Total Synthesis of Enamide-Containing Natural Products

Adele Elisa Pasqua M.Sc

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School of Chemistry

College of Science and Engineering

University of Glasgow

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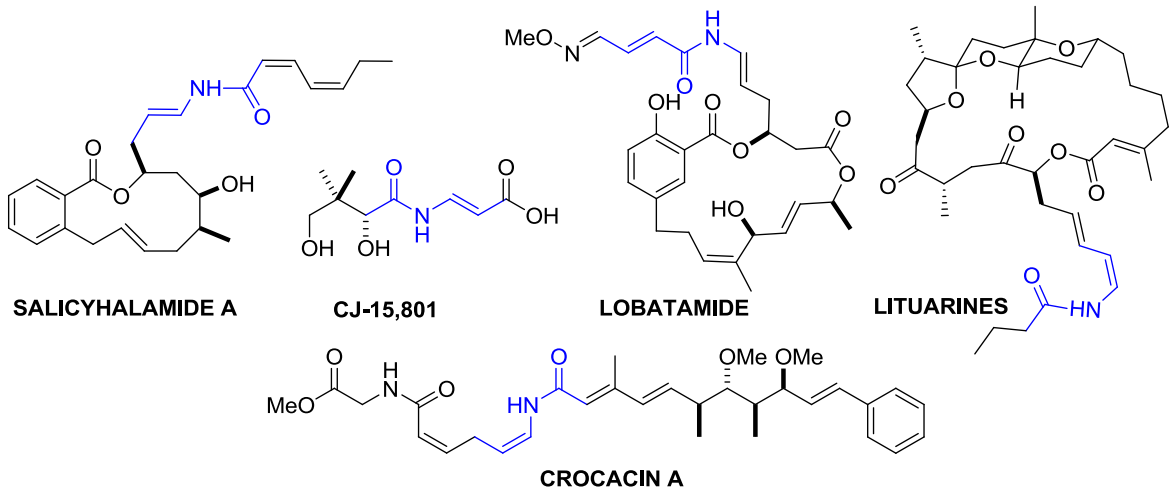
A nonno Vincenzo

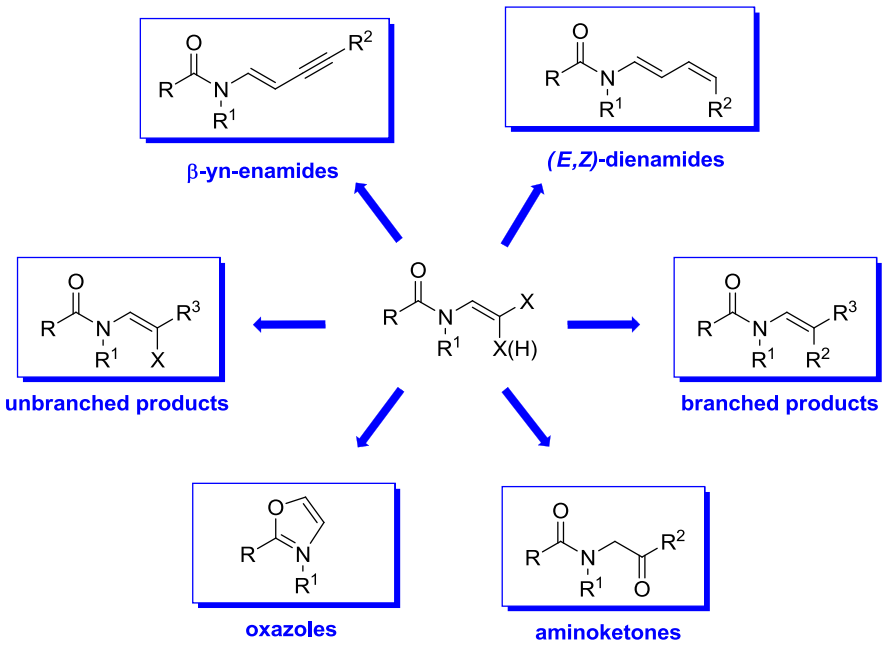
Abstract

Enamides are an important class of functional group commonly present in natural products and drug candidates. In particular, enamides and dienamides are common in many anti-parasitic and anti-cancer natural products and pharmaceutical drug leads.

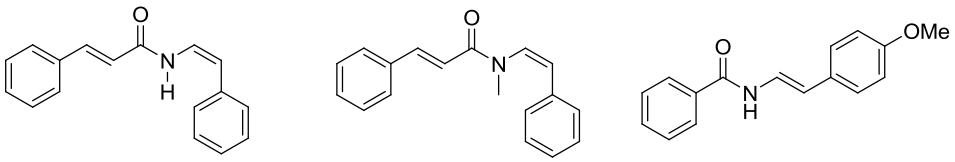


The enamide moiety is strictly related to the biological activity of such compounds as it is directly involved in their mode of action. Due to the great importance of the enamide moiety in biological and medicinal chemistry, a deep interest has risen in the synthetic community in the past two decades and a wide variety of methodologies for the preparation of enamides have been developed so far. However, current methods suffer from poor efficiency and stereocontrol, in particular in the case of the thermodynamically unfavoured *(Z)*-enamides.

The work reported herein details the development of a new methodology for the stereoselective synthesis of β-halo-enamides and β,β-dihalo-enamides from which it is possible to synthesise, *via* Pd-mediated cross-coupling reactions, more complex structures, such as β-yn-enamides, stereodefined *(E,Z)*-dienamides and branched products. In addition, oxazoles can be achieved *via* basic treatment of β-halo-enamides.

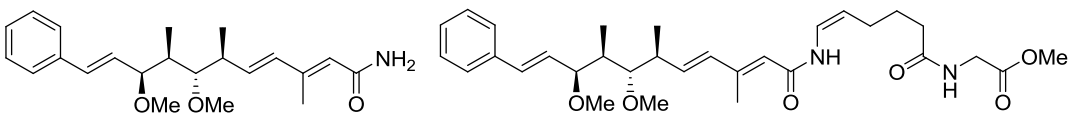


The methodology has been successfully applied to the total syntheses of simple enamide-containing natural products, such as lansiumamide A, lansiumamide B and alatamide.



LANSIUMAMIDE A **LANSIUMAMIDE B** **ALATAMIDE**

The total synthesis of a more complex family of enamide-containing natural products, such as the antifungal, antibiotic and cytotoxic crocacins, was also explored. The attention was focused firstly on (+)-crocacin C that is the primary amide and can be envisioned as the synthetic precursor of the other crocacins, and secondly on (+)-crocacin D, that is the most active and promising of the family. Two novel syntheses of (+)-crocacin C and (+)-crocacin D are therefore reported.



(+)-crocacin C **(+)-crocacin D**

The synthesis of simplified unnatural analogues with some promising insecticidal activity is also described.

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Acknowledgements

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Author Declaration

This thesis represents the original work of Adele Elisa Pasqua unless explicitly stated otherwise in the text. The research upon which it is based was carried out at the University of Glasgow, under the supervision of Dr. Rodolfo Marquez, during the period October 2009 to September 2012. Portions of the work described herein have been published elsewhere as listed below.

- **"Fast, Economic and Green Synthesis of *N*-Formylated Benzotriazoles"**
  Pasqua A. E.; Matheson M.; Sewell A. L.; Marquez R. *Org. Process. Res. Dev*. **2011**, *15*, 467.
- **" Regioselective Synthesis of β-iodo-enamides and β-yn-enamides"**
  Pasqua A. E.; Thomas L. H.; James J. Crawford.; Marquez R. *Tetrahedron* **2011**, *67*, 7611.
- **"Protecting Group Free, Stereo-controlled Synthesis of β-halo-enamides"**
  Pasqua A. E.; James J. Crawford.; Long D. L.; Marquez R. *J. Org. Chem.* **2012**, *77*, 2149.
- **"Formal Synthesis of (+)-Crocacin C"**
  Pasqua A. E.; Ferrari F. D.; James J. Crawford.; Marquez R. *Tetrahedron Lett.* **2012**, *53*, 2114.
- **"Step-Economic Synthesis of (+)-Crocacin C: A Concise Crotylboronation/[3,3]-Sigmatropic Rearrangement Approach"**
  Pasqua A. E.; Ferrari F. D.; Hamman C.; Liu Y.; James J. Crawford.; Marquez R. *J. Org. Chem.* **2012**, *77*, 6989.

Adele Elisa Pasqua

Dr. Rodolfo Marquez

Abbreviations

4Å-MS	4 Ångström molecular sieves
9-BBN	9-Borabicyclo(3.3.1)nonane
Ac	Acetate
acac	Acetylacetone
AIBN	Azobis*iso*butyronitrile
BAIB	bis(acetoxy)iodobenzene
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
brsm	Based on recovered starting material
bs	Broad singlet
Bu	Butyl
Bz	Benzoyl
CAN	Cerium Ammonium Nitrate
cat.	Catalytic
CBS	Corey-Bakshi-Shibata
Cbz	Carboxybenzyl
CI	Chemical Ionisation
cm	Centimetre(s)
cod	Cyclooctadienyl
conc.	Concentrated
COSY	Correlation Spectroscopy
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
d	Doublet
DAD	Diode-Array-Detected
dba	Dibenzylideneacetone
DBE	Double bonds equivalents
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide

dcypb	1,4-bis(dicyclohexylphosphino)butane
dd	Doublet of doublets
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DEAD	Diethyl azodicarboxylate
DET	Diethyltartrate
DIBAL-H	Di*iso*butylaluminium hydride
DIC	*N,N'*-diisopropylcarbodiimide
DIPEA	Di*iso*propylethyl amine
DIPT	Diisopropyl tartrate
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethylsulfoxide
DPPA	Diphenylphosphoryl azide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
dt	Doublet of triplets
EC	Effective concentration
EDCi	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
ee	Enantiomeric excess
EI	Electron ionisation
eq	Equivalent(s)
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron withdrawing group
FAB	Fast atom bombardment
GII	Grubbs II
gem	Geminal
Gly	Glycine
h	Hour
HBTU	*O*-Benzotriazole-*N*,*N*,*N'*,*N'*-tetramethyl-uronium-hexafluorophosphate
HGII	Hoveyda-Grubbs II

HMBC	Heteronuclear multiple bond correlation
HMDS	Bis(trimethylsilyl)amide
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear multiple quantum correlation
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	Hydroxybenzotriazole
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
i	*iso*
IC_{50}	Half maximal inhibition concentration
Ipc	Isopinocampheyl
IR	Infrared
L	Ligand
L.A.	Lewis acid
LDA	Lithium di*iso*propylamide
m	Multiplet
M	Molar
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
Mes	Mesityl
met	Metallyl
MIDA	*N*-methyliminodiacetic acid
min	Minutes
mL	Millilitre(s)
mM	Millimolar
mmol	Millimole
MOM	Methoxymethyl
MPLC	Medium-performance liquid chromatography
Ms	Methanesulfonyl
MU	Mass units
MW	Microwave
n	Normal
Napth	Naphthalide
NBS	*N*-Bromosuccinimide

NCS	*N*-Chlorosuccinimide
nM	Nanomolar
NMI	*N*-methyl imidazole
NMM	*N*-methylmorpholine
NMP	*N*-methyl pyrrolidone
NMR	Nuclear magnetic resonance
n*O*e	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
NXS	*N*-Halosuccinimide
P2-Ni	Nickel boride (Ni_2B)
PDC	Pyridinium dichromate
Ph	Phenyl
Piv	Pivaloyl
PMB	*para*-Methoxybenzyl
ppm	Parts per million
PPTS	Pyridinium p-toluenesulfonate
Pr	Propyl
Py	Pyridine
q	Quartet
quint	Quintet
RP	Reverse phase
RT	Room temperature
s	Singlet
SAE	Sharpless asymmetric epoxidation
SPhos	2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl
t	Triplet
t	*tert*
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
TC	Thiophene-2-carboxylate
TEA	Triethylamine

TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
Teoc	2-(trimethylsilyl)ethoxy carbonyl
TES	Triethylsilyl
tert	Tertiary
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid/trifluoroacetyl
THF	Tetrahydrofuran
TIPS	Tri*iso*propylsilyl
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMG	Tetramethylguanidine
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl
*p*TsOH	*p*-Toluenesulfonic acid
UV	Ultraviolet

CHAPTER I

1 Introduction

1.1 Enamides

Enamides show a good balance of stability and reactivity, a combination which accounts for their increasing importance in organic synthesis and medicinal chemistry. Enamides offer a wide variety of alternatives for the inclusion of nitrogen-based moiety into organic systems. These compounds can be seen as electron-deficient enamines, in which the alkene is substituted with a nitrogen functionality containing an electron withdrawing group such as imidazolidinone, oxazolidinone, lactam or amide. If we consider the cyclic systems the enamide double bond is constrained within a heterocycle, but if we consider the acyclic systems, where there is a β-substituted *N*-alkenyl side chain, both *(E)*- and *(Z)*-isomers can occur (**Figure 1**). In fact, one of the major problems associated with the preliminary syntheses of enamides was the lack of configurational control, together with low yields.

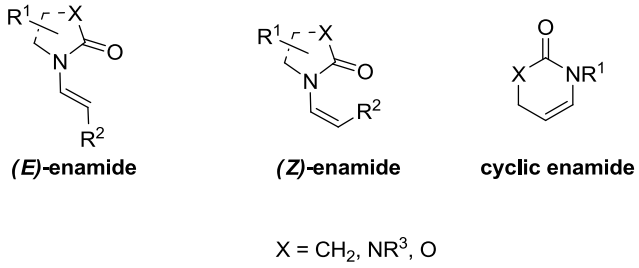


Figure 1. Different types of enamides.

Enamides are an important class of functional group due to their high reactivity which allows their use in the preparation of heterocyclic compounds.

Enamides show nucleophilic reactivity due to the enamine character (stabilised by the EWG) (**Figure 2**) and often reactivity in similar fashion to simple C=C bonds, behaviour which provides further options for the incorporation of *N*-functionality into complex systems.

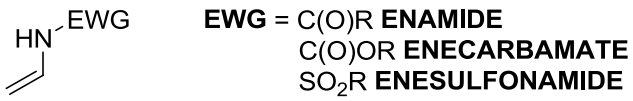


Figure 2. Nucleophilic reactivity of enamides.

Enamides are also often present in natural products and drug candidates. In particular, enamides and dienamides are common in a number of anti-parasitic and anti-cancer natural products and pharmaceutical drug leads[1a,b] (**Figure 3**).

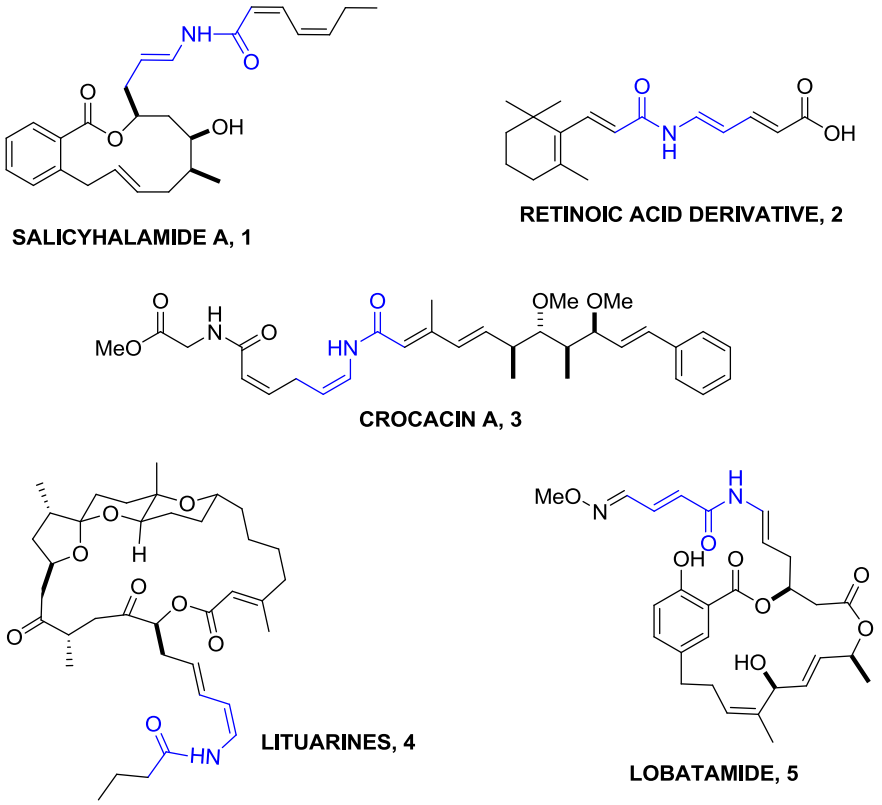


Figure 3. Enamides in natural and pharmaceutical products.

The enamide moiety is often responsible for the biological activity observed in those compounds through direct involvement in their mode of action. Mechanistically, it has been postulated that protonation of the enamide moiety leads to the highly electrophilic *N*-acyliminium ion which, in turn, can undergo

enzymatic nucleophilic attack to form the conjugated adduct responsible for activity.

A typical example of the important role played by the enamide moiety in the biological activity of natural products is represented by the comparison of the IC_{50} of the potent anti-cancer agent salicylihalamide A **1**, with two analogues **6** and **7**. In analogue **6**, in which the enamide moiety is preserved, the biological activity remains almost unaltered, while in the analogue **7** which lacks of the enamide moiety the biological activity against human cancer cells is severely reduced[2] (**Figure 4**).

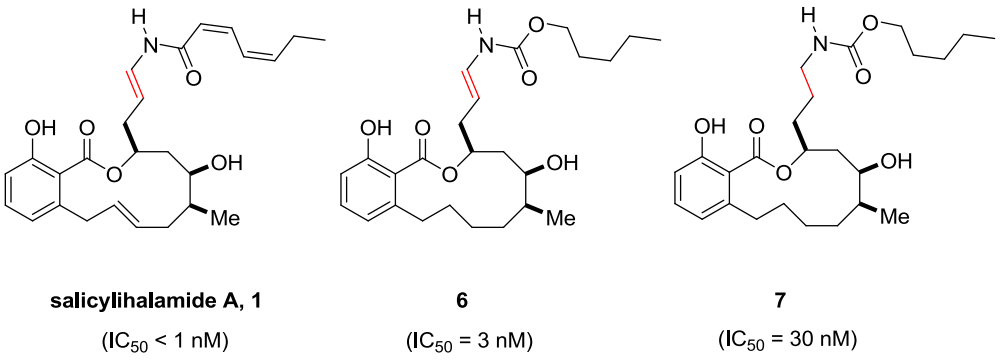


Figure 4. Importance of the enamide moiety for biological activity.

1.2 Methods of synthesis of enamides

Three major approaches have been considered for the synthesis of enamides. The most straightforward disconnection is through cleavage of the carbonyl C-N bond, which implies *N*-acylation of an enamine, or its equivalent.

The second disconnection is across the double bond which can be obtained in many ways including the elimination of either α- or β-substituents from saturated starting materials, the condensation of amides and aldehydes, and transition-metal-catalysed isomerisations of common *N*-allylated amides.

The third disconnection involves the scission of the N-C bond, which can be formed by coupling reactions using transition-metal-chemistry (**Figure 5**).

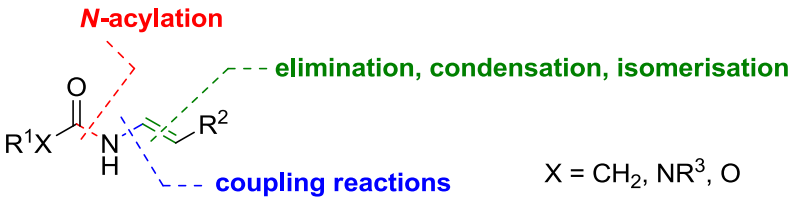


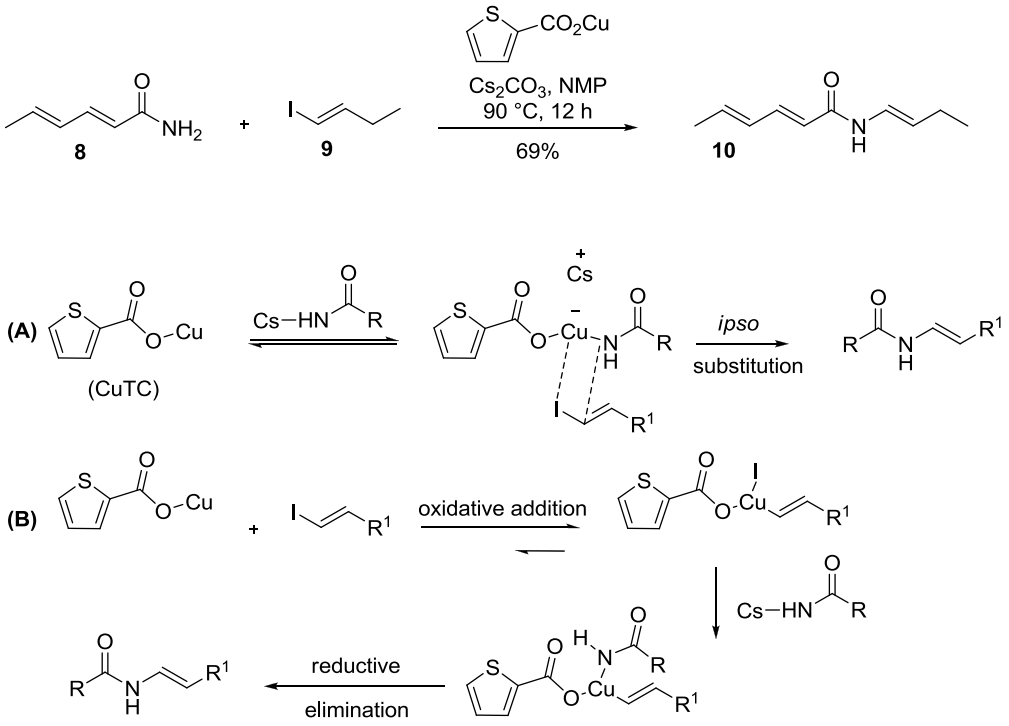
Figure 5. Three major disconnections in the enamides.

Reflecting their importance, a wide variety of methods for the synthesis of enamides has been developed in recent years. The following is a selection of the most common and representative approaches taken to date.[3a]

Some of the methodologies are based on *N*-acylation reactions, such as the acylation of imines; other strategies are based on cross- coupling reactions, such as the palladium(II)-catalysed amidation of alkenes and the copper(I)-catalysed coupling of vinyl iodides and amides; finally, there are methods involving elimination reactions such as the Peterson olefination.

Copper(I)-catalysed coupling of vinyl iodides and amides (Porco)

Porco and co-workers, in 2000, proposed a copper(I)-catalysed coupling of vinyl iodides and amides for the synthesis of enamides,[3a,b] as shown in **Scheme 1**.



Scheme 1. Porco's synthesis of enamides and proposed mechanisms.

Through the application of this methodology, a large variety of *(E)*-enamides were prepared in moderate to good yields. The most commonly used coupling agent for this reaction is Liebeskind's copper(I) thiophene carboxylate (CuTC) while the base of choice is cesium carbonate. The mechanism of the transformation has not yet been proven, however two hypotheses have been proposed. The first hypothesis is that the cesium carboxamide reacts with the CuTC to form a cuprate-like intermediate which, in turn, interacts with the vinyl iodide to give, *via* four-centered *ipso*-substitution, the final product. A second, more recently postulated mechanism, involves the oxidative addition of the vinyl iodide unit to the CuTC complex, followed by displacement of a copper iodide intermediate by the cesium carboxamide and final reductive elimination (**Scheme 1**). Porco's methodology has proven suitable for the introduction of enamide moieties under mild conditions, making it a very useful tool even during the late stages of a

synthesis. This procedure was applied during the syntheses of the salicylate enamide macrolides, a novel class of antitumor natural products such as lobatamides A-F,[4a,b] oximidines I-III,[5a,b] and CJ-12,950.[6]

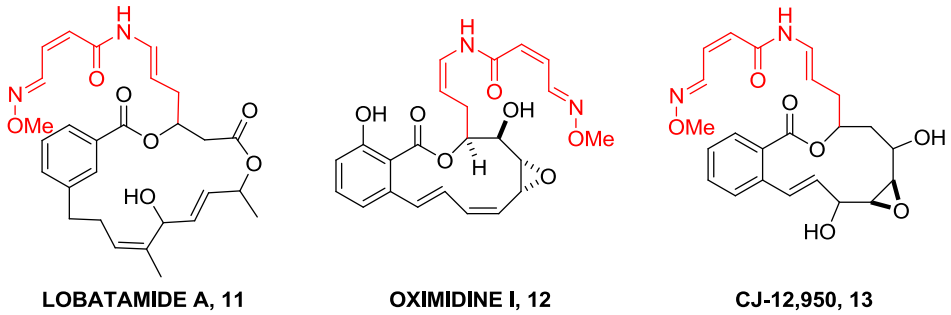


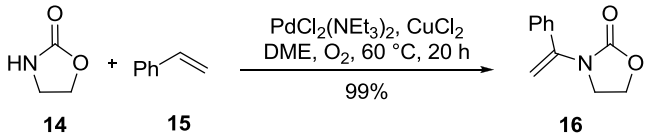
Figure 6. Application of Porco's procedure in total synthesis.

Buchwald later reported a copper(I)-catalysed coupling for the synthesis of enamides based on the use of vinyl iodides or bromides using *N,N'*-dimethyl ethylenediamine as a ligand.[7] Buchwald's method was an improvement on the Porco procedure as it allowed for the generation of *(Z)*-enamides. A year later, Ma and co-workers developed a variation of Buchwald's methodology based on the use of a different ligand, *N,N*-dimethylglycine.[8] The most recent variation on this approach was introduced by Batey and it is based on the use of potassium alkenyltrifluoroborates, which are extremely stable salts and can be used in copper(I)-catalysed cross-coupling reactions with amides to generate *(E)*-enamides in excellent yields under mild, base-free conditions.[9]

Palladium(II)-catalysed amidation of alkenes (Stahl)

In 2003, Stahl's group introduced the first general method for the intermolecular oxidative amination of styrenes.[10] Stahl method involves a palladium(II)-catalysed coupling in the presence of molecular oxygen as the stoichiometric oxidant, compatible with a wide variety of nitrogen nucleophiles, such as oxazolidin-2-one, pyrrolidinone and phthalimide. The catalytic activity can be enhanced by a catalytic amount of Brønsted base (Et_3N) in the reaction, and, in addition, the regioselectivity can be tuned as the base is believed to provide the driving force to

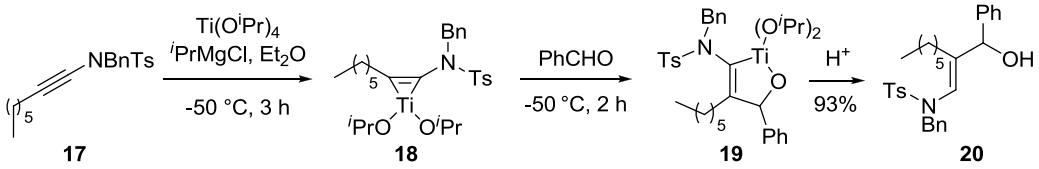
achieve the Markovnikov product. Unfortunately, the mechanistic details of this transformation have not yet been established. This methodology was used to access 3-(1-phenylvinyl)oxazolidin-2-one in one step and in excellent yield (**Scheme 2**).



Scheme 2. Stahl's oxidative amination of styrenes.

Titanium(II)-mediated coupling of ynamides and aldehydes (Sato)

In 2003, Sato proposed a novel synthesis of enamides *via* the titanium(II)-mediated coupling of ynamides and yne-sulfonamides with either carbonyl compounds or alkynes. The stereochemical outcome of the transformation depends on an intermediate ynamide-titanium complex, which couples with an aldehyde in a regio- and stereoselective fashion so as to afford a single stereodefined trisubstituted enamide[11] (**Scheme 3**).

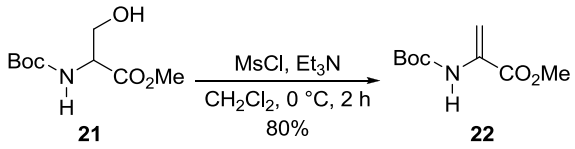


Scheme 3. Sato's synthesis of enamides.

Base-promoted elimination of substituted alcohols (Collier, Campbell)

Collier and Campbell developed a base-promoted elimination of substituted alcohols for the synthesis of enamides.[12] This method is based on the *in situ* generation of a mesylate intermediate starting from the amino ester **21** and its subsequent elimination (**Scheme 4**). Similar approaches have also been

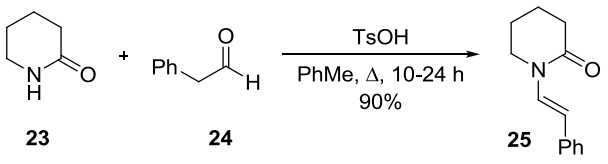
documented including the dehydration of free alcohols as well as eliminations involving glycosides, esters, and several other derivatives. The Collier and Campbell method proved to be a good strategy for the mild preparation of enantiopure, non-proteinogenic α-aminoacids, potential building blocks in natural and pharmaceutical products.



Scheme 4. Collier's synthesis of enamides.

Condensation of amides and aldehydes (Zezza, Smith)

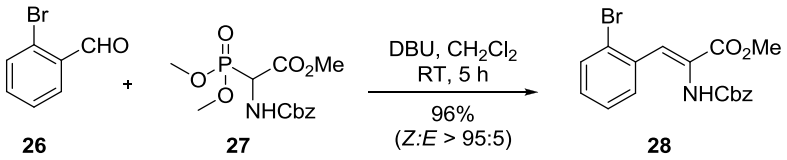
In 1987, Zezza and Smith introduced a simple synthesis of *(E)*-enamides by condensing lactams with aldehydes under mild conditions.[13] A large number of solvents, acids and reaction conditions were investigated, however toluene and a catalytic amount of 4-toluenesulfonic acid (with azeotropic removal of water) proved to be the best conditions. This methodology is useful for both aryl and alkyl aldehydes, which can easily undergo the condensation. In a typical example, piperidin-2-one **23** can be condensed with phenylacetaldehyde **24** to afford enamide **25** (**Scheme 5**).



Scheme 5. Smith's synthesis of enamides.

Alkenation *via* Horner-Woodsworth-Emmons conditions (Hruby)

In 2002, Hruby's group, reported the Horner-Wadsworth-Emmons alkenation of 2-bromobenzaldehyde **26** with phosphorylacetate **27**, which provided enamide **28** in high yield and good stereocontrol in favour of the *(Z)*-adduct[14] (**Scheme 6**).



Scheme 6. Hruby's synthesis of enamides.

This methodology was exploited in the total syntheses of (+)-sinefungin[15] **29** and azinomyzin A[16] **30** (**Figure 7**).

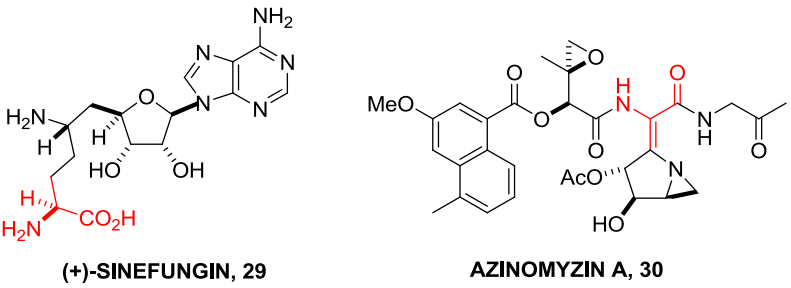
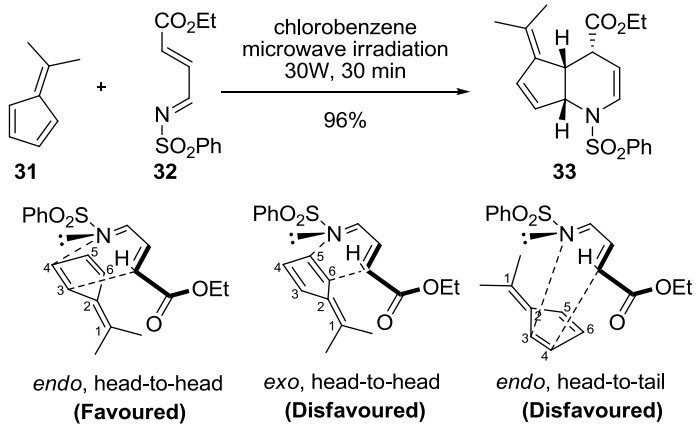


Figure 7. Targets accessed *via* HWE chemistry.

Hetero [4+2] cycloaddition (Hong)

In 2004, Hong proposed an inverse-electron-demand hetero-Diels-Alder approach for the synthesis of enamides. Hong's initial approach involves the reaction between *N*-sulfonyl-1-azabuta-1,3-diene **32** and dimethylfulvene **31**, to generate the cyclic enamide **33**. The process was particularly high yielding when promoted by microwave irradiation.[17] The reaction was both regio- and stereoselective and provided an efficient route to the cyclopenta[*b*]pyridine **33** (**Scheme 7**).

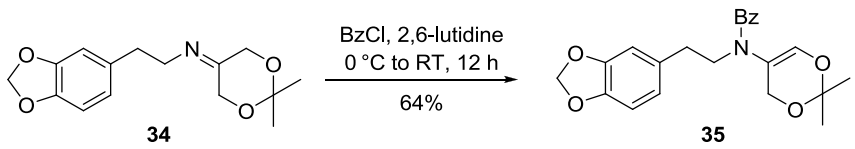


Scheme 7. Hong's inverse-electron-demand hetero-Diels-Alder.

Mechanistically, the cycloaddition occurs *via* an *endo*-head-to-head transition state. The *endo* transition state is aided by the presence of secondary orbital interactions between the azadiene and the C5-C6 double bond of the fulvene which stabilises the transition state. A second stabilising interaction between the ester carbonyl moiety and the C1-C2 double bond of the fulvene further reinforces the *endo* transitional bias. These orbital interactions are not feasible in the disfavoured *exo*-head-to-head and *endo*-head-to-tail transition states, respectively.

Acylation of imines (Funk)

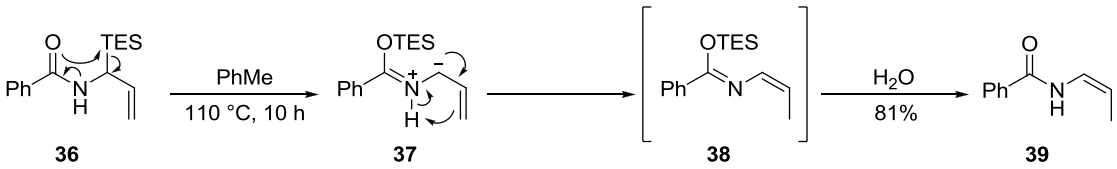
In 2001, Funk reported the *N*-acylation of imine **34** with benzoyl chloride to afford the enamide **35**[18] in reasonable yield (**Scheme 8**). A variety of 2,2-dimethyl-1,3-dioxane-derived enamides were obtained using these conditions.



Scheme 8. Funk's acylation of imines.

Dyotropic rearrangement (Danishefsky)

In 2004, Danishefsky reported a novel rearrangement of silylated amides into *(Z)*-enamides.[19] This rearrangement is a beautiful example of a formal, stepwise, thermally promoted 10-electron double-sigmatropic, or dyotropic, rearrangement. The transformation is based on a key, 1,4-silyl shift in which the triethylsilyl group is transferred from C to O. This TES migration leads to the formation of the allyl carbanion species **37** which then undergoes a 1,4-hydrogen shift to afford intermediate **38**. A final *N*-protonation affords the desired *cis*-enamide **39** (**Scheme 9**).



Scheme 9. Danishefsky's dyotropic rearrangement.

Despite the high temperature required, this methodology proved to be highly suitable for the introduction of *cis*-enamide moieties in complex targets. Danishefsky went to apply this methodology during the syntheses of the proteasome inhibitors TMC-95A **40** and TMC-95B **41** (**Figure 8**).[19]

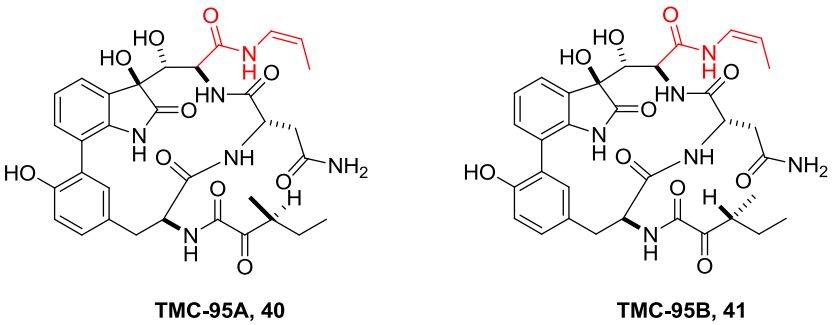
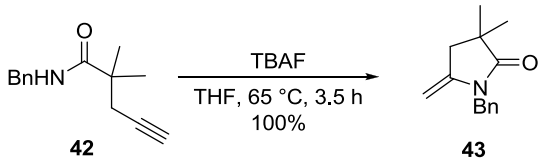


Figure 8. Danishefsky's proteasome inhibitor targets.

Amide additions to alkynes (Jacobi)

In 1996, Jacobi proposed a 5-*exo*-*dig* cyclisation promoted by tetrabutylammonium fluoride, leading from an acetylenic amide such as the alkynylated amide **42**, to the monocyclic enamide 5-methylenepyrrolidone **43** (**Scheme 10**).[20]



Scheme 10. Jacobi's synthesis of enamides.

This kind of cyclisation is particularly useful for highly substituted substrates, particularly those containing geminal dimethyl substituents, which cause the Thorpe-Ingold effect to take place. The *gem*-dimethyl substitution, leads to angle compression and reduction in the entropy of rotation in the open-chain compound, and subsequent increased strain, thus facilitating the cyclisation.

Cyclic enamides are useful intermediates for the synthesis of naturally occurring chlorins, isobacteriochlorins and corrins. Considering its mild conditions, the Jacobi methodology was applied to the syntheses of natural products such as the corrin cobrin acid **44**, which is a precursor of vitamin B12[20] (**Figure 9**).

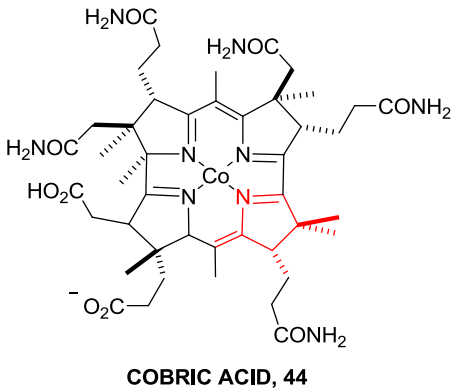
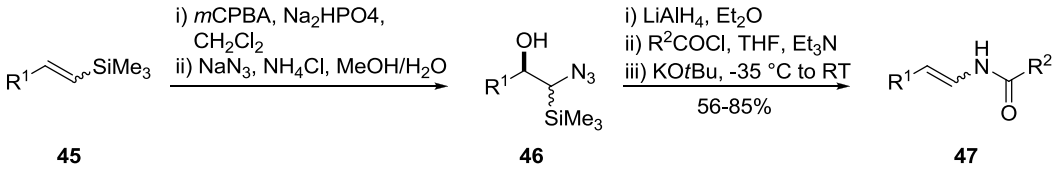


Figure 9. Cobric acid precursor of vitamin B_{12} (corrin).

Synthesis of enamides by a Peterson reaction manifold (Fürstner)

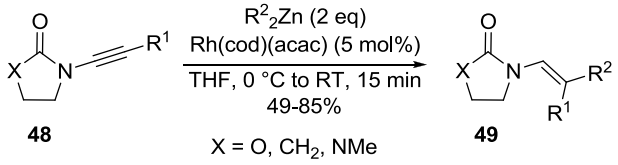
In 2001, Fürstner reported the stereoselective synthesis of enamides under mild, aprotic and basic conditions. Fürstner's methodology is based on a silicon-directed epoxide ring opening with sodium azide, followed by reduction of the resultant azide to the corresponding amine, *N*-acylation and Peterson elimination to afford enamide **47**. This methodology offers great stereocontrol and broad scope, but has the disadvantage of requiring a multi-step sequence.[21]



Scheme 11. Fürstner's synthesis of enamides.

Rhodium-catalysed carbozincation of ynamides (Lam)

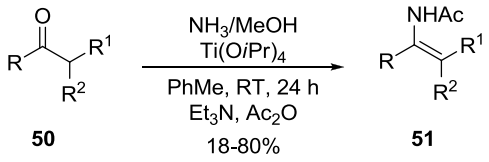
In 2008, Lam's group proposed an approach to the synthesis of multisubstituted enamides *via* carbometalation of cyclic ynamides using Rh(cod)(acac) as the catalyst and Me_2Zn, Et_2Zn or nBu_2Zn as reagent. The reaction proceeds smoothly in generally good yields and regioselectivity, but has a limited scope. In fact, when acyclic systems were considered there was loss of regiocontrol, leading to the formation of regioisomeric mixtures.[22a,b]



Scheme 12. Lam's carbometalation of ynamides.

Titanium-mediated conversion of ketones into enamides with ammonia and acetic anhydride (Reeves)

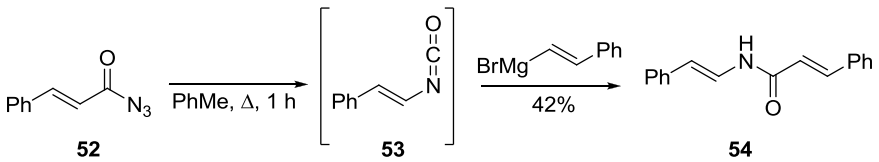
In 2012, Reeves introduced an unconventional Ti-mediated synthesis of *N*-acyl enamides with ammonia. Reeves' strategy is based on condensation of a ketone with ammonia to give either an imine or enamine, followed by *N*-acetylation with acetic anhydride. This has proven to be a reliable approach for the specific synthesis of *N*-acyl enamides.[23]



Scheme 13. Reeves' synthesis of enamides.

Organometallic addition to isocyanates (Taylor)

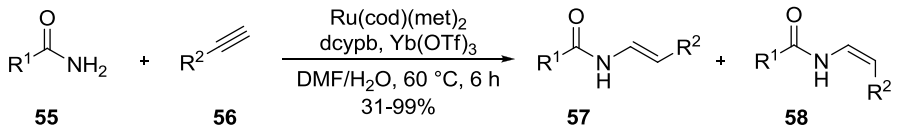
In 2000, Taylor and co-workers exploited Grignard additions to vinyl isocyanates for the preparation of unsaturated enamides. The sequence began with the Curtius rearrangement of acyl azide **52** to afford the corresponding vinyl isocyanate **53** which, in turn, was subjected to Grignard addition to generate the desired enamide **54** (**Scheme 14**). This procedure guaranteed good *(E)*-stereocontrol but was, however, a multi-step sequence which suffered from moderate to low overall yields from commercially available starting materials.[24]



Scheme 14. Taylor's addition to isocyanates.

Hydroamidation of alkynes (Gooßen)

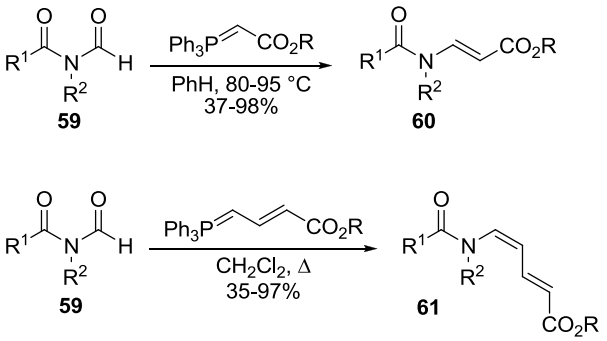
One of the most convergent and atom-efficient syntheses of enamides was proposed by Gooßen and is based on the ruthenium-catalysed *anti*-Markovnikov hydroamidation of terminal alkynes.[25] The choice of ligand determines the stereochemical outcome of the reaction with bulky ligands favouring the *(Z)*-isomer (**Scheme 15**).



Scheme 15. Gooßen's hydroamidation of alkynes.

Wittig-type olefination reactions (Marquez)

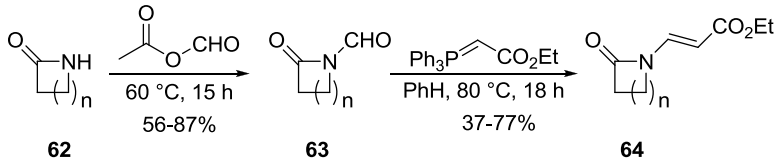
Previous work in the Marquez group focused on the exploitation of *N*-formyl imides as pseudoaldehydes. *N*-Formyl imides were found to easily undergo Wittig-type olefination reactions for the generation of enamides and dienamides in moderate to excellent yields and with fair to good stereocontrol.[1a-c]



Scheme 16. Marquez's synthesis of enamides and dienamides.

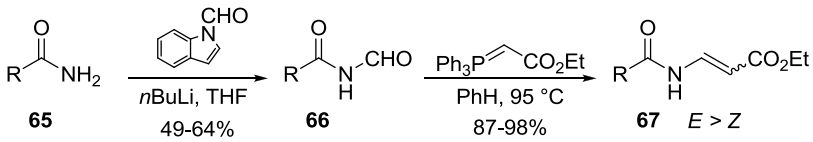
The project began in 2007 with the development of an efficient approach to the stereocontrolled synthesis of enamides starting from lactam and amide units through the use of intermediate imides.[1a,c] The formylation-olefination sequence

was initially applied to cyclic systems with fair overall yields and complete stereocontrol in favour of the *(E)*-isomers (**Scheme 17**).



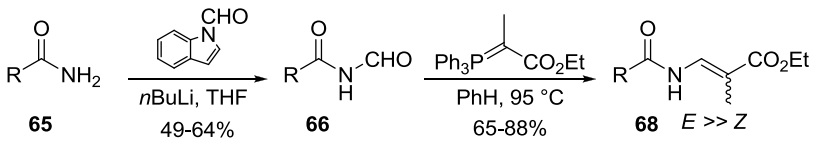
Scheme 17. Marquez's synthesis of cyclic enamides.

Subsequently, the methodology was applied to acyclic amides to afford the desired enamide products in fair overall yields and *E/Z* stereocontrol. The reduction in selectivity observed in the acyclic systems could potentially be explained by the starting imide geometry, however, the precise reason for this stereochemical outcome is so far not completely understood.



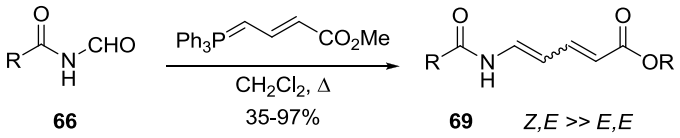
Scheme 18. Marquez's synthesis of acyclic enamides.

The same Wittig olefination was applied to the synthesis of trisubstituted acyclic *(E)*-enamides. Significantly, an increased selectivity was observed with respect to the disubstituted enamides, suggesting that the final *E/Z* product ratio arises due to the olefination transition state, rather than by the conformation of the starting imide alone (**Scheme 19**).



Scheme 19. Marquez's synthesis of trisubstituted acyclic enamides.

In 2009, the work was extended to the one-pot synthesis of dienamides starting from *N*-formyl imides and conjugated ylides. In all cases, the procedure afforded the *(Z,E)*-isomer as the major or sole isomer (**Scheme 20**). [1b]



Scheme 20. Marquez's synthesis of dienamides.

The generation of the *(Z,E)*-isomer was a surprising result as the major isomer was expected to be the *(E,E)*-dienamide, due to the use of a stabilised ylide which usually leads to the preferential formation of the thermodynamically stable *(E)* double bond. While no modeling studies have been carried out, there are some considerations that can be made. It was postulated that the presence of nitrogen in the starting imide could affect the transition state of the olefination leading to a different stereochemical outcome with respect to the typical result predicted for a traditional aldehyde/ylide system. The most plausible hypothesis, thus far, is that the nitrogen can be involved in hydrogen bonding interactions with the carbonyl oxygen of the ylide so to affect the transition state (**Figure 10**). [26]

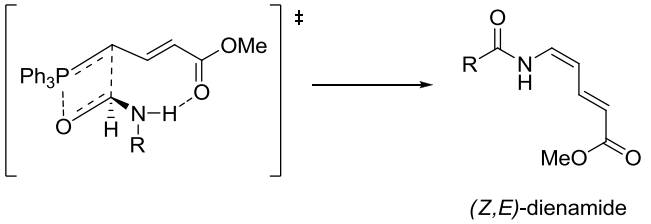
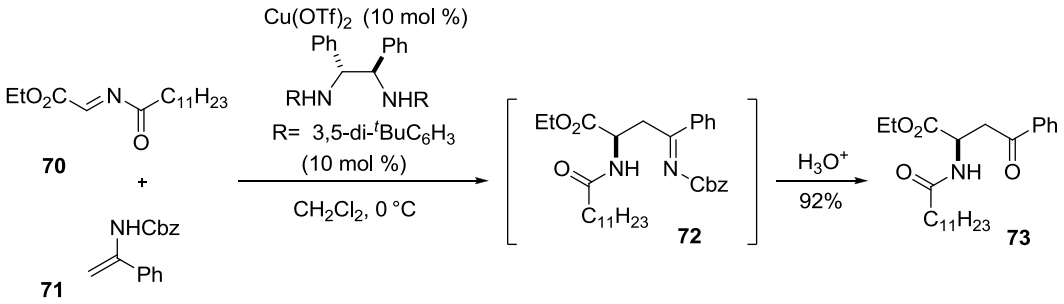


Figure 10. Marquez's proposed transition state for the synthesis of *(Z,E)*-dienamides.

1.3 The chemistry of enamides[27]

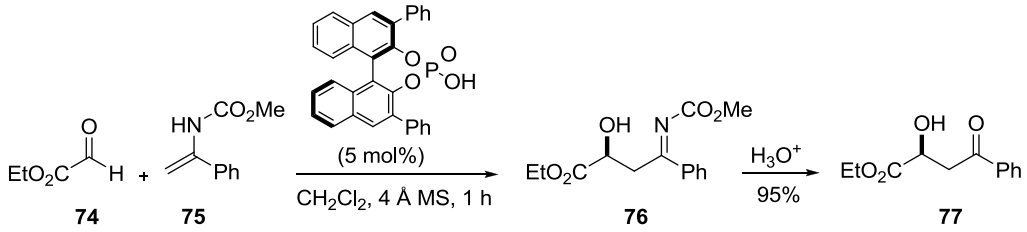
Enamides can be considered as functionalisable enamines, and for this reason they can participate in a wide variety of interesting transformations with electrophiles. Kobayashi's group was the first to introduce, in 2004, the enantioselective use of enamides as nucleophiles in copper(II)-catalysed reactions with aldehydes.[27a,b] This preliminary work suffered from low to medium levels of enantioselectivity. On the other hand, the same group optimised the methodology with the use of imine electrophiles, which allowed the formation of β-amino imines under similar chiral copper(II)-catalyst systems that failed with simple aldehydes. The reaction proceeded with excellent yield and high enantioselectivity (**Scheme 21**).



Scheme 21. Kobayashi's use of enamides as nucleophiles.

Kobayashi's procedure proved to be a robust strategy for the synthesis of optically active 1,3-diamine derivatives, which are useful building blocks for the synthesis of natural products and drug candidates. The detailed mechanism for the transformation has not been established yet, but the most plausible hypothesis involves an aza-ene type pathway.

Subsequently, in 2008, Terada proposed the use of enamides as excellent nucleophiles for chiral Brønsted acid promoted enantioselective additions to glyoxals.[28] The following is an example of the methodology applied to the organocatalytic synthesis of β-hydroxy ketone **77** using a Binol-based phosphonic acid catalyst (**Scheme 22**).



Scheme 22. Terada's enantioselective addition to glyoxals.

The high enantioselectivity of the reaction is strictly dependent on the two hydrogen-bonding interactions between the glyoxylate and the phosphoric acid. As a result, one enantiotopic face of the aldehyde (*Re* face) is shielded by a phenyl substituent while the opposite face (*Si* face) is completely free (**Figure 11**).

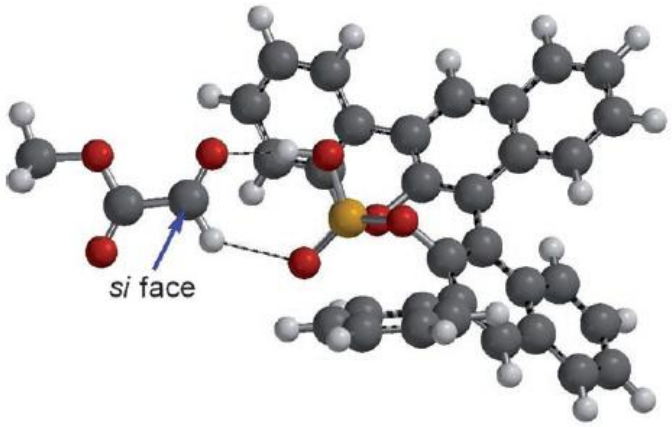
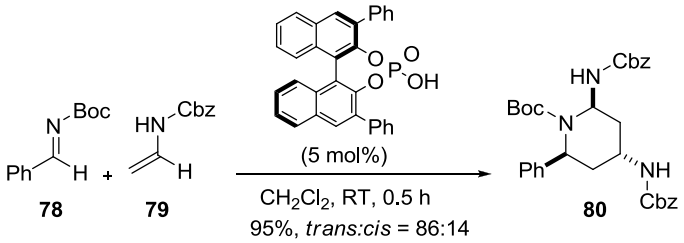


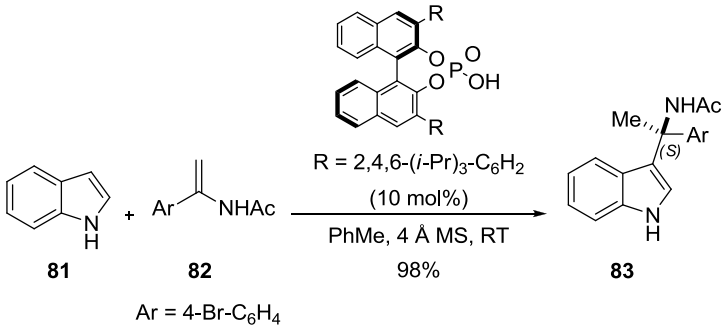
Figure 11. Nucleophilic attack from the *Si* face.

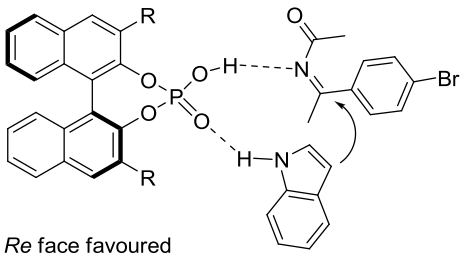
These initial studies have been optimised and expanded so to generate an impressive enantioselective synthesis of piperidines using aldimine **78** and enamide **79**. In this case, after the initial Mannich reaction of enamide **79** and imine **78**, the resulting β-amino imine product undergoes subsequent nucleophilic attack by a second equivalent of enamide **79**, followed by cyclisation to form the final piperidine **80** rapidly and in excellent yield and enantioselectivity[29] (**Scheme 23**).



Scheme 23. Terada's synthesis of piperidines.

Enamides can also be considered as good electrophiles. For example, Zhou in 2007, reported the use of chiral Brønsted acids to promote the conversion of enamides to chiral iminium ion electrophiles, which in turn, can participate to Friedel-Crafts reactions for the construction of quaternary carbon atoms[30] (**Scheme 24**).



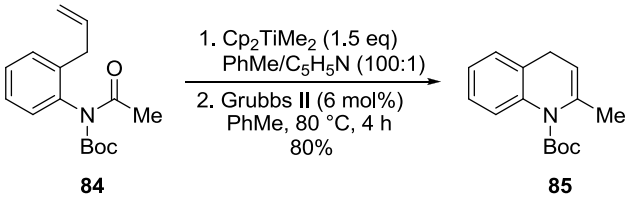


Scheme 24. Zhou's use of enamides as electrophiles.

The chiral Brønsted acid catalyst creates two hydrogen bond interactions with indole **81** and enamide **82**. The enamide is in equilibrium with the corresponding ketimine, which is activated upon protonation, so to accept nucleophilic attack of the indole from the *Re* face to afford the *(S)*-configuration of the stereocentre.

Enamides are also considered very useful substrates in a variety of transition metal mediated alkene transformations. For example, Bennasar demonstrated that enamides can participate in ring closing metathesis reactions, by proposing a one-

pot Petasis-methylenation of **84** followed by ring closing metathesis to afford the final dihydroquinoline **85** (**Scheme 25**).[31]



Scheme 25. Bennasar's use of enamides.

Bennasar's conditions have proven to be extremely useful and have formed part of key strategies towards the syntheses of complex natural products, such as paliurine and palau'amine, as reported by Evano[32a,b] and Overman[33] respectively (**Figure 12**).

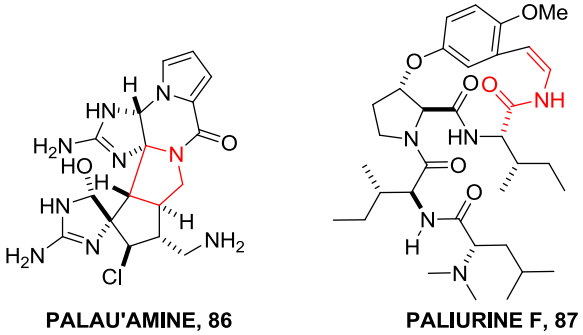
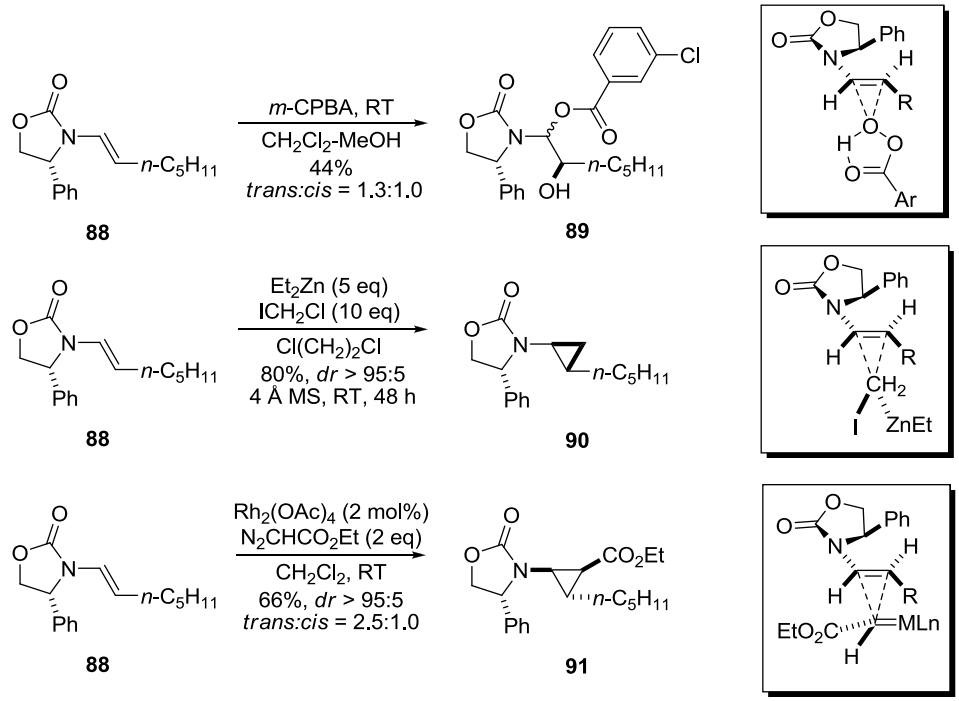


Figure 12. Evano and Overman targets accessed *via* Bennasar's chemistry.

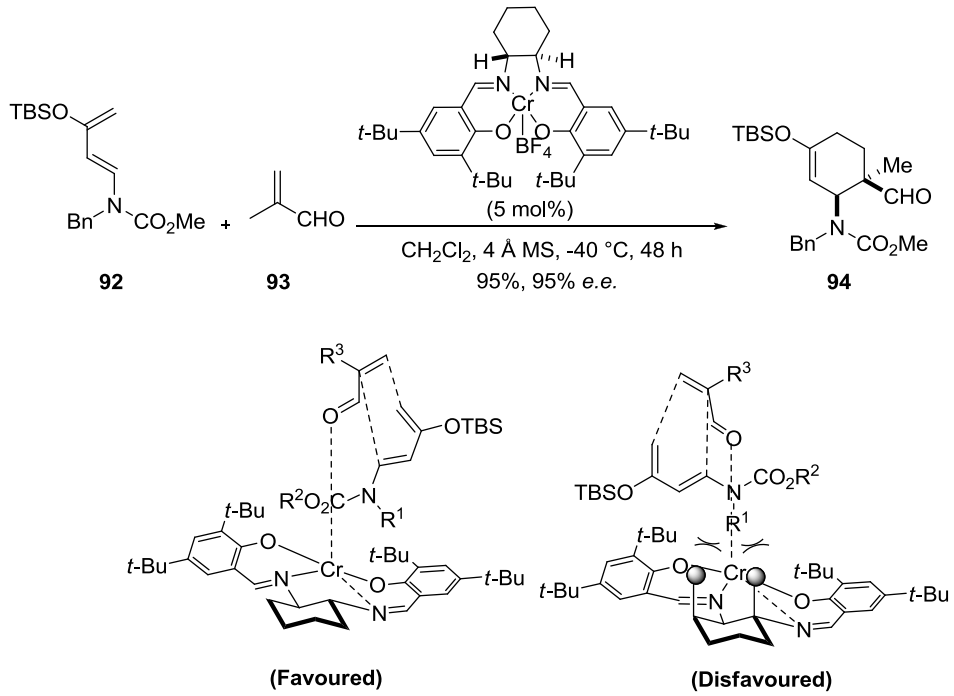
Hsung and co-workers have been pioneers in exploring the synthetic utility of enamides as substrates in organic transformations. In one of their initial studies, Hsung reported the treatment of oxazolidinone-derived enamide **88** with *m*CPBA to afford the corresponding epoxide, which subsequently underwent opening with *m*-chlorobenzoic acid to generate mono-acylated diol **89**.[34] Hsung has also been actively studying the cyclopropanation of chiral oxazolidinone enamides using a variety of conditions (i.e. Simmons-Smith), to generate the desired cyclopropyl adducts in high diastereoselectivity (**Scheme 26**).[35a,b]



Scheme 26. Hsung's use of enamides.

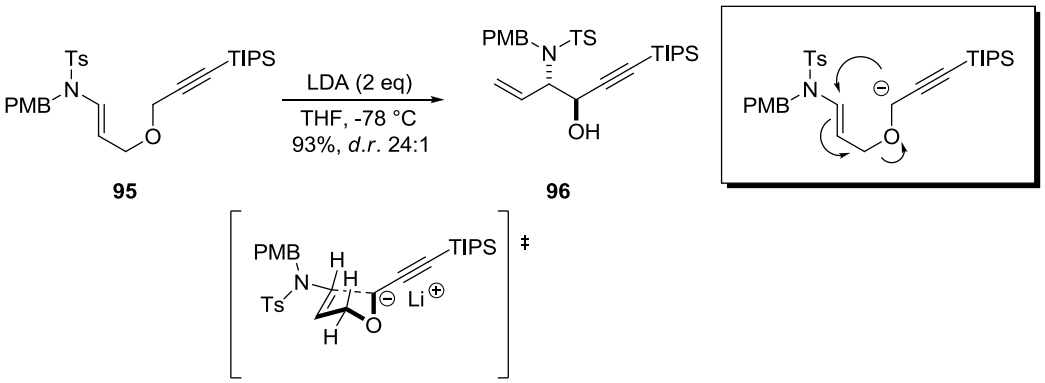
Recently, the use of enamides in pericyclic reactions has become an important area of research. Often, pericyclic reactions result in the transformation of the enamide Csp^2-N bond into a Csp^3-N bond, which allows the formation of new nitrogen containing stereocentres, and in an increase in the overall molecular complexity.

Rawal studied the use of enamides in Diels-Alder reactions as reactive dienes. The reaction was found to be highly *endo* selective, with no evidence of *exo* adduct. The process is catalysed by a Cr(III)-salen complex, which is also responsible for the stereochemical outcome of the reaction. Mechanistically, initial coordination of the chromium complex with the aldehyde unit **93** results in dienophile activation. At this point, diene **92** approaches dienophile **93** from the more readily accessible surface of the scaffold, (i.e. over the imine moiety and away from the bulky *tert*-butyl groups). The large steric bias results in single product formation (**Scheme 27**).[36]



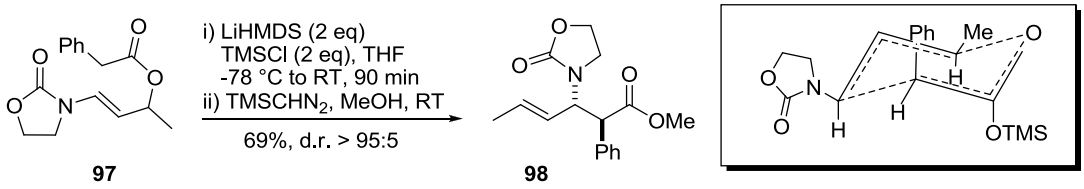
Scheme 27. Rawal's use of enamides in Diels-Alder reactions.

Meyer and Cossy proposed the first sigmatropic rearrangement which incorporated an enamide moiety. As part of their work, enamide **95** was converted to amino alcohol **96** by means of a [2,3]-Wittig rearrangement. Mechanistically, in order to understand the stereochemical outcome of the reaction, the envelope conformation of the five-membered ring transition state model, in which the alkynyl group occupies an *exo* orientation, must be considered (**Scheme 28**).[37]



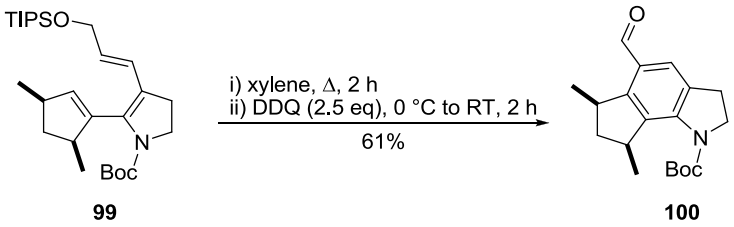
Scheme 28. Meyer and Cossy [2,3]-Wittig rearrangement of enamides.

In 2008, Carbery reported the use of enamides in the Ireland-Claisen [3,3]-rearrangement. In Carbery's approach, enamide **97** was cleanly rearranged into the desired allylic amine **98** in good yield and with very high diastereoselectivity (**Scheme 29**).[38]



Scheme 29. Carbery's Ireland-Claisen rearrangement of enamides.

Enamides have also proven to be highly valuable substrates in electrocyclic transformations. Funk subjected 2,3-pyrroline **99** to a thermal 6π-electrocyclic ring closure, which provided trikentrin alkaloid indole framework **100**. Mechanistically, the process consists of two steps: the first is an electrocyclic closure to give a diene intermediate, which subsequently undergoes aromatisation with concomitant oxidative desilylation to afford the indoline aldehyde **100** (**Scheme 30**).[39]



Scheme 30. Funk's use of enamides in a thermal 6π-electrocyclic ring closure.

The versatility of Funk's approach was demonstrated when it was applied to the syntheses of complex natural products such as welwistatin[40] **101** and dragmacidin E[41] **102**.

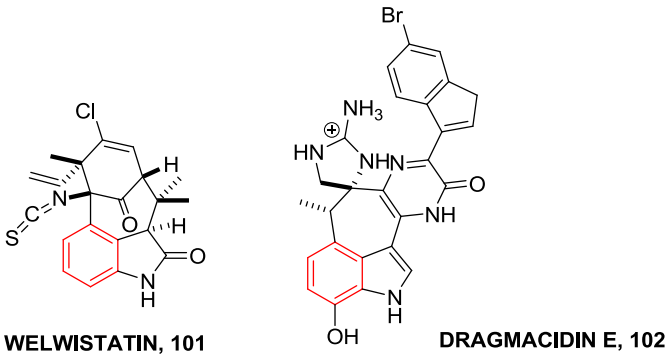
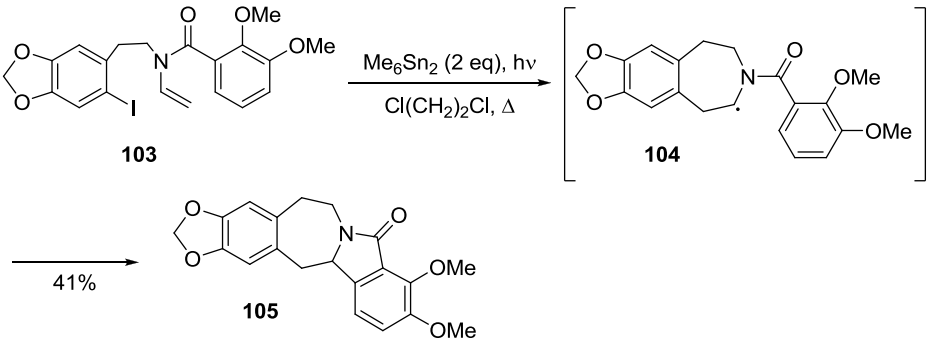


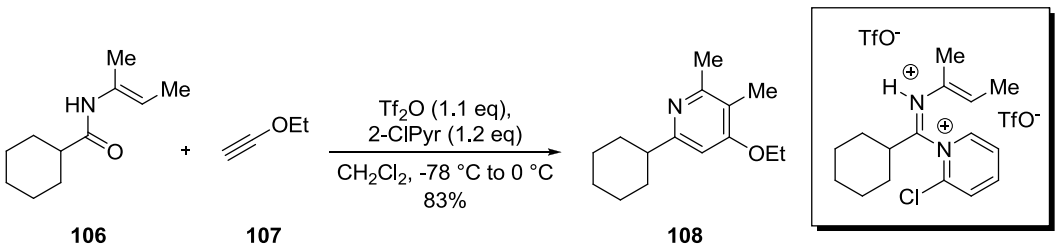
Figure 13. Targets accessed *via* Funk's chemistry.

Recently, enamides have also been used in radical transformations. One of the most significant examples in this area was proposed by Ishibashi during his synthesis of the alkaloid lennoxamine **105**. Ishibashi's synthesis proceeds *via* a radical 7-*endo* cyclisation followed by a homolytic aromatic substitution (**Scheme 31**).[42]



Scheme 31. Ishibashi's synthesis of lennoxamine.

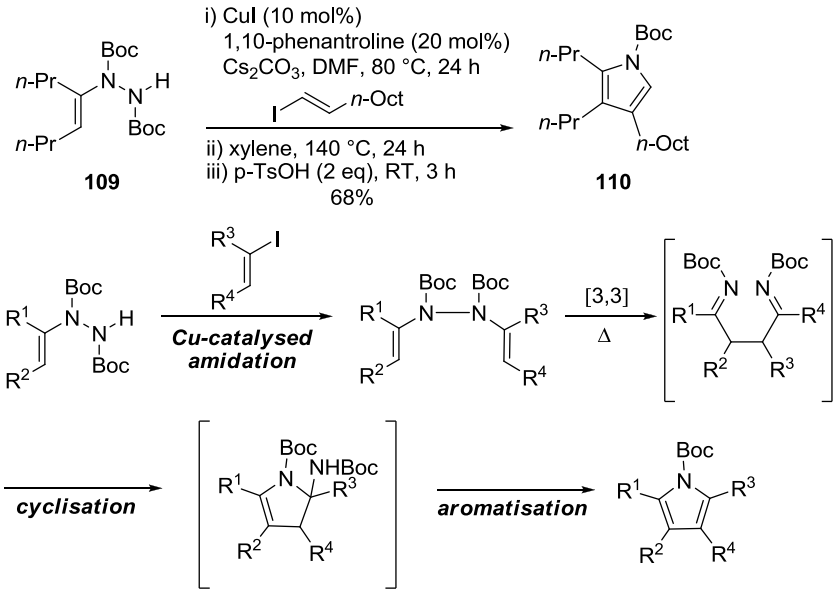
In recent years, enamides have gained importance as useful tools in the synthesis of heterocycles. In 2007, Movassaghi pioneered the use of enamides in the synthesis of pyridines (**Scheme 32**). In Movassaghi's strategy, enamides are converted to the corresponding *N*-vinyl iminium triflates, *via* activation by trifluoromethanesulfonic anhydride in the presence of 2-chloropyridine, to generate the putative iminium intermediate, which undergoes condensation with electron-rich hetero-substituted alkynes or alkenes to form substituted pyridines.[43]



Scheme 32. Movassaghi's synthesis of pyridines.

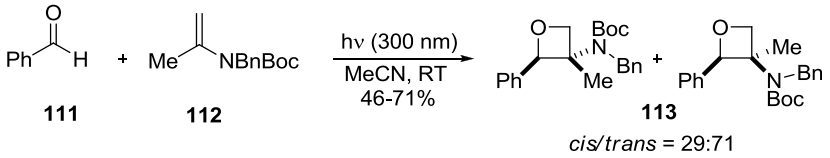
In the same year, Buchwald proposed a novel synthesis of pyrroles starting from bis-Boc-hydrazine. The process is based on two sequential copper(I)-catalysed vinylations to afford the resulting hydrazine bisenamide, which, in turn, undergoes

a [3,3]-sigmatropic rearrangement, followed by cyclisation and final aromatisation (**Scheme 33**).[44]



Scheme 33. Buchwald's synthesis of pyrroles.

Enamides have also been utilised in photochemistry, particularly as substrates in the Paternò-Büchi reaction. Using this approach, in 2001, Bach utilised enecarbamate **112** to form amino oxetanes **113** in good yield and with reasonable diastereocontrol (**Scheme 34**).[45]



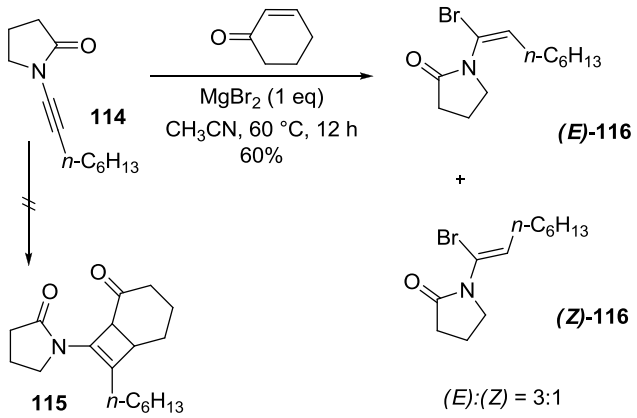
Scheme 34. Bach's use of enamides in the Paternò-Büchi reaction.

1.4 Halo-enamides

Halo-enamides are extremely versatile and useful enamide derivatives which can be utilised for the generation of highly functionalised intermediates in materials, synthetic and medicinal chemistry. However, despite their great potential to play a key role in the synthesis of more elaborated enamide derivatives, there remains a lack of reliable approaches and methods available for their efficient and practical synthesis.[3a]

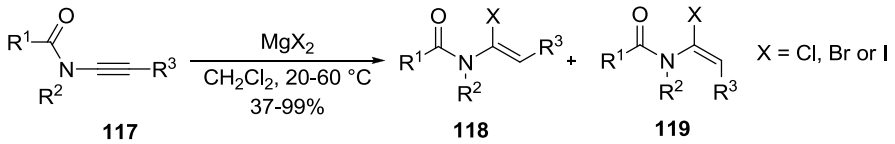
α-Halo-enamides

Most of the work on halo-enamides reported in the literature revolves around the synthesis of α-halo-enamides. Amongst the pioneers in the synthesis of halogenated enamides is Hsung who, in 2003, highlighted yet another synthetic utility of ynamides by reporting their unexpected hydrohalogenation in mild conditions with magnesium halide salts.[46] As part of Hsung's attempts to achieve the [2+2]-cycloaddition of ynamide **114** with cyclohexenone, $MgBr_2$ was added as Lewis acid catalyst. Although the reaction failed to afford the desired cycloadduct **115**, it generated the corresponding α-halo-enamide **116** in reasonable yield albeit with poor stereoselectivity (**Scheme 35**).



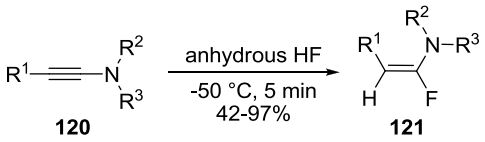
Scheme 35. Hsung's unexpected α-halogenation of ynamides.

Hsung reported that *in situ* generation of HX from the magnesium salt MgX_2 with serendipitous trace amounts of water in the reaction was responsible for the unexpected hydrohalogenation. Hsung was able to optimise the procedure as to generate α-halo-enamides in good yield and with excellent (*E)*-selectivity. No β-halo-enamides could be detected in Hsung's studies (**Scheme 36**).



Scheme 36. Hsung's α-halo-enamide synthesis from ynamides.

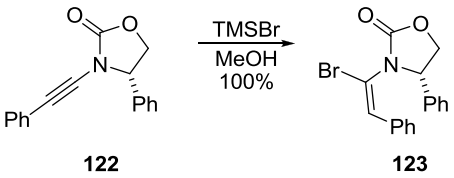
Interestingly, although Hsung's methodology was efficient for the introduction of chlorides, bromides and iodides, it was never used to achieve hydrofluorination. However, in 2012, Evano and co-workers introduced a new methodology for the regio- and stereoselective generation of *(E)*-α-fluoro-enamides *via* hydrofluorination of ynamides using anhydrous HF (**Scheme 37**).[47]



Scheme 37. Evano's hydrofluorination of ynamides.

Another example for the preparation of α-halo-enamides *via* hydrohalogenation of ynamides was recently reported by Flynn.

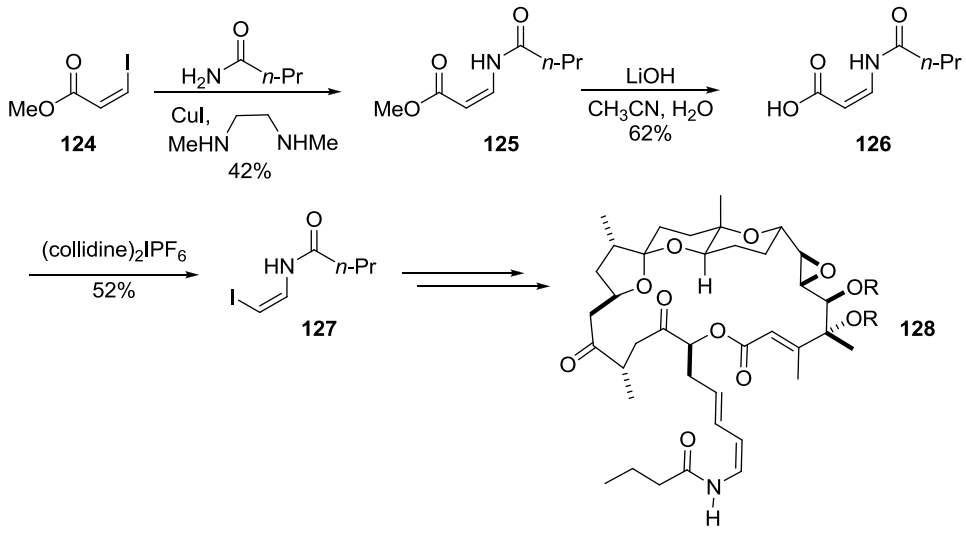
Flynn's approach is based on the use of HBr formed *in situ* from TMSBr and methanol (**Scheme 38**).[48]



Scheme 38. Flynn's hydrobromination of ynamides.

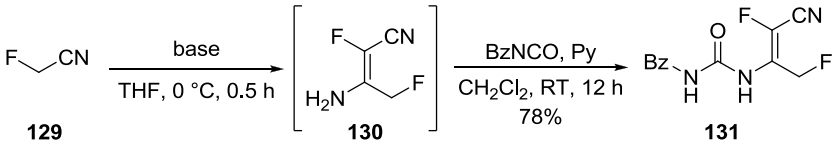
β-Halo-enamides

In contrast to α-halo-enamides, there have been only a small number of efficient methods for the synthesis of β-halo-enamides reported in literature. A typical example of the great difficulties involved in the preparation of these functionalities was presented by Smith in his synthesis of the lateral chain of the lituarines. The synthesis began with *cis*-2 iodomethylacrylate **124** which was converted into enamide **127** through a copper mediated coupling. Ester hydrolysis followed by iododecarboxylation then afforded the β-iodo-enamide **127** in a poor 14% yield over the non-trivial 3 step sequence (**Scheme 39**).[49]



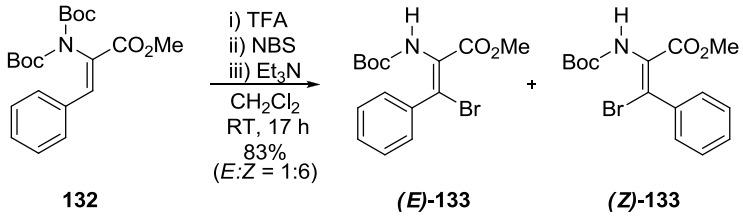
Scheme 39. Smith's synthesis of β-iodo-enamide **127**.

Then, in 2003, Trenkle reported a single example for the preparation of β-halo-enamide **131** based on the Thorpe condensation of difluoro-enamine **130**. The transformation required two steps and proceeded in good overall yield (**Scheme 40**).[50]



Scheme 40. Trenkle's synthesis of β-fluoro-enamide **131**.

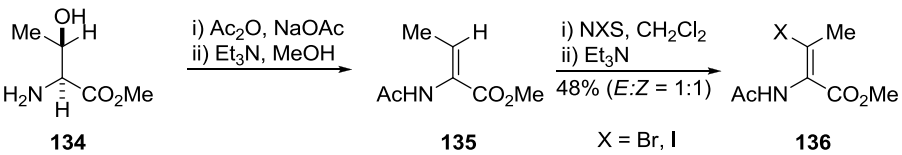
One year later, Ferreira and co-workers reported their studies on the antimicrobial benzo[*b*]thienyl dehydrophenylalanines, the preparation of which involved β-bromo-enamide **133** as a reactive intermediate. The halo-enamide was prepared by means of a three step sequence with moderate stereocontrol (**Scheme 41**).[51]



132 ***(E)*-133** ***(Z)*-133**

Scheme 41. Ferreira's synthesis of β-bromo-enamide **133**.

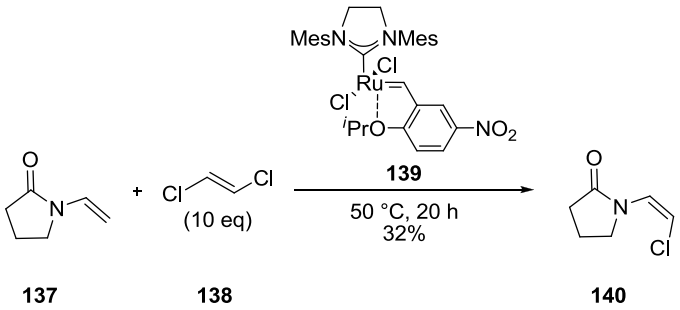
In 2004, Turner explored the use of β-halo-enamides as reactive intermediates for the preparation of branched amino acids. Turner's approach began with dehydration of L-threonine methyl ester **134** to afford the enoate intermediate **135** which, in turn, was halogenated to afford the corresponding enamide **136** in moderate yield. Unfortunately, Turner's approach resulted in enamide formation with no stereocontrol (**Scheme 42**).[52]



134 **135** **136**

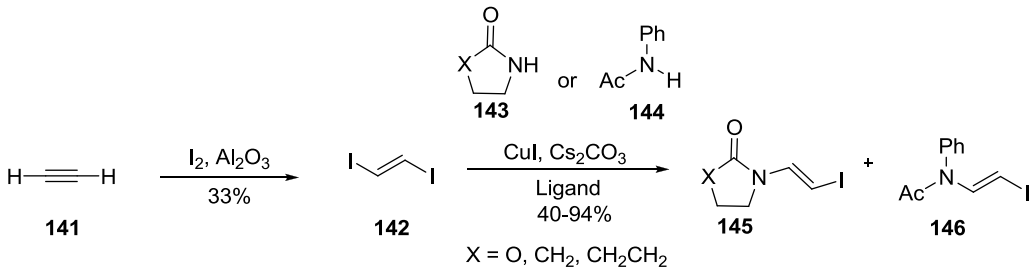
Scheme 42. Turner's synthesis of β-halo-enamides.

In 2008, Grela reported the first successful example of olefin cross-metathesis with chloroalkenes. Using this approach, Grela reported a single example of *(Z)*-β-halo-enamide formation using Grela's catalyst **139**. Grela's catalyst has been described as the boosted version of Hoveyda's catalysts. The reaction proceeds with complete stereocontrol, however, in poor yield and suffers from poor substrate scope (**Scheme 43**).[53]



Scheme 43. Grela's synthesis of β-halo-enamides.

Daoust, on the other hand, took advantage of copper promoted conditions to couple *trans*-1,2-diiodoethene **142** with both cyclic and acyclic amides to yield *(E)*-β-iodo-enamides **145** and **146** (**Scheme 44**). Unfortunately, Daoust's method requires the use of 1,2-diiodoethene **142**, for which only the synthesis of the *trans*-isomer has been reported.[54]

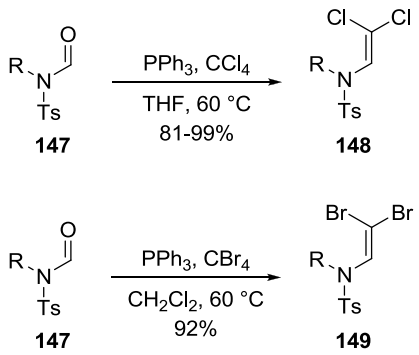


Scheme 44. Daoust's synthesis of *(E)*-β-iodo-enamides.

In conclusion, until now, the existing methodologies for the synthesis of β-halo-enamides are characterised by a series of drawbacks such as poor yields, lack of flexibility and stereocontrol, low substrate scope and often require multi-step procedures.

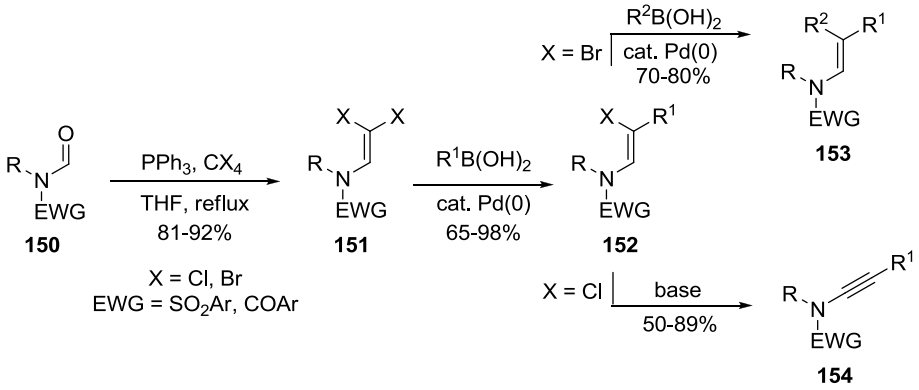
β,β-Dihalo-enamides

Although *gem*-dihalo-olefins have long been considered important and versatile building blocks in palladium-catalysed tandem reactions, nitrogen-substituted *gem*-dihalo-olefins did not receive great attention from the scientific community in the past. However, in the last two decades there has been a rise of interest in the exploitation of nitrogen-containing cyclic and acyclic systems and, thus far, some valid examples of the preparation of β,β-dihalo-enamides have been reported in literature. The first example of dihalo-enamide formation was reported in 2000 by Brückner during his synthesis of *N*-ethynyl-tosylamides. Brückner's approach is based on the use of Ramirez olefination conditions on *N*-formyl-tosylamides to generate dichloro- and dibromo-vinylamides in high yields (**Scheme 45**).[55]



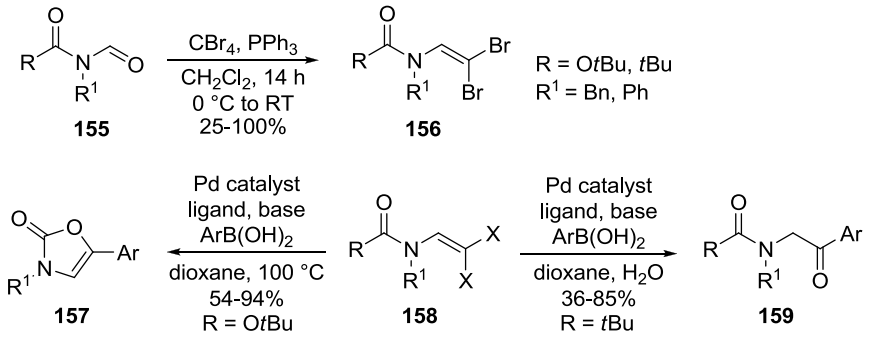
Scheme 45. Brückner's synthesis of β,β-dihalo-enamides.

A few years later, Cossy used β,β-dihalo-enamides for the preparation of branched enamides and ynamides. Cossy's β,β-dihalo-enamides were also accessed *via* Ramirez olefination conditions. Unfortunately, Cossy found the presence of an electron-withdrawing group on the nitrogen to be absolutely necessary for the success of the methodology, which somewhat limited the scope of the reaction (**Scheme 46**).[56]



Scheme 46. Cossy's use of β,β-dihalo-enamides.

In 2010, Lautens and co-workers also studied the synthesis of β,β-dibromo-enamides **156** through the Ramirez protocol and explored their reactivity. This led to the generation of 2-oxazolones **157** in moderate to excellent yield and α-aminoketones **159** in poor to good yield. Lautens corroborated that the Ramirez olefination is applicable only to *N*-protected *N*-formyl imides. Furthermore, only carbonyl derived protecting groups have proven suitable during the transformation (**Scheme 47**).[57]



Scheme 47. Lautens' methodology.

In conclusion, the synthesis of β,β-dihalo-enamides *via* Ramirez olefination proposed by Brückner, Cossy and Lautens proved to be an efficient methodology for the generation of specific *gem*-dihalo-enamides, but lacked a suitably wide scope due to the necessity of an electron-withdrawing protecting group on the nitrogen.

2 Results and Discussion

2.1 The Marquez group approach

Enamides, dienamides and en-ynamides are highly reactive and important building blocks in synthetic, biological and medicinal chemistry as well as materials science. Despite this extensive chemical breadth, there is the lack of a simple, high yielding and efficient method able to deliver these units quickly, and as single components.

The number of different approaches reported for the synthesis of enamides and dienamides reflects their importance and relevance as target units and functional intermediates in materials, synthetic, and medicinal chemistry. Unfortunately, the synthetic methodologies developed thus far enjoy varying degrees of success, particularly concerning the yield and control of double bond geometry. In a number of cases, no control over the geometry of the double bond generated is exhibited. β-Halo-enamides, on the other hand, are extremely versatile units, which provide a viable synthetic platform from which to generate elaborated enamide and dienamide structural units. Hence, reliable and effective methodology able to stereoselectively deliver *(E)*- and *(Z)*-β-halo-enamides would allow their widespread use. To date, synthetic approaches towards the synthesis of β-halo-enamides have been very limited with scarce flexibility, and have been focused on the synthesis of the *(E)*-isomers largely due to the availability of starting materials. Access to the corresponding *(Z)*-β-halo-enamides has proved to be highly challenging as there are no stereoselective synthetic methods currently available for their synthesis.

In the past few years, the Marquez group studies on the synthesis of enamides and dienamides have focused on the exploitation of *N*-formyl imides as reactive intermediates capable of undergoing Wittig-type olefination reactions for the generation of the desired products. On this basis, previous members of the group have developed reliable methodologies for the synthesis of *(E)*-enamides and *(Z,E)*-dienamides.[1a-c,26] However, despite the efficiency of such methods, in some

cases the stereocontrol of the double bond geometry was unsatisfactory, obtaining mixtures of double bond isomers.

Therefore, in order to address these issues, our project focused on the stereoselective synthesis of β-halo-enamides as reliable synthetic platforms from which to generate more elaborated moieties without problems related to stereocontrol (**Figure 14**).

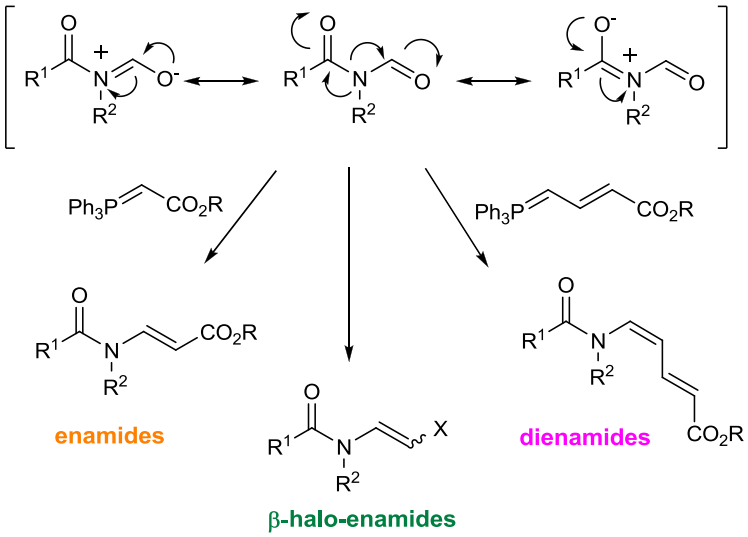


Figure 14. Marquez exploitation of *N*-formyl imides.

The project began with the generation of *N*-formyl imides, which can be readily prepared *via* simple formylation reactions starting from the corresponding lactams or acyclic amides (**Figure 15**).

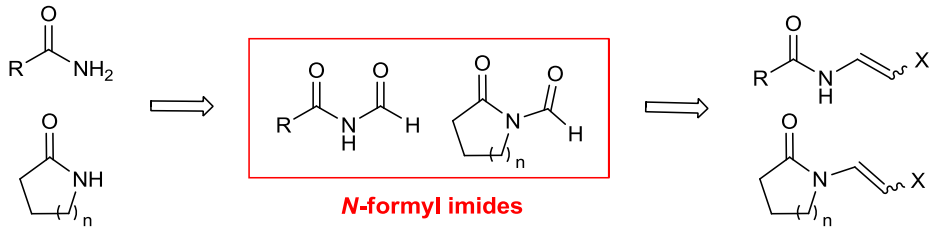
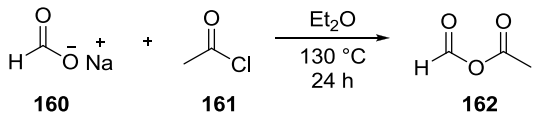


Figure 15. *N*-formyl imides as reactive intermediates.

2.2 *N*-Formyl imides from cyclic lactams

In order to explore the scope and limitations of our methodology, we took into consideration the use of both cyclic and acyclic amides. Lactams were chosen as the cyclic model units due to their affordability and availability in varying ring sizes. For the acyclic systems, a selection of aliphatic and aromatic, primary and secondary amides was considered. The formylation of the lactams was straightforward with the use of acetic formic anhydride as formylating agent. The anhydride was easily prepared by acetylating sodium formate (**Scheme 48**).[1a-c]



Scheme 48. Preparation of acetic formic anhydride.

Direct treatment of the lactam with the freshly prepared anhydride, afforded the desired *N*-formylimide. The formylation was straightforward and efficient, required minimum purification effort and provided the desired cyclic *N*-formyl imides, ready to be utilised in the subsequent halo-olefination reactions (**Table 1**).

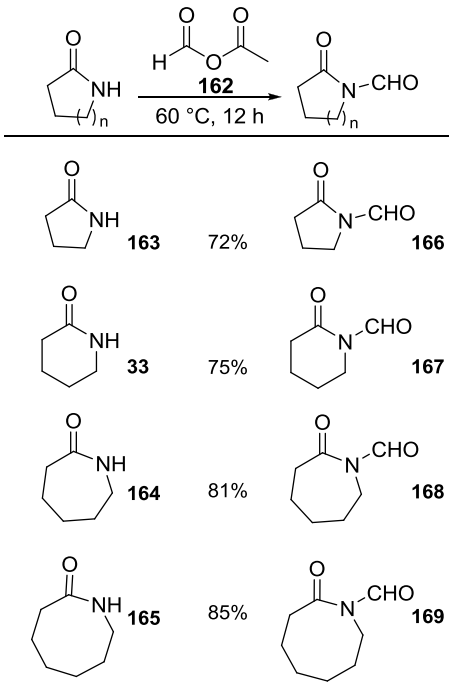


Table 1. Preparation of *N*-formyl imides from lactams.

2.3 Formylation

In contrast to the cyclic amides, which were easily formylated by treatment with acetic formic anhydride, the acyclic amides, due to their non nucleophilic character, required the use of stronger formylating conditions. For this reason, a series of formylating agents and experimental conditions were evaluated.

The formyl group itself has deep roots in organic chemistry and the term “formyl” derives from the Latin “formica”, meaning “ant”, as formic acid is one of the major components of ant fluids and tissues. The formyl carbonyl group shows a great polarisability due to its two components: a hard donor oxygen (hard base) and a reasonably hard acceptor carbon (hard acid). If the formyl group is attached to a heteroatom with a lone pair of electrons (like a nitrogen) the carbonyl carbon becomes softer. There has consistently been significant interest in the formyl moiety in organic synthesis with the aim to improve one carbon extension reactions. For such reasons, formylation is an integral part of organic, medicinal and biological chemistry both in industrial and academic settings. A reflection of this importance is the number of approaches and reagents that have been developed to achieve it (**Figure 16**).[58]

However, most of the formylating reagents developed to date suffer from a number of severe disadvantages which has drastically curtailed their use.

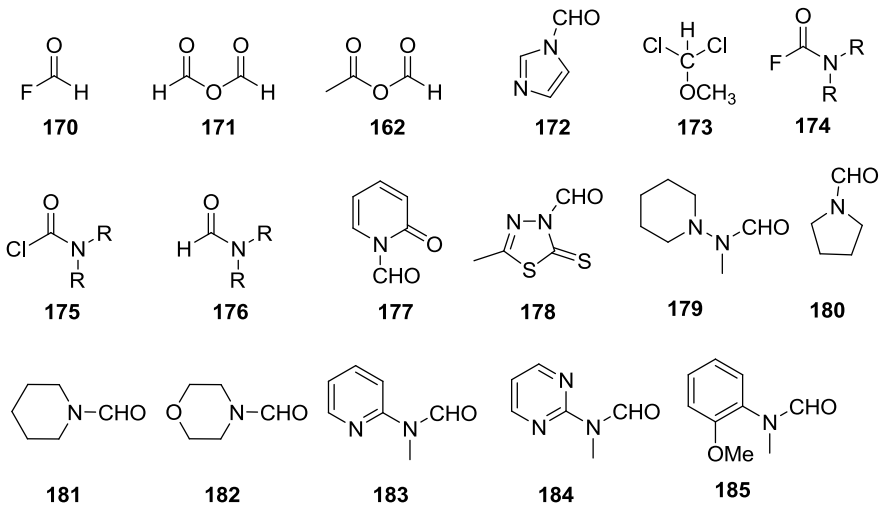
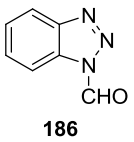


Figure 16. Traditional formylating agents.

The most common formylating agents, for example, formic halides and formic anhydrides tend to suffer from stability issues and degrade easily upon storage. Cyanomethyl formate is a very useful, however, difficult to prepare formylating agent.[59] Isopropenyl formate, on the other hand, is also a very fast and efficient reagent, but its synthesis requires a multi-step sequence. The ozonolysis of oxazoles also leads to formyl compounds but requires the use of ozone. Commercially available *N*-formylimidazole is a valuable formylating agent but is also very hygroscopic. Great instability also characterises *N*-formyl-4-pyridone and *N*-formyl-2-pyridone.[60a-d] Finally, coupling agents have also been used in conjunction with formic acid to achieve *N*- and *O*- formylation, however, the removal of the resultant side products is often labour intensive.[61] Among the others, Katrizky's *N*-formylbenzotriazole has proven to be a valuable, efficient, stable and easy to handle formylating agent.[62]

2.4 *N*-Formylbenzotriazole

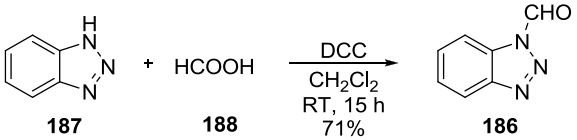
In 1994, Katrizky developed *N*-formylbenzotriazole **186** (**Figure 17**) as a stable and convenient formylating agent to achieve *N*- and *O*- formylation quickly and efficiently.



186

Figure 17. *N*-Formylbenzotriazole **186**.

N-Formylbenzotriazole has become, in a large number of cases, the reagent of choice to achieve the mild and selective formylation of alcohols, amines and even amides. Katrizky's method for the synthesis of *N*-formylbenzotriazole starts with benzotriazole which is coupled with formic acid in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) in anhydrous dichloromethane (**Scheme 49**).

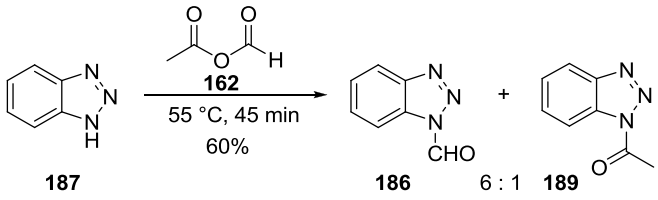


187 **188** **186**

Scheme 49. Katrizky's preparation of *N*-Formylbenzotriazole **186**.

Unfortunately, while the coupling proceeds quickly and efficiently, the separation of the desired *N*-formylbenzotriazole from the urea side product is non-trivial and requires repeated and lengthy purification by recrystallisation which severely decreases the isolated yield. Furthermore, even after repeated recrystallisation and trituration, the *N*-formylbenzotriazole obtained is often contaminated with urea by-products making the yields highly variable and often irreproducible. Efforts in our group to reduce the amount of urea side products by switching to *N,N'*-diisopropylcarbodiimide (DIC) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCi) failed to yield pure *N*-formylbenzotriazole in significant amounts and with the necessary purity. To solve such issues, a fast, efficient and environmentally friendly method for the synthesis of *N*-formylbenzotriazole had to be developed for the successful completion of this project.

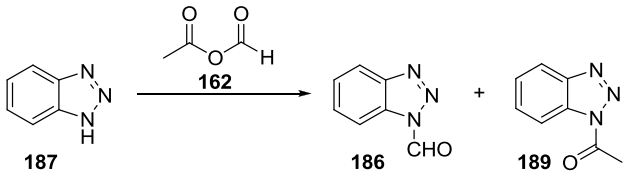
It was hypothesised that acetic formic anhydride **162** might effectively formylate benzotriazole **187** under mild conditions without the need for coupling agents and/or reaction additives. Thus, acetic formic anhydride was formed efficiently from acetic anhydride and formic acid, both under normal heating at 55 °C or at 80 °C under microwave conditions. The newly formed mixed anhydride was then treated with neat benzotriazole **187** at 55 °C. In our initial studies, the reaction mixture was dissolved in ethyl acetate, and the organic layer washed with water. Removal of the solvent under reduced pressure gave a white solid in 60% yield which consisted of *N*-formylbenzotriazole **186** and *N*-acetylbenzotriazole **189** in a 6:1 ratio, but most importantly, without any other side products (**Scheme 50**).



Scheme 50. Preliminary synthesis of *N*-formylbenzotriazole.

Optimisation of the transformation by lowering the temperature of formylation to 0 °C shifted the ratio to 44:1 in favour of the formylated adduct **186**. Further lowering of the temperature to -10 °C increased the selectivity and specificity of the reaction to afford *N*-formylbenzotriazole in a 160:1 ratio and with no detectable

side products. The lower reaction temperatures favour the preferential benzotriazole attack on the formyl as opposed to the more hindered acetyl carbonyl unit. This results in the selective ejection of acetate over a formate leaving group. Additionally, the yield was significantly improved (94%) by eliminating the workup procedure and simply removing the acetic acid by-product under reduced pressure (**Table 2**).

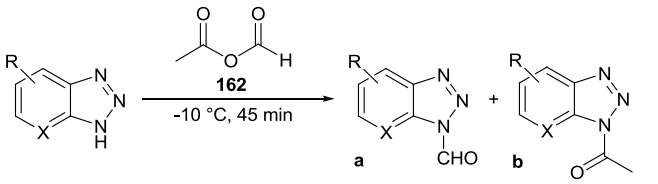


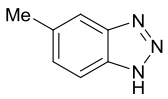
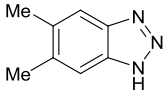
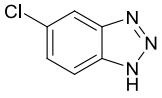
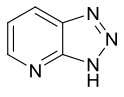
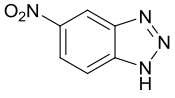
Conditions	Yield	Ratio (**186** : **189**)
55 °C, 45 min[i]	60%[iii]	6 : 1
0 °C, 45 min[i]	77%[iii]	44 : 1
-10 °C, 45 min[ii]	94%	160 : 1

i) Benzotriazole was added neat; *ii)* Benzotriazole was added as a 1M solution in THF; *iii)* Water was added as part of the workup procedure

Table 2. Optimisation of the synthesis.

Faced with such a dramatic improvement, the optimised mixed anhydride formylation conditions were also applied to a number of differently substituted benzotriazoles. In all cases, the formylation took place in excellent yield (**Table 3**).



Entry	Substrate		Yield	Ratio	
1		**190**	99%	43 : 1	**191a**[i] : **191b**
2		**192**	94%	193.6 : 1	**193a** : **193b**
3		**194**	99%	23 : 1	**195a**[ii] : **195b**
4		**196**	96%	5.4 : 1	**197a**[iii] : **197b**
5		**198**	90%	4.5 : 1	**199a**[iv] : **199b**

i) Obtained as a 1.6 : 1.0 mixture of regioisomers. *ii*) Obtained as a 2.5 : 1.0 mixture of regioisomers. *iii)* Obtained as a 12.0 : 1.0 mixture of regioisomers. *iv)* Obtained as a 5.7 : 1.0 mixture of regioisomers

Table 3. Synthesis of substituted *N*-formylbenzotriazoles.

As expected, formylation of unsymmetrical, 5-substituted benzotriazoles results in the formation of various ratios of formylated regioisomers depending on the electronic nature of the substituent group. The structure of the major regioisomer was established through selective NOESY studies (**Figure 18**).

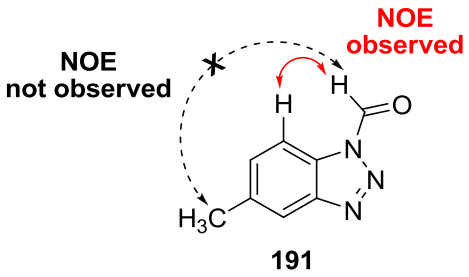
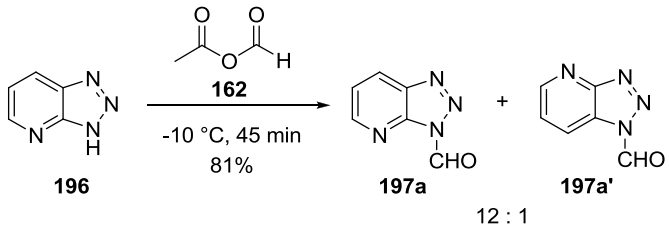


Figure 18. Selective NOE confirmation of the regioselectivity of the reaction.

Interestingly, the presence of electron withdrawing substituents on the benzotriazole unit resulted in a decrease in the formylation selectivity, presumably due to the lower reactivity of the benzotriazole core unit.

Acetic formic anhydride also formylated effectively the azo-analogue **197** (entry 4) in excellent yield and with good selectivity relative to the acetylated product. Interestingly, a 12:1 ratio of *N*-formylated regioisomers was obtained (**Scheme 51**).



Scheme 51. Synthesis of the azo-analogue **197**.

NOE studies show that formylation takes place preferentially on the same side as the pyridine ring's nitrogen. Indeed, no NOE interaction was observed between the formyl proton and any ring protons, indicating the presence of the formyl group adjacent to the heteroatom (**Figure 19**). The observed regioselectivity can be explained through a zwitterionic intermediate analogous to that proposed by Carpino for 1-hydroxy-7-azabenzotriazole (HOAt)[63] (**Figure 20**).

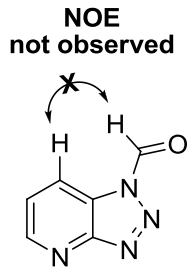


Figure 19. NOE confirmation of the regioselectivity of the reaction.

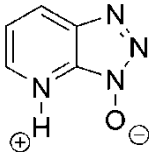
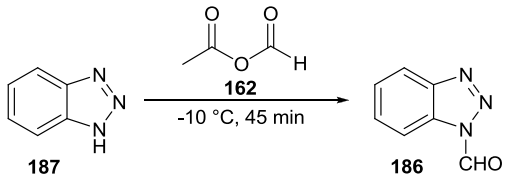


Figure 20. Carpino's zwitterionic intermediate.

Having explored the scope of the reaction conditions to formylate other benzotriazole systems, the feasibility for scaling the process up was then assessed (**Table 4**). We were pleased to see that increasing the scale of the reaction had minimal effect on the yield and the purity of the *N*-formylbenzotriazole **186** obtained. Most importantly, there was no product purification required regardless of the reaction scale. The volume of THF used was also significantly decreased by increasing the concentration of benzotriazole in THF up to 1.8 M without any significant drop in yield, purity or selectivity. Furthermore, preliminary results suggest that it might be possible to use non-anhydrous conditions during the formylation.



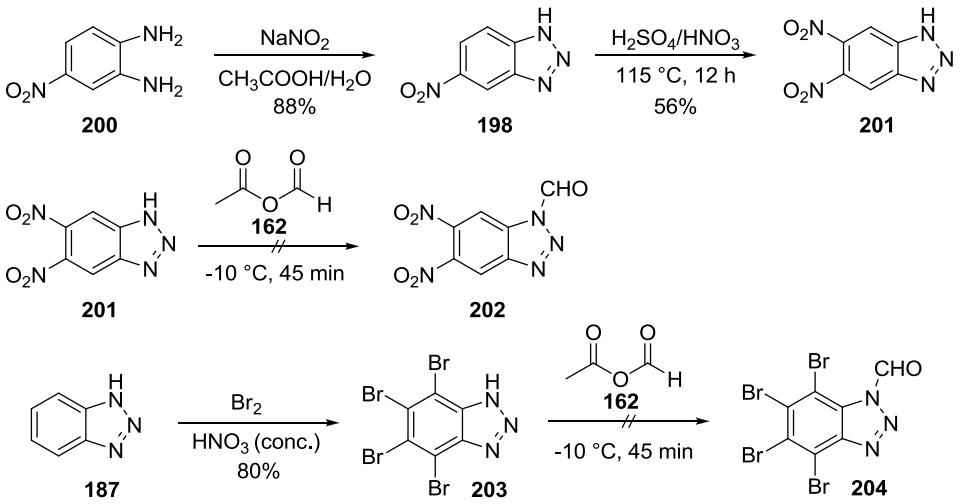
Entry	Amount	Yield	Purity
1	2.98 g[i]	94%	99+%
2	4.16 g[i]	96%	98.5%
3	13.09 g[i]	98%	99+%
4	29.00 g[ii]	99%	99+%
5	64.29 g[ii]	98.5%	98.5%

i) Added as a 1M soln in THF; *ii)* Added as a 1.8 M soln in THF.

Table 4. Scale-up of the reaction.

In summary, a fast, efficient, and environmentally friendly procedure for the synthesis of *N*-formylated benzotriazoles was developed. This method required very small amounts of organic solvent and produced acetic acid as the only significant side product. The THF used in the reaction mixture can be recovered during the evaporation step, thus causing minimal environmental impact and minimising costs. As a whole, this procedure represents a great improvement compared to other methods currently available for the synthesis of *N*-formylbenzotriazole in terms of cost, yield and overall efficiency.

Attention was then focused on the synthesis of the tetrabromo-derivative **204** and the dinitro-derivative **202**. It was expected that the symmetry of their structure would avoid the formation of mixtures of regioisomers and of special interest was the inductive and electronic nature of their substituents which should increase the reactivity. Disappointingly, while the synthesis of the starting materials **201** and **203** proceeded smoothly, their formylation was unsuccessful (**Scheme 52**).



Scheme 52. Efforts towards the synthesis of new *N*-formylbenzotriazoles.

2.5 *N*-Formyl imides from acyclic amides

Thanks to the development of this novel efficient procedure for the synthesis of highly pure *N*-formylbenzotriazole, it was possible to successfully subject a series of acyclic amides to our previously used formylation conditions.[1a-c]

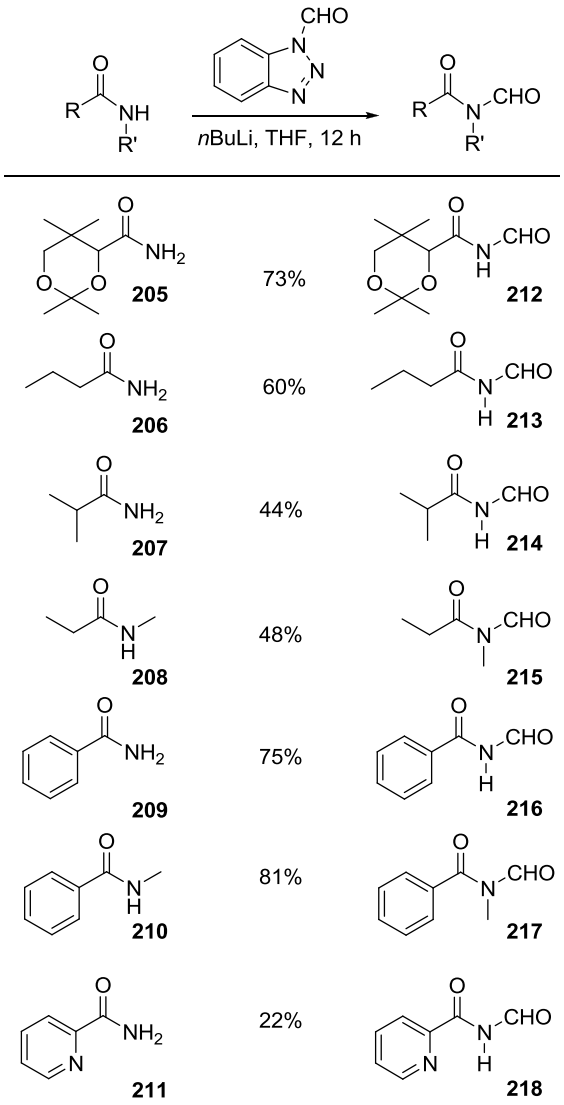


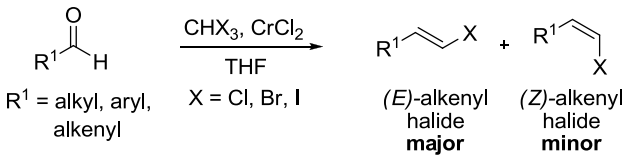
Table 5. Synthesis of acyclic *N*-formyl imides.

Apart from a few exceptions, the transformation was satisfactory and afforded the desired *N*-formyl imides in high purity, ready to be used in the subsequent step of halo-olefination.

2.6 Halo-enamides *via* Takai olefination

With the *N*-formyl imides in hand, we focused our efforts towards the development of an efficient approach to the regioselective synthesis of β-halo-enamides as well as a demonstration of their practical synthetic potential.

The first attempt was based on the Takai olefination to afford the respective β-iodo-enamides. This olefination reaction was introduced by Takai and Utimoto in 1987 and describes the simple and stereoselective conversion of an aldehyde to the resulting *(E)*-alkenyl halide, after treatment with a haloform-chromium(II)-chloride system. The organochromium species can be generated from iodoform, bromoform or chloroform and an excess of chromium(II) chloride (**Scheme 53**).[64a,b]



Scheme 53. Takai-Utimoto olefination.

The *E/Z* ratio depends on the haloform used (Cl>Br>I), with best selectivity observed when X = Cl. The rate of the reaction is also correlated to the haloform used: I>Br>Cl. Iodoform reacts rapidly at low temperatures (0 °C) while the other haloforms require higher temperatures to react.

The mechanistic details of this transformation are not yet completely known, however, a plausible hypothesis is that the reaction proceeds *via* geminal-dichromium intermediates, that are nucleophilic and attack the carbonyl compound to form a β-oxychromium intermediate, which then evolves towards the desired *(E)*-alkene (**Figure 21**).

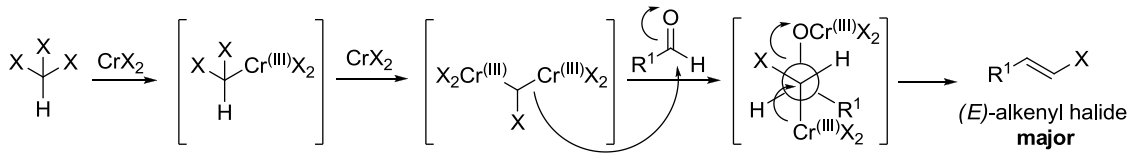
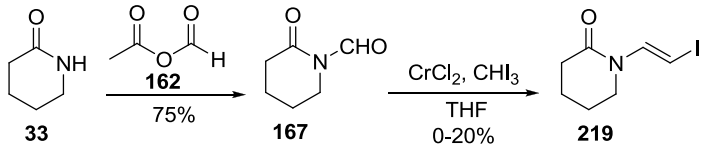


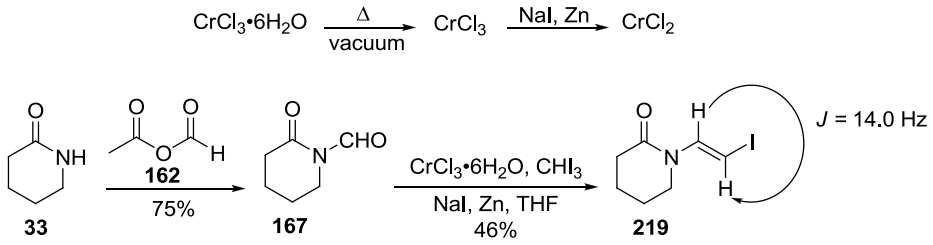
Figure 21. Mechanism of the Takai-Utimoto reaction.

Our initial studies began with valerolactam **33**, which was efficiently *N*-formylated using acetic formic anhydride **162** to generate the desired *N*-formyl imide **167** under our previously reported conditions.[1a-c] Treatment of *N*-formyl imide **167** under standard Takai conditions using commercially sourced chromium(II)chloride afforded the desired β-iodoenamide **219** in variable yields, and as inseparable mixtures of *(E)*- and *(Z)*- isomers. Unfortunately, the reaction proved to be highly dependent on the quality of the commercially sourced chromium(II)chloride employed. In a number of cases, the iodoolefination failed to yield any of the desired β-iodo-enamide adduct (**Scheme 54**).



Scheme 54. Takai olefination of *N*-formylimide **167**.

Faced with such an erratic procedure, a more reproducible and reliable method was sought. Gratifyingly, treatment of *N*-formyl imide **167** according to Auge's modification of the Takai reaction, in which chromium(III)chloride hydrate is reduced *in situ* using zinc, yielded the desired β-iodo-enamide **219** in moderate yield, and significantly, as a single *(E)*- double bond isomer (**Scheme 55**).[65]



Scheme 55. Auge's modification of Takai reaction.

The assignment of the double bond geometry of the newly formed β-iodo-enamide **219** was confirmed by both ^{1}H NMR and crystallographic analysis (**Figure 22**).

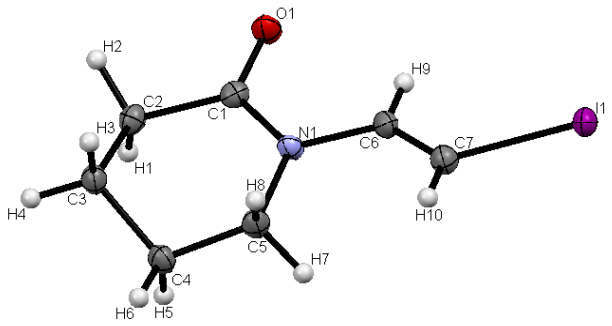


Figure 22. Crystal structure of β-iodo-enamide **219**.

Using the optimised conditions, a library of lactams were formylated and the resulting *N*-formyl imides **166-169** were treated under Auge's modified Takai conditions to generate the desired β-iodo-enamides **219-222** in moderate yield (**Table 6**). In all cases, only the *(E)*-isomer was detected both in the ^{1}H NMR of the crude reaction mixture and after purification by column chromatography.

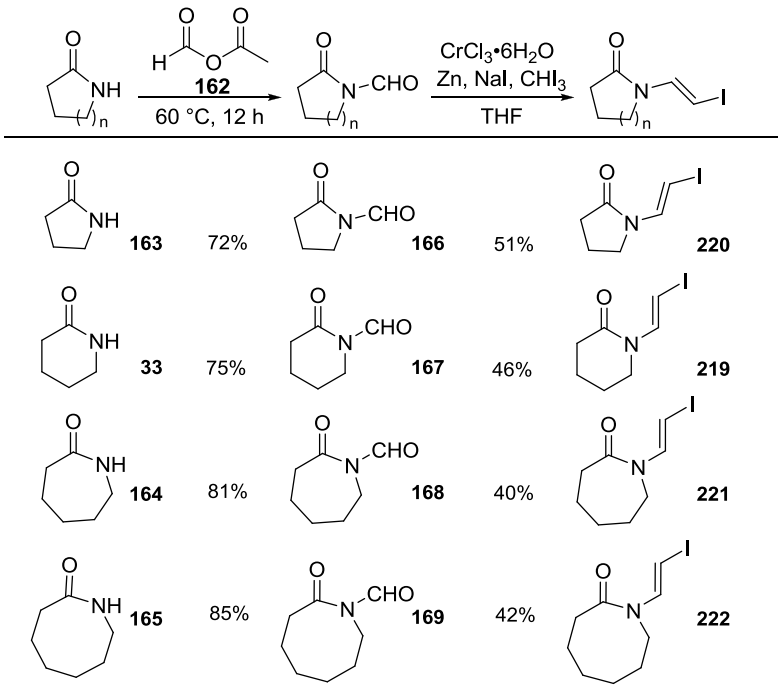


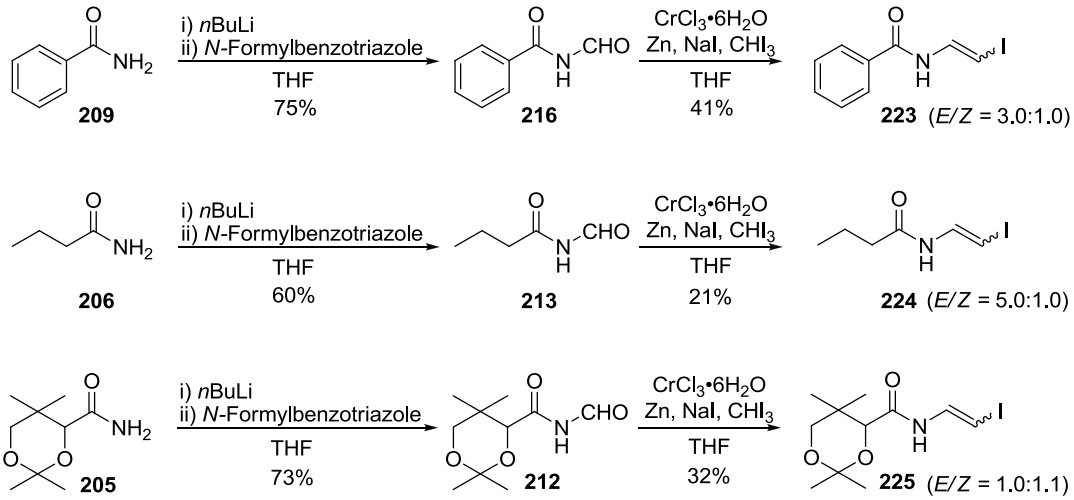
Table 6. Synthesis of β-iodo-enamides from cyclic *N*-formyl imides.

Having shown the ability of cyclic *N*-formyl imides to undergo iodoolefination, we became interested in exploring acyclic *N*-formyl imides as Takai olefination substrates. The idea of having an unprotected imide is very appealing as this

would avoid the need to subject the often unstable enamide derivatives to the generally incompatible conditions required for the removal of nitrogen protecting groups.

Thus, acyclic amides **205**, **206** and **209**, were *N*-formylated using *N*-formylbenzotriazole/*n*BuLi. The quality and the purity of *N*-formylbenzotriazole are essential for obtaining pure *N*-formyl imides in reproducible yields.

Iodoolefination of acyclic imides **212**, **213** and **216** under Auge's conditions however, yielded some very interesting and intriguing results. *N*-Formylbenzimide **216** and *N*-formylbutyrimide **216** yielded mixtures of *(E)/(Z)*-iodo-enamides **223** and **224** in which the *(E)*-iodo olefin was the major isomer. In the case of the dioxolane substituted *N*-formyl imide **212**, on the other hand, a nearly equal mixture of *(E)/(Z)* iodo-olefins **225** was obtained in which the *(Z)*-isomer was slightly predominant. Interestingly, the dioxolane derived *(E)*-iodoenamide ***225E*** proved to be unstable to normal separation conditions and underwent decomposition during the purification procedure (**Scheme 56**).



Scheme 56. Synthesis of β-iodo-enamides from acyclic *N*-formyl imides.

We believe that the marked difference in behaviour during the iodo-olefination between the lactam derived imides and the acylic cases can be attributed to the geometry of the *N*-formyl imide. In the lactam cases, the cyclic nature of the imide unit severely restricts the conformational flexibility of the imide unit, which in turn translates into the generation of a single *(E)*-iodo-olefin isomer.

In the case of the acyclic *N*-formyl imides, the situation is more complicated. Crystallographic data for *N*-formyl imides **216** and **212** suggest that the *N*-formyl carbonyl adopts a similar conformation within the two imides[1c] (**Figure 23**).

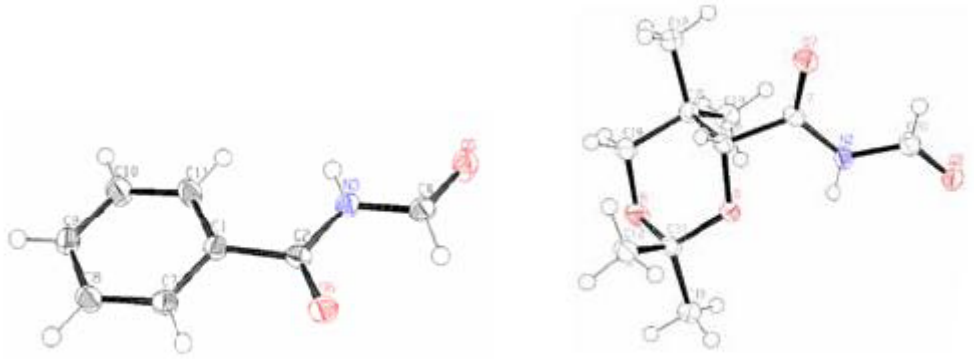


Figure 23. *N*-formylbenzimide **216** and dioxolane derived *N*-formylimide **212**.

This would imply that it is the rotational freedom of the imide unit along the bond between the internal carbonyl and the acyclic unit that determines the selectivity of the reaction. This would be consistent with the results observed in which the alkyl group in imide **212** exerts a slightly greater influence on the imide conformation than the flat aromatic substituent in imide **216**.

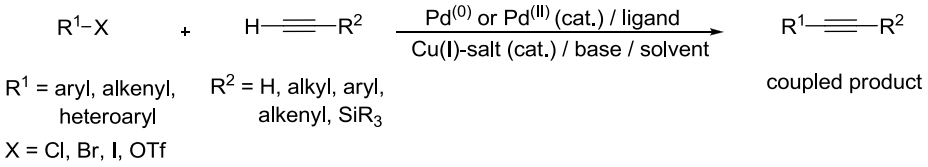
The geometry of *N*-formyl imide **212** on the other hand, is influenced by the conformation of the dioxolane ring as well as the potential interaction of the imide unit with the proximal oxygen of the ketal unit.

2.7 Sonogashira coupling

Having generated the desired β-halo-enamides, we were interested in their utility in combination with other methodologies (for example, metal mediated couplings) to generate novel, and diverse building units.

It was initially decided to evaluate the ability of β-iodo-enamides to undergo palladium-mediated Sonogashira couplings with the aim to generate novel β-yn-enamide units. It was reasoned that structurally constrained β-yn-enamides could have applications as reactive intermediates in both synthetic and medicinal organic chemistry. Furthermore, their defined molecular shape makes them potential candidates for the development of molecular tweezers and other structurally defined units in materials and supramolecular chemistry.

The Sonogashira coupling was introduced for the first time in 1975, when Sonogashira and co-workers reported the copper-palladium catalysed coupling of terminal alkynes with aryl and vinyl halides to give enynes (**Scheme 57**).



Scheme 57. Sonogashira coupling.

The copper(I) salt can be commercially available CuI or CuBr and is only needed in catalytic amounts (0.5-5 mol%) with respect to the halide or alkyne, often the base serves as the solvent, but occasionally a co-solvent is used. Crucially, the reaction does not require rigorous drying. The coupling is also stereospecific as it preserves the stereochemistry of the substrates in the products. The order of reactivity for aryl and vinyl halides is I~OTf>Br>>Cl. Although, almost all functional groups are tolerated, alkynes with conjugated EWG tend to rearrange to allenes. The large functional group tolerance has rendered the Sonogashira coupling extremely useful in the late stages of total synthesis. There are only few limitations to this methodology, such as the use of high temperatures for unreactive or bulky substrates and the potential side reactions of alkynes at high temperature.

The mechanism of the Sonogashira coupling follows the traditional pathway of oxidative addition and reductive elimination, however, some mechanistic details such as the catalytically active species remain unknown. The sequence begins with the generation of the $Pd^{(0)}$ species from a $Pd^{(II)}$ complex by reduction with the alkyne or with a phosphine ligand. The $Pd^{(0)}$ species is then subjected to oxidative addition with the aryl or vinyl halide, followed by transmetallation by the copper(I)-acetylide. Reductive elimination affords the desired coupled product and the cycle ends with the regeneration of the catalyst (**Figure 24**).[66]

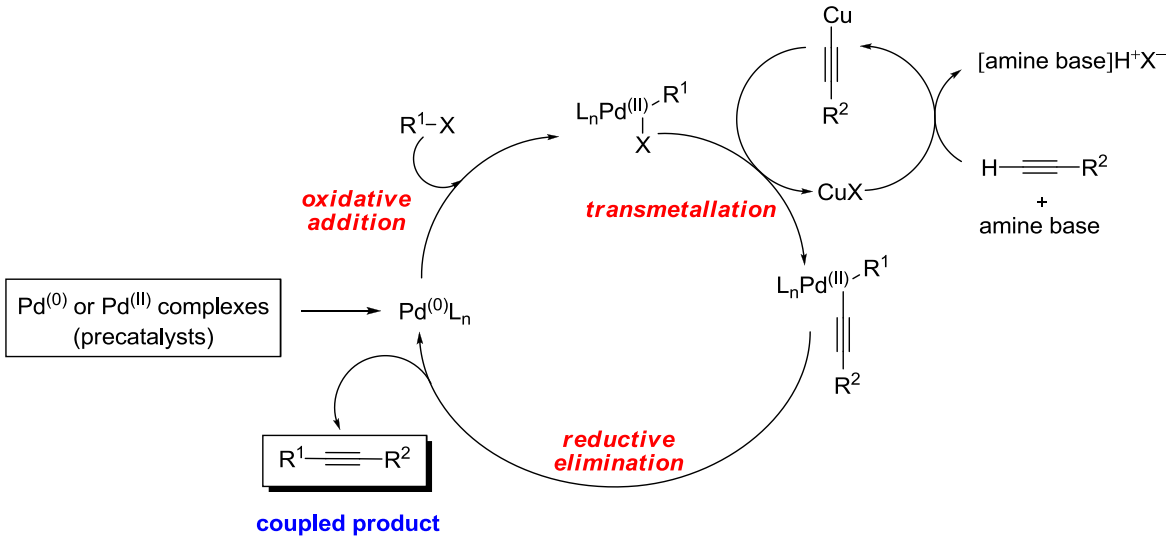
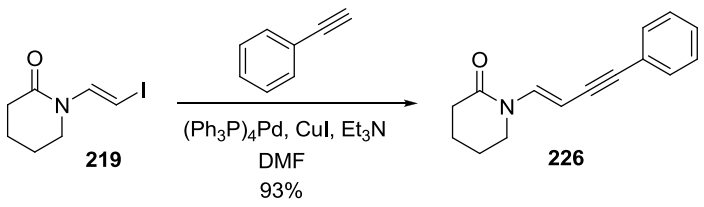


Figure 24. Sonogashira coupling's mechanism.

Initial Sonogashira coupling of β-iodo-enamide **219** with phenyl acetylene afforded the desired β-yn-enamide **226** in excellent yield and as a single isomer (**Scheme 58**). The structural assignment of the β-yn-enamide **226** was corroborated by X-ray crystallography (**Figure 25**).[67]



Scheme 58. Sonogashira coupling.

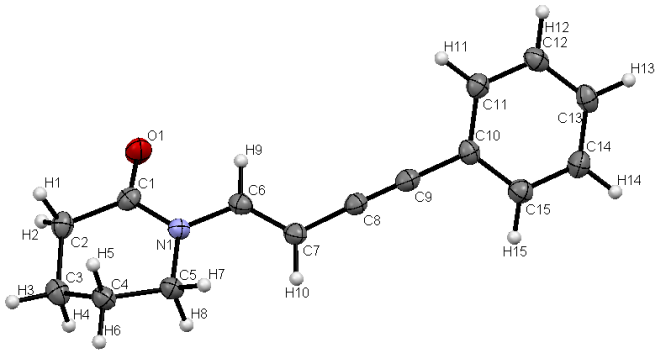


Figure 25. Crystal structure of compound **226**.

The excellent yield observed in the Sonogashira cross-coupling of β-iodo-enamide **226** and phenyl acetylene was then reproduced with a number of phenyl substituted acetylenes using both cyclic and acyclic β-iodo-enamides to generate the β-yn-enamides **227-232**. However, when alkyl substitued alkynes were used in the cross-coupling, a significant drop in the yield of the β-yn-enamides **231** and **232** obtained was observed. We believe that this difference in yield between the alkyl substituted and phenyl substituted alkyne β-yn-enamide products is due to the greater stability of the phenyl β-yn-enamide adducts obtained rather than due to the Sonogashira coupling itself (**Table 7**).

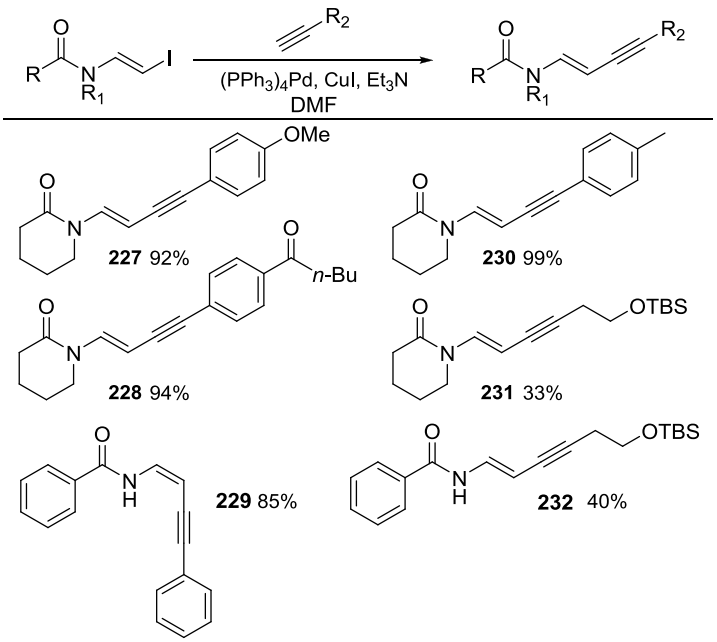
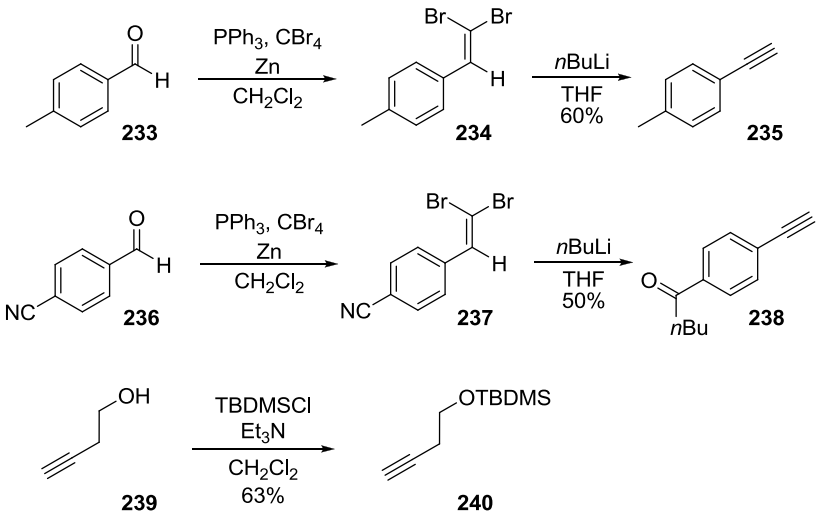


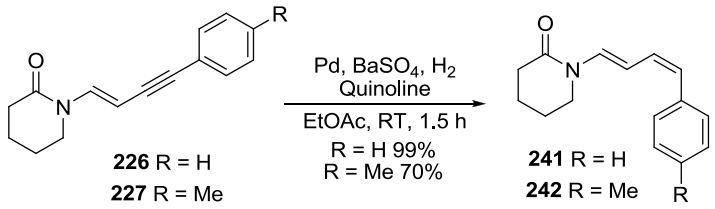
Table 7. β-yn-enamides.

The custom alkynes **235** and **238** used for the Sonogashira coupling were easily prepared following the traditional Corey-Fuchs procedure, while the alkyne **240** was prepared *via* TBDMS protection (**Scheme 59**).



Scheme 59. Custom alkynes for Sonogashira coupling studies.

Furthermore, preliminary evidence demonstrated that it is possible to selectively reduce the recently obtained β-yn-enamides to selectively generate *(E,Z)*-dienamides in excellent yield through catalytic hydrogenation (**Scheme 60**).



Scheme 60. Reduction of β-yn-enamides to *(E,Z)*-dienamides.

The stereochemistry of the dienamides obtained was confirmed *via* ^{1}H-NMR studies together with NOE studies. The observed *J* values of 14 Hz and 11 Hz are a clear indication of the geometry of the two double bonds in the *(E,Z)*-dienamides. In addition, NOE correlations were observed between the lactam ring and the aromatic ring, as well as between the protons of the dienamide moiety; those correlations are possible only in the presence of a *cis* double bond (**Figure 26**).

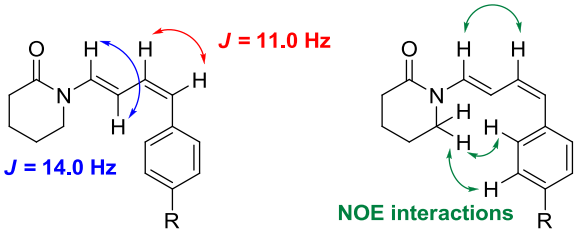


Figure 26. NMR observations.

In conclusion, we have developed a fast and efficient method which takes advantage of the pseudo-aldehyde behaviour of *N*-formyl imides to access β-halo-enamides in a single step, in moderate-good yields and without the need for nitrogen protecting groups. The β-halo-enamides can be easily functionalised into β-yn-enamides and dienamides in excellent yields and with complete selectivity.

We believe that this route complements and expands the methodologies currently available for the synthesis of β-haloenamides, β-yn-enamides and dienamides, and can be easily modified for the generation of novel structural motifs with potential applications in synthetic, biological, medicinal, supramolecular and materials chemistry.[68]

Despite these promising results, this route required the use of toxic chromium salts and was limited to the synthesis of *(E)*-halo-enamides. As a result, we next focused our attention on the development of a synthetic method for the *(Z)*-selective generation of β-halo-enamides.

2.8 Stork-Zhao olefination

Our initial approach to the synthesis of *(Z)*- β-halo-enamides was focused around the Stork-Zhao modification of the Wittig olefination.

The reaction of a phosphorus ylide with a carbonyl unit was introduced by Wittig and Gessler in 1953, and is considered the most widely recognised method for carbonyl olefination. The Wittig reaction is a *syn* elimination, driven by the strength of an oxygen-phosporus bond. The elimination step occurs from an *in situ* generated intermediate, which decomposes spontaneously.

Mechanistically, the reaction begins with a phosphonium salt that is deprotonated by a moderately strong base to form the corresponding ylide. The ylide is the nucleophilic species which attacks the carbonyl group to generate the intermediate betaine, which, in turn, evolves to the 4-membered ring oxaphosphetane intermediate. This species is very unstable and evolves spontaneously towards the desired alkene and the phosphine oxide as a by-product *via* elimination. The formation of the phosphorus-oxygen double bond is responsible for driving the reaction equilibrium towards product formation (**Figure 27**).[69a]

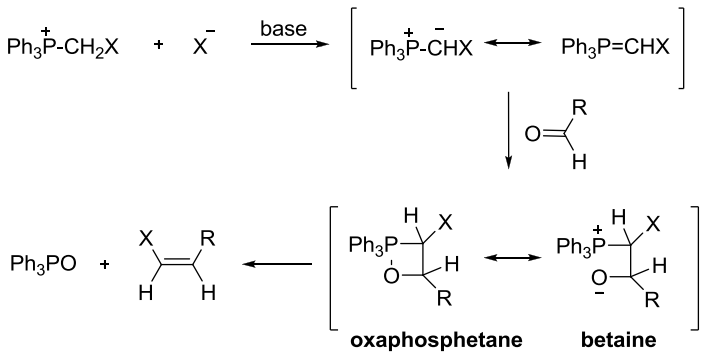


Figure 27. The Wittig-type olefination reaction.

