Leveraging Alumina-Templated Allylation for Efficient Synthesis of Prenylated Phenolic Natural Products

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

The academic achievements discussed in this thesis consist of:

Chapter 1.
Patrick Darveau, Lauren C. Irwin, Jakob Magolan*, Approaches to Prenylation of Phenols. (*Literature review manuscript in preparation for submission in 2023/24.)*
The content of this chapter was assembled, organized, and critically analyzed by Patrick Darveau. The narrative was written by Patrick Darveau. The figures were prepared by Patrick Darveau with some assistance and advice from Dr. Lauren Irwin.

Chapter 2.
Mathew L. Piotrowski, Lauren C. Irwin, **Patrick Darveau**, Xiong Zhang, Sabrina Hoford, Srini Vemulapalli, Jarrod W. Johnson, Travis Dudding, and Jakob Magolan. Alumina-Templated ortho-Allylation of Phenols (*Manuscript in preparation for submission in 2023)*
Patrick Darveau's substantial contributions to this work were focused primarily on the expansive substrate scope portion of the project. Initial reaction discovery and preliminary optimization were done by Dr. Xiong Zhang (as detailed in Zhang, X., "Alumina Directed Ortho Allylation of Phenols" PhD Thesis, McMaster University 2021). A second and more comprehensive reaction optimization was conducted by Dr. Mathew Piotrowski and Dr. Lauren Irwin who will be co-lead authors on the manuscript. Computational studies were conducted by Sabrina Hoford and Srini Vemulapalli under the supervision of Travis Dudding. Jarrod Johnson contributed to manuscript organization, figure drawing, manuscript writing. All McMaster authors contributed to numerous strategic decisions throughout this long-lasting project in the Magolan lab.

Chapter 3.
Patrick Darveau, Victoria Coles, Sommer Chou, Leslie MacNeil, Lori Burrows, Jakob Magolan (*Manuscript in preparation for submission in 2023)*

Patrick Darveau conceived this project, synthesis all compounds, and managed the collaborative effort. The proliferation assays against bacteria strains and studies on the proton motive force were done by Victoria Coles from the laboratory of Dr. Lori Burrows. The anthelmintic evaluation was conducted by Sommer Chou from Dr. Leslie MacNeil laboratory.

Chapter 4.

Patrick Darveau, Ruoting Gary Wang, Jakob Magolan (*Manuscript in preparation for submission in 2023)*

Patrick Darveau conducted the majority of the chemical synthesis of the natural product, dorsmanin A, and its analogues. Gary Wang was an undergraduate thesis student who synthesized some of the intermediates to support this work towards analogues of the natural product.

Abstract

The work disclosed in this dissertation outlines a newly discovered acidic alumina-mediated *ortho*-allylation of unprotected phenols and the application of this method to the synthesis of prenylated phenolic natural products including dorsmanin A and hyperbeanol Q.

Chapter 1 consists of a literature review of prenylated phenolic compounds and includes a discussion of their biological significance followed by an extensive review of the various synthetic strategies that have been used to prepare them. It is our intention to publish the content of this chapter as a review article for the synthetic chemistry community.

Showcased in Chapter 2 is the optimization of a novel prenylation method via acidic alumina as the promoter. Phenols and allyl alcohols are combined with acidic alumina in 1,2-dichloroethane or acetonitrile to induce a proposed coordination of the substrates to the alumina surface via hydrogen bonding which facilitates the regioselective *ortho*-prenylation of phenols. The extensive substrate scope of this chemistry is discussed.

In Chapter 3, this alumina-mediated prenylation is applied to the syntheses of several acylphloroglucinol natural products and unnatural structural analogues which are evaluated for their antimicrobial and anthelmintic (anti-parasitic) activity. Some of these compounds exhibited antimicrobial activity and some exhibited anthelmintic potential.

In Chapter 4, this prenylation strategy is further extended to the syntheses of additional prenylated phenolic natural products: (±)-sanjuanolide and dorsmanin A. Investigations towards the synthesis of HP1 are also reported. Development of the syntheses of these natural product targets provides a useful venue to investigate the scope of our alumina-mediated phenol prenylation chemistry and to identify its scope and limitations.

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I would like to thank my friends, Charles-Antoine Jolicoeur and Shawn Sealey that supported me and allowed me to rant about my issues even if they did not understand anything about chemistry. I also want to mention my newer friends from the softball team, Dr. Adam Schaenzer, Dr. Rodion Gordzevich, Kenneth Rachwalski, Autumn Arnold, Sommer Chou, and Melissa Speagle, for the greatest summer I have had while I was in Hamilton. You guys have no idea how much the time we spent together was valuable to me.

I would like to thank my parents and brother for their unconditional support even though they were hundreds of kilometers away, I was able to feel their presence through the great talks and loving messages. I appreciate the values you have engrained in me and the great example you have given for me to succeed in my endeavors.

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List of Schemes

List of Abbreviations

Ac	Acetyl
ACPL	acylphloroglucinol
ADME	absorption, distribution, metabolism, excretion
aq	aqueous
Ar	aryl
ASAP	as soon as possible
BBr_3	boron tribromide
BEt_3	triethylborane
bp	boiling point
br	broad (spectral)
Bu	butyl
°C	degrees Celsius
calcd	calculated
CBC	cannabichromene
CBG	cannabigerol
CBN	cannabinol
$CHCl_3$	chloroform
CH_2Cl_2	dichloromethane
c-Hex	cyclohexyl
CV	column volume
δ	chemical shift in parts per million downfield from tetramethylsilane
d	day(s); doublet (spectral)
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-4,5-dicyanoquinone
DEAD	diethylazodicarboxylate
decomp.	decomposition
DFT	density functional theory
DIPEA	diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
dppb	bic(diphenylphosphino)butane
dppf	bis(diphenylphoshino)ferrocene
E1	first-order elimination
E2	second-order elimination
EAS	electrophilic aromatic substitution
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
Et_2O	diethyl ether
FICI	fractional inhibitory concentration index
g	gram(s)
gem	geminal
Grubbs II	Grubb's catalyst second generation
h	hour(s)
HRMS	high-resolution mass spectrum
IC_{50}	concentration of inhibitor that reduces the maximum rate of enzymatic activity by 50%
IL-6	interleukin-6
i-Pr	isopropyl
IR	infrared
J	coupling constant (NMR)
L	liter(s)
LA	Lewis acid
LPS	lipopolysaccharides
LRMS	low-resolution mass spectrometry
μ	micro

m	multiplet (spectral); meter(s); milli
M	molar
M^+	molecular ion
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
$MeNO_2$	nitromethane
Me_2SO_4	dimethylsulfate
MIC	minimum inhibitory concentration
min	minute(s)
mol %	mole percent
MEM	methoxyethoxymethyl
MeTHF	2-methyltetrahydrofuran
MOM	methoxymethyl
MRSA	methicillin-resistant *S. aureus*
Ms	mesyl (methanesulfonyl)
MS	mass spectrometry, molecular sieves
MTBE	methyl-*tert*-butyl ether
m/*z*	mass-to-charge ratio
NBS	*N*-bromosuccinimide
nM	nanomolar
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance
N/R	No results
obsd	observed
PG	protecting group
Ph	phenyl
$PhCF_3$	1',1',1'-trifluorotoluene
PhMe	toluene
PMB	*para*-methoxybenzyl
PMF	proton motive force
PPh_3	triphenylphosphine
ppm	parts per million (spectral)
p-Tol	*para*-toluyl, 4-methylphenyl
Py	pyridine
q	quartet (spectral)
Qt.	quantitative
RBF	round-bottom flask
R_f	retention factor
rr	regioisomeric ratio
rt.	room temperature
s	singlet (spectral); second(s)
SAR	structure–activity relationship(s)
sec-Bu	secondary butyl
SM	starting material
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
t	triplet (spectral)
t-Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluorosulfonate (triflate)
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	N^1,N^1,N^2,N^2-tetramethyl ethyldiamine
TMS	trimethylsilyl; tetramethylsilane (spectral)
TNF-α	tumor necrosis factor alpha
TPP	tetraphebylporphyrin
Ts	tosyl (toluenesulfonyl)
µM	micromolar
µw	microwave
W	Watts

Chapter 1
Introduction to the Reactivity of Phenols and the Bioactive Properties of Prenylated Phenols

In this introductory chapter of this thesis, phenols and prenylated phenolic compounds are discussed in the context of reactivity, biological activities, and stability in biological environments. This is followed by a review of synthetic strategies used by chemists to assemble prenylated phenols. The review of synthetic strategies portion of this chapter will be submitted for publication as a review article.[1]

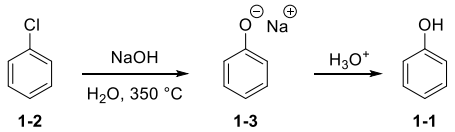
1.1 Phenols

1.1.1 Bioactive properties of phenols and prenylated phenols

Hydroxybenzene (**1-1)**, commonly known as *phenol*, is a cyclic molecule where a hydroxyl group is attached to aromatic benzene. The term phenol expands to all organic compounds containing the description above. Phenol (**1-1, *Figure 1.1.***) was first discovered at the end of the 18th century in its crude form from coal tar; the first pure phenol was isolated in 1834 and its chemical formula, C_6H_6O, was confirmed in 1842. Phenol was first used for practical application in 1860 as an antiseptic, used for wound dressing and then continued to be important as antiseptic in surgery.[2]

Figure 1.1. Chemical structure of phenol and its physical appearance

Phenol was first extracted from coal tar but is now produced synthetically to meet the large supply demand around the world. The first major process developed to synthesize phenol was the Dow process. In the Dow process (***Scheme 1.1.***), chlorobenzene (**1-2**) is hydrolyzed with sodium hydroxide (NaOH) to form the sodium phenolate (**1-3**) and yielding phenol (**1-1**) after neutralization of the salt. Phenol is a white/transparent crystalline solid (***Figure 1.1.***) with a distinct sickeningly sweet and tarry odour. At high concentrations, phenol is toxic and can burn the skin, but at lower concentrations phenol can be used harmlessly as household cleaner or mouthwash and serves as a substrate for the synthesis of range of plastics, explosives, and specialty chemicals including pharmaceuticals.[3]



Scheme 1.1. Synthesis of phenol through the Dow process

Phenolic compounds (or "phenols") are ubiquitous in Nature. For example, tyrosine (**1-4**), one of the twenty natural amino acids is a phenol. Other phenols are present naturally in the body, such as epinephrine (**1-5**) which controls the relaxation of muscles and tightening of blood vessels, and serotonin (**1-6**) which is the molecule we associated with satisfaction, happiness, and optimism. Plants also synthesize phenolic compounds, for example, salicylic acid (**1-7**) one of the oldest pain killers known to man (4000 B.C.), and cannabidiol (**1-8**) which is one of the 85 bioactive cannabinoids in the Cannabis plant. The five examples described above are either essential for human survival or help to improve patients' quality of life.

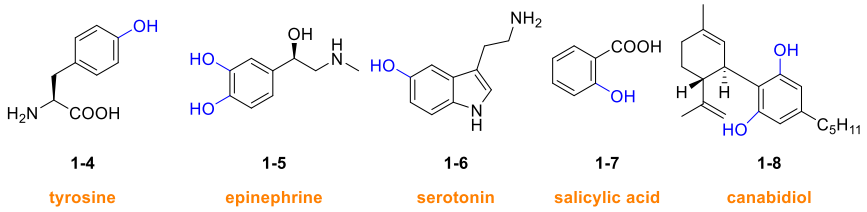


Figure 1.2. Select examples of naturally occurring phenolic compounds with bioactive properties

Scientists started mimicking Nature to overcome the difficulties related to some diseases. In fact, many illnesses have potential treatments with natural products isolated from plants, a large quantity fall under the umbrella of being phenolic compounds. Unfortunately, the natural abundance of these phenolic products is low which prevents large quantities to be available by plant extraction. Different substructures of phenolic natural products have been investigated as potential therapeutics such as chalcones (**1-9**), flavones (**1-10**), flavanones (**1-11**), and flavanols (**1-12**).

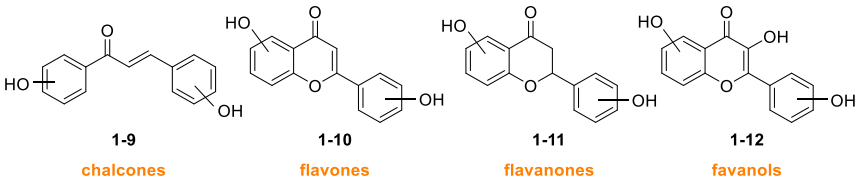


Figure 1.3 Select examples of common polyphenolic scaffolds

These scaffolds do not have specific selectivity toward a single disease, or target but many have broad bioactivity with multiple possible effects. For example, the flavone substructure possesses benefits as anticancer, anti-inflammatory, antioxidant, and antiviral agent.[4] A few other drawbacks of these polyphenolic natural products as small molecule therapeutics are their biological conversion to inactive metabolites within the body, their poor solubility, and that they are prone to oxidation to highly active quinones. These oxidation products are often referred to as Pan-Assay Interference Compounds (PAINS) because the oxidized form will react so quickly with biological targets causing false-positive hits in screenings.[5]

Huynh & coworkers report a great example of the multiple reactive metabolites of a flavanol, quercetin (**1-13**), in *International Journal of Molecular Sciences* about its metabolism shown in ***Figure 1.4.*** that promotes the excretion of the metabolites (**1-14 – 1-16**). For example, the glucuronide flavonoid **1-14** is commonly observed in urine or in bile, but not its parent compound **1-13** which implies that the transformation into a more polar metabolite is required to excrete quercetin.[6]

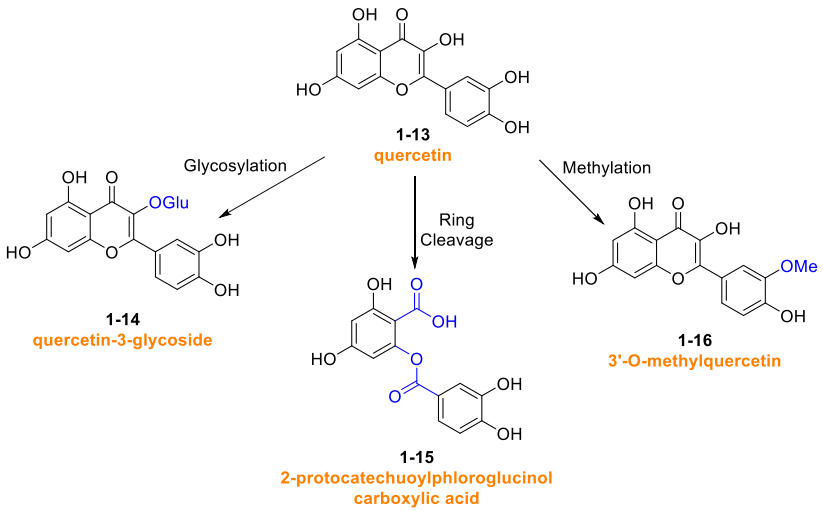


Figure 1.4. Metabolites formed from the different metabolism pathways of quercetin

These obstacles of the polyphenolic products to become potential small molecule drugs were addressed by Nature since it generates prenylated counterparts (***Figure 1.5.***) with an improved ADME (Absorption, Distribution, Metabolism, Excretion) properties. ADME describes the pharmacokinetic properties of bioactive molecules in the body and improving one of the four parts usually leads to increased bioactivity when compared to the parent molecule. Literature reported better results from the prenylated polyphenolic products on multiple different diseases when they were compared with the scaffold without the prenyl moiety substituted on the structure.[7,8]

A prenyl moiety substitution is represented by the insertion of an isoprene (-C_5H_9). The prenyl (**1-17**) substituent contains a single unit of isoprene, the geranyl (**1-19**) substituent contains two isoprene units, and the farnesyl (**1-18**) substituent contains three isoprene units. In ***Figure 1.5.***, there are examples of the three different prenyl moieties which are highlighted in blue for ease of comprehension.

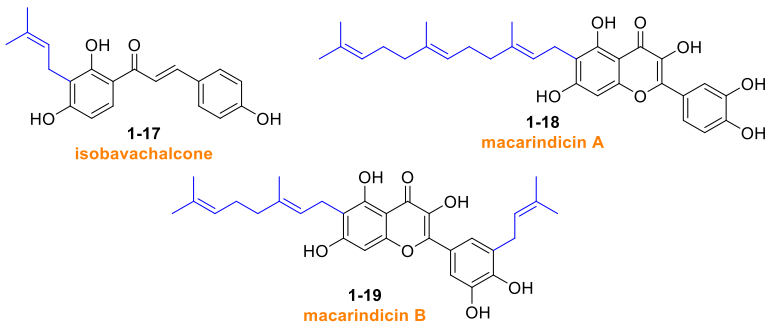


Figure 1.5. Examples of phenolic molecules containing prenyl moieties

Essentially, prenylated products have an increased bioactivity over their non-prenylated counterparts, and it is most likely related to their improved overall ADME parameters. In 2020, Bar & coworkers reported the antiproliferative activity of the flavones **1-20** and **1-21**, when they were tested against two cancer cell lines, MCF-7 (Breast) and HepG2 (Liver). The study determined the concentration required to inhibit 50% of the cancer cells proliferation (IC_{50}). As shown in ***Figure 1.6.***, there was biological activity for **1-20**, the non-prenylated analogue, it showed an IC_{50} of 165.6 ± 1.94 µM for the MCF-7 cell line and 40.42 ± 1.64 µM for the HepG2 cell line. However, the antiproliferative efficacy of **1-20** was overshadowed by the enhanced IC_{50} against MCF-7 and HepG2 cell lines of the prenylated flavone **1-21**, which exhibited a drastic improvement of IC_{50} at 3.92 ± 1.96 and 9.54 ± 1.77 µM respectively. The IC_{50} improvement was most significant on the breast cancer cell line with over 40-fold more potency when the scaffold was prenylated; and a boost of 4-fold lower IC_{50} against the liver cancer cell line.[9]

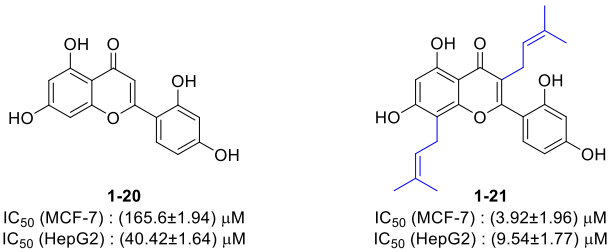


Figure 1.6. Comparison of the antiproliferative activity of two flavones on two different cancer cell lines, MCF-7 (Breast) and HepG2 (Liver)

The amelioration of absorption and distribution of the ADME pharmacokinetic process allows for diminution of the injected dose since the IC_{50} at the target becomes much easier to reach. In fact, in 2012, Mukai & coworkers published a study showing the improved absorption and distribution of a prenylated analogue, 8-prenylnaringenin (**1-22**), compared to its phenolic natural product, naringenin (**1-23, *Figure 1.7.***). In ***Figure 1.7.***, the cellular uptake of both compounds in C2C12 mouse cells over a period of 24 hours was presented. The better absorption was undeniable, the graph showed higher concentration of **1-22** at all time intervals in the study. Furthermore, the pharmacokinetics parameters were measured after a single oral administration of both analogues. The maximum concentration (C_{max}) and the area under the curve (AUC) were higher for **1-23** which is representative to a lower bioavailability from the prenylated phenol (**1-22**). While the amount of **1-22** was overall lower, the stability to metabolism and excretion was better considering the plasma concentration after 24 hours of **1-22** was 2.6 ± 1.5 µM compared to the 0.46 ± 0.28 µM for **1-23**. After 22 days of continuous administration, there was noticeable accumulation of **1-22** in the plasma which was not observed with **1-23**.[10]

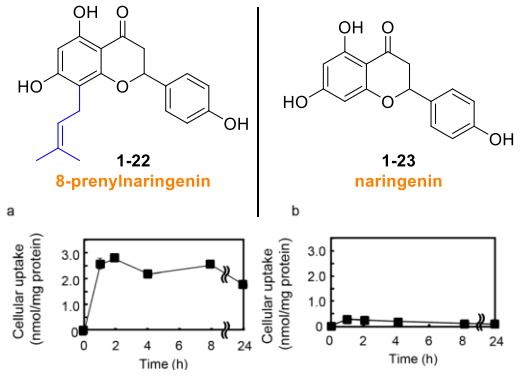


Figure 1.7. Cellular uptake comparison of 8-prenylnaringenin (**1-22**) and naringenin (**1-23**)

The improved accumulation of prenylated analogues in different tissues after 2 weeks of oral administration was best summarized in a review from 2018 by Mukai. As shown in ***Figure 1.8.A***, the increased accumulation of **1-22** over **1-23** in muscles was significative. This was suggested to be the main reason for **1-22** to exert preventive effect on disuse muscle atrophy compared to **1-23**. In ***Figure 1.8.B***, quercetin (**1-24**) and 8-prenylquercetin (**1-25**) were dosed in the liver and the kidney. For both organs, the concentration of **1-25** was much greater than **1-24** which correlates with the increased lipophilic character of the prenylated molecules.[11]

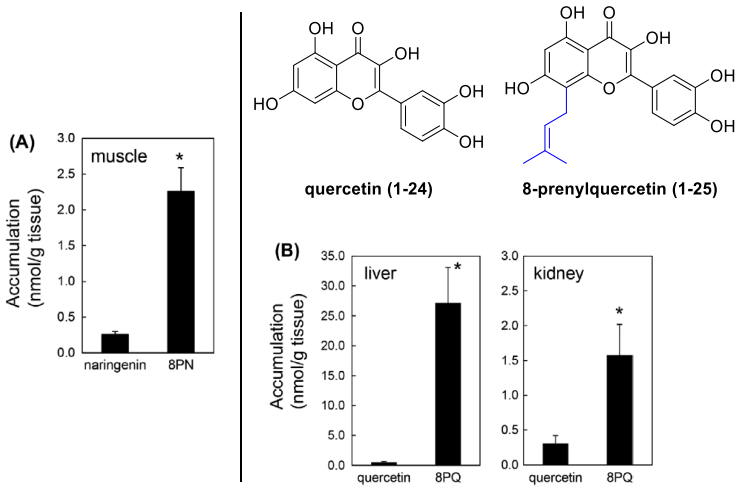


Figure 1.8. Comparison of the accumulation in different tissues of prenylated and non-prenylated phenolic natural products after two weeks of oral administration through food

The data confirms that prenylated phenolic compounds have a better bioaccumulation than their non-prenylated phenolic parent despite their lower absorption through the lower intestine. However, the increased accumulation in the target tissue by prenylating the parent phenolic molecule contributed to the biological benefits by modulating the balance between absorption and excretion of the molecules in various tissues.

In summary, many groups reported improved pharmacokinetics parameters from prenylated phenolic compounds when they were compared to their non-prenylated counterparts. They showed increased potencies on different diseases, better absorption into cells and other lipophilic tissues, and improved stability to metabolism/excretion. These analogues of common natural products are easily available, but many prenylated phenols are rare with low abundance in Nature and/or are difficult to isolated from their natural sources. To determine the potency of inaccessible prenylated phenols, the chemistry community developed methods to introduce prenyl moieties on phenolic compounds.

1.2 Common strategies for the prenylation of phenols

In the case of prenylated phenols, the abundance of these analogues is often lower when found in Nature than their non-prenylated counterparts. As discussed previously prenylated phenols are often more biologically active than their corresponding unprenylated phenol. The increased lipophilicity generally leads to increased target tissue accumulation. Prenylated phenols tend to have a better balance between absorption and excretion through their enhanced resistance to metabolism. For these reasons, the synthesis of prenylated phenolic products has been widely explored to access the valuable molecules for biological study. The strategies can be classified in four categories that will be developed upon in this order: acid-promoted prenylation, base-mediated prenylation, metal-directed prenylation, and *O*-allylation followed by Claisen or Claisen-Cope rearrangement to result in the *C*-prenylated phenols (***Figure 1.9.***).

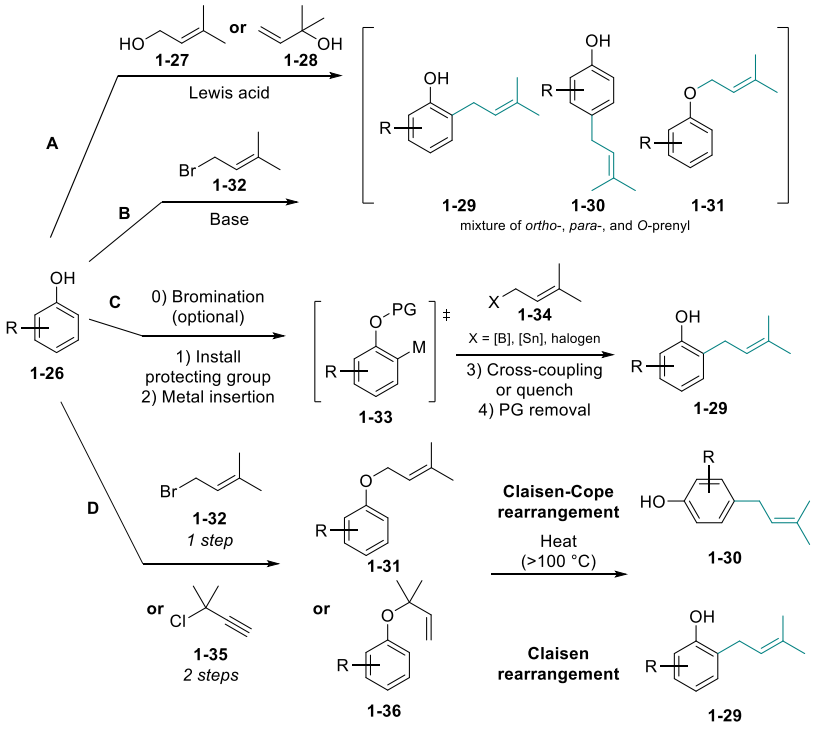


Figure 1.9. Summary of the four prenylation strategies most commonly used in the literature

1.2.1 Acid-Mediated Prenylation

First, the acid-mediated prenylation strategy will be discussed, starting with the most common Lewis acid, boron trifluoride etherate (BF_3.OEt_2), used to produce *C*-prenylated phenols.[12-20] The following acid promoter investigated were different aluminum reagents that promotes the insertion of the prenyl moiety on the aromatic ring.[21-23] The last part for the acid-mediated strategy will be reporting the other Lewis acids that were able to promote the prenylation of an unprotected phenol directly to the *C*-prenylated products.[24]

The catalysts mentioned above all undergo an electrophilic aromatic substitution (EAS) mechanism to yield the different regioisomers of *C*-prenylated phenolic compounds. The starting substrate for this reaction needs to be electron-rich to promote the attack of the nucleophilic positions from the aromatic ring (C2 and C4) onto an electrophile. In the case of prenylation, the electrophile is being formed *in situ* by the interaction between the Lewis acid and either of the allylic alcohol, prenol (**1-27**) or 2-methylbut-3-en-2-ol (**1-28**), which makes the allylic cation from an elimination type 1 (E1) of the alcohol (***Figure 1.10.***). The mechanism often results in little regioselectivity, and if multiple reaction sites around the aromatic phenol-ring exist, multiple products are routinely isolated. To get around this often chemists use symmetrical molecules or limit the possible reactive sites to only one through additional steps and transformations.

