Toward the Synthesis of Rimarikiamide A

By

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Abstract

Rimarikiamide A is a linear diterpenoid marine natural product featuring an unusual taurine structural moiety. Rimarikiamide A was isolated from the sea sponge *Latrunculia brevis* found in the Rimariki Islands in northern New Zealand, and was shown to elicit low μM cytotoxicity against HL-60 cells. Unfortunately, only 400 μg of rimarikiamide A was isolated from 700 g of sea sponge, making the characterisation of the two chiral centres impossible by spectroscopic means. To explore the full potential of rimarikiamide A as a therapeutic agent, the molecule must be synthesised in a stereoselective manner or from a starting material of known stereochemistry, fully characterised, and tested for biological activity. A Barbier coupling of two terpene units is required early in the proposed synthesis of Rimarikiamide A, and previous attempts have failed to generate the desired linear product. In this work, the suitability of a titanium-mediated Barbier coupling was investigated, and proved successful for the generation of the desired linear product.

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List of Abbreviations

BAIB	(Diacetoxyiodo)benzene
CAM	Ceric ammonium molybdate
COSY	Correlated spectroscopy
DCC	*N*,*N*-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMF	Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)- pyrimidinone
DMSO	Dimethyl sulfoxide
FDA	Food and Drug Administration
HEK Cells	Human embryonic kidney cells
HL-60 Cells	Human promyelocytic leukemia cells
HMBC	Heteronuclear multiple bond correlation
HPLC	High performance liquid chromatography
HRESIMS	High-resolution electrospray ionisation mass spectrometry
HSQC	Heteronuclear single-quantum coherance
IBX	2-Iodoxybenzoic acid
IC_{50}	Half maximum inhibitory concentration
IR	Infra-red
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PMB	*para*-methoxybenzyl
SET	Single electron transfer
TBAF	Tetrabutylammonium fluoride
TBS	Tert-butyldimethylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl or (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
THF	Tetrahydrofuran
TLC	Thin-layer chromatography

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1. Introduction

1.1 Natural products in treatment of disease

1.1.1 Function of natural products

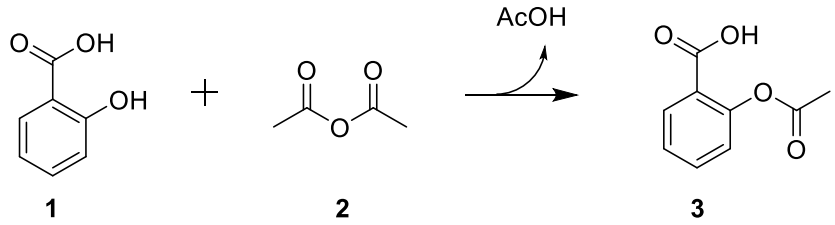
Natural products have played a vital role in the treatment of disease, and continue to provide medicinal chemists with inspiration for advancing modern drug discovery.[1] Natural products, or secondary metabolites, are not fundamental for survival but are produced by organisms to instil an evolutionary advantage over competitors or prey.[2] The generation of these compounds by the organism occurs through biosynthesis and typically, the first step in this process involves the breakdown of structurally complex molecules utilising catabolic pathways.[3] The products created during this process are reassembled to form important primary intermediates such as fatty acids, carbohydrates, peptides, and vitamins.[3] Primary intermediates are further functionalised into essential metabolites known as primary metabolites, which are often paramount for the survival of an organism.[3] Subsequent enzyme-mediated modification of primary metabolites leads to the generation of secondary metabolites (natural products). Natural products encompass several structural classes including polyketides, phenylpropanoids, alkaloids, and terpenoids.[4] These compounds are often structurally diverse and are capable of eliciting important biological responses; such examples are pheromones, anti-feedants, and cytotoxic agents. The biological relevance of these compounds has seen natural products make an invaluable contribution to the treatment of both infectious and cancerous disease.[1]

1.1.2 Natural products as drugs

Historically, natural products have provided an unrivalled solution to a plethora of diseases.[5] The earliest recorded use of natural products to treat ailments was in Mesopotamia (c.a. 2600 B.C.), through the creation of a variety of plant extracts such as those from poppy, cypress, myrrh, cedar, and liquorice.[6] All of the aforementioned plant extracts are still in use today for the treatment of conditions ranging from the common cold to parasitic infection.[6]

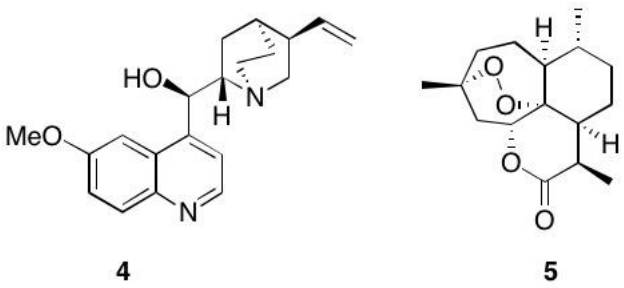
The origin of aspirin (**3**) provides a monumental example of natural product-based drug discovery.[7] Extracts obtained from the bark and leaves of the white willow tree (*Salix alba*) were used to treat fever and reduce pain for thousands of years.[7] The active ingredient of willow bark, salicin (**1**), was isolated in 1828 by Johann Buchner.[8] Salicin (**1**) was renamed salicylic acid by Raffaele Piria in 1838.[8] The acetylated version of salicylic acid was synthesised by the

Bayer Company in 1898, by reacting salicylic acid (**1**) with acetic anhydride (**2**) to form aspirin (**3**) (Scheme 1). Aspirin (**3**) provided a significantly more palatable alternative to salicylic acid without compromising the drug's efficacy.[8] The semi-synthetic route to aspirin (**3**) was commercialised by Bayer in 1899, and aspirin (**3**) has since become the most successful drug ever produced.[8]



*Scheme 1: Synthesis of aspirin (**3**) from salicylic acid (**1**)*

A more recent example of a natural product being successfully employed to combat disease is the use of artemisinin (**5**, Figure 1) to treat malaria. Before the discovery of artemisinin (**5**), the natural product quinine (**4**, Figure 1) was used as the frontline treatment of malaria until it was overtaken by synthetic derivatives in the 1930s.[9] Chloroquine was the most promising of these synthetic derivatives due to both its affordability and high efficacy.[10] However, prolonged over-use as a monotherapy instigated the rise of drug-resistance in malaria-endemic regions, and by 1960, North Vietnam and China were in dire need of an alternative.[9] The answer to this issue was found in an extract from the leaves of qinghao (*Artemisia annua L.*).[11] The bioactive compound present was isolated and identified in 1977 as artemisinin (**5**), a sesquiterpene lactone featuring an unusual peroxide bridge.[12] Since its discovery, both artemisinin (**5**) and its synthetic derivatives have shown success against both chloroquine resistant and multi-drug resistant *Plasmodium falciparum*, with few adverse side-effects.[13] To date, the World Health Organisation recognises artemisinin-based combination therapies as the gold-standard treatment of malaria.[14] The discovery of artemisinin (**5**) remains one of the most important in natural product history by reducing mortality rates globally by 20% and will continue to save millions of lives.[15]



4 **5**

*Figure 1: Structures of quinine (**4**) and artemisinin (**5**)*

1.1.3 Marine natural products

Terrestrial organisms are not the only source of natural products; marine environments contain a vast amount of undiscovered organisms and compounds.[16] From the years 1963-2013, there have been 24,662 isolated marine compounds recorded in literature.[17] Although most current therapeutics are terrestrial in origin, marine organisms tend to present a higher incidence of bioactivity compared to their terrestrial counterparts.[18] An example of this was found during a pre-clinical cytotoxicity screen conducted by the National Cancer Institute which showed that roughly 0.1% of terrestrial samples showed anti-tumour potential versus 1% of marine samples.[19]

By 2011 there were four U.S. Food and Drug Administration (FDA)-approved marine or marine-derived natural product drugs available on the market.[20] An early example of these drugs is cytarabine (**6**, Figure 2), a synthetic pyrimidine nucleoside derived from the Caribbean sea sponge (*Tethya crypta*) secondary metabolite spongothymidine.[21] Cytarabine (**6**) is a cytotoxic agent that inhibits both DNA polymerase and DNA synthesis through competition with intracellular deoxycytidine triphosphate. Cytarabine (**6**) was approved by the FDA in 1969 for the treatment of a range of acute leukemias.[22] Another marine-derived drug is ziconotide (**7**, Figure 2), a synthetic version of a 25-amino acid peptide, ω-conotoxin MVIIA, isolated from piscivorous marine snail (*Conus magus*) venom.[23] Ziconotide (**7**) is a potent analgesic, and unlike opioids, does not result in tolerance to the drug's effects.[24] The mechanism of action is through the reversible inhibition of N-type voltage-gated calcium channels involved in nociception, blocking the transmission of pain.[25] FDA approval for the management of severe chronic pain in terminally ill patients was granted in 2004.[26]

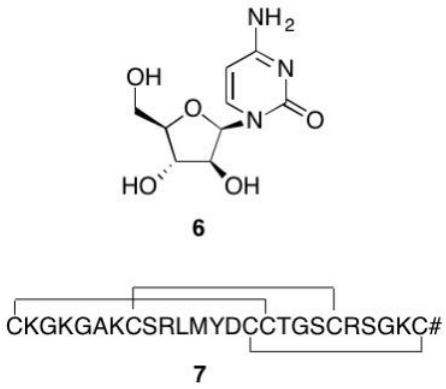


*Figure 2: Structures of cytarabine (**6**) and ziconotide (**7**)*

1.2 Rimarikiamide A

1.2.1 Isolation

The subject of the proposed research, rimarikiamide A (**8**, Figure 3), is a linear diterpenoid marine natural product featuring an unusual taurine structural moiety. Rimarikiamide A (**8**) was isolated from the sea sponge *Latrunculia brevis* found in the Rimariki Islands in northern New Zealand, by Nathaniel Dasyam working in the Keyzers research group at Victoria University of Wellington.[27]

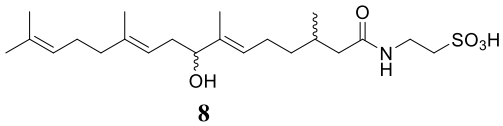


*Figure 3: Structure of rimarikiamide A (**8**)*

1.2.2 Structural elucidation

Partial structural elucidation of rimarikiamide A (**8**) was achieved using a combination of nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry. High-resolution electrospray ionisation mass spectroscopy (HRESIMS) revealed a m/z of 428.2469 and elemental analysis determined the chemical formula to be $C_{22}H_{39}NO_5S$, supporting the proposed chemical structure. Additionally, heteronuclear quantum coherence (HSQC) NMR experiments revealed the presence of 18 protonated and four non-protonated carbon atoms. Using 2D NMR experiments, it was determined that three of the non-protonated carbons were olefinic carbons (^{13}C NMR: 130.6, 134.9, and 137.4 ppm) while the remaining non-protonated

carbon was identified as a carbonyl carbon (^{13}C NMR 171.0 ppm). Finally, the linkage between the taurine group and the diterpenoid backbone was confirmed by a correlation observed between these two groups in the heteronuclear multiple bond correlation (HMBC) NMR spectrum. Unfortunately, only 400 μg of rimarikiamide A (**8**) was isolated from 700 g of sea sponge, making the characterisation of the two chiral centres impossible by spectroscopic means. The isolate was not crystalline so stereochemical identification by x-ray diffraction was not an option. These issues ultimately indicated the need for total synthesis in a stereoselective manner or from a starting material of known stereochemistry to define both relative and absolute configuration.

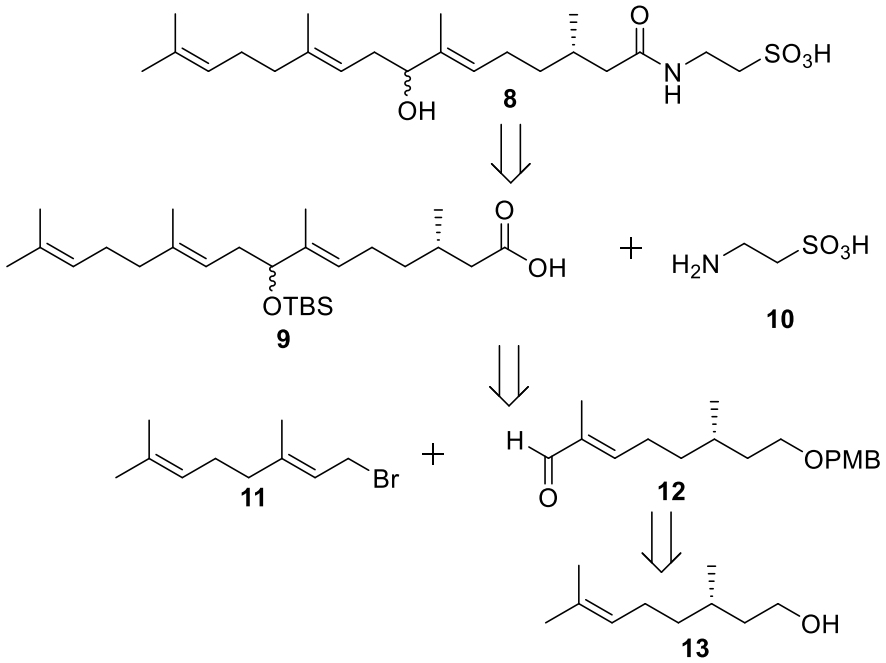
1.2.3 Preliminary biological evaluation

Preliminary biological evaluations were carried out on rimarikiamide A (**8**). These included cell toxicity assays using both HL-60, a human leukaemia cell line, and HEK cells, a healthy embryonic kidney cell line, to establish activity against cancerous cells versus healthy tissue. Mean IC_{50} values of 9.8 μM and 61.1 μM against these cell lines, respectively, were found. This difference in IC_{50} values indicates selective activity between cancerous and healthy cells and can be used to estimate a therapeutic index. A therapeutic index is a common measure of drug effectiveness, and can be established by the division of cytotoxicity by biological activity.[28] In the case of rimarikiamide A, the rough therapeutic index is calculated to be 6. This value suggests that rimarikiamide A may exhibit some specific *in vitro* anti-cancer activity, however further biological testing is needed to confirm this selectivity and establish the mode of action of rimarikiamide A (**8**).

