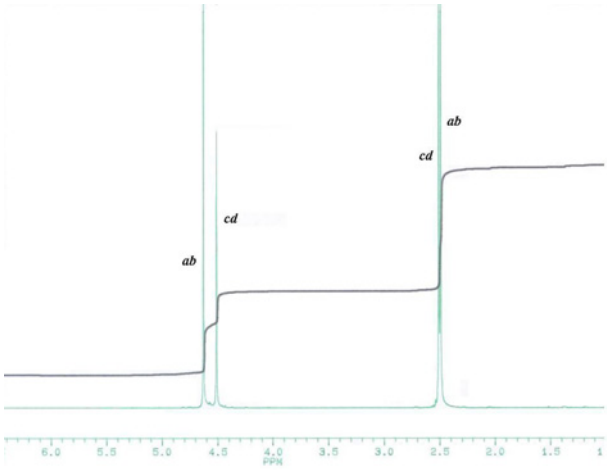


Fig.12 ^{1}H-NMR spectrum of a $CDCl_3$ solution of **77a**

Both external tautomer pairs of **77a** were also evident in the ^{13}C-NMR spectrum, with a clear separation of the peaks. The more intense signals are attributed to the major ***ab*** tautomer pair:

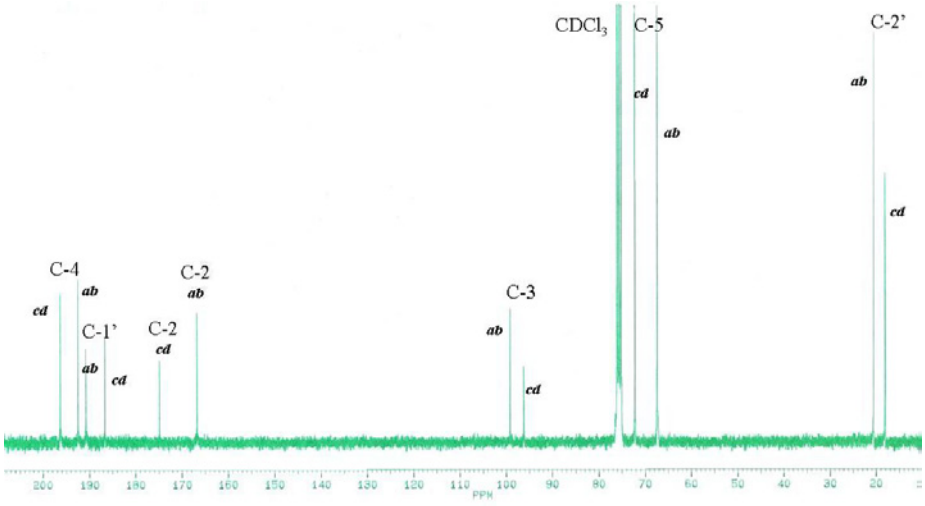


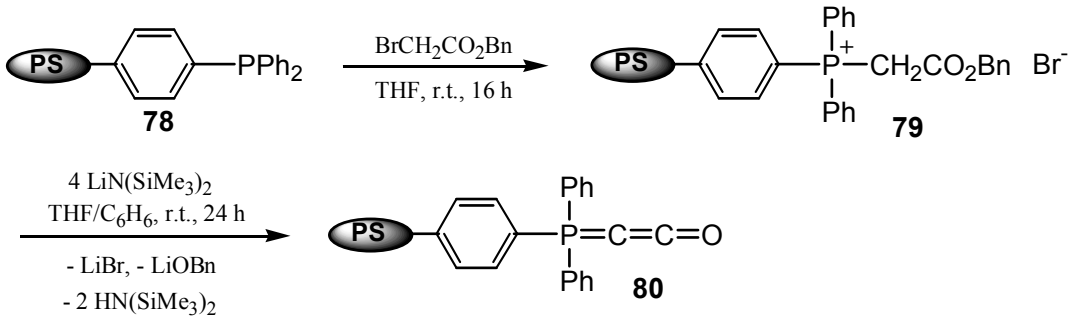
Fig.13 ^{13}C-NMR spectrum of a $CDCl_3$ solution of **77a**; see **Fig.11** for numbering key.

3-Acetyl-4-hydroxy-5-*n*-butyl-furan-2(5*H*)-one **77b** produced a similar trend to **77a** with a ***ab:cd*** ratio of 1.7:1.

The most striking difference between 3-acyl tetramic acids and 3-acyl tetronic acids is the position of equilibria between their external tautomers. The equilibria of the

tautomeric forms of **54b** were shifted towards the ***cd*** species, while the ***ab*** external tautomer pair of **77a** is predominant. It is likely that the decreased electron donating ability of the ring oxygen of furanones (in comparison to the nitrogen atom of pyrrol-2-ones) promotes hydrogen-bonding at the 4-carbonyl function by reducing the likelihood of hydrogen-bonding at the C-2 functionality.

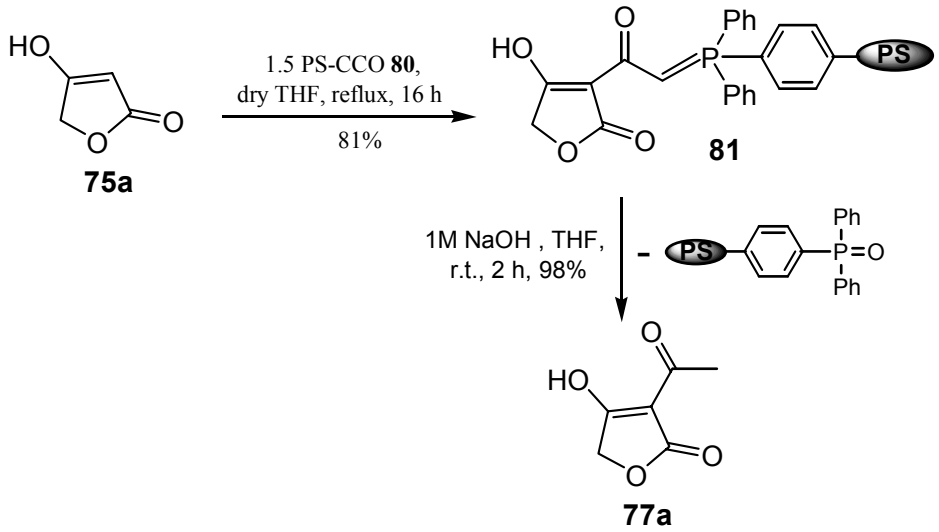
The acylation procedure with keteneylidenetriphenylphosphorane **1a** was also carried out using its polymer-supported (PS) variant **80**[90]. The polystyrene bound cumulated ylide **80** was prepared by alkylating resin-bound triphenylphosphine **78** with benzyl bromoacetate forming **79**, followed by treatment with lithium bis(trimethylsilyl)amide[90]:



Scheme 36 **PS** = polystyrene support of 100-200 mesh

The immobilised compounds described above were stirred in the reaction solvent for 10 - 15 min before addition of the remaining reagents, to allow swelling of the resin. This improves the overall yield of the reaction.

Immobilised ylide **80** reacted with **75a** in the same manner as Ph_3PCCO **1a**, at the 3-position of the furanone ring, generating **81**:



Scheme 37

An IR spectrum of the solid-supported compound **81** showed total disappearance of a peak at 2100cm^{-1} typical of **80**.

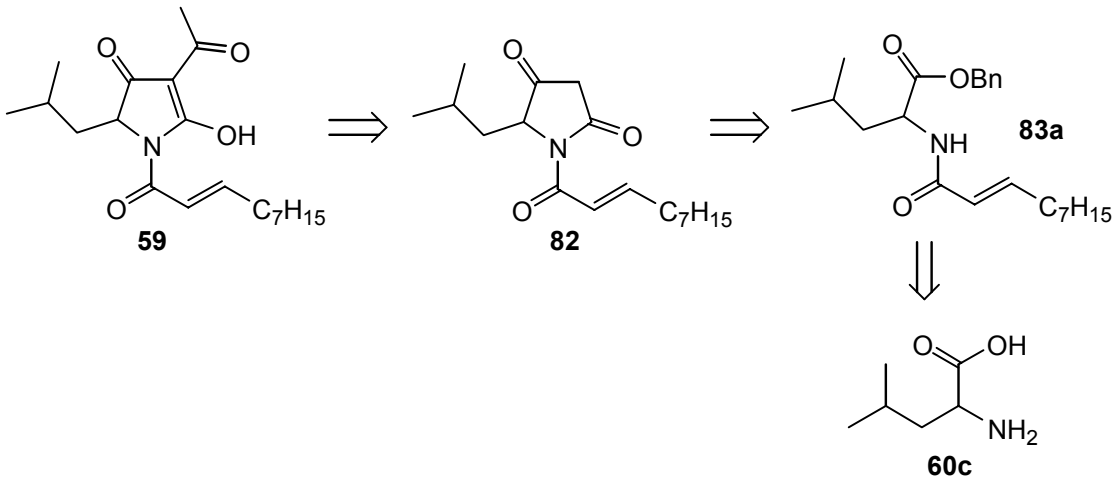
Hydrolysis of the 3-acylylidene portion of **81** was carried out by treatment with an excess of a 1M aqueous solution of NaOH at r.t. The resin-bound triphenylphosphine oxide was completely removed from the reaction mixture by filtration.

The acylation of tetronic acids using the cumulated ylide **1a** and the immobilised cumulated ylide **80** as acylating agents is a new, effective and highly efficient procedure which can be easily applied to larger scale reactions. The only drawback of this method of acylation is it's limitation to the addition of the acetyl residue, reducing the general flexibility of the total synthesis of **59** towards the preparation of analogues.

This acylation procedure was only deemed successful at the end of this project and was not used in the synthesis of reutericyclin **59**. Meanwhile another route towards the preparation of **59** was attempted.

2.3.3 Attempted synthesis 2 of reutericyclin

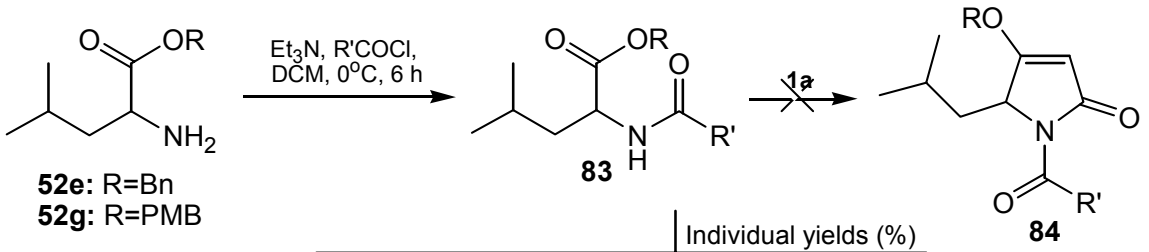
The second retrosynthetic approach to reutericyclin **59** involves N-functionalisation of a leucine ester, followed by ring closure to tetramic acid **82**:



Scheme 38

The ring closing step is expected to take place by the reaction of amide ester **83a** with cumulated ylide **1a**. This is a challenging concept as there have been no previous reports of such reactions. If this were to be successful, a range of N-functionalised tetramic acids could be effortlessly prepared.

Leucine esters **52e** and **52g** were prepared according to **Scheme 33** and were acylated with the corresponding chloride in methylene chloride:



52e: R=Bn
52g: R=PMB

	Individual yields (%)
83a: R=Bn, R'=$(CH)_2C_7H_{15}$	62
83b: R=PMB, R'=$(CH)_2C_7H_{15}$	55
83c: R=Bn, R'=Me	96
83d: R=Bn, R'=Et	95

Scheme 39

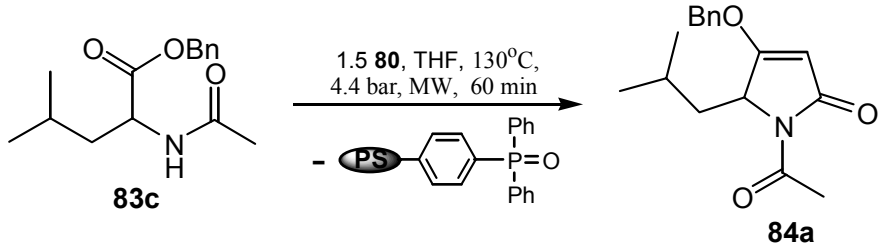
Benzyl and PMB protected amino esters **52** were prepared because deprotection is only carried out after the formation of the heterocycle and in the case of compounds **84** where R' is an α,β-unsaturated residue, hydrogenation conditions may disturb the double bond. Removal of the PMB protecting group requires a milder, non-hydrogenolytic procedure and may be a more attractive alternative when dealing with such molecules.

The less complex amide esters **83c** and **83d** were also prepared to test the feasibility of the ring-closing reaction, the NMR spectra of which would be easily interpreted and used as references for the reactions of the more complicated amide esters **83a** and **83b**.

Reaction of α-amido esters **83** with **1a** has not been reported before, although *Andrus et al*[91] have described the reaction of ylide **1a** with a BOC-protected amino aldehyde. This reaction was carried out at room temperature and both reagents were used in a 1:1 stoichiometric ratio with THF as the reaction solvent, furnishing the pyrrol-2-one in a 60% yield. These conditions were applied to the reaction of **83c** and **1a**, with the addition of a catalytic amount of benzoic acid, but no product was formed. Temperatures ranging from 60 to 140°C were tested with both standard reflux conditions and in a bomb tube, with reaction times of up to 48 h, but no reaction was detected. Microwave irradiation was also applied using THF or dichloroethane (DCE) as the reaction solvent, a range of pressures (1.6 – 15 bar) and temperatures up to 180°C were applied, but only the starting compounds were recovered.

As expected, the reactivity of the amide nitrogen of **83** towards ylide **1a** was significantly less than that of amino esters **52** (**Scheme 28**). The only explanation for the success of the reaction reported by *Andrus et al*[91] is that it proceeds via a different reaction mechanism in comparison to that of amino esters **52** with cumulated ylide **1a** (**Scheme 28**).

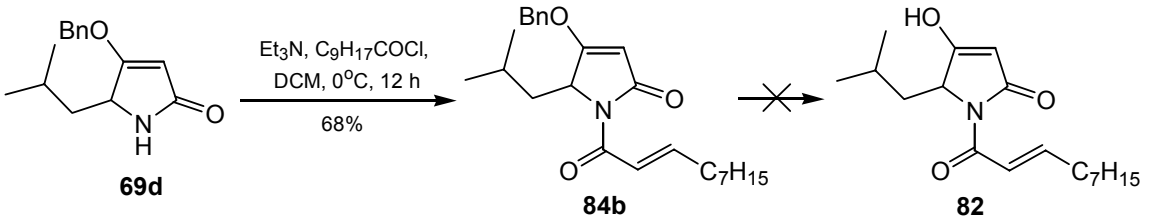
The reaction of **83c** with immobilised ylide **80** was tested with the addition of a catalytic amount of HBF_3 and was 'shaken' at 60°C for up to 72 h but no reaction took place. However, a new product was detected when the following conditions were applied:



Scheme 40

The primary indication of a reaction was the disappearance of the ylide peak (2100cm-1) of **80** in the IR spectrum of the solid-supported compound produced in the reaction and an IR spectrum of the reaction mixture showed the disappearance of the amide peak at 1650 cm^{-1} . A ^{1}H-NMR spectrum of the crude reaction mixture contained a new 'dd' signal at 4.15 ppm and a new singlet at 5.3 ppm which could be assigned to 5-H and 3-H respectively, of **84a**. The ^{13}C-NMR spectrum contained a new C-H signal at 94.1 ppm attributable to 3-H of the tetramate ring, this is a strong indication of ring closure and formation of the nitrogen heterocycle. A new signal above 169 ppm was also present which could be assigned to the carbonyl moiety at position-1. However, compound **84a** could not be obtained in a reasonable purity to report the results.

With little success in the reaction of α-amido esters **83** and cumulated ylide **1a**, this route to **59** was abandoned. Nonetheless, (±)-(*E*)-1-(dec-2-enoyl)-4-benzloxy-5-*iso*-butyl-pyrrol-2(*5H*)-one **84b** was easily prepared by acylation of the parent N*H*-4-benzyloxy tetramate **69d**:



Scheme 41

The presence of the pyrrol-2-one ring of **84b** and confirmation that tetramates do not react with electrophiles at their C-3, is clearly shown by a peak at 90 – 100 ppm in the ^{13}C-NMR spectrum of a $CDCl_3$ solution of **84b**:

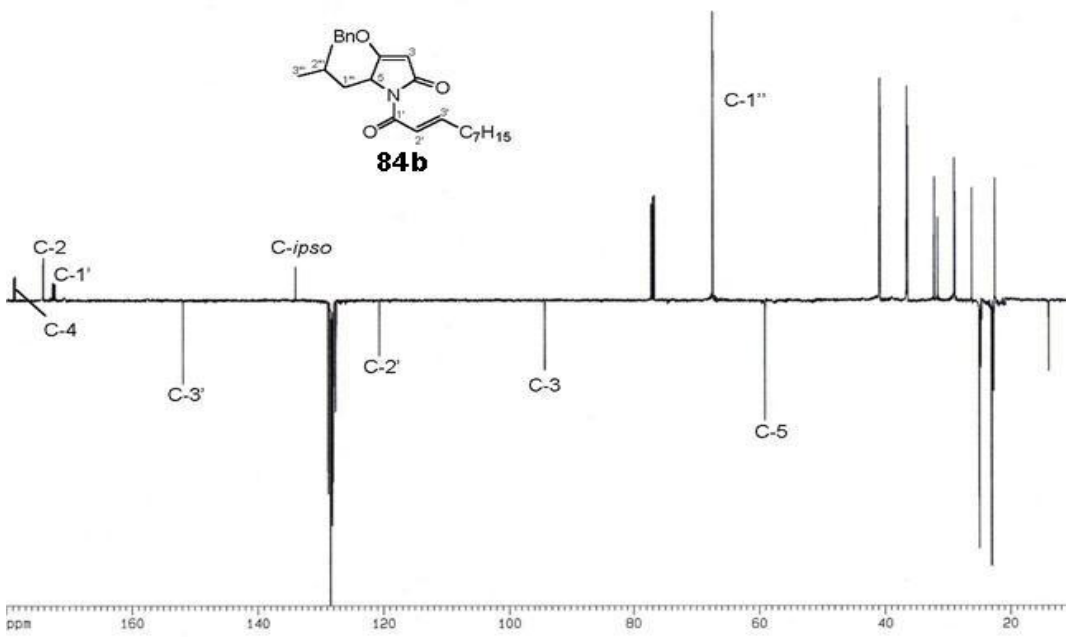
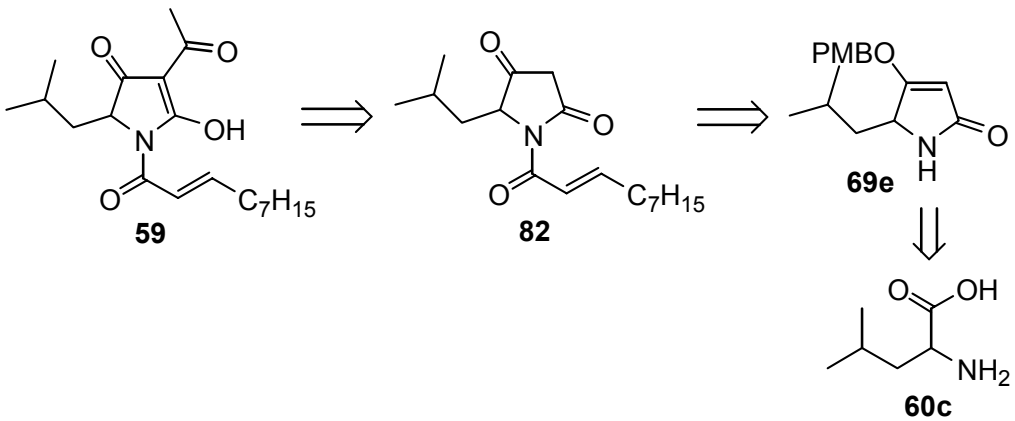


Fig.14 ^{13}C-NMR spectrum of a $CDCl_3$ solution of **84b**

Many attempts to remove the benzyl protecting group of **84b** in the presence of the N-substituent failed. Standard hydrogenation conditions were tested i.e. reactants in methanol under an atmosphere of hydrogen for 12 h in a sealed vessel, but only tetramate **84b** was recovered. An increase in temperature and pressure was applied, but molecule **84b** remained unchanged. There is no plausible explanation as to why this reaction has not been successful while the hydrogenolysis of N*H*-tetramates **69** occurs without difficulty. As a result, this approach to **59** was also abandoned.

2.3.4 Attempted synthesis 3 of reutericyclin

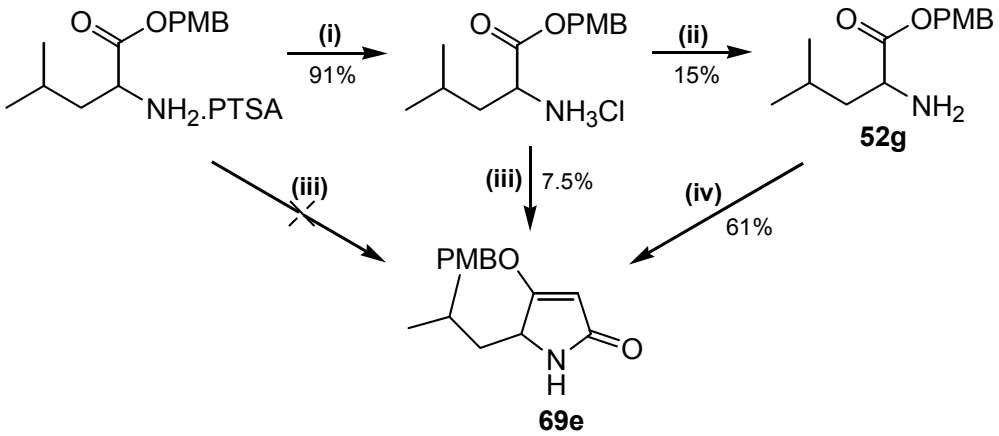
The final attempt to synthesise reutericyclin **59** involved the functionalisation of the pyrrolidine-2,4-dione nucleus at N-H and C-3 in two different steps:



Scheme 42

Employment of the PMB protecting group eliminates the aforementioned problem associated with deprotection of the benzyl group of the N-acylated tetramate. Acylation of tetramate **69e** should allow a selective N-acylation to take place, followed by 3-acylation of **82** to **59**.

The p-toluenesulfonate salt of *p*-methoxybenzyl-2-amino-4-methyl-pentanoate **52g** was prepared from *DL*-leucine **60c** according to **Scheme 27**. The subsequent conversion and deprotection of this salt resulted in poor yields (**Scheme 43**; steps (**i**) and (**ii**)). The final part of this 3-step esterification i.e. deprotection of the hydrochloride salt by treatment with 2.0M HCl in Et_2O, was not effective. Column chromatography was used in the purification of **52g** but the amino ester decomposed resulting in recovery of only the starting amino acid. Yields of no more than 15% were obtained:



Scheme 43 Reagents and conditions: (i) 2.0M HCl/Et_2O, $CHCl_3$, 0°C, 30 min. (ii) NH_3/DCM, $CHCl_3$, r.t. 1 h. (iii) 1.3 **1a**, THF, 90°C, 48 h. (iv) 1.3 **1a**, benzoic acid, THF, reflux, 24 h.

Steps were taken to bypass deprotection step **(ii)** by reaction of both the *p*-toluenesulfonate salt and the hydrochloride salt of **52g**, in turn, with keteneylidenetriphenylphosphorane **1a**. Ylide **1a** was expected to be basic enough to deprotonate the amino ester salts, inducing reaction at the ylide C^{β}. However, the PTSA salt of **52g** did not react at all with **1a**, while a small quantity of tetramate **69e** was generated from the hydrochloride salt, but poor yields were attained.

Further work:

- C-3 acylation of N-H tetramic acids with **1a** or immobilised ylide **80.**
- Preparation of **74**, followed by subsequent reactions to form **59**.

3. Tetronic acids and oligocyclic systems

3.1 Original work: Synthesis of Carlosic acid

3.1.1 Introduction

Tetronic acids possess a common 4-hydroxy-furan-2-one **75** nucleus with the possibility of a range of substitution patterns at C-3 and C-5 of the furanone ring. A large proportion of biologically active tetronic acids are substituted at C-3 with an acyl or alkyl residue, which plays a significant role in their activity. Tetronic acids are known to possess significant antibiotic, anticoagulant, anti-inflammatory, insecticidal and herbicidal activity[92], where Vitamin C and Penicillic acid[93] are two of the most important.

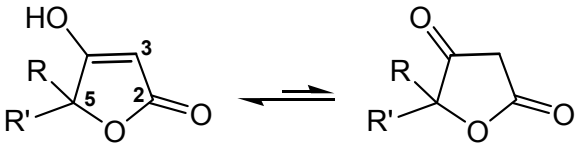
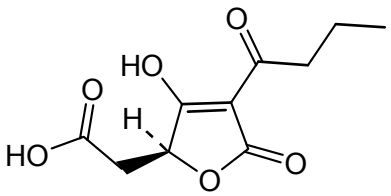


Fig.15 **75α** **75β**

As is the case with pyrrolidines, tetronic acids exist as the 3-enol tautomer **α** or the 2,4-diketo tautomer **β**. There is much speculation as to which of these tautomers predominates, especially in the presence of a 3-acyl residue. It is generally accepted that tetronic acids lean heavily towards the enol tautomer **α** because of their increased acidity in comparison to the N-analogue (tetramic acids).

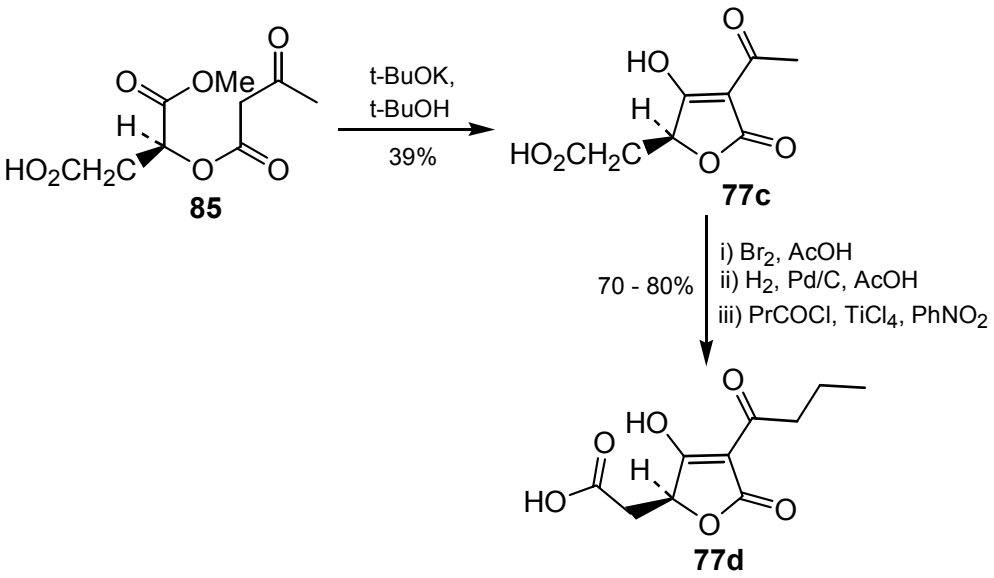
Tetronic acids appear structurally very similar to tetramic acids, but their chemical and physical properties are quite different, as are their tautomerisation patterns.

Carlosic acid, (*S*)-(2-Oxo-3-butanoyl-4-hydroxy-5-hydro-furan-5-yl)-acetic acid, **77d** is a highly functionalised tetronic acid and was first isolated from cultures of *Penicillium charlesii* by *Smith*[94] in 1934. One year later, the same group determined its structure and stereochemistry as the *S*-enantiomer:



77d

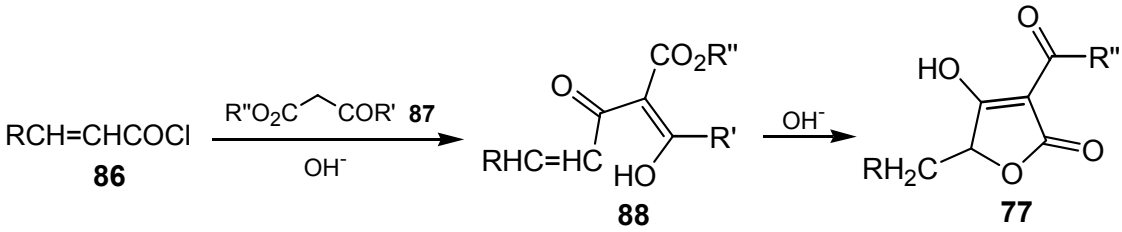
The first total synthesis of carlosic acid **77d** was successfully completed in 1974 by *Bloomer and Kappler*[95] by the base-induced ring closure of **85**:



Scheme 44

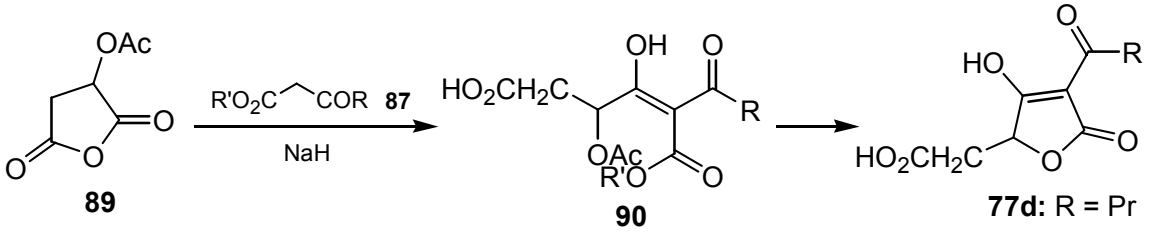
Only average yields were obtained for the preparation of **77d** using this methodology. Other approaches have since been employed to effectively prepare carlosic acid **77d**:

- β-oxo-ester **87** and an α,β-unsaturated acid chloride **86** underwent a condensation reaction when subjected to basic conditions, followed by ring closure and hydrolysis to the corresponding tetronic acid[96]:



Scheme 45

- α-Substituted malic acid anhydride **89** ring opens with carbon nucleophiles such as β-keto esters **87**, followed by deacetylation and cyclisation under basic, hydrolytic conditions to yield carlosic acid **77d**[97]:



Scheme 46

Carlosic acid **77d** is one of a family of fungal metabolites[98] and is thought to be a precursor to other functionalised tetronic acids[99]. It has been suggested, from

investigation of the biosynthetic pathway of such acids, that oxalacetate is the C_4-precursor[99].

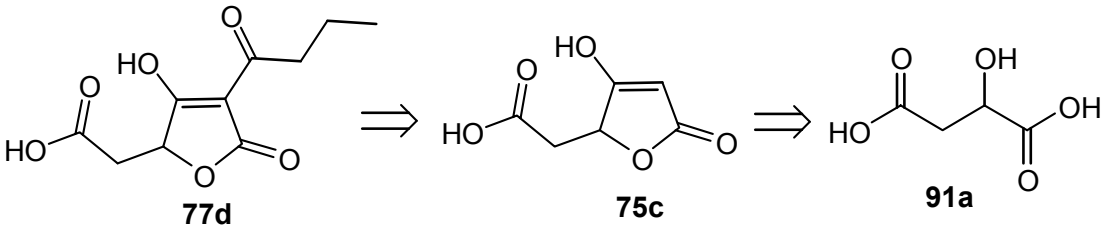
3.1.2 Aim of project

The purpose of this project was to develop a general method for the preparation of carlosic acid **77d** using keteneylidenetriphenylphosphorane **1a** to construct the furanone framework. A high-yielding, short synthesis with individual steps which are flexible towards the introduction of a range of substituents would be ideal, allowing the preparation of analogues. Most chiral compounds found in nature which are of pharmacological importance, are present as one specific enantiomer or diastereoisomer and so it is also important to consider the stereochemical aspect of the total synthesis.

It was hoped that the knowledge gained from working with tetramic acids could be applied, in part, to the tetronic acid system.

3.1.3 Total synthesis of carlosic acid 77d

The proposed retrosynthetic approach to carlosic acid **77d** involved construction of the furanone ring starting from α-hydroxy acid **91a**, followed by 3-acylation of the heterocyclic core:



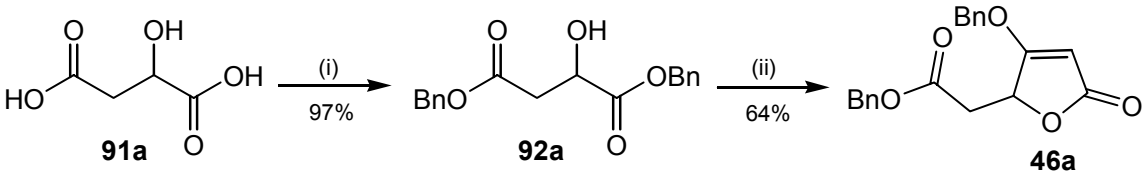
Scheme 47

The final step i.e. 3-acylation of **75c** could prove problematic due to the sensitive acid functionality present at C-5.

Carlosic acid **77d** is a particularly polar molecule and so it would be beneficial to mask the polar functionalities until as late as possible in the total synthesis.

The first step of the proposed synthesis involves nucleophilic attack of the α-hydroxy group of **91a** at C^{β} of ylide **1a**. It was therefore necessary to protect the acid functionalities of *DL*-malic acid **91a** by esterification with benzyl alcohol. The benzyl protecting group was chosen due to its stability and relatively mild deprotection conditions. Esterification using DBU, benzyl bromide and benzene as solvent produced

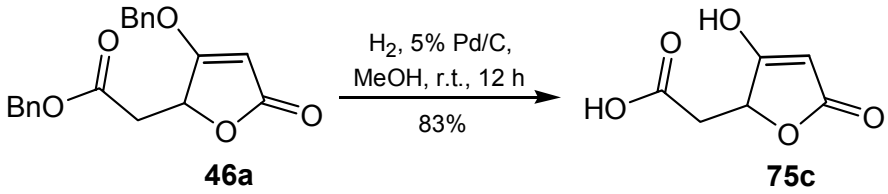
good yields of **91a** (75%) but an acid-catalysed esterification using an excess of benzyl alcohol was more effective:



Scheme 48 Reagents and conditions: (i) 6BnOH, PTSA, $CHCl_3$, reflux, 12 h. (ii) 1.3 **1a**, benzoic acid, THF, 16 h.

