A Flexible One-Step Synthesis of Dienamides: Approaches Towards a Total Synthesis of the Crocacins

Jennifer E. Mathieson (M. Sci)

A thesis submitted in fulfilment of the requirements of the degree of Master of Science

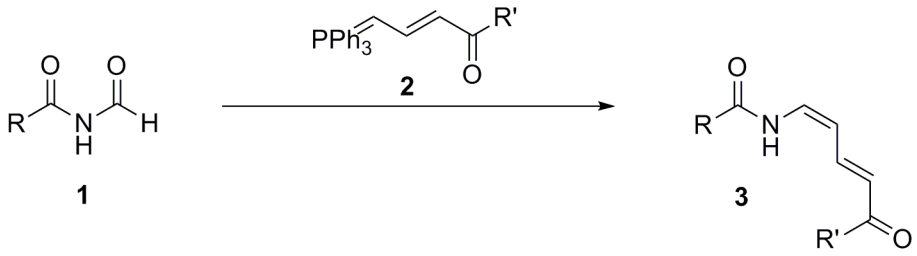
School of Chemistry
College of Science & Engineering
University of Glasgow

June 2012

Abstract

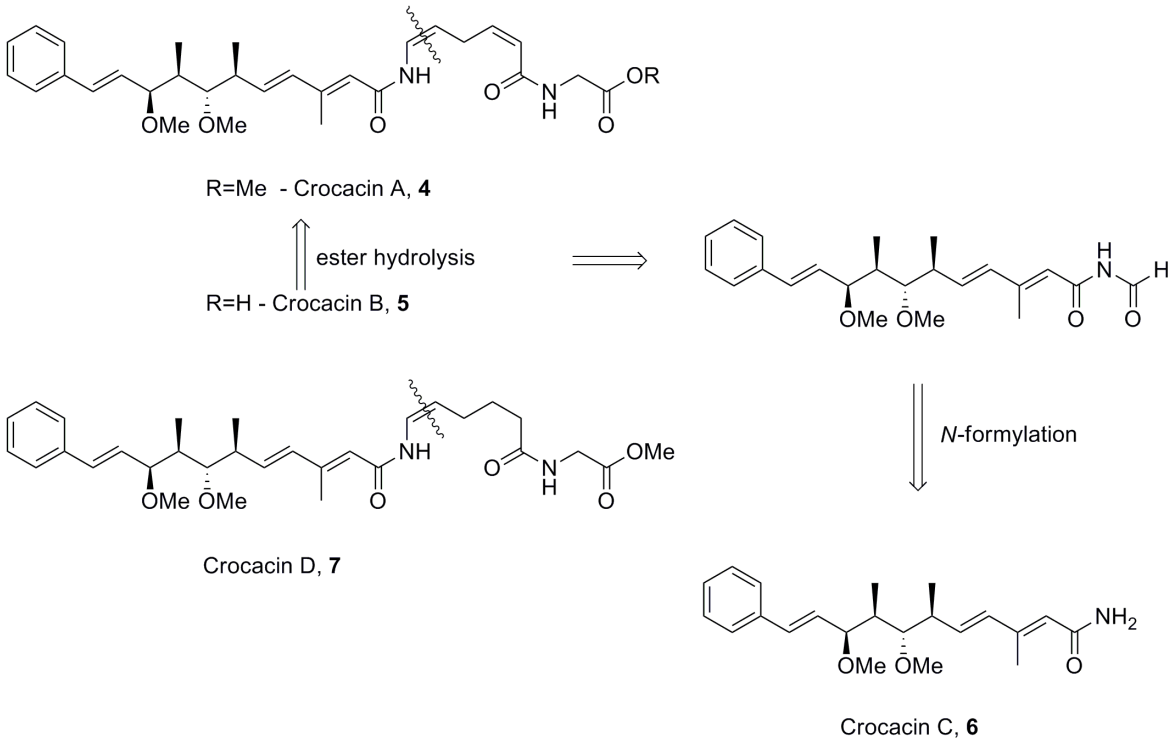
Dienamides are prevalent in many biologically active natural products and pharmaceutical drug leads. A number of different approaches have been reported for the synthesis of dienamides. These methods have varying degrees of success in terms of yield and selectivity. In particular, the control of double bond geometry presents a significant challenge. Presented, is an efficient one step synthesis of dienamide units starting from previously established *N*-formyl imide building blocks.

This approach presents an attractive alternative to other methods available currently in terms of the number of steps, yield and overall simplicity. The one-step approach to the synthesis of dienamides **3** relies on the olefination of *N*-formyl imides **1** through the use of the conjugated ylide **2** (Scheme 1). A number of final dienamide compounds have been synthesised, characterised and published thus far. In all cases the sole or major isomer observed was the (*Z,E*)-dienamide.



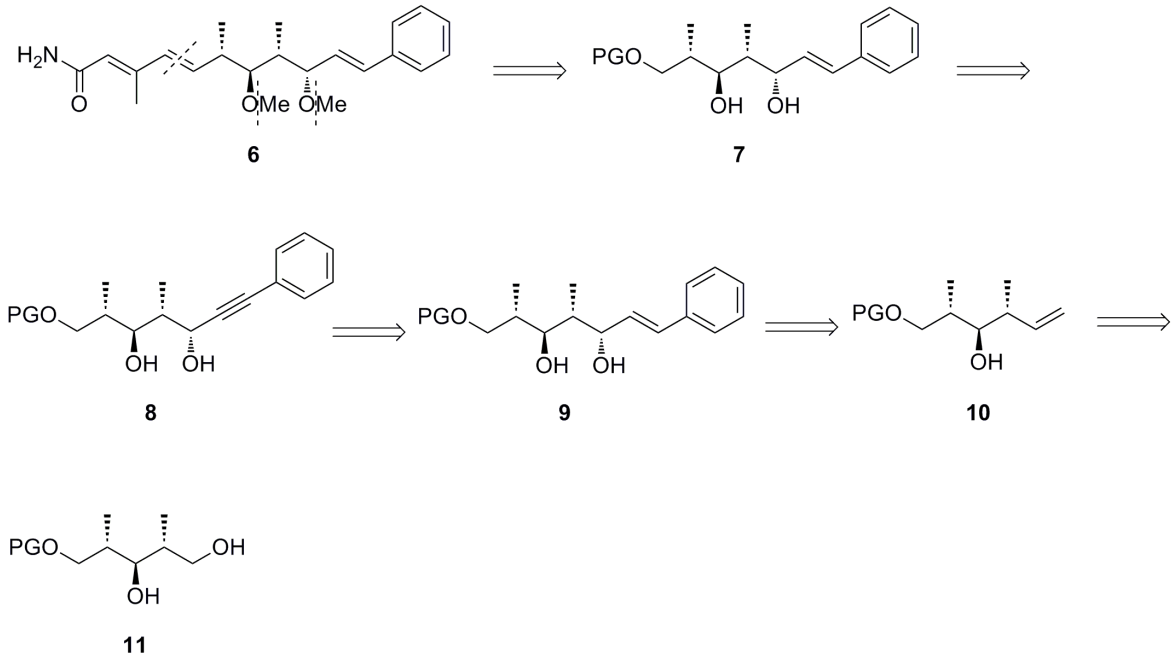
Scheme 1 Proposed one-step synthesis of dienamides

The Crocacins **4-7** are a group of linear dipeptides incorporating a reactive *N*-acyl enamine or enamide unit, crucial to their biological activity. Retrosynthetically, Crocacins A, B and D are derived from Crocacin C via an enamide linkage (Scheme 2).



Scheme 2 Convergent retrosynthesis of the Crocacins

It is proposed that Crocacins A, B and D can be synthesised from Crocacin C using the dienamide methodology developed previously. Although several syntheses of the individual members of the Crocacins have been reported, this method represents a potential route to a convergent synthesis for the whole family of compounds. Presented, are the approaches towards the total synthesis of Crocacin C.



PG = protecting group

Scheme 2a Retrosynthesis of Crocacin C

Contents

Author's Declaration

This thesis represents the original work of Jennifer Elaine Mathieson unless otherwise explicitly stated in the text. The research was carried out at the University of Glasgow during the period of October 2007 to September 2010 under the supervision of Dr Rudi Marquez, apart from the period of October 2009 to December 2009 when the research was carried out at AstraZeneca, Charnwood. Portions of the work described herein have been published elsewhere, as below:

Mathieson, J. E.; Crawford, J. J.; Schmidtmann, M.; Marquez, R., *Org. Biomol. Chem.* **2010**, 7, 2170

List of Abbreviations

Ac	acetyl
Ar	aryl
Bn	benzyl
br	broad
Bu	butyl
^{t}BuOH	*tert*-butanol
^{t}BuOOH	*tert*-butylhydroperoxide
Bz	benzoyl
°C	degrees centigrade
Cat	catalyst
CI	chemical ionisation
COSY	correlation spectroscopy
CSA	camphor sulfonic acid
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*-dicyclohexylcarbodiimide
DIC	diisopropylcarbodiimide
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DIPT	diisopropyltryptamine
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N,N'*-dimethyl-*N,N'*-trimethylene urea
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dppe	1,2-*bis*(diphenylphosphino)ethane
e.e.	enantiomeric excess
EI	electron impact
eq	equivalents
Et	ethyl

FAB	fast atom bombardment
FTIR	Fourier transform infrared
g	gram(s)
h	hours
HMBC	heteronuclear multiple bond correlation
^{1}H	proton
HPLC	high performance liquid chromatography
Hz	hertz
IC_{50}	half maximal inhibitory concentration
IR	infrared
J	NMR spectra coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
Kg	kilogram(s)
L	litre(s)
LC_{50}	median lethal dose
LDA	lithium diisopropylamide
µM	micromolar
M	molar
m	multiplet
*m*CPBA	*meta*-chloroperoxybenzoic acid
min(s)	minute(s)
mg	milligram(s)
MIC	minimal inhibitory concentration
MHz	megahertz
mL	millilitre(s)
mmol	millimole(s)
Me	methyl
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
m/z	mass to charge ratio
NaHMDS	sodium bis(trimethylsilyl)amide
nM	nanomolar
NMP	*N*-methyl pyrrolidone
NMR	nuclear magnetic resonance

NOE	nuclear Overhauser effect
o/n	overnight
OTf	trifluoromethane sulfonate
Ph	phenyl
PMB	*para*-methoxybenzoyl
ppm	parts per million
^{i}Pr	isopropyl
PTSA	*para*-toluenesulfonic acid
q	quartet
quin	quintet
RT	room temperature
s	singlet
SM	starting material
t	triplet
TASF	tris(dimethylamino)sulfonium-difluorotrimethylsilicate
TBHP	*tert*-butyl hydroperoxide
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TFP	tetrafluorophenyl
THP	tetrahydropyran
TIPS	*tri*-isopropylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethysilyl

1.0 Introduction

1.1 Dienamides

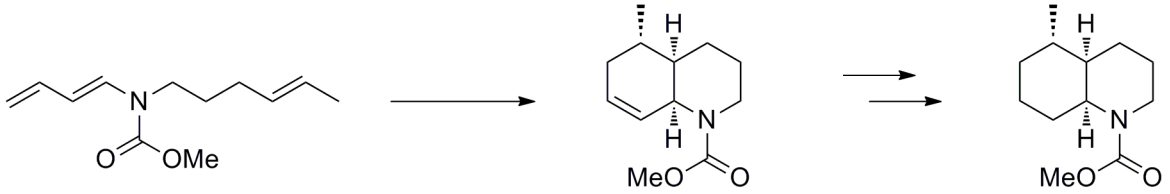
1.1.1 Significance and prevalence of dienamides in nature and in pharmaceutical chemistry

Dienamides are recognised as important structures. They are often used as reactive intermediates for a number of different reactions and are also present in the final structures of many natural products and pharmaceutical leads.[1]

1.1.1.1 Dienamides as reactive intermediates

Dienamides are structurally versatile and can be used as both electron rich and electron poor intermediates in a variety of reactions. In particular, they have been shown to react as electron-rich dienes in Diels-Alder reactions with electron-deficient dienophiles. The reaction is regioselective, giving only the product with 1,2-substitution of the electron-withdrawing group and the nitrogen substituent.

Much of the early work in this area was carried out in the Oppolzer group.[2] In their study of the synthesis of decahydroquinolines **14** they found that intramolecular cycloadditions could be directed towards the *exo* adduct when a dienamide **8** is present as the diene portion of the molecule (Scheme 3).



12 **13** **14**

Scheme 3 Oppolzer's cycloaddition of dienamides

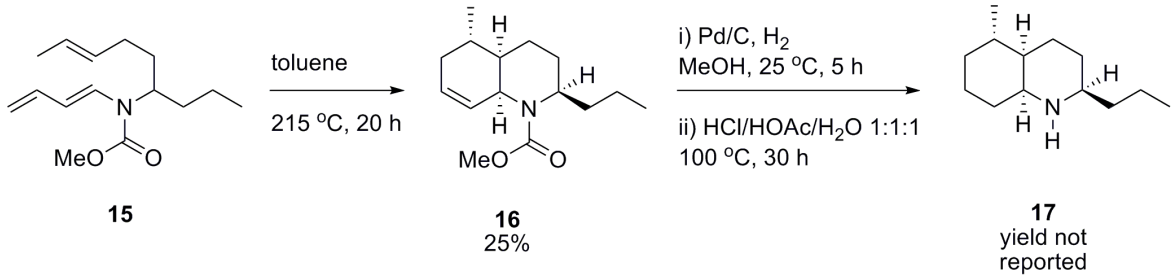
This method has been applied to natural product synthesis, most notably the early synthesis of (±)-Pumiliotoxin-C[1] **17** by the same group.[3] (Scheme 4) The

[1] For an excellent review of dienamides see: Tracey, M. R.; Hsung, R. P.; Antoline, J.; Kurtz, K. C. M.; Slafer, B. W.; Zhang, Y., *Science of Synthesis*, **2005**, 5, 387

[2] Oppolzer, W.; Fröstl, W., *Helv. Chim. Acta.*, **1975**, 58(2), 590

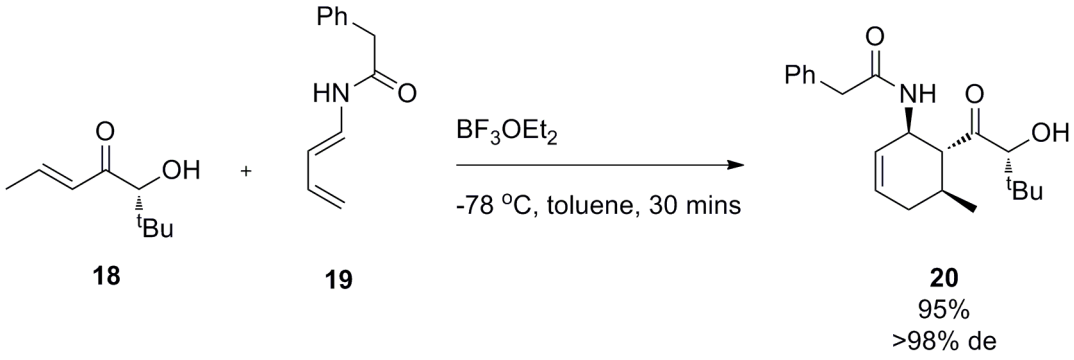
[3] Oppolzer, W.; Fröstl, W., *Helv. Chim. Acta*, **1975**, 58(2), 593

cycloaddition of key dienamide intermediate **15** was used as the penultimate step to complete a stereoselective, albeit racemic synthesis of the potent neurotoxin.



Scheme 4 Key steps in the synthesis of (±) Pumiliotoxin-C[1]

The first asymmetric Diels-Alder reaction employing a dienamide was reported by Masamune and co-workers in 1983 and involved the use of chiral dienophile **18**.[4] The dienophile was reacted with a variety of dienes, including dienamide **19** and gave complete control of stereochemistry in the final product **20** (Scheme 5)

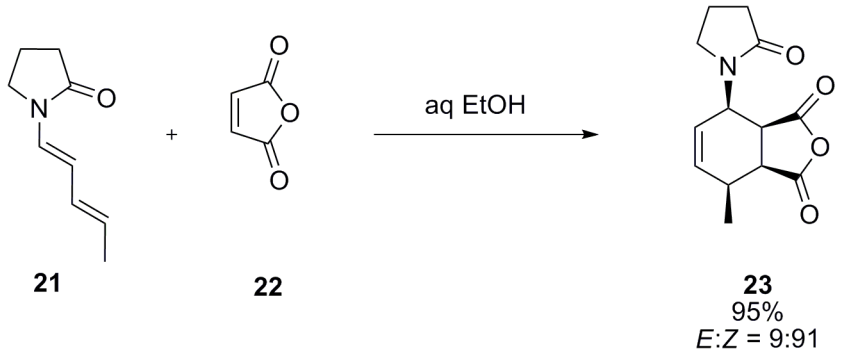


Scheme 5 Masamune's addition of a chiral dienophile to a dienamide

In 1988, Zezza and Smith published the first Diels-Alder reactions of dienamides derived from lactams.[5] The resulting *N*-1,3-dienyl lactams eg. **21** are available via a simple procedure whereby a lactam is reacted with an enolisable aldehyde in good yields and with a high degree of regio- and stereoselectivity. These then readily undergo Diels-Alder reactions with dienophiles such as maleic anhydride **22** to give the cycloaddition product **23** (Scheme 6).

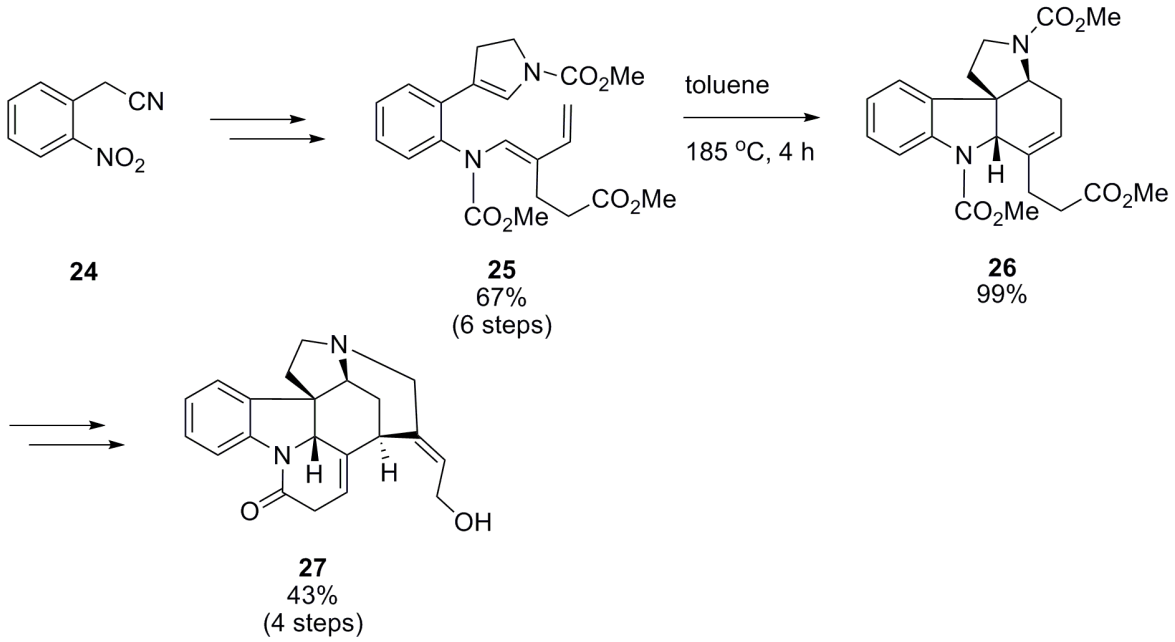
[4] Masamune, S.; Reed, L. A.; Davis, J. T.; Choy, W., *J. Org. Chem*., **1983**, 48, 4441

[5] Zezza, C. A.; Smith, M. B., *J. Org. Chem.*, **1988**, 53, 1161



Scheme 6 Zezza and Smith's use of *N*-1,3-dienyl lactams in Diels-Alder chemistry

More recently, in 1994, Rawal and co-workers reported the use of an intramolecular cycloaddition between a dienamide and an enamide **25** in their stereoselective synthesis of Strychnine **27** (Scheme 7).[6] This particular step furnished the desired intermediate **26** in quantitative yield and with complete stereocontrol, simultaneously establishing 3 of the stereocentres in the final structure.



Scheme 7 Key steps in the stereoselective synthesis of Strychnine

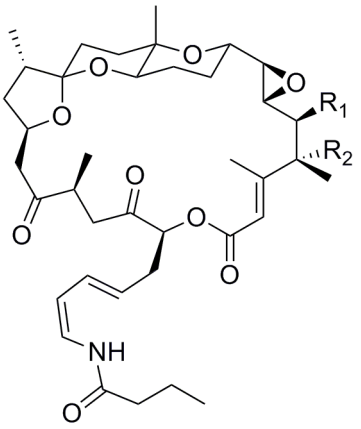
1.1.1.2 Dienamides in natural products

1.1.1.2.1 Lituarines

The Lituarines are a family of biologically active marine natural products (Fig 1). In 1992, Vidal and co-workers isolated the three members of the family, Lituarine A, B and C from the sea pen *Lituaria australasie*, which is found in the western region

[6] Rawal, V. H.; Iwasa, S., *J. Org. Chem.,* **1994**, 59, 2685

of the New Caledonian Lagoon, adjacent to the French territory of New Caledonia in the South-West Pacific Ocean.[7]



Lituarine A, **28** : $R_1 = R_2 = H$
Lituarine B, **29** : $R_1 = OAc$, $R_2 = OH$
Lituarine C, **30** : $R_1 = R_2 = OH$

Fig 1 The Lituarines

The Lituarines were subsequently found to inhibit the growth of the following fungi: *Fusarium oxysporum, Helminthosphorium turscicum, Penicillium italicum* and *Phytophtora parasitica.* Furthermore they showed significant cytotoxic activity towards KB cells. Lituarine B was the most active, with an IC_{50} value of 1-3 nM, though Lituarine A and C also showed significant activity with IC_{50} values of 5.5-7.5 nM and 7-9 nM respectively.

Structurally, the Lituarines are macrocyclic lactones with a side-chain consisting of a rare example of an acyclic conjugated dienamide. The dienamide itself has an unusual (*Z,E*) configuration. Due to the considerable biological activity combined with their rarity in nature (12.5 kg of sea pen furnished less than 25 mg of each compound) these structurally complex natural products are of great interest in terms of devising a synthetic route to them.

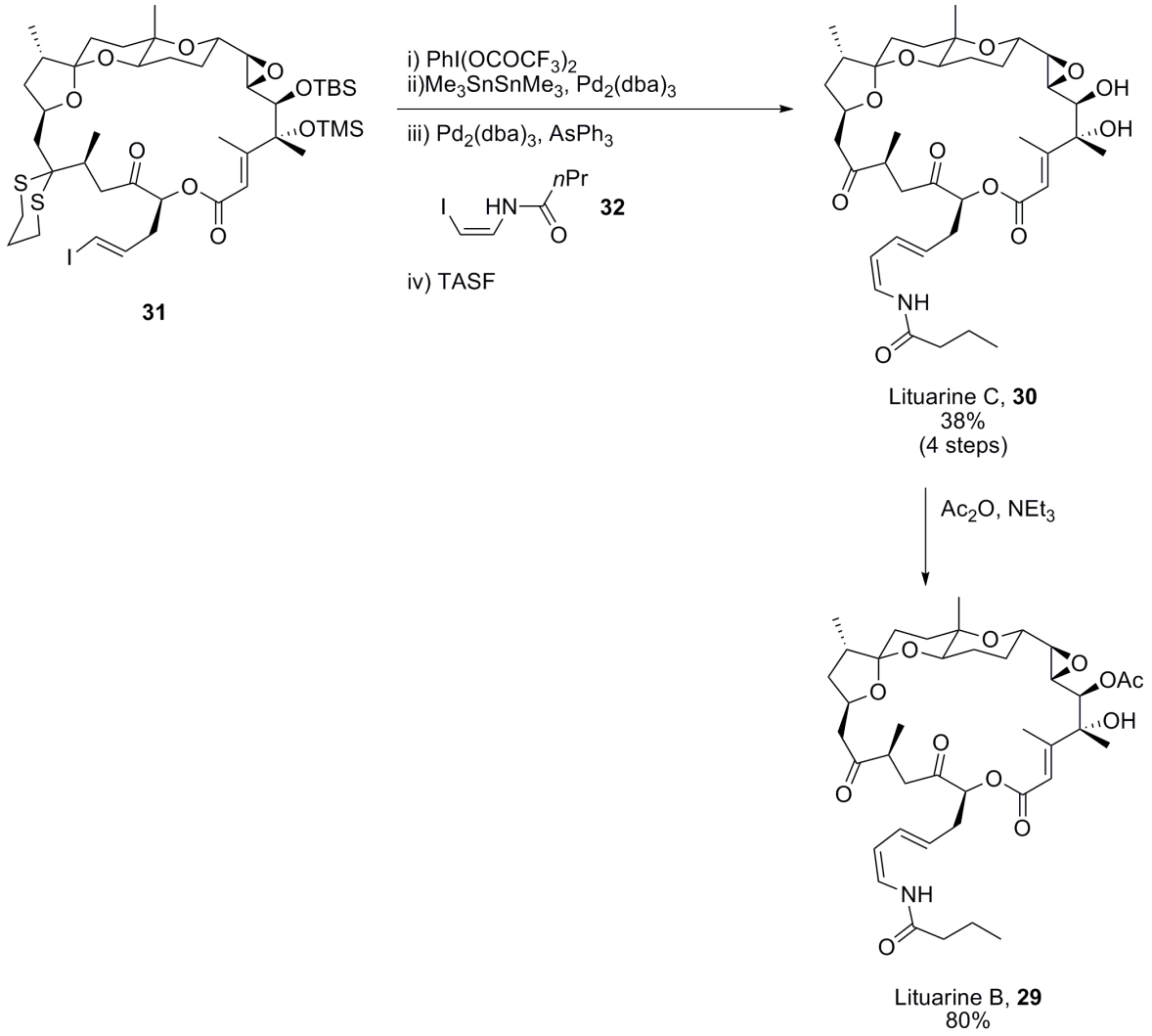
In 2008, Amos Smith and co-workers published a synthesis of Lituarine B and C.[8] The route developed involved the dienamide side-chain being introduced at a late stage in the synthesis via a Stille coupling reaction after synthesis of the macrocyclic core (Scheme 8).

Initially it was envisaged that the macrocyclic core would serve as the iodide coupling partner and the enamide unit stannylated in order to furnish a *Z* double bond when coupled to form the dienamide. However, it was found that stannylation

[7] Vidal, J P.; Escale, R., Girard, J P.; Rossi, J C., *J. Org. Chem.*, **1992**, 57, 5857

[8] Smith, A. B.; Walsh, S. P.; Frohn, M.; Duffey, M. O., *Org. Lett.*, **2005**, 7(1), 139; Smith, A. B.; Duffey, M. O.; Basu, K.; Walsh, S. P.; Suennemann, H. W.; Frohn, M., *J. Am. Chem. Soc.*, **2008**, 130, 422

of the *cis*-iodoenamide resulted in isomerisation to the *trans*-olefin. To overcome this problem the Stille coupling partners were reversed and a stannylation was performed on advanced intermediate **31** which was then coupled with *cis*-iodoenamide **32** to furnish the desired (*Z,E*)-dienamide unit

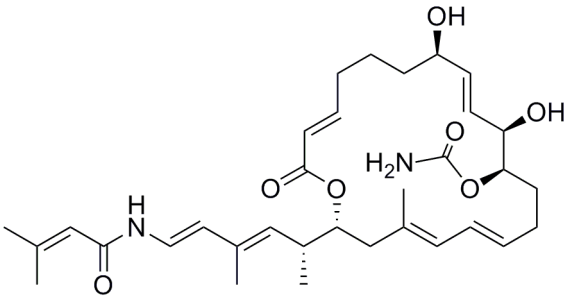


Scheme 8 Key steps in Smith's synthesis of Lituatine B and C

Removal of the silyl protecting groups gave Lituarine C **30** and Lituarine B **29** was accessed directly from Lituarine C via a regioselective acetylation of the hydroxyl adjacent to the epoxide. Although successful in terms of the final outcome, the synthesis of the dienamide unit was clearly not trivial and required a significant number of low-yielding and tricky steps.

1.1.1.2.2 Palmerolide A

Palmerolide A **33** (Fig 2 – proposed structure) is a marine polyketide macrolide, isolated in 2006 by Baker and co-workers from *Synoicum adareanum*, a circumpolar tunicate found in the waters around Anvers Island on the Antarctic Peninsula.[9]



Palmerolide A, **33**

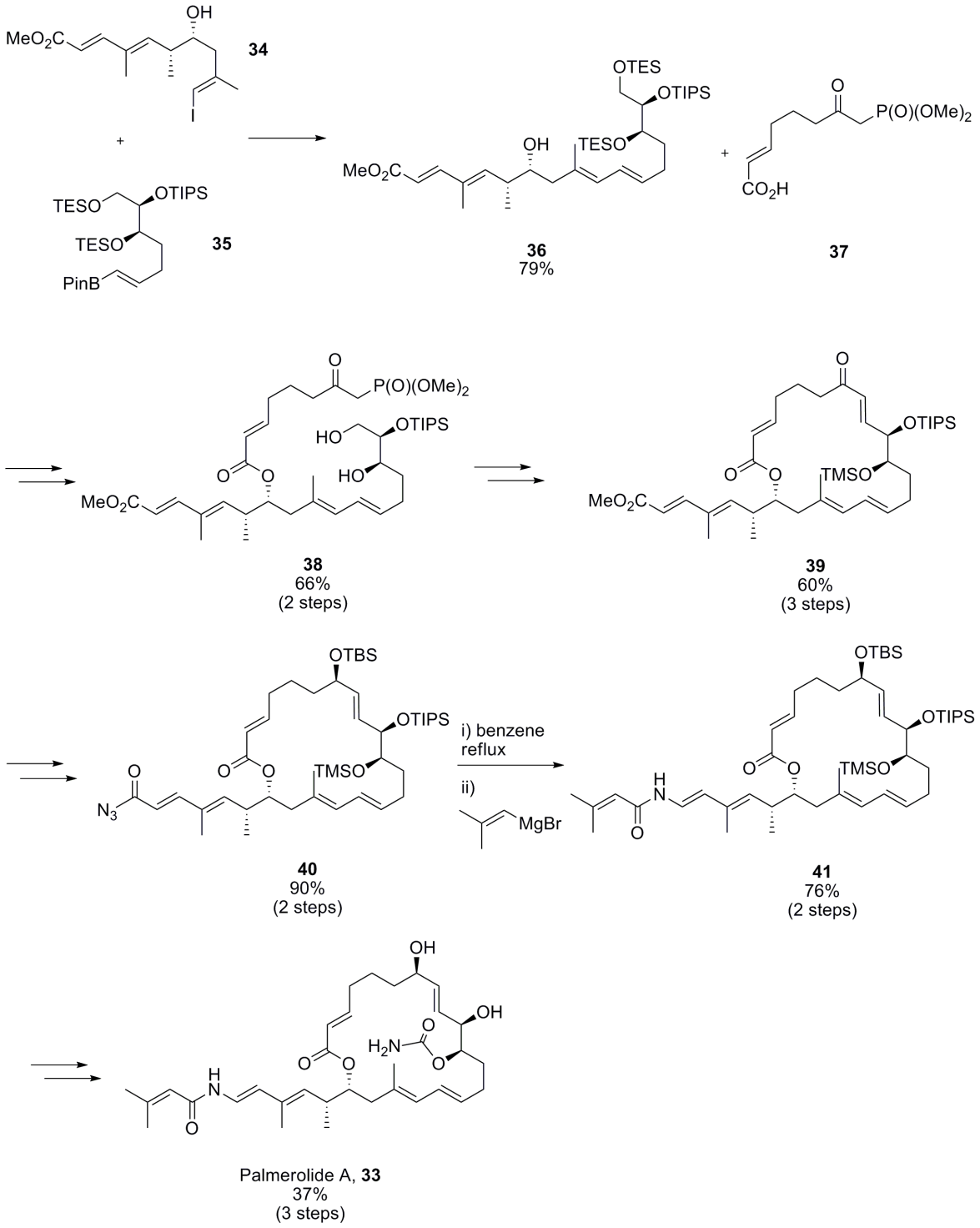
Fig 2 Original proposed structure of Palmerolide A

Palmerolide A has shown extremely positive results in targeting melanoma in the National Cancer Institute's 60 cell line panel (eg. UACC-62, LC_{50} = 18 nM). In addition to melanoma, Palmerolide A showed cytotoxic activity against one colon cancer cell line (HCC-2998, LC_{50} = 6.5 μM) and one renal cancer cell line (RXF 393, LC_{50} = μM), however in all other tested cell lines there was a lack of cytotoxicity, which shows a selectivity index of 10^3 for the most sensitive cells.

Structurally, Palmerolide A is a 20 membered macrolide with five chiral centres, a 1,3-diene system and an (*E,E*)-dienamide side-chain and as such presents a significant challenge to synthetic chemists. In 2007, De Brabander and co-workers published a total synthesis and structural revision of Palmerolide A.[10] The macrocycle was constructed via cross-coupling followed by a Horner-Wadsworth-Emmons reaction. The dienamide unit was installed in the final stages via a Curtius rearrangement and trapping of the isocyanate intermediate with 2-methylpropenylmagnesium bromide (Scheme 9).

[9] Diyabalanage, T.; Amster, C. D.; McClintock, J. B.; Baker, B. J., *J. Am Chem. Soc.*, **2006**, 128, 5630

[10] Jiang, X.; Liu, B.; Lebreton, S.; De Brabander, J. K., *J. Am Chem. Soc.*, **2007**, 129, 6386

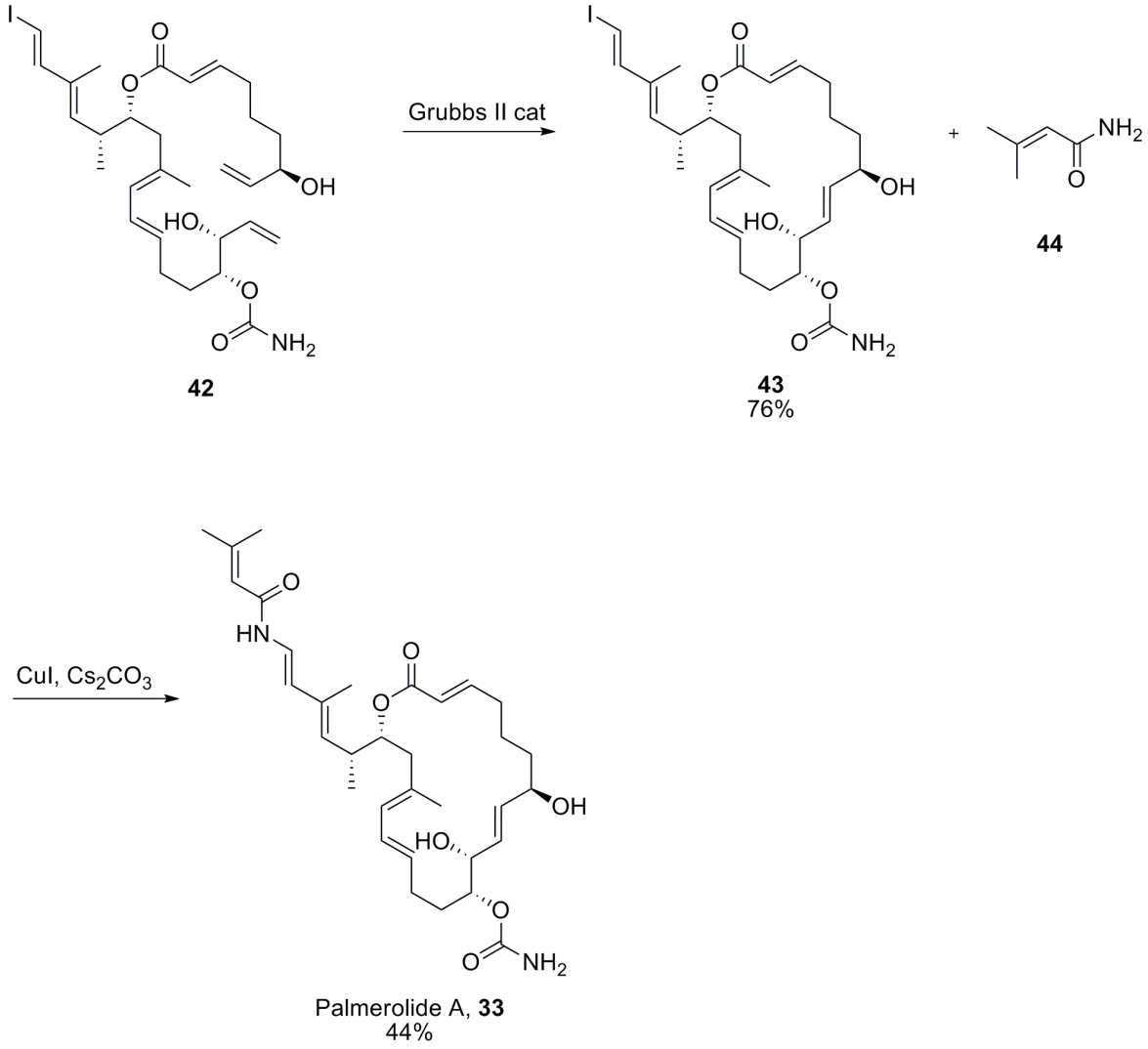


Scheme 9 Key steps in De Brabander's synthesis of Palmermolide A

In 2007, Nicolau and co-workers published a synthesis of both structures (original and revised) of Palmerolide A in a flexible synthesis that also allowed for synthesis of Palmerolide analogues.[11] The macrocycle was constructed from advanced intermediate **42** via a ring closing metathesis, where the *trans*-geometry was

[11] Nicolau, K. C.; Guduru, R.; Sun, Y-P.; Banerji, B.; Chen, D. Y-K., *Angew. Chem. Int. Ed.,* **2007**, 46, 5896

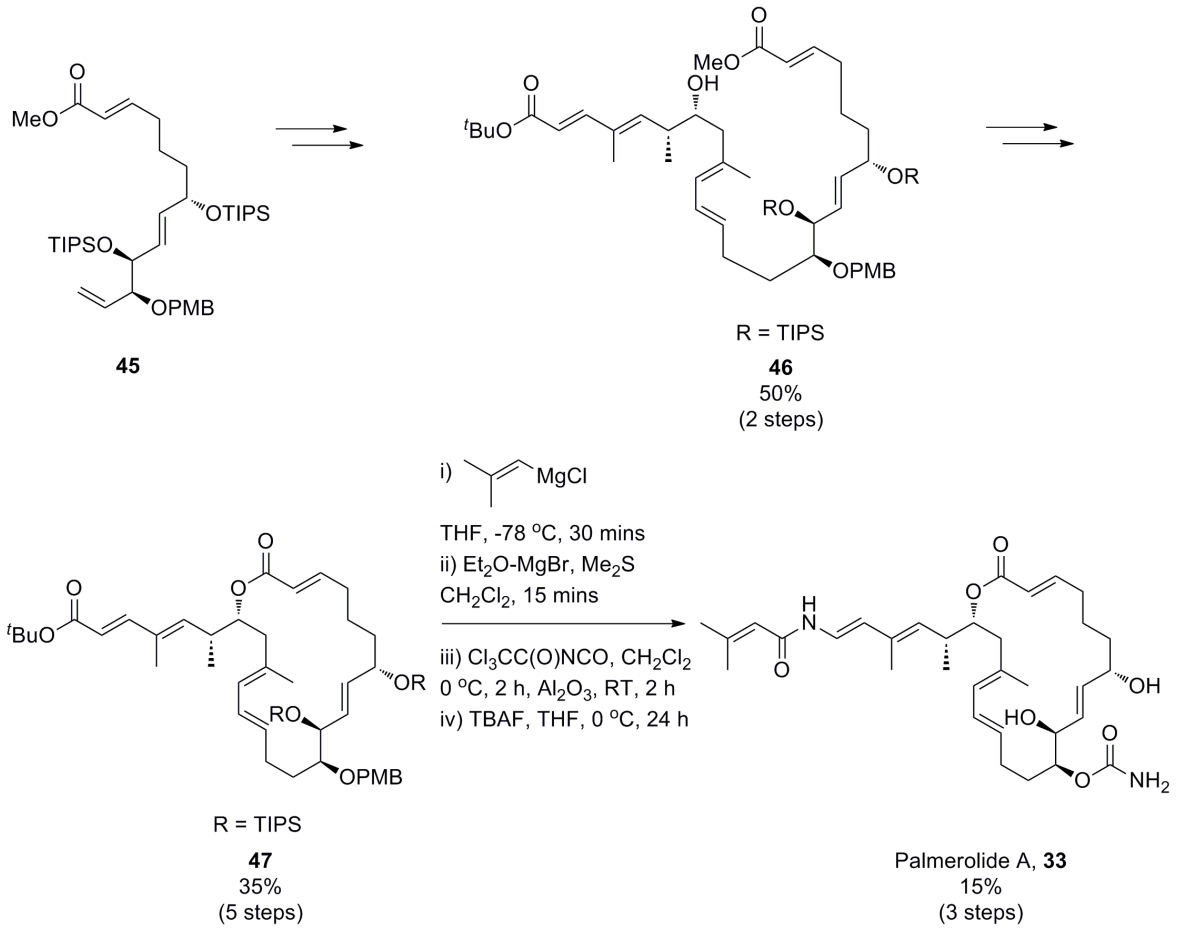
confirmed by NMR analysis and the dienamide unit was installed as the final step via the Buchwald copper-catalysed protocol (Scheme 10).



Scheme 10 Key steps in Nicaloau's synthesis of Palmerolide A

2009 saw the publication of Hall and co-worker's asymmetric synthesis which makes use of a Suzuki coupling and a Yamaguchi macrolactonisation to construct the macrocycle from advanced intermediates **45-47**.[12] A Curtius rearrangement analogous to the one employed previously by De Brabander is used to introduce the dienamide moiety (Scheme 11).

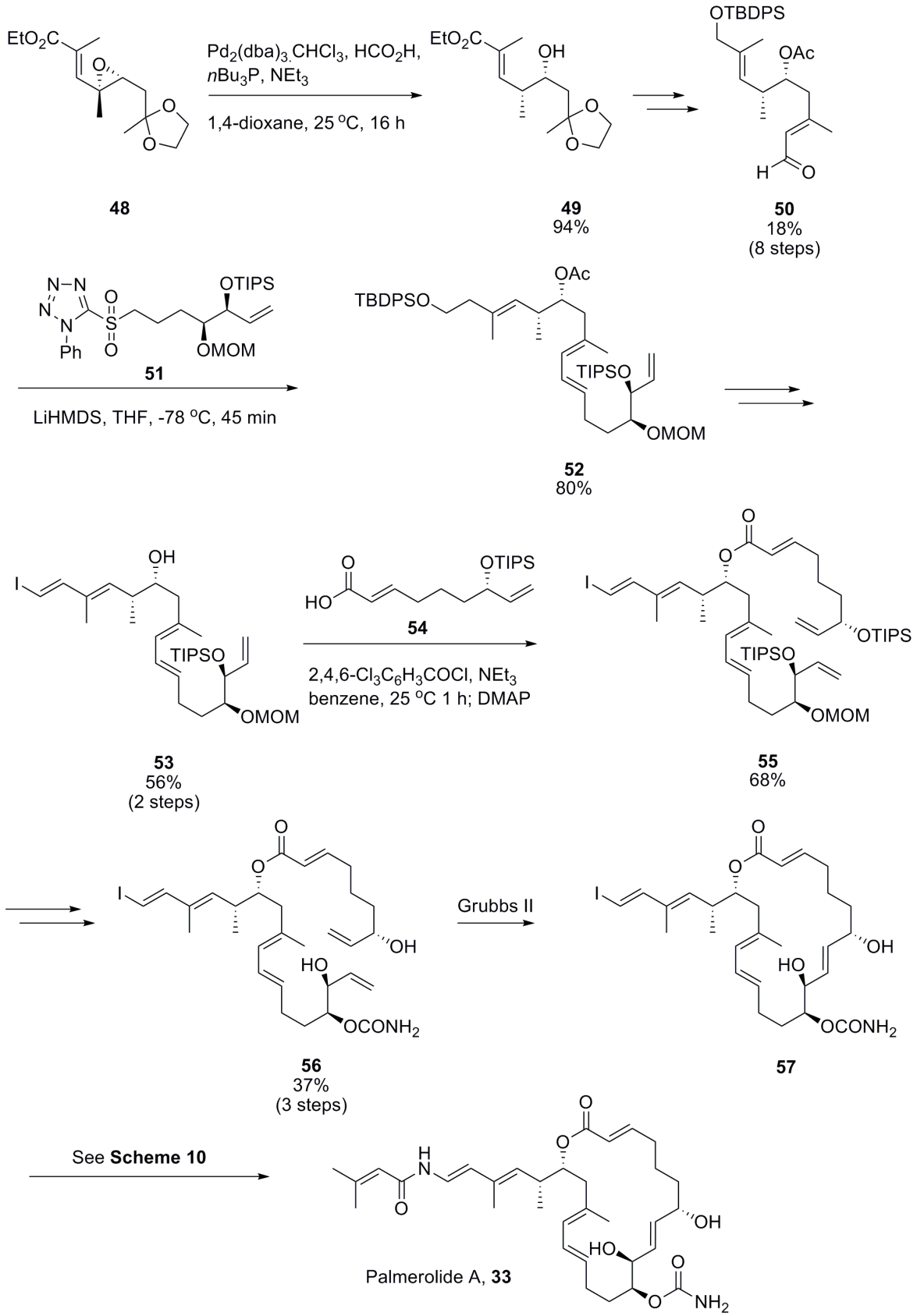
[12] Penner, M.; Rauniyar, V.; Kaspar, L. T.; Hall, D. G., *J. Am. Chem. Soc.,* **2009**, 131, 14216



Scheme 11 Key steps in Hall's synthesis of Palmerolide A

Most recently, in 2010, Kaliappan and co-workers published a formal synthesis of the key macrocycle iodide intermediate **57** of Nicolaou's synthesis in which key reactions include a Shimizu reaction to make intermediate **49** and a Julia-Kocienski olefination to couple the aldehyde to intermediate **51**.[13] The dienamide is then introduced using exactly the same Buchwald method as in Nicolaou's synthesis (Scheme 12).

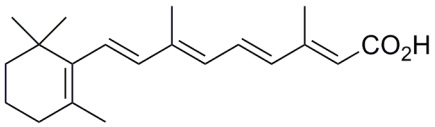
[13] Gowrisankar, P.; Pujari, S. A.; Kaliappan, K. P., *Chem. Eur. J.,* **2010**, 16, 5858



Scheme 12 Key steps in Kaliappan's synthesis of Palmerolide A

1.1.1.3 Dienamides in drug leads

Retinoic acid (all *trans*) **58** (Fig 3) and its isosteres, collectively known as retinoids, are active in the control of cellular differentiation and proliferation and in embryonic development. They have been used for chemotherapy treatment in the areas of dermatology and oncology.

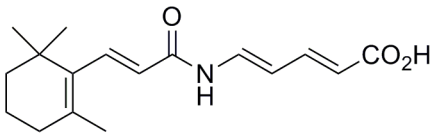


58

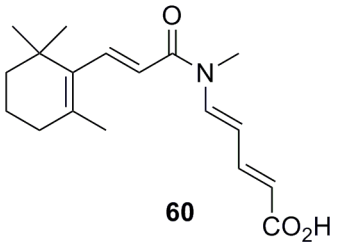
Fig 3 Retinoic acid (all *trans*)

A number of the retinoids, including retinoic acid itself have proved useful in the treatment of leukaemia and psoriasis. However their effectiveness is limited due to a number of side-effects caused, in part by their high hydrophobicity.

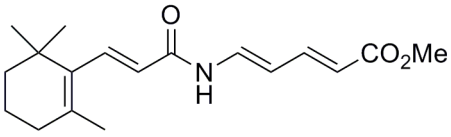
In 1995, Shudo and co-workers reported the synthesis of a number of retinoic acid derivatives, designed to have improved therapeutic indexes and reduce side-effects.[14] In particular, they found that introduction of an amide bond in place of the central olefinic bond of the pentaene system in retinoic acid served to reduce the hydrophobicity compared to the original structrure. As a result of this discovery a number of dienamide derivatives of retinoic acid **59-62** (Fig 4) were synthesised and tested against the human promyelocytic leukaemia cell line HL-60.



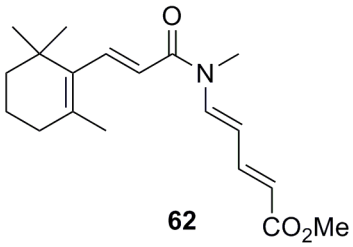
59



60



61



62

Fig 4 Dienamide derivatives of Retinoic acid

Their ability to induce differentiation of these cells to mature granulocytes was assessed and correlated with other known retinoids. The results for a small

[14] Shimasaki, H.; Kagechika, H.; Fukasawa, H.; Kawachi, E.; Shudo, K., *Chem. Pharm. Bull.,* **1995**, 43(1), 100

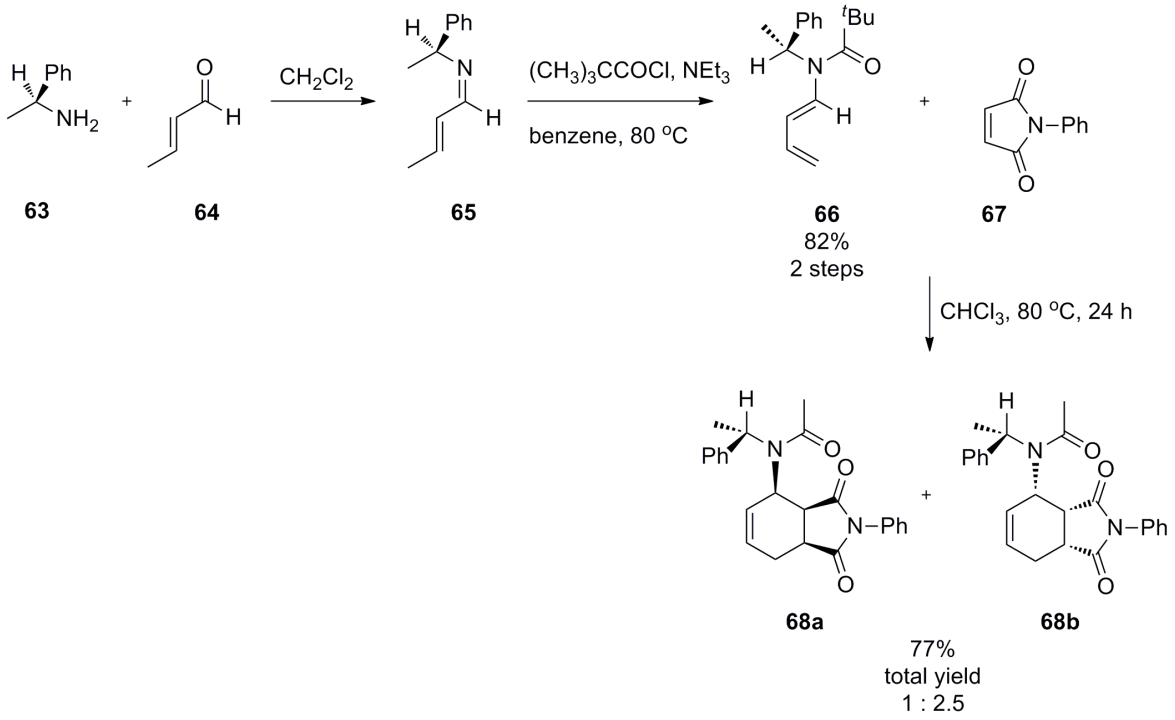
number of the dienamide derivatives were positive and in a couple of cases differentiation-inducing activity was observed at concentrations around 4.3-7.2 x 10^{-7} M.

