Towards the total synthesis of trichoether A

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**NANYANG
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**TOWARDS THE TOTAL SYNTHESIS
OF TRICHOETHER A**

KO WEITING

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2021

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

2021

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Abstract

This dissertation is divided into two chapters.

The first chapter describes the significance of polyene natural products in drug discovery. A short review that covers the different methodologies used to construct polyunsaturated motifs in natural products is reported herein. This chapter is mainly divided into two segments – direct olefination and cross-coupling reactions. The advantages and disadvantages of these reactions are reviewed and discussed.

The second chapter describes an approach towards the total asymmetric synthesis of trichoether A which involves three stages – the construction of the triene aliphatic chain fragment, the trisubstituted benzyl fragment, and the different approaches employed in unifying these two fragments in a convergent synthesis. The synthesis of the triene aliphatic chain features an optimisation of the alkynylation in a tricarbonyliron-dienyne complex. In the development of this optimisation step, a different electrophile was introduced to not only enhance the yield of the reaction, but also created an opportunity to avert the use of any hydroxyl protecting groups during the synthesis of the triene aliphatic chain. A subsequent regiospecific hydrostannylation across the internal alkyne was established. Completion of the aliphatic chain then ensued via a Suzuki coupling and Sharpless asymmetric dihydroxylation. The synthesis of the benzyl fragment emphasised the strategic use of C-H activation to install the respective substituent groups. In the final stage of the total synthesis, several coupling strategies for the ether construction as the key step were pursued. Both S_N2 and S_N1 reactions were described for the etherification step, but other protocols such as the use of Quinone Methide and ketal fragmentation were explored as well. While the partial chiral ketal reduction could deliver the ether bond formation, a model study was carried out to elucidate the mechanistic pathway of the ketal fragmentation strategy.

List of Abbreviations

α	Alpha
β	Beta
Ac	Acetyl
Boc	<i>tert</i> -Butyloxycarbonyl
Bn	Benzyl
Bu	Butyl
CAN	Ammonium cerium(IV) nitrate
Cy	Cyclohexyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
(DHQ) ₂ -PHAL	Hydroquinine 1,4-phthalazinediyl diether
DIBAL	Diisobutylaluminium hydride
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
Et	Ethyl
FDA	Food Drug Administration
<i>i</i>	Iso
LHMDS	Lithium bis(trimethylsilyl)amide

KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
Me	Methyl
MIDA	Methyliminodiacetate
Ms	Methanesulfonyl
NaHMDS	Sodium bis(trimethylsilyl)amide
NMO	4-Methylmorpholine N-oxide
NMR	Nuclear magnetic resonance
<i>p</i>	Para
PG	Protecting group
Ph	Phenyl
pin	Pinacol ester
Piv	Pivoyl
PMB	4-Methoxybenzyl
Pr	Propyl
PPTS	Pyridinium <i>p</i> -toluenesulfonate
PTSA	<i>p</i> -Toluenesulfonic acid
r.t.	Room temperature
SEM	Trimethylsilylethoxymethyl
Sia	Disiamyl
<i>t</i>	Tertiary
TBAB	Tetra- <i>n</i> -butylammonium bromide
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBS	<i>tert</i> -Butyldimethylsilyl
TC	Thiophene-2-carboxylate

TES	Triethylsilane
Tf	Triflate
TFP	Tri(2-furyl)phosphine
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin layer chromatography
TIPS	Triisopropylsilyl
TMS	Trimethylsilane
Ts	Tosyl
Xphos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Chapter 1 – Synthesis of Polyene Natural Products

1.1 Introduction

Polyene natural products are chemical entities produced by living organisms that contain at least three conjugating alkenyl units in the molecule. This class of compounds has gained much interest in the pharmaceutical industry due to its biological properties.

This review provides an insight into the potential of polyene natural products in drug discovery before delving into the different approaches used in constructing these polyunsaturated frameworks for a small selection of polyene natural products.

1.2 Drug Discovery in Polyene Natural Products

Natural products, just like any living organisms, have their characteristic traits. Not only do they have interesting names, but also possess unique molecular structures attributing to useful biological properties. The discovery of these molecules provides a vital source for revolutionary medicine, and inspiration for new drug leads as their derivatives can serve as potential candidates for important life-saving drugs. Since 1981, 24% out of 1881 FDA-approved drugs encompass natural products or derivatives thereof.¹ Some of the representative drug leads, in particular, are polyene natural products that possess quite a structurally diverse molecular structure.

A very simple class of hydrocarbon framework can be found in the family of carotenoids as the linear polyunsaturated chain is embedded in these molecules (Figure 1). For instance, retinol (**1**), commonly known as Vitamin A, has a conjugated pentaene framework which constitutes a conjugated four carbon-carbon double bond linear chain. Retinol (**1**) is not only essential for human growth and development, but also prevents Vitamin A deficiency that can result in xerophthalmia or night blindness. Analogous to retinol (**1**), retinal (**2**) is a receptor found in our eyes that allows us to read these words as light is converted into nerve impulses. β -Carotene (**3**), a dimer of retinol (**1**), is a red-

orange pigment prevalent in bright-coloured fruits and vegetables which will be converted to Vitamin A when ingested.

Figure 1. Polyene natural products in linear chain fashion.

These polyunsaturated natural products also come with interesting and complex molecular scaffolds such as macrolides. Often associated with antifungal properties, some of these polyene macrolides have not only shown broad applications in drug discovery, but also opened the window for clinically approved drugs to treat illnesses (Figure 2). The first successful antifungal antibiotic drug Nystatin (**4**) was developed by Brown and Hazen.² Originally named Fungicidin, Nystatin (**4**) was isolated from *Streptomyces noursei* in 1951.² This breakthrough led to the discovery of more polyene macrolides isolated from soil bacteria, especially from *Streptomyces*, for antifungal agents. Another well-known polyene macrolide, for instance, as an antifungal antibiotic drug is amphotericin B (**5**). Isolated from *Streptomyces nodosus* in 1955,³ this polyunsaturated antibiotic amphotericin B (**5**) is used to treat serious and life-threatening fungal infections. Rapamycin (**6**), a natural product isolated from *Streptomyces hygroscopicus* from a soil sample on Easter island,⁴ is a polyene macrolide used in the drug Sirolimus. It is not only an antifungal drug but also acts as an immunosuppressant that is prescribed for organ transplant recipients.

Figure 2. Clinically approved natural product derived drugs.

Careful thought and deliberation are needed when synthesising any polyene natural products. These polyunsaturated motifs are often sensitive to both protic and Lewis acid reagents. Furthermore, as the length of the polyene chain increases, the molecule becomes more unstable as it becomes more heat and light sensitive. The difficulty in constructing them extends further when it comes to controlling the stereochemistry of each double bond. Due to steric strain, *cis* alkenes are generally less stable than their *trans* counterparts. It is hence more challenging to synthesise the former as they are more susceptible to double bond isomerisation. When a specific isomer is required, the synthetic approach that results in a mixture of both *cis* and *trans* isomers will lead to a laborious purification process. Thus, it is imperative to use a reliable olefination approach that is both mild and functional group tolerant. It is also crucial to adopt a procedure that provides high geometrical purity.

A plenitude of synthetic methods to assemble polyene structures has been developed over the years. The general method to prepare alkenes is through the β -elimination process such as dehydration or dehalogenation. However, these protocols often require harsh conditions, and more importantly, they generally do not provide excellent regioselectivity and stereoselectivity. The most efficient and sought-after methods for alkene synthesis are those involving direct olefination of carbonyl compounds (Figure 3). Some of the familiar and established reactions for carbon-carbon double bond formations are the Wittig olefination, Horner-Wadsworth-Emmons reaction, and Julia olefination. Besides these traditional approaches, connecting two carbon-carbon double bond linkages through transition metal cross-coupling reactions is an alternative to assemble the polyunsaturated moiety (Figure 3).

Figure 3. Different strategies in constructing polyene framework.

While there are a few reviews on the synthesis of polyene natural products that have been reported,⁵ the objective of this critique herein aims to provide a short consideration of the general approaches adopted in forming polyenes. Since there are many possibilities in assembling polyunsaturated molecules, it is inevitable to see that there is a cross-function of protocols used in the total synthesis to improve the efficacy of the synthetic plan.

1.3 Direct Olefination

1.3.1 Wittig Olefination

Discovered by Wittig and Geissler in 1953,⁶ the Wittig olefination has become increasingly ubiquitous in organic synthesis.⁷ The mechanism of the Wittig olefination has been a controversial topic as it receives an intensive debate on the general pathway of the reaction. The Wittig reaction involves a carbonyl group and phosphorus ylide to attain the desired alkene with phosphine oxide as the by-product (Scheme 1). While Johnson listed a total of eight possible mechanisms in his review of the Wittig olefination,⁸ the mechanistic pathways suggested were either through the betaine intermediate or the four-membered cyclic oxaphosphetane intermediate (Scheme 1).⁹

Scheme 1. Suggested mechanisms of the Wittig olefination.

Wittig initially proposed that the reaction proceeds through an oxaphosphetane intermediate.⁶ However, a series of experimental observations led Wittig to recognise the involvement of a zwitterionic betaine intermediate during the reaction.¹⁰ Significant evidence was the isolation of β -hydroxyphosphonium salt upon the addition of acid to the Wittig reaction at low temperature. As the betaine was trapped with the formation of β -hydroxyphosphonium salt, it was postulated that the betaine adduct was generated *in situ* during the Wittig reaction. The mechanism was hence enumerated as a

nucleophilic addition of the phosphorus ylide to the carbonyl group to attain the betaine intermediate, before an irreversible elimination of the betaine intermediate to give the alkene and phosphine oxide by-product.^{7, 11} However, the driving force to generate the final products was contentious as betaine intermediate could proceed to form the oxaphosphetane before self-elimination to obtain alkene.

The use of the betaine intermediate to explain the mechanism of Wittig reaction was largely accepted until 1973 when Vedejs reported that oxaphosphetane is the only intermediate observed spectroscopically at low temperature.¹² He was the first to propose the direct irreversible [2 + 2] cycloaddition of the carbonyl and phosphonium ylide to obtain oxaphosphetane before an irreversible reverse cyclo-elimination of the oxaphosphetane to give alkene and phosphine oxide by-product. The lack of evidence of the betaine intermediate was further addressed by Aggarwal and Harvey.¹³ While most of the computational mechanistic studies were carried out in gas-phase models, Aggarwal and Harvey recognised the importance of both incorporating solvent effect in the endeavor to provide a detailed account of the Wittig mechanism and its selectivity in a salt-free Wittig reaction. Their computational work not only dismissed the intervention of betaine intermediates, which further reinforced the general mechanism of attaining oxaphosphetane as the intermediate, but also emphasised heavily that the selectivity of the Wittig product involves both the addition of the ylide to the carbonyls and the subsequent decomposition of the oxaphosphetane into products. Details of the mechanism on the *E/Z* selectivity of the alkenes, however, will not be discussed here. Aggarwal and Harvey modernised our understanding of the Wittig olefination and gave a complete insight of the mechanism by addressing the computational constraints faced.

All in all, what makes the Wittig reaction reliable is the retention of the double bond regioselectivity. Unlike the dehydration of alcohol in which a mixture of alkenes

will be obtained, the location of the double bond is fixed with respect to the carbonyl moiety. This well-established reaction can be seen in the classic example of the production of Vitamin A precursors from the leading supplier BASF. Employing Wittig olefination as the key step (Scheme 2), ylide (**7**) was treated with enal (**8**) to construct the tetraene framework in retinyl acetate (**9**).

Scheme 2. BASF's Wittig olefination to produce Vitamin A precursor.

Citreomontanin (**17**), a polyene pyrone isolated from *Penicillium* sp.,¹⁴ has a similar molecular structure as citreoviridin that is responsible for the acute cardiac beriberi in East Asia.¹⁵ In the synthesis of Citreomontanin (**17**), Pattenden and Patel orchestrated an iterative sequence to install the linear hexene chain using Wittig olefination (Scheme 3).¹⁶ Tiglinaldehyde (**10**) underwent the first Wittig olefination with phosphorus ylide (**11**) to construct the first alkene bond in diene (**12**). Upon an ester reduction followed by oxidation, dialenal (**13**) was treated with the same ylide (**11**) to prepare triene (**14**). In both Wittig olefination reactions, they were stereoselective and gave a pool of pure (*E*)-ester compounds. After transforming ester (**14**) into its corresponding ylide (**15**), Pattenden and co-workers performed the last Wittig reaction with pyrone (**16**) for the finale of citreomontanin (**17**) with all (*E*)-configuration in 2% yield.^{16b}

Scheme 3. Pattenden's total synthesis of citreomontanin.

While Pattenden *et. al.* attained pure (*E*)-citreomontanin (**17**) in the last synthetic step, they also attempted to switch the polarity partner between these intermediates for the final step to improve the yield of the natural product. Instead of having the ylide moiety on trienal (**15**) and aldehyde site on pyrone (**16**), the key functional groups were switched respectively as depicted in Scheme 4.^{16a} The Wittig olefination between ylide (**18**) and trienal (**19**) intermediates improved the yield significantly to 35%. However, a mixture of both (*E*)-citreomontanin (**17**) and the corresponding (*Z*)-isomer was obtained. Presumably, the yield improvement could stem from a less sterically hindered ylide (**18**) used as compared to the ylide (**15**). The reaction, however, did not lead to a geometrically pure Wittig end-product.

Scheme 4. Functional groups swapped in Pattenden's synthesis of citreomontanin.

While the examples above generally described how (*E*)-polyenes were synthesised, the preparation of (*Z*)-alkene was exemplified in the synthesis of leukotriene A methyl ester (**25**) by Baker and Clissold. A precursor for leukotriene D that triggers contraction in the bronchioles smooth lining, leukotriene A methyl ester (**25**) was constructed with a combination of both stabilised and non-stabilised ylide (Scheme 5).¹⁷ Aldehyde (**20**), which was prepared over a series of synthetic transformations starting from an economical reagent D-glucose, was treated with stabilised ylide (**21**) to obtain a mixture of both (*Z*)-dienal (**22**) and (*E*)-dienal (**23**). Interestingly, despite using a stabilised ylide, the major product was (*Z*)-dienal (**22**) which could be due to the sterically hindered epoxide moiety embedded in the chain. The (*Z*)-dienal (**22**) isomer was transformed into its corresponding (*E*)-dienal (**23**) with the treatment of iodine. Pioneered by Corey and co-workers,¹⁸ the installation of the last alkene with a *cis* configuration was followed through the use of an unstabilised ylide (**24**) to give leukotriene A methyl ester (**25**). On a side note, both the epoxide and ester remained intact despite the use of a strong base in the second Wittig olefination.

Scheme 5. Baker's total synthesis of leukotriene A methyl ester.

A drawback of the Wittig olefination is that the appropriate ylide must be prepared before the olefination step. Furthermore, a strong base is required to deprotonate the acidic proton on the phosphonium salt to generate the carbanion required for the Wittig olefination which might hamper the efficiency of the reaction. In the convergent synthesis of the novel neurogenic agent epolactaene (**30**) (Scheme 6), Kogen and his co-workers initially faced low yields of triene (**28**) when aldehyde (**26**) was treated with 2.4 equivalents of triphenylphosphonium salt (**27a**).¹⁹ The yield subsequently improved to 68% when they doubled the amount of phosphonium salt (**27a**) due to the decomposition of the ylide under the reaction conditions. Despite having moderate yields, a lack of stereoselectivity in the given Wittig olefination was observed. With the use of tributylphosphonium salt (**27b**), it afforded a higher percentage of (*E*)-isomer as compared to the former reaction. The completion of the total synthesis of epolactaene (**30**) was achieved with the deprotection of the TBS protecting group from the isolated pure (*E*)-triene (**28b**) isomer, followed by Dess-Martin oxidation with a lactam ring closure in a one-pot reaction.

Scheme 6. Kogen's synthesis of epolactaene.

Militarinone C (**37**) is a tetramic acid isolated in 2003 from an entomogenous fungus *Paecilomyces militaris*.²⁰ It encompasses a similar molecular structure as fumosorinone A which is a potential drug lead for type II diabetes,²¹ but the difference was that fumosorinone A was isolated from a different entomogenous fungus species *Isaria fumosorosea*.²² While both natural products have the same framework of a polyene chain and tetramic acid, militarinone C (**37**) contains a tetraene linear chain connected to the tetramic acid and fumosorinone A has a pentaene linear chain instead. Schobert and co-workers used the same strategy in synthesising these two natural products - militarinone C (**37**) and fumosorinone A.²³ The key difference, however, is that the polyunsaturated moiety in militarinone C (**37**) was installed purely using Wittig olefinations (Scheme 7) whereas HWE reactions were devised in the construction of fumosorinone A. Aldehyde (**31**) underwent the first Wittig olefination with ylide (**32**) to generate ester (**33**). The chain was subsequently extended by reducing the ester moiety (**33**) to the corresponding alcohol before oxidising it to attain aldehyde (**34**). Such an approach is not uncommon and in fact a perfect strategy to elongate the polyene

chain for subsequent Wittig olefinations. Aldehyde (**34**) was then treated with Meldrum's acid-derived ylide (**35**) to furnish the tetraene chain of ester (**36**). Due to the decomposition of ester (**36**) on silica, the crude mixture containing the by-product triphenylphosphine oxide was brought forward to the last two steps in achieve militarinone C (**37**). However, the phosphine oxide by-product contained within could have hindered the efficiency of the second last reaction as Schobert reported a low yield of 30%.

Scheme 7. Schobert's total synthesis of militarinone C.

The Wittig olefination has indeed proved to be one of the most valuable processes in making alkenes. Generally, the regioselective fashion of the reaction is definite in accordance with the position of the carbonyl groups. However, Wittig olefination does not often provide high stereoselectivity as both (*E*) and (*Z*)-isomers which might render difficult separation or necessitate the isomerisation of unwanted isomers. Furthermore, the unavoidable phosphine oxide by-product generated might

impede the purification process and reduce the efficiency of the reaction. However, the development of Wittig reaction for a greener and sustainable chemistry has been recently reported to overcome these limitations.²⁴ The selective reduction of phosphine oxide using silane reagents not only ameliorates the removal of phosphine oxide by-product, but also develops a catalytic Wittig reaction to enhance the scalability and practicality of the alkene synthesis. Despite the few challenges mentioned, the Wittig olefination, being the pioneering methodology in furnishing alkenes is still very useful in the field of total synthesis as it can reliably assemble highly complex structures.

1.3.2 Horner-Wadsworth-Emmons Reaction

The Horner-Wadsworth-Emmons (HWE) reaction is a modification of the Wittig olefination as it employs phosphonate ester reagents to generate alkenes. An advantage over the original Wittig olefination is the use of a milder base as the phosphonate ester deprotonates more easily to generate a stable carbanion through an enolate formation, while the generation of the ylide carbanion obligates the use of a strong base. This leads us to a second upside of the HWE reaction which would be the high (*E*)-selectivity as a result of the further stabilisation of the phosphonate via conjugation. Furthermore, the by-product phosphate salt can be easily removed through an aqueous extraction making the HWE reaction an impeccable reaction.

Nicolaou and co-workers had exemplified the use of HWE reactions thrice to install the heptaene chain in the total synthesis of the antifungal antibiotic amphotericin B (**5**) (Scheme 8).²⁵ The retrosynthesis began with the cleavage of the ester and alkene bond to give polyene (**38**) and polyol (**39**) fragments. The focus herein will only be on the construction of polyene (**39**) fragment to understand how Nicolaou elegantly built the polyunsaturated moiety using HWE reactions with only one phosphonate reagent (Scheme 9).

Scheme 8. Retrosynthesis of amphotericin B by Nicolaou.

The first HWE reaction was observed between aldehyde (**40**) and functionalised phosphonate (**41**) to attain triene (**42**). The reduction of the ester moiety to its corresponding alcohol preceded the oxidation of the hydroxyl group to prepare aldehyde precursor (**43**) for the second HWE reaction. The polyene chain was then further extended by resubmitting the aforementioned phosphonate (**41**) again with aldehyde (**43**) to give polyene (**44**). The aldehyde moiety was regenerated by repeating the reduction and oxidation procedures earlier. Even though the HWE reactions gave a minute amount of (*Z*)-isomers which can be purified chromatographically, the basic skeleton of amphotericin B (**5**) was crafted out perfectly with the repeated use of a single phosphonate reagent (**41**) in this total synthesis.

Scheme 9. Assembling of polyene fragment in Nicolaou's synthesis of amphotericin

B.

There is a plenitude of examples that employ HWE protocols in the total synthesis of polyene natural products as organic chemists reap the benefits of the outcome from the HWE reactions. In some instances, an amalgamation of the Wittig olefination and HWE procedures were utilised for installing the polyunsaturated chain. Waldmann and co-workers exploited the versatility of both ylides and phosphonate ester reagents in their convergent synthesis of cyclamenol A (**45**).²⁶ While intermediates (**46**) and (**47**) aided the macrolactamisation through pinacol coupling and amide formation (Scheme 10) which will not be discussed here in details, the highlight of this synthesis would be on the construction of the unsaturated bonds in these intermediates (Scheme 11).

Scheme 10. Retrosynthesis of cyclamenol A by Waldmann.

Diene (**50**) was first furnished through HWE reaction between aldehyde (**48**) and phosphonate ester (**49**) before reducing the ester moiety to attain alcohol (**51**). The second intermediate was then prepared through Wittig olefination between aldehyde (**52**) and ylide (**53**) using a strong base *n*-BuLi to give triene (**54**). A series of chemical transformations were then performed with the removal of the acetonide protecting group, followed by the protection of the secondary chiral alcohol to prevent decomposition of the diol due to the conjugated nature of the molecule. A one-pot reaction sequence then begins with a Swern oxidation to prepare the corresponding aldehyde *in situ* from its terminal alcohol, for the subsequent Wittig olefination with ylide (**56**). With triene (**57**) in hand, a series of chemical transformations were performed to prepare key intermediate (**47**) for the synthesis of cyclamenol A (**45**).

Scheme 11. Partial synthesis of cyclamenol A by Waldmann.

While HWE reactions are well-known for its (*E*)-selectivity and the examples above showed that the phosphonate reagents used predominately resulted in (*E*)-alkenes, it is also possible to obtain (*Z*)-olefins via a modified HWE reaction. Still and Gennari specially designed an electrophilic bis(trifluoroethyl)phosphonate ester to achieve high (*Z*)-stereoselectivity.²⁷ With the use of an electrophilic phosphonate ester, the rate-determining step of breaking down the oxaphosphetane intermediate is facile which results in excellent (*Z*)-selectivity. Menche and co-workers have exemplified the use of an electrophilic phosphonate ester in the synthesis of archazolid A (**58**) for the triene moiety in the macrolactone.²⁸ The approach in constructing archazolid A (**58**) relies on three main key reactions, namely aldol condensation, Heck reaction, and HWE reaction

with building blocks (**59**), (**60**), and (**61**) (Scheme 12). The main focus of discussion here will be the installation of the triene chain C9 to C14 which is predicated on the building block (**60**).

