

Synthesis and Anti-Parasitic Activity of Dehydrodieugenol B and Analogues

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A thesis submitted to the Board of the Faculty of Physical Sciences in partial
fulfilment of the requirements for the degree of

Doctor of Philosophy

Michaelmas Term 2020

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This thesis describes the optimisation of a copper-catalysed biaryl ether forming reaction, and its application in the synthesis of the anti-kinetoplastid natural products **1**, **2** and **4**, and towards **3**, isolated from the leaves of *Nectandra leucantha*.

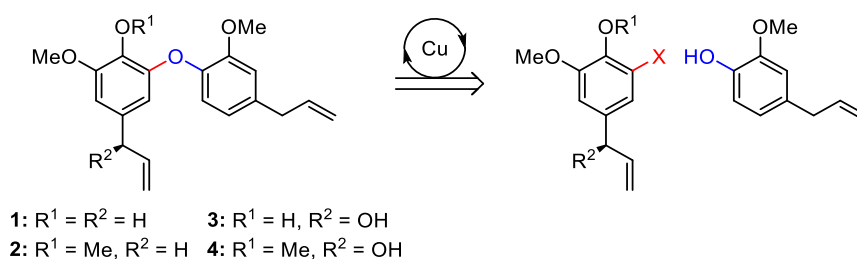


Figure I. Anti-kinetoplastid natural products **1** – **4** and the strategy for their synthesis.

The methodology developed for this synthesis was then applied to a number of synthetic analogues of **1** and **2**, including a deletion study on the biaryl ether core to ascertain the structure-activity relationship of the natural products, and more polar analogues aimed at improved the physicochemical properties of the natural product scaffold for further development.

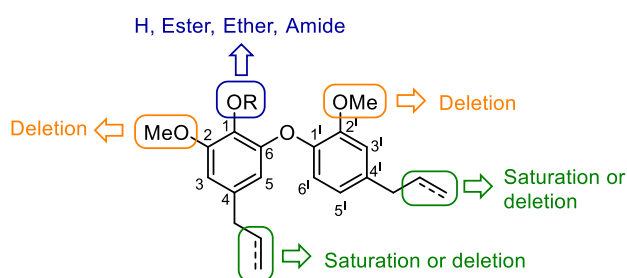


Figure II. Modifications performed on the natural product scaffold leading to synthetic analogues for the elucidation of SAR.

Finally, the analogues were tested for activity against the etiologic agents of the neglected tropical diseases leishmaniasis and Chagas disease, *Leishmania infantum* and *Trypanosoma cruzi*, as well as evaluation of their mammalian cytotoxicity. IC₅₀, CC₅₀ and Selectivity Indexes were calculated. A number of analogues were found to have enhanced activity and selectivity against both parasites, and the results enabled the elucidation of the structure-activity relationship of the natural products.

Acknowledgements

I would like to extend my gratitude to the following people, without whom completion of this thesis would not have been possible.

First, I thank Prof. Ed Anderson for the opportunity to work in his research group. His passion and expertise have been so valuable in my professional and personal development and I could not have asked for a more supportive and understanding mentor and teacher. I would also like to thank our collaborators; Prof João Lago and his student Dr Fernanda Sousa for getting the project off the ground, and Prof. André Tempone, for hosting me in São Paulo, welcoming me into his lab and giving me a crash course in parasitology!

I thank Prof. Martin Smith, Prof. Darren Dixon, and all at the SBMCDT for the funding that made this research possible. I would also like to thank the GCRF and Lady Margaret Hall Academic Development Fund for providing financial support for my visit to Brazil. My thanks go to all the technical staff in the Department of Chemistry in Oxford, and at Instituto Adolfo Lutz in São Paulo.

I thank Dr Joseph Tate at Syngenta for his support and mentorship and for hosting me at Jealotts Hill, and for all the technical staff for their support during my visit.

I am grateful to all of the EAA group, past and present, in particular to Dr Marius Haugland and Dr Pauline Pieper, for their synthesis expertise and advice, as well as their pastoral support. Thank you to Hannah Asiki for helping to bring through more coupling partners. Many thanks go to Thaís, Maiara R, and Maiara A, for looking after me during my first venture into parasitology, and for showing me the best food and drink São Paulo has to offer!

To Nada, my closest friend and ally, thank you for never giving up faith in me and for always cheering me on. Thank you for being there through even the darkest of days.

To Reece, for showing me the way out of the darkness and into the light.

To all of my family, in particular my Mum and Dad, my sisters Helen and Rosie, and my Aunt Georgina for the unconditional love, and personal and professional support. Their continued faith in me motivated me more than anything else.

Finally, I would like to dedicate this thesis to my late Nan and Grandad, Val and Bryan Meadows.

Oxford, December 2020

Claire Sear

*“Behind every successful woman
is herself.”*

List of Abbreviations and Symbols

4Å MS	4 Angstrom Molecular Sieves	DMSO	Dimethylsulfoxide
Ac	Acetyl	DNA	Deoxyribonucleic Acid
ADMET	Absorption, Distribution, Metabolism, Excretion, Toxicity	DNDi	Drugs for Neglected Diseases Initiative
Am.	Amastigote	dq	Doublet of Quartets
APCI	Atmospheric Pressure Chemical Ionisation	dt	Doublet of Triplets
Ar	Aryl	Eq	Equivalents
Asym. Red.	Asymmetric Reduction	EI	Electron Impact
ATR	Attenuated Total Reflection	ESI	Electrospray Ionisation
BBi	Bisbenzyltetrahydro-isoquinoline	FBS	Fetal Bovine Serum
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl	FDA	Food and Drugs Administration
Bn	Benzyl	GCRF	Global Challenges Research Fund
CC₅₀	50% Cytotoxic Concentration	HBA	Hydrogen Bond Acceptors
CI	Chemical Ionisation	HBD	Hydrogen Bond Donors
CL	Cutaneous Leishmaniasis	HMBC	Heteronuclear Multiple-Bond Correlation Spectroscopy
Conc.	Concentration	HRMS	High Resolution Mass Spectrometry
COSY	Homonuclear Correlation Spectroscopy	HSQC	Heteronuclear Single-Quantum Correlation Spectroscopy
DCM	Dichloromethane	IC₅₀	50% Inhibitory Concentration
Decomp.	Decomposition	IR	Infrared
δ	Chemical Shift	Isom.	Isomerised / Isomerisation
d	Doublet	J	Coupling Constant
dd	Doublet of Doublets	L-AmbB	Liposomal Amphotericin B
DIPEA	<i>N,N</i> -diisopropyl- <i>N</i> -ethylamine	<i>L. donovani</i>	<i>Leishmania donovani</i>
DME	Dimethoxyethane	<i>L. infantum</i>	<i>Leishmania infantum</i>
DMG.HCl	<i>N,N</i> -Dimethylglycine hydrochloride	Lit.	Literature
DMF	Dimethylformamide	LRMS	Low Resolution Mass Spectrometry
DMP	Dess – Martin Periodinane	m	Multiplet

MCL	Mucocutaneous leishmaniasis	RSM	Recovered Starting Material
MOM	Methoxymethyl	rt	Room Temperature
MP	Melting Point	SAR	Structure-Activity Relationship
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide	SBMCDT	Synthesis for Biology and Medicine Centre for Doctoral Training
MW	Molecular Weight	s	Singlet
m/z	Mass to Charge Ratio	SD	Standard Deviation
NA	Not Active	SE	Standard Error
NADH	Nicotinamide adenine dinucleotide	Sext	Sextet
ND	Not Determined	SI	Selectivity Index
NIS	<i>N</i> -Iodosuccinamide	SM	Starting Material
NMP	<i>N</i> -Methylpyrrolidinone	spp.	Species (plural)
NMR	Nuclear Magnetic Resonance	sp.	Species (singular)
NR	No Reaction	SSB	Sodium Stibogluconate
NTD	Neglected Tropical Disease	t	Triplet
on	Overnight	TBAF	<i>Tert</i> -Butylammonium Fluoride
Ox.	Oxidation	TBS	<i>Tert</i> -Butyldimethylsilyl
P	Product	<i>T. cruzi</i>	<i>Trypanosoma cruzi</i>
PAINs	Pan-Assay Interference	Tf	Triflate
PBS	Phosphate-Buffered Saline	THF	Tetrahydrofuran
PG	Protecting Group	TLC	Thin Layer Chromatography
PKDL	Post Kala-Azar Dermal Leishmaniasis	TMEDA	Tetramethylethylenediamine
PKPD	Pharmacokinetic / Pharmacodynamic	TMHD	2,2,6,6-Tetramethylheptane-3,5-dione
PMB	<i>Para</i> -Methoxybenzyl	TMS	Trimethylsilyl
Prom.	Promastigote	tPSA	Total Polar Surface Area
PTSA	<i>para</i> -Toluenesulfonic Acid	Tryp.	Trypomastigote
q	Quartet	UV	Ultraviolet
quin	Quintet	VL	Visceral Leishmaniasis
R	Generic Group	$\nu_{\max}$	Wavelength
R_f	Retention Factor	WHO	World Health Organisation
ROS	Reactive Oxygen Species	X	Halide

Table of Contents

Abstract	i
Acknowledgements	ii
List of Abbreviations and Symbols	iv
Table of Contents	vi
 1. Introduction	 1
1.1 Protozoan Parasitic Diseases	1
1.2 Anti-Kinetoplastid Drug Discovery	13
1.3 Anti-Parasitic Natural Products	15
1.4 Neolignan Biaryl Ether Natural Products	24
 2. Synthesis of Natural Products 1 – 4	 29
2.1 Retrosynthetic Strategy	29
2.2 Copper-Catalysed Biaryl Ether Formation on Sterically and Electronically Demanding Systems	31
2.3 Optimisation of Biaryl Ether Formation on a Model System	34
2.4 Synthesis of Halide Coupling Partners for 1 and 2	41
2.5 Coupling and Deprotection	43
2.6 Side Chain Installation Post-Ullmann Coupling	45
2.7 Alternative Protecting Groups for the Ullmann Coupling	51
2.8 Alternative Catalytic Systems	53
2.9 Studies Towards the Synthesis of 3 and 4	59
 3. Design and Synthesis of Analogues of 1 and 2	 67
3.1 Analogue Design	67
3.2 Analogue Synthesis	70
3.3 Chapter Summary and Future Work	78
 4. Anti-Parasitic Activity of Synthetic Analogues	 80
4.1 Mammalian Cytotoxicity	80
4.2 <i>Leishmania infantum</i> Intracellular Amastigote Assay	87
4.3 <i>Trypanosoma cruzi</i> Assays	90
4.4 <i>In silico</i> Predicted Physicochemical Properties	98
4.5 Mechanism of Action	100

5. Conclusions and Future Work	102
5.1 Learning More About the Best Analogues	102
5.2 Further Analogues	104
 6. Experimental	 107
6.1 Parasitology Assays.....	107
6.2 Synthesis of Compounds	110
6.3 NMR Spectra of Final Compounds	196
 7. References	 226

1. Introduction

1.1 Protozoan Parasitic Diseases

The word ‘parasite’ is derived from Latin ‘*parasītus*’ or Greek ‘*parásitos*’, meaning ‘to eat at another’s table’.¹ This derivation is appropriate, as a parasite is an organism which lives on or in another, known as the host, from which it obtains nutriment. The host, meanwhile, does not benefit at all. Parasites are responsible for numerous diseases worldwide, from tape worm to malaria. There are three main classes of parasites that can cause disease in humans: protozoa, helminths, and ectoparasites.² This thesis will focus on the protozoan parasites.

‘Protozoa’ is an informal term for a single-celled eukaryote, derived from the Greek ‘*prōtos*’, meaning ‘first’ and ‘*zōa*’ meaning ‘animals’. They often display animal-like properties, such as motility and predation, and lack a cell wall, as many plants and algae possess.³ Protozoan parasites fall broadly into four major classes; Sarcodina, Mastigophora, Ciliophora, and Sporozoa.² Within the mastigophora group is the sub-group, kinetoplastids. These parasites are defined by the presence of a kinetoplast, which is a network of circular DNA inside the mitochondrion. This group includes the two parasites which are the focus of this thesis; *Trypanosoma cruzi* and *Leishmania* spp., the etiologic agents of Chagas disease and leishmaniasis respectively⁴

1.1.1 The Leishmaniasis

The leishmaniasis are a group of neglected tropical diseases which affect humans and animals throughout the world. They are caused by over 20 species of the *Leishmania* parasites, and transmitted by the bite of female infected sand-flies. The leishmaniasis can be both anthroponotic, where humans are the main reservoir, or zoonotic, where animals are the reservoir. It is a common infection in dogs in particular.⁵

1.1.1.1 Visceral Leishmaniasis (VL)

Visceral Leishmaniasis (VL), also known as kala-azar ('black fever') in India, is the most serious form of the disease. Current estimates show an annual global incidence of 0.2 – 0.4 million people worldwide.⁶ Over 90% of all VL cases occur in the poorest areas of six countries: Brazil, India, South Sudan, Sudan, Ethiopia, and Bangladesh.⁷ The disease is caused exclusively by *L. donovani* in the subtropics of Asia and Africa, and *L. infantum* in the drier parts of Latin America and in the Mediterranean region, especially in Italy, France, and Spain, where the dog is the reservoir species and also the main victim.⁸ *L. infantum* instances have reduced in areas where living standards have improved, where *L. donovani* infection continues to result in VL epidemic outbreaks.⁹ The symptoms of VL are severe, and are a result of the parasite migrating from the site of infection to the internal organs. They include fever, significant weight-loss, hepatosplenomegaly, and anaemia. VL is almost certainly fatal if left untreated, with 20,000 – 30,000 deaths per year and the fatality rate in some developing countries reaching 100% in two years.^{10,11}

1.1.1.2 Post Kala-Azar Dermal Leishmaniasis (PKDL)

Post Kala-Azar Dermal Leishmaniasis is a complication arising from VL cases resulting from *L. donovani* infection. In 5% to 60% of cases, during or after treatment, dermatosis develops resulting in papal nodules on the skin infected with the parasite. These nodules are considered a reservoir for the parasite, particularly in interepidemic times.¹²

1.1.1.3 Cutaneous Leishmaniasis (CL) and Mucocutaneous Leishmaniasis (MCL)

Cutaneous Leishmaniasis (CL) is the most common and least serious form of *Leishmania* sp. infection. It is characterised by skin lesions at the site of the sand-fly bite, which can be painful and result in scarring and disfigurement. It is caused by numerous forms of the *Leishmania* parasite, dependent on the geographical region. There are 1.5 – 2 million cases worldwide, although it is likely that this is an underestimate due to asymptomatic infections and poor diagnosis. CL is endemic in 70 countries worldwide but 90% of cases are found in Afghanistan, Algeria, Brazil, Pakistan, Peru,

Saudi Arabia, and Syria.¹³ Despite the growing incidence worldwide, the low fatality rate means that CL is classed as a Neglected Tropical Disease (NTD), with little financial incentive to control the spread or find a cure for the disease.¹⁴ In immunocompromised cases, such as those with HIV/AIDS, CL is considered more serious as the parasite can visceralise and give rise to VL. As such, in areas where HIV and leishmaniasis overlap, the co-infection incidence is very high.¹⁵ Mucocutaneous leishmaniasis (MCL) is a potentially life-threatening condition resulting from CL, in which the lesions can lead to partial or total destruction of the mucous membranes of the nose, mouth, and throat cavities, occasionally leading to aspiration pneumonia. MCL can be severely disfiguring and lead to social rejection by the community (Figure 1).^{16,17}



Figure 1. Patient with lesion due to PKDL (left, image from ref. 16) and patient with MCL (right, image from WHO.int).

1.1.1.4 Parasite Life Cycle

The *Leishmania* parasite assumes two distinct forms at various stages of its life cycle. The promastigote form is the extracellular form that exists in the female sand-fly digestive tract. The promastigote cell body is elongated, with a long flagellum serving as a motility aid, presumably to allow the promastigote to migrate through the sand-fly gut and into the host at the point of infection. The intracellular amastigote form is assumed when the parasite enters the cells of the infected host, and retains the same cellular architecture as the promastigote, but has a drastically different morphology. The amastigote has a smaller, more spherical cell body and a short flagellum which has a sensory function.¹⁸ The amastigote is the form of the parasite assumed when infecting the human form, and therefore is the most clinically relevant of the two forms.

During the blood meal of the infected sand fly, the metacyclic promastigotes enter mammalian host cells and transform from promastigote to amastigote. Human immune macrophages are recruited to the site of the damage, and here they phagocytose the parasites, becoming infected. The promastigote is engulfed, forming the acidic parasitic vacuole (parasitophorous vacuole), affording the parasite some protection against the defence mechanisms of the host macrophage. Once inside the parasitic vacuole, differentiation to the amastigote morphology occurs, affording a smaller surface area / volume ratio for the parasite body, and providing further protection from the harsh environment within the macrophage. The slower growth rate of the amastigote vs the promastigote, and the reduced metabolic load as a result of its smaller size, mean the host macrophage cell is not overwhelmed, and survives longer as a host to the parasite.^{18,19} Whilst in the amastigote form, the parasite will multiply, and infect further cells. Because of this relationship, a key challenge when designing new therapies for leishmaniasis is to kill the parasite whilst maintaining the integrity of the host human macrophage.

When the sand fly bites a human and ingests the infected macrophages, differentiation from the amastigote to the promastigote occurs, likely as a result in changes of temperature and pH. Differentiation occurs within the parasitic vacuole. The flagellum and cell body elongate, and the parasite becomes motile once again.¹⁸

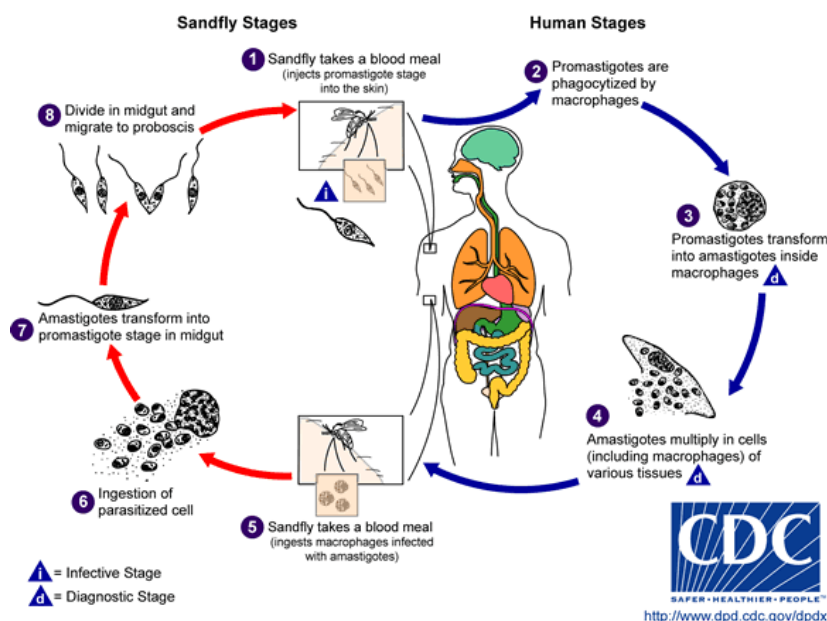


Figure 2. The *Leishmania* parasitic life cycle. Image taken from [cdc.gov](http://www.cdc.gov).⁶

1.1.1.5 Current Treatments for Leishmaniasis

In 1912, Brazilian researcher Gaspar de Oliveira Vianna discovered the efficacy of the emetic tartar (trivalent antimony) for leishmaniasis.²⁰ Pentavalent antimonials were then developed in 1945 and remain the first-in-line treatment for both VL and CL in most endemic countries. The most commonly used antimonials are sodium stibogluconate (**12**, Pentostam™, SSB) and *N*-methyl glucamine antimoniate (**13**, Glucantime™), and despite the long-time and widespread use of these drugs, until recently little was known about the structures, and their mechanisms of action are still poorly defined.²¹ They are thought to operate through one or a combination of three possible mechanisms: reduction from Sb(V) to the more active Sb(III) by both parasitic and mammalian thiols, intrinsic antileishmanial activity of Sb(V) through inhibition of macromolecular biosynthesis in the amastigote, or by modulation of the immune response by the mammalian host. In the last two decades, growing clinical resistance to pentavalent antimonial treatment has emerged, resulting in reduced efficacy of the drugs. Resistant parasites grew out of the North Bahir region of India where antimonial treatment was widely available and often misused – only 26% of cases were treated using the prescribed guidelines.¹⁵ Antimonial treatment is also marred by the presence of very significant side effects including cardiotoxicity and hepatotoxicity, as well as nausea, vomiting, weakness and myalgia, abdominal colic, diarrhoea, and skin rashes. As such, there is a clear and urgent need for a new generation of treatments.²¹

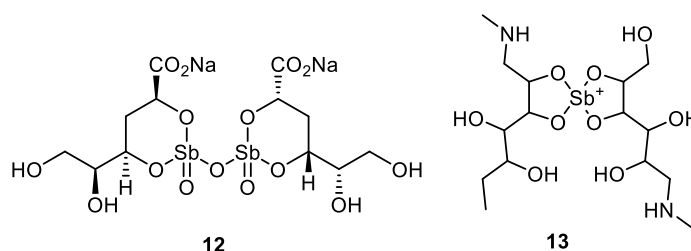


Figure 3. Sodium stibogluconate (left) and *N*-methyl glucamine antimoniate (right).

Drug repurposing is a common route to new anti-parasitic treatments, as a cheaper and more efficient way to bypass many of the safety testing procedures in modern pharmaceutical development. Originally developed as an antifungal agent, conventional amphotericin B (Am-B, **14**, Figure 4) is a common second in line treatment for leishmaniasis, particularly in India where resistance to

antimonials is common, and also Brazil where it is popular due to a large body of evidence to support its use.²² Amphotericin B causes a large influx of ions into the parasite cell body by increasing the permeability of the cell membrane, leading to parasite death. However, amphotericin B treatments suffer from long administrative regimes (typically 1 mg / kg every other day over 30 days) requiring hospitalisation, and also high levels of nephro- and hepato-toxicity and side effects such as nausea, weakness, headaches, weight gain, and hypotension. Hence, the effectiveness of conventional amphotericin B is limited outside of India. There is a large amount of interest in liposomal amphotericin B (L-AmB, Ambisome™) due to reduced toxicity, and it has shown promising results in clinical trials as a sole therapy and also in combination with other new therapies.^{23, 24} However, the high cost of these formulations means their use is limited in the poorer countries where leishmaniasis is most prevalent.²⁵

Pentamidine (**16**, Figure 4) is an antimicrobial used to treat pneumonia, and also other protozoan parasitic diseases such as African Trypanosomiasis. It has been shown to be effective against leishmaniasis cases caused by *L. braziliensis* and *L. guyanensis*.²⁶ It is thought to interfere with the parasite DNA synthesis, and through modifying the morphology of the kinetoplast, leading to parasite death. Again its efficacy is restricted by toxicity to pancreatic function and side effects such as nausea and vomiting, hypoglycaemia, hypotension, and diabetes, and parasitic resistance to the drug has been described.^{22, 27}

Miltefosine (**15**, Figure 4) is an alkyl-phospholipid that was originally developed for the treatment of cutaneous cancers and has subsequently been applied to the treatment of leishmaniasis. It is the first orally available treatment for the disease, including antimony-resistant strains. It cures 94% of cases and has a reasonable safety profile compared with other treatments.²⁸ It works by inhibition of phospholipid and sterol biosynthesis in the parasite. However, treatment with miltefosine is administered over a long period (28 days) which increases the risk of resistance developing. It has also show teratogenic properties, preventing its use in pregnant women.^{29, 25}

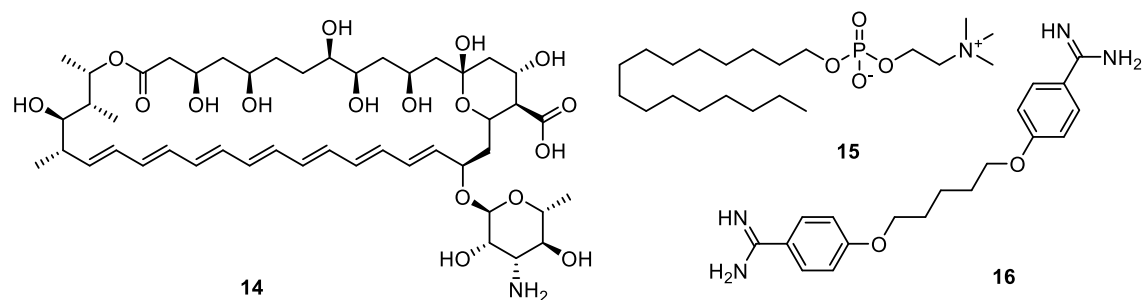


Figure 4. Amphotericin B (left), miltefosine (top right), and pentamidine (bottom right).

All of the current common therapies for leishmaniasis suffer from one or more of the following: poor safety profile, intolerable side effects, high cost, developing resistance. There is therefore an urgent need for new and effective treatments.¹⁶

1.1.1.6 Potential New Treatments for Leishmaniasis

Despite the challenges associated with treating leishmaniasis, there are a number of potential new therapies in the pipeline. Sitamaquine (**17**, Figure 5) is an 8-aminoquinoline originally developed for malaria, and after miltefosine, is the second orally administrated treatment for visceral leishmaniasis. It completed phase II clinical trials in India, Kenya, and Brazil, but showed nephrotoxicity at high doses, so research was suspended due to low efficacy at tolerated doses.³⁰ Azoles, such as fluconazole (**18**, Figure 5), itraconazole and ketoconazole are known to inhibit parasite ergosterol synthesis, and as such have been tested in numerous clinical trials for cutaneous leishmaniasis. However, the clinical trial results are mixed. A 6.5 – 8.0 mg / kg / day dose of fluconazole lasting 28 days was shown to have 22% cure rate, vs 53% for standard pentavalent antimonials.³¹ Fexinidazole (**19**, Figure 5) is a drug developed by the DNDi for the treatment of African Trypanosomiasis, or African Sleeping Sickness. Phase II clinical trials using fexinidazole in the treatment of VL in Sudan were promising but abandoned due to a lack of long-term efficacy – only three out of 14 patients remained cured after a six-month follow up.³² Because of the oral availability and also the studied safety profile of the drug, it is currently being investigated as a combination therapy with miltefosine.³³

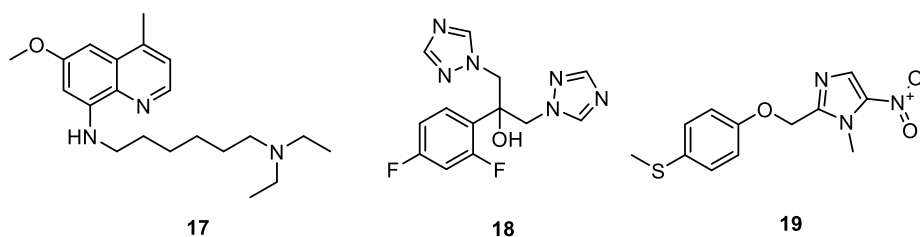


Figure 5. Sitamaquine (left), fluconazole (middle), and fexinidazole (right).

Local thermotherapy has also been shown to be an effective treatment for CL and is commonly studied, based on the observation that *Leishmania* spp. do not multiply *in vitro* at temperatures above 39 °C.³⁰ For example, in a trial in Peru, a low-cost heat pack at an initial temperature of 52 °C applied to the lesion for three minutes daily for 7 days, resulted in a 60 % cure rate.³⁴ Thermotherapy is desirable as it is low cost, requires little monitoring and has high adherence – the drawbacks are the risk of burns and the need for local anaesthesia and sterilisation.³⁵ Likewise, cryotherapy has been trialled for CL, causing parasite cell death *via* the formation of intracellular ice crystals.³⁰ Therapy involves the application of liquid nitrogen at -195 °C once or twice weekly for up to 6 weeks. Cryotherapy was found to have similar efficacy to Sb(V). However, it is associated with edema at the site of application, burning, and secondary infections.³⁶

Combination therapy is a popular option for treatment of leishmaniasis due to its success in other diseases such as HIV, malaria, and tuberculosis, and numerous combinations of drugs have been trialled, including SSB (**12**) and paromomycin, which was discovered during the epidemic of VL in southern Sudan in the 1980s, and has been used as a first-in-line treatment in Africa since 2002. Likewise, combination therapies employing L-AmB (**14**) and miltefosine (**15**) have been shown to be highly effective, with several trials reaching phase III and phase IV. These combination therapies require much shorter hospitalisation times than monotherapy with L-AmB – in most cases the L-AmB is administered in a single dose and the patient self-administers miltefosine for the remainder of the treatment.³³

1.1.2 Chagas Disease

Chagas disease (also referred to as American Trypanosomiasis) is endemic to Latin American but more recently has spread to other continents through mass human population movements, and now affects around six to seven million people worldwide.^{37,38} In the United States of America the disease is estimated to affect around 300,000 people, mostly among people originally from Latin America. However, the disease remains neglected due to the lack of understanding regarding identifying and managing infection.³⁹ It is caused by infection with the protozoan parasite *Trypanosoma cruzi*, and is spread most commonly through the bite of the triatomine (kissing) bug, but can also be transmitted through eating contaminated products, blood transfusions, and congenital transmission. Like leishmaniasis, it is both anthroponotic and zoonotic. The disease is characterised by two phases; the acute phase and the chronic phase.⁴⁰

1.1.2.1 Acute Phase

The acute phase of the disease occurs immediately after the insect bites, and lasts four to eight weeks. Usually a reaction occurs at the bite site, resulting in itchiness, allowing the parasite to migrate to the blood stream through wounds created by scratching. A classic sign is also edema of both eyelids, caused by migration of the parasite to the conjunctiva. This is usually accompanied by general malaise. In cases where transmission occurs through an oral route or blood transfusion, often the acute phase is asymptomatic but can be accompanied by fever. Splenomegaly and polylymphadenopathy have also been described.⁴⁰ It has been known since Carlos Chagas' pioneering studies that up to 60% of infected patients have no symptoms, suggesting cardiovascular or gastrointestinal involvement. In endemic areas, acute and serious cases of Chagas disease have shown myocardial involvement in approximately 80% of infected individuals. Mortality rates of 2 – 7% are described during an acute crisis and mortality is higher in children.^{41,42}

1.1.2.2 Chronic Phase

Following the acute phase, a latent phase is achieved where the patient is asymptomatic and an equilibrium is reached between the parasite load and the host immune response. However, the host remains infected and acts as a reservoir for the *T. cruzi* infection, and symptoms can develop later on. For example, cardiomyopathy can occur 10 – 20 years after the acute infection. Inflammation and fibrosis of the myocardium can lead to arrhythmias, thromboembolism, heart failure and sudden death. Also, in about 10% of patients with chronic Chagas disease, peripheral nervous system damage is observed. Diminished sensitivity to touch, particularly in the lower limbs, is one of the most common symptoms. *T. cruzi* infection can also lead to dysfunction of the digestive system, specifically by formation of Chagasic lesions in the digestive tract, most commonly resulting in mega-oesophagus and megacolon. The chronic phase of the disease will last for the rest of the patient's life.⁴⁰

1.1.2.3 Parasite Life Cycle

The *T. cruzi* parasitic cycle has four distinct parasite forms – the metacyclic and bloodstream trypomastigote forms, and the replicating amastigote and epimastigote forms. The epimastigote exists in the gut of the triatomine bug where it transforms into the metacyclic trypomastigote, and then is excreted onto the host skin when the insect takes a blood meal. The metacyclic trypomastigote will begin to invade cells at the site of the bite, by promoting lysozyme formation at the cell membrane and creating a parasitic vacuole. Once inside the cell, the trypomastigote differentiates into the amastigote form, which proliferates within the host cell. Once a high parasitic density is achieved, the amastigotes can transform into the bloodstream trypomastigote form and are released into the blood, where they can invade new cells in a similar fashion. Unlike the promastigote in *Leishmania* spp., this bloodstream trypomastigote form has clinical relevance as it is present in high density in an infected host. In the acute phase of infection, the amastigote form can also exist in the blood, particularly when cells are lysed prematurely. When the triatomine bug now takes a blood

meal from the mammalian host, it ingests a mixture of trypomastigote and amastigote forms, completing the life cycle of the parasite.⁴³

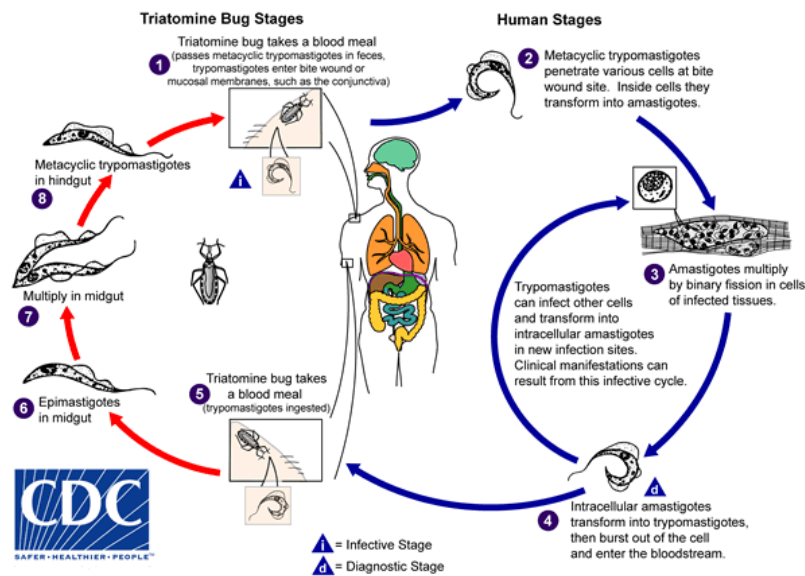


Figure 6. The *T. cruzi* parasitic life cycle. Image from cdc.gov.⁴⁴

1.1.2.4 Current Treatments for Chagas Disease

Nifurtimox (**20**, Figure 7) is a nitrofurantoin and was the first drug developed for the treatment of Chagas disease, as well as African Sleeping Sickness, in 1965. It is now on the World Health Organisation's (WHO) List of Essential Medicines and is provided by the WHO for free in regions where the disease is common. Its effectiveness varies depending on disease phase, patient age and geographical area. Typically, the best results are seen during the acute phase for children (cure rates of 88 – 100%) but the effectiveness of treatment in adults in the chronic phase is low (7 – 8%). The most common side effects include weight loss, paraesthesia, drowsiness or excitability, vomiting, intestinal cramps. There is also some evidence that incomplete treatment with nifurtimox has allowed resistant parasites to develop.^{45,46} Benznidazole (**21**, Figure 7) was developed towards the end of the 1970s and was shown to be similarly active against *T. cruzi* but with fewer side effects. However, like nifurtimox, it demonstrates very low cure rates in the chronic phase (8%) compared to the acute phase (76%).^{47,48} Success is also highly dependent on parasite strain and geographical location. There remain several unpleasant side effects to benznidazole including skin manifestations, paraesthesia, neuropathy and

agranulocytosis. In some cases, side effects have led to treatment interruption. The mechanism of action of these drugs is not well understood; they are thought to cause reductive stress in the parasite – the reduction of the nitro group to the nitro radical anion, then autooxidation of the radical produces highly toxic oxygen metabolites. *T. cruzi* has poor detoxification mechanisms for these reactive oxygen species (ROS), rendering the parasite highly susceptible to such metabolites compared with the mammalian host cells.⁴⁵ We can now project that 200,000 people living with Chagas disease will die from heart disease and related complications in the next five years. We urgently need to redouble our efforts to identify and treat young people who are still in the early stages of their illness, but ultimately we need to find better treatments and new cures.⁴⁹

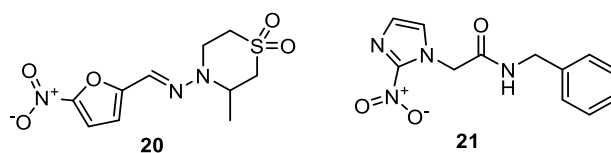


Figure 7. Left: nifurtimox and Right: benznidazole.

1.1.2.5 Potential New Therapies for Chagas Disease

Currently there are relatively few clinical trials ongoing for the treatment of Chagas disease. As with leishmaniasis, potential new therapies mostly arise out of repurposing old drugs or a combination of known therapies. Posaconazole (**22**, Figure 8) is a known, commercially available inhibitor of CYP51 – a fungal and protozoan cytochrome P450, and posaconazole is licensed for treating a number of fungal infections. After displaying promising anti *T. cruzi* activity *in vivo* and in murine models, the drug was moved into phase II clinical trials. However, the efficacy was found to be less than that of benznidazole, and the high cost of the drug hinders its use in developing countries in which Chagas disease is prevalent.⁵⁰ In contrast, ravuconazole (**23a**, Figure 8) is a known antifungal with a much simpler chemical structure and lower price, and displayed promising anti-parasitic activity in animal models. E1224 (**23b**, Figure 8) is a pro-drug that converts to ravuconazole in the body, leading to higher absorption and bioavailability. E1224 has a good safety profile and was effective in clearing *T. cruzi*. However the cure rate was low (8 – 31%) after one year of treatment.⁵¹

Research remains ongoing however, and a new trial is continuing from the Drugs for Neglected Diseases Initiative (DNDi) for a combination therapy with benznidazole and E1224.⁵² Amiodarone (**24**, Figure 8) is an anti-arrhythmic agent used to treat the symptoms of chronic cardiomyopathy associated with Chagas Disease. It has been shown to have direct activity against *T. cruzi* both *in vivo* and *in vitro*. This drug has the dual role of being both an anti-arrhythmic and an anti-infective agent. It has also since been used as a starting point to develop other more potent anti *T. cruzi* derivatives.⁵³ Fexinidazole (**19**), the antileishmanial drug, is also a potent antitrypanosomal agent and has shown high levels of parasitological cure in murine models against benznidazole-resistant strains, both in acute and chronic Chagas disease. Interestingly, it has also recently been shown that sulfone and sulfoxide metabolites of fexinidazole were more effective than either fexinidazole itself, or benznidazole.^{45,54}

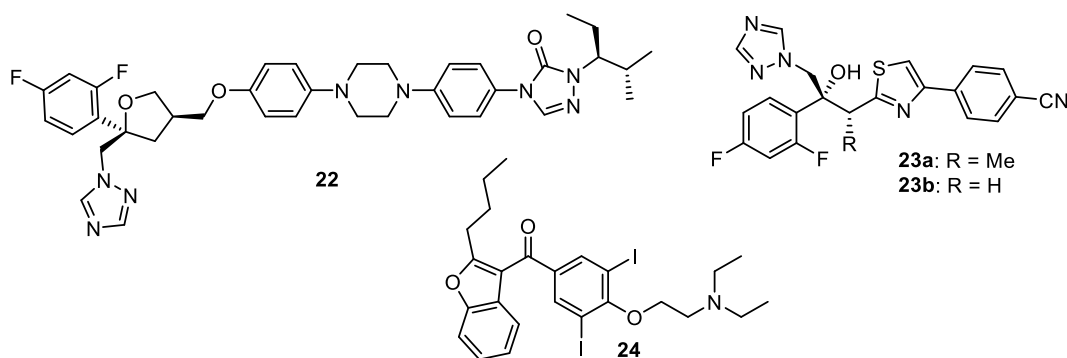


Figure 8. Posaconazole (**22**), ravuconazole (**23a**), E1224 (**23b**) and amiodarone (**24**).

1.2 Anti-kinetoplastid Drug Discovery

The Drugs for Neglected Diseases initiative (DNDi) is a patients' needs driven partnership which looks in particular at the kinetoplastid parasites *T. cruzi* and *L. donovani*, as well as *Trypanosoma brucei*, the related causal parasite of African Trypanosomiasis (African Sleeping Sickness).⁵⁵ Typically, many modern drug screening programs use a target-based approach where an essential protein in the parasite is validated and hits are identified using a high-throughput screen against that target.^{56,57} However despite the completion of the Tritryp program – the sequencing of the full genomes of these three parasites in 2005 – there remains a paucity of validated targets for screening

libraries against these diseases.⁵⁸ Most of the drugs in the field act *via* an unknown, or unclear at best, mechanism of action, and of the validated targets that do exist, none have led to new drug candidates in clinical research.⁵⁹

A similar problem is faced in many anti-infective drug discovery programs – antibiotic research at GlaxoSmithKline has recently reverted to using whole-cell screens and *in vivo* phenotypic assays as early in the discovery process as possible.^{57,60}

Similarly, the DNDi in collaboration with Institut Pasteur Korea and the University of Dublin have now developed high-content medium-throughput assays against the intracellular amastigotes of *T. cruzi* and *L. donovani*, where the host cells are infected with the parasite. These assays can differentiate between infected and non-infected host cells, as well as discriminate between parasite death due to specific pathogen killing, or due to host cell damage.^{57,61}

Due to the relative complexity of these assays and the medium-throughput, some selectivity is required when choosing libraries to screen. Typically screening libraries come from one of the following categories:⁵⁷

- Indication/repositioning libraries – compounds that have progressed to preclinical and clinical development for other indications
- Specific pharmacokinetic, absorption, distribution, metabolism, excretion criteria (PK/ADME)
- Known anti-infectives
- Target-based libraries such as protease or kinase inhibitors
- Diversity libraries where a smaller characteristic library is chosen to represent a much larger library

The hit-rates from such screens have so far been very low – around 0.1% for *L. donovani* and 0.3% for *T. cruzi*. This low hit rate is not surprising given the complexity of the assays. In order to reach a target in the amastigote, the compound must first pass through two host cell membranes, often in hostile environments such as low pH, and enter the parasitic vacuole where the amastigote resides.

L. donovani is a particularly challenging target as it has developed very specific strategies for survival inside the host cell, including slowed replication and reduced metabolism.^{62–64}

Because of these challenges, where the mechanism of action or structure-activity relationship is not known it is safer to rely on hit compounds with high potency in a whole-cell assay, and then carry out PK/ADME optimisation around the hit to improve *in vivo* efficacy. Table 1 indicates the criteria outlined by the DNDi for progressing compounds from hit to lead status.⁵⁷

Table 1. Hit and Lead criteria for progression of compounds.

Parameter	Hit <i>Leishmania</i> sp.	Hit <i>T. cruzi</i>	Lead <i>Leishmania</i> sp.	Lead <i>T. cruzi</i>
Activity	IC ₅₀ ≤ 10 μM in intracellular amastigote assay ^a	IC ₅₀ ≤ 10 μM in intracellular amastigote assay ^b	IC ₅₀ ≤ 1 μM ^c	IC ₅₀ 10 – 20 fold increase over Hit
Selectivity	10 fold vs mammalian cell line		Increased over Hit ≥ 50 fold more active vs mammalian cell line	

^a*L. donovani* or *L. infantum*. ^bTcVI (Tulahen) or TCII/Y strain. ^cAgainst a panel of clinical isolates and antimonial resistant strain.

1.3 Anti-parasitic Natural Products

Natural products have been used as medicines throughout history, from the use of folk medicines to treat ancient diseases, to present day herbal remedies, where natural products are employed in a relatively unrefined form. More recently, 50% of all FDA approved drugs are derived from chemical scaffolds provided by Nature, and antimicrobials and anticancer drugs probably even higher still. Natural products also have the benefit in drug discovery of rarely being defined as PAINS (Pan-Assay Interference Compounds). PAINS are molecules which can quickly be ruled out of the drug discovery process as they contain motifs likely to result in assay interference such as metal chelation and protein reactivity.⁶⁵ This, combined with the fruitful history of natural products in infectious diseases, makes them popular subjects of research for both leishmaniasis and Chagas disease.

1.3.1 Natural Products Active Against *Leishmania* spp.

Two of the current approved drugs for leishmaniasis are natural products – amphotericin B was originally isolated from soil bacterium *Streptomyces nodosus* and has been used as a broad-spectrum antibiotic, antifungal and anti-parasitic for over 50 years. Likewise, paromomycin was isolated from the bacteria *Streptomyces nodosus* in 1959. Natural product research against *Leishmania* spp. has been extensive and a number of compounds have progressed to pre-clinical animal models.

The following section comprises a review of selected natural products with notable *in vivo* activity against various *Leishmania* parasites, and can be broken down into the following subgroups: alkaloids, terpenoids, saponins, phenylpropanoids, flavonoids, lignoids, naphthoquinones, and iridoids.^{65,66}

γ -Fagarine (**25**, Figure 9) is an alkaloid isolated from *Helietta apiculata* and has shown a 97% reduction in liver parasite load in a BALB/c mice model administered orally at 10 mg kg⁻¹ over 15 days, superior to glucantime at 67% reduction.⁶⁷ Similarly, the medicinal plant *Peganum harmala*, which is used frequently in India for the treatment of parasitic diseases, produces pegamine hydrochloride (**26**, Figure 9) which has been shown to reduce the splenic parasite burden in hamsters by 88% at 200 mg kg⁻¹.⁶⁸ A third example is araguspongin C (**27**, Figure 9) isolated from marine sponge *Haliclona exigua*. This compound exhibited a 38% reduction in splenic parasite burden in a hamster model, when administered orally for five days at 100 mg kg⁻¹.⁶⁹

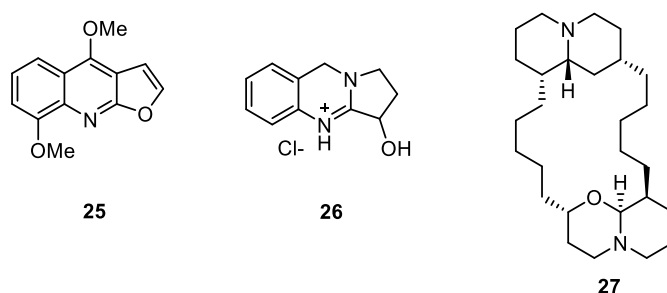


Figure 9. Alkaloid natural products with promising anti-leishmanial activity *in vivo*; γ -fagarine (left), pegamine hydrochloride (middle) and araguspongin C (right).

Two bisbenzoisoquinoline (BBI) natural products, berbamine (**28**, Figure 10) from *Berberis boliviana* and isotetradine (**29**) from *Limacopsis loangensis* were administered subcutaneously to BALB/c mice infected with *L. amazonensis* and *L. venezuelensis* at 100 mg kg⁻¹ day⁻¹. The lesion growth was found to be slower than the untreated mice in both cases.⁷⁰

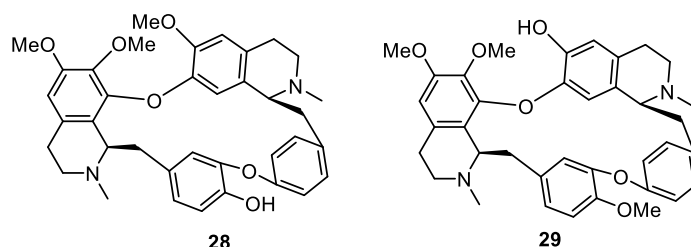


Figure 10. BBI natural products berbamine (left) and isotetradine (right).

The monoterpene limonene (**30**, Figure 11) has been shown to be a potent anti-parasitic compound. In a study of *L. amazonensis* infection in C57BL/6 mice, 100 mg kg⁻¹ day⁻¹ administered intrarectally for two weeks resulted in a parasite load reduction of 99% and a significant reduction in lesion size in 80% of the mice.⁷¹ Bisabolol, (**31**, Figure 11) isolated from chamomile, was administered orally to BALB/c mice infected with *L. infantum* at 200 mg kg⁻¹ for two weeks. It was found to reduce the spleen and liver parasite loads by 72% and 89% respectively and was shown to be at least as safe and effective as the standard drug, meglumine antimoniate.⁷² Finally, the diterpenoid lactone derivative **32** was found to be effective in reducing parasite loading in the spleen of golden hamsters infected with *L. donovani* by 88% at the highest dose tested of 250 mg kg⁻¹ administered orally for five days.⁷³

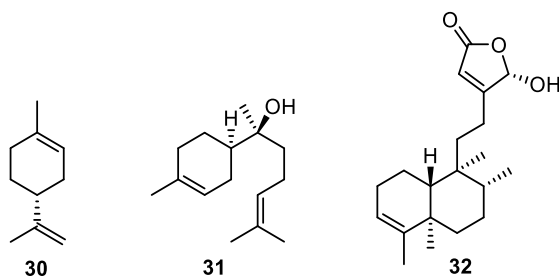


Figure 11. Terpenoid natural products with promising anti-leishmanial activity in vivo; limonene (left), (–)-α-bisabolol (middle) and 16a-hydroxycyclocleroda-3,13,14-Z-dien-15,16-olide (right).

Holothurin B (**34**, Figure 12) is a saponin natural product isolated from coral reef sea cucumber *Actinopyga lecanora*. It was administered orally to hamsters infected with *L. donovani* at 100 mg kg⁻¹ day⁻¹ for five days, which resulted in a parasite burden reduction of 72%. Related compound holothurin A (**33**) also showed moderate efficacy under the same regimen (45%).⁷⁴ Compound **35**, purified from a mixture of six related maesabalides isolated from *Maesa balansae*, showed a reduction in liver amastigote burden of 99% within seven days and 83% within 56 days of treatment, when administered prophylactically to *L. donovani* infected BALB/c mice.⁷⁵

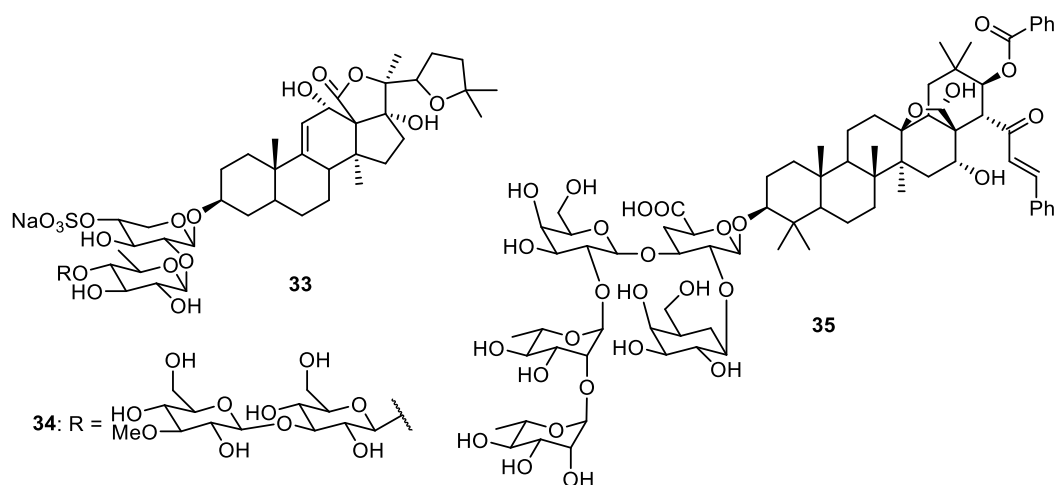


Figure 12. Saponin natural products with promising anti-leishmanial activity in vivo; holothurin A and B (**33** and **34**) and maesabalide (**35**).

A number of related flavonoid, lignoid and phenylpropanoid natural products have been shown to be effective anti-*Leishmania* agents. Calceolarioside A (**36**, Figure 13) is a glycoside phenylpropanoid isolated from the leaves of *Nyctanthe sarbortristis*. In golden hamsters infected with *L. donovani* it was administered intraperitoneally at 20 mg kg⁻¹ for 15 days and showed a reduction in spleen (84%) and liver (79%) parasite burden.⁷⁶

The flavonoid quercetin (**37**, Figure 13) has been isolated from a number of plant species was administered to golden hamsters with *L. donovani* infection at 5, 10, 20, 30 and 40 mg kg⁻¹ (orally, biweekly). Although this compound is a well know interference (PAINS) compound and can therefore not be considered a promising hit, it showed high level performance in *in vivo* tests following the sacrifice of the hamsters one month post administration, including showing prevention

of lipid peroxidation, prolonged red blood cell life span, higher prevention of reactive oxygen species (ROS) generation and decreased splenic parasite load. This compound was also administered orally to golden hamsters infected with *L. donovani* in a separate study at 14 mg kg⁻¹ twice a week for four weeks and reduced the splenic parasite load by 90%.⁷⁷

The lignoid lyoniside (**38**, Figure 13) was isolated from the stem bark of *Saraca indica* and was administered intraperitoneally to BALB/c mice infected with *L. donovani* twice a week for three weeks. It reduced parasite burden in the liver and spleen by 95% at 5.0 mg kg⁻¹ and showed low levels of cytotoxicity against the peritoneal murine macrophages. There is some evidence that this lignoid exhibits an immunomodulatory effect whereby the host cell immune response is enhanced to kill the parasite.⁷⁸

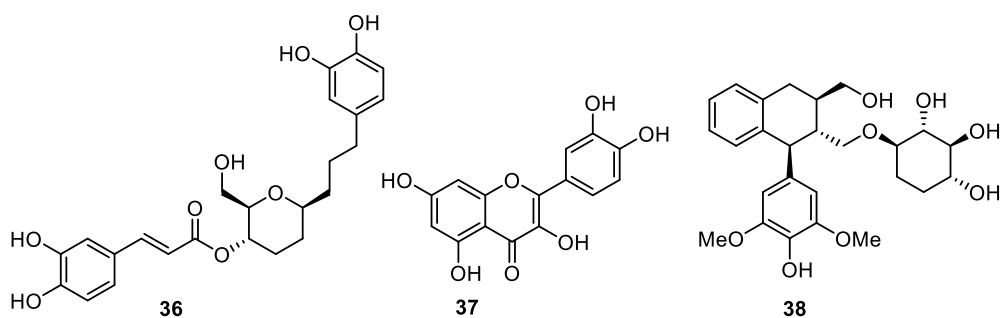


Figure 13. Calceolarioside A (left), quercetin **37** (middle) and lyoniside (right).

Certain naphthoquinones have also been shown to have promising anti-*Leishmania* activity against parasite forms which typically cause cutaneous leishmaniasis. 4-Hydroxy-1-tetralone (**39**, Figure 14) isolated from the stem barks of *Ampelocera edentula* was administered directly into the lesions of *L. amazonensis* and *L. venezuelensis* infected BALB/c mice at a single dose of 50 mg kg⁻¹, resulting in a lesion size reduction comparable to that of standard drug, Glucantime™, administered at a higher dose of 112 mg kg⁻¹.⁷⁹ Plumbagin (**40**), a related naphthoquinone, was used to treat BALB/c mice with *L. amazonensis* infection at 2.5 and 5.0 mgkg⁻¹day⁻¹ for two weeks and showed a reduction in parasite load of 38% with low toxicity.⁸⁰

The iridoid oleuropein (**41**, Figure 14) isolated from *Olea europaea* was administered to BALB/c mice infected with *L. donovani* intraperitoneally at 45, 15, and 5 mg kg⁻¹. Six weeks following

treatment completion a reduction in spleen parasite burden was observed of 96% at the lowest dose and >99% at the highest dose.⁸¹

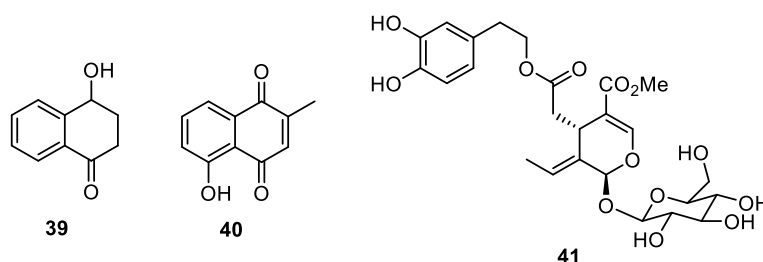


Figure 14. Naphthoquinones 4-hydroxy-1-tetralone (left) and plumbagin (middle), and iridoid oleuropein (right).

1.3.2 Natural products Active Against Chagas Disease

It has been reported that natural products research into Chagas disease has been less extensively studied in recent years.⁸² Izumi *et al.* extensively reviewed the screening of plant derived natural products, however few hit compounds make it through to further development.⁸³ This can be explained through the challenges associated with isolating and purifying enough active natural product to carry through to pre-clinical *in vivo* screening of successful hits, and as a result there is a need for improved purification and extraction methods, or a role for synthetic organic chemists to provide scaled-up routes.

The following section reviews a selection of natural products that have shown promising activity in initial screening against *T. cruzi*, often isolated by bio-guided fractionation of crude extracts.

A series of alkaloid natural products were isolated from bacteria *Bacillus pumilus*, with *N*-acetyl- β -oxotryptamine (**42**, Figure 15) showing the most promising antitrypanosomal activity, with an IC_{50} against *T. cruzi* of 19.4 μ M. This compound also showed low cytotoxicity against African green monkey kidney cells.⁸⁴ A series of 16 guanidine and pyrimidine alkaloids were isolated from marine sponge *Monanchora arbuscula* and three (**43**, **44**, and **45**, Figure 15) were shown to have very promising anti *T. cruzi* activity of 8, 2, and 7 μ M respectively, with some selectivity over the mammalian cell line.⁸⁵

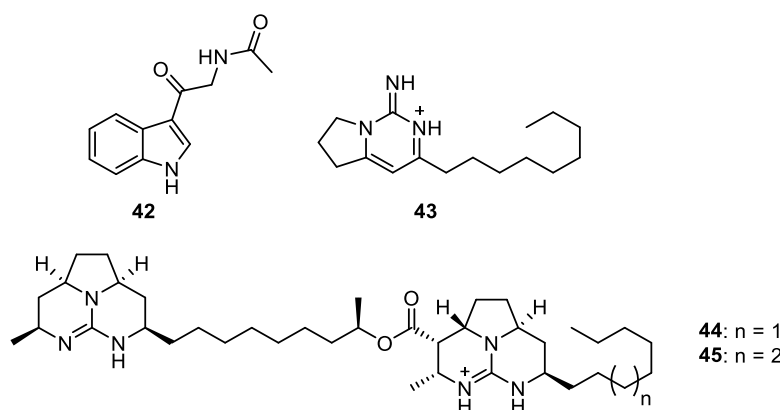


Figure 15. Alkaloid natural products with activity against *T. cruzi* intracellular amastigote forms.

In a 2017 study⁸⁶ a series of natural products isolated from marine sources were screened against a number of kinetoplastid parasites (Figure 16), and narciclasine (**46**), mefloquine hydrochloride (**47**), emetine dihydrochloride (**48**), and psammalpsin F (**49**) were all found to show low micromolar activity against *T. cruzi* (0.2, 4.0, 0.1, 5.6 μ M respectively) with moderate to good selectivity with the mammalian cell line (3T3).

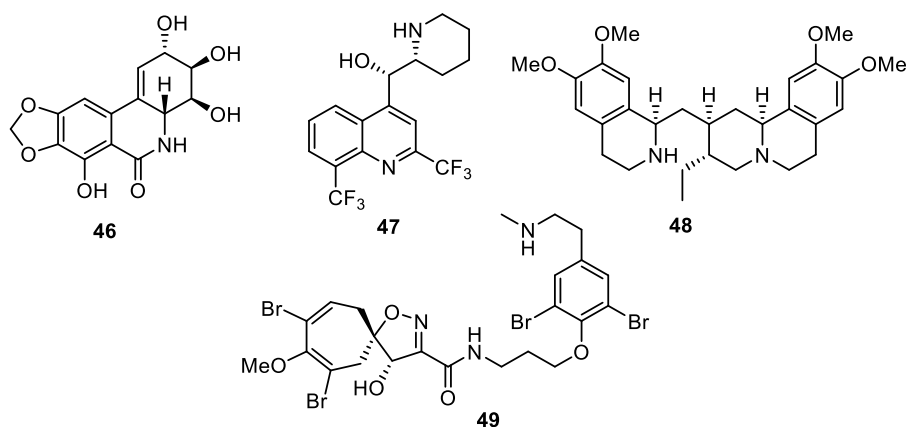


Figure 16. Marine natural products with good *T. cruzi* activity; Narciclasine (**46**), Mefloquine (**47**), emetine (**48**) and psammalpsin F (**49**).

A study on the tropical plant *Ancistrocladus tanzaniensis* led to the discovery of three alkaloid natural products (**50** to **52**, Figure 17) all of which exhibited low micromolar activity against *T. cruzi* and showed only weak cytotoxicity. The IC_{50} values reported are 1.7, 1.5, and 17.8 μ M respectively.⁸⁷ The same research group also isolated and characterised four phenylanthraquinone natural products from the roots of *Bulbine frutescens*. Of these four, three (**53** to **55**) showed promising activity against *T. cruzi* with IC_{50} values ranging from 7.6 to 33.1 μ M.

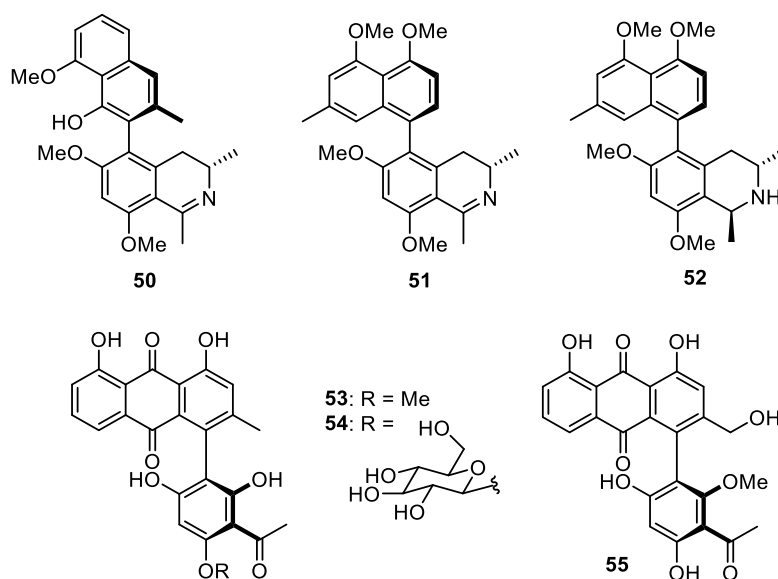


Figure 17. Anti-trypanosomal natural products from *Ancistrocladus tanzaniensis* (top), and from *Bulbine frutescens* (bottom).

Mbwambo *et al.* isolated a series of biflavonoid and xanthone natural products from the root bark of *Garcinia livingstonei* and four of them (**56** to **59**, Figure 18) showed low micromolar activity against *T. cruzi* of 5.7 μM , 7.0 μM and 4.0 μM respectively. However, **59** also showed high corresponding cytotoxicity against the MRC-5 cell line.⁸⁸

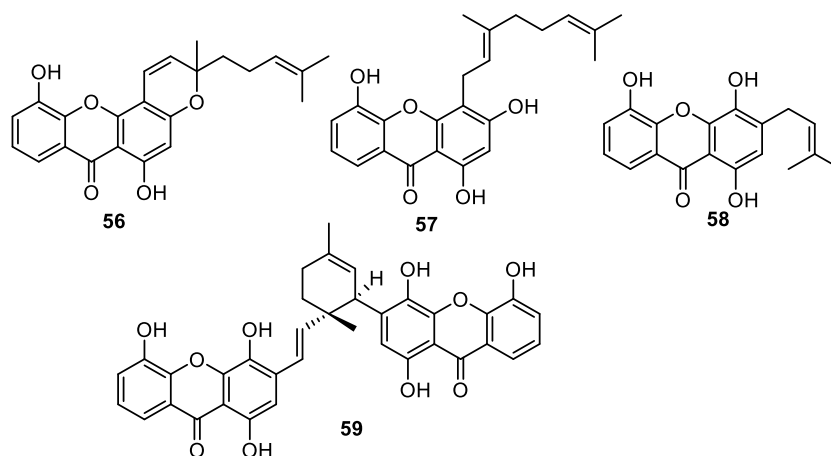


Figure 18. Biflavonoid anti-*T. cruzi* natural products discovered by Mbwambo *et al.*.⁸⁸

Three Bis-acetylene natural products were isolated from medicinal plant *Cussonia zimmermannii* and showed excellent activity against *T. cruzi* intracellular amastigotes (Figure 19). In particular those with the vinyl chain showed excellent potency and higher selectivity. The IC_{50} values reported for **60**, **61**, and **62** are 26 $\mu\text{g mL}^{-1}$ (SI 2.1), 0.7 $\mu\text{g mL}^{-1}$ (SI 12) and 0.4 $\mu\text{g mL}^{-1}$ (SI 58).⁸⁹

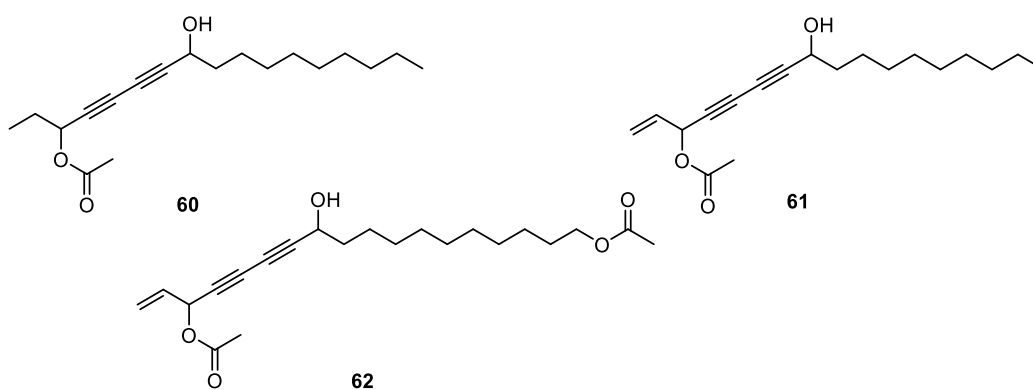


Figure 19. Bis-acetylene natural products from *Cussonia zimmermannii*.

Five new diterpene natural products from *Myospermum frutescens* were tested against intracellular amastigotes of *T. cruzi* and four (**63** to **66**) were shown to have very promising activity with low cytotoxicity against human foreskin fibroblasts. The IC_{50} values range from 16.6 - 25.9 μM , and CC_{50} values from 110 – 149 μM .⁹⁰

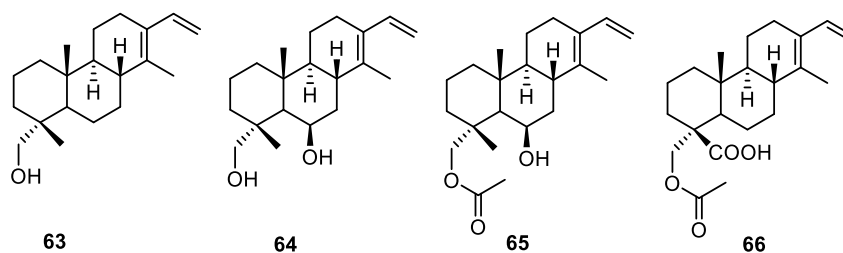


Figure 20. Diterpenoid natural products from *Myospermum frutescens*.

1.4 Neolignan Biaryl Ether Natural Products

Neolignan natural products are comprised of two linked 9-carbon units, each made up of a six-membered ring and three-carbon linear tail.⁹¹

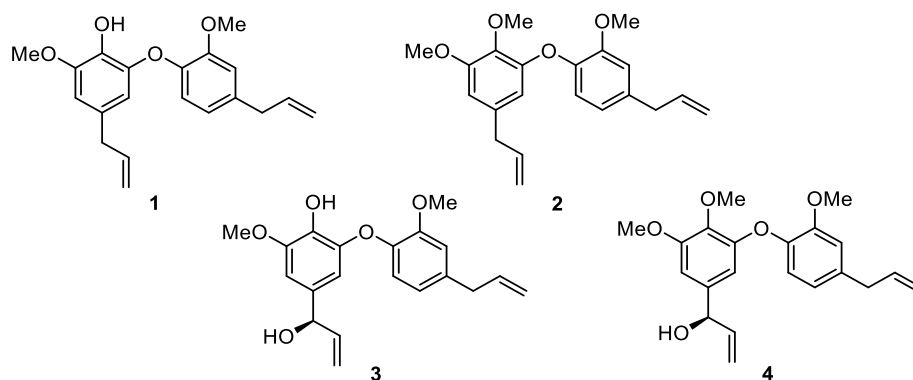


Figure 21. Biaryl ether neolignan natural products **1** to **4** from *Nectandra leucantha* shown to have promising activity against *L. donovani* and *T. cruzi*.

In 2015, in a study on the flowering plant *Nectandra leucantha*, our collaborators in the group of Prof. João Lago in São Paulo, isolated and characterised known biaryl ether pseudo-dimer dehydrodieugenol B (**1**) and three related natural products (**2** – **4**) by bio-guided fractionation. In collaboration with Prof. André Tempone, their promising activity against *L. donovani* was determined.⁹² Later in 2017, these compounds were found to also show promising antitrypanosomal activity.⁹³ All of these compounds show very low mammalian cytotoxicity which is essential for achieving selectivity in potential hits. These natural products are interesting compounds for semi-synthesis and further study as they contain two allyl side chains and a phenol as reactive handles for modification. Indeed, on a visit to our group in Oxford, Fernanda Sousa from the Lago group, synthesised a series of semi-synthetic analogues based on **1** and **2**, and found many of them to have promising activity against *T. cruzi* and *L. infantum*.^{94,95} The biological data obtained for the natural products **1** – **4** and the best semi-synthesis compounds **5** – **11** is shown in Table 2.

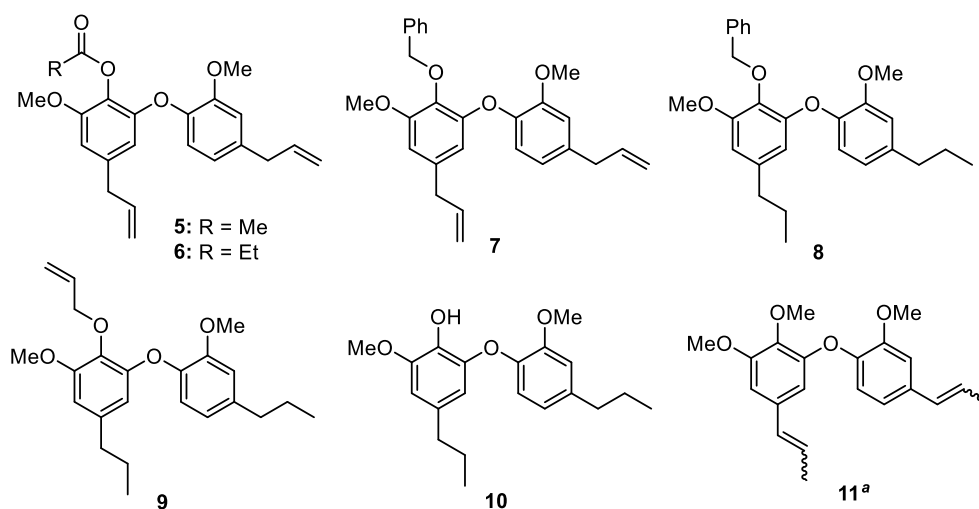


Figure 22. Seven semi-synthetic derivatives that showed the most promising anti *T. cruzi* and anti *Leishmania* spp. activity. ^aE / Z (5 : 1, comprising mixture of four regioisomers E/E, E/Z, Z/E, and Z/Z).

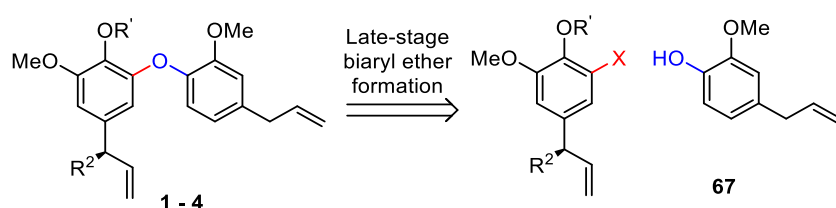
Table 2. Anti-parasitic activity of **1** – **11**.

Compound	<i>Leishmania</i> sp. ^d IC ₅₀ (± SD) / μM		<i>T. cruzi</i> IC ₅₀ (± SD) / μM		CC ₅₀ (± SD) / μM	SI	
	Promastigote	Amastigote	Trypomastigote	Amastigote		<i>Leishmania</i> sp. ^d	<i>T. cruzi</i>
1^a	NA	26.7 ± 9.0	38.6 ± 14.6	86.5 ± 18.0	>293.8	>11.0	>2.3
2^a	111.8 ± 19.3	17.8 ± 2.8	>100	NA	111.2 ± 11.2	6.25	ND
3^a	NA	101.9 ± 24.7	59.7 ± 51.6	33.6 ± 8.5	>292.1	>2.9	>5.9
4^a	ND	ND	39.2 ± 12.3	15.2 ± 7.0	>200	ND	>13.1
5^c	ND	ND	64.2 ± 8.2	8.0 ± 5.8	64.4 ± 4.2	ND	8.1
6^{b, c}	93.3 ± 8.4	35.9 ± 6.6	30.5 ± 10.4	10.0 ± 0.8	75.0 ± 13.8	2.1	7.5
7^c	ND	ND	>100	9.5 ± 1.3	>200	ND	>21.1
8^{b, c}	105.4 ± 9.4	6.1 ± 1.2	>100	7.5 ± 1.1	>200	>32.8	>26.6
9^c	ND	ND	>100	9.4 ± 3.9	>200	ND	>21.2
10^{b, c}	29.6 ± 2.3	21.7 ± 1.9	7.9 ± 0.7	>30	57.7 ± 1.1	2.7	ND
11^{b, c}	29.0 ± 0.2	34.5 ± 11.5	>100	12.2 ± 3.5	>200	>5.8	>16.4

IC₅₀: 50% Inhibitory Concentration; CC₅₀: 50% Cytotoxic Concentration; SI: Selectivity Index, given by the ratio between CC₅₀ in NCTC cells and IC₅₀ in intracellular amastigote assay. ^a*Leishmania* sp. data published in ref. 92, *T. cruzi* data published in ref. 93. ^b*Leishmania* data published in ref. 95. ^c*T. cruzi* data published in ref. 94. ^d*L. donovani* for **1** - **4**, *L. infantum* for **5**-**11**.

It became apparent very quickly in the design and synthesis of these analogues from **1** and **2** that their symmetry was a problem for selective modification of the two allyl side chains. Invariably there was no selectivity in the reactions on these double bonds owing to their similarity. This meant that there was no way to assess the anti-parasitic activity of non-symmetrical analogues using purely semi-synthesis.

An effective way to modify one ‘half’ independently of the other would be through a convergent total synthesis of the natural product, with a key step, late in the synthetic route, bringing together the two halves (Scheme 1). An obvious way to do this would be through formation of the biaryl ether linkage. With access to such a route, the two sides can therefore be modified independently prior to the coupling step, allowing access to a much larger library of fully synthetic, non-symmetrical derivatives. This route would also break the molecule down such that one half is derived from eugenol (**67**), itself a natural product with known anti-parasitic activity, which is very widely available and cheap.



Scheme 1. Proposed strategy towards the synthesis of natural products **1 – 4** and other fully synthetic analogues.

Another problem that arose from Sousa’s work was scale-up. As is common in natural product isolation, obtaining enough material to carry out *in vivo* mouse and hamster models in sufficient purity can be a challenge. A simple and scalable total synthesis would enable access to enough of the natural product and synthetic analogues to take the most promising compounds through to the next stage in development and optimisation.

What is clear from Sousa’s data are that saturation of the two allyl side chains is not only tolerated but in certain cases enhanced activity (**8, 9, 10**, Figure 22). However, as noted above, exploration of single side chain saturation was not possible using this semi-synthesis method. A total synthesis would allow us to probe the effect of saturation on activity in more detail. Also, it would enable a deletion study on the biaryl ether core – of the side chains themselves and also the methoxy and phenol groups – to determine which substituents are required for activity, and therefore elucidation of the structure-activity relationship. Sousa’s study also illustrated that the R’ phenolic ethers and esters showed good activity and that there is further scope for modifying this vector. This can also be achieved in a total synthesis where R’ serves as a protecting group in the biaryl ether forming step.

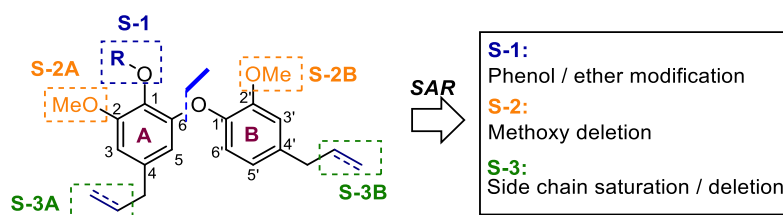


Figure 23. Potential areas of modification for the structure-activity relationship study of the biaryl ether natural products.

As with all potential therapeutics, achieving appropriate PK / ADME properties is essential for furthering hits through optimisation to leads and preclinical studies. Work by Dr Diedre Johns at Oregon State University predicted some of these properties on Sousa's compounds using *in silico* modelling.⁹⁶ The esters **5** and **6** (Figure 22) were flagged as a risk due the strong probability of being metabolised, and on the whole the compounds had high logP values and low solubility. However, all of the semi-synthesis compounds showed good *in silico* oral bioavailability and no similarity to PAINs compounds.⁹⁵ Suggestions from John's work as to how to improve certain ADMET properties included improving solubility and logP by removing functionality around the rings, and through adding polarity into the molecules by adding heteroatoms. Some of her recommendations are shown in Figure 24. Again, a fully synthetic route to the natural product biaryl ether core would allow such compounds to be synthesised and tested.