The stereochemical outcome of the reaction depends on the nature of the ylide employed. In fact, the stabilised ylides (so called because the negative charge is stabilised by an adjacent EWG) evolve towards *(E)*-alkenes and the unstabilised ylides, on the other hand, towards *(Z)*-alkenes. The *(Z)*-selectivity in Wittig reactions of unstabilised ylides can be explained through the stereoselective formation of the *syn* oxaphosphetane intermediate, followed by a stereospecific

elimination. The *syn* oxaphosphetane is favoured because the large substituents tend to orientate themselves as far as possible in the transition state (**Figure 28**).[69b]

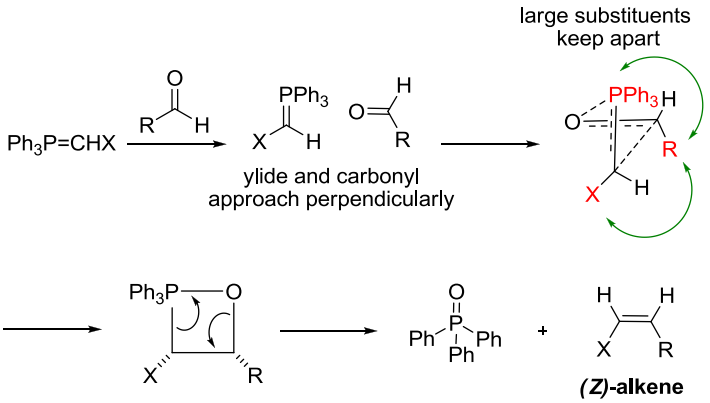
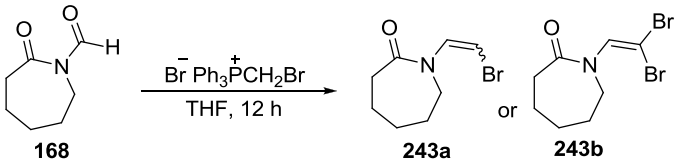


Figure 28. Stereoselectivity of the Stork-Zhao olefination reaction.

Our Stork-Zhao olefination studies began with the caprolactam derived *N*-formyl imide **168** which was treated under classic Stork-Zhao's olefination conditions[70] using bromomethylenetriphenylphosphorane[71a,b] and NaHMDS. Unfortunately, the reaction failed to generate the desired *(Z)*-bromo-enamide. After extensive experimentation, with a number of different bases and varying amounts of phosphonium salt, the desired *(Z)*-bromo-enamide was detected only in poor yields. However, using a 10-fold excess of phosphonium salt and switching the base to *t*BuOK, cleanly converted the *N*-formyl imide **168** into the unexpected dibromo-enamide **243b** in excellent yield (**Table 8**).

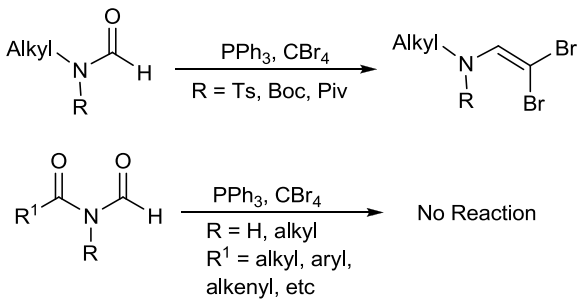


168 **243a** **243b**

Base	Br Ph$_3$PCH$_2$Br	T	Yield
NaHMDS (*2 eq*)	(*2 eq*)	RT	*No Reaction*
NaHMDS (*10 eq*)	(*10 eq*)	reflux	*No Reaction*
NaHMDS (*10 eq*)	(*10 eq*)	RT	**243a** 10% (*E*/*Z* 1:0)
KHMDS (*10 eq*)	(*10 eq*)	RT	**243a** 30% (*E*/*Z* 1:1)
LiHMDS (*10 eq*)	(*10 eq*)	RT	*No Reaction*
LiHMDS (*10 eq*)	(*10 eq*)	reflux	*No Reaction*
KO*t*Bu (*5 eq*)	(*5 eq*)	RT	**243b** 20% (60% brsm)
KO*t*Bu (*10 eq*)	(*10 eq*)	RT	**243b** 93%

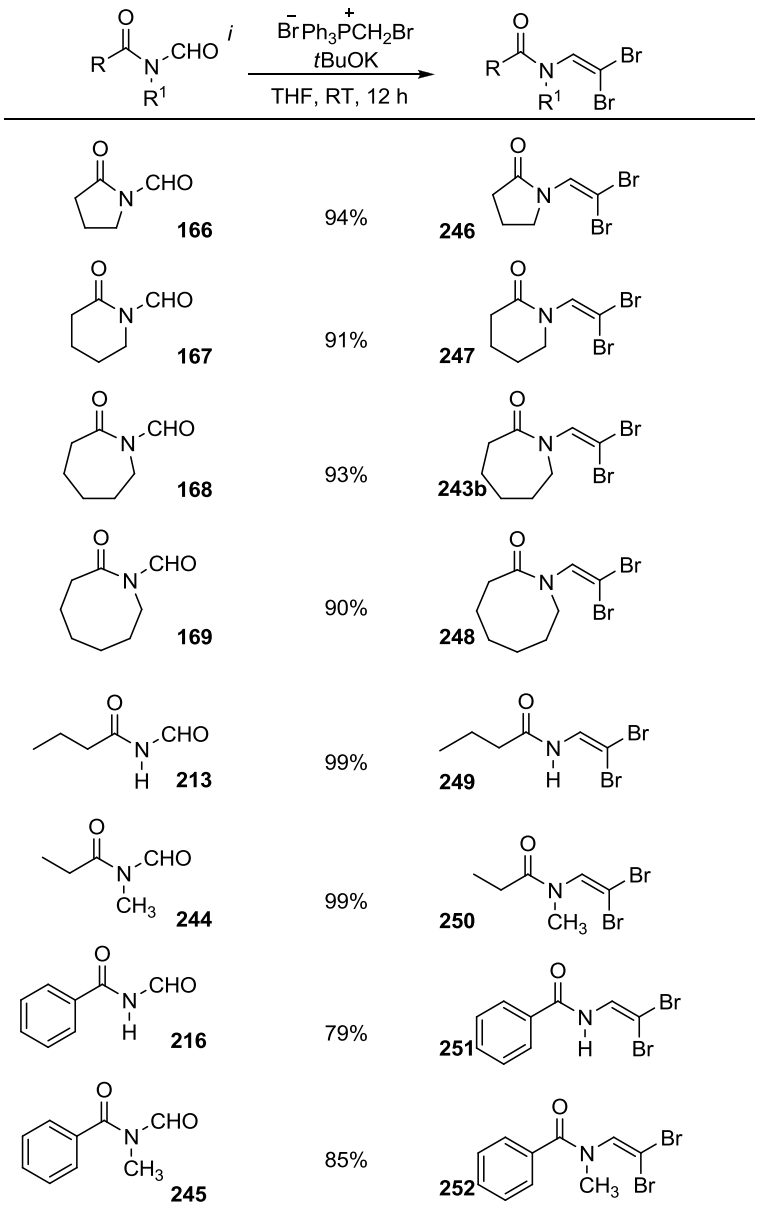
Table 8. Synthesis of β,β-dibromo-enamide **243b**.

Dibromo-enamides are well-known synthetic intermediates which have been previously accessed through the use of a Ramirez olefination.[55,56] Unfortunately, the Ramirez conditions are limited to the dibromo-olefination of tosyl-, Piv- and Boc- imides, and are not applicable to unprotected imide systems (**Scheme 61**). Indeed, Lautens reported that the *gem*-dibromination of formamides only works when an *N*-carbonyl protecting group (Boc or Piv) on the formamide is present.[57]



Scheme 61. Previous syntheses of β,β-dibromo-enamides.

Hence, the unexpected and high yielding imide dibromo-olefination reaction could provide a viable synthetic alternative for the synthesis of structurally diverse β,β-dibromo-enamide units. Significantly, consistently, excellent results were obtained when the same bromo-olefination conditions were applied to a wide variety of *N*-formyl imides (**Table 9**).

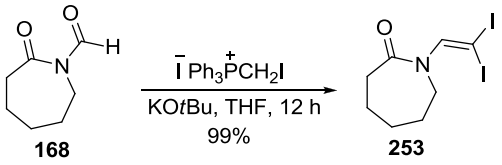


i)All reactions were conducted using 1 eq of N-formyl imide, 10 eq of salt and 10 eq of base in dry THF (0.33 M) at RT for 12 hours.

Table 9. Effect of imide substitution on dibromo-olefination.

Faced with such satisfying yields and scope for the synthesis of dibromo-enamides, we were curious to discover whether similar results could be obtained using iodomethylenetriphenylphosphorane. Initial iodo-olefination of *N*-formyl imide **168** matched the results obtained during the bromo-olefination, yielding diiodo-enamide **253** in excellent yield (**Scheme 62**).

The structure of the diiodoenamide **253** was corroborated by crystallographic analysis (**Figure 29**).



Scheme 62. Synthesis of β,β-diiodo-enamide **253**.

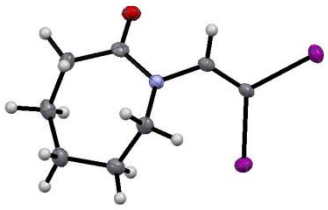
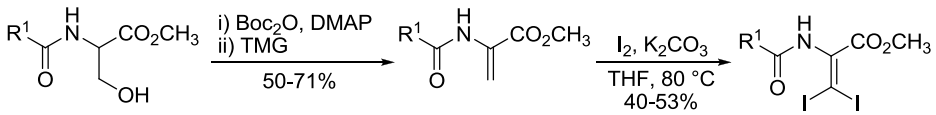


Figure 29. Crystal structure of diiodo-enamide **253**.

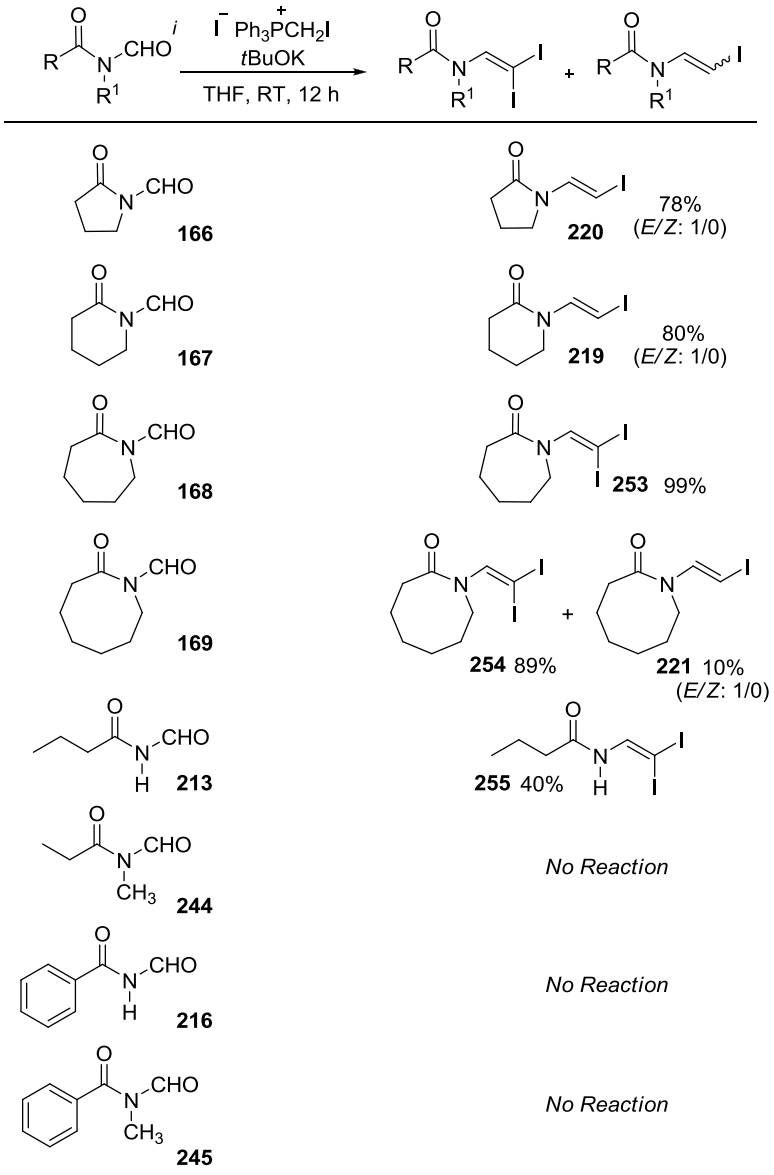
Currently, the only other report in the literature for the synthesis of β,β-diiodo-enamides is that of Ferreira and co-workers, who reported the generation of β,β-diiodo-enamides in highly variable yields by treatment of amino acid derived enamides with I_2 at 80 °C (**Scheme 63**).[72a,b]



Scheme 63. Ferreira's synthesis of β,β-diiodo-enamides.

Application of identical iodo-olefination conditions to the model group of *N*-formyl imides previously used demonstrated that the iodo-olefination is substrate dependent (**Table 9**), a fact previously noted by Ferreira in his enamide iodination studies. For instance, iodo-olefination of *N*-formyl imide **169** under the same conditions yielded the diiodo-enamide **254** together with traces of the unexpected *(E)*-iodo-enamide **221**. The iodo-olefination of the *N*-formyl imides **166** and **167** on the other hand resulted in the exclusive formation of β-iodo-enamides **220** and **219** respectively. In both instances, the reaction proceeded in good yield and with complete *(E)*-double bond selectivity.

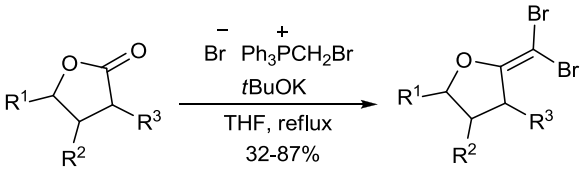
Interestingly, aromatic *N*-formyl imides (**216**, **245**) proved inert under the reaction conditions affording only starting materials, while the same *N*-formyl imides proceeded cleanly to generate the dibromo-enamide products. Furthermore, the steric environment surrounding the *N*-formyl group seems to influence the iodo-olefination significantly; for instance, whilst the butyramide derived imide **213** was diiodo-olefinated in working yields, *N*-methyl propionimide **244** failed to react under identical conditions.



i)All reactions were conducted using 1 eq of N-formyl imide, 10 eq of salt and 10 eq of base in dry THF (0.33M) at RT for 12 hours.

Table 9. Iodo-olefination of *N*-formyl imides.

This result was unexpected, as dihalo-olefins are seldom detected as side products during the olefination of ketones and aldehydes. The closest literature precedence for the formation of dibromo-enamide **243b** is the dibromo-olefination of lactones reported by Chapleur and co-workers (**Scheme 64**).[73]



Scheme 64. Chapleur's dibromo-olefination of lactones.

Mechanistically, the formation of the β,β-dibromo-enamides using bromomethylenetriphenylphosphorane could follow two potentially competing reaction pathways as proposed by Chapleur in explaining the lactone dibromoolefination. Initially, deprotonation of the phosphonium salt yields ylide **A** which then reacts with a second equivalent of the phosphonium salt to generate the dibromo-phosphonium unit **B** and methylene ylide **C**. Deprotonation of the dibromo phosphonium salt by either ylide **C** or *tert*-butoxide then yields the dibromomethylenetriphenylphosphorane **D** that can subsequently react with the *N*-formyl group of imide **168** to generate the observed dibromo-enamide **243b** (**Figure 30**).

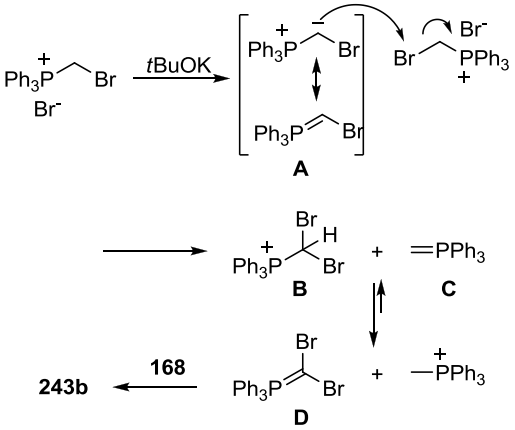
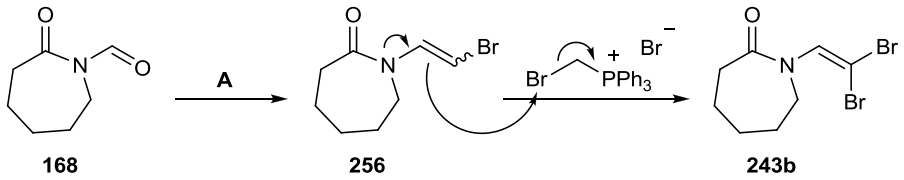


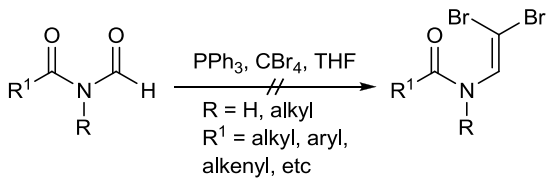
Figure 30. Chapleur's mechanism for *in-situ* generation of dibromomethylenetriphenylphosphorane **D**.

Alternatively the initial olefination of *N*-formyl imide **168** with bromomethylenetriphenylphosphorane **A** would yield bromo-enamide **256**, which then undergoes a second bromination to generate the observed dibromo-enamide intermediate **243b** (**Scheme 65**).



Scheme 65. Stepwise mechanism for synthesis of dibromo-enamides.

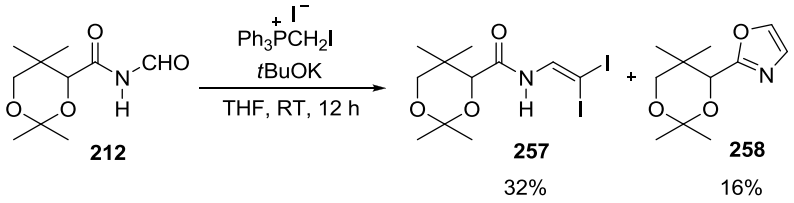
From a mechanistic point of view, the high yield isolation of iodo-enamides **219** and **220**, would suggest a different mechanism from that proposed by Chapleur, and would indicate that a step-wise process is taking place, and that the rate for the iodination step is highly dependent on the structural nature of the iodo-enamide intermediate generated. Alternatively, it could imply that *N*-formyl imides with very closely related structures have very different rates of reaction with ylides **A** or **D** and that the iodo-enamide products obtained from the reaction with ylide **A** are not intermediates in the pathway for the synthesis of diiodo-enamides. Circumstantial evidence for a stepwise process was provided by control experiments in which valeraldehyde generated the expected mono-halogenated olefin when subjected to the same reaction conditions, demonstrating the enamide nitrogen's pivotal role during the bromination step. Further indication that a stepwise pathway is taking place was provided by the fact that none of the *N*-formyl imides reacted with the dibromo ylide **D** generated through Ramirez olefination conditions (**Scheme 66**).



Scheme 66. Failed attempts of Ramirez olefination.

Additional mechanistic evidence for a step-wise process was provided by treatment of the pantolactone derived *N*-formyl imide **212** under the same

iodoolefination conditions, which resulted in the formation of diiodo-enamide **257** and oxazole **258** in good overall yield (**Scheme 67**). The structures of both diiodo-enamide and oxazole units were corroborated by crystallographic analysis (**Figure 31**).



Scheme 67. Iodo-olefination of pantolactone derived *N*-formyl imide **212**.

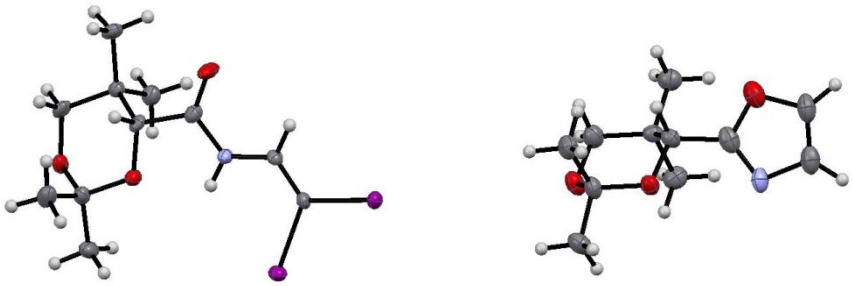
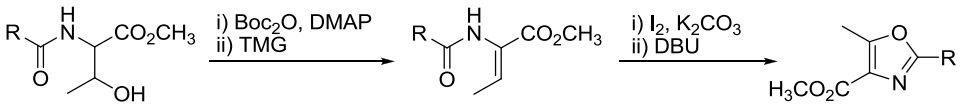


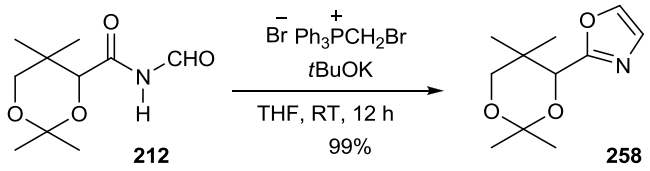
Figure 31. Crystal structures of diiodo-enamide **257** and oxazole **258**.

The oxazole unit was presumably generated through the intramolecular cyclisation of the iodo-enamide intermediate, in a process akin to that reported by Ferreira through the basic treatment of amino-acid derived β-iodo-enamides (**Scheme 68**).[72a,b]



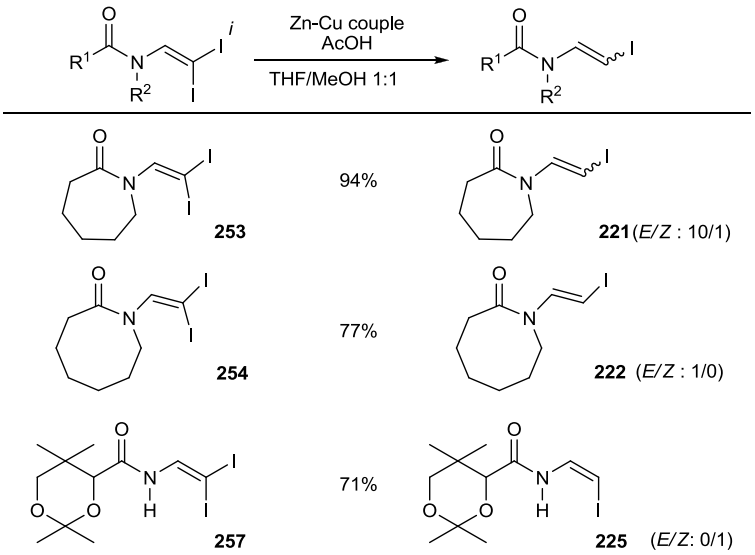
Scheme 68. Ferreira cyclisation of β-iodo-enamides.

Further evidence that ylide **A** is the reactive species was provided by the bromo-olefination of pantolactone derived *N*-formyl imide **212**, which yielded oxazole **258** in near quantitative yield under the same reaction conditions (**Scheme 69**). This would strongly suggest that the *N*-formyl imide **212** is first converted to a putative bromo-enamide intermediate which then undergoes cyclisation to generate oxazole **258**.



Scheme 69. One-step synthesis of oxazole **258**.

These results imply that, at least in the case of di-halo-enamide formation, a different mechanism is taking place from that proposed by Chapleur for the dibromo-olefination of lactones. Having successfully achieved a high yielding, flexible and reliable synthesis of β,β-dihalo-enamides, the key steroselective dehalogenations were attempted. Both for mechanistic reasons and for the stability displayed previously by *(E)*-β-iodo-enamides, it was decided to initially focus our attentions on the selective de-halogenation of the diiodo-enamide units. We were pleased to find that treatment of the diiodo-enamides with a Zn-Cu couple[74] proceeded cleanly to stereoselectively generate the *(E)*-β-iodo-enamides **221** and **222** in good yield (**Table 10**). Interestingly, in the case of the pantolactone derived iodo-enamide **257**, the *(Z)*-product was the sole isomer obtained. We believe that the opposite double bond geometry obtained in iodo-enamide **225** is the result of electronic interactions between the tetramethyl dioxolane ring and the enamide unit affecting the reactive conformation of diiodo-enamide **225**.

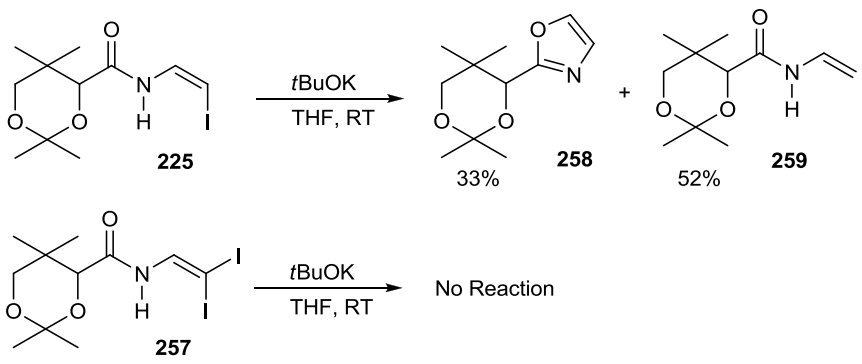


i)All reactions were conducted using 1 eq of diiodoenamide,30 eq of Zn-Cu couple and 100 eq of AcOH at 0 °C for 0.5 hours.

Table 10. Selective de-iodination of diiodo-enamides.

Crucially, having access to both the diiodo-enamide **257** and *(Z)*-iodo-enamide **225** provided the opportunity to further probe the mechanism of the halo-olefination taking place. It was proposed that if the step-wise mechanistic hypothesis was valid, basic treatment of iodo-enamide **225** should result in oxazole formation.

Gratifyingly, treatment of *(Z)*-iodo-enamide **225** under basic conditions yielded oxazole **258** together with traces of the de-halogenated enamide **259**. On the other hand, treatment of diiodo-enamide **257** under identical conditions gave only unreacted starting material (**Scheme 70**). This would support the theory that iodo-olefination of *N*-formyl imide **212** initially yields an iodo-enamide intermediate, which can then either undergo a second iodination to generate the diiodo-enamide **257** or a deprotonation-cyclisation to generate oxazole **258**.



Scheme 70. Synthesis of oxazole **258** from iodo-enamide **225**.

In addition to these mechanistic observations, there was also the support deriving from control experiments. The same reaction conditions were applied to simple aldehydes rather than *N*-formyl imides and the outcome of the reaction in these cases was, as expected, the generation of monohalo-olefins. This suggests that the nitrogen present in the *N*-formyl imides is involved in the mechanism of the dihalo-olefination reaction. Also the Ramirez olefination (in which it has been proven that the reactive species is **D**) was applied to the *N*-formylimide substrates, however without success, suggesting again that is not species **D** but species **A** which participates in our novel dihalo-olefination reaction (**Figure 32**).

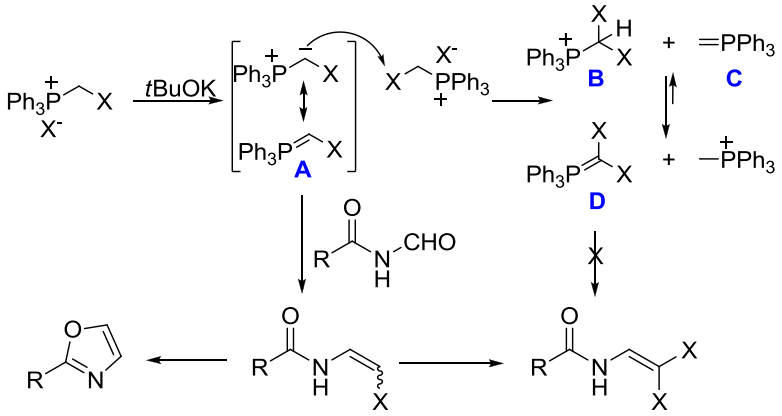
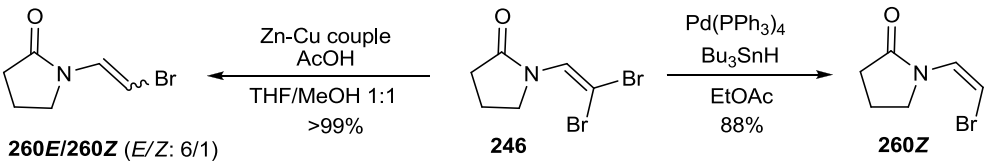


Figure 32. Suggested pathway of the dihalo-olefination reaction.

Final mechanistic observations, that again supported our hypothesis of a step-wise mechanism, derived from ^{31}P-NMR experiments in THF, which showed the presence of species **A** (δ ~ 13 ppm) and **C** (δ ~ 19 ppm) in the reaction mixture, but not **D**. In view of this evidence acquired, we have tentatively excluded Chaupleur's mechanistic proposal in favour of a step-wise mechanism.

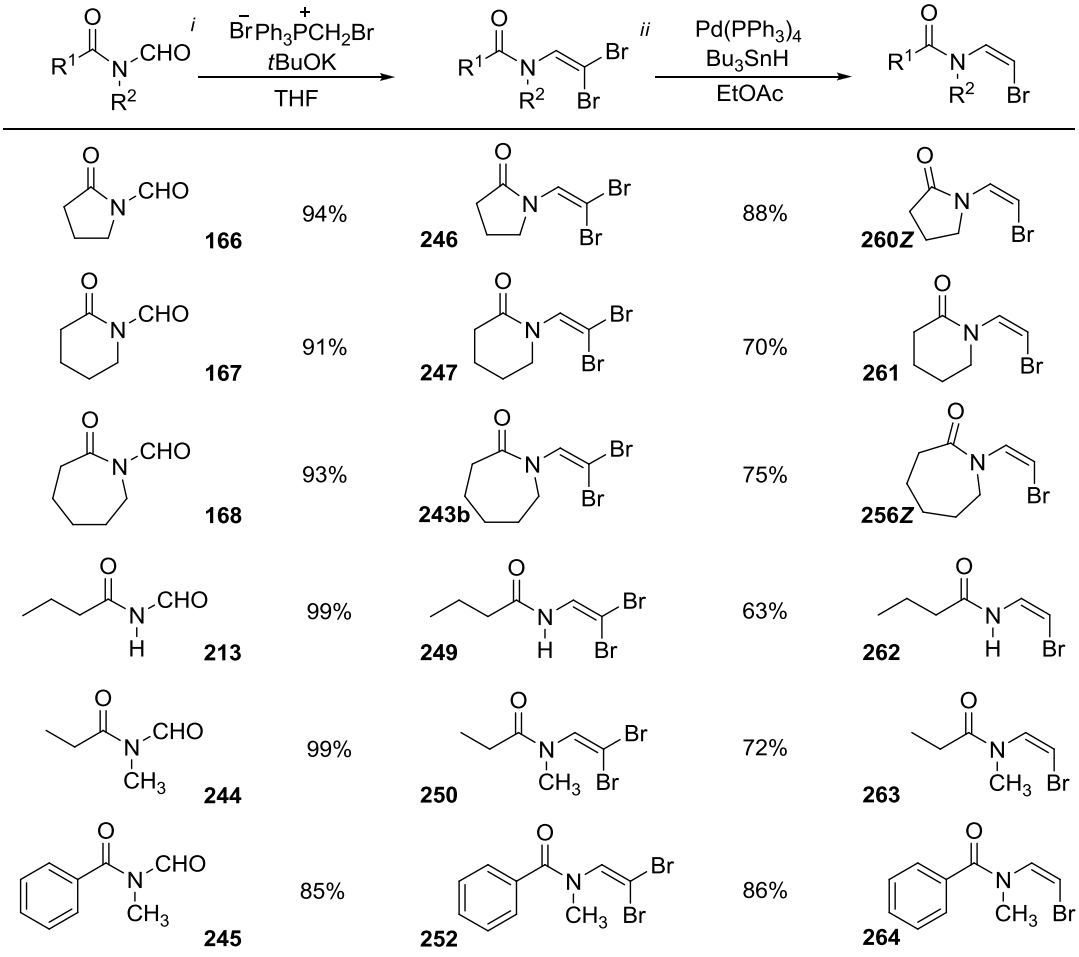
Having demonstrated the feasibility of carrying out selective dehalogenations on diiodo-enamides, analogous debromination, with the aim of accessing *(Z)*-β-bromo-enamides, was investigated.

Initial debromination attempts on dibromo-enamide **246** using Zn-Cu couple resulted in a 6:1 *(E:Z)* product ratio of β-bromo-enamides **260*E*/260*Z*** in quantitative yield (**Scheme 71**). Although this provides a highly efficient approach to the synthesis of *(E)*-halo-enamides, it did not provide us with the complete selectivity observed in the diiodo-enamide series. Crucially, however, treatment of dibromoenamide **246** using tributyltin hydride/palladium tetrakis[75] afforded the highly desired *(Z)*-β-bromo-enamide **260*Z*** in excellent yield and with complete diastereoselectivity (**Scheme 71**).



Scheme 71. Initial debromination attempts.

In order to ascertain the efficiency and selectivity for the synthesis of *(Z)*-bromo-enamide units, the reproducibility of the debromination conditions was assessed. We were pleased to find that in all cases, the reduction resulted in the desired *(Z)*-bromo enamides **256*Z*** and **260-264** in high yields and with complete stereocontrol (**Table 11**).



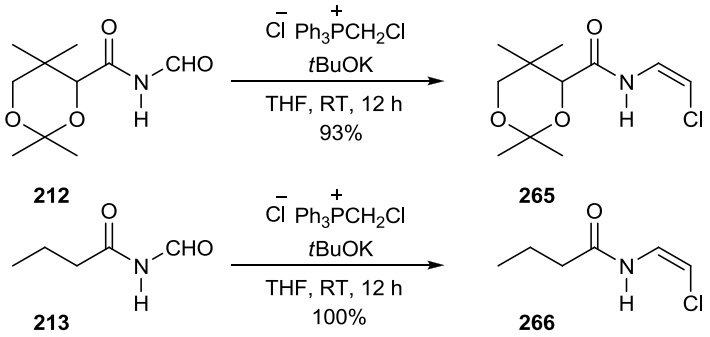
i)The reactions were conducted using 1 eq of N-Formyl imide, 10 eq of salt and 10 eq of base in dry THF (0.33 M) at RT for 12 hours. ii)The reactions were conducted using 1 eq of dibromo-enamide, 1.2 eq of Bu_3SnH and 0.1 eq of catalyst in dry EtOAc (16 mM) at RT for 12 hours.

Table 11. Stereoselective synthesis of *(Z)*-β-bromo-enamides.

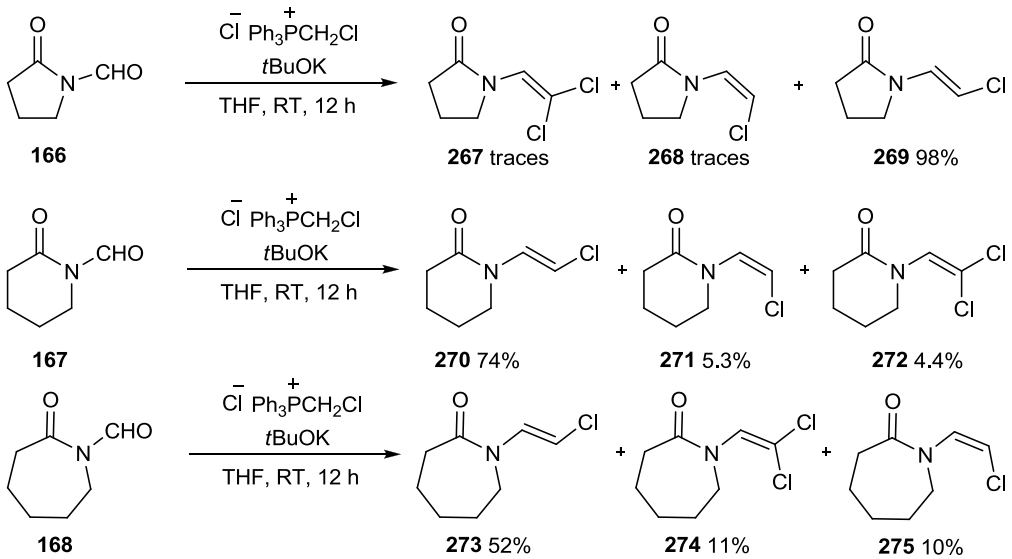
To complete our halo-enamide studies, β-chloro-enamides were also taken into consideration. In all cases, the methodology efficiently converted the *N*-formyl imides into halo-olefins, however, while in the case of the acyclic starting materials the only reaction products were the *(Z)*-β-chloro-enamides (**Scheme 72**), the

lactam systems afforded mixtures of *(Z)*-β-chloro-enamides, *(E)*-β-chloro-enamides and β,β-dichloro-enamides (**scheme 73**).

Further studies are necessary for the optimisation of the methodology.



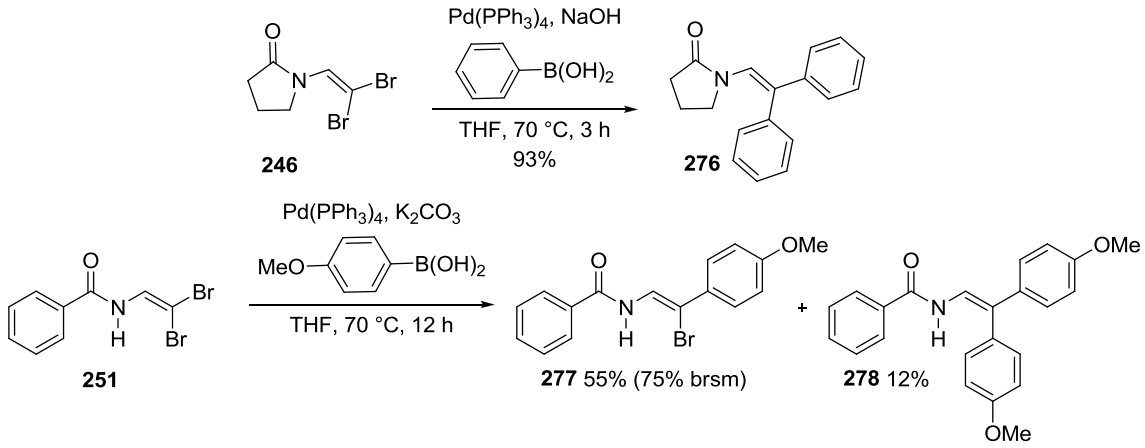
Scheme 72. Synthesis of *(Z)*-β-chloro-enamides.



Scheme 73. Synthesis of cyclic chloro-enamides.

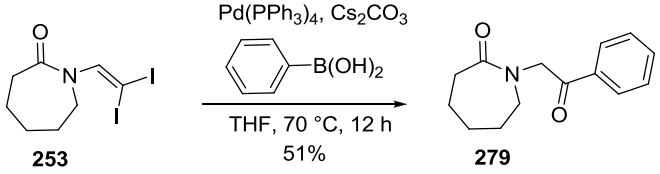
2.9 Potential and limitations of β-halo-enamides

Thus far, we have described two novel methods for the synthesis of β-halo-enamides as stereodefined reactive intermediates to be exploited in cross-coupling reactions for the generation of more elaborated enamide units. By using the Takai olefination reaction, we have shown the selective synthesis of *(E)*-β-iodo-enamides, which are robust and useful substrates in Sonogashira cross-couplings for the generation of β-yn-enamides and eventually *(E,Z)*-dienamides.
On the other hand, by using the Stork-Zhao olefination reaction, we have explored the synthesis of *gem*-dihalo-enamides. Such species have the potential to be flexible substrates for the synthesis of branched or unbranched products *via* Suzuki-Miyaura cross-coupling reactions. Indeed, reaction of both cyclic and acyclic dibromo-enamides, under Cossy's procedure,[56] yielded the desired cross-coupled adducts. Significantly, there was no need for nitrogen protection in the acyclic substrate (**Scheme 74**).



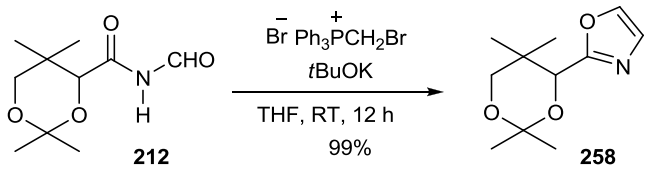
Scheme 74. Synthesis of branched and unbranched products.

Additionally, β,β-dihalo-enamides can also be exploited for the generation of aminoketones, following Lautens' protocol[57] (**Scheme 75**).



Scheme 75. Synthesis of aminoketones.

Finally, we have also observed the potential for acyclic β-halo-enamides to be useful substrates for a novel generation of oxazole products (**Scheme 76**).



Scheme 76. Synthesis of oxazoles.

For such reasons, we can conclude that β-halo-enamides and β,β-dihalo-enamides have great potential as key intermediates from which a series of important transformations can be developed. These substrates have shown a good reactivity in Csp^2-Csp and Csp^2-Csp^2 cross-couplings, with retention of the double bond geometry. Importantly, this methodology represents a protecting group-free strategy, an attractive feature not present in the existing examples reported so far in the literature (**Figure 33**).

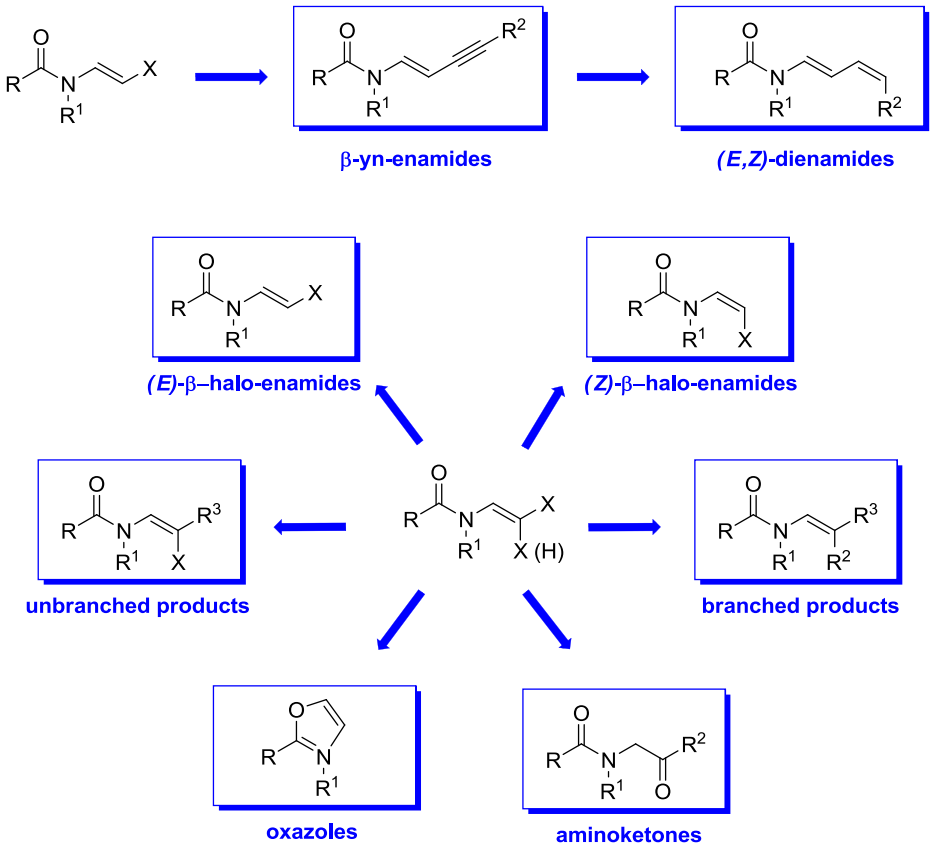
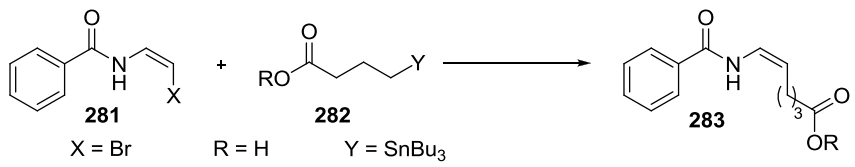


Figure 33. Synthetic potential of β-halo-enamides.

Thus far, we have explored the use of the β-halo-enamides in Csp^2-Csp (Sonogashira) and Csp^2-Csp^2 (Suzuki) cross-couplings. The next step, was to consider the reactivity of our novel β-halo-enamides in the more challenging Csp^2-Csp^3 cross-coupling reactions, which could be very useful in the total synthesis of natural products containing complex enamide moieties (for example, crocacin D as will be elucidated in the next chapter). To the best of our knowledge, there are no examples in the literature so far of Csp^2-Csp^3 cross-coupling reactions involving β-halo-enamides. In our preliminary studies, we took into consideration the use of *(Z)*-β-bromovinyl-benzamide **281** as a model system and we attempted the Stille coupling with a custom lateral chain **282**, initially following Echavarren's protocol.[76] A series of catalysts, additives, solvents and temperatures were explored, however, disappointingly, the reaction was unsuccessful in all cases, giving decomposition or in some cases (entry 1 and 2) a collateral dehalogenation to afford the undesired terminal olefin by-product **280** (**Table 12**).



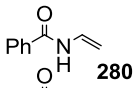
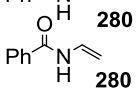
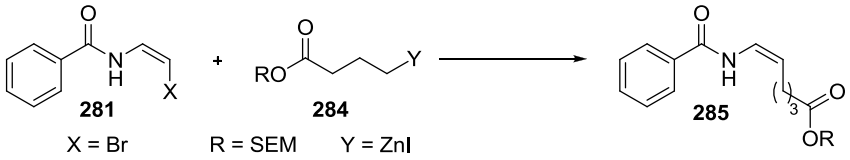
entry	catalyst	time (h)	additives	T (°C)	solvent	product
1	$Pd(PPh_3)_4$	3	-	60 °C (MW)	DMF	 **280**
2	$Pd(dppf)Cl_2$	4	-	100 °C (MW)	DMF	 **280**
3	$Pd(PPh_3)_4$	12	CuI	100 °C	DMF	decomposition
4	$Pd_2(dba)_3$	12	CsF, P(*n*Bu)$_3$	80 °C (MW)	dioxane	decomposition
5	PdCl(π-allyl)	48	TBAF, P(*n*Bu)$_3$	20 °C	THF	decomposition

Table 12. Efforts towards the Stille coupling.

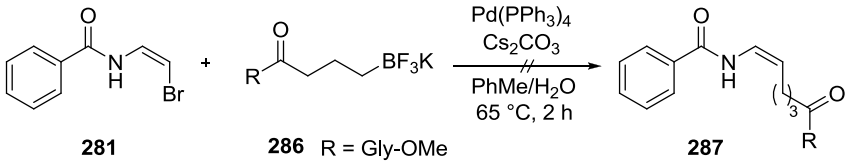
After the first unsuccessful attempts, Negishi coupling was also explored under Lipshutz's conditions.[77a,b] Again, the cross-coupling was unsuccessful, yielding either unreacted or isomerised starting material. In an additional case formation of the by-product **280** was also observed (**Table 13**).



entry	catalyst	time (h)	additives	T (°C)	solvent	product
1	$Pd(PPh_3)_2Cl_2$	48	TMEDA	20 °C	THF	isomerisation
2	$Pd(PPh_3)_2Cl_2$	72	TMEDA	20 °C	THF	**280**
3	$Pd(PPh_3)_2Cl_2$	12	NMI	20 °C	THF	unreacted SM
4	$Pd(PPh_3)_2Cl_2$	24	NMI	50 °C	THF/NMP	isomerisation

Table 13. Efforts towards the Negishi coupling.

Finally, a preliminary attempt to apply Molander's conditions of Suzuki cross-coupling to our model system was, likewise, unsuccessful, as generating only the undesired by-product **280** (**Scheme 77**).[78]



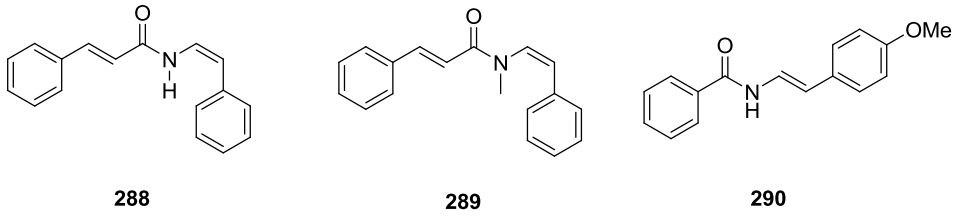
Scheme 77. Preliminary attempt of Suzuki coupling.

Thus, we have shown that β-halo-enamides and β,β-dihalo-enamides are excellent substrates for Csp^2-Csp^2 and Csp^2-Csp bond formation reactions to yield the desired enamides in good yield.

Unfortunately, successful Csp^2-Csp^3 cross-coupling of β-halo-enamides has proven rather elusive and remains a significant challenge.

2.10 Synthesis of Lansiumamides and Alatamide

Once our methodology for the synthesis of stereodefined β-halo-enamides was developed, a practical application of this novel procedure was explored. The methodology appeared to be particularly suitable for the total synthesis of three stereodefined enamide-containing natural products, namely lansiumamide A **288**, lansiumamide B **289** and alatamide **290** (**Figure 34**).



288 **289** **290**

Figure 34. Lansiumamide A **288**, B **289** and alatamide **290**.

Lansiumamide A **288** and B **289** are two cinnamamide derivatives isolated from the seeds of *Clausena lansium*, which is a plant native to China and Taiwan. Some parts of this plant have been used in traditional Chinese medicine as remedies against a variety of diseases and, in particular, the leaves are used for the treatment of asthma and gastro-intestinal diseases, while the seeds can also be used for the treatment of ulcers and acute or chronic gastro-intestinal inflamations (**Figure 35**).[79a-c]

Figure 35. *Clausena lansium* fruits and seeds.

In our retrosynthetic analysis, we envisioned lansiumamide B as deriving directly from lansiumamide A by direct methylation. Lansiumamide A, in turn, could be derived from the *(Z)*-β-bromo-enamide **292**, *via* Suzuki coupling with benzylboronic acid **293**. Enamide **292** could be easily obtained *via* the Pd/Bu_3SnH-mediated stereoselective debromination of β,β-dibromo-enamide **291**. The latter could be accessed through our dibromo-olefination methodology starting from *N*-formylimide **294**, which, in turn, could originate from *trans*-cinnamamide **295** *via* *N*-formylation (**Figure 36**).

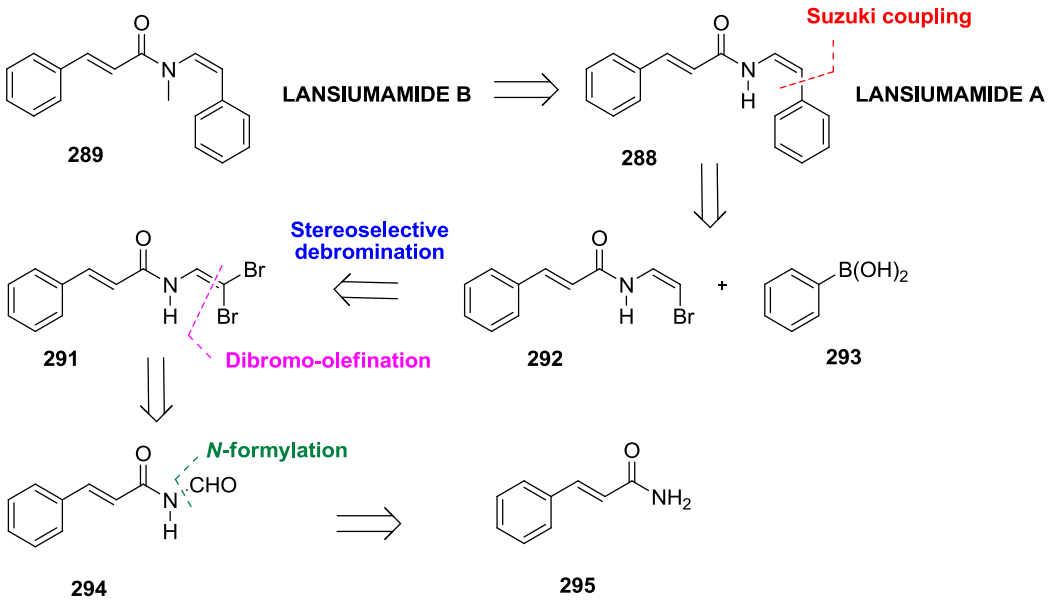
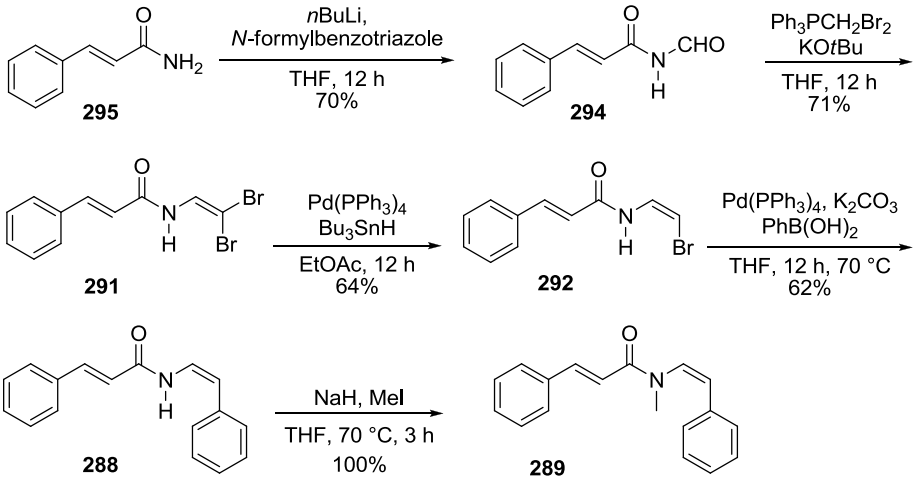


Figure 36. Retrosynthesis of lansiumamide A **288** and B **289**.

Our synthesis began with *trans*-cinnamamide **295** which was formylated with *N*-formylbenzotriazole to afford the *N*-formylimide **294** in good yield.

Treatment of imine **294** with (bromomethyl)triphenylphosphonium bromide and potassium *tert*-butoxide, cleanly afforded β,β-dibromo-enamide **291** in good yield. Stereoselective debromination of **291** yielded the *(Z)*-β-bromo-enamide **292** with complete stereocontrol. Coupling of halo-enamide **292** with phenylboronic acid **293** under Suzuki-Miyaura conditions gave lansiumamide A **288** in good yield and more importantly as a single double bond isomer. Methylation of lansiumamide A **288** afforded lansiumamide B **289** in quantitative yield (**Scheme 78**).



Scheme 78. Synthesis of lansiumamide A **288** and B **289**.

Alatamide **290** is a β-phenylethylamine-derived amide isolated from the aerial parts of the plant *Piper guayranum*, originating from both Trinidad and Tobago and Venezuela (**Figure 37**). Thus far, there have been no reports of medicinal uses of this plant.[80]

Figure 37. *Piper guayranum*.

The retrosynthetic analysis of alatamide **290** began with a Zn-Cu couple/CH_3COOH-mediated debromination of intermediate **277**. The latter, in turn, could be accessed *via* stereoselective Suzuki coupling of the β,β-dibromo-enamide **251** with boronic acid **297**. The *gem*-dihalo-enamide **251** could be derived from the corresponding *N*-formylimide **216** *via* dibromo-olefination.

N-Formylimide **216** could be accessed *via* formylation of benzamide **209** (**Figure 38**).

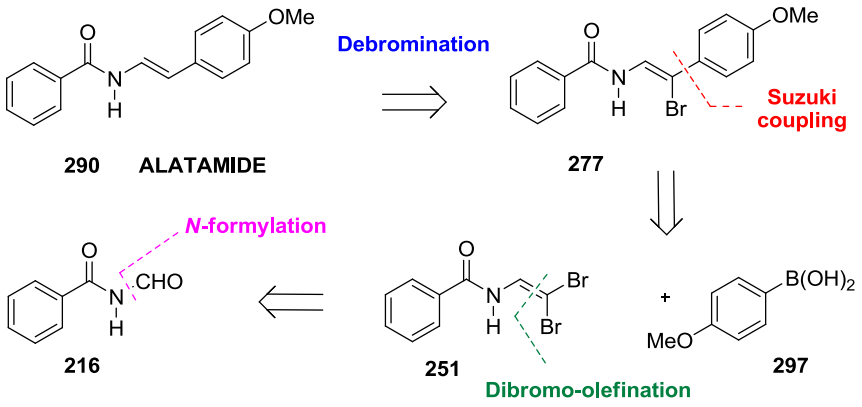
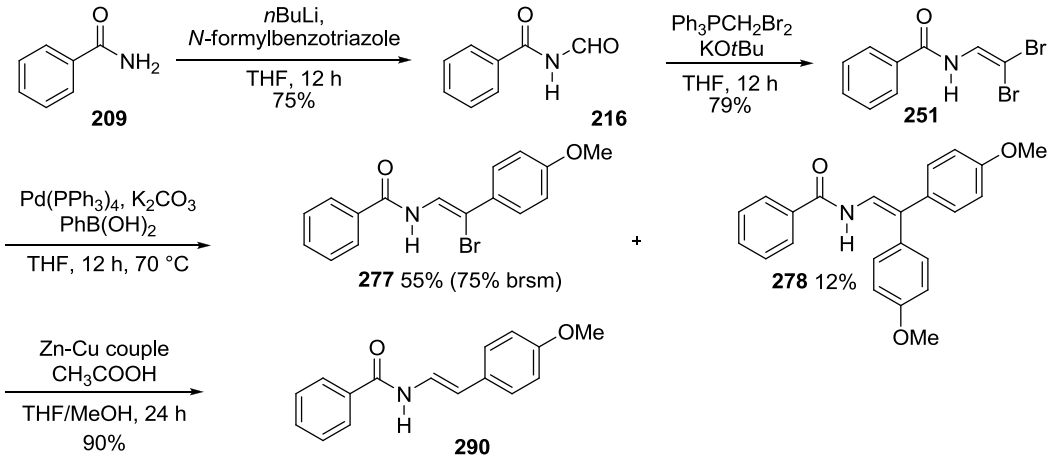


Figure 38. Retrosynthesis of alatamide.

Following our synthetic approach, benzamide **209** was successfully formylated to afford *N*-formylbenzimide **216** in good yield. *N*-Formylimide **216** was then subjected to our optimised dibromo-olefination conditions to yield the desired β,β-dibromo-enamide **251** in good yield. Suzuki cross-coupling of the dihalo-enamide **251** with boronic acid **298** afforded the desired enamide **277** in 55% yield (75% brsm) together with the undesired by-product **278** in 12% yield. Dehalogenation of enamide **277** with Zn-Cu couple/acetic acid yielded alatamide **290** in 90% yield (**Scheme 79**).

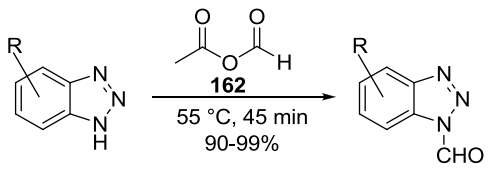


Scheme 79. Synthesis of alatamide **290**.

In conclusion, our methodology for the stereoselective preparation of β-halo-enamides, allowed the completion of the syntheses of three enamide-containing natural products in a simple and efficient fashion. The strategy compares favourably with the previous examples reported in the literature[2,21,24,25,81a,b] both for availability of the starting materials, costs, number of steps and overall yield.

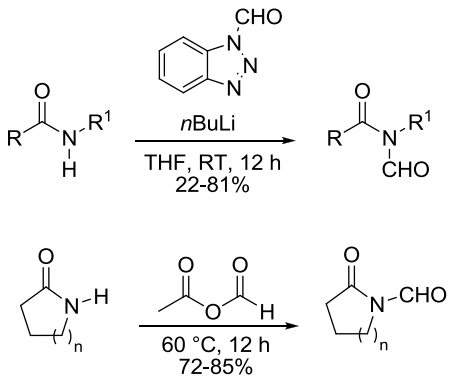
2.11 Summary and future work

In summary, an efficient and environmentally friendly procedure for the synthesis of *N*-formylbenzotriazole **186** and its derivatives has been developed. This method is considered green as it requires relatively small volumes of organic solvent and produces acetic acid as the only significant side product. The THF used in the reaction mixture can be recovered during the evaporation step, thus causing minimal environmental impact and minimising costs. The procedure represents a great improvement compared to other methods available currently for the synthesis of *N*-formylbenzotriazole in terms of cost, yield and overall efficiency (**Scheme 80**).



Scheme 80. Synthesis of *N*-formylbenzotriazoles.

Subsequently, the *N*-formylbenzotriazole so obtained has been exploited for the synthesis of *N*-formyl imides starting from acyclic commercial amides, while cyclic *N*-formyl imides have been prepared starting from commercial lactams and easily available acetic formic anhydride **162** (**Scheme 81**).



Scheme 81. Synthesis of *N*-formyl imides.

With the *N*-formyl imides in hand, we then developed a fast and efficient method, which takes advantage of the pseudo-aldehyde behaviour of *N*-formyl imides, to access β-halo-enamides in a single step, in moderate-good yields and without the need for nitrogen protecting groups. The approach hinges on the ability of *N*-formyl imides to undergo olefination reactions to generate enamides in good yield and most significantly without the need for nitrogen protection in acyclic cases. The β-halo-enamides, in turn, can be easily functionalised into β-yn-enamides and *(E,Z)*-dienamides in excellent yields and with complete stereoselectivity (**Figure 39**).

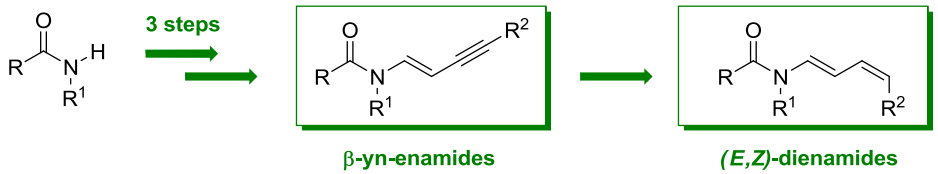


Figure 39. Synthesis of β-yn-enamides and *(E,Z)*-dienamides.

We have also developed a novel, protecting group-free, efficient and stereoselective approach to the generation of β-dihalo-enamides through the use of modified Stork-Zhao olefination conditions. Our results have shown that this methodology provides a robust synthetic platform from which *(Z)*- or *(E)*-enamides can be generated in good yields and with complete stereocontrol (**Figure 40**).

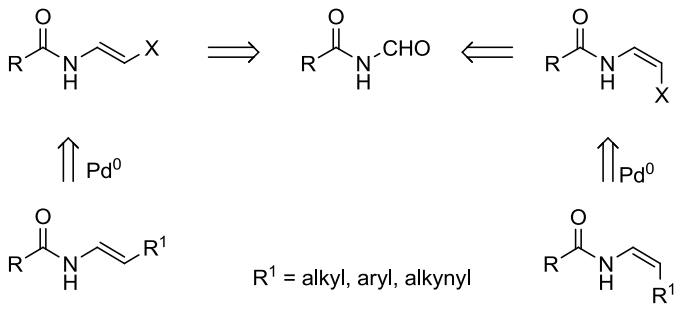


Figure 40. Proposed synthesis of β-halo-enamides from *N*-formyl imides.

The synthetic utility of the methodology has been proven through the efficient and stereoselective syntheses of three simple enamide-containing natural products, lansiumamide A **288**, B **289** and alatamide **290** (**Figure 41**).

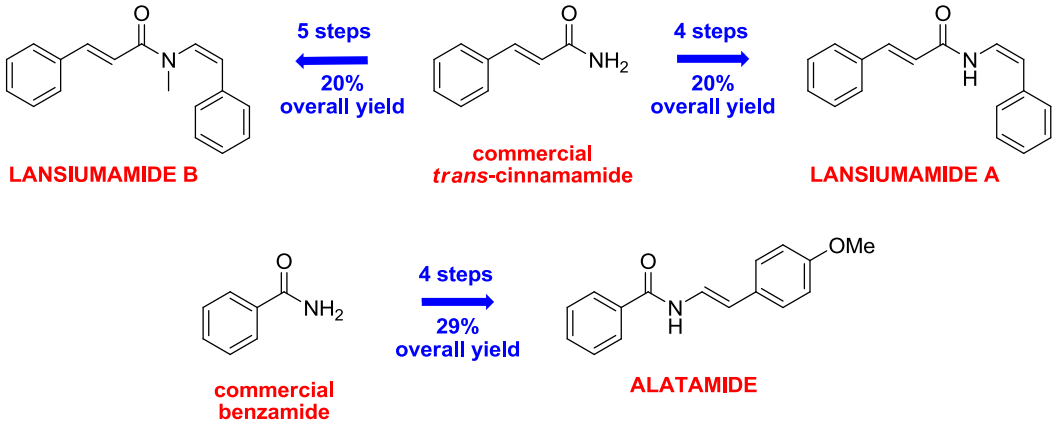


Figure 41. Synthesis of lansiumamide A, B and alatamide.

We have also obtained very promising results for the synthesis of oxazoles, however optimisation of these results is still necessary to expand the scope of this transformation (**Figure 42**).

Figure 42. Conversion of β-halo-enamides into oxazoles.

Finally, as all the attempts to couple the β-halo-enamides with alkylic substrates have proven unsuccessful thus far, hence, new efforts will be required to address and solve these issues (**Figure 43**).

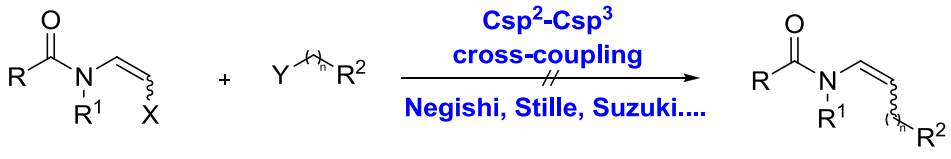
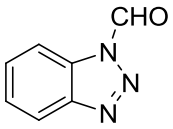


Figure 43. New efforts towards the Csp^2-Csp^3 cross-coupling.

3 Experimental

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Tetrahydrofuran (THF), diethyl ether, toluene and dichloromethane were purified through a Pure Solv 400-5MD solvent purification system (Innovative Technology, Inc). Anhydrous dimethylformamide, *N*-methylpyrrolidone, ethyl acetate, methanol and dioxane were purchased from Sigma-Aldrich. All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C using a Büchi Rotavapor. IR spectra were recorded neat using a JASCO FT/IR410 Fourier Transform spectrometer. Only significant absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}). Proton magnetic resonance spectra (^{1}H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were recorded using a Bruker DPX Avance400 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, m = multiplet, b = broad, dm = doublet of multiplet, dd = doublet of doublet, dt = doublet of triplet) and (3) coupling constant (*J*) quoted in Hertz to the nearest 0.1Hz. High resolution mass spectra were recorded on a JEOL JMS-700 spectrometer by electrospray (ESI), fast atom bombardment (FAB), electron impact (EI) and chemical ionisation (CI) mass spectrometer operating at a resolution of 15000 full widths at half height. Where a 100% peak was not observed in low resolution mass spectra the highest peak was taken to be 100%. Flash chromatography was performed using silica gel (Apollo Scientific Silica Gel 60, 40-63 mm) as the stationary phase. TLC was performed on aluminium sheets pre-coated with silica (Merck Silica Gel 60 F254). The plates were visualised by the quenching of UV fluorescence (λ_{max} 254 nm) and/or by staining with either anisaldehyde or potassium permanganate followed by heating.

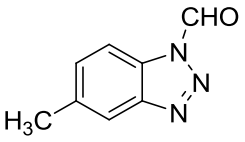
_N_-Formylbenzotriazole, 186

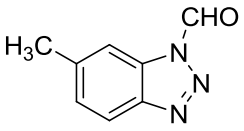


A solution of commercial grade acetic anhydride (4.72 mL, 50.0 mmol) was treated with 100% formic acid (3.80 mL, 100 mmol) at 0 °C and the resulting mixture was stirred at 80 °C for 45 minutes under microwave irradiation. The resulting crude anhydride mixture was then analysed by ^{1}H NMR and the yield of mixed anhydride **162** was obtained (42%, 21.0 mmol). The mixed anhydride was cooled down to -10 °C and the benzotriazole **187** (0.9 eq based on the amount of anhydride **162** generated, 2.25 g, 18.9 mmol) was added as a solution in anhydrous THF (25 mL). The resulting mixture was then stirred at -10 °C until complete as indicated by TLC analysis (45 minutes). The solvent was removed under vacuum to yield the desired *N*-formyl benzotriazole **186** without the need of purification in quantitative yield (2.78 g, 18.9 mmol). IR ν_{max} (film) 3105, 1723, 1604, 1595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.86 (1H, s, CHO), 8.26 (1H, d, *J* 8.0 Hz, CH_{Ar}), 8.18 (1H, dd, *J* 1.0, 8.0 Hz, CH_{Ar}), 7.71 (1H, ddd, *J* 1.0, 7.2, 8.2 Hz, CH_{Ar}), 7.59 (1H, ddd, *J* 1.0, 7.2, 8.2 Hz, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 159.7 (CO), 146.5 (C_{Ar}), 130.7 (CH_{Ar}), 129.8 (C_{Ar}), 127.0 (CH_{Ar}), 120.4 (CH_{Ar}), 113.6 (CH_{Ar}); HRMS (CI+/ISO) calc. for $C_7H_5N_3O$ $[M]^+$: 147.0433. Found 147.0435; m.p. 78-80 °C.

The characterisation matches with the data reported in literature:
Katrizky A. R.; Chang H. X.; Yang B. *Synthesis* **1995**, 503.

5-Methyl-*N*-formylbenzotriazole and 6-Methyl-*N*-formylbenzotriazole, 191





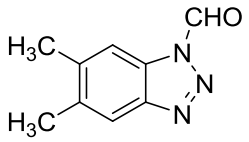
A solution of commercial grade acetic anhydride (4.72 mL, 50.0 mmol) was treated with 100% formic acid (3.80 mL, 100 mmol) at 0 °C and the resulting mixture was stirred under argon at 55 °C for 3 hours. The resulting crude anhydride mixture

was analysed by ^{1}H NMR and the yield of mixed anhydride **162** was obtained (47%, 23.3 mmol). The mixed anhydride was then cooled down to -10 °C and the 5-methyl-*1H*-benzo[*d*][1,2,3]triazole **190** (0.9 eq based on the amount of anhydride **162** generated, 2.80 g, 21.0 mmol) was then added as a solution in anhydrous THF (25 mL). The resulting mixture was stirred at -10 °C until complete as indicated by TLC analysis (45 minutes). The solvent was removed under vacuum to yield the desired product without the need of purification. The methyl substituted *N*-formylbenzotriazole **191** was obtained as a 1.6.:1.0 mixture of regioisomers in 99% yield (3.36 g, 20.8 mmol). IR ν_{max} (film) 2959, 2924, 1699, 1617, 1491, 1440, 1372, 1349, 1300, 1062 cm^{-1}; HRMS (ESI+) calc. for $C_8H_7N_3O$ $[M]^+$: 161.0589. Found 161.0592; m.p. 70-71 °C.

Major isomer (5-Methyl-N-formylbenzotriazole): ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.82 (1H, s, CHO)**,** 8.04 (1H, s, CH_{Ar}), 7.99 (1H, dd, *J* 0.5, 8.5 Hz, CH_{Ar}), 7.38 (1H, dd, *J* 1.1, 8.4 Hz, CH_{Ar}), 2.58 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 159.9 (CO), 145.1 (C_{Ar}), 142.0 (C_{Ar}), 130.3 (C_{Ar}), 128.9 (CH_{Ar}), 119.7 (CH_{Ar}), 113.1 (CH_{Ar}), 22.1 (CH_3).

Minor isomer (6-Methyl-N-formylbenzotriazole): ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.82 (1H, s, CHO)**,** 8.10 (1H, dd, *J* 0.4, 8.4 Hz, CH_{Ar}), 7.91 (1H, s, CH_{Ar}), 7.52 (1H, dd, *J* 1.0, 8.3 Hz, CH_{Ar}), 2.56 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 159.7 (CO), 147.1 (C_{Ar}), 137.4 (C_{Ar}), 132.5 (C_{Ar}), 128.2 (CH_{Ar}), 119.5 (CH_{Ar}), 112.9 (CH_{Ar}), 21.6 (CH_3).

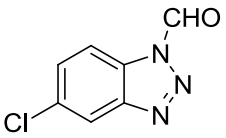
5,6-Dimethyl-*N*-formylbenzotriazole, 193

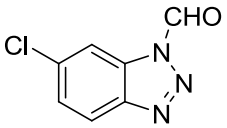


A solution of commercial grade acetic anhydride (4.72 mL, 50.0 mmol) was treated with 100% formic acid (3.80 mL, 100 mmol) at 0 °C and the resulting mixture was stirred at 80 °C for 45 minutes under microwave irradiation. The resulting crude anhydride mixture was analysed by ^{1}H NMR and the yield of mixed anhydride was obtained (42%, 21.0 mmol). The mixed anhydride **162** was then cooled down to -10 °C and the 5,6-dimethyl-*1H*-benzo[*d*][1,2,3]triazole **192** (0.9 eq based on the amount of anhydride **162** generated, 2.84 g, 18.9 mmol) was added as a solution

in anhydrous THF (25 mL). The resulting mixture was stirred at -10 °C until complete as indicated by TLC analysis (45 minutes). The solvent was removed under vacuum to yield the desired 5,6-dimethyl-*N*-formyl benzotriazole **193** without the need of purification in 94% yield (3.12 g, 17.8 mmol). IR ν_{max} (film) 3294, 2946, 2918, 2358, 1727, 1714, 1587, 1478, 1463, 1448, 1203, 1060 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.80 (1H, s, CHO), 8.01 (1H, s, CH_{Ar}), 7.88 (1H, s, CH_{Ar}), 2.47 (3H, s, CH_3), 2.45 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 159.8 (CO), 145.6 (C_{Ar}), 141.4 (C_{Ar}), 136.9 (C_{Ar}), 128.7 (C_{Ar}), 119.6 (CH_{Ar}), 113.2 (CH_{Ar}), 20.9 (CH_3), 20.5 (CH_3); HRMS (ESI+): calc. for $C_9H_9N_3O$ $[M]^+$: 175.0746. Found 175.0747; m.p. 110-111 °C.

5-Chloro-*N*-formylbenzotriazole and 6-Chloro-*N*-formylbenzotriazole, 195



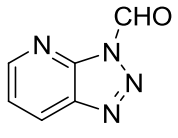


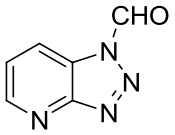
A solution of commercial grade acetic anhydride (4.72 mL, 50.0 mmol) was treated with 100% formic acid (3.80 mL, 100 mmol) at 0 °C and the resulting mixture was stirred under argon at 55 °C for 3 hours. The crude anhydride mixture was analysed by ^{1}H NMR and the yield of mixed anhydride **162** was obtained (42%, 21.0 mmol). The mixed anhydride was cooled down to -10 °C and the 6-chloro-1H-benzo[d][1,2,3]triazole **194** (0.9 eq based on the amount of anhydride **162** generated, 2.88 g, 18.8 mmol) was added as a THF solution (25 mL). The resulting mixture was stirred at -10 °C for 45 minutes. The solvent was removed under vacuum to yield the desired product without the need of purification. The chloro substituted *N*-formylbenzotriazole **195** was obtained as a 2.5:1.0 mixture of regioisomers in 99% yield (3.38 g, 18.6 mmol). IR ν_{max} (film) 3101, 3010, 2956, 2834, 1910, 1759, 1732, 1608, 1586, 1460, 1367, 1220 cm^{-1}; HRMS (ESI+): calc. for $C_7H_4N_3O^{35}Cl$ $[M]^+$: 181.0043. Found 181.0036; m.p. 88-90 °C.

Major isomer (5-Chloro-N-formylbenzotriazole): ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.82 (1H, s, CHO), 8.28 (1H, d, *J* 1.8 Hz, CH_{Ar}), 8.08 (1H, dd, *J* 0.5, 8.8 Hz, CH_{Ar}), 7.55 (1H, dd, *J* 1.9, 8.8 Hz, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 159.5 (CO), 145.0 (C_{Ar}), 137.5 (C_{Ar}), 130.5 (C_{Ar}), 128.1 (CH_{Ar}), 121.2 (CH_{Ar}), 113.7 (CH_{Ar}).

Minor isomer (6-Chloro-N-formylbenzotriazole): ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.83 (1H, s, CHO), 8.20 (1H, d, *J* 1.8 Hz, CH_{Ar}), 8.15 (1H, dd, *J* 0.6, 8.7 Hz, CH_{Ar}), 7.68 (1H, dd, *J* 1.8, 8.6 Hz, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 159.4 (CO), 143.5 (C_{Ar}), 132.8 (C_{Ar}), 131.5 (C_{Ar}), 128.6 (CH_{Ar}), 120.0 (CH_{Ar}), 114.3 (CH_{Ar}).

_N_-Formyl-4-azabenzotriazole and _N_-Formyl-7-azabenzotriazole, 197



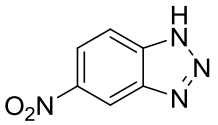


A solution of commercial grade acetic anhydride (4.72 mL, 50.0 mmol) was treated with 100% formic acid (3.80 mL, 100 mmol) at 0 °C and the resulting mixture was stirred at 80 °C for 45 minutes under microwave irradiation. The resulting crude anhydride mixture was analysed by ^{1}H NMR and the yield of mixed anhydride **162** was obtained (50%, 25.0 mmol). The mixed anhydride was then cooled down to -10 °C and the *1H*-[1,2,3]triazolo[4,5-*b*]pyridine **196** (0.9 eq based on the amount of anhydride **162** generated, 1.85 g, 22.5 mmol) was added as a solution in THF (25 mL). The resulting mixture was stirred at -10 °C until complete as indicated by TLC analysis (45 minutes). The solvent was removed under vacuum to yield the desired product without the need of purification. The *N*-formyl-aza-benzotriazole **197** was obtained as a 12.0:1.0 mixture of regioisomers in 96% yield (3.20 g, 21.6 mmol). IR ν_{max} (film) 2680, 1728, 1594, 1584, 1399, 1376, 1259, 1060 cm^{-1}; HRMS (CI+/ISO): calc. for $C_6H_5N_4O$ $[M+H]^+$: 149.0463. Found 149.0472; m.p. 103-105 °C.

Major isomer (N-Formyl-7-azabenzotriazole): ^{1}H NMR (400 MHz; DMSO-d_6): δ_H 10.03 (1H, s, CHO), 8.91 (1H, dd, *J* 1.5, 4.5 Hz, CH_{Ar}); 8.65 (1H, dd, *J* 1.4, 8.2 Hz, CH_{Ar}), 7.86 (1H, dd, *J* 4.5, 8.3 Hz, CH_{Ar}); ^{13}C-NMR (100 MHz; DMSO-d_6): δ_C 172.1 (CO), 163.1 (C_{Ar}), 149.7 (C_{Ar}), 144.8 (CH_{Ar}), 125.4 (CH_{Ar}), 123.3 (CH_{Ar}).

***Minor isomer (N-Formyl-4-azabenzotriazole)*:** ^{1}H-NMR (400 MHz; DMSO-d_6): δ_H 9.98 (1H, s, CHO), 8.87 (1H, dd, *J* 1.6, 4.4 Hz, CH_{Ar}); 8.64 (1H, dd, *J* 1.5, 8.3 Hz, CH_{Ar}), 7.81 (1H, dd, *J* 4.5, 8.3 Hz, CH_{Ar}); ^{13}C-NMR (100 MHz; DMSO-d_6): δ_C 172.0 (CO), 163.0 (C_{Ar}), 149.5 (C_{Ar}), 144.7 (CH_{Ar}), 125.4 (CH_{Ar}), 122.9 (CH_{Ar}).

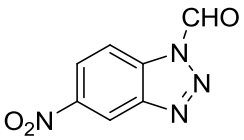
5-nitro-*1H*-benzo[*d*][1,2,3]triazole, 198

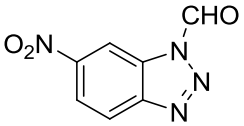


To a suspension of 4-nitro-1,2-phenylendiamine **200** (10.0 g, 65.0 mmol) in 15.7 mL of glacial acetic acid and 650 mL of cold distilled water, it was added dropwise and slowly a solution of sodium nitrite (4.50 g, 65.0 mmol) while stirring. The hot mixture was neutralised with a 5% solution of ammonia (117 mL) and cooled to allow the precipitation of the product. The product was filtered, washed with cold water and dried under vacuum at 80 °C overnight to afford the pure product **198** as a yellow solid in 88% yield (9.38 g, 57.2 mmol). ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 8.95 (1H, bd, *J* 1.2 Hz, CH_{Ar}), 8.39 (1H, dd, *J* 2.4, 9.2 Hz, CH_{Ar}), 7.92 (1H, d, *J* 8.8 Hz, CH_{Ar}); ^{1}H-NMR (400 MHz; DMSO-d_6): δ_H 8.95 (1H, dd, *J* 0.6, 1.7 Hz, CH_{Ar}), 8.33 (1H, dd, *J* 1.7, 9.1 Hz, CH_{Ar}), 8.12 (1H, dd, *J* 0.6, 9.1 Hz, CH_{Ar}); HRMS (EI+): calc. for $C_6H_4N_4O_2$ $[M]^+$: 164.0334. Found 164.0337.

The characterisation matches with the data reported in literature:
Larina L. I.; Milata V. *Magn. Reson. Chem*. **2009**, *47*, 142.

5-Nitro-*N*-formylbenzotriazole and 6-Nitro-*N*-formylbenzotriazole, 199





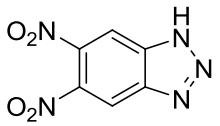
A solution of commercial grade acetic anhydride (4.72 mL, 50.0 mmol) was treated with 100% formic acid (3.80 mL, 100 mmol) at 0 °C and the resulting mixture was stirred under argon at 55 °C for 3 hours. The resulting crude anhydride mixture was analysed by ^{1}H NMR and the yield of mixed anhydride **162** was obtained (44%, 21.7 mmol). The mixed anhydride **162** was cooled down to -10 °C and the 6-nitro-*1H*-benzo[*d*][1,2,3]triazole **198** (0.9 eq based on the amount of anhydride **162** generated, 3.20 g, 19.5 mmol) was added as a solution in anhydrous THF (25 mL). The resulting mixture was stirred at -10 °C until complete as indicated by TLC analysis (45 minutes). The solvent was removed under vacuum to yield the

desired product without the need of purification. The nitro substituted *N*-formylbenzotriazoles **199** was obtained as a 5.7:1.0 mixture of regioisomers in 90% yield (3.37 g, 17.6 mmol). IR ν_{max} (film) 3173, 3098, 1751, 1742, 1618, 1520, 1339, 1205 cm^{-1}; HRMS (ESI+): calc. for $C_7H_4N_4O_3$ $[M]^+$: 192.0283. Found 192.0284; m.p. 210-211 °C.

Major isomer (5-Nitro-N-formylbenzotriazole): ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 9.90 (1H, s, CHO), 9.09 (1H, d, *J* 1.7 Hz, CH_{Ar}), 8.64 (1H, dd, *J* 2.0, 9.0 Hz, CH_{Ar}), 8.42 (1H, d, *J* 8.9 Hz, CH_{Ar}); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 159.2 (CO), 146.0 (C_{Ar}), 132.8 (C_{Ar}), 125.7 (CH_{Ar}), 117.2 (CH_{Ar}), 116.9 (C_{Ar}), 114.2 (CH_{Ar}).

Minor isomer (6-Nitro-N-formylbenzotriazole): ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 9.91 (1H, s, CHO), 9.05 (1H, d, *J* 1.8 Hz, CH_{Ar}), 8.56 (1H, dd, *J* 2.0, 9.0 Hz, CH_{Ar}), 8.45 (1H, d, *J* 9.5 Hz, CH_{Ar}); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 159.0 (CO), 146.5 (C_{Ar}), 125.3 (C_{Ar}), 122.1 (C_{Ar}), 121.4 (CH_{Ar}), 117.2 (CH_{Ar}), 110.3 (CH_{Ar}).

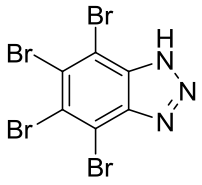
5,6-Dinitro-*1H*-benzo[*d*][1,2,3]triazole, 201



To a solution of 5-nitro-*1H*-benzo[*d*][1,2,3]triazole **198** (2.50 g, 15.0 mmol) in 30 mL of concentrated H_2SO_4 at 0 °C, 30 mL of HNO_3 (70%) were added dropwise in a period of 20 minutes. Stirring was continued for a further 15 minutes at 0 °C and then the resulting mixture was stirred at 115 °C overnight. The solution was cooled to room temperature and poured over ice to give a precipitate that was washed with distilled water and dried under vacuum at 80 °C overnight to afford the pure product **201** as a pale yellow solid in 56% yield (1.76 g, 8.40 mmol). ^{1}H-NMR (400 MHz; DMSO-d_6): δ_H 9.00 (2H, s, 2 x CH_{Ar}); HRMS (EI+): calc. for $C_6H_3N_5O_4$ $[M]^+$: 209.0185. Found 209.0182.

The characterisation matches with the data reported in literature:
McHugh C. J.; Tackley D. R.; Graham D. *Heterocycles* **2002**, *57*, 1461.

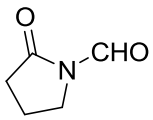
4,5,6,7-Tetrabromo-*1H*-benzo[*d*][1,2,3]triazole, 203



To a solution of benzotriazole **187** (1.20 g, 10.0 mmol) in concentrated HNO_3 (20 mL), bromine (3.33 mL, 65.0 mmol) was added dropwise and the resulting mixture was allowed to stir at reflux for 12 hours. The solution was allowed to cool to room temperature and the precipitate was washed with petroleum ether (20 mL), filtered and dried to afford a light yellow solid as pure product **203** in 80% yield (3.50 g, 8.00 mmol). ^{13}C-NMR (125 MHz; DMSO-d_6): δ_C 143.1 (C_{Ar}), 138.8 (C_{Ar}), 124.7 (C_{Ar}), 113.4 (C_{Ar}), 111.0 (C_{Ar}); HRMS (EI+): calc. for $C_6HN_3{}^{79}Br_4$ $[M]^+$: 430.6904. Found 430.6887.

The characterisation matches with the data reported in literature:
Borowski P.; Deinert J.; Schalinski S.; Bretner M.; Ginalski K.; Kulikowski T.; Sugar D. *Eur. J. Biochem.* **2003**, *270*, 1645.

2-Oxo-pyrrolidine-1-carbaldehyde, 166

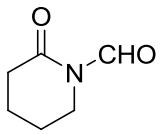


Sodium formate (30.0 g, 0.44 mol) was dried under vacuum at 130 °C for 24 hours. The dry sodium formate was suspended in dry diethyl ether (30 mL), and acetyl chloride (31.4 mL, 0.44 mol) was added quickly. The resulting solution was then stirred at room temperature under argon overnight. The reaction mixture was treated with the neat lactam 2-pyrrolidinone **163** (3.74 g, 44.0 mmol) and the solution was stirred at 60 °C overnight. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure to give a white solid which was taken up into dichloromethane (150 mL) and filtered to remove the insoluble salt by-product. The filtrate was washed with water (100 mL) and the aqueous phase was extracted into dichloromethane (50 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated under

reduced pressure to give a crude brown oil. Purification of the crude oil by flash column chromatography on silica gel (20% ethyl acetate in petroleum ether) gave the imide **166** as a colourless oil in 72% yield (3.58 g, 31.7 mmol). IR ν_{max} (film) 2969, 2903, 1744, 1686, 1395, 1350, 1321, 1292, 1240, 1219, 1194, 1018, 789, 731 and 650 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.07 (1H, s, CHO), 3.71 (2H, td, *J* 0.8, 7.2 Hz, CH_2N), 2.58 (2H, t, *J* 7.2 Hz, CH_2CO), 2.08 (2H, qn, *J* 7.2 Hz, CH_2); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 176.9 (CO), 160.3 (CHO), 42.1 (CH_2N), 33.2 (CH_2CO), 17.9 (CH_2); HRMS (EI+): calc. for $C_5H_7NO_2$ $[M]^+$: 113.0477. Found 113.0480.

The characterisation matches with the data reported in literature:
Villa M. V. J.; Targett S. M.; Barnes J. C.; Whittingham W. G.; Marquez R. *Org. Lett.* **2007**, *9*, 1631.

2-Oxo-piperidine-1-carbaldehyde, 167

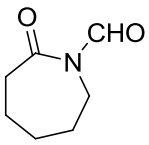


Sodium formate (30.0 g, 0.44 mol) was dried under vacuum at 130 °C for 24 hours. The dry sodium formate was suspended in dry diethyl ether (30 mL), and acetyl chloride (31.4 mL, 0.44 mol) was added quickly. The resulting solution was then stirred at room temperature under argon overnight. The reaction mixture was treated with the neat lactam δ-valerolactam **33** (4.36 g, 44.0 mmol) and the solution was stirred at 60 °C overnight. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure to give a white solid which was taken up in dichloromethane (150 mL) and filtered to remove the insoluble salt by-product. The filtrate was washed with water (100 mL) and the aqueous phase was extracted into dichloromethane (50 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude brown oil. Purification of the crude oil by flash column chromatography on silica gel (20% ethyl acetate in petroleum ether) gave the imide **167** as a colourless oil in 75% yield (4.19 g, 33.0 mmol). IR ν_{max} (film) 2953, 2880, 1713, 1684, 1479, 1460, 1396, 1368, 1342, 1331, 1290, 1281, 1231, 1155, 1090, 984 and 766 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.31 (1H, s, CHO),

3.50-3.47 (2H, bm, CH_2N), 2.47-2.42 (2H, m, CH_2CO), 1.78-1.68 (4H, bm, 2 x CH_2); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 170.9 (CO), 162.2 (CHO), 41.5 (CH_2N), 33.1 (CH_2CO), 22.3 (CH_2CH_2CO), 19.7 (CH_2CH_2N); HRMS (CI+/ISO): calc. for $C_6H_{10}NO_2$ $[M+H]^+$: 128.0712. Found 128.0709.

The characterisation matches with the data reported in literature:
Villa M. V. J.; Targett S. M.; Barnes J. C.; Whittingham W. G.; Marquez R. *Org. Lett.* **2007**, *9*, 1631.

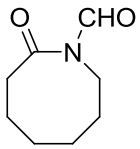
2-Oxo-azepane-1-carbaldehyde, 168



Sodium formate (30.0 g, 0.44 mol) was dried under vacuum at 130 °C for 24 hours. The dry sodium formate was suspended in dry diethyl ether (30 mL), and acetyl chloride (31.4 mL, 0.44 mol) was added quickly. The resulting solution was then stirred at room temperature under argon overnight. The reaction mixture was treated with the neat lactam ε-caprolactam **164** (4.98 g, 44.0 mmol) and the solution was stirred at 60 °C overnight. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure to give a white solid which was taken up in dichloromethane (150 mL) and filtered to remove the insoluble salt by-product. The filtrate was washed with water (100 mL) and the aqueous phase was extracted into dichloromethane (50 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude brown oil. Purification of the crude oil by flash column chromatography on silica gel (20% ethyl acetate in petroleum ether) gave the imide **168** as a colourless oil in 81% yield (5.03 g, 35.6 mmol). IR ν_{max} (film) 2932, 2861, 1718, 1682, 1462, 1437, 1348, 1331, 1261, 1213, 1179, 1153, 1082, 964, 905 and 849 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.40 (1H, s, CHO), 3.78 (2H, t, *J* 4.8 Hz, CH_2N), 2.70 (2H, t, *J* 4.8 Hz, CH_2CO), 1.83-1.68 (6H, m, 3 x CH_2); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 178.0 (CO), 162.2 (CHO), 40.2 (CH_2N), 38.3 (CH_2CO), 29.6 (CH_2CH_2CO), 28.6 (CH_2CH_2N), 23.6 (CH_2); HRMS (CI+/ISO): calc. for $C_7H_{12}NO_2$ $[M+H]^+$: 142.0868. Found 142.0864.

The characterisation matches with the data reported in literature:
Villa M. V. J.; Targett S. M.; Barnes J. C.; Whittingham W. G.; Marquez R. *Org. Lett.* **2007**, *9*, 1631.

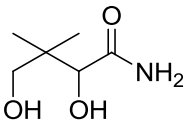
2-Oxo-azocane-1-carbaldehyde, 169



Sodium formate (30.0 g, 0.44 mol) was dried under vacuum at 130 °C for 24 hours. The dry sodium formate was suspended in dry diethyl ether (30 mL), and acetyl chloride (31.4 mL, 0.44 mol) was added quickly. The resulting solution was then stirred at room temperature under argon overnight. The reaction mixture was treated with the neat lactam 2-azacyclooctanone **165** (2.00 g, 16.0 mmol) and the solution was stirred at 60 °C overnight. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure to give a white solid which was taken up in dichloromethane (150 mL) and filtered to remove the insoluble salt by-product. The filtrate was washed with water (100 mL) and the aqueous phase was extracted into dichloromethane (50 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude brown oil. Purification of the crude oil by flash column chromatography on silica gel (20% ethyl acetate in petroleum ether) gave the imide **169** as a colourless oil in 85% yield (2.11 g, 13.6 mmol). IR ν_{max} (film) 2932, 2861, 1713, 1682, 1447, 1331, 1242, 1213, 1128, 1090, 914, 727 and 708 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.46 (1H, s, CHO), 3.85 (2H, t, *J* 6.0 Hz, CH_2N), 2.67 (2H, t, *J* 6.0 Hz, CH_2CO), 1.92 (2H, qn, *J* 6.0 Hz, CH_2CH_2CO), 1.72 (2H, qn, *J* 6.0 Hz, CH_2CH_2N), 1.63 (2H, qn, *J* 6.0 Hz, CH_2), 1.51 (2H, qn, *J* 6.0 Hz, CH_2); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 178.3 (CO), 162.6 (CHO), 40.5 (CH_2N), 35.1 (CH_2CO), 29.1 (CH_2CH_2CO), 28.6 (CH_2CH_2N), 25.9 (CH_2), 24.4 (CH_2); HRMS (CI+/ISO): calc. for $C_8H_{14}NO_2$ $[M+H]^+$: 156.1025. Found 156.1021.

The characterisation matches with the data reported in literature:
Villa M. V. J.; Targett S. M.; Barnes J. C.; Whittingham W. G.; Marquez R. *Org. Lett.* **2007**, *9*, 1631.

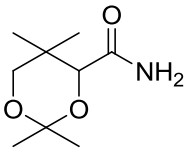
2,4-Dihydroxy-3,3-dimethylbutanamide



A 500-mL three-necked round bottom flask was loaded with pantolactone (20.0 g, 154 mmol) and liquid ammonia (200 mL) was allowed to drip through a condenser connected to a cylinder in the vessel. The reaction mixture was allowed to stir at room temperature overnight, and then it was allowed to dry under vacuum for 12 hours to afford the pure product as a white solid in 98% yield (22.1 g, 150 mmol). IR v_{max} (film) 3433, 3295, 3169, 3165, 2975, 2966, 1683, 1604, 1413, 1310, 1072, 1048, 1019, 979 and 693 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.11 (2H, s, NH_2), 5.22 (1H, d, *J* 5.6 Hz, OH), 4.49 (1H, t, *J* 5.6 Hz, OH), 3.62 (1H, d, *J* 5.6 Hz, *CH*OH), 3.36 (1H, dd, *J* 5.6, 10.4 Hz, C*H*HOH), 3.18 (1H, dd, *J* 5.6, 10.4 Hz, CH*H*OH), 0.82 (3H, s, CH_3), 0.81 (3H, s, CH_3); ^{13}C-NMR (100 MHz; DMSO-d_6): δ_C 175.5 (CO), 75.1 (CHOH), 68.0 (CH_2OH), 40.1 (C), 20.9 (CH_3), 20.4 (CH_3); HRMS (CI+/ISO): calc. for $C_6H_{14}NO_3$ $[M+H]^+$: 148.0974. Found 148.0972; m.p. 120-122 °C.

The characterisation matches with the data reported in literature:
Aquino F.; Pauling H.; Walter W.; Plattner D. A.; Bonrath W. *Synthesis* **2000**, *5*, 731.

2,2,5,5-Tetramethyl-1,3-dioxane-4-carboxamide, 205

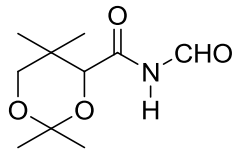


The 2,4-dihydroxy-3,3-dimethylbutanamide (2.94 g, 20.0 mmol) was suspended in a 1:1 mixture of acetone (45 mL) and dichloromethane (45 mL). Meanwhile, *p*-toluenesulfonic acid (100 mg, 0.60 mmol) and 2-methoxypropene (3.83 mL, 40.0 mmol) were dissolved in acetone (10 mL) and the resulting solution was cooled at 10 °C. The previously prepared amide suspension was added to give a dark red solution, which was allowed to stir at room temperature for 1 hour and then filtered to remove the resulting white precipitate. The filtrate was neutralised with NH_4Cl

saturated aqueous solution (100 mL) giving a transparent light green solution, which was separated, dried over Na_2SO_4, filtered and concentrated under vacuum to give a yellow oil as crude product. The crude product was purified through flash column chromatography on silica gel (2% methanol in dichloromethane) to afford a yellow solid as pure product **205** in 80% yield (3.00 g, 16.0 mmol). IR ν_{max} (film) 3475, 3276, 3143, 2988, 2971, 2867, 1695, 1406, 1375, 1370 and 1125 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.22 (1H, bs, N*H*H), 6.85 (1H, bs, NH*H*), 3.99 (1H, s, CH), 3.65 (1H, d, *J* 11.6 Hz, C*H*H), 3.18 (1H, d, *J* 11.6 Hz, *C*H*H*), 1.39 (3H, s, CH_3), 1.38 (3H, s, CH_3), 0.95 (3H, s, CH_3), 0.93 (3H, s, CH_3); ^{13}C-NMR (100 MHz; DMSO-d_6): δ_C 173.1 (CO), 98.7 (C), 76.5 (CH), 70.2 (CH_2O), 31.9 (C), 28.8 (CH_3), 21.3 (CH_3), 18.6 (CH_3), 18.3 (CH_3); LRMS (CI+/ISO): calc. for $C_9H_{18}NO_3$ $[M+H]^+$: 188.3.

The characterisation matches with the data reported in literature:
Aquino F.; Pauling H.; Walter W.; Plattner D. A.; Bonrath W. *Synthesis* **2000**, *5*, 731.

N-Formyl-2,2,5,5-tetramethyl-[1,3]dioxane-4-carboxylic acid amide, 212

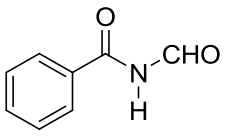


A solution of 2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide **205** (187 mg, 1.00 mmol) in anhydrous THF (10 mL) was cooled to 0 °C before being treated with *n*-BuLi (0.69 mL, 1.10 mmol, 1.6 M solution in hexanes). The reaction was then stirred at 0 °C for 5 minutes before being treated with *N*-formylbenzotriazole **186** (177 mg, 1.20 mmol). The resulting mixture was then allowed to warm up to room temperature and then stirred for a further 12 hours. The reaction was diluted with *t*-butylmethyl ether (10 mL), and quenched with a saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was then extracted with diethyl ether (3 × 20 mL) and the combined organic layers dried over Na_2SO_4. The solvent was removed under vacuum to afford the crude product, which was then purified by flash column chromatography on silica gel (from 10 to 20% ethyl acetate in petroleum ether) to afford the desired *N*-formyl imide **212** in 73% yield (157 mg,

0.73 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.10 (1H, d, *J* 10.5 Hz, CHO), 8.81 (1H, bd, *J* 10.5 Hz, NH), 4.13 (1H, s, CHO), 3.68 (1H, d, *J* 11.8 Hz, C*H*HO), 3.28 (1H, d, *J* 11.8 Hz, CH*H*O), 1.40 (3H, s, OCCH_3), 1.38 (3H, s, OCCH_3), 0.99 (3H, s, CCH_3), 0.98 (3H, s, CCH_3).

The characterisation matches with the data reported in literature:
Villa M. V. J.; Targett S. M.; Barnes J. C.; Whittingham W. G.; Marquez R. *Org. Lett.* **2007**, *9*, 1631.

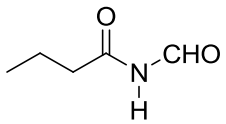
_N_-Formylbenzamide, 216



A solution of benzamide **209** (0.50 g, 4.13 mmol) in anhydrous THF (40 mL) was cooled to 0 °C before being treated with *n*-BuLi (3.1 mL, 4.96 mmol, 1.6 M solution in hexanes). The reaction was then stirred at 0 °C for 5 minutes before being treated with *N*-formylbenzotriazole **186** (0.91 g, 6.19 mmol). The resulting mixture was then allowed to warm up to room temperature and stir for a further 12 hours. The reaction was diluted with *t*-butylmethyl ether (20 mL), and quenched with a saturated aq. $NaHCO_3$ solution (40 mL). The aqueous phase was extracted with diethyl ether (3 × 40 mL) and the organic layers dried over Na_2SO_4. The solvent was removed under vacuum to afford the crude product, then purified by flash column chromatography on silica gel (from 10 to 20% ethyl acetate in petroleum ether) to afford the desired *N*-formyl imide **216** as a white solid in 75% yield (462 mg, 3.10 mmol). IR ν_{max} (film) 3414, 1728, 1683, 1463, 1364, 1252, 1208 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 9.38 (1H, d, *J* 9.8 Hz, CHO), 9.21 (1H, bd, *J* 9.8 Hz, NH), 7.92 (2H, dd, *J* 1.5, 6.6 Hz, 2 x *ortho* CH_{Ar}), 7.67 (1H, tt, *J* 1.2, 7.5 Hz, *para* CH_{Ar}), 7.55 (2H, td, *J* 1.5, 5.7 Hz, 2 x *meta* CH_{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 166.8 (CO), 164.9 (CHO), 134.1 (C_{Ar}), 131.2 (CH_{Ar}), 129.2 (CH_{Ar}), 128.2 (CH_{Ar}); HRMS (CI+/ISO) calc. for $C_8H_7NO_2$ $[M]^+$: 149.0477. Found: 149.0474.

The characterisation matches with the data reported in literature:
Villa M. V. J.; Targett S. M.; Barnes J. C.; Whittingham W. G.; Marquez R. *Org. Lett.* **2007**, *9*, 1631.

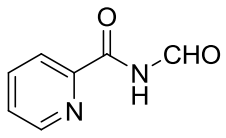
_N_-Formylbutyramide, 213



A solution of butyramide **206** (87.0 mg, 1.00 mmol) in anhydrous THF (10 mL) was cooled to 0 °C before being treated with *n*-BuLi (0.69 mL, 1.10 mmol, 1.6 M solution in hexanes). The reaction was then stirred at 0 °C for 5 minutes before being treated with *N*-formylbenzotriazole **186** (177 mg, 1.20 mmol). The resulting mixture was then allowed to warm up to room temperature and then stirred for a further 12 hours. The reaction was diluted with *t*-butylmethyl ether (10 mL), and quenched with a saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was then extracted with diethyl ether (3 × 20 mL) and the combined organic layers dried over Na_2SO_4. The solvent was removed under vacuum to afford the crude product, which was then purified by flash column chromatography on silica gel (from 10 to 20% ethyl acetate in petroleum ether) to afford the desired *N*-formyl imide **213** in 60% yield (69.0 mg, 0.60 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.73 (1H, bs, NH), 9.15 (1H, s, CHO), 2.40 (2H, t, *J* 7.3 Hz, CH_2CO), 1.80–1.70 (2H, m, CH_2), 1.03 (3H, t, *J* 7.3 Hz, CH_3).

The characterisation matches with the data reported in literature:
Mathieson J. E.; Crawford J. J.; Schmidtmann M.; Marquez R. *Org. Biomol. Chem.* **2009**, *7*, 2170.

_N_-Formylpicolinamide, 218

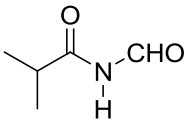


A solution of picolinamide **211** (122 mg, 1.00 mmol) in anhydrous THF (10 mL) was cooled to 0 °C before being treated with *n*-BuLi (0.69 mL, 1.10 mmol, 1.6 M solution in hexanes). The reaction was then stirred at 0 °C for 5 minutes before being treated with *N*-formylbenzotriazole **186** (177 mg, 1.20 mmol). The resulting mixture was then allowed to warm up to room temperature and then stirred for a further 12 hours. The reaction was diluted with *t*-butylmethyl ether (10 mL), and

quenched with a saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was then extracted with diethyl ether (3 × 20 mL) and the combined organic layers dried over Na_2SO_4. The solvent was removed under vacuum to afford the crude product, which was then purified by flash column chromatography on silica gel (from 10 to 20% ethyl acetate in petroleum ether) to afford the desired *N*-formyl imide **218** in 22% yield (33.0 mg, 0.22 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.32 (1H, bs, NH), 9.30 (1H, d, *J* 10.8 Hz, CHO), 8.51 (1H, d, *J* 5.0 Hz, CH_{Ar}), 8.23 (1H, d, *J* 7.8 Hz, CH_{Ar}), 7.90 (1H, td, *J* 1.7, 7.8 Hz, CH_{Ar}), 7.47 (1H, ddd, *J* 1.7, 5.0, 7.8 Hz, CH_{Ar}); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 164.5 (CO), 161.8 (CHO), 148.8 (CH_{Ar}), 147.2 (C_{Ar}), 137.8 (CH_{Ar}), 128.1 (CH_{Ar}), 123.3 (CH_{Ar}); HRMS (CI+/ISO): calc. for $C_7H_7N_2O_2$ $[M+H]^+$: 151.0508. Found 151.0510.

The characterisation matches with the data reported in literature:
Villa M. V. J.; Targett S. M.; Barnes J. C.; Whittingham W. G.; Marquez R. *Org. Lett.* **2007**, *9*, 1631.

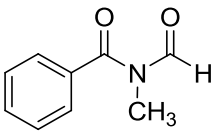
_N_-Formylisobutyramide, 214



A solution of isobutyramide **207** (87.0 mg, 1.00 mmol) in anhydrous THF (10 mL) was cooled to 0 °C before being treated with *n*-BuLi (0.69 mL, 1.10 mmol, 1.6 M solution in hexanes). The reaction was then stirred at 0 °C for 5 minutes before being treated with *N*-formylbenzotriazole **186** (177 mg, 1.20 mmol). The resulting mixture was then allowed to warm up to room temperature and then stirred for a further 12 hours. The reaction was diluted with *t*-butylmethyl ether (10 mL), and quenched with a saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was then extracted with diethyl ether (3 × 20 mL) and the combined organic layers dried over Na_2SO_4. The solvent was removed under vacuum to afford the crude product, which was then purified by flash column chromatography on silica gel (from 10 to 20% ethyl acetate in petroleum ether) to afford the desired *N*-formyl imide **214** in 44% yield (51.0 mg, 0.44 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.16 (1H, d, *J* 10.0 Hz, CHO), 8.58 (1H, bd, *J* 10.0 Hz, NH), 2.51-2.43 (1H, m, $CHMe_2$), 1.28 (6H, d, *J* 6.0 Hz, 2 × CH_3).

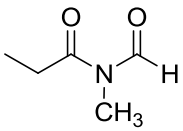
The characterisation matches with the data reported in literature:
Mathieson J. E.; Crawford J. J.; Schmidtmann M.; Marquez R. *Org. Biomol. Chem.* **2009**, *7*, 2170.

N-Formyl-*N*-methylbenzamide, 217



A 0 °C solution of *N*-methylbenzamide **210** (5.00 g, 37.0 mmol) in dry THF (100 mL) was treated by the dropwise addition of *n*-butyllithium (2.5 M in hexanes, 16.3 mL, 40.7 mmol). The resulting mixture was stirred at 0 °C for 1 hour and then treated with a solution of *N*-formylbenzotriazole **186** (6.53 g, 44.4 mmol) in THF (50 mL). The reaction mixture was then allowed to warm to room temperature and stirred for a further 12 hours. The mixture was diluted with *tert*-butyl methyl ether (100 mL) and quenched with saturated aqueous $NaHCO_3$ (100 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum to afford a crude brown oil. Purification of the crude residue by flash column chromatography on silica gel (from 0 to 20% ethyl acetate in hexane) gave the *N*-formylimide **217** as a yellow oil in 81% yield (4.80 g, 30.0 mmol). IR ν_{max} (film) 2935, 1722, 1654, 1600, 1413, 1338, 1274, 1043, 1022 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 8.90 (1H, s, CHO), 7.49−7.40 (5H, m, 5 × CH_{Ar}), 3.19 (3H, s, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 172.4 (CO), 164.3 (CHO), 133.4 (C_{Ar}), 132.0 (CH_{Ar}), 128.8 (CH_{Ar}), 128.7 (CH_{Ar}), 27.4 (CH_3); HRMS (CI+/ISO) calc. for $C_9H_{10}NO_2$ $[M+H]^+$: 164.0712. Found: 164.0714.

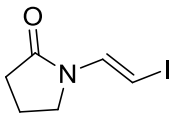
N-Formyl-*N*-methylpropionamide, 215



A 0 °C solution of *N*-methylpropionamide **208** (5.00 g, 57.5 mmol) in dry THF (100 mL) was treated by the dropwise addition of n-butyllithium (2.5 M in hexanes, 25.3

mL, 63.2 mmol). The resulting mixture was stirred at 0 °C for 1 hour and then treated with a solution of *N*-formylbenzotriazole **186** (10.2 g, 69.0 mmol) in THF (50 mL). The reaction mixture was then allowed to warm to room temperature and stirred for a further 12 hours. The mixture was diluted with *tert*-butyl methyl ether (100 mL) and quenched with saturated aqueous $NaHCO_3$ (100 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum to afford a crude brown oil. Purification of the crude residue by flash column chromatography on silica gel (from 0 to 20% ethyl acetate in hexane) gave the *N*-formylimide **215** as a yellow oil in 48% yield (3.20 g, 27.6 mmol). IR ν_{max} (film) 2985, 1722, 1668, 1452, 1417, 1365, 1265, 1051 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 9.14 (1H, s, CHO), 2.97 (3H, s, CH_3), 2.56 (2H, q, *J* 7.4 Hz, CH_2), 1.09 (3H, t, *J* 7.4 Hz, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 175.1 (CO), 162.4 (CHO), 28.1 (CH_2), 26.3 (NCH_3), 8.3 (CH_3); HRMS (CI+/ISO) calc. for $C_5H_{10}NO_2$ $[M+H]^+$: 116.0712. Found: 116.0707.

***(E)*-1-(2-Iodovinyl)pyrrolidin-2-one, 220**

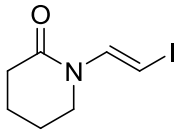


Method A: Chromium(III)chloride hexahydrate (2.85 g, 18.0 mmol) was placed in a two neck round bottom flask and was heated using a bunsen burner until the colour of the chromium(III)chloride changed from dark green to light green and then to purple. The purple chromium(III)chloride was then treated with zinc (0.59 g, 9.00 mmol) and NaI (2.25 g, 15.0 mmol), and the resulting mixture was stirred and heated under vacuum and for 15 minutes. The reaction mixture was then allowed to cool down to room temperature whilst still under vacuum and then placed under argon. The dry mixture was then suspended in anhydrous THF (30 mL) and the reaction mixture was stirred at room temperature for 10 minutes. A solution of *N*-formyl imide **166** (147 mg, 1.30 mmol) and iodoform (1.02 g, 2.60 mmol) in THF (15 mL) was then cannulated into the chromium mixture and the resulting brown suspension was stirred overnight at room temperature. The reaction was then quenched with saturated aqueous NaCl (30 mL), followed by saturated aqueous IDRANAL III® (30 mL) and the solution was allowed to stir at room temperature for 30 minutes before being extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was then purified by flash column chromatography on silica gel eluting with 10% ethyl acetate in petroleum ether to afford the desired product **220** as a yellow solid in 51% yield (156 mg, 0.66 mmol).

Method B: A suspension of (iodomethyl)triphenylphosphonium iodide (2.65 g, 5.00 mmol) in anhydrous THF (10 mL) was treated with potassium *tert*-butoxide (600 mg, 5.00 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of 2-oxopyrrolidin-1-carbaldehyde **166** (56.5 mg, 0.50 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with

diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum, and the crude residue was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the iodo-enamide **220** as a yellow solid in 78% yield (92.0 mg, 0.39 mmol). IR ν_{max} (film) 3057, 2957, 2917, 2889, 1685, 1607, 1480, 1457, 1263, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.59 (1H, d, *J* 15.0 Hz, NCH=), 5.37 (1H, d, *J* 15.0 Hz, =CHI), 3.51 (2H, t, *J* 7.1 Hz, CH_2N), 2.46 (2H, t, *J* 7.8 Hz, CH_2CO), 2.12 (2H, qn, *J* 7.5 Hz, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 172.3 (CO), 134.7 (NCH=), 55.0 (=CHI), 44.6 (CH_2N), 30.6 (CH_2CO), 17.4 (CH_2); HRMS (EI+) calc. for C_6H_8INO $[M]^+$ 236.9655. Found: 236.9651; m.p. 27-28 °C.

***(E)*-1-(2-Iodovinyl)piperidin-2-one, 219**

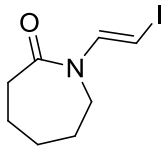


Method A: Chromium(III)chloride hexahydrate (1.70 g, 10.8 mmol) was placed in a two neck round bottom flask and was heated using a bunsen burner until the colour of the chromium(III)chloride changed from dark green to light green and then to purple. The purple chromium(III)chloride was then treated with zinc (352 mg, 5.38 mmol) and NaI (1.34 g, 8.97 mmol), and the resulting mixture was stirred and heated under vacuum and for 15 minutes. The reaction was then allowed to cool down to room temperature whilst still under vacuum and then placed under argon. The dry mixture was then suspended in anhydrous THF (30 mL) and the reaction mixture was stirred at room temperature for 10 minutes. A solution of *N*-formyl imide **167** (100 mg, 0.78 mmol) and iodoform (614 mg, 1.56 mmol) in THF (15 mL) was then cannulated into the chromium mixture and the resulting brown suspension was stirred overnight at room temperature.The reaction was then quenched with saturated aqueous NaCl (30 mL), followed by saturated aqueous IDRANAL III® (30 mL) and the solution was allowed to stir at room temperature for 30 minutes before being extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was then purified by flash column chromatography on

silica gel eluting with 10% ethyl acetate in petroleum ether to afford the desired product **219** as a yellow solid in 46% yield (90.0 mg, 0.36 mmol).

Method B: A suspension of (iodomethyl)triphenylphosphonium iodide (2.65 g, 5.00 mmol) in anhydrous THF (10 mL) was treated with potassium *tert*-butoxide (600 mg, 5.00 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of 2-oxopiperidin-1-carbaldehyde **167** (63.5 mg, 0.50 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum, and the crude residue was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the iodo-enamide **219** as a yellow solid in 80% yield (100 mg, 0.40 mmol). IR ν_{max} (film) 2924, 2854, 1651, 1599, 1458, 1404, 1296, 1257 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.11 (1H, d, *J* 14.0 Hz, NCH=), 5.44 (1H, d, *J* 14.0 Hz, =CHI), 3.41 (2H, t, *J* 6.0 Hz, CH_2N), 2.48 (2H, t, *J* 6.4 Hz, CH_2CO), 1.88-1.81 (2H, m, CH_2CH_2CO), 1.79-1.70 (2H, m, CH_2CH_2N); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 167.8 (CO), 137.7 (NCH=), 55.0 (=CHI), 45.0 (CH_2N), 32.8 (CH_2CO), 22.4 (CH_2CH_2CO), 20.6 (CH_2CH_2N); HRMS (CI+/ISO) calc. for $C_7H_{11}INO$ $[M+H]^+$:251.9886. Found: 251.9885; m.p. 31-33 °C.

(E)-1-(2-Iodovinyl)azepan-2-one, 221



Method A: Chromium(III)chloride hexahydrate (2.85 g, 18.0 mmol) was placed in a two neck round bottom flask and was heated using a bunsen burner until the colour of the chromium(III)chloride changed from dark green to light green and then to purple. The purple chromium(III)chloride was then treated with zinc (588 mg, 9.00 mmol) and NaI (2.25 g, 15.0 mmol), and the resulting mixture was stirred

and heated under vacuum and for 15 minutes. The reaction was then allowed to cool down to room temperature whilst still under vacuum and then placed under argon. The dry mixture was then suspended in anhydrous THF (30 mL) and the reaction mixture was stirred at room temperature for 10 minutes. A solution of *N*-formyl imide **168** (184 mg, 1.30 mmol) and iodoform (1.02 g, 2.60 mmol) in THF (15 mL) was then cannulated into the chromium mixture and the resulting brown suspension was stirred overnight at room temperature.The reaction was then quenched with saturated aqueous NaCl (30 mL), followed by saturated aqueous IDRANAL III® (30 mL) and the solution was allowed to stir at room temperature for 30 minutes before being extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was then purified by flash column chromatography on silica gel eluting with 10% ethyl acetate in petroleum ether to afford the desired product **221** as a yellow solid in 40% yield (137 mg, 0.52 mmol).

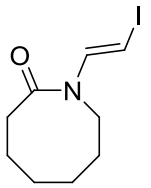
Method B: The dihaloenamide 1-(2,2-diiodovinyl)azepan-2-one **253** (380 mg, 0.97 mmol) was dissolved in an anhydrous MeOH/THF mixture (1:1, 20 mL total volume), and the resulting solution was cooled to 0 °C. The solution was treated with Zn−Cu couple (3.70 g, 29.1 mmol) and glacial acetic acid (5.9 mL, 97.0 mmol), and the resulting reaction mixture was stirred at 0 °C until completion by TLC analysis (30 minutes). The reaction was quenched with $NaHCO_3$ saturated aqueous solution (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over Na_2SO4 and concentrated under vacuum to afford the iodo enamides **221*E*** and **221*Z*** (10:1 ratio) as an inseparable mixture in 94% yield (240 mg, 0.91 mmol).

***(E)-1-(2-Iodovinyl)azepan-2-one* 221*E*:** IR (neat) ν_{max} 2930, 1658, 1602, 1476, 1389, 1325, 1191 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.84 (1H, d, *J* 13.7 Hz, NCH=), 5.51 (1H, d, *J* 14.2 Hz, =CHI), 3.57−3.52 (2H, m, CH_2N), 2.63−2.58 (2H, m, CH_2CO), 1.75−1.67 (6H, m, 3 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.5 (CO), 137.3 (NCH=), 55.0 (=CHI), 45.1 (CH_2N), 36.9 (CH_2CO), 29.4 (CH_2CH_2CO), 27.5 (CH_2CH_2N), 23.4 (CH_2); HRMS (CI/ISO) found $[M + H]^+$ 266.0042, $C_8H_{13}INO$ requires 266.0041; m.p. 35-36 °C.

***(Z)-1-(2-Iodovinyl)azepan-2-one* 221*Z*:** ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.45 (1H, d, *J* 6.3 Hz, NCH=), 5.83 (1H, d, *J* 6.9 Hz, =CHI), 3.76−3.73 (2H, m, CH_2N), 2.63−2.58 (2H, m, CH_2CO), 1.75−1.67 (6H, m, 3 × CH_2); ^{13}C NMR (100 MHz,

$CDCl_3$) δ_C 176.2 (CO), 138.6 (NCH=), 66.9 (=CHI), 49.5 (CH_2N), 37.4 (CH_2CO), 30.4 (CH_2CH_2CO), 29.8 (CH_2CH_2N), 23.3 (CH_2).

***(E)*-1-(2-Iodovinyl)azocan-2-one, 222**

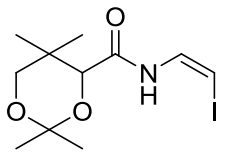


Method A: Chromium(III)chloride hexahydrate (2.85 g, 18.0 mmol) was placed in a two neck round bottom flask and was heated using a bunsen burner until the colour of the chromium(III)chloride changed from dark green to light green and then to purple. The purple chromium(III)chloride was treated with zinc (588 mg, 9.00 mmol) and NaI (2.25 g, 15.0 mmol), and the resulting mixture was stirred and heated under vacuum and for 15 minutes. The reaction was allowed to cool down to room temperature and was then suspended in anhydrous THF (30 mL) under argon and the reaction mixture was stirred at room temperature for 10 minutes. A solution of *N*-formyl imide **169** (201 mg, 1.30 mmol) and iodoform (1.02 g, 2.60 mmol) in THF (15 mL) was cannulated into the mixture and the resulting brown suspension was stirred overnight at room temperature. The reaction was quenched with saturated aqueous NaCl (30 mL), followed by saturated aqueous IDRANAL III® (30 mL) and the solution was allowed to stir at room temperature for 30 minutes before being extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was then purified by flash column chromatography on silica gel eluting with 10% ethyl acetate in petroleum ether to afford the desired product **222** as a yellow solid in 42% yield (150 mg, 0.54 mmol).

Method B: The dihaloenamide 1-(2,2-diiodovinyl)azocan-2-one **254** (405 mg, 1.00 mmol) was dissolved in an anhydrous MeOH/THF mixture (1:1, 20 mL total volume), and the resulting solution was cooled to 0 °C. The solution was treated with Zn−Cu couple (3.81 g, 30.0 mmol) and glacial acetic acid (6.1 mL, 100 mmol), and the resulting reaction mixture was stirred at 0 °C until completion by TLC analysis (30 minutes). The reaction was quenched with $NaHCO_3$ saturated aqueous solution (10 mL) and extracted with diethyl ether (3 × 10 mL). The

combined organic phases were dried over Na_2SO4 and concentrated under vacuum to afford the iodo enamide **222** as a white solid, which did not require any further purification, in 77% yield (215 mg, 0.771 mmol). IR ν_{max} (film) 3083, 2938, 2929, 2915, 1647, 1603, 1484, 1453, 1388, 1312 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.95 (1H, d, *J* 14.1 Hz, NCH=), 5.51 (1H, d, *J* 14.1 Hz, =CHI), 3.72 (2H, dd, *J* 5.8, 5.9 Hz, CH_2N), 2.63-2.56 (2H, m, CH_2CO), 1.88-1.78 (2H, m, CH_2CH_2CO), 1.73-1.68 (2H, m, CH_2CH_2N), 1.62-1.58 (2H, m, CH_2), 1.50-1.42 (2H, m, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 173.1 (CO), 136.2 (NCH=), 55.5 (=CHI), 43.6 (CH_2N), 34.3 (CH_2CO), 29.1 (CH_2CH_2CO), 27.9 (CH_2CH_2N), 26.4 (CH_2), 24.2 (CH_2); HRMS (CI+/ISO) calc. for $C_9H_{15}INO$ $[M+H]^+$: 280.0203. Found: 280.0198; m.p. 54-56 °C.

***(Z)-N*-(2-Iodovinyl)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide, 225**

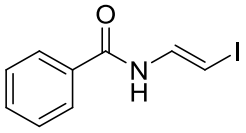


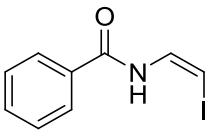
Method A: Chromium(III)chloride hexahydrate (2.85 g, 18.0 mmol) was heated using a bunsen burner until the colour of the chromium(III)chloride changed from dark green to light green and then to purple. The purple chromium(III)chloride was treated with zinc (588 mg, 9.00 mmol) and NaI (2.25 g, 15.0 mmol), and the resulting mixture was stirred and heated under vacuum and for 15 minutes. The reaction was allowed to cool down to room temperature and was then suspended in anhydrous THF (30 mL) under argon and the reaction mixture was stirred at room temperature for 10 minutes. A solution of *N*-formyl imide **212** (280 mg, 1.30 mmol) and iodoform (1.02 g, 2.60 mmol) in THF (15 mL) was cannulated into the mixture and the resulting brown suspension was stirred overnight at room temperature. The reaction was quenched with saturated aqueous NaCl (30 mL), followed by saturated aqueous IDRANAL III® (30 mL) and the solution was allowed to stir at room temperature for 30 minutes before being extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude 1.0/1.1 mixture of *E/Z* isomers. The crude oil was then purified by flash column chromatography on silica

gel eluting with 10% ethyl acetate in petroleum ether to afford the desired product **225** as a light yellow solid in 32% yield (140 mg, 0.41 mmol).

Method B: The dihaloenamide *N*-(2,2-diiodovinyl)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide **257** (160 mg, 0.34 mmol) was dissolved in an anhydrous MeOH/THF mixture (1:1, 10 mL total volume), and the resulting solution was cooled to 0 °C. The solution was treated with Zn−Cu couple (1.33 g, 10.3 mmol) and glacial acetic acid (2.1 mL, 34.4 mmol), and the resulting reaction mixture was stirred at 0 °C until completion by TLC analysis (30 minutes). The reaction was quenched with $NaHCO_3$ saturated aqueous solution (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over Na_2SO4 and concentrated under vacuum to afford the iodo enamide **225** as a yellow solid, which did not require any further purification, in 71% yield (0.08 g, 0.24 mmol). IR ν_{max} (film) 2988, 2956, 2872, 1699, 1626, 1464, 1375, 1285, 1235 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (1H, bd, *J* 11.0 Hz, NH), 7.28 (1H, dd, *J* 6.4, 11.2 Hz, NCH=), 5.42 (1H, d, *J* 6.4 Hz, =CHI), 4.17 (1H, s, CH), 3.72 (1H, d, *J* 11.8 Hz, C*H*HO), 3.32 (1H, d, *J* 11.8 Hz, CH*H*O), 1.54 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.05 (3H, s, CH_3), 1.04 (3H, s, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 167.6 (CO), 129.4 (NCH=), 99.4 (C), 77.2 (CH), 71.4 (CH_2), 61.4 (=CHI), 33.3 (C), 29.5 (CH_3), 21.9 (CH_3), 19.1 (CH_3), 18.8 (CH_3); HRMS (EI+) calc. for $C_{11}H_{18}INO_3$ $[M]^+$: 339.0331. Found: 339.0332; m.p. 109-110 °C.

(E)-N-(2-Iodovinyl)benzamide and *(Z)-N*-(2-Iodovinyl)benzamide, 223





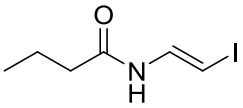
Chromium(III)chloride hexahydrate (2.20 g, 13.8 mmol) was placed in a two neck round bottom flask and was heated using a bunsen burner until the colour of the chromium(III)chloride changed from dark green to light green and then to purple. The purple chromium(III)chloride was then treated with zinc (452 mg, 6.90 mmol) and NaI (1.73 g, 11.5 mmol), and the resulting mixture was stirred and heated under vacuum and for 15 minutes. The reaction was then allowed to cool down to room temperature whilst still under vacuum and then placed under argon. The dry mixture was then suspended in anhydrous THF (30 mL) and the reaction mixture

was stirred at room temperature for 10 minutes. A solution of *N*-formyl imide **216** (149 mg, 1.00 mmol) and iodoform (0.78 g, 2.00 mmol) in THF (15 mL) was then cannulated into the chromium mixture and the resulting brown suspension was stirred overnight at room temperature.The reaction was then quenched with saturated aqueous NaCl (30 mL), followed by saturated aqueous IDRANAL III® (30 mL) and the solution was allowed to stir at room temperature for 30 minutes before being extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was then purified by flash column chromatography on silica gel eluting with 10% ethyl acetate in petroleum ether to afford the product as a yellow solid in 41% yield (113 mg, 0.42 mmol) in 3.0/1.0 mixture of *E/Z* isomers **223*E*** and **223*Z*** from which an analytical clean fraction of the isomer **223*E*** could be obtained.

Z isomer**:** ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.06 (1H, bs, NH), 7.89-7.84 (2H, m, 2 × CH_{Ar}), 7.62-7.48 (3H, m, 3 × CH_{Ar}), 7.40 (1H, d, *J* 6.7 Hz, NCH=), 5.49 (1H, d, *J* 6.7 Hz, =CHI).

E isomer**:** IR ν_{max} (film) 3299, 2929, 1687, 1652, 1620, 1508, 1464, 1283 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.96 (1H, app bd, *J* 8.9 Hz, NH), 7.79 (2H, app dd, *J* 1.4, 7.3 Hz, 2 × CH_{Ar}), 7.65 (1H, dd, *J* 10.1, 13.7 Hz, NCH=), 7.55 (1H, appt, *J* 7.3 Hz, 1 × CH_{Ar}), 7.46 (2H, appt, *J* 8.1 Hz, 2 × CH_{Ar}), 5.84 (1H, d, *J* 13.8 Hz, =CHI); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 164.3 (CO), 132.8 (NCH=)**,** 132.7 (C_{Ar}), 130.7 (CH_{Ar}), 129.1 (CH_{Ar}), 127.4 (CH_{Ar}), 61.2 (=CHI); HRMS (EI+) calc. for C_9H_8INO $[M]^+$: 272.9651. Found: 272.9654; m.p. 115-130 °C.

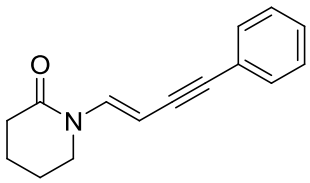
(E)-N-(2-Iodovinyl)butyramide, 224



Chromium(III)chloride hexahydrate (2.85 g, 18.0 mmol) was placed in a two neck round bottom flask and was heated using a bunsen burner until the colour of the chromium(III)chloride changed from dark green to light green and then to purple. The purple chromium(III)chloride was then treated with zinc (588 mg, 9.00 mmol) and NaI (2.25 g, 15.0 mmol), and the resulting mixture was stirred and heated under vacuum and for 15 minutes. The reaction was then allowed to cool down to room temperature whilst still under vacuum and then placed under argon. The dry

mixture was then suspended in anhydrous THF (30 mL) and the reaction mixture was stirred at room temperature for 10 minutes. A solution of *N*-formyl imide **213** (149 mg, 1.30 mmol) and iodoform (1.02 g, 2.60 mmol) in THF (15 mL) was then cannulated into the chromium mixture and the resulting brown suspension was stirred overnight at room temperature.The reaction was then quenched with saturated aqueous NaCl (30 mL), followed by saturated aqueous IDRANAL III® (30 mL) and the solution was allowed to stir at room temperature for 30 minutes before being extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude 5.0/1.0 mixture of *E/Z* isomers. The crude oil was then purified by flash column chromatography on silica gel eluting with 10% ethyl acetate in petroleum ether to afford the *E* isomer **224** as a yellow solid in 21% yield (65.0 mg, 0.27 mmol). IR ν_{max} (film) 3265, 2960, 1664, 1624, 1492, 1462, 1222 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.45 (1H, dd, *J* 10.6, 13.9 Hz, NCH=), 7.28 (1H, bs, NH), 5.64 (1H, d, *J* 13.9 Hz, =CHI), 2.20 (2H, t, *J* 7.3 Hz, CH_2CO), 1.68 (2H, sext, *J* 7.5 Hz, CH_2), 0.96 (3H, t, *J* 7.4 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 169.8 (CO), 133.7 (NCH=), 56.6 (=CHI), 38.3 (CH_2CO), 18.9 (CH_2), 13.8 (CH_3); HRMS (CI+/ISO) calc. for $C_6H_{11}INO$ $[M+H]^+$: 239.9885. Found: 239.9880; m.p. 85-90 °C.

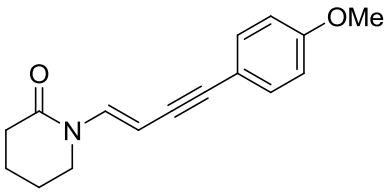
***(E)*-1-(4-Phenylbut-1-en-3-ynyl)piperidin-2-one, 226**



A 0.3 M solution of β-iodo-enamide **219** (0.06 g, 0.24 mmol) in DMF was treated with $Pd(PPh_3)_4$ (28.0 mg, 24.0 μmol) and the suspension was stirred at room temperature for 10 minutes. Then phenyl acetylene (132 μL, 1.20 mmol), CuI (10.0 mg, 48.0 μmol) and TEA (72.0 μL, 0.48 mmol) were sequentially added, and the resulting mixture was stirred at room temperature for 72 hours. The reaction mixture was quenched with distilled water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were then washed with water (10 × 20 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a brown residue. The crude product was purified by flash column chromatography on silica

gel eluting with 50/50 petroleum ether/dichloromethane + 5% diethyl ether to afford the pure β-yn-enamide product **226** as a yellow-brown solid in 93% yield (50.0 mg, 0.22 mmol). IR ν_{max} (film) 3086, 2939, 2877, 2198, 1728, 1658, 1612, 1458 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.02 (1H, d, *J* 14.8 Hz, NCH=), 7.37-7.32 (2H, m, 2 × CH_{Ar}), 7.26-7.17 (3H, m, 3 × CH_{Ar}), 5.21 (1H, d, *J* 14.8 Hz, =CHI), 3.43 (2H, t, *J* 6.0 Hz, CH_2N), 2.54 (2H, t, *J* 6.5 Hz, CH_2CO), 1.87 (2H, qn, *J* 6.2 Hz, CH_2CH_2CO), 1.75 (2H, qn, *J* 6.2 Hz, CH_2CH_2N); ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 168.2 (CO), 137.3 (NCH=), 131.3 (2 × *ortho* CH_{Ar}), 128.4 (2 × *meta* CH_{Ar}), 127.7 (*para* CH_{Ar}), 123.7 (C_{Ar}), 89.8 (=CH), 88.9 (=CH-C_{alkyne}), 87.4 (C_{alkyne}-Ar), 45.0 (CH_2N), 32.9 (CH_2CO), 22.4 (CH_2CH_2CO), 20.3 (CH_2CH_2N); HRMS (CI+/ISO) calc. for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1233. Found: 226.1232; m.p. 91-92 °C.

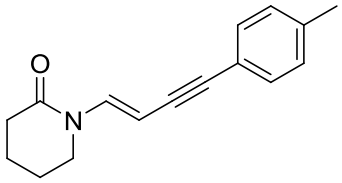
(E)-1-(4-(4-Methoxyphenyl)but-1-en-3-ynyl)piperidin-2-one, 227



A 0.3 M solution of β-iodo-enamide **219** (0.05 g, 199 μmol) in DMF was treated with $Pd(PPh_3)_4$ (23.0 mg, 19.0 μmol) and the suspension was stirred at room temperature for 10 minutes. Then 4-ethylanisole (132 mg, 995 μmol), CuI (7.00 mg, 38.0 μmol) and TEA (60.0 μL, 39.8 μmol) were sequentially added, and the resulting mixture was stirred at room temperature for 72 hours. The reaction mixture was quenched with distilled water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were then washed with water (10 × 20 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a brown residue. The crude product was purified by flash column chromatography on silica gel eluting with 50/50 petroleum ether/dichloromethane + 5% diethyl ether to afford the pure β-yn-enamide product **227** as a yellow-brown solid in 92% yield (47.0 mg, 0.18 mmol). IR ν_{max} (film) 3080, 2949, 2837, 2191, 1660, 1616, 1565, 1506, 1473 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.99 (1H, d, *J* 14.8 Hz, NCH=), 7.35 (2H, m, 2 × *ortho* CH_{Ar}), 6.83 (2H, m, 2 × *meta* CH_{Ar}), 5.20 (1H, d, *J* 14.8 Hz, =CH), 3.81 (3H, s, OCH_3), 3.43 (2H, t, *J* 6.0 Hz, CH_2N), 2.54 (2H, t, *J* 6.5 Hz, CH_2CO), 1.92 (2H, qn, *J* 6.2 Hz, CH_2CH_2CO), 1.80 (2H, qn, *J* 6.2 Hz, CH_2CH_2N); ^{13}C-NMR (125

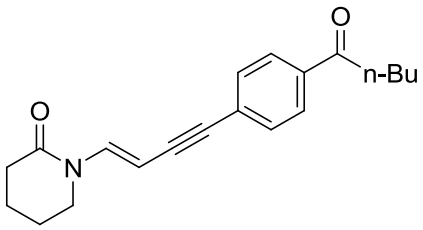
MHz, $CDCl_3$): δ_C 168.1 (CO), 159.2 (C_{Ar}-OMe), 136.7 (NCH=), 132.7 (2 × *ortho* CH_{Ar}), 115.9 (C_{Ar}), 114.0 (2 × *meta* CH_{Ar}), 90.2 (=CH), 88.8 (=CH-C_{alkyne}), 85.9 (C_{alkyne}-Ar), 55.3 (OCH_3), 45.0 (CH_2N), 33.0 (CH_2CO), 22.5 (CH_2CH_2CO), 20.4 (CH_2CH_2N); HRMS (EI+) calc. for $C_{16}H_{17}NO_2$ $[M]^+$: 255.1260. Found: 255.1259; m.p. 130-132 °C.

(E)-1-(4-*p*-Tolylbut-1-en-3-ynyl)piperidin-2-one, 230



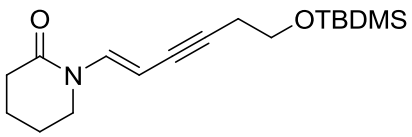
A 0.3 M solution of β-iodo-enamide **219** (0.05 g, 0.20 mmol) in DMF was treated with $Pd(PPh_3)_4$ (23.2 mg, 20.0 μmol) and the suspension was stirred at room temperature for 10 minutes. Then *p*-toluyl acetylene **235** (116 mg, 1.00 mmol), CuI (8.00 mg, 40.0 μmol) and TEA (61.0 μL, 40.0 μmol) were sequentially added, and the resulting mixture was stirred at room temperature for 72 hours. The reaction mixture was quenched with distilled water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were then washed with water (10 × 20 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a brown residue. The crude product was purified by flash column chromatography on silica gel eluting with 50/50 petroleum ether/dichloromethane + 5% diethyl ether to afford the pure β-yn-enamide product **230** as a yellow-brown solid in 99% yield (48.0 mg, 0.20 mmol). IR ν_{max} (film) 3086, 2955, 2924, 2877, 2191, 1666, 1620, 1504, 1458 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): δ_H 8.00 (1H, d, *J* 14.8 Hz, NCH=), 7.30 (2H, d, *J* 8.0 Hz, 2 × *ortho* CH_{Ar}), 7.10 (2H, d, *J* 7.6 Hz, 2 × *meta* CH_{Ar}), 5.20 (1H, d, *J* 14.8 Hz, =CH), 3.43 (2H, t, *J* 6.2 Hz, CH_2N), 2.54 (2H, t, *J* 6.6 Hz, CH_2CO), 2.34 (3H, s, CH_3), 1.94 (2H, qn, *J* 6.2 Hz, CH_2CH_2CO), 1.83 (2H, qn, *J* 6.2 Hz, CH_2CH_2N); ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 168.2 (CO), 137.8 (C_{Ar}-Me), 137.0 (NCH=), 131.1 (2 × *ortho* CH_{Ar}), 129.1 (2 × *meta* CH_{Ar}), 120.7 (C_{Ar}), 90.1 (CH=), 89.1 (CH-C_{alkyne}), 86.7 (C_{alkyne}-Ar), 45.0 (CH_2N), 33.0 (CH_2CO), 22.4 (CH_2CH_2CO), 21.5 (CH_3), 20.4 (CH_2CH_2N); HRMS (EI+) calc. for $C_{16}H_{17}NO$ $[M]^+$: 239.1311. Found: 239.1310; m.p. 147-148 °C.

_(E)_-1-(4-(4-Pentanoylphenyl)but-1-en-3-ynyl)piperidin-2-one, 228



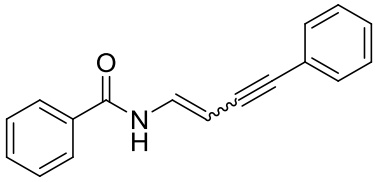
A 0.3 M solution of β-iodo-enamide **219** (35.0 mg, 139 μmol) in DMF was treated with $Pd(PPh_3)_4$ (16.0 mg, 14.0 μmol) and the suspension was stirred at room temperature for 10 minutes. Then 1-(4- ethynylphenyl)pentan-1-one **238** (130 mg, 0.70 mmol), CuI (5.00 mg, 28.0 μmol) and TEA (40.0 μL, 0.30 mmol) were sequentially added, and the resulting mixture was stirred at room temperature for 72 hours. The reaction mixture was quenched with distilled water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were then washed with water (10 × 20 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a brown residue. The crude product was purified by flash column chromatography on silica gel eluting with 50/50 petroleum ether/dichloromethane + 5% diethyl ether to afford the pure β-yn-enamide product **228** as a yellow-brown solid in 94% yield (40.0 mg, 0.13 mmol). IR ν_{max} (film) 3078, 3045, 2955, 2193, 1680, 1664, 1616, 1593, 1552, 1500 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ_H 8.07 (1H, d, *J* 14.9 Hz, NCH=), 7.89 (2H, d, *J* 8.7 Hz, 2 × *meta* CH_{Ar}), 7.47 (2H, d, *J* 8.7 Hz, 2 × *ortho* CH_{Ar}), 5.22 (1H, d, *J* 14.8 Hz, =CH), 3.45 (2H, t, *J* 6.0 Hz, CH_2N), 2.95 (2H, t, *J* 7.4 Hz, CH_2CO), 2.57 (2H, t, *J* 6.4 Hz, CH_2CO), 1.99-1.91 (2H, m, CH_2CH_2N), 1.89-1.82 (2H, m, CH_2CH_2CO), 1.71 (2H, app qn, *J* 7.1 Hz, CH_2CH_2CO), 1.41 (2H, app sextet, *J* 7.5 Hz, CH_2CH_3), 0.88 (3H, t, *J* 7.3 Hz, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 197.5 (CO), 168.5 (CON), 138.3 (*C*CO), 134.7 (NCH=), 131.2 (2 × *ortho* CH_{Ar}), 128.6 (C_{Ar}), 128.0 (2 × *meta* CH_{Ar}), 100.0 (C_{alkyne}-Ar), 95.4 (=CH), 89.3 (C_{alkyne}-CH=), 45.1 (CH_2N), 38.4 (CH_2CO), 33.0 (CH_2CO), 26.5 (CH_2CH_2N), 22.5 (CH_2CH_2CO), 22.4 (CH_2CH_3), 20.4 (CH_2CH_2CO), 14.0 (CH_3); HRMS (EI+) calc. for $C_{20}H_{23}NO_2$ [M]+: 309.1727. Found: 309.1729; m.p. 169-170 °C.