Scheme 12. Retrosynthesis of archazolid A by Menche.

Using Still-Gennari HWE-modified reaction, aldehyde (**62**) was treated with phosphonate (**63**) obtaining (*Z*)-enone (**64**) as the only isomer in excellent yield of 88% (Scheme 13). A second round of Stille-Gennari's modification of the HWE reaction was performed on aldehyde (**65**) to obtain the elongated enone (**66**) with a high (*Z*)-selectivity in 87% yield. Upon attaining enone (**66**), building block (**60**) was furnished through a reduction of the ester moiety and a subsequent oxidation of the resulting alcohol to its corresponding aldehyde.

providing (*E*)-alkene as the predominant product. One drawback of the Julia olefination is its low tolerance for reducible functional groups. A further refinement of this method was performed by his brother Sylvestre Julia in a one-pot reaction using benzothiazolyl sulfone (**68**) instead.³⁰ The mechanism of this modified Julia olefination differs from the classical process in the reductive elimination step. Upon nucleophilic attack of the benzothiazolyl sulfone carbanion to the aldehyde, the alkoxide would undergo a Smiles rearrangement-like mechanism *in situ* and spontaneously eliminate to give the alkene product together with sulphur dioxide and hydroxybenzothiazole as by-products. There is, however, one limitation to the modified Julia olefination which is the occurrence of aldehyde self-condensation even at low temperatures. Kocienski then further improved the modified process by utilising phenyl tetrazole sulfone (**69**).³¹ Also referred to as the Julia-Kocienski olefination, this reaction is not only highly *trans*-selective, but also reduces the propensity of aldehyde self-condensation as compared to Sylvestre's method.

Figure 4. Different types of sulfones for the connective double bond synthesis.

As mentioned previously, (-)-rapamycin (**6**) is an immunosuppressant that is essential for organ transplant recipients to prevent their immune system from attacking the donor's organ. This macrolide has received much attention owing to its biological properties and novel mechanism of action. Currently, Nicolaou,³² Schreiber,³³ Danishefsky,³⁴ Ley,³⁵ and Smith³⁶ have reported the total synthesis of (-)-rapamycin (**6**). Danishefsky and co-workers utilised the classic Julia olefination to form the trisubstituted (*E*)-olefin (Scheme 14).^{34b} Aldehyde (**70**) was treated with phenylsulfone

(**71**) before acylation of the resulting β -alkoxysulfone. Interestingly, the subsequent reductive elimination was not carried out in a one-pot reaction. In a stepwise fashion, the acetate group was eliminated to generate alkene (**72**). Upon reduction of the pivaloyl protecting group, the sulfone was subsequently reduced using sodium amalgam. Due to the inherent conjugate nature of the molecule, the alpha proton of the sulfone is more acidic than usual. Through elimination, alkene (**72**) would be tractable for the reduction process. In another strategy, Kocienski and co-workers performed a one-pot modified Julia olefination reaction instead to construct the triene fragment of (-)-rapamycin (**6**) using a functionalised benzothiazolyl sulfone (**74**) (Scheme 15).³⁷

Scheme 14. Partial synthesis of (-)-rapamycin by Danishefsky.

Scheme 15. Partial synthesis of (-)-rapamycin by Kocienski.

The Julia olefination or its modified version, however, is not always stereoselective which is a phenomenon similar to the Wittig reaction. Chaunopyran A (**78**), co-cultivated from two fungal strains of *Siphonaria sp.* mollusc, constitutes a tetrahydropyran ring attached to a linear triene chain.³⁸ Due to its innate instability of this molecule, Takahashi and co-workers utilised Julia-Kocienski olefination as the key step to construct the delicate triene chain (Scheme 16).³⁸ Although the Julia-Kocienski olefination is known for attaining high *trans* selectivity, various reaction conditions were examined between sulfone (**75**) and aldehyde (**76**) to attain the highest (*E*) : (*Z*) ratio. As the triene product attained is highly unstable, the mixture of triene (**77**) was desilylated before further purification using a reverse-phase HPLC to attain Chaunopyran A (**78**).

Scheme 16. Total synthesis of Chaunopyran A by Takahashi.

1.4 Adjoining C=C bond linkages

The palladium-catalysed cross-coupling reaction is currently considered one of the most powerful and general strategies in forming carbon-carbon bonds. Due to the method's highly efficacious nature in assembling building blocks, the extensive application of cross-coupling reactions in total synthesis became established. Unlike

direct olefination methods which were discussed earlier, cross-coupling reactions such as Suzuki, Stille, Hiyama, and Sonogashira are stereospecific. With the configurations of the alkenyl halide and organometallic building blocks fixed, they can be assembled reliably to furnish polyenes of high geometrical purity. The stereoselectivity, therefore, depends on the ability to access the coupling partners in stereochemically pure forms. Certainly, this rules out the possibility of a Heck reaction as beta-hydride elimination can lead to stereochemical issues. Furthermore, the cross-coupling reactions can be carried out in mostly mild conditions and have high functional group tolerance. The versatility of a cross-coupling reaction hence allows it to be the centerpiece to amalgamate two vinyl fragments into a polyene chain.

1.4.1 Stille coupling

The Stille coupling is extensively used in the synthesis of natural products owing to its mild and versatile reaction nature. Even though the drawback of using Stille coupling is the toxicity of the tin compounds used, the absolute control of stereoselectivity and mild conditions used places superiority over traditional olefination procedures. (+)-Mycotrienol (**82**), a natural product isolated from a fermented broth of *Streptomyces rishiriensis* T-23, exhibited potent antifungal activity.³⁹ Panek and Masse performed a final “stitch” in the macrocyclisation step through an intramolecular Stille coupling of two vinyl iodide terminals in amide (**79**) with (*E*)-bisstannylethene (**80**) to attain triene (**81**).⁴⁰ Following which, sequential reactions of oxidation and deprotection of the silyl groups gave them the desired (+)-mycotrienol (**82**) (Scheme 17). In fact, this approach was pioneered by Nicolaou’s group in their end game of total synthesis of (-)-rapamycin (**6**) (Scheme 18).³² Despite the low yield attained from the intramolecular double Stille coupling, it was a remarkable strategy as no protecting groups are required for alkene (**83**).

Scheme 17. Total synthesis of (+)-mycotrienol by Panek.

Scheme 18. Total synthesis of (-)-rapamycin by Nicolaou.

A one-pot Stille coupling can be found in the synthesis of Chivosazole F (**90**) by Paterson and co-workers (Scheme 19).⁴¹ The three fragments (**84**), (**85**), and (**86**) were initially installed through a stepwise process to construct triene (**87**). The synthetic steps were shortened by adding the respective fragments sequentially in a one-pot reaction to assemble the backbone structure of Chivosazole F (**90**) to attain triene (**87**) in an excellent yield of 80%. As Still-Gennari modified HWE reaction, as mentioned earlier, gives access to (*Z*)-olefins, the phosphonate group in triene (**87**) was treated with (*E*)-3-

(tributylstannyl)acrylaldehyde to obtain the corresponding (*Z*)-alkene as the major product. Upon oxidation of the terminal alcohol, the aldehyde moiety in intermediate (**88**) was subjected to a Stork-Zhao's olefination to attain (*Z*)-vinyl iodide (**89**) for subsequent intramolecular Stille coupling. Paterson and co-workers then performed a global deprotection of the silyl groups to attain Chivosazole F (**90**).

Scheme 19. Total synthesis of chivosazole F by Paterson.

1.4.2 Suzuki coupling

Despite the broad application of Stille coupling in organic synthesis, the main drawback of employing Stille coupling is the organotin halide by-product. It is not only toxic and harmful to the environment, but its polarity sometimes makes it difficult to remove from reaction mixtures. A similar chemistry that provides excellent stereoselectivity between two sp^2 centers but can overcome the above-mentioned problems is the Suzuki coupling. It involves the use of organohalide and borane reagents. An additional advantage of the Suzuki coupling over the Stille coupling is that the borane reagents used are both air and water stable. This can be seen in Suzuki's total synthesis of ($\pm$)-trisporal B (**91**) which delivered both high stereo- and regioselectivity (Scheme 20).⁴²

Scheme 20. Total synthesis of ($\pm$)-trisporal B by Suzuki.

In the earlier years of Suzuki coupling, Lewis bases used to promote transmetallation step were typically strong bases such as sodium ethoxide, which can be seen in the example of ($\pm$)-trisporal B (**91**). In order to improve the coupling reaction for greater functional group tolerance, a variety of mild bases have been adopted over

the years. In the recent and first total synthesis of (-)-exiguolide (**94**), Fuwa and co-workers installed the triene linear chain through a Suzuki coupling between vinyl iodide (**92**) and boronic ester (**93**) using silver oxide as the base (Scheme 21).⁴³

Scheme 21. Total synthesis of (-)-exiguolide by Fuma.

Burke and co-workers had successfully orchestrated a series of iterative cross-coupling reactions in the total synthesis of synechoxanthin (**102**) (Scheme 22).⁴⁴ Olefin (**95**) and (**96**) underwent a Stille coupling to prepare diene (**97**) with two different types of borane functional groups at each terminal end of the molecule – BMIDA and Bpin. It is an interesting strategy to install boranes of different electronic properties. As BMIDA is an electron-deficient boronic ester, it is less susceptible to undergo cross-coupling as compared to having a Bpin functionality. Since BMIDA is a poor cross-coupling partner, aryl iodide (**98**) would essentially be installed at the Bpin terminal of diene (**97**). BMIDA in diene (**99**) was then iodo-deborylated to obtain vinyl iodide (**100**) with complete retention of stereochemistry. The second Suzuki coupling was performed between diene (**97**) and vinyl iodide (**100**) to further elongate the polyene chain. Since synechoxanthin (**102**) is a dimer with an ethene linker, the end game of synechoxanthin (**102**) was achieved through (*E*)-1-bromo-2-iodoethene and two equivalents of boronic ester (**101**) in a one-pot reaction with three transformations taking place – a double

Suzuki coupling and a concomitant hydrolysis of the ester moieties. Throughout the entire synthesis of synechoxanthin (**102**), Burke took advantage of the electronics of the main metal group to influence the regioselectivity of the sp^2 - sp^2 coupling reactions.

Scheme 22. Total synthesis of synechoxanthin by Burke.

1.4.3 Hiyama coupling

Using organosilanes as the organometallic reagent, Hiyama cross-coupling reaction is another useful method to form polyenes. Similar to Stille and Suzuki coupling, Hiyama coupling is both regio- and stereospecific. However, in comparison to the former cross-coupling reactions, Hiyama coupling emerges as a more attractive option as organosilicon reagents are commercially cheaper and have low toxicity. Additionally, the Hiyama coupling has high chemical stability and requires mild reaction conditions.

RK-397 (**103**) is a polyene macrolide isolated from a soil bacteria *Streptomyces sp.* that exhibited excellent antifungal properties.⁴⁵ McDonald and Buroya accomplished the first total synthesis of RK-397 (**103**) in 2004.⁴⁶ Their main strategy to install the pentaene chain in the macrolide, which will not be discussed here in details, is through a combination of Stille coupling and HWE reaction. Subsequently, Denmark reported a convergent synthesis to assemble the polyol chain and pentaenoate backbone (**104**) in RK-397 (**103**) (Scheme 23).⁴⁷ While the endgame of RK-397 incorporates an HWE reaction and Yamaguchi esterification for the macrolactonisation, the main focus here will be looking into how Denmark achieved the pentaenoate fragment (**104**) through two Hiyama coupling reactions (Scheme 24).

Scheme 23. Retrosynthesis of RK-397 by Denmark.

Diene (**105**), prepared through a series of hydrosilylation reactions using Denmark's procedure, constitutes two differentiable silyl subunits at each terminal end of the molecule.⁴⁸ Using sodium hydride as the base to activate only the silanol group on diene (**105**), triene (**107**) was constructed with vinyl iodide (**106**) leaving the benzylsilane intact (Scheme 24). Despite attaining a good yield, this reaction gave poor diastereoselectivity and a mixture of alkene isomers was obtained. The polyene chain

was further elongated through a second Hiyama coupling using fluorides to activate benzylsilane on triene (**107**) to couple with ethyl (*E*)-3-iodopropenoate. Tetraene (**108**) had its THP ring deprotected and underwent isomerisation to attain a pure (*E*)-olefin before installing the phosphonate group to generate tetraene (**104**). Utilising the mechanistic duality of diene (**105**), Denmark successfully performed a sequential Hiyama cross-coupling reaction to assemble the polyene chain in RK-397 (**103**).

Scheme 24. Partial synthesis of RK-7 by Denmark.

1.4.4 Sonogashira coupling

In the event a (*Z*)-olefin is embedded in the natural product, the alkene can be installed using the above cross-coupling methods with a (*Z*)-configured organometallic species. However, preparing the appropriate (*Z*)-organometallic coupling partner sometimes may be cumbersome. An alternative method is to introduce Sonogashira coupling into the synthetic plan. Upon installation of an internal alkyne through Sonogashira coupling, a (*Z*)-olefin can be prepared using Lindlar catalyst through a *syn*-hydrogenation across the alkyne bond. Nicolaou and co-workers took advantage of the chemistry of Sonogashira coupling to design a stereocontrolled total synthesis of Lipoxin A (**114**) (Scheme 25).⁴⁹ A metabolite of arachidonic acid in human leukocytes,⁵⁰ Lipoxin A is a linear carboxylic chain that contains an (*E*),(*E*),(*Z*),(*E*) tetraene geometry

configuration. The diene moiety in enyne (**109**) was installed by either Wittig olefination or HWE reaction, which we have discussed earlier, using ylide or phosphonate reagent respectively from the commercially available pentenynol. The unsaturated chain was further lengthened by exploiting Sonogashira coupling with alkenyl bromide (**110**) to give a stereodefined enyne (**111**) preceding the deprotection of the silyl groups. The *cis* configuration was built by stereoselectively reducing the alkyne using Lindlar catalyst to furnish alkene (**113**) without affecting other unsaturated bonds. Finally, hydrolysis of the ester moiety gave Lipoxin A (**114**) in good yield.

Scheme 25. Total synthesis of Lipoxin A by Nicolaou.

Another example of incorporating Sonogashira coupling in the preparation of (*Z*)-alkenes is seen in the total synthesis of (-)-disorazole **C**₁ (**121**) by Wipf's group (Scheme 26).⁵¹ The unique molecular architecture of this macrocycle is the innate symmetry of this natural product – a dimer. The key steps in achieving (-)-disorazole **C**₁

(**121**) are Sonogashira coupling, esterification, and Yamaguchi lactonisation (Scheme 26). Alkyne (**115**) and vinyl iodide (**116**) were submitted through a Sonogashira coupling, furnishing internal alkyne (**117**) in nearly quantitative yield. Interestingly, the alcohol in alkyne (**115**) did not require any protecting group during the process and was subsequently esterified with acid (**118**) that was prepared from vinyl iodide (**116**) through hydrolysis. The terminal vinyl iodide in alkene (**119**) was treated with alkyne (**115**) through a second Sonogashira coupling in excellent yield as well. The resulting internal alkyne (**120**) had essentially acquired the desired molecular framework. (-)-Disorazole C₁ (**121**) was then crafted out through a series of lactonisation, removal of PMB protecting group, and most importantly, a *cis*-reduction of the alkynes to obtain the appropriate (*Z*)-alkenes.

Scheme 26. Total synthesis of (-)-disorazole C₁ by Wipf.

1.5 Summary

This review has highlighted the main methods in constructing the polyunsaturated framework in natural products. From a general point of view, direct

olefination has absolute control over regioselectivity but suffered some drawbacks in installing polyenes. The Wittig olefination, for example, would require a strong base to activate the phosphonium ylides used. This limitation was overcome by the use of a Horner-Wadsworth-Emmons reaction with the use of mild bases on phosphonate esters. In addition, using phosphonate esters would predominately generate (*E*)-alkenes. Alternatively, employing Julia and modified Julia olefination would also give (*E*)-alkenes by coupling carbonyls with aryl sulfones. All these reactions, however, often generate isomers and could not provide pure alkene geometry which remains as an elusive goal in assembling polyene natural products.

The use of cross-coupling reactions has surpassed these traditional olefination approaches as it gives excellent stereoselectivity in mild conditions. The downside of utilising cross-coupling reaction is the need to use of a metal catalyst which is a significant problem in the pharmaceutical industry as a low limit of heavy metal impurities are allowed in manufacturing drugs. While different methodologies of building polyenes have been developed and progressed over the years, the main goal is to prepare a high regioselective and stereoselective alkenes.

Chapter 2 – Towards the total synthesis of trichoether A

2.1 Background of the trichoether family

The family of trichoether natural products was first isolated in 2014 from the deuteromycetous fungus *Trichobotrys effusa* in Taiwan.⁵² Chen *et. al.* discovered that the ethyl acetate extracts of the fermented broth of *Trichobotrys effusa* exhibited excellent inhibitory effects against the A549 lung cancer cell in the initial stage of pharmacological evaluation. Four known compounds, namely coriloxin,⁵³ zythiostromic acid A,⁵⁴ radicicol,⁵⁵ and 3,5-dihydroxytoluene, were isolated and the spectroscopic data of these compounds corresponded to their literature values. Four other unprecedented secondary metabolites (Figure 1), namely trichoethers A – D, were isolated in the same broth extract and found to have intriguing bioactivities with GI₅₀ values of 25.61, 19.32, 16.19, 24.31 µg/mL respectively on the A549 lung cancer cell.

The molecular architecture of trichoether A (**1**) features a triene aliphatic chain bearing two hydroxyl groups and an ether connecting to a phenol with three substituent groups *ortho* to each other. Revealing an optical activity of $[\alpha]^{27}_D +27.5$, this unique chiral natural product was found to contain two stereogenic centres on the aliphatic backbone which exhibit a *syn* relationship in a relative configuration. Interestingly, trichoethers B – D hold a similar chemical backbone as trichoether A. With the triene moiety and the trisubstituted phenol remaining intact, the stark difference in each trichoether natural product would reside at the tail end of the aliphatic chain. Encompassing only one stereogenic centre, trichoether B possesses both an aldehyde and a ketone on the skeleton of the molecule. However, with the optical rotation found to be close to 0, the stereochemistry at the ether position was elucidated to be in its racemate form. In addition to their similar aliphatic backbone, both trichoethers C and

D each constitute a THF ring. The elucidated structure of the THF ring in trichoether D was found to bear a partial resemblance to the structure of lachnellin B⁵⁶.

Figure 1. Aliphatic phenol ethers from *Trichobotrys effusa*.

2.2 Significance of the synthesis of Trichoether A

In retrospect, trichoether A (**1**) holds the root form of the molecular structure in the trichoether family. The rest of the three natural products are derivatives of trichoether A (**1**) which can be attained by modifying the synthetic pathway of trichoether A (**1**) accordingly. For instance, performing oxidation on the hydroxyl functional groups of the aliphatic chain in trichoether A (**1**) could simply attain trichoether B (Figure 1). The inherent versatility in its transformation to other natural products in the family indeed renders trichoether A (**1**) an attractive synthetic target. Furthermore, each molecular structure in the trichoether family was elucidated in its relative configuration. The motivation behind the total synthesis of trichoether A not only stems from affirming the molecular structure proposed by Chen *et. al.*, but also determining the absolute configuration with the chiroptical data provided. Notably, there are no successful reported syntheses of any trichoether natural products hitherto, serving as the primary inspiration behind this project.

2.3 Retrosynthesis analysis

The retrosynthesis of trichoether A (**1**) entails the disconnection of the ether bond leading to two synthetic targets – the aromatic (**2**) and aliphatic chain (**3**) fragment (Scheme 1). This poses a key synthetic challenge as the construction of these molecules involves both sterically hindered alcohol and highly substituted benzyl intermediate. Moreover, the difficulty of the synthesis extends further as the aliphatic chain (**3**) requires selective protection of two hydroxyl groups before etherification with the aromatic fragment (**2**).

Scheme 1. Retrosynthesis of trichoether A.

The installation of the diols at C8 and C9 position is envisioned to be prepared from an asymmetric dihydroxylation from tetraene (**4**). Since dihydroxylating a single alkene in a tetraene system would be synthetically challenging, the olefins from C2 to C7 will have to be protected to prevent any complications during the dihydroxylation process. In the discussion of the first Chapter about the different methods to construct polyenes, cross-coupling reaction proves to be more advantageous than direct olefination as it delivers excellent stereoselectivity and high geometrical purity of olefins. The application of a cross-coupling reaction can be incorporated to prepare

tetraene (4). Dienyne (5) will have to undergo a regioselective hydrometallation across the internal alkyne to access a cross-coupling reaction to install C8 – C9 alkene bond. In turn, dienyne (5) can be synthesised from dienyne (6) through an alkynylation, and dienyne (6) could be obtained by a transformation from sorbaldehyde (7) which is commercially available.

2.4 Results and Discussion

This section will be broken down into three different segments. It begins with the synthetic pathway towards the aliphatic chain fragment (3) before the discussion on how aromatic fragment (2) was constructed. Lastly, the different methodologies attempted in piecing both key fragments (2) and (3) together will then be reviewed for the completion of the desired natural product trichoether A (1).

2.4.1 Synthesis of the aliphatic chain fragment

Synthesis of precursor for diene complexation

Sorbaldehyde (7) was first treated with Corey-Fuchs reagent, ylide (8), to achieve the corresponding dienyne (10) from the alkyne generated. The Corey-Fuchs reaction, a two-step methodology, transforms an aldehyde to its terminal alkyne through a one-carbon homologation.⁵⁷ This protocol involves the preparation of dibromoolefin (9) precursor before treating it with lithium base to prepare the desired alkyne. As suggested by Corey and Fuchs, there are two approaches in synthesising dibromoolefin (9) – either a mixture of triphenylphosphine and tetrabromomethane in a ratio of 4 : 2; or a mixture of activated zinc, 2 equivalents each of triphenylphosphine and tetrabromomethane added to an equivalent of aldehyde.^{57a} The latter procedure was preferred as a lesser amount of triphenylphosphine was used, leading to a less laborious purification procedure. Besides, the latter procedure was reported to give higher yields than the former protocol of not using zinc.^{57a} Despite its poor atom economy, the Corey-

Fuchs reaction has been extensively used in the synthesis of alkyne as it often delivers high yield.⁵⁸

It is noteworthy that ylide (**8**), generated *in situ* with tetrabromomethane and triphenylphosphine, is water sensitive. Since the commercially available tetrabromomethane contains water, it is crucial to dry it under high vacuum. In addition, the solution of tetrabromomethane in anhydrous dichloromethane prepared was stored over activated molecular sieves to further remove any adventitious moisture before treating it with the rest of the reagents. The generated dibromoolefin precursor (**9**) was then treated with butyllithium through a Fritsch-Buttenberg-Weichell (FBW) rearrangement to generate the respective lithiated acetylide (Scheme 2). This creates an opportune moment to do a one-pot reaction by sequentially adding the electrophile – paraformaldehyde – with the lithiated acetylide generated. Propargyl alcohol (**10**) was hence afforded an excellent yield of 82% over two steps (Scheme 3).