1.3 Initial synthetic strategy

1.3.1 Previous retrosynthetic analysis

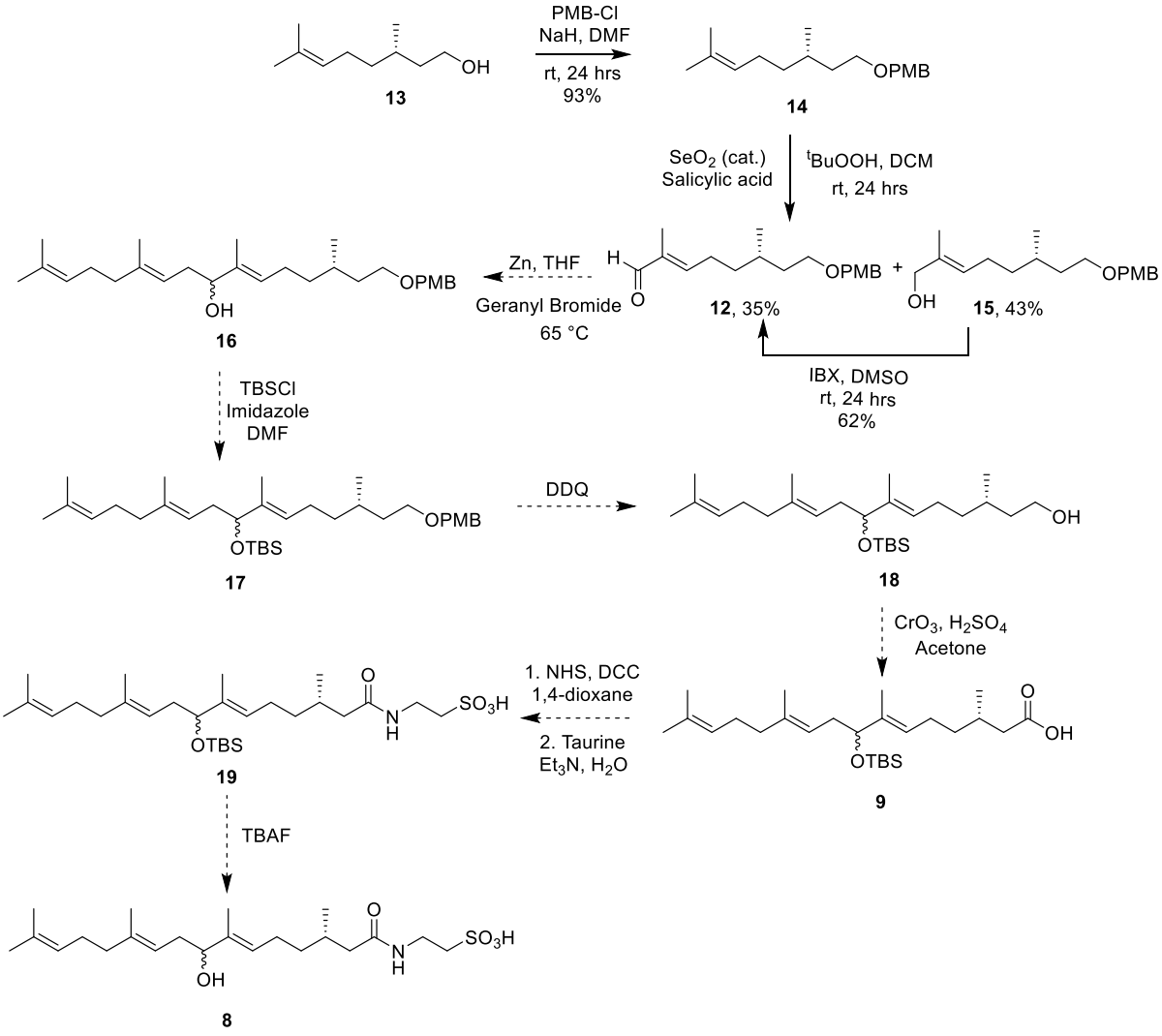
The previously proposed retrosynthetic analysis of the target diterpenoid **8** is outlined in Scheme 2.[29] It was anticipated that diterpenoid **8** could be synthesised via the coupling of taurine (**10**) to acid **9**.[30] Acid **9** could itself be prepared from PMB-protected aldehyde **12** through a Barbier coupling with geranyl bromide (**11**) followed by TBS protection, PMB deprotection, and the oxidation of the primary alcohol to the carboxylic acid.[31] Finally, PMB-protected α,β-unsaturated aldehyde **12** could be prepared from commercially available (*S*)-(-)-β-citronellol (**13**) through PMB protection followed by an allylic oxidation.[32]



*Scheme 2: Previous retrosynthetic strategy to rimarikiamide A (**8**)*

1.3.2 Previous forward synthesis

Previous attempts at the synthesis of rimarikiamide A (**8**) were carried out by several members of the Keyzers research group including Tessa Evans, Laura Walker, and Joel Cresser-Brown. The first step involved the protection of (*S*)-(-)-β-citronellol (**13**) with a *p*-methoxy benzyl ether (PMB) protecting group (Scheme 3). The reaction proceeded smoothly and gave the desired product **12** in excellent (93%) yield. Next, PMB-protected citronellol (**14**) was oxidised to give a mixture of the corresponding allylic alcohol (**15**, 43%) and α,β-unsaturated aldehyde (**12**, 35%) using selenium dioxide chemistry, as developed by Sharpless *et. al.*[32] The mixture was separated using standard chromatographic purification techniques and the remaining alcohol **15** was converted to aldehyde **12** using an IBX oxidation (62%). With the successful synthesis of aldehyde **12**, Walker and Cresser-Brown both published attempts at the coupling of aldehyde **12** with geranyl bromide (**11**) to give the desired diterpenoid backbone **16**. While these attempts were ultimately unsuccessful, a full description of the reaction conditions trialled is presented below. Had these attempts yielded any diterpenoid **16**, the newly formed alcohol **16** would have required protection with *tert*-butyldimethylsilyl ether (TBS) before continuing the synthesis. The TBS ether is easily introduced to the target molecule with TBS-Cl and imidazole, forming **17**. The selective deprotection of the primary hydroxyl group using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) would follow, yielding alcohol **18**. Following the deprotection step, the primary alcohol would be oxidised to form a carboxylic acid **9** using a Jones oxidation. Following a procedure reported by Ley *et. al.*, the carboxylic acid **9** would be activated through conversion to an *N*-hydroxysuccinic ester by reaction with *N*-hydroxysuccinimide.[30] The coupled product **19** will be formed via nucleophilic attack of taurine onto the activated ester. The final step in the initial proposed synthesis of rimarikiamide A (**8**) was the deprotection of the TBS protecting group using tetrabutylammonium fluoride (TBAF), to afford rimarikiamide A (**8**) as a mixture of two diastereomers which would be separated using HPLC.

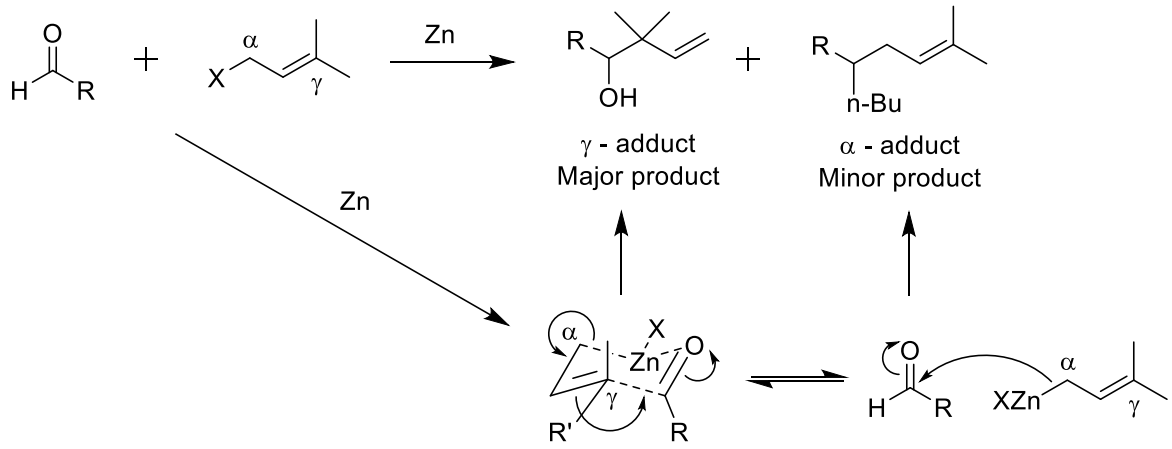


Scheme 3:Previous synthetic strategy

1.4 Previous work

1.4.1 Barbier coupling

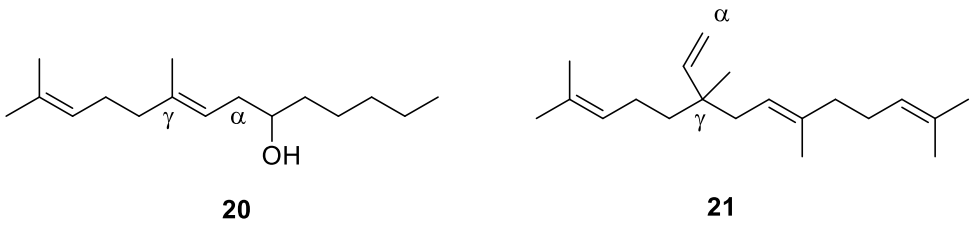
The Barbier reaction is a powerful tool for the synthesis of carbon-carbon bonds, as evidenced by the synthesis of several complex natural products.[33] This versatile technique featured as a key synthetic step in the previous attempts toward the synthesis of rimarikiamide A. Laura Walker of the Keyzers group previously carried out a Barbier coupling of geranyl bromide (**11**) with (S)-(-)-β-citronellol (**13**) using activated zinc.[34] Unfortunately, this produced a terminal (γ-) alkene instead of the desired linear (α-) product due to an allylic rearrangement (Scheme 4). This is a well-documented complication and is due to the divergent pathways available to zinc-mediated Barbier coupling reactions leading to mixtures of both the α- and γ-products .[35] According to the reaction mechanism, the α- adduct is formed through direct nucleophilic attack of the aldehyde with the Barbier reagent.[35] The γ- product however, is created through an allylic rearrangement of the Zn-intermediate followed by nucleophilic attack on the aldehyde.[35]



Scheme 4: Mechanism of formation of Barbier coupling adducts

Barbier reactions can be carried out in alcoholic solvents (instead of ether solvents) and are tolerant to water; though these benefits come at the cost of reactivity.[31] A recent investigation by Zhao *et. al.* sought to establish solvent effects for promoting the formation of the α- adduct using 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU).[36] Joel Cresser-Brown of the Keyzers group attempted the Barbier coupling following Zhao methodology using hexanal and geranyl bromide in DMPU as a model system.[36] Unfortunately, only the branched γ- self-

condensation product **21** was observed, instead of the desired α- adduct **20** (Figure 4).



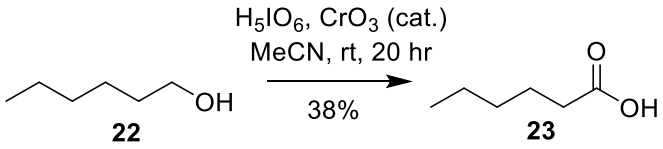
20 **21**

Figure 4: Observed Barbier coupling products

Other metals can also be used to promote the formation of the α- adduct such as indium and barium.[37] Cresser-Brown attempted the Barbier coupling using **12** and an allylbarium reagent. Cresser-Brown used 18-crown-6 ether as an additive, as it has been shown to increase α- adduct formation.[38] NMR spectroscopic analyses revealed that the reaction was unsuccessful and showed the presence of multiple byproducts that could not be purified.

1.4.2 Conversion of primary alcohol to acid

The conversion of a model primary alcohol to a carboxylic acid via Jones' oxidation was previously attempted by Laura Walker.[34] Hexanol (**22**) was used as a model substrate to generate hexanoic acid (**23**) in poor (37%) yield. Following this, Cresser-Brown attempted the same transformation using a catalytic chromium oxidation which also proved to be poorly yielding (38%, Scheme 5).[29] Attempts to oxidise (S)-(-)-β-citronellol (**13**) were attempted using similar methodologies with no indication of the acid being produced.



22 **23**

Scheme 5: Catalytic chromium oxidation

1.4.3 Taurine coupling

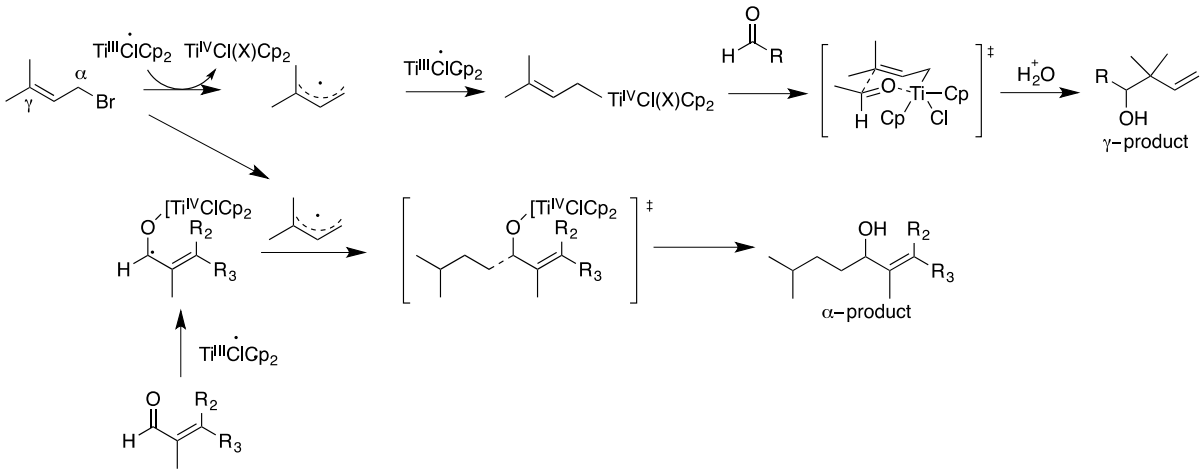
The taurine coupling step was previously investigated by Tessa Evans of the Keyzers research group using a model acid without success.[39] The first attempt used a procedure developed by Mirmura *et. al.* to generate an acid chloride using $SOCl_2$ followed by nucleophilic attack of taurine, which proved unsuccessful.[40] A subsequent attempt aiming to increase the electrophilicity of the carboxylic acid by transforming it to an oxybenzotriazole ester also failed due to the zwitterionic nature of taurine. Preliminary attempts by Joel Cresser-Brown on a model system utilising Ley methodology to form an *N*-hydroxysuccinic ester appeared moderately successful, though the methodology is yet to be attempted on the novel substrate.[30]

1.5 Proposed research

1.5.1 Titanium-mediated Barbier coupling

To circumvent the current issues surrounding the Barbier coupling alternative methodologies are needed to encourage α- selectivity. Allylation reactions are incredibly important in synthetic organic chemistry, and many different metals have been trialled in Barbier-type allylations.[41] Examples of metals that have been explored are Pb, Zn, Cr, Sn, In, and SmI_2, but unfortunately, using stoichiometric amounts of these can prove both costly and highly toxic.[33] Efforts have been made to investigate the potential of titanium, an abundant non-toxic equivalent.[42] Allyltitanium reagents have been proven to react with carbonyl compounds with significant diastereo-, enantio-, regio-, and chemoselectivities.[43]

Titanocene (III) complexes such as $[TiClCp_2]$ can be used to generate allyl radicals capable of reacting with a carbonyl containing compound.[44] Fortunately, $[TiClCp_2]$ is easily generated in-situ from commercially available $[TiCl_2Cp_2]$ and Mn dust in THF.[45] Allyltitanium Barbier-type coupling reactions are also capable of generating both α- and γ-adducts. However, there are many examples of α-prenylations that have shown unprecedented success through the employment of titanium, such as rosiridol and 12-hydroxysqualene.[33] The proposed reaction mechanism is similar to that of zinc-mediated Barbier coupling reactions, however, the α-adduct creation is through a prenyl radical pathway instead of a nucleophilic attack (Scheme 6).[46] Conversely, the γ- adduct is formed through the nucleophilic attack of the resulting organometallic prenyl-Ti^{IV} intermediate via a chair-like transition state similar to the one reported by Sato *et. al.*[47]

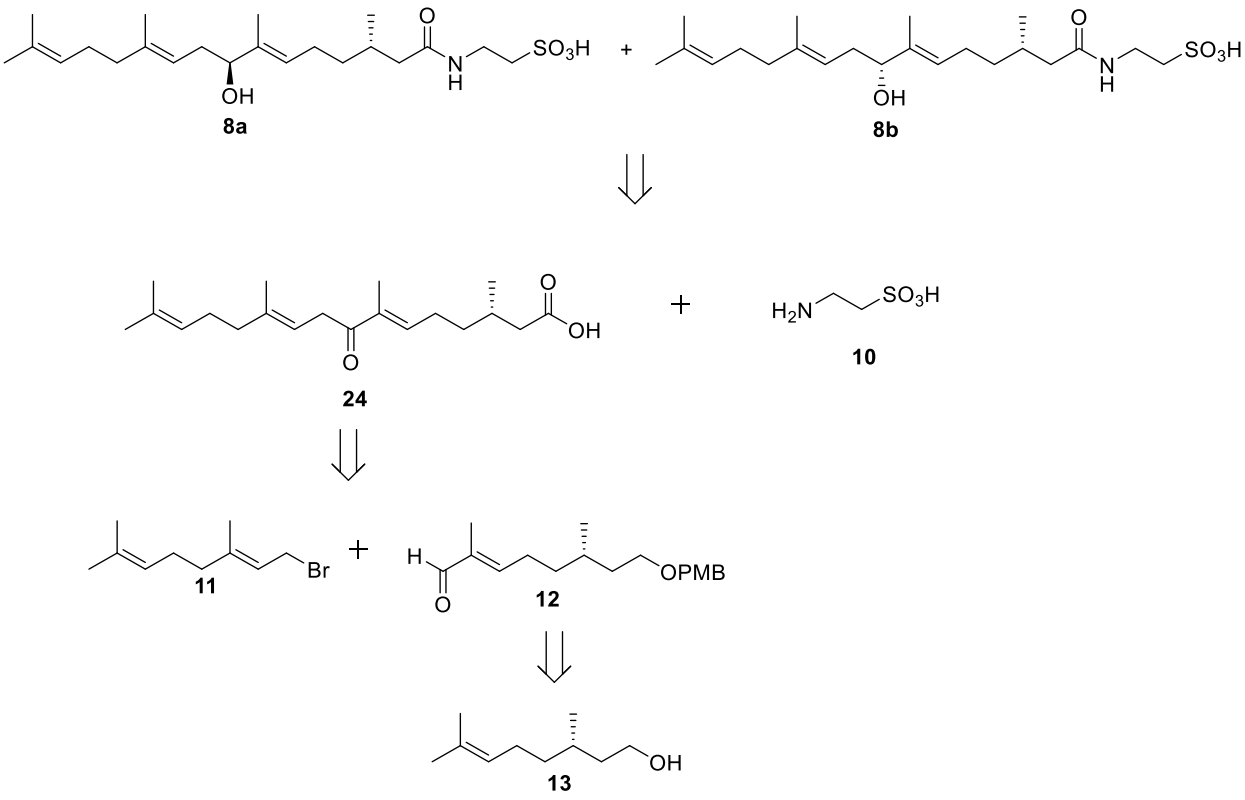


Scheme 6: Mechanism of formation of the α- and γ-prenylation products

For the synthesis of rimarikiamide A, the α,β-unsaturated aldehyde **12** will be coupled with geranyl bromide (**11**). Prior reports demonstrate that the prenyl-radical coupling will proceed fast and irreversibly due to conjugation, as the prenyl-radicals will not be trapped by [$TiClCp_2$] and will not form the prenyl-Ti^{IV} intermediate that encourages formation of the γ- adduct.[33] However, due to the α-substitution of substrate **12**, it is highly likely that steric hinderance will slow prenyl-radical coupling, causing a mixture of both α- and γ-adducts.[33] Fortunately, this will not be a large issue as any generation and purification of α- adducts will be considered a success in the scope of this project. The aim is to synthesise the natural product for structural and stereochemical confirmation, and a selective and high yielding route is a secondary consideration.