_(E)_-1-(6-(_tert_-Butyldimethylsilyloxy)hex-1-en-3-ynyl)piperidin-2-one, 231



A 0.3 M solution of β-iodo-enamide **219** (25.0 mg, 100 μmol) in DMF was treated with $Pd(PPh_3)_4$ (12.0 mg, 10.0 μmol) and the suspension was stirred at room temperature for 10 minutes. Then 1-(*tert*-butyldimethylsilyloxy)-3-butyne **240** (92.0 mg, 0.50 mmol), CuI (4.00 mg, 20.0 μmol) and TEA (30.0 μL, 0.20 mmol) were sequentially added, and the resulting mixture was stirred at room temperature for 72 hours. The reaction mixture was quenched with distilled water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were then washed with water (10 × 20 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a brown residue. The crude product was purified by flash column chromatography on silica gel eluting with 50/50 petroleum ether/dichloromethane + 5% diethyl ether to afford the pure β-yn-enamide product **231** as a yellow oil in 33% yield (10.2 mg, 33.0 μmol). IR ν_{max} (film) 2931, 2854, 2337, 1736, 1666, 1620 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.78 (1H, d, *J* 14.8 Hz, NCH=), 4.88 (1H, dm, *J* 14.8 Hz, =CH), 3.64 (2H, t, *J* 7.3 Hz, CH_2N), 3.28 (2H, t, *J* 6.3 Hz, CH_2CO), 2.43 (4H, m = 2 × t, 2 × CH_2), 1.81 (2H, qn, *J* 6.2 Hz, CH_2CH_2CO), 1.73 (2H, qn, *J* 6.2 Hz, CH_2CH_2N), 1.46 (6H, s, 2 × CH_3), 0.81 (9H, s, 3 × CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 168.5 (CO), 136.7 (NCH=), 90.2 (=CH), 90.0 (=CH-C_{alkyne}), 77.6 (C_{alkyne}), 62.1 (CH_2O), 44.9 (CH_2N), 32.9 (CH_2CO), 25.9 (3 × CH_3), 23.9 (CH_2CH_2O), 22.5 (CH_2CH_2CO), 20.4 (CH_2CH_2N), 18.4 (CMe_3), -5.2 (2 × CH_3); HRMS (CI+/ISO) calc. for $C_{17}H_{30}NO_2Si$ $[M+H]^+$: 308.2046. Found: 308.2051.

_N_-((_E_)-4-Phenyl-but-1-en-3-ynyl)-benzamide and _N_-((_Z_)-4-Phenyl-but-1-en-3-ynyl)-benzamide, 229

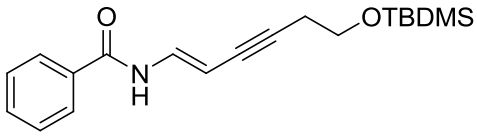


A 0.3 M solution of a 2:1 mixture of *E/Z* β-iodo-enamides **223** (55.0 mg, 201 µmol) in DMF was treated with $Pd(PPh_3)_4$ (23.0 mg, 21.0 µmol) and the suspension was stirred at room temperature for 10 minutes. Then phenyl acetylene (120 µL, 1.00 mmol), CuI (8.00 mg, 40.2 µmol) and TEA (60.0 µL, 0.40 mmol) were sequentially added, and the resulting mixture was stirred at room temperature for 72 hours. The reaction mixture was quenched with distilled water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were then washed with water (10 × 20 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a brown residue. The crude product was purified by flash column chromatography on silica gel eluting with 50/50 petroleum ether/dichloromethane + 5% diethyl ether to afford a 2:1 mixture of double bond isomers **229*E*** and **229*Z*** as a yellow oil in 85% yield (42.0 mg, 0.17 mmol) from which an analytical clean fraction of the isomer **229*E*** could be obtained.

***Z isomer*:** ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.97 (1H, bd, *J* 9.8 Hz, NH), 7.82 (1H, d, *J* 8.8 Hz, NCH=), 7.65 – 7.28 (10H, m, 10 × CH_{Ar}), 5.11 (1H, d, *J* 8.8 Hz, =CH).

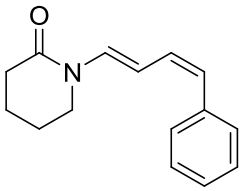
***E isomer*:** ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.98 (1H, bd, *J* 9.8 Hz, NH), 7.84 (2H, m, 2 × CH_{Ar}), 7.65-7.28 (9H, m, 8 × CH_{Ar} and NCH=), 5.56 (1H, d, *J* 14.5 Hz, =CH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 163.8 (CO), 133.1 (C_{Ar}), 132.5 (CH_{Ar}), 132.2 (CH_{Ar}), 131.3 (NCH=), 128.8 (CH_{Ar}), 128.5 (CH_{Ar}), 128.3 (CH_{Ar}), 127.2 (CH_{Ar}), 122.9 (C_{Ar}), 97.5 (C_{alkyne}), 89.9 (=CH), 83.5 (=CH-C_{alkyne}); IR ν_{max} (film) 3302, 2930, 2854, 2360, 1699, 1657, 1626, 1597, 1518, 1491 cm^{-1}; HRMS (CI+/ISO) calc. for $C_{17}H_{14}NO$ $[M+H]^+$: 248.1075. Found: 248.1074.

***N*-[*(E)*-6-(*tert*-Butyl-dimethyl-silanyloxy)-hex-1-en-3-ynyl]-benzamide, 232**



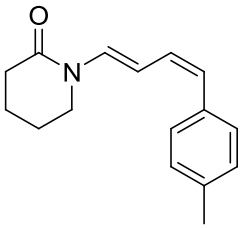
A 0.3 M solution of *(E)*-β-iodo-enamide **223** (55.0 mg, 201 μmol) in DMF was treated with $Pd(PPh_3)_4$ (20.0 mg, 17.0 μmol) and the suspension was stirred at room temperature for 10 minutes. Then 1-(*tert*-butyldimethylsilyloxy)-3-butyne **240** (153 mg, 325 μmol), CuI (7.00 mg, 33.0 μmol) and TEA (50.0 μL, 0.33 mmol) were sequentially added, and the resulting mixture was stirred at room temperature for 72 hours. The reaction mixture was quenched with distilled water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were then washed with water (10 × 20 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a brown residue. The crude product was purified by flash column chromatography on silica gel eluting with 50/50 petroleum ether/dichloromethane + 5% diethyl ether to afford the product **232** as a single isomer in 40% yield (153 mg, 0.47 mmol). IR ν_{max} (film) 3292, 2929, 2855, 2359, 1707, 1627, 1519, 1488, 1252, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.91 (1H, bd, *J* 10.6 Hz, NH), 7.79 (2H, d, *J* 6.8 Hz, 2 × CH_{Ar}), 7.58-7.39 (4H, m, NCH= and 3 × CH_{Ar}), 5.33 (1H, app dt, *J* 2.2, 14.4 Hz, =CH), 3.75 (2H, t, *J* 6.9 Hz, CH_2O), 2.54 (2H, app td, *J* 2.2, 7.1 Hz, CH_2), 0.91 (9H, s, 3 × CH_3), 0.09 (6H, s, 2 × CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 164.9 (CO), 133.4 (C_{Ar}), 132.4 (CH_{Ar}), 131.2 (NCH=), 128.9 (2 × CH_{Ar}), 127.3 (2 × CH_{Ar}), 93.2 (=CH), 88.2 (C_{alkyne}), 78.1 (C_{alkyne}), 62.6 (CH_2O), 26.8 (3 × CH_3), 24.2 (CH_2), 18.4 (C), -4.8 (2 × CH_3); HRMS (CI+/ISO) calc. for $C_{19}H_{28}NO_2Si$ $[M+H]^+$ 330.1889. Found: 330.1893.

1-((*1E*,3*Z*)-4-Phenylbuta-1,3-dienyl)piperidin-2-one, 241



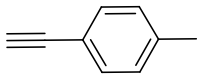
A solution of en-yne **226** (10.0 mg, 44.4 μmol) in anhydrous ethyl acetate (1 mL) containing 2% quinoline (v/v) was treated with Lindlar's catalyst® (10.0 mg) and the resulting mixture was placed under a hydrogen atmosphere. The reaction was then stirred at room temperature until completion by TLC analysis (1.5 hour). The solution was then filtered through Celite®, and washed several times with brine (10 × 10 mL) followed by and 10% aqueous HCl (1N, 10 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4. The solution was filtered and concentrated under vacuum to afford the desired *E,Z*-dienamide **241** as a yellow oil, which required no further purification, in 99% yield (10.0 mg, 44.0 μmol). IR ν_{max} (film) 2950, 2929, 1726, 1665, 1629, 1595, 1402 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.78 (1H, d, *J* 13.6 Hz, NCH=), 7.37-7.30 (5H, m, 5 × CH_{Ar}), 6.46 (1H, d, *J* 10.0 Hz, =CH), 6.33 (1H, dd, *J* 10.0, 16.0 Hz, CH=), 6.25 (1H, dd, *J* 13.6, 16.0 Hz, =CH), 3.44 (2H, t, *J* 6.1 Hz, CH_2N), 2.53 (2H, t, *J* 6.6 Hz, CH_2CO), 1.93-1.87 (2H, m, CH_2CH_2CO), 1.85-1.78 (2H, m, CH_2CH_2N); ^{1}H NMR (400 MHz, C_6D_6): δ_H 8.29 (1H, d, *J* 13.5 Hz, NCH=), 7.50-7.16 (5H, m, 5 × CH_{Ar}), 6.40-6.26 (3H, m, =CH and CH=CH), 2.70 (2H, t, *J* 6.1 Hz, CH_2N), 2.20 (2H, t, *J* 6.6 Hz, CH_2CO), 1.50-1.47 (2H, m, CH_2CH_2CO), 1.03-0.95 (2H, m, CH_2CH_2N); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 168.7 (CO), 132.2 (NCH=), 128.7 (CH=), 128.6 (C_{Ar}), 128.5 (CH_{Ar}), 128.3 (CH_{Ar}), 127.4 (CH_{Ar}), 126.6 (CH=), 107.8 (CH=), 45.5 (CH_2N), 33.1 (CH_2CO), 22.9 (CH_2CH_2CO), 20.7 (CH_2CH_2N); HRMS (EI+) calc. for $C_{15}H_{17}NO$ [M]+: 227.1310. Found: 227.1306.

1-((*1E*,3*Z*)-4-p-Tolylbuta-1,3-dienyl)piperidin-2-one, 242



A solution of en-yne **230** (11.2 mg, 46.9 µmol) in anhydrous ethyl acetate (1 mL) containing 2% quinoline (v/v) was treated with Lindlar's catalyst® (12.0 mg) and the resulting mixture was placed under a hydrogen atmosphere. The reaction was then stirred at room temperature until completion by TLC analysis (1.5 hour). The solution was then filtered through Celite®, and washed several times with brine (10 × 10 mL) followed by and 10% aqueous HCl (1N, 10 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4. The solution was filtered and concentrated under vacuum to afford the desired *E,Z*-dienamide **242** as a yellow oil, which required no further purification, in 79% yield (8.90 mg, 37.0 µmol). IR ν_{max} (film) 2951, 2937, 2919, 2895, 2875, 1654, 1625, 1595, 1510, 1477, 1458, 1402, 1345, 1329, 1305, 1287, 1267, 1252, 1178 and 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.71 (1H, d, *J* 13.6 Hz, NCH=), 7.15 (2H, d, *J* 8.0 Hz, 2 × *ortho* CH_{Ar}), 7.08 (2H, d, *J* 7.6 Hz, 2 × *meta* CH_{Ar}), 6.23 (1H, d, *J* 10.4 Hz, =CH), 6.20 (1H, dd, *J* 10.4, 16.8 Hz, CH=), 6.17 (1H, dd, *J* 14.0, 16.8 Hz, CH=), 3.37 (2H, t, *J* 6.0 Hz, CH_2N), 2.45 (2H, t, *J* 6.0 Hz, CH_2CO), 2.27 (3H, s, CH_3), 1.85-1.82 (2H, m, CH_2CH_2CO), 1.76-1.73 (2H, m, CH_2CH_2N); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 168.6 (CO), 136.3 (NCH=), 135.2 (C_{Ar}), 131.9 (C_{Ar}), 131.7 (CH_{Ar}), 130.1 (CH=), 129.1 (CH_{Ar}), 128.6 (CH=), 115.2 (CH=), 45.4 (CH_2N), 33.0 (CH_2CO), 22.5 (CH_2CH_2CO), 21.2 (CH_2CH_2N), 20.5 (CH_3); HRMS (EI+) calc. for $C_{16}H_{19}NO$ [M]+: 241.1467. Found: 241.1466.

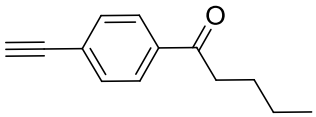
1-Ethynyl-4-methylbenzene, 235



To a suspension of triphenylphosphine (7.90 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in anhydrous dichloromethane (34 mL), under argon at 0 °C, a solution of carbon tetrabromide (9.95 g, 30.0 mmol) in anhydrous dichloromethane (7 mL) was added dropwise and the resulting mixture was allowed to stir at 0 °C for 20 minutes. *p*-Tolylaldehyde **233** (1.20 g, 10.0 mmol) in 7 mL of dry dichloromethane was added dropwise and the resulting mixture was allowed to warm to room temperature and to stir for 5 hours. Then the reaction mixture was poured into hexane, filtered to remove the precipitate, concentrated under reduced pressure and dissolved in anhydrous THF (20 mL). The solution was cooled to -78 °C and *n*BuLi (10.4 mL, 26.0 mmol, 2.5 M solution in hexanes) was added dropwise and the resulting mixture was allowed to stir until completion as indicated by TLC. The reaction was quenched with $NaHCO_3$ saturated aqueous solution (20 mL), extracted with diethyl ether (3 × 10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified by flash column chromatography on silica gel (petroleum ether) to afford the pure product **235** as a yellow oil in 60% yield (696 mg, 5.98 mmol). IR ν_{max} (film) 3295, 3049, 3025, 2956, 2917, 2857, 1594, 1508, 1448, 1373, 964, 808, 748, 707 and 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.31 (2H, d, *J* 8.0 Hz, 2 × *ortho* CH_{Ar}), 7.03 (2H, d, *J* 8.0 Hz, 2 × *meta* CH_{Ar}), 2.94 (1H, s, CH), 2.26 (3H, s, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 138.9 (C_{Ar}), 134.6 (CH_{Ar}), 129.4 (CH_{Ar}), 119.1 (C_{Ar}), 83.9 (CH), 76.5 (C), 21.5 (CH_3); HRMS (EI+) calc. for C_9H_8 [M]+: 116.0626. Found: 116.0627.

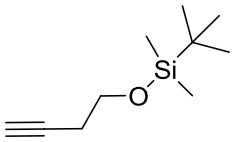
The characterisation matches with the data reported in literature:
Zhao M.; Kuang C.; Yang Q.; Cheng X. *Tetrahedron Lett.* **2011**, *52*, 992.

1-(4-Ethynylphenyl)pentan-1-one, 238



To a suspension of triphenylphosphine (7.90 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in anhydrous dichloromethane (34 mL), under argon at 0 °C, a solution of carbon tetrabromide (9.95 g, 30.0 mmol) in anhydrous dichloromethane (7 mL) was added dropwise and the resulting mixture was allowed to stir at 0 °C for 20 minutes. 4-Cyanobenzaldehyde **236** (1.31 g, 10.0 mmol) in 7 mL of dry dichloromethane was added dropwise and the resulting mixture was allowed to warm to room temperature and to stir for 5 hours. Then the reaction mixture was poured into hexane, filtered to remove the precipitate, concentrated under reduced pressure and dissolved in anhydrous THF (20 mL). The solution was cooled to -78 °C and *n*BuLi (10.4 mL, 26.0 mmol, 2.5 M solution in hexanes) was added dropwise and the resulting mixture was allowed to stir until completion as indicated by TLC. The reaction was quenched with $NaHCO_3$ saturated aqueous solution (20 mL), extracted with diethyl ether (3 × 10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford a brown oil as crude product. The crude product was purified by flash column chromatography on silica gel (petroleum ether) to afford the pure product **238** as a yellow solid in 50% yield (930 mg, 5.00 mmol). IR ν_{max} (film) 3233, 2955, 2901, 2870, 1674, 1597, 1551, 1458, 1404, 1373, 1343, 1273, 1204, 1180, 972, 856, 833, 795, 710 and 687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.84 (2H, dd, *J* 1.6, 8.0 Hz, 2 × *meta* CH_{Ar}), 7.50 (2H, dd, *J* 1.6, 8.0 Hz, 2 × *ortho* CH_{Ar}), 3.17 (1H, s, CH), 2.88 (2H, t, *J* 7.2 Hz, CH_2), 1.65 (2H, qn, *J* 7.2 Hz, CH_2), 1.33 (2H, sextet, *J* 7.2 Hz, CH_2), 0.88 (3H, t, *J* 7.2 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 199.8 (CO), 136.8 (C_{Ar}), 132.3 (CH_{Ar}), 127.9 (CH_{Ar}), 126.7 (C_{Ar}), 82.8 (C), 80.2 (CH), 38.4 (CH_2CO), 26.4 (CH_2), 22.5 (CH_2CH_3), 13.9 (CH_3); HRMS (CI+/ISO) calc. for $C_{13}H_{15}O$ [M+H]+: 187.1123. Found: 187.1124.

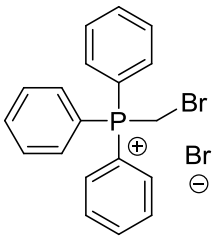
(But-3-ynyloxy)(*tert*-butyl)dimethylsilane, 240



To a solution of 3-butyn-1-ol **239** (2.50 g, 35.5 mmol) in anhydrous dichloromethane (36 mL), triethylamine (12.9 mL, 92.3 mmol) was added dropwise followed by TBDMSCl (5.89 g, 39.1 mmol) and the resulting mixture was allowed to stir at room temperature for 12 hours. The reaction was quenched with $NaHCO_3$ saturated aqueous solution (20 mL), extracted with diethyl ether (3 × 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a yellow oil as crude product. The product was purified by distillation under vacuum (95 °C/ 130 mmHg) to afford the pure product as a pale yellow oil in 25% yield (1.62 g, 8.80 mmol). IR ν_{max} (film) 3310, 2955, 2932, 2862, 1466, 1389, 1258, 1103, 1003, 918, 833, 779 and 633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.66 (2H, t, *J* 7.2 Hz, CH_2O), 2.32 (2H, td, *J* 2.4, 6.8 Hz, CH_2), 1.87 (1H, t, *J* 2.4 Hz, CH), 0.83 (9H, s, 3 × CH_3), 0.01 (6H, s, 2 × CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 80.4 (C), 68.3 (CH), 60.7 (CH_2O), 24.9 (3 × CH_3), 21.8 (CH_2), 17.4 (C), -5.0 (2 × CH_3); HRMS (CI+/ISO) calc. for $C_{10}H_{21}OSi$ [M+H]+: 185.1362. Found: 185.1363.

The characterisation matches with the data reported in literature:
Sneddon H. F.; Gaunt M. J.; Ley S. V. *Org. Lett.* **2003**, *5*, 1147.

(Bromomethyl)triphenylphosphonium bromide

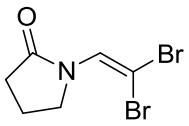


A solution of triphenylphosphine (60.0 g, 230 mmol) in dry toluene (100 mL) was treated with the dropwise addition of methylene bromide (21.0 mL, 300 mmol), and the resulting solution was stirred at 60 °C for 72 hours. The precipitate obtained was filtered, washed with toluene (5 × 100 mL), and dried under vacuum for 12 hours to yield 80.2 g, 184 mmol (80%) of bromomethyl)triphenylphosphonium

bromide as a white solid. IR (neat) ν_{max} 3047, 2987, 1589, 1481, 1437, 1340, 1116 cm^{-1}; ^{1}HNMR (400 MHz; DMSO-d_6) δ_H 7.99−7.93 (6H, m, 6 × *meta* CH_{Ar}), 7.84−7.79 (3H, m, 3 × *para* CH_{Ar}), 7.73−7.68 (6H, m, 6 × *ortho* CH_{Ar}), 5.88 (2H, d, *J* 5.4 Hz, CH_2); ^{13}C NMR (100 MHz; DMSO-d_6) δ_C 135.5, 134.4, 130.5, 116.6, 18.3; HRMS (FAB+) found $[M - Br]^+$ 355.0247, $C_{19}H_{17}P^{79}Br$ requires 355.0251; mp 220-222 °C (with decomposition).

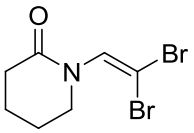
The characterisation matches with the data reported in literature:
Seyferth D.; Heeren J. K.; Singh D.; Grim S. O.; Hughes W. B. *J. Organometal. Chem.* **1966**, *5*, 267.

1-(2,2-Dibromovinyl)pyrrolidin-2-one, 246



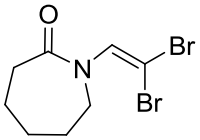
A suspension of (bromomethyl)-triphenylphosphonium bromide (2.20 g, 5.00 mmol) in anhydrous THF (10 mL) was treated with potassium *tert*-butoxide (600 mg, 5.00 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of 2-oxopyrrolidine-1-carbaldehyde **166** (56.5 mg, 0.50 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum, and the crude residue was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the dibromo-enamide **246** as a yellow oil in 94% (125 mg, 465 µmol). IR (neat) ν_{max} 3039, 2962, 2901, 1697, 1620, 1481, 1373 cm^{-1}; ^{1}HNMR (500 MHz; $CDCl_3$) δ_H 7.59 (1H, s, NCH=), 4.01 (2H, t, *J* 7.4 Hz, CH_2N), 2.39 (2H, t, *J* 8.2 Hz, CH_2CO), 2.09 (2H, qn, *J* 7.4 Hz, CH_2); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 174.7 (CO), 129.6 (NCH=), 74.0 (=CBr_2), 46.9 (CH_2N), 29.9 (CH_2CO), 18.9 (CH_2); HRMS (CI+) found $[M + H]^+$ 269.8957, $C_6H_8NO^{79}Br^{81}Br$ requires 269.8952.

1-(2,2-Dibromovinyl)piperidin-2-one, 247



A suspension of (bromomethyl)-triphenylphosphonium bromide (4.40 g, 10.0 mmol) in anhydrous THF (20 mL) was treated with potassium *tert*-butoxide (1.12 g, 10.0 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of 2-oxopiperidine-1-carbaldehyde **167** (127 mg, 1.00 mmol) in THF (10 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude brown oil residue was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the dibromo-enamide **247** as a yellow oil in 91% (258 mg, 912 µmol). IR (neat) ν_{max} 3047, 2947, 1658, 1612, 1473, 1404, 1260, 1255, 1219, 1157 cm^{-1}; ^{1}HNMR (500 MHz; $CDCl_3$) δ_H 7.40 (1H, s, NCH=), 3.64 (2H, t, *J* 4.8 Hz, CH_2N), 2.45 (2H, t, *J* 6.6 Hz, CH_2CO), 1.83 (4H, m, 2 × CH_2); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 169.9 (CO), 134.8 (NCH=), 85.9 (=CBr_2), 48.8 (CH_2N), 32.4 (CH_2CO), 23.1 (*C*$H_2$$CH_2CO$), 20.8 (*C*$H_2$$CH_2N$); HRMS (CI+) found $[M + H]^+$ 283.9102, $C_7H_{10}NO^{79}Br^{81}Br$ requires 283.9109.

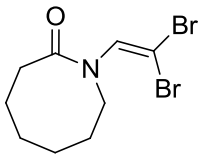
1-(2,2-Dibromovinyl)azepan-2-one, 243b



A suspension of (bromomethyl)-triphenylphosphonium bromide (2.20 g, 5.00 mmol) in anhydrous THF (10 mL) was treated with potassium *tert*-butoxide (600

mg, 5.00 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of 2-oxoazepan-1-carbaldehyde **168** (70.5 mg, 0.50 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude brown oil was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the dibromo-enamide **243b** as a yellow oil in 93% (139 mg, 468 μmol). IR (neat) ν_{max} 3039, 2928, 1658, 1435, 1392, 1257, 1207, 1188 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ_H 7.41 (1H, s, NCH=), 3.66 (2H, t, *J* 4.7 Hz, CH_2N), 2.58 (2H, t, *J* 6.4 Hz, CH_2CO), 1.84−1.80 (2H, m, CH_2CH_2CO), 1.77−1.73 (4H, m, 2 × CH_2); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 175.8 (CO), 135.8 (NCH=), 85.2 (=CBr_2), 50.2 (CH_2N), 37.3 (CH_2CO), 29.9 (CH_2CH_2CO), 29.4 (CH_2CH_2N), 23.2 (CH_2); HRMS (CI+) found $[M + H]^+$ 297.9261, $C_8H_{12}NO^{79}Br^{81}Br$ required 297.9265.

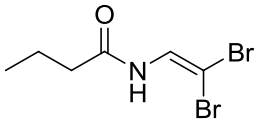
1-(2,2-Dibromovinyl)azocan-2-one, 248



A suspension of (bromomethyl)-triphenylphosphonium bromide (2.20 g, 5.00 mmol) in anhydrous THF (10 mL) was treated with potassium *tert*-butoxide (600 mg, 5.00 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of 2-oxoazocan-1-carbaldehyde **169** (77.5 mg, 0.50 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl

ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude brown oil was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the dibromo-enamide **248** as a yellow oil in 90% (140 mg, 0.45 mmol). IR (neat) ν_{max} 3039, 2928, 1712, 1658, 1454, 1396, 1361, 1207, 1192 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ_H 7.42 (1H, s, NCH=), 3.67 (2H, t, *J* 5.1 Hz, CH_2N), 2.59 (2H, t, *J* 6.4 Hz, CH_2CO), 1.85−1.80 (2H, m, CH_2CH_2CO), 1.78−1.68 (6H, m, 3 × CH_2); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 175.9 (CO), 135.8 (NCH=), 77.7 (=CBr_2), 50.2 (CH_2N), 37.3 (CH_2CO), 29.9 (CH_2CH_2CO), 29.4 (CH_2CH_2N), 26.3 (CH_2), 23.3 (CH_2); HRMS (CI+) found $[M + H]^+$ 311.9413, $C_9H_{14}NO^{79}Br^{81}Br$ required 311.9422.

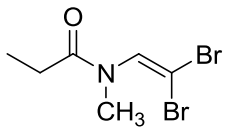
N-(2,2-Dibromovinyl)butyramide, 249



A suspension of (bromomethyl)-triphenylphosphonium bromide (2.20 g, 5.00 mmol) in anhydrous THF (10 mL) was treated with potassium *tert*-butoxide (600 mg, 5.00 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of *N*-formylbutyramide **213** (57.5 mg, 0.50 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude brown oil was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the dibromo-enamide **249** as a yellow solid in 99% (140 mg, 0.52 mmol). IR (neat) ν_{max} 3053, 2961, 1663, 1631, 1480, 1376, 1268, 1194 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ_H 7.61 (1H, d, *J* 11.6 Hz, NCH=), 7.13 (1H, bs, NH), 2.27 (2H, t, *J* 7.4 Hz, CH_2CO), 1.67 (2H, sextet, *J* 7.4 Hz, CH_2), 0.97 (3H, t, *J* 7.4 Hz, CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 169.5 (CO), 127.5 (NCH=), 73.7 (=CBr_2), 38.3 (CH_2CO), 18.7 (CH_2),

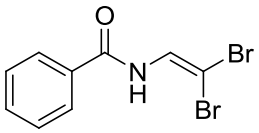
13.8 (CH_3); HRMS (CI+) found $[M + H]^+$ 271.9110, $C_6H_{10}NO^{79}Br^{81}Br$ required 271.9129; mp 66-67 °C.

N-(2,2-Dibromovinyl)-*N*-methylpropionamide, 250



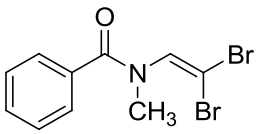
A suspension of (bromomethyl)-triphenylphosphonium bromide (4.40 g, 10.0 mmol) in anhydrous THF (20 mL) was treated with potassium *tert*-butoxide (1.12 g, 10.0 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of *N*-formyl-*N*-methylpropionamide **244** (115 mg, 1.00 mmol) in THF (10 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude brown oil was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the dibromo-enamide **250** as a yellow oil in quantitative yield (310 mg, 1.15 mmol). IR (neat) ν_{max} 2980, 2939, 1666, 1595, 1462, 1373, 1265, 1062 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ_H 7.06 (1H, s, NCH=), 3.01 (3H, s, N-CH_3), 2.24 (2H, q, *J* 7.6 Hz, CH_2), 1.07 (3H, t, *J* 7.4 Hz, CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 173.0 (CO), 135.5 (NCH=), 94.5 (=CBr_2), 33.7 (N-CH_3), 27.8 (CH_2), 9.1 (CH_3); HRMS (CI+) found $[M + H]^+$ 269.9130, $C_6H_{10}NO^{79}Br_2$ requires 269.9129.

_N_-(2,2-Dibromovinyl)benzamide, 251



A suspension of (bromomethyl)-triphenylphosphonium bromide (4.40 g, 10.0 mmol) in anhydrous THF (20 mL) was treated with potassium *tert*-butoxide (1.12 g, 10.0 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of *N*-formylbenzamide **216** (149 mg, 1.00 mmol) in THF (10 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude brown oil was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the dibromo-enamide **251** as a yellow solid in 79% (241 mg, 0.79 mmol). IR (neat) ν_{max} 3396, 3066, 1660, 1629, 1504, 1467, 1249, 848 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ_H 7.85−7.82 (4H, m, NCH=, NH, 2 × *ortho* CH_{Ar}), 7.59 (1H, tt, *J* 1.2, 6.8 Hz, *para* CH_{Ar}), 7.50 (2H, tm, *J* 7.6 Hz, 2 × *meta* CH_{Ar}); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 163.4 (CO), 132.9 (NCH=), 132.5 (C_{Ar}), 129.2 (CH_{Ar}), 127.8 (CH_{Ar}), 127.4 (CH_{Ar}), 75.0 ($=CBr_2$); HRMS (EI+) found $[M]^+$ 304.8883, $C_9H_7NO^{79}Br^{81}Br$ requires 304.8874; mp 60-61 °C.

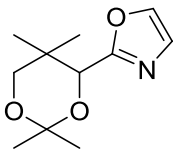
_N_-(2,2-Dibromovinyl)-_N_-methylbenzamide, 252



A suspension of (bromomethyl)-triphenylphosphonium bromide (4.40 g, 10.0 mmol) in anhydrous THF (20 mL) was treated with potassium *tert*-butoxide (1.12 g, 10.0 mmol), and the resulting bright orange suspension was allowed to stir at room

temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of *N*-formyl-*N*-methylbenzamide **245** (163 mg, 1.00 mmol) in THF (10 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude brown oil was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the dibromo-enamide **252** as a yellow solid in 85% (270 mg, 852 µmol). IR (neat) ν_{max} 3020, 2933, 1716, 1647, 1597, 1346, 1323 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ_H 7.52−7.47 (2H, m, 2 × *ortho* CH_{Ar}), 7.46−7.41 (1H, m, *para* CH_{Ar}), 7.40−7.36 (2H, m, 2 × *meta* CH_{Ar}), 7.09 (1H, bs, NCH=), 3.26 (3H, s, N-CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 170.5 (CO), 136.8 (NCH), 135.0 (C_{Ar}), 131.0 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (CH_{Ar}), 90.0 (=CBr_2), 34.9 (N-CH_3); HRMS (CI+) found $[M]^+$ 316.9045, $C_{10}H_9NO^{79}Br_2$ requires 316.9051; mp 79-80 °C.

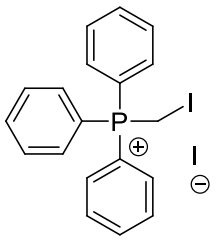
2-(2,2,5,5-Tetramethyl-1,3-dioxan-4-yl)oxazole, 258



A suspension of (bromomethyl)-triphenylphosphonium bromide (4.40 g, 10.0 mmol) in anhydrous THF (20 mL) was treated with potassium *tert*-butoxide (1.12 g, 10.0 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of *N*-formyl-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide **212** (108 mg, 0.50 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried

over Na_2SO_4, filtered, and concentrated under vacuum. The crude brown oil was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the dibromo-enamide **258** as a yellow solid in 99% (105 mg, 0.49 mmol). IR (neat) ν_{max} 3119, 2994, 2969, 1574, 1523, 1459, 1392, 1383, 1370, 1193, 1157 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.64 (1H, s, NCH), 7.09 (1H, s, OCH), 4.90 (1H, s, CH), 3.78 (1H, d, *J* 11.4 Hz, C*H*HO), 3.41 (1H, d, *J* 11.4 Hz, CH*H*O), 1.53 (3H, s, CH_3CO), 1.50 (3H, s, CH_3CO), 1.06 (3H, s, CH_3), 0.86 (3H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 161.2 (C), 138.9 (OCH), 127.0 (NCH), 99.7 (C), 74.8 (CH), 71.6 (CH_2O), 34.2 (C), 29.5 (CH_3CO), 21.8 (CH_3), 19.3 (CH_3), 18.7 (CH_3CO); HRMS (CI+) found $[M + H]^+$ 212.1282, $C_{11}H_{18}NO_3$ requires 212.1287; mp 68−70 °C.

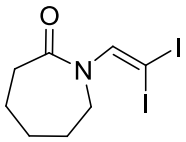
(Iodomethyl)triphenylphosphonium iodide



A solution of triphenylphosphine (30.0 g, 114 mmol) in dry toluene (50 mL) was treated dropwise with methylene iodide (12 mL, 149 mmol). The reaction mixture was allowed to stir at 60 °C for 72 hours, which caused a white precipitate to form. The suspension was then cooled down to room temperature, filtered and the white solid residue was washed several times with toluene (5 × 200 mL). The crude product was dried under vacuum for 12 hours to afford in 91% yield (55.0 g, 104 mmol) the phosphonium iodide as a pure white solid. IR (neat) ν_{max} 2994, 2970, 1575, 1459, 1392, 1383 cm^{-1}; ^1H NMR (400 MHz; DMSO-d_6) δ_H 7.98−7.81 (15H, m, 15 × CH_{Ar}), 5.10 (2H, d, *J* 8.5 Hz, CH_2); ^{13}C NMR (100 MHz; DMSO-d_6) δ_C 136.1, 134.7, 131.0, 118.8, −15.4; HRMS (FAB+) found $[M - I]^+$ 403.0110, $C_{19}H_{17}PI$ requires 403.0113; mp 235-237 °C.

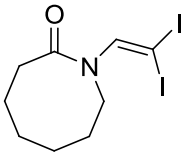
The characterisation matches with the data reported in literature:
Aquino F.; Pauling H.; Walter W.; Plattner D. A.; Bonrath W. *Synthesis* **2000**, *5*, 731.

1-(2,2-Diiodovinyl)azepan-2-one, 253



A suspension of (iodomethyl)triphenylphosphonium iodide (5.30 g, 10.0 mmol) in anhydrous THF (20 mL) was treated with potassium *tert*-butoxide (1.12 g, 10.0 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of 2-oxoazepane-1-carbaldehyde **168** (141 mg, 1.00 mmol) in THF (10 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum, and the crude residue was purified by flash column chromatography on silica gel (80:20 hexane:ethyl acetate) to afford the diiodo-enamide **253** as a yellow solid in 99% yield (390 mg, 0.99 mmol). IR (neat) ν_{max} 3010, 2930, 2910, 1646, 1587, 1464, 1443, cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.73 (1H, s, NCH=), 3.64 (2H, t, *J* 4.4 Hz, CH_2N), 2.58−2.55 (2H, m, CH_2CO), 1.83−1.74 (6H, m, 3 × CH_2); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 175.4 (CO), 147.3 (NCH=), 50.6 (CH_2N), 37.4 (CH_2CO), 31.7 (*C*H_2CH_2CO), 29.9 (*C*H_2CH_2N), 22.8 (CH_2), 14.0 (=CI_2); HRMS (CI+) found $[M+H]^+$ 391.9003, $C_8H_{12}NOI_2$ requires 391.9008; mp 74-75 °C.

1-(2,2-Diiodovinyl)azocan-2-one, 254



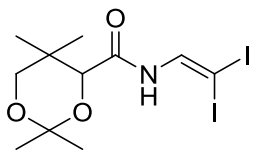
A suspension of (iodomethyl)triphenylphosphonium iodide (5.30 g, 10.0 mmol) in anhydrous THF (20 mL) was treated with potassium *tert*-butoxide (1.12 g, 10.0 mmol), and the resulting bright orange suspension was allowed to stir at room

temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of 2-oxoazocane-1-carbaldehyde **169** (155 mg, 1.00 mmol) in THF (10 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum, and the crude residue was purified by flash column chromatography on silica gel (80:20 hexane:ethyl acetate) to afford 386 mg of an inseparable 13:1 mixture of diiodo-enamide **254** (89%, 361 mg, 0.89 mmol) and *(E)*-iodoenamide **221** (10%, 28.0 mg, 0.10 mmol).

***1-(2,2-Diiodovinyl)azocan-2-one*, 254:** IR (neat) ν_{max} 2916, 2852, 1628, 1617, 1588, 1472, 1444 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.56 (1H, s, NCH=), 3.78 (2H, t, *J* 5.6 Hz, CH_2N), 2.53 (2H, t, *J* 6.3 Hz, CH_2CO), 1.88−1.82 (2H, m, CH_2CH_2CO), 1.69−1.58 (4H, m, 2 × CH_2), 1.53−1.47 (2H, m, CH_2); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 175.6 (CO), 145.2 (NCH=), 47.0 (CH_2N), 34.3 (CH_2CO), 30.1 (CH_2CH_2CO), 28.8 (CH_2CH_2N), 26.3 (CH_2), 24.3 (CH_2), 13.1 (=CI_2); HRMS (CI+) found $[M + H]^+$ 405.9169, $C_9H_{14}NOI_2$ requires 405.9165.

***(E)-1-(2-Iodovinyl)azocan-2-one*, 221:** ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.95 (1H, d, *J* 14.0 Hz, NCH=), 5.52 (1H, d, *J* 14.0 Hz, =CHI).

N-(2,2-Diiodovinyl)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide, 257



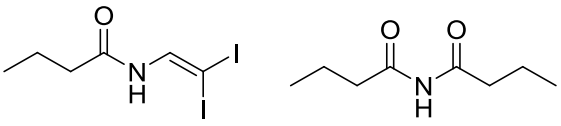
A suspension of (iodomethyl)triphenylphosphonium iodide (1.20 g, 2.25 mmol) in anhydrous THF (10 mL) was treated with potassium *tert*-butoxide (252 mg, 2.25 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of *N*-formyl-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide **212** (108 mg, 0.50 mmol) in THF

(5 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum, and the crude residue was purified by flash column chromatography on silica gel (80:20 hexane:ethyl acetate) to afford the diiodo-enamide **257** in 32% yield (74.0 mg, 0.16 mmol) and the oxazole **258** in 16% yield (17.0 mg, 0.08 mmol) as yellow solids.

***N-(2,2-Diiodovinyl)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide* 257:** IR (neat) ν_{max} 3351, 2836, 1686, 1612, 1465, 1384, 1379, 1094, 1050 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ_H 8.34 (1H, bd, *J* 10.8 Hz, NH), 7.76 (1H, d, *J* 11.4 Hz, NCH=), 4.14 (1H, s, CH), 3.71 (1H, d, *J* 11.7 Hz, C*H*HO), 3.32 (1H, d, *J* 11.7 Hz, CH*H*O), 1.51 (3H, s, CH_3CO), 1.45 (3H, s, CH_3CO), 1.03 (3H, s, CH_3), 1.02 (3H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 166.1 (CO), 136.4 (NCH=), 99.4 (C), 77.1 (CH), 71.4 (CH_2), 33.3 (C), 29.5 (CH_3), 22.9 (CH_3), 18.8 (CH_3), 19.1 (CH_3), −6.8 (=CI_2); HRMS (CI+) found $[M + H]^+$ 465.9372, $C_{11}H_{18}NO_3I_2$ requires 465.9376; mp 135-136 °C.

***2-(2,2,5,5-Tetramethyl-1,3-dioxan-4-yl)oxazole* 258:** ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.64 (1H, s, CH), 7.09 (1H, s, CH), 4.90 (1H, s, CH), 3.78 (1H, d, *J* 11.4 Hz, C*H*HO), 3.41 (1H, d, *J* 11.4 Hz, CH*H*O), 1.53 (3H, s, CH_3CO), 1.50 (3H, s, CH_3CO), 1.06 (3H, s, CH_3), 0.86 (3H, s, CH_3).

N-(2,2-Diiodovinyl)butyramide, 255 and *N*-Butyrylbutyramide



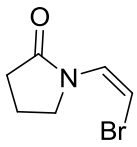
A suspension of (iodomethyl)triphenylphosphonium iodide (1.06 g, 2.00 mmol) in anhydrous THF (10 mL) was treated with potassium *tert*-butoxide (225 mg, 2.00 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of *N*-formyl-

butyramide **213** (57.5 mg, 0.50 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum, and the crude residue was purified by flash column chromatography on silica gel (80:20 hexane:ethyl acetate) to afford the diiodo-enamide **255** in 40% yield (73.0 mg, 0.20 mmol) and the *N*-butyrylbutyramide in 20% yield (15.7 mg, 0.10 mmol) as yellow solids.

***N-(2,2-Diiodovinyl)butyramide* 255:** IR (neat) ν_{max} 3264, 3179, 2963, 2878, 1728, 1505, 1373 and 1165 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ_H 8.06 (1H, bd, *J* 10.8 Hz, NCH=), 7.03 (1H, bd, *J* 8.4 Hz, NH), 2.29 (2H, t, *J* 7.2 Hz, CH_2), 1.70 (2H, app qn, *J* 7.2 Hz, CH_2), 1.00 (3H, t, *J* 7.2 Hz, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 168.9 (CO), 137.3 (NCH=), 39.3 (CH_2), 17.8 (CH_2), 13.6 (CH_3), −9.1 (=Cl_2); HRMS (EI+) found $[M]^+$ 364.8777, $C_6H_9NOI_2$ requires 364.8774; mp 59-60 °C.
***N-Butyrylbutyramide*:** ^1H NMR (400 MHz; $CDCl_3$) δ_H 8.04 (1H, bs, NH), 2.57 (4H, t, *J* 7.3 Hz, 2 × CH_2), 1.70 (4H, app qn, *J* 7.3 Hz, 2 × CH_2), 0.98 (6H, t, *J* 7.3 Hz, 2 × CH_3).

The characterisation matches with the data reported in literature:
Mohammadpoor-baltork I.; Tangestaninejad S.; Moghadam M.; Mirkhani V.; Nasr-Esfahani M. *J. Iran. Chem. Soc*. **2011**, *8*, 401.

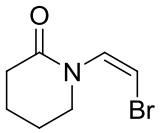
(Z)-1-(2-Bromovinyl)pyrrolidin-2-one, 260



A solution of 1-(2,2-dibromovinyl)pyrrolidin-2-one **246** (90.0 mg, 0.34 mmol) in anhydrous EtOAc (5 mL) was treated with $Pd(PPh_3)_4$ (39.0 mg, 0.03 mmol) and Bu_3SnH (0.11 mL, 0.40 mmol). The resulting reaction mixture was stirred at room temperature until completion as indicated by TLC analysis (12 hours). The reaction was diluted with hexane (15 mL), filtered through Celite®, and concentrated under

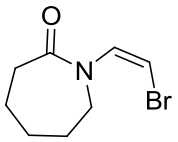
vacuum to afford a yellow oil as crude residue. The crude product was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the bromo-enamide **260** as a colourless oil in 88% yield (56.0 mg, 0.296 mmol). IR (neat) ν_{max} 2953, 1703, 1640, 1484, 1381, 1313, 1251 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.29 (1H, d, *J* 7.0 Hz, NCH=), 5.41 (1H, d, *J* 7.0 Hz, =CHBr), 4.14 (2H, t, *J* 7.2 Hz, CH_2N), 2.41 (2H, t, *J* 7.8 Hz, CH_2CO), 2.09 (2H, qn, *J* 7.4 Hz, CH_2); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 175.3 (CO), 126.2 (NCH=), 86.6 (=CHBr), 47.5 (CH_2N), 30.1 (*CH_2*CO), 18.8 (CH_2); HRMS (CI+) found $[M + H]^+$ 189.9865, $C_6H_9NO^{79}Br$ requires 189.9868.

(Z)-1-(2-Bromovinyl)piperidin-2-one, 261



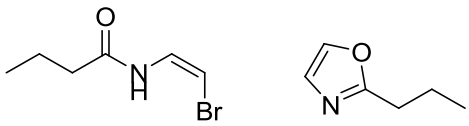
A solution of 1-(2,2-dibromovinyl)piperidin-2-one **247** (90.0 mg, 0.34 mmol) in anhydrous EtOAc (32 mL) was treated with $Pd(PPh_3)_4$ (70.0 mg, 0.06 mmol) and Bu_3SnH (0.2 mL, 0.71 mmol). The resulting reaction mixture was stirred at room temperature until completion as indicated by TLC analysis (12 hours). The reaction was diluted with hexane (30 mL), filtered through Celite®, and concentrated under vacuum to afford a yellow oil as crude residue. The crude product was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the bromo-enamide **261** as a colourless oil in 70% yield (86.0 mg, 424 µmol). IR (neat) ν_{max} 2953, 2877, 1656, 1626, 1477, 1460, 1427, 1406, 1269, 1172 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.37 (1H, d, *J* 6.5 Hz, NCH=), 5.74 (1H, d, *J* 6.5 Hz, =CHBr), 3.83−3.78 (2H, m, CH_2N), 2.51−2.46 (2H, m, CH_2CO), 1.89−1.79 (4H, m, 2 × CH_2); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 170.3 (CO), 131.6 (NCH=), 94.8 (=CHBr), 48.9 (CH_2N), 32.4 (*CH_2*CO), 23.1 (*CH_2*CH_2CO), 20.8 (*CH_2*CH_2N); HRMS (CI+) found $[M + H]^+$ 204.0026, $C_7H_{11}NO^{79}Br$ requires 204.0024.

_(Z)_-1-(2-Bromovinyl)azepan-2-one, 256_Z_



A solution of 1-(2,2-dibromovinyl)azepan-2-one **243b** (118 mg, 0.40 mmol) in anhydrous EtOAc (30 mL) was treated with $Pd(PPh_3)_4$ (46.0 mg, 0.04 mmol) and Bu_3SnH (0.13 mL, 0.48 mmol). The resulting reaction mixture was stirred at room temperature until completion as indicated by TLC analysis (12 hours). The reaction was diluted with hexane (30 mL), filtered through Celite®, and concentrated under vacuum to afford a yellow oil as crude residue. The crude product was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the bromo-enamide **256_Z_** as a colourless oil in 75% yield (65.0 mg, 0.30 mmol). IR (neat) ν_{max} 2929, 2856, 1739, 1666, 1627, 1394, 1332, 1321, 1190 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.29 (1H, d, *J* 6.3 Hz, NCH=), 5.73 (1H, d, *J* 6.3 Hz, =CHBr), 3.80−3.76 (2H, m, CH_2N), 2.63−2.61 (2H, m, CH_2CO), 1.90−1.81 (2H, m, CH_2CH_2CO), 1.79−1.71 (4H, m, 2 × CH_2); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 176.4 (CO), 132.6 (NCH=), 94.8 (=CHBr), 49.4 (CH_2N), 37.3 (CH_2CO), 29.9 (CH_2CH_2CO), 29.3 (CH_2CH_2N), 23.4 (CH_2); HRMS (CI+) found $[M + H]^+$ 218.0181, $C_8H_{13}NO^{79}Br$ requires 218.0181.

_(Z)-N-_(2-Bromovinyl)butyramide, 262 and 2-Propyloxazole



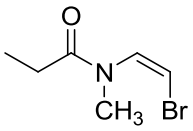
A solution of *N*-(2,2-dibromovinyl)-butyramide **249** (63.0 mg, 0.23 mmol) in anhydrous EtOAc (3 mL) was treated with $Pd(PPh_3)_4$ (27.0 mg, 0.02 mmol) and Bu_3SnH (0.10 mL, 0.28 mmol). The resulting reaction mixture was stirred at room temperature until completion as indicated by TLC analysis (12 hours). The reaction mixture was diluted with hexane (30 mL), filtered through Celite®, and concentrated under vacuum to afford a yellow oil as crude residue. The crude product was purified by flash column chromatography on silica gel (80:20

hexane/ethyl acetate) to afford the bromo-enamide **262** in 63% yield (28.0 mg, 147 µmol) and 2-propyloxazole in 37% yield (9.60 mg, 87.0 µmol) as colourless oils.

***(Z)-N-(2-Bromovinyl)butyramide* 262:** IR (neat) ν_{max} 2961, 1677, 1642, 1239, 1195, 678 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.40 (1H, dd, *J* 5.9, 10.9 Hz, NCH=), 7.32 (1H, bs, NH), 5.47 (1H, d, *J* 5.3 Hz, =CHBr), 2.30 (2H, t, *J* 7.3 Hz, CH_2CO), 1.71 (2H, sextet, *J* 7.4 Hz, CH_2), 0.99 (3H, t, *J* 7.4 Hz, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 169.5 (CO), 127.5 (NCH=), 88.3 (=CHBr), 38.4 (*CH_2*CO), 18.8 (CH_2), 13.8 (CH_3); HRMS (CI+) found $[M + H]^+$ 192.0018, $C_6H_{11}NO^{79}Br$ requires 192.0024.

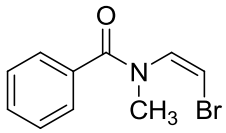
***2-Propyloxazole*:** ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.63 (1 H, d, *J* 10.9 Hz, CH), 7.08 (1 H, d, *J* 10.9 Hz, CH), 2.28 (2H, t, *J* 7.6 Hz, CH_2), 1.72 (2H, sextet, *J* 7.4 Hz, CH_2), 0.98 (3H, t, *J* 7.4 Hz, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 131.0 (C), 128.9 (CH), 125.4 (CH), 29.1 (CH_2), 23.1 (CH_2), 11.1 (CH_3); HRMS (CI+) found $[M + H]^+$ 112.0769, $C_6H_{10}NO$ requires 112.0762.

(Z)-N-(2-Bromovinyl)-*N*-methylpropionamide, 263



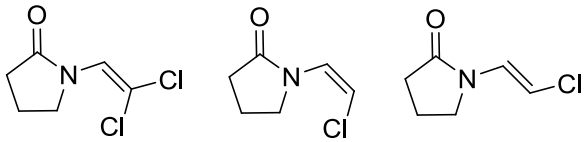
A solution of *N*-(2,2-dibromovinyl)-*N*-methylpropionamide **250** (117 mg, 0.43 mmol) in anhydrous EtOAc (10 mL) was treated with $Pd(PPh_3)_4$ (50.0 mg, 0.04 mmol) and Bu_3SnH (0.14 mL, 0.52 mmol). The resulting reaction mixture was stirred at room temperature until completion as indicated by TLC analysis (12 hours). The reaction was diluted with hexane (30 mL), filtered through Celite®, and concentrated under vacuum to afford a yellow oil as crude residue. The crude product was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the bromo-enamide **263** as a colourless oil in 72% yield (60.0 mg, 313 µmol). IR (neat) ν_{max} 3086, 3063, 2920, 1654, 1624, 1577, 1446, 1346, 1300, 1057 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ_H 6.95 (1H, bs, NCH=), 6.00 (1H, bs, =CHBr), 3.16 (3H, s, N-CH_3), 2.31−2.30 (2H, m, CH_2), 1.15−1.12 (3H, m, CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 173.6 (CO), 133.3 (NCH=), 102.3 (=CH), 34.0 (*CH_2*CO), 27.8 (CH_3), 9.2 (CH_3); HRMS (CI+) found $[M + H]^+$ 192.0015, $C_6H_{11}NO^{79}Br$ requires 192.0024.

_(Z)_-_N_-(2-Bromovinyl)-_N_-methylbenzamide, 264



A solution of *N*-(2,2-dibromovinyl)-*N*-methylbenzamide **252** (98.0 mg, 0.31 mmol) in anhydrous EtOAc (5 mL) was treated with $Pd(PPh_3)_4$ (36.0 mg, 0.03 mmol) and Bu_3SnH (0.10 mL, 0.37 mmol). The resulting reaction mixture was stirred at room temperature until completion as indicated by TLC analysis (12 hours). The reaction was diluted with hexane (30 mL), filtered through Celite®, and concentrated under vacuum to afford a yellow oil as crude residue. The crude product was purified by flash column chromatography on silica gel (80:20 hexane/ethyl acetate) to afford the bromo-enamide **264** as a colourless oil in 86% yield (63.0 mg, 264 µmol). IR (neat) ν_{max} 3086, 2982, 1666, 1631, 1612, 1462, 1423, 1377, 1276, 1057 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ_H 7.51−7.49 (2H, m, 2 × *ortho* CH_{Ar}), 7.46−7.43 (1H, m, *para* CH_{Ar}), 7.39−7.37 (2H, m, 2 × *meta* CH_{Ar}), 6.96 (1H, bs, NCH=), 5.73 (1H, d, *J* 6.0 Hz, =CHBr), 3.40 (3H, s, N-CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 171.4 (CO), 135.4 (C_{Ar}), 134.6 (NCH=), 130.9 (CH_{Ar}), 128.4 (CH_{Ar}), 128.5 (CH_{Ar}), 97.3 (=CHBr), 35.2 (N-CH_3); HRMS (CI+) found $[M + H]^+$ 240.0026, $C_{10}H_{11}NO^{79}Br$ requires 240.0024.

1-(2,2-Dichlorovinyl)pyrrolidin-2-one, 267 and _(E)/(Z)_-1-(2-Chlorovinyl) pyrrolidin-2-one, 268/269



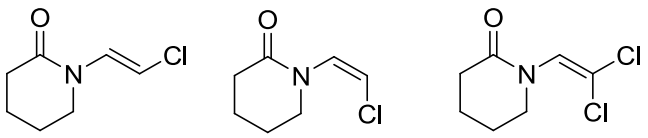
A suspension of (chloromethyl)triphenylphosphonium chloride (1.74 g, 5.00 mmol) in anhydrous THF (10 mL) was treated with potassium *tert*-butoxide (600 mg, 5.00 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of 2-oxopyrrolidine-1-carbaldehyde **166** (56.5 mg, 0.50 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature until TLC analysis showed

reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum, and the crude residue was purified by flash column chromatography on silica gel (80:20 hexane:ethyl acetate) to afford a first fraction consisting of a 1.0:1.7 mixture of the dichloro-enamide **267** and the *(Z)*-monochloro-enamide **268** (traces amounts) and a second clean fraction of the *(E)*-monochloro-enamide **269** in 98% yield (71.0 mg, 0.49 mmol) as a white solid.

***1-(2,2-Dichlorovinyl)pyrrolidin-2-one* 267:** IR (neat) ν_{max} 3094, 3057, 2965, 1705, 1645, 1379, 1333, 1277, 1256, 1225, 1165, 1026, 941, 918, 808 and 727 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ_H 7.15 (1H, s, NCH=), 3.97 (2H, t, *J* 6.7 Hz, CH_2N), 2.44-2.40 (2H, m, CH_2CO), 2.14-2.07 (2H, m, CH_2); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 174.7 (CO), 123.2 (NCH=), 108.3 (=CCl_2), 47.0 (CH_2N), 29.9 (*CH_2*CO), 18.8 (CH_2); HRMS (CI+) found $[M + H]^+$ 179.9980, $C_6H_8NO^{35}Cl_2$ requires 179.9983.

***(E)-1-(2-Chlorovinyl)pyrrolidin-2-one* 268:** IR (neat) ν_{max} 3071, 2969, 2897, 1692, 1628, 1481, 1458, 1398, 1329, 1292, 1217 and 939 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ_H 6.91 (1H, d, *J* 6.7 Hz, NCH=), 5.39 (1H, d, *J* 6.7 Hz, =CH), 4.10 (2H, t, *J* 6.7 Hz, CH_2N), 2.44-2.40 (2H, m, CH_2CO), 2.14-2.07 (2H, m, CH_2); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 175.1 (CO), 123.5 (NCH=), 100.1 (=CHCl), 47.7 (CH_2N), 29.9 (*CH_2*CO), 18.8 (CH_2); HRMS (CI+) found $[M + H]^+$ 146.0380, $C_6H_9NO^{35}Cl$ requires 146.0373; m.p. 45-46 °C.

_(E)_-1-(2-Chlorovinyl)piperidin-2-one, 270, _(Z)_-1-(2-Chlorovinyl)piperidin-2-one, 271 and 1-(2,2-Dichlorovinyl)piperidin-2-one, 272



A suspension of (chloromethyl)triphenylphosphonium chloride (1.74 g, 5.00 mmol) in anhydrous THF (10 mL) was treated with potassium *tert*-butoxide (600 mg, 5.00

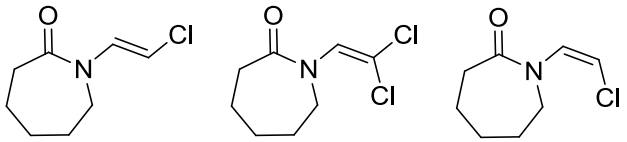
mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of 2-oxopiperidine-1-carbaldehyde **167** (63.5 mg, 0.50 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum, and the crude residue was purified by flash column chromatography on silica gel (80:20 hexane:ethyl acetate) to afford a 14.0:1.0:1.0 mixture of the *(E)*-monochloro-enamide **270** (74%, 58.8 mg, 0.37 mmol), *(Z)*-monochloro-enamide **271** (5.3%, 4.20 mg, 26.0 µmol) and the dichloro-enamide **272** (4.4%, 4.20 mg, 22.0 µmol) as a white solid (67.0 mg in total, 84% total yield).

***(E)-1-(2-Chlorovinyl)piperidin-2-one* 270:** IR (neat) ν_{max} 3090, 2957, 2866, 1655, 1618, 1472, 1456, 1431, 1410, 1346, 1331, 1287, 1271, 1231, 1177, 1167, 1090, 985, 953, 920, 891, 851, 827, 787 and 719 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ_H 7.77 (1H, d, *J* 13.4 Hz, NCH=), 5.67 (1H, d, *J* 12.7 Hz, =CH), 3.35 (2H, t, *J* 6.4 Hz, CH_2N), 2.48 (2H, t, *J* 6.4 Hz, CH_2CO), 1.92-1.78 (4H, m, 2 × CH_2); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 167.9 (CO), 130.2 (NCH=), 102.7 (=CHCl), 45.7 (CH_2N), 32.8 (CH_2CO), 22.5 (CH_2CH_2CO), 20.5 (CH_2CH_2N); HRMS (CI+) found $[M + H]^+$ 160.0523, $C_7H_{11}NO^{35}Cl$ requires 160.0529; m.p. 89-90 °C.

***(Z)-1-(2-Chlorovinyl)piperidin-2-one* 271:** ^1H NMR (500 MHz; $CDCl_3$) δ_H 7.02 (1H, d, *J* 6.5 Hz, NCH=), 5.61 (1H, d, *J* 6.6 Hz, =CH), 3.65-3.62 (2H, m, CH_2N), 2.50-2.46 (2H, m, CH_2CO), 1.92-1.78 (4H, m, 2 × CH_2).

***1-(2,2-Dichlorovinyl)piperidin-2-one* 272:** ^1H NMR (500 MHz; $CDCl_3$) δ_H 7.04 (1H, s, NCH=), 3.81-3.79 (2H, m, CH_2N), 2.50-2.46 (2H, m, CH_2CO), 1.92-1.78 (4H, m, 2 × CH_2).

_(E)_-1-(2-Chlorovinyl)azepan-2-one, 273, 1-(2,2-Dichlorovinyl)azepan-2-one, 274 and _(Z)_-1-(2-Chlorovinyl)azepan-2-one, 275



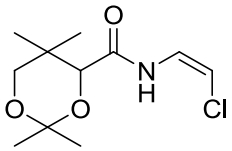
A suspension of (chloromethyl)triphenylphosphonium chloride (1.74 g, 5.00 mmol) in anhydrous THF (10 mL) was treated with potassium *tert*-butoxide (600 mg, 5.00 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of 2-oxoazepane-1-carbaldehyde **168** (70.6 mg, 0.50 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum, and the crude residue was purified by flash column chromatography on silica gel (80:20 hexane:ethyl acetate) to afford a 14.0:1.0:1.0 mixture of the *(E)*-monochloro-enamide **273** (52%, 44.8 mg, 0.26 mmol), dichloro-enamide **274** (11%, 11.2 mg, 54.0 µmol) and the *(Z)*-monochloro-enamide **275** (10%, 8.90 mg, 0.05 mmol) as a white solid (65.0 mg in total, 73% total yield).

***(E)-1-(2-Chlorovinyl)azepan-2-one* 273:** IR (neat) ν_{max} 3094, 2932, 2859, 1661, 1624, 1439, 1395, 1350, 1335, 1310, 1260, 1209, 1184, 1152, 1082, 1034, 972, 934 and 858 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ_H 7.45 (1H, d, *J* 12.7 Hz, NCH=), 5.79 (1H, d, *J* 12.7 Hz, =CH), 3.50-3.48 (2H, m, CH_2N), 2.59-2.55 (2H, m, CH_2CO), 1.74-1.64 (6H, m, 3 × CH_2); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 173.8 (CO), 130.3 (NCH=), 103.1 (=CHCl), 46.7 (CH_2N), 36.9 (CH_2CO), 29.4 (CH_2CH_2CO), 27.4 (CH_2CH_2N), 23.4 (CH_2); HRMS (CI+) found $[M + H]^+$ 174.0690, $C_8H_{13}NO^{35}Cl$ requires 174.0686; m.p. 90-92 °C.

***(Z)-1-(2-Chlorovinyl)azepan-2-one* 274:** ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 6.91 (1H, d, *J* 6.3 Hz, NCH=), 5.59 (1H, d, *J* 6.3 Hz, =CH), 3.75-3.73 (2H, m, CH_2N), 2.59-2.55 (2H, m, CH_2CO), 1.74-1.64 (6H, m, 3 × CH_2).

***1-(2,2-Dichlorovinyl)azepan-2-one* 275:** ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 6.98 (1H, s, NCH=), 3.63-3.61 (2H, m, CH_2N), 2.50-2.46 (2H, m, CH_2CO), 1.74-1.64 (6H, m, 3 × CH_2); HRMS (CI+) found $[M + H]^+$ 208.0293, $C_8H_{12}NO^{35}Cl_2$ requires 208.0296.

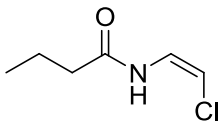
***(Z)-N*-(2-Chlorovinyl)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide, 265**



A suspension of (chloromethyl)triphenylphosphonium chloride (1.74 g, 5.00 mmol) in anhydrous THF (10 mL) was treated with potassium *tert*-butoxide (600 mg, 5.00 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of *N*-formyl-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide **212** (108 mg, 0.50 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum, and the crude residue was purified by flash column chromatography on silica gel (80:20 hexane:ethyl acetate) to afford the *(Z)*-monochloro-enamide **265** as a white gel in 93% yield (115 mg, 0.47 mmol). IR (neat) ν_{max} 3401, 2993, 2958, 2870, 1699, 1652, 1473, 1376, 1316, 1241, 1196, 1158, 1093, 1050, 1019, 903, 873, 768 and 757 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 8.53 (1H, bd, *J* 9.0 Hz, NH), 7.11 (1H, dd, *J* 5.8, 11.2 Hz, NCH=), 5.50 (1H, d, *J* 5.8 Hz, =CH), 4.17 (1H, s, CH), 3.70 (1H, d, *J* 11.9 Hz, C*H*HO), 3.31 (1H, d, *J* 11.9 Hz, CH*H*O), 1.51 (3H, s, CH_3CO), 1.45 (3H, s, CH_3CO), 1.04 (3H, s, CH_3), 1.02 (3H, s, CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 167.2 (CO), 121.8 (NCH=), 101.3 (=CHCl), 99.3 (C), 76.8 (CH), 71.3 (CH_2), 33.2 (C), 29.3 (CH_3),

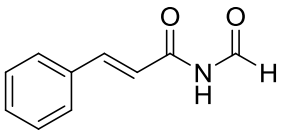
21.9 (CH_3), 18.9 (CH_3), 18.6 (CH_3); HRMS (CI+) found $[M + H]^+$ 248.1061, $C_{11}H_{19}NO_3{}^{35}Cl$ requires 248.1053.

***(Z)-N*-(2-Chlorovinyl)butyramide, 266**



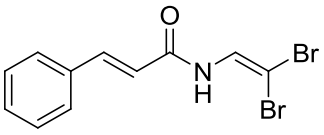
A suspension of (chloromethyl)triphenylphosphonium chloride (1.74 g, 5.00 mmol) in anhydrous THF (10 mL) was treated with potassium *tert*-butoxide (600 mg, 5.00 mmol), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 hours). The resulting brown suspension was then treated dropwise with a solution of *N*-formyl-butyramide **213** (57.5 mg, 0.50 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 hours). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum, and the crude residue was purified by flash column chromatography on silica gel (80:20 hexane:ethyl acetate) to afford the *(Z)*-monochloro-enamide **266** as a white gel in quantitative yield (74.0 mg, 0.50 mmol). IR (neat) ν_{max} 3284, 2966, 1675, 1649, 1483, 1316, 1241, 1191, 1115, 907, 763 and 702 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ_H 7.47-7.33 (1H, bs, NH), 7.16 (1H, dd, *J* 6.1, 11.1 Hz, NCH=), 5.42 (1H, d, *J* 5.7 Hz, =CHCl), 2.29 (2H, t, *J* 7.4 Hz, CH_2), 1.69 (2H, sextet, *J* 7.4 Hz, CH_2), 0.96 (3H, t, *J* 7.3 Hz, CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 170.3 (CO), 122.9 (NCH=), 99.7 (=CHCl), 38.4 (CH_2), 18.8 (CH_2), 13.8 (CH_3); HRMS (CI+) found $[M + H]^+$ 148.0528, $C_6H_{11}NO^{35}Cl$ required 148.0529.

_N_-Formylcinnamamide, 294



A solution of *trans*-cinnamamide **295** (147 mg, 1.00 mmol) in anhydrous THF (10 mL) was cooled to 0 °C before being treated with *n*-BuLi (0.75 mL, 1.20 mmol, 1.6 M solution in hexanes). The reaction was then stirred at 0 °C for 5 minutes before being treated with *N*-formylbenzotriazole **186** (221 mg, 1.50 mmol). The resulting mixture was then allowed to warm up to room temperature and stir for a further 12 hours. The reaction was diluted with *t*-butylmethyl ether (10 mL), and quenched with a saturated aq. $NaHCO_3$ solution (20 mL). The aqueous phase was then extracted with diethyl ether (3 × 20 mL) and the combined organic layers dried over Na_2SO_4. The solvent was removed under vacuum to afford the crude product, which was then purified by flash column chromatography on silica gel (from 10 to 20% ethyl acetate in petroleum ether) to afford the desired *N*-formyl imide **294** as a white solid in 70% yield (122 mg, 0.70 mmol). IR ν_{max} (film) 3167, 2940, 2347, 1730, 1670, 1624, 1491, 1479, 1449, 1366, 1319, 1209, 1134, 984, 812, 768, 756, 743, 710 and 679 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 9.52 (1H, bs, NH), 9.29 (1H, d, *J* 9.9 Hz, CHO), 7.84 (1H, d, *J* 16.6 Hz, CH=), 7.60-7.57 (2H, m, 2 × *ortho* CH_{Ar}), 7.44-7.42 (3H, m, 3 × *para and meta* CH_{Ar}), 6.54 (1H, d, *J* 16.1 Hz, =CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 165.5 (CO), 164.3 (CHO), 146.7 (CH=), 133.8 (C_{Ar}), 131.4 (CH_{Ar}), 129.2 (CH_{Ar}), 128.7 (CH_{Ar}), 118.0 (=CH); HRMS (EI+) calc. for $C_{10}H_9NO_2$ $[M]^+$: 175.0633. Found: 175.0636; m.p. 127-128 °C.

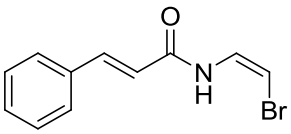
_N_-(2,2-Dibromovinyl)cinnamamide, 291



To a suspension of (bromomethyl)triphenylphosphonium bromide (573 mg, 1.31 mmol) in 2.5 mL of dry THF,under argon and at room temperature, the base potassium *tert*-butoxide (147 mg, 1.31 mmol) was added and the resulting bright yellow suspension was allowed to stir for 6 hours, till the appearance of a brown mixture that indicates the formation of the ylide. At this point, the *N*-formylcinnamamide **294** (23.0 mg, 0.13 mmol) in dry THF (1 mL) was added

dropwise and the resulting mixture was allowed to stir at room temperature for 12 hours. The reaction mixture was quenched with 2 mL of distilled water, then poured in hexane (5 mL) and filtered to eliminate the precipitate. The organic layer was so separated, while the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum to afford a brown oil as crude product, which was purified through flash column chromatography on silica gel (from 10 to 20% ethyl acetate in petroleum ether) to afford *N*-(2,2-dibromovinyl)cinnamamide **291** as a light yellow oil in 71% yield (31.0 mg, 94.0 µmol). IR ν_{max} (film) 3297, 3069, 2959, 2917, 2849, 1669, 1627, 1578, 1496, 1473, 1450, 1335, 1207, 977 and 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.71 (1H, d, *J* 15.5 Hz, CH=), 7.70 (1H, s, NCH=), 7.56-7.53 (2H, m, 2 × *ortho* CH_{Ar}), 7.41-7.39 (3H, m, 3 × *para and meta* CH_{Ar}), 7.24 (1H, bs, NH), 6.39 (1H, d, *J* 15.6 Hz, =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 162.1 (CO), 144.7 (CH=), 134.3 (C_{Ar}), 130.7 (NCH=), 129.1 (CH_{Ar}), 128.3 (CH_{Ar}), 127.8 (CH_{Ar}), 118.4 (=CH), 74.5 ($=CBr_2$); HRMS (CI+/ISO) calc. for $C_{11}H_9NO^{79}Br^{81}Br$ $[M]^+$: 330.9031. Found: 330.9032.

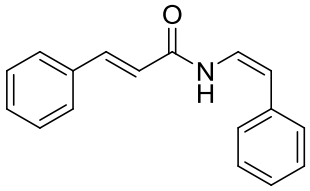
N-((*Z*)-2-Bromovinyl)cinnamamide, 292



To a solution of *N*-(2,2-dibromovinyl)cinnamamide **291** (31.0 mg, 94.0 µmol), in anhydrous ethyl acetate (1 mL), Bu_3SnH (27.5 mg, 95.0 µmol) was added in presence of the catalyst $Pd(PPh_3)_4$ (11.0 mg, 9.00 µmol). The reaction mixture was allowed to stir at room temperature for 18 hours, then it was diluted with hexane (5 mL), filtered through Celite® and concentrated under vacuum to afford a yellow oil as crude product. The crude was purified through flash column chromatography on silica gel (from 0 to 5% ethyl acetate in petroleum ether) to afford a colourless oil as pure product **292** in 64% yield (15.0 mg, 59.5 µmol). IR ν_{max} (film) 3271, 2975, 2927, 2854, 1674, 1642, 1629, 1498, 1480, 1449, 1382, 1337, 1298, 1236, 1181, 1169, 1115, 1073, 978, 915, 765, 758, 733, 716 and 679 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.77 (1H, d, *J* 15.3 Hz, CH=), 7.57-7.54 (4H, m, 2 × *ortho* CH_{Ar} and NH and NCH=), 7.41-7.39 (3H, m, 3 × *meta and para* CH_{Ar}), 6.49 (1H, d, *J* 16.1 Hz, =CH), 5.58 (1H, d, *J* 5.1 Hz, =CHBr); ^{13}C NMR (125

MHz, $CDCl_3$): δ_C 162.9 (CO), 144.2 (CH=), 134.6 (C_{Ar}), 130.5 (NCH=), 129.1 (CH_{Ar}), 127.4 (CH_{Ar}), 125.8 (CH_{Ar}), 119.2 (=CH), 89.1 (=CHBr); HRMS (CI+/ISO) calc. for $C_{11}H_{11}NO^{79}Br$ $[M+H]^+$: 252.0024. Found: 252.0023.

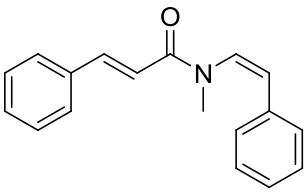
N-Styrylcinnamamide (LANSIUMAMIDE A), 288



To a solution of *N*-((*Z*)-2-bromovinyl)cinnamamide **292** (7.80 mg, 0.03 mmol) in anhydrous THF (1 mL), at room temperature and under argon, $Pd(PPh_3)_4$ (2.00 mg, 1.50 µmol), K_2CO_3 (25.5 mg, 0.19 mmol) and phenylboronic acid **293** (12.0 mg, 93.0 µmol) were added in one pot and the resulting mixture was allowed to stir for 12 hours at 70 °C. Then the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (5 mL) and filtered through Celite® to afford a dark red oil as crude product. The crude was purified through flash column chromatography on silica gel (10% ethyl acetate in hexane) to afford a yellow solid as pure product **288** in 62% yield (4.80 mg, 19.2 µmol). IR ν_{max} (film) 3300, 2955, 2923, 2852, 1737, 1669, 1647, 1628, 1506, 1480, 1467, 1450, 1443, 1260, 1204, 1172, 1028, 976, 763 and 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.79 (1H, bd, *J* 10.5 Hz, NH), 7.73 (1H, d, *J* 15.5 Hz, CH=), 7.53-7.44 (2H, m, 2 × CH_{Ar}), 7.42-7.25 (8H, m, 8 × CH_{Ar}), 7.13 (1H, dd, *J* 9.6 Hz, 11.3 Hz, CH=), 6.39 (1H, d, *J* 15.5 Hz, =CH), 5.84 (1H, d, *J* 9.6 Hz, =CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 163.2 (CO), 143.2 (CH=), 136.0 (C_{Ar}), 134.8 (C_{Ar}), 130.3 (CH_{Ar}), 129.3 (CH_{Ar}), 129.0 (CH_{Ar}), 128.2 (CH_{Ar}), 127.2 (CH_{Ar}), 122.6 (NCH=), 119.9 (=*CH*Ph), 110.8 (=*CH*CO); HRMS (EI+) calc. for $C_{17}H_{15}NO$ $[M]^+$: 249.1154. Found: 249.1149.

The characterisation matches with the data reported in literature:
Bayer A.; Maier M. E. Tetrahedron **2004**, *60*, 6665.

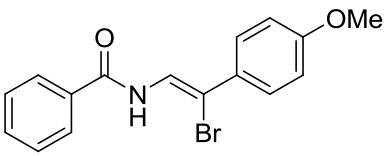
_N_-Methyl-_N_-styrylcinnamamide (LANSIUMAMIDE B), 289



To a solution of lansiumamide A **288** (17.0 mg, 0.07 mmol) in dry THF (1 mL), under argon and at 0 °C, NaH (3.00 mg, 71.0 µmol) was added and the resulting suspension was allowed to stir for 30 minutes. Then, iodomethane (5 µL, 0.08 mmol) was added and the resulting mixture was allowed to stir for 3 hours at 70 °C. The reaction was quenched with H_2O (1 mL) and extracted with diethyl ether (3 × 1 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum to afford a yellow oil as crude product, which was purified through flash column chromatography on silica gel (from 0 to 10% ethyl acetate in petroleum ether) to afford the pure product **289** as a pale yellow oil in quantitative yield (18.0 mg, 0.07 mmol). IR ν_{max} (film) 2956, 2923, 2853, 1742, 1660, 1639, 1600, 1450, 1428, 1375, 1362, 1259, 1235, 1218, 1178, 1114, 1086, 763 and 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.63 (1H, d, *J* 15.5 Hz, CH=), 7.45-7.44 (2H, m, 2 × CH_{Ar}), 7.34-7.21 (8H, m, 8 × CH_{Ar}), 6.93 (1H, d, *J* 15.5 Hz, =CH), 6.50 (1H, d, *J* 8.7 Hz, NCH=), 6.24 (1H, d, *J* 8.7 Hz, =CH), 3.09 (3H, s, N-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 166.6 (CO), 142.8 (CH=), 135.5 (C_{Ar}), 134.8 (C_{Ar}), 129.8 (CH_{Ar}), 129.2 (CH_{Ar}), 128.9 (CH_{Ar}), 128.8 (CH_{Ar}), 128.7 (NCH=), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 125.3 (=*CH*Ph), 118.7 (=*CH*CO), 34.7 (N-CH_3); HRMS (EI+) calc. for $C_{18}H_{17}NO$ $[M]^+$: 263.1310. Found: 263.1314.

The characterisation matches with the data reported in literature:
Bayer A.; Maier M. E. Tetrahedron **2004**, *60*, 6665.

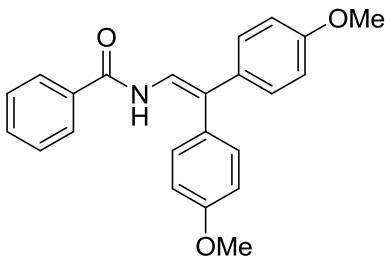
***(Z)-N*-(2-Bromo-2-(4-methoxyphenyl)vinyl)benzamide, 277**



To a solution of *N*-(2,2-dibromovinyl)benzamide **251** (37.0 mg, 0.12 mmol) in anhydrous THF (2.5 mL), at room temperature and under argon, $Pd(PPh_3)_4$ (8.00 mg, 7.00 µmol), K_2CO_3 (34.0 mg, 243 µmol) and 4-methoxyphenylboronic acid **297**

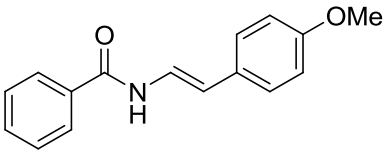
(18.4 mg, 121 µmol) were added in one pot and the resulting mixture was allowed to stir for 12 hours at 70 °C. Then the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (5 mL) and filtered through Celite® to afford a dark yellow solid as crude product. The crude was purified through flash column chromatography on silica gel (from 0 to 30% ethyl acetate in hexane) to afford a yellow solid as pure product **277** in 55% yield (75% brsm) (22.0 mg, 66.3 µmol) in addition to the disubstituted by-product *N*-(2,2-bis(4-methoxyphenyl) vinyl) benzamide **278** (5.00 mg, 14.0 µmol) in 12% yield. IR ν_{max} (film) 3414, 3068, 2956, 2917, 2848, 2364, 1678, 1642, 1605, 1511, 1502, 1468, 1442, 1298, 1281, 1251, 1178, 1113, 1100, 1028, 827 and 709 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.22 (1H, bd, *J* 9.0 Hz, NH), 7.90 (2H, dd, J 1.5, 7.2 Hz, 2 × CH_{Ar}), 7.73 (1H, d, *J* 7.3 Hz, =CH), 7.59 (1H, tt, *J* 1.2, 7.5 Hz, CH_{Ar}), 7.54-7.48 (4H, m, 4 × CH_{Ar}), 6.90 (2H, d, *J* 8.7 Hz, CH_{Ar}), 3.84 (3H, s, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 164.2 (CO), 160.1 (*C*-OMe), 133.4 (C_{Ar}), 132.6 (CH_{Ar}), 129.8 (C_{Ar}), 129.1 (CH_{Ar}), 128.6 (CH_{Ar}), 127.4 (CH_{Ar}), 120.9 (NCH=), 114.3 (CH_{Ar}), 108.8 (=CBr), 55.6 (OCH_3); HRMS (CI+/ISO) calc. for $C_{16}H_{15}NO_2{}^{79}Br$ $[M+H]^+$: 332.0286. Found: 332.0276.

N-(2,2-bis(4-Methoxyphenyl)vinyl)benzamide (BY-PRODUCT), 278



IR ν_{max} (film) 3429, 2922, 2850, 2366, 2339, 1729, 1671, 1635, 1605, 1576, 1511, 1503, 1472, 1435, 1363, 1208, 831 and 804 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.66-7.61 (2H, m, CH_{Ar}), 7.52-7.45 (2H, m, NH and CH_{Ar}), 7.42-7.39 (3H, m, CH= and CH_{Ar}), 7.27-7.25 (2H, m, CH_{Ar}), 7.21 (2H, d, *J* 8.7 Hz, CH_{Ar}), 7.03 (2H, d, *J* 8.7 Hz, CH_{Ar}), 6.84 (2H, d, *J* 8.9 Hz, CH_{Ar}), 3.88 (3H, s, OCH_3), 3.81 (3H, s, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 159.6 (CO), 159.2 (2 × C-OMe), 133.9 (C_{Ar}), 133.2 (C_{Ar}), 132.7 (C_{Ar}), 132.4 (CH_{Ar}), 132.0 (CH_{Ar}), 131.2 (CH_{Ar}), 128.9 (CH_{Ar}), 128.2 (CH_{Ar}), 127.1 (C), 118.8 (CH=), 115.1 (CH_{Ar}), 114.1 (CH_{Ar}), 55.3 (OCH_3), 55.2 (OCH_3); HRMS (CI+/ISO) calc. for $C_{23}H_{22}NO_3$ $[M+H]^+$: 360.1600. Found: 360.1597.

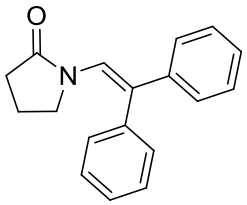
***(E)-N*-(4-Methoxystyryl)benzamide (ALATAMIDE), 290**



The *(Z)-N*-(2-bromo-2-(4-methoxyphenyl)vinyl)benzamide **277** (22.0 mg, 66.3 µmol) was dissolved in a mixture 1:1 of THF/MeOH (1 mL : 1 mL) and cooled to 0^{o}C. After 10 minutes Zn-Cu couple (253 mg, 1.99 mmol) was added together with glacial acetic acid (398 mg, 6.63 mmol). The mixture was allowed to stir for 24 hours and then washed with NH_4Cl aqueous saturated solution (2 mL) and extracted with diethyl ether (3 × 1 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum to afford the desired product **290** as a pale yellow solid without necessity of any further purification in 90% yield (15.0 mg, 59.7 µmol). IR v_{max} (film) 3322, 2969, 2955, 2924, 2853, 1658, 1506, 1456, 1443, 1366, 1246, 1231, 1217, 1207, 1177, 1032 and 943 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d_6): δ_H 9.79 (1H, bd, *J* 7.9 Hz, NH), 8.02 (2H, dd, *J* 1.4, 7.2 Hz, CH_{Ar}), 7.66 (1H, dd, *J* 10.2, 15.0 Hz, NCH=), 7.61 (1H, tt, *J* 1.3, 7.3 Hz, CH_{Ar}), 7.54 (2H, td, *J* 1.3, 7.7 Hz, CH_{Ar}), 7.38 (2H, dd, *J* 1.8, 6.8 Hz, CH_{Ar}), 6.93 (2H, dd, *J* 1.5, 8.8 Hz, CH_{Ar}), 6.45 (1H, d, *J* 16.0 Hz, =CH), 3.83 (3H, s, CH_3); ^{13}C NMR (125 MHz, Acetone-d_6): δ_C 165.5 (CO), 160.3 (C-OMe), 135.7 (C_{Ar}), 133.3 (C_{Ar}), 131.1 (CH_{Ar}), 130.1(CH_{Ar}), 129.0 (CH_{Ar}), 128.1 (CH_{Ar}), 123.9 (NCH=), 115.8 (=CH), 114.3 (CH_{Ar}), 56.3 (OCH_3); HRMS (EI+) calc. for $C_{16}H_{15}NO_2$ $[M]^+$: 253.1103. Found: 253.1106.

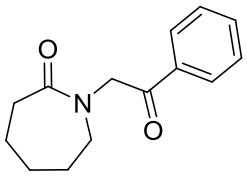
The characterisation matches with the data reported in literature:
Obrecht J.; Hellberg L.; Somanathan R. *J. Chem. Soc., Chem. Commun.* **1987**, *423*, 1219.

1-(2,2-Diphenylvinyl)pyrrolidin-2-one, 276



To a solution of 1-(2,2-dibromovinyl)pyrrolidin-2-one **246** (50.0 mg, 186 µmol) in anhydrous THF (4 mL), at room temperature and under argon, $Pd(PPh_3)_4$ (11.0 mg, 9.00 µmol), NaOH (1 M, 0.56 mmol) and phenylboronic acid (46.0 mg, 372 µmol) were added in one pot and the resulting mixture was allowed to stir for 3 hours at 70 °C. Then the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (5 mL) and filtered through Celite® to afford a dark yellow solid as crude product. The crude was purified through flash column chromatography on silica gel (from 10 to 15% ethyl acetate in petroleum ether) to afford a white solid as pure product **276** in 93% yield (46.0 mg, 175 µmol). *Rf*: 0.12 (20% EtOAc/PET); IR v_{max} (film) 1686, 1634, 1445, 1395, 1369, 1325, 1292, 1275, 1225, 903, 723, 702 and 648 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.31-7.13 (11 H, m, NCH= and 10 × CH_{Ar}), 2.93 (2H, t, *J* 6.9 Hz, CH_2N), 2.35 (2H, t, *J* 8.3 Hz, CH_2CO), 1.81 (2H, qn, *J* 7.2 Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 175.7 (CO), 141.6 (C_{Ar}), 138.9 (C_{Ar}), 130.9 (NCH=), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 127.7 (CH_{Ar}), 127.4 (CH_{Ar}), 127.1 (CH_{Ar}), 127.0 (CH_{Ar}), 122.6 (=C), 48.3 (CH_2N), 30.6 (CH_2CO), 18.9 (CH_2); HRMS (CI+/ISO) calc. for $C_{18}H_{18}NO$ $[M+H]^+$: 264.1388. Found: 264.1384; m.p. 106-107 °C.

1-(2-Oxo-2-phenylethyl)azepan-2-one, 279



To a solution of 1-(2,2-diiodovinyl)azepan-2-one **253** (110 mg, 281 µmol) in anhydrous THF (6 mL), at room temperature and under argon, $Pd(PPh_3)_4$ (33.0 mg, 0.03 mmol), Cs_2CO_3 (458 mg, 1.41 mmol) and phenylboronic acid (103 mg, 844 µmol) were added in one pot and the resulting mixture was allowed to stir for

12 hours at 70 °C. Then the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (10 mL) and filtered through Celite® to afford a dark yellow solid as crude product. The crude was purified through flash column chromatography on silica gel (from 30 to 50% ethyl acetate in petroleum ether) to afford a colourless oil as pure product **279** in 51% yield (33.0 mg, 0.14 mmol). IR v_{max} (film) 3486, 1707, 1638, 1439, 1421, 1360, 1221, 1121, 1092 and 723 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97-7.95 (2H, m, 2 × *ortho* CH_{Ar}), 7.61 (1H, tt, *J* 1.4, 7.5 Hz, *para* CH_{Ar}), 7.47 (2H, tt, *J* 1.7, 8.0 Hz, 2 × *meta* CH_{Ar}), 4.87 (2H, s, CH_2), 3.44-3.42 (2H, m, CH_2), 2.64-2.61 (2H, m, CH_2), 1.75-1.73 (6H, m, 3 × CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.2 (CO), 176.5 (CO), 135.4 (C_{Ar}), 133.7 (CH_{Ar}), 128.9 (CH_{Ar}), 128.2 (CH_{Ar}), 55.2 (CH_2), 51.1 (CH_2), 37.1 (CH_2CO), 30.2 (CH_2), 28.2 (CH_2), 23.5 (CH_2); LRMS (CI+/ISO): $C_{14}H_{18}NO_2$ $[M + H]^+$. Found: 232.3.

The characterisation matches with the data reported in literature:
Malmusi L.; Franchini S.; Mucci A.; Angeli P.; Gulini U.; Marucci G.; Brasili L. *Med. Chem. Res.* **1998**, *8*, 499.

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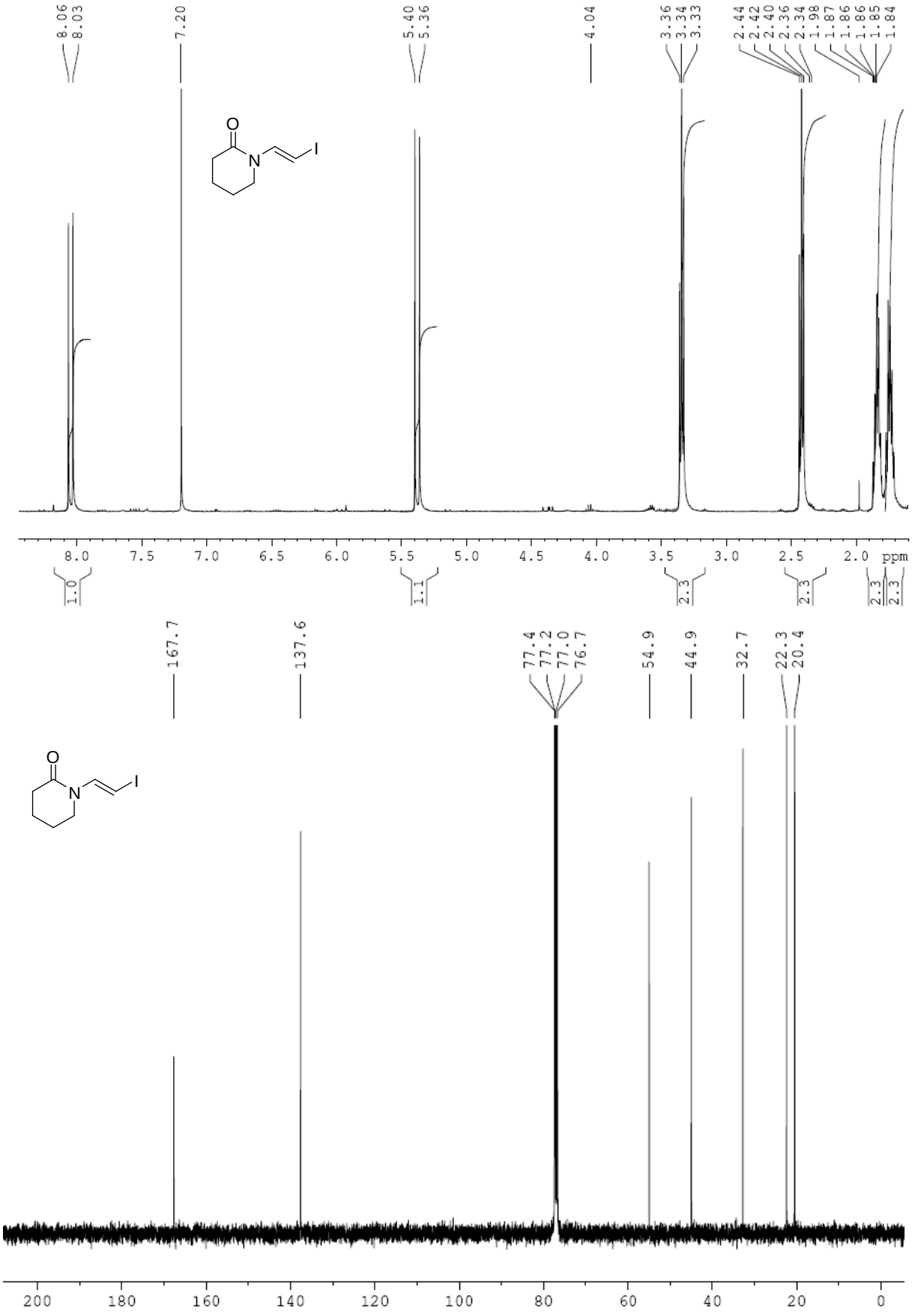
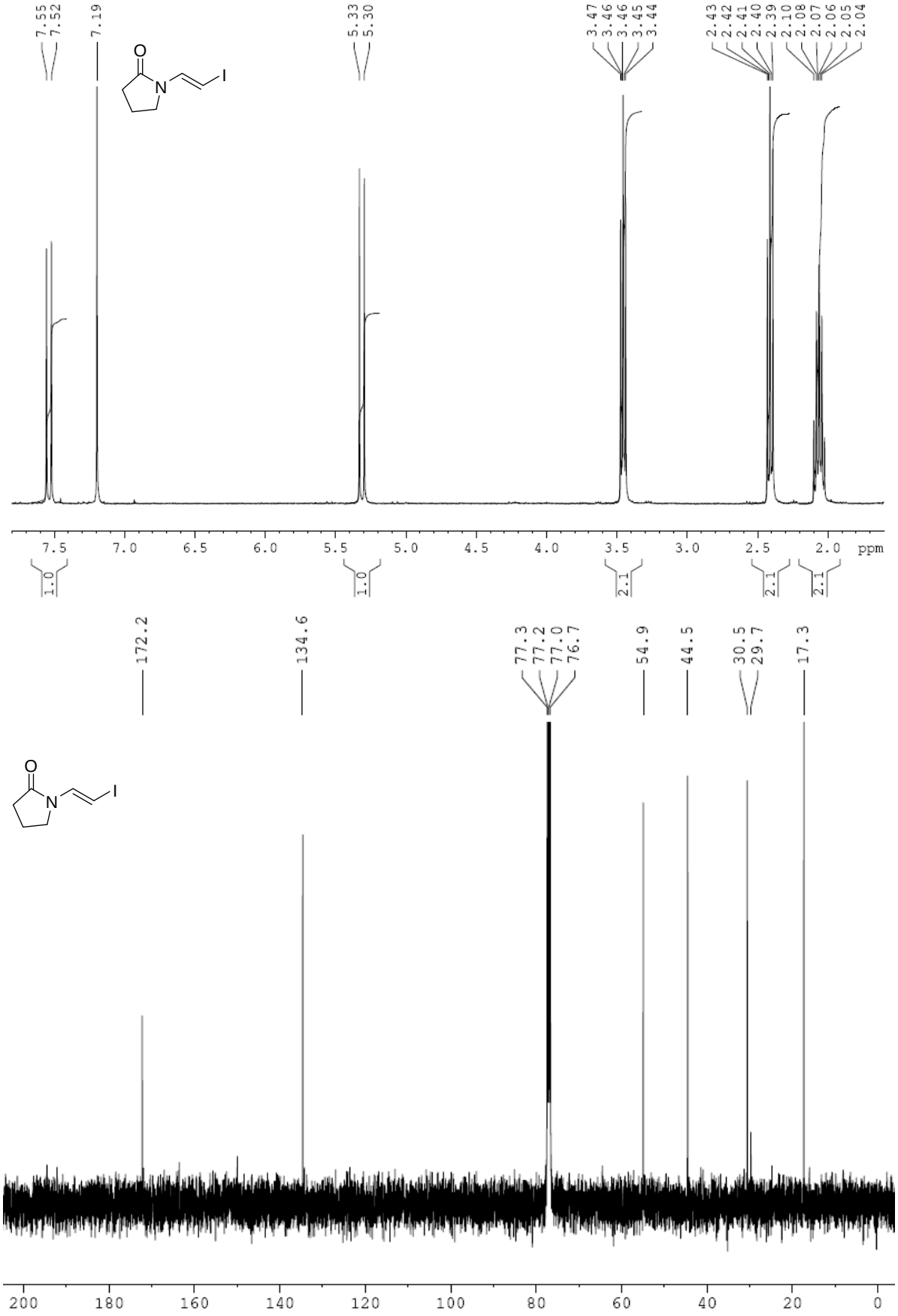
Appendices

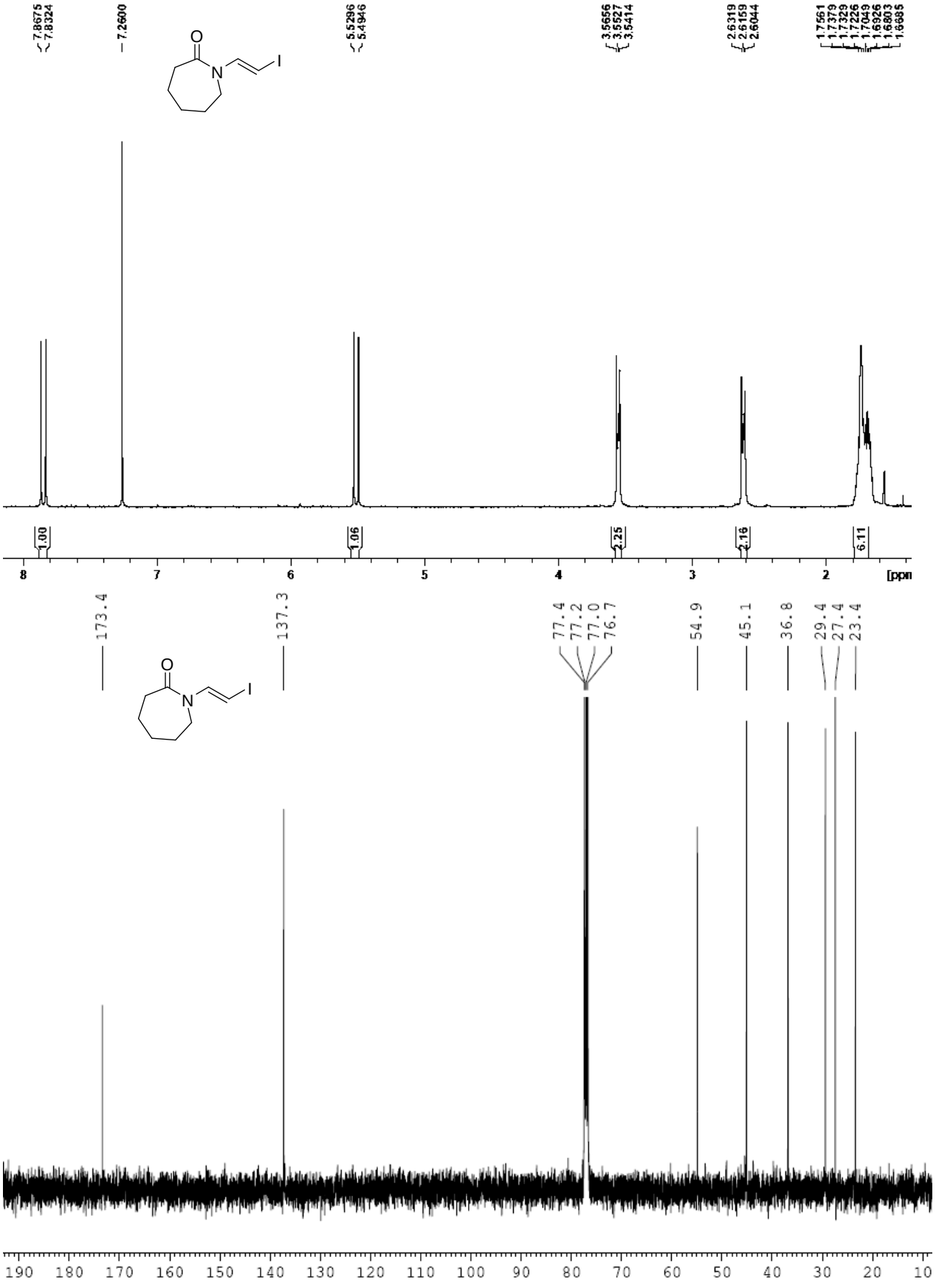
Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **219**



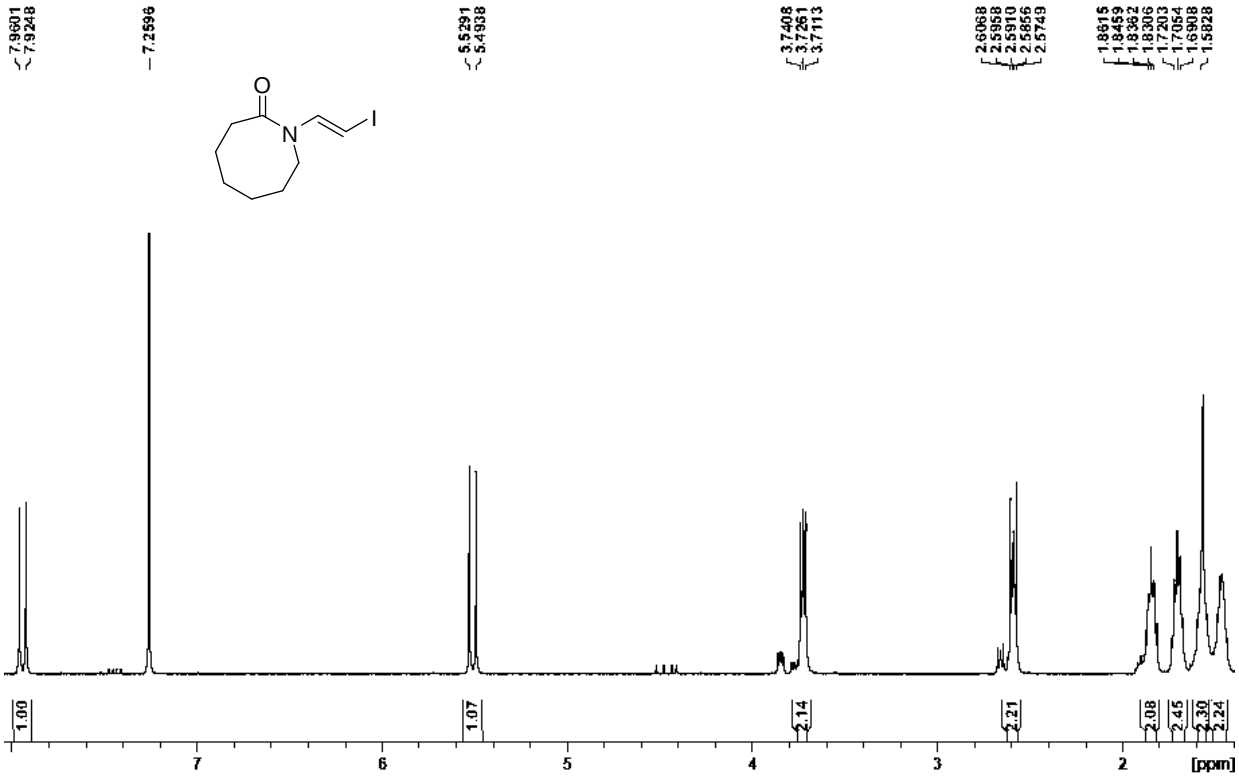
Appendix 2: ^{1}H and ^{13}C NMR spectra of compound **220**

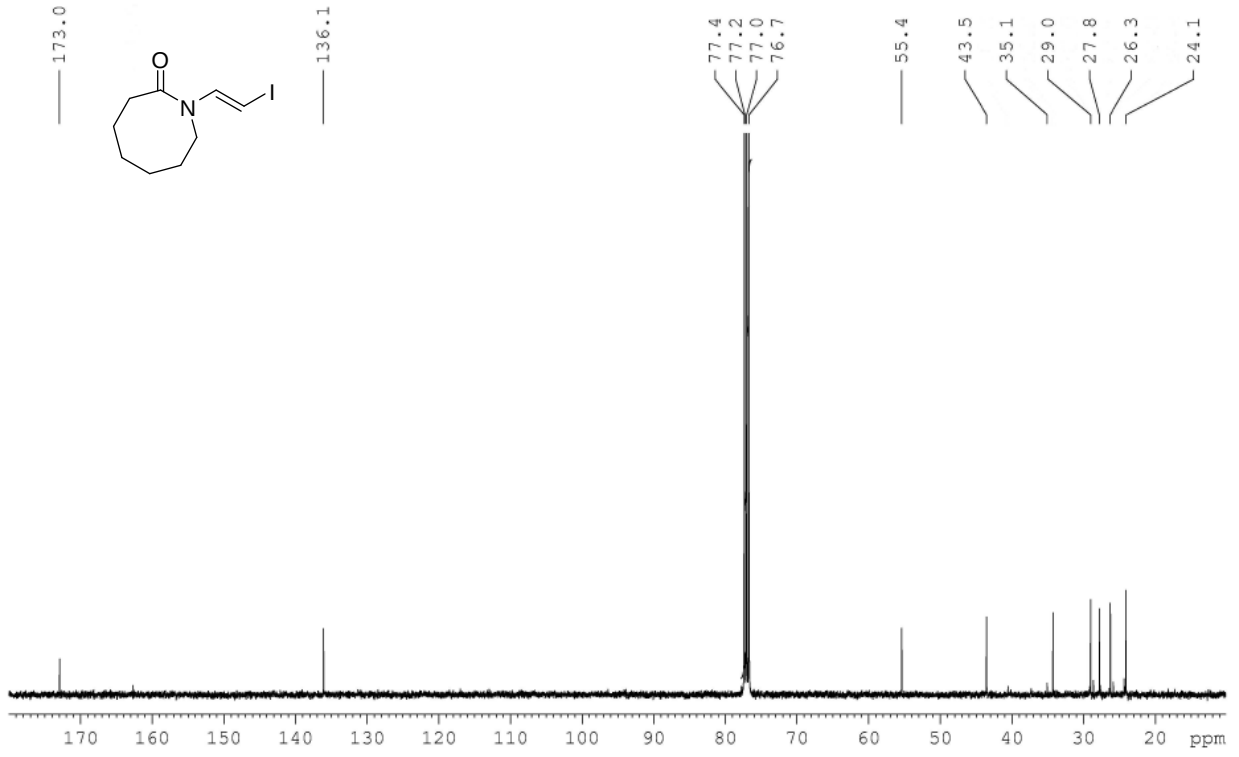


Appendix 3: ^{1}H and ^{13}C NMR spectra of compound **221**

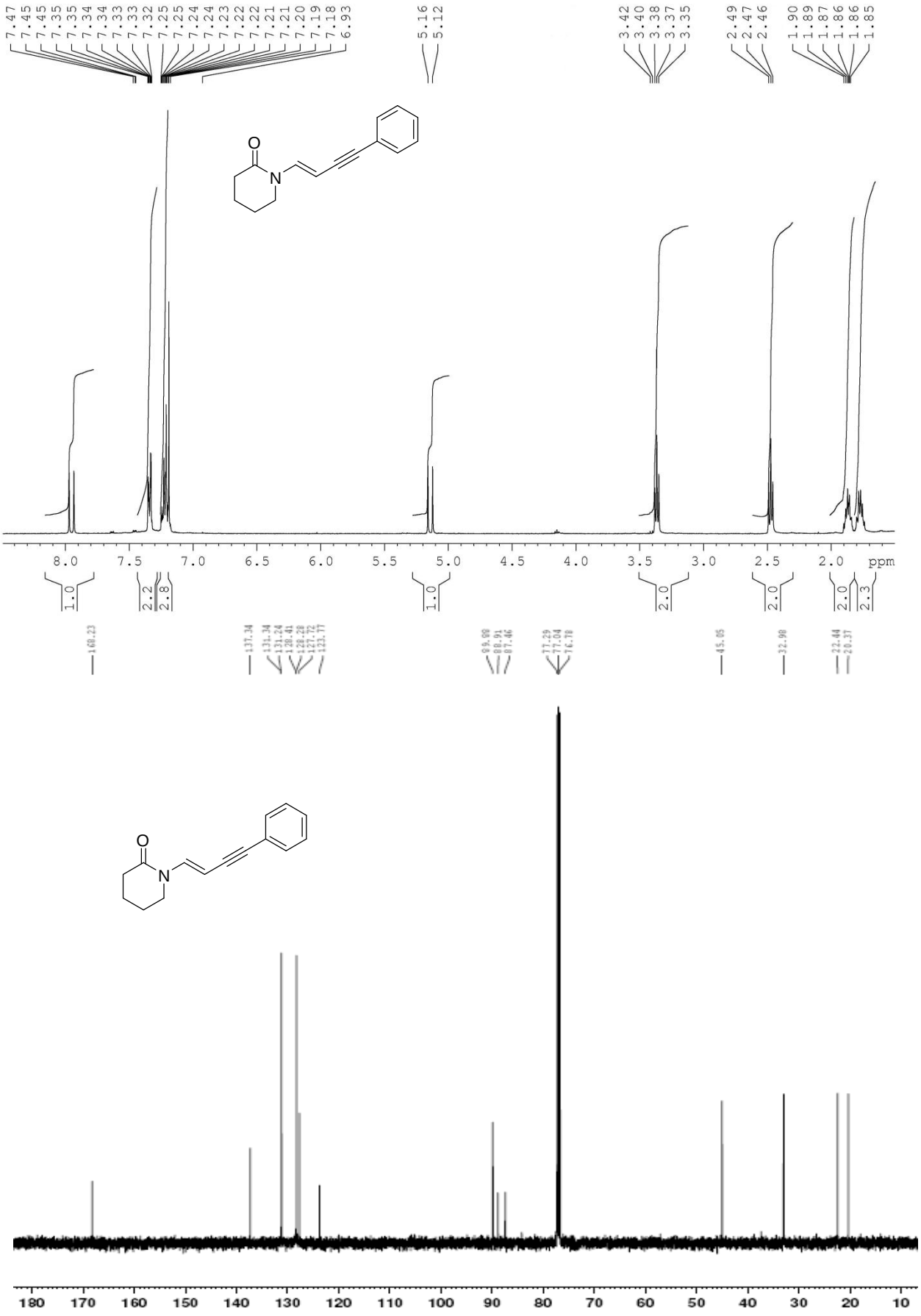


Appendix 4: ^{1}H and ^{13}C NMR spectra of compound **222**

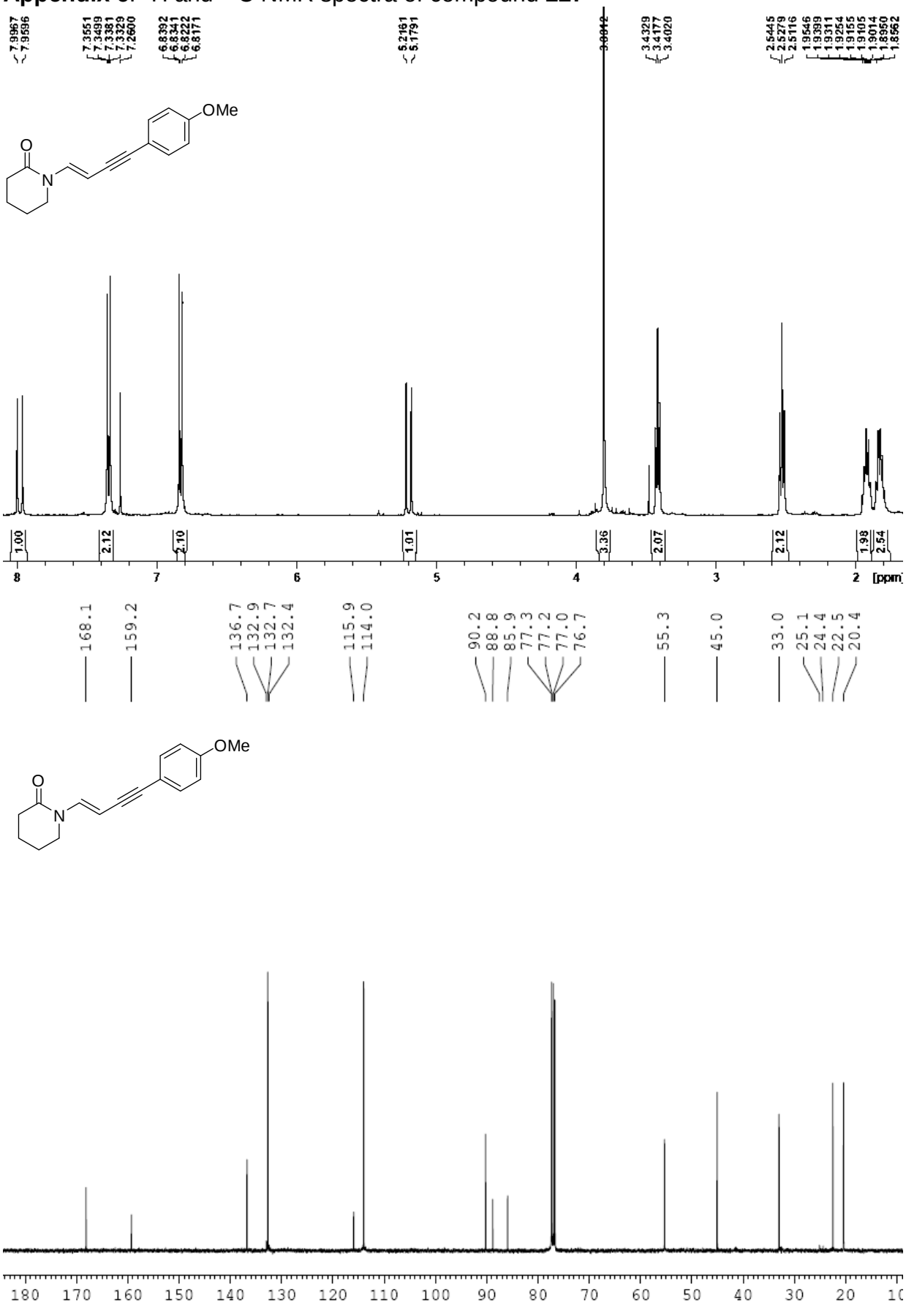




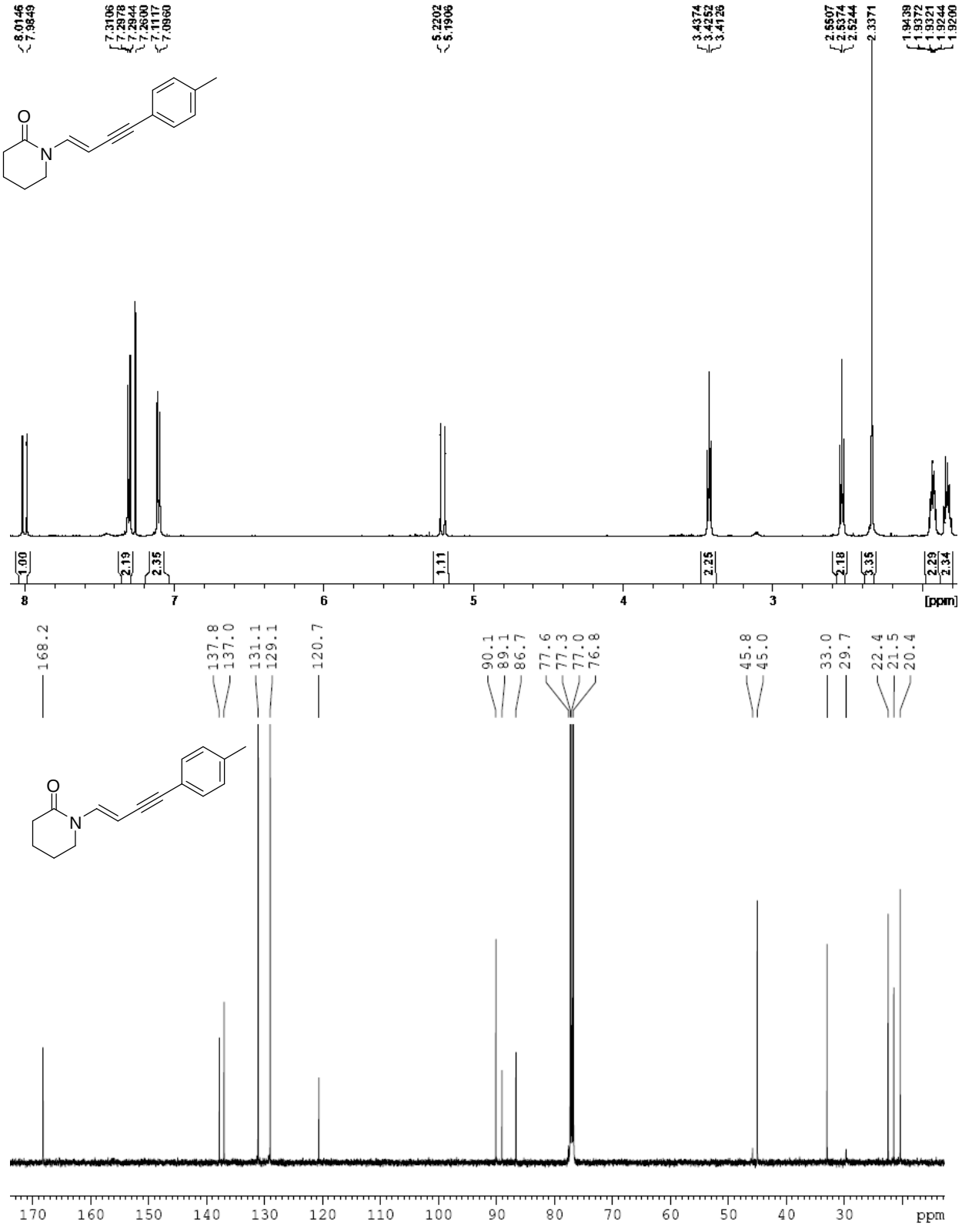
Appendix 5: ^{1}H and ^{13}C NMR spectra of compound **226**



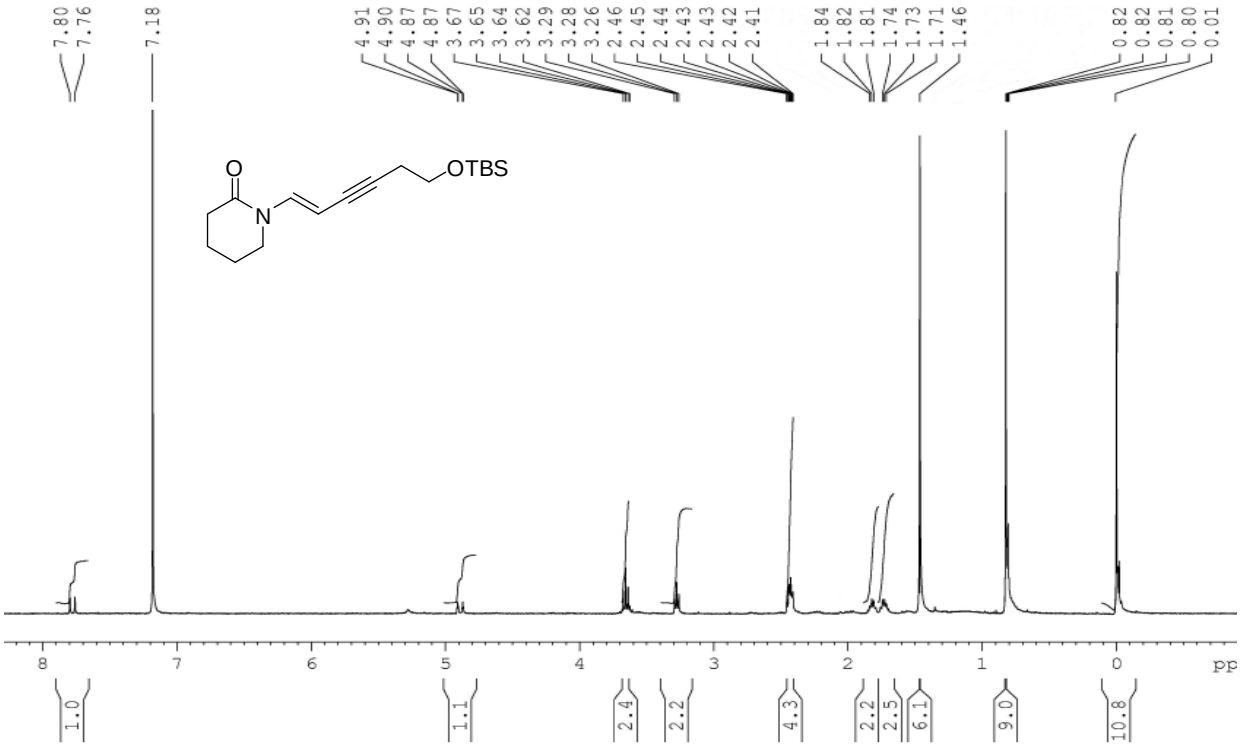
Appendix 6: ^{1}H and ^{13}C NMR spectra of compound **227**

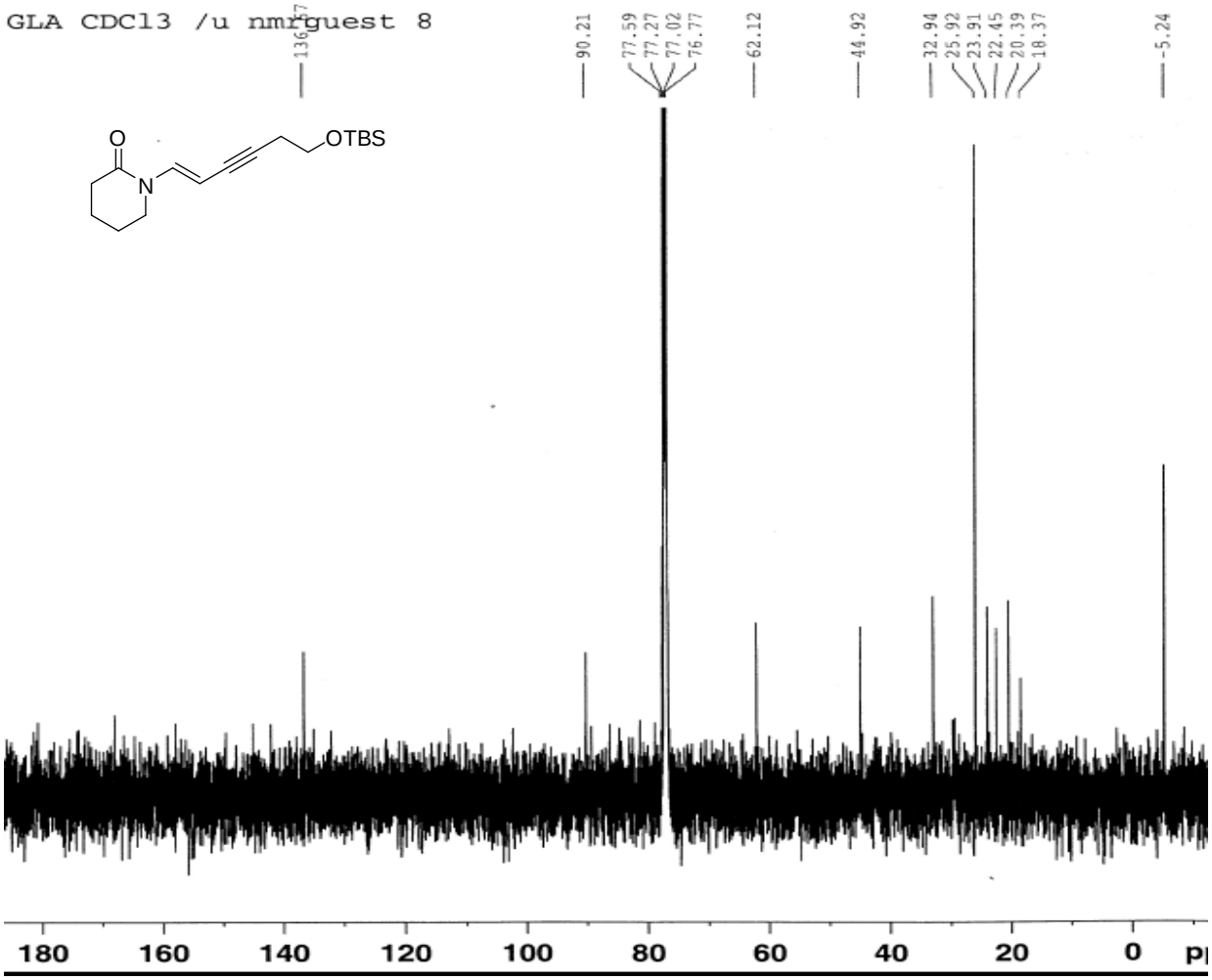


Appendix 7: ^{1}H and ^{13}C NMR spectra of compound **230**

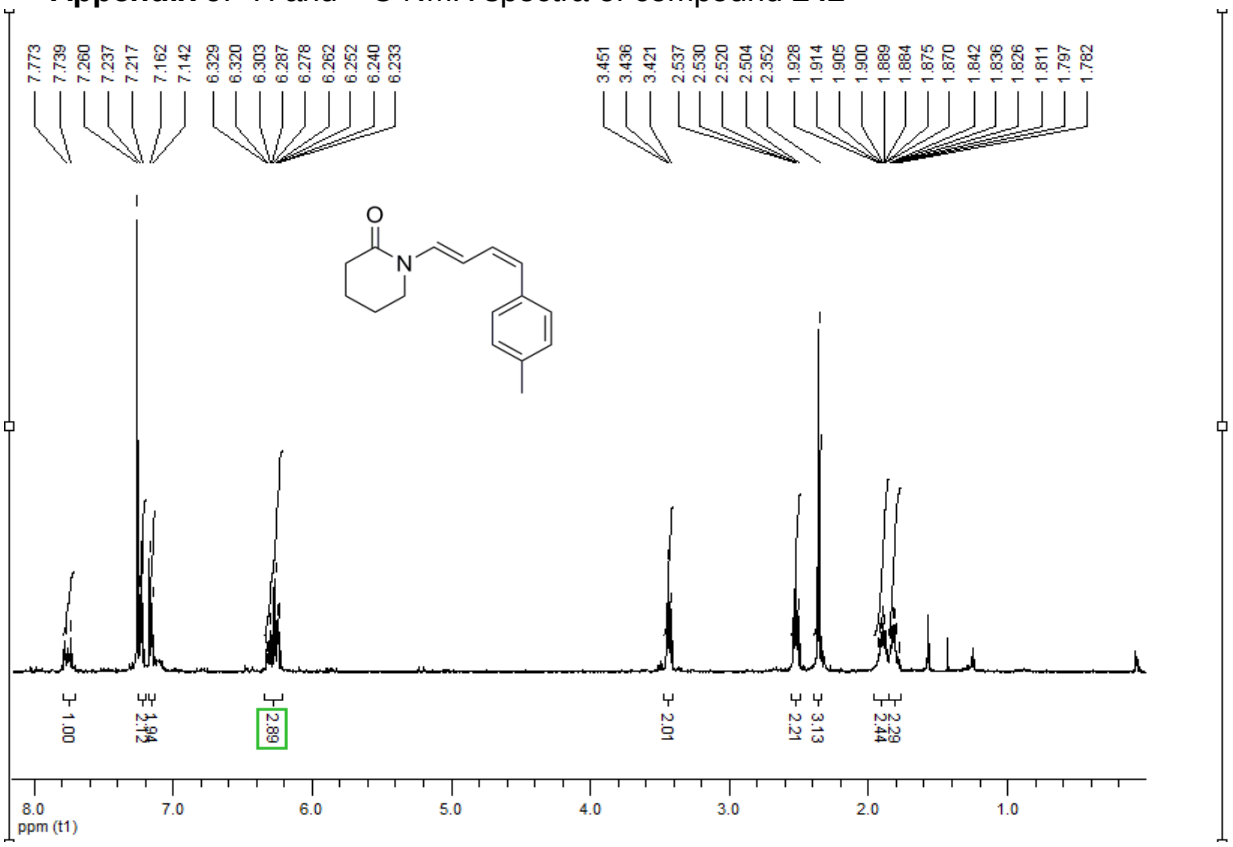


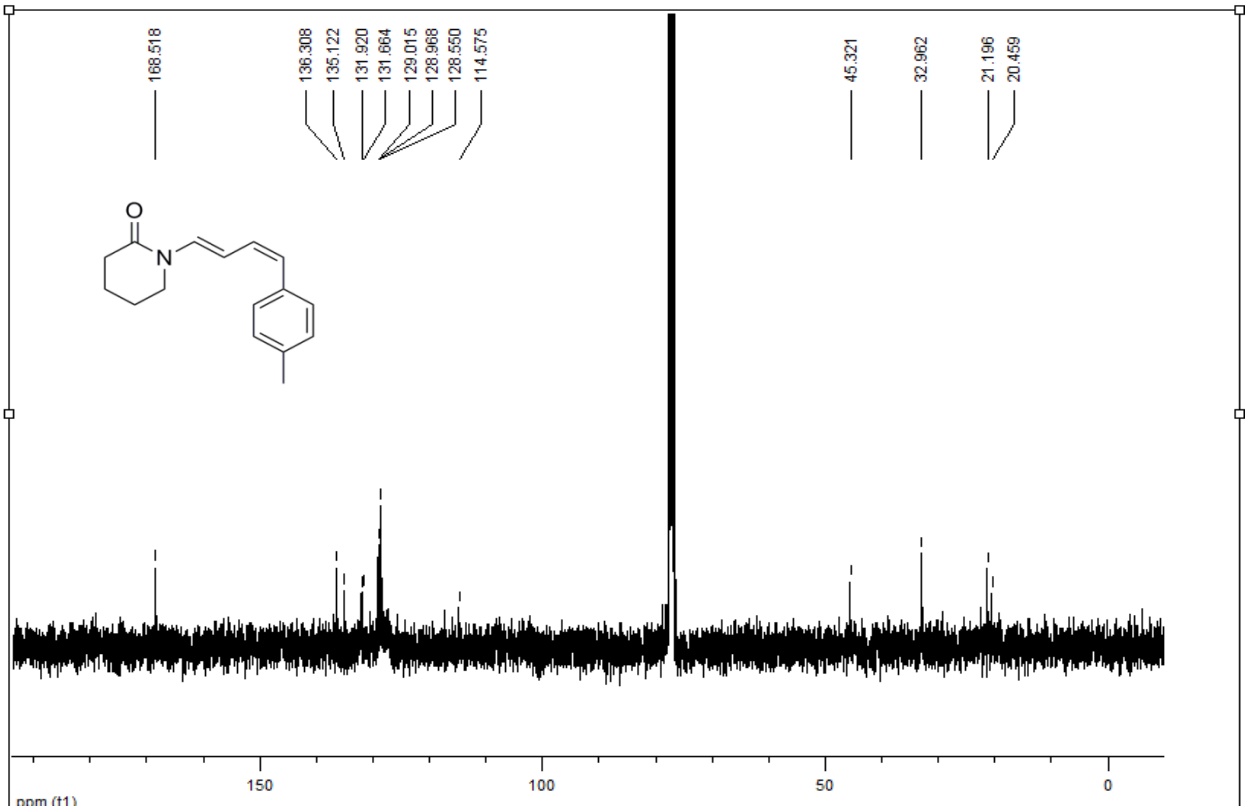
Appendix 8: ^{1}H and ^{13}C NMR spectra of compound **231**



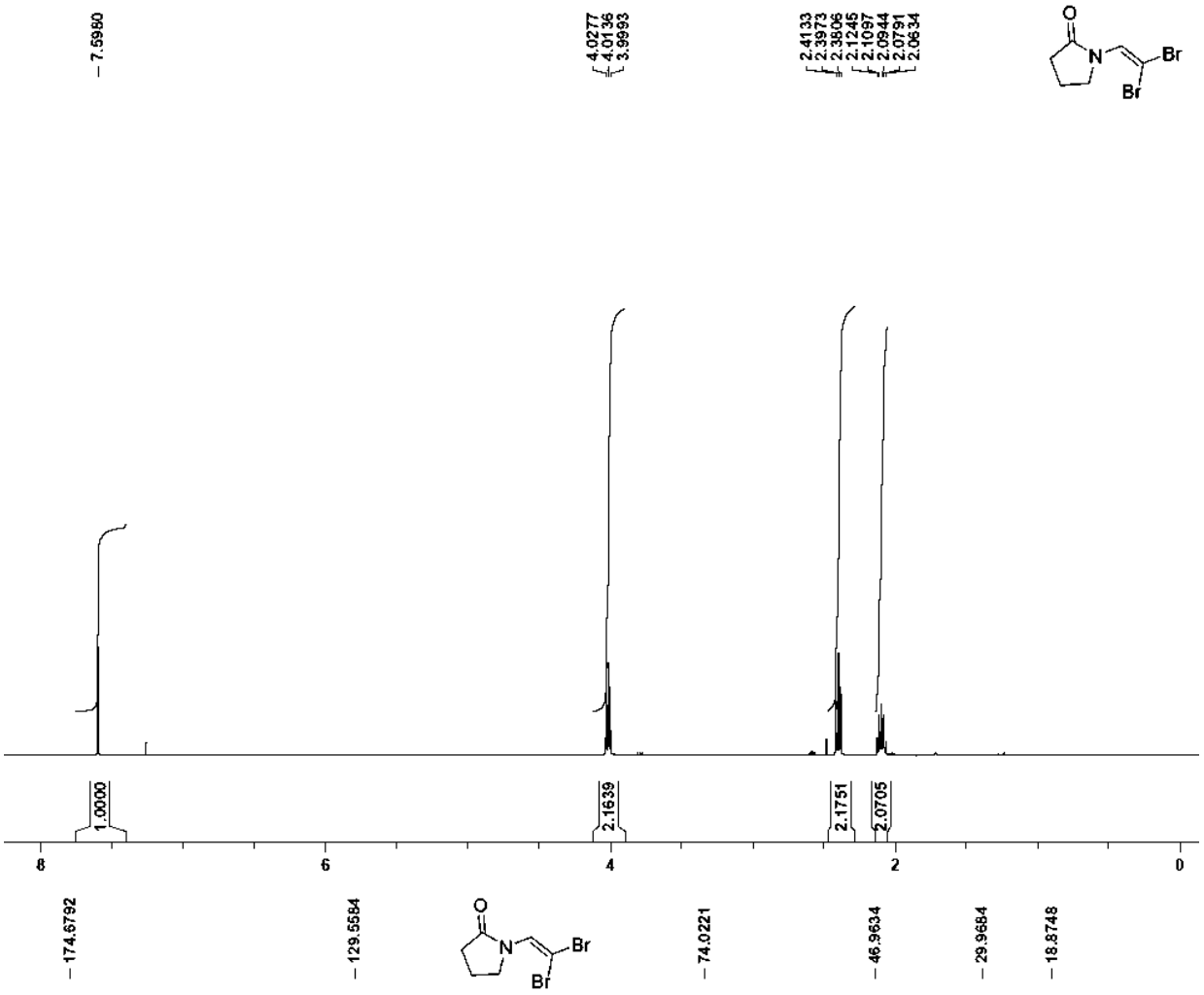


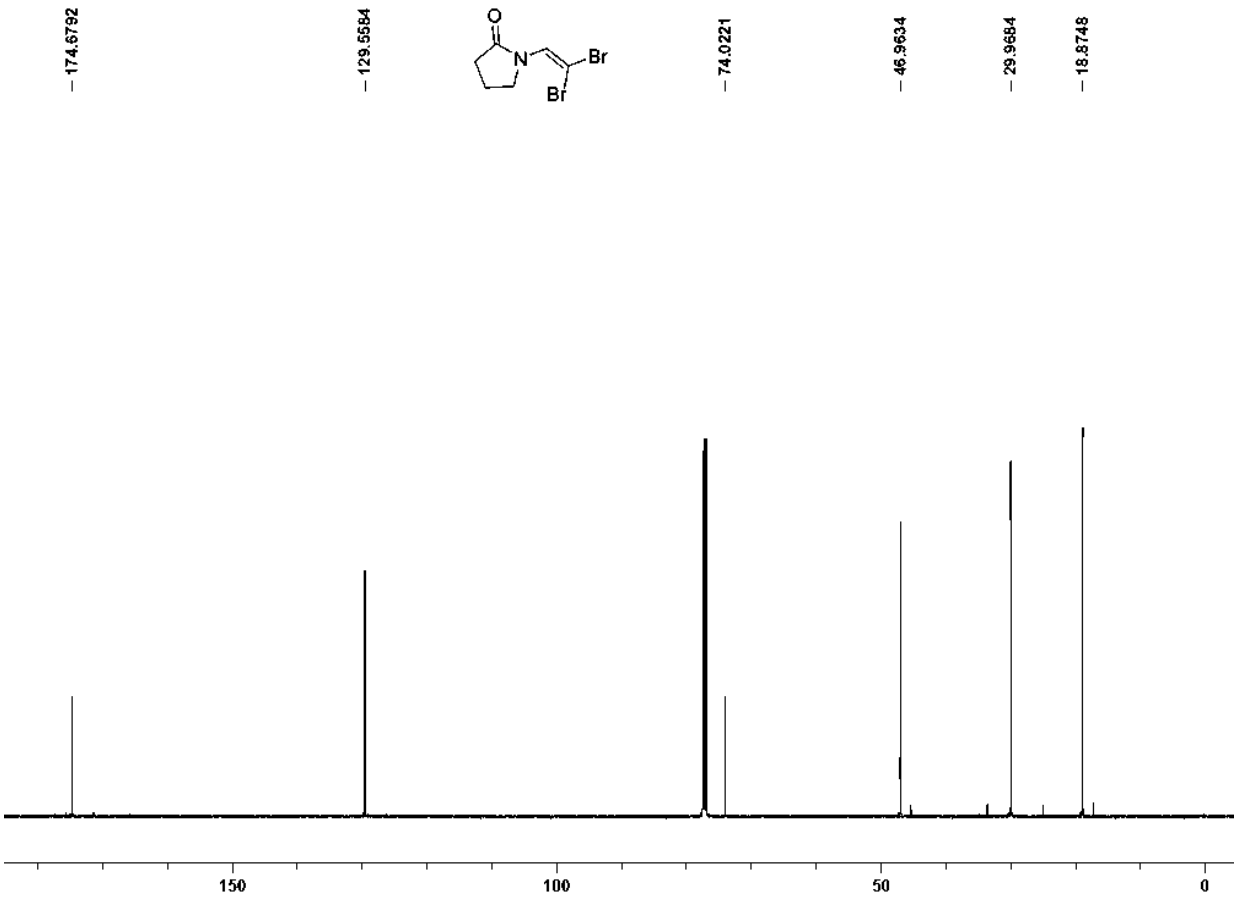
Appendix 9: ^{1}H and ^{13}C NMR spectra of compound **242**