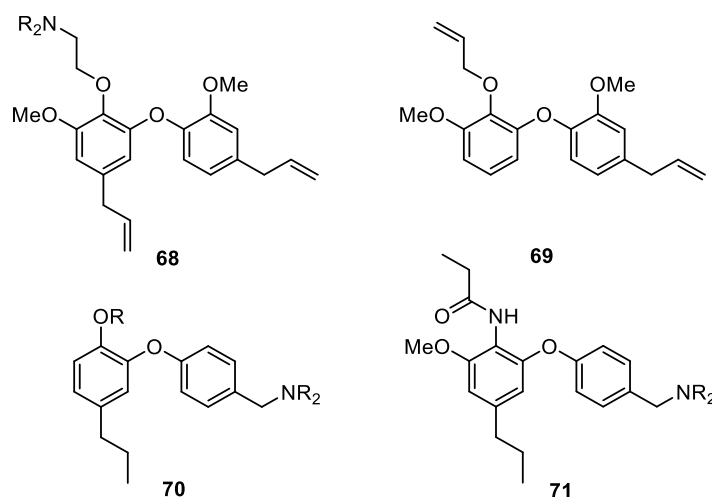


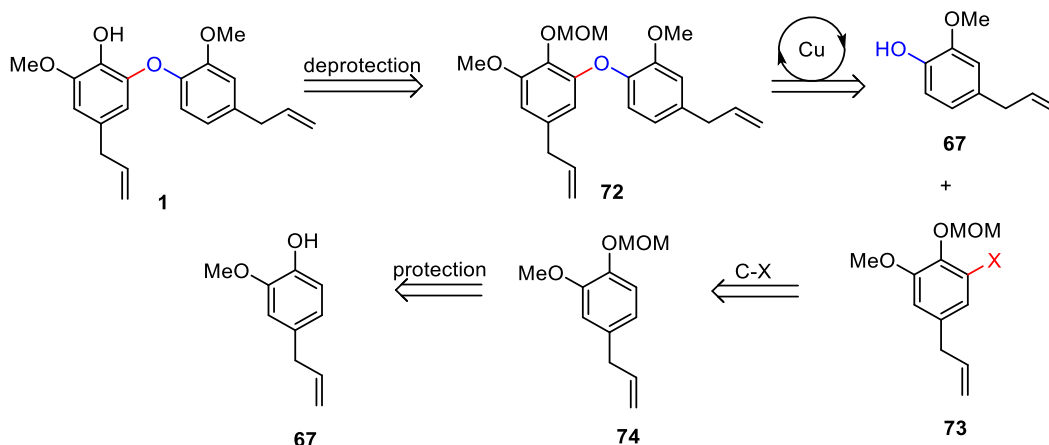
Figure 24. Analogues with improved predicted ADMET properties and therefore potential targets for synthesis.

This thesis describes the development of a synthetic route to the natural products **1**, **2**, and **4**, and towards the synthesis of **3**, including an extensive optimisation of the key biaryl ether forming step, and how this route was used to produce sufficient quantities of **5** for this compound to progress to *in vivo* murine models. It will then explore the design and synthesis of a series of fully synthetic natural product analogues using this route, with the emphasis on structure-activity relationship determination and some consideration of PK / ADME properties. Finally, it will describe the biological testing of these compounds in *L. infantum*, *T. cruzi*, and mammalian cytotoxicity assays to determine their IC₅₀ values and Selectivity Indexes, with an analysis on the key structural features of the natural products and their importance for activity.

2. Synthesis of Natural Products 1 – 4

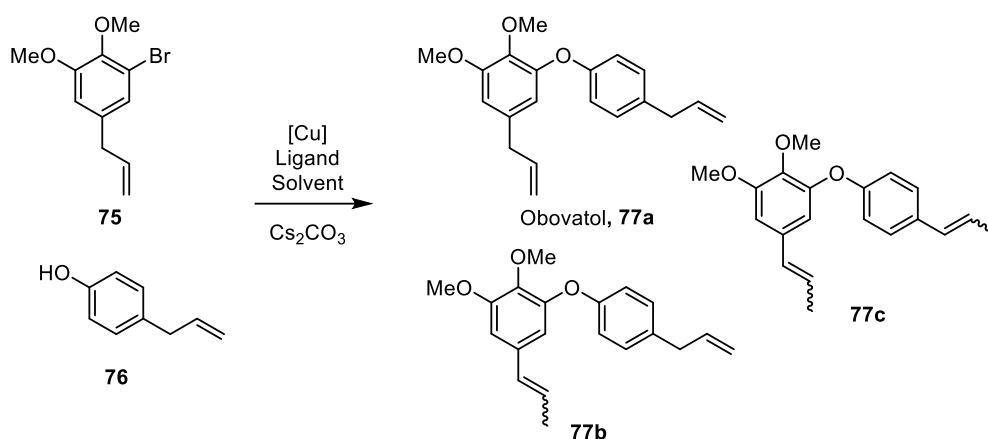
2.1 Retrosynthetic Strategy

The proposed strategy to synthesise the natural products is to form the biaryl ether linkage at a late stage in the synthesis (Scheme 2). Typically, this could be done by a nucleophilic aromatic substitution reaction, with a phenol as a nucleophile and a fluoride or chloride as a leaving group. However, this generally requires an electron deficient electrophilic arene, and in the systems of **1** – **4**, this is not the case. An alternative more suited to this system is to use a metal-mediated coupling approach to form the biaryl ether. Ullmann first reported the use of copper salts to effect these biaryl ether formation in 1904.⁹⁷ This is an attractive strategy towards our natural products because it enables the breakdown of the molecule into two halves as required, allowing access to a library of fully synthetic derivatives not accessible through semi-synthesis. The coupling partners required are also cheap and readily available, being eugenol for the right-hand side phenol, and a halide for the left-hand side which can be derived from eugenol, with the obvious route to this being through protection of the phenol with a coordinating protecting group such as MOM, followed by ortho-directed deprotonation/lithiation and quenching with an electrophilic source of halide. A further benefit of this type of coupling reaction is that it has been extensively studied in the literature and numerous catalyst and ligand systems now exist to facilitate this transformation on a variety of substrates, with tolerance of a diversity of electronics, sterics, and functional groups.^{98,99} Copper(I) salts themselves are also cheap compared to other metals which have been used for this transformation, such as palladium, making this reaction affordable, and also potentially scalable should we require access to the natural products in large quantities. Similarly, Cu-catalysed arylations often can be conducted ligand-free, or with simple, inexpensive ligands, compared with palladium chemistry for which the ligands are often expensive and structurally complex.



Scheme 2. Retrosynthesis of 1.

There are, however, three principal challenges associated with this strategy, the first being the electron-rich halide. A well-established trend in metal-catalysed arylation chemistry is that electron-donating groups on the phenol and electron withdrawing groups on the halide facilitate the reaction. In our system the more electron rich partner is the halide, and to reverse the polarity of the coupling would require less readily available starting materials and add multiple steps to the synthesis. It is also well established that *ortho*-substituents make this reaction more challenging due to steric constraints, and we require *ortho*-substituents on both partners. Chelating *ortho*-groups such as methoxy or acetal are more challenging still, as they have the ability to coordinate to the copper catalyst. Finally – and perhaps most crucially – these reactions are notoriously capricious. They can require high loadings of copper – often stoichiometric or in excess – basic reaction conditions, high temperatures, and long reaction times. It is well known that 1-propenylbenzene derivatives can isomerise under these conditions to the thermodynamically more stable 2-propenylbenzene.¹⁰⁰ This means that as well as the long reaction times and high copper loadings, there is a strong likelihood of formation of a mixture of 2-propenylbenzene by-products through base mediated isomerisation. Indeed, such side reactions have been reported on systems similar to ours. For example, in 2008, Kwak *et al.* screened a number of conditions for the synthesis of Obovatol (**77a**) and found mixtures of both singly and doubly isomerised products (Scheme 3, **77b** and **77c**). It was also found in their study that the left-hand side allyl group isomerised more rapidly than the right-hand side. Their best results were achieved using dioxane as the solvent and *N,N*-dimethylglycine as the ligand.¹⁰¹



Scheme 3. The synthesis of Obovatol by copper-catalysed biaryl ether formation giving rise to isomerised 2-propenyl products **77b** and **77c**.

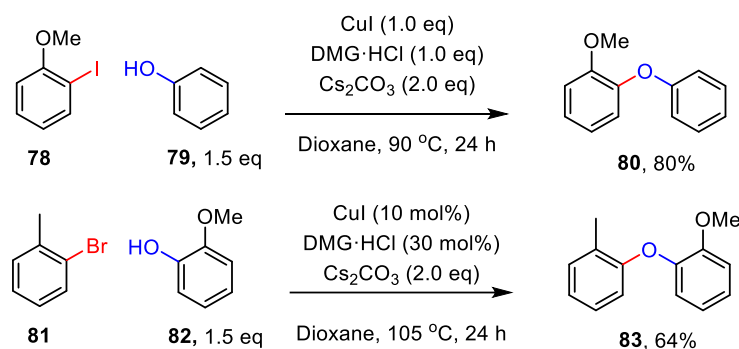
To overcome this problem in our system will require careful optimisation of base, temperature, solvent, catalyst, ligand, and reaction time. This also highlights a potential benefit of using copper, however, as other transition metals used for biaryl ether formation, such as palladium, iron, and nickel, have also been shown to themselves induce this allylbenzene isomerisation, whereas the use of copper to effect this transformation has not been reported.¹⁰⁰

2.2 Copper-Catalysed Biaryl Ether Formation on Sterically and Electronically Demanding Systems

A large number of conditions exist for using catalytic copper to achieve biaryl ether formation using a wide range of copper salts, ligands, solvents, and bases, and this subject has been extensively reviewed.^{98,99,102} However, conditions which can tolerate electron-rich halides and *ortho*-substituents are few and far between, and it is these systems which are of interest for us given the constraints of dehydrodieugenol B and its analogues. The following section includes a review of the systems which may be suitable and the results achieved for sterically and electronically demanding systems.

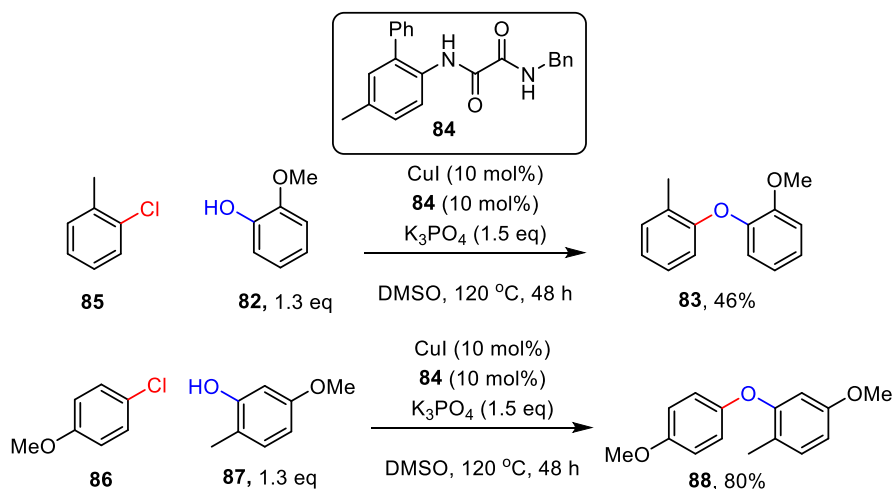
The conditions described by Dawei Ma using copper(I) iodide, *N,N*-dimethylglycine hydrochloride, and cesium carbonate in dioxane have been used extensively and were the chosen conditions for the

synthesis of obovatol described previously.^{101,103} These conditions have been found to tolerate electron rich halides and at least one *ortho* substituent, although higher copper(I) and ligand loadings were required in this case. In the coupling between 2-iodoanisole (**78**) and phenol (**79**), a yield of 80% of **80** was achieved using 1.0 eq. of copper and ligand, and the reaction of 2-bromotoluene (**81**) and guaiacol (**82**) gave 64% yield of **83** using 10 mol% of copper and 30 mol% of ligand at an elevated temperature of 105 °C. The success of these conditions in the synthesis of Obovatol makes them a potentially useful starting point for our synthesis of dehydrodieugenol B.¹⁰¹



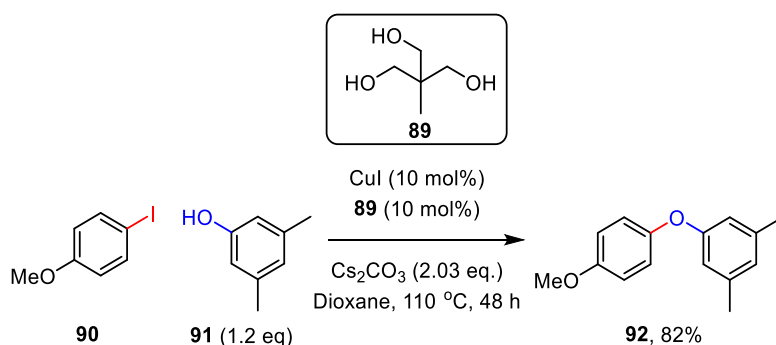
Scheme 4. Examples from Dawei Ma's paper where coupling of sterically and electronically demanding systems was achieved.¹⁰³

In 2016 Dawei Ma's group published a new set of conditions using an oxalamide ligand (**84**) for this transformation in which a chloride could be used as the halide coupling partner, which is unusual in these transformations and beneficial as chlorides are less expensive than bromides and iodides. Potassium phosphate was used as the base, again much cheaper than the more commonly used cesium carbonate. These conditions were successful on sterically and electronically demanding systems, albeit using a high temperature of 120 °C and long reaction times of 48 hours. These systems also required higher copper and ligand loadings than other less demanding systems (Scheme 5).



Scheme 5. Examples from Dawei Ma's paper where coupling of sterically and electronically demanding systems was achieved starting from the aryl chloride.¹⁰⁴

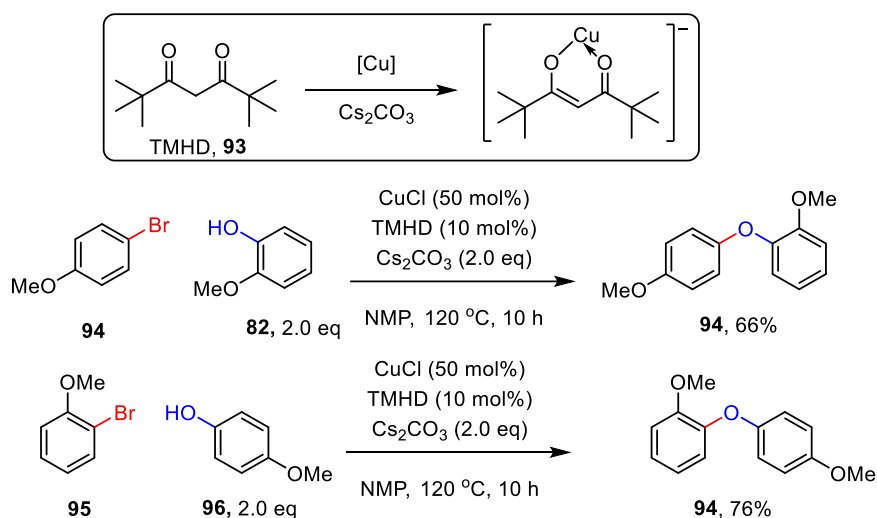
In 2006 Chen and Chen reported a new tripod ligand for these transformations.¹⁰⁵ 1,1,1-Tris(hydroxymethyl)ethane (**89**) proved a versatile ligand for the formation of C–O, C–N, and C–S bonds. These conditions benefit from a relatively low loading of copper(I) iodide (10 mol%) and ligand (10 mol%) and were shown to be effective on examples with *ortho* substituents and electron rich halides. For example, the coupling of 4-iodoanisole (**90**) with 2,4-dimethylphenol (**91**) gave an 82% yield of product (**92**, Scheme 6). An interesting observation is that while the solvent used for the C–O bond formation is dioxane, in the cases of C–N and C–S bond formation, a solvent mix of DMF / dioxane (1 : 9) was preferred.¹⁰⁵



Scheme 6. Examples from Chen and Chen's work using a tripod ligand to achieve coupling of sterically and electronically demanding systems.¹⁰⁵

Buck *et al.* at Merck published the use of diketone ligand 2,2,6,6-tetramethylheptane-3,5-dione (TMHD, **93**) as a means for accelerating the rate of the Ullmann coupling reaction in 2003.¹⁰⁶ This

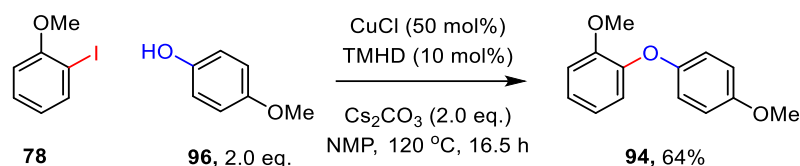
additive is deprotonated under the reaction conditions to form the corresponding enolate, and coordinates to the copper as a bidentate, anionic ‘LX’ type ligand. This ligand resulted in a rate acceleration for the coupling of 4-fluorophenol and 4-bromoanisole – an electronically challenging system – by 10 to 15 fold at 25 mol% loading of ligand. This additive therefore enables the coupling of substrates with *ortho* substituents on either the phenol or halide, and also with electron rich halides. These conditions are of clear relevance for our work on dehydrodieugenol B.



Scheme 7. Deprotonation and coordination of TMHD to copper(I), and examples from Buck's paper where coupling of sterically and electronically demanding systems was achieved.¹⁰⁶

2.3 Optimisation of Biaryl Ether Formation on a Model System

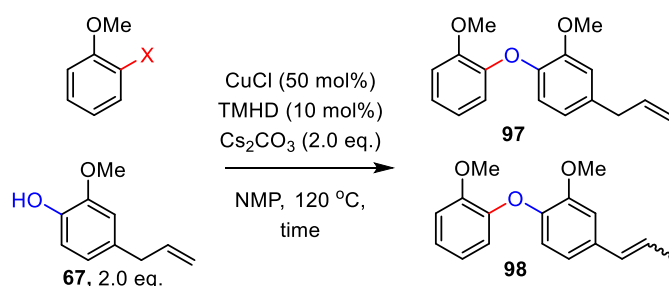
The conditions chosen for the initial optimisation of biaryl ether formation started using the copper and ligand system described by Buck *et al.*¹⁰⁶ These conditions were chosen as they had been shown to be very effective on electron rich and *ortho*-substituted phenols. Their procedure was trialled first on a system described directly in the paper to see if this could be reproduced in our lab. This reaction was carried out in a standard screw-cap vial using copper(I) chloride and cesium carbonate stored and weighed out in a glovebox. Pleasingly, this afforded a 64% yield (lit.¹⁰⁶ 76%). This result is shown in Scheme 8.



Scheme 8. Demonstration of the effectiveness of the chosen conditions in the presence of *ortho*-substituents and electron rich coupling partners.

Building on this result, we next modelled the natural product system. 2-Haloanisole was chosen for the halide partner as it contains an electron-donating, co-ordinating *ortho* substituent, and eugenol (**67**) was chosen as the phenol partner to directly mimic the natural product system. This would also allow us to determine whether the allyl side chain was tolerated, or liable to isomerisation under the conditions of the reaction (Table 3). 2-Bromo- and 2-iodoanisole were both submitted to the above conditions and the reaction was monitored by TLC. It was found immediately that the 2-iodoanisole (**78**, Entry 2) was consumed much more rapidly than 2-bromoanisole (**95**, Entry 1). In both cases, isomerisation to the 2-propenyl arene **98** was observed, which is not surprising given this reaction is heated to 120 °C for several hours with base. However, in the case of 2-iodoanisole, some of the required 1-propenyl product **97** was observed, which likely is due to the shorter reaction times. As a result of this, and also the slightly higher yield in this case, the iodide was chosen as the halide for the remainder of the optimisation.

Table 3. Influence of halide.

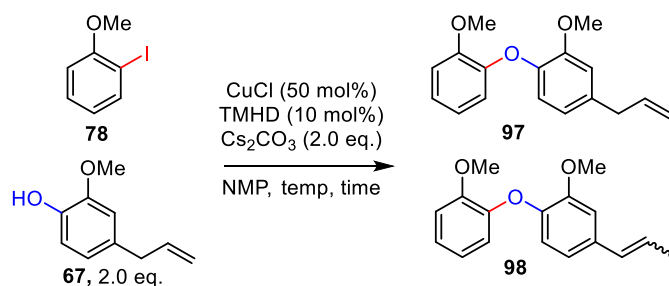


Entry	X	Time / h	Yield ^a / %	97 : 98 ^b
1	Br	42	25	0 : 1
2	I	15.5	35	1 : 2.5

^aCombined yield of **97** and **98**. ^bCalculated by ¹H NMR. **98** gave a mixture of *E* / *Z* (4 : 1).

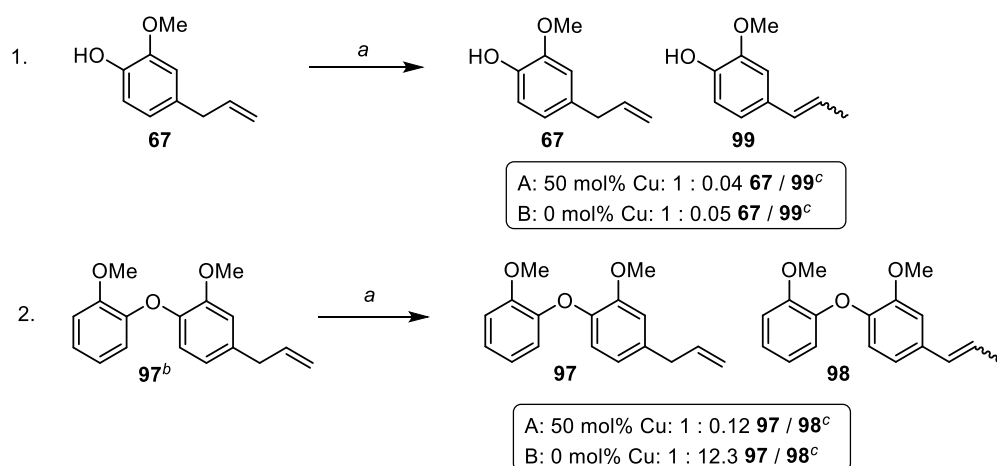
Use of the iodide **78** enabled a short reaction time and therefore gave some scope for potentially reducing the temperature in order to minimise the levels of undesired optimisation. The reaction was repeated at 100 °C and 90 °C and stopped after five hours to observe the conversion and levels of isomerisation. The reduction in temperature over the same time frame resulted in an increase in yield from 34% to 49% and a reduction in isomerisation from **97** / **98** 1 : 0.29 to 1 : 0.07 (Table 4, Entries 2 and 3). Leaving the reaction at 90 °C for 15 hours resulted in no real improvement in yield but increased the isomerisation to 1 : 0.54, which shows that extended reaction times favour the styrenyl product **98** (Entry 4). Decreasing the temperature further to 80 °C meant the reaction could be left overnight to go to completion and gave still only 1 : 0.07 **97** / **98** with 63% yield (Entry 5). These results illustrate the importance of both reaction time and temperature for isomerisation and conversion. Prolonged reaction times at elevated temperatures result in lower yields, likely due to decomposition of the starting materials. In these reactions, loss of the halide by reduction of the C–I bond is a common side reaction and indeed anisole was observed in the crude mixtures from this reaction. The difference between Entries 3 and 5 illustrates that reaction time can be extended to enable conversion at a lower temperature, whilst still minimising the isomerisation. As a result of this observation 80 °C was selected as the optimised temperature.

Table 4. Influence of temperature and reaction time on yield and isomerisation.



Entry	Temp. / °C	Time / h	Yield / %	97 : 98
1	120	42	25	0 : 1
2	100	5	34	1 : 0.29
3	90	5	49	1 : 0.07
4	90	15	45	1 : 0.54
5	80	15.5	63	1 : 0.07

Comparing entries 3 and 4 in Table 4 shows that the reaction at 90 °C gives similar yield of product regardless of reaction time, however the ratio of isomerised product **98** increases significantly. This suggests that under the reaction conditions, the product isomerises more readily than the eugenol precursor, and so leaving the product under the reaction conditions gives rise to high levels of isomerisation. To test this hypothesis, eugenol and a mixture of 1 : 0.07 **97** / **98** were submitted to the reaction conditions separately and in the absence of 2-iodoanisole. 100 °C was chosen as the temperature for this study to ensure that isomerisation would take place. Because it is known that transition metals can also facilitate this isomerisation,¹⁰⁰ eugenol and the product mixture were submitted to the reaction conditions independently with and without copper, so it could be determined whether copper was facilitating this isomerisation and if so, whether there was evidence to suggest that reducing the copper loading may be beneficial. The results of this study are shown in Scheme 9.



Scheme 9. Study on the extent of isomerisation. ^aCuCl (*X* mol%), TMHD (10 mol%), Cs₂CO₃ (2.0 eq), NMP, 100 °C, 20 h. ^b Submitted as a 1 : 0.07 mixture **97** : **98**. ^cCalculated from crude NMR. **98** and **99** give 1 : 0.25 *E* / *Z*.

The isomerisation ratios are calculated by comparison of the integrals of the doublet at 3.4 ppm corresponding to the CH₂, against the doublet of doublets at around 1.9 ppm corresponding to the propenyl CH₃ (Figure 25).

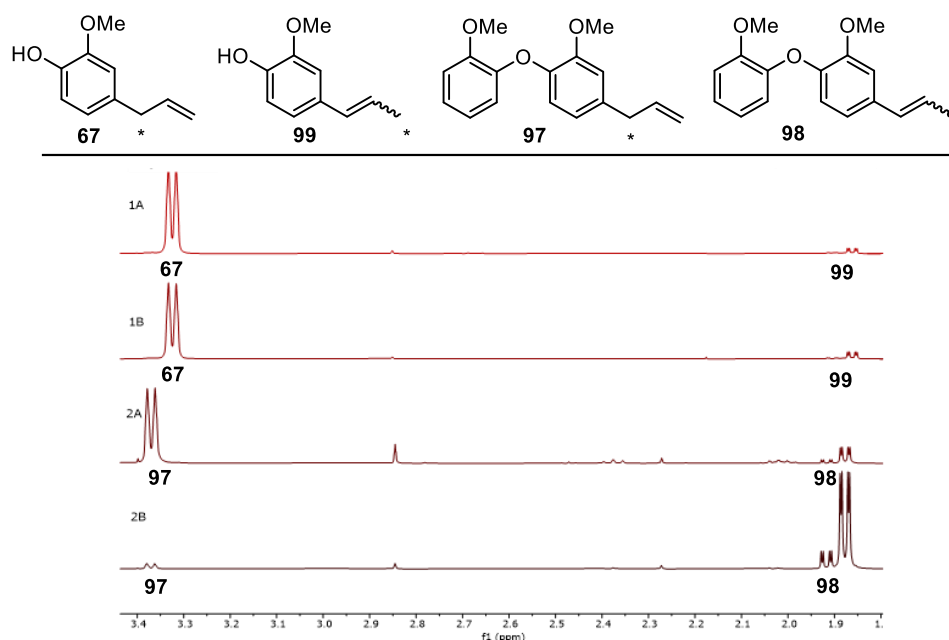
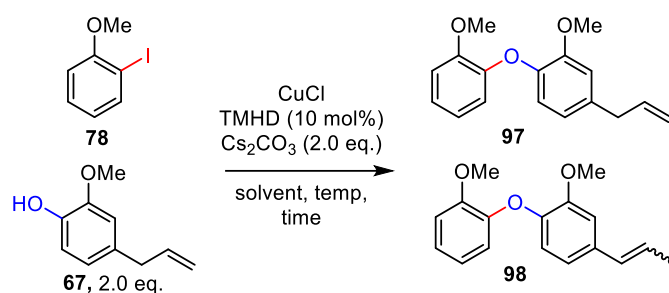


Figure 25. Crude NMR of entries 1A to 2B from Scheme 9. Conditions: CuCl (50 mol% for 1A and 2A, 0 mol% for 1B and 2B), TMHD (10 mol%), Cs₂CO₃ (2.0 eq), NMP, 100 °C, 20 h.

These data confirm that the product **97** isomerises more readily under the reaction conditions than the starting material **67**, as in entries 1A and 1B where eugenol was used, very little isomerisation was observed both with and without copper, whereas in 2A and 2B, there were more significant levels of the 2-propenyl product **98**. This is understandable as under the reaction conditions the phenol will be deprotonated to form the phenolate, and therefore a second deprotonation of the benzylic position is much less favourable. The more surprising discovery from these data are the influence of copper on the isomerisation. When comparing 1A and 1B, a small increase in isomerisation is observed in the absence of CuCl. However, comparing 2A and 2B clearly illustrates that in the absence of copper, almost complete isomerisation is observed. It is possible that this can be explained by the CuCl modulating the basicity of the carbonate – if a proportion of copper carbonate is formed *in situ* then this could be less basic than cesium carbonate in NMP. This means the overall basicity of the reaction is decreased and less isomerisation is observed. These data also confirmed that it is highly likely that the isomerisation in this system is base mediated, and not transition metal mediated.

This observation also rationalises the use of a high level of copper loading and justifies its continued use for the remainder of the optimisation. It also highlights the importance of controlling basicity to minimise this unwanted transformation.

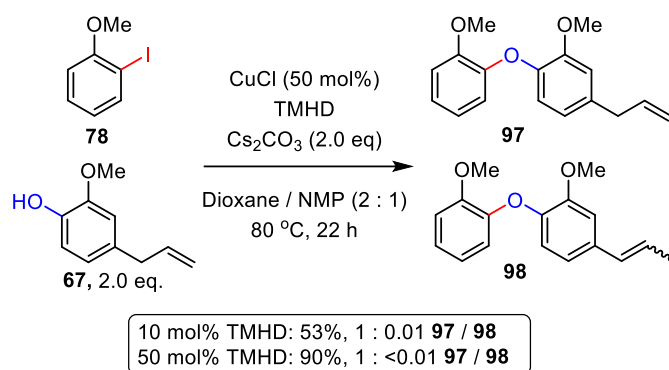
Base pKa is highly dependent on solvent so this was the next variable investigated for optimisation (Table 5). Typically, Ullmann couplings use high boiling, polar aprotic solvents. Dioxane has been shown to be effective at minimising isomerisation in Ullmann couplings where allylbenzenes are present.^{101,107} As a result this was chosen as an alternative solvent. At 80 °C, the reaction did not reach completion after 64 hours and gave only 37% yield of **97**. However, no isomerisation product (**98**) was observed (Table 5, Entry 2). Given this result, the temperature was increased to 100 °C. Although all starting material was consumed after 22 hours, there was no improvement in the yield, but pleasingly, no isomerisation was observed at this elevated temperature (Entry 3). To optimise this further, the dioxane was rigorously dried by distillation, and degassed by freeze-pump-thaw. However, this showed no marked increase in yield at either 80 or 100 °C (Entries 4 and 5). Toluene and DME were also tried as solvents that have been used in other Ullmann coupling systems, and although no isomerisation was observed in either case, conversion was very low (Entries 6 and 7). Given that the best yields were achieved with NMP and the lowest isomerisation with dioxane, a 1 : 1 mixture of those two solvents was tried. After 21 hours this solvent mixture gave a yield of 84% and an **97** / **98** ratio of 1 : 0.02 (Entry 8). Given this success, we experimented with reducing copper loading to 25 mol% (Entry 9), but this resulted in lower yield and a slight increase in isomerisation, so the high copper loading was maintained going forward. Increasing the proportion of dioxane to 2 : 1, led to a 53% yield, but only 1 : 0.01 isomerisation (Entry 10). This was considered an acceptable level of isomerisation whilst still maintaining a reasonable yield.

Table 5. Influence of temperature and reaction time on yield and isomerisation.

Entry	Solvent	CuCl / mol%	Temp / °C	Time / h	Yield / %	97 : 98
1	NMP	50	80	15.5	63	1 : 0.07
2	Dioxane	50	80	64	37	1 : 0
3	Dioxane	50	100	20	30	1 : 0
4	Dioxane ^a	50	80	42	34	1 : 0
5	Dioxane ^a	50	100	42	32	1 : 0.01
6	Toluene	50	80	42	14 ^b	1 : 0
7	DME	50	80	42	39 ^b	1 : 0
8	Dioxane / NMP (1 : 1)	50	80	24	84	1 : 0.02
9	Dioxane / NMP (1 : 1)	25	80	24	66	1 : 0.03
10	Dioxane / NMP (2 : 1)	50	80	24	53	1 : 0.01

^aDistilled and degassed. ^bNMR yield – not isolated.

Given the rate acceleration provided by TMHD reported by Buck *et al.*¹⁰⁶ it seemed likely that increasing the loading of this additive from 10 mol% to 50 mol% to match the loading of CuCl would further accelerate rate of the coupling. This proved to be true; under these optimised conditions a yield of 90% was obtained with negligible levels of isomerisation (Scheme 10).



Scheme 10. Influence of additive loading.

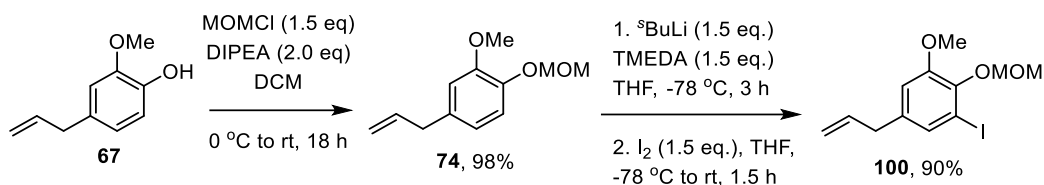
These optimised conditions enable the coupling of an electron-rich *ortho* substituted halide to an *ortho* substituted phenol, in high yields, and showing high tolerance for the isomerisable allyl benzene.

2.4 Synthesis of Halide Coupling Partners for **1** and **2**

The halide coupling partner required for the synthesis of natural products **1** and **2** is derived from eugenol and can be accessed in two steps. The first step is to protect the phenol with a MOM group. MOM was chosen as it should ensure direction of the subsequent iodination to the *ortho* position relative to this group, rather than the adjacent methoxy substituent. It should also be tolerated under the basic coupling conditions.

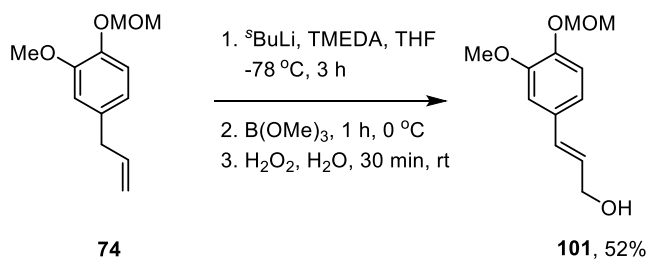
The iodination was initially troublesome and gave moderate yields of **100** using ^tBuLi to deprotonate and iodine to quench. This reaction was very sensitive to moisture as expected, and worked much better using distilled anhydrous THF and TMEDA. It was also important with this reaction to allow sufficient time for the deprotonation – three hours at -78 °C was optimal. This reaction was also highly sensitive to the nature of iodine used – iodination was only achieved when using anhydrous iodine beads, whereas iodine flakes led to recovery of starting material, presumably due to the presence of residual water. As might be expected, the iodination also worked much better on larger scale, and it was important to allow warming to room temperature to occur slowly over 90 minutes.

By careful optimisation of all these factors the iodination step could be achieved on multigram scale in 90% yield, giving the required halide **100** in 88% yield over two steps (Scheme 11).



Scheme 11. Synthesis of halide **100**.

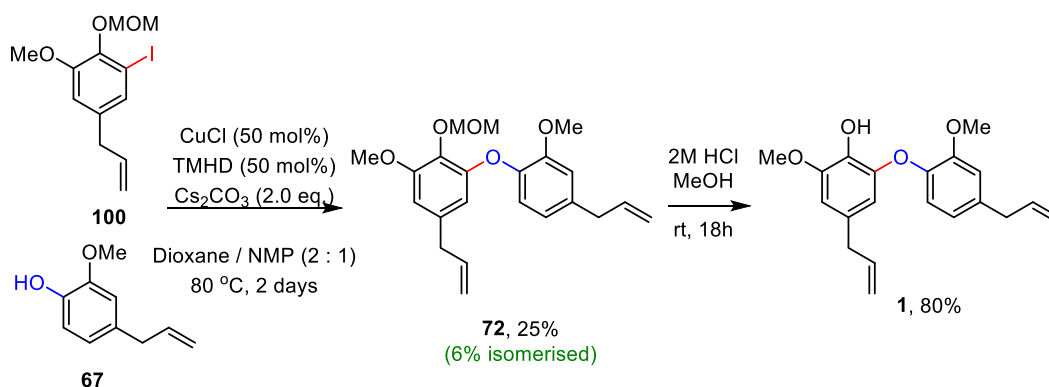
Equipped with the ability to selectively deprotonate the *ortho* position, we attempted quenching with alternative electrophiles. Installing a TMS group for example would enable an *ipso* substitution with an electrophilic iodine source to install the iodine, and negate any issues with iodine wetness in the quenching step. However, it was found that isomerisation of the double bond was observed under these conditions. This can be rationalised by the quenching with TMSCl being too slow, so as the reaction was allowed to slowly heat, the anion would deprotonate another molecule of starting material at the benzylic position, before being quenched with TMSCl . We also postulated that if we could install a hydroxy at this position, giving the phenol, we could access the phenol partner for the ‘reversed-polarity’ coupling. This was attempted by quenching with B(OMe)_3 and then treating with peroxide and water to convert the resulting boronate ester into the phenol. However, in our hands this gave undesired product **101** in 52% yield.



Scheme 12. Major product resulting from quench with B(OMe)_3 .

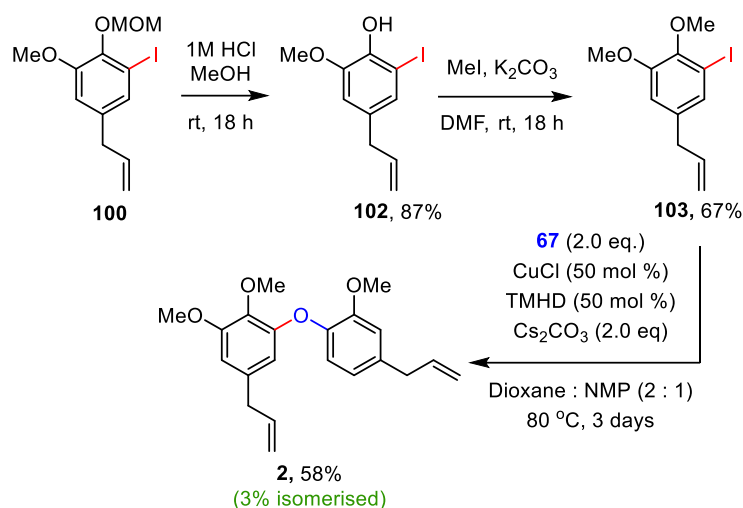
2.5 Coupling and Deprotection

With the desired halide in hand the coupling was attempted using conditions developed during the optimisation. The best result was achieved using the optimised results of 2 : 1 dioxane / NMP and 50 mol% of additive, however, the yield was only 25% of **72**. Examining the crude reaction mixture showed there were two main side reactions occurring – the MOM group appeared surprisingly labile under the reaction conditions, and reduction of the C–I bond was also observed, resulting in **74**. This is a well-known side reaction of Ullmann coupling so is not altogether surprising, although disappointing as this side reaction was not observed under the optimised conditions of the model system. However, with some **72** in hand, deprotection of the MOM group could be achieved using mild acidic conditions to give **1** in good yield (Scheme 12).



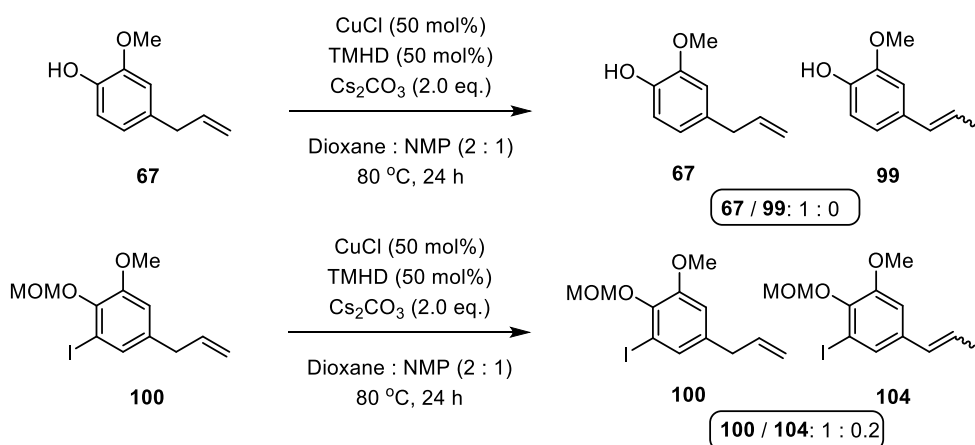
Scheme 12. Coupling reaction on natural product system and deprotection to afford **1**.

Because of the lability of the MOM group, the methyl ether natural product **2** was synthesised by deprotection of the MOM group from **100** before coupling, and replacing it with the methyl group to give **103**. This coupling proceeded in a much more satisfactory yield of 52%, albeit with some isomerisation (Scheme 13).



Scheme 13. Synthesis of 2.

Significantly more isomerisation was observed in the case of both natural product systems compared with the model system. This is also consistent with the observation made in the synthesis of obovatol that the more electron rich allylbenzene on the left hand side isomerises more readily.¹⁰¹ To test this hypothesis both coupling partners (**67** and **100**) were submitted independently to the optimised reaction conditions. Although this is not a perfect model, since as previously discussed, the product likely isomerises more rapidly than the starting materials, it gives an idea of which allyl group is more prone to isomerisation. The results of this study are shown in Scheme 14, and show that the allyl group corresponding to the left-hand side is more readily isomerised.



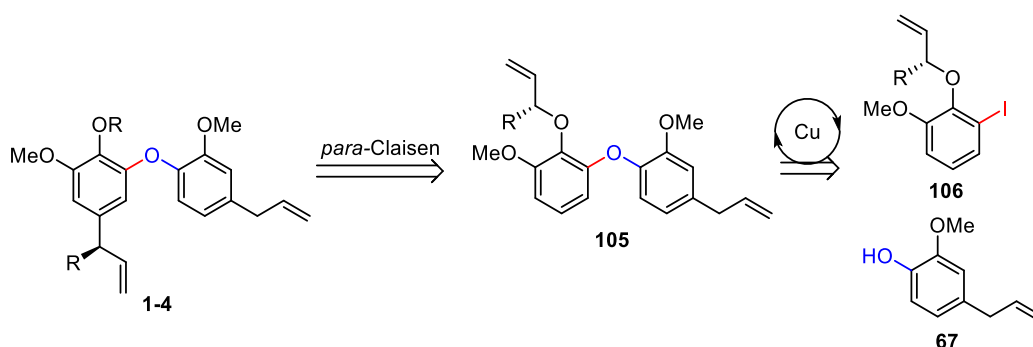
Scheme 14. Left-hand side vs right-hand side isomerisation.

2.6 Side Chain Installation Post-Ullmann Coupling

An alternative solution that would avoid the uncertainty over potential allyl-propenyl isomerisation would be to introduce this side chain after the coupling step. Also, given the unexpected lability of the MOM group, an alternative protecting group for this phenol could improve the yield in this step. The following section explores these strategies for optimising the natural product synthesis.

2.6.1 *Para*-Claisen Approach

A good way to achieve both of the proposed solutions with only one modification is to ‘protect’ the phenol with an allyl chain for the coupling, and perform a *para*-Claisen rearrangement as the final step, to simultaneously deprotect the phenol and install the allyl side chain on the left-hand side. This is of particular utility in our system as both *ortho* positions are blocked, forcing the rearrangement to go to the desired *para* position.

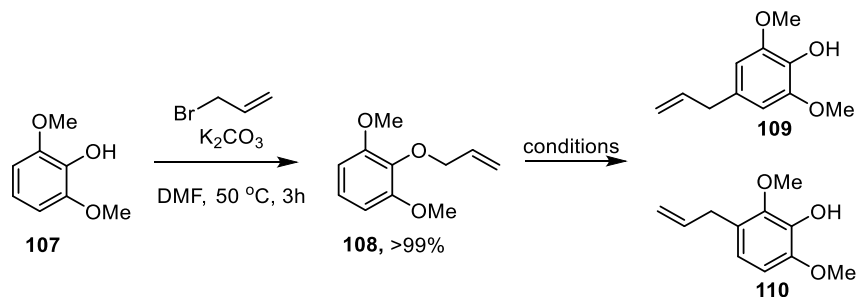


Scheme 15. Alternative *para*-Claisen approach to natural products 1-4.

To test the feasibility of this method the *para*-Claisen reaction was investigated on **108**, which was synthesised from 2,6-dimethoxyphenol and allylbromide in good yield (Table 6). Bi(OTf)₃ catalysed rearrangement,¹⁰⁸ while facile, gave a mixture of *para*- and *meta*- substituted products in our hands, the ratio of which was unchanged regardless of temperature or time (Entries 1 to 4). We believe this result derives from *in situ* formation of an allyl cation, and resulting Friedel–Crafts alkylation. It is possible for this mechanism to result in both *para* and *meta* substitution as although the phenol would be expected to be more strongly directing, the two methoxy groups work synergistically. However,

we were pleased to find that thermal rearrangement in 1,2-dichlorobenzene gave clean conversion to the *para*-substituted phenol (Entry 5).

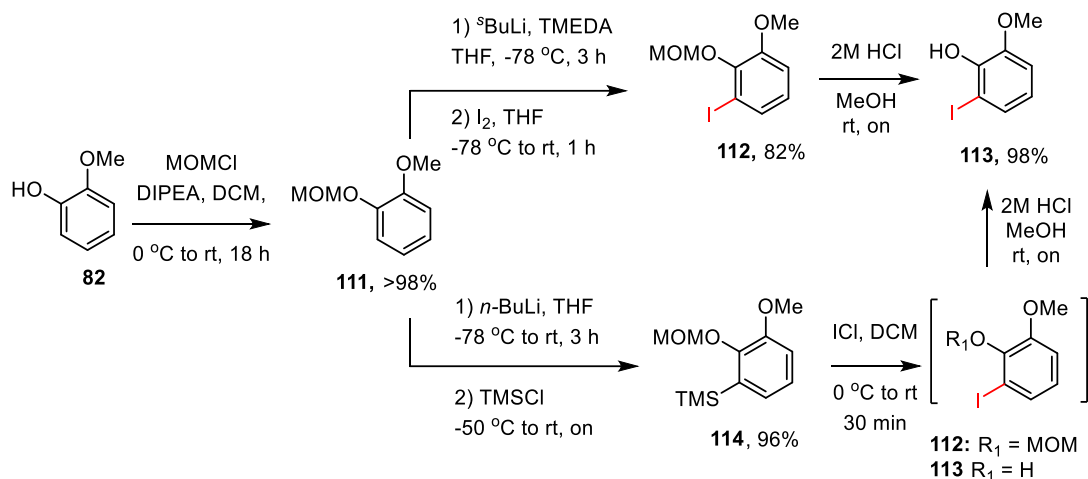
Table 6. *para*-Claisen rearrangement on a model substrate



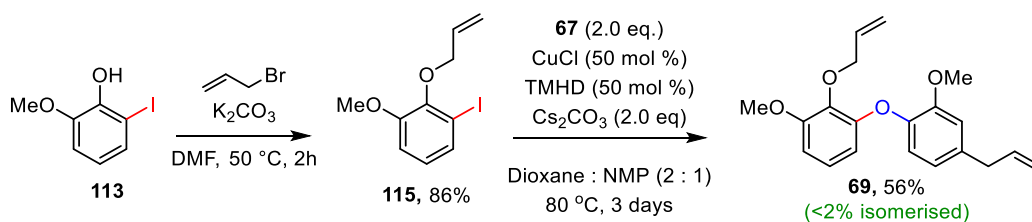
Entry	Conditions	109 : 110 ^a	Yield / %
1	Bi(OTf) ₃ (10 mol%), CH ₃ CN, 80 °C, 4 h	1 : 0.25	ND
2	Bi(OTf) ₃ (10 mol%), CH ₃ CN, 60 °C, 4 h	1 : 0.25	ND
3	Bi(OTf) ₃ (5 mol%), CH ₃ CN, 60 °C, 30 min	1 : 0.25	ND
4	Bi(OTf) ₃ (10 mol%), CH ₃ CN, 40 °C, 30 min	1 : 0.25	ND
5	1,2-Dichlorobenzene, 180 °C, 6 h	1 : 0	52%

^aRatio determined by NMR.

With this result in hand decided we decided to proceed with the natural product system. To synthesise the halide partner, guaiacol (**82**) was first protected as a MOM ether in good yield. This could then be iodinated in two ways, either directly by quenching the anion with iodine, or by quenching with TMS to give **114**, and carrying out an *ipso*-substitution. In the second case, the *ipso* substitution reaction also resulted in partial deprotection of the MOM to give the phenol **113**. Deprotection was complete in the usual way to give the phenol (Scheme 16).

Scheme 16. Synthesis of phenol **113**.

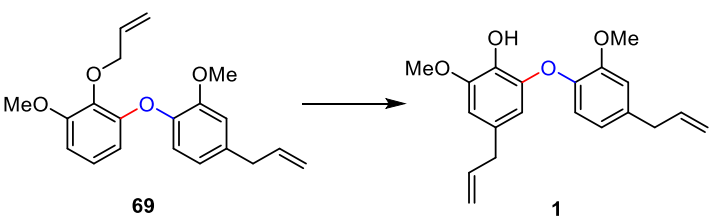
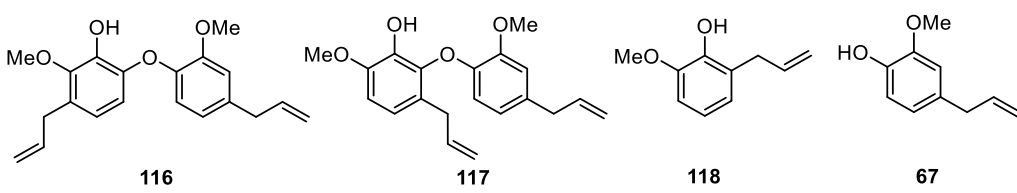
Allylation of the phenol with allyl bromide and potassium carbonate gave the required coupling partner **115**. With this in hand the coupling reaction was attempted using the optimised conditions described. This coupling gave a moderate yield of **69** (56%) but less isomerisation, as predicted (Scheme 17). Nonetheless, this yield is more than double that achieved in the coupling of the MOM protected halide **100**, and comparable with the methyl ether **103** for the synthesis of **2**. It also reduced the isomerisation to negligible levels, which justifies the additional deprotection and reprotection steps.

Scheme 17. Synthesis of *para*-Claisen substrate **116**.

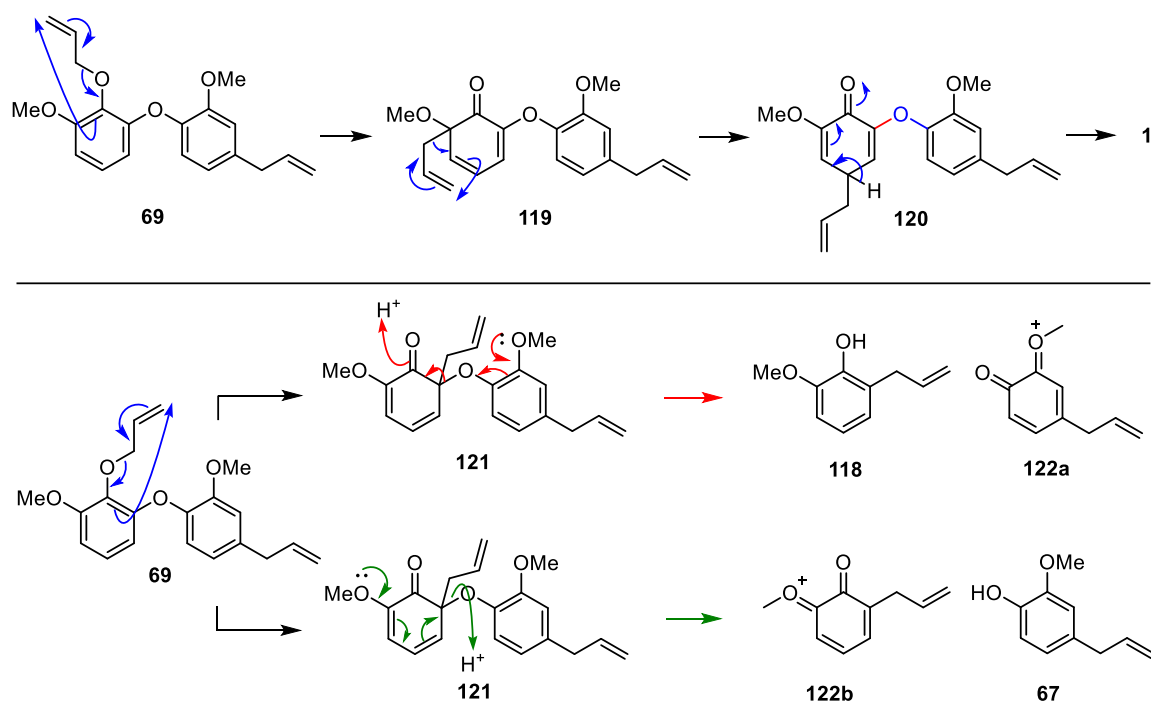
With the *para*-Claisen substrate in hand, the key rearrangement step was attempted (Table 7). Repeating the Lewis acid mediated conditions resulted in the same regioselectivity issues, giving a mixture of *meta*-allylated products **116** and **117** (Entry 1 and 2).^{108,109} Using a high-boiling solvent for the thermal reaction gave the best result of 28% of **1**, plus a mixture of **69** and eugenol **67** (Entry 3). Lowering the temperature by 20 °C resulting in the same mixture of products but also with some starting material present (Entry 4). Heating neat in a microwave for 75 min gave recovered starting

material, and in 1,2-dichlorobenzene the same fragmentation products as the thermal reaction (Entries 5 and 6).

Table 7. *para*-Claisen reaction products formed.

		
		
Entry	Conditions	Outcome
1	Bi(OTf) ₃ (10 mol %), CH ₃ CN, 80 °C, 4 h	1, 116, 117 , inseparable
2	BCl ₃ (1 eq.), DCM, rt, 2 h	1, 116, 117 , inseparable
3	1,2-dichlorobenzene, 180 °C, 6 h	28% 1 , 16% 118 , 28% 67
4	1,2-dichlorobenzene, 160 °C, 6 h	Mainly 69 and 1, 119, 67
5	180 °C, 75 min, μ v	69
6	1,2-dichlorobenzene, 180 °C, 75 min, μ v	1, 118, 67

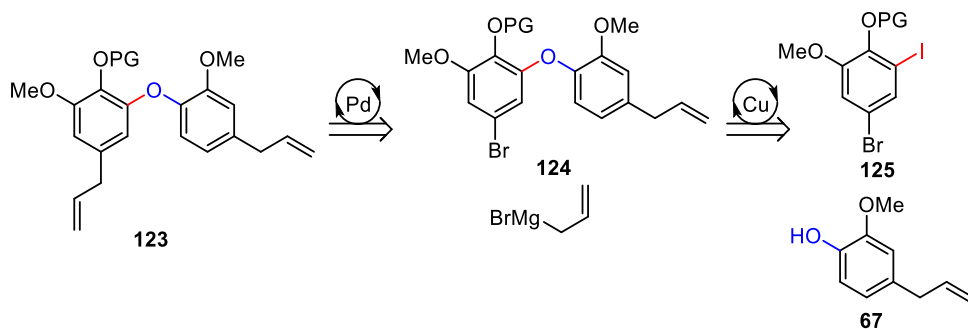
It is likely the side products **118** and **67** derive from the initial Claisen rearrangement clockwise to install the allyl group at the ortho-position (red arrows, Scheme 18). At this stage fragmentation may be possible by the mechanism shown in Scheme 18, resulting in **118** (red arrows) or **67** (green arrows), and by-products **122a** and **122b**. When the initial Claisen rearrangement occurs anti-clockwise (blue arrows, Scheme 18), fragmentation is not possible, and so the rearrangement continues to the required *para*-position, giving rise eventually to **1**.



Scheme 18. *para*-Claisen mechanism and decomposition pathways.

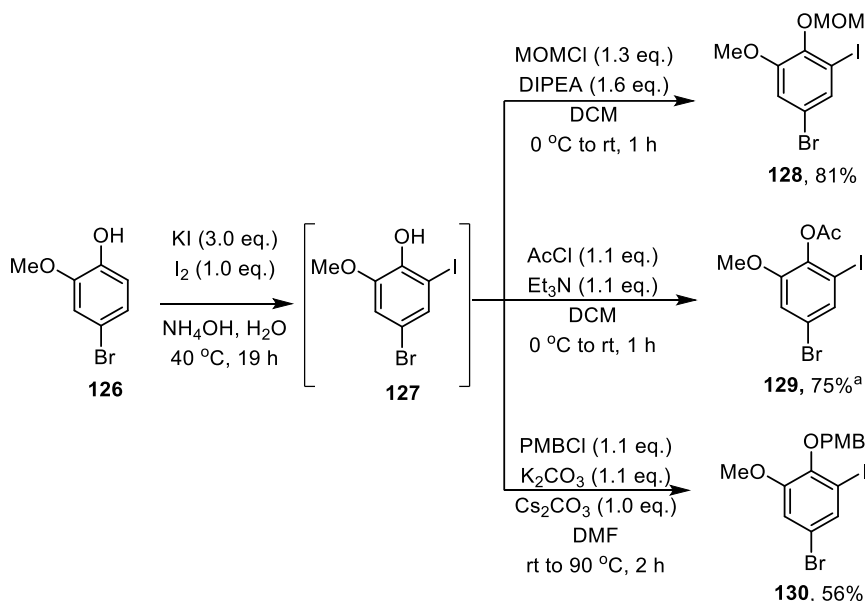
2.6.2 Bromide vs Iodide Selectivity in the Ullmann Coupling

If a bromide could be installed in place of the allyl chain on the left-hand side coupling partner, and selectivity could be achieved in the Ullmann coupling reaction, it is possible that the allyl group could be installed post Ullmann either by a palladium catalysed Kumada coupling with allyl magnesium bromide, as shown in Scheme 19, or by converting the bromide to a Grignard followed by reaction with allyl bromide. Given the evidence in the literature that bromides couple more slowly,^{104–106} and our initial result comparing the two halides in the model system, it is likely that in a substrate containing both an iodine and a bromine, the iodine will couple much more readily.



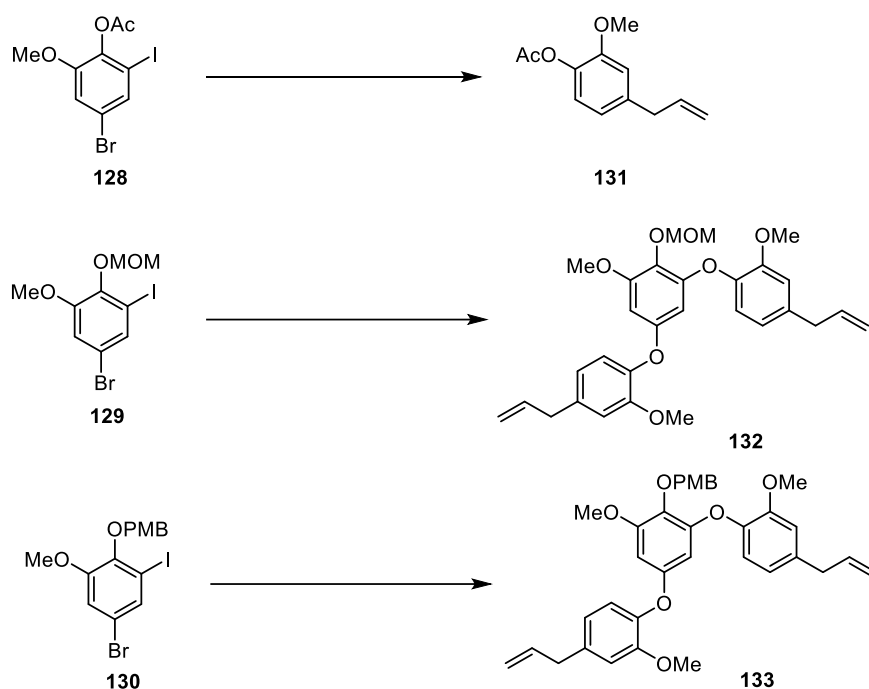
Scheme 19. *Installing the side-chain post-coupling.*

The iodobromoarene, **127** was synthesised from commercially available 2-methoxy-4-bromophenol (**126**) by iodinating ortho to the phenol. Three protecting groups were installed: MOM, acetate, and PMB (Scheme 20).



Scheme 20. Synthesis of the required coupling partners **128**-**130**. ^aNMR yield – synthesised as a 1 : 0.23 **129** / C–X reduction product and used without further purification.

The acetate **128** was soon found to be unsuitable in the coupling as the major product isolated from this reaction was acetate-protected eugenol **131**, where the protecting group had transferred onto the reacting phenol (Scheme 21). To our surprised, both the MOM and PMB protected substrates led to coupling at both positions as the major product (**132** and **133**), despite only using one equivalent of eugenol. This shows that the bromide in this system has comparable reactivity to the iodide which can be rationalised given that the bromide has no neighbouring substituents and is therefore more sterically accessible. Also present in this reaction mixture was a combination of proto-dehalogenated products in which one or both of the C–X bonds have been reduced. Promisingly, the PMB protecting group did not appear to be labile under the reaction conditions.



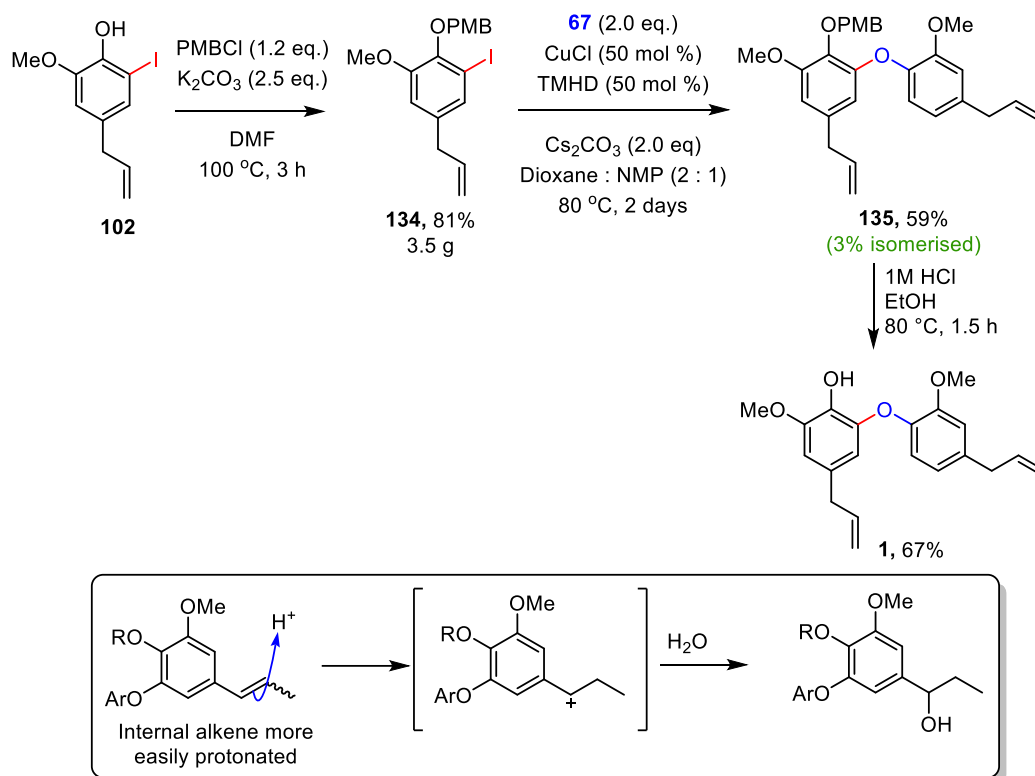
Scheme 21. Main products isolated from the coupling of halides **128-130**. Conditions: **67** (1.0 eq.), CuCl (50 mol%), TMHD (50 mol%), Cs₂CO₃ (2.0 eq.), dioxane / NMP (2 : 1), 80 °C, 24 h. Products not isolated – structures determined by crude NMR.

2.7 Alternative Protecting Groups for the Ullmann Coupling

As post-coupling installation of the left-hand side chain had proved troublesome, our attention turned to optimising the coupling by modifying the protecting group on the phenol. Ahead of trying new protecting groups, the free phenol **102** (Scheme 13) was used in the coupling to see if selectivity could be achieved, with eugenol being the more reactive phenol. This reaction gave some desired product, but also a complex mixture of other products that could not be separated. We concluded therefore that protection of this phenol was necessary.

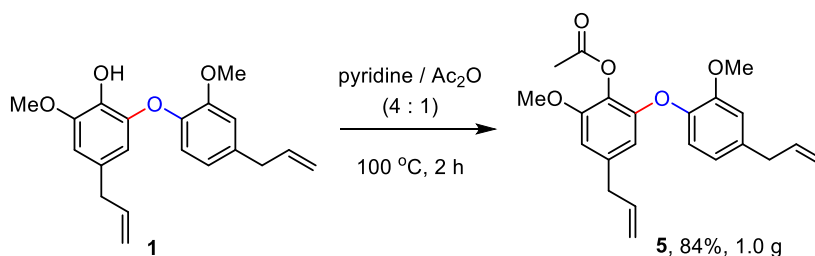
Given that the PMB group had been shown to not be labile in the previous section, and can be deprotected using mild acidic conditions, we chose this group to proceed. Protecting **102** using PMBCl proceeded to give an 81% yield of **134**, and when this halide was subjected to the coupling conditions, the reaction gave 59% of product **135**, with 3% isomerisation (Scheme 22). This was a vast improvement on the MOM protected phenol and comparable with the methyl ether analogue. When the PMB group was deprotected by heating with acid, the 2-propenyl side products were

hydrated under these conditions more readily than the less reactive 1-propenylbenzene. This effectively removed the by-product and gave clean natural product with no isomerisation present (Scheme 22).



Scheme 22. Top: synthesis of **1** using a PMB protecting group, and bottom: desirable side reaction resulting in selective hydration of 2-propenyl side-product.

At this stage in the project, compound **5** had been found to exhibit very promising activity against *T. cruzi*, eliminating 100% of the intracellular amastigotes in the cell-based assay, and de Sousa *et al.* were seeking to advance this compound into *in vivo* murine models, requiring at least 500 mg of pure compound. Using the synthetic method developed in this chapter we were able to scale up the synthesis to supply one gram of compound for these studies.⁹⁴



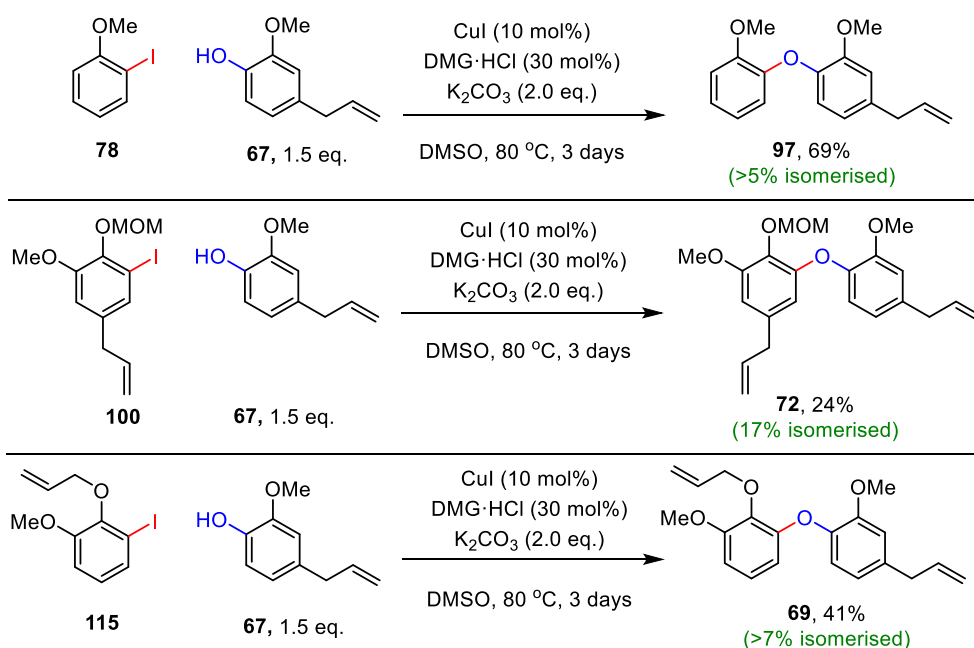
Scheme 23. Acetylation to afford 1 g of **5**.

2.8 Alternative Catalyst and Ligand Systems for the Ullmann Coupling

Although the Ullmann optimisation so far employed copper(I) chloride and TMHD, numerous copper and ligand systems exist for effecting C-O bond formation and many have been shown to be effective in electron rich and sterically demanding systems. A number of these were attempted on our model system and natural product systems.

2.8.1 Copper(I) Iodide with *N,N*-Dimethylglycine

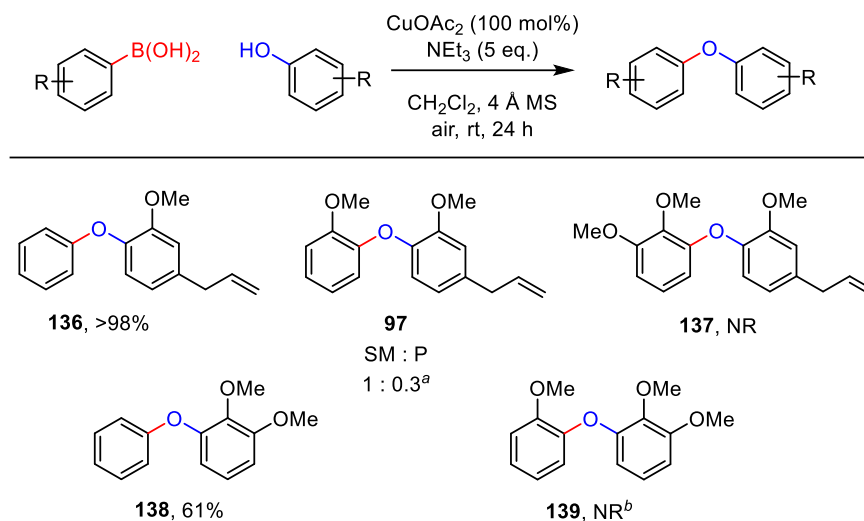
An extensive optimisation on the conditions described by Ma's group in 2003 was conducted by Dr Marius Haugland (Scheme 24).^{103,107} These conditions involve copper(I) iodide as the catalyst, with *N,N*-dimethylglycine hydrochloride (DMG·HCl) as the ligand, with cesium carbonate as base and dioxane as solvent. When optimised on the model system using eugenol (**67**) and 2-iodoanisole (**78**), DMSO was found to accelerate the rate of reaction compared to dioxane, allowing also a lower temperature and the use of the weaker and cheaper potassium carbonate as base. Higher loadings of copper(I) led to a greater yield and reduced levels of isomerisation, consistent with our previous studies. The best result of 69% yield of **97** was achieved using 10 mol% of CuI, 30 mol% of DMG·HCl, potassium carbonate (2.0 eq.), in DMSO at 80 °C for 72 hours. When these conditions were applied to the coupling of **100** and eugenol, however, only 24% yield was observed with a 1 : 0.2 mixture of desired product and a mixture of double bond regioisomers (Scheme 24). These conditions performed better using **115** as the halide, giving **69** in 41% yield.¹⁰⁷ Iridium and ruthenium catalysed photochemical C–O bond formation was also attempted on a model system as part of this work but only trace product was obtained in every case.¹⁰⁷



Scheme 24. Application of Dr. Haugland's conditions to model system (top) and natural product synthesis (middle)¹⁰⁷ and para-Claisen substrate **69** (bottom).

2.8.2 Chan-Lam Coupling

Chan-Lam couplings^{110,111} are a well-known method for C-O bond formation between a boronic acid and a phenol, using milder conditions than Ullmann coupling – they are usually conducted at room temperature in air, using an amine base – although, they require stoichiometric amounts of copper.¹¹² A number of model systems were tried to achieve a Chan-Lam coupling (Scheme 25), however, the success of the reaction declined significantly with the presence of any electron-donating group on the boronic acid (compound **97**, **137**, **139**). Equally, when attempting to synthesise the desired boronic acid partner for the synthesis of **1** and **2**, the palladium catalysed Miyaura borylation of the corresponding iodide (**100**) gave rise to double bond regioisomers. This is consistent with our prediction that palladium-catalysed C–O cross-couplings would be inappropriate for this system.¹⁰⁰



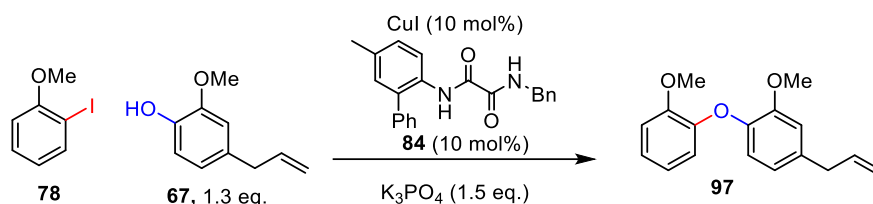
Scheme 25. Chan-Lam couplings on model systems. ^aBy NMR – not isolated. ^b36 °C, 48 h.

2.8.3 Copper(I) Iodide with Oxalamide Ligand

The oxalamide ligand (**84**, Table 8) described previously, developed by Ma and coworkers was first prepared according to the conditions described in the paper.¹⁰⁴ Reaction of methyl oxalyl chloride and 2-phenyl-4-methylaniline, followed by substitution of the resulting methyl ester with benzylamine, giving the ligand **84** in 67% overall yield.

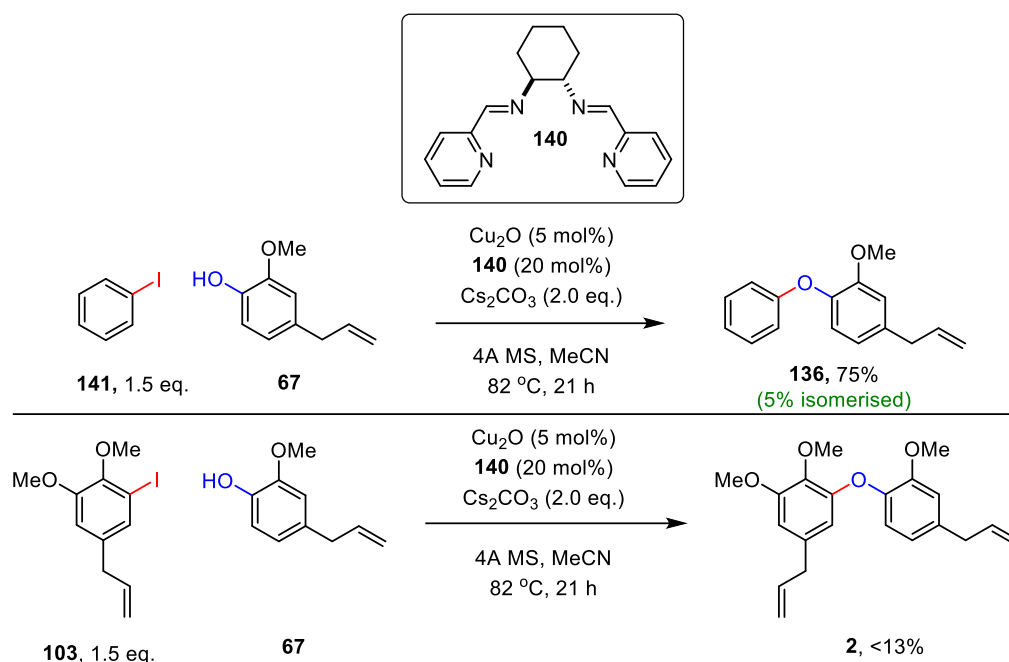
The literature coupling conditions were tried first on the model system using 2-iodoanisole as halide. Under the conditions described in the paper (Table 8, Entry 1) poor conversion and high isomerisation was observed. Reducing the reaction temperature and time to 100 °C for five hours (Entry 2) reduced the level of isomerisation but saw no increase in yield. Using a favoured dioxane / NMP (1 : 1) mixture at 80 °C for 24 hours also gave no noticeable improvement (Entry 3).

Table 8. Application of conditions to model substrate synthesis.

					
Entry	Solvent	Temp. / °C	Time / h	% Yield	% Isomerisation
1	DMSO	120	17	18	23
2	DMSO	100	5	15	2
3	Dioxane / NMP (1 : 1)	80	24	16	6

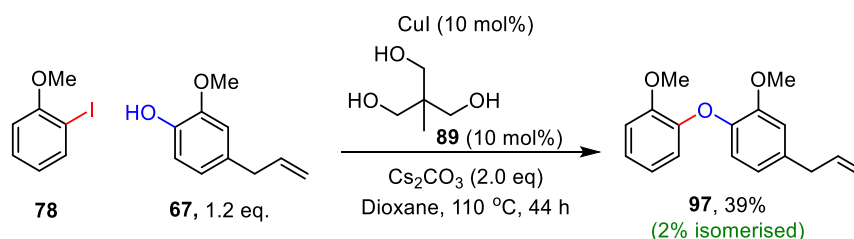
2.8.4 Other copper and ligand systems

Cristau *et al.* described the use of the Chxn-py-al ligand (**140**, Scheme 26) with copper(I) oxide for the formation of C–O bonds.¹¹³ This ligand is synthesised in one step from *rac*-trans-1,2-diaminocyclohexane and 2-pyridinecarboxaldehyde. The literature coupling conditions use an excess of halide and a cesium carbonate as the base, with acetonitrile as solvent. The reaction on a model system using phenyl iodide (**141**) and eugenol gave a promising result of 75% yield of **136** and 5% isomerisation. However, the conditions did not transfer well to the natural product system. Using the methyl ether as the halide (**103**), the reaction gave less than 12% yield of **2** (impure product) and 40% of proto-deiodinated starting material.



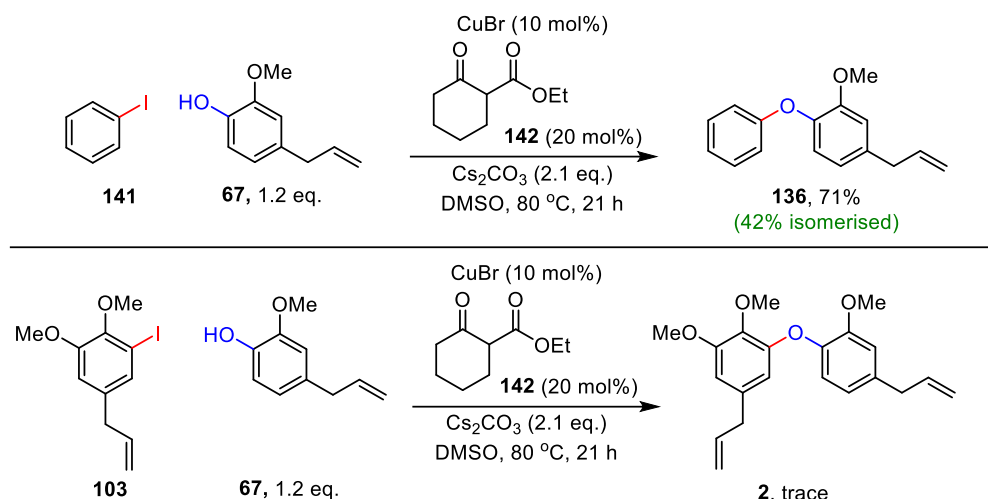
Scheme 26. Coupling reactions using conditions described by Christau et al.¹¹³

The tripod ligand 1,1,1-tris(hydroxymethyl)ethane (**89**) described by Chen and Chen¹⁰⁵ gave a moderate yield on the model substrate using 2-iodoanisole of 39% and only 2% isomerisation, using dioxane as the solvent and cesium carbonate as base (Scheme 27). While somewhat promising, it was decided that this system offered little advantage over TMHD, owing to the long reaction times and high temperatures required.



