The Design and Synthesis of Novel Potential Anti-malarial Compounds

by

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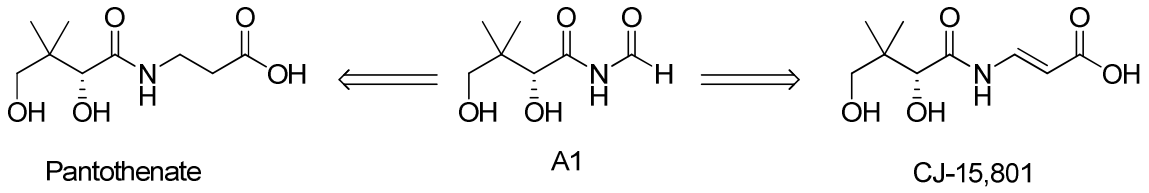
Abstract

The work contained in this thesis is split into two sections.
Each section covers a different biological pathway, its current importance as a potential drug target, and the syntheses towards a selection of natural products and analogues relevant to the pathway.

In Section A, the novel approach towards a new class of *N*-formyl amides is described. Furthermore, this new methodology is used to generate the imide intermediate A1. This imide is now considered a key intermediate in our synthesis of natural products CJ-15,801, Pantothenate, and the first generation of analogues based on CJ-15,801.



This section also covers the potential scope for *N*-formyl imides in chemical synthesis in general.

Section B describes two novel approaches towards non-mevalonate pathway (MEP) intermediates and inhibitors. The synthesis towards a previously unpublished 2,2-dimethyl MEP analogue, is described alongside the attempted generation MEP. The methodology described herein shows the use of Neighbouring Group Participation in intramolecular opening of epoxides, and how this can be applied to the generation of analogues.

Above all, the aim of this thesis is to open up new synthetic strategies towards potential inhibitors for individual biosynthetic pathways.

Acknowledgements

First and foremost I would like to thank my supervisor Dr Rudi Marquez for his tireless efforts and patience in his attempts to train an undergraduate biochemist to think like a postgraduate chemist.

Recognition must also go to Drs P. McGivern, N. Henry, S. Ghilagaber, B. Abbott and N. Shpiro for all their help and advice over the years.

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Final thanks must go to Mum, Dad and Nicola for putting up with me and providing support right to the end.

Abbreviations

2,2 DMEP	2,2 DiMethyl Erythritol Phosphate
Ac	acetyl
atm	atmosphere
ATP	Adenosine Triphosphate
Bn	benzyl
BnBr	benzylbromide
Bu	butyl
^{o}C	degrees Celsius
Ca	calcium
cat.	catalytic
CoA	Coenzyme A
Cu	copper
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DET	diethyl tartrate
DIBAL	diisobutylaluminium hydride
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMP	Dess-Martin Periodinane
DMSO	dimethylsulphoxide
DOXP	1-deoxy-D-xylulose 5 phosphate
e.e	enantiomeric excess
ERG8	phosphomevalonate kinase;
ERG10	acetoacetyl-CoA ligase;
ERG12	mevalonate kinase;
ERG13	2-hydroxy-3-methylglutaryl-CoA synthase (HMG-CoA synthase);
ERG20	farnesyl diphosphate synthase.
Et	ethyl
EtOAc	ethylacetate
g	gram
HMB-PP	(*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate
HMG1	2-hydroxy-3-methylglutaryl-CoA reductase 1
HMG2	2-hydroxy-3-methylglutaryl-CoA reductase 2
hr	hour
HRMS	high resolution mass spec
IDI1	isopentenyl pyrophosphate, dimethylallyl diphosphate isomerase;
IBX	2-iodoxybenzoic acid
IPP	isopentenyl pyrophosphate;
IR	infrared
ISPC	DOXP reductase
ISPD	4-diphosphocytidyl-2-C-methyl-D-erythritol synthase
ISPE	4-diphosphocytidyl-2-C-methyl-D-erythritol kinase
ISPF	2-C-methyl-D-erythritol 2,4-cyclodiphosphate synthase
ISPG	HMB-PP synthase
KHMDS	potassium (bistrimethylsilyl)amide
L.A	lewis acid
LAH	lithium aluminium hydride
liq.	liquid

mbar	millibar
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MEP	2-C-methyl-D-erythritol 4-phosphate
mg	milligram
MIC	Minimum Inhibitory Concentration
mL	millilitre
MVD1	diphosphomevalonate decarboxylase;
m/z	mass to charge ratio
n-	normal
NaH	sodium hydride
n-BuLi	*n*-butyllithium
NGP	neighbouring group participation
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
p-	para
*Pan*K	pantothenate kinase
PMB	*p*-methoxybenzyl
PPC	4'-phospho-*N*-pantothenoylcysteine
p-TsOH	*p*-toluenesulphonic acid
RDA	Recommended daily allowance
RT	room temperature
SAE	sharpless asymmetric epoxidation
SAR	structure activity relationships
TBAI	tert-butylammoniumiodide
TBS	*t*-butyldimethylsilyl
THF	tetrahydrofuran
TPAP	Tetrapropylammonium perruthenate
TMSOK	Potassium trimethylsilanolate
w/v	weight per volume
wt/wt	weight per weight

Contents

1 Malaria

1.1 Malaria: Discovery and Review

Malaria was first identified in 1880 by Alphonse Laveran, a French army surgeon working in Algeria. He documented the description of parasites in the red blood cells of a man showing symptoms of malaria. In 1886; Camillo Golgi established that there were at least two forms of the malaria. Within a decade further discoveries were documented. In 1898, Ronald Ross (a British officer in the Indian Medical Service), demonstrated that patients suffering from malaria could transmit the parasites to mosquitoes during a blood meal. All three were awarded the Nobel Prize for their discoveries in 1907, 1906, and 1902 respectively.

Since then malaria has continued to ravage third world countries. In addition to other threats such as the HIV/ AIDS virus, malaria has consistently contributed to the death toll in Africa and other endemic countries.

1.2 The Malarial Cycle

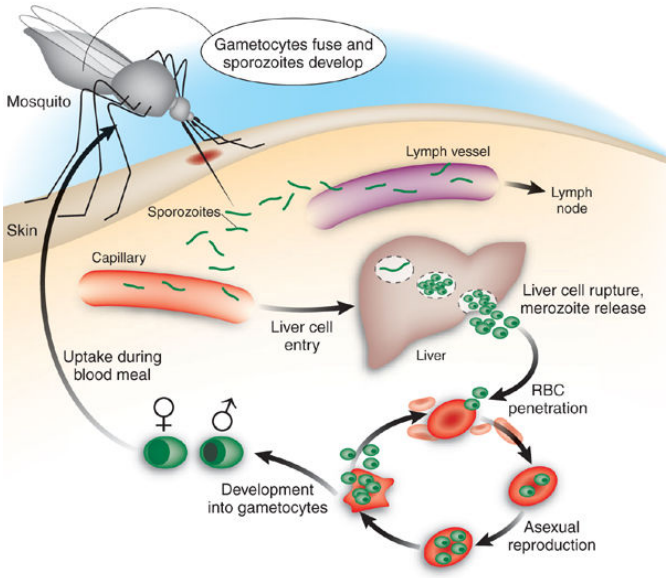


Figure 1.2.1 – The Malarial Cycle [1]

The cycle starts with sporozoites entering the bloodstream, and migrating to the liver. The sporozoites infect liver cells where they are undetected by the human immune system, and can multiply into merozoites. Merozoites then rupture the liver cells, and escape back into the bloodstream. Once in the bloodstream, the merozoites infect red blood cells and enter their erythrocytic stage. Whilst in the red blood cells they are again invisible to the human immune system, and develop into ring forms. From the ring form they transform into trophozoites to feed, then multinucleated schizonts to reproduce, then merozoites again. The merozoites rupture the blood cells and return to the bloodstream to infect more blood cells. Only the ring forms circulate in the bloodstream. The other red blood cells stick to the walls of small blood vessels using adhesive proteins on the infected cell surface, preventing them from being destroyed in the spleen.

Some merozoites turn into male and female gametocytes. If an infected person is bitten by a mosquito, the mosquito can pick up these gametocytes within the blood. Fertilization and sexual recombination of the parasite then occurs in the mosquito's gut, where new sporozoites develop and travel to the mosquito's salivary gland, completing the cycle.

There are 4 species of *Plasmodia* responsible for malaria. *Plasmodium falciparum*, *ovale*, *vivax*, and *malariae*. *Plasmodia* degrade the haemoglobin in red blood cells, to acquire the amino acids needed to construct its own protein. During this process, the parasite produces the toxic and soluble molecule haem, which it biocrystallizes to form haemozoin, a non-toxic molecule.

1.3 Malaria in Numbers

In past years it was thought there were at least 100 million deaths and 500 million further cases of malaria every year, worldwide.

Current estimates suggest that in 2002 the global burden of clinical malaria was in the area of 515 million cases. Approximately 60% of all cases of malaria occur among the poorest 20% of the world's population [(2)], and it is estimated that more than one-third of these cases occur in Asia, with around 3% occurring in the Americas.

The estimated cost to effectively control malaria in the 82 countries (of which 20 are listed below) with the highest burden is about $3.2 billion annually.

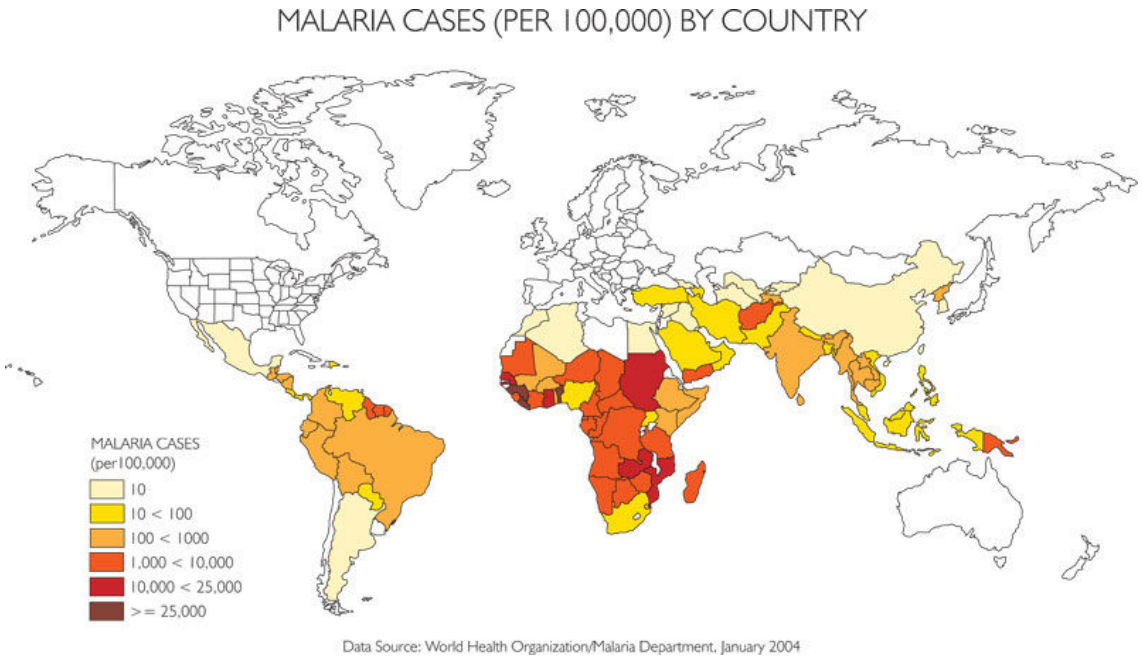


Figure 1.3.1- Population Density of Malaria cases

Rank	Country	Number	Year
1	Uganda	12,343,411	2003
2	Tanzania (United Rep. of)	10,712,526	2003
3	Mozambique	5,087,865	2003
4	Congo (Dem. Republic of)	4,386,638	2003
5	Ghana	3,552,869	2003
6	Sudan	3,084,320	2003
7	Malawi	2,853,317	2002
8	Nigeria	2,608,479	2003
9	Madagascar	2,114,400	2003
10	Zambia	2,010,185	2001

Rank	Country	Number	Year
11	Burundi	1,808,588	2002
12	India	1,781,336	2003
13	Burkina Faso	1,451,125	2002
14	Angola	1,409,328	2002
15	Zimbabwe	1,252,668	2002
16	Senegal	1,120,094	2000
17	Guinea	889,089	2000
18	Rwanda	856,233	2003
19	Mali	809,428	2003
20	Benin	779,041	2001

Table 1.3.1- Number of cases of malaria by country

Although most malaria cases occur among residents of countries where malaria is endemic (occurring on a constant basis), travellers to these countries can also be infected if bitten by an infected mosquito. This is one way in which malaria has appeared in non-endemic countries. Malaria can also occur among non-travelers in the form of congenital malaria (malaria passed from an infected mother to her child during pregnancy or birth), introduced malaria (malaria introduced in a non-endemic malaria region by an infected host), or transfusion-related malaria (malaria acquired during blood transfusions).

In the badly affected areas, children are the most threatened. The first two years of their life are the most dangerous, as they have not yet developed sufficient immunity. Malaria accounted for one in 10 deaths among children in developing countries in 2002.

The second most badly affected are pregnant women. Usual "western" problems associated with pregnancy (illness, anaemia) can be magnified due to malarial infection, and in some/ most cases cause death.

1.4 Diagnosis

The biggest fear is that current estimates of the scale of malaria are underestimated due to some people being infected and never finding a doctor. When these people do find a doctor, the list of diagnosis tools is limited. The most important diagnostic method is the recognition of malaria symptoms. These include:

- Fever
- Chills
- Headaches
- Nausea
- Profuse Sweating
- Muscle pain
- Fatigue

The only form of definitive diagnosis is through observation of parasites in the red blood cells under a microscope.

More advanced diagnostic tools include fluorescent staining, genetic probes and antigen detection in the form of a dip stick, but these methods are not widely used.

Malaria accounts for 10% of Africa's disease burden, and is thought to cost the African continent more than $12 billion annually. Therefore, due to the financial and sociological issues malaria gives rise to, the quest for an effective cure is an ongoing one.

1.5 Current Treatments

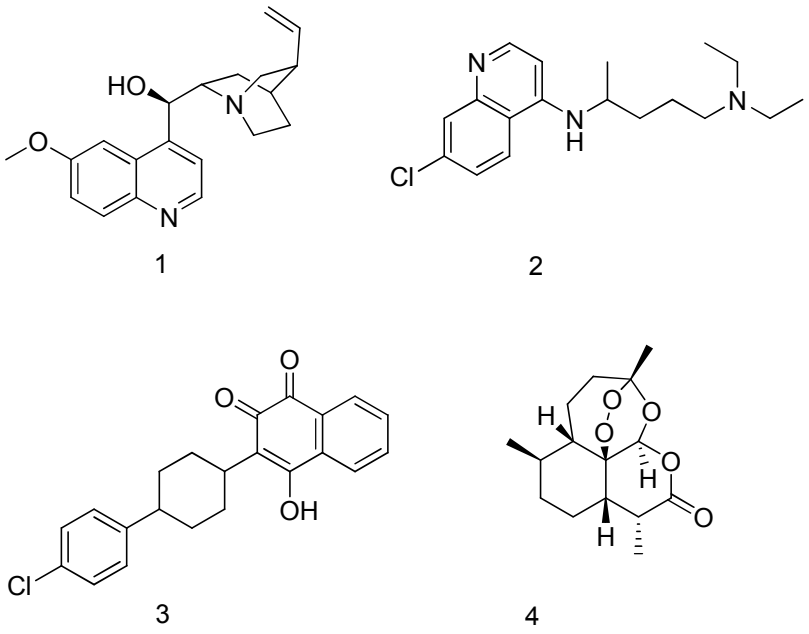


Figure 1.5.1

As malaria has been a problem as long as modern medicine has been practiced, a number of different treatments have been developed over the years.

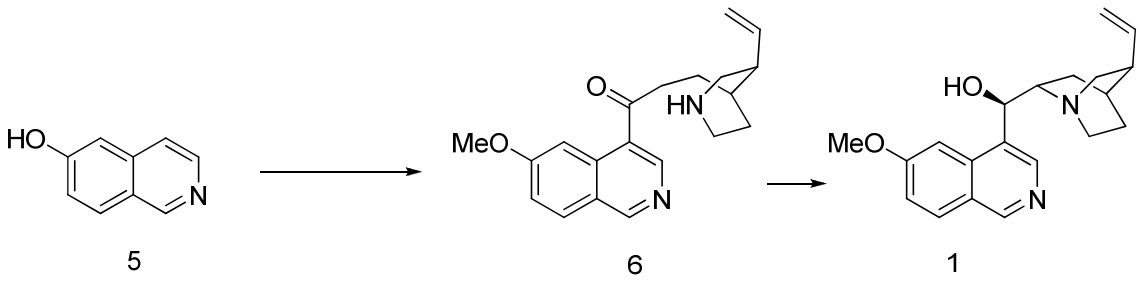
These include: Quinine, Chloroquine, Malarone and Artemisinin (Fig 1.5.1).

1.6 Quinine

Quinine (1) was extracted, isolated, and named in 1817 by French researchers Pierre Joseph Pelletier and Joseph Bienaimé Caventouin. It was extracted from the bark of the South American cinchona tree, and to this day Cinchona trees remain the only practical source of quinine. It contains two major fused-ring systems: The aromatic isoquinoline and the bicyclic quinuclidine.

Quinine inhibits haemozoin biocrystallization, increasing the levels of toxic haem in the parasites; resulting in parasite death.

The first formal synthesis was reported by Woodward [3] in 1944, and was later corroborated by modern techniques recently by Smith [4].



Scheme 1.6.1

However, no synthetic methods can compete with isolation of the alkaloid from natural sources with respect to economic efficiency.

The use of quinine does have its drawbacks. The FDA classes quinine as a Category X teratogen, as it is known to act as an abortifacient and cause birth defects in large doses. In the UK, the risks to the pregnancy are considered small, in comparison to the risk of death from *P. falciparum* malaria.

1.7 Chloroquine

Chloroquine (2) is a 4-aminoquinoline drug used in the treatment or prevention of malaria. The lysosomotropic character of chloroquine is believed to account for much of its anti-malarial activity; the drug concentrates in the acidic food vacuole of the parasite and interferes with essential processes.

Upon the production of haemozoin in the food vacuole, Chloroquine binds to haem (or FP) to form what is known as the FP-Chloroquine complex, this complex prevents further biocrystallization of haem and is highly toxic to the cell. The FP-Chloroquine complex disrupts membrane function, resulting in cell lysis. The parasite is then effectively flooded by its own metabolic products.

Chloroquine and related quinines have been associated with cases of retinal toxicity, particularly when provided at higher doses for longer time frames. Other side effects include stomach aches, itching, headaches and blurred vision. Increased doses can be fatal.

1.8 Malarone

Malarone (3) is a fixed preparation available from GSK. It is a mixture of Atovaquone (a hydroxy-1,4-naphthoquinone) and proguanil. Malarone has fewer side effects than other available treatments.

The dose is one tablet daily, starting one or two days before traveling into a malaria-endemic area. It is continued throughout the stay, and for another 7 days after returning from the malarious area. For this reason, the drug is considered expensive to use, and is generally only available to wealthier Westerners, travelling for short periods of time.

With such large amounts of treatments being made available, and their overly-inappropriate use, the widespread resistance to conventional anti-malarial drugs has

contributed to increasing morbidity and mortality. This continues to be an important public health challenge, particularly among countries in South and Southeast Asia and South America. The apparent emergence of malaria drug resistance in parts of Africa is also a growing concern.

Drug resistance has been confirmed in two of the four human malaria parasite species. Chloroquine resistant *P. falciparum* (CRPF) emerged as a major problem in the late 1950's and early 1960's in Southeast Asia, Oceania, and South America. Chloroquine resistant *P.vivax* (CRPV) malaria was identified in 1989 and has now also been found in Southeast Asia, the Indian subcontinent, and South America.

In the last half century chloroquine resistance has spread to nearly all areas of the world where *P.falciparum* malaria is transmitted. More concern is being generated over the fact that *P.falciparum* has also developed resistance to nearly all the currently available malaria drugs, such as sulfadoxine- pyrimethamine, mefloquine and quinine.

The emergence of drug resistance, high cost of production, or high toxicity has lead to the investigation of other compounds with therapeutic applications.

1.9 Artemisinin

One such compound is Artmesinin. Artemisinin (4) has been used in Chinese medicines for 2000 years, and was utilised as an antimalarial during the Vietnam War by Chinese soldiers.

These compounds produce a quick response in (and are well tolerated by) people with malaria. They have also been shown to be active against multi-drug resistant *P.falciparum* malaria. Artemisinin compounds are usually used in combination with other antimalarials

to treat the parasite as this can improve the efficiency of treatment and lead to reduced risk of the parasite developing resistance to the individual drugs in the combination.

Research is currently being undertaken to try and understand the mechanism of action of Artemisinin. It is thought that the iron in the haem generated in consumption of haemoglobin, reduces the peroxide bond in artemisinin; generating high-valent iron-oxo species. The subsequent reaction cascade produces reactive oxygen radicals, which damage the parasite leading to its death.

The total synthesis of Artemisinin has been performed using basic organic reagents [(5)].

As a response to increasing levels of antimalarial resistance, The World Health Organization (WHO) now recommends that all countries experiencing therapy resistant malaria cases to use combination therapies.

However, as artemisinin compounds are isolated from the plant *Artemisia annua*, the cultivation of the plants and production of the drugs takes at least eight months. Therefore the stockpile of drug must be guaranteed to be greater than any increased demand. This, coupled with its short shelf life of 3 years, makes it difficult to provide for people in remote areas.

Private/ Public partnerships are beginning to create solutions to the growing problem of malaria. Governments provide funding, removing the financial burden on private companies, and the private companies provide the research staff to find new compounds.

One example of such a private/ public partnership is the Medicines for Malaria Venture (MMV). With funding from the Gates Foundation, MMV strike up effective working relationships with companies such as Novartis and GSK, in the hope to provide new leads. One such lead is Triclosan (GSK) (8) which is currently used as an antibiotic, and has been shown to have anti- *P.falciparum* properties.

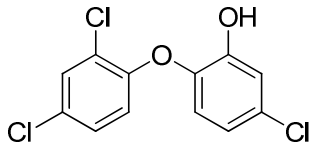


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Figure 1.9.1

The WHO now regularly publish lists of diagnostic tests that work, enabling healthcare workers to pick out best ones, in a bid to provide a much quicker and efficient diagnosis.

As more drugs are rolled out, our understanding of the biochemistry of malaria increases and development of known working drugs can be modified. With the emergence of further resistant strains, the need for new drugs and drug targets is ever more apparent. Until a vaccine is generated, the future of malaria chemotherapy lies in the development of non toxic, (and ultimately) cheap, treatments useful for combination therapies.

With the advancement of biochemical validation, new targets have been identified for potential new anti-malarial drugs. Two metabolic pathways in particular have been under investigation in recent years, the CoA biosynthetic and Non-mevalonate pathways.

2 Pantothenate, the CoA Biosynthetic Pathway, CJ-15,801 and enamides

2.1 The CoA Biosynthetic Pathway

Pantothenic acid, otherwise known as vitamin B_5, is a water-soluble vitamin whose name is derived from the Greek *pantothen* meaning "from everywhere". It gets this name due to the fact that small quantities of pantothenic acid are found in nearly every natural food source. Although no specific role has been determined, pantothenic acid deficiencies can result in fatigue, allergies, nausea, and abdominal pain. Any of these symptoms are quickly reversed by supplementation.

Biologically, pantothenic acid (9) is the starting substrate in the biosynthesis of coenzyme A (CoA), an enzyme cofactor necessary for a number of metabolic processes including the Citric Acid Cycle. Coenzyme A (14) plays a major role in the biosynthesis of many important compounds such as fatty acids, cholesterol, and acetylcholine. In certain bacteria, the ability to synthesize CoA comes from the necessity to import pantothenic acid from its surrounding environment to survive.

In vivo studies in both eukaryotic and bacterial cells show Coenzyme A is synthesized in a five-step process from pantothenate (Figure 2.1.1):

Pantothenate is phosphorylated to 4'-phosphopantothenate (10) by pantothenate kinase (Pan K). A cysteine is added to 4'-phosphopantothenate by the enzyme phosphopantothenoylcysteine synthetase to form 4'-phospho-*N*-pantothenoylcysteine (PPC) (11).

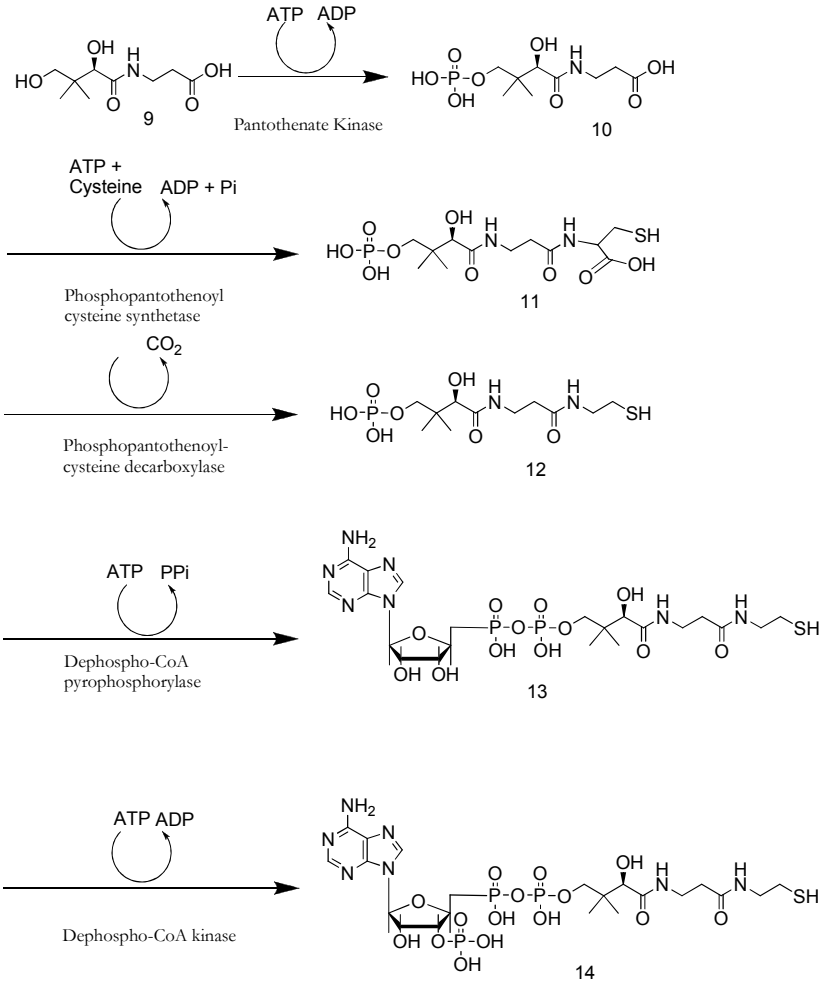


Figure 2.1.1- CoA biosynthetic pathway

PPC is then decarboxylated to 4'-phosphopantetheine (12) by phosphopantothenoyl-cysteine decarboxylase. Adenylation of 4'-phosphopantetheine by the enzyme phosphopantetheine adenylyl transferase generates dephospho-CoA (13). Finally, dephospho-CoA is phosphorylated using ATP to coenzyme A (14) by dephosphocoenzyme A kinase.

Studies have shown that the dextrorotatory (D)-(-) isomer of pantothenic acid is biologically active, whereas the levorotatory (L)-(+) form may antagonize the effects of the dextrorotatory isomer.[6]

2.2 Pantothenate

As pantothenic acid is needed to form CoA, and is necessary for so many biological roles, it is considered an essential nutrient to sustain life. Because of this, its commercial applications have become extremely diverse.

Although pantothenic acid can be found in numerous foods, no RDA has been proposed. However, it is possible to find Vit B_5 in many dietary supplements (as calcium-*D*-pantothenate), and a number of companies are now adding pantothenic acid to their beverages.

The cosmetic industry routinely add pantothenic acid to various cosmetic products, including shampoo, and advertise pantothenic acid additives. Studies have also shown that pantothenic acid has a positive effect on the treatment of acne [(7)].

Perhaps on a more important, and widely significant role, pantothenic acid has shown a measurable benefit on patients suffering from diabetes [(8)].

Due to the increased demand for pantothenic acid, there exist some industrial applications for a synthesis of this compound, although the emergence of the use of microbial cultures has been favoured over classic synthetic routes (Fig 2.3.1).

2.3 Synthesis of Pantothenate

2.3.1 Synthetic

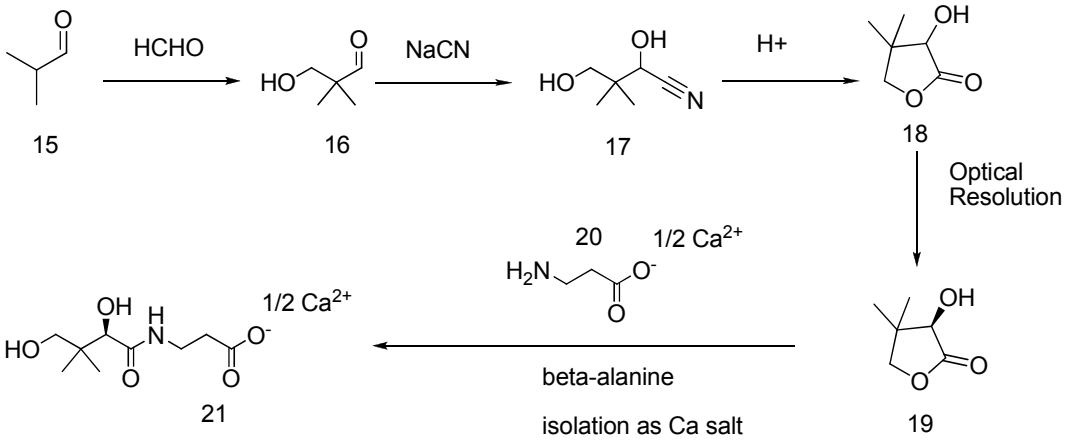


Figure 2.3.1- Current synthetic approach towards pantothenate

Vandamme [(9)] discusses the most efficient syntheses of pantothenic acid. Isobutyraldehyde (15) is reacted, first with formaldehyde, then sodium cyanide to generate cyanohydrin (17).

This is then cyclised to the racemic pantolactone (18). Optical resolution using quinine, quinidine, cinchonidine and brucine isolates the stereospecific (D)-(-)- pantolactone (19). Reaction with β-alanine provides pantothenic acid as the Ca salt (21). Although no yields were given, the limitations for production scale reactions are evident. The use of cyanide is dangerous on a large scale, but also the difficult optical resolution using numerous reagents is also a key limiting factor.

2.3.2 Microbial

To overcome these limitations on an industrial scale, a mixture of chemical and biochemical synthesis is used. The use of keto-reductase enzymes, such as *R.minuta* or *C.parapsilosis*, allows the generation of the enantiomerically pure pantolactone (19) from its respective keto-pantolactone (24). The ketopantolactone is generated in one pot using isobutyraldehyde (15) and formalin (22) as before; sodium methoxide, and diethyl oxalate (23). This produces the required ketopantolactone (24) in 81% yield. Introduction of the ketoreductases (along with glucose for energy) generates the optically pure (D)-(-)-pantolactone (19) in a molar yield of 100%.

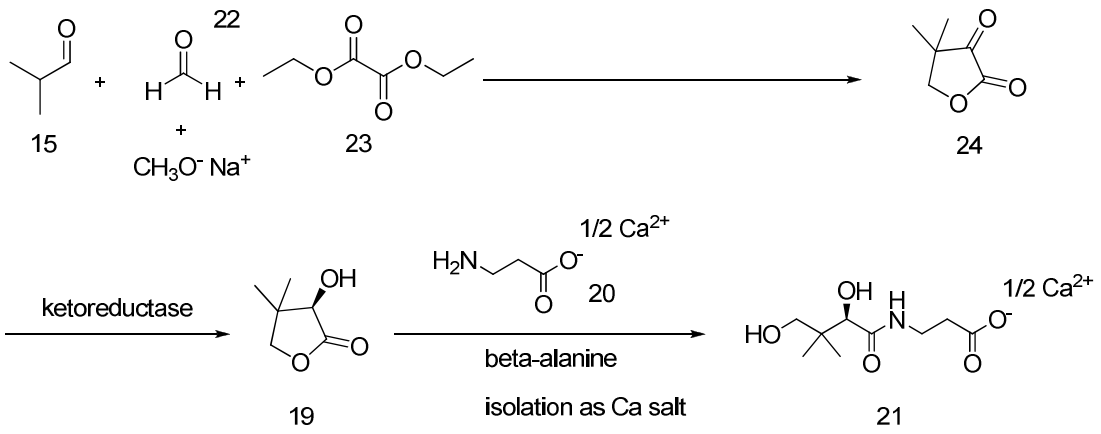


Figure 2.3.2- Current microbial approach towards pantothenate synthesis

Other enzymes have been used in reduction of ketopantolactone to the corresponding (D)-(-)-pantolactone including one isolated from *Pseudomonas maltophilia* 845 [10].

2.4 Pantothenate and CoA as Drug target

Numerous studies have shown that a range of bacteria are unable to synthesize CoA, and are therefore dependent on the transport of pantothenic acid from their environment [11]. The same dependence is exhibited in the malarial parasite *P. falciparum* also. It is now known that blood cells infected by Plasmodia, utilise new permeability pathways to bring in small molecules such as pantothenate, whereas uninfected cells do not exhibit these molecule permeability pathways [12, 13].

Work by Saliba has shown this pathway is validated in *P. falciparum* [14]. Lethal phenotypes, generated from gene disruption of the proteins in this pathway, demonstrate that the CoA biosynthetic pathway is essential in plasmodia. This, coupled with the fact that there is little sequence similarity between human PanK and its bacterial or malarial equivalent, provides us with a potential new drug target- necessary due to the emergence of drug resistant strains of *P. falciparum*.

2.4.1 Pantothenate analogues

For a review of a number of pantothenate analogues that have been developed as potential CoA biosynthesis inhibitors, please see Spry et al.[11]. A selection of these analogues are highlighted below (Fig.2.4.1).

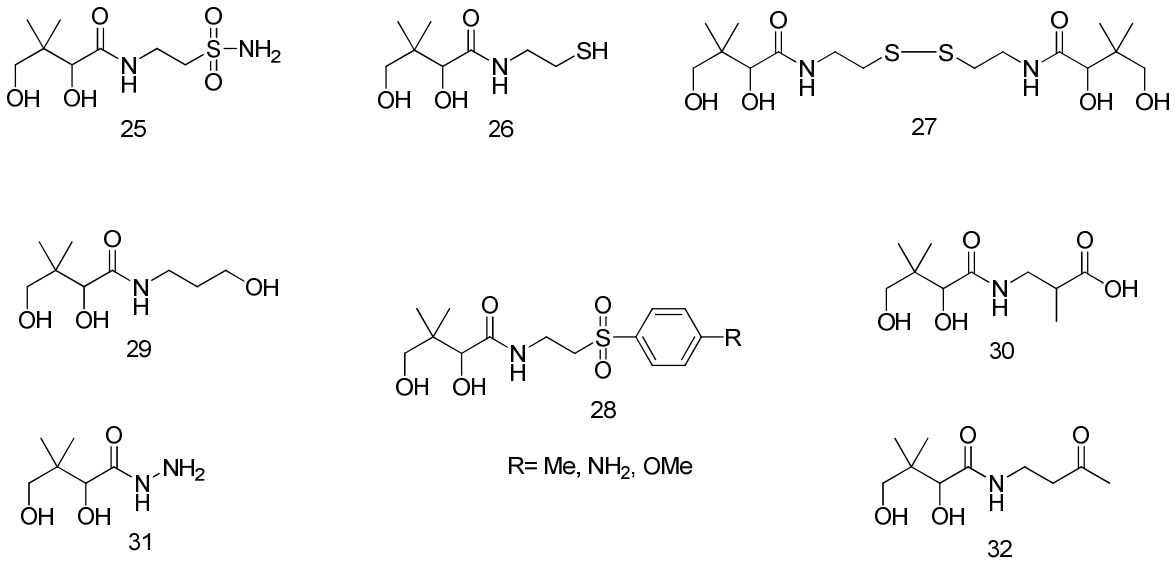


Figure 2.4.1- Range of current pantothenate derived analogues

Some of these analogues have clear structural similarities to pantothenate, such as the *N*-pantoylsubstituted amine (30) and methylpantothenone (32). Others are as varied as including sulphur; as in the pantoyltauramides (25-28).

It was observed that the inhibitory effect of these *N*-pantoyltauramides could be reversed by increasing levels of pantothenate available to the parasite. This finding demonstrated that the *N*-pantoyltauramides were acting as a CoA biosynthesis inhibitor, and validating this metabolic pathway as a drug target.

The pantoyltauramides were designed to reduce the water solubility of pantoyltaurine, whilst showing structural similarity to pantothenate. These compounds showed stronger inhibition than the pantoyltaurines they were designed to replace.

Methylpantothenone (32) showed some biological activity, but interestingly, its inhibition was not reversed by pantothenic acid. Although the idea of it being a non-competitive inhibitor was not discussed, the generation of similar compounds may prove to be of interest, as the phenylpantothenone derivative also proved to be active against a range of bacteria.

2.5 CJ-15,801

2.5.1 Isolation and characterisation

Figure 2.5.1- Structural similarities/ differences between pantothenate and CJ-15,801

One pantothenic acid analogue gaining some attention from biochemists (and chemists) over recent years is a natural product known as CJ-15,801 (33). Isolated from *Seimatosporum sp*. CL28611, this compound differs from pantothenate (9) only in the fact it has a double bond in the β-alanine moiety [15] (Fig 2.5.1).

Its activity as an inhibitor was limited against some bacteria, but was shown to be active against multidrug resistant *Staphylococcus aureus* with MIC values between 30 and 230μm.

CJ-15,801 has hence become a major target in the generation of potential new drug therapies.

2.5.2 CJ-15,801 Synthesis

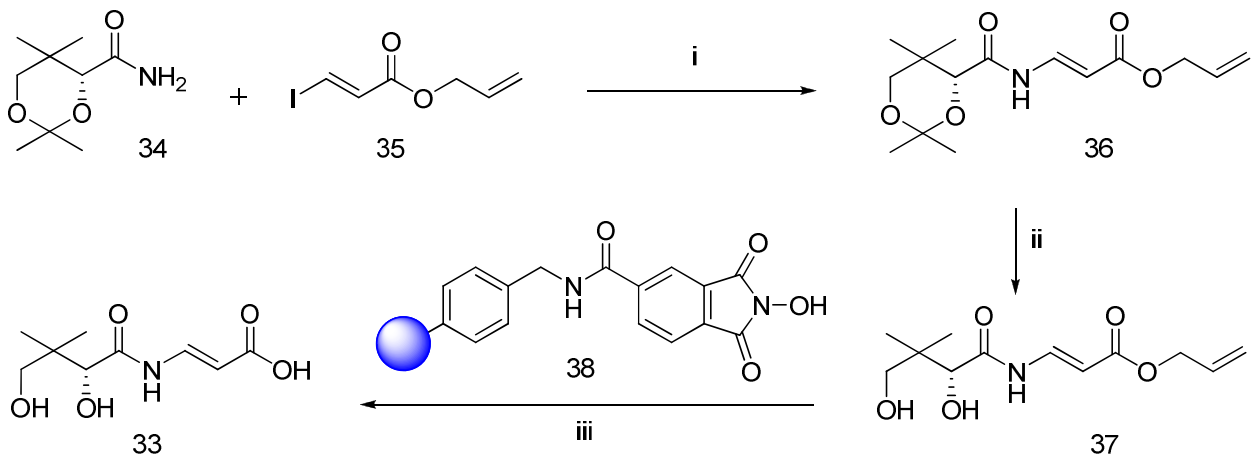
Although CJ-15,801 has only been relatively recently isolated, its promising biological profile, coupled with its interesting enamide bearing structure has already attracted the attention from highly revered chemists such as Porco and Nicolaou.

The first published synthesis of CJ-15,801 was done so by Porco and collaborators [16]. This synthesis requires the key coupling of a vinyl-halide (35) and an amide (34) under Cu catalysed conditions. The resulting enamide (36) has the allyl ester removed using a

synthesised solid supported reagent (38) to generate the required CJ-15,801 (33). Although successful, this synthesis has its limitations.

The vinyl halide synthesis from the regioselective hydroiodination of the corresponding alkyne is non-trivial, and this limits its use in wider situations.

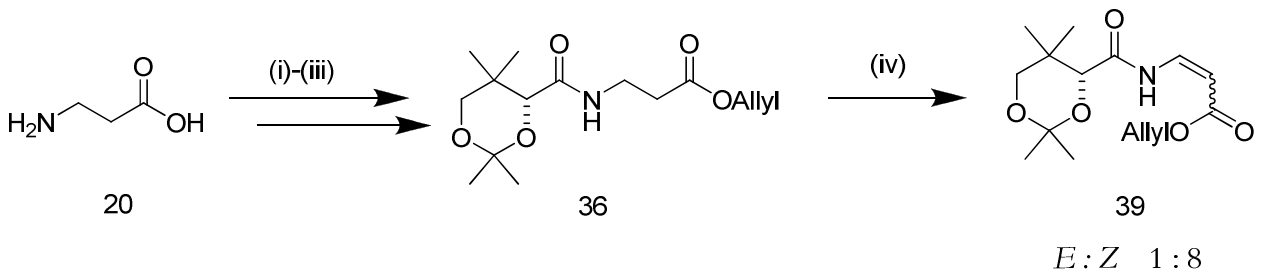
The approaches available for the synthesis of a substituted vinyl halide, also limits its use in the generation of potential CJ-15,801 analogues. The inclusion of an allyl ester is also an interesting one as it requires the use of the solid supported reagent for removal.