Reaction of **92a** with keteneylidenetriphenylphosphorane **1a** generated (±)-(2-oxo-4-benzyloxy-3,5-dihydro-furan-5-yl)-acetic acid-benzyl ester **46a** in good yields. Similar reactions have been shown to be stereoselective[45].

Smooth conversion of tetronate **46a** to the 'free' tetronic acid **75c** was achieved by a straight-forward hydrogenation with palladium on charcoal:



Scheme 49

75c was exclusively generated in the 3-enol tautomer form. Perhaps the orientation of the 5-acid residue and possible hydrogen-bonding between the 4-hydroxy and 5-carbonyl groups promote this. **Fig.16** shows the ^{13}C-NMR spectrum of a $CDCl_3$ solution of **75c** where 6 clear signals are evident, characteristic of the structure depicted in **Scheme 49**.

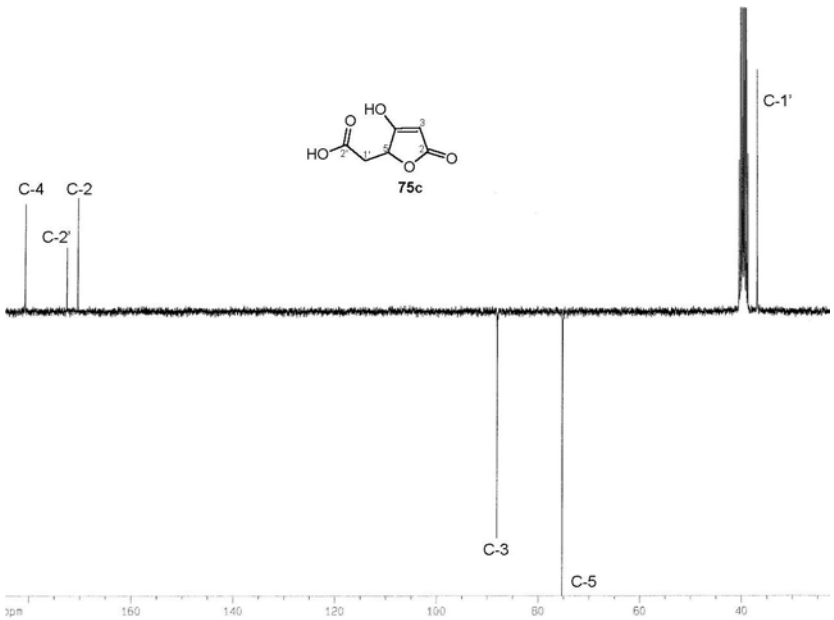
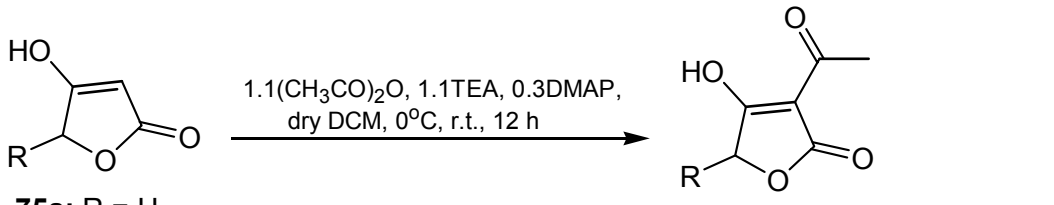


Fig.16 ^{13}C-NMR spectrum of $CDCl_3$ solution of **75c**

The final step of the total synthesis of carlosic acid **77d** involved 3-acylation of tetronic acid **75c**. Many 3-acylations of tetronic acids have been reported on 5,5-disubstituted tetronic acids with the use of strong bases[100], some 5-mono-substituted tetronic acids[101] and (2-oxo-4-hydroxy-3,5-dihydro-furan-5-yl)-methyl acetate[95,102], but no success has been reported with respect to the 3-acylation of **75c**. Therefore, a mild acylation procedure without the use of a strong base is needed for 3-acylation of **75c** or selective protection of the C-5 acid group followed by acylation and subsequent deprotection or use of a different starting α-hydroxy ester such as 2-hydroxy-butananedioic acid-1-benzyl-4-methylester.

Firstly, some mild acylation procedures were tested on systems **75a** and **75b**. Acylation using acetic acid, TEA, DMAP and DCC[103] proved unfruitful as virtually none of the 3-acyl tetronic acids **77** were isolated, but a method of acylation using acetic anhydride worked well with good yields.

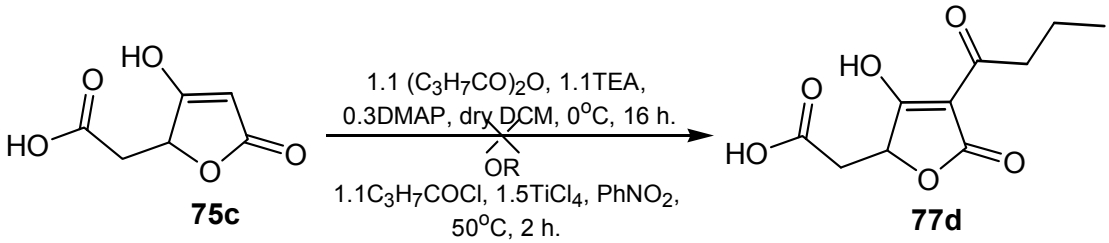


75a: R = H
75b: R = C_4H_9

	Individual yields (%)
77a: R = H	85
77b: R = C_4H_9	71

Scheme 50

This latter acylation technique was applied to **75c** in the hope that it would be mild enough to selectively react at C-3 of the furanone ring:



75c **77d**

Scheme 51

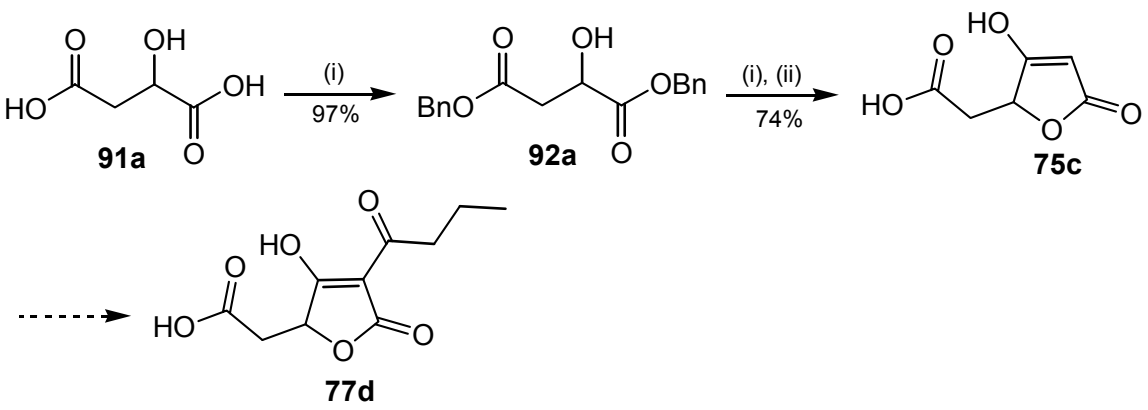
The results of the first acylation attempt are inconclusive: the ^{13}C-NMR spectrum revealed the disappearance of the signal for C-3 of **75c** at 90 ppm and C-3 of product **77d** around 115 ppm was also missing. A peak which could be attributable to the 5-methine group of a 1'-acylated product was also present. There was no ester signal around 1730cm^{-1} in the IR spectrum which rules out reaction of the 5-acid group. The mass spectrum gave numerous peaks greater than that expected for product **77d**.

A Friedel-Crafts acylation was also attempted using butanoyl chloride, $TiCl_4$ and nitrobenzene as the reaction solvent. This method has been successfully reported with reference to (2-oxo-4-hydroxy-3,5-dihydro-furan-5-yl)-methyl acetate[95,102], but when applied to system **75c** with milder reaction conditions and a more moderate temperature, none of the desired product or starting material was detected. It is difficult to propose exactly what reaction took place based on the spectral data obtained, but some possibilities are listed below:

- 3-acyl product **77d**: peak for 3-H in the ^{1}H-NMR spectrum (not attributable to **75c**), no corresponding mass peak in the mass spectrum and no signal above 170 ppm in the ^{13}C-NMR spectrum for C-3 (~180 ppm) and the 3-carbonyl function (~200 ppm). Therefore, it is unlikely **77d** was produced.
- 5-anhydride product: no anhydride peaks were evident in the IR spectrum, no corresponding mass peak in the mass spectrum and no signal around 80 ppm and 185 ppm in the ^{13}C-NMR spectrum for C-3 and C-4 respectively. These results conclude that none of this proposed product was formed.
- 4-O acylated product: too few signals downfield (above 160 ppm) in the ^{13}C-NMR spectrum and no corresponding peak in the mass spectrum suggest this product has not been formed. Although it could explain the presence of a peak around 5.5 ppm for 3-H in the ^{1}H-NMR spectrum which occurs at a higher frequency in comparison to the 3-H of **75c**.

As a result of the acylation attempts above, other methods must be considered or the 5-carboxylic residue must be protected and the resulting molecule acylated by a known procedure.

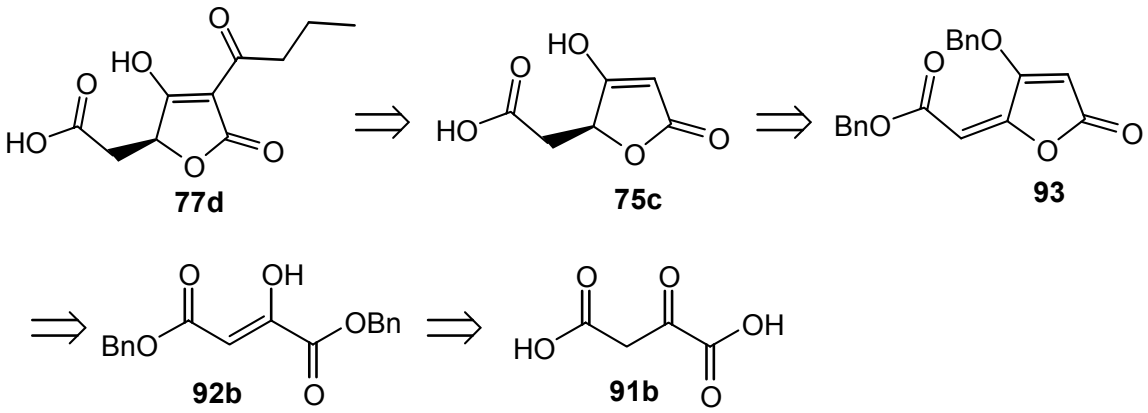
To date, the progress of the total synthesis of carlosic acid **77d** is as follows:



Scheme 52 *Reagents and conditions*: (i) 6BnOH, PTSA, $CHCl_3$, reflux, 12 h. (ii) 1.3 **1a**, benzoic acid, THF, 16 h. (iii) H_2, Pd/C, MeOH, r.t., 12 h.

3.1.4 Attempted stereoselective synthesis of carlosic acid 77d

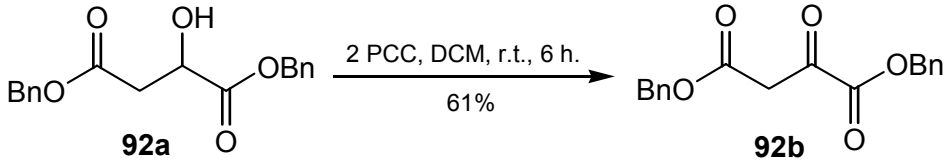
A stereoselective preparation of carlosic acid **77d** was also considered:



Scheme 53

A prochiral α-keto diester **92b** could be used to generate compound **93** containing an exocyclic double bond. Treatment of **93** with reductive conditions and a chiral catalyst should generate enantiopure **75c**.

The synthesis of α-keto ester **92b** was attempted by oxidation of α-hydroxy diester **92a**:

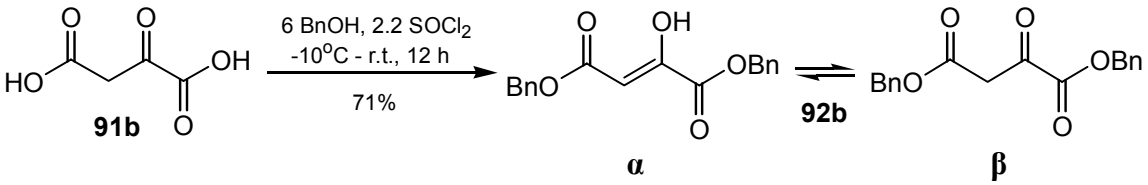


Scheme 54

This conversion was not straight-forward. Many well known oxidation procedures were tried out e.g. Swern, Pfitzner-Moffit and Jones oxidations but none were successful. However, oxidation using pyridinium chlorochromate (PCC) was most effective producing a reasonable yield of the desired product, which was unexpected as this technique is generally only applied to the oxidation of primary alcohols.

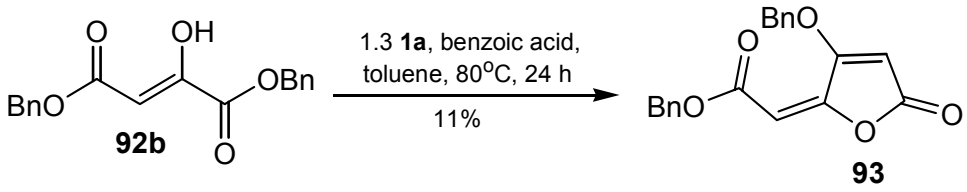
A straight-forward esterification of **91b** was also expected to effectively generate **92b**, although many attempts were unsuccessful. Acid-catalysed esterifications in both toluene and benzene were tested at temperatures up to 110°C; DBU and benzyl bromide in benzene; benzyl alcohol, PPh_3 and DIAD in THF, all gave negative results. Dibenzyl ether was detected in many of the product mixtures.

Esterification of oxalacetic acid **91b** was finally achieved after many attempts with a yield of 71% and a straight-forward work up, suitable for scale-up:



Scheme 55

Oxalacetic-dibenzylester **92b** reacted with keteneylidenetriphenylphosphorane **1a** generating **93**:



Scheme 56

A variety of reaction conditions were applied to the reaction above including a range of temperatures from 80 – 150°C, the use of different solvents (THF and toluene), reaction times were extended to 48 h and the reaction was carried out in a bomb-tube, but a maximum yield of only 11% was attained.

It was expected that if **92b** was used as an isomeric (keto-enol) mixture, the presence of the keto isomer **β** would hamper the reaction yields. Therefore, the reaction described in **Scheme 56** was tested using both an isomeric mixture of **92b** and the pure enol isomer **α**, but this made little difference to the outcome of the reaction. In many of the experiments, benzyl alcohol and **92b** were retrieved. It is more than surprising why this reaction met with such difficulty, while malic dibenzyl ester **92a** reacted smoothly with **1a**.

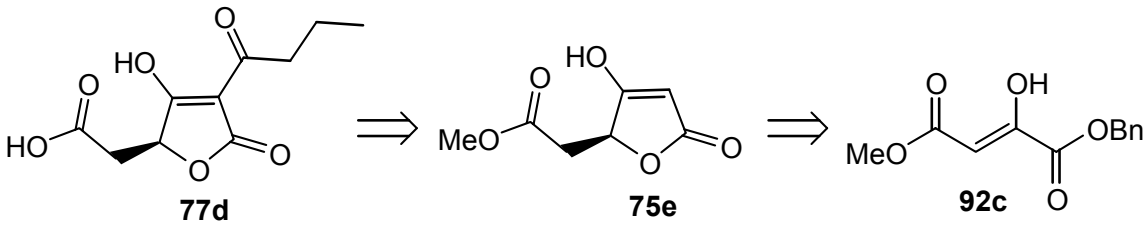
Keto-enol tautomerism could account for the detection of the starting ester **92b** in the reaction mixture, especially at elevated temperatures.

The inefficiency of this reaction could also result from ester exchange or carbon monoxide loss within the starting oxalacetic ester[104]. It has been well documented[105] that at high temperatures (~150°C) oxalacetic esters loose carbon monoxide forming the corresponding malonic ester. It is unlikely that the resulting malonic ester would enolise and react with ylide **1a**. This could explain why the experiment at 150°C in the bomb-tube was not successful. *Fitzhugh et al.*[104] described the ester exchange of oxalacetic esters with no CO loss at temperatures of 120°C, the mechanism for which is thought to operate via a 5-membered intermediate, from loss of a molecule of the corresponding alcohol. This could affect the course of the reaction in an unusual manner. This has not

been investigated in sufficient detail, with regard to this particular reaction, to offer a legitimate explanation.

Due to the poor yields produced in this ring-closing reaction (**Scheme 56**), this approach to the stereoselective synthesis of carlosic acid **77d** was abandoned.

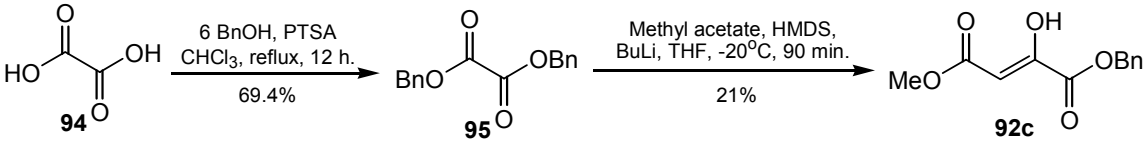
Another approach towards the preparation of (*S*)-carlosic acid **77d** was attempted by using 2-hydroxy-but-2-enedioic acid-1-benzylester-4-methylester **92c** as the starting ester:



Scheme 57

The initial reason for using an ester with two different protecting groups was to allow selective deprotection i.e. removal of the benzyl group in the presence of the methyl ester. This would allow acylation of **75e** using a previously described procedure[95,102]. Again, an α,β-unsaturated ester was used in order to introduce stereoselectivity into the total synthesis.

The preparation of **92c** was attempted using methyl acetate, oxalic dibenzyl ester **95**, KH and Et_3B, by formation of a potassium enoxyborate, but none of the desired product was formed. The reaction of methyl acetate, oxalic dibenzyl ester **95** and LDA was also tested, but the reaction failed. Various modifications were made to the reaction procedure, but this made no difference. Eventually, 2-hydroxy-but-2-enedioic acid-1-benzylester-4-methylester **92c** was prepared:



Scheme 58

Oxalic acid **94** was smoothly esterified with a three-fold excess of benzyl alcohol and a catalytic quantity of *p*-toluenesulfonic acid in chloroform, with the removal of water using a Dean-Stark apparatus. Oxalic dibenzyl ester **95** reacted successfully with the lithium enolate of methyl acetate, using the reagents and reaction conditions described in **Scheme 58**[106] to form compound **92c**.

Further work

- Explore other acylation possibilities for **75c** e.g. temporary protection of the acid functionality, followed by reaction with ylide **1a** or the immobilised cumulated ylide **80**.
- Reaction of **92c** with **1a** and hydrogenation to the 5-methylenemethylcarboxylate-furan-2(5*H*)-one **75e**, followed by 3-acylation.
- More in-depth study of the reaction products of oxalacetic dibenzyl ester **92b** with ylide **1a**, purify and characterise the compounds produced in the hope of establishing a theory for the lack of tetronate production.

3.2 Original work: Synthesis of highly substituted bicyclic and tricyclic systems

3.2.1 Introduction

Many naturally occurring compounds with interesting biological activites are composed of elaborate oligocyclic systems. Because of their unique skeletal complexity, these molecules are challenging target molecules for the synthetic chemist. Over the last century, much research has been carried out to search for a universal solution for the preparation of such compounds in the form of a general, short and efficient synthesis which would tolerate the presence of sensitive functionalities within the molecule. One such reaction is the intramolecular Diels-Alder [4π+2π] reaction which has gained importance for its efficiency and flexibility in the construction of bicyclic and tricyclic heterocycles.

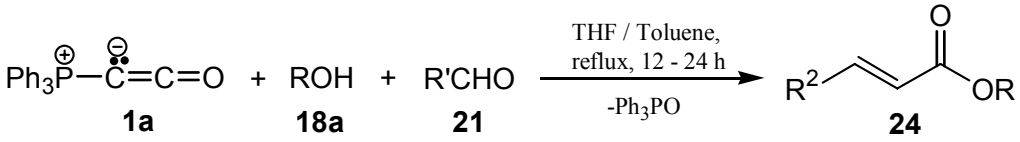
The Diels-Alder reaction was first discovered in 1928 by *Diels and Alder*[107] and has since been widely used and adapted to optimise the reaction rate, yield and selectivity of the reaction. This part of the project uses the Diels-Alder reaction to construct complex tricyclic systems from simple carboxylic acid derivatives.

The domino reaction, which also features in this part of the project, is a highly efficient and effective tool in the construction of larger, highly substituted molecules. A 'domino' reaction is defined as *a reaction which involves 2 or more bond-forming transformations which take place under the same reaction conditions without the*

addition of reagents or catalysts, and in which the subsequent reaction takes place as a direct result of the functionality(ies) formed in the previous step[77]. Domino reactions are useful to the synthetic chemist because two or more reactions take place as part of a 'one-pot' reaction, eliminating the need for isolation and purification of intermediates and so significantly reducing labour and costs.

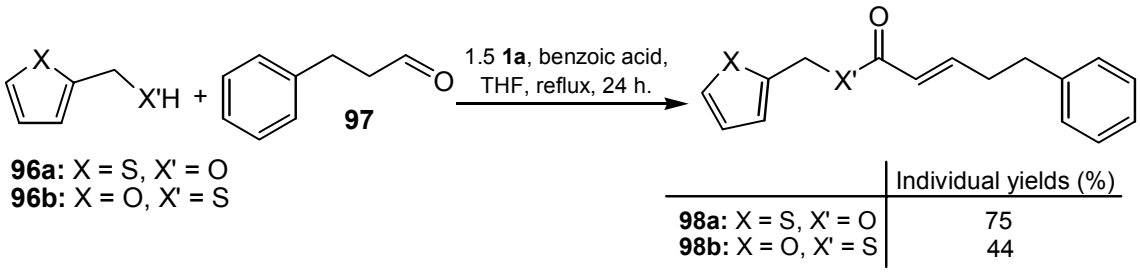
3.2.2 Carboxylic acid derivatives and their IMDA reaction products

A number of carboxylic acid derivatives were synthesised via a 3-component domino reaction, which was based on the greater reactivity of alcohols with keteneylidenetriphenylphosphorane **1a** in comparison to aldehydes:



Scheme 15

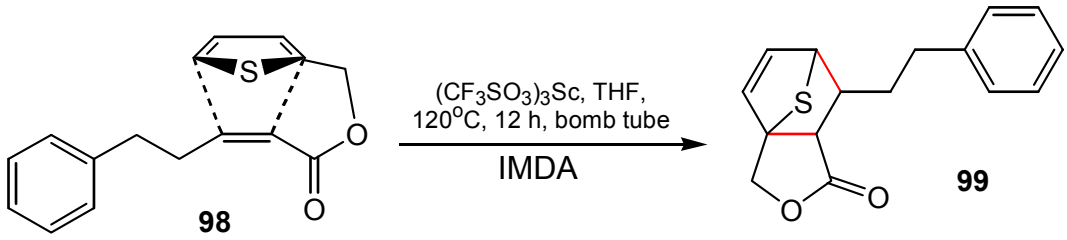
X-H acidic compounds **18a** react with ylide **1a** generating ester ylides, which in turn react with carbonyl compounds **21** via an intermolecular Wittig reaction forming α,β-unsaturated carboxylic compounds **24**. Compounds **98** were prepared using this approach by reacting **96**, 3-phenylpropanal **97** and ylide **1a**[108]:



Scheme 59

(*E*)-5-Phenyl-pent-2-enoic acid-thiophene-2'-yl-methyl ester **98a** and (*E*)-5-Phenyl-pent-2-enethioic acid-furan-2'-yl-methyl ester **98b** were obtained in average yields, with **98b** proving difficult to purify.

The objective of preparing compounds **98** was to subject them to the reagents and conditions needed to promote an intramolecular Diels-Alder reaction between the α,β-alkene and the diene system of the thiophene or furan ring to generate tricyclic systems **99**:



Scheme 60

This reaction is a 'type 1' intramolecular Diels-Alder (IMDA) [4π+2π] cycloaddition. Diels-Alder reactions[109] are classified into two types; type 1 and type 2, depending on the connectivity of the diene and dienophile within the reacting molecule. If the dienophile is attached to the diene at position 1, this is a 'type 1' IMDA reaction and the resulting molecule has a fused bicyclic structure:

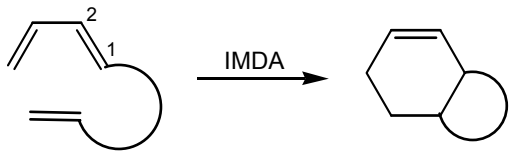


Fig.17

But if the dienophile is connected to the diene at position 2, a bridged bicyclic system containing a bridgehead double bond i.e. an anti-Bredt alkene, is produced and this is known as a 'type 2' reaction:

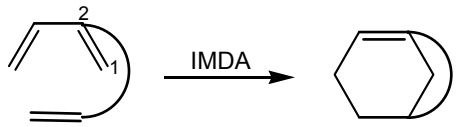


Fig.18

'Type 1' IMDA reactions are useful as they generate fused bicyclic systems from essentially acyclic compounds, few other reactions can boast of this transformation.

Many examples of Diels-Alder reactions in the gaseous state have been reported at temperatures of 400 - 500°C[110], while cycloadditions in solvents have been successfully carried out in sealed tubes at 170 - 250°C[110]. Because cycloaddition products similar to **99** are known to be especially susceptible to thermal cycloreversion[111], such high temperatures are not suitable. Therefore Lewis acid catalysts were considered, to enhance the efficiency and rate of cycloaddition reactions, with the use of moderate reaction temperatures. Their effect is thought to result from complexation with the electron-withdrawing group of the dienophile.

Two Lewis acid catalysts were tested in a variety of solvents, at a range of temperatures:

Experiment	Lewis-acid catalyst	Solvent	Temp. (^oC)	Reaction ?
1	$(CF_3SO_3)_3Sc$	THF	80	X
2	$(CF_3SO_3)_3Sc$	THF	120	☺
3	$(CF_3SO_3)_3Sc$	CH_3CN	r.t.	X
4	$(CF_3SO_3)_3Sc$	CH_3CN	reflux	X
5	$(CF_3SO_3)_3Y$	THF	150	X

Table 8 Reagents and reaction conditions applied to **Scheme 60**. Dry solvents were used and reaction times up to 12 h.

Some product was detected using the reagents and conditions in experiment 2 but yields of only 5 – 7% were obtained. Compound **99** was distinguishable from the ^{13}C-NMR spectrum; a new signal around 100 ppm was a clear indication of the formation of the furanone ring, while the downfield signal at approx. 170 ppm was assigned to C-4:

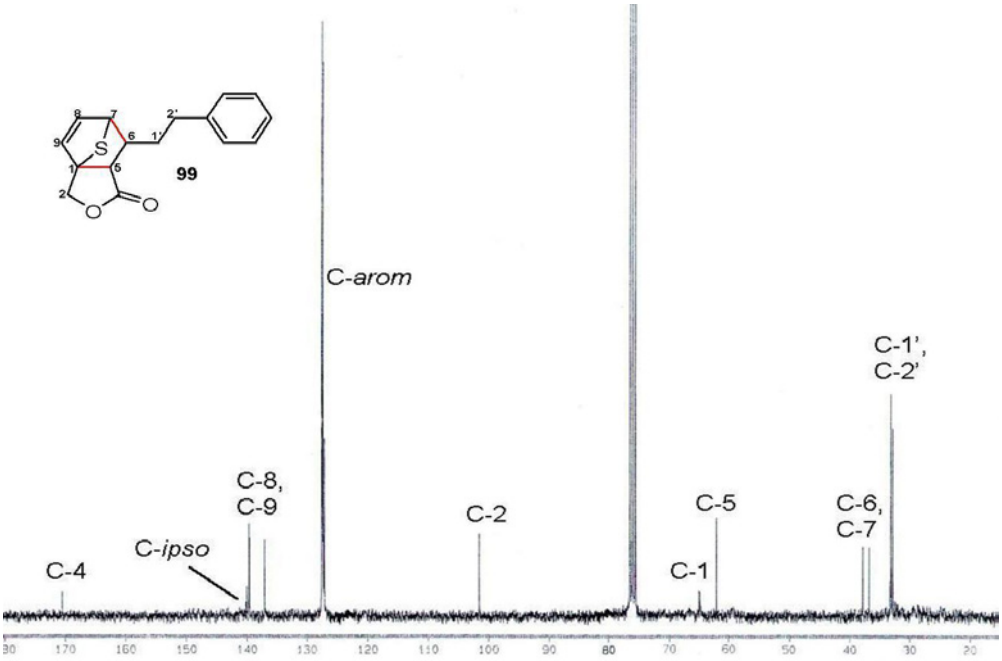
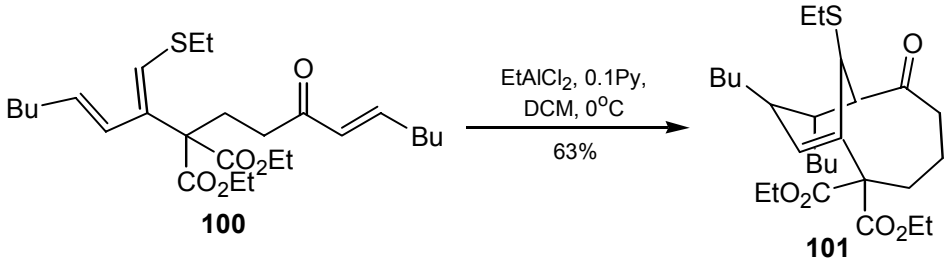


Fig.19 ^{13}C-NMR spectrum of a $CDCl_3$ solution of **99**

IMDA reactions of systems similar to **98** have been reported, with considerable success, using $EtAlCl_2$[112] as a Lewis acid with mild reaction conditions:

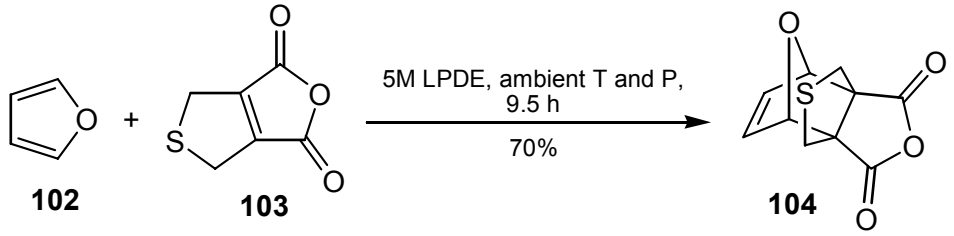


Scheme 61

Molecule **100** has an added advantage over **98** because of the substitution at the diene moiety (electron-donating butyl residue) and the dienophile is made more electrophilic by the presence of the β-oxo functionality, making it more reactive in an IMDA reaction. The furan and thiophene rings of compounds **98** are relatively poor Diels-Alder dienes due to their aromaticity. The electrons on the sulphur atom of the thiophene ring of **98a** are part of a sextet of electrons with delocalisation over the ring carbons. This provides the thiophene ring with added aromaticity and is therefore less likely to undergo addition reactions. This effect is less exaggerated in the furan derivative **98b**.

$EtAlCl_2$ was tested on system **98a** with the reagents and conditions described in **Scheme 61**, but no product **99** was detected. A range of temperatures from 0 – 65°C with reaction times of 2 – 12 h were also tested, but to no avail. A catalytic quantity of $EtAlCl_2$ with T = 110 - 180°C and microwave irradiation was also tried out, but again no product was formed.

The final attempt to drive this IMDA reaction involved the use of salt solutions in non-aqueous solvent. A 5M solution of lithium perchlorate ($LiClO_4$) in diethyl-ether (5M LPDE) has been reported to be one of the most effective solvent mediums for Diels-Alder reactions, showing an impressive acceleration in the rates of reactions, with reduced reaction times and enhanced yields[113]. The action of LPDE cannot be soley explained by the Lewis acid effect of Li^+ as this is considerably mitigated by the solvation effects of Et_2O, but its role has been attributed[109] to a combination of the formation of complexes between the $LiClO_4$ and Et_2O, polarity effects and internal pressure effects (pressure exerted by the LPDE medium on the diene and dienophile forcing them to react). One of the most impressive applications of this 'miracle medium' is used in the synthesis of cantharidin[113]:



102 **103** **104**

Scheme 62

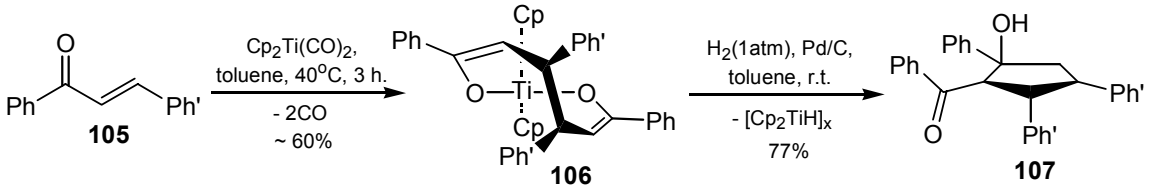
These encouraging results prompted the application of similar reaction conditions to the IMDA reaction of **98**. Reactions were carried out using 5M $LiClO_4$ in Et_2O with **98a** in dry THF from 0°C to reflux temperatures, but none of the desired product was detected.

Compound **98a** was oxidised using MCPBA (*m*-chloroperbenzoic acid) in an attempt to disturb the aromaticity of the thiophene ring and bring about a more effective IMDA reaction, but no Diels-Alder product **99** was detected.

The tether length between the diene and dienophile of **98a** may be too short to allow formation of the tricyclic product **99**. It has been reported[110] that bicycles with a tether length of four or five are much easier to prepare in comparison to those with a tether length of three. Acyclic compounds such as **98** form highly strained products with a high reaction activation energy. This energy of activation may not have been reached in these experiments. Steric hindrance by the phenyl group of **98a** could also have hindered the IMDA reaction.