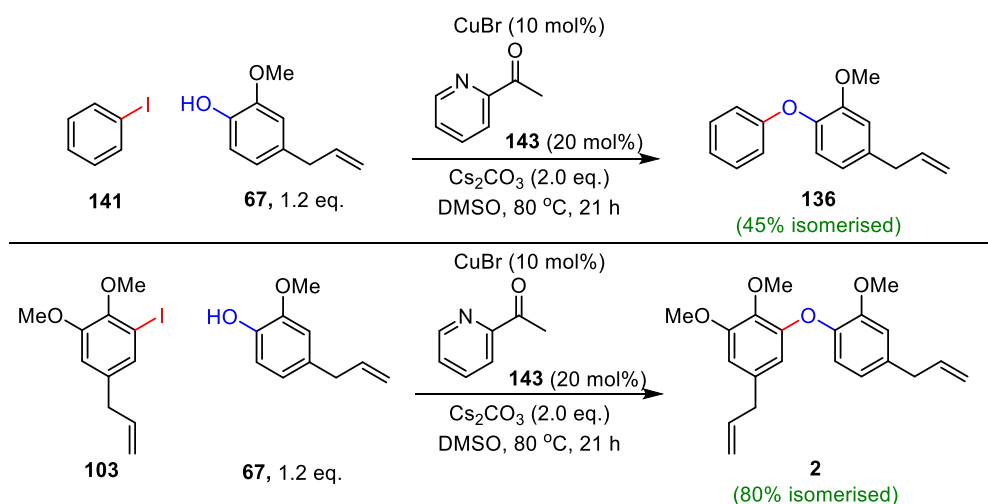
Scheme 27. Model coupling with 1,1,1-tris(hydroxymethyl)ethane (**89**) as ligand.

Lv and Bao described a β -ketoester **142** for the formation of C–S, C–N and C–O bonds with copper(I) bromide.¹¹⁴ In our hands this system worked well for a model system using phenyl iodide, albeit with quite high levels of isomerisation, but when applied to the synthesis of **2** using the methyl ether **103**, only trace amounts of product **2** could be identified in the crude NMR (Scheme 28).



Scheme 28. C-O bond formation using β -ketoester ligand described by Lv and Bao.¹¹⁴

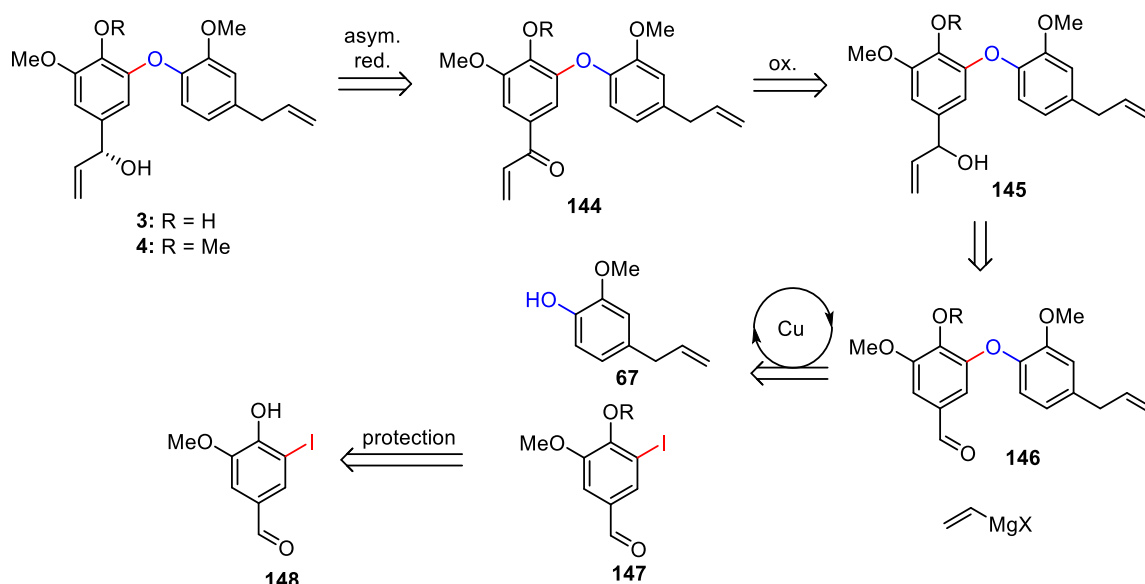
Zhang *et al.* described the use of 2-acetylpyridine (**143**) as a ligand for achieving copper-catalysed O-arylation of phenols with a range of phenol nucleophiles.¹¹⁵ In our hands these conditions were unsuccessful, leading to high levels of isomerisation even in a model system with no left-hand side allyl chain (Scheme 29). Owing to the presence of regioisomers in the crude NMR the products were not isolated in this case.



Scheme 29. C-O bond formation ligand described by Zhang *et al.*¹¹⁵

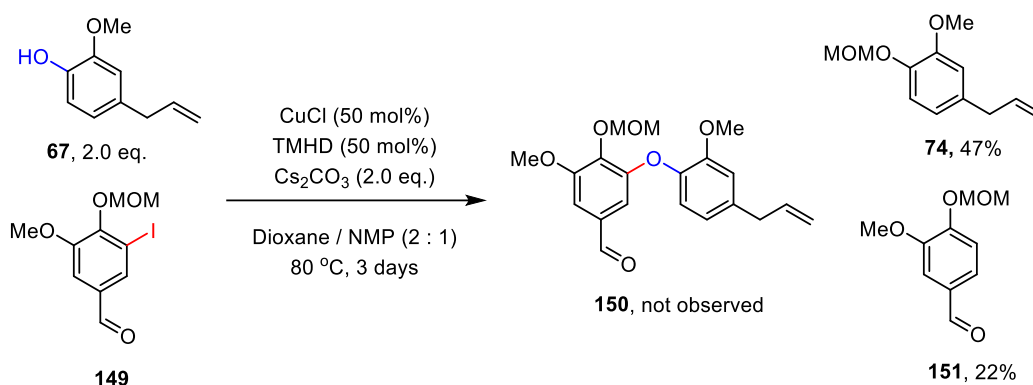
2.9 Studies Towards the Synthesis of **3** and **4**

The strategy for the synthesis of **3** and **4** involves a similar disconnection to that used for the other natural products; formation of the C-O bond through an Ullmann coupling strategy, with the allylic alcohol 'masked' as an aldehyde for the coupling step. This is an attractive strategy as 5-iodovanillin (**148**) is commercially available and inexpensive, and adds an electron withdrawing group to the halide coupling partner, making the electronics of the reaction more favourable. It would also allow incorporation of the stereocentre post-coupling through the addition of vinyl magnesium bromide, and subsequent oxidation and asymmetric reduction (Scheme 30).



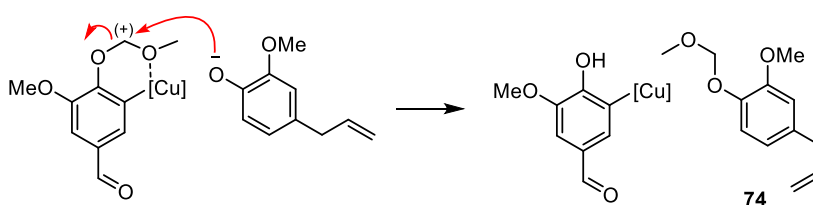
Scheme 30. Retrosynthetic strategy for **3** and **4**.

To synthesise **3**, MOM protected 5-iodovanillin (**149**) was prepared by Dr Marius Haugland.¹⁰⁷ The coupling of this iodide under the optimised conditions using TMHD gave rise to no desired product and two major side products; proto-deiodination of the halide to give MOM-protected vanillin **151**, and MOM-protected eugenol, **74** (Scheme 31).



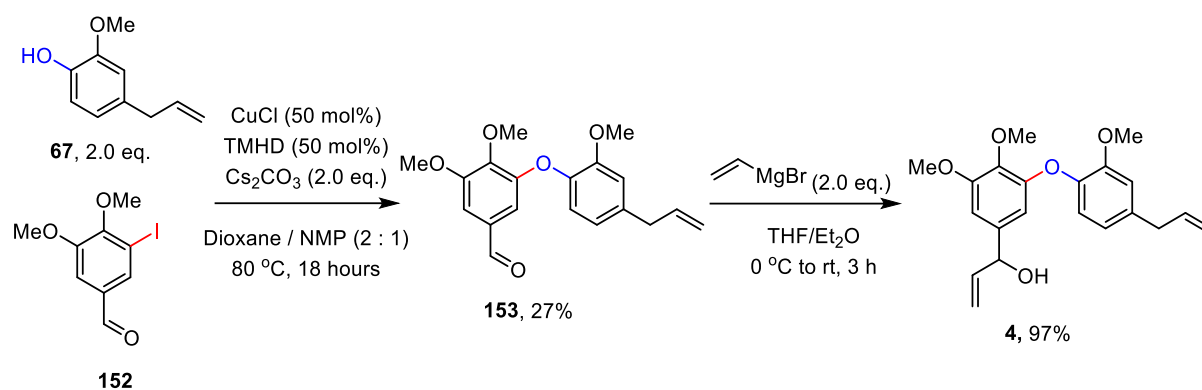
Scheme 31. Attempted coupling reaction towards **3**.

The formation of **151** is unsurprising as reduction is a common by-product in Ullmann coupling. However, MOM-protected eugenol **74** – which presumably arises from transfer of the MOM group from the halide partner to the reacting phenol (Scheme 32) – was unexpected. We had seen previously that the MOM group is labile in the coupling but this was the first time migration had been unequivocally observed. Interestingly, **74** was present as a by-product in the synthesis of **1** but in this system, it could have arisen from halide reduction. This observation suggests that it is possible that in the synthesis of **1**, MOM-eugenol is derived from two side reactions, rather than simply from iodide reduction.

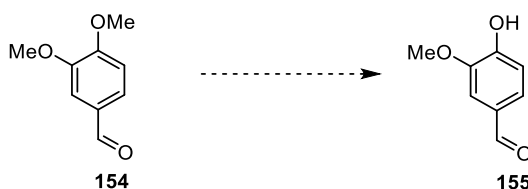


Scheme 32. Transfer of MOM from one phenol to the other.

The same coupling reaction with the phenol protected with a methyl group (**152**) – leading directly to the synthesis of **4** – was more successful, giving 27% yield of desired biaryl ether **153** (Scheme 33). The major side product in this reaction was again the reduction of the C–X bond. However, with some of **153** in hand, the Grignard addition to the aldehyde proceeded cleanly in good yield giving rise to racemic **4**. No isomerisation was observed in this Ullmann coupling which is unsurprising as **153** lacks the left-hand side double bond.

Scheme 33. Racemic synthesis of **4**.

Given the modest success of the methyl group as protecting group in the coupling, it was hypothesised that selective demethylation of the desired position to give **3** may be possible in this system, as the developing anion could be stabilised by resonance with the *para*-aldehyde, and indeed there were some limited examples of this in the literature.^{116,117} However in a model system on veratraldehyde (**154**) poor conversion was observed even with forcing conditions, so this strategy was abandoned (Table 9)

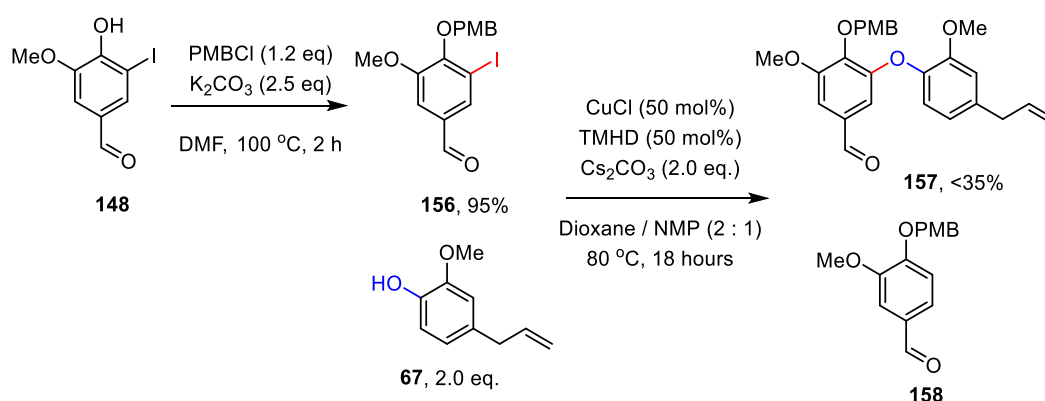
Table 9. Selective demethylation on veratraldehyde (**154**).

Entry	Conditions	Outcome
1	AlCl ₃ (2 eq), DCM, rt, on	NR
2	Piperidine : H ₂ O (1 : 1), reflux, 24 h	1 : 0.75 (154 : 155)

As with **1**, the free phenol **148** was also explored as a coupling partner. We expect the generated phenolate to be less likely to coordinate to copper, given the conjugation with the aldehyde, allowing some selectivity for the preferential reaction of eugenol. However, in the coupling of 5-iodovanillin

(**148**) directly with eugenol, rapid decomposition was observed and no product was observed, suggesting that it is necessary to have a protecting group on the phenol.

Having shown PMB to be a useful protecting group in the synthesis of **1**, the same protecting group was tried in this synthesis. PMB protection of 5-iodovanillin proceeded in good yield to give the desired iodide coupling partner **156**. However, Ullmann coupling gave rise to a 1 : 0.6 mixture of biaryl ether **157** : **158**, which unfortunately was inseparable and amounted to less than 35% of desired product. No migration of the PMB group was observed.



Scheme 34. Use of PMB protecting group in the synthesis of **3**.

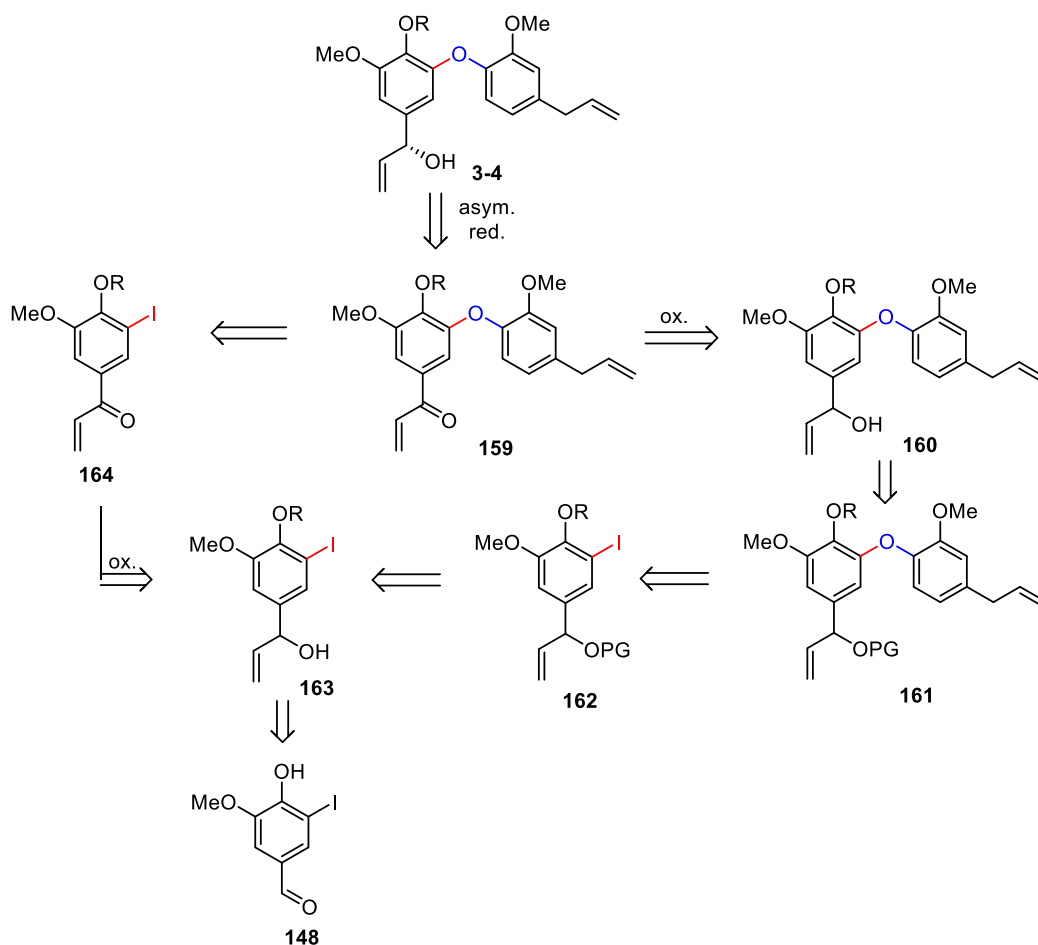
2.9.1 Protection of the Aldehyde for the Ullmann Coupling

Based on the examples described above, the presence of the aldehyde seems to promote reduction of the C–I bond. In light of this observation we decided to explore protection of the aldehyde. Commonly aldehydes are protected as an acetal, using ethylene glycol and PTSA. However, when modelling this protection on MOM-protected vanillin **151**, only 27% yield was achieved and the MOM group proved labile. Attempting to get around this by reversing the steps and protecting the aldehyde of vanillin before the phenol led to decomposition of vanillin so this strategy was abandoned.

An alternative method for ‘protecting’ the aldehyde for the coupling is to change the order of steps, so that Grignard addition takes place before the coupling. The alcohol resulting from Grignard

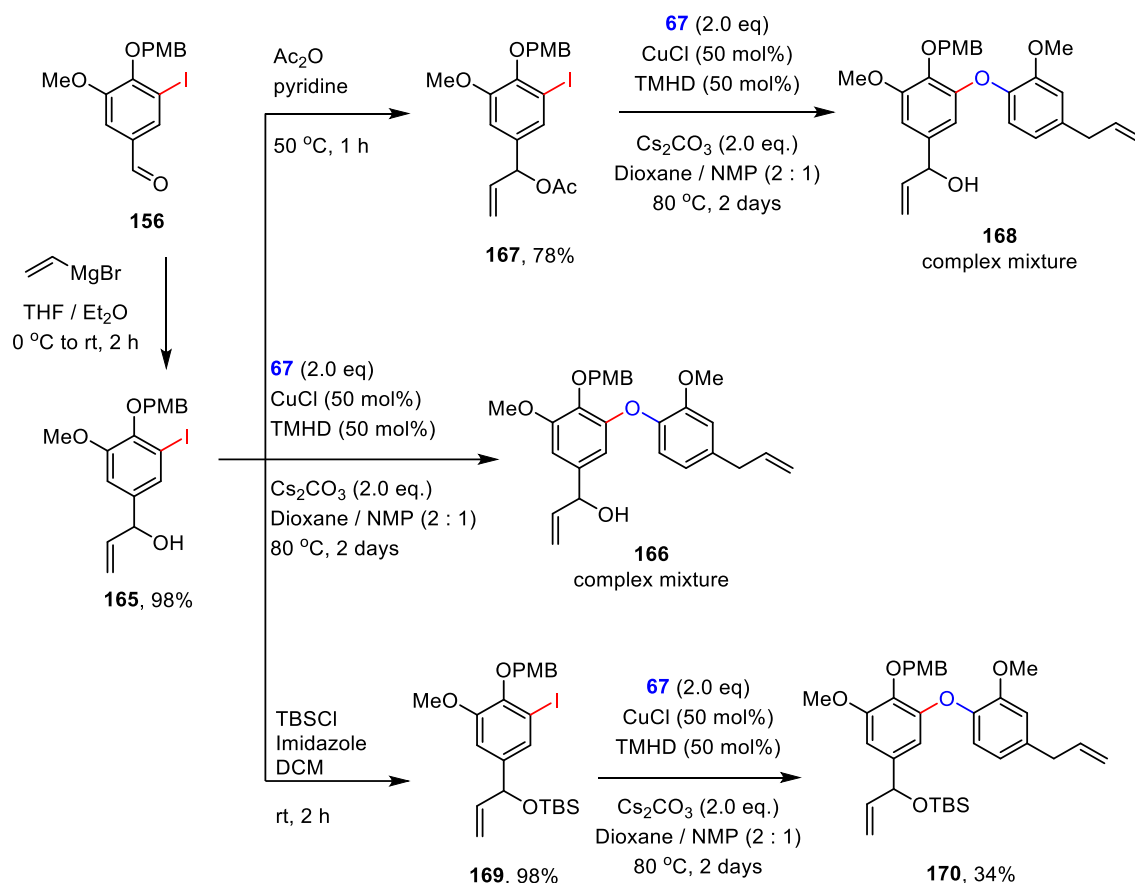
addition (**163**) can be either be protected (**162**), or oxidised to the ketone (**164**) ahead of coupling.

These possible strategies are outlined in Scheme 35.



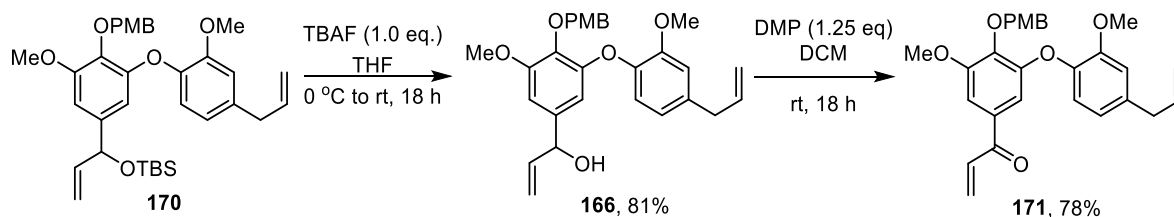
Scheme 35. Potential alternative routes to **3**.

With these strategies in mind a series of potential substrates for the synthesis were prepared. Grignard addition to **156** proceeded in 98% yield. Direct coupling of **165** with eugenol to give **166** was attempted but gave a complex mixture of inseparable products so it was decided that a protecting group for the allylic alcohol was necessary. This is a challenge as the protecting group needs to be tolerated in the coupling. The coupling was first attempted with an acetate protecting group on the alcohol (**167**), but this also gave a mixture of complex products, potentially owing to the lability of the acetate under the basic coupling conditions as seen previously. The most success was found using a TBS protecting group (**169**), which gave 34% of the required product **170** and no isomerisation. These results are summarised in Scheme 36.



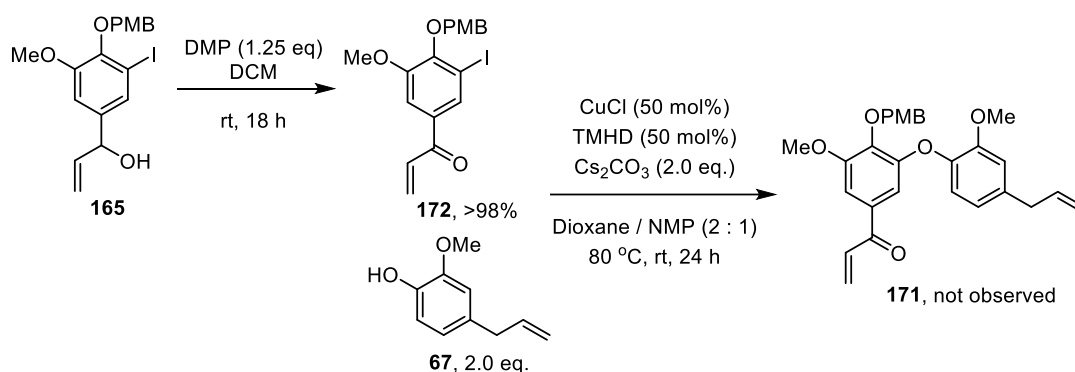
Scheme 36. Carrying out the Grignard addition before the biaryl ether formation.

With **170** in hand, deprotection of the TBS group could be achieved using TBAF in good yield, to afford the deprotected alcohol **166**, and oxidation was achieved using DMP to give the α,β -unsaturated ketone, **171** (Scheme 37).



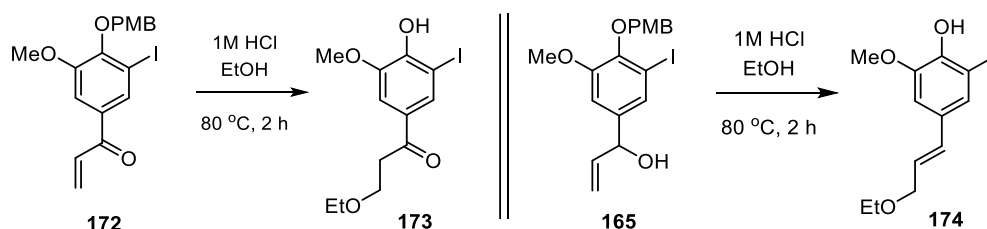
Scheme 37. Synthesis of **171**.

Synthesis of **171** was also attempted directly, through oxidation of iodide **165** with DMP to the ketone **172**, followed by coupling. This strategy is attractive as it avoids having to use a protecting group for the allylic alcohol at all. However, this gave a complex mixture in our hands, with addition of eugenol to the α,β -unsaturated ketone being one of the observed products (Scheme 38).



Scheme 38. Attempted synthesis of **171**.

Deprotection of the PMB group is also non-trivial in this system. It could feasibly be achieved at either **166**, **170**, or **171** stages of the synthesis, however, the allylic alcohol in **166** and **170** is likely to be labile under the acidic conditions used for the deprotection of the PMB group, and in **171** the α,β -unsaturated ketone is also potentially a reactive site under various conditions. Oxidative deprotection of the PMB ether is likely to lead to decomposition of the biaryl ether core, as it is itself an oxygen rich aromatic. Indeed, where the usual acidic deprotection conditions were tried on **172** or **165** as a model, addition of ethanol was observed as the major product (Scheme 39). Where other acids were used, no deprotection or decomposition was observed.



Scheme 39. Major products observed from PMB deprotection under acidic ethanolic conditions.

2.9.2 Future Work

Due to the COVID-19 pandemic, further attempts towards **3** and **4** were cut short, however, there remain a number of strategies for completing these targets that could be explored. Given the difficulties of deprotecting the PMB group once coupling with the oxygenated side chain is achieved, an alternative protecting group could be tried here that requires deprotection conditions compatible with the presence of the side chain functionality. Acetate and MOM protecting groups have already

been shown to be labile in the coupling reaction. Benzyl groups requiring hydrogenation to remove are incompatible with the allylic side chains. A silyl protecting group has potential to be a good choice, and will also enable global deprotection of both the phenol and the allylic alcohol in one step. However, there is some concern over the steric bulk of the *ortho*-substituent interfering with the Ullmann coupling reaction. There is also further potential for protecting the aldehyde as the acetal for the coupling as only one set of conditions were tried for this transformation. It is also possible that with a useful protecting group in hand, the order of steps can be changed so that the stereocentre is set ahead of the coupling, allowing for fewer manipulations post-coupling in the presence of additional complexity.

3. Design and Synthesis of Analogues of 1 and 2

The strategy developed towards **1** and **2** enables the modification of the two halves of the natural products independently. With such a route in hand, the design of new non-symmetric analogues is possible. For this project there are four key areas that can be explored using analogue design and synthesis:

1. Enhancing the potency and selectivity
2. Structure-activity relationship (SAR)
3. Physicochemical properties for improving ADMET/PKPD
4. Synthetic ease

With these goals in mind, a number of analogues can be designed to probe these areas and enhance the understanding of the anti-parasitic activity of the natural products. This chapter describes the design and synthesis of such analogues.

3.1 Analogue Design

3.1.1 Systematic and Modular Deletion Study

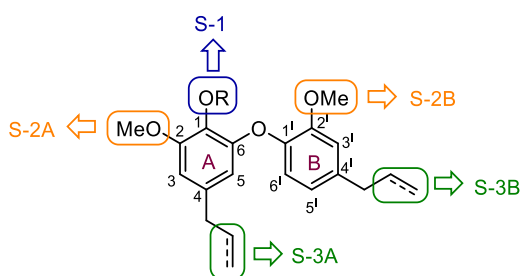


Figure 26. Nomenclature for describing substitution and deletion.

Where an active compound has a number of substituents or functional groups, it is possible to probe which of these are essential for the activity by designing a series of analogues where a single substituent is removed. In **1** and **2** there are five substituents on the biaryl ether core which could

feasibly be ‘deleted’ *via* the synthesis of analogues (**175** – **179**, Figure 27) resulting in a number of natural product matched pairs for SAR analysis. For the remainder of the discussion substitutions are named according to the following nomenclature: substitution at position 1 as S-1, substitution at positions 2 and 2' as S-2A and S-2B, and substitutions at positions 4 and 4' as S-3A and S-3B (Figure 26).

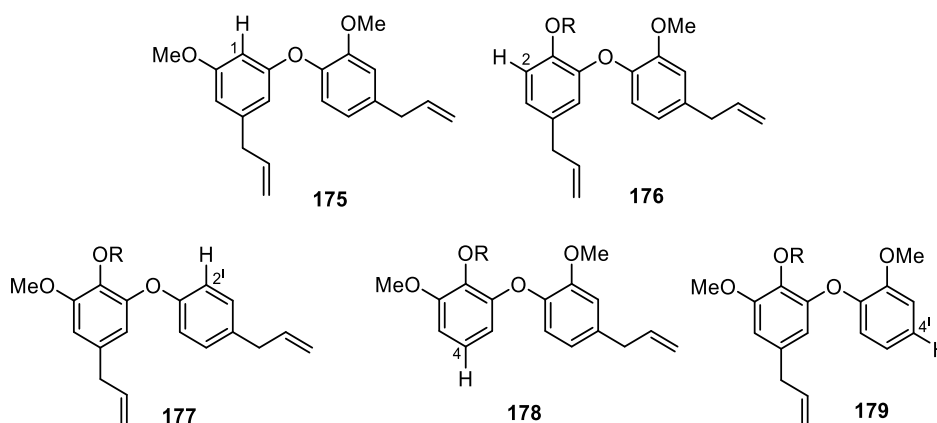


Figure 27. Systematic deletion of one substituent, resulting in a series of synthetic analogues.

As well as allowing the elucidation of the natural product structure-activity relationship, these analogues also enable some synthetic benefits. A deletion at either S-1 or S-2B position as in **175** and **177** will allow a reduction in the steric constraints in the coupling reaction. Deletions at S-1 will also see a notable reduction in the electron-richness of the halide coupling partner, also potentially facilitating the synthesis. As described in Chapter 2, the allylic side chains are troublesome in the synthesis and prone to isomerise, and so deletion of one of these – in particular the deletion at position S-3A (**178**) – is likely to be favourable for the synthesis. Unpublished work by Dr Diedre Johns also showed that removing some of these substituents, such as S-2 and S-3, may result in improved ADMET properties of the scaffolds, such as a reduction in logD and tPSA, and reduced MW.

3.1.2 Modification of Substituents

Obvious handles for modification of the natural products include the phenol and the allyl side chains. Work by Sousa *et al.* already showed that functionalisation of the S-1 vector led to notable improvements in selectivity and activity against both *T. cruzi* and *L. infantum*, with esters and benzyl

ethers giving promising results.^{94,95} The need for protection of this position in the synthesis of the natural products and any other phenolic analogues – such as the deletion study shown above – will give rise to a number of intermediates which may show promising activity, including with a PMB (135) or MOM (72) ether at this position. Given the particular success and interest in the acetate ester at this position (5), it would also be of interest to produce more analogues with this modification.

With a modular synthetic route in hand, single allyl chain modification is now possible whereas before this could only be done symmetrically. The fully saturated analogues in Sousa's work showed good activity^{94,95} and so synthesis of the singly saturated unsymmetrical analogues is a logical route to probe this effect further. It will also enable more straightforward synthesis as removing unsaturation at either S-3 position, but in particular S-3A (180), is likely to result in lower levels of isomerisation in the synthesis (Figure 28).

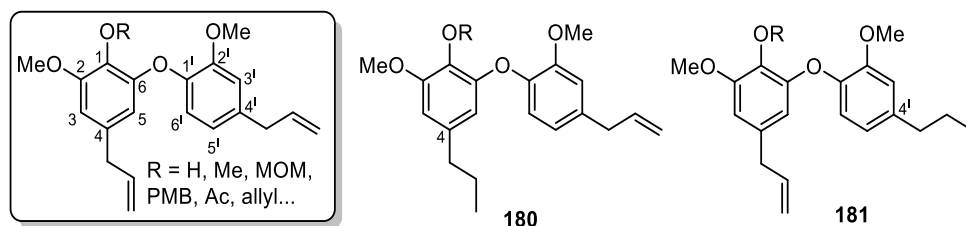


Figure 28. Analogues with new modifications at position 1, and asymmetrically saturated analogues.

3.1.3 Introducing Polarity to Improve Physicochemical properties

The natural products and semi-synthetic analogues synthesised and tested by Sousa and Amaral^{94,95} were found generally to have undesirable physicochemical properties, such as a high logP and low solubility. This can affect their toxicity profile and adsorption, metabolism, distribution and excretion (ADME). It also means they are liable to have off-target effects. Strategies to improve these properties suggested by Dr Diedre Johns' work include introducing heteroatoms on the substituents. The obvious way to achieve this is to replace the allylic side chain with an amine which could be achieved by installing this group before the coupling. 4' is the most attractive position for

this substitution (**184**) due to synthetic ease but it could feasibly be achieved on both sides. Likewise, the phenolic 1 position could be functionalised with an amine or an amide quite readily, as a semi-synthetic analogue directly from the natural product itself (**182** and **183**, Figure 29).

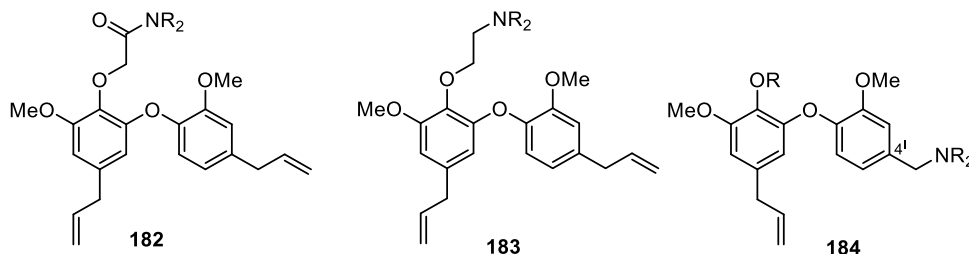
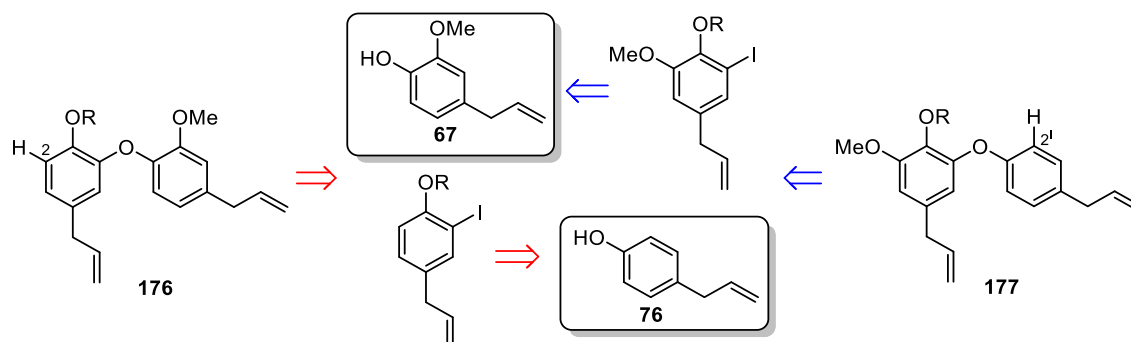


Figure 29. Adding polarity atoms to the natural product scaffold to improve physicochemical properties.

3.2 Analogue Synthesis

3.2.1 Deletion of Methoxy at S-2A and S-2B

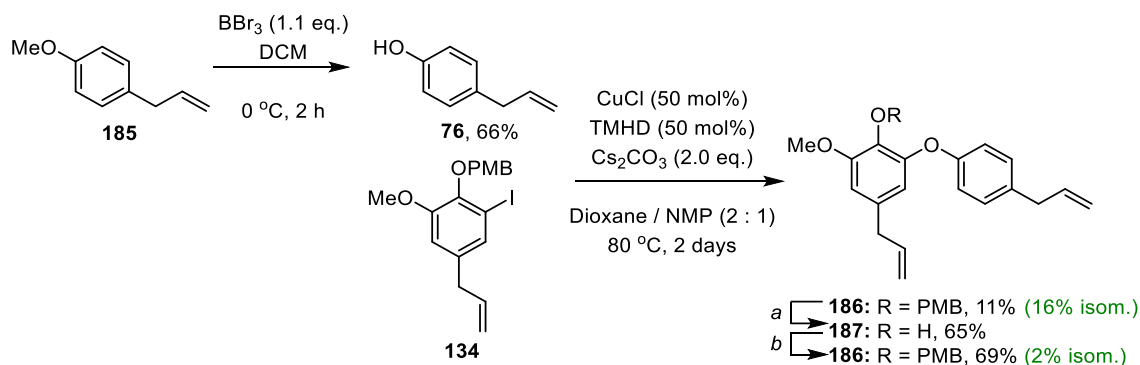
The analogues with the methoxy deletion at positions S-2A and S-2B require two common building blocks; eugenol (**67**) and 4-allylphenol (**76**, Scheme 40).



Scheme 40. Retrosynthesis for analogues missing the S-2 methoxy substituents.

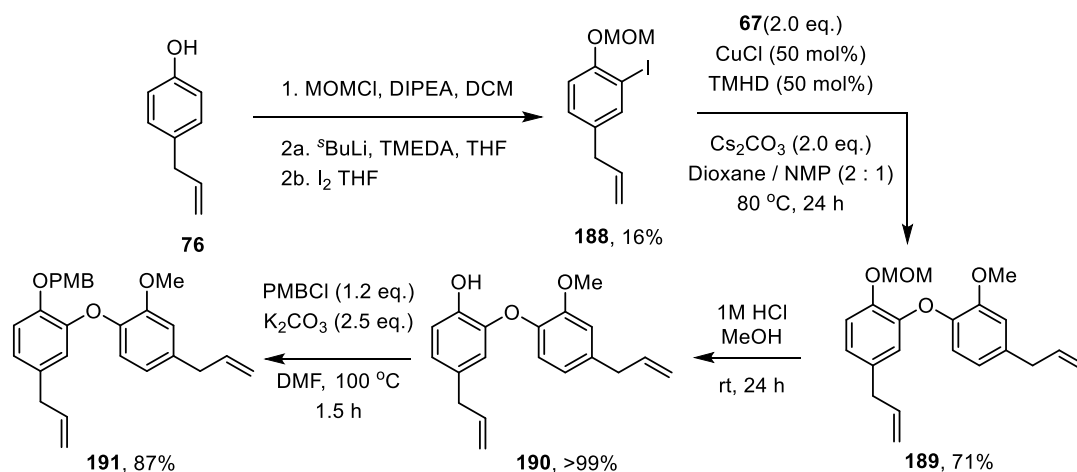
76 was obtained by demethylation of 4-allylanisole (**185**). **76** itself was surprisingly unstable and so subsequent reactions had to be carried out immediately. The coupling of **76** with previously described **134** was challenging, requiring long reaction times, and led to unusually high levels of isomerisation. The challenging nature of this particular coupling could be ascribed to the phenol – usually the electron rich partner – having ‘lost’ one of its electron-donating substituents and so

adding to the electronic challenge of the coupling. However, deprotection of the PMB group proceeded cleanly and allowed the double bond regioisomers to be reacted away through hydration as previously described. The PMB group could then be reinstated to provide the clean PMB ether analogue, **186**, for biological testing (Scheme 41).



Scheme 41. Synthesis of analogues **186** and **187**. ^a2M HCl, EtOH, 80 $^{\circ}\text{C}$, 2 h. ^bPMBCl (1.2 eq.), K_2CO_3 (2.5 eq.), DMF, 100 $^{\circ}\text{C}$, 2 h.

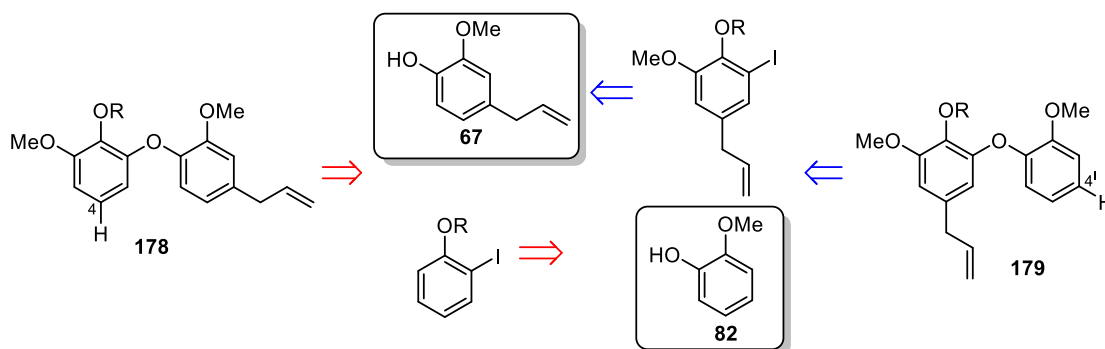
For the analogue with the methoxy deletion at the S-2A position, **76** was protected with MOM and then iodinated to give **188**. In this case, MOM was shown to be an effective protecting group in the coupling and this gave the highest yield seen for the biaryl ether formation so far (71% of **189**). This can be rationalised first by a steric argument – with the 2' methoxy group missing, the MOM can ‘swing’ out of the way of the catalytic copper centre making it less labile, and making the coupling reaction less sterically constrained. There is also an electronic argument; with an electron donating group missing from the halide the electronics of the reaction are now more favoured. The biaryl ether was deprotected under acidic conditions to give the phenol **190**, and protected with PMB to give an additional ether analogue **191** for exploring the 1' vector (Scheme 42).



Scheme 42. Synthesis of analogues 189 – 191.

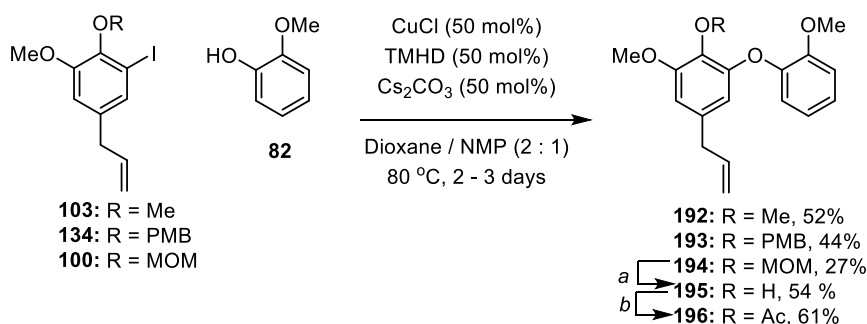
3.2.2 Deletion of Allyl at S-3A and S-3B

To remove the allyl chains at 4 and 4' to give **178** and **179** requires disconnection to guaiacol (**82**) and eugenol (**67**) as the key building blocks (Scheme 43).



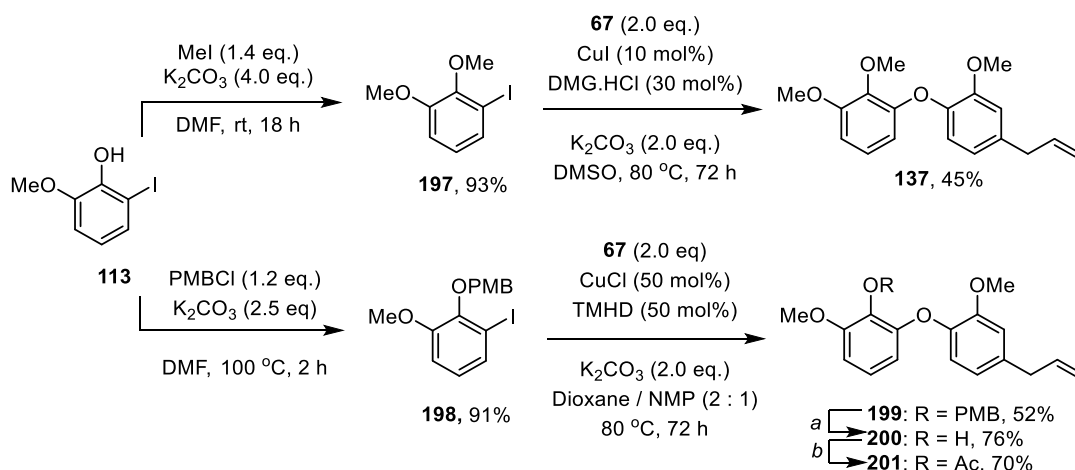
Scheme 43. Retrosynthesis for analogues missing the S-3 allyl substituents.

For the S-3B deletion, this requires the direct coupling of guaiacol with the halide (**100**, **103**, **134**) described previously. The methyl ether analogue was prepared from coupling of the methylated iodide **103**, and gave **192** in 52% yield. The PMB group gave **193** in 44% and the MOM protected halide **100** gave **194** in 27% yield. Deprotection afforded the phenol analogue **195** which could be functionalised to the acetate analogue, **196** (Scheme 44).



Scheme 44. Synthesis of 4' allyl group deleted analogues **192** - **196**. ^a1 M HCl, MeOH, rt, 18 h. ^bAc₂O, pyridine, 100 °C, 2 h.

For the analogues with the left-hand side allyl missing (S-3A), the halide coupling partner was synthesised from guaiacol as described in Chapter 2 for the *para*-Claisen substrate. The phenol **113** was converted to the methyl ether **197**, and the subsequent coupling was carried out by Dr Marius Haugland using the optimised DMG·HCl coupling conditions to give **137**.¹⁰⁷ PMB protection of **113** enabled access to coupled PMB analogue **199** in 52% yield, and on deprotection, the phenol and acetate analogues **200** and **201** (Scheme 45). In this series the allyl-protected analogue (**69**) is also available as synthesised in Chapter 2.

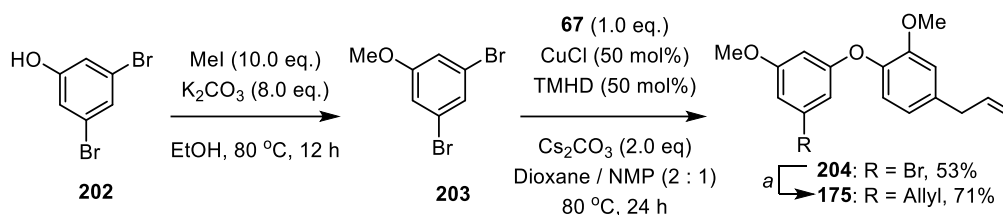


Scheme 45. Synthesis of S-3A allyl group deleted analogues **137**, **199** - **201**. ^a2 M HCl, EtOH, 80 °C, 2 h. ^bAc₂O, pyridine, 100 °C, 2 h.

3.2.3 Deletion of Phenol at S-1

The synthesis of the S-1 deleted analogue was carried out by Dr Pauline Pieper (Scheme 46), through methylation of 3,5-dibromophenol (**202**), followed by coupling of the resulting bromide **203** with

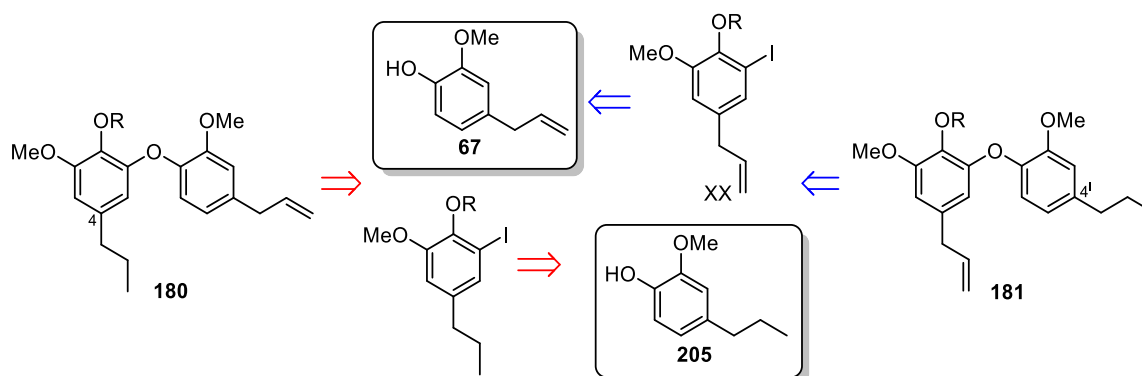
eugenol.¹¹⁸ This coupling to give **204** worked reasonably well despite being a bromide rather than an iodide, which can be explained in terms of the favourable steric effect of removing the *ortho* phenol, and also the presence of the second halide as an inductive electron withdrawing group. The allyl group was installed post-coupling through a palladium-catalysed Kumada coupling to form **175**, which interestingly validates the potential use of a bromide at this position for post-Ullmann side chain installation, provided the S-1 site is not substituted.



Scheme 46. Synthesis of S-1 deleted analogue **175** by Dr Pauline Pieper.¹¹⁸ ^aPd₂dba₂ (0.5 mol%), BINAP (1 mol%), allylMgBr (2.5 eq.). 80 °C, 6 h.

3.2.4 Saturation of a Single Side Chain at S-3A or S-3B

Saturation of the single saturated side chain requires eugenol and **205**, which can be made in one step through hydrogenation of eugenol (Scheme 47).

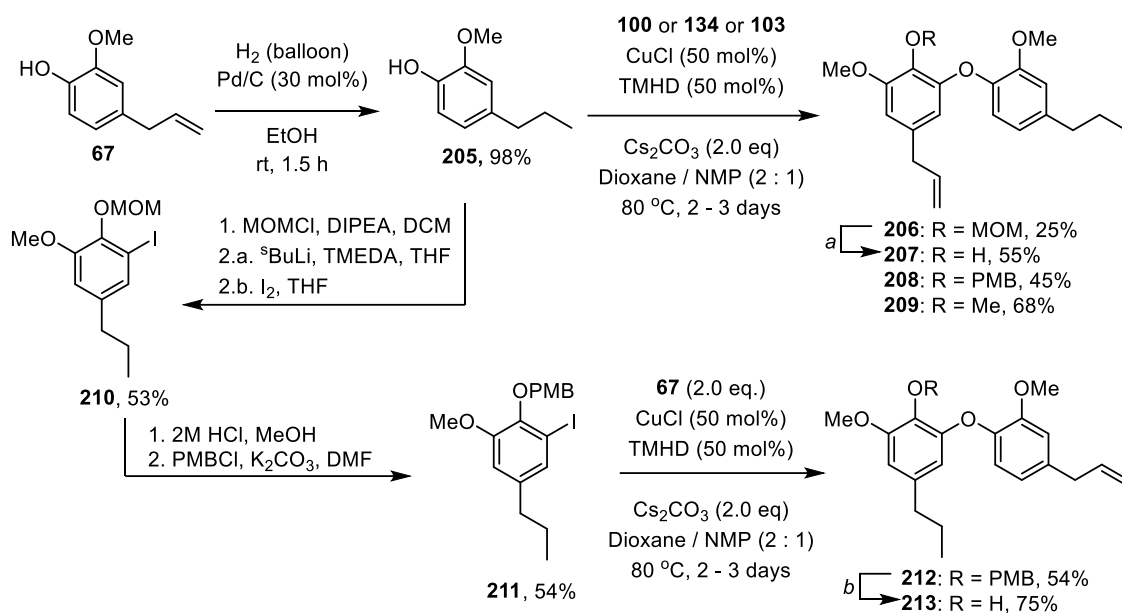


Scheme 47. Retrosynthesis for analogues with unsymmetrical saturation of the allyl side chains.

Coupling of **205** with the MOM protected iodide **100** gave 25% yield of the S-3B saturated analogue **206**, which could be deprotected to give the phenol **207**. Using PMB as the protecting group in the coupling gave **208** in 45% yield, and the methyl ether gave 68% of **209**. To achieve saturation at S-3B, **205** was protected as the MOM ether and iodinated to give **210**, and the MOM group replaced

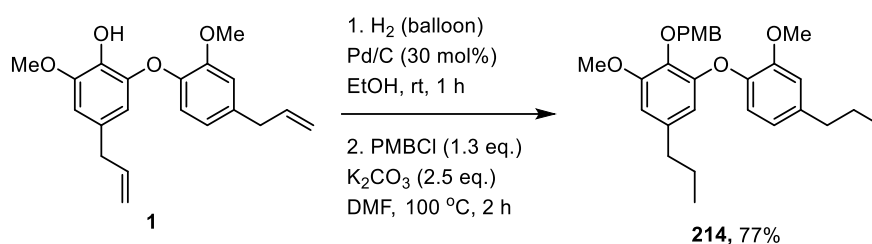
with a PMB group for the coupling (**211**), which gave 54% of the 4' saturated PMB analogue **212**.

Deprotection gave the corresponding phenol **213** (Scheme 48).



Scheme 48. Synthesis of analogues with a single side chain saturated (**206 – 109**, and **212 – 213**). ^a1 M HCl (aq), MeOH, rt, 18 h, ^b2M HCl (aq), EtOH, 80 °C, 2 h.

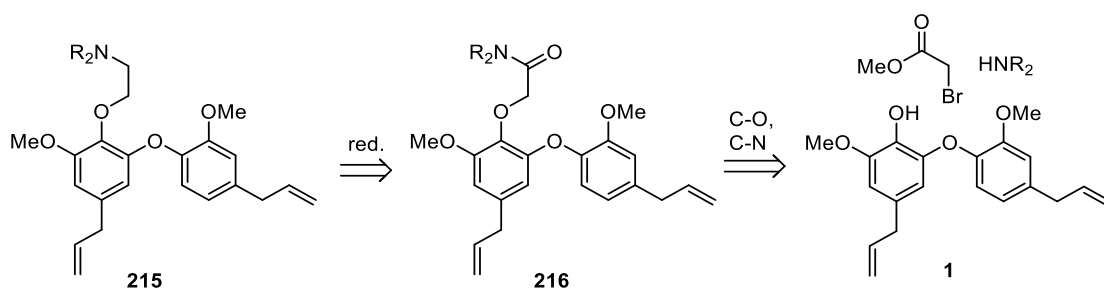
Sousa *et al.*⁹⁴ had not considered PMB ethers in their semi synthesis work, so to complete the series of saturated analogues for investigation, the fully saturated PMB ether analogue **214** was prepared through hydrogenation of **1**, then protection with a PMB group in good yield over two steps (Scheme 49).



Scheme 49. Synthesis of fully saturated PMB analogue **214**.

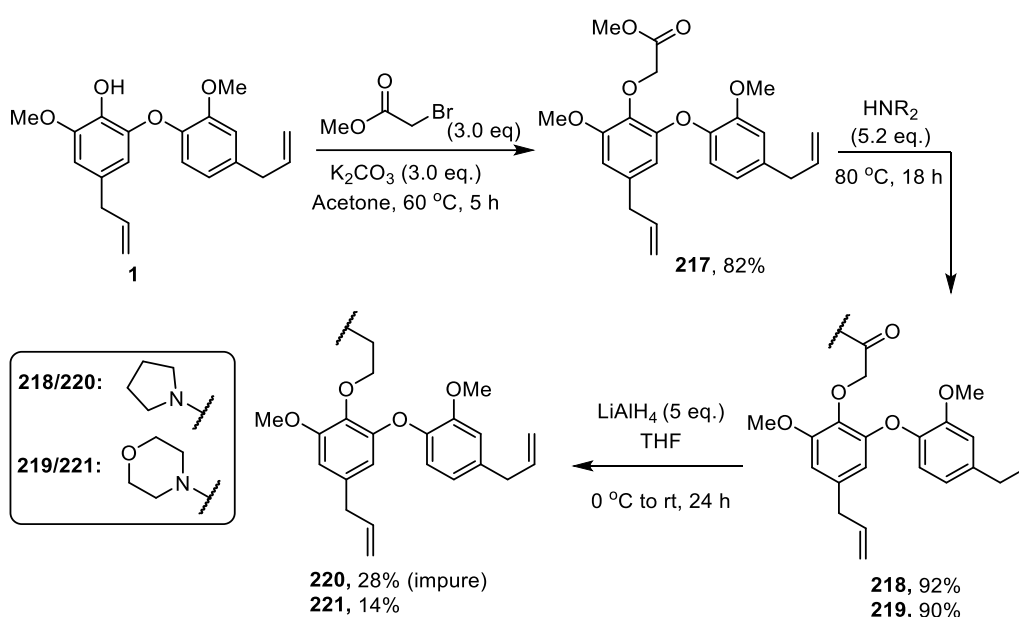
3.2.5 Nitrogen-Containing Sidechains at the S-1 Position

The proposed route to introduce amide and amine functionality at the S-1 position (**215** and **216**) is to use a two-carbon linker, readily installed using 2-bromomethylacetate *via* an $\text{S}_{\text{N}}2$ reaction with the **1**, followed by amide bond formation and then amide reduction (Scheme 50).



Scheme 50. Retrosynthesis for amide and amine containing analogues.

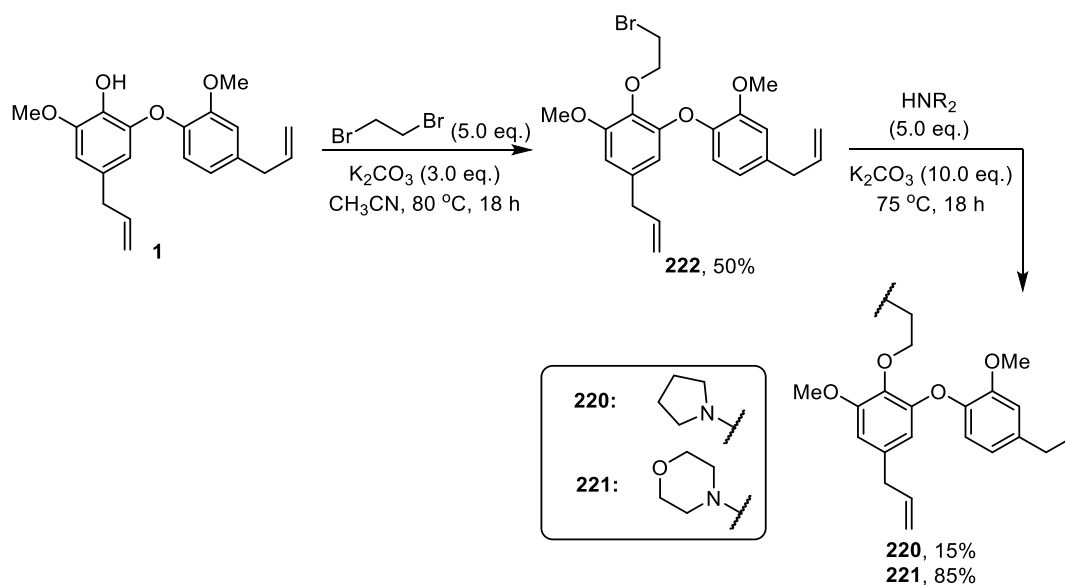
Morpholine and pyrrolidine were considered as the amine source as both are common nitrogen-containing heterocycles in drug discovery and have the potential to bring about the improvement in physicochemical properties required. The S_N2 reaction to install the two-carbon linker (**217**) and subsequent amide bond formation proceeded in good yield with both amine substrates **218** and **219**. However, the subsequent amide reduction to **220** and **221** was troublesome and gave very poor yield of the amine. In the case of pyrrolidine, an inseparable mixture of products was observed in very poor overall yield (Scheme 51).



Scheme 51. Synthesis of **218** – **221** via amide formation and reduction.

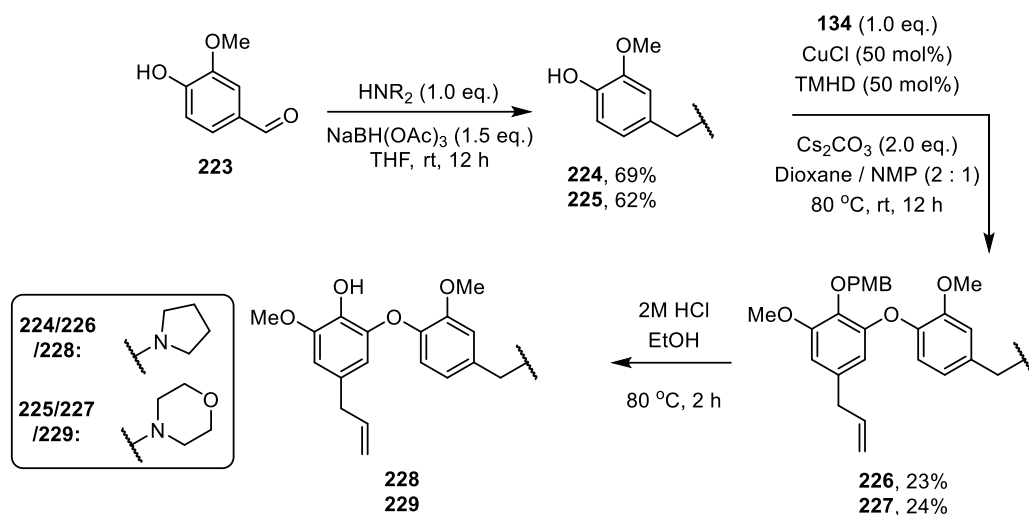
To overcome this challenge with the amide reduction step, an alternative strategy was employed for the preparation of the amines, using a double S_N2 reaction with 1,2-dibromoethane. The first S_N2 with the phenol nucleophile proceeded in moderate yield to give **222**. The second S_N2 reaction gave

a good yield again in the case of morpholine (**221**), but for pyrrolidine (**220**) the reaction rapidly turned black, and due to the high polarity of the product, required three columns to separate it from the baseline impurities. It is possible that the more nucleophilic amine in this reaction could be condensing with the acetone solvent, resulting in imine/enamine and aldol by-products. However sufficient quantities of amine required for testing could be obtained using this method (Scheme 52).



Scheme 52. Alternative synthesis of amines **220** and **221**, via a double S_N2 .

Four analogues with nitrogen containing heterocycles at the S-3B position were also synthesised by Dr Pauline Pieper and were submitted for testing against *T. cruzi* and *L. infantum* as part of this project (Scheme 53). The synthesis of these was achieved through reductive amination of vanillin (**223**) to give **224** and **225**, and then subsequent coupling to the corresponding PMB protected iodide **134**, using the optimised conditions described in Chapter 2, to give **226** and **227**. This was a promising result as it shows the coupling conditions can tolerate the presence of a free amine on the coupling partners. Deprotection of these compounds gave the free phenol analogues **228** and **229**,



Scheme 53. Synthesis of amines 226 – 229 by Dr Pauline Pieper.¹¹⁸

3.3 Chapter Summary and Future Work

The synthetic chemistry developed in Chapter two has proven to be applicable to a range of different substrates, with varying levels of substitution, oxidation, and functionality, including free amines. This has enabled the synthesis of 29 new analogues, which will enable us to probe the effects of each substituent on anti-parasitic activity as well as develop the physicochemical properties and improved safety profile required for potential therapeutics. The synthesis of these compounds has also shown how the removal of substituents can lead to a more straightforward synthesis, which can be useful for rapid and efficient generation of new analogues. For example, the coupling to generate compounds **190** and **191**, with a methoxy deletion at position S-2A, was a very efficient coupling and did not require a protecting group switch from MOM to PMB. If these analogues are found to be active in the assays this could be a useful starting point for further optimisation.

The majority of the analogues synthesised in this chapter aim to explore the importance of the structural features on the activity. It also describes to early stages of exploring the effect of adding polarity on both the synthesis and activity. Future work would aim to expand on this approach. There are a number of possible nitrogen-containing analogues which have not been described here and

could be synthesised using the current methodology or other existing methods. Some examples of potential nitrogen containing analogues not yet explored are shown in Figure 30.

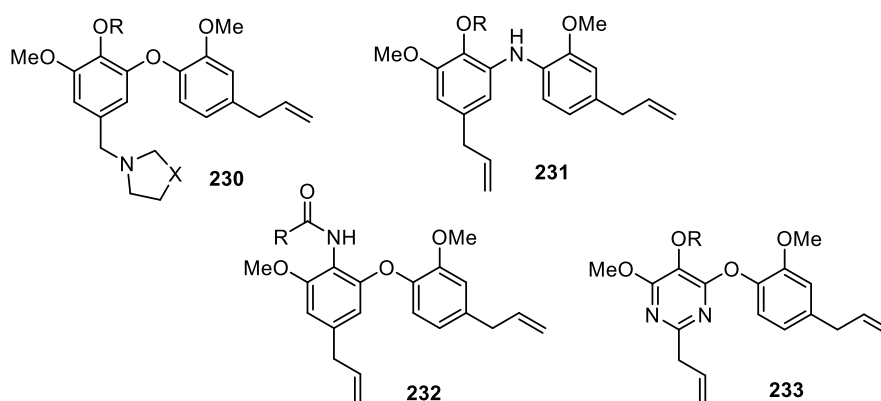


Figure 30. Potential analogues for future work, aimed at reducing logP and increasing solubility.

4. Anti-Parasitic Activity of Synthetic Analogues

The synthetic analogues described in the previous two chapters were sent to Prof. André Tempone at the Instituto Adolfo Lutz in São Paulo, Brazil, for biological evaluation. The IC₅₀ values were determined against the intracellular amastigote forms of *L. infantum* and the extracellular trypomastigotes and intracellular amastigote forms of *T. cruzi*. Mammalian cytotoxicity was also determined using NCTC (L929 cells, ATCC®) fibroblasts, allowing for the evaluation of CC₅₀ and therefore the Selectivity Index (SI). This chapter describes the biological assays run by the author of this thesis and discusses the structure-activity relationship of the natural products resulting from these data.

The modifications and their effects on activity were considered according to position of substitution; either S-1, S-2A and S-2B, or S-3A and S-3B.

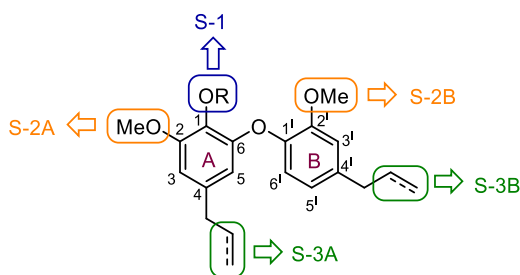


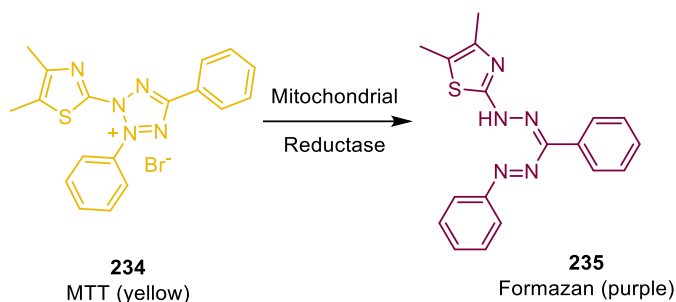
Figure 31. Nomenclature for describing substitution and deletion.

4.1 Mammalian Cytotoxicity

To measure the IC₅₀ (50% Inhibitory Concentration) of the compounds against the intracellular amastigote forms of both parasites, mammalian macrophages are infected with amastigotes and then treated with the compound in a phenotypic assay. As such, it is important to determine the toxicity of the compounds towards mammalian cells, so that if parasite inhibition is observed, it can be attributed to a specific effect by the compound and not simply blanket toxicity, or the host cell

becoming compromised. Equally important, as with all anti-infectives, is that toxicity is minimised to ensure pathogen inhibition with minimal side effects to the host.

For this assay, a 96 well plate is used and each compound is assigned two columns in the plate ($n = 2$). NCTC fibroblasts (mouse C3H/An areolar and adipose tissue) are distributed at a density of 6×10^4 per well. In an initial screen, the compounds to be tested are then applied to each well in a serial dilution descending the column, starting at 200 μM . After incubation for 48 hours the wells are treated with MTT. In living cells, MTT (**234**, yellow) is converted to formazan (**235**, purple/brown) by the enzyme mitochondrial reductase (Scheme 54). Compounds found to show toxicity below 200 μM are then subjected to a second assay where the CC_{50} (50% Cytotoxic Concentration) is determined by testing over a narrower range of concentrations based on the initial screen. The absorption is measured by a spectrophotometer which is converted to CC_{50} .



Scheme 54. Conversion of MTT to formazan in living cells, and corresponding colour change allowing CC_{50} to be determined.

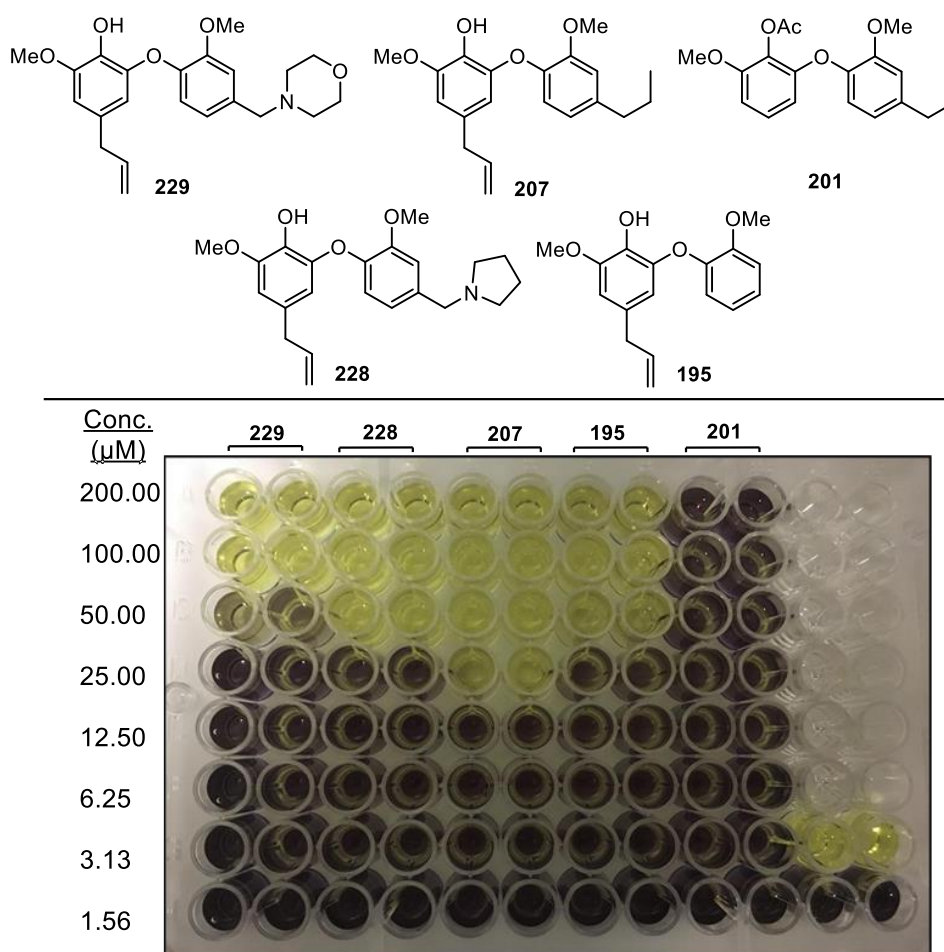
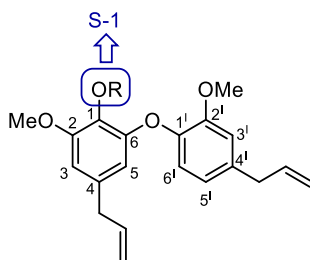


Figure 32. Cytotoxicity screen of five compounds, with concentration descending down the column, showing change in colour from yellow to brown in the case of living cells. Bottom right: negative control (no compound, living cells), top right; positive control (no cells).

4.1.1 S-1 Substitution

Table 10 shows the cytotoxicity data for the natural product analogues with a substitution at S-1. All other substituents are the same as the natural products **1** and **2**. For completeness, the data for these natural products are also shown as reported in the literature.^{92,93} Analogues **5** and **236** were synthesised in this thesis and their anti-*T. cruzi* activity is also reported in the literature.⁹⁴

Table 10. Cytotoxicity of natural products **1** and **2** and analogues substituted at the S-1 position.



Entry	Compound	S-1	CC ₅₀ / μM ($\pm$ SE)
1^a	1	OH	>200
2^a	2	OMe	>200
3	72	OMOM	>200
4	135	OPMB	>200
5^b	5	OAc	64.4 $\pm$ 2.1
6^b	236	OAllyl	>200
7	175	H	>200
8	218		52.9 $\pm$ 2.6
9	219		111.5 $\pm$ 4.1
10	220		24.9 $\pm$ 1.3
11	221		63.7 $\pm$ 0.1

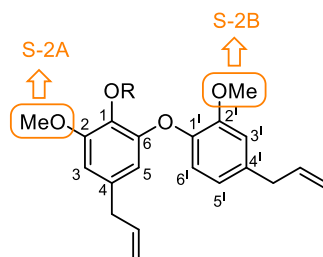
n = 4; CC₅₀: 50% Cytotoxic Concentration. ^aPublished in Ref. 92. ^bPublished in Ref 94.

Pleasingly, many of the compounds show no toxicity at all below 200 μM , and none show toxicity below 10 μM . Having an ether at this position such as allyl (**236**), PMB (**135**), or MOM (**72**) confers no toxicity, and the acetate ester **5** only moderate toxicity. Introducing amides or amines to this position does result in some toxicity (Entries 8 – 11).

4.1.2 S-2 Substitution

Table 11 shows the cytotoxicity data of all analogues with a substitution at S-2A or S-2B, including those with substitution variations at S-1 as well.

Table 11. Cytotoxicity of analogues substituted at the S-2 positions.



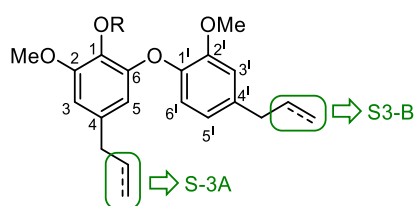
Entry	Compound	S-1	S-2A	S-2B	CC ₅₀ / μM ($\pm$ SE)
1	190	OH	H	OMe	128.6 $\pm$ 2.6
2	191	OPMB	H	OMe	>200
3	187	OH	OMe	H	123.4 $\pm$ 4.7
4	186	OPMB	OMe	H	>200

n = 4; CC₅₀: 50% Cytotoxic Concentration.

This table indicates that the removal of a methoxy group does not itself confer toxicity, however, when the phenol is not protected some toxicity is observed. This effect is the same regardless of which methoxy group is removed. This shows that this methoxy group has little effect on mammalian toxicity and that the phenol at S-1 is the more important substituent.

4.1.3 S-3 Substitution

Table 12 shows the cytotoxicity data of all analogues with substitution at either S-3A and S-3B. Data for **237** and **238** are known.⁹⁴

Table 12. Cytotoxicity of analogues substituted at the S-3 position.

Entry	Compound	S-1	S-3A	S-3B	CC ₅₀ / μM ($\pm$ SE)
1	200	OH	H	Allyl	>200
2	137	OMe	H	Allyl	>200
3	69	OAllyl	H	Allyl	>200
4	199	OPMB	H	Allyl	>200
5	201	OAc	H	Allyl	>200
6	195	OH	Allyl	H	31.6 $\pm$ 5.6
7	192	OMe	Allyl	H	>200
8	193	OPMB	Allyl	H	>200
9	196	OAc	Allyl	H	>200
10	213	OH	<i>n</i> -Propyl	Allyl	14.2 $\pm$ 0.1
11	212	OPMB	<i>n</i> -Propyl	Allyl	>200
12	207	OH	Allyl	<i>n</i> -Propyl	42.0 $\pm$ 1.9
13	209	OMe	Allyl	<i>n</i> -Propyl	>200
14	208	OPMB	Allyl	<i>n</i> -Propyl	>200
15 ^a	237	OH	<i>n</i> -Propyl	<i>n</i> -Propyl	57.7 $\pm$ 0.6
16 ^a	238	OMe	<i>n</i> -Propyl	<i>n</i> -Propyl	>200
17	214	OPMB	<i>n</i> -Propyl	<i>n</i> -Propyl	>200
18	228	OH	Allyl		43.3 $\pm$ 2.7
19	226	OPMB	Allyl		6.2 $\pm$ 0.6
20	229	OH	Allyl		51.4 $\pm$ 2.4
21	227	OPMB	Allyl		>200

n = 4; CC₅₀: 50% Cytotoxic Concentration. ^aPublished in Ref 94.

4.1.4 Discussion

In Tables 10 and 12 there is a consistent trend that free phenols at the S-1 position demonstrate measurable mammalian toxicity below 200 μ M. Substituting either of the methoxy groups at S-2 (Table 11) or the allyl groups at S-3 (Table 12) does not confer additional toxicity, as long as the phenol at S-1 is protected as an ether. In the case of the esters, some toxicity is observed in some cases and we hypothesise that this may be due to the ester being hydrolysed to the phenol in the cell. The non-toxicity of natural product **1** and compound **200** appears to be anomalous in these data, as these are the only free phenols that do not show toxicity below 200 μ M. Interestingly, compounds containing amides and amines were also found to demonstrate some mammalian toxicity, with the exception of **227**, the morpholine S-3 substituted analogue with PMB protection at S-1. In all instances the morpholine analogues showed lower toxicity than the corresponding pyrrolidine analogues.