Reagents/ Conditions: (i) $Cu(CH_3CN)_4PF_6$, Rb_2CO_3, 90%, (ii) $Bi(III)Cl_3$, aq. CH_3CN, 75%, (iii) **38**, $Pd(PPh_3)_4$, 35°C, 80%

Scheme 2.5.1

The second synthesis of CJ-15,801 was reported by Nicolaou [17]. This approach relies on the oxidation of amide (36) with Dess-Martin-Periodinane.



Reagents and conditions: (i) HCl, AllylOH, (ii) (D)-(-)-pantolactone, $NaHCO_3$, PhMe, reflux, 59%
(iii) 2-methoxypropene, *p*TsOH, 78% (iv) DMP, PhF, 85°C, 93%

Scheme 2.5.2

Nicolaou's IBX oxidation is believed to go through the following mechanism:

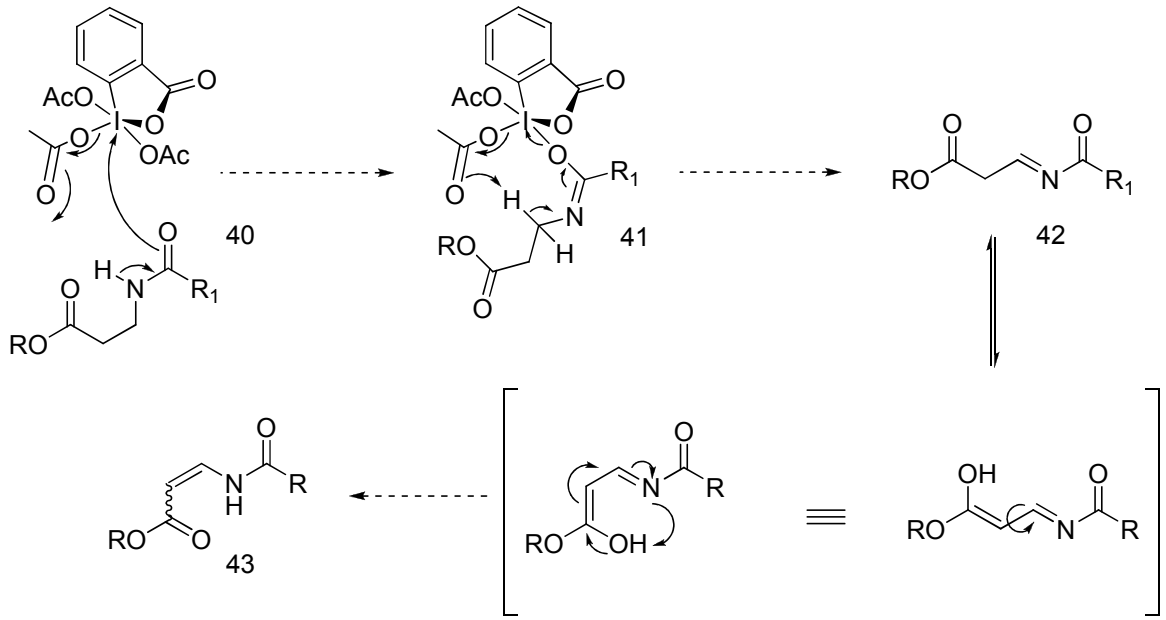


Figure 2.5.2- Mechanism for IBX oxidation to generate enamides

The first stage of the proposed mechanism involves the nucleophilic attack of the amide (40) onto the iodine core of the IBX reagent. Simultaneous release of an acetate group provides intermediate (41). After a spontaneous intramolecular rearrangement, Ac-IBA and AcOH are produced as side products, leaving the *N*-acyl imine intermediate (42). The

highly reactive intermediate is then transformed into imide (43). This occurs via tautomerization of intermediate (42) resulting in the enamide generation.

Although Nicolaou's approach successfully introduced the required enamide unit in a single step, from amide (36), the stereocontrol of the geometry of the enamide was non-existent. A 9:1 mixture of diastereomers was reported, in which the desired *E*- isomer was the minor product. Furthermore, Nicolaou uses the same allyl ester as the Porco synthesis, making this synthesis impractical.

In conclusion, the key difference between the growth promoter pantothenate and the inhibitor CJ-15,801, is the presence of its internal double bond. The synthesis proposed by Porco, was in fact derived from work performed on the synthesis of other enamides [18].

2.6 Enamides

Enamides are present as subunits in a variety of biologically active natural products and pharmaceutical drug lead compounds. Examples include the antibiotic CJ-15,801 (33), the lituarines (44) and crocacin A (45) (Figure 2.6.1).

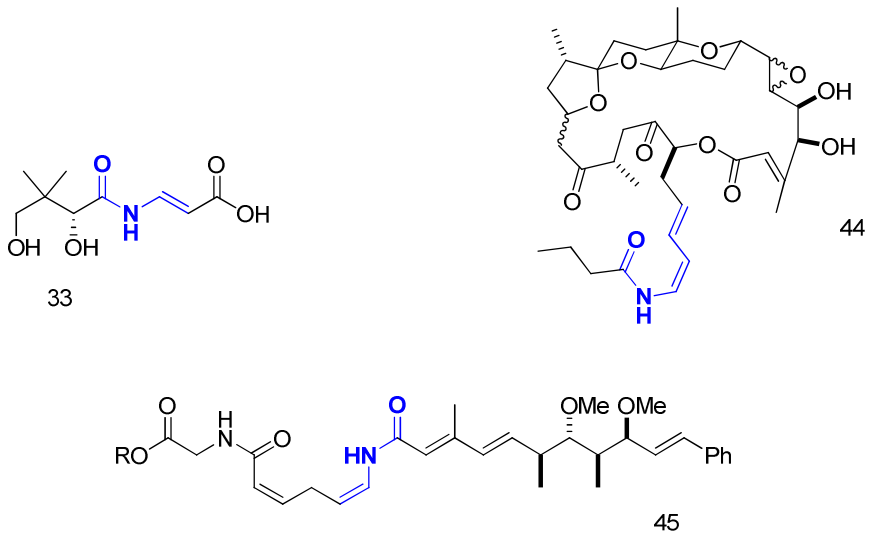


Figure 2.6.1- Range of known enamides

Enamides are considered highly reactive, thus making them key intermediates in the synthesis of a variety of heterocyclic compounds. It is due to this importance as both building blocks and target units, that a number of approaches to their synthesis have been investigated.

In the synthetic methods developed to date, varying degrees of success have been achieved when considering yield and control of the double bond stereochemistry; sometimes in the latter case, control is non-existent.

Such syntheses have made the following disconnections:

C-N (via N-acylation), N-C (coupling reaction with transition metal chemistry), C=C (condensation of amide and aldehyde) (Figure 2.6.2).

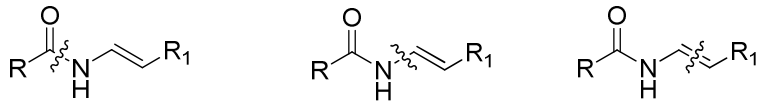


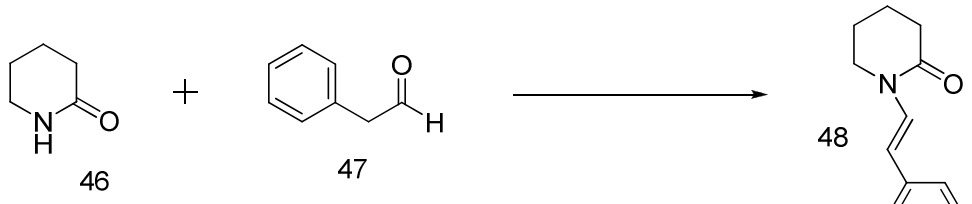
Figure 2.6.2- Enamide synthesis disconnections

2.7 Current Synthetic approaches to enamides

Based on the increased biological importance, a number of synthetic approaches have been developed for the synthesis of enamide units.

Early syntheses of enamides all occured under mild conditions, but to a reduced yield and efficiency. Since then, syntheses have focussed on increasing the yields and efficiencies. Current syntheses of enamides are varied, and all have respective advantages and disadvantages.

Zezza and Smith [19] have shown the successful condensation reaction of amide (46) and aldehyde (47) to generate the enamide (48).

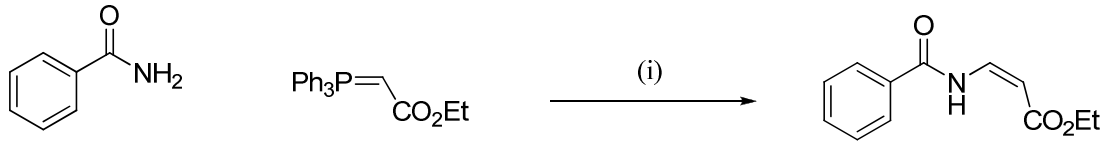


Reagents/ Conditions: (i) *p*TsOH, toluene, reflux, 90%

Scheme 2.7.1

Although this procedure is stereoselective, the option of influencing the reaction to generate either the *E* or *Z* isomer is not available. By relying on the use of the aldehyde to introduce the double bond, this synthesis is also limited to unsubstituted enamides and prevents the generation of potential analogues.

Kim and colleagues [20] have reported the successful palladium catalysed coupling of an ylide (50) and an amide (49), to generate the enamide (51). In contrast to the report by Zezza, this synthesis could allow the introduction of a substituted enamide unit, but appear to have no control for the generation of the *E* isomer.



Z : *E* >30:1

Reagents/ Conditions: (i) $PdCl_2(PhCN)_2$, CuCl, PhCl, O_2 (1 atm), 70°C, 70%

Scheme 2.7.2

For an excellent review on some of the current approaches to enamide synthesis please see Tracey *et al* [21].

The production of enamide-bearing natural products (and pharmaceutically relevant heterocyclic systems) would be far more attainable if there existed a reliable, flexible, and stereoselective procedure for their synthesis.

We therefore set out to develop an approach to the efficient and stereocontrolled synthesis of enamides, and then to apply this towards the synthesis of natural products pantothenate and CJ-15,801. It was also instrumental that the same approach would open up new areas towards the development of potential new analogues.

3 Synthesis of Enamides, CJ-15,801, analogues and Pantothenate

3.1 Enamides

As part of our novel approach, we envisioned the enamide units coming from the unprecedented olefination of the respective *N*-formylated amide (imide). The key to our approach lies in considering that the *N*-formyl unit could potentially behave as a pseudo-aldehyde unit, as opposed to a normal amide group. It was reasoned that the nitrogen lone pair would be effectively delocalised into the adjacent carbonyl. This delocalisation would render the *N*-formyl group to being significantly more reactive than a typical formamide.

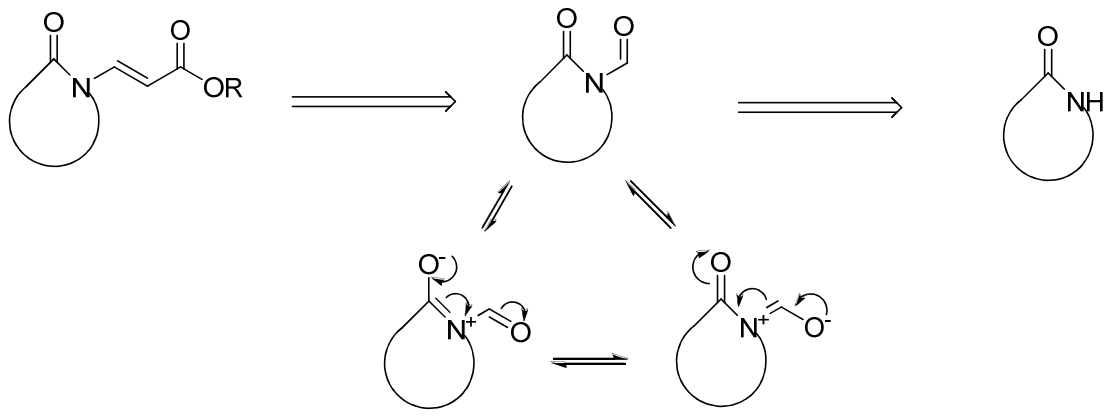


Figure 3.1.1- Resonance of imide giving rise to reactivity

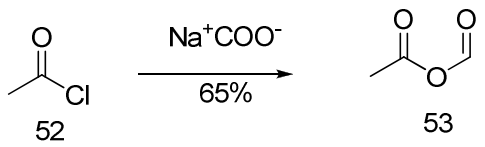
This approach would have the benefit of being able to take advantage of the myriad of aldehyde olefination conditions to stereoselectively generate polyfunctionalised enamides.

Unfortunately, the *N*-formylation of amides has not been that well documented [(22)], although an abundance of literature for amine formylation exists. This lead us to investigate whether the choice of reagents for use on amines could also be applied to amides.

3.1.1 Model Lactam systems

Our chosen model system was the Lactam family of compounds; due to their affordability and availability. The range of ring sizes available would help to investigate any potential limitations of our methodology.

Originally we attempted our amide formylation using known amine formylating agents such as ethyl chloroformate, but to no avail. We then investigated the use of mixed anhydrides, with formic-acetic anhydride (53) our mixed anhydride of choice [23]. Formic acid and acetic anhydride were pre-mixed before addition of the amide. The lack of formylated product suggested that as the mixed anhydride was being generated in situ, we could not be sure the full generation of the required mixed anhydride was occurring in the short time it was being pre-mixed for. Optimisation of the conditions included mixing formic acid and acetic anhydride at elevated temperature before addition of amide, and also the continued stirring of the reaction mixture at elevated temperature. Although the generation of the imide was apparent by ^{1}H NMR, we sought after a more effective method of generating our formic-acetic anhydride.

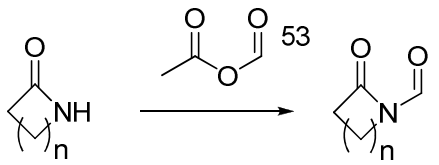


52 53

Scheme 3.1.1

Fife and co-workers [24] describe a way of generating mixed anhydrides, which cleanly generated our acetic-formic anhydride (53). This mixed anhydride was also stable at room temperature for many weeks.

Once the acetic-formic anhydride was produced, the attempted formylation of a range of simple lactams was performed. Azetidinone (n = 1) to 1-aza-2-cyclooctanone (n = 6) membered units were formylated (Table 3.1.1) [25].

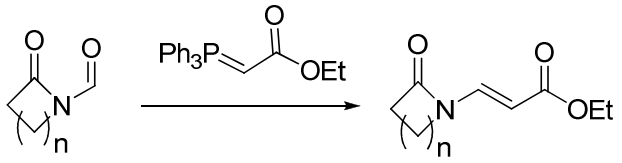


	n=	yield
54	1	56%
55	2	75%
56	3	80%
57	4	85%
58	5	70%
59	6	87%

Table 3.1.1- Lactam formylations

Ring size appeared to have a marginal effect on the yield of the formylation, the bigger the lactam ring, the greater the yield. The yields discovered could be considered surprising, as β-lactams are distinguished for their inability to delocalise, and therefore more formylation product expected, however we have no satisfying explanation for this loss of yield.

Having successfully synthesized the imine intermediates, the pivotal Wittig olefination was then attempted using a commercially available Wittig salt ethoxycarbonylmethylene triphenylphosphorane [25].



	n=	yield	*E*:*Z*
60	1	77%	*E* only
61	2	66%	*E* only
62	3	47%	*E* only
63	4	55%	*E* only
64	5	37%	*E* only
65	6	57%	*E* only

Table 3.1.2- Lactam Wittig Olefinations

It was gratifying to observe that the olefination proceeded in good yield and excellent *E* selectivity (Table 3.1.2).

The double bond geometry was assigned based on the alkene coupling constant (J = 14.4 Hz), on 2-dimensional nOe.

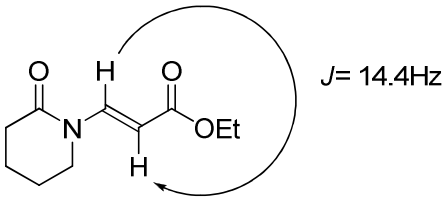


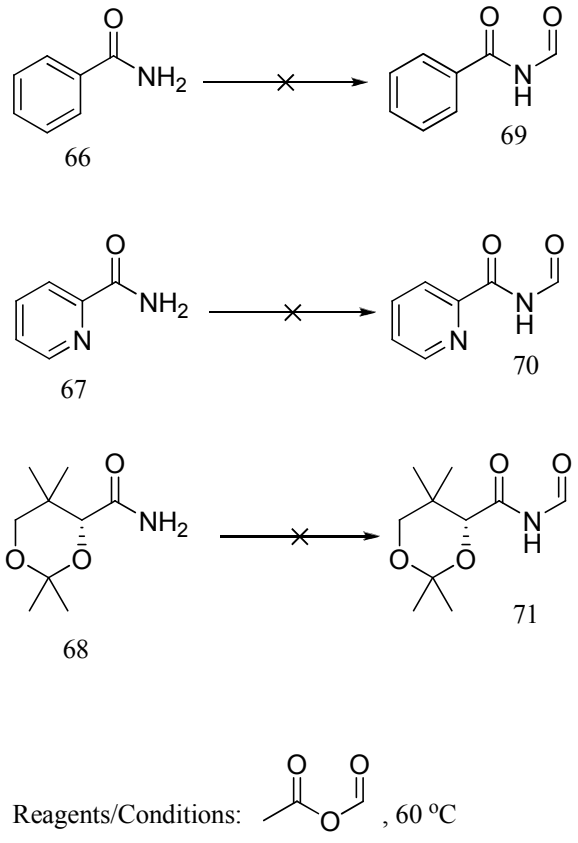
Figure 3.1.2- Coupling constant for *E* isomer characterization

Interestingly, it appears that even numbered rings generated a lower un-optimised yield than the odd numbered rings.

3.1.2 Acyclic Systems

Having developed a set of successful conditions for the synthesis of lactam derived enamides, we looked to expand the scope of the methodology. We were particularly keen to explore their application to acyclic systems, as the naturally occurring enamides are generally acyclic also.

For our acyclic model systems it was decided to focus on commercially available Benzamide (66) and Picolinamide (67), in addition to (*D*-) pantolactone derived amide (68).



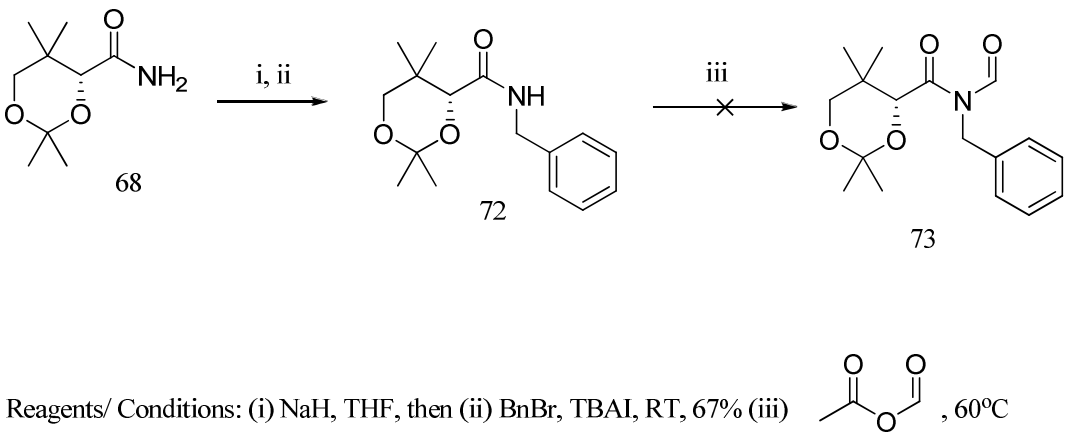
Scheme 3.1.2

We proceeded to use the conditions already established for our lactams, in an attempt to formylate each of the three amides (66-68). The mixed anhydride was mixed at high temperature as before, with the amide being added after a period of time. Initially, the only evidence of formylation returned by this method was by NMR, with a small peak present

towards the high end of ^{1}H NMR (~9 ppm). Despite attempts to optimise these conditions, no further formylation was observed.

The noticeable difference in efficiencies between our model lactam and model acyclic systems, prompted us to consider that the secondary nature of the lactams may have been contributing to the increased efficiency over the primary acyclic systems.

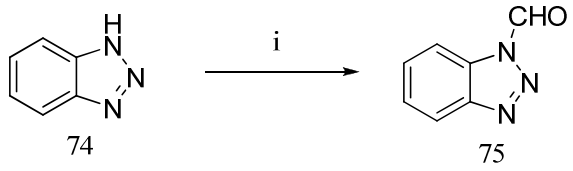
As such, it was decided to generate the secondary amide (72) from the protection of (D)-(-)-pantolactone derived amide (68). The choice of a benzyl group as a protecting group was based on the feasibility of the removal of this group at a later stage.



Scheme 3.1.3

Despite repeated experimentation, amide (72) failed to be formylated using mixed anhydride. Faced with this set back, we turned back to the literature where the use of *N*-formylbenzotriazole as an amine formylating agent has been described by Katritzky and co-workers [26].

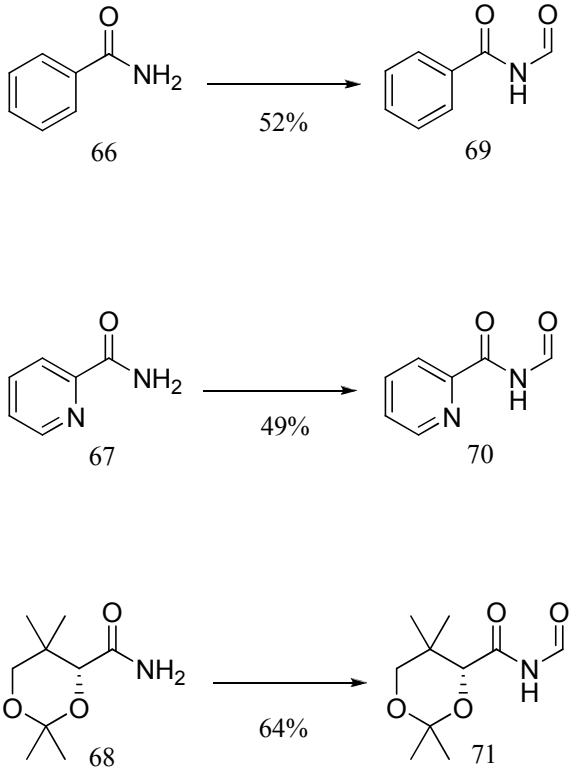
The *N*-formylbenzotriazole was prepared in the same manner as in the literature. Benzotriazole (74) was mixed with formic acid in the presence of DCC, then recrystallised from DCM to afford the desired formylating agent (75). This formylating agent could then be stored at room temperature for weeks with no loss of activity.



Reagents/ Conditions: (i) Formic Acid, DCC, 63%

Scheme 3.1.4

Whereas before, our initial formylations were relying on the nucleophillic attack of the nitrogen lone pair on the mixed anhydride, this method uses more aggressive conditions by deprotonation of the amide with *n*-BuLi before introduction of *N*-formylbenzotriazole as the formylating agent.



Reagents/ Conditions: (i) *n*-BuLi 1.6 M, THF, *N*-formylbenzotriazole, RT.

Scheme 3.1.5

The imides (69, 70 and 71) were generated in good yields [25], and their structures corroborated by X-ray analysis. Benzamide (Fig 3.1.3), Picolinamide (Fig 3.1.4) and pantolactone derived (Fig 3.1.5) are shown below.

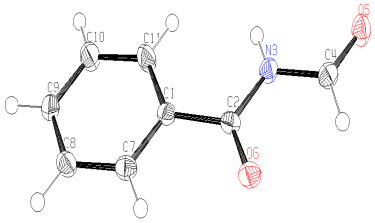


Figure 3.1.3- Benzamide derived imide (69)

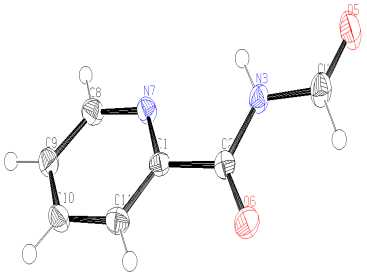


Figure 3.1.4- Picolinamide derived imide (70)

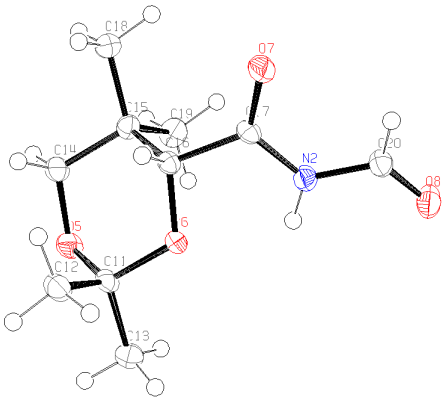
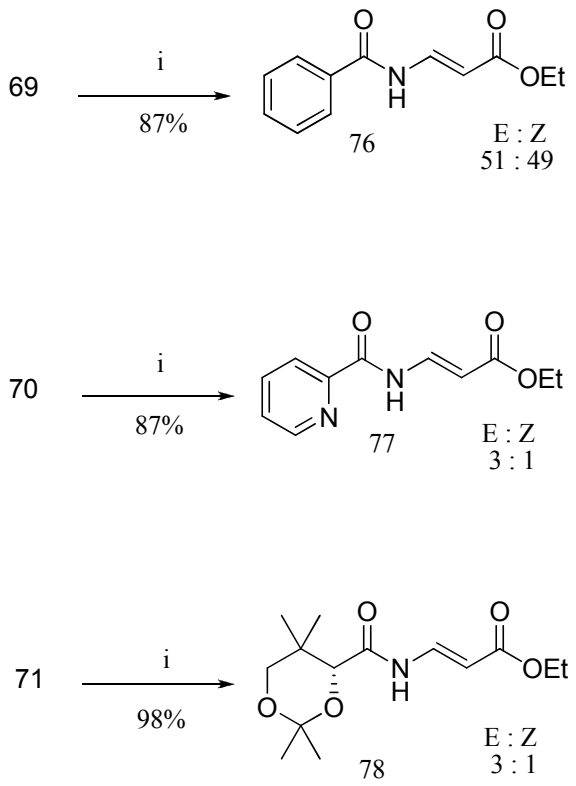


Figure 3.1.5- Pantolactone derived imide

Subjecting the acyclic imides (69-71) to the same Wittig-olefination conditions as those used for the synthesis of the lactam derived enamides, generated the desired enamides (76, 77, and 78).



Reagents/ Conditions: (i) PPh_3COOEt, 95 ^oC

Scheme 3.1.6

Satisfyingly, the respective enamides were obtained in much higher yields than previous lactam examples [25]. Furthermore, the conditions were still exhibiting *E* selectivity, albeit with lower selectivity than the lactam examples. This lower selectivity could potentially be explained by the starting imide geometry, although at this point the reason is still not completely clear.

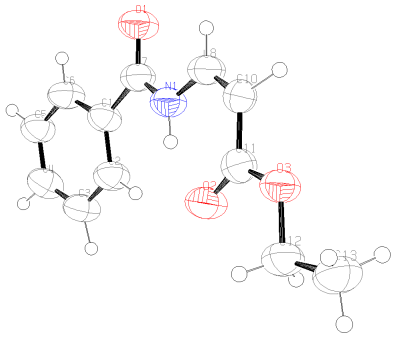


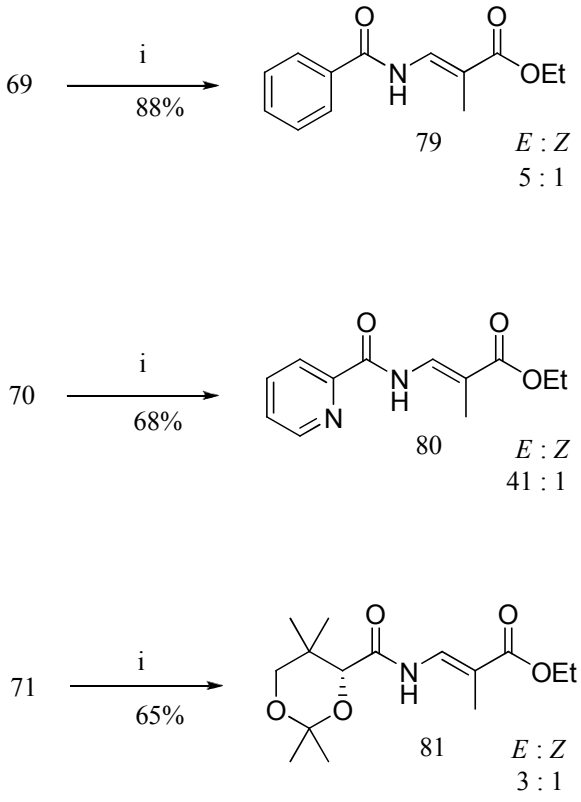
Figure 3.1.6- Benzamide derived enamide (76*Z*)

Additionally, the structure of (76*Z*) was determined by X-ray analysis (Fig 3.1.7), and matches that of the previously reported data [20].

3.2 Substituted Enamides

Having successfully generated the unsubstituted *E*-enamides, we focussed our attention on the generation of substituted enamides. Until now, there had been minimal literature precedence for substituted enamide synthesis [21].

As part of our approach, we attempted the olefination using the substituted ylide 1-carbethoxyethylidene triphenylphosphorane, which could allow us to explore the feasibility of generating substituted enamides whilst exploring their selectivity.



Reagents/ Conditions: (i) PPh_3CCH_3COOEt, 95 °C

Scheme 3.2.1

We were delighted to observe that selectivity had been maintained, and in some cases increased over those observed for the unsubstituted ylide.

Although the yields had decreased, they were still satisfactory enough for us to consider this an effective generation of the enamide functionalities.

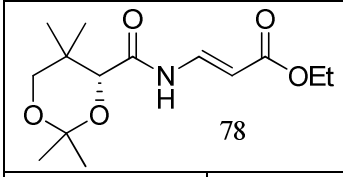
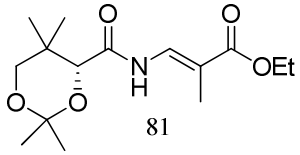
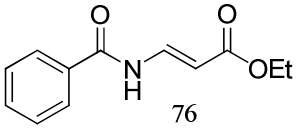
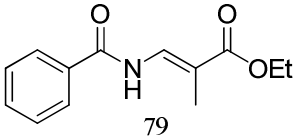
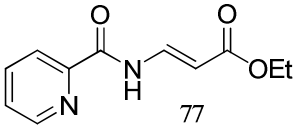
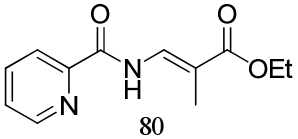
Unsubstituted		Substituted	
 78		 81	
Yield 98%	*E* : *Z* 3:1	Yield 65%	*E* : *Z* 3:1
 76		 79	
Yield 87%	*E* : *Z* 51:49	Yield 88%	*E* : *Z* 5:1
 77		 80	
Yield 87%	*E* : *Z* 3:1	Yield 68%	*E* : *Z* 41:1

Table 3.2.1- Comparison of effects on yield and selectivity by double bond substitution

Although a small range of data has been compiled to date, there are some preliminary conclusions that can be drawn from it.

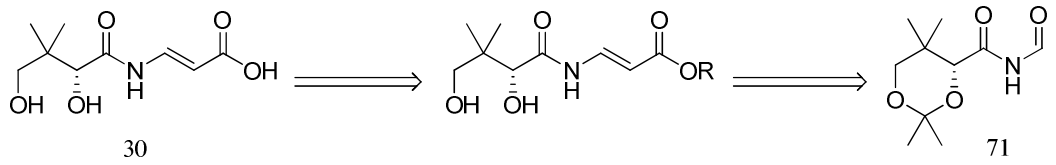
As the aromaticity of the imide increases, the *E* selectivity appears to decrease. Increasing substitution appears to decreases yield, whilst simultaneously increasing selectivity.

This can be attributable to the stability of the ylide during the Wittig olefination.

The introduction of the substituted enamide functionality could prove to be significant; if used to assess their use as analogues for existing enamides such as the crocacins and lituarines discussed earlier.

3.3 CJ-15,801

Having demonstrated the successful stereoselective generation of enamides from their imide precursors, we set out to attempt the novel synthesis of CJ-15,801 (33).



Scheme 3.3.1

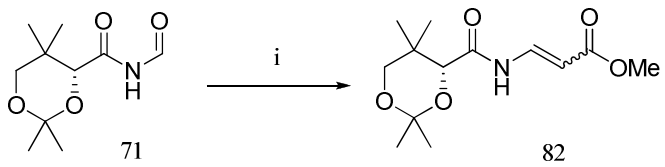
As part of our approach, we envisioned using a similar formylation/ olefination strategy as before to introduce the conjugated ester which could selectively be deprotected (Scheme 3.3.1). By utilising the same starting material, it was proposed that we could selectively deprotect the ketal in the presence of the ester, or alternatively investigate the removal of the ester group to generate the free acid in the presence of the ketal.

We felt one of the restrictions in the Porco and Nicolaou procedures was in the final deprotection step. In trying to remove the allyl ester, the need for a complicated solid supported reagent was needed; a reagent that needed synthesising itself.

To avoid the problems posed by deprotections, we decided to introduce a range of different esters. The theory being that each one would require different, but ultimately simple, de-protection procedures. This would therefore enable us to investigate and optimise the final deprotection step.

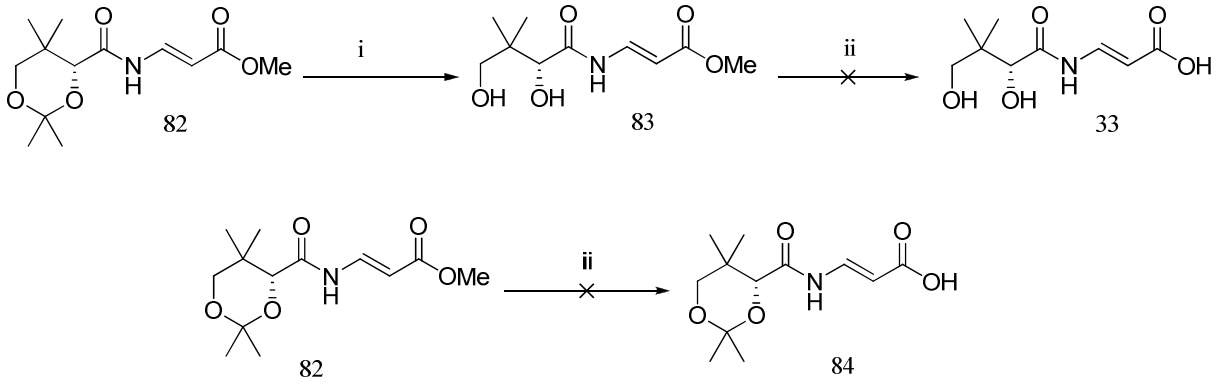
We were particularly intrigued by the work of Still and co-workers [27] which shows the simple deprotection of esters using TMSOK. This procedure could be utilised in the deprotection of simple esters such as methyl and ethyl esters, which could be generated from their commercially available ylides. The advantage of this approach is that the deprotection could be performed before or after ketal deprotection at the opposite end of the molecule.

Imide (71) was synthesised from (D)-(-)-pantolactone as described earlier. Treatment of imide (71) with the stabilised ylide methyltriphenylphosphoranylidene acetate gave the methyl ester (82). Ketal deprotection was performed using $BiCl_3$ with a catalytic amount of water, generating the desired free diol (83) in good yield [29]. TMSOK treatment of ester (83) failed to generate the acid (33) largely due to the starting material being insoluble in THF. The insoluble nature of the diol in the chosen solvent system prompted us to attempt the ester removal before the ketal removal. Treatment of ketal (82) with TMSOK (up to 5eq) failed to return any of the desired acid (84), only starting material.



Reagents/ Conditions: (i) $PPh_3CHCOOMe$, 95 ºC, 91%, *E* : *Z* 2:1

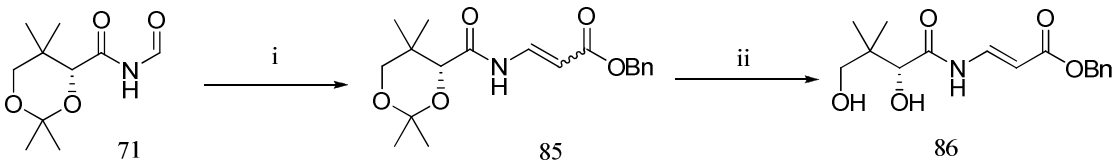
Scheme 3.3.2



Reagents/ Conditions: (i) $Bi(III)Cl_3$, H_2O, MeCN, 50% (ii) TMSOK

Scheme 3.3.3

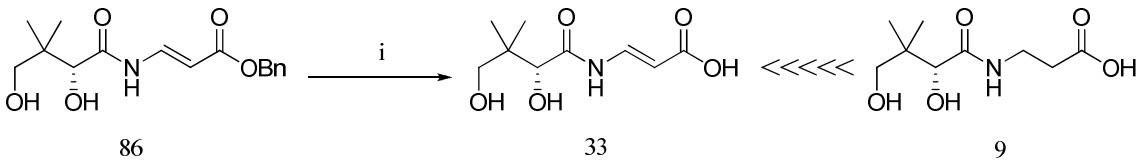
Not to be deterred by the difficulties encountered using the deprotection conditions, alternative esters and their corresponding deprotection conditions were explored. Initially we turned our attentions to using a benzyl ester unit. The benzyl ester would have the advantage of potentially being removed by hydrogen transfer-hydrogenolysis conditions.



Reagents/ Conditions: (i) $PPh_3CHCOOBn$, 95 °C, 87%, *E* : *Z* 3:1 (ii) $Bi(III)Cl_3$, H_2O, MeCN, 88%

Scheme 3.3.4

Olefination of imide (71) with the stabilised ylide benzyltriphenylphosphoranylidene gave the benzyl ester containing enamide (85) in good yield and as a 3:1 mixture of *E*: *Z* isomers. Before attempting the hydrogenolysis of the benzyl group, the ketal group was removed in good yield using our previously employed conditions, to give diol (86). A controlled hydrogen transfer hydrogenolysis was then attempted, using ammonium formate and Pd/C, to remove the benzyl ester in the presence of the double bond. The crude NMR showed a 1:1 ratio of CJ-15,801 (33): Pantothenic Acid (9). Extensive experimentation was carried out to see if the conditions could be adapted to increase the rate of benzyl group hydrogenolysis relative to that of double bond reduction. Disappointingly, it appeared that the rate of reduction of the double bond was faster than the desired ester hydrogenolysis, evident by the significant increase in the ratio of pantothenate upon increased amounts of sodium formate used.

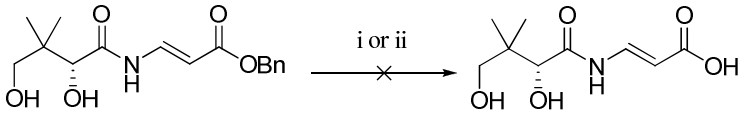


86 33 9

Reagents/ Conditions: (i) $NH_4^+COO^-$ (1.1-3.3eq), Pd/C, MeOH

Scheme 3.3.5

We then decided to change source of hydrogen to formic acid and then cyclohexene in a bid to slow down the rate of reduction. However, the adjusted conditions yielded similar results to earlier conditions.



86 33

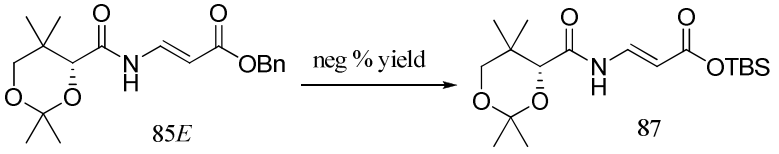
Reagents/ Conditions: (i) HCOOH, Pd/C, MeOH (ii) Cyclohexene, Pd/C, MeOH

Scheme 3.3.6

Further experimentation included changing the type of catalyst, and also the amounts used. These still failed to selectively cleave the benzyl ester without reducing the double bond.

Having failed to cleave the benzyl group, a new approach was devised. Literature evidence [30] suggests that benzyl esters can be converted to TBS esters by treatment with TBS-silane and palladium catalyst. The conversion of the benzyl esters into the corresponding TBS ester would be an attractive one, as this would allow the TBS and ketal to be removed simultaneously by treatment with acid.

Conversion of the benzyl ester (85) to the TBS ester (87) was performed, but returned little to no product.



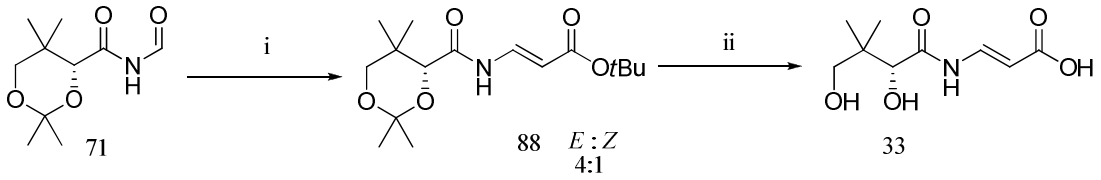
Reagents/ Conditions: (i) TBDMS-H, $Pd(OAc)_2$, Et_3N

Scheme 3.3.7

The low yield and unnecessary additional step was not considered beneficial to the synthesis, and therefore an alternative was sought after.

