Samroiymycins - an Interdisciplinary study of a novel anti-malarial drug

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**SAMROIYOTMYCINS – AN INTERDISCIPLINARY STUDY
OF A NOVEL ANTI-MALARIAL DRUG**

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**INTERDISCIPLINARY GRADUATE SCHOOL
PhD PROGRAMME IN HEALTHY SOCIETY @HEALTHTECH NTU**

2020

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**Interdisciplinary Graduate School
Research in Healthy Society @ HealthTech NTU**

**A thesis submitted to the Nanyang Technological University in
partial fulfilment of the requirement for the degree of
Doctor of Philosophy**

2020

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Abbreviations

BINAP – 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

Boc – *tert*-Butyloxycarbonyl

CBS – Corey-Bakshi-Shibata catalyst

CSA – Camphorsulphonic acid

DBU – 1,8-Diazabicyclo(5.4.0)undec-7-ene

DCE – 1, 2-Dichloroethane

DCM – Dichloromethane

DIAD – Diisopropylazodicarboxylate

DIOP – *O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

DMAP – 4-(Dimethylamino)pyridine

DMF – Dimethylformamide

DIBAL or DIBAL-H – Diisobutylaluminium hydride

DPPB – 1,4-Bis(diphenylphosphino)butane

HWE – Horner-Wadsworth-Emmons

IBX – 2-iodoxybenzoic acid

IC₅₀ – Half maximal inhibitory concentration

ID₅₀ – Infectious dose, 50%

IPrAuCl – Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I)

LUMO – Lowest Unoccupied Molecular Orbital

NMR – Nuclear Magnetic Resonance

NOESY – Nuclear Overhauser effect Spectroscopy

NMO – 4-Methylmorpholine *N*-oxide solution

OTs – Tosylate

PMB – 4-methoxybenzyl

p-TSA – *para*-toluenesulfonic acid monohydrate

PPTS – Pyridinium *para*-toluenesulfonate

RBF – Round bottomed flask

SEGPLHOS - 4,4'-Bi-1,3-benzodioxole-5,5'-diylbis(diphenylphosphane)

TBAB – Tetra (*n*-butyl) ammonium bromide

TBAF – Tetra (*n*-butyl) ammonium fluoride

TBAI – Tetra (*n*-butyl) ammonium iodide

TBS – *tert*-Butyldimethylsilyl

THF – Tetrahydrofuran

THP – Tetrahydropyranyl

TosMIC – *p*-toluenesulfonylmethyl isocyanide

TLC – Thin Layer Chromatography

Abstract

Samroiyotmycins A and B are closely related complex dimeric macrocycles containing 2-unsubstituted oxazole units. Furthermore, biological studies showed that they had anti-malarial activity and were active against a multi-drug resistant strain of *Plasmodium falciparum*.¹ Hence, they are lead compounds for further investigation to both improve activity and determine if their activity towards the parasite is novel. To our knowledge, there has been no reports of both molecules synthesised in the literature since their isolation and synthesis is the only way to obtain sufficient samples for further studies given its scarcity from natural sources. Herein, a synthetic route to the Samroiyotmycins was devised, successfully furnishing the 2-unsubstituted oxazole moiety using a novel and highly regioselective gold-catalysed 5-*exo-dig* cyclisation of alkynamides.

Chapter 1

INTRODUCTION

The study of natural products encompasses the discovery and elucidation of potential natural products from biological sources. It also involves the development of a novel synthetic route towards a viable target natural molecule and the subsequent implementation of assays to study its mechanism of biological activity towards certain diseases. It has been estimated that more than 50% of existing drugs of all types were inspired by natural products.³ Furthermore, it is through the discovery of new natural products that provide structures which reveal new molecular targets in the parasites. Many new natural product discoveries therefore probe further research and studies by medicinal chemists. However, these natural molecules are available from nature and only in small amounts from where they are isolated. Chemical synthesis then becomes the only means to access useful quantities of these important materials for further biological assays. Being an integral field of scientific research, natural product chemistry provides a valuable insight in the discovery of biological properties based on the myriad of structures and functionalities present among naturally occurring compounds.

However, it is known that the isolation of new natural compounds can often prove to be laborious due to the limited biological resources available from nature and the vast amounts of organic solvent needed during the extraction process. The additional effort of needing to chemically isolate and identify novel structures from known compounds in the mixture further increases the labour. Thus, it is not just the construction of natural products, but also their analogues that effectually provide opportunities to discover unprecedented chemistry during the synthetic process, thus widening the scope of improved and new chemical methodologies for chemists. By modifying certain key functional groups on a natural compound, we allow the discovery of natural product analogues and studying their biological attributes could

provide chemists with knowledge on how varying molecular functionalities could have an impact on their biological activity.⁴ Increasingly, total synthetic chemists over the years have been approaching diverted-total synthesis, which was first introduced by Danishefsky.⁵ This approach involves preparing structurally diverse natural product analogues either from a completely different scheme or from late-stage intermediates. In many total organic syntheses, late-stage intermediates serve as templates for integrating structural variation to generate a series of analogues.^{6, 7} Such a strategy is also how different strains of a certain natural product are prepared from a common moiety, also known as collective or unified synthesis.^{8, 9} With the ever-changing and accelerating field of biology-oriented synthesis¹⁰ in interdisciplinary research, it is imminent that diverted total synthesis will become more prominent in the future of natural product discovery.

This chapter of the thesis probes the investigation into an efficient synthetic pathway towards the synthesis of Samroiyotmycins A and B, both strains of a recently isolated natural compound¹ that exhibits anti-malarial activity towards the multi-drug resistant strain of malaria *Plasmodium falciparum* K1, as well as molecular biology studies towards the drug's efficiency in targeting the strain. The synthesis of an analogue of Samroiyotmycin A based on a functional group variant is also described in the subsequent chapter.

1.1. Significance of Malaria & Anti-malarial Natural Products

The World Health Organisation has reported 200 million cases of Malaria and over 500,000 deaths in 2013 itself². Up until today, Malaria remains a major threat to human health in certain parts of the world, particularly in developing countries. With five species of the *Plasmodium* parasite responsible for the disease, the *Plasmodium falciparum* parasite is the most pervasive strain in Sub-Saharan Africa and *Plasmodium vivax* being the most ubiquitous in non-African countries. To date, Africa has had the biggest proportion of Malaria cases and deaths of any continent at approximately 90%.

Even though *Plasmodium falciparum* malaria infections are symptomatic, it is noteworthy that transmission intensity is highly heterogeneous over short geographic distances and that low transmission areas tend to contain small foci of higher transmission intensity which serve as sources of infection¹¹. Delving on the differences in aspects of the *Plasmodium Falciparum* strain from the other three human malarias, the need to uncover more efficient and potent anti-malarial drugs is accentuated. The key differences are that gametocyte formation is delayed with respect to the peak growth of asexual stages and that mature gametocytes in the blood are resistant to most of the anti-malarial drugs, which affect the asexual stages¹². This adds to the concern as the developing sexual stages of *Plasmodium Falciparum*, are also the stages responsible for transmitting human malaria. The developing sexual stages remain contained in the microvasculature for roughly 10 days before maturing into distinct male and female gametocytes which are responsible for parasitic transmission and are also largely resilient to most anti-malarial drugs. Long duration of infections and partially effective drugs could further lead to an increase in the growth of gametocytes in falciparum malaria¹³. This in turn, leads to an increase in the prevalence of malaria since peak transmissibility correlates roughly with peak gametocytaemia¹⁴.

Isolated from the cinchona tree bark in 1820, Quinine, being the first and most effective anti-malarial drug, has had its long run as a front-line treatment for severe cases of malaria, up until 2006. Drug resistance of malaria to quinine was first reported in the 1980s and as of 2006, rendering it not as an option of first choice, but a treatment option only when artemisinins were not available. There were other well-established derivatives of quinine such as Chloroquine and Mefloquine (Figure 1), discovered between the period of 1920 and 1980s, but were later found to be inefficient due to the development of resistant parasitic strains and occurrence of adverse side effects¹⁵.

Figure 1. Structures of Quinine and some of its derivatives

Artemisinin was first isolated in 1971 from the plant *Artemisia annua* and found to have powerful combative properties against Malaria¹⁶ (Figure 2). The most accepted theory for its mechanism of action is that the molecule is activated by haem to generate free radicals which subsequently destroys the proteins required for parasite growth¹⁷. For several decades since, Artemisinin and its derived analogues have been intrinsic in the battle against malaria. However, in 2008, the first reported case of Malaria resistance to Artemisinin was reported¹⁸ and a decade later, the matter of concern became pronounced when there were already more than 30 individual cases of Artemisinin resistance in Southeast Asia¹⁹.

Figure 2. Artemisinin

Given that the prolific resistance to currently used anti-malarial drugs, including Quinine and Artemisinin, is becoming widespread, the search for novel and more effective drugs is needed. The future towards efficacious malarial combat lies in perpetuating the discovery of anti-malarial natural products that fulfil essential criteria such as having novel modes of action with no cross-resistance to current drugs, single-dose cures and imperatively, demonstrating activity against both the asexual blood stages and the mature gametocytes responsible for malarial transmission²⁰.

The recent discovery of naturally-occurring molecules Samroiyotmycins A & B by Dramaev and co-workers¹ have probed the need for interdisciplinary research into the total synthesis of both molecules and biological assays (which will be further discussed below) to determine their potential activity towards *Plasmodium Falciparum*.

1.2. Biological source & significance of Samroiymycins

Figure 3. The Samroiymycins

Samroiymycins A & B (Figure 3) were both isolated from *Streptomyces spp.*, a soil microorganism collected in Khao Sam Roi Yot National Park in Thailand. Interestingly, Samroiymycin B exhibited both moderate anti-malarial and anti-fungal activity while the other strain exhibited only anti-malarial activity. Samroiymycins A and B were biologically active against a multi-resistant strain of *Plasmodium falciparum* with IC₅₀ values of 3.65 and 3.16 µg/ml respectively. Structural determination highlighted that both Samroiymycins were closely related dimeric macrocycles with a complex structure and should be structurally related to the 16 membered macrolide Conglobatin which is also a scaffold containing the oxazole motif²¹. However, Conglobatin displayed negative biological activities towards antifungal, antibacterial, antiprotozoal and antitumor²². On the contrary, Vermiculin, the 16-membered macrolide devoid of an oxazole motif displayed immunosuppressive results²³. The 2-unsubstituted oxazole motif can be found in a number of other natural products, including Conglobatin, the Inthomycins and the Oxazolomycins^{24, 25} (Figure 4). In light of that, these natural molecules are therefore lead compounds for further biological investigation and for the development of new synthetic methodology valuable to organic and medicinal chemists.

Conglobatin

Vermiculin

Figure 4. Structures of Conglobatin & Vermiculin

1.3. Project Aims

The purpose of the project described herein is to devise an efficient and accessible total synthetic route to Samroiyotmycins **A** and **B**. The significance of this project is in the challenge of devising an efficient synthetic approach towards both dimeric macrocycles **A** and **B**. Furthermore, there is also the additional challenge foreseen in conceiving a strategy for the precise macrocyclic construction of Samroiyotmycin **B** in the final step of synthesis (Scheme 2.1), due to its unsymmetrical nature since the R group is Hydrogen instead (Figure 3).

The synthesis also involves developing novel synthetic chemistry along the way for the construction of 2-unsubstituted oxazole and catalytic asymmetric carbon-carbon bond formation (C1-C2) involving boron and silicon heterocycles.

Upon successfully synthesising both Samroiyotmycins **A** and **B**, they will be brought to Prof. Bozdech's lab for in-vitro biological assays to test for anti-malarial activity against the *Plasmodium Falciparum* K1 parasitic strain. Constant sample volumes of parasitized human erythrocytes would be added to culture mediums with different concentrations of the Samroiyotmycin strain that are bound to plasma proteins in the culture medium. Hence, by measuring the uptake of [G-³H] hypoxanthine by the parasites at various concentrations of the drug strain in each culture medium, the ID₅₀ values could be determined and correlated to the extent of the anti-malarial activity of Samroiyotmycin (**A** & **B**). The implementation of Cellular Thermal Shift Assay (CETSA) will also be employed to study and quantify the extent of binding between the synthesised natural product and the protein target of the malaria parasite²⁶.

Figure 5. CETSA

By determining the increase in temperature or thermal shift (ΔT_m) at which the drug-bound protein denatures as compared to the unbound protein of the parasite, the extent of successful binding between the drug and the protein of the parasite can be determined (Figure 5).

In addition, molecular biology studies will be performed to study the drug's ability to target the protein of the parasitic strain. This is crucial as the *Plasmodium falciparum* parasitic strain requires [G-³H] hypoxanthine for nucleic acid synthesis and energy metabolism and by targeting the protein of the parasitic strain, the uptake of hypoxanthine by the parasite would be suppressed. By measuring the suppression of the [G-³H] hypoxanthine into the nucleic acid of the parasite, the extent of anti-malarial activity can be demonstrated²⁷.

Furthermore, analogues of Samroiymycin would be synthesised (Section 1.4) and the results of these analogue studies will yield both structure-activity information, and show which positions can be modified for biological probe studies, such as affinity labelling.

1.4. Analog syntheses and studies

Figure 6. Positions for modification for analogue synthesis

In addition, further analogue studies invoking the oxazole moiety will be probed (shown in Figure 6) such as the synthesis of Phenyl-analogue (Figure 7), as well as the use of other phosphonoacids with different R groups will allow the installation of alternative substituents at C2 position for a diverted total synthesis research.

Figure 7. Analog involving absence of oxazole moiety

Additionally, the cross metathesis of secondary alcohol **2.1.8** (Scheme 2.1) with varying acrylate esters will give different acyclic analogues **1.4.1** and **1.4.2** (Figure 8) which studies could be conducted with regards to the degree which the natural product can be simplified without loss of activity.

Figure 8. Possible acyclic analogues

1.5. Theory of synthetic approach towards oxazole-containing moieties

The first reported synthesis of oxazole was reported by Zinin in 1840 during the synthesis of a compound that he named as azobenzil²⁸. It was formed from a reaction between benzil and ethanolic ammonia (Scheme 1.1).

Scheme 1.1. First oxazole synthesis by Zinin

It was reported that ethyl benzoate was produced concomitantly in the reaction and added that it accounted for the formation of azobenzil. However, it was not clearly explained as to how that was the case. Subsequently in 1883, Japp confirmed the structure and molecular formula of azobenzil as 2, 4, 5-triphenyloxazole as shown above. The reaction mechanism was suggested by Japp to be one that first involves decomposition of a portion of benzil in alcoholic ammonia to give ethylic benzoate and benzaldehyde. The benzaldehyde then subsequently reacts with a second portion of benzil and ammonia in stoichiometrically equivalent ratio to give azobenzil²⁹. This was subsequently tested by Japp in his experimental procedure which was reported that his proposed mechanism for the reaction was highly probable. However, this reaction poses several disadvantages by nature as slight amounts of moisture would result in the formation of benzoic acid as the by-product, which would correspond to a lesser amount of benzaldehyde formed and thus affecting the reaction yield of azobenzil. In addition, it was also stated that in the second step, if benzil were to react with two molecules of ammonia, the by-product called Lophine would be formed instead (Figure 9), leading to lower yields of azobenzil.

Figure 9. Structure of Lophine

In the late 1800s, Emil Fischer discovered the synthesis of 2, 5-disubstituted oxazoles by passing HCl gas through an absolute ether solution of an aromatic aldehyde and cyanohydrin (Scheme 1.2)³⁰.

Scheme 1.2. Fischer oxazole synthesis

Exemplary yields were obtained but the reaction is still unfavourable due to the use of toxic and corrosive HCl gas and also the substrate scope was only limited to aryl substituted substrates.

Since then, there have been many reported literature methods for synthesising oxazoles in the 1900s³¹. One of the traditional approaches to a convenient synthesis of parent oxazole was designed by Brederick and Bangert in 1962 (Scheme 1.3)³². The first step of the synthesis requires the reaction between formamide and ethyl α -hydroxysuccinate to give diethyl oxazole-4, 5-dicarboxylate. This ester was then subjected to hydrolysis with ether-ethanolic NaOH and subsequent treatment of the acid salt formed with quinoline in the presence of copper oxide with heating results in decarboxylation of the dicarboxylate to give oxazole in average yields (30 – 50%).

Scheme 1.3. Synthesis of parent oxazole by Brederick and Bangert³³

Despite being a convenient synthetic procedure to affording 2-unsubstituted oxazole, it is however an inefficient process since it requires harsh conditions such as high temperatures during the first step with formamide and α -hydroxyketones. This results in low to average yields of the oxazole obtained at the end of the synthesis^{34, 35}. Furthermore, the likelihood of inaccessibility to the glyoxylate starting material poses an additional challenge to the synthetic route.

Soon after, these disadvantages were overcome by Schöllkopf and Schröder in their strategy to synthesise 2-unsubstituted oxazoles in moderate to good yields by reacting α -metalated isocyanides with functionalised carboxylic acid derivatives (Scheme 1.4)^{35, 36}. This strategy not only provides a more facile access to oxazoles under milder conditions, it also enables a wide variety of functionalisation, from alkyls to aryls and heteroaryl, on the synthesised oxazole at the 4- and 5- positions in good yields (52 – 76%). In addition, the use of more conveniently accessible isocyanides and carboxylic derivatives such as acid chlorides and aldehydes reduces the challenge to obtain 2-unsubstituted oxazoles.

Scheme 1.4. Synthesis of 4- and 5- substituted oxazoles

In addition, Van Leusen and co-workers began researching on the synthesis of sulfonylmethyl isocyanides and their vast utility in designing 4- or 5-substituted oxazoles. Furthermore, it was reported that tosylmethyl isocyanide (TosMIC) can be easily obtained through simple chemical conversions such as sulfonylation of the α -lithiated isocyanide with tosyl fluoride. Hence, the Van Leusen oxazole synthesis³⁷ was devised as a popular and strategic approach to synthesising 2-unsubstituted oxazoles from aldehydes by reaction with TosMIC (Scheme 1.5). This reaction provides a facile access to 2-unsubstituted oxazoles owing to the unique reactivity of TOSMIC, which contains acidic protons on the carbon α to the isocyano and sulfonate group. Furthermore, the presence of a carbene-like carbon on the isocyanide group makes it susceptible to oxidation, which is a driving force for the C-O bond formation in the oxazole synthesis.

Scheme 1.5. Van Leusen oxazole synthesis

1.6. Synthetic examples of oxazole motif in prominent Natural Products

The oxazole moiety is an important and prevalent subunit in many biologically active natural product molecules³⁸. Furthermore, some natural compounds containing oxazole heterocycles exhibit antiviral, antibacterial and antineuropathic activity, which further demonstrates the essence of the oxazole unit in medicinal chemistry³⁹. One such popular scaffold is the natural product known as Bengazole A (Figure 10). The total synthesis of Bengazole A was first achieved by Chandrasekhar and Sudhakar⁴⁰ in 2009. It was identified and isolated by Crews et al.⁴¹ as a bisoxazole sugar hybrid from the marine sponge *Jaspidae fijiisponge*.

Figure 10. Bengazole A

Interestingly, the 2, 4-disubstituted oxazole unit in Bengazole A was achieved by subjecting the alcohol intermediate to oxidation, followed by a Robinson-Gabriel type oxazole formation under Panek and Beresis conditions⁴² (Scheme 1.6), giving the oxazole motif in average yield over two steps (54%).

Scheme 1.6. Robinson-Gabriel type oxazole formation

Another prominent example of an oxazole-containing natural product scaffold is the total synthesis of (+)-Inthomycin B (Figure 11) by Webb et al.⁴³ Inthomycin B, like other members of the Inthomycin family, contains a main 2-unsubstituted oxazole unit.

Figure 11. (+)-Inthomycin B

The construction of the first oxazole fragment was achieved using the Van Leusen's reaction conditions as shown in scheme 1.7, giving ethyl-5-oxazolecarboxylate in excellent yield (86%). However, one of the drawbacks is that rigorously anhydrous conditions have to be employed, otherwise reaction yields would be compromised.

Scheme 1.7. Van Leusen's oxazole formation in (+)-Inthomycin B synthesis

1.7. Analysis of adopted methodology towards 2-unsubstituted oxazole moiety

Based on our proposed synthetic scheme, the 2-unsubstituted oxazole intermediate **2.1.4** was prepared using gold (I) catalysed intramolecular cyclization of the internal alkyne **2.1.3**. The Van Leusen reaction was however, inappropriate for the synthesis of the oxazole as it would require a β -keto substituted aldehyde as substrate which could pose problems for the reaction in terms of regioselectivity. Furthermore, accessibility to β -keto substituted aldehyde substrates would be challenging and hence reduce the efficiency of the overall oxazole synthesis. Thus, our attention was brought to the employment of an active cationic gold catalytic species which would be more efficient in enabling a facile 5-*exo-dig* intramolecular cyclization of propargyl amide **2.1.3** to furnish 2-unsubstituted oxazole **2.1.4** (Scheme 1.8).

Scheme 1.8. Gold (I) catalysed intramolecular cycloisomerization

The use of catalytic cationic gold species in cycloisomerisation reactions to form heterocycles have been prevalent since the past decade⁴⁴. Before the discovery of cationic gold species used in efficient cyclizations of propargylic amides, Hacksell et al.⁴⁵ demonstrated that propargylic amides could undergo a 5-*exo-dig* cyclization to oxazoles under basic reaction conditions. Until then cyclization could only be achieved by harsh reaction conditions such as strongly acidic reagents or high temperatures or both⁴⁶. Recently, cationic gold species have been known to be effective catalysts for the electrophilic activation of alkynes toward

carbon and heteroatom nucleophiles⁴⁷. This could be due to the lower LUMO properties and poor back-donation of cationic gold (I) species. However, the appropriate choice of ligand, counterion and choice of solvent used in gold catalysis is also essential to the catalytic efficiency and yield of the reaction⁴⁸. In recent years, the use of cationic gold species for intramolecular cycloisomerisation of propargyl amides to form oxazoles have been a focus of interest. Amongst the active catalysts such as palladium, copper, silver and gold known to catalyse the formation of oxazoles, gold(I) catalysis has been shown to be generally most efficient and can proceed under mild reaction conditions⁴⁹. Many years ago, Costa et al.⁵⁰ performed an oxidative carbonylation of disubstituted prop-2-yncarboxamides to the corresponding oxazolines in the presence of catalytic Pd(II) species. The Pd(II) species was likely to have catalysed the reaction by activating the triple bond electrophilically. Since the use of cationic gold is much more effective in electrophilic activation of alkynes, Hashmi and co-workers then researched and reported on the cyclization of propargyl amides using Au (III) species⁵¹. The use of AuCl₃ in 5 mol% catalytic loading in the presence of DCM or MeCN smoothly enabled the cycloisomerization of terminal propargylic amides (Scheme 1.9) in average to excellent yields (48 – 95%).

Scheme 1.9. Gold (III) catalysed cycloisomerization of terminal propargylic amides

The exocyclic olefin intermediate could be identified in the reaction via ¹H NMR and is crucial in demonstrating that the last step of the mechanism involves isomerisation from the exocyclic olefin to the oxazole product.

Soon after, Hashmi et al.⁴⁹ subsequently demonstrated the cyclization of internal propargylic amides to synthesise substituted alkylideneoxazolines and their corresponding oxazines in the presence of IPrAuCl / AgOTs and THF as the catalyst and solvent system respectively (Scheme 1.10). They reported average to excellent yields of oxazolines (12 – 78%) obtained from the reaction and average yields of corresponding oxazines (10 – 35%).

Scheme 1.10. Gold (I) catalysed cycloisomerization of non-terminal propargylic amides

It is likely the gold carbene catalytic system used in the reaction was generated by the highly stable catalytic species IPrAuOTs in situ. Besides being more stable than other non-carbene incorporated Au(I) catalysts, the incorporation of a carbene ligand onto the cationic Au(I) center makes the catalyst more electron-rich, due to the strong electron-donating effect of the carbene. This could promote the proto-deauration step of the reaction mechanism since many reactions catalysed by gold(I) have reported rate-determining proto-deauration steps⁵². More importantly, it was noted that the electronic and steric properties of the corresponding R and R' groups on the internal alkyne and amide respectively, the ligand and the counterion on the catalyst could affect the regioselectivity of the reaction and also the likelihood of

isomerisation of the oxazolines into oxazoles. Furthermore, the presence of methylene protons on the propargylic amide substrate may promote isomerisation of oxazoline to oxazole, albeit lower reaction yields obtained due to a lack of Thorpe-Ingold effect as compared to substrates with functional groups substituted on the methylene carbon.

However, despite the existing literature that demonstrated syntheses of 2,5-disubstituted oxazoles, oxazolines and oxazines using cationic gold catalysts, there has been no literature on the synthesis of 2-unsubstituted oxazoles using active cationic gold catalysts. In addition, the formation of 2-unsubstituted oxazoles using catalytic intramolecular cyclization from a propargylic formamide substrate has not been reported before.

Thus, I have decided to venture into the use of catalytically active gold(I) species to furnish 2-unsubstituted oxazole **2.1.4** from the alkynamide intermediate **2.1.3** in our synthetic route (Scheme **1.8**).