3.2.3 Highly substituted cyclopentanols and their reactions

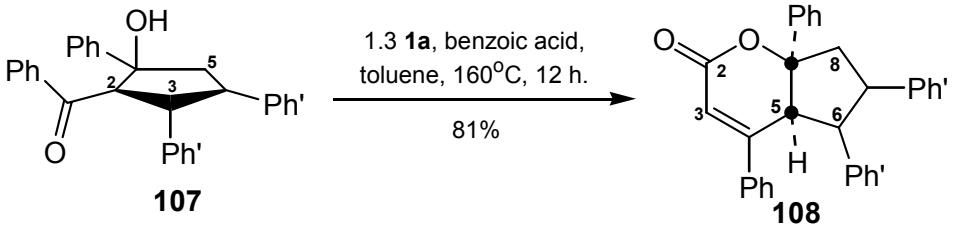
This part of the project deals with the use of metallacycles in the synthesis of highly substituted bicyclic systems. Many nine membered titanacycles have been successfully synthesised and characterised but most lack carbon in their metallacycle e.g.TiS_8[114]. Therefore, carbon-rich titana-2,9-dioxacyclonona-3,7-dienes were prepared by past group members by reaction of two equivalents of an α,β-unsaturated ketone **105** with $Cp_2Ti(CO)_2$ using mild, non-basic conditions[115]:



Scheme 63

Hydrogenolytic cleavage of titanocycle **106** drove an intramolecular aldol addition reaction and exclusive formation of the highly substituted cyclopentanol **107**[115]. These reductive conditions promoted ring contraction of **106** to **107**.

cis-1-Phenyl-2-phenylcarbonyl-3,4-diphenylcyclopentan-1-ol **107** with keteneylidenetriphenylphosphorane **1a**[116] was tested in different solvents (THF, toluene and xylene), with and without a catalytic quantity of benzoic acid and a range of temperatures was applied (60 - 120°C), but no reaction took place. NMR experiments suggested that a molecule of water was lost from **107** leaving the cyclopenta-1,5-ene system which could not react with ylide **1a**. Eventually the reaction was successfully carried out in a bomb-tube at 160°C generating the fused bicyclic system **108**:



Scheme 64

The reaction took place via a domino style reaction, where **107** adds to **1a** followed by an intramolecular Wittig alkenation to close the second ring. **108** was easily identified by a signal at 115 ppm in its ^{13}C-NMR spectrum for C-3 and with the disappearance of the carbonyl peak of **107** at 205 ppm. The disappearance of the hydroxy signal in the IR-spectrum of **107** was also a clear indication of a successful reaction. **Fig.20** shows the ^{1}H-NMR spectrum of a $CDCl_3$ solution of **108**, which clearly shows a new signal at approx. 6.2 ppm for 3-H and the disappearance of peaks at 4.5 and 5.3 ppm for 2-H and O-H of **107** respectively.

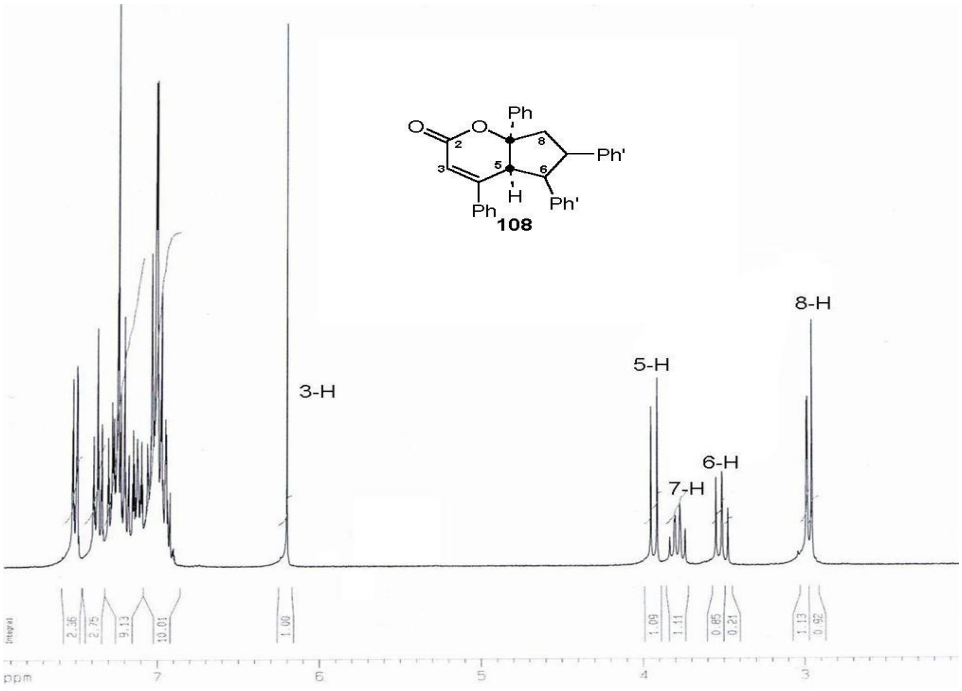


Fig.20 ^{13}C-NMR of a $CDCl_3$ solution of **108**

Further work

- Water has been reported as having a special effect on Diels-Alder reactions[117] by significantly enhancing their reaction rates. This enhancement can thus be

further magnified by addition of ionic solutes[118] e.g. LiCl, $LiClO_4$. This could be tested on systems **98a** and **98b** (**Scheme 60**).

- Test the IMDA reactions of derivatives of **98** with a larger tether length and replacing the phenyl moiety with a less bulky group.
- Test IMDA reactions in an autoclave under pressure, as this has been shown to promote similar reactions[119].

4. Experimental

Methods and materials

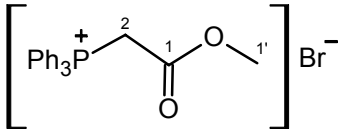
Melting points were recorded on a Gallenkamp or a Wagner & Munz apparatus and are uncorrected. IR spectra were recorded on a Bruker FT-IR Vector 22; Perkin Elmer 983G coupled to a Perkin Elmer 3700 Data Station and a Perkin Elmer 1605 FT-IR as potassium bromide discs or as films on sodium chloride plates. Nuclear Magnetic Resonance (NMR) spectra were recorded using Bruker DPX-300, DPX-500 and Jeol JNM-EX-270-FT spectrometers with Xwin-NMR data system, version 3. Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (internal, ^{1}H- and ^{13}C-NMR) or H_3PO_4 (85%, external, ^{31}P-NMR) as standards and coupling constants (J) are reported in Hertz (Hz). Mass spectra were recorded on a Double Focusing Triple Sector VG Auto Spectrometer and a Double Focusing Finnigan MAT 95 Spectrometer with MAT SS 300 data system (EI). Microanalyses were recorded using a Perkin Elmer 2400 CHN and Heraues CHN Mikromonar elemental analyser. Analytical GC was recorded using a United Technologies Packard Model 438S with DB-5 silica column (J&W Scientific) and Shimadzu C-R3A integrator. Microwave reactions were carried out in a CEM Discoverer Microwave. The silica gel used in column chromatography was Merck silica gel 60, particle size 0.063 – 0.2mm (70 – 230 mesh). TLC analyses were carried out using Polygram® SIL G / UV254 0.2mm silica plates and a UV lamp or developing solution (conc. H_2SO_4, 6mL; $Ce(SO_4)_2$, 1.0g; $12MoO_3.H_3PO_4$, 2.5g and H_2O, 94mL).

All solvents were obtained from Merck and were pre-distilled before use, some were rigorously dried: CH_2Cl_2 and $CHCl_3$, PO_5 (20g in 1L); MeOH, Mg turnings (2.5g in 500mL); toluene, THF, benzene, EtOH and Et_2O, sodium (7g in 1L).

Compounds in *italics* were available within our working group and have been included for spectroscopic comparisons. See references for protocols.

4.1 Synthesis of Keteneylidenetriphenylphosphorane 1a[87,120]

Carbomethoxymethyl-triphenylphosphoniumbromide 14[121]



Triphenylphosphine (262g, 1.0mol) was dissolved in toluene (1200mL) and methyl bromoacetate (152g, 1.0mmol) was added dropwise over a 30 min period. The reaction mixture was stirred for 24 h at r.t. forming a white precipitate (the progress of which was monitored by TLC). The solid was filtered using a Büchner apparatus, washed thoroughly with toluene (~500mL) and rinsed with Et_2O (~1000mL). The solvent was removed under reduced pressure and dried on an oil pump yielding carbomethoxymethyl-triphenylphosphoniumbromide **14** as a white solid (348.8g, 0.84mol, 84%).

MF : $C_{21}H_{20}O_2PBr$

MW : 415.27

MP = 162°C (Lit. mp.: 163°C [121]).

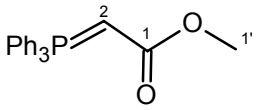
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 3.57 (s, 3H, 1'-H), 5.55 (d, $^2J_{PH}$ = 13.40Hz, 2H, 2-H), 7.5-7.9 (m, 15H, Ph-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 33.1 (d, $^1J_{PC}$ = 58.0Hz, CH_2; C-2), 55.1 (CH_3; C-1'), 117.9 (d, $^1J_{PC}$ = 85.3Hz, C^q; C-*ipso*), 131.3 (d, $^3J_{PC}$ = 12.62Hz, *m*-CH; C-*arom*), 133.8 (d, $^2J_{PC}$ = 10.91Hz, *o*-CH; C-*arom*), 134.9 (CH; *p*-CH; C-*arom*), 166.6 (C^q; C-1).

^{31}P-NMR (121.5MHz, $CDCl_3$); δ(ppm) = 21.69

IR (KBr); ν(cm^{-1}) = 3004(w), 2798(m), 2731(w), 1721(s), 1585(w), 1486(w), 1434(m), 1320(m), 1197(m), 1107(s), 994(w), 875(m), 800(w), 752(m), 724(m), 688(m).

Carbomethoxymethylene-triphenylphosphorane 15a[121]



Carbomethoxymethyl-triphenylphosphoniumbromide **14** (349g, 0.84mol) was dissolved in distilled water (4500mL), cooled to 4°C and 2M NaOH was added dropwise until the reaction mixture reached a pH of 7. A white precipitate was produced which was filtered using a Büchner filter and washed with a large quantity of water. The remaining solid was dissolved in DCM, the organic layer was separated from the aqueous phase, dried over $MgSO_4$, filtered and the solvent was removed on a rotary evaporator. The product was recrystallised from toluene yielding carbomethoxymethylene-triphenylphosphorane **15a** as a white, fluffy solid (221.9g, 0.66mol, 79%).

MF : $C_{21}H_{19}O_2P$

MW : 334.36

MP = 163.6 – 164.2°C (Lit. mp.: 163°C [121])

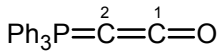
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 2.90 (d, $^{2}J_{PH}$ = 11.1, 1H, 2-H), 3.45 (s, 3H, 1'-H), 7.4–7.7 (m, 15H, Ph-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 28.2 (d, $^{1}J_{PC}$ = 126.15Hz, CH; C-2), 46.0 (CH_3; C-1'), 127.5 (d, $^{1}J_{PC}$ = 94.0Hz, C^q; C-*ipso*), 128.3 (d, $^{3}J_{PC}$ = 12.64Hz, *m*-CH; C-*arom*), 130.7 (*p*-CH; C-*arom*), 133.0 (d, $^{2}J_{PC}$ = 10.10Hz, *o*-CH; C-*arom*), 171.2 (d, $^{2}J_{PC}$ = 15.78Hz, C^q; C-1).

^{31}P-NMR (121.5MHz, $CDCl_3$); δ(ppm) = 16.97, 18.81.

MS (EI, 70eV); m/z (%) = 334 (46) [M^+], 333 (100) [M^+-1], 303 (44) [M^+-CH_3O^-], 275 (20) [M^+-$CH_3CO_2^-$], 77 (6) [$C_6H_5^+$].

Keteneylidenetriphenylphosphorane 1a[120]



To a solution of sodium amide (25.8g, 0.66mol) in dry benzene (1500mL), hexamethyldisilazane (HMDS; 106.6g, 0.66mol) was added and refluxed for 2 h. The resulting orange/brown solution was cooled, carbomethoxymethylene-triphenylphosphorane **15a** (220.7g, 0.66mol) was added and the reaction mixture was heated to 60°C for 24 – 48 h. Completion of the reaction was indicated by the cessation of ammonia production. The warm solution was filtered under argon, using a heated Schlenk filter apparatus embedded with basic alumina (approx. 2 cm depth) to remove sodium methoxide. It was vital that the solution was kept warm (~50°C) during filtration to avoid premature crystallisation of the product. The filtrate was reduced to one tenth its original volume under reduced pressure (oil pump with additional collecting chambers), dry Et_2O (~500mL) was added and the solution was cooled to -10°C for 24 h. The yellow solid formed was collected on a Schlenk filter apparatus, under argon, and washed thoroughly with dry Et_2O (750 – 1000mL) until the filtrate became neutral. The product was recrystallised from benzene yielding **1a** as a pale yellow solid (143.7g, 0.48mol, 72%).

MF : $C_{20}H_{15}OP$

MW : 302.31

MP = 173.5 – 174.9°C (Lit. mp.: 173°C [120c])

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 10.5 (d, $^{1}J_{PC}$ = 189.1Hz, C^q; C-2), 128.2 (d, $^{3}J_{PC}$ = 11.68Hz, *m*-CH; C-*arom*), 129.0 (d, $^{1}J_{PC}$ = 95.13Hz, C^q; C-*ipso*), 133.0 (*p*-CH; C-*arom*), 134.7 (d, $^{2}J_{PC}$ = 11.27Hz, *o*-CH; C-*arom*), 144.6 (d, $^{2}J_{PC}$ = 44.3Hz, C^q; C-1).

IR (KBr); ν(cm^{-1}) = 2099(s), 1625(m), 1435(m), 1108(m).

^{31}P-NMR (121.5MHz, $CDCl_3$); δ(ppm) = 5.95

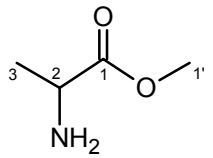
4.2 Synthesis of Amino Esters

4.2.1 Synthesis of methyl and ethyl amino esters

General procedure: The amino acid (10mmol) was added to a cold, stirring solution (-10°C; ice/salt bath) of thionyl chloride (11mmol) in dry alcohol (5mL), which was slowly warmed to room temperature and heated to 50°C for 3 h. An additional quantity of thionyl chloride (3mmol) was added and stirred for a further 30 min. The solvent was removed under reduced pressure producing a salt. Acetone was added, the solid was filtered using a Büchner funnel and washed thoroughly with acetone.

A slurry of the amino ester hydrochloride salt (8mmol) in $CHCl_3$ (10-15mL) was treated with 18% NH_3/DCM solution (1.7mL) and stirred at room temperature for 60 min. The white precipitate formed was filtered off using a Büchner apparatus and washed thoroughly with DCM. The solvent was removed from the filtrate using a rotary evaporator and carefully dried on an oil pump for some minutes, producing a viscous oil.

(±)-Methyl-2-amino-propanoate 52b



The reaction of *DL*-alanine **60a** (4.46g, 50mmol) and thionyl chloride in dry methanol (25mL) yielded the methyl-2-amino-propanoate hydrochloride salt of **52b** as a brilliant-white solid (5.95g, 42.6mmol, 85%):

MP = 155.7 – 156.3°C (decomp.).

IR (KBr); ν(cm^{-1}) = 2955(s), 2721(m), 2651(w), 2600(w), 2527(w), 1748(s), 1598(m), 1525(m), 1455(m), 1333(m), 1256(s), 1216(m), 1117(m), 1005(w), 979(w), 906(w), 838(w), 755(w), 618(w).

Treatment of the hydrochloride salt of **52b** (3.91g, 28mmol) in $CHCl_3$ with NH_3/DCM solution (5.88mL) produced (±)-methyl-2-amino-propanoate **52b** as a pale yellow oil (2.53g, 24.5mmol, 88%); R_f = 0.47 (EtOAc).

MF : $C_4H_9NO_2$

MW : 103.12

BP : 37 - 40°C, P = 14 Torr (Lit. b.p.: 38°C, P = 14 Torr[122])

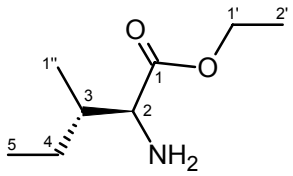
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 1.26 (d, $^3J_{HH}$ = 7.04Hz, 3H, 3-H), 1.7 (broad s, 2H, NH_2), 3.5 (q, $^3J_{HH}$ = 7.04Hz, 1H, 2-H), 3.7 (s, 3H, 1'-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 20.6 (CH_3; C-3), 50.6 (CH; C-2), 51.9 (CH_3; C-1'), 176.9 (C^q; C-1).

IR (film, NaCl); ν(cm^{-1}) = 3379(m), 3311(m), 2979(m), 1738(s), 1604(m), 1454(m), 1375(m), 1319(m), 1202(s), 1065(s), 981(m), 877(m), 830(m), 758(m).

MS (EI, 70eV); m/z (%) = 103 (6) [M^+], 88 (32) [M^+-CH_3], 44 (100) [CO_2].

(*2S*,*3S*)-Ethyl-2-amino-3-methyl-pentanoate 52c



The reaction of (*2S*,*3S*)-2-amino-3-methyl-pentanoic acid (*L*-isoleucine) **60b** (2.63g, 20mmol) and thionyl chloride in dry ethanol (10mL) produced ethyl-2-amino-3-methyl-pentanoate hydrochloride as a white salt (3.42g, 17.5mmol, 87.4%). Treatment of this hydrochloride salt (3.33g, 17mmol) in $CHCl_3$ with NH_3/DCM solution, followed by purification using column chromatography yielded (*2S*,*3S*)-ethyl-2-amino-3-methyl-pentanoate **52c** as a clear oil (2.24g, 14.1mmol, 83%); R_f = 0.65 (EtOAc).

MF : $C_8H_{17}NO_2$

MW : 159.23

BP : 193 - 196°C, P = 760 Torr (Lit. b.p.: 191.4 ± 13.0°C, P = 760 Torr[123])

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.88 (t, $^3J_{HH}$ = 7.2Hz, 3H, 5-H), 0.9 (d, $^3J_{HH}$ = 6.8Hz, 3H, 1''-H), 1.12 (m, 1H, 4-H), 1.24 (t, $^3J_{HH}$ = 7.0Hz, 3H, 2'-H), 1.42 (m, 1H, 4-H), 1.9 (m, 1H, 3-H), 3.52 (m, 1H, 2-H), 4.16 (q, $^3J_{HH}$ = 7.0Hz, 2H, 1'-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 14.2, 15.4, 17.4 (CH_3; C-5, C-2', C-1''), 25.1 (CH_2; C-4), 38.0 (CH; C-3), 56.5 (CH; C-2), 61.1 (CH_2; C-1'), 174.4 (C^q; C-1).

IR (film, NaCl); ν(cm^{-1}) = 3386(m), 2967(s), 2934(s), 2878(s), 1732(s), 1664(s), 1511(m), 1460(s), 1380(m), 1334(m), 1194(s), 1147(m), 1026(m), 965(w), 847(w), 737(w).

MS (EI, 70eV); m/z (%) = 159 (10) [M^+], 129 (51) [M^+-C_2H_6], 44 (100) [CO_2].

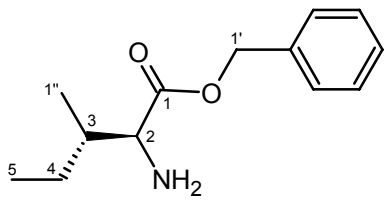
4.2.2 Synthesis of benzyl and *p*-methoxybenzyl amino esters

General procedure: An amino acid (10mmol), anhydrous *p*-toluenesulfonic acid **61** (10mmol) and *p*-toluenesulfonyl chloride **62** (12mmol) were added to the corresponding alcohol (20mL) with stirring, and refluxed for 2 h[74]. The excess alcohol was removed by distillation while the reaction mixture was still warm and the resulting viscous liquid was directly added to cold Et_2O (300mL) and refridgerated for 2 - 4 h. The white precipitate produced was filtered and washed well with cold Et_2O.

A slurry of the *p*-toluenesulfonate salt (9mmol) in $CHCl_3$ (25mL) was treated with a cold solution of HCl in Et_2O (2.0M; 4.5mL), the reaction vessel was lightly sealed and the mixture was left stirring for 30 min. An additional quantity of HCl in ether (2M; 2.3mL) was added to ensure a complete reaction. Et_2O (300mL) was added to the reaction flask and refridgerated for 3 - 5 h. The white precipitate formed was filtered using a Büchner filter and washed with a little cold Et_2O generating the corresponding amino ester hydrochloride salt.

A slurry of the amino ester hydrochloride salt (8mmol) in chloroform (10mL) was cooled to 0^oC, treated with an excess of NH_3/DCM solution (2.0mL; small excess prevents dissolution of the ammonium chloride precipitate in DCM) and left stirring for 60 min. Completion of the reaction was indicated by the formation of a fine white precipitate which was filtered off using a Büchner filter funnel and washed with a small quantity of dichloromethane. The solvent was removed from the filtrate using a rotary evaporator and the resulting oil was carefully dried using an oil pump, for a few minutes only. In some cases, the DCM was completely removed before filtration, the product was dissolved in toluene and filtered. This prevented contamination with NH_4Cl.

(*2S*,*3S*)-Benzyl-2-amino-3-methyl-pentanoate 52d



(*2S*,*3S*)-2-amino-3-methyl-pentanoic acid (*L*-isoleucine) **60b** (2.63g, 20mmol), anhydrous *p*-toluenesulfonic acid **61** and *p*-toluenesulfonyl chloride **62** in benzyl alcohol yielded benzyl-2-amino-3-methyl-pentanoate *p*-toluenesulfonate as a white salt (7.76g, 19.7mmol, 99%).

MP = 144 - 146^oC (Lit. m.p.: 153^oC[124]).

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.72 (t, $^3J_{HH}$ = 7.34Hz, 3H, 5-H), 0.82 (d, $^3J_{HH}$ = 6.84Hz, 3H, 1''-H), 1.2 (m, 2H, 4-H), 1.84 (m, 1H, 3-H), 2.27 (s, 3H, CH_3, PTSA), 3.91 (m, 1H, 2-H), 5.0 (dd, $^2J_{HH}$ = 12.2Hz, 2H, 1'-H), 7.03 (d, $^3J_{HH}$ = 8.1Hz, 2H, *m*Ph-H, PTSA), 7.23 (m, 5H, Ph-H), 7.71 (d, $^3J_{HH}$ = 8.1Hz, 2H, *o*Ph-H, PTSA), 7.89 (s, 1H, N-H), 8.1 (s, 1H, O-H, PTSA).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 11.4 (CH_3; C-5), 14.2 (CH_3; C-1''), 21.3 (CH_3; PTSA), 21.6 (CH_2; C-4), 36.3 (CH; C-3), 57.3 (CH; C-2), 67.7 (CH_2; C-1'), 126.5-128.5 (CH; C-*arom*), 134.8, 140.3 (C^q; C-*ipso*), 171.4 (C^q; C-1).

IR (KBr); ν(cm^{-1}) = 3024(s), 2976(s), 2916(s), 1745(m), 1602(m), 1494(s), 1451(s), 1382(m), 1262(m), 1173(s), 1117(s), 1074(s), 1030(m).

The *p*-toluenesulfonate salt of **52d** (7.67g, 19.5mmol) was treated with 2M HCl/Et_2O producing benzyl-2-amino-3-methyl-pentanoate hydrochloride as a white salt (4.98g, 19.3mmol, 99%).

MP = 178 - 180°C (decomp.).

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.72 (t, $^3J_{HH}$ = 7.35Hz, 3H, 5-H), 0.82 (d, $^3J_{HH}$ = 6.87Hz, 3H, 1''-H), 1.14 (m, 1H, 4-H), 1.3 (m, 1H, 4-H), 1.91 (m, 1H, 3-H), 3.99 (d, $^3J_{HH}$ = 4.47Hz, 1H, 2-H), 5.18 (dd, $^2J_{HH}$ = 12.2Hz, 2H, 1'-H), 7.1-7.5 (m, 5H, Ph-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 11.4 (CH_3; C-5), 14.6 (CH_3; C-1''), 21.7 (CH_2; C-4), 36.7 (CH; C-3), 57.7 (CH; C-2), 68.0 (CH_2; C-1'), 126.6-129.2 (CH; C-*arom*), 135.3 (C^q; C-*ipso*), 169.0 (C^q; C-1).

IR (KBr); ν(cm^{-1}) = 2967(m), 2930(m), 2875(w), 1745(s), 1622(w), 1528(m), 1263(m), 1184(s), 1127(m), 1038(m), 1014(m), 814(m).

Benzyl-2-amino-3-methyl-pentanoate hydrochloride (4.95g, 19.2mmol) was treated with NH_3/DCM generating (*2S,3S*)-benzyl-2-amino-3-methyl-pentanoate **52d** as a colourless oil (3.61g, 16.3mmol, 84.9%).

MF : $C_{13}H_{19}NO_2$

MW : 221.30

BP : > 200°C, P = 760 Torr (Lit. b.p.: 302.5 ± 17.0°C, P = 760 Torr[125])

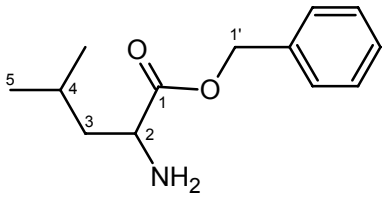
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.77 (t, $^3J_{HH}$ = 7.4Hz, 3H, 5-H), 0.84 (d, $^3J_{HH}$ = 6.87Hz, 3H, 1''-H), 1.13 (m, 1H, 4-H), 1.30 (m, 1H, 4-H), 1.73 (m, 1H, 3-H), 3.11 (broad s, 1H, N-H), 3.46 (d, $^3J_{HH}$ = 4.68, 1H, 2-H), 5.07 (2d, $^2J_{HH}$ = 12.23Hz, 2H, 1'-H), 7.27 (m, 5H, Ph-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 11.6 (CH_3; C-5), 15.8 (CH_3; C-1''), 24.6 (CH_2; C-4), 39.1 (CH; C-3), 59.2 (CH; C-2), 66.4 (CH_2; C-1'), 127.9, 128.0, 128.2, 128.3, 128.6 (CH; C-*arom*), 135.8 (C^q; C-*ipso*), 175.5 (C^q; C-1).

IR (film, NaCl); ν(cm^{-1}) = 3387(m), 3322(w), 3091(w), 3067(w), 3034(w), 2963(s), 2934(m), 2876(m), 1732(s), 1606(w), 1498(m), 1456(m), 1382(m), 1263(m), 1215(s), 1166(s), 1029(m).

MS (EI, 70eV); m/z (%) = 221 (5) [M^+], 130 (68) [M^+-$C_6H_5CH_2^+$], 115 (11) [130-CH_3^+], 91 (65) [$C_6H_5CH_2^+$], 86 (100) [130-CO_2], 44 (51) [CO_2].

(±)-Benzyl-2-amino-4-methyl-pentanoate 52e



(±)-2-Amino-4-methyl-pentanoic acid (*DL*-leucine) **60c** (2.63g, 20mmol), anhydrous *p*-toluenesulfonic acid **61** and *p*-toluenesulfonyl chloride **62** in benzyl alcohol yielded benzyl-2-amino-4-methyl-pentanoate *p*-toluenesulfonate salt as a white, fluffy solid (7.66g, 19.5mmol, 97%).

MP = 145 – 145.4°C (decomp.).

IR (KBr); ν(cm^{-1}) = 3055(m), 2967(m), 1745(m), 1611(w), 1527(m), 1458(w), 1395(w), 1214(s), 1183(s), 1126(m), 1067(m), 1012(m), 815(w), 748(w), 679(m), 568(m).

The *p*-toluenesulfonate salt of **52e** (7.6g, 19.3mmol) was treated with 2M HCl/Et_2O producing the corresponding white hydrochloride salt (4.84g, 18.8mmol, 97%).

MP = 178 – 181°C (decomp.).

IR (KBr); ν(cm^{-1}) = 2967(m), 1746(s), 1611(w), 1527(m), 1458(w), 1395(w), 1304(w), 1215(s), 1183(s), 1126(m), 1037(m), 1012(m), 815(w), 747(w), 678(m), 568(m).

Benzyl-2-amino-4-methyl-pentanoate hydrochloride (4.76g, 18.5mmol) treated with NH_3/DCM (5mL) produced (±)-benzyl-2-amino-4-methyl-pentanoate **52e** as a clear oil (3.48g, 15.7mmol, 85%); R_f = 0.4 (1:1 EtOAc-hexane).

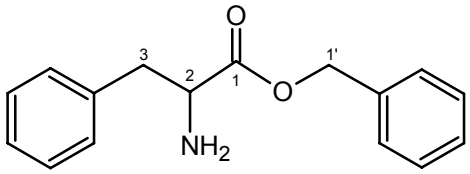
MF : $C_{13}H_{19}NO_2$

MW : 221.30

BP : > 200°C, P = 760 Torr (Lit. b.p.: 302.5 ± 17.0°C, P = 760 Torr[126])

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.88 (d, $^{3}J_{HH}$ = 6.5Hz, 3H, 5-H), 0.93 (d, $^{3}J_{HH}$ = 6.5Hz, 3H, 5-H), 1.32-1.39 (m, 1H, 3-H), 1.45-1.53 (m, 1H, 3-H), 1.66-1.69 (m, 1H, 4-H), 3.4 (dd, $^{3}J_{HH}$ = 5.67, 8.64Hz, 1H, 2-H), 5.06 (s, 2H, 1'-H), 7.2-7.3 (m, 5H, Ph-H).
^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 21.0, 21.9 (CH_3; C-5), 23.9 (CH; C-4), 43.2 (CH_2; C-3), 51.9 (CH; C-2), 65.5 (CH_2; C-1'), 127.2, 127.3, 127.4, 127.5, 127.8 (CH; C-*arom*), 134.8 (C^q; C-*ipso*), 175.5 (C^q; C-1).
IR (film, NaCl); ν(cm^{-1}) = 3375(m), 3301(m), 3088(w), 3059(m), 3037(m), 2963(s), 2868(s), 1733(s), 1608(m), 1498(m), 1468(m), 1390(m), 1368(m), 1324(w), 1265(m), 1162(s), 1081(w), 1007(m), 963(m), 868(w), 838(w), 816(m), 750(m), 699(m).
MS (EI, 70eV); m/z (%) = 222 (3) [M^++1], 129 (11) [M^+-$C_6H_5CH_3$], 91 (79) [$C_6H_5CH_2^+$], 86 (100) [M^+-$PhCH_2CO_2^-$], 44 (76) [CO_2].

(±)-Benzyl-2-amino-3-phenyl-propanoate 52f



(±)-2-Amino-3-phenyl-propanoic acid (*DL*-phenylalanine) **60d** (3.31g, 20mmol), anhydrous *p*-toluenesulfonic acid **61** and *p*-toluenesulfonyl chloride **62** in benzyl alcohol yielded a white *p*-toluenesulfonate salt (8.15g, 19mmol, 95%).
MP = 149.7 - 150.6°C (decomp.).
IR (KBr); ν(cm^{-1}) = 3459(w), 3032(m), 1741(s), 1606(w), 1522(m), 1454(w), 1403(w), 1208(s), 1176(s), 1126(s), 1036(m), 1010(m), 815(w), 742(w), 679(m), 569(m).

Benzyl-2-amino-3-phenyl-propanoate *p*-toluenesulfonate salt (8.0g, 18.7mmol) treated with 2M HCl/Et_2O produced a white hydrochloride salt (5.02g, 17.2mmol, 92%);
MP = 195 - 198°C (decomp.).
IR (KBr); ν(cm^{-1}) = 2855(s), 1749(s), 1606(m), 1489(s), 1454(m), 1405(m), 1369(m), 1228(s), 1194(m), 1156(w), 1102(w), 1076(w), 1054(w), 987(w), 940(w), 908(w), 739(m), 700(s).

Benzyl-2-amino-3-phenyl-propanoate hydrochloride (4.9g, 16.8mmol) was treated with NH_3/DCM (5mL) producing (±)-benzyl-2-amino-3-phenyl-propanoate **52f** as a cloudy, viscous oil (3.82g, 14.97mmol, 89%).
MF : $C_{16}H_{17}NO_2$

MW : 255.31

BP : > 200°C, P = 760 Torr (Lit. b.p.: 382.8 ± 27.0°C, P = 760 Torr[127])

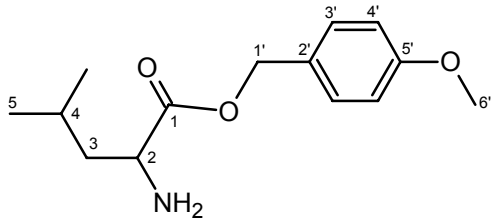
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 1.51 (broad s, 1H, N-H), 3.0 (dd, $^2J_{HH}$ = 13.5Hz, $^3J_{HH}$ = 7.5Hz, 1H, 3-H), 3.1 (dd, $^2J_{HH}$ = 13.5, $^3J_{HH}$ = 5.6Hz, 1H, 3-H), 3.77 (dd, $^3J_{HH}$ = 7.5, 5.6Hz, 1H, 2-H), 5.13 (s, 2H, 1'-H), 7.13-7.36 (m, 10H, Ph-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 40.7 (CH_2; C-3), 55.6 (CH; C-2), 66.8 (CH_2; C-1'), 126.8-129.8 (CH; C-*arom*), 135.6, 136.8 (C^q; C-*ipso*), 174.54 (C^q; C-1).

IR (film, NaCl); ν(cm^{-1}) = 3380(m), 3064(w), 3030(m), 2952(w), 1733(s), 1604(w), 1497(m), 1455(m), 1261(m), 1214(m), 1172(s), 1105(w), 1073(w), 1024(w), 1001(w), 911(w), 839(w), 742(m), 694(s).

MS (EI, 70eV); m/z (%) = 255 (3) [M^+], 163 (65) [M^+-$PhCH_3$], 86 (24) [163-$C_6H_5^+$], 77 (100) [$C_6H_5^+$].

(±)-*p*-Methoxybenzyl-2-amino-4-methyl-pentanoate 52g



(±)-2-Amino-4-methyl-pentanoic acid (*DL*-leucine) **60c** (2.63g, 20mmol), anhydrous *p*-toluenesulfonic acid **61** and *p*-toluenesulfonyl chloride **62** in *p*-methoxybenzyl alcohol yielded *p*-methoxybenzyl-2-amino-4-methyl-pentanoate *p*-toluenesulfonate salt as a white solid (5.93g, 14mmol, 70%).

MP = 141.6 - 143.0°C (decomp.).

IR (KBr); ν(cm^{-1}) = 3417(w), 3039(m), 2959(s), 1732(s), 1613(w), 1545(m), 1451(w), 1298(w), 1230(s), 1194(s), 1169(s), 1131(s), 1038(m), 1013(m), 919(w), 813(w), 681(m).

p-Methoxybenzyl-2-amino-4-methyl-pentanoate *p*-toluenesulfonate (5.89g, 13.9mmol) treated with 2M HCl/Et_2O produced a hydrochloride salt of **52g** as a white solid (3.92g, 13.6mmol, 98%).