The notion of being able to perform a global deprotection step inspired us to use a *t*-butyl ester as an alternative protecting group. Literature precedence suggested that a *t*-butyl ester can be hydrolysed under acidic conditions [31], and we were optimistic the ketal could be removed under the same acidic conditions [32].

Gratifyingly, when ester (88) was stirred with formic acid, the clear generation of the free acid was achieved, along with the liberation of the free diol to give CJ-15,801 (33).



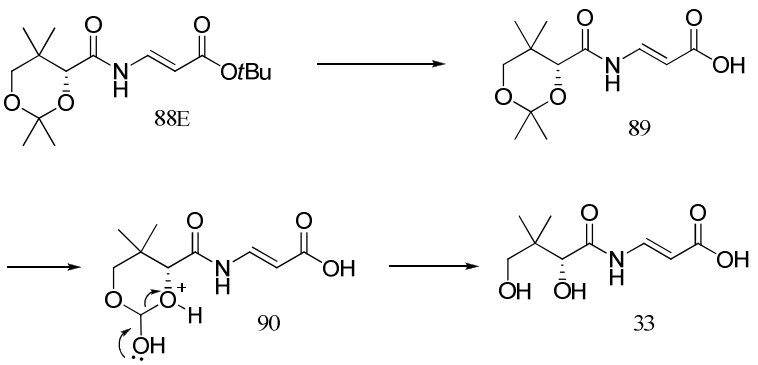
Reagents/ Conditions: (i) $PPh_3CHCOOtBu$, 95 °C, 85% (ii) Formic acid, RT, 20%

Scheme 3.3.8

3.3.1 Mechanism of Reaction

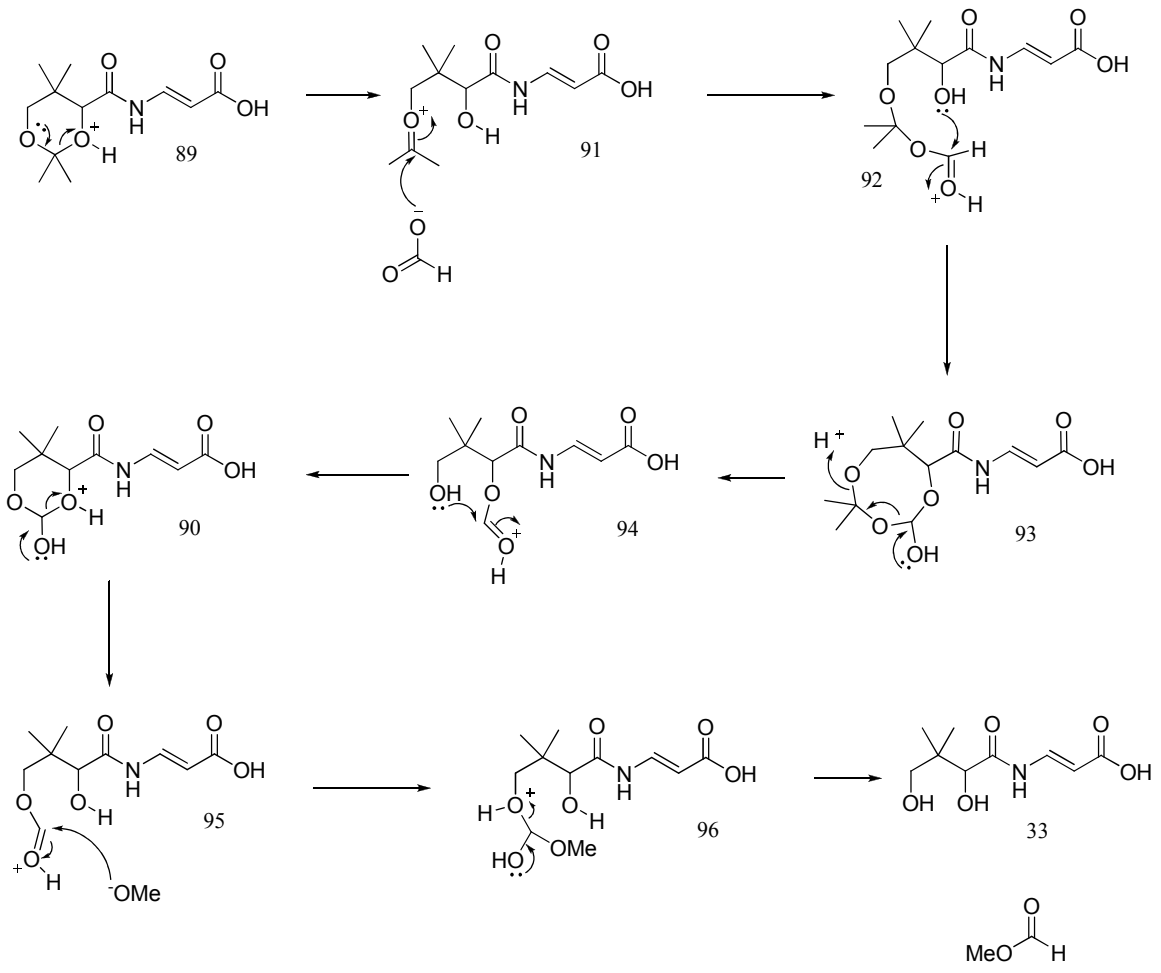
Interestingly, during the deprotection step, it was noticed that the NMR of the crude compound did not match that of the compound after column chromatography. Furthermore it was noticed that the R_f of the compound had also changed significantly. Treatment of the crude mixture with catalytic acidic methanol also caused the R_f and NMR to change to that

of the required product. We can propose that the ketal is converted to the free diol through a stable orthoester-type intermediate (90) formed by the association of formic acid with the free diol. This intermediate is only then completely hydrolysed upon the addition of acidic methanol.



Scheme 3.3.9

A possible mechanism for this process involves:



Scheme 3.3.10

After removal of the *t*Bu group, protonation of the ketal (89) causes its spontaneous degradation to intermediate (90). This occurs via the formation of the unstable intermediate (93). Addition of acidic MeOH allows protonation of the hemi-orthoester (90), and the free methoxide ion removing the formate group generating CJ-15,801 (33) and methyl formate sideproduct.

The structure of CJ-15, 801 was corroborated by comparison of NMR and optical rotation data previously reported [16].

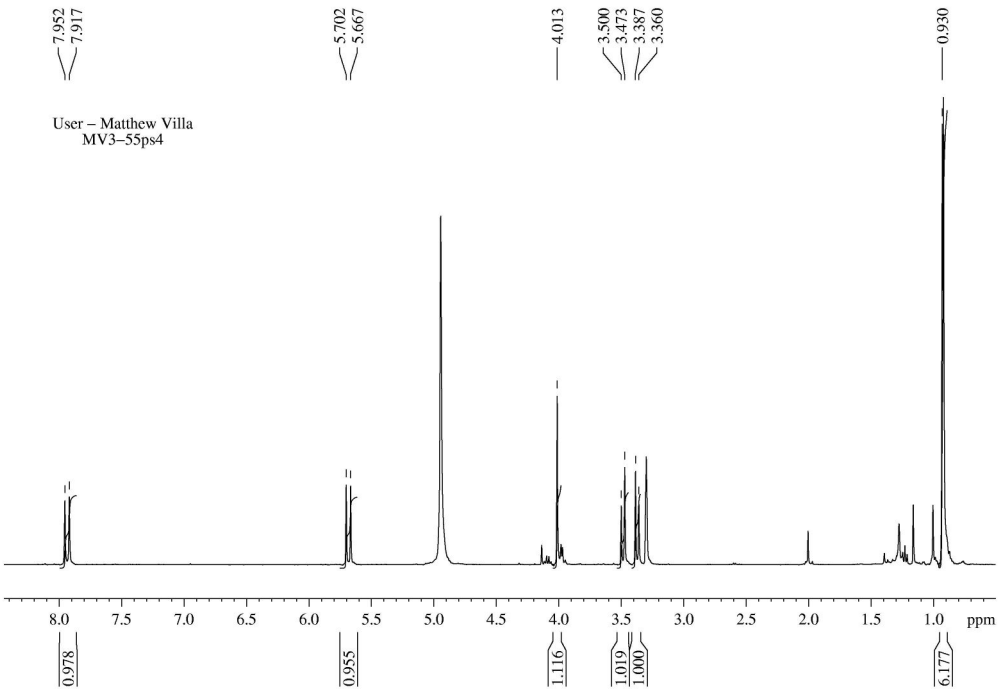


Figure 3.3.1- ^{1}H NMR product CJ-15,801 (33)

^{1}H NMR (300 MHz, CD_3OD) of natural CJ-15,801

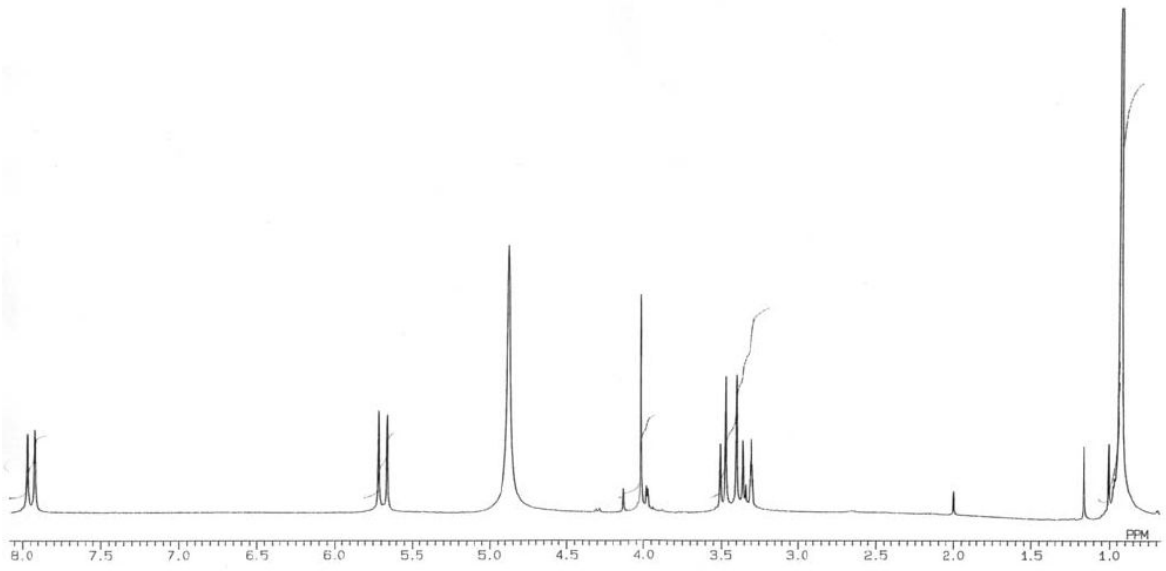
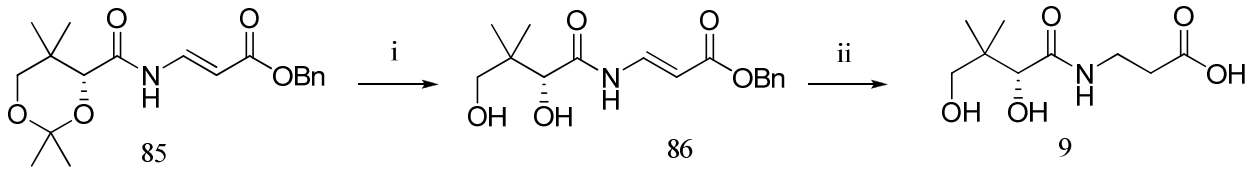


Figure 3.3.2- ^{1}H NMR natural CJ-15,801 [16]

3.4 Synthesis of Pantothenate

After observing over-reduction of our benzyl ester whilst trying to produce CJ-15,801, it was decided that optimisation of this process would provide us with viable and efficient access to the production of pantothenic acid.

Enamide (85) was subjected to standard $BiCl_3$ ketal deprotection conditions, liberating the free diol in good yield. Hydrogenation using (H_2 Pd/C) was then performed on ester (86) generating pantothenic acid (9) in good overall yield.

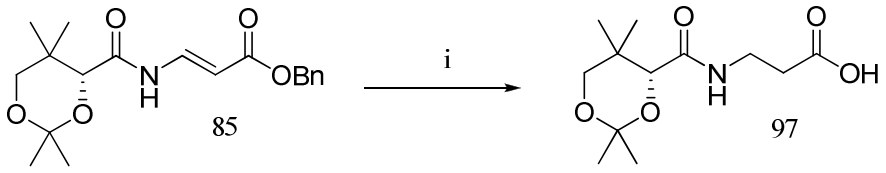


Reagents/ Conditions: (i) $Bi(III)Cl_3$, H_2O, MeCN, 88% (ii) H_2 atm, Pd/C, RT, 83%

Scheme 3.4.1

Although this procedure was initially performed on the isolated *E* isomer, the conditions were then applied to a mixture of the *E* and *Z* benzyl ester bearing enamides to generate (D)-(-)-pantothenic acid in comparable yield to the isolated esters.

Having completed the synthesis of pantothenic acid, it was decided that the enamide (85) could be subjected to hydrogenation conditions without the removal of the ketal protecting group. As Pantothenic acid is a growth promoter, it is possible that this ketal protected analogue (97) may be useful to determine structure activity relationships (SAR). We believe this is one of the most efficient chemical syntheses towards (D)-(-)-pantothenic acid without isolation as the Ca salt to date. Furthermore, our approach also allows for the synthesis of (L)-(+)-pantothenic acid by simply switching the pantolactone starting material.



Reagents/ Conditions: (i) H_2 atm, Pd/C, 85%

Scheme 3.4.2

3.5 CJ-15,801 analogues

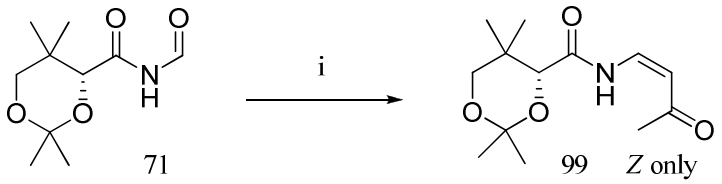
The current syntheses in literature for CJ-15,801 only focus on the target molecule. However, as this compound exhibits inhibitory activity against the validated CoA biosynthesis target PanK, we decided to utilise our enamide procedure for the synthesis of new potential inhibitors based on CJ-15,801 framework.

Our approach relies on the Wittig Olefination of imide (71) with a number of different ylides which would help retain the key enamide functionality whilst exploring potential hydrogen bond donor/ acceptors.

The vast majority of pantothenic acid analogues developed previously showed some success through modification of the β-alanine moiety. However, the fact that these analogues were designed before the discovery of CJ-15,801, the decision was made to focus on a different class of inhibitors. In our design, we decided to combine the enamide characteristic of CJ-15,801, along with a drastically modified β-alanine moiety.

3.5.1 Ketone

Methylpantothenone (32) derived analogues have shown reasonable success in plasmodia studies [11], hence our initial studies focussed on the synthesis of an enamide bearing analogue. The treatment of imide (71) under the same Wittig conditions as before, using the ketone containing ylide (94) generated the desired enone analogue in good yield and as a single *Z* isomer (99).



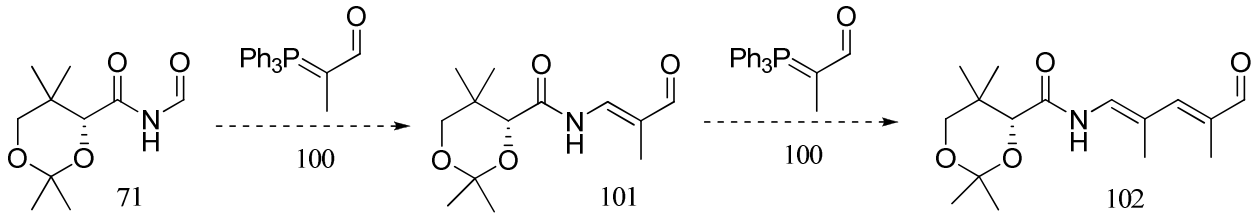
Reagents/ Conditions: (i) $PPh_3CHCOCH_3$, 95 °C, 65%

Scheme 3.5.1

3.5.2 Aldehyde

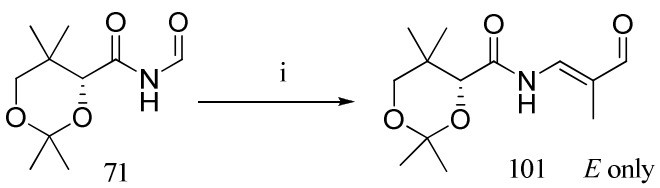
N-pantoylsubstituted amides have also shown promising anti-parasitic activities [11]. A closely related analogue would be the aldehyde bearing CJ-15,801 analogue (101). This was interesting as we are introducing a substituted double bond in addition to an aldehyde functionality.

Although this analogue could potentially be accessed through the Wittig olefination of imide (71) with ylide (100), there were concerns that a double Wittig olefination could take place which would generate the potentially unstable dienamide unit (102).



Scheme 3.5.2

Gratifyingly, the treatment of imide (71) with ylide (100) gave the desired enamide (101) in good yield and as a single *E* isomer. Although the yields are lower than the previous ester analogues, no dienamide side products were observed either in the aldehyde or the methyl ketone cases.



Reagents/ Conditions: (i) PPh_3CCH_3COH, 95 ^oC, 62%

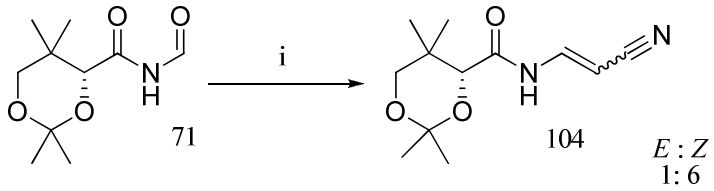
Scheme 3.5.3

It was also noted that in the example of the aldehyde, starting material was still present after reaction completion. This, coupled with the reduced yield of the ketone and aldehyde examples, could be attributed to the Wittig reagent reacting with itself.

3.5.3 Nitrile

Finally, the synthesis of nitrile bearing enamide (104) was attempted. The choice of nitrile unit emanated from its potential use not only as inhibitor, but also as a versatile handle opening up a range of further analogues including aldehydes and amines.

The treatment of imide (71) with the ylide (103) afforded the enamide (104) in excellent yield, and again with a predominance of the *Z* enamide.



Reagents/ Conditions: (i) PPh_3CHCN, 95 ^oC, 93%,

Scheme 3.5.4

This reversal of selectivity could potentially be explained by difference between the hybridisation of the ester carbon and that of the nitrile carbon. Our results would suggest that the delocalisation of the phosphorus-carbon bond is more effective with the ester carbonyl than with the nitrile group. The reduced delocalisation would effectively make the nitrile ylide behave more like an unstabilised ylide, (Figure 3.5.5) thus favouring the *Z*-olefin.

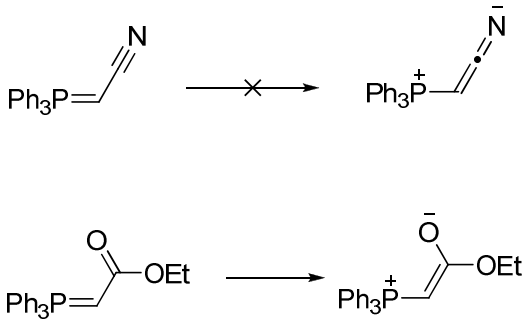


Figure 3.5.5- Comparison of ylides giving rise to observed selectivities

4 Biological Assessment

Having achieved the synthesis of a number of CJ-15,801 analogues, a number of compounds were sent for testing in the labarotories of Dr. Kevin Saliba at ANU. These compounds were tested against the Plasmodium parasite. These included compounds from our lactam, benzamide, picolinamide, and pantolactone derived enamides.

4.1 Selection Rationale

Although *Pf* PanK has not been characterized [33], information from SARs with bacterial PanK [34-36] has lead to the generation of potential inhibitors for this class of kinases. Our decision to generate and test compounds based on CJ-15,801 came from the same SARs as these investigations coupled with the known antiplasmodial activity of CJ-15,801 [10].

A number of aspects of the structure of pantothenate, and its affinity for *E.Coli* PanK (Fig 4.1.1 [10]) were considered as part of the selection process, before the compounds were sent for testing:

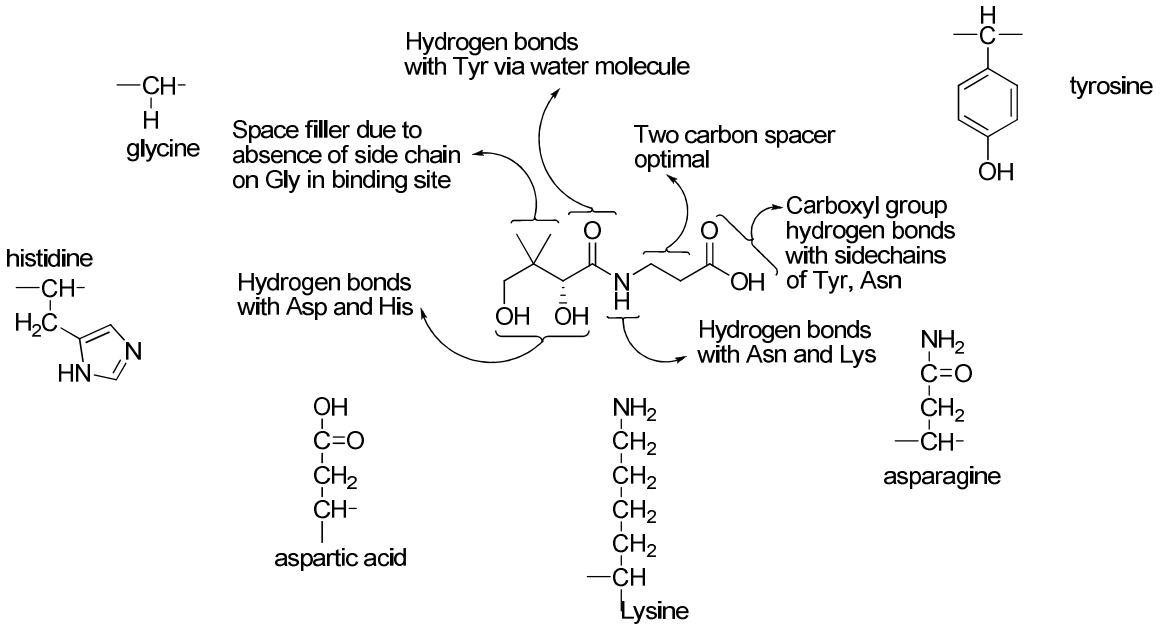


Figure 4.1.1- Known structure activity relationships of pantothenate and PanK

4.2 Lactam derived Enamides

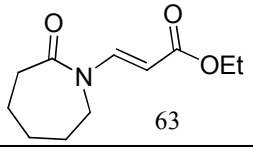
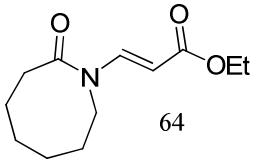
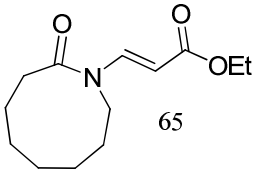
Entry	Structure	Average IC_{50} (μm)	No. repeats	Std. Dev.	clogP
1	 63	196	1	N/A	0.94
2	 64	98	1	N/A	1.36
3	 65	55	1	N/A	1.78

Table 4.2.1- Testing results for lactam derived enamides against whole parasite lysate

In the case of the lactam derived analogues, the activities observed were very surprising as these compounds only share the enamide functionality with the naturally occurring CJ-15,801, and no pantoyl functionality. It seems that the size of the lactam ring increases a uniform increase in the compound's inhibition. This higher potency may be attributed to a

couple of possible factors. The increase in size may be affecting the compounds ability to pass through cell membranes. Alternatively, the ring might be filling space in the target active site.

4.3 Benzamide derived Enamides

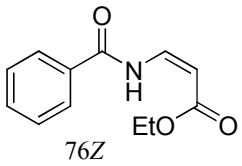
Entry	Structure	Average IC_{50} (μm)	No. repeats	Std. Dev.	clogP
4	 76*Z*	141	2	17	1.63

Table 4.3.1- Testing results for lactam derived enamides against whole parasite lysate

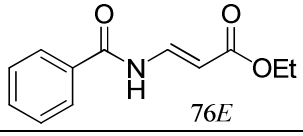
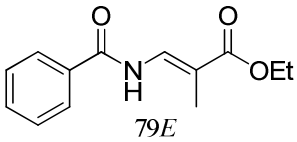
Entry	Structure	Average IC_{50} (μm)	No. repeats	Std. Dev.	clogP
5	 76*E*	183	2	6	1.63
6	 79*E*	139	2	5	1.98

Table 4.3.2- Testing results for lactam derived enamides against whole parasite lysate

The benzamide derived analogues proved to be weaker inhibitors than the lactam analogues. Interestingly, the *Z* isomer appears to be a better inhibitor than the *E* isomer (Entries 4 and 5).

Furthermore, comparison of entries 5 and 6 also shows greater inhibition when the double bond is trisubstituted. This could be attributable to a “tighter-fit” scenario similar to that seen with the lactam examples.

4.4 Picolinamide derived Enamides

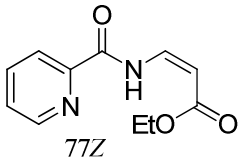
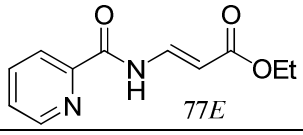
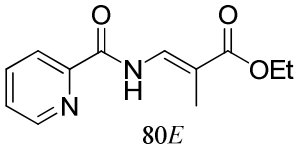
Entry	Structure	Average IC_{50} (μm)	No. repeats	Std. Dev.	clogP
7	 77*Z*	185	2	9	0.71
8	 77*E*	>200	2	N/A	0.71
9	 80*E*	125	2	7	1.06

Table 4.4.1- Testing results for lactam derived enamides against whole parasite lysate

As with the benzamide derived enamides, the picolinamides show a similar pattern of inhibition. Although the differences between the *Z* and *E* isomers are masked by the fact the *E* isomer inhibition is outside the upper limit, it still appears the *Z* isomer is a more potent inhibitor. However, the difference between the methyl substituted analogue (Entry 9) and the *Z* enamide (Entry 7) is more marked than that observed for benzamide derived analogues.

4.5 Pantolactone derived Enamides

The CJ-15,801 related analogues on the other hand provided the most interesting results. By comparing the esters in entries (11, 13 and 14) we can see that the increase in size of the ester group, generates an increase in inhibition. This could be due to the lipophyllic effect of the ester, helping the compound to pass through the cell wall. Alternatively, the larger group can be responsible for increasing the interactions with the biological target's active site.

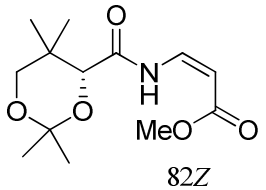
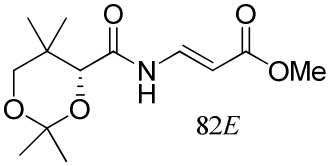
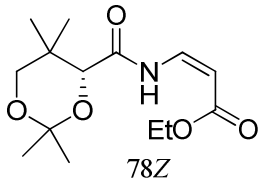
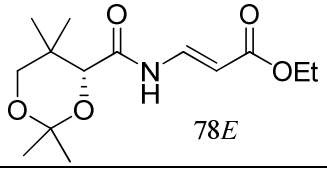
Entry	Structure	Average IC_{50} (μm)	No. repeats	Std. Dev.	clogP
10	 82*Z*	>200	1	N/A	0.90
11	 82*E*	>200	1	N/A	0.90
12	 78*Z*	172	1	N/A	1.24
13	 78*E*	158	1	N/A	1.24

Table 4.5.1- Testing results for methyl and ethyl ester containing enamides against whole parasite lysate

The pantolactone derived enamides appear to show different trends to the previously mentioned benzamide and picolinamide examples. Whereas before, the *Z* was better than *E*, in entries 12 and 13 we can see that the *E* isomer is slightly better inhibitor than *Z* in the un-substituted model.

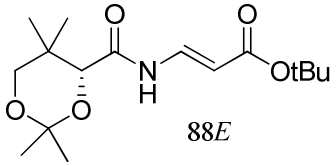
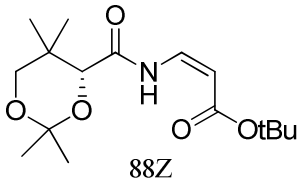
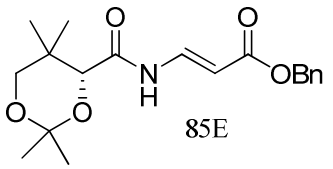
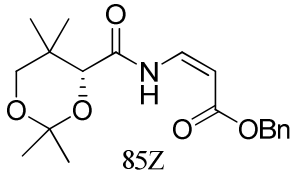
Entry	Structure	Average IC_{50} (μm)	No. repeats	Std. Dev.	clogP
14	 88*E*	124	2	3	1.77
15	 88Z	4	2	0.6	1.77
16	 85E	118	2	67	2.63
17	 85Z	63	2	2	2.63

Table 4.5.2- Testing results for larger ester containing enamides against whole parasite lysate

In addition to the increase in inhibition the increase in ester size generates, another trend also appears. Comparison of entries 16 and 17 show that as the size of the ester is increased, the predominance of the *Z* ester as the better inhibitor is far more apparent. The same increase in inhibition of the *Z* over the *E* isomer is also exhibited in entries 18 and 19. We were also pleased to see that the inclusion of a benzyl ester (entries 16 and 17) improved its inhibition against the whole parasite over the previous enamides. As *E. Coli* PanK I has two phenylalanine side residues [(34)] present just beyond the carboxylate end of pantothenate, we believe similar residues in *Pf* PanK may be interacting via ring stacking with the benzyl ester.

The most successful lead to date is Entry 15. A high inhibition was demonstrated against the whole parasite, possibly due to the increased size of the ester group as before. Again, the added lipophilicity of the *Z* isomer appears to make it more potent than its *E* counterpart (Entry 14). This compound will now require testing against the parasite lysate Pan K assays.

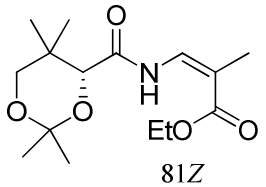
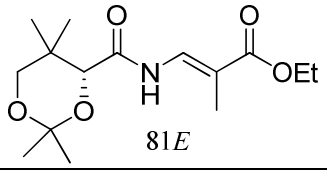
Entry	Structure	Average IC_{50} (μm)	No. repeats	Std. Dev.	clogP
18	 81*Z*	86	1	N/A	1.59
19	 81*E*	110	2	9	1.06

Table 4.5.3- Testing results for substituted enamides against whole parasite lysate

The generation of the substituted enamide (81) opened up the investigation for substituted enamides; as potential analogues of their unsubstituted counterpart. Comparison of entries 12, 13, 18 and 19 suggest that increasing the substitution of the double bond not only increases the inhibition of the compound, but also switches the predominant inhibitor from the *E* isomer to the *Z*.

The changes in inhibition observed imply that the molecular size added, through increasing the ester size or the double bond substitution, is perhaps providing a space filling/ lipophillic effect. To understand this effect in its entirety, further testing against specific isoforms of PanK needs to be performed.

4.6 CJ-15,801 Analogues

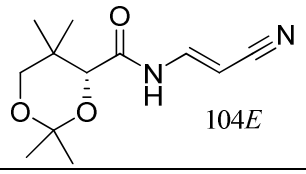
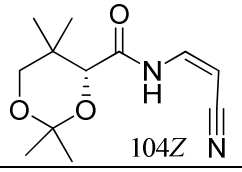
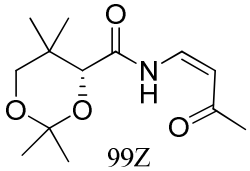
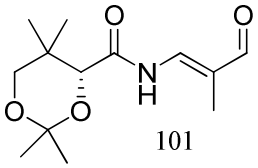
Entry	Structure	Average IC_{50} (μm)	No. repeats	Std. Dev.	clogP
20	 104*E*	163	1	N/A	1.11
21	 104*Z*	179	1	N/A	1.11
22	 99Z	>200	2	N/A	0.49
23	 101	42	1	N/A	0.72

Table 4.6.1- Testing results for CJ-15,801 analogues against whole parasite lysate

The results from the non-ester bearing compounds were intriguing. The nitrile containing enamide (entries 20 and 21), although not as good as some of the other analogues, was still showing some comparable activity. Although this compound does not contain the carboxyl group the other compounds (and CJ-15,801) contain, the nitrile may well be providing hydrogen bonding much like the carboxyl group in pantothenate, CJ-15,801 and other compounds tested.

After the initial success of methyl pantothenone in earlier trials[10] we were interested in the methylpantothenone's enamide counterpart (entry 22). However, the *Z* isomer provided no worthwhile results.

Our excitement was instead focussed on our aldehyde containing analog (entry 23). It not only showed some activity, but was almost as efficient as CJ-15,801 (IC_{50} 39μM). This is probably due to the presence of the aldehyde group acting as a more reactive electrophile than the ester.

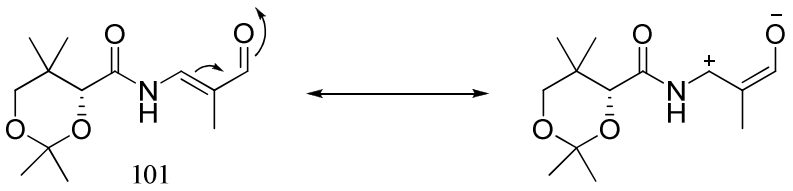
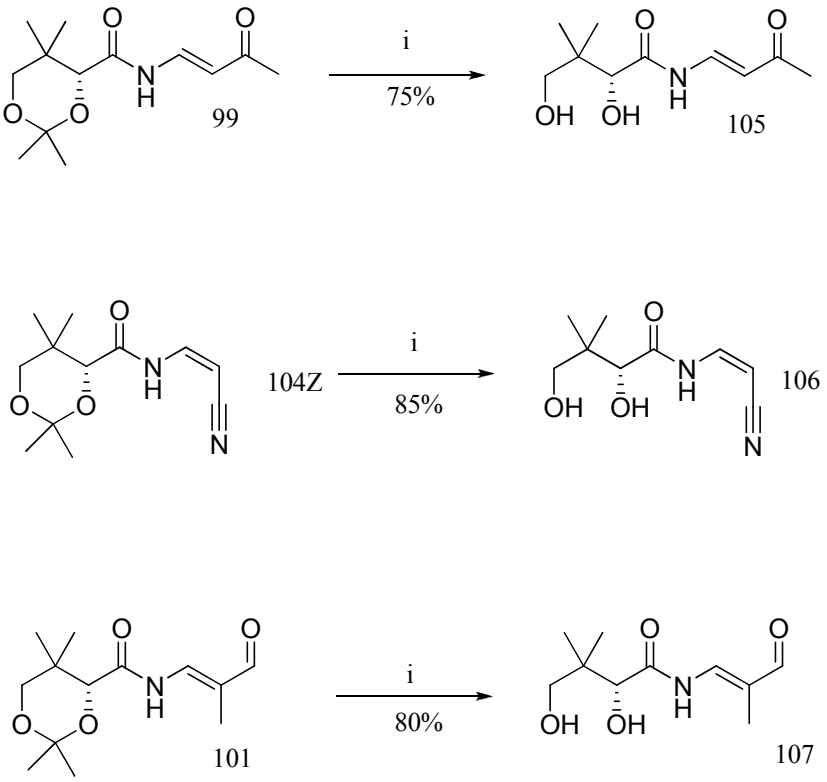


Figure 4.6.1

4.6.1 Deprotections

Encouraged by the positive preliminary test results obtained with the ketal protected enamides, the decision was taken to remove the ketal next to unmask the free 1,3-diol. It was decided that these free diols could be considered a second class of inhibitors bearing a closer resemblance to pantothenic acid, and ideally increase the binding interaction would translate into a corresponding decrease of inhibitory concentration.

Treatment of enamides (99, 101, and 104) with $BiCl_3$ / cat.H_2O gave the desired free diol containing enamides (105, 106 and 107) in excellent yield for all 3 cases.



Reagents/ Conditions: (i) $Bi(III)Cl_3$, H_2O, MeCN

Scheme 4.6.1

Testing of the deprotected diols against the same whole parasite assays as before, returned some intriguing results (Table 4.6.2).

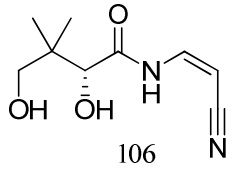
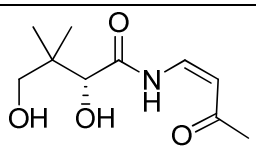
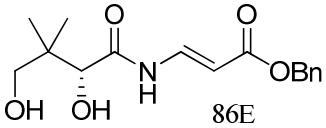
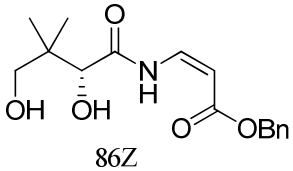
Entry	Structure	Average IC_{50} (μm)	No. repeats	Std. Dev.	clogP
24	 106	>200	2	N/A	-0.24
25	 105	>200	2	N/A	-0.87
26	 86E	9	2	0.7	1.28
27	 86Z	68	2	5	1.28

Table 4.6.2- Testing results for deprotected enamides against whole parasite lysate

Comparison of entries 21 and 24 clearly shows that the removal of the ketal group makes the compound less effective against the whole parasite when compared with its ketal protected form. This is possibly due to increased hydrophilicity preventing it from entering the parasite.

Entries 16, 17, 26 and 27 show a very interesting result. In the case of the *Z* isomer (entries 16 and 26), the removal of the ketal slightly reduced inhibition as expected. However, when the ketal was removed from the *E* isomer (entries 17 and 27), the inhibition increased drastically.

It might be possible that the combination of the free diol, the *E* enamide, and the benzyl ester provide the right balance of hydrophilicity/ hydrophobicity to maintain a high level of the compound in the parasite.

Until now, the compounds described have only been tested against parasite lysate. As the Plasmodium genome contains two different PanK enzymes, we are still unsure as to which is being inhibited. More comprehensive testing would enable more information on the compound target enzyme, and enable further structure activity relationships to be determined.

4.7 Further analogue generation

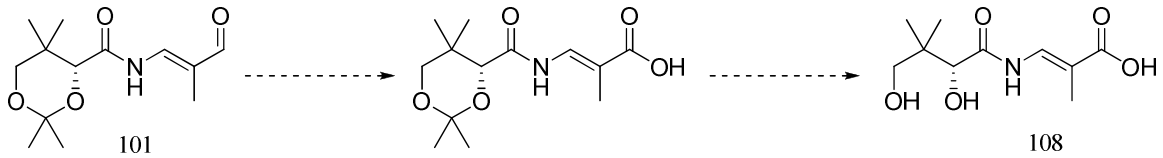
A number of preliminary conclusions can be drawn from the biological data, with some apparent trends bringing the inhibition levels below 100μM.

It appears that space filling such as increased lactam size, changing configuration from *E* to *Z*, or the inclusion of methyl substituted double bonds appears to improve inhibition.

This leads to a number of questions: Can the inhibition of CJ-15,801 be improved by incorporating these characteristics? Can previous pantothenate analogues' inhibition be improved simply through the introduction of an enamide double bond?

4.7.1 Future CJ-15,801 analogues

With the apparent increase in inhibition exhibited by the methyl substituted enamides generated earlier, the incorporation of a methyl group into the CJ-15,801 may see improved inhibition.



Scheme 4.7.1

Oxidation of aldehyde (101) would provide the methyl substituted CJ-15,801 intermediate which, after ketal deprotection, could provide the CJ-15,801 analogue (108). Alternatively, the further functionalisation of the enamide nitrogen (109) may see further space filling potential (Fig 4.7.1).

In addition to these, the synthesis and testing of *Z*- CJ-15,801 (110) may also be worth considering, as testing results appear to exhibit slightly higher inhibition from the *Z* enamides in comparison to their *E* counterpart.

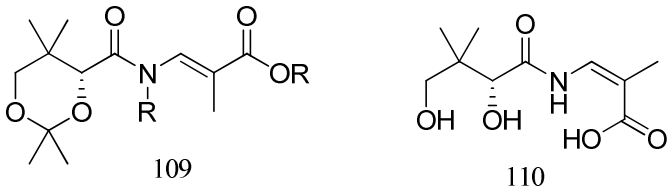
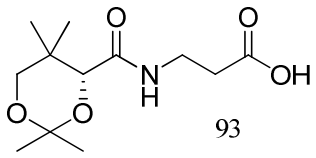


Figure 4.7.1

4.7.2 Pantothenate analogues

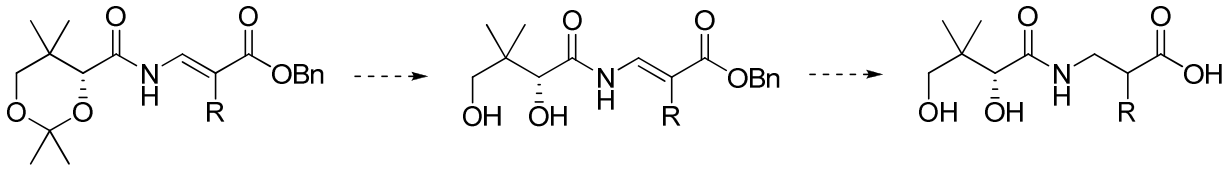
The quest for further inhibitors/ analogues is an ongoing one. Pantothenate is still a widely chosen lead for such analogues [37]. In addition to ketal protected Pantothenate (97), our process provides access to a further generation of analogues. By generating the relevant

substituted ylides, the generation of substituted enamides could see the generation of the branch chained pantothenate (R= CH_3) (Scheme 4.7.3) already shown to be biologically active [11] or further branch chained derivatives.