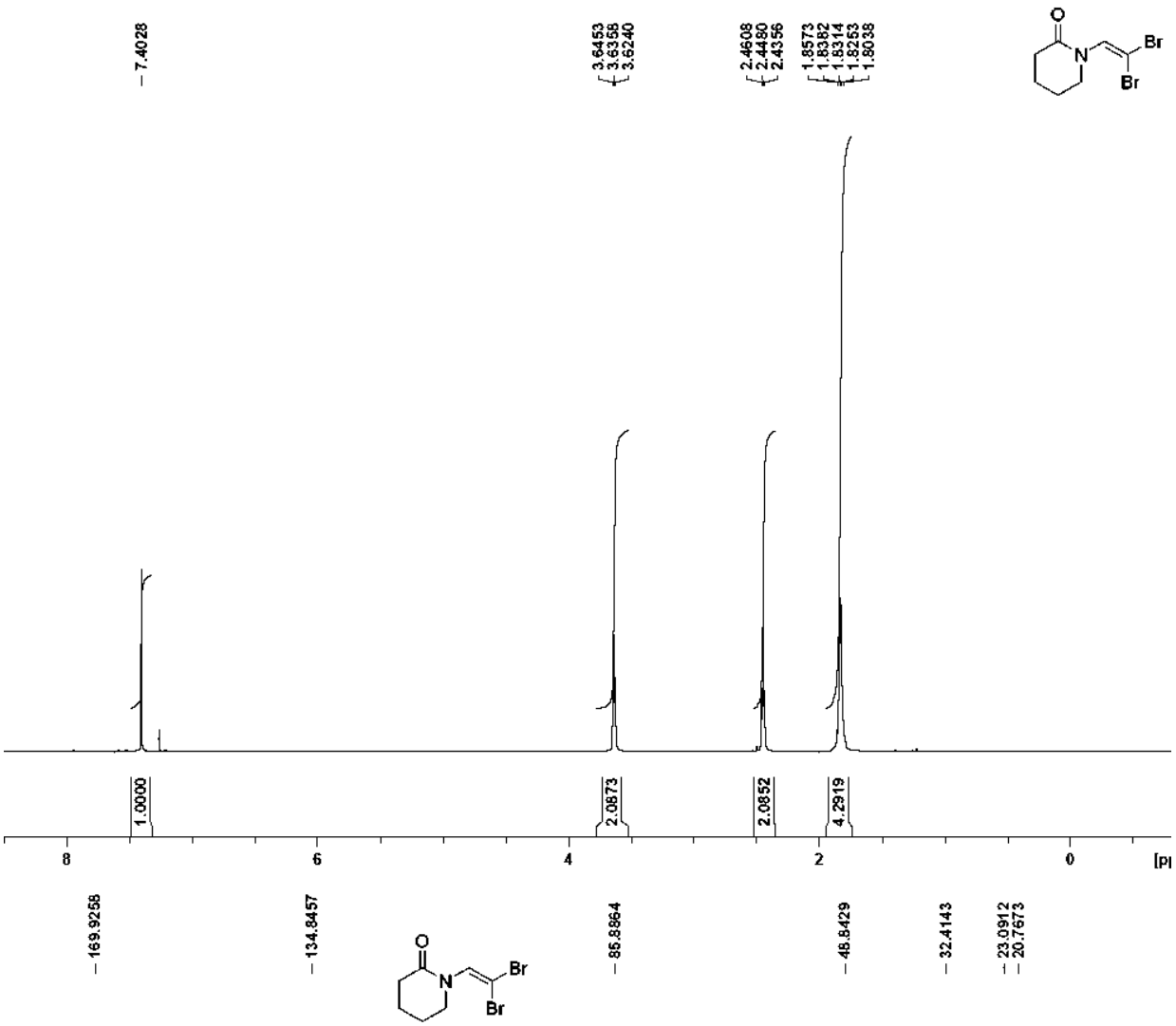


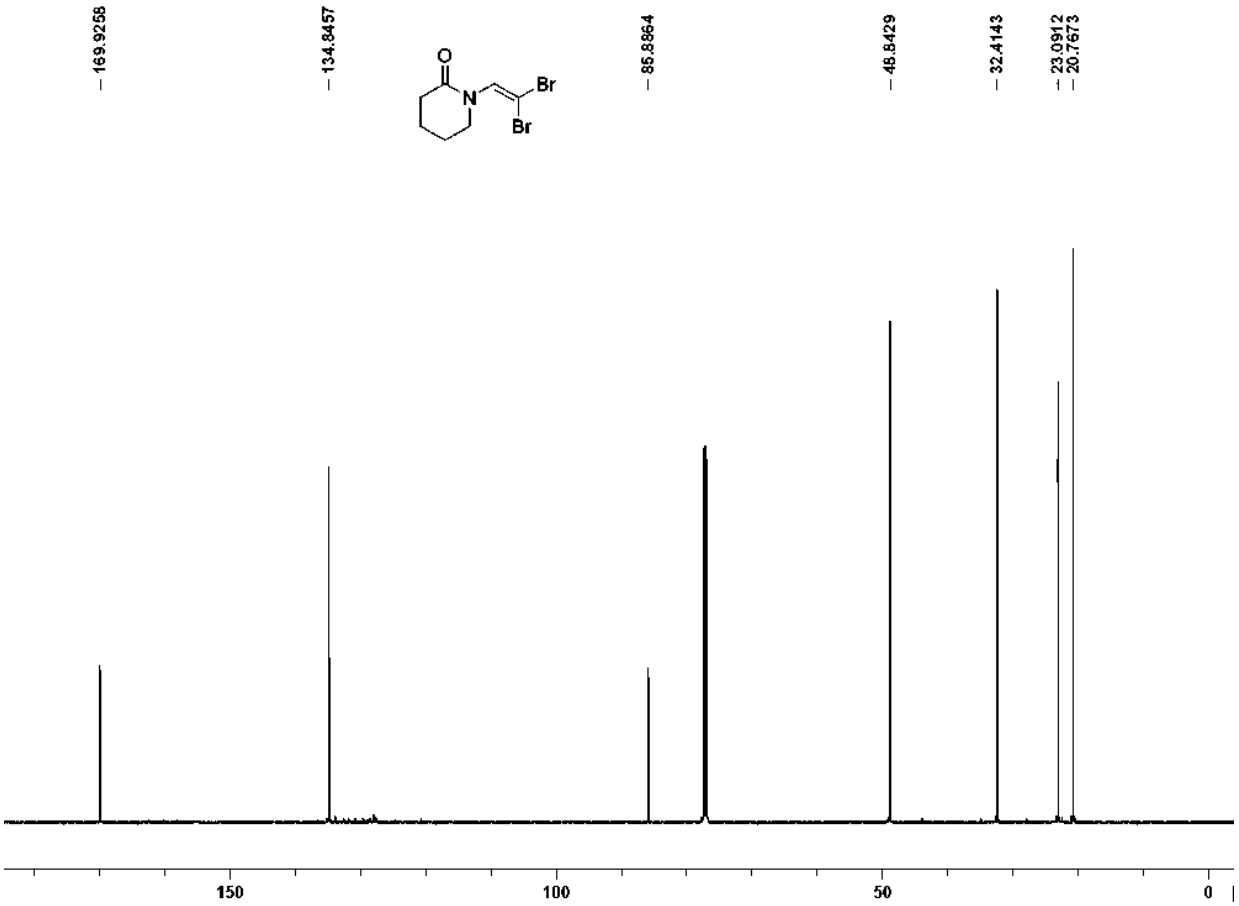
Appendix 10: ^{1}H and ^{13}C NMR spectra of compound **246**



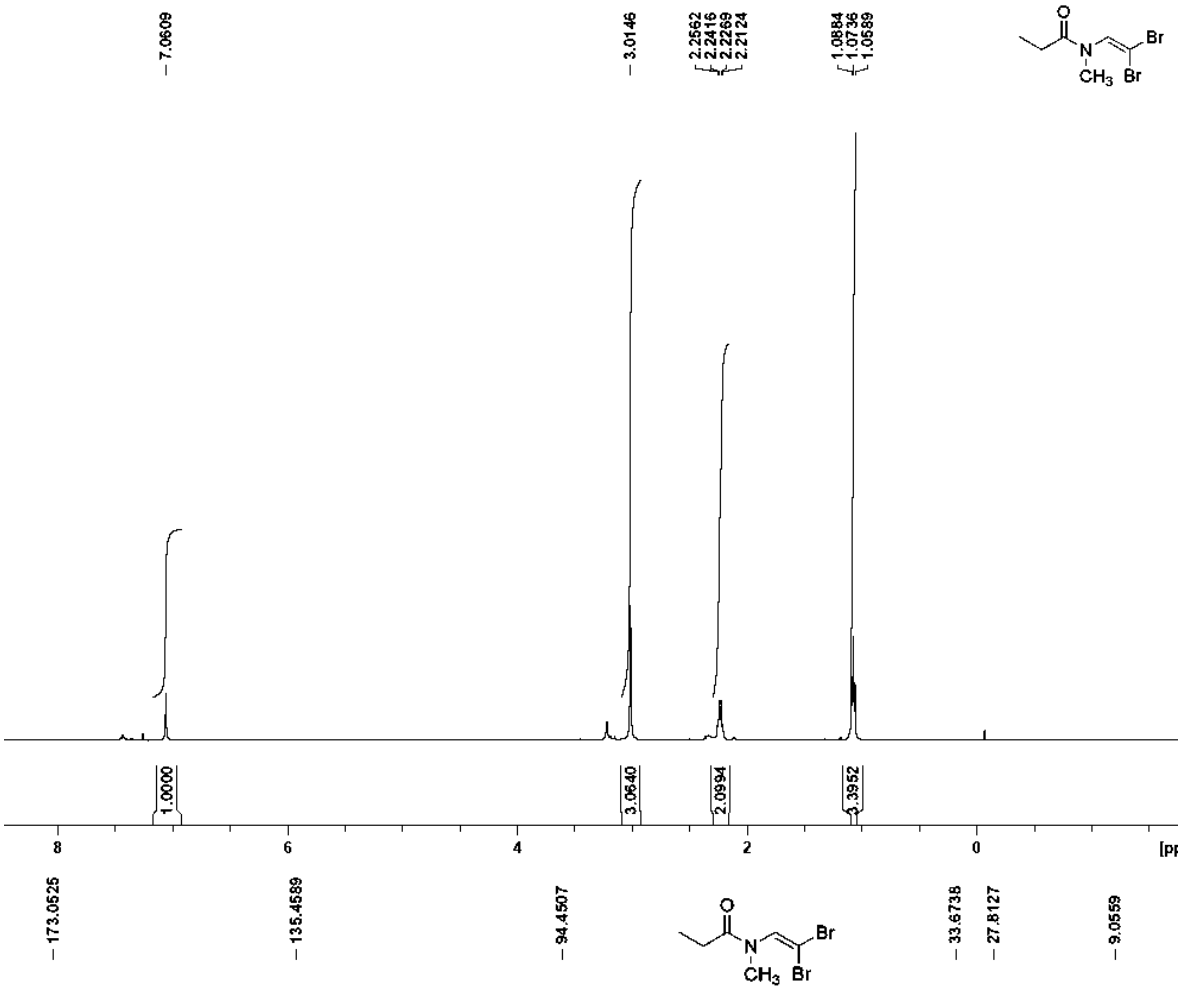


Appendix 11: ^{1}H and ^{13}C NMR spectra of compound **247**

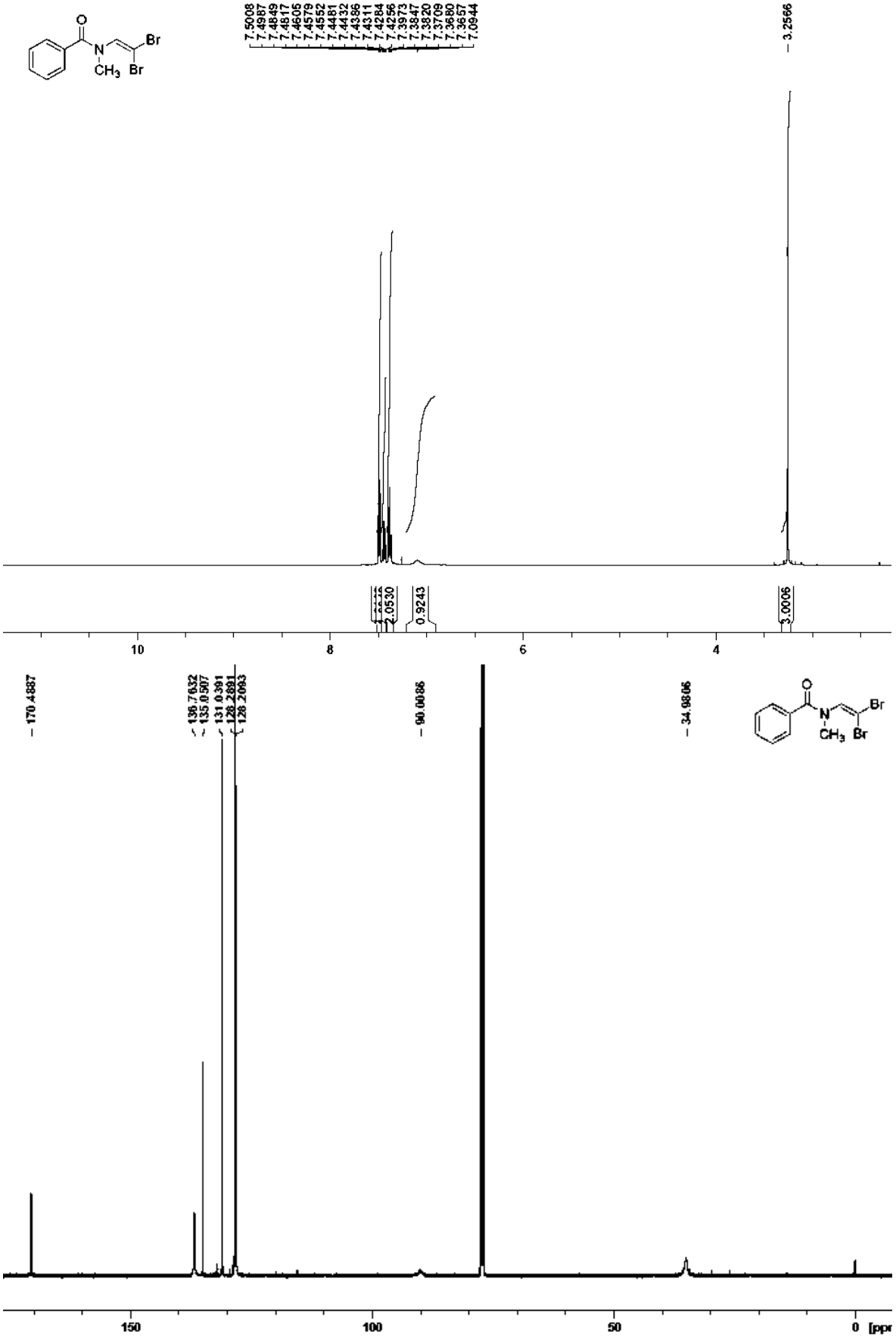




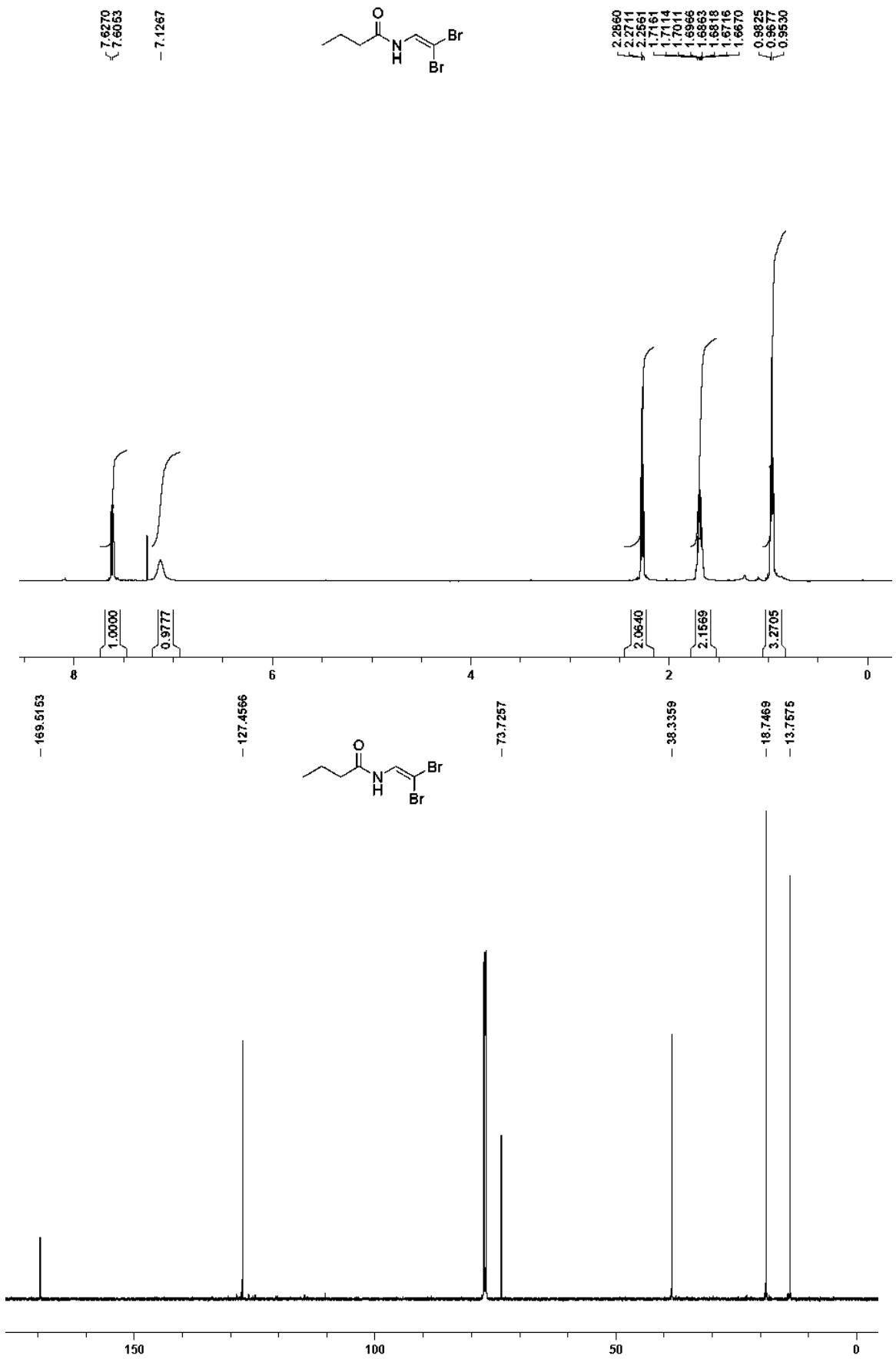
Appendix 12: ^{1}H and ^{13}C NMR spectra of compound **250**



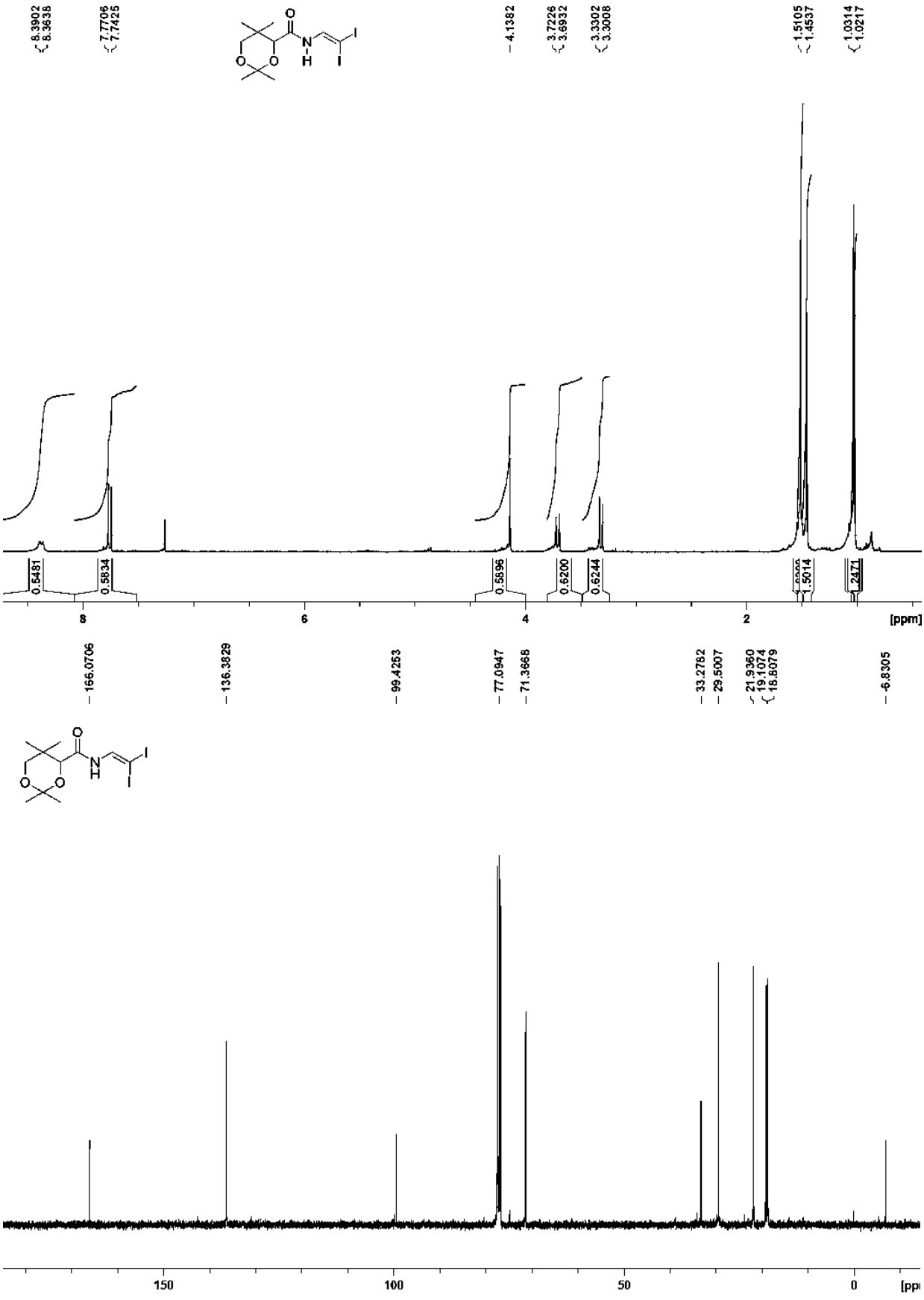
Appendix 13: ^{1}H and ^{13}C NMR spectra of compound **252**



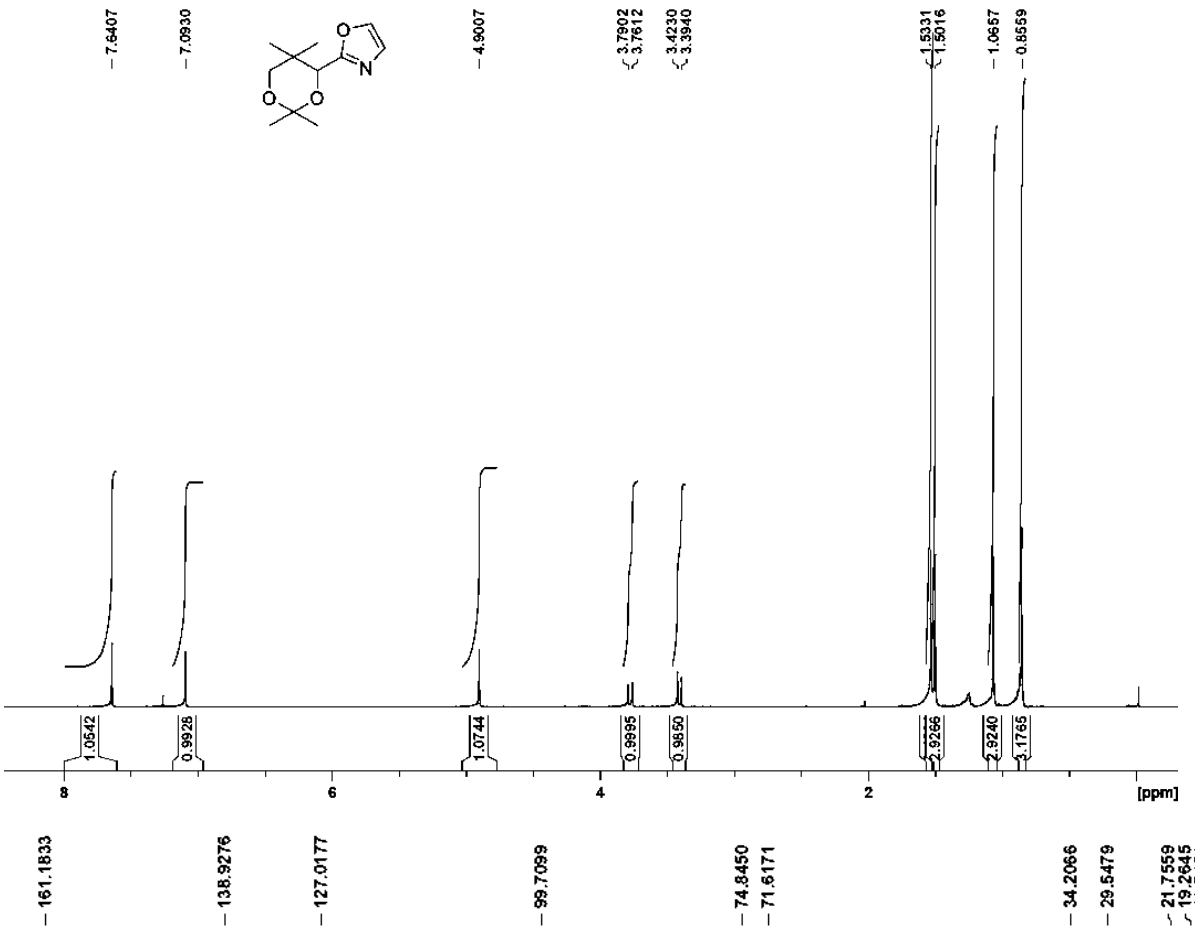
Appendix 14: ^{1}H and ^{13}C NMR spectra of compound **249**

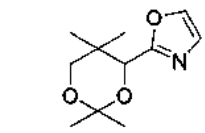


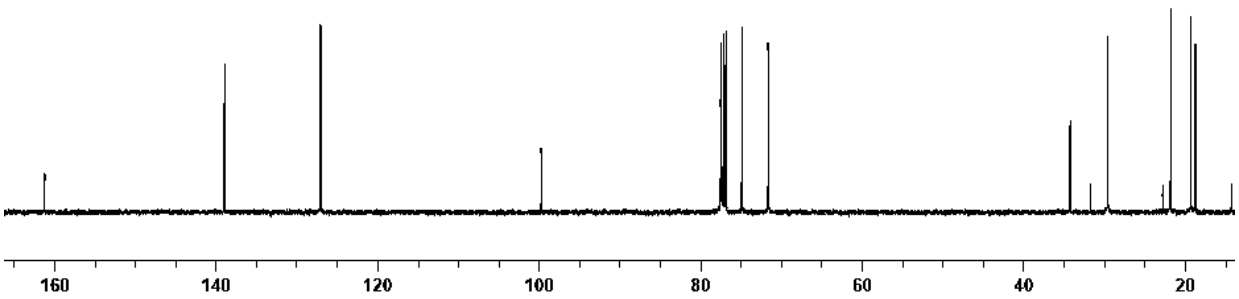
Appendix 15: ^{1}H and ^{13}C NMR spectra of compound **257**



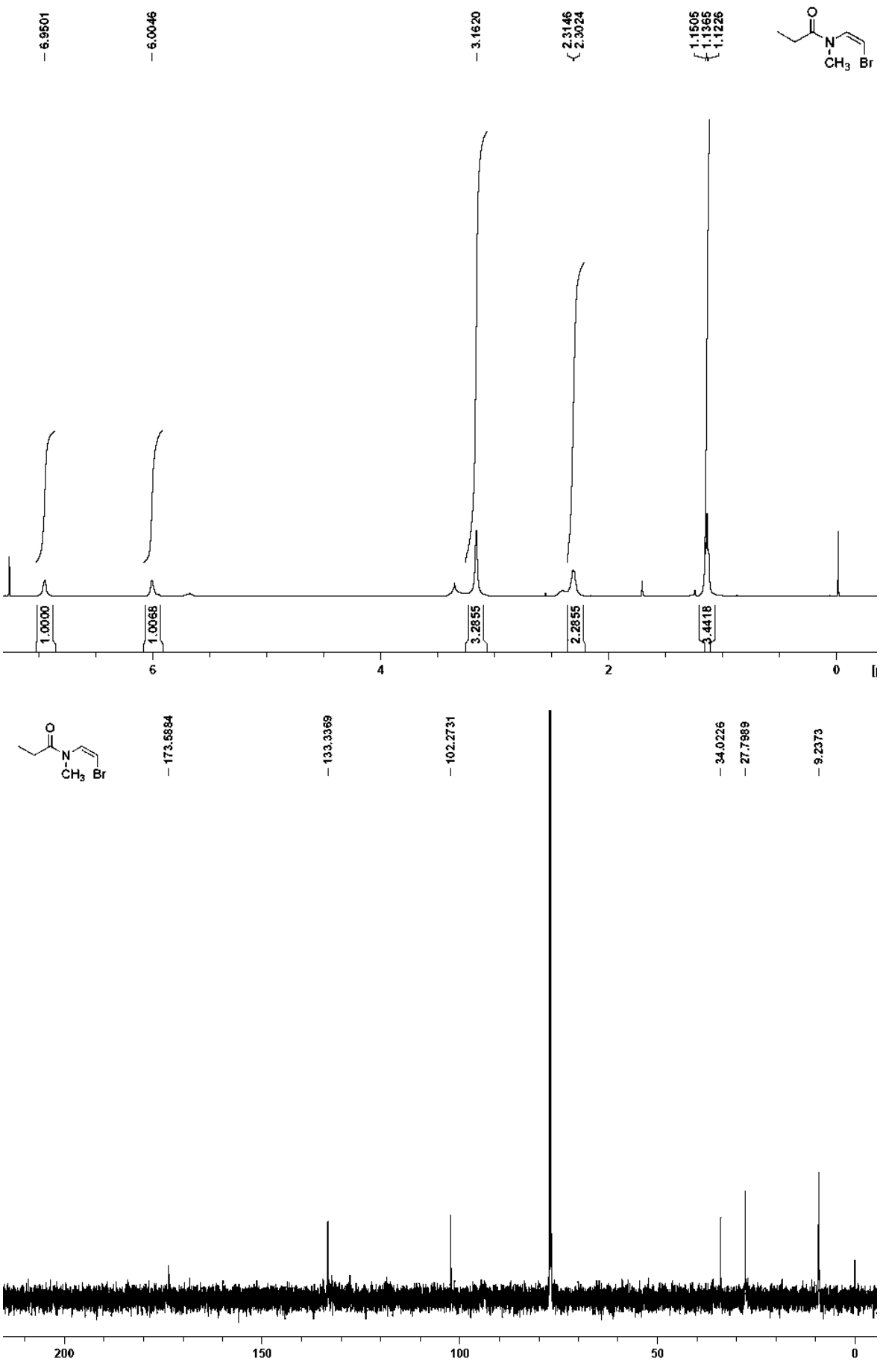
Appendix 16: ^{1}H and ^{13}C NMR spectra of compound **258**



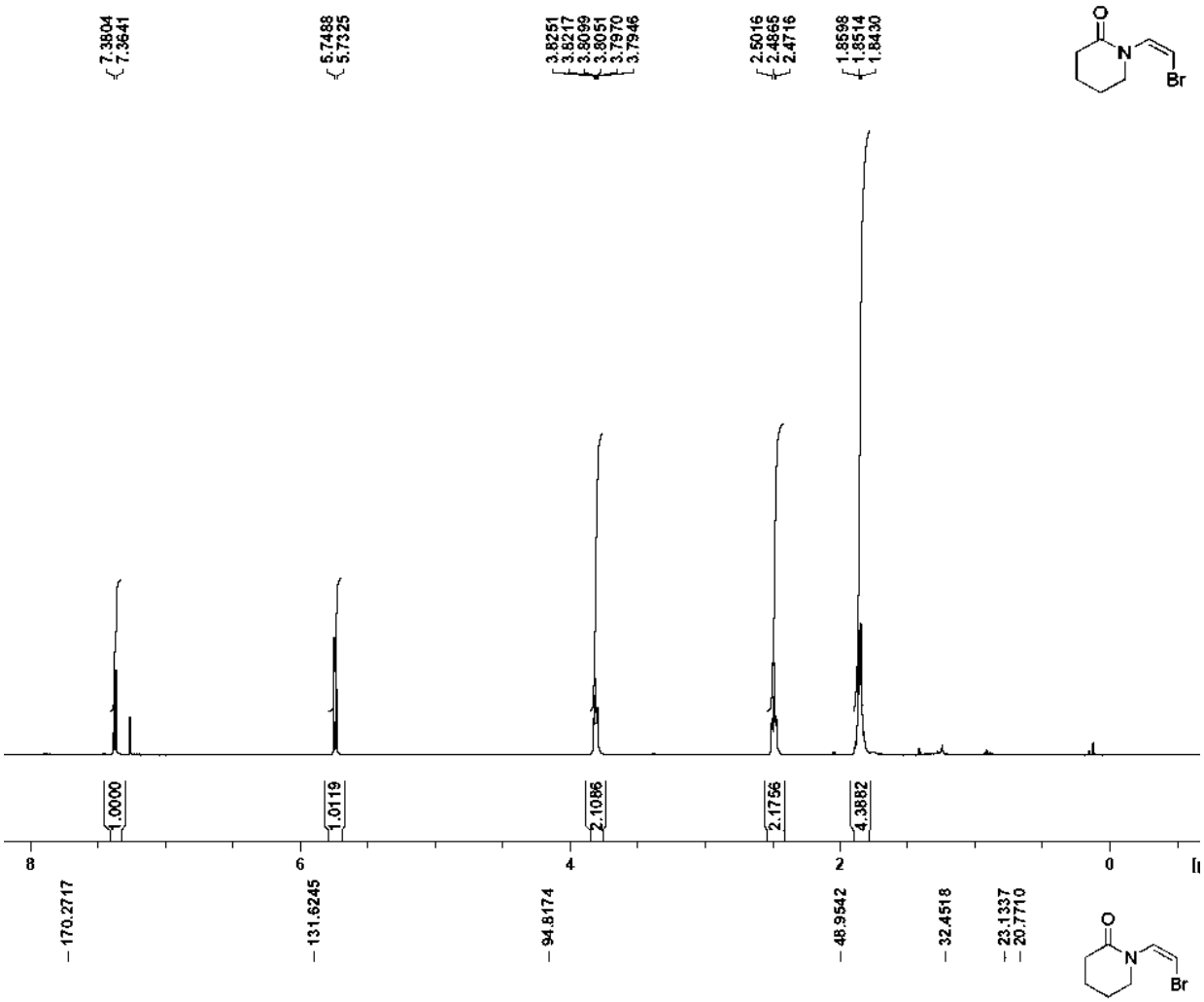


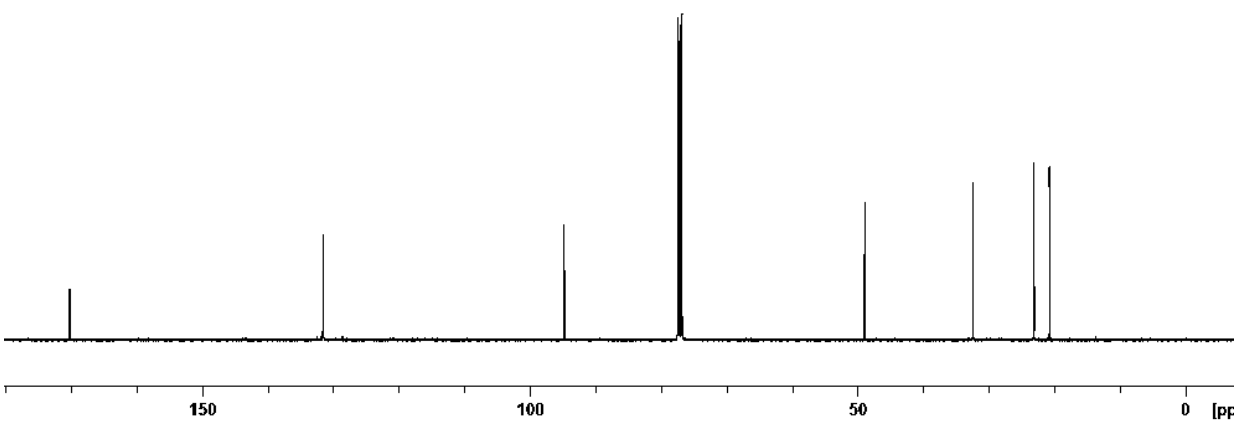


Appendix 17: ^{1}H and ^{13}C NMR spectra of compound **263**

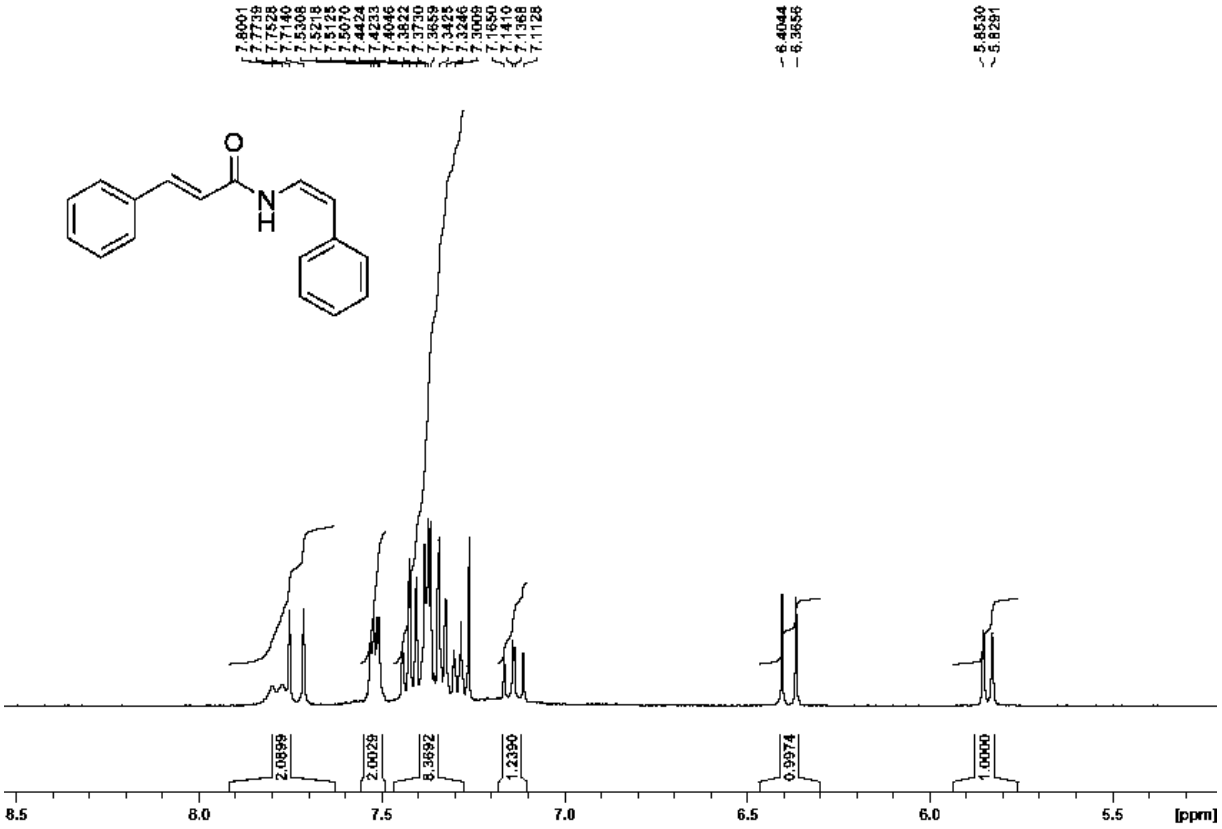


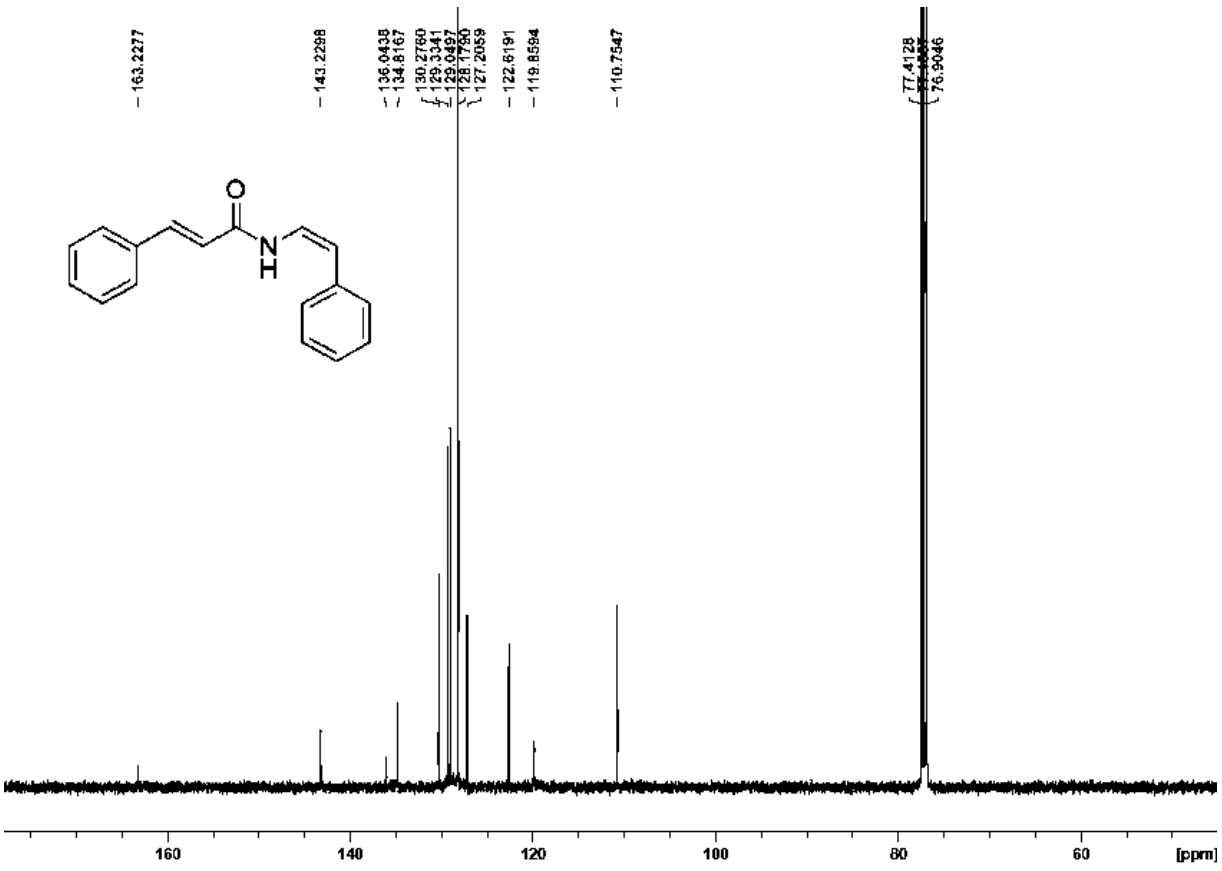
Appendix 18: ^{1}H and ^{13}C NMR spectra of compound **261**





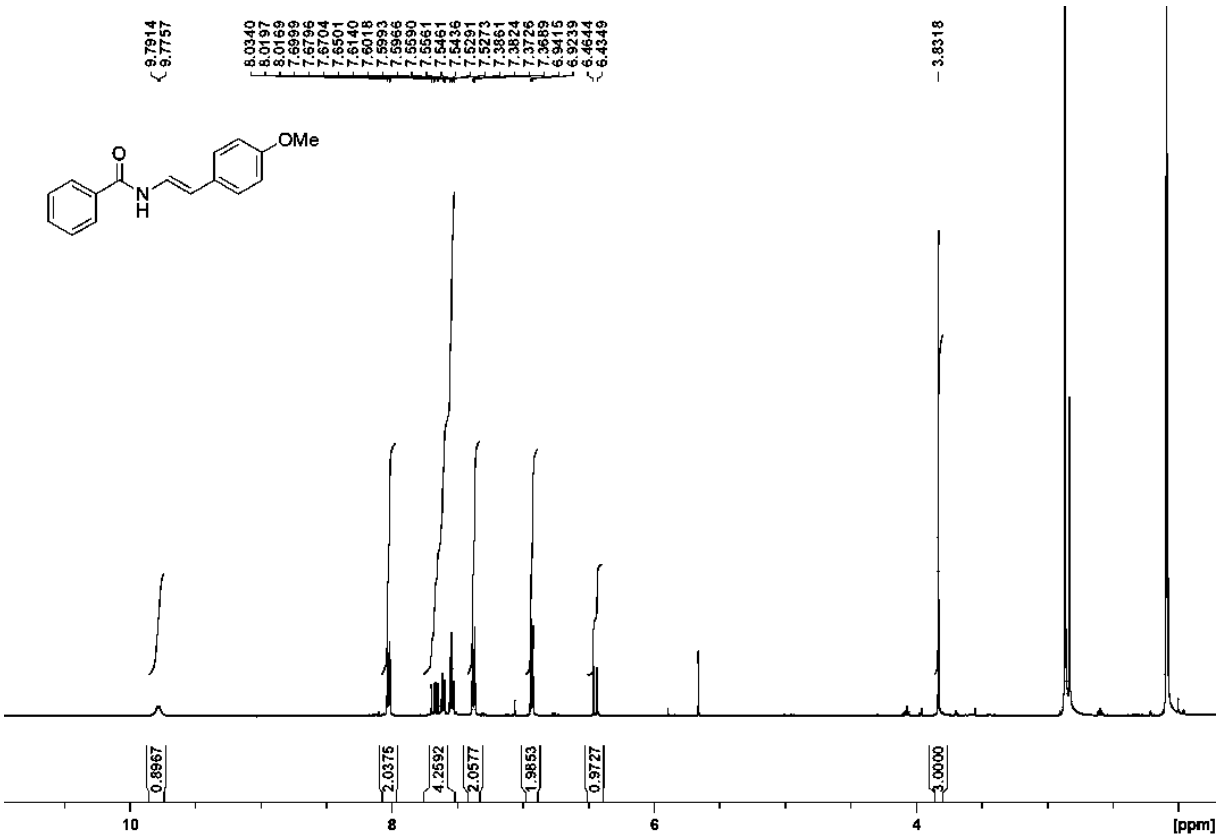
Appendix 19: ^{1}H and ^{13}C NMR spectra of compound **288**

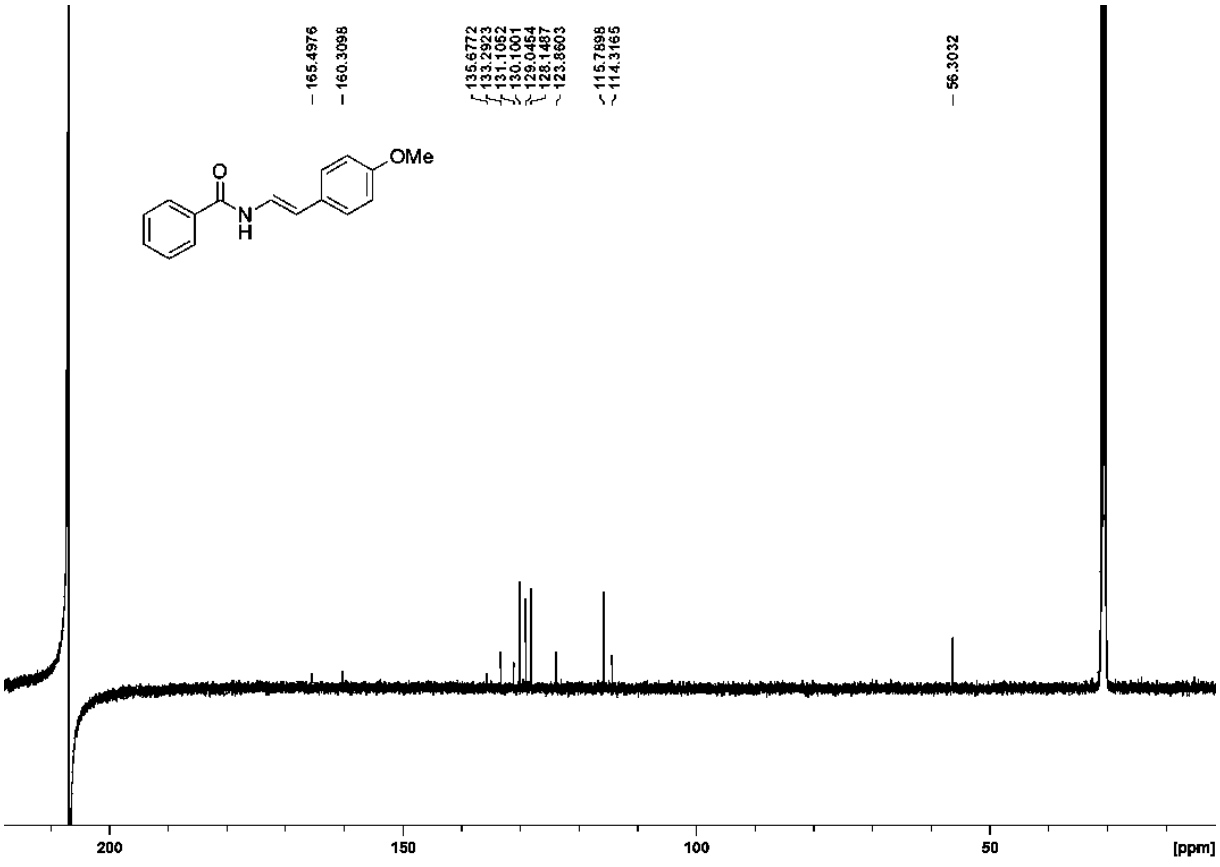




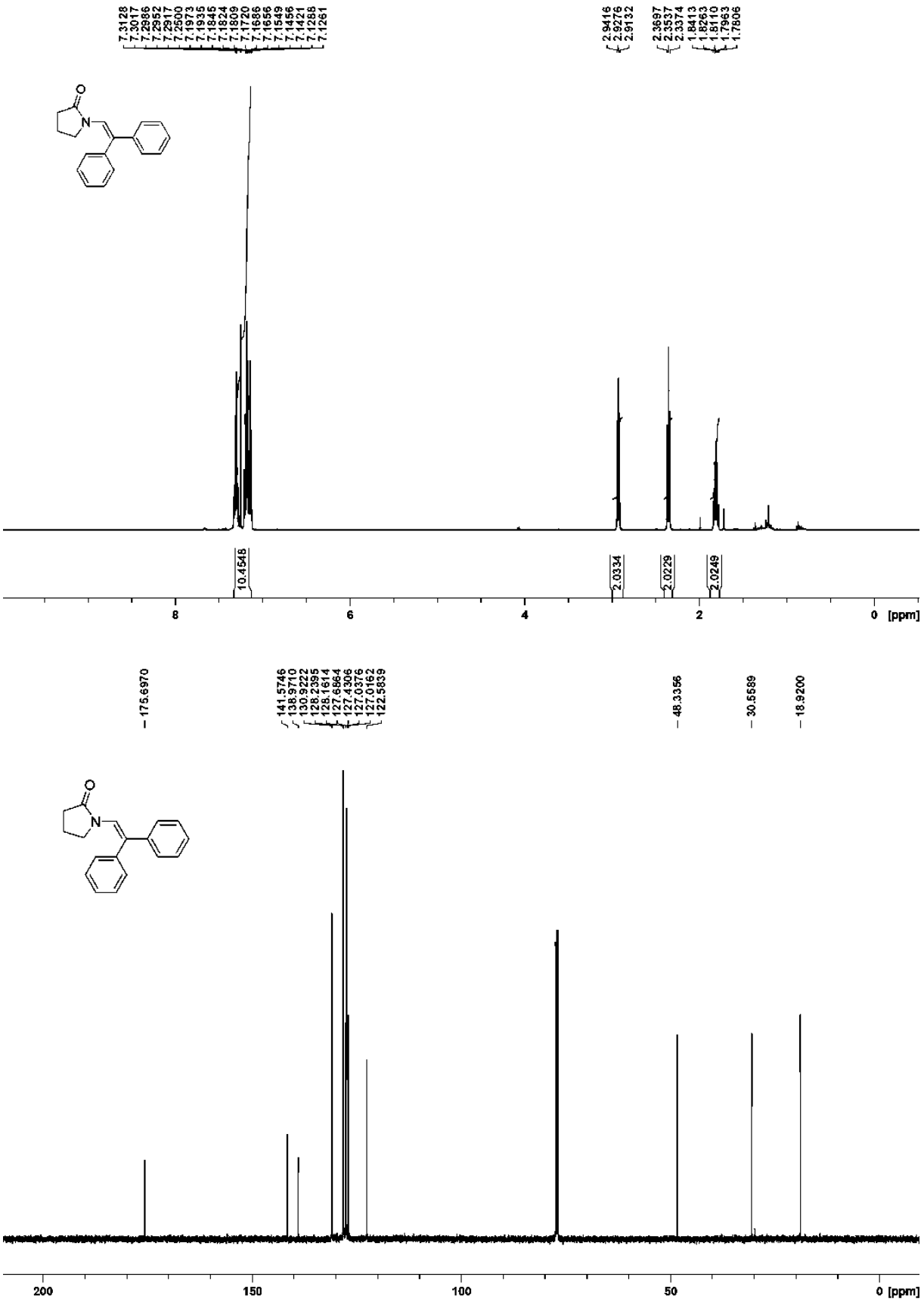
Appendix 20: ^{1}H and ^{13}C NMR spectra of compound **289**

Appendix 21: ^{1}H and ^{13}C NMR spectra of compound **290**

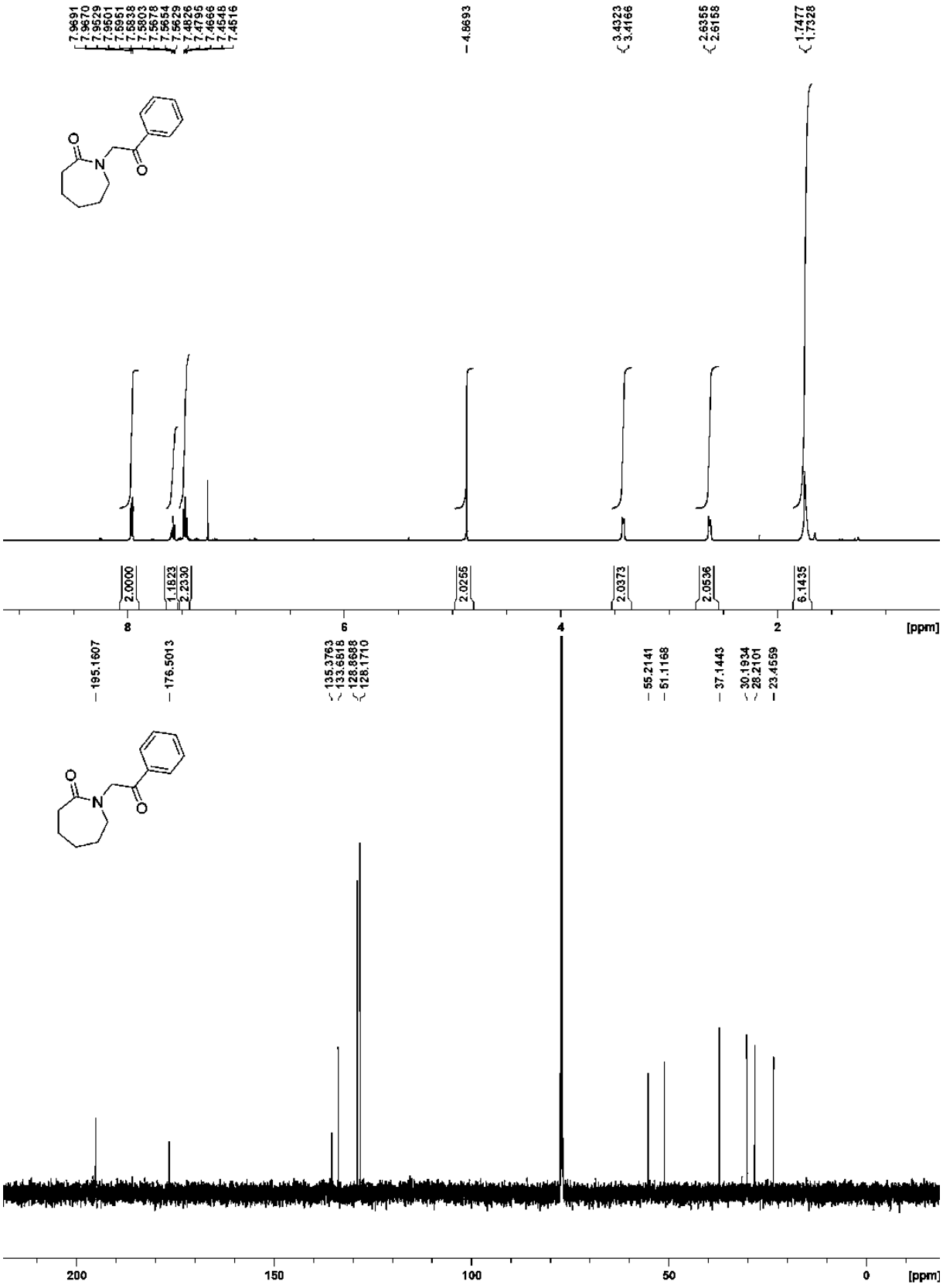




Appendix 22: ^{1}H and ^{13}C NMR spectra of compound **276**



Appendix 23: ^{1}H and ^{13}C NMR spectra of compound **279**



Appendix 24: X-ray crystallography of compound **219**

Table 1. Crystal data and structure refinement for compound 219.

Empirical formula	**C7 H10 I N O**
Formula weight	**251.06**
_cell_length_a	**10.2578(9)**
_cell_length_b	**15.9675(16)**
_cell_length_c	**9.9684(10)**
_cell_angle_alpha	**90**
_cell_angle_beta	**93.715(3)**
_cell_angle_gamma	**90**
_cell_volume	**1629.3(3)**
_cell_formula_units_Z	**8**
_cell_measurement_temperature	**100(2)**
_cell_measurement_reflns_used	**8841**
_cell_measurement_theta_min	**6.08**
_cell_measurement_theta_max	**55.17**
_exptl_crystal_description	**block**
_exptl_crystal_colour	**colourless**
_exptl_crystal_size_max	**0.3**
_exptl_crystal_size_mid	**0.2**
_exptl_crystal_size_min	**0.1**
_exptl_crystal_density_diffrn	**2.047**
_exptl_crystal_density_method	**'not measured'**
_exptl_crystal_F_000	**960**
_exptl_absorpt_coefficient_mu	**3.864**
_exptl_absorpt_correction_type	**multi-scan**
_exptl_absorpt_correction_T_min	**0.7004**
_exptl_absorpt_correction_T_max	**1.000**
_exptl_absorpt_process_details	**'CrystalClear 1.4.0 (Rigaku, 2008)'**
_diffrn_ambient_temperature	**100(2)**
_diffrn_radiation_type	**MoK\a**
_diffrn_radiation_wavelength	**0.71075**
_diffrn_radiation_monochromator	**graphite**
_diffrn_reflns_number	**10183**
_diffrn_reflns_av_R_equivalents	**0.035**
_diffrn_reflns_av_unetl/netl	**0.0271**
_diffrn_reflns_theta_min	**3.04**
_diffrn_reflns_theta_max	**27.47**
_diffrn_reflns_theta_full	**27.47**
_diffrn_measured_fraction_theta_max	**0.997**
_diffrn_measured_fraction_theta_full	**0.997**
_diffrn_reflns_limit_h_min	**-13**
_diffrn_reflns_limit_h_max	**13**
_diffrn_reflns_limit_k_min	**-20**
_diffrn_reflns_limit_k_max	**20**
_diffrn_reflns_limit_l_min	**-12**
_diffrn_reflns_limit_l_max	**12**
_reflns_number_total	**1873**
_reflns_number_gt	**1635**
_reflns_threshold_expression	**>2\s(I)**
_refine_ls_structure_factor_coef	**Fsqd**
_refine_ls_matrix_type	**full**
_refine_ls_R_factor_all	**0.0277**
_refine_ls_R_factor_gt	**0.0238**
_refine_ls_wR_factor_ref	**0.058**
_refine_ls_goodness_of_fit_ref	**1.231**

_refine_ls_restrained_S_all	1.231
_refine_ls_number_reflns	1873
_refine_ls_number_parameters	131
_refine_ls_number_restraints	0
_refine_ls_hydrogen_treatment	refall
_refine_ls_weighting_scheme	calc
_refine_ls_weighting_details	'calc w=1/[\s^2^(Fo^2^)+(0.0252P)^2^+1.7860P] where P=(Fo^2^+2Fc^2^)/3'
_refine_ls_shift/su_max	0.001
_refine_ls_shift/su_mean	0
_refine_diff_density_max	0.828
_refine_diff_density_min	-0.832
_refine_diff_density_rms	0.141
_refine_ls_extinction_method	none

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound 219. U(eq) is defined as one third of the trace of the orthogonalised Uij tensor.

	x	y	z	U(eq)
I1	0.698582(18)	-0.022335(11)	0.313183(18)	0.01739(8)
O1	0.6963(2)	0.31368(14)	0.2913(2)	0.0201(5)
N1	0.5777(2)	0.22957(15)	0.4200(2)	0.0151(5)
C4	0.4102(3)	0.29393(19)	0.5576(3)	0.0193(6)
C1	0.6178(3)	0.30692(18)	0.3780(3)	0.0156(6)
C3	0.4990(3)	0.37021(19)	0.5729(3)	0.0187(6)
C2	0.5598(3)	0.38404(18)	0.4392(3)	0.0181(6)
C6	0.6307(3)	0.15784(18)	0.3630(3)	0.0166(6)
C5	0.4886(3)	0.21642(18)	0.5294(3)	0.0188(6)
C7	0.6178(3)	0.08012(19)	0.4082(3)	0.0186(6)
H1	0.495(3)	0.402(2)	0.375(3)	0.013(8)
H5	0.342(3)	0.306(2)	0.490(3)	0.013(8)
H3	0.569(3)	0.360(2)	0.644(3)	0.017(8)
H8	0.543(3)	0.197(2)	0.609(3)	0.019(9)
H10	0.580(4)	0.066(3)	0.485(4)	0.029(10)
H6	0.368(3)	0.287(2)	0.631(4)	0.018(9)
H7	0.429(3)	0.171(2)	0.496(3)	0.020(9)
H9	0.677(3)	0.168(2)	0.295(3)	0.018(9)
H4	0.456(4)	0.420(3)	0.602(4)	0.030(10)
H2	0.631(3)	0.428(2)	0.446(3)	0.026(9)

Table 3. Bond lengths [A] and angles [deg] for compound 219.

I1 C7	**2.089(3)**
O1 C1	**1.224(4)**
N1 C1	**1.376(4)**
N1 C6	**1.404(4)**
N1 C5	**1.482(4)**
C4 C5	**1.512(4)**
C4 C3	**1.523(4)**
C4 H5	**0.96(3)**
C4 H6	**0.88(4)**
C1 C2	**1.513(4)**
C3 C2	**1.524(4)**
C3 H3	**0.99(3)**
C3 H4	**0.96(4)**
C2 H1	**0.94(3)**
C2 H2	**1.01(4)**
C6 C7	**1.330(4)**
C6 H9	**0.87(3)**
C5 H8	**0.99(3)**
C5 H7	**0.99(4)**
C7 H10	**0.91(4)**
C1 N1 C6	**118.5(2)**
C1 N1 C5	**124.2(3)**
C6 N1 C5	**117.1(2)**
C5 C4 C3	**110.6(3)**
C5 C4 H5	**114(2)**
C3 C4 H5	**109(2)**
C5 C4 H6	**110(2)**
C3 C4 H6	**110(2)**
H5 C4 H6	**104(3)**
O1 C1 N1	**121.2(3)**
O1 C1 C2	**120.5(3)**
N1 C1 C2	**118.3(3)**
C4 C3 C2	**107.7(3)**
C4 C3 H3	**110.5(19)**
C2 C3 H3	**108.9(19)**
C4 C3 H4	**114(2)**
C2 C3 H4	**111(2)**
H3 C3 H4	**104(3)**
C1 C2 C3	**115.4(2)**
C1 C2 H1	**105(2)**
C3 C2 H1	**110(2)**
C1 C2 H2	**107(2)**
C3 C2 H2	**112(2)**
H1 C2 H2	**108(3)**
C7 C6 N1	**125.0(3)**
C7 C6 H9	**121(2)**
N1 C6 H9	**114(3)**
N1 C5 C4	**112.4(3)**
N1 C5 H8	**106.9(19)**
C4 C5 H8	**113(2)**
N1 C5 H7	**105(2)**
C4 C5 H7	**109(2)**
H8 C5 H7	**110(3)**
C6 C7 I1	**121.7(2)**
C6 C7 H10	**125(3)**
I1 C7 H10	**113(3)**

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for compound 219.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U12	U13	U23
I1	0.01807(13)	0.01316(11)	0.02106(13)	0.00090(7)	0.00204(8)	-0.00199(7)
O1	0.0213(11)	0.0172(10)	0.0226(11)	-0.0004(8)	0.0083(9)	0.0015(8)
N1	0.0151(12)	0.0127(11)	0.0180(12)	0.0007(9)	0.0058(10)	0.0023(9)
C4	0.0208(16)	0.0185(14)	0.0194(15)	0.0008(12)	0.0068(13)	-0.0018(12)
C1	0.0156(14)	0.0156(13)	0.0153(14)	-0.0005(11)	-0.0009(11)	0.0023(11)
C3	0.0214(15)	0.0155(13)	0.0196(15)	0.0010(12)	0.0044(13)	-0.0023(11)
C2	0.0211(15)	0.0138(13)	0.0191(15)	-0.0001(12)	0.0002(13)	0.0009(12)
C6	0.0169(15)	0.0173(14)	0.0158(14)	-0.0009(12)	0.0032(12)	-0.0031(11)
C5	0.0226(16)	0.0147(13)	0.0199(15)	-0.0011(12)	0.0075(13)	0.0018(11)
C7	0.0200(15)	0.0171(14)	0.0188(15)	0.0015(12)	0.0027(12)	-0.0006(11)

Appendix 25: X-ray crystallography of compound **226**

Table 1. Crystal data and structure refinement for compound 226.

Empirical formula	**C15 H15 N O**
Formula weight	**225.28**
_cell_length_a	**11.5713(3)**
_cell_length_b	**8.1426(2)**
_cell_length_c	**12.6750(3)**
_cell_angle_alpha	**90**
_cell_angle_beta	**92.5340(10)**
_cell_angle_gamma	**90**
_cell_volume	**1193.08(5)**
_cell_formula_units_Z	**4**
_cell_measurement_temperature	**100(2)**
_exptl_crystal_density_diffrn	**1.254**
_exptl_crystal_density_method	**'not measured'**
_exptl_crystal_F_000	**480**
_exptl_absorpt_coefficient_mu	**0.078**
_exptl_absorpt_correction_type	**multi-scan**
_exptl_absorpt_process_details	**'SADABS, Bruker(2001)'**
_exptl_absorpt_correction_T_min	**0.4303**
_exptl_absorpt_correction_T_max	**0.7454**
_diffrn_ambient_temperature	**100(2)**
_diffrn_radiation_type	**MoK\a**
_diffrn_radiation_wavelength	**0.71073**
_diffrn_radiation_monochromator	**graphite**
_diffrn_measurement_device_type	**KappaCCD**
_diffrn_measurement_method	**'CCD; rotation images'**
_diffrn_reflns_number	**9801**
_diffrn_reflns_av_R_equivalents	**0.0816**
_diffrn_reflns_av_unetI/netI	**0.085**
_diffrn_reflns_theta_min	**1.76**
_diffrn_reflns_theta_max	**27.47**
_diffrn_reflns_theta_full	**27.47**
_diffrn_measured_fraction_theta_max	**0.998**
_diffrn_measured_fraction_theta_full	**0.998**
_diffrn_reflns_limit_h_min	**-15**
_diffrn_reflns_limit_h_max	**15**
_diffrn_reflns_limit_k_min	**-10**
_diffrn_reflns_limit_k_max	**10**
_diffrn_reflns_limit_l_min	**-16**
_diffrn_reflns_limit_l_max	**16**
_reflns_number_total	**2735**
_reflns_number_gt	**1590**
_reflns_threshold_expression	**>2\s(I)**
_refine_ls_structure_factor_coef	**Fsqd**
_refine_ls_matrix_type	**full**
_refine_ls_R_factor_all	**0.0991**
_refine_ls_R_factor_gt	**0.0416**
_refine_ls_wR_factor_ref	**0.0809**
_refine_ls_goodness_of_fit_ref	**0.917**
_refine_ls_restrained_S_all	**0.917**
_refine_ls_number_reflns	**2735**
_refine_ls_number_parameters	**214**
_refine_ls_number_restraints	**0**
_refine_ls_hydrogen_treatment	**refall**
_refine_ls_weighting_scheme	**calc**
_refine_ls_weighting_details	

'calc w=1/[\s^2^(Fo^2^)+(0.0297P)^2^+0.0000P] where P=(Fo^2^+2Fc^2^)/3'	
_refine_ls_shift/su_max	**0**
_refine_ls_shift/su_mean	**0**
_refine_diff_density_max	**0.183**
_refine_diff_density_min	**-0.207**
_refine_diff_density_rms	**0.039**
_refine_ls_extinction_method	**none**

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound 226. U(eq) is defined as one third of the trace of the orthogonalised Uij tensor.

	x	y	z	U(eq)
H9	0.6315(11)	0.1549(16)	0.5031(10)	0.022(4)
H1	0.3001(11)	0.3149(16)	0.6055(10)	0.028(4)
H14	1.1654(11)	-0.1034(16)	0.1760(11)	0.032(4)
H6	0.2080(12)	0.2277(15)	0.3294(10)	0.025(4)
H15	0.9714(12)	-0.0134(17)	0.1841(11)	0.030(4)
H8	0.4062(11)	0.2750(16)	0.3022(10)	0.026(4)
H10	0.5758(11)	0.0902(16)	0.2788(10)	0.028(4)
H11	0.9640(12)	-0.1754(17)	0.4890(10)	0.030(4)
H2	0.3495(11)	0.4894(17)	0.5817(10)	0.023(4)
H12	1.1614(12)	-0.2595(16)	0.4828(10)	0.026(4)
H4	0.2824(11)	0.4828(17)	0.4035(10)	0.029(4)
H13	1.2609(13)	-0.2209(17)	0.3252(10)	0.033(4)
H5	0.2408(11)	0.1347(17)	0.4415(10)	0.029(4)
H7	0.3977(11)	0.0829(17)	0.3300(10)	0.032(4)
H3	0.1767(12)	0.4175(16)	0.4700(9)	0.028(4)
N1	0.47280(10)	0.21927(13)	0.44771(8)	0.0220(3)
O1	0.53122(9)	0.32723(13)	0.60609(7)	0.0341(3)
C8	0.73551(13)	0.02119(17)	0.34543(10)	0.0239(4)
C9	0.83189(13)	-0.03234(18)	0.34102(10)	0.0249(4)
C12	1.12010(13)	-0.20986(17)	0.41955(12)	0.0270(4)
C1	0.45395(13)	0.30957(17)	0.53732(11)	0.0243(4)
C7	0.62187(12)	0.08902(18)	0.34784(11)	0.0245(4)
C5	0.38622(12)	0.1996(2)	0.35957(11)	0.0255(4)
C6	0.58223(13)	0.15113(18)	0.43706(11)	0.0237(4)
C13	1.17984(14)	-0.18802(18)	0.32840(12)	0.0281(4)
C11	1.00601(13)	-0.16192(18)	0.42405(12)	0.0260(4)
C2	0.33670(13)	0.3837(2)	0.55005(12)	0.0268(4)
C10	0.94954(12)	-0.08861(17)	0.33648(11)	0.0241(3)
C14	1.12404(13)	-0.11603(18)	0.24125(12)	0.0290(4)
C4	0.26460(13)	0.22897(19)	0.39344(12)	0.0273(4)
C15	1.01050(13)	-0.06593(19)	0.24468(12)	0.0282(4)
C3	0.25821(14)	0.39125(19)	0.45136(12)	0.0288(4)

Table 3. Bond lengths [A] and angles [deg] for compound 226.

N1 C1	**1.3784(17)**
N1 C6	**1.3944(17)**
N1 C5	**1.4760(17)**
O1 C1	**1.2292(16)**
C8 C9	**1.2010(19)**
C8 C7	**1.4278(19)**
C9 C10	**1.4399(19)**
C12 C11	**1.380(2)**
C12 C13	**1.384(2)**
C12 H12	**1.000(13)**
C1 C2	**1.500(2)**
C7 C6	**1.3383(19)**
C7 H10	**1.004(13)**
C5 C4	**1.508(2)**
C5 H8	**0.987(13)**
C5 H7	**1.033(14)**
C6 H9	**0.993(12)**
C13 C14	**1.385(2)**
C13 H13	**0.978(14)**
C11 C10	**1.3968(19)**
C11 H11	**0.980(13)**
C2 C3	**1.514(2)**
C2 H1	**1.007(13)**
C2 H2	**0.958(13)**
C10 C15	**1.3994(19)**
C14 C15	**1.378(2)**
C14 H14	**0.979(13)**
C4 C3	**1.515(2)**
C4 H6	**1.020(14)**
C4 H5	**1.025(13)**
C15 H15	**0.973(14)**
C3 H4	**1.008(14)**
C3 H3	**1.006(13)**
C1 N1 C6	**118.00(12)**
C1 N1 C5	**123.68(12)**
C6 N1 C5	**118.20(11)**
C9 C8 C7	**177.96(15)**
C8 C9 C10	**177.24(16)**
C11 C12 C13	**120.81(15)**
C11 C12 H12	**120.3(7)**
C13 C12 H12	**118.8(7)**
O1 C1 N1	**120.66(13)**
O1 C1 C2	**120.63(13)**
N1 C1 C2	**118.69(13)**
C6 C7 C8	**120.98(14)**
C6 C7 H10	**122.9(7)**
C8 C7 H10	**116.1(7)**
N1 C5 C4	**112.21(12)**
N1 C5 H8	**108.5(8)**
C4 C5 H8	**111.3(8)**
N1 C5 H7	**106.3(7)**
C4 C5 H7	**112.7(7)**
H8 C5 H7	**105.4(10)**
C7 C6 N1	**125.37(14)**
C7 C6 H9	**121.3(7)**
N1 C6 H9	**113.3(7)**
C12 C13 C14	**119.20(14)**
C12 C13 H13	**121.0(8)**
C14 C13 H13	**119.8(8)**
C12 C11 C10	**120.18(14)**

C12 C11 H11	120.9(8)
C10 C11 H11	118.9(8)
C1 C2 C3	116.09(13)
C1 C2 H1	105.2(8)
C3 C2 H1	110.1(8)
C1 C2 H2	106.4(8)
C3 C2 H2	112.6(8)
H1 C2 H2	105.7(10)
C11 C10 C15	118.80(14)
C11 C10 C9	120.94(13)
C15 C10 C9	120.23(13)
C15 C14 C13	120.78(15)
C15 C14 H14	119.9(8)
C13 C14 H14	119.3(8)
C5 C4 C3	110.01(13)
C5 C4 H6	110.2(7)
C3 C4 H6	110.5(7)
C5 C4 H5	109.2(7)
C3 C4 H5	110.2(7)
H6 C4 H5	106.6(10)
C14 C15 C10	120.23(15)
C14 C15 H15	121.1(8)
C10 C15 H15	118.7(8)
C2 C3 C4	108.94(13)
C2 C3 H4	110.8(8)
C4 C3 H4	109.4(8)
C2 C3 H3	110.4(7)
C4 C3 H3	111.4(8)
H4 C3 H3	105.8(11)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for compound 226.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U12	U13	U23
N1	0.0215(7)	0.0241(7)	0.0203(6)	0.0005(6)	0.0001(5)	0.0003(5)
O1	0.0302(6)	0.0445(7)	0.0274(6)	0.0003(5)	-0.0028(5)	-0.0083(5)
C8	0.0274(9)	0.0234(9)	0.0209(8)	-0.0004(7)	0.0015(6)	0.0018(6)
C9	0.0307(9)	0.0230(9)	0.0209(8)	-0.0016(7)	0.0007(7)	0.0006(6)
C12	0.0295(9)	0.0211(9)	0.0300(9)	0.0029(7)	-0.0041(7)	-0.0029(7)
C1	0.0266(9)	0.0236(9)	0.0231(8)	-0.0044(7)	0.0031(7)	0.0008(7)
C7	0.0241(9)	0.0252(9)	0.0241(8)	0.0012(7)	0.0002(7)	0.0031(7)
C5	0.0235(9)	0.0285(10)	0.0243(8)	0.0011(7)	-0.0015(7)	0.0006(7)
C6	0.0240(9)	0.0226(9)	0.0243(8)	-0.0003(7)	-0.0007(7)	0.0031(7)
C13	0.0231(9)	0.0249(9)	0.0360(9)	0.0020(7)	0.0003(7)	-0.0079(7)
C11	0.0287(9)	0.0224(9)	0.0269(8)	-0.0002(7)	0.0022(7)	-0.0027(7)
C2	0.0276(9)	0.0226(10)	0.0306(9)	-0.0006(7)	0.0057(7)	-0.0030(7)
C10	0.0236(9)	0.0204(8)	0.0281(8)	0.0005(7)	0.0008(6)	-0.0033(7)
C14	0.0274(9)	0.0314(10)	0.0288(9)	-0.0009(7)	0.0063(7)	-0.0034(7)
C4	0.0248(9)	0.0283(10)	0.0285(9)	0.0018(8)	-0.0022(7)	0.0004(7)
C15	0.0294(9)	0.0267(9)	0.0285(9)	0.0012(8)	-0.0007(7)	-0.0001(7)
C3	0.0238(9)	0.0270(9)	0.0358(9)	0.0009(7)	0.0026(7)	0.0012(8)

Appendix 26: X-ray crystallography of compound **253**

Table 1. Crystal data and structure refinement for compound 253

Empirical formula	**C8 H11 I2 N O**	
Formula weight	**390.98**	
Temperature	**150(2) K**	
Wavelength	**0.71073 A**	
Crystal system, space group	**Monoclinic, P2(1)/c**	
Unit cell dimensions	**a = 6.9197(2) A** **b = 14.4321(4) A** **c = 10.8204(4) A**	**alpha = 90 deg.** **beta = 100.536(3) deg.** **gamma = 90 deg.**
Volume	**1062.37(6) A^3**	
Z, Calculated density	**4, 2.444 Mg/m^3**	
Absorption coefficient	**5.88 mm^-1**	
F(000)	**720**	
Crystal size	**0.21 x 0.07 x 0.03 mm**	
Theta range for data collection	**2.99 to 26.00 deg.**	
Limiting indices	**-8<=h<=8, -17<=k<=17, -12<=l<=13**	
Reflections collected / unique	**8621 / 2085 [R(int) = 0.0456]**	
Completeness to theta = 26.00	**99.6 %**	
Absorption correction	**Analytical**	
Max. and min. transmission	**0.828 and 0.513**	
Refinement method	**Full-matrix least-squares on F^2**	
Data / restraints / parameters	**2085 / 0 / 109**	
Goodness-of-fit on F^2	**1.046**	
Final R indices [I>2sigma(I)]	**R1 = 0.0248, wR2 = 0.0407**	
R indices (all data)	**R1 = 0.0345, wR2 = 0.0440**	
Extinction coefficient	**none**	
Largest diff. peak and hole	**0.62 and -0.60 e.A^-3**	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound 253. U(eq) is defined as one third of the trace of the orthogonalised Uij tensor.

	x	y	z	U(eq)
I(1)	4014(1)	5775(1)	8249(1)	23(1)
I(2)	7529(1)	4022(1)	7894(1)	24(1)
O(1)	10647(4)	7217(2)	8360(3)	24(1)
N(1)	8369(4)	6791(2)	9500(3)	17(1)
C(1)	9728(5)	7401(3)	9193(4)	19(1)
C(2)	9973(6)	8304(3)	9888(4)	24(1)
C(3)	8148(6)	8931(3)	9578(4)	26(1)
C(4)	6633(6)	8727(3)	10399(4)	27(1)
C(5)	5772(5)	7757(3)	10235(4)	25(1)
C(6)	7252(6)	6969(3)	10516(4)	22(1)
C(7)	8442(5)	5885(3)	9008(4)	17(1)
C(8)	6941(5)	5344(3)	8529(4)	18(1)

Table 3. Bond lengths [A] and angles [deg] for compound 253.

I(1)-C(8)	2.087(4)
I(2)-C(8)	2.093(4)
O(1)-C(1)	1.223(5)
N(1)-C(1)	1.372(5)
N(1)-C(7)	1.416(5)
N(1)-C(6)	1.477(5)
C(1)-C(2)	1.499(5)
C(2)-C(3)	1.540(5)
C(3)-C(4)	1.522(6)
C(4)-C(5)	1.518(5)
C(5)-C(6)	1.524(5)
C(7)-C(8)	1.327(5)
C(1)-N(1)-C(7)	115.4(3)
C(1)-N(1)-C(6)	122.9(3)
C(7)-N(1)-C(6)	120.0(3)
O(1)-C(1)-N(1)	120.7(4)
O(1)-C(1)-C(2)	122.1(4)
N(1)-C(1)-C(2)	117.1(4)
C(1)-C(2)-C(3)	112.8(3)
C(4)-C(3)-C(2)	112.6(3)
C(5)-C(4)-C(3)	114.1(4)
C(4)-C(5)-C(6)	115.5(3)
N(1)-C(6)-C(5)	113.9(3)
C(8)-C(7)-N(1)	127.7(3)
C(7)-C(8)-I(1)	123.4(3)
C(7)-C(8)-I(2)	118.7(3)
I(1)-C(8)-I(2)	117.76(18)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for compound 253.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
I(1)	17(1)	26(1)	26(1)	-1(1)	4(1)	1(1)
I(2)	27(1)	18(1)	26(1)	-3(1)	3(1)	3(1)
O(1)	21(1)	26(2)	28(2)	2(1)	11(1)	1(1)
N(1)	18(2)	16(2)	18(2)	1(2)	5(1)	2(1)
C(1)	16(2)	19(2)	20(3)	7(2)	0(2)	6(2)
C(2)	27(2)	21(2)	26(3)	-2(2)	7(2)	-7(2)
C(3)	34(2)	17(2)	27(3)	1(2)	5(2)	2(2)
C(4)	32(2)	20(2)	29(3)	-1(2)	8(2)	1(2)
C(5)	25(2)	25(2)	27(3)	1(2)	9(2)	3(2)
C(6)	26(2)	24(2)	19(2)	-2(2)	8(2)	-2(2)
C(7)	18(2)	18(2)	17(2)	2(2)	5(2)	4(2)
C(8)	19(2)	16(2)	19(2)	1(2)	7(2)	5(2)

Appendix 27: X-ray crystallography of compound **257**

Table 1. Crystal data and structure refinement for compound 257.

Empirical formula	**C11 H17 I2 N O3**
Formula weight	**465.06**
Temperature	**150(2) K**
Wavelength	**0.71073 A**
Crystal system, space group	**Orthorhombic, P2(1)2(1)2(1)**
Unit cell dimensions	**a = 7.9762(2) A alpha = 90 deg.** **b = 13.5692(5) A beta = 90 deg.** **c = 14.1525(5) A gamma = 90 deg.**
Volume	**1531.73(9) A^3**
Z, Calculated density	**4, 2.017 Mg/m^3**
Absorption coefficient	**4.104 mm^-1**
F(000)	**880**
Crystal size	**0.24 x 0.24 x 0.07 mm**
Theta range for data collection	**2.88 to 26.00 deg.**
Limiting indices	**-9<=h<=9, -16<=k<=16, -17<=l<=17**
Reflections collected / unique	**13046 / 2996 [R(int) = 0.0428]**
Completeness to theta = 26.00	**99.8 %**
Absorption correction	**Analytical**
Max. and min. transmission	**0.770 and 0.466**
Refinement method	**Full-matrix least-squares on F^2**
Data / restraints / parameters	**2996 / 1 / 161**
Goodness-of-fit on F^2	**1.027**
Final R indices [I>2sigma(I)]	**R1 = 0.0227, wR2 = 0.0452**
R indices (all data)	**R1 = 0.0257, wR2 = 0.0463**
Absolute structure parameter	**-0.01(3)**
Extinction coefficient	**none**
Largest diff. peak and hole	**0.37 and -0.58 e.A^-3**

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound 257. U(eq) is defined as one third of the trace of the orthogonalised Uij tensor.

	x	y	z	U(eq)
I(1)	7373(1)	2863(1)	4421(1)	24(1)
I(2)	7326(1)	254(1)	4291(1)	23(1)
O(1)	7454(4)	3909(2)	7427(2)	22(1)
O(2)	8280(3)	5159(2)	8461(2)	24(1)
O(3)	8095(4)	1411(2)	8010(2)	38(1)
C(1)	7650(5)	3150(3)	8123(2)	20(1)
C(2)	9047(4)	3448(3)	8824(3)	19(1)
C(3)	8533(5)	4456(3)	9194(3)	24(1)
C(4)	7056(5)	4863(3)	7786(3)	24(1)
C(5)	9130(5)	2742(4)	9665(3)	28(1)
C(6)	10736(5)	3505(4)	8323(3)	28(1)
C(7)	7234(6)	5560(3)	6956(3)	31(1)
C(8)	5290(5)	4893(4)	8197(3)	33(1)
C(9)	7923(5)	2192(3)	7596(3)	24(1)
C(10)	7873(4)	1458(3)	6041(2)	18(1)
C(11)	7617(5)	1510(3)	5117(2)	19(1)
N(1)	7919(4)	2264(3)	6640(2)	21(1)

Table 3. Bond lengths [A] and angles [deg] for compound 257

I(1)-C(11)	**2.093(4)**
I(2)-C(11)	**2.080(4)**
O(1)-C(4)	**1.426(5)**
O(1)-C(1)	**1.434(4)**
O(2)-C(3)	**1.423(5)**
O(2)-C(4)	**1.424(4)**
O(3)-C(9)	**1.219(5)**
C(1)-C(9)	**1.515(5)**
C(1)-C(2)	**1.546(5)**
C(1)-H(1)	**1.0000**
C(2)-C(3)	**1.522(6)**
C(2)-C(6)	**1.524(5)**
C(2)-C(5)	**1.530(5)**
C(3)-H(3A)	**0.9900**
C(3)-H(3B)	**0.9900**
C(4)-C(7)	**1.514(6)**
C(4)-C(8)	**1.524(5)**
C(5)-H(5A)	**0.9800**
C(5)-H(5B)	**0.9800**
C(5)-H(5C)	**0.9800**
C(6)-H(6A)	**0.9800**
C(6)-H(6B)	**0.9800**
C(6)-H(6C)	**0.9800**
C(7)-H(7A)	**0.9800**
C(7)-H(7B)	**0.9800**
C(7)-H(7C)	**0.9800**
C(8)-H(8A)	**0.9800**
C(8)-H(8B)	**0.9800**
C(8)-H(8C)	**0.9800**
C(9)-N(1)	**1.356(5)**
C(10)-C(11)	**1.326(5)**
C(10)-N(1)	**1.384(5)**
C(10)-H(10)	**0.9500**
N(1)-H(1A)	**0.850(18)**
C(4)-O(1)-C(1)	**115.6(2)**
C(3)-O(2)-C(4)	**113.4(3)**
O(1)-C(1)-C(9)	**107.1(3)**
O(1)-C(1)-C(2)	**109.3(3)**

C(9)-C(1)-C(2)	**115.9(3)**
O(1)-C(1)-H(1)	**108.1**
C(9)-C(1)-H(1)	**108.1**
C(2)-C(1)-H(1)	**108.1**
C(3)-C(2)-C(6)	**110.7(4)**
C(3)-C(2)-C(5)	**107.9(3)**
C(6)-C(2)-C(5)	**110.8(3)**
C(3)-C(2)-C(1)	**105.2(3)**
C(6)-C(2)-C(1)	**110.6(3)**
C(5)-C(2)-C(1)	**111.5(3)**
O(2)-C(3)-C(2)	**112.9(3)**
O(2)-C(3)-H(3A)	**109.0**
C(2)-C(3)-H(3A)	**109.0**
O(2)-C(3)-H(3B)	**109.0**
C(2)-C(3)-H(3B)	**109.0**
H(3A)-C(3)-H(3B)	**107.8**
O(2)-C(4)-O(1)	**110.0(3)**
O(2)-C(4)-C(7)	**106.3(3)**
O(1)-C(4)-C(7)	**105.6(3)**
O(2)-C(4)-C(8)	**111.7(3)**
O(1)-C(4)-C(8)	**111.4(3)**
C(7)-C(4)-C(8)	**111.5(4)**
C(2)-C(5)-H(5A)	**109.5**
C(2)-C(5)-H(5B)	**109.5**
H(5A)-C(5)-H(5B)	**109.5**
C(2)-C(5)-H(5C)	**109.5**
H(5A)-C(5)-H(5C)	**109.5**
H(5B)-C(5)-H(5C)	**109.5**
C(2)-C(6)-H(6A)	**109.5**
C(2)-C(6)-H(6B)	**109.5**
H(6A)-C(6)-H(6B)	**109.5**
C(2)-C(6)-H(6C)	**109.5**
H(6A)-C(6)-H(6C)	**109.5**
H(6B)-C(6)-H(6C)	**109.5**
C(4)-C(7)-H(7A)	**109.5**
C(4)-C(7)-H(7B)	**109.5**
H(7A)-C(7)-H(7B)	**109.5**
C(4)-C(7)-H(7C)	**109.5**
H(7A)-C(7)-H(7C)	**109.5**
H(7B)-C(7)-H(7C)	**109.5**
C(4)-C(8)-H(8A)	**109.5**

C(4)-C(8)-H(8B)	**109.5**
H(8A)-C(8)-H(8B)	**109.5**
C(4)-C(8)-H(8C)	**109.5**
H(8A)-C(8)-H(8C)	**109.5**
H(8B)-C(8)-H(8C)	**109.5**
O(3)-C(9)-N(1)	**122.9(4)**
O(3)-C(9)-C(1)	**121.7(3)**
N(1)-C(9)-C(1)	**115.4(4)**
C(11)-C(10)-N(1)	**124.5(4)**
C(11)-C(10)-H(10)	**117.8**
N(1)-C(10)-H(10)	**117.8**
C(10)-C(11)-I(2)	**121.9(3)**
C(10)-C(11)-I(1)	**121.7(3)**
I(2)-C(11)-I(1)	**116.39(15)**
C(9)-N(1)-C(10)	**123.6(4)**
C(9)-N(1)-H(1A)	**116(3)**
C(10)-N(1)-H(1A)	**118(3)**

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for compound 257.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
I(1)	33(1)	19(1)	21(1)	4(1)	-2(1)	1(1)
I(2)	31(1)	19(1)	19(1)	-3(1)	-3(1)	1(1)
O(1)	32(2)	18(1)	17(1)	0(1)	-2(2)	-1(2)
O(2)	28(1)	19(2)	24(2)	-7(1)	-6(1)	1(1)
O(3)	78(2)	20(2)	17(2)	3(1)	-7(2)	-5(2)
C(1)	24(2)	23(2)	12(2)	0(2)	4(2)	-4(2)
C(2)	22(2)	19(2)	17(2)	0(2)	-1(2)	-1(2)
C(3)	28(2)	29(3)	15(2)	-4(2)	-7(2)	-2(2)
C(4)	27(2)	22(3)	22(2)	-5(2)	-5(2)	3(2)
C(5)	37(2)	31(3)	17(2)	4(2)	-7(2)	-3(2)
C(6)	27(2)	31(3)	26(2)	-3(2)	0(2)	1(2)
C(7)	48(3)	20(2)	26(2)	2(2)	-7(2)	4(2)
C(8)	26(2)	45(3)	28(2)	-8(2)	-4(2)	8(2)
C(9)	29(2)	24(3)	18(2)	-2(2)	0(2)	-4(2)
C(10)	22(2)	12(2)	20(2)	1(2)	0(2)	-2(2)
C(11)	23(2)	14(2)	19(2)	-2(1)	0(2)	1(3)
N(1)	32(2)	14(2)	15(2)	1(1)	0(1)	0(2)

Appendix 28: X-ray crystallography of compound **258**

Table 1. Crystal data and structure refinement for compound 258.

Empirical formula	**C11 H17 N O3**	
Formula weight	**211.26**	
Temperature	**150(2) K**	
Wavelength	**0.71073 A**	
Crystal system, space group	**Triclinic, P-1**	
Unit cell dimensions	**a = 5.8915(4) A** **b = 6.4911(4) A** **c = 8.4228(5) A**	**alpha = 107.971(6) deg.** **beta = 101.168(6) deg.** **gamma =105.691(6)deg.**
Volume	**281.14(3) A^3**	
Z, Calculated density	**1, 1.248 Mg/m^3**	
Absorption coefficient	**0.090 mm^-1**	
F(000)	**114**	
Crystal size	**0.33 x 0.17 x 0.13 mm**	
Theta range for data collection	**3.52 to 25.69 deg.**	
Limiting indices	**-7<=h<=7, -7<=k<=7, -10<=l<=10**	
Reflections collected / unique	**4450 / 2052 [R(int) = 0.0397]**	
Completeness to theta = 25.69	**99.6 %**	
Absorption correction	**Analytical**	
Max. and min. transmission	**0.990 and 0.978**	
Refinement method	**Full-matrix least-squares on F^2**	
Data / restraints / parameters	**2052 / 3 / 141**	
Goodness-of-fit on F^2	**1.026**	
Final R indices [I>2sigma(I)]	**R1 = 0.0473, wR2 = 0.0920**	
R indices (all data)	**R1 = 0.0680, wR2 = 0.1022**	
Absolute structure parameter	**0.4(13)**	
Extinction coefficient	**none**	
Largest diff. peak and hole	**0.15 and -0.21 e.A^-3**	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound 258. U(eq) is defined as one third of the trace of the orthogonalised Uij tensor.

	x	y	z	U(eq)
O(1)	6372(3)	6651(3)	7835(2)	27(1)
C(1)	6426(4)	8293(4)	9433(3)	25(1)
C(5)	6476(5)	12309(5)	10936(3)	34(1)
C(3)	4682(5)	10217(5)	7725(3)	33(1)
O(2)	4661(3)	8464(3)	6182(2)	34(1)
C(2)	6757(4)	10668(4)	9302(3)	24(1)
C(4)	4435(5)	6318(4)	6343(3)	29(1)
O(3)	8051(3)	8614(3)	12411(2)	40(1)
C(8)	4983(6)	4887(5)	4771(4)	37(1)
C(7)	1906(5)	5118(5)	6436(4)	36(1)
C(6)	9245(5)	11736(5)	9054(4)	34(1)
C(9)	8412(5)	8323(4)	10850(3)	32(1)
C(10)	11669(6)	8334(5)	12453(4)	37(1)
C(11)	10166(5)	8612(5)	13425(4)	38(1)
N(1)	10516(4)	8136(4)	10783(3)	30(1)

Table 3. Bond lengths [A] and angles [deg] for compound 258.

O(1)-C(1)	1.424(3)
O(1)-C(4)	1.439(3)
C(1)-C(9)	1.492(4)
C(1)-C(2)	1.542(3)
C(1)-H(1)	1.0000
C(5)-C(2)	1.528(4)
C(5)-H(5A)	0.9800
C(5)-H(5B)	0.9800
C(5)-H(5C)	0.9800
C(3)-O(2)	1.434(3)
C(3)-C(2)	1.511(3)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
O(2)-C(4)	1.414(3)
C(2)-C(6)	1.527(4)
C(4)-C(7)	1.512(4)
C(4)-C(8)	1.513(4)
O(3)-C(9)	1.336(3)
O(3)-C(11)	1.368(3)
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(7)-H(7A)	0.9800
C(7)-H(7B)	0.9800
C(7)-H(7C)	0.9800
C(6)-H(6A)	0.9800
C(6)-H(6B)	0.9800
C(6)-H(6C)	0.9800
C(9)-N(1)	1.288(3)
C(10)-C(11)	1.328(4)
C(10)-N(1)	1.389(3)
C(10)-H(10)	0.9500
C(11)-H(11)	0.9500
C(1)-O(1)-C(4)	113.56(19)
O(1)-C(1)-C(9)	106.8(2)
O(1)-C(1)-C(2)	110.7(2)
C(9)-C(1)-C(2)	114.39(19)
O(1)-C(1)-H(1)	108.3
C(9)-C(1)-H(1)	108.3
C(2)-C(1)-H(1)	108.3
C(2)-C(5)-H(5A)	109.5
C(2)-C(5)-H(5B)	109.5
H(5A)-C(5)-H(5B)	109.5
C(2)-C(5)-H(5C)	109.5
H(5A)-C(5)-H(5C)	109.5
H(5B)-C(5)-H(5C)	109.5
O(2)-C(3)-C(2)	111.8(2)
O(2)-C(3)-H(3A)	109.3
C(2)-C(3)-H(3A)	109.3
O(2)-C(3)-H(3B)	109.3
C(2)-C(3)-H(3B)	109.3
H(3A)-C(3)-H(3B)	107.9
C(4)-O(2)-C(3)	113.85(19)
C(3)-C(2)-C(6)	109.7(2)
C(3)-C(2)-C(5)	109.1(2)
C(6)-C(2)-C(5)	110.2(2)
C(3)-C(2)-C(1)	105.64(19)
C(6)-C(2)-C(1)	112.3(2)
C(5)-C(2)-C(1)	109.8(2)

O(2)-C(4)-O(1)	**109.77(19)**
O(2)-C(4)-C(7)	**112.3(2)**
O(1)-C(4)-C(7)	**111.6(2)**
O(2)-C(4)-C(8)	**105.9(2)**
O(1)-C(4)-C(8)	**105.1(2)**
C(7)-C(4)-C(8)	**111.8(2)**
C(9)-O(3)-C(11)	**104.6(2)**
C(4)-C(8)-H(8A)	**109.5**
C(4)-C(8)-H(8B)	**109.5**
H(8A)-C(8)-H(8B)	**109.5**
C(4)-C(8)-H(8C)	**109.5**
H(8A)-C(8)-H(8C)	**109.5**
H(8B)-C(8)-H(8C)	**109.5**
C(4)-C(7)-H(7A)	**109.5**
C(4)-C(7)-H(7B)	**109.5**
H(7A)-C(7)-H(7B)	**109.5**
C(4)-C(7)-H(7C)	**109.5**
H(7A)-C(7)-H(7C)	**109.5**
H(7B)-C(7)-H(7C)	**109.5**
C(2)-C(6)-H(6A)	**109.5**
C(2)-C(6)-H(6B)	**109.5**
H(6A)-C(6)-H(6B)	**109.5**
C(2)-C(6)-H(6C)	**109.5**
H(6A)-C(6)-H(6C)	**109.5**
H(6B)-C(6)-H(6C)	**109.5**
N(1)-C(9)-O(3)	**113.9(2)**
N(1)-C(9)-C(1)	**128.0(2)**
O(3)-C(9)-C(1)	**118.1(2)**
C(11)-C(10)-N(1)	**108.8(3)**
C(11)-C(10)-H(10)	**125.6**
N(1)-C(10)-H(10)	**125.6**
C(10)-C(11)-O(3)	**108.1(3)**
C(10)-C(11)-H(11)	**125.9**
O(3)-C(11)-H(11)	**125.9**
C(9)-N(1)-C(10)	**104.6(2)**

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for compound 258.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	32(1)	26(1)	22(1)	7(1)	5(1)	13(1)
C(1)	30(1)	23(1)	22(1)	8(1)	8(1)	9(1)
C(5)	38(2)	29(2)	36(2)	12(1)	13(1)	13(1)
C(3)	39(2)	30(2)	31(2)	13(1)	8(1)	17(1)
O(2)	47(1)	32(1)	24(1)	14(1)	6(1)	17(1)
C(2)	29(1)	23(1)	26(2)	11(1)	12(1)	13(1)
C(4)	32(1)	30(2)	21(1)	10(1)	2(1)	11(1)
O(3)	47(1)	40(1)	30(1)	15(1)	5(1)	12(1)
C(8)	45(2)	39(2)	25(1)	10(1)	13(1)	14(1)
C(7)	31(2)	38(2)	30(2)	9(1)	3(1)	9(1)
C(6)	33(2)	29(2)	42(2)	17(1)	14(1)	11(1)
C(9)	42(2)	22(2)	28(2)	12(1)	4(1)	6(1)
C(10)	38(2)	30(2)	37(2)	16(1)	-2(2)	7(1)
C(11)	37(2)	37(2)	32(2)	17(1)	-3(2)	8(1)
N(1)	31(1)	31(1)	28(1)	16(1)	2(1)	10(1)

CHAPTER II

1 Introduction

1.1 The family of the crocacins

Isolation and structural elucidation

The crocacins are a family of four antifungal and highly cytotoxic metabolites extracted from myxobacteria of the genus *Chondromyces*. The first isolation was performed in 1994 from the strain Cm c3 of *Chondromyces crocatus* by Jansen, Höfle and Reichenbach[1] at GBF in Braunschweig and yielded the compound now known as crocacin A, initially named simply as crocacin. In 1999, Jansen and co-workers identified the presence of three different members of the family in the original extract from the strains Cm c1, Cm c2, Cm c3, Cm c4, Cm c5 and Cm c7 of *Chondromyces crocatus,* together with the isolation of a fourth crocacin from the strain Cm p17 of *Chondromyces pediculatus*. To date there are four members of the crocacin family:

- crocacin A, B, C *(Chondromyces crocatus);*
- crocacin D (*Chondromyces pediculatus).*

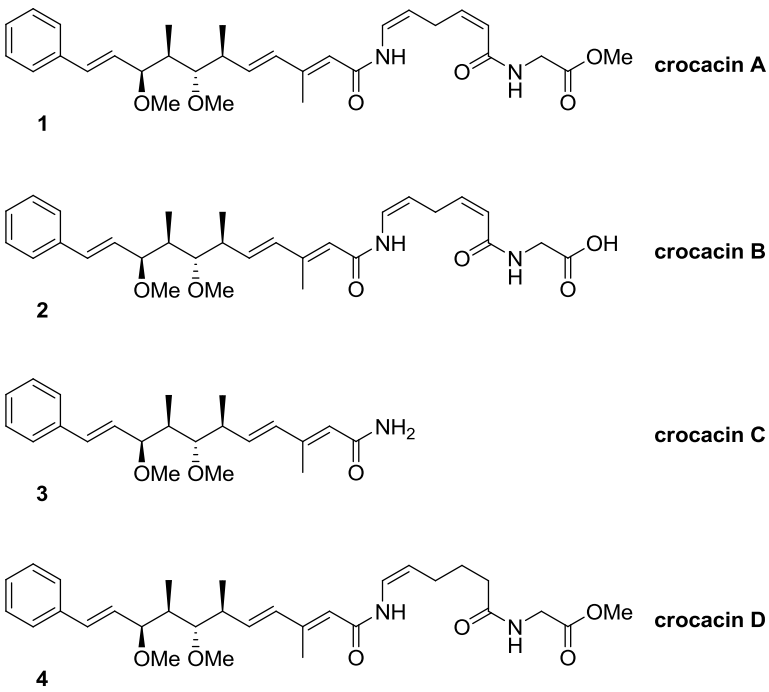


Figure 1. The family of the crocacins.

The extraction yield from the shaken cultures was quite low, in fact the major component, crocacin A, was produced in yields of only 20 mg/L.

The crocacins A, B and C were isolated from the acetone extract of wet cell mass of *C. crocatus* using both Sephadex LH-20 and RP-18 silica gel. Considering the significant destruction of important co-metabolites upon silica-gel chromatography, this step was avoided in the new separation procedure.

Crocacin D, on the other hand, was isolated from shaken cultures of *C. pediculatus,* strain Cm p17, by extraction from both cell mass and amberlite XAD 16 adsorbent resin and purification *via* RP-MPLC.

All four crocacins were obtained as pure colourless amorphous solids.

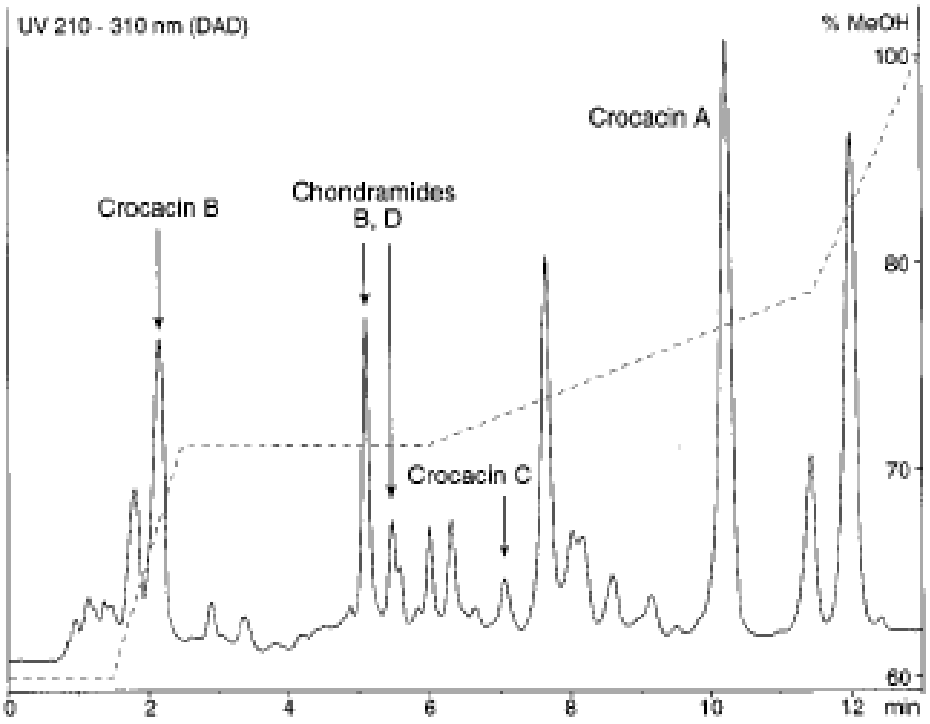


Figure 2. Typical RP-HPLC of an extract of *Chondromyces crocatus*.

Structurally, crocacins A, B and D are unusual dipeptides consisting of glycine and a 6-aminohexenoic or –hexadienoic acid, *N*-substituted by a complex polyketide-derived acyl residue, while crocacin C is the primary amide.

In 1999, Jansen and co-workers, together with the isolation and identification also provided the structural elucidation of the crocacins.[2] The most abundant compound, (+)-crocacin A **1**, was considered for the elucidation of the basic

structure of the crocacin family. The EI-HRMS analysis furnished a molecular ion of m/z 538 from which it was possible to obtain the elemental composition $C_{31}H_{42}N_2O_6$. This formula implies the presence of 12 double bonds equivalents. After UV analysis, which showed broad absorption bands at 254 nm and 291 nm, the DBEs were assigned to different chromophores. The IR analysis put in evidence the presence of ester and amide moieties, due to the intense carbonyl absorptions at 1747 and 1649 cm^{-1} respectively, together with NH broad bands at 3392 and 3252 cm^{-1}. The carbon backbone of the molecule was established by ^{1}H-NMR, ^{13}C-NMR and 2D-NMR experiments (COSY, HMQC). In addition, the relative positions of the secondary amide bonds, the methyl ester and the ether residues were established by long-range correlation spectra (HMBC). On the other hand, NOE correlations between the methyl group at C-13 and 15-H and between 12-H and 14-H, were exploited to establish the (*E*) configuration of the Δ^{12} double bond, while for all the other double bonds (Δ^{5}, Δ^{8}, Δ^{14}, Δ^{20}) the simple analysis of the vicinal coupling constants was sufficient. The values of the other observed ^{1}H vicinal coupling constants in the C-15 to C-20 segment, together with the calculated torsion angles obtained *via* MM^{+} calculations, and further NOE studies, clarified the relative configuration of the asymmetric centres in (+)-crocacin A (**Figure 3**).

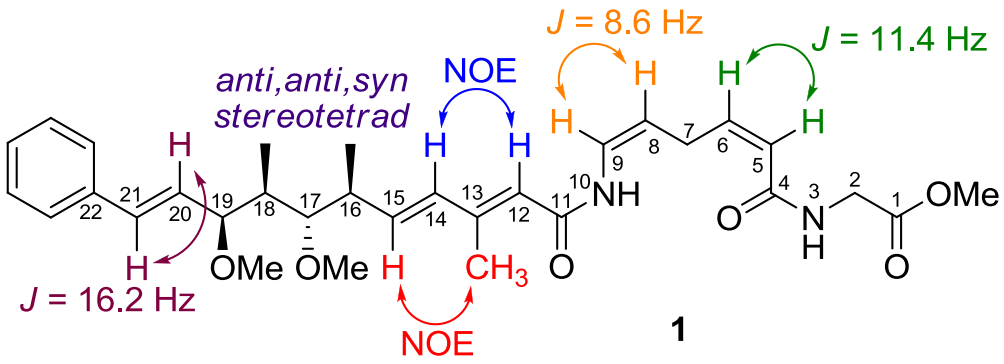


Figure 3. Structural elucidation of the (+)-crocacin A **1**.

Through NMR analysis it was possible to identify the free carboxylic acid moiety of crocacin B **2** by the lack of the methoxyl group signal, as was corroborated by EI-HRMS analysis, which provided a molecular ion of m/z 524 and elemental composition $C_{30}H_{40}N_2O_6$.

The structure of crocacin C **3** was identified *via* NMR analysis due to the lack of signals corresponding to the entire lateral chain, and due to the presence of the

primary amide moiety, confirmed by IR (1655 and 1600 cm^{-1}). In addition, these data were corroborated by HRMS analysis which provided a molecular ion of m/z 357 and elemental composition $C_{22}H_{31}NO_3$.

Finally, the structure of crocacin D **4** was established by evident comparison with the NMR spectra of crocacin A **1**. The crocacin D spectra indicated the lack of the Δ^5 double bond. The structure analysis was corroborated by EI-HRMS studies, which gave the molecular ion of m/z 540 and the elemental composition $C_{31}H_{44}N_2O_6$.

Biological properties

Jansen and co-workers disclosed the biological properties of the crocacin family in 1994. In their studies it was observed that *S. cerevisiae* became less sensitive to the crocacins if grown in the presence of glucose. Since *S. cerevisiae* can metabolise sugars by fermentation, the antagonistic effect of glucose suggested that the crocacins might interfere with the respirative energy metabolism. This is the order of activity against yeasts:

- crocacin A (MIC 10 mg/L)
- crocacin B (MIC 12.5 µgm/L)
- crocacin C (MIC 100 mg/L)
- crocacin D (MIC 1.4 ng/L)

The crocacins have also shown toxicity in L929 mouse fibroblast cell culture. A different order of activity is observed in this case:

- crocacin A (IC_{50} 0.2 mg/L)
- crocacin B (IC_{50} 40 mg/L)
- crocacin C (IC_{50} 140 mg/L)
- crocacin D (IC_{50} 0.06 mg/L)

In all cases, crocacin D proved to be the most active and promising compound of the family, while crocacin C is essentially inactive. This observation led to the hypothesis that the *(Z)*-enamide moiety present in the lateral chain of the crocacins may be responsible for the biological activity.

Speculative proposals on the mode of action have been made suggesting that protonation occurs at the enamide moiety, followed by nucleophilic attack onto the resulting *N*-acyliminium ion to form a conjugate with the enzyme. The biological activity of the crocacins was confirmed in 2008 by Crowley who showed that the activity of the crocacins was due to the inhibition of the electron flow within the cytochrome *bc1* segment (complex III) of the respiratory chain. The cytochrome *bc1* complex is a fundamental element of the respiratory chain, responsible for electron transfer from quinol to cytochrome *c* and the movement of protons across the inner mitochondrial membrane. Crowley's group published a series of molecular modelling studies[3a-d] based on crystallographic data which showed that the capability of crocacin A to inhibit the electron flow was related to the interaction with complex III through the following specific bonds (**Figure 4**):

- the *(Z)*-enamide carbonyl accepts a hydrogen bond from the Nε of the residue His161 in the enzyme;
- the *(Z)*-enamide linking group adopts a hair-pin conformation due to intramolecular hydrogen bonding between the two amide groups;
- the glycine nitrogen donates a hydrogen bond to the carbonyl group of the residue Met138;
- the glycine ester oxygen accepts a hydrogen bond from the backbone nitrogen of the residue Glu271.

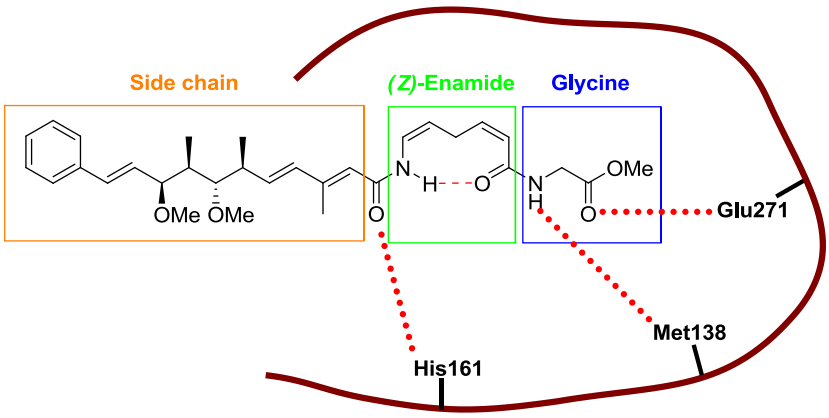


Figure 4. Binding moieties in crocacin A **1** structure.

Inhibitors of the cytochrome *bc1* complex are of great interest, both as potential biologically active molecules for the control of fungal diseases, and also as tools for probing the structure and function of the proteins involved in the respiratory electron transport chain. The aim of Crowley and co-workers was to design synthetic analogues of the natural fungicidal crocacins for potential exploitation as

agricultural fungicidal agents. The rationale behind this was that important fungicidals such as stigmatellin **5** and azoxystrobin **6** are also inhibitors of cytochrome *bc1* complex (**Figure 5**). Since the crocacins are good inhibitors of the electron transport chain at the same level and have shown fungicidal activity, they could potentially be leads for new agricultural fungicides.

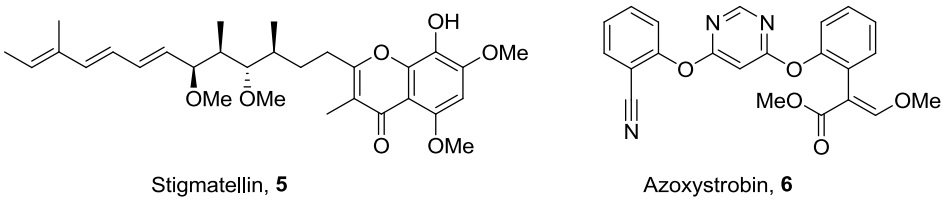


Figure 5. Other mitochondrial respiration inhibitors.

The crocacins display fungicidal activity against a number of plant pathogens including *Blumeria graminis, Mycosphaerella graminicola, Phytophthora infestans, Palsmopara viticola and Puccinia triticina*, *Puccinia recondita* and *Septoria nodorum.* Unfortunately, despite this interesting biological profile, the naturally occurring crocacins are characterised by great fragility which forbids their exploitation for agricultural purposes due to their instability to the field conditions. In simulated sunlight tests both crocacins A and D showed very poor photostability with 50% of parent compound being lost within 7 and 37 minutes, respectively.

Hence it is no surprise that unnatural analogues have been designed as potential crop protection agents. The first class of analogues were designed with simplified liphophilic side chains. These regions were considered to be unrelated to the biological activity of the molecule. The second class of analogues was based on modification of the linker segment, which is characterised by rigid and sterically undemanding nature (**Figure 6**). Disappointingly, despite slight improvements in terms of stability and activity with respect to the natural products (for example entry 4 and 5), it was not deemed, by Syngenta, to be sufficient to allow industrialisation of the compounds (**Table 1**).

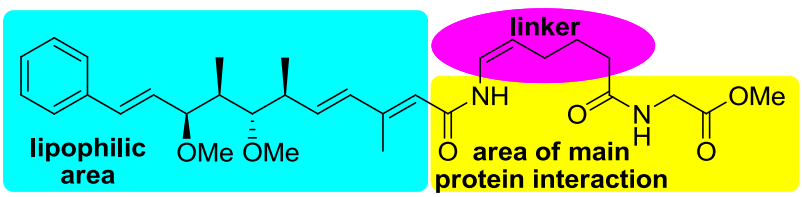


Figure 6. Classification of molecule functions in (+)-crocacin D **4**.

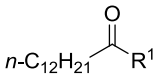
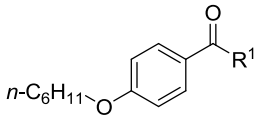
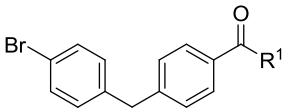
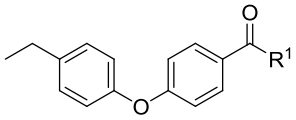
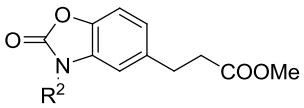
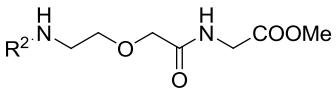
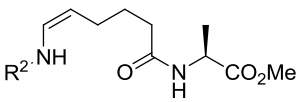
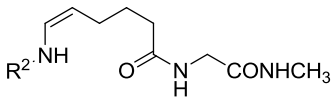
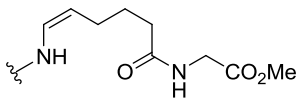
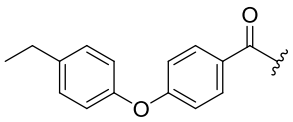
Entry	Analogue	EC90 Vine downey mildow/ppm	IC50 NADH oxidase/nM
1	(+)-crocacin D	25	36
2		>100	24
3		>100	21
4		10	17
5		25	9
6		>100	140
7		>100	230
8		>100	210
9		>100	880
	R^1 = 	R^2 = 	

Table 1. Biological efficacy of analogues of (+)-crocacin D **4**.

However, despite the lack of current industrial interest, the crocacins remain a source of significant synthetic interest both due to their biological potential and interesting structural features.

1.2 Previous syntheses of (+)-crocacin C

Rizzacasa's approaches (2000)

Rizzacasa reported the first enantioselective total synthesis of (+)-crocacin C **3** in 2000.[4] Retrosynthetically, Rizzacasa proposed the first disconnection at the C1-C5 *(E,E)*-dienamide moiety, which was envisioned as originating through the Stille coupling between the custom lateral chain **7** and the vinyl stannane intermediate **8**. The vinyl stannane **8** could be obtained *via* Hodgson's chromium-mediated vinylstannylation, while the C8-C9 bond could be obtained using Paterson's asymmetric *syn*-aldol reaction starting from cinnamaldehyde **9** and the dipropionate synthon **10**. Finally, ketone **10** could be obtained in 3 steps from the commercial Roche ester **11** (**Figure 7**).

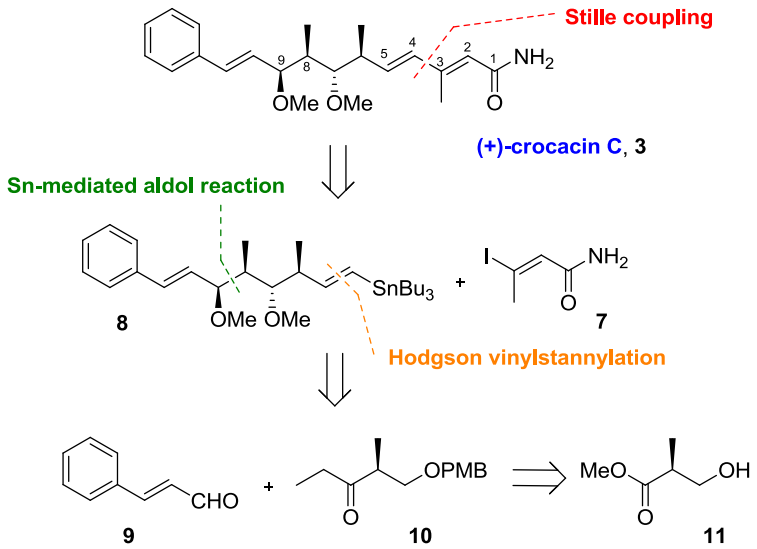
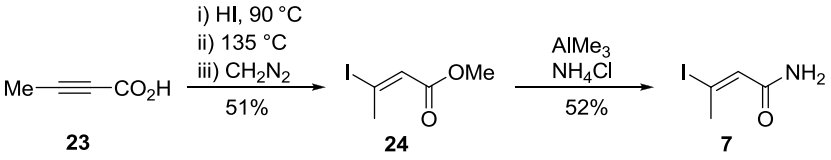


Figure 7. Retrosynthetic analysis of (+)-crocacin C by Rizzacasa.

Rizzacasa's synthesis began with commercially available *(S)*-Roche ester **11** which was converted into the corresponding Weinreb amide **12** and then protected to afford the PMB-ether **14**. The latter was treated with ethyl magnesium bromide to afford the intermediate **10** which then underwent a Sn(II)-mediated *syn*-aldol reaction following Paterson's protocol. This step involved the formation of the *(Z)*-Sn(II)-enolate from the intermediate **10** and its addition to the commercial *trans*-cinnamaldehyde **9** to afford the *syn-syn* adduct **15** in very good yield and with excellent diastereomeric excess. β-hydroxyketone **15** was then subjected to

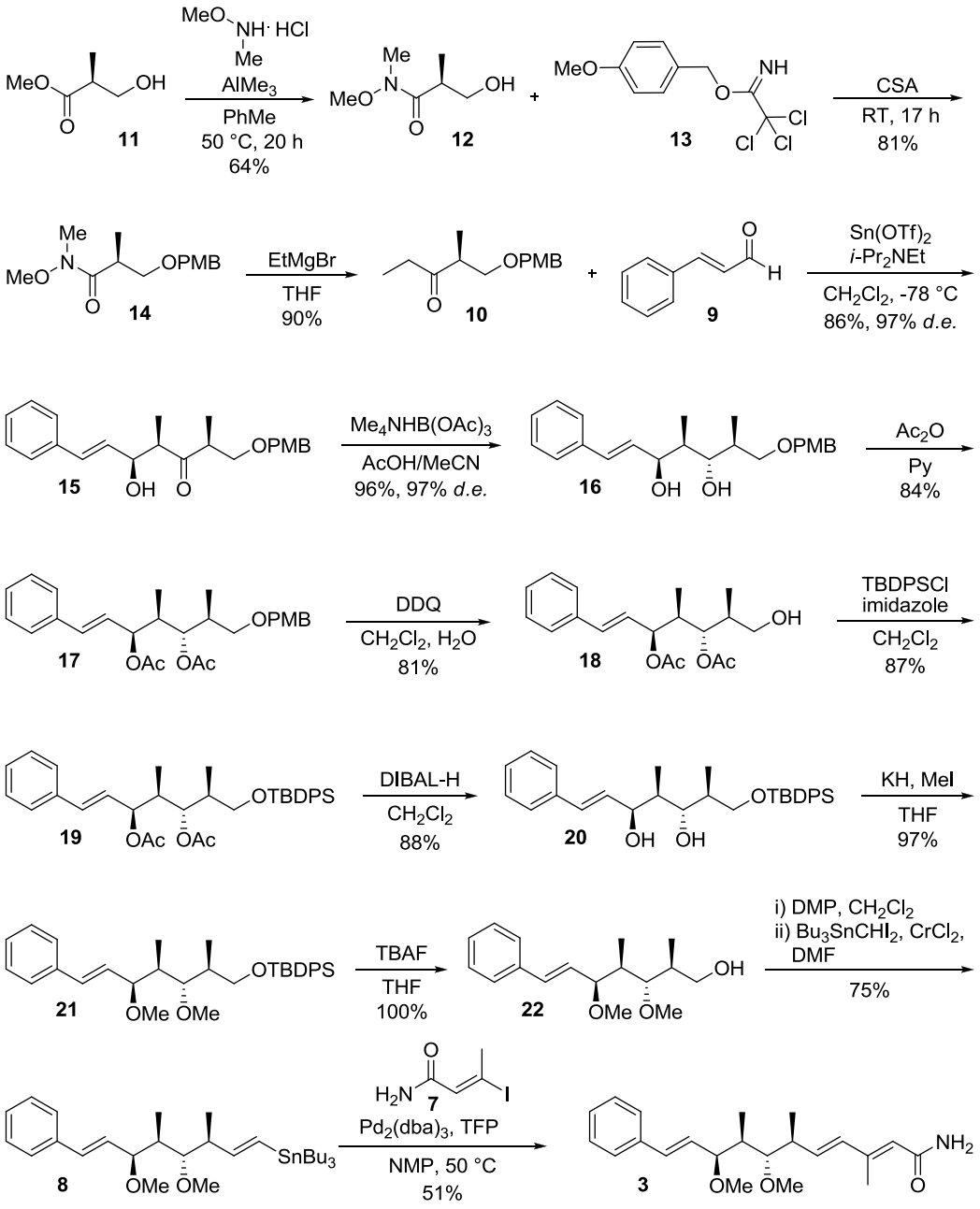
reagent controlled reductive conditions to provide the *anti*-diol **16** in excellent yield and with complete diastereocontrol. The stereochemistry of diol **16** was confirmed *via* ^{13}C-NMR studies on the corresponding acetonide following Rychnovsky's protocol. At this point, due to issues involving PMB group removal in the latter stages of the synthesis, an unfortunate protecting group interconversion was necessary. Thus, diol **16** was acetylated and the PMB group removed *via* DDQ treatment to afford the primary alcohol **18**, which was then reprotected with a TBDPS group. Reductive removal of the acetates, followed by methylation of the resultant diol **20**, afforded the dimethyl ether **21**, which was desilylated to give the free alcohol **22**. The latter was subjected to careful oxidation and subsequent chromium-mediated vinylstannylation following Hodgson's procedure to afford the *(E)*-stannane **8**. The final step involved a Stille coupling between stannane intermediate **8** and the custom lateral chain **7** (**Scheme 2**). The iodide lateral chain **7** was obtained in four steps from tetrolic acid **23**. Initial addition of HI to the alkyne unit generated the *(Z)*-acid which was subjected to thermal isomerisation to give a 70:30 mixture of *E:Z* isomers. Methylation using diazomethane then gave the pure *(E)*-ester **24** which was finally converted into the amide **7** with an overall yield of 27% (**Scheme 1**).



Scheme 1. Rizzacasa's synthesis of the lateral chain **7**.

Finally the key Stille coupling was carried out to afford, after purification by flash column chromatography and HPLC, (+)-crocacin C **3**.

Rizzacasa's synthesis was crucial in establishing the absolute stereochemistry of the natural product.

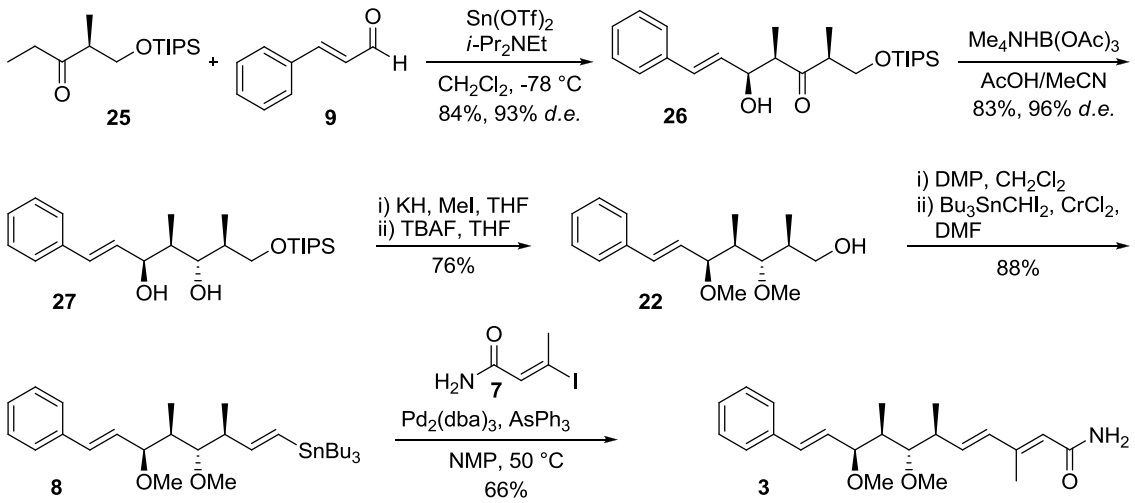


Scheme 2. Rizzacasa's first generation synthesis of (+)-crocacin C, **3**.

Due to the unforeseen issues related to the PMB protecting group stability, and the necessity for interconversion which elongated the total synthesis of (+)-crocacin C, Rizzacasa developed an optimised approach.[4,5] As part of this second generation synthesis, a more convenient TIPS protecting group was used in place of the PMB group. Rizzacasa's second generation synthesis began with ketone **25** which underwent a Sn(II)-mediated *syn*-aldol reaction, followed by stereoselective *anti*-reduction, to yield diol **27**. Bismethylation of diol **27** followed by TBAF removal of the silyl protecting group yielded free alcohol **22**. This new synthetic sequence

effectively saved four steps with respect to the first generation synthesis. Successively, DMP oxidation of alcohol **22** followed by chromium-mediated vinylstannylation afforded stannane **8**. The final Stille coupling was also optimised, which resulted in the replacement of the trifurylphosphine ligand with triphenylarsine in order to obtain the final target in a much improved 66% yield.

In conclusion, Rizzacasa's improved second generation synthesis yielded (+)-crocacin C **3** in 10 steps and 17% overall yield from commercially available starting materials.



Scheme 3. Rizzacasa's second generation synthesis of (+)-crocacin C, **3**.

Chakraborty's approach (2001)

Shortly after the publication of Rizzacasa's initial total synthesis of (+)-crocacin C **3**, Chakraborty reported a new independent approach.[6] In his retrosynthetic analysis, Chakraborty envisioned (+)-crocacin C as originating through a HWE olefination between aldehyde **28** and the custom lateral chain **29** to incorporate the C4-C5 double bond. Aldehyde **28**, in turn, could be obtained from allylic alcohol **30** *via* Sharpless asymmetric epoxidation followed by a regioselective cuprate-mediated epoxide opening. Alcohol **30** could be accessed through a Crimmins' *syn*-aldol Ti(IV)-mediated reaction between *N*-acylthiazolidinethione **31** and cinnamaldehyde **9** (**Figure 8**).

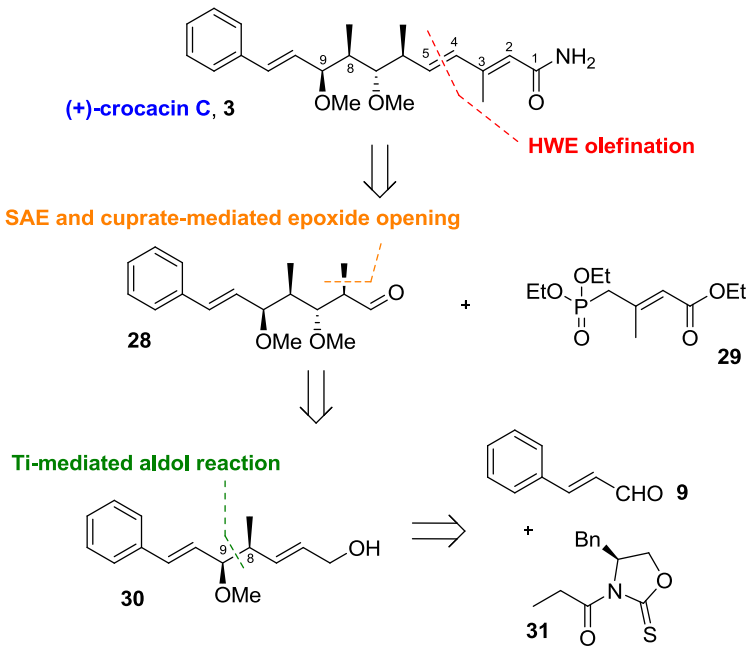
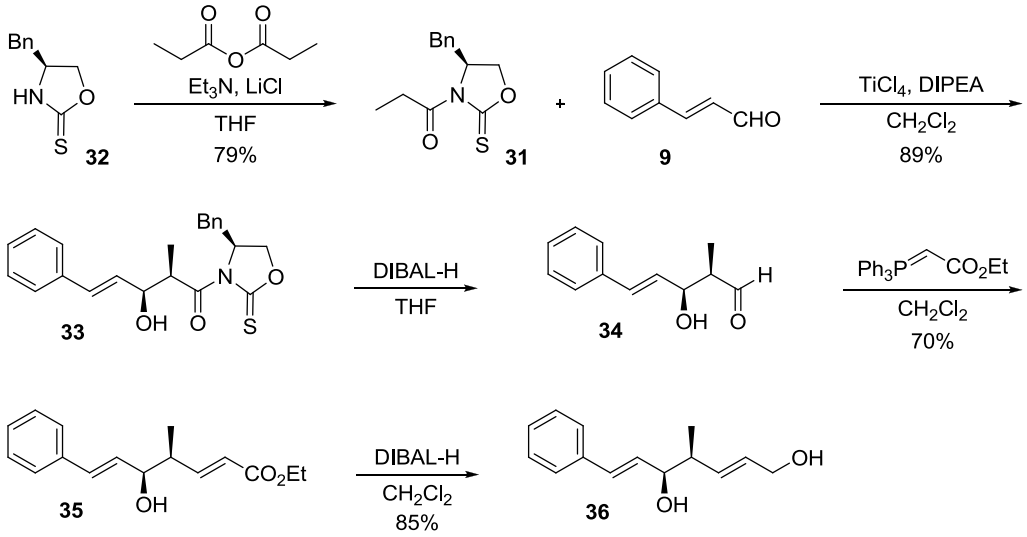


Figure 8. Retrosynthetic analysis of (+)-crocacin C by Chakraborty.

Chakraborty's synthesis began with the chiral oxazolidinethione **32** which was *N*-acylated to give propanoyl oxazolidinethione **31**. The latter was converted into the titanium enolate and was condensed with *trans*-cinnamaldehyde **9** *via* Crimmins' *syn*-aldol Ti(IV)-mediated conditions to afford alcohol **33**. Removal of the chiral auxiliary by DIBAL-H reduction afforded the corresponding aldehyde **34** which was then subjected to a Wittig olefination to afford the α,β-unsaturated ester **35** as a single *(E)*-isomer. DIBAL-H reduction of enoate **35** yielded alcohol **36** (**Scheme 4**).

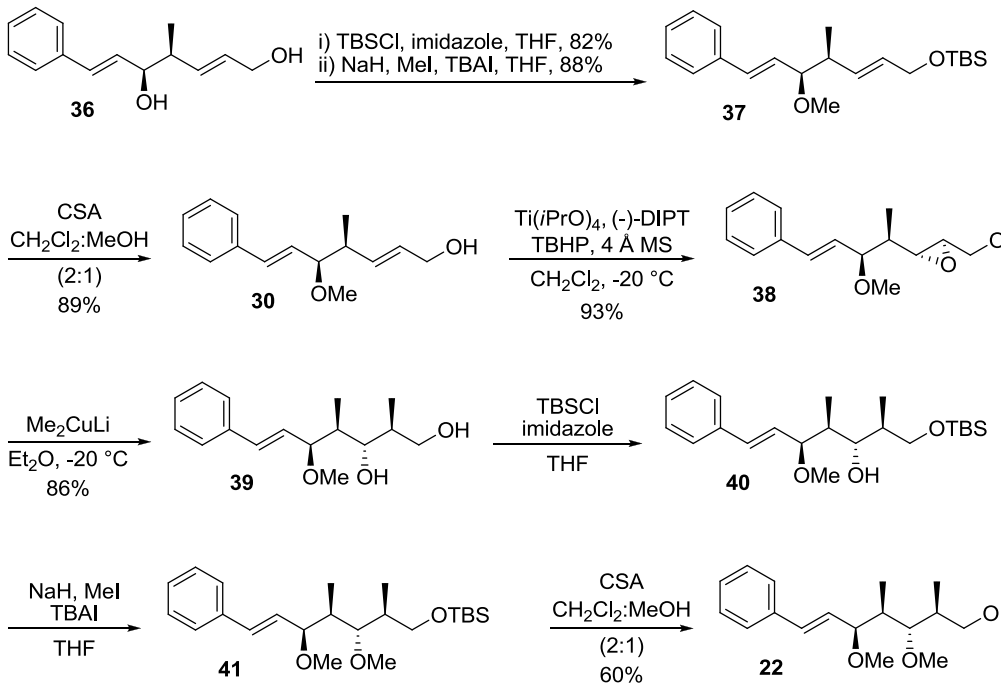


Scheme 4. Chakraborty's synthesis of intermediate **36**.

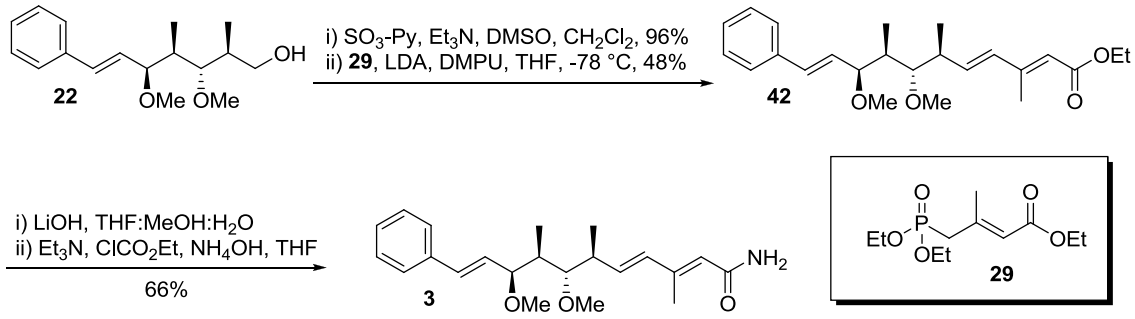
Selective silylation of the primary alcohol followed by methylation of the secondary alcohol afforded the differentially protected diol **37**. Selective silyl group removal afforded *(E)*-allylic alcohol **30** which was subjected to Sharpless asymmetric epoxidation to give the desired epoxy alcohol **38** in excellent yield and as a single diastereoisomer. The C6-C7 stereocentres were then accessed *via* regioselective opening of the epoxide using lithium dimethylcuprate. The selectivity was attributed to the presence of a more bulky substituent which directed the attack to the less hindered position to give the desired 1,3-diol **39**. Regioselective silylation of the primary alcohol afforded the TBS-ether **40**, which upon methylation afforded differentially protected triol **41**. Desilylation by CSA afforded primary alcohol **22** (**Scheme 5**).

Alcohol **22**, upon Parikh-Doering oxidation, yielded aldehyde **28**. Horner-Wadsworth-Emmons olefination of aldehyde **28** gave the *(E)*-conjugated ethyl ester **42**. Finally, saponification with lithium hydroxide, followed by activation of the resulting carboxylic acid and amidation afforded (+)-crocacin C **3** (**Scheme 6**).

In a nutshell, Chakraborty's synthesis of (+)-crocacin C was achieved in 17 steps with an overall yield of ~ 4% from commercially available starting materials.



Scheme 5. Chakraborty's synthesis of intermediate **22**.



Scheme 6. Chakraborty's completion of the synthesis of (+)-crocacin C, **3**.

Dias's approach (2001)

Several months after Chakraborty's synthesis was published, Dias' and co-workers also published their total synthesis of (+)-crocacin C **3**.[7] Dias' retrosynthetic analysis was influenced by Rizzacasa's work and started with the Stille coupling between the vinyl iodide **43** and the custom lateral chain **44** to generate the C3-C4 bond. In order to generate the vinyl iodide **43**, two disconnections were considered; the first involved a Takai olefination while the second involved a *m*CPBA epoxidation/cuprate-mediated epoxide opening sequence, starting from allylic alcohol **36**. The latter was thought as being accessed *via* Evans aldol reaction between the *N*-propionyl oxazolidinone **45** and *trans*-cinnamaldehyde **9** (**Figure 9**).

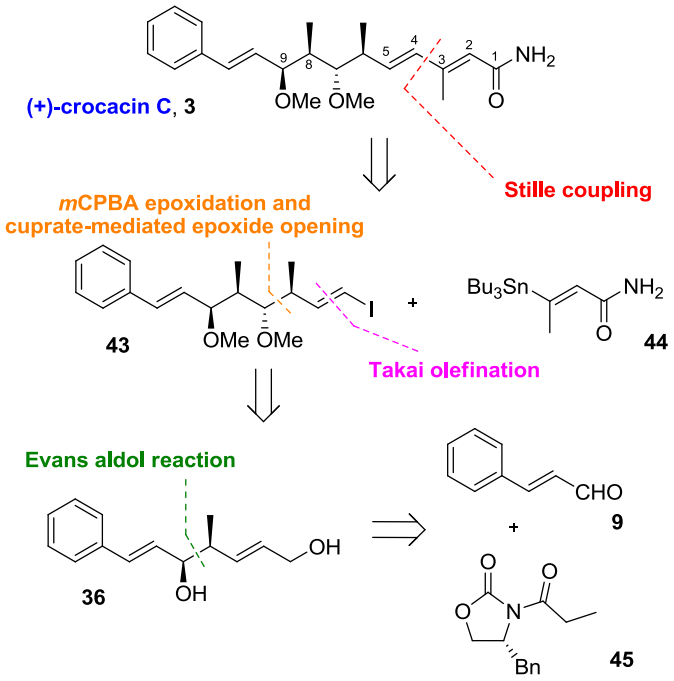
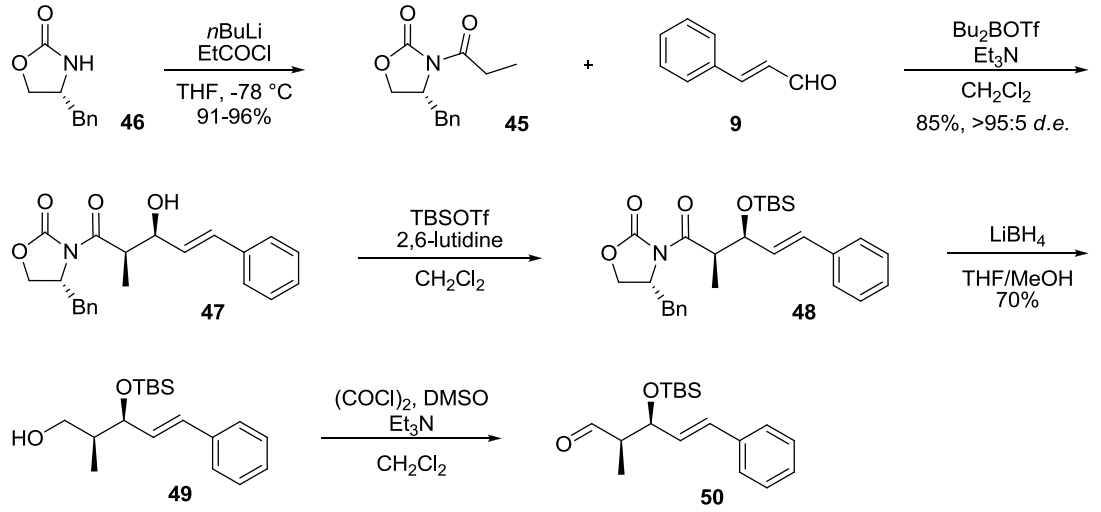


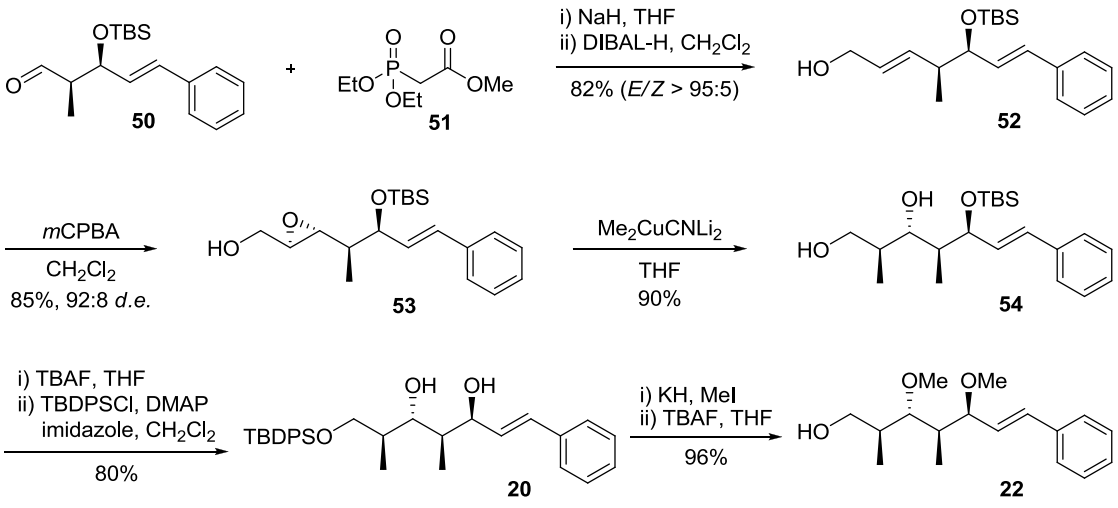
Figure 9. Retrosynthetic analysis of (+)-crocacin C by Dias.