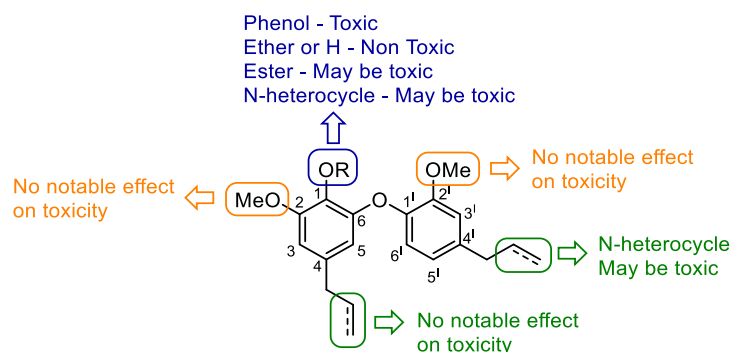


Figure 33. Summary of substituents and effect on mammalian toxicity.

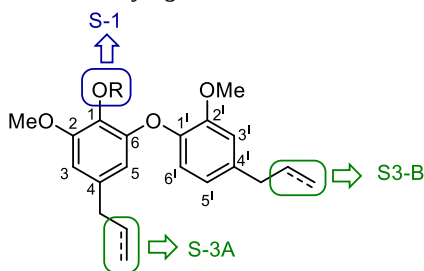
Demonstrating mammalian toxicity raises a red flag for compounds but does not rule them out as potential hits, provided they demonstrate a significantly lower IC_{50} than their CC_{50} in the intracellular amastigote assays, such that the selectivity index is greater than 10.

4.2 *Leishmania infantum* Intracellular Amastigote Assay

4.2.1 Assay description and results

Whereas for *T. cruzi*, both the trypomastigote and amastigote form are important for therapeutic use, in *Leishmania* spp. infections the amastigote form is the most clinically relevant. The assay involves removing peritoneal macrophages from BALB/c mice and infecting them with *L. infantum* amastigotes, maintained in and harvested from the spleen of infected golden hamsters, and purified by differential centrifugation. A 16 well plate slide is treated with 1×10^5 macrophages which are infected with amastigotes in a 10 : 1 parasite / macrophage ratio. >90% infection must be achieved for the assay to be valid. The infected cells are then treated with the compound at varying concentrations and visualised through a light microscope. The total number of cells, total number of infected cells, and total number of intracellular amastigotes are counted at the different concentrations to calculate IC₅₀. Miltefosine is used as the standard, and untreated macrophages as the negative control.

Because of the time-consuming nature of the assay and the animal sacrifice required, all analogues were initially screened at 10 μ M and 30 μ M only. Those with no significant parasite inhibition at 30 μ M could be discounted as inactive, having only used two wells of macrophages and amastigotes per compound, instead of the 16 wells required for the IC₅₀ calculation. This initial screen resulted in seven hits which were carried forward to the IC₅₀ calculation. The seven compounds with their IC₅₀ values, cytotoxicity and SI are shown in Table 13. The natural products **1** and **2** are also listed for comparison.

Table 13. Analogues with activity against *L. infantum* intracellular amastigotes.

Entry	Compound	S-1	S-3-A	S-3B	IC ₅₀ μM (± SE)	CC ₅₀ μM (± SE)	SI
1 ^a	1	OH	Allyl	Allyl	26.7 ± 4.5	>293.8	>11.0
2 ^a	2	OMe	Allyl	Allyl	17.8 ± 1.4	111.2 ± 5.6	6.23
3	218		Allyl	Allyl	20.3 ± 3.0	52.9 ± 7.6	2.6
4	220		Allyl	Allyl	4.1 ± 0.6	24.9 ± 1.3	6.0
5	221		Allyl	Allyl	9.6 ± 1.8	63.7 ± 0.1	6.6
6	69	OAllyl	H	Allyl	23.7 ± 1.2	>200	>8.4
7	212	OPMB	<i>n</i> -Propyl	Allyl	14.3 ± 1.4	>200	>14
8	196	OAc	Allyl	H	29.1 ± 1.5	>200	>6.9
9	193	OPMB	Allyl	H	37.1 ± 2.8	>200	>5.4
10	227	OPMB	Allyl		9.7 ± 1.0	>200	>20.6
11	Miltefosine	-	-	-	5.1 ± 0.3	119.7 ± 2.1	18.4

n = 4; IC₅₀: 50% Inhibitory Concentration; CC₅₀: 50% Cytotoxic Concentration; SI: Selectivity Index, given by the ratio between CC₅₀ in NCTC cells and IC₅₀ in intracellular amastigote assay. ^aPublished in Ref. 92 against *L. donovani*.

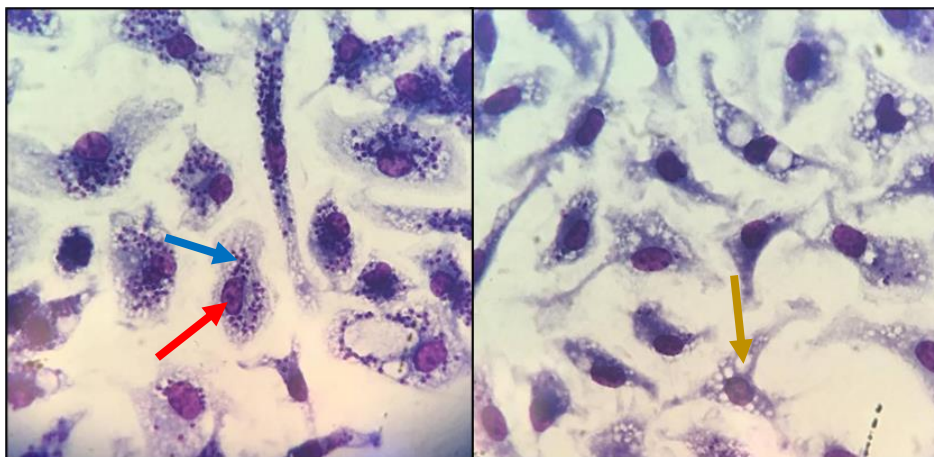


Figure 34. Antileishmanial activity of compound **196**. Giemsa-stained cells were observed in a light microscope (magnification 1000 $\times$). Left; Negative control - murine peritoneal macrophages infected with *L. infantum* amastigotes. Blue arrow = *L. infantum* amastigotes, red arrow = macrophage nucleus. Right; After incubation with 40 μ M compound **196** for 96 h, demonstrating almost complete elimination of parasite infection whilst maintaining macrophage integrity at this concentration. Yellow arrow = empty parasitophorous vacuole.

4.2.2 Discussion

The two most promising compounds in this assay are **212** and **227**. Both of these compounds show moderate activity against *L. infantum* with low toxicity and therefore high selectivity. At the higher concentrations tested, these compounds also demonstrate complete elimination of the parasite from the macrophages while maintaining integrity of the mammalian cell. Compounds containing nitrogen heterocycles at S-1 (**218**, **220**, and **221**) were found to demonstrate low μ M activity but these compounds also show high toxicity and therefore low selectivity for the parasite over the host. Interestingly, the amines at this position (**220** and **221**) showed higher selectivity than the amide (**218**) that was also active, with the morpholine amine being the most promising of this group. In all cases where an S-2 deletion was made to either side, no activity was observed, suggesting that it is important to have a substituent at these positions for activity. A deletion or substitution to an H or *n*-propyl at S-3A could be tolerated and some analogues with this modification showed good activity (**69** and **212**). An S-3B deletion was also tolerated, again with the presence of an ether or ester at S-1 (**196** and **193**), and replacing S3-B with a morpholine resulted in an excellent compound with low micromolar activity and high selectivity (**227**). The compounds with *n*-propyl at S-3B were found to be inactive.

Compound **227** meets the DNDi criteria for a hit ($IC_{50} < 10 \mu M$, $SI > 10$) and compound **212** comes very close. Both compounds contain a PMB ether at S-1 which suggests that functionalising this vector reduces toxicity and increases potency. The morpholine ring on the side chain gave excellent potency and selectivity and likely has improved PKPD properties (see below for further discussion of this).

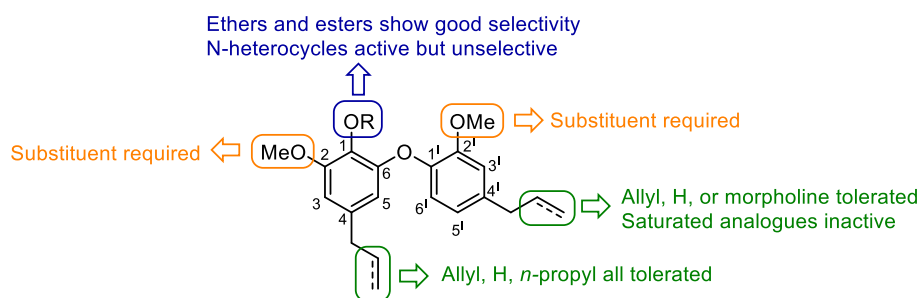


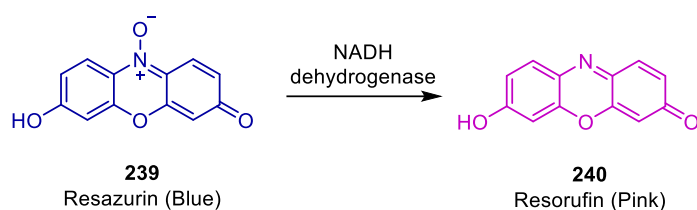
Figure 35. Summary of substituents and effect on *L. infantum* amastigote activity.

4.3 *Trypanosoma cruzi* Assays

4.3.1 Trypomastigote Assay

For *T. cruzi*, the blood trypomastigote form of the parasite is clinically relevant, in particular in the acute stage of the disease where blood parasite levels are high, and therefore both parasite forms are considered when evaluating the pharmaceutical relevance of potential anti-parasitics.

The trypomastigote assay, like the cytotoxicity assay, is a colorimetric assay carried out in a 96 well plate, with two rows allocated to each compound. Trypomastigotes are used at a density of 1×10^6 per well. Again, an initial screen is carried out on each compound in a twofold serial dilution of eight concentrations, starting at $150 \mu M$. After incubating with compound, the cells are treated with resazurin (**239**), a blue dye which is converted to resorufin (**240**, pink) by NADH dehydrogenase in living parasites. Compounds found to show significant activity below $150 \mu M$ were submitted to a second assay testing over a narrower range of concentrations to calculate IC_{50} .



Scheme 55. Conversion of resazurin to resorufin in living trypanomastigotes, and corresponding colour change allowing IC_{50} to be determined.

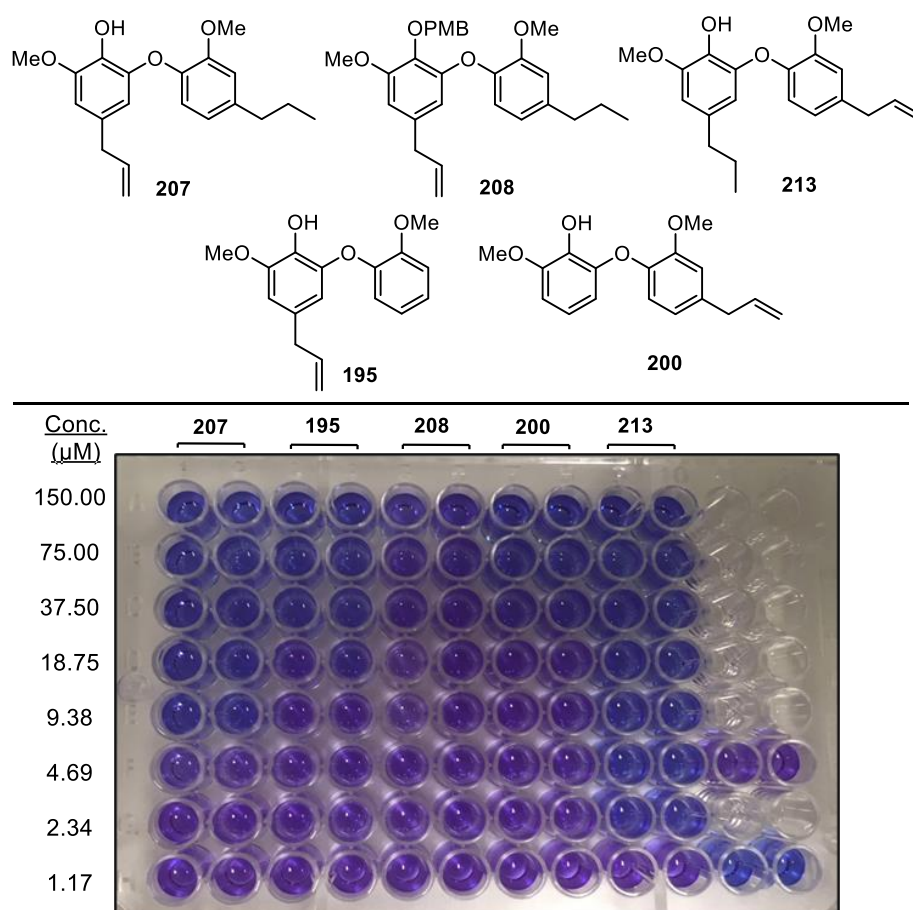


Figure 36. Trypanomastigote screen of 5 compounds, with concentration descending down the column, showing change in colour from blue for dead parasites and purple in living parasites. Top right: negative control (no compound), bottom right; positive control (no cells).

4.3.2 Intracellular Amastigote Assay

Although the trypanomastigote activity is important in Chagas disease, the intracellular amastigote assay is the most clinically relevant and the basis on which selectivity is calculated and potential hits are identified. As with *L. infantum*, this assay is also the most challenging and time consuming.

It is conducted in a similar manner to the *L. infantum* amastigote assay; murine peritoneal macrophages are seeded at 1×10^6 cells per well in a 16 well plate slide and infected, this time with the trypomastigote form of the parasite (10 : 1 parasite / macrophage ratio) which differentiates to the amastigote form on infection. >90% infection should be established, and the infected cells are then incubated with the compounds for 48 h at a range of concentrations. The slides are then visualised by light microscopy and the infection index calculated by counting the total number of macrophages, the number of infected macrophages, and the number of amastigotes at each concentration. Benznidazole is used as the standard drug and untreated infected macrophages as a negative control.

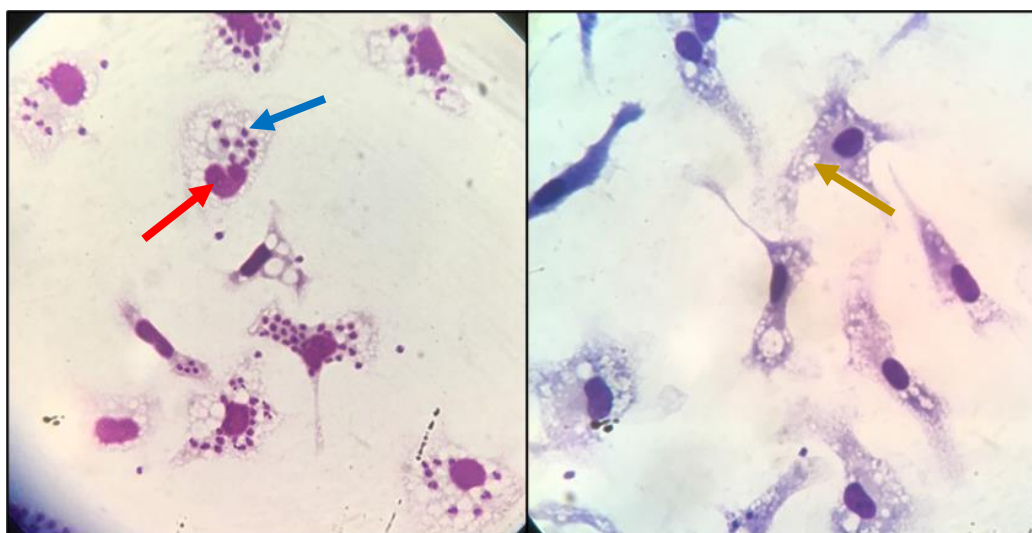
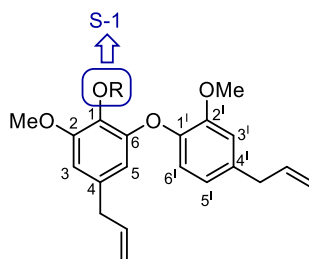


Figure 37. Antitrypanosomal activity of compound **137**. Giemsa-stained cells were observed in a light microscope (magnification 1000 $\times$). Left; Negative control - murine peritoneal macrophages infected with *T. cruzi* amastigotes. Blue arrow = *T. cruzi* amastigote. Red arrow = macrophage nucleus. Right; After incubation with 40 μ M compound **137** for 48 h, demonstrating almost complete elimination of parasite infection whilst maintaining macrophage integrity at this concentration. Yellow arrow = empty parasitophorous vacuole.

4.3.3 Assay results

The results for both trypomastigote and amastigote assays are shown in Tables 14 to 16. As with the cytotoxicity assay, the tables are grouped according to substitutions made on the biaryl ether scaffold (S1, S2-A and S2-B, and S3-A and S3-B). The selectivity index is calculated based on the intracellular amastigote IC₅₀ and the cytotoxicity data. The natural products **1** and **2** are included for comparison.⁹³ Data for **5** and **236 – 238** is known.⁹⁴

Table 14. T. cruzi assay data for compounds with a S-1 modification.

Entry	Compound	S-1	IC ₅₀ / μ M ($\pm$ SE)		CC ₅₀ / μ M ($\pm$ SE)	SI
			Tryp.	Am.		
1^a	1	H	38.6 $\pm$ 4.2	86.5 $\pm$ 8.1	>200	>2.3
2^a	2	OMe	NA	NA	>200	ND
3	72	OMOM	6.5 $\pm$ 2.5	24.4 $\pm$ 5.2	>200	>8.2
4	135	OPMB	NA	4.0 $\pm$ 0.7	>200	>50
5^b	5	OAc	64.2 $\pm$ 4.1	8.0 $\pm$ 2.9	64.4 $\pm$ 2.1	8.1
6^b	236	OAllyl	NA	NA	>200	ND
7	175	H	NA	10.9 $\pm$ 3.3	>200	>18.3
8	218		6.7 $\pm$ 2.9	4.3 $\pm$ 0.5	52.9 $\pm$ 7.6	12.3
9	219		18.7 $\pm$ 0.04	6.4 $\pm$ 1.5	111.5 $\pm$ 4.1	17.4
10	220		10.7 $\pm$ 1.7	4.3 $\pm$ 1.4	24.9 $\pm$ 1.3	5.8
11	221		7.8 $\pm$ 1.8	5.8 $\pm$ 2.0	63.7 $\pm$ 0.1	11.0
12	Benznidazole	-	17.7 $\pm$ 1.0	5.0 $\pm$ 1.3	190.6 $\pm$ 6.7	38.1

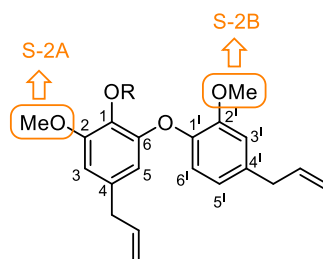
n = 4; IC₅₀: 50% Inhibitory Concentration; CC₅₀: 50% Cytotoxic Concentration; SI: Selectivity Index, given by the ratio between CC₅₀ in NCTC cells and IC₅₀ in intracellular amastigote assay. ^aPublished in Ref. 93.

^bPublished in Ref 94.

With one exception (compound **236**) all of the compounds with an S-1 modification showed improved activity against the intracellular amastigotes over the natural products **1** and **2**, which confirms that functionalising this vector is beneficial for activity. In particular the PMB protected natural product, **135**, showed low micromolar activity against the amastigotes and excellent selectivity, being approximately 20-fold more potent than the natural product and comparable with

benznidazole, a drug in clinical use against Chagas diseases. Interestingly, the deletion of this group altogether as demonstrated by compound **175** also led to a marked improvement in activity. This may suggest that substitution is not necessary at all, which could lead to improved synthetic ease. However, as this is the only analogue tested with this particular modification, further analogue synthesis would be necessary to validate whether this group is or is not required for activity. Compounds containing amides or amines at this position were also found to be highly potent against both forms of the parasite. Compound **219** (morpholine amide) is particularly promising as it shows lower mammalian toxicity and therefore higher selectivity. When comparing morpholine with pyrrolidine directly, the morpholine analogues tend to show higher selectivity.

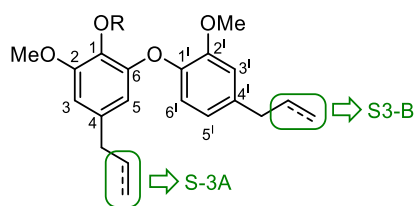
Table 15. *T. cruzi* assay data for compounds with a S-2 modification.



Entry	Compound	S-1	S-2A	S-2B	IC ₅₀ / μ M ($\pm$ SE)		CC ₅₀ / μ M ($\pm$ SE)	SI
					Tryp.	Am.		
1	190	OH	H	OMe	2.5 $\pm$ 0.7	7.7 $\pm$ 0.7	128.6 $\pm$ 2.6	16.7
2	191	OPMB	H	OMe	NA	11.6 $\pm$ 4.2	>200	>17.2
3	187	OH	OMe	H	4.6 $\pm$ 1.5	22.5 $\pm$ 9.4	123.4 $\pm$ 4.7	5.5
4	186	OPMB	OMe	H	NA	11.0 $\pm$ 1.2	>200	>18.2
5	Benznidazole	-	-	-	17.7 $\pm$ 1.0	5.0 $\pm$ 0.8	190.6 $\pm$ 6.7	38.1

n = 4; IC₅₀: 50% Inhibitory Concentration; CC₅₀: 50% Cytotoxic Concentration; SI: Selectivity Index, given by the ratio between CC₅₀ in NCTC cells and IC₅₀ in intracellular amastigote assay.

The effect of S-3 deletion was studied through analogues **190/191** (A ring) and **187/186** (B ring). In all cases, appreciable activity was observed against the amastigote form of the parasite, and also against trypomastigotes for the free phenols, albeit again at a cost of mammalian toxicity. Given the improved efficiency of Ullmann coupling of the iodide required for the synthesis of **190** and **191**, which lack the A-ring methoxy substituent, this deletion may again offer synthetic benefit for access to further natural product analogues.

Table 16. T. cruzi assay data for compounds with a S-3 modification.

Entry	Compound	S-1	S-3A	S-3B	IC ₅₀ / μ M ($\pm$ SE)		CC ₅₀ / μ M ($\pm$ SE)	SI
					Tryp.	Am.		
1	200	OH	H	Allyl	NA	NA	>200	ND
2	137	OMe	H	Allyl	63.1 $\pm$ 3.1	25.7 $\pm$ 6.1	>200	>7.8
3	69	OAllyl	H	Allyl	NA	NA	>200	ND
4	199	OPMB	H	Allyl	NA	NA	>200	ND
5	201	OAc	H	Allyl	NA	NA	>200	ND
6	195	OH	Allyl	H	30.6 $\pm$ 1.3	NA	31.6 $\pm$ 6.7	ND
7	192	OMe	Allyl	H	20.3 $\pm$ 0.2	NA	>200	ND
8	193	OPMB	Allyl	H	NA	NA	>200	ND
9	196	OAc	Allyl	H	NA	NA	>200	ND
10	213	OH	<i>n</i> -Propyl	Allyl	4.6 $\pm$ 1.9	10.5 $\pm$ 4.2	14.2 $\pm$ 0.1	1.3
11	212	OPMB	<i>n</i> -Propyl	Allyl	NA	13.4 $\pm$ 2.6	>200	>14.9
12	207	OH	Allyl	<i>n</i> -Propyl	7.6 $\pm$ 1.0	16.6 $\pm$ 0.5	42.0 $\pm$ 1.9	2.5
13	209	OMe	Allyl	<i>n</i> -Propyl	21.9 $\pm$ 3.1	11.7 $\pm$ 3.5	>200	>17.1
14	208	OPMB	Allyl	<i>n</i> -Propyl	NA	8.6 $\pm$ 1.1	>200	>23.3
15 ^a	237	OH	<i>n</i> -Propyl	<i>n</i> -Propyl	7.9 $\pm$ 0.4	NA	57.7 $\pm$ 0.6	ND
16 ^a	238	OMe	<i>n</i> -Propyl	<i>n</i> -Propyl	NA	13.3 $\pm$ 0.6	>200	>15.0
17	214	OPMB	<i>n</i> -Propyl	<i>n</i> -Propyl	NA	5.5 $\pm$ 1.8	>200	>36.4
18	228	OH	Allyl		NA	NA	43.3 $\pm$ 2.7	ND
19	226	OPMB	Allyl		7.4 $\pm$ 0.0	NA	6.2 $\pm$ 0.6	ND
20	229	OH	Allyl		NA	NA	51.4 $\pm$ 2.4	ND
21	227	OPMB	Allyl		NA	9.2 $\pm$ 1.2	>200	>21.7
22	Benzimidazole	-	-	-	17.7 $\pm$ 1.0	5.0 $\pm$ 0.8	190.6 $\pm$ 6.7	38.1

n = 4; IC₅₀: 50% Inhibitory Concentration; CC₅₀: 50% Cytotoxic Concentration; SI: Selectivity Index, given by the ratio between CC₅₀ in NCTC cells and IC₅₀ in intracellular amastigote assay.

^aPublished in Ref 94.

It is clear from Table 16 that deletion either of the S-3 side chains results in a significant reduction in activity against the intracellular amastigote form of the parasite (Entries 1 to 9), with **137** being the only active compound in this series. This activity is also interesting as it is an improvement on the native methylated natural product **2**, which is inactive, so it may be possible that this analogue operates *via* a different mechanism of action. Only three compounds in this group show activity against the trypomastigote form; **137**, **195** which also shows toxicity to mammalian cells, and **192**, which shows reduced activity relative to the analogues with both side chains present.

Consistent activity and selectivity against the intracellular amastigotes were observed in compounds where one or both of the side-chains is saturated (Entries 10 to 17). This is a pleasing result, as from a synthetic perspective these compounds are less likely (in the case of S-3A saturation) or unable to suffer from isomerisation during Ullmann coupling in their synthesis, so it is possible to propose further analogues with this modification that are more readily accessible through synthesis and likely to still be active. Trypomastigote activity was observed in the phenols **213** and **207**, and methylated analogue **209**, which was the only non-toxic compound in this group to show trypomastigote activity. Interestingly, introducing an amine to the right-hand side did not lead to active compounds against the amastigote form, with the exception of compound **227**, which also shows excellent activity and selectivity.

4.3.4 Discussion of Structure-Activity Relationship

The DNDi criteria for a promising hit compound include having no more than eight synthetic steps (all of these compounds meet this criteria), an $IC_{50} < 10 \mu M$ in the amastigote assay and a $SI > 10$. Eight of the compounds tested meet all three of these criteria, showing potency and selectivity equivalent to or greater than the pharmaceutical agent benznidazole, with a further seven showing $IC_{50} < 15 \mu M$. Only the analogues possessing free phenols or polar side chains show toxicity, with some of them showing high enough potency to still be selective. In general, lower activity was observed against the trypomastigotes than the amastigotes, which may suggest the compounds' mode

of action is implicated in amastigote replication (as the trypomastigote form is not replicative) or that the effect is immunomodulatory – the compound activates the macrophage immune response, in addition to any direct effect on the parasite.

The following trends against the amastigote form of *T. cruzi* emerge from the SAR study:

1. The S-1 substituent may not be crucial (Table 14, compound **175**) but can also accommodate functionalisation with various ether groups, which in general exhibit reduced toxicity compared to equivalent phenols. The most potent analogues feature benzylic ethers at this position, suggesting there is significant scope for further exploration of this substituent vector.
2. Both amides and the morpholine amine at S-1 (**218**, **219**, and **221**), although showing some toxicity, also show low micromolar activity, such that the selectivity index is > 10.
3. Either of the S-2 methoxy groups may be removed without significant effect on anti-parasitic activity, which is likely to be of utility from a synthetic perspective (Table 15, Scheme 42, compound **191**).
4. The presence of both S-3 side chains is important for activity, although one or both may be saturated. Again, this is likely to be useful from a synthetic perspective.

In all, this series shows that the dehydrodieugenol B framework offers a robust platform for further analogue design.

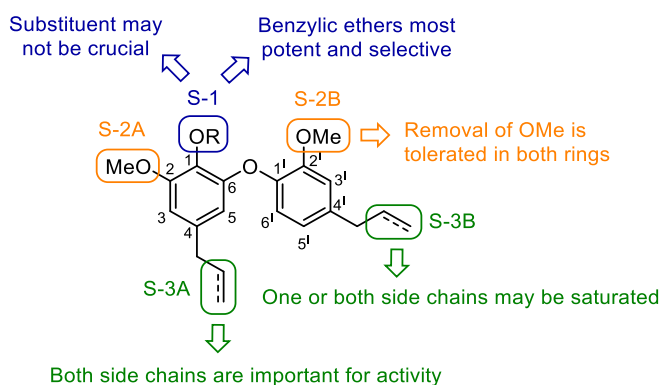
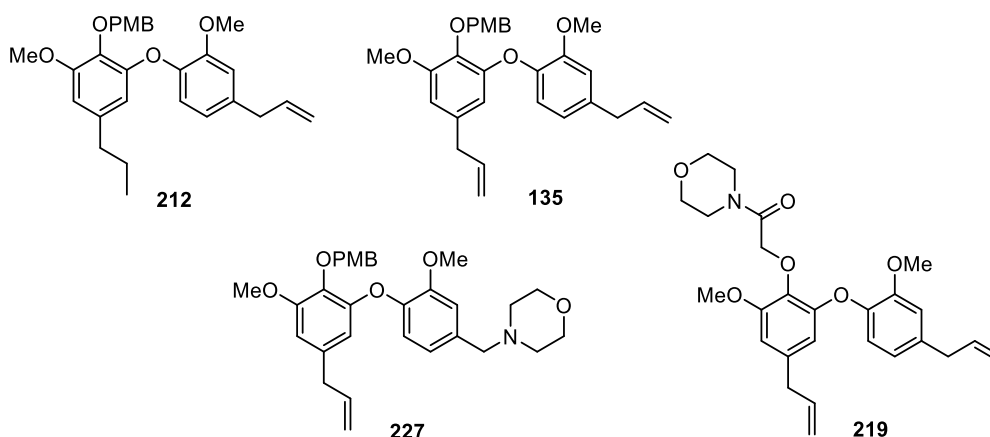


Figure 38. Summary of SAR for *T. cruzi*.

4.4 *In silico* Predicted Physicochemical properties

The natural products and the synthetic analogues designed by Sousa are known to have certain undesirable physicochemical properties when assessing drug-likeness, such as high logP and low solubility.⁹⁵ Compounds **218** – **221** and **226** – **229** were designed with the aim to improve the physicochemical properties whilst still including some of the structural features and overall scaffold. To assess whether this was achieved in this study, two of the ‘best’ compounds from each disease were selected for *in silico* analysis – one a direct natural product analogue and one with a modification designed to improve physicochemical properties. The properties of these compounds was predicted using FAF-Drug4⁹⁶ and the results are displayed in Table 17.

Table 17. In silico Predicted physicochemical properties from FAF-Drugs4.⁹⁶ IC_{50} and SI values are those corresponding to intracellular amastigote assay.



	212	227	135	219
IC_{50} <i>L. infantum</i> / μ M	14.3 $\pm$ 1.4	9.7 $\pm$ 1.0	-	-
IC_{50} <i>T. cruzi</i> / μ M	-	-	4.0 $\pm$ 0.7	6.4 $\pm$ 1.5
SI	>14	>20.6	>50	17.4
MW	448.55	505.6	446.53	453.53
logP	7.24	5.36	6.97	4.66
logD (pH 7.4)	7.07	5.36	6.76	4.10
logS	-6.60	-5.74	-6.42	-5.00
tPSA	46.15	58.62	46.15	66.46
HBD	0	0	0	0
HBA	5	7	5	7
Lipinski violations	1	2	1	0
Solubility mg L ⁻¹	613.17	1618.04	727.95	3054.56

In general, introduction of the morpholine heterocycle, either at S-3B or S-1, results in a reduction in logP and logD, an increase in logS, solubility, and tPSA. There are all beneficial changes when considering the drug-likeness of the compounds. Compound **219** shows the most favourable qualities, the only one with a logP lower than 5 and a significantly higher solubility than the others. It is also the only compound to show no violations of the Lipinski rules. Comparing **212** and **135**

shows that having unsaturation on both rings is slightly beneficial for some properties such as solubility and logP but not so much that it would be essential to maintain full unsaturation for an effective compound. Comparing **227** and **219** shows that the amide contributes more to improving the properties than the amine, but this is not a direct comparison as the position of the functionality may also be relevant. All four of these compounds also maintained the benefits of the natural product and semi-synthetic analogues – they show no activity in the PAINS filters and show good oral bioavailability. Overall, the modifications made to introduce polarity by functionalising S-3B and S-1 with a polar group had the desired effect of increasing predicted polarity and solubility, whilst also retaining the potency and selectivity in some cases. There is now potentially scope to improve these properties further making similar modifications to the other side chains, or to the biaryl ether scaffold itself.

4.5 Mechanism of Action

Although the mechanism of action of the analogues against the two diseases is unknown, there is some evidence in the literature that may point towards potential targets. The following section summarises the work in the literature to elucidate the mechanism of action of the following four compounds on the two parasite forms (Figure 39), and how this may relate to the work described in this thesis.

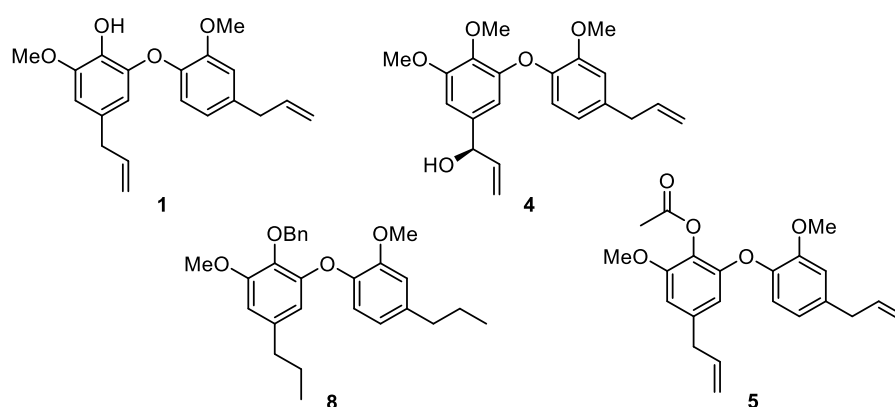


Figure 39. Natural products and semi-synthetic analogues where research on the mechanism of action is known.^{92–95}

4.5.1 *Leishmania*

In 2019, Amaral *et al.* reported on four semi-synthetic analogues and their studies of the mechanism of action.⁹⁵ These compounds are built around the same scaffold as the synthetic analogues discussed in this chapter and therefore are likely to operate by a similar mechanism of action. Compound **8**, selected as the best compound in this series, demonstrated an intense depolarisation of the *L. infantum* plasma membrane – an effect that is harmful to the parasite by affecting metabolite transportation and acquisition of nutrients. This compound also demonstrated intense depolarisation of the mitochondrial membrane, and caused swelling of the mitochondria and loss of cristae. Unlike mammalian cells, kinetoplastids present only a single-mitochondrion which is required for survival, so mitochondrial targets are of particular relevance for potential therapeutics. There was also some evidence in this work that compound **8** may impair DNA replication.

Initial studies on the three natural products **1** to **4** also suggested that the compounds acted on the parasite by an immunomodulatory effect – causing parasite death indirectly by up-regulating the immune response of the parasite. Compounds **1** and **8** have both been shown to affect the levels of cytokines IL-10, MCP-1 and TNF, all of which are known to be important in host cell activation.

4.5.2 *Trypanosoma cruzi*

Similarly, compound **4** was shown considerably alter the parasite plasma membrane permeability, together with mitochondrial dysfunction, in the trypomastigote of *T. cruzi*.⁹³ Interestingly, in the 2019 semi synthesis study compound **5** did not have the same effect on the plasma membrane suggesting that the presence of the acetate and lack of side chain hydroxyl alters the compound's affinity for the plasma membrane.⁹⁴ For our best compounds, further work would be needed to elucidate the effect of a PMB ether at the S-1 position. Consistent with the studies on *Leishmania infantum*, a strong depolarisation of the mitochondrial membrane was observed in compound **5**, again implying that the anti-parasitic effect of this group of compounds may be a result of mitochondrial impairment, however further studies on the compounds will be required to confirm this.

5. Conclusions and Future Work

The work described in this thesis has led to a robust synthetic strategy based on an Ullmann biaryl ether formation for the synthesis of a number of synthetic small molecules based on the dehydrodieugenol B scaffold, which is known to have potent anti-*Leishmania* and anti-*Trypanosoma* activity. The optimisation of this route has enabled the design and synthesis of a series of analogues, elucidation of the structure-activity relationship of the core scaffold, and also improving the predicted physicochemical properties of the compounds. This series included a number of compounds with much improved potency and selectivity against both parasites compared with the natural products, and a series of potential hit compounds for further exploration.

This work has also enabled the elucidation of a detailed structure-activity relationship whereby the importance of certain structural features for activity could be identified. We have shown that in general, phenols show higher mammalian cytotoxicity than corresponding ethers. In *L. infantum* infection, maintaining S-2 substitution is essential for activity whereas in *T. cruzi* this is not essential, and is a modification that may lead to improved synthetic ease when designing further analogues. Likewise, in *L. infantum* it is possible to remove one of the S-3 side chains and retain activity, and to saturate one of them in *T. cruzi*. Both of these modifications can be employed going forward, leading to more synthetically accessible analogues. We have also shown that predicted physicochemical properties can easily be improved by introducing polarity to the molecule using relatively simple chemistry at the positions that tolerate modification, with selectivity and potency being maintained in some cases.

5.1 Learning More About the Most Active and Selective Analogues

Given the low micromolar activity of some of the best analogues against both diseases, and also the very high selectivity, some of the compounds contained here are very promising hits, and it would therefore be desirable to learn more about their *in vivo* activity and mechanism of action. In the case

of *Leishmania infantum*, compound **227** is of particular interest both because of its potency and selectivity but also because of its improved predicted physicochemical properties. Similarly, in *T. cruzi* infection compound **135** shows by far the highest potency and selectivity. These compounds could therefore be taken to the next stage of development and tested in animal models of parasite infection, probing their toxicity and efficacy in reducing parasite burden.

These compounds could also be used in mechanism of action studies. As previously described, some research into the mechanism of action of the natural product and semi-synthetic analogues is ongoing and early work suggests a parasite mitochondrial target in the case of both diseases. Similar studies on the best compound in this work would be an obvious next step to see if they follow this trend. As described in Chapter 1, finding specific binding targets for these parasites has so far proven to be very difficult and has not resulted in any leads for the treatment of these diseases. However, there is work ongoing to validate protein targets for therapeutic use. For rational future analogue design and optimisation, it would be invaluable to understand the mechanism of action of these compounds at a molecular level. Identifying the molecular target could feasibly be achieved using a pull-down experiment whereby the inhibitor is immobilised onto a gel and used to ‘pull down’ the target to which it binds from a cell lysate. Similar strategies have been employed against related parasite *Trypanosoma brucei* with some success^{119–121}. The targets can also be identified using a knock-out experiment whereby essential proteins are identified through engineering parasites with the protein missing to see if the parasite can survive.

With a target known, it may be possible to obtain a crystal structure, probe binding affinity, as well as understand how inhibition of the target can affect the parasite. This can also enable a more directed design of analogues with structural features aimed at improving binding, and also a more high-throughput assay to enable the screening of larger libraries and more rapid identification and optimisation of hits.

5.2 Further Analogues

Given all we have learned about the necessity of structural features and the utility of including polarity in the molecules, a new round of analogues can now be designed that combine these structural features with the synthetic ease associated with the removal or modification of certain substituents. For example, for *L. infantum* the most potent compounds included saturation at S-3A in one case (**212**), and a morpholine at S-3B in another (**227**). A useful analogue may involve combining these two modifications into one compound (**239**, Figure 40). Also, we are yet to consider introducing polarity at S-3A in this study so analogues could be derived from this modification as well (**241**). We have also seen that a side chain at either S-3 position may not be essential so removing this could improve physicochemical properties and reduce molecular weight while maintaining potency (**240** and **242**).

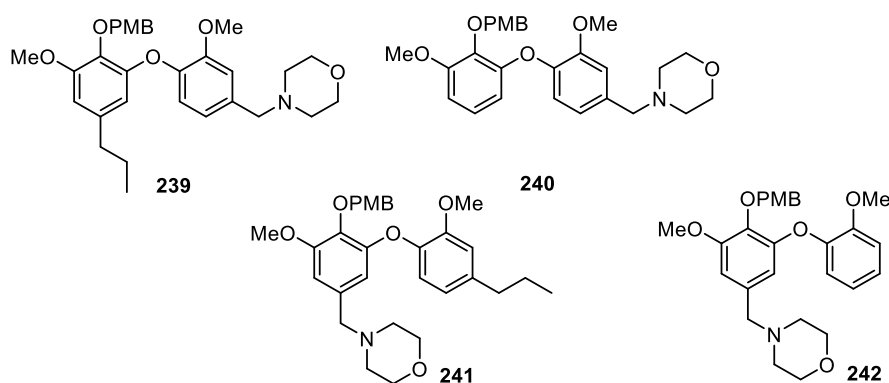


Figure 40. Potential new analogues for testing against *L. infantum*.

For *T. cruzi* infection we have learned that having a methoxy at the S-2 position is not essential for activity, and that its removal allows for a much more facile coupling step in the synthesis. We also learned that saturation of S-3A gives rise to a potent compound that reduces the likelihood of troublesome isomerisation at this position in the Ullmann coupling. We know that having a morpholine amide at S-1 leads to an improvement in physicochemical properties and a very potent compound. It is therefore possible to combine these modifications in a number of ways, leading to a more efficient synthesis and potent compounds with better physicochemical properties (**243** to **245**, Figure 41). There is also scope for varying the nature of the amine – we discovered that pyrrolidine

exhibited a much higher mammalian cytotoxicity than morpholine so it is clear that the nature of this amine is important and modifications to it could be easily explored using the synthetic route described.

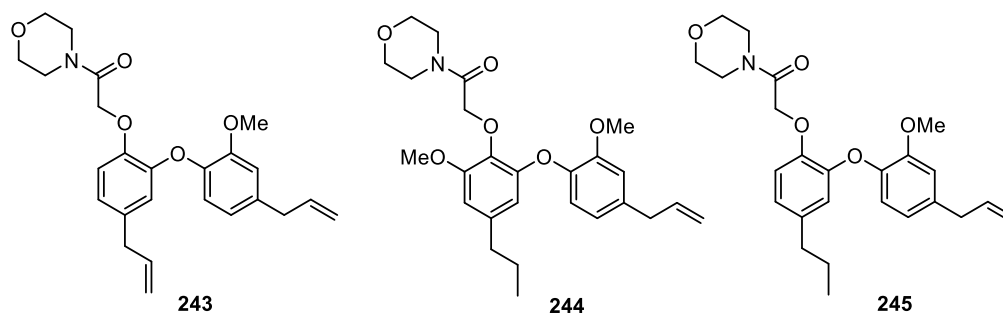


Figure 41. Potential new analogues for testing against *T. cruzi*, combining the synthetic ease associated with substituent deletion or modification with the potency and polarity associated with the amide group.

Although the PMB group has been shown to be very effective for potency and selectivity, it is not a particularly useful group in therapeutics as it is susceptible to metabolism in the body – it can be removed easily with mild acid or oxidising conditions. However, what it shows us is that functionalising this vector is useful, and other groups tested, such as benzyl and allyl ethers, have confirmed this. Some new analogues could therefore feasibly be designed for both diseases to incorporate some of the side chain modifications that have been shown to be useful, with a less troublesome ether at S-1 (246 to 249, Figure 42).

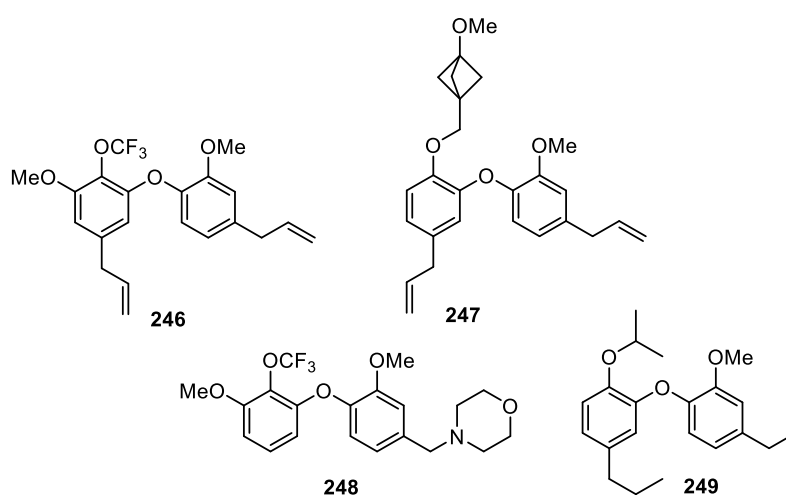


Figure 42. Potential new analogues combining an alternative ether at S-1 with other modifications shown to be effective in this study.

Finally, this work began the process of optimisation of drug-like properties of the potent analogues by looking at the S-1 and S-3B positions. However, there is much scope for introducing polarity on to the scaffolds at other sites, including S3-A (**253**), the biaryl ether linkage itself (**251**), or through substituting any of the aromatic rings with heterocycles (**250**, **252**, Figure 43).

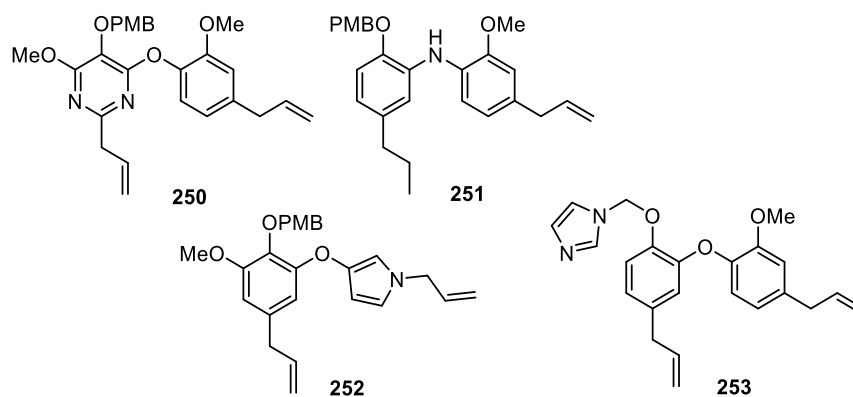


Figure 43. Potential new analogues designed with the aim of improving solubility and logP.

6. Experimental

6.1 Parasitology Assays

Ethics Statement

Male golden hamsters (*Mesocricetus auratus*, 120 g) and female BALB/c mice (20 g) were obtained from the animal breeding facility at the Instituto Adolfo Lutz – São Paulo, Brazil. The animals were maintained in sterilized cages under a controlled environment, receiving water and food *ad libitum*. All procedures performed were previously approved by the Animal Care and Use Committee from Instituto Adolfo Lutz – Secretary of Health of Sao Paulo State (Project Number CTC 21H/2015, CEUA 04/2016) in agreement with the Guide for the Care and Use of Laboratory Animals from the National Academy of Sciences.

Parasites and mammalian cell maintenance

L. infantum amastigotes were obtained from the spleen of golden hamsters previously infected, and purified by differential centrifugation.¹²² Trypomastigotes of *T. cruzi* (Y strain) were maintained in Rhesus monkey kidney cells (LLC-MK2 - ATCC CCL 7), cultivated in RPMI 1640 medium supplemented with 2% fetal calf serum at 37 °C in a 5% CO₂ humidified incubator. Peritoneal macrophages were collected by washing the peritoneal cavity of BALB/c mice with RPMI 1640 medium (Sigma-Aldrich) supplemented with 10% FBS, and were maintained at 37 °C in a 5% CO₂ humidified incubator. Murine fibroblasts NCTC (clone L929, ATCC, mouse C3H/An areolar and adipose tissue) were maintained in RPMI 1640 supplemented with 10% FBS at 37 °C in a 5% CO₂ humidified incubator.

Evaluation of *in vitro* anti-*L. infantum* activity

Peritoneal macrophages (1×10^5 cell / well) in 16-well slide chambers (NUNC) were infected with amastigotes at a ratio of 10 : 1 (amastigotes / macrophage) and treated with compounds (60 to 10 μ M) for 96 h. The slides were fixed with MeOH, stained with Giemsa, and observed under a light microscope (EVOS M5000, Thermo, USA) with digital image acquirement. The 50% inhibitory concentration (IC_{50}) values were determined by the infection index.¹²³ >90% infection of macrophages was established in this assay.

Evaluation of *in vitro* anti-*T. cruzi* activity

Trypomastigotes. LLC-MK2-derived trypomastigotes were seeded (1×10^6 cells / well) in 96-well plates and incubated with the compounds serially diluted twofold (up to 100 μ M) for 24 h in RPMI 1640 medium at 37 °C in a 5% CO₂ humidified incubator. Subsequently, resazurin (0.011% in PBS) was added to check the parasite viability, for 24 h.¹²⁴ The optical density was determined in the FilterMax F5 (Molecular Devices) at 570 nm. Benznidazole was used as standard.

Amastigotes. Peritoneal macrophages (1×10^5 cells / well), collected from the peritoneal cavity of BALB/c mice, were seeded in 16-well chamber slide (NUNC, Thermo Fisher Scientific) and infected with trypomastigotes (10 : 1, parasite / macrophage ratio). After 2 h, the compounds (in concentrations 30 - 0.23 μ M) were incubated with infected macrophages for 48 h at 37 °C in a 5% CO₂ humidified incubator. The slides were fixed with MeOH, stained with Giemsa, and observed under a light microscope (EVOS M5000, Thermo, USA) with digital image acquirement. The 50% inhibitory concentration (IC_{50}) values were determined by the infection index.⁹⁴ >90% infection of macrophages was established in this assay.

Evaluation of *in vitro* mammalian toxicity

Fibroblast NCTC cells (clone 929, mouse C3H/An areolar and adipose tissue) (6×10^4 cells / well) were seeded in 96-well plates and incubated with the compounds (200 – 1.56 μ M) for 48 h at 37 °C in a 5% CO₂ humidified incubator. The 50% cytotoxic concentration (CC₅₀) was determined by MTT colorimetric assay.¹²⁵ The Selectivity Index (SI) was determined as CC₅₀ / IC₅₀ against amastigotes.

Statistical analysis

The determination of the CC₅₀ and IC₅₀ values was obtained from sigmoid dose-response curves. The statistical significance (p value) between the samples was evaluated through the One-way ANOVA method using the Tukey's Multiple Comparison test. All analyses were performed using Graph Pad Prism 5.0 software. The samples were tested in duplicate and the assays were repeated at least twice.

In silico Physical-Chemical Properties

Pharmacokinetic and toxicological risks were predicted *in silico* using web-based server FAF-Drugs4.⁹⁶ The FAF-Drugs4 suite includes models for the prediction of physiochemical properties, solubility, oral bioavailability, drug likeness, phospholipidosis, PAINs compounds, and Lilly Med Chem Rules. The Lilly MedChem Rules consist of 275 descriptors developed by Lilly using experimental data collected over 18 years. The rules were developed to identify compounds that may interfere with biological assays such as promiscuous, fluorescent, or unstable compounds.¹²⁶

6.2 Synthesis of Compounds

6.2.1 General Considerations

Solvents and Reagents

Dichloromethane, dioxane, tetrahydrofuran, and dimethylformamide were dried by passing through an activated alumina column under argon in a solvent dispenser. All other reagents were used as received. Cesium carbonate, copper(I) chloride and copper(I) iodide were weighed out in a glove box under nitrogen. Petrol refers to the fraction of petroleum ether which boils in the range 40 – 60 °C. Brine refers to a saturated aqueous solution of NaCl.

Reactions

All reactions were carried out under an atmosphere of argon or nitrogen unless otherwise stated. Oven-dried glassware was used for reactions requiring anhydrous conditions.

Chromatography

Thin-layer chromatography was performed on Merck aluminium-backed DC 60 F254 0.2 mm precoated plates, which were visualised with UV fluorescence and staining with potassium(VII) manganate or vanillin. Flash column chromatography was performed on MN Kieselgel 60M (particle size 40 – 63 µm), with the solvent system used in parentheses.

Infrared Spectroscopy

Infrared spectra were recorded on a Bruker Tensor 27 Fourier transform spectrometer, as a thin film on a diamond ATR module.

NMR Spectroscopy

¹H NMR spectra were recorded at 200, 250, 400 or 500 MHz on Bruker DPX 200, DPX 250, DPX 400, DQX400, AVN 400, DRX500 and AVII 500 spectrometers. ¹³C NMR spectra were recorded at 101 MHz or 125 MHz on Bruker DQX 400, AVN 400, DRX500 or ACII 500 (with ¹³C cryoprobe) spectrometers. Chemical shifts (δ_{H} and δ_{C}) are expressed in parts per million (ppm), referenced to the residual solvent peak of CDCl₃ (7.26 ppm). Coupling constants (J) are reported to the nearest 0.1 Hz and are uncorrected. Spectra are assigned based on chemical shift, coupling constants, COSY,

HSQC and HMBC data and / or comparison with similar compounds. Splitting patterns are described using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), sext. (sextet).

Mass spectrometry

Low-resolution mass spectra (m/z) were performed on a Micromass LCT Premier Open Access. High resolution mass spectra were recorded under ESI or EI conditions on a Bruker MicroTOF.

Melting Points

Melting points were obtained using a Griffin melting point apparatus and are uncorrected.

Heating

For reactions that require heating, an oil bath was employed. The temperature was monitored via a temperature probe plugged into the stirrer plate.

6.2.2 General Synthetic Methods

General Method A: MOM Protection of Phenols

A solution of phenol (1.0 eq) in DCM (0.2 M) was cooled to 0 °C and chloromethyl methyl ether was added (1.5 eq), followed by dropwise addition of DIPEA (2.0 eq) and the reaction was allowed to reach room temperature. It was stirred until TLC showed consumption of phenol, after which time the reaction was transferred to a separating funnel and washed with 0.5 M HCl, water, brine, and 1 M NaOH, before being dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*.

General Method B: *Ortho*-Iodination of Protected Phenols

To a solution of protected phenol (1.0 eq) and TMEDA (1.5 eq) in anhydrous THF (0.6 M) at -78 °C was added sBuLi (1.3 M in hexanes, 1.5 eq) dropwise. The resulting dark red solution was stirred at -78 °C for three hours, before the dropwise addition of a solution of iodine (1.5 eq) in anhydrous THF (4.5 M). After the addition of iodine was complete, the reaction was allowed to warm to room temperature over 90 minutes, before being quenched with 10% aqueous $Na_2S_2O_5$ solution. The organic layer was removed, and the aqueous layer extracted with DCM. The combined organic layers

were washed with saturated aqueous NH_4Cl solution, brine, and then dried over MgSO_4 , filtered, and the solvent removed *in vacuo*.

General Method C: MOM – Deprotection of Phenols

The protected phenol (1.0 eq) was dissolved in MeOH (0.03 M) and 2M aqueous HCl (0.1 v/v) was added. The reaction was stirred at room temperature overnight. The reaction was brought to pH 5 by addition of 1M aqueous NaOH. The product was then extracted with EtOAc. The organic layers were combined, dried over MgSO_4 , filtered, and the solvent removed *in vacuo*.

General Method D: Optimised Biaryl Ether Formation

To a vial containing NMP (5 M *wrt* halide) and phenol (2.0 eq) was added cesium carbonate (2.0 eq), and the vial was evacuated and backfilled with nitrogen gas three times. Halide (1.0 eq), TMHD (0.5 eq) and copper(I) chloride (0.5 eq) were added and the vial was evacuated and backfilled with nitrogen gas three times, before addition of dioxane (2.5 M *wrt* halide). The vial was then sealed and heated to 80 °C and stirred until TLC showed consumption of the halide. After this time, the reaction was cooled to room temperature and diluted with Et_2O . The reaction mixture was filtered through celite, and the filter cake washed with Et_2O . The filtrate was washed with NH_4OH , water, 1 M aqueous NaOH solution, and brine, and the organic layer was dried over MgSO_4 , filtered, and the solvent removed *in vacuo*.

General Method E: Allylation of Phenols

To a solution of phenol (1.0 eq) in DMF (1 M) was added potassium carbonate (2.5 eq), followed by allyl bromide (1.5 eq) and the reaction heated to 50 °C and stirred for 3 hours. The reaction was then diluted with EtOAc and then washed with water, and the organic layer was dried over MgSO_4 , filtered, and the solvent removed *in vacuo*.

General Method F: Methylation of Phenols

To a solution of phenol (1.0 eq) in anhydrous DMF (0.7 M) was added potassium carbonate (4.0 eq), followed by dropwise addition of methyl iodide (1.4 eq). The reaction was stirred at room

temperature overnight, before being diluted with EtOAc, and washed with water and 1M NaOH. The organic layer was dried over MgSO₄, filtered, and the solvent removed *in vacuo*.

General Method G: Chan-Lam Coupling

To a solution of phenol (1.0 eq) in anhydrous DCM (0.13 M) was added 4Å molecular sieves, copper(II) acetate (1.0 eq) and triethylamine (5.0 eq), and the resulting mixture was stirred at room temperature under air for 20 minutes, before addition of boronic acid (2.0 eq). The reaction was stirred at room temperature under air for 30 hours, before being filtered through a pad of celite. The filtrate was washed with saturated NH₄Cl solution, and brine. The organic layer was dried over MgSO₄, filtered, and the solvent removed *in vacuo*.

General Method H: Grignard Addition to Aldehyde

To a flask containing a solution of aldehyde (1.0 eq) in diethyl ether (0.2 M) was added vinylmagnesium bromide (1 M in THF, 2.0 eq) dropwise at 0 °C. The reaction was then allowed to heat to room temperature and was stirred for three hours. After this time, the reaction was quenched with water, and the product extracted with diethyl ether. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and the solvent removed *in vacuo*.

General Method I: PMB-Protection of Phenols

To a flask containing a solution of phenol (1.0 eq) in anhydrous DMF (0.13 M) was added potassium carbonate (2.5 eq). PMBCl (1.2 eq) was added dropwise with vigorous stirring. The reaction was heated to 100 °C and stirred for two hours, or until TLC showed consumption of the phenol, after which time the reaction was cooled to room temperature and partitioned between EtOAc and water. The organic phase was washed with water and then brine, dried over MgSO₄, filtered, and the solvent removed *in vacuo*.

General Method J: PMB-Deprotection of Phenols

To a flask containing a solution of PMB-protected phenol (1.0 eq) in ethanol (0.05 M) was added 1M aqueous HCl (0.02 M) and the reaction was heated to 80 °C until TLC showed consumption of

the protected phenol, after which time the reaction was cooled to room temperature, and partitioned between water and EtOAc. The product was extracted with EtOAc and the combined organic layers were washed with brine, then dried over MgSO_4 and the solvent removed *in vacuo*.

General Method K: Hydrogenation of Alkenes

A flask containing a suspension of Pd/C (10% w/w, 0.3 eq) in ethanol (0.06 M) was evacuated of air and flushed with hydrogen (balloon) three times. The suspension was stirred vigorously under the hydrogen atmosphere for 15 minutes, before addition of the alkene (1.0 eq). The reaction was stirred under hydrogen until TLC showed consumption of the starting material. The mixture was then filtered through a pad of celite, and the filtrate dried over MgSO_4 and the solvent removed *in vacuo*.

General Method L: Acylation of Phenols

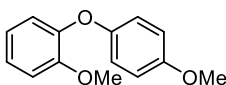
To a solution of phenol (1.0 eq) in pyridine (23.0 eq) was added acetic anhydride (7.5 eq) and the reaction heated to 100 °C with stirring. After two hours, the reaction was cooled to room temperature, and quenched with ice. The reaction was acidified by dropwise addition of 1M aqueous HCl. The produce was extracted with EtOAc and the organic layers combined and washed with 1M aqueous HCl and brine, before being dried over MgSO_4 , filtered, and the solvent removed *in vacuo*.

General Method M: Allylation of Phenols

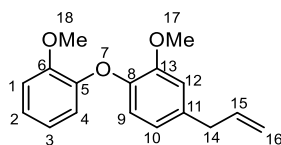
To a solution of phenol (1.0 eq) in DMF (1 M) was added potassium carbonate (2.5 eq) followed by dropwise addition of allyl bromide (1.5 eq). The reaction as heated to 50 °C and stirred until TLC indicated consumption of the starting material. The reaction was then cooled to room temperature and diluted with EtOAc, then washed with water, dried over MgSO_4 , filtered, and the solvent removed *in vacuo*.

6.2.3 Synthesis and Characterisation of Compounds

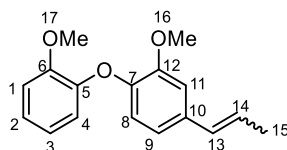
Methoxy-2-(4-methoxyphenoxy)benzene, **94**



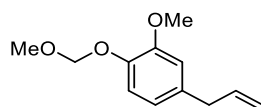
The compound was synthesised according to the literature procedure described by Buck *et al.*¹⁰⁶ To a vial containing NMP (1.7 mL) and 4-methoxyphenol (248 mg, 2.0 mmol, 2.0 eq) was added cesium carbonate (652 mg, 2.0 mmol, 2.0 eq), and the vial was evacuated and backfilled with nitrogen gas three times. 2-Iodoanisole (130 μ L, 1.0 mmol, 1.0 eq), TMHD (21 μ L, 0.1 mmol, 0.1 eq) and copper(I) chloride (50 mg, 0.5 mmol, 0.5 eq) were added and the vial was evacuated and backfilled with nitrogen gas three times. The vial was then sealed and heated to 120 °C and stirred overnight. After 16.5 hours, the reaction was cooled to room temperature and diluted with Et₂O (2 mL). The reaction mixture was filtered through celite, and the filter cake washed with Et₂O (3 $\times$ 2 mL). The filtrate was washed with water (10 mL), 1M aqueous NaOH solution (3 $\times$ 10 mL), brine (10 mL), and the organic layer dried over MgSO₄, filtered, and the solvent removed *in vacuo*. The crude residue was purified by recrystallization from petrol, to afford **94** (148 mg, 0.64 mmol, 64%) as an off-white crystalline solid; MP 64 – 67 °C (petrol); Lit.¹⁰⁶ 77 – 80 °C; *R*_f 0.26 (petrol / EtOAc (9 : 1)); ¹H NMR (400 MHz, CDCl₃) δ _H 7.06 (ddd, *J* = 8.1, 6.5, 2.4 Hz, 1H), 7.01–6.97 (m, 1H), 6.96–6.90 (m, 2H), 6.90–6.82 (m, 4H), 3.88 (s, 3H), 3.79 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ _C 155.5, 151.1, 150.9, 145.7, 123.9, 121.1, 119.5, 119.3, 114.8, 112.7, 56.1, 55.8; HRMS (EI⁺) calc. for C₁₄H₁₄O₃ [M]⁺ 230.0943, found 230.0945. The experimental data are in good agreement with that described in the literature.¹⁰⁶

4-Allyl-2-methoxy-1-(2-methoxyphenoxy)benzene, 97

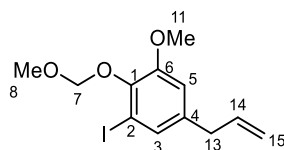
The product was prepared according to General Method D, using 2-iodoanisole (130 μ L, 1.0 mmol, 1.0 eq), eugenol (308 μ L, 2.0 mmol, 2.0 eq), copper(I) chloride (99 mg, 0.5 mmol, 0.5 eq), TMHD (104 μ L, 0.5 mmol, 0.5 eq), cesium carbonate (652 mg, 2.0 mmol, 2.0 eq), NMP (0.6 mL) and dioxane (1.2 mL). The reaction was complete after 2 days. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 9 : 1), to afford **97** (240 mg, 0.90 mmol, 90%) as an off-white waxy solid; R_f 0.19 (petrol / EtOAc (9 : 1)); IR (thin film, $\nu_{\max}$ / cm^{-1}) 3008, 2963, 2836, 1639, 1589, 1499, 1465, 1250, 1214, 1176; ^1H NMR (500 MHz, CDCl_3) δ_{H} 7.04 (ddd, J = 8.1, 7.3, 1.7 Hz, 1H, H2), 6.97 (dd, J = 8.1, 1.7 Hz, 1H, H1), 6.85 (ddd, J = 8.1, 7.3, 1.7 Hz, 1H, H3), 6.82–6.75 (m, 3H, H4, H9, H12), 6.69 (dd, J = 8.1, 2.0 Hz, 1H, H10), 5.99 (ddt, J = 16.8, 10.0, 6.7 Hz, 1H, H15), 5.17–5.04 (m, 2H, H16), 3.87 (s, 3H, H17), 3.84 (s, 3H, H18), 3.37 (dt, J = 6.7, 1.4 Hz, 2H, H14); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 150.6, 150.4, 146.5, 144.0, 137.5, 136.1, 123.6, 120.9, 120.8, 119.2, 118.3, 116.0, 113.0, 112.5, 56.1, 56.0, 40.1; HRMS (EI $^{+}$) calc. for $\text{C}_{17}\text{H}_{18}\text{O}_3$ $[\text{M}]^{+}$ 270.1256, found 270.1257.

2-Methoxy-1-(2-methoxyphenoxy)-4-(prop-1-en-1-yl)benzene, 98

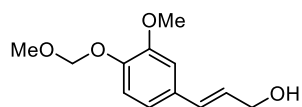
The compound was synthesised according to a modified literature procedure based on that described by Buck *et al.*¹⁰⁶ To a vial containing NMP (1.7 mL) and eugenol (308 μ L, 2.0 mmol, 2.0 eq) was added cesium carbonate (652 mg, 2.0 mmol, 2.0 eq), and the vial was evacuated and backfilled with nitrogen gas three times. 2-Bromoanisole (125 μ L, 1.0 mmol, 1.0 eq), TMHD (21 μ L, 0.1 mmol, 0.1 eq) and copper(I) chloride (50 mg, 0.5 mmol, 0.5 eq) were added and the vial was evacuated and backfilled with nitrogen gas three times. The vial was then sealed and heated to 120 °C and stirred for two days. The reaction was cooled to room temperature and diluted with Et₂O (2 mL). The reaction mixture was filtered through celite, and the filter cake washed with Et₂O (3 $\times$ 2 mL). The filtrate was washed with water (10 mL), 1M NaOH solution (3 $\times$ 10 mL), brine (10 mL), and the organic layer dried (MgSO₄), filtered, and the solvent removed *in vacuo*. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 9 : 1), to afford **98** (68 mg, 0.25 mmol, 25%, *cis* / *trans* (1 : 0.3)) as an off-white waxy solid; *R*_f 0.19 (petrol / EtOAc (9 : 1)); IR (thin film, ν_{max} / cm⁻¹); 3006, 2935, 2836, 2360, 186, 1499, 1455, 1300, 1252, 1216, 1176, 1126, 1113, 1030; ¹H NMR (400 MHz, CDCl₃) δ_{H} 7.16–6.64 (m, 7H, H1, H2, H3, H4, H8, H9, H11), 6.37 (d, *J* = 15.5 Hz, 1H, H13), 6.17 (dq, *J* = 15.5, 6.5 Hz, 1H, H14 *trans*), 5.76 (dq, *J* = 14.1, 7.2 Hz, 0.3H H14 *cis*), 3.86 (m, 6H, H16, H17), 1.93 (d, *J* = 7.2 Hz, 1H H16 *cis*), 1.88 (d, *J* = 6.3 Hz, 2H, H16 *trans*); ¹³C NMR (101 MHz, CDCl₃, some peaks overlapping due to E/Z mixtures) δ_{C} 150.5, 150.4, 150.0, 146.1, 146.0, 144.9, 144.6, 134.1, 133.5, 130.6, 129.5, 126.2, 124.9, 123.9, 123.7, 121.4, 120.9, 118.9, 118.9, 118.6, 118.3, 113.2, 112.5, 112.5, 109.7, 55.9, 29.8, 18.5, 14.8; HRMS (ES+) calc. for C₁₇H₁₉O₃ [M+H]⁺ 271.1329, found 270.1329.

4-Allyl-2-methoxy-1-(methoxymethoxy)benzene, 74

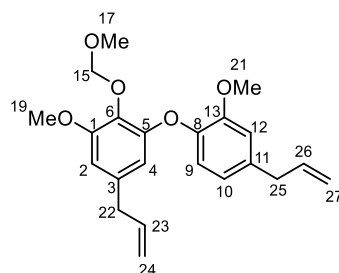
The product was prepared according to General Method A, using eugenol (2.2 mL, 14.4 mmol, 1.0 eq), MOMCl (1.6 mL, 21.6 mmol, 1.5 eq), DIPEA (5.0 mL, 28.8 mmol, 2.0 eq) and DCM (100 mL). The reaction was complete after 18 hours to afford on work-up **74** (2.97 g, 14.3 mmol, 99%) as an orange oil, which was used without further purification; R_f 0.47 (petrol / EtOAc (4 : 1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.07 (d, J = 8.0 Hz, 1H), 6.75–6.68 (m, 2H), 5.95 (ddt, J = 16.9, 10.0, 6.7 Hz, 1H), 5.20 (s, 2H), 5.12–5.04 (m, 2H), 3.87 (s, 3H), 3.51 (s, 3H), 3.36–3.32 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 149.8, 144.8, 137.6, 134.6, 120.7, 116.7, 115.8, 112.3, 95.7, 56.2, 55.9, 40.0; HRMS (EI+) calc. for $\text{C}_{12}\text{H}_{16}\text{O}_3$ $[\text{M}]^+$ 208.1099, found 208.1094. Experimental data are in good agreement with that described in the literature.¹⁰⁹

5-Allyl-1-iodo-3-methoxy-2-(methoxymethoxy)benzene, 100

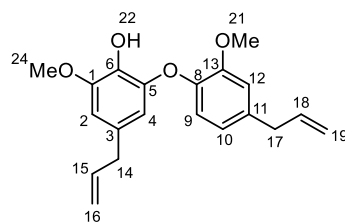
The product was prepared according to General Method B, using 4-allyl-2-methoxy-1-(methoxymethoxy)benzene, **74** (1.26 g, 6.05 mmol, 1.0 eq), TMEDA (1.36 mL, 9.07 mmol, 1.5 eq) ^sBuLi (1.3 M in hexanes, 1.15 mL, 1.5 mmol, 1.5 eq), iodine (2.3 g, 9.07 mmol, 1.5 eq) and THF (10 + 2 mL). The crude residue was purified via flash column chromatography (petrol / EtOAc (1 : 0 → 19 : 1)) to afford **100** (1.31 g, 3.92 mmol, 65%) as a colourless oil; *R_f* 0.24 (petrol / EtOAc (9 : 1)); IR (thin film, ν_{max} / cm^{-1}) 3078, 2963, 2824, 1561, 1480, 1461, 1411, 1314, 1158, 1139, 1076, 1041; ¹H NMR (500 MHz, CDCl₃) δ_{H} 7.20 (d, *J* = 1.9 Hz, 1H, H3), 6.70 (d, *J* = 1.8 Hz, 1H, H5), 5.97–5.84 (m, 1H, H14), 5.13 (s, 2H, H7), 5.13–5.06 (m, 2H, H15), 3.81 (s, 3H, H8), 3.67 (s, 3H, H11), 3.30 (d, *J* = 6.8 Hz 2H, H13); ¹³C NMR (125 MHz, CDCl₃) δ_{C} 152.2, 144.2, 138.3, 136.7, 130.8, 116.6, 113.4, 98.8, 92.7, 58.5, 56.0, 39.5; HRMS (ES⁺) calc. for C₁₂H₁₅IO₃Na [M+Na]⁺ 356.9958, found 356.9956.

(E)-3-(3-Methoxy-4-(methoxymethoxy)phenyl)prop-2-en-1-ol, 101

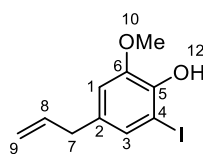
To a solution containing TMEDA (165 μ L, 1.1 mmol, 1.1 eq) in anhydrous THF (2 mL) at 0 $^{\circ}$ C was added a solution of n BuLi (1.6 M in hexanes, 0.69 mL, 1.1 mmol, 1.1 eq) dropwise. The resulting solution was added dropwise to a solution of 4-allyl-2-methoxy-1-(methoxymethoxy)benzene, **74** (208 mg, 1.0 mmol, 1.0 eq) in anhydrous THF (2 mL) at 0 $^{\circ}$ C. The resulting mixture was stirred for 1 hour at 0 $^{\circ}$ C before the dropwise addition of trimethylborate (111 μ L, 1.0 mmol, 1.0 eq). This was stirred for a further 1 hour at 0 $^{\circ}$ C. It was then allowed to heat to room temperature, before addition of 30% aqueous H_2O_2 (0.3 mL). The reaction was stirred for 30 minutes. After this time, water (5 mL) was added and the organic layer removed. The aqueous layer was extracted with Et_2O (2 $\times$ 5 mL). The combined organic layers were dried over MgSO_4 , filtered, and the solvent removed *in vacuo*. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (9 : 1 $\rightarrow$ 1 : 1)), to afford **101** (117.4 mg, 0.52 mmol, 52%) as a yellow oil; R_f 0.24 (petrol / EtOAc (1 : 1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.09 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.89 (dd, J = 8.2, 2.0 Hz, 1H), 6.54 (dt, J = 15.8, 1.5 Hz, 1H), 6.25 (dt, J = 15.8, 5.8 Hz, 1H), 5.22 (s, 2H), 4.30 (dd, J = 5.8, 1.4 Hz, 2H), 3.88 (s, 3H), 3.50 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 149.8, 146.4, 131.4, 131.0, 127.3, 119.7, 116.3, 109.5, 95.5, 63.9, 56.3, 55.9; LRMS (ES-) calc for $\text{C}_{12}\text{H}_{15}\text{O}_4$ [$\text{M}-\text{H}$] $^-$ 223.0, found 223.0. Experimental data are in good agreement with that reported in the literature.¹²⁷

5-Allyl-1-(4-allyl-2-methoxyphenoxy)-3-methoxy-2-(methoxymethoxy)benzene, **72**

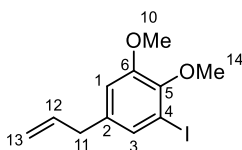
The product was prepared according to General Method D, using 5-allyl-1-iodo-3-methoxy-2-(methoxymethoxy)benzene, **100** (100 mg, 0.3 mmol, 1.0 eq), eugenol (92 μ L, 0.6 mmol, 2.0 eq), copper(I) chloride (15 mg, 0.15 mmol, 0.5 eq), TMHD (31 μ L, 0.15 mmol, 0.5 eq), cesium carbonate (195 mg, 0.6 mmol, 2.0 eq), NMP (0.17 mL) and dioxane (0.33 mL). The reaction was complete after 2 days. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 9 : 1), to afford **72** (34 mg, 0.09 mmol, 31%) as a pale yellow oil; R_f 0.16 (petrol / EtOAc (9 : 1)); IR (thin film, $\nu_{\max}$ / cm^{-1}) 3078, 2839, 1639, 1606, 1505, 1466, 1333, 1265, 1156, 1035; ^1H NMR (500 MHz, CDCl_3) δ_{H} 6.82 (d, J = 8.1 Hz, 1H, H9), 6.79 (d, J = 2.0 Hz, 1H, H12), 6.70 (ddt, J = 8.1, 1.9, 0.6 Hz, 1H, H2), 6.49 (d, J = 1.9 Hz, 1H, 2), 6.27–6.24 (m, 1H, 26, H4), 5.98 (ddt, J = 16.8, 10.1, 6.7 Hz, 1H, H26), 5.92–5.80 (m, 1H, H23), 5.17 (s, 2H, H15), 5.14–5.00 (m, 4H, H24, H27), 3.86 (s, 3H, H19), 3.82 (s, 3H, H21), 3.57 (s, 3H, H17), 3.37 (dt, J = 6.8, 1.5 Hz, 2H, H22), 3.23 (dt, J = 6.6, 1.4 Hz, 2H, H25); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 153.7, 150.9, 150.7, 143.9, 137.5, 137.2, 136.2, 136.2, 134.5, 120.9, 119.7, 116.0, 116.0, 113.1, 111.2, 107.3, 98.5, 57.2, 56.1, 56.0, 40.2, 40.1; HRMS (ES $^{+}$) calc. for $\text{C}_{22}\text{H}_{27}\text{O}_5$ $[\text{M}+\text{H}]^{+}$ 371.1853, found 371.1850.

Dihydrodieugenol B, **1**

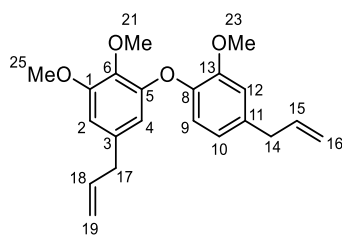
The product was prepared according to General Method C, using 5-allyl-1-(4-allyl-2-methoxyphenoxy)-3-methoxy-2-(methoxymethoxy)benzene, **72** (28 mg, 0.08 mmol, 1.0 eq), 2 M aqueous HCl (0.25 mL), and methanol (2.5 mL). The crude residue was purified *via* flash column chromatography (petrol / EtOAc (9 : 1 → 7 : 3) to give **1** (13 mg, 0.04 mmol, 52%) as a yellow oil; R_f 0.16 (petrol / EtOAc (9 : 1)); IR (thin film, $\nu_{\max}$ / cm^{-1}) 3078, 2839, 1639, 1505, 1466, 1333, 1265, 1233, 1213, 1035; ^1H NMR (500 MHz, CDCl_3) δ_{H} 6.82 (d, J = 8.1 Hz, 1H, H9), 6.79 (d, J = 2.0 Hz, 1H, H12), 6.70 (ddt, J = 8.1, 1.9, 0.6 Hz, 1H, H2), 6.49 (d, J = 1.9 Hz, 1H, 2), 6.27–6.24 (m, 1H, 26, H4), 5.98 (ddt, J = 16.8, 10.1, 6.7 Hz, 1H, H26), 5.92–5.80 (m, 1H, H23), 5.17 (s, 2H, H15), 5.14–5.00 (m, 4H, H24, H27), 3.86 (s, 3H, H19), 3.82 (s, 3H, H21), 3.57 (s, 3H, H17), 3.37 (dt, J = 6.8, 1.5 Hz, 2H, H22), 3.23 (dt, J = 6.6, 1.4 Hz, 2H, H25); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 153.7, 150.9, 150.7, 143.9, 137.5, 137.2, 136.2, 136.2, 134.5, 120.9, 119.7, 116.0, 116.0, 113.1, 111.2, 107.3, 98.5, 57.2, 56.1, 56.0, 40.2, 40.1; HRMS (ES⁺) calc. for $\text{C}_{22}\text{H}_{27}\text{O}_5$ $[\text{M}+\text{H}]^+$ 371.1853, found 371.1850. Experimental data are in good agreement with that described in the literature for the isolated natural product.⁹²

4-Allyl-2-iodo-6-methoxyphenol, 102

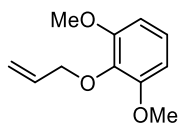
The product was prepared according to General Method C using 5-allyl-1-iodo-3-methoxy-2-(methoxymethoxy)benzene, **100** (1.3 g, 3.9 mmol, 1.0 eq), 1M aqueous HCl (10 mL) and MeOH (100 mL). The reaction was complete after 18 hours to afford **102** (987 mg, 3.4 mmol, 87% crude) as a pale yellow waxy solid, which was used without further purification. A sample was purified for analysis *via* flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 4 : 1) to afford a colourless wax; R_f 0.37 (petrol / EtOAc (4 : 1); IR (thin film, $\nu_{\max}$ / cm^{-1}); 3077, 2916, 2849, 1581, 1492, 1462, 1419, 1361, 1274, 1176, 1043; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.12 (s, 1H, H1), 6.65 (s, 1H, H3), 5.96 (s, 1H, H12), 5.95–5.84 (m, 1H, H8), 5.12–5.04 (m, 2H, H9), 3.87 (s, 3H, H10), 3.28 (d, J = 6.6 Hz, 2H, H7); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 145.9, 144.0, 137.1, 133.7, 130.1, 116.2, 111.3, 81.2, 56.2, 39.4; HRMS (ES-) calc. for $\text{C}_{10}\text{H}_{10}\text{IO}_2$ $[\text{M}-\text{H}]^-$ 288.9725, found 288.9715.