Chapter 2

SYNTHETIC PROPOSAL AND PRELIMINARY RESULTS

2.1. First Synthetic Route towards synthesis of Samroiyotmycins

The initial proposed synthetic route for both Samroiyotmycins is specifically designed to involve using catalysis for five key reaction steps and completing the entire synthesis in just eleven steps, minimising the use of protecting groups (Scheme **2.1**). One of the most essential key steps lies in the construction of the 2-unsubstituted oxazole moiety via an envisioned intramolecular cycloisomerization of our propargylic formamide substrate in the presence of an active gold (I) catalyst as shown below in the proposed scheme. This idea was predicated and inspired by the prevalent work of Hashmi et al.⁵³ in the efficient methodology of forming 2,5-substituted oxazoles using gold (I) catalysts of varying ligands and counterions in recent years.

Scheme **2.1**. Proposed synthetic route of the Samroiymycins

The proposed synthesis begins with the construction of the precursor **2.1.3** to the 2-unsubstituted oxazole moiety. The initial step features a facile *N*-alkylation of propargyl

bromide with sodium diformylamide⁵⁴ to give imide **2.1.1**, which would then be coupled with methacrolloyl chloride via Sonogashira coupling⁵⁵ to give the adduct **2.1.2**. The adduct will then be subjected to alcoholysis to give the corresponding ynone **2.1.3**. Subsequently, the ynone is then subjected to a key catalytic cyclization step to yield the corresponding oxazole intermediate **2.1.4**. Catalytic asymmetric reduction^{56, 57} of the oxazole will give chiral allylic alcohol **2.1.5**. This is then followed by either diastereoselective hydrosilylation⁵⁸ or hydroboration⁵⁹ to give either silacycle **2.1.6** or boracycle **2.1.7** respectively. The subsequent synthesis would then feature another key step involving catalytic allylation with either Hiyama conditions – if silacycle **2.1.6** was made, or Suzuki conditions – if boracycle **2.1.7** was made in the previous step. This would extend the chain and form the secondary alcohol **2.1.8**. Given the less frequent utilization of Hiyama or Suzuki coupling in aliphatic chemistry⁶⁰ relative to their usage in constructions of bonds in aryl system coupled with the fact that these reactions have never been used with boron or silicon heterocycle derivatives^{58, 61}, this step here would be a novel contribution to the field. Esterification with phosphonoacids **2.1.9ab**⁶² will give the phosphonates **2.1.10ab** which would then be subjected to cross-metathesis⁶³ to give aldehydes **2.1.11ab**. Finally, the last key step involving macrodimerisation under controlled Horner-Wadsworth-Emmons conditions⁶⁴ will directly yield Samroiymycin A **2.1.12a**. The unsymmetrical Samroiymycin B will be prepared by the Horner-Wadsworth-Emmons coupling of aldehydes **2.1.11a** and **2.1.11b**, which will be synthetically challenging as precise conditions have to be researched to ensure predominant hetero-coupling over any homo-coupling of the aldehydes.

2.2. Results from Initial proposed synthetic scheme

The first step of the synthesis began with a highly facile *N*-alkylation reaction between commercially available propargyl bromide and Sodium Diformylamide in anhydrous MeCN as solvent (Scheme 2.2). The diformylamide salt was easily prepared according to the procedure that was reported by Han et al.⁵⁴

Scheme 2.2. *N*-alkylation of propargyl bromide

After varying a few reaction conditions (Table 2-1), the imide **2.1.1** was obtained in an excellent yield of 93% (entry 2).

Table 2-1: Optimisation of *N*-alkylation reaction

Entry ^a	Propargyl bromide (equiv)	NaN(CHO) ₂ (equiv)	Duration (hr)	Temp. (°C)	Yield ^b
1	1	1.2	5	80	45
2	1.2	1	5.5	90	93
3 ^c	1.2	1	24	r.t.	45

^aAll reactions were done in 0.2M concentration of sodium diformylamide in absolute MeCN. Propargyl bromide was added at room temperature before the reaction was heated. ^bIsolated yield. ^cReaction was done in the presence of TBAB as phase-transfer catalyst and anhydrous THF.

It was noted from the results obtained in Table 2-1 that propargyl bromide has to be added in excess and also the reaction has to be performed at reflux for optimum reaction yield. It was

also observed from the crude ^1H NMR and TLC analysis of entry **1**, the use of excess sodium diformylamide led to the observed formation of formamide **2.1.1'** as the by-product (Figure 12) and also a decrease in the yield of imide **2.1.1** obtained, along with slight unreacted propargyl bromide. It is postulated that this could likely be due to the presence of adventitious moisture present in the reaction as a result of the highly hygroscopic nature of the sodium diformylamide reagent. Therefore, it is possible that **2.1.1'** is formed as a result of *in situ* hydrolysis of either the diformylamide salt or the hydrolysis of imide product **2.1.1**. Hence, it is essential that the reaction was to be conducted under rigorously anhydrous conditions as much as possible in order to reduce the amount of by-product **2.1.1'** formed in the reaction. Furthermore, changing the excess reagent to propargyl bromide instead and heating the reaction at reflux (entry **2**) induced a significant improvement in the reaction yield (45 – 93%), with reaction conditions in entry **2** even applicable on gram scale. On an additional note, when the same reaction was attempted in the presence of a phase-transfer catalyst TBAB at room temperature in dry THF, the reaction proceeded sluggishly, giving only moderate yield (42%) accompanied with moderate amounts of by-product **2.1.1'** (35%). Apart from the possibility of adventitious moisture present in the TBAB reagent that could have affected the reaction yield of **2.1.1** (entry **3**), it is apparent that reflux conditions were necessary for the reaction to proceed efficiently with exemplary yield.

Figure 12. *N*-formylpropargylamide by-product

Subsequently, imide **2.1.1** was subjected to a Sonogashira coupling with methacryloyl chloride under mild reaction conditions to give the internal alkyne adduct **2.1.2** (Scheme 2.3).

Scheme 2.3. Sonogashira coupling

For this step, average to excellent yields (35 – 85%) of the internal alkyne adduct **2.1.2** (Table 2-2) were obtained.

Table 2-2: Optimisation of Sonogashira coupling

Entry ^a	Acyl chloride (equiv)	Et ₃ N (equiv)	PdCl ₂ (PPh ₃) ₂ (mol %)	CuI (mol %)	Duration (hr)	Temp (°C)	Yield ^b
1	1.1	1.1	5	10	18	r.t.	24
2	1.0	1.5	2	4	O.N.	r.t.	28
3 ^c	1.5	1.25	2	4	3.5h	r.t. - 70	87
4 ^c	1.5	1.25	2	4	6	r.t.	85 ^d

^aAll reactions were done in 0.2M concentration of imide **1** in absolute THF. Triethylamine was added before the acid chloride and alkyne addition. ^bIsolated yield. ^cReaction was done with triethylamine added last and dropwise over 25 minutes. ^dReaction performed on gram scale.

Our first attempt at this reaction (entry **1**) unexpectedly gave less than promising yields (24%) of the desired alkyne adduct **2.1.2**. Upon analysis of the crude proton NMR spectrum, a second set of peaks corresponding to the vinyl protons were observed slightly downfield from those of the desired product. It was possibly due to the competing nucleophilic reaction between triethylamine and the acid chloride, hence affecting the yield of the desired product

obtained. When the reaction was repeated (entries **3** & **4**) but with triethylamine added dropwise slowly after the acid chloride and alkyne substrate **2.1.1** has been added to the mixture containing the catalysts, the reaction yield of the alkyne adduct improved significantly (28 – 87%). Therefore, this demonstrates that the slow addition of triethylamine at the last step reduces the extent of its possible side reaction with the acid chloride, allowing the Sonogashira coupling to proceed more efficiently.

After which, the alkyne adduct **2.1.2** was subjected to a direct ethanolysis on the imide functional group in the presence of a basic polymer resin (Amberlyst-26) in ethanol to furnish the alkynamide **2.1.3** (Scheme **2.4**).

Scheme **2.4**. Imide ethanolysis of **2.1.2**

Initially, a similar hydrolysis approach mentioned by Han et al. which uses potassium hydroxide as the basic catalyst instead of Amberlyst-26 was attempted. The reaction, however, proved to be less efficient as proton NMR analysis of the reaction crude revealed several other signals in addition to those of the product **2.1.3**. Hence, it was likely that the KOH might have been too strong as a base, resulting in possible nucleophilic side reactions on the carbonyl group. Considering the use of a milder base, Amberlyst-26 was used instead since it is a basic polymer resin and also facilitates the ease of reaction work-up to just filtration over celite. It was monitored from TLC analysis that the reaction was greatly slowed when Amberlyst-26 was used but moderate to good yields of product **2.1.3** were obtained (42 – 76%).

Table 2-3: Optimisation of imide ethanolysis

Entry ^a	Amberlyst-26 (wt. %)	Solvent	Duration (hr)	Yield ^b
1	9	EtOH	44	76
2	12	EtOH	72	66
3	18	EtOH	20	42
4	10	MeOH	48	50
5 ^c	10	MeOH	> 96	- ^d

^aAll reactions were done with 40g/L concentration of A-26 resin in alcoholic solvent at room temperature.

^bIsolated yield. ^cReaction was done in the presence of Amberlyst-15 acidic resin. ^dMinimal conversion based on crude proton NMR analysis.

Despite longer reaction times required as compared to the method suggested by Han et al., the use of Amberlyst-26 rendered the reactions more straightforward and afforded cleaner crude proton NMR spectra. Upon obtaining exemplary yield of alkynamide **2.1.3** in the first entry, the effect of higher Amberlyst-26 concentrations on the reaction yield was investigated, while maintaining the same solvent used and temperature (entries **2** & **3**). However, higher concentrations seemed to have an adverse effect on the yields and resulted in unidentified by-products in the reaction mixture. The use of a more acidic and nucleophilic solvent MeOH with Amberlyst-26 also resulted in a decrease in reaction yield (entry **4**) albeit giving complete reaction in much shorter reaction time. It is possible that the greater nucleophilicity of the *in-situ* generated methoxide ion as compared to the ethoxide ion resulted in a nucleophilic addition on the carbonyl group of alkyne substrate, leading to diminished yields. Additionally, switching to the use of an acidic polymer resin as catalyst led to a much slower reaction which eventually gave no further conversion even after stirring for more than 5 days (entry **5**).

With the alkyne substrate **2.1.3** in hand, several catalytic and reaction conditions to furnish the key oxazole intermediate **2.1.4** via a 5-*exo-dig* intramolecular cyclisation (Scheme **2.5**) were explored. Extensive studies were recently carried out by Hashmi's group on intramolecular cyclizations of propargylic amides to 2-substituted oxazoles using cationic gold. Thus, experiments using cationic gold catalysts were carried out to determine if their efficiency were applicable in the cyclization of our substrate **2.1.3** since no literature has reported the gold catalysed cyclisation of a formamide substrate to furnish 2-unsubstituted oxazoles.

Scheme **2.5**. 5-*exo-dig* cyclization of formamide **2.1.3**

Overall, after experimenting with much catalytic variations, ligands, counterions and reaction conditions, the oxazole intermediate **2.1.4** was obtained at a best possible yield of 72%.

Table **2-4**: Optimisation of gold catalysed intramolecular cyclization

Entry ^a	Au catalyst (mol %)	Silver salt (mol %)	Solvent	Duration (hr)	Temp (°C)	Yield ^b
1	PPh ₃ AuCl / (5)	AgOTf (5)	DCM	19	r.t.	12
2	PPh ₃ AuCl / (5)	AgSbF ₆ (5)	DCM	96	r.t.	19

3	Johnphos(NCMe) AuSbF ₆ (5)	-	DCM	72	r.t. - 50	29 ^e
4 ^c	Johnphos(NCMe) AuSbF ₆ (5)	-	DCE	89	80	35
5	Silica gel (300 wt. %)	-	DCM	24	r.t.	-
6	AuCl ₃ (5)	-	DCM	84	r.t.	- ^d
7	AuCl ₃ (5)	-	MeCN	72	50	- ^{d, e}
8	JohnphosAuNTf ₂ (5)	-	DCM	72	reflux	17
9	XPhosAuNTf ₂ (5)	-	DCM	72	r.t.	- ^f
10	Me ₃ PAuCl (5)	AgOTf (5)	DCM	48	r.t.	- ^f
11	(C ₆ F ₅) ₃ PAuCl (5)	AgOTf (5)	DCM	40	r.t.	-
12	(C ₆ F ₅) ₃ PAuCl (5)	AgSbF ₆ (5)	DCE	72	r.t. – 80	20
13	(<i>p</i> - CF ₃ C ₆ H ₄) ₃ PAuCl (5)	AgOTf (5)	DCM	84	r.t.	- ^d

14	JohnphosAuCl (5)	AgOTf (5)	DCM	72	r.t.	20 ^e
15	JohnphosAuCl (5)	AgOTs (5)	DCE	18	80	72
16	-	AgNO ₃ (10)	MeCN	48	r.t.	40
17	-	AgNO ₃ (20)	MeCN	19	r.t.	47

^aAll reactions were done in 0.25M concentration of alkynamide **2.1.3** in absolute solvent. ^bIsolated yield. ^cReaction was done in the presence of 1.2 equiv of AcOH. ^dCatalytic decomposition was observed. ^eYield estimated from crude proton NMR using dibromomethane as the internal standard. ^fReaction was inconclusive based on TLC and ¹H NMR analysis of crude.

Our initial efforts of using cationic Ph₃PAuOTf as the active catalytic system turned out to give undesirable results (entries **1** & **2**). In addition, following Hashmi's protocol of using cationic AuCl₃ as the catalyst (entries **6** & **7**) also proved to be inefficient in our case, since low reaction conversion was observed even after heating for prolonged reaction times and decomposition of AuCl₃ occurred. Therefore, it was debatable whether the low reaction yields was the result of poor electronic activation of the alkyne by the catalyst, slow protodeauration rates or possibly low nucleophilicity of the formyl group resulting in lower cyclization tendency.

In entries **3** & **4**, the use of a highly stable gold complex made by Echavarren et al. merely increased the reaction yields slightly (12 – 35%), albeit with prolonged reaction times. This could be because of enhanced catalyst stability from the phenyl ring of the biphenyl group which could exhibit weak π interactions with the Au centre⁶⁵. Thus, the catalytic turnover of the reaction would be greatly enhanced. However, including stoichiometric equivalents of an

acidic medium did not serve to improve the efficiency of the reaction in any way, which meant that slow protodeauration rate was unlikely the reason for the low reaction yield.

Hence, there was a need to screen the effect of using gold catalysts with enhanced Lewis acidities on the reaction. In entries **10** to **13**, several reactions were gradually performed by varying different electron-withdrawing ligands attached to the cationic gold centre. Despite the efforts, it was realised that increasing the Lewis acidity of the active gold catalyst had no benign effect on the reaction yields. Furthermore, varying the counterions of the active gold species within these reactions had no significant improvement despite running the reaction under forcing conditions (entry **12**). Hence, it was postulated that the cause for the sluggish reaction rate was likely not inefficient electrophilic activation of the alkyne by the catalyst.

This led to the question of whether the cyclisation was impeded by poor nucleophilicity of the formyl oxygen of substrate **2.1.3** since cyclisation of internal alkynamide substrates have been shown to proceed efficiently in the presence of various active gold species.

Since the Johnphos ligand provides an increased stability to the gold catalyst, the effect of using other counterions was investigated. In 2008, Ujaque and co-workers demonstrated the impact of the triflate counterion in assisting the tautomerisation of the positively charged carbamate intermediate (**I**, **II**) and the resulting $\text{NH}=\text{C}-\text{OH}$ tautomer underwent protodeauration efficiently to give the hydroaminated product⁶⁶ (Scheme **2.5.1**).

Scheme **2.5.1**. Counterion effect in intermolecular hydroamination of dienes

Thus, an experiment was performed using JohnphosAuCl and AgOTf as the catalyst and triflate source respectively (entry **14**). However, it was again an inefficient catalyst system for the reaction as only 20% crude yield of the oxazole was obtained and no further conversion was observed after prolonged stirring. Subsequently, a recent study by Zuccaccia and co-workers⁶⁷ was delved into. They performed an intramolecular 5-*endo-dig* *O*-addition of a hydroxyl group to the alkyne to form THF rings (Scheme **2.5.2**). During the computational studies that were performed in the process, they reported that the use of highly coordinating OTs⁻ counterion in the gold catalysed process is capable of facilitating the nucleophilic attack of the alcohol moiety to the gold-activated alkyne via a hydrogen bond interaction with the H atom of the –OH group (**III**, **IV**). This enhanced the nucleophilic character of the hydroxyl group.

Scheme **2.5.2**. Role of counterion in gold catalysed hydroalkoxylation of alkynes ($\text{X} = \text{OTs}$)

Considering that the tosylate anion is more coordinating to the Au centre, the overall stability of the active gold catalyst is also enhanced, albeit the less dissociating nature of OTs^- could affect the overall catalytic efficiency. Our reaction was thus repeated with Johnphos as the ligand **L** and AgOTs as the counterion source. To our delight, the reaction yield improved vastly to 72% (entry **15**) with more than 90% conversion based on crude ^1H NMR analysis. In this reaction, reflux conditions were necessary to overcome the drawback of the less dissociative nature of tosylate ion. It was predicted that the tosylate ion could have coordinated to the proton on the $-\text{NH}$ group, thus indirectly enhancing the nucleophilicity of the formyl oxygen by stabilising and favouring the formate intermediate **VII** (Scheme **2.6**).

Scheme **2.6**. Hydrogen-bond interaction of tosylate ion with formate hydrogen

From here on, the racemic route of the synthesis was proceeded with. Reduction of the ketone functional group with DIBAL-H gave racemic alcohol **2.1.5** (Scheme **2.7**).

Scheme 2.7. Reduction of ketone **2.1.4**

When the reaction was performed in slight excess of DIBAL-H in anhydrous DCM at -78 degrees, moderate yield (47%) was obtained even after running the reaction for 5 hours at that temperature. This was surprising given the fact that the soft nature of DIBAL-H as a reducing agent is to be highly chemoselective in reducing only the carbonyl group. Furthermore, the use of DCM over THF as the reaction solvent enhances the reactivity of DIBAL-H since the coordinating ability of THF via the oxygen to the Al of DIBAL makes the reducing agent less 'naked'. Exemplary yield (81%) was then achieved when the same reaction was repeated and stirred at -78 degrees for 40 mins, followed by overnight stirring at -40 degrees since it was noted that the reaction was actually progressing slower than expected. It was postulated that the sluggish reaction could be due to a possible coordination between the Lewis basic N atom of the oxazole moiety and the Al centre, thus hindering the reactivity of DIBAL.

Before the crucial coupling reaction of either silacycle **2.1.6** or boracycle **2.1.7** with allyl halide was investigated, it was essential to research on methods to achieve either of the intermediates. Protection of the hydroxyl group in allylic alcohol **2.1.5** was necessary prior to hydroboration of the substrate. Experiments to achieve the boracycle was first tested at this point of the synthesis (Scheme 2.8). TBS-protection of allylic alcohol **2.1.5** gave the intermediate allylic silyl ether **2.1.5'** which was isolated in 87% yield.

5	Rh(CO)(Fu ₃ P) ₂ Cl (3)	HBcat (1.2)	24	r.t. – 60	- ^c
6	[Ir(cod)Cl] ₂ / DPPB (2.5 / 5)	HBcat (1.2)	48	r.t.	- ^c
7	Rh(CO)(PPh ₃) ₂ Cl (3)	HBpin (1.2)	48	r.t.	- ^c
8	Wilkinson's (3)	HBpin (1.2)	48	r.t.	- ^c
9	Rh(CO)(Fu ₃ P) ₂ Cl (3)	HBpin (1.2)	48	r.t. - 60	- ^d

^aAll reactions were done in 0.3M concentration of allylic silyl ether **5'** in absolute THF. ^bIsolated yield. ^cOnly starting material was observed. ^dUnidentified side product observed in the crude mixture according to proton NMR of crude mixture.

Furthermore, switching to the use of Ir(I) catalysts did not give any hydroborated product, even with pinacolborane. It was postulated that the presence of the Lewis basic N in the oxazole could possibly have interfered with the reaction by coordinating to the Rh(I) catalyst, thus greatly impeding the catalytic activity.

Since the path for hydroboration was then at a standstill, efforts were redirected to experimenting on the path of intramolecular hydrosilylation to synthesise silacycle **2.1.6** (Scheme **2.9**).

Scheme **2.9**. Synthesis of silacycle **2.1.6**

When allylic alcohol was subjected to silylation with dimethylchlorosilane, the allylic dimethylsilyl ether was obtained in 11:1 ratio with respect to the alcohol based on proton NMR analysis of the crude mixture. The solvent-dried crude mixture was then directly subjected to intramolecular hydrosilylation under catalytic conditions in strictly anhydrous DCM as solvent (Table 2-6).

Table 2-6: Optimisation of intramolecular hydrosilylation

Entry ^a	Catalyst (mol %)	Duration (hr)	Temp. (°C)	Yield
1	PtCl ₂ / (5)	16	r.t.	- ^b
2	Rh(CO) ₂ (acac) / (5)	16	r.t.	- ^b

^aAll reactions were done in 0.3M concentration of allylic silyl ether crude in absolute DCM. ^bStarting material allylic alcohol **2.1.5** was obtained.

The initial hydrosilylation experiments conducted turned out to be unsatisfactory as when PtCl₂ or a Rh(I) active catalyst was used, the substrate simply reverted back to the allylic alcohol **2.1.5**. This is possibly because of the highly labile dimethylsilyl group of the allylic ether in the crude mixture, possibly resulting in a cleavage of the Si-O bond in the Pt(IV)-intermediate formed after oxidative addition of the silane, following with a β-hydride elimination to regenerate the allylic alcohol.

Subsequently, efforts were directed towards preparing allylic silyl ethers with bulkier groups on the Silicon for the intramolecular hydrosilylation in an attempt to minimise the possibility of proto-desilylation occurring (Table 2-7).

Table 2-7: Optimisation of intramolecular hydrosilylation

Entry ^a	Silane	Isolated yield of 6' (%)	Catalyst used / (mol %)	Duration	Temp (°C)	Yield (%)
1	<i>i</i> Pr ₂ Cl SiH	72	PtCl ₂ (C ₂ H ₄) ₂ (5)	20h	r.t.	- ^c
2	<i>i</i> Pr ₂ Cl SiH	72	PtCl ₂ (5)	20h	r.t.	- ^b
3	Ph ₂ Cl SiH	< 10	PtCl ₂ (5)	20h	r.t.	- ^b

^aAll reactions were done in 0.3M concentration of allylic silyl ether crude in absolute DCM. ^bStarting material allylic alcohol **5** was obtained. ^cThe reaction mixture was inconclusive based on ¹H NMR analysis of the crude.

Despite obtaining the desired allylic silyl ethers in good yields (72%), the ensuing intramolecular hydrosilylation with these substrates did not attribute any success towards the desired silacycle **2.1.6** (entries 1 – 3). In most cases, it seemed protodesilylation of the substrate proceeded faster than the desired reaction pathway and in the case where Zeise's dimer was used as the catalyst, the reaction resulted in a mixture of protodesilylated substrate **2.1.5**, starting material allylic silyl ether **2.1.6'** and some slight unidentified compound in the crude as analysed by ¹H NMR. It was predicted that in both cases of hydroboration and intramolecular hydrosilylation, the oxazole functional group would be the main culprit in not only poisoning the active catalysts, but also interfering with the actual catalytic activity of the desired reaction pathway.

Therefore, the synthetic route proposed (Scheme **2.1**) had to be revised in a way that furnishes the key oxazole moiety at a later stage, so as to prevent complications in the key reactions of the synthesis that could be caused by the oxazole.

2.3. Oxazolone synthesis

To do so, it was proposed based on modifications to the previous synthetic scheme which involves optimising the first gold-catalysed cycloisomerisation key step towards the oxazolone motif **2.3.3** (Scheme **2.10**).

Scheme **2.10**. Modified synthetic scheme for synthesis of Samroiymycins

The oxazolone key intermediate **2.3.3** would be the essential building block for further transformations along the synthesis as the lone-pair on the Nitrogen is now delocalised within the amide functionality of the cyclic structure. Therefore, it was postulated that such an intermediate posed a better and efficient synthesis along the route. Upon reaching the macrocyclic analogue of Samroiyotmycin, it was envisaged that the oxazole moiety could be developed by triflating the C=O bond of the amide group in the oxazolone on both ends of the macrocycle, followed by coupling with a hydride species such as Bu₃SnH under suitable catalytic conditions to yield the final Samroiyotmycin molecule.

Thus far, slight progress have been made towards the initial portions of the synthesis, up until the formation of allylic alcohol **2.3.4**.

Firstly, mono-Boc-protection of the commercially available propargylamine afforded the Boc-protected propargylamine in quantitative yield for an exemplary start. Subsequently, amine **2.3.1** was then subjected to Sonogashira reaction with methacryloyl chloride under similar conditions as optimised in the previous scheme (Table **2-8**, entry **4**). Gratifyingly, the alkyne adduct was furnished in an exemplary 81% yield. With that, optimal conditions were investigated to effect the key *5-exo-dig* cycloisomerisation of alkyne **2.3.2** to give the desired oxazolone product **2.3.3** (Table **2-8**).