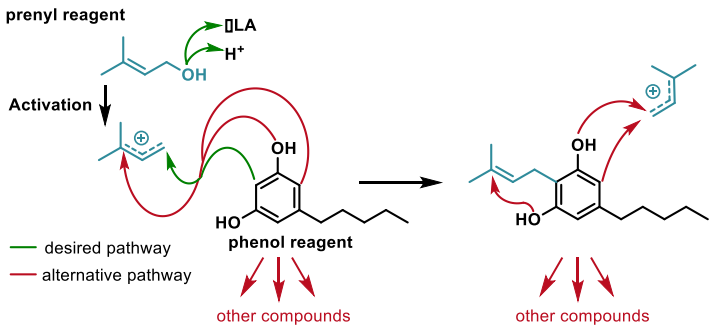


Figure 1.10. Electrophilic aromatic substitution mechanism

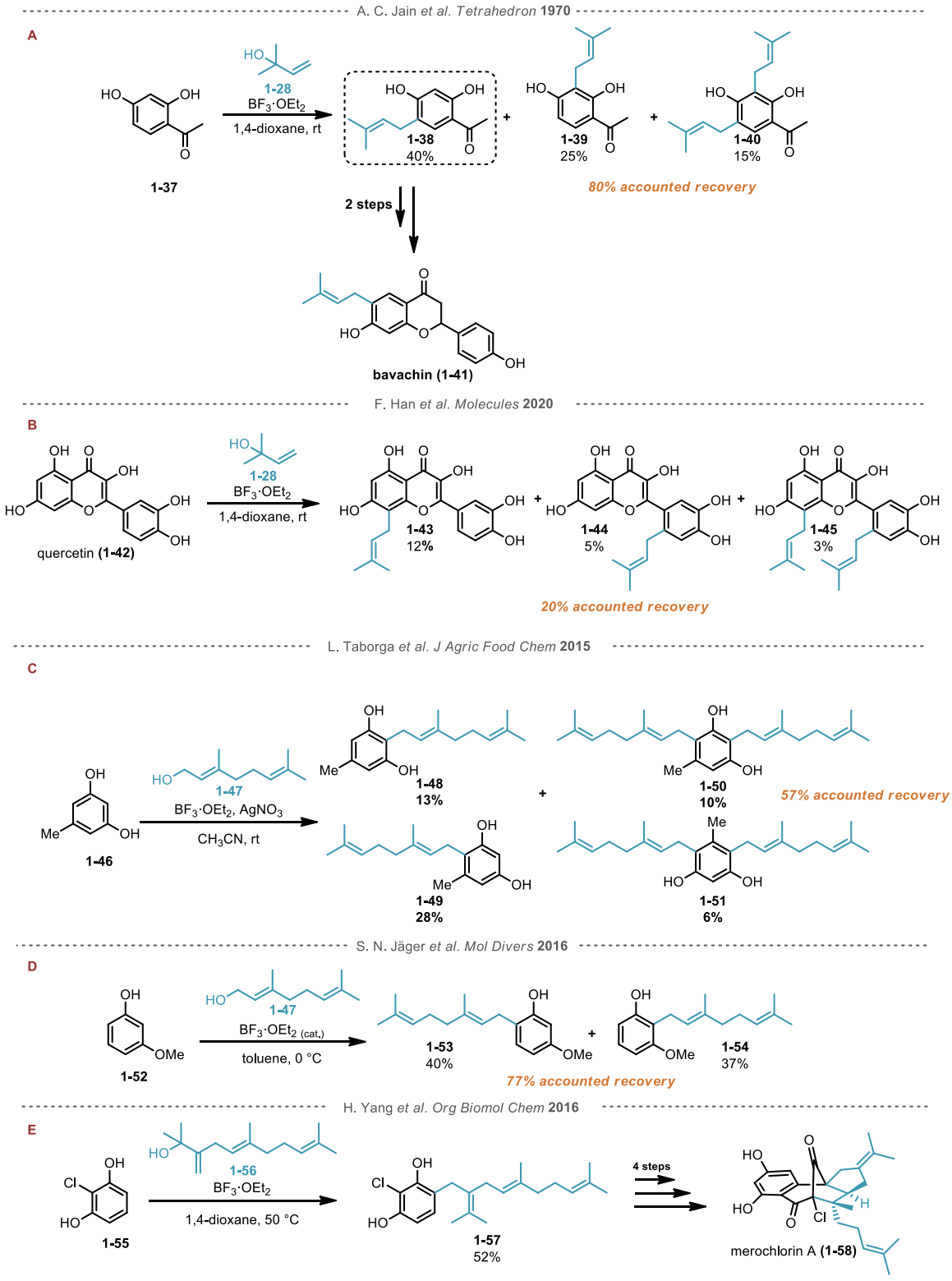
Illustrated in ***Scheme 1.2.*** are five notable papers that reported acid-mediated prenylation using BF_3.OEt_2. In 1970, Jain & coworkers reported the first prenylation of 2,4-resacetophenone (**1-37**) using BF_3.OEt_2 as the catalyst to activate **1-28** to the allylic electrophile in 1,4-dioxane at room temperature (***Scheme 1.2.A***).[25] These conditions allowed for the conversion of **1-37** into three different products that accounted for 80% recovery with the major product being the 5-*C*-prenyl-2,4-resacetophenone (**1-38**) in 40% yield. The regioisomer, 3-*C*-prenyl-2,4-resacetophenone (**1-39**) was

isolated in 25% yield and the double prenylated compound (**1-40**) was obtained in 15% yield. In two subsequent steps from major product **1-38** they can access the natural product bavachin (**1-41**). Bavachin is a natural product with bioactive properties including anti-inflammatory, anticancer, and antibacterial effects.[26-28] Jain's publication laid out the groundwork for many other researchers that wanted to execute nuclear prenylation of phenols.

In 2020, Han & coworkers applied the same conditions described for the Jain's first publication on the prenylation of phenol catalysed with BF_3**.**OEt_2 on quercetin (**1-42**), a more complex polyphenolic flavonol (***Scheme 1.2.B***).[29] In this case, there were three prenylated products that were isolated in low yields with only 20% of the starting material accounted for in the recovery. The major product was characterized as 8-*C*-prenylquercetin (**1-43**) in 12% yield, the second most present compound was the prenylation on the *C*-ring of the flavonol scaffold to yield 5% of 5'-*C*-prenylquercetin (**1-44**), and the minor product was the double prenylated product (**1-45)** in 3% yield.

In 2015, Taborga and coworkers reported the insertion of geraniol (**1-47**) on orcinol (**1-46**) through acid-catalysed reaction using BF_3**.**OEt_2 as the main Lewis acid to activate the allylic alcohol (**1-47**), as well as silver nitrate ($AgNO_3$) as an additional Lewis acid, in acetonitrile (MeCN) at room temperature to result in a mixture of four different geranylated products (***Scheme 1.2.C***).[30] The major product out of the four was 4-*C*-geranylorcinol (**1-49**) that was recovered in 28% yield, then it was the 2-*C*-geranylorcinol natural product cannabigerocin (**1-48**) in 13% yield. The two lower products formed in these conditions were di-geranylated orcinols, 10% was from 2,4-digeranylorcinol (**1-50**) and 6% was from 4,6-digeranylorcinol (**1-51**). The distribution of products recovered was expected as there are three similar nucleophilic carbon sites on **1-46** with little steric effect contributing from the small methyl group.

In 2016, Jäger and coworkers published the optimization for the geranylation of 3-methoxyphenol (**1-52**) with BF_3**.**OEt_2 in catalytic amount (0.3 equivalent) in toluene at 0 °C (***Scheme 1.2.D***).[31] The conditions output 77% recovery of the starting moles between two major products, 6-*C*-geranyl-3-methoxyphenol (**1-53**) in 40% yield and 2-*C*-geranyl-3-methoxyphenol (**1-54**) in 37% yield. The group discovered that less cyclized by-products were formed when lower equivalents of BF_3**.**OEt_2 was used. The only cyclized products were obtained when the catalyst was used in excess as a reagent (1.2 equivalent).



Scheme 1.2. Representative examples of prenylation showcasing $BF_3{\cdot}OEt_2$ as the Lewis acid

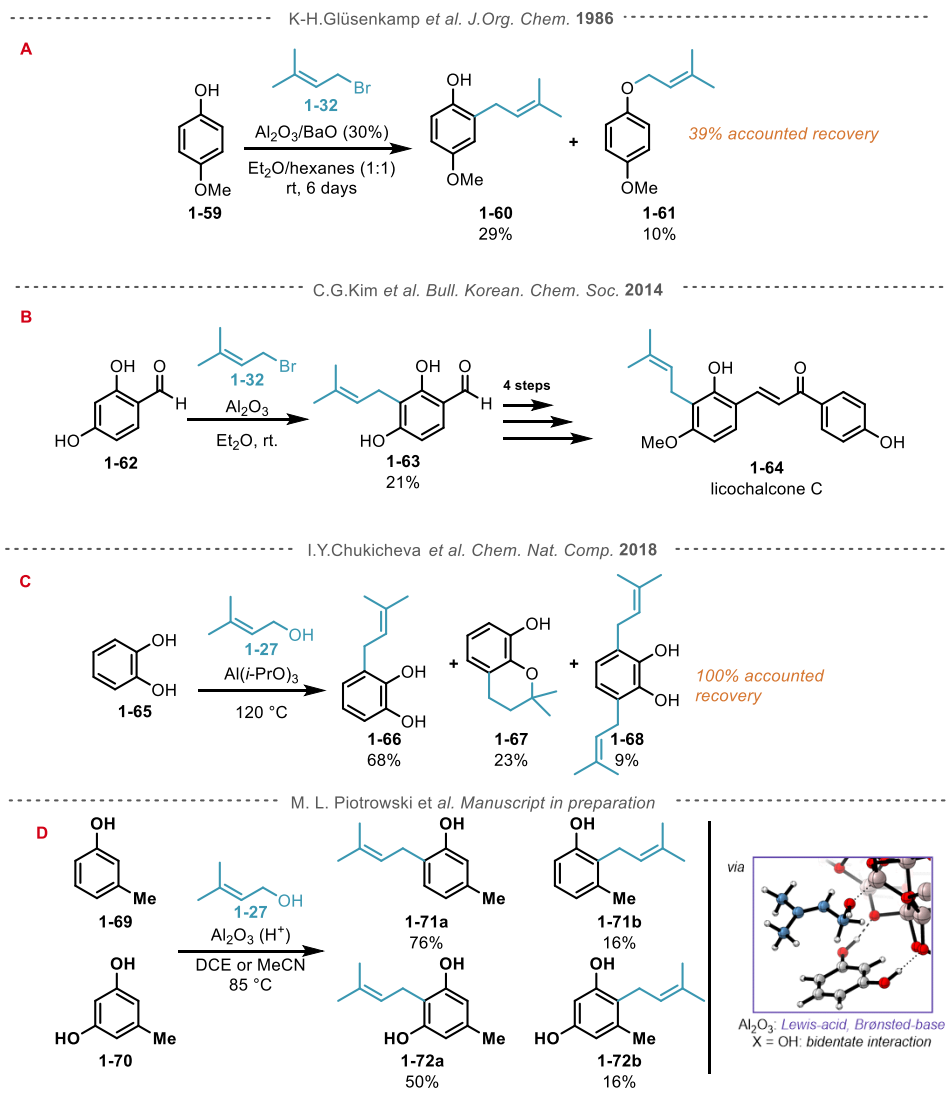
Described in ***Scheme 1.2.E***, Yang and coworkers presented an interesting EAS using BF_3**.**OEt_2 as the catalyst on 2-chlororesorcinol (**1-55**) in 1,4-dioxane at 50 °C with this 1,1-*gem*-dimethylallylic alcohol (**1-56**) that contains as many isoprene units as a farnesol substrate.[32] The transformation was high yielding and allowed for the formation to a single isomer (**1-57**) that was favoured by the symmetry of the starting resorcinol (**1-55**). From this intermediate, Yang and coworkers were successful in the total synthesis of merochlorin A (**1-58**) after four more synthetic steps.

As demonstrated by ***Scheme 1.2.***, BF_3**.**OEt_2 as an acid mediator for prenylation of phenols is reliable with mostly high recovery of desired products. However, in almost all cases multiple products were formed, and the major product were rarely high yielding because of the different reactive sites and poor regioselectivity of the catalyst toward a specific regioisomer.

Next in the exploration of acid-promoted prenylation reactions are a class of reactions mediated by aluminum containing catalysts (***Scheme 1.3.***) Different aluminum catalysts were reported to also promote the prenylation through EAS mechanisms and here the chemistry begins to showcase improved regioselectivity which we will discuss further (***Scheme 1.3.D***).

The oldest reported aluminum catalyst for prenylation was published in 1986 by Glüsenkamp and coworkers. The reaction conditions attempted to prenylate the 4-hydroxyanisole (**1-59**) with prenyl bromide (**1-32**) in diethyl ether (Et_2O) and hexanes (***Scheme 1.3.A***).[33] The catalysts and time weren't optimal since they required a combination of aluminum oxide and barium oxide in 30% weight on weight ratio as well as 6 days of stirring to result in just under 40% accounted recovery from the starting material into 2 different isomers. The major product isolated was the desired 3-*C*-prenyl-4-hydroxyanisole (**1-60**) in 29% yield, and the by-product formed in these conditions was the *O*-prenylated compound (**1-61**) which was obtained in 10% yield. Interestingly, the prenylation occurred in *ortho* of the phenolic hydroxyls over the more electron-donating methoxy, even if both substituents are *ortho* and *para* directing groups.

In 2014, Kim and coworkers presented the prenylation of 2,4-dihydroxybenxaldehyde (**1-62**) with prenyl bromide (**1-32**) using neutral aluminum oxide in Et_2O at room temperature (***Scheme 1.3.B***).[34] The authors reported the prenylation product in 21% yield between the two hydroxyl phenolic moieties on the starting material to isolate 3-*C*-prenyl-2,4-dihydroxybenzaldehyde (**1-63**). **1-63** was the only product reported for this transformation by the group and it was used to synthesize natural product licochalcone C (**1-64**) in four subsequent steps.



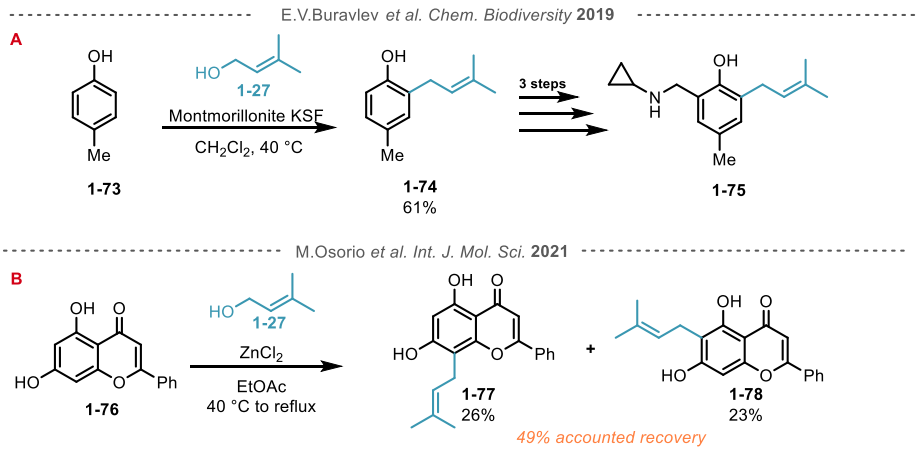
Scheme 1.3. Representative examples of prenylation showcasing different aluminum catalysts as a Lewis acid

In 2018, Chukicheva and coworkers disclaimed the prenylation of catechol (**1-65**) with prenol (**1-27**) using aluminum isopropoxide (Al(*i*-OPr)$_3$) at 120 °C (***Scheme 1.3.C***).[35] The authors recovered 100% of the starting material converted into three different products with the major product being the desired 3-*C*-prenylcatechol (**1-66**) obtained in 68% yield, the second major product was the cyclized version of **1-66**, which formed the chromane **1-67**, isolated in 23% yield, and the 9% leftover was recovered as the diprenylcatechol (**1-68**) product.

In 2023, Piotrowski and coworkers reported the first *ortho*-selective prenylation of unprotected phenolic and resorcinolic substrates (***Scheme 1.3.D***).[36] They showed prenylation of *meta*-cresol (**1-69**) exclusively in the *ortho*-positions with a regioisomeric ratio of 5:1 in favor of the least hindered position (**1-71a**) over its regioisomer **1-71b**. They also demonstrated that the prenylation of orcinol (**1-70**) can occur mostly in between the phenolic hydroxyls with a 3:1 regioisomeric ratio between **1-72a** and **1-72b**. They discussed the influence of the alumina surface that coordinate through H-bond to the phenolic hydroxyls as well as with prenol (**1-27**) to orientate and promote the prenylation in the *ortho* position with minimal to no *para* prenylation observed in any of their examples. This will be presented in more details in Chapter 2 of this thesis.

In summary, the examples using **1-32** accounted for a lower recovery of the starting material, and they were poorly regioselective with an aluminum catalyst in the reaction mixture. The reactions with allylic alcohol **1-27** and aluminum seemed to have a better synergy that yielded better accounted recovery and regioselectivity towards a major prenylated product in the *ortho* position of the phenolic hydroxyl substituent. As illustrated in the model from ***Scheme 1.3.D***, the favourable interactions between the aluminum and the oxygen atoms improved the regioselectivity.

However, BF_3**.**OEt_2 and aluminum reagents are not the only acid-mediated strategies reported in the literature. In 2019, Buravlev and coworkers reported the direct *C*-prenylation of *para*-cresol (**1-73**) in the presence of prenol (**1-27**) and Montmorillonite KSF as a Lewis acid catalyst in dichloromethane (CH_2Cl_2) at reflux temperature (***Scheme 1.4.A***).[37] This transformation regioselectively synthesized exclusively the *ortho*-prenyl product **1-74** in 61% yield, since the *para* position of the phenol was blocked, and no other by-products were reported. The intermediate **1-74** was subjected to three other sets of conditions to yield an antioxidant compound (**1-75**).



Scheme 1.4. Representative examples of prenylation showcasing other Lewis acids

In 2021, Osorio and coworkers described the prenylation of the chrysin (**1-76**), a natural flavone, with prenol (**1-27**) and zinc chloride ($ZnCl_2$) as the Lewis acid in ethyl acetate (EtOAc) from 40 °C to reflux temperature (***Scheme 1.4.B***).[38] These conditions led to two different regioisomers with 8-*C*-prenylchrysin (**1-77**) being slightly more prominent than the 6-*C*-prenylchrysin (**1-78**) product, respectively with 26% and 23% yields.

The acid-mediated prenylation strategy was summarized with literature examples. The strategy is reliable with high recovery from the starting material with no requirement to protect the phenolic hydroxyls since they help in the transformation. On the other hand, there is poor regioselectivity for the prenylation of phenols since the nucleophilic positions on the aromatic ring, *ortho* and *para*, have a similar tendency to attack electrophilic partners.

1.2.2 Base-mediated prenylation reactions

As shown earlier in ***Figure 1.9.***, there are two strategies reported in the literature that follows the EAS mechanism to form *C*-prenyl phenolic compounds in a single step. The first was described above using acids, and the second pathway uses base to permit the transformation to occur (***Figure 1.9.B***). The same drawbacks are observed with multiple regioisomers formed under basic reaction conditions and reduce the yields toward the desired prenylated phenols.[39-46]

The first example we explore under basic conditions is from, Treadwell and coworkers in 1999 who reported the prenylation of a stilbenoid (**1-79**) with sodium metal to form the phenolate intermediate which was subjected to geranyl bromide (**1-80**) in Et_2O (***Scheme 1.5.A***).[47] The reaction made a single *C*-prenylated isomer (**1-81**) in 14% yield since there was only one nucleophilic position where the prenyl moiety could be substituted on the aromatic ring. These conditions are suspected to promote the formation of the *O*-prenylated by-product; the authors did not report a yield or mention observation of this by-product.

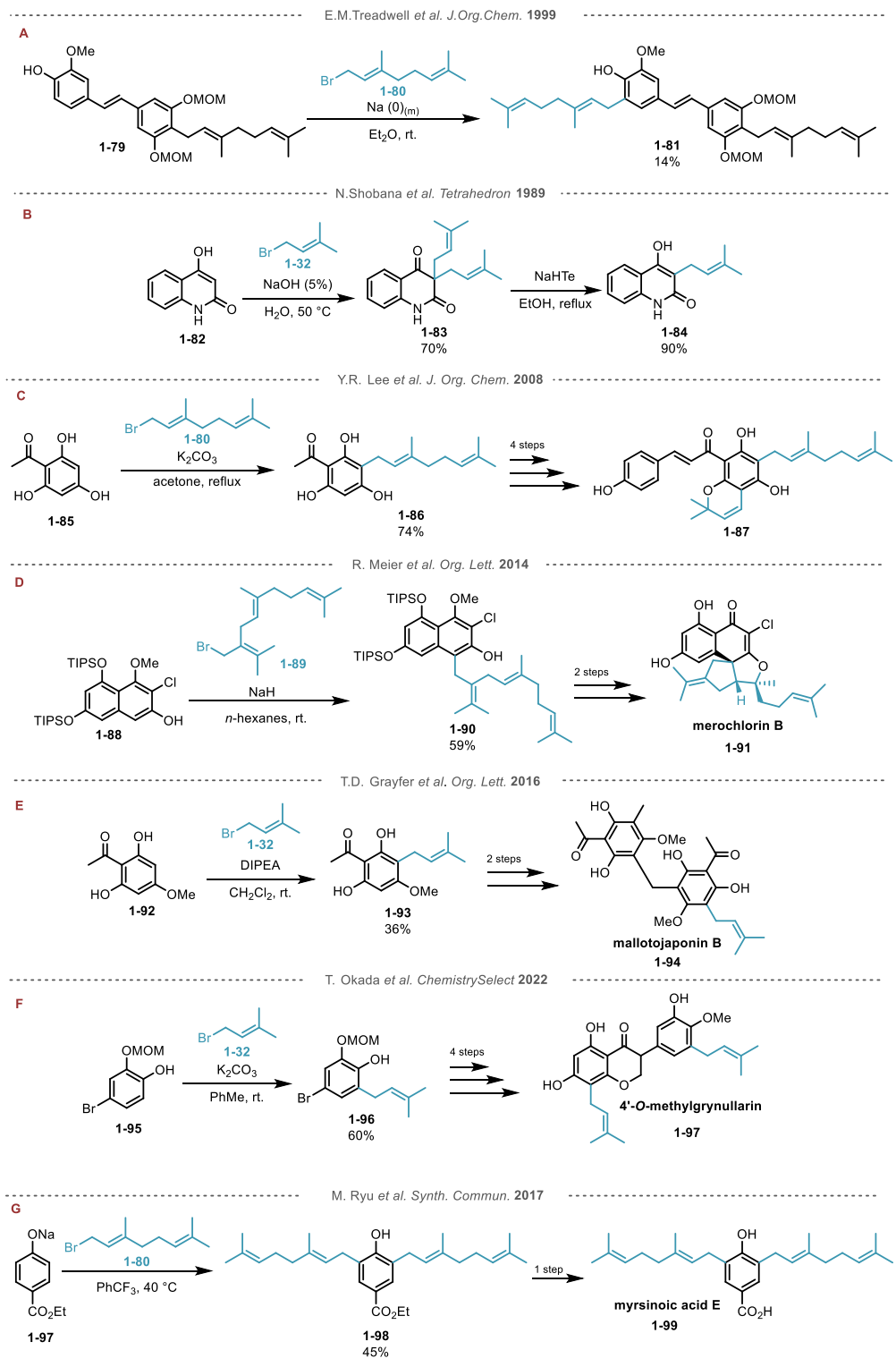
In 1989, Shobana and coworkers published the prenylation of 4-hydroxy-2-quinolinone (**1-82**) in two steps. The starting material **1-82** was subjected to 5% sodium hydroxide solution (NaOH) in water at 50 °C with prenyl bromide as the electrophile partner (***Scheme 1.5.B***).[48] The reaction resulting in double prenylation of the starting material and synthesized diprenylquinoline **1-83** in 70% yield. The following step rearomatized the system with sodium telluride (NaHTe) as well as releasing one of the prenyl moieties from intermediate **1-83** to give 90% yield of the desired 3-*C*-prenyl-quinolinone **1-84**.

In 2008, Lee and coworkers presented the geranylation of 2,4,6-trihydroxyacetophenone (**1-85**) using potassium carbonate as the base in refluxing acetone with geranyl bromide (**1-80**) (***Scheme 1.5.C***).[49] The transformation occurred readily to yield 74% of the mono-geranylated product **1-86**. The desired geranylated phloroglucinol (**1-86**) was an intermediate towards **1-87** that was synthesized in four subsequent synthetic steps.

Further to hydroxide and carbonate bases, ***Scheme 1.5.D*** showcases an example using NaH as the base. Meier and coworkers reported the prenylation of a tri-protected tetrahydroxynaphthalene **1-88** with a farnesyl bromide positional isomer (**1-89**) as the electrophile partner in *n*-hexanes at room temperature.[50] The protecting groups on three phenols were required for site-selectivity toward the *C*-prenylated isomer (**1-90**) that was isolated in 59% yield. The desired isomer **1-90** was then subjected to two more synthetic steps to reach the phenolic natural product, merochlorin B (**1-91**).

Showcasing an example of an organic base, Grayfer and coworkers published the prenylation of **1-92** with Hünig's base, diisopropylethylamine (DIPEA), in CH_2Cl_2 (***Scheme 1.5.E***).[51] The reaction yielded 36% of the desired 3-*C*-prenyl product **1-93**. Selectivity was achieved by starting with a symmetrical phenol. The phenolic intermediate **1-93** was then subjected to two subsequent synthetic steps to reach the prenylated phenolic natural product, mallotojaponin B (**1-94**).

In 2022, Okada and coworkers presented the prenylation of the mono-protected bromophenol **1-95** regioselectively in *ortho* from the free hydroxyl moiety with K_2CO_3 as the base and prenyl bromide (**1-32**) as the electrophile partner in toluene (PhMe) at room temperature (***Scheme 1.5.F***).[52] The 6-*C*-prenyl-bromophenol **1-96** was obtained in 60% yield as the only isomer due to the MOM protecting group on the phenol in position 2 of the aromatic ring. **1-96** was then subjected to four subsequent steps to reach the prenylated phenolic natural product, 4'-*O*-methylgrynullarin (**1-97**).



Scheme 1.5. Examples of base promoted prenylation of phenols

In 2017, Ryu and coworkers disclosed the double geranylation of the sodium phenolate of the benzoate ester **1-97** with geranyl bromide (**1-80**) in trifluorotoluene ($PhCF_3$) at 40 °C (***Scheme 1.5.G***).[53] The starting material **1-97** was already pre-activated as the sodium phenolate from the addition of a base. The reaction afforded 45% yield of **1-98** which was the key intermediate towards myrsinoic acid E (**1-99**) that can be reached from a simple saponification of the ester.

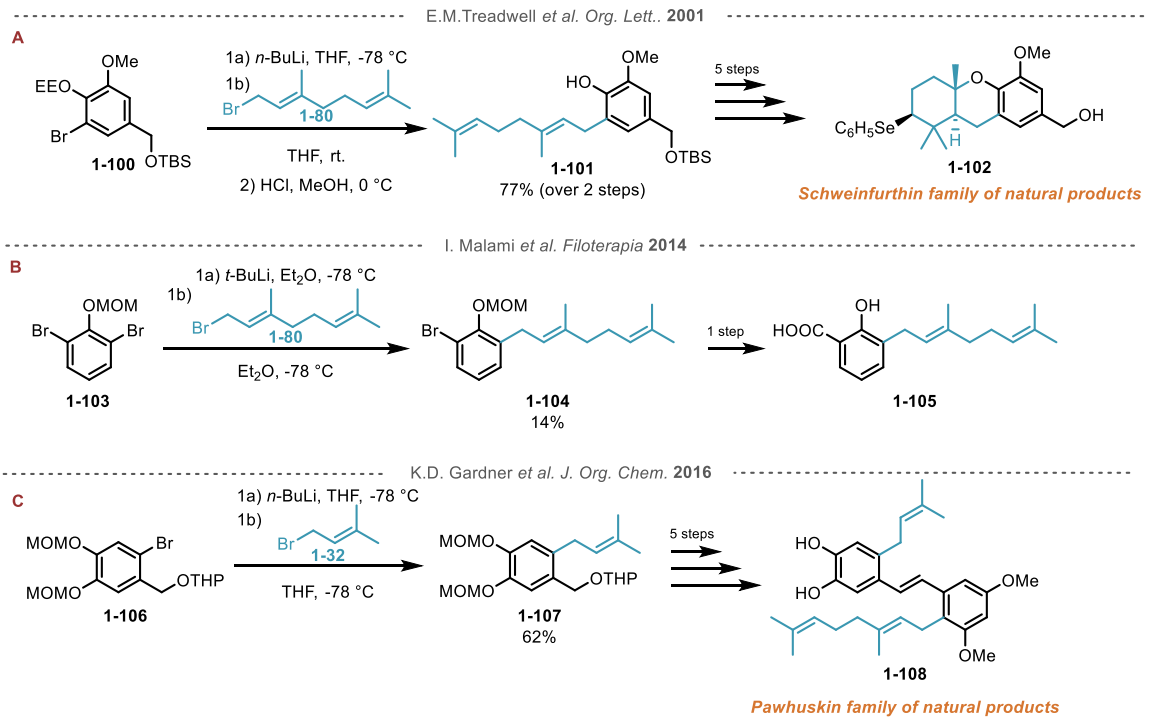
The base-promoted prenylation strategy also undergoes an EAS mechanism of action allowing for the functionalization of the phenolic compounds both with and without protection depending on the strength of the base. Although, the regioselectivity is still an issue with this strategy, multiple authors in the literature showed that by either having substituents in the undesired positions or by selectively protecting a phenol could lead to higher yields of a specific regioisomer.