5-Allyl-1-iodo-2,3-dimethoxybenzene, 103

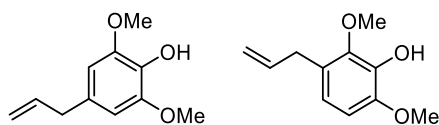
The product was prepared according to General Method F using 4-allyl-2-iodo-6-methoxyphenol, **102** (443 mg, 1.52 mmol, 1.0 eq), methyl iodide (133 μ L, 2.13 mmol, 1.4 eq), potassium carbonate (842 mg, 6.09 mmol, 4.0 eq), and DMF (2.2 mL). The crude residue was purified *via* flash column chromatography (petrol / Et₂O (19 : 1)) to afford **103** (309 mg, 1.0 mmol, 67%) as a colourless oil; *R*_f 0.51 (petrol / EtOAc (9 : 1)); IR (neat, ν_{max} / cm^{-1}) 2933, 1638, 1590, 1560, 1481, 1425, 1408, 1267, 1180, 1043; ¹H NMR (400 MHz, CDCl₃) δ_{H} 7.17 (d, *J* = 1.9 Hz, 1H, H1), 6.70 (d, *J* = 1.9 Hz, 1H, H3), 5.91 (ddt, *J* = 16.1, 10.9, 7.1 Hz, 1H, H12), 5.14–5.05 (m, 2H, H13), 3.84 (s, 3H, H10), 3.80 (s, 3H, H14), 3.29 (dt, *J* = 7.1, 1.6 Hz, 2H, H11); ¹³C NMR (101 MHz, CDCl₃) δ_{C} 152.5, 147.3, 138.2, 136.7, 130.2, 116.5, 113.3, 92.4, 60.5, 56.0, 39.5; HRMS (Methane CI) calc. for C₁₁H₁₄IO₂ [M+H]⁺ 305.0033, found 305.0033.

Methyldehydrodieugenol B, **2**

The product was prepared according to General Method D, using 5-allyl-1-iodo-2,3-dimethoxybenzene, **103** (152 mg, 0.5 mmol, 1.0 eq), eugenol (154 μ L, 1.0 mmol, 2.0 eq), copper(I) chloride (25 mg, 0.25 mmol, 0.5 eq), TMHD (52 μ L, 0.25 mmol, 0.5 eq), cesium carbonate (326 mg, 1.0 mmol, 2.0 eq), NMP (0.3 mL) and dioxane (0.6 mL). The reaction was complete after 3 days. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 9 : 1)), to afford **2** (99 mg, 0.29 mmol, 58%) as a colourless oil; R_f 0.24 (petrol / EtOAc (9 : 1)); IR (thin film, $\nu_{\max}$ / cm^{-1}) 2850, 2361, 1638, 1587, 1507, 1452, 1266, 1233, 1130, 1036; ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.85–6.78 (m, 2H, H9, H12), 6.69 (dd, J = 8.2, 1.9 Hz, 1H, H10), 6.48 (d, J = 1.9 Hz, 1H, H2), 6.27 (d, J = 1.9 Hz, 1H, H4), 6.04–5.82 (m, 2H, H15, H18), 5.15–4.97 (m, 4H, H16, H19), 3.87 (s, 6H, H25, H21), 3.83 (s, 3H, H23), 3.37 (d, J = 6.7 Hz, 2H, H14), 3.24 (d, J = 6.6 Hz, 2H, H17); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 153.6, 150.7, 144.3, 138.2, 137.5, 137.2, 136.1, 135.7, 120.9, 119.6, 116.0, 116.0, 113.2, 111.5, 107.4, 61.2, 56.2, 56.0, 40.2, 40.1; HRMS (ES $^{+}$) calc. for $\text{C}_{21}\text{H}_{24}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^{+}$ 363.1572, found 363.1572. Experimental data are in good agreement with that described in the literature for the isolated natural product.⁹²

2-(Allyloxy)-1,3-dimethoxybenzene, 108

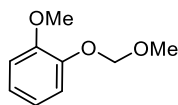
The product was prepared according to General Method M using 2,6-dimethoxyphenol (1.54 g, 10 mmol, 1.0 eq), allyl bromide (1.3 mL, 15 mmol, 1.5 eq), potassium carbonate (3.46 g, 25 mmol, 2.5 eq) and DMF (10 mL). The reaction was complete after three hours to afford on work-up **108** (1.93 g, 10 mmol, > 98%) as a yellow oil which was used without further purification; R_f 0.42 (petrol / EtOAc (9 : 1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.99 (t, J = 8.4 Hz, 1H), 6.58 (d, J = 8.4 Hz, 2H), 6.12 (ddt, J = 17.2, 10.3, 6.1 Hz, 1H), 5.30 (dq, J = 17.2, 1.6 Hz, 1H), 5.18 (ddt, J = 10.3, 2.0, 1.3 Hz, 1H), 4.52 (dt, J = 6.1, 1.3 Hz, 2H), 3.85 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 153.9, 136.9, 134.7, 123.8, 117.8, 105.4, 100.1, 74.3, 56.2; LRMS (ES^+) calc. for $\text{C}_{11}\text{H}_{15}\text{O}_3$ $[\text{M}+\text{H}]^+$ 195.0, found 195.0. Experimental data are in good agreement with that described in the literature.¹²⁸

4-Allyl-2,6-dimethoxyphenol, **109**, and 3-allyl-2,6-dimethoxyphenol, **110**

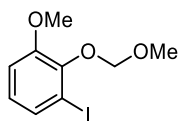
The product was prepared according to the literature produced described by Gawali *et al.*¹²⁹ **108** (194 mg, 1.0 mmol 1.0 eq) was heated to reflux in dry CH₃CN (3.2 mL) with bismuth triflate (66 mg, 0.1 mmol, 0.01 eq) for four hours. The reaction mixture was cooled to room temperature and filtered through a small pad of silica and washed with DCM. The filtrate was concentrated and purified *via* flash column chromatography (petrol / Et₂O (1 : 0 → 7 : 3)) to give **109** (61 mg, 0.314 mmol, 31%) as a pale yellow oil, and **110** (16.2 mg, 0.083 mmol, 8%) as a pale yellow oil.

109: *R_f* 0.20 (petrol / EtOAc (7 : 3)); ¹H NMR (400 MHz, CDCl₃) δ_H 6.41 (s, 2H), 5.95 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H), 5.39 (s, 1H), 5.14–5.02 (m, 2H), 3.87 (s, 6H), 3.32 (d, *J* = 6.7 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ_C 147.1, 137.7, 133.1, 131.2, 115.8, 105.2, 56.4, 40.5; LRMS (ES⁺) calc. for C₁₁H₁₄O₃Na [M+Na]⁺ 217.1, found 217.0. Experimental data are in good agreement with that described in the literature.¹²⁹

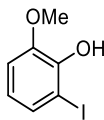
110: *R_f* 0.23 (petrol / EtOAc (9 : 1)); IR (thin film, ν_{max} / cm⁻¹) 3513, 2928, 2837, 2360, 2341, 1638, 1617, 1495, 1289, 1087; ¹H NMR (400 MHz, CDCl₃) δ_H 6.64 (dt, *J* = 8.4, 0.5 Hz, 1H, aromatic CH), 6.61 (d, *J* = 8.4 Hz, 1H, aromatic CH), 6.02–5.90 (m, 1H, CHCH₂), 5.54 (d, *J* = 1.8 Hz, 1H, OH), 5.09–5.00 (m, 2H, CHCH₂), 3.87 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 3.38–3.33 (m, 2H, ArCH₂CH); ¹³C NMR (101 MHz, CDCl₃) δ_C 146.4, 145.4, 138.8, 137.7, 126.3, 119.7, 115.5, 106.6, 60.8, 56.4, 33.8; HRMS (ES⁺) calc. for C₁₁H₁₄O₃Na [M+Na]⁺ 217.0835, found 217.0838.

1-Methoxy-2-(methoxymethoxy)benzene, 111

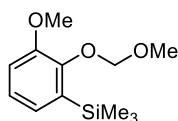
The product was prepared according to General Method A, using guaiacol (3.3 mL, 29.7 mmol, 1.0 eq), DIPEA (8.3 mL, 47.6 mmol, 1.6 eq), MOMCl (2.9 mL, 38.7 mmol, 1.3 eq), and DCM (35 mL) the reaction was complete after 18 hours to afford **111** (2.99g, 29.7 mmol, 99%) as a yellow oil, which was used without further purification; R_f 0.36 (petrol / EtOAc (9 : 1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.19–7.12 (m, 1H), 7.03–6.94 (m, 1H), 6.93–6.81 (m, 2H), 5.22 (s, 2H), 3.86 (s, 3H), 3.51 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 149.7, 146.5, 122.5, 120.9, 116.5, 111.8, 95.5, 56.1, 55.8. Experimental data are in good agreement with that described in the literature.¹⁰⁹

1-Iodo-3-methoxy-2-(methoxymethoxy)benzene, **112**

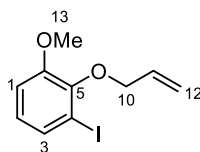
The product was prepared according to General Method B, using 1-methoxy-2-(methoxymethoxy)benzene, **111** (2.1 g, 10 mmol, 1.0 eq), ⁵Buli (1.3 M in hexanes, 12 mL, 15 mmol, 1.5 eq), TMEDA (2.3 mL, 15 mmol, 1.5 eq), iodine (3.8 g, 15 mmol, 1.5 eq) and THF (15 + 5 mL). The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 → 4 : 1)) to afford **112** (2.1 g, 7.1 mmol, 71%) as a colourless oil; ; *R_f* 0.54 (pentane / EtOAc (9 : 1)); ¹H NMR (400 MHz, CDCl₃) δ_H 7.37 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.88 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.79 (td, *J* = 8.2, 1.4 Hz, 1H), 5.17 (s, 2H), 3.83 (s, 3H), 3.68 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ_C 152.6, 146.0, 131.1, 126.0, 112.9, 98.8, 92.8, 58.5, 56.1; HRMS (APCI) calc. for C₉H₁₀O₃I [M-H]⁺ 292.9680, found 292.9673. The experimental data are in good agreement with that described in the literature.¹³⁰

2-Iodo-6-methoxyphenol, 113

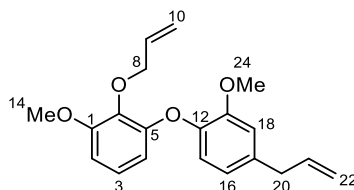
The product was prepared according to General Method C, using 1-iodo-3-methoxy-2-(methoxymethoxy)benzene, **112** (3.0 g, 10.2 mmol, 1.0 eq), 2M aqueous HCl (30 mL) and methanol (150 mL). The reaction was complete after 15 hours to afford on work up **113** (2.5 g, 10.1 mmol, 98%) as a white solid; MP 46 – 49 °C, Lit.¹³¹ 47 – 49 °C; R_f 0.41 (pentane / EtOAc (4 : 1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.28 (dd, $J = 8.1, 1.4$ Hz, 1H), 6.81 (dd, $J = 8.1, 1.4$ Hz, 1H), 6.62 (t, $J = 8.1, 1\text{H}$), 6.14 (s, 1H), 3.86 (d, $J = 1.4$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 146.2, 145.7, 130.6, 121.7, 110.7, 81.5, 56.3; HRMS (ES-) calc. for $\text{C}_7\text{H}_6\text{O}_2\text{I}$ $[\text{M}-\text{H}]^-$ 248.9418, found 248.9420. The experimental data are in good agreement with that described in the literature.¹³¹

(3-Methoxy-2-(methoxymethoxy)phenyl)trimethylsilane, 114

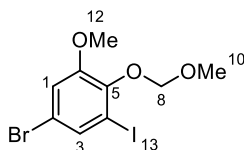
A solution containing 1-methoxy-2-(methoxymethoxy)benzene, **111** (1.7 g, 10 mmol, 1.0 eq) in anhydrous THF (20 mL) was cooled to $-78\text{ }^{\circ}\text{C}$ and n-butyllithium (2.5 M in hexanes, 6 mL, 15 mmol, 1.5 eq) was added dropwise. After stirring for 1 hour, the reaction was heated to $0\text{ }^{\circ}\text{C}$, and stirred for a further 1 hour, before being heated to room temperature. After 1 hour, the reaction was cooled to $-50\text{ }^{\circ}\text{C}$ and TMSCl (2.54 mL, 20 mmol, 2.0 eq) was added dropwise. The reaction was then allowed to warm to room temperature and was stirred overnight, after which time it was quenched with saturated aqueous NH_4Cl (20 mL). The organic layer was removed, and the aqueous layer extracted with diethyl ether ($3 \times 20\text{ mL}$). The organic layers were combined and washed with water (50 mL) and brine (50 mL), then dried over MgSO_4 , filtered, and the solvent removed *in vacuo* to afford **114** (2.19 g, 9.12 mmol, 91% (crude)) as a yellow oil which was used without further purification. A sample was purified for analysis via flash column chromatography (petrol / Et_2O (1 : 0 $\rightarrow$ 9 : 1)) to afford a colourless oil; R_f 0.43 (petrol / Et_2O (9 : 1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.08 (t, $J = 7.8\text{ Hz}$, 1H), 7.02 (d, $J = 7.8\text{ Hz}$, 1H), 6.96 (d, $J = 7.8\text{ Hz}$, 1H), 5.17 (s, 2H), 3.85 (s, 3H), 3.62 (s, 3H), 0.34 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 151.3, 150.4, 133.5, 126.7, 124.1, 114.0, 98.7, 57.7, 55.7, -0.3; LRMS (ES $^-$) calc. for $\text{C}_{14}\text{H}_{14}\text{O}_3\text{Na}$ $[\text{M}-\text{H}]^-$ $\text{C}_{12}\text{H}_{19}\text{O}_3\text{Si}$ 239.1, found 239.0. Experimental data are in good agreement with that reported in the literature.¹⁰⁹

2-(Allyloxy)-1-iodo-3-methoxybenzene, 115

The product was prepared according to General Method M, using 2-iodo-6-methoxyphenol, **113** (100 mg, 0.4 mmol, 1.0 eq), potassium carbonate (138 mg, 1.0 mmol, 2.5 eq), allyl bromide (52 μ L, 0.6 mmol, 1.5 eq), and DMF (0.4 mL). The reaction was complete after three hours. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 19 : 1)) to afford **115** (60 mg, 0.2 mmol, 52%) as a colourless oil; R_f 0.44 (petrol / EtOAc (9 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2937, 1578, 1467, 1445, 1433, 1419, 1355, 1292, 1259, 1221, 1176, 1142, 1078, 1029; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.35 (dt, J = 7.9, 1.1 Hz, 1H, H1), 6.88 (dd, J = 8.2, 1.1 Hz, 1H, H3), 6.79 (t, J = 8.2 Hz, 1H, H2), 6.25–6.10 (m, 1H, H11), 5.41 (dq, J = 17.1, 1.3 Hz, 1H, H12), 5.31–5.20 (m, 1H, H12), 4.52 (dt, J = 5.7, 1.3 Hz, 2H, H10), 3.84 (s, 3H, H13); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 153.0, 147.9, 134.0, 130.7, 126.0, 118.2, 112.8, 93.3, 74.0, 56.1; HRMS (Methane CI) calc. for $\text{C}_{10}\text{H}_{12}\text{IO}_2$ $[\text{M}+\text{H}]^+$ 290.9876, found 290.9864.

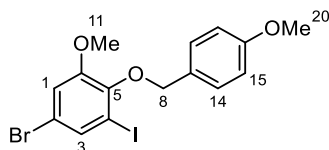
1-(4-Allyl-2-methoxyphenoxy)-2-(allyloxy)-3-methoxybenzene, 69

The product was prepared according to General Method D, using 2-(allyloxy)-1-iodo-3-methoxybenzene, **115** (1.00 g, 3.45 mmol, 1.0 eq), eugenol (1.06 mL, 6.89 mmol, 2.0 eq), copper(I) chloride (171 mg, 1.72 mmol, 0.5 eq), TMHD (360 μ L, 1.72 mmol, 0.5 eq), cesium carbonate (2.25 g, 6.89 mmol, 2.0 eq), NMP (2.0 mL), and dioxane (4.0 mL). The reaction was complete after 3 days. The crude residue was purified via flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 9 : 1), to afford **69** (635 mg, 1.95 mmol, 52%) as a colourless oil; R_f 0.29 (petrol / EtOAc (9 : 1)); IR (thin film, $\nu_{\max}$ / cm^{-1}) 2936, 2361, 1594, 1507, 1491, 1471, 1439, 1419, 1265, 1244, 1211, 1153, 1128, 1083, 1035; ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.90 (t, J = 8.3 Hz, 1H, H3), 6.82 (d, J = 8.1 Hz, 1H, H15), 6.80 (d, J = 1.9 Hz, 1H, H18), 6.70 (dd, J = 8.1, 1.9 Hz, 1H, H16), 6.65 (dd, J = 8.3, 1.4 Hz, 1H, H4), 6.42 (dd, J = 8.3, 1.4 Hz, 1H, H2), 6.07 (ddt, J = 17.2, 10.4, 6.0 Hz, 1H, H9), 5.97 (ddt, J = 16.8, 10.1, 6.7 Hz, 1H, H21), 5.26 (dq, J = 17.2, 1.6 Hz, 1H, H10), 5.16–5.05 (m, 3H, H10, H22), 4.60 (dt, J = 6.1, 1.3 Hz, 2H, H8), 3.87 (s, 3H, H14), 3.82 (s, 3H, H24), 3.37 (dt, J = 6.7, 1.4 Hz, 2H, H20); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 154.2, 151.5, 150.8, 144.1, 138.5, 137.5, 136.3, 134.7, 123.5, 120.9, 119.9, 117.6, 116.0, 113.2, 111.2, 107.0, 74.4, 56.3, 56.1, 40.1; HRMS (ES⁺) calc. for $\text{C}_{20}\text{H}_{23}\text{O}_4$ $[\text{M}+\text{H}]^+$ 327.1591, found 327.1589.

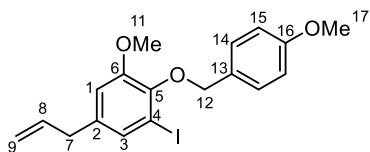
5-Bromo-1-iodo-3-methoxy-2-(methoxymethoxy)benzene, 128

To a solution of 4-bromo-2-methoxyphenol **126** (2.03 g, 10.0 mmol, 1.00 eq.) in aqueous ammonia (70 mL) was added a solution of iodine (2.54 g, 10.0 mmol, 1.00 eq.) and potassium iodide (4.98 g, 30.0 mmol, 3.00 eq.) in water (17 mL). The resulting mixture was heated to 40 °C and stirred overnight. After this time, the reaction was acidified to pH 7 using 5M HCl solution. The product was then extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with 10% aqueous Na₂S₂O₃ solution (200 mL) and brine (200 mL). The organic layer was dried over MgSO₄, filtered, and the solvent removed *in vacuo*. The crude residue was filtered through a short pad of silica (petrol / EtOAc (4 : 1)) to afford 4-bromo-1-iodo-6-methoxyphenol, **127** (2.00 g, 6.08 mmol, 61% crude) which was used without further purification.

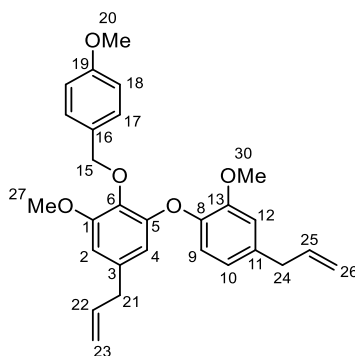
The product was then synthesised according to General Method A using crude 4-bromo-1-iodo-6-methoxyphenol, **127** (1.00 g, 3.04 mmol, 1.00 eq), MOMCl (0.300 mL, 3.95 mmol, 1.30 eq), DIPEA (0.850 mL, 4.86 mmol, 1.60 eq.) and DCM (3.6 mL). The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 → 19 : 1)) to afford **128** (959 mg, 2.57 mmol, 85%) as a colourless oil; *R*_f 0.33 (petrol / EtOAc (9 : 1)); IR (neat, *v*_{max} / cm⁻¹) 2936, 1568, 1460, 1435, 1389, 1282, 1252, 1228, 1204, 1155, 1075, 1028; ¹H NMR (400 MHz, CDCl₃) δ_H 7.50 (d, *J* = 2.2 Hz, 1H, H1), 7.00 (d, *J* = 2.2 Hz, 1H, H3), 5.14 (s, 2H, H8), 3.82 (s, 3H, H12), 3.65 (s, 3H, H10); ¹³C NMR (100 MHz, CDCl₃) δ_C 152.6, 145.5, 132.9, 117.6, 116.3, 98.8, 93.1, 58.6, 56.3; HRMS (APCI) calc. for C₉H₁₁O₃Br¹²⁷I [M+H]⁺ 372.8931, found 372.8932.

5-Bromo-1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, 130

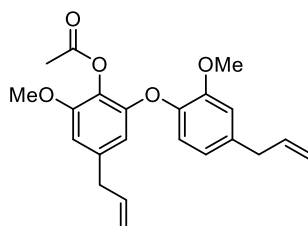
The product was prepared according to General Method I using crude 4-bromo-1-iodo-6-methoxyphenol, **127** (1.00 g, 3.04 mmol, 1.00 eq), potassium carbonate (462 mg, 3.34 mmol, 1.10 eq) PMBCl (453 μ L, 3.34 mmol, 1.10 eq) and DMF (15 mL). The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 19 : 1)) to afford **130** (762 mg, 1.70 mmol, 56%) as a colourless crystalline solid; MP 69 — 72 $^{\circ}$ C; R_f 0.31 (petrol / EtOAc (9 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2931, 2830, 1587, 1513, 1462, 1390, 1377, 1285, 1247, 1218, 1169, 1109, 1031; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.49 (d, J = 2.1 Hz, 1H, H1), 7.48 – 7.44 (m, 2H, H15), 7.01 (d, J = 2.1 Hz, 1H, H3), 6.93 – 6.88 (m, 2H, H14), 4.93 (s, 2H, H8), 3.85 (s, 3H, H20), 3.82 (s, 3H, H11); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 159.8, 153.2, 147.3, 132.6, 130.6, 129.0, 117.5, 116.3, 113.8, 93.6, 74.5, 56.4, 55.4; HRMS (APCI) calc. for $\text{C}_{15}\text{H}_{13}\text{O}_3\text{Br}^{127}\text{I} [\text{M}]^+$ 446.9087, found 446.9090.

5-Allyl-1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, 134

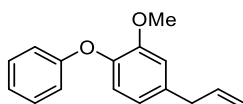
The product was prepared according to General Method I, using 4-allyl-2-iodo-6-methoxyphenol, **102** (500 mg, 1.72 mmol, 1.00 eq), *para*-methoxybenzyl chloride (280 μ L, 2.07 mmol, 1.20 eq), potassium carbonate (596 mg, 4.31, mmol, 2.5 eq) and DMF (13 mL). The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 19 : 1)) to afford **134** (570mg, 1.39 mmol, 81%) as a colourless oil; R_f 0.53 (petrol / EtOAc (9 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2934, 2835, 1638, 1612, 1513, 1461, 1409, 1372, 1266, 1248, 1227, 1173, 1141, 1039; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.50 (d, J = 8.3 Hz, 2H, H14), 7.19 (d, J = 1.9 Hz, 1H, H1), 6.94 – 6.89 (m, 2H, H15), 6.71 (d, J = 1.7 Hz, 1H, H3), 5.93 (dddd, J = 19.1, 9.6, 7.4, 6.2 Hz, 1H, H8), 5.14 – 5.07 (m, 2H, H9), 4.91 (s, 2H, H12), 3.85 (s, 3H, H17), 3.82 (s, 3H, H11), 3.31 (d, J = 6.7 Hz, 2H, H7); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 159.6, 152.7, 146.2, 138.2, 136.8, 130.5, 130.4, 129.5, 116.6, 113.8, 113.4, 93.2, 74.4, 56.1, 55.4, 39.6; HRMS (APCI) calc. for $\text{C}_{18}\text{H}_{20}\text{IO}_3$ $[\text{M}+\text{H}]^+$ 411.0452, found 446.0450.

5-Allyl-1-(4-allyl-2-methoxyphenoxy)-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, **135**

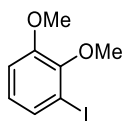
The product was prepared according to General Method D, 5-allyl-1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, **134** (1.23 g, 3.0 mmol, 1.0 eq), eugenol (921 μL , 6.0 mmol, 2.0 eq), copper(I) chloride (148 mg, 1.5 mmol, 0.5 eq), TMHD (312 μL , 1.5 mmol, 0.5 eq), cesium carbonate (1.95 mg, 6.0 mmol, 2.0 eq), NMP (2.0 mL) and dioxane (4.0 mL). The reaction was complete after 3 days. The crude residue was purified *via* flash column chromatography (petrol : EtOAc (1 : 0 $\rightarrow$ 4 : 1)), to afford **135** (765 mg, 1.78 mmol, 59%) as a pale yellow oil; R_f 0.21 (petrol / EtOAc (9 : 1)); IR (neat, ν_{max} / cm^{-1}) 3002, 2837, 1610, 1506, 1462, 1374, 1231, 1151, 1090, 1034; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.34 – 7.26 (m, 2H, H18), 6.84 – 6.77 (m, 3H, H9, H17), 6.74 (dd, J = 8.1, 1.6 Hz, 1H, H10), 6.67 (s, 1H, H12), 6.48 (d, J = 1.9 Hz, 1H, H2), 6.31 (d, J = 1.8 Hz, 1H, H4), 6.07 – 5.81 (m, 2H, H22, H25), 5.15 – 4.99 (m, 4H, H23, H26), 4.97 (s, 2H, H15), 3.82 (m, 6H, H20, H28), 3.78 (d, J = 1.6 Hz, 3H, H27), 3.37 (d, J = 6.8 Hz, 2H, H21), 3.24 (d, J = 6.6 Hz, 2H, H24); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 159.3, 154.0, 150.8, 150.5, 144.5, 137.6, 137.3, 137.1, 135.8, 135.8, 130.3, 130.2, 120.9, 119.2, 116.0, 116.0, 113.5, 113.1, 111.8, 107.7, 74.8, 56.2, 56.1, 55.4, 40.2, 40.1; HRMS (APCI) calc. for $\text{C}_{28}\text{H}_{31}\text{O}_5$ $[\text{M}+\text{H}]^+$ 447.2166, found 447.2164.

4-Allyl-2-(4-allyl-2-methoxyphenoxy)-6-methoxyphenyl acetate, 5

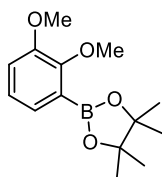
The product was prepared according to General Method L, using dehydrodieugenol B, **1** (262 mg, 0.800 mmol, 1.00 eq), pyridine (1.50 mL, 18.5 mmol, 23.0 eq) and added acetic anhydride (569 μ L, 6.02 mmol, 7.50 eq). The crude residue was purified via flash column chromatography (pentane / EtOAc (4 : 1)), to afford **5** (248 mg, 0.673 mmol, 84%) as a pale yellow oil; R_f 0.17 (petrol / EtOAc (9 : 1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.87 (d, J = 8.1 Hz, 1H), 6.79 (d, J = 2.0 Hz, 1H), 6.74 – 6.67 (m, 1H), 6.50 (d, J = 1.8 Hz, 1H), 6.27 (d, J = 1.8 Hz, 1H), 6.04 – 5.93 (m, 1H), 5.93 – 5.81 (m, 1H), 5.15 – 5.00 (m, 4H), 3.83 (s, 3H), 3.82 (s, 3H), 3.37 (dt, J = 6.7, 1.5 Hz, 2H), 3.26 (dt, J = 6.7, 1.4 Hz, 2H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 168.8, 152.5, 151.1, 150.4, 143.7, 138.5, 137.4, 136.9, 136.9, 128.7, 121.1, 120.7, 116.3, 116.1, 113.3, 110.7, 106.9, 56.3, 56.2, 40.4, 40.1, 20.6; LRMS (ES⁺) calc. for $\text{C}_{22}\text{H}_{24}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 391.2, found 391.2. The experimental data are in good agreement with that described in the literature.⁹⁴

4-Allyl-2-methoxy-1-phenoxybenzene, 136

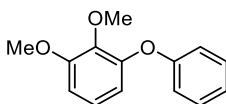
The product was prepared according to General Method G, using eugenol (154 μ L, 1.0 mmol, 1.0 eq), DCM (7.5 mL), 4 Å molecular sieves, copper(II) acetate (182 mg, 1.0 mmol, 1.0 eq), triethylamine (697 μ L, 5.0 mmol, 5.0 eq), and phenylboronic acid (244 mg, 2.0 mmol, 2.0 eq). The reaction was complete after 24 hours. The crude residue was purified *via* flash column chromatography (petrol / Et₂O (9 : 1)) to afford **136** (240 mg, 1.0 mmol, > 98%) as a colourless oil; *R_f* 0.42 (petrol / EtOAc (19 : 1)); ¹H NMR (400 MHz, CDCl₃) δ_{H} 7.31–7.23 (m, 2H), 7.02 (ddt, *J* = 8.5, 7.4, 1.1 Hz, 1H), 6.96–6.91 (m, 2H), 6.90 (s, 1H), 6.83 (d, *J* = 1.9 Hz, 1H), 6.75 (ddd, *J* = 8.1, 2.0, 0.8 Hz, 1H), 5.99 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1H), 5.19–5.05 (m, 2H), 3.82 (s, 3H), 3.39 (dd, *J* = 6.7, 1.6 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ_{C} 158.3, 151.5, 143.2, 137.4, 137.1, 129.6, 122.4, 121.3, 121.1, 117.1, 116.2, 113.2, 56.1, 40.2; HRMS (ES⁺) calc. for C₁₆H₁₆O₂Na [M+Na]⁺ 263.1043, found 263.1044. Experimental data are in good agreement with that described in the literature.¹³²

1-Iodo-2,3-dimethoxybenzene, 197

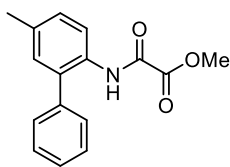
The product was prepared according to General Method F using 2-iodo-6-methoxyphenol, **113** (300 mg, 1.2 mmol, 1.0 eq), methyl iodide (105 μ L, 1.7 mmol, 1.4 eq), potassium carbonate (663 mg, 4.8 mmol, 4.0 eq) and DMF (1.75 mL). The reaction was complete after 20 hours to afford on work up **197** (296 mg, 1.1 mmol, 93%) as a colourless wax; R_f 0.49 (pentane / diethyl ether (4 : 1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.34 (dd, $J = 7.9, 1.5$ Hz, 1H), 6.88 (dd, $J = 8.2, 1.5$ Hz, 1H), 6.79 (t, $J = 8.1$ Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 153.0, 149.1, 130.6, 126.0, 112.9, 92.7, 60.5, 56.0; HRMS (EI) calc. for $\text{C}_8\text{H}_9\text{O}_2\text{I}$ $[\text{M}]^+$ 263.9642, found 263.9643. The experimental data are in good agreement with that described in the literature.¹³³

2-(2,3-Dimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, S1

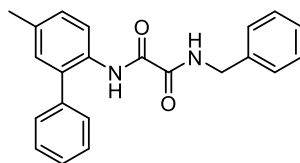
To a solution of 1-iodo-2,3-dimethoxybenzene, **197** (264 mg, 1.0 mmol, 1.0 eq) in anhydrous acetonitrile (3 mL) was added $\text{PdCl}_2(\text{dppf})_2$ (30 mg, 0.04 mmol, 4 mol%), and trimethylamine (892 μL , 6.4 mmol, 6.4 eq) at room temperature, followed by dropwise addition of pinacol borane (435 μL , 3.0 mmol, 3.0 eq). The reaction was heated to reflux, and stirred for 24 hours, after which time it was cooled to room temperature and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (10 mL) and washed with water (10 mL). The organic phase was dried over MgSO_4 , filtered, and the solvent removed *in vacuo*. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (9 : 1)) to afford **S1** (214 mg, 0.81 mmol, 81%) as a white solid; MP 37 – 40 °C; R_f 0.37 (petrol / EtOAc (4 : 1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.26 – 7.23 (m, 1H), 7.05 (dd, J = 8.0, 7.3 Hz, 1H), 7.00 (dd, J = 8.1, 1.8 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 1.35 (s, 12H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 154.6, 152.7, 127.7, 124.1, 115.8, 83.7, 61.9, 56.2, 25.0; HRMS (APCI) calc. for $\text{C}_{14}\text{H}_{22}\text{O}_4\text{B}$ $[\text{M}+\text{H}]^+$ 265.1606, found 265.1606. The experimental data are in good agreement with that reported in the literature.¹³⁴

1,2-Dimethoxy-3-phenoxybenzene, 138

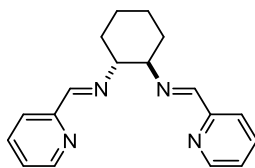
The product was prepared according to General Method G using 2,3-dimethoxyphenol (130 μ L, 1.0 mmol, 1.0 eq), DCM (7.5 mL), 4Å molecular sieves, copper(II) acetate (182 mg, 1.0 mmol, 1.0 eq), triethylamine (697 μ L, 5.0 mmol, 5.0 eq.), and phenylboronic acid (244 mg, 2.0 mmol, 2.0 eq). The reaction was complete after 30 hours. The crude residue was purified *via* flash column chromatography (petrol / Et₂O (9 : 1)) to afford **138** (142 mg, 0.61 mmol, 61%) as a colourless oil; *R_f* 0.29 (petrol / Et₂O (9 : 1)); ¹H NMR (400 MHz, CDCl₃) δ_{H} 7.34–7.27 (m, 2H), 7.06 (td, *J* = 7.3, 1.1 Hz, 1H), 7.02–6.93 (m, 3H), 6.73 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.60 (dd, *J* = 8.3, 1.5 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ_{C} 157.9, 154.2, 149.9, 141.2, 129.7, 123.7, 122.8, 117.6, 113.6, 108.0, 61.2, 56.3; LRMS (ES⁺) calc. for C₁₄H₁₄O₃Na [M+Na]⁺ 253.1, found 253.0. Experimental data are in good agreement with that described in the literature.¹³⁵

Methyl 2-((5-methyl-[1,1'-biphenyl]-2-yl)amino)-2-oxoacetate, S2

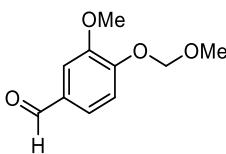
To a solution of 5-methyl-[1,1'-biphenyl]-2-amine (96% pure, 333 mg, 1.744 mmol, 1.0 eq) in anhydrous THF (8.7 mL) was added triethylamine (292 μ L, 2.093 mmol, 1.2 eq). The resulting mixture was cooled to 0 $^{\circ}$ C before dropwise addition of methyloxalyl chloride (177 μ L, 1.919 mmol, 1.1 eq). The reaction was warmed to room temperature and stirred for one hour, after which time the reaction was filtered to remove the resulting solid, and the filter cake washed with THF. The solvent was removed *in vacuo*, and the crude residue was purified by recrystallisation from methanol, to afford **S2** (313 mg, 1.162 mmol, 67%) as a colourless crystalline solid; MP 120 – 123 $^{\circ}$ C (MeOH); R_f 0.19 (petrol / EtOAc (4 : 1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 9.01 (s, 1H), 8.32 (d, J = 8.3 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.47 – 7.41 (m, 1H), 7.40 – 7.35 (m, 2H), 7.22 (ddt, J = 8.4, 2.1, 0.7 Hz, 1H), 7.14 – 7.11 (m, 1H), 3.87 (s, 3H), 2.38 (d, J = 0.8 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 161.5, 153.4, 137.5, 135.3, 132.8, 130.9, 129.3, 128.4, 120.7, 54.0, 21.1; LRMS (ES-) calc for $\text{C}_{16}\text{H}_{14}\text{NO}_3$ $[\text{M}-\text{H}]^-$ 268.1, found 268.1. Experimental data are in good agreement with that described in the literature.¹⁰⁴

N*¹-Benzyl-*N*²-(5-methyl-[1,1'-biphenyl]-2-yl)oxalamide, **84*

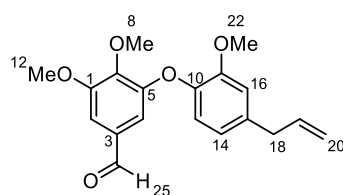
To a solution of methyl 2-((5-methyl-[1,1'-biphenyl]-2-yl)amino)-2-oxoacetate, **S2** (311 mg, 1.153 mmol, 1.0 eq) in THF (1.2 mL) was added benzylamine (152 μ L, 1.384 mmol, 1.2 eq), and the reaction heated to 70 °C and stirred for one hour. After this time, the reaction was cooled to room temperature, then placed in a freezer, and the resulting solid obtained by filtration, affording **84** (398 mg, 1.15 mmol, >99%) as a colourless crystalline solid; MP 139 – 141 °C (THF); *R*_f 0.32 (petrol / EtOAc (4 : 1)); ¹H NMR (400 MHz, CDCl₃) δ _H 9.39 (s, 1H), 8.21 (d, *J* = 8.3 Hz, 1H), 7.79 (t, *J* = 6.2 Hz, 1H), 7.49 – 7.02 (m, 13H), 4.39 (d, *J* = 6.1 Hz, 2H), 2.29 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ _C 160.0, 157.2, 137.5, 136.8, 135.1, 133.0, 131.1, 131.0, 129.3, 129.2, 129.1, 128.9, 128.4, 128.0, 127.9, 120.4, 44.0, 21.1; HRMS (ES⁺) calc. for C₂₂H₂₁O₂N₂ [M+H]⁺ 345.1598, found 345.1587. Experimental data are in good agreement with that described in the literature.¹⁰⁴

***Trans*-1,2-bis(2'-pyridylidenamino)-cyclohexane (Chxn-Py-Al), 140**

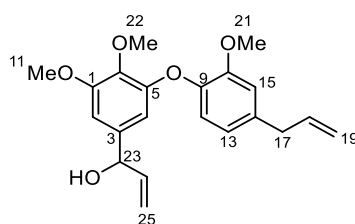
To a solution of 2-pyridylaldehyde (6.66 mL, 70.0 mmol, 2.0 eq.) in ethanol (50 mL) were successively added anhydrous magnesium sulphate (12.65 g, 105.1 mmol, 3.0 eq) and rac-*trans*-1,2-diaminocyclohexane (4.2 mL, 35.0 mmol, 1.0 eq). The mixture was stirred for 20 hours at room temperature, then heated at reflux for two hours and 30 minutes, and filtered through a frit while still hot. The solid was discarded and the filtrate was concentrated *in vacuo*. The residue was recrystallized from ethanol to give **140** (5.8 g, 19.8 mmol, 56%) as an off-white crystalline solid; MP 131 – 134 °C (EtOH), Lit.¹¹³ 140 – 141 °C; R_f 0.50 (EtOAc); ^1H NMR (400 MHz, CDCl_3) δ_{H} 8.51 (ddd, $J = 4.8, 1.8, 0.9$ Hz, 2H), 8.29 (s, 2H), 7.85 (dt, $J = 7.8, 1.1$ Hz, 2H), 7.63 – 7.58 (m, 2H), 7.18 (ddd, $J = 7.5, 4.9, 1.3$ Hz, 2H), 3.58 – 3.43 (m, 2H), 1.94 – 1.70 (m, 6H), 1.58 – 1.38 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 161.4, 154.6, 149.2, 136.4, 124.5, 121.3, 73.5, 32.7, 24.3; LRMS (ES⁺) calc. for $\text{C}_{18}\text{H}_{21}\text{N}_4$ $[\text{M}+\text{H}]^+$ 293.2, found 293.1. Experimental data are in good agreement with that reported in the literature.¹¹³

3-Methoxy-4-(methoxymethoxy)benzaldehyde, 151

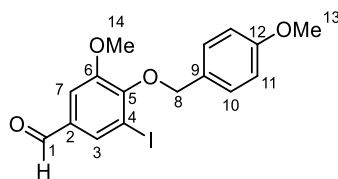
The product was prepared according to General Method A, using vanillin (776 mg, 5.10 mmol, 1.0 eq), DIPEA (1.42 mL, 6.63 mmol, 1.3 eq), MOMCl (503 μ L, 8.16 mmol, 1.5 eq) and DCM (6.4 mL). The reaction was complete after 18 hours to afford on work up **151** (0.99 g, 5.05 mmol, 99%) as an off-white solid which was used without further purification; MP 34 – 37 °C, Lit.¹²⁷ 40 °C; R_f 0.17 (petrol / EtOAc (4 : 1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 9.73 (s, 1H), 7.36-7.27 (m, 2H), 7.19-7.10 (m, 1H), 5.21 (s, 2H), 3.82 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 190.7, 151.8, 149.9, 130.9, 126.1, 114.5, 109.3, 94.8, 56.3, 55.8; HRMS (APCI) calc. for $\text{C}_{10}\text{H}_{13}\text{O}_4$ $[\text{M}+\text{H}]^+$ 197.0808, found 197.0808. The experimental data are in good agreement with that described in the literature.¹⁰⁹

3-(4-Allyl-2-methoxyphenoxy)-4,5-dimethoxybenzaldehyde, 153

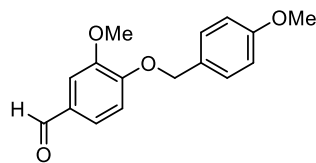
The product was prepared according to General Method D, using 3-iodo-4,5-dimethoxybenzaldehyde, **152** (146 mg, 0.5 mmol, 1.0 eq), eugenol (154 μ L, 1.0 mmol, 2.0 eq), copper(I) chloride (25 mg, 0.25 mmol, 0.5 eq), TMHD (52 μ L, 0.25 mmol, 0.5 eq), cesium carbonate (326 mg, 1.0 mmol, 2.0 eq), NMP (0.3 mL) and dioxane (0.6 mL). The reaction was complete after 24 hours. The crude residue was purified *via* flash column chromatography (petrol / Et₂O (1 : 1 $\rightarrow$ 3 : 7), to afford **153** (44 mg, 0.13 mmol, 27%) as a white solid; MP 59 – 62 °C; *R_f* 0.28 (petrol / Et₂O (1 : 1)); IR (thin film, ν_{max} / cm^{-1}) 2938, 2361, 1693, 1585, 1506, 1455, 1327, 1267, 1152, 1091; ¹H NMR (400 MHz, CDCl₃) δ_{H} 9.72 (s, 1H, H₂₅), 7.18 (d, *J* = 1.8 Hz, 1H, H₂), 6.91 (d, *J* = 8.1 Hz, 1H, H₁₃), 6.87 (d, *J* = 1.8 Hz, 1H, H₄), 6.83 (d, *J* = 1.3 Hz, 1H, H₁₆), 6.76 (dt, *J* = 8.1, 1.3 Hz, 1H, H₁₄), 5.99 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H, H₁₉), 5.18–5.03 (m, 2H, H₂₀), 4.03 (s, 3H, H₈), 3.95 (s, 3H, H₁₂), 3.79 (s, 3H, H₂₂), 3.40 (d, *J* = 6.7, Hz, 2H, H₁₈); ¹³C NMR (101 MHz, CDCl₃) δ_{C} 191.0, 154.2, 151.8, 151.1, 144.8, 142.7, 137.7, 137.3, 131.6, 121.1, 121.0, 116.3, 113.4, 113.3, 106.1, 61.3, 56.5, 56.0, 40.2; HRMS (ES⁺) calc. for C₁₉H₂₁O₅ [M+H]⁺ 329.1389, found 329.1393.

(±)-1-(3-(4-Allyl-2-methoxyphenoxy)-4,5-dimethoxyphenyl)prop-2-en-1-ol, 4

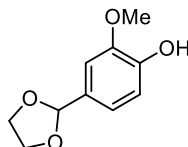
The product was prepared according to General Method H, using 3-(4-allyl-2-methoxyphenoxy)-4,5-dimethoxybenzaldehyde, **153** (24 mg, 0.073 mmol, 1.0 eq), diethyl ether (0.3 mL), and vinylmagnesium bromide (1M in THF, 146 μ L, 0.15 mmol, 2.0 eq). The crude residue was purified *via* flash column chromatography (petrol / EtOAc (7 : 3)), to afford **4** (25 mg, 0.071 mmol, 97%) as a pale yellow oil; R_f 0.16 (petrol / EtOAc (7 : 3)); IR (thin film, $\nu_{\max}$ / cm^{-1}) 3468, 2920, 2851, 2361, 2342, 1638, 1589, 1507, 1463, 1421, 1326, 1266, 1214, 1152, 1130, 1092, 1034; ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.83–6.78 (m, 2H, H12, H15), 6.72–6.67 (m, 2H, H2, H4), 6.44 (dd, J = 2.0, 0.6 Hz, 1H, H13), 6.05–5.90 (m, 2H, H18, H24), 5.28 (dt, J = 17.1, 1.4 Hz, 1H, H23), 5.17–5.02 (m, 4H, H19, H26), 3.89 (s, 3H, H11), 3.88 (s, 3H, H22), 3.82 (s, 3H, H21), 3.39–3.35 (m, 2H, H17); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 153.7, 150.9, 150.7, 143.9, 137.5, 137.2, 136.2, 136.2, 134.5, 120.9, 119.7, 116.0, 116.0, 113.1, 111.2, 107.3, 98.5, 57.2, 56.1, 56.0, 40.2, 40.1; HRMS (ES⁺) calc. for $\text{C}_{21}\text{H}_{25}\text{O}_5$ $[\text{M}+\text{H}]^+$ 357.1697, found 357.1770.

3-Iodo-5-methoxy-4-((4-methoxybenzyl)oxy)benzaldehyde, 156

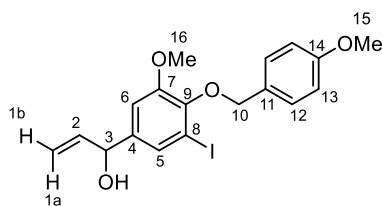
The product was prepared according to General Method I, using 5-iodovanillin (556 mg, 2.0 mmol, 1.0 eq), DMF (15 mL), potassium carbonate (691 mg, 5.0 mmol, 2.5 eq), and PMBCl (325 μ L, 2.4 mmol, 1.2 eq). The crude residue was purified *via* flash column chromatography (pentane / EtOAc (9 : 1)) to afford **156** (760 mg, 1.9 mmol, 95%) as a white solid; MP 59 – 62 °C (pentane); R_f 0.17 (pentane / EtOAc (9 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2935, 2732, 1691, 1612, 1513, 1412, 1458, 1241, 1137, 1033; ^1H NMR (CDCl_3 , 400 MHz) δ_{H} 9.80 (s, 1H, 1H), 7.82 (d, J = 1.8 Hz, 1H, H3), 7.50 – 7.42 (m, 2H, H10), 7.40 (d, J = 1.8 Hz, 1H, H7), 6.92 – 6.87 (m, 2H, H11), 5.08 (s, 2H, H8), 3.93 (s, 3H, H13), 3.80 (s, 3H, H14); ^{13}C NMR (CDCl_3 , 101 MHz) δ_{C} 189.2, 159.8, 153.1, 152.9, 134.9, 133.9, 130.6, 128.6, 113.8, 111.0, 93.1, 74.6, 56.2, 55.3; HRMS (APCI) calc. for $\text{C}_{16}\text{H}_{16}\text{O}_4\text{I}$ $[\text{M}+\text{H}]^+$ 399.0088, found 399.0084.

3-Methoxy-4-((4-methoxybenzyl)oxy)benzaldehyde, 158

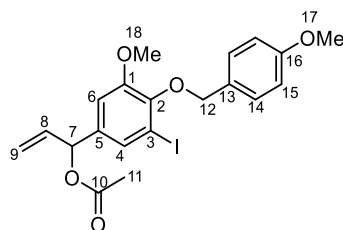
The product was prepared according to General Method I, using vanillin (1.52 g, 10.0 mmol, 1.0 eq), PMBCl (1.90 mL, 12.0 mmol, 1.2 eq), potassium carbonate (3.50 g, 25.0 mmol, 2.5 eq) and DMF (75 mL). The reaction was complete after 90 minutes, and the crude residue was purified by recrystallisation from ethanol to afford **158** (2.28 g, 8.4 mmol, 84 %) as a white crystalline solid; MP 107 – 110 °C (EtOH), Lit.¹³⁶ 100 – 102 °C ; R_f 0.14 (pentane / EtOAc (9 : 1)); ^1H NMR (CDCl_3 , 400 MHz) δ_{H} 9.75 (s, 1H), 7.35 – 7.24 (m, 4H), 6.92 (d, J = 8.1 Hz, 1H), 6.86 – 6.77 (m, 2H), 5.08 (s, 2H), 3.84 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (CDCl_3 , 101 MHz) 191.1, 159.7, 153.8, 150.2, 130.3, 129.2, 128.1, 126.8, 114.2, 112.5, 109.3, 70.8, 56.2, 55.4; HRMS (ES⁺) calc. for $\text{C}_{16}\text{H}_{16}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 295.0941, found 295.0940. The experimental data are in good agreement with that described in the literature.¹³⁶

4-(1,3-Dioxolan-2-yl)-2-methoxyphenol, S3

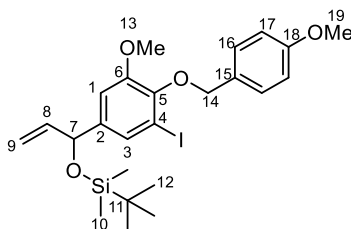
3-Methoxy-4-(methoxymethoxy)benzaldehyde, **151** (408 mg, 2.08 mmol, 1.0 eq), PPTS (12 mg, 0.06 mmol, 0.03 eq) and ethanediol (290 μ L, 5.20 mmol, 2.5 eq) were dissolved in toluene (12 mL) and the reaction heated to reflux and stirred overnight. The reaction was then cooled to room temperature and added dropwise to 2 M aqueous Na_2CO_3 (10 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (7 : 3)) to afford **S3** (112 mg, 0.575 mmol, 27%) as a colourless solid; MP: 56 – 59 $^\circ\text{C}$; R_f 0.24 (petrol / EtOAc (7 : 3)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.03 – 6.95 (m, 2H), 6.90 (d, J = 8.0 Hz, 1H), 5.80 (s, 1H), 5.73 (s, 1H), 4.20 – 4.07 (m, 2H), 4.09 – 3.95 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 146.6, 129.6, 120.1, 114.2, 108.6, 103.9, 65.9, 56.0; LRMS (ES $^+$) calc. for $\text{C}_{10}\text{H}_{12}\text{O}_4\text{K}$ $[\text{M}+\text{K}]^+$ 235.0, found 235.0. Experimental data are in good agreement with that described in the literature.¹³⁷

1-(3-Iodo-5-methoxy-4-((4-methoxybenzyl)oxy)phenyl)Prop-2-en-1-ol, 165

The product was prepared according to General Method H, using 3-iodo-5-methoxy-4-((4-methoxybenzyl)oxy)benzaldehyde, **156** (6.0 g, 15.1 mmol, 1.0 eq), vinylmagnesium bromide (43 mL, 30.1 mmol, 2.0 eq) and diethyl ether (30 mL). The crude residue was purified *via* flash column chromatography (cyclohexane / EtOAc (1 : 0 → 7 : 3)) to afford **165** (5.7 g, 13.2 mmol, 88%) as a white solid; MP 60 – 63 °C; R_f 0.23 (pentane / EtOAc (7 : 3)); IR (neat, $\nu_{\max}$ / cm^{-1}) 3486, 2937, 2836, 1611, 1514, 1462, 1408, 1248, 1173, 1136; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.53 – 7.46 (m, 2H, H12), 7.32 (dd, J = 1.8, 0.6 Hz, 1H, H5), 6.94 – 6.88 (m, 3H, H6, H13), 5.98 (ddd, J = 17.1, 10.3, 6.1 Hz, 1H, H2), 5.33 (dt, J = 17.1, 1.4 Hz, 1H, H1a), 5.20 (dt, J = 10.3, 1.4 Hz, 1H, H1b), 5.07 (d, J = 6.0 Hz, 1H, H3), 4.92 (s, 2H, H10), 3.85 (s, 3H, H15), 3.81 (s, 3H, H16); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 160.0, 152.8, 147.0, 140.7, 139.7, 130.5, 129.2, 128.3, 115.7, 113.7, 110.9, 93.1, 74.3, 74.3, 56.1, 55.4; HRMS (ES^+) calc. for $\text{C}_{18}\text{H}_{19}\text{O}_4\text{INa}$ $[\text{M}+\text{Na}]^+$ 449.0220, found 449.0220.

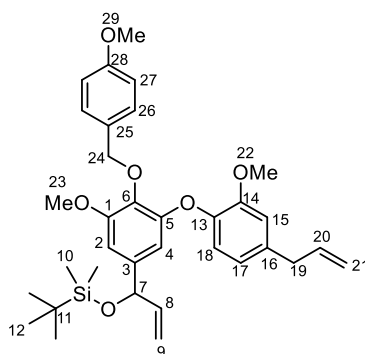
1-(3-Methoxy-4-((4-methoxybenzyl)oxy)phenyl)allyl acetate, 167

To a solution of 1-(3-iodo-5-methoxy-4-((4-methoxybenzyl)oxy)phenyl)prop-2-en-1-ol, **165** (1.00 g, 2.35 mmol, 1.0 eq) in pyridine (5 mL) was added acetic anhydride (311 μ L, 3.05 mmol, 1.3 eq) and the reaction was stirred at 50 °C under nitrogen for one hour, after which time TLC showed the reaction was complete. The reaction was cooled to room temperature, and quenched with ice. The reaction was acidified to pH 5 using 1M aqueous HCl. The product was extracted with EtOAc (3 $\times$ 10 mL) and the combined organic layers were washed with 1M aqueous HCl (20 mL) and brine (20 mL) before being dried over MgSO₄, filtered, and the solvent removed *in vacuo*. The crude residue was purified *via* flash column chromatography (cyclohexane / EtOAc (1 : 0 $\rightarrow$ 4 : 1)) to afford **167** (852 mg, 1.82 mmol, 78%) as a colourless oil; *R*_f 0.20 (pentane / EtOAc (9 : 1)); IR (neat, ν_{max} / cm⁻¹) 3013, 2836, 1738, 1644, 1588, 1514, 1462, 1360, 1226, 1144; ; ¹H NMR (400 MHz, CDCl₃) δ_{H} 7.54 – 7.46 (m, 2H, H14), 7.35 (d, *J* = 1.9, Hz, 1H, H4), 6.94 – 6.89 (m, 2H, H15), 6.87 (d, *J* = 1.9 Hz, 1H, H6), 6.16 (dt, *J* = 5.9, 1.4 Hz, 1H, H7), 5.96 (ddd, *J* = 17.1, 10.4, 5.8 Hz, 1H, H8), 5.35 – 5.24 (m, 2H, H9), 4.93 (s, 2H, H12), 3.87 (s, 3H, H17), 3.82 (s, 3H, H18), 2.13 (s, 3H, H11); ¹³C NMR (101 MHz, CDCl₃) δ_{C} 170.0, 159.7, 152.8, 147.8, 136.8, 135.8, 130.5, 129.8, 117.4, 113.8, 112.1, 93.3, 77.2, 75.2, 74.4, 56.2, 55.4, 21.4; HRMS (ES⁺) calc. for C₂₀H₂₁O₅INa [M+Na]⁺ 491.0326, found 491.0325.

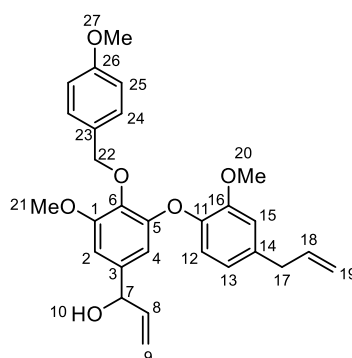
Tert*-butyl((1-(3-iodo-5-methoxy-4-((4-methoxybenzyl)oxy)phenyl)allyl)oxy)dimethylsilane,*169**

To a solution of 1-(3-iodo-5-methoxy-4-((4-methoxybenzyl)oxy)phenyl)prop-2-en-1-ol, **165** (100 mg, 0.24 mmol, 1.0 eq) in DCM (0.3 mL) was added TBSCl (36 mg, 0.24 mmol, 1.0 eq) and imidazole (19 mg, 0.28 mmol, 1.2 eq) at room temperature under nitrogen. The reaction was stirred for two hours, after which time TLC indicated consumption of the starting material. The reaction was quenched with water (2.0 mL) and the product extracted with DCM (3 × 2 mL), then the combined organic phases dried over MgSO₄ and the solvent removed *in vacuo* to afford **169** (1.25 g, 0.23 mmol, 98%) as a colourless oil; *R_f* 0.51 (pentane / EtOAc (9 : 1)); IR (neat, ν_{max} / cm⁻¹) 3012, 2836, 1738, 1644, 1513, 1461, 1370, 1226, 1144, 1041; ¹H NMR (400 MHz, CDCl₃) δ_{H} 7.54 – 7.46 (m, 2H, H15), 7.28 (d, *J* = 1.8 Hz, 1H, H1), 6.94 (d, *J* = 1.8 Hz, 1H, H3), 6.93 – 6.88 (m, 2H, H16), 5.88 (ddd, *J* = 17.0, 10.2, 5.9 Hz, 1H, H8), 5.29 (dt, *J* = 17.0, 1.5 Hz, 1H, H9^{trans}), 5.10 (dt, *J* = 10.1, 1.4 Hz, 1H, H9^{cis}), 5.07 (d, *J* = 5.9 Hz, 1H, H7), 4.93 (s, 2H, H14), 3.85 (s, 3H, H19), 3.82 (s, 3H, H13), 0.93 (s, 9H, H12), 0.08 (s, 3H, H10), 0.02 (s, 3H, H10); ¹³C NMR (101 MHz, CDCl₃) δ_{C} 159.6, 152.8, 146.6, 141.1, 130.5, 129.5, 128.0, 127.7, 114.2, 113.8, 110.6, 94.5, 75.0, 74.3, 56.0, 55.4, 26.0, 18.5, -4.5, -4.7; HRMS (ES⁺) calc. for C₂₄H₃₃O₄ISiNa [M+Na]⁺ 563.1085, found 563.1085.

((1-(3-(4-Allyl-2-methoxyphenoxy)-5-methoxy-4-((4-methoxybenzyl)oxy)phenyl)allyl)oxy)(tert-butyl)Dimethylsilane, **170**

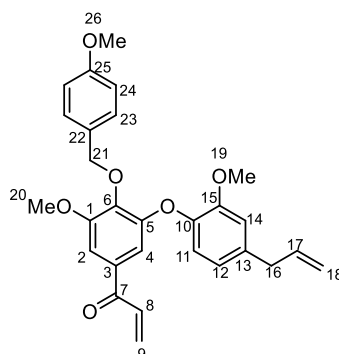


The product was prepared according to General Method D, using *tert*-butyl((1-(3-iodo-5-methoxy-4-((4-methoxybenzyl)oxy)phenyl)allyl)oxy)dimethylsilane, **169** (541 mg, 1.0 mmol, 1.0 eq), eugenol (308 μ L, 2.0 mmol, 2.0 eq), copper(I) chloride (50 mg, 0.5 mmol, 0.5 eq), TMHD (104 μ L, 0.5 mmol, 0.5 eq), cesium carbonate (654 mg, 2.0 mmol, 2.0 eq), NMP (0.6 mL) and dioxane (1.2 mL). The reaction was complete after four days. The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 $\rightarrow$ 9 : 1)) to afford **170** (195 mg, 0.34 mmol, 34%) as a colourless oil; R_f 0.42 (pentane / EtOAc (9 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2944, 2932, 1639, 1508, 1463, 1420, 1361, 1250, 1150, 1091; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.34 – 7.28 (m, 2H, H26), 6.83 – 6.79 (m, 2H, H27), 6.78 (d, J = 2.0 Hz, 1H, H15), 6.75 (d, J = 8.1 Hz, 1H, H18), 6.68 (dd, J = 7.9, 1.8 Hz, 1H, H17), 6.63 (d, J = 1.9 Hz, 1H, H2), 6.44 (d, J = 1.9 Hz, 1H, H4), 6.04 – 5.92 (m, 1H, H20), 5.85 (ddd, J = 17.0, 10.2, 5.9 Hz, 1H, H8), 5.21 (dt, J = 17.0, 1.6 Hz, 1H, H9^{trans}), 5.15 – 5.07 (m, 2H, H21), 5.04 (dt, J = 10.2, 1.5 Hz, 1H, H9^{cis}), 5.01 – 4.98 (m, 3H, H24, H7), 3.81 (s, 3H, H23), 3.80 (s, 3H, H29), 3.78 (s, 3H, H22), 3.37 (dt, J = 6.7, 1.5 Hz, 2H, H19), 0.85 (s, 9H, H12), 0.02 (s, 3H, H10), -0.06 (s, 3H, H10); ^{13}C NMR (101 MHz, CDCl_3) δ_{H} 159.3, 154.0, 150.8, 150.6, 144.2, 141.3, 139.4, 137.6, 137.3, 136.0, 130.3, 120.9, 119.6, 115.9, 113.8, 113.5, 113.0, 109.0, 104.6, 75.6, 74.7, 56.2, 56.0, 55.4, 40.1, 25.9, 18.4, -4.6, -4.8; HRMS (ES⁺) calc. for $\text{C}_{34}\text{H}_{44}\text{O}_6\text{SiNa}$ [$\text{M}+\text{Na}$]⁺ 599.2799, found 599.2797.

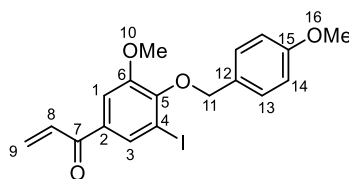
1-(3-(4-Allyl-2-methoxyphenoxy)-5-methoxy-4-((4-methoxybenzyl)oxy)phenyl)Prop-2-en-1-ol,**166**

To a solution of ((1-(3-(4-allyl-2-methoxyphenoxy)-5-methoxy-4-((4-methoxybenzyl)oxy)phenyl)allyl)oxy)(tert-butyl)dimethylsilane, **170** (180 mg, 0.31 mmol, 1.0 eq) in anhydrous THF (2.0 mL) at 0 °C was added TBAF (1M in THF, 0.31 mmol, 1.0 eq) dropwise and the reaction allowed to warm to room temperature over 24 hours, after which time TLC indicated consumption of the starting material. The crude residue was adsorbed directly onto celite and purified *via* flash column chromatography (pentane / EtOAc (1 : 0 → 3 : 2)) to afford **166** (117 mg, 0.25 mmol, 81%) as a colourless oil; R_f 0.35 (pentane / EtOAc (3 : 2)); IR (neat, $\nu_{\max}$ / cm^{-1}) 3481, 2936, 1587, 1507, 1453, 1374, 1248, 1174, 1090, 1033; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.34 – 7.28 (m, 2H, H24), 6.84 – 6.78 (m, 3H, H15, H25), 6.75 (d, J = 8.1 Hz, 1H, H12), 6.68 (m, 2H, H2, H13), 6.47 (d, J = 1.9 Hz, 1H, H4), 6.04 – 5.91 (m, 2H, H8, H18), 5.28 (dt, J = 17.1, 1.4 Hz, 1H, H9^{trans}), 5.16 (dt, J = 10.3, 1.3 Hz, 1H, H9^{cis}), 5.13 – 5.07 (m, 2H, 19), 5.05 (d, J = 5.9 Hz, 1H, H7), 5.00 (s, 2H, H22), 3.84 (s, 3H H21), 3.81 (s, 3H, H27), 3.78 (s, 3H, H20), 3.37 (dt, J = 6.8, 1.5 Hz, 2H, H17); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 159.4, 154.3, 151.0, 150.6, 144.2, 140.0, 138.3, 138.1, 137.6, 136.1, 130.3, 130.1, 120.9, 119.4, 116.0, 115.4, 113.6, 113.1, 109.6, 105.1, 75.6, 74.8, 56.3, 56.1, 55.4, 40.1; HRMS (ES⁺) calc. for $\text{C}_{28}\text{H}_{30}\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 485.1935, found 485.1934.

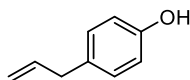
1-(3-(4-Allyl-2-methoxyphenoxy)-5-methoxy-4-((4-methoxybenzyl)oxy)phenyl)Prop-2-en-1-one, 171



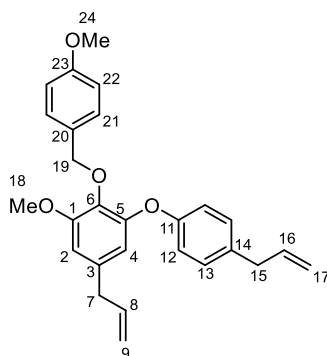
To a solution of 1-(3-(4-allyl-2-methoxyphenoxy)-5-methoxy-4-((4-methoxybenzyl)oxy)phenyl)prop-2-en-1-ol, **166** (100 mg, 0.22 mmol, 1.0 eq) in DCM (0.7 mL) was added Dess-Martin periodinane (115 mg, 0.27 mmol, 1.25 eq) and the reaction stirred at room temperature. After 18 hours, TLC showed consumption of the starting material. The product was adsorbed onto celite and purified *via* flash column chromatography (pentane / EtOAc (1 : 0 → 3 : 2)) to afford **171** (78 mg, 0.17 mmol, 78%) as a colourless oil; R_f 0.53 (pentane / EtOAc (3 : 2)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2937, 1667, 1610, 1507, 1463, 1416, 1329, 1246, 1163, 1033; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.37 – 7.32 (m, 2H, H23), 7.31 (d, J = 2.0 Hz, 1H, H2), 7.06 (d, J = 2.0 Hz, 1H, H4), 7.00 (dd, J = 17.1, 10.5 Hz, 1H, H8), 6.86 – 6.82 (m, 3H, H24, H14), 6.79 (d, J = 8.1 Hz, 1H, H11), 6.73 (dd, J = 8.1, 1.9 Hz, 1H, H12), 6.39 (dd, J = 17.0, 1.8 Hz, 1H, H9^{trans}), 6.01 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H, H17), 5.85 (dd, J = 10.5, 1.8 Hz, 1H, H9^{cis}), 5.17 – 5.10 (m, 4H, H18, H21), 3.93 (s, 3H, H20), 3.83 (s, 3H, H19), 3.81 (s, 3H, H26), 3.41 (dt, J = 6.7, 1.5 Hz, 2H, H16); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 189.4, 158.6, 154.2, 150.8, 150.6, 143.4, 142.8, 137.3, 136.7, 132.4, 131.9, 130.2, 129.9, 129.5, 120.9, 119.7, 116.0, 113.5, 113.1, 112.3, 107.0, 74.7, 56.3, 55.9, 55.3, 40.0; HRMS (ES⁺) calc. for $\text{C}_{28}\text{H}_{29}\text{O}_6$ $[\text{M}+\text{H}]^+$ 461.1959, found 461.1961.

1-(3-Iodo-5-methoxy-4-((4-methoxybenzyl)oxy)phenyl)Prop-2-en-1-one, 172

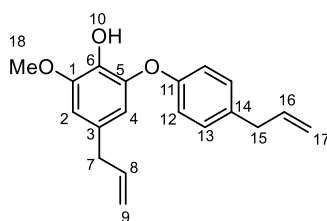
To a solution of 1-(3-iodo-5-methoxy-4-((4-methoxybenzyl)oxy)phenyl)prop-2-en-1-ol, **165** (426 mg, 1.0 mmol, 1.0 eq) in dichloromethane (3.3 mL) as added Dess-Martin periodinane (530 mg, 1.25 mmol, 1.25 eq), and the reaction stirred at room temperature. After 18 hours, TLC showed consumption of the starting material. The product was adsorbed onto celite and purified *via* flash column chromatography (pentane / EtOAc (1 : 0 → 7 : 3)) to afford **172** (422 mg, 0.99 mmol, 99%) as a white solid; MP 79 – 82 °C; R_f 0.47 (pentane / EtOAc (7 : 3)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2920, 1663, 1603, 1512, 1459, 1395, 1311, 1236, 1141, 1022; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.93 (d, J = 1.9 Hz, 1H, H1), 7.53 (d, J = 1.9 Hz, 1H, H3), 7.51 – 7.43 (m, 2H, H13), 7.11 (dd, J = 17.0, 10.5 Hz, 1H, H8), 6.94 – 6.86 (m, 2H, H13), 6.45 (dd, J = 17.0, 1.7 Hz, 1H, H9^{trans}), 5.92 (dd, J = 10.5, 1.7 Hz, 1H, H9^{cis}), 5.07 (s, 2H, H11), 3.94 (s, 3H, H10), 3.81 (s, 3H, H16); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 188.5, 159.8, 152.8, 151.9, 135.3, 132.2, 131.7, 130.6, 130.5, 128.8, 113.8, 112.5, 92.8, 74.6, 56.2, 55.4; HRMS (ES⁺) calc. for $\text{C}_{18}\text{H}_{17}\text{O}_4\text{INa}$ $[\text{M}+\text{Na}]^+$ 447.0064, found 447.0065.

4-Allylphenol, 76

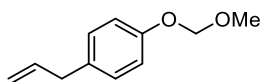
To a solution of 4-allylanisole (1.54 mL, 10.0 mmol, 1.0 eq) in DCM (50 mL) at 0 °C was added boron tribromide (1.0 M in dichloromethane, 11.0 mL, 11.0 mmol, 1.1 eq) dropwise. The reaction was stirred for two hours at 0 °C before being quenched with water. The product was extracted with dichloromethane (3 × 50 mL), before being dried over MgSO₄ and the solvent removed *in vacuo*. The crude residue was dissolved in diethyl ether (20 mL) and washed with 1M aqueous NaOH (3 × 20 mL). The combined aqueous phase was then acidified to pH 5 with 5M aqueous HCl. The product was extracted with diethyl ether (3 × 20 mL) and the combined organic phases were dried over MgSO₄, filtered, and the solvent removed *in vacuo* to afford 4-allylphenol, **76** (887 mg, 6.6 mmol, 66 %) as a colourless oil; *R_f* 0.61 (pentane / EtOAc (4 : 1)); ¹H NMR (400 MHz, CDCl₃) δ_H 7.01 – 6.93 (m, 2H), 6.73 – 6.65 (m, 2H), 5.94 – 5.79 (m, 1H), 5.03 – 4.91 (m, 2H), 3.23 (d, *J* = 6.7 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ_C 153.8, 137.9, 132.3, 128.9, 115.5, 115.3, 39.4; HRMS (ES⁺) calc. for C₉H₉O [M-H]⁺ 133.0659, found 133.0657. The experimental data are in good agreement with that described in the literature.¹³⁸

5-Allyl-1-(4-allylphenoxy)-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, **186**

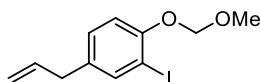
The product was prepared according to General Method D, using 5-allyl-1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, **134** (205 mg, 0.5 mmol, 1.0 eq), 4-allylphenol, **76** (134 mg, 1.0 mmol, 2.0 eq), copper(I) chloride (25 mg, 0.25 mmol, 0.5 eq), cesium carbonate (326 mg, 1.0 mmol, 2.0 eq), TMHD (52 μ L, 0.25 mmol, 0.5 eq), NMP (0.3 mL) and dioxane (0.6 mL). The reaction was complete after two days. The crude residue was purified *via* flash column chromatography (pentane / diethyl ether (1 : 0 $\rightarrow$ 9 : 1)) to afford **186** (58 mg, 0.14 mmol, 28%) as a colourless oil; R_f 0.62 (pentane / EtOAc (4 : 1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.17 – 7.12 (m, 2H), 7.06 – 6.98 (m, 2H), 6.82 – 6.75 (m, 2H), 6.74 – 6.68 (m, 2H), 6.46 (dd, J = 4.3, 2.0 Hz, 1H), 6.35 (d, J = 2.1 Hz, 1H), 5.95 – 5.76 (m, 2H), 5.04 – 4.93 (m, 4H), 4.84 (s, 2H), 3.78 (s, 3H), 3.70 (s, 3H), 3.28 (dd, J = 6.7, 1.6 Hz, 2H), 3.20 (dt, J = 6.7, 1.5 Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 159.3, 156.2, 154.1, 149.8, 137.7, 137.0, 136.0, 134.0, 130.1, 129.9, 129.6, 129.5, 117.4, 116.1, 115.6, 113.5, 113.3, 108.2, 73.7, 56.1, 55.2, 40.1, 39.5; HRMS (ES^+) calc. for $\text{C}_{27}\text{H}_{28}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 439.1880, found 439.1879.

4-Allyl-2-(4-allylphenoxy)-6-methoxyphenol, 187

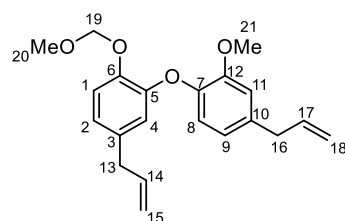
The product was prepared according to General Method J, using 5-allyl-1-(4-allylphenoxy)-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, **186** (57 mg, 0.14 mmol, 1.0 eq), 1M aqueous HCl (1.2 mL) and ethanol (2.5 mL). The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 $\rightarrow$ 4 : 1)) to afford **187** (14 mg, 0.05 mmol, 34%) as a pale yellow oil; R_f 0.44 (pentane / EtOAc (4 : 1)); IR (thin film, $\nu_{\max}$ / cm^{-1}) 3325, 2361, 1601, 1505, 1453, 1433, 1314, 1222, 1147, 1083; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.08 – 7.00 (m, 2H, H12), 6.90 – 6.80 (m, 2H, H13), 6.46 (d, J = 1.9 Hz, 1H, H2), 6.36 (d, J = 1.8 Hz, 1H, H4), 5.96 – 5.75 (m, 2H, H8, H16), 5.34 (s, 1H, H10), 5.05 – 4.92 (m, 4H, H9, H17), 3.83 (s, 3H, H18), 3.28 (dt, J = 6.7, 1.5 Hz, 2H, H15), 3.18 (dt, J = 6.6, 1.6 Hz, 2H, H7); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 155.8, 147.9, 143.1, 137.6, 137.3, 135.6, 134.5, 131.5, 129.7, 117.4, 115.9, 115.7, 113.0, 107.3, 56.3, 39.9, 39.5; HRMS (ES⁺) calc. for $\text{C}_{19}\text{H}_{21}\text{O}_3$ $[\text{M}+\text{H}]^+$ 297.1485. The experimental data are in good agreement with that described in the literature.¹⁰¹

1-Allyl-4-(methoxymethoxy)Benzene, S4

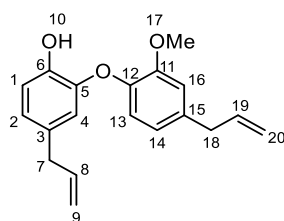
The product was prepared according to General Method A, using 4-allylphenol, **76** (134 mg, 1.0 mmol, 1.0 eq), MOMCl (99 μ L, 1.3 mmol, 1.3 eq), DIPEA (280 μ L, 1.6 mmol, 1.6 eq) and dichloromethane (1.2 mL). The reaction was complete after 24 hours. The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 $\rightarrow$ 98 : 2)) to afford **S4** (49 mg, 0.27 mmol, 27%) as a colourless oil; R_f 0.26 (pentane / diethyl ether (98 : 2)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.12 (d, J = 8.2 Hz, 2H), 6.99 (d, J = 8.3 Hz, 2H), 5.96 (ddtd, J = 16.9, 10.0, 6.6, 1.1 Hz, 1H), 5.16 (s, 2H), 5.12 – 5.02 (m, 2H), 3.49 (s, 3H), 3.35 (d, J = 6.6 Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 155.8, 137.9, 133.6, 129.7, 116.4, 115.7, 94.7, 56.0, 39.5; HRMS (APCI) calc. for $\text{C}_{12}\text{H}_{15}\text{O}_2$ $[\text{M}+\text{H}]^+$ 191.1067, found 191.1069. The experimental data are in good agreement with that described in the literature.¹³⁹

4-Allyl-2-iodo-1-(methoxymethoxy)benzene, 188

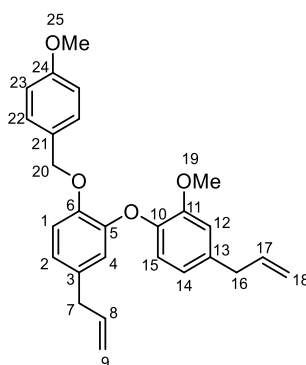
The product was prepared according to General Method B, using 1-allyl-4-(methoxymethoxy)benzene, **S4** (535 mg, 3.0 mmol, 1.0 eq), ^sBuLi (1.3 M in hexanes, 3.5 mL, 4.5 mmol, 1.5 eq), TMEDA (675 μ L, 4.5 mmol, 1.5 eq), iodine (1.1 g, 4.5 mmol, 1.4 eq) and THF (4 + 2 mL) to give on work-up **189** (529 mg, 1.7 mmol, 58 %) as a yellow oil; R_f 0.81 (pentane / EtOAc (4 : 1)); ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, J = 2.1 Hz, 1H), 7.09 (dd, J = 8.4, 2.2 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 5.97 – 5.86 (m, 1H), 5.21 (s, 2H), 5.11 – 5.02 (m, 2H), 3.51 (s, 3H), 3.30 (d, J = 6.7 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ_c 154.5, 139.5, 137.1, 135.7, 129.7, 116.3, 115.0, 95.2, 87.4, 56.1, 38.9; HRMS (APCI) calc. for C₁₁H₁₃O₂I [M+H]⁺ 303.9955, found 303.9960. The experimental data are in good agreement with that described in the literature.¹⁴⁰

4-Allyl-1-(5-allyl-2-(methoxymethoxy)phenoxy)-2-methoxybenzene, **189**

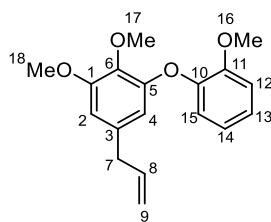
The product was prepared according to General Method D, using 4-allyl-2-iodo-1-(methoxymethoxy)benzene, **188** (100 mg, 0.33 mmol, 1.0 eq), eugenol (101 μ L, 0.66 mmol, 2.0 eq), copper(I) chloride (16 mg, 0.16 mmol, 0.5 eq), cesium carbonate (214 mg, 0.66 mmol, 2.0 eq), TMHD (34 μ L, 0.16 mmol, 0.5 eq), NMP (0.2 mL) and dioxane (0.4 mL). The reaction was complete after 2 days. The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 $\rightarrow$ 9 : 1)) to afford **189** (79 mg, 0.23 mmol, 71%) as a colourless oil; R_f 0.48 (pentane / EtOAc (4 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2901, 2828, 1592, 1505, 1421, 1256, 1212, 1153, 1128, 1076; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.13 (d, J = 8.3 Hz, 1H, H1), 6.84 (dd, J = 8.3, 1.8 Hz, 1H, H2), 6.80 (d, J = 1.8 Hz, 1H, H4), 6.75 (d, J = 8.1 Hz, 1H, H8), 6.70 – 6.66 (m, 2H, H9, H11), 5.98 (ddt, J = 16.3, 9.6, 6.4 Hz, 1H, H17), 5.88 (ddt, J = 17.5, 9.5, 6.6 Hz, 1H, H14), 5.18 (s, 2H, H19), 5.14 – 4.96 (m, 4H, H15, H18), 3.84 (s, 3H, H21), 3.45 (s, 3H, H20), 3.37 (dt, J = 6.7, 1.5 Hz, 2H, H16), 3.25 (dt, J = 6.6, 1.5 Hz, 2H, H13); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 150.4, 147.1, 146.3, 144.4, 137.6, 137.5, 135.9, 134.8, 123.8, 120.8, 119.5, 118.8, 117.8, 116.0, 115.8, 113.0, 95.7, 56.3, 56.0, 40.1, 39.5; HRMS (ES $^{+}$) calc. for $\text{C}_{21}\text{H}_{24}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^{+}$ 363.1567, found 363.1566.