MP = 182 - 184°C (decomp.).

IR (KBr); ν(cm^{-1}) = 2959(s), 1735(s), 1608(w), 1543(m), 1452(w), 1300(w), 1228(s), 1164(s), 1128(s), 1038(m), 1013(m), 919(w), 813(w), 681(m), 569(m).

p-Methoxybenzyl-2-amino-4-methyl-pentanoate hydrochloride (3.89g, 13.5mmol) wastreated with NH_3/DCM generating (±)-*p*-methoxybenzyl-2-amino-4-methyl-pentanoate **52g** as a yellow oil (510mg, 2.0mmol, 15%).

MF : $C_{14}H_{21}NO_3$

MW : 251.33

BP : > 200°C, P = 760 Torr

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.89 (d, $^3J_{HH}$ = 7.0Hz, 3H, 5-H), 0.93 (d, $^3J_{HH}$ = 7.0Hz, 3H, 5-H), 1.29-1.34 (m, 1H, 3-H), 1.37-1.42 (m, 1H, 3H), 1.63-1.67 (m, 1H, 4-H), 3.46 (dd, $^3J_{HH}$ = 5.5, 8.5Hz, 1H, 2-H), 3.79 (s, 3H, 6'-H), 5.07 (s, 2H, 1'-H), 6.9 (d, $^3J_{HH}$ = 8.9Hz, 2H, 4'-H), 7.26 (d, $^3J_{HH}$ = 8.9Hz, 2H, 3'-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 21.6, 21.9 (CH_3; C-5), 24.5 (CH; C-4), 42.0 (CH_2; C-3), 55.2 (CH_3; C-6'), 55.4 (CH; C-2), 67.0 (CH_2; C-1'), 113.6, 113.8 (CH; C-4'), 127.4 (C^q; C-2'), 129.6, 130.1 (CH; C-3'), 159.7 (C^q; C-5'), 173.5 (C^q; C-1).

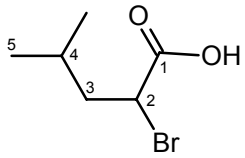
IR (film, NaCl); ν(cm^{-1}) = 3421(m), 2926(m), 2856(w), 1738(s), 1632(w), 1455(m), 1375(w), 1262(s), 1075(s), 1025(s), 800(s).

MS (EI, 70eV); m/z (%) = 251 (4) [M^+], 121 (84) [$CH_3OC_6H_4CH_2^+$], 86 (46) [M^+-$CH_3OC_6H_4CH_2CO_2H$], 78 (14) [C_6H_6], 77 (11) [$C_6H_5^+$], 44 (100) [CO_2].

CHN = Required for $C_{14}H_{21}NO_3$: C, 66.91%; H, 8.42%; N, 5.57. Found: C, 66.79%; H, 8.49%; N, 5.32%.

4.3 Synthesis of α-bromo acids and esters

2-Bromo-4-methyl-pentanoic acid 109



(±)-2-Amino-4-methyl-pentanoic acid (*DL*-leucine) **60c** (1.64g, 12.6mmol) was added, with stirring, to a cooled solution (0°C) of KBr (9.0g, 75.6mol) in 3M H_2SO_4 (49mL). Sodium nitrite (2.35g, 34mmol) was added and a reflux condenser containing metal parts was attached with an outlet tube to the back of the fume hood. The mixture was left stirring for 90 min at 0°C. Et_2O (~25mL) was added to the reaction mixture and left stirring for a further 60 min. The organic phase was separated and the aqueous solution was extracted with Et_2O (3 x 15mL). The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure using an oil pump. The product, a red

oil, was distilled using a Kugelrohr distillation yielding 2-bromo-4-methyl-pentanoic acid **109** as a yellow oil (1.34g, 6.87mmol, 55%).

MF : $C_6H_{11}O_2Br$

MW : 195.06

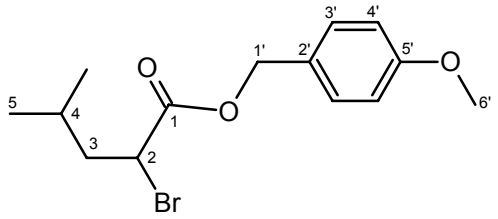
BP : 103°C, 0.1 Torr (Lit. b.p.: 76-79°C, P = 0.2 Torr[128])

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.93 (d, $^3J_{HH}$ = 6.4Hz, 3H, 5-H), 0.97 (d, $^3J_{HH}$ = 6.4Hz, 3H, 5-H), 1.2-1.6 (m, 1H, 4-H), 1.77-1.95 (m, 2H, 3-H), 4.27 (dd, $^3J_{HH}$ = 7.5, 7.86Hz, 1H, 2-H), 9.5 (broad s, 1H, O-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 21.9, 22.7 (CH_3; C-5), 26.7 (CH; C-4), 43.6 (CH_2; C-3), 43.8 (CH; C-2), 176.5 (C^q; C-1).

IR (film, NaCl); ν(cm^{-1}) = 2861(s), 2673(w), 1720(s), 1514(w), 1464(m), 1422(m), 1261(s), 1171(m), 1115(m), 1029(m), 923(w), 875(w), 802(m).

***p*-Methoxybenzyl-2-bromo-4-methyl-pentanoate 110**



2-Bromo-4-methyl-pentanoic acid **109** (1.17g, 6mmol), *p*-methoxybenzyl alcohol (2.27mL, 18mmol) and DMAP (2-5mg) were added together in dry THF (~75mL) and cooled (0°C). DCC (1.24g, 6mmol) was added slowly, the mixture was warmed to r.t. and left stirring for 12 h. A white precipitate was produced which was filtered off using a Büchner funnel, a little DCM was added to the filtrate and washed thoroughly with i) 0.5M HCl (2 x 25mL), ii) saturated $NaHCO_3$ solution (25mL) and iii) H_2O (50mL). The organic solution was dried over $MgSO_4$, concentrated *in vacuo* using the rotary evaporator and purified using column chromatography affording *p*-methoxybenzyl-2-bromo-4-methyl-pentanoate **110** as a brown oil (1.53g, 4.86mmol, 81%); R_f = 0.56 (1:8 Et_2O-hexane).

MF : $C_{14}H_{19}O_3Br$

MW : 315.21

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.85 (d, $^3J_{HH}$ = 6.4Hz, 3H, 5-H), 0.88 (d, $^3J_{HH}$ = 6.4Hz, 3H, 5-H), 1.32-1.65 (m, 1H, 4-H), 1.80-1.83 (m, 2H, 3-H), 3.73 (s, 3H, 6'-H), 4.2 (dd, $^3J_{HH}$ = 7.5, 7.86Hz, 1H, 2-H), 5.06 (s, 2H, 1'-H), 6.82 (dd, $^3J_{HH}$ = 9.55Hz, 2H, 4'-H), 7.24 (dd, $^3J_{HH}$ = 9.55Hz, 2H, 3'-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 21.1, 21.3 (CH_3; C-5), 25.4 (CH; C-4), 42.4 (CH_2; C-3), 43.7 (CH; C-2), 54.2 (CH_3; C-6'), 66.4 (CH_2; C-1'), 112.9 (CH; C-4'), 126.3 (C^q; C-2'), 129.1 (CH; C-3'), 158.8 (C^q; C-5'), 168.9 (C^q; C-1).

IR (film, NaCl); ν(cm^{-1}) = 2934(s), 1734(s), 1695(s), 1612(s), 1586(w), 1513(s), 1463(m), 1413(w), 1302(m), 1248(s), 1174(m), 1110(w), 1042(s), 817(m), 753(w).

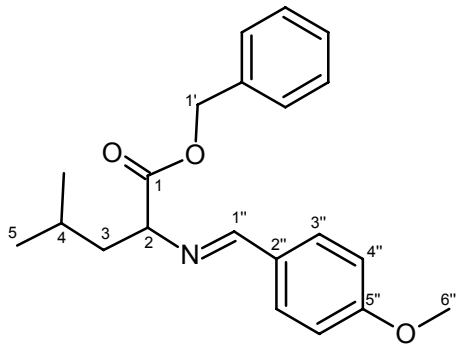
MS (EI, 70eV); m/z (%) = 177 (41) [M^+-$CH_3OC_6H_4CH_2OH$], 97 (54) [177-Br^-], 69 (100) [97-CO].

CHN = Required for $C_{14}H_{19}O_3Br$: C, 53.35%; H, 6.08%. Found: C, 52.96%; H, 5.91%.

4.4 Synthesis of N-substituted leucine esters

4.4.1 Synthesis of α-imine and α-amino esters

(±)-Benzyl-2-[(4-methoxy-benzylidine)-amino]-4-methyl-pentanoate 111



(±)-Benzyl-2-amino-4-methyl-pentanoate **52e** (332mg, 1.5mmol) and 4-methoxybenzaldehyde (216mg, 1.8mmol) in dry toluene (25 - 30mL) was heated to reflux with the azeotropic removal of water, for 8 h. The reaction mixture was cooled, the solvent was removed using a rotary evaporator and the residual aldehyde was removed via distillation. (±)-Benzyl-2-[(4-methoxy-benzylidine)-amino]-4-methyl-pentanoate **111** was produced as a pale yellow oil (365mg, 1.1mmol, 72%).

MF : $C_{21}H_{25}NO_3$

MW : 339.44

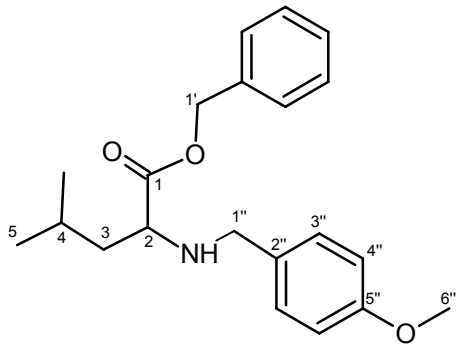
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.80 (d, $^3J_{HH}$ = 6.6Hz, 3H, 5-H), 0.85 (d, $^3J_{HH}$ = 6.6Hz, 3H, 5-H), 1.18-1.24 (m, 1H, 3-H), 1.44-1.53 (m, 1H, 3-H), 1.69-1.83 (m, 1H, 4-H), 3.75 (s, 3H, 6"-H), 4.0 (dd, $^3J_{HH}$ = 5.85, 8.55Hz, 1H, 2-H), 5.1 (s, 2H, 1'-H), 6.84 (d, $^3J_{HH}$ = 8.7Hz, 2H, 4"-H), 7.2-7.3 (m, 5H, Ph-H), 7.63 (d, $^3J_{HH}$ = 8.7Hz, 2H, 3"-H), 8.13 (s, 1H, 1"-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 21.5, 21.9 (CH_3; C-5), 25.2 (CH; C-4), 40.0 (CH_2; C-3), 60.1 (CH_3; C-6"), 62.8 (CH; C-2), 66.9 (CH_2; C-1'), 112.3, 112.8 (CH; C-4"), 127.2 (C^q; C-2"), 127.6-129.9 (CH; C-*arom* and C-3"), 133.2 (C^q; C-*ipso*, Bn), 159.0 (C^q; C-5"), 171.7 (CH; C-1"), 173.0 (C^q; C-1).

IR (film, NaCl); ν(cm^{-1}) = 3033(m), 2956(s), 2938(m), 2831(m), 1737(s), 1660(s), 1511(m), 1444(m), 1245(s), 1179(s), 1156(m), 1038(m), 827(m), 751(m), 699(w).

CHN = Required for $C_{21}H_{25}NO_3$: C, 74.31%; H, 7.42%; N, 4.13. Found: C, 73.16%; H, 7.43%; N, 4.05%.

(±)-Benzyl-2-[4-methoxy-benzylamino]-4-methyl-pentanoate 112



(±)-Benzyl-2-[(4-methoxy-benzylidine)-amino]-4-methyl-pentanoate **111** (325mg, 1.0mmol) was dissolved in dry MeOH (~50mL), cooled to -10°C (ice/salt) and $NaBH_4$ (45.4mg, 1.2mmol) was added. The reaction mixture was maintained at -10 °C, with stirring for 1 h.; progress of the reaction was monitored using TLC. The mixture was brought to r.t. and DCM was added (~50mL). The organic layer was separated out, washed with water (2 x 30mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure yielding (±)-benzyl-2-[4-methoxy-benzylamino]-4-methyl-pentanoate **112** as a colourless oil (305mg, 0.89mmol, 89.4%).

MF : $C_{21}H_{27}NO_3$

MW : 341.45

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.75 (d, $^3J_{HH}$ = 6.60Hz, 3H, 5-H), 0.82 (d, $^3J_{HH}$ = 6.60Hz, 3H, 5-H), 1.13-1.25 (m, 1H, 3-H), 1.36-1.42 (m, 1H, 3-H), 1.64-1.70 (m, 1H, 4-H), 3.25 (t, $^3J_{HH}$ = 7.3Hz, 1H, 2-H), 3.68 (dd, $^2J_{HH}$ = 12.6Hz, 1H, 1"-H), 3.71 (s, 3H, 6"-H), 5.1 (s, 1H, 1'-H), 6.75 (d, $^3J_{HH}$ = 8.6Hz, 2H, 4"-H), 7.11 (d, $^3J_{HH}$ = 8.6Hz, 2H, 3"-H), 7.3 (m, 5H, Ph-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 21.2, 21.7 (CH_3; C-5), 25.3 (CH; C-4), 41.7 (CH_2; C-3), 50.5 (CH_2; C-1"), 54.2 (CH_3; C-6"), 58.2 (CH; C-2), 65.3 (CH_2; C-1'),

112.7 (CH; C-4"), 127.3-128.4 (CH; C-*arom* and C^q; C-2"), 128.4 (CH; C-3"), 133.9 (C^q; C-*ipso*, Bn), 157.6 (C^q; C-5"), 174.9 (C^q; C-1).

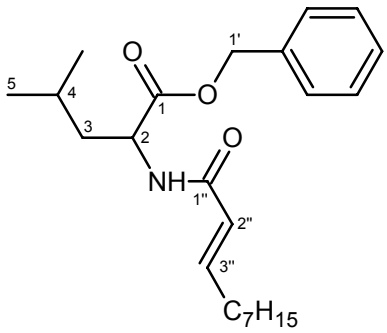
IR (film, NaCl); ν(cm^{-1}) = 3166(w), 3034(m), 2956(s), 2946(m), 2845(m), 2835(w), 1741(s), 1512(m), 1445(m), 1248(s), 1179(s), 1149(m), 1036(m), 828(m), 753(m), 690(w).

CHN = Required for $C_{21}H_{27}NO_3$: C, 73.87%; H, 7.97%; N, 4.10. Found: C, 73.59%; H, 7.99%; N, 4.06%.

4.4.2 Synthesis of N-acyl leucine esters

The amino ester (10mmol) was dissolved in dry DCM (25mL), cooled to -10°C (ice/salt) and triethylamine (11mmol) was added dropwise, with stirring. After some minutes, the corresponding chloride was added (12mmol) and left to stir for a further 4 h. A precipitate formed, which was removed via filtration (Büchner funnel) and washed well with DCM. The solvent was removed from the filtrate under reduced pressure and dried on an oil pump, generating the amide esters as oils. Where specified, column chromatography was also used as a purification technique.

(±)-(*E*)-Benzyl-2-(dec-2-enoylamino)-4-methyl-pentanoate 83a



(±)-Benzyl-2-amino-4-methyl-pentanoate **52e** (200mg, 0.9mmol) and *(E)*-dec-2-enoyl chloride produced (±)-(*E*)-benzyl-2-(dec-2-enoylamino)-4-methyl-pentanoate **83a** as a yellow oil (198mg, 0.53mmol, 62%), R_f = 0.87 (1:3 EtOAc-hexane).

MF : $C_{23}H_{35}NO_3$

MW : 373.54

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.85 (d, $^3J_{HH}$ = 6.8Hz, 3H, 5-H), 0.88 (t, $^3J_{HH}$ = 6.58Hz, 3H, 10"-H), 0.92 (d, $^3J_{HH}$ = 6.8Hz, 3H, 5-H), 1.26-1.65 (m, 13H, 3-H, 4-H, 5" – 9"-H), 2.26 (dt, $^3J_{HH}$ = 7.6, 7.7Hz, 2H, 4"-H), 4.6 (dd, $^3J_{HH}$ = 5.75, 8.76Hz, 1H, 2-H),

5.2 (s, 2H, 1'-H), 5.8 (dt, $^3J_{HH}$ = 15.6Hz, $^4J_{HH}$ = 1.57Hz, 1H, 2"-H), 7.1 (dt, $^3J_{HH}$ = 7.7, 15.6Hz, 1H, 3"-H), 7.30-7.35 (m, 5H, Ph-H).

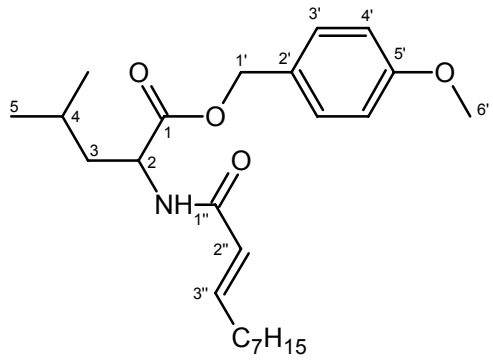
^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 14.0 (CH_3; C-10"), 22.0, 23.1 (CH_3; C-5), 24.1 (CH; C-4), 28.0, 28.9, 29.0, 29.1, 31.6, 31.7, 32.2 (CH_2; C-4" - C-9"), 43.6 (CH_2; C-3), 52.6 (CH; C-2), 66.7 (CH_2; C-1'), 121.3 (CH; C-2"), 126.9, 127.6 (CH; *o*C-*arom*), 128.2, 128.3, 128.5 (CH; *m*, *p*C-*arom*), 135.6 (C^q; C-*ipso*), 150.7 (CH; C-3"), 170.4 (C^q; C-1"), 175.8 (C^q; C-1).

IR (film, NaCl); ν(cm^{-1}) = 3309(m), 2957(s), 2928(s), 2857(s), 1743(s), 1699(s), 1654(s), 1519(w), 1467(w), 1420(m), 1380(w), 1283(m), 1216(w), 1156(m), 980(m), 748(m), 698(m).

MS (EI, 70eV); m/z (%) = 373 (3) [M^+], 357 (100) [M^+-CH_4], 272 (4) [357-$C_6H_{13}^+$], 180 (5) [272- $PhCH_3$], 91 (19) [$PhCH_2^+$].

CHN = Required for $C_{23}H_{35}NO_3$: C, 73.96%; H, 9.45%; N, 3.75. Found: C, 73.49%; H, 9.26%; N, 3.54%.

(±)-(*E*)-*p*-Methoxybenzyl-2-(dec-2-enoylamino)-4-methyl-pentanoate 83b



(±)-*p*-Methoxybenzyl-2-amino-4-methyl-pentanoate **52g** (150mg, 0.60mmol) and decenoyl chloride produced a brown residue which was purified using column chromatography yielding (±)-(*E*)-*p*-methoxybenzyl-2-(dec-2-enoylamino)-4-methyl-pentanoate **83b** as a brown oil (133mg, 0.33mmol, 55%); R_f = 0.84 (1:3 EtOAc-hexane).

N.B. PMB esters decomposed on the 'normal'* silica chromatography column and so the silica was first washed with 3% Et_3N/DCM, followed by a thorough washing with 1:3 EtOAc-hexane. *see methods and materials

MF : $C_{24}H_{37}NO_4$

MW : 403.56

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.89 (t, $^3J_{HH}$ = 6.7Hz, 3H, 10"-H), 0.91 (d, $^3J_{HH}$ = 6.85Hz, 3H, 5-H), 0.92 (d, $^3J_{HH}$ = 6.85Hz, 3H, 5-H), 1.26-1.71 (m, 13H, 3-H, 4-H, 5" – 9"-H), 2.26 (dt, $^3J_{HH}$ = 7.6, 7.7Hz, 2H, 4"-H), 3.8 (s, 3H, 6'-H), 4.7 (dd, $^3J_{HH}$ = 5.69,

8.72Hz, 1H, 2-H), 5.1 (s, 2H, 1'-H), 5.8 (d, $^3J_{HH}$ = 15.3Hz, 1H, 2"-H), 6.82 (dt, $^3J_{HH}$ = 7.6, 15.3Hz, 1H, 3"-H), 6.85 (d, $^3J_{HH}$ = 8.6Hz, 2H, 4'-H), 7.3 (d, $^3J_{HH}$ = 8.6Hz, 2H, 3'-H).

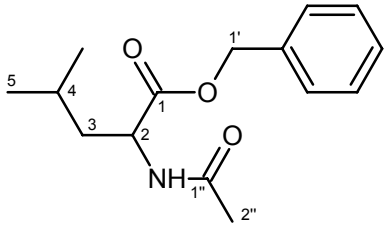
^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 14.1 (CH_3; C-10"), 22.0 (CH_2; C-9"), 22.6, 22.8 (CH_3; C-5), 24.8 (CH; C-4), 28.2, 29.0, 29.1, 31.3, 32.1 (CH_2; C-4" – 8"), 43.9 (CH_2; C-3), 52.7 (CH; C-2), 55.3 (CH_3; C-6'), 66.9 (CH_2; C-1'), 113.7, 113.9 (CH; C-4'), 121.9 (CH; C-2"), 127.5 (C^q; C-2'), 130.1 (CH; C-3'), 148.9 (CH; C-3"), 159.7 (C^q; C-5'), 168.6 (C^q; C-1"), 175.1 (C^q; C-1).

IR (film, NaCl); ν(cm^{-1}) = 3307(w), 2961(s), 2875(s), 1740(s), 1650(s), 1532(s), 1450(w), 1424(w), 1384(m), 1348(m), 1283(w), 1217(s), 1187(s), 1154(s), 1060(w), 972(m), 751(m), 698(m).

MS (EI, 70eV); m/z (%) = 403 (2) [M^+], 372 (100) [M^+-CH_3O], 356 (70) [372-CH_4], 329 (6) [372-$C_3H_7^-$], 273 (2) [372-$C_7H_{15}^-$], 91 (82) [$PhCH_2^+$].

CHN = Required for $C_{24}H_{37}NO_4$: C, 71.43%; H, 9.24%; N, 3.47. Found: C, 71.06%; H, 9.27%; N, 3.12%.

(±)-Benzyl-2-acetylamino-4-methyl-pentanoate 83c



(±)-Benzyl-2-amino-4-methyl-pentanoate **52e** (615mg, 2.78mmol) and acetyl chloride produced (±)-benzyl-2-acetylamino-4-methyl-pentanoate **83c** as a yellow oil (706mg, 2.68mmol, 96.4%); R_f = 0.37 (1:1 EtOAc-hexane).

MF : $C_{15}H_{21}NO_3$

MW : 263.34

BP : > 200°C, P = 760 Torr (Lit. b.p.: 405.4 ± 20.0°C, P = 760 Torr[33])

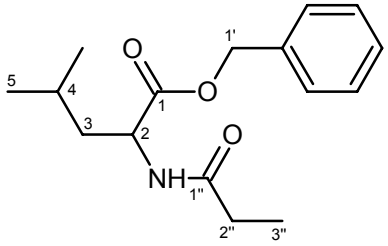
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.89 (d, $^3J_{HH}$ = 6.56Hz, 3H, 5-H), 0.90 (d, $^3J_{HH}$ = 6.56Hz, 3H, 5-H), 1.29-1.42 (m, 2H, 3-H), 1.48-1.59 (m, 1H, 4-H), 1.98 (s, 3H, 2"-H), 4.66 (td, $^3J_{HH}$ = 5.48, 5.94, 6.44Hz, 1H, 2-H), 5.13 (s, 2H, 1'-H), 6.01 (d, $^3J_{HH}$ = 6.44Hz, 1H, N-H), 7.29-7.34 (m, 5H, Ph-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 21.9, 22.7 (CH_3; C-5), 23.0 (CH; C-4), 24.8 (CH_3; C-2"), 41.5 (CH_2; C-3), 50.8 (CH; C-2), 66.9 (CH_2; C-1'), 128.1, 128.3, 128.5 (CH; C-*arom*), 135.3 (C^q; C-*ipso*), 169.8 (C^q; C-1), 173.1 (C^q; C-1").

IR (film, NaCl); ν(cm^{-1}) = 3282(m), 3065(m), 3035(m), 2958(s), 2871(m), 1744(s), 1654(s), 1545(s), 1455(m), 1371(m), 1336(w), 1273(m), 1192(m), 1153(s), 1081(w), 1030(w), 1002(m), 963(m), 921(w), 823(w), 747(m), 697(m), 599(m).

MS (EI, 70eV); m/z (%) = 263 (14) [M^+], 172 (1.5) [M^+-$C_6H_5CH_2^+$], 128 (64) [172-CO_2], 91 (49) [$C_6H_5CH_2^+$], 86 (100) [128-C_3H_6].

(±)-Benzyl-2-propionylamino-4-methyl-pentanoate 83d



(±)-Benzyl-2-amino-4-methyl-pentanoate **52e** (637mg, 2.88mmol) and propyl chloride produced (±)-benzyl-2-propionylamino-4-methyl-pentanoate **83d** as a clear oil (759mg, 2.74mmol, 95%); R_f = 0.62 (1:1 EtOAc-hexane).

MF : $C_{16}H_{23}NO_3$

MW : 277.36

BP : > 200°C, P = 760 Torr

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.89 (d, $^3J_{HH}$ = 6.2Hz, 3H, 5-H), 0.89 (d, $^3J_{HH}$ = 6.2Hz, 3H, 5-H), 1.12 (t, $^3J_{HH}$ = 7.6Hz, 3H, 3"-H), 1.47-1.65 (m, 3H, 3-H, 4-H), 2.22 (q, $^3J_{HH}$ = 7.6Hz, 2H, 2"-H), 4.6 (td, $^3J_{HH}$ = 5.13, 6.0, 6.6Hz, 1H, 2-H), 5.13 (dd, $^2J_{HH}$ = 12.3Hz, 2H, 1'-H), 5.88 (d, $^3J_{HH}$ = 6.6Hz, 1H, N-H), 7.33 (m, 5H, Ph-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 9.6 (CH_3; C-3"), 21.9, 22.7 (CH_3; C-5), 23.5 (CH; C-4), 24.8 (CH_2; C-2"), 41.7 (CH_2; C-3), 50.6 (CH; C-2), 66.9 (CH_2; C-1'), 128.1, 128.3, 128.5 (CH; C-*arom*), 135.3 (C^q; C-*ipso*), 173.1, 173.5 (C^q; C-1, C-1").

IR (film, NaCl); ν(cm^{-1}) = 3307(s), 3064(w), 2960(m), 2877(m), 1735(s), 1650(s), 1540(s), 1456(m), 1426(w), 1385(m), 1348(m), 1284(m), 1246(m), 1221(m), 1183(s), 1153(m), 1060(w), 946(w), 913(w), 884(w), 756(m), 700(m).

MS (EI, 70eV); m/z (%) = 277 (6) [M^+], 186 (1) [277-$C_6H_5CH_2^+$], 142 (20) [186-CO_2], 91 (19) [$C_6H_5CH_2^+$], 86 (100) [142- C_4H_8], 44 (7) [CO_2].

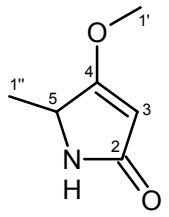
CHN = Required for $C_{16}H_{23}NO_3$: C, 69.29%; H, 8.36%; N, 5.05. Found: C, 69.24%; H, 8.38%; N, 5.0%.

4.5 Synthesis of pyrrol-2-ones

4.5.1 Synthesis of 4-alkoxy and 4-benzyloxy-pyrrol-2(5*H*)-ones

General procedure: The amino ester (10mmol) was added to a stirring solution of keteneylidenetriphenylphosphorane **1a** (13mmol) and a catalytic amount of benzoic acid (1-2mg) in dry THF (50mL). The reaction mixture was heated to reflux for 24 h with the exclusion of air and moisture. The resulting solution was cooled and the solvent was removed under reduced pressure. The crude residue was purified using column chromatography employing the solvent system indicated and recrystallised where possible.

(±)-4-Methoxy-5-methyl-pyrrol-2(5*H*)-one 69a



(±)-Methyl-2-amino-propanoate **52b** (1.03g, 10mmol), keteneylidenetriphenylphosphorane **1a** (3.93g, 13mmol) and benzoic acid (1-2mg) in dry THF (50mL) produced (±)-4-methoxy-5-methyl-pyrrol-2(5*H*)-one **69a** as pale orange crystals (0.90g, 7.11mmol, 71%); R_f = 0.16 (EtOAc).

MF : $C_6H_9NO_2$

MW : 127.14

MP : 111 - 115°C

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 1.33 (d, $^3J_{HH}$ = 6.75Hz, 3H, 1''-H), 3.80 (s, 3H, 1'-H), 4.10 (q, $^3J_{HH}$ = 6.75Hz, 1H, 5-H), 4.99 (s, 1H, 3-H), 5.60 (broad s, 1H, N-H).

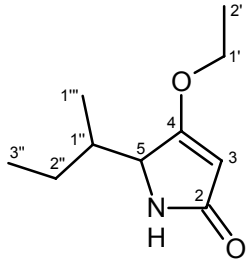
^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 17.7 (CH_3; C-1''), 53.2 (CH; C-5), 55.18 (CH_3; C-1'), 92.7 (CH; C-3), 174.4 (C^q; C-2), 179.3 (C^q; C-4).

IR (KBr); ν(cm^{-1}) = 3209(m), 3104(m), 2974(w), 2947(w), 2903(w), 1671(s), 1618(s), 1455(w), 1376(m), 1359(m), 1320(w), 1315(w), 1233(m), 1210(m), 1177(w), 1121(w), 1048(w), 992(m), 944(w), 831(m).

MS (EI, 70eV); m/z (%) = 127 (93) [M^+], 112 (100) [M^+-CH_3], 96 (66) [M^+-CH_3O], 68 (79) [96-C_2H_4].

CHN = Required for $C_6H_9NO_2$: C, 56.68%; H, 7.14%; N, 11.02. Found: C, 56.60%; H, 7.11%; N, 10.84%.

(±)-4-Ethoxy-5-*sec*-butyl-pyrrol-2(5*H*)-one 69b



(*2S,3S*)-ethyl-2-amino-3-methyl-pentanoate **52c** (1.59g, 10mmol), keteneylidenetriphenylphosphorane **1a** (3.93g, 13mmol) and benzoic acid in dry THF (50mL) produced a brown residue which was purified using column chromatography followed by stirring in refluxing ether for 2 h. A mixture of diastereoisomers (*5S,1''S*)- and (*5R,1''S*)-4-ethoxy-5-*sec*-butyl-pyrrol-2(5*H*)-one **69b** were generated as a shiny white solid (1.03g, 5.6mmol, 56%), R_f = 0.74 (1:9 MeOH-EtOAc), in a 1:4.25 ratio.

MF : $C_{10}H_{17}NO_2$

MW : 183.25

MP : 166 - 169°C

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.69 (d, $^3J_{HH}$ = 6.78Hz, 3H, 1'''-H, *isomer i*), 0.89 (t, $^3J_{HH}$ = 7.40Hz, 3H, 3''-H, *isomer i*), 0.95 (d, $^3J_{HH}$ = 6.99Hz, 3H, 1'''-H, *isomer ii*), 0.98 (t, $^3J_{HH}$ = 7.44Hz, 3H, 3''-H, *isomer ii*), 1.21 (t, $^3J_{HH}$ = 7.0Hz, 3H, 2'-H), 1.37-1.42 (m, 2H, 2''-H), 1.83-1.85 (m, 1H, 1''-H), 3.48 (q, $^3J_{HH}$ = 7.0Hz, 2H, 1'-H), 3.94-3.99 (m, 1H, 5-H, *isomer i*), 4.0-4.08 (m, 1H, 5-H, *isomer ii*), 4.99 (s, 1H, 3-H), 5.35 (s, 1H, N-H, *isomer i*), 5.39 (s, 1H, N-H, *isomer ii*).

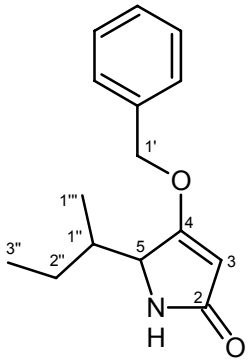
^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 11.9, 12.0, 14.1, 15.7, 15.8 (CH_3; C-2', C-3'', C-1'''), 23.2, 27.1 (CH_2; C-2''), 35.6, 36.4 (CH; C-1''), 61.0, 62.3 (CH; C-5), 67.0, 67.1 (CH_2; C-1'), 94.3, 94.5 (CH; C-3), 173.0, 173.2 (C^q; C-2), 174.0, 174.3 (C^q; C-4).

IR (KBr); ν(cm^{-1}) = 3186(m), 3065(w), 2960(m), 2927(m), 2871(w), 1677(s), 1613(s), 1468(w), 1371(m), 1339(s), 1210(s), 1105(w), 1032(m), 895(w), 879(w), 823(m), 807(m), 758(m).

MS (EI, 70eV); m/z (%) = 183 (25) [M^+], 167 (7) [M^+-CH_4], 126 (100) [M^+-$C_4H_9^+$], 99 (80), 69 (20).

CHN = Required for $C_{10}H_{17}NO_2$: C, 65.54%; H, 9.35%; N, 7.64. Found: C, 65.37%; H, 9.28%; N, 7.31%.

(±)-4-Benzyloxy-5-*sec*-butyl-pyrrol-2(5*H*)-one 69c



(*2S*,*3S*)-Benzyl-2-amino-3-methyl-pentanoate **52d** (3.32g, 15mmol), keteneylidenetriphenylphosphorane **1a** (5.90g, 19.5mmol) and benzoic acid in dry THF (75mL) produced a brown oil which was purified using column chromatography, washed with a hexane-ethyl acetate mixture and recrystallised from EtOAc yielding a mixture of diastereomers (*5S,1''S*)- and (*5R,1''S*)-4-benzyloxy-5-*sec*-butyl-pyrrol-2(5*H*)-one **69c** as a white solid (1.40g, 5.72mmol, 43%); R_f = 0.32 (EtOAc), in a 1:1 ratio.