Table **2-8**: Optimisation of *5-exo-dig* cycloisomerisation

Entry ^a	Au cat. (mol %)	Ag salt (mol %)	Solvent	Duration (hr)	Temp . (°C)	Yield ^b
1	AuCl ₃ / (5)	-	MeCN	24	50	- ^{c, d}
2	JohnphosAuCl / (5)	AgOTs (5)	DCE	2	65	97

^aAll reactions were done in 0.25M concentration of alkyne **2.3.2** in absolute solvent (except entry **1** where wet MeCN was used). ^bIsolated yield. ^cStarting material was recovered. ^dCatalytic decomposition was observed.

When the reaction was conducted under Hashmi's proposed reaction conditions for his cyclisation of terminal propargyl amides, the reaction did not proceed at all in terms of conversion, at most minute. However, it was worth noting that in Hashmi's results, it was mentioned that the use of Au(III) could not work for non-terminal propargylic substrates as well and was left unexplained. Hence, it was decided to exploit the use of similar reaction conditions previously optimised for the 5-*exo-dig* cycloisomerisation of formamide in Scheme 6. It was then indeed gratifying to observe a huge improvement to the reaction results as almost full conversion was observed after heating only at 65°C and for only 2 hours, to afford an excellent yield of 97% of the desired oxazolone intermediate. This indeed shows that the Boc-protected propargylic substrate was much more reactive to cycloisomerisation catalysed by cationic gold (I) due to its increased nucleophilicity of the carbamoyl group and enhanced electron-donating inductive effect caused by the *tert*-butyl group. Furthermore, cyclisation of the previous formamide substrate **2.1.3** (Scheme 2.5) proceeded comparatively slower and gave relatively lower yield of cyclised product as compared to the cycloisomerisation mentioned above. This could possibly be attributed to the oxazole product upon forming from the cyclisation of the formamide, coordinating to the active Au(I) catalyst in the reaction concurrently as the catalyst is catalysing the reaction, thus poisoning its catalytic activity and deteriorating the reaction yield of oxazole **2.1.4** in Scheme 2.5. Additionally, it is once again highlighted in the cycloisomerisation of amide **2.3.2**, that the combination of JohnphosAuCl and AgOTs is a highly efficient catalyst and counterion source respectively in terms of catalytic turnover number and the capability of the tosylate ion to induce *exo*- to *endo*- double bond isomerisation upon cyclisation.

Subsequently, the synthesis was continued with racemic reduction of the oxazolone intermediate with DIBAL-H to achieve the allylic alcohol **2.3.4**. However, when the DIBAL-H mediated reduction was performed under conditions similar to the previous scheme

(Scheme 2.7), the reaction proceeded very slowly and took 2 days to effect near complete consumption of starting material **2.3.3** even when stirring from -40°C to 0°C over two days. Upon analysis of the crude material after Rochelle's work-up, ¹H NMR revealed the reaction mixture to be thoroughly messy and indistinguishable between desired product and unwanted peaks. Furthermore, column chromatography resulted in the isolated allylic alcohol **2.3.4** only in 23% yield and was later analysed by ¹H NMR which found it to be impure and chemically inaccurate from what would be the expected chemical shifts of the molecule. It was postulated that this could likely be due to coordination of the Rochelle's salt to the oxazolone moiety of the product or likely coordination of the carbonyl group of the oxazolone functionality to the Al center of DIBAL-H due to resonance ability of the amide group in the cyclic structure of oxazolone **2.3.3**. This could thus lead to side reactions and decreased yield of **2.3.4** and even severely slow down the reduction of the carbonyl group as observed in our experiment.

Reduction under Luche's conditions⁶⁸ was then utilised and the alcohol was gratifyingly obtained in 76% yield.

Scheme 2.11. Reduction of ketone **2.3.3** and subsequent para-methoxybenzylation

Subsequently protection of alcohol **2.3.4** was then followed before testing out hydroboration (Scheme 2.11). Initial efforts to protect the alcohol with TBSOTf were mostly unsuccessful as a mixture of unidentified compounds along with the desired TBS-ether in the reaction crude was observed based on ¹H NMR analysis. It was postulated that this could be due to side reactions occurring such as silylation of the carbonyl group on the oxazolone since the TBSOTf is after all, a potent lewis acidic silylating agent. Hence, our attention was shifted to

another bulky protecting group, PMB, since it can also be conveniently installed and removed when needed during the synthesis (Scheme **2.11**). However, under many conditions attempted, the best only yielded an average of 46% as the para-methoxybenzylated ether **2.3.5**. Nonetheless, the alkene was tested for its feasibility towards hydroboration which is a key step of the synthesis.

Scheme **2.12**. Hydroboration

However, efforts were futile in hydroborating the alkene even after stirring the mixture with $\text{Rh}(\text{CO})(\text{PPh}_3)_2\text{Cl}$ or $\text{Rh}(\text{CO})(\text{Fu}_3\text{P})_2\text{Cl}$ catalysts over prolonged periods (Scheme **2.12**). It was postulated that the possible likelihood in this scenario was the oxazolone moiety may again have coordinated to the active Rh catalytic centre and hindered the catalytic process of hydroboration.

2.4. Proposed synthesis towards Phenyl-analogue of Samroiyotmycin

In order to determine if the oxazole moiety was interfering with the hydroboration process, hydroboration was performed on the analog substrate of **2.1.5'** which contains a phenyl ring in replacement of the oxazole group. To achieve the analog substrate **2.4.2**, the following synthetic scheme was performed (Scheme **2.13**), which began with methacrolein as the commercially available starting material.

Scheme **2.13**. Hydroboration studies on Ph-analog substrate **2.4.2**

Methacrolein was first subjected to a Grignard addition with benzyl magnesium chloride⁶⁹ to give the corresponding allylic alcohol **2.4.1** in excellent yield (81%). It was noted that benzyl magnesium chloride was strongly favoured over the bromide option of the Grignard since preparation of benzyl magnesium bromide often leads to the occurrence of unwanted Wurtz coupling products. Subsequent TBS-protection of the hydroxyl group under similar conditions reported in the previous section (Scheme **2.8**) afforded the analogue substrate **2.4.2** in excellent yield (87%).

The analogue substrate was then subjected to Rh(I)-catalysed hydroboration with pinacolborane (Table 2-9) as the boron source as resulting boranes would be more stable and easily purified as compared to those products derived from catecholborane.

Table 2-9: Optimisation of analogue substrate hydroboration

Entry ^a	Catalyst (mol %)	Duration (hr)	Temp. (°C)	Yield ^b
1	Wilkinson's / (5)	3.5	r.t.	- ^c
2 ^d	Rh(CO)(PPh ₃) ₂ Cl / (5)	2	r.t.	73

^aAll reactions were done in 0.25M concentration of analog substrate **2.4.2** in absolute DCM. ^bIsolated yield.

^cStarting material **2.4.2** was obtained. ^dReaction was performed with HBPin added before the addition of substrate **2.4.2**.

Interestingly, when the reaction was performed in the presence of Wilkinson's catalyst, no conversion of the substrate was observed even after 3 hours, beyond which catalytic decomposition was observed in the reaction mixture. However, when the same reaction was performed with Rh(CO)(PPh₃)₂Cl as catalyst, the reaction proceeded smoothly and afforded the corresponding borane **2.4.3** in exemplary yield (73%). This could possibly be due to the steric hindrance of the substrate posed by the *tert*-butylsiloxy group which could hinder coordination of the C=C bond to the Rh(III) centre after oxidative addition of HBpin on the catalyst. Furthermore, the replacement of one PPh₃ ligand with the CO ligand minimises the steric conflict experienced by the alkene substrate **2.4.2** when coordinating to the Rh(III) catalytic intermediate since PPh₃ is much bulkier than CO as a ligand. This indeed proves our hypothesis that the presence of the oxazole moiety in the substrate employed in the previous hydroboration (Scheme 2.8) was the cause for the unsuccessful reaction.

To our delight, only one diastereomer was obtained in the reaction based on TLC and ¹H NMR analyses of the reaction crude, which would imply that the hydroboration is highly

diastereoselective. However, the challenge still remains in determining the exact diastereomer (*syn* or *anti*) that was obtained from the reaction as the borane product **2.4.3** exists as an oil, rendering it difficult to recrystallize. Furthermore, it would be impossible to determine the stereochemical relationship between both stereogenic centres using NOESY as the product is an acyclic molecule with free rotation around all of the bonds in question.

Hence, further transformations have to be performed on the borane adduct in order to achieve an intermediate which we could definitively prove the stereochemical relationship from. An idea was then conceived to methodically transform the borane into a highly polar 1,3-diol compound which would likely crystallize and the diastereomeric relationship could then be determined by X-ray crystallography.

Figure 13. X-ray structure of *syn*-**2.4.4.1**

Further reactions were performed from then, which involved an oxidation followed by a subsequent deprotection of the TBS-group to form diol **2.4.4.1** which could be recrystallized using ether and hexane as the recrystallization solvents (Scheme 2.14). Based on X-ray crystallographic analysis of the crystalline sample of **2.4.4.1**, we ascertained the exact

diastereomeric structure of **2.4.4.1** to be the *syn*-diastereomer (Figure 13). This was a gratifying result as it ascertains that the alkene substrate **2.4.2** underwent highly diastereoselective hydroboration to form exclusively the *syn*-diastereomers of pinacol boronate ester **2.4.3**.

Scheme 2.14. Diol formation from borane **2.4.3**

Subsequently, we then went on to investigate optimal reaction conditions for Suzuki coupling of pinacol boronate ester **2.4.3** with allylic bromide in order to achieve the coupled adduct **2.4.7** (Scheme 2.15).

Scheme 2.15. Diol formation from borane **2.4.3**

Table 2-10: Optimisation of Suzuki coupling

Entry ^a	Catalyst (mol %)	Ligand (mol %)	Base (equiv)	Solvent	Additive (equiv)	T (°C)	Yield
1	PdCl ₂ (PPh ₃) ₂	-	Na ₂ CO ₃	THF	-	60	SM
	(5)		.10H ₂ O				
			(7)				

2	PdCl ₂ (dppf) (5)	-	K ₂ CO ₃ (3)	DMF- H ₂ O	2	80	SM (65)
3	PdCl ₂ (dppf) (5)	-	Cs ₂ CO ₃ (2)	THF	-	80	SM
4	PdCl ₂ (dppf) (5)	-	KO ^t Bu (2)	THF	-	80	SM (50) ^b
5	Pd(OAc) ₂ (5)	PPh ₃ (20)	K ₂ CO ₃ (3)	THF- EtOH	-	80	SM
6	Pd(OAc) ₂ (2)	SPhos (4)	Cs ₂ CO ₃ (2)	THF- H ₂ O	-	80	SM
7	Pd(OAc) ₂ (5)	SPhos (10)	CsOH.H ₂ O (3)	PhMe- H ₂ O	-	100	SM
8 ^c	Pd(OAc) ₂ (3)	SPhos (6)	CsOH.H ₂ O (3)	PhMe- H ₂ O	-	100	SM (2) ^d
9	PdCl ₂ (dppf) (5)	-	KOH (3)	Dioxane -H ₂ O	Ag ₂ O (2)	80	SM (30) ^d

10	PdCl ₂ (dppf) (5)	-	KO ^t Bu (2)	DME	Ag ₂ O (2)	85	SM
11	Pd(OAc) ₂ (5)	C ₁₁ H ₂₁ N 2.BF ₄ (4)	KF (1.25)	THF- H ₂ O	18- Crown- 6 (1.25)	50	SM
12	Pd ₂ (dba) ₃ (5)	P ^t Bu ₃ (15)	CsOH.H 2O (2)	DMF	Ag ₂ O (3)	100	SM ^b
13	PdCl ₂ (dppf) (5)	-	Cs ₂ CO ₃ (2)	DMF- THF- H ₂ O	Ag ₂ O (2)	100	SM
14	Pd ₂ (dba) ₃ (5)	P ^t Bu ₃ (15)	CsOH.H 2O (2)	Dioxane -H ₂ O	Ag ₂ O (2)	80	SM ^b

^aAll reactions were done in 0.3M concentration of substrate **2.4.3** in organic solvent. ^bSome unidentified by-product was isolated as well. ^cReaction was performed with allyl acetate instead of allyl bromide. ^dAlcohol by-product **2.4.4** was isolated.

In general, multiple attempts at the Suzuki coupling reaction came to naught in terms of progress in generating the product **2.4.7**. In almost every attempt, it was observed that the starting material pinacolboronate ester **2.4.3** was retrieved in more than 50% yield and being the only compound observed in the crude of the reaction, no conversion to the desired product

was observed. Furthermore, even reactions under the use of strong bases such as CsOH and Cs₂CO₃ did not lead to any conversion at all.

Since oxidative addition with allylic bromide is very rapid in the catalytic pathway, we postulated that the transmetallation step could be a problem in the catalytic cycle, presumably due to insufficient nucleophilic character of the organoboronate ester **2.4.3**, causing the inability of the formation of desired product. This postulation is made based on the hypothesis of the catalysis going through the ‘Palladium-hydroxide’ species⁷⁰. Additionally, there is the possibility of the difficulty in the formation of the borate complex via nucleophilic attack of the base species to the Boron centre of the pinacolboronate ester, hence stopping the catalytic pathway at that stage before transmetallation could proceed with the Palladium-halide complex after oxidative addition⁷¹.

However, even subjecting the reaction to the use of strong bases and higher temperatures (80 – 100°C), no conversion of the starting material was observed as well. This could possibly be due to the low electrophilic character of the Boron centre in the substrate, caused by the inductively electron-donating character of the pinacol and the alkyl groups, which could make transmetallating sp³-hybridised pinacolboronate esters inherently difficult.

Certain reaction conditions (entries **8 – 9**), however, have been found to generate the unexpected alcohol by-product **2.4.4**, albeit in minimal yields, which would only be generated via oxidative conditions such as H₂O₂ in the presence of a base under normal circumstances.

Foreseeing the need for an alternative sp³-sp³ coupling strategy, we then turned our attention to an interesting Cu(II)-catalysed “Kumada-like” coupling that was utilised by Kambe and co-workers⁷². According to their work, they devised an efficient C-C coupling between linear aliphatic halides and Grignard reagents in the presence of CuCl₂ in only ppm quantities, in the presence of a necessary alkyne ligand. Hence, we attempted to apply similar conditions to

achieve desired allylation in our case (Scheme 2.17). Since it was simpler to obtain the allyl Grignard reagent, it was thus necessary to convert our boronate ester **2.4.3** to a primary halide. The conversion to alkyl iodide **2.4.6** was done over three steps, namely oxidation of the boronate ester **2.4.3** to alcohol **2.4.4**, followed by mesylation to give **2.4.5** and a subsequent Finkelstein iodination to furnish the iodide **2.4.6** (Scheme 2.16).

Scheme 2.16. Iodide formation from borane **2.4.3**

Scheme 2.17. Cu(II)- catalysed allylation of iodide **2.4.6**

Table 2-11: Optimisation of Cu(II)-catalysed allylation

Entry ^a	Catalyst	Ligand	Grignard	Conc	T (°C)	Dura	Conver
	(mol %)	(equiv)	(equiv)	(M)		-tion	-sion
							(%) ^b

1	CuCl ₂ (25 mol ppm)	(1.0)	1.1	0.3	r.t.	24h	minimal
2	CuCl ₂ (1000 mol ppm)	(1.0)	K ₂ CO ₃ (3)	0.3	r.t.	36h	31
3	CuCl ₂ (5)	(1.0)	1.1	0.25	r.t.	24h	63
4	Cu(OTf) ₂ (5)	(S)- BINAP (0.1)	1.1	0.25	r.t.	24h	SM
5	CuCl ₂ (5)	(1.0)	1.5 (added over 5 mins)	0.1	-10°C (20mins r.t.	25h	quant.
6	CuCl ₂ (5)	(1.0)	1.5 (added over 10 mins)	0.1	-10 – r.t.	25h	SM
7 ^c	CuCl ₂ (5)	(1.0)	1.5 (added over 5 mins)	0.1	0°C (20mins) then r.t.	25h	quant.

^aAll reactions were done in anhydrous THF as the solvent. ^bConversion was determined based on crude NMR after work-up. ^cReaction was performed on a 500mg scale of substrate.

Based on the results obtained in above Table **2-11**, it was observed that the best results were obtained in entry **7**. However, it was later discovered that while the reaction was efficient in a small scale, it gave only 50% conversion in gram scales and hence we had to devise an alternative to remedy this problem. It was later discovered that Hu and co-workers had done a similar reaction but used CuCl instead and in the absence of a ligand, efficiently furnished similar coupling between complicated primary or secondary halides with primary or secondary Grignard reagents (Scheme **2.18**)⁷³. Since Kambe's coupling strategy using CuCl₂ was capricious on larger scales, we employed conditions used by Hu et al. instead and had managed to effect the allylation in excellent yields in gram scales for our case with an added gainfulness of a shorter reaction time required.

Scheme **2.18**. Cu(I)- catalysed allylation of iodide **2.4.6**

Subsequent deprotection of the TBS ether was performed to obtain the alcohol **2.4.8** in an excellent yield of 84% in the presence of catalytic acetyl chloride and methanol (Scheme **2.19**).

Scheme **2.19**. TBS deprotection

Subsequent esterification of the alcohol with phosphono-acetic acids **2.1.9ab** furnished the corresponding esters **2.4.9ab** in excellent yields (87 – 89%, Scheme 2.20).

Scheme 2.20. Esterification of alcohol to phosphono-acetate ester

Subsequent cross-metathesis of alkene **2.4.9ab** with crotonaldehyde in the presence of Grubbs Second generation catalyst efficiently yielded the corresponding (*E*)-en-aldehydes **2.4.10ab** both in 66% and 71% yields respectively (Scheme 2.21).

Scheme 2.21. Cross-metathesis

It was noted that the proton on the β -carbon to the aldehyde had a distinct doublet of triplet splitting pattern and its coupling constant with the α proton was calculated to be 16Hz. This meant that the relationship between the two protons were *trans* in geometry.

With the (*E*)-enal intermediate in hand, it was finally subjected to Horner-Wadsworth-Emmons dimerization in order to achieve the phenyl-analogue of Samroiymycin A (Scheme 2.22). Several reaction conditions were tried to effect the reaction as shown in Table 2-12.

Scheme **2.22**. Final step towards synthesis of Samroiymycin-analogue A

Table **2-12**: Optimisation of Honer-Wadsworth-Emmons Dimerization of **2.4.10a**

Entry ^a	Base (eq)	Additive (eq)	Solvent	Addition time over syringe pump (h)	T (°C)	Dura-tion	Yield (%) ^b
1	K ₂ CO ₃ (3.0)	18-Crown-6 (1.4)	PhMe	-	60 - 70	6h	- ^c
2	DBU (3.0)	LiCl (3.0)	THF	4	r.t.	5.5h	- ^c
3	DBU (3.0)	LiCl (3.0)	MeCN	1	0	18	- ^c
4	DBU (3.0)	LiCl (3.0)	MeCN	1	0	15	- ^e
5	Ba(OH) ₂	-	Dioxane/H ₂ O (40:1)	-	70	6	- ^e
6	Ba(OH) ₂ (4.0)	-	THF/H ₂ O (40:1)	3	r.t.	6	Complex mixture

7	Ba(OH) ₂ (3.6)	-	THF/H ₂ O (40:1)	5	0 - r.t.	26	Complex mixture
8	KO ^t Bu (2.2)	-	THF	-	0	13	- ^c
9	NaH (3.0)	-	THF	3	r.t.	7	27 ^g
10	NaH (4.0)	15-Crown-5 (0.48)	C ₆ H ₆	-	r.t.	1.25	12
11 ^d	NaH (2.7)	15-Crown-5 (0.27)	PhMe	6	0 - r.t.	7.5	56

^aAll reactions were done in anhydrous conditions. ^bYield was based on isolated product upon column chromatography. ^cDecomposition was observed in the reaction mixture based on crude NMR as the spectrum was too messy to be elucidated. ^dReaction was done in 0.015M concentration of the substrate in the said solvent. ^eProton NMR of reaction crude shows majority of Starting material remaining. ^fReaction was done using **2.4.10b** as the substrate. ^gIsolated product was not fully pure.

It was observed that initial efforts to effect the macrocyclic dimerization under standard basic conditions such as K₂CO₃ and DBU led to mostly decomposed mixtures as observed from the ¹H NMR analysis of the reaction crudes. It is likely that the reaction is sensitive to elevated temperatures above ambient conditions, which when conducted led to undesirable reaction outcomes (entries **1 – 3**).

We then proceeded to attempt the protocol published by Sinisterra in which Ba(OH)₂ was deemed an efficient catalyst for intermolecular Horner-Wadsworth-Emmons reaction. It was postulated in his case that the surface of Ba(OH)₂ provides active sites for the adsorption of the carbonyl and phosphonate substrates via coordination of the oxygen to the catalytic surface. The oxaphosphetane intermediate is generated on the surface which is then liberated as the desired alkene product, with the assistance of a small portion of water in the reaction, regenerating the catalyst. However, this efficiency was not observed when applied to our

substrate as complex mixtures were obtained according to ^1H NMR analysis. This could possibly be due to the difficulty in controlling the reactivity of the $\text{Ba}(\text{OH})_2$ in catalysing a head-to-tail dimerization of our substrate since the possibilities of forming linear polymers or even larger macrocyclic polymers are probable.

Our attention was then turned to the use of sodium hydride as the base of choice to effect the double Horner-Emmons reaction using conditions adopted by Hoyer and co-workers in 2000 in their total synthesis of (-)-Cylindrocyclophane A. It was observed from their experiments that the use of Masamune olefination conditions (similar to entries **2** - **4**) would yield their macrocyclic product in modest yield, but as a complicated mixture of *EE*, *EZ*, and *ZZ*-isomers. It was postulated that isomerization of any of the isomers is unlikely under either of the above Horner-Emmons olefination conditions, but rather, emerges as a result of a kinetically-controlled event. Hence, we proceeded to perform our double macrocyclic Horner-Emmons olefination using NaH in Benzene with catalytic amounts of 15-Crown-5, the very set of conditions that effectively yielded pure *EE*-isomer for Hoyer's synthesis⁷⁴. However, it was observed that despite complete consumption of the starting material in a short period of time as observed by TLC, the isolated yield of the desired analogue was only 12%. Thus, it was decided that the substrate has to be added in low proportions over a significant period of time as it is possible that side reactions were occurring in the previous attempt (entry **10**). As such, the conditions adopted by Hoyer et al., were made milder in entry **11** by modifying the amount of base and crown ether ligand added, changing the solvent to a slightly less polar variant, toluene and performing the reaction at zero degrees during which the substrate was added gradually over a six hour period via syringe pump. Gratifyingly, full conversion of the substrate was achieved as observed by TLC after stirring the reaction for 7.5h and the desired phenyl-analogue was obtained in 56% yield, as a mixture of D/L- and meso-isomers.

We further analysed the coupling constant of the proton at the α position to the ester of the synthesised macrocycle and deduced it to be 16 Hz, which meant that the geometry of the newly formed C=C bond from the dimerization was *trans*. Since the geometry of the C=C bond in the enal **2.4.10a** was predominantly *trans* based on previous calculations, we postulated that the isolated phenyl-analogue was the desired *EE*-isomer.

Overall, we successfully achieved the synthesis of the *Ph*-analogue of Samroiyotmycin A in a good overall yield of 13% over **11** steps (Scheme **2.23**).

Scheme 2.23. Overall synthesis of Phenyl-analogue **2.4.11a**

Chapter 3

RESULTS AND DISCUSSION TOWARDS SYNTHESIS OF SAMROIYOTMYCINS

3.1. Model study of a late-stage establishment of the oxazole moiety

We then subsequently turned our efforts towards testing the idea of using Van Leusen's method³⁴ to establish the oxazole moiety at a possibly later stage in the synthetic plan. This was so that we could avoid the oxazole presence interfering with any reactions involving transition metal catalysts in the early stages of the synthesis. To determine the feasibility of the Van Leusen's approach in our route, we tested the hypothesis on a model substrate.

(Scheme 3.2)

Scheme 3.2. Model studies with TosMIC

Grignard addition of allyl magnesium bromide on hexanal afforded the alcohol in excellent yield. Subsequently, acetylation of the secondary alcohol gave the acetate in 90% yield and ozonolysis of the alkene generated the model aldehyde substrate in exemplary yield. However,

Van Leusen's reaction of the beta-acetylated aldehyde substrate with TosMIC did not give any oxazole. Instead, it resulted in the elimination of the acetate group, resulting in alkene formation. This meant that installing the oxazole functionality on an intermediate aldehyde at a later stage using Van Leusen's synthesis would not be feasible in our synthetic plan towards the natural product.

3.2. Synthetic strategy towards synthesis of Samroiyotmycins from 2-(oxazol-5-yl)acetaldehyde intermediate

Therefore, we switched our strategy for the synthesis once again, this time envisioning a synthetic strategy that would lead towards a key intermediate which is 2-(oxazol-5-yl)acetaldehyde as shown in figure **14** below.