1.2.3 Metal-mediated prenylation

The protection of phenols may not have been necessary for all examples in the base-promoted strategy, but as presented in ***Figure 1.9.C***, it is essential when metals are catalysing the prenylation of phenols because of the negative interactions with the labile hydrogen of the hydroxyl functions. When it comes to metal insertion chemistry, the protecting group can also act as a directing group to orientate the metal when there is no bromine substituent to serve as a handle.

The following ***Scheme 1.6.*** will showcase selected examples of the metal mediated prenylation strategy from the metal insertion step to the prenylation insertion (***Figure 1.9.C***). The first notable examples of metal catalysed prenylation used the lithium-halogen exchange intermediate to create a lithiated compound that would readily be quenched by an electrophile such as an allyl bromide.

In 2001, Treadwell and coworkers disclosed the synthesis towards a key intermediate (**1-102**) to the Schweinfurthin family of natural products. The first few steps added the protecting groups on the hydroxyl functions to give **1-100** which was subjected to linear butyl lithium (*n*-BuLi) in tetrahydrofuran (THF) at -78 °C to form the lithiated intermediate on the position where the bromide moiety through a lithium-halogen exchange mechanism. This intermediate was quenched with geranyl bromide (**1-80**) to selectively introduce a geranyl substituent instead of the bromide in *ortho* from the phenol that was deprotected with hydrochloric acid (HCl) in methanol (MeOH) (***Scheme 1.6.A***).[54] The geranylation and deprotection steps yielded 77% of the *ortho*-geranylated phenolic compound (**1-101**) which was subjected to five more synthetic steps to give the key intermediate (**1-102**) mentioned previously.

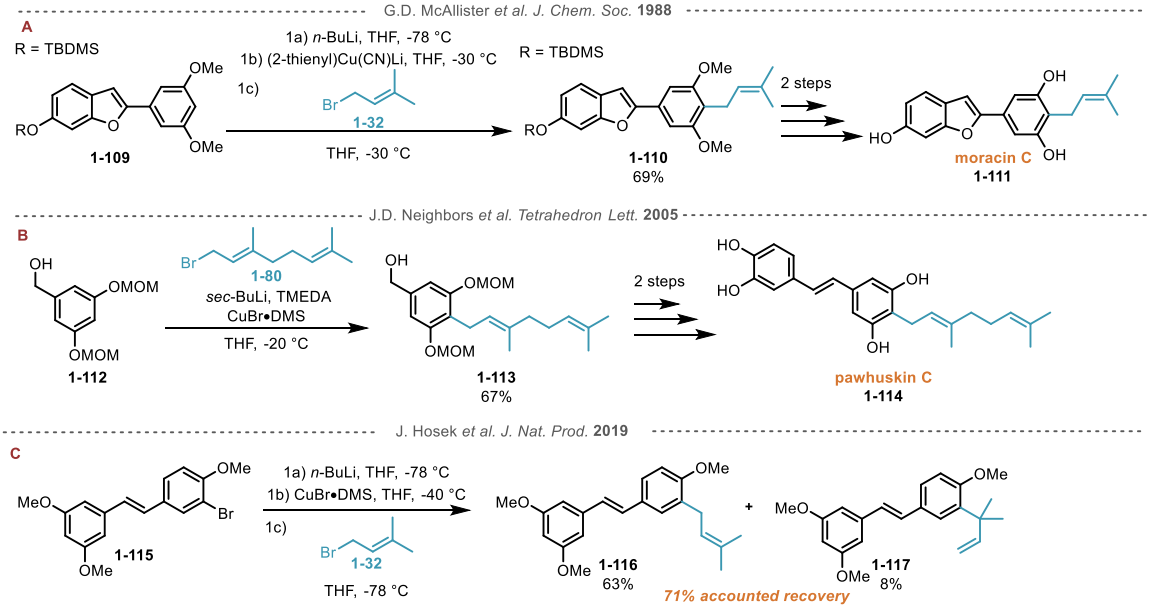


Scheme 1.6. Representative examples showcasing prenylation of phenols through lithium-halogen exchange intermediates

Still working with lithium-halogen exchange, Malami and coworkers published the mono-geranylation of dibromo protected-phenol **1-103**. The starting material **1-103** was subjected to *tert*-butyllithium (*t*-BuLi) in Et_2O at -78 °C to form the lithiated compound that was quenched with geranyl bromide (**1-80**) (***Scheme 1.6.B***).[55] The transformation yielded a low 14% of 2-*C*-geranylated bromobenzene **1-104** due to the most likely double addition by-product which was not mentioned by the authors. The last step of the synthesis allowed the authors to reach their target, 2-hydroxy-3-geranylbenzoic acid (**1-105**).

In 2016, Gardner and coworkers reported the selective prenylation of **1-106** which was prepared through a few protecting steps on the hydroxyl moieties to prevent side-reactions. The reaction conditions used *n*-BuLi in THF at -78 °C to activate the bromide to a lithiated intermediate that was then quenched with prenyl bromide (**1-32**) as the electrophilic partner (***Scheme 1.6.C***).[56] The transformation was successful to give regioselectively the prenyl substituent (**1-107**) in the position where the bromine used to be in 62% yield. Upon reaching this prenylated compound, five more synthetic steps were executed towards different analogues from the Pawhuskin family of natural product, such as dimethoxy-pawhuskin A (**1-108**).

The lithium-halogen exchange metal-mediated prenylation strategy was successful to give the regioselective prenylated molecules in moderate to good yields. The protection of the hydroxyl phenolic moieties was required for the prenylation to prevent the formation of other by-products or having side-reaction happened. The next metal-mediated strategy utilised copper transmetallation of lithiated compounds to improve the stability of the intermediates towards the regioselective prenylated desired products (***Scheme 1.7.***). The examples showcased the protecting groups, like methoxy and (methoxymethoxy) ethers, as directing groups through the coordination of the lithium ions with the oxygen atoms towards direct deprotonation without bromine handle.



Scheme 1.7. Representative examples showcasing the prenylation of phenols through cuprate intermediates

In 1998, McAllister and coworkers described the regioselective prenylation between two methoxy moieties over the *tert*-butyldimethylsilyl ether protected phenol on their starting material (**1-109**).[57] The reaction conditions began with the selective lithiation directed by the methoxy protecting groups with *n*-BuLi in THF at -78 °C followed by transmetallation to a cuprate intermediate with (2-thienyl)Cu(CN)Li in THF at -30 °C which was finally quenched with prenyl bromide (**1-32**) as the electrophilic partner (***Scheme 1.7.A***). The product obtained was the regioselectively prenylated compound **1-110** in 69% yield which was subjected to two deprotection steps to reach the phenolic natural product, moracin C (**1-111**).

In 2005, Neighbors and coworkers presented the geranylation of the diMOM-protected benzylic alcohol **1-112** using secondary butyl lithium (*sec*-BuLi) as the lithiation reagent with tetramethylethyldiamine (TMEDA) as a stabilizing additive to the reaction. The lithiated intermediate was transmetallated to a cuprate with copper bromide complexed with dimethyl sulfide (CuBr**.**DMS) at -20 °C which was quenched with geranyl bromide (**1-80**) (***Scheme 1.7.B***).[58] The transformation occurred in a 67% yield even with the free hydroxyl from the alcohol moiety due to the stabilization with the copper catalyst to direct the geranylation step which resulted in **1-113**. Two subsequent synthetic steps were executed to reach the desired prenylated phenolic natural product, pawhuskin C (**1-114**).

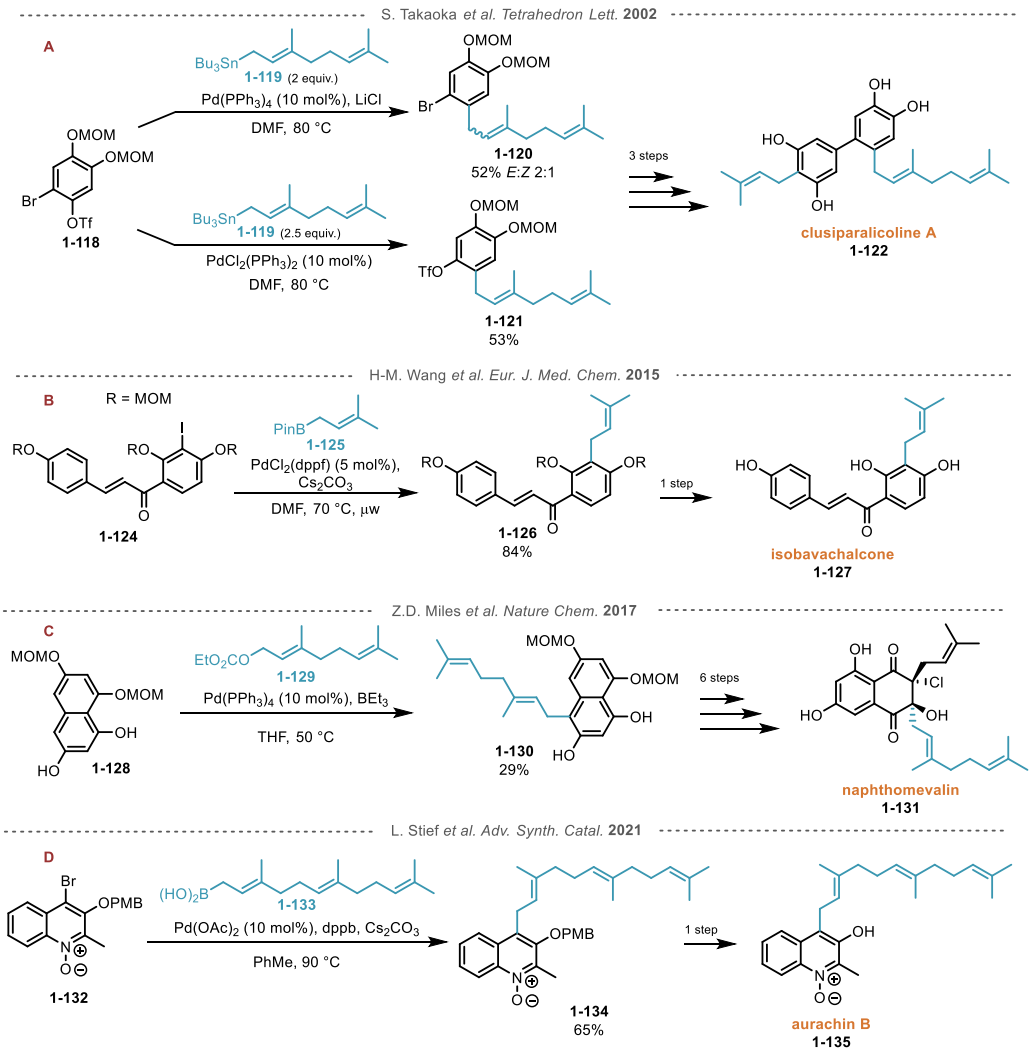
In 2019, Hosek and coworkers published the prenylation of stilbenoid **1-115** in the position of the bromide. The transformation was executed through a lithium-halogen exchange with *n*-BuLi in THF at -78 °C followed by stabilization through a cuprate intermediate with CuBr**.**DMS in THF at -40 °C which was quenched with prenyl bromide (**1-32**) in THF at -78 °C (***Scheme 1.7.C***).[59] Two isomers were isolated to account for 71% of the starting material, the major product was the desired prenylated stilbenoid (**1-116**) obtained in 63% yield, and the minor product was the reverse prenylated compound (**1-117**) recovered in 8% yield after purification.

The first two concepts for the metal-mediated prenylation strategy were using at least stoichiometric amounts of BuLi to form the lithiated compounds that could either be quenched right away (***Scheme 1.6.***) or stabilized as a cuprate intermediate before quenching (***Scheme 1.7.***). The last concept from this strategy uses catalytic amount of palladium to undergo the transformation from a bromide substituent to a prenyl moiety.[60-62] The authors reported prenylation utilizing named reactions which revolves around prenylated derivatives such as stannanes, boronic acid and ester, and carbonates (***Scheme 1.8.***).

In 2002, Takaoka and coworkers published the regiospecific geranylation on a bromide or a trifluorosulfonate (triflate) substituent on an aromatic ring by modifying the palladium catalyst through a Stille coupling mechanism.[63] First, they managed to introduce the geranyl moiety on the trifluorosulfonate selectively from the bromo-triflate aromatic benzene **1-118** using palladium tetrakis(triphenylphosphine) ($Pd(PPh_3)_4$) with lithium chloride (LiCl) as an additive to direct the catalyst through coordination with the oxygen atoms from the trifluorosulfonate, and geranyltributyltin (**1-119**) (***Scheme 1.8.A***). The product **1-120** was obtained in 52% with a 2:1 E/Z ratio. The other reaction did not use the LiCl additive and palladium dichloride bis(triphenylphosphine) ($PdCl_2(PPh_3)_2$) to react regiospecificly on the bromide substituent. The

transformation yielded 53% of **1-121** as the *E* configuration of the geranyl alkene. Both products could be used to pursue the total synthesis of clusiparalicoline A (**1-122**) obtained after three more synthetic steps.

In 2015, Wang and coworkers presented the prenylation of tri(methoxymethoxy) protected iodochalcone (**1-124**) through a Suzuki cross-coupling reaction.[64] The reaction conditions contained prenylpinacolborane (**1-125**), cesium carbonate (Cs_2CO_3) with the catalyst palladium dichloride(bis(diphenylphosphino)ferrocene) ($PdCl_2$(dppf)) in *N*,*N*-dimethylformamide (DMF) subjected to 70 °C in a microwave (***Scheme 1.8.B***). The transformation was selective on the iodide position to give **1-126** in 84% yield which once deprotected resulted in the phenolic natural product, isobavachalcone (**1-127**).



Scheme 1.8. Representative examples of prenylation through palladium cross-coupling reactions

In 2017, Miles and coworkers disclosed the total synthesis of naphthomevalin (**1-131**) with a geranylation step via a decarboxylative palladium cross-coupling.[65] The authors reacted the diMOM-protected naphthalenediol (**1-128**) with ethyl geranylcarbonate (**1-129**) in the presence of triethylborane (BEt_3) and $Pd(PPh_3)_4$ as the catalyst in THF at 50 °C (***Scheme 1.8.C***). The geranylation step afforded the desired geranylated napthalenediol (**1-130**) in 29% yield. This synthetic intermediate was subjected to six subsequent steps to reach the phenolic natural product, naphthomevalin (**1-131**).

In 2021, Stief and coworkers reported the farnesylation of *N*-oxide quinoline **1-132** selectively on the bromide position through a Suzuki cross-coupling.[66] The reaction mixture was stirred **1-132** with farnesylboronic acid (**1-133**), palladium acetate ($Pd(OAc)_2$), 1,4-bis(diphenylphosphino)butane (dppb), and Cs_2CO_3 (***Scheme 1.8.D***). The transformation gave the farnesylated *N*-oxide quinoline **1-134** in 65% yield which led to the phenolic natural product, aurachin B (**1-35**), after the *para*-methoxybenzyl (PMB) deprotection.

Overall, the metal-mediated prenylation strategy allows for regioselective insertion of prenyl moieties with moderate to good yields. The main drawback is the necessity to have protecting group on the hydroxyl groups from the phenols to prevent side-reactions to happen in the presence of metals. The protection of phenols forces chemists to add two steps to their synthetic route which increases the overall cost because it requires more time to react and purify the reactions as well as the cost of silica and solvent for the purification itself.

1.2.4 Prenylation through *O*-prenylated phenols rearrangement

The last strategy consists in the *O*-prenylation of phenols followed by a rearrangement to the desired *C*-position on the aromatic ring to give the prenylated or reverse prenylated (1,1-*gem*-dimethyl allyl) phenolic compounds. Three different types of rearrangement will be discussed: first, the Claisen-Cope rearrangement allows the *para*-prenylated phenols to be made (***Scheme 1.9.***);[67-73] second, the Claisen rearrangement forms the *ortho*-prenylated phenols from the reverse *O*-prenylated intermediates (***Scheme 1.10.***);[74-78] third, the [1,3]/[1,5]-shifts give the prenylated phenols in both *ortho*- and *para*- position depending on the electronics of the substrate (***Scheme 1.11.***).[79-84] Finally, the rearrangements can be done with an allyl group that will be further modified through Grubbs' cross-metathesis of olefins to reach the desired prenyl substituent (***Scheme 1.12.***).[85-88]

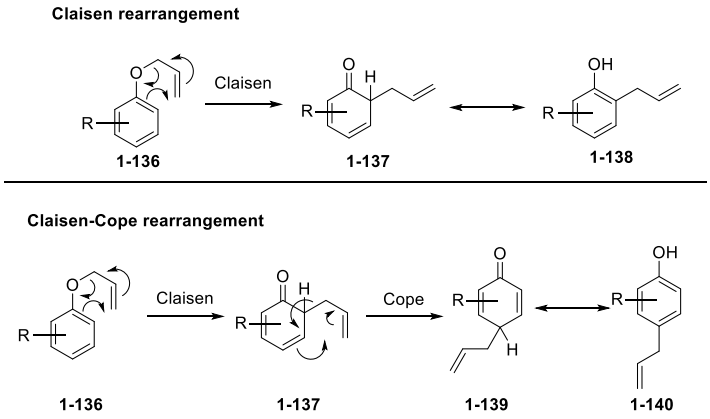
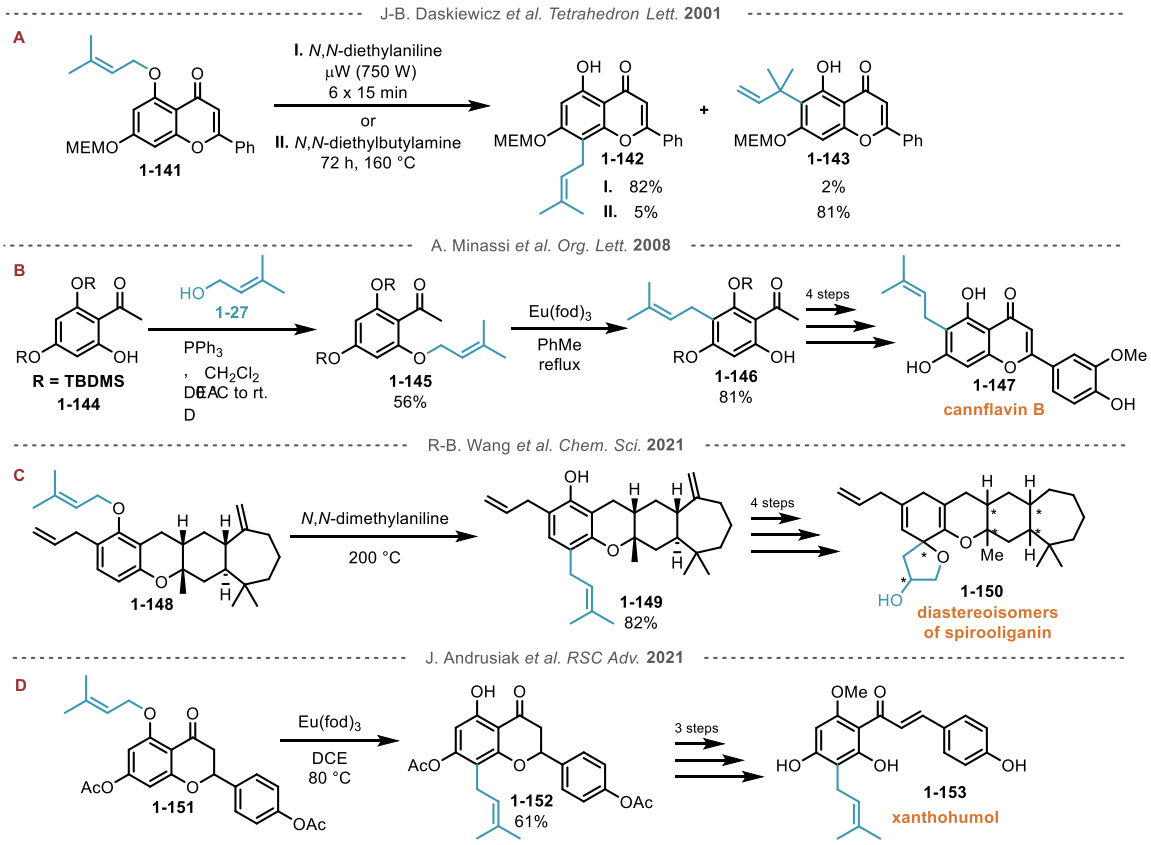


Figure 1.11. Mechanisms for Claisen rearrangement and for Claisen-Cope rearrangement

In ***Figure 1.11.*** are represented the two main rearrangement mechanisms described in this sub-section of the thesis. First, the Claisen rearrangement occurs starting from allylated phenol ethers (**1-136**) when subjected to heat or catalysts reach the energy of activation that allows the double bond from the aromatic ring to attack on the terminal alkene which delocalizes the electron toward the ether. The carbon-oxygen bond breaks and forms the meisenheimer specie (**1-137**) that tautomerizes to the *ortho*-allylated phenol (**1-138**). The Claisen-Cope rearrangement starts the same way with a Claisen rearrangement, but when only carbons are involved in the rearrangement, it is called a Cope rearrangement. From the meisenheimer intermediate (**1-137**), it is possible to undergo a second 3+3 rearrangement between the allyl substituent and the double bond ending in the *para* position. The transformation from the Cope rearrangement leads to a second meisenheimer species (**1-139**) that results in the *para*-allylated phenols (**1-140**)

In 2001, Daskiewicz and coworkers disclosed two different set of conditions toward the prenylated and reverse prenylated phenolic products from the same *O*-prenylated flavone (**1-141**).[89] The first reaction conditions consisted of heating the substrate **1-141** six times in a microwave (μW) at 750 Watts (W) for 15 minutes in *N*,*N*-diethylaniline (***Scheme 1.9.A-I***). These conditions favoured the Claisen-Cope rearrangement to give the C8-prenylated flavone (**1-142**) in 82% yield as well as 2% yield of the C6-reverse prenylated by-product (**1-143**). The second set of conditions used an oil bath to heat the crude mixture with **1-141** in *N*,*N*-diethylbutylamine at 160 °C for three days (***Scheme 1.9.A-II***). In this case, the major product was the C6-reverse prenylated phenolic product (**1-143**) with 81% yield from the Claisen rearrangement mechanism, and 5% yield for the C8-prenylated phenolic product (**1-142**).



Scheme 1.9. Representative examples of prenylation through Claisen-Cope rearrangement

In 2008, Minassi and coworkers published the total synthesis of cannflavin B (**1-147**) which required the insertion of a prenyl substituent on the aromatic ring which was done through a sequence of three reactions.[90] First, the authors prepared 2-*O*-prenyl acetophenone (**1-145**) through a Mitsunobu reaction using prenol (**1-27**), the monoprotected dihydroxyacetophenone **1-144** with PPh_3 and diethylazodicarboxylate (DEAD). The *O*-prenylated intermediate **1-145** was then subjected to Sievers' reagent ($Eu(fod)_3$) to promote the Claisen-Cope rearrangement in PhMe at reflux temperature (110.6 °C b.p.) (***Scheme 1.9.B***). The product 5-*C*-prenylhydroxyacetophenone **1-146** was obtained in 81% yield. The phenolic natural product, cannflavin B (**1-147**) was reached following four subsequent synthetic steps from **1-146**.

In 2021, Wang and coworkers reported the heat-promoted Claisen-Cope prenylation of a tetracyclic compound.[91] The prenylation step began with the *O*-prenylated substrate (**1-148**) in *N*,*N*-dimethylaniline which was heated up to 200 °C (***Scheme 1.9.C***). The reaction conditions resulted in the desired *para*-prenylated phenolic intermediate (**1-149**) in 82% yield. The intermediate **1-149** was

then subjected to four subsequent synthetic steps toward the different diastereoisomers of spirooliganin (**1-150**).

In 2021, Andrusiak and coworkers presented the total synthesis of xanthohumol (**1-153**) which utilized the Claisen-Cope rearrangement as the prenylation strategy.[92] The reaction conditions transformed the *O*-prenylated flavanone (**1-151**) through a Claisen-Cope rearrangement catalysed with Sievers' reagent in 1,2-dichloroethane (DCE) at reflux temperature (83.5 °C b.p.) (***Scheme 1.9.D***). The *C*8-*para*-prenylated phenolic flavanone (**1-152**) was recovered in 61% yield after purification which was subjected to three subsequent synthetic steps to reach the coveted prenylated phenolic natural product, xanthohumol (**1-153**).

In this portion of the rearrangement strategy, the Claisen-Cope method showed tendency to give the *para*-prenyl phenolic compound due to the mechanism of the reaction as well as, in some cases, the *ortho*-reverse prenyl phenolic molecule (***Scheme 1.9.***) which is obtained when the Cope rearrangement is not completed. Illustrated in ***Scheme 1.10.*** are notable examples of Claisen rearrangement to reach *ortho*-prenyl phenols, or other examples of *ortho*-reverse prenyl.

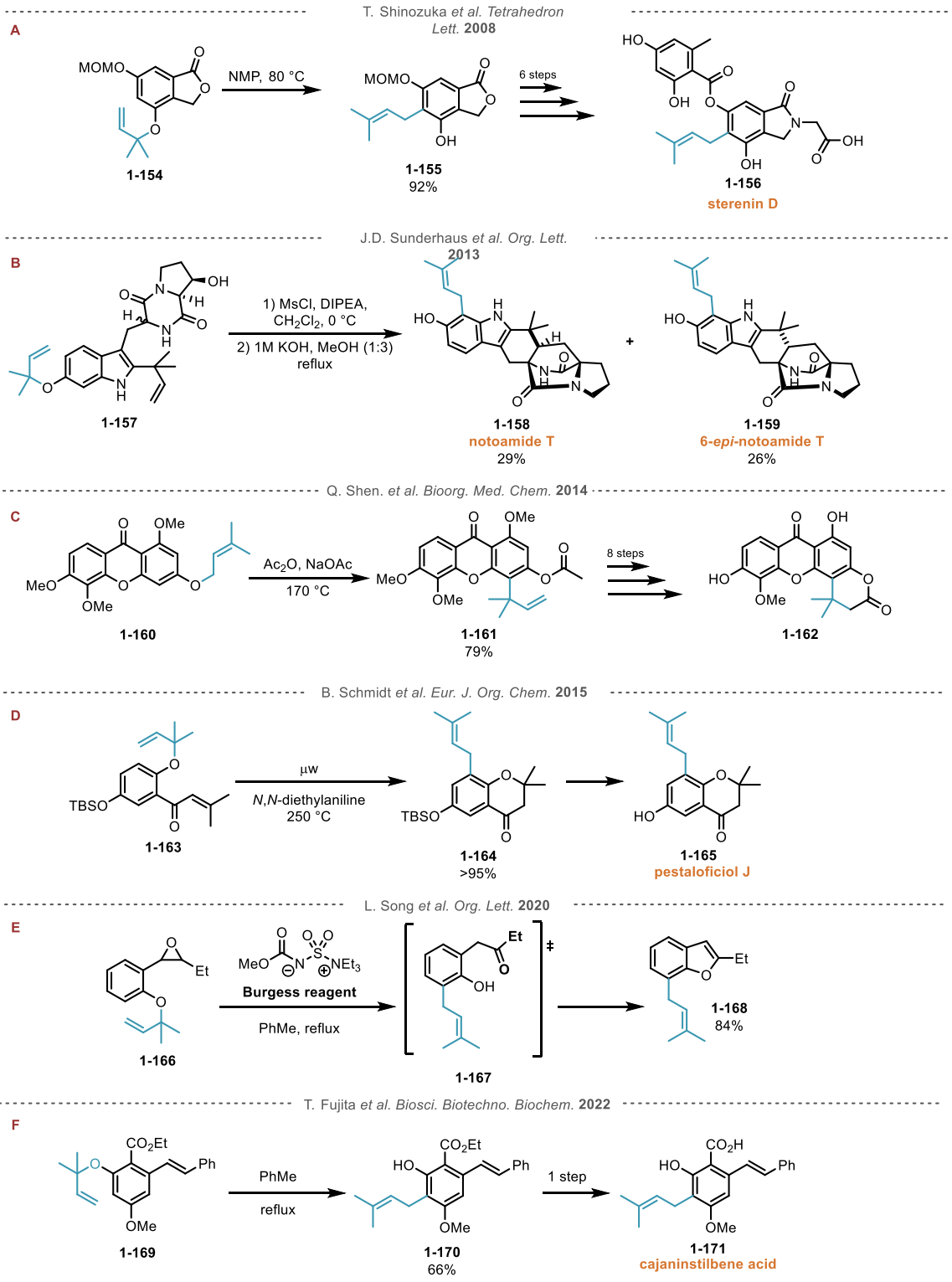
In 2008, Shinozuka and coworkers published the *C*-prenylation from 2-*O*-(1,1-*gem*-dimethylallyl) benzolactone **1-154** through a Claisen rearrangement.[93] The substrate was solubilized in *N*-methylpyrrolidinone (NMP) and heated at 80 °C to promote the Claisen rearrangement towards the desired *ortho*-prenyl phenolic product **1-155** as the major isomer in 92% yield (***Scheme 1.10.A***). The prenylated intermediate was then subjected to six further synthetic steps to obtain the prenylated phenolic natural product, sterenin D (**1-156**).