93

Scheme 4.7.2



Scheme 4.7.3

However, testing so far has been against the parasite, not the target enzyme. Thus, we still don't know how these compounds are working. The rational approach, therefore, would be to test these compounds against the PanK enzyme, in an attempt to elucidate the mode of inhibition.

Further testing could then provide more information on the identification of the receptor, and this information coupled with modelling crystallography could help provide new structure activity relationships and drive the generation of a new library of compounds.

5 Conclusions and Further Work

The successful generation of a unique class of *N*-imide intermediates has been reported. These *N*-imides have provided access to naturally occurring enamide functionalities – most notably the unique total synthesis of natural antimicrobial CJ-15,801 and previously unreported analogues.
Additionally, the apparent behaviour of *N*-formyl imides as "pseudo aldehydes" has opened up a number of reactions traditionally only accessible through aldehydes.

Although time constraints prevented us from exploring a number of these reactions in depth, the initial results suggest that *N*-formyl imides have significant potential in synthetic chemistry. Some are highlighted below.

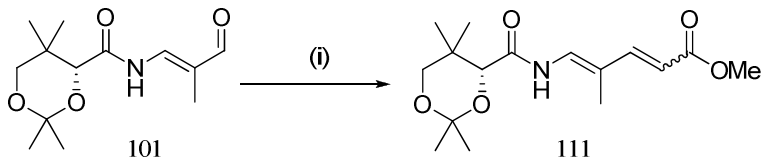
5.1 Dienamides

Dienamides provide a difficult synthetic challenge, requiring the introduction of a diene unit with the correct selectivity. Furthermore, the use of dienamides in Diels-Alder reactions makes them very useful intermediates.

There have been a number of approaches to the synthesis of dienamides [21].
However, the difficulty endured with the control of stereoselectivity and yield lead us to consider an alternative, more general approach to generating a dienamide unit.

As discussed earlier, one concern with the generation of the enamide (101) was the possibility of a double Wittig reaction occurring. However, in the synthesis of dienamides we decided to exploit enamide (101)'s ability to undergo a second Wittig olefination.

Enamide (101) was reacted with methyltriphenylphosphoranylidene acetate under the same olefination conditions used before. Although the scale of the reaction was small (0.2mmol) preliminary ^{1}H NMR of the crude product mixture shows evidence of the presence of the diene unit (111).



Reagents/ Conditions: (i) $PPh_3CHCOOMe$, benzene, 95ºC

Scheme 5.1.1

Despite its initial success, a number of issues need to be addressed as part of this approach. A possible limitation exists in that the initial enamide (101) is produced as an *E* only isomer. This limits the available dienamides to *E*, *E* and *E*, *Z* .

A possible way to circumvent this problem would be to generate the *Z* isomer of an aldehyde bearing enamide, and use this as the starting material. This could be done by using Ando or Stille-Gennari conditions [38-40].

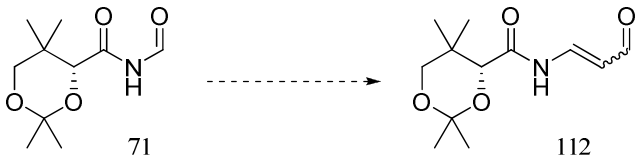


Figure 5.1.1

Alternatively, it would also be possible to perform a DIBAL reduction of the nitrile bearing enamide (104). This would generate the enamide (112) and allow for a two-step Wittig olefination.

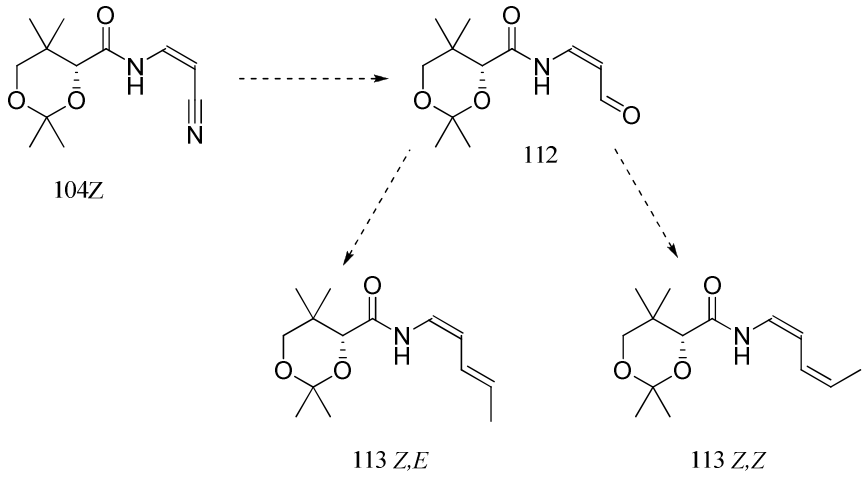
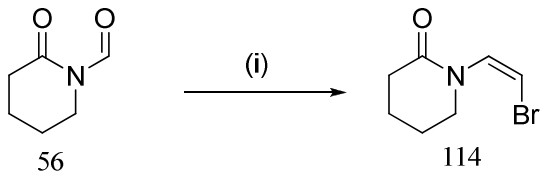


Figure 5.1.2

Any of these approaches would open the way for the possible selective generation of *Z*, *E* and *Z*, *Z* dienamides.

5.2 Ene-ynes

Enynes are another class of compounds which could potentially be generated from *N*-formyl imides, this time through the generation of haloenamide intermediates.
We have shown that the use of unstabilized ylide conditions [41] can be used to generate vinyl halide (114) from imide (56).



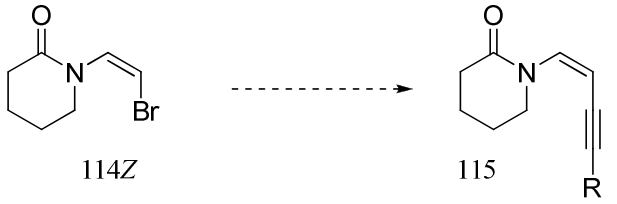
Reagents/ Conditions: (i) PPh_3CHBr, 25%, *Z* only

Scheme 5.2.1

The unstabilized ylide bromomethyl triphenylphosphonium bromide was treated with KHMDS before addition of imide (56) to generate the sole *Z* isomer of the *N*-vinylhalide (114).

Although not yet optimised, this reaction appears to return expected results for an aldehyde, i.e. the *Z* isomer being the major isomer.

Having obtained the required halide, this opens up the possibility of generating ene-ynes suitable for Pd^0 mediated Sonagashira couplings [21].



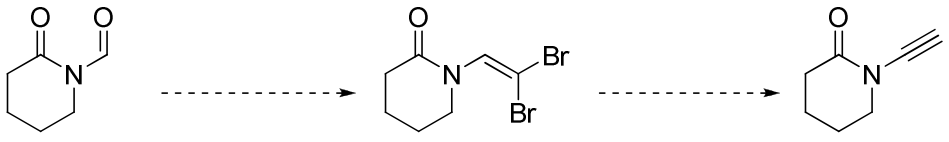
114*Z* 115

Scheme 5.2.2

5.3 Ynamides

Ynamides are another prospective functional group that can be prepared from our *N*-formyl imide intermediates.

However, until now there exists no universal method for the synthesis of ynamides.



56 116 117

Scheme 5.3.1

Generation of the dihalo-enamide (116) via Cory-Fuchs and subsequent Fritsch rearrangement could lead to the preparation of ynamide (117) giving rise to a general method for the functionalisation of amides with *N*-alkyne groups [42].

Before starting this project, we hypothesised that a large range of different *N*-functionalised compounds would be available from one key intermediate. The reactivity of imides observed to date suggests that *N*-formyl imides may well be that intermediate. The future for *N*-functionalisation through imide intermediates is now under investigation in the Marquez group (*publication in print*).

6 Section A: Experimental

General Information. All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Anhydrous DMF was purchased from Aldrich Chemical Co. Tetrahydrofuran (THF), diethyl ether, and dichloromethane (DCM) were purified through a Pure Solv 400-5MD solvent purification system (Innovative Technology, Inc). All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C using a Büchi Rotavapor.

IR spectra were recorded as thin films on NaCl plates using a Jasco FT/IR 4100 Fourier Transform spectrometer. Only significant absorptions (ν^{max}) are reported in wavenumbers (cm^{-1}) with the following abbreviations used to describe absorption intensity: w, weak; m, medium; s, strong and br, broad.

Proton magnetic resonance spectra (^{1}H-NMR) were recorded at 300MHz or 400MHz using a Bruker DPX Avance300 or 400 instrument, respectively. Chemical shifts (δ_H) are reported in parts per million (ppm), and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad), and (3) coupling constant (J) quoted in Hertz to the nearest 0.5Hz. Carbon magnetic resonance spectra (^{13}C) were recorded at 75MHz or 100MHz using a Bruker DPX Avance300 or 400 instrument respectively. Chemical shifts (δ_C) are quoted in parts per million (ppm) and are referenced to the appropriate solvent peak.

High resolution mass spectra were recorded on a JEOL JMS-700 spectrometer by electrospray ionisation mass spectrometer operating at a resolution of 15000 full widths at half height.

Flash chromatography was performed using silica gel (Apollo Scientific Silica Gel 60, 40-63 micron) as the stationary phase. TLC was performed on aluminium sheets pre-coated with silica (Merck Silica Gel 60 F_{254}). The plates were visualised by the quenching of UV fluorescence (λ_{max}254nm) and/or by staining with either anisaldehyde, potassium permanganate or iodine followed by heating.

All cLogP values were calculated using Chemoffice Chemdraw Version 10.

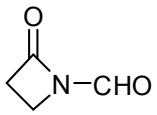
Any biological testing was performed by Dr C. Spry at the Australian National University, Australia, to the following procedures:

For whole parasite testing , *in vitro P. falciparum* growth assays were set up in 96-well microtitre plates (NUNC) starting with ring-stage *P. falciparum*-infected erythrocytes. Test compounds were initially dissolved in dimethylsulfoxide (DMSO), and then diluted in complete medium. The concentration of DMSO introduced into the assay never exceeded 0.01 % (v/v). Two-fold serial dilutions of the test compounds in complete medium were added to the wells of the plates in duplicate or triplicate (final well volume 100 µL). A suspension of infected erythrocytes (2 % haematocrit and 1 % parasitemia) was prepared in complete medium and 100 µL of this suspension added to the wells (final well volume 200 µL, haematocrit 1 %, parasitemia 1 %). Wells containing uninfected erythrocytes (1 % haematocrit) served as blank controls and wells containing infected erythrocytes (2 % haematocrit and 1 % parasitemia) in the absence of any drugs served as an estimate of 100 % parasite growth. The plates were then incubated at 37 ^{o}C under an atmosphere of 96 % nitrogen, 3 % carbon dioxide and 1 % oxygen for 96 h. To investigate specificity in some experiments the medium was supplemented with 100 µM pantothenate. Following the 48 or 96 h, the cells in the microtitre plates were resuspended before 100 µL from each well was transferred to a second 96-well microtitre plate containing 100 µL of Sybr Green I (0.2 µL/mL; Molecular Probes, Inc) in lysis buffer (20 mM Tris, pH 7.5; 5 mM EDTA; 0.008 % (w/v) saponin; 0.08 % (v/v) Triton X-100) per well. The cells were mixed with the buffer, and the fluorescence in the wells of the microtitre plates measured using a FLUOstar OPTIMA multidetection microplate reader from BMG LABTECH.

For PanK testing, Parasites were diluted 1/10 in a 10 mM Tris buffer (pH 7.4) and triturated 10 times through a 25-gauge needle. The lysate was then clarified by three centrifugation steps at 2000*g* for 30 min. At the end of each centrifugation step, the supernatant was transferred to a new tube. The lysates were stored at -20°C, and aliquots were thawed when required. The assay was performed in 50 µl volumes in a 96-well microtiter plate. The phosphorylation reaction was commenced by adding the lysate (125 µl/ml) to a solution containing 50 mM Tris, 5 mM ATP, 5mM MgCl2, and 0.1 µCi/ml [^{14}C]pantothenate in the absence or presence of the testing compound (200 µM). The reaction was terminated at predetermined time points by the addition of 5 µl of acetic acid (10% v/v). The phosphorylated [^{14}C]pantothenate was separated from the nonphosphorylated species by binding the phosphorylated [^{14}C]pantothenate to DE-81 filters contained in a 96-well Unifilter plate (Whatman, Florham Park, NJ). A 50 µl volume of the reaction solution was transferred into the Unifilter plate and was allowed to dry. The nonphosphorylated [^{14}C]pantothenate was removed by three washes, each with 200 µl of a solution of ethanol/acetic acid/water (95:1:4; v/v/v). The filters were allowed to dry before being soaked in 30 µl of scintillation fluid (Microscint; PerkinElmer Life and Analytical Sciences). The radioactivity was measured in a Top-Count scintillation counter (PerkinElmer Life and Analytical Sciences).

Representative Procedures.

General Procedure (A) for the Synthesis of Lactam Derived *N*-Formyl Imides (54-59). A mixture of formic acid (0.1 mol) and acetic acid (0.1 mol) was heated under argon at 55 ^{o}C for 3 hours. In each case, the lactam (0.01 mmol) was then added, and the resulting reaction mixture stirred at 60 ^{o}C for 15 hours. The reaction solution was then cooled to room temperature and the excess mixed anhydride removed under vacuum (10 mbar). The resulting crude product was then suspended in ethyl acetate (10 mL) and the resulting solution filtered through a plug of neutral alumina to afford the desired lactam derived *n*-formyl imides **(54-59).**



2-Oxo-azetidine-1-carbaldehyde, (54).

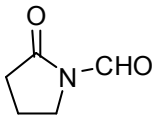
Prepared as per procedure A, using Azetidinone (213mg) to generate imide **(54)** (551mg, 56%)

^{1}H NMR (400MHz, $CDCl_3$) δ: 8.60 (1H, s, O=C*H*), 3.60 (2H, m, N-CH_2), 3.10 (2H, m, CH_2C=O).

NMR (100MHz, $CDCl_3$) δ: 166.0 (O=*C*H), 156.3 (N*C*=O), 22.1 (*C*H_2), 20.5 (*C*H_2).

IR ν_{max}(film)/cm^{-1} 2981 (s), 1830 (s), 1652(s).

HRMS calcd for $C_4H_5O_2N$ (M+ ·): 99.0320. Found 99.0321.



2-Oxo-pyrrolidine-1-carbaldehyde, (55).

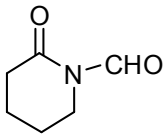
Prepared as per procedure A, using pyrrolidinone (851mg) to generate imide **(55)** (848mg, 75%)

^{1}H NMR (400MHz, $CDCl_3$) δ: 9.01 (1H, s, O=C*H*), 3.67 (2H, td, *J* = 7.3, 0.8 Hz, N-CH_2), 2.54 (2H, t, *J* = 7.9 Hz, CH_2C=O), 2.07 (2H, m, CH_2).

^{13}C NMR (100MHz, $CDCl_3$) δ: 176.8 (O=CH), 160.3 (NC=O), 42.1 (CH_2), 32.2 (CH_2), 17.8 (CH_2).

IR ν_{max}(film)/cm^{-1} 2905 (s), 1750 (s), 1698 (s), 1351 (s), 1300 (m).

HRMS calcd for $C_5H_7O_2N$ (M+ ·): 113.0477. Found 113.0479.



2-Oxo-piperidine-1-carbaldehyde, (56).

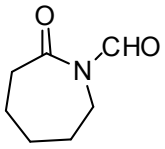
Prepared as per procedure A, using valerolactam (991mg) to generate imide **(56)** (1.02g, 80%)

^{1}H NMR (400MHz, $CDCl_3$) δ: 9.42 (1H, s, O=C*H*), 3.55 (2H, bs, N-CH_2), 2.55 (2H, bm, CH_2C=O), 1.80 (4H, bm, 2x CH_2).

^{13}C NMR (100MHz, $CDCl_3$) δ: 173.2 (O=C*H*), 162.8 (NC=O), 41.6 (CH_2), 33.3(CH_2), 21.7(CH_2), 19.9(CH_2).

IR ν_{max}(film)/cm^{-1} 2958 (s), 1690 (s), 1717 (s).

HRMS calcd for $C_6H_{10}O_2N$ ($M+H^+$): 128.0712. Found 128.0710.



2-Oxo-azepane-1-carbaldehyde, (57).

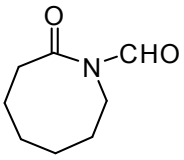
Prepared as per procedure A, using E-caprolactam (1.13g) to generate imide **(57)** (1.19g, 85%)

^{1}H NMR (400MHz, $CDCl_3$) δ: 9.41 (1H, s, O=C*H*), 3.81 (2H, m, N-CH_2), 2.70 (2H, m, CH_2C=O), 1.81 (4H, m, 2x CH_2), 1.71 (2H, m, CH_2).

^{13}C NMR (100MHz, $CDCl_3$) δ: 178.1(O=C*H*), 162.2 (NC=O), 40.2(N*C*H_2), 38.3(O=C*C*H_2), 29.6(CH_2), 28.6(CH_2), 23.6(CH_2).

IR ν_{max}(film)/cm^{-1} 2986 (s), 1700 (s), 1695 (s).

HRMS calcd for $C_7H_{12}O_2N$ ($M+H^+$): 142.0868. Found 142.0870.



2-Oxo-azocane-1-carbaldehyde, (58).

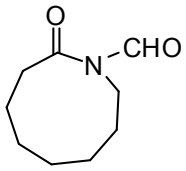
Prepared as per procedure A, using aza-2-cyclooctanone (1.27g) to generate imide **(58)** (1.08g, 70%)

^{1}H NMR (400MHz, $CDCl_3$) δ: 9.39 (1H, s, O=C*H*), 3.77 (2H, m, N-CH_2), 2.59 (2H, m, CH_2C=O), 1.85 (2H, m, CH_2), 1.65 (2H, m, CH_2), 1.50 (2H, m, CH_2), 1.45 (2H, m, CH_2).

^{13}C NMR (100MHz, $CDCl_3$) δ: 178.3(O=C*H*), 162.6 (NC=O), 40.5(NCH_2), 35.0(O=C*C*H_2), 29.0(CH_2), 28.6(CH_2), 25.8(CH_2), 24.3(CH_2).

IR ν_{max}(film)/cm^{-1} 2935 (s), 1652 (s), 1635 (s).

HRMS calcd for $C_8H_{14}O_2N$ ($M+H^+$): 156.1025. Found 156.1024.



2-Oxo-azonane-1-carbaldehyde, (59).

Prepared as per procedure A, using 2-azacyclononanone (1.41g) to generate imide **(54)** (1.48g, 87%)

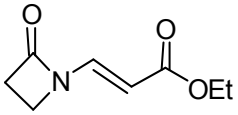
^{1}H NMR (400MHz, $CDCl_3$) δ: 9.35 (1H, s, O=C*H*), 3.75 (2H, m, N-CH_2), 2.61 (2H, m, CH_2C=O), 1.84 (2H, m, CH_2), 1.65 (2H, m, CH_2), 1.55 (2H, m, CH_2), 1.47 (4H, m, CH_2).

^{13}C NMR (100MHz, $CDCl_3$) δ: 178.8 (O=C*H*), 162.9 (NC=O), 42.3(NCH_2), 36.2 (O=C*C*H_2, 28.1(CH_2), 27.1(CH_2), 25.1 (2x CH_2), 22.5(CH_2).

IR ν_{max}(film)/cm^{-1} 2932 (s), 1695 (s), 1635 (s).

HRMS calcd for $C_9H_{16}O_2N$ ($M+H^+$): 170.1181. Found 170.1182.

General Procedure (B) for the Synthesis of Lactam Derived Enamides (60-65). In each case, a solution of the lactam derived *n*-formyl imide (1.0 mmol) in benzene (10 mL) was treated with ethoxycarbonylmethylene triphenylphosphorane (3.0 mmol) and the resulting homogeneous mixture heated to 80^{o}C for 18 hours. Once the reaction was complete by TLC analysis, the solvent was then removed *in vacuo* to generate a semi-solid crude residue. Purification of the crude product by flash column chromatography (silica gel, 30% EtOAc in 40-60 petroleum ether) proceeded to generate the desired lactam derived *E*-enamides **(60-65)**, as a single double bond isomer in each case.



(*E*)-3-(2-Oxo-azetidin-1-yl)-acrylic acid ethyl ester, (60).

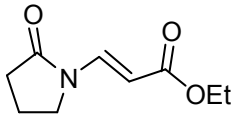
Imide **(54)** (127mg) was added to a solution of ethoxycarbonylmethylene triphenylphosphorane in benzene as per procedure B to generate enamide **(60)** (166mg, 77%) as a single *E* isomer.

^{1}H NMR (400MHz, $CDCl_3$) δ: 7.65 (1H, d, *J* = 14.0 Hz, *H*C=CH), 5.20 (1H, d, *J* = 14.0 Hz, HC=C*H*), 4.12 (2H, q, *J* = 7.1 Hz, OCH_2CH$_3$), 3.45 (2H, t, *J* = 4.9 Hz, N-CH_2), 3.09 (2H, t, *J* = 4.9 Hz, CH_2C=O), 1.20 (3H, t, *J* = 7.1 Hz, OCH$_2$CH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 166.9 (OC=O), 164.9 (NC=O), 134.9 (*C*=C), 100.0 (C=*C*), 60.3 (O*C*H$_2$CH$_3$) , 38.8 (CH$_2$), 37.3 (CH$_2$), 14.3 (OCH$_2$*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3029 (m), 2983 (s), 1774 (s), 1701 (s), 1632 (s), 1178 (s).

HRMS calcd for $C_8H_{11}O_3N$ (M+ ·): 169.0739. Found 169.0738.



(*E*)-3-(2-Oxo-pyrrolidin-1-yl)-acrylic acid ethyl ester, (61).

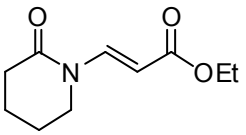
Imide **(55)** (105mg) was added to a solution of ethoxycarbonylmethylene triphenylphosphorane in benzene as per procedure B to generate enamide **(61)** (112mg, 66%) as a single *E* isomer.

^{1}H NMR (400MHz, $CDCl_3$) δ: 8.04 (1H, d, *J* = 14.3 Hz, *H*C=CH), 5.14 (1H, d, *J* = 14.2 Hz, HC=C*H*), 4.13 (2H, q, *J* = 7.1 Hz, OCH_2CH$_3$), 3.49 (2H, t, *J* = 7.2 Hz, N-CH_2), 2.49 (2H, t, *J* = 7.9 Hz, CH_2C=O), 2.1 (2H, appq, *J* = 7.5 Hz, CH_2), 1.23 (3H, t, *J* = 7.1 Hz, OCH$_2$CH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 174.2 (OC=O), 167.1 (NC=O), 137.2 (C=*C*), 100.8 (*C*=C), 60.2 (O*C*H$_2$CH$_3$), 44.9 (CH$_2$), 30.9 (CH$_2$), 17.4 (CH$_2$), 14.3 (OCH$_2$*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3049 (s), 2981 (s), 1728 (s), 1699 (s), 1630 (m), 1260 (m), 1159 (m).

HRMS calcd for $C_9H_{13}O_3N$ (M+ ·): 183.0895. Found 183.0888.



(*E*)-3-(2-Oxo-piperidin-1-yl)-acrylic acid ethyl ester, (62).

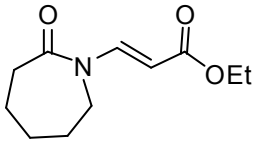
Imide **(56)** (188mg) was added to a solution of ethoxycarbonylmethylene triphenylphosphorane in benzene as per procedure B to generate enamide **(62)** (122mg, 42%) as a single *E* isomer.

^{1}H NMR (400MHz, $CDCl_3$) δ: 8.65 (1H, d, *J* = 14.5 Hz, *H*C=CH), 5.30 (1H, d, *J* = 14.5 Hz, HC=C*H*), 4.25 (2H, q, *J* = 7.1 Hz, OCH_2CH$_3$), 3.45 (2H, t, *J* = 6.1 Hz, N-CH_2), 2.60 (2H, t, *J* = 6.7 Hz, CH_2C=O), 1.88 (2H, m, CH_2), 1.78 (2H, m, CH_2), 1.30 (3H, t, *J* = 7.1 Hz, OCH$_2$CH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 169.5 (OC=O), 167.4 (NC=O), 140.7 (C=*C*), 100.0 (*C*=C), 60.1 (O*C*H$_2$CH$_3$), 45.6 (CH_2), 33.1 (CH_2), 22.4 (CH_2), 20.2 (CH_2), 14.4 (OCH$_2$*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3057 (s), 2957 (s), 1708 (s), 1683 (s), 1622 (s), 1255 (s), 1159 (m).

HRMS calcd for $C_{10}H_{15}O_3N$ (M+ ·): 197.1052. Found 197.1050.



(*E*)-3-(2-Oxo-azepan-1-yl)-acrylic acid ethyl ester, (63).

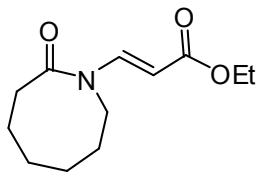
Imide **(57)** (191mg) was added to a solution of ethoxycarbonylmethylene triphenylphosphorane in benzene as per procedure B to generate enamide **(63)** (155mg, 55%) as a single *E* isomer.

^{1}H NMR (400MHz, $CDCl_3$) δ: 8.39 (1H, d, *J* = 14.5 Hz, *H*C=CH), 5.22 (1H, d, *J* = 14.4 Hz, HC=C*H*), 4.15 (2H, q, *J* = 7.1 Hz, OCH_2CH$_3$), 3.55 (2H, m, CH_2), 2.64 (2H, m, CH_2), 1.70 (6H, m, 3x CH_2), 1.25 (3H, t, *J* = 7.06 Hz, OCH$_2$CH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 174.8 (OC=O), 167.7 (NC=O), 140.7 (C=*C*), 98.8 (*C*=C), 60.0 (O*C*H$_2$CH$_3$), 45.4 (CH_2), 37.0 (CH_2), 29.1 (CH_2), 27.2 (CH_2), 23.4 (CH_2), 14.3 (OCH$_2$*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3069 (s), 2936 (s),1706 (s), 1684 (s), 1621 (s), 1173 (s), 1148 (m).

HRMS calcd for $C_{11}H_{17}O_3N$ (M+ ·): 211.1208. Found 211.1207.



(*E*)-3-(2-Oxo-azocan-1-yl)-acrylic acid ethyl ester, (64).

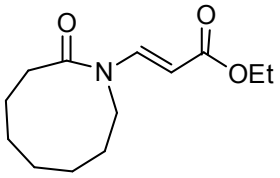
Imide **(58)** (214mg) was added to a solution of ethoxycarbonylmethylene triphenylphosphorane in benzene as per procedure B to generate enamide **(64)** (114mg, 37%) as a single *E* isomer.

^{1}H NMR (400MHz, $CDCl_3$) δ: 8.45 (1H, d, *J* = 14.6 Hz, *H*C=CH), 5.25 (1H, d, *J* = 14.6 Hz, HC=C*H*), 4.15 (2H, q, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 3.75 (2H, m, C*H*$_2$), 2.60 (2H, m, C*H*$_2$), 1.80 (2H, m, C*H*$_2$), 1.65(2H, m, C*H*$_2$), 1.50 (2H, m, C*H*$_2$), 1.40 (2H, m, C*H*$_2$), 1.22 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$).

^{13}C NMR (100MHz, $CDCl_3$) δ: 174.6 (OC=O), 167.6 (NC=O), 139.6 (C=*C*), 100.2 (*C*=C), 60.1 (O*C*H$_2$CH$_3$), 44.0 (CH$_2$), 34.5 (CH$_2$), 29.0 (CH$_2$), 27.2 (CH$_2$), 26.1 (CH$_2$), 24.0 (CH$_2$), 14.4 (OCH$_2$*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3048 (m), 2935 (s), 1702 (s), 1678 (s), 1621 (s), 1130 (s).

HRMS calcd for $C_{12}H_{19}O_3N$ (M+ ·): 225.1365. Found 225.1364.



(*E*)-3-(2-Oxo-azonan-1-yl)-acrylic acid ethyl ester, (65).

Imide **(59)** (219mg) was added to a solution of ethoxycarbonylmethylene triphenylphosphorane in benzene as per procedure B to generate enamide **(65)** (176mg, 57%) as a single *E* isomer.

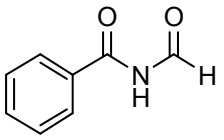
^{1}H NMR (400MHz, $CDCl_3$) δ: 8.45 (1H, d, *J* = 14.6 Hz, *H*C=CH), 5.21 (1H, d, *J* = 14.6 Hz, HC=C*H*), 4.14 (2H, q, *J* = 7.1 Hz, OCH_2CH$_3$), 3.74 (2H, m, CH_2), 2.50 (2H, m, CH_2), 1.80 (2H, m, CH_2), 1.70 (2H, m, CH_2), 1.50 (2H, m, CH_2), 1.40 (4H, m, 2x CH_2), 1.25 (3H, t, *J* = 7.1 Hz, OCH$_2$CH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 175.5 (OC=O), 167.6 (NC=O), 140.0 (C=*C*), 100.3 (*C*=C), 60.1 O*C*H$_2$CH$_3$), 45.7 (CH$_2$), 35.2 (CH$_2$), 28.1 (CH$_2$), 25.3 (CH$_2$), 25.2 (CH$_2$), 25.1 (CH$_2$), 22.2 (CH$_2$), 14.4 (OCH$_2$*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3045 (s), 2931 (s), 1703 (s), 1676 (s), 1620 (s), 1155 (m).

HRMS calcd for $C_{13}H_{21}O_3N$ (M+ ·): 239.1521. Found 239.1524.

General Procedure (C) for the Synthesis of *N*-Formyl Imides, (69-71). A solution of the acyclic amide (1 mmol) in anhydrous THF (10 mL) was cooled to 0 °C before being treated with *n*-BuLi (1.1 mmol, 1.6 M solution in hexanes). The reaction mixture was then stirred at 0 °C for 5 minutes before being treated with *N*-formylbenzotriazole (1.2 mmol). The resulting mixture was then allowed to warm up to room temperature and then stirred for a further 2 hours. The reaction mixture was diluted with *t*-butylmethyl ether (10 mL), and quenched with a saturated aq. $NaHCO_3$ solution (10 mL). The aqueous phase was then extracted with diethyl ether (3 x 20 mL) and the combined organic layers dried over Na_2SO_4. The solvent was removed under vacuum to afford the crude product, which was then purified by flash column chromatography (silica gel, 10% to 20% ethyl acetate in 40-60 petroleum ether) to afford the desired *N*-formyl imides **(69-71)**.



***N*-Formylbenzamide, (69)**.

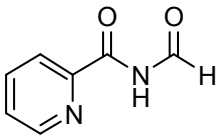
n-BuLi (1.88 mL) and *N*-formylbenzotriazole (756 mg) were added to a solution of benzamide (519 mg) in THF as per procedure C, to generate the imide **(69)** (333 mg, 52%).

^{1}H NMR (400MHz, $CDCl_3$) δ: 10.36 (1H, bd, *J* = 7.7 Hz, N*H*), 9.33 (1H, d, *J* = 9.5 Hz, O=C*H*), 7.91 (2H, m, 2x Ar*H*), 7.56 (1H, m, Ar*H*), 7.46 (2H, m, 2x Ar*H*).

^{13}C NMR (100MHz, $CDCl_3$) δ: 165.8 (NC=O), 164.1 (O=CH), 132.9 (ArC q), 130.0 (ArC), 128.0 (ArC), 127.1 (ArC).

IR ν_{max}(film)/cm^{-1} 3414 (m), 3029 (s), 1728 (s), 1683 (s), 1463 (s), 1364 (m), 1252 (s), 1208 (s).

HRMS calcd for $C_8H_7O_2N$ (M+ ·): 149.0477. Found 149.0474.



***N*-Formylpicolinamide, (70)**.

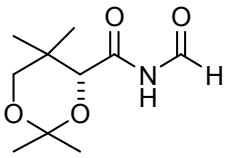
n-BuLi (1.80 mL) and *N*-formylbenzotriazole (726 mg) were added to a solution of picolinamide (502 mg) in THF as per procedure C, to generate the imide **(70)** (389 mg, 49%).

^{1}H NMR (400MHz, $CDCl_3$) δ: 10.3 (1H, bs, N*H*), 9.26 (1H, d, *J* = 10.6 Hz, O=C*H*), 8.58 (1H, dm, *J* = 4.8 Hz, Ar*H*), 8.19 (1H, dm, *J* = 7.8 Hz, Ar*H*), 7.89 (1H, td, *J* = 7.7, 1.7 Hz, Ar*H*), 7.53 (1H, ddd, *J* = 7.6, 4.7, 1.1 Hz, Ar*H*).

^{13}C NMR (100MHz, $CDCl_3$) δ: 164.4 (NC=O), 161.8 (O=CH), 148.7 (ArC q), 147.1 (ArC), 137.8 (ArC), 128.1 (ArC), 123.3 (ArC).

IR ν_{max}(film)/cm^{-1} 3347 (s), 3029 (s), 2926 (s), 1736 (s), 1697 (s), 1462 (m), 1367 (s), 1183 (m).

HRMS calcd for $C_7H_6O_2N_2$ (M+ ·): 150.0427. Found 150.0429.



_N_-Formyl-(_R_)-2,2,5,5-tetramethyl-[1,3]dioxane-4-carboxylic acid amide, (71).

n-BuLi (1.37 mL) and *N*-formylbenzotriazole (551 mg) were added to a solution of (*D*-) pantolactone derived amide (591 mg) in THF as per procedure C, to generate the imide **(71)** (431 mg, 64%).

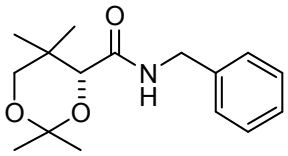
^{1}H NMR (400MHz, $CDCl_3$) δ: 9.08 (1H, d, *J* = 10.4 Hz, O=C*H*), 8.80 (1H, bs, N*H*), 4.12 (1H, s, C*H*(O)), 3.65 (1H, d, *J* = 11.8 Hz, $C_{HA,\ HB}$), 3.27 (1H, d, *J* = 11.8 Hz, $C_{HA,\ HB}$), 1.41 (3H, s, OCCH_3), 1.39 (3H, s, OCCH_3), 0.99 (3H, s, CCH_3), 0.98 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 170.6 (O=CH), 161.4 (NC=O), 99.7 (O*C*CH_3), 77.0 (CH(O)) , 71.1 (OCH_2), 33.3 (*C*CH_3), 29.3 (OC*C*H_3), 21.7 (OC*C*H_3), 18.9 (C*C*H_3), 18.6 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3385 (s), 2874 (s), 1743 (s), 1699 (s).

HRMS calcd for $C_{10}H_{18}O_4N$ ($M+H^+$): 216.1236. Found 216.1233.

$[\alpha]_D$ +48.0 (c = 1.4, $CHCl_3$).



_N_-Benzyl-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide, (72)

A solution of amide **(68)** (191 mg, 1.01mmol) in THF (5 mL) was added to a suspension of previously washed sodium hydride (60% oil dispersion, (81mg) in dry THF (5 mL) at 0 ^{o}C. After generation of H_2 subsided, the mixture was stirred for 30 min at 0 ^{o}C. Benzyl bromide was then added (0.24ml, 2.0mmol), followed by tetrabutylammonium iodide (37mg, 0.1mmol) at 0 ^{o}C. The reaction was allowed to warm up to room temperature over 1 hr, and was then stirred for a further 2hrs. The reaction mixture was then extracted with EtOAc (20mL) and water (15 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent evaporated under vacuum to give a crude oil which was purified by flash column chromatography (silica gel, 20% EtOAc in 40-60 petroleum ether) to afford *N*-benzyl amide **(72)**, as a clear oil (185mg, 67%).

^{1}H NMR (400MHz, $CDCl_3$) δ: 7.24 (5H, m, 5x Ar*H*), 6.80 (1H, bs, N*H*), 4.39 (2H, s, Bn*H*), 4.09 (1H,s, C*H*(O)), 3.63 (1H, d, *J* = 11.7 Hz, $C_{HA, HB}$), 3.22 (1H, d, *J* = 11.7 Hz, $C_{HA, HB}$), 1.36 (6H, s, 2x OCCH_3), 1.01 (3H, s, CCH_3), 0.95 (3H, s, CCH_3).

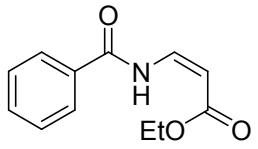
^{13}C NMR (100MHz, $CDCl_3$) δ: 169.7 (NC=O), 138.3 (ArC q), 128.7 (2x ArC), 127.6 (2x ArC), 127.4 (ArC) , 99.1 (O*C*CH_3), 77.3 (CH(O)), 71.5 (NCH_2), 42.6 (OCH_2), 33.2 (*C*CH_3), 29.5 (OC*C*H_3), 22.2(OC*C*H_3), 19.0 (C*C*H_3), 18.7(C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3322 (s), 3032(s), 2992 (s), 1716 (s), 1649 (s), 1460 (s).

HRMS calcd for $C_{16}H_{23}O_3N$ (M+ ·): 277.1678. Found 277.1677.

$[\alpha]_D$ +103.0 (c = 1.2, $CHCl_3$).

General Procedure (D) for the Synthesis of Acyclic Enamides (76-78). A solution of *N*-formyl imide **(69-71)** (1.0 mmol) in benzene (10 mL) was treated with ethoxycarbonylmethylene triphenylphosphorane (3.0 mmol) and the resulting mixture heated to 95 ^{o}C for 19 hours. Upon reaction completion as indicated by TLC analysis, the solvent was removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 30% EtOAc in 40-60 petroleum ether) to afford the desired enamides **(76-78)**.



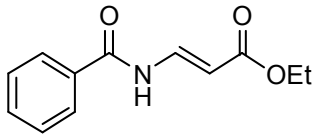
(*Z*)-3-Benzoylamino-acrylic acid ethyl ester, (76*Z*).

Imide **(69)** (184mg) was added to a solution of ethoxycarbonylmethylene triphenylphosphorane in benzene as per procedure D to generate enamide **(76)** (236mg, 87%) as a mixture of *E* and *Z* isomers, *E*:*Z* ratio 51: 49.

^{1}H NMR (400MHz, $CDCl_3$) δ: 11.5 (1H, bs, N*H*), 7.90 (2H, m, 2x Ar*H*), 7.68 (1H, dd, *J* = 9.1, 8.8 Hz, *H*C=CH), 7.53 (1H, m, Ar*H*), 7.44 (2H, m, 2x Ar*H*), 5.20 (1H, d, *J* = 8.8 Hz, HC=C*H*), 4.17 (2H, q, *J* = 7.1 Hz, OC$H_2$$CH_3$), 1.27 (3H, t, *J* = 7.1 Hz, OCH_2CH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 169.6 (OC=O), 164.5 (NC=O), 138.8 (ArC q), 132.9 (ArC), 132.2 (C=*C*), 128.9 (ArC), 127.7 (ArC), 97.2 (*C*=C), 60.3 (O*C*$H_2$$CH_3$), 14.3 ($OCH_2$*C*$H_3$).

IR ν_{max}(film)/cm^{-1} 3337 (s), 3056(s), 2985 (s), 1679 (s), 1627 (s), 1396 (m), 1381 (m), 1210 (m), 739 (s). HRMS calcd for $C_{12}H_{13}O_3N$ (M+ ·): 219. 0895. Found 219. 0898.



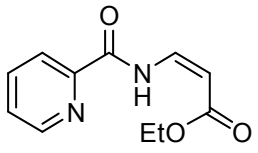
(*E*)-3-Benzoylamino-acrylic acid ethyl ester, (76*E*).

^{1}H NMR (400MHz, $CDCl_3$) δ: 8.28 (1H, dd, *J* = 14.1, 11.8 Hz, *H*C=CH), 8.08 (1H, bd, *J* = 11.8 Hz, N*H*), 7.88 (2H, m, 2x Ar*H*), 7.64 (1H, m, Ar*H*), 7.54 (2H, m, 2x Ar*H*), 5.65 (1H, d, *J* = 14.1 Hz, HC=C*H*), 4.25 (2H, q, *J* = 7.1 Hz, OC$H_2$$CH_3$), 1.33 (3H, t, *J* = 7.1 Hz, OCH_2CH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 167.3 (OC=O), 164.9 (NC=O), 137.9 (ArC q), 132.9 (ArC), 132.3 (C=*C*), 128.9 (ArC), 127.5 (ArC), 102.5 (*C*=C), 60.3 (O*C*$H_2$$CH_3$), 14.4 ($OCH_2$*C*$H_3$).