Figure **14**. Structure of 2-(oxazol-5-yl)acetaldehyde

Subsequent transformations from the aldehyde would then ensue towards the synthesis of Samroiyotmycins **A** and **B**. (Scheme **3.3**)

Scheme 3.3. Alternative strategy towards synthesis of Samroiymotmycins from 2-(oxazol-5-yl)acetaldehyde

It was proposed that if the 5-oxazolylacetaldehyde intermediate **3.3.7** was generated, the left end of the fragment could be further functionalised by performing either an asymmetric Aldol⁷⁵ or Krische⁷⁶ reaction to generate the corresponding alcohols as their anti-diastereomeric forms. Depending on which reaction was employed, subsequent simple transformations could be performed to generate the iodide intermediate which could then undergo a Cu(I)-catalysed allylation to extend the chain of the intermediate, as demonstrated previously in Scheme 2.18. A Mitsunobu esterification⁷⁷ could then be conveniently used to generate the subsequent ester as the syn-diastereomer, which could then be extended on the terminal alkene via cross-metathesis to generate the en-al moieties, each as the final key

precursor for participating in the macrocyclic Horner-Wadsworth-Emmons reaction towards the Samroiymycins.

We began our strategy towards the acetaldehyde intermediate following the given strategy as shown below in Scheme 3.3.1.

Scheme 3.3.1. Strategy towards the establishment of 2-(oxazol-5-yl)acetaldehyde

Our efforts proved successful in the initial stages where we were able to obtain the THP-ether **3.3.1** in excellent yield of 83%, up until the formation of the formamide **3.3.5**. Due to its high polarity, it was used directly in its crude form for the oxidation step since THP-removal gave a sufficiently clean crude result based on proton NMR. However, all efforts to oxidise the

alcohol moiety to aldehyde **3.3.6** failed. In most cases, using IBX or the Dess-Martin reagent led to very low conversions and the observation of unidentified peaks in the crude NMR spectrum which was inconclusive and challenging to analyse. Using Swern oxidation conditions⁷⁸ or even the Parikh-Doering protocol⁷⁹ led to likely side reactions occurring on the aldehyde product formed since we observed multiple aldehyde peaks in the NMR spectrum. This could possibly be due to an unstable nature of the envisioned aldehyde **3.3.6** since the transformation of the alcohol to aldehyde renders the substrate more electrophilic on the beta position of the triple bond. Hence, this could result in a higher tendency for side reactions to occur on the resultant compound if it was formed.

Attempts were made to subject the formamide **3.3.4** directly to cyclisation conditions that were previously established using JohnphosAuCl and AgOTs. (Scheme 2.5) However, no conversion to the desired acetaldehyde was observed at all and in most cases, varying the silver salts did not help either. Prolonged stirring and heating led to decomposition of the catalyst in most cases.

Scheme 3.3.2. Modified strategy towards synthesis of 2-(oxazol-5-yl)acetaldehyde

It was postulated that the substrate **3.3.4** employed for the cyclisation here was insufficiently electrophilic at the C2-position as labelled in scheme 3.3.2. Hence, intramolecular nucleophilic approach by the formyl group was disfavoured in the above-mentioned scenario, as compared to the substrate previously employed for the gold(I)-catalysed cyclisation in Scheme 2.5. Faced with yet another debacle, we devised an alternative strategy towards the formation of the desired acetaldehyde (Scheme 3.3.3).

Scheme 3.3.3. Modified strategy towards synthesis of 2-(oxazol-5-yl)acetaldehyde

In this scheme, we began our synthetic ideation from the work of Ley et al.⁸⁰ in his total syntheses of bisoxazole natural products Bengazoles A & B. Using TosMIC as the starting material, performing a Van Leusen's reaction according to Ley's protocol with ethyl glyoxylate to afforded the corresponding ethyl-5-oxazole carboxylate **3.3.7** in excellent yield. Subsequent reduction using lithium aluminium hydride afforded the alcohol **3.3.8** in 74% yield. A mesylation reaction was done before performing an S_N2 cyanation to achieve the desired nitrile **3.3.10**. However, it was later realised that the mesylate was highly unstable and inconvenient to purify and handle. Additionally, subjecting the crude mesylate directly with

KCN in DMF at 70°C led to an inconclusive proton NMR spectrum observed from the crude mixture. Only 55% yield of the pure mesylate was obtained during purification, which could be due to decomposition on silica gel. In addition, when the mesylate was subjected to standard cyanation conditions, low yields were obtained from the reaction (15 - 35% yield). To avert the unstable mesylate, the alcohol was converted to the corresponding chloride first before subjecting to cyanation, affording the nitrile in 75% yield over 2 steps. However, subsequent reduction of the nitrile to the acetaldehyde proved to be dismayingly unsuccessful as minimal conversion of the nitrile to the aldehyde was observed. Even after carrying out the reduction several times at elevated temperatures, ranging from -78°C to ambient conditions, the yield of the aldehyde obtained was still too low.

Despite the standstill faced with reducing nitrile **3.3.10**, we decided to perform a methoxycarbonylation on chloride **3.3.9** to achieve the corresponding ester **3.3.11** before reducing it to our desired acetaldehyde (Scheme **3.3.4**), an idea inspired by the synthesis of Curvulone B previously done in our group⁸¹. We were delighted to observe an efficient chlorination-carbonylation from alcohol **3.3.8** to ester **3.3.11** with 76% yield over two steps.

Scheme **3.3.4**. Modified strategy towards synthesis of 2-(oxazol-5-yl)acetaldehyde via ester **3.3.11**

However, it was observed that all attempts to partially reduce the ester to aldehyde has proven to be cumbersome as the result tends to be a mixture of both the desired aldehyde, alcohol and even unreacted starting material. Furthermore, reacting the ester with DIBAL-H while

maintaining it at -78°C showed no conversion of the ester at all, even after stirring for 4 hours. To overcome this problem, a transformation of the methyl ester **3.3.11** to a dimethyl Weinreb ketone **3.3.12** was performed and reduction of the Weinreb amide was attempted.

Scheme **3.3.5**. Modified strategy towards synthesis of 2-(oxazol-5-yl)acetaldehyde via amide **3.3.12**

However, all attempts to furnish the acetaldehyde proved again to be unexpectedly challenging, especially with the formation of both the aldehyde as the minor compound as well as the suspected formation of an enamine by-product based on ^1H NMR analysis of the crude mixture. (Scheme **3.3.5**) When the reaction was elevated to -10°C , it was postulated that multiple side reactions occurred as multiple aldehyde peaks were observed in the crude ^1H NMR spectrum. Furthermore, both the aldehyde product and enamine by-product were inseparable via column chromatography. An attempt to isomerize the enamine to the desired aldehyde *in-situ* by stirring the mixture of compounds in a weakly acidic medium such as silica gel resulted in a complicated reaction outcome with an incomprehensible ^1H NMR spectrum of the reaction crude.

Since obtaining the aldehyde was inconvenient, reducing the ester **3.3.11** to its corresponding alcohol followed by a re-oxidation to generate the desired aldehyde **3.3.6** was deemed as the subsequent logical approach (Scheme **3.3.6**).

Scheme **3.3.6**. Reduction of ester **3.3.11** to alcohol

Scheme **3.3.7**. Alcohol oxidation attempts to aldehyde **3.3.7**

However, to our dismay, attempts to oxidise the alcohol to aldehyde either resulted in intricate reaction outcomes or denied conversion of starting material. (Scheme **3.3.7**) For the Swern oxidation reaction attempted, it was postulated that side reactions occurred as a result of the likely unstable nature of the acetaldehyde. The installed aldehyde functional group on the product would cause the alpha proton to become acidic, possibly leading to intermolecular polymeric nucleophilic reactions.

3.2.1. Attempt on Krische allylation of 5-oxazolyethanol intermediate

Furthermore, we also attempted a Krische allylation of the alcohol but no reaction was observed at all (Scheme 3.2.1.1). The Lewis basic nature of the nitrogen atom on the heterocyclic core might have coordinated to the iridium catalytic centre, rendering it ineffective for the reaction.

Scheme 3.2.1.1. Krische Allylation

Since the above strategies did not succeed as expected, we shifted our attention towards another synthetic layout where we began from a racemic approach before targeting it diastereoselectively and a strategy that avoided the use of transition metal catalysed reactions due to the inhibitory effect of the oxazole moiety.

3.3. Racemic strategy towards synthesis of Samroiymycins

Scheme 3.4.1. Racemic strategy towards synthesis of Samroiymycins

The synthesis (Scheme 3.4.1) began with diethyl methylmalonate and alkylation at the alpha carbon with butenyl bromide, yielding the homoallylic alkene **3.4.1** quantitatively on gram

scale. Hydrolysis then afforded the malonic acid **3.4.2** cleanly in excellent yield upon work-up, which is then decarboxylated neatly at elevated temperatures overnight, giving the mono-acid **3.4.3** in 81% yield upon column chromatography. However, it came to our attention that when the decarboxylation was done on gram scales, we observed the presence of a side product corresponding to the double bond isomerisation of the terminal alkene product **3.4.3** in the reaction crude. We postulated that this isomerisation likely occurred due to the presence of residual HCl present from the work-up of the previous hydrolysis step, hence resulting in the subsequent acid-catalysed and heat induced double bond isomerisation of the alkene.

Scheme **3.4.1.1**. Decarboxylation step

Thus, it was decided that the decarboxylation had to be performed in the presence of a sub-stoichiometric quantity of collidine as base to sequester any residual HCl in the malonic acid substrate from the hydrolysis work-up. To our delight, the performance of the decarboxylation was back to exemplary standards, affording the mono-acid **3.4.3** in near quantitative yield in a shorter duration and without any isomerisation observed (Scheme **3.4.1.1**).

The acid **3.4.3** was then reacted with *N,O*-dimethylhydroxylamine hydrochloride to afford the Weinreb ketone **3.4.4** in good yield. However, the subsequent step where the Weinreb ketone was subjected to olefin metathesis with acrolein diethyl acetal afforded good yields of the

internal alkene but with poor selectivity of 3:1 (*E*:*Z*), despite controlling the addition rate of the Grubbs II catalyst via the use of a syringe pump. Moreover, changing the catalyst to Grubbs I resulted in yield erosion. It was also noted that side product was observed in every metathesis which corresponded to the internal alkene with deprotected acetal group. (Figure 15) This was possibly due to the labile nature of the acyclic acetal protecting group.

Figure 15. Structure of En-al

Hence, we decided to change the coupling reagent to 2-vinyl-1,3-dioxolane, which possesses a cyclic acetal group and would hence presumably be more stable.

Scheme 3.4.2. Modified strategy towards synthesis of Samroiymycins

It was a delight at first to see a great improvement in not only the metathesis yield but also the metathesis selectivity towards the *E*-alkene. (Scheme 3.4.2) Subsequent nucleophilic

addition of 3.4.5.1 with the *in-situ* generated lithium-acetylide anion afforded the ynone in 56% yield with a small amount of impurity present. On closer inspection, the impurity present in the isolated ynone product was deduced to be an aldehyde side-product, likely as a result of *in-situ* deprotection of the dioxolane group during column chromatography. Nonetheless, we decided to proceed with the next step, which was where our efforts came to a standstill when we tried to remove the TBS group.

Table 3-1: Optimisation of TBS-deprotection of 3.4.6

Entry ^a	Reagent (eq)	Solvent	T (°C)	Duration	Ratio of en-al : desired product ^b
1	TBAF.3H ₂ O (1.5)	THF	r.t.	0.5h	- ^c
2	0.67M TBAF (buffered with K ₂ HPO ₄)	THF	0 - r.t.	2.5h	1:1
3	Amberlyst-15	Ethylene glycol	r.t.	20	En-al product (with other unknown compounds)
4	PPTS (0.3)	Ethylene glycol	r.t.	overnight	- ^d

^aAll reactions were done in anhydrous conditions (except in entries 1 and 2). ^bRatio was calculated based on ¹H NMR of reaction crude mixture. ^cDecomposition was observed in the reaction mixture based on crude NMR as the spectrum was too messy to be elucidated. ^dRatio of 3:1 mixture of dioxolane:enal with the TBS-group intact was observed from the crude ¹H NMR.

It was postulated that when we used TBAF.3H₂O for the deprotection, the highly sensitive ynone functionality present in our molecule could possibly pose as a Michael acceptor for nucleophilic attack by the fluoride ion. Hence, the reaction led to an inconclusive proton NMR

spectrum of the reaction crude, as it was likely that multiple side reactions have occurred in the system.

Switching to the use of an acidic condition to remove the TBS group was tricky as the acetal group was also deprotected under acidic conditions, generating the en-al side product. (Scheme **3.4.2**) In spite of that, when a solution of TBAF.3H₂O buffered with K₂HPO₄ was used⁸², there was still a 1:1 mixture of the desired product and the unwanted side en-al product (TBS- and acetal deprotected) in the crude mixture upon reaction work-up. We postulated that the use of ethylene glycol as the solvent would enable the use of an acidic medium for TBS-deprotection as excess glycol would re-install the protection on the aldehyde in case the dioxolane was removed. However, when the theory was experimented, the method proved to be inefficient as the en-al product was still obtained as the major component of the crude mixture. (entry **3**)

Nonetheless, we switched our strategy for the synthesis once again and modified scheme **3.4.1** to a strategy that first encompasses the functionalization of the right-end of intermediate **3.4.4** into the 2-unsubstituted oxazole moiety, before installing the aldehyde functionality on the left terminal of the molecule.

Chapter 4

COMPLETE SYNTHESIS OF *RAC*-SAMROIYOTMYCINS

4.1. Revised strategy towards synthesis of Samroiyyotmycins

Since the pre-installation of the α,β -unsaturated aldehyde moiety on the left end of the Weinreb amide intermediate proved to be inconvenient for further transformations along the synthesis, it was decided that the route of transforming the right-end of the fragment towards the envisioned oxazole before extending the left end of the chain would be more efficacious.

Scheme 4.1.1. Modified racemic strategy towards synthesis of Samroyotmycins

According to the proposed scheme **4.1.1** above, the synthesis begins in a similar fashion to that previously employed (Scheme **3.4.1**) from the malonate alkylation step, up until the construction of Weinreb amide intermediate **3.4.4**. From this point, instead of performing cross metathesis on the alkene functionality, synthetic plans were made to functionalise and transform the Weinreb amide into the envisioned 2-unsubstituted oxazole moiety. In scheme **3.4.2**, it was observed that while propargylation of the Weinreb amide using *tert*-butyldimethylsilyl propargyl ether was efficient in terms of conversion, it was less than stellar based on isolated yield of the alkyne and reproducibility of the result. Based on Deuterium labelling experiments, it was noted that the conversion of the TBS-propargyl ether to lithium acetylide species using *n*-butyl lithium was erratic and very sensitive to temperature changes as well as the quality of the *n*-butyl lithium used. Hence, we decided to alter the propargyl ether to one with a THP group instead as the procedure for such a propargylation was decidedly more convenient and does not involve the use of *n*-butyl lithium. Subsequent deprotection of the tetrahydropyranyl group followed by transformation of the hydroxyl into the formamide group via nucleophilic substitution and subsequent alcoholysis will set up the formamide group on the molecule ready for the oxazole formation. The intramolecular cyclisation to the 2-unsubstituted oxazole can be attained by employing the well-established gold catalysed methodology derived from the previous synthesis of the oxazole intermediate **2.1.4** (Scheme **2.5**). Further transformations on ketone group can be performed to install the phosphonoacetate group for the HWE reaction in the latter part of the synthetic scheme. From this point, it is understood that from previous hydroboration attempts (Table **2-5**), the oxazole group tends to interfere with many transition metal-catalysed processes. We intend to utilise a Lewis acid additive in the cross metathesis step, envisioning its ability in pre-coordinating to the oxazole before introducing the Grubbs II catalyst. In case that the above strategy fails, the alternative strategy is to transform the present alkene functional group into an aldehyde,

a suitable partner for a subsequent Wittig reaction with the commercially available formylmethylene triphenylphosphorane ylid to generate the desired enal intermediate **4.1.8a** as the key precursor for the macrocyclic Horner-Wadsworth-Emmons dimerization towards the Samroiyotmycin A. Additionally, Horner-Wadsworth-Emmons coupling of enal intermediates **4.1.8a** and **4.1.8b** will produce the unsymmetrical Samroiyotmycin B.

Scheme **4.1.2**. Propargylation of Weinreb amide intermediate

Delving into the propargylation step towards the installation of the internal alkyne (Scheme **4.1.2**), we have decided to employ the *in situ* formation of the propargylic organomagnesium species which is more nucleophilic and is hence able to effect the propargylation step above more efficiently relative to the use of a lithium-acetylide species. However, the desired alkyne product was inseparable from the use of the propargyl-THP ether reagent and since excess amounts of the reagent were needed to effect full conversion, we proceeded on to the subsequent step of removing the THP group.

Table 4-1: Optimisation of THP-deprotection of **ynone intermediate crude**

Entry	Reagent (eq)	Solvent	T (°C)	Duration	Yield of 4.1.1 ^a (%)
1	Amberlyst-15 (15% w/w)	MeOH	r.t.	8h	- ^b
2	PPTS (0.1)	EtOH	55	3	46
3	PPTS (0.09)	EtOH	55	3.5	73 ^c
4	PPTS (0.09)	2-PrOH	60	6	86

^aAll reported yields were calculated based on isolated product after column chromatography. ^bCrude mixture showed presence of side product corresponding to double-bond isomerization of desired product. ^cYield decreased significantly when experiment was performed on gram scale.

It was observed that when we subjected the crude ynone intermediate to Amberlyst-15 in methanol, the reaction medium became too acidic and not only deprotected the intermediate, but also induced double bond isomerization of the product. Hence, the next sensible alternative was to use PPTS as the acidic catalyst instead since it is a mild yet efficient acid source for deprotection of acid-sensitive protecting groups. Indeed, from entries **2 – 4**, it was clearly demonstrated that catalytic amounts of PPTS were sufficient to induce full deprotection of the THP-intermediate without any trace of isomerization. It was however noted that while excellent yield of the desired alcohol was obtained when Ethanol was used as the solvent, the yield deteriorated upon conducting the reaction at larger scales. It was postulated that the use of large amounts of ethanol on large scales could have caused a Michael reaction on the ynone product due to its good Michael acceptor ability. By changing the solvent to isopropanol which is less nucleophilic in nature, the amount of side product

stemming from the unwanted Michael addition was significantly reduced and the yield of alcohol obtained was excellent, even on gram scale.

Scheme 4.1.3. Imidation of ynone intermediate 4.1.1

Subsequently, the alcohol intermediate 4.1.1 was subjected to mesylation and then nucleophilic substitution with sodium diformylamide to install the imide moiety as the precursor for the formamide group (Scheme 4.1.3). However, the imide installation process was not as straightforward as expected, as can be seen from the results in Table 4-2.

Table 4-2: Optimisation of imidation of ynone intermediate 4.1.1

Entry	Reagent (eq)	Solvent	T (°C)	Duration	Yield of imide ^a (%)
1	NaN(CHO) ₂ (1.5)	MeCN	r.t. - 80	5.5h	- ^b
2	NaN(CHO) ₂ (1.5) + TBAI (0.1)	MeCN	r.t.	Overnight	- ^b

^aAll reported yields were calculated based on isolated product after column chromatography. ^bProton NMR of crude mixture was inconclusive due to multiple peaks corresponding to side products.

It was observed from the ¹H NMR of the crude of both reactions that despite the complete conversion of the mesylate starting material and the evidence of the peak corresponding the imide protons, there were multiple other peaks corresponding to side products that rendered the spectrum too complicated for elucidation. This was likely once again due to the presence of the unmasked ynone functionality present in the substrate as a Michael acceptor, resulting

in possible side reactions soon as the diformylamide nucleophile was introduced in the reaction. Hence, we decided to mask the carbonyl group as a 1,3-dioxolane, hoping to avoid the possibility of Michael addition occurring on the substrate (Scheme 4.1.4).

Scheme 4.1.4. Protection of 4.1.1 as 1,3-dioxolane 4.1.2

Table 4-2: Optimisation of ketone protection of ynone intermediate 4.1.1

Entry	Reagent (eq)	catalyst	Solvent	T (°C)	Duration	Yield of imide ^a (%)
1	Ethylene glycol (1.1)	PPTS (0.1)	PhMe	Reflux	overnight	10 ^b
2	Ethylene glycol (1.2)	PPTS (0.1)	C ₆ H ₆	Reflux	Overnight	47 ^b
3	2-methoxy-1,3-dioxolane (1.5)	PPTS (0.1)	DCM	r.t.	Overnight	- ^b
4	2-methoxy-1,3-dioxolane (1.5)	PPTS (0.1)	DCM	reflux	Overnight	- ^b
5	2-methoxy-1,3-dioxolane (1.5)	Amberlyst-15 (80% w/w)	DCM	0 – r.t.	Overnight	- ^b
6	2-methoxy-1,3-dioxolane (1.5)	CSA (0.1)	DCM	reflux	Overnight	- ^b

7	2-methoxy- 1,3-dioxolane (1.5)	<i>p</i> -TSA (0.1)	DCM	0	Overnight	13 ^b
6	2-methoxy- 1,3-dioxolane (1.5)	<i>p</i> -TSA (0.1)	DCM	r.t.	6h	65

^aAll reported yields were calculated based on isolated product after column chromatography. ^bProton NMR of crude mixture showed significant presence of unreacted starting material.

The protection of the ketone group as the 1,3-dioxolane proved to be unexpectedly cumbersome as well. When ethylene glycol was used as the reagent, refluxing the reaction fitted with a Dean-Stark trap overnight with Benzene, gave moderate yield of the dioxolane (entry **2**), despite the presence of unreacted ketone in the mixture. Thus, the decision to switch the reagent to 2-methoxy-1,3-dioxolane was made since it is more superior and efficient as a reagent for carbonyl protection than ethylene glycol due to the mild conditions required for the ketalization⁸³. Upon experimentation with several acidic catalysts and temperatures, it was found that only the use of *p*-TSA was sufficient to induce ketalization of the ketone in good yield. However, the presence of the hydroxyl group in our substrate caused complications in the reaction yield as the hydroxyl group of the product likely reacted with the generated methyl formate *in-situ*, resulting in the formation of the formate ester side product in small quantity. Fortuitously, the formate ester side product can be hydrolysed under mild basic conditions to regenerate the product alcohol high quantitatively (Scheme **4.1.4**), resulting in an overall yield of 65% of the dioxolane **4.1.2**. There were also some other indecipherable side products in detected in the mixture, likely caused by the sensitivity of the hydroxyl group of the product. Nonetheless, even after several attempts to modify the reaction conditions, the optimal yield of the dioxolane remains as obtained in entry **6** and was sufficient for further synthesis, in spite of the yield erosion as a result of ineluctable formation of side products.

The alcohol **4.1.2** obtained in hand was then subjected to imide formation again as shown below in scheme **4.1.5**.

Scheme **4.1.5**. Imidation of alcohol intermediate **4.1.2**

While the almost complete conversion of the mesylate was observed based on ¹H NMR crude analysis, only moderate yields of the imide was isolated (16%), alongside average quantity (41%) of formamide, likely formed as a result of *in situ* cleavage of the imide product. In addition, some slight amount of formate ester was observed, possibly carried over as impurity from the previous protection step after column chromatography, since the polarity of the alcohol and formate ester was rather close. There were also other peaks observed in the ¹H NMR analysis of the reaction crude that were inconclusive and likely formed as a result of decomposition in the reaction.

Thus, we decided to devise an alternative method to install the formamide group efficiently on the substrate. Utilizing the alcohol **4.1.2**, a Mitsunobu phthaloylation was performed, rendering the formation of phthalimide **4.1.3**, in quantitative yield upon purification. The phthalimide was then subjected to hydrazinolysis utilizing Huang Min-lon's protocol, yielding the intermediate amine which was then formylated by refluxing the amine in excess ethyl formate neatly overnight. The resulting desired formamide **4.1.4** was obtained in an excellent yield of 76% over both steps (Scheme **4.1.6**).

Scheme **4.1.6**. Formylation of alcohol intermediate **4.1.2**

At this point, attempts were made to subject the formamide **4.1.4** directly to cyclisation conditions that were previously established using JohnphosAuCl and AgOTs (Scheme **4.1.7**). However, only average yield (36%) of the desired oxazole was obtained with remaining unreacted starting material based on ^1H NMR analysis of the reaction crude (Table **4-3**, entry 1).

Scheme **4.1.7**. Cycloisomerisation of formamide intermediate **4.1.4**

Table **4-3**: Optimisation of gold catalysed intramolecular cycloisomerisation of **4.1.4**

Entry ^a	Au catalyst (mol %)	Silver salt (mol %)	Solvent	Duration (hr)	Temp (°C)	Yield ^b
1	JohnphosAuCl (5)	AgOTs	DCE	O.N.	70	36

(5)

2	JohnphosAuCl (5)	AgOTf	DCE	O.N.	70	-
	(5)					
3	JohnphosAuCl (5)	AgNO ₃	DCE	O.N.	70	-
	(5)					
4	AuCl ₃ (5)	-	MeCN	O.N.	50	- ^{c, d}
5	(<i>p</i> -CF ₃ C ₆ H ₄) ₃ PAuCl (5)	AgOTs	DCE	4	r.t. -	33 ^e
	(5)				70	
6	(<i>p</i> -CF ₃ C ₆ H ₄) ₃ PAuCl (5)	AgOTs	MeNO ₂	O.N.	45	38 ^f
	(5)					
7	Johnphos(NCMe)AuSbF ₆	-	DCE	O.N.	80	-
	(5)					

^aAll reactions were done in 0.25M concentration of alkynamide **4.1.4** in absolute solvent. ^bIsolated yield. ^cCatalytic decomposition was observed. ^dReaction was inconclusive based on TLC and ¹H NMR analysis of crude. ^eConversion estimated from crude proton NMR using integral ratio of product peaks relative to starting material peaks. ^fSome slight impurity was observed in the isolated compound.