MF : $C_{15}H_{19}NO_2$

MW : 245.32

MP : 113.5 - 114.6°C

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.68 (d, $^3J_{HH}$ = 6.8Hz, 3H, 1'''-H, *isomer i*), 0.87 (t, $^3J_{HH}$ = 7.4Hz, 3H, 3''-H, *isomer i*), 0.93 (d, $^3J_{HH}$ = 7.0Hz, 3H, 1'''-H, *isomer ii*), 0.96 (t, $^3J_{HH}$ = 7.9Hz, 3H, 3''-H, *isomer ii*), 1.34-1.39 (m, 2H, 2''-H), 1.78-1.82 (m, 1H, 1''-H), 4.08 (d, $^3J_{HH}$ = 7.12Hz, 1H, 5-H, *isomer i*), 4.15 (d, $^3J_{HH}$ = 7.14Hz, 1H, 5-H, *isomer ii*), 4.97 (dd, $^2J_{HH}$ = 11.62Hz, 2H, 1'-H), 5.11 (s, 1H, 3-H), 6.48 (s, 1H, N-H, *isomer i*), 6.57 (s, 1H, N-H, *isomer ii*), 7.38 (m, 5H, Ph-H).

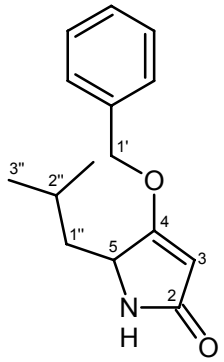
^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 11.97, 12.02, 12.06, 15.7 (CH_3; C-3'', C-1'''), 23.05, 27.06 (CH_2; C-2''), 35.70, 36.38 (CH; C-1''), 61.44, 62.75 (CH; C-5), 72.98, 73.07 (CH_2; C-1'), 95.43, 95.65 (CH; C-3), 127.73 - 128.71 (CH; C-*arom*), 134.93, 134.96 (C^q; C-*ipso*), 175.01, 175.28 (C^q; C-2), 176.19, 176.36 (C^q; C-4).

IR (KBr); ν(cm^{-1}) = 3194(w), 3068(w), 2960(w), 2869(w), 1684(s), 1652(m), 1619(s), 1558(m), 1540(w), 1521(w), 1507(w), 1457(w), 1384(w), 1340(m), 1261(w), 1185(w), 1028(w).

MS (EI, 70eV); m/z (%) = 246 (18) [M^++1], 245 (26) [M^+], 154 (33) [M^+- $C_6H_5CH_2^+$], 98 (30) [154-C_4H_8], 92 (64) [$C_6H_5CH_3$], 91 (58) [$C_6H_5CH_2^+$], 86 (100), 69 (43).

CHN = Required for $C_{15}H_{19}NO_2$: C, 73.44%; H, 7.81%; N, 5.71. Found: C, 73.01%; H, 7.29%; N, 5.56%.

(±)-4-Benzyloxy-5-*iso*-butyl-pyrrol-2(5*H*)-one 69d



(±)-Benzyl-2-amino-4-methyl-pentanoate **52e** (3.32g, 15mmol), keteneylidenetriphenylphosphorane **1a** (5.90g, 19.5mmol) and benzoic acid in dry THF (75mL) produced a brown oil which was purified using column chromatography, washed with a hexane-EtOAc mixture and recrystallised from Et_2O yielding (±)-4-benzyloxy-5-*iso*-butyl-pyrrol-2(5*H*)-one **69d** as a white solid (1.77g, 7.2mmol, 62%); R_f = 0.22 (EtOAc).

MF : $C_{15}H_{19}NO_2$

MW : 245.32

MP : 115 - 115.2°C

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.96 (d, $^3J_{HH}$ = 6.3Hz, 3H, 3"-H), 0.98 (d, $^3J_{HH}$ = 6.3Hz, 3H, 3"-H), 1.40 (m, 2H, 1"-H), 1.71 (m, 1H, 2"-H), 4.11 (dd, $^3J_{HH}$ = 3.64, 7.45Hz, 1H, 5-H), 4.97 (dd, $^2J_{HH}$ = 11.62Hz, 2H, 1'-H), 5.1 (s, 1H, 3-H), 5.58 (s, 1H, N-H), 7.39 (m, 5H, Ph-H).

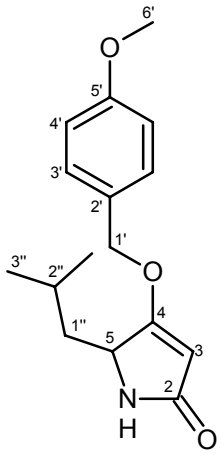
^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 21.8, 23.5 (CH_3; C-3"), 25.7 (CH; C-2"), 41.4 (CH_2; C-1"), 56.2 (CH; C-5), 73.1 (CH_2; C-1'), 94.3 (CH; C-3), 127.8, 128.7, 128.8 (CH; C-*arom*), 134.8 (C^q; C-*ipso*), 174.0 (C^q; C-2), 177.6 (C^q; C-4).

IR (KBr); ν(cm^{-1}) = 3196(w), 3068(s), 2959(m), 2869(m), 1681(s), 1620(m), 1455(w), 1341(m), 1226(w), 1186(w), 991(m), 821(m).

MS (EI, 70eV); m/z (%) = 246 (7) [M^++1], 245 (6) [M^+], 215 (4) [M^+-C_2H_6], 202 (11) [M^+-$C_3H_7^+$], 189 (19) [M^+-C_4H_8], 123 (21) [215- $C_6H_5CH_3$], 122 (93), 106 (23) [123-OH^-], 105 (93) [123-H_2O], 91 (77) [$C_6H_5CH_2^+$], 86 (9), 77 (100) [$C_6H_5^+$].

CHN = Required for $C_{15}H_{19}NO_2$: C, 73.44%; H, 7.81%; N, 5.71. Found: C, 70.99%; H, 7.54%; N, 5.41%.

(±)-4-*p*-Methoxybenzyloxy-5-*iso*-butyl-pyrrol-2(5*H*)-one 69e



(±)-*p*-Methoxybenzyl-2-amino-4-methyl-pentanoate hydrochloride (576mg, 2.0mmol), keteneylidenetriphenylphosphorane **1a** (786mg, 2.6mmol) and benzoic acid (1-2mg) in dry THF (25mL) for 48 h yielded (±)-4-*p*-methoxybenzyloxy-5-*iso*-butyl-pyrrol-2(5*H*)-one **69e** as an orange oil (41.38mg, 0.15mmol, 8%); R_f = 0.61 (1:1 EtOAc-hexane).

MF : $C_{16}H_{21}NO_3$

MW : 275.35

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.94 (d, $^3J_{HH}$ = 6.6Hz, 3H, 3"-H), 0.97 (d, $^3J_{HH}$ = 6.6Hz, 3H, 3"-H), 1.55 (m, 2H, 1"-H), 2.45 (m, 1H, 2"-H), 3.80 (s, 3H, 6'-H), 4.06 (dd, $^3J_{HH}$ = 3.47, 7.5Hz, 1H, 5-H), 4.58 (s, 2H, 1'-H), 5.12 (s, 1H, 3-H), 6.88 and 6.90 (2 x d, $^3J_{HH}$ = 8.7Hz, 2H, 4'-H), 7.29 and 7.32 (2 x d, $^3J_{HH}$ = 8.7Hz, 2H, 3'-H).

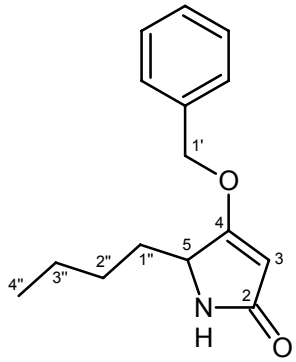
^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 22.1, 22.9 (CH_3; C-3"), 26.3 (CH; C-2"), 41.8 (CH_2; C-1"), 55.3 (CH_3; C-6'), 56.4 (CH; C-5), 72.7 (CH_2; C-1'), 94.6 (CH; C-3), 113.7, 114.1 (CH; C-4'), 129.8, 132.2 (CH; C-3'), 131.1 (C^q; C-2'), 152.0 (C^q; C-5'), 175.3, (C^q; C-2), 179.5 (C^q; C-4).

IR (film, NaCl); ν(cm^{-1}) = 3188(w), 2955(m), 2928(m), 2867(w), 1678(m), 1614(s), 1515(w), 1438(w), 1382(m), 1259(s), 1186(m), 1115(m), 725(m), 688(m).

MS (EI, 70eV); m/z (%) = 275 (8) [M^+], 154 (3) [M^+-$CH_3OC_6H_4CH_2^+$], 121 (100) [$CH_3OC_6H_4CH_2^+$], 112 (39) [154-C_3H_6].

CHN = Required for $C_{16}H_{21}NO_3$: C, 69.79%; H, 7.69%; N, 5.09. Found: C, 69.48%; H, 7.82%; N, 4.83%.

4-Benzyloxy-5-n-butyl-pyrrol-2(5H)-one[96] 69f



MF : $C_{15}H_{19}NO_2$

MW : 245.37

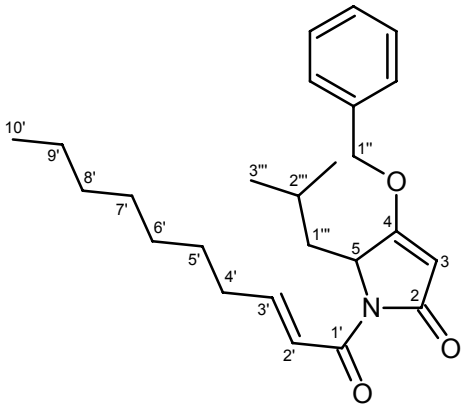
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.81 (t, $^3J_{HH}$ = 7.0Hz, 3H, 4"-H), 1.18-1.28 (m, 4H, 2"-H, 3"-H), 1.45-1.51 (m, 1H, 1"-H), 1.72-1.77 (m, 1H, 1"-H), 4.0 (dd, $^3J_{HH}$ = 7.41, 7.56Hz, 1H, 5-H), 4.9 (dd, $^2J_{HH}$ = 11.7Hz, 2H, 1'-H), 5.0 (s, 1H, 3-H), 7.0 (s, 1H, N-H), 7.24-7.39 (m, 5H, Ph-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 13.1 (CH_3; C-4"), 22.0 (CH_2; C-3"), 26.0 (CH_2; C-2"), 30.6 (CH_2; C-1"), 56.9 (CH; C-5), 72.0 (CH_2; C-1'), 94.4 (CH; C-3), 126.7, 126.8, 127.6, 127.7 (CH; C-*arom*), 133.9 (C^q; C-*ipso*), 173.8 (C^q; C-2), 176.1 (C^q; C-4).

IR (KBr); ν(cm^{-1}) = 3192(m), 3065(w), 2961(m), 2936(m), 2871(w), 2855(w), 1672(s), 1613(s), 1457(m), 1436(w), 1395(w), 1333(s), 1205(m), 1113(m), 1024(w), 976(w), 952(w), 912(w), 810(m), 742(m), 718(w), 697(m).

4.5.2 Synthesis of 1-acyl-4-benzyloxy-pyrrol-2(5*H*)-ones

(±)-(*E*)-1-(Dec-2-enoyl)-4-benzyloxy-5-*i*-butyl-pyrrol-2(5*H*)-one 84b



A solution of (±)-4-benzyloxy-5-*iso*-butyl-pyrrol-2(5*H*)-one **69d** (100mg, 0.41mmol) in dry methylene chloride (5mL) was cooled to -20 °C (CCl_4/CO_2), TEA (63µL, 0.45mmol)

was added, stirred for 1 - 2 min., followed by the addition of decenoyl chloride (84mg, 0.45mmol). The reaction mixture was slowly brought to r.t., stirred for 6 h and the crude product was purified by dissolution in hexane generating (±)-(*E*)-1-(dec-2-enoyl)-4-benzyloxy-5-*i*-butyl-pyrrol-2(5*H*)-one **84b** as a yellow-brown oil (111mg, 0.28mmol, 68%); R_f = 0.42 (1:3 EtOAc-hexane).

MF : $C_{25}H_{35}NO_3$

MW : 397.56

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.82-0.93 (m, 9H, 3'''-H, 10'-H), 1.21-1.29 (m, 6H, 7'-H, 8'-H, 9'-H), 1.36-1.44 (m, 2H, 1'''-H), 1.64-1.72 (m, 2H, 6'-H), 1.86-1.91 (m, 2H, 5'-H), 2.18-2.32 (m, 2H, 4'-H), 2.87-2.98 (m, 1H, 2'''-H), 4.0 (d, $^3J_{HH}$ = 15.1Hz, 1H, 2'-H), 4.72 (dd, $^3J_{HH}$ = 4.29, 7.66Hz, 1H, 5-H), 5.14 (dd, $^2J_{HH}$ = 12.2Hz, 2H, 1''-H), 5.16 (s, 1H, 3-H), 5.78 (dt, $^3J_{HH}$ = 15.1, 7.5Hz, 1H, 3'-H), 7.30-7.34 (m, 5H, Ph-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 13.7 (CH_3; C-10'), 22.6 (CH_2; C-9'), 22.9, 23.4 (CH_3; C-3'''), 23.9 (CH; C-2'''), 27.8-39.0 (CH_2; C-1''', C-4' – 8'), 55.8 (CH; C-5), 67.5 (CH_2; C-1''), 94.3 (CH; C-3), 120.6 (CH; C-2'), 127.6-128.93 (CH; C-*arom*), 135.2 (C^q; C-*ipso*), 152.1 (CH; C-3'), 157.4 (C^q; C-1'), 174.1 (C^q; C-2), 178.71 (C^q; C-4).

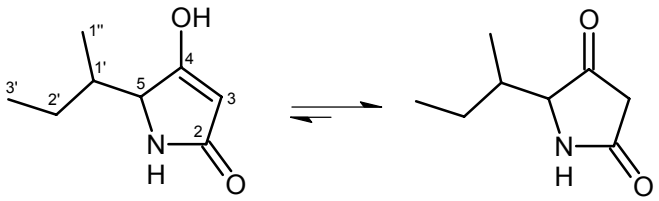
IR (KBr); ν(cm^{-1}) = 2998(m), 2959(m), 1680(s), 1639(m), 1620(m), 1515(w), 1457(w), 1428(w), 1345(m), 1283(m), 1221(w), 1182(w), 981(m), 831(m).

MS (EI, 70eV); m/z (%) = 398 (5) [M^+], 382 (62) [M^+-CH_4], 299 (9) [M^+-$C_7H_{15}^+$], 255 (4) [299-C_3H_8], 164 (77) [255-$C_6H_5CH_2^+$], 92 (77) [$C_6H_5CH_3$], 77 (100) [$C_6H_5^+$].

CHN = Required for $C_{25}H_{35}NO_3$: C, 75.530%; H, 8.874%; N, 3.523. Found: C, 75.461%; H, 8.99%; N, 3.102%.

4.5.3 Synthesis of N*H*-pyrrolidine-2,4-diones

(±)-5-*sec*-Butyl-pyrrolidine-2,4-dione 51b



α **β**

To a solution of (±)-4-benzyloxy-5-*sec*-butyl-pyrrol-2(5*H*)-one **69c** (300mg, 1.2mmol) in methanol (25mL), palladium on charcoal (30mg) was added and the reaction vessel was evacuated and purged with H_2 three times. The reaction mixture was left stirring under an atmosphere of H_2 for 12 h. The solution was filtered over celite (4cm depth), washed

with methanol (monitored with TLC), the solvent was removed under reduced pressure and the residue was dried using an oil pump. (±)-5-*sec*-Butyl-pyrrolidine-2,4-dione **51b** was produced as a white solid (183mg, 1.18mmol, 98%) with a diastereomeric ratio 1:1. The tautomers were easily separated by washing with ethyl acetate: tautomer **β** dissolved readily while tautomer **α** was only partially soluble in methanol. Depending on the purity of the starting **69c**, it was necessary to purify **51b** by gently refluxing in hexane, followed by recrystallisation using pet. ether (40^o - 60^o) to yield white crystals.

MF : $C_8H_{13}NO_2$

MW : 155.20

MP : 116.2 - 117.7°C (Lit. m.p.; 117.5 - 119°C[53])

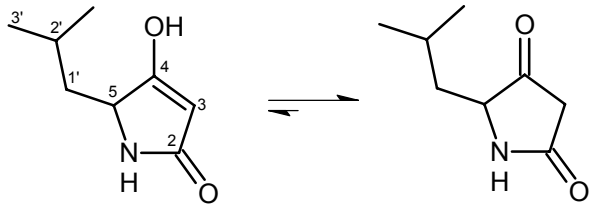
^{1}H-NMR (300MHz); δ(ppm) = **tautomer α** (CD_3OD)**:** 0.93 (2 x t, $^3J_{HH}$ = 7.4Hz, 3H, 3'-H), 0.99 (2 x d, $^3J_{HH}$ = 7.2Hz, 3H, 1''-H), 1.28 (2 x dq, $^3J_{HH}$ = 7.4, 7.5Hz, 1H, 2'-H), 1.49 (2 x dq, $^3J_{HH}$ = 4.2, 7.4Hz, 1H, 2'-H), 2.0 (m incl. ddt, $^3J_{HH}$ = 4.0, 4.2, 7.2, 7.5Hz, 1H, 1'-H), 3.97 (2 x d, $^3J_{HH}$ = 4.0Hz, 1H, 5-H), 5.62 (2 x s, 1H, 3-H), 5.81 (2 x broad s, 1H, N-H). **tautomer β** ($CDCl_3$)**:** 0.92 (2 x t, $^3J_{HH}$ = 7.4Hz, 3H, 3'-H), 1.02 (2 x d, $^3J_{HH}$ = 7.1Hz, 3H, 1''-H), 1.2-1.45 (m incl. dq, $^3J_{HH}$ = 4.03, 7.4Hz, 2H, 2'-H), 1.7-1.9 (m, 1H, 1'-H), 3.21 (s, 2H, 3-H), 3.92 (2 x d, $^3J_{HH}$ = 3.9Hz, 1H, 5-H), 7.7-7.9 (2 x broad s, 1H, N-H).

^{13}C-NMR (125MHz); δ(ppm) = **tautomer α** (CD_3OD)**:** 12.4, 12.9 (CH_3; C-3'), 15.4, 16.8 (CH_3; C-1''), 26.2, 26.8 (CH_2; C-2'), 36.4, 37.0 (CH; C-1'), 59.6, 61.1 (CH; C-5), 97.6, 97.8 (CH; C-3), 173.2, 173.4 (C^q; C-2), 190.1, 190.7 (C^q; C-4). **tautomer β** ($CDCl_3$)**:** 12.4, 12.8 (CH_3; C-3'), 14.5, 15.9 (CH_3; C-1''), 26.8 (CH_2; C-2'), 37.9 (CH; C-1'), 39.0, 39.4 (CH_2; C-3), 63.2, 64.7 (CH; C-5), 179.4 (C^q; C-2), 210.2, 210.6 (C^q; C-4).

IR (KBr); ν(cm^{-1}) = **tautomer α:** 3420(w), 3228(w), 2966(m), 2933(m), 2878(w), 2391(w), 1681(s), 1635(s), 1561(s), 1465(w), 1379(m), 1311(m), 1211(w), 1125(w), 805(m), 766(w), 719(w). **tautomer β:** 3302(w), 2969(s), 2919(m), 2871(m), 1767(m), 1675(s), 1616(s), 1438(m), 1381(m), 1305(m), 1177(m), 1121(s), 1089(m), 1049(s), 879(w), 807(w).

MS (EI, 70eV); m/z (%) = 156 (9) [M^++1], 128 (58) [156-C_2H_4], 100 (80) [156-C_4H_8], 72 (44) [100-CO], 57 (57), 29 (100).

(±)-5-*iso*-Butyl-5*H*-pyrrolidine-2,4-dione 51c



α **β**

Using the preceeding protocol, (±)-4-benzyloxy-5-*iso*-butyl-pyrrol-2(5*H*)-one **69d** (200mg, 0.82mmol) with Pd/C (20mg) in methanol (15 - 20mL), under a H_2 atmosphere for 12 h yielded (±)-5-*iso*-butyl-pyrrolidine-2,4-dione **51c** (123mg, 0.79mmol, 96%) as a white solid in a tautomer ratio **α**:**β** 1:2.3.

MF : $C_8H_{13}NO_2$

MW : 155.20

MP : 107.5 - 110°C

^{1}H-NMR (300MHz, CD_3OD); δ(ppm) = **tautomer α:** 0.98 (2 x d, $^3J_{HH}$ = 6.4Hz, 6H, 3'-H), 1.50 (dd, $^3J_{HH}$ = 4.2, 9.4Hz, 1H, 1'-H), 1.65 (dd, $^3J_{HH}$ = 4.4, 9.0Hz, 1H, 1'-H), 1.78 (m, 1H, 2'-H), 4.28 (dd, $^3J_{HH}$ = 4.4, 9.4Hz, 1H, 5-H), 5.71 (d, $^4J_{HH}$ = 1.52Hz, 1H, 3-H), 7.8 (broad s, 1H, N-H). **tautomer β:** 0.98 (2 x d, $^3J_{HH}$ = 6.4Hz, 6H, 3'-H), 1.51 (dd, $^3J_{HH}$ = 4.2, 9.4Hz, 1H, 1'-H), 1.65 (dd, $^3J_{HH}$ = 4.4, 9.0Hz, 1H, 1'-H), 1.76 (m, 1H, 2'-H), 3.0 (d, $^4J_{HH}$ = 2.61Hz, 2H, 3-H), 4.04 (dd, $^3J_{HH}$ = 4.4, 9.4Hz, 1H, 5-H), 7.8 (broad s, 1H, N-H).

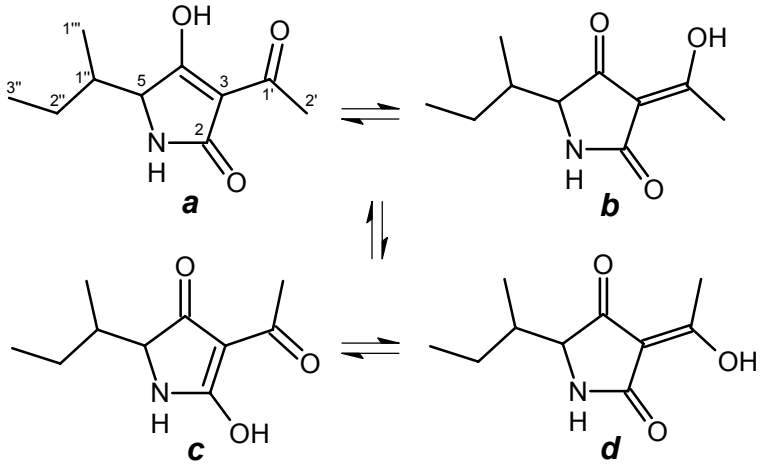
^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = **tautomer α:** 15.6 (CH_3; C-3'), 25.3 (CH; C-2'), 39.3 (CH_2; C-1'), 59.1 (CH; C-5), 91.8 (CH_2; C-3), 171.5 (C^q; C-2), 190.6 (C^q; C-4). **tautomer β:** 15.4 (CH_3; C-3'), 25.1 (CH; C-2'), 40.9 (CH_2; C-1'), 41.6 (CH_2; C-3), 63.2 (CH; C-5), 179.0 (C^q; C-2), 208.2 (C^q; C-4).

IR (KBr); ν(cm^{-1}) = **tautomer α:** 3225(w), 2969(m), 2931(m), 2919(w), 2877(w), 1683(s), 1635(s), 1560(m), 1463(w), 1371(m), 1309(m), 1215(w), 1126(w), 806(m), 714(m), 699(w). **tautomer β:** 3449(w), 2969(s), 2930(m), 2873(m), 1767(m), 1695(s), 1626(s), 1550(m), 1448(m), 1381(m), 1305(m), 1197(m), 1121(s), 1090(m), 1044(m), 877(w), 801(w), 751(w).

MS (EI, 70eV); m/z (%) = 155 (7) [M^+], 140 (31) [M^+-CH_3^+], 111 (64) [140-$C_2H_5^+$], 100 (91) [M^+-$C_4H_7^+$], 99 (29) [M^+-C_4H_8], 71 (100).

CHN; Required for $C_8H_{13}NO_2$: C, 61.91%; H, 8.44%. Found: C, 61.64%; H, 8.66%.

(±)-3-Acetyl-4-hydroxy-5-*sec*-butyl-pyrrol-2-(5*H*)-one 54b



(±)-5-*sec*-Butyl-pyrrolidine-2,4-dione **51b** (120mg, 0.77mmol) was added to a stirring solution of $BF_3.OEt_2$ (5mL), followed by the addition of acetyl chloride (166µL, 2.31mmol). The mixture was heated for 8 h (T = 75°C), after which an additional quantity of acyl chloride was added (55µL, 0.77mmol) and heated for a further 2 h. The cooled reaction mixture was added to water (10mL) and extracted with EtOAc (3 x 15mL). The organic layer was extracted with NaOH solution (5% w/v; 2 x 10mL), washed with chloroform (2 x 10mL) and acidified with conc. HCl to pH 5. The aqueous phase was extracted with chloroform (3 x 10mL), dried over $MgSO_4$ and concentrated using a rotary evaporator[83b]. (±)-3-Acetyl-4-hydroxy-5-*sec*-butyl-pyrrol-2(5*H*)-one (Tenuazonic acid) **54b** was recrystallised using pet. ether (40° - 60°) yielding a beige solid (81.4mg, 0.41mmol, 53.6%) in an tautomer ratio ***ab*:*cd*** 3:1.

MF : $C_{10}H_{15}NO_3$

MW : 197.23

MP : 143°C (Lit. m.p.: 145 - 151°C[53])

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.9 – 1.0 (m, 6H, 3''-H, 1'''-H), 1.23 (m, 2H, 2''-H), 1.9 (m, 1H, 1''-H), 2.43 and 2.48 (2 x s, 3H, 2'-H), 3.75^a and 3.77^a (2 x d, $^3J_{HH}$ = 4.2, 4.7Hz, 1H, 5-H), 3.94^b and 3.96^b (2 x d, $^3J_{HH}$ = 4.28, 4.7Hz, 1H, 5-H), 6.24^b and 6.25^b (2 x s, 1H, N-H), 6.43^a and 6.44^a (2 x s, 1H, N-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 13.2, 13.4 (CH_3; C-3''), 15.9, 16.3 (CH_3; C-1'''), 19.5, 20.3 (CH_3; C-2'), 26.6, 26.9 (CH_2; C-2''), 36.9, 37.4, 37.9, 38.2 (CH; C-1''), 64.8^b, 65.2^b (CH; C-5), 67.1^a, 67.6^a (CH; C-5), 100.3 (C^q; C-3), 171.2^b (C^q; C-2), 175.0^a (C^q; C-2), 184.2^a (C^q; C-1'), 188.7^b (C^q; C-1'), 194.7^a, 194.8^a (C^q; C-4), 199.4^b, 199.5^b (C^q; C-4).

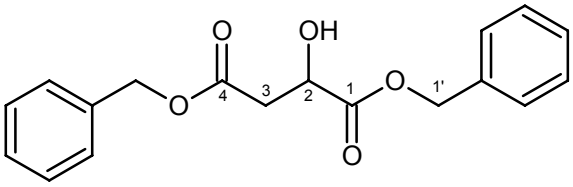
^{a} Peaks of higher intensity, ^{b} Peaks of lower intensity for a given carbon atom.

IR (KBr); ν(cm^{-1}) = 3433(m), 2966(m), 2929(w), 2872(w), 1781(w), 1769(s), 1696(s), 1628(s), 1438(m), 1382(m), 1310(w), 1181(m), 1123(m), 1079(m).

MS (EI, 70eV); m/z (%) = 198 (5) [MH^+], 141 (77) [198-$C_4H_9^+$].

4.6 Synthesis of Carboxylic diesters

(±)-2-Hydroxy-butanedioic acid-dibenzyl ester 92a



(±)-2-Hydroxy-butanedioic acid **91a** (0.67g, 5.0mmol) and benzyl alcohol (3.11ml, 30mmol) were added to dry chloroform (50mL), a Dean-Stark apparatus was fitted and the mixture was heated to reflux for 6 h. The excess benzyl alcohol was removed by distillation, $CHCl_3$ (20mL) was added, the organic solution was washed with water (3 x 20mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography was used to purify the crude mixture to 2-hydroxy-butanedioic acid-dibenzyl ester **92a** as a clear oil (1.52g, 4.84mmol, 97%); R_f = 0.85 (1:2 EtOAc-hexane).

MF : $C_{18}H_{18}O_5$

MW : 314.34

BP : > 200°C, P = 760 Torr (Lit. b.p.: 474.6 ± 35.0°C, P = 760 Torr[129])

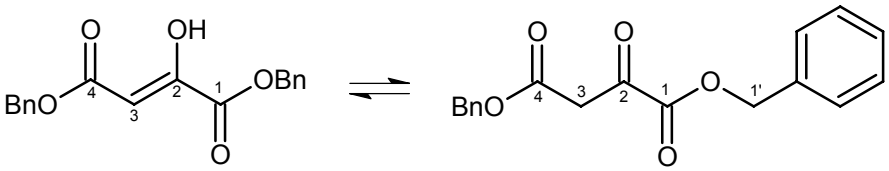
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 2.83 (dd, $^2J_{HH}$ = 16.6Hz, $^3J_{HH}$ = 6.0Hz, 1H, 3-H), 2.91 (dd, $^2J_{HH}$ = 16.6Hz, $^3J_{HH}$ = 4.7Hz, 1H, 3-H), 3.32 (d, $^3J_{HH}$ = 5.21Hz, 1H, O-H), 4.5 (dd, $^3J_{HH}$ = 4.7, 6.0Hz, 1H, 2-H), 5.11 and 5.17 (2 x s, 4H, 1'-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 38.6 (CH_2; C-3), 66.7 (CH_2; C-1'), 67.3 (CH; C-2), 67.6 (CH_2; C-1'), 126.9-128.6 (CH; C-*arom*), 134.9, 135.4 (C^q; C-*ipso*), 170.2 (C^q; C-4), 173.1 (C^q; C-1).

IR (film, NaCl); ν(cm^{-1}) = 3488(m), 3063(w), 3033(w), 2952(w), 2890(w), 1740(s), 1498(m), 1456(m), 1383(m), 1355(m), 1268(s), 1167(s), 1106(s), 1039(m), 992(m), 912(m), 824(w), 745(s), 699(s).

MS (EI, 70eV); m/z (%) = 314 (5) [M^+], 223 (41) [M^+-$C_6H_5CH_2^+$], 132 (3) [223-$C_6H_5CH_2^+$], 91 (100) [$C_6H_5CH_2^+$].

2-Hydroxy-but-2-enedioic acid-dibenzyl ester 92b



α **β**

Benzyl alcohol (2.38mL, 0.023mol) was cooled to -10°C (ice/salt) and thionyl chloride (0.79mL, 9.17mmol) was added dropwise (WITH CARE), with stirring. 2-Hydroxy-but-2-enedioic acid **91b** (0.5g, 3.79mmol) was added slowly and the solution was brought to r.t. The reaction mixture was stirred for 4 h, after which an additional quantity of thionyl chloride (0.11mL, 1.26mmol) was added and left stirring for a further 2 h. A yellow solution was produced, the solvent was removed under reduced pressure and the crude material was purified using column chromatography generating 2-hydroxy-but-2-enedioic acid-dibenzyl ester **92b** as a yellow oil (0.84g, 2.69mmol, 71%); R_f = 0.89 (1:1 EtOAc-hexane). Tautomer **α** (white solid) and tautomer **β** (yellow oil) were easily separated by washing with a hexane-Et_2O mixture.

MF : $C_{18}H_{16}O_5$

MW : 312.32

MP : 59.8 – 60.7°C

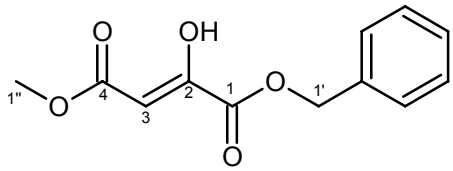
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = **tautomer α** : 5.23 (d, $^2J_{HH}$ = 14.5Hz, 2H, 1'-H), 5.25 (d, $^2J_{HH}$ = 16.4Hz, 2H, 1'-H), 6.1 (s, 1H, 3-H), 7.22-7.39 (m, 10H, Ph-H). **tautomer β** : 4.65 (s, 2H, 3-H), 6.23 (s, 2H, 1'-H), 6.38 (s, 2H, 1'-H), 7.33-7.58 (m, 10H, Ph-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = **tautomer α** : 66.9, 67.9 (CH_2; C-1'), 97.0 (CH; C-3), 126.9 (CH; *p*C-*arom*), 128.1-128.7 (CH; C-*arom*), 134.7, 134.9 (C^q; C-*ipso*), 159.3 (C^q; C-2), 161.4 (C^q; C-1), 171.5 (C^q; C-4). **tautomer β** : 32.8 (CH_2; C-3), 66.5, 67.1 (CH_2; C-1'), 127.9-129.1 and 133.0-134.2 (CH; C-*arom*), 135.7, 136.0 (C^q; C-*ipso*), 166.9 (C^q; C-1), 170.4 (C^q; C-4), 185.9 (C^q; C-2).

IR (KBr); ν(cm^{-1}) = **tautomer α** : 3494(m), 3064(m), 3034(m), 2956(m), 1796(s), 1740(s), 1684(m), 1497(m), 1454(m), 1381(m), 1255(s), 1003(m), 744(s), 697(s). **tautomer β** : 3034(w), 2924(w), 2853(w), 1726(s), 1652(w), 1497(w), 1455(w), 1378(w), 1320(m), 1272(s), 1163(s), 1002(m), 910(w), 734(m), 697(m).

MS (EI, 70eV); m/z (%) = 312 (10) [M^+], 221 (3) [M^+-$C_6H_5CH_2^+$], 206 (7) [M^+-C_6H_5CHO], 107 (14) [$C_6H_5CH_2O^-$], 92 (53) [$C_6H_5CH_3$], 91 (100) [$C_6H_5CH_2^+$], 77 (6) [$C_6H_5^+$].

2-Hydroxy-but-2-enedioic acid-1-benzylester-4-methylester 92c



Hexamethyldisilazane (HMDS, $(Me_3Si)_2NH$; 0.21mL, 1.02mmol) in dry THF (1.0mL) was cooled to 0°C (ice bath) and BuLi (1.6M in hexane; 0.9mL, 1.44mmol) was added dropwise over a 5 min period, with the exclusion of air and moisture and with stirring. This solution was cooled to -78°C (dry ice/acetone), methyl ethanoate (80µl, 1.0mmol) was added dropwise and stirred at -78°C for 30 min. This solution was added dropwise to a stirring solution of dibenzyl oxalate **95** (273mg, 1.01mmol) in dry THF (3.0mL), under an argon atmosphere. The reaction mixture was brought to -20°C (dry ice/MeOH) and stirred for 30 min, after which conc. HCl (80µl) and water (2.5mL) was added. The neutral solution was brought to pH 2 with the addition of conc. HCl (~2 drops) and extracted with Et_2O (5 x 2mL)[106a]. The solvent was removed *in vacuo* and dried over $MgSO_4$. The crude material was purified using column chromatography producing 2-hydroxy-but-2-enedioic acid-1-benzylester-4-methylester **92c** as a yellow oil (50mg, 0.2mmol, 21%), R_f = 0.28 (1:1 EtOAc-hexane).