1.1.2 Current methods for synthesis of dienamides

Although no general synthesis of dienamides exists, there have been many methods published for furnishing the dienamide unit, either in natural product synthesis or for use as reactive intermediates.

1.1.2.1 Condensation Methods

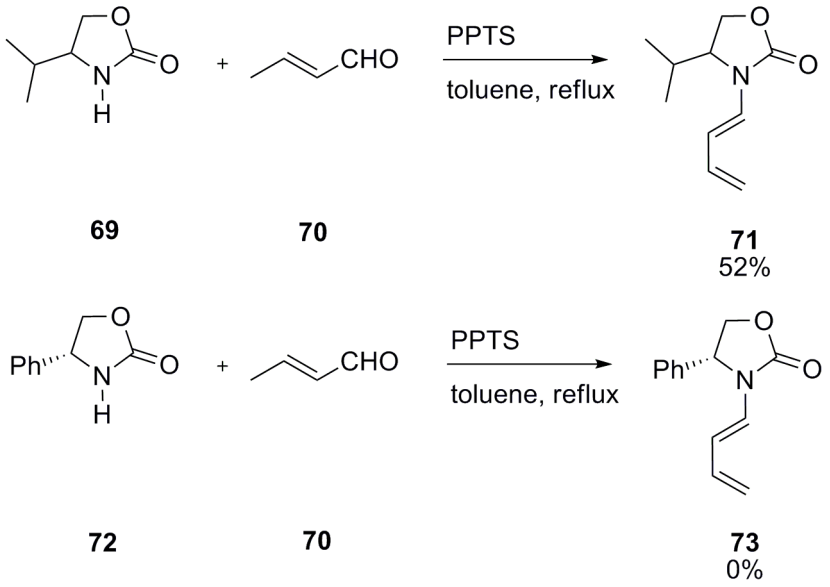
In their studies of regioselective Diels-Alder reactions of *N*-substituted dienes in 2001, Stevenson and co-workers were required to synthesise a series of chiral dienamides.[15] They achieved this initially through a condensation reaction between a chiral amine **63** and a simple aldehyde **64**. This reaction gave an imine **65**, which on reaction with trimethylacetyl chloride and triethylamine in refluxing benzene gave the chiral dienamide **66** in 82% yield. This was then available to undergo Diels-Alder cycloadditions with dienophiles e.g **67** (Scheme 13).



Scheme 13 Stevenson's synthesis of chiral dienamide **66** for Diels-Alder chemistry

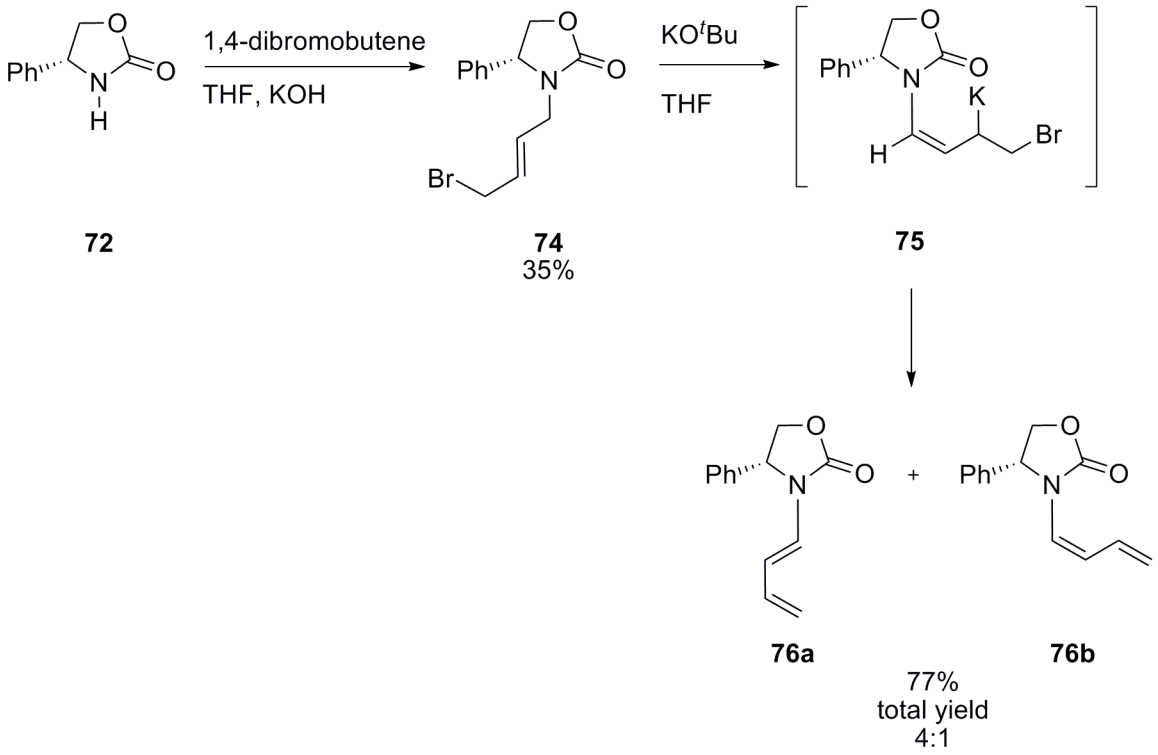
[15] McAlonan, H.; Murphy, J. P.; Niewenhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J.; Thompson, N., *J. Chem. Soc., Perkin Trans. 1.*, **2002**, 69

The next stage of the investigation involved studies of oxazolidinone-derived dienes and they found that a racemic oxazolidinone **69** readily condensed with crotonaldehyde **70** to give the diene **71**. However, attempts to synthesise enantio-enriched analogues **72** via the same methods were unsuccessful (Scheme 14). A different approach to the chiral oxazolidinone-derived dienamides was required.



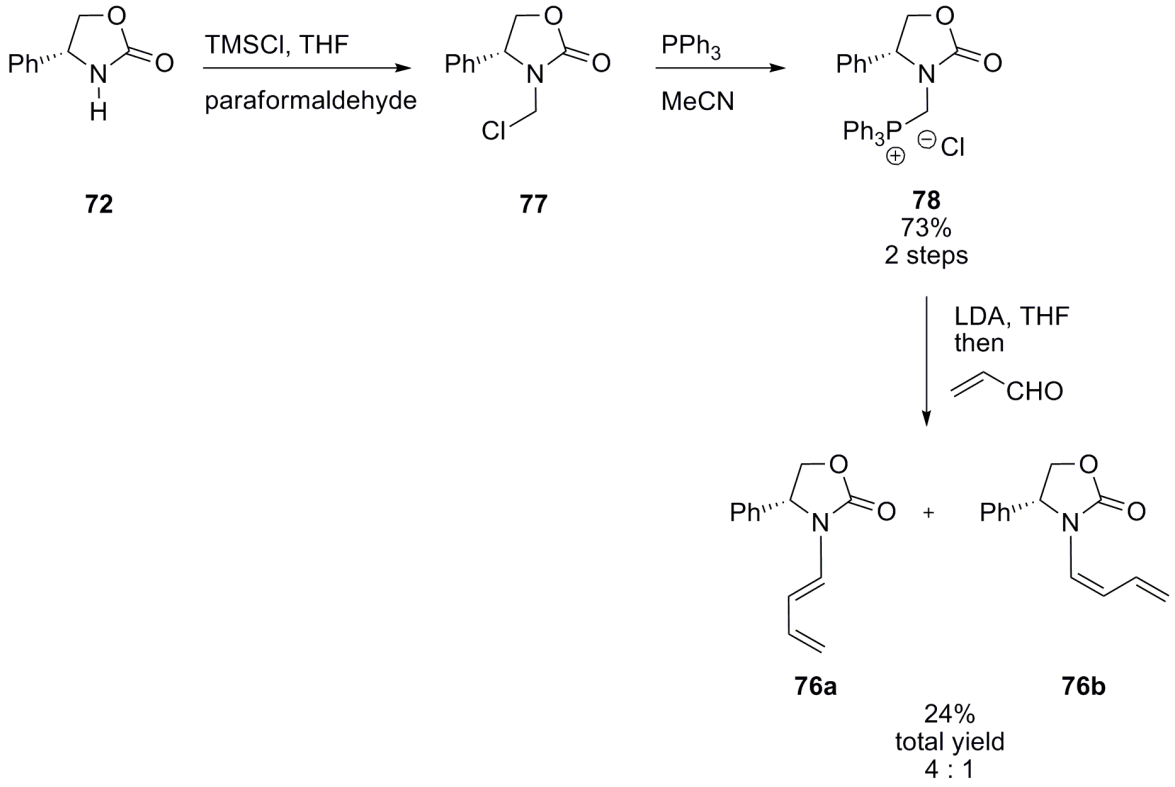
Scheme 14 Stevenson's synthesis of oxazalidinone-derived dienamides

They first investigated a dehydrobromination sequence whereby alkylation of the chiral oxazolidinone **72** followed by dehydrobromination gave a mixture of the *Z*- and *E*-dienes **76a-b** (Scheme 15). Attempts to isomerise the *Z*-diene **76b** to the *E*-diene **76a** were unsuccessful, despite extensive experimentation. It was found that only the *E*-dienes were reactive to Diels-Alder conditions, after which the unreacted *Z*-diene was separated from the cycloaddition product.



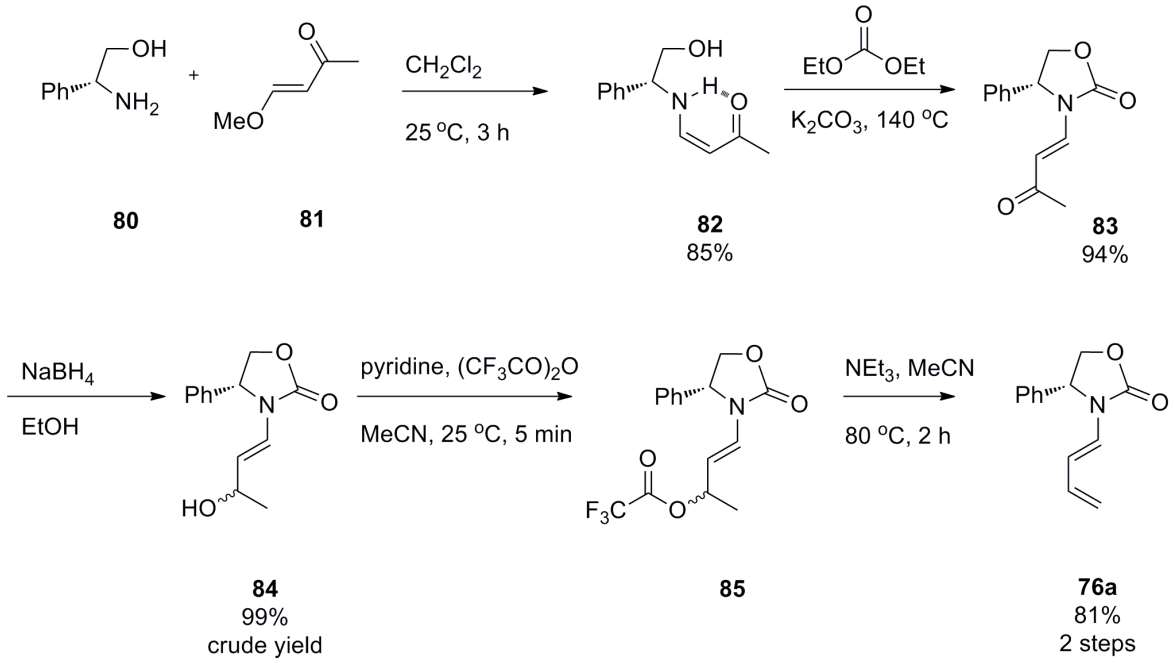
Scheme 15 Stevenson's synthesis of chiral oxazolidinone-derived dienamides using dehydrobromination

Next, an approach involving Wittig chemistry was examined (Scheme 16). The phosphonium salt **78** was prepared readily via treatment of the chloromethyl-oxazolidinone **77** with triphenylphosphine. This was followed by deprotonation and addition of acrolein to give the products **76a-b** in a 4:1 mixture of *Z*- and *E*-dienes in a poor 24% yield. This method was not investigated any further due to the undesired *Z*-diene being the major isomer produced.



Scheme 16 Stevenson's synthesis of chiral oxazolidinone-derived dienamides using Wittig chemistry

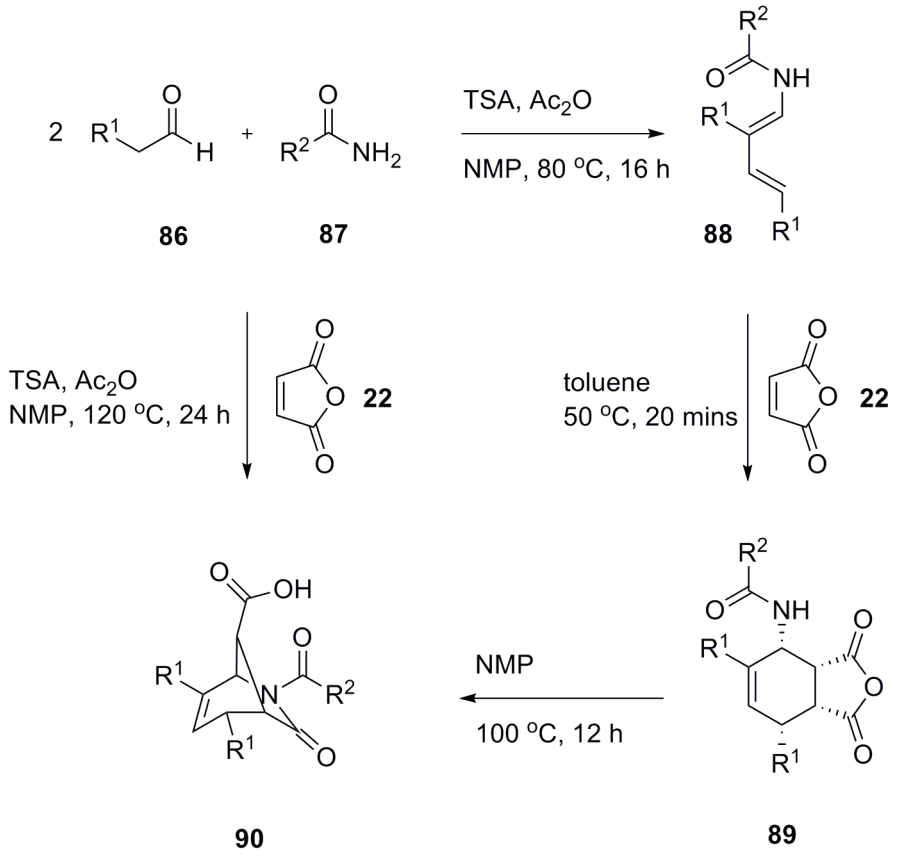
Finally, a successful approach to the *E*-diene was achieved through step-wise incorporation of the double bonds. The *E*-enamide double bond was introduced first during assembly of the oxazalidinone **83**, followed by elimination to establish the second double bond (Scheme 17).



Scheme 17 Stevenson's step-wise synthesis of chiral oxazolidinone-derived dienamides

It is clear from the reports that synthesis of the dienamide intermediates was not straightforward and no single method was found that could be applied to synthesis all the structures required. Often a mixture of stereoisomers was obtained and yields were moderate at best. There is no indication of whether they attempted to extend the methods to furnish anything other than a terminal dienamide.

Around the same time, Beller and co-workers developed a multi-component coupling protocol for the synthesis of substituted 1-amido-2-cyclohexenes **89** involving the condensation of simple aldehydes and amides to give dienamide intermediates **88** followed by Diels-Alder addition to maleic anhydride **22** and intramolecular amidation to yield the desired product **90** (Scheme 18).[16]



Scheme 18 Beller's synthesis of dienamide intermediates

Optimisation of the conditions for condensation proved that use of either *N*-methyl pyrolidinone or dimethylformamide as a solvent was important and a catalytic amount of *p*-toluenesulfonic acid plus stoichiometric amounts of acetic anhydride accelerated the reaction.

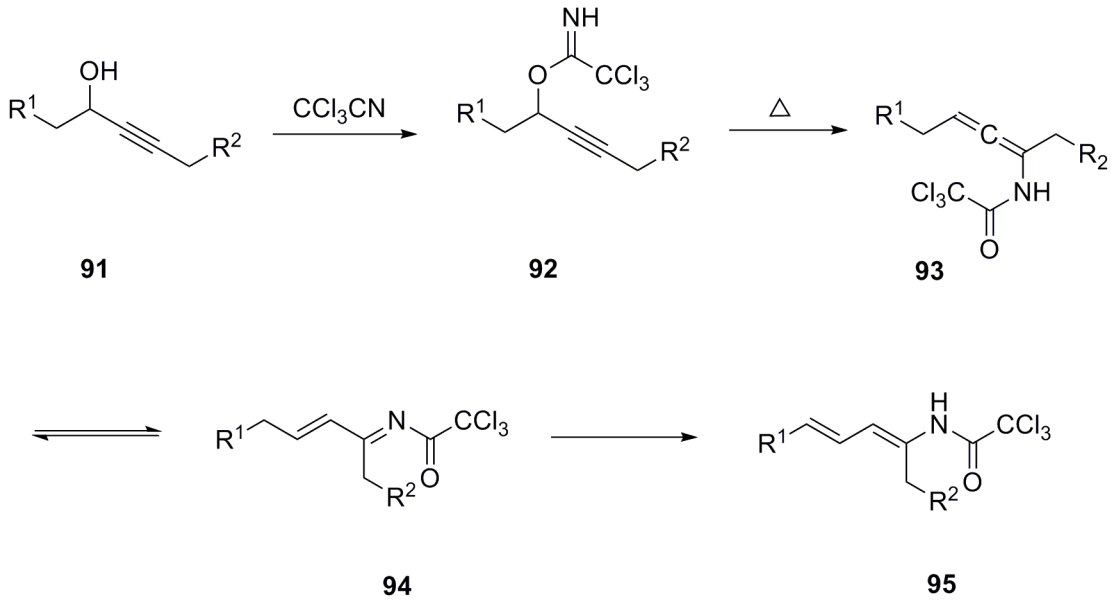
[16] Neumann, H.; von Wangelin, A. J.; Gördes, D.; Spannenberg, A.; Baumann, W.; Beller M., *Tetrahedron*, **2002**, 58, 2381

However the optimised conditions reported only gave 30% isolated yield of the all-*trans* isomer. The following two steps had respective yields of 96% and 89%, however the poor yield of the initial condensation step resulted in the overall yield of the final product being 26%.

It was found that adopting a one-pot procedure for the sequence eliminated the need for intermediate isolation and purification and increased the yield to 69% (also shown in Scheme 18). The one-pot procedure increased both the yield and efficiency of synthesis of these particular targets. However, in terms of isolation of the dienamides, this is clearly not a viable method.

1.1.2.2 Rearrangement Methods

In 1976 Overman and co-workers reported a new route to trichloroacetamido-1,3-dienes **95** via a thermolytic rearrangement of propargylic trichloroacetimidates **92**, made in turn by a simple condensation reaction between the corresponding propargylic alcohol **91** and trichloroacetonitrile.[17] Thermolysis results in a rearrangement of the nitrogen and oxygen of the imidate **94** to afford the resulting 1,3-dienamide (Scheme 19).



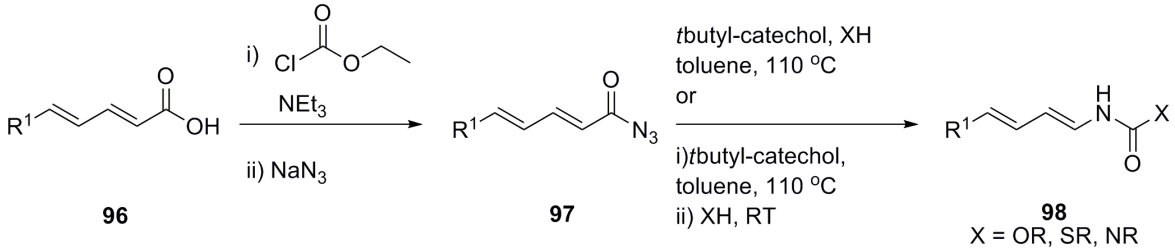
Scheme 19 Overman's synthesis of trichloroacetimido-1,3-dienes

These rearrangements occur in a range of yields and in varying degrees of stereoselectivity. Some of the products were applied to Diels-Alder reactions with a number of dienophiles. Reactivity was relatively low, however, and this was attributed to the electron-withdrawing nature of the trichloroacetyl substituent. The

[17] Overman, L. E.; Clizbe, L. A., *J. Am. Chem. Soc.*, **1976**, 2352

trichloroacetyl group can be easily removed before or after the Diels-Alder reaction by treatment with dilute base and as such gives access to a range of amino-1,3-dienes as well as the dienamides.

A few years later, Overman reported a new route to more reactive dienamides for Diels-Alder chemistry via a modified Curtius rearrangement of conjugated dienoic acids **96** (Scheme 20).[18]



96 **97** **98**

Scheme 20 Overman's synthesis of dienamides by Curtius rearrangement

Dienoic acids **96** are converted to acyl azides **97**, via their mixed anhydrides, and these were treated directly with the free radical inhibitor 4-*tert*-butylcatechol. The resulting product was either trapped by an *in situ* trapping agent (e.g. *tert*-butyl alcohol or benzyl alcohol) or cooled to room temperature before the trapping agent was added. The procedure used was dependant on the product being made. For example, in the preparation of diene ureas, the *in situ* trapping was problematic due to the decomposition of the product at elevated temperatures.

1.1.2.3 Metal-mediated Methods

In 1998, the group of Won-Hun Ham from Korea reported an interesting side-reaction in their synthesis of a side chain of Taxol.[19]

They were attempting to convert amino acetate **99** to an oxazoline via a palladium-catalysed cyclisation, however a mixture of the desired oxazoline **100** and the elimination product dienamide **101** was observed (Scheme 21). On investigation of conditions it was found that 1 mol% of $Pd_2(dba)_3$ and 4 mol% dppe with sodium hydride gave exclusively the elimination by-product, thought to originate from elimination of the allyl acetate via a π-allyl intermediate.

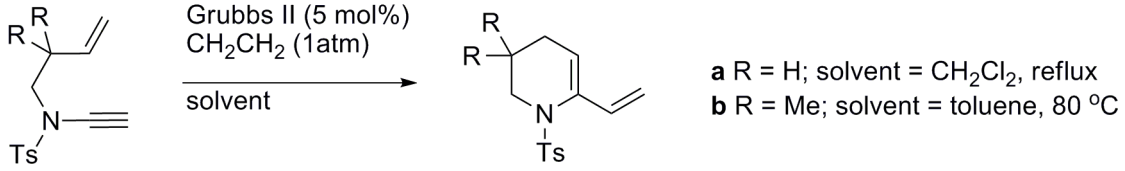
[18] Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P J., *J. Org. Chem.*, **1978**, 43(11), 2164

[19] Lee, K L.; Kim, Y H.; Park, M S.; Ham, W H., *Tetrahedron Lett.*, **1998**, 39, 8129

	99	**100**	**101**
i) $Pd(PPh_3)_4$ (5mol%), NaH DMF, 25 ^oC, 8 h		30%	45%
ii) $Pd_2dba\text{-}CHCl_3$ (1mol%), dppe (4 mol%) NaH, DMF, 25 ^oC, 8 h		0%	90%

Scheme 21 Dienamide side-product from the synthesis of a side chain of Taxol

In 2002, Mori and co-workers published a route to cyclic dienamides **103** via the ruthenium-catalysed ring-closing metathesis of an ene-ynamide **102** (Scheme 22).[20] They found that using 2nd generation Grubbs catalyst gave higher yields and shorter reaction times than the 1st generation Grubbs catalyst attempted initially. Interestingly, for the synthesis of piperidine derivatives via unsubstituted ene-ynamides, toluene at 80°C gave better results than refluxing dichloromethane, however for substituted ene-ynamides, the reverse is true.

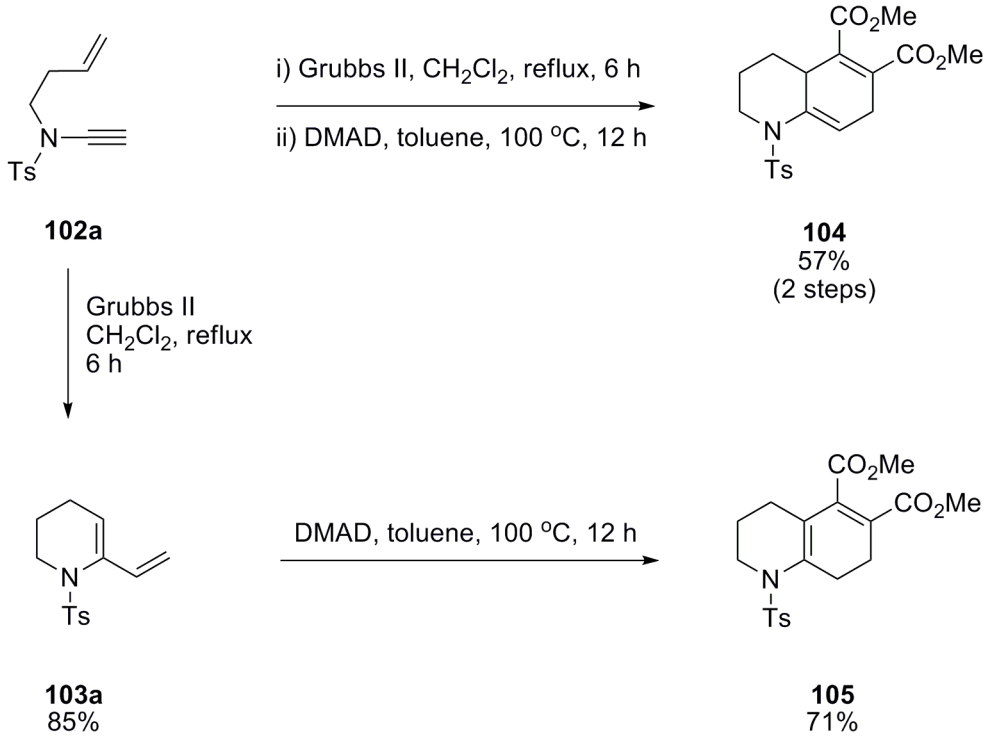


102 **103**

Scheme 22 Mori's synthesis of cyclic dienamides via metathesis

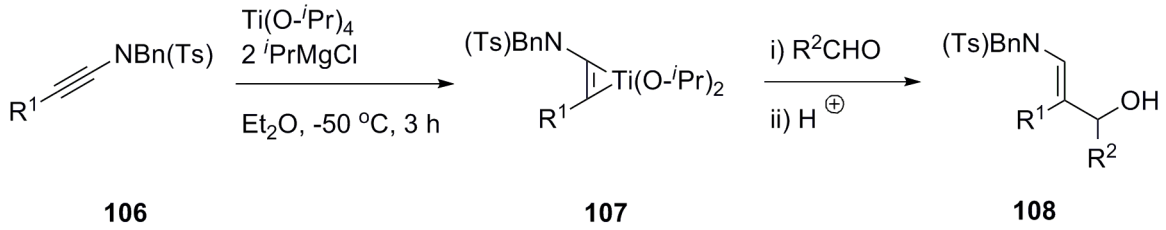
These cyclisation products were successfully applied to Diels-Alder reaction conditions to give bi- or even tri-cyclic products. Treatment of the crude product from ring-closing metathesis of **102a** with dimethyl acetylenedicarboxylate (DMAD) gave quinoline derivative **104**. However, if the methathesis product **103a** is isolated before the cyclisation step then the isomerisation product **105** is the only product isolated (Scheme 23).

[20] Saito, N.; Sato, Y.; Mori, M., *Org. Lett.*, **2002**, 4(5), 803



Scheme 23 Application of cyclic dienamides in Diels-Alder chemistry

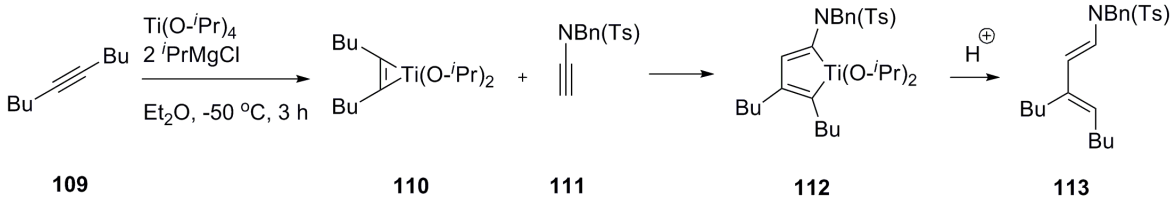
At around the same time, Sato and co-workers reported a synthesis of enamides and dienamides via a titanium-mediated coupling of ynamides with carbonyl compounds.[21] Acetylenes **106** were treated with titanium(IV) isopropoxide and isopropylmagnesium chloride to generate an ynamide-titanium complex **107**, which gives enamides on hydrolysis. These complexes can be treated with carbonyl compounds to give a stereoselective route to tri-substituted enamides **108** (Scheme 24).



Scheme 24 Sato's synthesis of enamides from ynamides

The acetylene-titanium complexes **110** can also be coupled with terminal ynamides **111** in a highly regio- and stereo-selective fashion to give dienamides **113** after hydrolysis as before (Scheme 25). Deuteriolysis in place of hydrolysis allowed the structures to be determined unambiguously through NMR analysis.

[21] Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F., *Org. Lett.*, **2003**, 5(1), 67

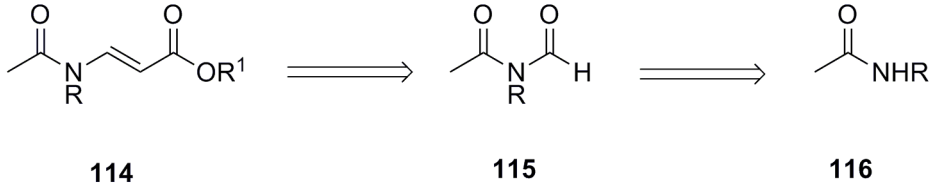


Scheme 25 Sato's synthesis of dienamides from terminal ynamides

This is a versatile reaction and the authors have proved this by showing that acetylene, dialkylacetylene, diphenylacetylene, silylacetylene and acetylinic esters and amides could all be used successfully in the coupling reaction. In the dienamide synthesis both (sulfonylamino)- and (benzoylamino)acetylenes could be used as the second coupling partner to give a wide variety of dienamides. In most cases the products were furnished as single regio- and stereoisomers.

1.1.3 Previous work in the Group

Recently in the Marquez group, studies have been made towards an efficient and stereocontrolled synthesis of enamides **114**.[22] These efforts were focused on a study of the unprecedented Wittig olefination of *N*-formyl imides **115**. The imides in turn are derived from the corresponding amide or lactam **116** (Scheme 26).



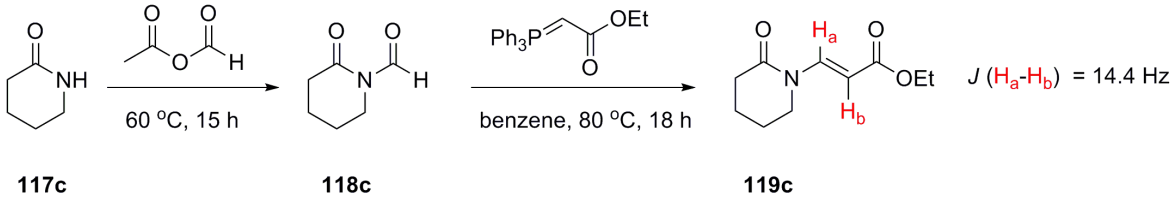
Scheme 26 Retrosynthesis of enamides

The decision to examine this reaction was due to the apparent propensity of the *N*-formyl imide unit to behave in a similar fashion to an aldehyde. Although at first glance it might seem that the lone pair on the nitrogen would decrease the reactivity of the formyl group in much the same way as in a formamide unit, it was postulated that the original amide or lactam carbonyl would delocalise enough of the electron density on the lone pair to make the formyl group sufficiently reactive.
It was proposed that this method would give access to a variety functionalised enamides and that the large selection of Wittig-type olefination reactions already

[22] Villa, M. V. J.; Targett, S. M.; Barnes, J. C.; Whittingham, W. G.; Marquez, R., *Org. Lett.*, **2007**, 9(9), 1631

established in the literature would allow the configuration of the double bond to be controlled completely.

Initial studies began with a 6-membered lactam unit **117c** and this was formylated under literature conditions using acetic formic anhydride.[23] Treatment of the resulting *N*-formyl imide **118c** with ethyl triphenylphosphonoacetate in benzene gave the *E*-enamide **119c** in good yield and as a single isomer (Scheme 27).

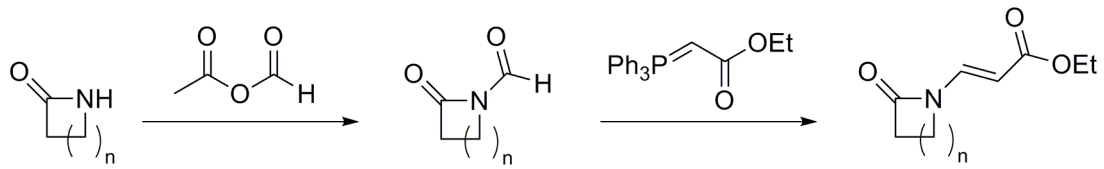


117c **118c** **119c**

Scheme 27 Synthesis of enamides and confirmation of stereochemistry

The stereochemistry was determined unequivocally through ^{1}H NMR spectroscopy (alkene coupling constant : J = 14.4 Hz), 2D NOE experiments and also through X-ray crystallography.

These conditions were then successfully applied to a number of *N*-formyl lactams **118a-f** (from 4-membered to 9-membered) giving the desired *E*-enamides **119a-f** in moderate to good yield and as a single isomer in all cases (Scheme 28).



117 **118** **119**

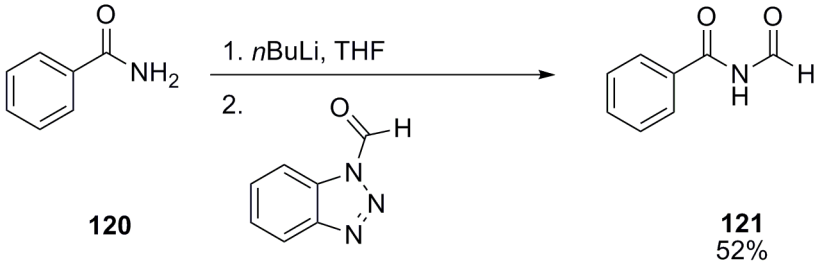
a	n = 1	77%
b	n = 2	66%
c	n = 3	47%
d	n = 4	55%
e	n = 5	37%
f	n = 6	57%

Scheme 28 Synthesis of enamides from *N*-formyl lactams

In addition to the studies of *N*-formyl lactams, a number of *N*-formyl amides were also prepared. Formylation of the parent amides, however, was not successful under the previous mixed anhydride conditions. Instead, the *N*-formyl amides were generated via formylation by *N*-formyl benzotriazole, a stable formylating reagent

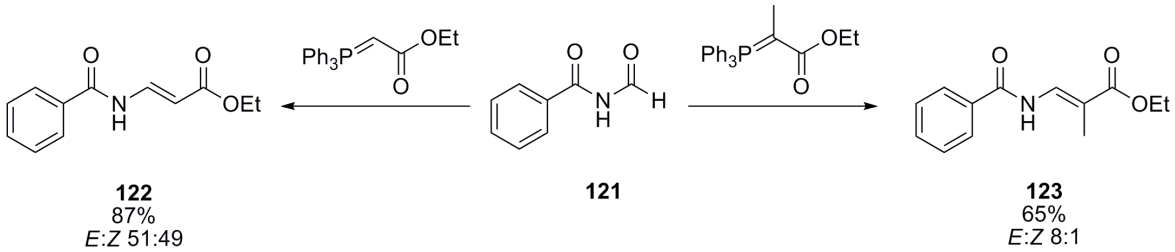
[23] Strazzolini, P.; Giumanini, A. G.; Cauci, S., *Tetrahedron*, **1990**, 46(4), 1081

made from a coupling reaction between benzotriazole and formic acid.[24] For example, benzamide **120** was formylated in good yield (Scheme 29).



Scheme 29 Formylation of benzamide

The *N*-formyl amides not only reacted satisfactorily under the previously developed olefination conditions, but also reacted with a methyl substituted phosphorous ylide to give 2-substituted enamides e.g **123**, also in good yields (Scheme 30). 2-substitued enamides had previously been difficult to obtain with any degree of stereocontrol through previous methods.



Scheme 30 Synthesis of di- and tri-substituted enamides

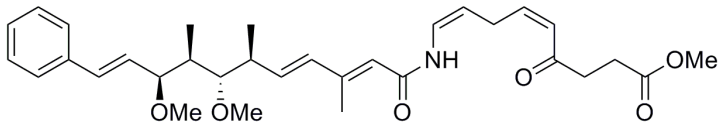
This work, done previously by the group indicates that *N*-formyl imides can provide access to a number of enamides with good control over olefin geometry, thus laying foundations for further development of this methodology.

[24] Katritzky, A. R.; Chang, H X.; Yang, B., *Synthesis*, **1995**, 503

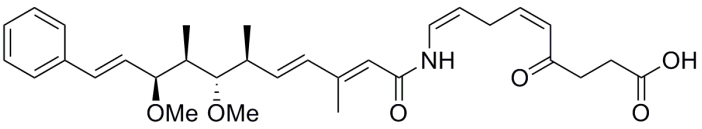
1.2 The Crocacins

1.2.1 Isolation and Structure Elucidation

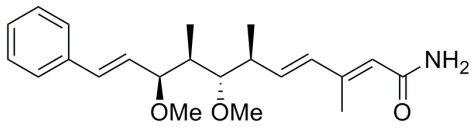
The Crocacins are a family of four antifungal and highly cytotoxic metabolites found in myxobacteria of the genus *Chondromyces*. Crocacins A-C were isolated from *Chondromyces crocatus* and Crocacin D from *Chondromyces pediculatus*.[25] Structurally, Crocacins A, B and D are unusual linear dipeptides containing a highly reactive *N*-acyl enamide unit. Crocacin C is a primary amide derivative of the other three more structurally complex members of the family (Fig 5).



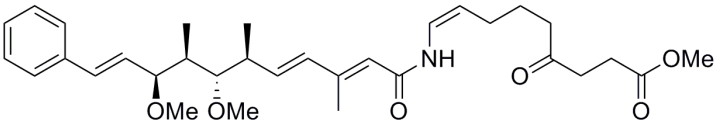
Crocacin A, **4**



Crocacin B. **5**



Crocacin C, **6**



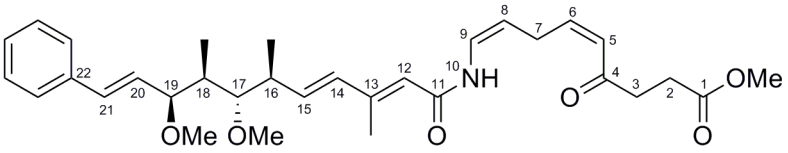
Crocacin D, **7**

Fig 5 The Crocacin family

In 1999, Jansen and co-workers reported the first isolation and structural elucidation of all four members of the family, where previously it was believed to be a single compound, Crocacin.[26] The Jansen group first assigned the structure of Crocacin A **4**, the main product from *C. Crocatus* via a variety of techniques (Fig 6).

[25] Kunze, B.; Jansen, R.; Höfle G.; Reichenbach, H., *J. Antibiot.*, **1994**, 47(8), 881

[26] Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Höfle, G., *Eur. J. Chem.*, **1999**, 1085



4

Fig 6 Crocacin A

The elemental composition was elucidated by HR-EI mass spectrometry, giving a *m/z* value of 538 which corresponded to the formula $C_{31}H_{42}N_2O_6$ implying 12 double bond equivalents. The characteristic UV spectrum allowed assignment of these to the appropriate chromophores. Ester and amide bonds were indicated by intense carbonyl signals and broad NH bands in the IR spectrum. The carbon backbone structure was confirmed and assigned by ^{1}H NMR and ^{13}C NMR and correlated by COSY and HMQC NMR spectroscopy. Long range correlation through HMBC spectroscopy allowed the assignment of the attached methyl ester and ether residues. The two *E* double bond configurations were confirmed via NOE experiments between the methyl group at C13 and 15-H and between 12-H and 14-H. The two *Z* double bonds were assigned via the vicinal coupling constants between 8-H and 9-H and 5-H and 6-H . The information gathered from the various experiments also allowed a relative configuration to be assigned, based on the four stereocentres at C-16, C-17, C-18 and C-19.

The structure of Crocacin B **5** was deduced from the absence of the 1-methoxy group in the ^{1}H NMR spectrum, and its highly polar behaviour in both TLC and HPLC analysis allowed the assumption that it existed as the free carboxylic acid.

The lower value result for the mass spectrometry, coupled with the absence of all the NMR signals belonging to the unsaturated amino acid and glycyl ester moieties of Crocacin A allowed the structure of Crocacin C **6** to be elucidated, the primary amide bond being characterised through the appropriate absorption bands in the IR spectrum.

Mass spectrometry showed Crocacin D **7** to contain 2 more hydrogen atoms than Crocacin A. The saturated bond between C-5 and C-6 was obvious from the lack of two olefin signals and addition of two methylene signals when comparing the NMR spectra.

1.2.2 Biological Properties

The Crocacins display a wide range of biological activities, showing high activity against fungi, yeast and animal cell cultures.[25]

Initial studies of the myxbacteria strains *C. Crocatus* and *C. Pediculatus* suggest that they are a rich source of electron transport inhibitors. The Crocacins in particular are believed to interfere specifically at the bc_1 segment (complex III) and further tests pointed to an interaction with *cytochrome b*.

On isolation and testing of the individual members of the Crocacin family, Crocacin A was found to be a moderate inhibitor of gram positive bacteria and showed high activity against the growth of fungi and yeast cultures. By far the most powerful of the four is Crocacin D, which has an MIC of 1.4 ng/mL against *Saccharomyces cerevisiae* and an IC_{50} value of 60 µg/mL for toxicity in L929 mouse fibroblast cell cultures.[26]

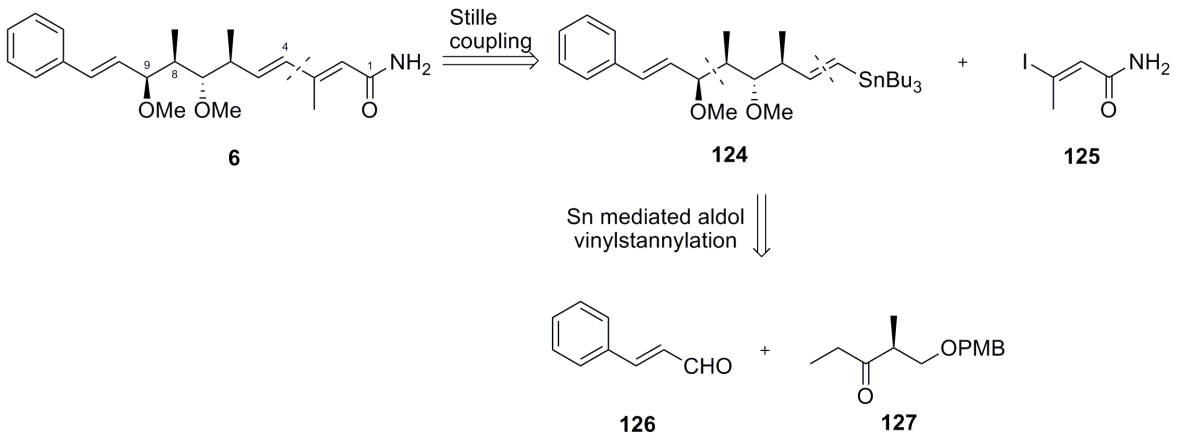
1.2.3 Previous Syntheses of Crocacin C

Crocacin C is the simplest of the family in terms of structure and therefore there have been a number of total syntheses reported. In spite of its relatively simple structure at first glance, synthesis of this compound is challenging, in particular due to the 4 adjacent stereocentres.

1.2.3.1 Rizzacasa *et al.* – 2000

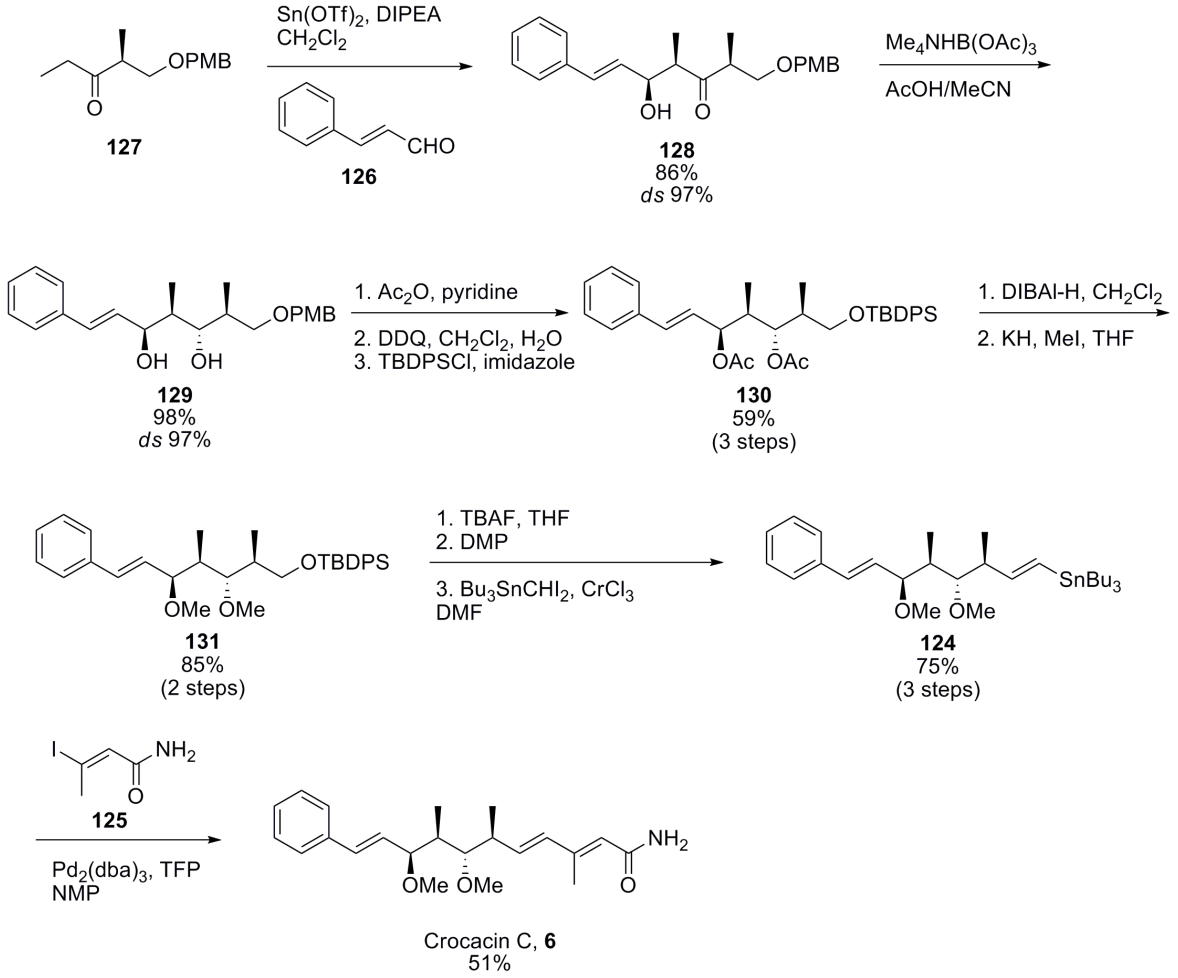
The first asymmetric total synthesis of Crocacin C was reported in 2000 by Rizzacasa and co-workers.[27] The key steps in the synthesis were the stereoselective formation of the (*E,E*)-diene via a Stille coupling and a substrate controlled aldol reaction, using Paterson's methodology, to furnish the *syn* stereocentres at C8 and C9 (Scheme 31).

[27] Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A., *Org. Lett.* **2000**, 2(21), 3365



Scheme 31 Rizzacasa's retrosynthesis of Crocacin C

The synthesis began with the tin-mediated aldol reaction of known intermediate **127** and *trans*-cinnamaldehyde **126** giving the *syn-syn* product **128** in excellent yield and with high diastereoselectivity. Stereoselective reduction of the ketone using tetramethylammonium triacetoxyborohydride furnished the *anti*-diol **129** and thus completed the stereotetrad (Scheme 32).