IR ν_{max}(film)/cm^{-1} 3400 (s), 3033 (m), 2993 (s), 1694 (s), 1639 (s), 1095 (m), 1051 (m), 908 (s).

HRMS calcd for $C_{12}H_{13}O_3N$ (M+ ·): 219.0895. Found 219.0897.



(*Z*)-3-[(Pyridine-3-carbonyl)-amino]-acrylic acid ethyl ester, (77*Z*).

Imide **(70)** (112mg) was added to a solution of ethoxycarbonylmethylene triphenylphosphorane in benzene as per procedure D to generate enamide **(77)** (143mg, 87%) as a mixture of *E* and *Z* isomers, *E*:*Z* ratio 3: 1.

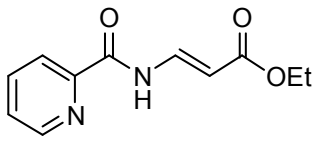
^{1}H NMR (400MHz, $CDCl_3$) δ: 12.35 (1H, bs, N*H*), 8.67 (1H, dm, *J* = 4.7 Hz, Ar*H*), 8.18 (1H, dt, *J* = 7.8, 1.0 Hz, Ar*H*), 7.83 (1H, td, *J* = 7.7, 1.7 Hz, Ar*H*), 7.60 (1H, dd, *J* = 11.9, 8.9 Hz, *H*C=CH),

7.44 (1H, ddd, *J* = 7.6, 4.7, 1.2 Hz, Ar*H*), 5.22 (1H, d, *J* = 8.8 Hz, HC=C*H*), 4.21 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 1.28 (3H, t, *J* = 7.17 Hz, OCH$_2$CH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 168.6 (OC=O), 162.9 (NC=O), 148.9 (ArC q), 148.5 (ArC), 137.5 (ArC), 137.0 (C=*C*), 127.2 (ArC), 123.3 (ArC), 98.4 (*C*=C), 60.3 (O*C*H$_2$CH$_3$), 14.4 (OCH$_2$*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3424 (s), 3078 (s), 2985 (s), 1688 (s), 1625 (s), 1204 (m), 735 (s).

HRMS calcd for $C_{11}H_{12}O_3N_2$ (M+ ·): 220.0848. Found 220. 0850.



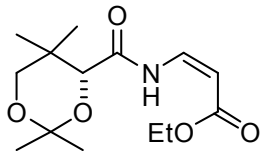
(*E*)-3-[(Pyridine-3-carbonyl)-amino]-acrylic acid ethyl ester, (77*E*)

^{1}H NMR (400MHz, $CDCl_3$) δ: 10.05 (1H, bd, *J* = 10.4 Hz, N*H*), 8.66 (1H, dm, *J* = 4.8 Hz, Ar*H*), 8.29 (1H, dm, *J* = 7.8 Hz, Ar*H*), 8.22 (1H, dd, *J* = 14.2, 12.2 Hz, *H*C=CH), 7.95 (1H, td, *J* = 7.7, 1.7 Hz, Ar*H*), 7.57 (1H, ddd, *J* = 7.6, 4.8, 1.2 Hz, Ar*H*), 5.76 (1H, d, *J* = 14.2 Hz, HC=C*H*), 4.26 (2H, q, *J* = 7.1 Hz, OCH_2CH$_3$), 1.35 (3H, t, *J* = 7.12 Hz, OCH$_2$CH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 167.3 (OC=O), 162.2 (NC=O), 148.4 (ArC q), 147.9 (ArC), 137.8 (ArC), 136.8 (C=*C*), 127.4 (ArC), 123.1 (ArC), 103.3 (*C*=C), 60.3 (O*C*H$_2$CH$_3$), 14.4 (OCH$_2$*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3274 (s), 3034 (m), 2971 (s), 1694 (s), 1637 (s), 1498 (s), 1150 (m).

HRMS calcd for $C_{11}H_{12}O_3N_2$ (M+ ·): 220.0848. Found 220.0847.



(*Z*)-3-[((*R*)-2,2,5,5-Tetramethyl-[1,3]dioxane-4-carbonyl)-amino]-acrylic acid ethyl ester, (78*Z*).

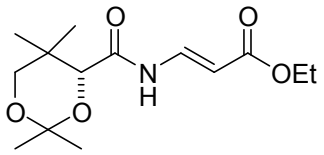
Imide **(71)** (69mg) was added to a solution of ethoxycarbonylmethylene triphenylphosphorane in benzene as per procedure D to generate enamide **(78)** (89mg, 98%) as a mixture of *E* and *Z* isomers, *E*:*Z* ratio 3: 1.

^{1}H NMR (400MHz, $CDCl_3$) δ: 11.05 (1H, bs, N*H*), 7.36 (1H, dd, *J* = 11.8, 8.9 Hz, *H*C=CH), 5.10 (1H, d, *J* = 8.9 Hz, HC=C*H*), 4.14 (1H, s, C*H*(O)), 4.13 (2H, q, *J* = 7.4 Hz, OCH_2CH$_3$), 3.66 (1H, d, *J* = 11.7 Hz, $C_{HA,\ HB}$), 3.26 (1H, d, *J* = 11.7 Hz, $C_{HA,\ HB}$), 1.52 (3H, s, OCCH_3), 1.40 (3H, s, OCCH_3), 1.23 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3), 0.98 (3H, s, CCH_3), 0.97 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 168.7 (NC=O), 168.2 (OC=O), 135.9 (C=*C*), 99.3 (*C*=C), 98.1 (O*C*CH$_3$), 76.7 (O*C*H$_2$CH$_3$), 71.3 (OCH$_2$), 60.1 (CH(O)), 33.3 (*C*CH$_3$), 29.3 (OC*C*H$_3$), 21.9 (OC*C*H$_3$), 19.0 (C*C*H$_3$), 18.6 (C*C*H$_3$), 14.3 (OCH$_2$*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3402 (s), 3012 (s), 2992 (s), 1690 (s), 1629 (s), 1197 (s), 731 (s).

HRMS calcd for $C_{14}H_{23}O_5N$ (M+ ·): 285.1576. Found 285.1574.



(*E*)-3-[((*R*)-2,2,5,5-Tetramethyl-[1,3]dioxane-4-carbonyl)-amino]-acrylic acid ethyl ester, (78*E*).

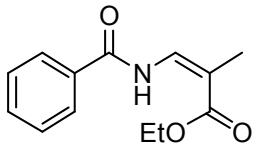
^{1}H NMR (400MHz, $CDCl_3$) δ: 8.35 (1H, bd, *J* = 11.9 Hz, N*H*), 7.91 (1H, dd, *J* = 11.9, 14.2 Hz, *H*C=CH), 5.25 (1H, d, *J* = 14.2 Hz, HC=C*H*), 4.13 (1H, s, C*H*(O)), 4.12 (2H, q, *J* = 7.1 Hz, OCH_2CH$_3$), 3.65 (1H, d, *J* = 11.8 Hz, $C_{HA,\ HB}$), 3.25 (1H, d, *J* = 11.8 Hz, $C_{HA,\ HB}$), 1.44 (3H, s, OCCH_3), 1.38 (3H, s, OCCH_3), 1.21 (3H, t, *J* = 7.1 Hz, OCH$_2$CH_3), 0.98 (3H, s, CCH_3), 0.94 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 166.9 (NC=O), 166.1 (OC=O), 134.8 (C=*C*), 102.1 (*C*=C), 98.5 (O*C*CH$_3$), 77.2 (O*C*H$_2$CH$_3$), 70.2 (OCH$_2$), 59.1 (CH(O)), 32.3 (*C*CH$_3$), 28.4 (OC*C*H$_3$), 20.8 (OC*C*H$_3$), 17.8 (C*C*H$_3$), 17.6 (C*C*H$_3$), 13.3 (OCH$_2$*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3399 (s), 3056 (s), 2993 (s), 1716 (s), 1639 (s), 910 (s), 733 (m). HRMS calcd for $C_{14}H_{23}O_5N$ (M+ ·): 285.1576. Found 285.1572. $[\alpha]_D$ +45.6 (c = 0.5, $CHCl_3$).

General Procedure (E) for the Synthesis of Acyclic Methyl-Enamides (79-81). A solution of *n*-formyl imide (1.0 mmol) in benzene (10 mL) was treated with 1-carbethoxyethylidene

triphenylphosphorane (3.0 mmol) and the resulting mixture heated to 95 °C for 19 hours. Upon reaction completion as indicated by TLC analysis, the solvent was removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 30% EtOAc in 40-60 petroleum ether) to afford the desired enamides **(79-81).**



(*Z*)-3-Benzoylamino-2-methyl-acrylic acid ethyl ester, (79*Z*).

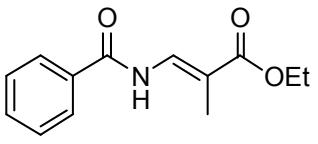
Imide **(69)** (150mg) was added to a solution of 1-carbethoxyethylidene triphenylphosphorane in benzene as per procedure D to generate enamide **(79)** (205mg, 88%) as a mixture of *E* and *Z* isomers, *E*:*Z* ratio 5: 1.

^{1}H NMR (400MHz, $CDCl_3$) δ: 11.40 (1H, d, *J* = 10.8 Hz, N*H*), 7.87 (2H, m, 2x Ar*H*), 7.56 (1H, dd, *J* = 10.9, 1.2 Hz, *H*C=CH), 7.49 (1H, m, Ar*H*), 7.42 (2H, m,2x Ar*H*), 4.20 (2H, q, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 1.85 (3H, d, *J* = 1.3 Hz, =CC*H*$_3$), 1.29 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$).

^{13}C NMR (100MHz, $CDCl_3$) δ: 169.0 (OC=O), 168.1 (NC=O), 134.3 (ArC q). 132.3 (ArC), 131.6 (C=*C*), 127.8 (ArC x2), 126.5 (ArC x2), 104.6 (*C*=C), 59.6 (O*C*H$_2$CH$_3$), 16.3 (OCH$_2$*C*H$_3$), 13.2 (C=C*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3335 (s), 3078 (m), 2983 (s), 1684 (s), 1649 (s), 1267 (m), 1133 (s).

HRMS calcd for $C_{13}H_{15}O_3N$ (M+ ·): 233.1052. Found 233.1053.



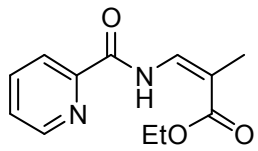
(*E*)-3-Benzoylamino-2-methyl-acrylic acid ethyl ester, (79*E*)

^{1}H NMR (400MHz, $CDCl_3$) δ: 8.19 (1H, bd, *J* = 11.7 Hz, N*H*), 8.10 (1H, dd, *J* = 11.6, 1.2 Hz, *H*C=C), 7.73 (2H, m, 2x Ar*H*), 7.45 (1H, m, Ar*H*), 7.34 (2H, m, 2x Ar*H*), 4.09 (2H, q, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 1.82 (3H, d, *J* = 1.3 Hz, =CC*H*$_3$), 1.20 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$).

^{13}C NMR (100MHz, $CDCl_3$) δ: 168.1 (OC=O), 164.5 (NC=O), 132.8 (ArC q), 132.7 (ArC), 131.9 (C=*C*), 128.9 (ArC x2), 127.3 (ArC x2), 109.0 (*C*=C), 60.6 (O*C*$H_2$$CH_3$), 14.4 (OCH$_2$*C*$H_3$), 10.8 (C=C*C*$H_3$).

IR ν_{max}(film)/cm^{-1} 3335 (s), 3015 (s), 2983 (s), 1684 (s), 1649 (s), 1267 (m), 1133 (s).

HRMS calcd for $C_{13}H_{15}O_3N$ (M+ ·): 233.1052. Found 233.1053.



(*Z*)-2-Methyl-3-[(pyridine-3-carbonyl)-amino]-acrylic acid ethyl ester, (80*Z*).

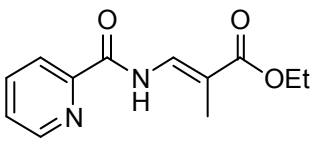
Imide **(70)** (158mg) was added to a solution of 1-carbethoxyethylidene triphenylphosphorane in benzene as per procedure D to generate enamide **(80)** (175mg, 68%) as a mixture of *E* and *Z* isomers, *E*:*Z* ratio 41: 1.

^{1}H NMR (400MHz, $CDCl_3$) δ: 8.64 (1H, dm, *J* = 4.8 Hz, Ar*H*), 8.17 (1H, dt, *J* = 7.8, 1.1 Hz, Ar*H*), 7.82 (1H, td, *J* = 7.7, 1.7 Hz, Ar*H*), 7.49 (1H, dq, *J* = 11.8, 1.3 Hz, *H*C=C), 7.41 (1H, ddd, *J* = 7.6, 4.7, 1.1 Hz, Ar*H*), 4.25 (2H, q, *J* = 7.2 Hz, OC*H*$_2$$CH_3$), 1.87 (3H, d, *J* = 1.3 Hz, =CC*H*$_3$), 1.20 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$).

^{13}C NMR (100MHz, $CDCl_3$) δ: 167.9 (OC=O), 161.3 (NC=O), 147.9 (ArC q), 147.8 (ArC), 136.3 (ArC), 132.4 (C=*C*), 125.8 (ArC), 122.1 (ArC), 105.9 (*C*=C), 59.5 (O*C*$H_2$$CH_3$), 15.5 (OCH$_2$*C*$H_3$), 13.3 (C=C*C*$H_3$).

IR ν_{max}(film)/cm^{-1} 3391 (s), 3012 (s), 2963 (s), 1694 (s), 1632 (s), 996 (s).

HRMS calcd for $C_{12}H_{14}O_3N_2$ (M+ ·): 234.1004. Found 234.1007.



(*E*)-2-Methyl-3-[(pyridine-3-carbonyl)-amino]-acrylic acid ethyl ester, (80*E*).

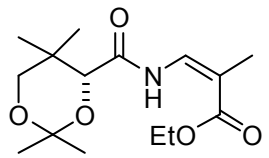
^{1}H NMR (400MHz, $CDCl_3$) δ: 9.87 (1H, d, *J*= 12.4 Hz, N*H*), 8.52 (1H, dm, *J* = 4.8 Hz, Ar*H*), 8.14 (1H, dm, *J*= 7.8 Hz, Ar*H*), 8.06 (1H, dq *J* = 12.5, 1.3 Hz, *H*C=C), 7.82 (1H, td, *J* = 7.7, 1.6 Hz,

Ar*H*), 7.45 (1H, ddd, *J* = 7.6, 4.7, 1.2 Hz, Ar*H*), 4.15 (2H, q, *J* = 7.1 Hz, OCH_2CH$_3$), 1.89 (3H, d, *J* = 1.4 Hz, =CCH_3), 1.22 (3H, t, *J* = 7.1 Hz, OCH$_2$CH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 168.2 (OC=O), 161.7 (NC=O), 148.4 (ArC q), 148.3 (ArC), 137.7 (ArC), 131.05 (C=*C*), 127.2 (ArC), 123.0 (ArC), 109.9 (*C*=C), 60.52 (O*C*H$_2$CH$_3$), 14.43 (OCH$_2$*C*H$_3$), 10.84 (C=C*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3367 (s), 3018 (m), 2986 (s), 1692 (s), 1652 (s), 1498 (s), 1265 (m).

HRMS calcd for $C_{12}H_{14}O_3N_2$ (M+ ·): 234.1004. Found 234.1006.



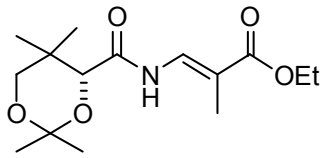
(*Z*)-2-Methyl-3-[((*R*)-2,2,5,5-tetramethyl-[1,3]dioxane-4-carbonyl)-amino]-acrylic acid ethyl ester, (81*Z*).

Imide **(71)** (186mg) was added to a solution of 1-carbethoxyethylidene triphenylphosphorane in benzene as per procedure D to generate enamide **(81)** (175mg, 65%) as a mixture of *E* and *Z* isomers, *E*:*Z* ratio 3: 1

^{1}H NMR (400MHz, $CDCl_3$) δ: 10.9 (1H, bd, *J* = 12.4 Hz, N*H*), 7.26 (1H, dd, *J* = 11.5, 1.3 Hz, *H*C=C), 4.18 (2H, qd, *J* = 7.2, 1.4 Hz, OCH_2CH$_3$)), 4.13 (1H, s, C*H*(O)), 3.66 (1H, d, *J* = 11.7 Hz, C$_{HA,\ HB}$), 3.26 (1H, d, *J* = 11.7 Hz, C$_{HA,\ HB}$), 1.79 (3H, d, *J* = 1.3 Hz, CH_3), 1.51 (3H, s, OCCH_3), 1.39 (3H, s, OCCH_3), 1.25 (3H, t, *J* = 7.1 Hz, OCH$_2$CH_3), 0.98 (3H, s, CCH_3), 0.96 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 167.6 (NC=O), 167.3 (OC=O), 131.3 (C=*C*), 105.5 (*C*=C), 98.2 (O*C*CH$_3$), 75.7 (O*C*H$_2$CH$_3$), 70.4 (OCH$_2$), 60.1 (CH(O)), 32.2 (*C*CH$_3$), 28.4 (OC*C*H$_3$), 20.9 (OC*C*H$_3$), 18.0 (C*C*H$_3$), 17.6 (C*C*H$_3$), 15.4 (C=C*C*H$_3$), 13.4 (OCH$_2$*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3410 (s), 3036 (m), 2992 (s), 1695 (s), 1652 (s). HRMS calcd for $C_{15}H_{25}O_5N$ (M+ ·): 299.1733. Found 299.1735. $[\alpha]_D$ +62.1 (c = 1.1, $CHCl_3$).

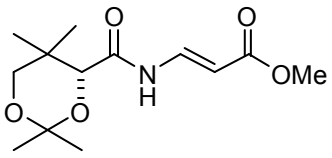


(*E*)-2-Methyl-3-[((*R*)-2,2,5,5-tetramethyl-[1,3]dioxane-4-carbonyl)-amino]-acrylic acid ethyl ester, (81*E*).

^{1}H NMR (400MHz, $CDCl_3$) δ: 8.25 (1H, bd, *J* = 12.3, N*H*), 7.86 (1H, dq, *J* = 12.3, 1.4 Hz, *H*C=C), 4.14 (1H, s, C*H*(O)), 4.10 (2H, qd, *J* = 7.2, 1.2 Hz, OCH_2CH$_3$)), 3.64 (1H, d, *J* = 11.8 Hz, $C_{HA,\ HB}$), 3.22 (1H, d, *J* = 11.8 Hz, $C_{HA,\ HB}$), 1.71 (3H, d, *J* = 1.4 Hz, =CCH_3), 1.41 (3H, s, OCCH_3), 1.39 (3H, s, OCCH_3), 1.25 (3H, t, *J* = 7.1 Hz, OCH$_2$CH_3), 0.97 (3H, s, CCH_3), 0.91 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 168.0 (NC=O), 167.4 (OC=O), 130.1 (C=*C*), 109.2 (*C*=C), 99.3 (O*C*CH$_3$), 77.2 (O*C*H$_2$CH$_3$), 71.2 (OCH$_2$), 60.5 (CH(O)), 33.2 (*C*CH$_3$), 29.4 (OC*C*H$_3$), 21.8 (OC*C*H$_3$), 18.8 (C*C*H$_3$), 18.6 (C*C*H$_3$), 14.38 (C=C*C*H$_3$), 10.4 (OCH$_2$*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3410 (s), 3028 (s), 2992 (s), 1695 (s), 1652 (s). HRMS calcd for $C_{15}H_{25}O_5N$ (M+·): 299.1733. Found 299.1735. $[\alpha]_D$ +40.7 (c = 1.1, $CHCl_3$).



(*R*,*E*)-Methyl 3-(2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamido)acrylate, (82*E*).

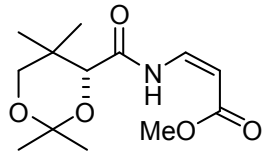
A solution of *N*-formyl imide **(71)** (193mg, 0.89 mmol) in benzene (10 mL) was treated with methyltriphenylphosphoranylidene acetate (888mg, 2.7 mmol) and the resulting mixture heated to 95 ^{o}C for 19 hours. Upon reaction completion as indicated by TLC analysis, the solvent was removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 30% EtOAc in 40-60 petroleum ether) to afford the desired enamide **(82)** (220mg, 91%) as a mixture of *E* and *Z* isomers, *E*: *Z* ratio 2:1.

^{1}H NMR (400MHz, $CDCl_3$) δ: 8.42 (1H, bd, *J* = 12.0 Hz, N*H*), 8.01 (1H, dd, *J* = 12.0, 14.2 Hz, *H*C=CH), 5.62 (1H, d, *J* = 14.2 Hz, HC=C*H*), 4.22 (1H, s, C*H*(O)), , 3.73 (4H, m, OCH_3 and $C_{HA,}$

$_{HB}$), 3.34 (1H, d, *J* = 11.8 Hz, $C_{HA, HB}$), 1.54 (3H, s, OCCH_3), 1.47 (3H, s, OCCH_3), 1.07 (3H, s, CCH_3), 1.03 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 167.9 (NC=O), 167.6 (OC=O), 136.2 (*C*=C), 102.5 (C=*C*), 99.6 (O*C*CH_3), 77.2 (O*C*H_3), 71.3 (CH_2), 51.4 (CH(O)), 33.4 (*C*CH_3), 29.5 (OC*C*H_3), 21.9 (OC*C*H_3), 18.8 (C*C*H_3), 18.7 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3330 (s), 3016 (s), 2992 (s), 2954 (s), 1720 (s), 1640 (s). HRMS calcd for $C_{13}H_{22}O_5N$ ($M+H^+$): 272.1498. Found 272.1494. $[\alpha]_D$ +137.6 (c = 1.0, $CHCl_3$).

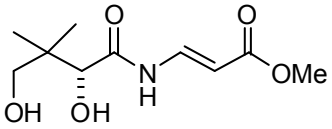


(*R*,*Z*)-Methyl 3-(2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamido)acrylate, (82*Z*).

^{1}H NMR (400MHz, $CDCl_3$) δ: 11.02 (1H, bd, *J* = 11.7Hz, N*H*), 7.37 (1H, dd, *J* = 9.0, 11.7 Hz, *H*C=CH), 5.11 (1H, d, *J* = 8.9 Hz, HC=C*H*), 4.15 (1H, s, C*H*(O)), , 3.67 (4H, m, OCH_3 and $C_{HA, HB}$), 3.26 (1H, d, *J* = 11.7 Hz, $C_{HA, HB}$), 1.53 (3H, s, OCCH_3), 1.41 (3H, s, OCCH_3), 0.98 (3H, s, CCH_3), 0.97 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 168.8 (NC=O), 168.6 (OC=O), 136.1 (*C*=C), 99.3 (O*C*CH_3), 97.6 (C=*C*), 77.3 (O*C*H_3), 71.3 (CH_2), 51.3 (CH(O)), 33.3 (*C*CH_3), 29.4 (OC*C*H_3), 21.9 (OC*C*H_3), 19.0 (C*C*H_3), 18.6 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3325 (s), 3056 (s), 2955 (s), 1696 (s), 1629 (s). HRMS calcd for $C_{13}H_{22}O_5N$ ($M+H^+$): 272.1498. Found 272.1501. $[\alpha]_D$ +108.0 (c = 1.1, $CHCl_3$).



(*R*,*E*)-Methyl 3-(2,4-dihydroxy-3,3-dimethylbutanamido)acrylate, (83*E*).

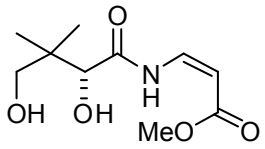
A solution of enamide **(82*E*)** (391mg, 1.44 mmol) in MeCN (12 mL) was treated with Bi (III)Cl_3 (45mg, 0.14 mmol) and H_2O (4 drops) and stirred at room temperature for 3hrs. Upon completion

by TLC analysis, the reaction was quenched with $NaHCO_3$ (2 mL) and stirred for a further 20mins. After this time, the mixture was filtered through Celite, dried over Na_2SO_4, filtered a second time, and then the solvent removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 30% EtOAc in 40-60 petroleum ether) to afford the desired diol **(83*E*)** (73mg, 50%).

^{1}H NMR (400MHz, $CDCl_3$) δ: 7.99 (1H, d, *J* = 14.2 Hz, *H*C=CH), 5.78 (1H, d, *J* = 14.2 Hz, HC=C*H*), 4.05 (1H, s, C*H*(O)), 3.74 (3H, s, OCH_3), 3.52 (1H, d, *J* = 10.9 Hz, $C_{HA,\ HB}$), 3.41 (1H, d, *J* = 10.9 Hz, $C_{HA,\ HB}$), 0.96 (3H, s, CCH_3), 0.95 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 175.1 (NC=O), 170.2 (OC=O), 138.9 (*C*=C), 102.5 (C=*C*), 77.1 (CH(O)), 69.8 (CH_2), 51.9 (O*C*H_3), 40.8 (*C*CH_3), 21.5 (C*C*H_3), 20.5 (C*C*H_3)

IR ν_{max}(film)/cm^{-1} 3291 (s), 3068 (s), 2992 (s), 1721 (s), 1670 (s), 1169 (s). HRMS calcd for $C_{10}H_{18}O_5N$ ($M+H^+$): 232.1185. Found 232.1184. $[\alpha]_D$ +131.7 (c = 1.4, $CHCl_3$).



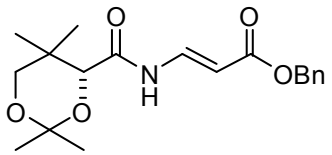
(*R*,*Z*)-Methyl 3-(2,4-dihydroxy-3,3-dimethylbutanamido)acrylate, (83*Z*).

A solution of enamide **(82*Z*)** (154mg, 0.57 mmol) in MeCN (6 mL) was treated with Bi (III)Cl_3 (89mg, 0.28 mmol) and H_2O (4drops) and stirred at room temperature for 3hrs. Upon completion by TLC analysis, the reaction was quenched with $NaHCO_3$ (1.5ml) and stirred for a further 20mins. After this time, the mixture was filtered over Celite, dried over Na_2SO_4 , filtered a second time, and then the solvent removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 30% EtOAc in 40-60 petroleum ether) to afford the desired diol, **(83*Z*).**

^{1}H NMR (400MHz, $CDCl_3$) δ: 7.47 (1H, d, *J* = 9.1 Hz, *H*C=CH), 5.24 (1H, d, *J* = 8.9 Hz, HC=C*H*), 4.09 (1H, s, C*H*(O)), 3.75 (3H, s, OCH_3), 3.53 (1H, d, *J* = 10.8 Hz, $C_{HA,\ HB}$), 3.44 (1H, d, *J* = 10.8 Hz, $C_{HA,\ HB}$), 0.97 (3H, s, CCH_3), 0.96 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 174.6 (NC=O), 170.3 (OC=O), 137.6(*C*=C), 98.0(C=*C*), 76.7(CH(O)), 69.8 (CH_2), 51.8(O*C*H_3), 40.9(*C*CH_3), 21.4(C*C*H_3), 20.6(C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3321 (s), 3019 (s), 2956 (s), 1721 (s), 1650 (s). HRMS calcd for $C_{10}H_{18}O_5N$ ($M+H^+$): 232.1185. Found 232.1188. $[\alpha]_D$ +120.7 (c = 1.3, $CHCl_3$).



(*R*,*E*)-Benzyl-3-(2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamido)acrylate, (85*E*).

A solution of *n*-formyl imide **(71)** (2.162g, 9.9 mmol) in benzene (100 mL) was treated with benzyltriphenylphosphoranylidene (12.3g, 0.03 mol) and the resulting mixture heated to 95 ^oC for 19 hours. Upon reaction completion as indicated by TLC analysis, the solvent was removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 30% EtOAc in 40-60 petroleum ether) to afford the desired enamides **(85)** (2.99g, 87%) as a mixture of *E* and *Z* isomers *E*: *Z* ratio 3: 1.

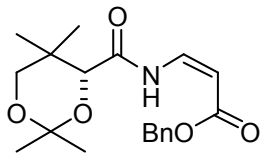
^{1}H NMR (400MHz, $CDCl_3$) δ: 8.44 (1H, bd, *J* = 12.1, N*H*), 8.04 (1H, dd, *J* = 14.2, 12.1 Hz, *H*C=CH), 7.37 (5H, m, 5x Ar*H*), 5.68 (1H, d, *J* = 14.2 Hz, HC=C*H*), 5.22 (2H, s, Bn*H*), 4.23 (1H, s, C*H*(O)), 3.74 (1H, d, *J* = 11.8 Hz, $C_{HA,\ HB}$), 3.34 (1H, d, *J* = 11.8 Hz, $C_{HA,\ HB}$), 1.54 (3H, s, OCCH_3), 1.48 (3H, s, OCCH_3), 1.08 (3H, s, CCH_3), 1.03 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 167.9 (NC=O), 166.9 (OC=O), 136.4 (*C*=C), 136.2 (ArC q), 128.5 (C=*C*), 128.2 (2x Ar*C*), 128.1 (2x ArC), 102.7 (ArC), 99.6 (O*C*CH_3), 77.2 (CH(O)), 71.3 (Bn-CH_2), 66.0 (CH_2), 33.4 (*C*CH_3), 29.5 (OC*C*H_3), 21.9 (OC*C*H_3), 18.8 (C*C*H_3), 18.7 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3332 (s), 3057(s), 2992 (s), 2959 (s), 2872 (s), 1716 (s), 1637 (s), 1496 (s).

HRMS calcd for $C_{19}H_{26}O_5N$ ($M+H^+$): 348.1811. Found 348.1812.

$[\alpha]_D$ +125.1 (c = 1.1, $CHCl_3$).



(*R*,*Z*)-Benzyl 3-(2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamido)acrylate, (85*Z*).

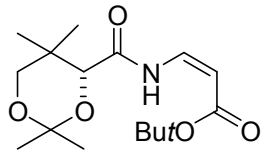
^{1}H NMR (400MHz, $CDCl_3$) δ: 11.19 (1H, bd, *J* = 11.5, N*H*), 7.49 (1H, dd, *J* = 11.7, 9.0 Hz, *H*C=CH), 7.39 (5H, m, 5x Ar*H*), 5.26 (1H, d, *J* = 8.9 Hz, HC=C*H*), 5.22 (2H, s, Bn*H*), 4.25 (1H, s, C*H*(O)), 3.77 (1H, d, *J* = 11.7 Hz, $C_{HA,\ HB}$), 3.37 (1H, d, *J* = 11.7 Hz, $C_{HA,\ HB}$), 1.63 (3H, s, OCCH_3), 1.51 (3H, s, OCCH_3), 1.09 (3H, s, CCH_3), 1.08 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 168.8 (N*C*=O), 168.1(O*C*=O), 136.6 (*C*=C), 135.9 (ArC q), 128.6 (2x ArC), 128.3 (C=*C*), 128.2 (2x ArC), 99.3 (O*C*CH_3), 97.6 (*C*=C), 77.3 (CH(O)), 71.3 (CH_2), 65.9 (CH_2), 33.3 (*C*CH_3), 29.3 (OC*C*H_3), 21.9 (OC*C*H_3), 19.0 (C*C*H_3), 18.6 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3329 (s), 3067 (s), 2992 (s), 2957 (s), 2872 (s), 1712 (s), 1692 (s).

HRMS calcd for $C_{19}H_{26}O_5N$ ($M+H^+$): 348.1811. Found 348.1809.

$[\alpha]_D$ +75.6 (c = 0.9, $CHCl_3$)



(*R*,*Z*)-*tert*-Butyl 3-(2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamido)acrylate, (88*Z*).

A solution of *n*-formyl imide **(71)** (500mg, 2.3 mmol) in benzene (20 mL) was treated with *t*-butoxycarbonylmethylene triphenylphosphorane (2.59g, 6.9 mmol) and the resulting mixture heated to 95 ^{o}C for 19 hrs. Upon reaction completion as indicated by TLC analysis, the solvent was removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 30% EtOAc in 40-60 petroleum ether) to afford the desired enamides **(88)** (614mg, 85%) as a mixture of *E* and *Z* isomers *E*: *Z* ratio 4:1.

^{1}H NMR (400MHz, $CDCl_3$) δ: 11.19 (1H, bd, *J* = 11.1 Hz, N*H*), 7.35 (1H, dd, *J* = 11.5, 8.9 Hz, *H*C=CH), 5.08 (1H, d, *J* = 9.0 Hz, HC=C*H*), 4.19 (1H, s, C*H*(O)), 3.72 (1H, d, *J* = 11.7 Hz, $C_{HA,}$

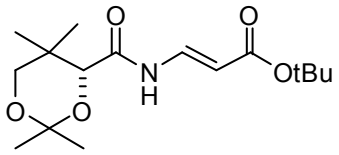
$_{HB}$), 3.32 (1H, d, *J* = 11.7 Hz, $C_{HA,\ HB}$), 1.58 (3H, s, OCCH_3), 1.49 (9H, s, C(CH_3)$_3$), 1.47 (3H, s, OCCH_3), 1.05 (6H, s, 2x CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ:. 168.8 (NC=O), 167.8 (OC=O), 135.1 (*C*=C), 99.9 (C=*C*), 99.2 (O*C*CH$_3$), 80.5 (*C* (CH$_3$)$_3$), 77.3 (CH(O)), 71.4 (CH_2), 33.2 (*C*CH$_3$), 29.3 (OC*C*H$_3$), 28.3 (CH$_3$ x2), 21.9 (OC*C*H$_3$), 19.1 (C*C*H$_3$), 18.6 (C*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3320 (s), 3019(s), 2980 (s), 2872 (s), 1686 (s), 1628 (s).

HRMS calcd for $C_{16}H_{28}O_5N$ ($M+H^+$): 314.1967. Found 314.1965.

$[\alpha]_D$ +85.5 (c = 1.9, $CHCl_3$).



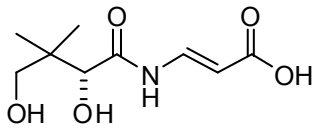
(*R*,*E*)-*tert*-Butyl 3-(2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamido)acrylate, (88*E*).

^{1}H NMR (400MHz, $CDCl_3$) δ: 8.46 (1H, bd, *J* = 11.8 Hz, N*H*), 7.76 (1H, dd, *J* = 11.7, 14.2 Hz, *H*C=CH), 5.48 (1H, d, *J* = 14.2 Hz, HC=C*H*), 4.10 (1H, s, C*H*(O)), 3.61 (1H, d, *J* = 11.8 Hz, $C_{HA,\ HB}$), 3.20 (1H, d, *J* = 11.8 Hz, $C_{HA,\ HB}$), 1.39 (3H, s, OCCH_3), 1.38 (9H, s, C(CH_3)$_3$), 1.35 (3H, s, OCCH_3), 0.95 (3H, s, CCH_3), 0.91 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 167.9 (NC=O), 166.4 (OC=O), 134.9 (*C*=C), 105.1 (*C*=C), 99.5 (O*C*CH$_3$), 80.2 (*C*(CH$_3$)$_3$), 77.2 (CH(O)), 71.3 (CH_2), 33.4 (*C*CH$_3$), 29.5 (OC*C*H$_3$), 28.2 (CH$_3$ x2), 21.9 (OC*C*H$_3$), 20.2 (CH$_3$), 18.8 (C*C*H$_3$), 18.7 (C*C*H$_3$)

IR ν_{max}(film)/cm^{-1} 3336 (s), 3028 (s), 2976 (s), 1709 (s), 1638 (s) 1499 (s).

HRMS calcd for $C_{16}H_{28}O_5N$ ($M+H^+$): 314.1967. Found 314.1971. $[\alpha]_D$ +105.9 (c = 1.5, $CHCl_3$).



(*R*,*E*)-3-(2,4-Dihydroxy-3,3-dimethylbutanamido)acrylic acid, CJ-15,801 (30).

A solution of (*R*,*E*)-*tert*-butyl 3-(2,4-dihydroxy-3,3-dimethylbutanamido)acrylate **(33)** (195mg, 0.62 mmol) in formic acid (7 mL) was stirred at room temperature for 90 mins. After this time, the excess formic acid was removed under vacuum. The crude residue was then taken up into MeOH (7 mL) and *p*-toluenesulfonic acid added (11mg, 0.062 mmol) and the resulting mixture stirred for 75 mins. After this time, the solvent was removed under vacuum, and the crude residue purified by flash column chromatography (silica gel, 50% EtOAc in 40-60 petroleum ether) to afford CJ-15,801 **(33)** in 20% yield. All spectral data matches literature (*Org. Lett.* **2004**, 6, 27).

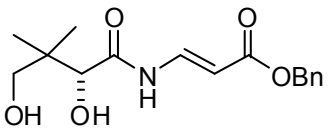
^{1}H NMR (400MHz, MeOD) δ: 7.94 (1H, d, *J* = 14.2 Hz, *H*C=CH), 5.69 (1H, d, *J* = 14.2 Hz, HC=C*H*), 4.02 (1H, s, C*H*(O)), 3.50 (1H, d, *J* = 10.9 Hz, $C_{HA, HB}$), 3.38 (1H, d, *J* = 10.9 Hz, $C_{HA, HB}$), 0.94 (3H, s, CCH_3), 0.93 (3H, s, CCH_3).

^{13}C NMR (100MHz, MeOD) δ: 173.4 (OC=O), 170.4 (NC=O), 137.1 (*C*=C), 102.1 (C=*C*), 75.6 (CH(O)), 68.2 (CH_2), 39.2 (*C*CH_3), 19.9 (C*C*H_3), 18.8 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3398 (br), 3011 (s), 2952 (s), 1774 (s), 1639 (s).

HRMS calcd for $C_9H_{15}O_5N$ ($M+H^+$): 218.1028 Found 218.1025.

$[\alpha]_D$ +58.0 (c = 0.6, MeOH).



(*R*,*E*)-Benzyl 3-(2,4-dihydroxy-3,3-dimethylbutanamido)acrylate, (86*E*)

A solution of enamide (**85*E***) (1.01g, 2.9 mmol) in MeCN (40 mL) was treated with Bi(III)Cl_3 (92mg, 0.29 mmol) and H_2O (6drops) and stirred at room temperature for 3hrs. Upon completion by TLC analysis, the reaction was quenched with $NaHCO_3$ (7ml) and stirred for a further 20mins. After this time, the mixture was filtered over Celite, dried over Na_2SO_4 filtered a second time, and then the solvent removed under vacuum. The crude residue was then purified by flash column

chromatography (silica gel, 10% to 50% EtOAc in 40-60 petroleum ether) to afford the desired diol **(86*E*)**.

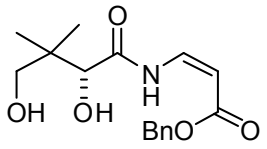
^{1}H NMR (400MHz, $CDCl_3$) δ: 8.04 (1H, bd, *J* = 14.2Hz, *H*C=CH), 7.34 (5H, m, 5x Ar*H*), 5.83 (1H, d, *J* = 14.2Hz, HC=C*H*), 5.18 (2H, s, Bn*H*), 4.11 (1H, s, C*H*(O)), 3.52 (1H, d, *J* = 10.9 Hz, $C_{HA,\ HB}$), 3.42 (1H, d, *J* = 10.9 Hz, $C_{HA,\ HB}$), 0.97 (3H, s, CCH_3), 0.96 (3H, s, CCH_3)

^{13}C NMR (100MHz, $CDCl_3$) δ: 175.1 (NC=O), 169.5 (OC=O), 139.2 (ArC), 137.8 (ArC q), 129.6 (2x ArC), 129.5 (CH(O)), 129.2 (2x ArC), 102.7 (*C*=C), 77.12 (C=*C*), 69.9 (CH_2), 67.1 (CH_2), 40.9 (*C*CH_3), 21.6 (C*C*H_3), 20.6 (C*C*H_3)

IR ν_{max}(film)/cm^{-1} 3327 (s), 3045 (s), 2962 (s), 1698 (s), 1634 (s).

HRMS calcd for $C_{16}H_{22}O_5N$ ($M+H^+$): 308.1498. Found 308.1501.

$[\alpha]_D$ +75.0 (c = 1.8, $CHCl_3$).



(*R*,*Z*)-Benzyl 3-(2,4-dihydroxy-3,3-dimethylbutanamido)acrylate, (86*Z*)

A solution of enamide **(85*Z*)** (1.11g, 3.2 mmol) in MeCN (40 mL) was treated with Bi(III)Cl_3 (100mg, 0.32 mmol) and H_2O (6drops) and stirred at room temperature for 3hrs. Upon completion by TLC analysis, the reaction was quenched with $NaHCO_3$ (7ml) and stirred for a further 20mins. After this time, the mixture was filtered over Celite, dried over Na_2SO_4 filtered a second time, and then the solvent removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 50% EtOAc in 40-60 petroleum ether) to afford the desired diol **(86*Z*)**.