4-Allyl-2-(4-allyl-2-methoxyphenoxy)phenol, 190

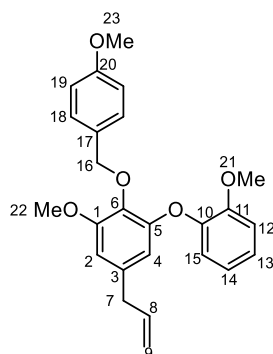
The product was prepared according to General Method C, using 4-allyl-1-(5-allyl-2-(methoxymethoxy)phenoxy)-2-methoxybenzene, **189** (50 mg, 0.15 mmol, 1.0 eq), 1 M aqueous HCl (0.3 mL) and methanol (1.4 mL). The reaction was complete after 24 hours to afford on work-up **190** (44 mg, 0.15 mmol, >99%) as a colourless oil; R_f 0.56 (pentane / EtOAc (4 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 3437, 2917, 1596, 1506, 1434, 1360, 1264, 1215, 1186, 1126; ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.98 (d, J = 8.1 Hz, 1H, H1), 6.92 (d, J = 8.2 Hz, 1H, H13), 6.85 – 6.78 (m, 2H, H4, H14), 6.75 (dd, J = 8.1, 2.0 Hz, 1H, H2), 6.71 (d, J = 2.1 Hz, 1H, H16), 6.08 (s, 1H, H10), 6.04 – 5.81 (m, 2H, H8, H19), 5.15 – 5.06 (m, 2H, H20), 5.05 – 4.96 (m, 2H, H9), 3.86 (s, 3H, H17), 3.38 (dt, J = 6.7, 1.5 Hz, 2H, H18), 3.27 – 3.21 (m, 2H, H7); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 150.8, 145.7, 144.8, 143.9, 137.7, 137.3, 137.3, 132.4, 124.5, 121.2, 120.6, 118.6, 116.3, 115.9, 115.7, 113.0, 56.1, 40.1, 39.6; HRMS (ES^+) calc. for $\text{C}_{19}\text{H}_{20}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 319.1305, found 319.1305.

4-Allyl-1-(5-allyl-2-((4-methoxybenzyl)oxy)phenoxy)-2-methoxybenzene, 191

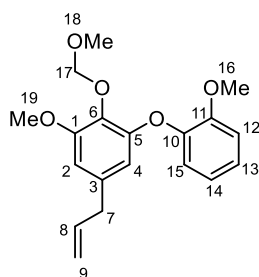
The product was prepared according to General Method I, using 4-allyl-2-(4-allyl-2-methoxyphenoxy)phenol, **190** (50 mg, 0.17 mmol, 1.0 eq), PMBCl (28 μ L, 0.20 mmol, 1.2 eq), potassium carbonate (58 mg, 0.42 mmol, 2.5 eq) and DMF (1.3 mL). The reaction was complete after 90 minutes. The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 $\rightarrow$ 9 : 1)) to afford **191** (61 mg, 0.15 mmol, 87%) as a colourless oil; R_f 0.69 (pentane / EtOAc (4 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 3075, 2915, 1612, 1505, 1463, 1421, 1247, 1211, 1129, 1033; ^1H NMR (400 MHz, CDCl_3 , δ_{H} 7.20 – 7.10 (m, 2H, H22), 6.91 (d, J = 8.2 Hz, 1H, H1), 6.86 – 6.78 (m, 5H, H23, H2, H14), 6.74 – 6.63 (m, 2H, H12, H4), 6.07 – 5.83 (m, 2H, H8, H17), 5.16 – 4.96 (m, 6H, H9, H18, H20), 3.83 (s, 3H, H19), 3.79 (s, 3H, H25), 3.38 (dt, J = 6.7, 1.5 Hz, 2H, H16), 3.27 (dt, J = 6.7, 1.6 Hz, 2H, H7); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 159.3, 150.2, 148.2, 146.6, 145.4, 137.7, 137.6, 135.3, 133.7, 129.6, 129.0, 124.0, 120.8, 120.7, 118.0, 115.9, 115.9, 115.8, 113.8, 113.3, 71.2, 56.2, 55.4, 40.1, 39.5; HRMS (ES^+) calc. for $\text{C}_{27}\text{H}_{28}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 439.1880, found 439.1879.

5-Allyl-1,2-dimethoxy-3-(2-methoxyphenoxy)benzene, **192**

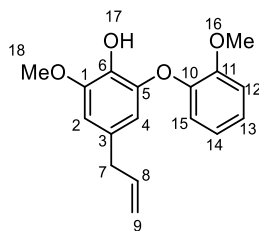
The product was prepared according to General Method D, using 5-allyl-1-iodo-2,3-dimethoxybenzene **103** (152 mg, 0.50 mmol, 1.0 eq), guaiacol (110 μ L, 1.0 mmol, 2.0 eq), copper(I) chloride (25 mg, 0.25 mmol, 0.5 eq), TMHD (52 μ L, 0.25 mmol, 0.5 eq), cesium carbonate (326 mg, 1.0 mmol, 2.0 eq), NMP (0.3 mL) and dioxane (0.6 mL). The reaction was complete after two days. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 4 : 1)) to afford **192** (77 mg, 0.28 mmol, 52%) as a colourless oil; R_f 0.24 (petrol / EtOAc (9 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2938, 2835, 1580, 1454, 1424, 1255, 1207, 1176, 1115, 1026; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.04 – 6.95 (m, J = 4.4 Hz, 1H, H13), 6.90 (d, J = 8.1 Hz, 1H, H12), 6.82 – 6.78 (m, 2H, H14, H15), 6.43 (d, J = 1.8 Hz, 1H, H2), 6.23 (d, J = 1.8 Hz, 1H, H4), 5.81 (m, 1H, H8), 5.01 – 4.91 (m, 2H, H9), 3.80 (s, 3H, H17), 3.79 (s, 3H, H16), 3.78 (s, 3H, H18), 3.17 (d, J = 6.7 Hz, 2H, H7); ^{13}C NMR (101 MHz, CDCl_3) δ 153.6, 150.7, 150.3, 146.0, 138.2, 137.1, 135.6, 123.9, 120.9, 119.3, 116.0, 112.7, 111.7, 107.5, 61.0, 56.1, 56.0, 40.1; HRMS (APCI) calc. for $\text{C}_{18}\text{H}_{21}\text{O}_4$ $[\text{M}+\text{H}]^+$ 301.1434, found 301.1433.

5-Allyl-1-methoxy-2-((4-methoxybenzyl)oxy)-3-(2-methoxyphenoxy)benzene, **193**

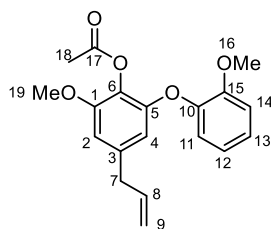
The product was prepared according to General Method D using 5-allyl-1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, **134** (410 mg, 1.0 mmol, 1.0 eq), guaiacol (110 μ L, 2.0 mmol, 2.0 eq), copper(I) chloride (50 mg, 0.5 mmol, 0.5 eq), TMHD (104 μ L, 0.5 mmol, 0.5 eq), cesium carbonate (652 mg, 2.0 mmol, 2.0 eq), NMP (0.6 mL) and dioxane (1.2 mL). The reaction was complete after 2 days. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 4 : 1)) to afford **193** (180 mg, 0.44 mmol, 44%) as a colourless oil; R_f 0.18 (pentane / diethyl ether (9 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2936, 2836, 1581, 1500, 1456, 1373, 1303, 1253, 1145, 1091; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.32 – 7.27 (m, 2H, H18), 7.10 – 7.01 (m, 1H, H13), 6.97 (d, J = 8.0 Hz, 1H, H12), 6.86 (td, J = 7.6, 1.4 Hz, 1H, H14), 6.83 – 6.78 (m, 3H, H15, H19), 6.50 (d, J = 1.8 Hz, 1H, H2), 6.35 (d, J = 1.8 Hz, 1H, H4), 5.97 – 5.82 (m, 1H, H8), 5.06 – 5.00 (m, 2H, H9), 4.98 (s, 2H, H16), 3.84 (s, 3H, H23), 3.83 (s, 3H, H21), 3.78 (s, 3H, H22), 3.26 (d, J = 6.6 Hz, 2H, H7); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 159.2, 154.0, 150.4, 150.3, 146.3, 137.1, 135.3, 130.2, 130.2, 130.1, 123.6, 120.9, 118.9, 116.0, 113.4, 112.6, 112.1, 107.8, 74.7, 56.1, 56.0, 55.2, 40.1; HRMS (ES $^{+}$) calc. for $\text{C}_{25}\text{H}_{27}\text{O}_5$ $[\text{M}+\text{H}]^{+}$ 407.1853, found 407.1855.

5-Allyl-1-methoxy-2-(methoxymethoxy)-3-(2-methoxyphenoxy)benzene, **194**

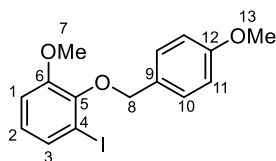
The product was prepared according to General Method D, using 5-allyl-1-iodo-3-methoxy-2-(methoxymethoxy)benzene, **100** (81 mg, 0.24 mmol, 1.0 eq), guaiacol (53 μ L, 0.49 mmol, 2.0 eq), copper(I) chloride (12 mg, 0.12 mmol, 0.5 eq), TMHD (25 μ L, 0.12 mmol, 0.5 eq), cesium carbonate (159 mg, 0.49 mmol, 2.0 eq), NMP (0.15 mL) and dioxane (0.3 mL). The reaction was complete after three days. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 4 : 1)) to afford **194** (22 mg, 0.51 mmol, 27%) as a colourless oil; R_f 0.22 (petrol / EtOAc (9 : 1)); IR (thin film, $\nu_{\max}$ / cm^{-1}) 2936, 2838, 1638, 1501, 1454, 1333, 1302, 1255, 1177, 1079; ^1H NMR (CDCl_3 , 400 MHz) δ_{H} 7.12 – 7.03 (m, 1H, H13), 6.98 (d, J = 8.1 Hz, 1H, H15), 6.94 – 6.83 (m, 2H, H12, H14), 6.50 (d, J = 1.9 Hz, 1H, H2), 6.29 (d, J = 1.9 Hz, 1H, H4), 5.95 – 5.80 (m, 1H, H8), 5.16 (s, 2H, H17), 5.08 – 4.98 (m, 2H, H9), 3.86 (s, 3H, H16), 3.84 (s, 3H, H19), 3.56 (s, 3H, H18), 3.24 (d, J = 6.7 Hz, 2H, H7); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 153.8, 150.8, 150.6, 145.8, 137.1, 136.3, 134.7, 124.1, 121.1, 119.5, 116.1, 112.7, 111.6, 107.5, 98.5, 57.2, 56.1, 56.0, 40.2; HRMS (ES^+) calc. for $\text{C}_{19}\text{H}_{22}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 353.1359, found 353.1356.

4-Allyl-2-methoxy-6-(2-methoxyphenoxy)phenol, 195

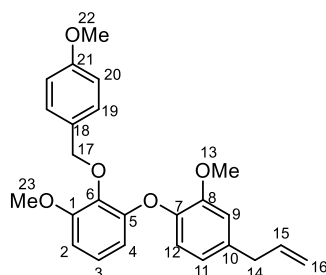
The product was prepared according to General Method C, using 5-allyl-1-methoxy-2-(methoxymethoxy)-3-(2-methoxyphenoxy)benzene, **194** (22 mg, 0.07 mmol, 1.0 eq), 2M aqueous HCl (0.2 mL) and methanol (2.0 mL). The reaction was complete after 20 hours. The crude residue was purified *via* flash column chromatography (pentane / EtOAc (4 : 1)) to afford **195** (10 mg, 0.04 mmol, 54%) as a pale yellow oil; R_f 0.36 (petrol / EtOAc (7 : 3)); IR (thin film, $\nu_{\max}$ / cm^{-1}) 3448, 2920, 1588, 1500, 1455, 1434, 1310, 1254, 1177, 1083; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.09 (td, J = 7.7, 1.6 Hz, 1H, H14), 7.02 – 6.92 (m, 2H, H12, H15), 6.89 (td, J = 7.6, 1.4 Hz, 1H, H13), 6.51 (d, J = 1.9 Hz, 1H, H2), 6.42 (d, J = 1.7 Hz, 1H, H4), 5.97 – 5.83 (m, 1H, H8), 5.80 (s, 1H, H17), 5.11 – 4.96 (m, 2H, H9), 3.90 (s, 3H, H18), 3.89 (s, 3H, H16), 3.25 (d, J = 6.6 Hz, 2H, H7); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 150.6, 148.0, 146.2, 144.2, 137.5, 135.4, 131.3, 124.4, 121.1, 119.4, 115.9, 112.6, 112.3, 107.5, 56.4, 56.1, 40.0; HRMS (ES⁺) calc. for $\text{C}_{17}\text{H}_{18}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 309.1097, found 309.1097.

4-Allyl-2-methoxy-6-(2-methoxyphenoxy)phenyl acetate, 196

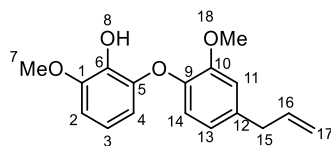
The product was prepared according to General Method L, using 4-allyl-2-methoxy-6-(2-methoxyphenoxy)phenol, **195** (87 mg, 0.29 mmol, 1.0 eq), pyridine (546 μ L, 6.8 mmol, 23.0 eq), acetic anhydride (215 μ L, 2.28 mmol, 7.5 eq). The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 $\rightarrow$ 4 : 1)), to afford **196** (59 mg, 0.18 mmol, 61%) as a white solid; MP 74 – 77 $^{\circ}$ C (pentane); R_f 0.46 (petrol / EtOAc (4 : 1)); IR (thin film, $\nu_{\max}$ / cm^{-1}) 2918, 1762, 1610, 1499, 1437, 1364, 1306, 1256, 1161, 1116, 1094; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.02 (td, J = 8.1, 1.9 Hz, 1H, H12), 6.88 (m, 2H, H11, H14), 6.80 (td, J = 7.6, 1.5 Hz, 1H, H13), 6.44 (d, J = 1.8 Hz, 1H, H2), 6.21 (d, J = 1.8 Hz, 1H, H4), 5.80 (ddt, J = 16.0, 10.9, 6.7 Hz, 1H, H8), 5.01 – 4.92 (m, 2H, H9), 3.75 (s, 3H, H16), 3.74 (s, 3H, H19), 3.18 (d, J = 6.7 Hz, 2H, H7), 2.15 (s, 3H, H18); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 168.6, 152.4, 151.1, 150.0, 145.4, 138.5, 136.8, 124.7, 121.1, 120.6, 116.3, 112.9, 110.8, 106.9, 56.2, 56.1, 40.3, 20.4; HRMS (ES $^{+}$) calc. for $\text{C}_{19}\text{H}_{21}\text{O}_5$ $[\text{M}+\text{H}]^{+}$ 329.1384 found 329.1382.

1-Iodo-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, 198

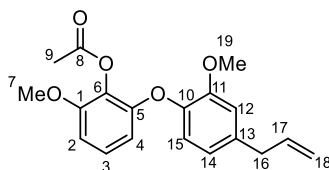
The product was prepared according to General Method I, using 2-iodo-6-methoxyphenol, **113** (2.0 g, 8.0 mmol, 1.0 eq), PMBCl (1.3 mL, 9.6 mmol, 1.2 eq), potassium carbonate (2.8 g, 20.0 mmol, 2.5 eq) and DMF (50 mL). The reaction was complete after two hours. The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 → 9 : 1)) to afford **198** (2.7 g, 7.3 mmol, 91%) as a colourless oil; R_f 0.39 (petrol / EtOAc (4 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2936, 2835, 1612, 1513, 1465, 1371, 1293, 1248, 1110, 1029; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.57 – 7.50 (m, 2H, H10), 7.39 (d, J = 7.8 Hz, 1H, H1), 6.98 – 6.89 (m, 3H, H3, H11), 6.83 (t, J = 8.1, 1H, H2), 4.98 (s, 2H, H8), 3.89 (s, 3H, H7), 3.85 (s, 3H, H13); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 159.6, 153.1, 147.8, 130.7, 130.4, 129.3, 126.0, 113.7, 112.8, 93.3, 74.2, 56.0, 55.3; HRMS (ES^+) calc. for $\text{C}_{15}\text{H}_{15}\text{O}_3\text{INa}$ $[\text{M}+\text{Na}]^+$ 392.9958, found 392.9956.

1-(4-Allyl-2-methoxyphenoxy)-3-Methoxy-2-((4-methoxybenzyl)oxy)benzene, 199

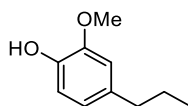
The product was prepared according to General Method D, using 1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, **198** (1.0 g, 2.7 mmol, 1.0 eq), eugenol (831 μ L, 5.4 mmol, 2.0 eq), copper(I) chloride (134 mg, 1.4 mmol, 0.5 eq), cesium carbonate (1.76 g, 5.4 mmol, 2.0 eq), TMHD (249 μ L, 1.4 mmol, 0.5 eq), NMP (2.0 mL) and dioxane (4.0 mL). The reaction was complete after three days. The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 $\rightarrow$ 4 : 1)) to afford **199** (575 mg, 1.4 mmol, 52%) as a colourless oil; R_f 0.15 (pentane / diethyl ether (4 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2937, 2836, 1588, 1708, 1469, 1419, 1373, 1243, 1152, 1033; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.38 – 7.28 (m, 2H, H20), 6.91 (t, J = 8.3 Hz, 1H, H3), 6.85 – 6.76 (m, 4H, H9, H12, H19), 6.70 (dd, J = 8.1, 2.0 Hz, 1H, H11), 6.65 (dd, J = 8.3, 1.4 Hz, 1H, H2), 6.45 (dd, J = 8.3, 1.6 Hz, 1H, H4), 5.99 (ddt, J = 16.8, 10.1, 6.7 Hz, 1H, H15), 5.15–5.07 (m, 2H, H16), 5.04 (s, 2H, H17), 3.84 (s, 3H, H22), 3.82 (s, 3H, H13), 3.79 (s, 3H, H23), 3.38 (dd, J = 6.6, 1.6 Hz, 2H, H14); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 159.4, 154.4, 151.5, 150.8, 149.4, 144.2, 138.7, 137.6, 136.2, 130.3, 123.5, 120.9, 119.7, 116.0, 113.5, 113.2, 111.3, 107.2, 74.7, 56.3, 56.1, 55.4, 40.8; HRMS (ES $^-$) calc. for $\text{C}_{25}\text{H}_{25}\text{O}_5$ $[\text{M}-\text{H}]^-$ 405.1708, found 405.1705.

2-(4-Allyl-2-methoxyphenoxy)-6-Methoxyphenol, 200

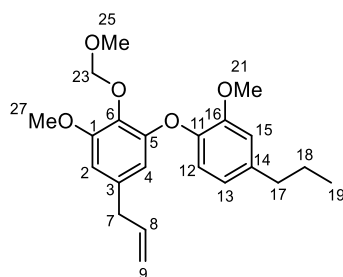
The product was prepared according to General Method J, using 1-(4-allyl-2-methoxyphenoxy)-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, **199** (74 mg, 0.19 mmol, 1.0 eq), 1M aqueous HCl (1.5 mL) and ethanol (3.8 mL). The reaction was complete after two hours. The crude residue was purified via flash column chromatography (pentane / EtOAc (1 : 0 → 4 : 1)) to afford **200** (39 mg, 0.14 mmol, 76%) as a colourless oil; R_f 0.33 (pentane / EtOAc (4 : 1)); IR (thin film, $\nu_{\max}$ / cm^{-1}) 3502, 2936, 1595, 1505, 1476, 1358, 1261, 1152, 1073, 1033; ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.91 (d, J = 8.1 Hz, 1H, H14), 6.80 (s, 1H, H11), 6.78 – 6.68 (m, 2H, H3, H13), 6.66 (d, J = 8.2 Hz, 1H, H2), 6.54 (d, J = 8.2 Hz, 1H, H4), 6.06 – 5.89 (m, 2H, H8, H16), 5.14 – 5.05 (m, 2H, H17), 3.90 (s, 3H, H18), 3.85 (s, 3H, H7), 3.37 (d, J = 6.7 Hz, 2H, H15); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 150.6, 148.2, 145.1, 144.1, 137.3, 137.1, 136.8, 120.9, 120.0, 119.1, 116.1, 113.0, 111.6, 106.8, 56.4, 56.1, 40.1; HRMS (ES⁺) calc. for $\text{C}_{17}\text{H}_{18}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 309.1097, found 309.1097.

2-(4-Allyl-2-methoxyphenoxy)-6-Methoxyphenyl acetate, 201

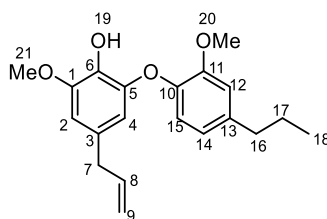
The product was prepared according to General Method L, using 2-(4-allyl-2-methoxyphenoxy)-6-methoxyphenol, **200** (39 mg, 0.14 mmol, 1.0 eq), pyridine (254 μ L, 3.15 mmol, 23.0 eq) and acetic anhydride (97 μ L, 1.03 mmol, 7.50 eq). The reaction was complete after two hours. The crude residue was purified *via* flash column chromatography (pentane / EtOAc (9 : 1)), to afford **201** (32 mg, 0.10 mmol, 70%) as an off-white solid; MP 82 – 85 $^{\circ}$ C; R_f 0.41 (pentane / ethyl acetate (4 : 1)); IR (thin film, $\nu_{\max}$ / cm^{-1}) 2917, 1760, 1505, 1474, 1418, 1251, 1212, 1178, 1083, 1030; ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.95 (dd, J = 9.0, 7.7 Hz, 1H, H3), 6.82 (d, J = 8.1 Hz, 1H, H15), 6.72 (d, J = 2.0 Hz, 1H, H12), 6.64 (dd, J = 8.1, 1.9 Hz, 1H, H2), 6.59 (d, J = 8.4 Hz, 1H, H14), 6.32 (dd, J = 8.6, 1.4 Hz, 1H, H4), 5.89 (ddt, J = 16.8, 10.3, 6.7 Hz, 1H, H17), 5.07 – 5.00 (m, 2H, H18), 3.76 (s, 3H, H7), 3.73 (s, 3H, H19), 3.29 (d, J = 6.6 Hz, 2H, H18), 2.20 (d, J = 1.3 Hz, 3H, H9); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 168.6, 152.4, 151.1, 150.0, 145.4, 138.5, 136.8, 128.7, 124.7, 121.1, 120.6, 116.3, 112.9, 110.8, 106.9, 56.2, 56.1, 40.3, 20.4; HRMS (ES^+) calc. for $\text{C}_{19}\text{H}_{21}\text{O}_5$ $[\text{M}+\text{H}]^+$ 329.1384, found 329.1384.

2-Methoxy-4-propylphenol, 205

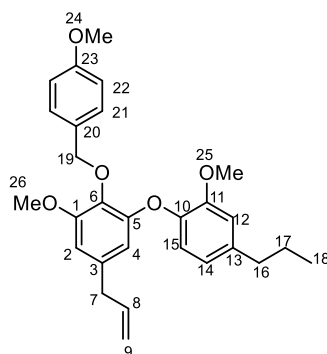
The product was prepared according to General Method K, using eugenol (770 μ L, 5.00 mmol, 1.00 eq), Pd/C (10% w/w, 1.60 g, 1.50 mmol, 0.30 eq) and ethanol (75 mL). The reaction was complete after 90 minutes to afford **205** (775 mg, 4.67 mmol, 93%) as a pale yellow oil which was used without further purification; R_f 0.36 (petrol / EtOAc (9 : 1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.84 (d, J = 7.8 Hz, 1H), 6.71 – 6.65 (m, 2H), 5.48 (dd, J = 5.5, 1.6 Hz, 1H), 3.88 (s, 3H), 2.52 (t, J = 7.4 Hz, 2H), 1.62 (h, J = 7.4 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 146.4, 143.6, 134.8, 121.1, 114.2, 111.1, 56.0, 37.9, 25.0, 14.0; HRMS (APCI) calc. for $\text{C}_{10}\text{H}_{13}\text{O}_2$ $[\text{M}-\text{H}]^-$ 165.0921, found 446.0917. The experimental data are in good agreement with that described in the literature.¹⁴¹

5-Allyl-1-methoxy-3-(2-methoxy-4-propylphenoxy)-2-(methoxymethoxy)benzene, **206**

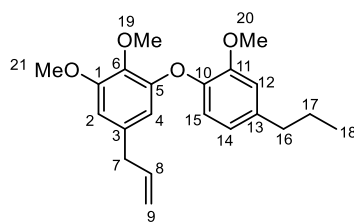
The product was prepared according to General Method D, using 5-Allyl-1-iodo-3-methoxy-2-(methoxymethoxy)benzene, **100** (167 mg, 0.5 mmol, 1.00 eq), 2-methoxy-4-propylphenol, **205** (167 mg, 1.0 mmol, 2.0eq), copper(I) chloride (25 mg, 0.25 mmol, 0.50 eq), TMHD (52 μ L, 0.25 mmol, 0.50 eq), cesium carbonate (326 mg, 1.0 mmol, 2.00 eq), NMP (0.3 mL) and dioxane (0.6 mL). The reaction was complete after two days. The crude residue was purified *via* flash column chromatography (petrol : EtOAc (1 : 0 $\rightarrow$ 4 : 1)), to afford **206** (47 mg, 0.126 mmol, 25%) as a pale yellow oil; R_f 0.25 (petrol / EtOAc (9 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2959, 2872, 1679, 1588, 1463, 1426, 1378, 1231, 1155, 1035; ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.83 – 6.77 (m, 2H, H12, H15), 6.68 (dd, J = 8.1, 1.8 Hz, 1H, H13), 6.50 – 6.45 (m, 1H, H2), 6.25 (d, J = 1.8 Hz, 1H, H4), 5.87 (ddt, J = 16.9, 10.4, 6.7 Hz, 1H, H8), 5.17 (d, J = 1.2 Hz, 2H, H23), 5.06 – 4.98 (m, 2H, H9), 3.86 (s, 3H, H21), 3.82 (s, 3H, H25), 3.57 (s, 3H, H27), 3.23 (d, J = 6.6 Hz, 2H, H7), 2.56 (t, J = 7.7 Hz, 2H, H17), 1.65 (sext, J = 7.4 Hz, 2H, H18), 0.95 (t, J = 7.3 Hz, 3H, H19); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 153.7, 151.0, 150.6, 143.5, 139.0, 137.2, 136.2, 134.4, 120.8, 119.6, 116.0, 113.0, 111.1, 107.2, 98.5, 57.2, 56.1, 56.0, 40.3, 38.0, 24.8, 14.0; HRMS (APCI) calc. for $\text{C}_{22}\text{H}_{38}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 395.1837, found 395.1829.

4-Allyl-2-methoxy-6-(2-methoxy-4-propylphenoxy)phenol, 207

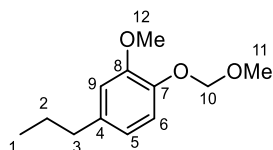
The product was prepared according to General Method C, using 5-allyl-1-methoxy-3-(2-methoxy-4-propylphenoxy)-2-(methoxymethoxy)benzene, **206** (47 mg, 0.13 mmol, 1.0 eq) 2M aqueous HCl (0.4 mL) and methanol (4 mL). The reaction was complete after 24 hours. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 7 : 3)) to afford **207** (22 mg, 0.07 mmol, 55%) as a colourless oil; R_f 0.30 (petrol / EtOAc (7 : 3)); IR (thin film, $\nu_{\max}$ / cm^{-1}) 3448, 2958, 2870, 1638, 1508, 1453, 1311, 1254, 1128, 1033; ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.88 (d, J = 8.1 Hz, 1H, H15), 6.79 (d, J = 1.9 Hz, 1H, H12), 6.69 (dd, J = 8.1, 1.9 Hz, 1H, H14), 6.49 (s, 1H, H2), 6.41 (s, 1H, H4), 5.97 – 5.82 (m, 2H, H8, H19), 5.08 – 4.99 (m, 2H, H9), 3.89 (s, 3H, H20), 3.87 (s, 3H, H21), 3.24 (d, J = 6.6 Hz, 2H, H7), 2.56 (t, J = 7.7 Hz, 2H, H16), 1.64 (sext, J = 7.4 Hz, 2H, H17), 0.95 (t, J = 7.3 Hz, 3H, H18); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 150.3, 147.9, 144.7, 143.9, 139.4, 137.6, 135.3, 131.1, 120.8, 119.6, 115.8, 112.9, 112.0, 107.3, 56.3, 56.1, 40.0, 38.0, 24.8, 14.0; HRMS (ES⁺) calc. for $\text{C}_{20}\text{H}_{25}\text{O}_4$ $[\text{M}+\text{H}]^+$ 329.1747, found 329.1748.

5-Allyl-1-methoxy-3-(2-methoxy-4-propylphenoxy)-2-((4-methoxybenzyl)oxy)benzene, **208**

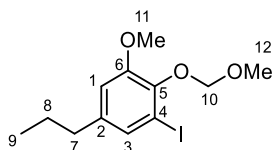
The product was prepared according to General Method D using 5-allyl-1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, **134** (205 mg, 0.5 mmol, 1.0 eq), 2-methoxy-4-propylphenol, **205** (166 mg, 1.0 mmol, 2.0 eq), copper(I) chloride (25 mg, 0.25 mmol, 0.5 eq), TMHD (52 μ L, 0.25 mmol, 0.5 eq), cesium carbonate (326 mg, 1.0 mmol, 2.0 eq), NMP (0.3 mL) and dioxane (0.6 mL). The reaction was complete after three days. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 4 : 1)) to afford **208** (100 mg, 0.22 mmol, 45%) as a colourless oil; R_f 0.23 (pentane / diethyl ether (4 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2957, 2933, 2360, 1587, 1511, 1463, 1375, 1265, 1232, 1155; ^1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.27 (m, 2H, H21), 6.83 – 6.79 (m, 2H, H22), 6.78 (d, J = 2.0 Hz, 1H, H12), 6.74 (d, J = 8.1 Hz, 2H, H15), 6.66 (dd, J = 8.2, 1.9 Hz, 1H, H14), 6.47 (d, J = 1.9 Hz, 1H, H2), 6.31 (d, J = 1.9 Hz, 1H, H4), 5.89 (ddt, J = 17.6, 9.5, 6.7 Hz, 1H, H8), 5.06 – 4.99 (m, 2H, H9), 4.98 (s, 2H, H19), 3.82 (s, 6H, H25, H24), 3.78 (s, 3H, H26), 3.25 (dt, J = 6.7, 1.5 Hz, 2H, H7), 2.56 (dd, J = 8.6, 6.7 Hz, 2H, H16), 1.65 (sext, J = 7.5 Hz, 2H, H17), 0.96 (t, J = 7.3 Hz, 3H, H18); ^{13}C NMR (101 MHz, CDCl_3) δ_c 159.4, 154.0, 150.9, 150.4, 144.1, 138.7, 137.3, 137.1, 135.7, 130.4, 130.2, 120.7, 119.2, 116.0, 113.5, 113.1, 111.8, 107.6, 74.8, 56.3, 56.1, 55.4, 40.2, 38.0, 24.8, 14.0; HRMS (ES+) calc. for $\text{C}_{28}\text{H}_{33}\text{O}_5$ $[\text{M}+\text{H}]^+$ 449.2323, found 449.2322.

5-Allyl-1,2-dimethoxy-3-(2-methoxy-4-propylphenoxy)benzene, **209**

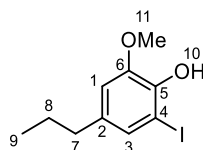
The product was prepared according to General Method D, using 5-allyl-1-iodo-2,3-dimethoxybenzene, **103** (152 mg, 0.50 mmol, 1.0 eq), 2-methoxy-4-propylphenol, **205** (166 mg, 1.0 mmol, 2.0 eq), copper(I) chloride (25 mg, 0.25 mmol, 0.5 eq), TMHD (52 μ L, 0.25 mmol, 0.5 eq), cesium carbonate (326 mg, 1.0 mmol, 2.0 eq), NMP (0.3 mL) and dioxane (0.6 mL). The reaction was complete after two days. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 4 : 1)) to afford **209** (117 mg, 0.34 mmol, 68%) as a pale yellow oil; R_f 0.30 (petrol / EtOAc (9 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2958, 2933, 1586, 1452, 1423, 1333, 1265, 1154, 1129, 1091; ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.84 – 6.79 (m, 2H, H15, H12), 6.71 (dd, J = 8.1, 1.9 Hz, 1H, H14), 6.50 (d, J = 1.9 Hz, 1H, H2), 6.29 (d, J = 1.9 Hz, 1H, H4), 5.90 (ddt, J = 16.0, 10.7, 6.7 Hz, 1H, H8), 5.10 – 5.00 (m, 2H, H9), 3.90 (s, 3H, H20), 3.89 (s, 3H, H19), 3.86 (s, 3H, H21), 3.26 (dt, J = 6.7, 1.5 Hz, 2H, H7), 2.59 (dd, J = 8.6, 6.7 Hz, 2H, H16), 1.73 – 1.62 (m, 2H, H17), 0.98 (t, J = 7.3 Hz, 3H, H18); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 153.5, 150.8, 150.5, 143.7, 138.8, 138.0, 137.1, 135.5, 120.6, 119.4, 115.9, 113.0, 111.3, 107.2, 61.0, 56.1, 56.0, 40.1, 37.9, 24.6, 13.8; HRMS (ES $^{+}$) calc. for $\text{C}_{21}\text{H}_{27}\text{O}_4$ $[\text{M}+\text{H}]^{+}$ 343.1904, found 343.1900. for $\text{C}_{19}\text{H}_{21}\text{O}_5$ $[\text{M}+\text{H}]^{+}$ 329.1384, found 329.1384.

2-Methoxy-1-(methoxymethoxy)-4-propylbenzene, S5

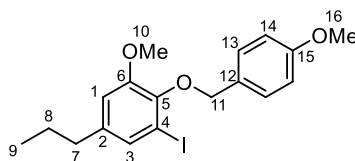
The product was prepared according to General Method A, using 2-methoxy-4-propylphenol, **205** (200 mg, 1.2 mmol, 1.0 eq), MOMCl (119 μ L, 1.6 mmol, 1.3 eq), DIPEA (335 μ L, 1.9 mmol, 1.6 eq) and DCM (1.4 mL). The reaction was complete after 20 hours, to afford on work up **S5** (225 mg, 1.1 mmol, 89%) as a yellow oil; R_f 0.54 (pentane / EtOAc (9 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2957, 2872, 1512, 1464, 1418, 1378, 1262, 1226, 1134, 1035; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.05 (d, J = 8.1 Hz, 1H, H6), 6.72 (s, 1H, H9), 6.70 (d, J = 8.1 Hz, 1H, H5), 5.19 (s, 2H, H10), 3.87 (s, 3H, H11), 3.51 (s, 3H, H12), 2.53 (t, J = 7.7 Hz, 2H, H3), 1.63 (h, J = 7.5 Hz, 2H, H2), 0.94 (t, J = 7.3 Hz, 3H, H1); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 149.7, 144.5, 137.4, 120.6, 116.7, 112.3, 95.8, 56.2, 55.9, 37.9, 24.8, 14.0; HRMS (Ammonia CI) calc. for $\text{C}_{12}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$ 211.1329, found 211.1327.

1-Iodo-3-methoxy-2-(methoxymethoxy)-5-propylbenzene, 210

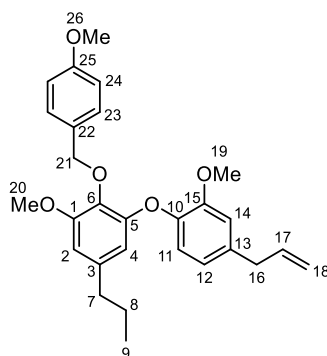
The product was prepared according to General Method B, using 2-methoxy-1-(methoxymethoxy)-4-propylbenzene, **S5** (150 mg, 0.7 mmol, 1.0 eq), ^sBuLi (1.3 M in hexanes, 0.82 mL, 1.1 mmol, 1.5 eq), TMEDA (160 μ L, 1.1 mmol, 1.5 eq), iodine (272 mg, 1.1 mmol, 1.5 eq) and THF (1.0 + 0.3 mL). The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 $\rightarrow$ 9 : 1)) to afford **210** (192 mg, 0.6 mmol, 60 %) as a pale yellow oil; ; R_f 0.65 (pentane / EtOAc (4 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2958, 2870, 1591, 1560, 1462, 1340, 1265, 1200, 1158, 1142; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.19 (d, J = 1.9 Hz, 1H, H1), 6.68 (d, J = 2.0 Hz, 1H, H3), 5.12 (s, 2H, H10), 3.82 (s, 3H, H11), 3.67 (s, 3H, H12), 2.48 (dd, J = 8.6, 6.7 Hz, 2H, H7), 1.67 – 1.55 (m, 2H, H8), 0.93 (t, J = 7.3 Hz, 4H, H9); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 152.1, 143.9, 141.0, 130.7, 113.7, 98.8, 92.5, 58.5, 56.0, 37.5, 24.6, 13.9; HRMS (ES⁺) calc. for $\text{C}_{12}\text{H}_{17}\text{O}_3\text{INa}$ $[\text{M}+\text{Na}]^+$ 358.0115, found 359.0116.

2-Iodo-6-methoxy-4-propylphenol, S6

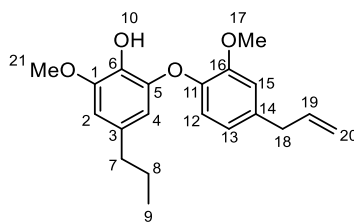
The product was prepared according to General Method C, using 1-iodo-3-methoxy-2-(methoxymethoxy)-5-propylbenzene, **210** (192 mg, 0.6 mmol, 1.0 eq), 2M aqueous HCl (1.7 mL) and methanol (8.4 mL). The reaction was complete after 20 hours. The crude residue was purified *via* flash column chromatography (pentane / diethyl ether (9 : 1 $\rightarrow$ 4 : 1)) to afford **S6** (129 mg, 0.4 mmol, 77%) as a colourless wax; R_f 0.31 (pentane / diethyl ether (4 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 3481, 2997, 1602, 1493, 1462, 1360, 1272, 1173, 1095, 1044; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.04 (s, 1H, H1), 6.56 (s, 1H, H3), 5.84 (s, 1H, H10), 3.79 (s, 3H, H11), 2.40 (t, J = 7.7 Hz, 2H, H7), 1.52 (h, J = 7.3 Hz, 2H, H8), 0.85 (t, J = 7.3 Hz, 3H, H9); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 145.8, 143.6, 136.4, 130.0, 111.2, 81.1, 56.2, 37.3, 24.7, 13.7; HRMS (ES $^-$) calc. for $\text{C}_{10}\text{H}_{12}\text{O}_2\text{I}$ $[\text{M}-\text{H}]^-$ 290.9888, found 290.9887.

1-Iodo-3-methoxy-2-((4-methoxybenzyl)oxy)-5-propylbenzene, 211

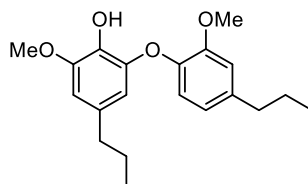
The product was prepared according to General Method I, using 2-iodo-6-methoxy-4-propylphenol, **S6** (128 mg, 0.44 mmol, 1.0 eq), PMBCl (71 μ L, 0.53 mmol, 1.2 eq), potassium carbonate (151 mg, 1.10 mmol, 2.5 eq) and DMF (3.3 mL). The reaction was complete after four hours. The crude residue was purified *via* flash column chromatography (pentane / diethyl ether (1 : 0 $\rightarrow$ 9 : 1)) to afford **211** (126 mg, 0.31 mmol, 70%), as a colourless wax; R_f 0.40 (pentane / EtOAc (9 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 3003, 2831, 1611, 1559, 1512, 1460, 1303, 1248, 1171, 1034; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.55 – 7.47 (m, 2H, H13), 7.19 (d, J = 1.8 Hz, 1H, H1), 6.96 – 6.88 (m, 2H, H14), 6.71 (d, J = 1.9 Hz, 1H, H3), 4.92 (s, 2H, H11), 3.85 (s, 3H, H16), 3.82 (s, 3H, H10), 2.50 (dd, J = 8.6, 6.7 Hz, 2H, H7), 1.63 (h, J = 7.6 Hz, 2H, H8), 0.95 (t, J = 7.3 Hz, 3H, H9); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 159.6, 152.6, 145.9, 140.9, 130.4, 130.4, 129.2, 113.8, 113.4, 93.0, 73.9, 56.1, 55.4, 37.5, 23.9, 13.9; HRMS (ES⁺) calc. for $\text{C}_{18}\text{H}_{21}\text{O}_3\text{INa}$ $[\text{M}+\text{Na}]^+$ 435.0428, found 435.0427.

1-(4-Allyl-2-methoxyphenoxy)-3-Methoxy-2-((4-methoxybenzyl)oxy)-5-propylbenzene, 212

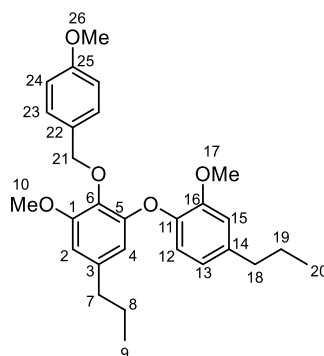
The product was prepared according to General Method D, using 1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)-5-propylbenzene, **211** (95 mg, 0.23 mmol, 1.0 eq), eugenol (71 μ L, 0.46 mmol, 2.0 eq), copper(I) chloride (11 mg, 0.12 mmol, 0.5 eq), TMHD (24 μ L, 0.12 mmol, 0.5 eq), cesium carbonate (151 mg, 0.46 mmol, 2.0 eq), NMP (0.14 mL) and dioxane (0.28 mL). The reaction was complete after three days. The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 $\rightarrow$ 4 : 1)) to afford **212** (56 mg, 0.12 mmol, 54%) as a white solid; MP 52 – 55 $^{\circ}$ C (pentane); R_f 0.23 (pentane / EtOAc (9 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 3001, 2870, 1609, 1506, 1463, 1421, 1375, 1248, 1152, 1080; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.35 – 7.27 (m, 2H, H23), 6.84 – 6.77 (m, 3H, H14, H24), 6.74 (d, J = 8.1 Hz, 1H, H11), 6.67 (dd, J = 8.1, 1.9 Hz, 1H, H12), 6.47 (d, J = 1.9 Hz, 1H, H2), 6.31 (d, J = 1.9 Hz, 1H, H4), 5.98 (ddt, J = 16.8, 10.1, 6.7 Hz, 1H, H17), 5.15 – 5.04 (m, 2H, H18), 4.97 (s, 2H, H21), 3.82 (s, 3H, H26), 3.82 (s, 3H, H19), 3.78 (s, 3H, H20), 3.37 (dt, J = 6.8, 1.5 Hz, 2H, H16), 2.44 (dd, J = 8.6, 6.7 Hz, 2H, H7), 1.56 (dq, J = 13.7, 7.4 Hz, 2H, H8), 0.89 (t, J = 7.3 Hz, 3H, H9); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 159.3, 153.9, 150.5, 150.4, 144.7, 138.5, 137.7, 136.8, 135.7, 130.4, 130.2, 120.8, 119.0, 116.0, 113.5, 113.0, 111.8, 107.7, 74.8, 56.2, 56.1, 55.4, 40.1, 38.2, 24.6, 13.9; HRMS (ES $^{+}$) calc. for $\text{C}_{28}\text{H}_{33}\text{O}_5$ $[\text{M}+\text{H}]^{+}$ 449.2323, found 449.2329.

2-(4-Allyl-2-methoxyphenoxy)-6-Methoxy-4-propylphenol, 213

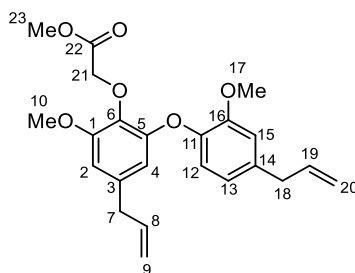
The product was prepared according to General Method J, using 1-(4-allyl-2-methoxyphenoxy)-3-methoxy-2-((4-methoxybenzyl)oxy)-5-propylbenzene, **212** (30 mg, 0.07 mmol, 1.0 eq), 1M aqueous HCl (0.5 mL) and ethanol (1.4 mL). The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 $\rightarrow$ 4 : 1)) to **213** (17 mg, 0.05 mmol, 75%) as a colourless oil; R_f 0.32 (pentane / EtOAc (4 : 1)); IR (thin film, $\nu_{\max}$ / cm^{-1}) 3441, 2931, 1596, 1507, 1452, 1431, 1309, 1238, 1151, 1092; ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.88 (d, J = 8.1 Hz, 1H, H12), 6.80 (d, J = 2.0 Hz, 1H, H15), 6.70 (dd, J = 8.1, 1.9 Hz, 1H, H13), 6.49 (d, J = 1.8 Hz, 1H, H2), 6.39 (d, J = 1.9 Hz, 1H, H4), 5.97 (ddt, J = 16.9, 10.1, 6.7 Hz, 1H, H19), 5.79 (s, 1H, H10), 5.15 – 5.04 (m, 2H, H20), 3.89 (s, 3H, H21), 3.87 (s, 3H, H17), 3.37 (dt, J = 6.7, 1.6 Hz, 2H, H18), 2.44 (dd, J = 8.6, 6.7 Hz, 2H, H7), 1.55 (dq, J = 16.0, 7.6 Hz, 2H, H8), 0.89 (t, J = 7.3 Hz, 3H, H9); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 150.5, 147.4, 144.4, 144.3, 137.4, 136.4, 134.9, 134.0, 120.9, 119.5, 116.1, 112.9, 111.8, 107.3, 56.3, 56.1, 40.1, 38.0, 24.8, 13.8; HRMS (ES $^{+}$) calc. for $\text{C}_{20}\text{H}_{25}\text{O}_4$ $[\text{M}+\text{H}]^{+}$ 329.1747, found 329.1747.

2-Methoxy-6-(2-methoxy-4-propylphenoxy)-4-propylphenol, 237

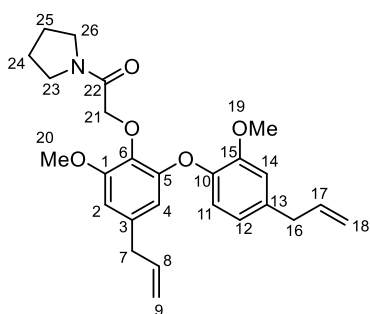
The product was prepared according to General Method K, using dehydrodieugenol B, **1** (50 mg, 0.15 mmol, 1.0 eq), hydrogen (balloon), Pd/C (10% w/w, 5.0 mmol, 0.05 mmol, 0.3 eq) and ethanol (2.5 mL). The reaction was complete after one hour to afford **237** (51 mg, 0.15 mmol, >99%) as a colourless oil; R_f 0.31 (pentane / EtOAc (4 : 1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.87 (d, J = 8.1 Hz, 1H), 6.79 (d, J = 1.9 Hz, 1H), 6.69 (dd, J = 8.1, 2.0 Hz, 1H), 6.49 (d, J = 1.8 Hz, 1H), 6.40 (d, J = 1.8 Hz, 1H), 5.85 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.56 (dd, J = 8.6, 6.7 Hz, 2H), 2.44 (dd, J = 8.6, 6.7 Hz, 2H), 1.64 (h, J = 7.2 Hz, 2H), 1.55 (h, J = 7.6 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 150.3, 147.8, 144.5, 144.0, 139.2, 135.0, 133.9, 120.8, 119.9, 112.9, 111.8, 107.3, 56.3, 56.1, 38.0, 24.8, 24.8, 14.0, 13.8; LRMS (ES⁺) calc. for $\text{C}_{20}\text{H}_{26}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 353.2, found 353.2. The experimental data are in good agreement with that described in the literature.⁹⁴

1-Methoxy-3-(2-methoxy-4-propylphenoxy)-2-((4-methoxybenzyl)oxy)-5-propylbenzene, 214

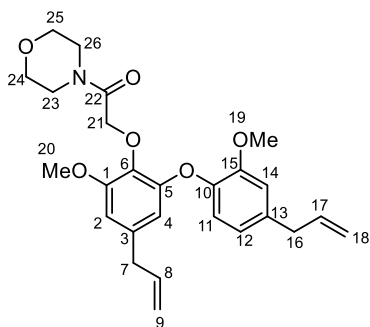
The product was prepared according to General Method I, using 2-methoxy-6-(2-methoxy-4-propylphenoxy)-4-propylphenol, **237** (50 mg, 0.15 mmol, 1.0 eq), PMBCl (25 μ L, 0.18 mmol, 1.3 eq), potassium carbonate (53 mg, 0.38 mmol, 2.5 eq) and DMF (1.3 mL). The reaction was complete after two hours. The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 $\rightarrow$ 9 : 1)) to afford **214** (53 mg, 0.12 mmol, 77%) as a white solid; MP 56 – 59 $^{\circ}$ C; R_f 0.69 (pentane / EtOAc (4 : 1)); IR (neat, $\nu_{\max}$ / cm^{-1}) 2957, 2860, 1607, 1505, 1437, 1376, 1298, 1220, 1173, 1077; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.34 – 7.27 (m, 2H, H23), 6.82 – 6.79 (m, 2H, H24), 6.78 (d, J = 1.9 Hz, 1H, H15), 6.73 (d, J = 8.2 Hz, 2H, H12), 6.66 (dd, J = 8.1, 1.9 Hz, 1H, H13), 6.47 (d, J = 1.9 Hz, 1H, H2), 6.31 (d, J = 1.9 Hz, 1H, H4), 4.97 (s, 2H, H21), 3.82 (s, 6H, H17, H26), 3.78 (s, 3H, H10), 2.56 (dd, J = 8.6, 6.7 Hz, 2H, H18), 2.45 (dd, J = 8.6, 6.7 Hz, 2H, H7), 1.65 (sext, J = 7.3 Hz, 2H, H19), 1.55 (sext, J = 7.4 Hz, 2H, H8), 0.96 (t, J = 7.3 Hz, 3H, H20), 0.89 (t, J = 7.3 Hz, 3H, H9); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 159.3, 153.8, 150.6, 150.3, 144.3, 138.5, 138.5, 136.4, 130.4, 130.2, 120.7, 118.9, 113.5, 113.1, 111.7, 107.6, 74.8, 56.2, 56.1, 55.4, 38.2, 38.0, 24.8, 24.6, 14.0, 13.9; HRMS (ES+) calc. for $\text{C}_{28}\text{H}_{35}\text{O}_5$ $[\text{M}+\text{H}]^+$ 451.2479, found 451.2479. HRMS (ES+) calc. for $\text{C}_{28}\text{H}_{35}\text{O}_5$ $[\text{M}+\text{H}]^+$ 451.2479, found 451.2479.

Methyl 2-(4-allyl-2-(4-allyl-2-methoxyphenoxy)-6-methoxyphenoxy)acetate, 217

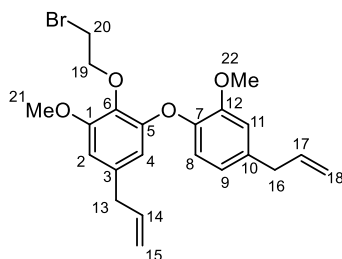
To a flask containing a solution of dihydrodieugenol B, **1** (50 mg, 0.15 mmol, 1.0 eq) in acetone (0.25 mL) was added potassium carbonate (32 mg, 0.23 mmol, 1.5 eq) and methyl bromoacetate (22 μ L, 0.23 mmol, 1.5 eq). The reaction was stirred at room temperature for 20 hours, after which time an additions portion of potassium carbonate (32 mg, 0.23 mmol, 1.5 eq) and methyl bromoacetate (22 μ L, 0.23 mmol, 1.5 eq) were added. After a further four hours, TLC showed consumption of the atarting material. The reaction mixture was filtered through a pad of celite, and the filtrate dried over MgSO_4 and the solvent removed *in vacuo*. The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 $\rightarrow$ 4 : 1)) to afford **217** (60 mg, 0.15 mmol, 98%) as a colourless oil; R_f 0.31 (pentane / EtOAc (4 : 1)); IR (neat, ν_{max} / cm^{-1}) 2919, 2850, 2361, 1766, 1738, 1589, 1507, 1428, 1212, 1152; ^1H NMR (400 MHz, CDCl_3) δ 6.84 (d, J = 8.1 Hz, 1H, H12), 6.78 (d, J = 1.9 Hz, 1H, H15), 6.70 (dd, J = 7.9, 2.0, 1H, H13), 6.46 (d, J = 1.9 Hz, 1H, H2), 6.23 (d, J = 1.8 Hz, 1H, H4), 5.97 (ddt, J = 16.9, 10.1, 6.7 Hz, 1H, H19), 5.86 (ddt, J = 17.5, 9.5, 6.6 Hz, 1H, H8), 5.17 – 4.95 (m, 4H, H9, H20), 4.68 (s, 2H, H21), 3.84 (s, 3H, H17), 3.80 (s, 3H, H10), 3.73 (s, 3H, H23), 3.36 (dt, J = 6.6, 1.5 Hz, 2H, H7), 3.22 (dt, J = 6.7, 1.5, 2H, H18); ^{13}C NMR (101 MHz, CDCl_3) δ_c 170.0, 153.2, 150.8, 150.5, 143.7, 137.5, 137.1, 136.5, 136.1, 136.0, 120.9, 120.1, 116.1, 116.0, 113.2, 111.0, 107.3, 69.8, 56.3, 56.0, 52.0, 40.2, 40.1; HRMS (ES^+) calc. for $\text{C}_{23}\text{H}_{27}\text{O}_6$ $[\text{M}+\text{H}]^+$ 399.1802, found 399.1795.

2-(4-Allyl-2-(4-allyl-2-methoxyphenoxy)-6-methoxyphenoxy)-1-(pyrrolidin-1-yl)Ethan-1-one,**218**

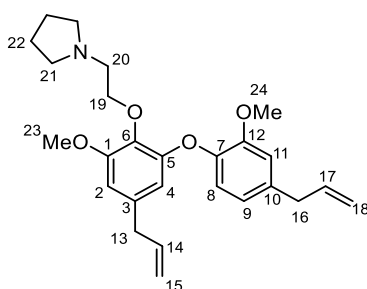
Methyl 2-(4-allyl-2-(4-allyl-2-methoxyphenoxy)-6-methoxyphenoxy)acetate, **217** (40 mg, 0.10 mmol, 1.0 eq) was stirred with pyrrolidine (44 μ L, 0.52 mmol, 5.2 eq) at 60 °C for 24 hours, after which time TLC showed consumption of the starting material. The reaction was cooled to room temperature and dissolved in EtOAc (5 mL), and washed with saturated aqueous NH_4Cl (3×5 mL). The organic layer was dried over MgSO_4 , filtered, and the solvent removed *in vacuo*. The crude residue was purified via flash column chromatography (pentane / EtOAc (1 : 0 $\rightarrow$ 3 : 7)) to afford **218** (41 mg, 0.09 mmol, 92%) as a pale yellow oil; R_f 0.14 (pentane / EtOAc (1 : 1)); IR (thin film, ν_{max} / cm^{-1}) 2923, 1639, 1588, 1505, 1451, 1426, 1265, 1212, 1152, 1091; ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.80 (d, J = 8.1 Hz, 1H, H11), 6.78 (d, J = 2.3 Hz, 1H, H14), 6.69 (dd, J = 8.1, 2.0 Hz, 1H, H12), 6.48 (d, J = 1.9 Hz, 1H, H2), 6.26 (d, J = 1.9 Hz, 1H, H4), 5.97 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H, H17), 5.87 (ddt, J = 17.5, 9.5, 6.6 Hz, 1H, H8), 5.14 – 4.97 (m, 4H, H9, H18), 4.63 (s, 2H, H21), 3.85 (s, 3H, H20), 3.81 (s, 3H, H19), 3.59 (t, J = 6.7 Hz, 2H, H23), 3.43 (t, J = 6.8 Hz, 2H, H24), 3.36 (dt, J = 6.8, 1.5 Hz, 2H, H16), 3.22 (dt, J = 6.6, 1.6 Hz, 2H, H7), 1.88 – 1.79 (m, 2H, H26), 1.79 – 1.70 (m, 2H, H23); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 167.1, 153.6, 150.6, 150.5, 144.2, 137.5, 137.1, 136.4, 136.3, 136.2, 121.0, 119.5, 116.1, 116.0, 113.1, 111.5, 107.6, 73.0, 56.3, 56.1, 46.2, 46.2, 40.2, 40.1, 26.4, 24.0; HRMS (ES^+) calc. for $\text{C}_{26}\text{H}_{32}\text{O}_5\text{N}$ $[\text{M}+\text{H}]^+$ 438.2275, found 438.2271.

2-(4-Allyl-2-(4-allyl-2-methoxyphenoxy)-6-methoxyphenoxy)-1-Morpholinoethan-1-one, 219

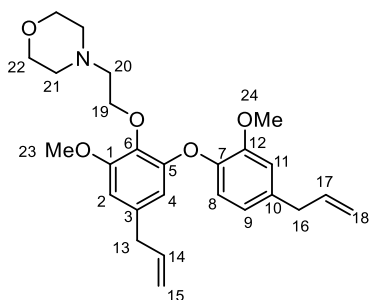
Methyl 2-(4-allyl-2-(4-allyl-2-methoxyphenoxy)-6-methoxyphenoxy)acetate, **217** (40 mg, 0.10 mmol, 1.0 eq) was stirred with morpholine (46 μ L, 0.52 mmol, 5.2 eq) at 60 °C for 24 hours, after which time TLC showed consumption of the starting material. The reaction was cooled to room temperature and dissolved in EtOAc (5 mL), and washed with saturated aqueous NH_4Cl (3×5 mL). The organic layer was dried over MgSO_4 , filtered, and the solvent removed *in vacuo*. The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 $\rightarrow$ 3 : 7)) to afford **219** (46 mg, 0.10 mmol, >99%) as a colourless oil; R_f 0.29 (pentane / EtOAc (1 : 1)); IR (thin film, ν_{max} / cm^{-1}) 2921, 2854, 1649, 1589, 1506, 1452, 1267, 1212, 1152, 1091; ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.82 – 6.75 (m, 2H, H11, H14), 6.70 (dd, J = 8.1, 1.9 Hz, 1H, H12), 6.48 (d, J = 1.9 Hz, 1H, H2), 6.25 (d, J = 1.9 Hz, 1H, H4), 5.97 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H, H17), 5.92 – 5.80 (m, 1H, H8), 5.14 – 4.97 (m, 4H, H9, H18), 4.66 (s, 2H, H21), 3.85 (s, 3H, H19), 3.82 (s, 3H, H20), 3.79 – 3.72 (m, 2H, H26), 3.65 – 3.59 (m, 2H, H23), 3.58 – 3.51 (m, 5H, H24), 3.37 (dt, J = 6.7, 1.7 Hz, 2H, H16), 3.23 (dt, J = 6.7, 1.6 Hz, 2H, H7); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 167.1, 154.4, 150.0, 144.4, 137.4, 137.0, 136.8, 136.5, 136.1, 121.0, 119.5, 116.2, 116.2, 113.1, 111.3, 107.5, 72.7, 67.1, 66.9, 56.2, 56.0, 46.3, 42.5, 40.2, 40.1; HRMS (ES $^{+}$) calc. for $\text{C}_{26}\text{H}_{32}\text{O}_6\text{N}$ $[\text{M}+\text{H}]^{+}$ 454.2224, found 454.2224.

5-Allyl-1-(4-allyl-2-methoxyphenoxy)-2-(2-bromoethoxy)-3-methoxybenzene, **222**

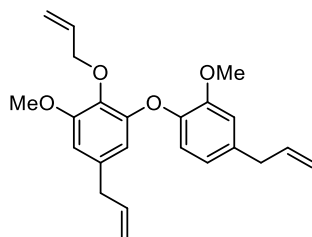
To a solution of dehydrodieugenol B, **1** (109 mg, 0.33 mmol, 1.0 eq) in acetonitrile (1.7 mL) was added potassium carbonate (138 mg, 1.00 mmol, 3.0 eq) and 1,2-dibromoethane (144 μ L, 1.67 mmol, 5.0 eq) and the resulting suspension was heated to 80 $^{\circ}$ C. After 18 hours, the reaction was cooled to room temperature, filtered, and the solvent removed *in vacuo*. The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 $\rightarrow$ 4 : 1)) to afford **222** (72 mg, 0.17 mmol, 50%) as a pale yellow oil; R_f 0.40 (pentane / EtOAc (4 : 1)); IR (thin film, $\nu_{\max}$ / cm^{-1}) 2935, 2360, 1638, 1587, 1595, 1424, 1266, 1187, 1152, 1092; ^1H NMR (400 MHz, CDCl_3) 6.74 (d, J = 8.1 Hz, 1H, H8), 6.73 (d, J = 1.9 Hz, 1H, H11), 6.63 (dd, J = 8.1, 2.0 Hz, 1H H9), 6.40 (d, J = 1.9 Hz, 1H, H2), 6.19 (d, J = 1.9 Hz, 1H, H4), 5.91 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H, H14), 5.86 – 5.74 (m, 1H, H17), 5.07 – 4.92 (m, 4H, H15, H19), 4.27 – 4.17 (m, 2H, H19), 3.78 (s, 3H, H21), 3.75 (s, 3H, H22), 3.51 – 3.43 (m, 2H, H20), 3.30 (dt, J = 6.7, 1.6 Hz, 2H, H16), 3.16 (dt, J = 6.7, 1.5 Hz, 2H, H13); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 153.5, 150.7, 150.6, 143.7, 137.4, 137.0, 136.3, 136.2, 136.1, 120.8, 119.7, 116.0, 115.9, 113.0, 111.0, 107.2, 72.7, 56.1, 55.9, 40.1, 40.0, 29.5; HRMS (ES $^{+}$) calc. for $\text{C}_{22}\text{H}_{26}\text{O}_4\text{Br}$ $[\text{M}+\text{H}]^{+}$ 433.1009, found 433.1010.

1-(2-(4-Allyl-2-(4-allyl-2-methoxyphenoxy)-6-methoxyphenoxy)ethyl)pyrrolidine, 220

To a solution of 5-allyl-1-(4-allyl-2-methoxyphenoxy)-2-(2-bromoethoxy)-3-methoxybenzene, **222** (35 mg, 0.08 mmol, 1.0 eq) in acetone (5 mL) was added potassium carbonate (112 mg, 0.80 mmol, 10.0 eq), potassium iodide (27 mg, 0.16 mmol, 2.0 eq) and pyrrolidine (34 μ L, 0.40 mmol, 5.0 eq). The reaction was stirred at 75 $^{\circ}$ C for 18 hours, before being cooled to room temperature and diluted with EtOAc (10 mL). The organic phase was washed with 0.1 M aqueous HCl (10 mL) and brine (10 mL), before being dried over MgSO_4 , filtered, and the solvent removed *in vacuo*. The crude residue was purified *via* flash column chromatography (DCM / MeOH (1 : 0 $\rightarrow$ 9 : 1)) to afford **220** (8 mg, 0.02 mmol, 23%) as a pale yellow oil; R_f 0.23 (DCM / MeOH (19 : 1)); IR (thin film, ν_{max} / cm^{-1}) 2919, 2850, 2361, 1589, 1507, 1463, 1428, 1266, 1212, 1154; ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.77 – 6.82 (m, 2H, H8, H11), 6.70 (dd, J = 8.1, 2.0 Hz, 1H, H9), 6.47 (d, J = 2.0 Hz, 1H, H2), 6.26 (d, J = 1.9 Hz, 1H, H4), 6.03 – 5.92 (m, 1H, H17), 5.92 – 5.82 (m, 1H, H14), 5.13 – 4.98 (m, 4H, H15, H18), 4.29 (t, J = 5.5 Hz, 2H, H20), 3.85 (s, 3H, H23), 3.82 (s, 3H, H24), 3.37 (dt, J = 6.7, 1.6 Hz, 2H, H16), 3.23 (dt, J = 6.6, 1.6 Hz, 2H, H13), 3.14 – 3.05 (m, 2H, H20), 3.04 – 2.89 (m, H21), 2.03 – 1.73 (m, 4H, H24); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 153.8, 150.6, 150.5, 144.4, 137.6, 137.2, 137.1, 136.0, 135.8, 120.9, 119.3, 116.1, 116.0, 113.1, 111.7, 107.6, 71.1, 56.2, 56.1, 55.4, 54.3, 40.2, 40.1; HRMS (ES $^{+}$) calc. for $\text{C}_{26}\text{H}_{34}\text{O}_4\text{N}$ $[\text{M}+\text{H}]^{+}$ 424.2482, found 424.2479.

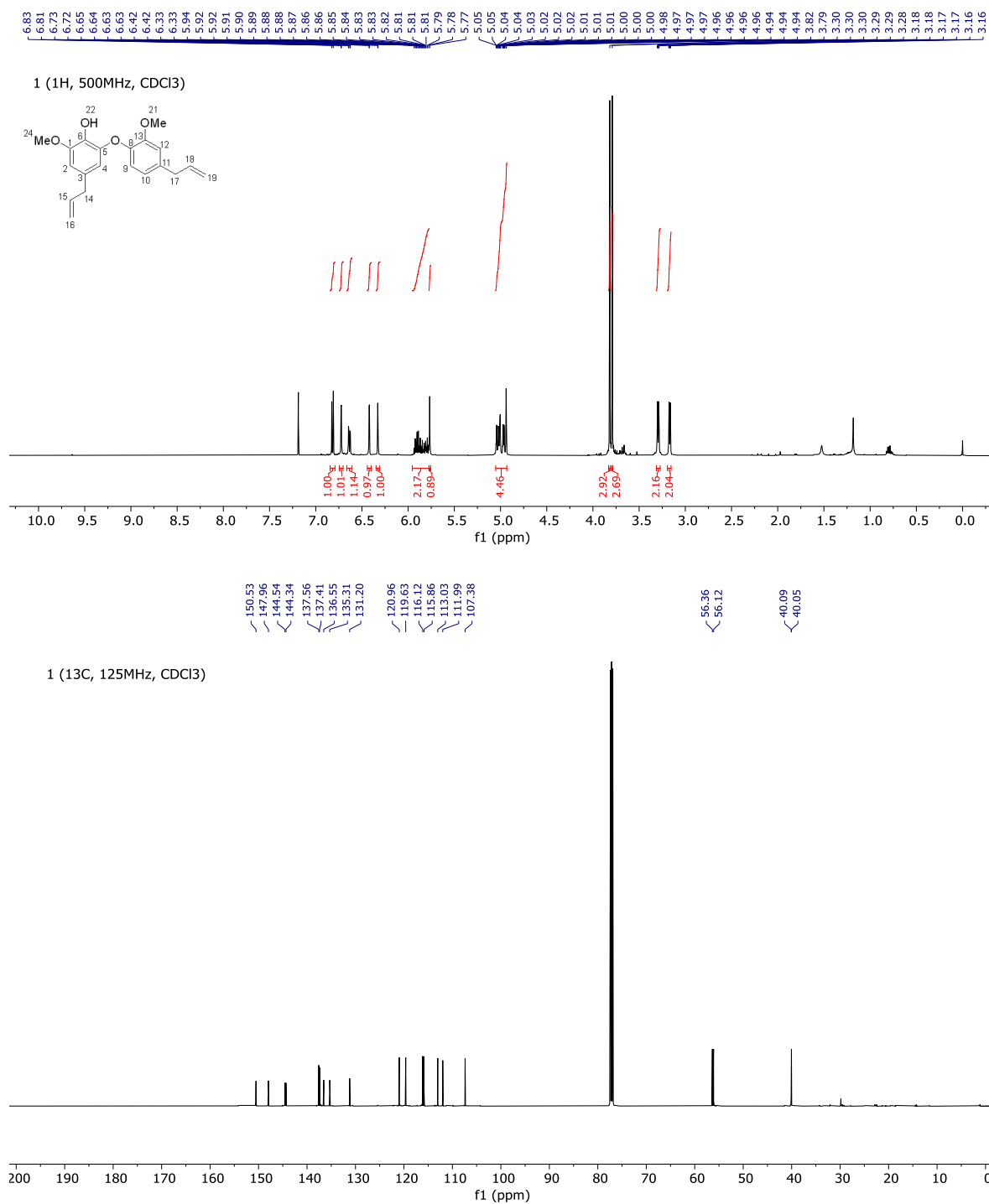
4-(2-(4-Allyl-2-(4-allyl-2-methoxyphenoxy)-6-methoxyphenoxy)ethyl)morpholine, 221

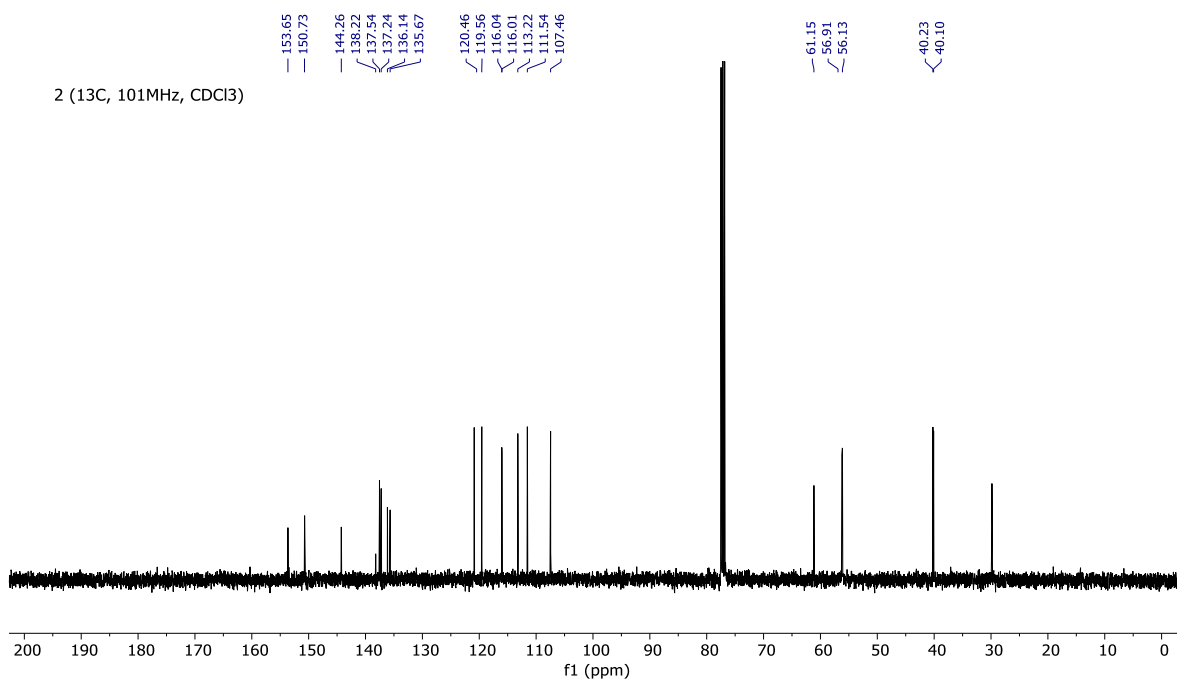
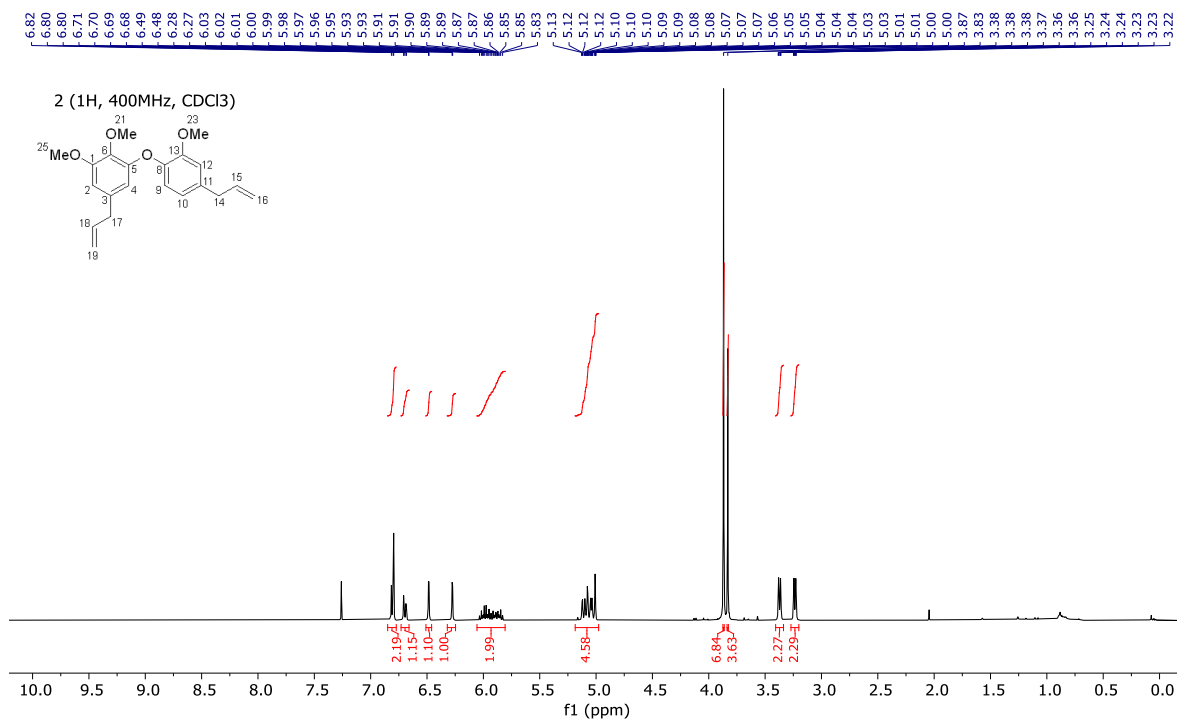
To a solution of 5-allyl-1-(4-allyl-2-methoxyphenoxy)-2-(2-bromoethoxy)-3-methoxybenzene, **222** (35 mg, 0.08 mmol, 1.0 eq) in acetone (5 mL) was added potassium carbonate (112 mg, 0.80 mmol, 10.0 eq), potassium iodide (27 mg, 0.16 mmol, 2.0 eq) and morpholine (35 μ L, 0.40 mmol, 5.0 eq). The reaction was stirred at 75 $^{\circ}$ C for 18 hours, before being cooled to room temperature and diluted with EtOAc (10 mL). The organic phase was washed with 0.1 M aqueous HCl (10 mL) and brine (10 mL), before being dried over MgSO_4 , filtered, and the solvent removed *in vacuo*. The crude residue was purified *via* flash column chromatography (pentane / EtOAc (1 : 0 $\rightarrow$ 0 : 1)) to afford **221** (30 mg, 0.07 mmol, 83%) as a colourless oil; R_f 0.30 (pentane / EtOAc (3 : 7)); IR (thin film, ν_{max} / cm^{-1}) 2921, 2851, 1586, 1505, 1452, 1425, 1330, 1265, 1151, 1092; ^1H NMR (400 MHz, CDCl_3) 6.78 (d, J = 2.0 Hz, 1H, H11), 6.75 (d, J = 8.1 Hz, 1H, H8), 6.67 (dd, J = 8.1, 1.9 Hz, 1H, H9), 6.48 (d, J = 2.0 Hz, 1H, H2), 6.31 (d, J = 1.9 Hz, 1H, H4), 6.03 – 5.91 (m, 1H, H17), 5.91 – 5.81 (m, 1H, H14), 5.14 – 4.98 (m, 4H, H15, H18), 4.12 (t, J = 5.7 Hz, 2H, H20), 3.69 – 3.62 (m, 4H, H21, H21), 3.36 (dd, J = 6.7, 1.6 Hz, 2H, H20), 3.24 (dt, J = 6.6, 1.5 Hz, 2H, H16), 2.69 (t, J = 5.7 Hz, 2H, H13), 2.53 – 2.46 (m, 4H, H22); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 153.8, 150.5, 150.3, 144.5, 137.5, 137.4, 137.2, 135.8, 135.8, 120.8, 118.9, 116.1, 116.0, 113.0, 112.0, 107.7, 70.5, 67.1, 58.4, 56.1, 56.0, 53.9, 40.2, 40.1; HRMS (ES $^{+}$) calc. for $\text{C}_{26}\text{H}_{34}\text{O}_5\text{N}$ $[\text{M}+\text{H}]^{+}$ 440.2431, found 440.2422.