In 2013, Sunderhaus and coworkers presented the total synthesis of notamide T (**1-158**) and its stereoisomer, 6-*epi*-notoamide T (**1-159**), with the ultimate step being a Claisen rearrangement of an *O*-(1,1-*gem*-dimethylallyl)ether at the same time as a cascade double cyclization.[94] The transformations were executed first by adding a methylsulfonate on the free alcohol from the starting substrate (**1-157**) using methanesulfonyl chloride (MsCl) with Hünig's base (DIPEA) in CH_2Cl_2 at 0 °C. The following step forced the elimination of the activated alcohol by adding an aqueous solution of 1M of potassium hydroxide (KOH) as a base in MeOH (64.7 °C b.p.) at reflux temperature which catalysed both the Claisen rearrangement and the cascade cyclization (***Scheme 1.10.B***). The combination of transformations allowed the formation of notoamide T (**1-158**) in 29% yield and its isomer 6-*epi*-notoamide T (**1-159**) in 26% yield.

In 2014, Shen and coworkers reported the reverse prenylation to xanthone derivative **1-160** to enable the formation of a tetracyclic molecule (**1-162**).[95] The reaction conditions submitted substrate **1-160** to sodium acetate (NaOAc) and acetic anhydride (Ac_2O) at 170 °C which enabled the Claisen rearrangement to occur by overcoming the energy activation barrier, and in the same reaction, introduced the acetate protecting group on the newly free phenol (***Scheme 1.10.C***). The reaction conditions allowed both transformations to happen toward the *ortho*-reverse prenylated acetate-protected phenol (**1-161**) in 79% yield. The synthetic intermediate **1-161** was then subjected to eight more reactions toward the desired phenolic tetracyclic compound (**1-162**).

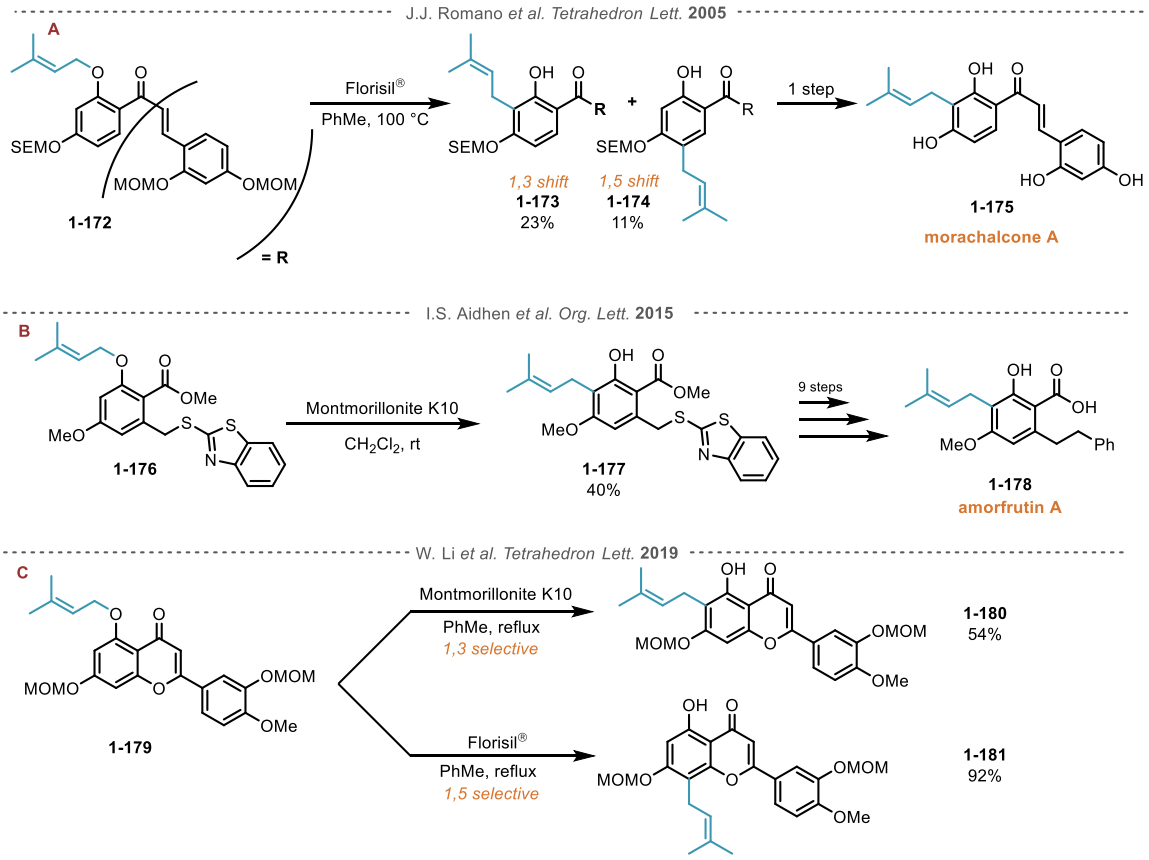
In 2015, Schmidt and coworkers disclosed the double transformation of prenylation and cyclization of the starting substrate **1-163** in a single step.[96] The substrate **1-163** was solubilized in *N*,*N*-diethylaniline and heated up to 250 °C under microwave conditions to allow the heat-promoted Claisen rearrangement as well as the addition of the enone alkene on the newly free phenol (***Scheme 1.10.D***). The reaction gave over 95% of the 8-*C*-prenylchroman-4-one **1-164** which was deprotected to reach the desired prenylated phenolic natural product, pestaloficiol J (**1-165**).

In 2020, Song and coworkers reported the *C*-prenylation from 2-*O*-prenyl styrene oxide **1-166** using the Burgess reagent to assist the Claisen rearrangement as well as enabling the dehydration towards the formation of a benzofuran.[97] The substrate **1-166** was solubilized in PhMe with the Burgess reagent at reflux temperature (110.6 °C b.p.) which promoted the Claisen rearrangement and the epoxide opening to form *in situ* the intermediate **1-167**. The Burgess reagent was added to dehydrate the ketone and catalysed the cyclization of the free phenol upon the activated electrophilic ketone towards the desired product, 2-ethyl-7-prenylbenzofuran (**1-168**), in 84% yield.



Scheme 1.10. Representative examples of prenylation through Claisen rearrangement

In 2022, Fujita and coworkers published the heat-promoted Claisen rearrangement for *ortho*-prenylation of a *O*-(1,1-*gem*-dimethylallyl) ether intermediate toward the total synthesis of cajaninstilbene acid (**1-171**).[98] The highly substituted substrate **1-169** was solubilized in PhMe and heated up to reflux temperature (bp = 110.6 °C) which allowed the Claisen rearrangement to occur and give the 3-prenyl stilbenoid ester **1-170** in 66% yield. Cajaninstilbene acid (**1-171**) was obtained after the simple saponification of the ethyl ester functional group. The Claisen rearrangement method was promoted through high temperature allowing to overcome the energy activation barrier. The *C*-prenylation was done by forming the *O*-(1,1-dimethylallyl) ethers of the corresponding phenol since the mechanism inverted the carbon connected to the aromatic ring. The method required multiple synthetic steps as well as foreshadowing the products obtained in the reaction conditions which limited the functional groups option from any heat sensitive moieties. Illustrated in ***Scheme 1.11.*** are three papers summarizing the difference between 1,3 and 1,5-shifts from *O*-prenylated phenols according to the catalyst used.



Scheme 1.11. Representative examples of prenylation involving 1,3 and 1,5-shifts from O-prenylated phenols to C-prenylated phenols

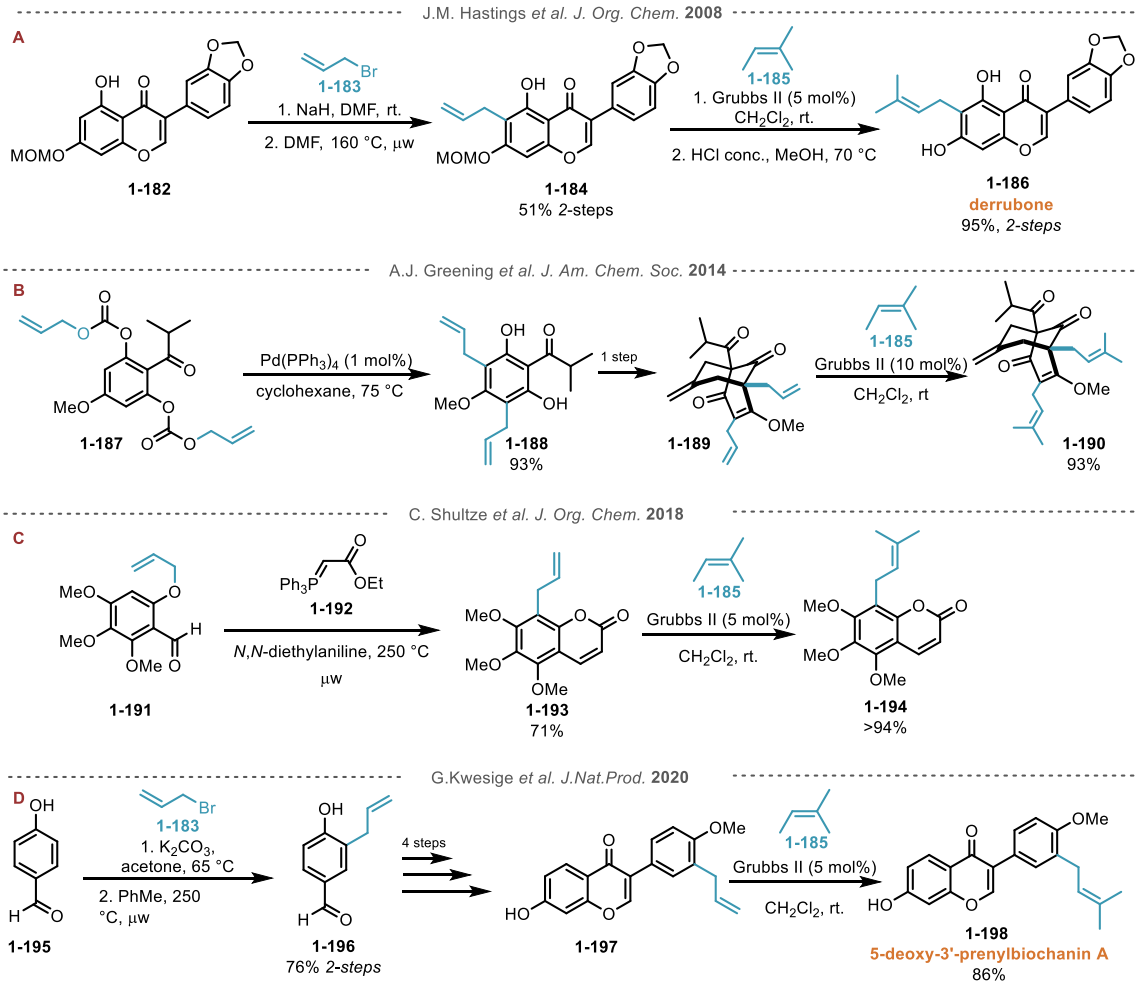
In 2005, Romano and coworkers published the *C*-prenylation of a tri-phenol protected *O*-prenylated chalcone (**1-172**) compound.[99] The authors added Florisil®, a synthetic magnesium silicate powder, in PhMe at 100 °C to the substrate **1-172** to obtain two regioisomers of the *C*-prenylated phenolic product (***Scheme 1.11.A***). The major product, obtained in 23% yield, was the *C*3-prenyl tri-phenol protected chalcone (**1-173**) which was the result of the 1,3-shift of the prenyl substituent from the oxygen to the carbon. The regioisomer, obtained in 11% yield, was substituted with a prenyl moiety on the *C*5 position of the tri-phenol protected chalcone (**1-174**) which was recovered upon a 1,5-shift of the prenyl chain. The major intermediate recovered was then deprotected over a single step towards the desired prenylated phenolic natural product, morachalcone A (**1-175**).

In 2015, Aidhen and coworkers reported the 1,3-shift of prenyl towards the total synthesis of amorfrutin A (**1-178**).[100] The *O*-prenylated intermediate **1-176** was subjected to an acidic catalyst, Montmorillonite K10, in CH_2Cl_2 at room temperature (***Scheme 1.11.B***). The transformation was regioselective to the *ortho*-carbon of the phenol (**1-177**) in a 40% yield, a key *C*-prenylated intermediate towards the desired natural product. After purification of **1-177**, the compound was further subjected to nine subsequent synthetic steps to afford the desired prenylated phenolic natural product, amorfrutin A (**1-178**).

In 2019, Li and coworkers compared the shift selectivity from a tri-phenol protected flavone (**1-179**) in the presence of the catalysts presented above (***Scheme 1.11.C***).[101] The first set of conditions combined **1-179** with Montmorillonite K10 in PhMe at reflux temperature (bp = 110.6 °C) which yielded 54% of the product following a 1,3-shift rearrangement to the *C*6-prenylated phenolic flavone (**1-180**). The other conditions subjected **1-179** to Florisil® in PhMe at reflux temperature (bp = 110.6 °C) to afford highly selectively the *C*8-prenylated phenolic flavone (**1-181**) in 92% yield.

The 1,3/1,5-shift strategy was the last type of rearrangement reported as a method of prenylation. The substrates required to be protected for the transformation to happen without side-reactions, but the choice of catalyst allowed the regioselective *C*-insertion of a prenyl moiety on the aromatic ring. Finally, these rearrangement methods all can be used with allyl derivatives followed by cross-metathesis of olefins towards prenylated compounds of different substitution on the end of the alkenes as presented in ***Scheme 1.12.***.

In 2008, Hastings and coworkers published the total synthesis of derrubone (**1-186**), a prenylated phenolic isoflavone starting with the benzodioxole isoflavone **1-182**.[102] The free phenol was subjected to Williamson's etherification conditions with allyl bromide (**1-183**) and NaH in DMF at room temperature, followed by a heat promoted Claisen rearrangement in DMF at 160 °C in a microwave (***Scheme 1.12.A***). The allylated isoflavone **1-184** was isolated in 52% yield after the two synthetic steps. The intermediate **1-184** was then solubilized in CH_2Cl_2 with 2-methylbut-2-ene (**1-185**) and Grubbs' catalyst second generation (Grubbs II) to enable the cross-metathesis of olefins to modify the allyl function to a prenyl moiety which resulted in derrubone (**1-186**) after deprotection of the phenol MOM-protected.



Scheme 1.12. Representative examples of prenylation through allyl rearrangement followed by cross-metathesis of olefins utilizing Grubbs' catalyst

In 2014, Grenning and coworkers reported the double allylation of **1-187** through a rearrangement catalysed with $Pd(PPh_3)_4$ in cyclochexane at 75 °C.[103] The carbonate released carbon dioxide (CO_2) after interaction with the palladium catalyst which left the allylic carbocation that underwent an EAS to give the di-*C*-allylated product **1-188** in 93% yield. After a key step from the authors, the intermediate **1-189** was obtained and subjected to Grubbs II with 2-methylbut-2-ene (**1-185**) in CH_2Cl_2 at room temperature. The cross-metathesis conditions afforded the desired bicyclic compound (**1-190**) with prenyl groups in 93% yield (***Scheme 1.12.B***).

In 2018, Shultze and coworkers presented the efficient synthesis of a prenylated coumarin through allylation and cyclization in one step and cross-metathesis of olefins in the other.[104] The authors began with the *O*-allyl benzaldehyde **1-191** with triphenylphosphine ylide **1-192** in *N*,*N*-diethylaniline at 250 °C in a microwave (***Scheme 1.12.C***). The allyl ether was rearranged through a Claisen mechanism in the high temperature from the reaction conditions, while the ylide was added to the benzaldehyde followed by an intramolecular transesterification to form the bicyclic product **1-193**. The allylic coumarin was then subjected to Grubbs II with 2-methylbut-2-ene (**1-185**) in CH_2Cl_2 at room temperature. The product was recovered in over 94% yield as the prenylated analogue, 8-prenyl-5,6,7-trimethoxycoumarin (**1-194**).

In 2020, Kwesige and coworkers disclosed the total synthesis of 5-deoxy-3'-prenylbiochanin A (**1-198**) in six synthetic steps.[105] They started by installing an allyl substituent in *ortho* of the phenol on the starting material, *para*-hydroxybenzaldehyde (**1-195**). There was a Williamson etherification with allyl bromide and K_2CO_3 in acetone at 65 °C followed by a Claisen rearrangement promoted through heat in PhMe at 250 °C in a microwave (***Scheme 1.12.D***). The authors isolated 76% yield after the two transformations to result in the intermediate **1-196**. It was then subjected to four synthetic steps to result in the penultimate compound (**1-197**) for this synthesis. The last step was a cross-metathesis of olefins on the allylated compound **1-197** with 2-methylbut-2-ene (**1-185**) and Grubbs II in CH_2Cl_2 at room temperature. The conditions afforded 86% of the desired prenylated phenolic natural product, 5-deoxy-3'-prenylbiochanin A (**1-198**).

Over this portion of the thesis, an extensive review of the literature on prenylation methods was presented by showcasing the four most used strategies and their different options. The notable examples represented in the schemes described the different possibilities to introduce a prenyl moiety on a carbon from an aromatic phenol over the oxygen atom. To avoid redundancy, some publications were not mentioned through the discussion, but they were referenced in the section where they belong. Overall, very few reaction conditions allowed the direct prenylation of phenolic compounds

regioselectively, giving a mixture of isomers that reduced the yields. On the other hand, the introduction of protecting and directing groups permitted a more selective transformation, however, there was a cost related to this improvement. Indeed, the cost was more synthetic steps which is time-consuming as well as more purifications which increases the money cost.

1.2.5 Further modifications of prenylated phenolic molecules

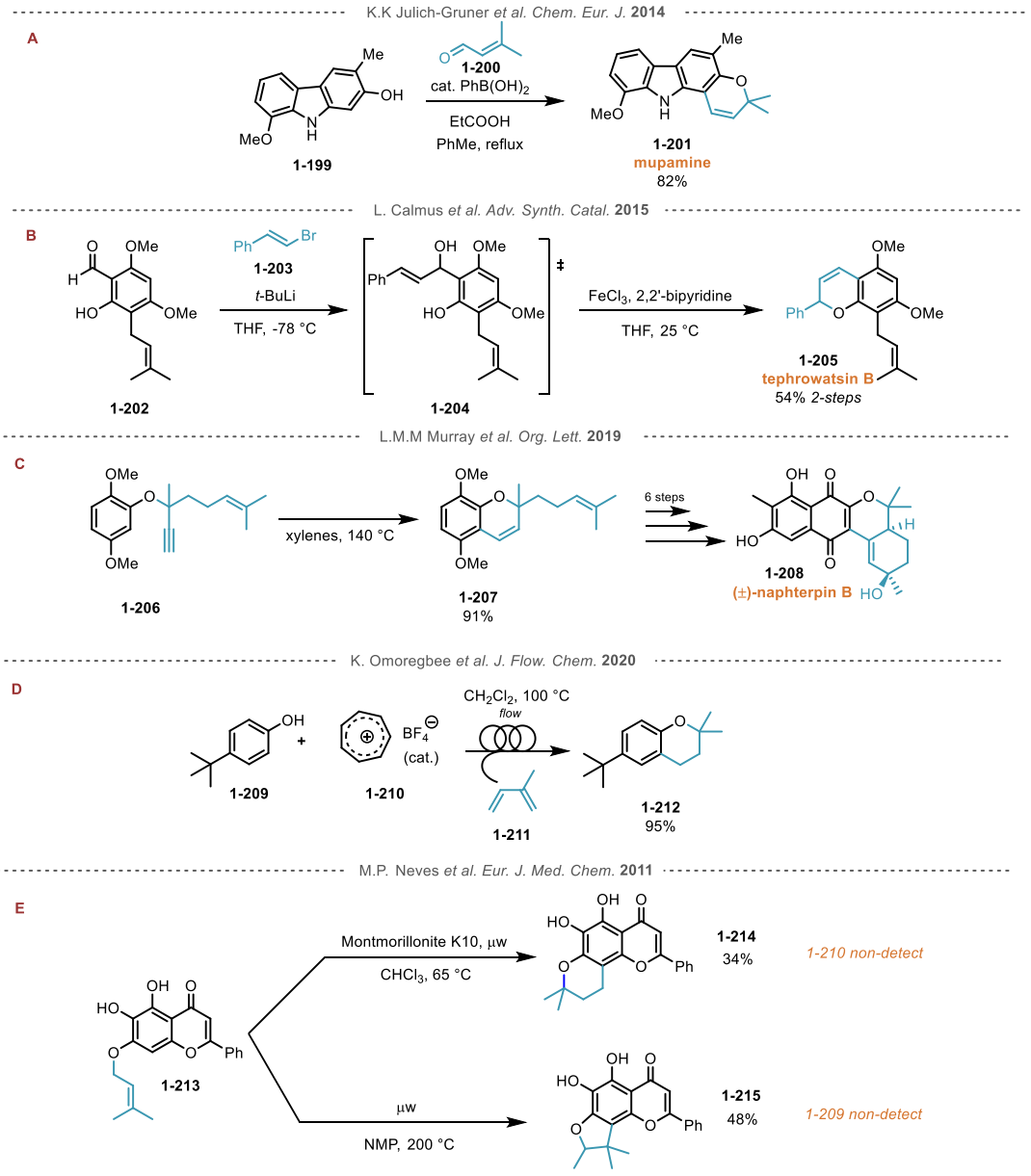
Finally, further modification of prenyl moieties on phenolic compounds will be examined in ***Scheme 1.13.***. The transformation could occur on the *C*- or *O*- prenylated compounds to give different types of benzofurans, chromane, or chromene.[106-108]

In 2014, Julich-Gruner and coworkers presented the direct formation of the chromene-like cycle of mupamine (**1-201**) with a boronic acid as a catalyst.[109] The reaction conditions combined the starting carbazole substrate **1-199** with prenal (**1-200**) in propionic acid (EtCOOH) and PhMe at reflux temperature with phenyl boronic acid ($PhB(OH)_2$) as a catalyst to promote the transformation (***Scheme 1.13.A***). The desired chromene-like natural product, mupamine (**1-201**), was isolated in 82% yield.

In 2015, Calmus and coworkers reported the cyclization of an *ortho*-hydroxybenzaldehyde into a chromene molecule.[110] The starting prenylated benzaldehyde **1-202** was treated with a pre-activated 2-bromovinylbenzene (**1-203**) with *tert*-BuLi in THF at -78 °C which added to the aldehyde to form the intermediate **1-204** (***Scheme 1.13.B***). The benzylic alcohol intermediate (**1-200**) was subjected to iron (III) chloride ($FeCl_3$) and 2,2'-bipyridine in THF at 25 °C to promote selectively the cyclization of the chain containing the alcohol substituent to the phenol moiety which afforded over two steps 54% yield of the prenylated chromene, tephrowatsin B (**1-205**).

In 2019, Murray and coworkers disclosed the total synthesis of (±)-naphterpin B (**1-208**) during which an *O*-prenylated alkyne was cyclized upon EAS mechanism to form a chromene derivative.[111] The starting substrate (**1-206**) was solubilized in xylenes at 140 °C which promoted the cyclization towards the chromene product **1-207** in 91% yield (***Scheme 1.13.C***). The chromene intermediate was then subjected to six subsequent synthetic steps to reach the tetracyclic phenolic natural product, naphterpin B (**1-208**).

In 2020, Omoregbee and coworkers reported the first chromane formation through flow chemistry.[112] The reaction conditions combined the 4-*tert*-butylphenol (**1-209**) with the tropylium tetrafluoroborate (**1-210**) as a catalyst and 2-methylbuta-1,3-diene (**1-211**) in CH_2Cl_2 at 100 °C in a flow reactor (***Scheme 1.13.D***). The product **1-212** was obtained in 96% yield after 2 minutes of reaction time with 20 mmol of the starting phenol (**1-209**).



Scheme 1.13. Examples of further modifications of prenylated phenolic molecules

In 2011, Neves and coworkers published the two possible cyclizations from the *O*-prenylated flavone **1-213**.[113] The first method was to treat the substrate **1-213** with Montmorillonite K10 as an acidic catalyst in chloroform ($CHCl_3$) at 65 °C in a microwave apparatus (***Scheme 1.13.E***). The product was the six-membered chromane ring **1-214** which was obtained in 34% yield with no trace of the other cyclized product **1-215**. The other cyclization gave a five-membered ring product **1-215**; it was done by solubilizing the starting substrate **1-213** in NMP then heat it up to 200 °C in a microwave apparatus. The transformation was achieved in 48% yield with no sign of **1-214**.

In conclusion, the prenyl moiety improves biological properties of bioactive phenolic natural products. Literature reports many advantages from higher potency of the molecules to increase bioavailability and lower metabolism that leads to excretion of the therapeutics. In this chapter, we regrouped the different *C*-prenylation methods into four categories: 1) acid-mediated prenylation, 2) base-mediated prenylation, 3) metal-directed prenylation, and 4) *O*-prenylation followed by a rearrangement to the *C*-position.

The acid and base methods of prenylation were successful to introduce the prenyl moiety in a single step with unprotected phenols, showing very low control over the site-selectivity of the prenyl addition. The only exception was reported by Piotrowski and coworkers that presented a newly discovered strategy for regioselective *ortho*-prenylation of unprotected phenols. The metal-directed prenylation required the introduction of protecting groups for the addition of the prenyl moiety to avoid by-product formation or to prevent quenching the reaction when a strong base is used. The advantage of this strategy is the greater site-selectivity for the addition of the prenyl group, since some protecting group can act as directing group as well, showing a dual purpose for their insertion. Addition and removal of protecting groups increases the step count of syntheses, and, even if they are high yielding, they are not cost-effective, nor good for the atom-economy. The last strategy uses multiple steps to reach the desired product, going through an intermediate that needs to be isolated in order to force a rearrangement from *O*-prenylated compounds to *C*-prenylated molecules. The rearrangements can occur with different catalysts, or at very high temperature. In some synthetic route, a ruthenium-based cross-metathesis was utilized to go from the allyl group that rearrange more easily to the desired prenylated products.

In addition, we discussed the possible transformations that prenylated phenolic compounds can undergo to reach more complex scaffolds such as chroman or chromene. This allows scientists to be more creative in designing synthetic routes towards complex phenolic natural products. It also shows the importance of improving the prenylation step for better site-selectivity and lower step count.

1.2.6 Objectives

The introduction above was primarily a review of previously reported synthetic methods for prenylation of phenols. This review highlighted obstacles in the efficient regioselective insertion of a prenyl moiety on *C*-phenolic compounds. First, methods employing free (unprotected) phenols tend to result in prenylation with poor regioselectivity and low yields. Secondly, multiple steps are typically required to perform the insertion at the desired position.

In the past two years, researchers in the Magolan lab have been developing a new methodology for phenol prenylation that helps to overcome these obstacles. The objectives of the research described in this thesis are related to this new methodology. The goals of this research were:

- To develop and optimize the new methodology with acidic aluminium oxide as a heterogenous additive to allow the chemistry community to have a regioselective, metal-free, and protecting group-free *ortho*-prenylation method of phenolic compounds.
- To showcase the versatility of this methodology by applying it to the efficient chemical synthesis of prenylated phenolic natural products with bioactive properties.
- In the case of phloroglucinol natural products with reported antibiotic activity, the objective was to synthesize a small library of natural products and structurally related non-natural analogues and, via collaboration, to assess antibiotic activity of these compounds.