Furthermore, upon conducting the reaction with varying catalytic combinations, the yield obtained did not improve (entries **2 – 4**). It was postulated that the presence of the dioxolane group has reduced the electron-withdrawing effect originally present more significantly due to the presence of the ketone group. Hence, the absence of the ketone functionality has likely resulted in lower electrophilicity of the alkyne and on the beta carbon of the alkyne, thus causing inefficient nucleophilic attack by the formamide on the beta carbon. To mitigate the possibility of such an issue, we also attempted the use of gold catalyst with an electron-withdrawing ligand such as (*p*-CF₃C₆H₄)₃PAuCl (entries **5 – 6**). The results were however, an insignificant improvement from the yield first obtained in entry **1**. This suggests that it was

highly due to the lack of an electron-withdrawing group conjugated to the alkyne, leading to the inefficient intramolecular nucleophilic attack within the substrate as mentioned above.

Hence, the ketone functional group was unmasked by removing the dioxolane group using catalytic amounts of *p*-TSA in bench acetone. With the ynone moiety **4.1.5** in hand, the intramolecular formamide cycloisomerisation was then conducted to furnish the 2-unsubstituted oxazole key intermediate **4.1.6** (Scheme 4.1.8).

Scheme 4.1.8. 5-*exo*-dig cycloisomerisation of formamide intermediate **4.1.5**

Table 4-4: Results for Au(I)-catalysed intramolecular cycloisomerization

Entry ^a	Au catalyst (mol %)	Silver salt (mol %)	Solvent	Duration (hr)	Temp (°C)	Yield ^b
1	JohnphosAuCl (10)	AgOTs (10)	THF	O.N.	r.t. - 60	49 ^c
2 ^d	JohnphosAuCl (10)	AgOTs (10)	DCE	O.N.	r.t. - 70	73

^aAll reactions were done in 0.25M concentration of alkynamide **4.1.5** in absolute solvent. ^bIsolated yield. ^c15% of formamide starting material was recovered. ^dReaction was done by first pre-stirring the formamide substrate with the gold chloride catalyst, followed by adding the silver salt and then heating.

When the reaction was done using similar conditions previously employed for the cyclisation of the formamide (Table 4-4, entry 1), the yield of the oxazole obtained was moderate with slight amounts of starting material unreacted. This was an unexpected outcome as the

postulated idea of a conjugated ynone that would make an ideal substrate for the intramolecular cyclisation was inconclusive. In a report by Echavarren et al.⁸⁴, it came to our attention that the use of JohnphosAuCl as the pre-catalyst and certain silver salts (AgNTf₂, AgBF₄, AgOTf, AgSbF₆) would lead to the formation chloride-bridged digold complexes that are substantially inactive and poor catalysts in the reaction, due to the low coordinating nature of these counterions. In such cases, excess amounts of the silver salts are needed to minimise the formation of these digold complexes and increase the formation of active [JohnphosAu]⁺X⁻ species in the solution, where X is the counterion. In summary, the sequence of addition of the silver salt could have an influence in reactivity if the substrate is unable to properly cleave the chloride-bridge. Although the influence of AgOTs on the formation of digold complexes was not examined, we began to wonder if the same phenomenon had occurred in our cycloisomerisation. Hence, the reaction was repeated (entry **2**) but with a procedure where the substrate was premixed with JohnphosAuCl for a set amount of time, followed by the addition of AgOTs sequentially. To our surprise, there was a great improvement in the isolated yield of the desired oxazole **4.1.6**.

With this key step essentially optimised, the oxazole intermediate **4.1.6** was subjected to the next step of synthesis where the ketone group was reduced to alcohol **4.1.7** with DIBAL-H in exemplary yield (Scheme **4.1.9**).

Scheme **4.1.9**. Reduction of ketone intermediate **4.1.6**

Subsequently in scheme **4.1.10**, the alcohol obtained was then esterified with phosphonoacetic acids **2.1.9a** and **2.1.9b** to generate the ester intermediates **4.1.8ab** in excellent yields.

Scheme **4.1.10**. Esterification of alcohol intermediate **4.1.7**

It was at this point however, that the efforts to install the *trans* en-al group on the alkene **4.1.8b** via cross-metathesis were unsuccessful in all cases and conditions tested (Scheme **4.1.11**, Table **4-5**).

Scheme **4.1.11**. Cross metathesis of ester intermediate **4.1.8b**

Table **4-5**: Attempts at cross metathesis of alkene intermediate **4.1.8b** with acrolein

Entry ^a	Catalyst (mol %)	Lewis acid (equiv)	Solvent	Duration (hr)	Temp . (°C)	Yield ^b
1	Grubbs II (5)	Ti(O ^{<i>i</i>} Pr) ₄ (0.15)	DCM	O.N.	Reflux	- ^c

2	Hoveyda- Grubbs II (5)	-	DCM / C ₆ F ₆ (5:3)	O.N.	40	- ^c
3	Grubbs II (5)	Ti(O ^{<i>i</i>} Pr) ₄ (1.1)	DCM	O.N.	40	- ^c
4 ^d	Grubbs II (5)	BF ₃ .OEt ₂ (2.0)	DCM	O.N.	Reflux	- ^e

^aAll reactions were done in 0.05M concentration of the alkene **4.1.8b** in absolute solvent. The substrate was pre-mixed with the lewis acid for an hour before adding the metathesis reagent, followed by the syringe-pump addition of the catalyst. ^bIsolated yield. ^cStarting material remains unreacted in the crude mixture. ^dReaction was done using 2-vinyl-1,3-dioxolane as the metathesis reagent instead of acrolein. ^eProton NMR spectrum of reaction crude was inconclusive.

It was expected that the presence of the oxazole moiety would interfere with the Grubbs' catalyst in the metathesis reaction likely via coordination of the Lewis basic Nitrogen to the Ruthenium centre. However, in our attempts to conduct the reaction in the presence of a Lewis acidic additive such as Ti(O^{*i*}Pr)₄, the metathesis was still inefficient and no conversion of starting material was observed in all cases. When boron trifluoride was used as the lewis acid, there was likely a reaction that occurred with the oxazole. However, the ¹H NMR spectrum of the reaction crude was inconclusive as the oxazole peaks were absent from the spectrum, indicating a possible side reaction that occurred between the oxazole and Lewis acid. Thus, it was unlikely that the desired alkene product was generated. Hence, it was decided that metathesis was an unsuitable method for installing the trans en-al moiety on the terminal alkene.

We attempted an ozonolysis on the alkene substrate **4.1.8b**, envisioning the formation of an intermediate aldehyde which could then be coupled with a formyl ylid, Ph₃PCHCHO, to give the desired enal **4.1.9b**. However in our case, the intermediate aldehyde was not formed based

on crude ^1H NMR analysis and instead, the oxazole peaks were missing from the spectrum again. It was later realised that ozonolysing conditions could chemically affect oxazoles as well, converting them into anhydrides, even at low temperatures⁸⁵.

Since ozonolysis was unsuitable as well, we devised an alternative methodology towards the desired en-al via a three step procedure. The alkenes **4.1.8ab** were individually subjected to a dihydroxylation to afford diol intermediates with quantitative conversion based on ^1H NMR analysis of the reaction crude, rendering both diols sufficiently pure for the next step. Subjecting the diols each to sodium periodate in silica gel⁸⁶ cleanly converts the both diols to the intermediate aldehydes in quantitative conversion as well based on ^1H NMR analysis of crude. The aldehydes obtained being sufficiently pure, were each subsequently subjected to Wittig reaction with (formylmethylene)triphenylphosphorane (Scheme **4.1.12**). Several conditions were investigated to effect full conversion of the aldehyde intermediate from **4.1.8b** to the desired en-al product **4.1.9b**.

Scheme **4.1.12**. Formation of en-al intermediates **4.1.9ab**

Table **4-6**: Optimisation of Wittig reaction between aldehyde intermediate with Ph_3PCHCHO

Entry ^a	Solvent	Duration (hr)	Temp. ($^\circ\text{C}$)	Yield of 4.1.9b ^b	Yield of 4.1.9a ^b
--------------------	---------	---------------	----------------------------	-------------------------------------	-------------------------------------

1	DCM	O.N.	r.t.	- ^d	-
2	DCM	O.N.	reflux	40 ^c	-
3	DCE	O.N.	90	- ^d	-
4 ^e	THF	24	100	32	50

^aAll reactions were done under anhydrous conditions with 1.2 eq of the ylid added. ^bIsolated yield. ^cConversion of the starting material to desired product was measured instead, based on proton NMR of the crude. ^dStarting material remains unreacted in the crude mixture. ^eReaction was done in a sealed tube and 1.25eq of the ylid was used.

As observed from Table 4-6, mild conditions were insufficient to effect full conversion of the aldehyde intermediate to the desired en-al products **4.1.9ab**. It was postulated that the reason for low conversions was due to the high stability of the formylmethylene ylid used in the Wittig reaction, resulting in the slow formation of the oxaphosphetane intermediate due to the possibly low reactivity of the ylid. Hence, attempts were made to increase the reaction temperature in order to effect reaction between the ylid and the alkene **4.1.8b** since formation of the oxaphosphetane intermediate is likely to be rate-determining and its collapse towards the desired alkene product and triphenylphosphine oxide is normally very fast.⁸⁷ Yet, when the reaction temperature was raised to 90°C by conducting the reaction in DCE, there was surprisingly no conversion of the starting material at all. However, when the reaction was conducted in THF at 100°C, full conversion was achieved with moderate yield of the desired en-al product **4.1.9b** (entry 4). When the same conditions were employed for the Wittig reaction of alkene **4.1.8a**, the desired en-al product **4.1.9a** was achieved in good yield (50% over 3 steps). This suggests that it was not just the reaction temperature that had a part to play in driving the reaction, but more importantly, the choice of solvent employed.

Finally, we placed our attention on the synthesis towards Samroiyotmycin A first, primarily due to its symmetric nature and would hence presumably be more convenient to furnish. By

subjecting the en-al intermediate **4.1.9a** to a controlled Horner-Wadsworth-Emmons dimerization, we envisioned that Samroiymycin A would be formed in an efficient methodology (Scheme **4.1.13**).

Scheme **4.1.13**. Horner-Wadsworth-Emmons dimerization of en-al **4.1.9a**

When similar conditions previously employed for the HWE-dimerization towards the Samroiymycin Analogue A (Scheme **2.22**; Table **2-12**, entry **11**) were executed for the scheme above, there was unexpectedly no reaction of the en-al starting material as observed from the ^1H NMR of the reaction crude. (Table **4-7**, entry **1**)

Table **4-7**: Optimisation of HWE-dimerization of aldehyde intermediate **4.1.9a**

Entry ^a	Base (eq)	Additive (eq)	Temp. (°C)	Solvent	Duration (h)	Yield of 4.1.10a ^b
1	NaH (2.5)	15-Cr-5 (0.25)	0 - r.t.	PhMe	O.N.	- ^d
2	NaH (3.0)	15-Cr-5 (0.3)	0 – r.t.	THF	6h	29

^aAll reactions were done under anhydrous conditions. ^bIsolated yield. ^cStarting material remains unreacted in the crude mixture.

It was postulated that the presence of the methyl group in the alpha position to the phosphonate functionality could have induced a steric effect, causing the HWE reaction to be inefficient in

entry **1**. Hence, when the solvent was switched from toluene to THF, the solubility of NaH was enhanced and was likely more potent in deprotonating the carbon alpha to the phosphonate group, thereby effecting the synthesis of *rac*-Samroiyotmycin A in good yield (entry **2**). The compound **4.1.10a** was isolated in 2 fractions as a mixture of *syn*, *anti* and *meso*-isomers upon column chromatography and were sufficiently pure based on the ¹H NMR spectrum of our synthesised compound, with respect to the ¹H NMR spectrum reported in the literature source¹.

4.2. Results from Bioassays of *rac*-Samroiymycin A & Phenyl-analogue

With the synthesised Samroiymycin A racemic compound and the phenyl-analogue at hand, the work was proceeded with bioassays conducted for both compounds, along with the oxazole intermediate **4.1.7**, as shown in figure **16** by Jerzy Dziekan Michel from the lab of Prof. Zbynek Bozdech in School of Biological Sciences (NTU, Singapore).

Figure **16**. Compounds submitted for bio-assays

According to the figure **17** below, the bar-chart created represents the generated IC₅₀ values from the bioassays for each of the compounds tested in figure **16** against *Plasmodium Falciparum K1* parasitic growth.

Figure 17. Bar-chart data showing IC₅₀ values (in μM)

The IC₅₀ values for each of the compounds were compared against the literature IC₅₀ value of enantiomerically pure Samroiyotmycin A (represented as “**Lit.**”) reported by Dramae et al. It can be seen that the racemic mixture of Samroiyotmycin A (labelled as “**mix**”) had a much higher IC₅₀ value (41.3 μM) compared to the actual enantiomerically pure natural product itself (7 μM). This was however, expected as we postulated that while the active isomer was within the racemic mixture itself, it is also possible that the other isomers present in the mixture were either inactive or possessed minimal anti-malarial activity against the parasitic culture. Hence, this could have caused the overall racemate to be several times less effective in inhibiting the parasitic growth. Our attention was very much brought to the bioassay result of the diastereomeric mixture of the Phenyl analogues (labelled as “**diphenyl**”) as the IC₅₀ value (11.2 μM) was unprecedentedly outstanding, compared to that of the racemic mixture and with consideration that it was not significantly different from that of the literature value. Considering the significantly large IC₅₀ value (264 μM) of the oxazole intermediate (labelled

as “**truncated**”), it was postulated that the presence of the oxazole moiety alone was unlikely to be responsible for the anti-malarial activity of the natural product itself, but rather the presence of the di-enoate Michael acceptor group in the molecule, as present in the compounds that were synthesised. It is also postulated that the electrophilic Michael acceptor group inhibits parasitic growth by forming covalent bonds to cysteine residues present in the protein of the parasite culture, much like the phenomenon of the well-known kinase inhibitor drug Afatinib that targets Non-Small Cell Lung Cancer (NSCLC) (Figure 18)⁹⁶.

Figure 18. Protein Kinase inhibitor drug, Afatinib

4.3. Conclusion & Future work

To sum up the progress and research that is exemplified in this thesis, we have developed a cogent and efficient synthesis towards Samroiyotmycin A in its racemic form in an overall yield of 2% over 18 steps. Throughout the syntheses described in Chapters 1 to 4, we have succeeded in the methodology of furnishing 2-unsubstituted oxazoles via a facile gold catalysed intramolecular 5-*exo-dig* cyclisation of the formamide group to an internal alkyne, (Schemes **2.6** & **4.1.8**) which was not reported in literature hitherto. This reaction highlighted the importance and versatility of gold catalysis in synthesising 2-unsubstituted oxazoles which is advantageous over other synthetic methods that may be substrate-limited or require harsh conditions to furnish 2-unsubstituted oxazoles.

In addition, we have devised an efficient and concise synthetic route towards the synthesis of a Phenyl-analogue of Samroiyotmycin (Scheme **2.23**) in an excellent overall yield of 13% over 11 steps, featuring a highly diastereoselective Rh(I)-catalysed hydroboration as the key step and an efficient Cu(I)-catalyzed coupling strategy to achieve a unique sp^3 - sp^3 coupling.

In future, work will be continued towards the synthesis of *rac*-Samroiyotmycin B **4.1.10b** by employing a carefully controlled HWE reaction between the phosphonates **4.1.9a** and **4.1.9b** both slowly added via the use of two syringe pumps. A sample of *rac*-Samroiyotmycin B **4.1.10b** will also be sent to Bozdech's biological lab for testing once it has been synthesised. Together with the synthesised compounds of *rac*-Samroiyotmycin A and the phenyl analogues, Cellular Thermal Shift Assay (CETSA) will be conducted on these compounds as well to determine the extent of binding of the drug to the protein of the parasite at varying conditions such as drug concentrations, buffer pH or ionic strength of the solution.

Future installations for this project will also involve devising an efficient asymmetric synthesis towards the formation of Samroiyotmycins A and B in their enantiomerically pure

forms, so as to compare their IC₅₀ values against that reported in the literature. Given that the unexpected exemplary IC₅₀ value of the phenyl-analogue sample, it is definitely worth looking into the asymmetric synthesis of individual D/L- and meso- isomers of the analogue. This is to determine which of the three isomers display the highest anti-malarial or possibly any other biological activity. Furthermore, the greater steric hindrance around the Michael acceptor in Samroiyotmycin A may also be the reason why it exhibits a lower cytotoxicity than Samroiyotmycin B, according to their cytotoxicity values published by Dramae et al.

To confirm the postulation of the di-enoate Michael acceptor as a possible inhibitory site against cysteine residues within the protein, it would also be important to look into the synthesis of acyclic analogues possessing the Michael acceptor moiety, further phenyl analogues of Samroiyotmycins such as one bearing only α , β -unsaturated esters in the macrocycle as well as molecules with other functional groups replacing the oxazole moiety (Figure 19). From the present data (Figure 17), it would be difficult to pin-point if the mechanism of action of the synthesised compounds involve a 1, 4 or 1, 6-addition. Hence, the synthesis of the following α , β and γ , δ -unsaturated compounds would ideally answer this question.

Figure 19. Molecules for future synthesis

EXPERIMENTAL SECTION

Reactions were carried out under inert atmosphere using Nitrogen in oven-dried glassware. Syringes and needles were also dried under vacuum prior to usage. Solvents Acetonitrile and 1, 2-Dichloroethane was distilled from CaH₂ under Nitrogen and collected over 4 Å molecular sieves. Dichloromethane was distilled from CaH₂ under Nitrogen and THF was distilled from a mixture of Sodium and Benzophenone under Nitrogen atmosphere. Toluene was distilled over sodium under inert atmosphere prior to use and dimethylformamide was distilled from CaH₂ under reduced pressure and collected over 4 Å molecular sieves. Triethylamine was stirred overnight with CaH₂ under Nitrogen, then distilled and collected over CaH₂ under inert atmosphere. Column chromatography was performed using silica 230-400 mesh.

NMR spectra were recorded in CDCl₃ or Acetone-D₆ using Bruker AV300, AV400, AV500, BBFO1 400, BBFO2 400, JEOL ECA 400 and ECA400SL spectrometers. Chemical shifts are given in ppm and coupling constants in Hz. The following abbreviations are introduced for the multiplicity of the signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet).

N-formyl-N-(prop-2-yn-1-yl)formamide 2.1.1

To a mixture containing sodium diformylamide (20 mmol, 1.90g) in absolute acetonitrile (4 mL) under Nitrogen atmosphere was added propargyl bromide (24 mmol, 2.1 mL) dropwise and the reaction was then stirred for 5.5 hours at 90°C. After which, the reaction was cooled to room temperature and filtered over celite. The filtrate was concentrated in vacuo and the crude mixture purified by flash chromatography (hexane : ethyl acetate = 70 : 30) on silica to give the desired compound **2.1.1** as a light yellow oil (93%).

¹H NMR (400 MHz, CDCl₃): δ 8.89 (s, 2H), 4.41 (s, 2H), 2.17 (s, 1H)

All data are consistent with that reported in literature⁵⁴.

N-formyl-N-(5-methyl-4-oxohex-5-en-2-yn-1-yl)formamide 2.1.2

To a mixture containing PdCl₂(PPh₃)₂ (0.014 mmol, 10.1 mg) and CuI (0.029 mmol, 5.4 mg) in absolute THF (2.6 mL) under Nitrogen atmosphere, was added methacryloyl chloride (1.08 mmol, 106 μL) followed by N-formyl-N-(prop-2-yn-1-yl)formamide (**2.1.1**) (0.720 mmol, 80 mg) in absolute THF (1 mL). The dark orange reaction mixture was then allowed to stir for one minute at room temperature. Triethylamine (0.9 mmol, 126 μL) was then added dropwise slowly to the stirring reaction mixture over 25 minutes and the reaction was then allowed to stir for 5.5 hours at ambient temperature. The crude mixture was then filtered over celite and the filtrate concentrated in vacuo, following which the crude was then purified by flash chromatography (hexane : ethyl acetate = 68 : 22) on silica to give the desired compound **2.1.2** as a yellow oil which crystallizes into yellow solids upon storage at -20°C (85%).

¹H NMR (400 MHz, CDCl₃): δ 8.91 (s, 2H), 6.37 (s, 1H), 6.05 (s, 1H), 4.61 (s, 2H), 1.88 (s, 3H)

¹³C NMR (400 MHz, CDCl₃): δ 179.27, 162.82, 144.71, 131.96, 85.00, 79.68, 27.81, 15.87

IR(neat) cm⁻¹: 1666.50, 1643.35

MS (ESI): *m/z* = 180.1 [M+H]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₉H₉NO₃: 180.0661; found: 180.0671.

Melting point (range): 56 – 60°C

N-(5-methyl-4-oxohex-5-en-2-yn-1-yl)formamide 2.1.3

To a solution of the imide **2.1.2** (0.719 mmol, 129 mg) in ethanol (290 μ L) was added Amberlyst-26 resin (11.6 mg) and the reaction was stirred to air at room temperature for 2 days. The reaction mixture was subsequently filtered over celite and concentrated in vacuo. The crude was purified by flash chromatography (hexane : ethyl acetate = 50 : 50) on silica to give the desired compound **2.1.3** as a yellow oil, which crystallizes into a light orange solid upon storage at -20°C (76%).

^1H NMR (400 MHz, CDCl_3): δ 8.24 (s, 1H (major rotamer)), 8.17 (d, J = 14.4 Hz, 1H (minor rotamer)), 6.42 (s, 1H (major rotamer)), 6.39 (s, 1H (minor rotamer)), 6.07 (s, 1H, (major rotamer)), 6.01 (brs, 1H), 4.32 (d, J = 5.6 Hz, 2H (major rotamer)), 4.25 (d, J = 6.2 Hz, 2H (minor rotamer)), 1.90 (s, 3H)

^{13}C NMR (400 MHz, CDCl_3): δ 179.79, 161.17, 144.71, 132.02, 87.96, 80.08, 27.84, 15.90

IR(neat) cm^{-1} : 3265.49, 2725.42, 2223.92, 1666.50, 1633.71

MS (ESI): m/z = 152.12 $[\text{M}+\text{H}]^+$.

HRMS (Q-Tof): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_8\text{H}_9\text{NO}_2$: 152.0712; found: 152.0703.

Melting point (range): 40 - 45 °C

3-methyl-1-(oxazol-5-yl)but-3-en-2-one **2.1.4**

To a flask containing JohnphosAuCl (0.0165 mmol, 8.8 mg) and AgOTs (0.0165 mmol, 4.6 mg) was added absolute DCE (0.8 mL) and the reaction mixture was allowed to stir for 35 minutes at room temperature under Nitrogen atmosphere. After which, a solution of N-(5-methyl-4-oxohex-5-en-2-yn-1-yl)formamide (**2.1.3**) (0.331 mmol, 50 mg) in absolute DCE (0.5 mL) was added dropwise to the reaction mixture and the reaction was stirred for 30 minutes at room temperature and then at 80°C overnight. The reaction mixture was then filtered through celite and the filtrate concentrated in vacuo. The crude was purified by flash chromatography (hexane : ethyl acetate = 60 : 40) on silica to give the desired compound **2.1.4** as a yellow oil (72%).

¹H NMR (400 MHz, CDCl₃): δ 7.83 (s, 1H), 6.99 (s, 1H), 6.07 (s, 1H), 5.92 (s, 1H), 4.12 (s, 2H), 1.92 (s, 3H)

¹³C NMR (400 MHz, CDCl₃): δ 195.25, 150.78, 146.06, 143.88, 126.26, 124.75, 34.59, 17.53

IR(neat) cm⁻¹: 1681.96, 1631.81

MS (ESI): *m/z* = 151.99 [M+H]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₈H₉NO₂: 152.0712; found: 152.0690.

3-methyl-1-(oxazol-5-yl)but-3-en-2-ol **2.1.5**

To a solution of 3-methyl-1-(oxazol-5-yl) but-3-en-2-one (**2.1.4**) (0.58 mmol, 88 mg) in absolute DCM (1.9 mL) at -78°C under Nitrogen atmosphere, was added DIBAL (1.0 M, 0.75 mL) dropwise over 15 minutes. The reaction was then stirred for a further 35 minutes at that temperature and subsequently at -40°C overnight. Methanol (1 mL) was then added to the reaction mixture at -40°C, followed by the addition of saturated Rochelle's solution (5 mL) and the mixture was warmed to room temperature and allowed to stir for another 2 hours. The mixture was then extracted with DCM (3 x 10 mL), following which the organic layers were combined and dried over MgSO₄ for 15 minutes, filtered and washed with DCM. The solvent was evaporated and the crude product was purified by flash chromatography (9:11 Hexane/Ethyl acetate) on silica to give the desired compound **2.1.5** as a light yellow oil (81%).