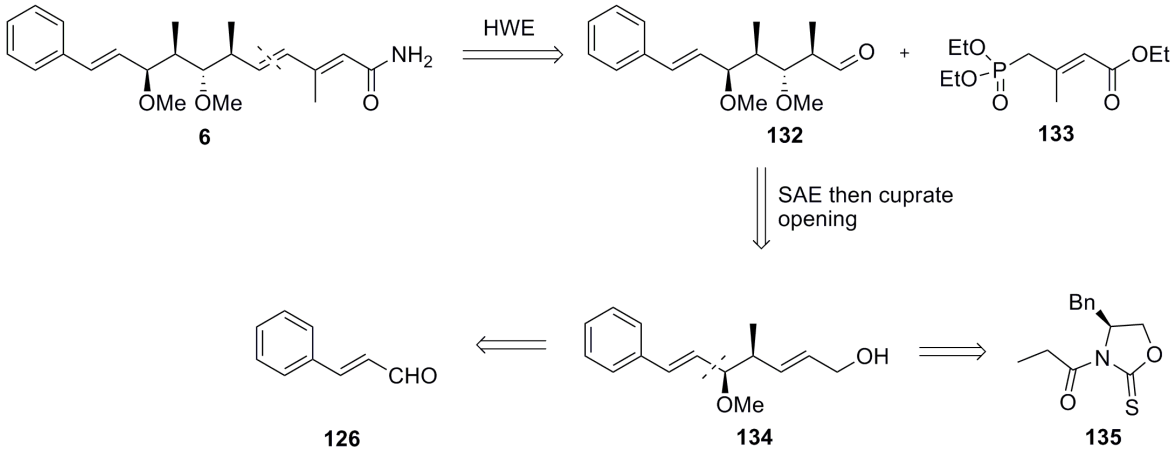
Scheme 32 Rizzacasa's synthesis of Crocacin C

At this stage removal of the PMB group was proving problematic. This was eventually overcome by acetylation of the diol, which gave the diacetate. Removal of the PMB group gave the primary alcohol, which was reprotected as a TBDPS ether **130** followed by reductive removal of the acetate groups. Methylation of the diol afforded the dimethyl ether in good yield. The next stage was desilylation followed by oxidation to give the aldehyde, which when treated with chromium-mediated vinylstannylation methods yielded the (*E*)-stannane **124**. The stannane was then coupled with the iodide **125** under palladium-catalysed conditions to afford Crocacin C.

As this was the first total synthesis of Crocacin C reported, the structure was therefore verified and it was found that the ^{1}H NMR, ^{13}C NMR, IR and UV spectra were identical to that of the natural product. In addition to this data, the optical rotation was comparable to that of natural Crocacin C.

1.2.3.2 Chakraborty *et al.* – 2001

At around the same time Chakraborty and co-workers also reported a total synthesis of Crocacin C.[28] Their strategy involved a Horner-Wadsworth-Emmons reaction to install the (*E*,*E*)-diene unit and a titanium-mediated Aldol reaction to furnish the adjacent stereocentres at C8 and C9. The remaining two stereocentres at C6 and C7 were produced via a Sharpless asymmetric epoxidation followed by selective opening of the epoxide using a lithium dimethyl cuprate (Scheme 33).



Scheme 33 Chakraborty's retrosynthesis of Crocacin C

Synthesis began with the asymmetric aldol addition between the titanium enolate derived from acyloxazolidinethione **135** and *trans*-cinnamaldehyde **126** to give the

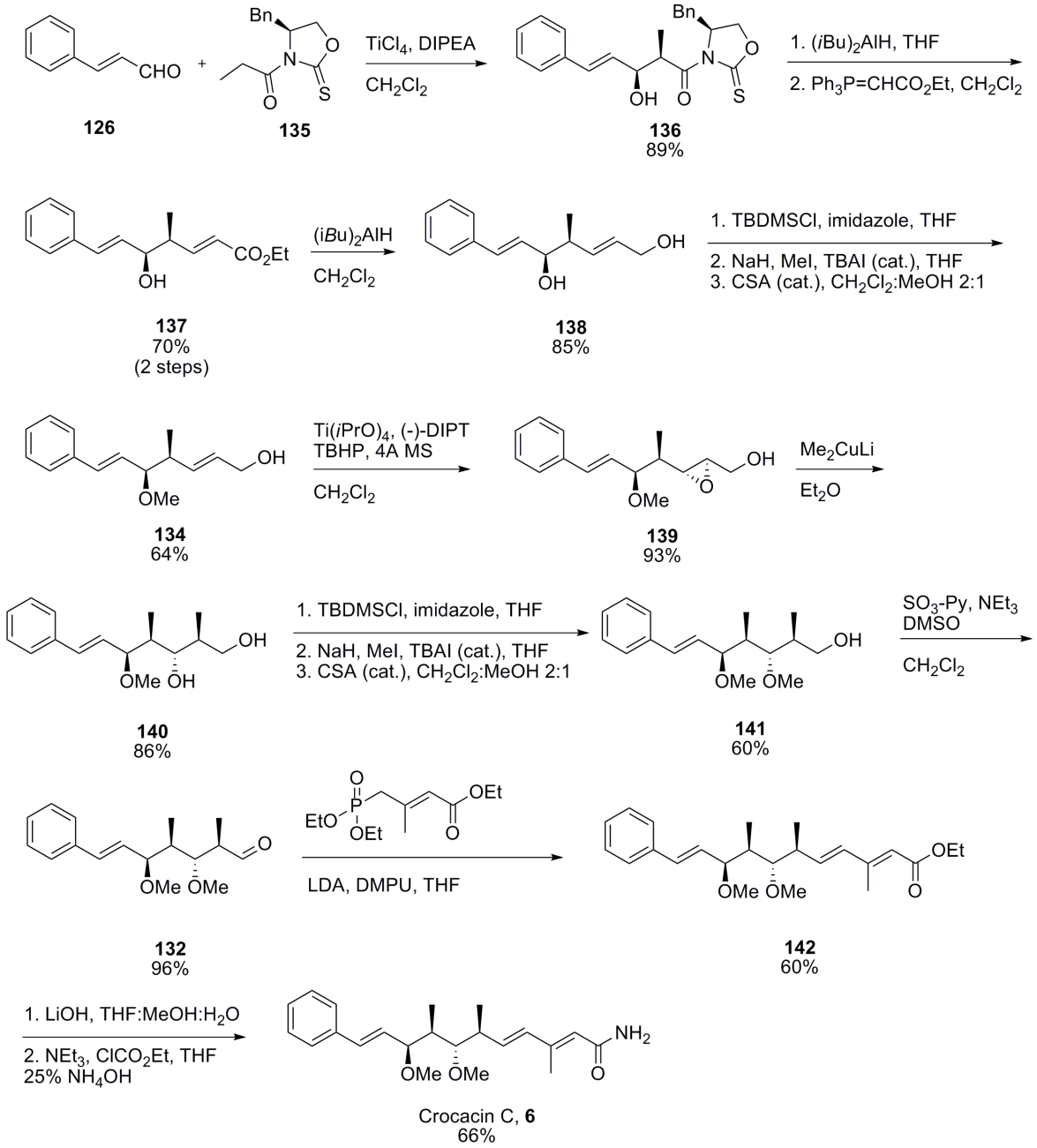
[28] Chakraborty, T. K.; Jayaprakesh, S., *Tetrahedron Lett.* **2001**, 42, 497

desired *syn* aldol product in good yield. Reduction of **136** with DIBAl-H followed by reaction of the intermediate aldehyde with a stabilised ylide gave the α,β-unsaturated ester **137** which was subsequently reduced to give the diol **138**.

In order to methylate the secondary alcohol, the primary alcohol was first selectively protected with a silyl group, allowing methylation of the secondary alcohol with sodium hydride and iodomethane. The silyl protecting group was then removed from the primary alcohol.

The allylic alcohol **134** was then subjected to Sharpless asymmetric epoxidation conditions using (-)-DIPT to yield the desired epoxy alcohol **139** which was then opened stereo- and regio-selectively using lithium dimethylcuprate. With the four stereocentres now in place the second secondary alcohol was then methylated using the same three steps as above for the previous secondary alcohol.

Next the primary alcohol was oxidised using SO_3-pyridine and the resultant aldehyde treated with a phosphonate ester under Horner-Wadsworth-Emmons conditions. Crocacin C was finally furnished via saponification of the ester **142** followed by conversion of the acid to the amide using a mixed anhydride method (Scheme 34).



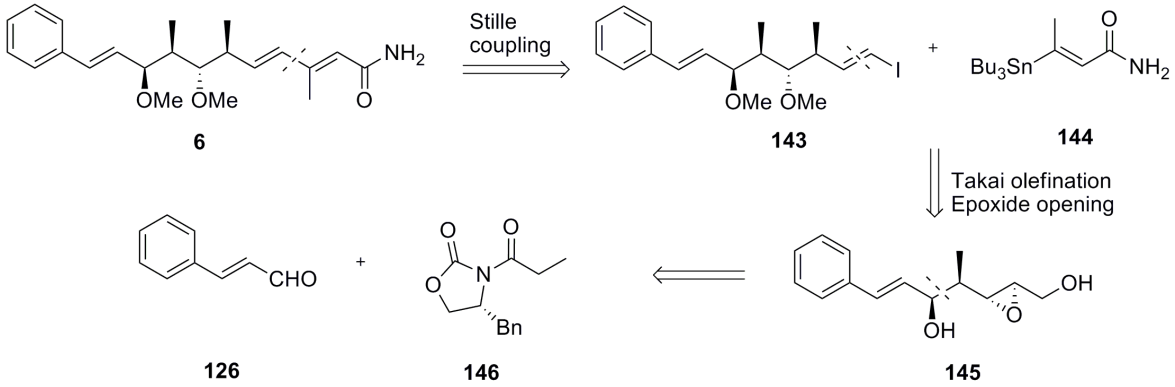
Scheme 34 Chakraborty's synthesis of Crocacin C

The product compared favourably with all the obtained data for the natural product Crocacin C. Step-wise methylation of the two secondary alcohols is an obvious disadvantage of this synthesis. Overall this simple functional group conversion involved 6 steps resulting in significant reduction of yield. It would have been more efficient if the methylation steps could have been carried out simultaneously.

1.2.3.3 Dias *et al.* – 2001

Also in 2001 Dias and co-workers published a total synthesis of Crocacin C.[29] The key steps in the synthesis were also featured in the earlier syntheses by Rizzacasa and Chakraborty.

The synthesis involves establishing the (*E,E*)-diene unit through a Takai olefination followed by a Stille coupling reaction and the four stereocentres were constructed by a boron-mediated Aldol reaction and a stereoselective epoxide opening (Scheme 35).



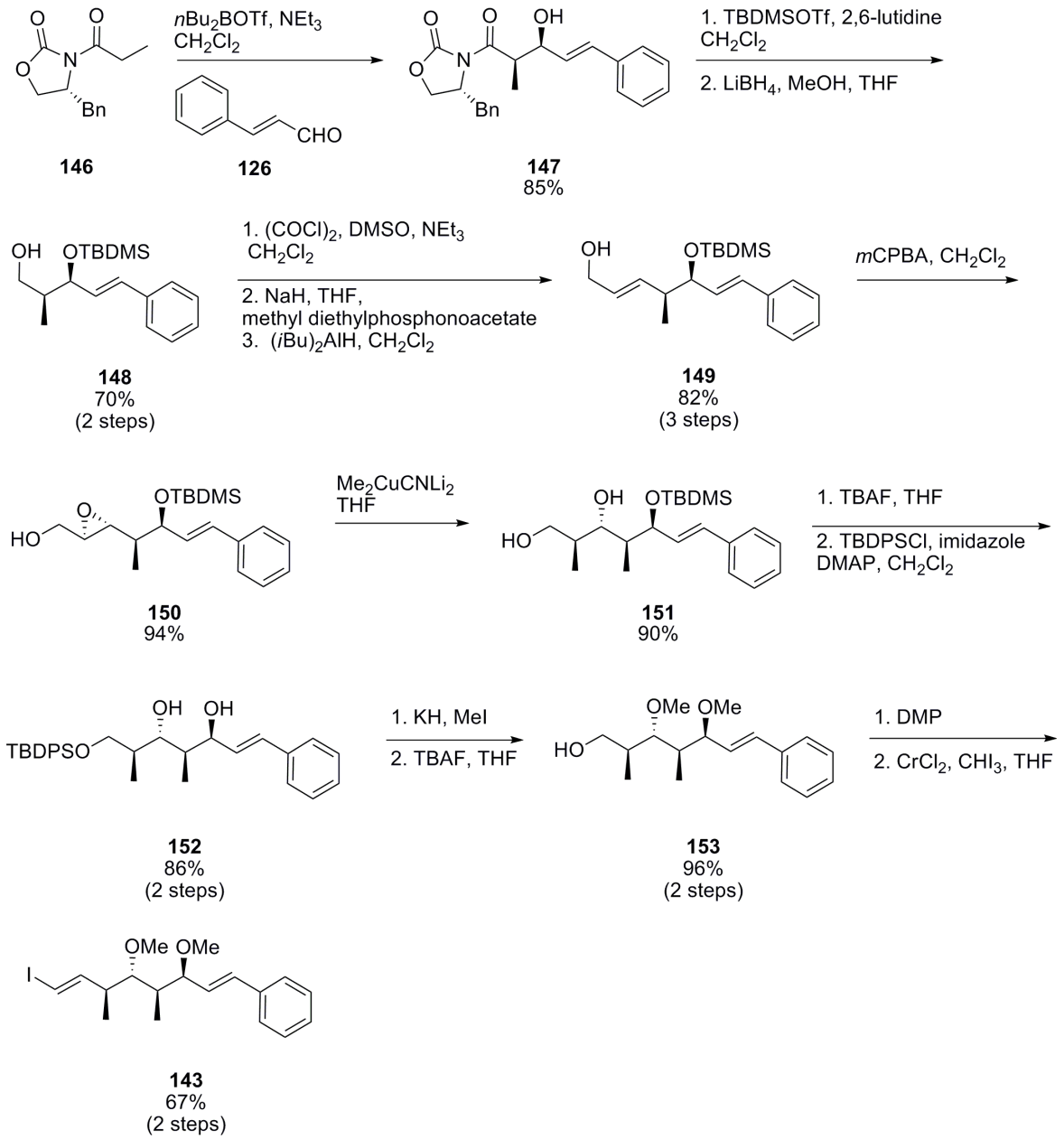
Scheme 35 Dias' retrosynthesis of Crocacin C

The synthesis began with (-)-acyloxazolidinone **146** which was prepared by acylation of the parent (+)-oxazolidinone via a procedure described by Evans.[30] This was subjected to asymmetric aldol addition via the boron enolate with *trans*-cinnamaldehyde **126**. Conversion to the primary alcohol **148** was achieved first by protection of the secondary alcohol and then removal of the oxazolidinone auxiliary by treatment with lithium borohydride.

The primary alcohol was then oxidised under Swern conditions and immediately reacted with diethylphosphonoacetate in a Horner-Wadsworth-Emmons olefination reaction. Reduction of the ester with DIBAl-H gave the allylic alcohol **149** which was epoxidised using *m*CPBA. The group were pleased to report that epoxidation proceeded with the desired stereo- and regio-selectivity, presumably due to steric effects of the bulky TBDMS group. The *anti*-epoxy alcohol **150** was then opened using $Me_2CuCNLi_2$ to give the diol **151** with the desired *anti-anti-syn* stereochemistry with respect to the four adjacent stereocentres.

[29] Dias, L. C.; de Oliveira, L. G., *Org. Lett.*, **2001**, 3(24), 3951

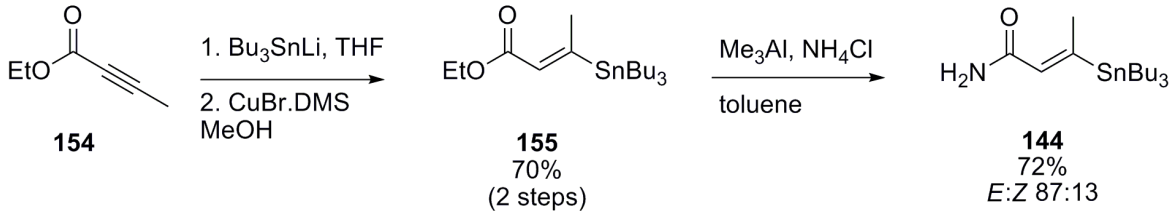
[30] Evans, D. A.; Gage, J. R., *Org. Synth.*, **1989**, 68, 83



Scheme 36 Synthesis of the iodide

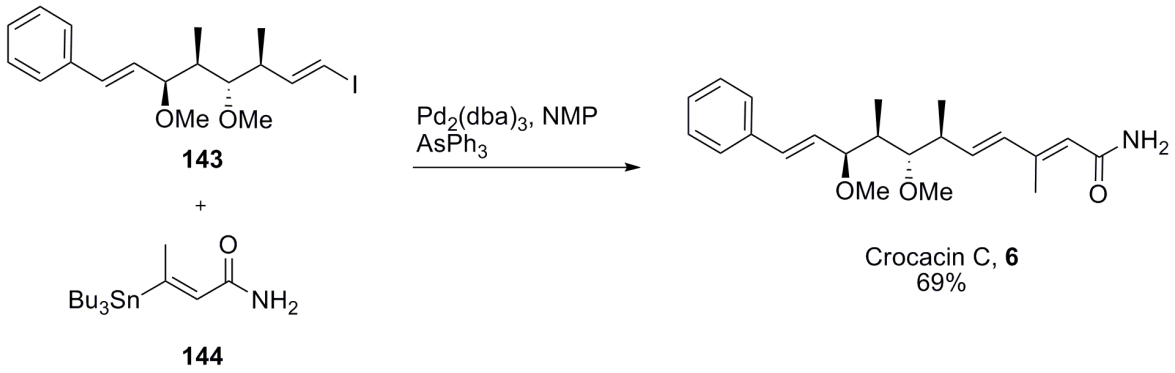
The secondary alcohol was then deprotected and the primary alcohol selectively protected followed by methylation of the two secondary alcohols with potassium hydride and iodomethane. Finally, removal of the silyl protecting group and oxidation of the primary alcohol **153** using Dess-Martin periodinane gave the aldehyde required to carry out the necessary Takai olefination to give the *E*-vinyl iodide **143** for the final coupling step (Scheme 36).

The second coupling partner, stannane **144**, was prepared via conjugate organo-stannyl cuprate addition to ethyl 2-butynoate followed by treatment with trimethylaluminium and ammonium chloride to convert the ester **155** to the amide (Scheme 37).



Scheme 37 Synthesis of the stannane

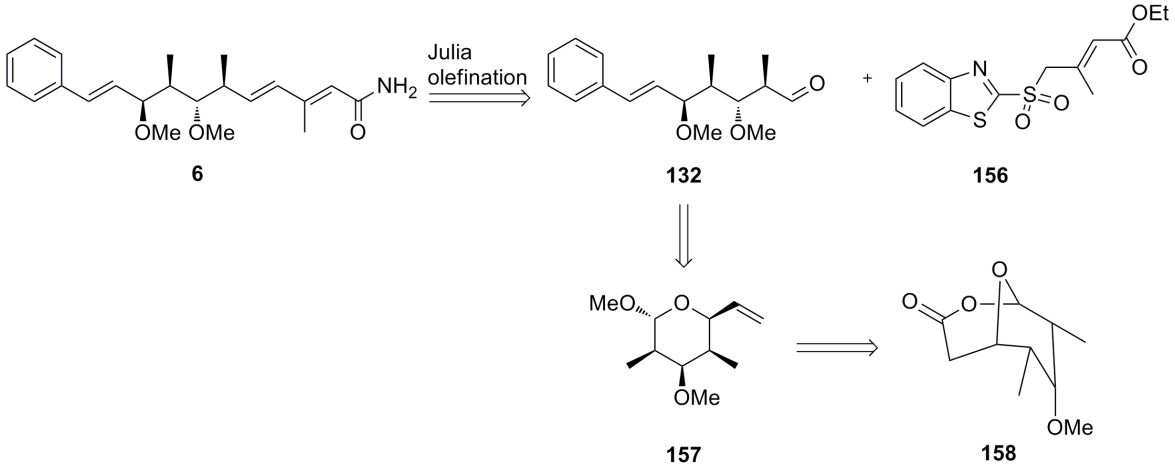
The two fragments were then coupled under Stille conditions to give Crocacin C which corresponded with all the physical data available for the natural product (Scheme 38).



Scheme 38 Completion of Dias' synthesis of Crocacin C

1.2.3.4 Yadav *et. al.* – 2007

A number of years later Yadav and co-workers reported a total synthesis of Crocacin C which was completely different from previous attempts in that it relied on desymmetrisation of a meso bicyclic dihydrofuran.[31] Key steps included asymmetric hydroboration, cross-metathesis and Julia olefination reactions (Scheme 39).

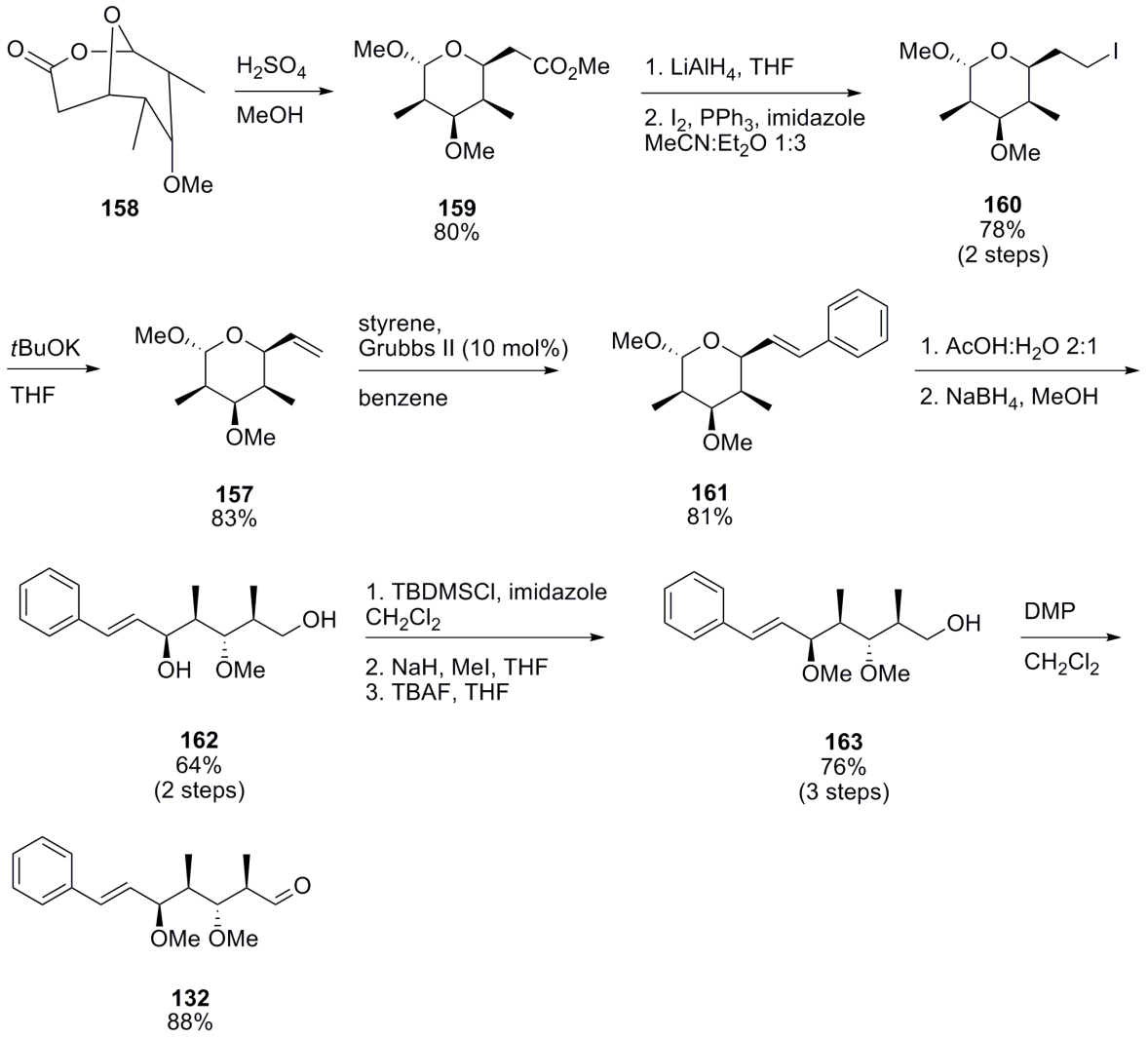


Scheme 39 Yadav's retrosynthesis of Crocacin C

[31] Yadav, J. S.; Venkatrem Reddy, P.; Chandraiah, L., *Tetrahedron Lett.,* **2007**, 48, 145

The first step involved acid-catalysed methanolysis of bicyclic lactone **158**, which yielded ester **159**. The ester was reduced with lithium aluminium hydride and the resultant alcohol converted to the iodide **160** using iodine, triphenylphosphine and imidazole. The iodide was eliminated under basic conditions to give olefin **157**.

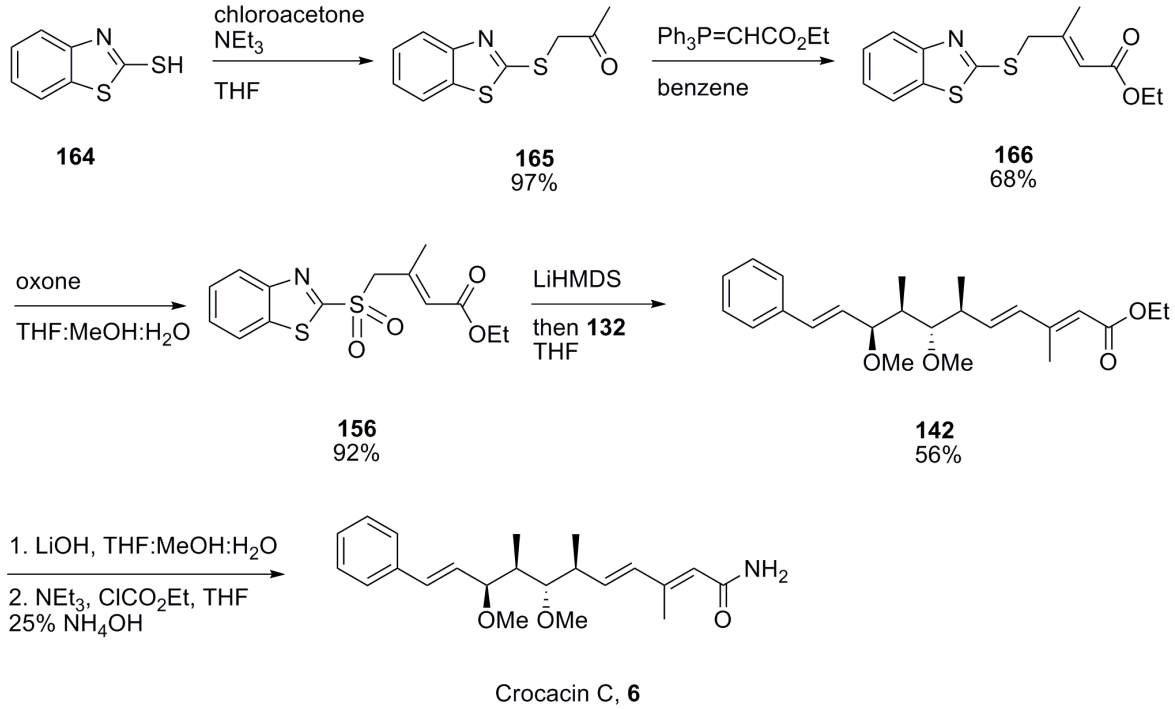
This was then coupled with styrene under cross metathesis conditions using Grubbs 2nd generation catalyst to give the *trans*-olefin **161**. The lactone ring was then opened via aqueous acetic acid-induced hydrolysis followed by sodium borohydride reduction of the lactol to give the diol **162**. Selective protection of the primary alcohol with a silyl group allowed the secondary alcohol to be methylated using sodium hydride and iodomethane. Deprotection then gave the alcohol **163** which was oxidised with Dess-Martin periodinane to give aldehyde **132** ready for the Julia olefination reaction (Scheme 40).



Scheme 40 Synthesis of aldehyde **132**

The sulfone for the Julia olefination was generated from mercaptobenzothiazole and chloroacetone to give intermediate **165** followed by Wittig olefination with a

stabilised ylide to give the α,β-unsaturated ester **166**. Finally, selective oxidation of the sulfide to the sulfone using oxone gave the second fragment for the final coupling reaction **156** (Scheme 41).



Scheme 41 Completion of Yadav's synthesis of Crocacin C

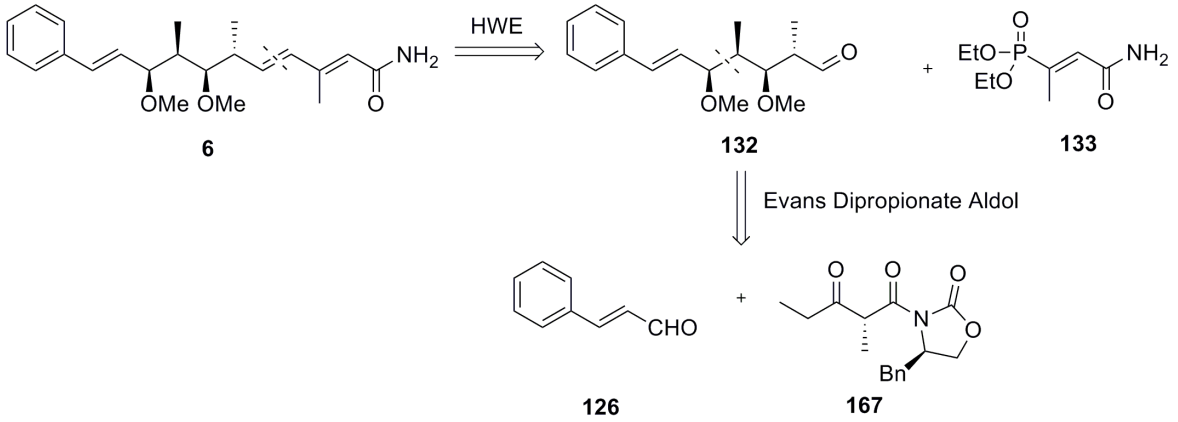
The sulfone was lithiated then treated with aldehyde **132** to give advanced intermediate ester **142**. Finally Crocacin C was furnished by following the methods previously developed by Chakraborty; saponification and formation of the amide by mixed anhydride methods.

In addition to synthesising Crocacin C, Yadav and co-workers claim that Crocacins A, B and D can be derived from the same advanced intermediate ester **142**, although to date nothing further has been published by this group on synthesis of any of these compounds.

1.2.3.5 Andrade *et al.* – 2008

In 2008, Andrade and co-workers published a much shorter route to Crocacin C than had previously been published.[32] The route eliminated the need for protecting groups, thus increasing the atom efficiency of the reaction significantly. Key steps involve a Horner-Wadsworth-Emmons olefination to install the (*E,E*)-diene unit and an Evans dipropionate aldol reaction to control the stereochemistry (Scheme 42).

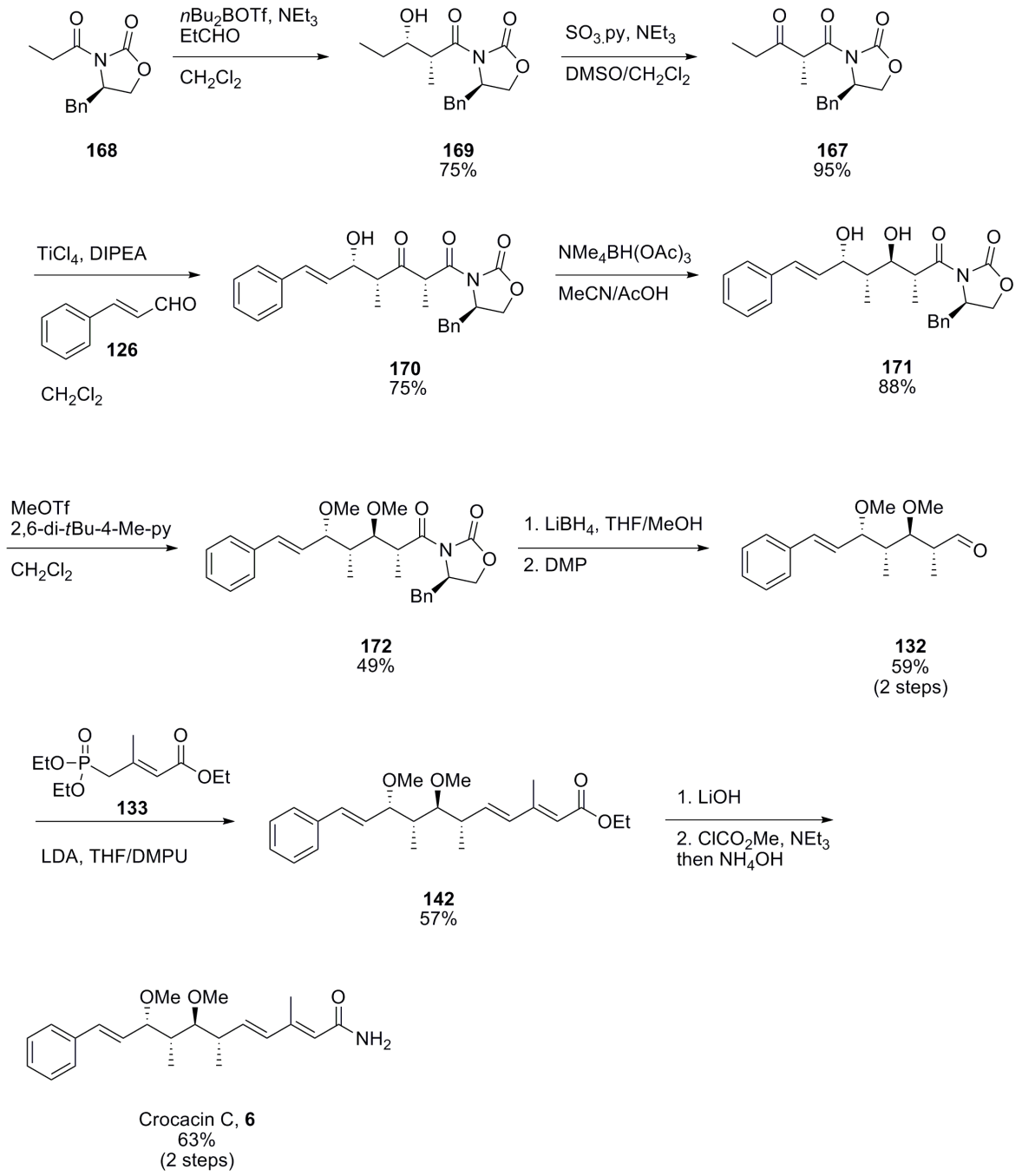
[32] Sirasani, G.; Paul, T., Andrade, R. B., *J. Org. Chem.*, **2008**, 73, 6386



Scheme 42 Andrade's retrosynthesis of Crocacin C

The first reaction in the synthesis was an Evans aldol reaction between oxazolidinone **168** and propionaldehyde followed by oxidation of the secondary alcohol **169** under Parikh-Doering conditions. Addition of *trans*-cinnamaldehyde **126** to the titanium enolate of **167** gave the desired *syn-syn* aldol product **170**.

The ketone was then stereoselectively reduced using tetramethylammonium triacetoxyborohydride to give the *anti*-1,3-diol **171** before methylating the two secondary alcohols with methyl triflate and 2,6-di-*tert*-butyl-4-methylpyridine. This reaction was relatively low yielding (49%), with the undesired elimination product being attributed to the remaining mass balance. The chiral auxiliary was then removed using lithium borohydride and the resulting primary alcohol oxidised using Dess-Martin periodinane.

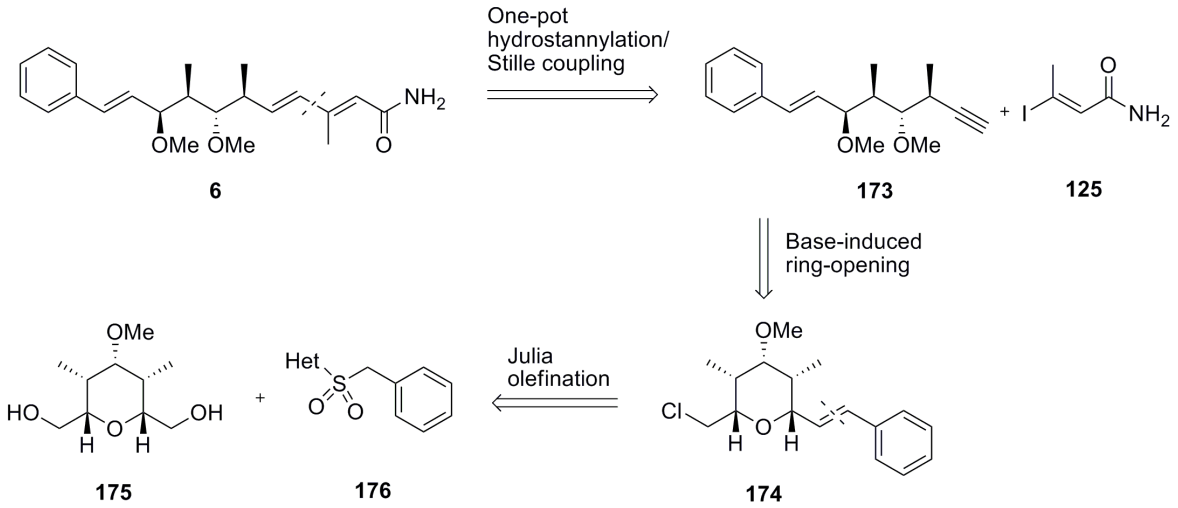


Scheme 43 Andrade's synthesis of Crocacin C

Finally aldehyde **132** was coupled to phosphonate ester **133** under Horner-Wadsworth-Emmons conditions and ester **142** was saponified and converted to the amide using lithium hydroxide followed by methyl chloroformate and aqueous ammonia to give Crocacin C (Scheme 43). This synthesis provided the shortest and most atom-efficient route of Crocacin C to date.

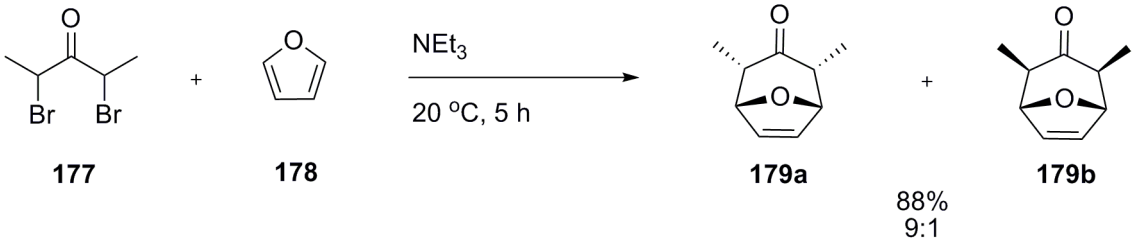
1.2.3.6 – Pons *et al.* – 2010

The most recent reported synthesis of Crocacin C to date was in 2010 from Pons and co-workers in which they used a combination of desymmetrisation of a *meso*-THP diol followed by a base-induced ring-opening to establish all four stereocentres at once (Scheme 44).[33]



Scheme 44 Pons' retrosynthesis of Crocacin C

The starting material, oxabycycle **179a** is made via a [4+3] cycloaddition between the oxoallyl cation of **177** and furan **178** (Scheme 45). The oxabicycle **179a** was then diastereoselectively reduced using sodium borohydride and the resulting secondary alcohol methylated under standard conditions to furnish **180**. Ozonolysis with a reductive work-up furnished the desired *meso*-diol, the achiral version of which was desymmetrised enzymatically using *Rhizomucor miehei* in diisopropyl ether and vinyl acetate.



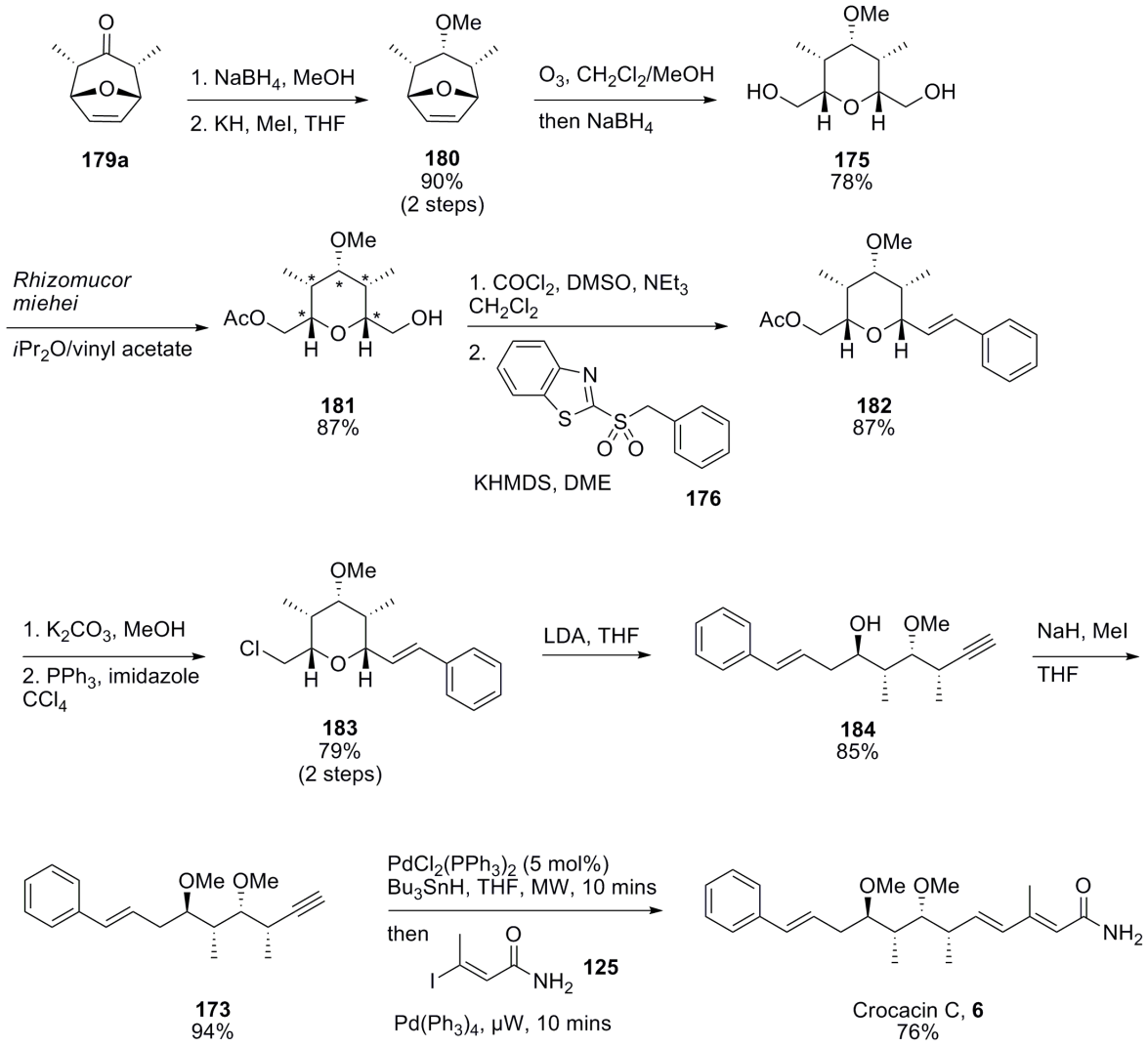
Scheme 45 Synthesis of the oxabicycle

The resulting mono-acetate **181** was subjected to standard Swern conditions to give the aldehyde which was immediately treated with sulfone **176** to give Julia olefination product **182** in an *E*:*Z* ratio of 87:13, the isomers of which were easily separated by column chromatography. The acetate was then removed under basic

[33] Candy, M.; Audran, G.; Bienayme, H.; Bressy, C.; Pons, J M., *J. Org. Chem.* **2010**, 75, 1354

conditions and the resulting primary alcohol treated with triphenylphosphine, imidazole and carbon tetrachloride to give chloride **183**.

This intermediate was then subjected to base-induced THP ring-opening to form alkyne **184**. The secondary alcohol was then methylated under standard conditions to give **173**.



Scheme 46 Pons' synthesis of Crocacin C

The final step of Crocacin C synthesis involved a one-pot palladium-catalysed hydrostannylation followed by a Stille coupling. This reaction was optimised and it was found that a microwave assisted procedure gave the best results (Scheme 46).

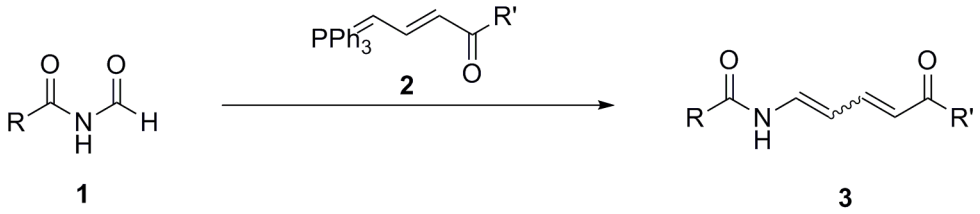
This synthesis makes use of hidden symmetry to give a very concise, protecting group-free strategy for the synthesis of Crocacin C, albeit involving a large amount of optimisation throughout.

2.0 Results and Discussion

2.1 Dienamides

The literature available on previous syntheses of dienamides suggests that each methodology presents its own range of disadvantages which limits the scope of the reactions. Issues of low yields, substrate limitation, poor stereocontrol and inefficiency in terms of the number of reaction steps need to be addressed in order to maximise the potential for synthesis of these important functionalities.

In the pursuit of an efficient synthesis of dienamides it is proposed that the scope of the group's previous work into the enamide methodology could be further widened to examine olefination of the imide precursor with an alkenyl ylide **2** (Scheme 47). This would generate the dienamide unit in a single step, with complete control of olefin geometry.



Scheme 47 Proposed one-step synthesis of dienamides

2.1.1 Synthesis of Dienamides

An efficient and flexible methodology for the synthesis of enamides using established Wittig chemistry has been proven to be successful.[34] In order to expand this methodology and explore its flexibility further in terms of a one-step synthesis of dienamides it was necessary to first build up a library of diverse imide coupling partners.

[34] Villa, M. V. J.; Targett, S. M.; Barnes, J. C.; Whittingham, W. G.; Marquez, R., *Org. Lett.*, **2007**, 9(9), 1631

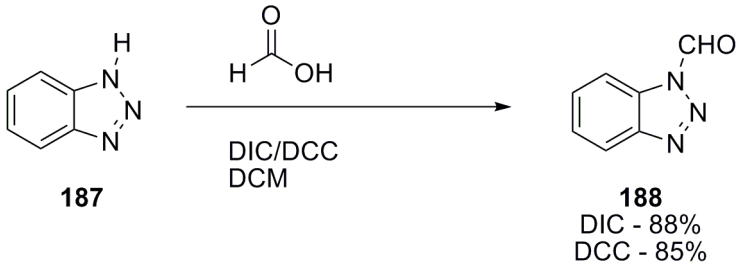
2.1.1.1 Synthesis of parent imides

The imides are derived from their corresponding amides or lactams via an *N*-formylation reaction (Scheme 48). As previously reported, amides can be formylated using *N*-formyl benzotriazole, a stable formylating reagent.[35]

Scheme 48 Preparation of *N*-formyl imides

The advantages of *N*-formyl benzotriazole over more conventional formylating reagents, such as formic halides, anhydrides and esters and formic acid is that it is reactive in both *N*- and *O*-formylation reactions and is also extremely stable. It can be stored in the fridge for months without decomposition. In terms of *N*-formylation it will react with both aromatic and aliphatic amines in good yield.

N-formyl benzotriazole **188** is prepared via a coupling reaction between commercially available benzotriazole **187** and formic acid using a coupling reagent such as DIC or DCC (Scheme 49).

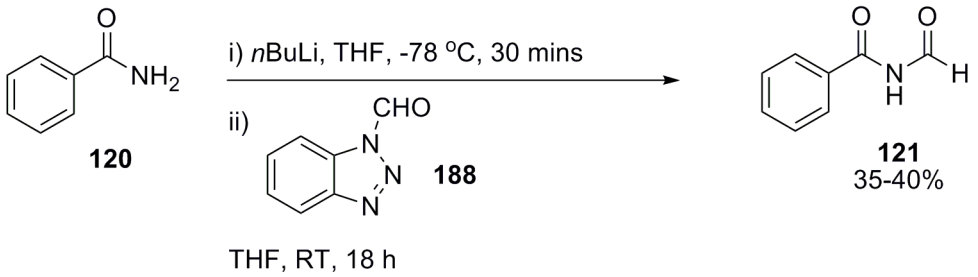


Scheme 49 Synthesis of *N*-formyl benzotriazole

Although the yields were comparable whether using DIC or DCC, it was found that the use of DIC gave problems at the purification stage in terms of removing the excess reagent. Optimisation found that use of DCC gave a much cleaner reaction with easier purification.

The first amide to be formylated was benzamide **120** and treatment with *N*-formylbenzotriazole gave the *N*-formyl benzamide **121** in consistently 35-40% yield (Scheme 50).

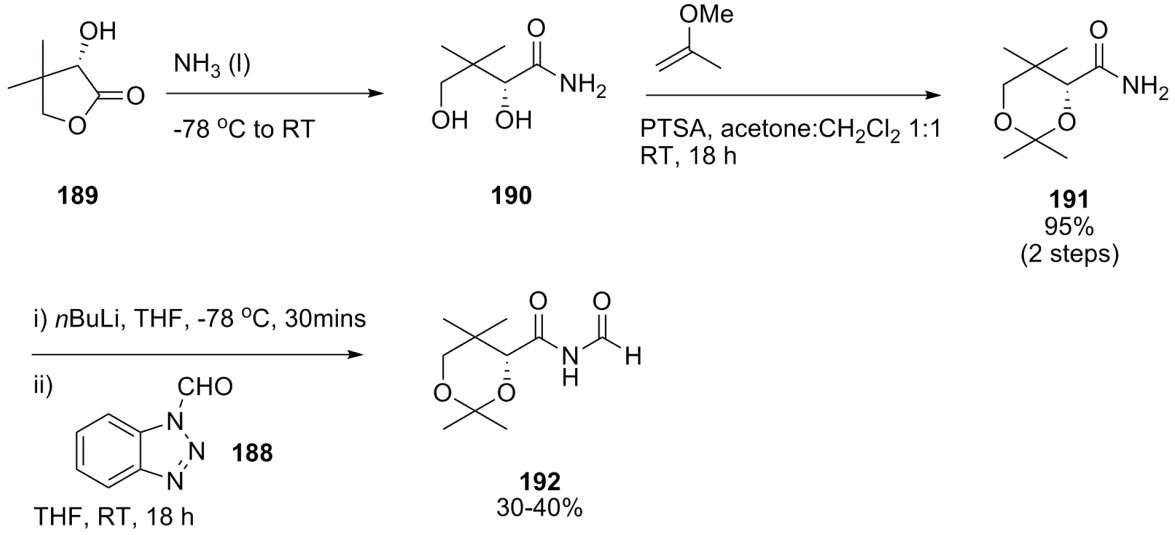
[35] Katritzky, A. R.; Chang, H, X.; Yang, B., *Synthesis*, **1995**, 503



Scheme 50 Formylation of benzamide

The next amide selected was one which had proved to be effective in the previous studies within in the group. It is an intermediate in the group's synthesis of enamide-bearing antibiotic CJ-15 801.[36]

Amide **191** is prepared by treatment of pantolactone **189** with liquid ammonia to generate diol **190**, which is taken directly onto the next step. Treatment of the diol **190** with 2-methoxypropene and a catalytic amount of PTSA gives the ketal-protected amide **191** in around 95% yield over two steps without the need for purification (Scheme 51).