Dias' synthesis began with commercially available (+)-*(R)*-oxazolidinone **46** which was *N*-acylated to afford the known (-)-acyloxazolidinone **45**. The *N*-propionyl oxazolidinone **45** was then converted into the corresponding boron enolate and was coupled with *trans*-cinnamaldehyde **9**, to yield the aldol adduct **47** in good yield and high diastereomeric ratio. TBS protection of the secondary alcohol followed by removal of the chiral auxiliary accessed the free primary alcohol **49**, which was subsequently oxidised under Swern conditions to afford the aldehyde **50** (**Scheme 7**).



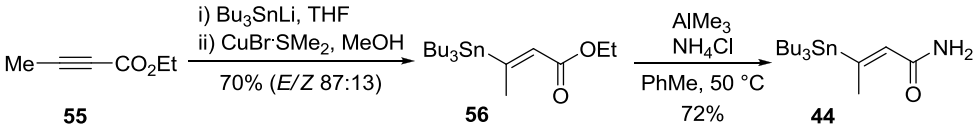
Scheme 7. Dias's synthesis of intermediate **50**.

HWE olefination of aldehyde **50** with phosphonate **51** afforded the α,β-unsaturated ester which was directly reduced to the corresponding *trans*-allylic alcohol **52** in high yield and good stereocontrol. Allylic alcohol **52** was subjected to a substrate controlled epoxidation to afford the epoxy alcohol **53** in good yield. Interestingly, the epoxidation proceeded with high regio- and diastereoselectivity from the opposite side of the TBS group to give the *anti*-epoxy alcohol **53** in high purity. Epoxide **53** was opened regioselectively with $Me_2CuCNLi_2$ to afford the *anti-anti-syn* diol **54**. Desilylation followed by regioselective TBDPS protection of the resulting primary alcohol, afforded the 1,3-diol **20**. Permethylation followed by TBAF desilylation gave the free primary alcohol **22** (**Scheme 8**).



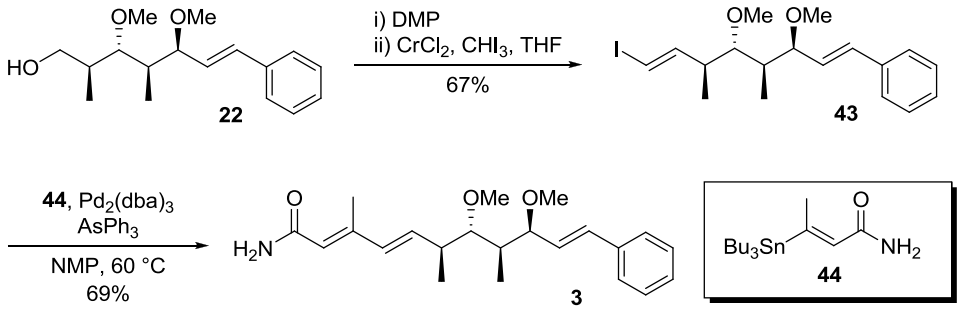
Scheme 8. Dias's synthesis of intermediate **22**.

The stannane containing lateral chain **44** was prepared starting from the commercially available ethyl 2-butynoate **55** which was subjected to a cuprate-mediated hydrostannylation to afford vinyl stannane **56**. The latter was finally converted into the primary amide **44** *via* amidation by ammonium chloride (**Scheme 9**).



Scheme 9. Dias's synthesis of the lateral chain **44**.

DMP oxidation of alcohol **22** followed by Takai olefination afforded *(E)*-vinyl iodide **43** in fair yield, however, with complete stereocontrol. The synthesis was completed with a Stille coupling between vinyl iodide **43** and stannane **44** using triphenyl arsine as the ligand, to access (+)-crocacin C **3** in 69% yield (**Scheme 10**). Dias' total synthesis of (+)-crocacin C **3** was completed in 16 steps from commercially available starting materials and in 8.5% overall yield.



Scheme 10. Dias's completion of the synthesis of (+)-crocacin C, **3**.

Andrade's approaches (2008-2010)

Andrade's approach to the synthesis of (+)-crocacin C was based on the chemoselective cross-metathesis between dienamide **58** and diene **57**.[8] Diene **57** was then dissected in two further places. The first proposed scission involved breaking the C6-C7 bond, which was proposed as originating through an asymmetric crotylboration *via* Brown's or Roush's reagent **60**. The second disconnection involved the construction of the C8-C9 bond through the Crimmins aldol condensation of propionate synthon **59** with *trans*-cinnamaldehyde **9** (**Figure 10**).

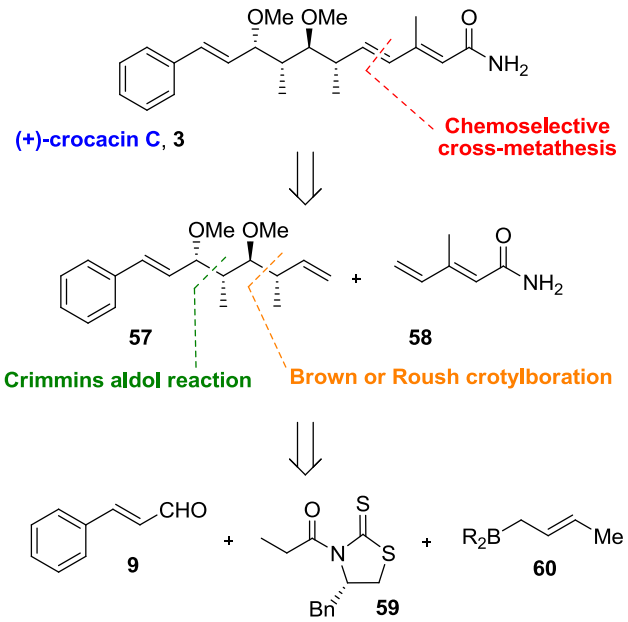
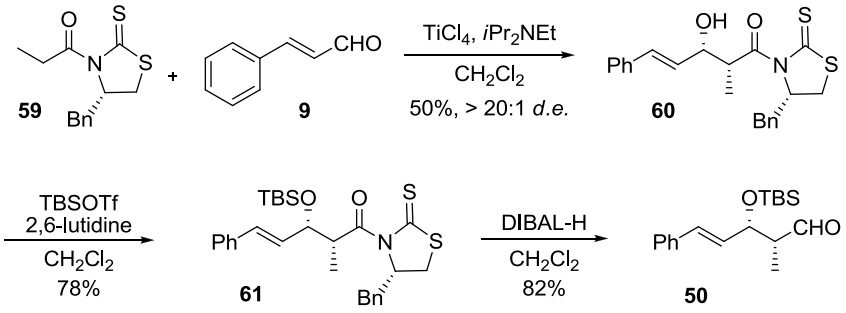


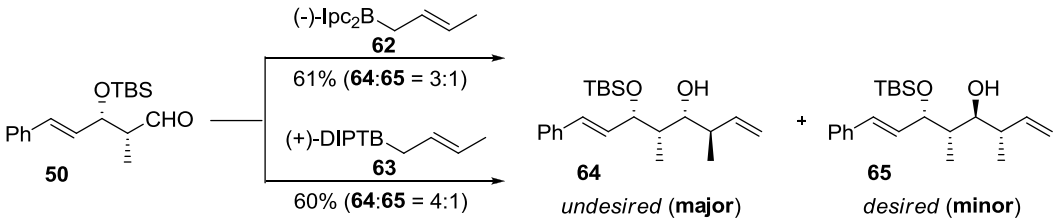
Figure 10. First generation retrosynthesis of (+)-crocacin C by Andrade.

As proposed, Andrade's synthesis began with a Crimmins aldol reaction between the readily available thiazolidinethione propionimide **59** and *trans*-cinnamaldehyde **9** to yield the *syn*-aldol adduct **60** in moderate yield and good diastereomeric excess. TBS protection of the primary alcohol followed by reductive removal of the chiral auxiliary, gave aldehyde **50** (**Scheme 11**).



Scheme 11. Andrade's synthesis of intermediate **50**.

Aldehyde **50** was subjected to asymmetric crotylboration conditions, initially, under Brown's and later under Roush's protocols. In both cases disappointing diastereomeric mixtures were obtained in which the undesired product **64** was formed preferentially (**Scheme 12**).



Scheme 12. Andrade's attempts of double asymmetric crotylborations.

Although Andrade's initial approach was rich in originality, the disappointing results in the crotylboration step led to a revised synthetic strategy, strongly influenced by Chakraborty's and Dias' syntheses. In the revised synthetic plan, Andrade maintained a highly convergent approach in which C4-C5 bond formation was built through a HWE olefination between the lateral chain **29** and aldehyde **28**. Aldehyde **28**, in turn, could be accessed *via* Evans' dipropionate aldol reaction between dipropionate synthon **66** and *trans*-cinnamaldehyde **9**, followed by a diastereoselective 1,3-*anti*-reduction (**Figure 11**).[9a,b]

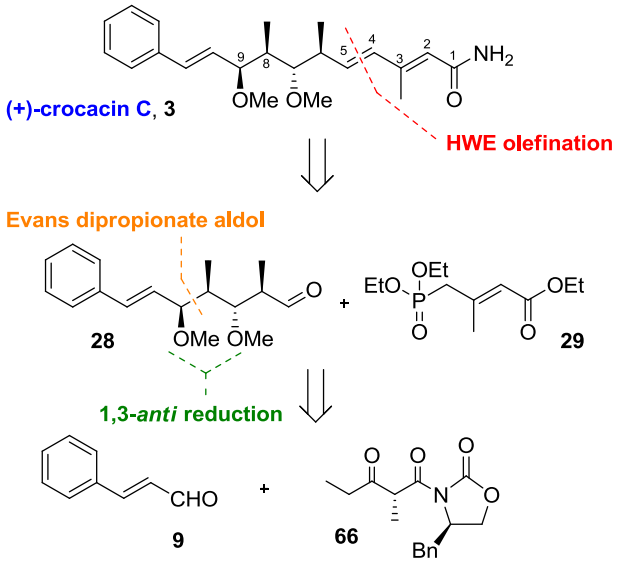
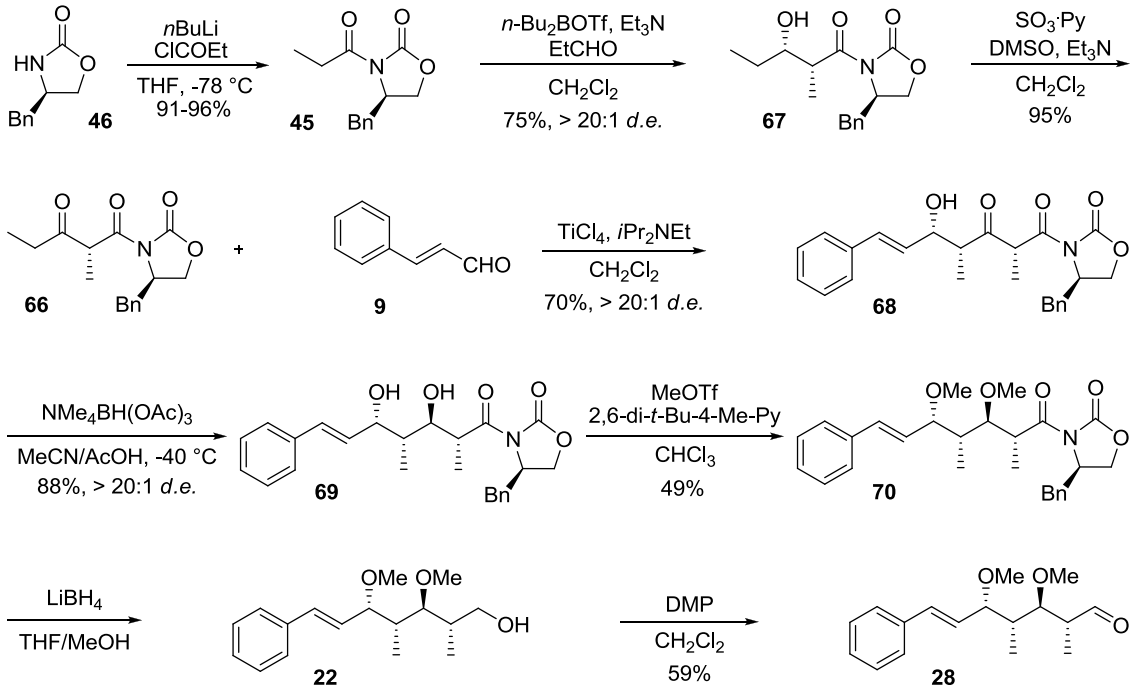


Figure 11. Andrade's second generation retrosynthesis of (+)-crocacin C, **3**.

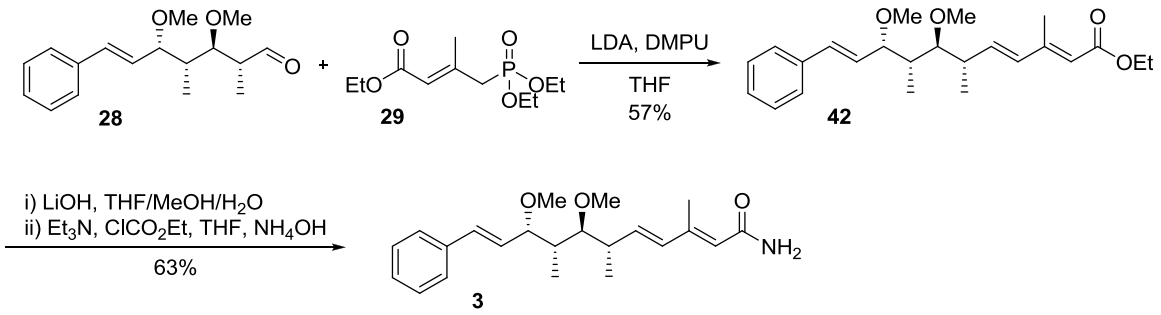
The revised synthesis showed a direct influence from both Rizzacasa's and Dias' approaches. It began with Evans' reagent **46** which was *N*-acylated to afford the oxazolidinone **45**. Oxazolidinone **45** was then subjected to aldol reaction with propionaldehyde, and the propionate intermediate subjected to a Parikh-Doering oxidation, to afford the dicarbonyl species **66**. The latter underwent Evans' asymmetric *syn*-aldol reaction with *trans*-cinnamaldehyde **9**, to yield the aldol product **68**. Stereoselective reagent controlled *anti*-reduction then completed the synthesis of the *anti,anti,syn* stereotetrad. Double methylation of the secondary alcohol moieties and reductive removal of the chiral auxiliary, yielded alcohol **22**. Finally, careful oxidation of alcohol **22**, afforded aldehyde **28** (**Scheme 13**).



Scheme 13. Andrade's synthesis of intermediate **28**.

For his endgame strategy Andrade adopted Chakraborty's procedure which involved HWE olefination between aldehyde **28** and phosphonate **29**, to give ester **42**. Saponification of the ester, activation of the resulting acid and amidation, afforded (+)-crocacin C (**Scheme 14**).

Andrade's protecting-group-free approach was able to generate (+)-crocacin C in ~ 4% overall yield over 11 steps.



Scheme 14. Andrade's completion of (+)-crocacin C, **3**.

Burke's approach (2008)

Burke reported a novel and original approach to the synthesis of (+)-crocacin C, based on the use of *N*-methyliminodiacetic acid (MIDA) boronates.[10] Burke introduced the use of MIDA boronates as very stable vinylboronic acid surrogates and, in order to prove the utility of this new methodology in natural product synthesis, he chose (+)-crocacin C as a suitable target. In his retrosynthetic analysis, Burke considered the C11-C12 bond as his first disconnection, involving a Suzuki coupling to incorporate the aromatic ring. The second disconnection was at the C3-C4 bond involving a Stille coupling between vinyl iodide **71** and the known stannane **44**, in a similar fashion to that reported by Dias. In the latter, two further disconnections were considered, one across the vinyl iodide moiety, involving a Takai olefination similar to Dias' approach, and the other at the C8-C9 bond involving a Paterson *syn*-aldol reaction following Rizzacasa's protocol. This led back to two simple intermediates, the acrolein MIDA boronate **72** and the dipropionate synthon **10** (**Figure 12**).

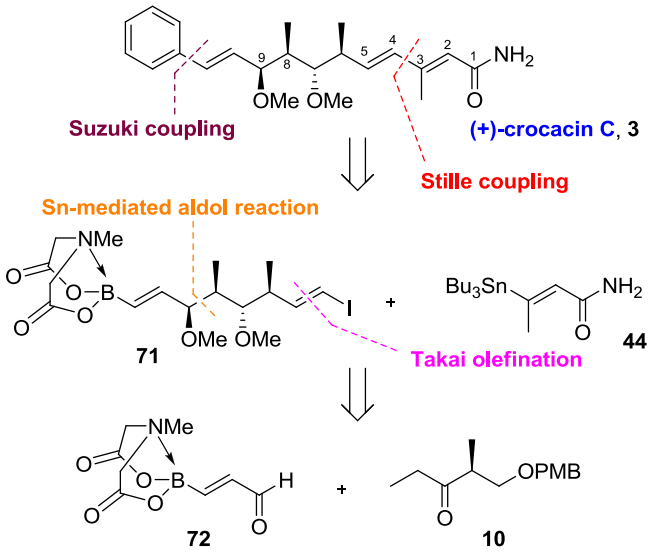
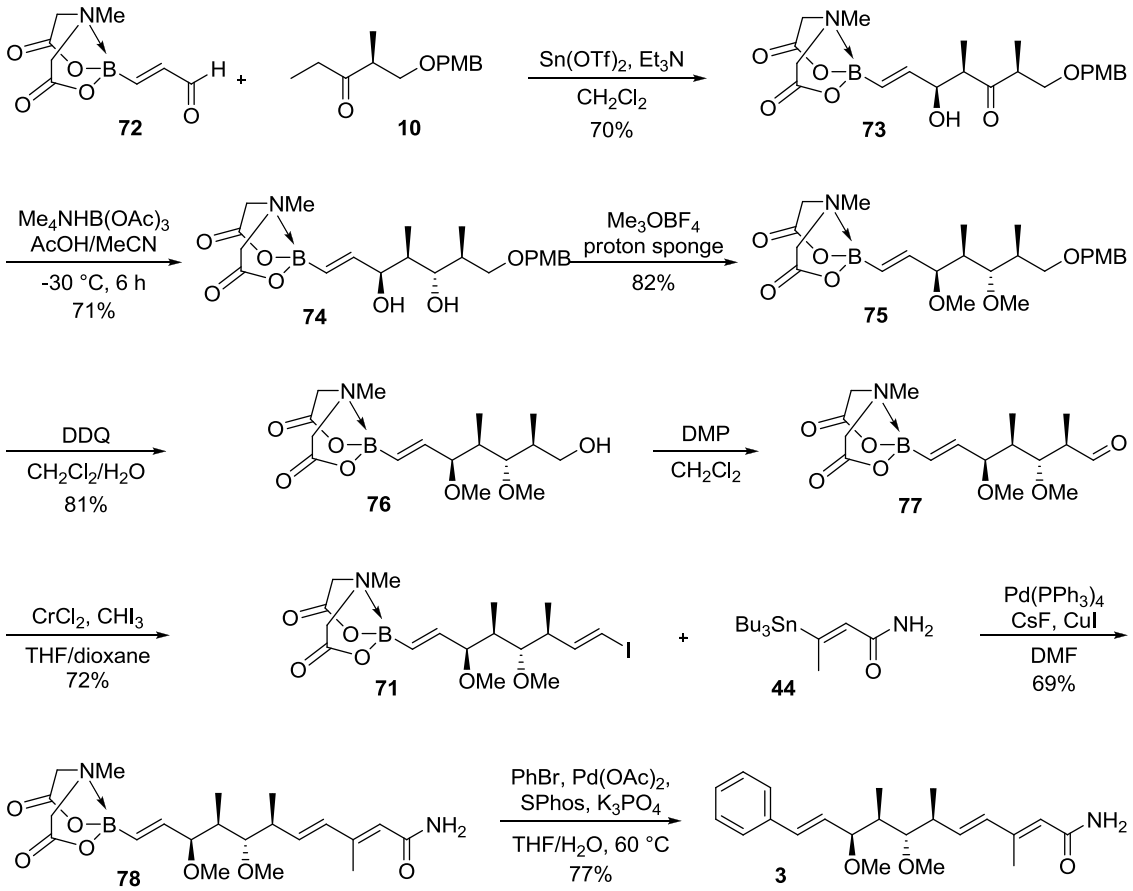


Figure 12. Retrosynthetic analysis of (+)-crocacin C by Burke.

Burke's synthesis began with acrolein MIDA boronate **72**, which was subjected to a Sn(II)-mediated *syn*-aldol reaction to generate the propionate **73**. Stereoselective *anti*-reduction of β-hydroxyketone afforded diol **74**, which was permethylated to yield dimethyl ether **75**. Removal of the PMB group, followed by

oxidation of the resulting primary alcohol **76**, yielded aldehyde **77**. Takai olefination of aldehyde **77** then yielded the key vinyl iodide unit **71**. Iodide **71** was then subjected to CsF/CuI-promoted Stille coupling conditions with stannane **44** to afford dienamide **78**. Finally, *in situ* boronic acid generation and Suzuki coupling between the MIDA boronate and bromobenzene, yielded (+)-crocacin C in 77% yield (**Scheme 15**). Burke's synthesis was achieved in 9 steps and 13% overall yield.



Scheme 15. Burke's synthesis of (+)-crocacin C, **3**.

Bressy and Pons' approach (2010)

In 2010, Bressy and Pons reported a convergent and protecting group-free synthesis of (+)-crocacin C.[11] Bressy ans Pons' synthesis hinged on formation of the C3-C4 bond through a one-pot hydrostannylation/Stille coupling procedure between the alkyne intermediate **79** and the lateral chain **7**. Alkyne **79**, in turn, could be derived from pyran **80** *via* base-induced ring opening. Pyran **80** could be accessed from a Julia-type olefination between sulfone **81** and the *meso*-THP diol **82**. Diol **82**, in turn, could be obtained from the oxabicycle *via* ozonolysis and reduction of the carbonyl moieties. Oxabicycle **83**, on the other hand, could originate from furan **84** *via* a [4+3]-cycloaddition with custom ketone **85** (**Figure 13**).

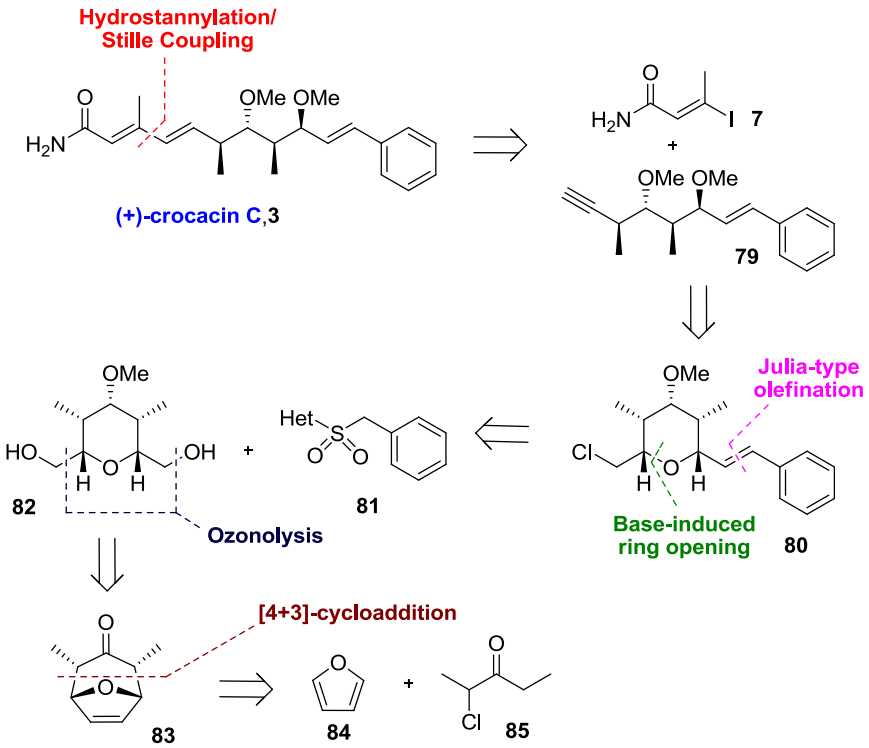
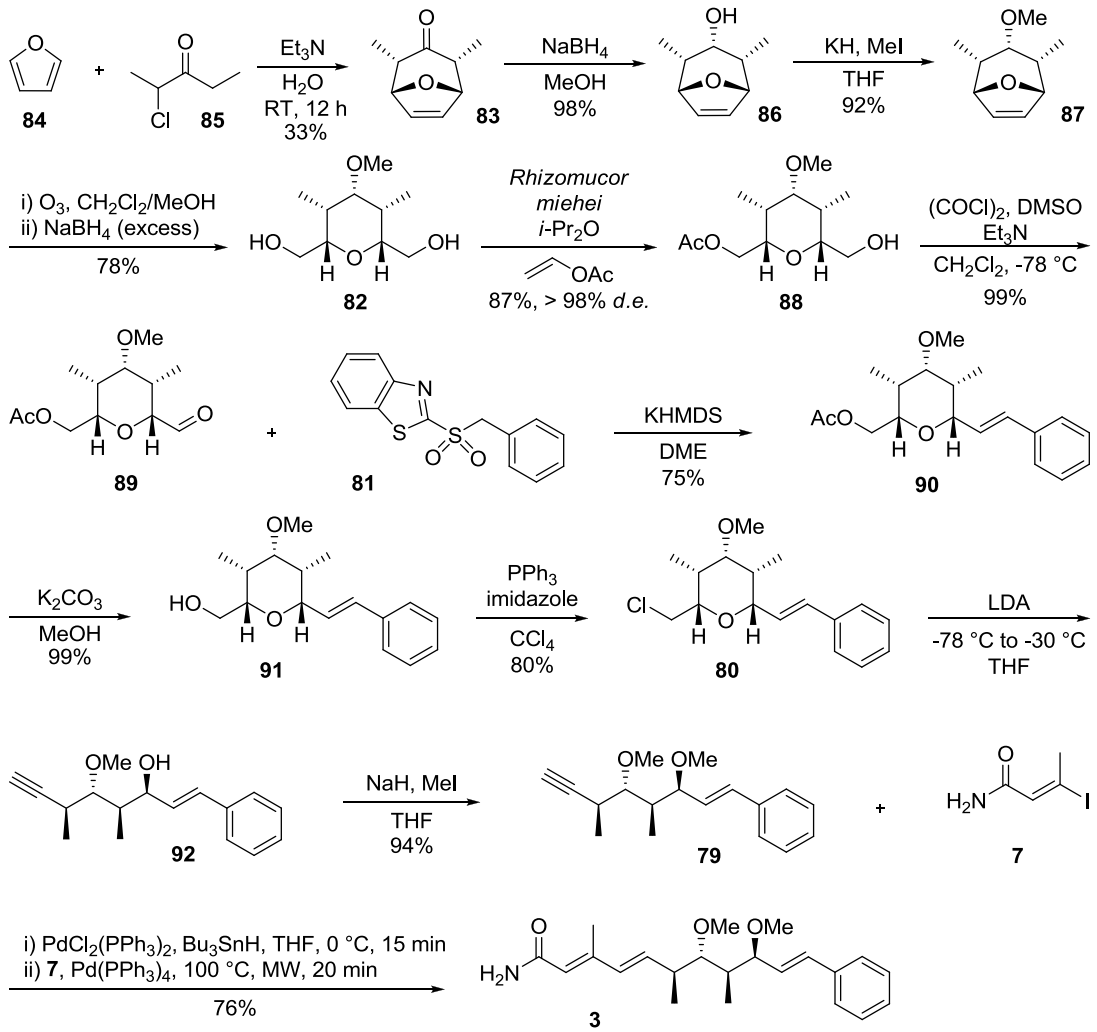


Figure 13. Retrosynthetic analysis of (+)-crocacin C by Bressy-Pons.

Bressy and Pons' synthesis began with a [4+3]-cycloaddition between furan **84** and 2-chloropentan-3-one **85** to afford oxabicycle **83**. The newly formed oxabicycle **83** was stereoselectively reduced and the resulting alcohol **86** was methylated to give methylether **87**. Methylether **87** was then subjected to an

ozonolysis-reduction sequence to afford *meso*-THP diol **82**, which was then converted, *via* enzymatic desymmetrisation, to monoacetate **88** in high yield and with excellent stereocontrol. Monoacetate **88** was oxidised to the corresponding aldehyde **89** under Swern conditions, and then subjected to a Julia-type olefination with sulfone **81** to afford olefin **90**. Acetate hydrolysis followed by chlorination of the resulting alcohol **91** gave chloride **80** which, upon base-induced THP ring opening and methylation, gave alkyne **79**. Alkyne **79** was finally subjected to a one-pot hydrostannylation and *in situ* Stille coupling with the known lateral chain **7**, to yield (+)-crocacin C **3**. Bressy-Pons' approach thus completed the synthesis in 14 steps and 8% overall yield from commercially available starting materials (**Scheme 16**).



Scheme 16. Bressy-Pons's synthesis of (+)-crocacin C, **3**.

Roush's approach (2012)

The most recent total synthesis of (+)-crocacin C was reported by Roush. The key step in Roush's approach was a mismatched double asymmetric δ-stannylcrotylboration to access the *anti,anti*-stereotriad in a stereoselective fashion.[12] Although attempts of mismatched double asymmetric crotylboration had previously been reported by Andrade with unsatisfactory results, Roush's newly developed methodology was able to solve the issues related to the intrinsic diastereofacial preference of the aldehyde substrate. Thus, in his retrosynthetic analysis, Roush envisioned (+)-crocacin C as originating through the Stille coupling between the known iodide **7** and stannane **8**. Stannane **8**, in turn, could be obtained *via* δ-stannylcrotylboration starting from chiral crotylborane reagent **93** and aldehyde **94**. Finally, aldehyde **94** could be prepared through an Evans' *syn*-aldol reaction between the acyl oxazolidinone **95** and *trans*-cinnamaldehyde **9** (**Figure 14**).

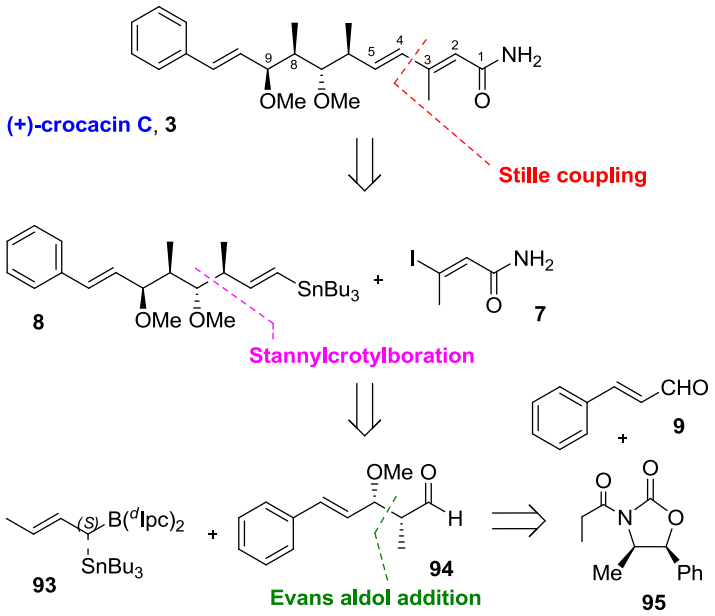
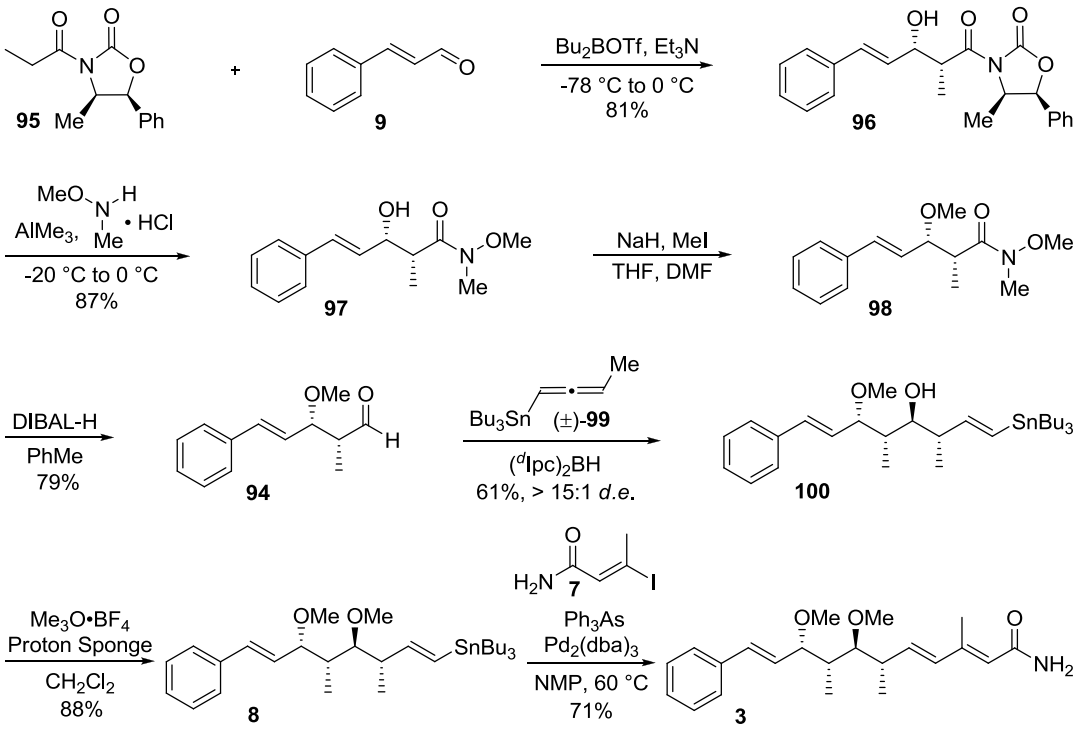


Figure 14. Retrosynthetic analysis of (+)-crocacin C by Roush.

Roush's synthesis began with acyl oxazolidinone **95** which was deprotonated to give the corresponding *(Z)*-enolate, which was subjected to an Evans' asymmetric *syn*-aldol addition with *trans*-cinnamaldehyde **9** to afford the aldol adduct **96**. Transamidation of unit **96** then yielded Weinreb amide **97**, which was methylated

and reduced to afford aldehyde **94**. Hydrostannylation of aldehyde **94** using the crotylborane reagent, obtained from the enantioselective hydroboration of racemic allenylstannane (±)-**99** with $(^{d}Ipc)_2BH$, yielded vinyl stannane **100** in fair yield and good diastereomeric excess. Methylation and final Stille coupling under Rizzacasa's conditions afforded the (+)-crocacin C in 71% yield (**Scheme 17**).

Roush's approach proved to be very efficient, yielding (+)-crocacin C in 20% overall yield over 7 steps on the longest linear sequence.



Scheme 17. Roush's synthesis of (+)-crocacin C, **3**.

1.3 Previous syntheses of (+)-crocacin D

Rizzacasa's approach (2002)

Rizzacasa and co-workers reported the first total synthesis of (+)-crocacin D **4**.[5] As part of his approach, Rizzacasa envisioned (+)-crocacin D as originating from acyl chloride **101** and the carbamate lateral chain **102**. Acyl chloride **101** was envisioned as originating using the same approach previously developed for (+)-crocacin C, which was utilised as a synthetic precursor of (+)-crocacin D. The lateral chain **102**, on the other hand, was envisioned as arising *via* addition of trimethylsilylethanol to isocyanate **103** (**Figure 15**).

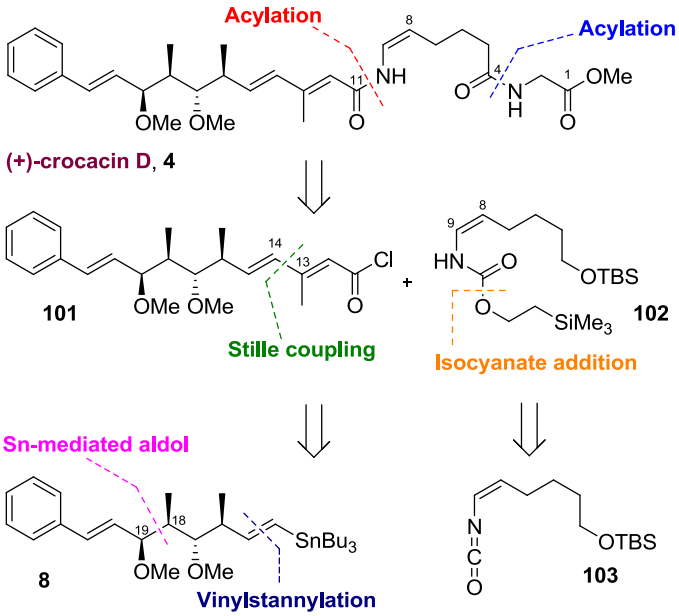
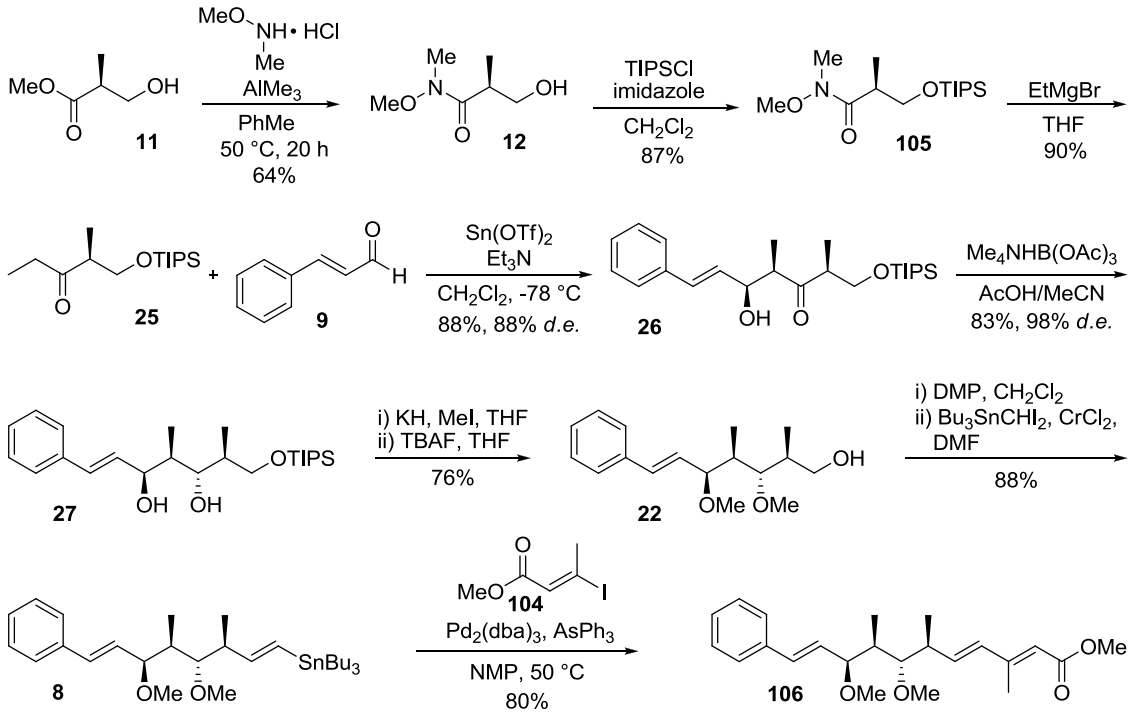


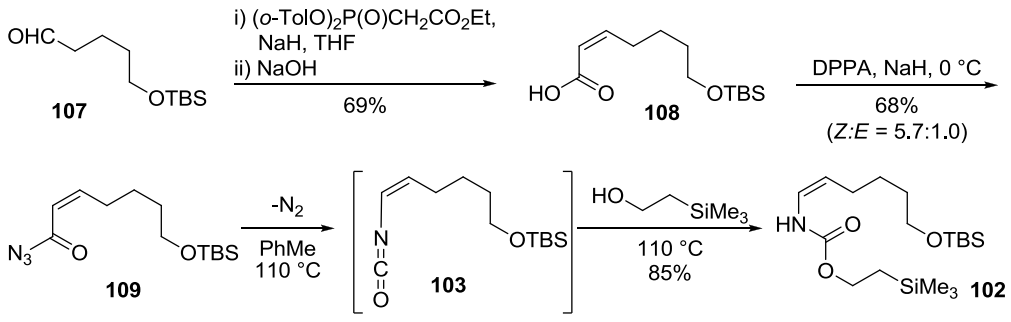
Figure 15. Retrosynthetic analysis of (+)-crocacin D by Rizzacasa.

Rizzacasa's synthesis of the left hand side of (+)-crocacin D paralleled his second generation approach for the total synthesis of (+)-crocacin C. However, upon accessing vinyl stannane **8**, a modified Stille coupling was carried out in order to generate methyl ester **106** (**Scheme 18**).



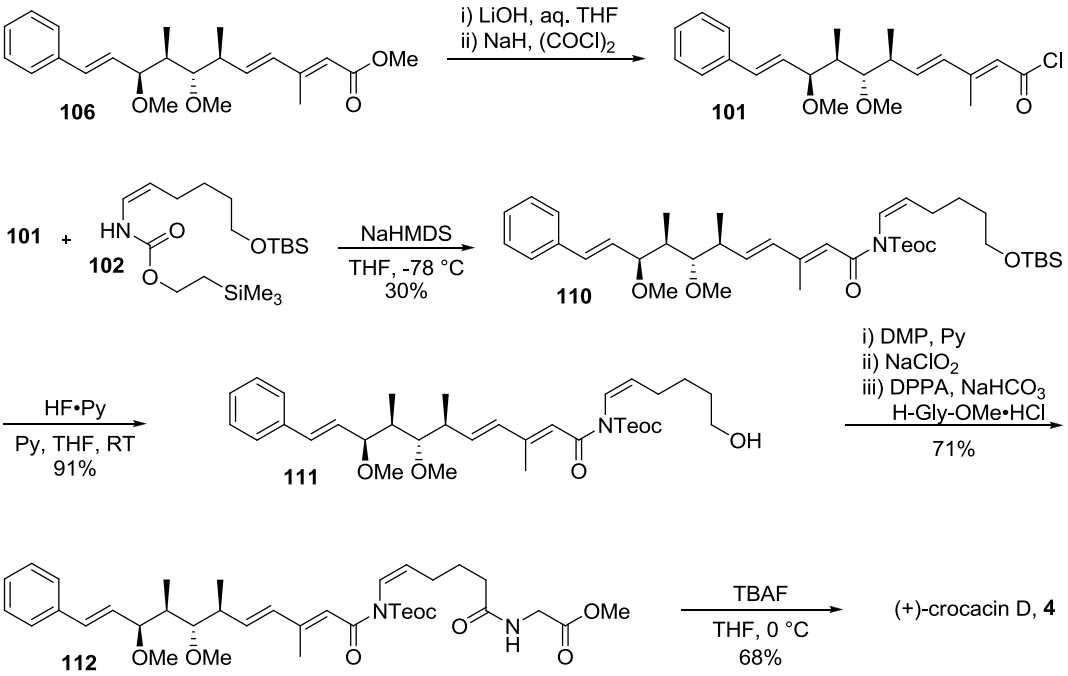
Scheme 18. Rizzacasa's synthesis of the intermediate **106**.

The synthesis of the *(Z)*-enamide containing right hand side of (+)-crocacin D began with the aldehyde **107**, which was subjected to an Ando olefination in order to generate the sensitive *(Z)*-α,β-unsaturated ester. Ester saponification yielded carboxylic acid **108**, which was then converted to acyl azide **109**. Curtius rearrangement of acyl azide **109** afforded the *(Z)*-vinyl isocyanate intermediate **103**, which upon treatment with trimethylsilylethanol yielded the key carbamate **102** (**Scheme 19**).



Scheme 19. Rizzacasa's synthesis of the intermediate **102**.

Rizzacasa's final steps towards the synthesis of (+)-crocacin D involved conversion of methyl ester **106** into acyl chloride **101**, and subsequent coupling with the lateral chain **102** (**Scheme 20**). Removal of the silyl protecting group followed by oxidation of the resulting alcohol to the corresponding carboxylic acid and DPPA-mediated coupling with glycine methyl ester led to the protected enamide **112**. Finally, Teoc deprotection afforded (+)-crocacin D in an overall yield of ~ 2% and in 18 steps on the longest linear sequence.



Scheme 20. Rizzacasa's synthesis of the (+)-crocacin D, **4**.

Chakraborty's approach (2002)

Shortly after Rizzacasa's synthesis, Chakraborty reported a total synthesis of (+)-crocacin D.[13] Chakraborty envisioned (+)-crocacin D as originating through a double disconnection approach in which the N3-C4 bond was incorporated through an amide linkage involving glycine and the C8-C9 double bond was generated through a Peterson elimination. The primary alcohol intermediate **113** on the other hand was thought as having originated through the coupling of carboxylic acid **114** and TMS-amine **115**. Carboxylic acid **114** could be synthesised following the same sequence previously developed by Chakraborty's group for the synthesis of (+)-crocacin C. Fragment **115** could be accessed *via* regioselective epoxide opening from the TMS-epoxide **116**. The latter could be obtained by alkene reduction and epoxidation from the known TMS-alkyne **117**.

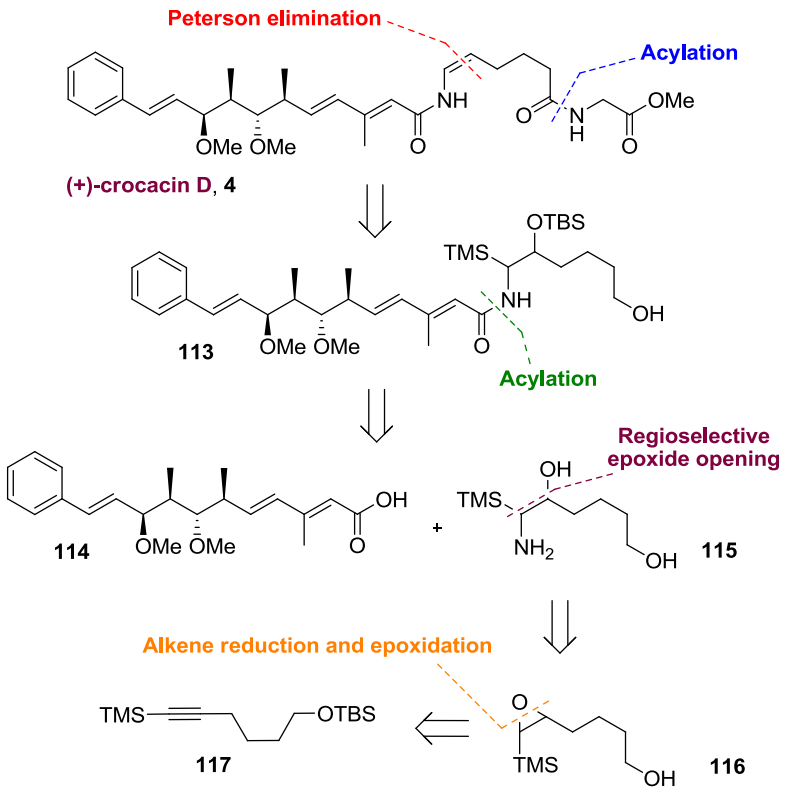
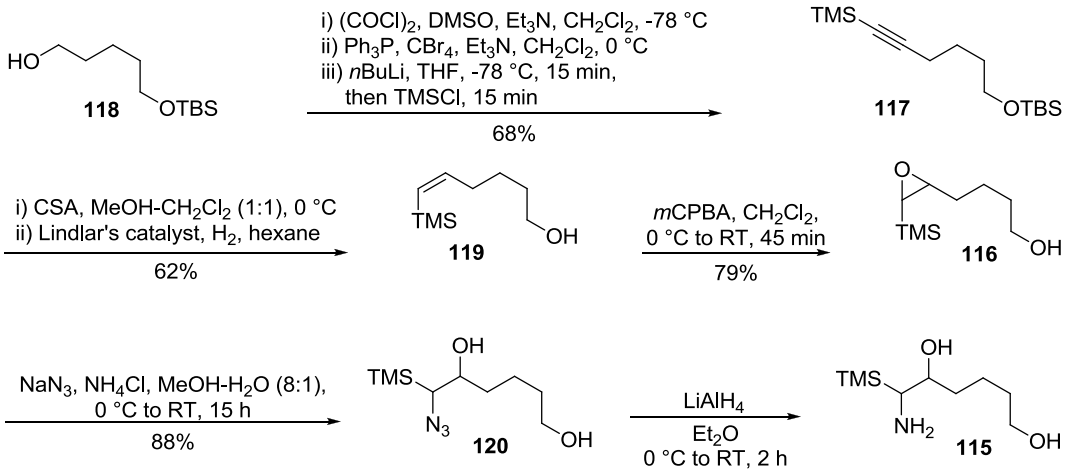


Figure 16. Retrosynthesis of the (+)-crocacin D by Chakraborty.

Chakraborty's synthesis began with the oxidation of alcohol **118** under Swern conditions to give the corresponding aldehyde, which was directly subjected to

Corey-Fuchs alkynylation to afford the TMS acetylide **117** (**Scheme 21**). TBS removal followed by partial hydrogenation of the alkyne afforded *(Z)*-vinylsilane **119**. Epoxidation of vinylsilane **119** and regioselective opening of the epoxide intermediate **116** with sodium azide gave the α-azido-β-hydroxyalkylsilane intermediate **120**. Reduction of the azide afforded the secondary amine **115**.

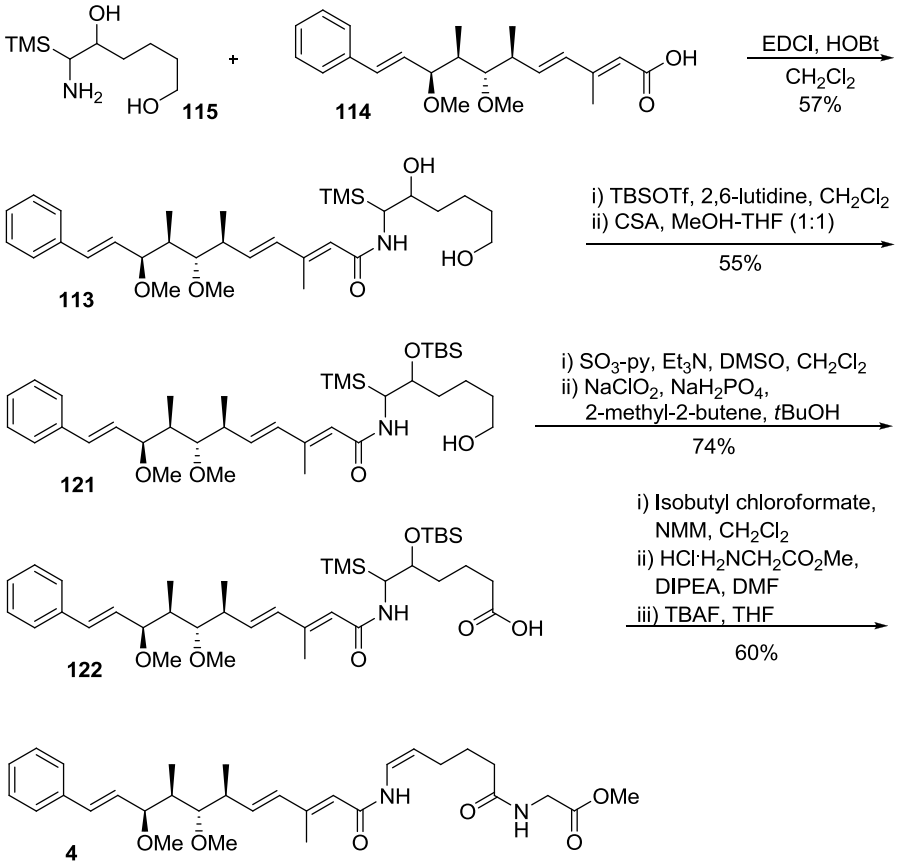


Scheme 21. Chakraborty's synthesis of the intermediate **115**.

Acylation of amine **115** with the known carboxylic acid **114**, yielded amide **113** which was globally protected before the primary alcohol was selectively unmasked (**Scheme 22**). Alcohol **121** was oxidised to yield carboxylic acid **122**, which was then coupled to glycine methyl ester *via* formation of the mixed anhydride.

Finally, a TBAF-mediated one-pot desilylation/Peterson elimination afforded (+)-crocacin D in 78% yield.

As a whole, Chakraborty's total synthesis of (+)-crocacin D was achieved in 24 steps and ~ 1% overall yield.



Scheme 22. Chakraborty's completion of the synthesis of (+)-crocacin D, **4**.

Dias's approach (2005)

A few years later, Dias reported a novel and more convergent approach to the total synthesis of (+)-crocacin D, based on Buchwald's copper-catalysed coupling of amides with vinyl halides.[14] Hence retrosynthetically, Dias envisioned (+)-crocacin D as originating through the copper-mediated coupling between (+)-crocacin C **3** and vinyl iodide **123**. Vinyl iodide **123** could in turn be generated through the peptide coupling of the carboxylic acid intermediate with glycine methyl ester and functional group manipulation (**Figure 17**).

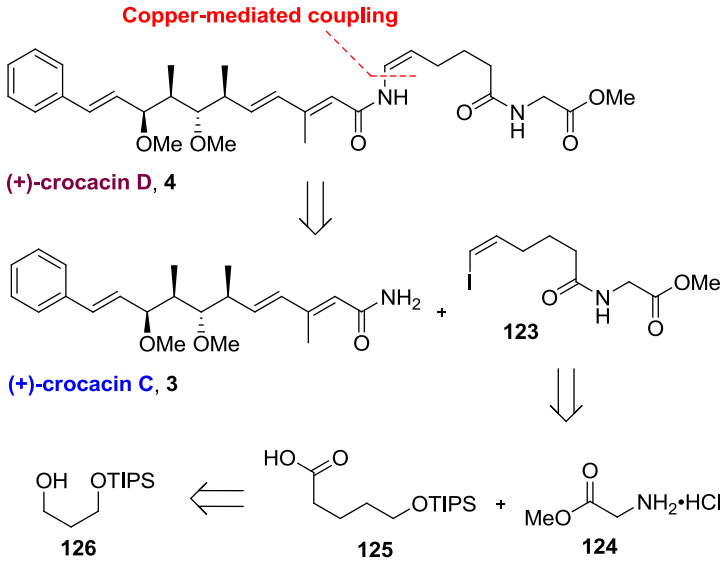
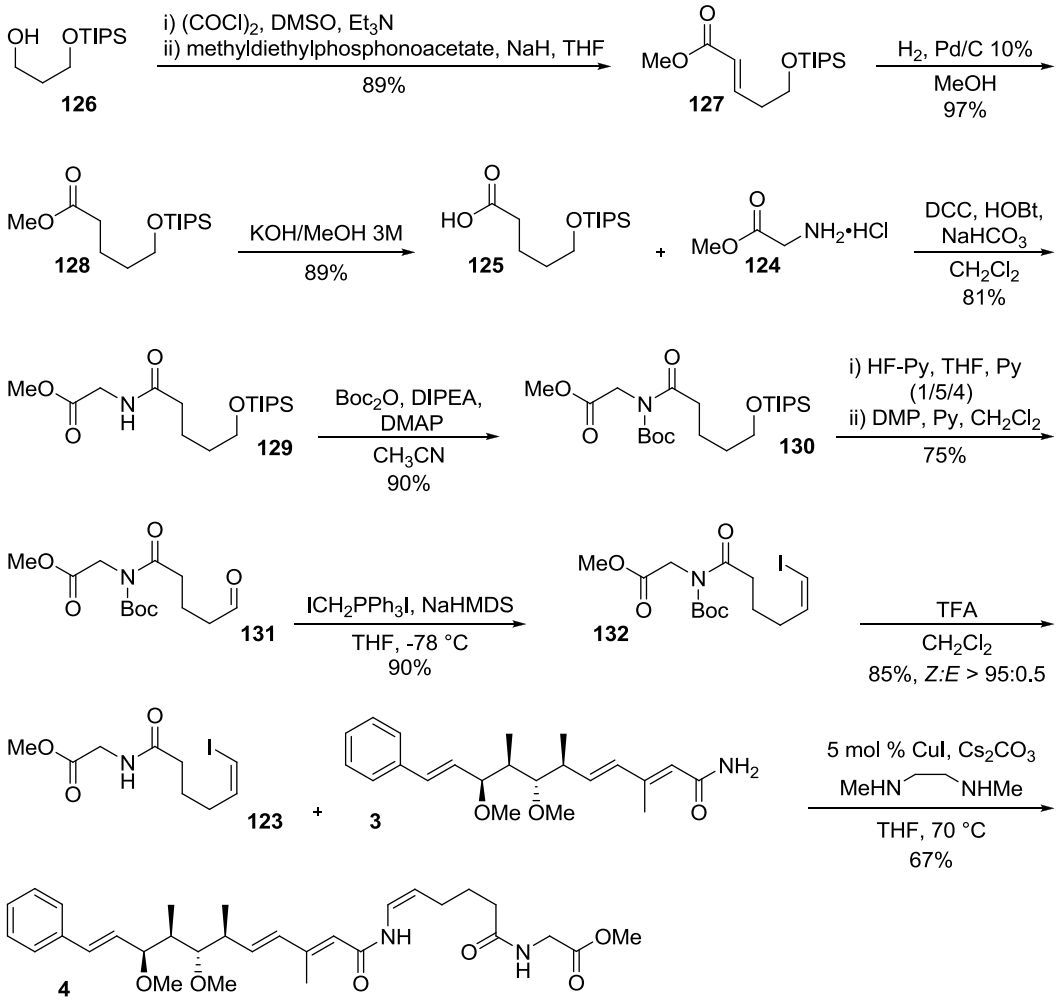


Figure 17. Retrosynthesis of (+)-crocacin D by Dias.

Dias' synthesis began with the Swern oxidation of alcohol **126** to the corresponding aldehyde followed by HWE olefination to give the *(E)*-enoate **127** (**Scheme 23**). Hydrogenation of the double bond followed by saponification afforded the carboxylic acid **125** which was then coupled with glycine methyl ester **124** to yield amide **129**. Boc protection of the secondary amide, desilylation and careful oxidation of the free alcohol, led to the aldehydic intermediate **131**. The latter was subjected to a *(Z)*-selective Stork-Zhao olefination to afford vinyl iodide **132**, which after Boc-removal using TFA, afforded the desired lateral chain **123**. The endgame strategy consisted of a copper-mediated cross-coupling between

(Z)-vinyl iodide **123** and (+)-crocacin C **3** under Buchwald's conditions to afford (+)-crocacin D in ~ 6% overall yield and 17 steps on the longest linear sequence.



Scheme 23. Dias's synthesis of (+)-crocacin D, **4**.

1.4 Previous syntheses of (+)-crocacin A

Rizzacasa's approach (2003)

Rizzacasa's group was, again, the first to report the total synthesis of (+)-crocacin A.[15] Rizzacasa's retrosynthetic analysis was very similar to that previously proposed for (+)-crocacin D. Hence Rizzacasa envisioned (+)-crocacin A as originating through the coupling of the known acyl chloride **101** and to the *(Z,Z)*-dienecarbamate **133**. Carbamate **133** could in turn be accessed *via* addition of trimethylsilylethanol to vinyl isocyanate **134**, which, on the orther hand, could be easily synthesised from the known 1,4-alkadiyne **135** (**Figure 18**).

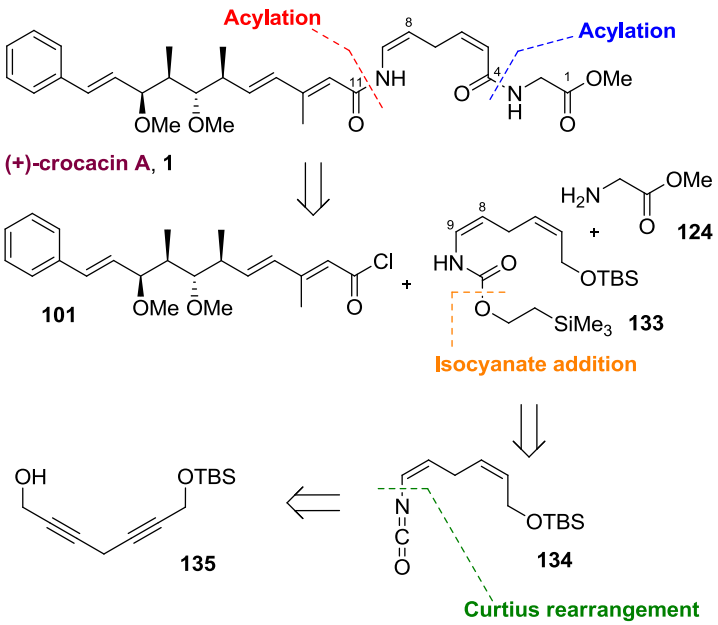
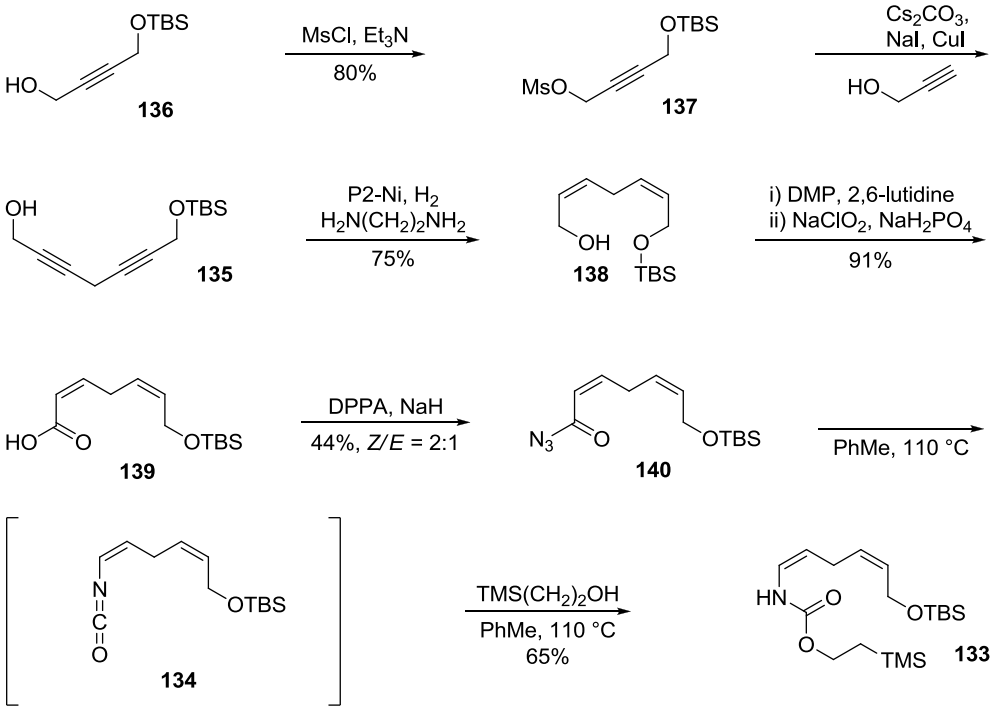


Figure 18. Retrosynthetic analysis of (+)-crocacin A by Rizzacasa.

Rizzacasa's synthesis began with the known alcohol **136** which was mesylated and subjected to a copper-mediated coupling to give the 1,4-alkadyine **135**. The sensitive intermediate **135** was partially reduced to the corresponding *(Z,Z)*-diene **138** using borohydride-reduced nickel catalyst (P-2Ni). The primary alcohol was then oxidised to carboxylic acid which, in turn, was converted to the corresponding azide **140** in moderate yield and with partial isomerisation of the double bonds (*Z/E* = 2:1). Azide **140** was then subjected to Curtius rearrangement conditions to give isocyanate **134** which was directly converted into carbamate **133** by treatment with trimethylsilylethanol (**Scheme 24**).

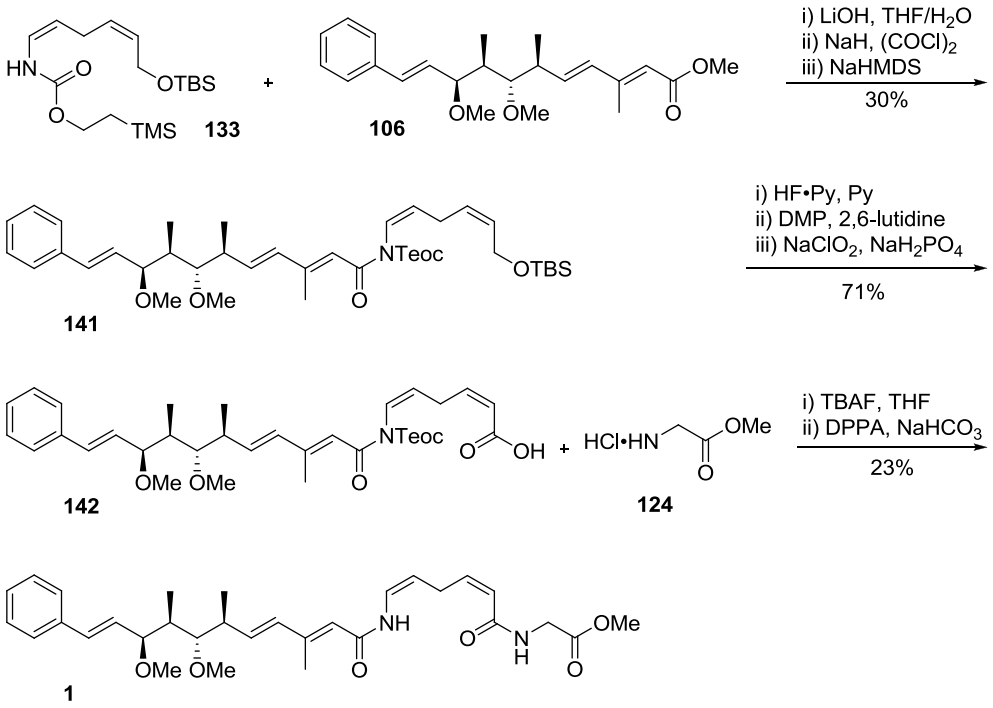


Scheme 24. Rizzacasa's synthesis of the intermediate **133**.

Rizzacasa's final steps towards the synthesis of (+)-crocacin A **1**, began with dienoate **106** which was converted into the corresponding acyl chloride and directly coupled to carbamate **133** to afford the resulting enamide **141** in low yield (**Scheme 25**).

Silyl group removal followed by oxidation of the primary alcohol yielded the corresponding carboxylic acid **142** which was TBAF deprotected and subsequently subjected to a DPPA-mediated coupling with glycine methyl ester **124** to afford (+)-crocacin A in 23% yield.

Overall, Rizzacasa's total synthesis of (+)-crocacin A **1** was completed in 1% yield and in 18 steps in the longest linear sequence.



Scheme 25. Rizzacasa's completion of (+)-crocacin A, **1**.

Chakraborty's approach (2003)

In the same year that Rizzacasa published his total synthesis of (+)-crocacin A **1**, Chakraborty also reported his own independent approach.[16] Chakraborty's retrosynthetic analysis hinged on an acylation reaction to generate the N3-C4 bond, while a Peterson elimination would establish the C8-C9 double bond (**Figure 19**). The allylic alcohol precursor **143**, on the other hand, was envisioned as being assembled through a new acylation reaction between carboxylic acid **114** and amine **144**. Amine **144** could be obtained by regioselective opening of epoxide **145** which, in turn, could be prepared *via* partial reduction and epoxidation from the known bis-alkyne **146**.

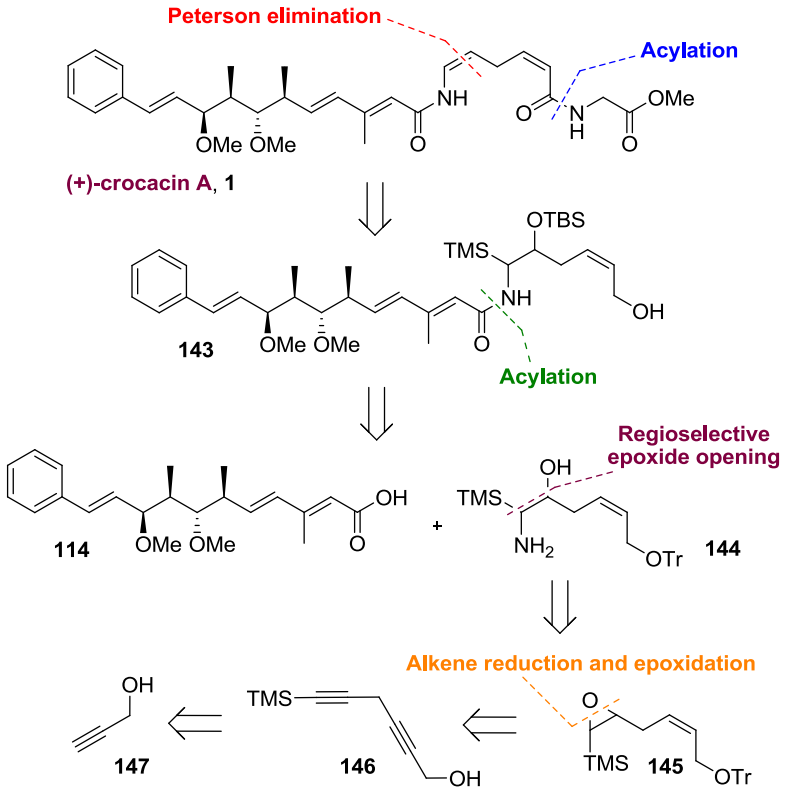
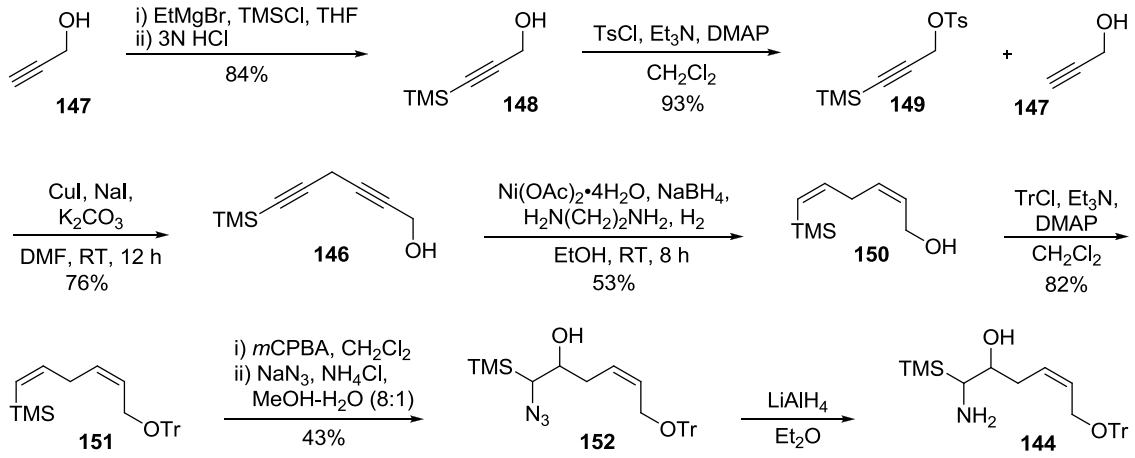


Figure 19. Retrosynthetic analysis of (+)-crocacin A by Chakraborty.

Chakraborty's synthesis began with silylation of propargylic alcohol **147** which was converted into the TMS-intermediate **148**. Tosylation of the primary alcohol position, followed by a copper-catalysed coupling with propargylic alcohol **147** afforded the diynyl intermediate **146**. Partial reduction of diynyl **146** gave *(Z,Z)*-dienenol **150**. Hydroxyl group tritylation and subsequent oxidation with *m*CPBA yielded the corresponding epoxide, which was regioselectively opened with

sodium azide to afford TMS-azide **152**. Finally, reduction of the azide **152** completed the synthesis of the lateral chain **144** (**Scheme 26**).

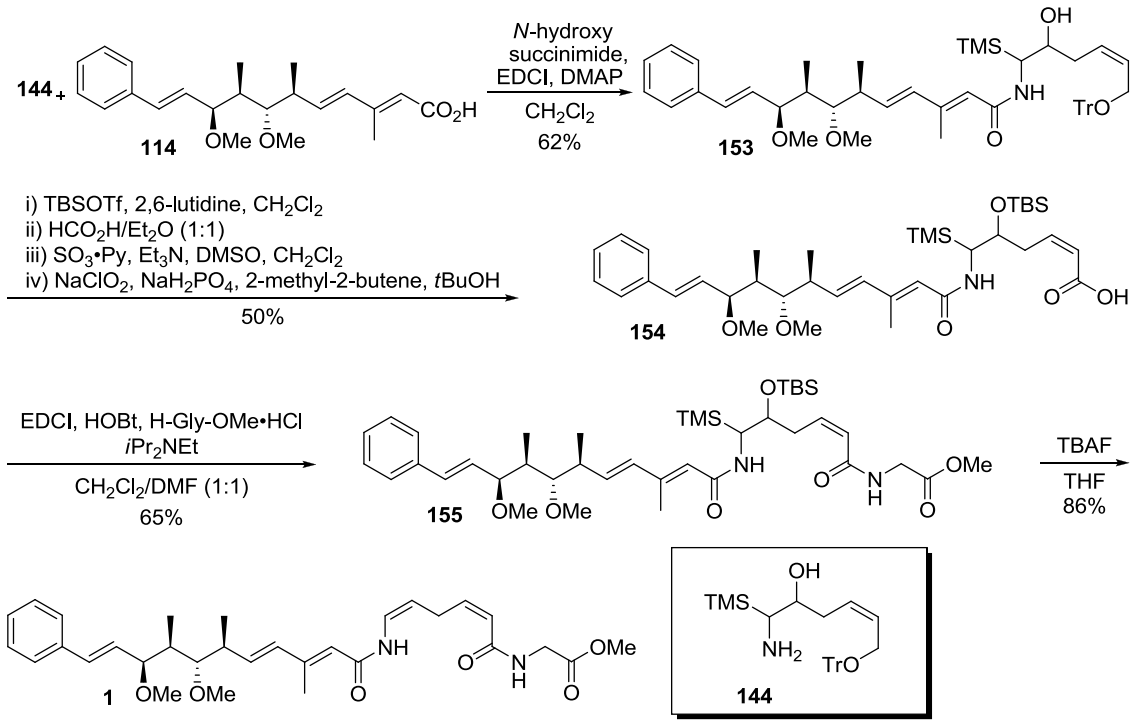


Scheme 26. Chakraborty's synthesis of the intermediate **144**.

The known carboxylic acid **114** was then subjected to an EDCI-mediated coupling with the amine lateral chain **144** to afford amide **153**. Protecting group manipulation followed by oxidation of the primary alcohol yielded carboxylic acid **154**.

EDCI-promoted peptide coupling with glycine methyl ester then afforded dipeptide **155**. Finally, a TBAF-mediated one-pot desilylation/Peterson olefination yielded (+)-crocacin A in 86% yield (**Scheme 27**).

In conclusion, Chakraborty's synthesis yielded (+)-crocacin A in ~1% yield and in 23 steps in the longest linear sequence.



Scheme 27. Chakraborty's completion of (+)-crocacin A, **1**.

1.5 Previous syntheses of (+)-crocacin B

To date, only one total synthesis of (+)-crocacin B **2** has been reported in literature by Rizzacasa and co-workers.[17] In 2003, Chakraborty's group attempted the synthesis of crocacin B from crocacin A *via* hydrolysis of the ester moiety, however, disappointingly, the saponification resulted in the exclusive formation of undesired side products.[16]

Rizzacasa's approach (2008)

Following Chakraborty's attempts, in 2008 Rizzacasa also attempted the direct synthesis of crocacin B *via* hydrolysis of crocacin A, but once again, the result proved disappointing. In fact, the base-mediated saponification led to complete degradation of the natural product. Faced with this initial drawback, Rizzacasa proposed a new synthetic strategy very similar to his previous approach to (+)-crocacin A. Crucially, however, Rizzacasa used the labile glycine TMSE ester **124** in place of glycine methyl ester **156** in order to overcome the issues involved in the final hydrolytic step (**Figure 20**).[17]

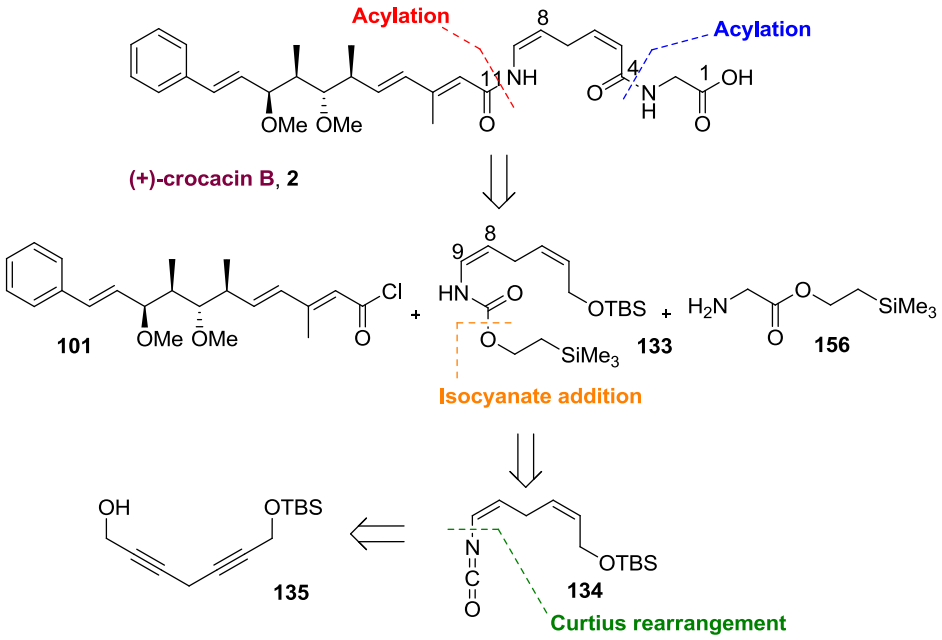
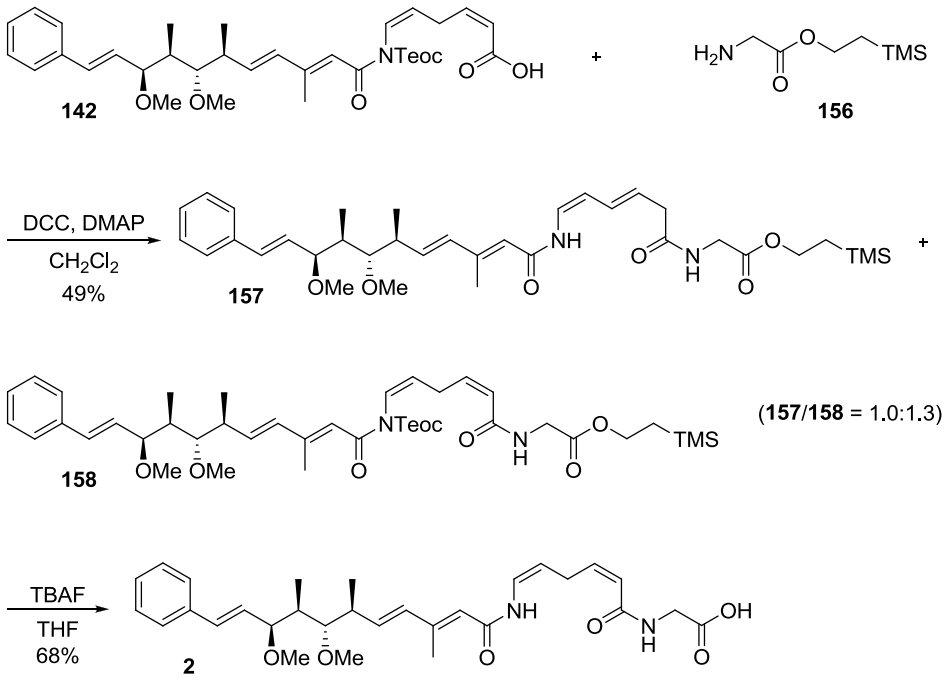


Figure 20. Retrosynthetic analysis of (+)-crocacin B by Rizzacasa.

Rizzacasa's synthesis began with the DCC-promoted coupling between the known carboxylic acid **142** and glycine TMSE ester **156** to afford enamide **158**. The coupling proceeded in low yield due to partial isomerisation of the C5-C6 double bond which resulted in formation of the undesired diene **157**. Practically, the product mixture was carried through to the final step, where treatment with TBAF removed the Teoc protecting group, yielding (+)-crocacin B **2** in 68% yield (**Scheme 28**).

Rizzacasa's approach yielded (+)-crocacin B in ~1% overall yield and required 15 steps in the longest linear sequence.



Scheme 28. Rizzacasa's synthesis of (+)-crocacin B, **2**.

2 Results and discussion

2.1 Formal synthesis of (+)-crocacin C

anti,anti-Stereotriad: hydroboration-oxidation approach

As part of our approach, several strategies were taken into consideration for the synthesis of (+)-crocacin C **3**. Our principal aim in all of these efforts was the development of a synthetic route which could easily access the primary amide of (+)-crocacin C as simply and quickly as possible and from which more complex derivatives could be explored. In addition, of course, the proposed synthetic route needed to be enantioselective, amenable to scale up, economically viable and capable of bringing some important elements of novelty with respect to the numerous previous syntheses of (+)-crocacin C currently reported in literature.

Our initial efforts towards the synthesis of (+)-crocacin C were based on a hydroboration-oxidation approach.[18] Thus, our retrosynthetic analysis began with a disconnection between the central core of the target, containing the four stereocentres, and the doubly conjugated lateral chain (**Figure 21**). This bond could be easily accessed through a HWE olefination between the corresponding aldehyde **28** and a diethylphosphonate intermediate **29**,[19] followed by functional group interconversion of the ester moiety into primary amide. Diethyl phosphonate **29** could be derived from a commercially available ethyl ester **159** in two straightforward steps of bromination and subsequent Michaelis-Arbuzov phosphonation following a well-known procedure.[20] The key aldehyde **28**, bearing the four stereocentres present in (+)-crocacin C, could be achieved *via* an asymmetric aldol addition to chiral aldehyde **160**. Aldehyde **160**, on the other hand, could be accessed *via* the substrate controlled hydroboration-oxidation of the α,β-unsaturated ester **161**, taking advantage of the indigenous chirality to introduce the two new stereocentres. Ester **161** could be accessed through Wittig olefination between aldehyde **163** and ylide **162**. Aldehyde **163** can be easily prepared from the commercially available Roche ester, *(S)*-methyl 3-hydroxy-2-

methylpropanoate **11**, which provides us with the first stereocentre of the target from the outset.

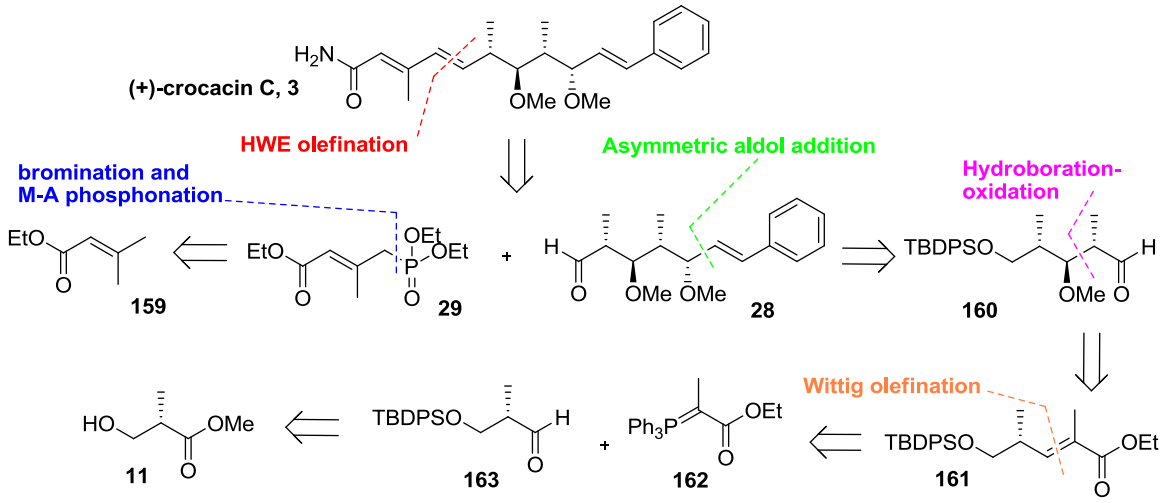
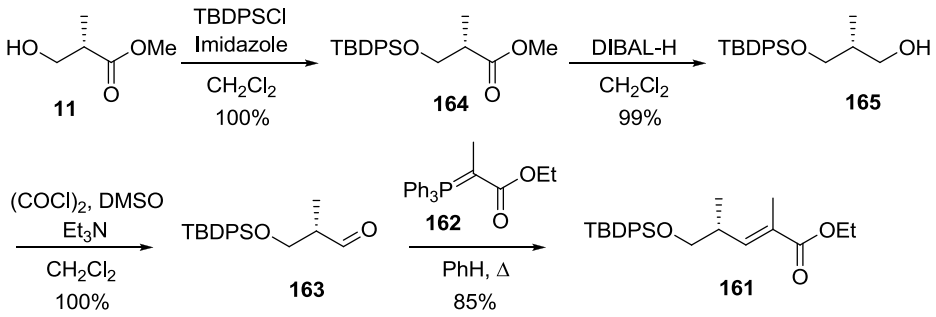


Figure 21. Retrosynthetic analysis of (+)-crocacin C *via* hydroboration approach.

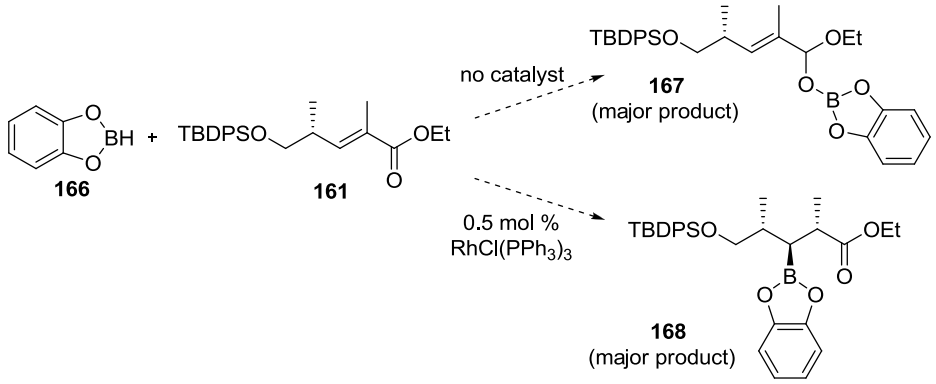
Our synthesis began with the TBDPS-protection of Roche ester **11**, followed by reduction of the ester moiety to yield primary alcohol **165**. Oxidation of the primary alcohol **165** under Swern conditions followed by Wittig olefination with ylide **162** afforded the desired conjugated ester intermediate **161**. These initial steps were extremely efficient and amenable to scale-up without problems of purity, epimerisation or drop in yields (>10 g scale) and accessed enoate **161** in excellent overall yield of 84% (**Scheme 29**).



Scheme 29. Route from the commercial Roche ester to the intermediate **161**.

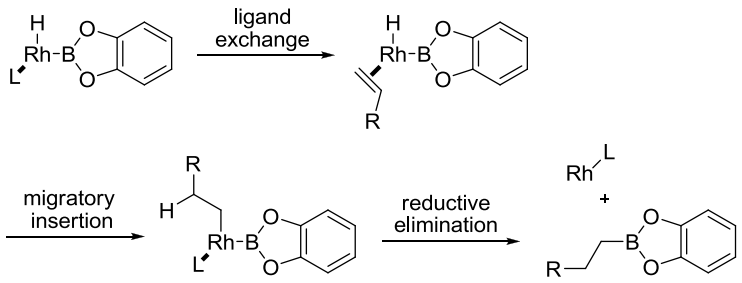
At this point, the hydroboration-oxidation strategy was ready to be tested on α,β-unsaturated ester **161**. The hydroboration step was performed in presence of a

catalytic amount of the Wilkinson's catalyst, $RhCl(PPh_3)_3$.[21] Literature reports have shown that small amounts of transition-metal complexes can accelerate the addition of boranes to alkenes under mild conditions and even at room temperature. In addition, the catalyst was expected to alter the chemoselectivity of the reaction in the case of multifunctional substrates. Studies made by Mannig and co-workers, have demonstrated that without Wilkinson's catalyst the borane tends to add preferentially to the carbonyl group of the ester **161**. However, in presence of 0.5 mol % of $RhCl(PPh_3)_3$, the hydroboration takes place preferentially at the double bond site.[22]



Scheme 30. Prediction of chemoselectivity in hydroborations.

The mechanism for the Rh-catalysed hydroboration reaction has not been fully established, but it is certainly fundamentally different from the corresponding uncatalysed processes. The most reasonable proposed mechanism is based on four phases (**Scheme 31**). The first step consists of the oxidative addition of the boron hydride to the metal, followed by ligand exchange in which the rhodium coordinates to the olefin. At this point, there is migratory insertion of the olefin into the rhodium hydride bond, followed by a final reductive elimination.



Scheme 31. Proposed mechanism for Rh-catalysed hydroborations.

On initial analysis, the stereoselective outcome of the reaction was predicted to be controlled by the chiral centre already present in our substrate **161**. This chiral centre was expected to direct preferential attack of the borane reagent from the *Si* face to avoid the steric hindrance of the methyl group (**Figure 22**).

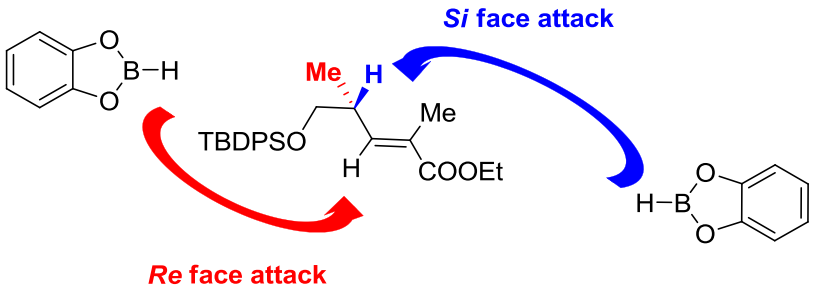


Figure 22. Predicted stereocontrol of the hydroboration reaction.

Thus, the α,β-unsaturated ester **161** was treated with different hydroborating agents, such as 9-BBN **169**, catecholborane **166** and pinacolborane **170** (**Figure 23**), using a wide range of reaction conditions (temperature, reaction time, presence or absence of microwave irradiation). Unfortunately, all attempts were unsuccessful returning only starting material (**Scheme 32, Table 2**).

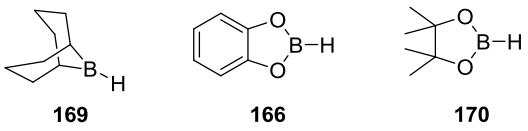
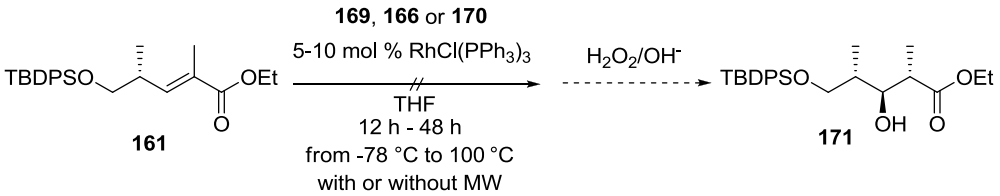


Figure 23. 9-BBN **169**, catecholborane **166**, pinacolborane **170**.

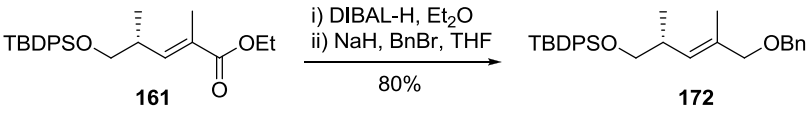


Scheme 32. Efforts towards hydroboration-oxidation.

Entry	Reagent	Time	Temperature	MW	mol % catalyst	Result
1	**169**	12 h	-78 °C	No	5 mol%	No reaction
2	**169**	24 h	RT	No	10 mol%	No reaction
3	**169**	48 h	100 °C	Yes	10 mol%	No reaction
4	**166**	12 h	-78 °C	No	5 mol%	No reaction
5	**166**	24 h	RT	No	10 mol%	No reaction
6	**166**	48 h	100 °C	Yes	10 mol%	No reaction
7	**170**	12 h	-78 °C	No	5 mol%	No reaction
8	**170**	24 h	RT	No	10 mol%	No reaction
9	**170**	48 h	100 °C	Yes	10 mol%	No reaction

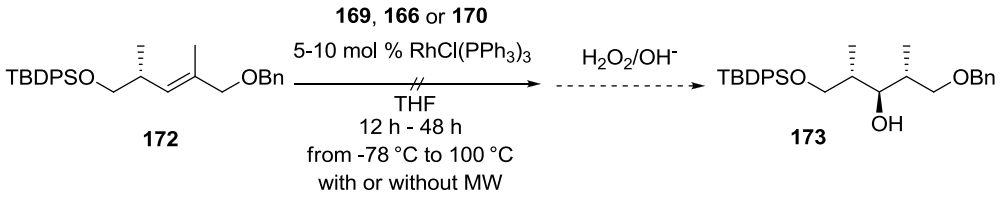
Table 2. Attempted conditions for the hydroboration-oxidation.

It was reasoned that the double bond was too electron-poor due to conjugation with the ester moiety and it therefore seemed necessary, in order to increase the reactivity of the alkene, to reduce the ester unit. Reduction of the ester moiety proceeded cleanly to yield the corresponding alcohol which was then protected as a benzyl ether (**Scheme 33**).



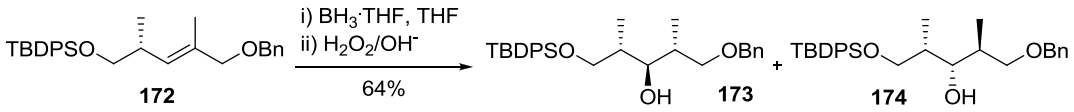
Scheme 33. Conversion to a more electron-rich system.

However, as in the case of the hydroboration of ester **161**, all attempts to achieve hydroboration proved unsuccessful, yielding only unreacted starting material (**Scheme 34**).



Scheme 34. Attempted hydroboration-oxidation of benzyl ether **172**.

On the other hand, when the hydroboration-oxidation sequence was performed using BH_3·THF, the reaction proceeded quickly and in fair yield. The observation that when bulky reagents such as 9-BBN, catecholborane and pinacolborane were used, the hydroboration did not take place at all, while with the use of the sterically undemanding reagent BH_3·THF the reaction was successful, suggested that steric factors exert more influence than electronic effects on the outcome of the reaction.
Unfortunately, even if BH_3·THF improved the efficiency of the reaction, the stereoselectivity was very poor, as the hydroboration-oxidation gave diastereomeric mixtures. When the reaction was performed at room temperature, a ratio of 3.5:1.0 in favour of the undesired isomer **174** was obtained.
Lowering the reaction temperature to -78 °C, resulted in a slight improvement in the ratio (1.8:1.0, **174**:**173**). However, the result was clearly not satisfactory (**Scheme 35**).



Scheme 35. BH_3·THF-mediated hydroboration-oxidation step.

Entry	Temperature	173/174
1	RT	1.0/3.5
2	-78 °C	1.0/1.8

Table 3. Effect of temperature on the stereocontrol.

The diastereoisomeric ratios obtained led us to reason that allylic strain ($A^{1,3}$ strain) might be controlling the facial selectivity of hydroboration.[23]
In our hydroboration-oxidation system, in fact, the conformation is clearly controlled by a *cis* substituent. The low-energy conformer is that in which the hydrogen eclipses the double bond (**A**), while steric interactions between the chiral methyl and the alkene methyl (*cis* substituent) prevent the orientation in which the chiral methyl group would eclipse the double bond (**B**). This conformational bias influences the facial selectivity of the hydroboration and is responsible for the diastereoisomeric ratio obtained (**Figure 24**).

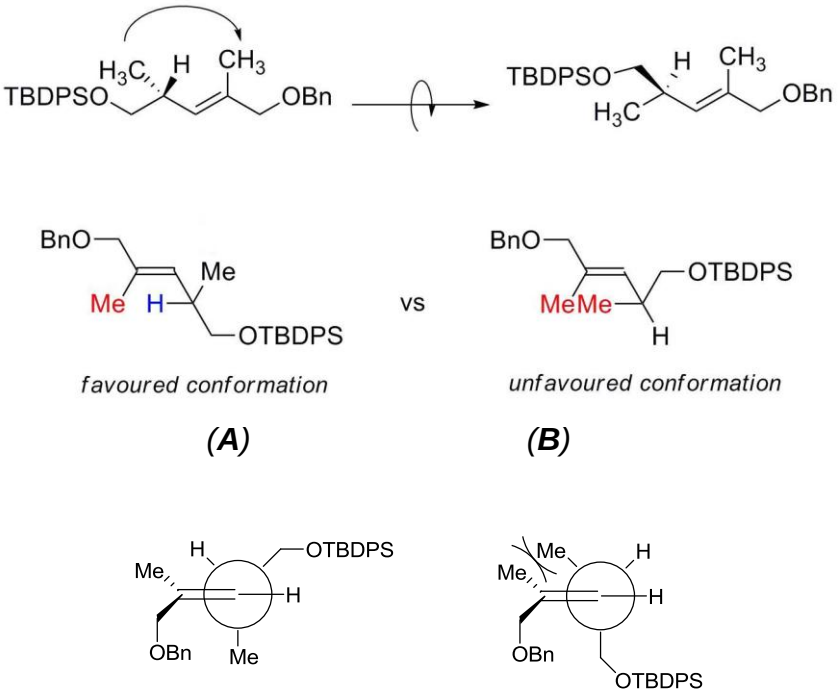


Figure 24. Allylic strain favours the undesired isomer **174**.

Taking into consideration the low selectivity associated with the hydroboration-oxidation approach further investigation in this route was abandoned in favour of new strategies.

anti,anti-Stereotriad: cuprate approach

In order to overcome the difficulties met in the previous strategy, a new synthetic route toward (+)-crocacin C, based on the exploitation of cuprate chemistry, was explored. Retrosynthetically, the first disconnection of this second strategy mirrors the previous approach, and involves a HWE olefination between aldehyde **28** and diethylphosphonate **29**.

In this revised approach, aldehyde **28** could be accessed from epoxide **175** *via* organocuprate to generate the *anti,anti* stereotriad. Epoxide **175**, in turn, could be obtained from α,β-unsaturated ester **176** *via* reduction to the corresponding allylic alcohol and subsequent Sharpless asymmetric epoxidation. Finally, the α,β-unsaturated ester **176** could be easily synthesised through a Swern

oxidation/Wittig olefination sequence starting from commercially available Roche ester, *(R)*-methyl 3-hydroxy-2-methylpropanoate **177** (**Figure 25**).

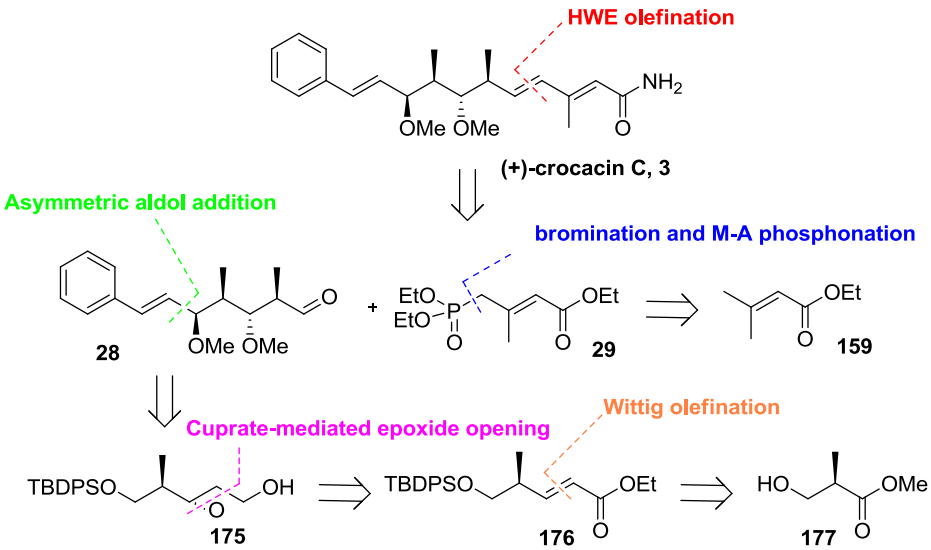
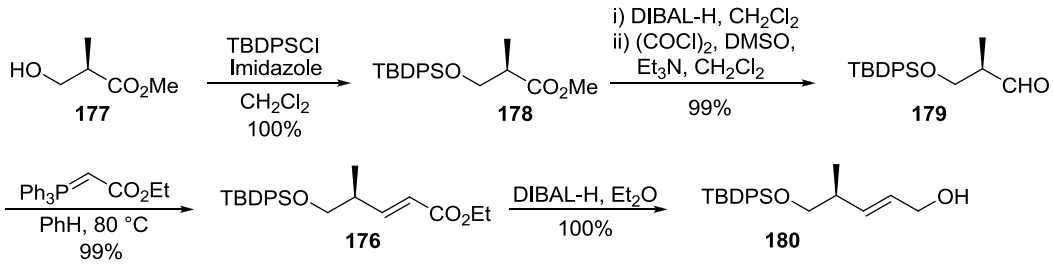


Figure 25. Second retrosynthetic analysis of crocacin C, **3**.

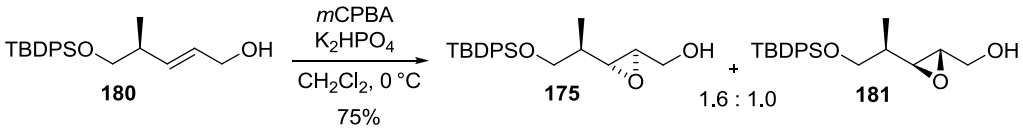
Synthetically, silyl protection of the *(R)*-Roche ester **177** yielded the TBDPS-ether **178** in excellent yield. DIBAL-H reduction of ester **178** followed by oxidation of the resulting primary alcohol afforded aldehyde **179** in excellent yield. Wittig olefination of aldehyde **179** with ethyl triphenylphosphonoacetate yielded the desired *(E)*-ethyl enoate **176** in near quantitative yield and as a single double bond isomer. DIBAL-H reduction of enoate **176** gave allylic alcohol **180**.



Scheme 36. Stereoselective synthesis of allylic alcohol **180**.

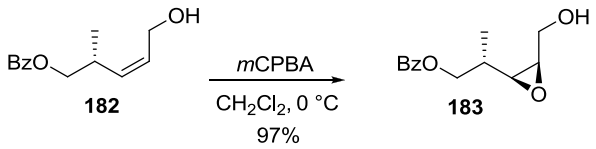
With the allylic alcohol **180** in hand, the epoxidation step was investigated. Epoxidation of this substrate under substrate controlled epoxidation conditions, using *m*CPBA and taking advantage of the chiral centre already present to direct the epoxidation, had been attempted previously within the Marquez group.[24] Disappointingly, the stereocontrol dictated by the methyl group was very poor, and

an unsatisfactory 1.6:1.0 mixture in favour of the desired diastereoisomer **175** was obtained (**Scheme 37**).



Scheme 37. Substrate controlled *m*CPBA epoxidation.

The rationale behind this result can be explained considering the work of Kishi and co-workers.[25] When *cis*-allylic alcohol **182** is the substrate of epoxidation using *m*CPBA, the desired isomer **183** is the only product of the reaction (**Scheme 38**). This is due to the fact that **A** is the preferred conformation assumed by the substrate as it minimises the steric compression present in the alternative eclipsed conformations **B** and **C** (**Figure 26**).



Scheme 38. Kishi epoxidation of *cis*-allylic alcohol **182**.

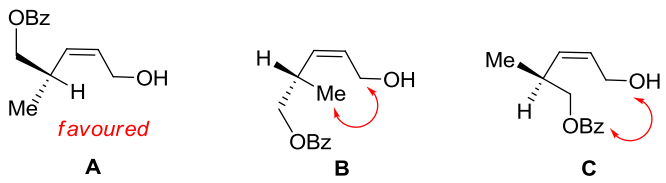
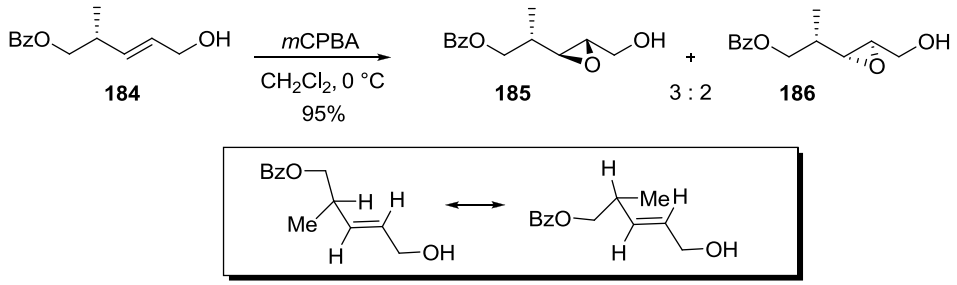


Figure 26. Conformations of *cis*-allylic alcohol **182**.

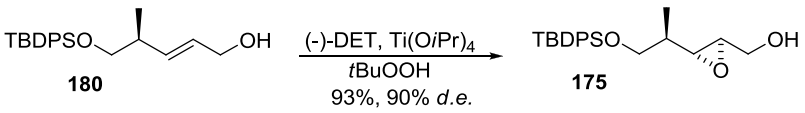
On the other hand, when Kishi's group performed the same reaction on the *trans*-allylic alcohol **184**, the stereocontrol was significantly reduced, and a 3:2 mixture of isomers was obtained (**Scheme 39**).



Scheme 39. Kishi epoxidation of *trans*-allylic alcohol **184**.

The lower stereoselectivity observed in the epoxidation of *trans*-allylic alcohol **184** could be attributed to a lower degree of preference of one conformation with respect to the others, as the *E* geometry of the double bond causes less steric compression.

Thus, *trans*-allylic alcohol **180** was deemed unsuitable to undergo substrate controlled epoxidation, and was instead subjected to a reagent controlled epoxidation under Sharpless conditions. Gratifyingly, the Sharpless asymmetric epoxidation of alkene **180** proceeded in excellent yield and with high diastereoselectivity to yield the *syn*-epoxy-alcohol **175** as an inseparable (95:5) mixture of diastereomers. This mixture of diastereoisomers was carried directly onto the next steps.



Scheme 40. Stereocontrolled synthesis of the epoxide **175**.

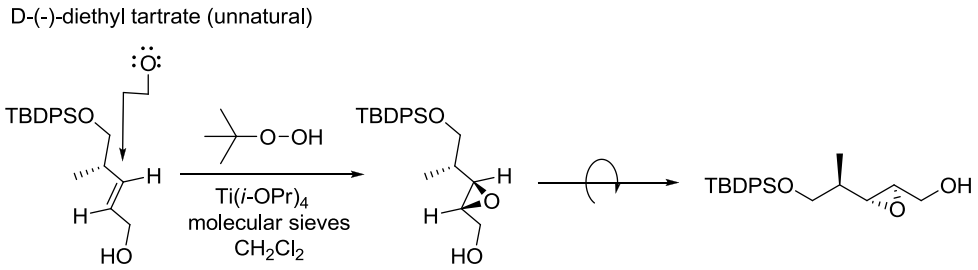
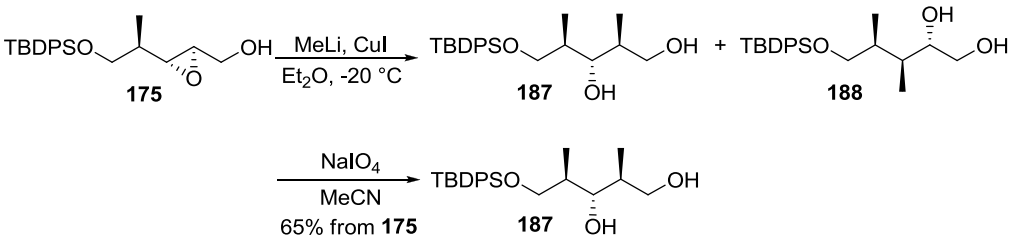


Figure 27. Application of the SAE to our substrate **180**.

In conclusion, the strategy led to the formation of the epoxide **175**, with excellent yield in all steps. The synthetic sequence is amenable to scale up and was able to deliver significant amounts of epoxide (>10 g) in relatively short amounts of time.

At this point, the regio- and stereoselective opening of 2,3-epoxy alcohol **175** with a methyl cuprate was attempted. It was reasoned that opening of epoxide would take place regioselectively at the C2 position due to both cuprate chelation with the free alcohol and steric hindrance exerted by the existing methyl group on the incoming nucleophile at the undesired position.

In our initial attempt, the epoxy-alcohol mixture was treated with the lower order Gilmans' reagent Me_2CuLi, under Nakamura's conditions, to yield the desired 1,3-diol **187** together with trace amounts of the 1,2-diol side product **188**.[26] The undesired diol was removed by treatment of the diastereomeric mixture with sodium periodate. This two step sequence yielded the desired 1,3-diol **187** in reasonable overall yield of 65% (**Scheme 41**). In later attempts, the two diastereoisomers were successfully separated by flash column chromatography.



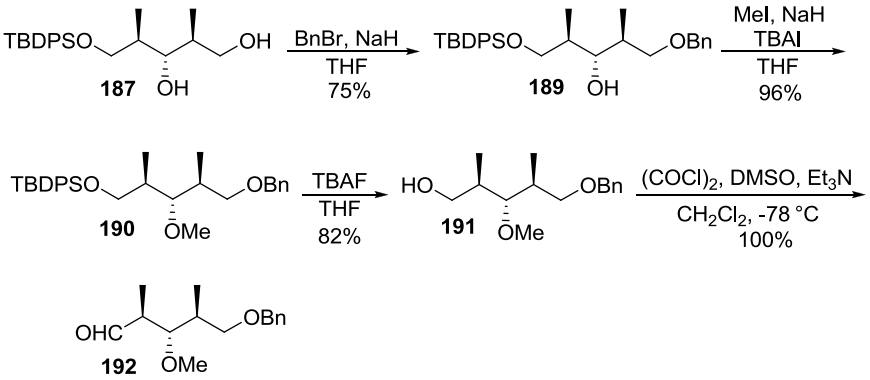
Scheme 41. Epoxide-opening *via* cuprate approach.

In order to improve the reaction yield, a more reactive higher order Lipshutz' cuprate, $Me_2Cu(CN)Li_2$ (in which the Cu-cluster contains an additional ligand), was utilised, following Dias' experimental conditions.[7] Despite an increased reaction rate with respect to the first order cuprate conditions, the reaction yield obtained was slightly lower (56%). Considering these results, Nakamura's procedure became the pivotal strategy for our synthesis.

The diastereomerically pure 1,3-diol **187** was then selectively benzylated and the resulting secondary alcohol **189** methylated to afford the differentially protected triol **190**. Desilylation of ether **190** using TBAF yielded the free primary alcohol

191 which was oxidised under Swern conditions to produce the desired aldehyde **192** in excellent yield.

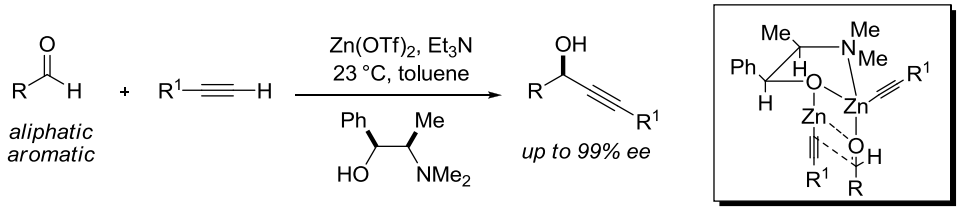
Until the arrival to aldehyde **192**, the synthetic route proceeded well, with reasonably good yields, and as such was considered a satisfactory improvement with respect to the previous disappointing hydroboration-oxidation approach.



Scheme 42. Conversion of 1,3-diol **187** to aldehyde **192**.

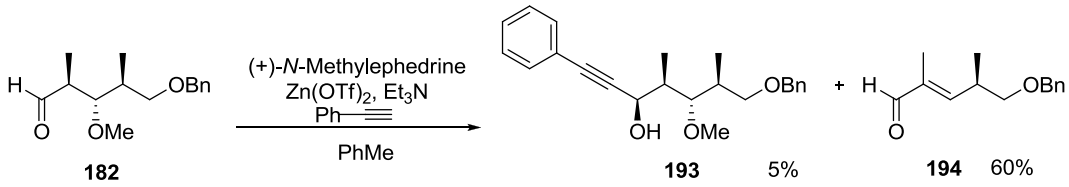
Strategies of coupling

With the aldehyde intermediate **192** in hand, several coupling approaches were explored for the introduction of the styrene moiety. A preliminary coupling attempt was based on Carreira's procedure which, if successful, would provide a one-pot stereoselective condensation of aldehyde **192** with the phenylacetylenic moiety. Carreira reported the enantioselective synthesis of propargylic alcohols by direct addition of terminal alkynes to aldehydes, under mild conditions and in the presence of either (+)- or (-)-*N*-methylephedrine as a chiral additive (**Scheme 43**).[27] Carreira's proposed mechanism involves the *in situ* generation of a zinc alkynylide as key step. The choice of chiral additive as a ligand for Zn(II) then determines the enantioselectivity of the reaction.



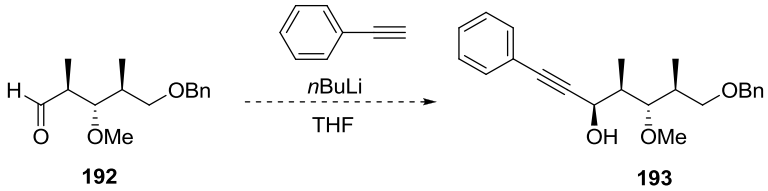
Scheme 43. Carreira's alkynylation of aldehydes.

Unfortunately, when Carreira's conditions were applied to aldehyde **182**, a disappointingly small percentage of aldehyde evolved toward the desired product **193**, the major product **194** being the result of collateral β-elimination.



Scheme 44. Application of Carreira's protocol to our substrate.

Considering the unfortunate results, Carreira's procedure was abandoned and subsequent efforts focused on a substrate controlled stereoselective coupling.



Scheme 45. Substrate-dependent proposed coupling.

The main concept in this new approach (**Scheme 45**) was to utilise a straightforward addition of the phenylacetylene moiety to the aldehyde intermediate **192**, without the use of chiral reagents, through the exploitation of the intrinsic directing-effects exerted by the substrate. The aldehyde intermediate **192** bears substituents at both the α and β positions and each of these stereocenters could potentially influence the stereochemistry of the nucleophilic addition.

This is a typical example of an integrated α,β-stereoinduction model as proposed by Evans.[28a,b] In fact, this revised model integrates the Felkin-Ahn and 1,3-asymmetric induction models and could be used to predict the stereoselective outcome of the reaction. Aldehyde **192** displays an *anti* relationship between the α-methyl and the β-alkoxy substituents, and based on Evans' model, the relative configurations of these substituents should mutually reinforce each other and result in preferential nucleophilic addition as to generate the *syn,anti*-adduct (**Figure 28**). This analysis leads to the conclusion that such a synergic effect should enhance the π-facial selectivity in the desired fashion.

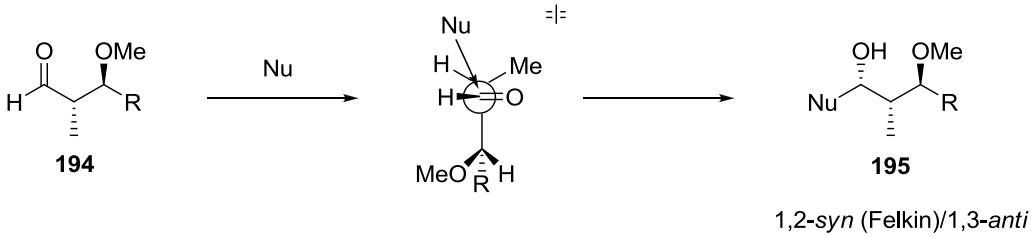


Figure 28. Evans merged α,β-stereoinduction polar model.

Alternatively, chelation control would afford a different result. In fact, as Evans shows in his studies, the chelate of the *anti*-substituted aldehyde reveals a non reinforcing nature of this stereochemical array. The chelate intermediate places the α and β substituents on opposite sides of the coordinated carbonyl. As the nucleophile approaches from the Felkin diastereoface, it encounters steric encumbrance from the α-methyl group (**Figure 29**), therefore addition to *anti*-substituted aldehydes would result in diminished stereoselectivity under chelate control.

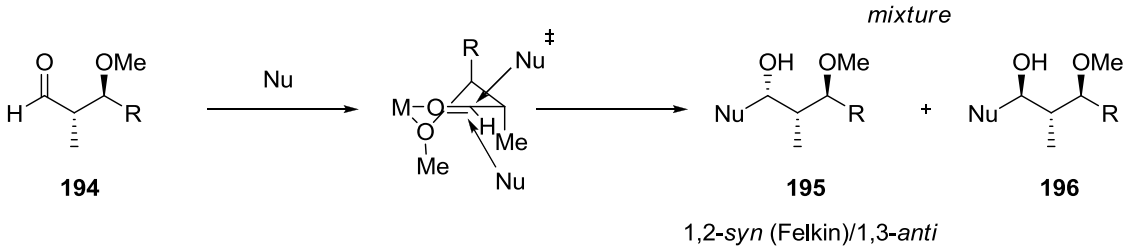
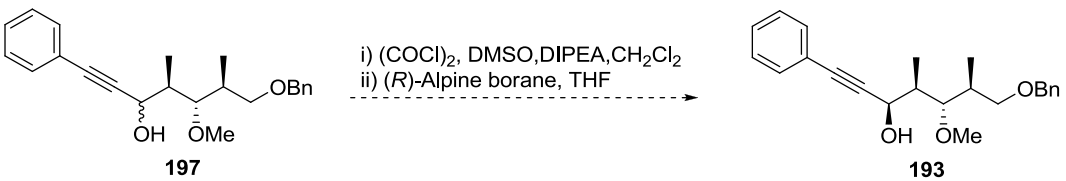


Figure 29. Evans merged α,β-stereoinduction chelate model.

However, it was reasoned that, even in case of unsatisfactory isomeric ratios in the products, an oxidation/stereoselective reduction sequence could be exploited following Midland's protocol to afford the desired product (**Scheme 46**).[29]



Scheme 46. Oxidation/stereoselective reduction proposed sequence.

The reduction of unhindered ketones, such as acetylenic ketones, using either enantiomer of B-3-pinanyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane®), known as the Midland reduction, provides a simple means of forming chiral, non racemic alcohols of known absolute configuration in high enantiomeric purity.

The reaction is widely applicable to ketones, however, on the basis of steric effects, in general, methyl ketones give the lowest selectivity. If the group adjacent to the ketone is a branched alkyl group or phenyl group, then the purity of the α-pinene becomes the limiting factor in obtaining high enantioselectivities. The reaction's selectivity is highly reliable and use of the same enantiomer of Alpine-Borane® consistently gives the same absolute configuration of the resulting alcohol. The reaction conditions are very mild and the reagent is chemoselective easily discriminating the acetylenic group from other unsaturated functionalities.

A major contributing factor to the degree of asymmetry observed in the alcohol products is the specificity of Alpine-Borane® for the substrate ketone. The ketone is postulated to approach the borane such that a boatlike transition state is formed. Two possible transition states are possible. The bulkier substituent could be accommodated in either an axial or an equatorial orientation. The preference for reduction by transition state **A** or transition state **B** would determine the absolute degree of asymmetry that could be introduced into the resulting alcohol (**Figure 30**). Other competing modes of reduction, *i.e.* dehydroboration-reduction, or the use of α-pinene of less than 100% *e.e.*, will lower the asymmetric induction observed.

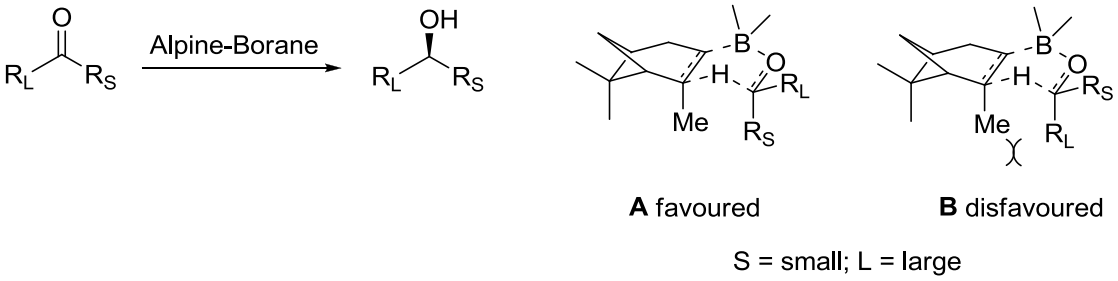
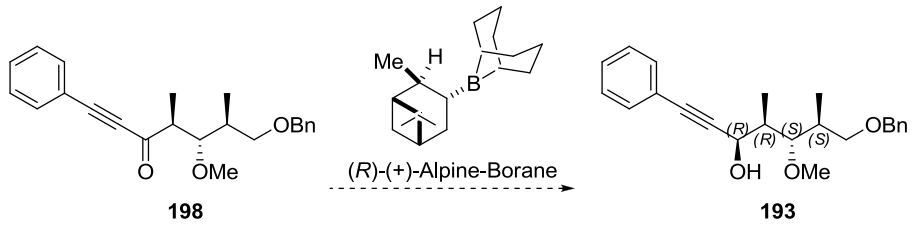


Figure 30. Transition-state model.

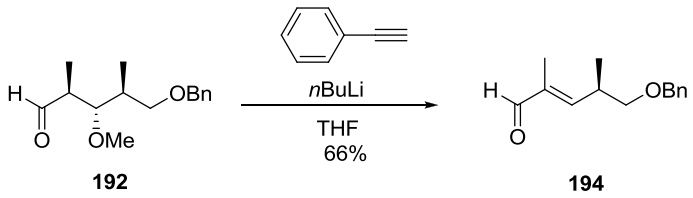
Orientating the ketone substituents into the proposed model transition state such that the smallest group occupies the pseudoaxial position, it is possible to predict the configuration of the asymmetric carbinol center generated. In our specific case,

considering the nature of the substituents present on each side of the ketone, it was expected that the desired isomer would be obtained using *(R)*-Alpine-Borane® (**Scheme 47**).



Scheme 47. Proposed use of *(R)*-Alpine-Borane®.

The applicability of this strategy, was tested on a small scale. Disappointingly, all attempts to introduce the phenyl acetylene unit resulted in β-elimination. These results mirror those encountered during the application of the Carreira methodology, further corroborating the unsuitability of this particular approach.



Scheme 48. New efforts toward the aldol addition.

At this stage an alternative strategy based on a Stille coupling between an acid chloride intermediate and an organotin reagent was considered.[30]

The palladium-catalysed coupling of acid chlorides with organotin reagents has been demonstrated as an efficient reaction to afford ketones in high yields. The reaction is quite general with respect to both coupling partners, the ketone product is formed rapidly under mild, neutral reaction conditions. Furthermore, a wide variety of functional groups can also be present on the acid chloride, including nitro, nitrile, haloaryl, methoxy, ester, and even aldehydes. In the proposed catalytic cycle for this reaction the active catalyst bis(triphenylphosphine) palladium(0) **2**, generated from benzylchlorobis(triphenylphosphine)palladium(II),

undergoes oxidative addition of the acid chloride to give the acylchloropalladium complex **3**. Transmetalation reaction between complex **3** and the organotin reagent yields the acylalkylpalladium(II) species **4**, which undergoes reductive elimination of the ketone and regenerates **2.** The transmetalation stage **3** - **4,** in the palladium-catalysed ketone synthesis, has been proposed to occur by the electrophilic attack of acylchloropalladium(II) complex **3** on the carbon bonded to tin (**Figure 31**).

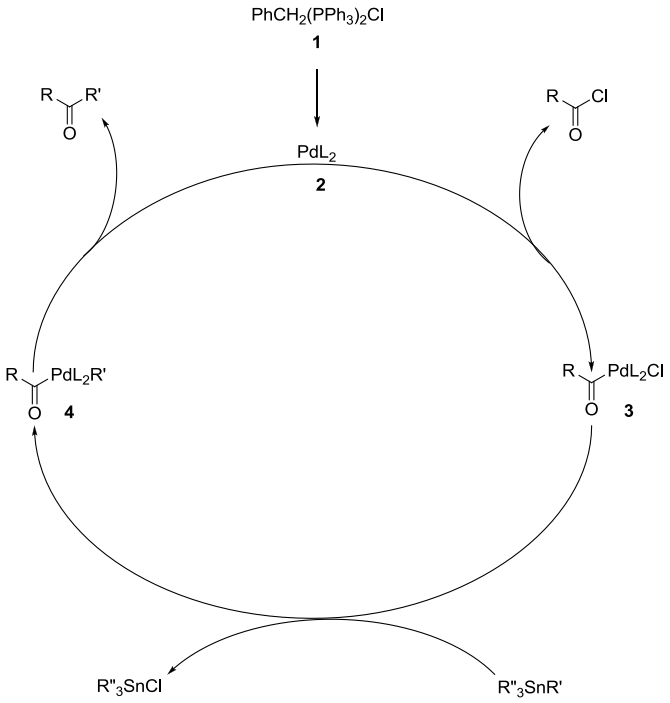
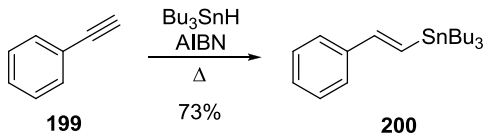


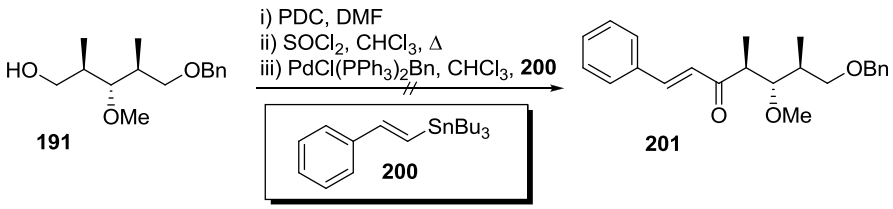
Figure 31. Catalytic cycle for the coupling reaction of acylchlorides with organotins.

Synthetically, this new approach began with the synthesis of the stannyl-fragment **200** which was easily synthesised from phenylacetylene **199** through treatment with tributyltin hydride and AIBN (**Scheme 49**).



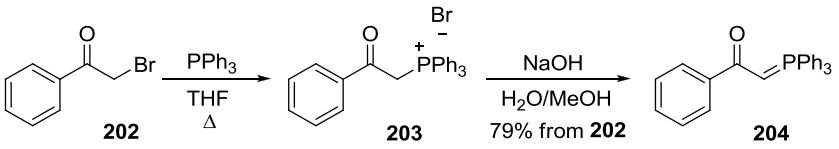
Scheme 49. Synthesis of the stannyl-intermediate **200**.

On the other hand, the acid chloride was generated starting from alcohol **191** *via* PDC oxidation to carboxylic acid, followed by conversion to chloride *via* treatment with $SOCl_2$. Unfortunately, formation of the acid chloride proved highly problematic due to the same β-elimination observed previously, which affected the purity of the acid chloride obtained. Nevertheless, the Stille coupling was attempted on the crude acyl chloride, however the reaction disappointingly resulted in complete decomposition of starting material with no product being detected (**Scheme 50**).



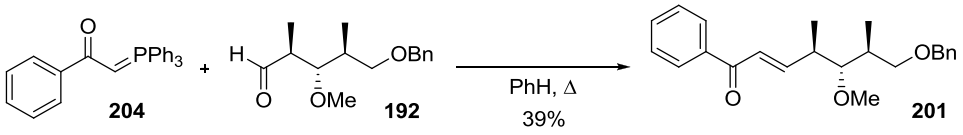
Scheme 50. Stille coupling attempt.

Faced with the difficulties encountered during the nucleophilic addition to both the aldehyde and acid chloride, a new approach was subsequently taken into consideration. Our new strategy was based on a Wittig olefination/[3,3]-sigmatropic rearrangement sequence. The first step required the synthesis of ylide **204** which was afforded in good yield using a simple procedure reported in literature (**Scheme 51**).[31]



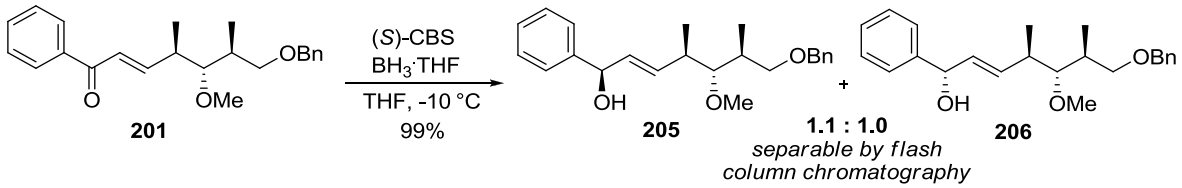
Scheme 51. Preparation of ylide **204**.

Olefination of aldehyde **192** with the stabilised phosphorane **204**, as expected, gave the desired *(E)*-enone **201** as a single double bond isomer, in moderate yield. The low yield could potentially be explained by the formation of the previously seen undesired β-elimination product **194**, although no side products were isolated (**Scheme 52**).



Scheme 52. Synthesis of enone **201** *via* Wittig olefination.

Stereoselective Corey-Bakshi-Shibata reduction of enone **201**,[32] proceeded with an excellent yield of 99%, however a disappointing 1.1:1.0 mixture of diastereoisomers in favour of the desired product **205** was obtained. Fortunately, this mixture was easily separable by flash column chromatography and the desired isomer **205** was obtained cleanly in fair yield (**Scheme 53**).



Scheme 53. Asymmetric reduction of enone **201**.

anti,anti,syn-Stereotetrad: [3,3]-sigmatropic rearrangement

The desired allylic alcohol **205** was acetylated to afford the intermediate **207** from which the key [3,3]-sigmatropic rearrangement of allylic acetates was explored.[33a-d] This transformation proceeds *via* a pericyclic reaction, characterised by the movement of a sigma bond from the 1 position to the relative 3 position. The reaction is so called because the newly formed σ bond has a 3,3 relationship to the former σ bond as shown below (**Figure 32**):

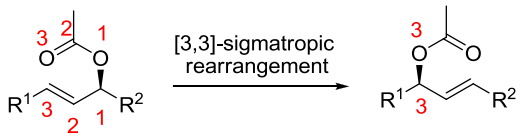


Figure 32. Bond movement in the [3,3]-sigmatropic rearrangement.

The process occurs in a concerted manner and is characterised by suprafacial symmetry as the new bond is formed on the same face as was the former. There are three components involved in this transformation: two non-conjugated π bonds, which must overlap, with a σ bond connecting the two. All of these components participate with two electrons each, with the pericyclic process taking place through a chair-like six-membered transition state as shown below (**Figure 33**):

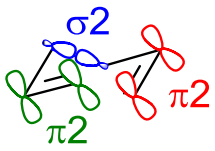


Figure 33. Orbital description in the [3,3]-sigmatropic rearrangement.

In our case, we considered a Pd(II)-catalysed rearrangement. The metal-catalysed rearrangement proceeds through a cyclisation-induced mechanism starting with the coordination of the metal to the alkene, followed by nucleophilic attack of the oxygen to form a six-membered ring, which finally collapses to generate the desired product (**Figure 34**).

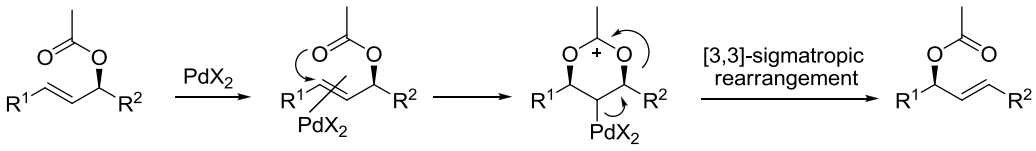
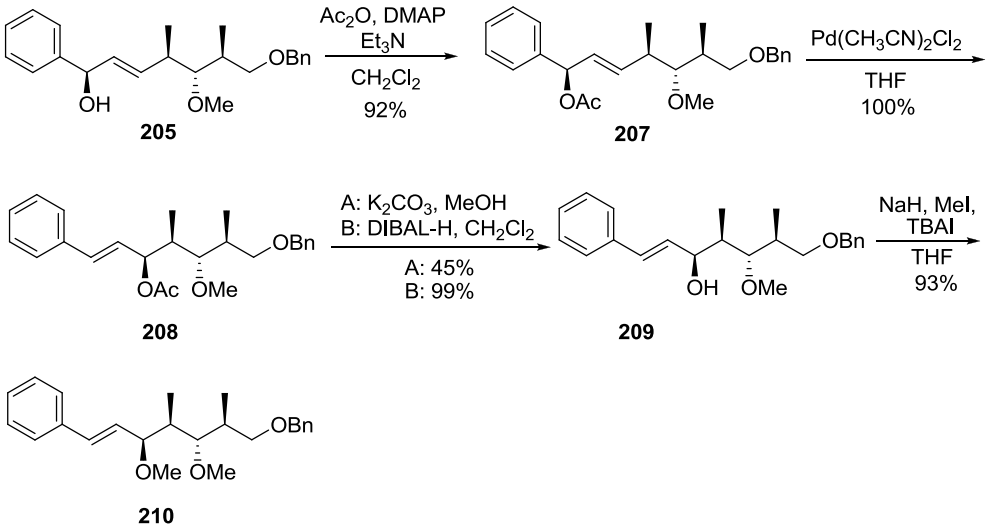


Figure 34. [3,3]-sigmatropic rearrangement.

Upon treatment with $PdCl_2(CH_3CN)_2$ under Overman's conditions, the acetate group of **207** was cleanly transposed to generate the *anti:anti:syn* adduct **208** in quantitative yield and as a single diastereomer. As this palladium(II)-catalysed sigmatropic rearrangement of allylic acetates is characterised by a suprafacial stereochemistry, there was complete transfer of chirality. After the Overman [3,3]-sigmatropic rearrangement, reduction of the acetate group was cleanly achieved using DIBAL-H in 99% yield. Subsequently, the resulting secondary alcohol **209** was methylated to afford the fully protected intermediate **210** (**Scheme 54**).

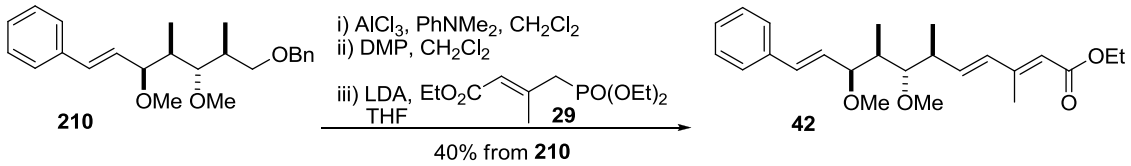
Thus far, this new approach had successfully incorporated each of the four chiral centres present in (+)-crocacin C.



Scheme 54. [3,3]-sigmatropic rearrangement approach.

Incorporation of the lateral chain of (+)-crocacin C *via* HWE olefination

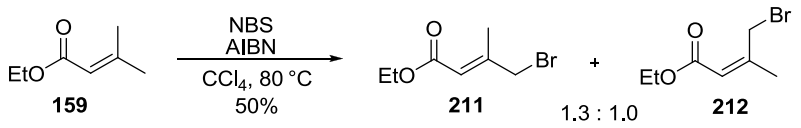
Benzyl-deprotection of intermediate **210**,[34] followed by careful DMP-oxidation[35] of the resulting primary alcohol and stereoselective Horner-Wadsworth-Emmons olefination with phosphonoacetate **29** successfully completed the formal synthesis of (+)-crocacin C (**Scheme 55**).



Scheme 55. Completion of the formal synthesis of (+)-crocacin C.

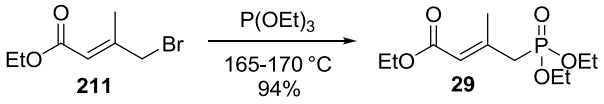
Phosphonate **29** was prepared in two steps from the commercially available ester ethyl 3-methylbut-2-enoate **159**. The initial bromination step afforded a 1.3:1.0 mixture of two isomers in favour of the desired product **211**. This mixture was

cleanly separated *via* column chromatography to afford the desired isomer **211** in 28% yield (**Scheme 56**).



Scheme 56. Bromination of the lateral chain.

Phosphonation of bromide **211** was performed following a Michaelis-Arbuzov procedure (**Figure 35**).[36] Thus, *(E)*-ethyl 4-bromo-3-methylbut-2-enoate **211** was heated with triethyl phosphite to afford the desired lateral chain *(E)*-ethyl 4-(diethoxyphosphoryl)-3-methylbut-2-enoate **29** in excellent yield (**Scheme 57**).



Scheme 57. Phosphonation of the lateral chain.

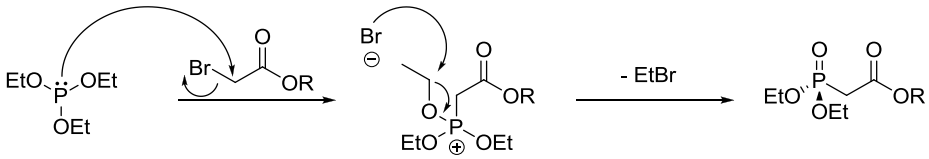
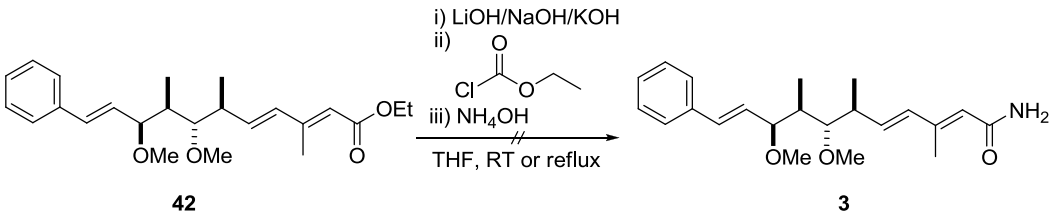


Figure 35. Michaelis-Arbuzov mechanism.

The spectral data and optical rotation of dienoate ester **42** is concurrent with that reported by Chakraborty and co-workers for the same advanced intermediate during their synthesis of (+)-crocacin C.[6] Gratifyingly, the HWE olefination proceeded with complete stereocontrol of the double bond geometry.

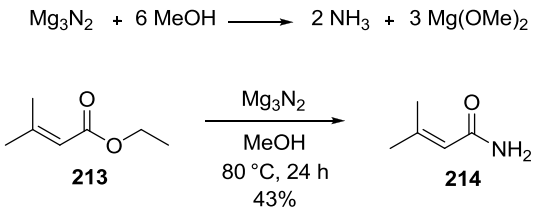
In summary, a novel formal synthesis of (+)-crocacin C was completed, taking advantage of a highly regio-selective cuprate addition to the epoxide and a diastereoselective [3,3]-sigmatropic rearrangement. The final steps to achieve a total synthesis of (+)-crocacin C required the functional group interconversion of ethyl ester **42**, into the (+)-crocacin C **3** amide. Initial attempts were based on the

saponification of ester **42** to the corresponding carboxylic acid, followed by activation with ethylchloroformate and subsequent treatment with ammonium hydroxide, following Chakraborty's procedure.[6] Unfortunately, this procedure was unsuccessful, likely due to issues encountered during the saponification step. Treatment of the ethyl ester **42** with NaOH, KOH or LiOH at room temperature failed to give satisfactory results, while carrying out the reaction in refluxing THF led to epimerisation and decomposition of the starting material (**Scheme 58**).

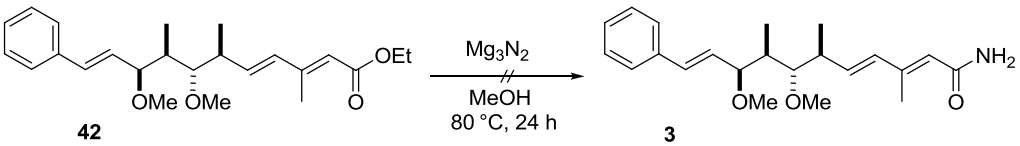


Scheme 58. Final functional group interconversion *via* saponification.

Application of Ley's conditions using magnesium nitride in methanol as a source of ammonia, proceeded in fair yield on a simple model system (**Scheme 59**).[37] Disappointingly, this methodology was unsuccessful on the more complex substrate **42** (**Scheme 60**).



Scheme 59. Magnesium nitride treatment in model system **213**.



Scheme 60. Final functional group interconversion *via* magnesium nitride.