1.5.2 Retrosynthetic analysis

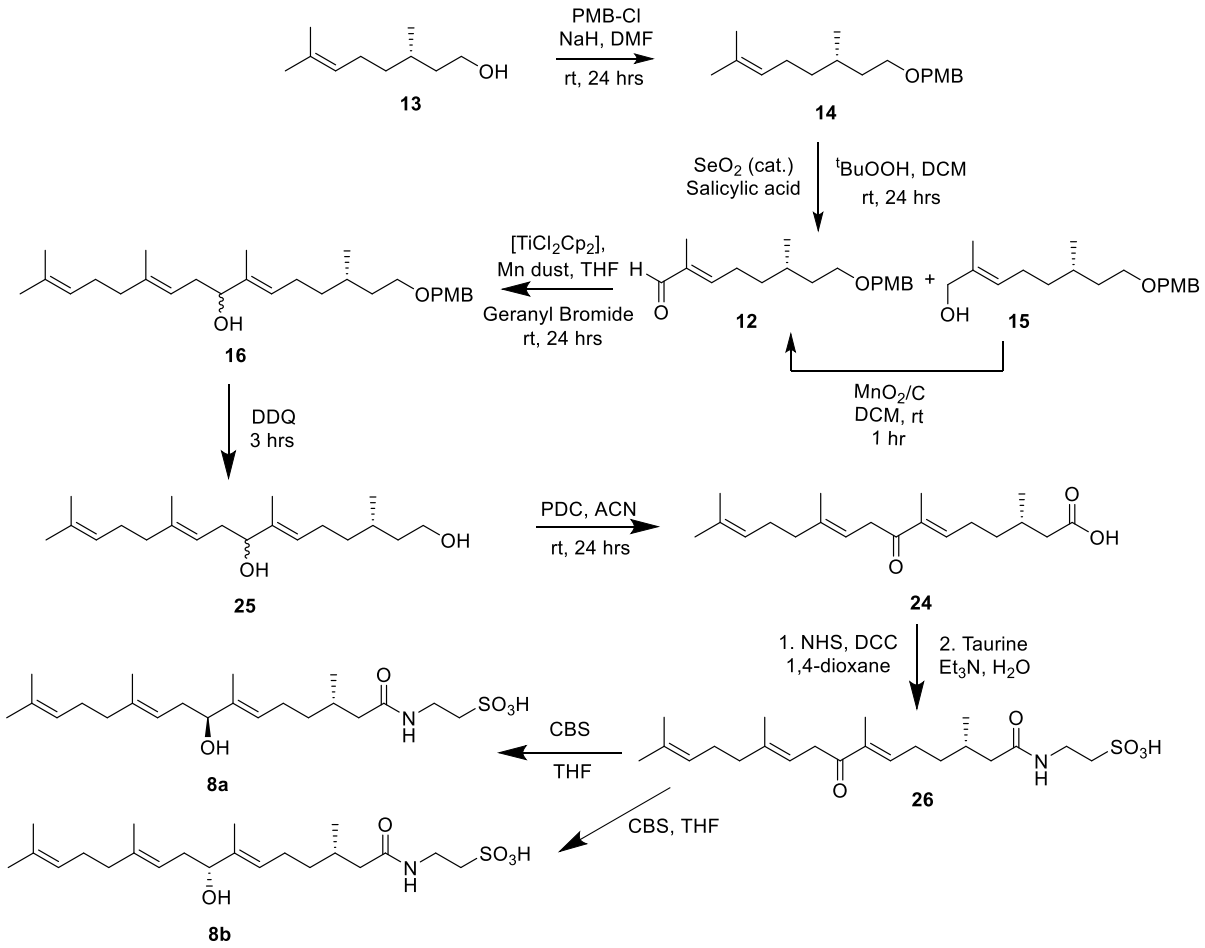
To synthesise rimarikiamide A (**8**), a retrosynthetic strategy was proposed whereby the taurine moiety (**10**) could be coupled to acid **24** using Ley methodology followed by the stereoselective reduction of the ketone functionality (Scheme 7).[30] The carboxylic acid **24**, could, in turn, be prepared through a global oxidation following the allyltitanium-mediated Barbier-type coupling of aldehyde **12** and commercially available geranyl bromide (**11**).[33] Finally, PMB-protected α,β-unsaturated aldehyde **11** could be prepared from commercially available (S)-(-)-β-citronellol (**13**) through PMB protection followed by a selenium dioxide oxidation.[32]



Scheme 7: Retrosynthesis of rimarikiamide A (8)

1.5.3 Alternate synthetic strategy

An alternative synthetic strategy was proposed whereby the first two synthetic steps remained the same as in the previous strategy (Scheme 8). The transformation from allylic alcohol **15** to aldehyde **12** would be achieved through a MnO_2 oxidation. Following this, the next step would be a Barbier coupling between α,β-unsaturated aldehyde **11** and commercially available geranyl bromide (**11**) to form the α-adduct **16**.[45] Next, the PMB protecting group of α-adduct **16** will be removed using the single electron oxidant, DDQ to afford the diol **25**.[48] The next step is the global oxidation of **25** via a PDC oxidation to the corresponding acid **24**.[49] Following a procedure reported by Ley *et. al.*, the carboxylic acid **24** can be activated through conversion to an *N*-hydroxysuccinic ester by reaction with *N*-hydroxysuccinimide and taurinated to form **26**.[30] Finally, the last synthetic step would be an enantioselective reduction of the ketone **26** to form **8a** and **8b**.[50] In this case, both forms of CBS must be used as it will be difficult to predict the synthetic outcome.



Scheme 8: Alternative synthetic strategy to rimarikiamide A (8)

1.6 Research objectives

To explore the full potential of rimarikiamide A as a therapeutic agent, the molecule must be synthesised, characterised, and tested for biological activity. As previously stated, the natural product displayed encouraging activity in preliminary biological assays. However, the main goal of this project is the successful synthesis and characterisation of the target natural product. To achieve this, a total synthetic strategy is proposed, which upon completion, will result in the generation of two diastereomers **(8a** and **8b**, Figure 5). The configuration at the methyl stereocenter is predefined using the commercially available chiral pool reagent (*S*)-(-)-β-citronellol. The configuration at the carbinol will be varied in order to determine the relative stereochemical relationship of the natural product.

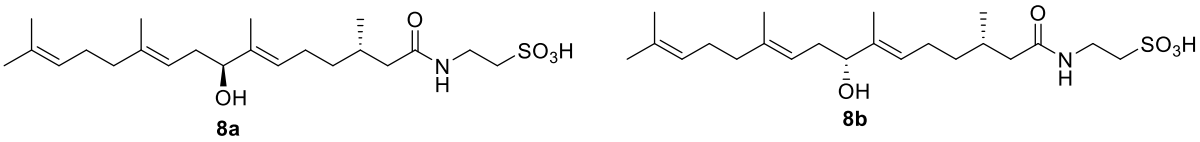


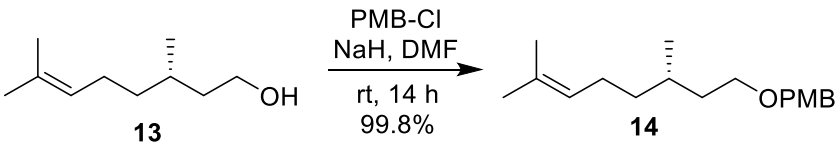
*Figure 5: Target diastereomers **8a** and **8b***

Once synthesised, the diastereomers can be separated using high pressure liquid chromatography (HPLC) and both the relative and absolute stereochemistry of the natural product can be defined through comparison with previously obtained NMR spectra and optical rotation data, respectively. Further biological evaluation can be carried out to determine the mode of action of rimarikiamide A, although this is outside the scope of this project. Previous attempts to achieve the total synthesis of rimarikiamide A have revealed many synthetic challenges that have resulted in failure to generate the desired products. More specifically, issues have arisen with the Barbier coupling and oxidation from the primary alcohol to the acid. Thus, any improvement to the aforementioned steps will be considered a large contribution toward the total synthesis of rimarikiamide A.

2. Results and Discussion

2.1 PMB protection of (S)-(-)-β-citronellol (13)

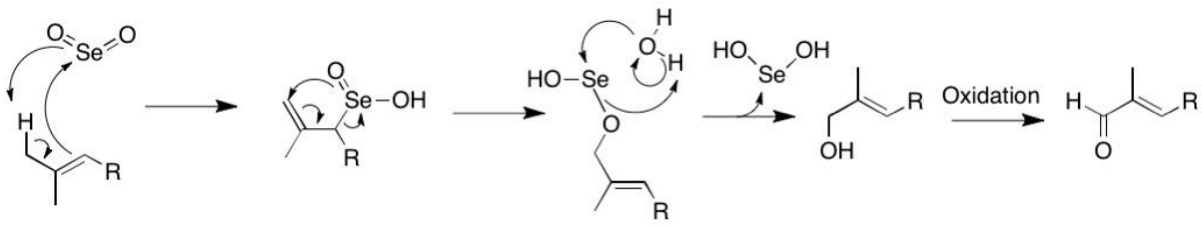
The first step of the proposed synthesis of rimarikiamide A (**8**) was the protection of the primary hydroxyl group on the commercially available chiral pool reagent (*S*)-(-)-β-citronellol (**13**) with a *p*-methoxy benzyl (PMB) protecting group (Scheme 9). Protecting groups are commonly employed to mask key functional groups until they are necessary for synthesis. Methoxy-substituted benzyl ethers are common protecting groups for hydroxyl groups, and are easier to cleave oxidatively than unsubstituted benzyl ethers.[48] PMB ether protecting groups have well defined conditions for both their addition to a molecule and their subsequent removal.[48] A PMB protecting group can be introduced in high yield, and is expected to remain unscathed for the synthetic steps required in this project, making its inclusion ideal within this synthetic strategy. Furthermore, there are literature procedures detailing the PMB protection of (*S*)-(-)-β-citronellol (**13**), thus making PMB an obvious choice for protecting group.[51] Reaction of (*S*)-(-)-β-citronellol (**13**) with PMB-Cl in the presence of sodium hydride provided the desired PMB protected product **14** in excellent (99.8%) yield. ^{1}H NMR spectral data was consistent with the expected product. In particular, aromatic signals at 7.26 and 6.88 ppm indicated that the PMB-protecting group had been successfully installed.



Scheme 9: PMB protection of (S)-(-)-β-citronellol (13)

2.2 Allylic Oxidation

The second step in the proposed synthesis of rimarikiamide A (**8**) was the oxidation of **14** to form the α,β-unsaturated aldehyde **12** using catalytic selenium dioxide chemistry, as developed by Sharpless *et. al.*[32] This method provided a reliable route to the required *E*-isomer of the aldehyde, as the subsequent synthetic step requires *E*-geometry for the integrity of the linear carbon chain.[32] The first mechanistic step is a cycloaddition involving selenium dioxide and the olefinic substituent (Scheme 10). The resulting allylic selenic acid undergoes a [2,3]-sigmatropic rearrangement. Hydrolysis of the selenium (II) intermediate resulted in the generation of an allylic alcohol **15** in 33%. Further oxidation of the allylic alcohol **15** yielded the desired α,β-unsaturated aldehyde **12** in moderate (47%) yield. NOESY experiments were previously carried out on α,β-unsaturated aldehyde **12**, revealing the major product as the *E*-isomer.[29] The allylic alcohol was characterised by ^{1}H NMR spectroscopy which showed the absence of the terminal methyl peak at 1.59 ppm and the presence of the CH_2-OH singlet at 3.98 ppm (Figure 6). In addition, the alkene proton previously at 5.09 ppm shifted downfield to 5.39 ppm indicating the presence of a functional group capable of eliciting deshielding effects. Finally, IR spectroscopy confirmed an OH-stretch at 3407 cm^{-1}.



Scheme 10: Selenium dioxide oxidation mechanism

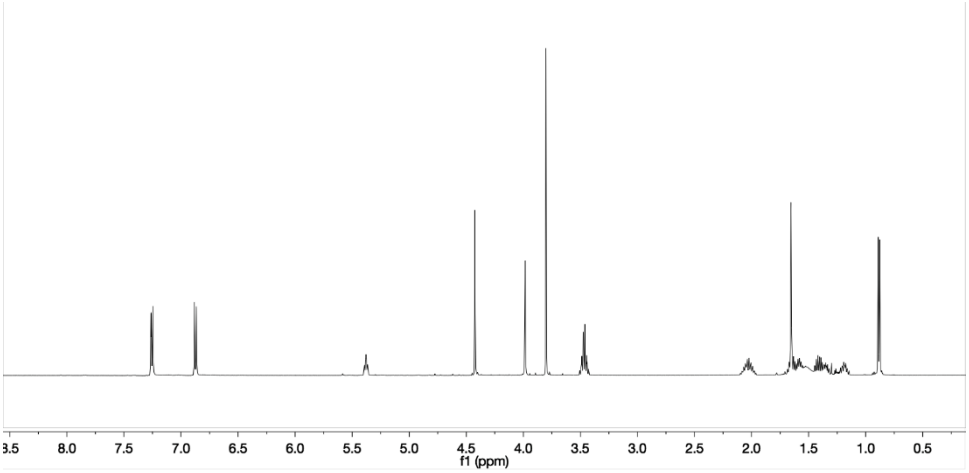
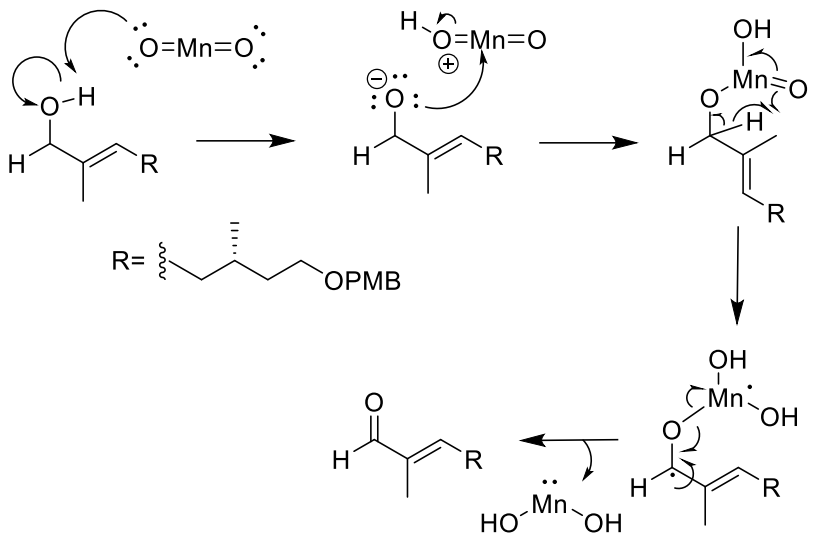


*Figure 6: ^{1}H NMR spectrum of allylic alcohol **15***

2.3 MnO_2 oxidation

Previous synthetic attempts oxidised the allylic alcohol **15** with IBX in DMSO to yield α,β-unsaturated aldehyde **12**. IBX however, is an undesirable reagent as it has the potential to be explosive.[52] So, to negate the need for an IBX oxidation, an alternative approach was trialled, and the allylic alcohol **15** was successfully oxidised to form α,β-unsaturated aldehyde **12** through oxidation by manganese dioxide. MnO_2 was generated from $KMnO_4$ and immobilised on activated carbon following a literature procedure.[53] The first proposed mechanistic step is the deprotonation of the hydroxyl proton by MnO_2 (Scheme 11). The alkoxide can then attack the electrophilic manganese centre, and this is followed by a radical-mediated oxidation process leading to the desired aldehyde **12**.