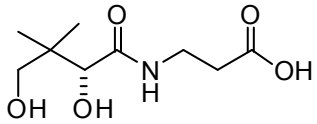
^{1}H NMR (400MHz, $CDCl_3$) δ: 7.49 (1H, d, *J* = 9.0Hz, *H*C=CH), 7.35 (5H, m, 5x Ar*H*), 5.26 (1H, d, *J* = 9.0Hz, HC=C*H*), 5.18 (2H, s, Bn*H*), 4.11 (1H, s, C*H*(O)), 3.53 (1H, d, *J* = 10.9 Hz, $C_{HA,\ HB}$), 3.44 (1H, d, *J* = 10.9 Hz, $C_{HA,\ HB}$), 0.97 (3H, s, CCH_3), 0.96 (3H, s, CCH_3)

^{13}C NMR (100MHz, $CDCl_3$) δ: 174.6 (NC=O), 169.5 (OC=O), 137.8 (*C*=C), 137.6 (ArC q), 129.6(2x ArC), 129.4 (2x ArC), 129.3 (CH(O)) , 98.8 (*C*=C), 76.8 (C=*C*), 69.9 (CH_2), 67.0 (CH_2), 40.9 (*C*CH_3), 21.4 (C*C*H_3), 20.7 (C*C*H_3)

IR ν_{max}(film)/cm^{-1} 3336 (s), 3028 (s), 2962 (s), 2876 (s), 1691 (s), 1626 (s), 1189 (s).

HRMS calcd for $C_{16}H_{22}O_5N$ ($M+H^+$): 308.1498. Found 308.1501

$[\alpha]_D$ +53.3 (c = 1.8, $CHCl_3$)



(*R*)-3-(2,4-Dihydroxy-3,3-dimethylbutanamido)propanoic acid, (9).

A solution of (*R*,*Z*)-benzyl 3-(2,4-dihydroxy-3,3-dimethylbutanamido)acrylate **(86*E*)** (218mg, 0.7 mmol) in MeOH (5 mL) was treated with Pd/C (10% *wt/wt*). The heterogenous mixture was then stirred under a H_2 atmosphere for 24hrs. Upon reaction completion as indicated by TLC analysis, the solvent was removed under vacuum. The crude residue was found by NMR to be the desired pantothenate **(9)** in 83% yield, with no further purification necessary.

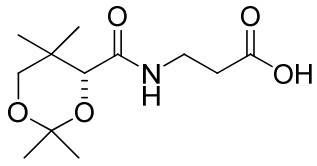
^{1}H NMR (400MHz, MeOD) δ: 3.92 (1H, s, C*H*(O)), 3.46 (4H, m, OCH_2 and NCH_2), 2.56 (2H, t, *J* = 6.4 Hz, CH_2), 0.94 (6H, s, 2x CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 176.1 (OC=O), 175.5 (NC=O), 77.3 (CH(O)), 70.4 (OCH_2), 40.4 (*C*CH_3), 35.8 (NCH_2), 34.8 (CH_2), 21.3 (C*C*H_3), 20.9 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3700 (v, br), 3023 (s), 2948 (s), 1721 (m), 1650 (s).

HRMS calcd for $C_9H_{17}O_5N$ (M+ ·): 219.1107. Found 219.1110.

$[\alpha]_D$ +82.4 (c = 1.3, MeOH).



(*R*)-3-(2,2,5,5-Tetramethyl-1,3-dioxane-4-carboxamido)propanoic acid, (97).

A solution of (*R*,*Z*)-benzyl 3-(2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamido)acrylate **(85)** (220mg, 6.3 mmol) in MeOH (5 mL) was treated with Pd/C (10% *wt/wt*). The heterogenous mixture was then stirred under a H_2 atmosphere for 24hrs. Upon reaction completion as indicated by TLC analysis at 24hrs, the solvent was removed under vacuum. The crude residue was found

by NMR to be the clean, desired ketal-pantothenate **(97)** in 85% yield, with no further purification necessary.

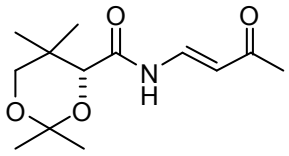
^{1}H NMR (400MHz, $CDCl_3$) δ: 7.07 (1H, t, *J* = 6.0Hz, N*H*), 4.13 (1H, s, C*H*(O)), 3.71 (1H, d, *J* = 11.7 Hz, $C_{HA,\ HB}$), 3.56 (2H, m, NCH_2), 3.30 (1H, d, *J* = 11.7 Hz, $C_{HA,\ HB}$), 2.63 (2H, t, *J* = 6.2Hz, CH_2), 1.48 (3H, s, OCCH_3), 1.45 (3H, s, OCCH_3), 1.05 (3H, s, CCH_3), 0.99 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 176.7 (OC=O), 170.2 (NC=O), 99.1 (O*C*CH_3), 77.1 (CH(O)), 71.4 (OCH_2), 34.1 (NCH_2), 33.9 (CH_2), 32.9 (*C*CH_3), 29.4 (OC*C*H_3), 22.0 (OC*C*H_3), 18.8 (C*C*H_3), 18.7 (C*C*H_3)

IR ν_{max}(film)/cm^{-1} 3420 (s), 2992 (br), 1731 (s), 1642 (s).

HRMS calcd for $C_{12}H_{22}O_5N$ ($M+H^+$): 260.1498. Found 260.1495.

$[\alpha]_D$ +104.0 (c = 1.2, MeOH).



(*R*,*E*)-2,2,5,5-Tetramethyl-*N*-(3-oxobut-1-enyl)-1,3-dioxane-4-carboxamide, (99).

A solution of *N*-formyl imide **(71)** (894mg, 4.1 mmol) in benzene (50 mL) was treated with triphenylphosphoranylidene-2-propanone (3.82g, 0.012 mmol) and the resulting mixture heated to 95 °C for 19 hours. Upon reaction completion as indicated by TLC analysis (19hrs), the solvent was removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 30% EtOAc in 40-60 petroleum ether) to afford the desired enamide **(99)** (682mg, 65%) as the *Z* only isomer.

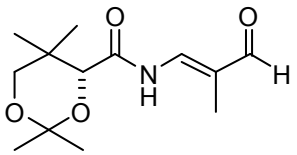
^{1}H NMR (400MHz, $CDCl_3$) δ: 11.95 (1H, bd, *J* = 9.7, N*H*), 7.33 (1H, dd, *J* = 11.5, 8.6 Hz, *H*C=CH), 5.58 (1H, d, *J* = 8.6 Hz, HC=C*H*), 4.20 (1H, s, C*H*(O)), 3.72 (1H, d, *J* = 11.7 Hz, $C_{HA,\ HB}$), 3.32 (1H, d, *J* = 11.7 Hz, $C_{HA,\ HB}$), 2.23 (3H, s, O=CCH_3), 1.65 (3H, s, OCCH_3), 1.45 (3H, s, OCCH_3), 1.01 (3H, s, CCH_3), 1.00 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 200.6 (O=*C*CH_3), 169.7 (NC=O), 135.1 (*C*=C), 105.3 (C=*C*), 99.3 (O*C*CH_3), 77.3 (O=C*C*H_3), 71.3 (CH_2), 33.3 (*C*CH_3), 30.7 (C*H*(O)), 29.4 (OC*C*H_3), 21.8 (O*C*CH_3), 19.0 (C*C*H_3), 18.6 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3290 (s), 3011 (s), 2961 (s), 1702 (s), 1588 (s).

HRMS calcd for $C_{13}H_{22}O_4N$ ($M+H^+$): 256.1549. Found 256.1541.

$[\alpha]_D$ +120.4 (c = 1.1, $CHCl_3$).



(*R*,*E*)-2,2,5,5-Tetramethyl-*N*-(3-oxobut-1-enyl)-1,3-dioxane-4-carboxamide, (101).

A solution of *n*-formyl imide **(71)** (895mg, 4.1 mmol) in benzene (50 mL) was treated with 2-triphenylphosphoranylidene propionaldehyde (3.82g, 0.012 mmol) and the resulting mixture was heated to 95 ^oC for 19 hrs. Upon reaction completion as indicated by TLC analysis (19hrs), the solvent was removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 30% EtOAc in 40-60 petroleum ether) to afford the desired enamide **(101)** (651mg, 62%) as the *E* only isomer.

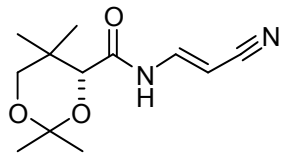
^{1}H NMR (400MHz, $CDCl_3$) δ: 9.32 (1H, s, O=C*H*), 8.59 (1H, bd, *J* = 12.0 Hz, N*H*), 7.58 (1H, d, *J* = 12.2 Hz, *H*C=C), 4.20 (1H, s, C*H*(O)), 3.68 (1H, d, *J* = 11.8 Hz, $C_{HA,\ HB}$), 3.28 (1H, d, *J* = 11.8 Hz, $C_{HA,\ HB}$), 1.68 (3H, s, =CCH_3), 1.47 (3H, s, OCCH_3), 1.41 (3H, s, OCCH_3), 1.01 (3H, s, CCH_3), 0.97 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 192.3 (O=CH), 167.7 (NC=O), 139.9 (*C*=C), 121.0 (C=*C*CH_3), 99.6 (O*C*CH_3), 77.4 (*C*H(O)), 71.2 (CH_2), 33.4 (*C*CH_3), 29.4 (C=*C*H_3), 21.8 ($OCCH_3$), 18.9 ($OCCH_3$), 18.7 (CCH_3), 7.4 (CCH_3).

IR ν_{max}(film)/cm^{-1} 3403 (s), 3012 (s), 2991 (s), 2960 (s), 2873 (s), 1716 (s), 1644 (s).

HRMS calcd for $C_{13}H_{22}O_4N$ ($M+H^+$): 256.1549. Found 256.1546.

$[\alpha]_D$ +123.1 (c = 1.4, $CHCl_3$).



(*R*,*E*)-*N*-(2-Cyanovinyl)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide (104*E*).

A solution of *n*-formyl imide **(71)** (806mg, 3.7mmol) in benzene (50 mL) was treated with triphenylphosphoranylidene acetonitrile (3.31g, 0.01 mmol) and the resulting mixture heated to 95 ^{o}C for 19 hours. Upon reaction completion as indicated by TLC analysis (20hrs), the solvent was removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 20% EtOAc in 40-60 petroleum ether) to afford the desired conjugated enamide **(104)** (822mg, 93%) as a mixture of *E* and *Z* isomers in a 1: 6 ratio.

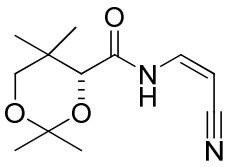
^{1}H NMR (400MHz, $CDCl_3$) δ: 8.45 (1H, bd, *J* = 10.7Hz, N*H*), 7.50 (1H, dd, *J* = 10.7, 14.7 Hz, *H*C=CH), 5.15 (1H, d, *J* = 14.7 Hz, HC=C*H*), 4.12 (1H, s, C*H*(O)), 3.65 (1H, d, *J* = 11.82Hz, $C_{HA,\ HB}$), 3.25 (1H, d, *J* = 11.81 Hz, $C_{HA,\ HB}$), 1.45 (3H, s, OCCH_3), 1.40 (3H, s, OCCH_3), 1.00 (3H, s, CCH_3), 0.95 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 167.8 (NC=O), 140.1 (C=*C*), 117.6 (C≡N), 99.7 ($OCCH_3$), 81.1 (*C*=C), 77.2 (CH(O)), 71.2 (OCH_2), 33.5 (*C*CH_3), 29.5 (OC*C*H_3), 21.8 (OC*C*H_3), 18.9 (C*C*H_3), 18.7 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3346 (s), 3025 (s), 2992 (s), 2219 (s), 1700 (s), 1623 (s).

HRMS calcd for $C_{12}H_{19}O_3N_2$ ($M+H^+$): 239.1396. Found 239.1399.

$[\alpha]_D$ +127.3 (c = 1.0, $CHCl_3$).



(*R*,*Z*)-*N*-(2-Cyanovinyl)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide, (104*Z*).

^{1}H NMR (400MHz, $CDCl_3$) δ: 9.00 (1H, bd, *J* = 10.9 Hz, N*H*), 7.56 (1H, dd, *J* = 10.9, 8.9 Hz, *H*C=CH), 4.71 (1H, d, *J* = 8.9 Hz, HC=C*H*), 4.25 (1H, s, C*H*(O)), 3.75 (1H, d, *J* = 11.8Hz, $C_{HA,\ HB}$),

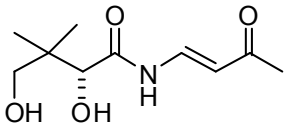
3.35 (1H, d, J = 11.8 Hz, $C_{HA,\ HB}$), 1.55 (3H, s, OCCH_3), 1.50 (3H, s, OCCH_3), 1.06 (3H, s, CCH_3), 1.05 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 167.8 (NC=O), 139.1 (C=*C*), 115.2 (C≡N), 99.7 ($OCCH_3$), 77.5 (*C*=C), 77.1 (CH(O)), 71.1 (OCH_2), 33.4 (*C*CH_3), 29.3 (OC*C*H_3), 21.8 (OC*C*H_3), 18.9 (C*C*H_3), 18.7 (C*C*H_3)

IR ν_{max}(film)/cm^{-1} 3374 (s), 2992 (s), 2962 (s), 2210 (s), 1719 (s), 1627 (s), 1478 (s)

HRMS calcd for $C_{12}H_{19}O_3N_2$ ($M+H^+$): 239.1396. Found 239.1400

$[\alpha]_D$ +110.8 (c = 1.3, $CHCl_3$).



(*R*,*E*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-oxobut-1-enyl)butanamide, (105).

A solution of enamide **(99)** (1.0 mmol) in MeCN (10 mL) was treated with Bi (III)Cl_3 (0.1 mmol) and H_2O (3drops) and stirred at room temperature for 3hrs. Upon completion by TLC analysis, the reaction was quenched with $NaHCO_3$ (4ml) and stirred for a further 20mins. After this time, the mixture was filtered over Celite, dried over Na_2SO_4 , filtered a second time, and then the solvent removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 50% EtOAc in 40-60 petroleum ether) to afford the desired diol **(105)**.

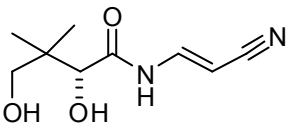
^{1}H NMR (400MHz, $CDCl_3$) δ: 7.31 (1H, dd, J = 11.4, 8.63 Hz, *H*C=CH), 5.53 (1H, d, J = 8.60 Hz, HC=C*H*), 4.14 (1H, d, J = 4.7 Hz, $C_{HA,\ HB}$), 3.87 (1H, d, J = 4.8 Hz, $C_{HA,\ HB}$), 3.51 (2H, m, CH(O) and OH), 2.44 (1H, bs, OH), 2.15 (3H, s, O=CCH_3), 0.98 (3H, s, CCH_3), 0.92 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 200.9 (O=*C*CH_3), 172.7 (N*C*=O), 135.5 (H*C*=CH), 105.4(HC=*C*H), 78.3 (O=C*C*H_3), 71.5(*C*H_2), 39.4(*C*CH_3), 30.8(*C*H(O)), 21.0 (C*C*H_3), 20.4 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3600 (s, br), 3281 (s), 3016 (s), 2949 (s), 1702 (s), 1588 (s), 1394 (s), 1099 (s).

HRMS calcd for $C_{10}H_{17}NO_4$ (M+ ·): 215.1158. Found 215.1152

$[\alpha]_D$ +84.3 (c = 0.9, $CHCl_3$).



(*R*,*E*)-*N*-(2-Cyanovinyl)-2,4-dihydroxy-3,3-dimethylbutanamide, (106*E*).

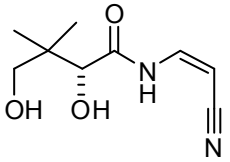
A solution of enamide **(104*E*)** (1.0 mmol) in MeCN (10 mL) was treated with Bi(III)Cl_3 (0.1 mmol) and H_2O (3drops) and stirred at room temperature for 3hrs. Upon completion by TLC analysis, the reaction was quenched with $NaHCO_3$ (4ml) and stirred for a further 20mins. After this time, the mixture was filtered over Celite, dried over Na_2SO_4 , filtered a second time, and then the solvent removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 50% EtOAc in 40-60 petroleum ether) to afford the desired diol **(106*E*)**.

^{1}H NMR (400MHz, $CDCl_3$) δ: 7.62 (1H, d, *J* = 14.7 Hz, HC=C*H*), 5.41 (1H, d, *J* = 14.7 Hz, *H*C=CH), 3.92 (1H, s, CH(O)), 3.49 (1H, d, *J* = 10.9 Hz, $C_{HA, HB}$), 3.40 (1H, d, *J* = 10.9 Hz, $C_{HA, HB}$), 1.31 (3H, s, CCH_3), 0.95 (3H, s, CCH_3).

IR ν_{max}(film)/cm^{-1} 3487 (s, br), 3140 (s), 2980 (s), 2190 (s), 1693 (s), 1580 (s).

HRMS calcd for $C_9H_{15}O_3N_2$ ($M+H^+$): 199.1083. Found 199.1087.

$[\alpha]_D$ +70.3 (c = 0.8, $CHCl_3$).



(*R*,*Z*)-*N*-(2-Cyanovinyl)-2,4-dihydroxy-3,3-dimethylbutanamide, (106*Z*).

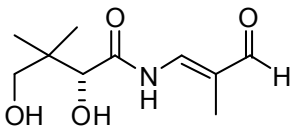
A solution of enamide **(104Z)** (124mg, 0.52 mmol) in MeCN (5 mL) was treated with Bi(III)Cl_3 (16mg, 0.05mmol) and H_2O (2drops) and stirred at room temperature for 3hrs. Upon completion by TLC analysis, the reaction was quenched with $NaHCO_3$ (4ml) and stirred for a further 20mins. After this time, the mixture was filtered over Celite, dried over Na_2SO_4 , filtered a second time, and then the solvent removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 50% EtOAc in 40-60 petroleum ether) to afford the desired diol **(106*Z*)**.

^{1}H NMR (400MHz, $CDCl_3$) δ: 9.49 (1H, bd, *J* = 10.8Hz), 7.60 (1H, dd, *J* = 12.3, 8.9 Hz), 4.72 (1H, d, *J* = 8.9 Hz), 4.27 (1H, s, C*H*(O)), 3.69 (1H, d, *J* = 10.7 Hz, $C_{HA,\ HB}$), 3.62 (1H, d, *J* = 10.7 Hz, $C_{HA,\ HB}$), 1.11 (3H, s, CCH_3), 1.02 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 173.5 (NC=O), 140.9 (*C*=C), 116.5 (C≡N), 77.3 (C=*C*), 76.4 (CH(O)), 69.5 (CH_2), 41.1 (*C*CH_3), 21.4 (C*C*H_3), 20.7 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3366 (s, br), 2965 (s), 2932 (s), 2213 (s), 1708 (s), 1628 (s), 1251 (s). HRMS calcd for $C_9H_{15}O_3N_2$ ($M+H^+$): 199.1083. Found 199.1087.

$[\alpha]_D$ +58.2 (c = 0.9, $CHCl_3$).



(*R*,*E*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(2-methyl-3-oxoprop-1-enyl)butanamide, (107).

A solution of enamide **(101)** (1.0 mmol) in MeCN (10 mL) was treated with Bi(III)Cl_3 (0.1 mmol) and H_2O (3drops) and stirred at room temperature for 3hrs. Upon completion by TLC analysis, the reaction was quenched with $NaHCO_3$ (4ml) and stirred for a further 20mins. After this time, the mixture was filtered over Celite, dried over Na_2SO_4 , filtered a second time, and then the solvent removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 50% EtOAc in 40-60 petroleum ether) to afford the desired diol **(107)**.

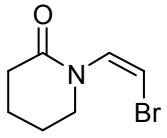
^{1}H NMR (400MHz, $CDCl_3$) δ: 9.35 (1H, s, O=C*H*), 7.76 (1H, s, C=C*H*), 4.19 (1H, s, C*H*(O)), 3.52 (1H, d, *J* = 10.9 Hz, $C_{HA,\ HB}$), 3.46 (1H, d, *J* = 10.9 Hz, $C_{HA,\ HB}$), 1.69 (3H, s, C=CCH_3), 1.00 (3H, s, CCH_3), 0.98 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 194.9 (CH(O)), 173.9 (NC=O), 143.1 (*C*=C), 122.0 (*C*=CH_3),76.9 (CH(O)), 69.6 (CH_2), 41.1 (*C*CH_3), 21.5 (C=C*C*H_3), 20.9 (C*C*H_3), 7.5 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3631 (s, br), 3298 (s), 2999 (s), 1716 (s), 1669 (s).

HRMS calcd for $C_{10}H_{17}NO_4$ (M+ ·): 215.1158. Found 215.1157.

$[\alpha]_D$ +80.7 (c = 1.0, $CHCl_3$).

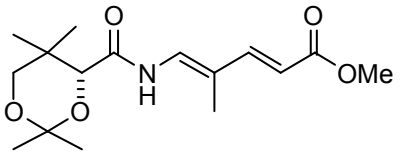


(*Z*)-1-(2-Bromovinyl)piperidin-2-one, (114).

A solution of bromomethyl triphenylphosphonium bromide (2.29g, 5.24mmol) in THF (8 mL) was stirred at -78 ^{o}C for 5mins. KHMDS (10.5 mL, 5.24mmol) was then added dropwise, before stirring for a further 10mins. Imide **(56)** (222mg, 1.75mmol) was then added as solution in THF (2 mL) at -78 ^{o}C. The reaction mixture was allowed to warm to room temperature and was stirred for 70hrs. After this time, the solvent was removed under vacuum, and the crude mixture was purified by flash column chromatography (silica gel, 30% EtOAc in 40-60 petroleum ether) to generate the halo-enamide **(114).**

^{1}H NMR (400MHz, $CDCl_3$) δ: 7.81 (1H, d, *J* = 13.2, *H*C=CH), 5.51 (1H, d, *J* = 13.2 Hz, HC=C*H*), 3.23 (2H, t, *J* = 6.2 Hz, N-CH_2), 2.34 (2H, t, *J* = 6.6 Hz, CH_2C=O), 1.71 (4H, m, 2x CH_2).

^{13}C NMR (100MHz, $CDCl_3$) δ: 167.8 (NC=O), 132.4 (C=*C*), 88.8 (*C*=C), 45.4 (NCH_2), 32.8 ($O{=}CCH_2$), 22.4 (CH_2), 20.5 (CH_2).



(*R*,2*E*,4*E*)-Methyl 4-methyl-5-(2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamido) penta-2,4-dienoate, (111).

A solution of aldehyde **(101)** (58mg, 0.23 mmol) in benzene (5 mL) was treated with methyl triphenylphosphoranylidene acetate (152mg, 0.45 mmol) and the resulting mixture heated to 95 ^{o}C for 18 hrs. Upon reaction completion as indicated by TLC analysis (18hrs), the solvent was removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 30% EtOAc in 40-60 petroleum ether) to afford the desired dienamide **(111)**.

^{1}H NMR (400MHz, $CDCl_3$) δ: 8.59 (1H, bd, *J* = 11.6Hz, N*H*), 7.49 (1H, d, *J* = 15.2 Hz, *H*C=CH), 6.88 (1H, d, *J* = 11.7 Hz, N-*H*C=C), 5.81 (1H, d, *J* = 15.2 Hz, HC=C*H*), 4.12 (1H, s, C*H*(O)), 3.71 (3H, s, OCH_3), 3.66 (1H, d, *J* = 11.7 Hz, $C_{HA,\ HB}$), 3.26 (1H, d, *J* = 11.7 Hz, $C_{HA,\ HB}$), 1.79 (3H, s, =CCH_3), 1.50 (3H, s, OCCH_3), 1.40 (3H, s, OCCH_3), 1.00 (3H, s, CCH_3), 0.96 (3H, s, CCH_3).

7 Isoprenoid Biosynthesis

Isoprenoids are key factor in a number of different metabolic pathways. They are utilised in processes such as cell membrane maintenance, hormone production, protein anchoring and *N*-glycosylation [43]. Isoprenoids have shared functionalities between eukaryotes and prokaryotes, for example ubiquinone (118) and menaquinone (119) being utilised in electron transport pathways. Some isoprenoids are species specific, for example dolichol (120), which plays a key role in post-translational modification in eukaryotes. Examples exist whereby different isoprenoids perform similar roles in different species. Cholesterol (121) in eukaryotes and hopanoids (122) in prokaryotes are both responsible for membrane stability. To understand whether these differences can be exploited in a drug design capacity, the method of biosynthesis needs to be understood.

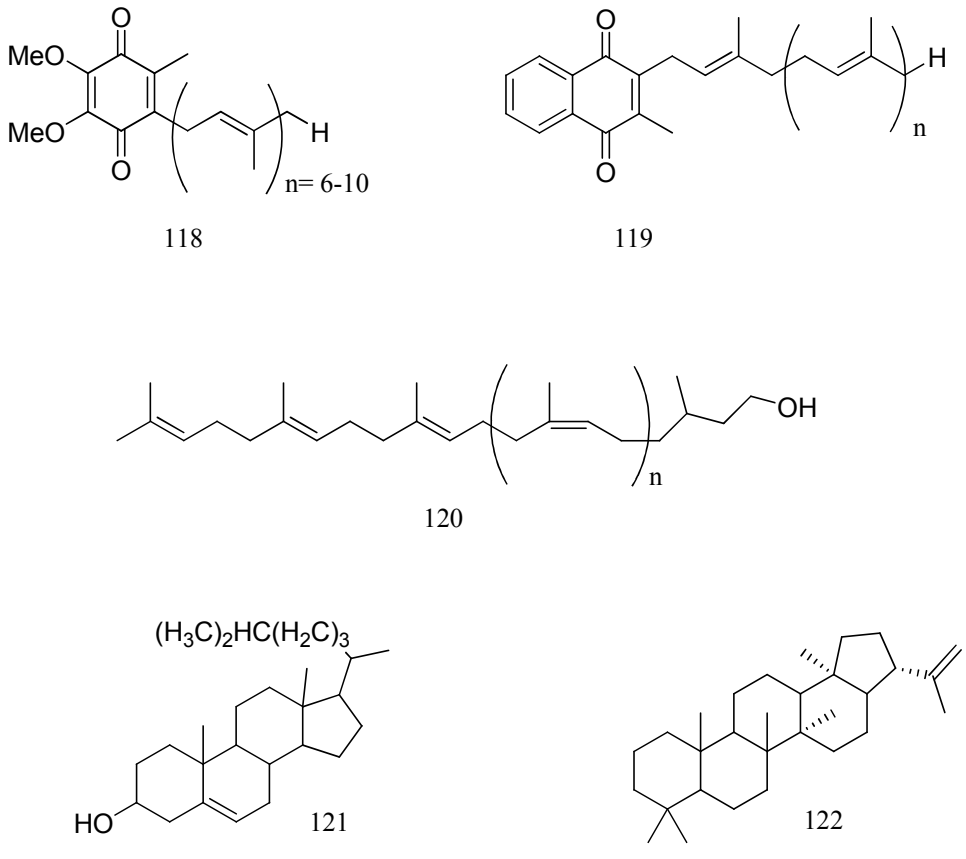


Figure 5.3.1- Various isoprenoids

7.1 The Mevalonate Pathway

For a long time the Mevalonate pathway was thought to be the only pathway for isoprenoid synthesis, and is considered an important metabolic pathway present in all higher eukaryotes, plants and many bacteria. It is responsible for the production of isopentenyl pyrophosphate (IPP, 129) and dimethylallyl pyrophosphate (DMAPP, 130). DMAPP and IPP form the base units for a range of isoprenoids [(44)].

Acetyl-CoA is acetylated by a thiolase ERG10 to generate acetoacetyl-CoA (124). HMG-CoA synthase (ERG13) then mediates the condensation reaction of acetoacetyl-CoA with a second acetyl- CoA molecule to form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) (125).

HMG-CoA reductase then facilitates the rate determining step of this pathway. HMG-CoA is reduced using NADPH to mevalonate (126), the key intermediate from which the pathway takes its name. This reaction occurs in the cytosol. Mevalonate is then phosphorylated by mevalonate kinase (ERG12) to generate 5-phosphomevalonate (127).

5-phosphomevalonate is then phosphorylated by phosphomevalonate kinase (ERG8) to yield 5-pyrophosphomevalonate (128).

Pyrophosphate (128) is decarboxylated to IPP (129) by mevalonate-5-pyrophosphate decarboxylase, before isomerisation to DMAP (130).

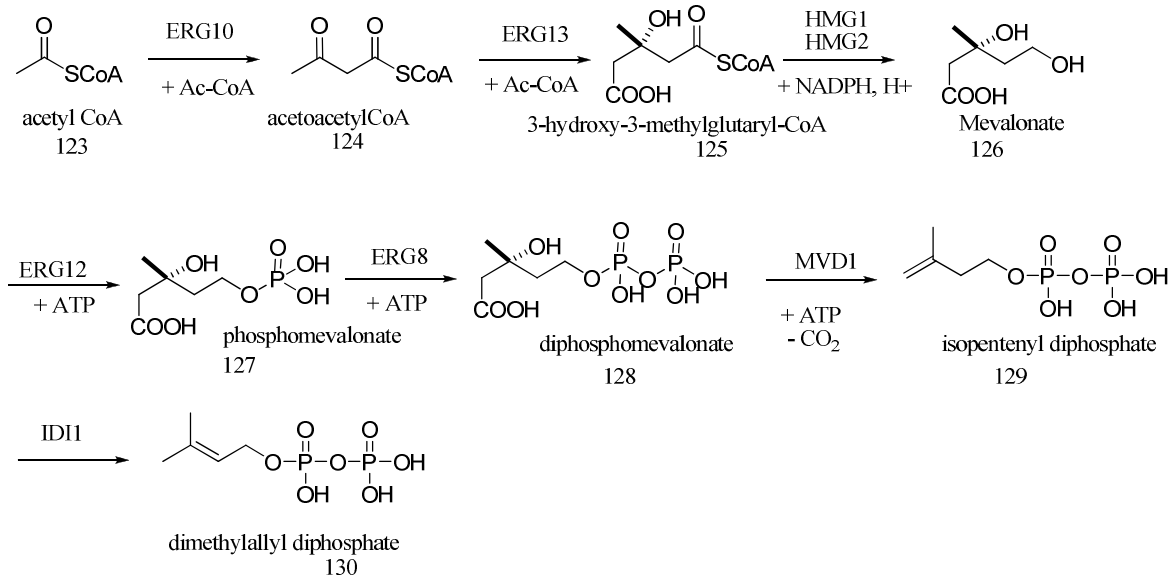


Figure 7.1.1- The Mevalonate pathway

7.2 The Non-Mevalonate Pathway

A second pathway for isoprenoid biosynthesis has been identified recently [45]. This second pathway has become widely referred to as the Non-mevalonate pathway or 2-*C*-methyl-D-erythritol 4-phosphate (MEP) pathway, due to the absence of mevalonate in the pathway.

A range of organisms utilise the MEP pathway for isoprenoid biosynthesis. These organisms include plants [46], along with many organisms responsible for disease such as: eubacteria (*Mycobacterium tuberculosis)* and Apicomplexan protozoa (*Plasmodium falciparum*) [47]. Crucially though, this pathway is not present in higher eukaryotes [48].

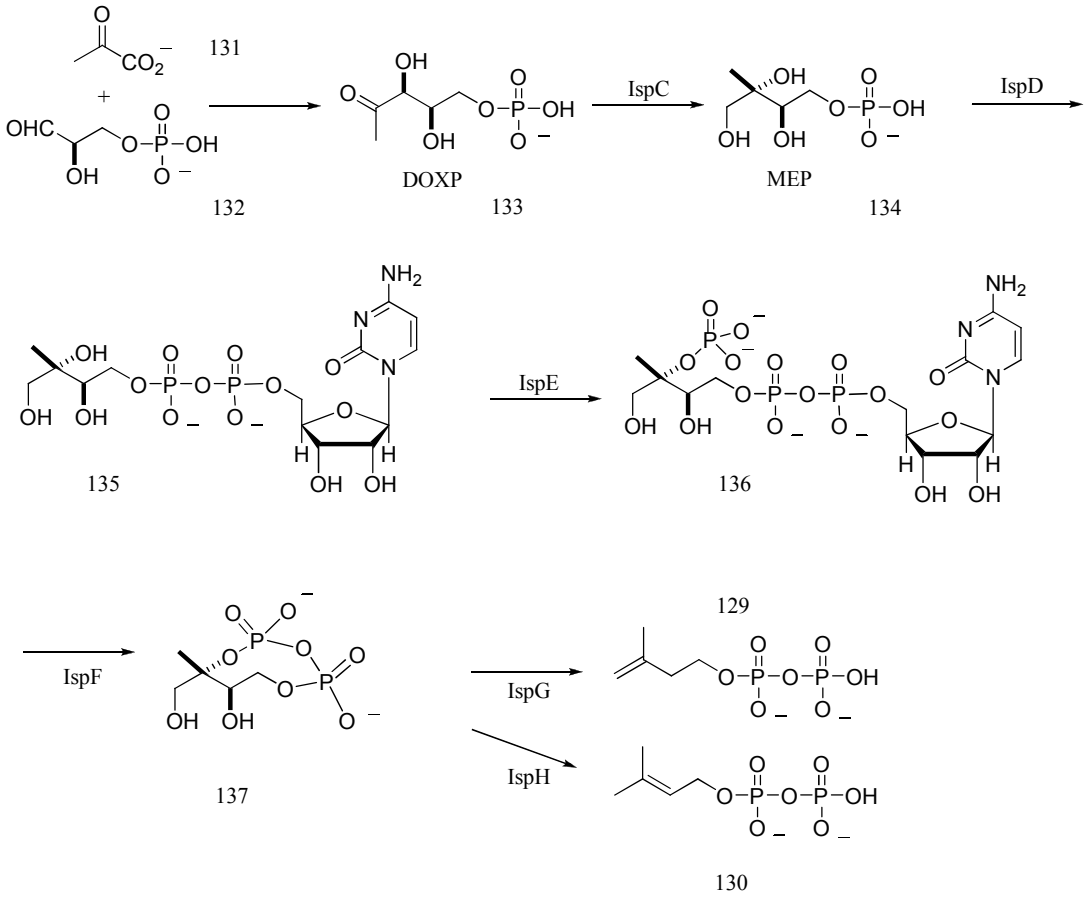


Figure 7.2.1- The Non-mevalonate (MEP) pathway

Thanks to the exquisite and extensive mechanistic studies of Rohmer [49-51] and Arigoni [52] with their respective co-workers, the MEP reaction pathway is known to start with the coupling of pyruvate (131) and glyceraldehyde 3-phosphate (132) by DOXP synthase (Dxs) to DOXP (133). DOXP (133) is then converted by IspC to 2-C-methyl-D-erythritol 4-phosphate (MEP) (134).

The next step involves the simultaneous conversion to a pyrophosphate and addition of a cytidine monophosphate group by IspD. Phosphorylation of the tertiary 2C-hydroxyl by IspE generates pyrophosphate (136). Cyclisation of the pyrophosphate to the cyclic diphosphate MecPP (137) by IspF then occurs.

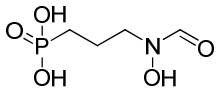
Finally, MEcPP is converted to (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP) by IspG, and HMB-PP is converted to IPP and DMAPP by HMB-PP reductase IspH [53].

The presence of the MEP pathway in pathogenic organisms, coupled with its apparent absence in humans or any other agriculturally important animal, provides us with an attractive drug target.

7.3 Validation and Characterisation

The importance of this pathway as a drug target has been confirmed through a number of investigations [54]. The generation of lethal phenotypes through knockout experiments, have shown the pathway to be essential for parasite survival [55, 56].

Chemically, the pathway has also been shown to be a feasible drug target due to the inhibition of DOXP Reductase by the known antibacterial Fosmidomycin (138) [57-59].



138

Figure 7.3.1

Structural studies have resolved the structure of the pathway enzymes along with their substrate interactions [60, 61].

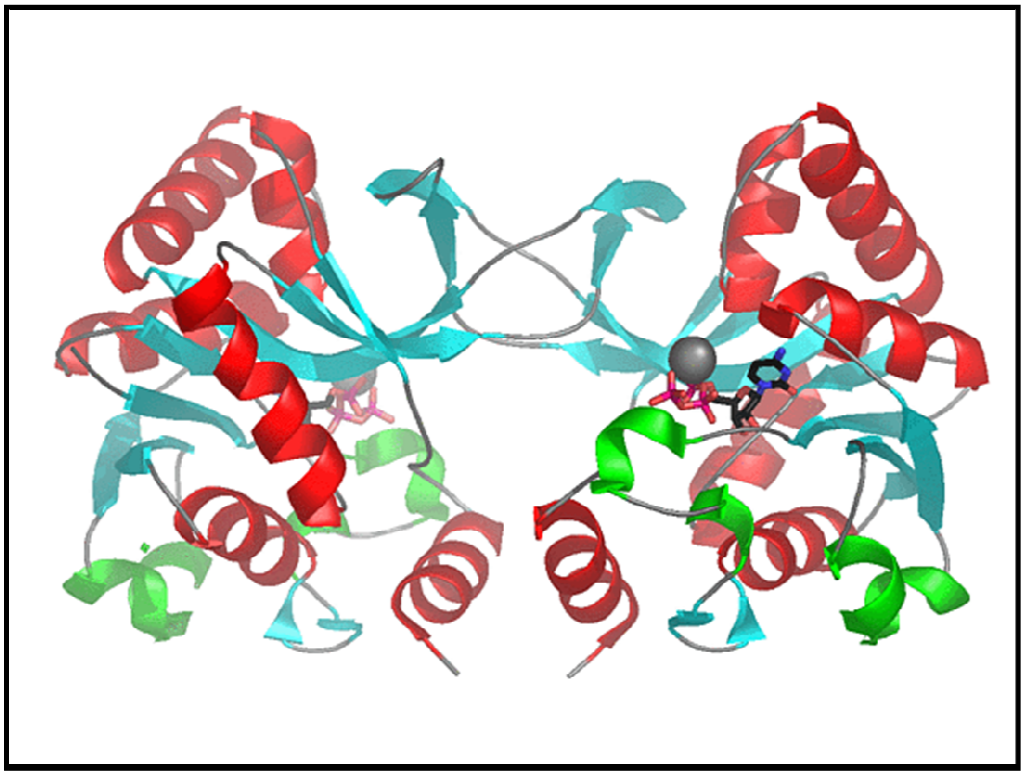


Figure 7.3.2- IspE complexed with substrate [60]

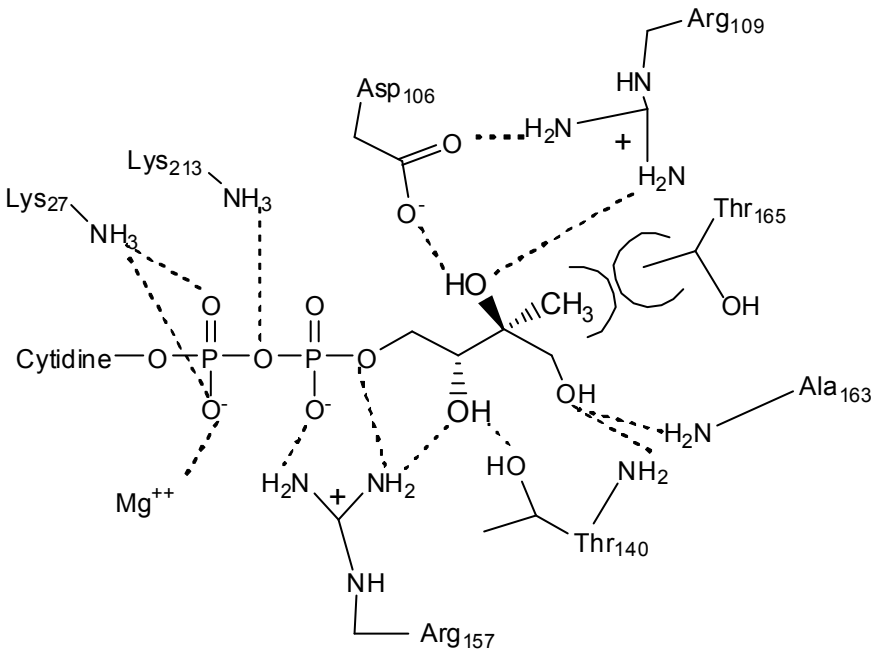
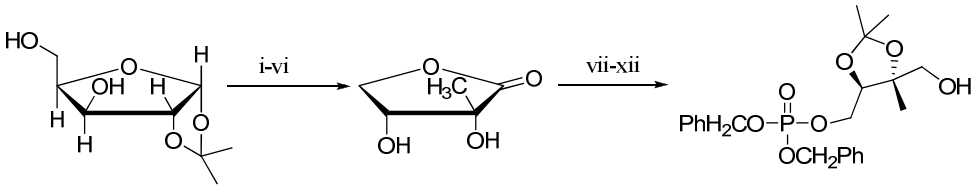


Figure 7.3.3- Interactions of IspE active site [60]

7.4 Previous syntheses

Due to the interest in the MEP pathway as a potential drug target, a range of syntheses of MEP have been published, using a variety of different approaches.

Kis K. and collaborators' synthesis of MEP began with the sugar (139) which allowed the incorporation of the relevant stereochemistry from the start [62].