2.2 Revised total synthesis of (+)-crocacin C

anti,anti-Stereotriad: crotylboronation approach

Despite the successful completion of a novel formal synthesis of (+)-crocacin C, the approach itself was deemed unsuitable for scale-up due to the number of steps required and its low overall efficiency. In addition, the final conversion of the ester moiety into the primary amide was unsuccessful under all attempted conditions. Challenged by this outcome, an alternative, more convergent route to (+)-crocacin C was devised. This led to the development of a second generation synthesis based on a crotylboronation/[3,3]-sigmatropic rearrangement approach. As shown in **Figure 36**, this revised strategy was much more concise with respect to the previous approaches. The foremost alteration considered was the introduction of the lateral chain directly as primary amide through a Stille coupling, thus avoiding the issues related to the final amide formation. The styrenyl moiety on the other hand was envisioned as originating through a cross-metathesis reaction followed by the highly successful [3,3]-sigmatropic rearrangement previously employed as part of our first generation synthesis. This led to the fragment **215** in which the iodo-olefin could be introduced *via* Takai olefination while the opposite terminal olefin could, in another significant alteration to the previous approach, be accessed by crotylboronation of aldehyde **163**.

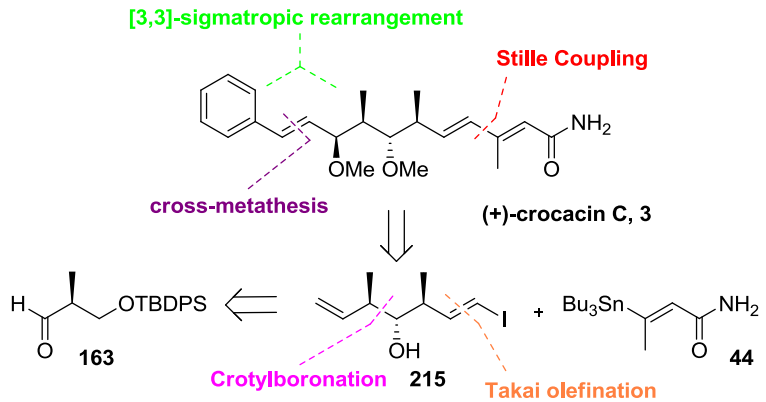
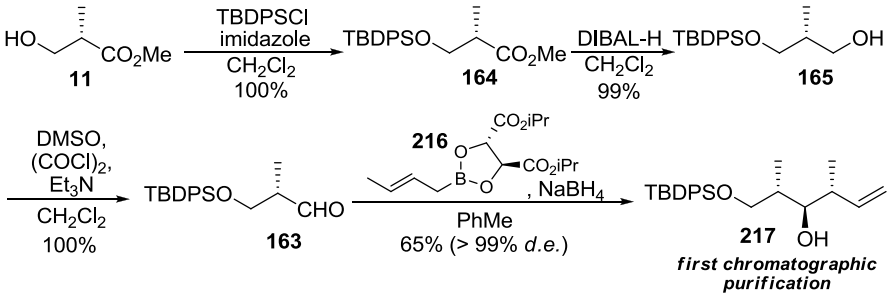


Figure 36. Second generation retrosynthesis of (+)-crocacin C, **3**.

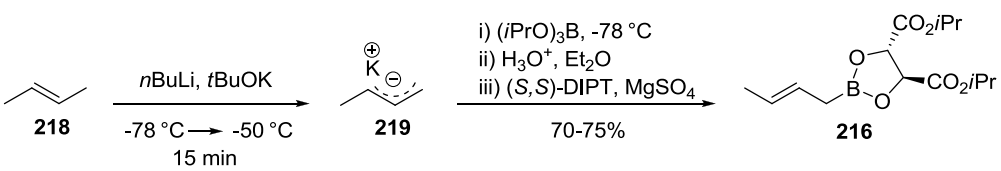
Our revised synthesis of (+)-crocacin C **3** began with Roche ester **11** which, *via* silyl protection and reduction-oxidation of the resultant methyl ester **164**, was converted to aldehyde **163.** The key diastereoselective crotylboronation of aldehyde **163** under Roush's conditions[38a,b] yielded the desired *anti,anti*-adduct **217**. These initial steps in the synthesis were straightforward, quick and high-yielding. It is noteworthy that the reaction sequence was amenable to scale-up (> 10 g) without significant drop in the yield and purity of the sample and, significantly, alcohol **217** was the first intermediate in the synthesis that required purification (**Scheme 61**).



Scheme 61. Synthesis of alcohol **217**.

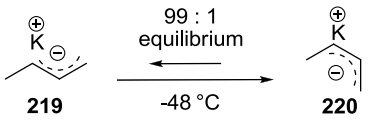
Roush's crotylboronation

The key step in our new approach was the pivotal crotylboronation that allowed the one pot insertion of two stereocentres to generate the challenging *anti,anti* stereotriad in a single transformation. The chiral reagent *(S,S)*-diisopropyl tartrate-modified *(E)*-crotylboronate **216** is well known in literature and can be prepared with high isomeric purity (> 98%) *via* metallation of *trans*-2-butene **218** with *n*-butyllithium and potassium *tert*-butoxide in tetrahydrofuran. The resultant *(E)*-crotylpotassium **219** can then be treated with triisopropylborate and esterified with *(S,S)*-DIPT.[38a]



Scheme 62. Roush synthesis of asymmetric crotylboronate **216**.

The first step involves *n*-butyllithium deprotonation of *trans*-2-butene while potassium *tert*-butoxide treatment subsequently affords a stabilised ion pair. In this phase, temperature control is extremely important. Schlosser's studies have shown that at -48 °C the crotylpotassium species exists as a 99:1 equilibrium in favour of the *(Z)* isomer (**Scheme 63**).[39]



Scheme 63. Importance of temperature control.

The *cis* isomer is favoured due to the *endo* transition state in which the protons of the terminal methyl group can contribute hydrogen-bonding with the anion. For this reason the reaction must be strictly carried at -50 °C, never above.

The choice of K^+ as counter-ion is also very important as allylpotassium species are fairly stable, undergoing configurational changes only very slowly.

With the chiral reagent *(S,S)*-DIPT **216** in hand, Roush's crotylboration was explored using the *(S)*-aldehyde **163**. This substrate pairing is an example of a mismatched double asymmetric combination. The desired diastereoisomer **217** is intrinsically disfavoured, displaying *anti*-Felkin relationship with respect to the aldehyde. However, through utilisation of the chiral auxiliary, it was possible to override the diastereofacial preference of the aldehyde (**Figure 37**).[38b]

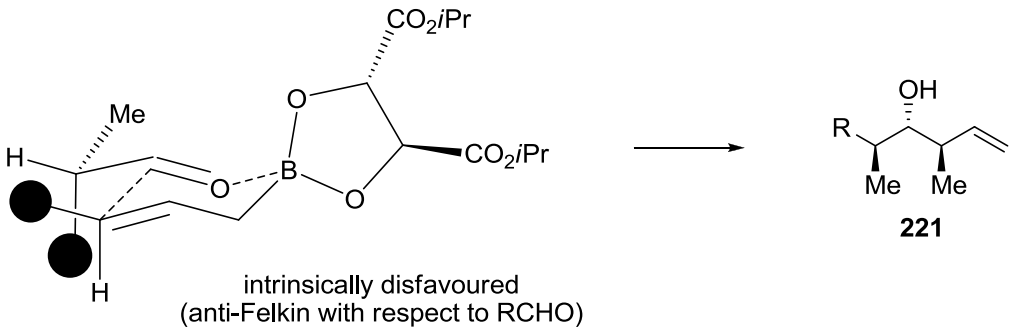
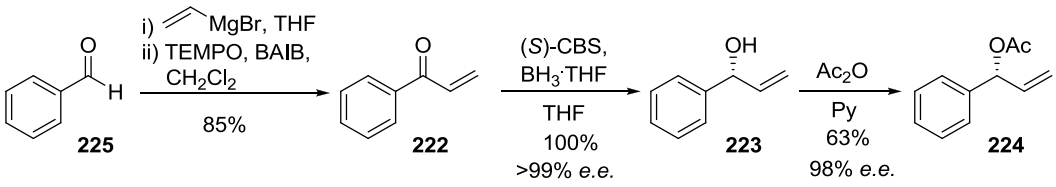


Figure 37. Mismatched double asymmetric crotylboration.

Significantly, Roush's crotylboronation did not only generate the desired *anti,anti*-adduct, but it also provided an olefinic handle from which a cross-metathesis could be explored.

Insertion of styrene moiety *via* cross-metathesis

In order to determine the maximum efficiency of our terminal olefin **217** in cross-metathesis reactions, three potential coupling partners were prepared: enone **222**, allylic alcohol **223** and allylic acetate **224**. Enone **222** was accessed *via* Grignard addition to benzaldehyde **225**, followed by oxidation of the resultant allylic alcohol with TEMPO/BAIB.[40] Enone **222** was stereoselectively reduced to the corresponding allylic alcohol **223** *via* Corey-Bakshi-Shibata reaction and finally, the allylic alcohol **223** was acetylated to afford the corresponding allylic acetate **224** (**Scheme 64**).



Scheme 64. Synthesis of the coupling partners **222, 223 and 224**.

With the desired coupling partners in hand, the cross-metathesis conditions were explored. Despite extensive experimentation, cross-metathesis of olefin **217** with either vinyl acetophenone **224** or its reduced form **223** proved to be extremely slow likely due to the low reactivity of both coupling partners. However, application of the cross-metathesis conditions recently reported by Donohoe using the Zhan-1B catalyst **226** (figure **226**) successfully coupled the two olefins **217** and **222** in good yield and with excellent stereocontrol to give the desired *(E)*-enone **227** (**Table 4** and **Scheme 65**).[41]

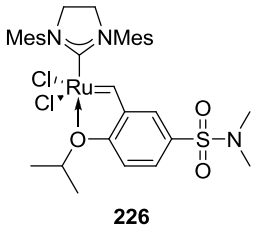
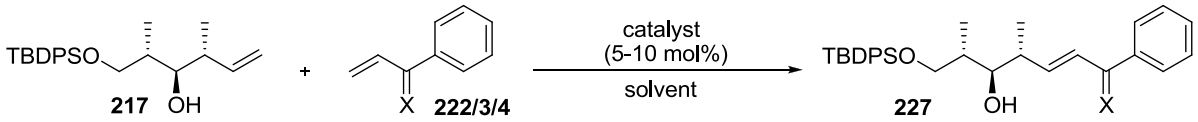
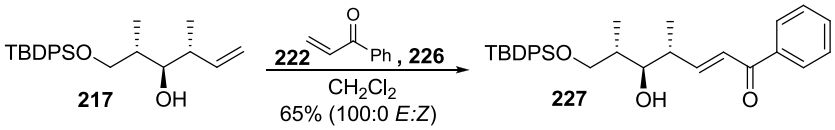


Figure 38. Zhan 1B catalyst **226**.



entry	eq **217**	eq **222/3/4**	X	conditions	**227** (%)
1	1.0	1.5	H, OAc	HGII, 0.1 M CH_2Cl_2, 40 °C, 12 h	Only poor homodimerisation
2	1.0	1.5	H, OAc	GII, 0.1 M CH_2Cl_2, 40 °C, 12 h	Only poor homodimerisation
3	1.0	3.0	H, OAc	GII, 0.1 M CH_2Cl_2, 45 °C, 24 h	Only poor homodimerisation
4	1.0	3.0	H, OAc	HGII, 0.05 M CH_2Cl_2, 80 °C, MW, 12 h	No rxn, SM epimerised
5	1.0	1.0	H, OH	GII, 0.05 M CH_2Cl_2, 80 °C, MW, 12 h	decomposition
6	1.0	3.0	H, OH	HGII, 0.1 M CH_2Cl_2, 80 °C, 2 h	decomposition
7	5.0	1.0	H, OAc	GII, 0.1 M CH_2Cl_2, 45 °C, 72 h	decomposition/ epimerisation
8	10.0	1.0	H, OAc	GII, 0.1 M toluene, 45 °C, 72 h	decomposition/ epimerisation
9	1.0	4.0	O	HGII, 0.2 M CH_2Cl_2, 50 °C, 120 h	21%
10	1.0	5.0	O	HGII, 0.25 M CH_2Cl_2, 40 °C, MW, 48 h	43%
11	1.0	5.0	O	HGII, 0.3 M CH_2Cl_2, 40 °C, 48 h	40%
12	1.0	5.0	O	Zhan 1B, 0.3 M CH_2Cl_2, 40 °C, 48 h	65%

Table 4. Cross-metathesis studies for the synthesis of enone **227**.



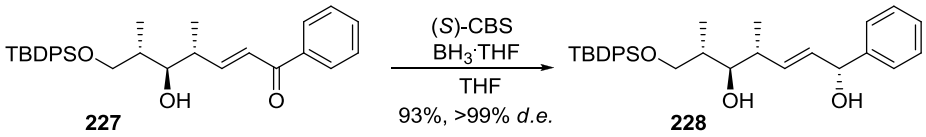
Scheme 65. Optimised synthesis of the enone **227**.

It is well documented that the more hindered and electron-poor the olefin, the less reactive it will be to cross-metathesis. Therefore a categorisation of different olefin types was disclosed. Olefins are ranked into four classes ranging from type I, electron-rich/unhindered olefins, to type IV, electron-poor/sterically demanding olefins.[42] In our specific case, the vinyl ketone **222**, deemed a type II olefin, and the secondary homoallylic alcohol **217**, a particularly hindered type II olefin, is considered a difficult borderline case. Although the reaction proved to be fairly slow for both homo- and hetero-dimerisation, it was successful as a result of three

positive factors: the first factor was the presence of the free alcohol in the coupling partner **217**. Such olefins bearing proximal alcohol groups have emerged as a special substrate class for cross-metathesis due to their enhanced levels of reactivity, likely due to hydrogen bonding with the chloride ligands on the metathesis catalyst.[43] The second positive factor was the use of the coupling partner **222**; such electron-deficient olefins are well known for their capability to undergo slow dimerisation in the presence of metathesis catalysts, hence enone **222** is an ideal coupling partner for cross-metathesis with terminal olefins. As a result, when this electron-poor substrate was used in excess (5 equivalents), the reaction proceeded efficiently and stereoselectively to generate the *(E)*-isomer.[44] Finally, the third factor was the choice of the modern and extremely powerful Zhan 1B catalyst, which shows increased reactivity due to the presence of a dimethylsulfonamide stabilising group and has proven effective even in the metathesis of poorly reactive substrates.

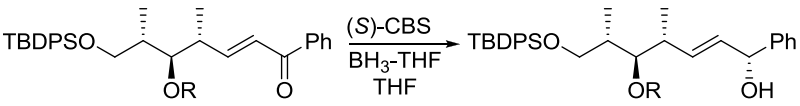
Corey-Bakshi-Shibata reduction of the enone 227

Subsequently, enone **227** was stereoselectively reduced *via* Corey-Bakshi-Shibata reduction to afford the desired allylic alcohol **228** in excellent yield and in >99% *d.e*. (**Scheme 66**).



Scheme 66. CBS reduction of the enone **227**.

Interestingly, we observed a long-range influence exerted by the homoallylic alcohol on the outcome of this reduction.[45a-c] For example, in the case of acetylated intermediate **229**, the alcohol **231** was observed as the major diastereomer in moderate yield. However, when the allylic alcohol was methylated **230**, the yield was improved significantly, but no stereocontrol was observed during the reduction. In the case of the unprotected alcohol **227**, the reduction proceeded with complete stereocontrol to generate the desired diol **228** (**Table 5**).



entry	R	T (°C)	isolated yield (%)		(*R*)/(*S*)
1	Ac **229**	- 40	40	**231**	1.0/2.0
2	Me **230**	- 10	99	**232**	1.1/1.0
3	H **227**	- 40	93	**228**	>99.0/1.0

Table 5. Long-range neighbouring group effects observed during CBS reductions.

Although the reasons for this remarkable change in behaviour are not completely clear, there are some observations that can be seen when considering the boat-like transition state involved in the process. Through computational and modelling studies, such as those reported by Meyer,[45c] it has become increasingly evident that the nonbonding interactions in the transition state of the process play a

complex role in the mediation of stereoselection. Computational studies proved that the cyclic arrangement of the transition state including the reductant borane and the carbonyl of the ketone to be reduced, (at least in the case of prochiral ketones bearing a small substituent with greater steric presence such as in our case) assumed a boat conformation, as was previously predicted by Evans.[45b] When the boat-like transition state is considered, it can be seen that the only neighbouring group of the CBS catalyst that is brought into close proximity with the substrate is the B-Me group. This suggests that this group may be involved in the stereoselectivity. Hence, it is possible that in the presence of the free alcohol, the co-ordination between the hydroxyl group and the oxazaborolidine is responsible for the enhancement in stereoselectivity observed, while when the methoxy or the acetyl moiety are present, the steric clash with the B-Me group creates an opposing effect on the stereocontrol (**Figure 39**).

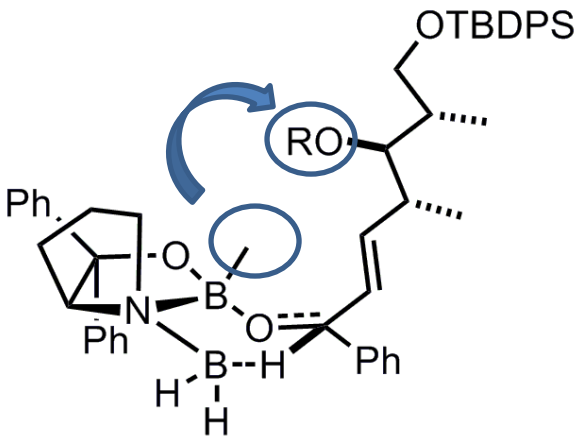
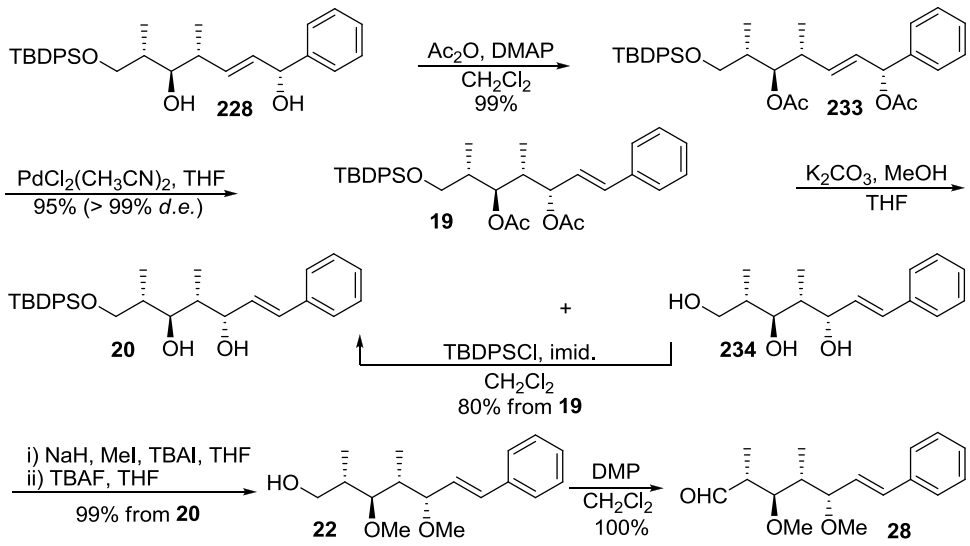


Figure 39. Long-range neighbouring group effects observed during CBS reductions.

[3,3]-Sigmatropic rearrangement

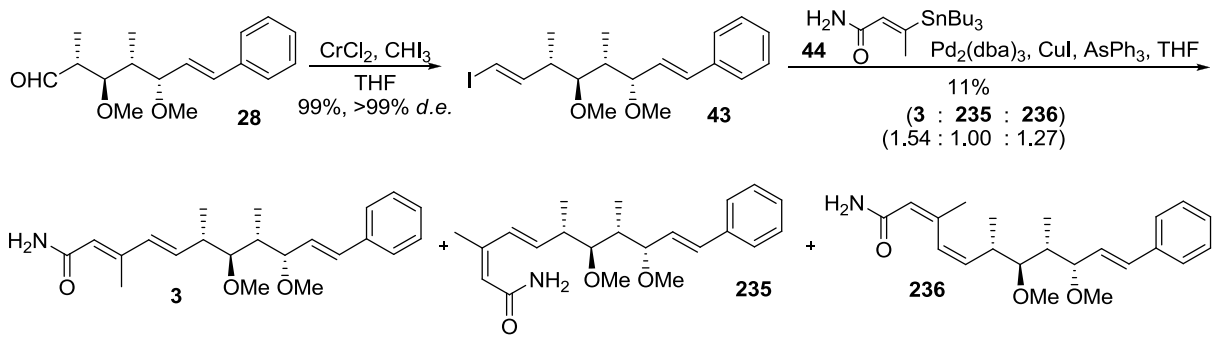
The newly generated diol **228** was then acetylated to afford *bis*-acetate **233**, allowing us to implement the key [3,3]-sigmatropic rearrangement. Gratifyingly, when treated with $PdCl_2(CH_3CN)_2$, the *bis*-acetate **233** gave the desired *anti,anti,syn*-product **19** as a single diastereomer in excellent yield. Hydrolysis of *bis*-acetate **19** generated the free diol **20** together with triol **234**, which was selectively reprotected to afford the desired diol **20** in very good overall yield. Methylation of diol **20** followed by silyl-group removal gave the desired alcohol **22** in near quantitative yield over the two steps. With alcohol **22** in hand, the final steps of the synthesis were explored. Careful oxidation of alcohol **22** generated aldehyde **28** (**Scheme 67**).



Scheme 67. Synthesis of alcohol **22**.

Lateral chain insertion *via* Stille coupling

As a consequence of the initial setback encountered in the previous strategy based on an HWE olefination for the introduction of the lateral chain, an alternative end game was required for the total synthesis of (+)-crocacin C **3**. In order to introduce the amide functionality without necessitating a final functional group interconversion, a strategy involving a metal-mediated coupling with the amide unit already in place was pursued. Thus, treatment of aldehyde **28** under Takai conditions[46] afforded the desired *(E)*-vinyl iodide **43** in excellent yield and with complete stereocontrol. With the *(E)*-iodo-alkene **43** in hand, Stille coupling with the stannyl enamide **44** afforded (+)-crocacin C **3** in poor yield, however, an exciting mixture of products containing two novel isomeric crocacin analogues **235** and **236** was also obtained (**Scheme 68**).



Scheme 68. Preliminary attempt of Stille coupling.

The structures of these novel analogues were assigned based on analysis of their 1D and 2D NMR spectra, and the double bond geometries were confirmed by NOE studies (**Figure 40**).

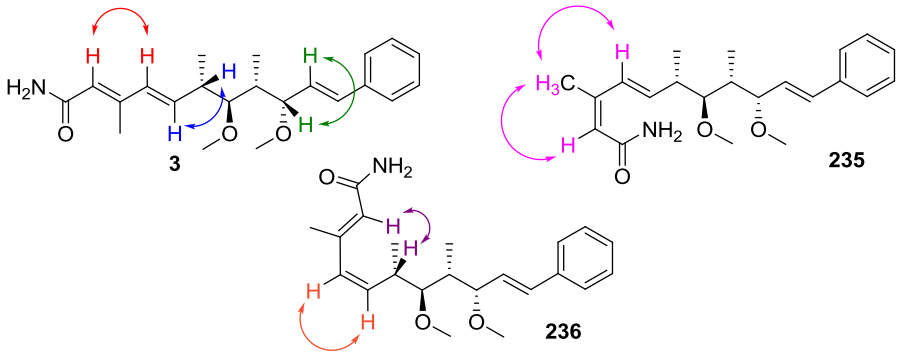
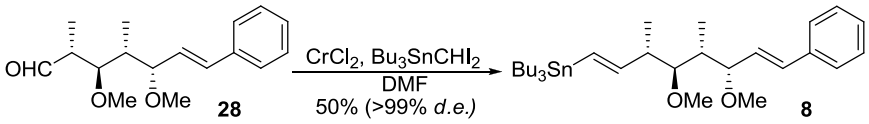


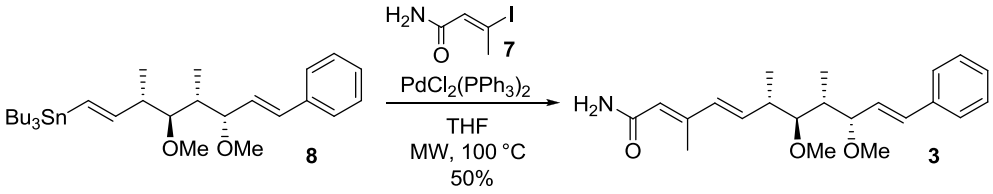
Figure 40. Observed NOEs.

The promising Stille coupling results prompted us to consider a reverse coupling strategy for the completion of the synthesis whereby the enamide unit would be introduced as the vinyl halide and the C4-C11 framework of (+)-crocacin C **3** would be brought forward as the vinyl stannane **8**. Conveniently, the synthesis of the key *(E)*-vinyl stannane **8** was achieved in one step through the Hodgson olefination of aldehyde **28** in moderate yield (**Scheme 69**).[47a,b]



Scheme 69. Hodgson olefination.

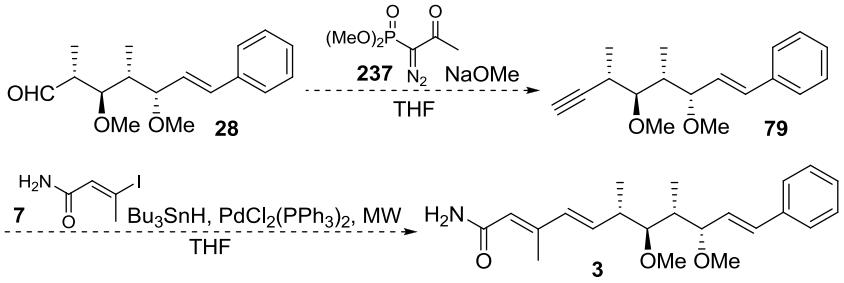
Microwave assisted Stille coupling of vinyl stannane **8** with the vinyl iodide bearing amide **7** then yielded (+)-crocacin C **3**. Importantly, (+)-crocacin C was isolated as a single double bond isomer in much improved yield with respect to the initial end-game strategy.



Scheme 70. Reverse Stille coupling strategy.

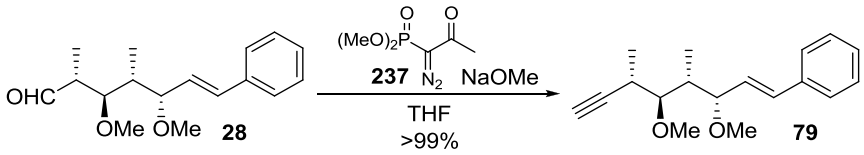
Although the Stille coupling of vinyl stannane **8** with vinyl iodide **7** yielded (+)-crocacin C **3** as a single alkene isomer, the process was not amenable to scale-up, often resulting in protodestannylation during purification of vinyl stannane **8**.

In a variant of the highly promising Stille coupling which would allow us to circumvent the protodestannylation issues, aldehyde **28** was envisioned as being converted into the corresponding alkyne **79,** which could then potentially undergo a one-pot Pd-catalysed hydrostannylation/Stille coupling reaction, following Malezka's protocol.



Scheme 71. Proposed one-pot procedure.

Following this new synthetic strategy, aldehyde **28** was subjected to Ohira-Bestmann homologation conditions to generate alkyne **79**. The homologation proceeded in quantitative yield to afford alkyne **79** after minimal purification (**Scheme 72**).[48a,b]



Scheme 72. Ohira-Bestmann homologation.

Mechanistically, the Ohira-Bestmann homologation is believed to occur *via* deacylation of the Ohira-Bestmann reagent by methoxide. The resulting carbanion then attacks the aldehyde to form an oxaphosphetane-type intermediate, which subsequently decomposes to afford a thermally unstable diazoalkene. The diazoalkene loses dinitrogen through α-elimination and the resulting alkylidenecarbene undergoes a 1,2-shift to give rise to the desired alkyne (**Figure 41**).

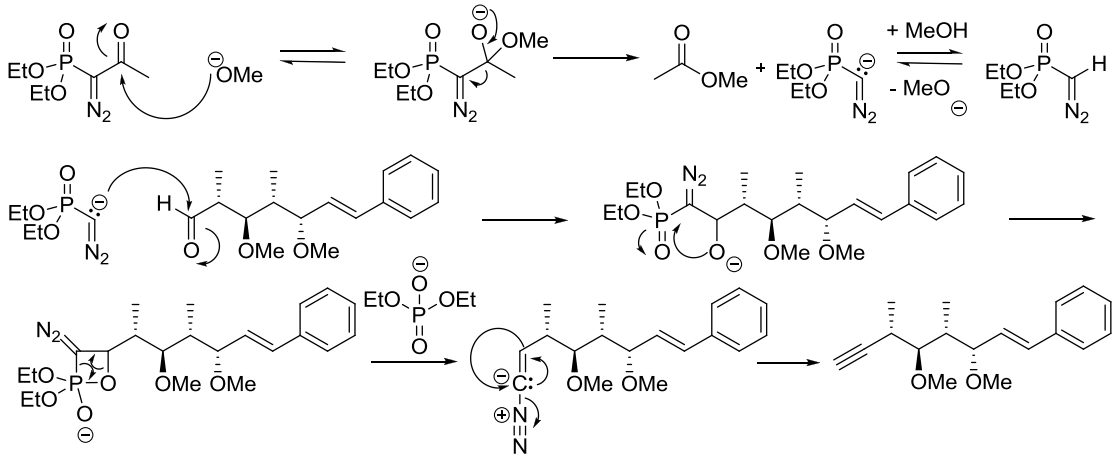


Figure 41. Ohira-Bestmann homologation mechanism.

Having alkyne **79** in place, the one-pot hydrostannylation/Stille coupling sequence developed by Maleczka[49] was considered. This strategy has proven to be an extremely convenient method which avoids any issues related to the isolation and purification of the stannane intermediate. Stannane intermediates can be prone to silica gel-mediated protonolysis, resulting in destannylation and as a consequence dramatic drop in yield and purity of the product. Conveniently, the catalyst used for the sequence, $Pd(II)Cl_2(PPh_3)_2$, is cheap, air stable and easily prepared, culminating in an extremely convenient overall process. The reactive species is formed *in situ via* reduction of Pd(II) to Pd(0) by tributyltin hydride (**Equation A**).

(**A**) $PdCl_2(PPh_3)_2 + 2\ Bu_3SnH \longrightarrow Pd(PPh_3)_2 + 2\ Bu_3SnCl + H_2$

The proposed mechanism of the reaction involves the oxidative addition of tributyltin hydride to the metal centre, followed by coordination of the alkyne which can undergo hydro-metallation. Final reductive elimination affords the desired organostannane; the process occurs with *cis* stereoselective addition leading to the desired *(E)*-isomer. As was shown by both Giubè[50] and Maleczka,[49] a good *(E)*-regioselectivity in this process depends on the presence of bulky propargylic substituents (**Figure 42**).[51]

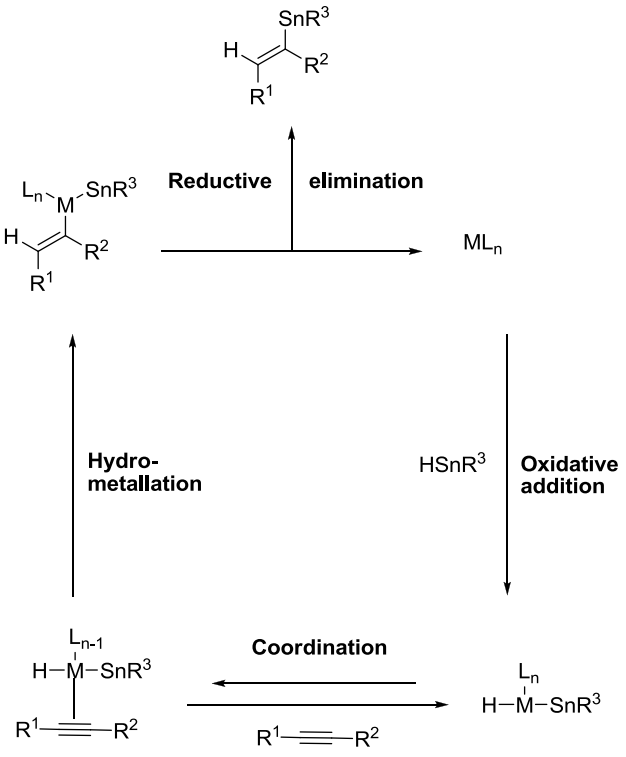
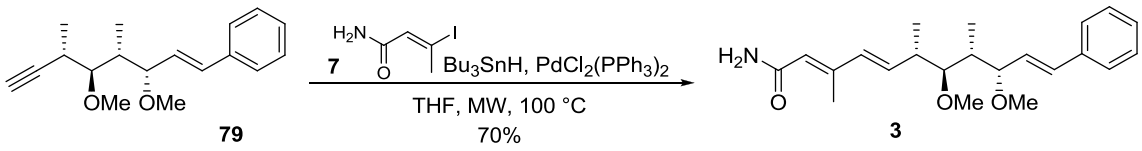


Figure 42. Mechanism of Pd-catalysed hydrostannation.

To our delight, *in situ* conversion of alkyne **79** into the *(E)*-vinyl stannane **8** with concomitant Stille coupling (with vinyl iodide **7**) using Bressy and Pons' conditions[11] afforded (+)-crocacin C **3** in high yield and as a single isomer. In our specific case the nature of the propargylic group provided enough steric hindrance to give complete *(E)*-stereocontrol.



Scheme 73. End-game strategy to (+)-crocacin C **3**.

Completion of the total synthesis of (+)-crocacin C

In conclusion, we have developed a reliable, flexible and highly efficient synthesis of (+)-crocacin C **3**. Our approach is amenable to scale-up and is able to generate (+)-crocacin C **3** in 14 steps (8 isolated intermediates) and 20% overall yield (89% yield per step) from commercially available Roche ester **11**. This represents a great improvement respect to our first approach in which a formal synthesis of our target up to the common intermediate **22** was completed in 16 isolated intermediates and with a modest 2.3% overall yield.

Our new approach exploits some interesting key steps never used before for the synthesis of the crocacins, such as a *(S,S)*-diisopropyl tartrate-modified *(E)*-crotylboronate mediated crotylboronation, a cross-metathesis coupling and a [3,3]-sigmatropic rearrangement of allylic acetates. The total synthesis compares favourably with the previous syntheses reported in literature.

2.3 Total synthesis of (+)-crocacin D

Imide/halo-olefination approach

With (+)-crocacin C in hand, we next considered the generation of the more complex members of the crocacin family and, in particular, (+)-crocacin D, which has proven to exhibit the widest and strongest biological activity. The initial project was based on the exploitation of the recently developed methodology of imide/halo-enamide formation that has been deeply discussed in the first section of this dissertation. On the basis of this plan, the free carboxamide (+)-crocacin C **3** could be considered as the starting point for the generation of the more complex (+)-crocacin A **1**, B **2** and D **4**. Formylation of the primary amide was envisioned using *N*-formylbenzotriazole as formylating agent. The resulting *N*-formylimide could be then stereoselectively converted into the *(Z)*-mono-halo-enamide **238**. At this point, the sp^2-sp^3 coupling of the custom lateral chain **239** should deliver the desired crocacins.

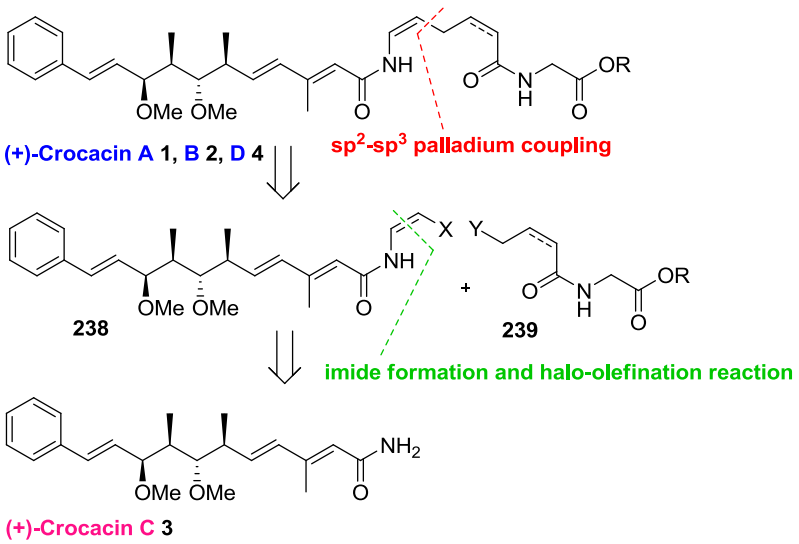
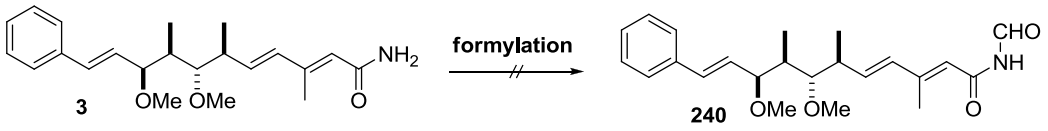


Figure 43. Retrosynthetic analysis of (+)-crocacin A **1**, B **2**, D **4**.

Despite the great potential of the project, this basic idea proved so far to be unsuccessful as a result of two main issues. Regardless of extensive experimentation, the first step of formylation *via N*-formylbenzotriazole (following the recently developed protocol) failed under several conditions. The use of *n*-

butyllithium as base proved to be too harsh and created problems of β-elimination, due to the highly conjugated nature of the system. The choice of a weaker base such as sodium hydride, led to epimerisation and isomerisation issues affording complex mixtures of difficult interpretation. The use of milder conditions, such as potassium *tert*-butoxide and microwave irradiation returned the unreacted starting material (**Table 6**).



entry	conditions	result
1	*n*BuLi, *N*-formylbenzotriazole, THF	β-elimination
2	NaH, *N*-formylbenzotriazole, THF	epimerisation/isomerisation
3	*t*BuOK, *N*-formylbenzotriazole, THF	unreacted starting material
4	*t*BuOK, *N*-formylbenzotriazole, THF MW, 40 °C	unreacted starting material

Table 6. Attempts of formylation of (+)-crocacin C **3**.

In addition to the issues related to amide formylation, subsequent steps pose severe challenges also. As described in the first section of this dissertation, the sp^2-sp^3 coupling of halo-enamides proved problematic under a variety of conditions (Stille, Suzuki, Negishi, Molander, Lipshutz).[52a-e] Indeed, to the best of our knowledge, there are no examples so far in the literature of successful couplings between a β-halo-enamide and a sp^3-alkyl chain. Therefore, even in the event of successful formylation and halo-olefination, the insertion of the lateral chain **239** on intermediate **238** would prove troublesome. In addition, it must be stressed that the crocacins are very fragile natural products, highly sensitive in particular to acidic conditions, light and moisture. As such, a stepwise approach does not seem conducive to their synthesis, as fragmentation issues may appear along the way. Thus, considering this initial setback, it was reasoned that the exploitation of an alternative approach based on the highly convergent insertion of the lateral chain on the precursor (+)-crocacin C would be optimal.

Ruthenium mediated coupling approach

The ruthenium-catalysed *anti*-Markovnikov hydroamidation of terminal alkynes first introduced by Gooßen and co-workers in 2005 is an atom-economic transformation in which the stereochemistry of the product depends on the nature of the ligands chosen for the catalyst.[53] Hence, both (*E*)- and (*Z*)-enamides can be prepared in a stereocontrolled fashion from the corresponding primary amides and custom terminal alkynes. The catalytically active species in such transformations are the phosphine-stabilised ruthenium(II) amides generated from the catalyst precursor [(cod)Ru(met)$_2$] after displacement of: a) the cyclooctadiene ligand (COD) with phosphine ligands; and b) the basic methallyl ligands with Yb(OTf)$_3$-acidified amides (**Figure 44**).

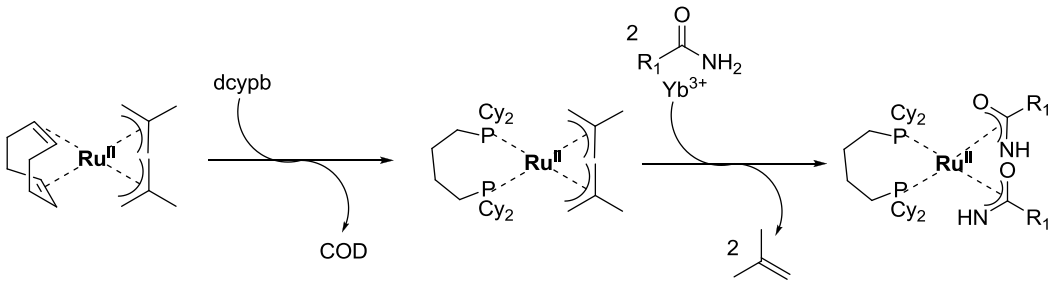


Figure 44. Activation of the catalyst.

A strong Lewis acid co-catalyst is necessary for the preferential activation of the N-H bond of the primary amide with respect to that of the resulting secondary amide product. Thus, the process terminates after a single vinylation even in presence of excess alkyne. The choice of DMF as solvent is almost compulsory as it is able to solubilise the co-catalyst without reducing its activity. In addition, the reaction conditions are very mild so that a variety of common functional groups are tolerated, including ester, ether, alkene, nitrile, nitro and halide moieties.

From a stereoselective point of view, the thermodynamically unfavoured *(Z)*-configured secondary enamides can be synthesised using a catalyst generated *in situ* from bis(2-methallyl)(cycloocta-1,5-diene)ruthenium(II), 1,4-bis(dicyclohexyl-phosphino)butane and ytterbium triflate. The thermodynamically favoured *(E)*-isomers, on the other hand, can be obtained by an *in situ* isomerisation of the *(Z)*-double bond mediated by triethylamine and molecular sieves. The strong

dependence of the stereocontrol of the reaction on the choice of ligand for the catalyst can be explained if we consider that the preferred orientation of the vinylidene moiety relative to the amide will occur depending on the steric bulk of the phosphines, **Figure 45**. The use of electron-rich, sterically demanding and chelating ligands leads to the formation of an *(E)*-ruthenium-enamide complex **B** which will afford the *(Z)*-isomers, while the use of less demanding ligands is necessary to afford the *(E)*-configured products.

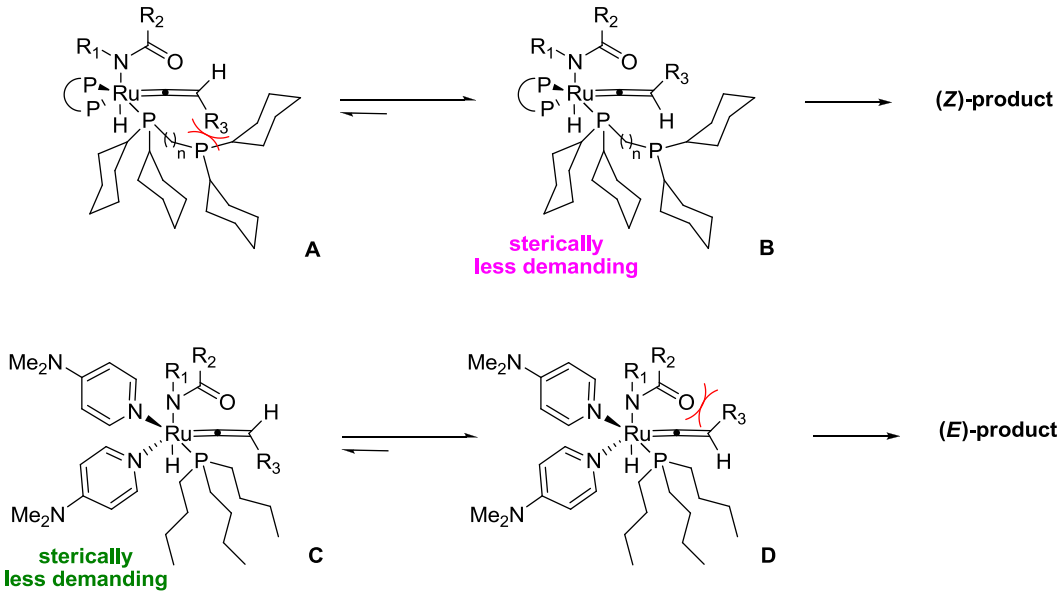


Figure 45. Ligand-dependent stereoselectivity of the coupling.

Although to date the mechanism of the process has not been completely proven, the most recent mechanistic investigation carried by Gooßen in 2011,[54] supports the presence of a ruthenium-hydride and ruthenium-vinylidene species as principal intermediates. Following this hypothesis, the first step can be considered the oxidative addition of the amide to an active Ru^0 species, followed by alkyne insertion into the ruthenium-hydride bond and then the vinyl-vinylidene rearrangement. Finally, nucleophilic attack of the amide to the α-carbon of the adduct and subsequent reductive elimination affords the *anti*-Markovnikov product (**Figure 46**).

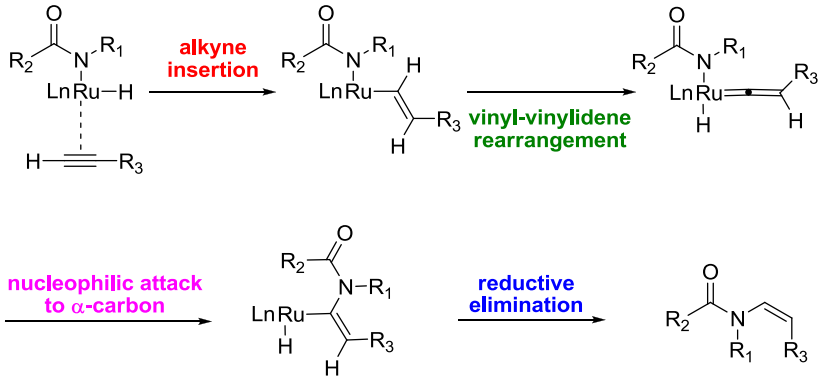


Figure 46. Mechanistic hypothesis.

On the basis of this methodology, (+)-crocacin D could be envisioned as originating from (+)-crocacin C through a ruthenium(II)-mediated coupling with alkyne **241** (**Figure 47**).

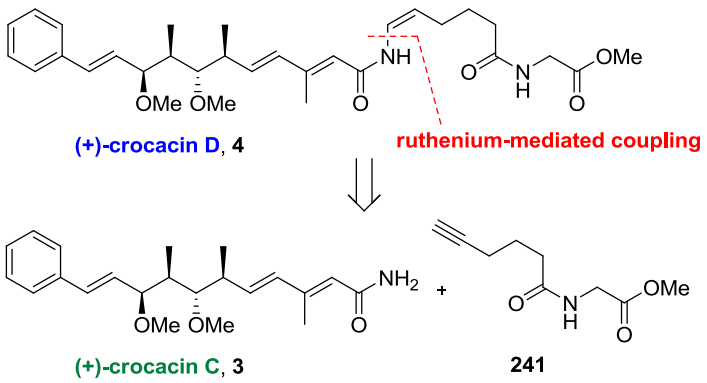
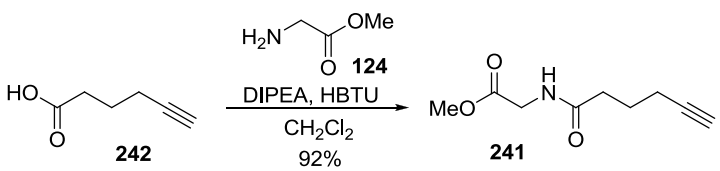


Figure 47. Retrosynthetic analysis of (+)-crocacin D *via* ruthenium-mediated coupling.

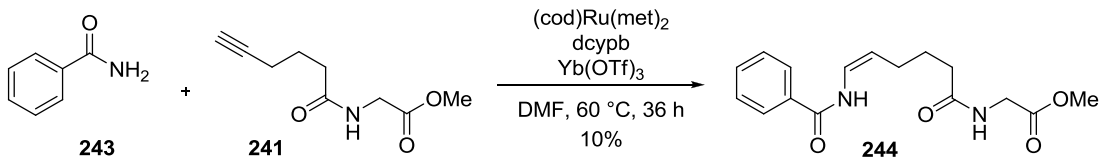
Synthetically, the alkyne derived lateral chain **241** was accessed in excellent yield in a very straightforward manner by the HBTU-mediated peptide coupling between carboxylic acid **242** and the glycine methyl ester **124** (**Scheme 74**).



Scheme 74. Synthesis of the alkyne lateral chain **241**.

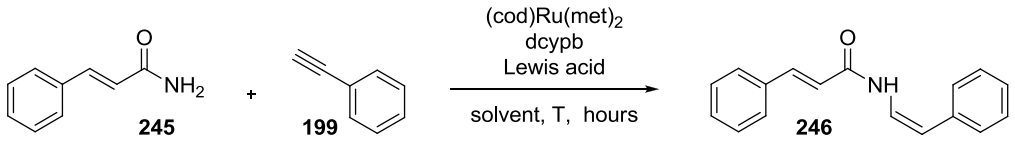
Once the desired lateral chain **241** was prepared, a preliminary coupling attempt was performed on a simple model system, the commercial benzamide **243** (**Scheme 75**).

Disappointingly, after 6 hours (according to the Gooßen protocol) no reaction had taken place at all. After 36 hours at 60 °C, the reaction afforded the desired product **244** in a very poor yield of 10%, while 90% of the starting material remained inert to these conditions and was recovered unreacted. Gooßen reported that the use of small amounts of water as a co-solvent proved decisive in the case of some very sluggish couplings. Therefore, the same reaction was repeated also in the presence of 6-8 equivalents of distilled water, relative to the amide substrate; however, even in this case the result was unsatisfactory as no product was isolated after 6, 12, 24 or 36 hours.



Scheme 75. First attempt of coupling on a model system.

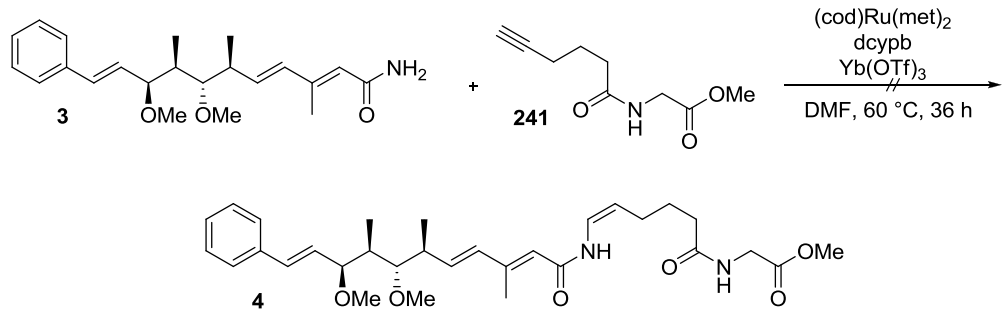
Considering these initial, unsatisfactory results, a second coupling attempt was performed on a different amide, the *trans*-cinnamamide **245**, using a simpler and more stable partner, phenylacetylene **199**. This combination was chosen in order to establish if the difficulty of the coupling could be attributed to an intrinsic lower reactivity of the custom lateral chain **241** with respect to other simpler alkynes. Disappointingly, also in this case, the coupling efficiency was excessively low (**Table 7**).



entry	catalyst % mol	Lewis acid	solvent	T	time	yield
1	5%	$Yb(OTf)_3$	DMF	60 °C	6 h	0%
2	10%	$Yb(OTf)_3$	DMF	60 °C	52 h	8%
3	10%	$Yb(OTf)_3$	DMF/H_2O	60 °C	52 h	3%
4	10%	$BF_3•OEt_2$	DMF	60 °C	24 h	0%

Table 7. Attempted Gooßen coupling on a simple model system.

Despite the unsatisfactory results when applied to the model systems, the Gooßen coupling was attempted on a very small scale between (+)-crocacin C **3** and alkyne **241**. As expected, the reaction did not proceed and the starting amide was recovered (**Scheme 76**).



Scheme 76. Attempted synthesis of (+)-crocacin D *via* Gooßen coupling.

Copper mediated coupling approach

In response to the initial set-back in the endgame strategy for the completion of the (+)-crocacin D **4**, another coupling approach was taken into consideration. In order to ensure as much convergence as possible, the revised synthetic strategy paralleled Dias' approach[14] and envisioned (+)-crocacin D **4** as being directly derived from (+)-crocacin C **3** through a Buchwald's copper(I)-mediated coupling with the *(Z)*-vinyl iodide **123** (**Figure 48**).[55]

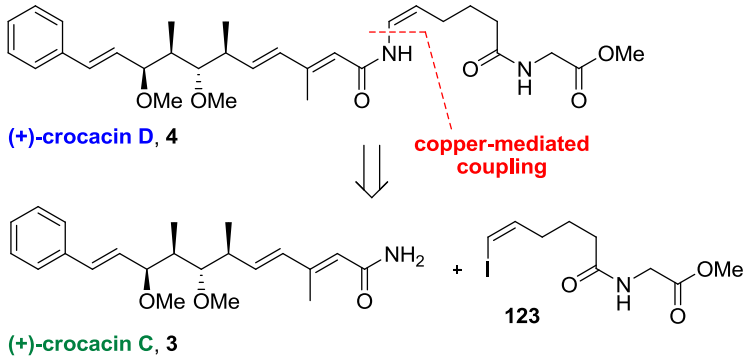
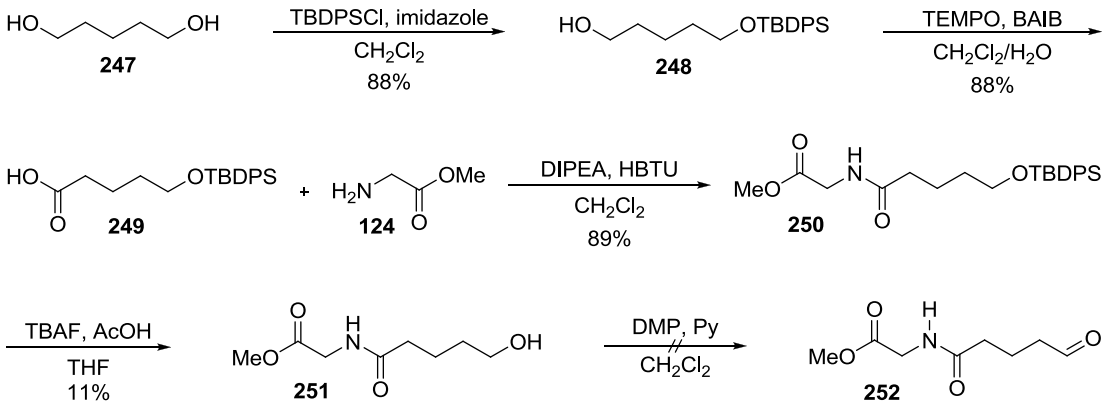


Figure 48. Retrosynthetic analysis of (+)-crocacin D *via* copper-mediated coupling.

The copper(I)-mediated coupling can be considered one of the mildest method for the introduction of an enamide moiety in a complex natural product, due to the use of a weak base, non-polar solvent, fairly low temperatures and catalytic amounts of copper. Although the mechanistic details of the coupling are not well established, recent studies have offered more clarity. In particular, it has been established *via* kinetic studies the role of the ligand involved. It has been postulated that the diamine ligand facilitates the amidation reaction because it does not allow the formation of multiply-ligated cuprate structures which would be otherwise unreactive, and instead stabilises the active species copper-amide complex.[55]

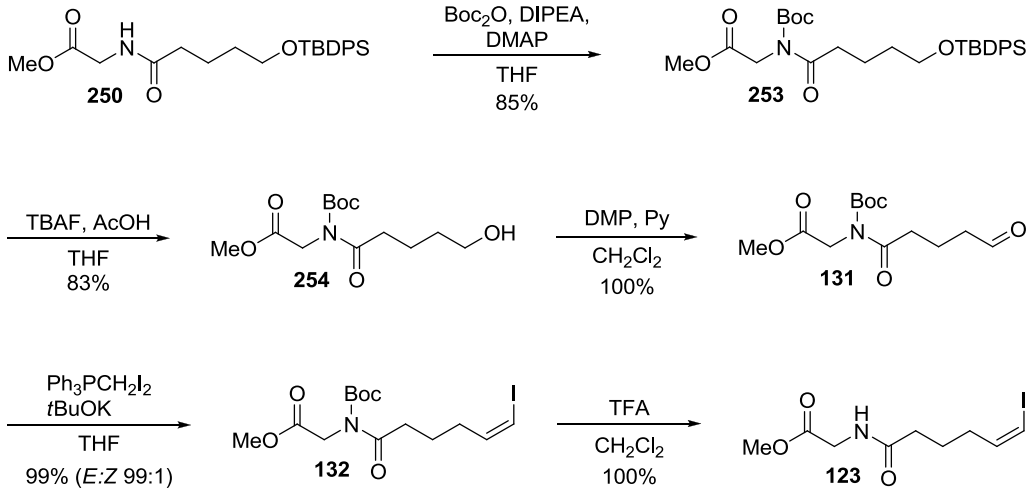
Synthesis of the key *(Z)*-vinyl iodide **123** began with 1,5-pentane-diol **247**, which was mono-protected as a TBDPS-ether **248** and then oxidised to afford the corresponding carboxylic acid **249** which was coupled with glycine methyl ester **124** to yield amide **250**. In our initial studies, desilylation of ether **250** in the presence of the unprotected amide moiety yielded alcohol **251** in 11% yield. The disappointing efficiency of the deprotection step was due in part to the excessive

polarity of the product which was difficult to separate from TBAF impurities even after repeated flash column chromatography. Oxidation of alcohol **251** by DMP and pyridine, however failed to yield any of the desired aldehyde **252** (**Scheme 77**).



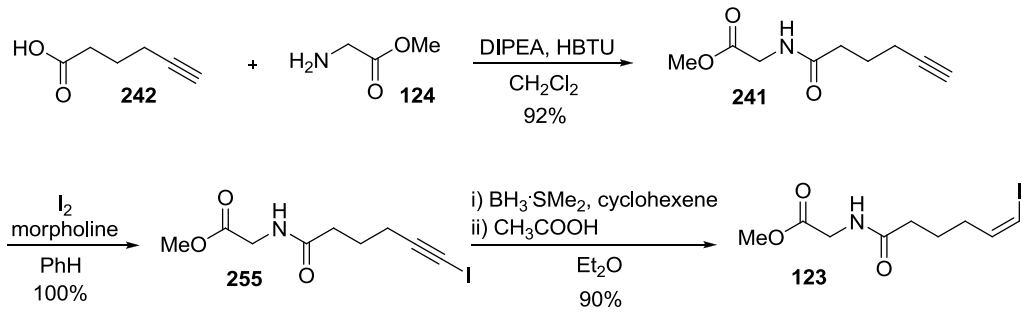
Scheme 77. Initial studies on the synthesis of the (+)-crocacin D lateral chain.

Faced with this initial set-back, the previous strategy was modified slightly; amide **250** was protected to afford the Boc-amide **253** (**Scheme 78**), which was then TBAF-desilylated to yield alcohol **254** without incident. The latter was oxidised to the corresponding aldehyde **131**, *via* treatment with DMP and pyridine, and was immediately converted to the *(Z)*-iodo-olefin **132** following the Stork-Zhao olefination protocol. Finally, Boc-removal with TFA afforded the desired lateral chain **123** in a total of 8 steps and 48% overall yield from diol **247**.



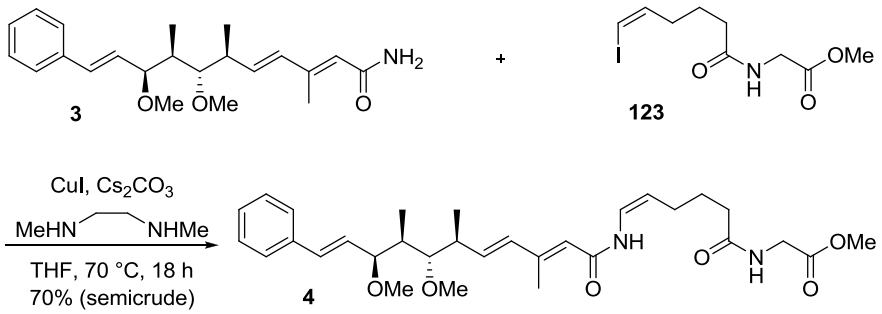
Scheme 78. Completion of the lateral chain **123**.

Despite the successful synthesis of the lateral chain **123**, a further round of optimisation was carried out. In the revised approach, commercially available carboxylic acid **242** underwent an HBTU-mediated coupling with glycine methyl ester, to yield amide **241** (**Scheme 79**). Alkyne **241** was then quantitatively converted to iodo-alkyne **255** by simple treatment with iodine and morpholine. Hydroboration-protonolysis of iodo-alkyne **255**, completed the synthesis of the iodo-alkene unit **123**. This new approach accessed the lateral chain in 3 steps with an excellent 83% overall yield, representing a significant improvement with respect to the previous strategy.



Scheme 79. Second generation synthesis of the lateral chain **123**.

With (+)-crocacin C **3** and *(Z)*-iodo-olefin **123** in hand, the final copper-mediated coupling was explored. The reaction was performed in the presence of caesium carbonate as the base, copper iodide as the catalyst, *N,N'*-dimethyl ethylenediamine as the ligand and THF as the solvent (**Scheme 80**). The reaction mixture was allowed to stir at 70 °C for 18 hours, and pleasantly afforded (+)-crocacin D **4**. Disappointingly, only a semi-crude yield (70%) could be established for the final step because the compound, due to its extremely low stability, decomposed during purification by HPLC. Nevertheless, NMR, IR and MS analysis of the semi-pure sample allowed the unequivocal identification of (+)-crocacin D **4**.



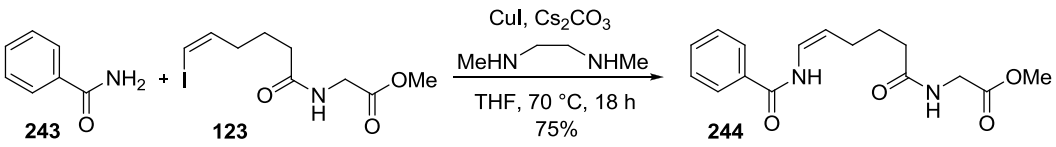
Scheme 80. Total synthesis of (+)-crocacin D, **4**.

In conclusion, the total synthesis of (+)-crocacin D has been completed in 15 steps (9 isolated intermediates) on the longest linear sequence which represents the shortest synthesis of (+)-crocacin D **4** to date from commercially available starting materials.

2.4 Unnatural analogues of (+)-crocacin D

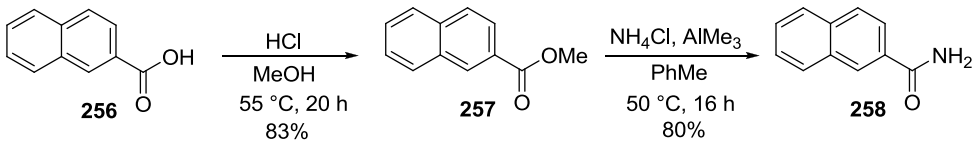
Given the success of the copper-mediated coupling for the synthesis of (+)-crocacin D, it was reasoned to use the same strategy for the preparation of a focused library of unnatural analogues of (+)-crocacin D. The rationale was that the lateral chain containing the *(Z)*-enamide moiety, which is believed to be responsible for the biological activity of the crocacins, remained unaltered, while the lipophilic section, was simplified.

Following the library rationale, the first unnatural analogue to be prepared was the benzamide-derived **244**. The copper-mediated coupling was successful and the compound displayed good stability, which allowed purification to afford the desired product in 75% yield (**Scheme 81**).



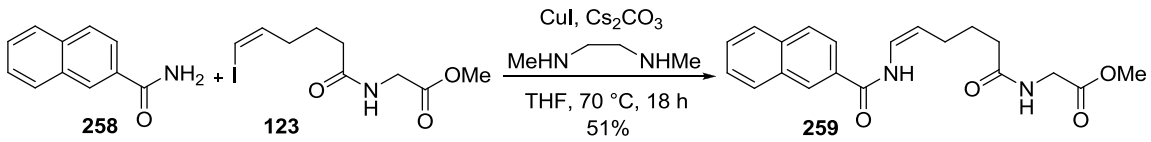
Scheme 81. Synthesis of analogue **244**.

In addition, in order to prepare other stable and simplified analogues, naphthoic acid **256** was taken into consideration due to the stability of the lipophilic portion derived from the presence of two aromatic rings. Hence, carboxylic acid **256** was at first converted into amide **258** *via* a simple two-step sequence in a moderate overall yield of 66% (**Scheme 82**).



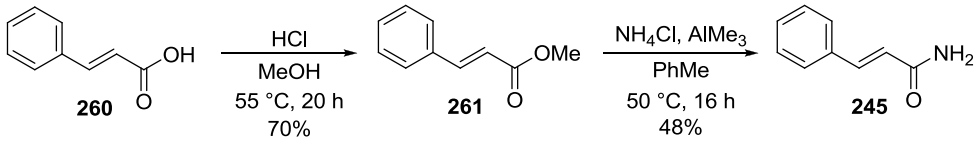
Scheme 82. Synthesis of amide **258**.

Amide **258** was then coupled with the lateral chain **123** *via* the same copper-mediated conditions to afford the desired analogue **259** (**Scheme 83**).



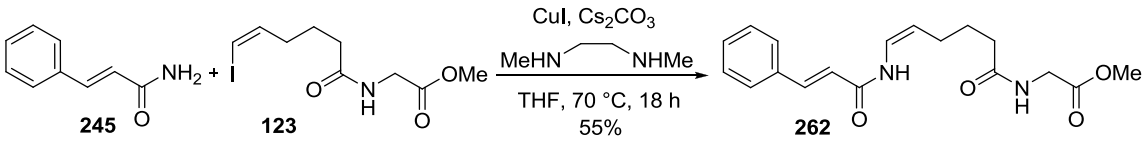
Scheme 83. Synthesis of analogue **259**.

Following the same basic principle, *trans*-cinnamic acid **260** was converted into the corresponding *trans*-cinnamamide **245** in working overall yield of 34% over the two steps (**Scheme 84**).



Scheme 84. Synthesis of amide **245**.

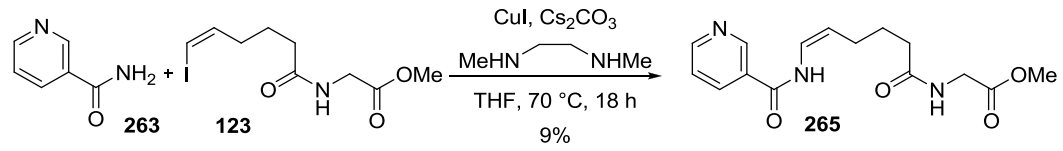
In turn, *trans*-cinnamamide **245** was subjected to a copper-mediated coupling with lateral chain **123** to afford the desired analogue **262** in fair yield (**Scheme 85**).



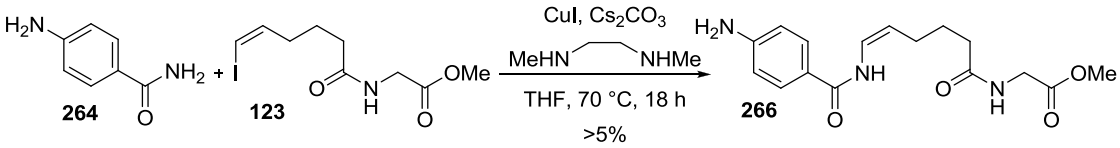
Scheme 85. Synthesis of analogue **262**.

In conclusion, the first three unnatural analogues **244**, **259** and **262** were prepared *via* straightforward transformations in good to moderate yields. Although the efficiency of the copper-mediated coupling was not excellent, it guaranteed complete stereocontrol of the *(Z)*-enamide moiety, so that the Buchwald coupling, in this context, proved to be the elected strategy for the preparation of simple analogues of (+)-crocacin D **4**. Following the same rationale, the library was expanded to incorporate various other analogues. For example, the commercial aromatic nicotinamide **263** and 4-aminobenzamide **264** were subjected to coupling with the custom lateral chain **123** to afford analogues **265** and **266** respectively. Disappointingly, these substrates proved to be almost completely unreactive towards the copper-mediated coupling, likely due to the presence of the nitrogen in the starting materials, which could contribute a deleterious effect on the outcome

of the reaction for electronic reasons (**Schemes 86** and **87**). Due to the extremely poor yields (calculated from the ^{1}H NMR of the crude mixture), the isolation of clean products from large amounts of unreacted starting materials was not achieved.



Scheme 86. Synthesis of analogue **265**.



Scheme 87. Synthesis of analogue **266**.

Additionally, a smaller non-aromatic substrate was also taken into consideration: 3-methylbut-2-enamide **267**. Successful coupling of amide **267** to the lateral chain **123** would provide access to the entire C1-C14 fragment of (+)-crocacin D, and would determine the activity of the C15-C27 complex polypropionate fragment (**Figure 49**).

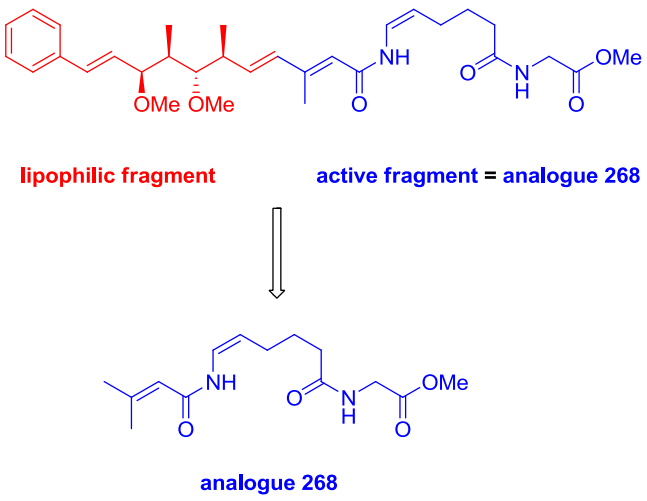
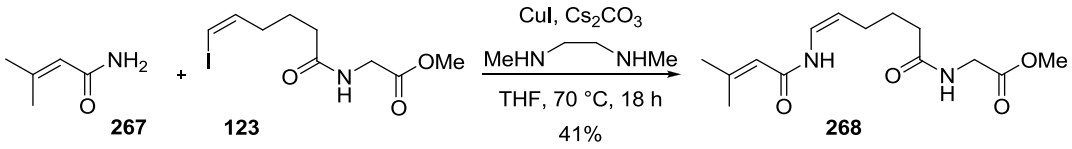


Figure 49. Structural analogies between the natural (+)-crocacin D and the unnatural analogue **268**.

In any event, the Cu(I)-mediated coupling afforded the desired enamide analogue **268** in a moderate 41% yield, however, disappointingly, the product suffered from a significant intrinsic instability which led to complete decomposition during the characterisation process (**Scheme 88**). This result suggested that the C1-C14 fragment of (+)-crocacin D, even if strictly involved in the biological activity of the molecule, does not exhibit the required characteristics of stability necessary to be considered an analogue of interest.



Scheme 88. Synthesis of analogue **268**.

The next step focused on the exploration of an “hybrid analogue”. The hybrid species was envisioned as deriving from the coupling between the C1-C9 fragment of (+)-crocacin D and the pantoyl moiety of CJ-15,801, an important pantothenic acid analogue involved in the inhibition of the CoA biosynthesis (**Figure 50**).[56] The rationale behind this idea was to explore the possibility of double, or enhanced, activity of the hybrid analogue due to its strong correlation to two important natural products.

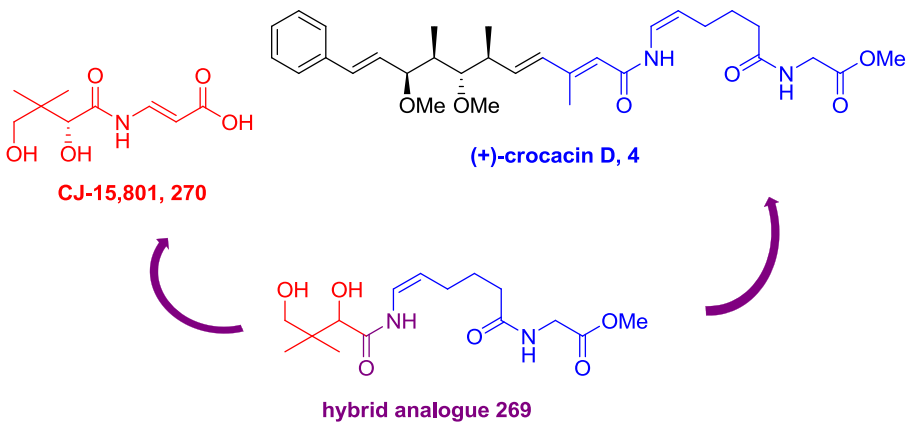
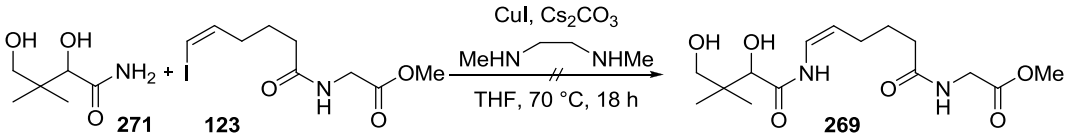


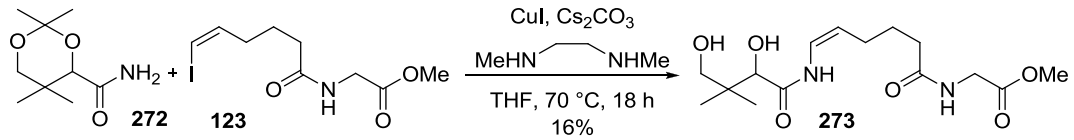
Figure 50. Structural features of the hybrid analogue **269**.

In our initial effort towards the synthesis of the hybrid analogue, the easily accessed 2,4-dihydroxy-3,3-dimethylbutanamide **271** was subjected to Buchwald coupling with custom lateral chain **123**. The coupling was unsuccessful and yielded a complex mixture, likely due to the presence of the two free alcohol moieties.



Scheme 89. First attempt of synthesis of the hybrid analogue **269**.

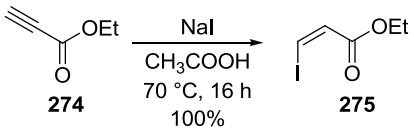
Considering the unsatisfactory outcome of this coupling on the unprotected substrate **271**, a similar reaction was carried out on the starting material **272** which has the 1,3-diol masked as an acetonide (**Scheme 90**). Interestingly, as shown by crude ^{1}H NMR analysis, the reaction conditions led to the complete removal of the acetonide group and only to a very low efficiency of coupling, while a significant amount of free carboxamide remained uncoupled. In addition, the product did not satisfy the requisites of stability necessary for a successful analogue as it decomposed upon purification. Hence, in order to study the biological activity of this interesting hybrid analogue, both the coupling procedure and purification protocol would require significant optimisation.



Scheme 90. Synthesis of the hybrid analogue **273**.

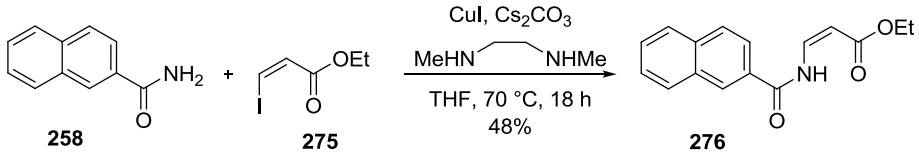
Finally, taking the satisfactory results of coupling and stability obtained with the analogues **259** and **262** into consideration, two further analogues based on the naphthyl- and *trans*-cinnamyl- frameworks were prepared. The variation in this case was concentrated to the lateral chain which maintained the biologically important *(Z)*-enamide moiety, but incorporated a simplified and more stable ester

functionality. The lateral chain **275** was prepared quantitatively in a single step from the commercial ethyl propionate **274** *via* hydroiodination (**Scheme 91**).[57]



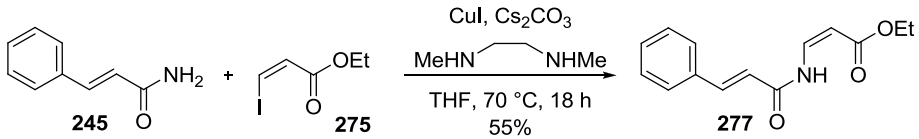
Scheme 91. Synthesis of iodo-enoate **275**.

With the *(Z)*-ethyl 3-iodoacrylate **275** in hand, coupling with 2-naphtamide **258** was carried out to afford the desired analogue **276** in reasonable yield (**Scheme 92**). Importantly, this analogue displayed good stability to the conditions of isolation and purification.



Scheme 92. Synthesis of analogue **276**.

In the same fashion, *trans*-cinnamamide **245** was coupled to the new lateral chain **275** in moderate yield and without problems of purification (**Scheme 93**).



Scheme 93. Synthesis of analogue **277**.

In summary, a small library of 9 unnatural analogues of (+)-crocacin D was prepared, however among those, only 5 compounds (analogues **244**, **259**, **262**, **276**, **277**) displayed the characteristics of stability necessary to be taken onto the next step of rigorous biological testing.

In order to determine the potential of the 5 stable analogues, they were subjected to a screening on the Discovery Early Screen (DES) platform against a range of weed species, insect pests and fungal pathogens by Syngenta (Jealott's Hill International Research Centre, Bracknell, UK). All testing was carried out in 96-well plates. In herbicide assays the compounds were tested for activity against *Arabidopsis thaliana* at 10ppm and *Poa annua* at 32ppm (**Table 8**). Test plates were stored for seven days in a controlled environment cabinet. Scores were given as 0 or 99, where 99 is any herbicidal effect, and 0 is no effect.

Test species	Treatment timing	Rate (ppm)
Arabidopsis thaliana	Pre emergence	10
Poa annua	Pre emergence	32

Table 8. Herbicide assays.

In insecticide assays the compounds were tested for activity against the aphid species, *Aphis gossypii*, in a leaf-disc assay at 1000ppm. The compounds were also evaluated at a rate of 5000ppm on *Plutella maculipennis* in an artificial diet assay and against the nematode species *Caenorhabditis elegans* in liquid culture at 10ppm (**Table 9**). The analogues were applied to feeding aphids, prior to infestation with *P. xylostella larvae*, or diluted into the *C. elegans* culture. Mortality was assessed relative to control wells using a 2 band system (0 or 99 where 99 is significant mortality and 0 is no significant effect), 5-9 days after the treatment depending on the assay. *C. elegans* were also assessed for symptomology.

Test species	Treatment type	Media	Rate (ppm)
Aphis gossypii	Feeding/contact	Leaf disc	1000
Plutella maculipennis	Feeding/contact	Artificial diet	5000
Caenorhabditis elegans	Feeding/contact	Liquid culture	10

Table 9. Insecticide assays.

In fungicidal assays, the compounds were evaluated in mycelial growth tests in artificial media against *Pythium dissimile, Alternaria solani, Botryotini cinerea* and *Gibberella zeae* at rates of 20ppm and 2ppm (**Table 10**).

Test species	Media	Rate (ppm)
Pythium dissimile	Semi-solid	20 and 2
Alternaria solani	Semi-solid	20 and 2
Botryotinia cinerea	Semi-solid	20 and 2
Gibberella zeae	Semi-solid	20 and 2

Table 10. Fungicide assays.

Leaf-piece assays were also conducted. The compounds were evaluated at 200ppm and 60ppm against *Phytophthora infestans* on tomato and 100ppm for *Uromyces vicae-fabae* on bean (**Table 11**). The analogues were applied prior to inoculation in the leaf-piece assays.

Test species	Host	Rate (ppm)
Pytophthora infestans	Tomato	200 and 60
Uromyces viciae-fabae	Bean	100

Table 11. Leaf-piece assays.

Mycelial growth or disease inhibition was assessed visually and scored using a 3 band system (0, 55 and 99 where 99 is total inhibition of hyphal growth/disease development, 55 is partial inhibition and 0 is no inhibition), 4-14 days after inoculation depending on the assay. Screening results are presented in **Tables 12**, **13** and **14**.

- **Herbicide**: the compounds tested were inactive on the herbicide screens.
- **Insecticide**: the majority of the analogues were inactive on the insecticide screens. However, interestingly, one compound, analogue **276**, proved to be highly active against the species *Nematode Caenorhabditis elegans*, and therefore showed a good potential for further investigation.

- **Fungicide**: Most of the compounds were inactive on the fungicide screens. Only analogue **259** showed a moderate activity against the species *Uromyces viciae-fabae*. Analogue **262**, on the other hand, showed low activity against *Uromyces viciae-fabae* and moderate activity against *Phytophtora infestans*. These results were not sufficient for further interest.

Tested compounds	*Arabidopsis thaliana*	*Poa annua*
Analogue **244**	0, 0, 0	0, 0, 0
Analogue **259**	0, 0, 0	0, 0, 0
Analogue **262**	0, 0, 0	0, 0, 0
Analogue **276**	0, 0, 0	0, 0, 0
Analogue **277**	0, 0, 0	0, 0, 0

Table 12. Herbicide effect.

Tested compounds	*Aphis gossypii*	*Plutella maculipennis*	*Caenorhabditis elegans*
Analogue **244**	0, 0, 0	0, 0, 0	0, 0, 0
Analogue **259**	0, 0, 0	0, 0, 0	0, 0, 0
Analogue **262**	0, 0, 0	0, 0, 0	0, 0, 0
Analogue **276**	0, 0, 0	0, 0, 0	**99, 99, 99**
Analogue **277**	0, 0, 0	0, 0, 0	0, 0, 0

Table 13. Insecticide effect.

Tested compounds	*Gibberella zeae*	*Botryotinia cinerea*	*Alternaria solani*	*Pythium dissimile*	*Uromyces viciae-fabae*	*Phytophtora infestans*
Analogue **244**	0, 0, 0	0, 0, 0	0, 0, 0	0, 0, 0	0, 0, 0	0, 0, 0
Analogue **259**	0, 0, 0	0, 0, 0	0, 0, 0	0, 0, 0	**55, 55, 55**	0, 0, 0
Analogue **262**	0, 0, 0	0, 0, 0	0, 0, 0	0, 0, 0	**0, 55, 27**	**99, 0, 49**
Analogue **276**	0, 0, 0	0, 0, 0	0, 0, 0	0, 0, 0	0, 0, 0	0, 0, 0
Analogue **277**	0, 0, 0	0, 0, 0	0, 0, 0	0, 0, 0	0, 0, 0	0, 0, 0

Table 14. Fungicide effect.

Positive control compounds were included in each test as appropriate: Azoxystrobin **278** and/or Prochloraz **279** for fungicide assays, Thiamethoxam **280** and Indoxacarb **281** for the insecticide assays and Norflurazon **282** for herbicide assays (**Figure 51**).

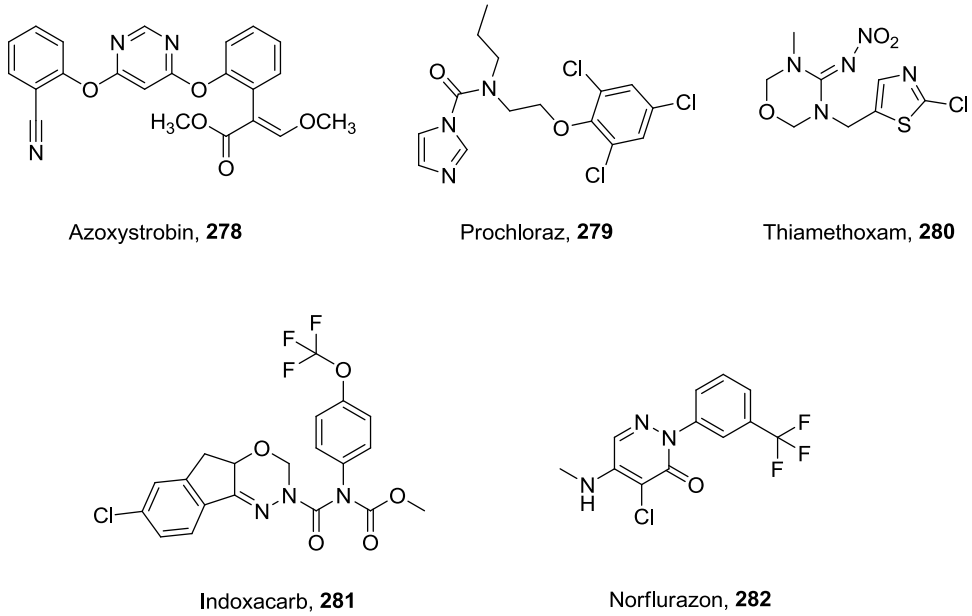


Figure 51. Positive control compounds.

2.5 Studies towards the synthesis of (+)-crocacin A, B

In parallel to the design of novel unnatural analogues, the total synthesis of (+)-crocacin A **1** and B **2** was also investigated. The retrosynthesis is very similar to the one followed for the synthesis of (+)-crocacin D and is based on a Buchwald Cu(I)-mediated coupling between (+)-crocacin C **3** and the lateral chain **283**, made more complex by the presence of a further *(Z)*-enamide moiety (**Figure 52**).

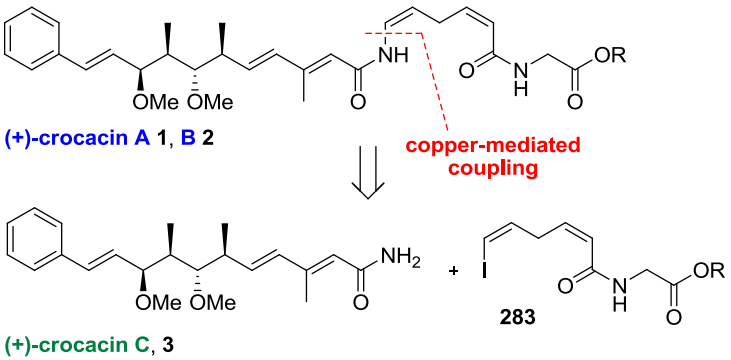
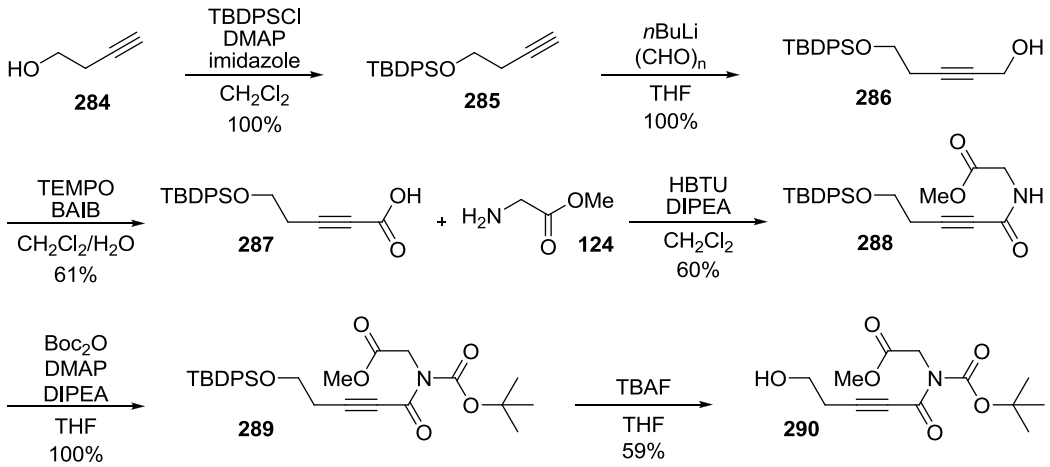


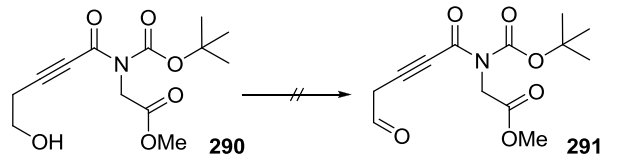
Figure 52. Retrosynthesis of (+)-crocacin A and B *via* copper-mediated coupling.

The synthesis of the (+)-crocacin A lateral chain **283** began with the TBDPS-protection of but-3-yn-1-ol **284** (**Scheme 94**). Alkyne lithiation followed by alkylation with *p*-formaldehyde yielded propargylic alcohol **286**. The alcohol moiety was then oxidised to the corresponding carboxylic acid **287** which was then subjected to an HBTU-mediated peptide coupling with glycine methyl ester **124** to afford dipeptide **288**. Boc-protection of the secondary amide followed by TBAF-mediated desilylation afforded the free homo-propargylic alcohol **290**.



Scheme 94. Efforts towards the synthesis of the crocacin A lateral chain **283**.

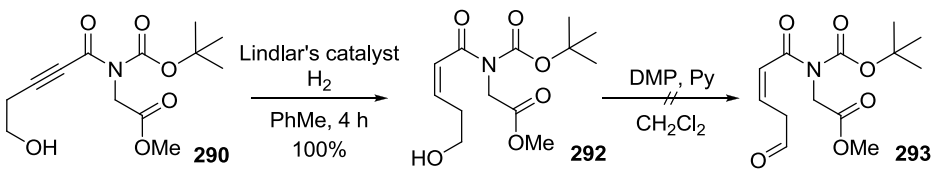
Surprisingly, however, oxidation of the propargylic alcohol unit proved difficult to achieve. Initial efforts, using TEMPO and BAIB, returned only unreacted starting material. The use of Swern oxidation conditions, resulted in a complex mixture of unidentifiable products which by ^{1}H NMR analysis of the crude product mixture appeared to show olefin migration. Due to the homo-propargylic alcohol's apparent fragility, milder oxidation conditions such as Dess-Martin Periodinane were attempted.[58] Unfortunately, in all cases, the starting material remained largely unreacted without any trace of product being detected by crude ^{1}H NMR (**Table 15**).



Entry	Conditions	Yield
1	TEMPO/BAIB/CH_2Cl_2	0%
2	$(COCl)_2$/DMSO/Et_3N/CH_2Cl_2	0%
3	DMP/Py/CH_2Cl_2	0%
4	DMP/$NaHCO_3$/CH_2Cl_2	0%

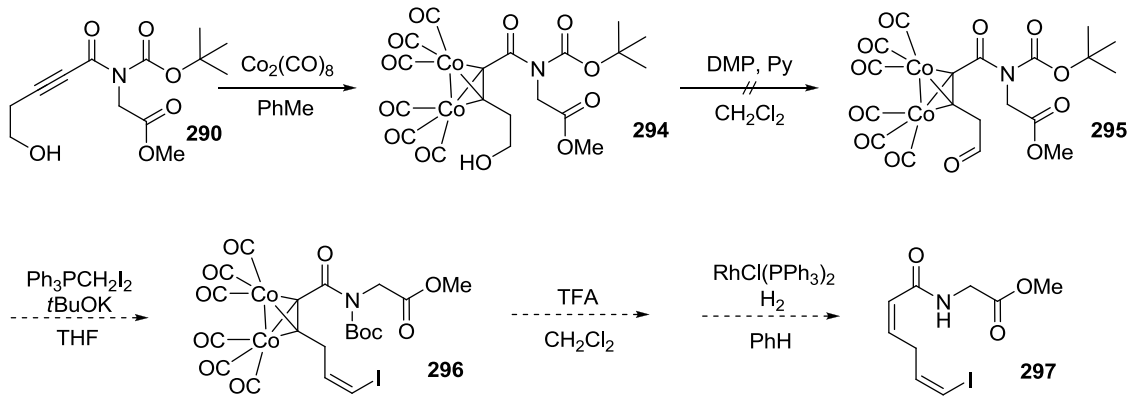
Table 15. Efforts towards the oxidation of propargylic alcohol **290**.

To combat the issues caused by the presence of the homo-propargylic moiety, partial reduction of the alkyne to *(Z)*-double bond *via* hydrogenation was performed to afford homoallylic alcohol **290**, which was in turn subjected to oxidation conditions in an effort to access the corresponding aldehyde intermediate **291**.[59] Unfortunately, the majority of the starting material remained unreacted, together with traces of by-product due to the migration of the double bond (**Scheme 95**).



Scheme 95. Partial reduction of homo-propargylic alcohol **290**.

To avoid issues of bond migration, it was decided to mask alkyne **290** by forming cobalt carbonyl complex **294** which then, in turn, was subjected to DMP oxidation.[60] Disappointingly, the oxidation of the dicobalt complex **294** was also unsuccessful (**Scheme 96**).



Scheme 96. Efforts towards the synthesis of the lateral chain **297**.

Unfortunately, time constrains prevented us from completing the synthesis of the desired lateral chain for (+)-crocacins A and B.

2.6 Summary and future work

In conclusion, a formal synthesis of (+)-crocacin C **3** was completed in 20 steps (16 isolated intermediates) and 2.3% overall yield (83% per step) from commercially available *(R)*-Roche ester **177**.

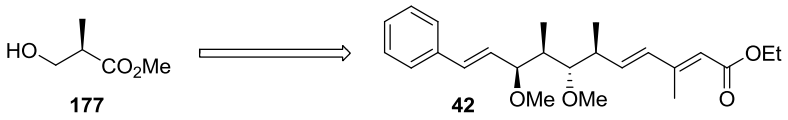


Figure 53. First generation formal synthesis of (+)-crocacin C, **3**.

After this initial result, which gave us the possibility to test the key steps of the process, such as the [3,3]-sigmatropic rearrangement, a second approach was developed which led to the completion of the total synthesis of (+)-crocacin C **3** in 14 steps (8 isolated intermediates) with a 20% overall yield (89% per step) from commercially available starting materials.

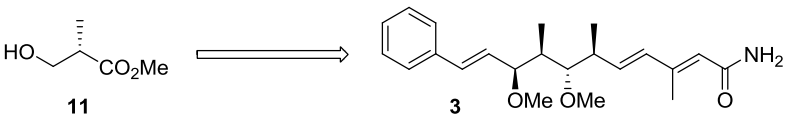


Figure 54. Second generation total synthesis of (+)-crocacin C, **3**.

Building on from the total synthesis of (+)-crocacin C **3**, the total synthesis of the bioactive (+)-crocacin D **4** was completed in 15 steps (9 isolated intermediates) and ~14% overall yield. This synthesis, based on the key Buchwald copper-mediated coupling between crocacin C **3** and vinyl iodide **123**, is the shortest synthesis of (+)-crocacin D reported to date.

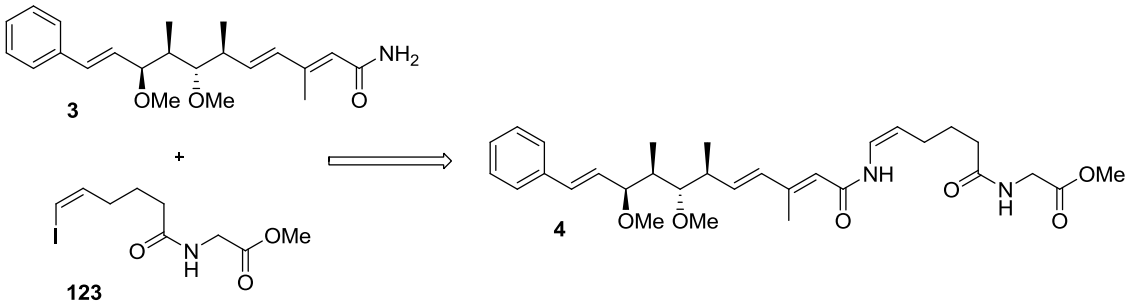


Figure 55. Total synthesis of (+)-crocacin D, **4**.

A mini-library of unnatural analogues of (+)-crocacin D was also developed, among which it is worthy to highlight analogue **276** for its high and promising anti-nematodal potential displayed during preliminary biological tests.

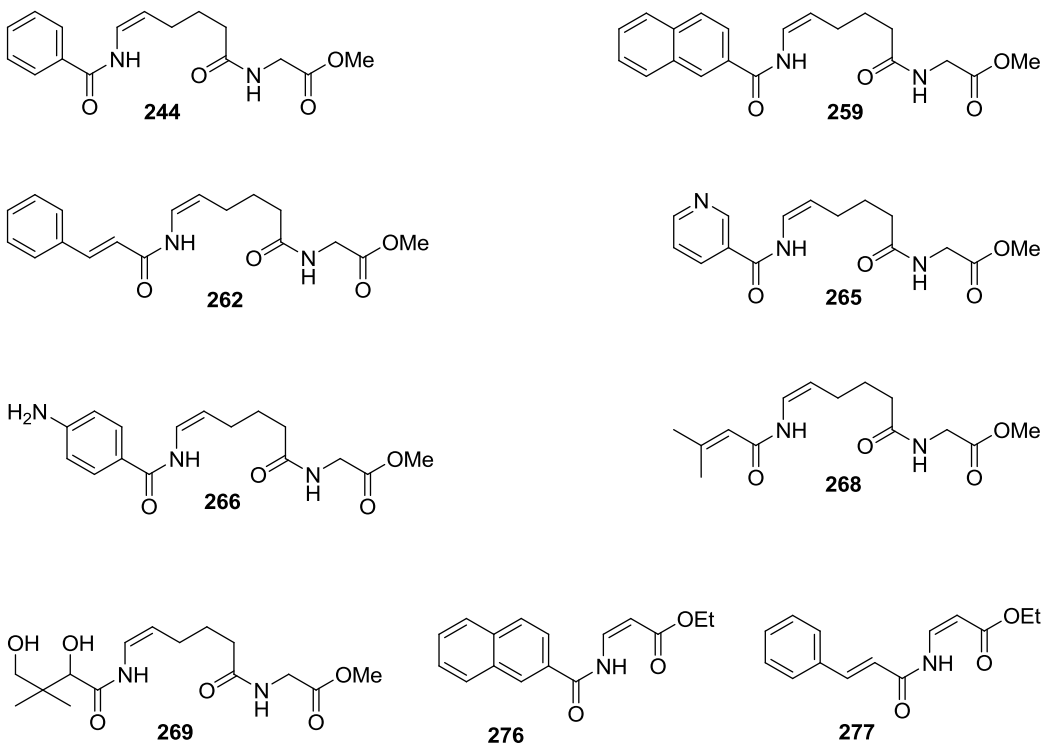


Figure 56. Analogues of (+)-crocacin D, **4**.

Besides, studies towards the synthesis of the lateral chain of the last two members of the crocacin family (crocacins A and B) are ongoing; 8 steps have been successfully completed, affording the intermediate **294**.

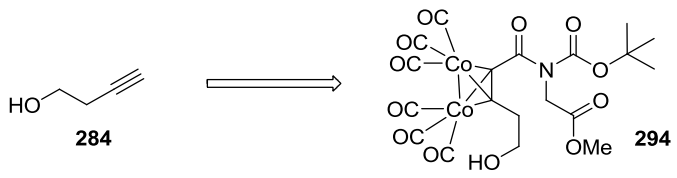


Figure 57. Studies towards the intermediate **294**.

Finally, (+)-crocacin D has shown a broad spectrum of biological activities, encompassing antibiotic, antifungal and cytotoxic properties in addition to its activity against plant pathogens. Hence, this natural product has been considered

a potential drug lead, not only for medicinal purposes but also for crop protection. However, despite this great potential, crocacin D has been deemed unsuitable for the harsh field conditions due to its intrinsic instability. Thus, the need for stable crocacin D analogues has become increasingly evident. Following on from the development of the dihalo-olefination methodology described in the first section of this dissertation, the design of stabilised and branched crocacin analogues, in an effort to overcome the stability issues is currently underway.

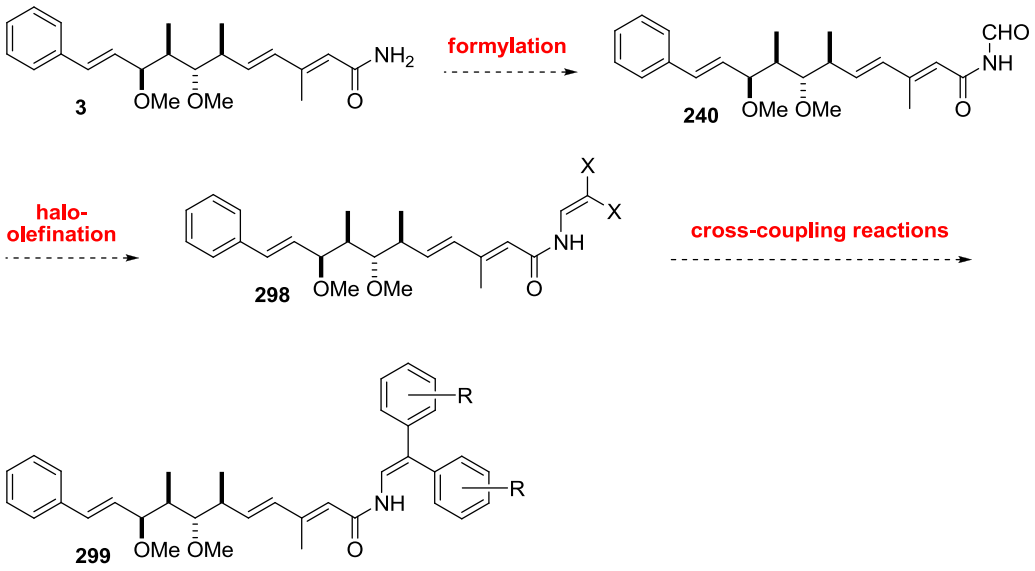
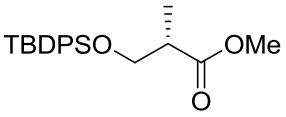


Figure 58. Stabilised crocacin analogues **299**.

3 Experimental

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Tetrahydrofuran (THF), diethyl ether, toluene and dichloromethane were purified through a Pure Solv 400-5MD solvent purification system (Innovative Technology, Inc). Anhydrous acetone, dimethylformamide, methanol, benzene and absolute ethanol were purchased from Sigma-Aldrich. All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C using a Büchi Rotavapor. IR spectra were recorded neat using a JASCO FT/IR410 Fourier Transform spectrometer. Only significant absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}). Proton magnetic resonance spectra (^{1}H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were recorded using a Bruker DPX Avance400 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, m = multiplet, b = broad, dm = doublet of multiplet, dd = doublet of doublet, dt = doublet of triplet) and (3) coupling constant (*J*) quoted in Hertz to the nearest 0.1Hz. High resolution mass spectra were recorded on a JEOL JMS-700 spectrometer by electrospray (ESI), fast atom bombardment (FAB), electron impact (EI) and chemical ionisation (CI) mass spectrometer operating at a resolution of 15000 full widths at half height. Where a 100% peak was not observed in low resolution mass spectra the highest peak was taken to be 100%. Flash chromatography was performed using silica gel (Apollo Scientific Silica Gel 60, 40-63 mm) as the stationary phase. TLC was performed on aluminium sheets pre-coated with silica (Merck Silica Gel 60 F254). The plates were visualised by the quenching of UV fluorescence (λ_{max} 254 nm) and/or by staining with either anisaldehyde or potassium permanganate followed by heating.

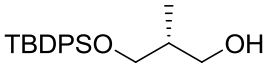
(S)-Methyl 3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanoate, 164



To a solution of *(S)*-methyl 3-hydroxy-2-methylpropanoate **11** (7.00 g, 59.3 mmol) and imidazole (4.80 g, 71.1 mmol) in dichloromethane (300 mL), cooled at 0 °C, TBDPSCl (17.0 mL, 65.2 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature and to stir for 12 hours. Then the reaction was quenched with 200 mL of $NaHCO_3$ saturated aqueous solution and extracted with dichloromethane (3 × 150 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated under vacuum to afford the product **164** as a colourless oil in a quantitative yield (21.2 g, 59.3 mmol). The crude product resulted clean without necessity of any further purification. R_f 0.44 (hexane:EtOAc, 9:1); $[\alpha]^{22}_D$ +6.8 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3073-2859, 1740, 1472, 1427, 1389, 1362, 1258, 1198, 1177, 1106, 824, 739, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.70-7.65 (4H, m, CH_{Ar}), 7.45-7.37 (6H, m, CH_{Ar}), 3.86 (1H, dd, *J* 6.9 Hz, 9.8 Hz, CH*H*), 3.76 (1H, dd, *J* 5.9 Hz, 9.8 Hz, C*H*H), 3.71 (3H, s, OCH_3), 2.79-2.68 (1H, m, CH), 1.18 (3H, d, *J* 7.0 Hz, CH_3), 1.06 (9H, s, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 175.5 (CO), 135.7 (CH_{Ar}), 133.6 (C_{Ar}), 129.8 (CH_{Ar}), 127.8 (CH_{Ar}), 66.0 (CH_2), 51.7 (OCH_3), 42.5 (CH), 26.8 (3 × CH_3), 19.4 (C), 13.6 (CH_3); HRMS (CI+/ISO) calc. for $C_{21}H_{29}O_3Si$ $[M+H]^+$: 357.1886. Found: 357.1888.

The characterisation matches with the data reported in literature:
Cossy J.; Bauer D.; Bellosta V. *Tetrahedron* **2002**, *58*, 5909.

(R)-3-(*tert*-Butyldiphenylsilyloxy)-2-methylpropan-1-ol, 165

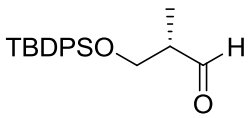


The *(S)*-methyl 3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanoate **164** (22.0 g, 61.7 mmol) was dissolved in dry dichloromethane (300 mL) and the solution was cooled at 0 °C. Then DIBAL-H (136 mL, 136 mmol, 1 M solution in hexane) was added dropwise and the reaction mixture was allowed to stir at 0 °C for 3 hours. The

reaction mixture was quenched carefully at 0 °C with 250 mL of a Rochelle's salt saturated aqueous solution added dropwise and the biphasic system was allowed to stir at room temperature for 12 hours. Then the organic layer was saved and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). All the organic layers were combined, washed with brine (300 mL) and dried over Na_2SO_4, filtered and concentrated under vacuum to afford a colourless oil as product **165** (20.1 g, 61.2 mmol) in 99% yield . The crude product resulted clean enough, without necessity of any further purification and very stable. (The batch was kept at -20 °C for several months without any decomposition or silyl migration issues, as proved by ^{1}H NMR analysis and optical rotation). R_f 0.29 (hexane:EtOAc, 9:1); $[\alpha]^{25}_D$ +4.0 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3387, 3073-2859, 1472, 1427, 1391, 1362, 1111, 1086, 1028, 939, 822, 802, 739, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.71-7.66 (4H, m, CH_{Ar}), 7.47-7.37 (6H, m, CH_{Ar}), 3.74 (1H, dd, *J* 4.5 Hz, 9.9 Hz, C*H*H), 3.68 (2H, bd, *J* 4.5 Hz, CH_2), 3.61 (1H, dd, *J* 7.7 Hz, 10.1 Hz, CH*H*), 2.56 (1H, bs, OH), 2.06-1.95 (1H, m, CH), 1.07 (9H, s, 3 × CH_3), 0.84 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 135.7 (CH_{Ar}), 134.9 (C_{Ar}), 129.9 (CH_{Ar}), 127.9 (CH_{Ar}), 68.9 (CH_2), 67.8 (CH_2), 37.4 (CH), 26.9 (3 × CH_3), 19.3 (C), 13.3 (CH_3); HRMS (CI+/ISO) calc. for $C_{20}H_{29}O_2Si$ $[M+H]^+$: 329.11937. Found: 329.1933.

The characterisation matches with the data reported in literature:
Cossy J.; Bauer D.; Bellosta V. *Tetrahedron* **2002**, *58*, 5909.

(S)-3-(*tert*-Butyldiphenylsilyloxy)-2-methylpropanal, 163

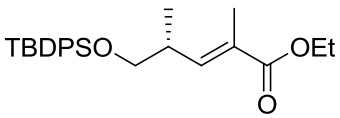


Oxalyl chloride (2.15 mL, 24.5 mmol) was dissolved in freshly distilled dichloromethane (195 mL) and the solution was cooled at -78 °C under argon. Then a solution of dimethylsulfoxide (3.5 mL, 49.0 mmol) in dichloromethane (8 mL) was added dropwise and stirred under argon at -78^{o}C for 30 minutes. A solution of *(R)*-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol **165** (4.02 g, 12.3 mmol) in dichloromethane (8 mL), was added dropwise and the reaction mixture was allowed to stir at -78 °C for 1 hour. Then the reaction mixture was quenched at -78 °C by dropwise addition of triethylamine (13.7 mL, 98.0 mmol) with the use of a

bleach trap and the obtained solution was allowed to stir at -78 °C for 10 minutes and at room temperature for 30 minutes. The solution was washed with 100 mL of $NaHCO_3$ aqueous saturated solution and extracted with dichloromethane (3 × 100 mL). The organic layers were collected, washed with 100 mL of brine, dried over Na_2SO_4, filtered and concentrated under vacuum to afford the product **163** as a yellow oil in quantitative yield (4.02 g, 12.3 mmol). The crude product was taken straight onto the next step without any further purification. R_f 0.38 (hexane:Et_2O, 9:1); $[\alpha]^{26}_D$ +5.0 (*c* 2.0, $CHCl_3$); IR ν_{max} (film) 3073-2720, 2114, 1738-1713, 1472, 1428, 1111, 1026, 1008, 808, 826, 739, 698, 689, 615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.77 (1H, d, *J* 1.7 Hz, CHO), 7.68-7.62 (4H, m, CH_{Ar}), 7.45-7.38 (6H, m, CH_{Ar}), 3.95-3.82 (2H, m, CH_2), 2.65-2.50 (1H, m, CH), 1.10 (3H, d, *J* 6.8 Hz, CH_3), 1.05 (9H, s, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 204.6 (CO), 135.7 (CH_{Ar}), 133.2 (C_{Ar}), 129.9 (CH_{Ar}), 127.9 (CH_{Ar}), 64.2 (CH_2), 48.9 (CH), 26.9 (3 × CH_3), 19.3 (C), 10.4 (CH_3); HRMS (CI+/ISO) calc. for $C_{20}H_{27}O_2Si$ $[M+H]^+$: 327.1780. Found: 327.1774.

The characterisation matches with the data reported in literature:
Cossy J.; Bauer D.; Bellosta V. *Tetrahedron* **2002**, *58*, 5909.

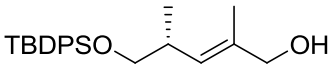
(R,E)-Ethyl 5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpent-2-enoate, 161



To a solution of *(S)*-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanal **163** (933 mg, 2.86 mmol) in benzene (10 mL), under argon at room temperature, ethyl 2-(triphenylphosphoranylidene) propanoate (2.60 g, 7.15 mmol) was added in one portion and the resulting mixture was heated at 80 °C and allowed to stir for 18 hours. Then the reaction mixture was allowed to cool to room temperature and the solvent was removed under vacuum to afford a yellow oil as crude product. The crude product was purified through flash column chromatography on silica gel (from 0 to 5% ethyl acetate in hexane) to afford the pure product **161** as a colourless oil in 85% yield (939 mg, 2.27 mmol). R_f 0.43 (hexane:EtOAc, 9:1); $[\alpha]^{26}_D$ -3.6 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3072, 2960, 2932, 2896, 2858, 1709, 1473, 1427, 1233, 1110, 1080, 1029, 823, 802, 739, 699, 689 and 615 cm^{-1}; ^1H NMR

(500 MHz, $CDCl_3$): δ_H 7.67-7.65 (4H, m, CH_{Ar}), 7.43-7.36 (6H, m, CH_{Ar}), 6.60 (1H, dq, *J* 1.4, 9.9 Hz, CH=), 4.20 (2H, q, *J* 7.6 Hz, CH_2), 3.55 (2H, dd, *J* 2.7, 6.4 Hz, CH_2), 2.77-2.73 (1H, m, CH), 1.81 (3H, d, *J* 1.4 Hz, CH_3), 1.29 (3H, t, *J* 7.6 Hz, CH_3), 1.05 (9H, s, 3 × CH_3), 1.04 (3H, d, *J* 6.6 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 168.4 (CO), 144.6 (CH=), 135.8 (CH_{Ar}), 133.8 (C_{Ar}), 129.8 (CH_{Ar}), 128.1 (C=), 127.8 (CH_{Ar}), 67.9 (CH_2), 60.6 (CH_2), 36.3 (CH), 26.9 (3 × CH_3), 19.4 (C), 16.5 (CH_3), 14.4 (CH_3), 12.7 (CH_3); HRMS (CI+/ISO) calc. for $C_{25}H_{35}O_3Si$ $[M+H]^+$: 411.2355. Found: 411.2350.

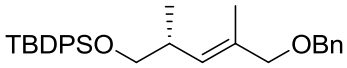
(R,E)-5-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylpent-2-en-1-ol



To a solution of *(R,E)*-ethyl 5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpent-2-enoate **163** (720 mg, 1.76 mmol) in dry diethyl ether (10 mL), under argon at 0 °C, DIBAL-H (3.9 mL, 3.90 mmol, 1M solution in diethyl ether) was added slowly dropwise and the resulting mixture was allowed to stir for 2 hours at 0 °C. The reaction mixture was quenched carefully at 0 °C with 10 mL of a Rochelle's salt saturated aqueous solution added dropwise and the biphasic system was allowed to stir at room temperature for 12 hours. Then the organic layer was saved and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). All the organic layers were combined and washed with brine (20 mL), then dried over Na_2SO_4, filtered and concentrated under vacuum to afford a colourless oil as product (650 mg, 1.76 mmol) in quantitative yield. The product resulted very clean without necessity of any further purification. R_f 0.6 (hexane:EtOAc, 6:4); $[\alpha]^{26}_D$ -16.80 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3341, 3071, 2960, 2932, 2855, 1427, 1389, 1111, 1072, 1003, 825, 787, 741, 702 and 610 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.66 (4H, dd, *J* 0.7, 7.3 Hz, CH_{Ar}), 7.44-7.36 (6H, m, CH_{Ar}), 5.16 (1H, dq, *J* 1.1, 9.4 Hz, CH=), 4.00 (2H, bs, CH_2O), 3.53-3.46 (2H, m, CH_2OSi), 2.69-2.59 (1H, m, CH), 1.62 (3H, d, *J* 1.1 Hz, CH_3), 1.58 (1H, bs, OH), 1.06 (9H, s, 3 × CH_3), 1.00 (3H, d, *J* 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 135.8 (CH_{Ar}), 135.7 (CH_{Ar}), 135.3 (C), 134.1 (C), 134.2 (C), 129.7 (CH_{Ar}), 129.6 (CH_{Ar}), 129.1 (CH=), 127.8 (CH_{Ar}), 127.7 (CH_{Ar}), 69.0 (CH_2), 68.6 (CH_2), 35.2 (CH), 27.0 (3 × CH_3), 19.4 (C), 17.4 (CH_3), 14.0 (CH_3); HRMS (CI+/ISO) calc. for $C_{23}H_{31}OSi$ $[M-OH]^+$: 351.2144. Found: 351.2145.

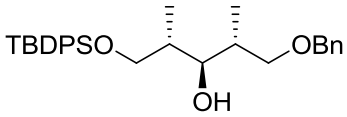
The characterisation matches with the data reported in literature:
Paterson I.; Tillyer R. D. *J. Org. Chem.* **1993**, *58*, 4182.

(R,E)-(5-(Benzyloxy)-2,4-dimethylpent-3-enyloxy)(*tert*-butyl)diphenylsilane, 172



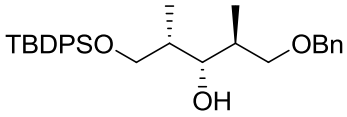
To a solution of *(R,E)*-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpent-2-en-1-ol (170 mg, 462 µmol) in dry THF (10 mL), under argon at 0 °C, sodium hydride (60% wt, 37.0 mg, 942 µmol) was added and the resulting suspension was allowed to stir for 30 minutes, then benzyl bromide (0.07 mL, 554 µmol) was added dropwise and the resulting mixture was allowed to warm to room temperature and to stir for 12 hours. The reaction was quenched with NH_4Cl saturated aqueous solution (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified through flash column chromatography on silica gel (from 0 to 20% ethyl acetate in hexane) to afford a colourless oil as pure product **172** in 94% yield (199 mg, 434 µmol). R_f 0.83 (hexane:EtOAc, 8:2); $[\alpha]^{25}_D$ -14.00 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3071, 2932, 2855, 2739, 1458, 1427, 1389, 1366, 1173, 1111, 1065, 826, 741, 694 and 610 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.69 (4H, dd, *J* 1.1, 7.6 Hz, CH_{Ar}), 7.46-7.27 (11H, m, CH_{Ar}), 5.25 (1H, dq, *J* 1.1, 9.3 Hz, CH=), 4.46 (2H, bs, CH_2Ph), 3.92-3.88 (2H, m, CH_2O), 3.56-3.44 (2H, m, CH_2OSi), 2.75-2.62 (1H, m, C*H*CH_3), 1.66 (3H, d, *J* 1.1 Hz, CH_3), 1.07 (9H, s, 3 × CH_3), 1.03 (3H, d, *J* 6.6 Hz, C*H*$_3$CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 138.8 (C), 135.8 (CH_{Ar}), 134.1 (C_{Ar}), 132.6 (=C), 131.3 (CH=), 129.7 (CH_{Ar}), 128.4 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 76.4 (CH_2), 71.5 (CH_2), 68.6 (CH_2), 35.3 (CH), 27.0 (3 × CH_3), 19.4 (C), 17.4 (CH_3), 14.3 (CH_3); HRMS (CI+/ISO) calc. for $C_{30}H_{39}O_2Si$ $[M+H]^+$: 459.2719. Found: 459.2720.

***(2R,3R,4S)*-1-(Benzyloxy)-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpentan-3-ol, 173**



and

***(2S,3S,4S)*-1-(Benzyloxy)-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpentan-3-ol, 174**



To a solution of *(R,E)*-(5-(benzyloxy)-2,4-dimethylpent-3-enyloxy)(*tert*-butyl)diphenylsilane **172** (38.0 mg, 83.0 µmol) in dry THF (1 mL), under argon at room temperature, BH_3·THF (0.25 mL, 0.25 mmol, 1 M solution in THF) was added dropwise and the resulting mixture was allowed to stir at room temperature for 12 hours. Then the reaction was quenched at 0 °C with 0.4 mL of NaOH 3 N aqueous solution and 0.4 mL of H_2O_2 (30%) and it was allowed to warm to room temperature. After 30 minutes it was extracted with diethyl ether (3 × 3 mL) and the organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford a pale yellow oil as crude product in 50% yield (20.0 mg, 42.0 µmol). The crude product without any further purification was analysed *via* ^{1}H NMR analysis and resulted in an inseparable mixture of *(2R,3R,4S)*-1-(benzyloxy)-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpentan-3-ol **173** and *(2S,3S,4S)*-1-(benzyloxy)-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethyl pentan -3-ol **174** in a 1:3.5 ratio in favour of the undesired compound (**174**). When the same reaction was performed at -78 °C, an inseparable mixture of *(2R,3R,4S)*-1-(benzyloxy)-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpentan-3-ol **173** and *(2S,3S,4S)*-1-(benzyloxy)-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethyl-pentan-3-ol **174** in a 1:1.8 ratio in favour of the undesired compound (**174**) was obtained with an overall yield of 64% (25.2 mg, 53.0 µmol).

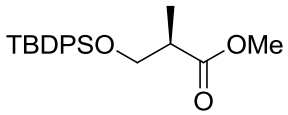
Minor isomer (desired product **173**): R_f 0.58 (hexane:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.75-7.63 (15H, m, CH_{Ar}), 4.51 (2H, s, CH_2Ph), 3.74 (2H, d, *J* 5.7 Hz, CH_2OBn), 3.60-3.45 (2H, m, CH_2OSi), 3.45-3.35 (1H, m, C*H*CH_3), 2.06-1.98 (1H, m, C*H*OH), 1.95-1.80 (1H, m, C*H*CH_3), 1.07 (9H, s, 3 × CH_3), 0.99 (3H, d, *J* 6.9 Hz, CH_3), 0.97 (3H, d, *J* 6.9 Hz, CH_3).

The characterisation matches with the data reported in literature:
Chandrasekhar S.; Yaragorla S. R.; Sreelakshmi L.; Reddy C. H. R. *Tetrahedron* **2008**, *64*, 5174.

Major isomer (undesired product **174**): R_f 0.58 (hexane:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.74-7.65 (5H, m, CH_{Ar}), 7.45-7.21 (10H, m, CH_{Ar}), 4.53 (2H, s, CH_2Ph), 3.76-3.62 (3H, m, CH_2OSi and C*H*CH_3), 3.57 (2H, d, *J* 5.8 Hz, CH_2OBn), 1.99-1.88 (1H, m, C*H*OH), 1.85-1.75 (1H, m, C*H*CH_3), 1.08 (9H, s, 3 × CH_3), 0.92 (3H, d, *J* 6.9 Hz, CH_3), 0.86 (3H, d, *J* 6.9 Hz, CH_3).

The characterisation matches with the data reported in literature:
Yasui K.; Tamura Y.; Nakatani T.; Kawada K.; Ohtani M. *J. Org. Chem.* **1995**, *60*, 7567.

(R)-Methyl 3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanoate, 178

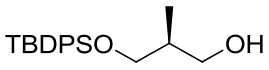


To a solution of (-)-methyl-D-β-hydroxyisobutyrate (2.50 g, 21.2 mmol) and imidazole (1.73 g, 25.4 mmol) in dichloromethane (120 mL), cooled at 0 °C, TBDPSCl (6.1 mL, 23.3 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature and to stir for 12 hours. Then the reaction was quenched with 100 mL of $NaHCO_3$ saturated aqueous solution and extracted with dichloromethane (3 × 50 mL). The organic layers were collected, dried over Na_2SO_4, filtrated and concentrated under vacuum to afford in a quantitative yield 7.60 g, 21.2 mmol of a colourless oil as product **178**. The product resulted very clean without necessity of any further purification. R_f 0.44 (hexane:EtOAc, 9:1); $[\alpha]^{25}_D$ -19.60 (c 2.0, $CHCl_3$); IR ν_{max} (film) 3073-2859, 1740, 1472, 1427, 1389, 1362, 1258, 1198, 1177, 1106, 824, 739 and 702 cm^{-1}; ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.70-7.67 (4H, m, CH_{Ar}), 7.47-7.39 (6H, m, CH_{Ar}), 3.86 (1H, dd, *J* 6.9, 9.8 Hz, C*H*H), 3.76 (1H, dd, *J* 5.9, 9.9 Hz, CH*H*), 3.71 (3H, s, OCH_3), 2.79-2.71 (1H, m, CH), 1.18 (3H, d, *J* 7.0 Hz, CH_3), 1.06 (9H, s, 3 × CH_3).
^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 175.7 (CO), 135.7 (CH_{Ar}), 133.6 (C_{Ar}), 129.8 (CH_{Ar}), 127.8 (CH_{Ar}), 66.1 (CH_2), 51.7 (OCH_3), 42.6 (CH), 26.8 (3 × CH_3), 19.3 (C),

13.6 (CH_3); HRMS (CI+/ISO) calc. for $C_{21}H_{29}O_3Si$ $[M+H]^+$: 357.1886. Found: 357.1888.

The characterisation matches with the data reported in literature:
Trost B. M.; Papillon J. P. N. *J. Am. Chem. Soc.* **2004**, *126*, 13618.

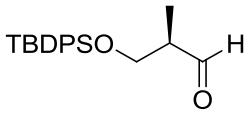
(S)-3-(*tert*-Butyldiphenylsilyloxy)-2-methylpropan-1-ol



The *(R)*-methyl 3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanoate **178** (7.60 g, 21.2 mmol) was dissolved in dry dichloromethane (91 mL) and the solution was cooled at 0 °C. Then a DIBAL-H (46.6 mL, 46.6 mmol, 1 M solution in hexane) was added dropwise and the reaction mixture was allowed to stir at 0 °C for 2 hours. The reaction mixture was quenched carefully at 0 °C with 100 mL of a Rochelle's salt saturated aqueous solution added dropwise and the biphasic system was allowed to stir at room temperature for 12 hours. Then the organic layer was saved and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). All the organic layers were combined and washed with brine (100 mL), then dried over Na_2SO_4, filtered and concentrated under vacuum to afford a colourless oil as product (7.00 g, 21.0 mmol) in 99% yield . The product resulted very clean without necessity of any further purification. R_f 0.29 (hexane:EtOAc, 9:1); $[\alpha]^{25}_D$ -8.00 (c 0.5, $CHCl_3$); IR ν_{max} (film) 3387, 3073-2859, 1472, 1427, 1391, 1362, 1111, 1086, 1028, 939, 822, 802, 739 and 698 cm^{-1}; ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.71-7.64 (4H, m, CH_{Ar}), 7.47-7.33 (6H, m, CH_{Ar}), 3.77-3.54 (4H, m, 2 × CH_2), 2.59 (1H, bs, OH), 2.05-1.95 (1H, m, CH), 1.07 (9H, s, 3 × CH_3), 0.83 (3H, d, *J* 6.7 Hz, CH_3); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 135.8 (CH_{Ar}), 133.3 (C_{Ar}), 129.9 (CH_{Ar}), 127.9 (CH_{Ar}), 68.9 (CH_2), 67.9 (CH_2), 37.4 (CH), 26.9 (3 × CH_3), 19.3 (C), 13.3 (CH_3); HRMS (CI+/ISO) calc. for $C_{20}H_{29}O_2Si$ $[M+H]^+$: 329.11937. Found: 329.1933.

The characterisation matches with the data reported in literature:
Robles O.; McDonald F. E. *Org. Lett.* **2008**, *10*, 1811.

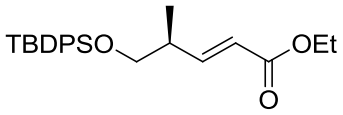
_(R)_-3-(_tert_-Butyldiphenylsilyloxy)-2-methylpropanal, 179



Oxalyl chloride (2.13 mL, 24.4 mmol) was dissolved in freshly distilled dichloromethane (195 ml) and the solution was cooled at -78 °C under argon. Then a solution of dimethylsulfoxide (3.46 mL, 48.7 mmol) in dichloromethane (8 mL) was added dropwise and stirred under argon at -78 °C for 30 minutes. Then a solution of *(S)*-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol (4.02 g, 12.3 mmol) in dichloromethane (8 mL), was added dropwise and the reaction mixture was allowed to stir at -78 °C for 1 hour. Then the reaction mixture was quenched at -78 °C by dropwise addition of triethylamine (13.6 mL, 97.4 mmol) with the use of a bleach trap and the obtained solution was allowed to stir at -78 °C for 10 minutes and then at room temperature for 30 minutes. Then the solution was washed with 100 mL of $NaHCO_3$ aqueous saturated solution and extracted with dichloromethane (3 × 100 mL). The organic layers were collected, washed with 100 mL of brine, dried over Na_2SO_4, filtered and concentrated under vacuum to afford the product **179** as a yellow oil in quantitative yield (4.33 g, 13.3 mmol). The crude product was taken straight onto the next step without any further purification. R_f 0.38 (hexane:Et_2O, 9:1); $[\alpha]^{25}_D$ -5.00 (c 2.0, $CHCl_3$); IR ν_{max} (film) 3073-2720, 2114, 1738-1713, 1472, 1428, 1111, 1026, 1008, 808, 826, 739, 698, 689 and 615 cm^{-1}; ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 9.76 (1H, s, CHO), 7.75-7.65 (4H, m, CH_{Ar}), 7.52-7.35 (6H, m, CH_{Ar}), 3.95-3.85 (2H, m, CH_2), 2.65-2.50 (1H, m, CH), 1.20 (3H, d, *J* 6.7 Hz, CH_3), 1.08 (9H, s, 3 × CH_3); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 204.5 (CO), 135.7 (CH_{Ar}), 133.2 (C_{Ar}), 129.8 (CH_{Ar}), 127.8 (CH_{Ar}), 64.2 (CH_2), 48.8 (CH), 26.8 (3 × CH_3), 19.1 (C), 10.3 (CH_3); HRMS (CI+/ISO) calc. for $C_{20}H_{27}O_2Si$ $[M+H]^+$: 327.1780. Found: 327.1774.

The characterisation matches with the data reported in literature:
Robles O.; McDonald F. E. *Org. Lett.* **2008**, *10*, 1811.

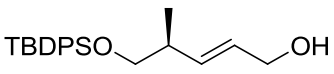
_(S,E)_-Ethyl 5-(_tert_-butyldiphenylsilyloxy)-4-methylpent-2-enoate, 176



(R)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanal **179** (10.7 g, 32.7 mmol) and (*tert*-butoxycarbonylmethylene)triphenylphosphorane (17.2 g, 49.2 mmol) were dissolved in benzene (60 mL) and the reaction mixture was allowed to stir at 80 °C for 12 hours. Then the solution was concentrated under vacuum to afford a brown oil as crude product. It was purified through flash column chromatography on silica gel (from 0 to 10% ethyl acetate in hexane) to afford a colourless oil as pure product **176** (13.0 g, 32.7 mmol) in quantitative yield. R_f 0.41 (hexane:EtOAc, 9:1); $[\alpha]^{25}_D$ -10.40 (c 1.0, $CHCl_3$); IR ν_{max} (film) 3416, 2961, 2859, 1717, 1653, 1472, 1427, 1368, 1267, 1182, 1111, 1094, 1034, 982, 824, 802, 741, 700, 689 and 613 cm^{-1}; ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.66-7.56 (4H, m, CH_{Ar}), 7.43-7.30 (6H, m, CH_{Ar}), 6.91 (1H, dd, *J* 7.5, 15.8 Hz, CH=), 5.80 (1H, dd, *J* 1.5, 15.8 Hz, EtOCOCH=), 4.17 (2H, q, *J* 7.1 Hz, CH_2), 3.60-3.53 (2H, m, CH_2), 2.61-2.42 (1H, m, CH), 1.29 (3H, t, *J* 7.0 Hz, CH_3), 1.12 (3H, d, *J* 6.7 Hz, CH_3), 1.01 (9H, s, 3 × CH_3); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 166.7 (CO), 152.8 (EtOCOCH=), 135.9 (CH_{Ar}), 133.6 (C_{Ar}), 130.0 (CH_{Ar}), 127.9 (CH_{Ar}), 121.5 (CH=), 67.6 (CH_2), 60.2 (CH_2), 39.1 (CH), 26.9 (3 × CH_3), 19.2 (C), 16.6 (CH_3), 14.3 (CH_3); HRMS (CI+/ISO) calc. for $C_{24}H_{33}O_3Si$ $[M+H]^+$: 397.2199. Found: 397.2203.

The characterisation matches with the data reported in literature:
Nicolaou K. C.; Schlawe D.; Kim D. W.; Longbottom D. A.; de Noronha R. G.; Lizos D. E.; Manam R. R.; Faulkner D. J. *Chem. Eur. J.* **2005**, *11*, 6197.

_(S,E)_-5-(_tert_-Butyldiphenylsilyloxy)-4-methylpent-2-en-1-ol, 180

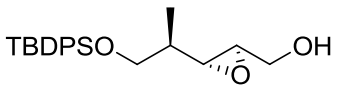


The *(S,E)*-ethyl 5-(*tert*-butyldiphenylsilyloxy)-4-methylpent-2-enoate **176** (13.7 g, 34.6 mmol) was dissolved in dry dichloromethane (180 mL) and the solution was cooled at 0 ° C. Then DIBAL-H (76.1 mL, 76.1 mmol, 1 M solution in hexane) was added dropwise and the reaction mixture was allowed to stir at 0 °C for 2 hours.

The reaction mixture was quenched carefully at 0 °C with 200 mL of a Rochelle's salt saturated aqueous solution added dropwise and the biphasic system was allowed to stir at room temperature for 12 hours. Then the organic layer was saved and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). All the organic layers were combined and washed with brine (200 mL), then dried over Na_2SO_4, filtered and concentrated under vacuum to afford a colourless oil as product **180** (12.4 g, 34.8 mmol) in quantitative yield . The product resulted very clean without necessity of any further purification. R_f 0.15 (hexane:EtOAc, 9:1); $[\alpha]^{25}_D$ -2.40 (c 1.0, $CHCl_3$); IR ν_{max} (film) 3323, 3071, 2959, 2858, 1589, 1473, 1427, 1389, 1362, 1105, 1083, 1007, 998, 970, 824, 806, 738, 699, 689 and 613 cm^{-1}; ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.66-7.58 (4H, m, CH_{Ar}), 7.42-7.28 (6H, m, CH_{Ar}), 5.64-5.54 (2H, m, CH=CH), 4.07-3.95 (2H, m), 3.57-3.43 (2H, *app* bt, *J* 4.8 Hz, CH_2), 2.50-2.27 (1H, m, CH), 1.30 (1H, bt, *J* 5.8 Hz, OH), 1.12 (9H, s, 3 × CH_3), 1.00 (3H, d, *J* 7.0 Hz, CH_3); (400 MHz; C_6D_6): δ_H 7.80-7.74 (4H, m, CH_{Ar}), 7.26-7.20 (6H, m, CH_{Ar}), 5.47-5.43 (2H, m, CH=CH), 3.80 (2H, t, *J* 5.1 Hz, C*H*$_2$OH), 3.57 (1H, dd, *J* 6.2, 9.7 Hz, C*H*HOSi), 3.48 (1H, dd, *J* 7.4, 9.9 Hz, CH*H*OSi), 2.42-2.29 (1H, m, CH), 1.18 (9H, s, 3 × CH_3), 0.99 (3H, d, *J* 6.7 Hz, CH_3); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 135.6 (CH_{Ar}), 135.5 (CH=), 133.9 (C_{Ar}), 129.6 (CH_{Ar}), 128.7 (CH_{Ar}), 127.6 (CH=), 68.5 (CH_2OSi), 63.9 (CH_2OH), 38.9 (CH), 26.9 (3 × CH_3), 19.3 (C), 16.4 (CH_3); HRMS (CI+/ISO) calc. for $C_{22}H_{29}OSi$ [M-OH]$^+$: 337.1988. Found: 337.1987.

The characterisation matches with the data reported in literature:
Chandrasekhar S.; Yaragorla S. R.; Sreelakshmi L.; Reddy C. H. R. *Tetrahedron* **2008**, *64*, 5174.

((*2R,3R*)-3-((*R*)-1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl)oxiran-2-yl)methanol, 175

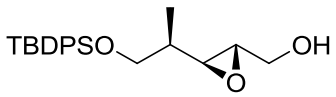


(-)-Diethyl tartrate (0.53 mL, 3.05 mmol) and powdered 4 Å molecular sieves (0.50 g) were suspended in freshly distilled dichloromethane (15 mL) and the resulting suspension was cooled at -20 °C and then treated with Ti(O-*i*Pr)$_4$ (0.76 mL, 2.54

mmol) followed by vigorous stirring for 20 minutes at -20 °C. Then TBHP (1.4 mL, 7.62 mmol) was added and the reaction mixture was stirred for 20 minutes at -20 °C. A solution of *(S,E)*-5-(*tert*-butyldiphenylsilyloxy)-4-methylpent-2-en-1-ol **180** (0.90 g, 2.54 mmol) in dichloromethane (5 mL) was finally added and the resulting mixture was stirred at -23 °C for 1 hour. The reaction mixture was diluted with diethyl ether (20 mL) and filtered through Celite® and silica gel. The solvent was removed under vacuum to afford a yellow-orange oil as crude product. The crude was purified by flash column chromatography on silica gel (from 10 to 40% ethyl acetate in hexane) to afford a colourless oil as pure product **175** (0.87 g, 2.35 mmol) in 93% yield, 90% *d.e.* R_f 0.29 (hexane:EtOAc, 7:3); $[\alpha]^{25}_D$ -9.60 (*c* 1.25, $CHCl_3$); IR ν_{max} (film) 3429, 2859, 1749, 1473, 1427, 1111, 1007, 824, 739, 699 and 614 cm^{-1}; ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.66-7.58 (4H, m, CH_{Ar}), 7.42-7.28 (6H, m, CH_{Ar}), 3.91-3.61 (4H, m, 2 × CH_2), 3.22-3.18 (2H, m, 2 × CH), 2.19 (1H, bs, OH), 1.81-1.68 (1H, m, C*H*CH_3), 1.11 (9H, s, 3 × CH_3), 1.01 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 135.6 (CH_{Ar}), 133.6 (C_{Ar}), 129.8 (CH_{Ar}), 127.8 (CH_{Ar}), 65.9 (CH_2OSi), 61.9 (CH_2OH), 57.5 (*C*HCHCH$_3$), 56.9 (*C*HCH$_2$OH), 37.8 (*C*HCH$_3$), 26.9 (3 × CH_3), 19.4 (C), 12.9 (CH_3); HRMS (CI+/ISO) calc. for $C_{22}H_{31}O_3Si$ $[M+H]^+$: 371.2042. Found: 371.2052.

The characterisation matches with the data reported in literature:
Chandrasekhar S.; Yaragorla S. R.; Sreelakshmi L.; Reddy C. H. R. *Tetrahedron* **2008**, *64*, 5174.

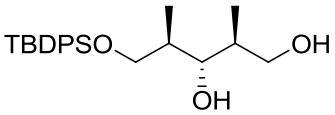
(*(2S,3S)*-3-(*(R)*-1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl)oxiran-2-yl) methanol, 181



^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.72-7.67 (4H, m, CH_{Ar}), 7.47-7.37 (6H, m, CH_{Ar}), 3.94-3.60 (4H, m, 2 × CH_2), 3.18-3.13 (1H, m, CH), 2.98-2.95 (1H, m, CH), 2.19 (1H, bs, OH), 1.75-1.65 (1H, m, C*H*CH_3), 1.07 (9H, s, 3 × CH_3), 0.99 (3H, d, *J* 7.0 Hz, CH_3).

The characterisation matches with the data reported in literature:
Fuwa H.; Sasaki M. *Org. Lett.* **2010**, *12*, 584.

***(2S,3S,4R)*-5-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylpentane-1,3-diol, 187**

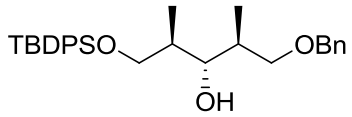


CuI (2.50 g, 13.2 mmol) was dissolved in dry diethyl ether (8 mL) and the solution was cooled at -23 °C, then a solution of methyllithium 1.5M (17.6 mL, 26.4 mmol) was added dropwise and stirred to afford a colourless solution. The solution was cooled at -45 °C and (*(2R,3R)*-3-(*(R)*-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)oxiran-2-yl)methanol **175** (0.49 g, 1.32 mmol) in dry diethyl ether (2 mL) was added dropwise. The reaction mixture was allowed to warm from -45 °C to -20 °C and left to stir for 12 hours. The reaction mixture was quenched with a 2:1 mixture of saturated NH_4Cl and 28% aqueous NH_3 (10 mL) and separated. The organic layer was washed with brine (10 mL) and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product was directly dissolved in 60% aqueous acetonitrile (10 mL) followed by slow addition of $NaIO_4$ (565 mg, 2.64 mmol) at 0 °C. After stirring for an hour at room temperature acetonitrile was removed under vacuum and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified by silica gel flash column chromatography (from 10 to 40% ethylacetate in hexane) to afford a colourless oil as pure product **187** (333 mg, 863 µmol) in 65% yield. R_f 0.40 (hexane:EtOAc, 6:4); $[\alpha]^{25}_D$ -5.60 (c 0.5, $CHCl_3$); IR ν_{max} (film) 3425, 2961, 2858, 2360, 1427, 1112, 1075, 984, 824, 740, 701, 692 and 613 cm^{-1}; ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.72-7.63 (4H, m, CH_{Ar}), 7.49-7.35 (6H, m, CH_{Ar}), 4.40 (1H, d, *J* 4.0 Hz, CHO*H*), 3.91-3.78 (2H, m, CH_2OSi), 3.70-3.46 (3H, m, C*H*OH and C*H*$_2$OH), 1.81-1.68 (2H, m, 2 × CH), 1.18-1.15 (1H, bm, CH_2O*H*), 1.09 (9H, s, 3 × CH_3), 1.02 (3H, d, *J* 7.0 Hz, CH_3), 0.96 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 135.7 (CH_{Ar}), 133.6 (C_{Ar}), 130.0 (CH_{Ar}), 127.9 (CH_{Ar}), 83.2 (CHOH), 68.3 (CH_2OH), 66.8 (CH_2OSi), 37.1 (CH), 36.7 (CH), 26.9 (3 × CH_3), 19.1 (C), 14.6 (CH_3), 13.5 (CH_3); HRMS (CI+/ISO) calc. for $C_{23}H_{35}O_3Si$ $[M+H]^+$: 387.2355. Found: 387.2361.

The characterisation matches with the data reported in literature:

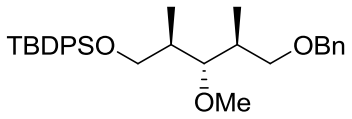
Chandrasekhar S.; Yaragorla S. R.; Sreelakshmi L.; Reddy C. H. R. *Tetrahedron* **2008**, *64*, 5174.

(2S,3S,4R)-1-(Benzyloxy)-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpentan-3-ol, 189



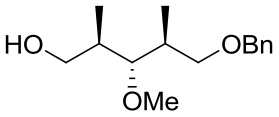
To a suspension of NaH (1.03 g, 25.7 mmol) in dry THF (150 mL) at 0 °C, a solution of *(2S,3S,4R)*-5-(tert-butyldiphenylsilyloxy)-2,4-dimethylpentane-1,3-diol **187** (3.30 g, 8.50 mmol) in THF (50 mL) was added. The resulting mixture was stirred at 0 °C for 30 minutes and then benzyl bromide (1.02 mL, 8.50 mmol) was added dropwise. The reaction mixture was allowed to stir at room temperature for 12 hours. The reaction was quenched with NH_4Cl saturated aqueous solution (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified by silica gel column chromatography (from 0 to 20% ethyl acetate in hexane) to afford a colourless oil as pure product **189** (3.35 g, 7.03 mmol) in 83% yield. R_f 0.64 (hexane:EtOAc, 8:2); $[\alpha]^{25}_D$ -4.80 (c 1.0, $CHCl_3$); IR ν_{max} (film) 3503, 2932, 2862, 1466, 1427, 1111, 1080, 995, 910, 818, 734, 694, 648 and 610 cm^{-1}; ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.86-7.63 (4H, m, CH_{Ar}), 7.41-7.21 (11H, m, CH_{Ar}), 4.46 (2H, s, CH_2Ph), 3.70 (2H, d, *J* 5.7 Hz, CH_2OSi), 3.60-3.45 (2H, m, CH_2OBn), 3.39 (1H, m, C*H*OH), 2.05-1.82 (2H, m, 2 × CH), 1.10 (1H, bs, OH), 1.06 (9H, s, 3 × CH_3), 0.95 (3H, d, *J* 6.9 Hz, CH_3), 0.93 (3H, d, *J* 6.9 Hz, CH_3); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 138.3 (C_{Ar}), 135.7 (CH_{Ar}), 135.2(CH_{Ar}), 133.3 (C_{Ar}), 129.7 (CH_{Ar}), 128.4 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 79.5 (CHOH), 73.6 (CH_2OBn), 73.4 (CH_2Ph), 67.3 (CH_2OSi), 37.8 (CH), 36.3 (CH), 26.9 (3 × CH_3), 19.2 (C), 15.1 (CH_3), 14.6 (CH_3); HRMS (CI+/ISO) calc. for $C_{30}H_{41}O_3Si$ $[M+H]^+$: 477.2825. Found: 477.2824.