Scheme 11: MnO_2 oxidation mechanism

Previous attempts to oxidise the allylic alcohol via IBX oxidation required silica flash chromatography of the product, ultimately lowering the yield of the reaction to 62% due to degradation of the aldehyde on silica. Utilising MnO_2/C alleviated the need for columning, as purification could be achieved by filtration over a pad of Celite ®. This method resulted in the generation of α,β-unsaturated aldehyde **12** in excellent (98%) yield. To confirm that α,β-unsaturated aldehyde **12** had been synthesised, standard spectroscopic techniques were utilised. More specifically, diagnostic peaks in the ^{1}H NMR spectrum included the aldehyde proton resonance at 9.37 ppm, and the absence of the CH_2-OH singlet at 3.98 ppm (Figure 7). Furthermore, IR spectroscopy showed a lack of the previously observed OH-stretch. Finally, spectroscopic data from both the allylic alcohol **15** and α,β-unsaturated aldehyde **12** matched data obtained from previous synthetic attempts.[29]

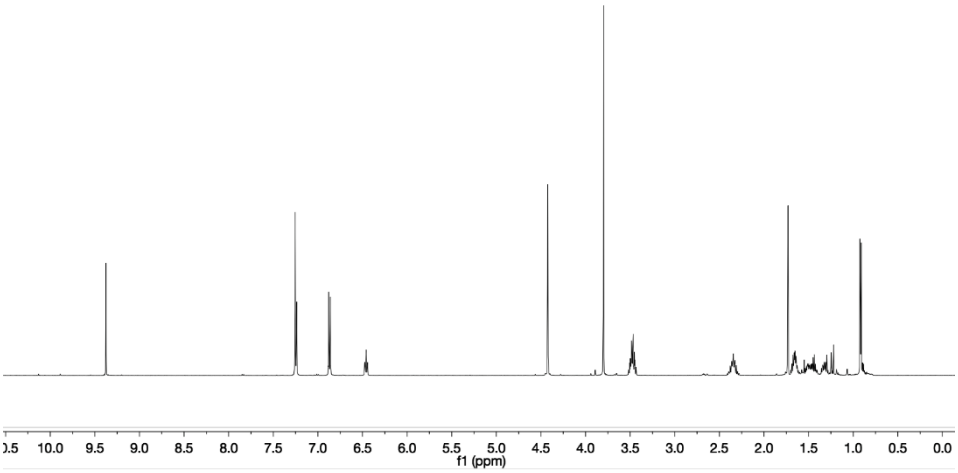
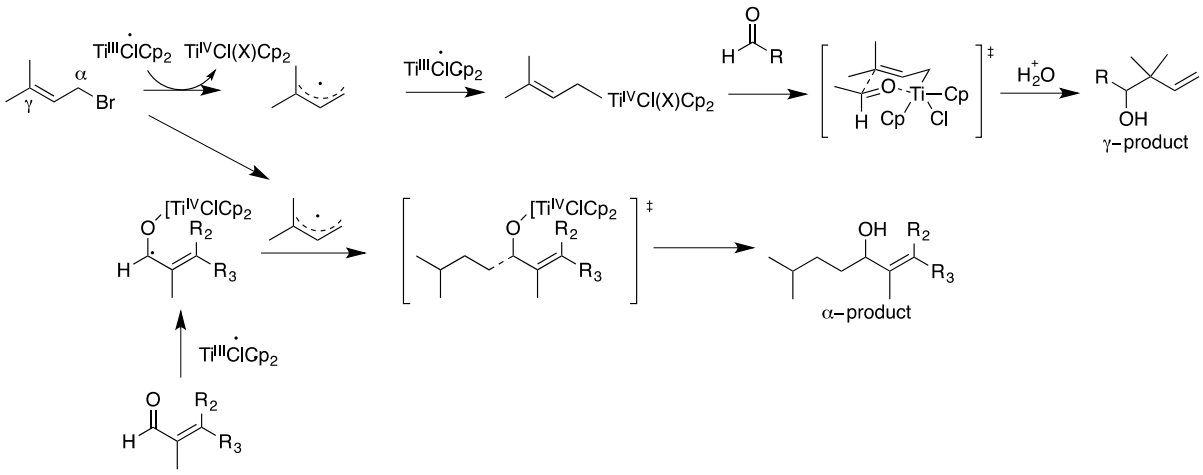


*Figure 7: ^{1}H NMR spectrum of aldehyde **12***

2.4 Ti-mediated Barbier coupling

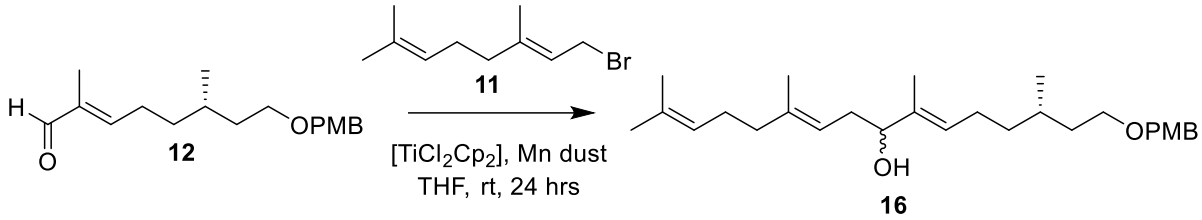
The fourth synthetic step in the total synthesis of rimarikiamide A was a Barbier coupling between α,β-unsaturated aldehyde **12** and commercially available geranyl bromide (**11**). Previous attempts at this coupling utilising allyl-zinc and allyl-barium reagents proved unsuccessful for the generation of the desired α-adduct on both model substrates and the synthesised aldehyde **12**. However, an extensive literature search revealed the use of allyl-titanium reagents for the Barbier-like coupling of similar substrates.[47] Allyl-titanium Barbier-like coupling reactions are also capable of producing both α- and γ-adducts (Scheme 12). Unlike allyl-zinc Barbier couplings, the α-adduct is created through a prenyl radical pathway instead of a direct nucleophilic attack. Conversely, the γ-product is formed by the nucleophilic attack of the organometallic prenyl-Ti intermediate via a chair-like transition state.



Scheme 12: Proposed formation of α- and γ-adducts in Ti-mediated Barbier-like couplings

The titanium reagent [$TiClCp_2$] was prepared in situ from commercially available [$TiCl_2Cp_2$] and Mn dust in THF as per a literature procedure.[45] The first attempt at the Ti-mediated coupling used 2.2 equivalents of [$TiCl_2Cp_2$] on a 50 mg scale with basic workup conditions (Table 1, entry 1). The ^{1}H NMR spectrum of the crude reaction mixture indicated a complex mixture of products including aldehyde starting material and the γ-adduct. Purification through silica flash chromatography afforded what was tentatively assigned as the eliminated α-adduct in extremely poor yield (<1 mg). Unfortunately, this resulted in the inability to collect data other than a ^{1}H NMR spectrum, thus preventing full characterisation. The second attempt used 2.2 equivalents of [$TiCl_2Cp_2$] on an 80 mg scale, with aqueous (pH = 7) conditions (Table 1, entry 2). Purification through silica flash chromatography, and characterisation through NMR spectroscopy revealed the presence of the α-adduct **16** in 3% yield. In addition, spectroscopic analysis showed no presence of the elimination product, suggesting that aqueous workup is beneficial. The ^{1}H NMR spectrum of the isolated material revealed the following diagnostic signals: aromatic protons of the PMB group at 7.26 and 6.87 ppm, three alkene resonances (5.37, 5.09, 5.08 ppm), CH_2-OPMB at 4.42 ppm, and the CH-OH signal at 3.97 ppm (Figure 8). Additionally, an HMBC correlation between the CH-OH proton and the adjacent alkenes confirm that the aldehyde **12** and geranyl bromide (**11**) were successfully coupled to afford **16** (Figure 9).

Table 1 Ti-mediated coupling conditions



Entry	Eq. $[TiCl_2Cp_2]$	Workup Conditions	Scale	Outcome
1	2.2	Basic (sat. aqueous $NaHCO_3$)	50 mg	γ only
2	2.2	Aqueous (pH = 7)	80 mg	α = 3%
3	4.4	Aqueous (pH = 7)	117 mg	α = 17%
4	4.4	Aqueous (pH = 7)	786 mg	α = 6%

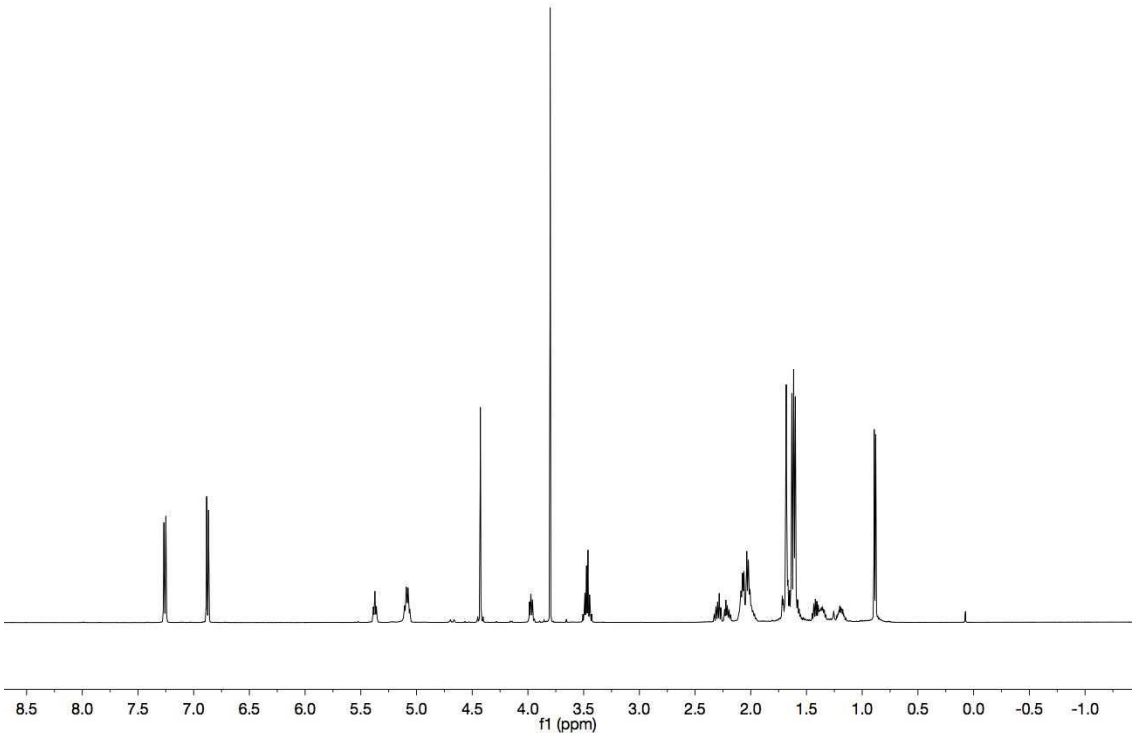


*Figure 8: ^1H NMR of coupled product **16***

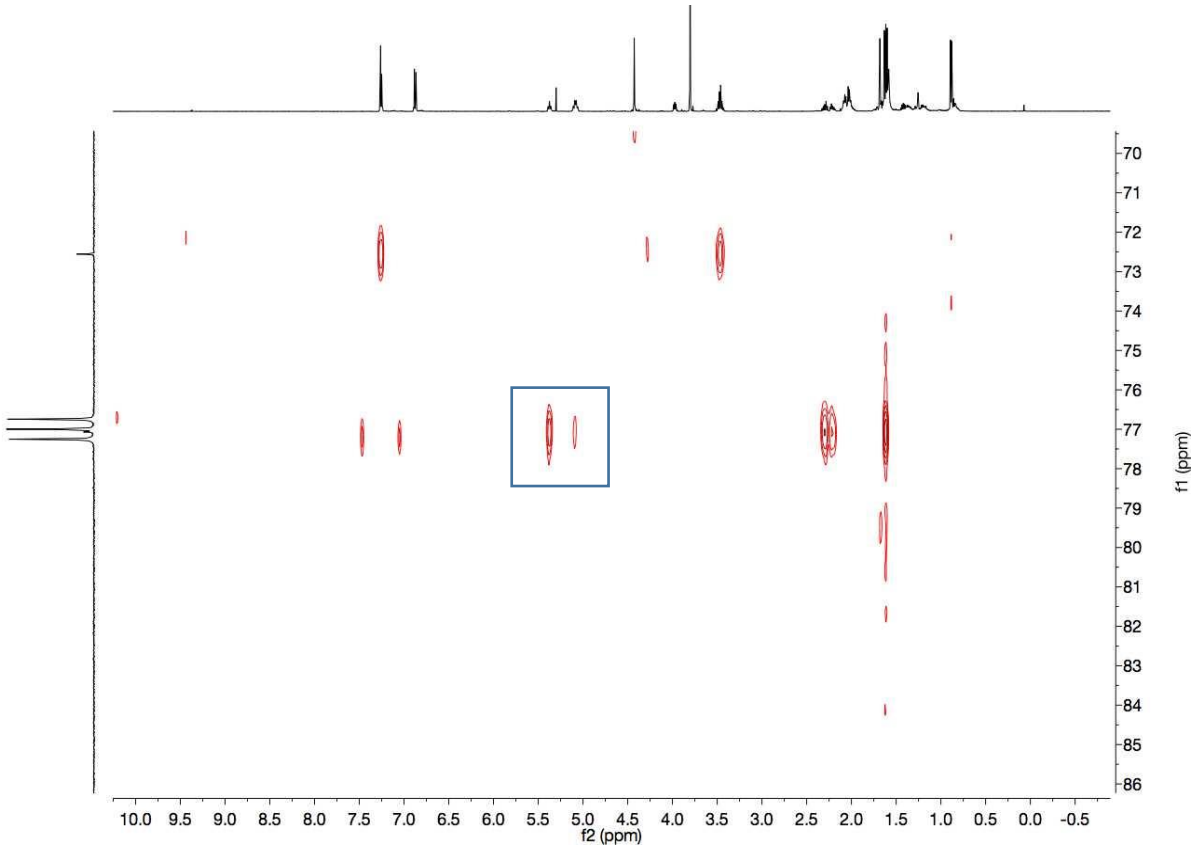
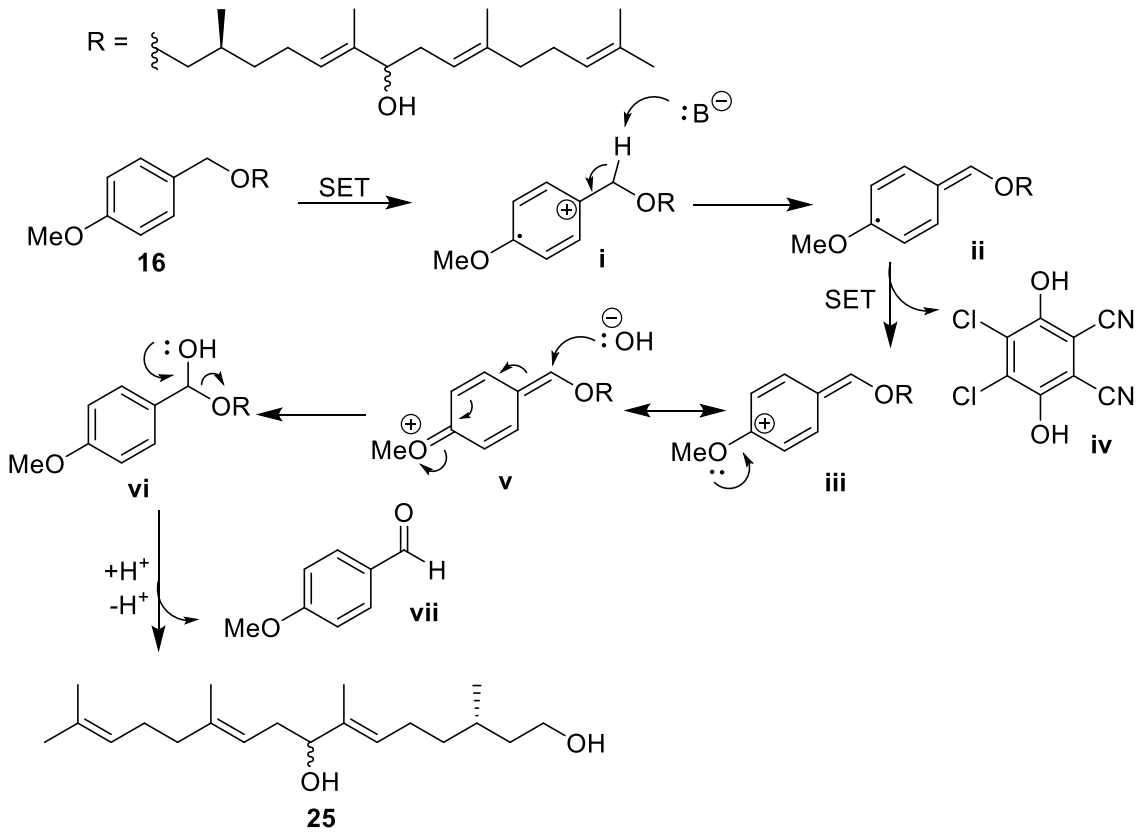