MF : $C_{12}H_{12}O_5$

MW : 236.22

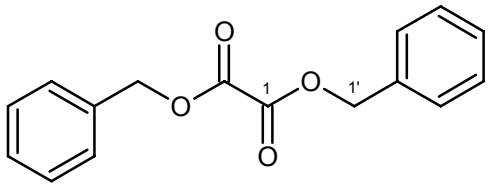
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 3.8 (s, 3H, 1"-H), 5.3 (s, 2H, 1'-H), 7.3 (m, 5H, Ph-H), 11.6 (s, 1H, O-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 52.1 (CH_3; C-1"), 64.8 (CH_2; C-1'), 96.7 (CH; C-3), 126.8 (CH; *p*C-*arom*), 128.3-128.6 (CH; *o*, *m*C-*arom*), 140.8 (C^q; C-*ipso*), 158.0 (C^q; C-2), 162.2 (C^q; C-1), 172.1 (C^q; C-4).

IR (film, NaCl); ν(cm^{-1}) = 3495(s), 3031(m), 2969(m), 2935(w), 1742(s), 1489(s), 1456(s), 1386(s), 1341(s), 1167(m), 1105(s), 1098(w), 1044(m), 982(m), 916(s), 749(s), 698(s).

MS (EI, 70eV); m/z (%) = 263 (2) [M^+], 171 (56) [M^+-$C_6H_5CH_3$], 128 (26), 91 (100) [$C_6H_5CH_2^+$], 44 (9) [CO_2].

Acetic-dioic acid-dibenzylester 95



Acetic-dioic acid (Oxalic acid) **94** (1.5g, 16.7mmol), benzyl alcohol (10.38mL, 0.1mol) and a catalytic quantity of *p*-toluenesulfonic acid **61** were heated to reflux in dry chloroform (50mL) with the extraction of water, for 3 - 4 h. The solvent was removed *in vacuo* and the excess benzyl alcohol was removed via distillation. Chloroform (15mL) was added to the crude product, shaken up with water (2 x 20mL), dried over Na_2SO_4 and the solvent was removed using a rotary evaporator. Acetic-dioic acid-dibenzylester **95** was recrystallised from hexane-DCM yielding a white solid (3.13g, 11.58mmol, 69%).

MF : $C_{16}H_{14}O_4$

MW : 270.28

MP : 80 – 81°C (Lit. m.p.: 80°C[130])

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 5.3 (s, 4H, 1'-H), 7.4 (m, 10H, Ph-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 68.3 (CH_2; C-1'), 128.2-128.6 (CH; C-*arom*), 134.1 (C^q; C-*ipso*), 157.3 (C^q; C-1).

IR (KBr); ν(cm^{-1}) = 3034(w), 1747(s), 1454(m), 1372(m), 1311(m), 1163(s), 903(w).

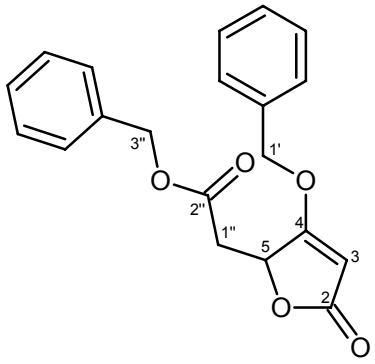
MS (EI, 70eV); m/z (%) = 270 (81) [M^+], 179 (3) [M^+-$C_6H_5CH_2^+$], 91 (100) [$C_6H_5CH_2^+$], 88 (21) [179-$C_6H_5CH_2^+$].

4.7 Synthesis of furan-2-ones

4.7.1 Synthesis of 4-benzyloxy-furan-2-ones

General procedure: The α-hydroxy-ester (10 mmol), keteneylidenetriphenylphosphorane **1a** (13 mmol) and a catalytic amount of benzoic acid (1-2mg) in dry THF (50mL) were heated to reflux for 16 h (unless otherwise indicated), with the exclusion of air and moisture. The solvent was removed from the cooled reaction mixture under reduced pressure and the crude material was purified using column chromatography with the solvent systems indicated.

(±)-(2-Oxo-4-benzyloxy-3,5-dihydro-furan-5-yl)-acetic acid-benzylester 46a



(±)-2-Hydroxy-butanedioc acid-dibenzylester **92a** (1.5g, 4.77mmol), keteneylidenetriphenylphosphorane **1a** (1.87g, 6.20mmol) and a catalytic amount of benzoic acid in dry toluene (50mL) generated (±)-(2-oxo-4-benzyloxy-3,5-dihydro-furan-5-yl)-acetic acid-benzylester **46a** as a yellow oil (1.04g, 3.08mmol, 64%); R_f = 0.94 (1:1 EtOAc-hexane).

MF : $C_{20}H_{18}O_5$

MW : 338.36

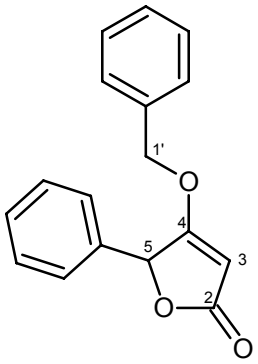
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 2.70 (dd, $^2J_{HH}$ = 16.2Hz, $^3J_{HH}$ = 8.1, 1H, 1"-H), 2.93 (dd, $^2J_{HH}$ = 16.2Hz, $^3J_{HH}$ = 4.3, 1H, 1"-H), 4.9 (dd, $^2J_{HH}$ = 11.5Hz, 2H, 1'-H), 5.04 (s, 1H, 3-H), 5.07 (s, 2H, 3"-H), 5.22 (dd, $^3J_{HH}$ = 4.3, 8.1Hz, 1H, 5-H), 7.30-7.39 (m, 10H, Ph-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 36.1 (CH_2; C-1"), 66.1 (CH_2; C-3"), 73.7 (CH_2; C-1'), 74.0 (CH; C-5), 89.0 (CH; C-3), 127.0-128.2 (CH; C-*arom*), 132.6, 134.2 (C^q; C-*ipso*), 167.6 (C^q; C-2), 170.7 (C^q; C-2"), 178.6 (C^q; C-4).

IR (film, NaCl); ν(cm^{-1}) = 3122(w), 3064(w), 3034(m), 2953(m), 1740(s), 1630(s), 1498(m), 1456(m), 1387(m), 1347(m), 1316(s), 1234(s), 1166(s), 1100(m), 1043(m), 985(m), 927(m), 867(w), 808(m), 740(m), 699(m).

MS (EI, 70eV); m/z (%) = 338 (8) [M^+], 247 (20) [M^+-$C_6H_5CH_2^+$], 141 (12) [247-C_6H_5CHO], 107 (17) [$C_6H_5CH_2O^-$], 91 (100) [$C_6H_5CH_2^+$].

4-Benzyloxy-5-phenyl-furan-2(5H)-one ***46b***[87]



MF : $C_{17}H_{14}O_3$

MW : 266.30

MP : 98°C (Lit. m.p.: 98°C[87])

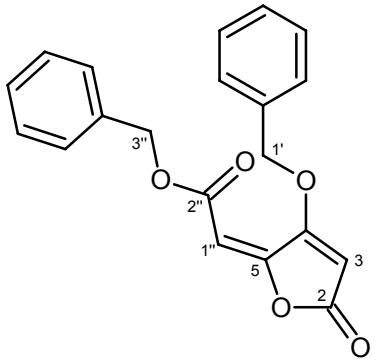
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 5.0 (dd, $^2J_{HH}$ = 13.2Hz, 2H, 1'-H), 5.2 (s, 1H, 3-H), 5.7 (s, 1H, 5-H), 7.15-7.4 (m, 10H, Ph-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 74.4 (CH_2; C-1'), 80.3 (CH; C-3), 89.3 (CH; C-5), 126.6-129.3 (CH; C-*arom*), 133.7, 134.0 (C^q; C-*ipso*), 172.5 (C^q; C-2), 180.1 (C^q; C-4).

IR (film, NaCl); ν(cm^{-1}) = 3101(w), 3029(w), 2913(w), 1725(s), 1635(s), 1605(s), 1445(m), 1337(m), 805(m), 751(m), 685(w).

MS (EI, 70eV); m/z (%) = 266 (28) [M^+], 222 (7), 175 (7) [M^+-$C_6H_5CH_2^+$], 148 (5), 107 (15), 91 (100) [$C_6H_5CH_2^+$].

(2-Oxo-3*H*-4-benzyloxy-furan-5-ylidene)-acetic acid-benzylester 93



2-Hydroxy-but-2-enedioic acid-dibenzylester **92b** (273mg, 0.87mmol), keteneylidenetriphenylphosphorane **1a** (342mg, 1.13mmol) and a catalytic amount of benzoic acid in dry THF (10mL) were heated to reflux for 48 h producing (2-oxo-3*H*-4-benzyloxy-furan-5-ylidene)-acetic acid-benzylester **93** as a cloudy oil (32mg, 0.096mmol, 21%), R_f = 0.94 (1:1 EtOAc-hexane).

MF : $C_{20}H_{16}O_5$

MW : 336.34

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 5.0 (s, 1H 3-H), 5.05 (dd, $^{2}J_{HH}$ = 11.2Hz, 2H, 1'-H), 5.11 (s, 1H 1"-H), 5.22 (dd, $^{2}J_{HH}$ = 14.0Hz, 2H, 3"-H), 7.28-7.52 (m, 10H, Ph-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 66.2 (CH_2; C-1'), 66.7 (CH_2; C-3"), 82.9 (CH; C-1"), 84.8 (CH; C-3), 127.8-129.2 and 133.4-134.2 (CH; C-*arom*), 135.9, 136.3 (C^q; C-*ipso*), 150.1 (C^q; C-5), 165.9 (C^q; C-2"), 167.9 (C^q; C-4), 189.1 (C^q; C-2).

IR (film, NaCl); ν(cm^{-1}) = 3123(w), 3065(m), 3034(m), 2949(w), 1740(s), 1631(s), 1583(w), 1498(w), 1455(m), 1388(m), 1363(m), 1347(m), 1317(s), 1270(m), 1234(s), 1168(s), 1100(w), 1042(m), 984(m), 928(m), 867(w), 807(m), 748(m), 700(m).

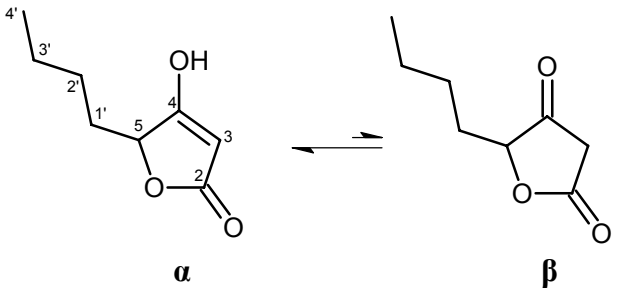
MS (EI, 70eV); m/z (%) = 336 (2) [M^+], 334 (13), 315 (9), 271 (18), 243 (42) [334-$C_6H_5CH_2^+$], 225 (13), 201 (8) [243-CO_2], 181 (17), 91 (100) [$C_6H_5CH_2^+$].

4.7.2 Synthesis of 4-hydroxy-furan-2(5*H*)-ones

4.7.2.1 Synthesis of 4-hydroxy-5-substituted-furan-2(5*H*)-ones

General procedure: To a stirring solution of 4-benzyloxy-5-substituted-furan-2(5*H*)-one (200mg) in dry methanol (10mL), palladium on charcoal was added (20mg), the reaction vessel was tightly sealed and evacuated and purged with H_2 three times. Finally, the reaction mixture was left stirring under an atmosphere of H_2 for 12 h. The solution was filtered over celite (4cm depth), washed with copious quantities of methanol (monitored with TLC), the solvent was removed under reduced pressure and dried using an oil pump. The 'free' tetronic acids were generally produced as white or lightly coloured solids which were recrystallised using the solvent systems indicated.

4-Hydroxy-5-*n*-butyl-furan-2(5*H*)-one 75b



α **β**

A solution of 4-benzyloxy-5-*n*-butyl-furan-2(5*H*)-one **46c**[89] (1.5g, 4.76mmol) in dry methanol (75mL) treated with 5% Pd/C (150mg) yielded 4-hydroxy-5-*n*-butyl-furan-2(5*H*)-one **75b** as a white solid (685mg, 4.39mmol, 92%) in a **α**:**β** tautomer ratio of 3:1.

MF : $C_8H_{12}O_3$

MW : 156.18

MP : 78.5 – 79.8 (Lit. m.p.: 79 - 80°C[87])

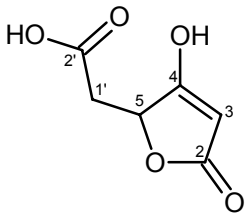
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.91 (t, $^3J_{HH}$ = 7.1Hz, 3H, 4'-H, **β**), 0.93 (t, $^3J_{HH}$ = 7.1Hz, 3H, 4'-H, **α**), 1.3-1.48 (m, 4H, 2'-H, 3'-H), 1.55-1.83 (m, 1H, 1'-H), 1.86-2.0 (m, 1H, 1'-H), 3.2 (dd, $^4J_{HH}$ = 1.09Hz, 2H, 3-H, **β**), 4.63 (qd, $^3J_{HH}$ = 4.6, 7.6Hz, $^4J_{HH}$ = 1.09Hz, 1H, 5-H, **β**), 4.8 (dd, $^3J_{HH}$ = 3.8, 7.6Hz, 1H, 5-H, **α**), 5.0 (s, 1H, 3-H, **α**).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 13.7, 13.8 (CH_3; C-4'), 22.1, 22.3 (CH_2; C-3'), 26.3, 26.5 (CH_2; C-2'), 31.0 (CH_2; C-1', **β**), 31.2 (CH_2; C-1', **α**), 37.5 (CH_2; C-3, **β**), 80.5 (CH; C-5, **α**), 86.4 (CH; C-5, **β**), 89.0 (CH; C-3, **α**), 170.0 (C^q; C-2, **α**), 177.7 (C^q; C-2, **β**), 183.5 (C^q; C-4, **α**), 205.8 (C^q; C-4, **β**).

IR (KBr); ν(cm^{-1}) = 3440(s), 2999(m), 2926(m), 2878(m), 1712(s), 1630(s), 1565(m), 1450(w), 1375(m), 1310(m), 1275(w), 1162(m), 1069(m), 806(m).

MS (EI, 70eV); m/z (%) = 156 (14) [M^+], 140 (28) [156-CH_4], 114 (55) [M^+-C_3H_6], 70 (9) [114-CO_2], 44 (100) [CO_2].

(±)-(2-Oxo-4-hydroxy-3,5-dihydro-furan-5-yl)-acetic acid 75c



(2-Oxo-4-benzyloxy-3,5-dihydro-furan-5-yl)-acetic acid-benzylester **46a** (676mg, 2.0mmol) and Pd/C (67mg) in dry methanol (35mL) generated (2-oxo-4-hydroxy-3,5-dihydro-furan-5-yl)-acetic acid **75c** which was recrystallised from benzene-acetic acid yielding a beige solid (262mg, 1.66mmol, 83%). **75c** was produced exclusively as the 3-enol tautomer.

MF : $C_6H_6O_5$

MW : 158.11

MP : 190 – 192 (Lit. m.p.: 187 - 191°C[96])

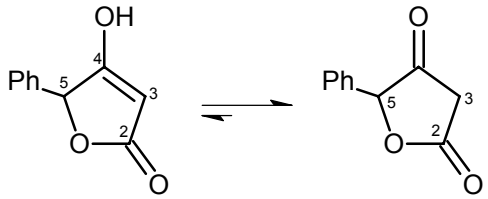
^{1}H-NMR (500MHz, d^6-DMSO); δ(ppm) = 2.35 (dd, $^2J_{HH}$ = 16.2Hz, $^3J_{HH}$ = 8.5, 1H, 1'-H), 2.77 (dd, $^2J_{HH}$ = 16.2Hz, $^3J_{HH}$ = 3.2, 1H, 1'-H), 4.83 (s, 1H, 3-H), 4.97 (dd, $^3J_{HH}$ = 3.2, 8.5Hz, 1H, 5-H).

^{13}C-NMR (125MHz, d^6-DMSO); δ(ppm) = 37.4 (CH_2; C-1'), 75.6 (CH; C-5), 87.4 (CH; C-3), 171.1 (C^q; C-2), 173.5 (C^q; C-4), 182.4 (C^q; C-2').

IR (KBr); ν(cm^{-1}) = 3415(m), 3128(w), 2932(w), 2691(w), 1717(s), 1695(m), 1627(s), 1575(s), 1435(w), 1397(w), 1340(w), 1283(m), 1200(w), 1172(w), 1092(w), 1031(m), 950(w), 875(w), 813(w).

MS (EI, 70eV); m/z (%) = 158 (19) [M^+], 140 (35) [M^+-H_2O], 112 (65) [140-CO], 43 (62), 42 (100).

4-Hydroxy-5-phenyl-furan-2(5*H*)-one 75d



α **β**

A solution of 4-benzyloxy-5-phenyl-furan-2(5*H*)-one **46b** (400mg, 1.5mmol) in dry methanol (20mL) was treated with 5% Pd/C (40mg) yielding 5-phenyl-furanone-2,4-dione **75d** as a beige solid (211mg, 1.35mmol, 90%) in a **α**:**β** tautomer ratio of 1:5.5.

MF : $C_{10}H_8O_3$

MW : 176.17

MP : 124 - 126°C (Lit. m.p.: 126 - 128°C[131])

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 2.53 (dd, $^2J_{HH}$ = 16.8Hz, 2H, 3-H, **β**), 4.2 (m, 1H, 5-H), 5.27 (d, $^4J_{HH}$ = 1.84Hz, 1H, 3-H, **α**), 7.13-7.25 (m, 5H, Ph-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 42.9 (CH_2; C-3, **β**), 65.9 (CH; C-5, **α**), 68.9 (CH; C-5, **β**), 72.2 (CH; C-3, **α**), 126.8-129.4 (CH; C-*arom*), 135.7, 137.3 (C^q; C-*ipso*), 173.8, 177.2 (C^q; C-2), 185.4 (C^q; C-4, **α**), 204.6 (C^q; C-4, **β**).

IR (KBr); ν(cm^{-1}) = 3207(m), 3028(m), 2919(m), 2668(m), 1720(s), 1636(m), 1493(w), 1441(m), 1261(s), 1157(w), 1158(m), 1076(s), 1039(m), 919(w), 819(w), 747(m), 697(m), 641(m).

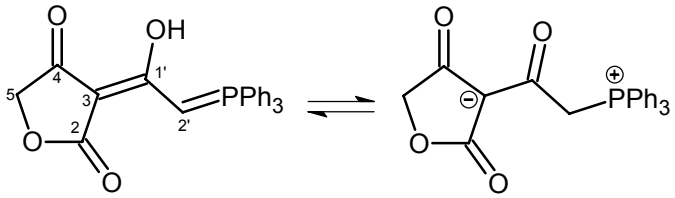
MS (EI, 70eV); m/z (%) = 134 (17) [M^+-CO_2], 105 (100), 92 (21) [$C_6H_5CH_3$], 91 (52) [$C_6H_5CH_2^+$], 43 (22) [134-$C_6H_5CH_2^+$].

4.7.2.2 Synthesis of 3-acylylidene-5*H*-furanone-2,4-diones[87]

The tetronic acid (10mmol) was added to a stirring solution of keteneylidenetriphenylphosphorane **1a** (13 mmol) in THF (50mL) and heated to reflux for 16 h, under an argon atmosphere. The reaction mixture was allowed to cool, the product precipitated out of solution and was filtered using a Büchner funnel. The

precipitate was thoroughly washed with THF and dried using an oil pump, yielding the corresponding 3-acylylidene tetronic acid.

3-(1′-hydroxy-ethylylidenetriphenylphosphoran-2′-yl)-5*H*$_2$-furanone-2,4-dione 76a



α **β**

4-Hydroxy-furan-2(5*H*)-one **75a** (1.0g, 10mmol) and keteneylidenetriphenylphosphorane **1a** (3.93g, 13mmol) in THF (50mL) yielded 3-(1′-hydroxy-ethylylidenetriphenylphosphoran-2′-yl)-5*H*$_2$-furanone-2,4-dione **76a** as a white solid (3.38g, 8.4mmol, 84%).

MF : $C_{24}H_{19}O_4P$

MW : 402.39

MP : > 200°C (decomp.), (Lit. m.p.: > 200°C (decomp.)[87]).

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 3.93 and 4.16 (2 x s, 2H, 5-H), 5.04 (d, $^2J_{PH}$ = 13.06Hz, 2H, 2'-H), 7.67 (m, 18H, Ph-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 35.7 (d, $^1J_{PC}$ = 54.34Hz, CH_2; C-2', **β**), 68.3, 70.2 (CH_2; C-5, **β**), 77.8 (CH_2; C-5, **α**), 97.5 (C^q; C-3, **β**), 119.7 (d, $^1J_{PC}$ = 88.37Hz, C^q; C-*ipso*, **β**), 124.1 (d, $^1J_{PC}$ = 92.0Hz, C^q; C-*ipso*, **α**), 129.8, 130.3 (2 x d, $^2J_{PC}$ = 12.60, 12.91Hz, CH; *o*C-*arom*), 133.5, 134.3 (2 x d, $^3J_{PC}$ = 10.26, 10.34Hz, CH; *m*C-*arom*), 135.0, 135.6 (CH; *p*C-*arom*), 179.3, 195.7 (C^q; C-2, C-4).

Percentages in brackets refer to the relative intensities of the peaks.

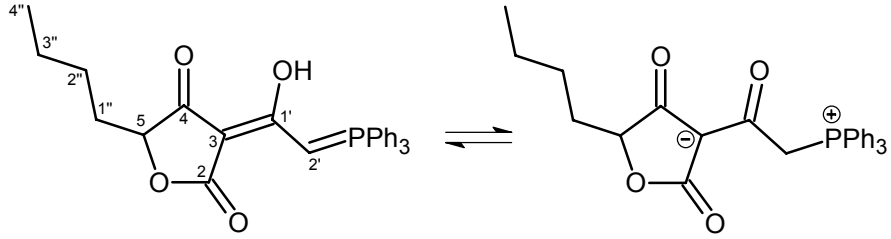
^{31}P-NMR (121.5MHz, H_3PO_{4ext}, $CDCl_3$); δ(ppm) = 15.85 (20.4%, **α**), 22.28 (24%, **β**), 23.11 (55.6%, **β**).

^{31}P-NMR (121.5MHz, H_3PO_{4ext}, d^6-DMSO); δ(ppm) = 20.88 (53.5%, **β**), 21.3 (46.5%, **β**).

IR (KBr); ν(cm^{-1}) = 3444(m), 3061(w), 2931(w), 1737(s), 1657(s), 1629(s), 1600(s), 1485(m), 1436(s), 1320(w), 1271(w), 1227(w), 1188(w), 1163(w), 1110(m), 1048(m), 1011(w), 930(m), 857(w).

MS (EI, 70eV); m/z (%) = 402 (10) [M^+], 384 (31), 369 (77), 353 (24), 275 (13) [$(C_6H_5)_3PCH^+$], 127 (32) [M^+-$(C_6H_5)_3PCH^+$], 101 (56), 100 (20) [$C_4H_4O_3$], 99 (30) [$C_4H_3O_3^-$], 78 (100) [C_6H_6].

3-(1′hydroxy-ethylylidenetriphenylphosphoran-2'-yl)-5-*n*-butyl-furanone-2,4-dione 76b[87]



α **β**

Reaction of 5-*n*-butyl-4-hydroxy-furan-2(5*H*)-one **75b** (1.0g, 6.4mmol) and keteneylidenetriphenylphosphorane **1a** (2.5g, 8.3mmol) in THF (30mL) generated 3-(1′-hydroxy-ethylylidenetriphenylphosphoran-2'-yl)-5-*n*-butyl-furanone-2,4-dione **76b** as a white solid (2.08g, 4.5mmol, 71%).

MF : $C_{28}H_{27}O_4P$

MW : 458.49

MP : > 195°C (decomp.), (Lit. m.p.: > 192°C (decomp.)[87]).

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.84 and 0.86 (2 x t, $^3J_{HH}$ = 7.2, 7.5Hz, 3H, 4"-H), 1.3-2.2 (m, 6H, 1"-H, 2"-H, 3"-H), 4.2 and 4.45 (2 x dd, $^3J_{HH}$ = 7.3, 7.7, 8.0Hz, 1H, 5-H), 5.10 and 5.12 (d and s, $^2J_{PH}$ = 13.63Hz, 1H, 2'-H), 7.5-7.8 (m, 18H, Ph-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 13.9, 14.0 (CH_3; C-4"), 22.5, 22.6 (CH_2; C-3"), 26.9, 27.0 (CH_2; C-2"), 31.4, 31.6 (CH_2; C-1"), 34.9 (d, $^1J_{PC}$ = 53.58Hz, CH_2; C-2', **β**), 56.6 (d, $^1J_{PC}$ = 105.71Hz, CH; C-2', **α**), 80.5, 81.1 (CH; C-5, **β**), 83.4 (CH; C-5, **α**), 97.5, 100.3 (C^q; C-3), 119.2 (d, $^1J_{PC}$ = 88.6Hz, C^q; C-*ipso*, **β**), 123.9 (d, $^1J_{PC}$ = 92.0Hz, C^q; C-*ipso*, **α**), 128.9 (d, $^3J_{PC}$ = 12.5Hz, CH; *o*C-*arom*, **α**), 129.4 and 130.0 (2 x d, $^3J_{PC}$ = 12.75, 12.83Hz, CH; *o*C-*arom*, **β**), 133.0 (CH; *m*C-*arom*, **α**), 133.2 and 134.0 (2 x d, $^2J_{PC}$ = 10.3, 10.7Hz, CH; *m*C-*arom*, **β**), 133.6 (CH; *p*C-*arom*, **α**), 134.7 (CH; *p*C-*arom*, **β**), 164.9, 173.4, 177.6, 179.4 (C^q; C-2, C-4 & C-1').

Percentages in brackets refer to the relative intensities of the peaks.

^{31}P-NMR (121.5MHz, $CDCl_3$); δ(ppm) = 16.09 (32.48%, **α**), 22.22 (3.22%, **β**), 23.25 (64.3%, **β**).

^{31}P-NMR (121.5MHz, d^6-DMSO); δ(ppm) = 23.81 (**β**).

IR (KBr); ν(cm^{-1}) = 3449(m), 2927(m), 1728(s), 1629(s), 1438(s), 1110(m), 751(m), 515(m).

MS (EI, 70eV); m/z (%) = 458 (6) [M^+], 384 (49), 369 (14), 353 (43), 275 (23) [$(C_6H_5)_3PCH^+$], 157 (7) [$C_8H_{13}O_3^+$], 127 (55) [157-C_2H_6], 115 (50) [157-C_3H_6], 101 (100) [115-CH_3^+], 99 (37) [$C_4H_3O_3^-$].

4.7.2.3 Synthesis of 3-acetyl-4-hydroxy-furan-2(5*H*)-ones

PROTOCOL 1[103]: The tetronic acid **75** (5mmol) and TEA (5.5mmol) in $CHCl_3$ (25mL) was cooled to 0°C (ice bath), followed by the addition of DMAP (0.15mmol) and acetic anhydride (5.5mmol). After stirring for 10min at 0°C, the reaction mixture was brought to r.t. and stirred for a further 12 h. The resulting solution was washed well with 5% HCl solution (10mL x 3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The solid material was recrystallised using the solvent system indicated, generating the 3-acetyl tetronic acid as a pale-coloured solid.

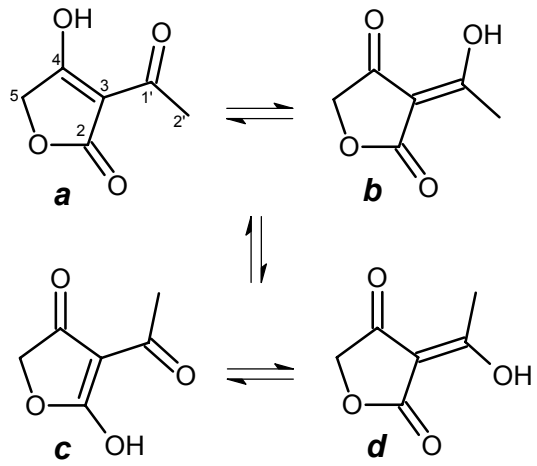
PROTOCOL 2: A solution of the 3-acylylidene tetronic acid **76** (5mmol) in THF (25mL) was treated with aqueous NaOH solution (2M; 10mL) and stirred for 2 h at r.t. The reaction mixture was concentrated under reduced pressure, water (20mL) was added to the solid material and acidified to pH 4 with the addition of conc. HCl. This aqueous solution was extracted with EtOAc (3 x 10mL), the combined organic fractions were washed with water (15mL x 2), dried over Na_2SO_4 and the solvent was removed *in vacuo*. The remaining solid was stirred in DCM (15mL) for 10-15 min at r.t., filtered (Büchner apparatus) and the solvent was removed using a rotary evaporator. The resulting solid was dried on an oil pump yielding pure 3-acetyl-tetronic acid.

PROTOCOL 3: The tetronic acid **75** (5mmol) was added to a stirring solution of immobilised keteneylidenetriphenylphosphorane* **80** (PS-CCO; 7.5mmol) in dry THF (25mL) and heated to reflux for 16h, with the exclusion of air and moisture. The reaction mixture was filtered using a Büchner filter and the solid residue was thoroughly washed with THF. The IR spectrum of this solid shows the disappearance of the ylide peak at 2100cm^{-1} indicating a reaction.

2M NaOH solution (10mL) was added to the immobilised 3-acylylide tetronic acid in THF (25mL) and stirred at r.t. for 2 h. The reaction mixture was filtered (Büchner filter), washed thoroughly with THF and the filtrate was concentrated under reduced pressure. Water (20mL) was added to the solid material and acidified to pH 4 with the addition of conc. HCl. This aqueous solution was extracted with EtOAc (3 x 10mL), the combined organic fractions were washed with water (20mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. The solid was dried using an oil pump yielding pure 3-acetyl-tetronic acid.

*PS-CCO must be stirred in THF for 10-15min before the addition of the reactant(s) to allow swelling of the resin for a successful reaction.

3-Acetyl-4-hydroxy-furan-2(5*H*)-one 77a



Protocol 1: 4-Hydroxy-furan-2(5*H*)-one **75a** (200mg, 2.0mmol), TEA (0.31mL, 2.2mmol), DMAP (80mg, 0.66mmol) and acetic anhydride (0.21mL, 2.2mmol) yielded 3-acetyl-4-hydroxy-furan-2-one **77a** as a yellow solid (242mg, 1.70mmol, 85%).

Protocol 2: A solution of 3-(1'-hydroxy-ethylylidenetriphenylphosphoran-2'-yl)-*5H*$_2$-furan-2,4-dione **76a** (250mg, 0.62mmol) in THF treated with aqueous NaOH solution yielded 3-acetyl-4-hydroxy-furan-2-one **77a** as a yellow solid (85mg, 5.98mmol, 96%).

Protocol 3: 4-Hydroxy-furan-2(5*H*)-one **75a** (200mg, 2.0mmol) and immobilised keteneylidenetriphenylphosphorane **80** (1.14g, 3.0mmol) yielded 3-acetyl-4-hydroxy-furan-2-one **77a** as a yellow solid (85mg, 5.98mmol, 98%).

The average tautomer ratio produced was ***ab***:***cd*** 1.6:1.

MF : $C_6H_6O_4$

MW : 142.11

MP : 80 – 81°C (Lit. mp.; 78 - 80.2°C[132])

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = ***ab*** *tautomer pair*: 2.49 (s, 3H, 2'-H), 4.62 (s, 2H, 5-H). ***cd*** *tautomer pair*: 2.51 (s, 3H, 2'-H), 4.51 (s, 1H, 5-H).

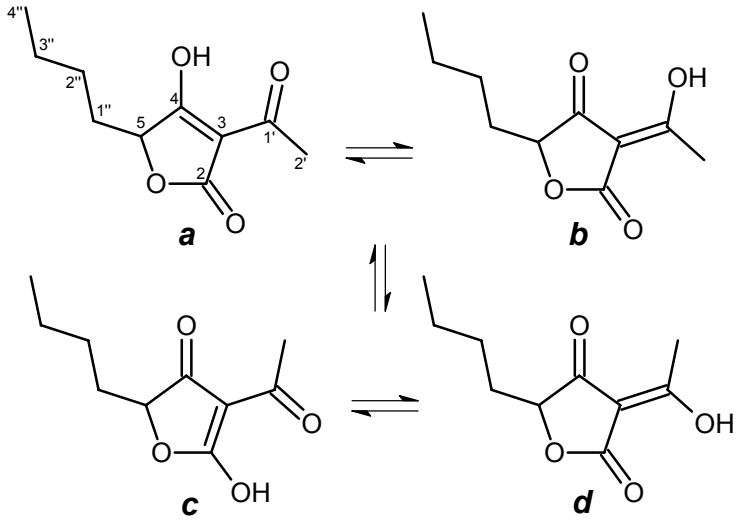
^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = ***ab*** *tautomer pair*: 21.1 (CH_3; C-2'), 67.8 (CH_2; C-5), 99.6 (C^q; C-3), 167.3 (C^q; C-2), 191.3 (C^q; C-1'), 196.8 (C^q; C-4). ***cd*** *tautomer pair*: 18.6 (CH_3; C-2'), 72.7 (CH_2; C-5), 96.7 (C^q; C-3), 175.3 (C^q; C-2), 187.1 (C^q; C-1'), 193.0 (C^q; C-4).

IR (KBr); ν(cm^{-1}) = 3113(m), 1758(s), 1668(s), 1594(s), 1463(m), 1432(m), 1344(m), 1285(m), 1227(w), 1151(s), 1010(s), 829(m).

MS (EI, 70eV); m/z (%) = 142 (100) [M^+], 127 (76), 124 (33), 99 (3) [M^+-CO_2], 84 (85) [99-CH_3^+], 69 (49), 43 (66).

CHN; Required for $C_6H_6O_4$: C, 50.71%; H, 4.26%. Found: C, 50.67%; H, 4.36%.