(*(2R,3S,4S)*-5-(Benzyloxy)-3-methoxy-2,4-dimethylpentyloxy)(*tert*-butyl) diphenylsilane, 190



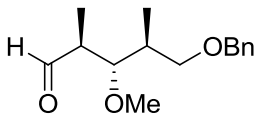
To a suspension of NaH (1.40 g, 35.0 mmol) in dry THF (25 mL), a solution of *(2S,3S,4R)*-1-(benzyloxy)-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpentan-3-ol **189** (3.30 g, 7.00 mmol) in THF (25 mL) was added and the resulting mixture was allowed to stir at room temperature for 15 minutes. Then iodomethane (4.4 mL, 70.0 mmol) and TBAI (0.26 g, 0.70 mmol) were added and the reaction mixture was let to stir at 60 °C for 12 hours. The reaction was quenched with a saturated solution of NH_4Cl (50 mL) and the 2 layers were separated. The organic layer was washed with brine (50 mL) and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The organic layers were mixed, dried over Na_2SO_4, filtered and concentrated under vacuum to afford a pale yellow oil as crude product. The crude product was purified by silica gel flash column chromatography (5% ethyl acetate in hexane) to afford a colourless oil as pure product **190** (3.30 g, 6.74 mmol) in 96% yield. R_f 0.39 (hexane:EtOAc, 9.5:0.5); $[\alpha]^{25}_D$ -4.00 (c 0.5, $CHCl_3$); IR ν_{max} (film) 3071, 2963, 2855, 1612, 1466, 1427, 1080, 995, 1003, 826, 741, 694 and 610 cm^{-1}; ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.86-7.63 (4H, m, CH_{Ar}), 7.41-7.21 (11H, m, CH_{Ar}), 4.46 (2H, s, CH_2Ph), 3.59 (1H, dd, *J* 4.4, 9.6 Hz, C*H*HOSi), 3.49 (1H, dd, *J* 6.8, 10.0 Hz, CH*H*OSi), 3.47 (3H, s, OCH_3), 3.35-3.42 (2H, m, CH_2OBn), 2.93 (1H, *app* t, *J* 6.4 Hz, CHOMe), 2.05-1.82 (2H, m, 2 × CH), 0.92 (9H, s, 3 × CH_3), 0.82 (3H, d, *J* 7.0 Hz, CH_3), 0.78 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 138.9 (C_{Ar}), 135.7 (CH_{Ar}), 135.5 (CH_{Ar}), 133.9 (C_{Ar}), 129.6 (CH_{Ar}), 128.4 (CH_{Ar}), 127.5 (CH_{Ar}), 127.3 (CH_{Ar}), 85.8 (CHOMe), 73.1 (CH_2Ph), 72.2 (CH_2OBn), 65.2 (CH_2OSi), 61.2 (OCH_3), 37.9 (CH), 36.1 (CH), 26.9 (3 × CH_3), 19.2 (C), 15.7 (CH_3), 15.1 (CH_3); HRMS (CI+/ISO) calc. for $C_{31}H_{43}O_3Si$ $[M+H]^+$: 491.2981. Found: 491.2985.

***(2R,3R,4S)*-5-(Benzyloxy)-3-methoxy-2,4-dimethylpentan-1-ol, 191**



(*(2R,3S,4S)*-5-(benzyloxy)-3-methoxy-2,4-dimethylpentyloxy)(*tert*-butyl) diphenyl silane **190** (525 mg, 1.07 mmol) was dissolved in dry THF (15 mL) under argon and the solution obtained was cooled at 0 °C. Then TBAF (2.7 mL, 2.70 mmol, 1 M solution in THF) was added dropwise and the reaction mixture was allowed to stir at room temperature for 12 hours. The reaction was quenched with distilled water (15 mL), extracted with diethyl ether (3 × 20 mL), washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow/colourless oil as crude product. The crude product was purified by silica gel flash column chromatography (from 10 to 40% ethyl acetate in hexane) to afford a colourless oil as pure product **191** (0.22 g, 873 µmol) in 82% yield. R_f 0.14 (hexane:EtOAc, 8:2); $[\alpha]^{25}_D$ +3.20 (c 1.0, $CHCl_3$); IR ν_{max} (film) 3433, 2924, 1458, 1366, 1088, 1026, 978, 903, 741 and 694 cm^{-1}; ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.41-7.32 (5H, m, CH_{Ar}), 4.50 (2H, s, CH_2Ph), 3.75 (1H, dd, *J* 4.4 Hz, 9.6 Hz, C*H*HOH), 3.65-3.45 (3H, m, CH*H*OH and CH_2OBn), 3.38 (3H, s, OCH_3), 2.93 (1H, *app* t, *J* 6.4 Hz, CHOMe), 2.89 (1H, bs, OH), 2.05-1.82 (2H, m, 2 × CH), 0.82 (3H, d, *J* 6.9 Hz, CH_3), 0.78 (3H, d, *J* 6.9 Hz, CH_3); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 138.6 (C_{Ar}), 128.4 (CH_{Ar}), 127.9 (CH_{Ar}), 127.5 (CH_{Ar}), 89.1 (CHOMe), 73.1 (CH_2OPh), 72.2 (CH_2OBn), 65.6 (CH_2OH), 61.1 (OCH_3), 37.4 (CH), 36.4 (CH), 15.1 (CH_3), 14.6 (CH_3); HRMS (CI+/ISO) calc. for $C_{15}H_{25}O_3$ $[M+H]^+$: 253.1804. Found: 253.1805.

***(2S,3S,4S)*-5-(Benzyloxy)-3-methoxy-2,4-dimethylpentanal, 192**

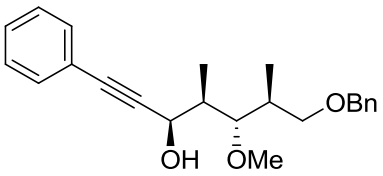


Oxalyl chloride (0.10 mL, 1.08 mmol) was dissolved in freshly distilled dichloromethane (2 mL) and the solution was cooled at -78 °C under argon. Then a solution of dimethylsulfoxide (0.16 mL, 2.16 mmol) in dichloromethane (2 mL) was added dropwise and stirred under argon at -78 °C for 30 minutes. Then a solution of *(S)*-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol **191** (136 mg, 0.54

mmol) in dichloromethane (3 mL), was added dropwise and the reaction mixture was allowed to stir at -78 °C for 1 hour. Then the reaction mixture was quenched at -78 °C by dropwise addition of triethylamine (0.6 mL, 4.32 mmol) with the use of a bleach trap and the obtained solution was allowed to stir at -78 °C for 10 minutes and then at room temperature for 30 minutes. Then the solution was washed with 10 mL of $NaHCO_3$ aqueous saturated solution and extracted with dichloromethane (3 × 10 mL). The organic layers were collected, washed with 10 mL of brine, dried over Na_2SO_4, filtered and concentrated under vacuum to afford the product **192** as a yellow oil in quantitative yield (135 mg, 0.54 mmol). The crude product was taken straight onto the next step without any further purification.

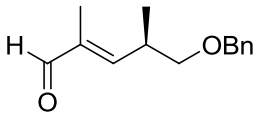
^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 9.76 (1H, s, CHO), 7.40-7.32 (5H, m, CH_{Ar}), 4.50 (2H, s, CH_2Ph), 3.54-3.46 (2H, m, CH_2OBn), 3.38 (3H, s, OCH_3), 3.41-3.37 (1H, m, CHOMe), 2.69-2.61 (1H, m, CH), 2.11-2.05 (1H, m, CH), 1.14 (3H, d, *J* 6.8 Hz, CH_3), 0.98 (3H, d, *J* 6.8 Hz, CH_3).

***(3R,4R,5S,6S)*-7-(Benzyloxy)-5-methoxy-4,6-dimethyl-1-phenylhept-1-yn-3-ol, 193**



and

***(R,E)*-5-(Benzyloxy)-2,4-dimethylpent-2-enal, 194**



To a suspension of zinc triflate (673 mg, 1.85 mmol) and (+)-*N*-methylephedrine (343 mg, 1.91 mmol) in dry toluene (3 mL), under argon at room temperature, triethylamine (0.3 mL, 1.91 mmol) was added dropwise and the resulting mixture was allowed to stir at room temperature for 2 hours. Then phenylacetylene (0.1 mL, 0.74 mmol) was added by syringe in one portion and the reaction mixture was allowed to stir for 15 minutes. Finally, a solution of *(2S,3S,4S)*-5-(benzyloxy)-3-methoxy-2,4-dimethylpentanal **192** (154 mg, 615 µmol) in 2 mL of dry toluene was added in one portion by syringe and the resulting mixture was allowed to stir at 60

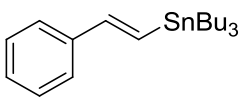
°C for 48 hours. Then, the reaction was quenched with NH_4Cl saturated aqueous solution (5 mL) and extracted with ethyl acetate (4 × 5 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum to afford a yellow-brown oil as crude product. The crude product was purified through flash column chromatography (from 0 to 30% diethyl ether in hexane) to afford the desired product **193** as a colourless oil in 5% yield (10.0 mg, 28.4 µmol), and the secondary product **194** as a pale yellow oil in 60% yield (80.0 mg, 367 µmol).

***Desired product* 193:** $[\alpha]^{26}_D$ -4.40 (*c* 0.1, $CHCl_3$); IR ν_{max} (film) 3047, 2964, 2939, 2859, 1490, 1454, 1365, 1215, 1085, 1070, 1028, 970, 752, 737 and 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47-7.27 (10H, m, CH_{Ar}), 4.70 (1H, dd, *J* 2.4, 6.8 Hz, *CH*OH), 4.52 (2H, s, CH_2Ph), 4.11 (1H, d, *J* 6.8 Hz, OH), 3.60-3.56 (1H, m, CH), 3.55 (3H, s, OCH_3), 3.47-3.42 (2H, m, CH_2OBn), 2.27-2.11 (2H, m, 2 × CH), 1.17 (3H, d, *J* 6.8 Hz, CH_3), 1.12 (3H, d, *J* 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5 (C_{Ar}), 131.7 (CH_{Ar}), 131.6 (CH_{Ar}), 128.4 (CH_{Ar}), 128.2 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 123.0 (C_{Ar}), 89.3 (C), 88.2 (CHOMe), 85.3 (C), 73.2 (CH_2OBn), 70.2 (CH_2Ph), 66.4 (CHOH), 60.9 (OCH_3), 40.5 ($CHCH_3$), 36.5 ($CHCH_3$), 15.6 (CH_3), 14.6 (CH_3); HRMS (CI+/ISO) calc. for $C_{23}H_{27}O_2$ $[M\text{-}OH]^+$: 335.2011. Found: 335.2012.

***Undesired Byproduct* 194:** $[\alpha]^{26}_D$ +20.10 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 9.40 (1H, s, CHO), 7.37-7.26 (5H, m, CH_{Ar}), 6.34 (1H, dq, *J* 2.0, 9.6 Hz, CH=), 4.52 (2H, s, CH_2Ph), 3.48-3.40 (2H, m, CH_2OBn), 3.07-3.00 (1H, m, $CHCH_3$), 1.78 (3H, s, CH_3), 1.09 (3H, d, *J* 9.0 Hz, CH_3).

The characterisation matches with the data reported in literature:
Meyers A. I.; Babiak K. A.; Campbell A. L.; Comins D. L.; Fleming M. P.; Henning R.; Heuschmann M.; Hudspeth J. P.; Kane J. M.; Reider P. J.; Roland D. M.; Shimizu K.; Tomioka K.; Walkup R. D. *J. Am. Chem. Soc.* **1983**, *105*, 5015.

(E)-Tributyl(styryl)stannane, 200

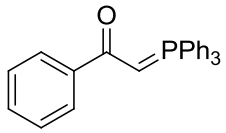


To a mixture of phenylacetylene **199** (2.1 mL, 19.0 mmol) and AIBN (0.14 g, 85.0 µmol), under argon at room temperature, tributyltin hydride (5.4 mL, 20.0 mmol)

was added dropwise and the resulting mixture was allowed to stir at 50 °C for 24 hours. The reaction was allowed to cool to room temperature to afford a yellow oil as crude product. The crude product was purified by distillation under vacuum (b.p. 134 °C, 0.1 mmHg) to afford the pure product **200** as a colourless oil in 73% yield (5.42 g, 13.8 mmol). ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.21-7.42 (5H, m, CH_{Ar}), 6.93 (2H, s, CH=CH), 1.60-0.66 (27H, m, 9 × CH_2 and 3 × CH_3); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 146.0 (CH=), 138.7 (C_{Ar}), 129.3 (CH_{Ar}), 128.3 (CH_{Ar}), 127.3 (CH_{Ar}), 125.9 (CH=), 29.2 (CH_2), 27.4 (CH_2), 13.8 (CH_2), 9.7 (CH_3).

The characterisation matches the data reported in literature:
Labadie J. W.; Stille J. K. *J. Am. Chem. Soc*. **1983**, *105*, 6129.

2-Phenyl(triphenylphosphoranylidene)ethan-2-one, 204

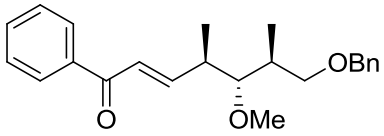


Triphenylphosphine (2.62 g, 10.0 mmol) and 2-bromo-1-phenylethanone (1.99 g, 10.0 mmol) were dissolved in dry THF (250 mL) under argon and the resulting mixture was allowed to stir at reflux for 4 hours. Then the mixture was allowed to cool to room temperature and the white precipitate was collected by filtration and washed with diethyl ether (100 mL) to afford the (2-oxo-2-phenylethyl)triphenylphosphonium salt **203**. ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 8.35-8.30 (2H, m, CH_{Ar}), 7.89-7.48 (18H, m, CH_{Ar}), 6.35 (2H, d, *J* 12.0 Hz, CH_2). The salt **203** was immediately dissolved in a mixture of methanol and H_2O (100 mL + 100 mL) and treated with an aqueous solution of NaOH 2 N (100 mL). The resulting mixture was allowed to stir at room temperature for 12 hours, then the methanol was removed under reduced pressure while the aqueous phase was extracted with chloroform (3 × 100 mL). The organic layer was wahed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford a light yellow solid as pure product **204** in 79% yield over the two steps (3.00 g, 7.90 mmol). IR ν_{max} (film) 1587, 1524, 1512, 1483, 1435, 1385, 1103, 891, 872, 843, 748, 712 and 689 cm^{-1}; ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.98-7.97 (2H, m, CH_{Ar}), 7.75-7.35 (18H, m, CH_{Ar}), 4.43 (1H, d, *J* 24.4 Hz, CH=); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 184.0 (CO), 133.2 (C_{Ar}), 132.1 (C_{Ar}), 129.4 (CH_{Ar}), 128.9 (CH_{Ar}), 128.8

(CH_{Ar}), 127.7 (CH_{Ar}), 126.9 (CH_{Ar}), 126.6 (CH_{Ar}), 50.0 (CH=); HRMS (CI+/ISO) calc. for $C_{26}H_{22}OP$ $[M+H]^+$: 381.1408. Found: 381.1408; m.p.184-185 °C.

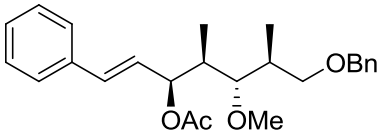
The characterisation matches the data reported in literature:
Babu K. S.; Li X. C.; Jacob M. R.; Zhang Q. F.; Kahn S. I.; Ferreira D.; Clark A. M. *J. Med. Chem*. **2006**, *49*, 7877.

***(4R,5R,6S,E)*-7-(Benzyloxy)-5-methoxy-4,6-dimethyl-1-phenylhept-2-en-1-one, 201**



(2S,3S,4S)-5-(benzyloxy)-3-methoxy-2,4-dimethylpentanal **192** (135 mg, 0.54 mmol) and 2-phenyl(triphenylphosphoranylidene)ethan-2-one **204** (616 mg, 1.62 mmol) were dissolved in benzene (3 mL) and the reaction mixture was allowed to stir at 85 °C for 96 hours. Then the solution was concentrated under vacuum to afford a beige oil as crude product. The crude product was purified through flash column chromatography on silica gel (from 0 to 10% ethyl acetate in hexane) to afford a colourless oil as pure product **201** (73.0 mg, 0.21 mmol) in 39% yield. R_f 0.12 (hexane:Et_2O, 9:1); $[\alpha]^{26}_D$ +2.80 (c 1.0, $CHCl_3$); IR ν_{max} (film) 2967, 2932, 2911, 2874, 2859, 2359, 1767, 1669, 1653, 1618, 1597, 1580, 1449, 1364, 1252, 1215, 1090, 1047, 1015, 986, 974, 916, 845, 822, 775 and 735 cm^{-1}; ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.93-7.89 (2H, m, CH_{Ar}), 7.58-7.51 (1H, m, CH_{Ar}), 7.50-7.43 (2H, m, CH_{Ar}), 7.37-7.32 (5H, m, CH_{Ar}), 7.09 (1H, dd, *J* 8.6, 15.7 Hz, CH=), 6.84 (1H, d, *J* 15.7 Hz, COCH=), 4.50 (2H, s, CH_2Ph), 3.52-3.50 (2H, m, CH_2OBn), 3.42 (3H, s, OCH_3), 3.13-3.10 (1H, m, CHOMe), 2.76-2.70 (1H, m, CH), 1.96-1.88 (1H, m, CH), 1.21 (3H, d, *J* 6.8 Hz, CH_3), 1.01 (3H, d, *J* 6.9 Hz, CH_3); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 191.3 (CO), 151.2 (CH=), 138.8 (C_{Ar}), 138.2 (C_{Ar}), 132.7 (CH_{Ar}), 128.7 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 126.0 (CO*C*H=) 87.0 (CHOMe), 73.4 (CH_2Ph), 72.4 (CH_2OBn), 61.3 (OCH_3), 40.3 (CHMe), 37.3 (CHMe), 17.6 (CH_3), 15.1 (CH_3); HRMS (CI+/ISO) calc. for $C_{23}H_{29}O_3$ $[M+H]^+$: 353.2117. Found: 353.2112.

_(3S,4S,5S,6S,E)_-7-(Benzyloxy)-5-methoxy-4,6-dimethyl-1-phenylhept-1-en-3-yl acetate, 208

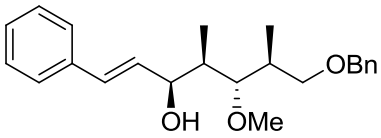


_(S)_-2-Methyl-CBS-oxazaborilidine (300 mg, 1.08 mmol) was dissolved in dry THF (12 mL) and cooled to -10 °C. Then BH_3·THF (1.08 mL, 1.08 mmol, 1 M solution in THF) was added. After 30 minutes, a solution of _(4R,5R,6S,E)_-7-(benzyloxy)-5-methoxy-4,6-dimethyl-1-phenylhept-2-en-1-one **201** (312 mg, 0.88 mmol) was added and the reaction mixture was stirred at -10 °C for 1 hour. Evaporation of the solvent afforded a yellow oil as crude product, which was purified through flash column chromatography on silica gel (from 0 to 30% diethyl ether in hexane) to afford a colourless oil as pure product **205** (163 mg, 0.46 mmol) in 52% yield. _(1R,4R,5R,6S,E)_-7-(benzyloxy)-5-methoxy-4,6-dimethyl-1-phenylhept-2-en-1-ol **205** (163 mg, 0.46 mmol) was immediately dissolved in dry dichloromethane (6 mL), under argon at room temperature, and acetic anhydride (0.12 mL, 1.32 mmol), triethylamine (0.30 mL, 1.76 mmol) and DMAP (5.0 mg, 0.04 mmol) were added. The reaction mixture was allowed to stir at room temperature for 12 hours. Then the solvent was removed under vacuum to afford a yellow-brown oil as crude product (166 mg, 0.42 mmol, 92%), which was taken straight onto the next step without any further purification. ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.36-7.26 (10H, m, CH_{Ar}), 6.24 (1H, dd, _J_ 1.2, 6.4 Hz, CHOAc), 5.80 (1H, dd, _J_ 10.0, 15.6 Hz, CH=), 5.63 (1H, dd, _J_ 10.0, 15.6 Hz, CH=), 4.48 (2H, s, CH_2Ph), 3.55-3.42 (2H, m, CH_2OBn), 3.37 (3H, s, OCH_3), 2.98-2.94 (1H, m, CHOMe), 2.10 (3H, s, $OCOCH_3$), 1.95-1.78 (2H, m, 2 × CH), 1.10 (3H, d, _J_ 6.9 Hz, CH_3), 1.06 (3H, d, _J_ 6.9 Hz, CH_3).

(1_R_,4_R_,5_R_,6_S_,_E_)-7-(benzyloxy)-5-methoxy-4,6-dimethyl-1-phenylhept-2-enyl acetate **207** (166 mg, 0.42 mmol), and $PdCl_2(CH_3CN)_2$ (6.30 mg, 21.2 µmol) were dissolved in dry THF (2.1 mL) and the resulting mixture was allowed to stir at room temperature for 12 hours. Then it was filtered through Celite® and washed with ethyl acetate as eluent (40 mL). The eluate was concentrated under vacuum to afford a yellow-brown oil as crude product. The crude was purified through flash column chromatography on silica gel (from 0 to 30% ethyl acetate in hexane) to afford a yellow oil as pure product **208** (166 mg, 0.42 mmol) in quantitative yield.

^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.41-7.27 (10H, m, CH_{Ar}), 6.63 (1H, d, *J* 15.4 Hz, CH=), 6.17 (1H, dd, *J* 9.3, 15.8 Hz, CH=), 4.53-4.46 (3H, m, CHOAc and CH_2Ph), 3.61-3.55 (2H, m, CH_2OBn), 3.41 (3H, s, OCH_3), 3.39-3.35 (1H, m, CHOMe), 3.06-2.98 (2H, m, 2 × CH), 2.12 (3H, s, $OCOCH_3$), 1.10 (3H, d, *J* 6.9 Hz, CH_3), 0.99 (3H, d, *J* 6.9 Hz, CH_3).

***(3S,4R,5S,6S,E)*-7-(Benzyloxy)-5-methoxy-4,6-dimethyl-1-phenylhept-1-en-3-ol, 209**



Method A

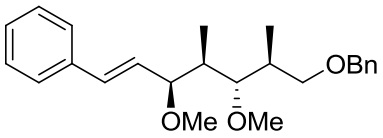
(3S,4S,5S,6S,E)-7-(benzyloxy)-5-methoxy-4,6-dimethyl-1-phenylhept-1-en-3-yl acetate **208** (0.04 g, 101 µmol) was dissolved in methanol/H_2O (1 mL/1 mL) in presence of K_2CO_3 (42.0 mg, 30.3 µmol) and the resulting mixture was allowed to stir at room temperature for 2 hours. The reaction was quenched with H_2O (2 mL) and extracted with ethyl acetate (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified by silica gel flash column chromatography (from 0 to 15% ethyl acetate in hexane) to afford a colourless oil as pure product **209** (15.5 mg, 45.0 µmol) in 45% yield.

Method B

(3S,4S,5S,6S,E)-7-(benzyloxy)-5-methoxy-4,6-dimethyl-1-phenylhept-1-en-3-yl acetate **208** (126 mg, 0.32 mmol) was dissolved in dry dichloromethane (5.25 mL) and the solution was cooled to 0 °C and stirred for 10 minutes. Then DIBAL-H (0.71 mL, 709 µmol, 1 M solution in hexane) was added dropwise and the resulting mixture was allowed to stir at 0 °C for 2 hours. The reaction mixture was quenched carefully at 0 °C with 10 mL of a Rochelle's salt saturated aqueous solution added dropwise and the biphasic system was allowed to stir at room temperature for 12 hours. Then the organic layer was saved and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). All the organic layers were combined and washed with brine (50 mL), then dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow thick oil/solid as crude product. The crude product was quickly washed through a pad of silica gel (30% ethyl acetate in hexane) to afford

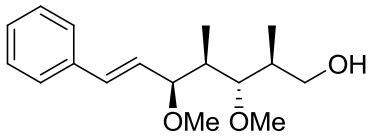
a yellow oil as semi pure product **209** in 99% yield (112 mg, 317 µmol). $[\alpha]^{26}_{D}$ +2.00 (c 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.43-7.25 (10H, m, CH_{Ar}), 6.62 (1H, d, *J* 15.9 Hz, CH=), 6.25 (1H, dd, *J* 6.9, 15.9 Hz, CH=), 4.53 (2H, s, CH_2Ph), 4.33 (1H, *app* t, *J* 7.3 Hz, C*H*OH), 3.63-3.56 (1H, m, C*H*HOBn), 3.53 (3H, s, OCH_3), 3.48-3.42 (1H, m, CH*H*OBn), 3.18 (1H, dd, *J* 4.7, 7.2 Hz, CHOMe), 2.22-2.19 (1H, m, CH), 2.06-2.01 (1H, m, CH), 1.63 (1H, bs, OH), 1.12 (3H, d, *J* 7.0 Hz, CH_3), 0.95 (3H, d, *J* 7.0 Hz, CH_3).

***((3S,4R,5S,6S,E)*-7-(Benzyloxy)-3,5-dimethoxy-4,6-dimethylhept-1-enyl) benzene, 210**



To a suspension of NaH (50.3 mg, 1.26 mmol) in dry THF (2 mL), a solution of *(3S,4R,5S,6S,E)*-7-(benzyloxy)-5-methoxy-4,6-dimethyl-1-phenylhept-1-en-3-ol **209** (112 mg, 317 µmol) in dry THF (10 mL) was added and the resulting mixture was left to stir at room temperature for 10 minutes. Then iodomethane (0.16 mL, 2.52 mmol) and TBAI (13.5 mg, 25.5 µmol) were added and the reaction mixture was allowed to stir at 60 °C for 12 hours. The reaction was quenched with a saturated aqueous solution of NH_4Cl (8 mL) and the two layers were separated. The organic layer was washed with brine (8 mL) and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow oil as crude product **210** (109 mg, 295 µmol, 93% yield). ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 7.41-7.23 (10H, m, CH_{Ar}), 6.56 (1H, d, *J* 16.0 Hz, CH=), 6.18 (1H, dd, *J* 7.2, 15.9 Hz, CH=), 4.48 (2H, s, CH_2Ph), 4.05 (1H, dd, *J* 2.5, 7.4 Hz, CHOMe), 3.60 (2H, m, CH_2OBn), 3.50 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 3.20 (1H, dd, *J* 2.4, 9.3 Hz, CHOMe), 2.17-2.09 (1H, m, CH), 1.84-1.77 (1H, m, CH), 1.14 (3H, d, *J* 7.1 Hz, CH_3), 0.93 (3H, d, *J* 7.1 Hz, CH_3).

***(2S,3S,4R,5S,E)*-3,5-Dimethoxy-2,4-dimethyl-7-phenylhept-6-en-1-ol, 22**



((3S,4R,5S,6S,E)-7-(benzyloxy)-3,5-dimethoxy-4,6-dimethylhept-1-enyl) benzene, **210** (109 mg, 295 µmol) and *N,N*-dimethylaniline (122 mg, 912 mmol) were dissolved in dry dichloromethane (15 mL) and aluminum trichloride (0.15 mL, 0.91 mmol) was added. The resulting mixture was allowed to stir at room temperature for 12 hours. The reaction was quenched with distilled water (30 mL), extracted with ethyl acetate (3 × 20 mL), washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford a pale yellow oil as crude product. The crude product was purified by silica gel column chromatography (from 0 to 30% ethyl acetate in hexane) to afford a colourless oil as pure product **22** (14.8 mg, 53.1 µmol) in 18% yield. R_f 0.14 (hexane:EtOAc, 8:2); $[\alpha]^{22}_D$ -5.2 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3440, 2972, 2935, 2831, 1497, 1449, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.43-7.39 (2H, m, CH_{Ar}), 7.36-7.31 (2H, m, CH_{Ar}), 7.27-7.23 (1H, m, CH_{Ar}), 6.58 (1H, d, *J* 16.3 Hz, CH=), 6.19 (1H, dd, *J* 7.1, 15.8 Hz, CH=), 4.08-4.05 (1H, m, CHOMe), 3.89-3.82 (1H, m, C*H*HOH), 3.57-3.51 (1H, m, CHOMe), 3.53 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 3.29 (1H, dd, *J* 2.7, 9.4 Hz, CH*H*OH), 2.92-2.87 (1H, m, OH), 1.92-1.82 (2H, m, 2 × CH), 1.21 (3H, d, *J* 7.2 Hz, CH_3), 0.91 (3H, d, *J* 7.2 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 136.9 (C_{Ar}), 132.3 (CH=), 129.5 (CH=), 128.8 (CH_{Ar}), 127.8 (CH_{Ar}), 126.6 (CH_{Ar}), 88.6 (CHOMe), 81.3 (CHOMe), 64.7 (CH_2OH), 61.8 (OCH_3), 56.5 (OCH_3), 42.5 (CH), 35.9 (CH), 16.4 (CH_3), 10.5 (CH_3); HRMS (ESI+) calc. for $C_{17}H_{26}O_3Na$ $[M+Na]^+$: 301.1774. Found: 301.1772.

The characterisation matches with the data reported in literature:

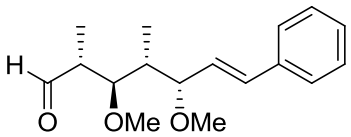
Feutrill J. T.; Lilly M. J.; Rizzacasa M. A. *Org. Lett*. **2000**, *2*, 3365.

Dias L. C.; de Oliveira L. G. *Org. Lett*. **2001**, *3*, 3951.

Chakraborty T. K.; Jayaprakash S.; Laxman P. *Tetrahedron* **2001**, *57*, 9461.

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

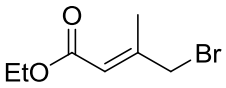
***(2R,3R,4R,5S,E)*-3,5-Dimethoxy-2,4-dimethyl-7-phenylhept-6-enal, 28**



To a solution of *(2S,3S,4R,5S,E)*-3,5-dimethoxy-2,4-dimethyl-7-phenylhept-6-en-1-ol **22** (30.0 mg, 108 µmol) in 2 mL of dry dichloromethane, DMP (92.0 mg, 216 µmol) was added and the resulting mixture was allowed to stir under argon at room temperature until completion as indicated by TLC analysis (40 minutes). Then, $Na_2S_2O_3$ aqueous saturated solution (2 mL), $NaHCO_3$ aqueous saturated solution (2 mL) and diethyl ether (5 mL) were added and the resulting mixture was stirred for a further 20 minutes at room temperature. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 5 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum to afford a pale yellow oil as crude product **28** (29.8 mg, 108 µmol), which was taken straight onto the next step without any further purification. R_f 0.37 (hexane:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.77 (1H, d, *J* 1.8 Hz, CHO), 7.43-7.23 (5H, m, CH_{Ar}), 6.57 (1H, d, *J* 16.0 Hz, CH=), 6.15 (1H, dd, *J* 7.3, 16.0 Hz, CH=), 4.08 (1H, dd, *J* 2.4, 7.6 Hz, CHOMe), 3.55 (1H, dd, *J* 2.6, 9.3 Hz, CHOMe), 3.49 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 2.73-2.65 (1H, m, CH), 1.93-1.82 (1H, m, CH), 1.20 (3H, d, *J* 7.1 Hz, CH_3), 0.87 (3H, d, *J* 7.1 Hz, CH_3).

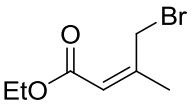
The characterisation matches with the data reported in literature:
Chakraborty T. K.; Jayaprakash S.; Laxman P. *Tetrahedron* **2001**, *57*, 9461.

***(E)*-Ethyl 4-bromo-3-methylbut-2-enoate, 211**



and

***(Z)*-Ethyl 4-bromo-3-methylbut-2-enoate, 212**



To a solution of ethyl 3-methylbut-2-enoate (5.42 mL, 39.0 mmol) in carbon tetrachloride (64 mL), were added *N*-bromosuccinimide (7.50 g, 42.5 mmol) and AIBN (10.0 mg, 61.0 µmol) and the resulting mixture was allowed to stir at 80 °C for 3 hours. Then the reaction mixture was allowed to cool to room temperature, it was filtered and the filtrate washed with chloroform (50 mL). The organic layers were combined and washed with Na_2SO_3 saturated aqueous solution (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified through flash column chromatography on silica gel (from 0 to 1.5% diethyl ether in hexane) to afford the desired product **211** as a colourless oil in 28% yield (2.25 g, 10.9 mmol) and the undesired isomer **212** as a colourless oil in 22% yield (1.77 g, 8.58 mmol).

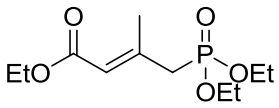
***Desired isomer* 211:** IR ν_{max} (film) 1719, 1651, 1445, 1369, 1282, 1231, 1157, 1042, 891, 863 and 736 cm^{-1}; ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 5.96 (1H, q, *J* 1.2 Hz, CH=), 4.17 (2H, q, *J* 7.0 Hz, CH_2), 3.93 (2H, s, CH_2Br), 2.27 (3H, d, *J* 1.2 Hz, CH_3), 1.28 (3H, t, *J* 7.0 Hz, CH_3); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 166.1 (CO), 152.5 (C), 119.7 (CH=), 60.3 (CH_2), 38.4 (CH_2Br), 17.3 (CH_3), 14.4 (CH_3); HRMS (CI+/ISO) calc. for $C_7H_{11}O_2Br$ $[M]^+$: 205.9942. Found: 205.9938.

***Undesired isomer* 212:** ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 5.74 (1H, q, *J* 1.2 Hz, CH=), 4.53 (2H, s, CH_2Br), 4.15 (2H, q, *J* 7.2 Hz, CH_2), 2.01 (3H, d, *J* 1.2 Hz, CH_3), 1.26 (3H, t, *J* 7.2 Hz, CH_3).

The characterisation matches with the data reported in literature:
Mata E.; Thomas E. J. *J. Chem. Soc. Perkin Trans. 1* **1995**, 785.

.

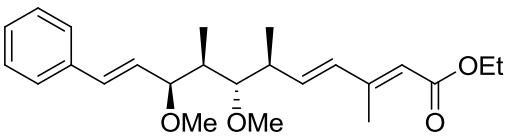
***(E)*-Ethyl 4-(diethoxyphosphoryl)-3-methylbut-2-enoate, 29**



To the neat *(E)*-ethyl 4-bromo-3-methylbut-2-enoate **211** (1.30 g, 6.31 mmol) was added triethyl phosphite (1.65 mL, 9.50 mmol) and the resulting mixture was allowed to stir at 170 °C for 1 hour. The crude brown oil so obtained was distilled under vacuum (180 °C, 1 mbar) to afford the desired product **29** as a colourless oil in 94% yield (1.55 g, 5.90 mmol). IR ν_{max} (film) 1713, 1647, 1444, 1392, 1352, 1211, 1144, 1097, 1018, 958, 854 and 778 cm^{-1}; ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 5.75-5.71 (1H, m, CH=), 4.16-3.99 (6H, m, 3 × CH_2), 2.63 (2H, d, *J* 23.5 Hz, CH_2), 2.25 (3H, dd, *J* 1.3, 3,5 Hz, CH_3), 1.30-1.20 (9H, m = overlapping t, 3 × CH_3); ^{13}C-NMR (100 MHz; $CDCl_3$): δ_C 166.1 (CO), 149.7 (C=), 120.2 (CH=), 62.3 (CH_2), 59.8 (2 × CH_2), 39.3 (CH_2), 20.1 (CH_3), 16.5 (2 × CH_3), 14.4 (CH_3); HRMS (CI+/ISO) calc. for $C_{11}H_{21}O_5P$ $[M]^+$: 264.1127. Found: 264.1126.

The characterisation matches with the data reported in literature:
Mata E.; Thomas E. J. *J. Chem. Soc. Perkin Trans. 1* **1995**, 785.

***(2E,4E,6S,7S,8R,9S,10E)*-Ethyl 7,9-dimethoxy-3,6,8-trimethyl-11-phenyl undeca-2,4,10-trienoate, 42**

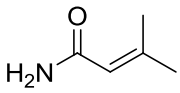


To a solution of diisopropylamine (0.03 mL, 216 µmol) in dry THF (1 mL), under argon at -78 °C, *n*BuLi (0.09 mL, 216 µmol, 2.5 M in hexanes) was added dropwise and the resulting mixture was allowed to stir at -78 °C for 30 minutes, then DMPU (0.16 mL) was added and the reaction mixture was stirred for 5 minutes. A solution of *(2R,3R,4R,5S,E)*-3,5-dimethoxy-2,4-dimethyl-7-phenylhept-6-enal **28** (30.0 mg, 108 µmol) and *(E)*-ethyl 4-(diethoxyphosphoryl)-3-methylbut-2-enoate **211** (57.0 mg, 216 µmol) in dry THF (1 mL) was added dropwise and the resulting mixture was allowed to stir at -78 °C for 12 hours. The reaction was

quenched with NH_4Cl saturated aqueous solution (5 mL) at -78 °C and then it was allowed to warm to room temperature, diluted with ethyl acetate (5 mL), washed with brine (5 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified through flash column chromatography on silica gel (from 0 to 10% ethyl acetate in hexane) to afford the pure product **42** as a pale yellow oil in 86% yield (36.0 mg, 93.0 µmol). R_f 0.31 (hexane:EtOAc, 9:1); $[\alpha]^{19}_D$ − 10.00 (*c* 0.2, $CHCl_3$); ^{1}H-NMR (500 MHz; $CDCl_3$): δ_H 7.32 (2H, d, *J* 8.1 Hz, 2 × CH_{Ar}), 7.24 (2H, dd, *J* 7.1, 8.3 Hz, 2 × CH_{Ar}), 7.16 (1H, m, CH_{Ar}), 6.48 (1H, d, *J* 16.1 Hz, CH=), 6.13-6.02 (2H, m, 2 × CH=), 6.08 (1H, d, *J* 15.9 Hz, CH=), 5.60 (1H, d, *J* 1.0 Hz, CH=), 4.07 (2H, q, *J* 6.8 Hz, CH_2), 4.02-3.96 (1H, m, CHOMe), 3.46 (3H, s, OCH_3), 3.25 (3H, s, OCH_3), 3.12 (1H, dd, *J* 1.8, 9.9 Hz, CHOMe), 2.54-2.46 (1H, m, CHMe), 2.17 (3H, d, *J* 1.0 Hz, CH_3), 1.56-1.45 (1H, m, CHMe), 1.21 (3H, t, *J* 6.8 Hz, CH_3), 1.17 (3H, d, *J* 6.9 Hz, CH_3), 0.88 (3H, d, *J* 6.9 Hz, CH_3); ^{13}C-NMR (125 MHz; $CDCl_3$): δ_C 167.3 (CO), 152.2 (C=), 137.9 (CH=), 136.7(CH_{Ar}), 133.9 (C_{Ar}), 132.7 (CH_{Ar}), 129.2 (CH=), 128.4 (CH=), 127.5 (CH_{Ar}), 125.7 (CH=), 118.8 (CH=), 87.1 (CHOMe), 81.9 (CHOMe), 61.5 (CH_2), 60.0 (OCH_3), 56.6 (OCH_3), 43.6 (CHMe), 40.9 (CHMe), 19.2 (CH_3), 14.4 (CH_3), 13.9 (CH_3), 10.2 (CH_3).

The characterisation matches with the data reported in literature:
Chakraborty T. K.; Jayaprakash S.; Laxman P. *Tetrahedron* **2001**, *57*, 9461.

3-Methylbut-2-enamide, 214

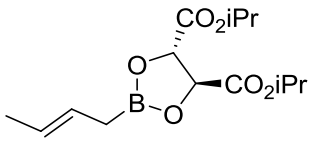


To a solution of ethyl-3,3-dimethyl-acrylate (0.1 mL, 0.70 mmol) in dry methanol (2.25 mL) in a 2-5 mL microwave vial, at 0 °C under argon, magnesium nitride (0.36 g, 3.50 mmol) was added in one portion and the vial was immediately sealed and allowed to warm to room temperature in 1 hour. The initial beige-brown suspension gradually becomes white during this time. When the vial reaches room temperature, it is transferred in an oil bath and heated at 80 °C for 24 hours. The crude product is directly purified thorugh flash column chromatography on silica gel (from 50 to 100% ethyl acetate in hexane) to afford the pure product **214** as a

white solid in 43% yield (26.0 mg, 0.30 mmol). IR ν_{max} (film) 3366, 3169, 2980, 2940, 2918, 2753, 1670, 1607, 1454, 1433, 1404, 1368, 1325, 1310, 1188, 1103, 1078, 980, 957, 939, 854, 797, 714 and 679 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.62 (1H, sept, *J* 1.3 Hz, CH=), 5.60 (1H, bs, NH), 5.39 (1H, bs, NH), 2.14 (3H, d, *J* 1.3 Hz, CH_3 *trans*), 1.84 (3H, d, *J* 1.3 Hz, CH_3 *cis*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1 (CO), 152.8 (C=), 117.6 (CH=), 27.3 (CH_3 *trans*), 19.9 (CH_3 *cis*); HRMS (CI+/ISO) calc. for $C_5H_{10}ON$ $[M+H]^+$: 100.0762. Found: 100.0759; m.p. 97-98 °C.

The characterisation matches with the data reported in literature:
Mathieson J. E.; Crawford J. J.; Schmidtmann M.; Marquez R. *Org. Biomol. Chem.* **2009**, *7*, 2170.

(4S,5S)-Diisopropyl-2-(*(E)*-but-2-enyl)-1,3,2-dioxaborolane-4,5-dicarboxylate, 216

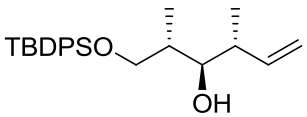


An oven-dried 100-mL, three-necked, round bottomed flask equipped with a magnetic stir bar and a thermometer was charged with potassium *tert*-butoxide (2.85 g, 25.3 mmol) and dry THF (30 mL). The resulting solution was flushed with argon and cooled to -78 °C, then *trans*-2-butene **218** (2.5 mL, 26.8 mmol) (previously condensed from a gas lecture bottle into a rubber-stoppered 10-mL graduated vial immersed in a -78 °C dry-ice/acetone bath) was added *via* canula. *n*BuLi (10.12 mL, 25.3 mmol) was added dropwise in a period of 20 minutes so that the internal temperature never rose above -65 °C. After the completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm until -50 °C. The reaction mixture is kept at -50 °C for exactly 15 minutes and then was immediately recooled to -78 °C. Triisopropylborate (5.8 mL, 25.3 mmol) was added dropwise in a period of 20 minutes avoiding that the internal temperature goes above -65 °C. After the completion of the addition, the reaction mixture was stirred at -78 °C for other 10 minutes and then immediately poured in a 250-mL separatory funnel containing 50 mL of aqueous 1N HCl saturated with NaCl. The aqueous layer was adjusted at pH 1.00 using 1N HCl aqueous solution and then *(S,S)*-DIPT (5.25 mL, 25.3 mmol) in dry diethyl ether (10 mL) was added

to the funnel. The phases were separated and the aqueous phase was extracted again with diethyl ether (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ for 3 hours at room temperature, then filtered and concentrated under vacuum (it is necessary to stir under vacuum till the removal of any residual of THF), to afford the product **216** as a colourless oil in 75% yield (5.60 g, 18.9 mmol). The product was stored at -20 °C as a 1.0 M solution in dry toluene. $[\alpha]^{26}_{D}$ +1.58 (*c* 4.0, $CHCl_3$); ^{1}H-NMR (400 MHz; $CDCl_3$): δ_H 5.65-5.55 (1H, m, =CH), 5.45-5.35 (1H, m, CH=), 4.81-5.02 (2H, m, 2 × CH), 4.90 (2H, s, 2 × CH), 1.85 (2H, bd, *J* 6.4 Hz, CH_2), 1.55 (3H, d, *J* 6.4 Hz, CH_3), 0.93 (12H, d, *J* 6.4 Hz, 4 × CH_3).

The characterisation matches with the data reported in literature:
Roush W. R.; Ando K.; Powers D. B.; Palkowitz A. D.; Halterman R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.

***(2S,3R,4R)*-1-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylhex-5-en-3-ol, 217**

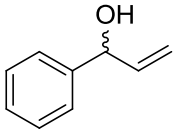


To a slurry of 300 mg of 4 Å powdered molecular sieves (previously dried under vacuum with the heat gun) in 15 mL of dry toluene under argon at room temperature, was added *(4S,5S)*-diisopropyl 2-(*(E)*-but-2-enyl)-1,3,2-dioxaborolane-4,5-dicarboxylate **216** (13.8 mL, 13.8 mmol, 1.0 M solution in dry toluene). After being stirred for 10 minutes at room temperature, the mixture was cooled to -78 °C. A solution of aldehyde *(S)*-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanal **163** (crude, theoretically 3.00 g, 9.20 mmol) in 15 mL of dry toluene was then introduced dropwise via cannula over a 20 minutes period. After the addition was complete, the solution was maintained at -78 °C for 16 hours. Excess ethanolic $NaBH_4$ (200 mg in 3 mL of absolute ethanol) was then added dropwise via pipet and the solution was allowed to warm to 0 °C. Then the reaction mixture was diluted with 25 mL of 1 N NaOH and stirred vigorously for 2 hours. The layers were separated and the aqueous layer was extracted with diethyl ether (5 × 150 mL). The organic layers were combined, dried over K_2CO_3 and concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified by three rounds of silica gel flash column chromatography (from 0 to 10% diethyl ether in hexane) to afford a colourless oil as pure product

217 in 65% yield (2.30 g, 6.00 mmol). R_f 0.32 (hexane:Et_2O, 9:1); $[\alpha]^{28}_D$ +14.6 (*c* 4.0, $CHCl_3$); {Lit.[38] $[\alpha]^{20}_D$ +26.2 (*c* 0.8, $CHCl_3$)}; IR ν_{max} (film) 3050, 2062, 1430, 1210, 1010, 915, 864, 702, 610, 420, 350 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.59-7.56 (4H, m, CH_{Ar}), 7.36-7.24 (6H, m, CH_{Ar}), 5.86 (1H, ddd, *J* 2.1, 8.4, 10.5 Hz, CH=), 5.00-4.94 (2H, m, $=CH_2$), 3.66-3.58 (2H, m, CH_2OSi), 3.39 (1H, dd, *J* 0.6, 3.3 Hz, OH), 3.36-3.32 (1H, m, C*H*OH), 2.33-2.22 (1H, m, CH), 1.77-1.70 (1H, m, CH), 1.02 (3H, d, *J* 7.0 Hz, CH_3), 0.97 (9H, s, 3 × CH_3), 0.72 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 139.9 (CH=), 135.7 (CH_{Ar}), 132.9 (C_{Ar}), 129.9 (CH_{Ar}), 127.8 (CH_{Ar}), 115.2 ($=CH_2$), 79.7 (CHOH), 68.9 (CH_2OSi), 41.2 (CHMe), 37.9 (CHMe), 26.9 (3 × CH_3), 19.1 (C), 17.8 (CH_3), 13.6 (CH_3); HRMS (CI+/ISO) calc. for $C_{24}H_{35}O_2Si$ $[M+H]^+$: 383.2406. Found: 383.2410.

The characterisation matches with the data reported in literature:
Roush W. R.; Palkowitz A. D.; Ando K. *J. Am. Chem. Soc*. **1990**, *112*, 6348.

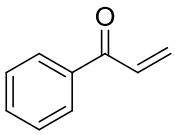
1-Phenylprop-2-en-1-ol



Vinylmagnesium bromide (47.1 mL, 47.1 mmol, 1.0 M in THF) was added dropwise to a solution of benzaldehyde **225** (5.00 g, 47.1 mmol) in 250 mL of dry THF at 0 °C. After 10 minutes the reaction mixture was allowed to warm to room temperature and stirred for 4 hours. Then the reaction was quenched by addition of 200 mL of NH_4Cl aqueous saturated solution and extracted with diethyl ether (3 × 150 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford a yellow oil as crude product in quantitative yield (6.23 g, 47.1 mmol). The crude product was taken directly onto the next step without any further purification. R_f 0.21 (hexane:Et_2O, 8:2); IR ν_{max} (film) 3371, 1667, 1451, 1119, 950, 865, 780, 706, 630, 410, 360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.38-7.36 (5H, m, CH_{Ar}), 6.05 (1H, ddd, *J* 6.1, 10.3, 17.1 Hz, CH=), 5.38-5.33 (1H, m, C*H*OH), 5.22-5.17 (2H, m, $=CH_2$), 4.66 (1H, bs, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 142.7 (CH=), 140.3 (C_{Ar}), 128.7 (CH_{Ar}), 127.8 (CH_{Ar}), 126.4 (CH_{Ar}), 115.2 ($=CH_2$), 75.4 (CHOH); HRMS (EI+) calc. for $C_9H_{10}O$ $[M]^+$: 134.0732. Found: 134.0733.

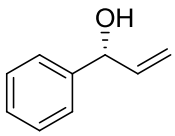
The characterisation matches the data reported in literature:
Tamura S.; Shiomi A.; Kaneko M.; Ye Y.; Yoshida M.; Yoshikawa M.; Kimura T.; Kobayashi M.; Murakami N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2555.

1-Phenylprop-2-en-1-one, 222



The alcohol 1-phenylprop-2-en-1-ol (crude, theoretically 6.23 g, 47.1 mmol) was dissolved in 500 mL of dry dichloromethane under argon at room temperature. TEMPO (147 mg, 0.94 mmol) and iodobenzene diacetate (38.0 g, 118 mmol) were added and the resulting mixture was allowed to stir at room temperature for 12 hours. The reaction mixture was quenched by addition of $Na_2S_2O_3$ aqueous saturated solution (300 mL) and left to stir for 1 hour. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 200 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum to afford an orange-yellow oil as crude product. The crude product was purified by silica gel flash column chromatography (from 0 to 20% Et_2O in hexane) to afford a yellow oil as pure product **222** in 85% yield (5.30 g, 40.1 mmol). R_f 0.37 (hexane:Et_2O, 8:2); IR ν_{max} (film) 2967, 2932, 2874, 1768, 1668, 1618, 1449, 1364, 1252, 1215, 1090, 1015, 916, 775, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.97-7.93 (2H, m, CH_{Ar}), 7.60-7.56 (1H, m, CH_{Ar}), 7.49-7.47 (2H, m, CH_{Ar}), 7.16 (1H, dd, *J* 10.6, 17.1 Hz, CH=), 6.45 (1H, dd, *J* 1.7, 17.1 Hz, =C*H*H), 5.94 (1H, dd, *J* 1.7, 10.6 Hz, =CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 191.2 (CO), 137.5 (C_{Ar}), 133.1 (CH_{Ar}), 132.6 (CH=), 130.3 ($=CH_2$), 128.8 (CH_{Ar}), 128.7 (CH_{Ar}); HRMS (CI+/ISO) calc. for C_9H_9O $[M+H]^+$: 133.0653. Found: 133.0650.

***(R)*-1-Phenylprop-2-en-1-ol, 223**

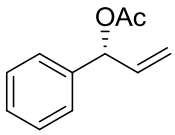


To a solution of *(S)*-2-methyl-CBS-oxazaborilidine (514 mg, 1.52 mmol) in dry THF (4 mL), under argon at room temperature, BH_3·THF (1.86 mL, 1.86 mmol, 1.0 M solution in THF) was added dropwise and the resulting mixture was allowed to stir at room temperature for 30 minutes, then it was cooled to -40 °C and a solution of

1-phenylprop-2-en-1-one **222** (0.20 g, 1.52 mmol) in dry THF (4 mL) was added dropwise. The resulting mixture was allowed to stir at -40 °C for 4 hours and then it was immediately concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified through flash column chromatography on silica gel (from 0 to 30% ethyl acetate in hexane) to afford the pure product **223** as a colourless oil in quantitative yield (204 mg, 1.52 mmol). $[\alpha]^{25}_{D}$ +1.60 (*c* 1.0, $CHCl_3$); {Lit. $[\alpha]^{20}_{D}$ +1.30 (*c* 1.0, $CHCl_3$); >99% *e.e.*}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.42-7.24 (5H, m, CH_{Ar}), 6.04 (1H, ddd, *J* 5.7, 10.4, 17.1 Hz, CH=), 5.34 (1H, ddd, *J* 1.8, 1.8 Hz, 17.1 Hz, CH=), 5.20-5.15 (2H, m, CH and CH=), 2.03 (1H, bs, OH).

The characterisation matches the data reported in literature:
Duveen D. I.; J. Kenyon *J. Chem. Soc.* **1939**, 1697.
Davis F. A.; Stringer O. D.; McCauley Jr. J. P. *Tetrahedron* **1985**, *41*, 4747.
Lin H.; Liu Y.; Wu Z. L. *Chem. Commun*. **2011**, *47*, 2610.
Kanbayashi N.; Onitsuka K. *Angew. Chem. Int. Ed.* **2011**, *50*, 5197.

(R)-1-Phenylallyl acetate, 224

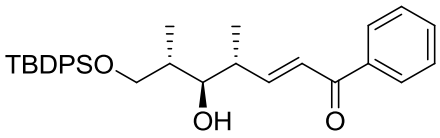


To a solution of *(R)*-1-phenylprop-2-en-1-ol **223** (0.20 g, 1.52 mmol) in pyridine (28 mL), at room temperature under argon, acetic anhydride (7.1 mL, 75.0 mmol) was added and the resulting mixture was allowed to stir at room temperature for 12 hours. The reaction was quenched with NH_4Cl saturated aqueous solution (30 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified through flash column chromatography on silica gel (from 0 to 5% diethyl ether in hexane) to afford the pure product **224** as a colourless oil in 90% yield (0.24 g, 1.37 mmol). R_f 0.47 (hexane:Et_2O, 8:2); $[\alpha]^{26}_{D}$ +25.0 (*c* 1.0, $CHCl_3$); {Lit. $[\alpha]^{25}_{D}$ +30.42 (*c* 0.48, $CHCl_3$); 96% *e.e.*}; IR ν_{max} (film) 3033, 2925, 2363, 1739, 1494, 1456, 1370, 1227, 1201, 1100, 1074, 1019, 983, 931, 925, 846, 759, 749 and 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.38-7.33 (5H, m, CH_{Ar}), 6.27 (1H, dt, *J* 1.4, 5.9 Hz, CH), 6.01 (1H,

ddd, *J* 6.0, 10.5, 17.0 Hz, CH=), 5.29 (1H, dt, *J* 1.4, 17.0 Hz, CH=), 5.25 (1H, dt, *J* 1.4, 10.5 Hz, CH=), 2.12 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 169.9 (CO), 138.9 (C_{Ar}), 136.3 (CH=), 128.6 (CH_{Ar}), 128.2 (CH_{Ar}), 127.1 (CH_{Ar}), 116.9 (CH=), 76.2 (CHOAc), 21.3 (CH_3); HRMS (CI+/ISO) calc. for $C_{11}H_{12}O_2$ $[M+H]^+$: 176.0837. Found: 176.0840.

The characterisation matches the data reported in literature:
Duveen D. I.; J. Kenyon *J. Chem. Soc.* **1939**, 1697.
Chen P.; Xiang P. *Tetrahedron Lett.* **2011**, *52*, 5758.
Kanbayashi N.; Onitsuka K. *Angew. Chem. Int. Ed.* **2011**, *50*, 5197.

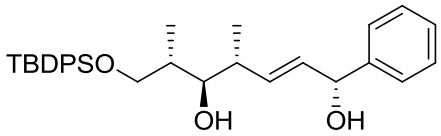
(4R,5R,6S,E)-7-(*tert*-Butyldiphenylsilyloxy)-5-hydroxy-4,6-dimethyl-1-phenylhept-2-en-1-one, 227



A 0.5 – 2 mL microwave vial, fitted with a magnetic follower, was charged with Zhan 1B catalyst **226** (15.0 mg – 5 mol%). The vial was sealed with a rubber septum and purged with argon. Then a solution of the homoallylic alcohol *(2S,3R,4R)*-1-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhex-5-en-3-ol **217** (145 mg, 379 μmol) and of the α,β-enone 1-phenylprop-2-en-1-one **222** (250 mg, 1.90 mmol) in 1.5 mL of freeze-thaw degassed dichloromethane were added and the resulting green solution was stirred at 40 °C for 12 hours. After this period a further portion of Zhan 1B catalyst **226** (15.0 mg – 5 mol%) in 1.5 mL of freeze-thaw degassed dichloromethane was added and the brown solution was stirred for an additional 12 hours. Then the reaction mixture was allowed to cool to room temperature and it was concentrated under vacuum to afford a dark brown oil as crude product. The crude product was purified by silica gel flash column chromatography (from 0 to 20% ethyl acetate in hexane) to afford a pale yellow oil as pure product **227** in 65% yield (120 mg, 0.25 mmol). R_f 0.29 (hexane:EtOAc, 8:2); $[\alpha]^{25}_D$ +188.6 (*c* 0.1, $CHCl_3$); IR ν_{max} (film) 3450, 2974, 2931, 2857, 1670, 1618, 1473, 1428, 1112, 998, 823, 741, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.95-7.91 (2H, m, CH_{Ar}), 7.69-7.65 (4H, m, CH_{Ar}), 7.49-7.36 (9H, m, CH_{Ar}), 7.20

(1H, dd, *J* 8.6, 15.8 Hz, CH=), 6.86 (1H, d, *J* 15.7 Hz, =CHCO), 3.96 (1H, d, *J* 2.7 Hz, OH), 3.74 (1H, dd, *J* 4.0, 10.4 Hz, C*H*HOSi), 3.66 (1H, dd, *J* 8.5, 10.5 Hz, CH*H*OSi), 3.61-3.58 (1H, m, C*H*OH), 2.69-2.61 (1H, m, CHMe), 1.88-1.80 (1H, m, CHMe), 1.23 (3H, d, *J* 6.9 Hz, CH_3), 1.05 (9H, s, 3 × CH_3), 0.80 (3H, d, *J* 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 191.5 (CO), 151.2 (CH=), 138.2 (C_{Ar}), 135.8 (CH_{Ar}), 132.8 (C_{Ar}), 132.7 (CH_{Ar}), 130.1 (CH_{Ar}), 128.8 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 126.9 (=CHCO), 80.2 (CHOH), 69.6 (CH_2OSi), 40.7 (CHMe), 38.0 (CHMe), 26.9 (3 × CH_3), 19.2 (C), 17.4 (CH_3), 13.6 (CH_3); HRMS (EI+) calc. for $C_{31}H_{37}O_2Si$ $[M\text{-}OH]^+$: 469.2563. Found: 469.2557.

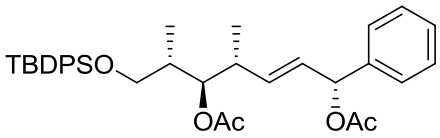
(1R,4R,5R,6S,E)-7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-1-phenylhept-2-ene-1,5-diol, 228



(S)-CBS (348 mg, 1.25 mmol) was dissolved in 15 mL of dry THF under argon at room temperature and BH_3·THF (1.25 mL, 1.25 mmol, 1.0 M solution in THF) was added dropwise. The resulting mixture was vigorously stirred at room temperature for 0.5 hours, then it was cooled at -40 °C and *(4R,5R,6S,E)*-7-(*tert*-butyldiphenylsilyloxy)-5-hydroxy-4,6-dimethyl-1-phenylhept-2-en-1-one **227** (500 mg, 1.03 mmol) in 15 mL of dry THF was added dropwise. The reaction mixture was allowed to stir at -40 °C till complete disappearance of the starting material by TLC (4 – 5 hours), then it was quenched with 10 mL of methanol and concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified by silica gel flash column chromatography (from 10 to 40% ethyl acetate in hexane) to afford a colourless yellow oil as pure product **228** in 93% yield (467 mg, 0.96 mmol). R_f 0.19 (hexane:EtOAc, 8:2); $[\alpha]^{25}_D$ -4.8 (*c* 0.1, $CHCl_3$); IR ν_{max} (film) 2974, 2931, 2859, 1473, 1428, 1383, 1112, 986, 823, 741, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.69-7.65 (4H, m, CH_{Ar}), 7.46-7.43 (2H, m, CH_{Ar}), 7.42-7.37 (6H, m, CH_{Ar}), 7.36-7.32 (2H, m, CH_{Ar}), 7.29-7.25 (1H, m, CH_{Ar}), 5.93 (1H, ddd, *J* 0.9, 8.5, 15.6 Hz, CH=), 5.69 (1H, ddd, *J* 0.7, 7.1, 15.6 Hz, =CH), 5.22 (1H, dd, *J* 3.4, 6.9 Hz, C*H*OH), 3.72-3.64 (3H, m, CH_2OSi and OH), 3.46-3.43 (1H, m, C*H*OH), 2.40-2.36 (1H, m, CHMe), 2.03 (1H, d, *J* 3.6 Hz, OH), 1.81-1.75 (1H, m, CHMe),

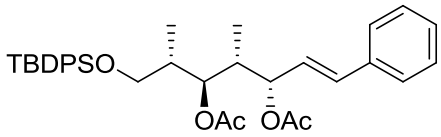
1.13 (3H, d, *J* 7.0 Hz, CH_3), 1.06 (9H, s, 3 × CH_3), 0.74 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 143.5 (C_{Ar}), 135.8 (CH=), 135.6 (=CH), 133.3 (C_{Ar}), 130.0 (CH_{Ar}), 128.6 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 127.6 (CH_{Ar}), 126.2 (CH_{Ar}), 80.2 (CHOH), 75.3 (CHOH), 69.2 (CH_2OSi), 39.8 (CHMe), 37.9 (CHMe), 26.9 (3 × CH_3), 19.2 (C), 18.1 (CH_3), 13.6 (CH_3); HRMS (ESI+) calc. for $C_{31}H_{37}OSi$ [M-H_2O-OH]$^+$: 453.2608. Found: 453.2609.

(1R,4R,5R,6S,E)-7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-1-phenylhept-2-ene-1,5-diyl diacetate, 233



To a solution of *(1R,4R,5R,6S,E)*-7-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyl-1-phenylhept-2-ene-1,5-diol **228** (500 mg, 873 mmol) in 50 mL of dry dichloromethane, acetic anhydride (1.0 mL, 10.5 mmol) and DMAP (11.0 mg, 873 µmol) were added and the reaction mixture was allowed to stir at room temperature for 12 hours. Then the solvent was removed under vacuum to afford a yellow-brown oil as crude product. The crude product was purified by silica gel flash column chromatography (from 0 to 20% ethyl acetate in hexane) to afford a colourless oil as pure product **233** (495 mg, 864 mmol) in 99% yield. R_f 0.46 (hexane:EtOAc, 8:2); $[\alpha]^{25}_D$ -8.4 (*c* 0.1, $CHCl_3$); IR ν_{max} (film) 2974, 2963, 2928, 2857, 2360, 2343, 1739, 1472, 1428, 1370, 1233, 1112, 10018, 964, 824, 756, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.66-7.61 (4H, m, CH_{Ar}), 7.45-7.27 (11H, m, CH_{Ar}), 6.18 (1H, bd, *J* 4.6 Hz, CHOAc), 5.61-5.58 (2H, m, CH=CH), 4.76 (1H, *app* t, *J* 6.2 Hz, CHOAc), 3.61 (1H, dd, *J* 4.5 Hz, 10.0 Hz, C*H*HOSi), 3.43 (1H, dd, *J* 7.5, 9.5 Hz, CH*H*OSi), 2.59-2.46 (1H, m, CHMe), 2.08 (3H, s, $COCH_3$), 1.99-1.89 (1H, m, CHMe), 1.73 (3H, s, $COCH_3$), 1.04 (9H, s, 3 × CH_3), 0.95 (3H, d, *J* 6.8 Hz, CH_3), 0.91 (3H, d, *J* 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 170.7 (CO), 170.1 (CO), 139.8 (C_{Ar}), 135.8 (CH=), 135.4 (CH_{Ar}), 133.8 (C_{Ar}), 129.7 (=CH), 129.4 (CH_{Ar}), 128.7 (CH_{Ar}), 128.1 (CH_{Ar}), 127.7 (CH_{Ar}), 126.9 (CH_{Ar}), 77.9 (CHOAc), 76.2 (CHOAc), 64.9 (CH_2OSi), 39.0 (CHMe), 37.2 (CHMe), 26.9 (3 × CH_3), 21.5 (CO*C*H_3), 20.7 (CO*C*H_3), 19.3 (C), 17.5 (CH_3), 14.5 (CH_3); HRMS (ESI+) calc. for $C_{31}H_{37}OSi$ [M-AcOH-OAc]$^+$: 453.2608. Found: 453.2606.

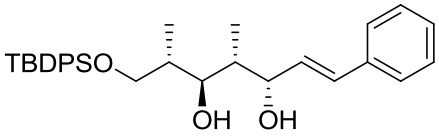
***(3S,4R,5S,6S,E)*-7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-1-phenylhept-1-ene-3,5-diyl diacetate, 19**



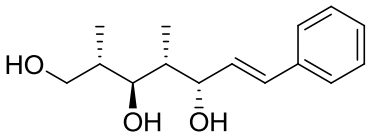
(1R,4R,5R,6S,E)-7-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyl-1-phenylhept-2-ene-1,5-diyl diacetate **233** (420 mg, 733 µmol) and $PdCl_2(CH_3CN)_2$ (10.0 mg, 37.0 mmol, 5 mol%) were dissolved in dry THF (30 mL) and the resulting mixture was allowed to stir at room temperature for 12 hours. Then it was filtered through Celite® and washed with ethyl acetate as eluent (50 mL). The eluate was concentrated under vacuum to afford a yellow-brown oil as crude product. The crude product was purified by silica gel flash column chromatography (from 0 to 20% ethyl acetate in hexane) to afford a yellow oil as pure product **19** (399 mg, 696 µmol) in 95% yield. R_f 0.54 (hexane:EtOAc, 8:2); $[\alpha]^{25}_D$ -7.6 (*c* 0.1, $CHCl_3$); IR ν_{max} (film) 3071, 2961, 2932, 2857, 1739, 1237, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.70-7.65 (4H, m, CH_{Ar}), 7.42-7.37 (6H, m, CH_{Ar}), 7.35-7.21 (5H, m, CH_{Ar}), 6.46 (1H, dd, *J* 1.0, 16.1 Hz, CH=), 6.06 (1H, dd, *J* 5.8, 15.9 Hz, =CH), 5.53-5.49 (1H, m, CHOAc), 4.94 (1H, dd, *J* 3.2, 9.7 Hz, CHOAc), 3.76 (1H, dd, *J* 6.1, 10.2 Hz, C*H*HOSi), 3.47 (1H, dd, *J* 6.8, 10.3 Hz, CH*H*OSi), 2.32-2.25 (1H, m, CHMe), 2.21-2.13 (1H, m, CHMe), 2.08 (3H, s, $COCH_3$), 1.99 (3H, s, $COCH_3$), 1.04 (9H, s, 3 × CH_3), 0.96 (3H, d, *J* 6.9 Hz, CH_3), 0.94 (3H, d, *J* 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 170.8 (CO), 170.6 (CO), 136.6 (C_{Ar}), 135.6 (CH_{Ar}), 133.8 (CH=), 133.7 (C_{Ar}), 131.8 (CH_{Ar}), 129.7 (CH_{Ar}), 128.7 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (=CH), 126.9 (CH_{Ar}), 76.3 (CHOAc), 73.0 (CHOAc), 64.7 (CH_2OSi), 38.9 (CHMe), 36.8 (CHMe), 26.9 (3 × CH_3), 21.3 ($COCH_3$), 20.9 ($COCH_3$), 19.3 (C), 15.3 (CH_3), 11.1 (CH_3); HRMS (ESI+) calc. for $C_{35}H_{44}O_5NaSi$ $[M+Na]^+$: 595.2850. Found: 595.2852.

The characterisation matches with the data reported in literature:
Feutrill J. T.; Lilly M. J.; Rizzacasa M. A. *Org. Lett*. **2000**, *2*, 3365.

***(3S,4R,5S,6S,E)*-7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-1-phenylhept-1-ene-3,5-diol, 20**



***(2S,3S,4R,5S,E)*-2,4-Dimethyl-7-phenylhept-6-ene-1,3,5-triol, 234**

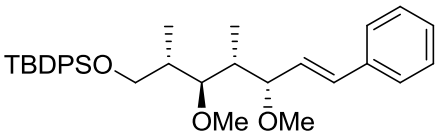


To a stirred solution of *(3S,4R,5S,6S,E)*-7-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyl-1-phenylhept-1-ene-3,5-diyl diacetate **19** (195 mg, 341 µmol) in 10 mL of methanol, 1.7 mL of K_2CO_3 1.0 M in H_2O was added dropwise and the resulting mixture was allowed to stir at room temperature for 12 hours. Then the reaction was quenched by addition of NH_4Cl saturated aqueous solution (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford a pale yellow oil as crude product. The crude product was purified by silica gel flash column chromatography (80:20 hexane/ethyl acetate, then 60/40 hexane/ethyl acetate) to afford a colourless oil as pure product **20** (3.00 mg, 68.0 µmol) in 20% yield and also as a pale yellow oil the triol **234** (51.0 mg, 205 µmol), a secondary product, due to loss of the TBDPS group. The triol was selectively reprotected at the primary alcohol. To a stirred solution of the triol (51.0 mg, 205 µmol) and imidazole (18.0 mg, 267 µmol) in 1 mL of dry dichloromethane, under argon at -5 °C, TBDPSCl (62.0 mg, 226 µmol) in 1 mL of dry dichloromethane was added dropwise and the resulting mixture was allowed to stir at -5 °C till complete disappearance of the starting material by TLC (15 minutes – 40 minutes). The reaction was quenched by addition of H_2O (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and concentrated under vacuum to afford the silyl ether **20** as a colourless oil in 60% yield (100 mg, 205 µmol). The total yield for the silyl ether over the two steps was of 80% (133 mg, 272 µmol). R_f 0.60 (hexane:EtOAc, 7:3); $[\alpha]^{27}_D$ +3.6 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3418, 3072, 2963, 2932, 2855, 1427, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.70-7.67 (4H, m, CH_{Ar}), 7.49-7.40 (8H, m, CH_{Ar}), 7.34-7.19 (3H, m, CH_{Ar}), 6.66 (1H, dd, *J* 1.2, 15.9 Hz, =CH), 6.26 (1H, dd, *J* 5.4, 15.9 Hz, CH=), 4.78 (1H, d, *J* 2.8 Hz, OH),

4.73-4.68 (1H, m, C*H*OH), 4.28 (1H, d, *J* 2.8 Hz, OH), 3.87 (1 H, dd, *J* 3.7, 10.3 Hz, C*H*HOSi), 3.75-3.70 (1H, m, C*H*OH), 3.67 (1H, dd, *J* 7.6, 10.3 Hz, CH*H*OSi), 2.14-2.04 (1H, m, CHMe), 1.99-1.89 (1H, m, CHMe), 1.07 (9H, s, 3 × CH_3), 1.04 (3H, d, *J* 7.2 Hz, CH_3), 0.86 (3H, d, *J* 7.2 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 137.4 (C_{Ar}), 135.8 (CH_{Ar}), 135.7 (C_{Ar}), 132.6 (=CH), 132.5 (CH_{Ar}), 131.2 (CH_{Ar}), 130.2 (CH_{Ar}), 128.6 (CH_{Ar}), 127.4 (CH=), 126.6 (CH_{Ar}), 82.2 (CHOH), 73.0 (CHOH), 69.5 (CH_2OSi), 39.9 (CHMe), 36.9 (CHMe), 26.9 (3 × CH_3), 19.2 (C), 13.9 (CH_3), 11.9 (CH_3); HRMS (ESI+) calc. for $C_{31}H_{37}OSi$ [M-H_2O-OH]$^+$: 453.2608. Found: 453.2609.

The characterisation of the diol **20** matches with the literature data:
Feutrill J. T.; Lilly M. J.; Rizzacasa M. A. *Org. Lett*. **2000**, *2*, 3365.
The characterisation of the triol **234** matches with the literature data:
Dias L. C.; de Oliveira L. G. *Org. Lett*. **2001**, *3*, 3951.

tert-Butyl(_(2S,3S,4R,5S,E)_-3,5-dimethoxy-2,4-dimethyl-7-phenylhept-6-enyloxy)diphenylsilane

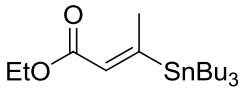


To a suspension of NaH (85.0 mg, 2.13 mmol) in dry THF (2 mL), a solution of *(3S,4R,5S,6S,E)*-7-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyl-1-phenylhept-1-ene-3,5-diol **20** (130 mg, 266 µmol) in dry THF (2 mL) was added and the resulting mixture was allowed to stir at room temperature for 10 minutes. Then iodomethane (0.3 mL, 4.26 mmol) and TBAI (8.00 mg, 21.3 µmol) were added and the reaction mixture was let to stir at 60 °C for 12 hours. The reaction was quenched with a saturated solution of NH_4Cl (5 mL) and the two layers were separated. The organic layer was washed with brine (5 mL) and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The organic layers were mixed, dried over Na_2SO_4, filtered and concentrated under vacuum to afford a pale yellow oil as crude product. The crude product resulted clean without necessity of any further purification. R_f 0.62 (hexane:EtOAc, 8:2); $[\alpha]^{27}_D$ -20.80 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.71-7.66 (4H, m, CH_{Ar}), 7.45-7.23 (11H, m, CH_{Ar}), 6.54 (1H, d, *J* 16.0 Hz, CH=), 6.14 (1H, dd, *J* 7.2, 16.0 Hz, =CH), 4.03 (1H, dd, *J* 2.0,

7.2 Hz, CHOMe), 3.77 (1H, dd, *J* 5.3, 10.0 Hz, CHOMe), 3.58 (1H, dd, *J* 7.9, 9.9 Hz, C*H*HOSi), 3.47 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 3.21 (1H, dd, *J* 2.6, 9.3 Hz, CH*H*OSi), 2.09-1.99 (1H, m, CHMe), 1.81-1.71 (1H, m, CHMe), 1.15 (3H, d, *J* 7.0 Hz, CH_3), 1.05 (9H, s, 3 × CH_3), 0.83 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 137.1 (C_{Ar}), 135.8 (CH_{Ar}), 135.7 (C_{Ar}), 131.8 (CH=), 129.7 (CH_{Ar}), 129.6 (CH_{Ar}), 128.7 (CH_{Ar}), 127.7 (=CH), 127.6 (CH_{Ar}), 126.5 (CH_{Ar}), 85.6 (CHOMe), 81.5 (CHOMe), 64.9 (CH_2OSi), 61.5 (OCH_3), 56.6 (OCH_3), 41.8 (CHMe), 38.1 (CHMe), 27.0 (3 × CH_3), 19.4 (C), 16.0 (CH_3), 10.5 (CH_3).

The characterisation matches with the literature data:
Feutrill J. T.; Lilly M. J.; Rizzacasa M. A. *Org. Lett*. **2000**, *2*, 3365.
Dias L. C.; de Oliveira L. G. *Org. Lett*. **2001**, *3*, 3951.

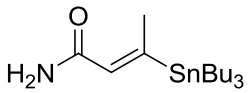
(E)-Ethyl 3-(tributylstannyl)but-2-enoate



To a solution of diisopropylamine (0.3 mL, 1.87 mmol) in 1 mL of dry THF at 0 °C under argon, *n*Buli (1.2 mL, 1.87 mmol, 1.6 M in hexanes) was added dropwise and the resulting mixture was allowed to stir for 10 minutes. Then tributyltin hydride (0.5 mL, 1.78 mmol) was added dropwise and the resulting mixture was cooled at -50 °C. At this point the reaction mixture was added to a suspension of $CuBr{\cdot}Me_2S$ (368 mg, 1.78 mmol) in 2 mL of dry THF at -50 °C and the reaction was allowed to stir for 30 minutes. Then a precooled solution of ethyl-2-butynoate (100 mg, 892 µmol) and dry methanol (0.01 mL, 1.52 mmol) in 3 mL of dry THF was added to the cuprate at -95 °C and the resulting mixture was stirred for 30 minutes, then it was warmed at -78 °C and stirred for an additional 2 hours. The reaction was quenched with 5% aqueous NH_4OH (5 mL), the organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified by silica gel flash column chromatography (hexane) to afford a colourless oil as pure product (343 mg, 0.86 mmol) in 96% yield. R_f 0.08 (hexane); IR ν_{max} (film) 2957, 2925, 2852, 1714, 1599, 1464, 1377, 1366, 1338, 1258, 1164, 1099, 1039, 960,

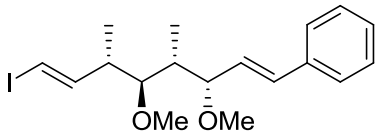
862, 689, 664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.96 (1H, q, *J* 1.8 Hz, CH=), 4.16 (2H, q, *J* 7.1 Hz, CH_2), 2.39 (3H, d, *J* 1.9 Hz, CH_3), 1.54-1.45 (6H, m, 3 × CH_2), 1.34-1.27 (9H, m, 3 × CH_2 and CH_3), 0.97-0.93 (6H, m, 3 × CH_2), 0.93 (9H, t, *J* 7.3 Hz, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.4 (CO), 164.6 (C=), 128.2 (CH=), 59.7 (CH_2OEt), 29.1 (3 × CH_2), 27.5 (3 × CH_2), 22.5 (CH_3), 14.5 (3 × CH_2), 13.8 (3 × CH_3), 9.5 (CH_3); HRMS (ESI) calc. for $C_{18}H_{37}O_2Sn$ $[M+H]^+$: 405.1810. Found: 405.1813.

(E)-3-(Tributylstannyl)but-2-enamide, 44



To a suspension of NH_4Cl (170 mg, 3.18 mmol) in dry toluene (10 mL) under argon at 0 °C was added dropwise a solution of $AlMe_3$ (1.6 mL, 3.18 mmol, 2 M in toluene) and the resulting solution was allowed to warm to room temperature and then recooled to 0 °C. A solution of *(E)*-ethyl 3-(tributylstannyl)but-2-enoate (343 mg, 0.86 mmol) in dry toluene (5 mL) was added and the mixture was heated at 50 °C for 16 hours. The reaction was diluted with ethyl acetate (10 mL) and quenched at 0 °C by addition of 10% HCl in saturated NaCl aqueous solution (20 mL). The organic phase was washed with $NaHCO_3$ saturated aqueous solution (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford a pale yellow thick oil as crude product. The crude product was purified by silica gel flash column chromatography (20% ethyl acetate in hexane) to afford a white solid as pure product **44** (124 mg, 0.38 mmol) in 78% yield. R_f 0.62 (EtOAc); IR v_{max} (film) 3402, 3202, 2955, 2924, 2847, 2361, 1659, 1597, 1458, 1397, 1312, 1072, 1312, 1072, 1003, 872, 733, 687 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 5.92 (1H, q, *J* 1.7 Hz, CH=), 5.64 (1H, bs, N*H*H), 5.39 (1H, bs, NH*H*), 2.35 (3H, d, *J* 1.8 Hz, CH_3), 1.54-1.44 (6H, m, 3 × CH_2), 1.35-1.27 (6H, m, 3 × CH_2), 0.96-0.92 (6H, m, 3 × CH_2), 0.88 (9H, t, *J* 7.3 Hz, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 167.6 (CO), 162.9 (C=), 130.5 (CH=), 29.1 (3 × CH_2), 27.5 (3 × CH_2), 22.2 (3 × CH_2), 13.8 (3 × CH_3), 9.5 (CH_3); HRMS (ESI) calc. for $C_{16}H_{34}ONSn$ $[M+H]^+$: 376.1657. Found: 376.1651; mp: 32-33 °C.

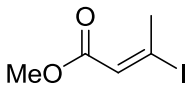
(*(1E,3S,4R,5S,6S,7E)*-8-Iodo-3,5-dimethoxy-4,6-dimethylocta-1,7-dienyl)benzene, 43



To a stirred suspension of anhydrous $CrCl_2$ (226 mg, 1.84 mmol, gently flame dried under vacuum), in dry THF (2 mL) under argon, at room temperature, a solution of the aldehyde *(2R,3R,4R,5S,E)*-3,5-dimethoxy-2,4-dimethyl-7-phenylhept-6-enal **28** (29.8 mg, 108 µmol) and iodoform (255 mg, 0.65 mmol) in 1 mL of dry THF was added *via* cannula. The resulting brown mixture was stirred in the dark at room temperature until completion as indicated by TLC analysis (30 minutes). The reaction mixture was quenched by addition of H_2O (5 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a yellow solid as crude product. The crude product was purified by silica gel flash column chromatography (from 0 to 5% ethyl acetate in hexane) to afford a white solid as pure product **43** (43.0 mg, 107 µmol) in 99% yield. R_f 0.64 (hexane:EtOAc, 7.5:2.5); $[\alpha]^{24}_D$ +1.84 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 2963, 2924, 2361, 2334, 1728, 1651, 1585, 1597, 1497, 1451, 1335, 1188, 1088, 972, 748, 694 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ_H 7.24-7.04 (5H, m, CH_{Ar}), 6.77 (1H, dd, *J* 9.2, 14.5 Hz, CH=), 6.44 (1H, d, *J* 16.0 Hz, =CHPh), 6.04 (1H, dd, *J* 7.0, 16.0 Hz, CH=), 5.74 (1H, d, *J* 14.6 Hz, =CHI), 4.09 (1H, dd, *J* 1.0, 11.5 Hz, CHOMe), 3.31 (3H, s, OCH_3), 3.16 (3H, s, OCH_3), 3.02 (1H, dd, *J* 2.1, 9.9 Hz, CHOMe), 2.23-2.12 (1H, m, CHMe), 1.71-1.60 (1H, m, CHMe), 0.94 (3H, d, *J* 7.0 Hz, CH_3), 0.83 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, C_6D_6): δ_C 147.9 (CH=), 137.2 (C_{Ar}), 132.1 (CH_{Ar}), 129.5 (CH=), 128.6 (CH_{Ar}), 128.4 (=CHPh), 126.7 (CH_{Ar}), 85.9 (CHOMe), 80.9 (=CHI), 75.1 (CHOMe), 61.1 (OCH_3), 55.9 (OCH_3), 43.5 (CHMe), 42.7 (CHMe), 18.2 (CH_3), 9.8 (CH_3).

The characterisation matches with the literature data:
Dias L. C.; de Oliveira L. G. *Org. Lett*. **2001**, *3*, 3951.

***(E)*-Methyl 3-iodobut-2-enoate, 104**

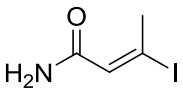


Method A: A 5 mL-flask was loaded with but-2-ynoic acid (0.50 g, 5.95 mmol) and HI 55% (0.977 mL, 7.14 mmol) and it was allowed to stir at 90 °C for 4 hours. The product was filtered, washed with cold water (10 mL) and dried under vacuum overnight to provide *(Z)*-3-iodobut-2-enoic acid as light yellow needles in 78% yield (984 mg, 4.64 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 11.73 (1H, bs, OH), 6.36 (1H, q, *J* 1.3 Hz, CH=), 2.74 (3H, d, *J* 1.3 Hz, CH_3). A 10 mL-sealed tube was loaded with *(Z)*-3-iodobut-2-enoic acid (984 mg, 4.64 mmol) and it was heated at 135 °C for 48 hours to provide a mixture of *(E)*-3-iodobut-2-enoic acid and *(Z)*-3-iodobut-2-enoic acid (*E/Z* ratio: 1.7/1.0) in a total quantitative yield (984 mg, 4.64 mmol). *(E)*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 11.73 (1H, bs, OH), 6.68 (1H, q, *J* 1.3 Hz, CH=), 3.00 (3H, d, *J* 1.3 Hz, CH_3). The mixture of the two isomers was dissolved in dry THF (50 mL), Cs_2CO_3 (1.51 g, 4.64 mmol) was added and the resulting suspension was allowed to stir under argon at room temperature for 5 minutes, then iodomethane (0.6 mL, 9.28 mmol) was added and the reaction mixture was allowed to stir at room temperature for 12 hours. The reaction was quenched with NH_4Cl saturated aqueous solution (30 mL), the organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (100 mL) and concentrated under vacuum to afford a brown-yellow thick oil as crude product. Interestingly, as proved by ^{1}H NMR analysis of the crude, the product was a mixture of *(E)*-methyl 3-iodobut-2-enoate and *(Z)*-methyl 3-iodobut-2-enoate in a very good ratio (*E/Z* ratio: 15/1) in favour of the desired isomer. The crude product was purified by silica gel flash column chromatography (5% ethyl acetate in petroleum ether) to afford a white solid as pure product (210 mg, 929 µmol) in 32% yield.

Method B: To a suspension of CuCN (1.25 g, 14.0 mmol) in anhydrous THF (30 mL), under argon at -78 °C, tributyltin hydride (7.53 mL, 28.0 mmol) was added dropwise, followed by the careful addition of *n*BuLi (11.2 mL, 28.0 mmol) and the resulting mixture was allowed to stir at -78 °C for 1 hour. Then a solution of but-2-ynoic acid (0.51 g, 6.07 mmol) in 12 mL of THF was added and the resulting mixture was allowed to stir at -78 °C for 3 hours. The reaction was quenched with

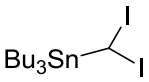
NH_4Cl saturated aqueous solution (40 mL), extracted with diethyl ether (3 × 20 mL), washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow oil as crude product, which was carried directly onto the next step without purification (82% yield, 1.87 g, 4.99 mmol). *(E)*-3-(tributylstannyl)but-2-enoic acid (1.87 g, 4.99 mmol) was dissolved in anhydrous diethyl ether (24 mL) and it was cooled to 0 °C. Iodine (1.50 g, 5.76 mmol) was added in one portion and the resulting mixture was allowed to stir room temperature for 2 hours. The reaction was quenched with KF saturated aqueous solution (25 mL) and $Na_2S_2O_3$ saturated aqueous solution (25 mL), it was extracted with diethyl ether (3 × 20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow oil as crude product which was taken directly onto the next step without any further purification (96%, 1.02 g, 4.80 mmol). *(E)*-3-iodobut-2-enoic acid (1.02 g, 4.80 mmol) was dissolved in 50 mL of anhydrous THF and the solution was cooled to 0 °C. Cs_2CO_3 (1.57 g, 4.80 mmol) was added in one portion and the resulting mixture was allowed to stir under argon at room temperature for 1 hour, then iodomethane (0.60 mL, 9.60 mmol) was added and the reaction mixture was allowed to stir at room temperature for 12 hours. The reaction was quenched with NH_4Cl saturated aqueous solution (50 mL), the organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (150 mL) and concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified by silica gel flash column chromatography (5% ethyl acetate in petroleum ether) to afford a white solid as pure product (549 mg, 2.43 mmol) in 51% yield. (40% yield over the 3 steps). R_f 0.6 (PE:EtOAc, 9.5:0.5); IR ν_{max} (film) 2954, 2922, 2853, 1718, 1617, 1456, 1444, 1331, 1263, 1176, 1073, 907 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 6.64 (1H, q, *J* 1.5 Hz, CH=), 3.70 (3H, s, OCH_3), 2.98 (3H, d, *J* 1.5 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 164.6 (CO), 131.0 (C), 120.7 (CH=), 51.4 (OCH_3), 31.0 (CH_3); HRMS (CI+/ISO) calc. for $C_5H_8O_2I$ $[M+H]^+$: 226.9569. Found: 226.9566.

***(E)*-3-Iodobut-2-enamide, 7**



To a suspension of ammonium chloride (488 mg, 9.10 mmol) in dry toluene (8.5 mL) under argon at 0 °C, $AlMe_3$ (4.55 mL, 0.10 mmol, 2.0 M solution in toluene) was added dropwise and the resulting solution was allowed to warm to room temperature. After this period, the reaction was recooled to 0 °C and (*E*)-methyl 3-iodobut-2-enoate (206 mg, 0.91 mmol) was added. The resulting mixture was stirred at 50 °C for 16 hours. The reaction mixture was diluted with ethyl acetate (10 mL) and quenched at 0 °C by addition of 10% HCl in saturated NaCl (20 mL) and the organic layer was washed with $NaHCO_3$ saturated aqueous solution (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a pale yellow oil as crude product. The crude product was purified by silica gel flash column chromatography (1:1 petroleum ether/ethyl acetate) to afford a white solid as pure product **7** (97.0 mg, 0.46 mmol) in 50% yield. R_f 0.27 (PE:EtOAc, 1:1); IR ν_{max} (film) 3354, 3181, 2359, 2330, 1651, 1597, 1397, 1364, 1302, 1067 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 6.58 (1H, q, *J* 1.5 Hz, CH=), 5.31 (2H, bs, NH_2), 2.99 (3H, d, *J* 1.5 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 165.7 (CO), 132.5 (C), 117.6 (CH=), 30.7 (CH_3); HRMS (CI+/ISO) calc. for C_4H_7ONI $[M+H]^+$: 211.9572. Found: 211.9574; mp: 105-106 °C.

Tributyl(diiodomethyl)stannane

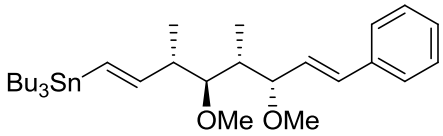


To a solution of $Bu_3SnCHBr_2$ (300 mg, 0.65 mmol) in anhydrous acetone (4 mL), sodium iodide (390 mg, 2.60 mmol) was added and the reaction mixture was allowed to stir at room temperature in absence of light for 24 hours. The reaction mixture was concentrated, then diluted with hexane (5 mL) and filtered. The resultant solution was concentrated under vacuum in absence of light, diluted with chloroform (5 mL), refiltered and reconcentrated under vacuum in absence of light to afford a light yellow oil as product in quantitative yield (361 mg, 0.65 mmol). R_f 0.50 (PE); ^1H NMR (500 MHz, $CDCl_3$): δ_H 4.25 (1H, s, CHI_2), 1.64-1.58 (6H, m, 3 ×

CH_2), 1.33 (6H, sextet, *J* 7.2 Hz, 3 × CH_2), 1.12-1.09 (6H, m, 3 × CH_2), 0.92 (9H, t, *J* 7.2 Hz, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 28.6 (3 × CH_2), 27.5 (CHI_2), 15.7 (3 × CH_2), 13.8 (3 × CH_3), 13.1 (3 × CH_2).

The characterisation matches the data reported in literature:
Hodgson D. M.; Boulton L. T.; Maw G. M.*Tetrahedron* **1995**, *51*, 3713; Hodgson D. M.; Foley A. M.; Boulton L. T.; Lovell P. J.; Maw G. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2911.

Tributyl(*(1E,3S,4S,5R,6S,7E)*-4,6-dimethoxy-3,5-dimethyl-8-phenylocta-1,7-dienyl)stannane, 8

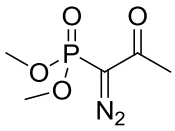


To a stirred bright green suspension of anhydrous $CrCl_2$ (135 mg, 1.10 mmol, gently flame dried under vacuum), in freeze/thaw degassed DMF (1 mL) under argon, at 0 °C, in absence of light, a solution of the aldehyde *(2R,3R,4R,5S,E)*-3,5-dimethoxy-2,4-dimethyl-7-phenylhept-6-enal **28** (21.8 mg, 0.08 mmol) in freeze/thaw degassed DMF (1 mL) containing freshly prepared diiodomethyl tributyltin (120 mg, 0.22 mmol) was added *via* cannula. The resulting mixture was allowed to warm to room temperature in the dark until completion as indicated by TLC analysis (10 hours). The reaction mixture was quenched by addition of H_2O (5 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified by fast vacuum filtration on silica gel (90:10 hexane/ethyl acetate + 1% Et_3N) to afford a pale yellow oil as pure product **8** (22.3 mg, 0.04 mmol) in 50% yield. R_f 0.47 (PE:EtOAc, 40:1, 1% Et_3N); $[\alpha]^{25}_D$ +18.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.40-7.20 (5H, m, CH_{Ar}), 6.57 (1H, d, *J* 16.2 Hz, CH=), 6.17 (1H, dd, *J* 6.9, 16.2 Hz, =CH), 5.96 (1H, dd, *J* 7.2, 19.2 Hz, =CH), 5.86 (1H, d, *J* 19.2 Hz, CH=), 4.11 (1H, dd, *J* 1.1, 7.2 Hz, CHOMe), 3.53 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 3.14 (1H, dd, *J* 2.4, 10.2 Hz, CHOMe), 2.46 (1H, m, CHMe), 1.63 (1H, m, CHMe), 1.51-1.41 (6H, m, 3 × CH_2), 1.33-1.21 (12H, m, 6 × CH_2), 1.15 (3H, d, *J* 7.1 Hz, CH_3), 0.85 (3H, d, *J* 7.1 Hz,

CH_3), 0.84 (9H, t, *J* 7.2 Hz, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 150.5 (CH=), 137.1 (C_{Ar}), 131.8 (=CH), 129.7 (CH_{Ar}), 128.7 (CH=), 127.5 (CH_{Ar}), 127.2 (=CH), 126.5 (CH_{Ar}), 86.4 (CHOMe), 81.4 (CHOMe), 61.3 (OCH_3), 56.7 (OCH_3), 44.9 (CHMe), 42.7 (CHMe), 29.3 (3 × CH_2), 27.4 (3 × CH_2), 18.5 (CH_3), 13.8 (3 × CH_2), 9.6 (3 × CH_3), 9.5 (CH_3).

The characterisation matches with the data reported in literature:
Feutrill J. T.; Lilly M. J.; Rizzacasa M. A. *Org. Lett*. **2000**, *2*, 3365.

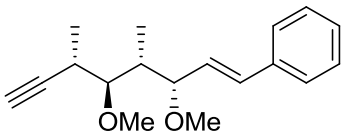
Ohira-Bestmann reagent: Dimethyl 1-diazo-2-oxopropylphosphonate, 237



To a solution of dimethyl (2-oxopropyl)phosphonate (5.00 g, 30.0 mmol) in dry acetonitrile (50 mL) under argon at 0 °C, K_2CO_3 (4.58 g, 33.0 mmol) and tosyl azide (6.53 g, 33.0 mmol) were added sequentially and the resulting mixture was allowed to stir at room temperature for 3 hours. The solvent was removed in vacuo and the crude dissolved in dichloromethane (50 mL) and washed with water (50 mL) and brine (50 mL) sequentially, dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified through flash column chromatography on silica gel (from 0 to 30% ethyl acetate in petroleum ether) to afford the product **237** in quantitative yield (5.80 g, 30.0 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.82 (6H, bd, *J* 12.0 Hz, 2 × CH_3), 2.23 (3H, bs, CH_3).

The characterisation matches with the data reported in literature:
Callant P.; D'Haenens L.; Vandewalle M. *Synth.Commun*. **1984**, *14*, 155.
Ghosh A. K.; Bischoff A.; Cappiello J. *Eur. J. Org. Chem*. **2003**, *5*, 821.

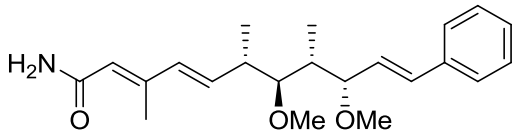
(*(3S,4R,5S,6S,E)*-3,5-Dimethoxy-4,6-dimethyloct-1-ene-7-ynyl)benzene, 79



To a cooled (-78 °C) solution of Ohira-Bestmann's reagent **237** (138 mg, 0.72 mmol) in dry THF (2.5 mL) was added NaOMe (0.17 mL, 25% in methanol, 0.72 mmol) dropwise. After stirring for 20 minutes a solution of aldehyde **28** (50.0 mg, 0.18 mmol) in dry THF (2.5 mL) was added dropwise. The reaction mixture was allowed to slowly warm to room temperature over 30 minutes and quenched with saturated aqueous NH_4Cl (5 mL). The mixture was then diluted with H_2O (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a yellow oil as crude product. An initial round of flash column chromatography (from 0 to 10% ethyl acetate in hexane) followed by a second round (1:1 petroleum ether/dichloromethane) afforded the pure product **79** (49.0 mg, 0.18 mmol, >99%) as a white solid. R_f 0.55 (hexane:EtOAc, 8:2); $[\alpha]^{27}_D$ +24.4 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.42-7.40 (2H, m, CH_{Ar}), 7.34-7.31 (2H, m, CH_{Ar}), 7.26-7.23 (1H, m, CH_{Ar}), 6.59 (1H, d, *J* 16.0 Hz, CH=), 6.20 (1H, dd, *J* 7.2, 16.0 Hz, =CH), 4.15 (1H, ddd, *J* 1.1, 2.2, 7.2 Hz, CHOMe), 3.57 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 3.15 (1H, dd, *J* 2.5, 9.9 Hz, CHOMe), 2.77 (1H, m, CHMe), 2.06 (1H, d, *J* 2.5 Hz, CH_{alkyne}), 1.99-1.93 (1H, m, CHMe), 1.35 (3H, d, *J* 7.1 Hz, CH_3), 0.93 (3H, d, *J* 7.1 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 136.9 (C_{Ar}), 132.2 (CH=), 129.4 (=CH), 128.7 (CH_{Ar}), 127.7 (CH_{Ar}), 126.5 (CH_{Ar}), 85.1 (C_{alkyne}), 84.9 (CHOMe), 81.1 (CHOMe), 70.1 (CH_{alkyne}), 61.5 (OCH_3), 56.6 (OCH_3), 42.9 (CHMe), 29.6 (CHMe), 18.4 (CH_3), 10.1 (CH_3).

The characterisation matches with the data reported in literature:
Candy M.; Audran G.; Bienayme H.; Bressy C.; Pons J.-M. *J. Org. Chem.* **2010**, *75*, 1354.

(+)-crocacin C: *(2E,4E,6S,7S,8R,9S,10E)*-7,9-Dimethoxy-3,6,8-trimethyl-11-phenylundeca-2,4,10-trienamide, 3



Method A: To a solution of (*(1E,3S,4R,5S,6S,7E)*-8-iodo-3,5-dimethoxy-4,6-dimethylocta-1,7-dienyl)benzene **43** (43.0 mg, 107 µmol) and *(E)*-3-(tributylstannyl)but-2-enamide **44** (45.0 mg, 120 µmol) in anhydrous THF (7 mL), under argon at room temperature, CuI (3.40 mg, 0.65 mmol), $AsPh_3$ (4.50 mg, 15.0 µmol) and $Pd_2(dba)_3$ (6.00 mg, 6.00 µmol) were added and the reaction mixture was allowed to stir at 60 °C for 6 hours. Then the reaction was quenched with H_2O (5 mL), diluted with diethyl ether (5 mL) and the two phases were separated. The organic layer was washed with brine (5 mL) and dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow oil as crude product. The sample was purified on a Varian HPLC from Agilent Technologies (Santa Clara, CA, USA) equipped with SD-1 pumps, a model 325 UV−vis detector, a model 410 autosampler, and a model 701 fraction collector. Mobile phase A was water with 0.1% ammonium hydroxide and mobile phase B was acetonitrile. The flow rate was 60 mL/min. The method started at 40% B for 1 min, then raised to 80% B over the next 9 min, was held at 80% B for another minute, then raised to 95% B in 0.2 min, held at 95% for 1.5 min, then lowered back to 40% B in 0.2 min, and held at 40% B for an additional 1.5 min. The column was a 30 mm × 100 mm, 10 µm Gemini-NX from Phenomenex (Torrance, CA, USA). The UV collection was done using a wavelength of 254 nm. (+)-Crocacin C **3** eluted at 6.2 min. (+)-Crocacin C and the two isomeric *(Z)* analogues **235** and **236** were isolated in a 1.54/1.00/1.27 ratio, in a total yield of 11% (11.8 µmol, 4.20 mg total weight).

Method B: In a flame-dried 2 – 5 mL MW vial, under argon, at room temperature, the stannane **8** (22.3 mg, 0.04 mmol) and the vinyl iodide **7** (13.0 mg, 43.6 µmol) were dissolved in 2 mL of freeze-thaw degassed THF and the catalyst $PdCl_2(PPh_3)_2$ (1.40 mg, 2.00 µmol, 5 mol%). The vial was submitted to MW irradiation (15 minutes, 100 °C), then the reaction was filtered and concentrated under vacuum to afford a brown oil as crude product. The crude product was

purified by silica gel column chromatography (1:1 petroleum ether/ethyl acetate) to afford (+)-crocacin C **3** as a white solid (7.00 mg, 19.6 µmol) in 50% yield.

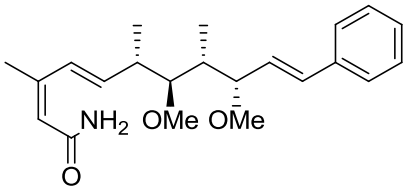
Method C: In a flame-dried 5 mL microwave vial under an inert atmosphere, a solution of alkyne **79** (50.0 mg, 184 µmol) in anhydrous THF (2.5 mL) was degassed by three freeze−pump−thaw cycles. $PdCl_2(Ph_3P)_2$ (7.00 mg, 10.3 µmol) was then incorporated, and the solution was cooled to 0 °C before tributyltin hydride (56.0 µL, 203 µmol) was added dropwise. The resultant brown solution was stirred at 0 °C until the starting material was consumed as indicated by TLC (25 minutes). Vinyl iodide **7** (42.0 mg, 197 µmol) was added, and the solution was heated to 100 °C in a microwave reactor for 15 minutes. The reaction mixture was filtered through a small pad of silica using ethyl acetate as the eluent (10 mL), and the filtrate was concentrated in vacuo to give crude yellow oil. Purification of the crude residue by flash column chromatography on silica gel (elution gradient 1:1 PE/EtOAc to 2:3 PE/EtOAc) afforded (+)-crocacin C **3** as a white solid in 70% yield (46.0 mg, 129 µmol). R_f 0.25 (PE:EtOAc, 1:1); $[\alpha]^{26}_D$ +54.0 (*c* 0.1, MeOH); {Lit.[2] $[\alpha]^{22}_D$ +52.2 (*c* 0.3, MeOH); Lit.[4] $[\alpha]^{19}_D$ +61.3 (*c* 0.3, MeOH); Lit.[6] $[\alpha]^{20}_D$ +53.8 (*c* 0.2, MeOH); Lit.[8] $[\alpha]^{20}_D$ +59.8 (*c* 0.31, MeOH); Lit.[10] $[\alpha]^{23}_D$ +46.3 (*c* 0.3, MeOH); Lit.[11] $[\alpha]^{25}_D$ +56.2 (*c* 0.5, MeOH); Lit.[12] $[\alpha]^{23.5}_D$ +56.8 (*c* 0.3, MeOH)}; IR ν_{max} (film) 3479, 3395, 3343, 3184, 2963, 2926, 1655, 1601, 1449, 1368, 1261, 1088, 972 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6): δ_H 7.47 (2H, d, *J* 8.0 Hz, CH_{Ar}), 7.32 (2H, dd, *J* 7.5, 8.0 Hz, CH_{Ar}), 7.23 (1H, dd, *J* 7.5, 7.5 Hz, CH_{Ar}), 6.70 (1H, bs, N*H*H), 6.59 (1H, d, *J* 16.0 Hz, CH=), 6.26 (1H, dd, *J* 7.3, 16.1 Hz, =CH), 6.13 (1H, bs, NH*H*), 6.12-6.04 (2H, m, CH=CH), 5.80 (1H, s, CH=), 4.08 (1H, ddd, *J* 1.0, 2.4, 7.2 Hz, CHOMe), 3.52 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 3.16 (1H, dd, *J* 2.0, 9.6 Hz, CHOMe), 2.58 (1H, ddq, *J* 2.2, 6.8, 8.1 Hz, CHMe), 2.22 (3H, d, *J* 1.1 Hz, CH_3), 1.56 (1H, ddq, *J* 2.5, 7.0, 9.5 Hz, CHMe), 1.17 (3H, d, *J* 6.9 Hz, CH_3), 0.85 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, acetone-d_6): δ_C 169.0 (CO), 148.1 (C=), 137.9 (C_{Ar}), 137.0 (CH=), 135.1 (CH=), 132.6 (CH=), 130.5 (CH=), 129.4 (CH_{Ar}), 128.3 (CH_{Ar}), 127.3 (CH_{Ar}), 122.1 (CH=), 87.1 (CHOMe), 81.8 (CHOMe), 61.5 (OCH_3), 56.5 (OCH_3), 43.5 (CHMe), 40.8 (CHMe), 19.3 (CH_3), 13.5 (CH_3), 10.1 (CH_3); HRMS (FAB+) calc. for $C_{22}H_{31}O_3NNa$ $[M+Na]^+$: 380.2202. Found: 380.2207; mp: 95-100 °C.

The characterisation matches with the data reported in literature:
Feutrill J. T.; Lilly M. J.; Rizzacasa M. A. *Org. Lett*. **2000**, *2*, 3365.

Dias L. C.; de Oliveira L. G. *Org. Lett*. **2001**, *3*, 3951.

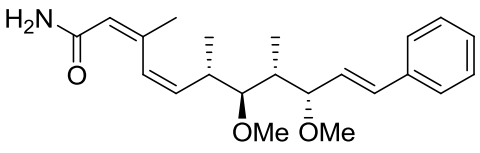
Candy M.; Audran G.; Bienayme H.; Bressy C.; Pons J.-M. *J. Org. Chem.* **2010**, *75*, 1354.

(2Z,4E,6S,7S,8R,9S,10E)-7,9-Dimethoxy-3,6,8-trimethyl-11-phenylundeca-2,4,10-trienamide, 235



$[\alpha]^{26}_{D}$ +32.0 (*c* 0.1, MeOH); IR ν_{max} (film) 3460, 3391, 3339, 3086, 2972, 2928, 1659, 1595, 1456, 1321, 1261, 1085, 1024, 750, 694, 677 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): δ_H 7.82 (1H, d, *J* 16.3 Hz, CH=), 7.51-7.47 (2H, m, CH_{Ar}), 7.38-7.29 (2H, m, CH_{Ar}), 7.25-7.21 (1H, m, CH_{Ar}), 6.71 (1H, bs, N*H*H), 6.59 (1H, d, *J* 16.0 Hz, CH=), 6.26 (1H, dd, *J* 7.1, 15.9 Hz, CH=), 6.07 (1H, bs, NH*H*), 6.05 (1H, dd, *J* 9.0, 16.2 Hz, CH=), 5.69 (1H, bs, CH=), 4.09-4.07 (1H, m, CHOMe), 3.54 (3H, s, OCH_3), 3.30 (3H, s, OCH_3), 3.18 (1H, dd, *J* 2.1, 9.6 Hz, CHOMe), 2.65-2.55 (1H, m, CHMe), 1.90 (3H, d, *J* 1.0 Hz, CH_3), 1.58-1.52 (1H, m, CHMe), 1.18 (3H, d, *J* 7.2 Hz, CH_3), 0.86 (3H, d, *J* 7.2 Hz, CH_3); ^{13}C NMR (125 MHz, acetone-d_6): δ_C 169.0 (CO), 146.9 (C=), 137.9 (CH=), 137.8 (C_{Ar}), 132.7 (CH=), 130.5 (CH=), 129.4 (CH_{Ar}), 129.3 (CH=), 128.3 (CH_{Ar}), 127.3 (CH_{Ar}), 120.1 (CH=), 87.2 (CHOMe), 81.9 (CHOMe), 61.5 (OCH_3), 56.5 (OCH_3), 43.5 (CHMe), 41.2 (CHMe), 21.0 (CH_3), 19.3 (CH_3), 10.1 (CH_3).

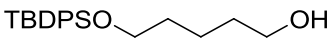
(2Z,4Z,6S,7S,8R,9S,10E)-7,9-Dimethoxy-3,6,8-trimethyl-11-phenylundeca-2,4,10-trienamide, 236



$[\alpha]^{26}_{D}$ -44.0 (*c* 0.1, MeOH); IR ν_{max} (film) 3460, 3391, 3339, 3086, 2972, 2928, 1659, 1595, 1456, 1368, 1296, 1088, 1017, 747, 669 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): δ_H 7.50-7.47 (2H, m, CH_{Ar}), 7.35-7.31 (2H, m, CH_{Ar}), 7.26-7.23 (1H, m, CH_{Ar}), 6.83 (1H, bs, N*H*H), 6.60 (1H, d, *J* 16.0 Hz, CH=), 6.26 (1H, dd, *J* 7.4, 16.1 Hz, CH=), 6.14 (1H, bs, NH*H*), 5.89 (1H, d, *J* 12.1 Hz, CH=), 5.84 (1H, s,

CH=), 5.60 (1H, dd, *J* 11.3, 12.2 Hz, CH=), 4.05-4.02 (1H, m, CHOMe), 3.52 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 3.10 (1H, dd, *J* 2.2, 9.6 Hz, CHOMe), 3.07-2.98 (1H, m, CHMe), 2.20 (3H, d, *J* 1.1 Hz, CH_3), 1.58-1.50 (1H, m, CHMe), 1.18 (3H, d, *J* 7.3 Hz, CH_3), 0.79 (3H, d, *J* 7.3 Hz, CH_3); ^{13}C NMR (125 MHz, acetone-d_6): δ_C 168.7 (CO), 148.9 (C=), 137.8 (CH=), 134.9 (C_{Ar}), 133.0 (CH=), 132.8 (CH=), 130.6 (CH_{Ar}), 129.4 (CH=), 128.4 (CH_{Ar}), 127.3 (CH_{Ar}), 121.3 (CH=), 86.9 (CHOMe), 81.9 (CHOMe), 61.6 (OCH_3), 56.4 (OCH_3), 43.8 (CHMe), 36.0 (CHMe), 19.7 (CH_3), 19.5 (CH_3), 10.0 (CH_3).

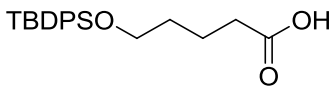
5-(*tert*-Butyldiphenylsilyloxy)pentan-1-ol, 248



To a solution of imidazole (477 mg, 7.00 mmol) in dichloromethane (50 mL) at 0°C under argon, was added pentane-1,5-diol **245** (1.05 mL, 10.0 mmol) and the reaction mixture was stirred for 5 minutes. Then TBDPSCl (0.87 mL, 3.33 mmol) was added dropwise and the resulting mixture was allowed to warm to room temperature and to stir for 12 hours. The reaction was quenched with 50 mL of NH_4Cl saturated aqueous solution and extracted with dichloromethane (3 × 50 mL). The organic layers were collected, washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum to afford the crude product as a yellow oil. The crude product was purified by flash column chromatography on silica gel (EtOAc:PE, from 0:1 to 2:8) to afford the clean product **246** as a colourless oil in 88% yield (1.00 g, 2.92 mmol). R_f 0.21 (PE:EtOAc, 9:1); IR ν_{max} (film) 3335, 2932, 2896, 2858, 2358, 1473, 1427, 1111, 998, 823, 739, 700, 687 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.68-7.65 (4H, m, CH_{Ar}), 7.44-7.36 (6H, m, CH_{Ar}), 3.67 (2H, t, *J* 6.5 Hz, CH_2OSi), 3.62 (2H, dd, *J* 6.5, 11.1 Hz, CH_2OH), 1.62-1.52 (4H, m, 2 × CH_2), 1.46-1.39 (2H, m, CH_2), 1.22 (1H, bt, *J* 4.8 Hz, OH), 1.05 (9H, s, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 135.7 (CH_{Ar}), 134.2 (C_{Ar}), 129.7 (CH_{Ar}), 127.7 (CH_{Ar}), 63.9 (CH_2OSi), 63.1 (CH_2OH), 32.6 (CH_2), 32.4 (CH_2), 27.0 (3 × CH_3), 22.1 (CH_2), 19.4 (C); HRMS (CI+/ISO) calc. for $C_{21}H_{31}O_2Si$ $[M+H]^+$: 343.2093. Found: 343.2097.

The characterisation matches with the literature data:
Young I. S.; Kerr M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465.

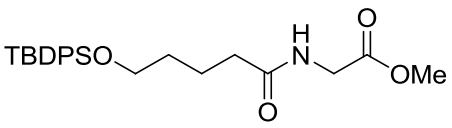
5-(*tert*-Butyldiphenylsilyloxy)pentanoic acid, 249



To a solution of 5-(*tert*-butyldiphenylsilyloxy)pentan-1-ol **246** (1.00 g, 2.92 mmol) in dichloromethane (3 mL) and H_2O (3 mL), cooled at 0 °C, TEMPO (90.0 mg, 0.58 mmol) and BAIB (2.07 g, 6.42 mmol) were added and the reaction mixture was allowed to warm to room temperature and to stir for 12 hours. Then the reaction was quenched with 10 mL of $Na_2S_2O_3$ saturated aqueous solution and extracted with dichloromethane (3 × 10 mL) and ethyl acetate (3 × 10 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated under vacuum to afford the crude product as an orange oil. The crude product was purified by flash column chromatography (EtOAc:PE, from 0:1 to 2:8) to afford the clean product **247** as a colourless oil in 76% yield (0.79 g, 2.22 mmol). R_f 0.25 (PE:EtOAc, 8:2); IR ν_{max} (film) 3070, 2953, 2931, 2891, 2858, 2343, 1706, 1473, 1427, 1390, 1362, 1293, 1245, 1105, 1091, 823, 797, 740, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 11.46 (1H, bs, COOH), 7.73-7.68 (4H, m, CH_{Ar}), 7.47-7.39 (6H, m, CH_{Ar}), 3.72 (2H, t, *J* 6.2 Hz, CH_2OSi), 2.40 (2H, t, *J* 8.2 Hz, CH_2COO), 1.79 (2H, qn, *J* 7.6 Hz, CH_2), 1.68-1.62 (2H, m, CH_2), 1.09 (9H, s, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 180.3 (COOH), 135.7 (CH_{Ar}), 134.0 (C_{Ar}), 129.7 (CH_{Ar}), 127.8 (CH_{Ar}), 63.4 (CH_2OSi), 33.9 (CH_2COOH), 31.9 (CH_2), 26.9 (3 × CH_3), 21.3 (CH_2), 19.3 (C); HRMS (CI+/ISO) calc. for $C_{21}H_{29}O_3Si$ $[M+H]^+$: 357.1886. Found: 357.1883.

The characterisation matches with the literature data:
Jacobi P. A.; Li Y. *Org. Lett.* **2003**, *5*, 701.

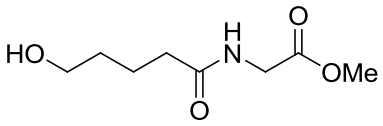
Methyl 2-(5-(*tert*-butyldiphenylsilyloxy)pentanamido)acetate, 250



To a solution of 5-(*tert*-butyldiphenylsilyloxy)pentanoic acid **247** (0.79 g, 2.22 mmol), glycine methylester **124** (335 mg, 2.66 mmol) and HBTU (1.01 g, 2.66 mmol) in dichloromethane (20 mL) under argon, DIPEA (1.0 mL, 5.55 mmol) was

added dropwise and the reaction mixture was allowed to stir for 12 hours. Then the reaction was quenched with 20 mL of NH_4Cl saturated aqueous solution and extracted with diethyl ether (3 × 20 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated under vacuum to afford the crude product as a yellow oil. The crude product was purified by flash column chromatography on silica gel (EtOAc:PE, from 0:1 to 2:8) to afford the clean product **248** as a pale yellow oil in 89% yield (0.84 g, 1.97 mmol). R_f 0.40 (PE:EtOAc, 1:1); IR ν_{max} (film) 3312, 3072, 2953, 2931, 2856, 1756, 1652, 1531, 1473, 1427, 1389, 1362, 1204, 1177, 1105 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.71-7.62 (4H, m, CH_{Ar}), 7.45-7.35 (6H, m, CH_{Ar}), 6.00 (1H, bs, NH), 4.02 (2H, d, *J* 5.7 Hz, CH_2N), 3.75 (3H, s, OCH_3), 3.68 (2H, t, *J* 6.7 Hz, CH_2OSi), 2.23 (2H, t, *J* 8.1 Hz, CH_2CO), 1.75 (2H, qn, *J* 7.7 Hz, CH_2), 1.65-1.57 (2H, m, CH_2), 1.05 (9H, s, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 173.2 (CONH), 170.6 (COO), 135.7 (CH_{Ar}), 134.0 (C_{Ar}), 129.7 (CH_{Ar}), 127.7 (CH_{Ar}), 63.6 (CH_2OSi), 52.4 (OCH_3), 41.3 (CH_2N), 36.1 (CH_2CO), 31.9 (CH_2), 26.9 (3 × CH_3), 22.1 (CH_2), 19.3 (C); HRMS (CI+/ISO) calc. for $C_{24}H_{34}O_4NSi$ $[M+H]^+$: 428.2257. Found: 428.2258.

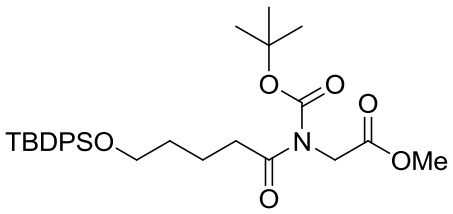
Methyl 2-(5-hydroxypentanamido)acetate, 251



To a solution of methyl 2-(5-(*tert*-butyldiphenylsilyloxy)pentanamido)acetate **248** (0.83 g, 1.94 mmol) in anhydrous THF (20 mL) under argon at 0 °C, TBAF (4.90 mL, 4.90 mmol, 1.0 M solution in THF) was added dropwise and the reaction mixture was allowed to stir for 12 hours. Then the reaction was quenched with 20 mL of distilled water and extracted with diethyl ether (3 × 20 mL), ethyl acetate (3 × 20 mL) and dichloromethane (3 × 20 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated under vacuum to afford the crude product as a yellow oil. The crude product was purified by flash column chromatography on silica gel (EtOAc:methanol:Et_3N, 1:1:1) to afford the clean product **249** as a light yellow thick oil in 11% yield (0.04 g, 212 µmol). IR ν_{max} (film) 3312, 2955, 2920, 2851, 1740, 1651, 1549, 1462, 1362, 1260, 1207, 1182, 1121, 1078, 978, 820 and 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.05 (1H, bt, *J* 5.6

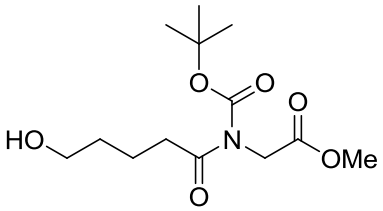
Hz, NH), 6.10 (1H, bs, OH), 3.97 (2H, d, *J* 5.6 Hz, CH_2N), 3.59 (3H, s, OCH_3), 3.55 (2H, t, *J* 6.4 Hz, CH_2O), 2.26 (2H, t, *J* 7.6 Hz, CH_2CO), 1.82-1.54 (4H, m, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.8 (CONH), 169.9 (COO), 62.3 (CH_2OH), 52.7 (OCH_3), 41.0 (CH_2N), 36.1 (CH_2CO), 31.5 (CH_2), 22.0 (CH_2); HRMS (CI+/ISO) calc. for $C_8H_{16}O_4N$ $[M+H]^+$: 190.1079. Found: 190.1079.

Methyl 2-(*N*-(*tert*-butoxycarbonyl)-5-(*tert*-butyldiphenylsilyloxy) pentanamido)acetate, 253



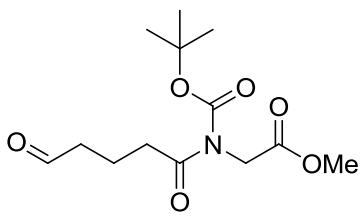
To a solution of methyl 2-(5-(*tert*-butyldiphenylsilyloxy)pentanamido)acetate **248** (3.60 g, 8.43 mmol) in THF (37 mL), under argon and cooled at 0 °C , DIPEA (6.00 mL, 33.7 mmol), DMAP (21.0 mg, 33.7 mmol) and Boc_2O (7.40 g, 33.7 mmol) were added and the reaction mixture was allowed to warm to room temperature and to stir for 4 hours. Then the reaction was washed with 20 mL of brine and extracted with diethyl ether (3 × 20 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated under vacuum to afford the crude product as a yellow oil. The crude product was purified by flash column chromatography on silica gel (from 0 to 10% ethyl acetate in hexane) to afford the clean product **251** as a colourless oil in 85% yield (3.80 g, 7.20 mmol). R_f 0.24 (hexane:EtOAc, 9:1); IR ν_{max} (film) 2932, 2858, 2360, 1757, 1742, 1700, 1690, 1473, 1428, 1369, 1336, 1209, 1146, 1106, 1092, 1036, 987, 856, 823, 778, 740, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.71-7.67 (4H, m, CH_{Ar}), 7.44-7.37 (6H, m, CH_{Ar}), 4.47 (2H, s, CH_2N), 3.74 (3H, s, OCH_3), 3.71 (2H, t, *J* 6.3 Hz, CH_2OSi), 2.96 (2H, t, *J* 7.4 Hz, CH_2CO), 1.82-1.74 (2H, m, CH_2), 1.68-1.61 (2H, m, CH_2), 1.51 (9H, s, 3 × CH_3), 1.06 (9H, s, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 175.6 (CON), 169.6 (COOMe), 152.2 (COO*t*Bu), 135.6 (CH_{Ar}), 134.1 (C_{Ar}), 129.6 (CH_{Ar}), 127.7 (CH_{Ar}), 83.7 (C), 63.7 (CH_2OSi), 52.2 (OCH_3), 45.2 (CH_2N), 37.8 (CH_2CO), 32.1 (CH_2), 27.9 (3 × CH_3), 26.9 (3 × CH_3), 21.5 (CH_2), 19.3 (C); HRMS (CI+/ISO) calc. for $C_{29}H_{42}O_6NSi$ $[M+H]^+$: 528.2781. Found: 528.2772.

Methyl 2-(*N*-(*tert*-butoxycarbonyl)-5-hydroxypentanamido)acetate, 254



To a solution of methyl 2-(*N*-(*tert*-butoxycarbonyl)-5-(*tert*-butyldiphenylsilyloxy) pentanamido) acetate **251** (3.80 g, 7.20 mmol) in THF (50 mL), under argon and at 0 °C , was added dropwise a solution of HF-Py/Py/THF (10 mL: 40 mL: 50 mL) and the reaction mixture was allowed to warm to room temperature and to stir for 15 hours. Then the reaction was quenched at 0 °C with 1.60 g of $NaHCO_3$ in powder. The resulting mixture was allowed to stir for 10 minutes, then it was filtered and concentrated under vacuum to afford the crude product as a colourless oil. The crude product was purified by flash column chromatography on silica gel (from 50 to 100% ethyl acetate in hexane) to afford the clean product **252** as a colourless oil in 60% yield (1.24 g, 4.30 mmol). R_f 0.10 (hexane:EtOAc, 7:3); IR ν_{max} (film) 3445, 2953, 2364, 1743, 1684, 1439, 1371, 1339, 1214, 1149, 1079, 1140, 985, 855, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 4.45 (2H, s, CH_2N), 3.73 (3H, s, OCH_3), 3.68-3.63 (2H, bm, CH_2O), 2.97 (2H, t, *J* 7.5 Hz, CH_2CO), 1.79-1.72 (2H, m, CH_2), 1.69-1.66 (1H, bm, OH), 1.65-1.59 (2H, m, CH_2), 1.49 (9H, s, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 175.8 (CO), 169.7 (CO), 152.3 (CO), 84.0 (C), 62.4 (CH_2O), 52.3 (OCH_3), 45.3 (CH_2N), 37.6 (CH_2CO), 32.1 (CH_2), 28.0 (3 × CH_3), 21.1 (CH_2); HRMS (CI+/ISO) calc. for $C_{13}H_{24}O_6N$ $[M+H]^+$: 290.1604. Found: 290.1596.

Methyl 2-(*N*-(*tert*-butoxycarbonyl)-5-oxopentanamido)acetate, 131

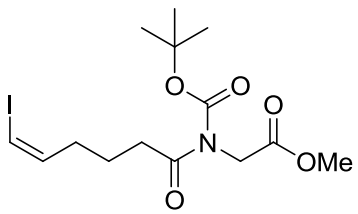


To a solution of methyl 2-(*N*-(*tert*-butoxycarbonyl)-5-hydroxypentanamido)acetate **252** (100 mg, 346 µmol) in dichloromethane (1 mL), under argon and cooled at 0

°C, TEMPO (11.0 mg, 0.07 mmol) and BAIB (245 mg, 0.76 mmol) were added and the reaction mixture was allowed to warm to room temperature and to stir for 1 hour. Then the reaction was quenched with 1 mL of $Na_2S_2O_3$ saturated aqueous solution and extracted with diethyl ether (3 × 1 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated under vacuum to afford the crude product as an orange oil. The crude product was purified by flash column chromatography on silica gel (from 0 to 40% diethyl ether in hexane) to afford the clean product **131** as a colourless oil in 71% yield (70.0 mg, 244 µmol). R_f 0.37 (hexane: EtOAc, 7:3); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 9.76 (1H, bt, *J* 1.4 Hz, CHO), 4.43 (2H, s, CH_2N), 3.72 (3H, s, OCH_3), 2.99 (2H, t, *J* 7.1 Hz, CH_2CO), 2.52 (2H, dt, *J* 1.4, 7.2 Hz, CH_2CHO), 1.98 (2H, qn, *J* 7.2 Hz, CH_2), 1.48 (9H, s, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 202.1 (CHO), 175.0 (CON), 169.6 (COOMe), 152.2 (COO*t*Bu), 84.1 (C), 52.3 (OCH_3), 45.3 (CH_2N), 43.2 (CH_2CHO), 37.1 (CH_2), 28.0 (3 × CH_3), 17.6 (CH_2).

The characterisation matches the data reported in literature:
Dias L. C.; de Oliveira L. G. *Org. Lett*. **2001**, *3*, 3951.

***(Z)*-Methyl 2-(*N*-(*tert*-butoxycarbonyl)-6-iodohex-5-enamido)acetate, 132**

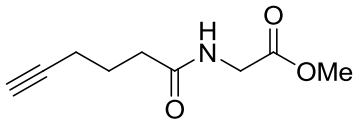


To a suspension of $Ph_3PCH_2I_2$ (186 mg, 0.35 mmol) in THF (3 mL), under argon, potassium *tert*-butoxide (31.0 mg, 0.25 mmol) was added and the reaction mixture was allowed to stir for 10 minutes at room temperature and then it was cooled to -78 °C. The aldehyde methyl 2-(*N*-(*tert*-butoxycarbonyl)-5-oxopentanamido)acetate **131** (20.0 mg, 0.07 mmol) in THF (2 mL) was added dropwise and the resulting mixture was allowed to stir at -78 °C for 3 hours. Then the reaction was quenched with 5 mL of NH_4Cl saturated aqueous solution and extracted with dichloromethane (3 × 5 mL) and diethyl ether (3 × 5 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated under vacuum to afford the crude product as a yellow-brown solid. The crude product was purified by flash

column chromatography on silica gel (from 0 to 20% ethyl acetate in hexane) to afford the clean product **132** as a white thick oil in quantitative yield (30.0 mg, 0.07 mmol). R_f 0.37 (hexane:EtOAc, 8:2); IR ν_{max} (film) 2953, 2916, 2849, 2357, 1740, 1700, 1686, 1457, 1437, 1369, 1337, 1208, 1146, 1075, 1034, 986, 856, 778 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 6.23 (1H, d, *J* 7.2 Hz, =CHI), 6.19 (1H, q, *J* 7.0 Hz, CH=), 4.46 (2H, s, CH_2N), 3.73 (3H, s, OCH_3), 2.98 (2H, t, *J* 7.5 Hz, CH_2CO), 2.21 (2H, q, *J* 7.3 Hz, CH_2), 1.81 (2H, qn, *J* 7.3 Hz, CH_2), 1.50 (9H, s, 3 × CH_3); (500 MHz, C_6D_6): δ_H 5.83 (1H, dt, *J* 1.4, 7.3 Hz, =CHI), 5.66 (1H, q, *J* 7.1 Hz, CH=), 4.43 (2H, s, CH_2N), 3.23 (3H, s, OCH_3), 2.84 (2H, t, *J* 7.1 Hz, CH_2CO), 2.03 (2H, dq, *J* 1.2, 7.3 Hz, CH_2), 1.69 (2H, qn, *J* 7.6 Hz, CH_2), 1.28 (9H, s, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 175.4 (CON), 169.6 (COOMe), 152.3 (COO*t*Bu), 140.8 (CH=), 84.0 (C), 83.2 (=CHI), 52.3 (OCH_3), 45.4 (CH_2N), 37.4 (CH_2CO), 34.2 (CH_2CH=), 28.1 (3 × CH_3), 23.4 (CH_2); HRMS (CI+/ISO) calc. for $C_{14}H_{23}O_5NI$ $[M+H]^+$: 412.0621. Found: 412.0613.

The characterisation matches the data reported in literature:
Dias L. C.; de Oliveira L. G. *Org. Lett*. **2001**, *3*, 3951.

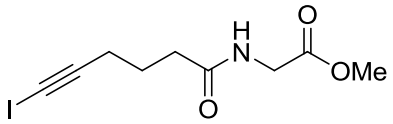
Methyl 2-hex-5-ynamidoacetate, 241



To a solution of hex-5-ynoic acid **242** (1.00 g, 8.93 mmol), glycine methylester **124** (1.35 g, 10.7 mmol) and HBTU (4.07 g, 10.7 mmol) in dichloromethane (25 mL) under argon, DIPEA (3.9 mL, 22.3 mmol) was added dropwise and the reaction mixture was allowed to stir for 16 hours. Then the reaction was quenched with 25 mL of NH_4Cl saturated aqueous solution and extracted with diethylether (3 × 25 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated under vacuum to afford the crude product as a yellow oil. The crude product was purified by flash column chromatography on silica gel (from 0 to 30% ethyl acetate in petroleum ether) to afford the clean product **241** as a colourless oil in 92% yield (1.5 g, 8.19 mmol). R_f 0.55 (EtOAc); IR ν_{max} (film) 3284, 2954, 1743, 1652, 1539, 1436, 1409, 1370, 1205, 1181, 1038, 1010, 982, 639 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 6.37 (1H, bs, NH), 3.97 (2H, d, *J* 5.2 Hz, CH_2N), 3.69 (3H, s,

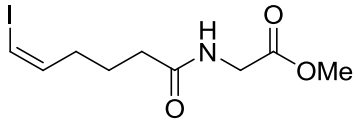
OCH_3), 2.34 (2H, t, *J* 7.3 Hz, CH_2CO), 2.21 (2H, td, *J* 2.6, 6.8 Hz, CH_2CH_{alkyne}), 1.94 (1H, t, *J* 2.7 Hz, CH_{alkyne}), 1.81 (2H, qn, *J* 7.2 Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 172.7 (CON), 170.5 (COO), 83.5 (C_{alkyne}), 69.2 (CH_{alkyne}), 52.3 (OCH_3), 41.2 (CH_2N), 34.6 (CH_2CO), 24.1 (CH_2), 17.8 (CH_2CH_{alkyne}); HRMS (CI+/ISO) calc. for $C_9H_{13}O_3N$ $[M]^+$: 183.0895. Found: 183.0894.

Methyl 2-(6-iodohex-5-ynamido)acetate, 255



To a solution of methyl 2-hex-5-ynamido acetate **241** (100 mg, 546 µmol) and iodine (208 mg, 819 µmol) in benzene (5 mL), under argon, morpholine (0.24 mL, 2.73 mmol) was added dropwise and the reaction mixture was allowed to stir at 45 °C for 12 hours. Then the reaction was allowed to cool to room temperature and it was filtered and extracted with diethyl ether (3 × 5 mL). The organic layers were collected, washed with brine (20 mL), $NaHCO_3$ saturated aqueous solution (20 mL), $Na_2S_2O_3$ saturated aqueous solution (20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford the crude product **253** as a yellow thick oil in a quantitative yield (169 mg, 546 µmol). The crude product was carried through without any further purification. R_f 0.32 (PE:EtOAc, 1:1); ^1H NMR (500 MHz, $CDCl_3$): δ_H 5.91 (1H, bs, NH), 4.05 (2H, d, *J* 5.4 Hz, CH_2N), 3.77 (3H, s, OCH_3), 2.47 (2H, t, *J* 7.0 Hz, CH_2C), 2.37 (2H, t, *J* 7.0 Hz, CH_2CO), 1.88 (2H, qn, *J* 7.0 Hz, CH_2).

***(Z)*-Methyl 2-(6-iodohex-5-enamido)acetate, 123**



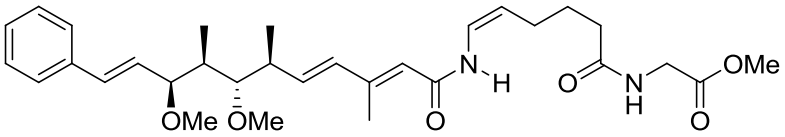
Method A: To a solution of *(Z)*-methyl 2-(*N*-(*tert*-butoxycarbonyl)-6-iodohex-5-enamido)acetate **132** (30.0 mg, 0.07 mmol) in dichloromethane (300 mL), under argon, TFA (2.0 mL) was added dropwise and the resulting mixture was allowed to stir at room temperature for 24 hours. Then the reaction mixture was concentrated under vacuum to afford the crude product as a yellow oil. The crude product was

purified by flash column chromatography on silica gel (from 0 to 40% ethyl acetate in hexane) to afford the clean product **123** as a colourless oil in quantitative yield (22.0 mg, 0.07 mmol).

Method B: To a solution of $BH_3{\cdot}SMe_2$ (0.16 mL, 324 µmol) in diethyl ether (5 mL), cooled at 0 °C and under argon, cyclohexene (0.07 mL, 648 µmol) was added dropwise and the reaction mixture was allowed to warm to room temperature and to stir for 1 hour. The resulting white suspension was cooled to 0 °C and a solution of methyl 2-(6-iodohex-5-ynamido)acetate **253** (100 mg, 324 µmol) in dry diethyl ether (3 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature and to stir for 1 hour. Then the reaction mixture was recooled to 0 °C and it was quenched with 0.2 mL of glacial acetic acid. The resulting mixture was allowed to stir at room temperature for 2 hours, then it was washed with H_2O (10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford the crude product as an orange oil. The crude product was purified by flash column chromatography on silica gel (from 0 to 40% ethyl acetate in hexane) to afford the clean product **123** as a colourless oil in 90% yield (91.0 mg, 293 µmol). R_f 0.21 (PE:EtOAc, 1:1); IR ν_{max} (film) 3287, 3082, 2949, 1748, 1649, 1537, 1456, 1437, 1406, 1370, 1288, 1269, 1202, 1179, 1152, 1036, 982, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 6.25 (1H, dt, *J* 1.2, 7.4 Hz, =CHI), 6.16 (1H, q, *J* 7.0 Hz, CH=), 5.98 (1H, bs, NH), 4.06 (2H, d, *J* 4.4 Hz, CH_2N), 3.77 (3H, s, OCH_3), 2.28 (2H, t, *J* 7.6 Hz, CH_2CO), 2.21 (2H, dq, *J* 1.0, 7.3 Hz, C*H*$_2$CH=), 1.81 (2H, qn, *J* 7.4 Hz, CH_2); (500 MHz, C_6D_6): δ_H 5.85 (1H, dt, *J* 1.3, 7.3 Hz, =CHI), 5.63 (1H, q, *J* 6.9 Hz, CH=), 5.11 (1H, bs, NH), 3.73 (2H, d, *J* 5.0 Hz, CH_2N), 3.20 (3H, s, OCH_3), 1.97 (2H, dq, *J* 1.3, 7.3 Hz, C*H*$_2$CH=), 1.69 (2H, t, *J* 7.6 Hz, CH_2CO), 1.60-1.54 (2H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 172.7 (CON), 170.6 (COO), 140.4 (CH=), 83.5 (=CHI), 52.5 (OCH_3), 41.4 (CH_2N), 35.5 (CH_2CO), 34.2 (*C*H_2CH=), 23.8 (CH_2); HRMS (CI+/ISO) calc. for $C_9H_{15}O_3NI$ $[M+H]^+$: 312.0097. Found: 312.0099.

The characterisation matches the data reported in literature:
Dias L. C.; de Oliveira L. G. *Org. Lett*. **2001**, *3*, 3951.

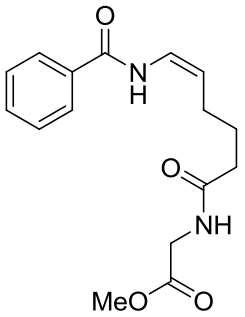
(+)-crocacin D: Methyl 2-((*Z*)-6-((*2E,4E,6S,7S,8R,9S,10E*)-7,9-dimethoxy-3,6,8-trimethyl-11-phenylundeca-2,4,10-trienamido)hex-5-enamido)acetate, 4



To a suspension of (+)-crocacin C **3** (8.50 mg, 24.0 µmol), cesium carbonate (7.40 mg, 23.0 µmol), CuI (1.00 mg, 5.00 µmol) and *N,N'*-dimethyl ethylenediamine (1 µL, 9.50 µmol) in degassed and dry THF (0.5 mL) in a 2.0-5.0 mL microwave vial, a solution of *(Z)*-methyl 2-(6-iodohex-5-enamido)acetate **123** (6.60 mg, 21.0 µmol) in degassed and dry THF (0.5 mL) was added dropwise and the reaction mixture was allowed stir at 70 °C for 24 hours. The resulting blue-purple suspension was diluted with 1 mL of ethyl acetate and filtered through a short pad of silica gel (previously deactivated with Et_3N) using EtOAc (10 mL) as eluent. Then the filtrate was concentrated under vacuum to afford a green-yellow oil as crude product. The crude product was purified by flash column chromatography on silica gel previously deactivated with triethylamine (EtOAc:DCM:Et_3N, 2.9:7:0.1) to afford the semipure product **4** as a yellow gum in 70% yield (8.00 mg, 15.0 µmol). R_f 0.38 (EtOAc:PE:Et_3N 4.9:5:0.1); IR ν_{max} (film) 3302, 2924, 1744, 1653, 1603, 1514, 1262, 1089 and 972 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6): δ_H 9.21 (1H, bd, *J* 10.5 Hz, NH), 7.61-7.52 (1H, m, NH), 7.51 (2H, d, *J* 7.3 Hz, 2 × *ortho* CH_{Ar}), 7.35 (2H, dd, *J* 7.4, 7.4 Hz, 2 × *meta* CH_{Ar}), 7.27 (1H, dd, *J* 7.4, 7.4 Hz, *para* CH_{Ar}), 6.80 (1H, dd, *J* 9.0, 10.4 Hz, CH=), 6.62 (1H, d, *J* 16.0 Hz, PhCH=), 6.29 (1H, dd, *J* 7.3, 16.1 Hz, CH=), 6.15-6.10 (2H, m, CH=CH), 5.95 (1H, d, *J* 1.0 Hz, CH=), 4.71 (1H, dt, *J* 7.3, 9.0 Hz, CH=), 4.12 (1H, dd, *J* 1.6, 7.4 Hz, CHOMe), 3.98 (2H, d, *J* 6.0 Hz, CH_2N), 3.71 (3H, s, OCH_3), 3.56 (3H, s, OCH_3), 3.30 (3H, s, OCH_3), 3.22 (1H, dd, *J* 2.4, 9.5 Hz, CHOMe), 2.65-2.57 (1H, m, CHMe), 2.31 (3H, d, *J* 1.0 Hz, CH_3), 2.29 (2H, t, *J* 7.1 Hz, CH_2CO), 2.11 (2H, dt, *J* 6.8, 7.2 Hz, CH_2), 1.67 (2H, tt, *J* 6.8, 7.2 Hz, CH_2), 1.56-1.55 (1H, m, CHMe), 1.22 (3H, d, *J* 6.8 Hz, CH_3), 0.91 (3H, d, *J* 7.1 Hz, CH_3); LRMS (ES+): $[M+H]^+$: 541.8; $[M+Na]^+$: 563.8

The characterisation matches the data reported in literature:
Dias L. C.; de Oliveira L. G. *Org. Lett*. **2001**, *3*, 3951.

***(Z)*-Methyl 2-(6-benzamidohex-5-enamido)acetate, 244**



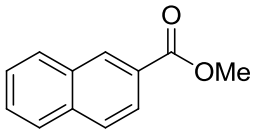
Method A: To a suspension of benzamide **243** (5.30 mg, 44.0 µmol), cesium carbonate (14.0 mg, 44.0 µmol), CuI (1.00 mg, 5.00 µmol) and *N,N'*-dimethyl ethylenediamine (1 µL, 9.50 µmol) in degassed and dry THF (0.5 mL) in a 2.0-5.0 mL microwave vial, a solution of *(Z)*-methyl 2-(6-iodohex-5-enamido)acetate **123** (10.0 mg, 38.0 µmol) in degassed and dry THF (0.5 mL) was added dropwise and the reaction mixture was allowed stir at 70 °C for 24 hours. The resulting blue-purple suspension was diluted with 1 mL of EtOAc and filtered through a short pad of silica gel (previously deactivated with Et_3N) using EtOAc as eluent. Then the filtrate was concentrated under vacuum to afford a green-yellow oil as crude product. The crude product was purified by flash column chromatography (EtOAc:DCM:Et_3N, 2.9:7:0.1) to afford the clean product **244** as a white gum in 75% yield (10.0 mg, 33.0 µmol).