*Figure 9: HMBC of coupled product **16***

With a small amount of α-adduct in hand, TLC analyses allowed a reliable method for isocratic purification on silica gel to be determined. This included trialling a series of PE/EtOAc running solvents (25:1, 20:1, 14:1, 10:1, 9:1), ultimately revealing 9:1 as the best running solvent to achieve isocratic separation. The next attempt at the coupling used double the amount of Ti-reagent (4.4 eq.) on a 117 mg scale with aqueous workup conditions (Table 1, entry 3). Isocratic purification isolated the α-adduct **16** in modest (17%) yield. The final attempt used 4.4 equivalents on a much larger scale (786 mg) with aqueous workup conditions (Table 1, entry 4). Unfortunately, these conditions resulted in a lower yield of α-adduct **16** (6%), most likely due to scale. In summary, it was determined that coupling reactions using 4.4 eq. of $[TiCl_2Cp_2]$ on a moderate scale (~100 mg) with aqueous workup conditions were the highest yielding (Table 1, entry 3). Previous attempts to synthesise the α-adduct failed to generate and separate the desired product. As such, the synthesis and purification of the desired product was considered the main milestone of this project.

2.5 PMB deprotection

Next, the PMB protecting group of α-adduct **16** was removed using the single electron oxidant, DDQ. While benzyl ethers are typically removed using hydrogenolysis, the presence of double bonds within α-adduct **16** restricts the use of this methodology. Additionally, the *p*-methoxy moiety present in PMB-ethers stabilises the cationic intermediate formed during the DDQ deprotection, making the use of DDQ a more suitable deprotection strategy. The first mechanistic step of the PMB removal involves a single electron transfer (SET) from α-adduct **16** to DDQ, thereby giving the radical cationic species **i** (Scheme 13). Abstraction of the benzylic proton followed by a second SET gives cationic species iii. Here, the cation is resonance stabilised (**v**), thereby facilitating the oxidation of the benzyl ether. Nucleophilic attack by hydroxide at the benzylic position quenches the positive charge and gives hemiacetal **vi**. Finally, formation of anisaldehyde (**vii**) results in the leaving of diol **25**.



Scheme 13: PMB deprotection reaction mechanism

Accordingly, α-adduct **16** was treated with DDQ and water in DCM, which led to the cleavage of the PMB group to give the diol **25** in moderate (33%) yield. The successful PMB deprotection of coupled product **16** was confirmed through spectroscopic means. The ^{1}H NMR spectrum revealed the absence of all previously observed PMB peaks such as the aromatic protons at 7.26 and 6.87 ppm, the benzylic-CH_2 peak at 4.42 ppm, and the OMe peak at 3.80 ppm (Figure 10).

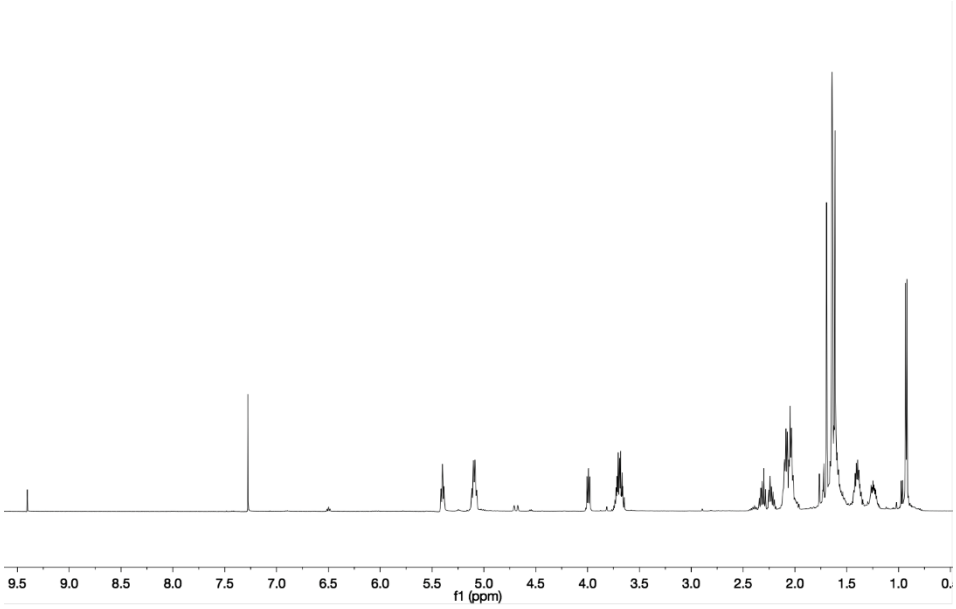


*Figure 10: ^{1}H NMR spectrum of diol **25***

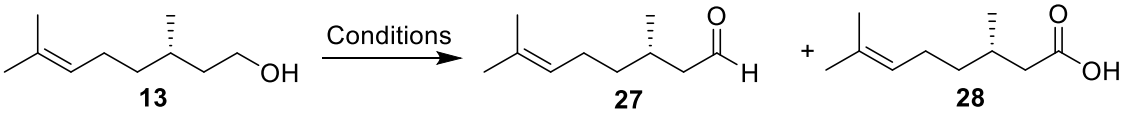
2.6 Oxidation of primary alcohol

With diol **25** in hand, the next synthetic step was the global oxidation of both the primary and secondary alcohols. With only small quantities of **25** available, optimisation of reaction conditions on a model substrate was necessary. The original starting material (*S*)-(-)-β-citronellol was selected to explore the parameters necessary to oxidise the primary alcohol to the corresponding acid. Relatively mild conditions were desirable to prevent olefinic oxidation or elimination reactions from occurring on the actual substrate **25**.

Several reaction conditions were employed in an attempt to convert (*S*)-(-)-β-citronellol (**13**) to its corresponding acid (**28**, Table 2). First pyridinium chlorochromate (PCC) (3.5 equiv) was added to a solution of **13** in DMF/H_2O (9:1, 5 mL) and left to stir at room temperature (entry 1). After 24 hours, the reaction mixture was acidified and extracted with diethyl ether.

Unfortunately, only starting material was isolated from the reaction mixture. Next, the reaction was repeated with acetonitrile in place of DMF. (entry 2).[49] Once again, only (*S*)-(-)-β-citronellol (**13**) was isolated from the reaction mixture. At this point, it was proposed that PCC may not be a suitable oxidant for this model system and instead a TEMPO-BAIB oxidation was attempted. Thus, BAIB (2.6 equiv) was added to a solution of **13** and TEMPO (cat.) in acetonitrile and water at room temperature for 24 hours (entry 3). TLC analyses of the reaction mixture showed an abundance of starting material **13** and a small amount of aldehyde **27** when stained with cerium ammonium molybdate (CAM). The reaction was repeated using more equivalents of BAIB (4 equiv), but showed the same disappointing result (entry 4). Satisfied that TEMPO-BAIB may not be appropriate for this model substrate, pyridinium dichromate (PDC) was trialled. PDC oxidations are more mild than PCC oxidations, and are particularly suitable for acid sensitive substrates.[54] PCC (4 equiv) was added to a solution of **13** in acetonitrile and water at room temperature for 24 hours. TLC analyses only revealed the presence of starting material **13** (entry 5). The reaction was repeated using more equivalents of PDC (10 equiv), and an acid-base reaction quench was performed, yielding starting material and the desired acid **28** with a small amount of impurity.

Table 2 Attempts to oxidise (*S*)-(-)-β-citronellol (**13**)



13 **27** **28**

Entry	Conditions	Result
1	PCC (3.5 eq.), DMF/H_2O, rt	Isolated **13**
2	PCC (4 eq.), ACN/H_2O, rt	Isolated **13**
3	TEMPO (cat.), BAIB (2.6 eq.), ACN/H_2O, rt	**13 + 27***
4	TEMPO (cat.), BAIB (4 eq.), ACN/H_2O, rt	**13 + 27***
5	PDC (4 eq.), ACN/H_2O, rt	**13***
6	PDC (10 eq.), ACN/H_2O, rt	**13 + 28**$^{+}$

*Based on TLC analysis

$^{+}$Separated with a small amount of impurity

3. Conclusions and Future Prospects

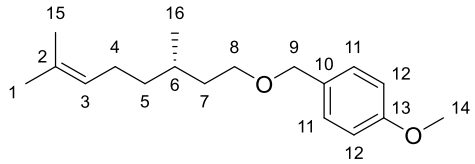
This Masters project aimed to contribute to development of the total synthesis of rimarikiamide A (**8**), and to establish both the relative and absolute stereochemical configurations of the natural product. Accordingly, all previously successful synthetic steps were further optimised including the PMB protection where the yield was improved from 93% to 99.8%, the allylic oxidation from 35% to 47%. An alternative oxidation strategy to IBX was employed to oxidise the allylic alcohol to the α,β-unsaturated aldehyde using MnO_2/C. This increased the yield of the reaction from 62% to 98% without the need for purification through flash silica chromatography. An alternative methodology was trialled to overcome issues surrounding the Barbier coupling step of the synthesis. Specifically, a Ti-mediated α-prenylation was successfully employed to generate the desired linear product **16** in 17% yield. Some investigation into the optimal conditions required for the reaction were carried out, and an isocratic purification method was developed. A PMB deprotection using DDQ was successfully employed, although in moderate (33%) yield. Finally, a model substrate was used to establish the best conditions needed for the global oxidation step. Firstly, PCC was trialled and it was found that only starting material was recovered, with no indication aldehyde or carboxylic acid formation. Next, a TEMPO-BAIB oxidation was employed and TLC analyses revealed an abundance of starting material and some aldehyde product, but again no acid after varying reaction conditions. Finally, PDC was used and upon the addition of ten equivalents, a small amount of the desired acid was formed. Unfortunately, further optimisation is required as the reaction was extremely low yielding.

Further optimisation of the Barbier coupling step is worth exploring, particularly with the inclusion of agents capable of regenerating the active catalyst such as 2,4,6-collidine and Me_3SiCl. Unfortunately, due to time constraints, the global oxidation of the real substrate, taurination, and enantioselective reduction were not attempted. Although, these steps should be the focus of future investigations. Furthermore, Mosher acid analysis to determine the absolute stereochemistry of the two diastereomers will be necessary. Finally, if purification by silica gel chromatography is not possible, HPLC separation will be required.

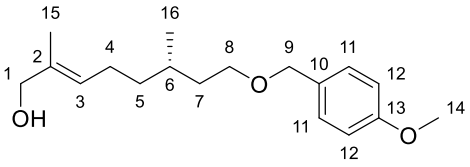
4. Experimental

4.1 General Experimental Procedures

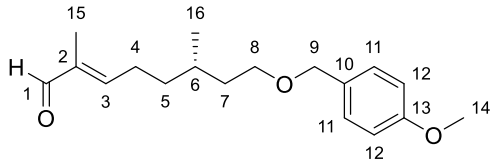
Unless otherwise stated, all reactions were performed at room temperature under an atmosphere of argon. DCM, THF, and Diethyl ether were obtained from a PureSolv (Innotive Technologies). PMB-Cl (Sigma Aldrich), DMF (Acros), NaH (Sigma Aldrich), *S*-citronellol (Sigma Aldrich), Magnesium sulphate (Pure Science), Salicylic acid (homebrew), ^{t}BuOOH (Sigma Aldrich), Sodium thiosulphate (Vickers), Hexanes (Fischer), Ethyl Acetate (Fischer), MnO_2/C (homebrew), Mn dust (Sigma Aldrich), $TiCl_2Cp_2$ (Sigma Aldrich), Geranyl bromide (homebrew), DDQ (Sigma Aldrich), and $NaHSO_3$ (homebrew) were used as received. All solvents were removed via concentration under reduced pressure. Reactions were monitored by TLC analysis on silica gel coated plastic sheets (0.2 mm, Polygram SIL G/UV254). Visualisation was achieved by UV irradiation (254 nm) and staining. High resolution mass spectrometry was recorded using an Agilent 6530 Accurate-mass Q-TOF LC/MS mass spectrometer with an Agilent Jet Stream ESI source, operating in positive mode. Optical rotations were recorded using a Perkin-Elmer polarimeter at the sodium D-line (589 nm); concentrations are given in g/100 mL. Infrared spectra were recorded as thin films using a Bruker Tensor 27 FTIR Spectrometer and are reported in wave numbers (cm^{-1}). Column chromatography was carried out using silica gel 60 (220-240 mesh). NMR spectra were recorded at 20 °C in $CDCl_3$ using a Varian INOVA operating at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. Chemical shifts (δ) are listed in ppm relative to the solvent residual peak. Subsequent peak assignments were performed using COSY, HSQC, and HMBC 2D-experiments. Proton signal multiplicity is quoted as s = singlet, d = doublet, t = triplet, m = multiplet.