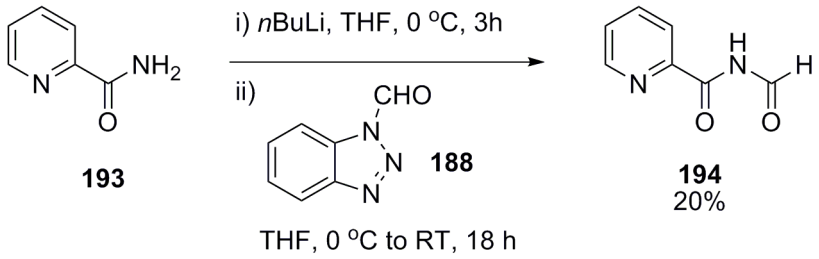


Scheme 51 Synthesis of *N*-formyl imide from pantolactone

Finally amide **191** is treated with *N*-formyl benzotriazole **188** using identical conditions to that of the benzamide formylation to give the imide **192** with a consistent yield of 30-40%.

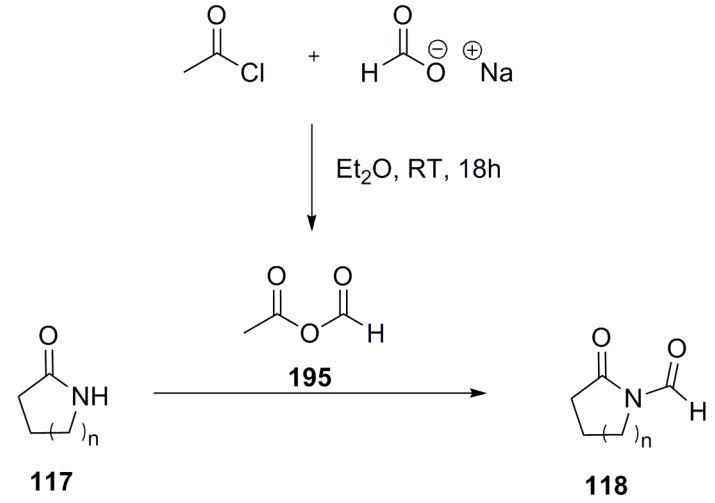
A second aromatic amide, picolinamide **193**, was chosen as the next example. Formylation with *N*-formyl benzotriazole **188** was low-yielding, giving only 20% of the expected material. (Scheme 52) No optimisation was attempted however, as no further material was required.

[36] Sewell, A.L.; Villa, M. V. J., Matheson, M.; Whittingham, W. G.; Marquez, R., *Org. Lett.*, **2011**, 13, 800



Scheme 52 Synthesis of picolinamide-drived *N*-formyl imide

In order to fully demonstrate the flexibility of the methodology it was necessary to make as diverse a library of imide starting materials as possible and as such, in addition to aliphatic and aromatic acyclic amides, a selection of cyclic amides or lactams of varying ring-size were formylated. It had previously been established that lactams cannot be formylated under *N*-formyl benzotriazole conditions. This observation could be attributed to the difference between formylating a primary amide and a secondary amide. The lactams are secondary amides and the nitrogen atom is more hindered, making it more difficult for bulky reagents such as *n*-butyllithium and *N*-formyl benzotriazole to react. As an alternative, lactams were treated with a mixed anhydride **195**, made *in situ* from acetyl chloride and sodium formate (Scheme 53).



Scheme 53 Synthesis of *N*-formyl lactams

The lactams which were formylated under these conditions are detailed in Table 1. The low yields observed for the smaller *N*-formyl lactams could be attributed to the low boiling points of the products and therefore loss of material during solvent removal under vacuum.

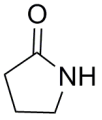
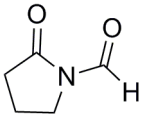
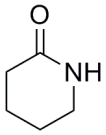
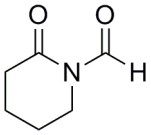
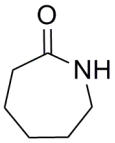
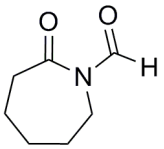
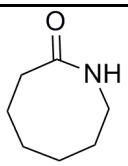
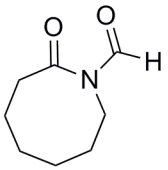
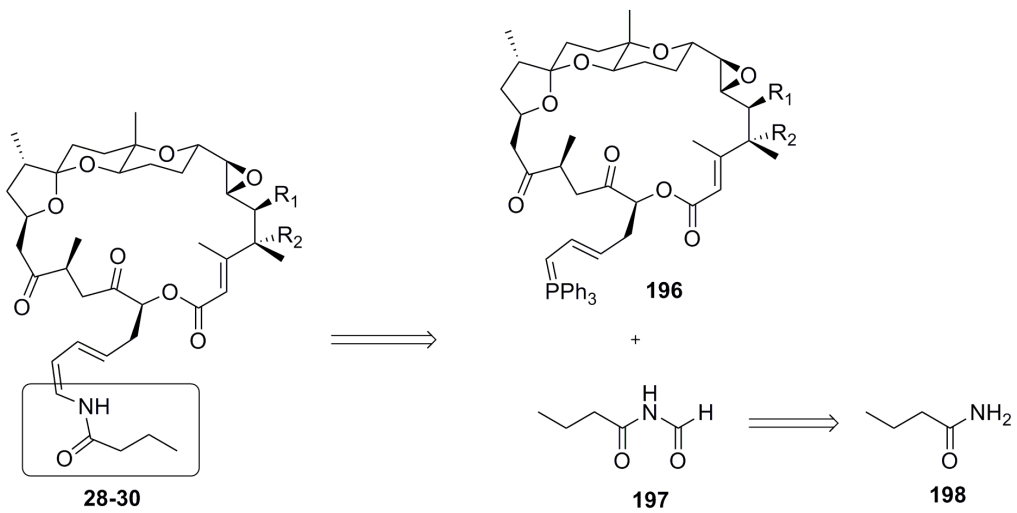
Starting Lactam (117b-e)	Product (118b-e)	Yield
		12%
		16%
		60%
		25%

Table 1 Yields for *N*-formyl lactam synthesis

The reasons for developing this methodology include demonstrating a potential convenient route to establishing dienamide units in natural products. In order to illustrate this further, some dienamide-containing natural products were identified and imides which could be potential synthons in their retrosynthesis were prepared.

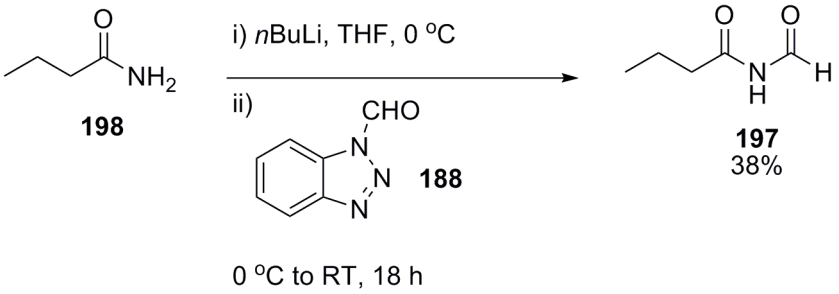
In particular, butyramide **198** is a simple, readily available aliphatic amide but the dienamide derived from butyramide is present in the lituarine family of natural products **28-30** and could potentially be formed from an olefination reaction of the corresponding *N*-formyl imide **197** (Scheme 54).



Scheme 54 Butyramide-derived dienamide present in the Lituarines

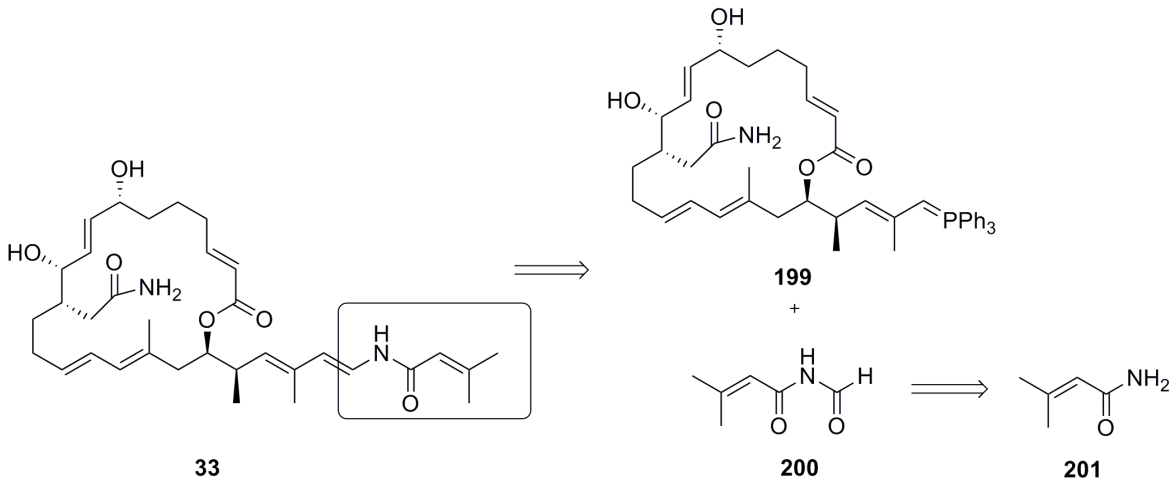
The dienamide moiety present in the lituarines has an *E*,*Z* configuration. Conventionally, a Wittig reaction with a stabilised ylide would be expected to produce an *E* double bond as the major product and in this case would therefore form an *E*,*E* dienamide as the major isomer. Taking advantage of the many reagent-controlled variations of the Wittig reaction that have proven to favour formation of the *Z* double bond could potentially give a degree of stereocontrol over the dienamide formation in this case.

Imide **197** was therefore prepared by reaction of butyramide **198** with *N*-formyl benzotriazole **188** in 38% yield (Scheme 55).



Scheme 55 Synthesis of butyramide-derived *N*-formyl imide

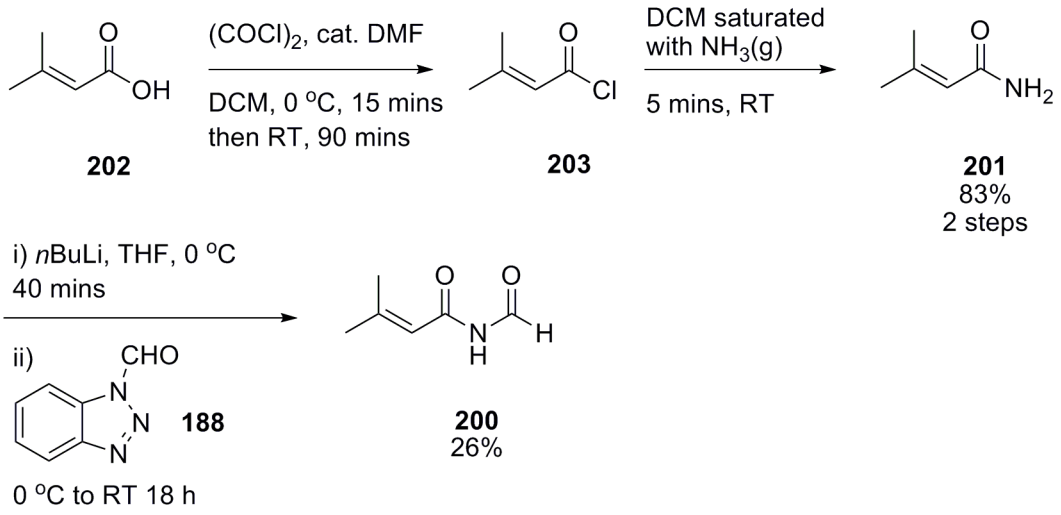
Another obvious candidate to potentially benefit from this methodology is Palmerolide A **33**, which contains an olefinic dienamide side-chain. It was envisaged that theoretically a similar approach could be adopted to install the dienamide moiety as was suggested for the lituarines (Scheme 56).



Scheme 56 Presence of olefinic dienamide in Palmerolide A

In this case the dienamide unit has an *E,E* configuration. This should be easily achievable through use of stabilised Wittig conditions or even Horner-Wadsworth-Emmons chemistry as is reported widely in the literature.

The parent amide, 3,3-dimethylacrylamide **201** is not readily available. 3,3-dimethylacrylic acid **202**, however, is commercially available and can be easily converted to the amide via the acid chloride **203** by treatment with oxalyl chloride followed by ammonia. This gave the desired amide in 83% yield over 2 steps, which was formylated using *N*-formyl benzotriazole **188** to give the *N*-formyl imide **200** in 26% yield (Scheme 57).

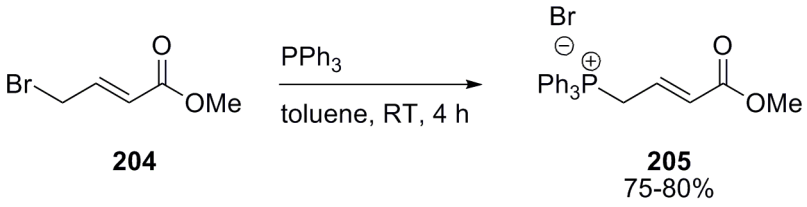


Scheme 57 Synthesis of olefinic *N*-formyl imide

At this stage a library of *N*-formyl imides had been constructed, which contained both aromatic and aliphatic examples, as well as examples derived from cyclic lactams. In addition, examples have been deliberately included that apply directly to the synthesis of dienamide-containing natural products.

2.1.1.2 Wittig Chemistry

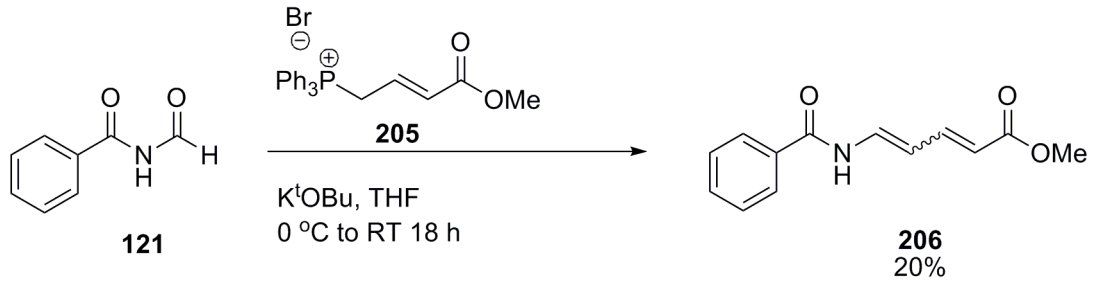
Before initial Wittig experiments on the imide precursors could start, a suitable phosphorous ylide partner was constructed. In order to install the dienamide functionality in one step the ylide partner should have one alkene functionality already in place. A phosphonium salt **205** was envisioned containing an *E*-alkene conjugated with a simple methyl or ethyl ester.



Scheme 58 Synthesis of conjugated phosphonium salt

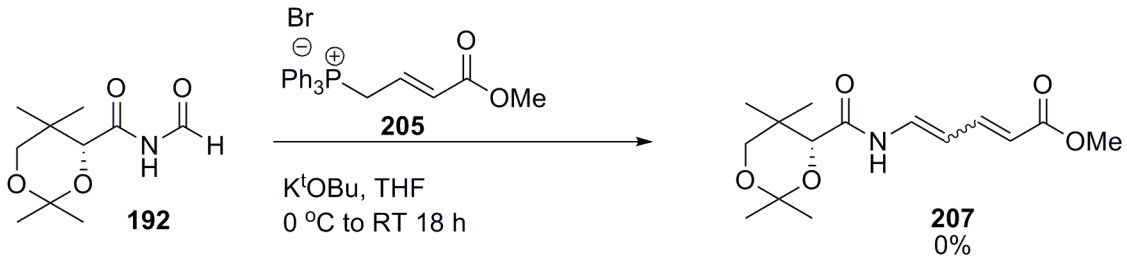
Phosphonium salt **205** was prepared from commercially available methyl 4-bromocrotonate, **204** by reaction with triphenylphosphine in consistently 75-80% yield (Scheme 58).

The phosphonium salt was then reacted with the benzamide-derived imide **121** after deprotonation with potassium *tert*-butoxide (Scheme 59). Analysis by TLC appeared to show complete consumption of starting material, however only 20% of the desired dienamide product **206** was isolated. Whilst it was encouraging to isolate the dienamide, the yield was disappointingly low.



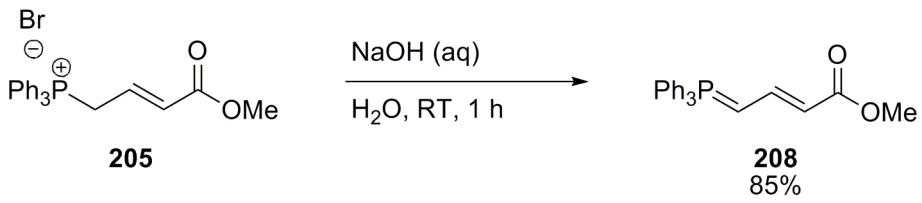
Scheme 59 Wittig reaction with conjugated phosphonium salt

A second imide, the pantolactone-derived imide **192**, was reacted under the same conditions (Scheme 60). After 48 hours, no reaction was observed.



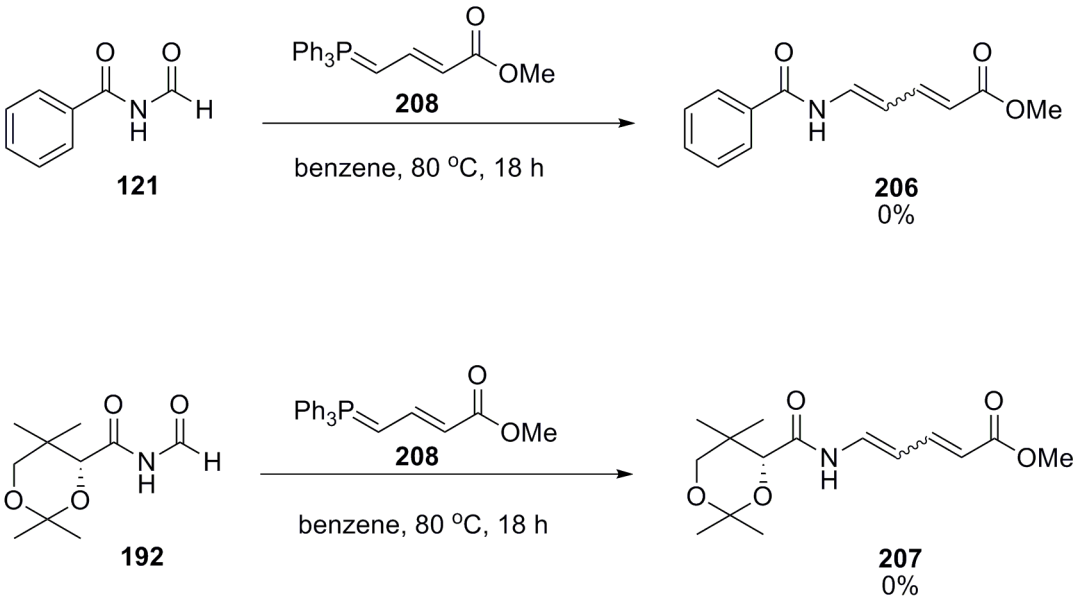
Scheme 60 Wittig reaction with conjugated phosphonium salt

It was postulated that the problem with the reaction may lie with the deprotonation of the phosphonium salt. To overcome this, the salt was deprotonated separately and the ylide **208** isolated before reaction with the imides (Scheme 61). The salt was dissolved in water and treated with a 1M solution of aqueous sodium hydroxide. The product precipitated out immediately upon addition of the base and was isolated to give the ylide as an orange solid in 85% yield.



Scheme 61 Deprotonation of phosphonium salt to give conjugated ylide

Benzene has proved to be an efficient solvent for Wittig reactions involving imides and preformed ylides in previous studies within the group. However reaction of both the benzamide **121** and pantolactone-derived imides **192** with ylide **208** in benzene gave no reaction by TLC analysis (Scheme 62).

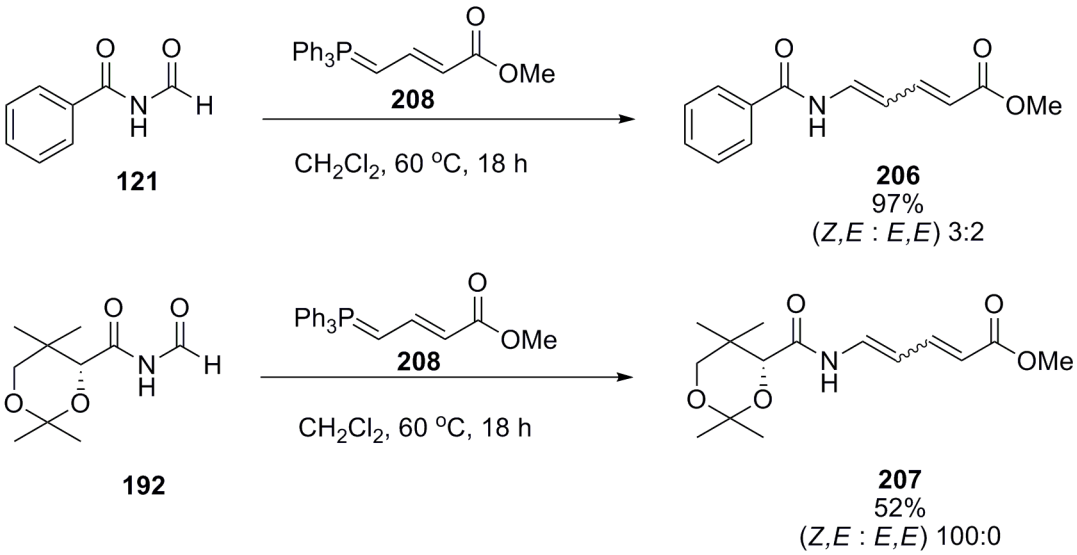


Scheme 62 Wittig reactions in benzene

Bergdahl, in 2007 claimed that water had proved to be an effective solvent for a variety of stabilised Wittig reactions.[37] This is in spite of the poor solubility issues that consistently arise when using water as a solvent in organic reactions. The author believes that hydrophobic interactions play a role in the accelerated reaction rates and notes that in particular, aromatic and long chain aliphatic aldehydes reacting with triphenylphosphoranes give the highest yields. These findings were an attractive prospect given the significant environmental and cost advantages involved in the use of water over more conventional organic solvents.

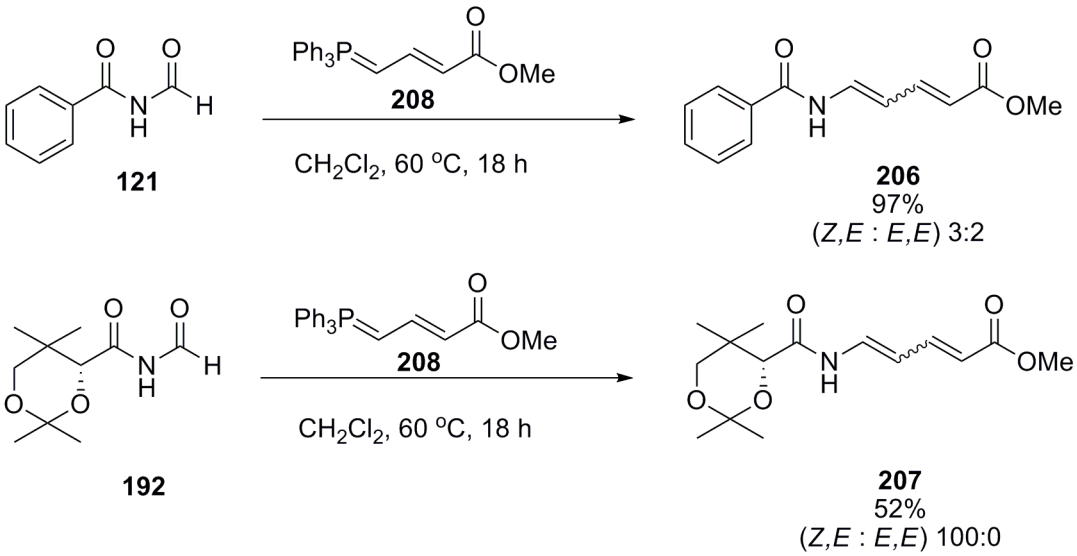
A trial of these conditions gave a 35% yield from the Wittig reaction on the pantolactone-derived imide **192** but gave no reaction with the benzamide-derived imide **121** (Scheme 63). These results were disappointing, however this was the first time these reactions had been attempted using *N*-formyl imides instead of the traditional aldehyde coupling partners.

[37] El-Batta, A.; Jiang, C.; Zhao, W.; Anness, R.; Cooksy, A. L.; Bergdahl, M., *J. Org. Chem*., **2007**, *72*, 5244



Scheme 63 Wittig reactions in water

A small screening of solvents was next carried out using both the benzamide and pantolactone-derived imides. Disappointingly, refluxing THF and toluene both appeared to give decomposition of the starting material. However, when the reactions were carried out in dichloromethane at reflux for 18 hours overnight the result was a 52% yield of the pantolactone-derived dienamide **207** and a very encouraging 97% yield of the benzamide-derived dienamide **206** (Scheme 64).



Scheme 64 Wittig reactions in dichloromethane

Following the discovery of dichloromethane as the most suitable solvent for these reactions, the remaining imides in the library were subjected to the same conditions. The corresponding dienamides **209-214** were all successfully isolated after column chromatography in varying yields, detailed in Table 2.

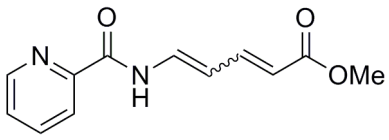
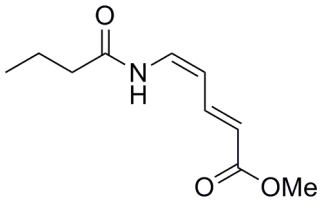
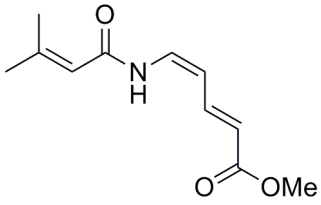
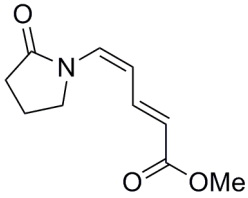
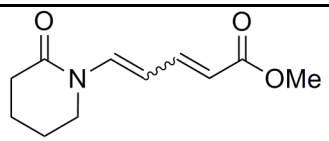
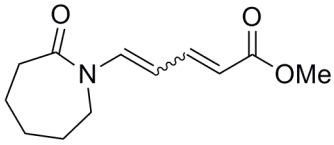
Dienamide Product (209-214)	Yield	*Z,E*:*E,E* ratio
	87%	3:1
	42%	100% *Z,E*
	41%	100% *Z,E*
	56%	100% *Z,E*
	35%	10:1
	56%	3:1

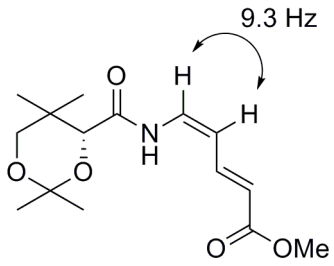
Table 2 Yields of dienamides

In the majority of cases, a single isomer was observed to be present by ^{1}H NMR spectroscopy. However, in the case of the aromatic examples, namely the benzamide **206** and picolinamide-derived **209** dienamides there appeared to be a mixture of stereoisomers apparent in the corresponding region of the ^{1}H NMR spectrum. In the case of the benzamide-derived dienamide **206** these isomers were successfully isolated by careful column chromatography and there was found to be a 3:2 mixture present.

Literature precedence shows that olefination reactions between aldehydes and the conjugated ylide employed in these studies form dienes with a marked preference for the *E,E*-isomer. This would correspond with the fact that the ylide is stabilised and formation of the thermodynamically stable *E* double bond is the most

theoretically probable. Therefore in these studies it was expected that the major isomer would be the *E,E*-dienamide, owing to retention of the original *E* double bond present in the ylide and formation of the most stable conformation of the new double bond.

However, we were surprised to discover, through initial analysis of the ^{1}H NMR spectra of the products, that the preference for these reactions was actually to form the *Z,E*-dienamide. The coupling constants for the new double bonds formed was in fact in the region of 8-10 Hz, a standard value for protons present in a *Z* double bond formation, as demonstrated for the pantolactone-derived dienamide **207** (Fig 7).

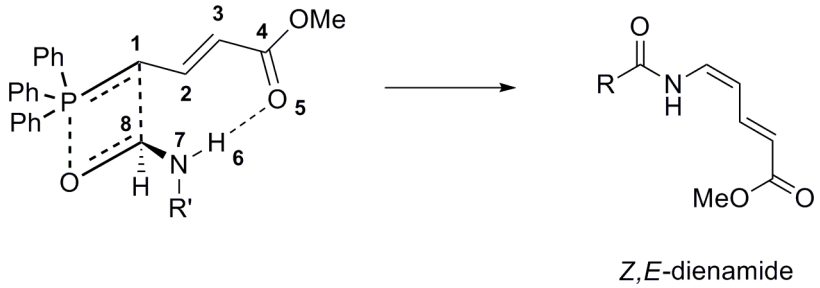


207 (*Z,E*)

Fig. 7 Confirmation of stereochemistry

Through analysis of the NMR spectra, it was found that this was the case for all the dienamides produced. When only a single isomer was formed, coupling constants confirmed it to be the *Z,E*-isomer and in the case of a mixture of isomers being isolated, the major isomer was again the *Z,E*-dienamide in all cases.

As no modelling studies have been carried out for the reactions of *N*-formyl imides and conjugated ylides there can only be assumptions made about the preferential formation of the *Z*,*E*-dienamide over the *E,E*-dienamide. It is possible that the presence of the nitrogen atom in the imide is having an effect on the transition state. This could allow for the possibility of further interactions that are not possible from a simple aldehyde/ylide transition state. An obvious example of these interactions is hydrogen bonding. If the hydrogen on the imide nitrogen were to form a hydrogen bond with the carbonyl oxygen on the ylide then a transition state as shown in Fig. 89 would be formed.



Z,E-dienamide

Fig. 8 Proposed transition state for formation of (*Z,E*)-dienamides

The resulting transition state formed would be more stable than one formed by simple Van der Waal's forces as the hydrogen bond is a much stronger non-bonding interaction. Due to the conjugation of the ylide, the transition state would take the form of an eight membered ring. As there is already a fixed *trans* double bond present in the ylide then it follows that the new double bond formed must adopt a *cis* formation as an eight-membered ring cannot incorporate two stable conjugated *trans* double bonds. Using this theory, a *E,E*-dienamide can only be formed if the cyclic transition state is much larger, which is not possible from the bonding interactions available in the transition state.

To further confirm this, a crystal structure of the pantolactone-derived dienamide **207** was obtained, which shows unequivocally the presence of the *Z,E* dienamide by clear demonstration of a *Z* double bond formation between C10-C11 (Fig. 9).

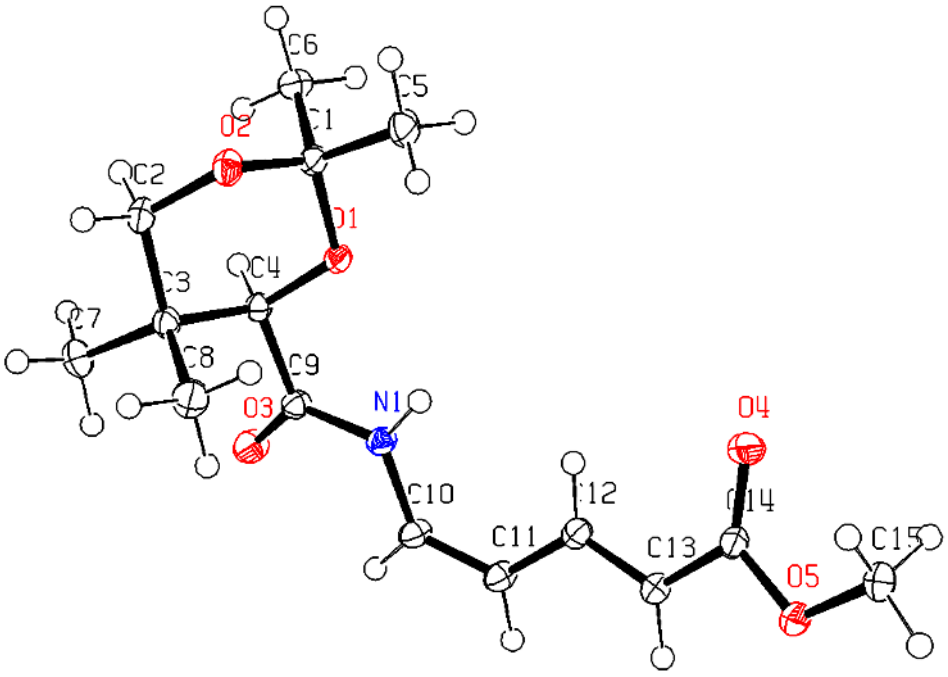


Fig 9 Crystal structure of pantolactone-derived dienamide

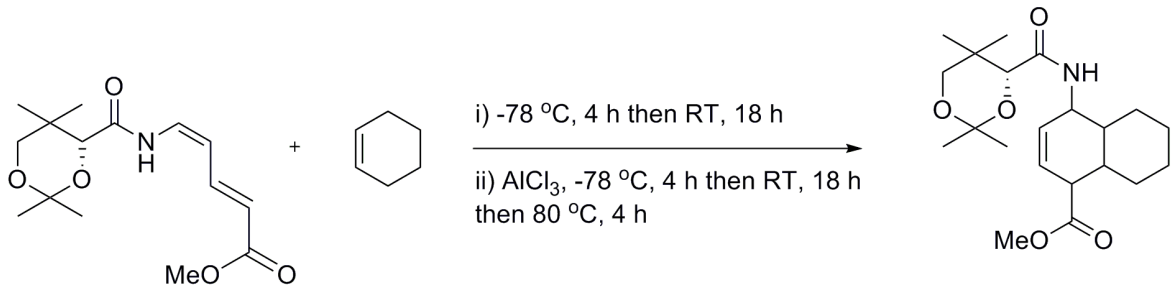
.

2.1.2 Applications of Dienamides in Synthesis

After the dienamides had been synthesised the next natural step was to explore how they behaved under different conditions. As was reported in the introduction to this thesis, one of the most common reactions for a dienamide to undergo in the literature is as the diene partner in a cycloaddition reaction.

2.1.2.1 Diels-Alder Chemistry

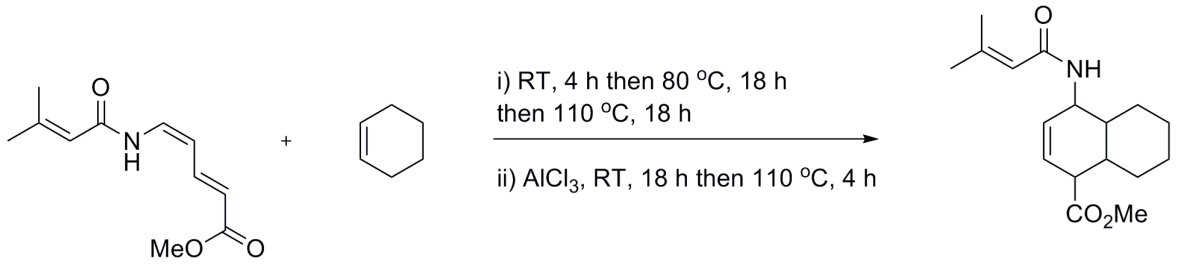
In the initial experiments pantolactone-derived dienamide **207** was treated with cyclohexene **215** at -78 °C and stirred for 4 hours before warming to room temperature overnight (Scheme 65). When TLC analysis showed no reaction, the mixture was cooled back down to -78 °C and treated with the Lewis acid catalyst, aluminium chloride before allowing to warm to room temperature overnight once more. A final attempt was made by heating the reaction mixture to 80 °C for 4 hours but the reaction did not proceed.



207 (*Z,E*) **215** **216** 0%

Scheme 65 Diels-Alder chemistry

The next step was to explore whether a higher temperature would be more effective in producing a reaction. For this purpose, olefinic dienamide **211** was taken up in cyclohexene **215** and initially stirred at room temperature (Scheme 66). When TLC analysis showed no reaction after 4 hours the temperature was increased to reflux (80 °C) overnight. Again, no reaction was evident by TLC so in order to increase the temperature beyond reflux the reaction mixture was transferred to a sealed tube and heated to 110 °C overnight once more. When this showed no signs of reaction a Lewis acid catalyst, aluminium chloride was added to the reaction mixture and stirred at room temperature overnight before eventually increasing the temperature to 110 °C in a sealed tube again.

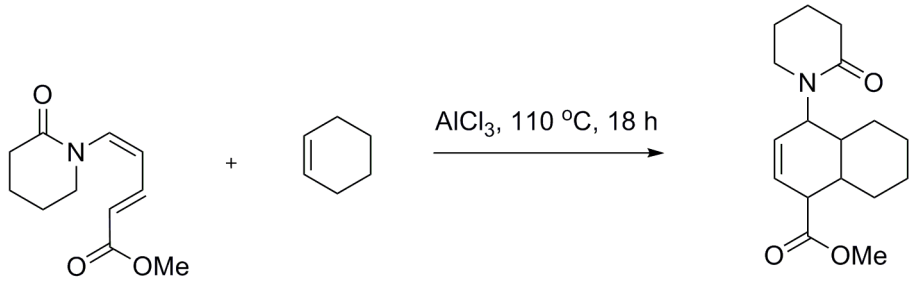


211 (*Z,E*) **215** **217**
0%

Scheme 66 Diels-Alder chemistry

None of these conditions proved successful in producing any cycloaddition product, in fact despite the attempt to force the reaction to proceed by employing harsher conditions, only starting material was observed by TLC analysis.

Once again, a different dienamide, lactam-derived dienamide **213** was treated with aluminium chloride and cyclohexene **215** in a sealed tube at 110 °C overnight but TLC showed no reaction (Scheme 67). As before, only starting material was observed.

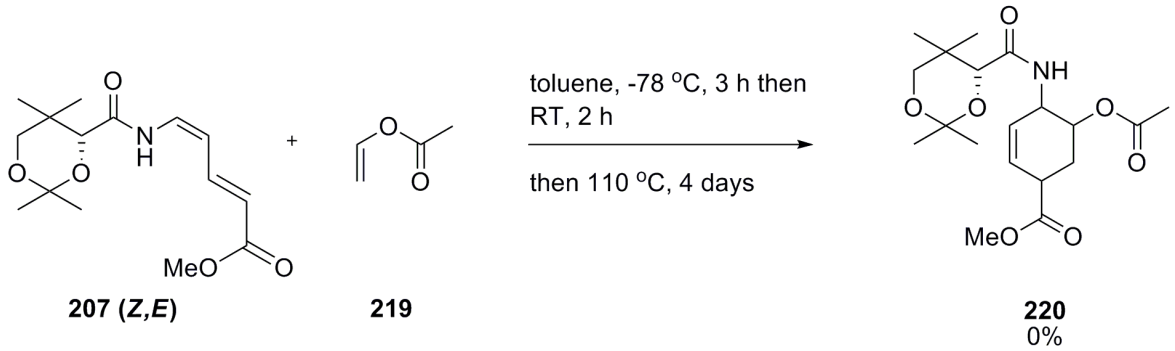


213 (*Z,E*) **215** **218**
0%

Scheme 67 Diels-Alder chemistry

Cyclohexene was proving to be very unsuccessful as a dienophile in these reactions. Cyclohexene is an electron neutral dienophile so next an electron withdrawing and an electron donating dienophile were selected in order to vary the substrates and get a clearer idea of what would be the most reactive dienophile for these types of reactions.

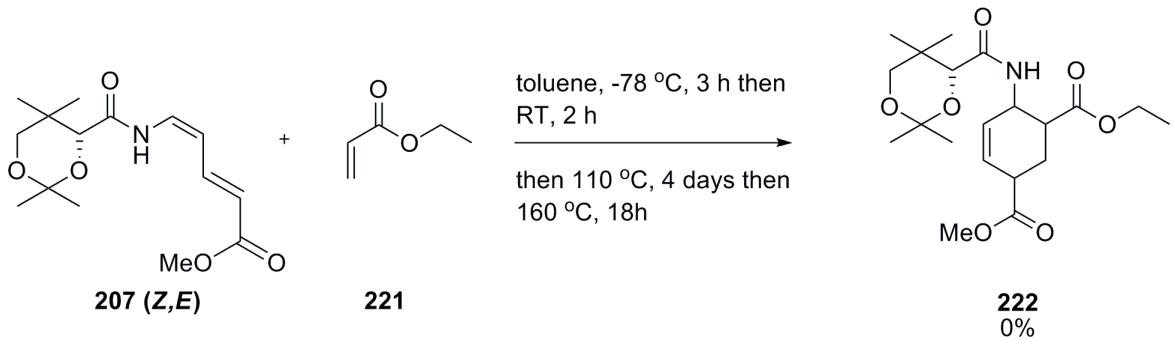
The pantolactone-derived dienamide **207** was reacted, first with vinyl acetate **219** in toluene at -78 °C for 3 hours before warming to room temperature (Scheme 68). When no reaction occurred the temperature was increased to reflux (110 °C) and the reaction mixture stirred for 4 days at this temperature. Only starting material was observed, once again.



207 (*Z,E*) **219** **220**
0%

Scheme 68 Diels-Alder chemistry

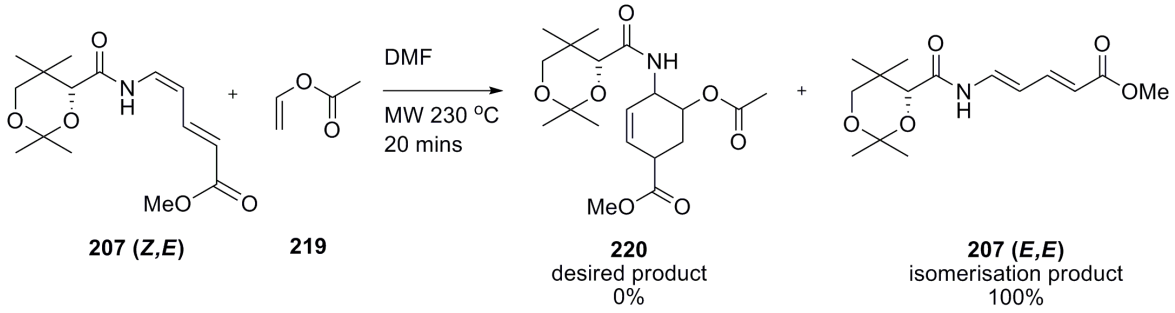
Next, the pantolactone-derived dienamide **207** was reacted with ethyl acrylate **221** in toluene at -78 °C for 3 hours followed by room temperature for 2 hours and then 110 °C for 4 days (Scheme 69). A last attempt was made to push the reaction to go by transferring the mixture to a sealed tube and heating to 160 °C overnight. Even these harsh conditions produced nothing more than starting material by TLC analysis.



207 (*Z,E*) **221** **222**
0%

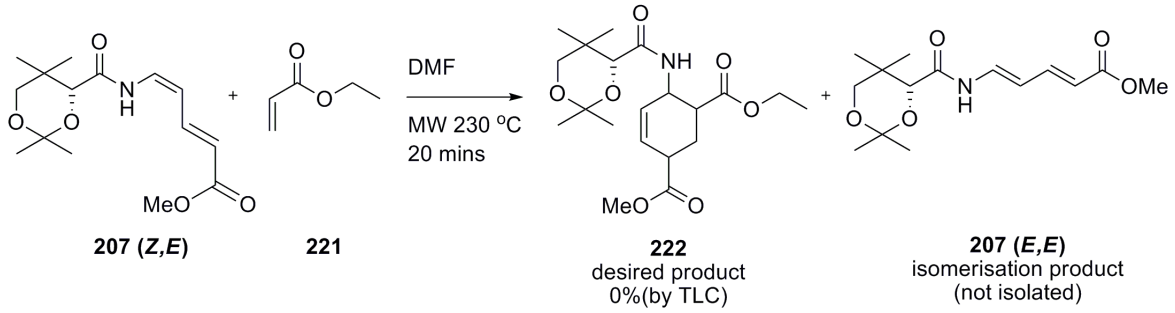
Scheme 69 Diels-Alder chemistry

Microwave heating has proved, in the past to be an efficient method for Diels-Alder reactions. So the pantolactone-derived dienamide **207** was combined with vinyl acetate **219** in dimethylformamide and heated to 230 °C in the microwave for 20 minutes (Scheme 70). By TLC analysis a new spot had formed which was isolated. ^{1}H NMR spectroscopy seemed to show that the new product was not the cycloaddition product but rather the result of an isomerisation of the dienamide to the *E,E* isomer.



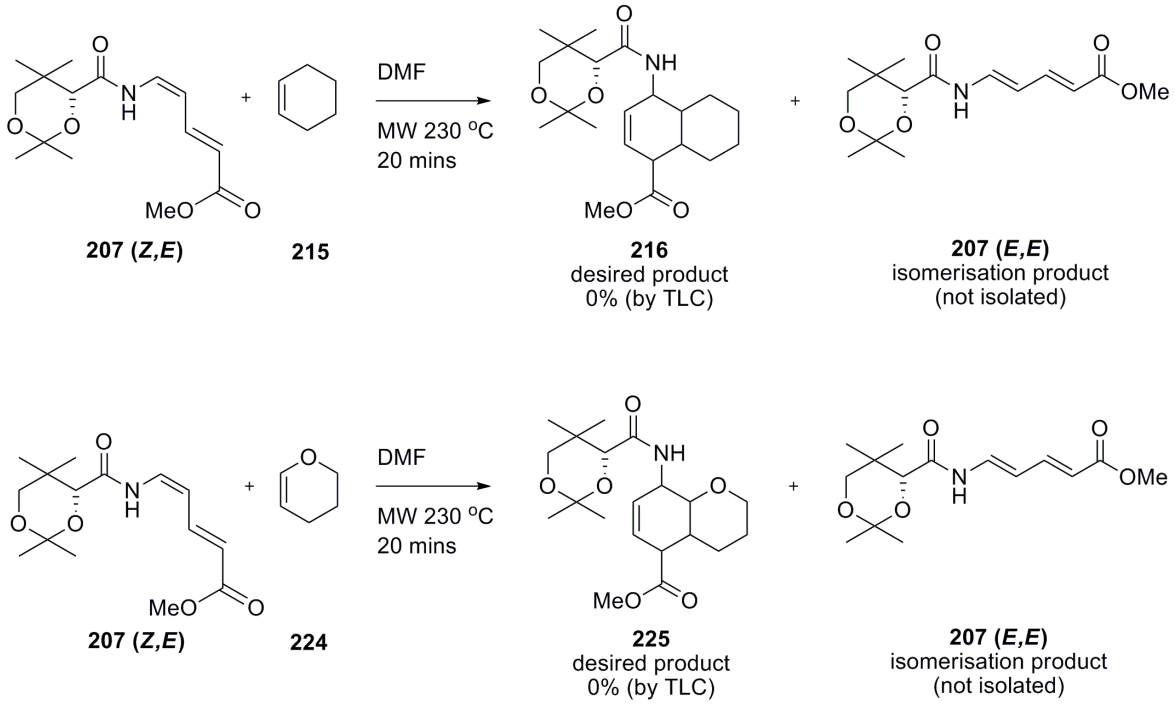
Scheme 70 Diels-Alder chemistry

Similarly, reaction of dienamide **207** with ethyl acrylate **221** under the same conditions also produced the same results (Scheme 71).



Scheme 71 Diels-Alder chemistry

Furthermore, reaction of dienamide **207** with both cyclohexene **215** and dihydropyran **224** under the same conditions gave the same results (Scheme 72).



Scheme 72 Diels-Alder chemistry

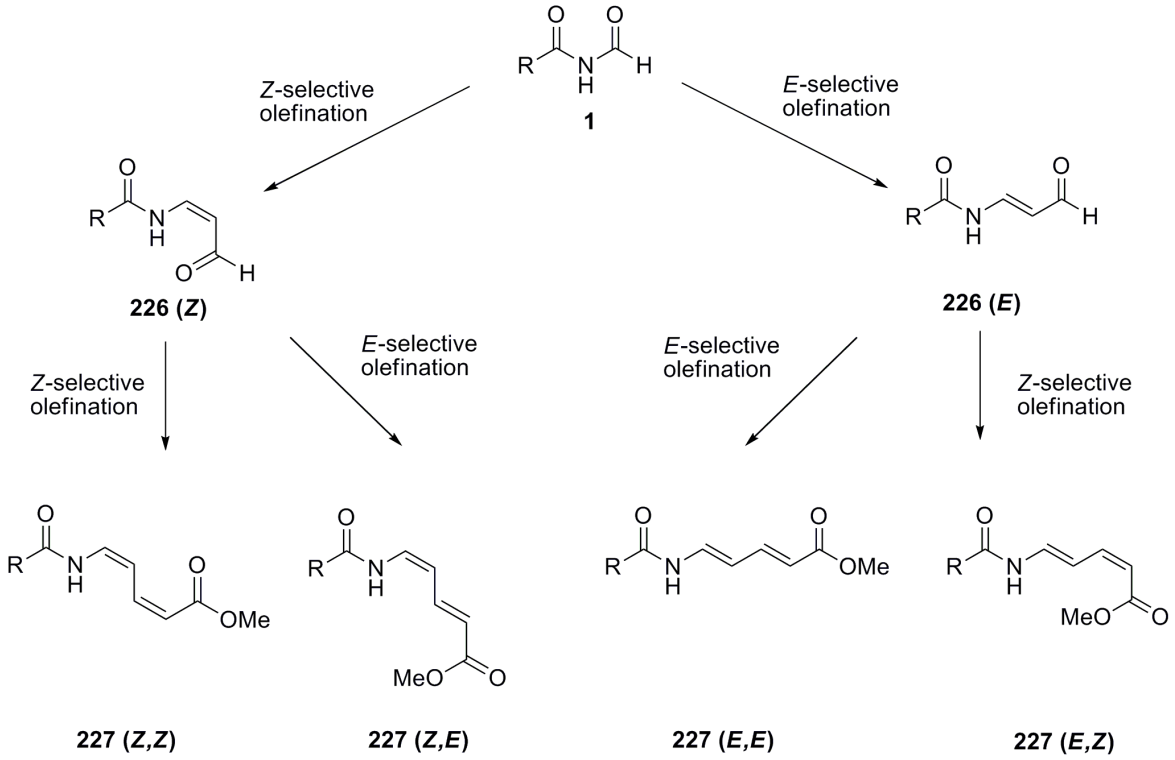
The *E,E*-dienamide is the most stable isomer, meaning that it is the thermodynamic product of the olefination reactions. This explains why, under the harsh heating conditions of the microwave, thermal isomerisation from *Z,E* to *E,E* should occur. In the original Wittig olefination reactions, the conditions were clearly not amenable for complete thermal isomerisation and so the main product was the kinetic *Z,E* isomer.