¹H NMR (400 MHz, CDCl₃): δ 7.80 (s, 1H), 6.89 (s, 1H), 4.99 (s, 1H), 4.89 (s, 1H), 4.38 (t, *J* = 6.2 Hz, 1H), 2.95 (ddd, *J*₁ = 20.0 Hz, *J*₂ = 6.0 Hz, 2H), 1.87 (s, 1H), 1.79 (s, 3H)

¹³C NMR (400 MHz, CDCl₃): δ 150.47, 149.88, 146.16, 123.62, 112.02, 73.71, 31.86, 17.76

IR(neat) cm⁻¹: 3361.98, 1653.02

MS (ESI): *m/z* = 153.98 [M+H]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₈H₁₁NO₂: 154.0868; found: 154.0838.

5-(2-((tert-butyldimethylsilyl)oxy)-3-methylbut-3-en-1-yl)oxazole **2.1.5'**

To a solution of 3-methyl-1-(oxazol-5-yl)but-3-en-2-ol (**2.1.5**) (0.653 mmol, 100 mg) in absolute DCM (2.1 mL) was added 2,6-lutidine (1.18 mmol, 137 μ L) dropwise. After which, TBSOTf (0.783 mmol, 180 μ L) was then added dropwise over 15 minutes to the stirred mixture at 0°C and the reaction was stirred at 0°C for 2 hours. The reaction mixture was subsequently quenched with saturated sodium bicarbonate solution (3 mL) at 0°C and stirred for a further 15 minutes at room temperature, before extracting with DCM (3 x 15 mL). The organic layers were combined and dried over MgSO₄ for 15 minutes, filtered and washed with DCM. The solvent was evaporated and the crude product was purified by flash chromatography (93:7 Hexane/Ethyl acetate) on silica to give the desired compound **2.1.5'** as a colourless oil (87%).

¹H NMR (400 MHz, CDCl₃): 7.77 (s, 1H), 6.82 (s, 1H), 4.90 (d, J = 0.8 Hz, 1H), 4.80 (s, J = 1.4 Hz, 1H), 4.31 (td, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H), 2.84 (m, 2H), 1.73 (s, 3H), 0.83 (s, 9H), -0.06 (s, 3H), -0.13 (s, 3H)

¹³C NMR (400 MHz, CDCl₃): δ 150.07, 149.99, 146.49, 123.81, 111.71, 74.97, 33.19, 25.64, 18.06, 17.01, -5.07, -5.55

IR(neat) cm⁻¹: 1653.02, 1606.73

MS (ESI): m/z = 268.19 [M+H]⁺

HRMS (Q-ToF): m/z [M+H]⁺ calcd for C₁₄H₂₅NO₂Si: 268.1701; found: 268.1748.

tert-butyl prop-2-yn-1-ylcarbamate **2.3.1**

To a solution of propargylamine (2 mmol, 110 mg) in H₂O (2 mL) was added di-tert-butyl dicarbonate (2.2 mmol, 480mg) and the mixture was allowed to stir at room temperature vigorously as effervescence was evolved during the reaction. After 70 minutes, the reaction was extracted with ether (4 x 12 mL) and the organic layers were dried over MgSO₄ and concentrated to give a yellow oil (99%) which solidifies at -20°C into a yellow solid.

¹H NMR (400 MHz, CDCl₃): δ 4.71 (s, 1H), 3.93 (s, 2H), 2.22 (t, *J* = 2.5 Hz, 1H), 1.48 (s, 9H).

¹³C NMR (400 MHz, CDCl₃): δ 155.31, 80.16, 79.87, 71.11, 30.25, 28.27.

All data are consistent with that reported in literature⁸⁸.

tert-butyl (5-methyl-4-oxohex-5-en-2-yn-1-yl)carbamate **2.3.2**

To a solution of the bis(triphenylphosphine)dichloro Palladium (II) (0.0129 mmol, 9 mg) and Copper(I) iodide (0.0258 mmol, 4.9mg) in anhydrous THF (3.2mL), was added methacryloyl chloride (0.966 mmol, 94 μL) and then tert-butyl prop-2-yn-1-ylcarbamate **2.3.1** (0.644 mmol, 100mg) under Nitrogen at ambient temperature. After which, triethylamine (0.805 mmol, 112 μL) was added dropwise to the reaction with stirring over 25 minutes using a syringe pump at room temperature. The reaction was then stirred for 4 hours at room temperature, and then filtered over celite and washed with ether (3 x 10 mL). The filtrate was then concentrated in

vacuo and then purified by column chromatography (10:1 Hexane/Ethyl Acetate) to give the product as a yellow oil (81%) which solidifies at -20°C into a yellow solid.

¹H NMR (400 MHz, CDCl₃): δ 6.43 (s, 1H), 6.05 (t, *J* = 1.1 Hz, 1H), 4.79 (brs, 1H), 4.15 – 4.10 (m, 2H), 1.90 (s, 3H), 1.46 (s, 9H).

¹³C NMR (400 MHz, CDCl₃): δ 179.68, 155.27, 144.80, 131.42, 89.14, 80.29, 79.90, 30.59, 28.25, 15.91.

IR(neat) cm⁻¹: 3361.93, 3097.68, 2725.42, 2222.00, 1732.08, 1714.72, 1645.28, 1600.92

MS (ESI): *m/z* = 246.11 [M+Na]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₁₂H₁₇NO₃: 224.1287; found: 224.1289.

5-(3-methyl-2-oxobut-3-en-1-yl) oxazol-2(3H)-one **2.3.3**

To a degassed, oven-dried 2-necked flask fitted with a reflux condenser was charged with the JohnphosAuCl catalyst (0.0224 mmol, 11.9mg) and AgOTs (0.0224 mmol, 6.3mg) in anhydrous dichloroethane (0.8mL) under N₂. The mixture was then stirred at room temperature for 45 minutes, during which precipitation was observed. After which, a solution of the tert-butyl (5-methyl-4-oxohex-5-en-2-yn-1-yl)carbamate **2.3.2** (0.448 mmol, 100mg) in anhydrous DCE (1mL) was added to the reaction mixture and the reaction was stirred for 30 minutes at room temperature before being heated at 65°C for 2.5 hours. The mixture was then cooled to room temperature and filtered over celite and washed with DCM. The filtrate

was subsequently concentrated in vacuo to give a brownish oily solid, which was purified on silica gel (Hexane:Ethyl Acetate 7:3) to give a yellowish powder (97%).

¹H NMR (400 MHz, CDCl₃): δ 6.62 (t, *J* = 2.0 Hz, 1H), 6.12 (brs, 1H), 5.93 (s, 1H), 5.78 (d, *J* = 1.3 Hz, 1H), 4.73 (d, *J* = 2.0 Hz, 2H), 1.93 (s, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 191.75, 164.06, 155.34, 145.32, 124.14, 97.96, 47.61, 17.56.

IR(neat) cm⁻¹: 1787.08, 1674.24, 1599.02

MS (ESI): *m/z* = 190.00 [M+Na]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₈H₉NO₃: 168.0655; found: 168.0668.

Melting point (range): 115 – 121°C

5-(2-hydroxy-3-methylbut-3-en-1-yl)oxazol-2(3H)-one 2.3.4

To an oven-dried 25mL RBF was charged with the ketone **2.3.3** (0.42 mmol, 69.5 mg) in absolute methanol (2.5mL) containing a stir bar and fitted with a drying tube. Cerium (III) Chloride heptahydrate (0.83 mmol, 310 mg) was added to the reaction mixture, followed by the addition of Sodium borohydride (0.83 mmol, 31.4 mg) portionwise over 5 minutes with stirring at 0°C. The reaction mixture was then allowed to warm to room temperature and stirred for 25 minutes, before being quenched with saturated ammonium chloride (5 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic layers were then dried over Magnesium Sulphate, filtered and then concentrated in vacuo to give a crude oil. Subsequent

purification on silica gel (3:1 Ethyl acetate/Hexane) gave the product as a yellowish solid (76%).

¹H NMR (400 MHz, CDCl₃): δ 7.03 (s, 1H), 5.11 (dt, *J* = 8.4, 2.6 Hz, 1H), 5.06 – 4.95 (m, 1H), 4.76 (s, 1H), 4.58 (d, *J* = 8.4 Hz, 1H), 4.47 – 4.29 (m, 2H), 2.85 (brs, 1H), 1.72 (s, 3H).

IR(neat) cm⁻¹: 3429.49, 1766.83, 1641.45

MS (ESI): *m/z* = 192.05 [M+Na]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₈H₁₁NO₃: 170.0812; found: 170.0848.

5-(2-((4-methoxybenzyl)oxy)-3-methylbut-3-en-1-yl)oxazol-2(3H)-one **2.3.5**

To an oven-dried 50 mL RBF containing a solution of the allylic alcohol **2.3.4** (0.26 mmol, 44 mg) in absolute DCM (0.8 mL), was added p-TSA (0.026 mmol, 4.5 mg) and then pyridine (0.026 mmol, 2.1 μL) and lastly benzyl 2,2,2-trichloroacetimidate (0.52 mmol, 108 μL). The reaction was then stirred at room temperature for 3 days, then subsequently quenched with saturated NaHCO₃ and extracted with DCM (3 x 6 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated in vacuo and purified on silica gel via column chromatography (9 : 11 Ethyl Acetate/Hexane) to give the product as a yellow oil (46%).

¹H NMR (400 MHz, CDCl₃): δ 7.34 – 7.19 (m, 3H), 6.89 (t, *J* = 7.1 Hz, 2H), 5.27 (d, *J* = 7.1 Hz, 1H), 4.97 (d, *J* = 3.3 Hz, 2H), 4.35 (dd, *J* = 48.2 Hz, 11.5 Hz, 2H), 4.22 (d, *J* = 7.3 Hz, 2H), 4.18 (d, *J* = 1.3 Hz, 1H), 3.79 (s, 3H), 1.73 (s, 3H).

3-methyl-1-phenylbut-3-en-2-ol 2.4.1

To a suspension of activated Magnesium turnings (26.7 mmol, 0.648 g) in absolute ether (18 mL) under N₂ was added benzyl chloride (24.3 mmol, 2.8 mL) dropwise at room temperature, at a rate which the solution begins to gently reflux. The reaction was stirred at room temperature for an hour and then refluxed for a further 15 to 30 minutes before being cooled to ambient temperature. To another oven-dried degassed RBF containing a solution of methacrolein (14.3 mmol, 1.2 mL) in absolute THF (3.6 mL) at -10°C, was added a solution of the BnMgCl (1.3M, 12.4 mL) dropwise over 15 minutes. The reaction was then stirred at room temperature for an hour before being quenched with saturated ammonium chloride and extracted with ether (4 x 12 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated in vacuo and then purified on silica gel via column chromatography (8:92 Ethyl acetate/Hexane) to give the product as a colourless oil (82%).

¹H NMR (400 MHz, CDCl₃): 7.43-7.10 (m, 5H), 4.97 (d, *J* = 0.7 Hz, 1H), 4.88 (d, *J* = 1.3 Hz, 1H), 4.37-4.24 (m, 1H), 2.86 (ddd, *J*₁ = 13.7 Hz, *J*₂ = 8.7 Hz, *J*₃ = 4.4 Hz, 2H), 1.83 (s, 3H), 1.62 (d, *J* = 3.2 Hz, 1H)

¹³C NMR (400 MHz, CDCl₃): δ 146.82, 138.48, 129.45, 128.48, 126.51, 111.41, 76.59, 42.19, 18.14.

All data are consistent with that reported in literature⁸⁹.

tert-butyldimethyl((3-methyl-1-phenylbut-3-en-2-yl)oxy)silane 2.4.2

To a solution of 3-methyl-1-phenylbut-3-en-2-ol (**2.4.1**) (0.653 mmol, 100 mg) in absolute DCM (2.1 mL) was added 2,6-lutidine (1.18 mmol, 137 μ L) dropwise. After which, TBSOTf (0.783 mmol, 180 μ L) was then added dropwise over 15 minutes to the stirred mixture at 0°C and the reaction was stirred at 0°C for 2 hours. The reaction mixture was subsequently quenched with saturated sodium bicarbonate solution (3 mL) at 0°C and stirred for a further 5 minutes at room temperature. The mixture was then extracted with ether (3 x 5 mL) and the combined organic layers were dried over MgSO₄. The mixture was then filtered and the filtrate was concentrated in vacuo to give a crude oil. The crude was subsequently purified on silica gel by column chromatography (100% Hexane) to give the product as a colourless oil (87%).

¹H NMR (400 MHz, CDCl₃): 7.22 (dt, J = 7.7, 5.2 Hz, 5H), 4.79 (d, J = 30.6 Hz, 2H), 4.19 – 4.15 (m, 1H), 2.79 – 2.69 (m, 2H), 1.76 (s, 3H), 0.80 (s, 9H), -0.15 (s, 3H), -0.31 (s, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 147.65, 139.35, 129.85, 128.00, 126.06, 110.86, 78.50, 43.73, 25.84, 18.19, 17.49, -2.88, -5.07.

IR(neat) cm⁻¹: 3086.11, 3066.82, 3028.24, 2885.51, 2856.58, 1647.21, 1635.64, 1494.83, 1454.33, 1253.73.

MS (ESI): m/z = 299.31 [M+Na]⁺

HRMS (Q-Tof): m/z [M+H]⁺ calcd for C₁₇H₂₈OSi: 277.1988; found: 277.1996.

tert-butyl dimethyl(((2R,3R)-3-methyl-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-yl)oxy)silane 2.4.3 (relative stereochemistry)

To a degassed, oven-dried 25 mL RBF was added Rh(CO)(PPh₃)₂Cl (8.9 μmol, 6.2 mg), followed by a solution of the alkene **2.4.2** (0.445 mmol, 123 mg) in absolute THF (1.8 mL). To the stirred mixture was then added HBPIn (0.534 mmol, 78 μL) dropwise and the mixture was then stirred at room temperature for 2 hours. Upon reaction completion as confirmed by TLC, the mixture was then exposed to air for a few minutes, concentrated in vacuo and then purified on silica gel via column chromatography (1:49 Ethyl acetate/Hexane) to give the product as a colourless viscous oil (73%).

¹H NMR (400 MHz, CDCl₃): δ 7.28 – 7.11 (m, 5H), 3.82 – 3.71 (m, 1H), 2.66 (ddd, *J* = 21.0, 13.5, 6.5 Hz, 2H), 1.87 – 1.75 (m, 1H), 1.20 (s, 12H), 1.03 – 0.85 (m, 2H), 0.94 (d, *J* = 8.0 Hz, 3H), 0.83 (s, 9H), 0.67 (dd, *J* = 15.6, 9.9 Hz, 1H), -0.06 (s, 3H), -0.31 (s, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 140.01, 129.74, 128.08, 125.81, 82.75, 78.40, 40.33, 34.02, 26.02, 24.89, 24.80, 18.15, 16.66, -4.52, -4.86.

IR(neat) cm⁻¹: 3412.08, 3086.11, 3064.89, 1494.83, 1456.26, 1371.39, 1315.45, 1255.66, 1215.15

MS (ESI): *m/z* = 405.10 [M+H]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₂₃H₄₁BO₃Si: 405.2996; found: 405.3005.

(2R,3R)-2-methyl-4-phenylbutane-1,3-diol 2.4.4.1 (relative stereochemistry)

To a solution of the pinacolboronate ester **2.4.3** (0.235 mmol, 95 mg) in bench methanol (0.35 mL) at 0°C, was added a solution of 3M NaOH (1.41 mmol, 0.47 mL) dropwise with stirring. After which, H₂O₂ solution (0.587 mmol, 60 µL, 30% w/w) was added dropwise to the mixture at 0°C and the reaction was stirred at room temperature for 5 hours or till TLC indicated complete consumption of the starting material. The reaction was then quenched with water and 2M HCl, then extracted with ethyl acetate (4 x 5 mL). The combined organic layers were then dried over MgSO₄, filtered and concentrated in vacuo to give the crude alcohol a pale yellow oil. The crude alcohol was then dissolved in a solution of THF (3.2 mL) and TBAF.3H₂O (0.352 mmol, 111 mg) was added in one portion to the mixture and the reaction was stirred at room temperature for 3 hours. After which, the reaction mixture was then concentrated in vacuo and purified immediately on silica gel via column chromatography (2 : 3 Ethyl acetate/Hexane) to give the diol as a white crystalline solid.

¹H NMR (400 MHz, CDCl₃): 7.36 – 7.18 (m, 5H), 4.08 (t, *J* = 6.0 Hz, 1H), 3.74 (s, 2H), 2.78 (d, *J* = 6.9 Hz, 2H), 2.20 (s, 1H), 2.08 (s, 1H), 1.93 – 1.81 (m, 1H), 1.05 (d, *J* = 7.1 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 138.71, 129.28, 128.64, 126.51, 75.45, 67.10, 40.65, 38.55, 10.22

X-ray crystallography: *refer to appendix*

All data are consistent with that reported in literature⁹⁰.

(2R,3R)-3-((tert-butyldimethylsilyl)oxy)-2-methyl-4-phenylbutyl methanesulfonate

2.4.5 (relative stereochemistry)

To a degassed, oven-dried 25 mL RBF containing a solution of the crude alcohol (0.405 mmol, 119 mg) obtained from the hydrolysis of **2.4.3** in absolute DCM (1.2 mL), was added anhydrous triethylamine (0.608 mmol, 85 μ L) at 0°C. After which, methanesulfonyl chloride (0.527 mmol, 41 μ L) was added dropwise over 10 minutes at that temperature and the reaction was then stirred at 0°C for 1 hour and 45 minutes. The reaction was then quenched with saturated NaHCO₃ and extracted with DCM (3 x 5 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated in vacuo and then purified on silica gel via column chromatography (1:19 Ethyl acetate/Hexane) to give the product as a colourless oil (99%).

¹H NMR (400 MHz, CDCl₃): δ 7.32 – 7.11 (m, 5H), 4.13 (ddd, J = 52.2, 9.5, 7.0 Hz, 2H), 4.00 (td, J = 7.1, 2.5 Hz, 1H), 2.90 (s, 3H), 2.82 – 2.68 (m, 2H), 1.93 (ddd, J = 13.9, 6.9, 2.5 Hz, 1H), 1.01 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.01 (s, 3H), -0.16 (s, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 138.42, 129.41, 128.47, 126.41, 73.14, 72.14, 40.61, 37.23, 37.05, 25.89, 18.06, 10.35, -4.68, -4.84.

IR(neat) cm⁻¹: 3086.11, 3064.89, 3028.24, 1627.92, 1604.77, 1354.03, 1336.67, 1116.78, 1099.43

MS (ESI): m/z = 395.21 [M+Na]⁺

HRMS (Q-Tof): m/z [M+H]⁺ calcd for C₁₈H₃₂O₄SSi: 373.1869; found: 373.1862.

tert-butyl(((2R,3S)-4-iodo-3-methyl-1-phenylbutan-2-yl)oxy)dimethylsilane 2.4.6

(relative stereochemistry)

To a 25 mL RBF containing the mesylate **2.4.5** (1.29 mmol, 481 mg) in acetone (1.3 mL), was added sodium iodide (2.32 mmol, 348 mg) and sodium sulphite (21 mg). The mixture was then stirred in the dark with reflux for 6 hours. The reaction was then quenched with saturated sodium thiosulphate and extracted with ether (3 x 6 mL). The combined organic layers were dried over MgSO_4 , filtered, concentrated in vacuo and then purified on silica gel via column chromatography (1:99 Ethyl acetate/Hexane) to give the product as a colourless oil (81%).

^1H NMR (400 MHz, CDCl_3): δ 7.31 – 7.12 (m, 5H), 4.02 (td, $J = 7.0, 2.7$ Hz, 1H), 3.17 (ddd, $J = 17.1, 9.5, 7.0$ Hz, 2H), 2.76 – 2.69 (m, 2H), 1.77 (ddd, $J = 14.2, 7.1, 2.7$ Hz, 1H), 1.06 (d, $J = 6.8$ Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), -0.15 (s, 3H).

^{13}C NMR (400 MHz, CDCl_3): δ 138.55, 129.45, 128.44, 128.30, 126.35, 75.49, 40.76, 40.62, 25.99, 18.15, 14.53, 12.50, -4.46, -4.59.

IR(neat) cm^{-1} : 3107.32, 3086.11, 3062.96, 3026.31, 1604.77, 1255.66, 516.92

MS (ESI): $m/z = 427.39$ $[\text{M}+\text{Na}]^+$

HRMS (Q-ToF): m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{29}\text{IOSi}$: 427.0930; found: 425.1481.

(2R,3R)-3-methyl-1-phenylhept-6-en-2-ol 2.4.8 (relative stereochemistry)

To a degassed, oven-dried 25 mL RBF was added CuCl (0.069 mmol, 6.9 mg), followed by a solution of the iodide **2.4.6** (1.39 mmol, 560 mg) in absolute THF (4.2 mL) at ambient temperature. After which, allyl magnesium chloride (2M, 0.97 mL) was added dropwise to the solution with stirring and the reaction was subsequently stirred for 4 to 6 hours at room temperature. The reaction was then quenched with saturated ammonium chloride and then extracted with ether (4 x 10 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo to give the alkene product as a pale yellow crude oil which was sufficient pure based on ¹H NMR. The crude alkene was then redissolved in methanol (4.2 mL) and acetyl chloride (0.208 mmol, 15 μL) was then added dropwise to the solution at 0°C through a fitted drying tube. The reaction was then stirred from 0°C to room temperature gradually over 5 hours and then quenched with saturated NaHCO₃ and extracted with ether (4 x 8 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated in vacuo and purified on silica gel via column chromatography (1:9 Ethyl acetate/Hexane) to give the product as a colourless oil (82%).

¹H NMR (400 MHz, CDCl₃): δ 7.40 – 7.18 (m, 5H), 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.09 – 4.89 (m, 2H), 3.75 (dd, *J* = 9.2, 3.3 Hz, 1H), 2.73 (ddd, *J* = 22.9, 13.6, 6.6 Hz, 2H), 2.22 – 2.00 (m, 2H), 1.70 – 1.57 (m, 2H), 1.39 (d, *J* = 4.0 Hz, 1H), 1.34 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 139.37, 138.96, 129.36, 128.55, 126.34, 114.46, 75.86, 41.06, 37.31, 32.54, 31.58, 13.79.

IR(neat) cm⁻¹: 3427.51, 3419.79, 1639.49

MS (ESI): $m/z = 205.11$ $[M+H]^+$

HRMS (Q-Tof): m/z $[M+H]^+$ calcd for $C_{14}H_{20}O$: 205.1592; found: 205.1586.

(2R,3R)-3-methyl-1-phenylhept-6-en-2-yl 2-(diethoxyphosphoryl)acetate 2.4.9a

(relative stereochemistry)

To an oven-dried flask fitted with a drying tube, containing a solution of diethyl phosphonoacetic acid (1.11 mmol, 217 mg) in anhydrous DCM (3.7 mL) was added oxalyl chloride (3.3 mmol, 281 μ L) dropwise at room temperature. Absolute DMF (20 μ L) was then added dropwise and effervescence was observed. The reaction was then stirred at ambient temperature for 1 hour and then concentrated in vacuo to give a yellow oil. The crude oil was then azeotroped with dry benzene thrice, then redissolved in absolute THF (2.8 mL) under N_2 atmosphere to give a 0.4M solution of the acid chloride. To another oven-dried, degassed 25 mL RBF containing a solution of the alcohol **2.4.8** (0.37 mmol, 76.5 mg) in absolute THF (6.5 mL) at 0°C was added pyridine (1.9 mmol, 155 μ L), followed by the acetyl chloride solution dropwise over 10 minutes. The mixture was then stirred at 0°C for 15 minutes then at ambient temperature for 2.5 hours. The reaction was subsequently quenched with saturated $NaHCO_3$ and extracted with ethyl acetate (4 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated in vacuo and purified on silica gel via column chromatography (2:3 Ethyl acetate/Hexane) to give the product as a colourless oil (87%).

¹H NMR (400 MHz, CDCl₃): δ 7.35 – 7.14 (m, 5H), 5.72 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.15 (td, *J* = 7.1, 3.4 Hz, 1H), 4.99 – 4.84 (m, 2H), 4.22 – 4.04 (m, 4H), 3.01 – 2.76 (m, 4H), 2.15 – 1.95 (m, 2H), 1.67 (s, 1H), 1.50 (dt, *J* = 9.3, 5.0 Hz, 1H), 1.32 (td, *J* = 7.1, 3.5 Hz, 7H), 1.01 (d, *J* = 6.8 Hz, 6H).

¹³C NMR (400 MHz, CDCl₃): δ 165.27, 138.40, 137.60, 129.21, 128.39, 126.44, 114.61, 78.80, 62.51, 37.67, 34.99, 34.64, 33.65, 32.21, 31.23, 16.31, 13.78.

IR(neat) cm⁻¹: 1732.08, 1639.49, 1604.77, 1114.86

MS (ESI): *m/z* = 383.11 [M+H]⁺

HRMS (Q-ToF): *m/z* [M+H]⁺ calcd for C₂₀H₃₁O₅P: 383.1987; found: 383.2002.