Scheme 2. FBW rearrangement in Corey-Fuchs reaction.

Scheme 3.

As the enyne chain in propargyl alcohol (**10**) *en route* in constructing the skeleton of trichoether A (**1**), the internal alkyne moiety will have to undergo a hydrometallation and the regioselectivity of installing the metal hydride across an unsymmetrical internal alkyne will be an issue. Ferreira and co-workers demonstrated the use of substituent effects to achieve a highly regioselective platinum-catalysed hydrosilylation of internal alkynes.⁵⁹ Amidst the variety of ynone substrates, Ferreira reported that hydrosilylation of these internal alkynes not only gave good yields, but also more importantly produced excellent regioselectivity for α -silylenones with respect to the ketone moiety (Scheme 4).^{59a} This is consistent with the Chalk-Harrod mechanism for platinum-catalysed hydrosilylation as the hydride is delivered to the more electron-deficient carbon on the internal alkyne as it coordinated with the platinum complex (Scheme 5).⁶⁰

Scheme 4. Ferreira's platinum-catalysed hydrosilylation of ynones.

Scheme 5. Chalk-Harrod mechanism of hydrosilylation.

However, the selectivity of α -silylenones diminished dramatically with oxygenation at the propargylic position due to the inductive effects of these functional groups. A similar observation occurred when Ferreira and co-workers attempted to treat a series of methyl ynoates to the same hydrosilylation conditions.^{59b} Methyl ynoates containing aliphatic groups produced high selectivity for α -silylenoates. On the other hand, compounds bearing an electron-withdrawing oxygen substituent – such as acetate or THP group – at the propargylic position drastically affected the regioselectivity (Scheme 6). Even though the regioselectivity of the α -silylenoates was governed by the electron-withdrawing methyl ester moiety, Ferreira explored the possibility of having oxygen substituents at the propargylic position could induce a polarisation comparable to the electronic influence of the ester group.

Scheme 6. Poor selectivity observed in Ferreira's platinum-catalysed hydrosilylations.

We can conceptualise Ferreira's idea in our work as their substrate scope did not include the effects of platinum-catalysed hydrosilylation on dienyne substrates. This will allow us to understand if conjugate effects can influence the regioselectivity of asymmetric alkynes through hydrosilylation. Besides, as we transformed the alcohol group in dienyne (**10**) into an acetate correspondingly to give dienyne (**11**) (Scheme 3), we can exploit the electronic influence of having an oxygen substituent at the propargylic position to aid us in attaining high α -2-silylallylic acetate (**12**) (Figure 2).

Figure 2. Hypothesis of hydrosilylation through electronic influence.

Diene complexation with Fe₂(CO)₉

As mentioned in the retrosynthesis of trichoether A (**1**) (Scheme 1), there will be a regioselectivity issue during the asymmetric dihydroxylation step in tetraene (**4**) intermediate. It is hence imperative to protect the diene system in propargyl acetate (**11**) to prevent any complications during that stage. Generally, the standard tool in protecting a conjugated diene would be to coordinate it to a tricarbonyliron fragment. As the conjugated diene acts as a π -donating ligand to the tricarbonyliron fragment, the resulting tricarbonyl(η^4 -diene)iron complex would be less prone to reactions such as hydrogenation or dihydroxylation. This methodology has played a pivotal role in protecting unsaturated systems which is found to be useful in organic reactions.⁶¹

The preparation of tricarbonyliron-diene complex from its corresponding diene has been well-precedented.⁶² The complexation can be achieved by either thermal or photolytic conditions depending on the source of binary iron carbonyl reagent used (Figure 3). Pentacarbonyliron, being the cheapest and most stable iron carbonyl reagent,

was used by Reihlen and co-workers to synthesise the first tricarbonyliron-diene complex.⁶³ However, pentacarbonyliron is not very reactive and would require harsh conditions such as the use of high temperature or irradiation by UV light for the dissociative process to occur. Nonacarbonyldiiron, on the other hand, is a more reactive reagent, and the tricarbonyliron-diene complex can be simply obtained through sonication. Unlike pentacarbonyliron which is a highly toxic and volatile liquid, nonacarbonyldiiron comes in a solid form that makes it easier and safer to handle. The most reactive binary iron carbonyl compound would be the dodecacarbonyltriiron. Despite the rapid complexation with even milder conditions employed such as heating at reflux, dodecacarbonyltriiron sublimes easily and decomposes to pyrophoric iron upon exposure to air. Therefore, the best option was to use nonacarbonyldiiron as it is not only easy to handle, but also reactive enough to give us the corresponding tricarbonyliron-diene complex.

Figure 3. Different binary iron carbonyl reagents for diene ligand complexation.

Since the complexation of dienes using iron complexes in an enyne system has not been reported, it is worthwhile to attempt this synthesis for it will be an efficient method to selectively protect the diene moiety in the presence of an alkyne functionality. After several attempts, the ultrasound-assisted reaction of dienyne (**11**) with nonacarbonyldiiron, however, gave no reaction, and the starting material was recovered. Likewise, sonication with dienyne (**10**) and nonacarbonyldiiron afforded the same result.

The presence of competitive binding between the alkyne and diene in the system could have nullified the complexation of π -donating ligand with the iron carbonyl.⁶⁴

Donaldson⁶⁵ and Ley⁶⁶ have well exemplified the use of ultrasound in the complexation of 2,4-dienals with nonacarbonyldiiron. Adopting the same strategy, sorbaldehyde (**7**) was then sonicated with nonacarbonyldiiron using an ultrasound cleaning bath to prepare the corresponding tricarbonyliron complex (**13**). It was observed that the quality of the nonacarbonyldiiron reagent used would greatly affect the yield of the tricarbonyliron complex (**13**), which can range from as low as 30% to as high as 89% (Scheme 7). The grade of the nonacarbonyldiiron depends on the amount of pyrophoric iron contained in the bottle. There was an instance in which a newly arrived bottle of nonacarbonyldiiron contained a presumably large content of pyrophoric iron that led to an ignition upon opening the reagent bottle. The strategy in synthesising the aliphatic chain of trichoether A (**1**) remains despite the difficulties faced at the initial stage.

Scheme 7.

Based on the ¹H-NMR spectrum of tricarbonyliron complex (**13**), only two out of four protons were found resonating in the chemical shift range of 6.0 – 5.0 ppm that is typically observed for olefinic protons. There was an unusually large upfield shift for the other two diene protons resonating at 2.0 – 1.0 ppm. This is due to the bonding interaction between the diene and the iron, and the predominant involvement of the magnetic anisotropy effect caused by the carbonyl groups.⁶⁷ A ring current is induced around the aromatic diene, and the anisotropic field generated opposes the applied

magnetic field. This results in H^a and H^b to be more shielded and causing an upfield shift in resonance (Figure 4).

Figure 4. Magnetic anisotropy effect on tricarbonyliron complex.

Alkynylation in iron complex

Since Corey-Fuchs reaction proceeded smoothly (Scheme 3) and a good yield was attained for dienyne (**10**), the same methodology can be applied to triironcarbonyliron complex (**13**) in preparing its corresponding alkyne. Unfortunately, after treating triironcarbonyliron complex (**13**) with ylide (**8**) that was generated *in situ* from triphenylphosphine and tetrabromomethane, precipitation of iron was observed during the reaction. Triironcarbonyliron complex (**13**) could have possibly decomposed in the reaction even before the formation of the desired dibromoolefin. It was then proven evidently from the ^1H -NMR analysis that small peaks of sorbaldehyde (**7**) were observed from the crude mixture upon working up of the reaction.

An alternative in transforming an aldehyde to its terminal alkyne correspondingly in a one-pot reaction is to use α -diazophosphonate such as the Seyferth-Gilbert reagent (**14**) or the Ohira-Bestmann reagent (**15**) (Figure 5).^{58, 68} Despite the similar functionality of these reagents, the protocol of using the Seyferth-Gilbert reagent (**14**) requires harsh conditions such as a strong base.⁶⁹ Whereas the Ohira-Bestmann reagent (**15**), a modified version of the Seyferth-Gilbert reagent (**14**), requires only mild reaction conditions and is well tolerated by most functional groups. This is thus

advantageous in any organic synthesis especially for tricarbonyliron complex (**13**) since decomposition was observed with the harsh conditions used in the Corey-Fuchs reaction.

Figure 5. α -Diazophosphonate reagents.

The preparation of the Ohira-Bestmann derivative reagent involves two steps (Scheme 8) Diethylphosphonate (**17**) was first synthesised by the Arbuzov reaction using chloroacetone (**16**) and triethylphosphite. The diazo group was then introduced by treating diethylphosphonate (**17**) with triethylamine and tosyl azide to generate Ohira-Bestmann derivative (**18**).⁷⁰

Scheme 8.

The methoxide ion, produced from potassium carbonate in methanol, reacts with Ohira-Bestmann derivative (**18**) to generate a carbanion phosphonate *in situ* (Scheme 10). This nucleophile would then attack the aldehyde forming an oxaphosphetane-type intermediate that breaks down to form a diazoalkene. This diazoalkene loses nitrogen and the resultant carbene once again undergoes FBW rearrangement – similar to the mechanism in Corey-Fuchs reaction (Scheme 2) – to give rise to the corresponding alkyne. Alkyne (**19**) was successfully prepared from tricarbonyliron complex (**13**) and Ohira-Bestmann derivative (**18**) with a good yield of 70% (Scheme 9).

Alkyne (**19**) was then treated with butyllithium and paraformaldehyde in THF at -78°C in accordance with the original plan to obtain the corresponding propargyl alcohol. However, the highest yield obtained for this reaction condition was only 12% after several attempts (Table 1, Entry 1). The low yield might stem from the incompleteness of deprotonation of the alkyne (**19**). Additionally, cracking of the oligomeric chain in paraformaldehyde might also pose a challenge. Hence, a deuteration test was first performed to investigate the optimum reaction conditions on the deprotonation of alkyne (**19**) by trying out different bases and temperature (Table 1). This optimisation allows us to first understand the effectiveness of the various bases in the deprotonation process rather than to search for a suitable electrophile which is akin to finding a needle in a haystack.

Table 1. Conditions for deprotonation of alkyne (**19**).

$ \begin{array}{ccc} \text{Me}-\text{CH}=\text{CH}-\text{C}(\text{Fe}(\text{CO})_3)\equiv\text{H} & \xrightarrow[\text{THF}]{\text{Base, electrophile}} & \text{Me}-\text{CH}=\text{CH}-\text{C}(\text{Fe}(\text{CO})_3)\equiv\text{R} \\ \mathbf{19} & & \end{array} $					
Entry ^a	Base	Electrophile	Temperature (°C)	R	Yield ^b (%)
1	<i>n</i> -BuLi	Paraformaldehyde	-78 – r.t.	CH ₂ OH	12
2	<i>n</i> -BuLi	D ₂ O	-78	D	5 ^c
3	LDA	D ₂ O	-78	D	S.M.
4	LHMDS	D ₂ O	-78	D	S.M.
5	<i>n</i> -BuLi	D ₂ O	0	D	- ^d
6	<i>n</i> -BuLi	D ₂ O	-40	D	70 ^c
7	<i>n</i> -BuLi	Paraformaldehyde	-40	CH ₂ OH	10
8	<i>n</i> -BuLi	Methyl chloroformate	-78	CO ₂ Me	30
9	<i>n</i> -BuLi	Methyl chloroformate	-40	CO ₂ Me	82

General conditions: ^a Substrate **19** (0.4 mmol); base (1.2 eq.); electrophile (1.5 eq.); THF (1.2 mL). ^b Isolated yield. ^c Deuterium incorporation was determined by ¹H-NMR spectroscopy. ^d starting material decomposed.

Firstly, among the bases that were screened through, butyllithium was the best reagent to deprotonate alkyne (**19**) despite low conversion to the deuterated product at -78°C (Table 1, Entry 2 – 4). Secondly, the temperature of the reaction mixture plays a pivotal role in generating stable lithium acetylide species. It was discovered that the reaction did not proceed to completion when deprotonated at -78°C, whereas adding base to alkyne (**19**) at 0°C led to a decomposition of the starting material (Table 1, Entry 5). As the results showed that the reaction was temperature-sensitive, it was hence postulated that the temperature for deprotonation had to be monitored carefully. After several optimisations, the deuteration test showed that the optimum condition was to generate the lithium acetylide at -40°C while maintaining the reaction at this temperature upon the addition of deuterium oxide. However, when paraformaldehyde was employed

bromide. As such, hydrometallation is a straightforward route to introduce the metal hydride across the alkyne bond of ynoate (**20**) to generate the organometallic moiety. Amongst a plethora of hydrometallation applications that have been reported over the years, only the use of hydrosilylation and hydrostannylation on ynoate (**20**) will be deliberated in this dissertation.

Hydrosilylation is one of the most useful catalytic reactions in the industry and in generating organosilane intermediates in organic chemistry.⁷¹ Since silanes are relatively cheap, hydrosilylation is an attractive option to attempt. In addition, the by-product of a Hiyama coupling from the synthesised organosilanes has low toxicity and can be removed easily through column chromatography. Ynoate (**20**) was thus treated with diethoxymethylsilane using PtCl_2 as the catalyst. Surprisingly, protodesilylation was observed, resulting in the formation of triene (**21**) (Scheme 12). Even in the presence of a more facile catalyst, such as Ziese's dimer, the alkyne was still reduced.

Scheme 12.

Since hydrosilylation did not deliver us the desired organosilane product, organotin chemistry was turned to as an alternative method in building the organometallic intermediate species. Rossi and co-workers reported a highly regioselective palladium-mediated hydrostannylation of alkylynoates with the stannyl group predominately inserted α to the carbonyl.⁷² Envisioned to achieve the same results as Rossi, ynoate (**20**) was hydrostannylated with the same reaction conditions used by the group and the ratio of the organostanne isomers obtained was determined by ^1H -NMR spectroscopy. H^a in the desired stannylester (**22- α**) will appear as doublet as it

couples with the neighboring olefin proton, whereas a singlet peak from H^b in stannylester (**22-β**) would be anticipated since there is no neighboring proton for a resonance coupling (Figure 6).

Figure 6. The hydrostannylated isomers (α and β)

Surprisingly, it was observed that the ratio of α -stannylester (**22-α**) to β -stannylester (**22-β**) in the crude ¹H-NMR spectroscopy was 1 : 1.31, which was unlike the high regioselectivity results attained in Rossi's hydrostannylation. A possible reason for the poor selectivity towards stannylester (**22-α**) could be due to the competitive electron-withdrawing group between the ester functional group and the dienes complexed with tricarbonyliron adjunct. Intrigued by the result, the reaction condition was further optimised by varying the steric and electron properties of the tertiary phosphine of the palladium catalyst (Table 2).

Table 2. Optimisation for hydrostannylation of ynoate (**20**).

Entry ^a	Catalyst	Ligand	Yield ^b (%)	Ratio (α : β) ^c
1	Pd(PPh ₃) ₄	-	97	1 : 1.31
2	PdCp(cinn)	-	96	1 : 1.65
3	Pd(OAc) ₂	TFP	98	1 : 1.48
4	PdCl ₂ (PEt ₃) ₂	-	96	1 : 0.87
5	PdCl ₂ (PCy ₃) ₂	-	96	1 : 0.34
6	PdCp(cinn)	P(<i>t</i> -Bu) ₃	97	1 : 1.18
7	Pd(dppf)Cl ₂	-	95	1 : 0.8

General conditions: ^a Substrate **20** (0.2 mmol); HSnBu₃ (2 eq.); [Pd] catalyst (10 mol%); ligand (20 mol%); THF (0.6 mL). ^b Isolated yield. ^c Ratio was determined by ¹H-NMR spectroscopy.

A control experiment with the use of palladium(0) catalyst with no ligands was first conducted to help us understand the effects of ligand on the regioselectivity of the hydrostannylation. Sources of palladium(0) catalyst would include Pd(dba)₂ and Pd₂(dba)₃CHCl₃. However, these catalysts decompose easily and often contain palladium metal nanoparticle impurities.⁷³ This would in turn impact the outcome and reproducibility of the reaction. PdCp(cinn), pioneered by Baird and co-workers, is an alternative source of palladium(0) catalyst and an efficacious precursor for Pd(0)-catalysed cross-coupling reactions.⁷⁴ Without any use of ligand, the hydrostannylation reaction led to a higher amount of stannylester (**22-β**) (Table 2, Entry 2). The use of electron-withdrawing ligands, as shown in Entries 1 and 3 (Table 2), did not ameliorate the desired selectivity towards stannylester (**22-α**). This led us to the hypothesis that electron-donating phosphine ligands might alter the regioselectivity. To our delight, incorporating electron-donating phosphine ligands in the catalyst, such as PEt₃ and PCy₃,

favoured a higher percentage of the stannylester (**22- α**) isomer (Table 2, Entry 4 and 5). However, when P(*t*-Bu)₃ was used as the ligand, selectivity towards the α -regioisomer deteriorated.

These results showed that the phosphine ligand's electronics and steric bulk could influence the selectivity towards the stannylester (**22- α**) isomer. In order to further understand the different reaction outcomes, we attempted to find a correlation between the yield of the stannylester (**22- α**) isomer and the physical properties of each ligand. Keay and co-workers reviewed on the quantification of the physical properties of different phosphine ligands.⁷⁵ Two charts were plotted according to the data provided by Keay – the stannylester (**22- α**) ratio against the Tolman cone angle (Figure 7) and the stretching frequency of the ligand (Figure 8). The Tolman cone angle would help to categorise the phosphine ligand according to its size. The greater the Tolman cone angle, the more sterically hindered the phosphine ligand.

As shown in Figure 7, the random plotted results showed that there was no correlation between the regioselectivity and the steric bulk of the phosphine ligands. On the other hand, the electron donor ability of the ligand will be governed by the stretching frequencies of CO from the monosubstituted transition-metal carbonyls with the phosphine ligand. The phosphine ligands with high electron donor ability will result in lower CO stretching frequency due to the greater degree of back-bonding from the metal center to the π^* orbital of the CO ligand.

The results in Figure 8 showed that in general, as the stretching frequency of the CO ligand decreases, the percentage of stannylester (**22- α**) isomer increases. This implies that as the phosphine ligands become more electron-donating, the hydrostannylation becomes more regioselective at the α -position. Interestingly, an anomaly was observed as the percentage of stannylester (**22- α**) drops with the use of

$P(t\text{-Bu})_3$ ligand. According to the electronic parameter provided by Keay and co-workers, $P(t\text{-Bu})_3$ gives a slightly smaller CO stretching frequency than PCy_3 does, which meant that $P(t\text{-Bu})_3$ is more electron-donating than PCy_3 . However, the tremendous dip of the percentage of stannylester (**22- α**) could indicate that the steric bulk of $P(t\text{-Bu})_3$ possibly distorted the expected result though the trend predicts that a more electron-donating ligand favours a more regioselective hydrostannylation. Since PCy_3 delivered the best α -regioisomer result with a ratio of 1 : 0.34 (Table 2, Entry 5), the ligand was used in the palladium-catalysed hydrostannylation reaction with ynoate (**20**).

Figure 7. Percentage of (**22- α**) against Tolman Cone angle.

Figure 8. Percentage of (22- α) against stretching frequency of CO.

Even though the mechanism of hydrostannylation is not fully understood, we could attempt to rationalise the mechanistic details from the results attained. The catalytic cycle essentially involves oxidative addition, hydrometallation upon coordination of the catalyst to the alkyne, and lastly reductive elimination.⁷⁶ There are two possibilities on how the hydrometallation will occur – either inserting hydride or the tin group across the alkyne bond. Assuming that the palladium-catalysed hydrostannylation proceeds through a Chalk-Harrod mechanism in which the hydride will be inserted across the internal alkyne bond, there are two potential intermediates (A or B) can be formed during the catalytic cycle (Scheme 13). From our plotted data above, the hydrostannylation is mostly influenced by the electronic properties of the phosphine ligands instead of its steric bulk. A mechanistic viewpoint that can possibly explain these results will be through an electronic polarisation of the π alkyne bond from the alkyne's substituent groups to effect the hydride insertion.⁷⁷ As the ester moiety is an electron-withdrawing group, the hydride will be delivered to the more electron-deficient alkyne

carbon atom (δ^{++}). With a more electron-donating phosphine ligand on the palladium complex, the hydride will be more susceptible to proceed towards intermediate A and attain the desired stannylester (**22- α**).

Scheme 13. Plausible hydrostannylation mechanism.

Cross-coupling

The organostannane (**22**) mixture was subsequently submitted to a Stille coupling with *trans*-1-bromopropene to obtain the desired coupling product. However, after several attempts with different catalysts, solvents, and variation of additives, no cross-coupling reaction took place. In some cases, side products were obtained but could not be identified or elucidated (Table 3). A possible reason for these disappointing results could be due to the bulkiness of the tricarbonyliron moiety that prevented the rate-determining transmetallation step from occurring.

Table 3. Stille coupling optimisation.

Entry ^a	Catalyst	Ligand	Solvent	Additive	Temperature (°C)	Yield (%)
1	Pd(PPh ₃) ₄	-	THF	-	r.t.	-
2	Pd(PPh ₃) ₄	-	THF	TBAF	80	-
3	Pd(OAc) ₂	XPhos	THF	TBAF	r.t.	-
4	PdCp(cinn)	TFP	THF	TBAF	r.t.	-
5	PdCp(cinn)	TFP	DMF	TBAF	r.t.	-
6	PdCp(cinn)	Ph ₃ As	DMF	TBAF	r.t.	-
7	Pd(OAc) ₂	P(<i>t</i> -Bu) ₃	THF	TBAF	r.t.	-

General conditions: ^a Substrate mixture **22** (0.4 mmol); bromopropene (1 eq.); [Pd] catalyst (5 mol%); ligand (10 mol%); solvent (1.2 mL).