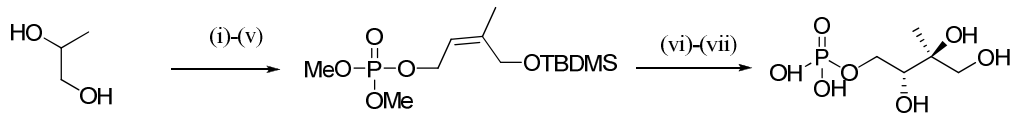
139 140 141

Reagents/ Conditions: (i)$Pb(OOCCH_3)_4$, DCM, 0 °C, (ii)(1) CH_3MgI, Et_2O, 25 °C, (2) H_2O, NH_4Cl (iii) RuO_2, $NaIO_4$, K_2CO_3, $CHCl_3/H_2O$, 25 °C, (iv) $(CH_3)_3SiCN$, KCN, 18-crown-6, DCM, 25 °C (v) HCl (25%), H_2O, EtOH, 80 °C (vi) HCOOH (60%), 80 °C, (vii) CH_3COCH_3, $ZnCl_2$, 25 °C, (viii) (1) DIBAL, THF, (2) H_2O, -78 °C, (ix) $PhCH_2ONH_2$, pyridine, DCM, 25 °C, (x) (1) $(PhCH_2O)_3P$, I_2, DCM, (2) $(PhCH_2O)_2POI$, pyridine, DCM, -20 °C, (xi) (1) O_3, pyridine, DCM, -78 °C, (2) CH_3SCH_3, -78 °C, (xii) $NaBH_4$, MeOH

Scheme 7.4.1

Kis' approach was tailored towards the introduction of radiolabelled isotopes, and no derivatives were reported.

MEP intermediates have also been synthesised from small linear starting materials. Work published by Koppisch described the synthesis of MEP using a synthesis starting with from 1-methyl ethylene glycol (142) and comprising 7 linear steps [63]. This approach hinged around intermediate (143).

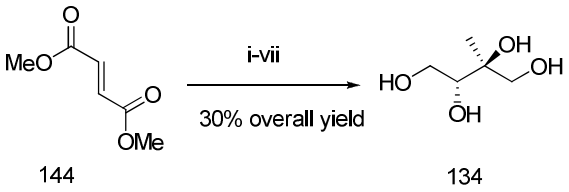


142 143 134

Reagents/ Conditions: (i) TBDMSCl, N-ethyldiisopropylamine, DCM (ii)TPAP, NMO, DCM (iii) KH, (2,2,2-trifluoroethyl)methoxycarbonylmethylphosphonate, THF, -20 °C (iv) DIBAL, DCM, -40 °C; (v) dimethyl chlorophosphate, DMAP, DCM (vi) modified AD-mix â, t-BuOH/H_2O, $NaHCO_3$, 0 °C (vii) TMSBr/ H_2O; HCl.

Scheme 7.4.2

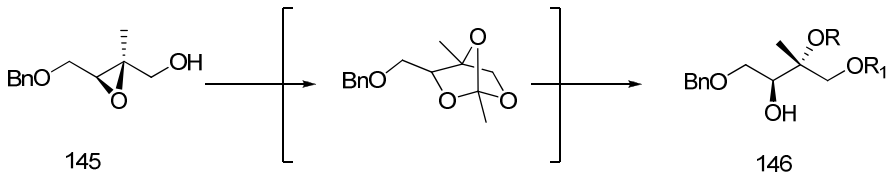
Epoxides have also been used as key intermediates in MEP synthesis. Independent work by Fontana and Giner, have used a Sharpless asymmetric epoxidation to generate key epoxide intermediates with the relevant MEP stereochemistry in place. A regioselective opening of the epoxide then generates the required MEP framework [64, 65], in the development of synthetic routes towards MEP [66] and other pathway intermediates [67].



Reagents/ Conditions: (i)O_3, $Ph_3PC(CH_3)CHO$ (ii)$NaBH_4$ (iii)BnBr, NaH, THF (iv) DIBAL, -78°C, THF (v) Ti (*i*-PrO)$_4$, (+)-DET, *t*-BuOOH, -23°C in DCM (vi) *t*-BuOH, 0.5 N NaOH, H_2O, 75°C (vii) Pd:C, H_2

Scheme 7.4.3

Giner [65] utilises an acid mediated rearrangement to generate the intermediate orthoester (145a). The breakdown of this orthoester intermediate generates a mixture of the mono-protected diols.



Scheme 7.4.4

Until recently the main focus was on the synthesis of MEP, due to its small size, and densely packed functionality. However, recently the generation of analogues has become the main focus.

7.5 Current Analogues/ Inhibitors

With the emergence of drug resistance, the quest for new compounds for which resistance cannot be evolved is an ongoing one. When one pathway enzyme is knocked out, the parasite can develop a way round it. This can occur by single point mutations in the enzyme, or by utilising other enzymes to perform the task.

Alongside the known syntheses of MEP, the synthesis of known MEP pathway inhibitors are few and far between. Only reports on Fosmidomycin (138) and its analogue FR00098 (147) were known until recently [68].

Figure 7.5.1- Known MEP pathway inhibitors

Coates and colleagues [69, 70] have reported a new synthesis of MEP (134), along with the pyrophosphate (137), and two analogues (149 and 150). This approach relies on the dioxanone derived key intermediate (148).

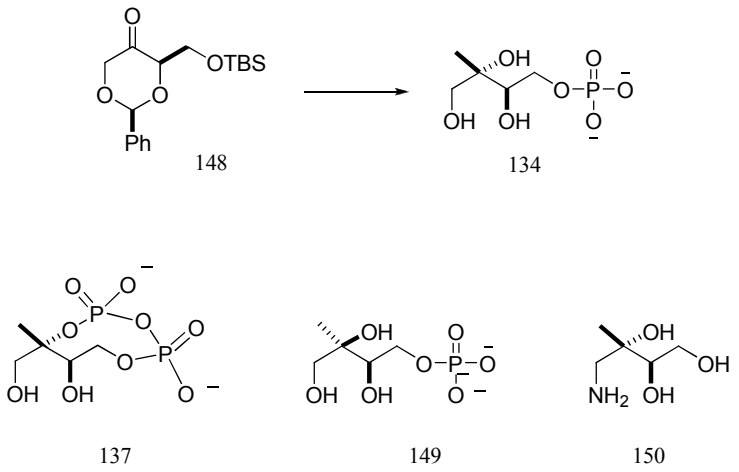
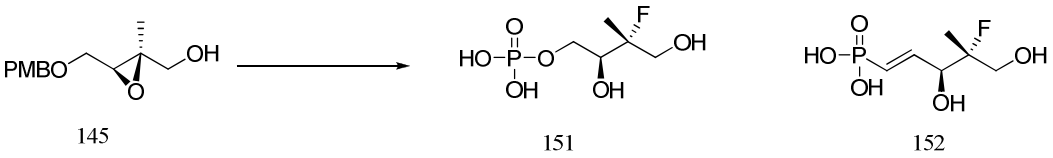


Figure 7.5.2- MEP pathway intermediates/ inhibitors currently synthesised

A number of collaborators have also started to exploit the abundance of crystal structure data to begin to generate inhibitors based on analogues of the cytidyl group present in the substrate for IspE [71].

Our group recently published the synthesis of 2-fluoro MEP (151) [72] and the conjugated analogue (152). This approach took advantage of a key epoxide intermediate (144). Analogue (152) has been successfully co-crystallised with IspC (unpublished data).



Reagents/ Conditions: (i) TEA.3HF, 100ºC; (ii) TBSOTf, 2,6-lutidine, 0ºC; (iii) $SnCl_4$, PhSH, 0ºC; (iv) $(EtO)_2P(O)I$, Py; (v) 90% TFA, 0ºC; (vi) TMSBr, DCM, 0ºC.

Scheme 7.5.1

Efforts in our group have been focussed on targeting Isp D, Isp E, and Isp F using C-2 isosteres for the MEP 2-hydroxy group.

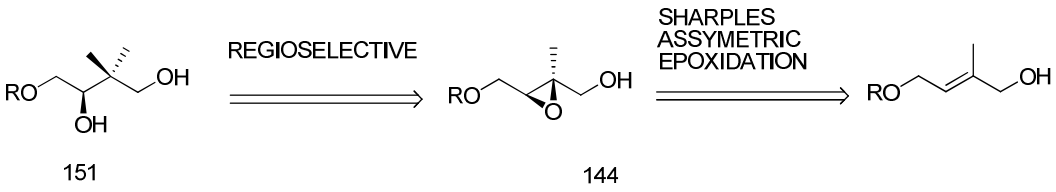
The reason behind this is the availability of crystallographic data for these three enzymes, along with the pathway implications they present.

In our approach towards MEP inhibitors, we reasoned that a hydroxyl group isostere at the C2 position could potentially inhibit Isp E from the outset. Failing that, the resemblance of the compound to MEP would potentially allow it to be turned over by Isp E and F to generate the corresponding cyclic diphosphate. This diphosphate could then in turn act as an inhibitor for Isp G and H enzymes.

We were therefore keen to see if one compound could act as an inhibitor in 3 consecutive enzymes, and possibly reduce the chances of resistance developing.

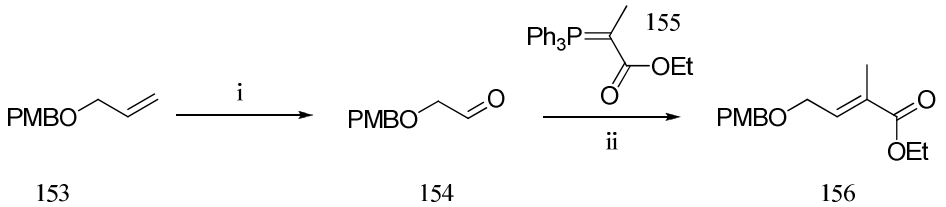
8 Synthesis of 2, 2-Dimethyl MEP

Our initial target for an MEP analogue was the replacement of the MEP 2-hydroxy group with a methyl isostere.We reasoned that this would provide us with a compound that resembled MEP in spatial size, with no ability to be phosphorylated by Isp E. The synthesis would also allow the later generation of MEP from the same intermediate, epoxide (145).



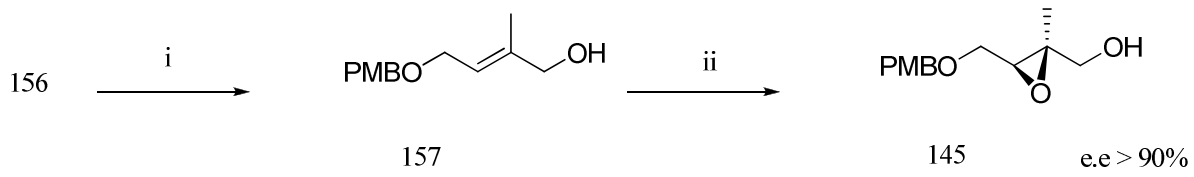
Scheme 7.5.1

Our synthesis began with the protection of readily available PMB alcohol as the allyl ether (153) in excellent yield. Ozonolysis of allyl ether (153) afforded the aldehyde (154), again in good yield. Wittig olefination of aldehyde (154) using ylide (155) generated the *E*-conjugated ester (156) as a single diastereomer.



Reagents/ Conditions: (i) O_3, -78°C, 72% (ii) Ylide 155, benzene, reflux, 73%

Scheme 7.5.2



Reagents/ Conditions: (i) LAH, dry ether, 0°C, 86% (ii) D(-)DIPT, titanium(IV) isopropoxide, 4A molecular sieves, an. DCM, -23°C. *t*-BuOOH (64%).

Scheme 7.5.3

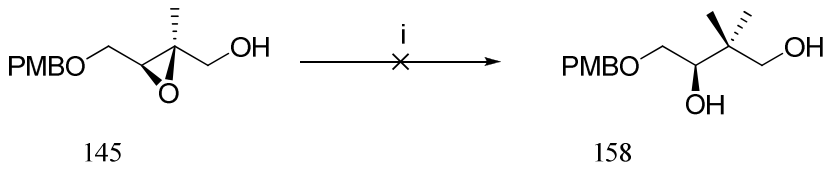
Lithium aluminium hydride reduction of ester (156) generated the required allylic alcohol (157) in good yield.

Finally, epoxidation of the allylic alcohol (157) under Sharpless Assymetric Epoxidation conditions [72] afforded the epoxyalcohol (145) in good yield and good *e.e.*

8.1 Epoxide Opening

Based on literature examples [72] the decision was made to attempt the generation of a 2,2-dimethyl analogue by opening the epoxide directly.

Our approach towards the desired 2,2- dimethyl analogue commenced with the attempted opening of epoxide (145) using Me_3Al, under a number different conditions [73, 74], to the 2,2 dimethyl MEP analogue (158).



Reagents/ Conditions: (i) Me_3Al 3eq- 10eq

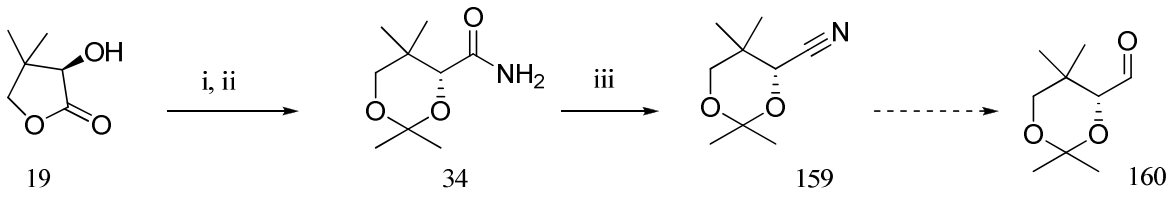
Scheme 8.1.1

Disappointingly, continued adaptation of these conditions returned either starting material or a mixture of degraded products of no further interest.

Due to the investigation into the synthesis of CJ-15,801, the existence of the commercially available (S)-(+)-pantolactone, was recognised as having the required methyl and hydroxyl groups in the correct stereochemistry for a 2,2-dimethyl MEP analogue.

Although the correct stereochemistry for MEP is provided by (S)-(+)-pantolactone, the relative expense of this compound in relation to its (R)-(-) enantiomer meant establishing the synthetic route with (R)-(-)-pantolactone, and subsequently applying this to the more expensive (S)-(+) enantiomer.

To access the corresponding alcohol intermediate (161) needed for 2,2-DMEP generation, ketal amide (34) was resynthesized using the same conditions as before [75]. (*D*-) pantolactone (19) was opened using liquid ammonia, and the resulting diol was protected as the ketal (34). Amide (34) was then dehydrated using cyanuric chloride to generate the nitrile (159). Unfortunately the reaction proceeded in too low yield to generate enough nitrile to attempt the reduction to aldehyde (160).



19 34 159 160

Reagents/ Conditions: (i) NH_3 (l), -78°C, 99% (ii) 2-methoxypropene, *p*TsOH, 52%
(iii) cyanuric chloride, TBME/ DMF, 17%

Scheme 8.1.2

We were keen to access the aldehyde (160), as it would provide us a handle for a further range of analogues through relatively simple approaches.

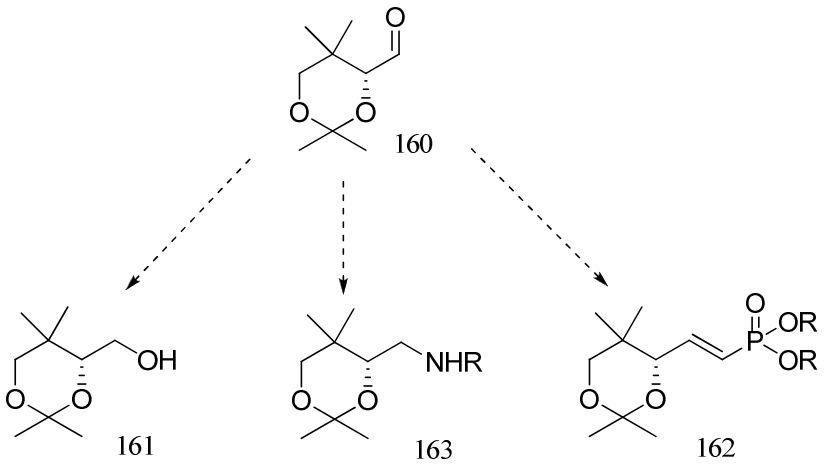
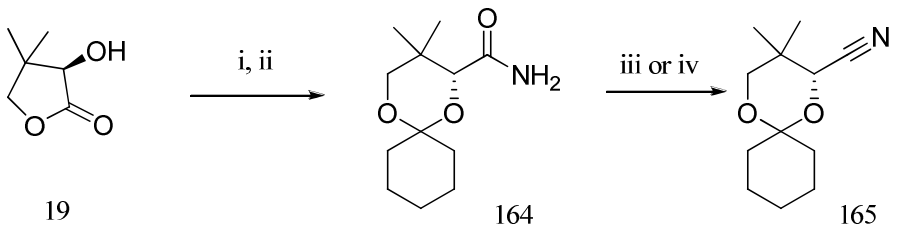


Figure 8.1.1

It was reasoned that the low yield encountered during the dehydration step could be accounted for by the small size of the nitrile produced (159), and its likely volatility during solvent removal under vacuum. Therefore, a decision was made to increase the molecular weight of the molecule, in an attempt to reduce its volatility.



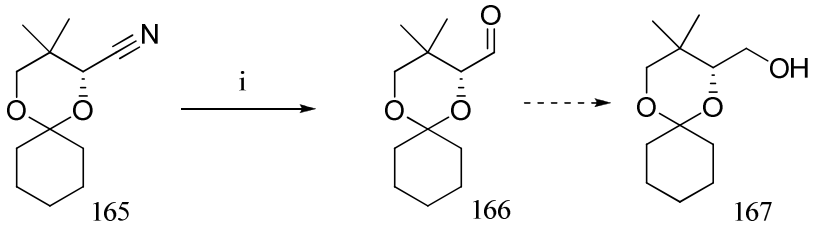
Reagents/ Conditions: (i) NH_3 (l), -78°C (ii) Cyclohexanone diethyl acetal, *p*TsOH, 59% (2 steps) (iii) Burgess reagent, 84%, (iv) cyanuric chloride, TBME/ DMF, 65%

Scheme 8.1.3

Our modified approach began with opening (D)-(-)-pantolactone with liquid ammonia, and the resulting diol intermediate was protected using cyclohexanone diethyl acetal to generate the bulkier cyclohexyl-ketal (164) in good yield.

Faced with the low yield of the cyanuric chloride dehydration, an alternative dehydration procedure was required. Claremon and Phillips [76] report the use of

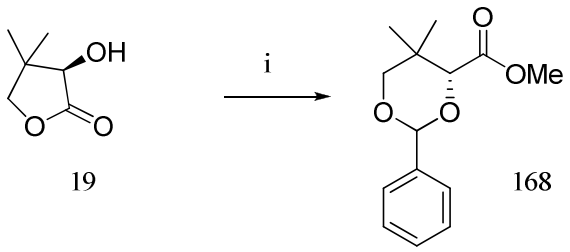
methoxycarbonylsulfamoyl triethylammonium hydroxide inner salt (Burgess Reagent) to dehydrate amides. However, although a greatly improved yield over our previous cyanuric chloride dehydration, the high expense of Burgess Reagent meant its long term use was not feasible. We therefore returned to the previously used cyanuric chloride approach. Dehydration of the amide (164) to the nitrile (165) was achieved in improved yield. With the successful generation of nitrile (165), focus was returned to reducing to the aldehyde (166) in good yield [77].



Reagents/ Conditions: (i) DIBAL, 0°C, 57%

Scheme 8.1.4

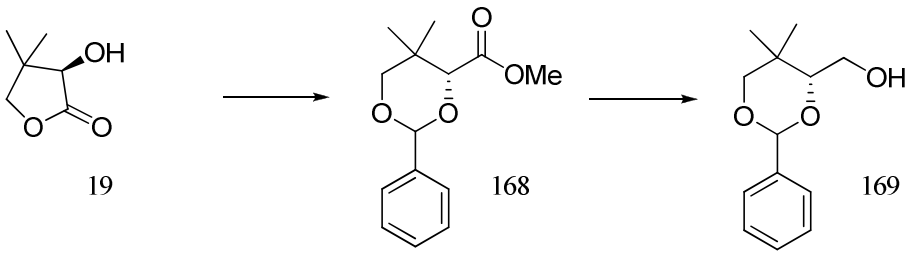
Although the yield for this approach was acceptable, it still involved a significant number of steps. A new approach was based on work of Oniciu and colleagues [78], who reported the conversion of pantolactone (19) to the corresponding ester (168), in a single step and in good yield.



Reagents/ Conditions: (i) Benzaldehyde dimethyl acetal, *p*TsOH, dioxane, 36%

Scheme 8.1.5

Treatment of (D)-(-)-pantolactone with benzaldehyde dimethyl acetal successfully generated ester (168), which was then subsequently reduced with LAH to afford the alcohol (169) in reasonable yield over the 2 step sequence.



Reagents/ Conditions: (i) Benzaldehyde dimethyl acetal, *p*TsOH, dioxane, 37% (ii) LAH, 0°C, 65%

Scheme 8.1.6

Advantages of this approach over the previous one include the fact that there are less steps involved to generate the alcohol (169) or its corresponding aldehyde. The structure of ester (168) was corroborated using X-ray analysis.

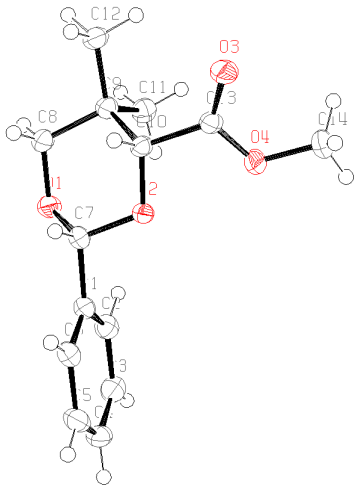
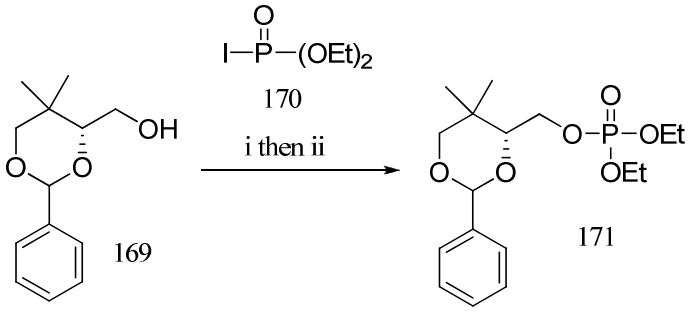


Figure 8.1.2- Crystal structure ester (168)

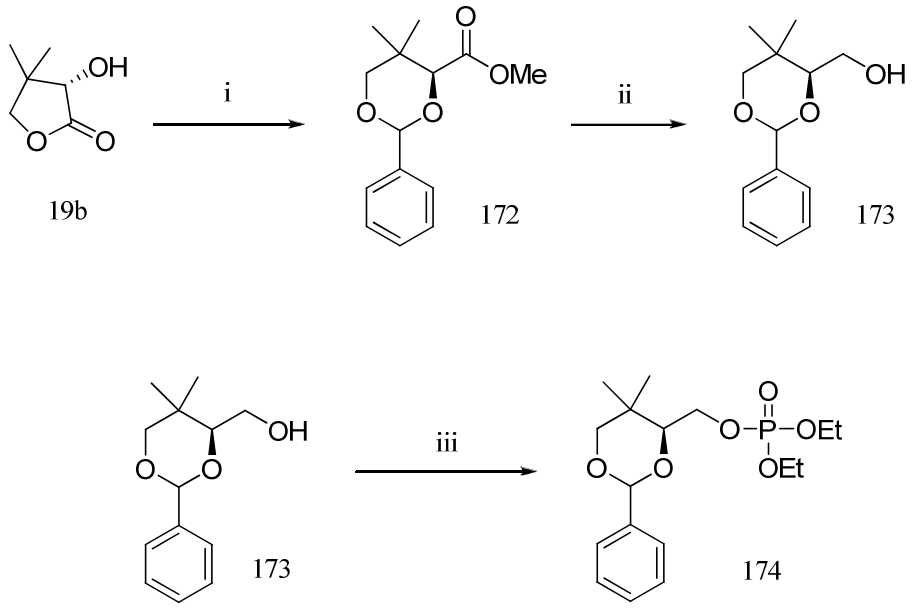
Alcohol (169) was then phosphorylated in a single step using conditions [72] previously used in our group, to generate diethyl phosphate (171).



Reagents/ Conditions: (i) Iodine, triethyl phosphite, DCM, 0°C generates **170** then (ii), pyridine, DCM, RT, 30%

Scheme 8.1.7

Having successfully generated the phosphate (171), the same synthetic sequence was applied to (S)-(+)-pantolactone, providing the correct enantiomer for 2,2 DMEP.



Reagents/ Conditions: (i) Benzaldehyde dimethyl acetal, *p*TsOH dioxane, 50%
(ii) LAH, 0°C, 52%, (iii) Iodine, triethyl phosphite, DCM, 0°C then (iv), pyridine, DCM, RT, 30%

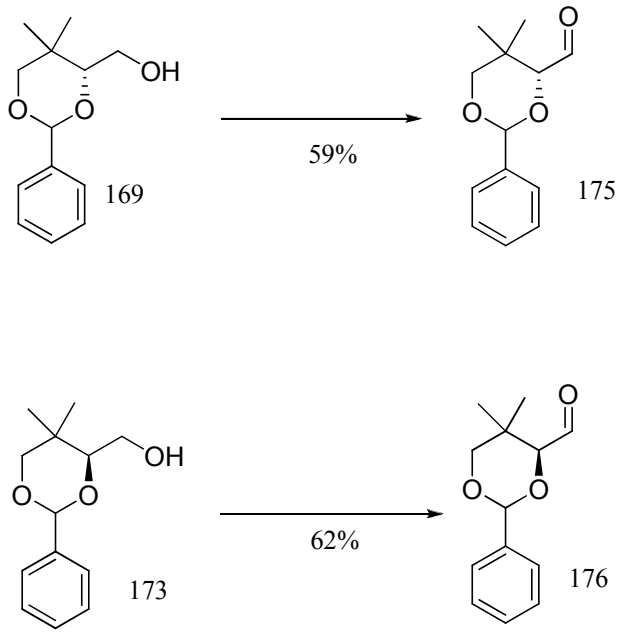
Scheme 8.1.8

Unfortunately, due to time constraints, the global deprotection of diethyl phosphates (171) and (174) could not be explored to our satisfaction. This was considered unfortunate, as we

are confident the synthesis of this potential MEP pathway inhibitor can be completed shortly.

8.2 Other analogues

In addition to the generation of MEP analogues at the 2- hydroxy position, the modification of the phosphate unit was explored.

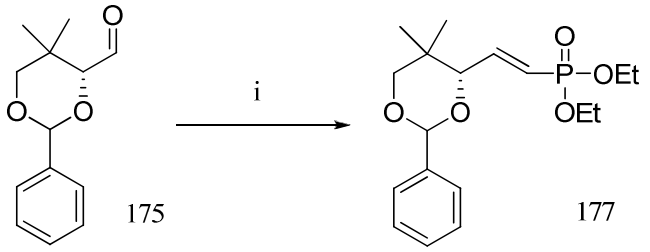


Reagents/ Conditions: (i) DMSO, oxalyl chloride, -78 ^{o}C (ii) Et_3N, RT

Scheme 8.2.1

Our synthesis of the new analogues began with the Swern oxidation of alcohols (169) and (173) to provide the corresponding aldehydes (175 and 176) in good yield. As discussed earlier, these aldehyde units could be key intermediates for the parallel generation of analogues.

Our initial analogue target was the phosphonate (177) due to its potential ability to undergo irreversible bonding through a Michael-like addition process, not dissimilar to the enamide examples discussed earlier. Aldehyde (175) was reacted with tetraethylmethylene diphosphonate to successfully generate the protected phosphonate (177) in reasonable yield.



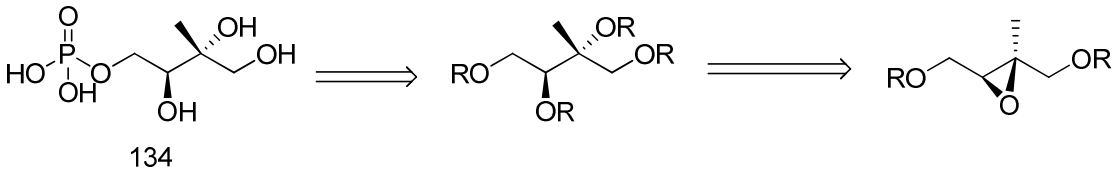
175 177

Reagents/ Conditions: (i) *n*-BuLi, tetraethylmethylene diphosphonate, THF, -78 ^{o}C, 49%

Scheme 8.2.2

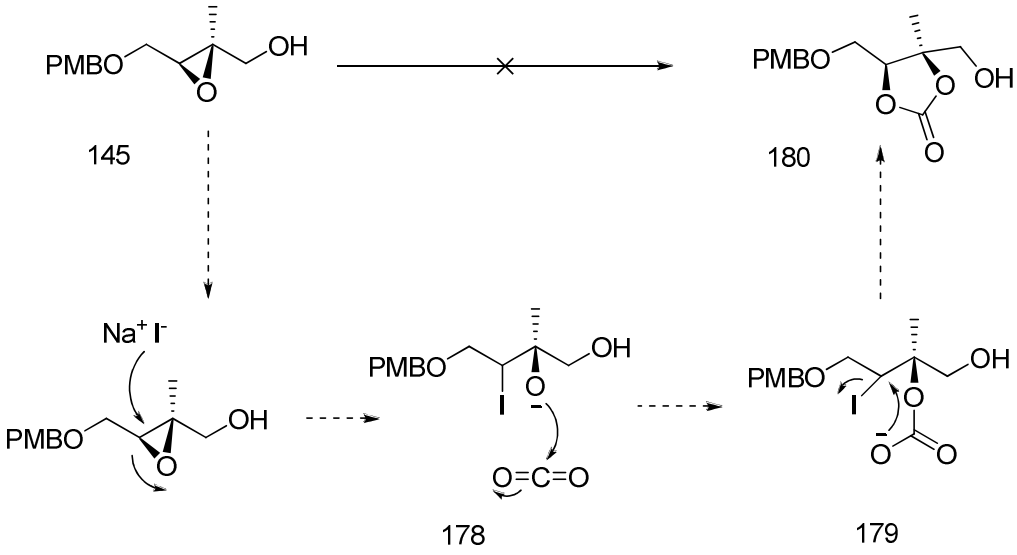
9 Synthesis of MEP

Simultaneous to the 2,2 DMEP synthesis, a parallel approach to the synthesis of MEP itself was investigated.



Scheme 8.2.1

We envisioned MEP as the result of a regioselective opening of an epoxide (Scheme 8.2.1). Our synthesis began with the previously synthesised epoxide (145) which was treated with NaI and CO_2 [79]. It was envisioned that epoxide (145) would be initially opened at the least hindered position by NaI to generate alkoxide (178). Alkoxide (178) would then trap the CO_2 present in the reaction, to generate anion (179) which would then perform an intramolecular S_N2 reaction to generate carbonate (180).

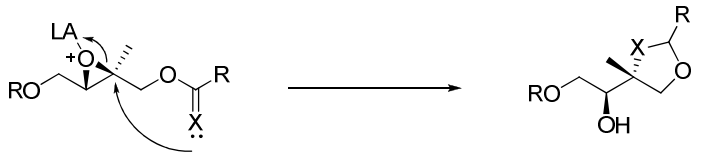


Scheme 8.2.2

More traditional epoxide opening methods were also investigated but failed to open the epoxide. NH_4OAc and Ti *i*OPr [80] and H^+ /H_2O [81].

9.1 Opening epoxides via NGP

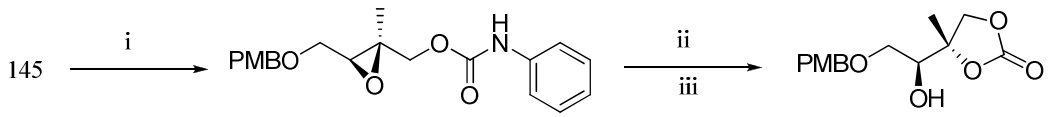
Faced with the failure of intermolecular methods to generate the desired erythrol, our modified approach considered the incorporation of an additional functional group, which could be utilised in a Neighbouring Group Participation epoxide opening.



Scheme 9.1.1

Previous reports have shown that epoxides can be opened selectively under Lewis Acid mediated conditions to their corresponding carbonates [82-85].

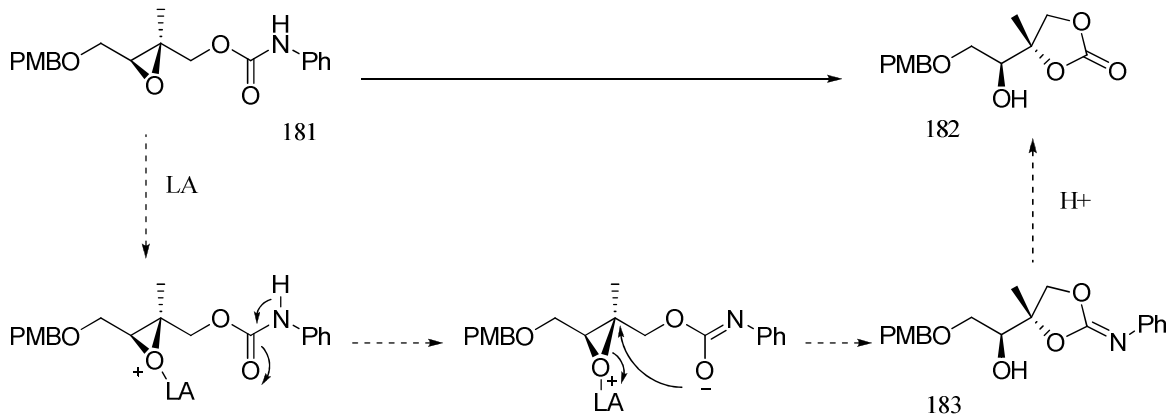
Epoxy alcohol (145) was treated with phenyl isocyanate to generate the carbamate (181). Gratifyingly, cyclisation in the presence of diethylaluminiumchloride generated the carbonate (182).



Reagents/ Conditions: (i) Et_3N, phenylisocyanate, 72% (ii) Et_2AlCl, Et_2O/ DCM, 0°C, (iii) 0.5M HCl, RT 10mins, 27%

Scheme 9.1.2

Mechanistically, the reaction proceeds through the intramolecular attack of the carbamate carbonyl on the Lewis Acid coordinated epoxide, to generate imine (183). Acid hydrolysis of the imine affords the carbonate (182).



Scheme 9.1.3

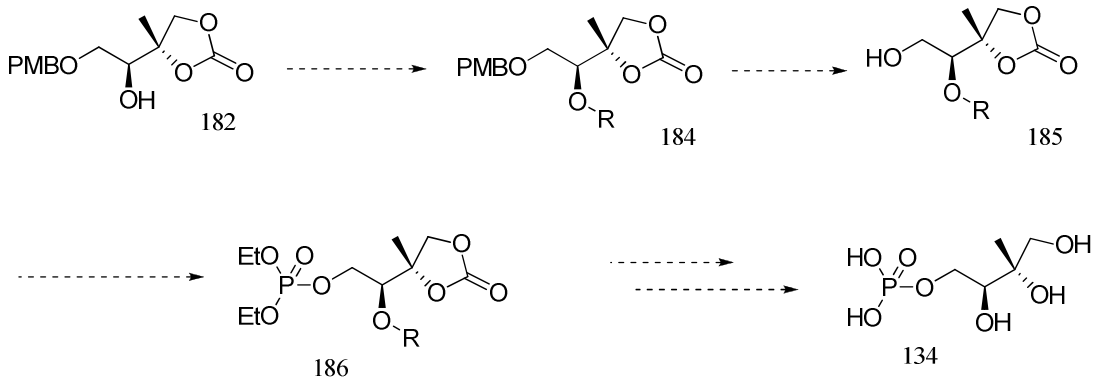
10 Conclusions and Further Work

The synthesis of 2, 2-DMEP from a lactone has been started, alongside the initial investigation into the generation of previously unpublished MEP pathway inhibitors. A parallel synthesis of MEP has also been initiated. By utilising neighbouring group participation, the ability to open the key epoxide intramolecularly under Lewis Acid conditions has been demonstrated and has opened up the opportunity to use this methodology to generate MEP and further 2-hydroxy isosteres. The key intermediate in this approach has all stereocentres in place and differentially protected hydroxyl groups.

10.1 Further Work: MEP

Having successfully generated carbonate (182) we were then keen to progress to the latter stages of our proposed approach.

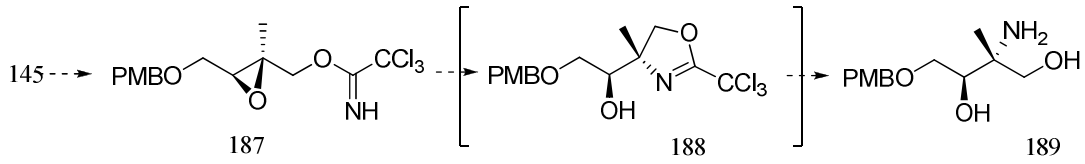
The generation of carbonate (182) proved to be a key intermediate in our approach to MEP. Although time constraints prevented us from moving this synthesis further forward, we reasoned we could follow literature methods already established within the group [72] to complete the transformation of the carbonate (182) to the final compound MEP (134).



Scheme 10.1.1

After the successful opening of the epoxide using NGP and Lewis acid conditions, we would like to explore the introduction of an amine isostere at the C-2 position. This could

be performed by protecting the epoxyalcohol (145) as the trichloroacetimidate (187). Rearrangement under Lewis acid conditions would then afford the amine (189) via the intermediate (188).



Scheme 10.1.2

10.2 Further Work: 2,2- DMEP

Molecular modelling studies carried out in the Hunter group at the University of Dundee, has suggested that a number of amines could be potential cytidyl mimics (Fig 10.2.1).

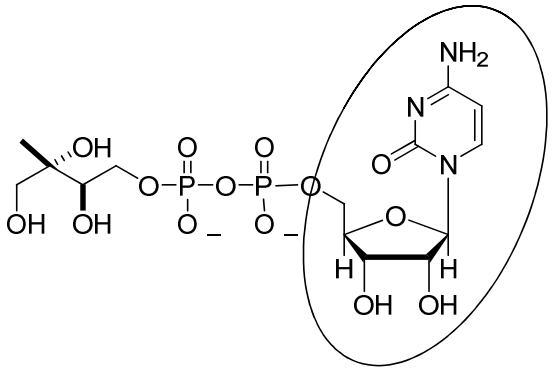
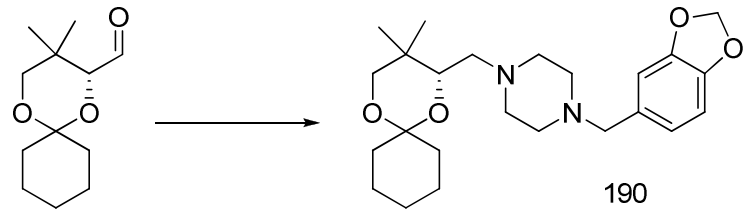


Figure 10.2.1

Preliminary data suggests that when aldehyde (166) was stirred with 1-piperonylpiperazine and sodium triacetoxyborohydride the amine (190) is generated in reasonable yield.



Reagents/ Conditions: (i) 1-piperonylpiperazine, Sodium triacetoxyborohydride, DCE, 40%

Scheme 10.2.1

Therefore, we would like to explore the generation of further amines utilising reductive amination conditions [86]. These new conditions could be used to generate a range of amines (Fig 10.2.2) from their corresponding, commercially available amines (Fig 10.2.2), selected for their potential as cytidyl mimics.

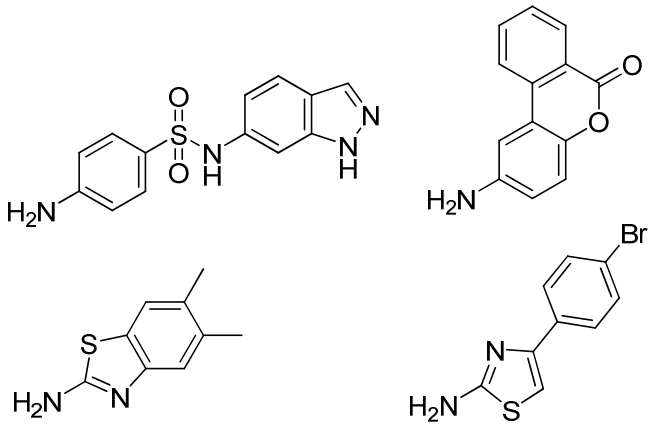
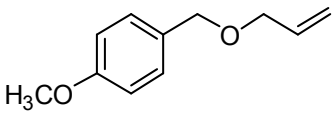


Figure 10.2.2- Potential cytidyl mimics available for reductive aminations

11 Section B: Experimental

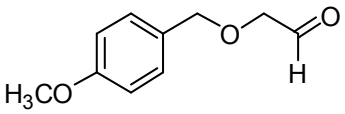
General Information. As in Section A experimental.



1-(Allyloxymethyl)-4-methoxybenzene, (153).

A solution of 1-(allyloxymethyl)-4-methoxybenzene (6.96g**,** 0.05 mol) in THF (20 mL) was added to a suspension of previously washed sodium hydride as a 60% oil dispersion, (3.2g, 0.08 mol) in dry THF (150 mL) at 0 ^{o}C, and the mixture was stirred for 30 min. The reaction mixture was cooled to 0 ^{o}C before addition of allyl bromide (12.99 mL, 0.15mol) and tetrabutylammonium iodide (0.93g, 2.52 mmol). The reaction was allowed to warm up to room temperature and was then stirred overnight. The reaction mixture was then extracted with DCM (200 mL) and water (100 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent evaporated to give 1-allyloxymethyl-4-methoxybenzene **(153)** (8.8g, 98%).