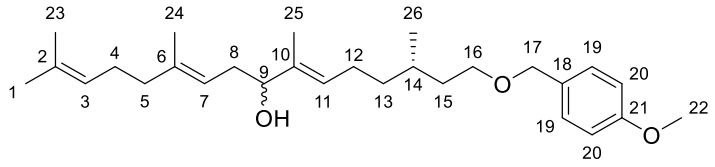
***S*)-1-(((3,7-Dimethyloct-6-en-1-yl)oxy)methyl)-4-methoxybenzene (14)** To a solution of *S*-citronellol (0.5 g, 3.2 mmol) in DMF (3 mL) at 0 °C, NaH (0.3 g, 12.2 mmol, 60% in mineral oil) was added slowly and the mixture stirred vigorously for 10 min. PMB-Cl (0.6 g, 3.5 mmol) was added portion-wise and the resulting pale yellow mixture was stirred for 14 h at room temperature. The reaction was quenched with the addition of 5 mL water, and the aqueous layer was washed with diethyl ether (3 x 10 mL). The combined organic fractions were washed with water (2 x 10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by silica flash chromatography (10% MeOH in DCM) to afford **14** as a pale-yellow oil (0.88 g, 3.2 mmol, 99.8%). $[\alpha]_D^{20}$ = -2.0 (c = 1.0, CH_2Cl_2); IR (film): ν_{max} = 2922, 2835, 1613, 1512, 1457, 1376, 1301, 1245, 1172, 1093, 1037 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, $J_{11,12}$ = 8.7 Hz, 2H, H-11), 6.88 (d, $J_{12,11}$ = 8.7 Hz, 2H, H-12), 5.09 (t, $J_{3,4}$ = 7.2 Hz, 1H, H-3), 4.43 (s, 2H, H-9), 3.80 (s, 3H, H-14), 3.47 (m, 2H, H-8), 1.97 (m, 2H, H-4), 1.68 (s, 3H, H-15), 1.65 (m, 1H, H-7a), 1.60 (s, 3H, H-1), 1.57 (m, 1H, H-6), 1.42 (m, 1H, H-7b), 1.32 (m, 1H, H-5a), 1.15 (m, 1H, H-5b), 0.88 (d, $J_{16\text{-}6}$ = 6.7Hz, 3H, H-16); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9 (C-13), 131.1 (C-2), 130.8 (C-10), 129.2 (C-11), 124.8 (C-3), 113.7 (C-12), 72.5 (C-9), 68.4 (C-8), 55.2 (C-14), 37.2 (C-5), 36.7 (C-7), 29.6 (C-6), 25.7 (C-15), 25.5 (C-4), 19.5 (C-16), 17.6 (C-1); HRMS(ESI) *m/z* calculated for $[C_{18}H_{28}O_2+H]^+$: 277.2162, observed: 277.2153 (Δ -3.25 ppm). Spectral data matched those reported in literature.[46]



(*S*,*E*)-8-((4-Methoxybenzyl)oxy)-2,6-dimethyloct-2-en-1-ol (15) Selenium dioxide (0.15 g, 1.3 mmol) was added to a solution of salicylic acid (0.53 g, 3.85 mmol) in DCM (30 mL) and the mixture was stirred for 15 min. An aliquot of ^{t}BuOOH (13.13 mL) was added to the mixture and stirred for 15 min. A solution containing **14** (4.16 g, 15.1 mmol) in DCM (10 mL) was added slowly to the reaction mixture, and the resulting pale-yellow solution was stirred at room temperature for 36 h. The reaction was quenched with sodium thiosulfate, stirred for 1h, and extracted with DCM. The organic layer was washed with water (3 x 30 mL), brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by silica flash chromatography (0-60% hexanes : EtOAc) to afford **15** as a pale yellow oil (1.42 g, 4.9 mmol, 47%). $[\alpha]_D^{20}$ = -3.8 (c = 2.0, CH_2Cl_2); IR (film) ν_{max} = 3407 cm^{-1}, 2920, 2857, 1613, 1513, 1460, 1364, 1302, 1247, 1173, 1091, 1035; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, $J_{11\text{-}12}$ = 8.2 Hz, 2H, H-12), 6.88 (d, $J_{12\text{-}11}$ = 8.3 Hz, 2H, H-11), 5.38 (t, $J_{3,4}$ = 7.6 Hz, 1H, H-3), 4.43 (s, 2H, H-9), 3.99 (s, 2H, H-1), 3.80 (s, 3H, H-14), 3.46 (m, 2H, H-8), 2.03 (m, 2H, H-4), 1.65 (s, 3H, H-15), 1.63 (m, 1H, H-7a), 1.59 (m, 1H, H-6), 1.41 (m, 1H, H-7b), 1.34 (m, 1H, H-5a), 1.18 (m, 1H, H-5b), 0.88 (d, $J_{16\text{-}6}$ = 7.14 Hz, 3H, H-16); ^{13}C (125 MHz, $CDCl_3$) 158.9 (C-13), 131.0 (C-1), 130.7 (C-10), 129.2 (C-11), 124.8 (C-3), 113.7 (C-12), 72.5 (C-9), 68.4 (C-8), 55.2 (C-14), 37.2 (C-5), 36.7 (C-7), 29.5 (C-6), 25.7 (C-15), 25.5 (C-4), 19.5 (C-16), 17.6 (C-1); HRMS(ESI) *m/z* calculated for $[C_{18}H_{28}O_3+Na]^+$: 315.1931, observed: 315.1923 (Δ -2.51 ppm).



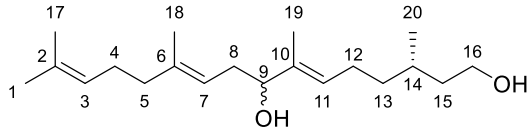
(*S*,*E*)-8-((4-Methoxybenzyl)oxy)-2,6-dimethyloct-2-enal (12) MnO_2/C (1.56 g) was added to a stirred solution of **15** (0.1 g, 0.34 mmol) in anhydrous DCM (12 mL) at room temperature for 60 min. The reaction mixture was filtered through a pad of Celite, and washed with DCM. The filtrate was concentrated under reduced pressure to yield the title compound (97 mg, 0.33 mmol, 98%) without further purification. $[\alpha]_D^{20}$ = -4.3 (c = 2.0, CH_2Cl_2); IR (film): ν_{max} = 2925 cm^{-1}, 2855, 1684, 1642, 1612, 1512, 1460, 1361, 1301, 1246, 1173, 1092, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1H, H-1), 7.25 (d, $J_{11\text{-}12}$ = 8.5 Hz, 2H, H-12), 6.87 (d, $J_{12\text{-}11}$ = 8.3 Hz, 2H, H-11), 6.46 (t, $J_{3,4}$ = 7.6 Hz, 1H, H-3), 4.43 (s, 2H, H-9), 3.80 (s, 3H, H-14), 3.48 (m, 2H, H-8), 2.35 (m, 2H, H-4), 1.73 (s, 3H, H-15), 1.67 (m, 1H, H-7a), 1.65 (m, 1H, H-6), 1.51 (m, 1H, H-7b), 1.33 (m, 1H, H-5a), 1.30 (m, 1H, H-5b), 0.92 (d, , $J_{16\text{-}6}$ = 6.54 Hz, 3H, H-16); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.3 (C-1), 159.1 (C-13), 154.9 (C-3), 139.2 (C-2), 130.6 (C-10), 129.2 (C-11), 113.7 (C-12), 72.6 (C-9), 68.0 (C-8), 55.2 (C-14), 36.6 (C-5), 35.5 (C-7), 29.7 (C-6), 26.5 (C-15), 19.3 (C-16), 9.15 (C-15); HRMS(ESI) *m/z* calculated for $[C_{18}H_{27}O_3]^+$: 291.1955, observed: 291.1949 (Δ -2.06 ppm).



(3*S*,6*E*,10*E*)-1-((4-Methoxybenzyl)oxy)-3,7,11,15-tetramethylhexadeca-6,10,14-trien-8-ol (16)

Manganese dust (0.39 g) was added to a mixture of [$TiCl_2Cp_2$] (0.44 g, 2 mmol) in strictly deoxygenated THF (2 mL). The reaction mixture was stirred for 30 min at room temperature until a dark green colour change was observed. The reaction was cooled to 0 °C, and a solution of **12** (0.117g, 0.4 mmol) and geranyl bromide (0.104 g, 0.5 mmol) in THF (1 mL) was added dropwise to the reaction mixture over 30 min. The reaction mixture was allowed to slowly warm to room temperature, and stirred for 48 h. The reaction was quenched through the addition of water, and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel (9:1, PE/EtOAc) to afford **16** as a colourless oil (110 mg, 0.26 mmol, 17%). IR (film): ν_{max} = 3453 cm^{-1}, 2925, 2857, 1713, 1586, 1513, 1456, 1376, 1302, 1248, 1095, 1037; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, $J_{19\text{-}20}$ = 9.2 Hz, 2H, H-19), 6.87 (d, $J_{20\text{-}19}$ = 8.3 Hz, 2H, H-20), 5.37 (t, $J_{11\text{-}12}$ = 7.6 Hz, 1H, H-11), 5.08 (m, 2H, H-3 and H-7), 4.43 (s, 2H, H-17), 3.97 (t, $J_{9\text{-}8}$ = 6.8 Hz, 1H, H-9), 3.8 (s, 3H, H-22), 3.47 (m, 2H, H-16), 2.29 (m, 1H, H-8a), 2.21 (m, 1H, H-8b), 2.07 (m, 2H, H-4), 2.03 (m, 2H, H-15), 2.02 (m, 2H, H-12), 1.68 (s, 3H, H-1), 1.66 (m, 2H, H-15), 1.63 (s, 3H, H-24), 1.62 (s, 3H, H-25), 1.60 (s, 3H, H-23), 1.58 (m, 1H, H-14), 1.40 (m, 1H, 13a), 1.19 (m, 1H, 13b), 0.89 (d, $J_{26\text{-}14}$ = 7.9 Hz, 3H, H-26); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0 (C-21), 138.3 (C-6), 136.3 (C-10), 131.5 (C-2), 130.7 (C-18), 129.2 (C-19), 126.5 (C-11), 124.1 (C-3), 120.0 (C-7), 113.6 (C-20), 76.9 (C-9), 72.5 (C-17), 68.3 (C-16), 55.2 (C-22), 39.8 (C-4), 36.8 (C-13), 36.6 (C-15), 34.1 (C-8), 29.6 (C-14), 26.5 (C-5), 25.7 (C-1), 25.0 (C-12), 19.5 (C-26), 17.7 (C-23), 16.3 (C-24), 11.7 (C-25); HRMS(ESI) *m/z* calculated for $[C_{28}H_{44}O_3+NH_4]^+$: 446.3600, observed: 446.3600

(Δ 0 ppm).



(3*S*,6*E*,10*E*)-3,7,11,15-Tetramethylhexadeca-6,10,14-triene-1,8-diol (25)

A solution of **16** (0.073 g, 0.17 mmol) in DCM (2 mL) was treated with water (120 μL) and cooled to 0 °C. DDQ (0.022 g, 0.10 mmol) was added to the reaction mixture, and the solution was allowed to warm to room temperature with constant stirring for 2.5 h. The reaction was cooled to 0 °C again, and quenched with 40% aqueous $NaHSO_3$ solution (0.5 mL) and water (2 mL). After stirring for 15 min, water (20 mL) and DCM (20 mL) were added, and the layers were separated. The aqueous layer was extracted with DCM (3 x 20 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel (3:1 PE/EtOAc) and gave **25** as a colourless oil (17 mg, 0.055 mmol, 33%). IR (film): ν_{max} = 3348 cm^{-1}, 2916, 2856, 1686, 1449, 1377, 1325, 1251, 1052, 1010; ^1H NMR (500 MHz, $CDCl_3$) δ 5.38 (t, $J_{11\text{-}12}$ = 6.9 Hz, 1H, H-11), 5.12-5.03 (complex m, 2H, H-3 and H-7), 3.97 (t, $J_{9\text{-}8}$ = 6.9 Hz, 1H, H-9), 3.68 (m, 2H, H-16), 2.30 (m, 1H, H-8a), 2.22 (m, 1H, H-8b), 2.07 (m, 2H, H-4), 2.04 (m, 2H, H-15), 2.02 (m, 2H, H-12), 1.70 (m, 1H, H-15a), 1.68 (s, 3H, H-1), 1.63 (s, 3H, H-18), 1.62 (s, 3H, H-19), 1.60 (s, 3H, H-17), 1.38 (m, 1H, H-13a), 1.35 (m, 1H, H-15b), 1.23 (m, 1H, H-13b), 0.91 (d, $J_{20\text{-}14}$ = 6.5 Hz, 3H, H-20); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5 (C-6), 136.5 (C-10), 131.6 (C-2), 126.4 (C-11), 124.1 (C-3), 120.0 (C-7), 77.2 (C-9), 61.2 (C-16), 39.97 (C-4), 39.93 (C-15), 36.9 (C-13), 34.2 (C-8), 29.3 (C-14), 26.7 (C-5), 25.9 (C-1), 25.1 (C-12), 19.7 (C-20), 17.8 (C-17), 16.4 (C-18), 11.9 (C-19); HRMS(ESI) *m/z* calculated for $[C_{20}H_{36}O_2+Na]^+$: 331.2608, observed 331.2592 (Δ -4.8 ppm).

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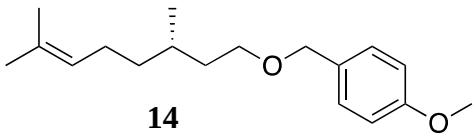
Appendix



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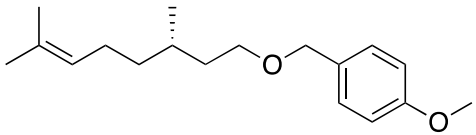

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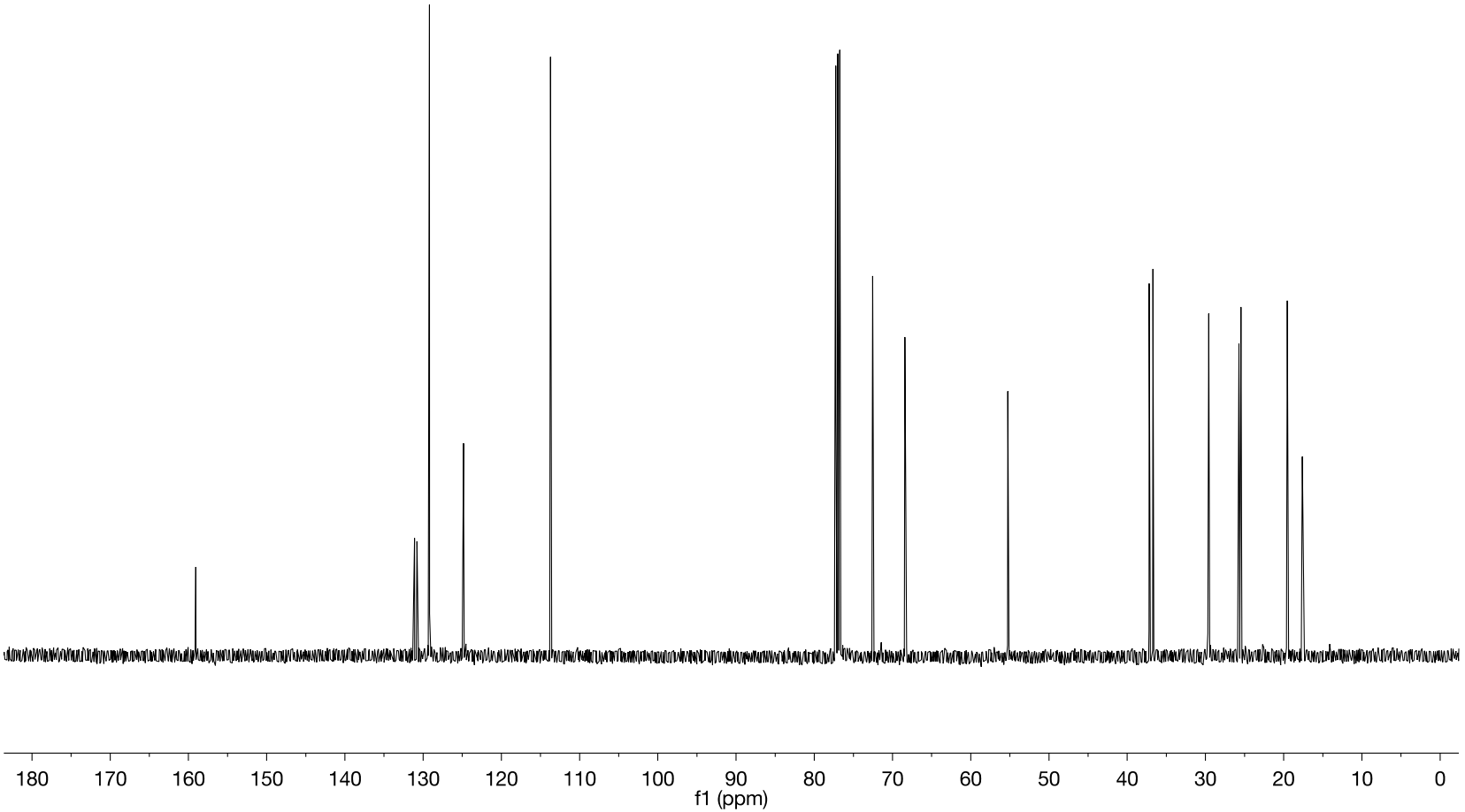