Undeterred, a different strategy to install the propenyl chain was explored. In Rossi's quest of preparing a stereoselective hydrostannylation for 2-alkynoates, the organotin product was stereospecifically converted to its corresponding iodo-alkenoates at room temperature after several failed attempts of Stille coupling. Following the same procedure, the organostannane (**22**) mixture will be iodo-destannylated followed by a palladium-catalysed Suzuki coupling with propenyl boronate. The mixture of tin isomers (**22**) was then treated with an equimolar amount of iodine to convert them into their corresponding iodo-derivatives. However, decomplexation of the tricarbonyliron moiety was observed when the reaction was performed at room temperature. Iodine could have possibly acted as an oxidising agent resulting in the facile decomposition of the iron complex. Gratifyingly, the oxidation process was impeded, and the desired iodo-derivatives (**23**) and (**24**) were attained upon lowering the temperature to -78°C.

The mixture of tin isomers (**22**), which initially had similar R_f values, were inseparable through column chromatography after several attempts. To our delight, we could subsequently separate the two different iodo-derived isomers upon the iodo-destannylation step. Upon purification, a COSY NMR experiment was conducted to ensure that the correct major isomer was obtained. Since the COSY NMR experiment helps us understand the correlations of protons through chemical bonds, H^a and H^b should exhibit a correlation as these two proton resonances are mutually coupled within the desired iodo-compound (**23**) (Figure 9). On the contrary, there would be no correlation between H^d and H^b from the undesired compound (**24**).

Figure 9. Iodo-derivatives obtained after iodo-destannylation.

It is imperative to first differentiate the two diene protons H^b and H^c that were shifted upfield from the magnetic anisotropy effect as mentioned earlier (Figure 4). By identifying the chemical shift for H^b , we will understand if there is any proton coupling effect with it. The methyl group, with a characteristic doublet of chemical shift at 1.49 ppm, shows a correlation with the multiplet H^c at the range of 1.72 – 1.66 ppm (Figure 10). Hence, the next upfield diene proton with a doublet of doublet at 2.71 ppm would correspond to H^b which shows interactions with two protons – a doublet, and a doublet of doublet in the alkene region. Logically, H^a should appear as a doublet if it interacts with H^b and this was proven evidently from the COSY NMR spectrum. As such, the major product was indeed vinyl iodide (**23**). This in turn reflected that our hydrostannylation using PCy_3 as the ligand gave us the highest stannylester (**22- α**) regioisomer yield.

Figure 10. COSY NMR experiment on vinyl iodide (**23**).

The iodo intermediate (**23**) had to be freshly prepared in dark conditions as they were light-sensitive compounds and decomposed easily. The vinyl iodide (**23**) generated was then submitted immediately to a palladium-catalysed Suzuki reaction to give alkene (**25**) (Scheme 14). Though sodium hydroxide was used as the base, the ester functional group remained intact under these conditions. Also, the alkene installed remained as (*Z*)-geometry as the cross-coupling Suzuki reaction is stereospecific.

Scheme 14.

Asymmetric dihydroxylation (AD)

According to the design of our retrosynthesis (Scheme 1), the four alkenes in intermediate (**4**) are susceptible to a dihydroxylation reaction. Two of the alkenes are currently protected with tricarbonyliron group which makes this diene unreactive to dihydroxylation as the olefin donates its π -electrons to the tricarbonyl moiety. Since AD favours electron-rich alkenes, the idea of installing an ester moiety remains influential in selectively dihydroxylating the (*E*)-disubstituted olefin which was just attached via Suzuki coupling.⁷⁸ Thus, alkene (**25**) would not face any complications during the AD process. Furthermore, upon installation of the diols across the carbon double bond, the ester moiety would fit in aptly and elegantly in the subsequently intramolecular cyclisation to form a five-membered lactone ring. This also addresses the key issue of

selectively protecting one of the two hydroxyl groups which was mentioned in the retrosynthetic analysis (Scheme 1).

As emphasised earlier, the molecular structure of trichoether A (**1**) reported was not in its absolute configuration. Spectroscopical evidence provided by Chen *et. al.* proved that the relative configuration of the protons at the stereogenic centres were in the *erythro* form. Thus, whichever the choice of AD-mix is arbitrary. As there is no known exception of the stereochemistry in Sharpless asymmetric dihydroxylation in every alkene, the enantiofacial selectivity of the asymmetric dihydroxylation is well predicted from his mnemonic device (Figure 11).⁷⁹ While the southwest quadrant is well-suited to accommodate large groups, the northeast quadrant is relatively opened for substituents on the olefin of moderate size. More importantly, the southeast quadrant resides a proton as compared to the slight steric barrier of the northwest quadrant of the device. With the alkene positioned accordingly to these constraints, the dihydroxylation can follow accordingly to the well-known Sharpless mnemonic device with the AD- β on the top face or the AD- α at the bottom face. With the enantiofacial selectivity determined using Sharpless mnemonic device, the absolute configuration of the synthesised natural product will be delivered. The confirmation of the right choice of reagent used can then only be proven upon the completion of the total synthesis, where the optical activity of the synthesised trichoether A (**1**) could be compared against the chiroptical data provided by Chen *et. al.*

Figure 11. Sharpless's asymmetric dihydroxylation

Alkene (**25**) was first treated using Sharpless asymmetric dihydroxylation condition using the commercially available premixed AD-mix α . Surprisingly, the starting material alkene (**25**) was mostly recovered, and the highest yield of lactone (**29**) attained was only 7%. This could be due to the low concentration of potassium osmate in the commercial premix which resulted in incompleteness of the reaction. Hence, the loading of the osmate catalyst was increased together with the use of AD-mix α . The reaction saw a slight improvement as a mixture of starting material alkene (**25**), uncyclised diols (**28**), and cyclised lactone (**29**) was observed. Instead of using potassium ferricyanide as the oxidant pioneered by Tsuji and co-workers,⁸⁰ we also attempted using NMO as the oxidant using Upjohn's condition.⁸¹ Even though it was reported that using potassium ferricyanide as the stoichiometric reoxidant surpasses over NMO in the AD such as higher catalytic turnover and *ee* ratio,⁸² it is worthwhile to investigate if the use of NMO would improve our reaction. However, it was observed that bubbles of gas were evolved during the reaction using Upjohn's conditions. From the crude ¹H-NMR analysis, the tricarbonyliron moiety was removed from alkene (**25**).

With the evidence gathered from the experimental results, it was deduced that NMO (**27**) oxidant led to an oxidative decomplexation and released carbon dioxide gas as the by-product (Scheme 15).⁸³

Scheme 15. Mechanism of oxidative decomplexation using NMO as co-oxidant.

Since Sharpless dihydroxylation gave us the desired products but at a low yield, the AD-mix formulation was modified to further push the reaction to completion. With a stoichiometric amount of methanesulfonamide, the mixture was modified with the base potassium carbonate and potassium ferricyanide co-oxidant increased to 3 equivalents each. Furthermore, while the osmate catalyst was increased to 2 mol%, the chiral ligand (DHQ)₂-PHAL was also increased to 10 mol% as the alkaloid ligands play a crucial role in accelerating the AD process.⁸⁴ Providentially, the starting material was fully consumed. Even though there was a slight amount of unidentified side product formed, uncyclised diols (**28**) being the major product, and lactone (**29**) were both obtained (Scheme 16). The slow rate of cyclisation could be due to the biphasic nature of the reaction as the base was trapped in the aqueous layer which inhibited the

formation of the lactone. In addition, the bulky tricarbonyl iron moiety could have also decelerated the cyclisation.

Thus, an extra step was needed for the formation of lactone (**29**) from the uncyclised diol (**28**). Potassium carbonate, acting as a mild base, was initially used with THF for the closure of the lactone ring. However, due to the solubility issue between the carbonate and THF solvent, the starting material was retrieved. A catalytic amount of potassium *tert*-butoxide was used instead and gratifyingly, the desired lactone (**29**) was formed in excellent yield (Scheme 16).

Scheme 16.

Tricarbonyliron diene complexes exhibit planar chirality. Given that tetraene (**25**) is racemic, asymmetric dihydroxylation would be expected to give rise to four stereoisomeric diols. There would be two pairs of enantiomers, and two pairs of diastereomers (Figure 12). We, therefore, opted to determine the stereoselectivity of the dihydroxylation at a later point, which is after oxidative demetallation.

Figure 12. Four possible isomeric diols from Sharpless dihydroxylation

2.4.2 Synthesis of the aromatic substituent

The molecular architecture of trichoether (**1**) bears a highly substituted aryl moiety comprising all *ortho*-, *meta*- and *para*- substituents. Prudent planning is hence called for in synthesising the aromatic building block (**2**) (Scheme 1) to prevent over substitution of the aromatic ring. Traditionally, the introduction of any substituent groups on the aromatic ring mostly relies on the use of a Friedel-Crafts reaction.⁸⁵ Regardless of alkylation or acylation, the regioselectivity of this electrophilic substitution reaction is greatly dependent on the nature of the substituent groups attached to the aromatic ring. Despite it being a convenient synthetic tool for carbon-carbon bond construction on the aromatic moiety, there are certain limitations posed by this reaction. The Friedel-Crafts alkylation reaction, for instance, does not work if the aromatic motif encompasses a pre-attached strongly electron-withdrawing group. Furthermore, there is also a possibility that over substitution can occur since the resultant compound is more activated than the starting material.

The approach to circumvent these problems is to employ a transition metal catalysed C-H functionalisation reaction. Direct functionalisation of C-H bonds has emerged as a powerful strategy to install carbon-carbon or carbon-heteroatom bonds.⁸⁶ Such cutting-edge methodology is very attractive as it not only maximises atom-economy in the synthesis of new building blocks, but also simplifies the overall chemical synthesis. With the use of a directing group to install a new substituent on the aromatic ring, the possibility of an over substitution can be eliminated. This is hence a viable strategy to adopt in constructing the aromatic building block (**2**).

Two possible approaches were considered to prepare the aromatic coupling partner (**2**) for the aliphatic chain (Scheme 17). The most efficient way would be to perform a direct C-H activation on salicylic acid to attach the propyl alkyl chain. Alternatively, direct C-H hydroxylation on the propyl benzoic acid precursor, which can be obtained from the commercially available 2-iodobenzoic acid, will also pave the way towards attaining the desired aromatic intermediate (**2**).

Scheme 17. Different approaches in assembling (**2**).

Direct C-H activation on salicylic acid

The synthetic plan began with an *ortho*-alkylation of salicylic acid through C-H functionalisation. Gooßen and co-workers developed an *ortho* C-H functionalisation directed by a carboxylate moiety using $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$.⁸⁷ The reaction conditions

used are not only mild, but also promotes regiospecific C-H allylation. In addition, this methodology will immediately give us all three desired *ortho*, *meta*, *para* substitutions with the right reagents used. Before adopting this strategy to construct our desired aromatic building block (**2**), methyl salicylate (**30**) was first protected with SEMCl to furnish benzoate (**31**) as the acidic phenol moiety might compete with the base-assisted carboxylate-directed *ortho*- C-H allylation. Benzoate (**31**) underwent methanolysis to furnish benzoic acid (**32**) for the subsequent C-H functionalisation reaction using Goossen's protocol. However, instead of acquiring the corresponding allylated benzoic acid, the SEM protecting group had been lost and gave benzoic acid (**33**) in only 10% yield (Scheme 18).

It was postulated that the C-H allylation process had occurred since benzoic acid (**33**) was obtained from the reaction. In the mechanism of the catalytic cycle, the by-product acetic acid was sufficiently acidic enough to cleave the SEM protecting group *in-situ* in the allylated benzoic acid. However, this was insufficient to account for the low reaction yield as the deprotected benzoic acid (**33**) would be achieved in higher yield should the allylation process occur. A possible reason for the low yield from the C-H allylation process could be due to the acetic acid by-product which might have deprotected the SEM group in benzoic acid (**32**). With the SEM protecting group was lost in benzoic acid (**32**), the free phenol moiety and carboxylic acid could bind to the ruthenium catalyst and impede any C-H activation process.

Scheme 18.

Thus, a more robust protecting group was chosen instead since the SEM protecting group is too labile for the carboxylate-directed *ortho*- C-H allylation reaction. PMB was chosen to be the protecting group as it can be cleaved via treatment with DDQ or CAN, without affecting the conjugated triene system towards the synthesis of trichoether A (**1**). Once again, the phenol substituent in methyl salicylate benzoic acid (**30**) underwent a PMB protection to give benzoate (**34**). After methanolysis of benzoate (**34**), benzoic acid (**35**) was then treated with the C-H allylation protocol, affording the desired carboxylic acid (**36**) with 25% yield (Scheme 19). Most of the starting material benzoic acid (**35**) was retrieved. Baffled by the results, an attempt to improve the yield by optimising the reaction conditions but this was the best result achieved. The failure of the direct alkylation on the salicylic acid thus prompted the search for another strategy to prepare the desired aromatic building block (**2**).

Scheme 19.

Hydroxylation of arenes using carboxylic acid as directing group

The second approach, as mentioned earlier in Scheme 17, would be to perform a C-H hydroxylation on propyl benzoic acid to generate the phenol substituent group. In 2009, Yu and co-workers successfully developed a palladium-catalysed *ortho*-hydroxylation on a wide array of substituted benzoic acids using oxygen gas.⁸⁸ The benzoic acid moiety acts as a directing group to insert the oxygen atom to give the corresponding hydroxylated product. The idea that no special ligand was required, yet able to install the desired phenol substituent group, intrigued us to employ this methodology in our work.

Phthalic anhydride (**37**) was treated with copper bromide and ethylmagnesium bromide to induce a ring-opening of the lactone to prepare 2-propionylbenzoic acid for the *ortho*-hydroxylation.⁸⁹ However, the reaction was somewhat challenging despite following the procedure closely. A mixture of an alkylated ketone (**38**) and di-alkylated benzyl alcohol (**39**) was obtained from the reaction (Scheme 20). The Grignard reagent led to a facile ring-opening of the anhydride to give the alkylated ketone in benzoic acid (**38**). Unfortunately, the anticipated ketone moiety in benzoic acid (**38**) underwent a

second nucleophilic attack from the Grignard reagent as well, leading to the double addition alcohol (**39**). There were also other unidentified by-products that were consistent with the data reported. Despite an extensive survey of reaction parameters, no promising results were obtained, and this prompted us to devise another route to introduce the alkyl chain on the aromatic building block (**2**).

Scheme 20.

2-Iodobenzoate (**41**), which was prepared from its corresponding benzoic acid (**40**) by Fischer esterification, was then subjected to a Sonogashira coupling with propyne gas to afford alkyne (**42**) (Scheme 21). Alternatively, 2-iodobenzoate (**41**) can be allylated using allylmagnesium bromide to give alkene (**43**).⁹⁰ Both pathways gave good yields and it was not of great concern on which specific route to take since both intermediates ultimately were to be hydrogenated to attain the desired propyl chain in ester (**44**). Ester (**44**) was then methanolysed with lithium hydroxide to give carboxylic acid (**45**) in quantitative yield.

Scheme 21.

Carboxylic acid (**45**) was then submitted to a direct hydroxylation using Yu's protocol.⁸⁸ A good yield of 75% for carboxylic acid (**46**) was obtained from the *ortho*-C-H hydroxylation. Carboxylic acid (**46**) was subsequently reduced using lithium aluminium hydride to give the corresponding alcohol (**47**) (Scheme 22).

Scheme 22.

Selective SEM protection

Alcohol (**47**) was then submitted to a SEM protection using SEMCl and potassium carbonate in acetone. However, to our surprise, the benzyl alcohol substituent was protected instead and resulted in a good yield of 70% for phenol (**49**) (Table 4, Entry 1). According to Greene, the standard protocol to protect phenol with the SEM group would be to use DIPEA in dichloromethane.⁹¹ Interestingly, utilising this condition in our case did not provide enough selectivity which led to a mixture of the desired benzyl alcohol (**48**) and phenol (**49**) in a 1 : 1 ratio (Table 4, Entry 2).

Intrigued by the result, an attempt of using bases of various strengths was used to investigate any possible correlation between the basicity and regioselectivity of the protection. DIPEA, being a stronger base than potassium carbonate, gave at least our desired benzyl alcohol (**48**) despite poor selectivity towards the phenol protection. Aiming to improve the yield of benzyl alcohol (**48**), the condition was tuned by using a stronger base such as sodium hydroxide. However, as SEMCl is moisture sensitive, it was degraded in the solvent mixture of dioxane and water, and the starting material arene (**47**) was retained. In order to ensure that the inorganic hydroxide ion can fully deprotonate the phenol without the use of water, a phase transfer catalyst TBAB was used in toluene to facilitate the deprotonation process. However, the yield of the desired protected phenol product deteriorated as shown in Entry 4 (Table 4).

Table 4. Optimisation in the protection of phenol in arene (**47**) using different bases.

Entry ^a	Base	Additive	Solvent	Temperature (°C)	48 (%)	49 (%)
1	K ₂ CO ₃	-	acetone	50	-	70
2 ^b	DIPEA	-	CH ₂ Cl ₂	0	50	50
3 ^b	NaOH	-	dioxane/H ₂ O	r.t.	-	-
4 ^b	NaOH	TBAB	toluene	r.t.	20	65

General conditions: ^a Substrate **47** (0.6 mmol); SEMCl (1 eq.); base (1 eq.); additive (10 mol%); solvent (2 mL). ^b Ratio was determined by ¹H-NMR spectroscopy.

This setback was quickly addressed by re-examining our approach in light of carboxylic acid (**46**). Given the difficulty in selectively protecting the phenol moiety over the benzyl alcohol in the same molecule, this would imply that it will also be a challenge to protect only the phenol group carboxylic acid (**46**). Instead of searching and surveying through different approaches to selectively protect the phenol, it was decided that both the phenol and acid moieties in carboxylic acid (**46**) would be protected with SEM. Even though this was not an atom-efficient process, the goal was ultimately to get the desired aromatic coupling partner for the aliphatic chain in trichoether A (**1**). Carboxylic acid (**46**) was successfully converted to arene (**50**), followed by a reduction of the ester group to obtain alcohol (**48**) (Scheme 23).

Alcohol (**48**) was then converted to a good leaving group before coupling with the key intermediate aliphatic chain. Upon submission of alcohol (**48**) with methanesulfonyl chloride in dichloromethane, its corresponding chloride (**51**) was obtained instead of the expected mesylate product. It was postulated that the highly electron-rich aromatic ring resulting from both the propyl chain and the SEM protecting group enhanced the electron density in the system. As such, once the mesylate group

was formed, it was immediately displaced by the chloride and generated chloride (**51**) in a good yield of 80% (Scheme 23). Interestingly, it was also possible to generate the desired mesylate (**52**) by using a less polar solvent such as diethyl ether. The chloride ion generated will be trapped and was precipitated out as the triethylamine hydrochloride salt in the reaction mixture.

Scheme 23.

In fact, both chloride (**51**) and mesylate (**52**) will be useful for the synthesis of trichoether A (**1**). However, mesylate (**52**) is an unstable compound and decomposes easily due to the facile displacement of the leaving group caused by the electron-rich aromatic ring. Hence, mesylate (**52**) should be freshly prepared and used immediately.

2.4.3 Coupling of aromatic and aliphatic substituents

SN2 reaction

The convergent synthesis of trichoether A (**1**) began with etherification between lactone tricarbonyliron complex (**29**) and chloride (**51**) using silver oxide. The silver ion would coordinate with the chloride leaving group to facilitate the benzylation process.

However, no reaction occurred despite varying the solvent system used. Interestingly, only lactone tricarbonyliron complex (**29**) was recovered after the reaction (Table 5, Entry 1 and 2). The benzylating agent chloride (**51**) could have decomposed in the reaction which resulted in no recovery of the aromatic building block.

The Williamson ether synthesis was also attempted for the coupling reaction of both key intermediates (**29**) and (**51**) (Table 5, Entry 3). Although there were no promising results in attaining the desired product, lactone tricarbonyliron complex (**29**) was fortunately retained without any hydrolysis of the ester moiety. Not surprisingly, chloride (**51**) was irretrievable after the reaction. The decomposition of chloride (**51**) could be attributed to a possible halide exchange between the chloride leaving group and bromide ion in the TBAB phase transfer catalyst. The corresponding benzyl bromide would therefore be formed *in situ* during the reaction, and its decomposition of it was faster than the formation of the desired product.

Table 5 Different conditions used to couple the aliphatic chain and aromatic fragment.

Entry ^a	Base	Additive	Solvent	Temperature (°C)	Yield
1	AgO	-	MeCN	r.t.	- ^b
2	AgO	-	DMF	r.t.	- ^b
3	NaOH	TBAB	toluene	r.t.	- ^b
4	NaH	-	THF	0 – r.t.	- ^c
5	NaH	-	THF	0 – 60	- ^c
6	NaH	-	DMF	0 – r.t.	- ^c
7	NaH	-	DMF	0 – 60	- ^c
8	NaH	KI	DMF	r.t.	- ^b

General conditions: ^a Substrate **29** (0.3 mmol); substrate **51** (1.2 eq.); base (1.1 eq.), additive (10 mol%), solvent (1 mL). ^b Decomposition of chloride (**51**). ^c Both starting materials recovered.

Despite using a stronger base such as sodium hydride, the etherification did not proceed successfully. In addition, both starting materials were retrieved even at elevated temperatures (Table 5, Entry 4 – 7). In Entry 7, adding additives such as potassium iodide resulted in the decomposition of chloride (**51**) as well. It is noteworthy that the reaction between lactone tricarbonyliron complex (**29**) and mesylate (**52**) was also performed with all the reaction conditions listed in Table 5. Similarly, only lactone tricarbonyliron complex (**29**) was retrieved upon purification. There was no recovery of mesylate (**52**) as the facile mesylate leaving group on the aryl ring led to a decomposition of the compound due to the high electron density in the aromatic system.

These failures brought us into thinking about whether lactone tricarbonyliron complex (**29**) could also pose a problem in the etherification process. The highly substituted hydroxyl motif is not only surrounded by the bulky tricarbonyliron moiety,

but the methyl group on the lactone site also creates a steric hindrance in preventing a nucleophilic substitution from taking place. These setbacks were then addressed by removing the bulky tricarbonyliron group using CAN. However, it led to a messy reaction and the product could not be elucidated upon purification. The oxidative decomplexation was then achieved by using trimethyl *N*-oxide to afford the corresponding lactone (**54**) successfully (Scheme 24).

Scheme 24.

At this juncture, the enantiomeric excess of lactone (**54**) can be determined via chiral HPLC since a pair of enantiomers was obtained through oxidative demetallation. The methodology to determine the enantiomeric excess would first require the preparation of the *R,R*- lactone enantiomers (Figure 13) with the use of chiral ligand $(\text{DHQD})_2\text{-PHAL}$ which is found in AD-mix β . The method of preparing the *RR*-lactone enantiomers would be essentially and conveniently be the same as the synthesis of lactone (**54**). By spiking *S,S* lactone (**54**) with the *R,R*-enantiomer, the enantiomeric excess of lactone (**54**) was then successfully determined via the chiral HPLC analysis.