(2R,3R)-3-methyl-1-phenylhept-6-en-2-yl 2-(diethoxyphosphoryl)propanoate 2.4.9b
(relative stereochemistry)

To an oven-dried flask fitted with a drying tube, containing a solution of 2-(diethoxyphosphoryl)propanoic acid (2.80 mmol, 589 mg) in anhydrous DCM (8.5 mL) was added oxalyl chloride (24.9 mmol, 2.1 mL) dropwise at room temperature. Absolute DMF (150 μL) was then added dropwise and effervescence was observed. The reaction was then stirred at ambient temperature for 1 hour and then concentrated in vacuo to give an orange oil. The crude oil was then azeotroped with dry benzene thrice, then redissolved in absolute THF (7 mL) under N₂ atmosphere to give a 0.4M solution of the acid chloride. To another oven-dried, degassed 25 mL RBF containing a solution of the alcohol **2.4.8** (0.934 mmol, 191 mg)

in absolute THF (16 mL) at 0°C was added pyridine (4.76 mmol, 385 μ L), followed by the acetyl chloride solution dropwise over 10 minutes. The mixture was then stirred at 0°C for 15 minutes then at ambient temperature for 5.5 hours. The reaction was subsequently quenched with saturated NaHCO₃ and extracted with ethyl acetate (4 x 12 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated in vacuo and purified on silica gel via column chromatography (9:11 Ethyl acetate/Hexane) to give the product as a colourless oil (86%).

¹H NMR (396 MHz, CDCl₃): δ 7.40 – 7.12 (m, 5H), 5.82 – 5.63 (m, 1H), 5.22 – 5.12 (m, 1H), 4.99 – 4.85 (m, 2H), 4.22 – 4.03 (m, 4H), 3.04 – 2.78 (m, 3H), 2.03 (qdd, J = 9.0, 7.8, 3.8 Hz, 2H), 1.76 – 1.62 (m, 1H), 1.51 (dddd, J = 15.2, 11.9, 8.3, 4.8 Hz, 1H), 1.43 – 1.18 (m, 10H), 1.02 (t, J = 6.8 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 169.28, 169.24, 169.13, 169.08, 138.47, 138.41, 137.72, 137.61, 129.25, 128.35, 128.33, 126.39, 114.57, 114.56, 78.41, 78.39, 62.53, 62.46, 40.39, 40.02, 39.05, 38.68, 37.91, 37.55, 35.00, 34.50, 32.30, 32.19, 31.25, 16.41, 16.35, 13.86, 13.73, 11.76, 11.70

IR(neat) cm⁻¹: 1775.51, 1733.07, 1640.49, 1604.80, 1171.78

MS (ESI): m/z = 397.18 [M+H]⁺

HRMS (Q-Tof): m/z [M+H]⁺ calcd for C₂₁H₃₃O₅P: 397.2144; found: 397.2142.

(2R,3R,E)-3-methyl-8-oxo-1-phenyloct-6-en-2-yl 2-(diethoxyphosphoryl)acetate 2.4.10a
(relative stereochemistry)

To a degassed 2-necked 25 mL RBF containing the alkene **2.4.9a** (0.392 mmol, 150 mg) in absolute DCM (0.4 mL) under constant N₂ flow, was added *trans*-crotonaldehyde (1.18 mmol, 97 μ L). After which, a solution of the Grubbs II catalyst (0.0196 mmol, 16.6 mg) in anhydrous DCM (0.4 mL) was added to the reaction over 4 hours dropwise using a syringe-pump while the reaction was stirred at reflux under N₂ flow. After the addition, the reaction was stirred for a further 2 hours at reflux under N₂ flow. Subsequently, the reaction was then filtered over celite, concentrated in vacuo and then purified on silica gel via column chromatography (9:11 Ethyl acetate/Hexane) to give the product as a purple oil (66%).

¹H NMR (400 MHz, CDCl₃): δ 9.44 (d, J = 7.9 Hz, 1H), 7.37 – 7.15 (m, 5H), 6.74 (dt, J = 15.6, 6.8 Hz, 1H), 6.05 (dd, J = 15.6, 7.9 Hz, 1H), 5.17 (td, J = 7.2, 2.9 Hz, 1H), 4.14 (dq, J = 14.2, 7.1, 4.0 Hz, 4H), 2.98 – 2.77 (m, 4H), 2.33 (dd, J = 15.2, 6.9 Hz, 2H), 1.76 – 1.59 (m, 2H), 1.47 – 1.23 (m, 7H), 1.04 (t, J = 7.1 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 193.90, 158.04, 137.28, 133.14, 129.16, 128.55, 126.67, 78.16, 62.61, 37.67, 35.07, 34.68, 33.71, 31.23, 30.26, 16.38, 13.72

IR(neat) cm⁻¹: 1946.21, 1733.07, 1688.71, 1635.66

MS (ESI): m/z = 411.23 [M+H]⁺

HRMS (Q-Tof): m/z [M+H]⁺ calcd for C₂₁H₃₁O₆P: 411.1937; found: 411.1912.

(2R,3R,E)-3-methyl-8-oxo-1-phenyloct-6-en-2-yl 2-(diethoxyphosphoryl)propanoate

2.4.10b (relative stereochemistry)

To a degassed 2-necked 25 mL RBF containing the alkene **2.4.9b** (0.397 mmol, 158 mg) in absolute DCM (0.4 mL) under constant N₂ flow, was added *trans*-crotonaldehyde (1.19 mmol, 99 µL). After which, a solution of the Grubbs II catalyst (0.0199 mmol, 16.9 mg) in anhydrous DCM (0.4 mL) was added to the reaction over 4 hours dropwise using a syringe-pump while the reaction was stirred at reflux under N₂ flow. After the addition, the reaction was stirred for a further 2 hours at reflux under N₂ flow. Subsequently, the reaction was then filtered over celite, concentrated in vacuo and then purified on silica gel via column chromatography (2:3 Ethyl acetate/Hexane) to give the product as a purple oil (71%).

¹H NMR (400 MHz, CDCl₃): δ 9.44 (dd, *J* = 7.9, 4.1 Hz, 1H), 7.33 – 7.14 (m, 5H), 6.74 (ddt, *J* = 15.6, 11.4, 6.8 Hz, 1H), 6.05 (dt, *J* = 15.0, 7.4 Hz, 1H), 5.19 (td, *J* = 7.1, 2.8 Hz, 1H), 4.19 – 4.05 (m, 4H), 3.03 – 2.77 (m, 3H), 2.39 – 2.26 (m, 2H), 1.74 – 1.60 (m, 2H), 1.49 – 1.19 (m, 10H), 1.06 (t, *J* = 6.8 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 193.91, 193.88, 169.42, 158.22, 158.05, 137.40, 137.28, 133.10, 129.21, 129.19, 128.50, 128.47, 126.61, 77.79, 77.73, 62.72, 62.66, 62.56, 62.47, 40.45, 40.05, 39.12, 38.72, 37.89, 37.57, 35.03, 34.55, 31.32, 31.21, 30.30, 30.27, 16.46, 16.40, 13.79, 13.66, 11.80, 11.74

IR(neat) cm⁻¹: 1991.54, 1729.21, 1683.89, 1635.66

MS (ESI): *m/z* = 425.25 [M+H]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₂₂H₃₃O₆P: 425.2093; found: 425.2023.

(3E,5E,9R,10R,13E,15E,19R,20R)-10,20-dibenzyl-9,19-dimethyl-1,11-dioxacycloicosa-3,5,13,15-tetraene-2,12-dione 2.4.11a (mixture of *meso*- and *D/L*-isomers)

To a degassed, oven-dried 2-necked 50 mL RBF containing sodium hydride (ca. 60% w/w in mineral oil, 0.71 mmol, 28 mg) was washed with anhydrous toluene twice (2 x 3 mL) to remove the oil layer. The sodium hydride was then redissolved in anhydrous toluene again (14 mL) in a N₂ atmosphere. To a separate flask containing a solution of the aldehyde **2.4.10a** (0.26 mmol, 107 mg) in anhydrous toluene (3 mL) was added 15-Crown-5 (0.183 mmol, 36 μ L) and this mixed solution was then added dropwise over 6 hours via a syringe pump to the 2-necked flask containing the sodium hydride suspension in toluene at 0°C. After the addition, the syringe was washed with a further 0.5 mL toluene and added to the reaction mixture entirely. The reaction was then allowed to stir from 0°C to room temperature over 1.5 hours and was then quenched with saturated ammonium chloride. The mixture was extracted with ethyl acetate (4 x 10 mL) and the combined organic layers were dried over MgSO₄. The mixture was then filtered, concentrated in vacuo and purified on silica gel via column chromatography (1:19 Ethyl acetate/Hexane) to give the analogue product (mixture of *D/L* and *meso* isomers) as a pale yellow oily solid that crystallises at -20°C (56%).

¹H NMR (pure *meso*-isomer) (400 MHz, CDCl₃): δ 7.37 – 7.02 (m, 10H), 6.21 – 5.89 (m, 4H), 5.72 (d, J = 15.3 Hz, 2H), 5.27 – 5.07 (m, 2H), 3.01 – 2.71 (m, 4H), 2.10 (dd, J = 33.0, 9.1 Hz, 4H), 1.68 (s, 2H), 1.58 – 1.39 (m, 4H), 1.38 – 1.13 (m, 2H), 1.03 (t, J = 5.8 Hz, 6H).

¹³C NMR (pure *meso*-isomer) (400 MHz, CDCl₃): δ 166.80, 145.26, 144.37, 138.12, 129.44, 128.65, 128.41, 126.64, 119.65, 37.62, 35.55, 35.31, 32.84, 32.38, 31.06, 14.40, 13.74.

IR(neat) cm^{-1} : 1705.07, 1635.64, 1610.56, 972.12

MS (ESI): $m/z = 535.36$ $[\text{M}+\text{Na}]^+$

HRMS (Q-Tof): m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{34}\text{H}_{40}\text{O}_4$: 535.2824; found: 535.2808.

Melting point (range): 342 – 346 °C

4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-ol 3.3.1

^1H NMR (400 MHz, CDCl_3): δ 4.81 (t, $J = 3.1$ Hz, 1H), 4.51 – 4.05 (m, 4H), 3.94 – 3.71 (m, 1H), 3.62 – 3.45 (m, 1H), 1.95 – 1.40 (m, 7H).

^{13}C NMR (400 MHz, CDCl_3): δ 96.89, 81.95, 62.01, 54.38, 50.80, 50.64, 30.19, 25.30, 18.92

All data are consistent with that reported in literature⁹¹.

N-formyl-N-(4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-yl)formamide 3.3.3

To a degassed, oven-dried 25 mL RBF was added the alcohol **3.3.1** (2.94 mmol, 500 mg) in absolute DCM (12 mL). The mixture was then placed in a 0°C bath and Et_3N (4.4 mmol, 0.614 mL) was then added to the mixture, followed by the dropwise addition of methane sulfonyl chloride (3.8 mmol, 0.3 mL) slowly. The reaction was then stirred at 0°C for 100 to 120 minutes, then subsequently with saturated NaHCO_3 and extracted with DCM (3 x 10 mL). The combined organic layers were dried over MgSO_4 , filtered, concentrated in vacuo and purified on silica gel via a short-path column chromatography (3:17 Ethyl acetate/Hexane) to

give the mesylate product as a yellow oil (92%) which is unstable and thus used immediately for the next step. To a degassed, oven-dried 25 mL 2-necked RBF containing sodium diformylamide (0.604 mmol, 57.4 mg) under N₂ atmosphere, was added a solution of the mesylate (0.403 mmol, 100 mg) in absolute MeCN (1 mL). The resulting mixture was then stirred at 90°C for c.a. 3 hours, before being cooled to room temperature. The suspension was then filtered over celite, the filtrate concentrated in vacuo and purified on column chromatography (7:13 Ethyl acetate/Hexane) to give the imide product as a yellow oil (62%) and the formamide product **3.3.4** (3:2 Ethyl acetate/Hexane) as a yellow oil (20%).

¹H NMR (400 MHz, CDCl₃): δ 8.86 (s, 2H), 4.76 (t, *J* = 3.2 Hz, 1H), 4.44 (s, 2H), 4.23 (q, *J* = 15.8 Hz, 2H), 3.88 – 3.43 (m, 2H), 1.93 – 1.45 (m, 6H).

¹³C NMR (400 MHz, CDCl₃): δ 162.74, 96.83, 78.69, 61.96, 54.07, 30.16, 28.16, 25.30, 18.96

IR(neat) cm⁻¹: 1680.99

MS (ESI): *m/z* = 226.20 [M+H]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₁₁H₁₅NO₄: 226.1079; found: 226.1106.

N-(4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-yl)formamide 3.3.4

To an oven-dried 10 mL RBF containing the imide **3.3.3** (0.227 mmol, 51.1 mg) in ethanol (0.6 mL) was added Amberlyst-26 (33 wt.%, 17.4 mg) in one portion and the suspension was stirred for 29 hours at room temperature. The mixture was then filtered over celite, the filtrate concentrated in vacuo and purified on silica gel via column chromatography (7:3 Ethyl acetate/Hexane) to give the product as a yellow oil (80%).

¹H NMR (400 MHz, CDCl₃): δ 8.18 (s, 1H, major rotamer), 8.13, (d, *J* = 12.0 Hz, 1H, minor rotamer), 5.75 (brs, 1H), 4.81 – 4.72 (m, 1H), 4.37 – 4.18 (m, 2H), 4.18 – 4.10 (m, 2H, major rotamer), 4.06 (dt, *J* = 6.0, 1.9 Hz, 1H, minor rotamer), 3.89 – 3.77 (m, 1H), 3.59 – 3.48 (m, 1H), 1.92 – 1.44 (m, 6H).

¹³C NMR (400 MHz, CDCl₃): δ 160.66, 97.09 (minor rotamer), 97.00 (major rotamer), 80.99, 79.68, 62.06, 54.24 (major rotamer), 54.15 (minor rotamer), 30.20, 28.14, 25.28, 19.02

IR(neat) cm⁻¹: 3042.76, 2237.46, 1723.43, 1673.28

MS (ESI): *m/z* = 220.10 [M+Na]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₁₀H₁₅NO₃: 198.1130; found: 198.1130.

Ethyl oxazole-5-carboxylate 3.3.7

¹H NMR (400 MHz, CDCl₃): δ 8.01 (s, 1H), 7.77 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 157.37, 153.49, 142.77, 132.93, 61.54, 14.01

All data are consistent with that reported in literature⁸⁰.

Oxazol-5-ylmethanol 3.3.8

¹H NMR (400 MHz, CDCl₃): δ 7.87 (s, 1H), 7.03 (s, 1H), 4.70 (s, 2H), 2.46 (brs, 1H).

¹³C NMR (400 MHz, CDCl₃): δ 151.93, 151.24, 123.17, 54.17

All data are consistent with that reported in literature⁸⁰.

2-(oxazol-5-yl)acetonitrile 3.3.10

¹H NMR (400 MHz, CDCl₃): δ 7.89 (s, 1H), 7.10 (s, 1H), 3.85 (d, *J* = 1.1 Hz, 2H).

All data are consistent with that reported in literature⁸⁰.

Methyl 2-(oxazol-5-yl)acetate 3.3.11

¹H NMR (400 MHz, CDCl₃): δ 7.77 (s, 1H), 6.93 (s, 1H), 3.69 (s, 2H), 3.67 (s, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 168.68, 150.87, 145.09, 124.71, 52.40, 31.26

All data are consistent with that reported in literature⁸⁰.

N-methoxy-N-methyl-2-(oxazol-5-yl)acetamide 3.3.12

To a degassed oven-dried 50 mL 2-necked RBF containing a solution of *N*, *O*-dimethylhydroxylamine hydrochloride (2.12 mmol, 207 mg) in anhydrous DCM (14 mL) at 0°C was added dimethylaluminium chloride (0.9M, 2.36 mL) dropwise and the reaction was then allowed to stir at ambient temperature for an hour. A solution of the ester **3.3.11** (0.708 mmol, 100 mg) in absolute DCM (6 mL) was then added dropwise at room temperature to the reaction mixture and was then subsequently stirred for another 30 minutes at ambient temperature. The reaction was then quenched with a pH 8 phosphate buffer (6.36 mL), stirred for another 10 minutes and then extracted with DCM (3 x 15 mL). The combined organic layers were dried over MgSO₄, filtered and then concentrated in vacuo to give the crude product as a yellow oil which was sufficiently pure (based on ¹H NMR) for the next step (79%).

¹H NMR (400 MHz, CDCl₃): δ 7.83 (s, 1H), 7.02 (s, 1H), 3.89 (s, 2H), 3.73 (s, 3H), 3.23 (s, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 168.72, 150.82, 146.17, 124.73, 61.47, 32.28, 29.58

IR(neat) cm⁻¹: 1658.81, 1510.29, 1182.38, 1103.30

MS (ESI): *m/z* = 193.04 [M+Na]⁺

Diethyl 2-(but-3-en-1-yl)-2-methylmalonate **3.4.1**

¹H NMR (400 MHz, CDCl₃): δ 5.79 (dq, *J* = 10.3, 6.2 Hz, 1H), 5.10 – 4.91 (m, 2H), 4.18 (q, *J* = 6.7 Hz, 4H), 2.04 – 1.91 (m, 4H), 1.39 (s, 3H), 1.25 (t, *J* = 8.0 Hz, 6H).

¹³C NMR (400 MHz, CDCl₃): δ 171.98, 137.57, 114.76, 60.95, 53.25, 34.63, 28.53, 19.70, 13.89

All data are consistent with that reported in literature⁹².

2-(but-3-en-1-yl)-2-methylmalonic acid 3.4.2

To a solution of the malonate **3.4.1** (14.6 mmol, 3.34 g) in a 4:1 THF/H₂O mixture (52 mL) was added LiOH·H₂O (36.6 mmol, 1.53 g) in one portion and the mixture was stirred at 70°C overnight. The mixture was then cooled to room temperature and acidified to pH = 1 with 37% w/w concentrated HCl, then extracted with ethyl acetate (5 x 20 mL) and the combined organic layers were concentrated in vacuo to give a yellow oil, which solidifies into a yellow solid when placed under high vacuum (88%).

¹H NMR (400 MHz, CDCl₃): δ 9.13 (brs, 2H), 5.79 (dq, *J* = 10.0, 6.2 Hz, 1H), 5.02 (dd, *J* = 28.8, 13.7 Hz, 2H), 2.14 – 1.87 (m, 4H), 1.50 (s, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 177.99, 137.15, 115.30, 53.57, 34.61, 28.56, 19.84

All data are consistent with that reported in literature⁹³.

2-methylhex-5-enoic acid 3.4.3

To a flask equipped with a water cooling condenser containing the malonic acid **3.4.2** (5.18 mmol, 892 mg) was added 2,4,6-collidine (1.3 mmol, 171 μ L) and the mixture was heated at 140°C for c.a. 4 hours under continuous N₂ flow, without any stirring required. Any product condensed on the condenser was then washed with ethyl acetate into the flask and the resultant solution was concentrated in vacuo. The crude was loaded directly onto silica gel and purified via column chromatography (7:93 Ethyl acetate/Hexane) to give the product as a colourless oil (98%).

¹H NMR (500 MHz, CDCl₃): δ 5.79 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.08 – 4.93 (m, 2H), 2.50 (dd, J = 14.0, 7.0 Hz, 1H), 2.11 (dd, J = 14.9, 7.2 Hz, 2H), 1.82 (dt, J = 15.3, 7.5 Hz, 1H), 1.53 (td, J = 14.0, 7.5 Hz, 1H), 1.20 (d, J = 10.0 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 1853.42, 137.63, 115.16, 38.70, 32.49, 31.19, 16.68

All data are consistent with that reported in literature⁹⁴.

N*-methoxy-*N*,2-dimethylhex-5-enamide **3.4.4*

¹H NMR (500 MHz, CDCl₃): δ 5.79 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.08 – 4.91 (m, 2H), 3.68 (s, 3H), 3.19 (s, 3H), 2.90 (s, 1H), 2.10 – 2.01 (m, 2H), 1.84 – 1.75 (m, 1H), 1.52 – 1.39 (m, 1H), 1.13 (d, J = 5.0 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 177.59, 138.17, 114.61, 77.39, 61.28, 34.36, 32.68, 32.09, 31.48, 17.27

All data are consistent with that reported in literature⁹⁵.

(E)-6-(1,3-dioxolan-2-yl)-N-methoxy-N,2-dimethylhex-5-enamide 3.4.5.1

To a degassed, oven-dried 2-necked 25 mL RBF fitted with a water cooling condenser containing a solution of the Weinreb amide **3.4.4** (0.534 mmol, 100 mg) in absolute DCM (1.7 mL), was added 2-vinyl-1,3-dioxolane (1.6 mmol, 160 μ L). The reaction was placed under constant N₂ flow and a solution of the Grubbs II catalyst (0.0267 mmol, 22.7 mg) in absolute DCM (1 mL) was then added dropwise over an hour via syringe pump with the reaction stirring at 45°C. The reaction was then continued stirring at the same temperature for a further 5 hours, before it was cooled to ambient temperature and filtered over celite. The filtrate was then concentrated in vacuo and purified on silica gel via column chromatography (1:3 Ethyl acetate/Hexane) to give the product as a dark purple oil (76%, predominantly *trans*).

¹H NMR (400 MHz, CDCl₃): δ 5.90 (dt, J = 15.4, 6.7 Hz, 1H), 5.57 – 5.40 (m, 1H), 5.18 (d, J = 8.0 Hz, 1H), 4.05 – 3.75 (m, 4H), 3.68 (s, 3H), 3.18 (s, 3H), 2.87 (s, 1H), 2.16 – 1.99 (m, 2H), 1.90 – 1.75 (m, 1H), 1.47 (td, J = 13.5, 7.4 Hz, 1H), 1.12 (d, J = 4.0 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 136.79, 126.85, 103.98, 64.83, 61.42, 34.42, 32.41, 29.76, 29.61, 22.61, 17.33

IR(neat) cm⁻¹: 1734.04, 1648.20, 1057.01

MS (ESI): m/z = 266.18 [M+Na]⁺

HRMS (Q-Tof): m/z [M+H]⁺ calcd for C₁₂H₂₁NO₄: 244.1549; found: 244.1572.

1-hydroxy-5-methylnon-8-en-2-yn-4-one 4.1.1

To a degassed, oven-dried 50 mL 2-necked RBF was charged with 2-(prop-2-yn-1-yloxy) tetrahydro-2H-pyran (8.4 mmol, 1.18 g) in absolute THF (12 mL) under a N₂ atmosphere. Ethyl magnesium bromide (3M in Et₂O, 2.79 mL) was then added dropwise at room temperature and the mixture was then refluxed for 1.5 hours at 70°C with stirring. After which, the mixture was then allowed to cool to ambient temperature and was then transferred via a syringe to another degassed, oven-dried flask containing a solution of the Weinreb amide **3.4.4** (3.51 mmol, 600 mg) in absolute THF (36 mL) placed under N₂ atmosphere at 0°C. The mixture was then allowed to stir from 0°C to room temperature over 4.5 hours. The mixture was subsequently quenched with saturated ammonium chloride, extracted thrice with ether (3 x 30 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated in vacuo and the crude redissolved in iso-propanol (67 mL) with a stir bar in another flask. To the mixture was then added PPTS (0.756 mmol, 190 mg) in one portion and the flask was fitted with an air condenser and drying tube. The reaction mixture was then stirred at 60°C for c.a. 6 hours, before being cooled to room temperature. Sodium bicarbonate powder was then added and the mixture was swirled a few times and then allowed to stand over 5 to 10 minutes. The mixture was then filtered over celite, the filtrate concentrated in vacuo and subsequently purified on silica gel via column chromatography (3:17 Ethyl acetate/Hexane) to give the product as a yellow oil (86% over two steps).

¹H NMR (400 MHz, CDCl₃): δ 5.78 (ddt, *J* = 16.8, 10.1, 6.5 Hz, 1H), 5.02 (t, *J* = 13.7 Hz, 2H), 4.46 (d, *J* = 6.3 Hz, 2H), 2.73 – 2.53 (m, 1H), 2.10 (dd, *J* = 22.8, 15.2 Hz, 2H), 1.88 (ddd, *J* = 17.2, 11.8, 6.4 Hz, 2H), 1.58 – 1.40 (m, 1H), 1.19 (d, *J* = 9.0 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 192.07, 137.54, 115.32, 91.63, 83.17, 50.38, 47.54, 31.48, 30.96, 15.62

IR(neat) cm⁻¹: 3429.49, 2213.35, 1670.38

MS (ESI): *m/z* = 189.08 [M+Na]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₁₀H₁₄O₂: 167.1072; found: 167.1085.

3-(2-(hex-5-en-2-yl)-1,3-dioxolan-2-yl)prop-2-yn-1-ol **4.1.2**

To an oven-dried 25 mL RBF containing the ketone **4.1.1** (1.03 mmol, 171 mg) in absolute DCM (5 mL), was added 2-methoxy-1, 3-dioxolane (1.55 mmol, 147 μL) and the flask was then fitted with a drying tube. *p*-TSA.H₂O (0.103 mmol, 19.6 mg) was then added to the reaction mixture in one portion and the reaction was then stirred for 6 hours at room temperature. The reaction was then subsequently quenched with saturated sodium bicarbonate and extracted with DCM (5 x 5 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated in vacuo and purified on silica gel via column chromatography (1:5 Ethyl acetate/Hexane) to give the dioxolane product as a dark orange oil (60%) and the formate ester side product (1:10 Ethyl acetate/Hexane) as a yellow oil (6%). The formate ester was then redissolved in ethanol (1 mL) another flask and Amberlyst-26 (2.25 mg) was added. The reaction was then stirred overnight at room temperature, then filtered over celite washing with DCM and concentrated in vacuo to give a light orange oil as the same dioxolane product (91%), totalling the overall yield of the dioxolane **4.1.2** to 65%.