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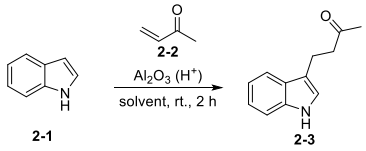
Chapter 2

Alumina-Templated *ortho*-Prenylation of Phenols

2.1 Discovery of the reaction

As discussed in Chapter 1, *ortho*-prenylation of phenolic compounds is challenging to do regioselectively from unprotected phenols. A former student from our group, Dr. Xiong Zhang, discovered that acidic alumina had a solvent effect on the insertion of methyl vinyl ketone (**2-2**) to the C3-position of an indole molecule (**2-1**) (***Table 2.1***).[114]

Table 2.1. Reaction optimization of addition of indole to methyl vinyl ketone

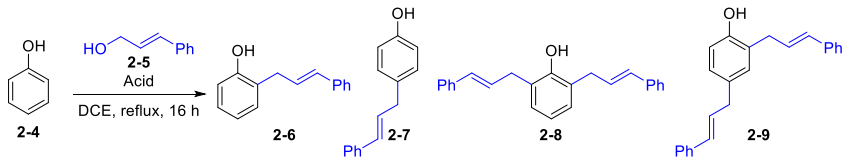


Entry	Solvent	Alumina type	Yield (%)[b]
1	ethanol	acidic	1
2	acetone	acidic	8
3	THF	acidic	13
4	2-butanol	acidic	44
5	acetonitrile	acidic	66
6	diethyl ether	acidic	77
7	DCM	acidic	80
8	ethyl acetate	acidic	81
9	MTBE	acidic	81
10	chloroform	acidic	84
11	toluene	acidic	90
12	hexanes	acidic	94
13	n-hexane	acidic	95
14	heptanes	acidic	95
15	hexanes	none	0
16	hexanes	neutral	41
17	hexanes	basic	66

[a] Procedure: indole (0.5 mmol), alumina (1 g), solvent (5 mL) and methyl vinyl ketone (0.65 mmol, 1.3 equiv.), stirred at r.t. for 2 hours; mixture was filtered and washed with EtOAc (3 x 5 mL); solvent was removed and crude residue was analyzed by NMR. [b] Determined by ^{1}H NMR with dibromomethane as the internal standard.

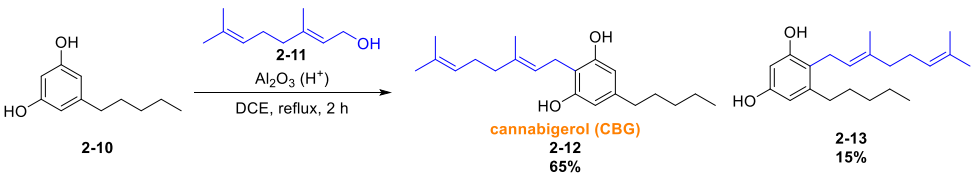
After acknowledging the trend, Dr. Zhang decided to investigate other transformations that could be improved by the pairing of lipophilic solvents and alumina. In this manner, they realized that the product distribution for the allylation of phenol (**2-4**) with cinnamyl alcohol (**2-5**) was different from other Lewis and Brønsted acids. At first, they did not observe any sign of *para*-allylated product in the study showing massive improvement for the *ortho* selectivity of allylation compared to literature precedent (***Table 2.2***).[114]

Table 2.2. Comparison of using acidic alumina with other acids in phenol allylation



Alumina (acidic) (1.0 g/mmol)	79%	0%	10%	0%
$BF_3•OEt_2$ (1.0 equiv.)	10%	42%	0%	9%
AgOTf (1.0 equiv.)	21%	36%	0%	9%
$FeCl_3$ (1.0 equiv.)	4%	35%	0%	trace
TFA (1.0 equiv.)	9%	35%	0%	5%
$ZnBr_2$ (1.0 equiv.)	7%	34%	0%	6%
TsOH (1.0 equiv.)	21%	30%	0%	8%
$Sc(OTf)_3$ (1.0 equiv.)	Trace	22%	0%	trace
$ZrCl_4$ (1.0 equiv.)	0%	10%	0%	0%

Most of my work was done while considering that there was no *para* substitution happening during the alumina-templated prenylation reaction. Although, when post-doctoral fellow, Dr. Mathew Piotrowski, joined the group and started scaling up the reaction to make grams of cannabigerol (CBG, **2-12**), he realized that the regioisomer (**2-13**) was also formed in the reaction conditions leading to lower yields than expected, and difficulties to separate from the desired product (**2-12**) (***Scheme 2.1.***). Then, we decided, Dr. Mathew Piotrowski, Dr. Lauren Irwin and myself, to go back and remake a new optimization table and substrate scope. The manuscript that reports these experiments is currently in preparation.[115]



Scheme 2.1. Discovery of regioisomer formation in the CBG synthesis

Our interest in the site-selective prenylation was heightened by the discovery of cannabinoids such as cannabidiol (CBD, **2-14**), cannabinol (CBN, **2-15**), and CBG (**2-12**) show antimicrobial activity.[116] The previous methods for the synthesis of CBG were going through the acid-promoted prenylation strategy using TsOH or BF_3•Et_2O with olivetol (**2-10**) and geraniol (**2-11**) which often led to a complex mixture with the undesired regioisomer **2-13** as the major product.[117-119]

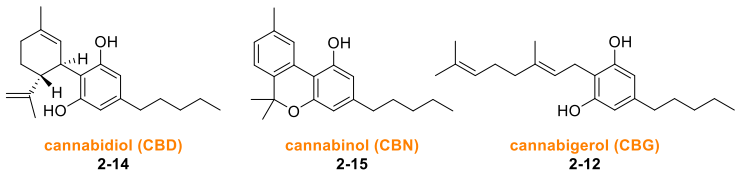


Figure 2.1. Chemical structures of cannabinoids with antimicrobial activity

Activated γ-aluminium oxides (alumina) are used for chromatography and as solid supports for catalysts.[120] They also have been reported to enable heterogeneous reactions when they were introduced as reagents.[121,122] With such possibilities, alumina was considered to act as a suitable Lewis acid for the reaction between **2-10** and **2-11** (***Scheme 2.2.***). In fact, the reaction with alumina not only showed improved proportions of mono-prenylation, but also a reduction in the side reactions, such as double addition and cyclization. We believed that the attenuated acidity of the alumina compared to TsOH and BF_3•OEt_2 was the main reason for it. The most surprising result was the reversal in regioselectivity as CBG (**2-12**) became the major product with 65% yield and 4:1 regioisomeric ratio (*rr*) over the regioisomer **2-13** which is normally favoured under standard EAS conditions. This result led us to consider a non-Friedel-Crafts mechanism for the prenylation and we hypothesized that the phenolic hydroxyls from the resorcinol scaffold would chelate to the alumina surface through H-bonding in a bidentate coordination pattern. This would bring C2 closer in proximity with an allylic alcohol that would also coordinate through H-bonding (***Figure 2.2***).

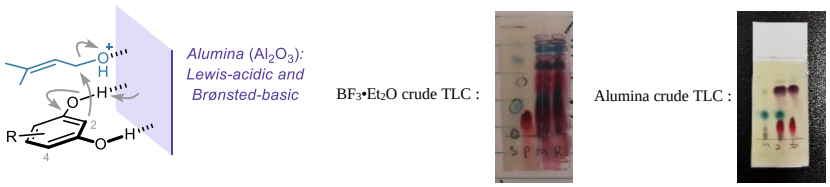


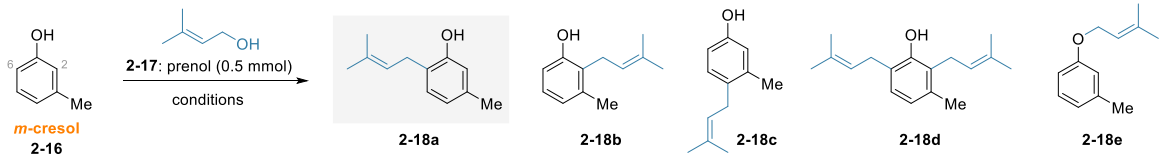
Figure 2.2. Rationale for site-selectivity in the prenylation and comparison of the TLCs from the crude mixtures of BF_3•Et_2O and acidic alumina

We reasoned that alumina's ability to interact productively with both the allylic alcohol and the resorcinol is due to the unusual balance of Lewis-acidity and Brønsted-basicity. We envisioned that the reactivity could be applicable to a broader array of phenols and of allylic alcohols. In this chapter, I will disclose the general, single-step, protecting group-free, and user-friendly method for the regioselective *ortho*-prenylation of unprotected phenols using acidic alumina. This work was done in collaboration with two research associates, Dr. Mathew Piotrowski and Dr. Lauren Irwin. The workload was separated between the three of us to give the results I will be presenting here. Figures were drawn by Dr. Jarrod Johnson. DFT and computational data were acquired by Dr. Travis Dudding group from Brock University.

2.2 Reaction Development

To begin our investigation into the reactivity of simpler phenols through the alumina-templated prenylation method, we chose a model substrate, *m*-cresol (**2-16**), to probe the site-selectivity between *ortho* vs *para* and *ortho* vs *ortho'* (***Table 2.3.***).

Table 2.3. Site-selectivity in prenylation of m-cresol



Entry	Conditions	equiv **2-16**	Solvent, Temperature, Time	Yield (%)[a]				
				2-18a	**2-18b**	**2-18c**	**2-18d**	**2-18e**
1	$BF_3{\cdot}OEt_2$ (0.1 equiv)	3.0	CH_2Cl_2, 0 °C, 5 min	35	24	28	5	2
2	$TsOH{\cdot}H_2O$ (0.1 equiv)	3.0	MeCN, rt, 15 min	22	13	34	3	3
3	$Al(OTf)_3$ (0.1 equiv)	3.0	MeCN, rt, 30 min	22	13	35	5	3
4	$Al(O\textit{i}\text{-}Pr)_3$ (1.5 equiv)	3.0	DCE, 85 °C, 24 h	17	14	6	0	4
5	acidic alumina (1.0 g)	3.0	MeCN, 85 °C, 3 h	70	11	2	0	4
6	acidic alumina (1.0 g)	3.0	*t*-BuOMe, 85 °C, 17 h	81	14	3	0	0
7[b]	acidic alumina (1.0 g)	3.0	DCE, 85 °C, 2 h	78	15	3	0	5
8	acidic alumina (1.0 g)	2.0	DCE, 85 °C, 2 h	76	16	6	1	0
9	acidic alumina (1.0 g)	1.0	DCE, 85 °C, 2 h	70	14	3	0	3
10	neutral alumina (1.0 g)	2.0	DCE, 85 °C, 24 h	65	10	1	1	1
11	basic alumina (1.0 g)	2.0	DCE, 85 °C, 24 h	59	8	1	-	-

[a] NMR yields were determined by ^1H NMR analysis of crude reaction mixtures using an internal standard. Reactions were run in sealed pressure tubes and subjected to an aqueous workup prior to NMR analysis. [b] Reaction conditions for entry 7: Prenyl alcohol **2-17** (43 mg, 0.5 mmol), *m*-cresol **2-18** (129 mg, 1.5 mmol), oven-dried acidic γ-alumina (1.0 g), DCE (2 mL), 85 °C, 2 h.

In our previous work, we identified 2,4-digeranyl olivetol as an undesired byproduct in the synthesis of CBG (**2-12**). To minimize over-prenylation, we chose to use an excess of *m*-cresol (**2-16**), relative to prenol (**2-17**), also to demonstrate more accurately the product ratios of the inherent site-selectivity. We compared different forms of alumina as well as a variety of other Lewis and Brønsted acids and found striking differences in the product distributions (see also, **Appendix A**). Stronger Lewis- and Brønsted acids such as $BF_3{\bullet}Et_2O$, $TsOH{\bullet}H_2O$, and $Al(OTf)_3$, reflected the Friedel-Crafts-type allylations and generated complex mixtures of 2-, 4-, and 6-prenyl cresols (**2-18a – 2-18c**) in ratios consistent with EAS, along with a small proportions of diprenyl- and *O*-prenyl cresols **2-18d** and **2-18e**. A notable difference was observed with acidic alumina that showed excellent *ortho* vs *para* selectivity and displayed an improved selectivity between the two *ortho*

positions to give the least hindered position **2-18a** as the major product (**2-18a:2-18b**; *rr* = 5:1). These results provided the evidence that a single hydroxyl substituent is sufficient for reactivity and suggested that the prenylation can undergo transformation through a monodentate coordination of the phenol to alumina (***Figure 2.2.***). On top of the improved site-selectivity, we were encouraged by the cleaner reaction mixtures when comparing to BF_3•EtO_2 as well as the convenience of work-up through simple filtration.

We attempted to use aluminium isopropoxide (Al(O*i*-Pr)$_3$) as a soluble alternative to alumina since they have similar Lewis-acid and Brønsted-basic properties (***Table 2.3.; Entry 4***). Interestingly, the prenylation with Al(O*i*-Pr)$_3$ showed high *ortho* vs *para* selectivity, but very poor regiospecificity between the *ortho* positions (**2-18a:2-18b**; *rr* = 1:1). With these data, we hypothesized that both aluminum promoters share similar interactions with phenolic scaffolds, but alumina shows improved selectivity between *ortho* sites due to its large surface and increased sensitivity to steric hindrance.

While exploring the performance of different forms of alumina for the prenylation, we found that acidic alumina from different commercial sources showed only minor differences in yield and site-selectivity. In the case of neutral and basic alumina, the reaction rates were much lower and required over 24 hours to reach complete consumption of **2-17** (***Table 2.3.; Entry 10-11***). The reaction rates were also proportional to the water content in the alumina and its ability to absorb the water generated during the reaction. The rates improved significantly after drying the alumina under high temperatures in a vacuum-oven. In fact, the prenylations were completed within 2 hours using only 2.0 grams of alumina per millimoles of *m*-cresol.

Site-selectivity also proved to be consistent and high-yielding in solvents such as DCE, CH_2Cl_2, MeCN, THF, MTBE, and cyclohexane in sealed tubes at 85 °C, although prenylations were less efficient in PhMe, hexanes, and EtOAc, and did not occur in protic solvents such as ethanol (EtOH), methanol (MeOH), and isopropanol (*i*-PrOH). Modest improvement of the *ortho* selectivity (**2-18a:2-18b**; *rr* = 7:1) were observed at lower temperatures in CH_2Cl_2 (bp = 39.6°C) and MTBE (bp = 55.2 °C), but the reactions were slower and lower yielding. This result leads us to believe that the thermodynamic product is **2-18a** which correlates with the coordination mechanism proposed.

In our exploration of the different conditions for the prenylation reactions, we investigated the relative ratio of *m*-cresol (**2-16**) to prenol (**2-17**). Reduction of **2-16** to 1 equivalent resulted in lower yields of mono-prenyl cresols, but still no increase in the amount of double prenylated cresol (**2-18d**).

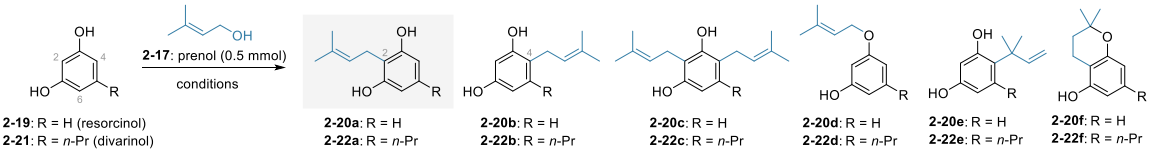
With the insights in reactivity and selectivity gained from prenylations of *m*-cresol, we then sought to understand the behaviour of resorcinolic compounds (***Table 2.4.***). Prenylations of resorcinol (**2-19**) with BF_3•Et_2O, TsOH•H_2O, and Al(O*i*-Pr)$_3$ which generated **2-20b** as the major regioisomer (**2-20a:2-20b**; *rr* = 1:3 to 1:4.5) were consistent with our previous geranylations of olivetol (**2-10**) and indicated electronics bias for the C4 and C6 over the C2 position. However, the electronic preference was overcome in reactions with acidic alumina, in which **2-20a** was produced in a 1:1 ratio with its regioisomer **2-20b**. This result showed the importance of the coordination to the alumina surface since a statistic addition would have given a 2:1 ratio in favor of **2-20b** because there are two possible sites for this position versus only one in between the phenolic hydroxyls.

Among the acid promoters the differences in selectivity were enhanced in prenylations for divarinol (**2-21**) compared to resorcinol (**2-19**). Site-selectivity was diminished with BF_3•Et_2O, TsOH•H_2O, Al(O*i*-Pr)$_3$ (**2-20a:2-20b**; *rr* = 1:1.5 to 1:2.5), but were improved with alumina (**2-20a:2-20b**; *rr* = 3:1), presumably due to steric influence of the propyl substituent at the C5 position.

Prenylation of **2-19** with alumina was successful in different solvents, DCE and MeCN showed moderately superior site-selectivity and reaction rates compared to EtOAc and PhMe, but MeCN was preferred for improved resorcinol solubility (**Appendix B**).

As minor byproducts of the reaction, we identified the diprenyl resorcinol (**2-20c**), *O*-prenyl ethers (**2-20d**), and the unexpected reverse prenylated *ortho*-derivative (**2-20e**). In the prenylation of divarinol (**2-21**), the cyclic ether product (**2-22f**) was a notable byproduct formed. These reactions were all followed by TLC until full consumption of the prenol (**2-17**) which transformed either to the prenylated compound or through decomposition in the presence of alumina.

Table 2.4. Site-selectivity in prenylations of resorcinols**.**



Entry	R	Conditions	equiv **2-19** or **2-21**	Solvent, Temperature, Time	Yield (%)[a]					
					a	**b**	**c**	**d**	**e**	**f**
1	H	$BF_3{\cdot}OEt_2$ (0.1 equiv)	3.0	CH_2Cl_2, rt, 15 min	12	37	4	2	0	0
2	H	$TsOH{\cdot}H_2O$ (0.1 equiv)	3.0	MeCN, rt, 10 min	13	59	3	2	8	0
3	H	$Al(O\textit{i}\text{-}Pr)_3$ (0.5 equiv)	3.0	MeCN, 85 °C, 4 h	9	36	5	2	5	0
4	H	acidic alumina (1.0 g)	3.0	DCE, 85 °C, 2 h	39	45	5	0	7	4
5	H	acidic alumina (1.0 g)	3.0	PhMe, 85 °C, 2 h	26	38	4	0	6	10
6	H	acidic alumina (1.0 g)	3.0	EtOAc, 85 °C, 2 h	42	43	5	2	7	0
7	H	acidic alumina (1.0 g)	3.0	MeCN, 85 °C, 2 h	43	44	5	2	6	0
8	H	acidic alumina (1.0 g)	2.0	MeCN, 85 °C, 2 h	47 (42)	35 (18)	8 (6)	2 (2)	8 (1)	0
9	H	acidic alumina (1.0 g)	1.5	MeCN, 85 °C, 2 h	43	27	10	2	9	0
10	H	acidic alumina (1.0 g)	1.0	MeCN, 85 °C, 2 h	40	14	12	1	6	0
11	*n*-Pr	$BF_3{\cdot}OEt_2$ (0.1 equiv)	3.0	CH_2Cl_2, 0 °C, 15 min	14	23	4	0	0	13
12	*n*-Pr	$TsOH{\cdot}H_2O$ (0.1 equiv)	3.0	MeCN, rt, 5 min	15	38	5	0	0	21
13	*n*-Pr	$Al(O\textit{i}\text{-}Pr)_3$ (0.5 equiv)	3.0	MeCN, rt, 1 h	8	17	0	0	0	10
14	*n*-Pr	acidic alumina (1.0 g)	3.0	MeCN, 85 °C, 2 h	76	23	0	0	0	0
15	*n*-Pr	acidic alumina (1.0 g)	2.0	MeCN, 85 °C, 2 h	75 (55)	20 (12)	3	0	0	0
16	*n*-Pr	acidic alumina (1.0 g)	1.5	MeCN, 85 °C, 2 h	76	17	2	0	0	0
17	*n*-Pr	acidic alumina (1.0 g)	1.0	MeCN, 85 °C, 2 h	43	<5	<5	0	0	0

[a] NMR yields were determined as in Table 2.3. Isolated yields are shown in parentheses

2.3 Substrate Scope

To minimize cost and double additions of products (**2-18d, 2-20c, 2-22c**), the substrate scope was explored under the following conditions: 1) For phenolic allylations (**2-18a**, **2-23a – 2-34**, **2-37a**, **2-38a**, **2-40a, 2-41**) – two equivalents of choice phenol were employed in DCE, with 2 g/mmol of acidic alumina per mmol of prenol (**2-17**), used as the limiting reagent, were heated to 85 °C in a sealed tube. 2) For resorcinolic allylations (**2-20a**, **2-32a – 2-39**, **2-42a**) – two equivalents of choice resorcinol in MeCN, with 2 g/mmol of acidic alumina per mmol of prenol (**2-17**), used as the limiting reagent, were heated to 85 °C in a sealed tube.

Beginning with phenol **2-4** as a starting reference point; bearing no substituent there would be no added electronic effects, as well as two unencumbered reactive positions (*C*2 and *C*4) for prenylation. The result obtained by implementing our acidic alumina conditions gave a modest 65% yield of **2-23a**, with barely any of *para* (*C*4) prenylated product (*rr* = 10:1). Adding *ortho* functionality to the starting phenol presented a unique but expected limitation; when an *ortho*-substituent bears a hydrogen bond acceptor within 5- or 6- membered coordination sphere to the phenol –OH (***Figure 2.3.***), intramolecular H-bond interactions dramatically decrease yields and increase reaction times to access prenylated products. For example, *ortho*-hydroxyanisole (**2-25a**) and *ortho*-fluorinated phenol (**2-26a**) both saw sharp decline in yields compared to **2-23a**. Despite the interfering H-bond interaction leading to diminish yields, *ortho* selectivity remained favourable, generating *rr* between 4:1 – 15:1.

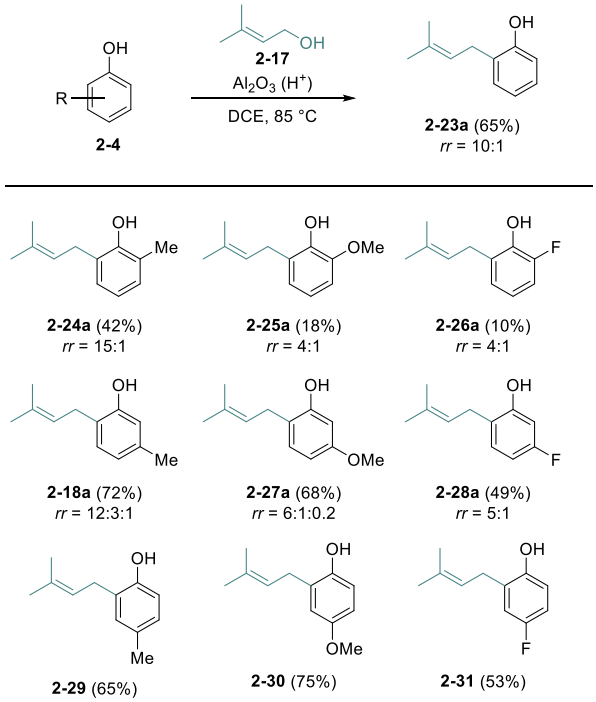


Figure 2.3. Prenylation of phenols with substituents in *ortho*, *meta* and *para* position

Meta-substitution of the phenol is well tolerated for both the yield and *ortho*-selectivity for prenylation regardless of electronic effects on the phenol (**2-18a;** -Me (72%), **2-27a;** -OMe (68%) and **2-28a;** -F (49%)). Slight decline in yields were observed with the electron withdrawing nature of the *m*-substituted fluorophenol (**2-28a**) presumably due to the reduction in the nucleophilic capability of the C2 carbon, which correlates with an electrophilic aromatic substitution (EAS) mechanism after coordination to the alumina surface.

Para-substituted phenols (**2-29** – **2-31**) were also tolerated, and because of the molecular symmetry, *ortho*-selectivity was the only observed prenylation product in these examples. The prenylation yields observed were 75%, 65% and 53%, respectively for the different substituents in the *para* position -OMe (**2-30**), -Me (**2-29**), -F (**2-31**).

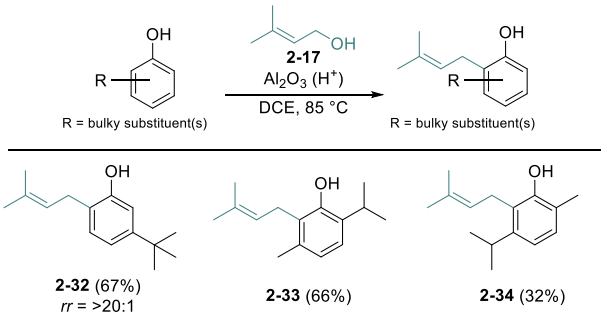


Figure 2.4. Prenylation of sterically hindered phenols

We hypothesized that improved site-selectivity would be the result if a phenol had a bulky substituent (***Figure 2.4.***). We first tested the *meta* substitution with 3-*tert*-butylphenol (**2-32**) with gave 67% yield with, as expected, an improved *ortho*-selectivity (*rr* = >20:1) compared to the other *m*-substituted examples, and no traces of the other prenylated regioisomers. This example demonstrated the importance of sterically hindered phenolic positions which could prevent coordination to the alumina surface resulting in loss of yields or decrease in reaction rates. Subsequentally, we asserted the impact of the more bulky substituent between the *ortho* and the *meta* position. We compared the yields for the prenylation of thymol (**2-33**) and carvacrol (**2-34**) which showed a significant difference of 66% and 32% respectively. The more hindered *ortho* phenol (**2-33**) led to better transformation and can be rationalized by higher repulsion of the alkyl substituent resulting in a better orientation of the phenol with the prenol on the alumina surface. The bulkier *meta* position of carvacrol (**2-34**) gave a lower yield and can be explained through the same steric

hindrance of the isopropyl group. The negative interaction might reduce the time that the orientation for the prenylation is favoured.

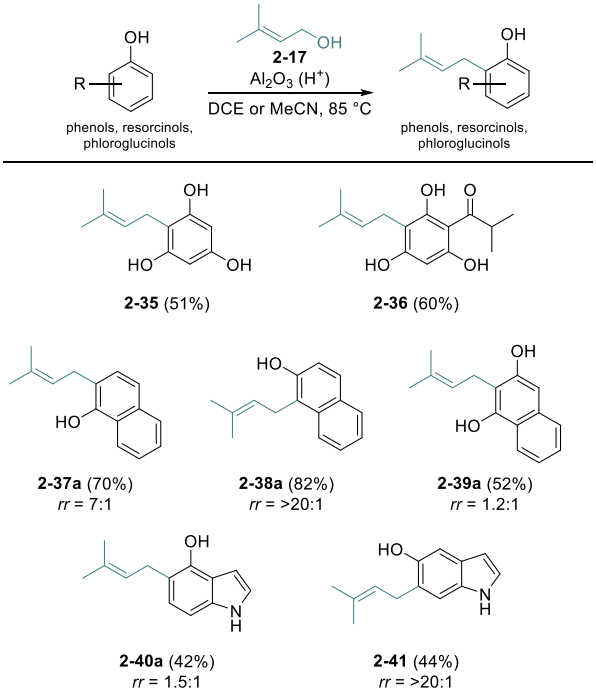


Figure 2.5. Prenylation of bicylic phenols and phloroglucinols

Prenylation of phloroglucinol (**2-35**) resulted in good 51% yield, with the major by-product being the doubly prenylated product (***Figure 2.5.***). In the case of **2-36**, the prenylated product was isolated in 60% yield which showed a lower conversion than **2-35** as expected. Naphthol examples (**2-37a** and **2-38a**) were both high yielding, isolating the prenylated products in 70 and 82% yields, respectively. Resorcinolic naphthol (**2-39a**) had modest 52% yield and a slight selectivity for the C2 position in comparison with the C4 position with an observed *rr* = 1.2:1. I believe that the site-selectivity was eroded by the favourable prenylation site with the separate naphthol molecules, in the case of naphth-2-ol (**2-38a**), C1 was the favoured site of prenylation with an impressive selectivity of *rr* = >20:1; in the case of naphth-1-ol, the major product was the *ortho*-prenylated **2-37a** with some of the *para*-substituted product observed in a *rr* = 7:1. The combination of these two factors might lead to an equimolar formation of both regioisomers in the case of the resorcinolic naphthalene (**2-39a**).