Figure 13. *R,R*-triene aliphatic lactone.

It was chromatographically challenging to separate the enantiomers as the peaks often overlapped despite varying the solvent parameters and concentration of the sample for analysis. After several attempts, the best chromatogram result was attained by using

a Diacel OJ-H column revealing that the compound had been obtained with a 71% *ee* (Figure 14). Unlike the (*E*)-olefins examples reviewed by Sharpless which gave high *ee*,⁷⁹ our dihydroxylation reaction (Scheme 16) furnished moderate enantioselectivity. The unusual nature of tetraene (**25**) could bring about an adverse effect on the enantioselectivity of the lactone.

Figure 14. Integration table of lactone (**54**) HPLC result.

Employing the reaction conditions listed in Table 5, etherification of lactone (**54**) and chloride (**51**), however, did not occur and the outcome of these results was similar to what was mentioned earlier. The synthesised mesylate (**52**) was thus used as the coupling agent and 29% yield of the desired ether (**54**) was serendipitously obtained (Scheme 25). Unfortunately, the reaction outcome was irreproducible and the isolation of the mesylate was a challenge. In addition, the window for etherification between lactone (**53**) and mesylate (**52**) was very narrow as the decomposition of mesylate in the reaction could be faster than the formation of the ether bond.

Scheme 25.

Dudley-like reagent

These unprecedented results prompted us to consider an alternative method for the etherification process. The conditions used earlier in fact undergo an S_N2 -type reaction between the alkali metal alkoxide generated from the strong base used and the benzyl halide agent. Alternatively, Dudley and co-workers developed a hydroxyl benzylation protocol using benzyloxypyridinium triflate salt, also known as the Dudley's reagent (**56**) (Figure 15), under mild and nearly neutral conditions.⁹² He proposed that the mechanism falls along the spectrum of S_N1 and S_N2 pathways but favoring the S_N1 process. Since our benzylation via the S_N2 methods did not give us any promising results, we worked towards the other end of the nucleophilic substitution spectrum by adopting Dudley's possible approach with an S_N1 strategy to assemble both the intricate aliphatic chain and sensitive aromatic building block.

Figure 15. Dudley's reagent

Benzyl alcohol (**48**), which was prepared earlier, underwent a nucleophilic aromatic substitution with 2-chloropyridine to give pyridine (**57**) in an excellent yield of 82% (Scheme 26).^{92a} It was then treated with methyl triflate to prepare the

benzylating salt reagent that is analogous to Dudley's reagent. However, the SEM protecting group falls off and phenol (**58**) was isolated instead of the corresponding pyridinium salt. This could be due to traces of triflic acid from the methyl triflate that likely caused the deprotection of the SEM group (Scheme 26).

Scheme 26.

Since the desired SEM protected pyridinium salt could not be prepared, it was generated *in situ* as the mixture of pyridine (**57**) and lactone tricarbonyliron complex (**29**) was treated with methyl triflate (Scheme 27). The desired ether product, however, was not attained and lactone tricarbonyliron complex (**29**) was recovered. Likewise, the same results were obtained when the mixture of less sterically hindered lactone (**54**) and pyridine (**57**) was treated with methyl triflate to generate the desired SEM protected pyridinium salt *in situ*. Not surprisingly, both lactone (**54**) and phenol (**58**) were isolated from the reactions as well. The SEM protecting group was too labile which led to a facile deprotection by the mildly acidic methyl triflate upon generating the pyridinium salt *in situ*.

Scheme 27.

In order to rectify the root of the problem, a more robust protecting group had to be used as the SEM protecting group had been compromising the etherification process. Carboxylic acid (**46**) was thus protected with the PMB group before reducing PMB ester (**59**) to its corresponding alcohol (**60**). Alcohol (**60**) was subsequently coupled with 2-chloropyridine which afforded pyridine (**61**) in good yield (Scheme 28).

Scheme 28.

Dudley and co-workers highlighted that when methyl triflate is treated with the pyridine that is attached to the PMB group, the pyridinium triflate salt (**62**) is unstable (Figure 16).⁹³ Despite being analogous to Dudley's reagent (**56**) (Figure 15), the electron-rich PMB group possibly could result in the unstable nature of pyridinium triflate salt (**62**). It was not a surprise that the attempt to prepare the pyridinium triflate salt (**63**) (Figure 16) was unsuccessful as it decomposed rapidly at room temperature. Hence, the earlier concept of generating the pyridinium salt *in situ* was executed again.

Figure 16. Unstable pyridinium triflate salt at room temperature.

When lactone tricarbonyliron complex (**29**) and pyridine (**61**) were treated with methyl triflate, a 6% yield of the desired ether was obtained (Scheme 29). Even though the $^1\text{H-NMR}$ spectrum from the purified product was slightly unclear, a rough elucidation of the $^1\text{H-NMR}$ and the mass spectrum obtained from LCMS indicated that the etherification did occur. Undeterred, the less sterically hindered lactone (**54**) and pyridine (**61**) were also treated with methyl triflate. To our delight, the yield of the expected ether product (**65**) improved to 30% (Scheme 29). However, the results were subsequently irreproducible which hindered us from progressing to the subsequent reactions.

Scheme 29.

Lepidine-Dudley's reagent

We aimed to improve the yield of the etherification process by changing the pyridine moiety to a lepidine group. Dudley pointed out that not only pyridinium triflate salt (**62**) (Figure 16) was unstable, but also the fact that it was insoluble in aromatic solvents which affected the reaction efficiency.⁹³ In order to counter this problem, Dudley prepared quinoline (**66**) by attaching a lepidine moiety to the PMB group (Figure

17). Though it is also unstable at room temperature, quinoline (**66**) is soluble in aromatic solvent which is crucial in improving the efficacy of the reaction.⁹³

Figure 17. Dudley's quinoline triflate salt as benzylating agent.

Understanding that the stability of electron-rich quinoline triflate salt is an issue, it will be prepared *in situ* instead of isolating it. Hence, the etherification process proceeded with treating lepidine (**67**), which was prepared from alcohol (**60**) and commercially available 2-chlorolepidine, and lactone tricarbonyl iron complex (**29**) with methyl triflate (Scheme 30). However, the reaction was very messy, and no conclusive result was obtained after several attempts. The same results were also obtained when the less sterically hindered lactone (**54**) was used for the etherification process.

Scheme 30.

Quinone Methide strategy

A new approach was then devised for the etherification between the aliphatic chain and the aromatic building block. *Ortho*-Quinone methides (*o*-QMs) have been used as important intermediates for the construction of complex natural products.⁹⁴ They are reactive species that undergo rapid re-aromatisation by a Diels-Alder reaction or a Michael addition of a nucleophile. As *o*-QMs are very reactive, they cannot be isolated and are always generated *in situ*. Several methods in generating *o*-QMs include thermolysis of benzocyclooxabutenes, a Grignard addition to an OBoc substrate, acid or base, and treatment of fluorides to a silyl-protected phenol moiety (Figure 18).

Figure 18. Different methods to generate *o*-QMs.

We have attempted base- and acid-mediated nucleophilic substitution for our etherification between the aliphatic chain and aromatic building block thus far. Among all the unsuccessful attempts, the highest yield obtained was in fact the reaction using the mildly acidic methyl triflate (Scheme 30). The acid-mediated conditions could therefore be used to our advantage to construct the desired ether compound by using the quinone methide strategy. As mentioned earlier, one of the protocols was to treat an unprotected phenol with acid to generate *o*-QMs. Without any protecting group on the

aryl moiety, there will be more “free” space to couple both key fragments together which could be beneficial to our ether synthesis.

Since a Diels-Alder reaction can occur between olefins and QMs, only lactone tricarbonyliron complex (**29**) will be used in this strategy to prevent any cycloaddition from taking place. Alcohol (**47**) and lactone tricarbonyliron complex (**29**) were initially treated with a mild Brønsted acid such as Amberlyst-15. It was observed based on ^1H -NMR spectrum that no reaction took place despite varying the temperature and solvent used. However, when a stronger Brønsted acid such as pyridinium *p*-toluenesulfonate, *p*-toluenesulfonic acid, or camphorsulfonic acid was used, the reaction became very sluggish. Even after purifying the crude product, no conclusive results could be made as the crude ^1H -NMR spectrum was indecipherable. Attempts to use different Lewis bases such as scandium triflate or ytterbium triflate to improve the reaction also gave inconclusive results.

Scheme 31. Attempts at etherification using different Lewis or Brønsted acid via *o*-QM.

Several side reactions could have intervened during the acid-mediated *o*-QM reactions. The hydroxyl group on lactone tricarbonyliron complex (**29**) could have undergone an elimination in the acidic conditions and decomposed during the reaction.

In addition, since *o*-QMs are extremely reactive transient species, there is a possibility for alcohol (**47**) to undergo polymerisation as well.

Other than using the acid-mediated *o*-QM strategy, the silyl protected phenol is an alternative precursor on generating *o*-QM intermediates. A fluoride-induced desilylation of the protected phenol will introduce a phenoxide anion intermediate which then undergoes a conjugate elimination of a leaving group such as a halide or nitrate esters. Aryl (**46**), which was prepared earlier during the C-H functionalisation step, was protected with TBS group to give aryl (**69**). Since there will be an issue of selectively protecting the phenol moiety as mentioned earlier, the phenol and carboxylic acid were both protected. The plan was to reduce the resultant ester functionality in aryl (**69**) and transform the corresponding alcohol into a better leaving group for the fluoride-mediated *o*-QM reaction. However, to our surprise, upon treating aryl (**69**) with LiAlH₄, not only was the ester moiety reduced but also the TBS protecting group was taken off to give alcohol (**47**). The ester reduction was also attempted with DIBAL but instead led to a messy reaction.

Since we were not able to prepare the desired *o*-silyloxybenzyl alcohol, the plan to generate the fluoride-induced QM from a leaving group could not be executed. Alternatively, both the phenol and alcohol sites can be protected with TBS group to generate *o*-QM *in situ* upon the treatment of a fluoride base. As exemplified by Marino and co-workers, the key step in the total synthesis of hexahydrocannabinol was an intramolecular Diels-Alder reaction from an *o*-QM through a slow desilylation of a bis-silylated hydroxyphenol.⁹⁵ Taking into consideration this concept of a 1,4-elimination process to make *o*-QM induced by desilylation *in situ*, this method could be advantageous to us in the etherification synthesis. Thus, after bis-silylating aryl (**47**) with TBS groups, aryl (**70**) was then treated with lactone tricarbonyliron complex (**29**)

with cesium fluoride in refluxing acetonitrile in accordance with Marino's procedure. However, to our disappointment, not only did we not get the desired ether (**68**), but the reaction outcome was also inconclusive.

Scheme 32.

Model study of ether synthesis by ketal reduction

Regardless of the different setbacks that were encountered, a new strategy was devised to bring these two key fragments together. The idea of employing the *o*-QM strategy earlier was to take advantage of having no protecting groups on the hydroxyphenol fragment to facilitate the etherification process. This method of having a protecting group-free hydroxyphenol fragment is handy as there will be lesser steric hindrance which would impel the formation of the desired ether molecule.

Since the *o*-QM chemistry does not work in our favor, an alternative method to utilise the protecting group free hydroxyphenol concept is to in turn use it as a “protecting group” for the aliphatic chain. The synthesis was thus redesigned by

installing aryl (**47**) on lactone (**71**) before the reduction of the ketal ring. However, there are a few concerns with regards to the asymmetric reduction of the ketal ring. The partial reduction of the unsymmetrical ketal moiety in intermediate (**72**) would pose a regioselectivity issue as it might give us either the desired ether (**68**) with the free phenol moiety or ether (**73**) with the free benzylic alcohol (Scheme 33). The stereoselectivity of the ether moiety upon the hydride attack is an added concern that needs to be addressed too, even though the stereochemistry of the ether bond will hypothetically retain as the hydride would be delivered on the less hindered site.

Scheme 33. Possible reaction outcomes from a chiral ketal reduction.

Interestingly, the study of such an asymmetric ketal reduction has not been reported. Hence, the next course of action would be to perform a model study to understand the regioselectivity of such a chiral ketal reduction. Cyclohexanone (**74**) was treated with salicylic alcohol (**75**) to give us ketal (**76**) (Scheme 34). Initial attempts with molecular sieves to trap the water by-product somehow gave low yields that range from 20 – 40% despite varying the acids used, such as PTSA, amberlyst-15, and PPTS. When trimethyl orthoformate was used as a water scavenger, the reaction yield saw a tremendous improvement to 76%.

Scheme 34.

Ketal (**76**) was subsequently reduced using DIBAL and gave a mixture of two products. One of the products was identified as *o*-Cresol – the by-product of the reaction. A plausible mechanism that could explain *o*-Cresol as one of the products is a ketal ring-opening from the cleavage of the carbon-oxygen bond assisted by the lone pair on the benzylic oxygen atom (Scheme 35). The hydride from the DIBAL attached to the phenoxide will be delivered to the benzyl carbon releasing the cyclohexanone as the leaving group. *o*-Cresol would then be obtained upon working up of the reaction.

Scheme 35. Plausible mechanism to attain by-product *o*-Cresol.

Nevertheless, the above mechanism did give us a clue that the ketal reduction might be in favor of us. If the hydride is delivered to the oxonium moiety in intermediate (**77**), the major product could be our desired ether (**78**) with a free phenol site. This deduction, however, cannot be a conclusive result as more information is required to

determine the structure of the main product. In order to differentiate between desired ether (**78**) and undesired ether (**79**), a 2D HMBC NMR experiment was carried out, allowing us to understand the long-range coupling of the benzylic proton on the aromatic ring and heteronuclear carbon atom. If the ketal reduction delivers the desired ether (**78**) as the main product, H_a will correlate with 4 carbon atoms – 3 carbon atoms from the aromatic ring and one quaternary carbon on the cyclohexyl ring. However, if the undesired ether (**79**) is attained from the ketal reduction, H_b itself will only correlate with 3 aromatic ring carbons (Figure 19).

Figure 19. Comparison of benzylic protons between two possible products from DIBAL reduction.

The benzylic protons in the ¹H-NMR spectrum appear as a sharp singlet with a chemical shift of 4.7 ppm. From the HMBC 2D NMR spectrum (Figure 20), the benzylic proton reflected 4 correlations across the carbon spectrum. This was indeed a useful piece of information to not only help us affirm that we have obtained the desired ether (**78**), but also the mechanism that explains *o*-cresol as the by-product is correct.

Figure 20. HMBC NMR experiment of the major product attained in ketal DIBAL reduction.

However, the key aliphatic fragment (**71**) contains a lactone moiety, which is also susceptible to reduction. The use of DIBAL as the reducing agent is seen as a double-edged sword. It can help to perform a global reduction of both the ketal and lactone moiety in a one-pot reaction, but could also possibly result in unexpected side reactions. Another model study was hence performed on the reduction of a ketal ring with an ester moiety in the system. Using the same conditions to “protect” the cyclohexanone group, methyl levulinate (**80**) was first treated with salicylic alcohol (**75**) to give ketal (**81**). Since esters are more susceptible to reduction than ketals, ketal (**81**) was first submitted to a DIBAL reduction at -78°C before elevating it to room temperature. Surprisingly, aryl (**82**) was obtained instead of the desired aryl (**83**). A plausible mechanism would be that the DIBAL reduction of the ester moiety preceded

the ketal ring-opening, and the *i*-propyl group on the DIBAL subsequently migrated to the benzyl carbon instead of the hydride.

Since the alkyl groups from the DIBAL reagent created complexity in the reaction, this calls for the use of an alternative hydride donor for the reduction of the ketal ring in the presence of the ester moiety had to be. Ketal (**81**) was therefore treated with alane as it is not only a powerful reducing agent, but also a promising hydride donor as it has three hydrogens attached to the aluminium centre. Fortunately, aryl (**83**) was the only product obtained from the reaction, proving the desirability of alane as a reducing agent. However, in any case, upon the reduction process on the actual substrates, there might a possibility that reducing the ester moiety can complicate the reaction.

The scope was further narrowed by exploring a hydride-transfer reagent that could selectively reduce the ketal ring without affecting the ester site. The use of triethylsilane and a Lewis acid such as scandium triflate, boron trifluoride, or titanium isopropoxide, is an effective reagent pair for the selective reduction of acetals. However, upon screening the different Lewis acid for the reduction, the reaction turned out to be very messy and no conclusive results can be obtained even after purification. Michael and co-workers reported using boranes and trimethylsilyl triflate as complementary reagents for the reductive opening of chiral ketals.⁹⁶ Interestingly, they discovered that esters were unaffected during the reduction process as they were screening the versatility of these reagents. Only borane-dimethyl sulphide complex proved to give good yields from the reductive ketal ring-opening while the use of borane-THF required harsher conditions. On top of this, treatment of ketals with borane-THF led to sluggish reactions and therefore gave lower yields. The promising aspect of this methodology lies in the use of mild conditions, and more importantly, the inertness of the ester group during the

reaction. Using Michael's protocol, ketal (**81**) was hence treated with the complimentary reagents at -78°C . Gratifyingly, aryl (**84**) was attained in an excellent yield of 70% with the ester moiety unimpaired.

Scheme 36.

Oxidation of hydroxyl substituent on lactone moiety

The free hydroxyl group in tricarbonyliron complex (**29**) was then subjected to oxidation to its corresponding ketone using Dess-Martin periodinane. With the use of hypervalent iodine, it is a fast and mild oxidation that is suitable for oxidation of substrates with sensitive functionalities. However, the reaction led to a messy and inconclusive result even after purifying the crude mixture. Bases, such as pyridine and sodium bicarbonate, were also added to the reaction presuming that the acetic acid by-product was responsible for the unexpected messy result. Nonetheless, the desired ketone (**71**), and signs of oxidative decomplexation of the tricarbonyl iron adjunct were observed in the ^1H -NMR crude spectrum. The tricarbonyliron complex (**29**) was also treated to another mild oxidation protocol which is the Swern oxidation. Despite

monitoring the temperature carefully to prevent any side reactions, the outcome of the result was once again messy and inconclusive.

Scheme 37. Unsuccessful oxidation of tricarbonyliron complex.

In the Dess Martin oxidation attempt on tricarbonyliron complex (**29**), demetallation of the iron complex gave us a hint that the tricarbonyl iron moiety could be the problem towards the oxidation process. In order to counter the problem of the oxidising agent attacking the tricarbonyl iron group, the hydroxyl group on lactone (**54**) was resubmitted to another round of Dess-Martin oxidation. Instead of obtaining the desired ketone as the product, the hydroxyl group was interestingly converted into its corresponding acetate (**85**) (Scheme 38).

Scheme 38.

The periodinane intermediate (**86**) will theoretically undergo a rearrangement with one of the acetates to liberate the desired corresponding ketone and acetic acid as the by-product. Even though the stereochemistry of the acetate group is not determined, a plausible explanation of attaining acetate (**85**) is that upon the deprotonation of the hydroxyperiodinane via base, the acetate ion performs an S_N2 attack on the intermediate (**87**) (Scheme 39). Lactone (**54**) was also subjected to a Swern oxidation, but an unidentified product was obtained.

Scheme 39. Mechanism of side product attained from Dess-Martin oxidation.

2.5 Conclusion

Despite being a few synthetic steps away from the natural product, it is unfortunate that the convergent synthesis of trichoether A (**1**) could not be completed due to time constraints. The pathway towards the total synthesis of this unprecedented natural product, however, had been paved. In a nutshell, the total asymmetric synthesis towards trichoether A (**1**) reported in this dissertation comprises of three stages – the synthesis of the triene aliphatic chain, the construction of the aryl ring, and the attempts made to furnish the natural product (Scheme 40).

In the first stage, the skeleton of trichoether A (**1**) was built from a diene complexation in sorbaldehyde (**7**) as the protection of diene in a conjugate system of dienyne substrates prove to be challenging. The synthesised tricarbonyliron-diene complex then proceeded through a homologation strategy to which the aldehyde functional group transformed to an alkyne. In the alkynylation optimisation step, the decision in the change of electrophile from paraformaldehyde to methyl chloroformate not only enhances the yield of the reaction, but the product ynoate (**20**) formed was

envisioned for an internal hydroxyl protection in the later stage of the synthesis. The development of the palladium-catalysed regioselective hydrostannylation using tricyclohexylphosphine as the ligand gave a mixture of inseparable isomers of both α - and β -stannyl ester isomers. The mechanism of the hydrostannylation reaction was explained through the endeavours made in finding the correlation between the regioselectivity and the physical properties of the phosphine ligands. The unsuccessful attempts of using Stille coupling for the mixture of stannyl ester isomers led to an iodo-destannylation method for an access to Suzuki coupling. It was fortunate that the desired vinyl iodide could be separated chromatographically in this reaction and was determined through a COSY NMR experiment. The desired vinyl iodide proceeded to a Suzuki coupling and a Sharpless asymmetric dihydroxylation. While the diol attained from the asymmetric dihydroxylation was expected, an intramolecular lactonisation was observed in the reaction as well. The ester moiety which was installed during the optimisation of the alkynylation step had performed a hydroxyl protection as intended.

The second stage of the total synthesis featured the use of C-H activation strategy to construct the key aryl ring sub-unit. As the substituent groups on trichoether A (**1**) are *ortho* to each other, there were two possible approaches to install the respective substituents. As the direct C-H activation on salicylic acid to introduce the alkyl substituent proved to be challenging, the alternative method was to install the phenol moiety from 2-iodobenzoic acid with the benzoic acid acting as the directing group. Once the substituents were furnished accordingly on the aryl ring sub-unit, the selective protection of a phenol in a hydroxybenzoic acid proves to be problematic which led to a global protection of these two functional groups.

Upon establishing both the key triene aliphatic chain and aryl ring sub-units, the final stage of the total synthesis commenced with ether synthesis employing $\text{S}_{\text{N}}2$

reactions. Despite varying several conditions, the etherification proved to be a very delicate step. The efficiency of the ether synthesis was slightly improved with the use of a more activated aryl coupling partner, benzyl mesylate, and a less sterically hindered triene aliphatic chain. In an endeavor to improve the yields, other aryl coupling derivatives were also attempted by exploring into S_N1 -like reactions with the intention of adopting Dudley's benzylation protocol. However, the yields of the etherified product were irreproducible due to the unstable nature of the highly electron rich aryl coupling partner which was attributed by both the protected phenol and propyl substituents. Since the proposed structure of trichoether A (**1**) contains a propyl chain on the aromatic ring, the electronic effects caused by the propyl substituent cannot be eliminated. The protecting group on the phenol was then speculated to be compromising the formation of the desired ether product. Without any use of protecting groups on the key aryl ring, the etherification strategy was explored by preparing Quinone-Methide *in situ* with the use of either mild acids or fluorides but the outcomes proved to be unsuccessful.