This line of investigation into Diels-Alder chemistry of dienophiles was halted at this stage due to time and reagent constraints. Despite the disappointing lack of cycloaddition product formation, the actual results pose some interesting questions that may be worth addressing in the future. Isomerisation of the *Z,E* products to the *E,E,* products under microwave conditions could be a useful tool for obtaining primarily the *E,E*-dienamide from the olefination reactions.

2.1.3 Other Reactions using *N*-formyl Imides

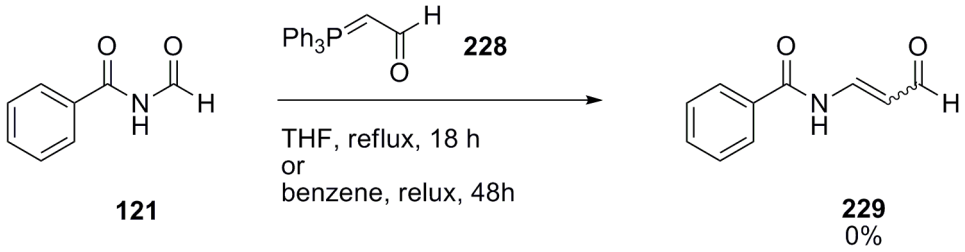
2.1.3.1 Olefination reactions

Although the one-step synthesis of dienamides using the conjugated ylide is clearly convenient and efficient, a step by step approach could also be used through use of two separate olefination reactions (Scheme 73). The advantages of this approach are that a better handle on the stereochemistry of the resulting enamides and dienamides could be achieved potentially.



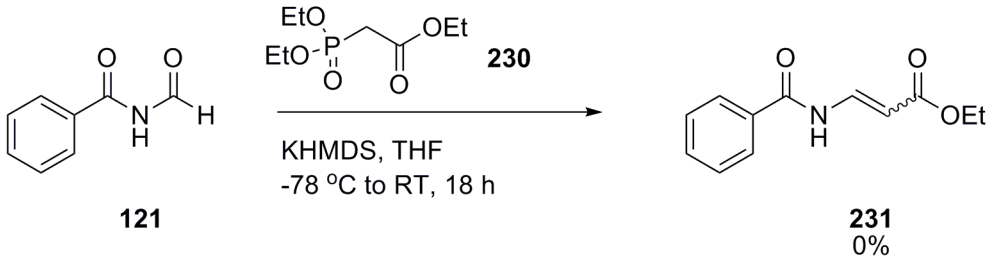
Scheme 73 Step-wise synthesis of dienamides

Benzamide-derived imide **121** was reacted first with (triphenylphosphine)acetaldehyde **228** in both THF and benzene (Scheme 74). Unfortunately neither of these reactions gave the desired aldehyde-substituted enamide, instead decomposition of the imide starting material occurred.



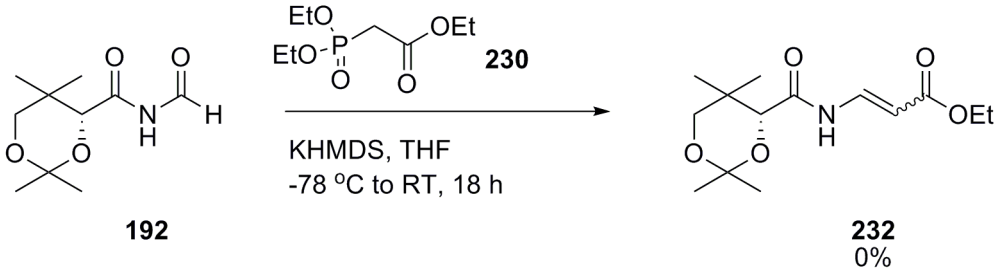
Scheme 74 Attempted synthesis of aldehyde-substituted enamide

Next, imide **121** was treated with triethylphosphonoacetate **230** and KHMDS under Horner-Wadsworth-Emmons conditions (Scheme 75). This reaction was also unsuccessful in producing the desire enamide, on this occasion starting material was recovered indicating no reaction had taken place at all.



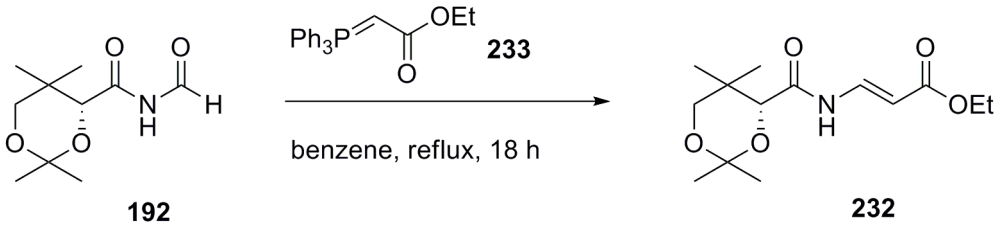
Scheme 75 Attempted Horner-Wadsworth-Emmons reaction

When changing the starting material to a different imide, in this case the pantolactone-derived imide **192**, Horner-Wadsworth-Emmons conditions also failed to produce the enamide, returning only unreacted starting material (Scheme 76).



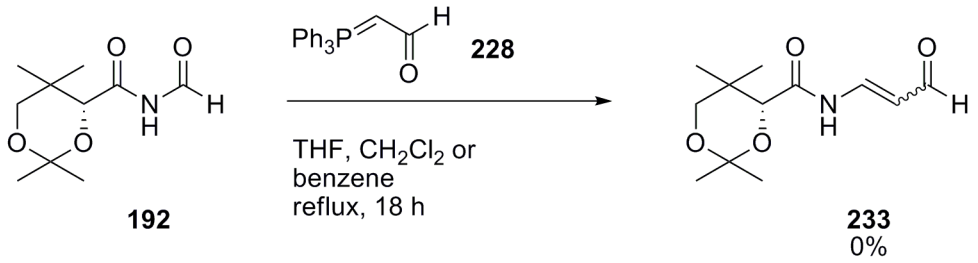
Scheme 76 Attempted Horner-Wadsworth-Emmons reaction

However, a reaction to produce the same product under Wittig conditions with ylide **233** yielded the enamide **232** on a test-scale, confirmed by the crude ^{1}H NMR spectrum (Scheme 77). This reaction had already been carried out previously in the group, its purpose was to prove that the imide itself was not the reason for the failure of the previous reactions.



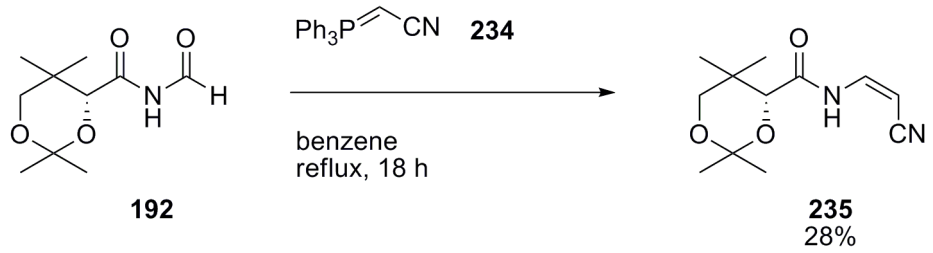
Scheme 77 Wittig reaction

Encouraged by this result, a reaction with the pantolactone-derived imide **192** and (triphenylphosphine)acetaldehyde **228** was set up (Scheme 78). Disappointingly, this failed to result in any of the desired enamide in THF, DCM or benzene.



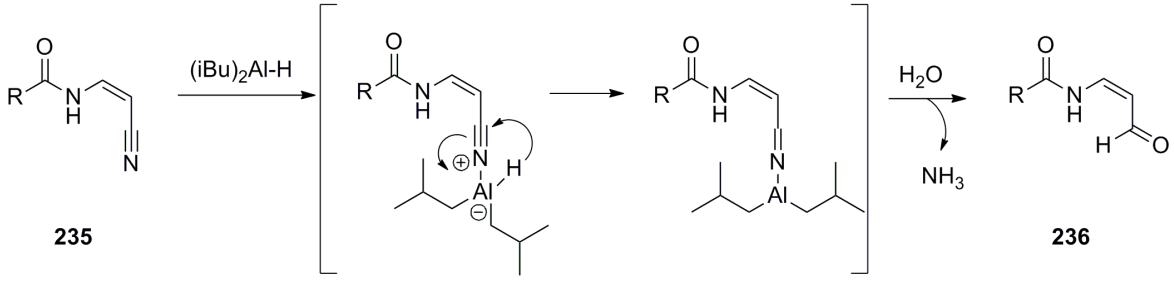
Scheme 78 Attempted synthesis of aldehyde-substituted enamide

Incorporation of a nitrile functionality, however was successful, using the ylide (triphenylphosphoranylidene)acetonitrile **234** in benzene, giving a 28% yield of enamide **235** after column chromatography (Scheme 79).



Scheme 79 Synthesis of nitrile-substituted enamide

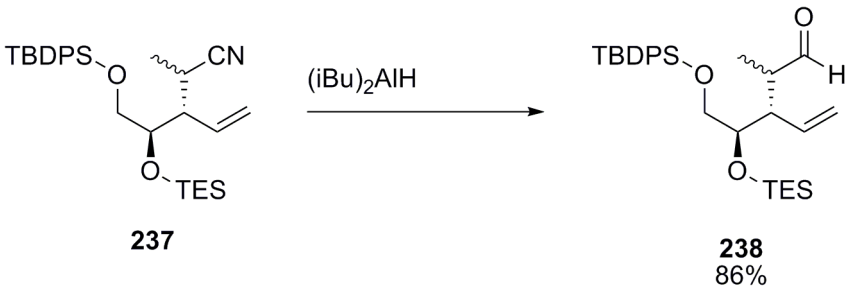
Interestingly, coupling constants between the two alkene protons in enamide **235** indicate that the product is in fact the *Z*-enamide. These results are analogous to an identical reaction previously carried out within the group where a 6:1 ratio of *Z* to *E* enamide was recovered.[38] This could prove useful for incorporating the *Z* configuration when constructing dienamides on a step by step basis. Historically, this has been more complicated than the *E*-isomer to synthesise. The nitrile functionality could be converted to the aldehyde by treatment with a reducing agent. The reducing agent must be chosen carefully as a strong reducing agent such as lithium aluminium hydride can reduce the nitrile completely to the amine. Use of diisobutylaluminium hydride followed by an aqueous work-up should give the aldehyde via an imine (Scheme 80).



Scheme 80 DiBAl-H-reduction of nitrile functionality

[38] Villa, M. V. J., *PhD Thesis* **2009**

An example of this reaction is in the synthesis of the Ritterazines, reported by Taber and co-workers where they use diisobutylaluminium hydride to reduce a nitrile **237** to the corresponding aldehyde **238** (Scheme 81). [39]



237 **238** 86%

Scheme 81 DiBAl-H reduction in a synthesis of the Ritterazines

Other methods of reducing nitriles to aldehydes include the Stephen reduction, where the nitrile is converted via the imide to an aldehyde using tin chloride and hydrogen chloride under anhydrous conditions[40] and reduction by Raney nickel, first reported by Backeberg and Staskun.[41]

This line of investigation was not pursued any further due to time constraints, however the evidence exists to support the idea of a step-wise synthesis of enamides with good control of stereochemistry as indicated in Scheme 73.

2.1.3.2 Ynamide formation

Ynamides are a relatively unexplored class of compounds in organic synthesis, however they are an attractive prospect for future research due to their enhanced stability over ynamines.[42] Formation of carbon-carbon triple bonds from *N*-formyl imides to give ynamides would be a useful reaction in this category and seems a logical step in the quest to fully explore the similarities in the reactivity patterns of *N*-formyl imides compared to aldehydes (Scheme 82).

[39] Taber, D. F.; Joerger, J-M., *J. Org. Chem.*, **2007**, 72, 3454

[40] Stephen, H., *J. Chem. Soc.*, **1925**, 127, 1874

[41] Backeberg, O. G.; Staskun, B., *J. Chem. Soc.*, **1962**, 2961

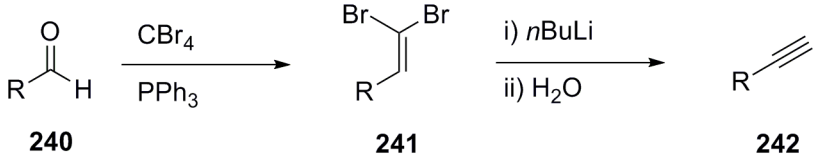
[42] Tracey, M. R.; Hsung, R. P.; Antoline, J.; Kurtz, K. C. M.; Slafer, B. W.; Zhang, Y., *Science of Synthesis*, **2005**, 5, 387

1 **239**

Scheme 82 Proposed ynamide synthesis

Historically, terminal alkynes have been formed from aldehydes via one of two main methods: the Corey-Fuchs reaction[43] or using Ohira-Bestmann chemistry, a variant of the Seyferth-Gilbert homologation.[44]

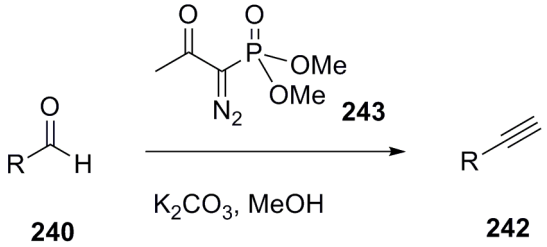
The Corey-Fuchs reaction is actually a series of reactions whereby a terminal alkyne **242** is synthesised from an aldehyde in via the corresponding 1,1-dibromoolefin **241** (Scheme 83).



240 **241** **242**

Scheme 83 Corey-Fuchs reaction

The Ohira-Bestmann reagent **243** or dimethyl-1-diazo-2-oxopropylphosphonate reacts with aldehydes **240** in the presence of potassium carbonate and methanol to give terminal alkynes **242** (Scheme 84).[45]



240 **242**

Scheme 84 Ohira-Bestmann reaction

On evaluation of the two methods it was decided that the first one to be examined would be the Ohira-Bestmann chemistry. This is due to the prospect of formation of the ynamide in a single step using a common reagent that can be synthesised in bulk and applied to a variety of different imide starting materials. The Corey-

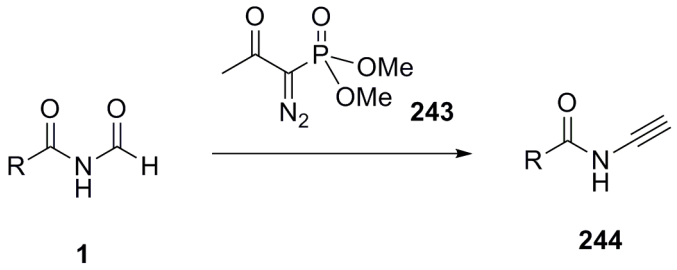
[43] Corey, E.J.; Fuchs, P. L., *Tetrahedron Lett.,* **1972**, 13, 3769

[44] a) Seyferth, D.; Marmor, R. S.; Hilbert, P., *J. Org. Chem.*, **1971**, 36, 1379, b) Gilbert, J. C.; Weewasooriya, U., *J. Org. Chem,* **1982**, 47, 1837

[45] Müller, S.; Liepold, B.; Roth, G.; Bestmann, H. J., *Synlett*, **1996**, 6, 521

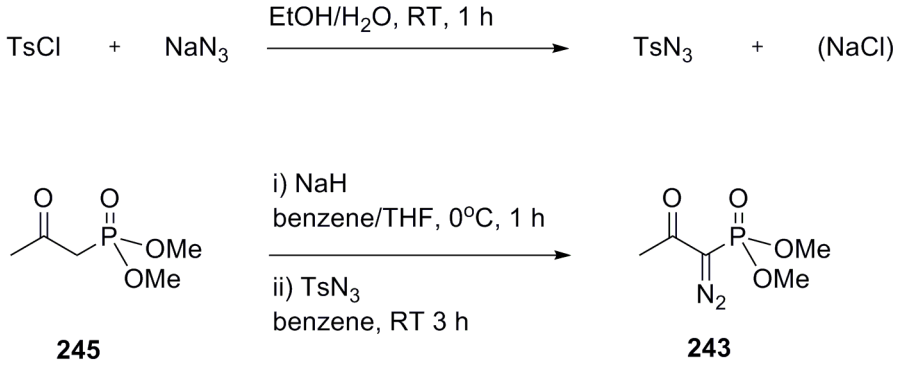
Fuchs method, on the other hand would require several different steps to obtain each different ynamide product.

Due to the propensity of *N*-formyl imides to behave in a similar fashion to aldehydes in olefination reactions, it was hoped that they would also react with the Ohira-Bestmann reagent to form terminal ynamides (Scheme 85).



Scheme 85 Proposed synthesis of ynamides using Ohira-Bestmann chemistry

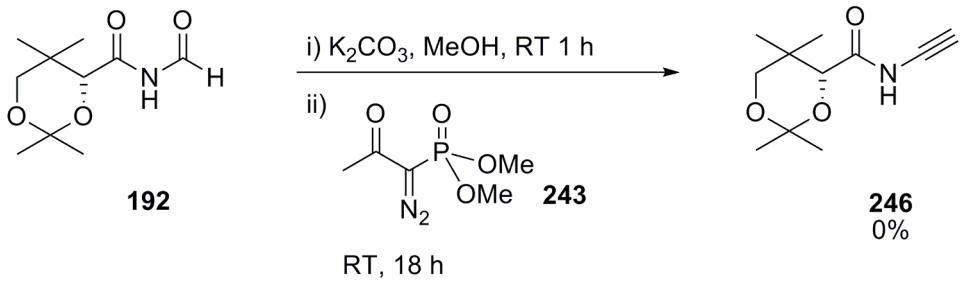
To make the Ohira-Bestmann reagent **243**, dimethyl (2-oxopropyl)phosphonate **245** is deprotonated and then treated with freshly prepared tosyl azide to give the reagent **243** in around 80-90% yield (Scheme 86).[46]



Scheme 86 Synthesis of Ohira-Bestmann reagent

Reaction of the pantolactone-derived imide **192** with potassium carbonate and then reagent **243** in methanol at room temperature overnight showed consumption of starting material by TLC analysis (Scheme 87). Unfortunately, neither the ^{1}H NMR spectrum nor an IR spectrum showed evidence of a terminal alkyne proton present in the crude reaction mixture.

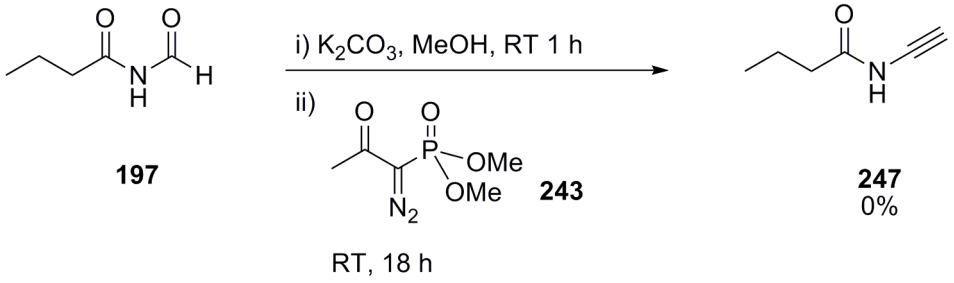
[46] Callant, P.; D'Haenens, L.; Van der Eycken, E.; Vandewalle, M., *Syn. Comm.*, **1984**, 14(2), 163



192 **243** **246** 0%

Scheme 87 Attempted ynamide synthesis

Similarly, reaction of butyramide-derived imide **197** under the same conditions, showed consumption of starting material by TLC analysis but no evidence of a terminal alkyne peak by NMR or IR analysis (Scheme 88).



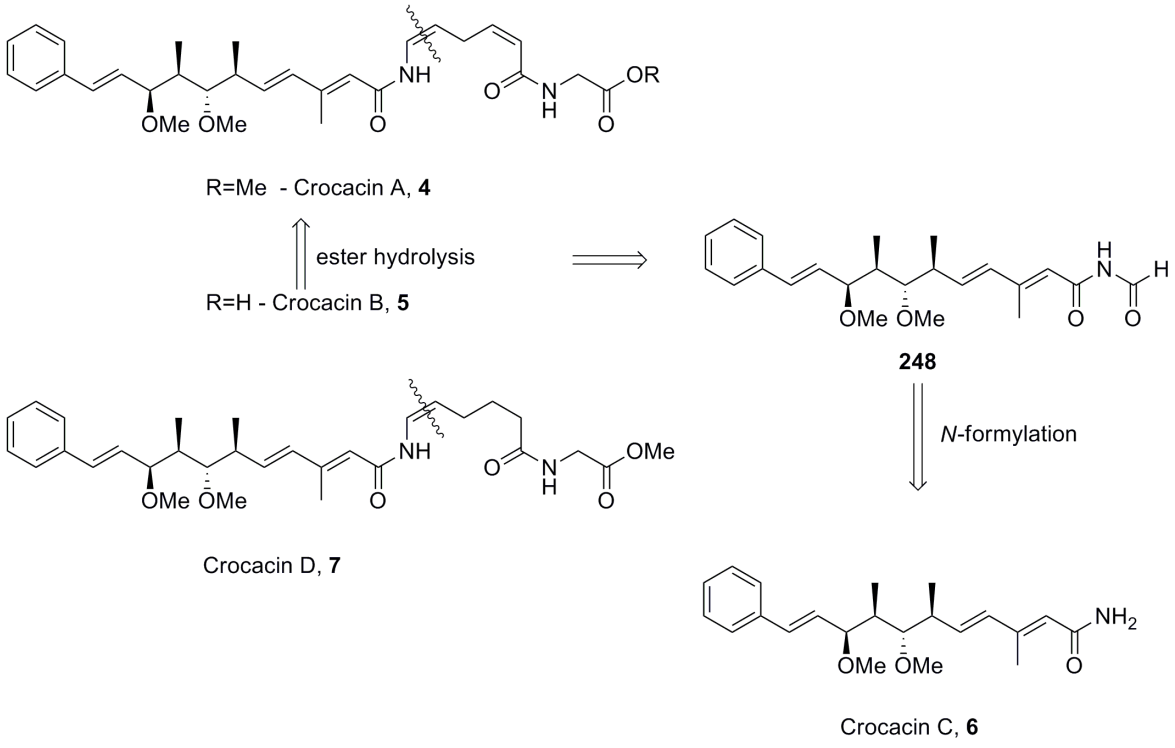
197 **243** **247** 0%

Scheme 88 Attempted ynamide synthesis

2.2 Crocacin C

Total synthesis of the Crocacins have been widely investigated and reported in the literature and many of the routes have proved to be inventive and elegant, however most of these syntheses have all been specific for a particular member of the Crocacin family.

The ultimate aim of this project was to establish a convergent synthesis of all four members of the family. Such an approach would be advantageous and efficient, especially in terms of exploring derivatives and analogues. It was envisaged that the enamide methodology that has previously been developed in the group could be exploited to allow Crocacins A, B and D to be synthesised via the more structurally simple Crocacin C (Scheme 89).

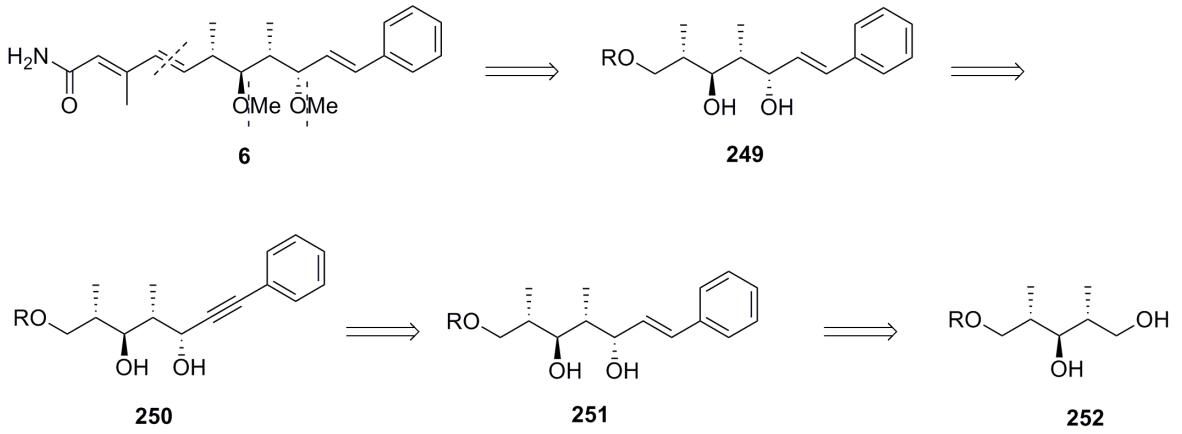


Scheme 89 Proposed convergent retrosynthesis of The Crocacin family

Efforts in the synthesis of Crocacin C **6** are therefore presented. The immediate aim of this synthesis was to use key elements of previously estabished syntheses but to explore a more efficient method of establishing the synthetically difficult core, which contains four adjacent stereocentres.

2.2.1 Retrosynthesis of Crocacin C

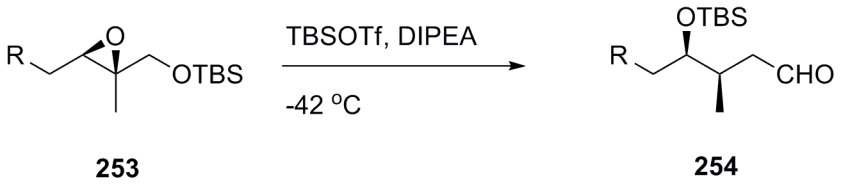
Initially, it was envisioned that Crocacin C could be disconnected to give protected alcohol **249**, in a similar fashion to previous literature examples (Scheme 90).[47,48] Further to this, the remaining *E*-alkene bond could be accessed via selective hydrogenation of alkyne **250** to give the *anti*-alkene **251** which in turn is disconnected via the aldehyde to alcohol **252**.



Scheme 90 Retrosynthesis of Crocacin C

The pivotal stage in the synthesis of Crocacin C is establishment of the key stereocentres in the core of the structure. Therefore the remaining retrosynthesis focuses on generating these with the correct stereochemistry in place.

It was initially envisioned that the central 2 stereocentres could be installed in one step by taking advantage of the non-aldol aldol rearrangement, published by Jung and co-workers in 1993 (Scheme 91).[49]



Scheme 91 Non-aldol aldol rearrangement

They reported a new method for synthesising diastereomeric aldol products **254** by a unique non-aldol route. The key step of this rearrangement involves an

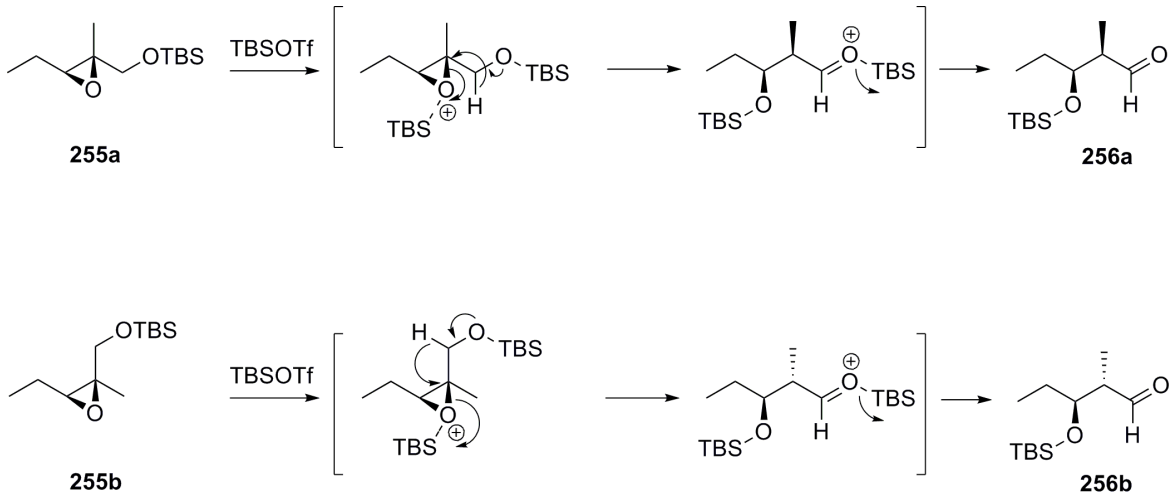
[47] Chakraborty, T. K.; Jayaprakesh, S., *Tetrahedron. Lett.* **2001**, 42, 497

[48] Sirasani, G.; Paul, T., Andrade, R. B., *J. Org. Chem.*, **2008**, 73, 6386

[49] Jung, M. E.; D'Amico, D.C., *J. Am. Chem. Soc.,* **1993**, 115, 12208

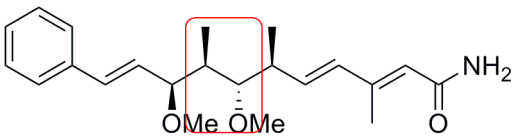
intramolecular hydride transfer from the methylene group on the silyl-protected epoxy alcohol to open the epoxide regio-selectively to generate the desired aldol products with inversion of configuration. It is believed that the mechanism of the reaction involves activation of the epoxide oxygen by the silyl triflate followed by intramolecular hydride transfer to generate the new stereocentre.

In order to obtain an *anti* relationship between the methyl group and the new secondary alcohol it is necessary to begin with the epoxy alcohol derived from the corresponding *Z*-alkene. The mechanism is illustrated in Scheme 92.



Scheme 92 Mechanism of the non-aldol aldol rearrangement

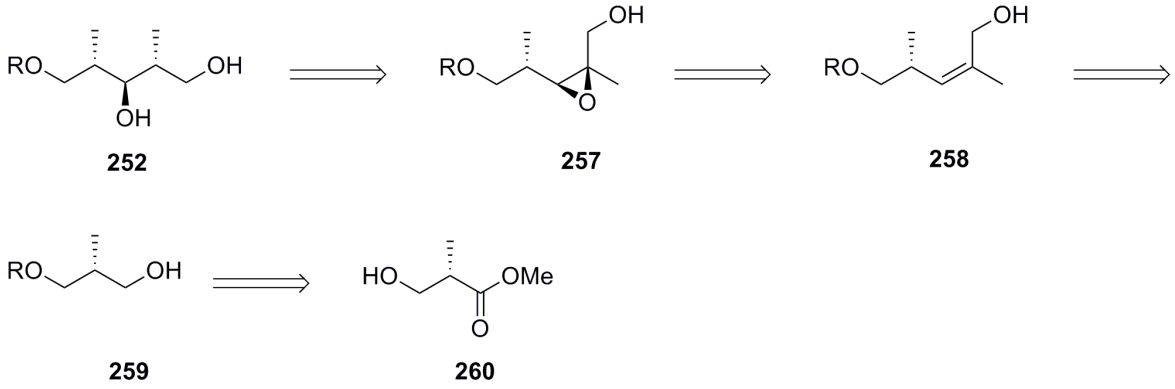
The synthesis of Crocacin C requires that an *anti*-configuration is established between the methyl group and the secondary alcohol (Fig 10). For this reason it is important to generate a *Z*-alkene earlier in the synthesis.



6

Fig. 10 Stereocentres in Crocacin C

Based on this method the remaining retrosynthesis is detailed in Scheme 93. This occurs via epoxide **257**, which in turn is accessed via allylic alcohol **258**. This is derived from alcohol **259** via oxidation and a *Z*-selective olefination reaction. Alcohol **259** is easily synthesised from commercially available (*S*)-(-)-3-hydroxy-2-methyl propionic acid methyl ester **260**.

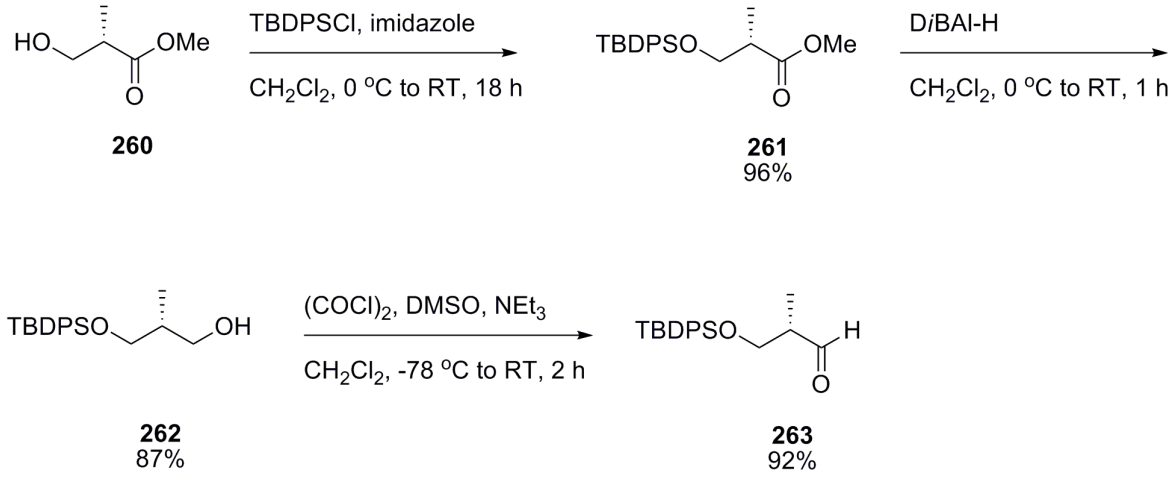


Scheme 93 Retrosynthesis of Crocacin C continued

2.2.2 Synthesis of the Core

2.2.2.1 The non-aldol aldol Approach

The synthesis began with commercially available (*S*)-(-)-3-hydroxy-2-methyl propionic acid methyl ester **260** which is first protected with a ^{t}butyldiphenylsilyl protecting group. [50,51] The reason for using this bulky protecting group is due to its stability when exposed to a wide-range of reaction conditions. The protecting group will have to remain in place for a large portion of the synthesis. This reaction proceeds in excellent yield to give ester **261** (Scheme 94).



Scheme 94 Synthesis of aldehyde intermediate

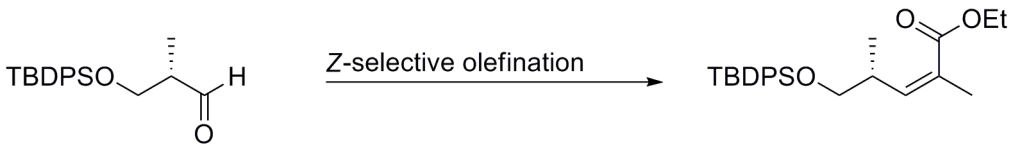
After protection, the ester functionality is reduced to the alcohol **262** using diisobutyl aluminium hydride and then oxidised back to the aldehyde **263** using Swern conditions in very good overall yield. An attempt to perform a direct reduction of the ester to the aldehyde using a controlled number of equivalents of

[50] Guan, Y.; Wu, J.; Sun, L.; Dai, W-M., *J. Org. Chem.*, **2007**, 72, 4953

[51] Canova, S.; Ballosta, V.; Bigot, A.; Mailliet, P.; Mignani, S.; Cossy, J., *Org. Lett.*, **2007**, 9(1), 145

diisobutyl aluminium hydride was unsuccessful in that it produced a mixture of the singly reduced aldehyde product and the doubly reduced alcohol product. This is likely to be due to the increased susceptibility to reduction of the aldehyde over the ester.

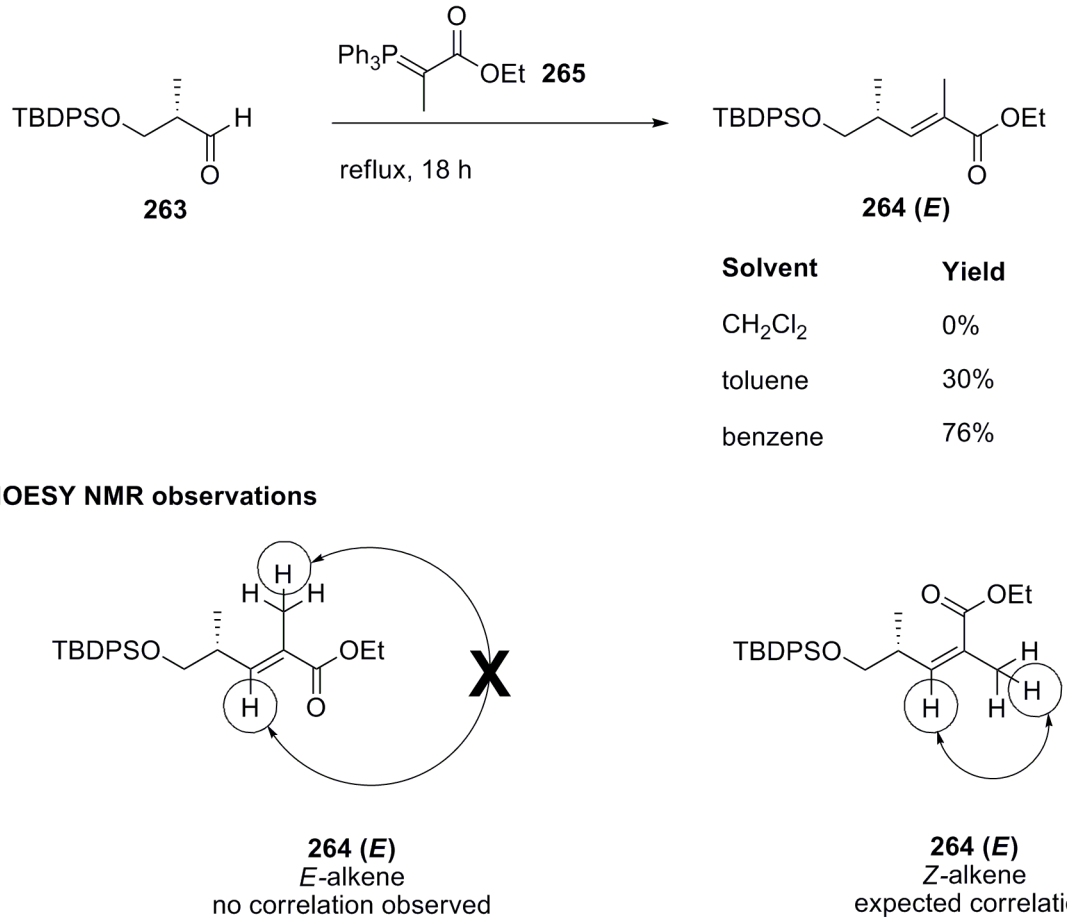
The next stage of the proposed synthesis involves a *Z*-selective olefination of aldehyde **263** to give tri-substituted *Z*-alkene **264** (Scheme 95).



263 **264(*Z*)**

Scheme 95 *Z*-selective olefination

A standard Wittig olefination using (carbethoxyethylidine)triphenylphosphorane **265** in DCM, benzene and toluene all gave exclusively the *E*-alkene in various yields (Scheme 96). This was determined by NOESY NMR experiments, whereby no correlation was observed between the alkene proton and the protons on the alkene methyl substituent. If a *Z*-alkene had been formed these protons would be in close enough proximity to each other to allow a correlation.

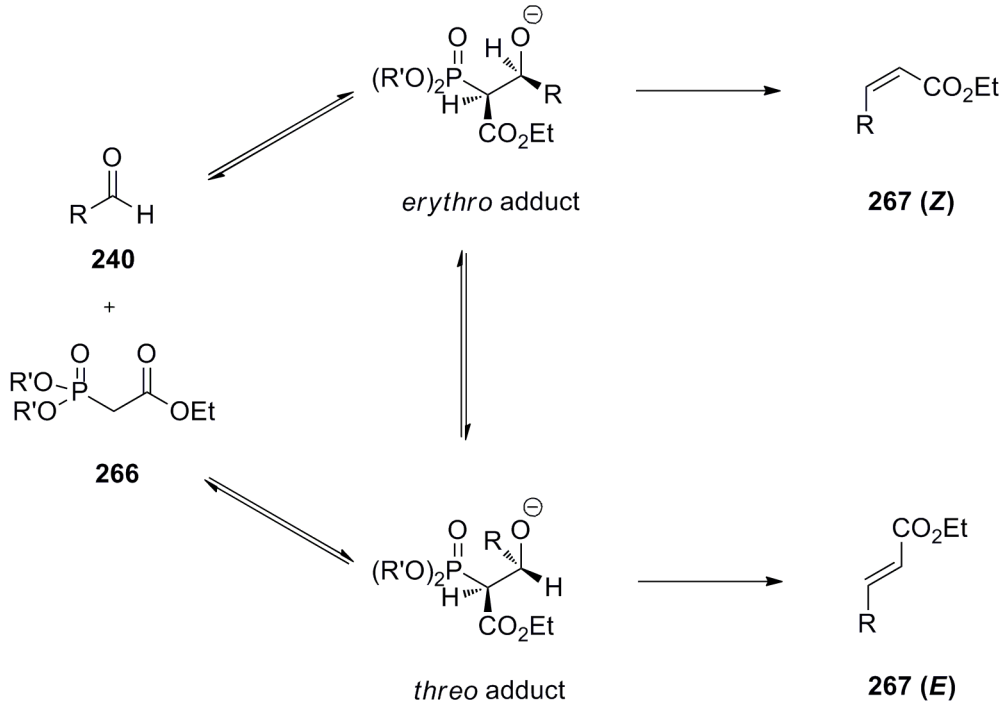


Scheme 96 Wittig olefination of aldehyde intermediate and confirmation of stereochemistry

In order to establish a reliable method for installing the *Z*-alkene it was necessary to explore the variety of *Z*-olefination techniques reported in the literature. The first reagent examined was Ando's variation of the Horner-Wadsworth-Emmons reagent, first reported in 1995.[52,53] The method involves using ethyl (diarylphosphono)acetate reagents **266** to increase the stability of the 4-membered transition state formed during the olefination process. The theory behind this lies in the electron-withdrawing properties of the diaryl substituents on the phosphorous. When an aldehyde reacts with a phosphorous ylide-type reagent, a reversible reaction occurs to form a four membered intermediate which then irreversibly collapses to form the olefin (Scheme 97).

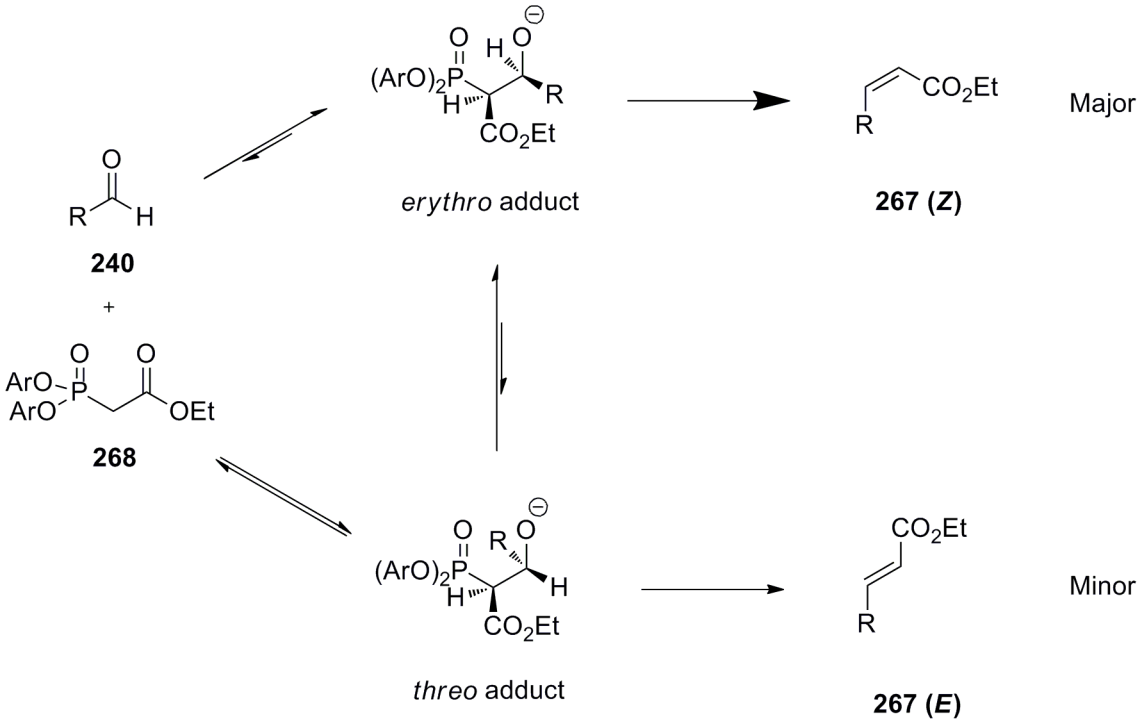
[52] Ando, K., *Tetrahedron Lett.*, **1995**, 36, 4105

[53] Ando, K., *J. Org. Chem.,* **1997**, 62, 1934



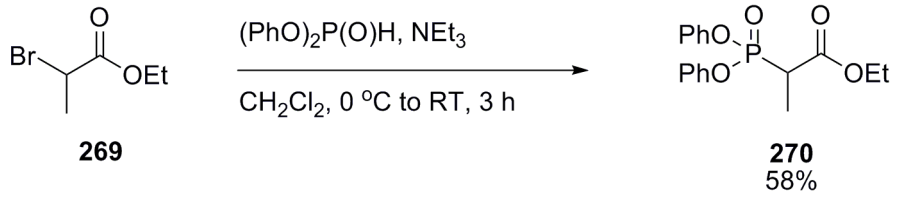
Scheme 97 Horner-Wadsworth-Emmons olefination

The *E*/*Z* configuration of the olefin is determined by the orientation of this transition state at the time of collapse. The *erythro* transition state is the kinetic product, *ie*. one that forms initially. This exists in equilibrium with the more thermodynamically stable *threo* transition state. Increased stability of this adduct accounts for the *E* olefin being the major product in standard Horner-Wadsworth-Emmons olefination reactions. However, in the case of the Ando reagent, the electron-withdrawing nature of the diaryl substituent increases the electrophilicity of the phosphorous in the transition state. Therefore the *erythro* adduct has increased reactivity for the irreversible olefin forming reaction and less opportunity to equilibrate with the *threo* adduct and also to decompose back to the original starting materials. The overall result is an increase in the formation of the *Z*-olefin **267 (*Z*)** (Scheme 98).



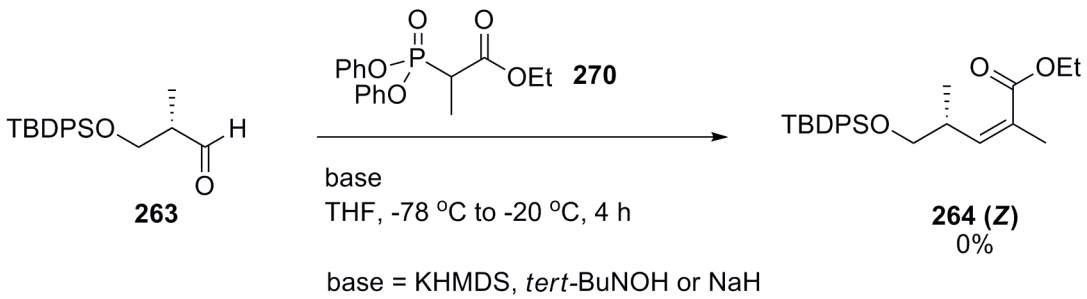
Scheme 98 Ando olefination

The corresponding reagent for the reaction in this synthesis was made by reacting ethyl 2-bromopropionate **269** with diphenylphosphite. The diphenylphosphonate ester **270** was isolated in 58% yield (Scheme 99).



Scheme 99 Synthesis of Ando reagent

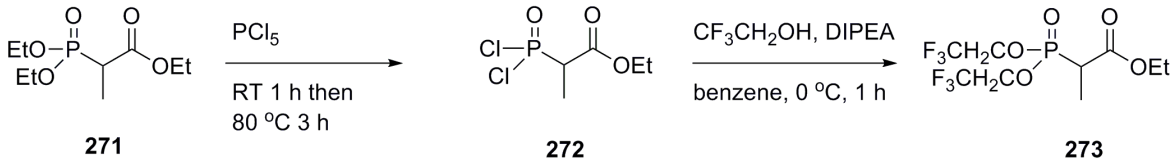
Aldehyde **263** was reacted with the newly synthesised Ando reagent **270** with several different bases to deprotonate the phosphonate ester. KHMDS, *tert*-butylammonium hydroxide and sodium hydride were all used but all of them resulted in only starting material being recovered (Scheme 100).



Scheme 100 Attempted Ando olefination

A different approach to *Z*-selective olefination was investigated and the next natural step was the Still-Gennari modification of the Horner-Wadsworth-Emmons reaction.[54] This method was reported in the literature more than ten years prior to Ando's paper, however the Ando reagent is much simpler to synthesise and thus was selected for the first attempts at Z-olefination. The principle behind the increased Z-selectivity in the Still-Gennari modified reaction are similar to Ando's in that increased electron withdrawing properties of the phosphorous substituents, in this case the trifluoroethyl ester lead to increased electrophilicity of the phosphorous and thus the reaction rate for olefin formation is faster than the equilibrium of the adducts. In addition to this, Still and Gennari report that use of a base possessing a minimally complexing counterion also contributes to the high rate of olefin formation. Thus the method favours use of strong bases combined with crown ethers, for example KHMDS with 18-crown-6, to completely remove the potassium counterion.