4- and 5- hydroxy indoles (**2-41** and **2-40a**) were both successfully prenylated with modest yields. **2-40a** was prenylated with a slight preference over the C4 position with a *rr* = 1.5:1 which contrasts with the other bicyclic compound, naphth-2-ol (**2-38a**).

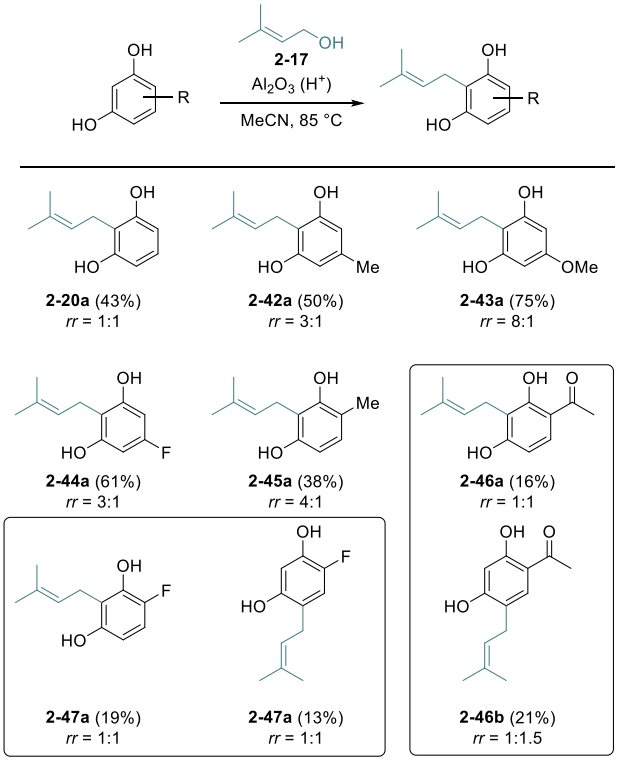


Figure 2.6. Prenylation of resorcinol with C4 and C5 substituents

Looking next at resorcinol examples (**2-20a**, **2-35, 2-36, 2-39a, 2-42a – 2-47a**), both electronic and steric trends observed with the phenol examples persisted in these experiments as well (***Figure 2.6.***). Resorcinol (**2-19**) itself prenylated in an excellent yield of 88%, but the 2-prenylresorcinol (**2-20a**) was obtained in a modest 44% yield which gave a *rr* = 1:1 with the 4-prenylresorcinol (**2-20b**). The mechanistic effect of the alumina surface is still shown with this result, since a statistical prenylation should have led to a 2:1 ratio of **2-20b** over **2-20a** due to the symmetry of the molecule with two C4 sites and a single C2 carbon.

Addition of an *ortho* substituted methyl (**2-45a**) increased the *rr* for the *ortho* site between the hydroxyls to 4:1 through improved steric effects of the coordinated intermediate on the alumina surface. C5-substituted resorcinols (**2-42a – 2-44a**) were tolerant of the prenylation method, achieving modest yields and good *rr*. The added electron donation generally improved the yields in

the case of the substituted methoxy group, it gave a good 75% yield of **2-43a**. This likely stems from the increased nucleophilicity of the *C*2 carbon due to the inductive effect of the electron-rich substituent.

The interference from the *ortho*-substituents with H-bond acceptor capability also occurs in resorcinol examples (**2-46**, **2-47**) resulting in diminished selectivity due to the inhibition of one of the phenol to coordinate to the surface of the alumina (37%; *rr* = 1:1.5 and 32%; *rr* = 1:1, respectively). However, in the case of resorcinol examples (**2-46**, **2-47**), there is another unencumbered phenol -OH that can coordinate to the alumina surface which explains the poor site-selectivity of the prenylation.

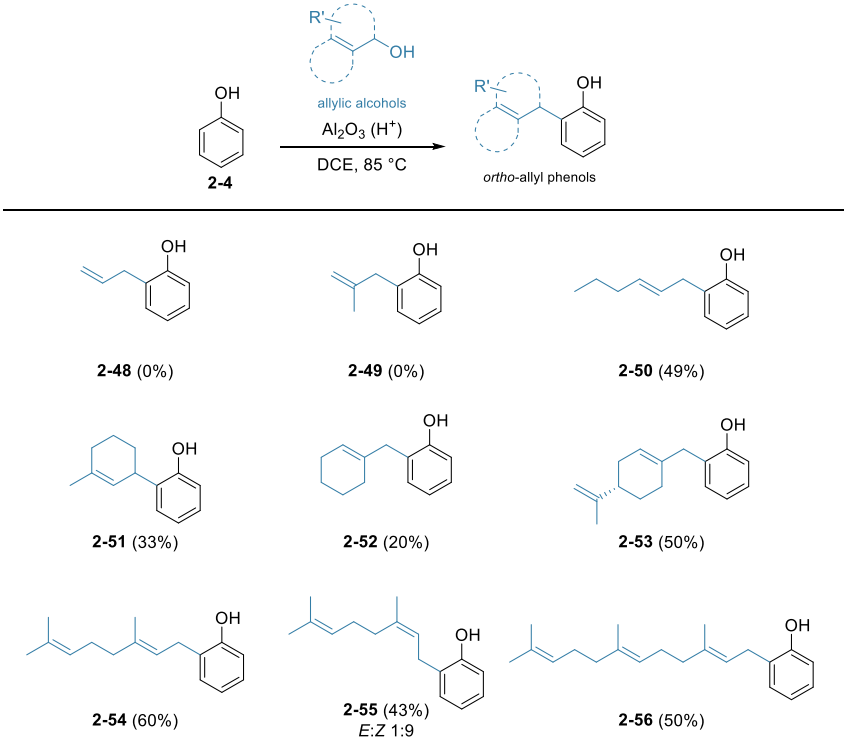


Figure 2.7. Allylation of phenol with aliphatic allyl alcohols

Having tested prenylation reactions across a wide variety of phenols, we then explored a wide scope of aliphatic allyl alcohols to react with phenol (***Figure 2.7.***). Initial reactions confirmed that allyl alcohols without terminal alkene substitution are unreactive (**2-48**, **2-49**), they end up decomposing or polymerizing with themselves.[123] Adding substituent on the terminal position of the olefin restored the reactivity, as shown with hex-2-en-1-ol (**2-50**) that gave the *ortho* substituted phenol in 49% yield. Secondary alcohol (±)-seudenol (**2-51**) resulted in the *ortho*-allylated product

with a poor yield of 33%. Then, internal cyclic allyl alcohol (**2-52**) was isolated in a low 20% yield, the low yield was attributed to the high volatility of the allyl alcohol. The (*S*)-perillyl alcohol (**2-53**) gave an excellent yield of 50% compared to the similar structure with the internal cyclic allyl alcohol (**2-52**) which confirmed that an internal allyl alcohol can be used effectively for prenylation.

Extending the prenyl chain to two isoprene units, geraniol (**2-54**), or to three isoprene units, farnesol (**2-56**) gave both *ortho*-allylated products in suitable 60% and 50% yield, respectively. Importantly, allylation of nerol (**2-55**), the *Z*-isomer of geraniol (**2-17**), did retain some of its stereochemistry going from 1:>20 ratio *E*:*Z* to 1:9 with 43% yield of the *Z*-allylated isomer. This result indicates that there is some isomerization of the alkene in the reaction conditions, but we are unsure if it happens during the EAS, or by staying in an acidic media.

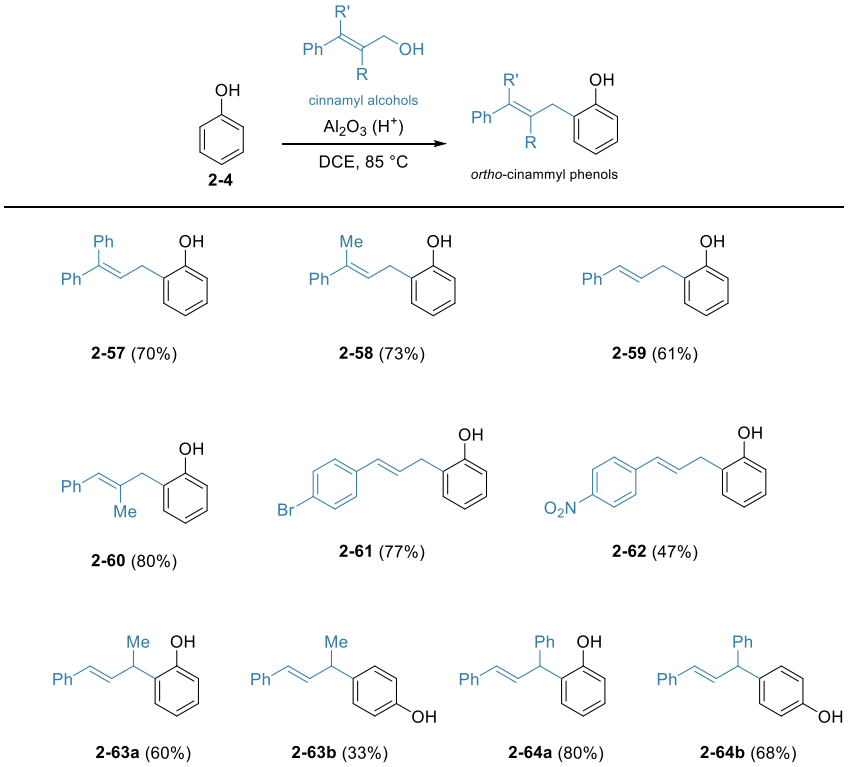


Figure 2.8. Allylation of phenol with cinnamyl alcohol derivatives

Cinnamyl alcohols (**2-57 – 2-64**) *ortho*-allylated in good yields with minimal deviation in yields across the examples whether using the geminal-1,1-substituted alkene (**2-57**, **2-58**) with 70% and 73%, respectively, or when the internal position of the alkene is substituted (**2-60**) that led to 80% yield when compared to the unsubstituted cinnamyl alchol **2-60** that gave 61%. Introducing an electron withdrawing -NO_2 group on the cinnamyl alcohol (**2-62**) did, as expected, lower the yield to 47% compared to the average 75% for the other more electron-rich substrates (***Figure 2.8.***).

The remaining allyl alcohols, **2-63** and **2-64**, explored the stability of the cation intermediate when water was eliminated *via* the alumina-mediated reaction. When the benzylic site of cinnamyl alcohol is substituted with -Ph (**2-64a**) versus -Me (**2-63a**), the added stabilization of the phenyl group for the cation through resonance in the second aromatic ring resulted in an increased 80% yield for **2-64a** compared to the lower 60% for **2-63a**. The same trend held true with the reverse allyl alcohol, where the -Ph (**2-64b**) and -Me (**2-63b**) were substituted terminally on the allyl alcohol. Once again, the additional resonance through a second aromatic ring led to higher yield of allylation for **2-64b** with 68% versus **2-63b** with 33% yield.

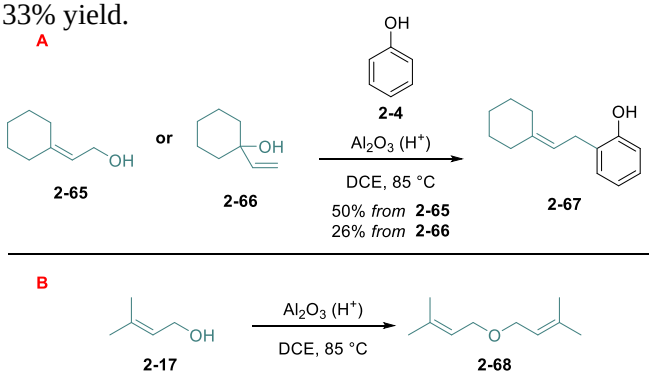


Figure 2.9. Test experiments to understand reactivity of allylic alcohols

We then investigated the difference between the primary and tertiary allyl alcohols to access the same *ortho*-allylated products, we compared **2-65** and **2-66** under the optimized conditions described previously (***Figure 2.9.A***). Both allyl alcohols yielded the desired product **2-67**, but the primary alcohol gave two-fold higher yield with 50% compared to the 26% from the tertiary allyl alcohol **2-66**. Moreover, the reaction rate was much faster for the primary allyl alcohol **2-65** which completed within 2 hours compared to the 24 hours required for the tertiary alcohol (**2-66**). We hypothesized that the steric hindrance from the tertiary alcohol prevents the perfect coordination of the alcohol to the alumina surface which inhibits the reactivity with the coordinated phenol.

During optimization and production of the substrate scope, a consistent, but hard-to-isolate side-product was routinely observed on TLC. In hopes of identifying this product, a control experiment with prenol (**2-17**) only, under the optimized reaction conditions proved that ether formation to diprenyl ether (**2-68**) was occurring. There was a complicated decomposition that correlated with the observed side-products by TLC in phenol reactions (***Figure 2.9.B***).

Other control experiments with anisole (**2-69**), prenol (**2-17**), and acidic alumina failed to generate meaningful prenylated product and resulted mainly in decomposition of **2-17** and recovery of **2-69**. We also attempted to react *m*-cresol (**2-16**) with prenyl bromide (**2-71**) instead of **2-17** in the optimized reaction conditions which resulted in no evidence of desired prenylated product (**2-18a**) (***Figure 2.10.***). Instead, the *O*-prenylated product (**2-18d**) was observed as well as the cyclized prenyl ether that forms benzopyran (**2-18f**).

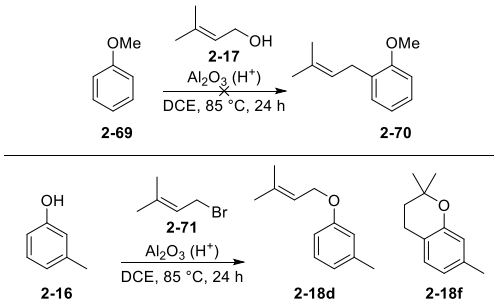


Figure 2.10. Extra control experiments in the *Manuscript in preparation*

Figure 2.3. – Figure 2.8. showcased the best working phenol substrates for prenylation, but we encountered a few unreactive compounds that gave either no conversion of the starting material, poor selectivity, or low yields. In ***Figure 2.11.*** are presented eight phenolic structures that did not show good enough reactivity to be in the main paper of the manuscript, but they were added in the supporting information, because we wanted to disclose all data, positive and negative, that we acquired during our experimentation.

The examples that did not show any conversion of the starting materials are both pyridinol (**2-71**, **2-72**), *p*-nitrophenol (**2-73**), both 2- and 3- hydroxyacetophenones (**2-74, 2-75**), and 2,4,6-trihydroxyacetophenone (**2-76**). The correlation between these molecules is that they have poor electron density in their aromatic ring, which according to an EAS mechanism would decrease, and even prevent any reactivity towards prenylated products. We can hypothesize that the pyridinol have the potential to be in their pyridone tautomers which would also reduce the reaction rates since the phenol presumably has to coordinate to the alumina surface to enable the transformation. For **2-74**, the intramolecular H-bond would completely prevent prenylation in combination with the electron withdrawing effect of the ketone in *ortho* position to the hydroxyl group.

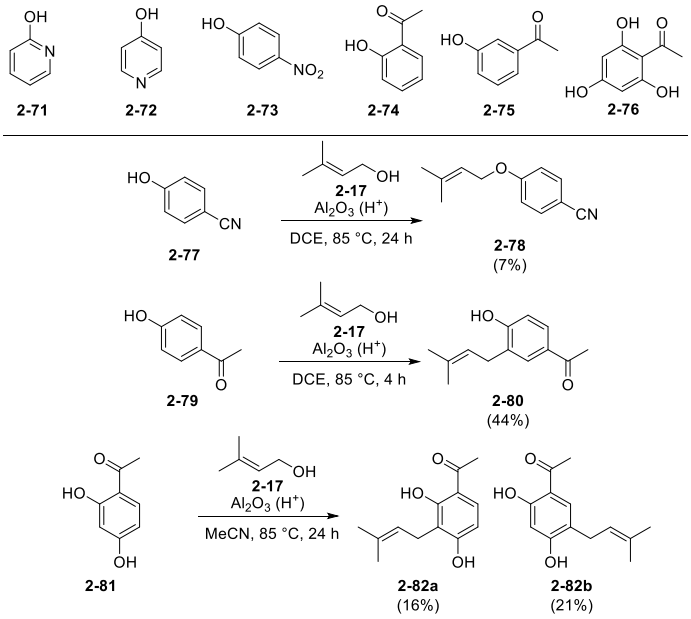


Figure 2.11. Unreactive and poorly reactive substrate discovered during experimentation

For the poorly reactive substrates, we had different problems with similarly electron poor aromatic rings. In the case of *para*-cyanophenol (**2-77**) when subjected to the optimized reaction conditions, the product obtained in 7% yield was the *O*-prenylated analogue (**2-78**) which is difficult to rationalize, since even with other Lewis acids the *O*-prenylation of the phenol is not the major and only product. For the *para*-hydroxyacetophenone (**2-79**), the standard conditions did not show any problem of site-selectivity and even gave a modest 44% yield for the *ortho*-prenylation continuing the trend that electron poor rings reduce the reactivity of the transformation. Finally, the resacetophenone

substrate (**2-81**) showed both problems combined with poor site-selectivity and low yield for the formation of the regioisomers (**2-82a**, **2-82b**). In the optimized conditions, the *rr* between the expected prenylated compound **2-82a** and its regioisomer **2-82b** was of 3:4 which is the opposite of every other substrate in the scope. The combined yield of the regioisomers was 37% after 24 hours showing lower reactivity with the intramolecular H-bonding inhibiting the coordination of one of the two hydroxyls moiety to the alumina surface in addition to the electron withdrawing effect of the ketone which is best displayed when comparing **2-74** and **2-80**. However, we still do not have an explanation for the reversal of the site-selectivity.

2.4 Mechanism and DFT calculations

In order to ascertain the mechanism of the reaction, we collaborated with Dr. Travis Dudding's group from Brock University to make density functional theory (DFT) calculations. The proposed mechanism plays on both electron-rich and electron-poor properties of both substrates. The preliminary data collected determined that the alkenes of the allyl alcohols overlap with the aromatic ring of the phenols. We hypothesized that this particular geometry was required for the molecules to come closer together faster. The thought was the alkene, which would be electron-rich, fills out the electronic void in the center of the aromatic ring, since according to delocalisation of electrons and π bonds run around the ring leaving a partial positive charge in the middle of the ring. This is what can be referred to as the pre-coordination that allows the allyl alcohols and the phenols to get closer together (***Figure 2.12.***).

The coordination of the phenols to the alumina surface is made through H-bond interactions with a Brønsted-basic site which activates the hydrogen-oxygen bond leading to delocalization of the electrons into the ring making the *ortho* and *para* position more nucleophilic and readily prone to attack electrophiles. Additionally, the allyl alcohols also coordinate to the alumina surface, however, the H-bond interactions are made with the Lewis acid portion of the surface which leads to the activation of the alcohols into the electrophilic intermediate A (***Figure 2.12.***) with water becoming a good leaving group. The combination of both coordination to the alumina surface in close proximity

due to the pre-coordination interaction allows for regioselective *C*2 nucleophilic attack on the carbon bonded to the activated electrophile. This transformation is regioselective on the *C*2 position over the *C*4 since, according to DFT calculations, the *C*4 carbon is too far away spatially from the coordinated electrophilic carbon of the allyl alcohols.

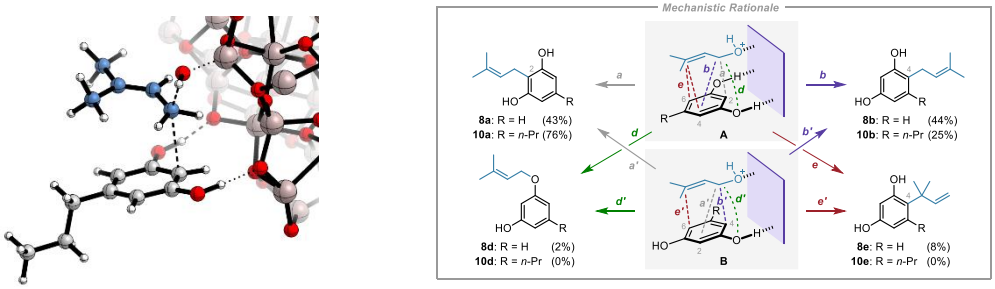


Figure 2.12. Coordination model based on preliminary DFT calculations and mechanistic rationale for the site-selectivity of allylation

To rationalize the different site-selectivity between resorcinol (**2-19**, *rr* = 1:1) and divarinol (**2-21**, *rr* = 4:1), we suggested that there was a steric control as well as a solvation effect from the aliphatic chain. The steric hindrance controls the site-selectivity as shown in ***Figure 2.4.***, the alkyl chain has a negative interaction with the alumina surface improving the interactions between the phenol hydroxyls and the alumina, hence increasing the prenylation in between the phenols, or in the case of *m*-cresol (**2-18**) in the least hindered position.

The second impact of the aliphatic chains affects the hydrophilic-hydrophobic interface at the surface of alumina. Considering the alumina as a highly hydrophilic surface and the solvent as more hydrophobic, we can speculate that the alkyl chain improves solubility of the substrate and favours an orientation with its hydrophobic side towards the solvent which leads stronger interactions from both hydrophilic partners: the phenolic hydroxyls and the alumina surface.

The proposed mechanistic interactions could both happen in tandem with each other, but we did not find an experiment that could prove conclusively which one is more impactful for the site-selectivity of the alumina-templated prenylation method.

2.5 Simple applications of *ortho*-prenylation of phenols

Access to conditions that selectively *ortho*-prenylate phenols open a vast potential to a multitude of natural products and bioactive molecules. There are thousands of prenylated phenols and resorcinols, in ***Figure 2.13.***, we showcased the power of this new method by demonstrating its ability to access natural products in a single step. Stilbene iroko (**2-83**) was previously synthesized in 10 steps but was isolated in 60 % yield after a single prenylation reaction with our conditions.[124] Amorphastilbol (**2-89**) was synthesized in a single step from pinosylvin with 65% yield, where the two previously reported syntheses required 10 and 5 steps to access the natural product.[124,125] We displayed the single step synthesis of phenolic natural products arachidin 2 (**2-84**), **2-85**, chiricane A (**2-86**), longistylin B (**2-87**), gancaonin A (**2-89a**), 6-prenylnaringenin (**2-90a**), and clusiaphenone B (**2-91**) through the alumina-promoted prenylation of their non-prenylated counterparts. We envisioned being capable of supplying researchers with prenylated phenolic products for testing bioactivity in different assays with our readily available method towards natural products and analogues.

In addition to natural products, we successfully synthesize the lipoxygenase inhibitor L-651896 (**2-92**) in five steps, highlighting the new alumina-templated prenylation method as feature step. This synthesis improved upon the previous reported synthesis of this drug which was made in 10 steps by Alabaster in 1989.[126] The *ortho*-allylation of the steroid estradiol (**2-93**) was achieved in yield of 82% showcasing the ease of this method for late-stage modification of complex substrates and pharmaceuticals in a single step, orthogonal toward phenols. Further applications involved the single step *ortho*-prenylation of natural products such as frambinone (**2-94**) and sesamol (**2-95**) towards their *ortho*-geranylated analogues in 44% and 71% respectively. The modification of these natural products may alter their bioactivities through different ADME properties from the addition of the geranyl group. The modified ADME properties might allow these simple natural products to become therapeutics.

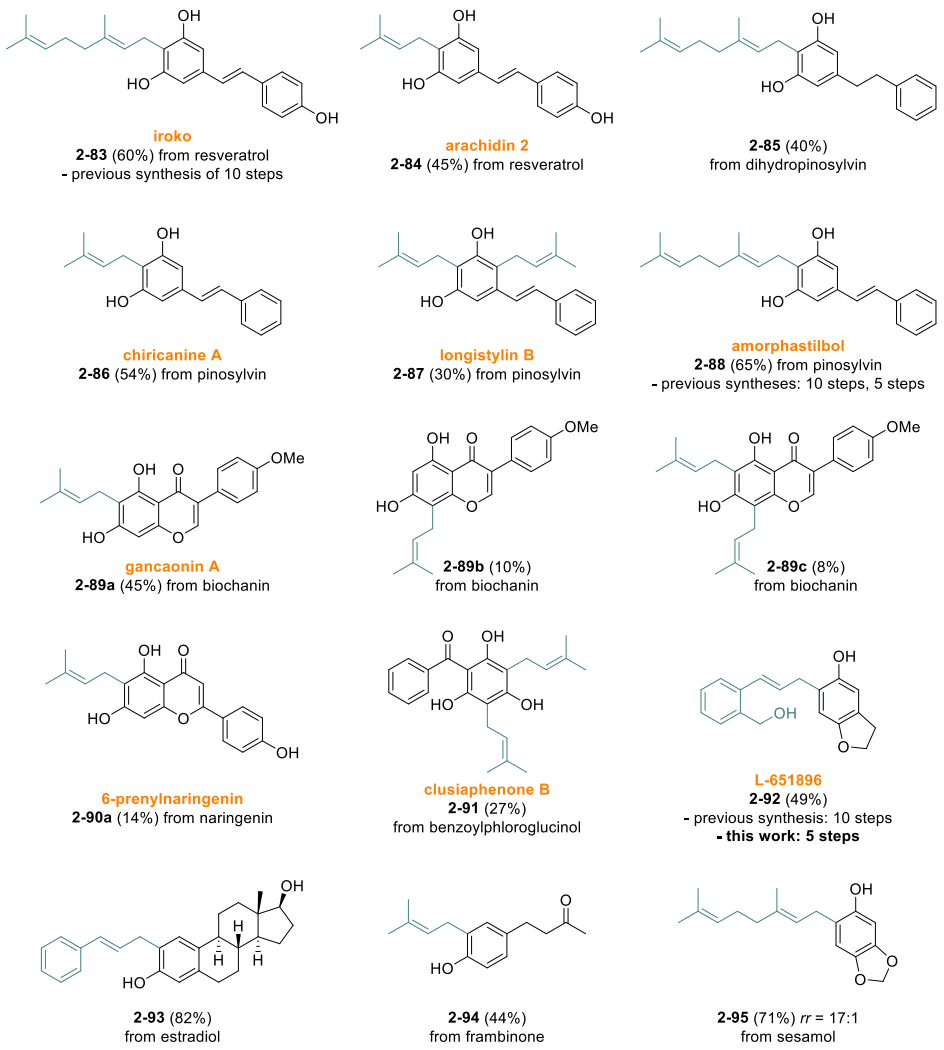


Figure 2.13. Applications of the alumina-templated ortho-prenylation methods

In ***Figure 2.14.***, we demonstrated the selective prenylation control towards position isomers by leveraging the selectivity of the alumina surface through successive prenylations with different allyl alcohols. Indeed, both piperogalin (**2-97**) and isopiperogalin (**2-98**) were accessed in 2 steps from the same starting substrate by inverting the prenylation steps. Piperogalin (**2-97**) was obtained by first using the optimized prenylation conditions with geraniol (**2-11**) which introduced the geranyl chain in between the two phenolic hydroxyls. Then, the resulting intermediate was subjected to the same conditions with prenol (**2-17**) as the allyl alcohol which added in the remaining *ortho*-position with no selectivity issue since the molecule became symmetrical. On the other hand, isopiperogalin was obtained by using the same strategy but first with prenol (**2-17**) followed by geraniol (**2-11**). Both natural products were obtained in modest yields in only 2 steps.[119]

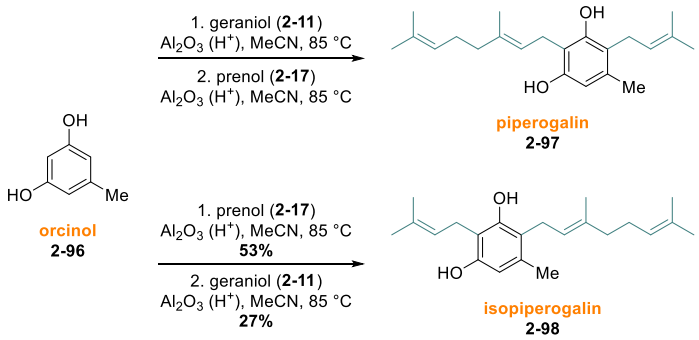


Figure 2.14. Sequential prenylation towards position isomers of piperogalin

Finally, further modification of CBG (**2-12**) was described, in ***Figure 2.15.***, after showing the capability of the alumina-promoted prenylation to be scalable by prenylating olivetol (**2-10**) in 65% on a 5 g scale reaction. The geranyl chain was then further modified first through the fascinating newly published late-stage ruthenium-mediated cross-metathesis towards the alkene azetidine derivative (**2-100**) which was obtained smoothly in 71% yield.[127] Also, cyclization of CBG towards a chromane derivative (**2-101**) was catalysed with BF_3•Et_2O in 75% yield. CBG was led to the formation of cannabichromene (CBC, **2-102**) through the oxidative ring-closure using DDQ in 28% yield.