Method B: To a suspension of benzamide **243** (24.0 mg, 0.20 mmol), (cod)Ru(met)$_2$ (3.20 mg, 1.00 µmol), Yb(OTf)$_3$ (5.00 mg, 8.00 µmol) and dcybd (5.40 mg, 12.0 µmol) in anhydrous DMF (0.6 mL), the alkyne **241** (73.0 mg, 0.40 mmol) was added and the resulting mixture was allowed to stir at 60 °C for 36 hours. Then the reaction was quenched with $NaHCO_3$ saturated aqueous solution (1 mL) and extracted with diethyl ether (3 × 2 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow solid as crude product. The crude product was purified by flash column chromatography (EtOAc:DCM:Et_3N, 2.9:7:0.1) to afford the clean product **244** as a white gum in 10% yield (6.10 mg, 0.02 mmol).

R_f 0.42 (EtOAc:PE:Et_3N 2.9:7:0.1); IR ν_{max} (film) 3304, 2953, 2923, 2854, 1745, 1646, 1515, 1484, 1457, 1437, 1375, 1281, 1207, 1030 and 708 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d$_6$): δ_H 9.67 (1H, bs, NH), 8.10 (2H, d, *J* 7.1 Hz, 2 × *ortho* CH_{Ar}), 7.75 (1H, bs, NH), 7.58 (1H, dd, *J* 7.1, 7.1 Hz, *para* CH_{Ar}), 7.52 (2H, dd, *J*

7.4, 7.4 Hz, 2 × *meta* CH_{Ar}), 7.01 (1H, td, *J* 1.0, 9.0 Hz, CH=), 4.89 (1H, q, *J* 8.2 Hz, =CH), 4.03 (2H, d, *J* 5.8 Hz, CH_2N), 3.66 (3H, s, OCH_3), 2.39-2.29 (4H, m, 2 × CH_2), 1.82-1.75 (2H, qn, *J* 6.6 Hz, CH_2); ^{13}C NMR (125 MHz, Acetone-d_6): δ_C 175.7 (CONH), 171.8 (COO), 166.0 (CONH), 135.8 (C_{Ar}), 133.1 (*para* CH_{Ar}), 129.8 (2 × *meta* CH_{Ar}), 129.5 (2 × *ortho* CH_{Ar}), 125.2 (CH=), 112.4 (=CH), 52.9 (OCH_3), 42.4 (CH_2N), 34.8 (CH_2CO), 26.9 (CH_2), 26.1 (CH_2); HRMS (EI+) calc. for $C_{16}H_{20}O_4N_2$ $[M]^+$: 304.1423. Found: 304.1417.

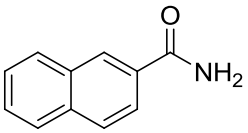
Methyl 2-naphthoate, 257



To a solution of naphtoic acid **256** (1.00 g, 5.80 mmol) in methanol (40 mL), concentrated hydrochloric acid (2 mL) was added and the resulting mixture was allowed to stir at 55 °C for 20 hours. Then the reaction was concentrated under vacuum, diluted with dichloromethane (40 mL) and washed with Na_2CO_3 saturated aqueous solution (2 × 50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to afford the product as a yellow oil. The crude product was purified by flash column chromatography on silica gel (from 0 to 30% ethyl acetate in hexane) to afford the clean product **257** as a white solid in 83% yield (899 mg, 4.83 mmol). R_f 0.81 (PE:EtOAc, 7:3); IR ν_{max} (film) 3070, 2949, 1709, 1470, 1437, 1352, 1292, 1231, 1199, 1155, 1130, 1099, 972, 961, 920, 878, 835, 781, 766 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 8.61 (1H, s, CH_{Ar}), 8.07 (1H, dd, *J* 1.6, 8.5 Hz, CH_{Ar}), 7.92 (1H, d, *J* 8.5 Hz, CH_{Ar}), 7.84 (2H, dd, *J* 4.3, 8.6 Hz, 2 × CH_{Ar}), 7.58-7.49 (2H, m, 2 × CH_{Ar}), 3.97 (3H, s, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 167.2 (CO), 135.5 (C_{Ar}), 132.5 (C_{Ar}), 131.0 (CH_{Ar}), 129.3 (CH_{Ar}), 128.2 (CH_{Ar}), 127.7 (CH_{Ar}), 127.4 (C_{Ar}), 126.6 (CH_{Ar}), 125.2 (CH_{Ar}), 52.2 (OCH_3); HRMS (CI+/ISO) calc. for $C_{12}H_{11}O_2$ $[M+H]^+$: 187.0759. Found: 187.0761; m.p. 70-71 °C.

The characterisation matches with the literature data:
Wu X. F. *Chem. Eur. J.* **2012**, *18*, 8912.

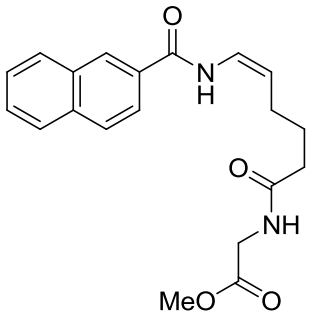
2-Naphthamide, 258



To a suspension of ammonium chloride (2.61 g, 48.3 mmol) in dry toluene (20 mL) at 0 °C, $AlMe_3$ (2.0 M solution in toluene, 24.2 mL, 48.3 mmol) was added dropwise and the resulting mixture was allowed to stir for 30 minutes, then a solution of methyl-2-naphtoate **257** (899 mg, 4.83 mmol) in dry toluene (20 mL) was added and the resulting mixture was allowed to stir at 50 °C for 16 hours. The reaction was cooled to 0 °C, quenched with 10 mL of HCl solution (1 N) and the organic layer was washed with $NaHCO_3$ saturated aqueous solution (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a pale yellow oil as crude product. The crude product was purified by silica gel flash column chromatography (1:1 PE/EtOAc) to afford a white solid as pure product **258** (659 mg, 3.85 mmol) in 80% yield. R_f 0.31 (EtOAc); IR ν_{max} (film) 3381, 3194, 1655, 1611, 1574, 1476, 1406, 1364, 1117, 916, 872, 839 and 787 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6): δ_H 8.56 (1H, s, CH_{Ar}), 8.09-7.99 (4H, m, CH_{Ar}), 7.67 (1H, bs, N*H*H), 7.63 (2H, *app* dqn, *J* 1.5, 6.8 Hz, CH_{Ar}), 7.69 (1H, bs, NH*H*); ^{13}C NMR (125 MHz, Acetone-d_6): δ_C 169.8 (CO), 136.5 (C_{Ar}), 134.4 (C_{Ar}), 133.5 (C_{Ar}), 130.6 (CH_{Ar}), 129.6 (CH_{Ar}), 129.5 (CH_{Ar}), 129.3 (CH_{Ar}), 129.2 (CH_{Ar}), 128.2 (CH_{Ar}), 126.1 (CH_{Ar}); HRMS (CI+/ISO) calc. for $C_{11}H_{10}ON$ $[M+H]^+$: 172.0762. Found: 172.0758; m.p. 189-190 °C

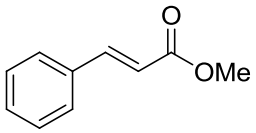
The characterisation matches with the literature data:
Cacchi S.; Misiti D.; La Torre F. *Synthesis* **1980**, *3*, 243.

_(Z)_-Methyl 2-(6-(2-naphthamido)hex-5-enamido)acetate, 259



To a suspension of 2-naphtamide **258** (30.0 mg, 175 µmol), cesium carbonate (57.0 mg, 175 µmol), CuI (1.70 mg, 8.80 µmol) and *N,N'*-dimethyl ethylenediamine (1.8 µL, 16.6 µmol) in degassed and dry THF (1 mL) in a 2.0-5.0 mL microwave vial, a solution of *(Z)*-methyl 2-(6-iodohex-5-enamido)acetate **123** (48.0 mg, 0.16 mmol) in degassed and dry THF (2 mL) was added dropwise and the reaction mixture was allowed stir at 70 °C for 18 hours. The resulting light-green suspension was diluted with 3 mL of ethyl acetate and filtered through a short pad of silica gel (previously deactivated with Et_3N) using ethyl acetate as eluent. Then the filtrate was concentrated under vacuum to afford a green-yellow oil as crude product. The crude product was purified by flash column chromatography on silica gel (EtOAc:DCM:Et_3N, 2.9:7:0.1) to afford the clean product **259** as a white gum in 51% yield (29.0 mg, 82.0 µmol). R_f 0.46 (EtOAc:PE:Et_3N 2.9:7:0.1); IR ν_{max} (film) 3300, 3071, 2951, 2928, 2855, 1748, 1647, 1520, 1499, 1437, 1370, 1294, 1204 and 1180 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6): δ_H 9.90 (1H, bd, *J* 7.2 Hz, NH), 8.78 (1H, s, CH_{Ar}), 8.17 (1H, dd, *J* 1.7, 8.6 Hz, CH_{Ar}), 8.09 (1H, d, *J* 7.7 Hz, CH_{Ar}), 8.02 (2H, d, *J* 9.0 Hz, 2 × CH_{Ar}), 7.81 (1H, bs, NH), 7.65 (2H, *app* dqn, *J* 1.5, 6.9 Hz, 2 × CH_{Ar}), 7.07 (1H, t, *J* 9.0 Hz, CH=), 4.93 (1H, q, *J* 8.6 Hz, =CH), 4.08 (2H, d, *J* 5.5 Hz, CH_2N), 3.59 (3H, s, OCH_3), 2.44-2.34 (4H, m, 2 × CH_2), 1.82 (2H, qn, *J* 6.9 Hz, CH_2); ^{13}C NMR (125 MHz, Acetone-d_6): δ_C 175.8 (CON), 171.8 (COO), 166.0 (CON), 136.6 (C_{Ar}), 134.4 (C_{Ar}), 132.9 (C_{Ar}), 130.7 (CH_{Ar}), 129.9 (CH_{Ar}), 129.5 (CH_{Ar}), 129.3 (CH_{Ar}), 129.2 (CH_{Ar}), 128.2 (CH_{Ar}), 126.3 (CH_{Ar}), 125.4 (CH=), 112.3 (=CH), 52.8 (OCH_3), 42.5 (CH_2N), 34.9 (CH_2CO), 26.9 (CH_2), 26.1 (CH_2); HRMS (CI+/ISO) calc. for $C_{20}H_{22}O_4N_2$ $[M]^+$: 354.1580. Found: 354.1581.

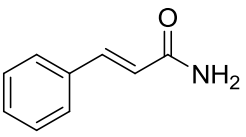
Methyl cinnamate, 261



To a solution of cinnamoic acid **260** (1.00 g, 6.76 mmol) in methanol (40 mL), concentrated hydrochloric acid (2 mL) was added and the resulting mixture was allowed to stir at 55 °C for 20 hours. Then the reaction was concentrated under vacuum, diluted with dichloromethane (40 mL) and washed with Na_2CO_3 saturated aqueous solution (2 × 50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to afford the product as a yellow oil. The crude product was purified by flash column chromatography on silica gel (from 0 to 30% ethyl acetate in hexane) to afford the clean product **261** as a light yellow solid in 70% yield (770 mg, 4.75 mmol). R_f 0.82 (EtOAc:PE, 3:7); IR ν_{max} (film) 2998, 2364, 1713, 1636, 1578, 1497, 1451, 1435, 1329, 1314, 1273, 1202, 1167, 978, 766, 731, 712 and 683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.68 (1H, d, *J* 15.9 Hz, CH=), 7.50-7.46 (2H, m, 2 × *ortho* CH_{Ar}), 7.36-7.32 (3H, m, 3 × *meta and para* CH_{Ar}), 6.43 (1H, d, *J* 16.2 Hz, =CH), 3.77 (3H, s, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 167.2 (CO), 144.7 (CH=), 134.3 (C_{Ar}), 130.2 (CH_{Ar}), 128.8 (CH_{Ar}), 128.0 (CH_{Ar}), 117.8 (=CH), 51.5 (OCH_3); HRMS (CI+/ISO) calc. for $C_{10}H_{11}O_2$ $[M+H]^+$: 163.0754. Found: 163.0762; m.p. 30-31 °C.

The characterisation matches with the literature data:
Hosangadi B. D.; Dave R. H. *Tetrahedron Lett.* **1996**, *37*, 6375.

Cinnamamide, 245

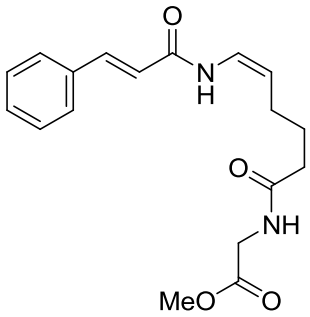


To a suspension of ammonium chloride (2.57 g, 47.5 mmol) in dry toluene (15 mL) at 0 °C, $AlMe_3$ (2 M solution in toluene, 23.8 mL, 47.5 mmol) was added dropwise and the resulting mixture was allowed to stir for 30 minutes, then a solution of methyl cinnamate **261** (770 mg, 4.75 mmol) in dry toluene (20 mL) was added and

the resulting mixture was allowed to stir at 50 °C for 16 hours. The reaction was cooled to 0 °C, quenched with 10 mL of HCl solution (1 N) and the organic layer was washed with $NaHCO_3$ saturated aqueous solution (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a pale yellow oil as crude product. The crude product was purified by silica gel flash column chromatography (1:1 PE/EtOAc) to afford a white solid as pure product **245** (337 mg, 2.29 mmol) in 48% yield. R_f 0.30 (EtOAc); IR ν_{max} (film) 3372, 3167, 1736, 1661, 1607, 1493, 1451, 1398, 1246, 1202, 1115, 968 and 698 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6): δ_H 7.62 (2H, dd, *J* 1.9, 7.9 Hz, 2 × *ortho* CH_{Ar}), 7.60 (1H, d, *J* 15.9 Hz, CH=), 7.46-7.37 (3H, m, 3 × *meta and para* CH_{Ar}), 7.14 (1H, bs, N*H*H), 6.78 (1H, d, *J* 15.8 Hz, =CH), 6.70 (1H, bs, NH*H*); ^{13}C NMR (125 MHz, Acetone-d_6): δ_C 168.6 (CO), 141.7 (CH=), 136.9 (C_{Ar}), 131.0 (CH_{Ar}), 130.5 (CH_{Ar}), 129.3 (CH_{Ar}), 123.3 (=CH); HRMS (CI+/ISO) calc. for $C_9H_{10}ON$ $[M+H]^+$: 148.0762. Found: 148.0764; m.p. 110-111 °C

The characterisation matches with the literature data:
Tian J.; Moeller K. D. *Org. Lett.* **2005**, *7*, 5381.

Methyl 2-(*(Z)*-6-cinnamamidohex-5-enamido)acetate, 262



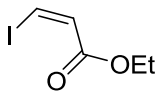
Method A: To a suspension of cinnamamide **245** (30.0 mg, 204 µmol), cesium carbonate (66.0 mg, 204 µmol), CuI (2.00 mg, 10.2 µmol) and *N,N'*-dimethyl ethylenediamine (2.2 µL, 20.4 µmol) in degassed and dry THF (1 mL) in a 2.0-5.0 mL microwave vial, a solution of *(Z)*-methyl 2-(6-iodohex-5-enamido)acetate **123** (55.0 mg, 186 µmol) in degassed and dry THF (2 mL) was added dropwise and the reaction mixture was allowed stir at 70 °C for 18 hours. The resulting pale blue suspension was diluted with 3 mL of ethyl acetate and filtered through a short pad of silica (previously deactivated with Et_3N) using ethyl acetate as eluent. Then the filtrate was concentrated under vacuum to afford a green-yellow oil as crude product. The crude product was purified by flash column chromatography on silica gel (EtOAc:DCM:Et_3N, 2.9:7:0.1) to afford the clean product **262** as a white gum in 55% yield (34.0 mg, 103 µmol).

Method B: To a suspension of *trans*-cinnamamide **245** (20.0 mg, 136 µmol), (cod)Ru(met)$_2$ (4.50 mg, 14.0 µmol), Yb(OTf)$_3$ (6.75 mg, 10.0 µmol) and dcybd (7.20 mg, 16.0 µmol) in anhydrous DMF (0.6 mL), the alkyne **241** (75.0 mg, 0.41 mmol) was added and the resulting mixture was allowed to stir at 60 °C for 52 hours. Then the reaction was quenched with $NaHCO_3$ saturated aqueous solution (1 mL) and extracted with diethyl ether (3 × 2 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow solid as crude product. The crude product was purified by flash column chromatography (EtOAc:DCM:Et_3N, 2.9:7:0.1) to afford the clean product **262** as a white gum in 8% yield (3.60 mg, 10.9 µmol).

R_f 0.21 (EtOAc:DCM:Et_3N 2.9:7:0.1); IR ν_{max} (film) 3297, 2951, 2361, 1750, 1651, 1520, 1206, 1182, 980, 766 and 682 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6): δ_H 9.59 (1H, bd, *J* 9.5 Hz, NH), 7.77 (1H, bs, NH), 7.66 (1H, d, *J* 15.9 Hz, CH=), 7.65-7.63 (2H, m, 2 × *ortho* CH_{Ar}), 7.49-7.40 (3H, m, 3 × *meta and para* CH_{Ar}), 6.91

(1H, t, *J* 8.9 Hz, CH=), 6.89 (1H, d, *J* 15.9 Hz, =CH), 4.84 (1H, q, *J* 8.6 Hz, =CH), 4.07 (2H, d, *J* 5.6 Hz, CH_2N), 3.71 (3H, s, OCH_3), 2.36 (2H, t, *J* 6.6 Hz, CH_2CO), 2.22 (2H, q, *J* 6.7 Hz, CH_2), 1.77 (2H, qn, *J* 6.7 Hz, CH_2); ^{13}C NMR (125 MHz, Acetone-d_6): δ_C 175.6 (CON), 171.9 (COO), 164.2 (CON), 142.1 (CH=), 137.0 (C_{Ar}), 131.2 (CH_{Ar}), 130.5 (CH_{Ar}), 129.3 (CH_{Ar}), 124.8 (CH=), 123.1 (=CH), 111.5 (=CH), 52.9 (OCH_3), 42.5 (CH_2N), 35.2 (CH_2CO), 26.8 (CH_2), 26.2 (CH_2); HRMS (CI+/ISO) calc. for $C_{18}H_{22}O_4N_2$ $[M]^+$: 330.1580. Found: 330.1577.

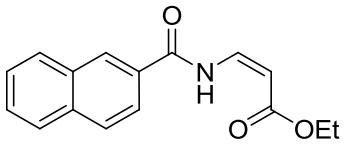
(Z)-Ethyl 3-iodoacrylate, 275



To a solution of ethyl propiolate **274** (1 mL, 9.85 mmol) in glacial acetic acid (5 mL), sodium iodide (1.50 g, 10.0 mmol) was added and the reaction mixture was allowed to warm to room 70 °C and to stir for 16 hours. Then the reaction was quenched with H_2O (5 mL) and NaOH (1N, 5 mL) and extracted with diethylether (3 × 5 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated under vacuum to afford the product as an orange oil in a quantitative yield (2.23 g, 9.85 mmol). The crude product **275** resulted clean without necessity of any further purification. R_f 0.59 (Et_2O:PE, 2.5:7.5); IR ν_{max} (film) 1721, 1597, 1321, 1192, 1159, 1024 and 804 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.31 (1H, d, *J* 8.8 Hz, IHC=), 6.74 (1H, d, *J* 8.9 Hz, =CH), 4.06 (2H, q, *J* 7.2 Hz, CH_2), 1.14 (3H, t, *J* 7.2 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 164.0 (CO), 129.6 (=CH), 94.7 (IHC=), 60.4 (CH_2), 13.9 (CH_3); HRMS (EI+) calc. for $C_5H_7O_2I$ $[M]^+$: 225.9491. Found: 225.9494.

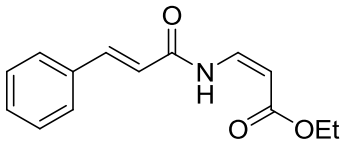
The characterisation matches with the literature data:
Trost B. M.; Papillon J. P. N.; Nussbaumer T. *J. Am. Chem. Soc.* **2005**, *127*, 17921.

_(Z)_-Ethyl 3-(2-naphthamido)acrylate, 276



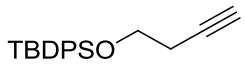
To a suspension of 2-naphtamide **258** (50.0 mg, 292 µmol), cesium carbonate (95.0 mg, 292 µmol), CuI (3.00 mg, 15.0 µmol) and *N,N'*-dimethyl ethylenediamine (3.2 µL, 30.0 µmol) in degassed and dry THF (2 mL) in a 2.0-5.0 mL microwave vial, a solution of *(Z)*-ethyl 3-iodoacrylate **275** (60.0 mg, 266 µmol) in degassed and dry THF (2 mL) was added dropwise and the reaction mixture was allowed stir at 70 °C for 18 hours. The resulting pale blue suspension was diluted with 4 mL of ethyl acetate and filtered through a short pad of silica (previously deactivated with Et_3N) using ethyl acetate as eluent. Then the filtrate was concentrated under vacuum to afford a green-yellow oil as crude product. The crude product was purified by flash column chromatography on silica gel (from 0 to 5% ethyl acetate in petroleum ether) to afford the clean product **276** as a pale yellow gum in 48% yield (34.3 mg, 128 µmol). R_f 0.16 (EtOAc:PE, 0.4:9.6); IR ν_{max} (film) 3327, 1678, 1622, 1487, 1397, 1381 and 1199 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6): δ_H 11.69 (1H, bd, *J* 8.8 Hz, NH), 8.59 (1H, s, CH_{Ar}), 8.20 (1H, d, *J* 7.9 Hz, CH_{Ar}), 8.17 (1H, d, *J* 8.9 Hz, CH_{Ar}), 8.09 (1H, d, *J* 7.6 Hz, CH_{Ar}), 8.03 (1H, dd, *J* 1.9, 8.5 Hz, CH_{Ar}), 7.86 (1H, dd, *J* 8.9, 11.1 Hz, CH=), 7.72 (2H, *app* dqn, *J* 1.6, 7.0 Hz, 2 × CH_{Ar}), 5.38 (1H, d, *J* 8.9 Hz, =CH), 4.31 (2H, q, *J* 7.1 Hz, CH_2), 1.36 (3H, t, *J* 7.1 Hz, CH_3); ^{13}C NMR (125 MHz, Acetone-d_6): δ_C 170.9 (CON), 165.5 (COO), 140.5 (CH=), 140.3 (CH_{Ar}), 137.1 (C_{Ar}), 134.4 (C_{Ar}), 131.4 (C_{Ar}), 130.9 (CH_{Ar}), 130.7 (CH_{Ar}), 130.2 (CH_{Ar}), 129.5 (CH_{Ar}), 128.9 (CH_{Ar}), 125.0 (CH_{Ar}), 98.5 (=CH), 61.7 (CH_2), 15.3 (CH_3); HRMS (CI+/ISO) calc. for $C_{16}H_{16}O_3N$ $[M+H]^+$: 270.1130. Found: 270.1136.

***(Z)*-Ethyl 3-cinnamamidoacrylate, 277**



To a suspension of cinnamamide **245** (50.0 mg, 0.34 mmol), cesium carbonate (111 mg, 0.34 mmol), CuI (3.10 mg, 16.0 µmol) and *N,N'*-dimethyl ethylenediamine (3.4 µL, 32.0 µmol) in degassed and dry THF (2 mL) in a 2.0-5.0 mL microwave vial, a solution of *(Z)*-ethyl 3-iodoacrylate **275** (70.0 mg, 0.31 mmol) in degassed and dry THF (2 mL) was added dropwise and the reaction mixture was allowed stir at 70 °C for 18 hours. The resulting pale blue suspension was diluted with 4 mL of ethyl acetate and filtered through a short pad of silica (previously deactivated with Et_3N) using ethyl acetate as eluent. Then the filtrate was concentrated under vacuum to afford a green-yellow oil as crude product. The crude product was purified by flash column chromatography on silica gel (from 0 to 5% ethyl acetate in petroleum ether) to afford the clean product **277** as a white gum in 55% yield (36.0 mg, 147 µmol). R_f 0.1 (EtOAc:PE, 0.4:9.6); IR ν_{max} (film) 3333, 2983, 1713, 1676, 1620, 1379, 1260, 1198 and 1138 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6): δ_H 10.65 (1H, bd, *J* 8.3 Hz, NH), 7.83-7.78 (2H, m, 2 × CH_{Ar}), 7.79 (1H, d, *J* 16.0 Hz, CH=), 7.69 (1H, dd, *J* 9.0, 11.4 Hz, CH=), 7.54-7.46 (3H, m, 3 × CH_{Ar}), 7.10 (1H, d, *J* 16.0 Hz, =CH), 5.24 (1H, d, *J* 9.2 Hz, =CH), 4.23 (2H, q, *J* 6.9 Hz, CH_2), 1.31 (3H, t, *J* 7.2 Hz, CH_3); ^{13}C NMR (125 MHz, Acetone-d_6): δ_C 170.2 (CON), 164.9 (COO), 145.4 (CH=), 139.9 (CH=), 136.4 (C_{Ar}), 131.9 (CH_{Ar}), 130.6 (CH_{Ar}), 129.9 (CH_{Ar}), 121.7 (=CH), 97.7 (=CH), 61.4 (CH_2), 15.3 (CH_3); HRMS (CI+/ISO) calc. for $C_{14}H_{16}O_3N$ $[M+H]^+$: 246.1130. Found: 246.1130.

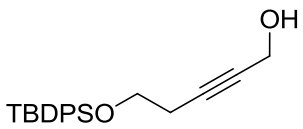
(But-3-ynyloxy)(*tert*-butyl)diphenylsilane, 285



To a solution of but-3-yn-1-ol **284** (2.00 g, 28.5 mmol), imidazole (2.72 g, 39.9 mmol) and DMAP (35.0 mg, 285 µmol) in dry dichloromethane (40 mL), under argon and at 0 °C, TBDPSCl (8.9 mL, 34.2 mmol) was added dropwise and the resulting mixture was allowed to warm to room temperature and to stir for 12 hours. Then the reaction was quenched by addition of 40 mL of distilled water. The aqueous phase was extracted with dichloromethane (3 × 50 mL) and the organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford a pale yellow oil as crude product. The crude product **285** was taken directly onto the next step without any further purification and the reaction was considered quantitative (8.79 g, 28.5 mmol). IR ν_{max} (film) 3308, 2957, 2932, 2859, 1738, 1472, 1427, 1385, 1362, 1217, 1105, 908, 822, 802, 733, 700 and 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.73-7.71 (4H, m, CH_{Ar}), 7.46-7.42 (6H, m, CH_{Ar}), 3.82 (2H, t, *J* 7.2 Hz, CH_2), 2.48 (2H, td, *J* 2.5, 7.0 Hz, CH_2CH_{alkyne}), 1.97 (1H, t, *J* 2.7 Hz, CH_{alkyne}), 1.10 (9H, s, 3 × CH_3); HRMS (CI+/ISO) calc. for $C_{20}H_{25}OSi$ $[M+H]^+$: 309.1675. Found: 309.1668.

The characterisation matches with the data reported in literature:
Ohtsuki K.; Matsuo K.; Yoshikawa T.; Moriya C.; Tomita-Yokotani K.; Shishido K.; Shindo M. *Org. Lett*. **2008**, *10*, 1247.

5-(*tert*-Butyldiphenylsilyloxy)pent-2-yn-1-ol, 286

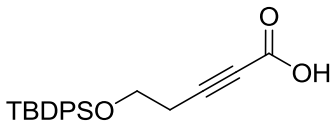


To a solution of (but-3-ynyloxy)(*tert*-butyl)diphenylsilane **285** (8.80 g, 28.5 mmol) in dry THF (80 mL), under argon at -78 °C, *n*-BuLi (11.98 mL, 29.9 mmol, 2.5 M solution in hexanes) was added dropwise and the resulting mixture was stirred at -78 °C for 30 minutes. Then paraformaldehyde (2.05 g, 68.5 mmol) was added in one portion and the resulting mixture was allowed to warm to room temperature and to stir for 3 hours. The reaction was quenched by addition of distilled water

(100 mL), it was diluted with diethyl ether (100 mL) and washed with brine (100 mL). The organic phase was dried over Na_2SO_4 and concentrated under vacuum to afford a yellow-orange oil as crude product. The crude product was purified through flash column chromatography on silica gel (from 0 to 20% ethyl acetate in hexane) to afford the pure product **286** as a yellow oil in quantitative yield (9.66 g, 28.5 mmol). R_f 0.44 (hexane:EtOAc, 8:2); IR ν_{max} (film) 3381, 2953, 2932, 2859, 2363, 2249, 1736, 1589, 1472, 1427, 1385, 1362, 1105, 1007, 999, 908, 822, 731, 700 and 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.74-7.72 (4H, m, CH_{Ar}), 7.47-7.41 (6H, m, CH_{Ar}), 4.21-4.20 (2H, m, CH_2OH), 3.82 (2H, t, *J* 7.3 Hz, CH_2OSi), 2.54-2.51 (2H, m, CH_2), 1.99-1.97 (1H, m, OH), 1.12 (9H, s, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 135.7 (CH_{Ar}), 133.7 (C_{Ar}), 129.8 (CH_{Ar}), 127.8 (CH_{Ar}), 83.4 (C_{alkyne}), 79.7 (C_{alkyne}), 62.5 (CH_2OSi), 51.3 (CH_2OH), 26.9 (3 × CH_3), 22.9 (CH_2), 19.3 (C); HRMS (CI+/ISO) calc. for $C_{21}H_{27}O_2Si$ $[M+H]^+$: 339.1780. Found: 339.1781.

The characterisation matches with the literature data:
Chakraborty T. K.; Purkait S.; Sanjib D. *Tetrahedron* **2003**, *59*, 9127.

5-(*tert*-Butyldiphenylsilyloxy)pent-2-ynoic acid, 287

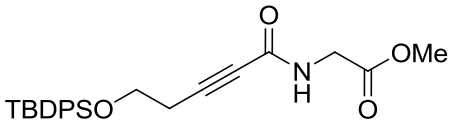


To a solution of 5-(*tert*-butyldiphenylsilyloxy)pent-2-yn-1-ol **286** (9.66 g, 28.5 mmol) in dichloromethane (30 mL) and distilled water (30 mL), under argon, TEMPO (892 mg, 5.71 mmol) and BAIB (20.2 g, 62.8 mmol) were added and the resulting mixture was allowed to stir at room temperature for 12 hours. Then the reaction was extracted with dichloromethane (3 × 30 mL) and ethyl acetate (3 × 30 mL). The organic layers were combined, dried over Na_2SO4 and concentrated under vacuum to afford an orange oil as crude product. The crude product was purified through flash column chromatography on silica gel (from 0 to 30% ethyl acetate in petroleum ether) to afford the pure product **287** as a yellow oil in 61% yield (6.20 g, 17.5 mmol). R_f 0.5 (PET:EtOAc, 7:3); IR ν_{max} (film) 2241, 1686, 1472, 1427, 1219, 1105, 910, 822, 735, 700 and 687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 11.21 (1H, bs, OH), 7.73-7.71 (4H, m, CH_{Ar}), 7.47-7.42 (6H, m, CH_{Ar}), 3.88 (2H,

t, *J* 6.8 Hz, OCH_2), 2.64 (2H, t, *J* 6.8 Hz, CH_2), 1.11 (9H, s, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 157.9 (CO), 135.7 (CH_{Ar}), 133.3 (C_{Ar}), 129.9 (CH_{Ar}), 127.9 (CH_{Ar}), 88.1 (C), 74.4 (C), 61.4 (CH_2O), 26.9 (3 × CH_3), 23.0 (CH_2), 19.3 (SiC); HRMS (CI+/ISO) calc. for $C_{20}H_{25}OSi$ $[M\text{-}CO_2+H]^+$: 309.1675. Found: 309.1678.

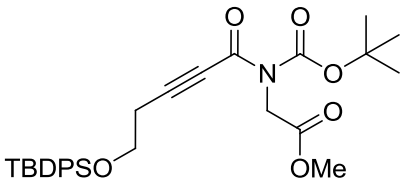
The characterisation matches with the literature data:
Wipf P.; Thomas H. *Org. Biomol. Chem.* **2005**, *3*, 31.

Methyl 2-(5-(*tert*-butyldiphenylsilyloxy)pent-2-ynamido)acetate, 288



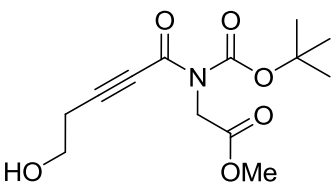
To a solution of 5-(*tert*-butyldiphenylsilyloxy)pent-2-ynoic acid **287** (5.85 g, 16.5 mmol), HBTU (7.51 g, 19.8 mmol) and glycine methyl ester **124** (2.49 g, 19.8 mmol) in dry dichloromethane (150 mL), under argon at 0 °C, DIPEA (7.2 mL, 41.3 mmol) was added dropwise and the resulting mixture was allowed to warm to room temperature and stir for 12 hours. The reaction was quenched with a saturated solution of NH_4Cl (100 mL) and extracted with diethyl ether (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum to afford a brown oil as crude product. The crude product was purified through flash column chromatography on silica gel (from 0 to 50% ethyl acetate in petroleum ether) to afford the pure product **288** as a yellow oil in 60% yield (4.61 g, 9.98 mmol). R_f 0.56 (PET:EtOAc, 1:1); IR ν_{max} (film) 1748, 1647, 1518, 1427, 1368, 1294, 1207, 1182, 1105, 908, 822, 729, 700 and 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.69-7.67 (4H, m, CH_{Ar}), 7.44-7.38 (6H, m, CH_{Ar}), 6.22 (1H, bs, NH), 4.05 (2H, d, *J* 5.3 Hz, NCH_2), 3.81 (2H, t, *J* 6.8 Hz, CH_2O), 3.75 (3H, s, OCH_3), 2.56 (2H, t, *J* 7.6 Hz, CH_2), 1.07 (9H, s, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 169.7 (CO), 153.2 (CO), 135.6 (CH_{Ar}), 133.4 (C_{Ar}), 129.9 (CH_{Ar}), 127.9 (CH_{Ar}), 85.6 (C), 75.9 (C), 61.5 (CH_2O), 52.6 (OCH_3), 41.4 (NCH_2), 26.9 (3 × CH_3), 22.9 (CH_2), 19.3 (SiC); HRMS (CI+/ISO) calc. for $C_{24}H_{30}O_4NSi$ $[M+H]^+$: 424.1944. Found: 424.1943.

Methyl 2-(*N*-(*tert*-butoxycarbonyl)-5-(*tert*-butyldiphenylsilyloxy)pent-2-ynamido)acetate, 289



To a solution of methyl 2-(5-(*tert*-butyldiphenylsilyloxy)pent-2-ynamido)acetate **288** (4.61 g, 9.98 mmol), DMAP (24.0 mg, 199 µmol) and Boc_2O (8.70 g, 39.9 mmol) in dry THF (40 mL), under argon at 0 °C, DIPEA (7 mL, 39.9 mmol) was added dropwise and the resulting mixture was allowed to warm to room temperature and to stir for 12 hours. Then the reaction mixture was poured in 50 mL of brine and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford a brown oil as crude product **289**. The crude product was taken directly onto the next step without any further purification. R_f 0.26 (Hexane:EtOAc, 8:2); IR ν_{max} (film) 1755, 1736, 1653, 1369, 1333, 1217, 1148, 1105, 908, 729, 700 and 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.71-7.67 (4H, m, CH_{Ar}), 7.44-7.38 (6H, m, CH_{Ar}), 4.46 (2H, s, NCH_2), 3.87 (2H, t, *J* 6.9 Hz, CH_2O), 3.69 (3H, s, OCH_3), 2.68 (2H, t, *J* 6.8 Hz, CH_2), 1.49 (9H, s, 3 × CH_3), 1.08 (9H, s, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 168.4 (CO), 152.9 (CO), 150.9 (CO), 135.4 (CH_{Ar}), 133.1 (C_{Ar}), 129.7 (CH_{Ar}), 127.7 (CH_{Ar}), 94.2 (C), 84.2 (C), 76.2 (C), 61.3 (CH_2O), 52.1 (OCH_3), 44.7 (NCH_2), 27.7 (3 × CH_3), 26.7 (3 × CH_3), 23.4 (CH_2), 19.0 (SiC).

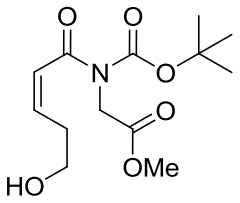
Methyl 2-(*N*-(*tert*-butoxycarbonyl)-5-hydroxypent-2-ynamido)acetate, 290



To a solution of methyl 2-(*N*-(*tert*-butoxycarbonyl)-5-(*tert*-butyldiphenyl silyloxy) pent-2-ynamido)acetate **289** (4.00 g, 7.12 mmol) in dry THF (25 mL), under argon at 0 °C, was added dropwise a mixture of glacial acetic acid (1.02 mL, 17.8 mmol) and TBAF (17.8 mL, 17.8 mmol, 1M solution in THF). The resulting mixture was allowed to warm to room temperature and stir for 12 hours. Then it was quenched

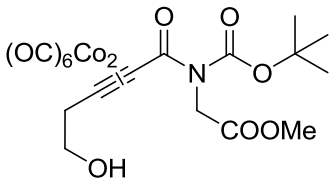
with distilled water (20 mL) and extracted with diethyl ether (20 mL), ethyl acetate (20 mL) and dichloromethane (20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford a yellow oil as crude product. The crude product was purified through flash column chromatography on silica gel (from 0 to 50% ethyl acetate in hexane) to afford a colourless oil as pure product **290** in 59% yield (1.20 g, 4.19 mmol). R_f 0.28 (hexane:EtOAc, 1:1); IR ν_{max} (film) 1736, 1651, 1369, 1331, 1217, 1144, 1117, 1053, 972, 914, 847, 775, 729 and 646 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 4.65 (1H, bs, OH), 4.27 (2H, s, NCH_2), 3.62 (2H, t, *J* 5.6 Hz, CH_2O), 3.64 (3H, s, OCH_3), 2.48 (2H, t, *J* 5.4 Hz, CH_2), 1.34 (9H, s, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 168.5 (CO), 152.7 (CO), 150.8 (CO), 94.8 (C), 84.6 (C), 76.4 (C), 59.6 (CH_2OH), 52.0 (CH_3), 44.5 (NCH_2), 27.5 (3 × CH_3), 23.5 (CH_2); HRMS (FAB+) calc. for $C_{13}H_{20}O_6N$ $[M+H]^+$: 286.1291. Found: 286.1286.

(Z)-Methyl 2-(*N*-(*tert*-butoxycarbonyl)-5-hydroxypent-2-enamido)acetate, 292



To a suspension of methyl 2-(*N*-(*tert*-butoxycarbonyl)-5-hydroxypent-2-ynamido)acetate **290** (189 mg, 663 µmol) and Lindlar's catalyst (3.50 mg, 332 µmol) in dry toluene (6 mL) was allowed to stir under H_2 atmosphere at room temperature for 4 hours. Then it was diluted with toluene (10 mL) and filtered through Celite® to afford the product **292** as a colourless thick oil in quantitative yield (0.19 g, 663 µmol). The crude product was very clean without necessity of any further purification. R_f 0.35 (hexane:EtOAc, 1:1); IR ν_{max} (film) 1739, 1733, 1680, 1438, 1419, 1369, 1337, 1205, 1143, 1051, 852 and 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 6.64 (1H, d, *J* 11.5 Hz, CH), 6.15 (1H, dt, *J* 8.0, 11.5 Hz, CH), 4.38 (2H, s, NCH_2), 3.68 (3H, s, OCH_3), 3.66 (2H, t, *J* 6.0 Hz, CH_2O), 2.45 (2H, q, *J* 6.0 Hz, CH_2), 1.43 (9H, s, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 169.3 (CO), 168.5 (CO), 151.9 (CO), 141.5 (CH), 125.9 (CH), 84.2 (C), 61.2 (CH_2), 52.2 (OCH_3), 45.1 (NCH_2), 31.9 (CH_2), 27.8 (3 × CH_3); HRMS (CI+/ISO) calc. for $C_{13}H_{22}O_6N$ $[M+H]^+$: 288.1447. Found: 288.1441.

Methyl 2-(*N*-(*tert*-butoxycarbonyl)-5-hydroxypent-2-ynamido)acetate-cobalt carbonyl complex, 293



To a solution of methyl 2-(*N*-(*tert*-butoxycarbonyl)-5-hydroxypent-2-ynamido) acetate **290** (0.15 g, 526 µmol) in toluene (5 mL), the cobalt carbonyl (0.36 g, 1.05 mmol) was added and the resulting suspension was allowed to stir at room temperature for 12 hours. Then, the resulting mixture was filtered through Celite® using toluene as eluent (20 mL), concentrated under vacuum to afford a light brown solid as crude product (0.29 g, 508 µmol, 97%). The crude product was carried through the next step without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.92 (2H, m, CH_2), 3.76 (3H, s, OCH_3), 3.65 (2H, m, CH_2), 1.52 (2H, m, CH_2), 1.48 (9H, s, 3 × CH_3).

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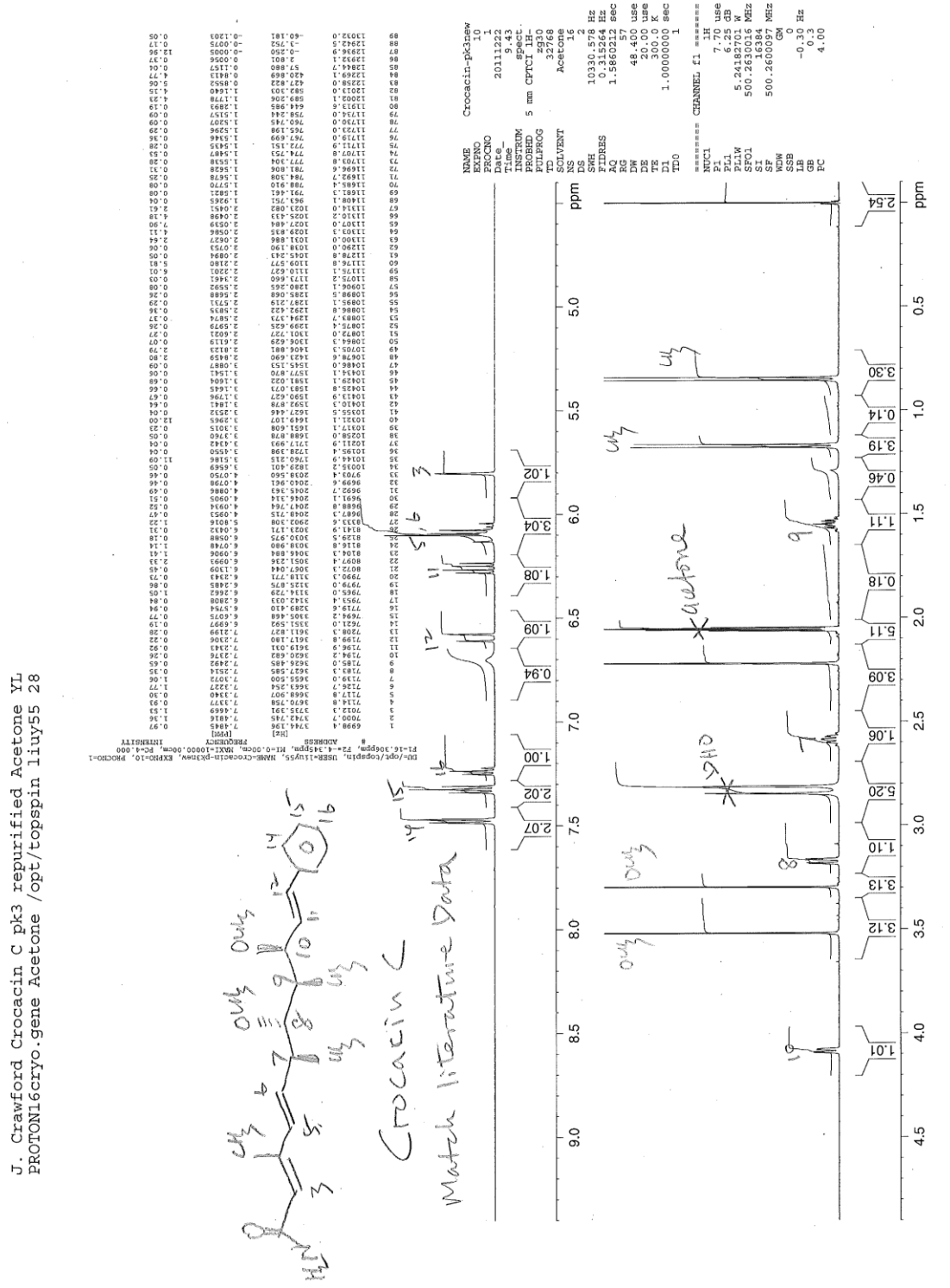
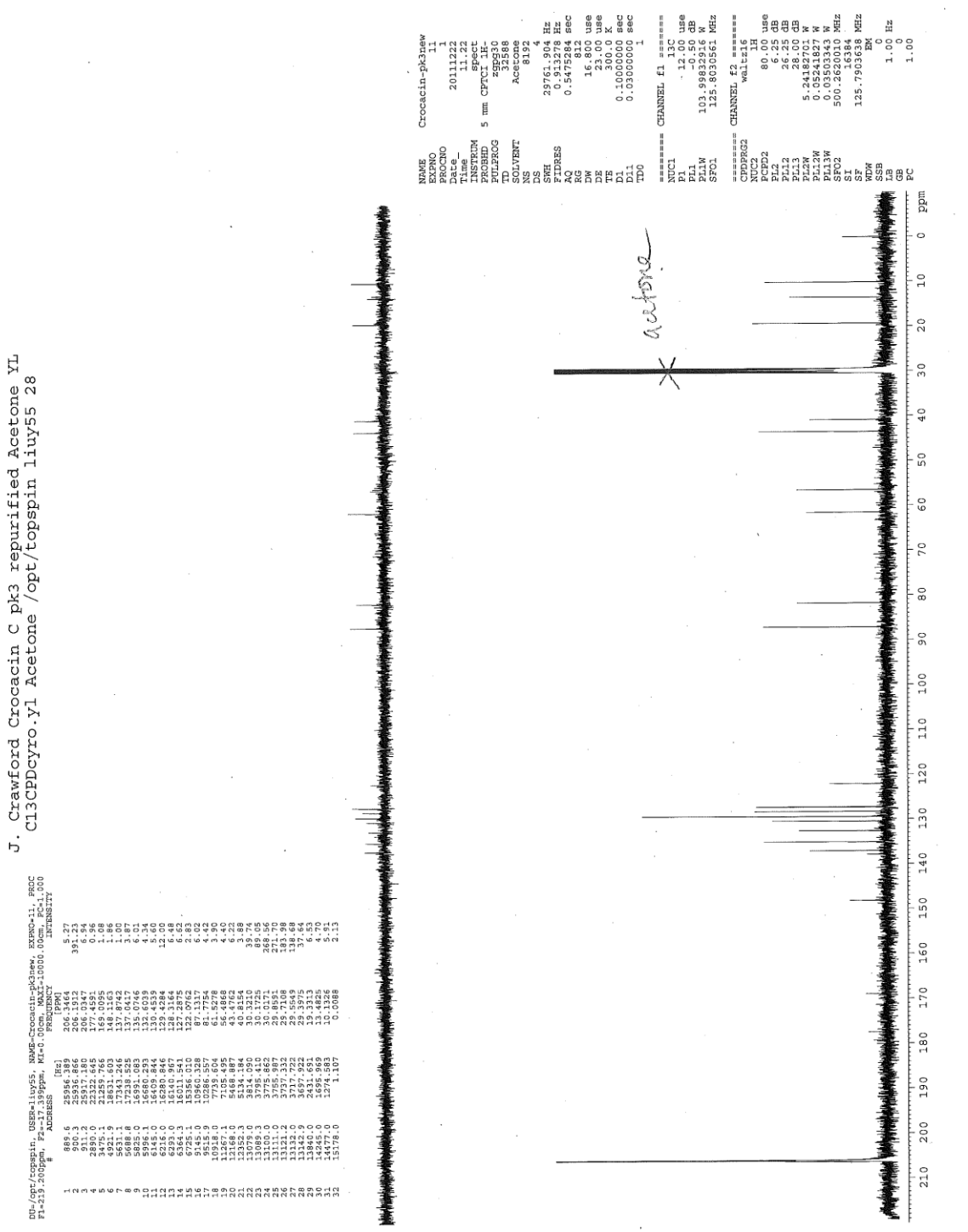
Appendices

Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **3**

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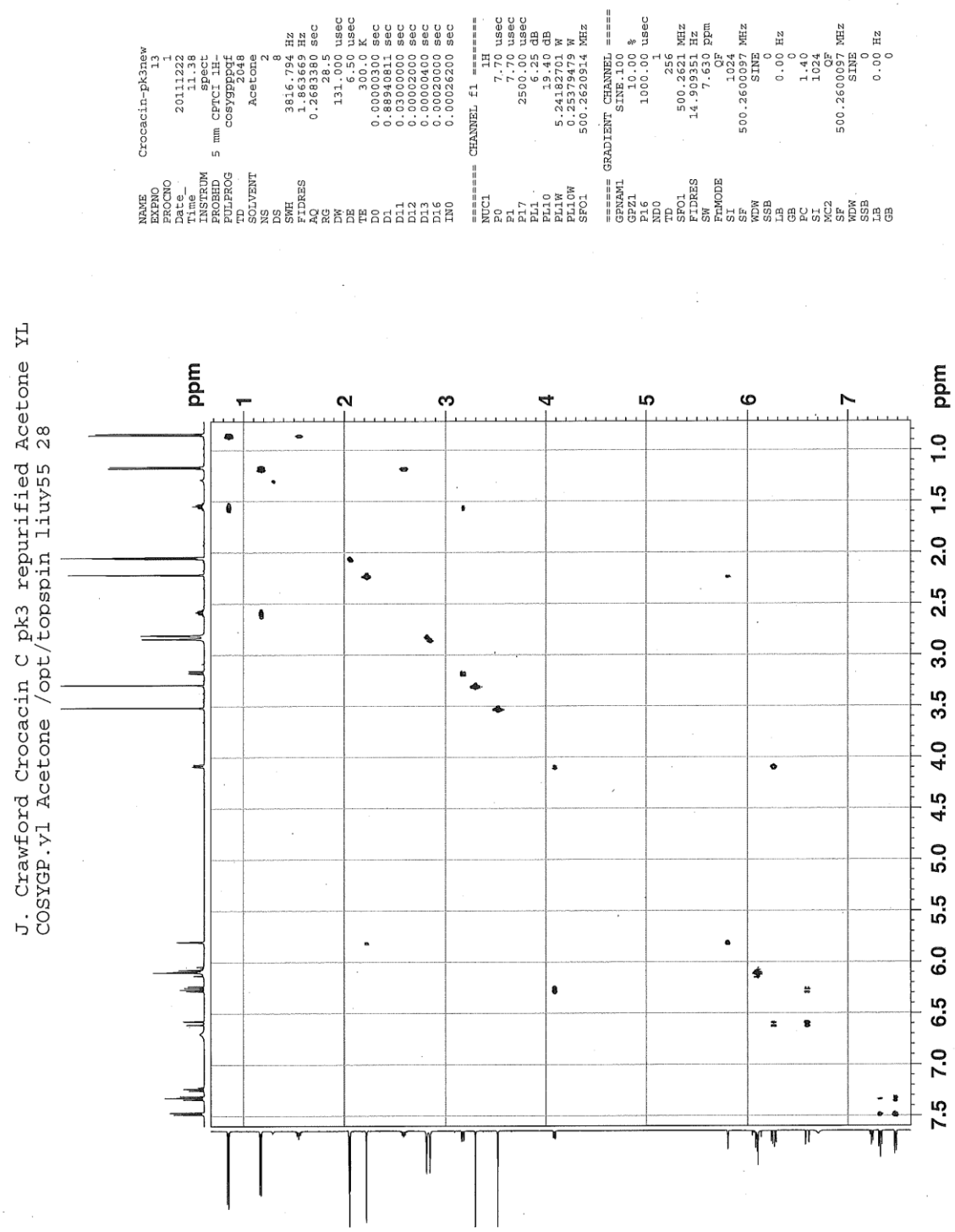
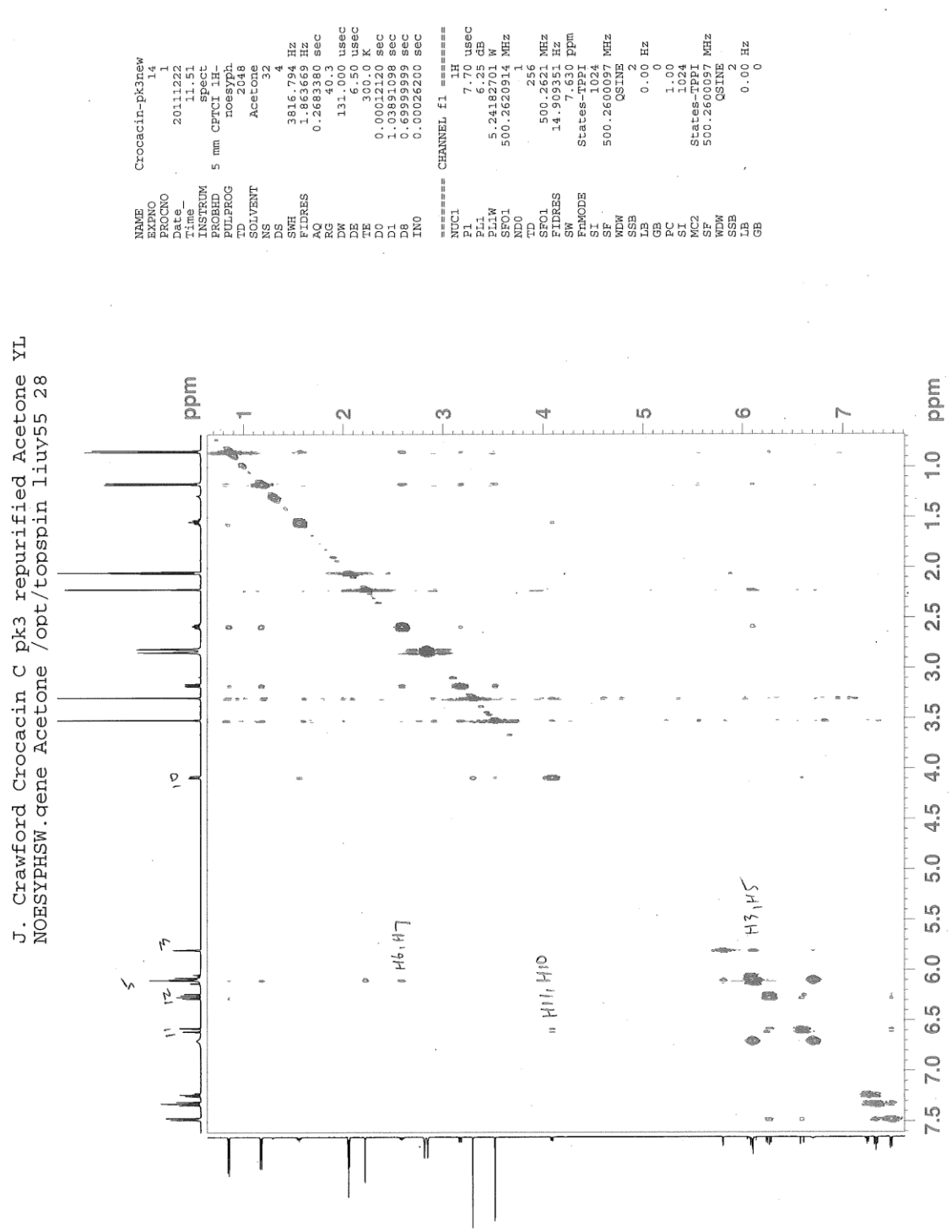
Acetone
ppm

Appendix 2: COSY, NOESY and HSQC NMR spectra of compound **3**

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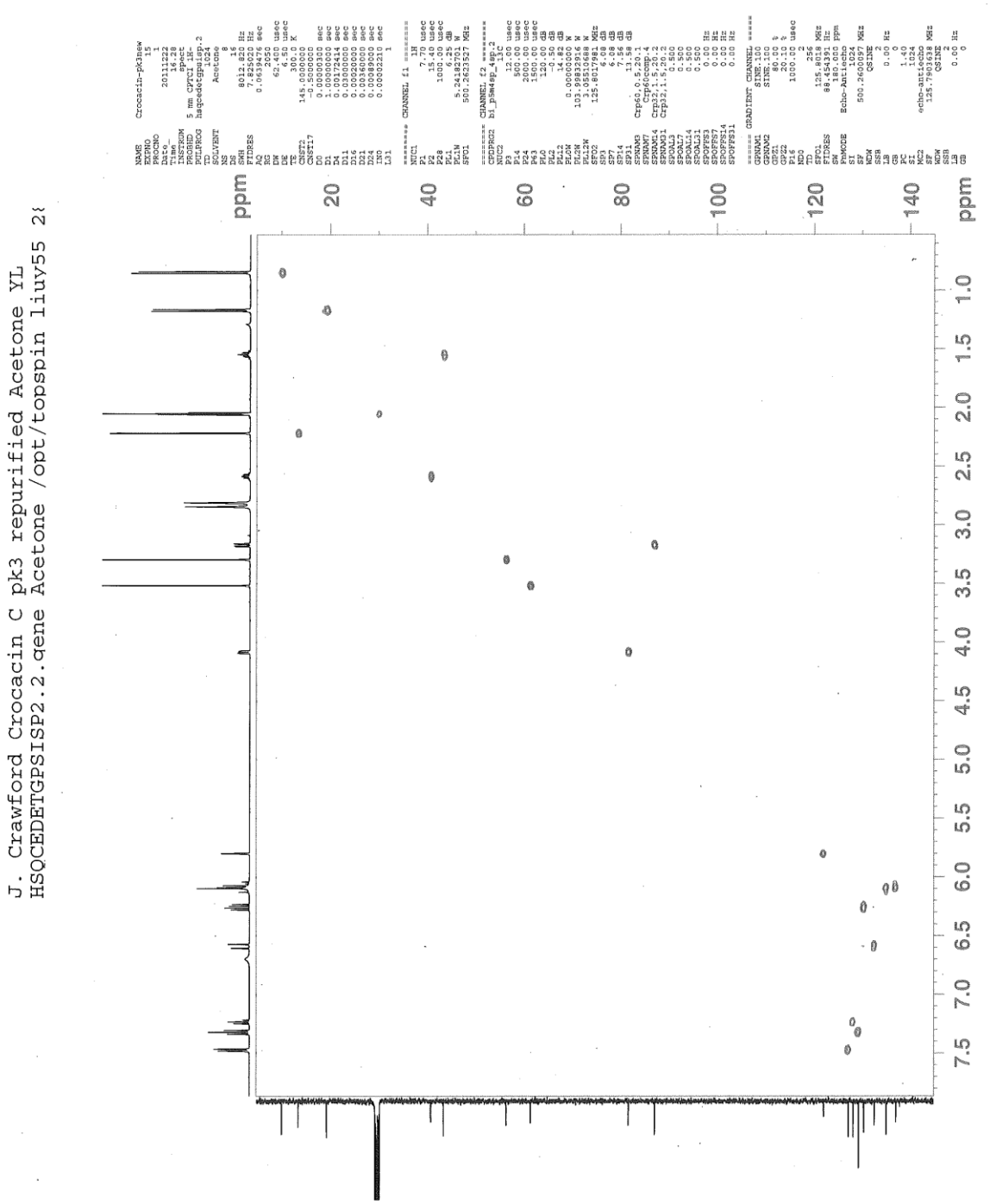
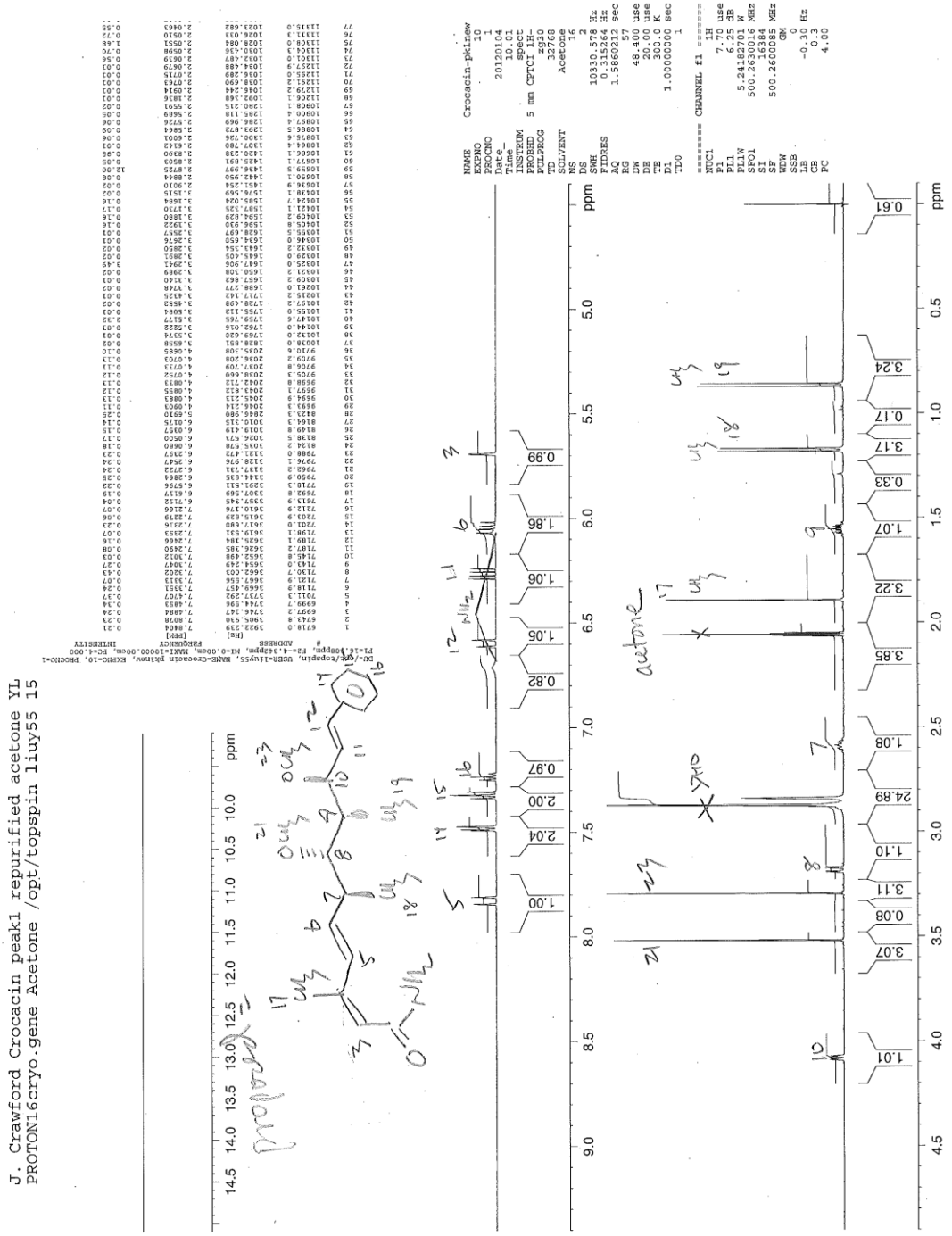
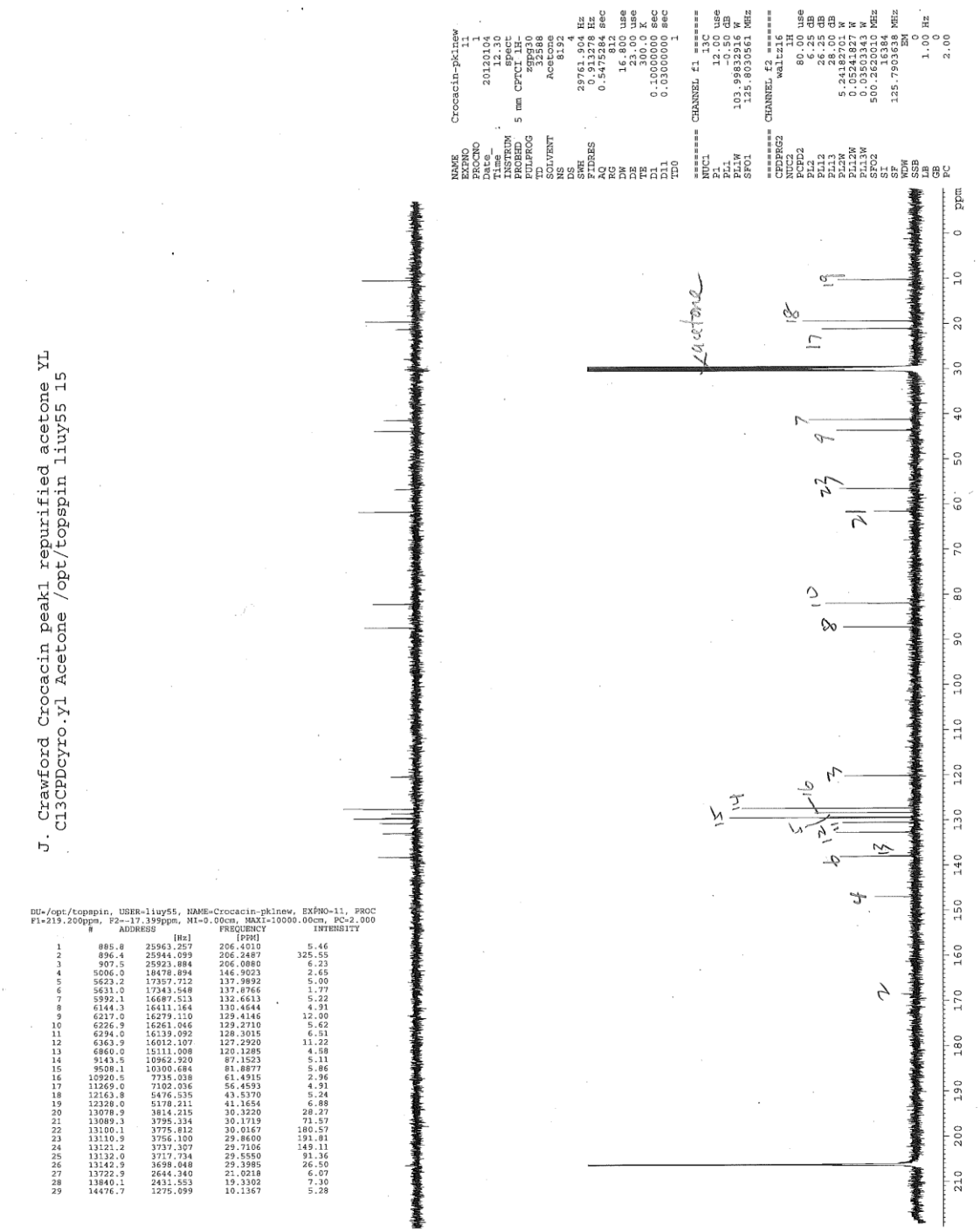
AQ 0.2683380 sec
RG 40.3
DW 131.000 usec
DE 6.50 usec
TE 300.0 K
D0 0.00012120 sec
D1 1.03891098 sec
D8 0.69999999 sec
IN0 0.00026200 sec
CHANNEL f1
NUC1 1H
P1 7.70 usec
PL1 6.25 dB
PL1W 5.24182701 W
SFO1 500.2620914 MHz
ND0 1
TD 256
SFO1 500.2621 MHz
FIDRES 14.909351 Hz
SW 7.630 ppm
FnMODE States-TPPI
SI 1024
SF 500.2600097 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0
PC 1.00
SI 1024
MC2 States-TPPI
SF 500.2600097 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0
ppm
ppm


J. Crawford Crocacin C pk3 repurified Acetone YL
HSQCEDETGPSISP2.2.qene Acetone /opt/topspin liuy55 2
ppm
ppm

Appendix 3: ^{1}H and ^{13}C NMR spectra of compound **235**



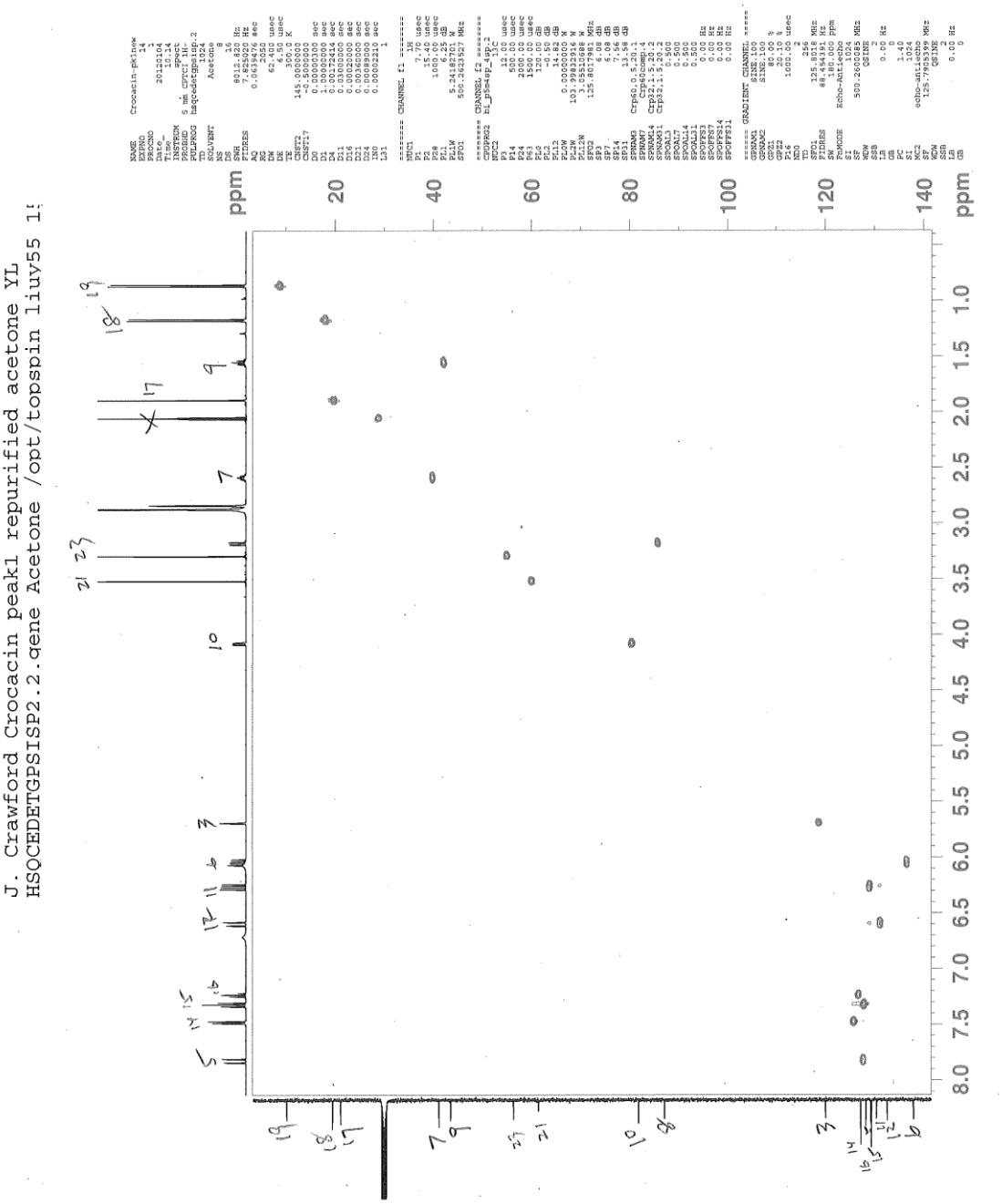


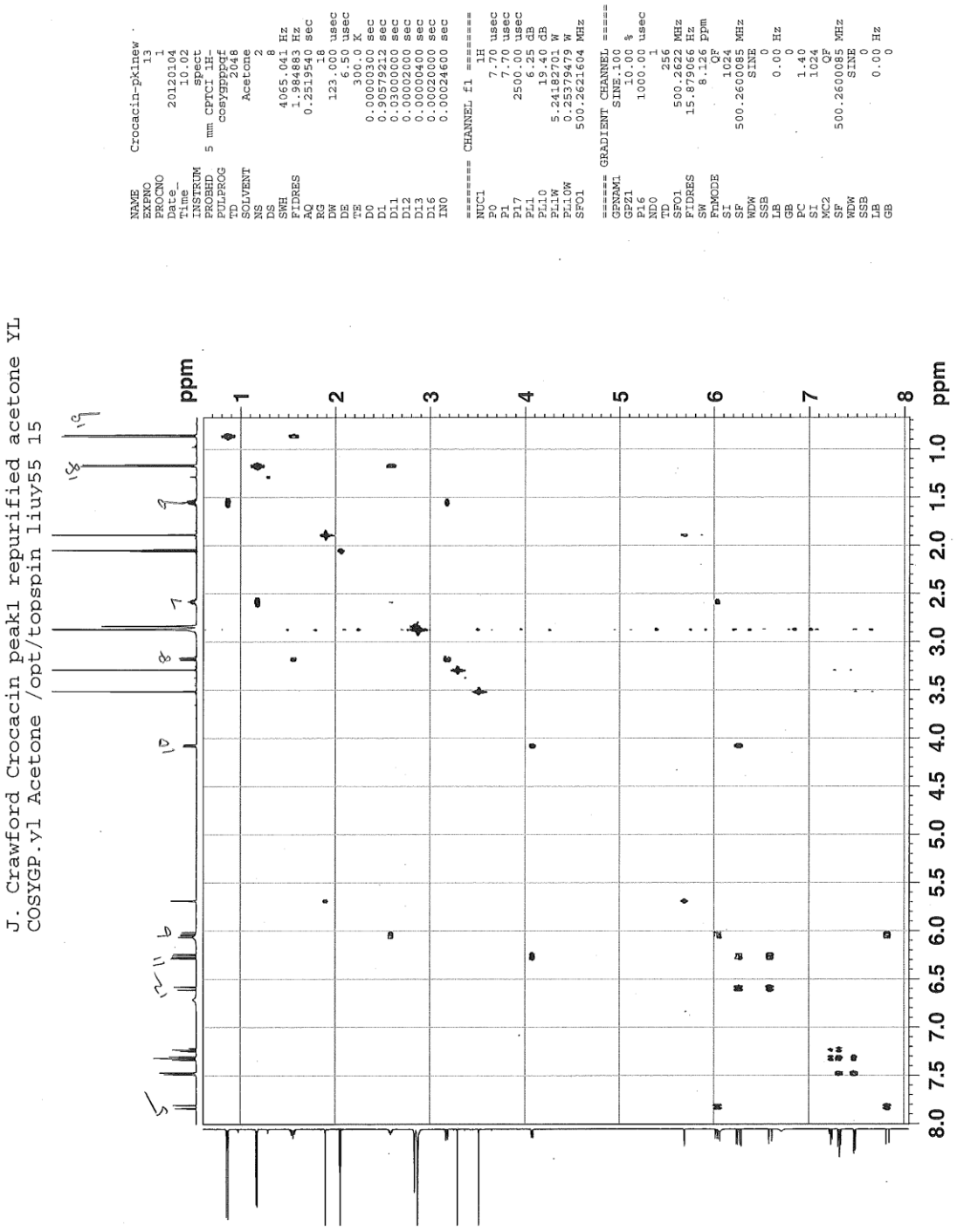
DU=/opt/topspin, USER=liuy55, NAME=Crocacin-pklnew, EXPNO=11, PROC
F1=219.200ppm, F2=-17.399ppm, MI=0.00cm, MAXI=10000.00cm, PC=2.000

#	ADDRESS	FREQUENCY [Hz]	FREQUENCY [PPM]	INTENSITY
1	885.8	25963.257	206.4010	5.46
2	896.4	25944.099	206.2487	325.55
3	907.5	25923.884	206.0880	6.23
4	5006.0	18478.894	146.9023	2.65
5	5623.2	17357.712	137.9892	5.00
6	5631.0	17343.548	137.8766	1.77
7	5992.1	16687.513	132.6613	5.22
8	6144.3	16411.164	130.4644	4.91
9	6217.0	16279.110	129.4146	12.00
10	6226.9	16261.046	129.2710	5.62
11	6294.0	16139.092	128.3015	6.51
12	6363.9	16012.107	127.2920	11.22
13	6860.0	15111.008	120.1285	4.58
14	9143.5	10962.920	87.1523	5.11
15	9508.1	10300.684	81.8877	5.86
16	10920.5	7735.038	61.4915	2.96
17	11269.0	7102.036	56.4593	4.91
18	12163.8	5476.535	43.5370	5.24
19	12328.0	5178.211	41.1654	6.88
20	13078.9	3814.215	30.3220	28.27
21	13089.3	3795.334	30.1719	71.57
22	13100.1	3775.812	30.0167	180.57
23	13110.9	3756.100	29.8600	191.81
24	13121.2	3737.307	29.7106	149.11
25	13132.0	3717.734	29.5550	91.36
26	13142.9	3698.048	29.3985	26.50
27	13722.9	2644.340	21.0218	6.07
28	13840.1	2431.553	19.3302	7.30
29	14476.7	1275.099	10.1367	5.28

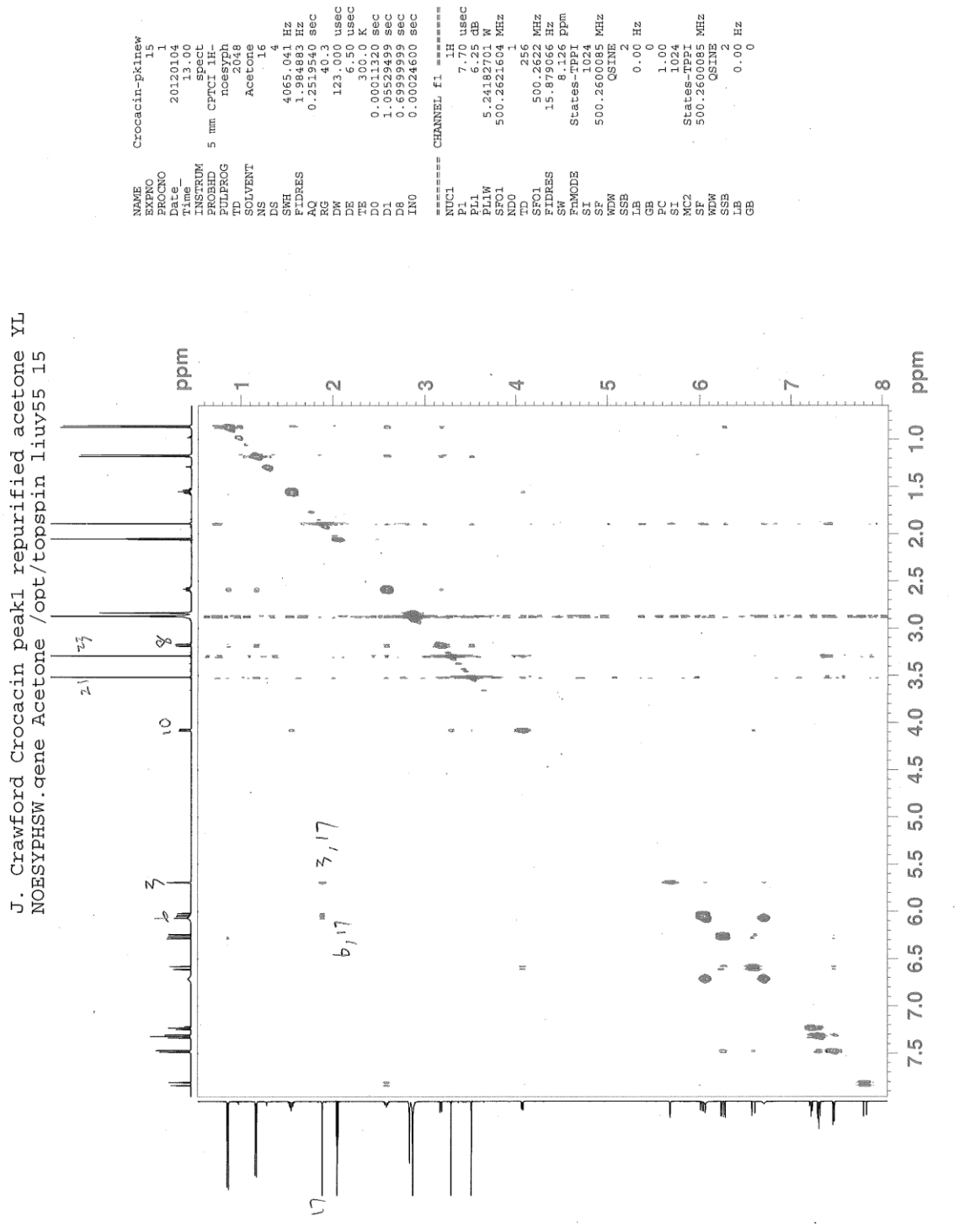
NAME	Crocacin-pklnew
EXPNO	11
PROCNO	1
Date_	20120104
Time	12.30
INSTRUM	spect
PROBHD	5 mm CPTCI 1H-
PULPROG	zgpg30
TD	32588
SOLVENT	Acetone
NS	8192
DS	4
SWH	29761.904 Hz
FIDRES	0.913278 Hz
AQ	0.5475284 sec
RG	812
DW	16.800 use
DE	23.00 use
TE	300.0 K
D1	0.10000000 sec
D11	0.03000000 sec
TD0	1
========	CHANNEL f1 ========
NUC1	13C
P1	12.50 use
PL1	0 dB
PL1W	103.99832916 W
SFO1	125.8030561 MHz
========	CHANNEL f2 ========
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 use
PL2	6.25 dB
PL12	26.25 dB
PL13	28.00 dB
PL2W	5.24182701 W
PL12W	0.05241827 W
PL13W	0.02503043 W
SFO2	500.2602013 MHz
SI	16384
SF	125.7903638 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	2.00

Appendix 4: HSQC, COSY and NOESY NMR spectra of compound **235**

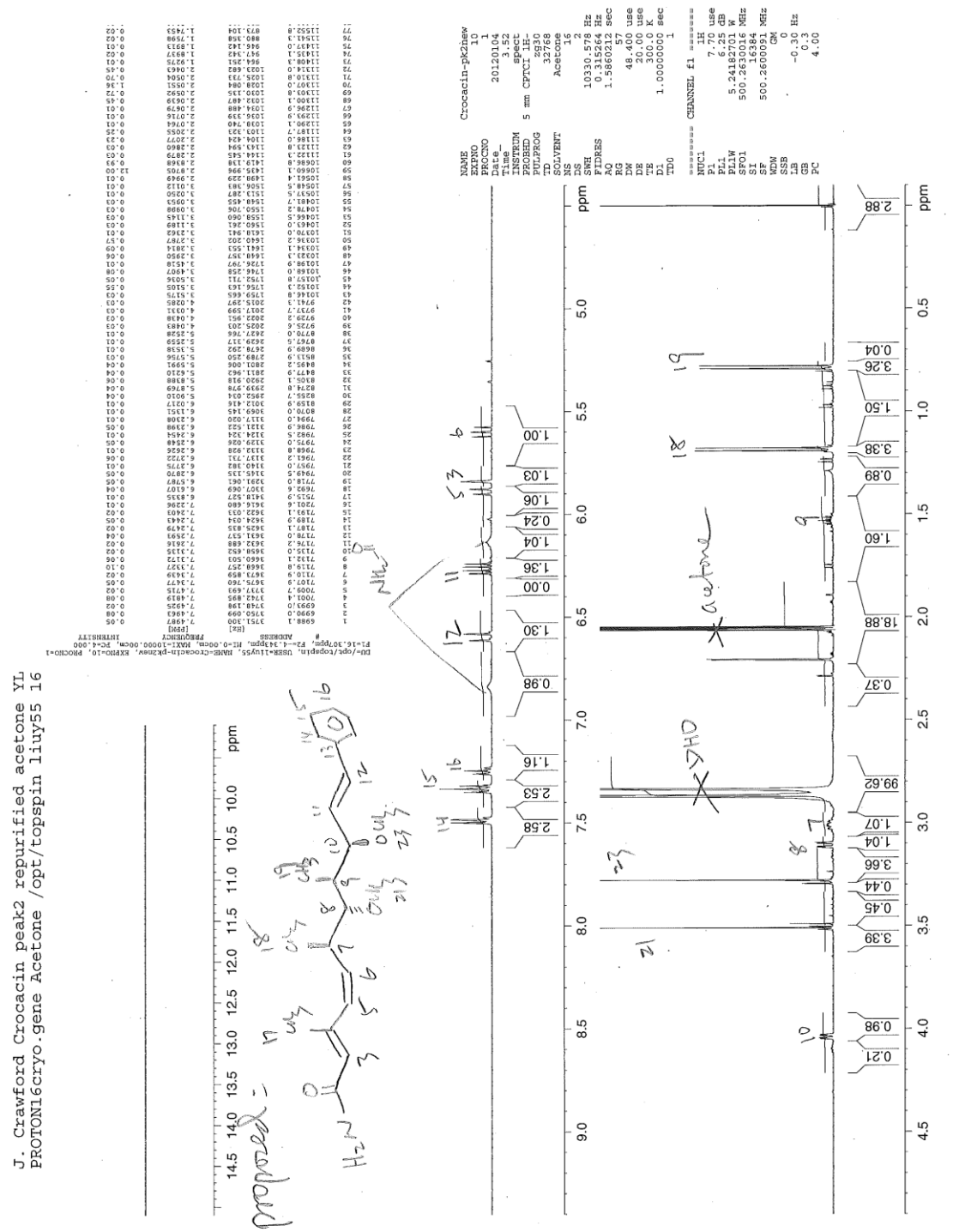


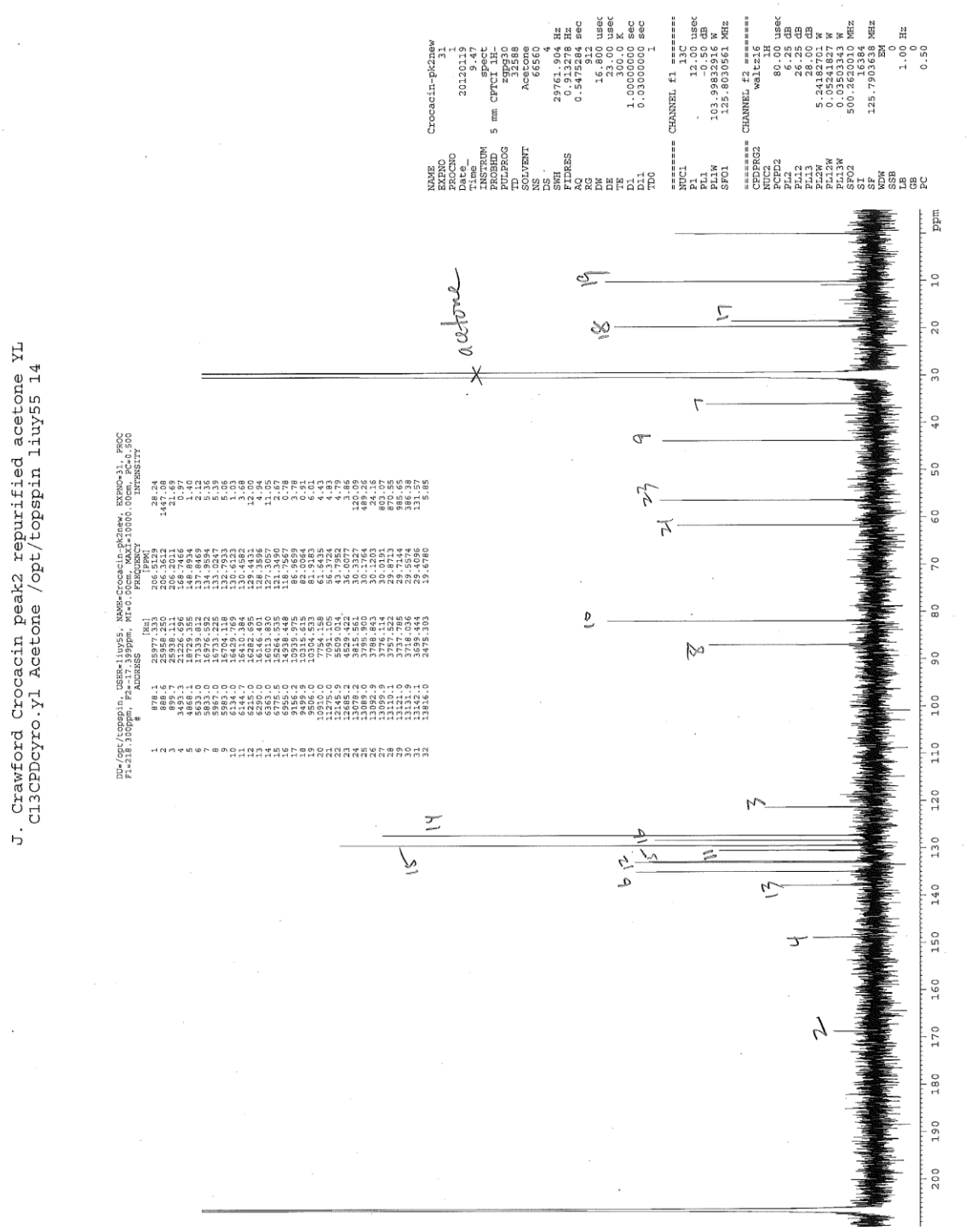


NAME	Crocacin-pk1new
EXPNO	13
PROCNO	1
Date_	20120104
Time	10.02
INSTRUM	spect
PROBHD	5 mm CPTCI 1H-
PULPROG	cosygppqf
TD	2048
SOLVENT	Acetone
NS	2
DS	8
SWH	4065.041 Hz
FIDRES	1.984883 Hz
AQ	0.2515540 sec
RG	18
DW	123.000 usec
DE	6.50 usec
TE	300.0 K
D0	0.00000300 sec
D1	0.90579212 sec
D11	0.03000000 sec
D12	0.00002000 sec
D13	0.00000400 sec
D16	0.00020000 sec
IN0	0.00024600 sec
========	CHANNEL f1 ========
NUC1	1H
P0	7.70 usec
P1	7.70 usec
P17	2500.00 usec
PL1	6.25 dB
PL10	19.40 dB
PL1W	5.24182701 W
PL10W	0.25379479 W
SFO1	500.2621604 MHz
======	GRADIENT CHANNEL =====
GPNAM1	SINE.100
GPZ1	10.00 %
P16	1000.00 usec
ND0	1
TD	256
SFO1	500.2622 MHz
FIDRES	15.879066 Hz
SW	8.126 ppm
FnMODE	QF
SI	1024
SF	500.2600085 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.40
SI	1024
MC2	QF
SF	500.2600085 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

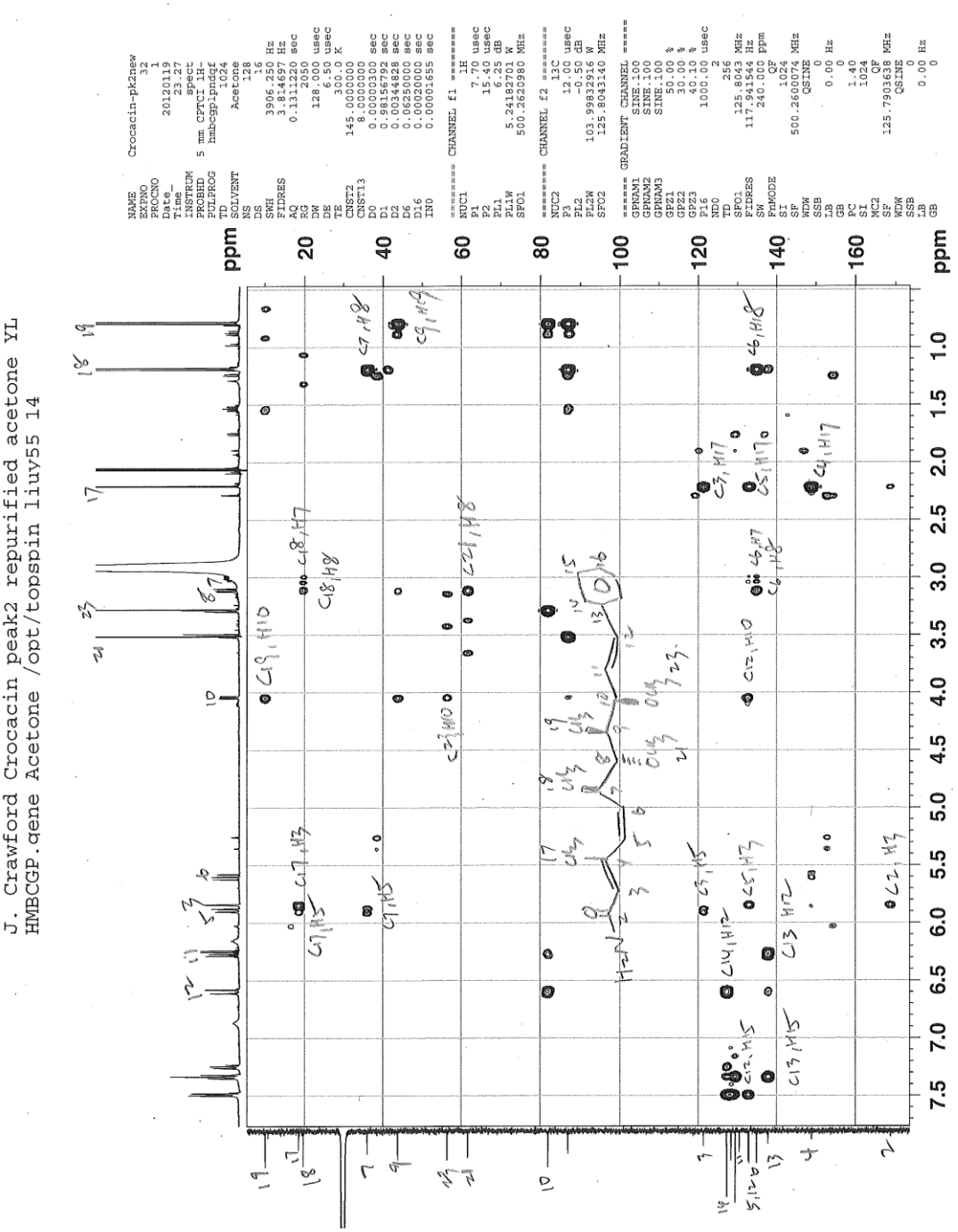

J. Crawford Crocacin peak1 repurified acetone YL
NOESYPHSW.qene Acetone /opt/topspin liuy55 15
NAME Crocacin-pk1new
EXPNO 15
PROCNO 1
Date_ 20120104
Time 13.00
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG noesyph
TD 2048
SOLVENT Acetone
NS 16
DS 4
SWH 4065.041 Hz
FIDRES 1.984883 Hz
AQ 0.2519540 sec
RG 40.3
DW 123.000 usec
DE 6.50 usec
TE 300.0 K
D0 0.00011320 sec
D1 1.05529499 sec
D8 0.69999999 sec
IN0 0.00024600 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.70 usec
PL1 6.25 dB
PL1W 5.24182701 W
SFO1 500.2621604 MHz
ND0 1
TD 256
SFO1 500.2622 MHz
FIDRES 15.879066 Hz
SW 8.126 ppm
FnMODE States-TPPI
SI 1024
SF 500.2600085 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0
PC 1.00
SI 1024
MC2 States-TPPI
SF 500.2600085 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0
ppm
1
2
3
4
5
6
7
8
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

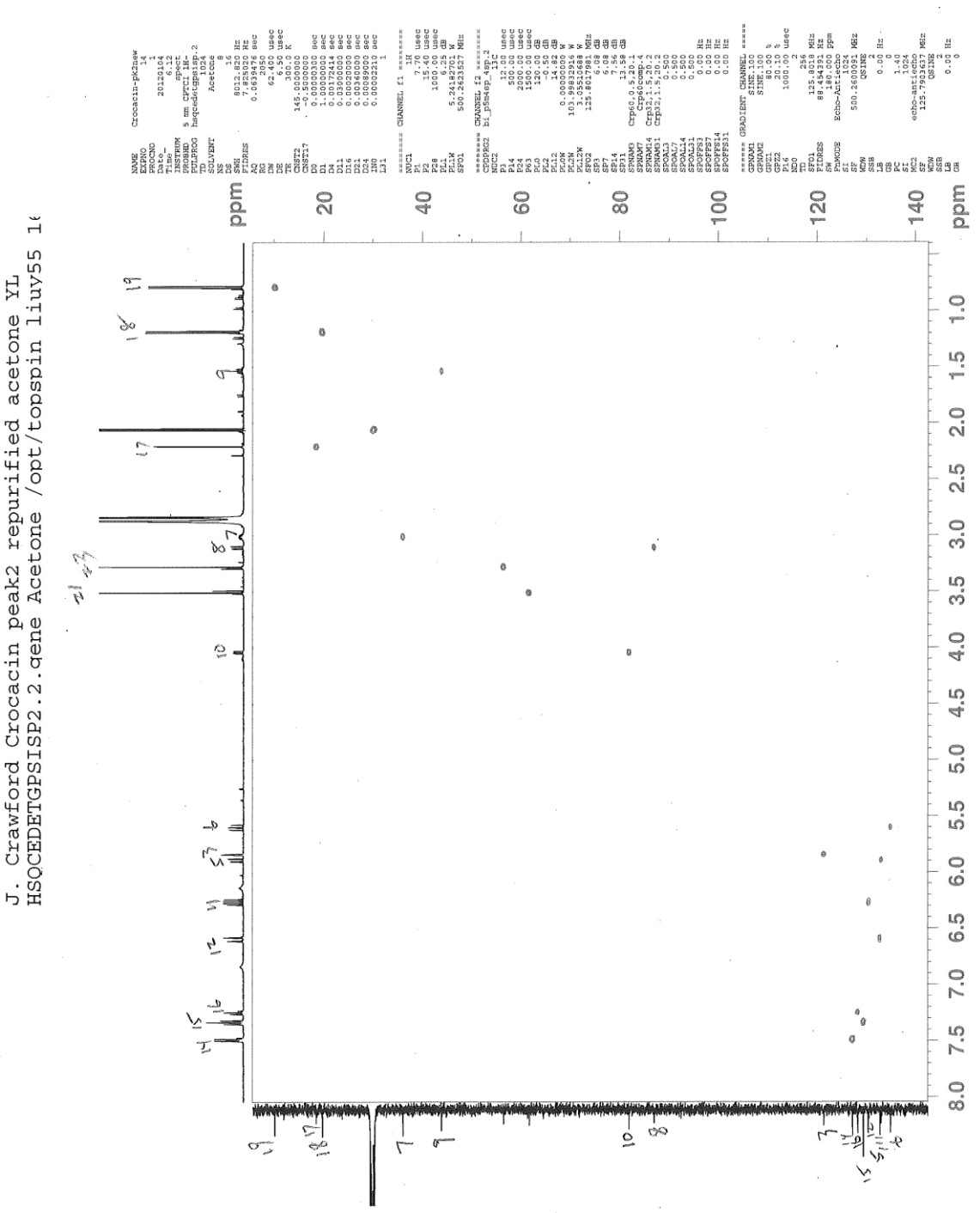
Appendix 5: ^{1}H and ^{13}C NMR spectra of compound **236**

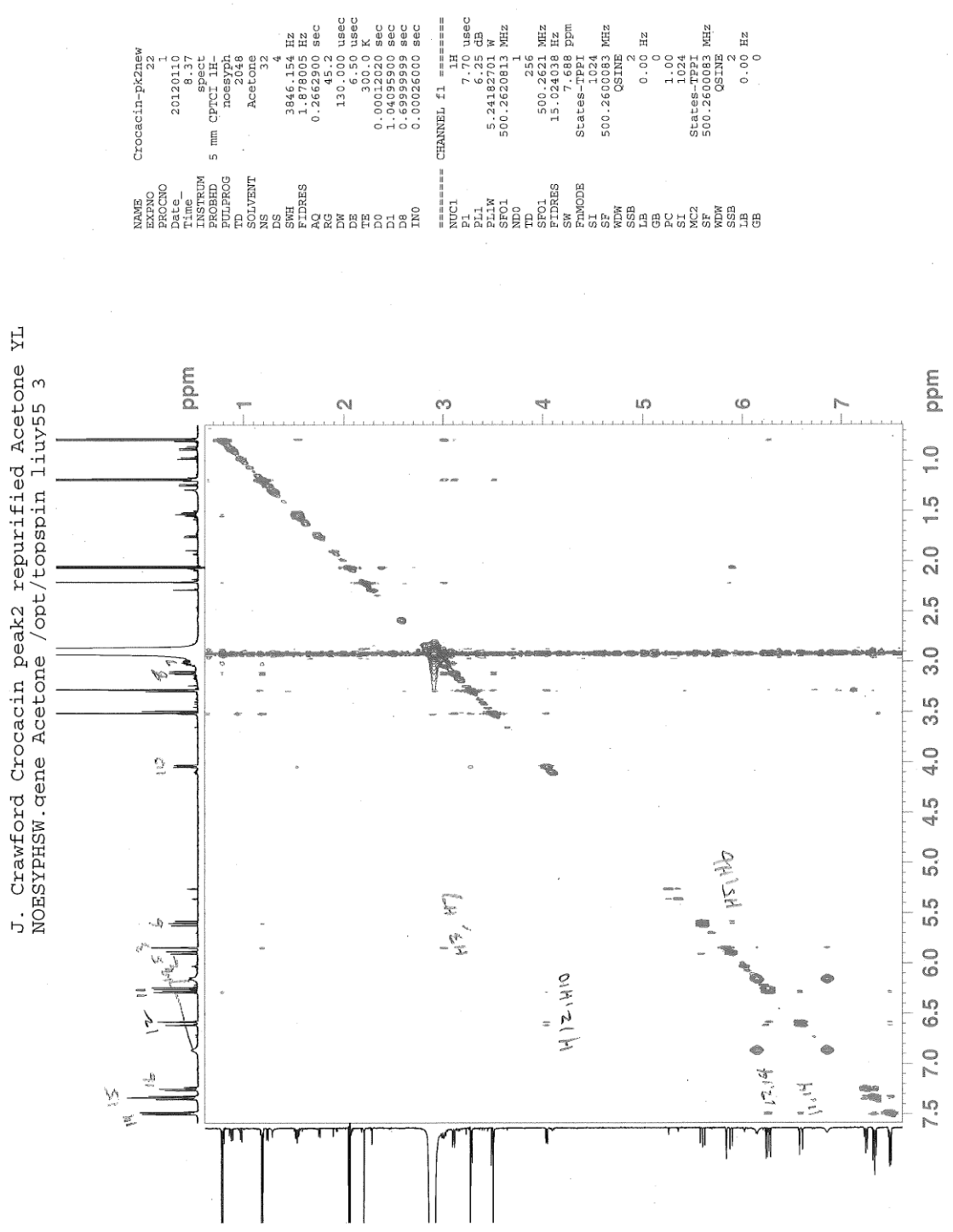



J. Crawford Crocacin peak2 repurified acetone YL
C13CPDcyro.yl Acetone /opt/topspin liuy55 14
acetone
ppm

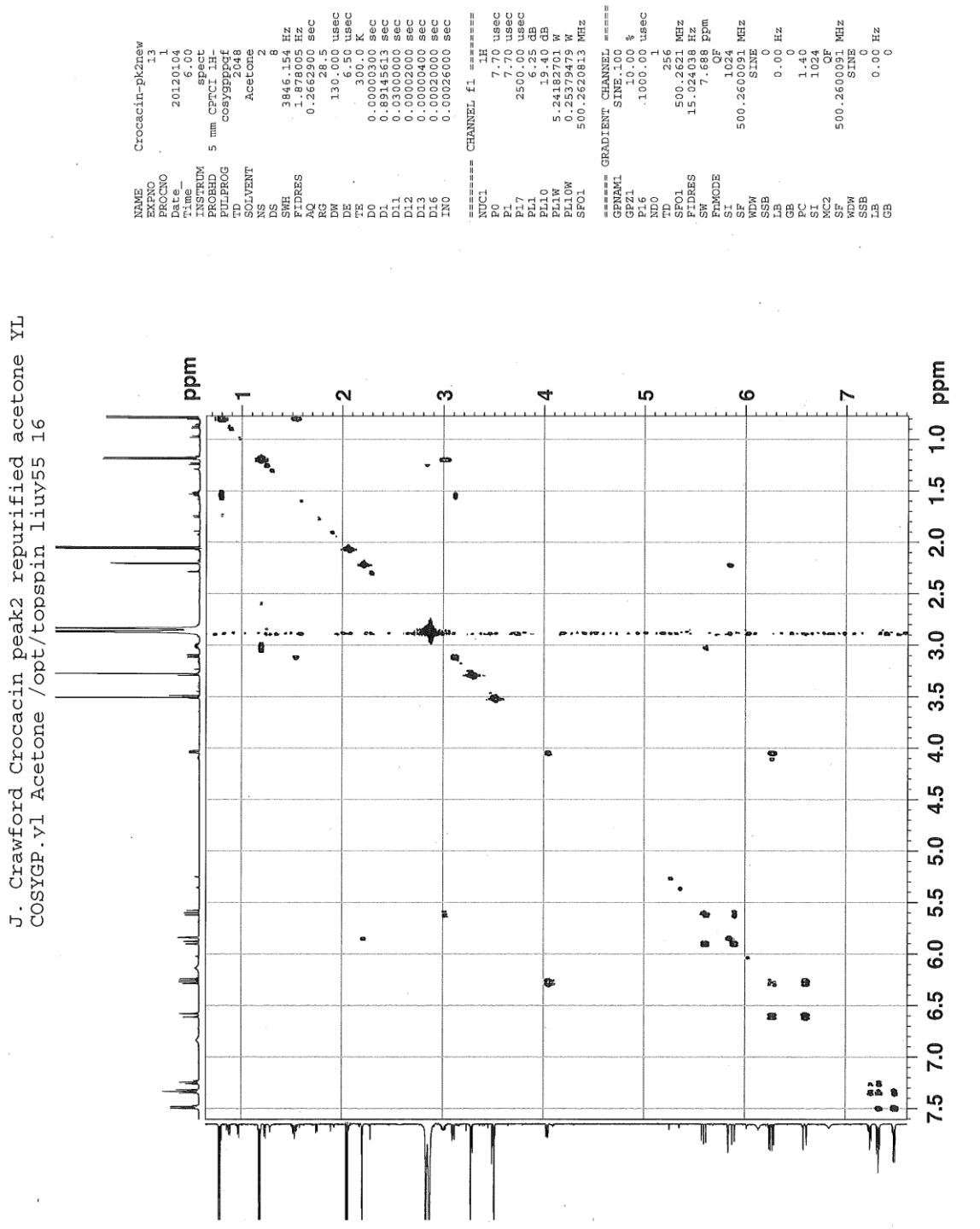
Appendix 6: HMBC, HSQC, NOESY and COESY NMR spectra of compound **236**



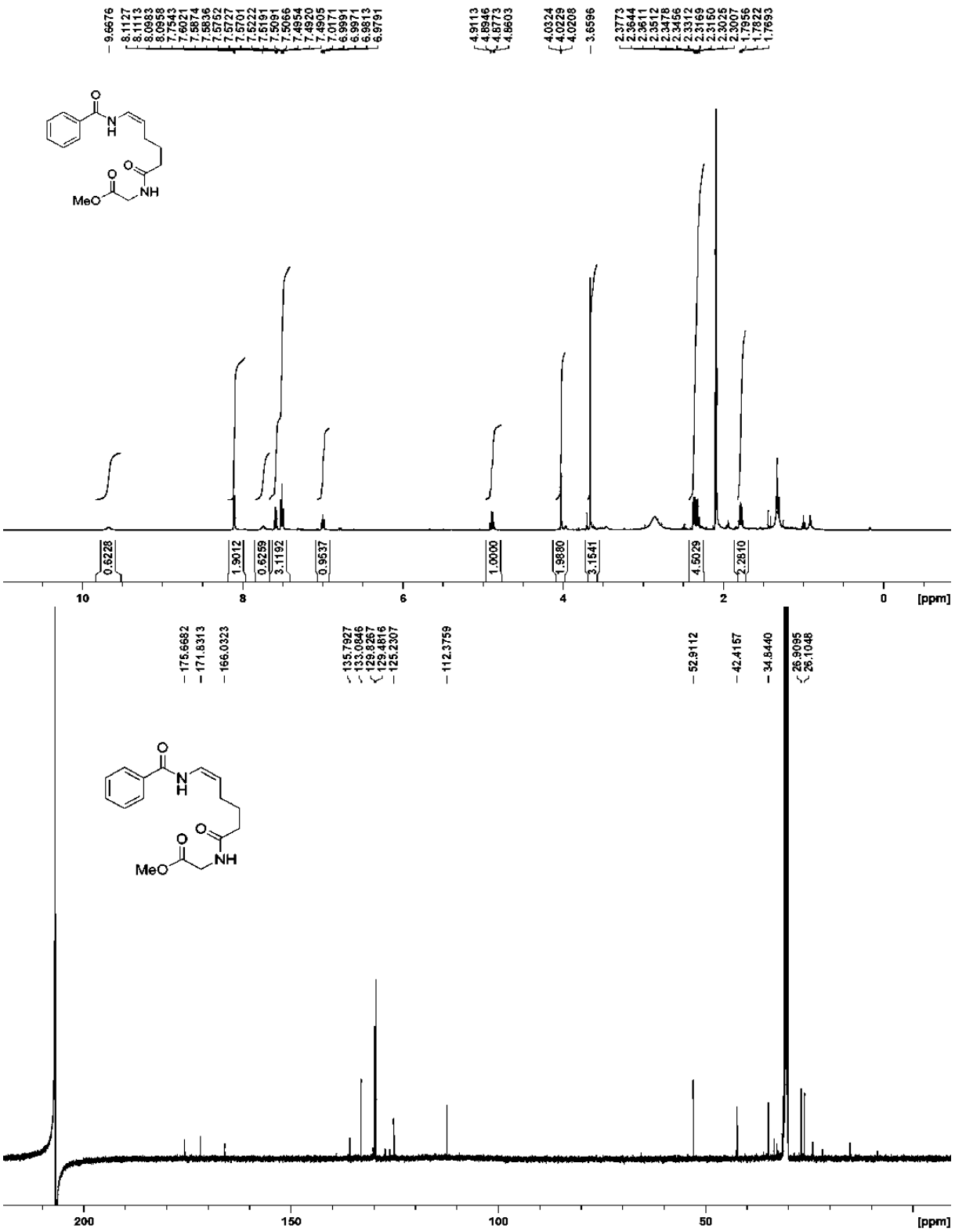

J. Crawford Crocacin peak2 repurified acetone YL
HSQCEDETGPSISP2.2.qene Acetone /opt/topspin liuy55 1(
ppm
20
40
60
80
100
120
140
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0



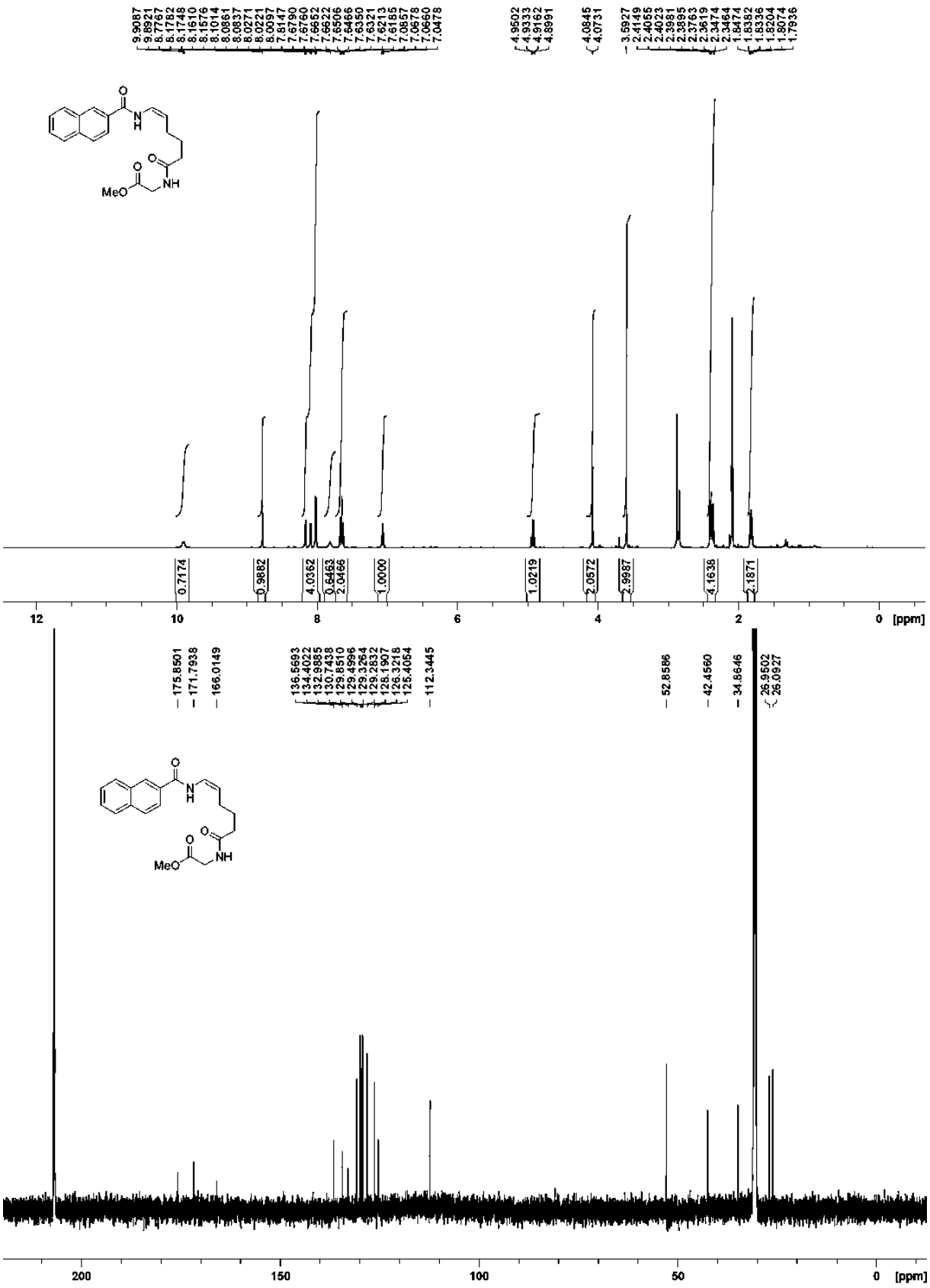

```
NAME            Crocacin-pK2new
EXPNO                        22
PROCNO                        1
Date_               20120110
Time_                     8.37
INSTRUM                   spect
PROBHD     5 mm CPTCI 1H-
PULPROG                 noesyph
TD                         2048
SOLVENT                 Acetone
NS                           32
DS                            4
SWH                  3846.154 Hz
FIDRES               1.878005 Hz
AQ                   0.2662900 sec
RG                         45.2
DW                    130.000 usec
DE                      6.50 usec
TE                     300.0 K
D0                   0.00012020 sec
D1                   1.04095900 sec
D8                   0.69999999 sec
IN0                  0.00026000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                       7.70 usec
PL1                      6.25 dB
PL1W                5.24182701 W
SFO1               500.2620813 MHz
ND0                           1
TD                          256
SFO1                 500.2621 MHz
FIDRES              15.024038 Hz
SW                       7.688 ppm
FnMODE              States-TPPI
SI                          1024
SF                 500.2600083 MHz
WDW                       QSINE
SSB                           2
LB                         0.00 Hz
GB                            0
PC                         1.00
SI                          1024
MC2                 States-TPPI
SF                 500.2600083 MHz
WDW                       QSINE
SSB                           2
LB                         0.00 Hz
GB                            0
```


J. Crawford Crocacin peak2 repurified acetone YL
COSYGP.yl Acetone /opt/topspin liuy55 16
ppm
1
2
3
4
5
6
7
ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
NAME Crocacin-pk2new
EXPNO 13
PROCNO 1
Date_ 20120104
Time 6.00
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG cosygppqf
TD 2048
SOLVENT Acetone
NS 2
DS 8
SWH 3846.154 Hz
FIDRES 1.878005 Hz
AQ 0.2662900 sec
RG 28.5
DW 130.000 usec
DE 6.50 usec
TE 300.0 K
D0 0.00000300 sec
D1 0.89145613 sec
D11 0.03000000 sec
D12 0.00002000 sec
D13 0.00000400 sec
D16 0.00020000 sec
IN0 0.00026000 sec
======== CHANNEL f1 ========
NUC1 1H
P0 7.70 usec
P1 7.70 usec
PL7 2500.00 usec
PL1 6.25 dB
PL10 19.40 dB
PL1W 5.24182701 W
PL10W 0.25379479 W
SFO1 500.2620813 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPZ1 10.00 %
P16 1000.00 usec
ND0 1
TD 256
SFO1 500.2621 MHz
FIDRES 15.024038 Hz
SW 7.688 ppm
FnMODE QF
SI 1024
SF 500.2600091 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0
PC 1.40
SI 1024
MC2 QF
SF 500.2600091 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0

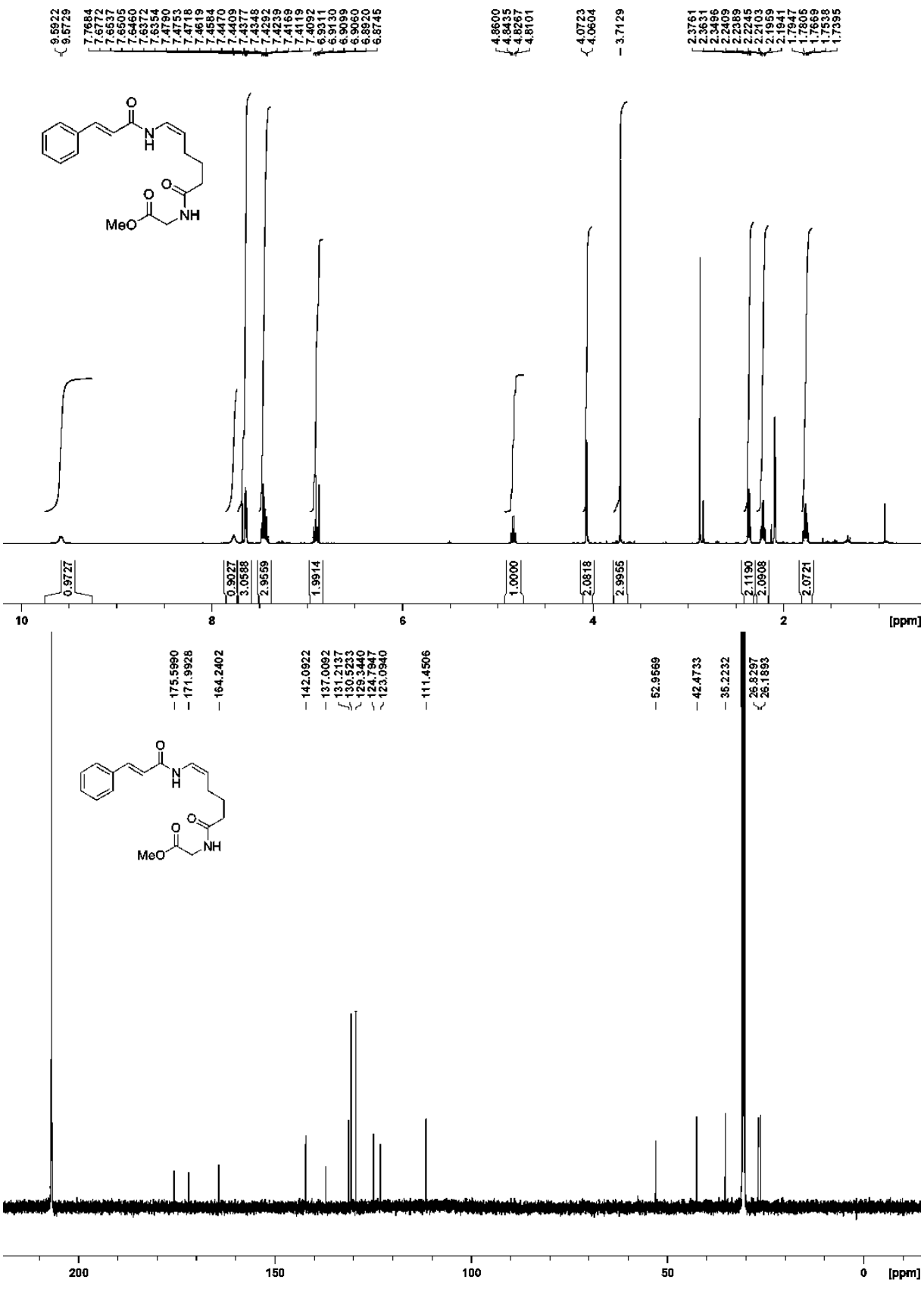
Appendix 7: ^{1}H and ^{13}C NMR spectra of compound **244**



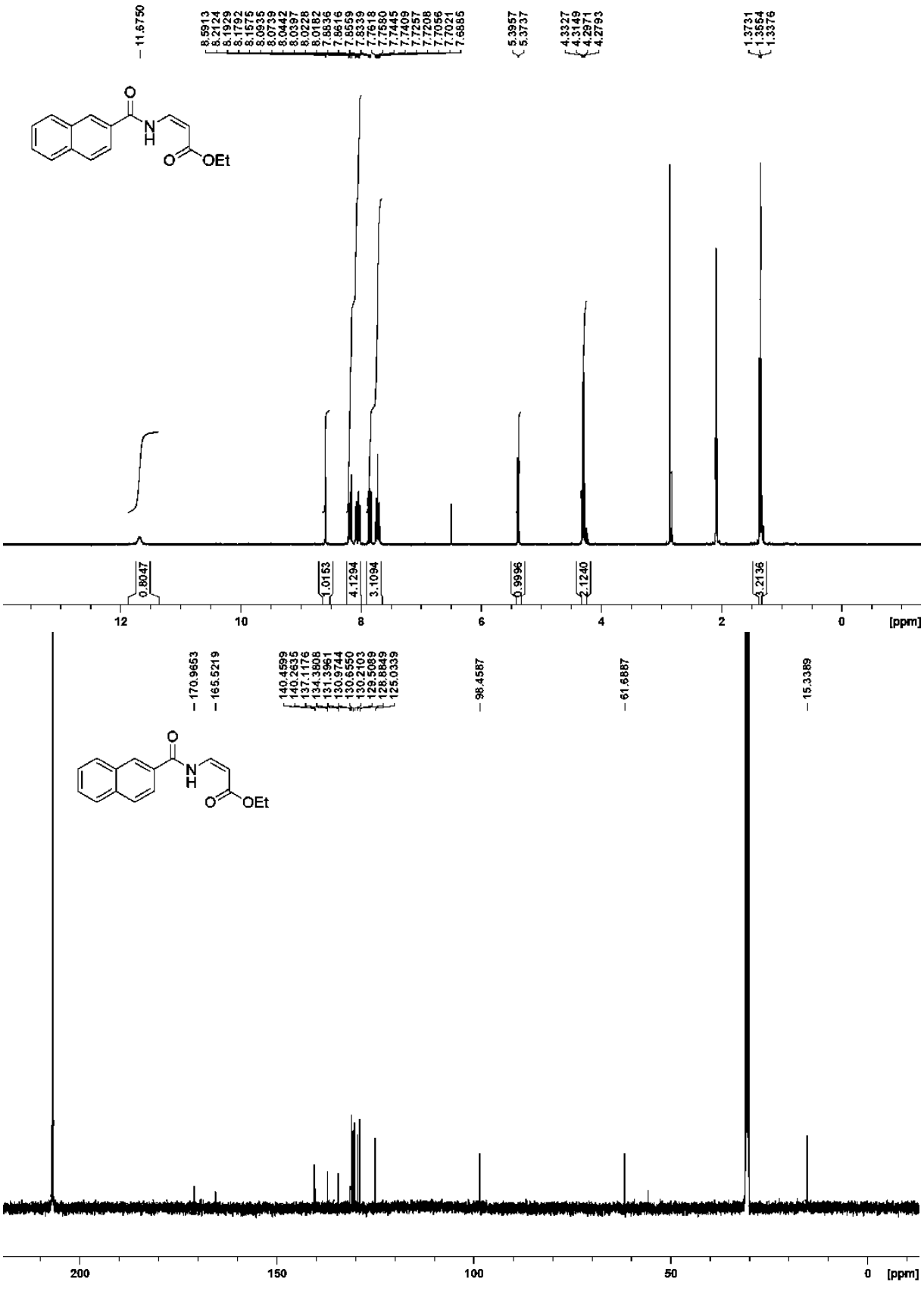
Appendix 8: ^{1}H and ^{13}C NMR spectra of compound **259**



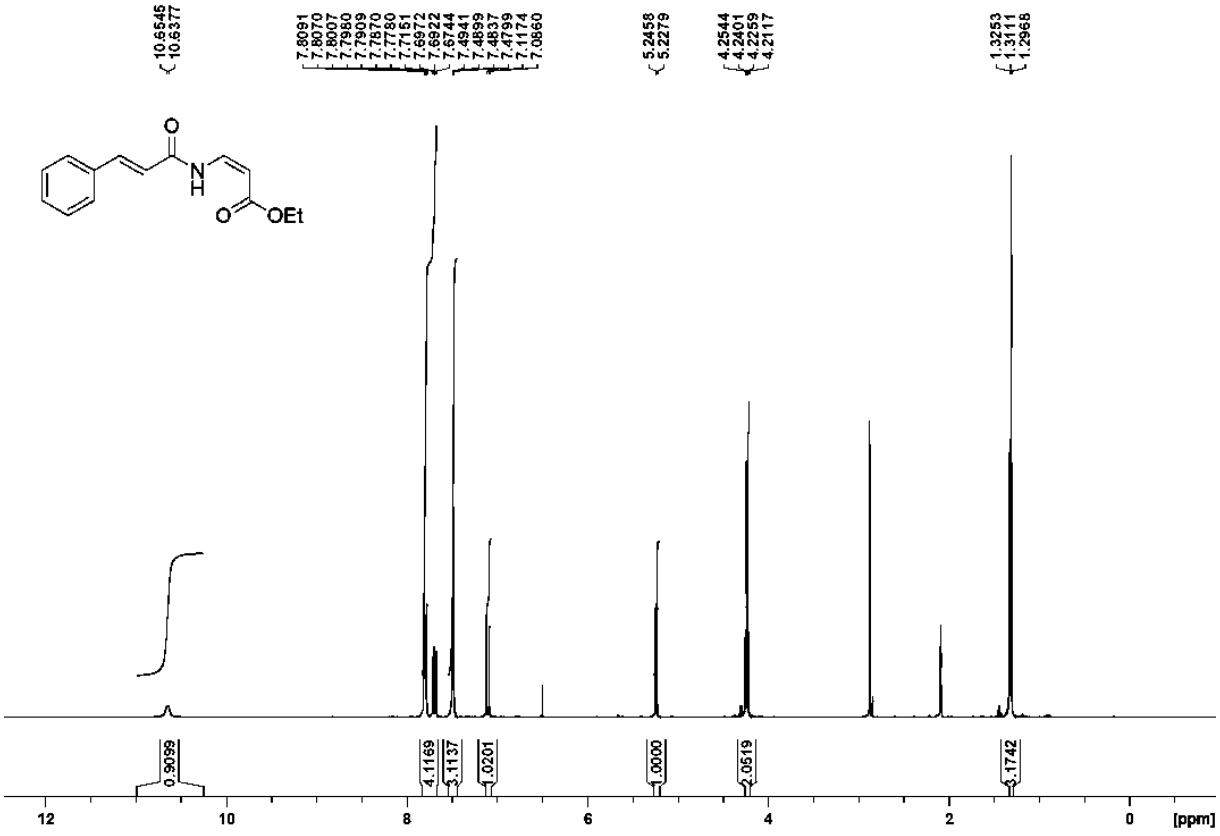
Appendix 9: ^{1}H and ^{13}C NMR spectra of compound **262**

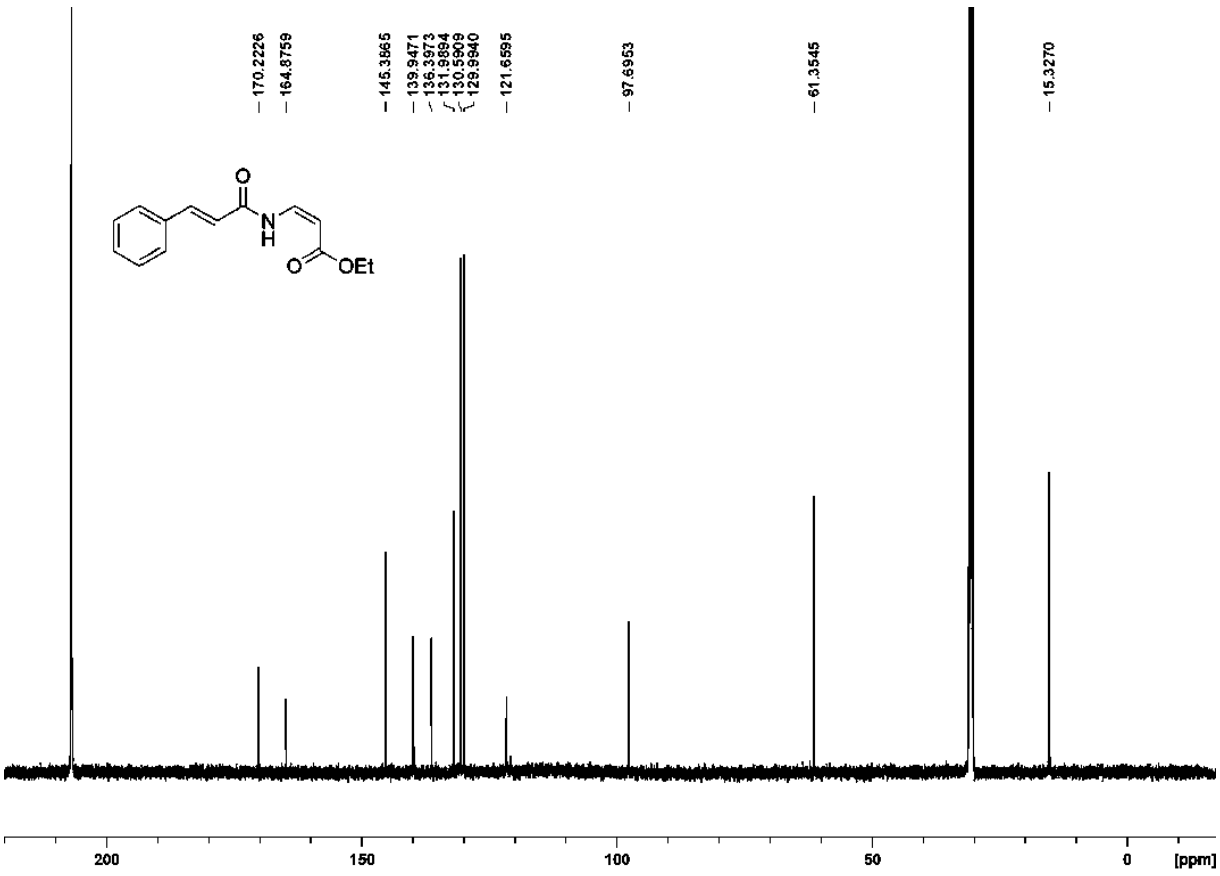


Appendix 10: ^{1}H and ^{13}C NMR spectra of compound **276**

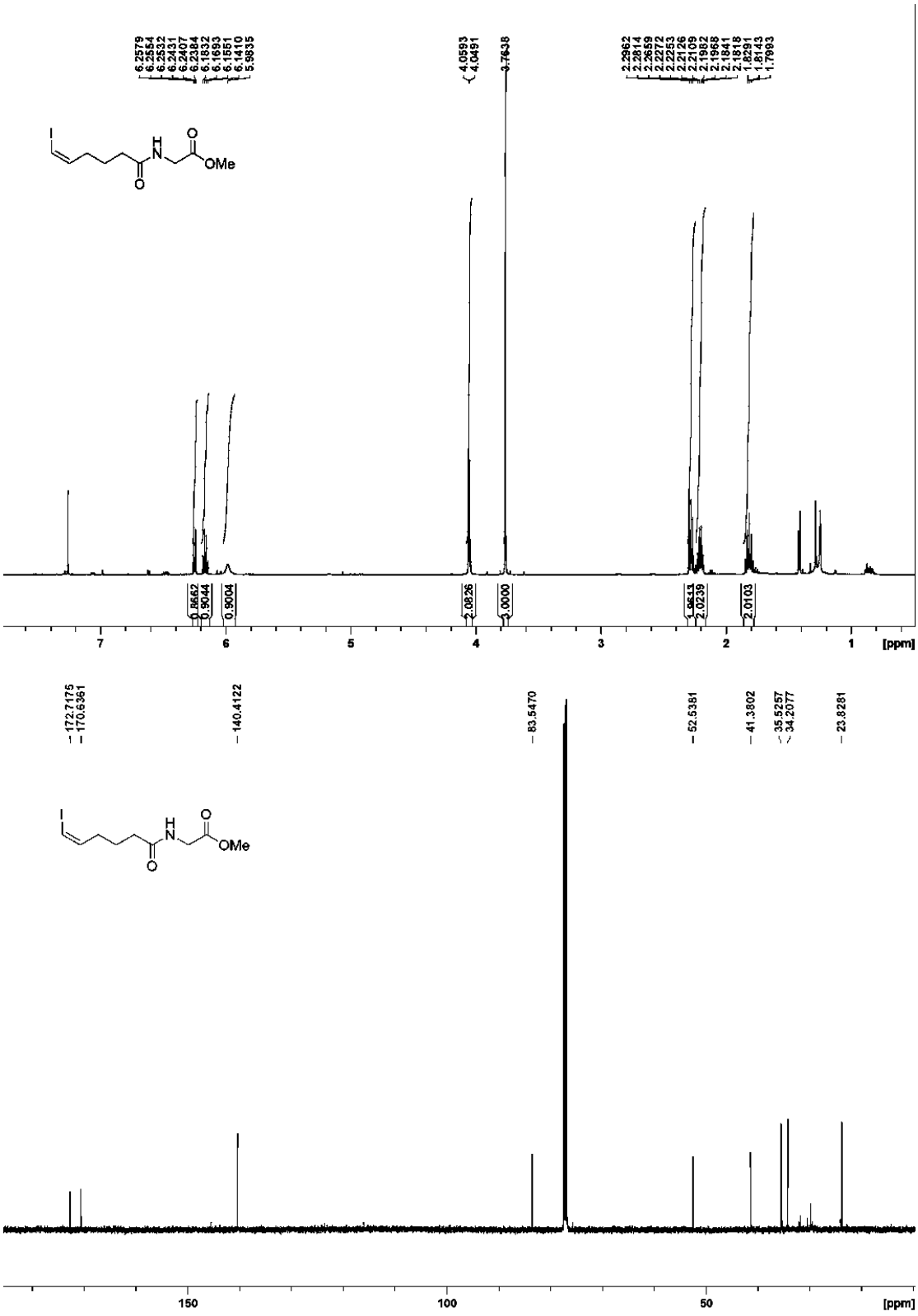


Appendix 11: ^{1}H and ^{13}C NMR spectra of compound **277**

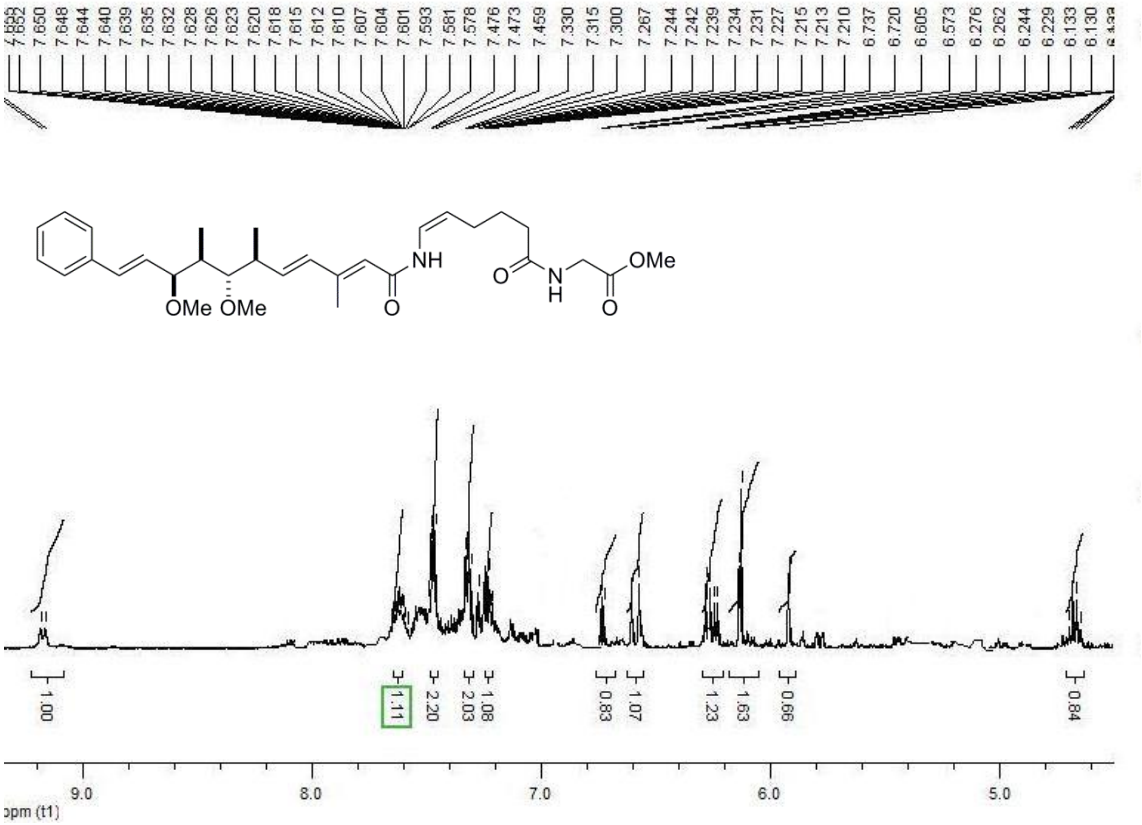


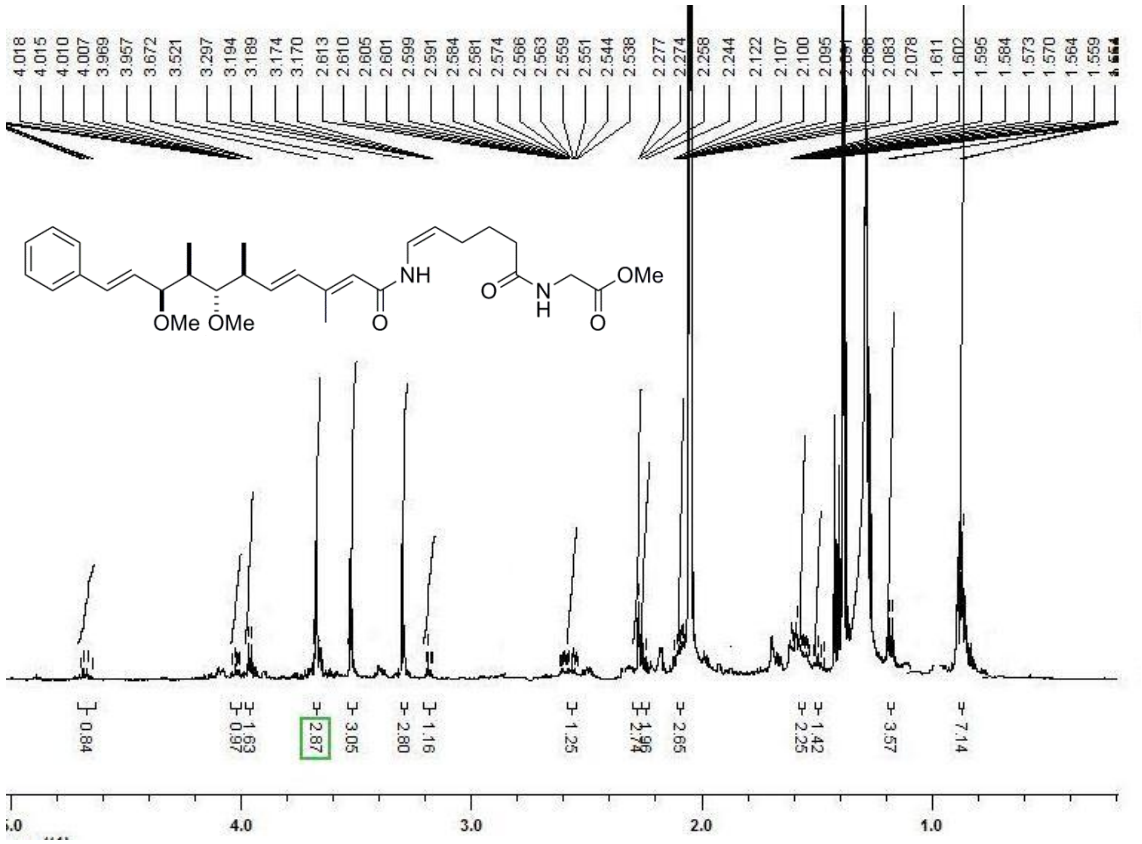


Appendix 12: ^{1}H and ^{13}C NMR spectra of compound **123**



Appendix 13: ^{1}H NMR spectrum (semicrude) of compound **4**





Appendix 14: LRMS and IR spectrum (semicrude) of compound **4**