The trifluoroethyl phosphonate ester is made in 2 steps from the Horner-Wadsworth-Emmons phosphonate ester. 2-ethylphosphonopropionate **271** was reacted with phosphorous pentachloride to give dichloride **272** and then with trifluoroethanol to give Still-Gennari reagent **273** (Scheme 101).

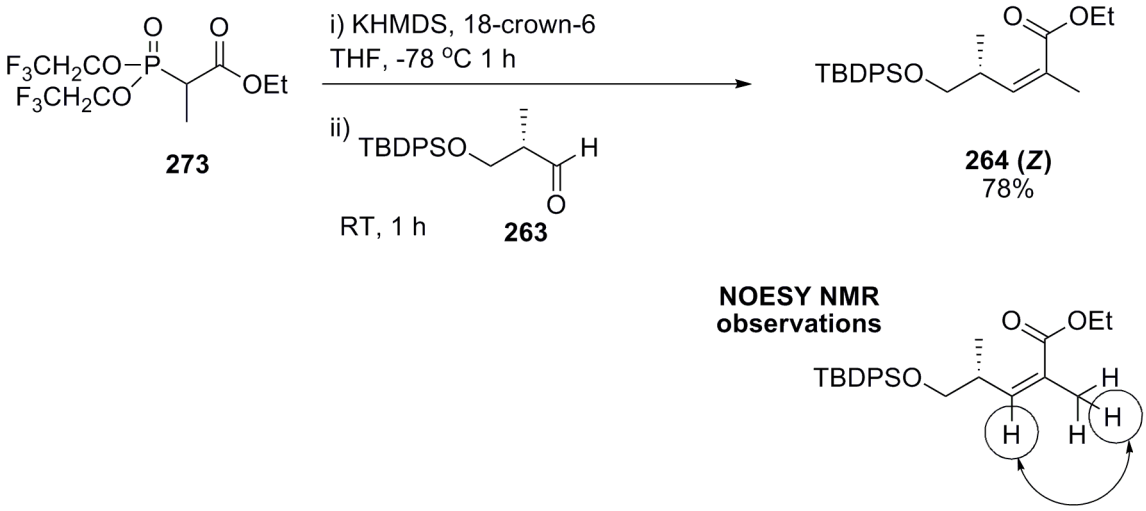


271 **272** **273**

Scheme 101 Synthesis of the Still-Gennari reagent

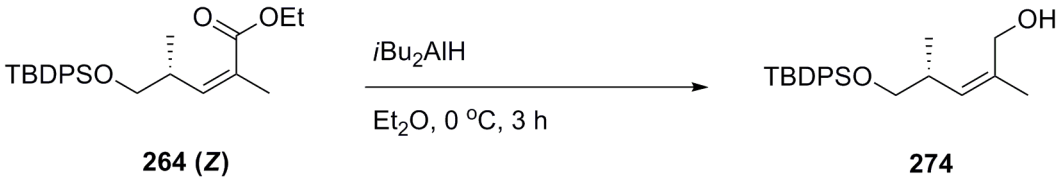
Olefination of aldehyde **263** under Still-Gennari conditions went successfully in 78% yield (Scheme 102). It was found that optimum results can be achieved by subjecting aldehyde **263** to column chromatography quickly before reacting immediately with phosphonate **273** as the aldehyde proved to be unstable. It is also important to remove all of the excess PCl_5 by distillation from step one of the synthesis of phosphonate **273,** as presence of this can hinder the reaction and lower the yield significantly. NOESY studies confirmed that desired *Z*-alkene **264 (*Z*)** was the sole product of the Still-Gennari olefination.

[54] Still, W.C.; Gennari, C., *Tetrahedron Lett.*, **1983**, 24(41), 4405



Scheme 102 Still-Gennari olefination of aldehyde intermediate and confirmation of stereochemistry

Once the *Z*-alkene had been established the next stage was to reduce the ester to give the allylic alcohol. This was initially achieved by using 2.2 equivalents of diisobutylaluminium hydride in diethyl ether and with an aqueous Rochelle's salt work-up. This gave allylic alcohol **274** in a modest 52% yield (Scheme 103).



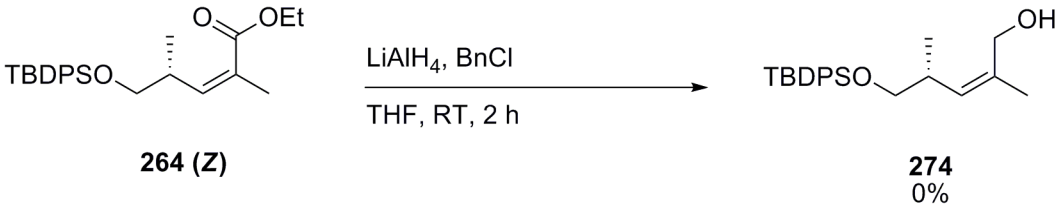
Scheme 103 Reduction of ester to allylic alcohol

It was felt, however, that this yield could be improved and therefore some optimisation was carried out. This is detailed in Table 3.

REAGENTS	TEMP (°C)	SOLVENT	WORK-UP	RESULT
***i*Bu$_2$AlH (2.2 eq)**	0	Et_2O	Rochelle's salt	52%
***i*Bu$_2$AlH (2.2 eq)**	0	DCM	Rochelle's salt	DECOMPOSITION
***i*Bu$_2$AlH (2.2 eq)**	0	Et_2O	NaOH	DECOMPOSITION
***i*Bu$_2$AlH (2.2 eq)**	0	DCM	NaOH	SM RECOVERED
***i*Bu$_2$AlH (2.2 eq)**	0	Et_2O	NH_4Cl	7%
***i*Bu$_2$AlH (2.2 eq)**	-20	toluene	H_2O	27%
***i*Bu$_2$AlH (3.0 eq)**	0	Et_2O	Rochelle's salt	75%
$LiAlH_4$ (0.3 eq)	-78	THF	NaOH	DECOMPOSITION
$LiAlH_4$ (1.2eq) + BnCl (1.2 eq)	RT	THF	H_2O	DECOMPOSITION

Table 3 Reduction conditions

Regarding the final entry in Table 3, the Wang group from China reported the use of lithium aluminium hydride and benzyl chloride as a method for reducing α,β-unsaturated esters to allylic alcohols.[55] They postulate that a reactive aluminium trihydride intermediate is formed which carries out the reduction. This method proved unsuccessful when applied to ester **264 (*Z*)**, resulting only in decomposition of starting material (Scheme 104).



264 (*Z*) **274** 0%

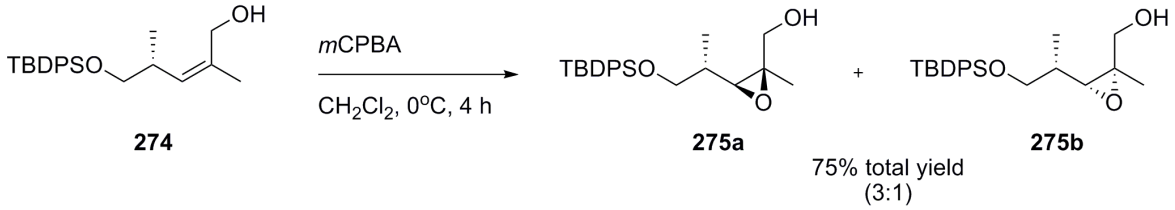
Scheme 104 Attempted lithium aluminium hydride reduction

By simply increasing the amount of diisobutylaluminium hydride to three equivalents under the same conditions in Scheme 103 that the yield can be increased to 75%.

The next steps involve epoxidation of the alkene and protection of the alcohol with a suitable silyl protecting group. Epoxidation using *m*CPBA achieved a 74% yield of the epoxide **275** but with a 3:1 mixture of diastereoisomers (Scheme 105). The configuration of these diastereoisomers will not be confirmed until later in the

[55] Wang, X.; Li, X.; Xue, J.; Zhao, Y.; Zhang, Y., *Tetrahedron Lett.* **2009**, 413

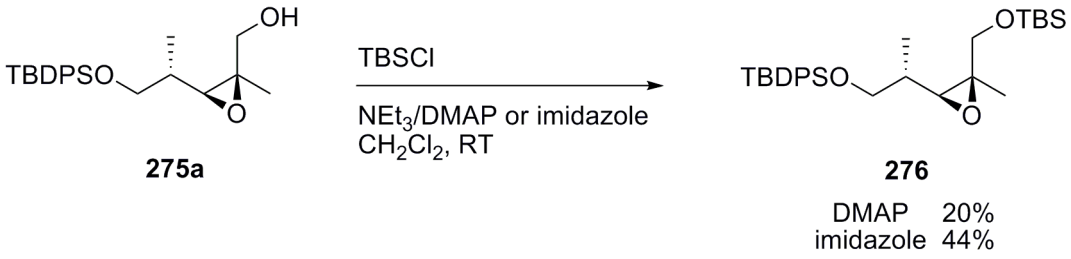
synthesis, athough literature precedence suggests that the desired *anti* diastereoisomer **275a** should be the major product.[56]



Scheme 105 Epoxidation of alliylic alcohol

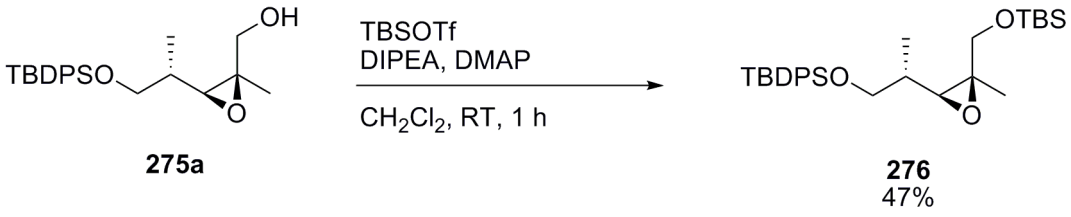
Addition of 3.0 equivalents of potassium phosphate dibasic to the reaction gave a much higher yield of 90% and there was also a marked increase in the proportion of diastereoisomers from 3:1 to 8:1.[57] These ratios were determined by examining the ^{1}H NMR spectrum before and after separation of the isomers by flash column chromatography. It was found that the epoxide proton had a small but marked difference in chemical shift between the major and minor diastereoisomer.

Various protection strategies were attempted for the silyl protection of epoxy alcohol **275a**. Protection with ^{t}butyldimethylsilyl chloride gave a 20% yield with triethylamine as the base and 44% with imidazole (Scheme 106).



Scheme 106 Silyl protection of epoxy-alcohol

Switching to the more reactive ^{t}butyldimethylsilyl trifluoromethansulfonate with diisopropylethylamine as the base only improved the yield to 47% (Scheme 107).

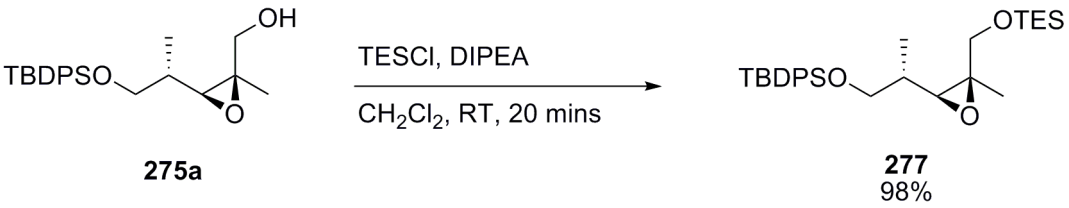


Scheme 107 Silyl protection of epoxy-alcohol

[56] Johnson, M. R.; Kishi, Y., *Tetrahedron Lett.,* **1979**, 45, 4347

[57] Jung, M. E.; D'Amico, D. C., *J. Am. Chem. Soc.*, **1997**, 119, 12150

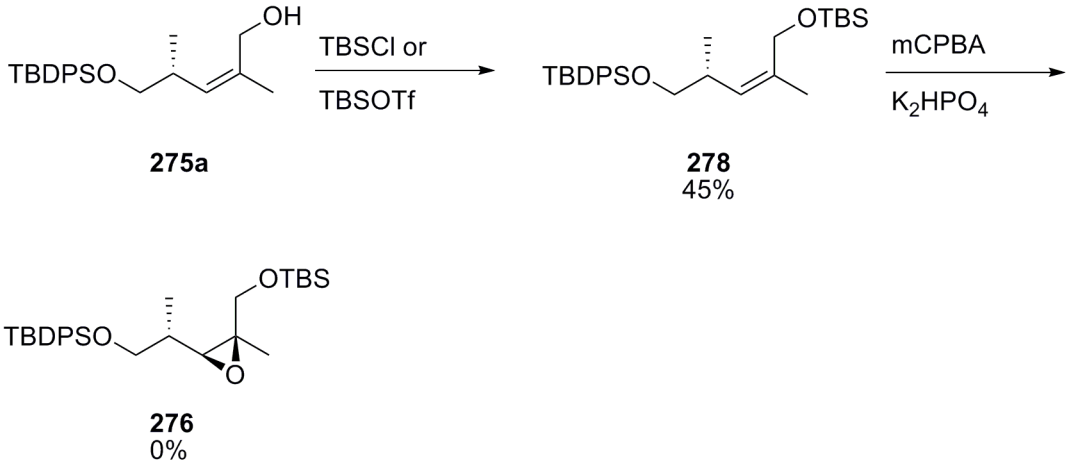
However, using triethylsilyl chloride with diisopropylethylamine gives an almost quantitative yield of protected epoxy alcohol **277** in only 20 minutes with no need for purification (Scheme 108). The increase in the yields for triethylsilyl protection compared to ^{t}butyldimethylsilyl protection could be explained by sterics. The larger ^{t}butyldimethylsilyl group may be encountering some hindrance when reacting with the hydroxyl group due to interactions with the methyl group. This will be particularly pronounced due to the fact that the epoxide is derived from a *Z*-alkene and the hydroxyl group is therefore closer to the methyl group. The smaller triethylsilyl group will meet fewer steric interactions and therefore give a higher yield of protected alcohol.



275a **277** 98%

Scheme 108 Silyl protection of epoxy-alcohol

The epoxidation and protection steps were also reversed to see if this would improve the yield. Protection of allylic alcohol **275a** with a ^{t}butyldimethylsilyl group worked in moderate yield, however epoxidation of the protected allylic alcohol **278** was unsuccessful in all attempts (Scheme 109).

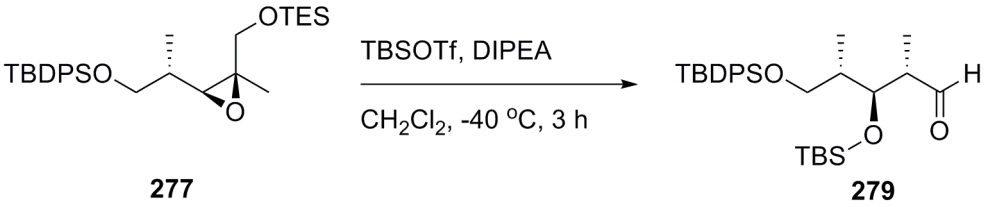


275a **278** 45%

276 0%

Scheme 109 Silyl protection then attempted epoxidation of allylic alcohol

With the protected epoxy-alcohol **277** in place, the next stage was to try out conditions for the non-aldol aldol rearrangement. It was anticipated that reaction of epoxy silyl alcohol **277** under standard non-aldol aldol conditions would generate aldehyde **279** (Scheme 110).



277 **279**

Scheme 110 Non-aldol aldol rearrangement conditions

Unfortunately no reaction was observed using these conditions. Lowering the temperature to -78 °C also gave no reaction. Switching to trimethylsilyl trifluoromethansulfonate at a range of temperatures from -100 °C to -40 °C also resulted in no reaction. Similarly, using triethyl trifluoromethansulfonate also failed to produce aldehyde **279**. In all cases no new product was observed by TLC analysis, only starting material was recovered.

These results were disappointing and it became clear that another route to give the correct stereocentres would have to be established.

2.2.2.2 The Cuprate Approach

It has been well known in recent years that dialkyl cuprates can open epoxides with a high degree of regio- and stereo-control and in mild conditions.[58,59] Lower order cuprates or Gilman cuprates of the formula R_2CuLi, where R represents an alkyl group, are formed from a reaction between a copper halide and an organolithium reagent. They are more stable than the corresponding mono-organocopper reagent and are the most widely used in synthesis. They transfer a single alkyl ligand during the reaction and for this reason can be uneconomical to use if the starting materials are expensive or not readily available.[60]

Higher order cuprates of the formula R_3Cu_2Li are made by altering the copper halide : organolithium ratio but are widely considered to be of little synthetic use, apart from some very specific applications. However, “higher order” cyanocuprates of the formula $R_2Cu(CN)Li_2$ are much more widely used. There is some debate as to whether these can truly be considered as higher order reagents. One argument has claimed that the cyanide is sigma-bonded to the copper ion, making the copper dianionic and that the addition of the CN ligand to the copper provides

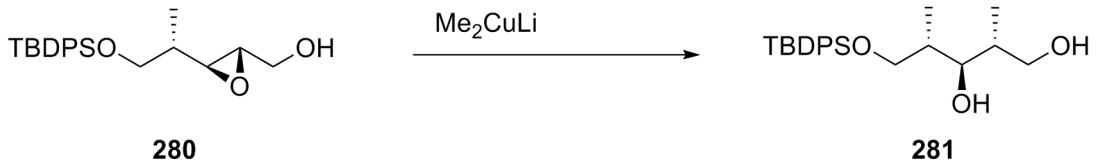
[58] Johnson, M. R.; Nakata, T.; Kishi, Y., *Tetrahedron Lett.*, **1979**, 45, 4343

[59] Lipshutz, B. H.; Kozlowski, J., Wilhelm, R. S., *J. Am. Chem. Soc*., **1982**, 104, 2305

[60] Lipshutz, B. H., *Organocopper Reagents : A Practical Approach*, Ed. Richard J. K. Taylor, Oxford University Press, **1994**, 105

appropriate *π*-acidity to allow a second organic ligand to coordinate with the copper, thus providing a third carbon-copper bond and therefore enforcing the term “higher order”.[61] Other arguments claim that the copper-cyanide bond does not truly exist and therefore the system cannot be called “higher order”.[62]
On the reactivity front there appears to be no set pattern in terms of which is more reactive between lower order cuprates and higher order cyanocuprates. The reactivity appears to be specific to the actual reaction and for that reason it may be necessary to try both in this project.

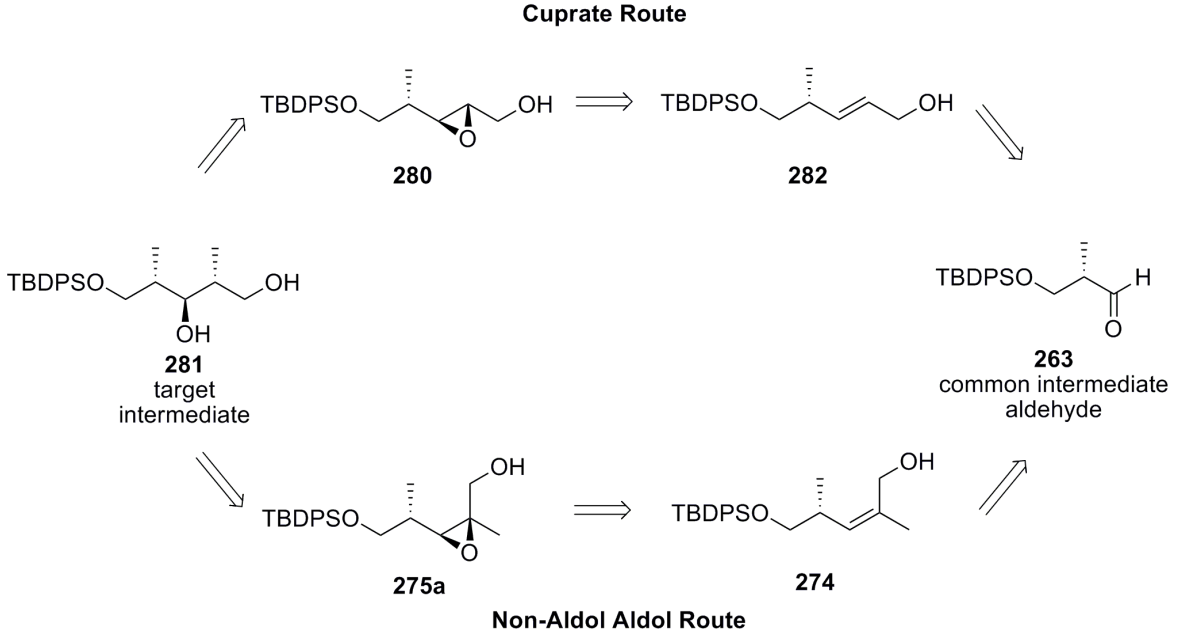
It was anticipated that the methyl group in Crocacin C could be introduced via the reaction of a lower order cuprate to the appropriate epoxide (Scheme 111).



280 **281**

Scheme 111 Proposed cuprate opening of epoxide

For this method, the epoxide required to give the correct stereochemical outcome is one derived from a disubstituted *E*-alkene **282**, as opposed to the trisubstituted *Z*-alkene required for the non-aldol aldol method. Aldehyde **263** however is a common intermediate for the two syntheses (Scheme 112).

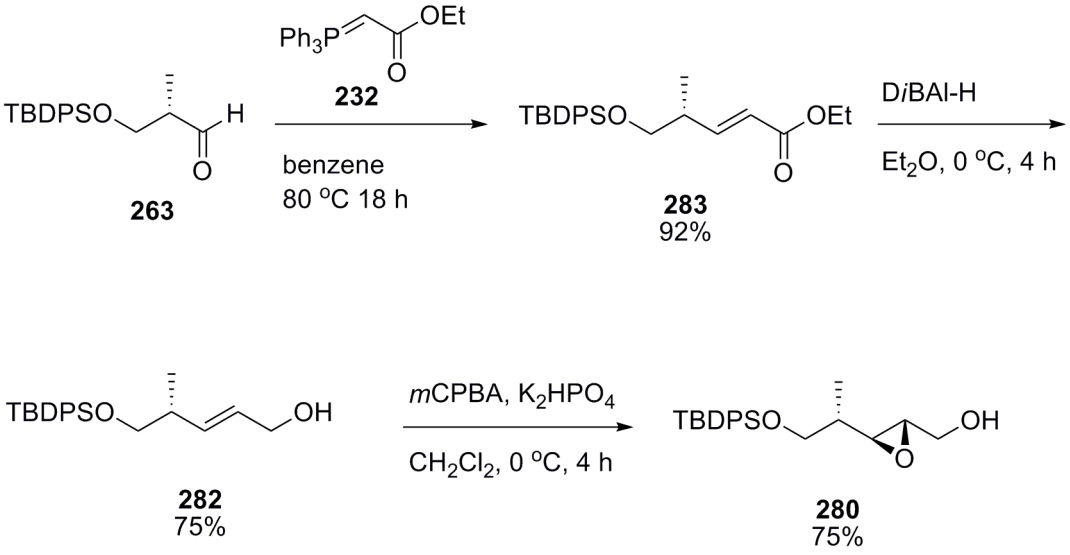


Scheme 112 Cuprate route vs non-aldol aldol route

[61] Lipshutz, B. H.; Sharma, S.; Ellsworth, E.L. *J. Am. Chem. Soc.* **1990**, *112*, 4032

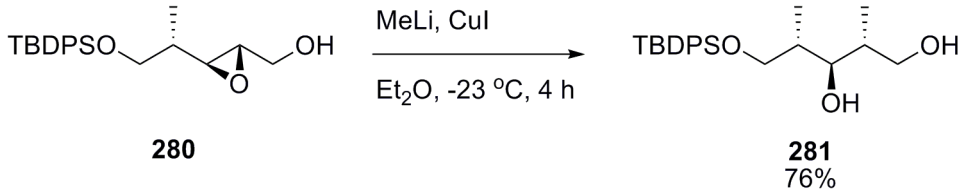
[62] Snyder, J. P.; Bertz, S.H. *J. Org. Chem.* **1995**, *60*, 4312

Aldehyde **263** was treated wth pre-formed ylide **232** and gave the desired *E*-alkene in excellent yield as confirmed by coupling constant calculations from ^{1}H NMR spectroscopy. Reduction of the *α,β*-unsaturated ester **283** to allylic alcohol **282** also gave good results, as did epoxidation under the same conditions as before to give **280**. A single diastereoisomer was isolated from the epoxidation step (Scheme 113).



Scheme 113 Revised synthesis of the epoxy-alcohol intermediate

The cuprate is made *in situ* from copper iodide and an alkyllithium. In this case methyllithium is required to give a cuprate of the formula Me_2CuLi. This reaction has been reported many times in the literature.[63] Including Chandrasekhar and co-workers' synthesis of (-)-Spongidepsin in which an identical intermediate is used in the synthesis (Scheme 114).[64]



Scheme 114 Opening of epoxide using cuprate conditions

[63] Examples of uses of dimethyl cuprates in total synthesis – a) Milbemycin D – Crimmins, M. T.; Al-awar, R. S.; Vallin I. M.; Hollis Jr., G.; O'Mahony, R.; Lever, J. G.; Bankaitis-Davis, D. M, *J. Am Chem. Soc.*, **1996**, 118, 7513, b) Crocacin D – Dias, L. C.; de Oliveira, L. G.; Vilcachagua, J. D.; Nigsch, F., *J. Org. Chem.*, **2005**, 70, 2225, c) Lomaiviticin A/B - Zhang, W.; Baranczak, A.; Sulikowski, G. A., *Org. Lett*., **2008**, 10(10), 1939,

[64] Chandrasekhar, S.; Yaragoria, S. R.; Sreelakshmi, L.; Reddy, C. R., *Tetrahedron*, **2008**, 64, 5174.

The paper reported a 76% yield of diol **281** by reacting 6.6 equivalents of copper iodide with 13.3 equivalents of methyllithium in dry diethyl ether at -23 °C for 30 minutes. The mixture was then cooled to -40 °C and epoxide **280** added as a solution in dry diethyl ether dropwise before warming back up to -23 °C and stirring for 5 hours. Following this method exactly gave no reaction at all by TLC analysis. Several different ratios of equivalents of copper iodide and methyllithium were also used at several different temperatures, however none of these sets of conditions achieved formation of the desired product. The ratios of reagents used are described in Table 4.

Reagents	Conditions
CuI (2.0eq), MeLi (4.0eq)	Et_2O, 0 °C, 3 h
CuI (2.3eq), MeLi (6.0eq)	Et_2O, 0 °C, 3 h
CuI (6.6eq), MeLi (13.3eq)	Et_2O, -40 °C, 5 h
CuI (4.0eq), MeLi (8.0eq)	THF, -78 °C, 3 h
CuCN (2.0eq), MeLi (4.0eq)	Et_2O, 0 °C, 3 h
CuCN (9.0eq, MeLi (17.0eq)	THF, -20 °C, 18 h
CuBr.Me_2S (4.0eq), MeLi (8.0eq	Et_2O, 0 °C, 3 h

Table 4 Attempted conditions for cuprate opening of epoxide

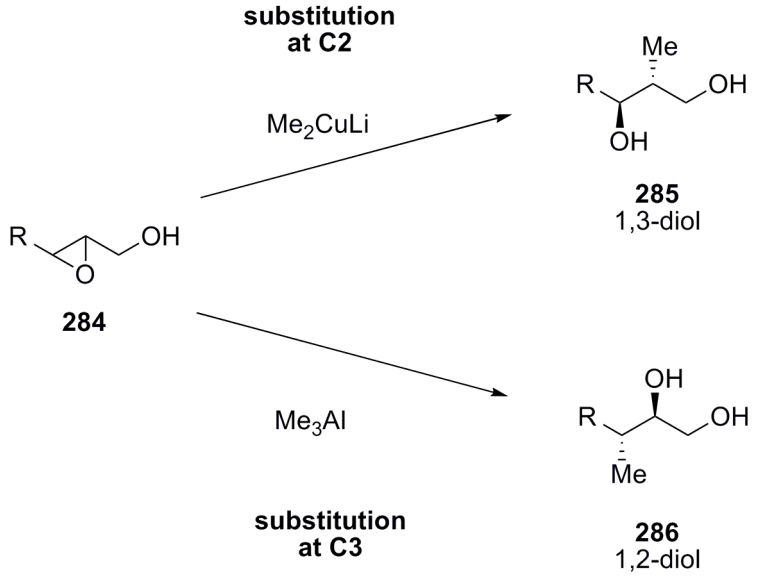
Attempts to synthesise a higher order cyanocuprate by using copper cyanide in place of copper iodide offered no improvement to the lack of reaction. A copper bromide dimethyl sulfide complex was also used following advice from a colleague, but gave no reaction either.

Optimisation was unsuccessful in all cases including the uses of methods such as titrating the methyllithium solution to gain the exact concentration and the use of molecular sieves to keep the solution as dry as possible.

Although these reactions have been well-reported in the literature, frustratingly they were not working in this case. It was decided that another new approach for this reaction was required.

2.2.2.3 An Alternative Epoxide Opening Approach

A different approach to the opening of epoxide **280** was briefly examined, using trimethylaluminium as an alternative source of the methyl group. Miyashita and co-workers reported an interesting development in their studies of nucleophilic substitution reactions of 2,3-epoxyalcohols **284**.[65] When treated with Gilman-type cuprates, as described in the previous section, 2,3-epoxyalcohols undergo nucleophilic substitution at the C2 position to selectively give the 1,3-diol product **285**. However, when treated with an organoaluminium reagent, such as trimethylaluminium, substitution occurs via the C3 position to give the 1,2-diol product **286** (Scheme 115).[66]

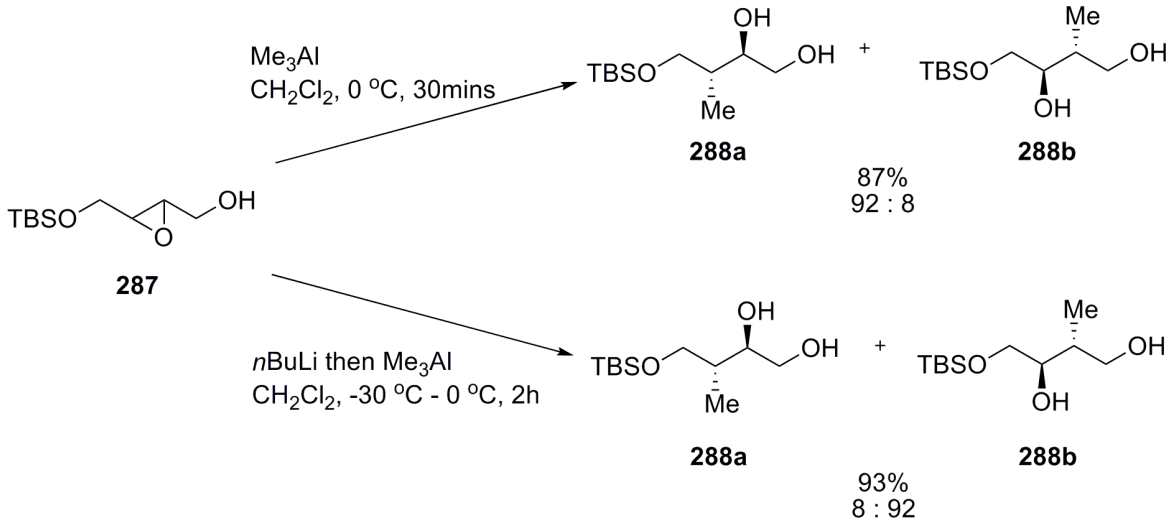


Scheme 115 Cuprate conditions vs trimethylaluminium conditions for epoxide opening

It was found that conventional treatment of 2,3-epoxyalcohol **287** with only trimethylaluminium gave almost exclusively the 1,2-diol **288a** as expected. However, they also found that pre-treatment of 2,3-epoxyalcohol **287** with *n*-butyllithium to form the lithium alkoxide before treatment with trimethylaluminium resulting in a complete reversal of regioselectivity, producing the 1,3-diol **288b** (Scheme 116).

[65] Sasaki, M.; Tanino, K.; Miyashita, M., *Org. Lett.*, **2001**, 3(11), 1765

[66] a) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H., *Tetrahedron Lett.*, **1982**, 3597 b) Roush, W. R.; Adam, M. A.; Peseckis, S. M., *Tetrahedron Lett.*, **1983**, 1377



Scheme 116 1,3-diol vs 1,2-diol formation

These results suggested that the reaction was proceeding via an aluminium-ate complex. Furthermore, they concluded that the second hydroxyl group in epoxide **287** was serving as an anchor and thereby controlling the regioselectivity further (Fig. 11).

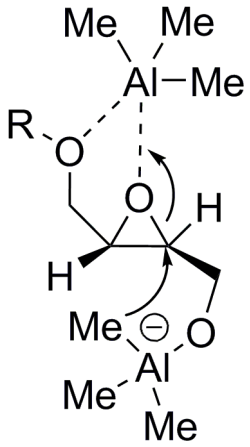
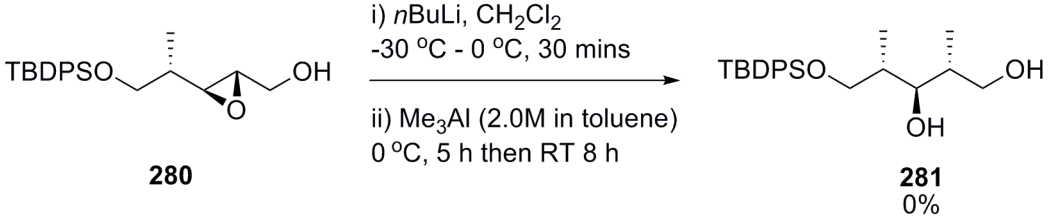


Fig. 11 Proposed aluminium-ate transition state in reaction of **287**

With these results in mind, the conditions were applied to the current synthesis. Epoxide **280** was treated with *n*-butyllithium before careful addition of trimethylaluminium (Scheme 117).



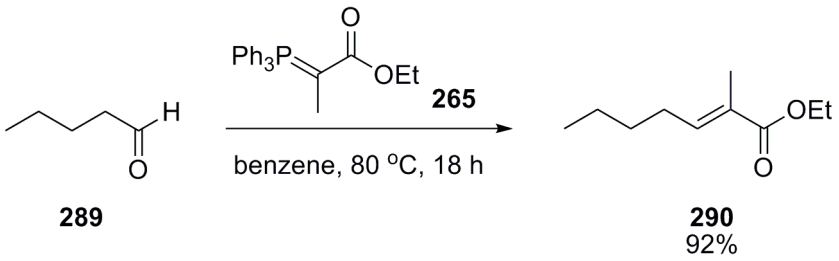
Scheme 117 Attempted trimethylaluminium reaction

Even after leaving the mixture to warm to room temperature overnight, no reaction was observed by TLC analysis. It could be argued that the second oxygen is too far away from the reaction site to have any control over regioselectivity in the mechanism, however this does not account for the fact that not even the traditional 1,2-diol was formed in the reaction. Due to time constraints, this line of investigation was not pursued any further.

2.2.2.4 The Samarium Diiodide Approach

In 1987 Inanaga and co-workers reported that *α,β*-epoxy esters could be selectively reduced to give *β*-hydroxy esters using samarium diiodide.[67] The mechanism for this reaction is unclear but it was reported that the presence of hexamethylphosphoramide (HMPA) in the reaction mixture accelerated the electron transfer, which is important for achieving a fast reaction rate. The presence of dimethylaminoethanol (DMAE) is also important as it not only acts as a proton source but also acts as a strong chelation agent to remove the Lewis acidic Sm(III) species from the reaction mixture. This prevents the samarium opening the ring in a non-regioselective manner and limits the formation of the undesired *α*-hydroxy derivative.

In order to ration the expensive chiral starting material, a test system for this method was developed starting with valeraldehyde **289**, a simple, short chain aldehyde. This was olefinated using (carbethoxyethylidine)triphenylphosphorane **265** as before to give tri-substituted *α,β*-unsaturated ester **290** in an excellent 92% yield (Scheme 118).

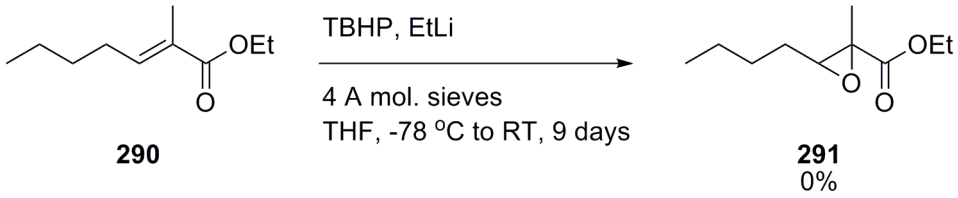


Scheme 118 Synthesis of *α,β*-unsaturated ester

The next step, epoxidation of *α,β*-unsaturated ester **290**, is not straightforward as the alkene is intrinsically electron-deficient due to the adjacent electron-withdrawing ester group. Rodriguez and co-workers reported a selective

[67] Otsubo, K.; Inanaga, J.; Yamaguchi, M., *Tetrahedron Lett.*, **1987**, 28(38), 4437

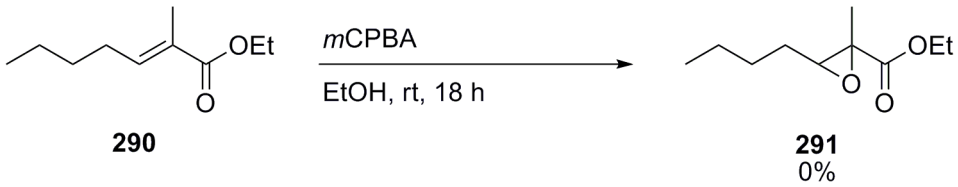
epoxidation of *α,β*-unsaturated esters using *t*butylhydroperoxide and ethyllithium.[68] It was reported, however that the reaction could take up to 7 days to go to completion. Ester **290** was reacted under the same conditions but no reaction was observed after 9 days (Scheme 119).



290 **291** 0%

Scheme 119 Attempted epoxidation of *α,β*-unsaturated ester

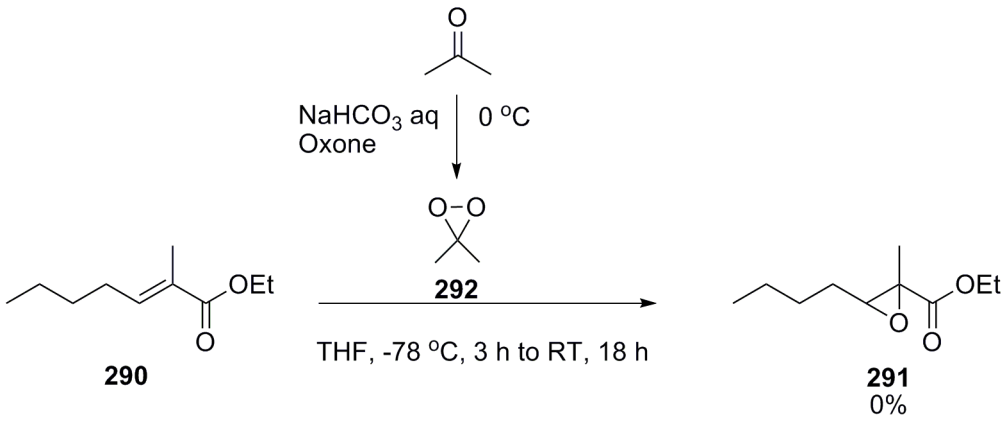
An attempt to epoxidise *α,β*-unsaturated ester **290** under standard *m*CPBA conditions was also unsuccessful (Scheme 120). This result was anticipated, however at this stage it was important to explore all possibilities for epoxidation.



290 **291** 0%

Scheme 120 Attempted epoxidation of *α,β*-unsaturated ester

Next, epoxidation using dimethyldioxirane, was attempted. Dimethyldioxirane **292** was made by reaction between potassium peroxymonosulfate (Oxone), aqueous sodium bicarbonate and acetone. The resulting solution was distilled under reduced pressure then reacted directly with ester **290** (Scheme 121). Once again, only starting material remained by TLC analysis.

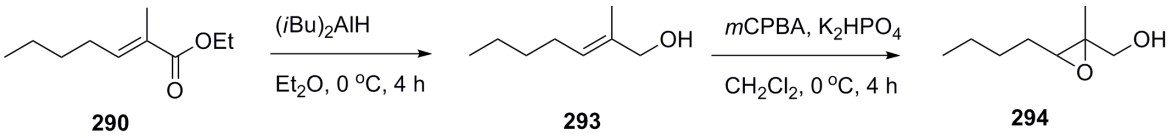


290 **291** 0%

Scheme 121 Attempted epoxidation of *α,β*-unsaturated ester

[68] López, I.; Rodriguez, S.; Izquierdo, J.; González, F., *J. Org. Chem.*, **2007**, 72, 6614

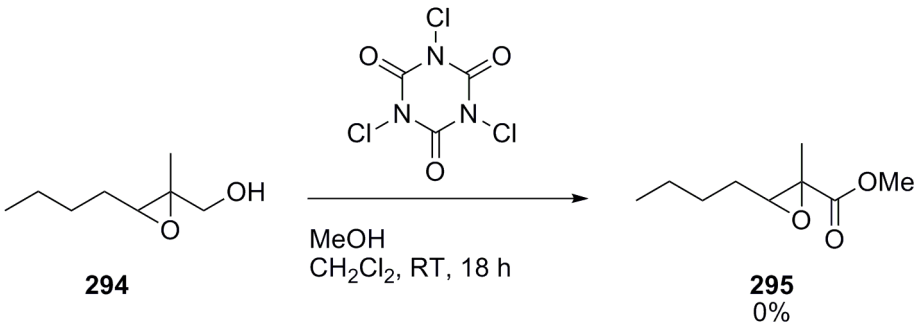
The above attempts show that epoxidation of *α,β*-unsaturated ester **290** was proving to be unsuccessful, therefore a different approach was required. Epoxidation of allylic alcohols has been much more successful in this project so this approach involved reducing the ester to the allylic alcohol **293** with diisobutylaluminium hydride and epoxidation under standard *m*CPBA conditions to give epoxy alcohol **294** (Scheme 122).



290 **293** **294**

Scheme 122 Synthesis of epoxy alcohol

In order to produce an *α,β*-epoxy ester to use as a starting material for the samarium diiodide method, the allylic alcohol would have to be oxidised. Hiegel and co-workers reported that it may be possible to oxidise the primary alcohol after the alkene has been epoxidised under mild conditions using trichloroisocyanuric acid and methanol (Scheme 123).[69] This reaction showed no indication of methyl ester formation, only decomposition of the starting material.



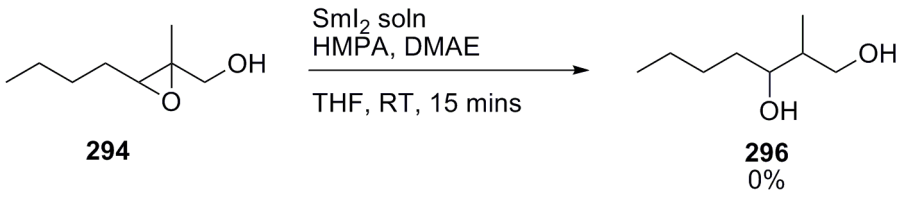
294 **295** 0%

Scheme 123 Attempted oxidation of epoxy alcohol

In order to cover all possible combinations of reactions, an effort was made to react epoxy alcohol **294** under the samarium diiodide conditions reported by Inanaga. First, a solution of samarium diiodide was preprared by reacting samarium metal with 1,2-diiodoethane in tetrahydrofuran. After heating gently for an hour the solution turned dark blue which indicated presence of samarium diiodide.

This was then reacted with epoxy alcohol **294** in the presence of HMPA and DMAE (Scheme 124). No reaction was observed by TLC analysis.

[69] Hiegel, G. A.; Gilley, C. B., *Synth. Commun.*, **2003**, 33, 2003



294 **296** 0%

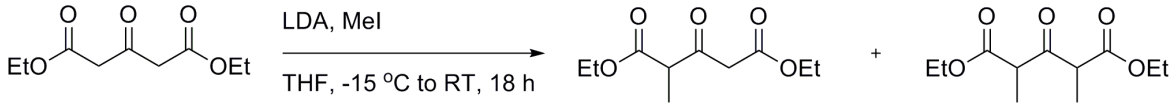
Scheme 124 Attempted epoxide opening with samarium diiodide

These results were not surprising as the paper suggested that the epoxide would have to be electron withdrawing in order for the samarium diiodide to react and indicate the importance of producing the *α,β*-unsaturated epoxide for this reaction to be successful. This line of investigation was not pursued any further.

2.2.2.5 The Racemic Approach – Direct methylation

It was becoming apparent that attempting to synthesise the core of Crocacin C enantioselectively was not proceeding as well as was hoped. As a result of this it was felt that a racemic synthesis might prove to be a little more straightforward. To this end a method of installing the four centres was devised starting from commercially available diethyl 1,3-acetonedicarboxylate **297**.

It was reported that mono-methylation of diester **297** was achieved by treatment with lithium diisopropylamide and one equivalent of iodomethane.[70] The mono-methylated product **298** was isolated in 47% yield along with 20% of the disubstituted product **299** (Scheme 125).

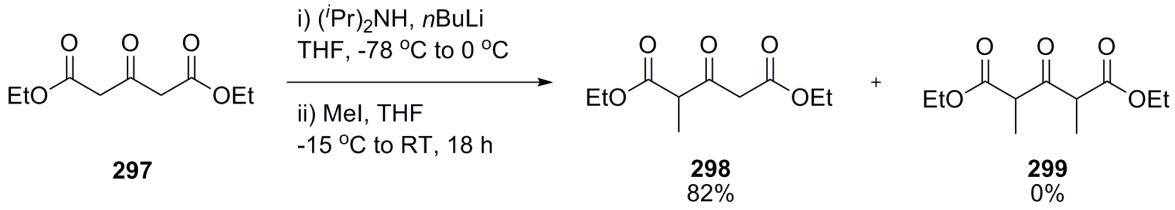


297 **298** 47% **299** 20%

Scheme 125 Methylation of diethyl 1,3-acetonediarboxylate

From these results it was postulated that by increasing the number of equivalents of LDA and iodomethane, an increase in the amount of disubstituted product could be achieved. Treatment of diester **297** with two equivalents of LDA, made *in*-situ from diisopropylamine and *n*-butyllithium followed by two equivalents of iodomethane gave a product which ^{1}H NMR spectroscopy unfortunately showed to be mono-methylated product **298** (Scheme 126).

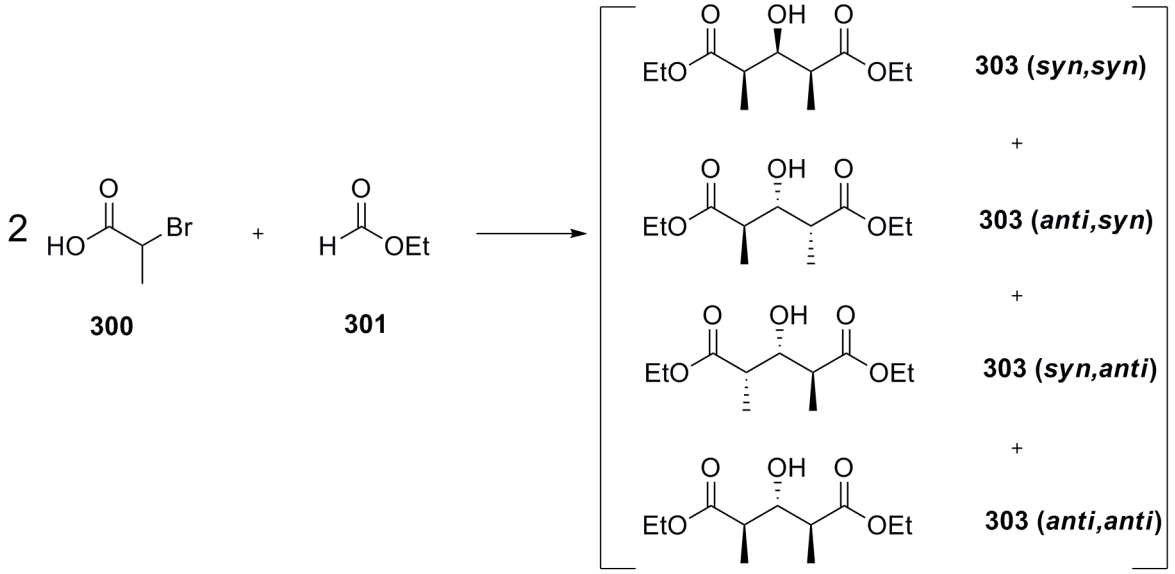
[70] Rozzell J. D.; Kambouakis, S., US patent no 2004/0053377, March 2004



Scheme 126 Methylation of diethyl 1,3-acetonediarboxylate

2.2.2.6 The Reformatsky Approach

An alternative method to direct methylation is to build up the stereocentres in the core in a step-wise fashion via a condensation reaction. In 1996 Uguen and co-workers reported the construction of a stereotriad from a Reformatsky-style condensation between two equivalents of ethyl bromo-propionate **300** and ethyl formate **301** (Scheme 127).[71]



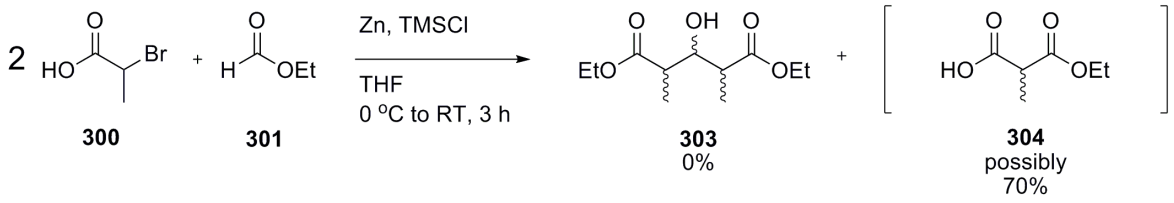
Scheme 127 Uguen's Reformatsky condensation of ethyl bromo-propionate and ethyl formate

They reported a 4:4:1 (*syn,syn*:*anti,syn*:*anti,anti)* mixture of the four diastereoisomers **303**, accounting for the fact that the symmetry of the product means that the *anti,syn* product is identical to the *syn,anti* product. These diastereoisomers were isolated by first performing a saponification of the esters to give the corresponding dicarboxylic acids. The *syn,syn* isomer was then isolated from this mixture by crystallisation in 40% yield. From the mother liquor, a racemic mixture of the *anti,syn* and *syn,anti* isomers were obtained after evaporation and crystallisation in a 40% yield. Finally, attempts to repeat the process from the second mother liquor to isolate the *anti,anti* isomer were unsuccessful, however

[71] Domon, L.; Vogeleisen, F.; Uguen, D., *Tetrahedron. Lett.,* **1996**, 37 (16), 2773

reduction of the residue gave a mixture of triols from which the *anti,anti* isomer was isolated by chromatography in a 9% overall yield.