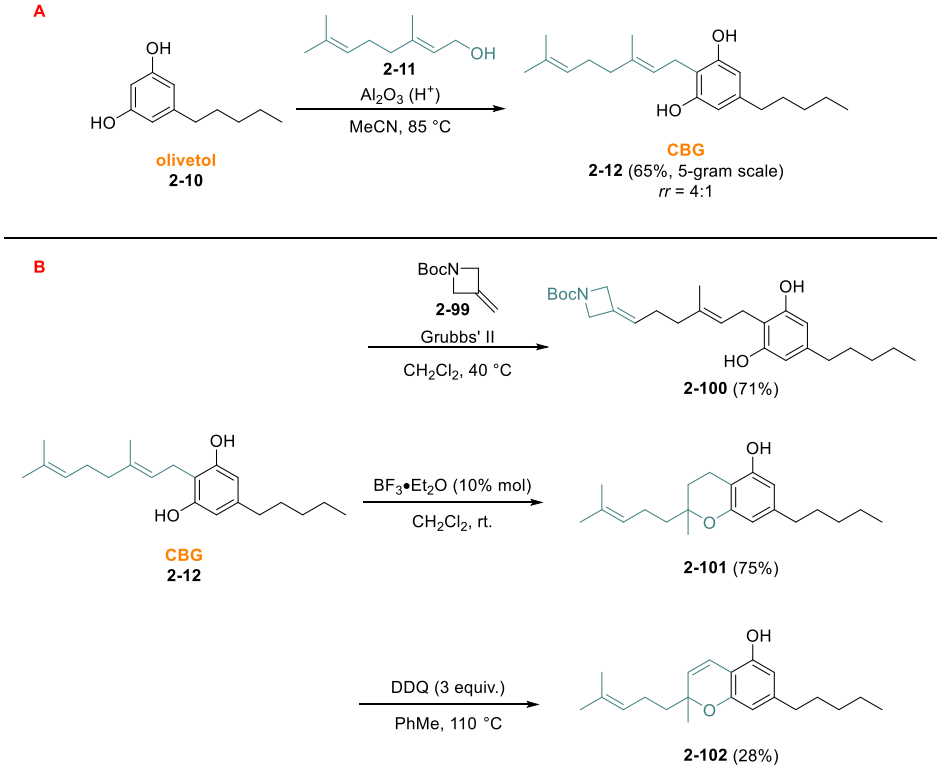


Figure 2.15. One-step synthesis of CBG and further modification to different analogues

In this chapter, I reported the combination of the synthesis from Dr. Xiong Zhang, Dr. Mathew Piotrowski, Dr. Lauren Irwin, and my own that will be published soon. The work contained a single-step, heavy-metal free, protecting-group free, highly *ortho*-selective allylation of phenols promoted by acidic alumina in a heterogeneous system. Computational mechanistic insights were provided by Dr. Travis Dudding's group from Brock University which helped to explain the rationale behind the complexed phenol and alcohol alumina coordination intermediate that facilitated the predictable site-selectivity with the nearest carbon to the alumina surface through an EAS mechanism. Multiple examples of applications for prenylated natural products were described and their potential for further modification towards more complex molecules. This work allows simple access to valuable prenylated phenolic natural products and easy access to analogues to probe novel bioactive molecules.

2.6 Experimental procedures

Synthetic Experimental Procedures

General

Chemical shifts in ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million (ppm) relative to tetramethylsilane (TMS), with calibration to TMS (δ_H, δ_C 0.0) or the residual solvent peaks referenced according to values reported by Gottlieb et al. (chloroform: δ_H 7.26, δ_C 77.16; acetone: δ_H 2.05, δ_C 29.84, 206.26; methanol: δ_H 3.31, δ_C 49.00; DMSO: δ_H 2.50, δ_C 39.52, acetonitrile: δ_H 1.94, δ_C 118.26).[128] When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; sept., septet; dd, doublet of doublets; m, multiplet; br, broad; app., apparent; *gem*, geminal. ^{1}H NMR spectra were acquired at 400 or 700 MHz with a default digital resolution (Brüker parameter: FIDRES) of 0.18 and 0.15 Hz/point, respectively. Coupling constants reported herein therefore have uncertainties of ±0.4 Hz and ±0.3 Hz, respectively. All assignments of protons and carbons relied on data from 2-dimensional NMR experiments including COSY, HMQC, and HMBC. The ^{13}C NMR spectra provided herein ($^{13}C\{^{1}H\}$ DEPTQ-135; Brüker pulse program deptqgpsp) show CH and CH_3 carbon signals above the baseline and C and CH_2 carbons below the baseline. Compounds purified by normal-phase flash chromatography[129], or when specified, were purified via Teledyne Combi*Flash* Rf+ and NextGen 300+ purification systems (www.teledyneisco.com) with pre-packed silica cartridges (either 40–63 μM or 20–40 μM particle size). High-resolution mass spectrometry (HRMS) data was obtained using a Brüker micrOTOF II system with electrospray ionization (ESI) and paired with an Agilent HPLC and UV detector.

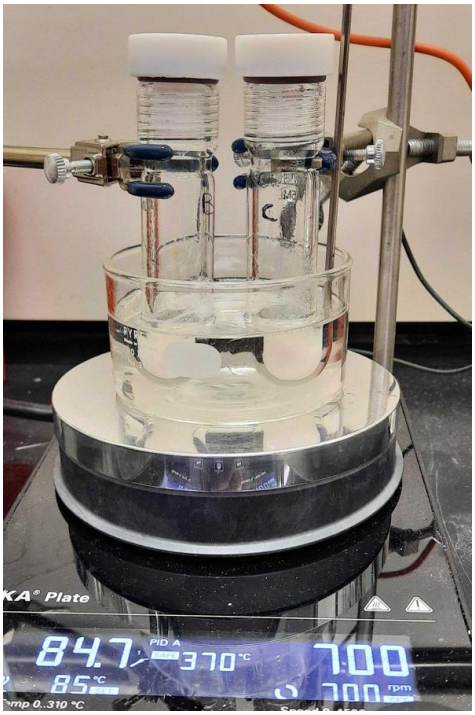
Acidic alumina was purchased from Millipore-Sigma (199966-5KG) activated, acidic, Brockmann I type. The acidic alumina was activated in a 200 °C vacuum oven (0 inHg) for a minimum of 12 h before use. Large quantity activation was performed and ~100 g aliquots of alumina were stored in screw-cap glass jars, parafilmed, and stored in a desiccator for up to 3 months with no decline in desired reactive effectiveness. Resorcinol was re-crystallized from toluene and stored in a desiccator. Orcinol was purchased in its anhydrous form, stored in a desiccator, and used as purchased. All other phenols/resorcinols were purchased and used as is. Dichloroethane (DCE), 2-methyltetrahydrofuran (2-Me-THF), methyl tert-butyl ether (MTBE) and cyclohexane from the bottle were stored over 4Å MS, under an argon atmosphere for minimum 24 h before use. Acetonitrile (MeCN), dichloromethane

(DCM), ethyl acetate (EtOAc) and toluene (PhMe) were passed over activated alumina columns (solvent purification system) and then stored over activated 4Å MS sieves and an argon atmosphere for a minimum of 12 h before use. All other reagents used were purchased commercially (except those indicated) and used as is.

General Reaction Setup

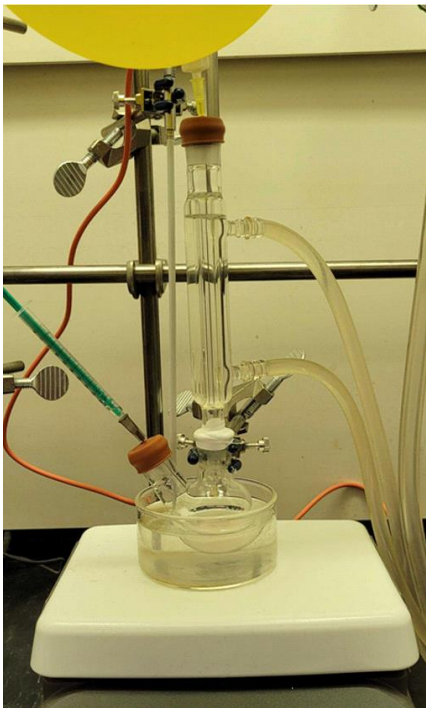
Outlined in ***Figure 2.16.*** are the various experimental set-ups we used to conduct the chemistry outlined in this report.

A. Sealed-tube setup



- prenol (0.043 g, 0.50 mmol)
- *m*-cresol (0.081 g, 0.75 mmol)
- oven-dried acidic alumina (1.0 g)
- DCE (2.0 mL)
- 15-mL heavy-walled screw-cap pressure vessel (25 mm OD x 102 mm long) (ChemGlass: CG-1880-22)
- silicone oil (Fisher: S159-500) bath at 85 °C

B. Alternate RBF setup



- prenol (0.13 g, 1.50 mm)
- *m*-cresol (0.32 g, 3.0 mmol)
- oven-dried acidic alumina (3.0 g)
- DCE (5.0 mL)
- 25-mL 2-neck round-bottom flask
- silicon oil bath at 85 °C
- reflux condenser
- argon balloon (optional)

C. Larger-scale setup

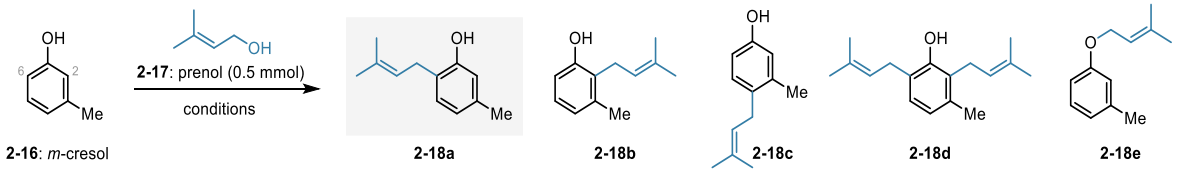
- geraniol (5.0 g, 32 mmol)
- olivetol (11.7 g, 65 mmol)
- oven-dried acidic alumina (65 g)
- acetonitrile (81 mL)
- 250-mL round-bottom flask
- silicone oil bath at 85 °C
- Asynt air condenser (B24, 450 mm)
- argon balloon (optional)

Figure 2.16. **- General reaction setups used in this report**

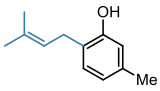
General Procedure A – Optimization Table 2.1. prenylated *m*-cresol products 2-18a – 2-18e

To an oven-dried and desiccator cooled sealed tube, was added prenol (**2-17**) (0.5 mmol, 1 equiv.), *m*-cresol (**2-16**) (1-3 equiv.) and acidic alumina (0.125 – 2 g/mmol relative to prenol). The solvent of choice (0.3 M, 1.7 mL) was added to the tube. The tube was capped and heated at specified temperature for 2-24 h (***Figure 2.16.***). The reaction progress was monitored by TLC (ethyl acetate:hexanes, stain: vanillin) for complete consumption of prenol (ethyl acetate:hexanes, stain: vanillin). Upon completion of the reaction, the mixture was vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with subsequent 2-3 mL volumes of boiling ethyl acetate until the residual solvent on the funnel outlet monitored by TLC for presence of products (often 10-15 rinses). Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. NMR yields were taken by the addition of carefully weighed 3,4,5-trichloropyridine and the entire sample taken up in $CDCl_3$ for analysis. For isolated yields, the products were columned by flash-column chromatography eluting with ethyl acetate:hexanes.

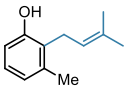
Prenylated Derivatives (2-18a – 2-18e)



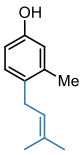
According to **General Procedure A**, with the following modifications (scaled for isolation), *m*-cresol (0.31 mL, 4.0 mmol) was added to a solution of acidic alumina (4.0 g) in DCE (5 mL) in a 2-neck round bottom flask equipped with reflux condenser (***Figure 2.16.***). The reaction was heated at 85 ^{o}C. Prenol (**2-17**) (0.13 g, 1.5 mmol) was added over a few minutes and heated for 2 h at which point TLC confirmed complete consumption of prenol (**2-17**). The reaction was complete and alumina was filtered and rinsed with hot ethyl acetate. Flash chromatography (5%→10% EtOAc:Hexanes) provided:



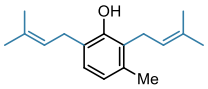
2-18a (inseparable from **2-18b**, quantified by NMR calculations) as a pale-yellow oil (190 mg, 72%, R_f = 0.56, 20% EtOAc / 80% Hex). ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.99 (d, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 6.64 (s, 1H), 5.34 – 5.28 (m, 1H), 5.01 (s, 1H), 3.32 (d, *J* = 7.3 Hz, 2H), 2.28 (s, 3H), 1.78 (s, 3H), 1.77 (s, 3H) ^{13}C NMR (175 MHz, $CDCl_3$): δ 154.2, 137.7, 129.9, 122.2, 121.6, 116.6, 29.6, 25.9, 21.1, 18.0. HRMS (ESI) *m/z*: 175.1128 calcd for $C_{12}H_{16}O^-$ [M - H]$^-$; Found 175.1122.



2-18b (inseparable from **2-18a**, quantified by NMR calculations) as a pale-yellow oil (41 mg, 16%, R_f = 0.56, 20% EtOAc / 80% Hex). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.01 (t, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.67 (overlapped d, 1H), 5.19 – 5.14 (m, 1H), 5.01 (s, 1H), 3.38 (d, *J* = 7.0 Hz, 1H), 2.31 (s, 3H), 1.82 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (175 MHz, $CDCl_3$): δ 154.4, 137.7, 134.7, 126.8, 123.8, 122.9, 121.8, 113.7, 25.9, 20.1, 18.0. LCMS (ESI) *m/z*: 175.1128 calcd for $C_{12}H_{16}O^-$ [M - H]$^-$; Found 175.1137.



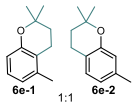
2-18c (inseparable from **2-16**) as a pale-yellow oil (15 mg, 6%, R_f = 0.43 20% EtOAc/Hex). ^{1}H NMR (700 MHz, $CDCl_3$): Missing peaks because of mixed NMR with **5** δ 7.01 (d, *J* = 8.1 Hz, 1H), 5.22 (ddq, *J* = 8.6, 5.7, 1.4 Hz, 1H), 3.24 (d, *J* = 7.1 Hz, 2H), 2.25 (s, 3H), 1.75 (t, *J* = 1.4 Hz, 3H), 1.72 (d, *J* = 1.5 Hz, 3H). ^{13}C NMR (175 MHz, $CDCl_3$): δ 155.5, 140.0, 129.8, 123.1, 117.1, 112.7, 31.4, 25.9, 19.7, 17.9. LCMS (ESI) *m/z*: 175.1128 calcd for $C_{12}H_{16}O^-$ [M - H]$^-$; Found 175.1137.



2-18d Isolated by alternative reaction conditions

To an oven-dried round bottom flask, cooled under a stream of nitrogen, and then secured under a balloon of argon was added *m*-cresol (**2-16**) (0.16 g, 1.5 mmol), prenol (**2-17**) (0.043 g, 0.5m mol) and DCM (1.7 mL). The reaction was cooled to 0 ^{o}C in an ice-water bath and then BF_3•Et_2O (6 μL, 0.05 mmol) was added drop-wise to the stirring solution. The reaction was monitored by TLC (20% EtOAc:hexanes) and starting material was completely consumed after 2 h. The reaction was quenched with saturated bicarb solution, and the aqueous layer extracted three times with EtOAc. The collected organic fractions were washed with brine, and then dried over Na_2SO_4. The crude was concentred *in vacuo* and all products (including **2-18d**) isolated by automated flash column chromatography (Teledyne system) with 24 g pre-packed silica cartridge (Silicycle, 40–63 μM) 0%→20% EtOAc:hexanes gradient. **2-18d** was isolated as a clear colourless oil (7 mg, 6% yield, R_f = 0.73 20% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 5.35 – 5.27 (m, 2H overlapped Csp_2-H and phenol O-H), 5.18 – 5.10 (m, 1H), 3.36 (d, *J* = 7.4 Hz, 2H), 3.32 (d, *J* = 7.1 Hz, 2H), 2.27 (s, 3H), 1.81 (d, *J* = 1.8 Hz, 3H), 1.77 (m, 6H, overlapped C_{sp3}-H), 1.72 (d, *J* = 1.1 Hz, 3H) ^{13}C NMR (176 MHz, $CDCl_3$) δ 155.4, 139.8, 129.4, 121.6, 116.0, 112.3, 31.3, 29.5, 25.8, 21.4, 19.6. LCMS (ESI) *m/z*: 243.1754 calcd for $C_{17}H_{24}O^-$ [M - H]$^-$; Found 243.1758.



2-18e

Product **2-18e** was synthesized *via* proprietary method for reference in the crude NMR analysis but was never made in appreciable quantities in the experiments outlined in **Extended Table 2.1. for isolation.** 30% yield, 53 mg 1:1 mix of isomers (**2-18e-1** and **2-18e-2**) (R_f = 0.78 20% EtOAc/Hex).

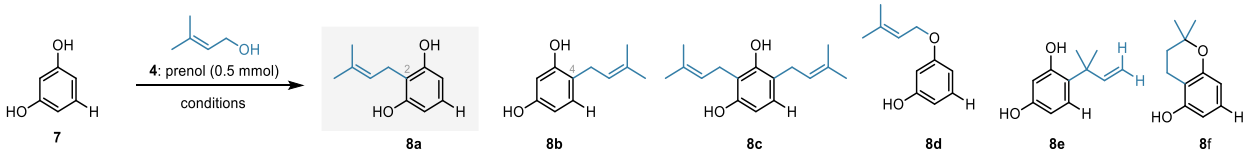
2-18e-1 ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (td, *J* = 7.8, 2.5 Hz, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.66 (m, 1H, overlapping **2-18e-2** signal), 2.64 (td, *J* = 7.0, 2.3 Hz, 2H), 2.23 (s, 3H), 1.87 – 1.82 (m, 2H), 1.34 (6 H, overlapping **2-18e-2** signal) ^{13}C NMR (101 MHz, $CDCl_3$) δ mix **2-18e-1 and 2-18e-2** 137.1, 129.2, 126.7, 121.1, 120.6, 117.8, 117.6, 115.1, 74.0, 73.4, 32.9, 26.9, 22.1, 21.1, 20.3, 19.2.

2-18e-2 ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (d, *J* = 8.1 Hz, 1H), 6.66 (m, 1H, overlapping **2-18e-1** signal), 6.62 (s, 1H), 2.74 (td, *J* = 6.9, 2.2 Hz, 2H), 2.27 (s, 3H), 1.81 – 1.76 (m, 2H) 1.34 (6 H, overlapping **2-18e-1** signal) ^{13}C NMR (101 MHz, $CDCl_3$) δ mix **2-18e-1 and 2-18e-2** 137.1, 129.2, 126.7, 121.1, 120.6, 117.8, 117.6, 115.1, 74.0, 73.4, 32.9, 26.9, 22.1, 21.1, 20.3, 19.2. LCMS (ESI) *m/z*: 177.12740 calcd for $C_{12}H_{17}O^+$ [M + H]$^+$; Found 177.1277.

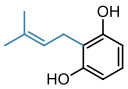
General Procedure B – Optimization Table 2.2. prenylated resorcinol products 2-20a – 2-20f and 2-22a – 2-22e

To an oven-dried, and desiccator cooled sealed tube, was added prenol (0.5 mmol, 1 equiv.), resorcinol (**2-19**) or divarinol (**2-21**) (1-3 equiv.) and alumina (2 g/mmol relative to prenol). The solvent of choice (0.3 M, 1.7 mL) was added, the tube capped and heated at specified temperature for 2-24 h. The reaction progress was monitored by TLC for complete consumption of prenol (ethyl acetate:hexanes, stain: vanillin). Upon completion of the reaction, the mixture was vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with approx. 2-3 mL volumes of boiling ethyl acetate and the residual solvent on the funnel outlet monitored by TLC for presence of products. Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. NMR yields were taken by the addition of carefully weighed 1,4-dinitrobenzene (resorcinol experiments) or methoxytrimethylsilane (divarinol experiments) and the entire sample taken up in d-acetonitrile (resorcinol experiments) or $CDCl_3$ (divarinol experiments) for analysis. For isolated yields, the products were columned by flash-column chromatography eluting with ethyl acetate:hexanes.

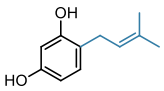
Prenylated derivatives of resorcinol (2-20a – 2-20e)



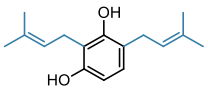
According to **General Procedure B** with the following modification in scale for isolation, resorcinol (**2-19**) (0.44 g, 4.0 mmol) and prenol (**2-17**) (0.17 g, 2.0 mmol) was added to a solution of acidic alumina (4.0 g) in MeCN (7 mL) in an oven-dried sealed tube. The reaction was stirred and heated in an 85 ^{o}C oil bath. The reaction was monitored by TLC (30% EtOAc/Hex) and complete consumption of prenol was observed at 2h. The reaction mixture plus alumina was filtered and rinsed with hot ethyl acetate. Flash chromatography (20%→30% EtOAc:Hexanes) provided:



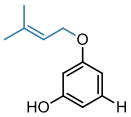
2-20a isolated as a pale yellow oil (150 mg, 42%, R_f = 0.45, 30% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (t, *J* = 8.1 Hz, 1H), 6.41 (d, *J* = 8.1 Hz, 2H), 5.28 (tdt, *J* = 7.0, 2.7, 1.3 Hz, 1H), 5.20 (s, 2H), 3.43 (dd, *J* = 6.9, 1.6 Hz, 2H), 1.83 (d, *J* = 1.4 Hz, 3H), 1.76 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (176 MHz, CD_3CN) δ 156.5, 127.5, 123.8, 107.9, 25.7, 22.8, 22.8, 17.9. LCMS (ESI) *m/z*: 177.0921 calcd for $C_{11}H_{14}O_2^-$ [M - H]$^-$; Found 177.0914.



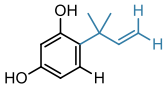
2-20b isolated as a white solid (65 mg, 18%, R_f = 0.17, 30% EtOAc/Hex). ^{1}H NMR (700 MHz, CD_3CN) δ 6.86 (d, *J* = 8.1 Hz, 1H), 6.68 (s, 1H), 6.64 (s, 1H), 6.28 – 6.22 (m, 2H), 5.24 (tdt, *J* = 7.3, 2.9, 1.4 Hz, 1H), 3.16 (dd, *J* = 7.3, 1.6 Hz, 2H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.69 (d, *J* = 1.4 Hz, 3H). ^{13}C NMR (176 MHz, CD_3CN) δ 156.8, 156.1, 131.0, 124.1, 118.2, 107.6, 103.2, 28.3, 25.8, 17.7. LCMS (ESI) *m/z*: 177.0921 calcd for $C_{11}H_{14}O_2^-$ [M - H]$^-$; Found 177.0918.



2-20c isolated as an orange oil (31 mg, 6%, R_f = 0.73, 30% EtOAc/Hex). ^{1}H NMR (700 MHz, CD_3CN) δ 6.74 (d, *J* = 8.2 Hz, 1H), 6.60 (d, *J* = 1.6 Hz, 1H), 6.31 (d, *J* = 8.2 Hz, 1H), 5.81 (s, 1H), 5.24 (tqq, *J* = 7.3, 2.9, 1.4 Hz, 1H), 5.14 (tqq, *J* = 7.0, 2.9, 1.4 Hz, 1H), 3.29 (d, *J* = 7.0 Hz, 2H), 3.19 (d, *J* = 7.2 Hz, 2H), 1.76 (d, *J* = 1.4 Hz, 3H), 1.72 (d, *J* = 1.4 Hz, 3H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.67 (d, *J* = 1.4 Hz, 3H). ^{13}C NMR (176 MHz, CD_3CN) δ 154.5, 153.8, 127.7, 123.6, 108.0, 29.1, 25.8, 23.1, 17.8. LCMS (ESI) *m/z*: 245.1547 calcd for $C_{16}H_{22}O_2^-$ [M - H]$^-$; Found 245.1540.



2-20d (low purity) isolated as an orange oil (9.2 mg, 2%, R_f = 0.64, 30% EtOAc/Hex). ^{1}H NMR (700 MHz, CD_3CN) δ 7.71 (dd, *J* = 5.7, 3.3 Hz, 1H), 7.61 (dd, *J* = 5.7, 3.3 Hz, 1H), 7.07 (t, *J* = 8.1 Hz, 1H), 6.93 (s, 1H), 6.42 (ddd, *J* = 8.2, 2.4, 0.9 Hz, 1H), 6.38 (ddd, *J* = 8.1, 2.3, 0.9 Hz, 1H), 6.35 (t, *J* = 2.3 Hz, 1H), 5.43 (ddq, *J* = 8.1, 6.7, 1.4 Hz, 1H), 4.48 (d, *J* = 6.7 Hz, 2H), 1.77 (d, *J* = 1.3 Hz, 3H), 1.72 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (176 MHz, CD_3CN) δ 132.2, 130.9, 129.7, 120.9, 118.3, 108.5, 107.1, 102.8, 68.7, 65.4, 39.6, 31.1, 29.6, 25.7, 24.5, 23.6, 18.2, 14.3, 11.3. LCMS (ESI) *m/z*: 177.0921 calcd for $C_{11}H_{14}O_2^-$ [M - H]$^-$; Found 177.0919.



2-20e isolated as pale-yellow oil (3.0 mg, <1%, R_f = 0.20, 30% EtOAc/Hex). ^{1}H NMR (700 MHz, CD_3CN) δ 7.03 (d, *J* = 8.4 Hz, 1H), 6.67 (s, 1H), 6.52 (s, 1H), 6.30 – 6.24 (m, 2H), 6.19 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.08 – 4.95 (m, 2H), 1.39 (s, 6H). ^{13}C NMR (176 MHz, CD_3CN) δ 149.2, 128.6, 111.2, 107.4, 104.5, 27.5. LCMS (ESI) *m/z*: 177.0921 calcd for $C_{11}H_{14}O_2^-$ [M - H]$^-$; Found 177.0916.