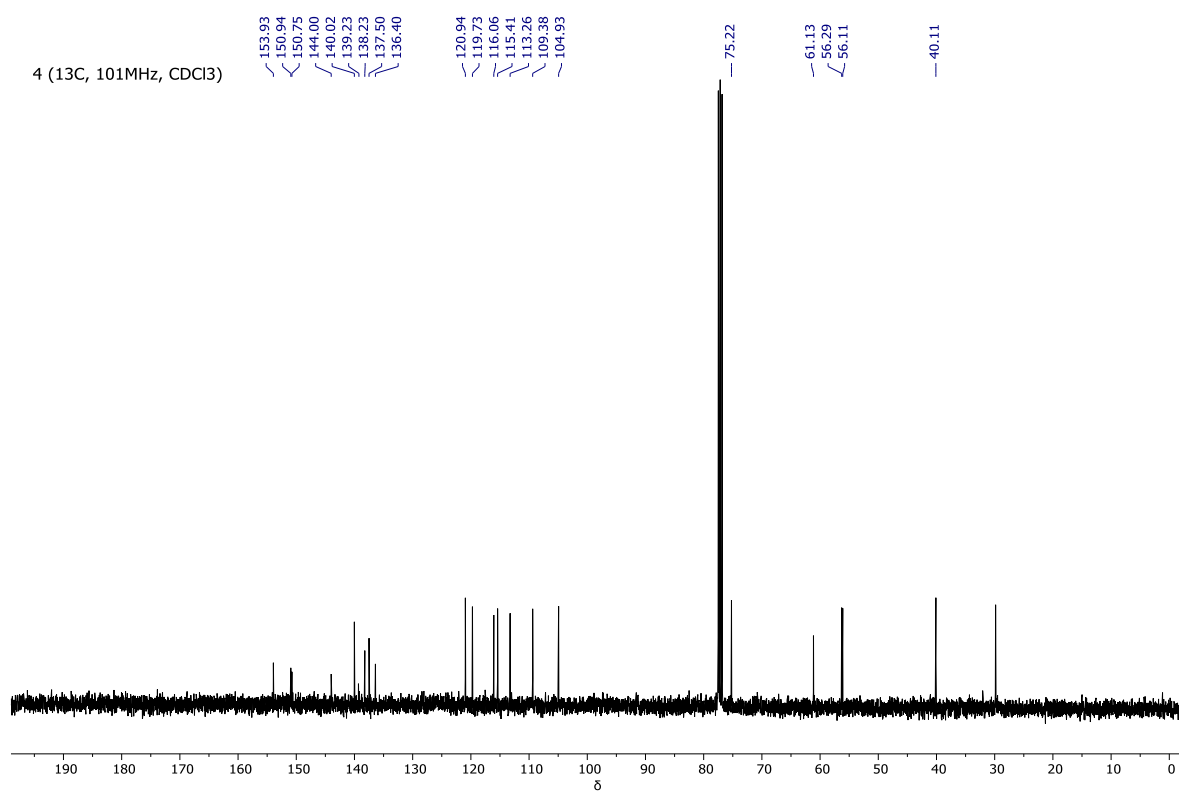
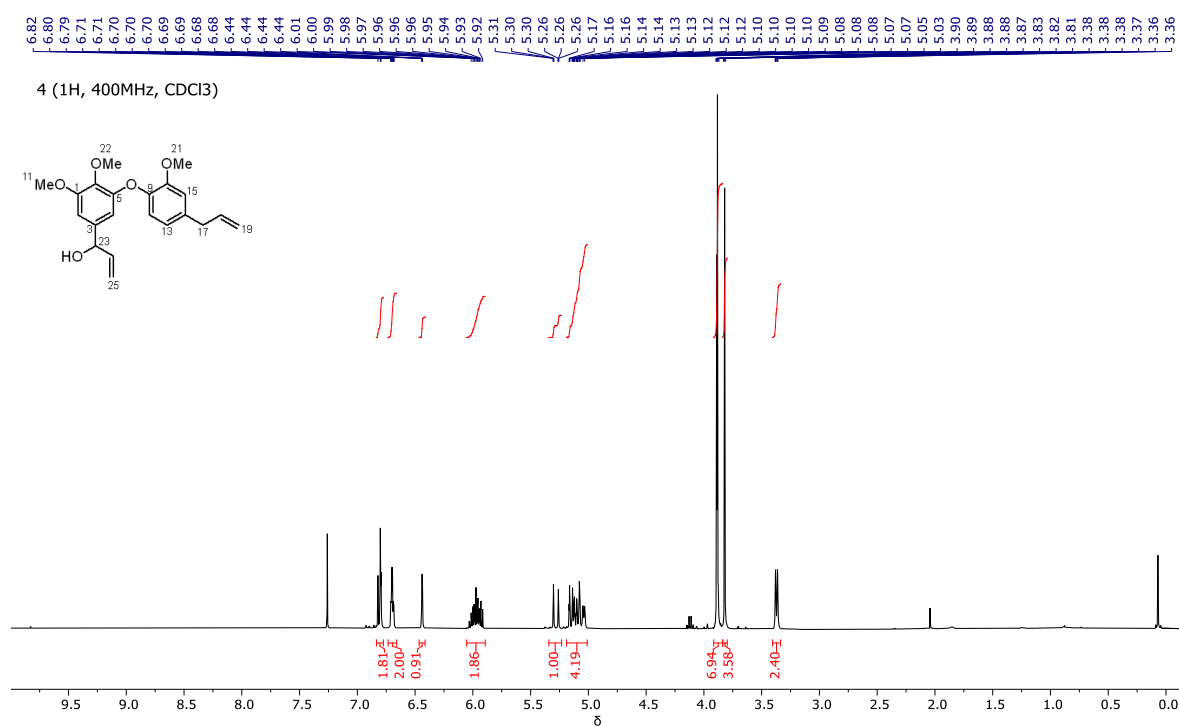
5-Allyl-1-(4-allyl-2-methoxyphenoxy)-2-(allyloxy)-3-methoxybenzene, 236

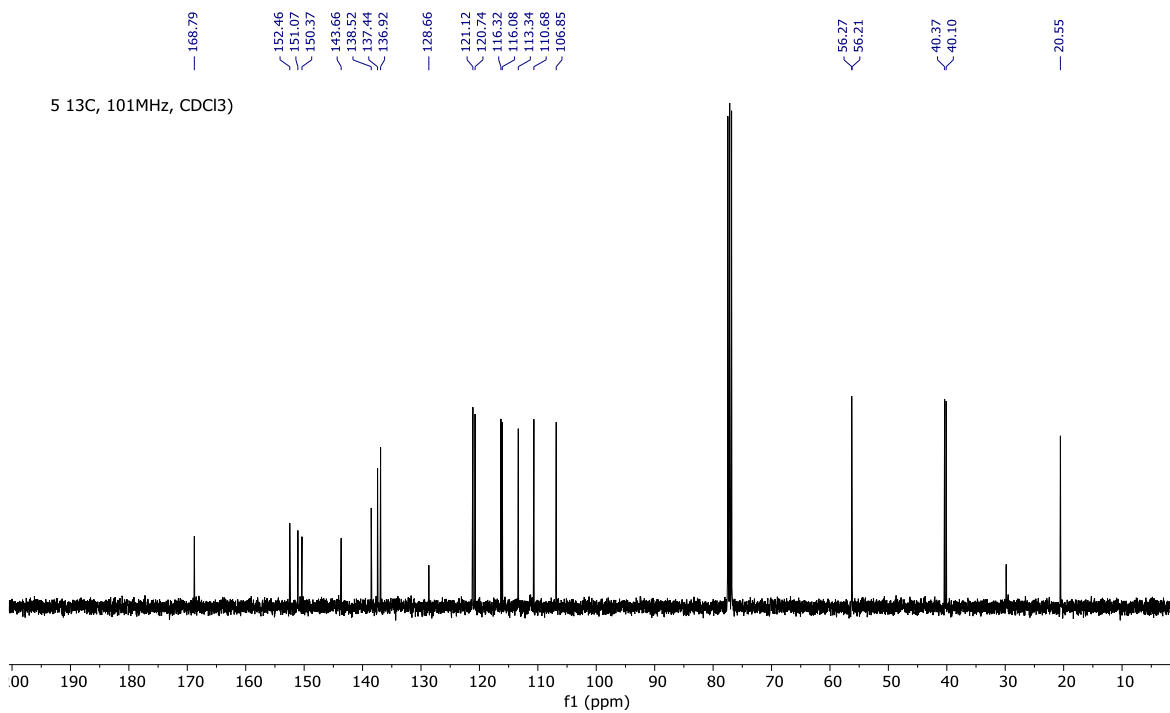
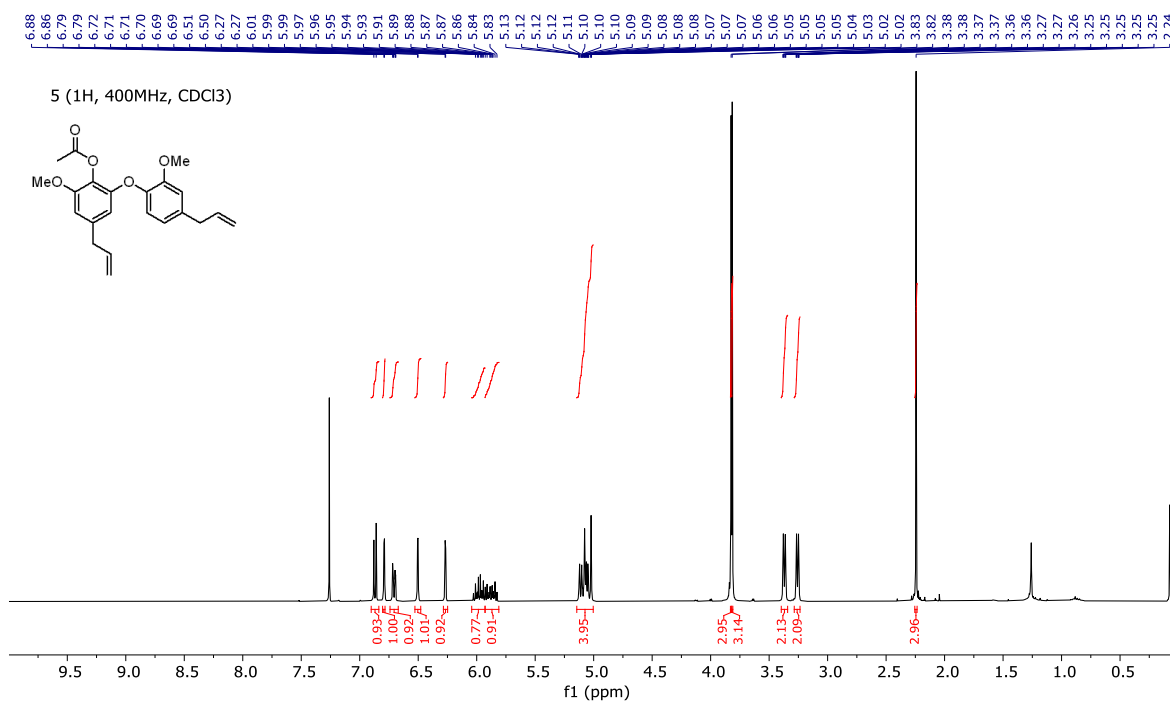
The product was prepared according to General Method M, using dehydrodieugenol B, **1** (50 mg, 0.15 mmol, 1.0 eq), allyl bromide (20 μ L, 0.23 mmol, 1.5 eq), potassium carbonate (53 mg, 0.38 mmol, 2.5 eq) and DMF (0.15 mL). The reaction was complete after 1.5 hours. The crude residue was purified *via* flash column chromatography (hexane / diethyl ether (9 : 1)) to afford **236** (52 mg, 0.14 mmol, 93%) as a colourless oil; R_f 0.81 (pentane / EtOAc (4 : 1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.79 (m, 2H), 6.69 (dd, J = 8.1, 1.9 Hz, 1H), 6.48 (d, J = 1.9 Hz, 1H), 6.30 (d, J = 1.9 Hz, 1H), 6.11 – 5.82 (m, 3H), 5.24 (dq, J = 17.2, 1.6 Hz, 1H), 5.16 – 4.98 (m, 5H), 4.55 (dt, J = 6.0, 1.4 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.37 (dt, J = 6.7, 1.6 Hz, 2H), 3.24 (dt, J = 6.6, 1.6 Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 153.9, 150.8, 150.6, 144.4, 137.5, 137.2, 136.8, 135.9, 135.7, 134.7, 120.8, 119.3, 117.5, 116.0, 115.9, 113.2, 111.6, 107.5, 56.2, 56.2, 56.1, 40.2, 40.0; HRMS (ES⁺) calc. for $\text{C}_{23}\text{H}_{27}\text{O}_4$ $[\text{M}+\text{H}]^+$ 367.1904, found 367.1902. The experimental data are in good agreement with that described in the literature.⁹⁴

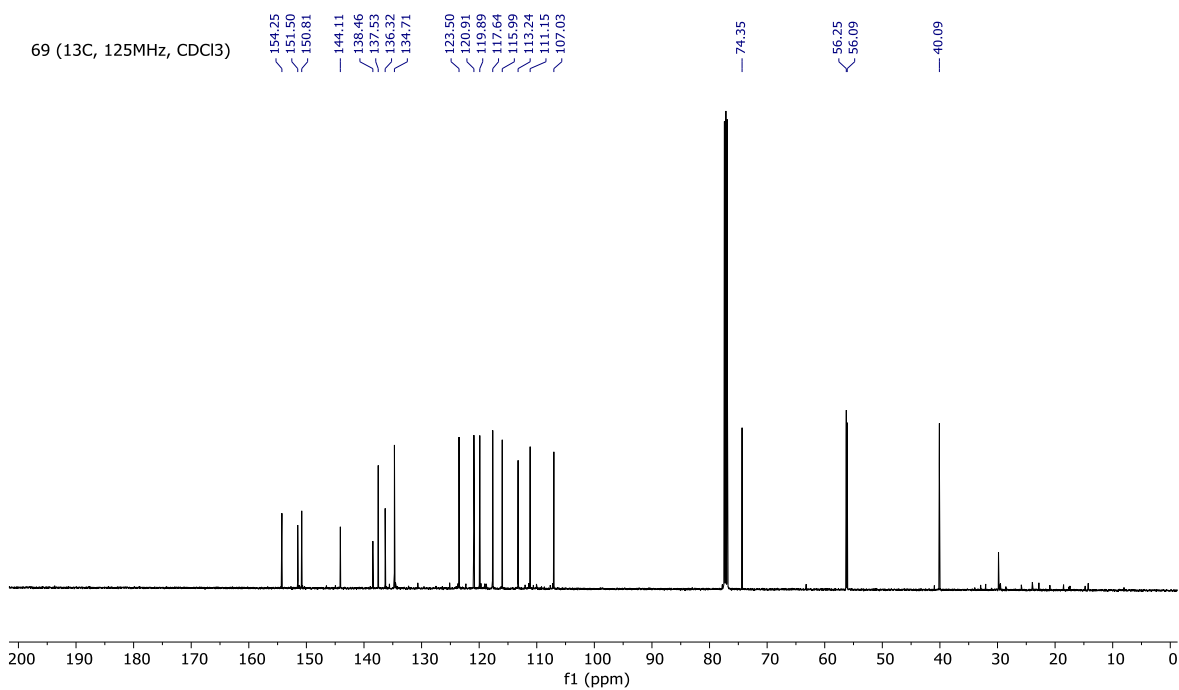
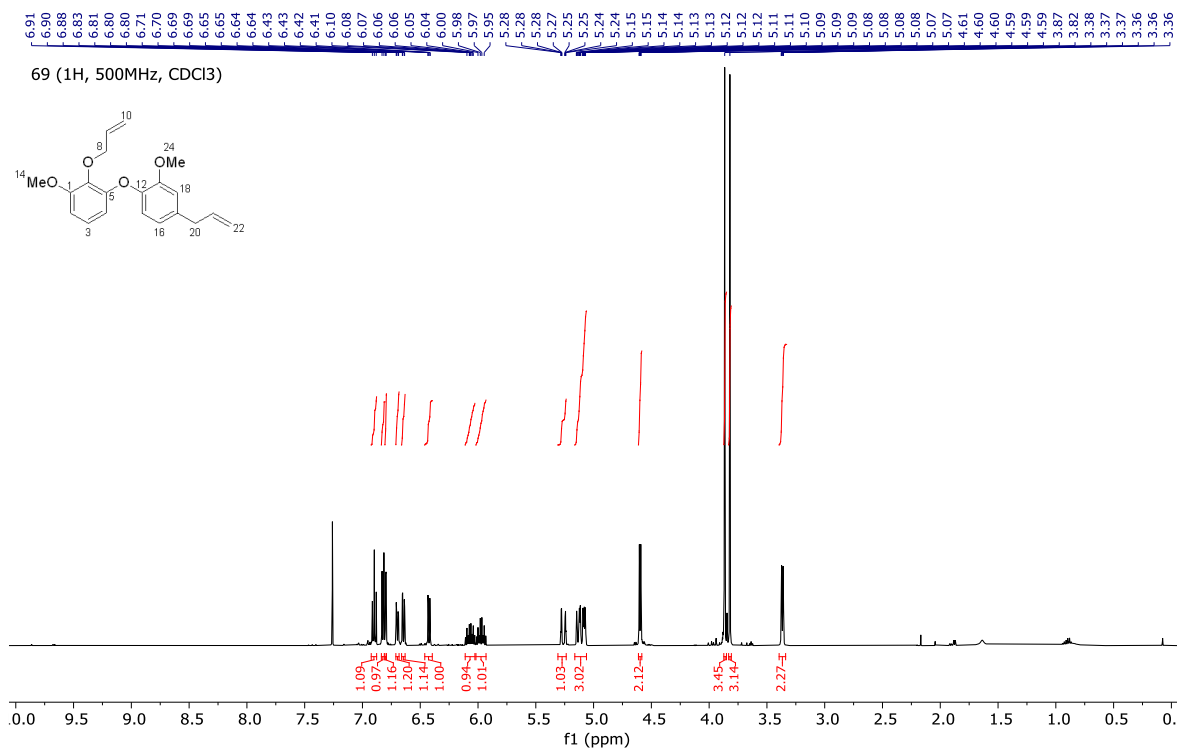
6.3 NMR Spectra of Final Compounds

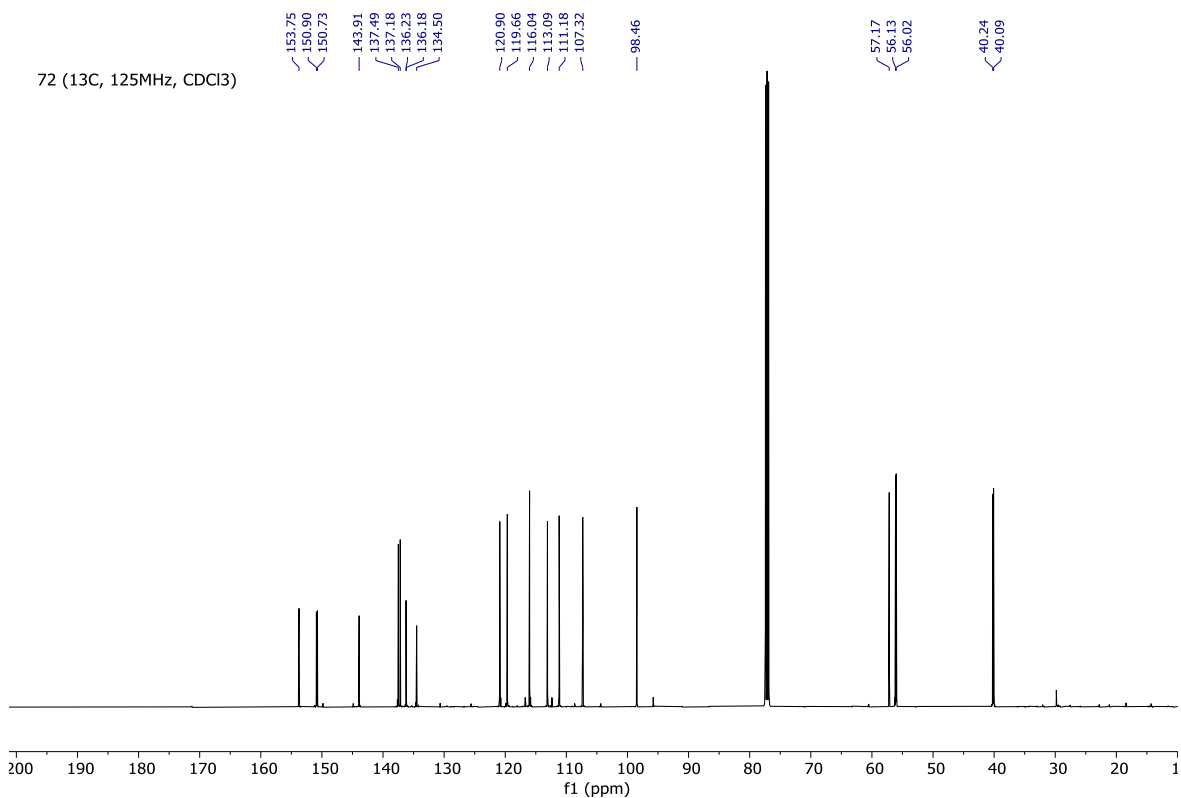
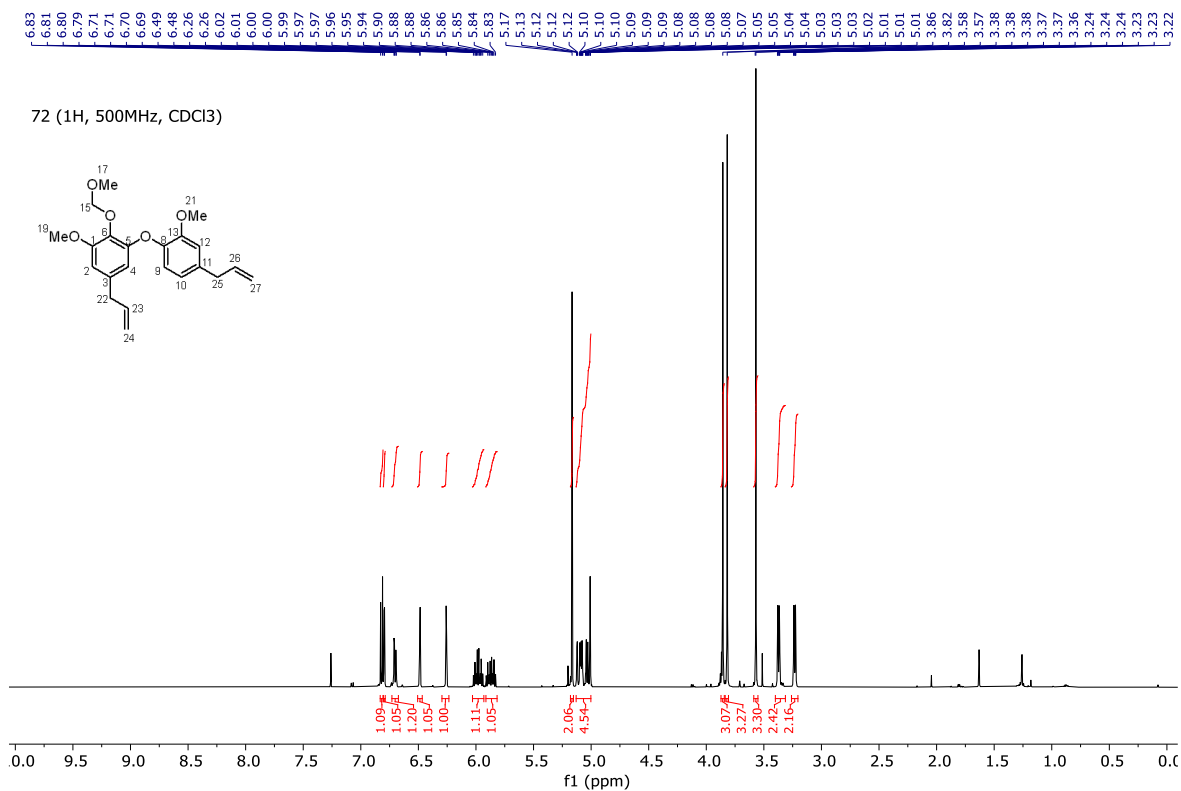


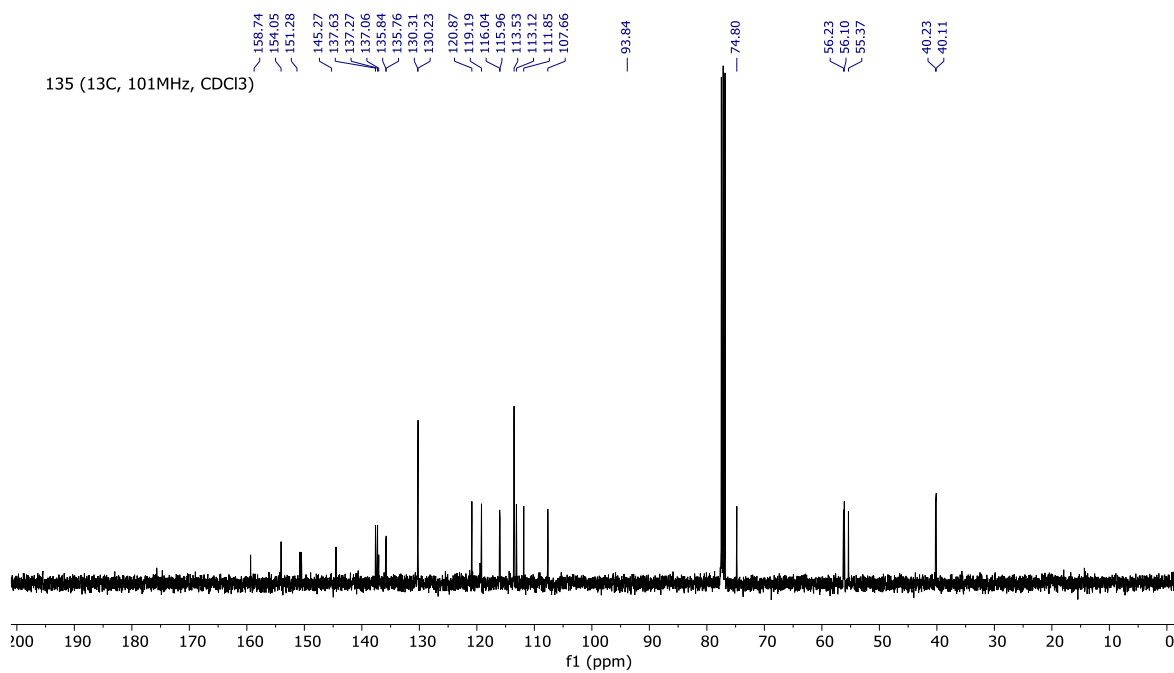
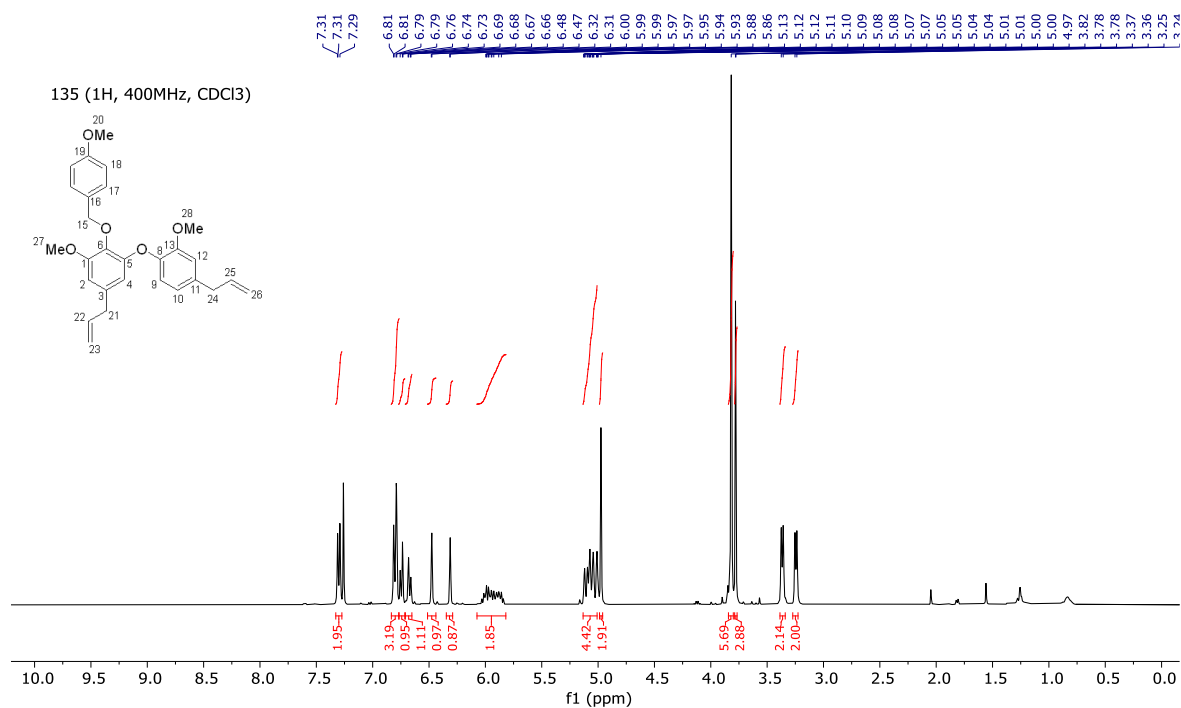


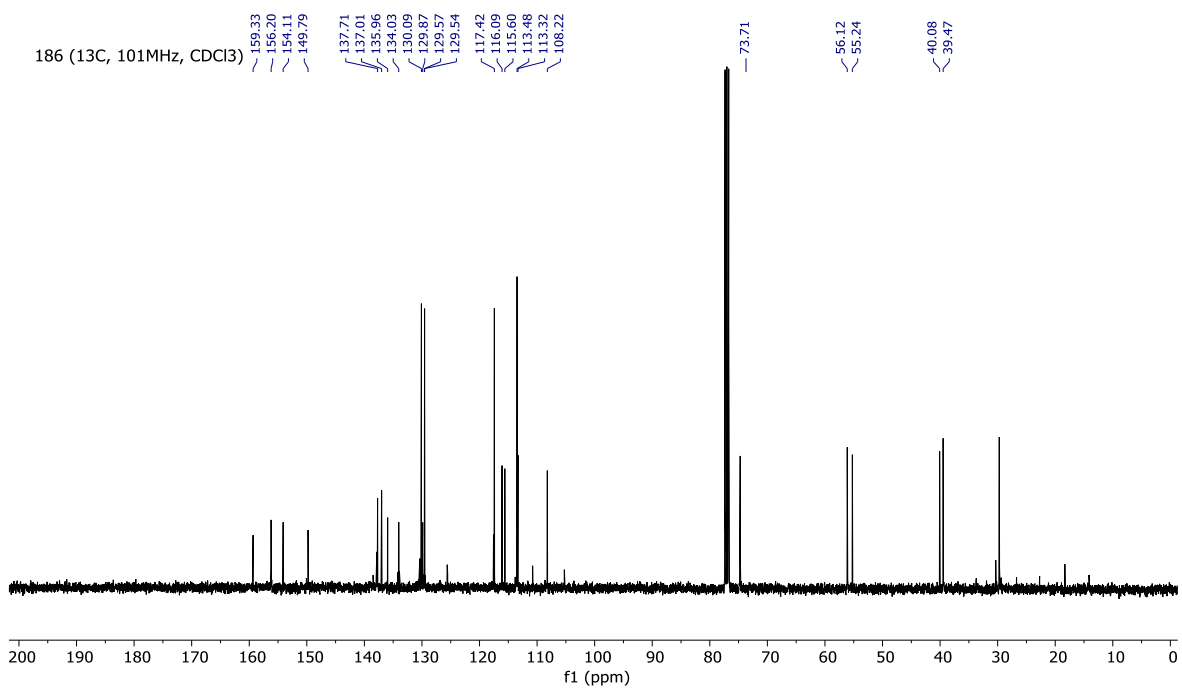
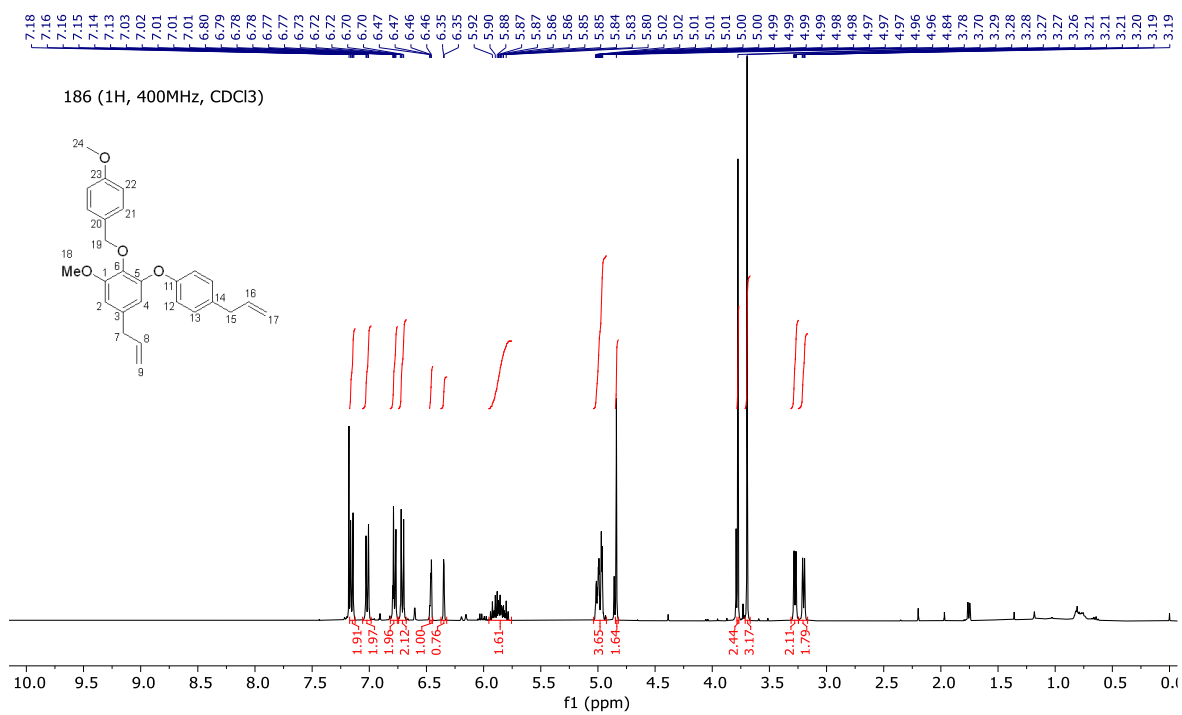


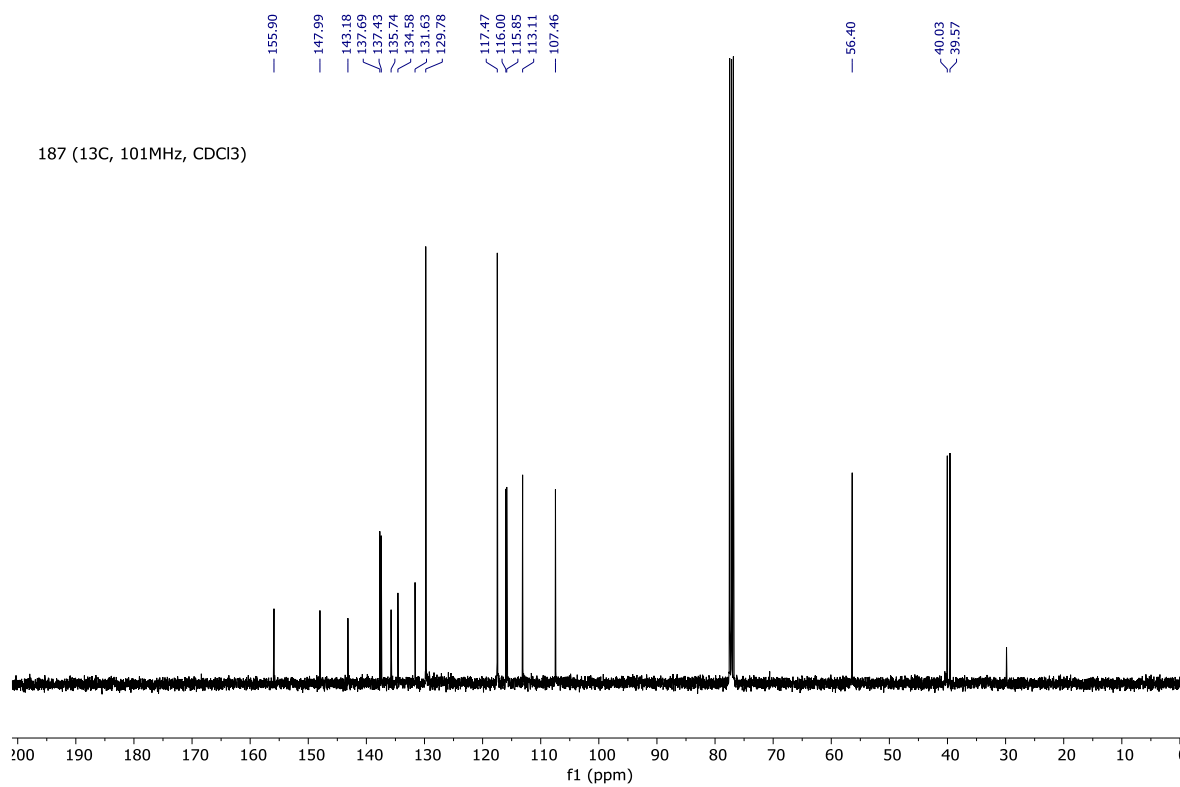
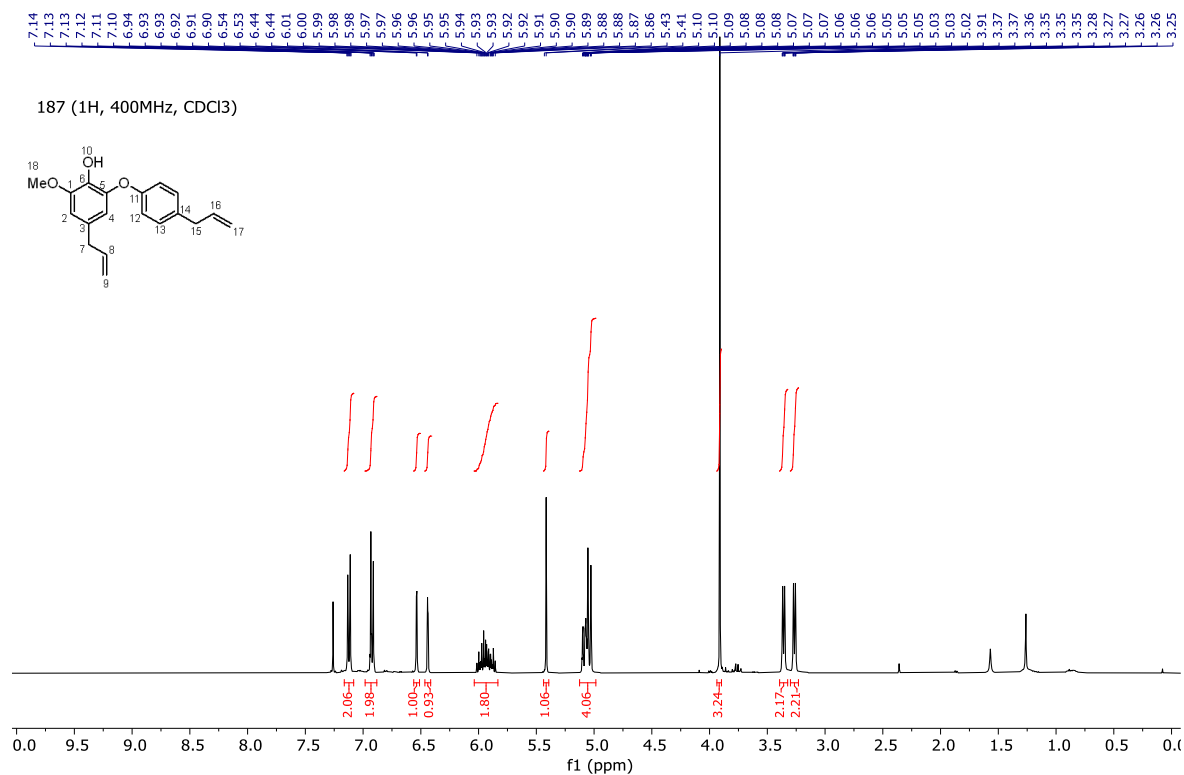


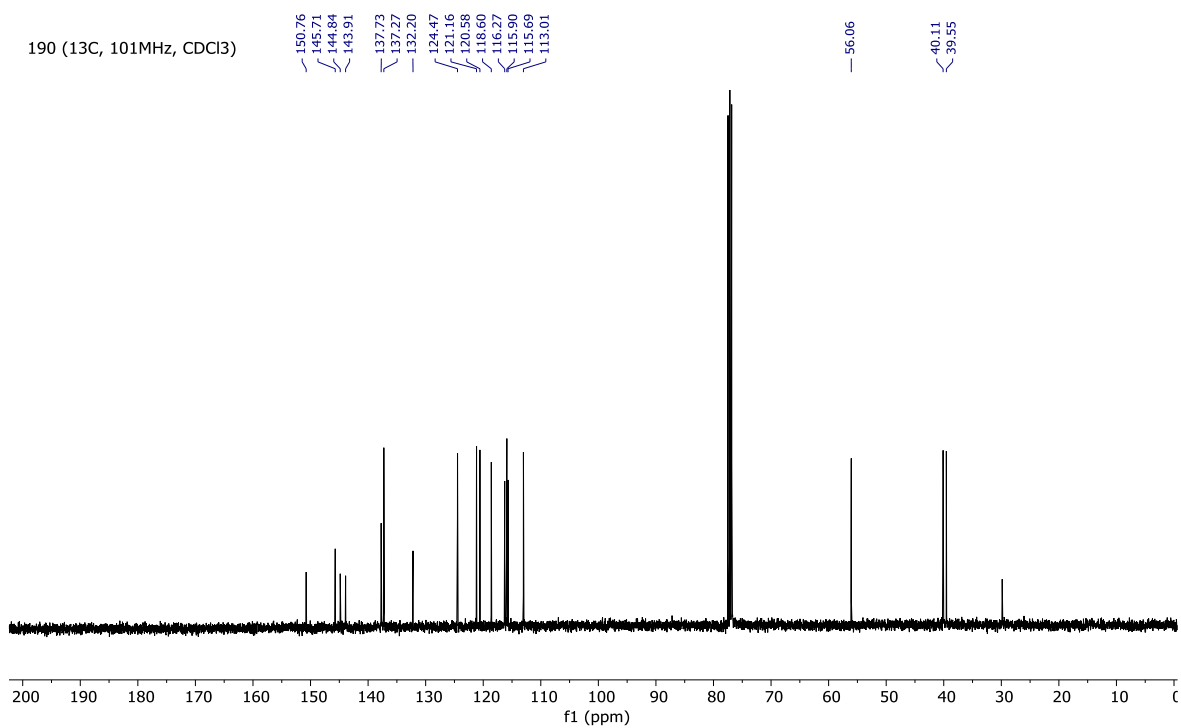
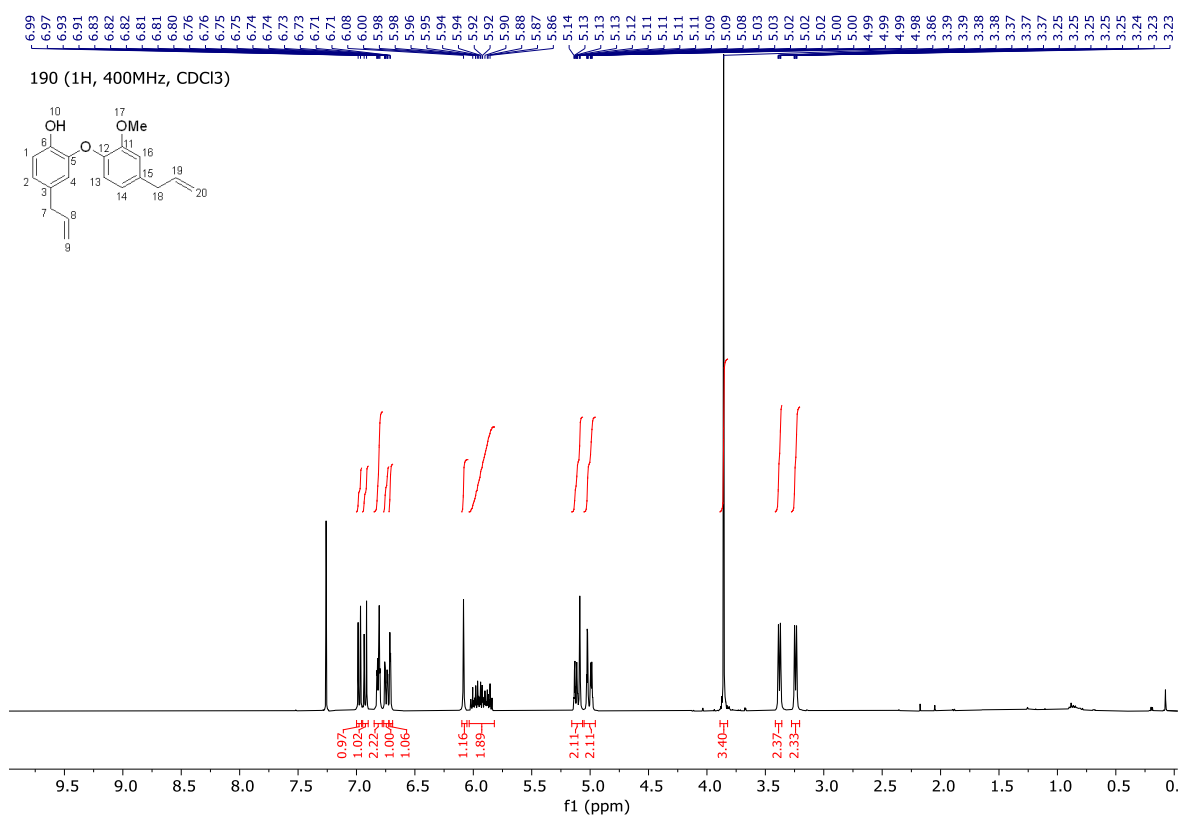


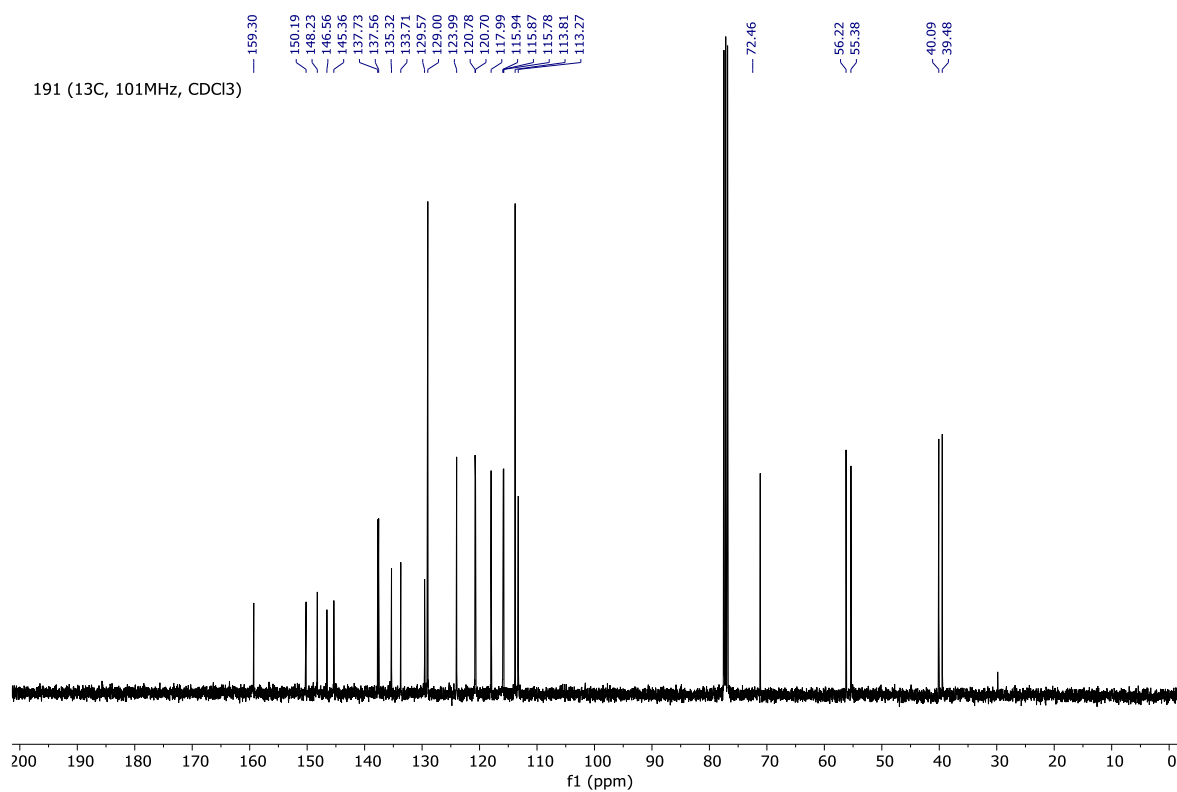
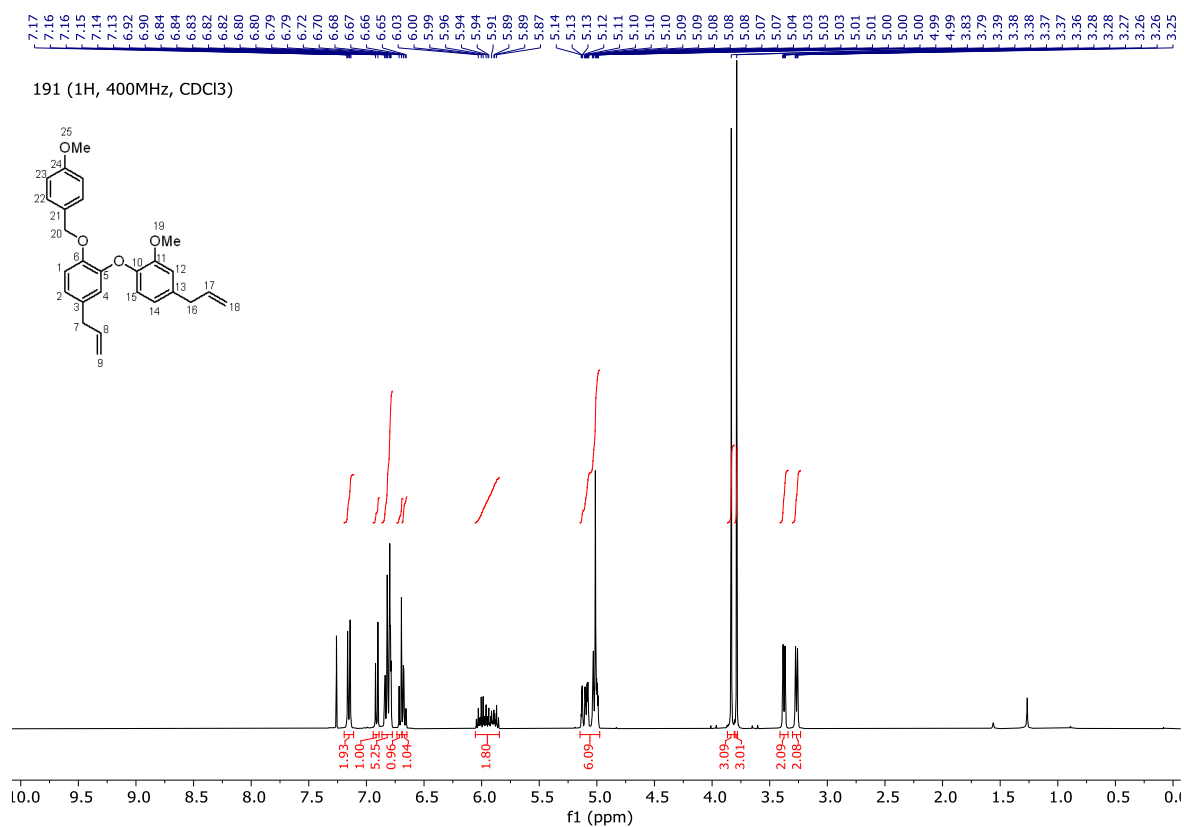


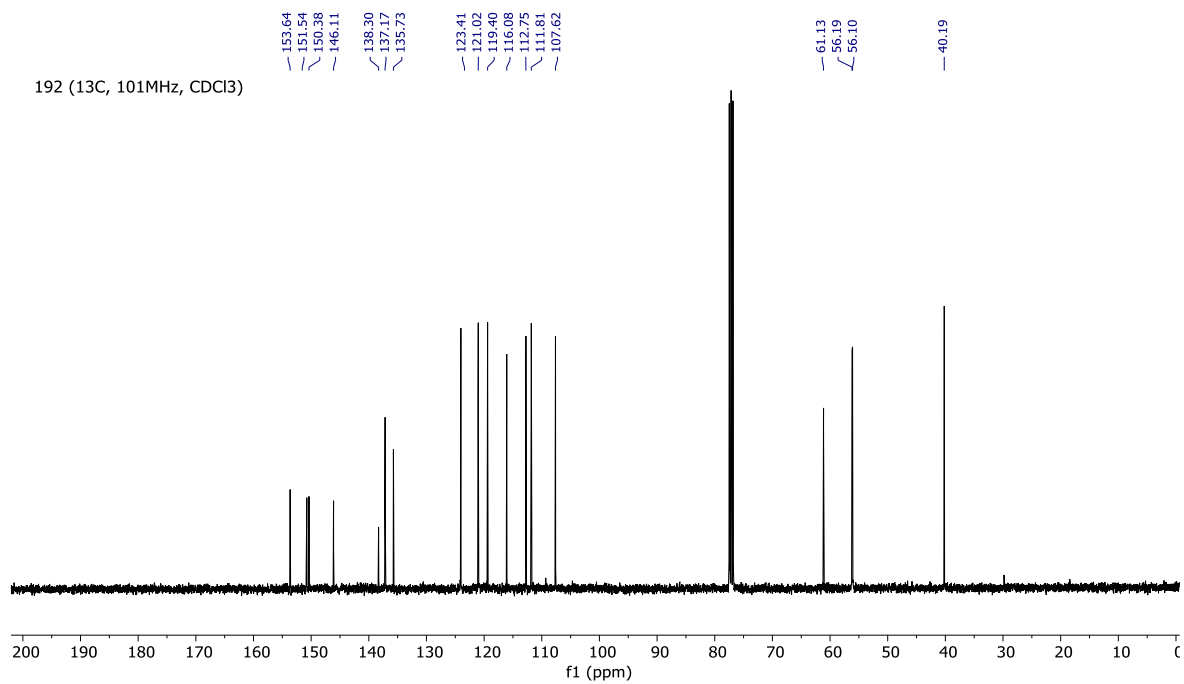
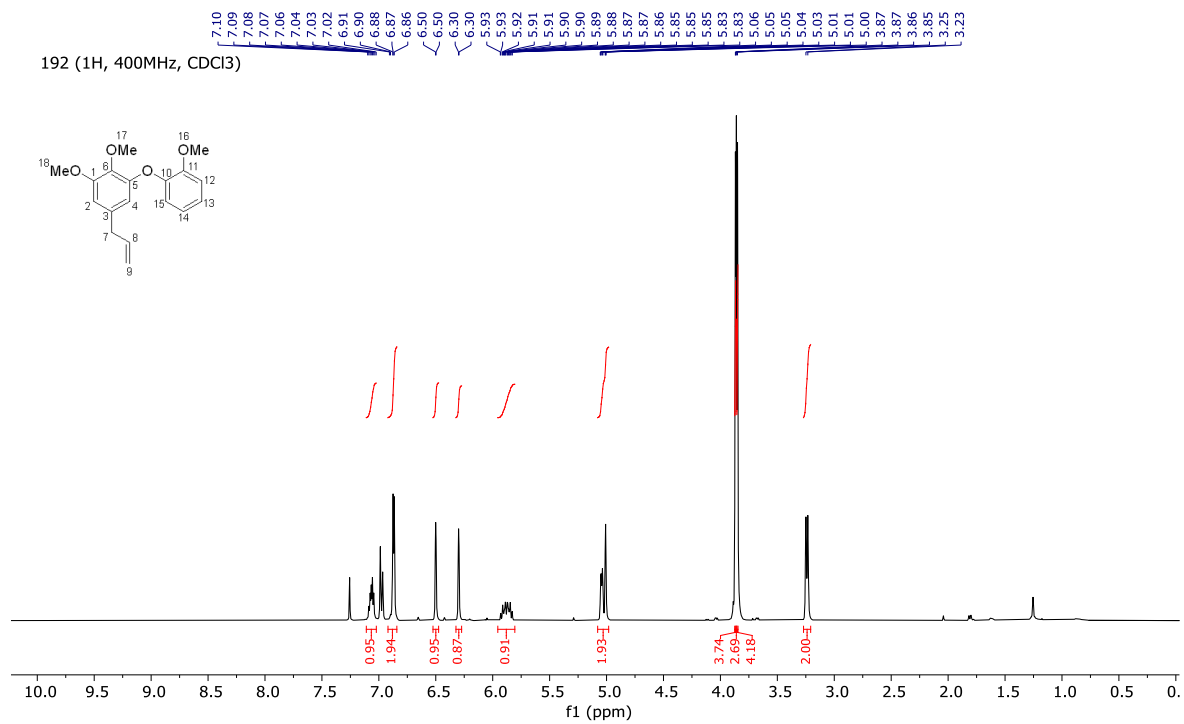


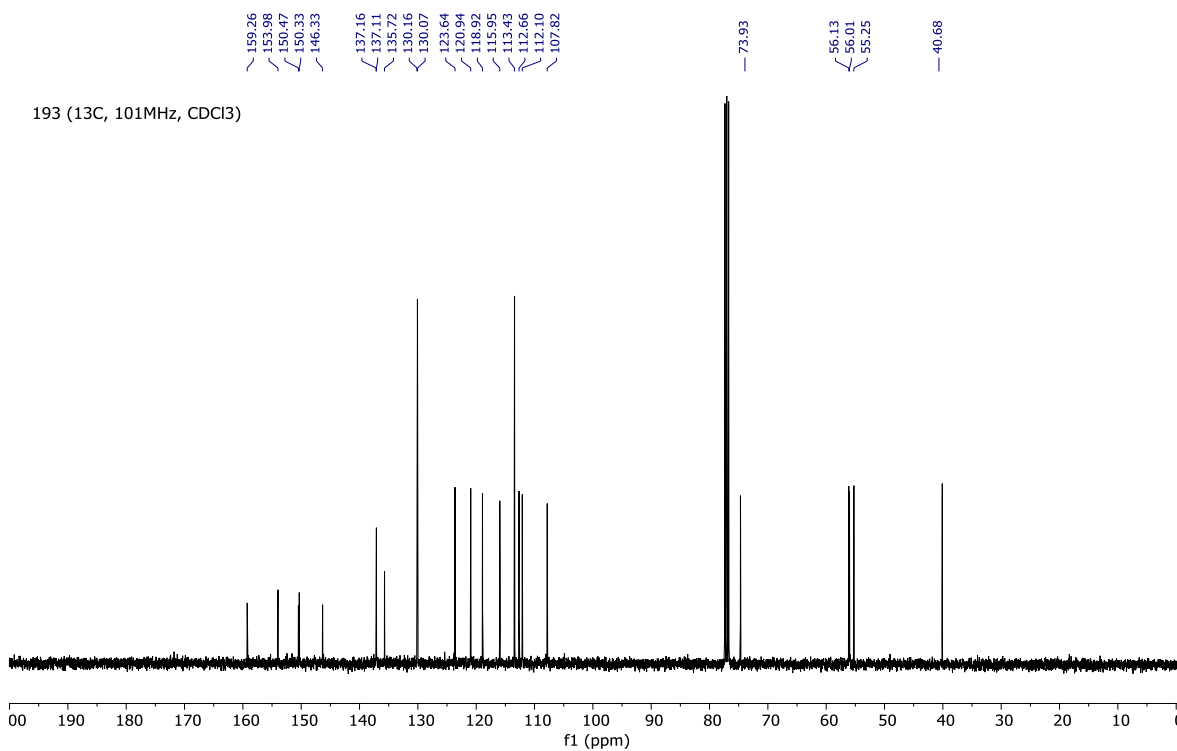
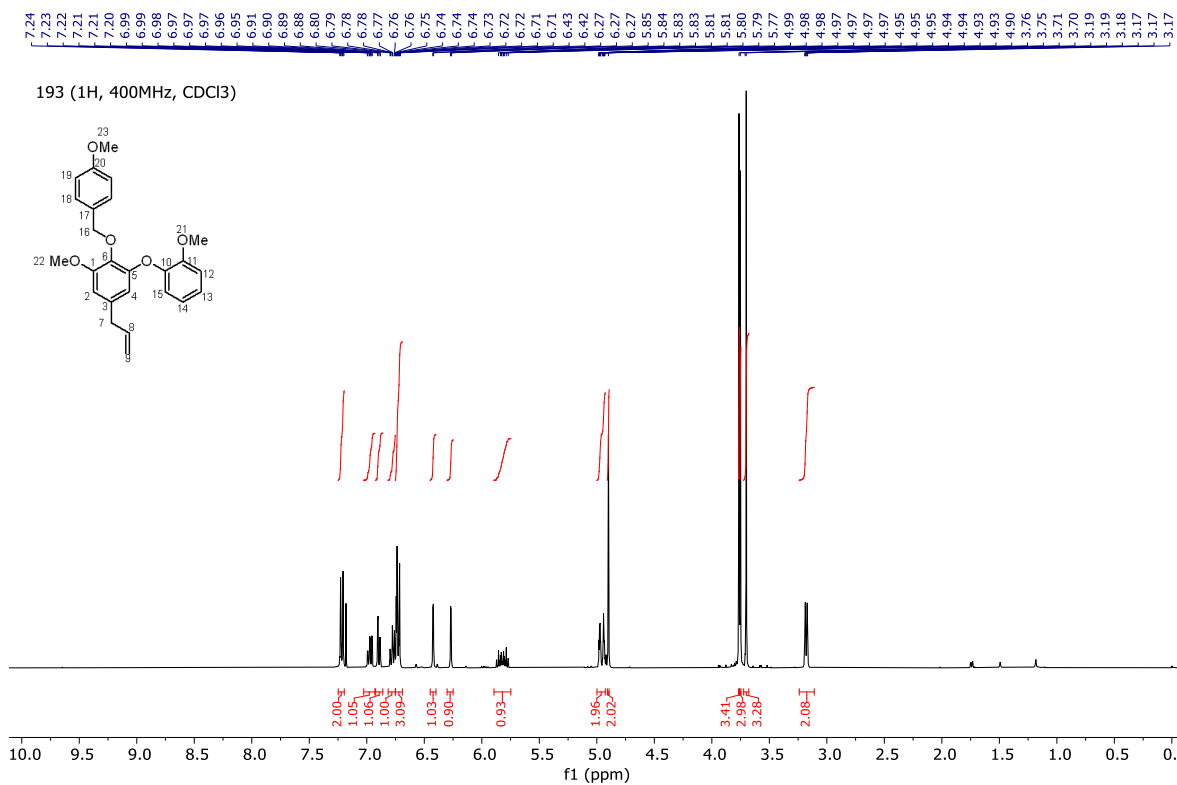


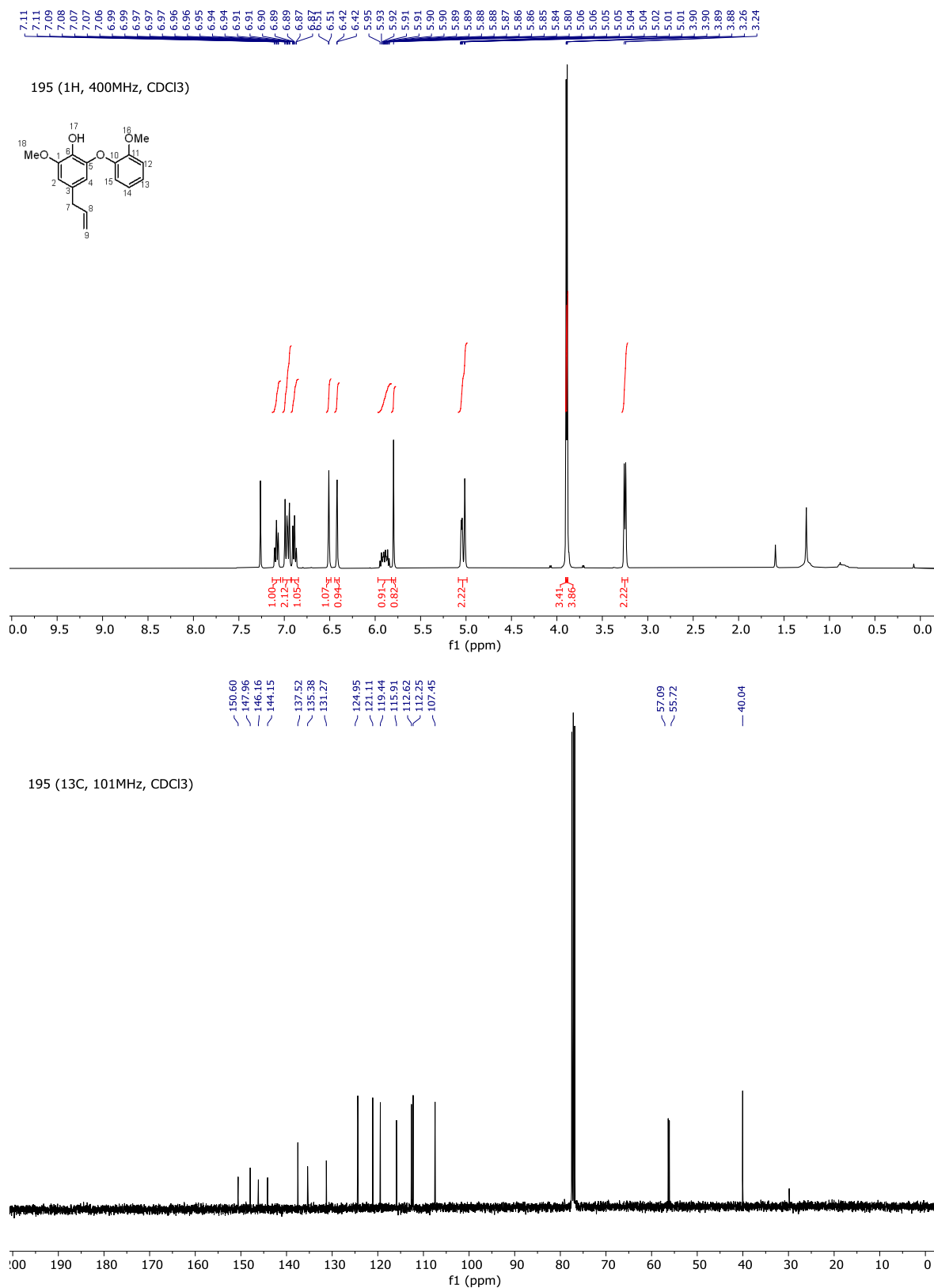


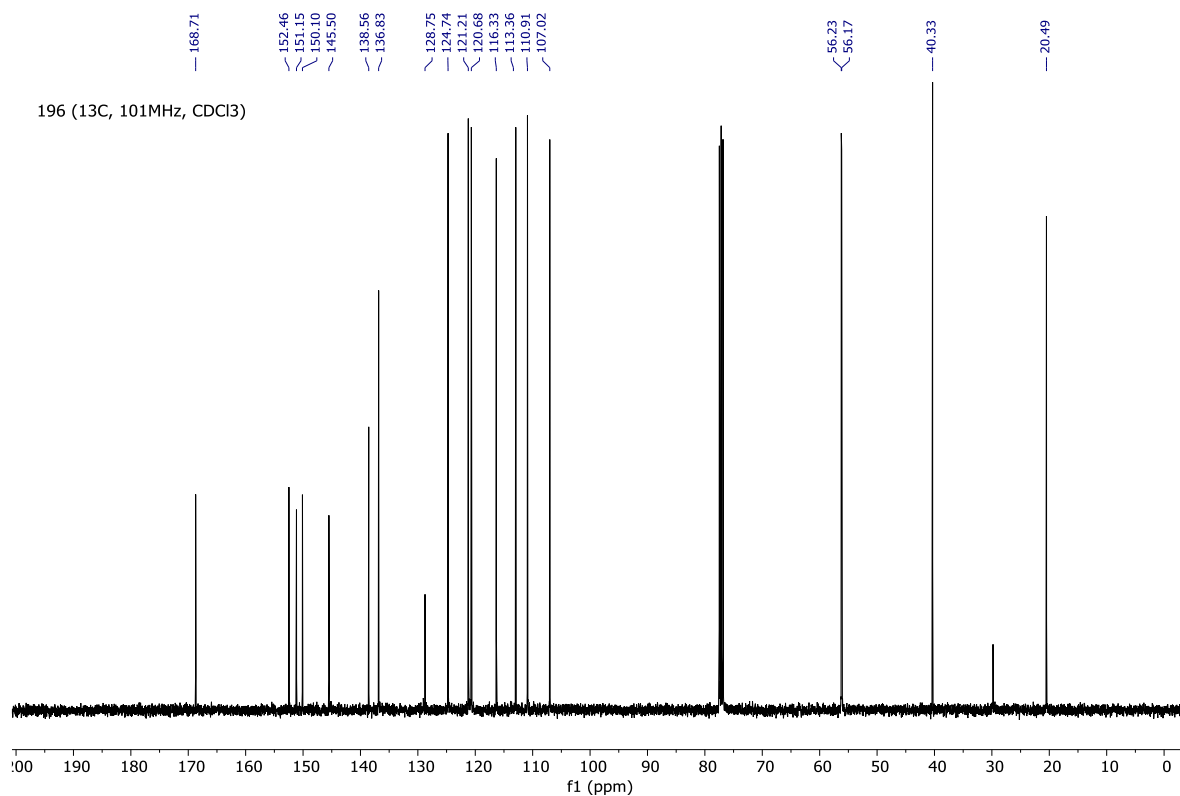
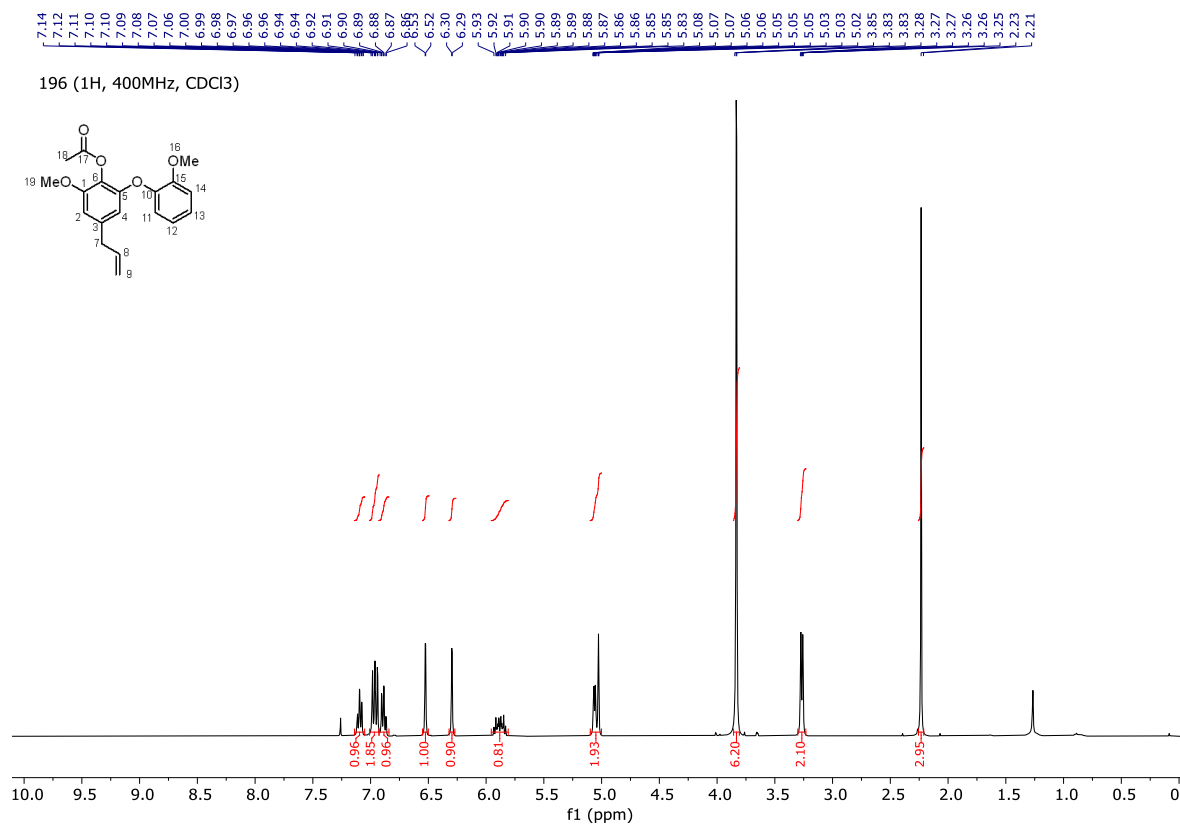


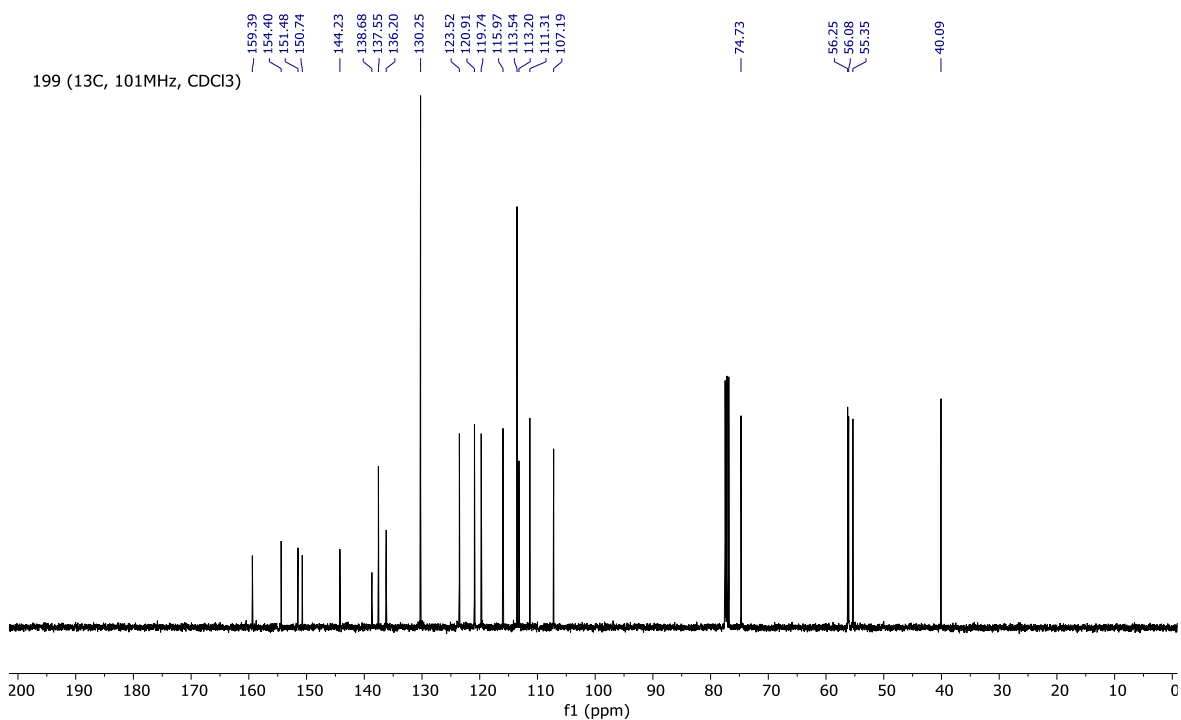
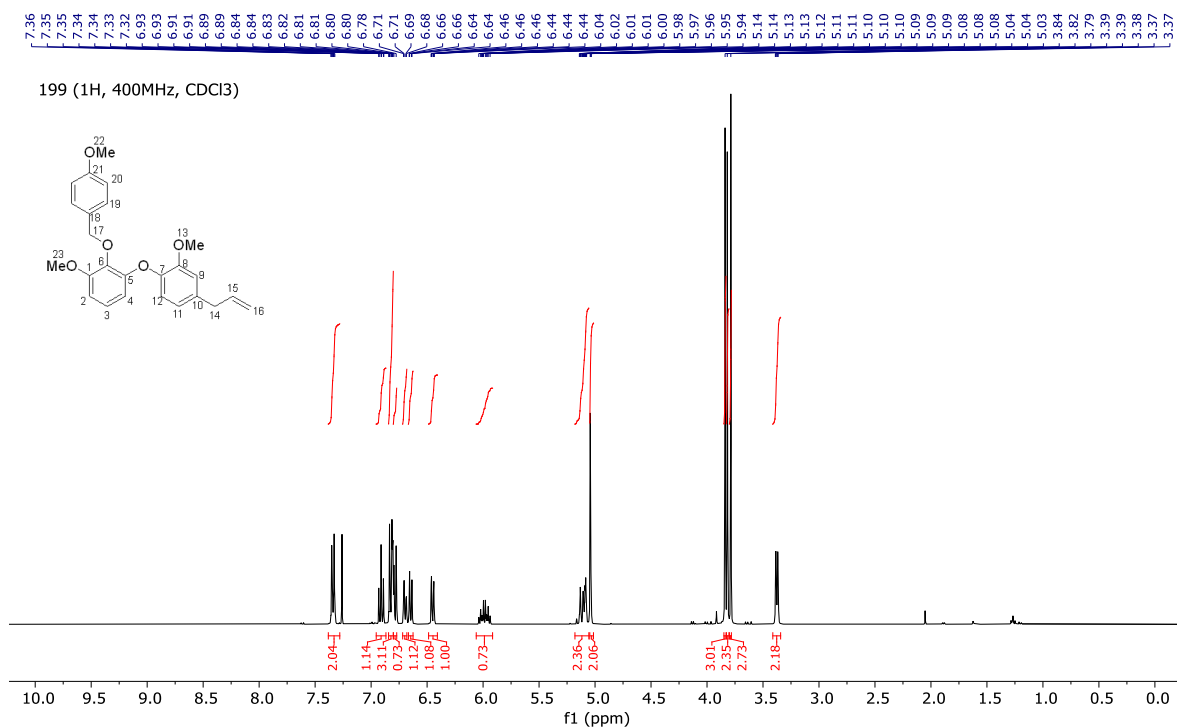