A complete change in the etherification methodology was envisaged by using a ketal fragmentation strategy with the use of DIBAL reagent in attaining the desired ether product. Model studies were carried to understand the mechanistic pathway of the partial reduction of chiral ketal substrates. Various hydride-transfer reagents were explored to selectively reduce the ketal moiety in the presence of the ester functional group. It was found that the complimentary reagents boranes and trimethylsilyl triflate were useful for the reductive opening of chiral ketals leaving the ester moiety intact. Should the oxidation of the secondary alcohol on the lactone to deliver the requisite ketone be successful, the total synthesis of trichoether A (**1**) can soon be completed.

2.6 Future work

Due to time constraints, there was no opportunity to further explore other oxidising agents. With hindsight, from the efforts in transforming the secondary alcohol to its corresponding ketone in tricarbonyliron complex (**29**), the tricarbonyl iron moiety could be impeding the oxidation process which brought us to the oxidation of a less hindered molecule – lactone (**54**). Even though two different oxidising agents were attempted for the secondary alcohol in lactone (**54**) and the desired product was not attained, there are a few other oxidising agents that can be explored to prepare the precursor for the ketal formation (Scheme 40). For example, considering our hypothesis that the acetate group displaces out the iodinate in intermediate (**87**), the use of IBX can be examined as the oxidising agent to prevent any acetate ion to deviate from the oxidation process. Also, manganese dioxide is a suitable candidate since it is selective in oxidising allylic alcohol which is already structurally built-in lactone (**54**). Other oxidants such as TEMPO or the use of Corey-Kim oxidation can be taken into consideration as well.

Should the oxidation of the secondary alcohol on lactone (**54**) goes wrong, an alternative method would be to introduce electron withdrawing protecting group on the key aryl sub-unit (Scheme 41). As we retrace our synthetic steps in the first few etherification process, the benzylating agent used in the S_N2 reaction or the Dudley-like reagent was electronically rich. This interfered with the ether synthesis as the benzylating agent decomposed during the process before the two key fragments can be attached. One possible method to counter this problem is to consider installing an electron withdrawing protecting group, such as acetate, to build the derivative of the Dudley's reagent.

Scheme 41.

2.7 Experimental

All moisture-sensitive reactions were carried out using oven-dried glassware (120 °C) under an atmosphere of nitrogen unless indicated otherwise. Reactions using ultrasound facilitation were done using an ultrasonic bath (1.75 L, 560 W; 30.0 cm width x 17.9 cm depth x 26.4 cm height).

Anhydrous THF and diethyl ether were distilled from sodium metal and benzophenone under nitrogen. Anhydrous toluene was distilled from sodium metal under nitrogen. Anhydrous acetonitrile, dichloromethane, DIPEA, and triethylamine were distilled from calcium hydride under nitrogen. Anhydrous dimethyl sulfoxide and *N, N*-dimethylformamide were distilled from calcium hydride under reduced pressure and stored over 4Å molecular sieves. Anhydrous methyl chloroformate was distilled from calcium chloride under nitrogen. Anhydrous methanol was distilled from activated magnesium under nitrogen. All other solvents and reagents that were used upon received.

Analytical TLC was carried out on glass plates (silica gel 60, F254). Column chromatography was performed on silica gel 230 – 400 mesh. All ¹H-NMR spectra were recorded either on Bruker Advance DPX 400 or 500 MHz, or on JEOL ECA 400 MHz in CDCl₃ solution. All ¹³C-NMR spectra were recorded using the same instrument at the corresponding frequency in CDCl₃ solution. Chemical shifts were reported in ppm with respect to TMS, and coupling constants were recorded in Hz. Infrared spectra were recorded on an FT-IR spectrometer and reported in wavenumbers (cm⁻¹).

(3E,5E)-1,1-Dibromohepta-1,3,5-triene⁹⁷ (9)

Dry carbon tetrabromide (6.01 g, 18.1 mmol) in anhydrous dichloromethane (15 mL) was transferred via a cannula into a stirring mixture containing triphenylphosphine (4.75 g, 18.1 mmol) and activated zinc dust (1.18 g, 18.1 mmol) under nitrogen in an ice bath. The reaction was warmed to room temperature and left to stir overnight. Sorbaldehyde (1.0 mL, 9.06 mmol) was then slowly added into the mixture at room temperature, and the reaction was left to stir for not more than 2 hours. The resulting mixture was filtered, washed with water (10 mL), and extracted with dichloromethane (10 mL x 3) respectively. The combined organic extracts were washed with brine, dried over magnesium sulphate, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica to give dibromoolefin (**9**) (1.94 g, 85%) as a yellow oil.

¹H NMR δ 6.92 (d, *J* = 10.3 Hz, 1H), 6.34 (dd, *J* = 14.8, 10.9 Hz, 1H), 6.18 – 6.02 (m, 2H), 5.88 (dq, *J* = 13.8, 6.9 Hz, 1H), 1.78 (d, *J* = 6.2 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 137.3, 136.5, 133.7, 131.4, 126.5, 89.9, 18.8.

(4E,6E)-Octa-4,6-dien-2-yn-1-ol⁹⁸ (10)

n-Butyllithium (6.3 mL, 10.1 mmol, 1.6 M in hexane) was slowly added to a solution of dibromoolefin (**9**) (1.94 g, 7.70 mmol) in anhydrous THF (23 mL) at -78°C under nitrogen. Upon stirring at -78°C for 1 hour, paraformaldehyde (694 mg, 23.1 mmol) was then added to the reaction mixture through a solid addition tube. The reaction was then slowly warmed to room temperature and left to stir overnight. Saturated aqueous ammonium chloride (10 mL) was added to quench the reaction. The mixture

was then extracted with ethyl acetate (15 mL x 3). The combined organic extracts were washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica to give propargyl alcohol (**10**) (879 mg, 93%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 6.56 (dd, *J* = 15.8, 11.2 Hz, 1H), 6.13 – 6.06 (m, 1H), 5.82 (dq, *J* = 14.0, 6.8 Hz, 1H), 5.49 (dd, *J* = 15.8, 0.6 Hz, 1H), 4.49 (s, 2H), 1.79 (d, *J* = 6.8 Hz, 3H), 1.69 – 1.51 (m, 1H).

¹³C NMR (100 MHz, CDCl₃) δ 142.8, 133.3, 131.0, 107.8, 88.8, 85.3, 51.8, 18.4.

(4*E*,6*E*)-Octa-4,6-dien-2-yn-1-yl acetate (11**)**

Acetic anhydride (816 μL, 8.63 mmol) was slowly added to a mixture of propargyl alcohol (**10**) (879 mg, 7.20 mmol), triethylamine (2.01 mL, 14.4 mmol) in anhydrous dichloromethane (21 mL) at 0°C. The reaction was then warmed to room temperature and left to stir overnight. Saturated aqueous ammonium chloride (10 mL) was added to quench the reaction. The mixture was then extracted with dichloromethane (10 mL x 3). The combined organic extracts were washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica to give acetate (**11**) (1.10 g, 93%) as a yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 6.57 (dd, *J* = 15.9, 10.8 Hz, 1H), 6.10 – 6.05 (m, 1H), 5.81 (dq, *J* = 13.8, 7.0 Hz, 1H), 5.45 (dd, *J* = 16.0, 0.5 Hz, 1H), 4.78 (d, *J* = 2.0 Hz, 2H), 2.08 (s, 3H), 1.77 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 170.4, 143.5, 133.6, 130.9, 107.4, 86.1, 84.3, 53.1, 20.8, 18.4.

FTIR (CH₂Cl₂, cm⁻¹): ν_{max} 2939, 2915, 2852, 2215, 1740, 1643.

MS (ESI): $m/z = 187.03$ $[M + Na]^+$.

HRMS (EI): Calculated for $C_{10}H_{13}O_2$ $[M + H]^+$: 165.0916; found: 165.0908; Calculated for $C_{10}H_{12}O_2Na$ $[M + Na]^+$: 187.0735; found: 187.0727.

Tricarbonyl[(2E,4E)-hexa-2,4-dienal]iron⁹⁹ (13)

The suspension of sorbaldehyde (1.50 mL, 13.6 mmol) and nonacarbonyldiiron (5.93 g, 16.3 mmol) in a mixture of Et_2O and THF (5 : 2, 40 mL) was sonolysed for 12 hours under nitrogen. The mixture was then concentrated under *vacuo*, and diluted with 10% Ethyl acetate/Hexane (50 mL) before filtering through a thick pad of Celite[®]. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (3% Ethyl acetate/Hexane) on silica to give aldehyde (**13**) (962 mg – 2.86 g, 30 – 89%) as a yellow oil. Spectral data for compound (**13**) corresponded to the values reported in the literature.⁹⁹

¹H NMR (400 MHz, $CDCl_3$) δ 9.26 (d, $J = 4.4$ Hz, 1H), 5.77 (dd, $J = 8.0, 4.8$ Hz, 1H), 5.30 (dd, $J = 8.8, 5.2$ Hz, 1H), 1.71 (qd, $J = 7.4, 6.4$ Hz, 1H), 1.51 (d, $J = 6.4$ Hz, 3H), 1.26 (dd, $J = 8.0, 4.4$ Hz, 1H).

¹³C NMR (100 MHz, $CDCl_3$) δ 196.3, 89.7, 81.4, 60.4, 54.8, 19.3.

FTIR (neat, cm^{-1}): ν_{max} 2972, 2859, 2731, 2050, 1985, 1736, 1682, 1495, 1460.

Diethyl (2-oxopropyl)phosphonate¹⁰⁰ (17)

A mixture of chloroacetone (4.30 mL, 53.5 mmol) and KI (8.87 g, 53.5 mmol) in a mixture of anhydrous acetonitrile and acetone solvent (1 : 1.3, 162 mL) was stirred for 30 minutes at room temperature. Triethylphosphite (9.16 mL, 53.5 mmol) was then added to the mixture, and refluxed for 4 hours. The reaction mixture was cooled to room

temperature before filtering the white precipitate. The solvent was removed under reduced pressure, and the crude product was distilled under *vacuo* (80°C, 0.2 Torr) to obtain phosphonate (**17**) as a colourless oil (9.54 g, 91%). Spectral data for compound (**17**) corresponded to the values reported in the literature.¹⁰⁰

¹H NMR (400 MHz, CDCl₃) δ 4.20 – 4.10 (m, 4H), 3.09 (d, *J* = 22.8 Hz, 2H), 2.33 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 200.0 (d, *J* = 6.0 Hz), 62.7 (d, *J* = 6.4 Hz), 44.1, 42.9, 31.5, 16.4 (d, *J* = 6.1 Hz).

³¹P NMR[¹H] (162 MHz, CDCl₃) δ 20.64.

Diethyl (1-diazo-2-oxopropyl)phosphonate¹⁰⁰ (**18**)

A mixture of phosphonate (**17**) (9.54 g, 49.1 mmol), tosyl azide (11.6 g, 59.0 mmol), and triethylamine (13.7 mL, 98.3 mmol) in anhydrous acetonitrile (150 mL) was stirred at room temperature for 20 hours. The mixture was then concentrated under *vacuo*, the crude residue was dissolved in minimal amount of dichloromethane before adding hexane. The yellow precipitate was filtered off through a pad of Celite[®], and the solvent of the filtrate was removed under reduced pressure. The crude product was purified by column chromatography (40% Ethyl acetate/Hexane) on silica to give diazophosphonate (**18**) as a yellow oil (7.67 g, 70%). Spectral data for compound (**18**) corresponded to the values reported in the literature.¹⁰⁰

¹H NMR (400 MHz, CDCl₃) δ 4.27 – 4.15 (m, 4H), 2.28 (s, 3H), 1.39 (t, *J* = 7.0 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 190.2, 63.7 (d, *J* = 5.8 Hz), 63.5 (5.5 Hz), 27.4, 16.3 (d, *J* = 6.7 Hz).

³¹P NMR[¹H] (162 MHz, CDCl₃) δ 11.93.

Tricarbonyl[(3E,5E)-hepta-3,5-dien-1-yne]iron (19)

Phosphonate (**18**) (7.44 g, 33.8 mmol) was slowly added to a mixture of aldehyde (**13**) (5.32 g, 22.5 mmol) and potassium carbonate (9.35 g, 67.6 mmol) in anhydrous methanol (65 mL) at room temperature under nitrogen. The mixture was then left to stir overnight. Saturated aqueous ammonium chloride (20 mL) was added to quench the reaction before concentrating under *vacuo*. The crude mixture was then extracted with ethyl acetate (15 mL x 3). The combined organic extracts were washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (3% Ethyl acetate/Hexane) to give alkyne (**19**) (3.68 g, 70%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 5.35 (ddd, *J* = 8.2, 4.8, 1.0 Hz, 1H), 5.08 (dd, *J* = 8.8, 4.8 Hz, 1H), 2.42 (d, *J* = 2.0 Hz, 1H), 1.41 (d, *J* = 6.0 Hz, 3H), 1.26 – 1.19 (m, 1H), 0.86 (ddd, *J* = 8.2, 2.0, 1.2 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃) δ 87.3, 85.7, 84.0, 71.9, 57.7, 36.5, 19.2.

FTIR (neat, cm⁻¹): ν_{max} 3308, 3017, 2970, 2918, 2859, 2102, 2046, 1965, 1456, 1437, 1381.

MS (ESI): *m/z* = 232.85 [M + H]⁺.

HRMS (EI): Calculated for C₁₀H₉O₃Fe [M + H]⁺: 232.9901; found: 232.9905.

Tricarbonyl[(4E,6E)-octa-4,6-dien-2-yn-1-ol]iron

n-Butyllithium (180 μL, 0.29 mmol, 1.6 M in hexane) was added slowly to a solution of alkyne (**19**) (56.0 mg, 0.24 mmol) in anhydrous THF (1 mL) under nitrogen

atmosphere at -40°C. The reaction mixture was left to stir at -40°C for an hour. Paraformaldehyde (36.3 mg, 1.21 mmol) was then added to the reaction mixture through a solid addition tube and left to stir for another 1.5 hours. Saturated aqueous ammonium chloride (15 mL) was added to quench the reaction before warming to room temperature. The mixture was then extracted with ethyl acetate (3 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (5% Ethyl acetate/Hexane) to give propargyl alcohol as a yellow oil (6.70 mg, 10%).

¹H NMR (400 MHz, CDCl₃) δ 5.31 (dd, *J* = 6.6, 4.8 Hz, 1H), 5.08 (dd, *J* = 7.0, 4.8 Hz, 1H), 4.24 (d, *J* = 3.6 Hz, 2H), 1.41 (d, *J* = 6.4 Hz, 3H), 1.29 – 1.19 (m, 1H), 0.95 – 0.86 (m, 1H).

¹³C NMR (100 MHz, CDCl₃) δ 87.8, 87.2, 83.7, 82.2, 57.7, 51.7, 37.1, 19.2.

FTIR (neat, cm⁻¹): ν_{max} 3360, 2918, 2860, 2214, 2039, 1954, 1456, 1381, 1013.

MS (ESI): *m/z* = 262.22 [M + H]⁺.

Tricarbonyl[methyl (4*E*,6*E*)-octa-4,6-dien-2-ynoate]iron (**20**)

n-Butyllithium (11.9 mL, 19.0 mmol, 1.6 M in hexane) was added slowly to a solution of alkyne (**19**) (3.68 g, 15.9 mmol) in anhydrous THF (48 mL) under nitrogen atmosphere at -40°C. The reaction mixture was left to stir for an hour at -40°C. Methyl chloroformate (1.84 mL, 23.8 mmol) was then added slowly to the mixture and left to stir for another 1.5 hours. Saturated aqueous ammonium chloride (15 mL) was added to quench the reaction before warming to room temperature. The mixture was then extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced

pressure, and the crude product was purified by column chromatography on silica (5% Ethyl acetate/Hexane) to give ester (**20**) as a yellow oil (3.78 g, 82%).

¹H NMR (400 MHz, CDCl₃) δ 5.47 (dd, *J* = 8.0, 4.8 Hz, 1H), 5.16 (dd, *J* = 8.4, 4.8 Hz, 1H), 3.74 (s, 3H), 1.45 – 1.37 (m, 4H), 0.50 (d, *J* = 8.0 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃) δ 154.4, 91.1, 88.5, 83.5, 75.3, 58.8, 52.6, 32.7, 19.2.

FTIR (neat, cm⁻¹): $\nu_{\max}$ 3021, 2955, 2859, 2208, 2050, 1977, 1713, 1495, 1435, 1381.

MS (ESI): *m/z* = 290.89 [M + H]⁺; 313.05 [M + Na]⁺.

HRMS (EI): Calculated for C₁₂H₁₁O₅Fe [M + H]⁺: 290.9956; found: 290.9948; Calculated for C₁₂H₁₀O₅FeNa [M + Na]⁺: 312.9775; found: 312.9773.

Mixture of Tricarbonyl[methyl (2*E*,4*E*,6*E*)-2-(tributylstannyl)octa-2,4,6-trienoate]iron and Tricarbonyl[methyl (2*E*,4*E*,6*E*)-3-(tributylstannyl)octa-2,4,6-trienoate]iron (22**)**

Tributyltin hydride (7.59 g, 26.1 mmol) was slowly added to a mixture of ester (**20**) (3.78 g, 13.0 mmol) and PdCl₂(PCy₃)₂ (962 mg, 1.30 mmol) in anhydrous THF (39 mL) under nitrogen at 0°C. The reaction was warmed to room temperature and stirred until no more starting material was detected by TLC analysis. The mixture was then concentrated under *vacuo*, and the crude residue was dissolved in hexane (20 mL) before filtering off the yellow precipitate through a pad of Celite[®]. The solvent of the filtrate was removed under reduced pressure. The crude product was purified by column chromatography (3% Ethyl acetate/Hexane with trace amount of triethylamine) on silica to give a mixture of stannylesters (**22**) as a yellow oil (7.29 g, 96%).

¹H NMR (400 MHz, CDCl₃) δ 6.03 (d, *J* = 10.8 Hz, 1H), 5.76 (d, *J* = 1.2 Hz, 1H), 5.23 (dd, *J* = 8.8, 4.8 Hz, 1H), 5.17 (dd, *J* = 9.6, 5.2 Hz, 1H), 5.11 (dd, *J* = 8.8, 5.2 Hz, 1H), 5.07 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.55 (d, *J* = 9.2 Hz, 1H), 2.79 (t, *J* = 19.6 Hz, 1H), 1.75 – 1.24 (m, 31H), 1.13 – 0.84 (m, 28 H).

¹³C NMR (100 MHz, CDCl₃) δ 211.9, 172.7, 170.9, 164.7, 155.8, 133.4, 125.2, 86.9, 86.8, 85.7, 83.9, 62.1, 58.4, 58.2, 56.3, 51.3, 51.0, 29.1, 29.0, 27.4, 27.3, 19.3, 19.2, 13.8, 13.7, 11.6, 10.4.

FTIR (neat, cm⁻¹): ν_{max} 2957, 2926, 2872, 2855, 2043, 1981, 1964, 1699, 1578, 1464, 1431, 1377, 1358, 1196, 1169.

MS (ESI): *m/z* = 583.00 [M + H]⁺; 605.10 [M + Na]⁺.

HRMS (EI): Calculated for C₂₄H₃₉O₅FeSn [M + H]⁺: 583.1169; found: 583.1172; Calculated for C₂₄H₃₈O₅FeSnNa [M + Na]⁺: 605.0988; found: 605.0995.

Tricarbonyl[methyl (2*E*,4*E*,6*E*)-2-iodoocta-2,4,6-trienoate]iron (23)

A solution of iodine (3.50 g, 13.8 mmol) in dichloromethane (50 mL) was added very slowly to a mixture of stannylester (**22**) (7.29 g, 12.5 mmol) in dichloromethane (15 mL) at -78°C under nitrogen. Upon stirring at -78°C for 30 minutes, saturated sodium thiosulphate (20 mL) was added to the reaction before warming it to room temperature for another two hours. The mixture was then extracted with dichloromethane (3 x 10 mL). The combined organic extracts were then concentrated under *vacuo*, and diluted with diethyl ether (15 mL). Potassium fluoride (1.46 g, 25.1 mmol) was added to the crude mixture, and was left to stir at room temperature for 1.5 hours. The mixture was then filtered through a pad of Celite[®] before removing the solvent under reduced pressure. The crude product was purified by column

chromatography on silica (3% Ethyl acetate/Hexane) to give vinyl iodide (**23**) as a yellow oil (4.21 g, 80%).

¹H NMR (400 MHz, CDCl₃) δ 6.85 (d, *J* = 10.8 Hz, 1H), 5.26 (dd, *J* = 8.4, 4.8 Hz, 1H), 5.08 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.79 (s, 3H), 2.71 (dd, *J* = 10.4, 9.2 Hz, 1H), 1.72 – 1.66 (m, 1H), 1.47 (d, *J* = 6.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 164.1, 159.4, 87.5, 83.7, 79.8, 59.1, 56.4, 53.2, 19.3.

FTIR (neat, cm⁻¹): ν_{max} 2951, 2045, 1965, 1731, 1694, 1574, 593.

MS (ESI): *m/z* = 418.76 [M + H]⁺.

HRMS (EI): Calculated for C₁₂H₁₂O₅FeI [M + H]⁺: 418.9079; found: 418.9055.

Tricarbonyl[methyl (2Z,4E,6E)-2-((E)-prop-1-en-1-yl)octa-2,4,6-trienoate]iron
(25)

A mixture of *trans*-1-propenylboronic acid MIDA ester (2.18 g, 11.1 mmol) and sodium hydroxide (1.21 g, 30.2 mmol) in THF and water (1 : 1, 15 mL) was stirred for 30 minutes under nitrogen at room temperature. The mixture was then transferred to a mixture of vinyl iodide (**23**) (4.21 g, 10.1 mmol), Pd(PPh₃)₄ (582 mg, 0.504 mmol), NaOH (403 mg, 10.1 mmol) in THF and water (1 : 1, 15 mL) through a cannula under nitrogen. The reaction was left to stir at room temperature for 16 hours. Saturated ammonium chloride (10 mL) was then added to the mixture to quench the reaction before filtering off the precipitate through a thick pad of Celite®. The filtrate was extracted with ethyl acetate (3 x 15 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (5% Ethyl acetate/Hexane) to give tetraene (**25**) as a yellow oil (2.91 g, 87%).