3-Acetyl-4-hydroxy-5-*n*-butyl-furan-2(5*H*)-one 77b



Protocol 1: 4-Hydroxy-5-*n*-butyl-furan-2(5*H*)-one **75b** (312mg, 2.0mmol), TEA (0.31mL, 2.2mmol), DMAP (80mg, 0.66mmol) and acetic anhydride (0.21mL, 2.2mmol) yielded 3-acetyl-4-hydroxy-5-*n*-butyl-furan-2-one **77b** as a white solid (282mg, 1.42mmol, 71%).

Protocol 2: A solution of 3-(1'-hydroxy-ethylidenetriphenylphosphoran-2'-yl)-4-hydroxy-5-*n*-butyl-furan-2(5*H*)-one **76b** (300mg, 0.65mmol) in THF treated with aqueous NaOH solution produced **77b** as a white solid (117mg, 0.59mmol, 90%).

The average tautomer ratio produced was ***ab***:***cd*** 1.7:1.

MF : $C_{10}H_{14}O_4$

MW : 198.23

MP : 54 – 54.5°C

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.89 (t, $^3J_{HH}$ = 7.1Hz, 3H, 4"-H, ***cd***), 0.91 (t, $^3J_{HH}$ = 7.1Hz, 3H, 4"-H, ***ab***), 1.31-1.51 (m, 4H, 2"-H, 3"-H), 1.63-1.78 (m, 2H, 1"-H, ***cd***), 1.88-1.99 (m, 2H, 1"-H, ***ab***), 2.52 (s, 3H, 2'-H), 4.61 (dd, $^3J_{HH}$ = 4.16, 7.33Hz, 1H, 5-H, ***cd***), 4.72 (dd, $^3J_{HH}$ = 4.16, 7.33Hz, 1H, 5-H, ***ab***).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 13.6 (CH_3; C-4"), 19.4 (CH_3; C-2'), 22.1, 22.2 (CH_2; C-3"), 26.3, 26.4 (CH_2; C-2"), 29.5, 30.8 (CH_2; C-1"), 79.8 (CH; C-5, ***ab***), 85.4 (CH; C-5, ***cd***), 98.0 (C^q; C-3, ***cd***), 100.6 (C^q; C-3, ***ab***), 167.8 (C^q; C-2, ***ab***), 176.0 (C^q; C-2, ***cd***), 188.0 (C^q; C-1', ***cd***), 194.2 (C^q; C-1', ***ab***), 195.0 (C^q; C-4, ***cd***), 199.6 (C^q; C-4, ***ab***).

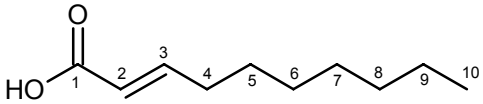
IR (KBr); ν(cm^{-1}) = 3099(m), 2960(s), 2857(m), 1752(s), 1666(s), 1451(m), 1364(m), 1280(w), 1239(w), 1156(m), 1073(m), 1012(m), 973(w), 887(w).

MS (EI, 70eV); m/z (%) = 198 (11) [M^+], 155 (12) [M^+-$C_3H_7^+$], 142 (100) [M^+-C_4H_8], 84 (61).

CHN; Required for $C_{10}H_{14}O_4$: C, 60.59%; H, 7.12%. Found: C, 60.70%; H, 7.25%.

4.8 Synthesis of α,β-unsaturated carboxylic acids and derivatives

(*E*)-Dec-2-enoic acid 113



Malonic acid (2.6g, 25mmol) was added to pyridine (6.04mL, 75mmol) and stirred for 5 min, followed by the addition of octanal (3.9mL, 25mmol) and a catalytic amount of piperidine. The reaction mixture was heated to reflux for 12 h. The product mixture was poured on an ice/conc. HCl mixture and the aqueous solution was extracted with Et_2O (3 x 25mL). The organic extract was washed with water, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude material was purified using column chromatography generating (*E*)-dec-2-enoic acid **113** as a clear oil (3.66g, 21.5mmol, 86%); R_f = 0.29 (1:5 EtOAc-hexane).

MF : $C_{10}H_{18}O_2$

MW : 170.25

BP : 101.5 – 103°C, P = 760 Torr (Lit. mp.; 102 – 103°C, P = 760 Torr [133])

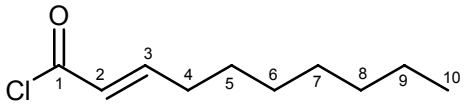
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.83 (t, $^3J_{HH}$ = 7.0Hz, 3H, 10-H), 1.2-1.4 (m, 10H, 5 - 9-H), 2.3 (dt, $^3J_{HH}$ = 7.1, 7.5Hz, 2H, 4-H), 5.8 (d, $^3J_{HH}$ = 15.4Hz, 1H, 2-H), 6.9 (dt, $^3J_{HH}$ = 7.1, 15.4Hz, 1H, 3-H), 11.4 (broad s, 1H, O-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 14.1 (CH_3; C-10), 22.6 (CH_2; C-9), 27.9 (CH_2; C-8), 29.0 (CH_2; C-7), 29.1 (CH_2; C-6), 31.7 (CH_2; C-5), 32.3 (CH_2; C-4), 120.5 (CH; C-2), 152.6 (CH; C-3), 172.0 (C^q; C-1).

IR (film, NaCl); ν(cm^{-1}) = 2928(s), 2857(s), 2676(s), 1698(s), 1651(s), 1466(m), 1421(s), 1286(s), 1225(m), 1124(w), 981(m), 940(m), 741(w), 701(w).

MS (EI, 70eV); m/z (%) = 171 (3) [MH^+], 155 (4) [M^+-CH_3^+], 127 (6) [M^+-$C_3H_7^+$], 114 (9) [M^+-C_4H_8], 99 (19) [M^+-$C_5H_{11}^+$], 86 (20) [M^+-C_6H_{12}], 73 (83) [$HO_2C(CH_2)_2^+$], 43 (100) [73-C_2H_6].

(*E*)-Dec-2-enoyl chloride 86a



(*E*)-Dec-2-enoic acid **113** (2.3g, 13.5mmol) and TEA (1.88mL, 13.5mmol) in THF (20mL) were stirred together for 15 min, followed by the dropwise addition of thionyl chloride (2.95mL, 40.5mmol). The mixture was stirred at r.t. for 12 h, followed by distillation yielding (*E*)-dec-2-enoyl chloride **86a** as a brown oil (3.66g, 11.6mmol, 86%).

MF : $C_{10}H_{17}OCl$

MW : 188.75

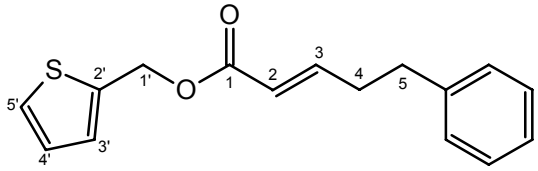
BP : 100 – 103°C, P = 2.5 Torr (Lit. mp.; 95 – 97°C, P = 2.5 Torr[134])

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.83 (t, $^3J_{HH}$ = 7.0Hz, 3H, 10-H), 1.24-1.40 (m, 8H, 6 – 9-H), 1.43-1.49 (m, 2H, 5-H), 2.1 (m, 2H, 4-H), 5.9 (d, $^3J_{HH}$ = 15.3Hz, 1H, 2-H), 7.1 (dt, $^3J_{HH}$ = 7.1, 15.3Hz, 1H, 3-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 14.1 (CH_3; C-10), 22.5 (CH_2; C-9), 27.8 (CH_2; C-8), 28.7 (CH_2; C-7), 28.9 (CH_2; C-6), 31.6 (CH_2; C-5), 32.3 (CH_2; C-4), 120.3 (CH; C-2), 153.1 (CH; C-3), 168.8 (C^q; C-1).

IR (film, NaCl); ν(cm^{-1}) = 1788(s), 1758(s), 1461(m), 1380(w), 1241(w), 1169(w), 1075(w), 1036(m), 985(m), 940(m), 731(m), 701(w).

(*E*)-5-Phenyl-pent-2-enoic acid-thiophen-2'-ylmethylester 98a[87]



2-Thiophenemethanol **96a** (0.35mL, 3.69mmol), dihydrocinnamaldehyde **97** (0.49mL, 3.69mmol) and keteneylidenetriphenylphosphorane **1a** (1.67g, 5.54mmol) in dry THF (25mL) were heated to reflux for 24 h with the exclusion of air and moisture. The solvent was removed from the cooled reaction mixture using a rotary evaporator and the crude product was purified using column chromatography yielding (*E*)-5-phenyl-pent-2-enoic acid-thiophen-2'-ylmethylester **98a** as a pale yellow solid (0.754g, 2.77mmol, 75%); R_f = 0.69 (1:4 Et_2O-hexane).

MF : $C_{16}H_{16}O_2S$

MW : 272.36

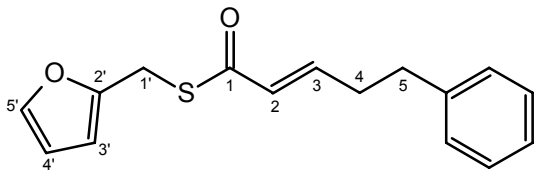
^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 2.51 (m, 2H, 4-H), 2.76 (t, $^{3}J_{HH}$ = 7.3Hz, 2H, 5-H), 5.31 (s, 2H, 1'-H), 5.86 (dt, $^{3}J_{HH}$ = 15.7Hz, $^{4}J_{HH}$ = 1.56Hz, 1H, 2-H), 6.98-7.5 (m, 9H, 3-H, 3'-H, 4'-H, 5'-H, Ph-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 34.4, 34.7 (CH_2; C-4, C-5), 60.8 (CH_2; C-1'), 121.8 (CH; C-2), 126.6, 127.2 (CH; C-4', C-5'), 128.5-129.0 (CH; C-*arom* and C-3'), 138.6, 141.2 (C^q; C-*ipso* and C-2'), 149.5 (CH; C-3), 166.5 (C^q; C-1).

IR (KBr); ν(cm^{-1}) = 3062(w), 3027(w), 2926(m), 2856(w), 1720(s), 1654(m), 1603(w), 1496(w), 1453(m), 1262(m), 1188(m), 1086(w), 1028(w), 975(w), 852(w), 804(w), 748(w), 700(s).

MS (EI, 70eV); m/z (%) = 272 (9) [M^+], 175 (5) [M^+- C_5H_5S], 159 (10) [M^+-$C_5H_5SO^+$], 158 (46) [M^+-C_5H_6SO], 113 (21) [$C_5H_5SO^+$], 97 (100) [$C_5H_5S^+$], 91 (78) [$C_7H_7^+$], 65 (35) [$C_5H_5^+$].

(*E*)-5-Phenyl-pent-2-enethioic acid-furan-2'-ylmethylester 98b[87]



2-Furylmethanethiol **96b** (0.4mL, 3.97mmol), dihydrocinnamaldehyde **97** (0.52mL, 3.97mmol) and keteneylidenetriphenylphosphorane **1a** (1.67g, 5.54mmol) in dry THF (25mL) were heated under reflux for 24 h with the exclusion of air and moisture. After cooling, the solvent was removed under reduced pressure and the crude product was purified using column chromatography yielding (*E*)-5-phenyl-pent-2-enethioic acid-furan-2'-ylmethylester **98b** as a pale yellow oil (0.476g, 1.75mmol, 44%); R_f = (1:1 Et_2O-hexane) 0.86.

MF : $C_{16}H_{16}O_2S$

MW : 272.36

BP : 116 – 117°C, P = 1 Torr (Lit. mp.; 116°C, P = 1 Torr[108]).

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 2.50-2.58 (m, 2H, 4-H), 2.79 (t, $^{3}J_{HH}$ = 7.1Hz, 1H, 5-H), 3.71 (dd, $^{3}J_{HH}$ = 14.8Hz, 2H, 1'-H), 6.15 (dt, $^{2}J_{HH}$ = 15.6Hz, $^{3}J_{HH}$ = 1.45Hz, 1H, 2-H), 7.1-7.3 (m, 9H, 3-H, 3'-H, 4'-H, 5'-H, Ph-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 30.5 (CH_2; C-4), 34.4, 34.6 (CH_2; C-5, C-1'), 108.2, 111.0 (CH; C-3', C-4'), 128.8-129.5 (CH; C-*arom*), 140.1 (C^q; C-*ipso*), 142.6, 142.8 (CH; C-2, C-5'), 149.8 (C^q; C-2'), 151.5 (CH; C-3), 185.4 (C^q; C-1).

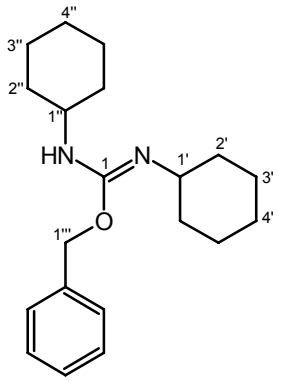
IR (KBr); ν(cm^{-1}) = 3026(w), 2927(m), 2857(m), 1719(s), 1671(s), 1498(m), 1428(m), 1250(w), 1145(s), 1008(m), 810(m), 700(s).

MS (EI, 70eV); m/z (%) = 272 (4) [M^+], 191 (19) [M^+- C_5H_5O], 159 (5) [M^+-C_5H_5SO], 158 (34) [M^+-C_5H_6SO], 91 (92) [$C_7H_7^+$], 81 (3) [$C_5H_5O^+$], 65 (14) [$C_5H_5^+$].

4.9 Synthesis of benzyl and *p*-methoxybenzyl-N,N'dicyclohexylisoureas[135]

General procedure: The alcohol (10mmol) was slowly added**,** with stirring, to CuCl (1-2mg) in N,N'-diisopropylcarbodiimide (10mmol). The mixture was warmed to 40°C and stirred for 30 min, followed by stirring for 5 h at r.t. Completion of the reaction was indicated by the disappearance if the diimide IR band at 2100cm^{-1} and appearance of the isourea band at 1660cm^{-1}. The reaction volume was doubled with hexane, filtered over neutral alumina (2-3 cm depth) and thoroughly washed with hexane. The solvent was removed using a rotary evaporator and dried using an oil pump producing an oil.

O-Benzyl-N,N′-dicyclohexylisourea 114a



N,N'-dicyclohexylcarbodiimide (1.99g, 9.65mmol) and benzyl alcohol (1.0mL, 9.65mmol) with a catalytic quantity of CuCl produced O-benzyl-N,N′-dicyclohexylisourea **114a** as a colourless oil (2.55g, 8.11mmol, 84%).

MF : $C_{20}H_{30}N_2O$

MW : 314.47

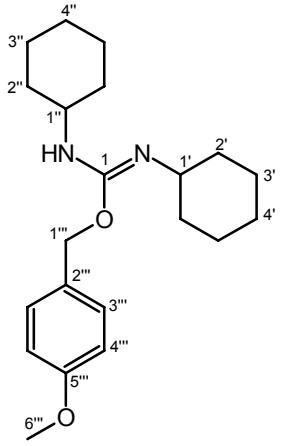
BP : 183 - 184°C, 0.05 Torr (Lit. b.p.: 184°C, 0.05 Torr [87])

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 1.1-1.25 and 1.5-1.84 (m, 20H, 2'-H, 3'-H, 4'-H, 2''-H, 3''-H, 4''-H), 3.0-3.3 (m, 2H, 1'-H, 1''-H), 4.95 (s, 2H, 1'''-H), 7.2-7.4 (m, 5H, Ph-H).

^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 25.0, 25.8, 26.1, 26.7, 33.9, 34.5 (CH_2; C-2', C-3', C-4', C-2'', C-3'', C-4''), 49.9 (CH; C-1''), 54.9 (CH; C-1'), 70.0 (CH_2; C-1'''), 127.3-129.1 (CH; C-*arom*), 131.7 (C^q; C-*ipso*), 155.2 (C^q; C-1).

IR (KBr); ν(cm^{-1}) = 3440(w), 3063(w), 3032(w), 2922(s), 2852(s), 1660(s), 1449(m), 1385(m), 1318(s), 1244(m), 1123(m), 1054(m), 889(w), 839(w), 801(w), 738(m), 700(m).

O-*p*-Methoxybenzyl-N,N′-dicyclohexylisourea 114b



N,N'-dicyclohexylcarbodiimide (2.06g, 10mmol) and *p*-methoxybenzyl alcohol (1.25mL, 10mmol) with a catalytic quantity of CuCl produced O-*p*-methoxybenzyl-N,N'-dicyclohexylisourea **114b** as a clear oil (2.76g, 8.25mmol, 80%).

MF : $C_{21}H_{32}N_2O_2$

MW : 344.5

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 0.72-1.76 (m, 20H, 2'-H, 3'-H, 4'-H, 2''-H, 3''-H, 4''-H), 3.2-3.5 (m, 5H, 1'-H, 1''-H, 6'''-H), 4.4 (s, 2H, 1'''-H), 6.74-6.8 (m, 2H, 4'''-H), 7.1-7.2 (m, 2H, 3'''-H).

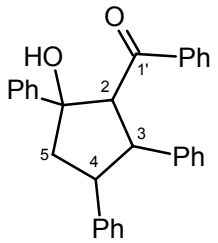
^{13}C-NMR (75.5MHz, $CDCl_3$); δ(ppm) = 25.0, 26.0, 26.3, 31.7, 33.4, 33.9 (CH_2; C-2', C-3', C-4', C-2'', C-3'', C-4''), 49.4 (CH; C-1''), 54.5 (CH; C-1'), 55.6 (CH_3; C-6'''), 71.9 (CH_2; C-1'''), 114.2, 114.6 (CH; C-4'''), 127.8, 129.8 (CH; C-3'''), 130.3 (C^q; C-2'''), 158.2 (C^q; C-1), 159.6 (C^q; C-5''').

IR (film, NaCl); ν(cm^{-1}) = 3001(m), 2933(s), 2841(s), 1712(w), 1679(s), 1611(s), 1512(s), 1460(s), 1358(m), 1300(s), 1248(s), 1176(s), 1079(s), 1035(s), 953(w), 820(s), 761(m), 709(w), 636(w), 585(m), 523(m).

4.10 Oligocyclic and polymer compounds

4.10.1 Synthesis of 2-acylcyclopentanols and bicyclic derivatives

cis-1-Phenyl-2-phenylcarbonyl-3,4-diphenylcyclopentan-1-ol ***107***[115]



MF : $C_{30}H_{26}O_2$

MW : 418.54

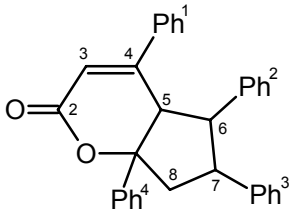
MP : 170.5 – 171.2°C

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = 2.52 (dd, $^2J_{HH}$ = 14.53Hz, $^3J_{HH}$ = 6.04Hz, 1H, 5-H), 2.93 (dd, $^2J_{HH}$ = 14.53Hz, $^3J_{HH}$ = 11.23Hz, 1H, 5-H), 3.74 (td, $^3J_{HH}$ = 6.04, 10.34, 11.23Hz, 1H, 4-H), 4.03 (dd, $^3J_{HH}$ = 10.34, 11.96Hz, 1H, 3-H), 4.46 (d, $^3J_{HH}$ = 11.96Hz, 1H, 2-H), 5.30 (s, 1H, OH), 6.95-8.06 (m, 20H, Ph-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 51.4 (CH_2; C-5), 51.5 (CH; C-4), 59.6 (CH; C-3), 63.5 (CH; C-2), 84.3 (C^q; C-1), 124.9-133.2 (CH; C-*arom*), 137.6, 139.8, 144.0, 145.3 (C^q; C-*ipso*), 205.0 (C^q; C-1').

IR (KBr); ν(cm^{-1}) = 3409(m), 3061(m), 3030(m), 2941(m), 1705(s), 1606(m), 1495(m), 1448(m), 1369(m), 1246(s), 1189(m), 1049(s), 987(m), 872(m), 759(s), 698(s).

4,6,7,9-Tetraphenyl-5,6,7,8-tetrahydro-cyclopenta[5.9]-pyran-2-one 108[116]



cis-1-Phenyl-2-phenylcarbonyl-3,4-diphenylcyclopentan-1-ol **107** (200mg, 0.48mmol), keteneylidenetriphenylphosphorane **1a** (189mg, 0.62mmol) and a catalytic amount of benzoic acid in dry toluene (7mL) were reacted in a sealed bomb tube at 160°C for 12 h. A dark brown solution was produced, the solvent was removed *in vacuo* and the crude material was purified using column chromatography producing 4,6,7,9-tetraphenyl-5,6,7,8-tetrahydro-cyclopenta[5.9]-pyran-2-one **108** which was recrystallised (hexane-DCM) to white crystals (172mg, 0.39mmol, 81%); R_f = 0.21 (1:4 Et_2O-hexane).

MF : $C_{32}H_{26}O_2$

MW : 442.56

MP : 187°C

^{1}H-NMR (500MHz, $CDCl_3$); δ(ppm) = 2.92 (dd, $^2J_{HH}$ = 15.3Hz, $^3J_{HH}$ = 7.3Hz, 1H, 8-H), 2.95 (dd, $^2J_{HH}$ = 15.3Hz, $^3J_{HH}$ = 10Hz, 1H, 8-H), 3.55 (dd, $^3J_{HH}$ = 10.9Hz, 11.3Hz, 1H, 6-H), 3.80 (td, $^3J_{HH}$ = 7.3, 10.0, 10.9Hz, 1H, 7-H), 3.93 (d, $^3J_{HH}$ = 11.3Hz, 1H, 5-H), 6.20 (s, 1H, 3-H), 6.95-7.52 (m, 20H, Ph-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 50.0 (CH_2; C-8), 50.9 (CH; C-7), 54.5 (CH; C-6), 62.5 (CH; C-5), 93.0 (C^q; C-9), 114.9 (CH; C-3), 124.9-129.8 (CH; C-*arom*), 136.0, 138.9, 141.7, 142.9 (C^q; C- *ipso*), 157.1 (C^q; C-4), 164.7 (C^q; C-2).

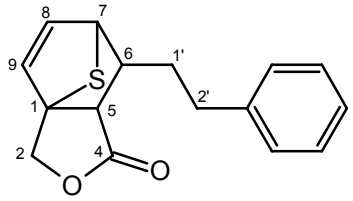
IR (KBr); ν(cm^{-1}) = 3432(w), 3060(w), 3030(w), 1704(s), 1606(w), 1495(w), 1448(w), 1366(w), 1317(w), 1268(m), 1188(w), 1052(m), 985(w), 872(w), 758(m), 698(s).

MS (EI, 70eV); m/z (%) = 442 (10) [M^+], 414 (9) [M^+-CO], 310 (9) [414-CH_2CHPh], 233 (100) [310-$C_6H_5^+$], 220 (33), 205 (13), 191 (19), 180 (29), 105 (55), 91 (20) [$PhCH_2^+$], 77 (40) [$C_6H_5^+$].

CHN; Required for $C_{32}H_{26}O_2$: C, 86.85%; H, 5.92%. Found: C, 87.12%; H, 5.93%.

4.10.2 Synthesis of tricyclic Diels-Alder product 99

6-Phenyl-3-oxa-10-thia-tricyclo[5.2.1.0$^{1.5}$]dec-8-en-4-one 99



(*E*)-5-Phenyl-pent-2-enoic acid-thiophen-2'-ylmethylester **98a** (100mg, 0.37mmol) in dry THF (10mL) was treated with a catalytic quantity of scandium trifluoromethanesulfonate ($(CF_3SO_3)_3Sc$) and heated to 120°C for 12 h. The cooled orange-yellow solution was purified using column chromatography generating a cloudy oil (27mg, 0.1mmol, 27%); R_f = 0.64 (1:5 EtOAc-hexane).

MF : $C_{16}H_{15}O_2S$

MW : 271.35

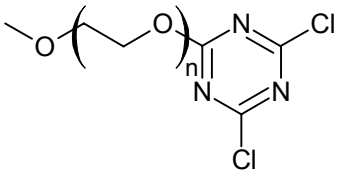
^{1}H-NMR (500MHz, $CDCl_3$); δ(ppm) = 0.8 (dd, $^3J_{HH}$ = 3.85, 7.14Hz, 1H, 1'-H), 1.22 (dd, $^3J_{HH}$ = 7.14, 8.73Hz, 1H, 1'-H), 2.47 (t, $^3J_{HH}$ = 7.14Hz, 2H, 2'-H), 2.88 (m, 1H, 6-H), 2.99 (d, $^3J_{HH}$ = 6.3Hz, 1H, 5-H), 3.78 (dd, $^3J_{HH}$ = 3.2, 5.68Hz, 1H, 7-H), 4.43 (dd,

$^{2}J_{HH}$ = 14.5Hz, 2H, 2-H), 6.0 (dd, $^{3}J_{HH}$ = 3.2, 6.35Hz, 1H, 8-H), 6.15 (d, $^{3}J_{HH}$ = 6.35Hz, 1H, 9-H), 7.1-7.24 (m, 5H, Ph-H).

^{13}C-NMR (125MHz, $CDCl_3$); δ(ppm) = 22.4, 31.3 (CH_2; C-1', C-2'), 36.8, 37.8 (CH; C-6, C-7), 62.1 (CH; C-5), 65.0 (C^q; C-1), 81.2 (CH_2; C-2), 126.9-128.4 (CH; C-*arom*), 137.1, 139.6 (CH; C-8, C-9), 141.7 (C^q; C-*ipso*), 171.81 (C^q; C-4).

4.10.3 Synthesis of polymer scavenger PEG-DCT[80]

Polyethyleneglycol-dichlorotriazine (PEG-DCT) 72a



A solution of butyl lithium (2M in hexane; 5mL) in benzene (10mL) with 1,10-phenanthroline (1-2mg) was titrated with a polyethyleneglycol-monomethylether solution (MeO-PEG; 3.5g in 100mL benzene), under argon, to reach a yellow end-point (8.3mL) which indicated a slight excess of MeO-PEG. The titrated solution was added dropwise to a stirring solution of cyanuric chloride (9.25g, 50mmol) in benzene (100mL), again with the absence of air and moisture and stirred for 1 h at r.t. The reaction solution was filtered to remove excess cyanuric chloride, dry hexane (300mL) was added and the product precipitated out of solution. The solid product was dissolved in dry toluene and re-precipitated (x 2) by the addition of dry hexane yielding PEG-dichlorotriazine (PEG-DCT) **72a** as a white solid.

NB It was crucial that all the solvents used were pre-distilled over a drying agent directly before use to ensure the removal of all moisture and water. It was vital that cyanuric chloride was recrystallised a number of times from toluene, also directly before use.

MP : > 200°C

For characterisation purposes only, PEG-dichlorotriazine (PEG-DCT) **72a** was derivatised:

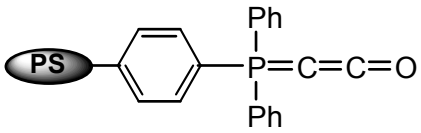
72a (200mg, 0.4mmol) and benzylamine (0.44mL, 10mmol) in dry acetonitrile (10mL) was heated to reflux for 24 h[79]. After cooling, the solvent was removed from the reaction mixture under vacuum (oil pump), hexane was added (2 x 25mL) and the product precipitated out yielding polyethyleneglycol-dibenzylaminotriazine **72b** as a white solid:

MP : > 200°C

^{1}H-NMR (300MHz, $CDCl_3$); δ(ppm) = key peaks: 3.3 (s, 3H, OCH_3), 3.9 (s, 4H, $PhCH_2$), 7.35 (m, 10H, Ph-H).

IR (KBr); ν(cm^{-1}) = 2999(m), 2941(m), 2782(w), 2662(s), 2603(s), 2490(s), 1477(s), 1437(s), 1391(s), 1321(w), 1185(s), 1160(m), 1136(s), 1100(w), 1068(m), 1024(m), 932(w), 981(m).

4.10.4 Synthesis of immobilised ylide 80[90]



Polystyrene-bound triphenylphosphane **78** (5.0g, 0.7mmol/g, 0.7mmol, 100-200 mesh, 1% divinylbenzene) in THF (20mL) was transfered to a fritted solid-phase reaction flask and shaken at r.t. for 60 min. Benzyl bromoacetate (6.46g, 28.2mmol) in THF (20mL) was added with the exclusion of air and moisture, and shaken for a further 16 h. The cooled reaction mixture was filtered (Büchner filter apparatus) and thoroughly washed with dry THF (3 x 15mL), Et_2O (2 x 15mL), DCM (3 x 15mL) and benzene (2 x 15mL). The pale yellow immobilised compound **79** was dried using an oil pump. Carbobenzyloxymethyl-triphenylphosphonium bromide **79** (0.53g, 0.5mmol) was washed with dry benzene (5mL) under argon, a 1:1 THF/benzene mixture was added (2mL), followed by treatment with lithium hexamethylsilazanide (335mg, 2.0mmol). This mixture was shaken for 24 h at r.t., after which filtration and washing with dry THF (3 x 25mL), benzene (3 x 25mL) and toluene (2 x 25mL), followed by drying *in vacuo* yielded the yellow resin bound compound **80**[90].

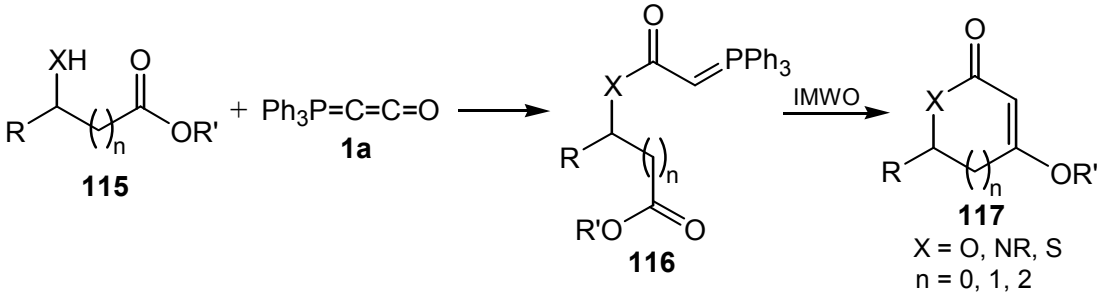
^{31}P-TOSS NMR (203 MHz, H_3PO_4 ext, $CDCl_3$): 4.97ppm[90]

5. Summary

Heterocycles of various ring sizes and containing different heteroatoms are the core of many biologically and pharmaceutically interesting compounds. The general objective of this project was to prepare a number of these biologically active nitrogen and oxygen heterocycles using phosphorus ylide keteneylidenetriphenylphosphorane **1a**.

Specific substituted pyrrolidine and furanone containing compounds were selected as target molecules and a number of retrosynthetic paths were proposed. The synthesis of these compounds was undertaken in order to find short, efficient routes towards their preparation, using individual reactions which were flexible with respect to the starting compounds which could be used, and towards the introduction of a variety of substituents.

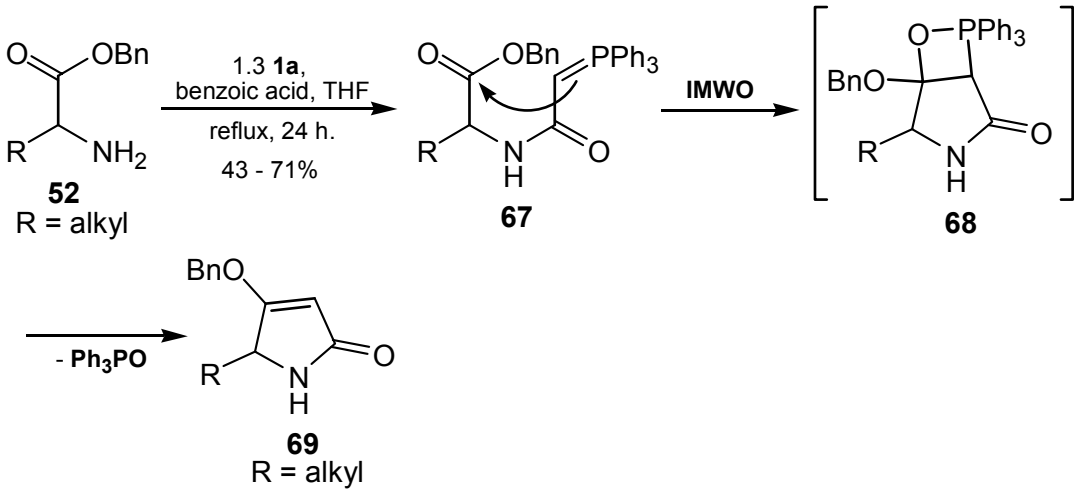
Keteneylidenetriphenylphosphorane **1a** was used as a 'C_2O building-block' because it reacts with derivatives of carboxylic acids bearing XH-acidic groups **115** such as –OH, -NHR or –SH giving rise to the formation of a variety of heterocycles **117**:



Scheme 65 General reaction of **1a** with XH-acidic esters **115**

The acidic group of the carboxylic acid derivative **115** adds across the $C^{\alpha}=C^{\beta}$ bond of ylide **1a** generating an acylylide intermediate **116**, which undergoes an intramolecular Wittig olefination (IMWO) reaction furnishing a range of unsaturated heterocycles **117**.

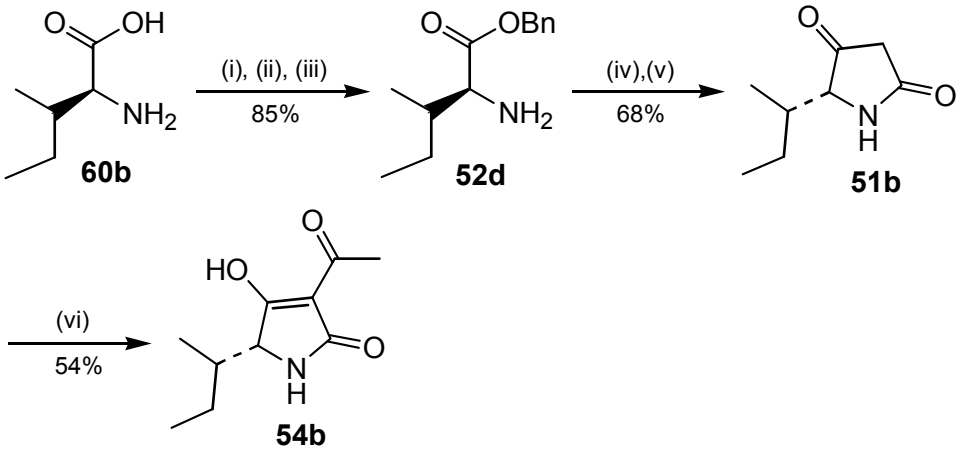
Using this general reaction scheme, keteneylidenetriphenylphosphorane **1a** and α-amino esters were used to prepare of a number of 4-alkoxy- and 4-benzyloxy-tetramates:



Scheme 28

NMR analyses revealed that, with respect to diastereomeric compounds where R = CH(Me)Et, the lactamisation sequence was not stereoselective. An average isomer ratio of 1:1 was found. Subsequent cleavage of the 4-ether function of compounds **69** furnished a range of 5-alkyl-tetramic acids (5-alkyl-pyrrolidine-2,4-diones).