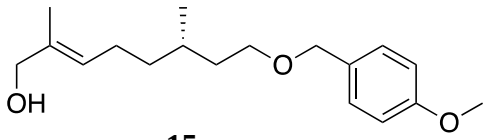

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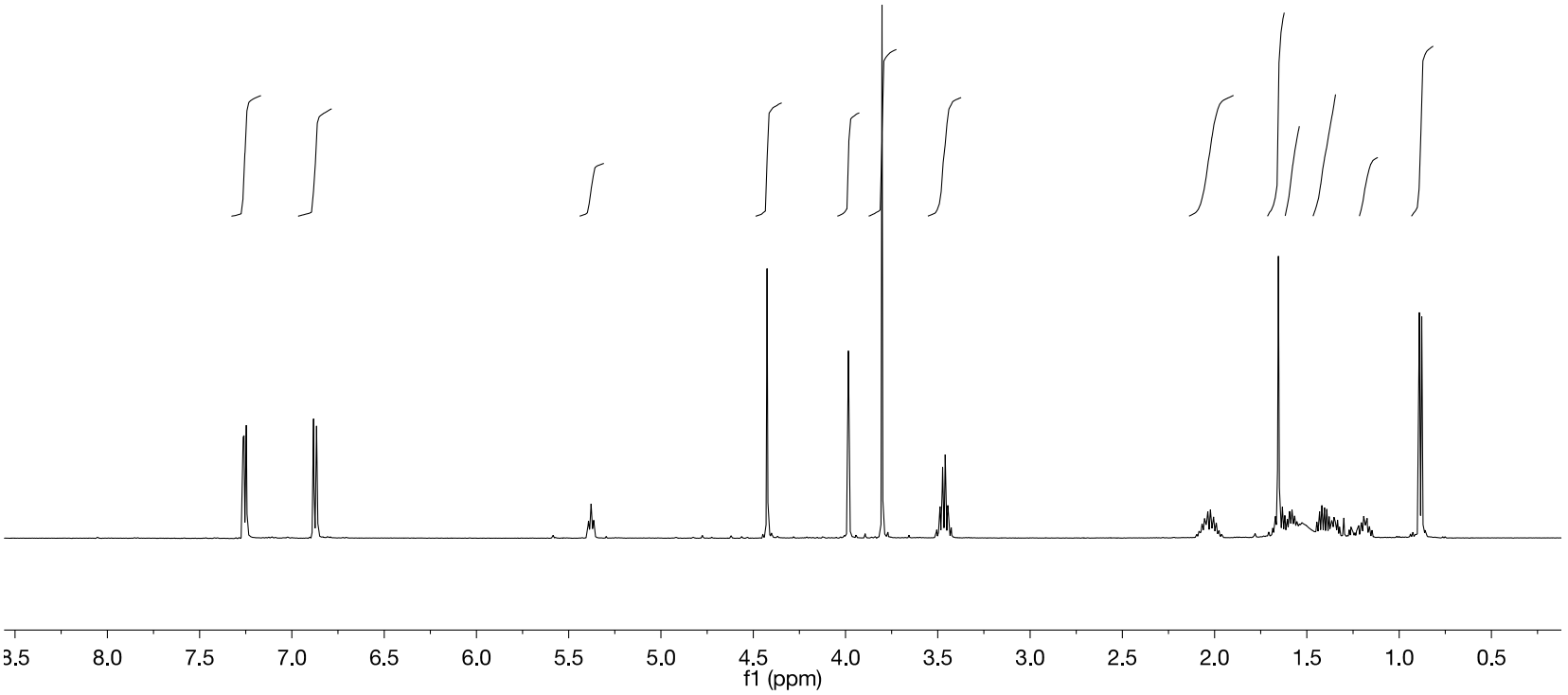

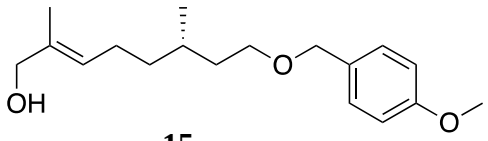

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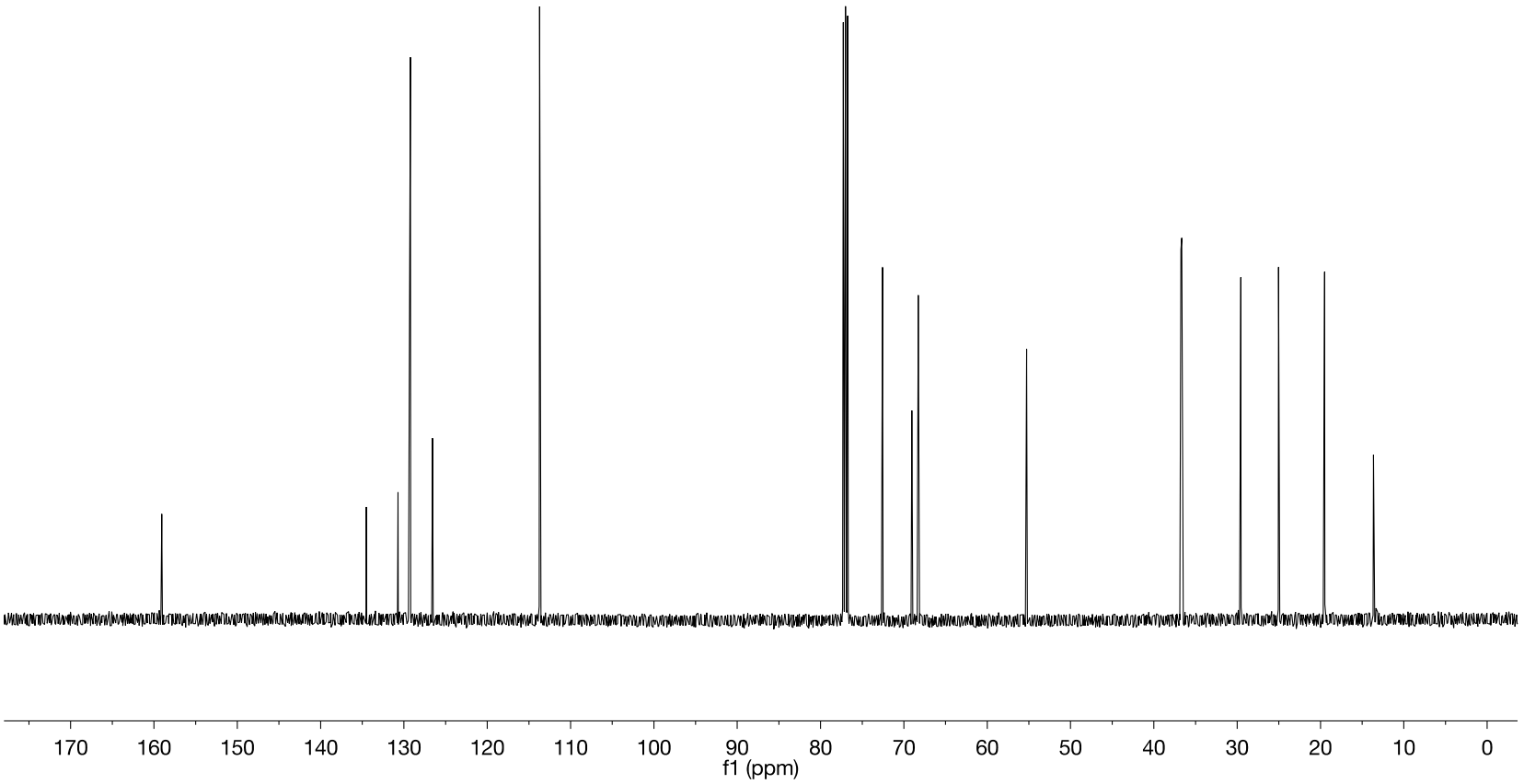

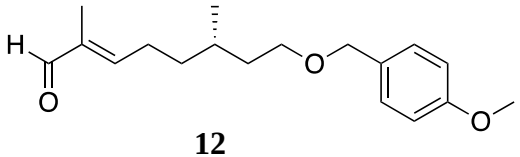

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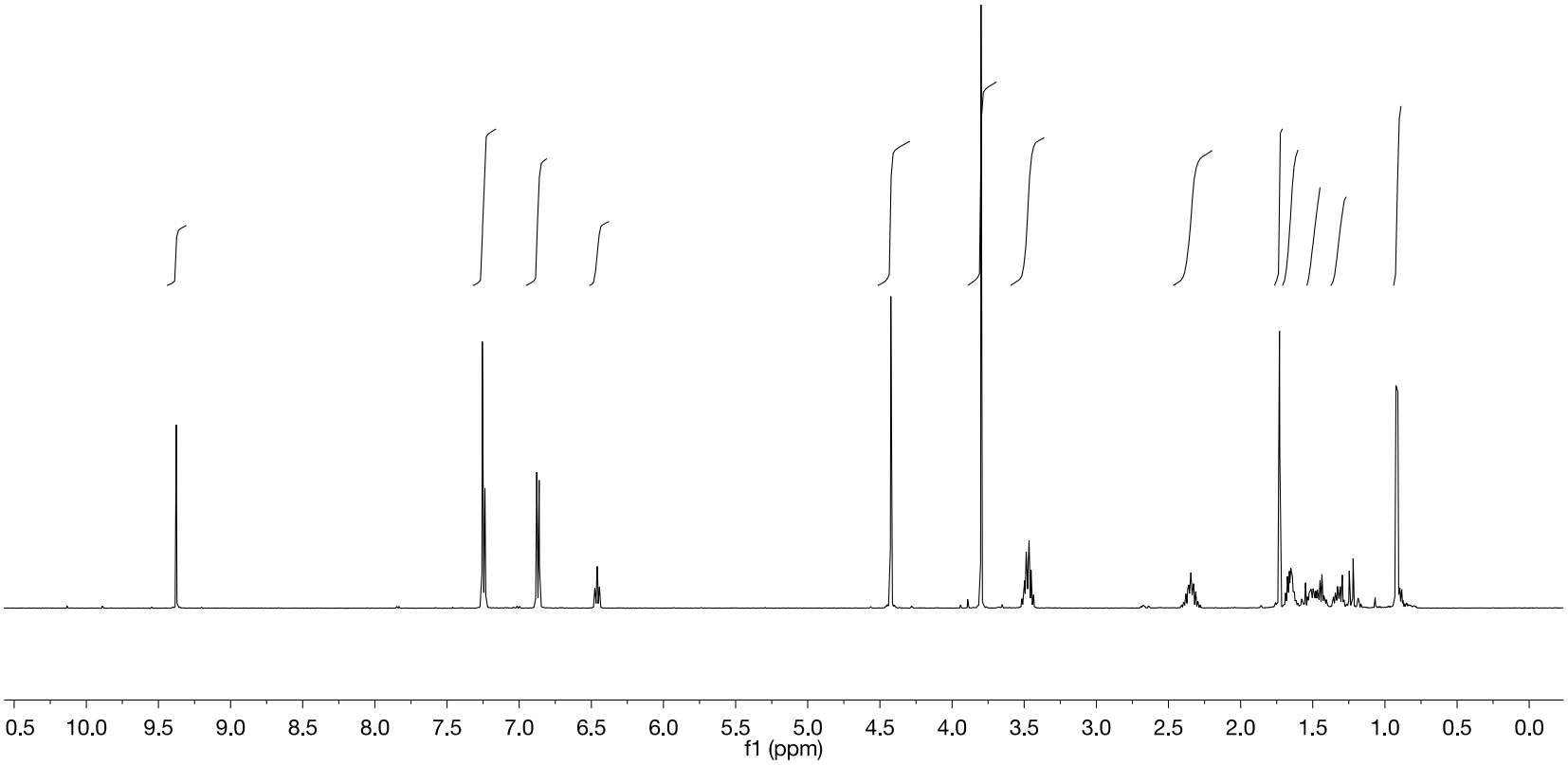

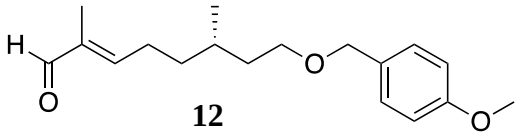

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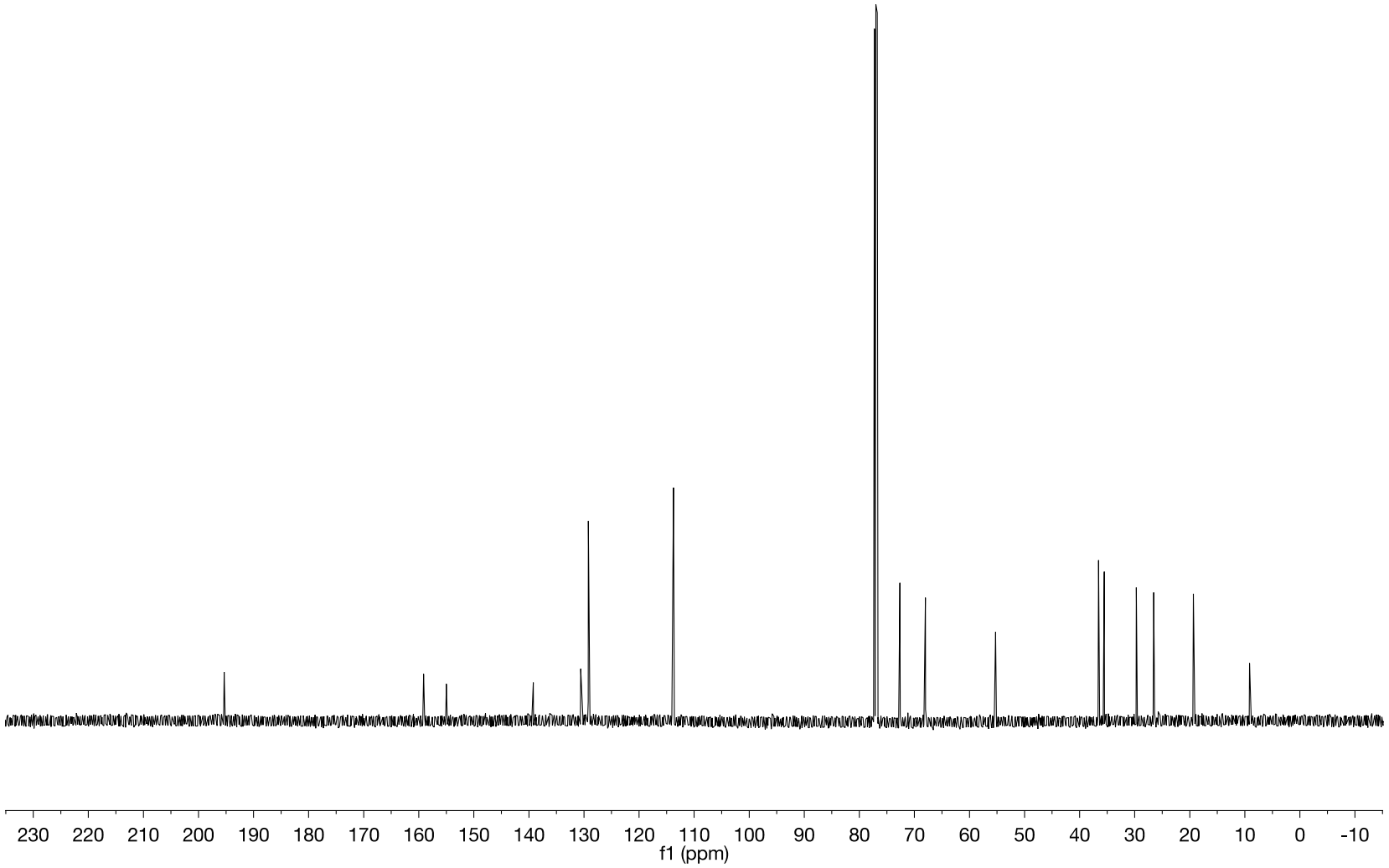