¹H NMR (400 MHz, CDCl₃) δ 6.06 – 6.02 (m, 1H), 5.90 – 5.80 (m, 2H), 5.25 (dd, *J* = 8.8, 4.8 Hz, 1H), 5.07 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.80 (s, 3H), 2.50 (dd, *J* = 10.4, 8.8 Hz, 1H), 1.74 (dd, *J* = 6.4, 1.6 Hz, 1H), 1.61 – 1.54 (m, 1H), 1.45 (d, *J* = 6.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 167.7, 140.3, 129.1, 128.7, 127.4, 86.6, 83.7, 58.2, 56.6, 51.6, 19.3, 18.8.

FTIR (neat, cm⁻¹): ν_{max} 2951, 2914, 2039, 1964, 1713, 1593, 1435, 1379, 1217.

Tricarbonyl[methyl (2Z,4E,6E)-2-((1S,2S)-1,2-dihydroxypropyl)octa-2,4,6-trienoate]iron (28)

Potassium ferricyanide (8.65 g, 26.3 mmol), potassium carbonate (3.63 g, 26.3 mmol), potassium osmate (58.3 mg, 0.175 mmol), (DHQ)₂PHAL (683 mg, 0.876 mmol) and methanesulfonamide (833 mg, 8.76 mmol) as added to a solution of tetraene (**25**) (2.91 g, 8.76 mmol) in *t*-butanol and water (1 : 1, 24 mL) at 0°C. The reaction was left to stir at 0°C for 24 hours. Saturated sodium sulfite (10 mL) was added to the mixture before warming the mixture to room temperature. The mixture was filtered through a pad of Celite[®]. The filtrate was extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (25% Ethyl acetate/Hexane) to give diol (**28**) as a yellow oil (1.92 g, 60%).

¹H NMR (400 MHz, CDCl₃) δ 6.20 (d, *J* = 10.8 Hz, 1H), 6.15 (d, *J* = 11.2 Hz, 1H), 5.31 (dd, *J* = 7.2, 5.2 Hz, 1H), 5.12 (dd, *J* = 7.0, 5.2 Hz, 1H), 4.13 (t, *J* = 5.6 Hz, 1H),

3.81 (s, 3H), 3.80 (s, 3H), 2.68 – 2.56 (m, 2H), 1.68 – 1.60 (m, 1H), 1.47 (d, $J = 6.4$ Hz, 3H), 1.12 (d, $J = 6.4$ Hz, 3H), 1.09 (d, $J = 6.4$ Hz, 3H), 0.88 – 0.84 (m, 4H).

FTIR (neat, cm^{-1}): ν_{max} 3416, 2976, 2039, 1989, 1954, 1694, 1614, 1435, 1381, 1223, 1132, 1032.

MS (ESI): $m/z = 389.16$ $[\text{M} + \text{Na}]^+$.

HRMS (EI): Calculated for $\text{C}_{15}\text{H}_{18}\text{O}_7\text{FeNa}$ $[\text{M} + \text{Na}]^+$: 389.0300; found: 389.0304.

Tricarbonyl[(4S,5S,Z)-3-((2E,4E)-hexa-2,4-dien-1-ylidene)-4-hydroxy-5-methyldihydrofuran-2(3H)-one]iron (29)

Potassium *tert*-butoxide (524 μL , 5.24 mmol) was slowly added to a solution of diol (**28**) (1.92 g, 5.24 mmol) in anhydrous THF (15 mL) under nitrogen at 0°C . The reaction mixture was left to stir at 0°C for 30 minutes. The reaction was then quenched with saturated ammonium chloride and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined, washed with brine, dried over MgSO_4 , and filtered. The solvent was removed under reduced pressure to obtain lactone (**29**) as a yellow oil (1.57 g, 90%).

^1H NMR (400 MHz, CDCl_3) δ 6.37 (d, $J = 11.2$ Hz, 1H), 5.34 (dd, $J = 6.8, 4.8$ Hz, 1H), 5.15 (dd, $J = 7.0, 4.8$ Hz, 1H), 4.65 – 4.49 (m, 2H), 3.11 – 3.03 (m, 1H), 1.94 – 1.87 (m, 1H), 1.49 (d, $J = 6.4$ Hz, 3H), 1.40 (d, $J = 6.4$ Hz, 3H).

MS (ESI): $m/z = 335.05$ $[\text{M} + \text{H}]^+$; 357.13 $[\text{M} + \text{Na}]^+$.

HRMS (EI): Calculated for $\text{C}_{14}\text{H}_{15}\text{O}_6\text{Fe}$ $[\text{M} + \text{H}]^+$: 335.0218; found: 335.0210;

Calculated for $\text{C}_{14}\text{H}_{14}\text{O}_6\text{FeNa}$ $[\text{M} + \text{Na}]^+$: 357.0037; found: 357.0030.

Methyl 2-((2-(trimethylsilyl)ethoxy)methoxy)benzoate¹⁰¹ (31)

SEMCl (1.02 mL, 5.79 mmol) was added to a mixture of methyl salicylate (500 μ L, 3.86 mmol) and DIPEA (2.02 mL, 11.6 mmol) in anhydrous dichloromethane (12 mL) at 0°C. The reaction was warmed to room temperature and stir for 18 hours. Water (10 mL) was then added to quench the reaction, and the mixture was extracted with dichloromethane (3 x 10 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (3% Ethyl acetate/Hexane) to give benzoate (**31**) as a colourless oil solid (1.03 g, 95%). Spectral data for compound (**31**) corresponded to the values reported in the literature.¹⁰¹

¹H NMR (400 MHz, CDCl₃) δ 7.77 (dd, J = 7.8, 1.8 Hz, 1H), 7.43 (ddd, J = 8.5, 7.3, 1.8 Hz, 1H), 7.22 (dd, J = 8.4, 0.8 Hz, 1H), 7.02 (td, J = 7.6, 0.8 Hz, 1H), 5.30 (s, 2H), 3.88 (s, 3H), 3.81 (t, J = 8.4 Hz, 2H), 0.96 (t, J = 8.2 Hz, 2H), 0.00 (s, 9H).

¹³C NMR (100 MHz, CDCl₃) δ 166.7, 156.9, 133.3, 131.4, 121.5, 121.4, 116.4, 93.6, 66.6, 52.0, 18.1, -1.4.

2-((2-(Trimethylsilyl)ethoxy)methoxy)benzoic acid¹⁰² (32)

The mixture of benzoate (**31**) (1.03 g, 3.65 mmol) and lithium hydroxide (105 mg, 4.38 mmol) in THF : methanol : water (3 : 1 : 1, 10 mL) was stirred at room temperature for 18 hours. The reaction mixture was then acidified with 2M HCl till pH 4 – 5 was achieved, and was extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, and filtered. The solvent

was removed under reduced pressure to give acid (**32**) as a yellow oil (878 mg, 90%).

Spectral data for compound (**32**) corresponded to the values reported in the literature.¹⁰²

¹H NMR (400 MHz, CDCl₃) δ 8.18 (dd, J = 7.8, 1.8 Hz, 1H), 7.54 (ddd, J = 8.5, 7.3, 1.8 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.17 (td, J = 7.6, 0.8 Hz, 1H), 5.46 (s, 2H), 3.82 (t, J = 8.4 Hz, 2H), 0.97 (t, J = 8.2 Hz, 2H), 0.00 (s, 9H).

¹³C NMR (100 MHz, CDCl₃) δ 165.7, 156.4, 135.1, 133.8, 123.1, 118.4, 115.2, 94.5, 68.0, 18.2, -1.3.

Methyl 2-((4-methoxybenzyl)oxy)benzoate¹⁰³ (34**)**

PMBCl (630 μ L, 4.63 mmol) was added to a mixture of methyl salicylate (500 μ L, 3.86 mmol) and potassium carbonate (799 mg, 5.79 mmol) in anhydrous acetone (9 mL) and left to reflux for 18 hours. The mixture was then allowed to cool to room temperature before adding saturated ammonium chloride (10 mL) to quench the reaction. The mixture was extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (5% Ethyl acetate/Hexane) to obtain benzoate (**34**) (815 mg, 78%). Spectral data for compound (**34**) corresponded to the values reported in the literature.¹⁰³

¹H NMR (400 MHz, CDCl₃) δ 7.79 (dd, J = 7.6, 2.0 Hz, 1H), 7.41 – 7.37 (m, 3H), 6.99 – 6.037 (m, 2H), 6.89 (dd, J = 6.8, 2.0 Hz, 2H), 5.08 (s, 2H), 3.86 (s, 3H), 3.77 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 166.8, 159.3, 158.2, 133.4, 131.7, 128.8, 128.5, 120.9, 120.5, 114.1, 113.9, 70.5, 55.2, 51.9.

2-((4-Methoxybenzyl)oxy)benzoic acid¹⁰⁴ (35)

The mixture of ester (34) (815 mg, 2.99 mmol) and sodium hydroxide (144 mg, 3.59 mmol) in dioxane : water (1 : 1, 9 mL) was heated for reflux for 18 hours. The reaction was then acidified with 2M HCl till pH 4 – 5 was achieved, and was extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure to give acid (35) as a yellow oil (732 mg, 95%).

¹H NMR (400 MHz, CDCl₃) δ 8.17 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.55 (ddd, *J* = 8.5, 7.3, 1.7 Hz, 1H), 7.37 – 7.34 (m, 2H), 7.15 – 7.10 (m, 2H), 6.95 – 6.92 (m, 2H), 5.21 (s, 2H), 3.81 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 165.6, 160.4, 157.5, 135.1, 133.8, 129.9, 126.3, 122.4, 118.2, 114.6, 113.3, 72.2, 55.4.

2-(3-Hydroxypentan-3-yl)benzoic acid (39)

Following a reported procedure,¹⁰⁵ ethyl magnesium bromide (1.24 mL, 3.71 mmol) was slowly added to a mixture of phthalic anhydride (500 mg, 3.38 mmol) and copper bromide (33.9 mg, 0.24 mmol) in THF (5 mL) at -20°C. The mixture was left to stir overnight at -20°C. The reaction was then allowed to warm to room temperature and was acidified with 2M HCl till pH2 was achieved. The mixture was extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica to give benzoic acid (39) as a white solid (721 mg, 10%).

¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.66 (td, *J* = 7.6, 1.2 Hz, 1H), 7.50 (td, *J* = 7.4, 1.2 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 2.10 (dq, *J* = 14.8, 7.4 Hz, 2H), 1.92 (dq, *J* = 14.8, 7.4 Hz, 2H), 0.71 (t, *J* = 7.4 Hz, 6H).

¹³C NMR (MHz, CDCl₃) δ 170.6, 152.1, 134.0, 129.0, 127.4, 125.7, 121.2, 91.0, 31.5, 7.66.

FTIR (neat, cm⁻¹): ν_{max} 3466, 1776, 1454, 1377, 1285, 1057.

MS (ESI): *m/z* = 191.23 [M – H₂O]⁺.

HRMS (EI): Calculated for C₁₂H₁₅O₂ [M – H₂O]⁺: 191.1072; found: 191.1044.

Methyl 2-iodobenzoate¹⁰⁶ (41)

A mixture of 2-iodobenzoic acid (10.32 g, 41.6 mmol) and concentrated sulfuric acid (5 mL) in methanol (120 mL) was left to reflux until no more starting material was detected by TLC analysis. The mixture was then cooled to room temperature, and saturated aqueous Na₂CO₃ was added till pH14 was achieved. The mixture was extracted with ethyl acetate (3 x 20 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure to obtain ester (**41**) as a colourless oil (10.72 g, 98%). Spectral data for compound (**41**) corresponded to the values reported in the literature.¹⁰⁶

¹H NMR (500 MHz, CDCl₃) δ 7.99 (d, *J* = 7.5 Hz, 1H), 7.80 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.15 (td, *J* = 7.8, 1.5 Hz, 1H), 3.93 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 167.1, 141.4, 135.3, 132.8, 131.1, 128.0, 94.2, 52.6.

Methyl 2-(prop-1-yn-1-yl)benzoate¹⁰⁷ (42)

A balloon of gaseous propyne was added to a mixture of ester (**41**) (1.24 g, 4.73 mmol, 1.0 eq.), PdCl₂(PPh₃)₂ (166 mg, 0.237 mmol, 5 mol%) and copper iodide (45.1 mg, 0.237 mmol, 5 mol%) in anhydrous DMF (15 mL) under inert atmosphere. DIPEA (990 μ L, 5.68 mmol, 1.2 eq.) was then slowly added to the reaction mixture and left to stir at room temperature for 3 hours. Saturated aqueous ammonium chloride (5 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were then extracted with water (3 x 20 mL), washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (5% Ethyl acetate/Hexane) to obtain alkyne (**42**) as a colourless oil (711 mg, 86%). Spectral data for compound (**42**) corresponded to the values reported in the literature.¹⁰⁷

¹H NMR (400 MHz, CDCl₃) δ 7.89 (dd, J = 8.0, 1.2 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.42 (td, J = 7.6, 1.6 Hz, 1H), 7.31 (td, J = 7.6, 1.2 Hz, 1H), 3.92 (s, 3H), 2.13 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 167.0, 134.4, 131.9, 131.7, 130.3, 127.3, 124.7, 91.6, 78.5, 52.3, 4.9.

Methyl 2-allylbenzoate¹⁰⁸ (**43**)

Following a reported procedure,⁹⁰ bromobutane (7.77 mL, 72.4 mmol, 2.0 eq.) was slowly added to a mixture of magnesium turnings (2.11 g, 86.8 mmol, 2.4 eq.) and an iodine crystal in THF (85 mL). The mixture was stirred for 15 minutes before cooling to -40°C. Ester (**41**) (9.48 g, 36.2 mmol, 1.0 eq.) was slowly added to the mixture and was left to stir at -40°C for 1.5 hours. A freshly prepared mixture of LiCl (3.07 g, 72.4 mmol, 2.0 eq.) and copper cyanide (3.24 g, 36.2 mmol, 1.0 eq.) in THF (210 mL) was cannulated into the mixture, and stirred for another 30 minutes before a slow addition

of allyl bromide (12.5 mL, 144.7 mmol, 4.0 eq.). The mixture was left to stir at -40°C for 15 minutes before quenching with aqueous NH₄OH. The mixture was warmed to room temperature before filtering over Celite®. The filtrate was extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (3% Ethyl acetate/Hexane) to obtain alkene (**43**) as a colourless oil (6.12 g, 96%). Spectral data for compound (**43**) corresponded to the values reported in the literature.¹⁰⁸

¹H NMR (400 MHz, CDCl₃) δ 7.87 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.44 (td, *J* = 7.5, 1.4, 1H), 7.29 – 7.25 (m, 2H), 6.01 (ddt, *J* = 16.7, 10.2, 6.4 Hz, 1H), 5.05 – 4.99 (m, 2H), 3.88 (s, 3H), 3.76 (d, *J* = 6.4 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃) δ 168.2, 141.7, 137.5, 132.2, 131.1, 130.7, 129.9, 126.3, 115.7, 52.1, 38.5.

Methyl 2-propylbenzoate¹⁰⁹ (44**)**

A balloon of gaseous hydrogen was added to a mixture of alkyne (**42**) (711 mg, 4.08 mmol) and palladium on carbon (43.4 mg, 0.408 mmol) in degassed methanol (12 mL) under inert atmosphere. The reaction was left to stir overnight at room temperature. The mixture was then filtered through Celite® after quenching with a stream of nitrogen gas into the solution. The solvent was evaporated under vacuum to obtain ester (**44**) as a yellow oil (698 mg, 96%).

Alternatively, a balloon of gaseous hydrogen was added to a mixture of alkene (**43**) (6.12 g, 34.7 mmol) and palladium on carbon (369 mg, 3.47 mmol) in degassed methanol (110 mL) under inert atmosphere. The reaction was left to stir overnight at

room temperature. The mixture was then filtered through Celite® after quenching with a stream of nitrogen gas into the solution. The solvent was evaporated under vacuum to obtain ester (**44**) as a yellow oil (6.03 g, 97%).

¹H NMR (500 MHz, CDCl₃) δ 7.85 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.41 (td, *J* = 7.5, 1.5 Hz, 1H), 7.26 – 7.22 (m, 2H), 3.89 (s, 3H), 2.92 (t, *J* = 7.8 Hz, 2H), 1.66 – 1.59 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 168.4, 144.6, 131.9, 131.1, 130.7, 129.7, 125.8, 52.0, 36.6, 25.0, 14.3.

2-Propylbenzoic acid¹¹⁰ (**45**)

A mixture of ester (**44**) (6.78, 38.0 mmol, 1.0 eq.) and lithium hydroxide (1.09 g, 45.7 mmol, 1.2 eq.) in dioxane: methanol: water (3: 1: 1, 110 mL) was left to reflux until no more starting material was detected by TLC analysis. The mixture was then cooled to room temperature and concentrated HCl was added till pH1 was achieved. The mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were then extracted with water (3 x 50 mL), washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure to obtain acid (**45**) as a white solid (6.23 g, quantitative yield). Spectral data for compound (**45**) corresponded to the values reported in the literature.¹¹⁰

m.p. 55 – 58°C.

¹H NMR (400 MHz, CDCl₃) δ 8.04 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.47 (td, *J* = 7.5, 1.4 Hz, 1H), 7.30 – 7.26 (m, 2H), 3.02 (t, *J* = 7.8 Hz, 2H), 1.72 – 1.62 (m, 2H), 0.99 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 173.4, 145.8, 132.9, 131.8, 131.4, 128.3, 126.0, 36.7, 25.0, 14.3.

2-Hydroxy-6-propylbenzoic acid¹¹¹ (46)

A balloon of gaseous oxygen was added to a solution of acid (**45**) (1.10 g, 6.70 mmol, 1.0 eq.), Pd(OAc)₂ (150 mg, 670 μmol, 10 mol%), KOAc (1.31 g, 13.4 mmol, 2.0 eq.), benzoquinone (724 mg, 6.70 mmol, 1.0 eq.) in *N,N*-dimethylacetamide (20 mL) under inert atmosphere. The solution was left to heat at 122°C for 24 hours. Minimal amount of ethyl acetate and a large amount of water was added to the mixture. The mixture was then filtered over a thick pad of Celite® and concentrated HCl was added to the filtrate till pH1 was achieved. The mixture was extracted with ethyl acetate (3 x 20 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (3% Ethyl acetate/Hexane) to obtain phenol (**46**) as a white solid (892 mg, 74%).

m.p. 105 – 107°C.

¹H NMR (400 MHz, CDCl₃) δ 11.15 (s, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 7.2 Hz, 1H), 2.97 (t, *J* = 7.8 Hz, 2H), 1.69 – 1.60 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 176.7, 163.7, 147.7, 135.6, 123.0, 116.1, 110.6, 38.5, 25.2, 14.3.

2-(Hydroxymethyl)-3-propylphenol¹¹² (47)

Lithium aluminium hydride (266 mg, 7.01 mmol) was slowly added to a solution of acid (**46**) (421 mg, 2.34 mmol) in anhydrous diethyl ether (10 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and left to stir overnight. The mixture was quenched with water (266 µL), NaOH (266 µL), and HCl till pH 2 sequentially. The mixture was then extracted with ethyl acetate (3 x 20 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure to obtain hydroxyphenol (**47**) as a colourless oil (311 mg, 80%).

¹H NMR (400 MHz, CDCl₃) δ 7.07 (t, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 2H), 4.85 (s, 2H), 2.52 (t, *J* = 7.8 Hz, 2H), 1.53 (tq, *J* = 7.6, 7.5 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 156.4, 141.3, 128.4, 123.0, 121.8, 114.3, 59.8, 35.3, 24.8, 14.1.

(2-Propyl-6-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)methanol (48**)**

Lithium aluminium hydride (254 mg, 6.70 mmol) was added to a solution of ester (**50**) (1.97 g, 4.47 mmol) in anhydrous Et₂O (15 mL) at 0°C. The reaction was then allowed to warm to room temperature and stirred for 2 hours. The mixture was quenched at 0°C with H₂O (254 µL), 2M NaOH (254 µL), H₂O (254 µL) sequentially. The white precipitate was filtered off, and the solvent of the filtrate was removed under reduced pressure. The crude product was purified by column chromatography (10% Ethyl acetate/Hexane) on silica to give benzyl alcohol (**48**) as a yellow oil (1.13 g, 85%).

¹H NMR (400 MHz, CDCl₃) δ 7.16 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 5.26 (s, 2H), 4.73 (s, 2H), 3.76 (t, *J* = 8.4 Hz, 2H), 2.68 (t, *J* = 7.8 Hz, 2H), 2.45 (s, 1H), 1.61 (tq, *J* = 7.5, 7.5 Hz, 2H), 0.99 – 0.94 (m, 5H), 0.00 (s, 9H).

¹³C NMR (100 MHz, CDCl₃) δ 156.5, 142.7, 128.7, 128.3, 123.6, 112.6, 93.7, 66.7, 57.2, 35.3, 25.2, 18.1, 14.2, -1.4.

MS (ESI): m/z = 297.10 [M + H]⁺; 319.17 [M + Na]⁺.

HRMS (EI): Calculated for C₁₆H₂₉O₃Si [M + H]⁺: 297.1886; found: 297.1898.

(2-((2-(Chloromethyl)-3-propylphenoxy)methoxy)ethyl)trimethylsilane (51)

Methanesulfonyl chloride (162 μL, 2.10 mmol) was slowly added to a mixture of benzyl alcohol (**48**) (565 mg, 1.91 mmol) and triethylamine (319 μL, 2.29 mmol) in anhydrous dichloromethane (6 mL) at 0°C. The reaction was maintained at 0°C for one hour, and water (3 mL) was added. The mixture was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were then washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure to obtain benzyl chloride (**51**) as a yellow oil (481 mg, 80%).

¹H NMR (400 MHz, CDCl₃) δ 7.20 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.86 (dd, J = 7.6, 0.4 Hz, 1H), 5.29 (s, 2H), 4.76 (s, 2H), 3.80 (t, J = 8.4 Hz, 2H), 2.70 (t, J = 8.0 Hz, 2H), 1.70 – 1.63 (m, 2H), 1.02 – 0.95 (m, 5H), 0.00 (s, 9H).

¹³C NMR (100 MHz, CDCl₃) δ 155.8, 143.5, 129.6, 124.8, 122.9, 112.0, 92.9, 66.5, 38.0, 34.8, 24.6, 18.2, 14.3, -1.3.

2-Propyl-6-((2-(trimethylsilyl)ethoxy)methoxy)benzyl methanesulfonate (52)

Methanesulfonyl chloride (162 μ L, 2.10 mmol) was slowly added to a mixture of benzyl alcohol (**48**) (565 mg, 1.91 mmol) and triethylamine (319 μ L, 2.29 mmol) in anhydrous diethyl ether (6 mL) at -25°C . The reaction was maintained at -25°C for one hour, and the white precipitate was filtered off. Water (3 mL) was added to the filtrate before extracting with dichloromethane (3 x 5 mL). The combined organic extracts were then washed with brine, dried over MgSO_4 , and filtered. The solvent was removed under reduced pressure to obtain mesylate (**52**) as a yellow oil (574 mg, 80%).