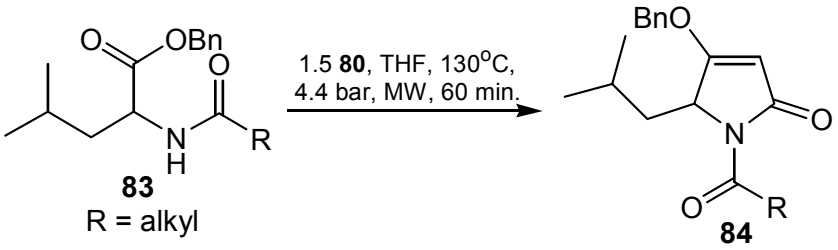
4-Hydroxy-5-*sec*-butyl-pyrrol-2(*5H*)-one **51b** was acylated producing (±)-3-acetyl-4-hydroxy-5-*sec*-butyl-pyrrol-2(5*H*)-one **54b**, also known as (±)-Tenuazonic acid. Complicated spectra were produced which illustrated the presence of two diastereoisomers (*5S,1''S*)- and (*5R,1''S*)-**54b** and four tautomeric species, which resulted from keto-enol tautomerisation of C-2 and C-4 and hydrogen-bonding of these groups with the 3-acyl residue.



Scheme 33 Total synthesis of **54b**: Reagents and conditions (i) BnOH, PTSA **61**, PTSCl **62**, 80°C, 2 h. (ii) HCl/Et_2O, $CHCl_3$, 0°C, 30 min. (iii) NH_3/DCM, $CHCl_3$, r.t. 60 min. (iv) 1.3 **1a**, benzoic acid, THF, reflux, 24 h. (v) H_2, 5% Pd/C, MeOH, r.t., 12 h. (vi) AcCl, $BF_3.OEt_2$, 80°C, 8 h.

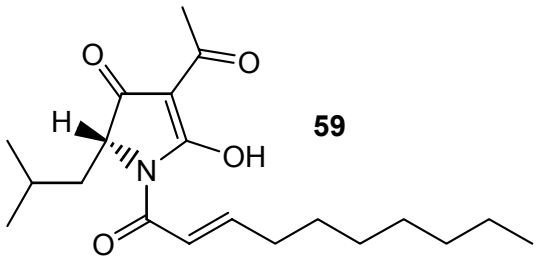
Tenuazonic acid **54b** has been shown to exhibit antibacterial and anti-viral activity, but its toxicity has impeded its clinical application to date[63-65].

The preparation of N-functionalised-5-alkyl-tetramic acids, such as reutericyclin **59**, was also investigated by reaction of α-amido esters **83** and ylide **1a**. The reaction was extremely sluggish due to the reduced acidity of the amide nitrogen in comparison to amino esters, but ring closure was found to occur using microwave irradiation:



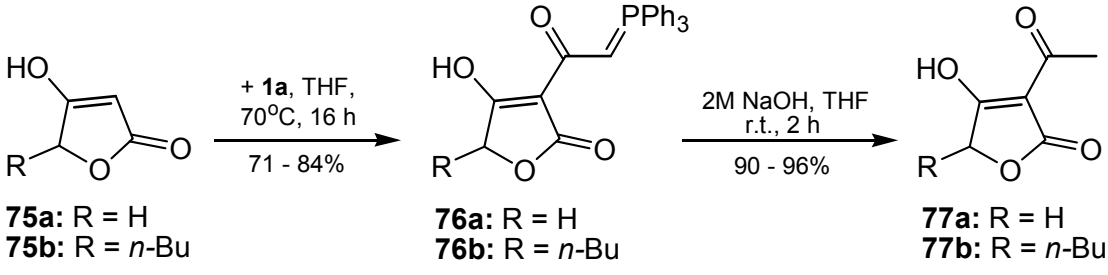
Scheme 40

Reutericyclin **59** has been isolated from a strain of lactic acid bacteria and possesses potential biological activity[68].



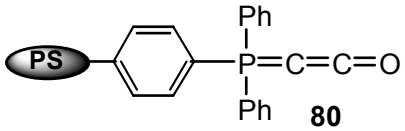
N-acyl tetramates were also synthesised by a straight-forward acylation of the 4-benzyloxy 5-alkyl tetramates **69**.

Whilst investigating other synthetic routes towards the preparation of **59**, the use of keteneylidenetriphenylphosphorane **1a** as an acylation agent was discovered. Reaction of simple tetronic acids, substituted and unsubstituted at the 5-position, with ylide **1a** generated 3-acylylidene-tetronic acids:



Scheme 35

A number of reagents and conditions were tested to bring about oxidative cleavage of the 3-acylylidene portion of **76** without disturbing the heterocycle and finally treatment with an aqueous 2M NaOH solution proved successful. The reaction was also carried out using the polymer-supported variant of ylide **1a** – **80** as the acylating agent.

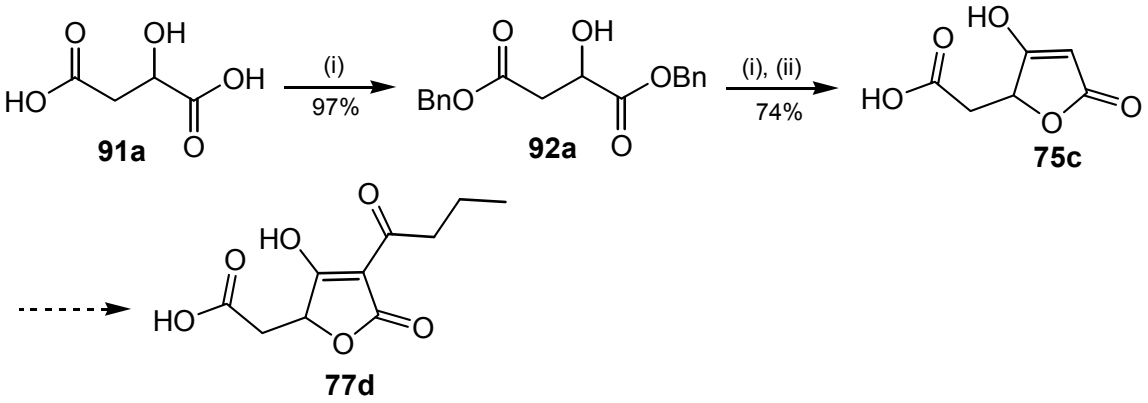


80

Both reactions were very efficient with minimal work-up and excellent yields.

In summation, a new and mild acylation procedure has been discovered to introduce an acetyl substituent to the tetronic acid and possibly tetramic acid nucleus.

The reaction of α-hydroxy-esters and keteneylidenetriphenylphosphorane **1a** was used in the construction of 4-benzyloxy-tetronates, following exposure to hydrogenolytic conditions to yield the corresponding tetronic acids:



91a **92a** **75c**

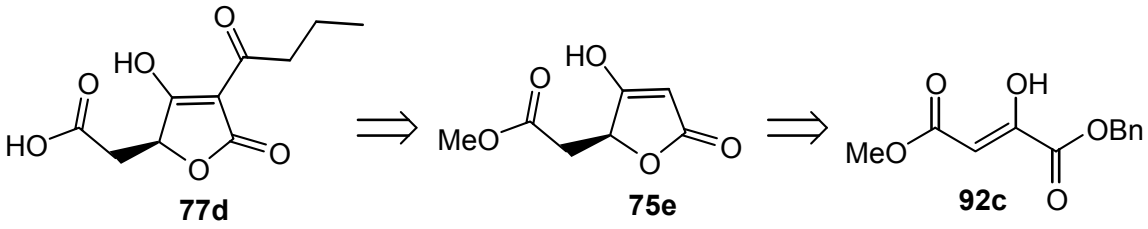
77d

Scheme 52 Reagents and conditions: (i) 6BnOH, PTSA, $CHCl_3$, reflux, 12 h. (ii) 1.3 **1a**, benzoic acid, THF, 16 h. (iii) H_2, Pd/C, MeOH, r.t., 12 h.

This reaction was used as part of the total synthesis of Carlosic acid **77d**, with the reaction of ylide **1a** and α-hydroxy-ester **92a** producing good yields. Carlosic acid **77d** is one of a family of fungal metabolites[98] and is believed to be a precursor to a number of other functionalised tetronic acids[99].

A number of 3-acyl-4-hydroxy-5-alkyl-furan-2-ones were prepared using a straight-forward acylation procedure consisting of the corresponding acid anhydride and the parent tetronic acid. However, this technique could not be applied to the synthesis of Carlosic acid **77d** due to the sensitive acid-functionality at C-5.

A stereoselective preparation of (*S*)-Carlosic acid **77d** was also considered:



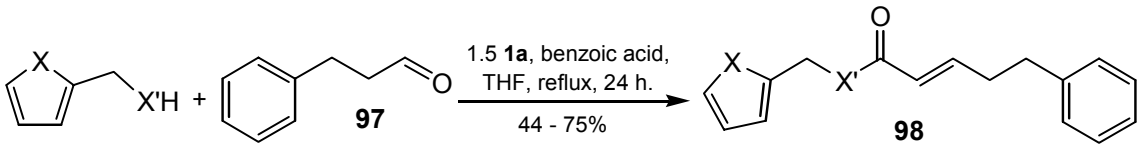
77d **75e** **92c**

Scheme 57

Use of an ester such as **92c**, containing two different protecting groups should allow regiospecific 3-acylation of **75e** in comparison to the 'free' acid **75c**.

Reaction of the prochiral precursor **92c** with ylide **1a** generated the corresponding tetronate with a 5-exocyclic double bond. Chiral reduction of this double bond with removal of the benzyl protecting group should produce optically active tetronic acid **75e**, but this approach was halted by the inefficiency of the lactonisation reaction (yields < 21%).

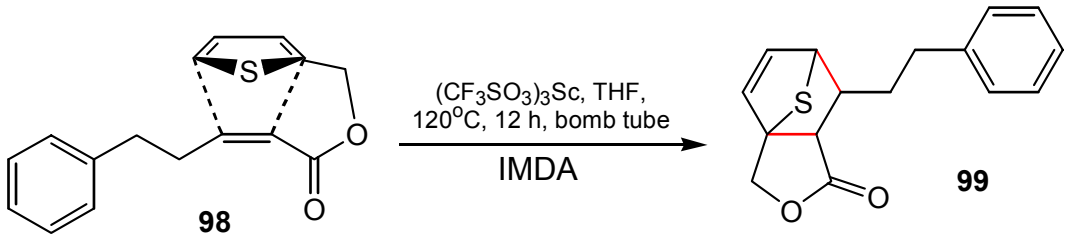
A number of α,β-unsaturated esters were prepared from the multi-component reaction of ylide **1a**, an alcohol **96a** or thiol **96b** and aldehyde **97**:



96a: X = S, X' = O
96b: X = O, X' = S

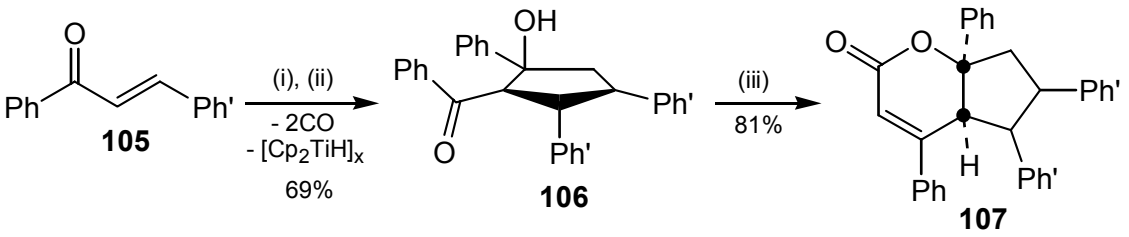
Scheme 59

An intramolecular Diels-Alder (IMDA) [4π+2π] cycloaddition reaction of compounds **96** was used in the construction of functionalised oligomers, such as **99**. Due to the thermal instability of the complex product **99**, a fine balance between the temperature and applied pressure drove the reaction:



Scheme 60

Highly substituted bicycles were also prepared starting from α,β-unsaturated ketones. Enone **105** reacted with $Cp_2Ti(CO)_2$ to generate a titanacycle, which was smoothly converted to **106** by a mild hydrogenation procedure[115].



Scheme 63 & 64 Reagents and conditions: (i) $Cp_2Ti(CO)_2$, toluene, 40°C, 3 h. (ii) H_2 (1 atm), Pd/C, toluene, r.t. (iii) 1.3 **1a**, benzoic acid, toluene, 160°C, 12 h.

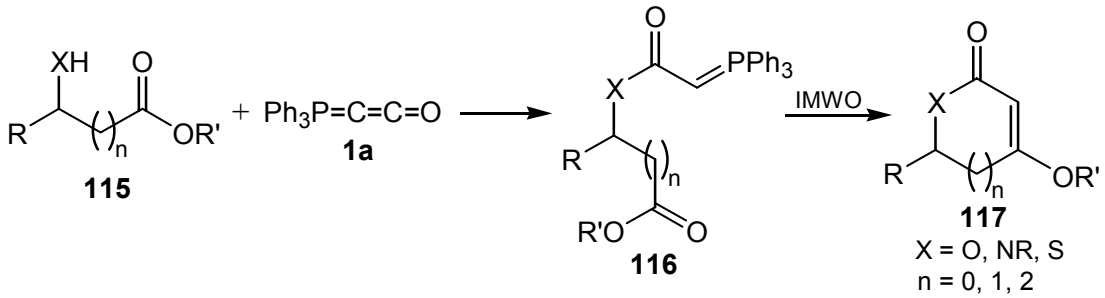
Taking advantage of the hydroxy and ketone functionalities within **106**, reaction with ylide **1a** led to the formation of the *cis*-annulated pyranone **107**.

5. Zusammenfassung

Heterocyclen mit unterschiedlichen Ringgruppen und verschiedenen Heteroatomen bilden das Grundgerüst vieler biologisch und pharmazeutisch interessanter Verbindungen. Das Hauptaugenmerk dieser Arbeit lag in der Herstellung einer Vielzahl von biologisch aktiven Stickstoff- und Sauerstoff-Heterocyclen mit Hilfe des Phosphorylids Ketenylidentriphenylphosphoran **1a**.

Als Zielmoleküle wurden speziell substituierte Pyrrolidine und Furanone ausgewählt, für die mehrere Retrosyntheserouten entwickelt wurden. Die Synthese dieser Verbindungen wurde unter den Gesichtspunkten einer kurzen und effizienten Route unternommen. Dabei wurden einzelne Reaktionen verwendet, die im Hinblick auf die Ausgangsverbindungen, und hinsichtlich der Einführung verschiedenster Substituenten sehr flexibel sind.

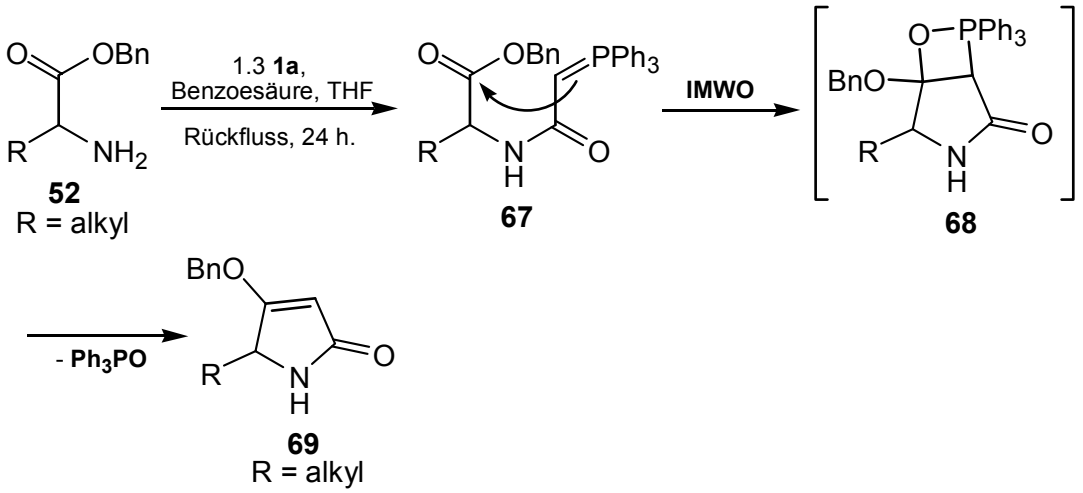
Ketenylidentriphenylphosphoran **1a** wurde als 'C_2O-Synthesebaustein' verwendet, weil es mit Carbonsäurederivaten die XH-acide Gruppen **115** wie -OH, -NHR oder -SH enthalten, unter Bildung einer Vielfalt von Heterocyclen **117** reagiert:



Scheme 65 Allgemeine Reaktion von **1a** mit XH-aciden Estern **115**

Zunächst addiert die Säuregruppe **115** an die C^{α}=C^{β} Bindung des Ylids **1a** unter Bildung einer Acylylid-Zwischenstufe **116**, die dann eine intramolekulare Wittig-Olefinierungsreaktion (IMWO) eingeht, welche zu einer Reihe von ungesättigten Heterocyclen **117** führt.

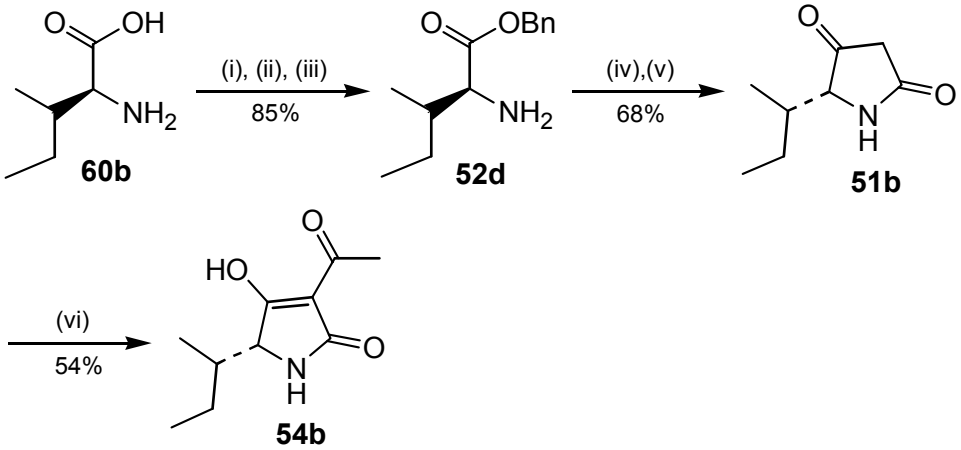
Unter Verwendung dieses allgemeinen Reaktionsschemas wurden durch Umsatz von Ketenylidentriphenylphosphoran **1a** mit α-Aminosäureestern eine Vielzahl von 4-Alkoxy- und 4-Benzyloxy-Tetramaten hergestellt:



Scheme 28

In Bezug auf diastereomere Verbindungen mit R = CH(Me)Et zeigten NMR-Analysen, dass die Lactamisierungssequenz nicht stereoselektiv verläuft. Es wurde ein Isomeren Verhältnis von 1:1 gefunden. Die ansschließende Abspaltung der 4-Etherfunktion von Verbindungen des Typs **69** lieferte eine Reihe von 5-Alkyltetramsäuren (5-Alkyl-pyrrolidine-2,4-dione).

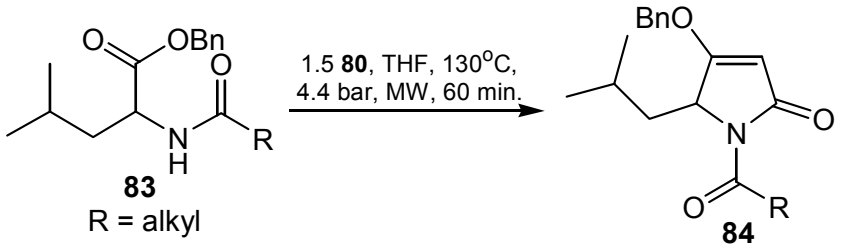
Die Acylierung von 4-Hydroxy-5-*sec*-butyl-pyrrol-2(*5H*)-on **51b** führte zu (±)-3-Acetyl-4-hydroxy-5-*sec*-butyl-pyrrol-2(5*H*)-on **54b**, die auch als (±)-Tenuazonsäure bekannt ist. Man erhielt komplizierte Spektren, was sich durch das Vorhandensein von zwei Diastereomeren (*5S,1''S*)- und (*5R,1''S*)-**54b** und vier tautomeren Spezies erklären lässt. Dies ist zurückzuführen auf Keto-Enol Tautomerie von C-2 und C-4 und Wasserstoffbrückenbindungen dieser Gruppen mit der 3-Acylfunktion.



Scheme 33 Totalsynthese von **54b**: Reagenzien und Bedingungen: (i) BzlOH, TosOH, TosCl, 80°C, 2 h. (ii) HCl/Et_2O, $CHCl_3$, 0°C, 30 min. (iii) NH_3/DCM, $CHCl_3$, r.t., 60 min. (iv) 1.3 **1a**, Benzoesäure, THF, Rückfluss, 24 h. (v) H_2, 5% Pd/C, MeOH, r.t., 12 h. (vi) AcCl, $BF_3.OEt_2$, 80°C, 8 h.

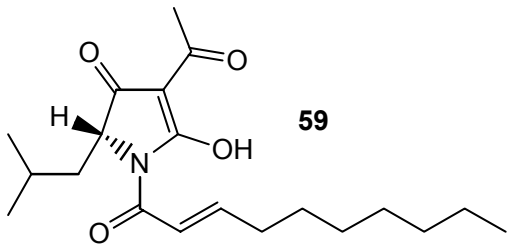
Es konnte gezeigt werden, dass Tenuazonsäure **54b** antibakterielle und anti-virale Eigenschaften besitzt, allerdings hat ihre Toxizität bis heute ihre klinische Anwendung verhindert[63-65].

Die Synthese von N-funktionalisierten 5-Alkyltetramsäuren **84** wurde durch Umsatz von α-Amidoestern **83** mit Ylid **1a** auch erforscht. Die Reaktion war sehr träge aufgrund der erniedrigten Acidität des Amidstickstoffs im Vergleich zu Aminosäureestern, konnte jedoch unter Mikrowellenbestrahlung erfolgreich durchgeführt werden:



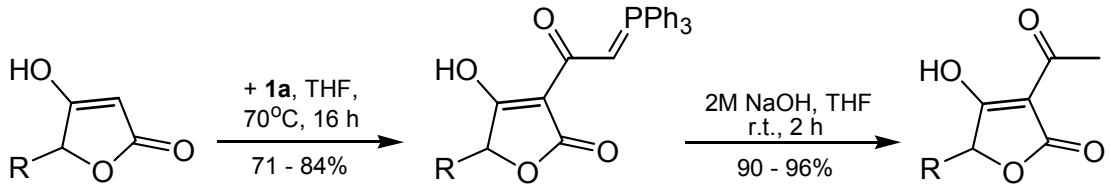
Scheme 40

Reutericyclin **59** wurde aus Milchsäurebakterienstämmen isoliert und besitzt hohe biologische Aktivität[68].



N-Acyltetramate wurden auch durch direkte Acylierung von 4-Benzyloxy-5-alkyl-tetramate **69** erzeugt.

Während andere Synthesewege zur Herstellung von Reutericyclin **59** erforscht wurden, wurde entdeckt, dass sich Ketenylidentriphenylphosphoran **1a** sehr gut als Acylierungsreagenz eignet. Die Reaktion von einfachen Tetronsäuren, bisubstituiert oder unsubstituiert an der 5-Position, mit Ylid **1a** lieferte 3-Acylylidentetronsäuren **76**:



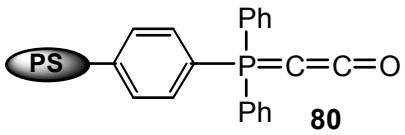
75a: R = H
75b: R = *n*-Bu

76a: R = H
76b: R = *n*-Bu

77a: R = H
77b: R = *n*-Bu

Scheme 35

Ein Vielzahl von Reagenzien und Reaktionsbedingungen wurde getestet, um eine oxidative Spaltung der 3-Acylyliden-Einheit von **76** zu entwickeln ohne den Heterocyclus zu zerstören. Schließlich war die Behandlung mit wässeriger 2M NaOH-Lösung erfolgreich. Die Reaktion wurde auch mit der polymer-gebundenen Variante von Ylid **1a** – **80** als Acylierungsmittel durchgeführt.

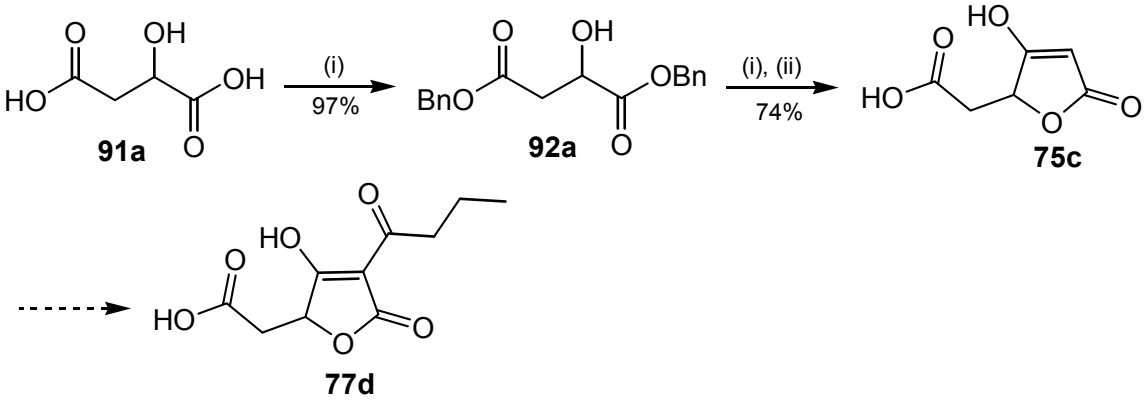


80

Beide Reaktionen waren sehr effizient, da nur geringe Aufarbeitung nötig war und sehr gut Ausbeuten erzielt wurden.

Zusammenfassend lässt sich festhalten, dass eine neue und milde Acylierungsmethode entdeckt wurde, die einen Acylierungssubstituenten an Tetronsäuren und wahrscheinlich auch Tetramsäuren einführt.

Die Reaktion von α-Hydroxyestern und Ketenylidentriphenylphosphoran **1a** wurde verwendet um 4-Benzyloxytetronate aufzubauen und deren anschließende Hydrierung liefert wie unten gezeigt die entsprechenden Tetronsäuren:



91a **92a** **75c**

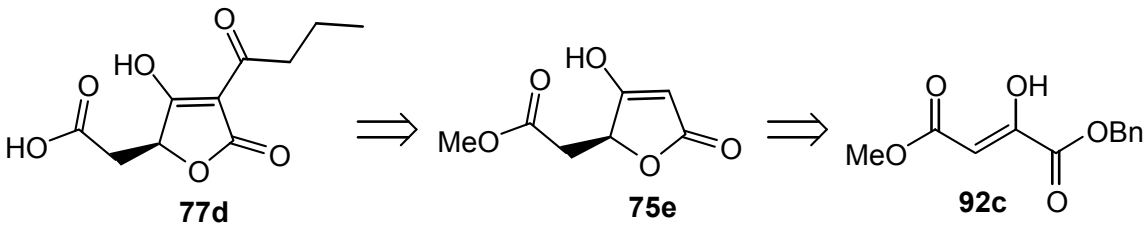
77d

Scheme 52 Reagenzien und Bedingungen: (i) 6TosOH, PTSA, $CHCl_3$, reflux, 12 h. (ii) 1.3 **1a**, Benzoesäure, THF, 16 h. (iii) H_2, Pd/C, MeOH, r.t., 12 h.

Die Reaktion wurde eingesetzt für die Totalsynthese von Carlosischer Säure **77d**. Dabei verlief der Umsatz von Ylid **1a** mit α-Hydroxyester **92a** in guten Ausbeuten.

Eine Reihe von 3-Acyl-5-alkyl-furan-2-onen wurde mittels einer einfachen Acylierungsmethode aus dem entsprechenden Carbonsäureanhydrid und dem Tetronsäuregrundgerüst hergestellt. Wegen der empfindlichen C-5 Säurefunktion konnte diese Technik jedoch nicht auf die Synthese von Carlosischer Säure **77d** übertragen werden.

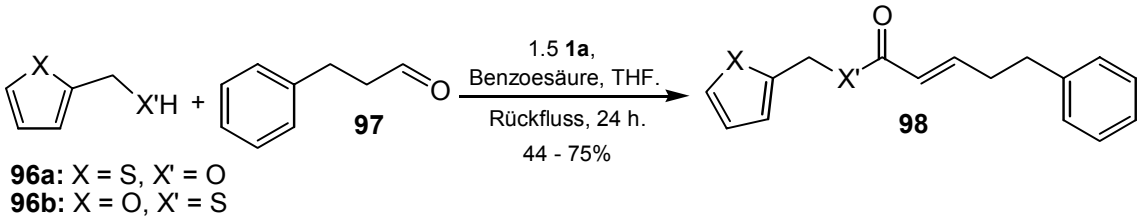
Eine stereoselektive Synthese von (*S*)-Carlosischer Säure **77d** wurde auch in Betracht gezogen:



Scheme 57

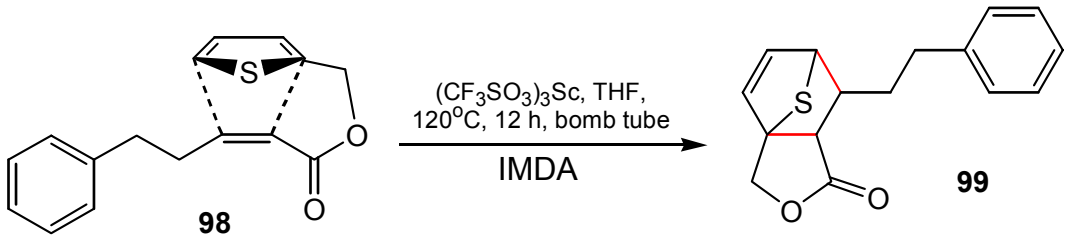
Bei Verwendung eines Esters wie **92c**, der zwei verschiedene Schutzgruppen enthält, wurde erwartet, dass die 3-Acylierung von **75e** im Vergleich zu der freien Säure **75c** regiospezifisch verläuft. Die Reaktion von prochiralen Vorstufen wie **92c** mit Ylid **1a** lieferte die entsprechenden Tetronate mit einer 5-exocyclischen Doppelbindung. Chirale Reduktion dieser Doppelbindung mit Entfernung der Benzylschutzgruppe sollte die optisch aktive Tetronsäure **75e** liefern, aber diese Methode wurde aufgrund der Ineffektivität der Lactonisierungsreaktion nicht weiter verfolgt.

Eine Vielzahl von α,β-ungesättigten Estern wurde durch die Multikomponentenreaktion von Ylid **1a**, Alkohol **96a** oder Thiol **96b** und Aldehyd **97** hergestellt:



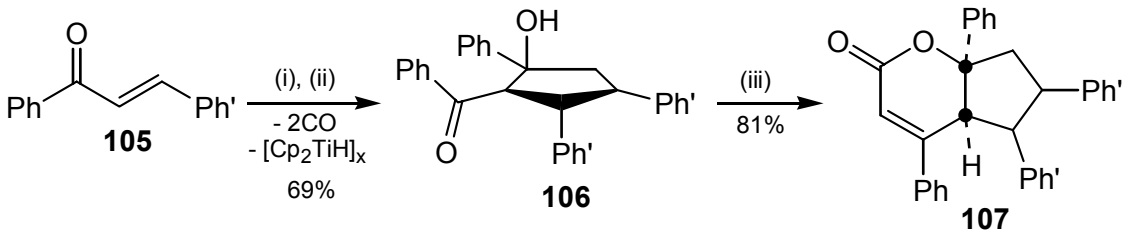
Scheme 59

Zur Konstruktion von funktionalisierten Oligomeren wie **99** wurde Verbindung **96** einer intramolekularen Diels-Alder (IMDA) [4π+2π] Cycloadditionsreaktion unterzogen. Wegen der thermischen Instabilität des Komplexprodukts **99**, führte nur eine feine Balance zwischen Temperatur und dem angewandten Druck zu einer Reaktion:



Scheme 60

Ausgehend von α,β-ungesättigten Ketonen wurden hochsubstituierte Bicyclen hergestellt. Enon **105** reagierte mit $Cp_2Ti(CO)_2$ unter Bildung eines Titancyclus, der sehr langsam durch eine milde Hydrierungsmethode zu **106** umgewandelt wurde[115].



Scheme 63 & 64 Reagenzien und Bedingungen: (i) $Cp_2Ti(CO)_2$, toluol, 40°C, 3 h. (ii) H_2 (1 atm), Pd/C, toluol, r.t. (iii) 1.3 **1a**, Benzoesäure, toluol, 160°C, 12 h.

Nützt man die Vorteile der Hydroxy- und Ketonfunktionalitäten in **106** aus, führt die Reaktion mit Ylid **1a** zur Bildung des *cis*-annulated Pyrons **107**.

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[2] In accordance with IUPAC nomenclature, ylides of type $R_3P=C=C=X$ are designated as phosphacumulene ylides, while those of type $R_3P=C=CR'_2$ are phosphaallene ylides[6].

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Publikationen:

1. Claire Melanophy, Rainer Schobert*, Faramarz Maaref, Frank Hampel, **Inorganica Chimica Acta**, **2003**, 355, 454.

'An unusual hydrogenolysis of titana-2,9-dioxacyclonona-3,7-dienes producing cis-2-acylcyclopentanols'

2. Claire Melanophy, Rainer Schobert*, Cartsen Jagusch, Gillian Mullen, **tbp**.

'Synthesis and reactions of polymer-bound $Ph_3P=C=C=O$: a quick route to tenuazonic acid and other optically active pure 5-substituted tetramates'

Erklärung

Die Arbeiten zur vorliegenden Dissertation wurden im Zeitraum von Oktober 1999 bis September 2001 an der School of Chemistry, Queens University of Belfast, und von Oktober 2001 bis Mai 2003 am Lehrstuhl für Organische Chemie I, Universität Bayreuth unter der Leitung von Herrn Prof. Dr. Rainer Schobert durchgeführt.

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