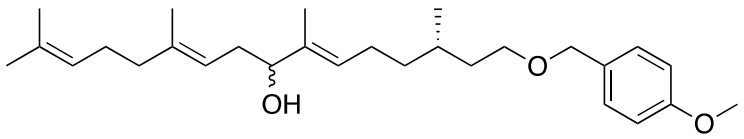

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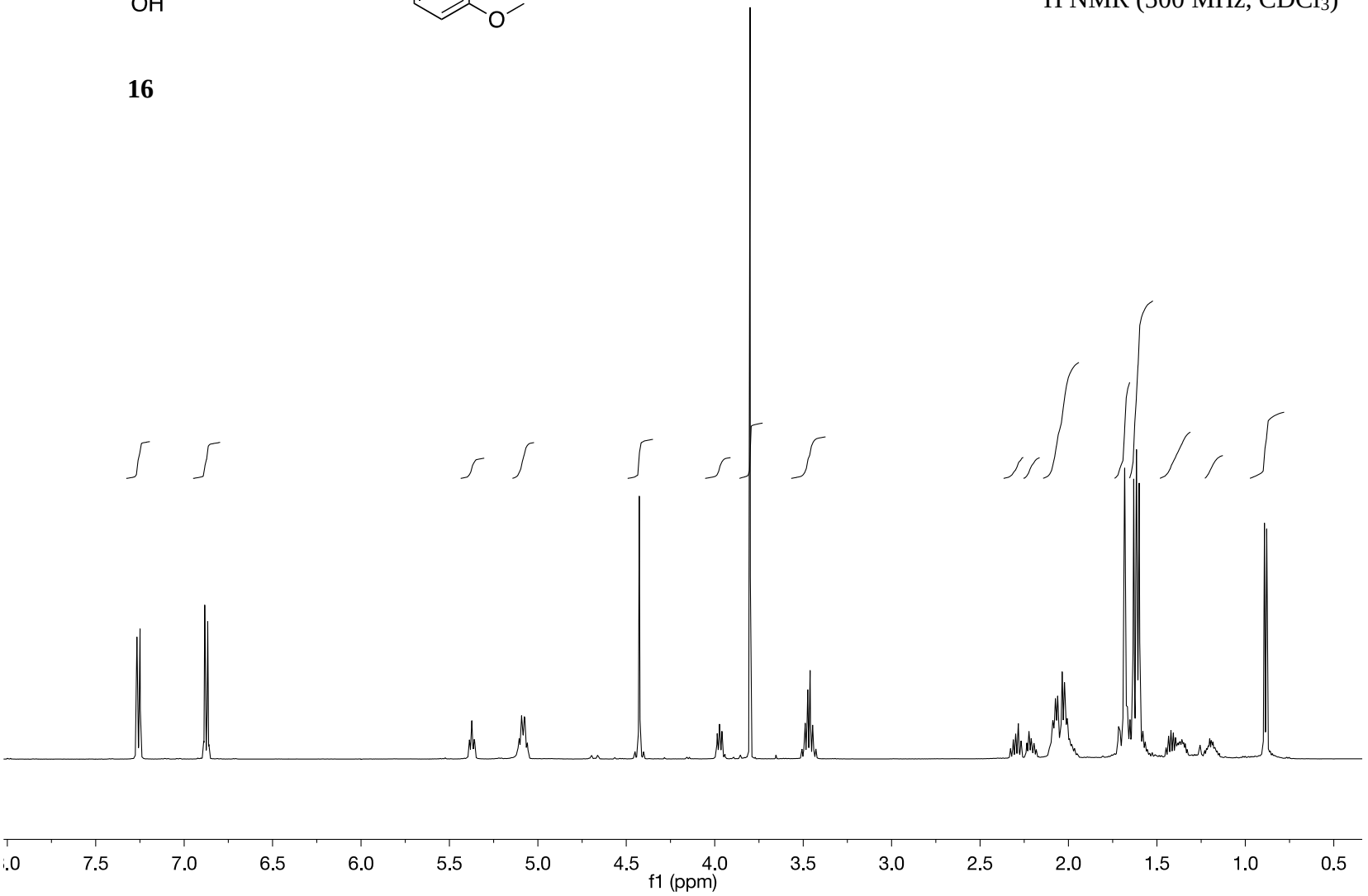
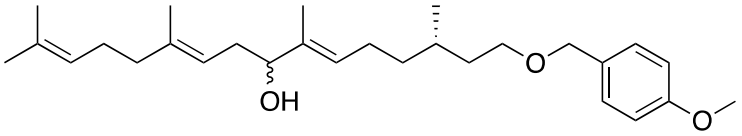
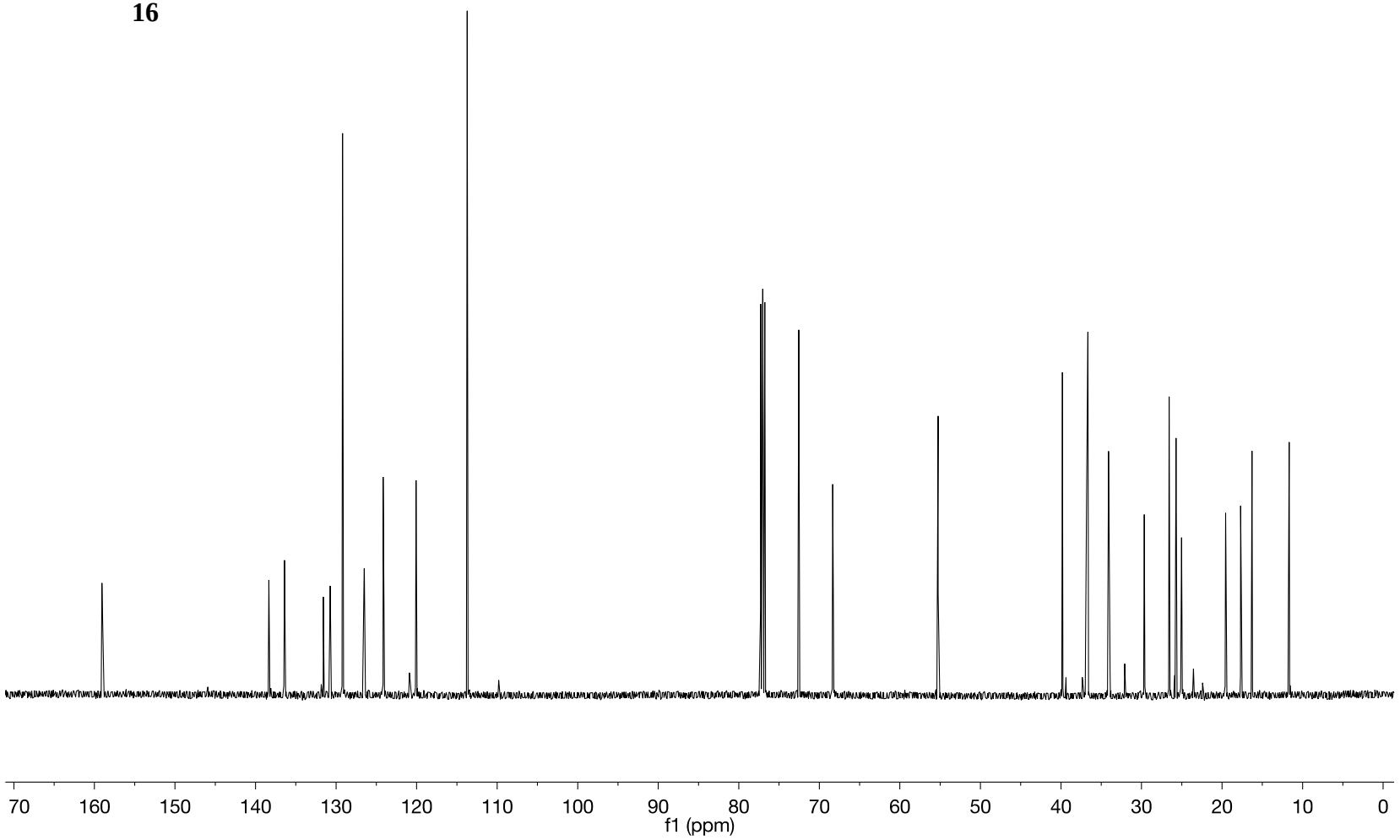
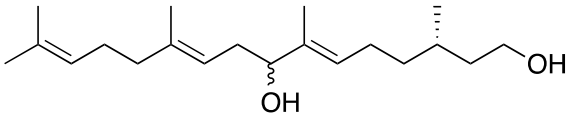




^{13}C NMR (125 MHz, $CDCl_3$)

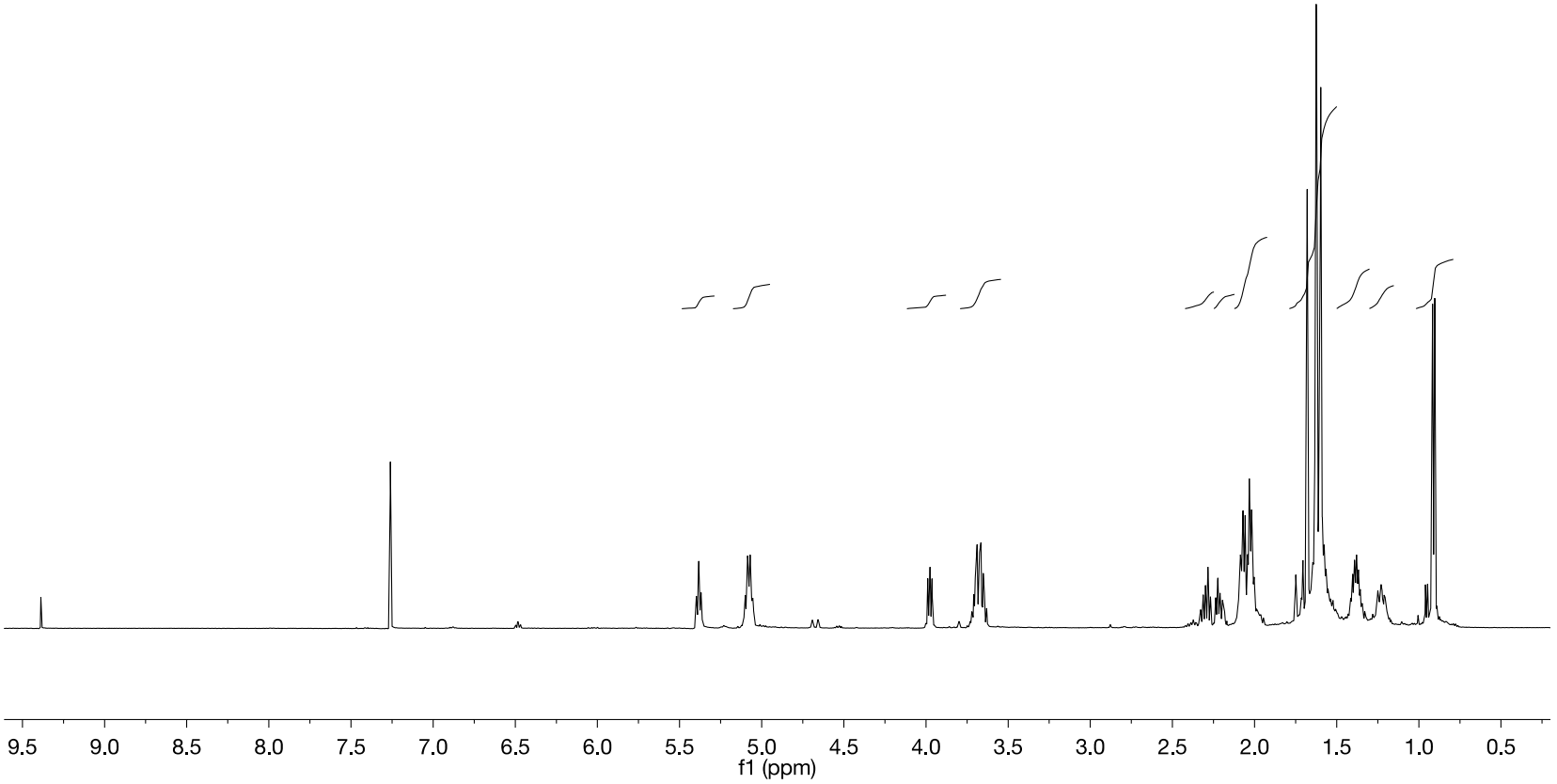
16

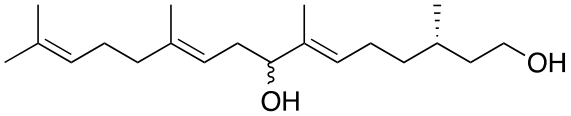




25

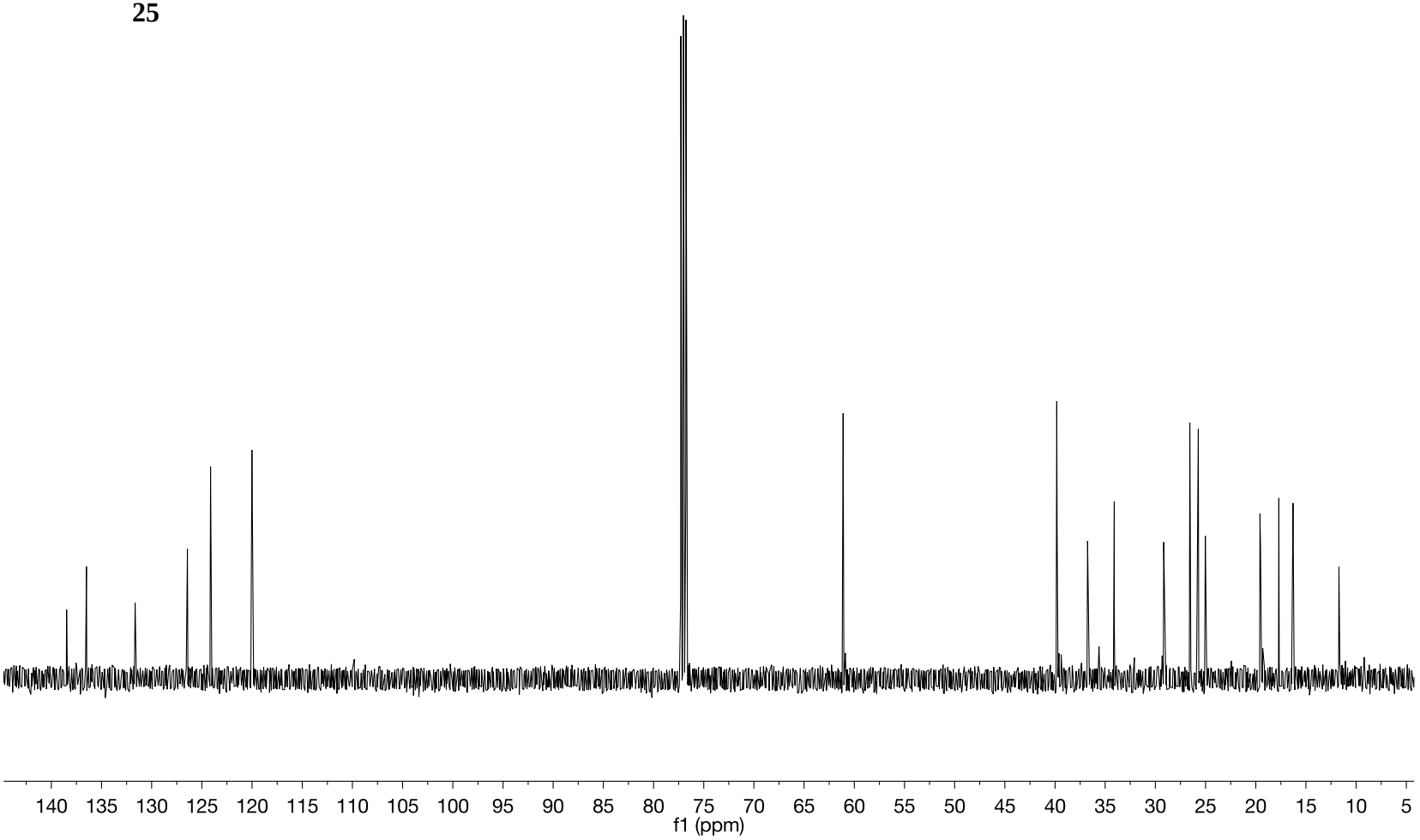
^{1}H NMR (500 MHz, $CDCl_3$)





25

^{13}C NMR (125 MHz, $CDCl_3$)



~x~