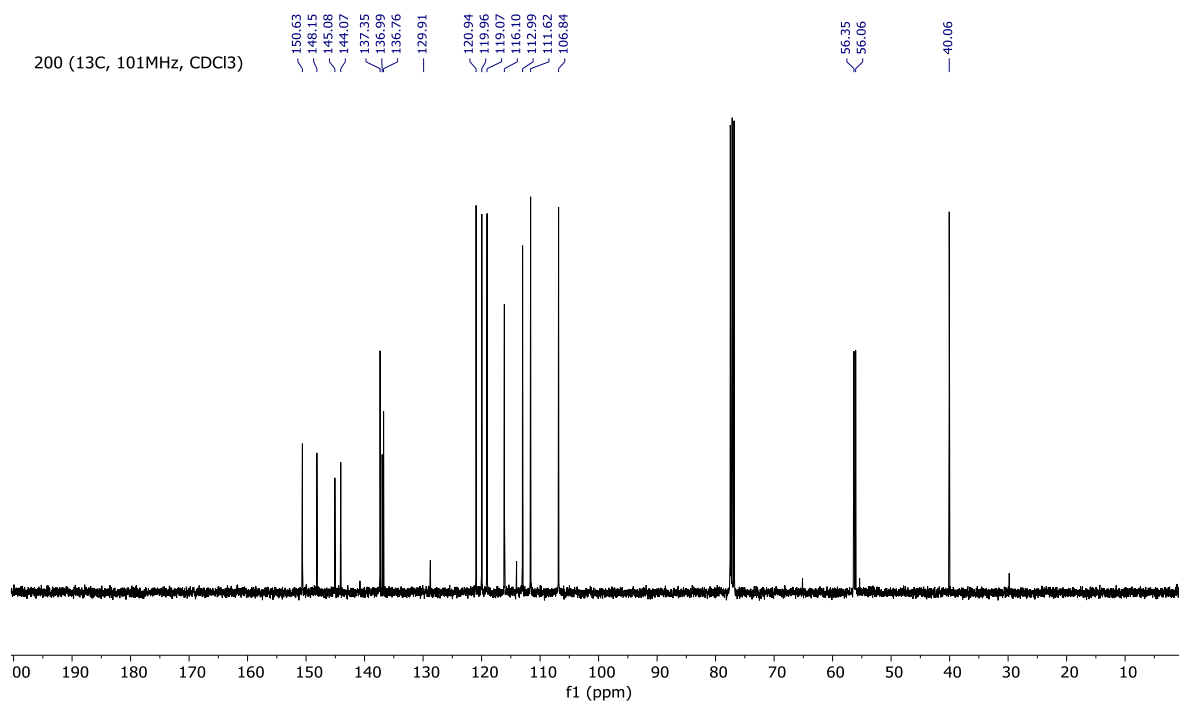
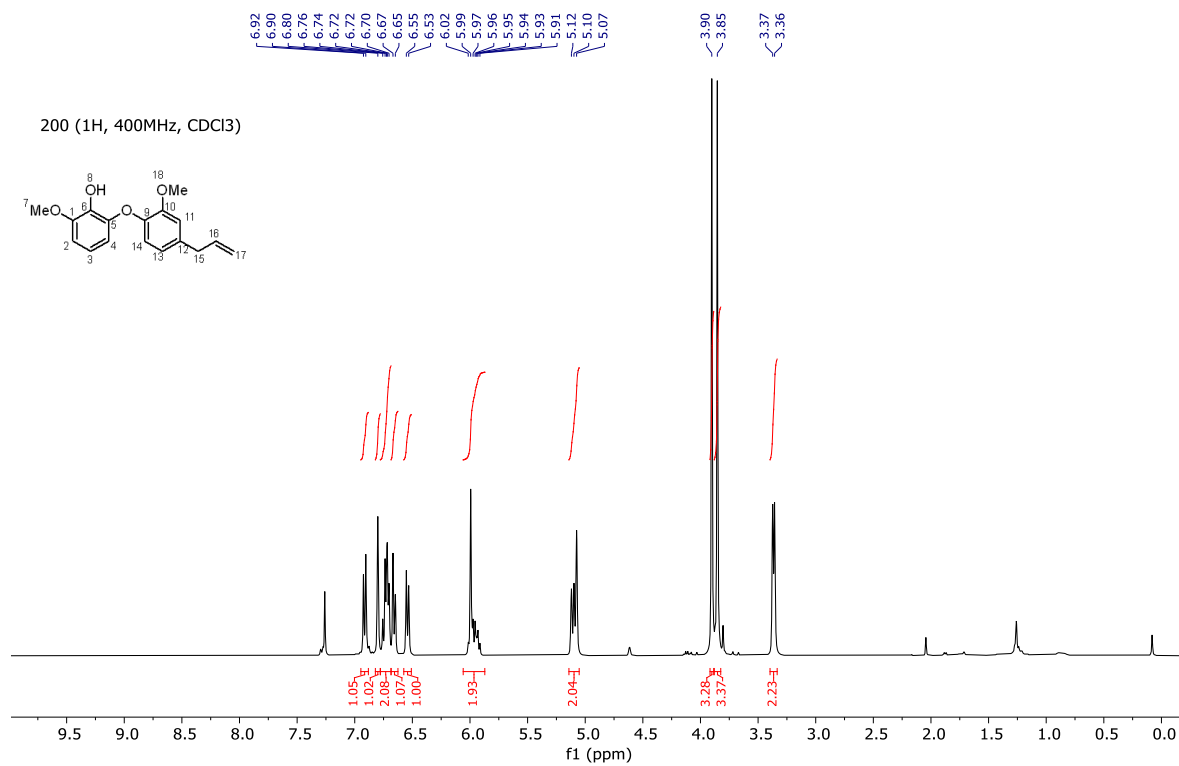


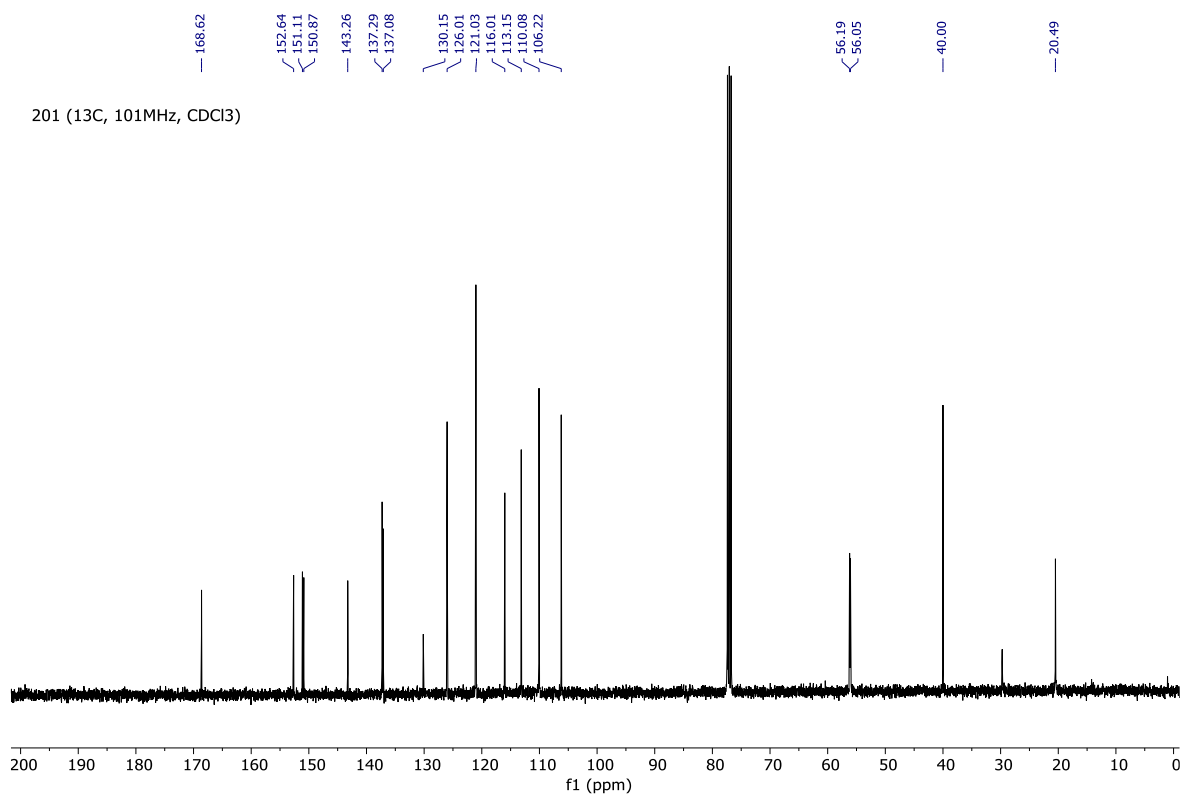
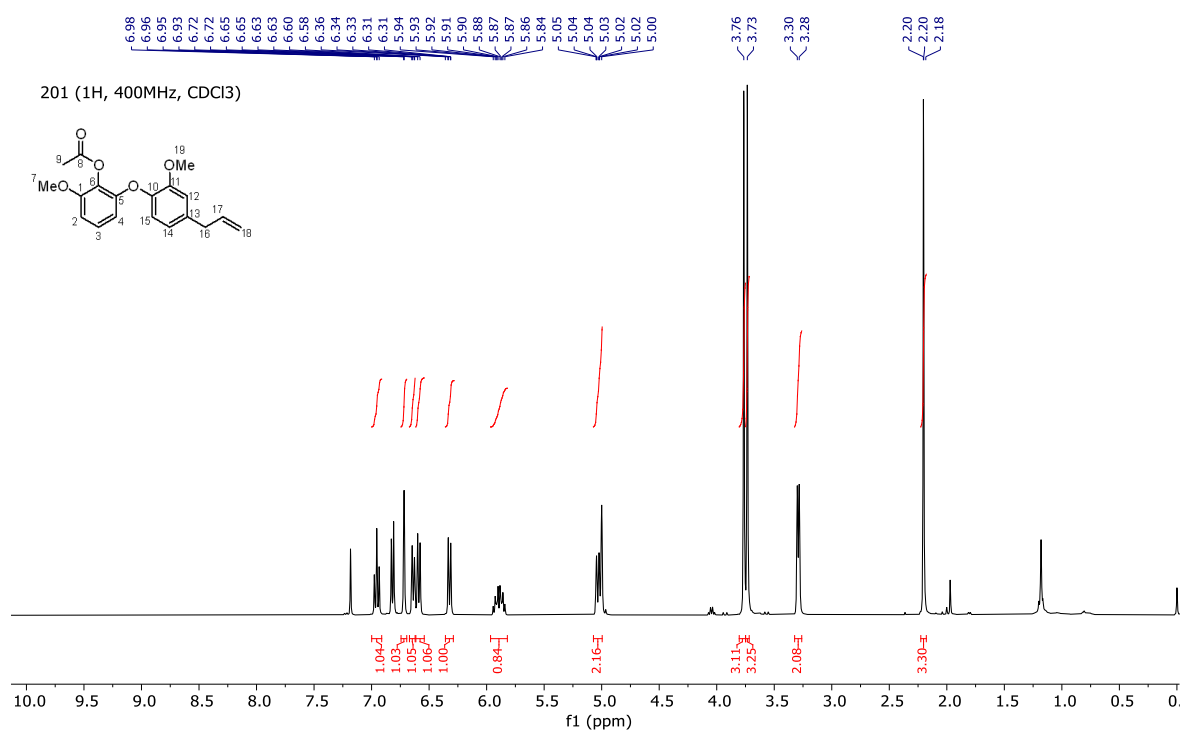


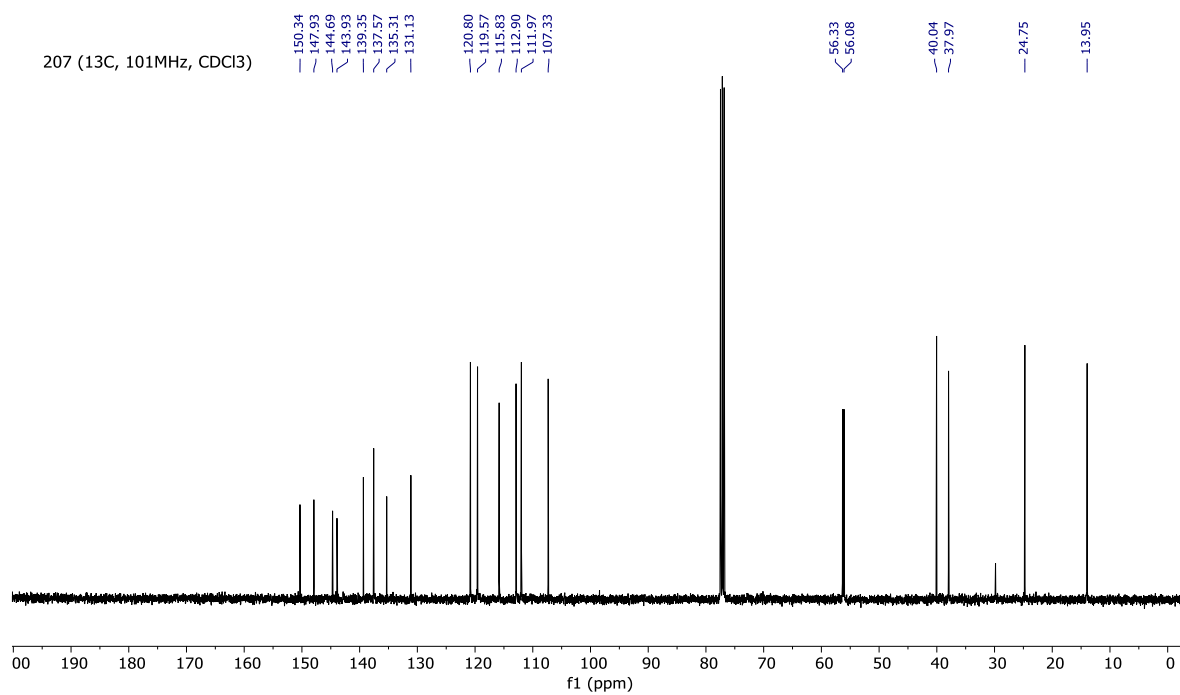
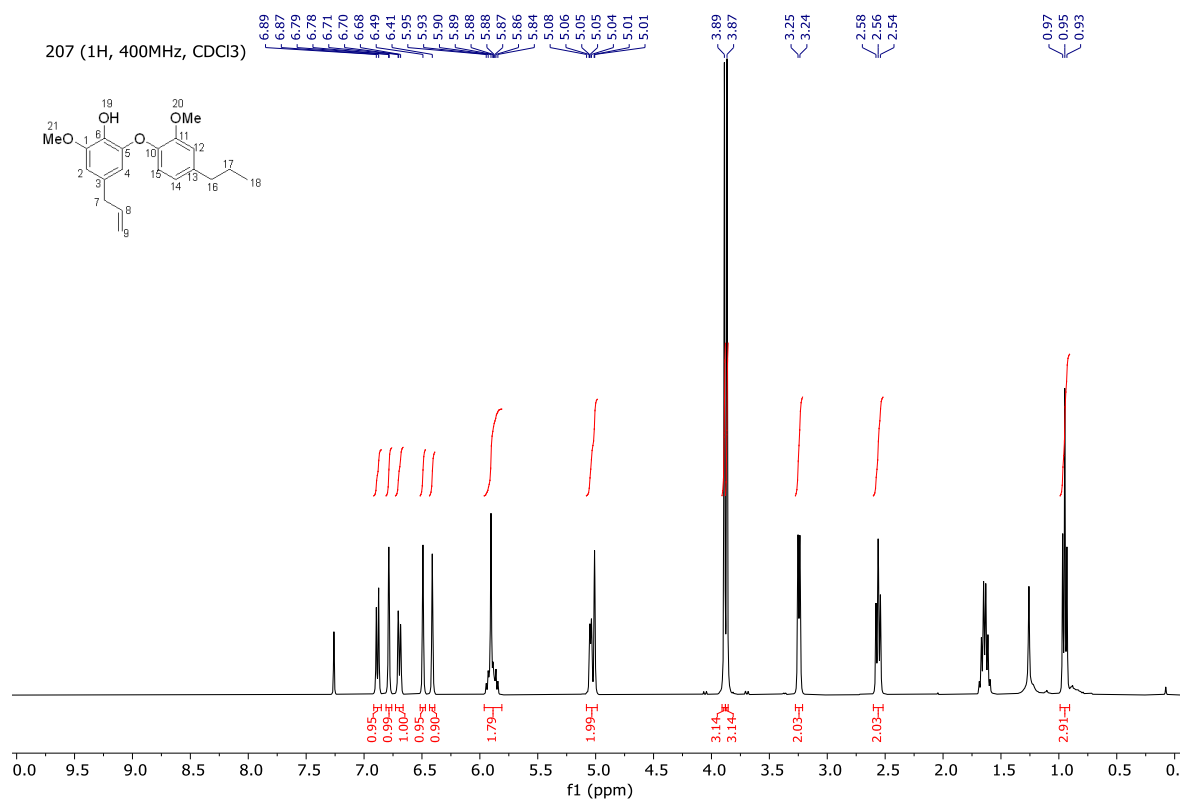


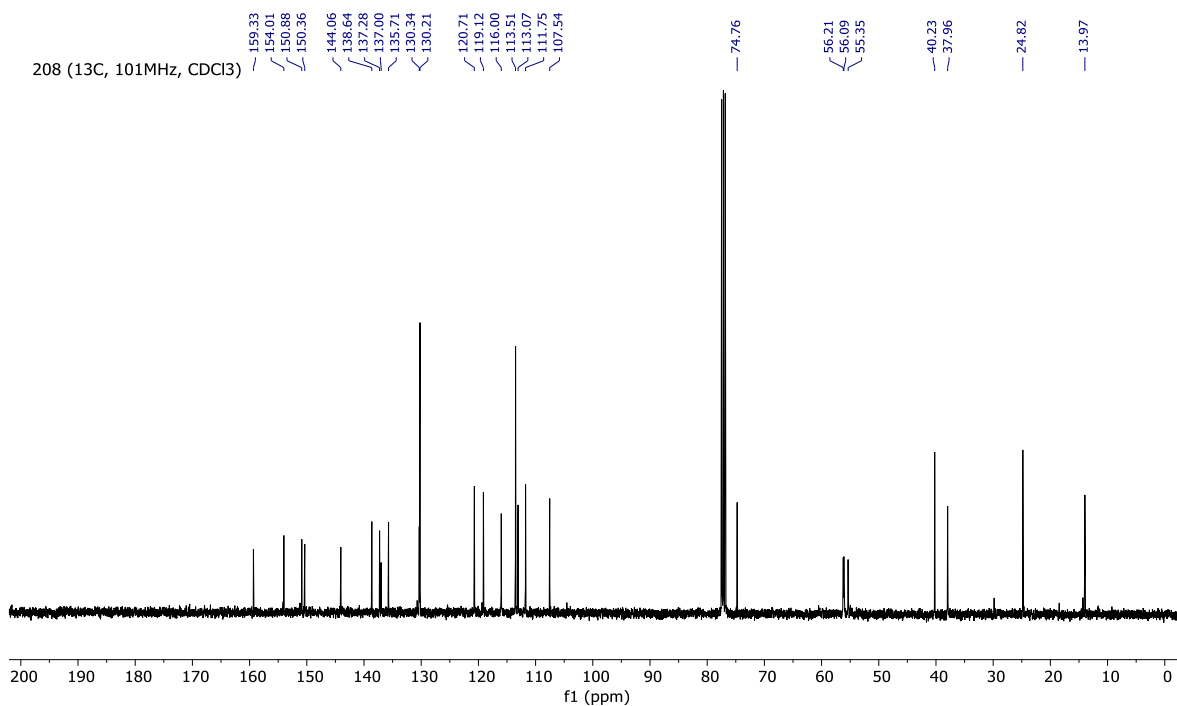
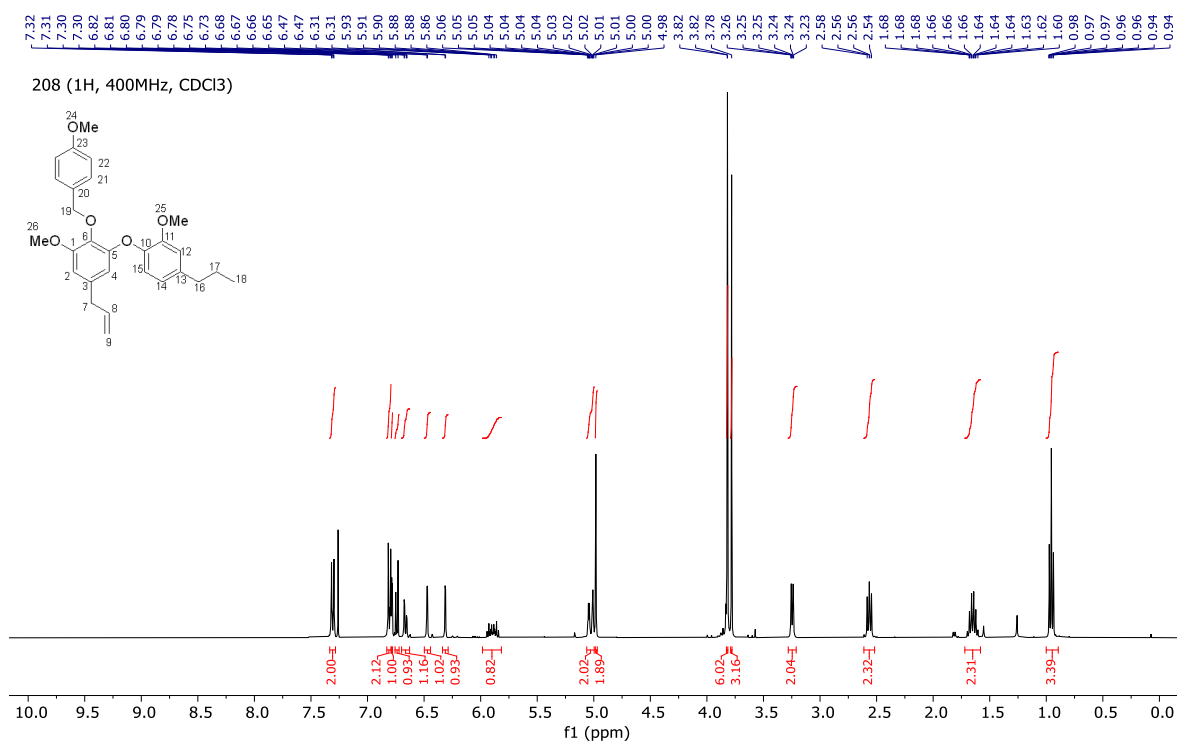


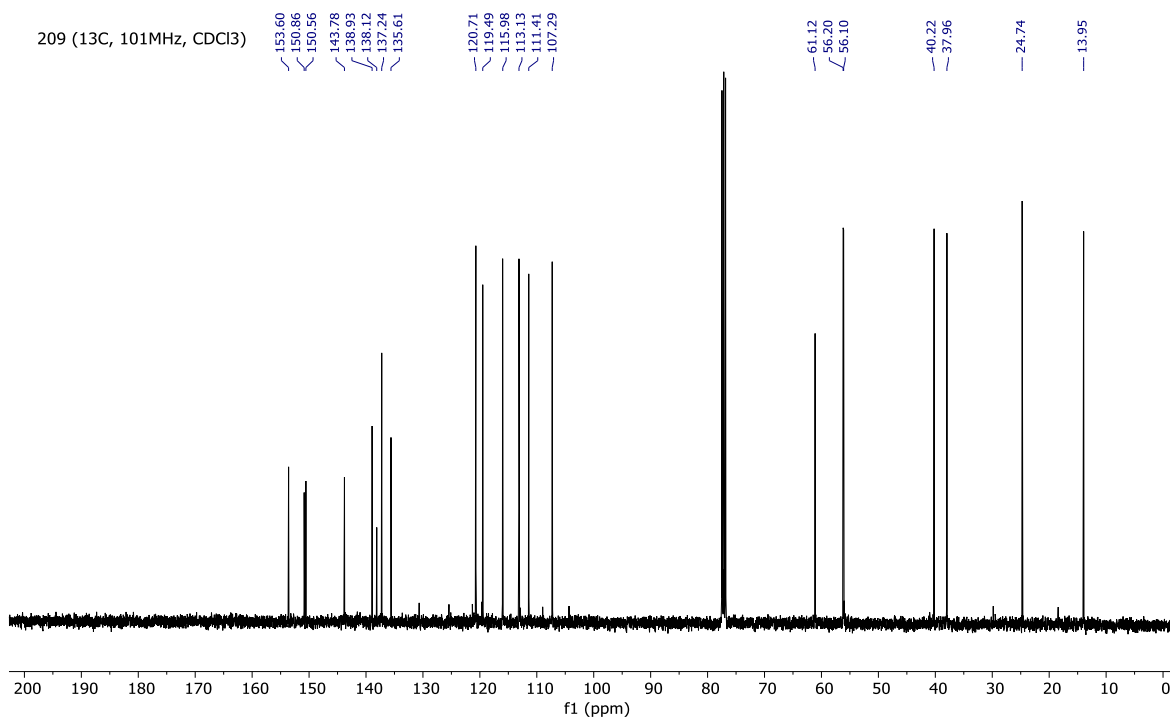
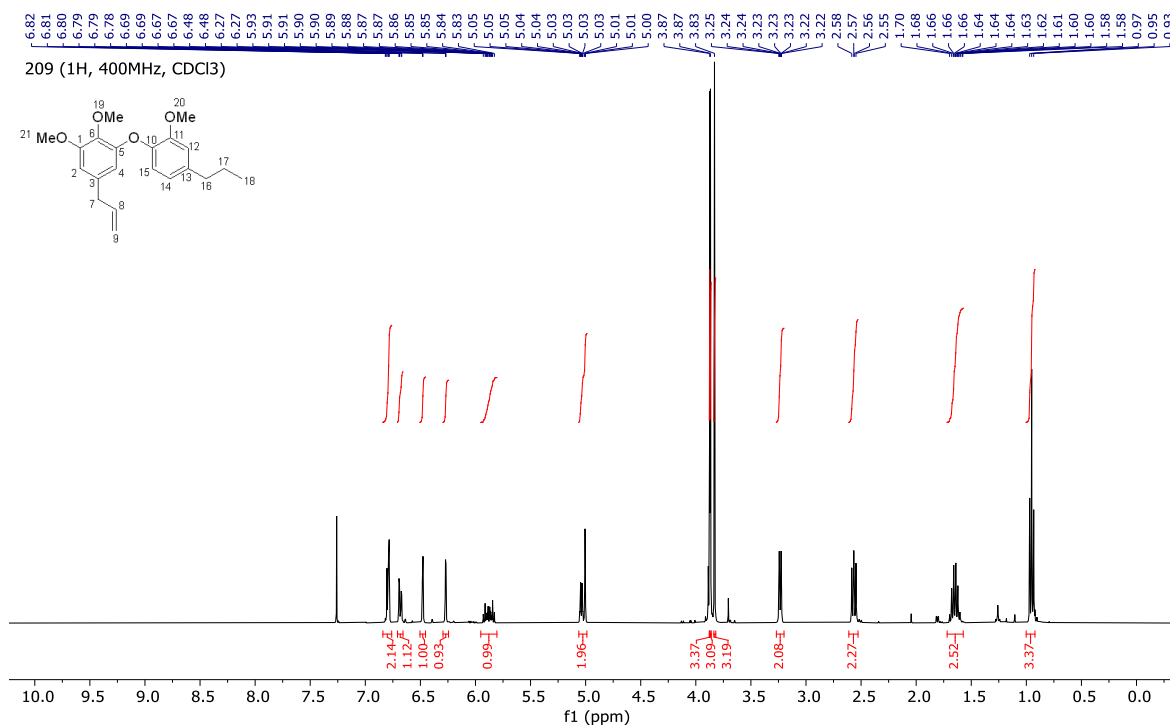


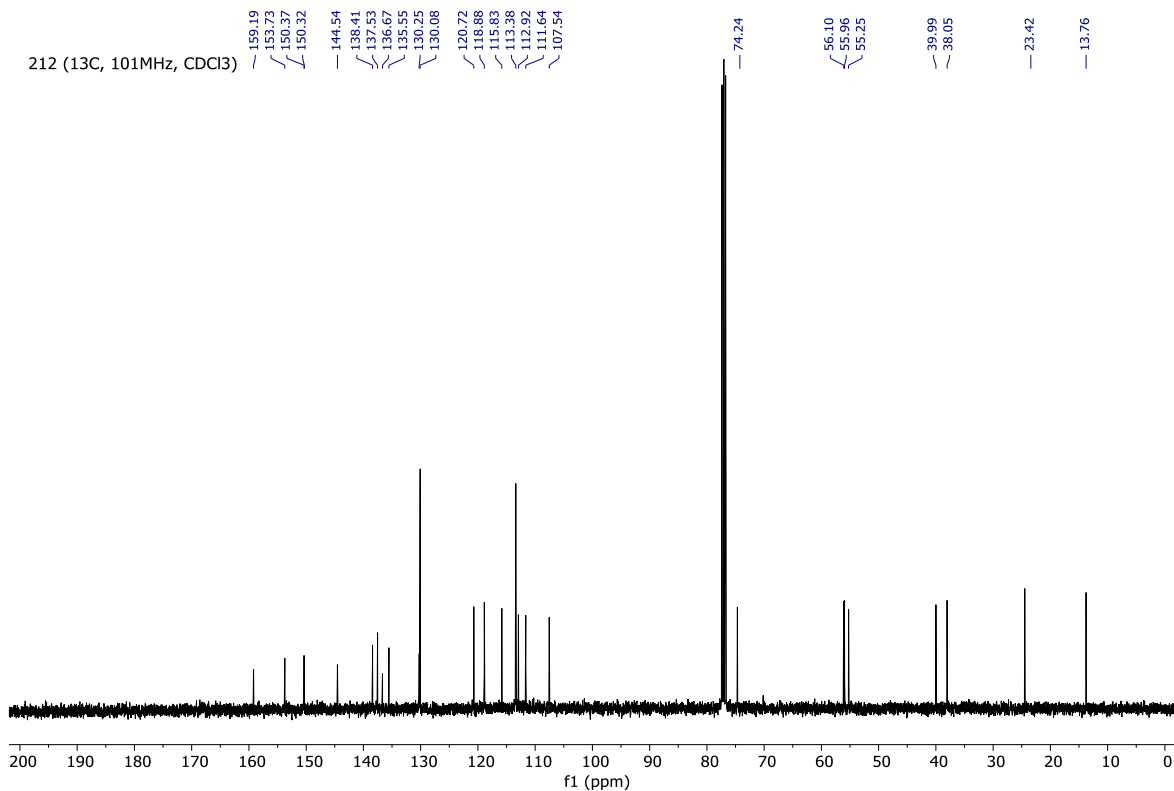
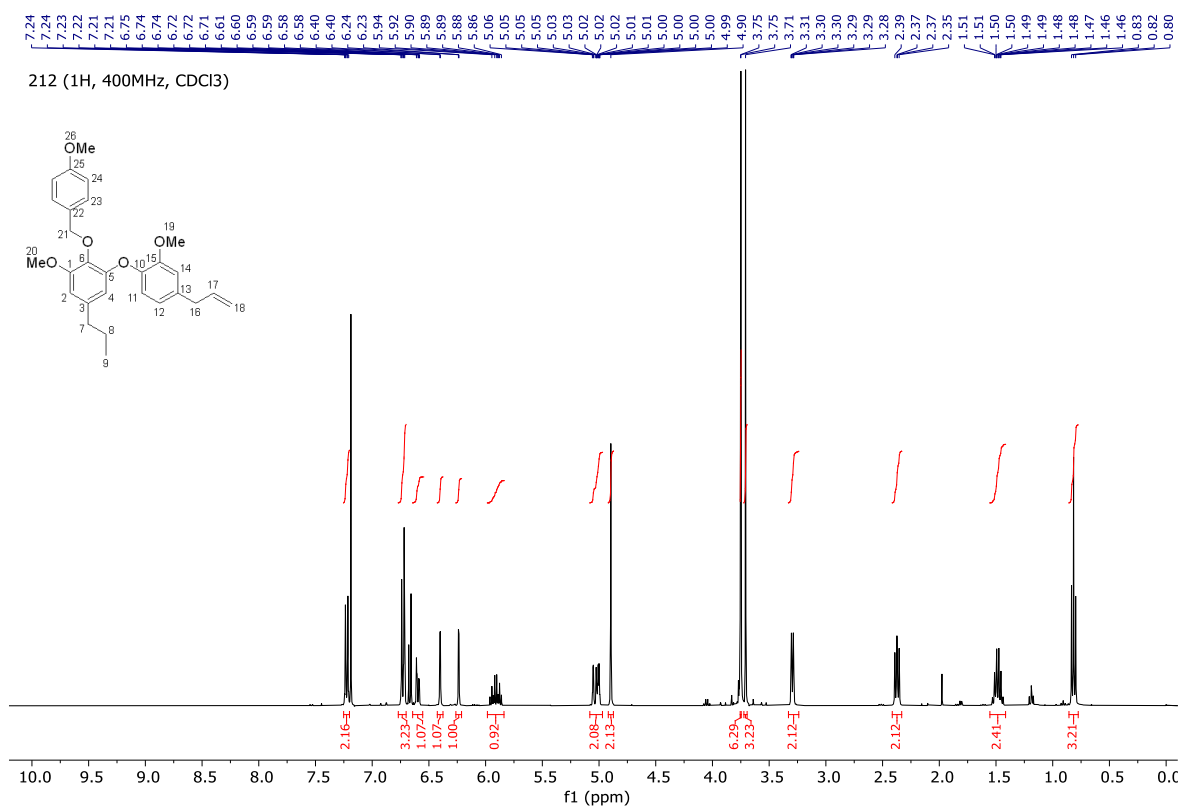


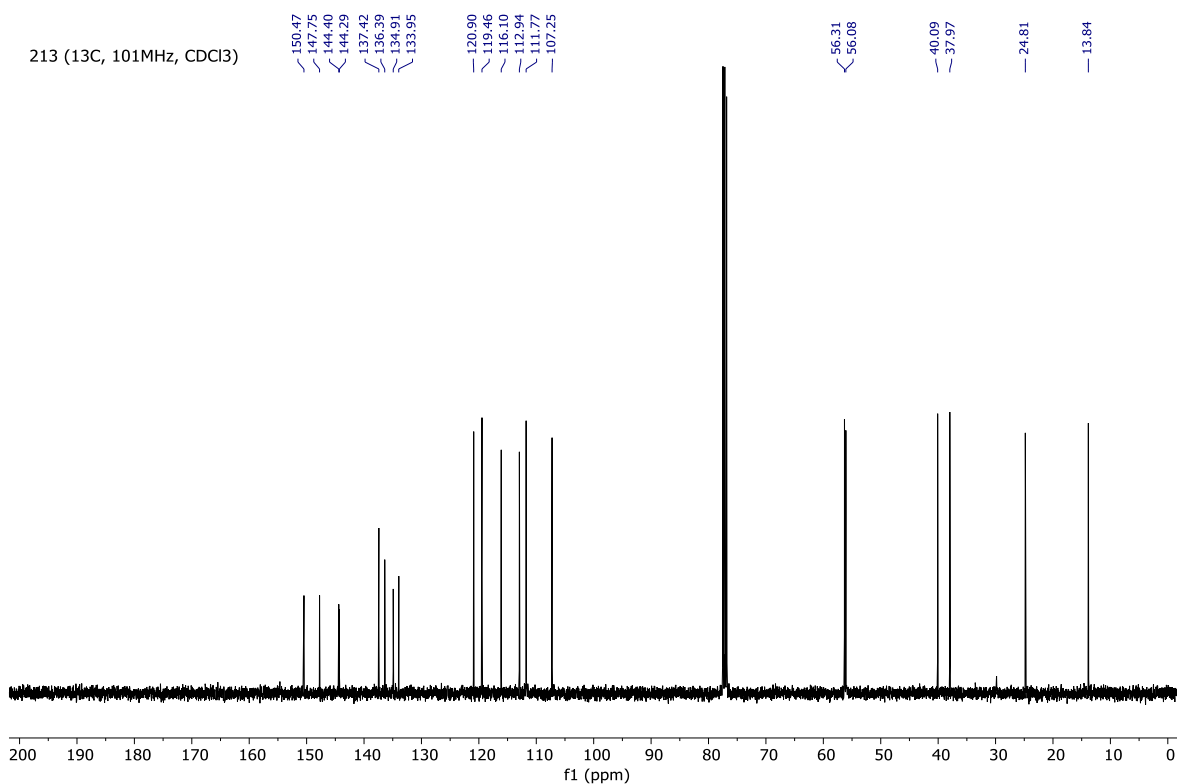
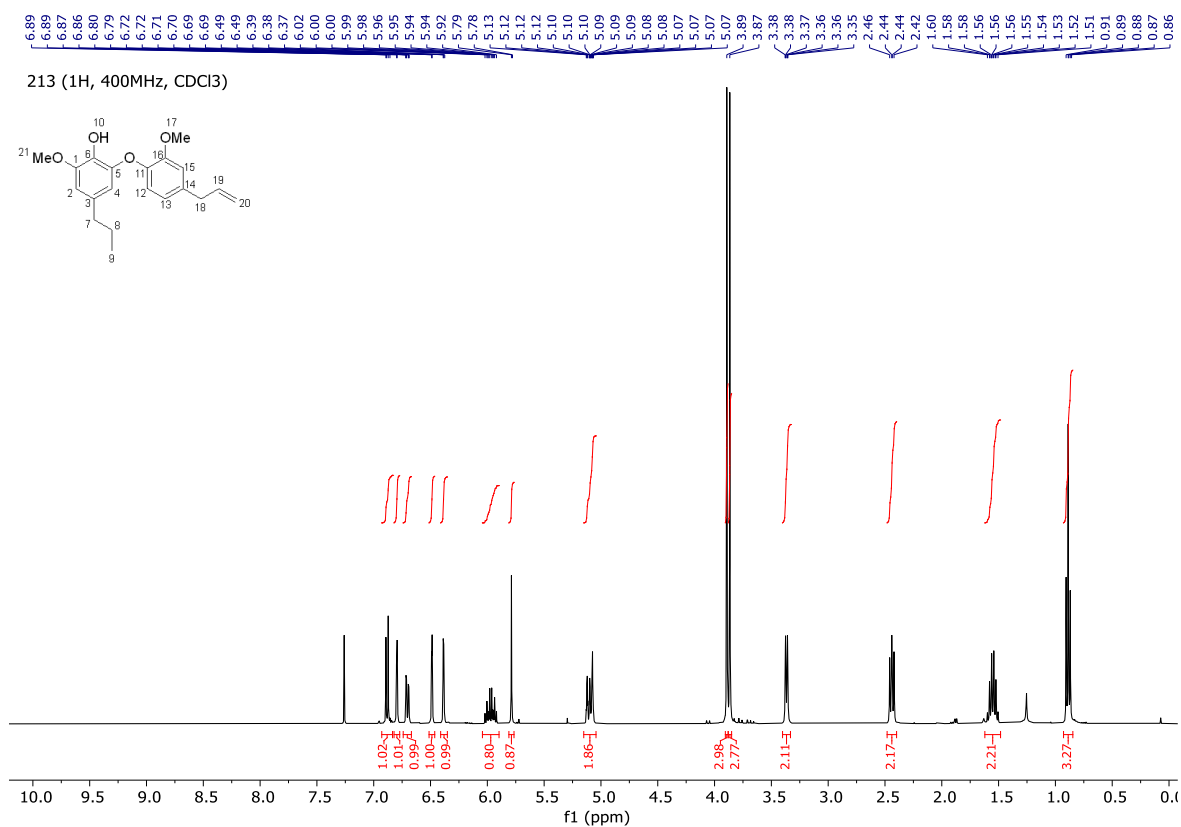


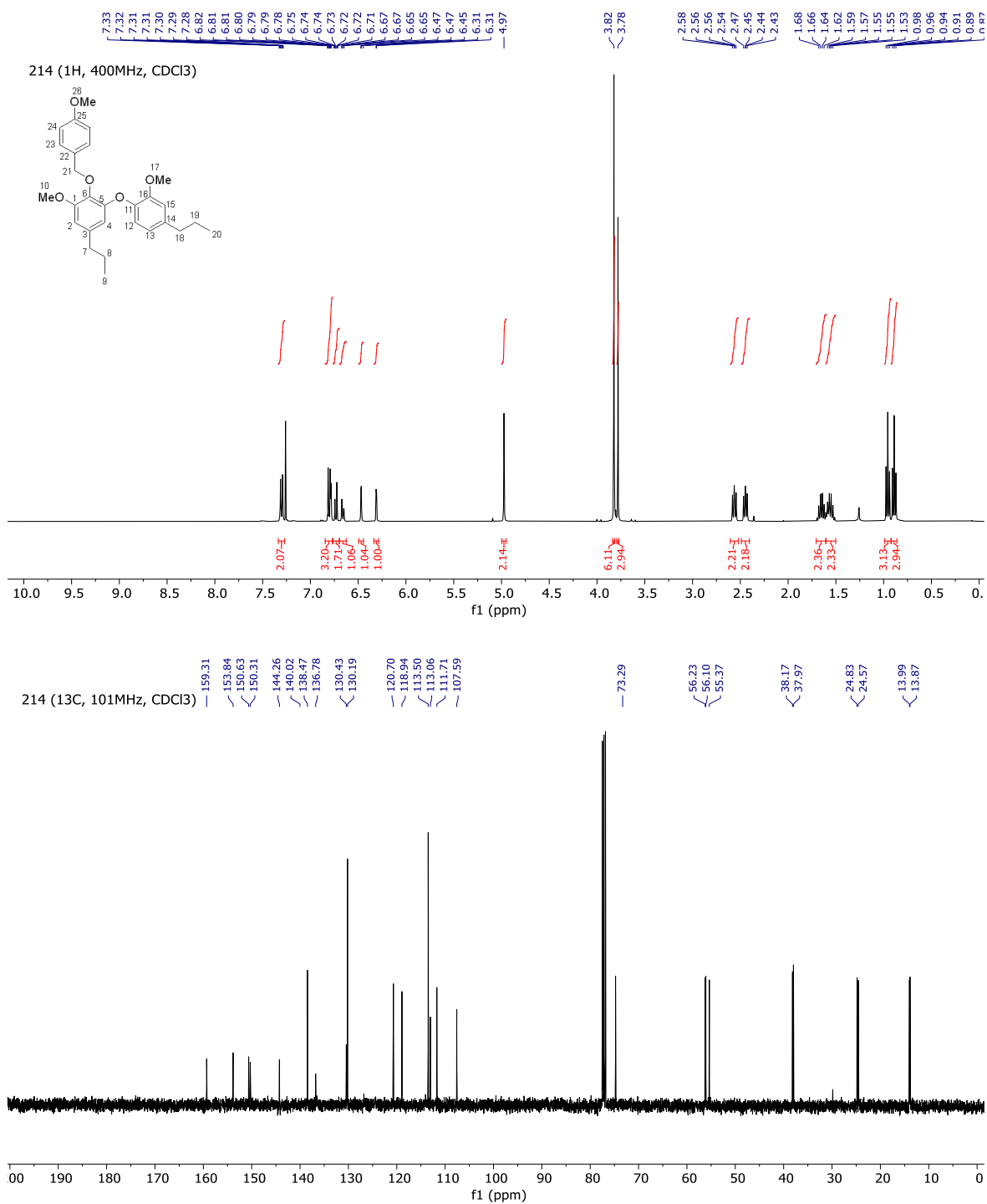


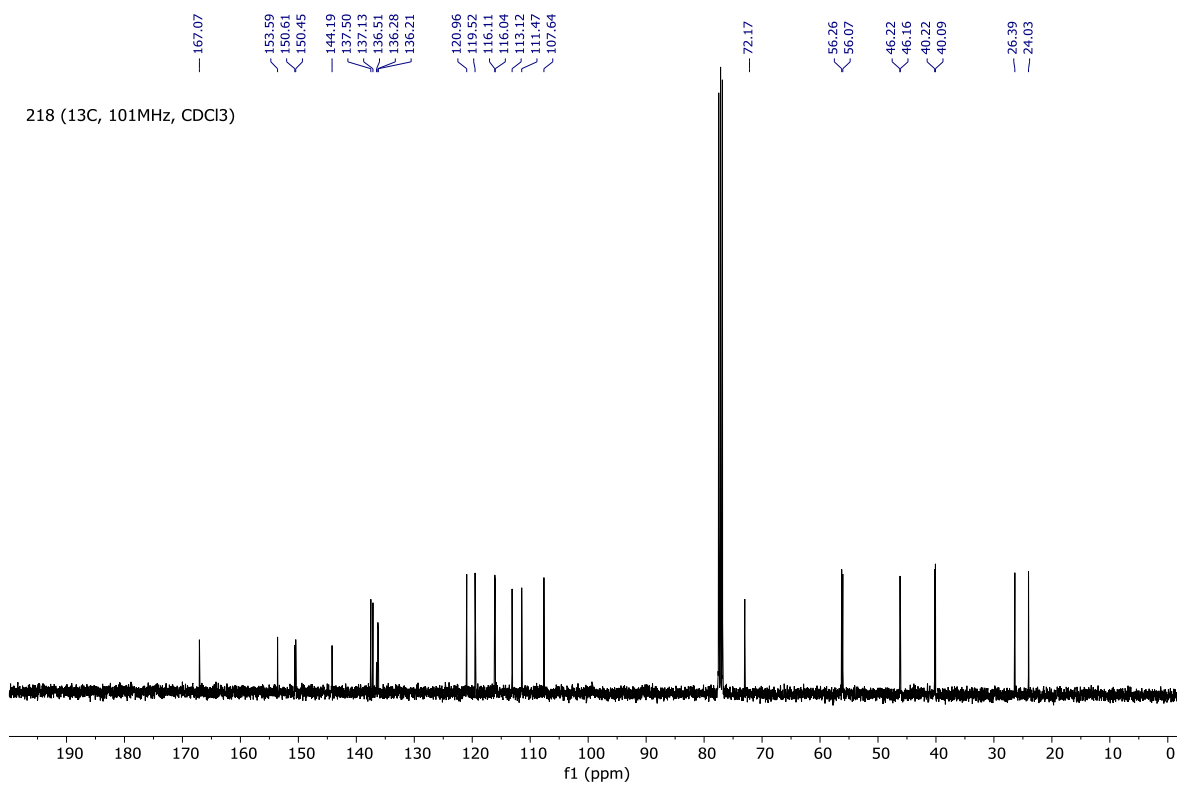
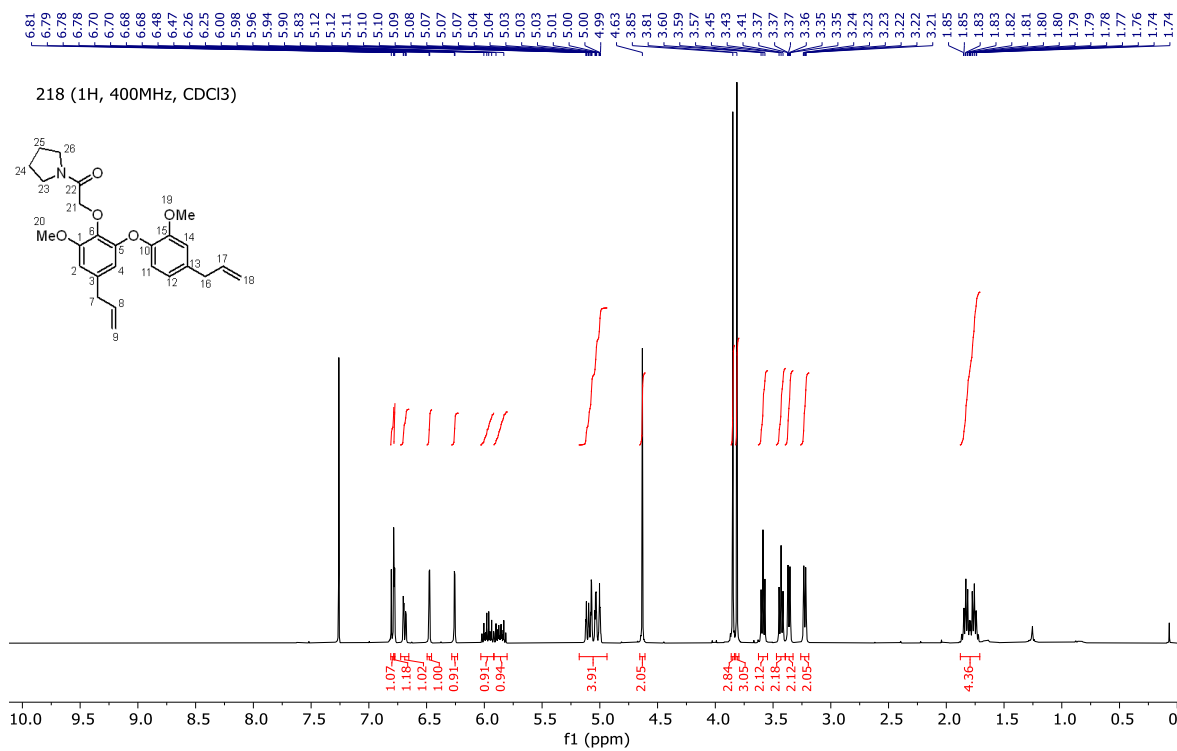


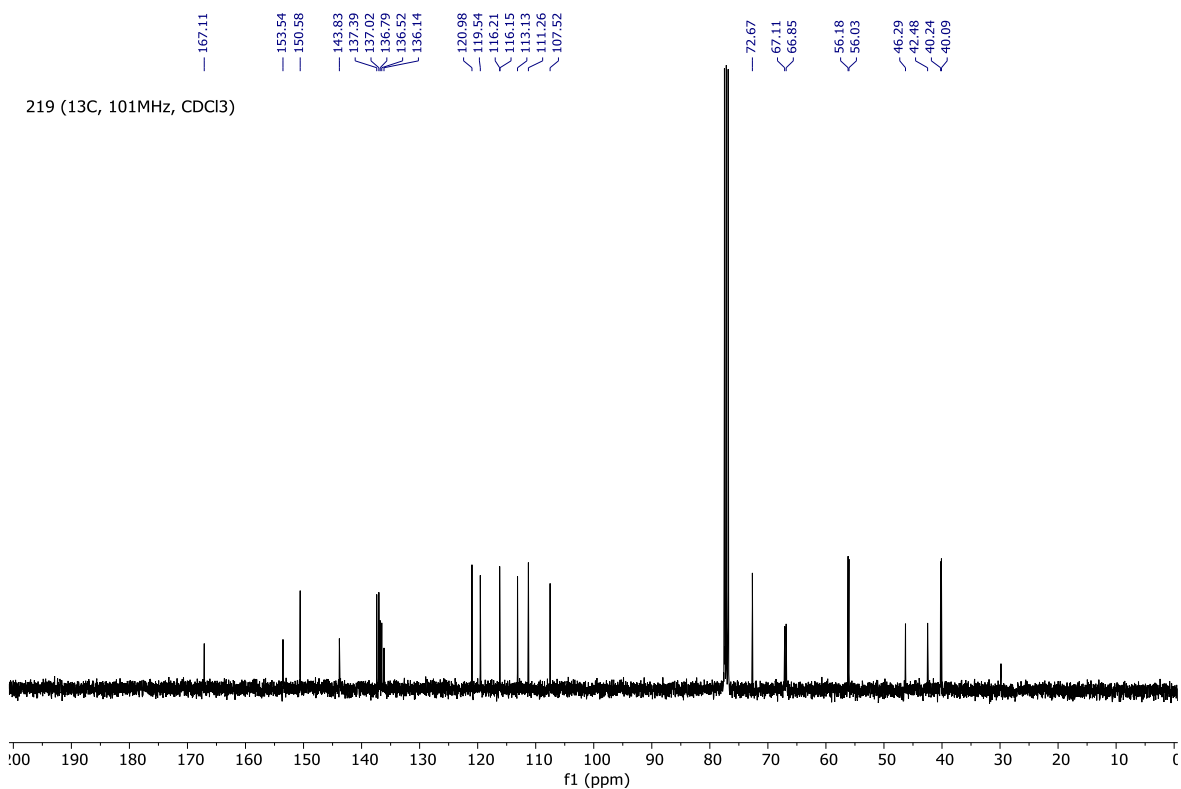
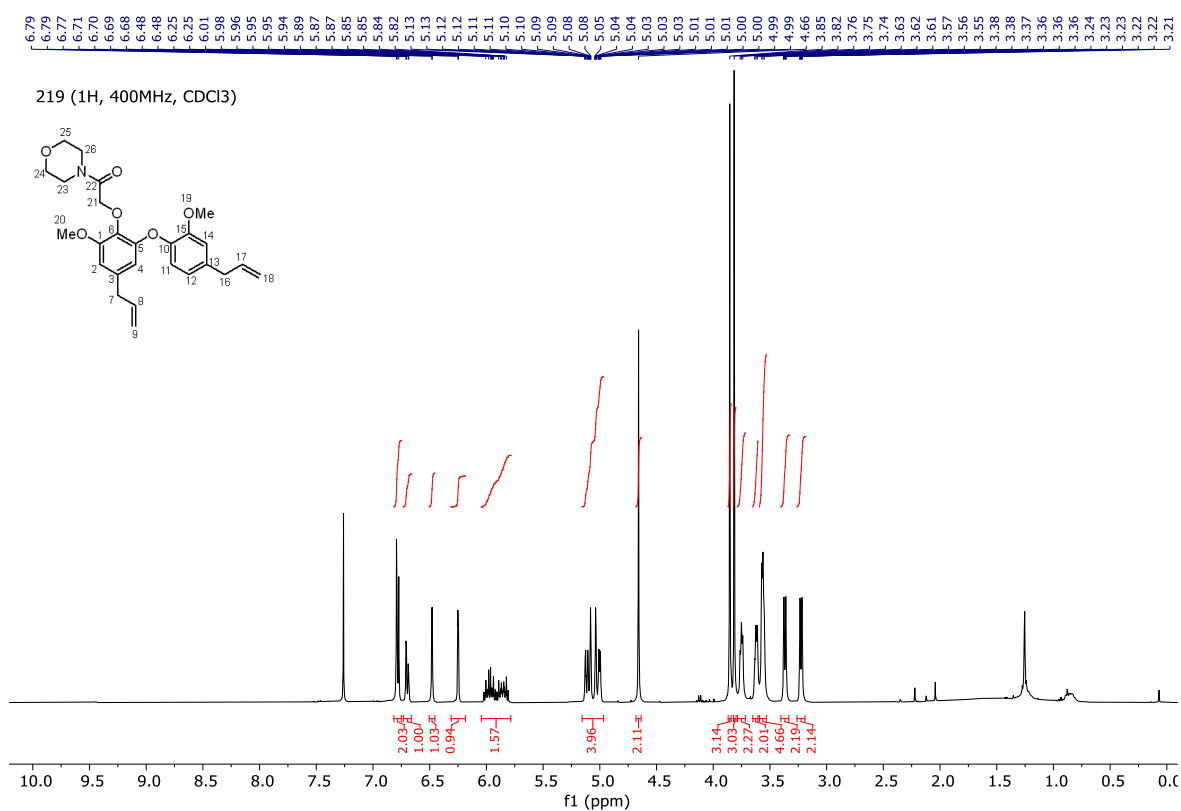


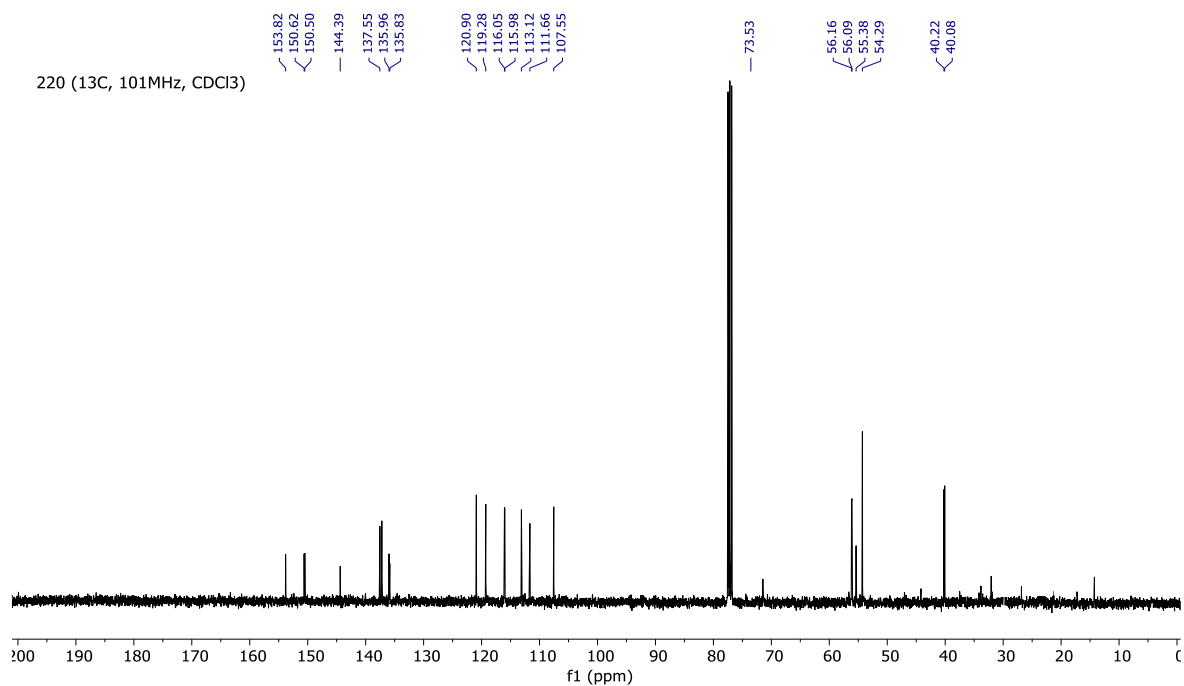
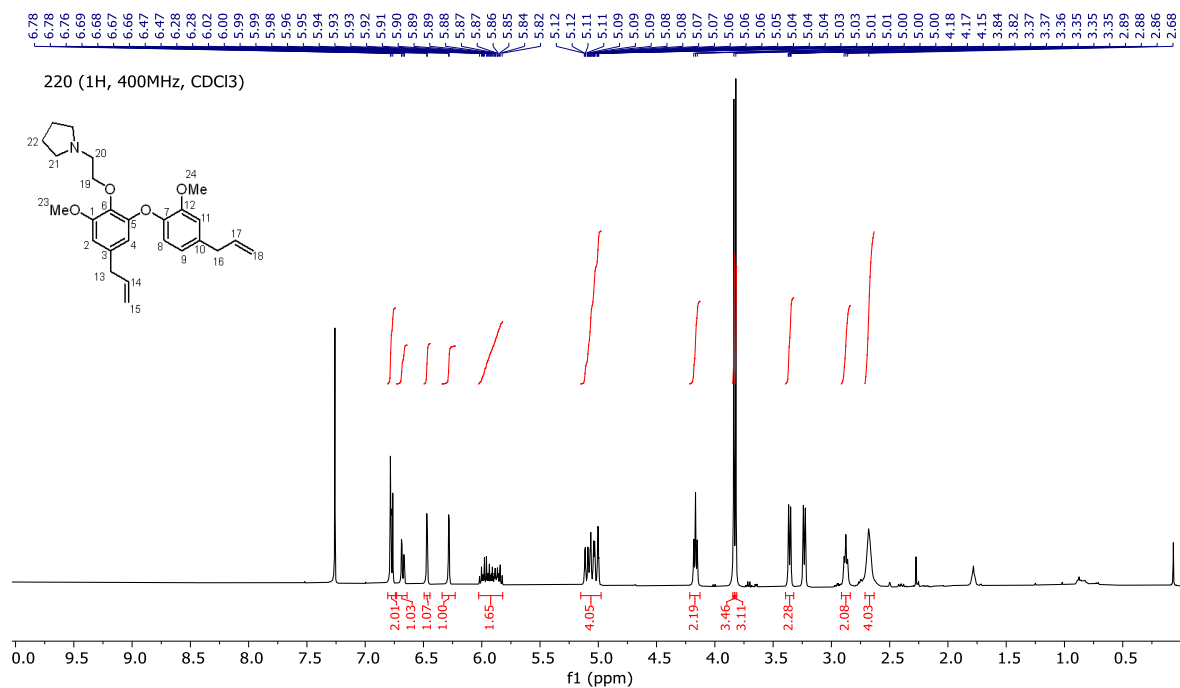


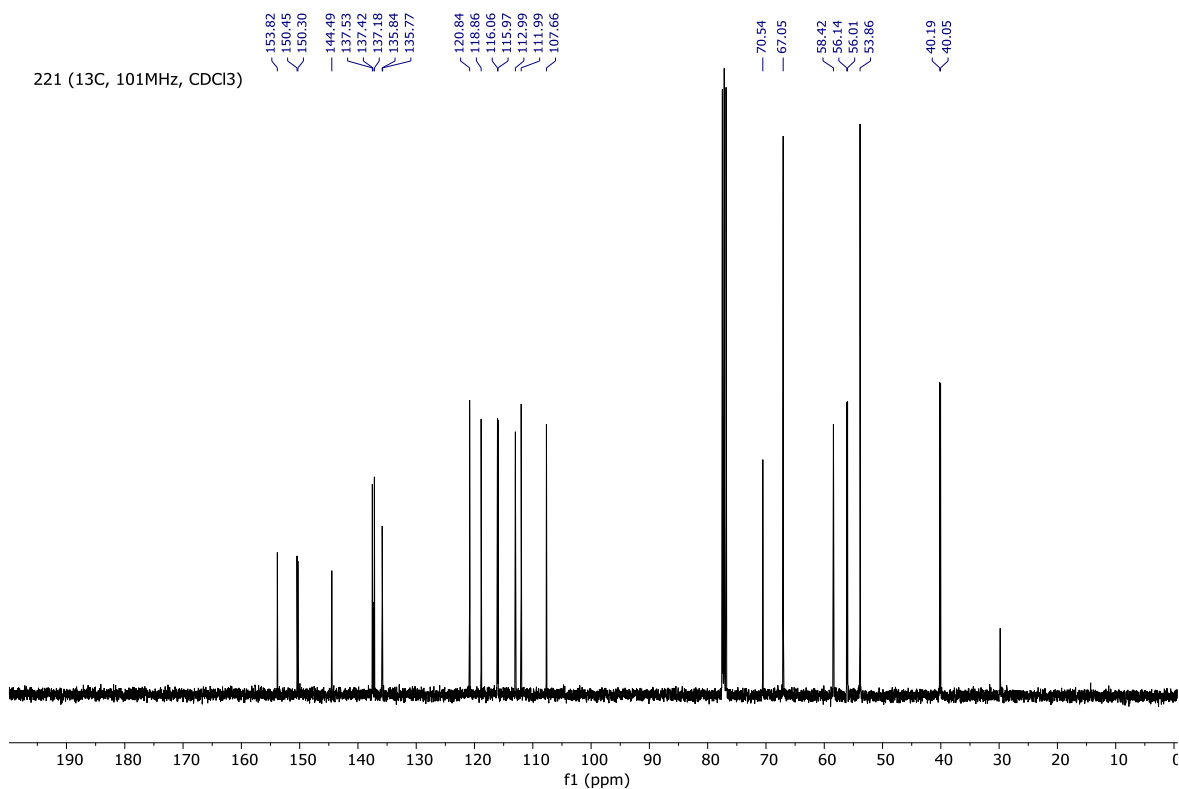
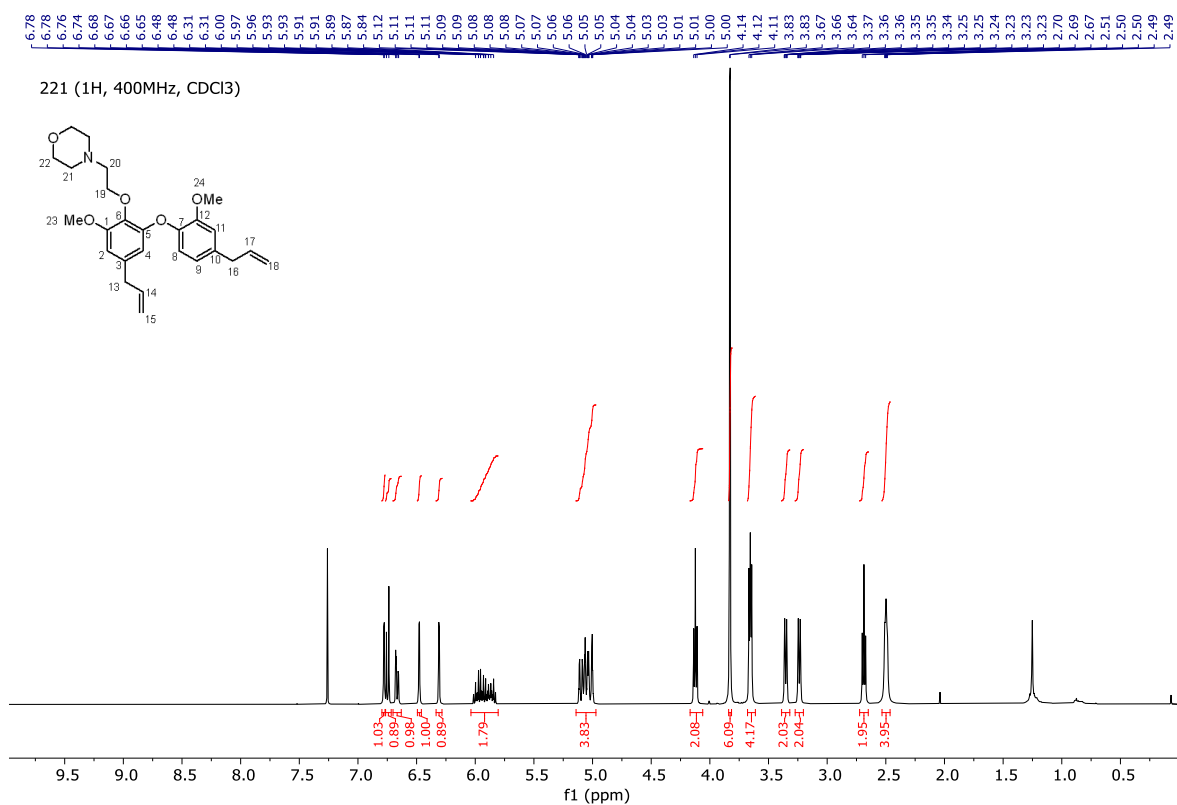


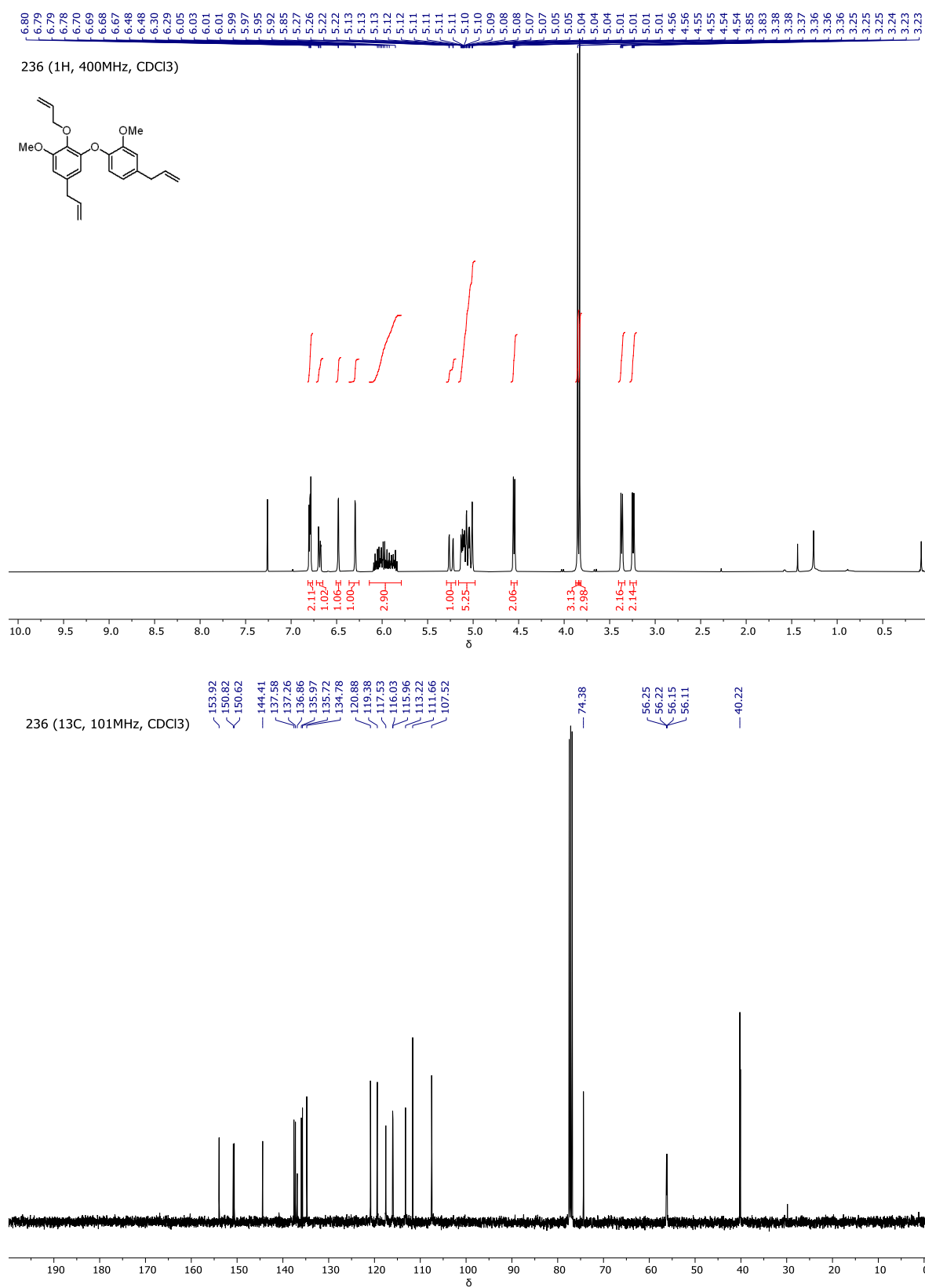


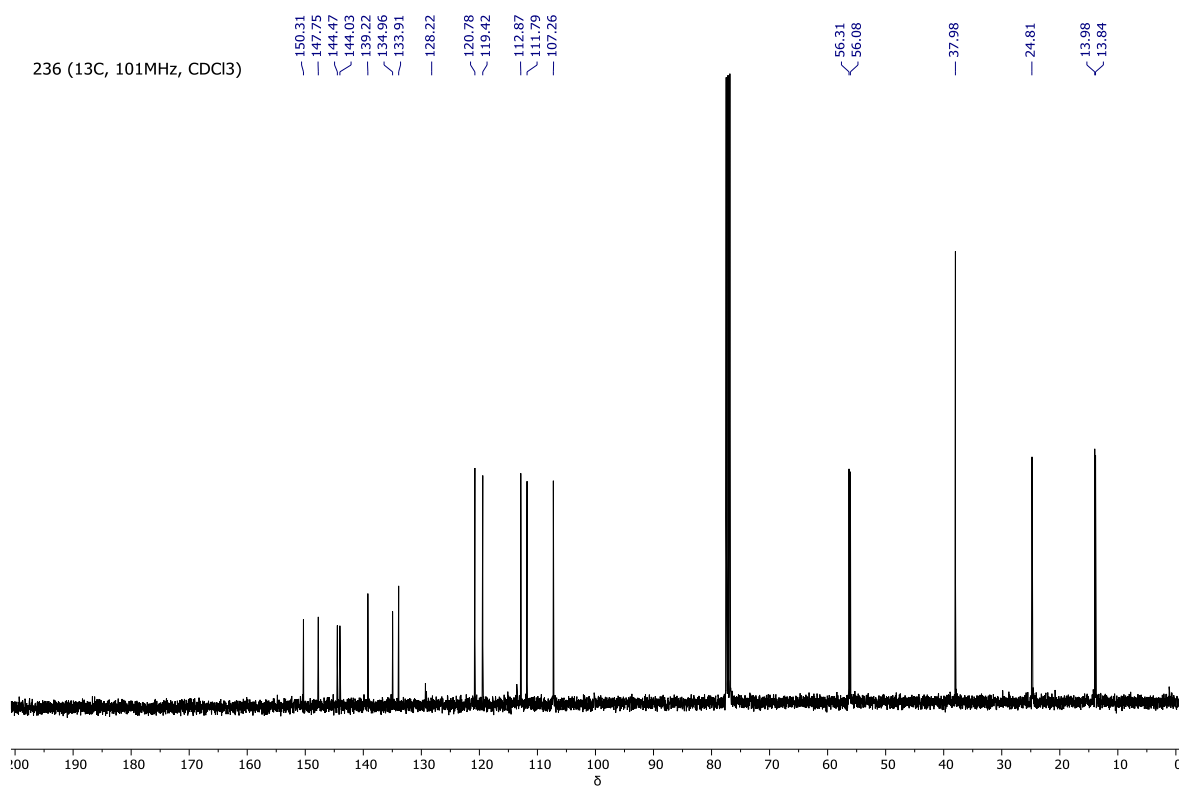
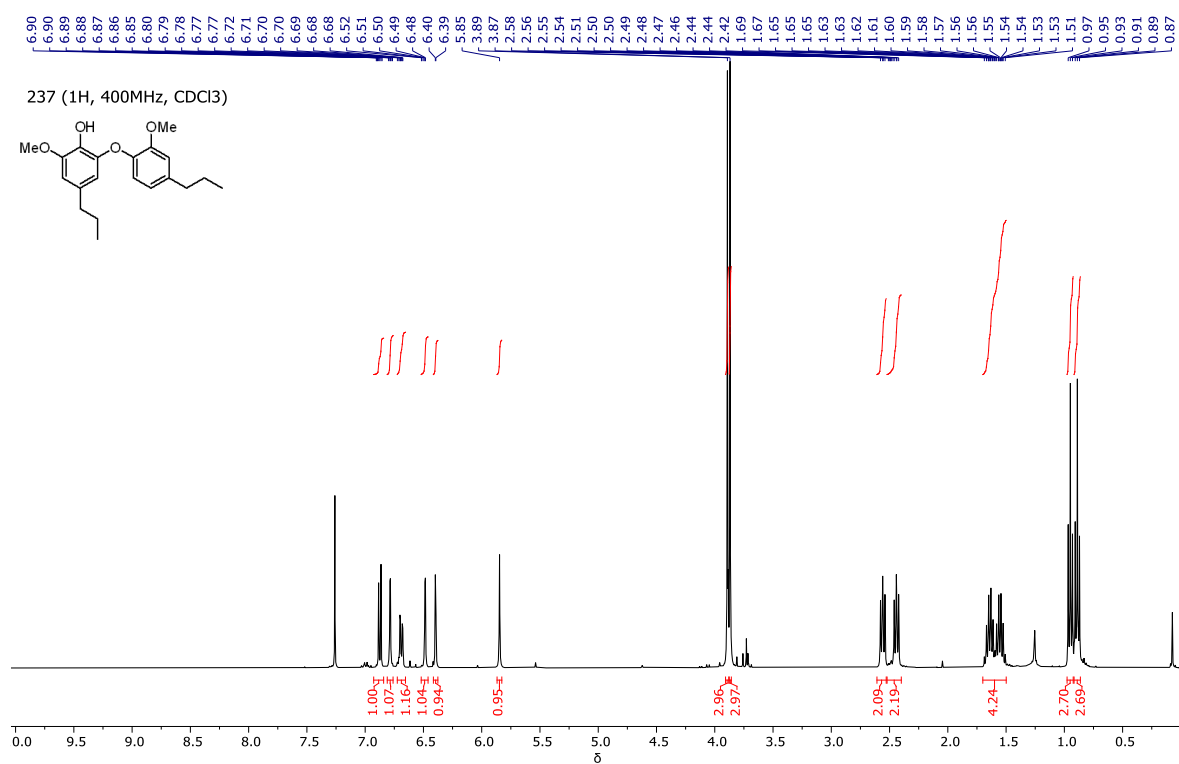












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