¹H NMR (400 MHz, CDCl₃): δ 5.81 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.12 – 4.90 (m, 2H), 4.32 (d, *J* = 4.4 Hz, 2H), 4.17 – 3.89 (m, 4H), 2.30 – 2.14 (m, 1H), 2.10 – 1.94 (m, 1H), 1.84 (ttd, *J* = 10.4, 7.0, 3.4 Hz, 2H), 1.39 – 1.19 (m, 2H), 1.06 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 138.62, 114.56, 106.31, 83.04, 82.26, 64.73, 64.65, 50.61, 41.00, 31.35, 30.22, 13.96

IR(neat) cm⁻¹: 3429.49, 2211.43, 1641.45, 1110.05

MS (ESI): *m/z* = 233.16 [M+Na]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₁₂H₁₈O₃: 211.1334; found: 211.1333.

2-(3-(2-(hex-5-en-2-yl)-1,3-dioxolan-2-yl)prop-2-yn-1-yl)isoindoline-1,3-dione 4.1.3

To a degassed, oven-dried 25 mL RBF was charged with phthalimide (0.618 mmol, 91 mg), triphenylphosphine (0.618 mmol, 162 mg), followed by a solution of the alcohol **4.1.2** (0.48 mmol, 100 mg) in absolute THF (5.3 mL) under a N₂ atmosphere. DIAD (0.62 mmol, 122 μL) was then added dropwise to the mixture in the dark and the reaction was then stirred overnight at room temperature. The mixture was then subsequently concentrated in vacuo and purified on silica gel directly via column chromatography (3:22 Ethyl acetate/Hexane) to give the product as a yellowish solid (quantitative).

¹H NMR (400 MHz, CDCl₃): δ 7.95 – 7.68 (m, 4H), 5.78 (ddt, *J* = 17.1, 10.1, 6.6 Hz, 1H), 5.07 – 4.85 (m, 2H), 4.49 (s, 2H), 4.17 – 3.86 (m, 4H), 2.22 – 1.95 (m, 2H), 1.85 – 1.75 (m, 2H), 1.28 (tdd, *J* = 9.3, 7.8, 4.2 Hz, 1H), 1.03 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 166.88, 138.67, 134.17, 131.98, 123.50, 114.45, 106.13, 80.20, 78.06, 64.67, 64.59, 40.85, 31.32, 30.15, 27.17, 13.96

IR(neat) cm⁻¹: 1772.61, 1721.50, 1640.49

MS (ESI): *m/z* = 340.19 [M+H]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₂₀H₂₁NO₄: 340.1549; found: 340.1569.

***N*-(3-(2-(hex-5-en-2-yl)-1,3-dioxolan-2-yl)prop-2-yn-1-yl)formamide 4.1.4**

To a flask containing a solution of the phthalimide **4.1.3** (0.532 mmol, 181 mg) in ethanol (2.4 mL) with a stir bar was added hydrazine monohydrate (2.39 mmol, 117 μ L) and the reaction was refluxed with stirring for 2.5 hours. The mixture was then allowed to cool to ambient temperature before it was filtered over celite and filtrate concentrated in vacuo to give a light yellow solid. To the flask containing the solid was then added ethyl formate (5.3 mL) and the reaction flask was fitted with a water condenser and a drying tube. The mixture was then heated to reflux at 60°C for 24 hours. It was then subsequently cooled to room temperature, concentrated in vacuo and then purified on silica gel via column chromatography (1:1 Ethyl acetate/Hexane) to give the product as a yellow oil (76%, over both steps).

¹H NMR (400 MHz, CDCl₃): δ 8.18 (s, 1H, major rotamer), 8.13 (d, *J* = 12.0 Hz, 1H), 5.86 – 5.76 (m, 1H), 5.69 (brs, 1H), 5.06 – 4.94 (m, 2H), 4.16 (dd, *J* = 5.4, 0.8 Hz, 2H, major rotamer), 4.12 (d, *J* = 8.0 Hz, 2H, minor rotamer), 4.09 – 3.94 (m, 4H), 2.24 – 2.11 (m, 1H), 2.09 – 1.95 (m, 1H), 1.83 (dtdd, *J* = 13.2, 10.0, 6.9, 3.4 Hz, 2H), 1.42 – 1.12 (m, 1H), 1.05 (d, *J* = 4.0 Hz, 3H, major rotamer), 1.03 (d, *J* = 4.0 Hz, 3H, minor rotamer).

¹³C NMR (400 MHz, CDCl₃): δ 160.61, 138.61, 114.60, 106.38, 106.24, 80.84, 80.72, 79.64, 79.53, 64.78, 64.76, 64.71, 41.65, 41.02, 31.34, 30.77, 30.23, 29.51, 27.86, 22.83, 14.05, 14.00

IR(neat) cm⁻¹: 3364.88, 2239.39, 1672.31, 1231.57, 1167.92, 1119.70, 1049.29

MS (ESI): *m/z* = 238.12 [M+H]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₁₃H₁₉NO₃: 238.1443; found: 238.1478.

***N*-(5-methyl-4-oxonon-8-en-2-yn-1-yl)formamide 4.1.5**

To a flask containing a solution of the dioxolane **4.1.4** (0.421 mmol, 100 mg) in bench acetone (2.1 mL), was added *p*-TSA.H₂O (0.0548 mmol, 10.4 mg) in one portion and the flask was fitted with an air condenser and stirred for a day. The reaction was then quenched with saturated NaHCO₃, diluted with some water and then extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated in vacuo and then purified on silica gel via column chromatography (1:1 Ethyl acetate/Hexane) to give the product as a yellow oil (77%).

¹H NMR (400 MHz, CDCl₃): δ 8.22 (s, 1H, major rotamer), 8.15 (d, *J* = 11.7 Hz, 1H, minor rotamer), 6.03 – 5.68 (m, 2H), 5.09 – 4.94 (m, 2H), 4.30 (dd, *J* = 5.6, 0.7 Hz, 2H, major rotamer), 4.22 (d, *J* = 6.2 Hz, 2H, minor rotamer), 2.66 – 2.50 (m, 1H), 2.23 (dt, *J* = 20.5, 8.5 Hz, 1H, minor rotamer), 2.15 – 1.98 (m, 2H, major rotamer), 1.88 (ddt, *J* = 13.6, 8.8, 6.7 Hz, 1H, major rotamer), 1.75 (m, 1H, minor rotamer), 1.49 (ddt, *J* = 20.1, 18.4, 9.2 Hz, 1H, major rotamer), 1.35 – 1.24 (m, 1H, minor rotamer), 1.17 (d, *J* = 7.0 Hz, 3H, major rotamer), 1.15 (d (overlapped), 3H, minor rotamer).

¹³C NMR (400 MHz, CDCl₃): δ 194.10, 191.28, 161.08, 137.76, 115.21, 96.17, 44.69, 40.01, 33.07, 31.28, 30.24, 17.68

IR(neat) cm⁻¹: 3403.45, 1674.24, 1626.98, 1196.85

MS (ESI): *m/z* = 194.14 [M+H]⁺

HRMS (Q-ToF): *m/z* [M+H]⁺ calcd for C₁₁H₁₅NO₂: 194.1392; found: 194.1430.

3-methyl-1-(oxazol-5-yl)hept-6-en-2-one 4.1.6

To an oven-dried degassed three necked 25 mL RBF fitted with a water condenser under N₂ containing JohnphosAuCl (0.0319 mmol, 16.9 mg) was added a solution of the formamide **4.1.5** (0.319 mmol, 61.6 mg) in absolute DCE (1.3 mL). The reaction was then stirred for thirty minutes at ambient temperature, at which point AgOTs (0.0319 mmol, 8.9 mg) was added in one portion to the reaction mixture via a solid addition tube and the reaction was then stirred for a further 45 minutes, before being heated to 70°C overnight. The reaction was then filtered over celite, the filtrate concentrated in vacuo and then loaded directly onto silica

gel and purified via column chromatography (7:13 Ethyl acetate/Hexane) to give the product as a yellow to light orange oil (73%).

¹H NMR (400 MHz, CDCl₃): δ 7.83 (s, 1H), 7.00 (s, 1H), 5.75 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.07 – 4.92 (m, 2H), 3.91 – 3.75 (m, 2H), 2.65 (dt, *J* = 15.0, 7.5 Hz, 1H), 2.09 – 1.98 (m, 2H), 1.82 (ddt, *J* = 13.8, 8.3, 6.9 Hz, 1H), 1.51 – 1.40 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 207.74, 150.72, 145.68, 137.64, 124.81, 115.29, 44.99, 37.91, 31.63, 31.16, 16.16

IR(neat) cm⁻¹: 1718.60, 1641.45, 1177.56, 1105.23

MS (ESI): *m/z* = 194.09 [M+H]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₁₁H₁₅NO₂: 194.1181; found: 194.1184.

3-methyl-1-(oxazol-5-yl)hept-6-en-2-ol **4.1.7**

To a degassed, oven-dried 2-necked 25 mL RBF containing a solution of the ketone **4.1.6** (0.796 mmol, 154 mg) in absolute DCM (2.6 mL) was added DIBAL-H (1M, 1.2 mL) dropwise at -78°C over 10 minutes. The reaction was stirred for 15 minutes at that temperature, then at -40°C overnight. It was then subsequently quenched with saturated Rochelle's salt and the mixture was stirred overnight, before it was extracted thrice (3 x 10 mL) with DCM. The combined organic layers were dried over MgSO₄, filtered, concentrated in vacuo and subsequently purified on silica gel via column chromatography (9:11 Ethyl acetate/Hexane) to give the product as a yellow oil (90%).

¹H NMR (400 MHz, CDCl₃): δ 7.81 (d, *J* = 2.0 Hz, 1H), 6.89 (d, *J* = 3.6 Hz, 1H), 5.81 (dtd, *J* = 21.4, 10.7, 6.6 Hz, 1H), 5.11 – 4.90 (m, 2H), 3.82 (d, *J* = 33.6 Hz, 1H), 2.96 – 2.71 (m, 2H), 2.26 – 1.96 (m, 2H), 1.66 – 1.61 (m, 2H), 1.40 – 1.16 (m, 2H), 0.97 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 150.75, 150.35, 138.67, 138.62, 123.38, 123.25, 114.60, 73.61, 72.71, 37.88, 37.35, 32.24, 31.34, 31.26, 31.07, 30.90, 30.09, 15.05, 13.46

IR(neat) cm⁻¹: 3416.96, 1640.49, 1608.66, 1050.26

MS (ESI): *m/z* = 196.13 [M+H]⁺

HRMS (Q-Tof): *m/z* [M+H]⁺ calcd for C₁₁H₁₇NO₂: 196.1338; found: 196.1323.

3-methyl-1-(oxazol-5-yl)hept-6-en-2-yl 2-(diethoxyphosphoryl)propanoate 4.1.8a

To an oven-dried flask fitted with a drying tube, containing a solution of 2-(diethoxyphosphoryl)propanoic acid (2.81 mmol, 590 mg) in anhydrous DCM (3.2 mL) was added oxalyl chloride (8.44 mmol, 0.71 mL) dropwise at room temperature. Absolute DMF (17 μL) was then added dropwise and effervescence was observed. The reaction was then stirred at ambient temperature for 1 hour and then concentrated in vacuo to give an orange oil. The crude oil was then redissolved in absolute THF (7 mL) under N₂ atmosphere to give a 0.4M solution of the acid chloride. To another oven-dried, degassed 50 mL RBF containing a solution of the alcohol **4.1.7** (0.948 mmol, 185 mg) in absolute THF (16 mL) at 0°C was added pyridine (4.74 mmol, 384 μL), followed by the acetyl chloride solution dropwise over 10 minutes. The mixture was then stirred at 0°C for 15 minutes then at ambient temperature

for 2.5 hours. The reaction was subsequently quenched with saturated NaHCO_3 and extracted with ethyl acetate (4 x 12 mL). The combined organic layers were dried over MgSO_4 , filtered, concentrated in vacuo and purified on silica gel via column chromatography (19:1 Ethyl acetate/Hexane) to give the product as a pale yellow oil (88%).

^1H NMR (300 MHz, CDCl_3): δ 7.78 (d, J = 1.3 Hz, 1H), 6.85 (d, J = 10.4 Hz, 1H), 5.89 – 5.64 (m, 1H), 5.27 – 4.88 (m, 3H), 4.26 – 4.03 (m, 4H), 3.08 – 2.83 (m, 3H), 2.34 – 1.95 (m, 2H), 1.64 (m, 3H), 1.46 – 1.10 (m, 9H), 0.99 (tt, J = 9.3, 4.6 Hz, 3H).

^{13}C NMR (400 MHz, CDCl_3): δ 171.09, 169.11, 169.00, 150.52, 138.21, 123.85, 123.76, 114.85, 114.81, 77.26, 76.20, 76.14, 75.17, 62.64, 62.60, 62.54, 60.35, 40.00, 38.91, 38.70, 35.36, 35.23, 35.12, 31.94, 31.86, 31.10, 31.05, 30.76, 28.00, 27.78, 26.91, 21.00, 16.39, 16.33, 14.88, 14.76, 14.16, 14.07, 13.76, 13.73

IR(neat) cm^{-1} : 1734.04, 1641.45, 1248.93, 1165.99, 1096.55

MS (ESI): m/z = 388.28 $[\text{M}+\text{H}]^+$

HRMS (Q-Tof): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{30}\text{NO}_6\text{P}$: 388.1701; found: 388.1746.

3-methyl-1-(oxazol-5-yl)hept-6-en-2-yl 2-(diethoxyphosphoryl)acetate 4.1.8b

To an oven-dried flask fitted with a drying tube, containing a solution of diethyl phosphonoacetic acid (2.04 mmol, 399 mg) in anhydrous DCM (2.3 mL) was added oxalyl chloride (6.1 mmol, 516 μL) dropwise at room temperature. Absolute DMF (12 μL) was then

added dropwise and effervescence was observed. The reaction was then stirred at ambient temperature for 1 hour and then concentrated in vacuo to give a yellow oil. The crude oil was then redissolved in absolute THF (3 mL) under N₂ atmosphere to make a solution of the acetyl chloride. To another oven-dried, degassed 25 mL RBF containing a solution of the alcohol **4.1.7** (0.688 mmol, 134 mg) in absolute THF (12 mL) at 0°C was added pyridine (3.44 mmol, 278 µL), followed by the acetyl chloride solution dropwise over 10 minutes. The mixture was then stirred at 0°C for 15 minutes then at ambient temperature for 2.5 hours. The reaction was subsequently quenched with saturated NaHCO₃ and extracted with ethyl acetate (4 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated in vacuo and purified on silica gel via column chromatography (19:1 Ethyl acetate/Hexane) to give the product as a light yellow oil (87%).

¹H NMR (400 MHz, CDCl₃): δ 7.79 (s, 1H), 6.87 (s, 1H), 5.86 – 5.69 (m, 1H), 5.22 – 4.91 (m, 3H), 4.24 – 4.09 (m, 4H), 3.05 – 2.81 (m, 4H), 2.34 – 1.97 (m, 2H), 1.76 (d, *J* = 30.2 Hz, 1H), 1.59 – 1.50 (m, 1H), 1.41 – 1.28 (m, 7H), 0.98 (ddd, *J* = 12.5, 8.1, 4.8 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 165.19, 165.14, 165.08, 150.57, 148.87, 148.77, 138.13, 123.79, 123.76, 114.88, 114.86, 77.29, 76.48, 75.52, 62.63, 62.58, 35.24, 35.17, 34.93, 33.60, 31.84, 31.06, 31.02, 30.78, 27.84, 26.86, 16.31, 16.25, 14.78, 13.99, 13.74

IR(neat) cm⁻¹: 1735.96, 1641.45, 1164.06, 1113.91

MS (ESI): *m/z* = 374.25 [M+H]⁺

HRMS (Q-ToF): *m/z* [M+Na]⁺ calcd for C₁₇H₂₈O₆NP: 396.1552; found: 396.1552.

(*E*)-3-methyl-1-(oxazol-5-yl)-8-oxooct-6-en-2-yl 2-(diethoxyphosphoryl)propanoate

4.1.9a

To a 10 mL RBF containing the alkene **4.1.8a** (0.297 mmol, 115 mg) in a 5:1 solution of acetone/H₂O mixture (2.8 mL) at 0°C, was added NMO (50% w/w, 0.594 mmol, 123 µL), followed by K₂OsO₄·2H₂O (0.0148 mmol, 5.5 mg) in one portion. The flask was then fitted with a glass stopper, then sealed with Teflon tape and the mixture was stirred at 0°C for four hours before being raised to room temperature and stirred overnight for 14 hours. The reaction was quenched with Na₂SO₃ solid, stirred for 30 minutes before adding water and extracting with ethyl acetate (5 x 10 mL) and washing with brine. The combined organic layers were dried over MgSO₄, filtered, concentrated in vacuo and was sufficiently pure according to ¹H NMR to be used directly in the next step without further purification. To a flask containing a suspension of silica (0.49 g) in DCM (3.9 mL) was added a 0.65 M solution of NaIO₄ (0.319 mmol, 0.49 mL) dropwise with stirring, whence a flaky suspension was formed. The crude diol obtained above was re-dissolved in DCM (0.49 mL) in a separate flask and this solution was added dropwise via a syringe to the silica suspension and the reaction was stirred for 15 to 20 minutes. The mixture was then subsequently filtered over celite, washing with DCM and the filtrate evaporated to give a pale yellow oil which was sufficiently pure according to ¹H NMR to be used directly in the next step without further purification. The crude aldehyde obtained from the second step was then redissolved in absolute THF (2.3 mL) in a flask under N₂ and this solution was added to a pressure tube containing Ph₃PCHCHO (0.319 mmol, 97.2 mg) under N₂. The tube was then sealed and heated to 100°C

for 24 hours with a blast shield placed in front of the reaction system. It was then subsequently cooled to room temperature, filtered over celite, concentrated in vacuo and purified on silica via column chromatography (Ethyl acetate) to give the product as a yellow oil (50%).

¹H NMR (400 MHz, CDCl₃): δ 9.55 – 9.48 (m, 1H), 7.79 (d, *J* = 2.0 Hz, 1H), 6.93 – 6.76 (m, 2H), 6.21 – 6.05 (m, 1H), 5.30 – 5.05 (m, 1H), 4.20 – 4.06 (m, 4H), 3.09 – 2.85 (m, 3H), 2.53 – 2.10 (m, 3H), 1.82 – 1.72 (m, 2H), 1.49 – 1.29 (m, 9H), 1.02 (dt, *J* = 13.5, 7.5 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 193.74, 193.70, 169.26, 169.20, 169.06, 169.01, 157.65, 157.46, 150.63, 148.73, 133.26, 133.24, 132.16, 132.06, 129.09, 128.56, 124.11, 123.97, 123.88, 77.24, 75.88, 75.81, 74.66, 74.58, 62.81, 62.74, 62.68, 62.61, 62.54, 60.35, 40.38, 40.08, 39.05, 38.75, 35.74, 35.61, 35.52, 35.45, 31.05, 30.94, 30.51, 30.22, 30.18, 29.94, 29.78, 29.67, 28.04, 27.85, 27.22, 27.08, 20.98, 16.41, 16.35, 15.00, 14.94, 14.18, 13.71, 13.67, 11.87, 11.81, 11.77, 11.71

IR(neat) cm⁻¹: 1738.86, 1653.02, 1242.18

MS (ESI): *m/z* = 416.27 [M+H]⁺

HRMS (Q-ToF): *m/z* [M+H]⁺ calcd for C₁₉H₃₀NO₇P: 416.1862; found: 416.1830.

(*E*)-3-methyl-1-(oxazol-5-yl)-8-oxooct-6-en-2-yl 2-(diethoxyphosphoryl)acetate 4.1.9b

To a 10 mL RBF containing the alkene **4.1.8b** (0.268 mmol, 100 mg) in a 5:1 solution of acetone/H₂O mixture (2.5 mL) at 0°C, was added NMO (50% w/w, 0.54 mmol, 111 μL),

followed by $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (0.0134 mmol, 4.9 mg) in one portion. The flask was then fitted with a glass stopper, then sealed with Teflon tape and the mixture was stirred at 0°C for four hours before being raised to room temperature and stirred overnight for 14 hours. The reaction was quenched with Na_2SO_3 solid, stirred for 30 minutes before adding water and extracting with ethyl acetate (5 x 10 mL) and washing with brine. The combined organic layers were dried over MgSO_4 , filtered, concentrated in vacuo and was sufficiently pure according to ^1H NMR to be used directly in the next step without further purification. To a flask containing a suspension of silica (0.54 g) in DCM (4.3 mL) was added a 0.65 M solution of NaIO_4 (0.348 mmol, 0.54 mL) dropwise with stirring, whence a flaky suspension was formed. The crude diol obtained above was redissolved in DCM (0.54 mL) in a separate flask and this solution was added dropwise via a syringe to the silica suspension and the reaction was stirred for 15 to 20 minutes. The mixture was then subsequently filtered over celite, washing with DCM and the filtrate evaporated to give a pale yellow oil which was sufficiently pure according to ^1H NMR to be used directly in the next step without further purification. The crude aldehyde obtained from the second step was then redissolved in absolute THF (2.5 mL) in a flask under N_2 and this solution was added to a pressure tube containing Ph_3PCHCHO (0.335 mmol, 102 mg) under N_2 . The tube was then sealed and heated to 100°C for 24 hours with a blast shield placed in front of the reaction system. It was then subsequently cooled to room temperature, filtered over celite, concentrated in vacuo and purified on silica via column chromatography (4:1 Ethyl acetate/DCM) to give the product as a yellow oil (32%).

^1H NMR (400 MHz, CDCl_3): δ 9.51 (dd, $J = 15.4, 9.5$ Hz, 1H), 7.79 (d, $J = 2.0$ Hz, 1H), 6.90 – 6.76 (m, 2H), 6.20 – 6.04 (m, 1H), 5.18 (dd, $J = 52.2, 4.3$ Hz, 1H), 4.18 – 4.05 (m, 4H), 3.09 – 2.85 (m, 3H), 2.52 – 2.08 (m, 2H), 1.77 (d, $J = 41.6$ Hz, 2H), 1.47 – 1.14 (m, 9H), 1.07 – 0.94 (m, 3H).

^{13}C NMR (400 MHz, CDCl_3): δ 193.84, 165.18, 157.65, 133.24, 123.98, 123.89, 76.13, 74.93, 62.78, 62.73, 62.68, 35.53, 35.45, 34.96, 33.62, 30.89, 30.18, 29.95, 29.77, 29.67, 27.87, 27.08, 16.35, 16.29, 14.91, 13.67

IR(neat) cm^{-1} : 1734.08, 1684.89, 1654.03, 1637.64, 1211.35, 1164.09

MS (ESI): m/z = 402.26 $[\text{M}+\text{H}]^+$

HRMS (Q-Tof): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{28}\text{NO}_7\text{P}$: 402.1682; found: 402.1681.

***rac*-Samroiymycin A 4.1.10a**

To a degassed, oven-dried 2-necked 25 mL RBF was added sodium hydride (60% w/w, 0.42 mmol, 17 mg) that was pre-washed with absolute PhMe to remove the oil layer. Absolute THF (7 mL) was then added. A solution of the enal **4.1.9a** (0.139 mmol, 58 mg) and 15-Crown-5 (0.042 mmol, 8.3 μL) in absolute THF (1.5 mL) was then added dropwise over 6 hours via a syringe pump to the reaction mixture at 0°C . During the addition, the mixture was maintained at 0°C for four hours, before being allowed to gradually warm to room temperature over the remaining 2 hours. The reaction was then quenched with saturated ammonium chloride at 0°C and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over MgSO_4 , filtered, concentrated in vacuo and then purified on silica gel via column chromatography to isolate two isomeric fractions of the product (9:11 Ethyl acetate/Hexane, then 9:1 Ethyl acetate/Hexane) each as an oily solid (29%).

¹H NMR (400 MHz, CDCl₃): δ 7.78 (s, 1H), 7.73 – 7.41 (m, 1H), 7.10 – 7.07 (m, 1H), 6.82 (s, 1H), 6.42 – 5.94 (m, 2H), 5.14 (d, *J* = 55.8 Hz, 1H), 3.13 – 2.83 (m, 2H), 2.37 – 1.95 (m, 2H), 1.95 – 1.66 (m, 3H), 1.37 – 1.11 (m, 3H), 1.02 – 0.99 (m, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 176.46, 167.97, 150.51, 149.12, 142.77, 132.16, 132.06, 131.95, 128.56, 128.44, 123.72, 35.66, 31.93, 30.57, 29.70, 14.11, 12.63, 1.02, -0.01

IR(neat) cm⁻¹: 1645.31

MS (ESI): *m/z* = 523.40 [M+H]⁺

HRMS (Q-Tof): *m/z* [M+Na]⁺ calcd for C₃₀H₃₈N₂O₆: 545.2628; found: 545.2638.

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APPENDIX

Figure 20. X-ray structure of 2.4.4.1