Spectral data matches those of literature reportings *Org. Biomol. Chem* **2007,** *5*, 97-102.

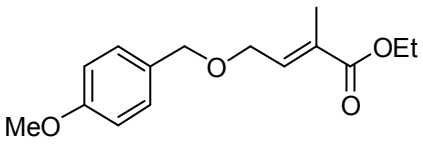


2-(4-Methoxybenzyloxy)acetaldehyde, (154).

A solution of 1-allyloxymethyl-4-methoxybenzene **(153)** (12.3g, 0.07 mol) in DCM (300 mL), was treated with ozone at −78 ^{o}C until the blue colour of ozone remained. At this point, argon was bubbled through until the blue colour disappeared. Methyl sulfide (102 mL, 1.38 mol) was then added to the solution and the resulting mixture stirred until TLC analysis indicated reaction completion (13hrs). The solvents were evaporated under vacuum, and the crude residue purified by

flash column chromatography (silica gel with 20-30% EtOAc in 40-60 petroleum ether)) to generate the desired aldehyde **(154)** as clear yellow oil (9.14g, 72%).

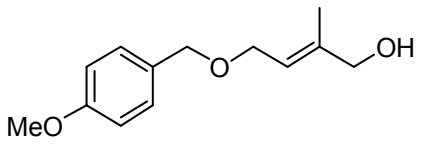
Spectral data matches those of literature reportings *Org. Biomol. Chem* **2007,** *5*, 97-102.



(*E*)-Ethyl 4-(4-methoxybenzyloxy)-2-methylbut-2-enoate, (156).

A solution of 2-(4-methoxybenzyloxy)acetaldehyde **(154)** (9.14g, 0.05mol) in toluene (300 mL) was treated with (carbethoxyethylidene) triphenylphosphorane (36.5g, 0.10 mol) and was refluxed overnight. The solvent was evaporated under vacuum, and the crude residue washed with diethyl ether. The mixture was then filtered to remove the solid triphenylphosphine oxide, and the filtrate was then evaporated under vacuum. Any remaining triphenylphosphine was removed by flash column chromatography (silica gel with 20-30% EtOAc in 40-60 petroleum ether)) to give (*E*)-ethyl 4-(4-methoxybenzyloxy)-2-methylbut-2-enoate **(156)** as the single *E* isomer (9.75g, 73%).

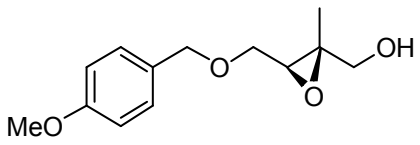
Spectral data matches those of literature reportings *Org. Biomol. Chem* **2007,** *5*, 97-102.



(*E*)-4-(4-Methoxybenzyloxy)-2-methylbut-2-en-1-ol, (157).

Lithium Aluminium Hydride (24.3 mL, 0.03mol) was added to a solution of (*E*)-ethyl 4-(4-methoxybenzyloxy)-2-methylbut-2-enoate **(156)** (6.65g, 0.025mol) in dry ether (80 mL) at 0 ^{o}C, and the resulting reaction mixture was stirred at 0 ^{o}C for 1 hr. Water (0.75 mL), $NaHCO_3$ (0.75ml) and water (2.5 mL) was added slowly, and the resulting white precipitate stirred for 1 hr at room temperature. The crude mixture was purified by flash column chromatography (silica gel with 10-20% EtOAc in 40-60 petroleum ether to afford (*E*)-4-(4-methoxybenzyloxy)-2-methylbut-2-en-1-ol as a light yellow oil **(157)** (4.81g, 86%).

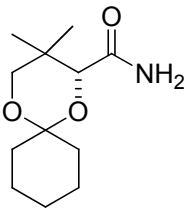
Spectral data matches those of literature reportings *Org. Biomol. Chem* **2007,** *5*, 97-102.



((2*S*,3*S*)-3-((4-Methoxybenzyloxy)methyl)-2-methyloxiran-2-yl)methanol, (145).

Diisopropyl-D-tartrate (0.11 mL, 0.52 mmol) and titanium (IV) isopropoxide (0.15 mL, 0.49 mmol) were added to a flask charged with activated powdered 4 A˚ molecular sieves (3 g) in dry dichloromethane (2 mL) at −23 ^{o}C. The mixture was stirred while *tert*-butyl hydroperoxide (0.57 mL, 3.11mmol) in dry dichloromethane (2 mL) was added dropwise, and the resulting solution was stirred for 30 min at −23 ◦C. A solution of (*E*)-4-(4-methoxybenzyloxy)-2-methylbut-2-en-1-ol **(157)** (316mg, 1.42 mmol) in dry dichloromethane (2 mL) was then added slowly, and the resulting reaction mixture was stirred for 6 hrs at −23 ^{o}C. The reaction was then quenched with water (11.9 g; 20 times the weight of the titanium(IV) isopropoxide used) and was stirred for a further 40 min, while allowing the suspension to warm to room temperature. To hydrolyse the tartrate, a 30% aqueous solution of sodium hydroxide saturated with sodium chloride was added and the biphasic mixture was stirred vigorously for 30 min. The mixture was filtered through a pad of silica and Celite to break up the emulsion, and the phases were separated. The aqueous phase was extracted with DCM (2 × 10 mL), the combined organic extracts were dried over Na_2SO_4 and the filtrate was evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with (silica gel with 25-40% EtOAc in 40-60 petroleum ether) to give [3-(4-methoxybenzyloxymethyl)-2-methyloxiranyl] methanol **(145)** (213mg, 64%, .90% *e.e*).

Spectral data matches those of literature reportings *Org. Biomol. Chem* **2007,** *5*, 97-102.



(*R*)-3,3-Dimethyl-1,5-dioxaspiro[5.5]undecane-2-carboxamide, (164).

p-Toluenesulphonic acid (516mg, 0.003mol) was added to a solution of amide (5.0g, 0.03mol) in DCM (80 mL). Cyclohexanone diethyl acetal was added (16.1 mL, 0.08mol). The reaction mixture was stirred at RT for 4.5hrs. The solvent was removed under vacuum, and the resulting oil was purified by flash column chromatography (silica gel with 30-50% EtOAc in 40-60 petroleum ether to afford (*R*)-3,3-dimethyl-1,5-dioxaspiro[5.5]undecane-2-carboxamide **(164)** as a white solid (4.52g, 66%).

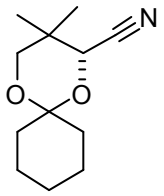
^{1}H NMR (400MHz, $CDCl_3$) δ: 6.47 (1H, bs, $N_{HA, HB}$), 5.64 (1H, bs, $N_{HA, HB}$), 4.06 (1H, s, C*H*(O)), 3.66 (1H, d, *J* = 11.7 Hz, $C_{HA, HB}$), 3.21 (1H, d, *J* = 11.7 Hz, $C_{HA, HB}$), 1.81 (2H, m, CH_2), 1.63 (2H, m, CH_2), 1.53 (2H, m, CH_2), 1.37 (4H, m, 2x CH_2), 1.00 (3H, s, CCH_3), 0.97 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 172.8 (NC=O), 99.2 (OCO), 76.5 (CH(O)), 70.7 (OCH_2), 38.3 (CH_2), 33.1 (*C*CH_3), 27.3 (CH_2), 25.6 (CH_2), 22.7 (CH_2), 22.4 (CH_2), 22.1 (C*C*H_3), 19.1 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3323 (s), 2978 (s), 1730 (s).

HRMS calcd for $C_{12}H_{21}NO_3$ ($M+H^+$): 227.1521 Found 228.1604.

$[\alpha]_D$ +204.4 (c = 1.0, $CHCl_3$)



(*R*)-3,3-Dimethyl-1,5-dioxaspiro[5.5]undecane-2-carbonitrile, (165).

A solution of Cyanuric chloride (156mg, 0.085mmol) in *t*-butylmethylether (5 mL) was added to a solution of (*R*)-3,3-dimethyl-1,5-dioxaspiro[5.5]undecane-2-carboxamide **(164)** (193mg, 0.85mmol) in DMF (5 mL). The reaction mixture was stirred for 16 hrs. The reaction mixture was neutralised with 28% NaOH (8 mL). The crude mixture was extracted with TBME (10 mL) and

water (10 mL). The organic layers were combined and dried over Na_2SO_4, and filtered. The solvent was removed under vacuum, and the resulting oil was purified by flash column chromatography (silica gel with 10-20% EtOAc in 40-60 petroleum ether to afford 3,3-dimethyl-1,5-dioxaspiro[5.5]undecane-2-carbonitrile as a clear oil **(165)** (116mg, 65%).

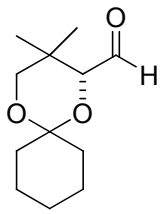
^{1}H NMR (400MHz, $CDCl_3$) δ: 4.53 (1H, s, C*H*(O)), 3.66 (1H, d, *J* = 11.9 Hz, $C_{HA,\ HB}$), 3.48 (1H, d, *J* = 11.8 Hz, $C_{HA,\ HB}$), 1.84 (2H, m, CH_2), 1.74 (2H, m, CH_2), 1.60 (2H, m, CH_2), 1.46 (4H, m, 2x CH_2).

^{13}C NMR (100MHz, $CDCl_3$) δ: 116.7 (C≡N), 100.1 (OCO), 68.7 (OCH_2), 68.6 (CH(O)), 42.0 (CH_2), 36.9 (CH_2), 33.2 (*C*CH_3), 27.9 (CH_2), 25.4 (CH_2), 22.3 (CH_2), 21.6 (C*C*H_3), 19.9 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 2995(s), 2250 (s).

HRMS calcd for $C_{12}H_{19}NO_2$ (M+ ·): 209.1416. Found 209.1419.

$[\alpha]_D$ +12.9 (c = 1.3, $CHCl_3$).



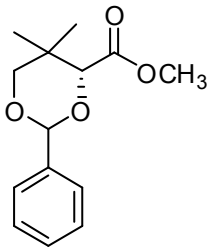
(*R*)-3,3-Dimethyl-1,5-dioxaspiro[5.5]undecane-2-carbaldehyde, (166).

Dibal (0.62 mL, 0.61mmol) was added to a solution of 3,3-dimethyl-1,5-dioxaspiro[5.5]undecane-2-carbonitrile **(165)** (116mg, 0.55mmol) in dry ether (5 mL) at 0 ^{o}C, and the resulting reaction mixture was stirred at 0 ^{o}C for 1 hr. The reaction mixture was allowed to warm to RT over 16 hrs. The reaction was worked up with Rochelles salt (2 mL), and the resulting white precipitate stirred for 1 hr at room temperature. The crude mixture was purified by flash column chromatography (silica gel with 10-20% EtOAc in 40-60 petroleum ether to afford 3,3-dimethyl-1,5-dioxaspiro[5.5]undecane-2-carbaldehyde as a clear oil **(166)** (66mg, 57%).

^{1}H NMR (400MHz, $CDCl_3$) δ: 9.58 (1H, s, O=C*H*), 3.96 (1H, s, C*H*(O)), 3.71 ((1H, d, *J* = 11.5 Hz, $C_{HA,\ HB}$), 3.26 (1H, d, *J* = 11.5 Hz, $C_{HA,\ HB}$), 1.86 (2H, m), 1.73 (2H, m), 1.62 (2H, m), 1.44 (4H, m), 1.12 (3H, s, CCH_3), 0.95 (3H, s, CCH_3)

^{13}C NMR (100MHz, $CDCl_3$) δ: 212.9 (O=CH), 76.5 (OCH_2), 75.8 (CH(O)), 69.3 (OCO), 43.9 (*C*CH_3), 41.9 (CH_2), 27.0 (CH_2), 24.9 (CH_2), 22.9 (CH_2), 22.1 (2x CH_2), 21.9 (CH_3), 18.8 (CH_3).

IR ν_{max}(film)/cm^{-1} 2982 (s), 2854 (s), 1752 (s). HRMS calcd for $C_{12}H_{20}O_3$ (M+ ·): 212.1412. Found 212.1417. $[\alpha]_D$ -5.091 (c = 1.1, $CHCl_3$).



(4*S*)-Methyl 5,5-dimethyl-2-phenyl-1,3-dioxane-4-carboxylate, (168).

A solution of pantolactone **(19)** (1.99g, 0.015mol) and benzaldehyde dimethyl acetal (3.9 mL, 0.026mol) in dioxane (5 mL) was treated with *p*-toluenesulphonic acid (58mg, 0.3 mmol) and the resulting mixture stirred at room temperature for 48hrs. Upon reaction completion as indicated by TLC analysis, the reaction was quenched with $NaHCO_3$ (2 mL) and stirred for a further 3hrs. After this time the the solution was diluted with Et_2O (15 mL), washed with $NaHCO_3$ (5 mL) and H_2O (10 mL) and brine (5 mL). The organic layer was separated and dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% EtOAc in 40-60 petroleum ether) to afford the desired ester **(168)** (1.39g, 37%).

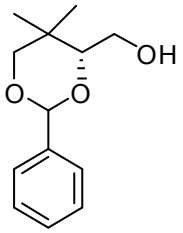
^{1}H NMR (400MHz, $CDCl_3$) δ: 7.58 (2H, dd, *J* = 7.6, 1.6 Hz, Ar*H* x2), 7.40 (3H, m, 3x Ar*H*), 5.54 (1H, s, OC*H*O), 4.31 (1H, s, C*H*(O)), 3.81 (3H, s, OCH_3), 3.80 (1H, d, *J* = 11.2 Hz, $C_{HA,\ HB}$), 3.73 (1H, d, *J* = 11.2 Hz, $C_{HA,\ HB}$), 1.25 (3H, s, CCH_3), 1.03 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 169.2 (OC=O), 137.7 (ArC q), 129.1 (ArC), 128.3 (2x ArC), 126.4 (2x ArC), 101.6 (OCO), 83.9 (CH(O)), 78.3 (OCH_2), 51.8 (OCH_3), 32.9 (*C*CH_3), 21.7 (C*C*H_3), 19.6 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 2959 (s), 2873 (s), 1735 (s), 1395 (s), 1371 (s).

HRMS calcd for $C_{14}H_{19}O_4$ ($M+H^+$): 251.1283. Found 251.1280.

$[\alpha]_D$ -40.2 (c = 1.7, $CHCl_3$).



(4*S*)-(5,5-Dimethyl-2-phenyl-1,3-dioxan-4-yl)methanol, (169).

A solution of ester **(168)** (1.12g, 4.5mmol) in diethylether (30 mL) was cooled to 0°C before being treated with $LiAlH_4$ (1.0M diethylether) (16 mL, 0.016mol). The mixture was stirred at 0°C for 10mins, warmed to room temperature and stirred for a further 2hrs. Upon reaction completion as indicated by TLC analysis, the reaction was quenched with the addition of H_2O (1 mL), 15% NaOH (1 mL), and H_2O (3 mL). The organic layer was extracted with ether (2x 20 mL) and the solvent was removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 30% EtOAc in 40-60 petroleum ether) to generate the desired alcohol **(169)** (652mg, 65%)

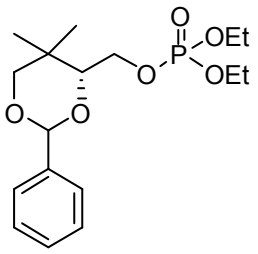
^{1}H NMR (400MHz, $CDCl_3$) δ: 7.41 (2H, dd, *J* = 7.6, 1.8 Hz, Ar*H* x2), 7.26 (3H, m, 3x Ar*H*), 5.35 (1H, s, OC*H*O), 3.48 (5H, m, 2x CH_2 and C*H*(O)), 2.55 (1H, bs, OH), 0.98 (3H, s, CCH_3), 0.68 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 138.3 (ArC q), 129.1 (ArC), 128.4 (2x ArC), 126.3 (2x ArC), 102.1 (OCO), 85.9 (CH(O)), 78.9 (HOCH_2), 61.6 (OCH_2), 31.6 (*C*CH_3), 21.4 (C*C*H_3), 19.2 (C*C*H_3)

IR ν_{max}(film)/cm^{-1} 3442 (br), 2958 (s), 2850 (s), 1393 (s).

HRMS calcd for $C_{13}H_{19}O_3$ ($M+H^+$): 223.1334. Found 223.1333.

$[\alpha]_D$ +19.3 (c = 1.6, $CHCl_3$).



(4*S*)-(5,5-Dimethyl-2-phenyl-1,3-dioxan-4-yl)methyl diethyl phosphate, (171).

Iodine (145mg, 0.6 mmol) was added to a solution of triethyl phosphite (0.11 mL, 0.67 mmol) in dry DCM (2 mL) at 0 ^{o}C, and the solution was stirred for 20 min at 0 ^{o}C and then for 1 hr at room temperature. The freshly made phosphorylation agent was then added slowly to a roundbottomed flask containing 5,5-dimethyl-2-phenyl-1,3-dioxan-4-yl)methanol (169) (124mg, 0.6 mmol) and pyridine (0.18 mL, 2.2 mmol) in dry DCM (3 mL) at −40 ^{o}C. The reaction was allowed to warm up to room temperature and stirred for 4 hr. The mixture was then washed with a solution of 3% $KHSO_4$ (5 mL), saturated $NaHCO_3$ (5 mL), and brine (5 mL). The organic layer was then extracted with DCM (2x 10 mL) dried over Na_2SO_4 and the solvent was removed under vacuum. The crude residue was then purified by flash chromatography on silica gel eluting with 20-30% EtOAc in 40-60 petroleum ether to give the expected phosphoric acid 5,5-dimethyl-2-phenyl-1,3-dioxan-4-yl)methyl diethyl phosphate **(171)** (215mg, 30%).

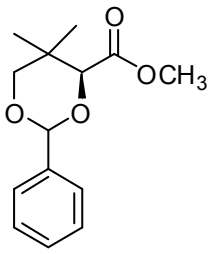
^{1}H NMR (400MHz, $CDCl_3$) δ: 7.52 (2H, dd, *J* = 7.5, 1.9 Hz, Ar*H* x2), 7.37 (3H, m, 3x Ar*H*), 5.52 (1H, s, OC*H*O), 4.21 (1H, ddd, *J* = 11.1, 6.1, 2.7 Hz, ($C_{HC,\ HD}$), 4.10 (5H, m, 2 x POCH_2CH$_3$ and $C_{HC,\ HD}$), 3.89 (1H, dd, *J* = 7.9, 2.6 Hz, CH(O)), 3.72 (1H, d, *J* = 11.2 Hz, $C_{HA,\ HB}$), 3.66 (1H, d, *J* = 11.3 Hz, $C_{HA,\ HB}$), 1.22 (3H, dt, *J* = 7.1, 1.0 Hz, POCH$_2$C*H*$_3$), 1.18 (3H, dt, *J* = 7.1, 1.0 Hz, POCH$_2$C*H*$_3$), 1.17 (3H, s, CC*H*$_3$), 0.91 (3H, s, CC*H*$_3$).

^{13}C NMR (100MHz, $CDCl_3$) δ: 138.2 (ArC q), 128.9 (ArC), 128.2 (2x ArC), 126.2 (2x ArC), 101.8 (OCO), 83.8 (CH(O)), 78.7 (OCH$_2$), 66.7 (O*C*H$_2$CH$_3$), 66.6 (O*C*H$_2$CH$_3$), 63.9 (O*C*H$_2$CH$_3$), 31.7 (*C*CH$_3$), 21.5 (C*C*H$_3$), 18.9 (C*C*H$_3$), 16.1 (OCH$_2$*C*H$_3$), 16.0 (OCH$_2$*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 2980 (s), 2910 (s), 2872 (s), 1468 (s).

HRMS calcd for $C_{17}H_{28}O_6P$ (M+H^{+}): 359.1624. Found 359.1621.

$[\alpha]_D$ +51.8 (c = 2.0, $CHCl_3$).



(4*R*)-Methyl 5,5-dimethyl-2-phenyl-1,3-dioxane-4-carboxylate, (172).

A solution of pantolactone **(19b)** (1.03g, 8mmol) and benzaldehyde dimethyl acetal (1.95 mL, 0.013mmol) in dioxane (5 mL) was treated with *p*-toluenesulphonic acid (30mg, 0.16mmol) and the resulting mixture stirred at room temperature for 48hrs. Upon reaction completion as indicated by TLC analysis, the reaction was quenched with $NaHCO_3$ (2 mL) and stirred for a further 3hrs. After this time the the solution was diluted with Et_2O (10 mL), washed with $NaHCO_3$ (5 mL), H_2O (5 mL) and brine (5 mL). The organic layer was separated and dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% EtOAc in 40-60 petroleum ether) to afford the desired ester **(172)** (1.00g, 50%).

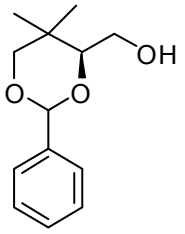
^{1}H NMR (400MHz, $CDCl_3$) δ: 7.55 (2H, dd, *J* = 7.7, 1.8 Hz, Ar*H* x2), 7.36 (3H, m, 3x Ar*H*), 5.49 (1H, s, OC*H*O), 4.27 (1H, s, C*H*(O)), 3.76 (1H, d, *J* = 11.3 Hz, $C_{HA,\ HB}$), 3.75 (3H, s, OCH_3), 3.68 (1H, d, *J* = 11.3 Hz, $C_{HA,\ HB}$), 1.21 (3H, s, CCH_3), 0.99 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 169.2 (OC=O), 137.7 (ArC q), 129.2 (ArC), 128.4 (2x ArC), 126.4 (2x ArC), 101.7 (OCO), 84.0 (CH(O)), 78.4 (OCH_2), 51.9 (OCH_3), 33.0 (CCH_3), 21.8 (CCH_3), 19.7 (CCH_3).

IR ν_{max}(film)/cm^{-1} 2959 (s), 2909 (s), 1735 (s), 1458 (s).

HRMS calcd for $C_{14}H_{19}O_4$ ($M+H^+$): 251.1283. Found 251.1282.

$[\alpha]_D$ +21.9 (c = 1.9, $CHCl_3$).



(4*R*)-(5,5-Dimethyl-2-phenyl-1,3-dioxan-4-yl)methanol, (173).

A solution of ester (**172**) (990mg, 4 mmol) in diethylether (10 mL) was cooled to 0°C before being treated with $LiAlH_4$ (1.0M diethylether) (14 mL, 0.014mol). The mixture was stirred at 0°C for 10mins, warmed to room temperature and stirred for a further 2hrs. Upon reaction completion as indicated by TLC analysis, the reaction was quenched with the addition of H_2O (0.5 mL), 15% NaOH (0.5 mL), and H_2O (1.5 mL). The organic layer was extracted with ether (2x 12 mL) and the solvent was removed under vacuum. The crude residue was then purified by flash column chromatography (silica gel, 10% to 30% EtOAc in 40-60 petroleum ether) to generate the desired alcohol (**173)** (458mg, 52%).

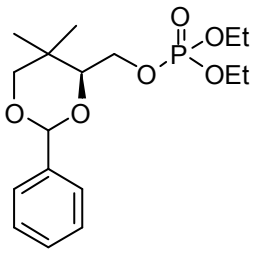
^{1}H NMR (400MHz, $CDCl_3$) δ: 7.55 (2H, dd, *J* = 7.6, 1.9 Hz, Ar*H* x2), 7.40 (3H, m, 3x Ar*H*), 5.53 (1H, s, OC*H*O), 3.71 (4H, m, OCH_2 and CH(O) and $C_{HA,\ HB}$), 3.63 (1H, d, *J* = 11.4 Hz, $C_{HA,\ HB}$), 2.24 (1H, bs, OH), 1.16 (3H, s, CCH_3), 0.86 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 136.9 (ArC q), 127.7 (ArC), 126.9 (2x ArC), 124.9 (2x ArC), 100.6 (OCO), 84.5 (CH(O)), 77.4 ($HOCH_2$), 59.9 (OCH_2), 30.1 (*C*CH_3), 19.9 (C*C*H_3), 17.7 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3450 (s), 2958 (s), 2850 (s), 1467 (s), 1393 (s), 1359 (s).

HRMS calcd for $C_{13}H_{18}O_3$ (M+ ·): 222.1256. Found 222.1253.

$[\alpha]_D$ -20.5 (c = 1.6, $CHCl_3$).



(4*R*)-(5,5-Dimethyl-2-phenyl-1,3-dioxan-4-yl)methyl diethyl phosphate, (174).

Iodine (375mg, 1.5 mmol) was added to a solution of triethyl phosphite (0.3 mL, 1.7 mmol) in dry DCM (2 mL) at 0 ^{o}C, and the solution was stirred for 20 min at 0 ^{o}C and then for 1 hr at room temperature. The freshly made phosphorylation agent was then added slowly to a roundbottomed flask containing 5,5-dimethyl-2-phenyl-1,3-dioxan-4-yl)methanol **(173)** (322mg, 1.5 mmol) and pyridine (0.47 mL, 6 mmol) in dry DCM (8 mL) at −40 ^{o}C. The reaction was allowed to warm up to room temperature and stirred for 4 hrs. The mixture was then washed with a solution of 3% $KHSO_4$ (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL). The organic layer was then extracted with DCM (2x 15 mL), dried over Na_2SO_4, and the solvent removed under vacuum. The crude residue was then purified by flash chromatography on silica gel eluting with 20-30% EtOAc in 40-60 petroleum ether to give the expected phosphoric acid 5,5-dimethyl-2-phenyl-1,3-dioxan-4-yl)methyl diethyl phosphate **(174)** (172mg, 32%).

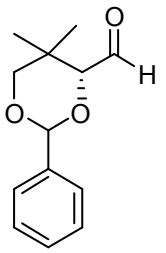
^{1}H NMR (400MHz, $CDCl_3$) δ: 7.43 (2H, dd, *J* = 7.6, 1.9 Hz, Ar*H* x2), 7.28 (3H, m, 3x Ar*H*), 5.43 (1H, s, OC*H*O), 4.12 (1H, ddd, *J* = 11.1, 6.1, 2.6 Hz, $C_{HC,\ HD}$), 4.01 (5H, m, $C_{HC,\ HD}$ and $POCH_2CH_3$ x2), 3.80 (1H, dd, *J* = 7.9, 2.6 Hz, CH(O)), 3.62 (1H, d, *J* = 11.2 Hz, $C_{HA,\ HB}$), 3.56 (1H, d, *J* = 11.2 Hz, $C_{HA,\ HB}$), 1.31 (3H, dt, *J* = 7.1, 1.0 Hz, $POCH_2CH_3$), 1.27 (3H, dt, *J* = 7.1, 1.0 Hz, $POCH_2CH_3$), 1.08 (3H, s, CCH_3), 0.82 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 138.2 (ArC q), 128.9 (ArC), 128.2 (2x ArC), 126.2 (2x ArC), 101.8 (OCO), 83.8 (CH(O)), 78.7 (OCH_2), 66.7 (OCH_2CH_3), 66.6 (OCH_2CH_3), 63.8 (OCH_2CH_3), 31.7(CCH_3), 21.5 (CCH_3), 18.9 (CCH_3), 16.1 (OCH_2CH_3), 16.0 (OCH_2CH_3).

IR ν_{max}(film)/cm^{-1} 2980 (s), 2910 (s), 2872 (s), 1468 (s).

HRMS calcd for $C_{17}H_{28}O_6P$ ($M+H^+$): 359.1624. Found 359.1627.

$[\alpha]_D$ -49.1 (c = 1.1, $CHCl_3$).



(4*S*)-5,5-Dimethyl-2-phenyl-1,3-dioxane-4-carbaldehyde, (175). DMSO (1.14 mL, 0.016mol) was added slowly to oxalyl chloride (7 mL, 0.014mol) at -78 °C. When addition was complete, the activated oxalyl chloride was stirred for 5mins at -78 °C. 5,5-dimethyl-2-phenyl-1,3-dioxan-4-yl)methanol **(169)** (2.35g, 0.011mol) was added as a DCM solution (30 mL) and stirred at -78 °C. After 1hr, Et_3N (4.28 mL, 0.031mol) was added, the solution warmed to RT, and stirred for a further 1hr. The reaction was worked up by addition of 1N HCl (1 mL), sat. $NaHCO_3$ (1 mL), H_2O (1 mL) and finally brine (1 mL). The organic layer was extracted with DCM, dried over Na_2SO_4, and the solvent removed under vacuum. The crude residue was then purified by flash chromatography on silica gel eluting with 5-20% EtOAc in 40-60 petroleum to generate the desired aldehyde **(175)** (1.43g, 59%).

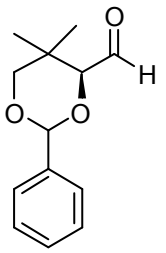
^{1}H NMR (400MHz, $CDCl_3$) δ: 9.59 (1H, d, *J* = 1.2, O=C*H*), 7.49 (2H, dd, *J* = 7.6, 1.7 Hz, Ar*H* x2), 7.33 (3H, m, 3x Ar*H*), 5.47 (1H, s, OC*H*O), 3.88 (1H, s, C*H*(O)), 3.65 (1H, d, *J* = 11.3 Hz, $C_{HA,\ HB}$), 3.59 (1H, d, *J* = 11.3 Hz, $C_{HA,\ HB}$), 1.17 (3H, s, CCH_3), 0.94 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 201.7 (O=CH), 137.6 (ArC q), 129.4 (ArC), 128.5 (ArC x2), 126.3 (ArC x2), 101.6 (OCO), 87.4 (CH(O)), 78.6 (OCH_2), 33.6 (*C*CH_3), 20.9 (C*C*H_3), 19.2 (C*C*H_3).

IR ν_{max}(film)/cm^{-1} 3468 (s), 2963 (s), 2856 (m), 1758 (s) 1468 (s), 1393 (s).

HRMS calcd for $C_{13}H_{17}O_3$ ($M+H^+$): 221.1178. Found 221.1187.

$[\alpha]_D$ +108.0 (c = 1.1, $CHCl_3$).



(4*R*)-5,5-Dimethyl-2-phenyl-1,3-dioxane-4-carbaldehyde, (176)

DMSO (0.05 mL, 0.67mmol) was added slowly to oxalyl chloride (0.3 mL, 0.6mmol) at -78 ^{o}C. When addition was complete, the activated oxalyl chloride was stirred for 5mins at -78 ^{o}C. ((4*R*)-5,5-dimethyl-2-phenyl-1,3-dioxan-4-yl)methanol **(173)** (99mg, 0.45mmol) was added as a DCM solution (3 mL) and stirred at -78 ^{o}C. After 1hr, Et_3N (0.18 mL, 1.3mmol) was added, the solution warmed to RT, and stirred for a further 1hr. The reaction was worked up by addition of 1N HCl (0.5 mL), sat. $NaHCO_3$ (0.5 mL), H_2O (0.5 mL) and finally brine (0.5 mL). The organic layer was extracted with DCM, dried over Na_2SO_4, and the solvent removed under vacuum. The crude residue was then purified by flash chromatography on silica gel eluting with 5-20% EtOAc in 40-60 petroleum to generate the desired aldehyde **(176)** (61mg, 62%).

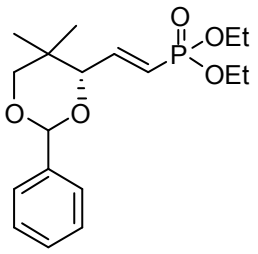
^{1}H NMR (400MHz, $CDCl_3$) δ: 9.71 (1H, d, *J* = 1.4 Hz, O=C*H*), 7.60 (2H, dd, *J* = 7.5, 1.9 Hz, Ar*H* x2), 7.44 (3H, m, 3x Ar*H*), 5.59 (1H, s, OC*H*O), 3.99 (1H, s, C*H*(O)), 3.77 (1H, d, *J* = 11.3 Hz, $C_{HA,\ HB}$), 3.70 (1H, d, *J* = 11.4 Hz, $C_{HA,\ HB}$), 1.28 (3H, s, CCH_3), 1.06 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 201.7(O=CH), 137.6 (ArC q), 129.4 (ArC), 128.5 (2x ArC), 126.3 (2x ArC), 101.6 (OCO), 87.4 (CH(O)), 78.6 (CH_2), 33.6 ($C$$CH_3$), 20.9 (C$C$$H_3$), 19.2 (C$C$$H_3$).

IR ν_{max}(film)/cm^{-1} 3468 (s), 2963 (s), 2832 (m), 1758 (s) 1468 (s), 1393 (s).

HRMS calcd for $C_{13}H_{17}O_3$ ($M+H^+$): 221.1178. Found 221.1176.

$[\alpha]_D$ -107.1 (c = 1.1, $CHCl_3$).



Diethyl-(*E*)-2-((4*R*)-5,5-dimethyl-2-phenyl-1,3-dioxan-4-yl)vinylphosphonate, (177).

n-BuLi (0.38 mL, 0.87mmol) was added slowly to a solution of tetraethylmethylene diphosphonate (0.29 mL, 1.2mmol) in THF (5 mL) at -78 ^{o}C, and stirred at -78 ^{o}C for 30mins. 5,5-dimethyl-2-phenyl-1,3-dioxane-4-carbaldehyde **(175)** (160mg, 7.3mmol) was then added as THF solution (5 mL) and continued to stir at -78 ^{o}C for 1hr. The reaction mixture was warmed to RT and stirred for a further 1hr. Workup was performed by addition of 10% *w/v* NH_4Cl (1 mL). The organic layer was extracted with EtOAc (2x 5 mL), the organic collections combined, dried over Na_2SO_4 and the solvent removed under vacuum. The crude oil was passed over a pad of silica to yield the desired phosphonate (**177**) (151mg, 49%).

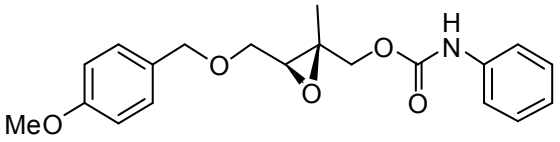
^{1}H NMR (400MHz, $CDCl_3$) δ: 7.44 (2H, dd, *J* = 7.6, 1.8 Hz, Ar*H* x2), 7.31 (3H, m, 3x Ar*H*), 6.76 (1H, ddd, *J* = 23.0, 17.1, 3.5 Hz, HC=C*H*), 5.97 (1H, ddd, *J* = 21.1, 17.1, 2.0 Hz, *H*C=CH), 5.46 (1H, s, OC*H*O), 4.14 (1H, dd, *J* = 5.5, 3.5 Hz, CH(O)), 4.00 (4H, m, 2x OCH_2CH$_3$)), 3.68 (1H, d, *J* = 11.1 Hz, $C_{HA,\ HB}$), 3.59 (1H, d, *J* = 11.2 Hz, $C_{HA,\ HB}$), 1.24 (6H, dt, *J* = 7.1, 3.7 Hz, 2x OCH$_2$CH_3), 1.01 (3H, s, CCH_3), 0.85 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 146.4 (C=*C*), 137.2 (ArC q), 127.9 (ArC), 127.2 (2x ArC), 125.2 (2x ArC), 100.6 (OCO), 82.9 (CH(O)), 82.7 (*C*=C), 77.3 (OCH$_2$), 60.8 (O*C*H$_2$CH$_3$), 60.7 (O*C*H$_2$CH$_3$), 32.4 (*C*CH$_3$), 20.3 (C*C*H$_3$), 18.0 (C*C*H$_3$), 15.4 (OCH$_2$*C*H$_3$), 15.3 (OCH$_2$*C*H$_3$).

IR ν_{max}(film)/cm^{-1} 3013 (s), 2973 (s), 2913 (s), 2870 (s), 1635 (s), 1466 (s).

HRMS calcd for $C_{18}H_{28}O_5P$ (M+H^{+}): 355.1674. Found 355.1675.

$[\alpha]_D$ -27.8 (c = 1.8, $CHCl_3$).



[(3*S*)-3-([(4-Methoxyphenyl)methoxy]methyl)-2-methyl oxiran-2-yl]methyl phenylcarbamate, (181).

To a solution of ((2*S*, 3*S*)-3-((4-methoxybenzyloxy)methyl)-2-methyloxiran-2-yl)methanol **(145)** (166mg, 0.69mmol) in dry DCM (3 mL), Et_3N (6 drops) was added and stirred for 20mins. After this time, phenylisocyanate (0.09 mL, 0.83mmol) was added and stirred for 2.5hrs. At completion by TLC analysis, the white precipitate was filtered through Celite, and the filtrate concentrated under vacuum. The crude residue was purified by flash column chromatography (silica gel with 10-20% EtOAc in 40-60 petroleum ether) to give ((2*S*, 3*S*)-3-((4-methoxybenzyloxy)methyl)-2-methyloxiran-2-yl)methyl phenylcarbamate **(181)** (179mg, 72%).

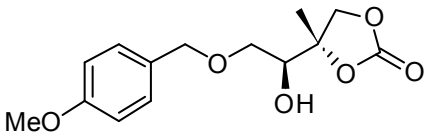
^{1}H NMR (400MHz, $CDCl_3$) δ: 7.26 (6H, m, 4x Ar*H* and 2x PMB-Ar*H*), 7.01 (1H, t, *J* = 7.3 Hz, Ar*H*), 6.81 (2H, d, *J* = 8.6 Hz, 2x PMB-Ar*H*), 4.50 (1H, d, *J* = 11.5 Hz, $BnC_{HA,\ HB}$), 4.40 (1H, d, *J* = 11.5 Hz, $BnC_{HA,\ HB}$), 4.23 (1H, d, *J* = 11.8 Hz, $C_{HC,\ HD}$), 3.99 (1H, d, *J* = 11.9 Hz, $C_{HC,\ HD}$), 3.73 (3H, s, OCH_3), 3.62 (1H, dd, *J* = 11.2, 4.6 Hz, $C_{HE,\ HF}$), 3.51 (1H, dd, *J* = 11.2, 6.0 Hz, $C_{HE,\ HF}$), 3.13 (1H, dd, *J* = 5.8, 4.8 Hz, CH(O)), 1.24 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 204.4 (ArC q), 159.4 (NC=O), 137.5 (ArC q), 129.8 (ArC q), 129.5 (2x ArC), 129.1 (2x ArC), 123.7 (ArC), 113.9 (2x ArC), 73.0 (CH_2), 68.2 (CH_2), 67.8 (CH_2), 59.1(OCH_3), 58.1 (CCH_3), 55.3 (CH(O)), 14.5 (CCH_3).

IR ν_{max}(film)/cm^{-1} 3319 (s), 2935 (s), 2857 (s), 1734 (s), 1214 (s).

HRMS calcd for $C_{20}H_{23}NO_5$ (M+ ·): 357.1576. Found 357.1572.

$[a]_D$ +7.1 (c = 1.4, $CHCl_3$).



(4*R*)-4-[(1*S*)-1-Hydroxy-2-[(4-methoxyphenyl)methoxy]ethyl]-4-methyl-1,3-dioxolan-2-one, (182).

A solution of [(3S)-3-([(4-methoxyphenyl)methoxy]methyl)-2-methyl oxiran-2-yl]methyl phenylcarbamate **(181)** (110mg, 0.31mmol) in (3:1 Et_2O : DCM) (4 mL) was stirred at 0 ^oC, before adding Et_2AlCl (0.92 mL, 0.92mmol) and stirring at 0 ^oC for a further 3hrs. After this time 0.5M HCl was added and stirred for 10mins. The solution was extracted with DCM (10 mL), washed with Brine (4 mL), $NaHCO_3$ (4 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated under vacuum. The crude residue was purified by flash column chromatography (silica gel with 10-20% EtOAc in 40-60 petroleum ether) to give (*S*)-4-((*S*)-1-hydroxy-2-(4-methoxybenzyloxy)ethyl)-4-methyl-1,3-dioxolan-2-one **(182)** as a clear oil (23mg, 27%).

^1H NMR (400MHz, $CDCl_3$) δ: 7.15 (2H, d, *J* = 8.6 Hz, 2x Ar*H*)), 6.82 (2H, d, *J* = 8.6 Hz, 2x Ar*H*), 4.61 (1H, d, *J* = 8.8 Hz, $C_{HA,\ HB}$), 4.43 (1H, d, *J* = 11.4 Hz, $C_{HC,\ HD}$), 4.33 (1H, d, *J* = 11.4 Hz, $C_{HC,\ HD}$), 3.95 (1H, d, *J* = 8.8 Hz, $C_{HA,\ HB}$), 3.84 (1H, bdd, *J* = 7.2, 4.5 Hz, CH(O)), 3.74 (3H, s, OCH_3), 3.56 (1H, dd, *J* = 10.3, 2.7 Hz, $C_{HE,\ HF}$), 3.45 (1H, dd, *J* = 10.3, 5.0 Hz, $C_{HE,\ HF}$), 2.92 (1H, d, *J* = 4.6 Hz, OH), 1.35 (3H, s, CCH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ: 159.5 (ArC q), 154.6 (C=O), 129.7 (ArC q), 129.5 (ArC x2), 114.1 (ArC x2), 84.5 (CCH_3), 73.5 (CH_2), 72.9 (CH(O)), 71.9 (CH_2), 69.3 (CH_2), 55.3 (OCH_3), 21.2 (CH_3).

IR νmax(film)/cm^{-1} 3397 (s, br), 1770(s), 1600 (s), 1570 (s).

HRMS calcd for $C_{14}H_{18}O_6$ (M+ ·): 282.1103. Found 282.1100.

$[a]_D$ +10.5 (c = 1.2, $CHCl_3$).

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