^1H NMR (400 MHz, CDCl_3) δ 7.28 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 5.41 (s, 2H), 5.27 (s, 2H), 3.77 (t, J = 8.4 Hz, 2H), 2.99 (s, 3H), 2.70 (t, J = 7.8 Hz, 2H), 1.68 – 1.56 (m, 2H), 1.00 – 0.94 (m, 5H), 0.00 (s, 9H).

(4S,5S,Z)-3-((2E,4E)-Hexa-2,4-dien-1-ylidene)-4-hydroxy-5-methyldihydrofuran-2(3o)-one (54**)**

A mixture of trimethyl *N*-oxide (2.89 g, 38.5 mmol) and lactone complex (**29**) (1.17 g, 3.50 mmol) in acetonitrile (11 mL) was stirred under nitrogen for 18 hours. The mixture was filtered through a pad of Celite[®], and the filtrate was concentrated under *vacuo*. The crude mixture was purified by column chromatography on silica (30% Ethyl acetate/Hexane) to obtain triene (**54**) as a yellow oil (471 mg, 69%).

^1H NMR (400 MHz, CDCl_3) δ 7.44 (dd, J = 13.4, 12.0 Hz, 1H), 6.88 (d, J = 11.6 Hz, 1H), 6.56 (dd, J = 13.0, 11.2 Hz, 1H), 6.28 (t, J = 13.4 Hz, 1H), 6.02 (dd, J = 11.0, 6.8 Hz, 1H), 4.73 (t, J = 5.8 Hz, 1H), 4.61 – 4.55 (m, 1H), 1.86 (d, J = 7.2 Hz, 3H), 1.70 (d, J = 6.4 Hz, 1H), 1.41 (d, J = 6.4 Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 169.3, 144.2, 144.1, 137.2, 131.7, 125.4, 125.0, 78.3, 71.6, 18.8, 14.4.

MS (ESI): $m/z = 195.17 [M + H]^+$; $217.21 [M + Na]^+$.

HRMS (EI): Calculated for $C_{11}H_{15}O_3 [M + H]^+$: 195.1021; found: 195.1017.

4-Methoxybenzyl 2-((4-methoxybenzyl)oxy)-6-propylbenzoate (**59**)

Potassium carbonate (1.94 g, 14.0 mmol) was added to a solution of hydroxybenzoic acid (**46**) (1.10 g, 6.10 mmol) in anhydrous DMF (18 mL). The mixture was heated at 80°C for 15 minutes before the addition of 4-methoxybenzyl chloride (2.20 g, 14.0 mmol). The reaction was left to stir at 80°C for 18 hours. Saturated aqueous ammonium chloride (10 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were then extracted with water (3 x 20 mL), washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (5% Ethyl acetate/Hexane) to obtain ester (**59**) as a colourless oil (2.32 g, 90%).

1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 4H), 7.20 (t, $J = 8.0$ Hz, 1H), 6.86 (d, $J = 8.8$ Hz, 2H), 6.81 – 6.76 (m, 4H), 5.26 (s, 2H), 4.97 (s, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 2.48 (t, $J = 7.8$ Hz, 2H), 1.54 (tq, $J = 7.5, 7.5$ Hz, 2H), 0.85 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 159.7, 159.4, 155.6, 141.3, 130.5, 130.2, 129.0, 128.9, 128.1, 124.3, 121.9, 113.9, 113.9, 110.1, 70.3, 66.8, 55.3, 35.5, 24.4, 14.1.

FTIR (neat, cm^{-1}): ν_{max} 2959, 2870, 2835, 1728, 1612, 1584, 1514, 1462, 1377, 1246, 1175, 1099, 1034, 826.

MS (ESI): $m/z = 421.01 [M + H]^+$; $443.27 [M + Na]^+$.

HRMS (EI): Calculated for $C_{26}H_{29}O_5 [M + H]^+$: 421.2015; found: 421.1987.

(2-((4-Methoxybenzyl)oxy)-6-propylphenyl)methanol (60)

Lithium aluminium hydride (628 mg, 16.6 mmol) was slowly added to a solution of ester (**59**) (2.32 g, 5.52 mmol) in anhydrous diethyl ether (20 mL) at 0°C. The reaction mixture was warmed to room temperature and left to stir overnight. The mixture was quenched with water (628 µL), NaOH (628 µL), and water (628 µL) sequentially. The mixture was filtered through Celite®, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica (5% Ethyl acetate/Hexane) to obtain lepidine (**60**) as a colourless oil (1.34 g, 85%).

¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, *J* = 8.8 Hz, 2H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.93 – 6.89 (m, 2H), 6.82 (t, *J* = 6.8 Hz, 2H), 5.01 (s, 2H), 4.73 (s, 2H), 3.80 (s, 3H), 2.66 (t, *J* = 7.8 Hz, 2H), 1.59 (tq, *J* = 7.5, 7.5 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 159.7, 157.7, 142.6, 129.2, 128.9, 128.5, 127.5, 122.7, 114.2, 109.7, 70.2, 57.6, 55.4, 35.4, 25.2, 14.2.

FTIR (neat, cm⁻¹): ν_{max} 3418, 2959, 2932, 2870, 1614, 1584, 1514, 1454, 1379, 1302, 1246, 1175, 1111, 1084, 1034, 822.

MS (ESI): *m/z* = 309.24 [M + Na]⁺.

HRMS (EI): Calculated for C₁₈H₂₂O₃Na [M + Na]⁺: 309.1467; found: 309.1505.

2-((2-((4-Methoxybenzyl)oxy)-6-propylbenzyl)oxy)pyridine (61)

A mixture of benzyl alcohol (**60**) (519 mg, 1.81 mmol), 2-chloropyridine (172 µL, 1.81 mmol), potassium hydroxide (339 mg, 6.04 mmol), and 18-crown-6 (24.0 mg,

0.091 mmol) in anhydrous toluene (3 mL) was heated at reflux for 1 hour using a Dean-Stark trap. The reaction was then allowed to cool to room temperature before removing the solvent under reduced pressure. The crude product was purified by column chromatography on silica (3% Ethyl acetate/Hexane) to obtain lepidine (**61**) as a colourless oil (589 mg, 89%).

¹H NMR (400 MHz, CDCl₃) δ 8.20 (dd, J = 5.2, 1.2 Hz, 1H), 7.54 (ddd, J = 8.5, 6.9, 1.7 Hz, 1H), 7.27 – 7.21 (m, 3H), 6.88 – 6.78 (m, 5H), 6.73 (d, J = 8.4 Hz, 1H), 5.51 (s, 2H), 5.01 (s, 2H), 3.76 (s, 3H), 2.68 (t, J = 7.8 Hz, 2H), 1.64 (tq, J = 7.4, 7.5 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 164.3, 159.2, 158.1, 147.0, 144.8, 138.5, 129.5, 129.4, 128.7, 123.7, 122.4, 116.6, 113.9, 111.5, 110.3, 70.3, 59.4, 55.4, 35.2, 25.0, 14.3.

FTIR (neat, cm⁻¹): $\nu_{\max}$ 2957, 2932, 2870, 1593, 1568, 1514, 1429, 1364.

MS (ESI): m/z = 386.19 [M + Na]⁺.

HRMS (EI): Calculated for C₂₃H₂₆NO₃ [M + H]⁺: 364.1913; found: 364.1920.

2-((2-((4-Methoxybenzyl)oxy)-6-propylbenzyl)oxy)-4-methylquinoline (**67**)

A mixture of benzyl alcohol (**60**) (562 mg, 1.96 mmol), 2-chlorolepidine (348 mg, 1.96 mmol), potassium hydroxide (363 mg, 6.48 mmol), and 18-crown-6 (25.9 mg, 0.098 mmol) in anhydrous toluene (5 mL) was heated at reflux for 1 hour using a Dean-Stark trap. The reaction was then allowed to cool to room temperature before removing the solvent under reduced pressure. The crude product was purified by column chromatography on silica (3% Ethyl acetate/Hexane) to obtain lepidine (**67**) as a colourless oil (716 mg, 85%).

¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.83 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.60 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.37 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.24 – 7.21 (m, 3H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 6.72, 1H), 6.67 – 6.65 (m, 2H), 5.71 (s, 2H), 4.99 (s, 2H), 3.66 (s, 3H), 2.73 (t, *J* = 7.8 Hz, 2H), 2.55 (d, *J* = 0.8 Hz, 3H), 1.66 (tq, *J* = 7.6, 7.6 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 162.3, 159.1, 158.1, 146.8, 146.5, 144.8, 129.4, 129.3, 129.2, 128.6, 127.9, 125.5, 123.9, 123.7, 123.6, 122.4, 113.8, 113.5, 110.3, 70.2, 59.2, 55.2, 35.2, 25.1, 18.7, 14.3.

FTIR (neat, cm⁻¹): ν_{max} 2959, 2932, 2870, 2835, 1738, 1614, 1584, 1574, 1514, 1468, 1396, 1329, 1312, 1246, 1184, 1130, 1111, 1088, 1040, 1018, 853, 822, 760.

MS (ESI): *m/z* = 428.06 [M + H]⁺.

HRMS (EI): Calculated for C₂₈H₃₀NO₃ [M + H]⁺: 428.2226; found: 428.2202.

***tert*-Butyldimethylsilyl 2-((*tert*-butyldimethylsilyl)oxy)-6-propylbenzoate (**69**)**

tert-Butyldimethylsilyl chloride (258 mg, 1.71 mmol) was added to a mixture of hydroxybenzoic acid (**46**) (103 mg, 0.572 mmol) and imidazole (97.3 mg, 1.43 mmol) in anhydrous DMF (2 mL) at 0°C. The reaction was allowed to warm to room temperature and left to stir for 16 hours. Saturated aqueous ammonium chloride (5 mL) was added to quench the reaction. The mixture was then extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were then extracted with water (3 x 10 mL), washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (5% Ethyl acetate/Hexane) to obtain aryl (**69**) as a colourless oil (198 mg, 85%).

¹H NMR (400 MHz, CDCl₃) δ 7.12 (t, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 2.57 – 2.53 (m, 2H), 1.66 – 1.56 (m, 2H), 0.97 (s, 9H), 0.95 (s, 9H), 0.39 (s, 6H), 0.23 (s, 6H).

MS (ESI): *m/z* = 431.19 [M + Na]⁺.

HRMS (EI): Calculated for C₂₂H₄₁O₃Si₂ [M + H]⁺: 409.2594; found: 409.2592.

***tert*-Butyl((2-((*tert*-butyldimethylsilyl)oxy)-6-propylbenzyl)oxy)dimethylsilane
(70)**

tert-Butyldimethylsilyl chloride (1.23 g, 8.16 mmol) was added to a mixture of hydroxyphenol (**47**) (452 mg, 2.72 mmol) and imidazole (463 mg, 6.80 mmol) in anhydrous DMF (8 mL) at 0°C. The reaction was allowed to warm to room temperature, and left to stir for 16 hours. Saturated aqueous ammonium chloride (5 mL) was added to quench the reaction. The mixture was then extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were then extracted with water (3 x 10 mL), washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (5% Ethyl acetate/Hexane) to obtain aryl (**70**) as a colourless oil (927 mg, 86%).

¹H NMR (400 MHz, CDCl₃) δ 7.07 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 4.78 (s, 2H), 2.70 (t, *J* = 8.0 Hz, 2H), 1.70 – 1.60 (m, 2H), 1.02 – 0.98 (m, 12H), 0.91 (s, 9H), 0.23 (s, 6H), 0.10 (s, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 153.7, 144.9, 129.1, 128.2, 122.4, 116.5, 56.6, 34.9, 26.1, 26.0, 25.9, 24.7, 18.5, 14.5, -3.9, -5.1.

FTIR (CH₂Cl₂, cm⁻¹): ν_{max} 2957, 2931, 2857, 1582, 1464, 1268, 1268, 1052.

MS (ESI): *m/z* = 395.23 [M + H]⁺, 417.26 [M + Na]⁺.

HRMS (EI): Calculated for C₂₂H₄₂O₂Si₂Na [M + Na]⁺: 417.2621; found: 417.2614.

4H-Spiro[benzo[d][1,3]dioxine-2,1'-cyclohexane]¹¹³ (76)

A mixture of cyclohexanone (1.60 mL, 15.4 mmol), salicylic alcohol (2.68 g, 21.6 mmol), trimethyl orthoformate (1.69 mL, 15.4 mmol), amberlyst-15 in anhydrous toluene (45 mL) was left to stir for 16 hours at room temperature. The mixture was then filtered over a pad of Celite®, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica (3% Ethyl acetate/Hexane) to obtain ketal (**76**) as a colourless oil (2.41 g, 76%). Spectral data for compound (**76**) corresponded to the values reported in the literature.¹¹³

¹H NMR (400 MHz, CDCl₃) δ 7.14 (ddd, *J* = 8.1, 1.6, 0.8 Hz, 1H), 6.94 (d, *J* = 6.8 Hz, 1H), 6.90 – 6.83 (m, 2H), 4.82 (s, 2H), 1.81 (t, *J* = 6.2 Hz, 4H), 1.70 – 1.57 (m, 4H), 1.51 – 1.45 (m, 2H).

¹³C NMR (100 MHz, CDCl₃) δ 151.2, 128.1, 124.7, 120.3, 120.1, 117.2, 99.8, 60.3, 33.6, 25.5, 22.6.

2-((Cyclohexyloxy)methyl)phenol (78)

DIBAL (605 μL, 1 M in toluene) was slowly added to a solution of ketal (**76**) (103 mg, 0.504 mmol) in anhydrous dichloromethane (1.5 mL) at 0°C under nitrogen. The reaction mixture was warmed to room temperature and stirred for 16 hours. Methanol (2 mL) was added to quench the excess DIBAL. Saturated aqueous Rochelle's salt (5 mL) was added, and the mixture was stirred for another 2 hours. The mixture was

then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (3% Ethyl acetate/Hexane) to obtain phenol (**78**) as a colourless oil (67.1 mg, 65%).

¹H NMR (400 MHz, CDCl₃) δ 8.01 (s, 1H), 7.18 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.82 (t, J = 7.4 Hz, 1H), 4.74 (s, 2H), 3.48 – 3.42 (m, 1H), 1.95 – 1.92 (m, 2H), 1.76 – 1.72 (m, 2H), 1.53 – 1.49 (m, 1H), 1.44 – 1.36 (m, 2H), 1.33 – 1.22 (m, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 156.7, 129.3, 127.8, 122.8, 119.8, 116.6, 77.6, 69.7, 31.9, 25.7, 23.9.

***o*-Cresol¹¹⁴**

o-Cresol, a by-product obtained in the reduction of ketal (**76**) (103 mg, 0.504 mmol) using DIBAL (605 μ L, 1 M in toluene) in anhydrous dichloromethane (1.5 mL) at 0°C under nitrogen, was obtained as a colourless oil (15 mg). Spectral data for this compound corresponded to the values reported in the literature.¹¹⁴

¹H NMR (400 MHz, CDCl₃) δ 7.13 – 7.06 (m, 2H), 6.84 (t, J = 7.4 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 4.73 (s, 1H), 2.25 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 153.9, 131.2, 127.3, 123.8, 120.9, 115.0, 15.8.

Methyl 3-(2-methyl-4H-benzo[d][1,3]dioxin-2-yl)propanoate (81**)**

A mixture of methyl levulinate (1.50 mL, 12.1 mmol), salicylic alcohol (2.11 g, 16.9 mmol), trimethyl orthoformate (1.18 mL, 12.1 mmol), amberlyst-15 in anhydrous toluene (36 mL) was left to stir for 16 hours at room temperature. The mixture was then filtered over a pad of Celite[®], and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica (3% Ethyl acetate/Hexane) to obtain ketal (**81**) as a colourless oil (190 mg, 6%).

¹H NMR (400 MHz, CDCl₃) δ 7.15 (td, $J = 7.7, 1.0$ Hz, 1H), 6.96 (d, $J = 6.4$ Hz, 1H), 6.89 (td, $J = 7.4, 0.8$ Hz, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 4.88 (d, $J = 15.2$ Hz, 1H), 4.79 (d, $J = 15.2$ Hz, 1H), 3.67 (s, 3H), 2.54 (t, $J = 7.8$ Hz, 2H), 2.21 – 2.16 (m, 2H), 1.48 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 174.1, 151.1, 128.3, 124.7, 120.6, 119.4, 117.2, 100.0, 60.8, 51.8, 34.2, 28.3, 21.9.

2-Isopentylphenol¹¹⁵ (**82**)

DIBAL (1.64 mL, 1.64 mmol) was slowly added to a solution of ketal (**81**) (125 mg, 529 μ mol) in anhydrous dichloromethane (1.0 mL) at -78°C under nitrogen. The reaction mixture was stirred for 1 hour at -78°C before warming to room temperature and stirred for another 16 hours. Methanol (1.0 mL) was added to quench the excess DIBAL. Saturated aqueous Rochelle's salt (2.0 mL) was added, and the mixture was stirred for another 2 hours. The mixture was then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (3% Ethyl acetate/Hexane) to obtain

phenol (**82**) as a colourless oil (31.2 mg, 48%). Spectral data for compound (**82**) corresponded to the values reported in the literature.¹¹⁵

¹H NMR (400 MHz, CDCl₃) δ 7.12 (d, J = 7.2 Hz, 1H), 7.07 (td, J = 7.7, 1.2 Hz, 1H), 6.86 (td, J = 7.4, 0.8 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 4.66 (d, J = 1.2 Hz, 1H), 2.60 (t, J = 8.2 Hz, 2H), 1.66 – 1.58 (m, 1H), 1.53 – 1.47 (m, 2H), 0.95 (d, J = 6.4 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 153.5, 130.2, 128.9, 127.1, 121.0, 115.3, 39.1, 28.1, 27.9, 22.7.

2-(((5-Hydroxypentan-2-yl)oxy)methyl)phenol (83**)**

Lithium aluminium hydride (201 mg, 5.29 mmol) was slowly added to a mixture of aluminium trichloride (212 mg, 1.59 mmol) in anhydrous diethyl ether (3 mL) at 0°C. Maintaining at this temperature, to this mixture was added a solution of ketal (**81**) (125 mg, 529 mmol) in anhydrous ether (1 mL). The reaction was warmed to room temperature for 2 hours. The mixture was cooled to room temperature and was carefully quenched with ether and 2M HCl. The precipitate was then removed through Buchner filtration. The mixture was then extracted with diethyl ether (3 x 5 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (3% Ethyl acetate/Hexane) to obtain phenol (**83**) as a colourless oil (44.9 mg, 69%).

¹H NMR (400 MHz, CDCl₃) δ 7.72 (s, 1H), 7.20 (td, J = 7.8, 1.6 Hz, 1H), 7.00 (dd, J = 7.0, 1.2 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.83 (dd, J = 7.5, 1.2 Hz, 1H), 4.78 (d, J = 12.0 Hz, 1H), 4.66 (d, J = 12.4 Hz, 1H), 3.72 – 3.66 (m, 3H), 1.70 – 1.61 (m, 4H), 1.25 (d, J = 6.4 Hz, 3H).

Methyl 4-((2-hydroxybenzyl)oxy)pentanoate (**84**)

Trimethylsilyl trifluoromethanesulfonate (85 μ L, 0.467 mmol), borane dimethyl sulphide (8 μ L, 0.467 mmol) were added respectively to a solution of ketal (**81**) (92.0 mg, 0.389 mmol) in anhydrous dichloromethane (1.5 mL) at -78°C . The reaction was left to stir at -78°C for 2 hours before quenching with saturated sodium bicarbonate (3 mL). The mixture was then warmed to room temperature and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine, dried over MgSO_4 , and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica (15% Ethyl acetate/Hexane) to obtain phenol (**84**) as a colourless oil (64.9 mg, 70%).

^1H NMR (400 MHz, CDCl_3) δ 7.52 (s, 1H), 7.20 (td, $J = 7.7, 1.4$ Hz, 1H), 7.01 (d, $J = 7.2$ Hz, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 6.83 (td, $J = 7.4, 0.8$ Hz, 1H), 4.75 (d, $J = 12.4$ Hz, 1H), 4.63 (d, $J = 12.0$ Hz, 1H), 3.69 – 3.61 (m, 4H), 2.41 (td, $J = 7.3, 1.8$ Hz, 2H), 1.92 – 1.86 (m, 2H), 1.25 (d, $J = 6.0$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 174.0, 156.4, 129.5, 128.2, 122.7, 120.0, 116.7, 74.9, 70.1, 51.8, 31.4, 30.0, 19.3.

IR (neat) 3387, 2970, 1736, 1597, 1491, 1456, 1375, 1344, 1242, 1177, 1136, 1086, 1034, 756.

MS (ESI): $m/z = 239.11$ [$\text{C}_{13}\text{H}_{18}\text{O}_4 + \text{H}$] $^+$, 261.20 [$\text{C}_{13}\text{H}_{18}\text{O}_4 + \text{Na}$] $^+$.

HRMS (ESI): Calculated for $\text{C}_{13}\text{H}_{19}\text{O}_4$ [$\text{M} + \text{H}$] $^+$: 239.1283; found: 239.1281.

(2*S*,3*R*,*Z*)-4-((2*E*,4*E*)-Hexa-2,4-dien-1-ylidene)-2-methyl-5-oxotetrahydrofuran-3-yl acetate (85)

DMP (132 mg, 0.309 mmol) was added to a mixture of triene (**54**) (50 mg, 0.257 mmol) and pyridine (20 μ L, 0.257 mmol) in anhydrous dichloromethane (1 mL). The mixture was stirred for thirty minutes at room temperature before extracting with dichloromethane (3 x 3 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and filtered. The solvent was removed under reduced pressure to give the crude product as a yellow oil (25 mg, 50%). Due to lack of data, the stereochemistry of the acetate group is tentatively assigned in this configuration.

¹H NMR (400 MHz, CDCl₃) δ 7.45 (dd, J = 13.4, 11.2 Hz, 1H), 7.31 (d, J = 1.6 Hz, 1H), 7.15 (dd, J = 13.2, 11.2, 1H), 6.62 (d, J = 15.6 Hz, 1H), 6.34 (d, J = 15.6 Hz, 1H), 5.12 (dd, J = 10.2, 6.8 Hz, 1H), 2.31 (s, 3H), 1.63 (s, 1H), 1.48 (d, J = 6.8 Hz, 3H).

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