In an attempt to recreate this, zinc dust was treated with chlorotrimethylsilane followed by ethyl 2-bromopropionate **300** and ethyl formate **301** (Scheme 128). Initial ^{1}H NMR results seemed to suggest that only one addition had taken place to give ester **304**. However, this could not be confirmed as the NMR spectrum could also point to a mixture of the two starting materials.

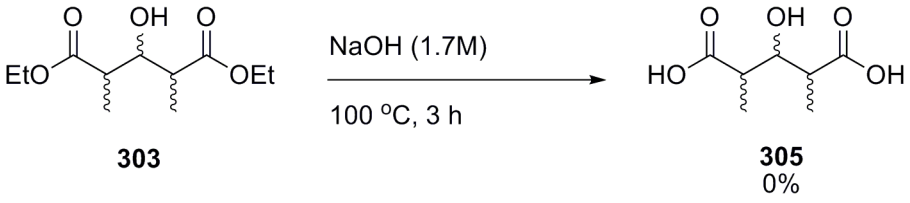


300 **301** **303** 0% **304** possibly 70%

Scheme 128 Attempted Reformatsky condensation

Further investigation suggested that activation of the zinc dust might be necessary in order to encourage the reaction to proceed.[72] This was carried out and the reaction in Scheme 128 repeated. The resulting crude material was purified by column chromatography to give an inseparable mixture of diastereoisomers in 40% yield. From the ^{1}H NMR of the mixture it was impossible to tell the ratio of diastereoisomers present in the mixture.

In order to repeat the separation reported by Uguen and co-workers, the diester **303** would first have to be saponified to give the corresponding dicarboxylic acid **305** (Scheme 129).



303 **305** 0%

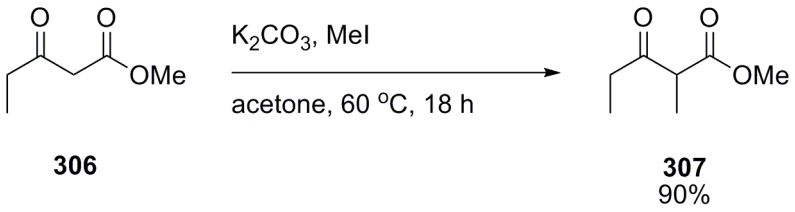
Scheme 129 Attempted saponification of diester

Unfortunately this reaction was unsuccessful in that no change was observed by TLC analysis. On evaluation of this route it seemed that the purification method was very complicated and laborious balanced with the small amount of useful material that could be expected if the isolation was successful. This route was therefore abandoned in favour of what was hoped to be a more controlled set of reactions.

[72] Shriner, R. L.; Neumann, F. W., *Organic Syntheses Coll. Vol. 3,* **1955**, p 73 and *Vol. 26,* **1946**, p 7

2.2.2.7 The Aldol Approach

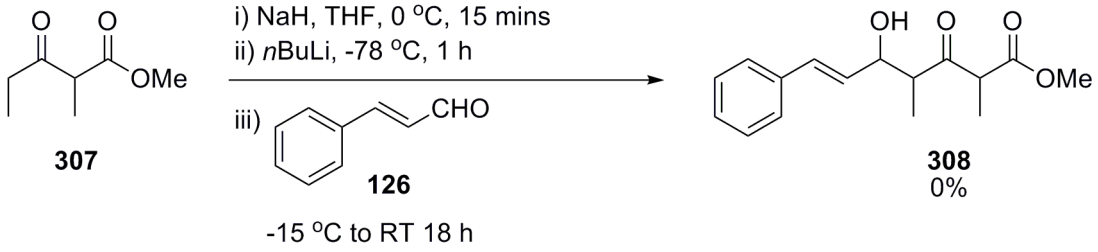
This new approach to the racemic synthesis of Crocacin C was envisioned to occur via an aldol addition to a dicarbonyl compound. First, commercially available methyl propionyl acetate **306** was selectively methylated by removal of the most acidic proton between the two carbonyl groups using a mild base and addition of iodomethane to give intermediate **307** in excellent 90% yield without the need for purification (Scheme 130).[73]



306 **307** 90%

Scheme 130 Methylation of methyl propionyl acetate

The methylated product **307** was then treated with sodium hydride followed by *n*-butyllithium then *trans*-cinnamaldehyde **126** in an attempt to perform an aldol addition. A similar reaction was used by Trauner and co-workers in 2005 during their synthesis of Elysiapyrones A and B.[74] The use of two separate bases was to first remove the most acidic proton, between the two carbonyls and then remove the second most acidic proton, at the desired site of addition (Scheme 131).



307 **126** **308** 0%

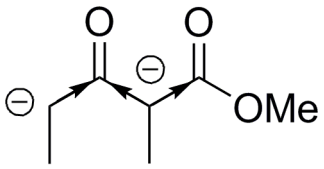
-15 °C to RT 18 h

Scheme 131 Attempted aldol addition of *trans*-cinnamaldehyde

It was reasoned that the desired addition site would be the most reactive of the two anions, this is due to the stabilisation of the first anion by the two carbonyl groups. The second anion has only one carbonyl adjacent to provide stabilisation and this is already involved with stabilising the first (Fig 12).

[73] Kalaitzakis, D.; Kambourakis, S.; Rozzell, D. J.; Smonou, I. *Tetrahedron Asymmetry*, **2007**, 18, 2418

[74] Barbarow, J. E.; Miller, A. K.; Trauner, D. *Org. Lett.*, **2005**, 7(14), 2901

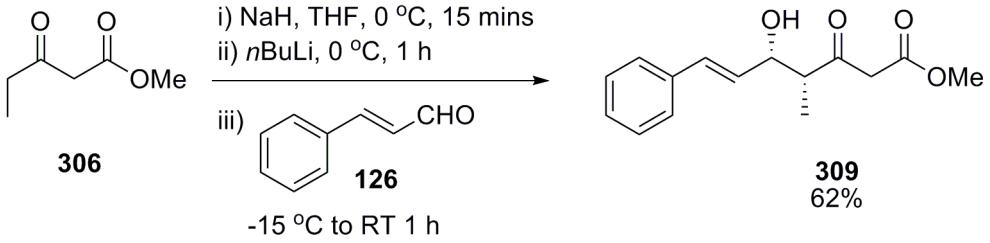


307

Fig. 12 Reactivity of *α*-carbons

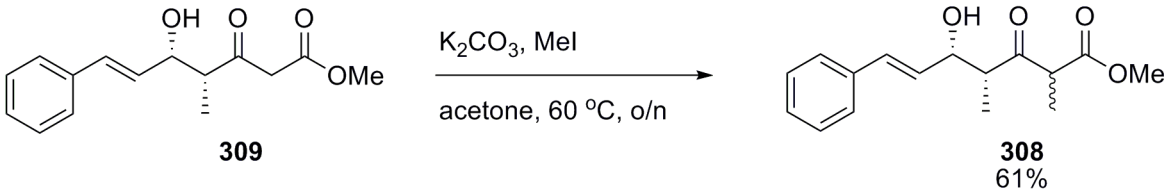
Unfortunately several attempts at this reaction proved to be unsuccessful. Changing the bases to *n*-butyllithium followed by *t*-butyllithium was also ineffective. To rectify this problem, the methylation and Aldol steps were reversed, with the aldol addition being performed directly on the methyl propionyl acetate **306**. This reaction has precedence in the literature, when Kobayashi and co-workers used it in their synthesis of 9-methoxystrobilurin-type β-substituted β-methoxyacrylates in 2002.[75]

This reaction was performed several times with yields ranging from 38% to 62% after column chromatography and the product **309** was observed as a single diastereoisomer (Scheme 132).



Scheme 132 Aldol addition of methyl propionyl ester

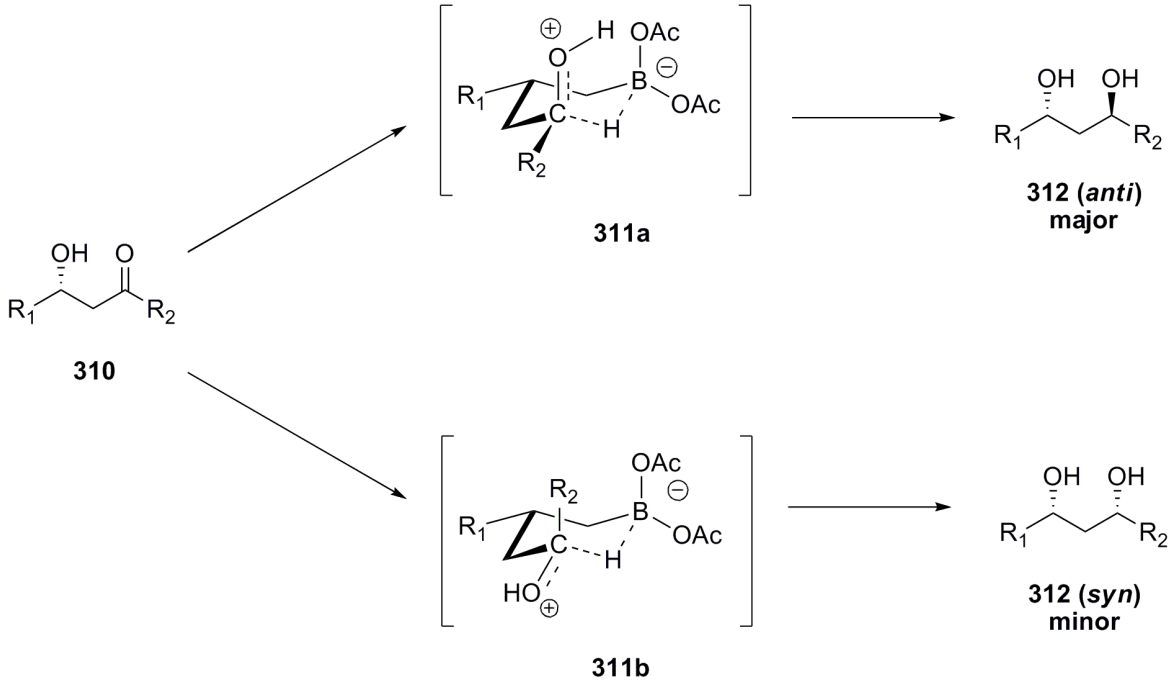
The aldol product **309** was treated with potassium carbonate then iodomethane to give methylated product **308**. It was found that purification of the iodomethane by passing it through a short plug of neutral alumina increased the yield from 20-30% to 61% (Scheme 133).



Scheme 133 Methylation of Aldol product

[75] Uchiro, H.; Nagasawa, K.; Kotake, T.; Hasegawa, D.; Tomita, A.; Kobayashi, S. *Biorg. & Med. Chem. Lett.*, **2002**, 12, 2821

Synthesis continues with a selective reduction of the ketone to give an *anti*-diol, which was achieved using tetramethylammonium triacetoxyborohydride. Evans first reported this reducing agent in 1988 as a method of reducing acyclic *β*-hydroxy ketones to their corresponding *anti*-diols with high diastereoselectivity.[76] The rationalisation behind this selectivity can be explained by examining the transition state of the reaction (Scheme 134).

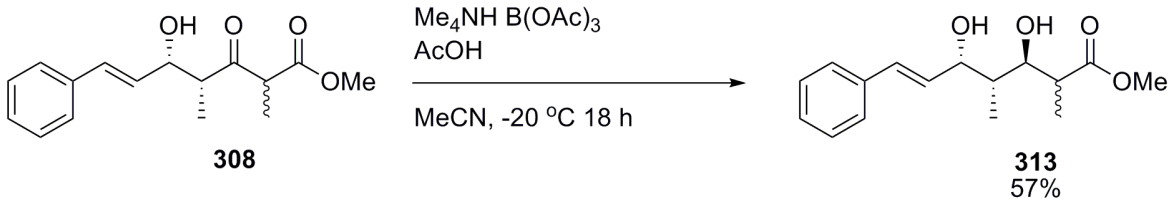


Scheme 134 Transition states for tetramethylammonium triacetoxyborohydride reduction

Exchange of the acetoxy ligand between the reducing agent and the substrate hydroxyl is assumed to take place before the actual reduction. This is supported by evidence that carbonyl reduction does not take place in the absence of the hydroxyl group in the starting ketone. The two chair-like transition states illustrated in Scheme 134 are thought to be in competition with each other. The 1,3-diaxial interactions of the R_2 group with the OAc ligand in **311b** should be more destabilising to the transition state than the analogous 1,3-diaxial interactions of the HO^+ group with the OAc ligand in **311a**. Therefore the favoured transition state is **311a**, leading to the *anti*-diol **312 (*anti*)** being the major product. The diol is produced via a combination between intramolecular hydride delivery and activation by acid catalysis.

Ketone **308** was successfuly reduced by tetramethylammonium triacetoxyborohydride to give the diol in 57% (Scheme 136).

[76] Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.*, **1988**, 110, 3560



308 **313** 57%

Scheme 135 Reduction of ketone to 1,2-diol

At this stage time constraints meant that the synthesis could not be continued any further.

3.0 Conclusion and Future Work

3.1 Dienamides

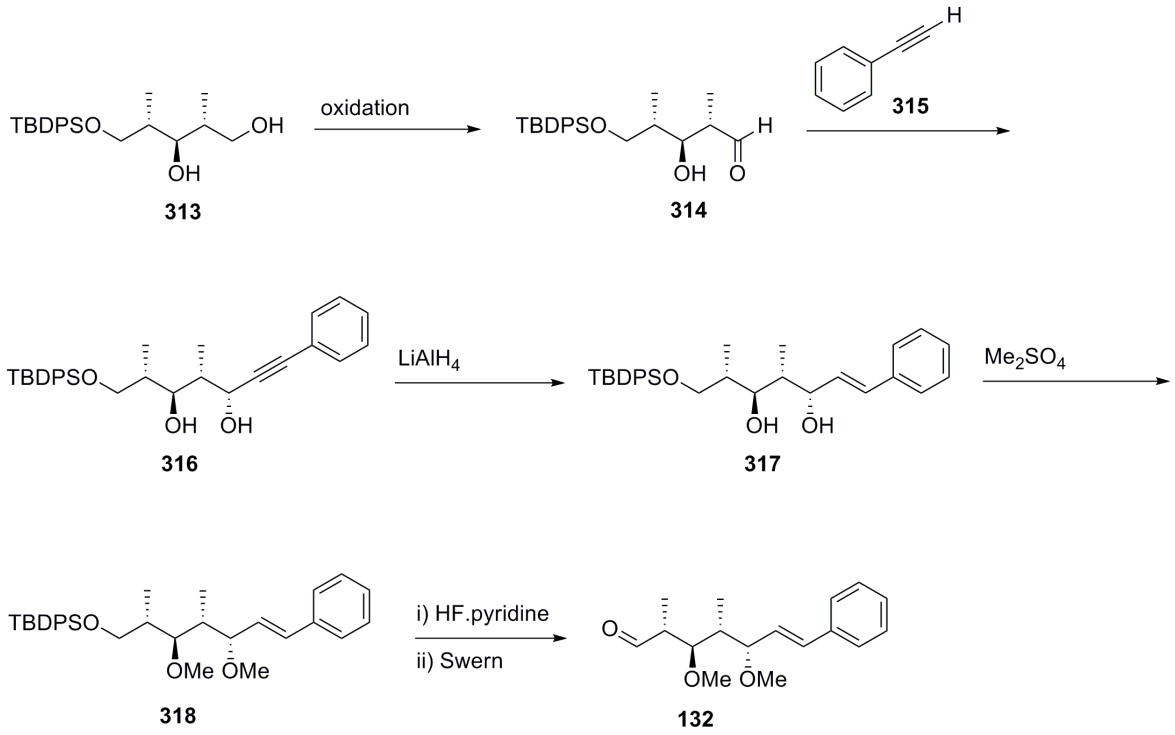
A varied library of *Z*,*E*-dienamides were synthesised in one-step which reinforces the versatility and potential of *N*-formyl imides as synthetic intermediates. The methodology is fast, flexible and amenable to dienamides not readily accessible through other methods. The potential use for this methodology could extend from a convenient method of preparing a range of dienamides for use as reactive intermediates in other studies to installing dienamide units within natural products.

3.2 The Crocacins

A significant portion of the structure of Crocacin C was synthesised, though due to time constraints and problems with certain reactions, neither the stereoselective nor racemic syntheses of Crocacin C were completed. This is unfortunate but detailed below are the plans for finishing the synthesis, plus the future vision for completion of synthesis of the rest of the Crocacin family.

3.2.1 Stereoselective Synthesis

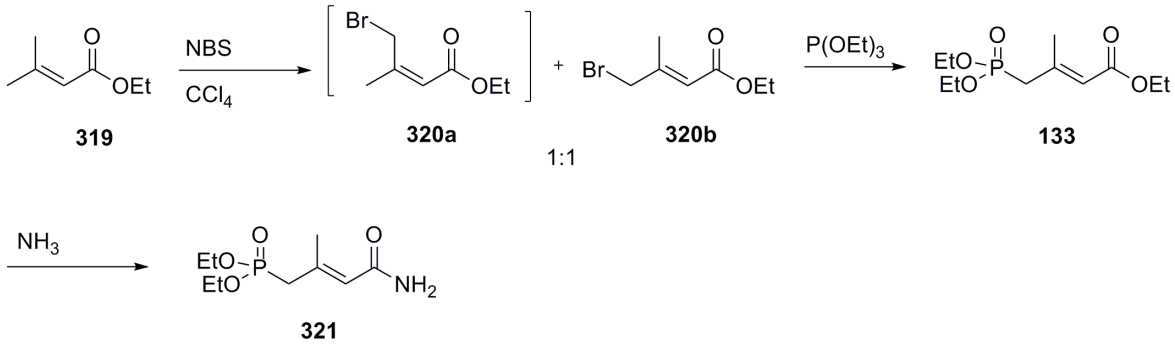
The stumbling block for this synthesis was opening of the epoxide to establish the stereocentres in the middle portion of the molecule. It was expected and accepted that this was going to be the most challenging part of the synthesis and it is therefore expected that completion of the synthesis beyond this step should be relatively straightforward (Scheme 137).



Scheme 137 Proposed completion of stereoselctive synthesis

The first step would be selective oxidation of the primary alcohol over the secondary alcohol to give aldehyde **314**, which would then be reacted with the alkyne **315** plus a base which it is hoped would react stereoselectively to give the anti diol **316**. The alkyne could be reduced selectively to the *trans* alkene, followed by methylation of the two secondary alcohols to give di-methyl ether **318**. Deprotection of the bulky silyl protecting group, probably with hydrogen fluoride followed by oxidation to give the final intermediate, aldehyde **132**.

The final step in the proposed synthesis of Crocacin C is a Horner-Wadsworth-Emmons reaction on aldehyde **132** to install the last section. In order to complete the synthesis, the Horner-Wadsworth-Emmons reagent **321** must be prepared. This is a procedure known in the literature (Scheme 138).[77]

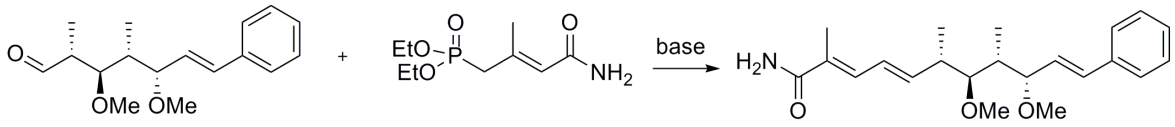


Scheme 138 Synthesis of Horner-Wadsworth-Emmons reagent

[77] Mata, E. G.; Thomas, E. J., *J. Chem. Soc., Perkin Trans. 1*, **1995**, 785

Commercially available ester **319** is brominated with *N*-bromosuccinimide and should produce a 1:1 mixture of regioisomers which should be separable by column chromatography. The desired regioisomer **320b** would then be treated with diethylphosphite to give phosphonate ester **133** which is treated with ammonia to convert the ester to amide **321**.

The final step involves treating aldehyde **132** with phosphonate ester **133** in the presence of base to give Crocacin C **6** (Scheme 139).



132 **133** Crocacin C, **6**

Scheme 139 Horner-Wadsworth-Emmons reaction to complete Crocacin C synthesis

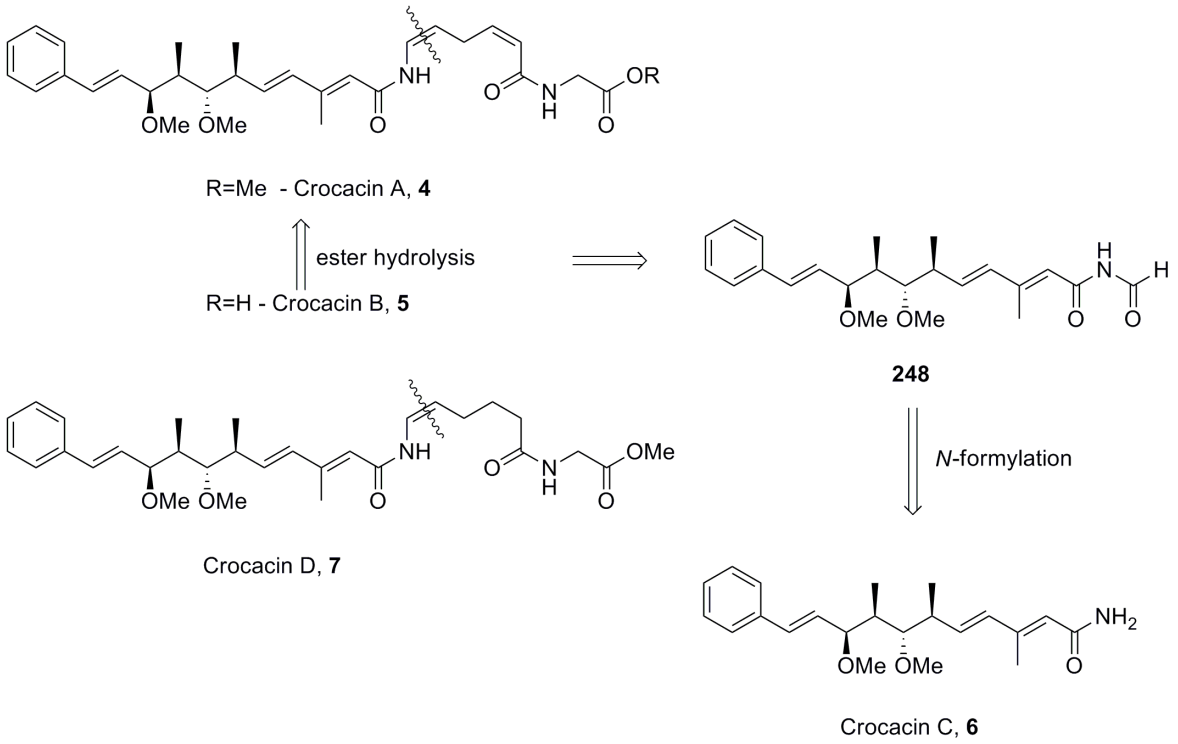
3.2.2 A Convergent Synthesis of the the Crocacin Family

As mentioned, the ultimate aim of this project was to establish a convergent synthesis of the four members of the Crocacin family, taking advantage of their closely related structures.

In particular, it has been noted that Crocacins A, B and D derive from the structurally simpler Crocacin C via an enamide linkage.

It is proposed that Crocacins A, B and D can be synthesised from Crocacin C using the enamide/dienamide methodology reported thus far (Scheme 140).[78]

[78] Mathieson, J. E.; Crawford, J.J.; Schmidtmann, M.; Marquez, R., *Org. Biomol. Chem.*, **2010**, 7, 2170



Scheme 140 Proposed convergent retrosynthesis of the Crocacin family

Carrying out an *N*-formylation of the amide functionality of Crocacin C should allow for an olefination reaction to take place to furnish the structures of the more complex family members. Crocacin B, in turn can be synthesised from Crocacin A via a simple ester hydrolysis.

4.0 Experimental

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. 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 Buchi Rotavapor, unless otherwise stated.

IR spectra were recorded as thin films on NaCl plates using a JASCO FT/IR410 Fourier Transform spectrometer. Only significant absorptions (λ_{max}) are reported in wavenumbers (cm^{-1}).

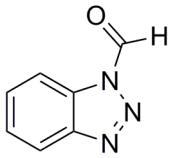
Proton magnetic resonance spectra (^{1}H NMR) and carbon magnetic spectra (^{13}C NMR) were respectively recorded at 400MHz and 100MHz using a Bruker DPX Advance400 instrument. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, b = broad), (3) coupling constant (*J*) quoted in Hertz to the nearest 0.1 Hz.

High resolution mass spectra were recorded on a JEOL JMS-700 spectrometer by electrospray (EI), chemical ionisation (CI) and fast atom bombardment (FAB) mass spectrometer operating at a resolution of 15000 full widths at half height.

Flash chromatography was performed using silica gel (Flurochem 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, iodine or cerium ammonium molybdate followed by heating.

4.1 Dienamides

N-formyl benzotriazole 188[35]



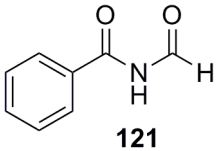
188

A suspension of benzotriazole (10.0 g, 83.9 mmol) in dichloromethane (200 mL) was cooled to 0 ºC in an ice bath and formic acid (3.8 mL, 101 mmol) and diisopropylcarbodiimide (18.2 mL, 118 mmol) were added sequentially. The reaction mixture was warmed up slowly to room temperature and stirred for 18 hours.

The resulting white precipitate was removed by filtration and the filtrate concentrated under reduced pressure to give a crude white solid. The white solid was triturated in a solution of 30% ethyl acetate in petroleum ether (400 mL total vol.) and the remaining white solid was removed by filtration. The filtrate was concentrated *in vacuo* to give 10.7 g (88%) of the desired *N*-formyl benzotriazole **188** as a white solid.

^{1}H NMR ($CDCl_3$) : δ = 9.80 (1H, s, *CHO*), 8.18 (1H, d, *J* = 8.2 Hz, *aromatic CH*), 8.09 (1H, d, *J* = 8.2 Hz, *aromatic CH*), 7.64 (1H, td, *J* = 8.1, 0.8 Hz, *aromatic CH*), 7.51 (1H, dt, *J* = 8.2, 0.8 Hz, *aromatic CH*) ^{13}C NMR ($CDCl_3$) : δ = 159.7, 164.5, 130.7, 129.8, 127.0, 120.4, 113.6 HRMS – found 147.0435, calc for $C_7H_5N_3O$ 147.0433

N-formylbenzamide 121



121

A suspension of benzamide (3.83 g, 31.6 mmol) in tetrahydrofuran (30 mL) at -78 ºC was treated with *n*-butyllithium (2.5 M in hexane, 13.9 mL, 34.8 mmol) and the resulting mixture was allowed to warm up to room temperature over 3 hours. The reaction was cooled back down to -78 ºC and a solution of *N*-formyl benzotriazole

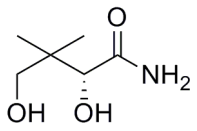
[35] Katritzky, A. R.; Chang, H, X.; Yang, B., *Synthesis*, **1995**, 503

188 (5.58 g, 37.9 mmol) in tetrahydrofuran (30 mL) was added. The mixture was allowed to warm up to room temperature and stirred for 18 hours.

The reaction mixture was diluted with *t*-butyl methyl ether (30 mL), washed with aqueous saturated sodium bicarbonate solution (60 mL) and extracted into diethyl ether (2 x 60 mL). The combined organic phases were washed with water (60 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a crude white solid. Purification of the crude white solid by flash chromatography (silica gel, 10% ethyl acetate in petroleum ether) gave the desired imide **121** as a white solid (1.68 g, 36%).

^{1}H NMR ($CDCl_3$) : δ = 9.40 (1H, d, *J* = 9.6 Hz, *CHO*), 8.96 (1H, bs, *NH*), 7.92 (1H, d, *J* = 7.2 Hz, *aromatic CH*), 7.70 (2H, t, *J* = 7.6 Hz, *aromatic CH*), 7.58 (2H, t, *J* = 7.6 Hz, *aromatic* CH) ^{13}C NMR ($CDCl_3$) : δ = 164.0, 163.9, 133.9, 131.1, 129.1, 127.9 HRMS - found 150.1321, calc for $C_8H_7NO_2$ 150.1309

(*R*)-2,4-dihydroxy-3,3-dimethylbutanamide 190

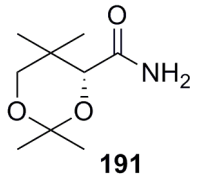


190

A round-bottomed flask charged with *D*-pantolactone (20.0 g, 15.4 mmol) was treated with liquid ammonia (100 mL) at -78 ºC. The reaction mixture was refluxed at -78 ºC for 2 hours before being allowed to warm up to room temperature over 48 hours during which time the ammonia evaporated. The resulting white solid was taken up in dichloromethane (100 mL) and concentrated *in vacuo* to remove any remaining traces of ammonia, giving the desired amide **190** as a white solid (22.5 g, 99%) without the need for further purification.

^{1}H NMR ($CDCl_3$) : δ = 6.65 (1H, bs, NH_2), 5.51 (1H, bs, NH_2), 4.12 (1H, s, *CH*), 3.65 (1H, d, *J* = 11.1 Hz, CH_2), 3.57 (1H, d, *J* = 11.1 Hz, CH_2), 1.11 (3H, s, CH_3), 0.99 (3H, s, CH_3).

(*R*)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide 191

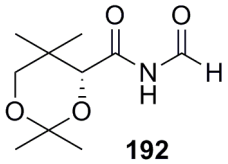


191

A suspension of amide **190** (4.00 g, 27.2 mmol) in a mixture of dichloromethane and acetone (1:1, 80 mL total volume) was stirred at room temperature until homogenous (10 minutes). The solution was treated with 2-methoxypropene (3.90 mL, 40.8 mmol) and the resulting mixture was stirred for a further 10 minutes at room temperature. A catalytic amount of *para*-toluene sulfonic acid (150 mg, 0.8 mmol) was added and the reaction mixture stirred at room temperature for a further 2 hours. The reaction mixture was concentrated *in vacuo* to give a brown oil which, on drying under high vacuum for 18 hours gave the protected amide product as an off-white solid (4.85 g, 96%). The crude product **191** was used in the next step without the need for further purification.

^{1}H NMR ($CDCl_3$) : δ = 6.49 (1H, bs, *NH_2*), 6.07 (1H, bs, *NH_2*), 4.10 (1H, s, *CH*), 3.70 (1H, d, *J* = 11.8 Hz, *CH_2*), 3.31 (1H, d, *J* = 11.8 Hz, *CH_2*), 1.47 (3H, s, *CH_3*), 1.44 (3H, s, *CH_3*), 1.06 (3H, s, *CH_3*), 1.02 (3H, s, *CH_3*)

(*R*)-*N*-formyl-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide 192



192

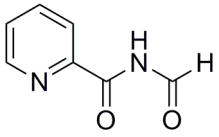
A suspension of the protected amide **191** (3.84 g, 20.5 mmol) in tetrahydrofuran (50 mL) at -78 ºC was treated with *n*-butyllithium (2.5 M in hexanes, 9.02 mL, 22.5 mmol) and the reaction mixture was stirred for 3 hours. A solution of *N*-formyl benzotriazole **188** (3.80 g, 25.8 mmol) in tetrahydrofuran (30 mL) was added and the resulting mixture was allowed to warm up to room temperature and stirred for 18 hours.

The reaction mixture was diluted with *t*-butyl methyl ether (20 mL) and quenched with water (50 mL). The organic phase was washed with water (50 mL) and the combined aqueous phases were extracted into diethyl ether (2 x 20 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a dark brown oil. Purification of the crude brown oil by flash chromatography (silica gel, 15% ethyl acetate in petroleum ether) gave

the imide **192** as a white solid (1.91 g, 43%) after drying under high vacuum overnight.

^{1}H NMR ($CDCl_3$) : δ = 9.18 (1H, d, *J* = 10.1 Hz, *CHO*), 8.92 (1H, bs, *NH*), 4.23 (1H, s, *CH*), 3.75 (1H, d, *J* = 11.7 Hz, CH_2), 3.37 (1H, d, *J* = 11.7 Hz, CH_2), 1.53 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.11 (3H, s, CH_3), 1.07 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) : δ = 170.7, 161.7, 99.8, 71.2, 33.1, 29.4, 21.8, 18.7 HRMS found 216.0197, calc for $C_{10}H_{17}NO_4$ 216.0191

_N_-formylpicolinamide 194



194

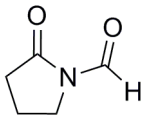
A suspension of picolinamide (2.00 g, 16.4 mmol) in tetrahydrofuran (40 mL) at -78 ºC was treated with *n*-butyllithium (2.5 M in hexanes, 7.20 mL, 18.0 mmol) and the reaction mixture was allowed to warm up to room temperature over 3 hours. The reaction was cooled back down to -78 ºC and a solution of *N*-formyl benzotriazole (3.22 g, 21.9 mmol) in tetrahydrofuran (20 mL) was added. The mixture was allowed to warm up to room temperature and stirred for 18 hours overnight.

The reaction mixture was diluted with *t*-butylmethyl ether (10 mL), washed with aqueous saturated sodium bicarbonate solution (10 mL) and extracted into diethyl ether (2 x 10 mL). The combined organic phases were washed with water (10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a crude white solid. Purification of the crude white solid by flash chromatography (silica gel, 10% ethyl acetate in petroleum ether) gave the desired imide **194** as a white solid (485 mg, 20%).

^{1}H NMR ($CDCl_3$) : δ = 10.40 (1H, bs, *NH*), 9.40 (1H, d, *J* = 10.6 Hz, *CHO*), 8.68 (1H, d, J = 4.5 Hz, *aromatic CH*), 8.33 (1H, d, *J* = 7.8 Hz, *aromatic CH*), 7.98 (1H, dt, *J* = 7.8, 1.5 Hz, *aromatic CH*), 7.61 (1H, dt, *J* = 5.8, 1.0 Hz, *aromatic CH*) ^{13}C NMR ($CDCl_3$) : δ = 164.4, 161.7, 148.6, 147.1, 138.0, 128.2, 123.3 HRMS found 151.0463, calc for $C_7H_6N_2O_2$ 151.0428.

General procedure for the fomylation of lactams

2-oxopyrrolidine-1-carbaldehyde 118b



118b

Sodium formate (30.0 g, 44.1 mmol) was dried under vacuum at 130 ºC for 24 hours. The dry sodium formate was taken up in dry diethyl ether (30 mL) and acetyl chloride (31.4 mL, 44.1 mmol) was added quickly. The reaction mixture was stirred at room temperature under argon overnight.

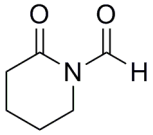
The reaction mixture was treated with pyrollidinone (3.34 mL, 4.40 mmol) and the solution was stirred at 60ºC overnight.

The reaction mixture was cooled down to room temperature and filtered to remove the insoluble salt by-product then concentrated *in vacuo* to give a crude brown oil.

Purification of the crude oil by flash chromatography (silica gel, 20% ethyl acetate in petroleum ether) gave the desired imide **118b** as a colourless oil (0.58 g, 12 %).

^{1}H NMR ($CDCl_3$) : δ = 9.11 (1H, s, *CHO*), 3.75 (2H, t, *J* = 7.2 Hz, CH_2), 2.62 (2H, t, *J* = 8.1 Hz, CH_2), 2.15 (2H, qn, *J* = 7.8 Hz, CH_2) ^{13}C NMR ($CDCl_3$) : δ = 176.9, 160.3, 45.3, 32.1, 17.8 HRMS found 114.1287, calc for $C_5H_7NO_2$ 114.1280

2-oxopiperidine-1-carbaldehyde 118c

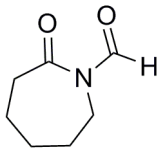


118c

Imide **118c** was prepared following the same procedure as above, starting from sodium formate (30.0 g, 44.1 mmol), acetyl chloride (31.4 mL) and valerolactam (4.36 g, 4.40 mmol) to give 0.93 g (17%) of product **118c** after flash chromatography.

^{1}H NMR ($CDCl_3$) : δ - 9.53 (1H, s, *CHO*), 3.65 (2H, bt, *J* = 4.6 Hz, CH_2), 2.62 (2H, bt, *J* = 6.9 Hz, CH_2), 1.88 (4H, appqn, *J* = 3.4 Hz, *2 x* CH_2) ^{13}C NMR ($CDCl_3$) : δ = 173.3, 162.9, 41.9, 33.4, 21.8, 20.3 HRMS found 128.1612, calc for $C_6H_9NO_2$ 128.1617

2-oxoazepane-1-carbaldehyde 118d

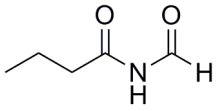


118d

Imide **118d** was prepared following the same procedure as above, starting from sodium formate (13.0 g, 19.1 mmol), acetyl chloride (13.6 mL, 19.1 mmol) and caprolactam (2.15 g, 1.9 mmol) to give 1.62 g (60%) of product **118d** after flash chromatography.

^{1}H NMR ($CDCl_3$) : δ = 9.11 (1H, s, *CHO*), 3.75 (2H, m, *CH_2*), 2.69-2.72 (2H, m *CH_2*), 1.81-1.83 (4H, m *2 x CH_2*), 1.71-1.72 (2H, m, *CH_2*) ^{13}C NMR ($CDCl_3$) : δ = 178.0, 162.1, 39.6, 37.9, 29.3, 28.7, 23.3 HRMS found 142.1623, calc for $C_7H_{11}NO_2$ 142.1628.

***N*-formylbutyramide 197**



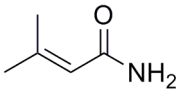
197

To a suspension of butyramide (1.00 g, 11.5 mmol) in tetrahydrofuran (10 mL) at 0 ºC was added *n*-butyllithium (2.5 M in hexanes, 3.10 mL, 12.6 mmol) and the reaction mixture stirred for 1 hour. The reaction mixture was cooled down to 0 ºC and a solution of *N*-formyl benzotriazole **188** (2.00 g, 13.8 mmol) in tetrahydrofuran (10 mL) was added and the resulting solution allowed to warm to room temperature and stirred for 18 hours overnight.

The reaction mixture was diluted with diethyl ether (20 mL) and filtered to remove the white precipitate. The filtrate was concentrated *in vacuo* to give a pale yellow oil. Purification of the crude oil by flash chromatography (silica gel, 20% ethyl acetate in petroleum ether) gave the desired imide **197** as a colourless oil (0.45 g, 34%).

^{1}H NMR ($CDCl_3$) : δ = 9.15 (1H, s, *CHO*), 2.40 (2H, t, *J* = 7.3 Hz, *CH_2*), 1.70-1.80 (2H, m, *CH_2*), 1.03 (3H, t, *J* = 7.3 Hz, *CH_3*) ^{13}C NMR ($CDCl_3$) : δ = 173.8, 163.6, 33.4, 17.8, 13.6 HRMS found 116.1985, calc for $C_5H_9NO_2$ 116.1667 ν_{max} (neat)/cm $^{-1}$ 2968, 1746, 1689

3-methylbut-2-enamide 201

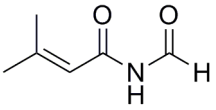


201

A suspension of 3,3-dimethylacrylic acid (2.00 g, 19.9 mmol) in dichloromethane (50 mL) was cooled to 0 ºC in an ice-bath before treating with a catalytic amount of dimethylformamide (20 µL). Oxalyl chloride (1.77 mL, 20.9 mmol) was then added dropwise over 2 minutes. The reaction mixture was stirred at 0 ºC for 15 minutes before being allowed to warm up to room temperature, then stirred for a further 90 minutes. Dichloromethane (50 mL), which had been saturated with ammonia gas for 1 hour was added via cannula. After 5 minutes the reaction mixture was quenched with water (40 mL) and the aqueous phase was extracted with dichloromethane (2 x 30 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the desired amide **201** as a yellow solid (1.46 g, 83%), which could be used without any further purification.

^{1}H NMR ($CDCl_3$) : δ = 5.56 (1H, sept, *J* = 1.2 Hz, *alkene CH*), 5.35 (2H, bs, *NH*$_2$), 2.09 (3H, d, *J* = 1.2 Hz, *CH*$_3$), 1.79 (3H, d, *J* = 1.2 Hz, *CH*$_3$) ^{13}C NMR ($CDCl_3$) : δ = 168.4, 151.5, 116.6, 26.2, 18.8 HRMS found 99.0681 calc for C_5H_9NO 99.0684 ν_{max} (neat)/cm $^{-1}$ 3360, 3292, 3174, 1674, 1610 cm $^{-1}$

***N*-formyl-3-methylbut-2-enamide 200**



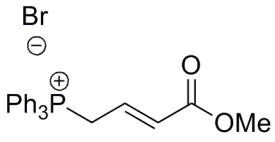
200

To a suspension of vacuum-dried amide **201** (0.50 g, 50.4 mmol) in tetrahydrofuran (10 mL) at 0 ºC was added *n*-butyllithium (2.5 M in hexanes, 2.5 mL, 55.5 mmol) and the reaction mixture was stirred for 90 minutes. The reaction mixture was cooled down to 0 ºC, a solution of *N*-formyl benzotriazole **188** (0.89 g, 60.5mmol) in tetrahydrofuran (10 mL) was added and the resulting solution was allowed to warm to room temperature then stirred for 18 hours overnight. The reaction mixture was diluted with *t*-butylmethyl ether (5 mL), quenched with water (15 mL) and the aqueous phase was extracted with diethyl ether (2 x 10 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a crude brown oil. Purification of the crude brown oil

by flash chromatography (silica gel, 15% ethyl acetate in petroleum ether) gave the desired imide **200** as a yellow solid (0.17 g, 26%).

^{1}H NMR ($CDCl_3$) : δ = 9.09 (1H, d, *J* = 10.1 Hz, *CHO*), 8.65 (1H, bs, *NH*), 5.60 (1H, s, *CH*), 2.18 (3H, d, *J* = 1.2 Hz, CH_3), 1.90 (3H, d, *J* = 1.2 Hz, CH_3) ^{13}C NMR ($CDCl_3$) : δ = 163.4, 160.9, 129.3, 116.0, 27.9, 20.2 HRMS found 128.0998, calc for $C_6H_9NO_2$ 128.0967 ν_{max} (neat)/cm $^{-1}$ 3084, 2933, 1722, 1660, 1633 cm $^{-1}$

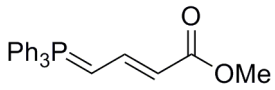
(*E*)-(4-methoxy-4-oxobut-2-en-1-yl)triphenylphosphonium bromide 205



205

A suspension of triphenylphosphine (11.3 g, 43.0 mmol) in toluene (50 mL) was treated with methyl 4-bromocrotonate (5.00 mL, 42.0 mmol) and the reaction mixture was stirred at room temperature for 4 hours. The resulting precipitate was removed by filtration and the filtrate was concentrated *in vacuo* to give the phosphonium salt **205** as a white solid (11.4 g, 62%), which was taken directly onto the next step without any purification.

(*E*)-methyl 4-(triphenylphosphoranylidene)but-2-enoate 208

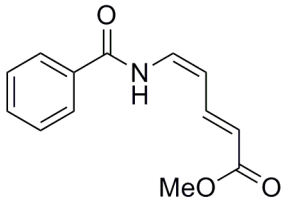


208

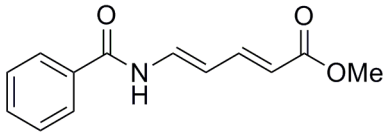
Phosphonium salt **205** (11.40 g, 26.0 mmol) was taken up in water (200 mL) and stirred until homogenous (12 hours). Aqueous sodium hydroxide (100 mL) was added dropwise, which caused a yellow precipitate to form immediately. The reaction mixture was extracted with dichloromethane (3 x 200 mL) and the combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the product **208** as an orange solid. The crude orange solid was ground using a pestle and mortar and dried under high vacuum overnight. The fine powder obtained could be used in the subsequent steps without any further purification (6.89 g, 74 %).

General Conditions for the synthesis of dienamides

(2E,4Z)-methyl 5-benzamidopenta-2,4-dienoate 206



206 (*Z,E*)



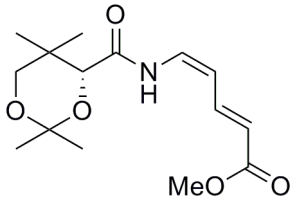
206 (*E,E*)

A suspension of imide **121** (0.10 g, 0.7 mmol) in dichloromethane (10 mL) was treated with ylide **208** (0.73 g, 2.1 mmol) and the resulting suspension was refluxed overnight. The reaction mixture was concentrated *in vacuo* to give a crude brown oil. Purification of the crude oil by flash chromatography (silica gel, 10% ethyl acetate in petroleum ether + 1% triethylamine) afforded the desired dienamide products **206** as a separable 3:2 mixture in 100% overall yield (0.15 g).

206 (*Z,E*) ^{1}H NMR ($CDCl_3$) : δ = 8.33 (1H, bd, *J* = 8.6 Hz, *"cis alkene" CH*), 7.89–7.90 (1H, m, *aromatic CH*), 7.61–7.67 (4H, m, *4 x aromatic CH*), 7.30 (1H, dd, *J* = 10.9, 9.6 Hz, *"cis alkene" CH*), 5.97 (1H, d, *J* = 14.9 Hz, *"trans alkene" CH*), 5.66 (1H, dd, *J* = 12.3, 9.0 Hz, *"trans alkene" CH*), 3.73 (3H, s, *OCH_3*) ^{13}C NMR ($CDCl_3$) : δ = 167.7, 164.4, 136.6, 132.9, 132.7, 128.9, 128.6, 127.4, 119.4, 107.6, 51.7 HRMS found 231.0899, calc for $C_{13}H_{13}NO_3$ 231.0895 ν_{max} (neat)/cm^{-1} - 3308.0, 1683.9, 1666.5, 1626.0, 1602.9

206 (*E,E*) ^{1}H NMR ($CDCl_3$) : δ = 7.99 (1H, bd, *J* = 12.3 Hz, *alkene CH*), 7.85–7.87 (1H, m, *aromatic CH*), 7.51–7.64 (4H, m, *4 x aromatic CH*), 7.41 (1H, dd, *J* = 15.2, 11.4 Hz, *alkene CH*), 6.12 (1H, dd, *J* = 14.1, 11.9 Hz, *alkene CH*), 5.86 (1H, d, *J* = 15.2 Hz, *alkene CH*), 3.78 (3H, s, *OCH_3*) ^{13}C NMR ($CDCl_3$) : δ = 166.6, 163.5, 142.5, 132.1, 131.6, 127.8, 126.3, 116.9, 110.2, 50.5 HRMS found 231.0897, calc for $C_{13}H_{13}NO_3$ 231.0895 ν_{max} (neat)/cm^{-1} 3304.1, 1670.4, 1622.2, 1608.7, 1583.6 cm^{1}.

(2E,4Z)-methyl 5-((*R*)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamido)penta-2,4-dienoate 207

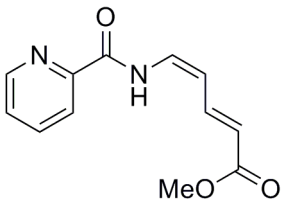


207 (*Z,E*)

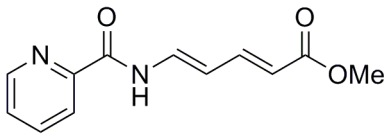
Dienamide **207** was prepared following the same procedure as above, starting with imide **192** (0.20 g, 0.93 mmol) and ylide **208** (1.00 g, 2.8 mmol) to give the product **207** (0.15 g, 52%) as a single stereoisomer after flash chromatography.

^{1}H NMR ($CDCl_3$) : δ = 8.73 (1H, bd, *J* = 11.9 Hz, *NH*), 7.46 (1H, dd, *J* = 14.5, 12.6 Hz, *"trans alkene" CH*), 7.03 (1H, dd, *J* = 11.5, 9.4 Hz, *"cis alkene" CH*), 5.93 (1H, d, *J* = 14.9 Hz, *"trans alkene" CH*), 5.58 (1H, dd, *J* = 11.7, 9.3 Hz, *"cis alkene" CH*), 4.24 (1H, s, *CH*), 3.80 (3H, s, *OCH_3*), 3.75 (1H, d, *J* = 12.4 Hz, *CH_2*), 3.36 (1H, d, *J* = 12.4 Hz, *CH_2*), 1.60 (3H, s, *CH_3*), 1.50 (3H, s, *CH_3*), 1.10 (3H, s, *CH_3*), 1.06 (3H, s, *CH_3*) ^{13}C NMR ($CDCl_3$) : δ = 167.5, 167.1, 136.3, 126.7, 119.6, 107.7, 99.6, 76.7, 71.3, 51.7, 33.4, 29.4, 22.0, 18.9, 18.7 HRMS found 297.1572, calc for $C_{15}H_{23}NO_5$ 297.1576 ν_{max} (neat)/cm^{-1} 2962.8, 1699.3, 1660.8, 1626.0 cm^{-1} $[\alpha]_D$ +3.84 (c = 1.0, $CHCl_3$).

(2E,4Z)-methyl 5-(picolinamido)penta-2,4-dienoate 209



209 (*Z,E*)



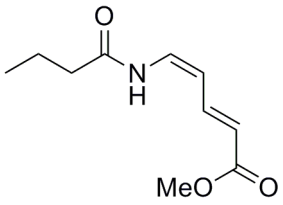
209 (*E,E*)

Dienamides **209** were prepared following the same procedure as above, starting with imide **194** (0.10 g, 0.66 mmol) and ylide **188** (0.72 g, 2.0 mmol) to give the products **209** (0.13 g, 87%) as an inseparable mixture of stereoisomers after flash chromatography.

^{1}H NMR ($CDCl_3$) : δ = **209 (*Z,E*)** 10.27 (1H, bd, *J* = 11.5 Hz, *NH*), 7.82–7.86 (2H, m, *2 x aromatic CH*), 7.65 (1H, dd, *J* = 12.2, 14.9 Hz, *"trans alkene" CH*), 7.39–7.47 (2H, m, *2 x aromatic CH*), 7.14 (1H, dd, *J* = 11.7, 9.1 Hz, *"cis alkene" CH*), 5.88 (1H, d, *J* = 14.9 Hz, *"trans alkene" CH*), 5.59 (1H, dd, *J* = 8.9, 12.2 Hz, *"cis alkene" CH*), 3.73 (3H, s, *OCH_3*) **209 (*E,E*)** 9.88 (1H, bd, *J* = 10.4 Hz, *NH*), 8.52–8.60 (2H, m, *2 x aromatic CH*), 8.15 (2H, m, *2 x aromatic CH*), 7.39–7.47 (1H, dd,

J = 15.2, 11.3 Hz, *"trans alkene" CH*), 7.33 (1H, dd, *J* = 13.2, 11.0, Hz, *"trans alkene" CH*), 6.11 (1H, dd, *J* = 13.3, 11.3 Hz, *"trans alkene" CH*), 5.78 (1H, d, *J* = 15.2 Hz, *"trans alkene" CH*), 3.68 (3H, s, *OCH_3*) ^{13}C NMR ($CDCl_3$) : δ = 167.6, 161.3, 148.4, 148.3, 137.7, 136.7, 127.6, 127.1, 122.8, 119.5, 108.3, 51.6 HRMS found 232.0850, calc for $C_{12}H_{12}N_2O_3$ 232.0848 ν_{max} (neat)/cm^{-1} 3362, 1705, 1627, 1618 cm^{-1}.

(2E,4Z)-methyl 5-butyramidopenta-2,4-dienoate 210

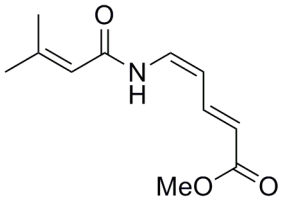


210 (*Z,E*)

Dienamide **210** was prepared following the same procedure as above, starting with imide **197** (0.10 g, 0.87 mmol) and ylide **208** (0.94 g, 2.6 mmol) to give the product **210** (0.07 g, 42%) as a single stereoisomer after flash chromatography.

^{1}H NMR ($CDCl_3$) : δ = 8.36 (1H, bd, *J* = 11.2 Hz, *NH*) *7.*54 (1H, dd, *J* = 14.8, 12.1 Hz, *"trans alkene" CH*), 6.99 (1H, dd, *J* = 11.8, 9.0 Hz, "*cis alkene" CH*), 5.80 (1H, d, *J* = 14.9 Hz, *"trans alkene" CH*), 5.42 (1H, d, *J* = 12.2, 9.0 Hz, *"cis alkene" CH*), 3.70 (3H, s, *OCH_3*), 2.25 (2H, t, *J* = 7.3 Hz, *CH_2*), 1.60–1.71 (2H, m, *CH_2*), 0.92 (3H, t, *J* = 7.4 Hz, *CH_3*) ^{13}C NMR ($CDCl_3$) : δ = 170.9, 168.0, 137.6, 128.7, 118.4, 106.3, 51.1, 38.4, 18.8, 13.7 HRMS found 198.1128, calc for $C_9H_{15}NO_3$ 198.1130 ν_{max} (neat)/cm^{-1} 2987, 1707, 1629 cm^{-1}

(2E,4Z)-methyl 5-(3-methylbut-2-enamido)penta-2,4-dienoate 211



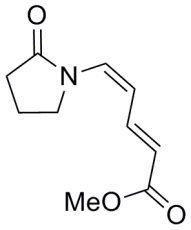
211 (*Z,E*)

Dienamide **211** was prepared following the same procedure as above, starting with imide **200** (0.17 g, 1.3 mmol) and ylide **208** (1.40 g, 3.9 mmol) to give the product **211** (0.11 g, 41%) as a single stereoisomer after flash chromatography.

^{1}H NMR ($CDCl_3$) : δ = 7.71 (1H, bd, *J* = 11.6 Hz, *NH*), 7.47 (1H, ddd, *J* = 14.9, 12.2, 0.9 Hz, *"trans alkene" CH*), 7.06 (1H, dd, *J* = 11.8, 9.0 Hz, *"cis alkene" CH*), 5.78 (1H, d, *J* = 14.9 Hz, *"trans alkene" CH*), 5.63 (1H, bs, *trisubstitued alkene*

CH), 5.42 (1H, dd, *J* = 12.2, 9.0 Hz, *"cis alkene" CH*), 3.68 (3H, s, OCH_3), 2.16 (3H, d, *J* = 0.8 Hz, CH_3), 1.85 (3H, d, *J* = 1.2 Hz, CH_3) ^{13}C NMR ($CDCl_3$) : δ = 168.0, 163.3, 137.2, 129.0, 125.9, 118.3, 117.1, 105.9, 51.8, 27.9, 20.5 HRMS found 210.1128, calc for $C_{11}H_{15}NO_3$ 210.1130 ν_{max} (neat)/cm^{-1} 3010, 1730, 1701, 1658, 1639, 1624 cm^{-1}.

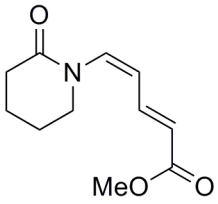
(2E,4Z)-methyl 5-(2-oxopyrrolidin-1-yl)penta-2,4-dienoate 212



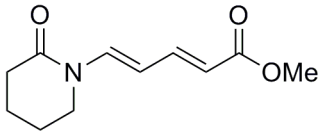
212 (*Z,E*)

Dienamide **212** was prepared following the same procedure as above, starting with imide **117b** (0.10 g, 0.8 mmol) and ylide **208** (0.92 g, 2.5 mmol) to give the product **212** (0.09 g, 56%) as a single stereoisomer after flash chromatography.
^{1}H NMR ($CDCl_3$) : δ = 7.65 (1H, appt, *J* = 13.6 Hz, *"trans alkene" CH*), 6.85 (1H, d, *J* = 9.9 Hz, *"cis alkene" CH*), 5.76 (1H, d, *J* = 14.9 Hz, *"trans alkene" CH*), 5.46 (1H, dd, *J* = 12.3, 10.6 Hz, *"cis alkene" CH*), 3.93 (2H, t, *J* = 7.1 Hz, CH_2), 3.68 (3H, s, OCH_3), 2.42 (2H, t, *J* = 8.1Hz, CH_2), 2.11 (2H, qn, *J* = 7.5Hz, CH_2) ^{13}C NMR ($CDCl_3$) : δ = 174.8, 167.7, 138.9, 128.0, 119.8, 107.5, 51.6, 48.8, 29.8, 18.2 HRMS found 195.0898, calc for $C_{10}H_{13}NO_3$ 195.0895 ν_{max} (neat)/cm^{-1} 1749, 1699, 1614 cm^{-1}

(2E,4Z)-methyl 5-(2-oxopiperidin-1-yl)penta-2,4-dienoate 213



213 (*Z,E*)

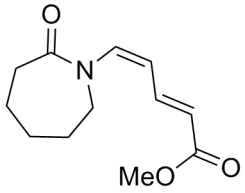


213 (*E,E*)

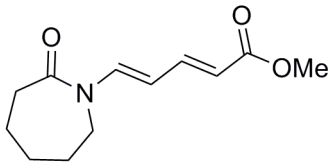
Dienamides **213** were prepared following the same procedure as above, starting with imide **117c** (0.20 g, 1.60 mmol) and ylide **208** (1.70 g, 4.70 mmol) to give the products **213** (0.11 g, 35%) as an inseparable mixture of stereoisomers after flash chromatography.
^{1}H NMR ($CDCl_3$) : δ = **213 (*Z,E*)** 7.56 (1H, appt, *J* = 13.4 Hz, *"trans alkene" CH*), 7.04 (1H, d, *J* = 9.8 Hz, *"cis alkene" CH*), 5.74 (1H, d, *J* = 14.9 Hz, *"trans alkene"*

CH), 5.54 (1H, dd, *J* = 12.1, 10.6 Hz, *"cis alkene" CH*), 3.73 (2H, *J* = 5.6 Hz, CH_2), 3.70 (3H, s, OCH_3), 2.48 (2H, t, *J* = 5.8 Hz, CH_2), 1.75 -1.85 (4H, m, *2 x* CH_2). **213 (*E,E*)** characteristic peaks 7.87 (1H, d, *J* = 14.5 Hz, *"trans alkene" CH*), 7.32 (1H, dd, *J* = 15.6, 10.8 Hz, *"trans alkene" CH*) ^{13}C NMR ($CDCl_3$) : δ = **213 (*Z,E*)** 169.9, 167.6, 139.2, 133.0, 120.7, 111.3, 51.6, 50.8, 32.6, 23.3, 20.8 **213 (*E,E*)** 168.9, 167.6, 144.5, 136.6, 117.7, 108.4, 51.4, 45.4, 33.0, 22.4, 20.3 HRMS found 209.1057, calc for $C_{11}H_{15}NO_3$ 209.1052 ν_{max} (neat)/cm^{-1} 1707, 1660, 1614 cm^{-1}.

(2E,4Z)-methyl 5-(2-oxoazepan-1-yl)penta-2,4-dienoate 214



214 (*Z,E*)

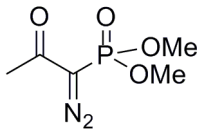


214 (*E,E*)

Dienamides **214** were prepared following the same procedure as above, starting with imide **117d** (0.20 g, 1.40 mmol) and ylide **208** (1.60 g, 4.30 mmol) to give the products **214** (0.18 g, 56%) as an inseparable mixture of stereoisomers after flash chromatography.

^{1}H NMR ($CDCl_3$) : δ = **214 (*Z,E*)** 7.40 (1H, ddd, *J* =15.1, 12.1, 1.0 Hz, *"trans alkene" CH*), 6.85 (1H, d, *J* = 9.1 Hz, *"cis alkene" CH*), 5.79 (1H, d, *J* = 15.1 Hz, *"trans alkene" CH*), 5.58 (1H, ddd, *J* = 12.1, 9.0, 0.7 Hz, *"cis alkene" CH*), 3.68 (3H, s, OCH_3), 3.66–3.69 (2H, m, CH_2), 2.57–2.62 (2H, m, CH_2), 1.77–1.80 (2H, m, CH_2), 1.70–1.75 (4H, m, *2 x* CH_2) **214 (*E,E*)** 7.66 (1H, d, *J* = 14.5 Hz, *"trans alkene" CH*), 7.32 (1H, ddd, *J* = 15.0, 11.1, 0.8 Hz, *"trans alkene" CH*), 5.71 (1H, d, *J* = 14.9 Hz, *"trans alkene" CH*), 5.70 (1H, appt, *J* = 12.0 Hz, *"trans alkene" CH*), 3.66 (3H, s, OCH_3), 3.66–3.69 (2H, m, CH_2), 2.57–2.62 (2H, m, CH_2), 1.77–1.80 (2H, m, CH_2), 1.70–1.75 (4H, m, *2 x* CH_2) ^{13}C NMR ($CDCl_3$) : δ = **214 (*Z,E*)** 176.0, 167.4, 138.5, 135.4, 120.7, 113.2, 51.7, 37.3, 37.1, 29.6, 28.8, 23.4. **214 (*E,E*** 174.5, 167.7, 144.8, 136.7, 117.0, 107.7, 51.4, 45.3, 37.0, 29.3, 27.4, 23.5 HRMS found 224.1284, calc for $C_{12}H_{17}NO_3$ 224.1287 ν_{max} (neat)/cm^{-1} 1708, 1662, 1653, 1624 cm^{-1}.

Conditions for the synthesis of dimethyl 1-diazo-2-oxopropylphosphonate 243



243

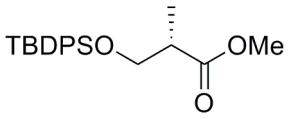
A suspension of recrystallised tosyl chloride (2.00 g, 10.5 mmol) in ethanol (12 mL) was treated with a solution of sodium azide (0.82 g, 12.6 mmol) in water (3 mL) and the reaction mixture was stirred for 1 hour before being allowed to stand for 1 hour at room temperature. The reaction mixture was poured onto water (50 mL) and the oily layer separated and washed with water (3 x 5 mL). This was then dried over anhydrous sodium sulfate to give tosyl azide in 28% yield (572 mg). This was characterised by IR spectroscopy (azide signal) and ^{1}H NMR spectroscopy (tosyl signals).

A suspension of sodium hydride (washed with petroleum ethers and dried under vacuum, 0.07 g, 2.90 mmol) in benzene : tetrahydrofuran (1:1 mixture, 4.0 mL total vol.) was cooled in an ice-bath and treated with dimethyl (2-oxopropyl) phosphonate (0.16 mL, 1.20 mmol). A solution of the previously prepared tosyl azide (0.58 g, 2.90 mmol) in benzene (8 mL) was added and the reaction mixture allowed to warm to room temperature. After 2.5 hours the reaction mixture was filtered through celite and the filtrate concentrated *in vacuo* to give a brown oil. The crude oil was purified by flash chromatography (silica gel, 5% ethyl acetate in petroleum ethers then 1:1 dichloromethane : methanol) to give the desired product **243** as a colourless oil (0.2 g, 90%).

^{1}H NMR ($CDCl_3$) : δ = 2.29 (s, 3H, *CH_3*), 3.87 (d, 6H, *J* = 16.0 Hz, *2 x OCH_3*)

4.2 Crocacin C

(*S*)-methyl 3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropanoate 261

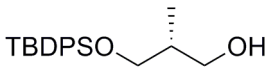


261

To a solution of (*S*)-(-)-3-hydoxy-2-methyl propionic acid methyl ester (5.00 mL, 45.1 mmol) in dichloromethane (50 mL) at 0 ºC was added imidazole (3.38 g, 49.6 mmol) and *t*-butyldiphenylsilyl chloride (11.7 mL, 45.1 mmol) dropwise. The reaction mixture was warmed to room temperature and then stirred overnight. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (40 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic phases were washed with saturated aqueous ammonium chloride solution (40 mL), dried over anhydrous sodium sulfate and the solvent was removed *in vacuo* to give the desired protected ester **261** as an analytically pure colourless oil (15.4 g, 96%).

^{1}H NMR ($CDCl_3$) : δ = 7.57-7.59 (4H, m, *4 x aromatic CH*), 7.29-7.38 (6H, m, *6 x aromatic CH*), 3.63-3.77 (2H, m, CH_2), 3.61 (3H, s, OCH_3), 2.62-2.67 (1H, m, *CH*), 1.08 (3H, d, *J* = 7.2 Hz, CH_3), 0.96 (9H, s, *3 x* ^{t}*Bu* CH_3) ^{13}C NMR ($CDCl_3$) : δ = 175.4, 135.6, 133.6, 129.7, 127.7, 51.6, 66.0, 42.5, 26.8, 19.3, 13.5 HRMS found 357.5448, calc for $C_{21}H_{38}O_3Si$ 357.5450 ν_{max} (neat)/cm^{-1} 1739, 2858, 2931 $[\alpha]_D$ -161.6 (c = 1.0, $CHCl_3$)

(*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropan-1-ol 262



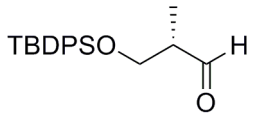
262

To a suspension of ester **261** (2.00g, 5.60 mmol) in dichloromethane (20 mL) at 0 ºC was added diisobutylaluminium hydride (1.0 M in hexanes, 12.3 mL, 12.3 mmol) dropwise and the reaction mixture was stirred at 0 ºC. After 1 hour the reaction mixture was quenched with a saturated aqueous solution of Rochelle's Salt (20 mL) and stirred at room temperature until two clear layers formed (3 hours). The layers were separated and the aqueous phase extracted with ethyl acetate (2 x 20 mL). The combined organic phases were dried over anhydrous sodium sulfate and the solvent removed *in vacuo* to give a crude colourless oil.

Purification by flash chromatography (silica gel, 10% ethyl acetate in petroleum ether) gave the desired primary alcohol **262** as a colourless oil (1.60g, 87%).

^{1}H NMR ($CDCl_3$) : δ = 7.59-7.61 (4H, m, *4 x aromatic CH*), 7.31-7.39 (6H, m, *6 x aromatic CH*), 3.49-3.67 (4H, m, *2 x* CH_2), 2.46-2.49 (1H, m*, CH)*, 0.99 (9H, s, *3 x* ^{t}*Bu* CH_3), 0.75 (3H, d, *J* = 7.2 Hz, CH_3) ^{13}C NMR ($CDCl_3$) : δ = 135.6, 133.2, 129.8, 127.8, 68.6, 67.5, 36.1, 26.7, 18.9, 13.3 HRMS found 329.5348, calc for $C_{20}H_{28}O_2Si$ 329.5346 ν_{max} (neat)/cm^{-1} 1739.8, 2858.6, 2929.9, 2958.9 $[\alpha]_D$ -58.00 (c = 1.0, $CHCl_3$)

(*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropanal 263



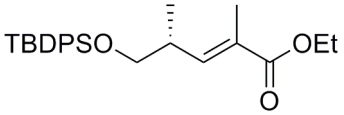
263

To a suspension of oxalyl chloride (1.65 mL, 19.5 mmol) in dichloromethane (20 mL) at -78 ºC was added dimethylsulfoxide (2.77 mL, 39.0 mmol) and the mixture was stirred for 5 minutes before a solution of alcohol **262** (3.20 g, 9.80 mmol) in dichloromethane (30 mL) was added. The reaction mixture was stirred at -78 ºC for 1 hour before triethylamine (10.9 mL, 78.0 mmol) was added and the mixture warmed to room temperature. After 1 hour at room temperature the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (30 mL). The aqueous phase was extracted with dichloromethane (2 x 30 mL) and combined organic phases washed with brine (40 mL) before drying over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give a crude yellow oil. The crude oil was purified by column chromatography (silica gel, 20% ethyl acetate in petroleum ether) to give the desired aldehyde **263** as a yellow oil (2.91 g, 92%).

^{1}H NMR ($CDCl_3$) : δ = 9.69 (1H, d, *J* = 1.7 Hz, *CHO*), 7.56-7.58 (4H, m, *4 x aromatic CH*), 7.30-7.40 (6H, m, *6 x aromatic CH*), 3.75-3.85 (2H, m, CH_2), 2.61 (1H, m*, CH*), 1.03 (3H, d, *J* = 6.9 Hz*,* CH_3), 0.97 (9H, s, *3 x* ^{t}*Bu* CH_3)

NB. The product is unstable and therefore it was taken directly onto the next step without further analysis.

(*R,E*)-ethyl 5-((*tert*-butyldiphenylsilyl)oxy)-2,4-dimethylpent-2-enoate 264 (*E*)



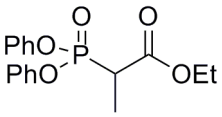
264 (*E*)

To a suspension of aldehyde **263** (0.20 g, 0.60 mmol) in benzene (10 mL) was added (carbethoxyethylidene)triphenylphosphorane (0.67 g, 0.18 mmol) and the reaction mixture heated to reflux overnight. The solvent was removed *in vacuo* to give a crude yellow oil. Purification of this crude oil by flash chromatography (silica gel, 10% ethyl acetate in petroleum ether) gave the *E*-conjugated ester **264 (*E*)** as a single isomer in the form of a colourless oil (0.18 g, 76%).

^{1}H NMR ($CDCl_3$) : δ = 7.57-7.59 (4H, m, *4 x aromatic CH*), 7.29-7.37 (6H, m, *6 x aromatic CH*), 6.51 (1H, d, *J* = 9.7 Hz, *alkene CH*), 4.08-4.14 (2H, m, *CH_2*), 3.47 (2H, d, *J* = 6.8 Hz, *ethyl CH_2*), 2.63-2.71 (1H, m, *CH*), 1.73 (3H, s, *ethyl CH_3*), 1.22 (3H, t, *J* = 7.4 Hz, *CH_3*), 0.97 (9H, s, *3 x ^{t}Bu CH_3*)

^{13}C NMR ($CDCl_3$) : δ = 167.3, 143.5, 134.6, 128.6, 126.6, 119.6, 114.3, 75.7, 66.7, 59.5, 35.1, 25.8, 15.3, 13.3, 11.6 HRMS found 411.6365, calc for $C_{25}H_{34}O_3Si$ 411.6366 ν_{max} (neat)/cm^{-1} 1694.0, 1700.8, 2859.6, 2963.2 $[\alpha]_D$ -2.400 (c = 1.0, $CHCl_3$)

Ethyl 2-(diphenoxyphosphoryl)propanoate 270

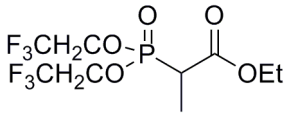


270

A suspension of diphenylphosphite (3.83 mL, 20.0 mmol) in dichloromethane (20 mL) was cooled to 0 °C in an ice-bath before treating with ethyl 2-bromopropionate (2.60 mL, 20.0 mmol) and triethylamine (3.90 mL, 28.0 mmol). The reaction mixture was stirred at 0 °C for 30 minutes before removing the ice-bath and stirring at room temperature for a further 2 hours. The mixture was quenched with water (20 mL) and the aqueous phase was extracted into a mixture of ethyl acetate : hexane (3:1, 80 mL total volume). The combined organic phases were washed with saturated brine (20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a colourless oil. This was purified by flash chromatography (silica gel, 10% ethyl acetate in petroleum ether) to give the desired product **270** as a colourless oil (3.86 g, 58%).

^{1}H NMR ($CDCl_3$) – δ : 7.17-7.37 (m, 10H, *10 x aromatic CH*), 4.39 (q, 1H, *J* = 8.0 Hz, *CH*), 4.27 (q, 2H, *J* = 8.0 Hz, *ethyl* CH_2), 1.86 (d, 3H, *J* = 8.0 Hz, *ethyl* CH_3), 1.34 (t, 3H, *J* = 8.0 Hz, CH_3)

Ethyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)propanoate 273

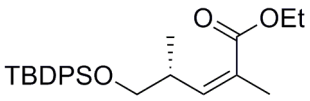


273

Triethyl 2-phosphonoacetate (10.0 g, 4.20 mmol) was cooled to 0 ºC and treated with phosphorous pentachloride (21.8 g, 10.5 mmol). The neat mixture was stirred at room temperature for 1 hour followed by 3 hours at 75 ºC. Distillation removed the $POCl_3$ by-product and excess PCl_5 (RT-80ºC, 20mm-0.1mm), affording the dichloride intermediate as a clear oil. This was dissolved in benzene (60 mL) and cooled to 0 ºC before treating with a solution of trifluoroethanol (5.13 mL, 7.01 mmol) and *N,N*-diisopropylethylamine (12.20 mL, 7.01 mmol) in benzene (20 mL). The reaction mixture was stirred at 0 ºC for 1 hour before removing the solvent *in vacuo* to give a crude yellow oil. Purification by flash chromatography (silica gel, 50% ethyl acetate in petroleum ether) gave the desired (trifluoroethyl)phosphonate ester **273** as a pale yellow oil (6.89 g, 47%).

^{1}H NMR ($CDCl_3$) – δ : 4.14-4.55 (6H, m, *3 x* CH_2), 3.30-3.41 (m, 1H, *CH*), 1.29-1.50 (m, 6H, *2 x* CH_3)

(*R,Z*)-ethyl 5-((*tert*-butyldiphenylsilyl)oxy)-2,4-dimethylpent-2-enoate 264 (*Z*)



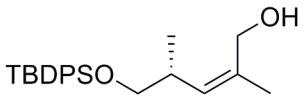
264 (*Z*)

To a suspension of Still-Gennari reagent **273** (5.95 g, 17.2 mmol) in tetrahydrofuran (60 mL) at -78 ºC was added potassium hexamethyldisilazine (0.5 M in toluene, 32.4 mL, 1.61 mmol) and 18-crown-6 (recrystallised from acetonitrile, 22.7 g, 86.0 mmol) and the reaction mixture stirred at -78 ºC for 1 hour. A solution of aldehyde **263** (3.30 g, 10.1 mmol) in tetrahydrofuran (20 mL) was added and the reaction mixture allowed to warm to room temperature. After 1 hour at room temperature the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (40 mL) and the aqueous phase extracted into hexane (2 x 50 mL). Combined organic phases were dried over anhydrous sodium sulfate and the solvent removed *in vacuo* to give a crude brown oil. Purification by column

chromatography (silica gel, 20% ethyl acetate in petroleum ether) gave the *Z*-conjugated ester **264 (*Z*)** as a single isomer in the form of a pale yellow oil (3.25 g, 78%).

^{1}H NMR ($CDCl_3$) : δ = 7.57-7.58 (4H, m, *4 x aromatic CH*), 7.30-7.34 (6H, m, *6 x aromatic CH*), 5.69 (1H, d, *alkene CH*), 3.47 (2H, d, *J* = 9.6 Hz, *ethyl* CH_2), 3.31-3.33 (2H, m, CH_2), 1.82-1.89 (4H, m, *alkene* CH_3 + *CH*), 1.18-1.22 (3H, m, *ethyl* CH_3), 0.97 (9H, s, *3 x* ^{t}*Bu* CH_3), 0.76-0.80 (3H, m, CH_3) ^{13}C NMR ($CDCl_3$) : δ = 168.1, 145.2, 135.7, 133.9, 127.8, 127.6, 127.3, 68.3, 60.1, 36.3, 28.8, 20.9, 19.3, 16.9, 14.3 HRMS found 433.6175, calc for $C_{25}H_{34}O_3Si$ 433.6184 ν_{max} (neat)/cm^{-1} 1589.9, 1694.5, 2587.1, 2930.4 $[\alpha]_D$ -13.200 (c = 1.0, $CHCl_3$)

(*R,Z*)-5-((*tert*-butyldiphenylsilyl)oxy)-2,4-dimethylpent-2-en-1-ol 274

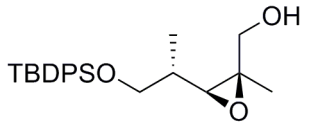


274

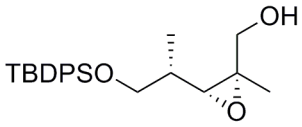
To a suspension of ester **264 (*Z*)** (1.20 g, 2.92 mmol) in diethyl ether (40 mL) was cooled to 0 ºC before treating with diisobutylaluminium hydride (1.0M in hexanes, 8.80 mL, 8.77 mmol) and the mixture stirred at 0 ºC for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of Rochelle's salt (40 mL) and stirred at room temperature until two clear layers had formed (3 hours). The layers were separated and the aqueous phase extracted into ethyl acetate (2 x 20 mL). The combined organic phases were dried over anhydrous sodium sulfate and the solvent removed *in vacuo* to give a crude yellow oil. Purification by flash chromatography (silica gel, 20% ethyl acetate in petroleum ether) gave the desired allylic alcohol **274** as a pale yellow oil (0.82 g, 75%).

^{1}H NMR ($CDCl_3$) : δ = 7.51-7.54 (4H, m, *4 x aromatic CH*), 7.24-7.30 (6H, m, *6 x aromatic CH*), 4.90 (1H, d, *J* = 9.9 Hz, *alkene CH*), 4.01-4.04 (1H, m, CH_2-*OH*), 3.78-3.83 (1H, m, CH_2-*OH*), 3.43-3.38 (1H, m, CH_2), 3.15-3.19 (1H, m, CH_2), 2.64-2.68 (1H, m, *CH*), 1.69 (3H, s, CH_3), 0.91 (9H, s, *3 x* ^{t}*Bu* CH_3), 0.76 (3H, d, *J* = 6.7 Hz, CH_3) ^{13}C NMR ($CDCl_3$) : δ = 135.9, 133.4, 131.8, 129.7, 127.7, 68.8, 35.0, 26.9, 22.0, 19.2, 17.5 HRMS found 368.2176 calc for $C_{23}H_{32}O_2Si$ 368.2172

((*2R,3S*)-3-((*S*)-1-((tert-butyldiphenylsilyl)oxy)propan-2-yl)-2-methyloxiran-2-yl)methanol 275



275a



275b

To a suspension of allylic alcohol **274** (0.50 g, 1.40 mmol) in dichloromethane (10 mL) was added potassium phosphate dibasic (0.93 g, 4.10 mmol) and the reaction mixture cooled down to -5 ºC. A solution of *m*-chloroperbenzoic acid (0.40 g, 1.60 mmol) in dichloromethane (10 mL) was added dropwise and the reaction mixture stirred at -5 ºC for 4 hours. The reaction mixture was quenched with a saturated aqueous solution of sodium thiosulphate (20 mL) and allowed to warm to room temperature. After 1 hour at room temperature the mixture was poured onto a diethyl ether : water mixture (2:1, 60 mL total volume) and the aqueous phase extracted into diethyl ether (2 x 20 mL). The combined organic phases were dried over anhydrous sodium sulfate and the solvent removed *in vacuo* to give a crude colourless oil. Purification by flash chromatography gave two diastereoisomers **275a-b** as two separable colourless oils (0.47 g, 90% total yield). The ratio of the two products is 3:1 although the stereochemistry of each has still to be determined.

Major diastereoisomer:

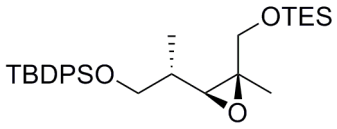
^{1}H NMR ($CDCl_3$) : δ = 7.59-7.61 (4H, m, *4 x aromatic CH*), 7.29-7.37 (6H, m, *6 x aromatic CH*), 3.51-3.69 (4H, m, *2 x* CH_2), 2.71 (1H, d, *J* = 9.5 Hz, *epoxide CH*), 1.57-1.63 (1H, m, *CH*), 1.33 (3H, s, CH_3), 0.99-1.01 (12H, m, *3 x* ^{t}*Bu* CH_3 + CH_3)

Minor diastereoisomer:

^{1}H NMR ($CDCl_3$) : δ = 7.68-7.70 (4H, m, *4 x aromatic CH*), 7.42-7.51 (6H, m, *6 x aromatic CH*), 3.76 (1H, d, *J* = 11.7 Hz, CH_2), 3.61-3.65 (2H, m, CH_2), 3.44 (1H, t, *J* = 10.0 Hz, CH_2), 2.63 (1H, d, *J* = 9.6 Hz, *epoxide CH*), 1.87-1.94 (1H, m, *CH*), 1.52 (3H, s, CH_3), 1.10 (9H, s, *3 x* ^{t}*Bu* CH_3), 0.98 (3H, d, *J* = 6.7 Hz, CH_3)

^{13}C NMR ($CDCl_3$) : δ = 135.2, 131.4, 131.2, 129.9, 129.6, 73.9, 67.5, 67.1, 61.7, 33.1, 28.4, 26.4, 20.5, 14.1 HRMS found 384.2119 calc for $C_{23}H_{32}O_3Si$ 384.2123

tert-butyl((_S_)-2-((_2S,3R_)-3-methyl-3-(((triethylsilyl)oxy)methyl)oxiran-2-yl)propoxy)diphenylsilane 277

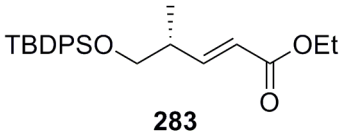


277

To a solution of epoxide **275a** (0.79 g, 2.10 mmol) in dichloromethane (20 mL) at room temperature was added *N,N*-diisopropylethylamine (0.54 mL, 3.10 mmol) and a catalytic amount of diaminopyridine (10 mg). The reaction mixture was treated with triethylchlorosilane (0.41 mL, 2.50 mmol) and stirred at room temperature for 20 minutes. The reaction mixture was diluted with diethyl ether (10 mL) and shaken with 0.2 M pH 5.5 phosphate buffer (20 mL). The organic phase was washed with water (20 mL), 0.2 M pH 7.0 phosphate buffer (20 mL) and brine (20 mL) before drying over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give a crude colourless oil which was filtered through a plug of silica gel (DCM wash) to give the desired protected epoxy alcohol **277** as a colourless oil (1.00 g, 98%).

^{1}H NMR ($CDCl_3$) : δ = 7.56-7.61 (4H, m, *4 x aromatic CH*), 7.28-7.36 (6H, m, *6 x aromatic CH*), 3.44-3.72 (4H, m, *2 x CH_2*), 2.63 (1H, d, *J* = 9.4 Hz, *epoxide CH*), 1.58-1.66 (1H, m, *CH*), 1.29 (3H, s, *CH_3*), 0.99 (9H, s, *3 x ^{t}Bu CH_3*), 0.81-0.91 (12H, m, *3 x ethyl CH_3 + CH_3*), 0.51-0.57 (6H, m, *3 x ethyl CH_2*) ^{13}C NMR ($CDCl_3$) : δ = 139.6, 138.3, 138.1, 133.2, 127.3, 125.6, 75.3, 67.2, 61.5, 32.4, 29.3, 24.5, 20.1, 14.6, 12.1, 11.7, 11.3, 7.1 HRMS found 498.2983, calc for $C_{29}H_{46}O_3Si_2$ 498.2985

(_R,E_)-ethyl 5-(_tert_-butyldiphenylsilyloxy)-4-methylpent-2-enoate 283

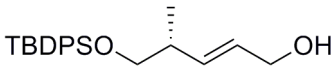


283

A suspension of aldehyde **263** (1.59g, 4.90 mmol) in benzene (20 mL) was added (carbethoxymethylene) triphenyl phosphorane (5.10g, 14.6 mmol) and the reaction mixture was refluxed at 80 °C for 18 hours overnight. The reaction mixture was concentrated *in vacuo* to give a crude brown oil. This was purified by flash chromatography (silica gel, 20% ethyl acetate in petroleum ethers) to give *α,β*-unsaturated ester **283** as a pale brown oil (1.78 g, 92%).

^{1}H NMR ($CDCl_3$) : δ = 7.56-7.58 (m, 4H, *4 x aromatic CH*), 7.29-7.33 (m, 6H, *6 x aromatic CH*), 6.89 (q, 1H, *J* = 8.0 Hz, *alkene CH*), 4.12 (q, 2H, *J* = 8.0 Hz, CH_2), 3.50 (q, 2H, *J* = 4.0 Hz, CH_2), 2.48-2.54 (m, 4H, *CH + alkene* CH_3), 1.19-1.24 (m, 6H, *2 x* CH_3), 0.98 (s, 9H, *3 x* ^{t}*Bu* CH_3) ^{13}C NMR ($CDCl_3$) : δ = 167.9, 147.3, 134.6, 130.1, 129.6, 123.7, 71.2, 62.5, 38.9, 32.3, 27.4, 17.5, 14.2, 13.6 HRMS found 410.2274, calc for $C_{25}H_{34}O_3Si$ 410.2277

Conditions for the synthesis of (R,E)-5-(tert-butyldiphenylsilyloxy)-4-methylpent-2-en-1-ol 282

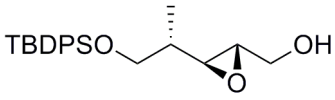


282

A suspension of ester **283** (1.15 g, 3.00 mmol) in diethyl ether (30 mL) was cooled to 0 °C in an ice-bath and treated with diisobutylaluminium hydride (1.0M in hexanes, 9.00 mL, 9.00 mmol) and the reaction mixture stirred for 2 hours at 0 °C before being allowed to warm to room temperature overnight. The reaction mixture was quenched by addition of saturated aqueous Rochelle's salt (30 mL) and stirred at room temperature for 1 hour. The aqueous phase was extracted into ethyl acetate (2 x 30 mL) and the combined organic phases were dried over anhydrous sodium sulphate before concentrating *in vacuo* to give a colourless oil. This was purified by flash chromatography (silica gel, 20% ethyl acetate in petroleum ethers) to give the desired allylic alcohol **282** as a colourless oil (0.80 g, 75%).

^{1}H NMR ($CDCl_3$) : δ = 7.68-7.69 (m, 4H, *4 x aromatic CH*), 7.39-7.48 (m, 6H, *6 x aromatic CH*), 5.65-5.68 (m, 1H, alkene *CH*), 4.10 (bs, 2H, CH_2-*OH*), 3.51-3.61 (m, 2H, CH_2), 2.41-2.47 (m, 1H, *CH*), 1.08 (s, 9H, *3 x* ^{t}*Bu* CH_3), 1.07 (m - obscured, 6H, *2 x* CH_3) ^{13}C NMR ($CDCl_3$) : δ = 134.5, 132.1, 130.0, 129.8, 125.8, 70.2, 69.8, 38.9, 22.1, 37.2, 17.8, 13.2 HRMS found 368.2171 calc for $C_{23}H_{32}O_2Si$ 368.2172

((*2S,3S*)-3-((*S*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)oxiran-2-yl)methanol 280



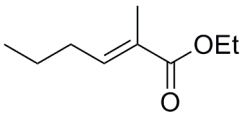
280

A suspension of allylic alcohol **282** (0.49 g, 1.40 mmol) in dichloromethane (10 mL) was cooled to 0 °C in an ice-bath before treating with potassium phosphate

dibasic (0.99 g, 4.30 mmol) and a solution of *m*-chloroperbenzoic acid (0.43 g, 1.70 mmol) in dichloromethane (10 mL) and reaction mixture stirred at 0 °C for 3 hours. Reaction mixture was then quenched with aqueous sodium thiosulfate solution (20 mL) and stirred at room temperature for 30 minutes. The mixture was then poured onto a diethyl ether : water mixture (1:1, 40 mL total volume) and the aqueous phase extracted into a further 20 mL diethyl ether. The combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a colourless oil. This was purified by flash chromatography (silica gel, 20% ethyl acetate in petroleum ethers) to give the desired epoxide **280** as a colourless oil (0.40 g, 75%) and as a single diastereoisomer.

^{1}H NMR ($CDCl_3$) : δ = 7.67-7.7 (m, 4H, *4 x aromatic CH*), 7.40-7.46 (m, 6H, *6 x aromatic CH*), 3.97 (d, 1H, *J* = 12.0 Hz, CH_2), 3.62-3.74 (m, 1H, CH_2), 2.95-3.12 (m, 2H, CH_2), 2.65 (s, 1H, *epoxide CH*) 1.66-1.77 (m, 1H, *CH*), 1.09 (s, 9H, *3 x* ^{t}*Bu* CH_3), 1.02 (app. t, 3H, CH_3)

(*E*)-ethyl 2-methylhept-2-enoate 290

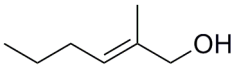


290

A suspension of valeraldehyde (0.71 mL, 6.6 mmol) in benzene (30 mL) was treated with (carbethoxyethylidene) triphenylphosphorane (7.25 g, 20.0 mmol) and the reaction mixture was refluxed at 80 °C for 18 hours overnight. The reaction mixture was concentrated *in vacuo* to give a crude yellow solid. This was purified by flash chromatography (silica gel, 20% ethyl acetate in petroleum ethers) to give the desired *α,β*-unsaturated ester **290** as a colourless oil (1.17 g, 100%).

^{1}H NMR ($CDCl_3$) : δ = 6.47-6.49 (m, 1H, *alkene CH*), 4.09-4.19 (m, 2H, CH_2), 2.11-2.18 (s, 3H, *alkene* CH_3), 2.01-2.08 (m, 2H, *ethyl* CH_2), 1.39-1.45 (m, 2H, CH_2), 1.32-1.27 (m, 3H, *ethyl* CH_3), 0.89-0.95 (m, 3H, CH_3) ^{13}C NMR ($CDCl_3$) : δ = 167.4, 140.4, 128.3, 52.6, 29.8, 23.3, 17.3, 16.9 HRMS found 156.1146, calc for $C_9H_{16}O_2$ 156.1150

(*E*)-2-methylhept-2-en-1-ol 293

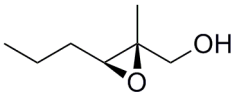


293

A suspension of ester **290** (0.50 g, 2.90 mmol) in diethyl ether (20 mL) was cooled to 0 °C in an ice-bath and treated with diisobutylaluminium hydride (1.0M in hexanes, 8.80 mL, 8.80 mmol) and the reaction mixture stirred at 0 °C for 4 hours. The reaction mixture was quenched with methanol and treated with celite (1.00 g) and sodium sulphate decahydrate (1.00 g) before stirring at room temperature for 30 minutes. The solids were removed by filtration and the filtrate concentrated *in vacuo* to give a colourless oil. This was purified by flash chromatography (silica gel, 20% ethyl acetate in petroleum ethers) to give the desired allylic alcohol **293** as a colourless oil (0.10 g, 27%).

^{1}H NMR ($CDCl_3$) : δ = 5.12-5.05 (m, 1H, *alkene CH*), 4.35 (s, 3H, *alkene* CH_3), 2.24-2.16 (m, 2H, CH_2), 1.78 (s, 3H, CH_3), 1.38-1.45 (m, 2H, CH_2), 0.89-1.01 (m, 3H, CH_3) ^{13}C NMR ($CDCl_3$) : δ = 135.6, 128.2, 70.2, 29.3, 22.7, 12.4, 14.6 HRMS found 114.1048 calc for $C_7H_{14}O$ 114.1045

(3-butyl-2-methyloxiran-2-yl)methanol 294



294

A suspension of allylic alcohol **293** (0.15 g, 1.20 mmol) in dichloromethane (20 mL) was cooled to 0 °C in an ice-bath before treating with potassium phosphate dibasic (0.81 g, 3.50 mmol) and a solution of *m*-chloroperbenzoic acid (0.35 g, 1.40 mmol) in dichloromethane (10 mL). Reaction mixture was stirred at 0 °C for 4 hours before quenching with aqueous sodium thiosulfate solution (20 mL) and stirring at room temperature for 1 hour. The mixture was poured onto a diethyl ether : water mixture (1:1, 40 mL total volume) and the aqueous phase extracted into diethyl ether (20 mL). Combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a colourless oil. This was purified by flash chromatography (silica gel, 20% ethyl acetate in petroleum ethers) to give the desired epoxide **294** as a colourless oil (0.06 g, 43%).

^{1}H NMR ($CDCl_3$) : δ = 3.76-3.51 (m, 2H, CH_2), 2.50-2.54 (m, 1H, *epoxide CH*), 1.28-1.43 (m, 4H, *2 x* CH_2), 1.31 (s, 3H, *epoxide* CH_3), 1.09-1.14 (m, 3H, CH_3) ^{13}C NMR ($CDCl_3$) : δ = 67.3, 64.5, 62.5, 31.3, 24.5, 22.3, 14.5

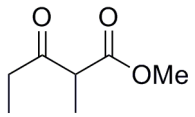
HRMS found 130.1002, calc for $C_7H_{14}O_2$ 130.0994

Samarium diiodide

1,2-diiodoethane was purified by dissolving in diethyl ether and washing with aqueous sodium thiosulfate then brine before drying over anhydrous sodium sulfate and concentrating *in vacuo*. It was stored under argon in the fridge until ready for use.

To an oven-dried round bottom flask was added samarium metal (0.38 g, 2.50 mmol) and the flask flushed with argon. 1,2-diiodoethane (0.56 g, 2.0 mmol) was added and the flask flushed once more with argon. Tetrahydrofuran (20 mL) was added and the reaction mixture heated gently in a water bath. After 1 hour the solution turned dark blue, indicating reaction completion. The solution was stored under argon in the fridge in the absence of light.

Methyl 2-methyl-3-oxopentanoate 307

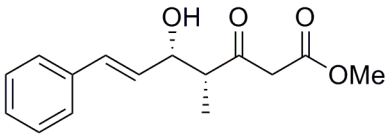


307

A suspension of potassium carbonate (1.93 g, 14.0 mmol) in acetone (20 mL) was treated with methyl propionyl acetate (1.88 mL, 15.0 mmol) and the reaction mixture stirred for 5 minutes before addition of iodomethane (1.15 mL, 18.0 mmol). The reaction mixture was refluxed at 60 °C overnight. The mixture was diluted with diethyl ether (20 mL) and filtered to remove the precipitate. The filtrate was concentrated *in vacuo* to give the desired product **307** as an orange oil (1.81 g, 90%).

^{1}H NMR ($CDCl_3$) : δ = 3.65 (s, 3H, *CH_3*), 3.47-3.51 (m, 1H, *CH*), 2.39-2.60 (m, 2H, *CH_2*), 1.25-1.30 (m, 3H, *CH_3*), 0.97-1.06 (m, 3H, *CH_3*) ^{13}C NMR ($CDCl_3$) : δ = 208.6, 171.0, 52.5, 52.2, 34.7, 12.8, 7.5 HRMS found 144.0783 calc for $C_7H1_2O_3$ 144.0786

(*4R,5S,E*)-methyl 5-hydroxy-4-methyl-3-oxo-7-phenylhept-6-enoate 309

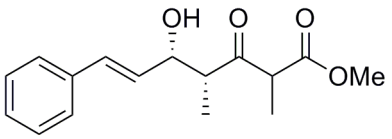


309

A suspension of sodium hydride (washed in petroleum ethers and dried under vacuum, 0.30 g, 12.6 mmol) in tetrahydrofuran (40 mL) was cooled to 0 °C in an ice-bath and treated with methyl propionyl acetate (1.50 mL, 10.5 mmol). The mixture was stirred for 5 minutes until the bubbling had stopped. The ice-bath was removed and the mixture stirred at room temperature for 10 minutes. The ice-bath was replaced again and the mixture treated with *n*-butyllithium (2.5M in hexanes, 5.04 mL, 12.6 mmol). The reaction mixture was stirred at 0 °C for 30 minutes. A solution of *trans*-cinnemaldehyde (1.32 mL, 10.5 mmol) in tetrahydrofuran (20 mL) was then added and the reaction mixture allowed to warm to room temperature and stirred for 1 hour. The mixture was diluted with diethyl ether (40 mL) and quenched with water (100 mL). The aqueous phase was extracted into diethyl ether (2 x 100 mL) and the combined organic phases were dried over anhydrous sodium sulfate before concentrating *in vacuo* to give a crude yellow oil. This was taken up in dichloromethane (20 mL) and pre-absorbed onto silica gel. The crude material was purified by flash chromatography (silica gel, 5% ethyl acetate in dichloromethane + 1% triethylamine) to give the desired product **309** as a yellow oil (1.04 g, 38%) and as a single diastereoisomer.

^{1}H NMR ($CDCl_3$) : δ = 7.34-7.56 (m, 5H, *5 x aromatic CH*), 6.67 (d, 1H, *J* = 12.4 Hz, *alkene CH*), 6.34 (dd, 1H, *J* = 12.5, 0.4 Hz, *alkene CH*), 2.76 (m, 1H, *CH*), 3.72 (s, 3H, *OCH_3*), 3.52 (s, 2H, *CH_2*), 2.87 (m, 1H, *CH*), 1.08-1.13 (m, 3H, *CH_3*) ^{13}C NMR ($CDCl_3$) : δ = 207.3, 168.7, 138.3, 129.3, 128.7, 128.2, 127.9, 72.3, 51.6, 50.2, 47.2, 13.2 HRMS found 262.1210 calc for $C_{15}H_{18}O_4$ 262.1205

(4R,5S,E)-methyl 5-hydroxy-2,4-dimethyl-3-oxo-7-phenylhept-6-enoate 308



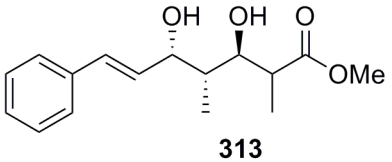
308

A suspension of *β*-keto ester **309** (1.75 g, 7.00 mmol) in acetone (100 mL) was treated with potassium carbonate (0.90 g, 6.30 mmol) and the reaction mixture was stirred at room temperature for 10 minutes before addition of iodomethane

(purified first by passing through a short plug of basic alumina, 0.52 mL, 8.40 mmol). The reaction mixture was refluxed at 60 °C for 18 hours overnight. The reaction was diluted with diethyl ether (100 mL) and filtered to remove the precipitate before concentrating the filtrate *in vacuo* to give a yellow oil. This was taken up in dichloromethane (30 mL) and pre-absorbed onto silica gel. The crude material was purified by flash chromatography (silica gel, 5% ethyl acetate + 5% toluene in dichloromethane + 1% triethylamine) to give the desired product **308** as a yellow oil (1.12 g, 61%).

^{1}H NMR ($CDCl_3$) : δ = 7.28-7.32 (m, 5H, *5 x aromatic CH*), 6.67 (d, 1H, *J* = 12.4 Hz, *alkene CH*), 6.34 (dd, 1H, *J* = 12.4, 0.4 Hz, *alkene CH*), 4.18-4.21 (m, 1H, *CH*), 3.75 (s, 3H, *OCH_3*), 3.45 (m, 1H, *CH*), 2.61-2.65 (m, 1H, *CH*), 1.17-1.19 (m, 3H, *CH_3*), 0.89-0.93 (s, 3H, *CH_3*) ^{13}C NMR ($CDCl_3$) : δ = 210.4, 171.3, 135.9, 128.3, 127.3, 126.9, 126.2, 125.3, 74.2, 51.4, 48.8, 48.3, 12.3, 11.3 HRMS found 276.1364 calc for $C_{16}H_{20}O_4$ 276.1362

(3R,4R,5S,E)-methyl 3,5-dihydroxy-2,4-dimethyl-7-phenylhept-6-enoate 313



313

A suspension of tetramethylammonium triacetoxyborohydride (2.57 g, 9.80 mmol) in acetonitrile (30 mL) was treated with acetic acid (10 mL) and the reaction mixture stirred at room temperature for 30 minutes. The reaction was then cooled down to -40 °C and treated with a solution of ketone **308** (0.30 g, 1.1 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at -40 °C for 1 hour and the homogenous mixture was transferred to the freezer to be stored, under argon, for 18 hours overnight. The reaction mixture was allowed to warm to room temperature and quenched by addition of saturated aqueous Rochelle's salt (40 mL). After stirring for 30 minutes the mixture was poured onto a mixture of saturated aqueous sodium bicarbonate : dichloromethane (1:1, 80 mL total volume). The aqueous phase was extracted into dichloromethane (2 x 50 mL) and the combined organic phases were dried over anhydrous sodium sulfate before concentrating *in vacuo* to give a crude yellow oil. This was purified by flash chromatography (silica gel, 5% ethyl acetate + 5% toluene in dichloromethane + 1% triethylamine) to give the desired diol **313** as a yellow oil (2.41 g, 89%).

^{1}H NMR ($CDCl_3$) : δ = 7.23-7.35 (m, 5H, *5 x aromatic CH*), 6.67 (d, 1H, *J* = 11.9 Hz, *alkene CH*), 6.21 (dd, 1H, *J* = 12.0, 0.9 Hz, *alkene CH*), 3.79-3.84 (m, 2H, *2 x CH*), 3.74 (s, 3H, *OCH_3*), 2.49-2.53 (m, 1H, *CH*), 1.90-1.94 (m, 1H, *CH*), 1.23-1.25 (m, 3H, *CH_3*), 0.88-0.93 (m, 3H, *CH_3*) ^{13}C NMR ($CDCl_3$) : δ = 176.3, 137.8, 128.4, 127.8, 127.4, 125.6, 125.2, 71.2, 70.9, 53.5, 46.2, 42.3, 14.6, 9.3 HRMS found 278.1523 calc for $C_{16}H_{22}O_4$ 278.1518