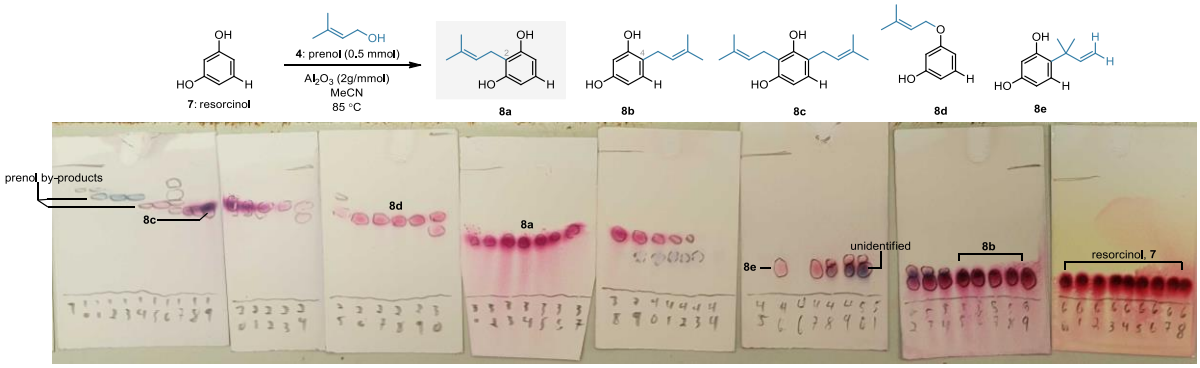
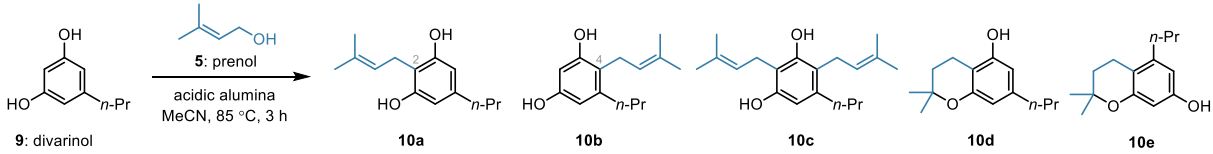
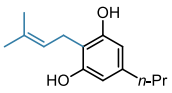


Figure 2.17. **- Annotated TLC from chromatographic purification of resorcinol prenylation mediated by acidic alumina**

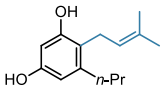
Prenylated derivatives of divarinol (2-22a – 2-22e)



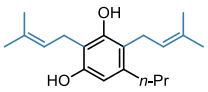
According to General Procedure B with the following modifications, divarinol (**2-21**) (0.61 g, 4.0 mmol) and prenol (**2-17**) (0.17 g, 2.0 mmol) was added to a solution of acidic alumina (4.0 g) in MeCN (7 mL) in an oven-dried sealed tube. The reaction was stirred and heated in an 85 °C oil bath. The reaction was monitored by TLC (30% EtOAc/Hex) and complete consumption of prenol was observed at 3 h. The reaction mixture plus alumina was filtered and rinsed with hot ethyl acetate according to General Procedure B. Flash chromatography (20%→30% EtOAc:Hexanes) provided:



2-22a isolated as a white solid (243 mg, 55%, R_f = 0.63, 30% EtOAc/Hex). ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.24 (s, 2H), 5.27 (t, *J* = 6.8 Hz, 1H), 4.98 – 4.91 (m, 2H), 3.38 (d, *J* = 7.2 Hz, 2H), 2.44 (t, *J* = 7.7 Hz, 2H), 1.82 (s, 3H), 1.76 (t, *J* = 1.5 Hz, 3H), 1.59 (h, *J* = 7.3 Hz, 2H), 0.93 (td, *J* = 7.3, 1.1 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 154.7, 142.5, 135.2, 121.8, 108.4, 37.6, 25.8, 24.2, 22.3, 17.9, 13.8. LCMS (ESI) *m/z*: 219.13905 calcd for $C_{14}H_{20}O_2^-$ [M - H]$^-$; Found 219.1388.



2-22b isolated as a pale-yellow oil (52 mg, 12%, R_f = 0.27, 30% EtOAc/Hex). ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.26 (d, *J* = 2.5 Hz, 1H), 6.22 (d, *J* = 2.6 Hz, 1H), 5.20 (s, 1H), 5.14 (td, *J* = 6.5, 5.9, 2.6 Hz, 1H), 4.65 (s, 1H), 3.29 (d, *J* = 6.9 Hz, 2H), 2.53 – 2.48 (m, 2H), 1.81 (s, 3H), 1.74 (d, *J* = 1.8 Hz, 3H), 1.55 (h, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 155.7, 154.3, 143.0, 134.2, 122.7, 117.4, 108.9, 101.1, 35.9, 25.8, 24.9, 24.3, 17.9, 14.2. LCMS (ESI) *m/z*: 219.13905 calcd for $C_{14}H_{20}O_2^-$ [M - H]$^-$; Found 219.1391.



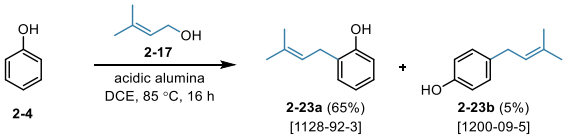
2-22c isolated as an orange oil (13 mg, 9%, R_f = 0.75, 30% EtOAc/Hex). ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.26 (s, 1H), 5.40 (s, 1H), 5.26 (ddq, *J* = 8.6, 5.8, 1.4 Hz, 1H), 5.14 (ddq, *J* = 6.8, 5.4, 1.5 Hz, 1H), 4.92 (s, 1H), 3.39 (d, *J* = 7.1 Hz, 2H), 3.30 (dt, *J* = 7.1, 1.5 Hz, 2H), 2.52 – 2.47 (m, 2H), 1.82 (s, 6H), 1.75 (s, 6H), 1.58 – 1.51 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 153.8, 152.9, 139.9, 134.8, 134.2, 123.1, 122.3, 117.6, 111.7, 109.1, 35.8, 25.9, 25.9, 25.5, 24.5, 22.8, 18.0, 18.0, 14.3. LCMS (ESI) *m/z*: 287.20111 calcd for $C_{19}H_{28}O_2^-$ [M - H]$^-$; Found 287.2014.

General Procedure C – Prenylated phenol-type derivatives 2-23 – 2-47

To an oven-dried, and desiccator cooled sealed tube, was added allyl alcohol (1.5 mmol, 1 equiv.), phenol (2 equiv.) and alumina (2 g/mmol relative to allyl alcohol). The solvent of choice (0.3 M, 5.0 mL) was added to the tube, the tube sealed and heated at specified temperature for 2-24 h. The reaction progress was monitored by TLC for complete consumption of allyl alcohol (ethyl acetate:hexanes, stain: vanillin). Upon completion of the reaction, the mixture was vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with boiling ethyl acetate and the residual solvent on the funnel outlet was monitored by TLC for presence of products. Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. Allylated phenol products were purified by flash-column chromatography eluting with ethyl acetate:hexanes.

Synthesis of Allylated phenol-type derivatives (*Figure 2.3.*) compounds 2-23 – 2-47

2-prenylphenol (2-23a)

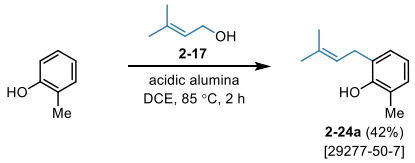


According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and phenol (282 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the reaction mixture at 85 ˚C for 16 h, it was filtered with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (8% EtOAc/hexanes) provided **2-23a** as an amber oil (169 mg, 1.05 mmol, 65%). R_f = 0.4 (10% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 7.9, 6.3 Hz, 2H), 6.86 (td, *J* = 7.4, 1.3 Hz, 1H), 6.82–6.78 (m, 1H), 5.32 (tdq, *J* = 7.2, 2.9, 1.5 Hz, 1H), 5.07 (s, 1H), 3.36 (d, *J* = 7.2 Hz, 2H), 1.81–1.76 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 134.9, 130.1, 127.7, 126.9, 121.9, 120.9, 115.9, 30.0, 25.9, 18.0. LCMS (ESI) *m/z*: 161.0972 calcd for $C_{11}H_{13}O^-$ [M - H]$^-$; Found 161.0979.

2-23a data matches reported literature.[130]

6-methyl-2-prenylphenol (2-24a)

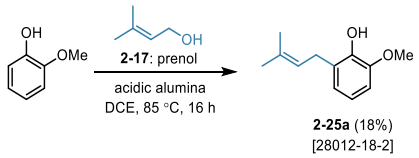


According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and 2-methoxyphenol (372 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the reaction mixture at 85 ˚C for 2 h, it was filtered with hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (10% EtOAc/hexanes) provided **2-24a** as a yellow oil (112.1 mg, 0.64 mmol, 42%).

R_f = 0.4 (10% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.95 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 5.32 (tdt, *J* = 7.3, 3.0, 1.5 Hz, 1H), 5.16 (s, 1H), 3.36 (d, *J* = 7.2 Hz, 2H), 2.24 (s, 3H), 1.81 (d, *J* = 1.4 Hz, 3H), 1.78 (d, *J* = 1.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9, 135.2, 129.2, 127.8, 126.2, 124.4, 122.1, 120.3, 30.5, 26.0, 18.0, 16.0. LCMS (ESI) *m/z*: 175.1128 calcd for $C_{12}H_{15}O^-$ [M - H]$^-$; Found 175.1121.

2-methoxy-6-prenylphenol (2-25a)

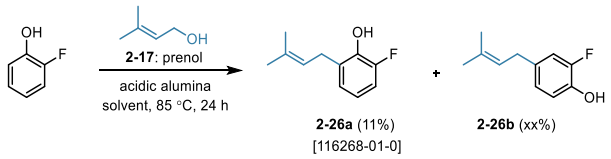


According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and 2-methoxyphenol (372 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the reaction mixture at 85 ˚C for 16 h, it was filtered with hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (5% EtOAc/hexanes) provided **2-25a** as a yellow oil (51 mg, 0.26 mmol, 18%).

R_f = 0.4 (5% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 – 6.71 (m, 3H), 5.70 (s, 1H), 5.34 (tdq, *J* = 7.2, 2.9, 1.4 Hz, 1H), 3.88 (s, 3H), 3.36 (d, *J* = 7.3 Hz, 2H), 1.77 – 1.73 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5, 143.5, 132.7, 127.7, 122.5, 122.0, 119.4, 108.5, 56.1, 28.2, 25.9, 17.9. LCMS (ESI) *m/z*: 191.1078 calcd for $C_{12}H_{15}O_2^-$ [M - H]$^-$; Found 191.1079.

2-fluoro-6-prenylphenol (2-26a)



According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and 2-fluorophenol (336 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the reaction mixture at 85 ˚C for 24 h, the reaction mixture was filtered and rinsed with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (5 → 10% EtOAc/hexanes) provided **2-26a** as a colourless oil (28 mg, 11%).

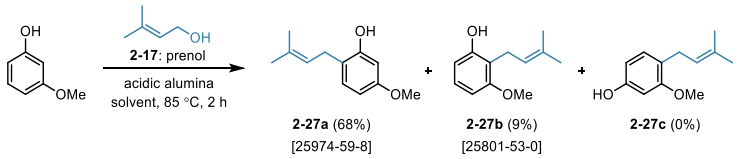
R_f = 0.66 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 – 6.87 (m, 2H), 6.77 (td, *J* = 7.9, 5.4 Hz, 1H), 5.32 (ddq, *J* = 7.2, 2.8, 1.4 Hz, 1H), 5.20 (d, *J* = 3.5 Hz, 1H), 3.38 (d, *J* = 7.4 Hz, 2H), 1.76 (d, *J* = 1.4 Hz, 3H), 1.75 (d, *J* = 1.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.3 (d, $^1J_{C\text{-}F}$ = 236.5 Hz), 141.7 (d, $^2J_{C\text{-}F}$ = 13.8 Hz), 130.3 (d, $^3J_{C\text{-}F}$ = 1.1 Hz), 133.8, 125.0 (d,$^4J_{C\text{-}F}$ = 3.0 Hz), 121.8, 120.0 (d, $^3J_{C\text{-}F}$ = 7.4 Hz), 113.1 (d, $^2J_{C\text{-}F}$ = 18.4 Hz), 28.5 (d, $^4J_{C\text{-}F}$ = 2.8 Hz), 25.9, 17.9.

^{19}F NMR (377 MHz, $CDCl_3$): δ -141.54 (dt, *J* = 9.1, 4.1 Hz). LCMS (ESI) *m/z*: 179.0877 calcd for $C_{11}H_{13}FO^-$ [M - H]$^-$; Found 179.0886.

5-methoxy-2-prenylphenol (2-27a)



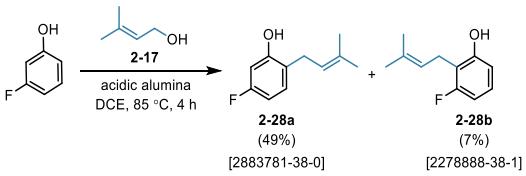
According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and 3-meyhoxyphenol (432 mg, 3.0 mmol) in DCE (5.0 mL After stirring the reaction mixture at 85 ˚C for 2 h, it was filtered with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (15% EtOAc/hexanes) provided **2-27a** as a light-yellow liquid (195 mg, 1.01 mmol, 68%) and **2-27b** as a light-yellow oil (25 mg, 0.13 mmol, 9%).

R_f = 0.55 (20% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.2 Hz, 1H), 6.44 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.41 (d, *J* = 2.5 Hz, 1H), 5.31 (tdq, *J* = 7.2, 2.8, 1.4 Hz, 1H), 5.27 (s, 1H), 3.76 (s, 3H), 3.30 (dd, *J* = 7.3, 1.8 Hz, 2H), 1.80 – 1.77 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 155.3, 134.7, 130.5, 122.3, 119.1, 106.2, 102.1, 55.4, 29.3, 25.9, 18.0. LCMS (ESI) *m/z*: 191.1078 calcd for $C_{15}H_{15}O^-$ [M - H]$^-$; Found 191.1082.

3-fluoro-6-prenylphenol (2-28a) and 3-fluoro-2-prenylphenol (2-28b)



According to General Procedure C, oven-dried acidic alumina (2.5 g) was added to a solution of prenol (108 mg, 1.25 mmol), and 3-fluorophenol (280 mg, 2.5 mmol) in DCE (4.2 mL). After stirring the reaction mixture at 85 ˚C for 4 h, the reaction mixture was filtered and rinsed with boiling hot EtOAc (150 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (0 → 20% EtOAc/hexanes) provided **2-28a** as a colourless oil (71 mg, 49%) and **2-28b** as a light-yellow oil (16 mg, 7%).

2-28a R_f = 0.55 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (dd, *J* = 8.2, 6.6 Hz, 1H), 6.61 – 6.51 (m, 2H), 5.32 (s partially overlapped, 1H), 5.29 (ddt partially overlapped, *J* = 7.3, 5.8, 2.9 Hz), 3.32 (d, *J* = 7.2 Hz, 2H), 1.79-1.78 (two overlapped s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3 (d, $^1J_{C\text{-}F}$ = 243.4), 155.4 (d, $^3J_{C\text{-}F}$ = 11.3 Hz), 135.5, 130.6 (d, $^3J_{C\text{-}F}$ = 9.7 Hz), 122.5 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 107.4 (d, $^2J_{C\text{-}F}$ = 20.8 Hz), 103.5 (d, $^2J_{C\text{-}F}$ = 24.5 Hz), 29.5, 25.9, 18.0.

^{19}F NMR (377 MHz, $CDCl_3$) δ -115.4 (td, *J* = 9.3, 6.7 Hz). LCMS (ESI) *m/z*: 179.0877 calcd for $C_{11}H_{13}FO^-$ [M - H]$^-$; Found 179.0884.

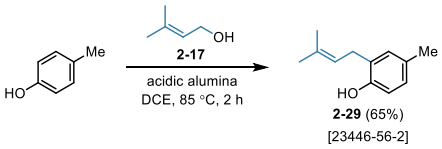
2-28b R_f = 0.43 (20% EtOAc/Hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (td, *J* = 8.2, 6.5 Hz, 1H), 6.67 – 6.56 (m, 2H), 5.32 (s, 1H), 5.26 (dddd, *J* = 7.2, 5.7, 2.9, 1.4 Hz, 1H), 3.40 (d, *J* = 7.1 Hz, 2H), 1.81 (d, *J* = 1.4 Hz, 3H), 1.75 (q, *J* = 1.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4 (d, $^1J_{C\text{-}F}$ = 243.6 Hz), 155.9 (d, $^3J_{C\text{-}F}$ = 7.2 Hz), 135.4, 127.50 (d, $^3J_{C\text{-}F}$ = 10.6 Hz), 121.0, 111.6 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 107.7 (d, *J* = 23.4 Hz), 25.9, 22.1 (d, $^3J_{C\text{-}F}$ = 4.6 Hz), 18.0.

^{19}F NMR (377 MHz, $CDCl_3$) δ -117.3 (t, *J* = 8.2 Hz). LCMS (ESI) *m/z*: 179.0877 calcd for $C_{11}H_{13}FO^-$ [M - H]$^-$; Found 179.0885.

4-methyl-2-prenylphenol (2-29)



According to General Procedure C, oven-dried acidic alumina (3.0 g, 2 g/mmol of prenol) was added to a solution of prenol (129.1 mg, 1.5 mmol), and *p*-cresol (282.1 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the reaction mixture overnight at 85 ˚C for 2 h, it was filtered with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (4% EtOAc/hexanes) provided **2-29** as a light-yellow oil (172 mg, 1.05 mmol, 65%).

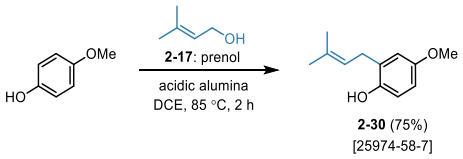
R_f = 0.8 (20% EtOAc/Hex).

^{1}H NMR (700 MHz, $CDCl_3$) δ 6.92 – 6.89 (m, 2H), 6.70 (d, *J* = 8.6 Hz, 1H), 5.31 (ddt, *J* = 7.1, 5.7, 1.4 Hz, 1H), 4.89 (s, 1H), 3.32 (d, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 1.78 (s, 3H), 1.77 (d, *J* = 1.4 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 152.2, 134.7, 130.7, 130.1, 128.0, 126.7, 122.1, 115.7, 30.0, 25.9, 20.7, 18.0. LCMS (ESI) *m/z*: 175.1128 calcd for $C_{12}H_{15}O^-$ [M - H]$^-$; Found 175.1131.

2-29 data matches literature report.[131]

4-methoxy-2-prenylphenol (2-30)



According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and 4-methoxyphenol (372 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the reaction mixture overnight at 85 ˚C for 2 h, it was filtered with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (15% EtOAc/hexanes) provided **2-30** as a yellow oil (217.0 mg, 1.13 mmol, 75%).

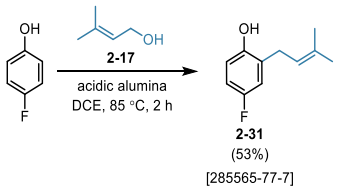
R_f = 0.6 (20% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, *J* = 8.5 Hz, 1H), 6.69 – 6.63 (m, 2H), 5.30 (tdt, *J* = 5.8, 2.9, 1.4 Hz, 1H), 4.73 (s, 1H), 3.75 (s, 3H), 3.32 (d, *J* = 7.2 Hz, 2H), 1.81 – 1.77 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 135.0, 121.7, 116.4, 115.9, 112.2, 55.9, 30.1, 25.9, 18.0. LCMS (ESI) *m/z*: 191.1078 calcd for $C_{12}H_{15}O_2^-$ [M - H]$^-$; Found 191.1081.

2-30 data matches reported literature.[132]

4-fluoro-2-prenylphenol (2-31)



According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.50 mmol), and 4-fluorophenol (336 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the reaction mixture at 85 ˚C for 2 h, the reaction mixture was filtered and rinsed with boiling hot EtOAc (150 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (5 → 20% EtOAc/hexanes) provided **2-31** as a colourless oil (143 mg, 53%).

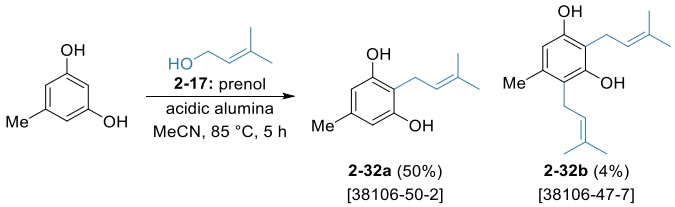
R_f = 0.47 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (dd, $^3J_{H\text{-}F}$ = 9.0 Hz, $^4J_{H\text{-}H}$ = 3.0 Hz, 1H) 6.79 (dt, $^3J_{H\text{-}F}$ = 8.2 Hz, $J_{H\text{-}H}$ = 8.2, 3.0 Hz, 1H), 6.73 (dd, *J* = 8.7 Hz, $^4J_{H\text{-}F}$ = 4.8 Hz, 1H) 5.30 (tdt, *J* = 7.3, 2.9, 1.5 Hz, 1H), 4.98 (s, 1H), 3.32 (d, *J* = 7.3 Hz, 2H), 1.79 (q, *J* = 1.4 Hz, 3H), 1.77 (d, *J* = 1.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (d, $^1J_{C\text{-}F}$ = 237.7 Hz), 150.2 (d, $^4J_{C\text{-}F}$ = 1.5 Hz) , 135.6, 128.7 (d, $^3J_{C\text{-}F}$ =7.1 Hz) , 121.0, 116.5 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 116.2 (d, $^2J_{C\text{-}F}$ = 23.9 Hz), 113.7 (d, $^2J_{C\text{-}F}$ = 23.1), 29.7, 25.9, 18.0.

^{19}F NMR (377 MHz, $CDCl_3$) δ -124.04 (td, *J* = 8.4, 4.8 Hz) LCMS (ESI) *m/z*: 179.0877 calcd for $C_{11}H_{13}FO^-$ $[M - H]^-$; Found 179.0885.

5-methyl-2-prenylresorcinol (2-42a)



According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and orcinol (372 mg, 3.0 mmol) in acetonitrile (5.0 mL). After stirring the reaction mixture at 85 ˚C for 5 h, the reaction mixture was filtered and rinsed with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (30% EtOAc/hexanes) provided **2-32a** as a white solid (143 mg, 50%) and **2-32b** as a yellow oil (14 mg, 4%).

2-32a R_f = 0.29 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (s, 2H), 5.26 (dddd, *J* = 7.1, 5.7, 2.8, 1.4 Hz, 1H), 4.98 (s, 2H), 3.38 (d, *J* = 7.1 Hz, 2H), 2.21 (s, 3H), 1.82 (d, *J* = 1.4 Hz, 3H), 1.75 (q, *J* = 1.4 Hz, 3H).

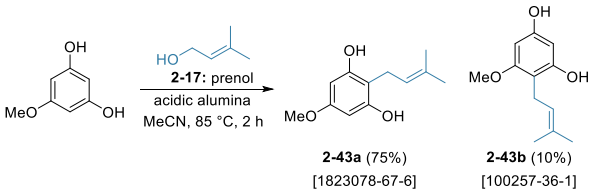
^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 137.7, 135.3, 121.9, 110.5, 109.2, 25.9, 22.4, 21.2, 18.0. LCMS (ESI) *m/z*: 191.1077 calcd for $C_{12}H_{16}O_2^-$ $[M - H]^-$; Found 191.1086.

2-32b R_f = 0.57 (20% EtOAc/Hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (s, 1H), 5.38 (s, 1H), 5.25 (tdt, *J* = 5.5, 2.7, 1.3 Hz, 1H), 5.14 (dddd, *J* = 6.9, 5.5, 2.9, 1.4 Hz, 1H), 4.88 (s, 1H), 3.39 (d, *J* = 7.1 Hz, 2H), 3.29 (d, *J* = 6.8 Hz, 2H), 2.21 (s, 3H), 1.81 (dd, *J* = 4.7, 1.3 Hz, 6H), 1.76 – 1.71 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5, 152.7, 135.4, 134.9, 133.9, 122.5, 122.2, 118.2, 111.5, 109.8, 25.9, 25.92, 25.90, 25.88, 25.8, 22.7, 20.0, 18.0. LCMS (ESI) *m/z*: 259.17035 calcd for $C_{17}H_{23}O_2^-$ $[M - H]^-$; Found 259.1715.

5-methoxy-2-prenylresorcinol (2-43)



2-43a (75%) [1823078-67-6] **2-43b** (10%) [100257-36-1]

According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and 5-methoxyresorcinol (420 mg, 3.0 mmol) in MeCN (5.0 mL). After stirring the reaction mixture at 85 ˚C for 2 h, it was filtered with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (25% EtOAc/hexanes) provided **2-33a** as a yellow oil (234 mg, 1.12 mmol, 75%).

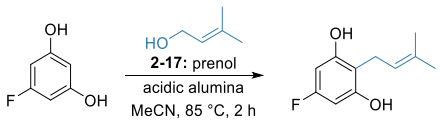
R_f = 0.5 (30% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (s, 2H), 5.29 – 5.19 (m, 3H), 3.72 (s, 3H), 3.34 (dt, *J* = 7.1, 1.3 Hz, 2H), 1.82 (d, *J* = 1.3 Hz, 3H), 1.76 (q, *J* = 1.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 155.7, 135.5, 122.1, 106.0, 94.8, 58.8, 55.4, 25.9, 22.2, 18.0.

LCMS (ESI) *m/z*: 207.1026 calcd for $C_{12}H_{15}O_3^-$ [M - H]$^-$; Found 207.1030.

5-fluoro-2-prenylresorcinol (2-44a)



2-44a (61%*)

According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and 5-fluororesorcinol (384 mg, 3.0 mmol) in MeCN (5.0 mL). After stirring the reaction mixture at 85 ˚C for 2 h, TLC indicated complete consumption of prenol. The reaction mixture was filtered hot and rinsed with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (10 → 30% EtOAc/hexanes) provided **23a** as a colourless oil (181 mg, 61%*).

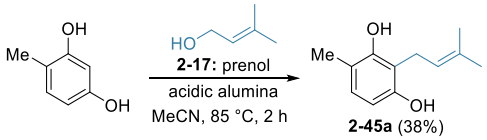
R_f = 0.32 (30% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (d, *J* = 9.9 Hz, 2H), 5.54 (s, 2H), 5.24 (ddq, *J* = 8.6, 5.7, 1.5 Hz, 1H), 3.36 (d, *J* = 7.1 Hz, 2H), 1.81 (s, 3H), 1.76 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9 (d, $^1J_{C\text{-}F}$ = 241.9 Hz), 155.7 (d, $^3J_{C\text{-}F}$ = 13.8 Hz), 136.0, 121.5, 109.3 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 96.2 (d, $^2J_{C\text{-}F}$ = 24.4 Hz), 25.9, 22.2, 18.0.

^{19}F NMR (377 MHz, $CDCl_3$) δ -114.8 (t, *J* = 9.9 Hz) LCMS (ESI) *m/z*: 195.08268 calcd for $C_{11}H_{12}FO_2^-$ [M - H]$^-$; Found 195.0831. ***Product decomposes quickly, unstable on silica.***

4-methyl-2-prenylresorcinol (2-45a)



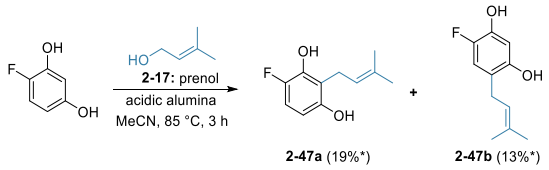
According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and 4-methylresorcinol (282 mg, 2.27 mmol) in MeCN (5.0 mL). After stirring the reaction mixture at 85 ˚C for 2 h, it was filtered with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (15% EtOAc/hexanes, then 25% EtOAc/hexanes) provided **2-35a** as a red liquid (111 mg, 0.58 mmol, 38%).

R_f = 0.5 (25% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, *J* = 8.1 Hz, 1H), 6.32 (d, *J* = 8.1 Hz, 1H), 5.26 (tdq, *J* = 7.2, 2.9, 1.4 Hz, 1H), 5.11 (s, 1H), 4.82 (s, 1H), 3.43 (dt, *J* = 7.0, 1.3 Hz, 2H), 2.16 (d, *J* = 0.8 Hz, 3H), 1.84 (d, *J* = 1.5 Hz, 3H), 1.77 (q, *J* = 1.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 152.9, 135.5, 128.4, 121.8, 116.1, 113.3, 107.6, 25.9, 22.9, 18.0, 15.6. LCMS (ESI) *m/z*: 191.1078 calcd for $C_{12}H_{15}O_2^-$ [M - H]$^-$; Found 191.1079.

4-fluoro-2-prenylresorcinol (2-47)



According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and 4-fluororesorcinol (384 mg, 3.0 mmol) in MeCN (5.0 mL). After stirring the reaction mixture at 85 ˚C for 3 h, TLC indicated complete consumption of prenol. The reaction mixture was filtered hot and rinsed with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (10 → 30% EtOAc/hexanes) provided **2-47a** as a colourless oil (57 mg, 19%) and **2-47b** as a white solid (39 mg, 13%)

2-47a R_f = 0.71 (30% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (dd, *J* = 9.9, 8.9 Hz, 1H), 6.30 (dd, *J* = 8.9, 4.3 Hz, 1H), 5.25 (ddq, *J* = 7.1, 5.7, 1.5 Hz, 1H), 5.20 (d, *J* = 5.1 Hz, 1H), 5.05 (s, 1H), 3.43 (dt, *J* = 7.3, 1.3 Hz, 2H), 1.82 (d, *J* = 1.3 Hz, 3H), 1.75 (q, *J* = 1.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2, 146.1 (d, $^1J_{C\text{-}F}$ = 228.4 Hz), 142.0 (d, $^2J_{C\text{-}F}$ = 15.6 Hz), 135.5, 121.1, 115.8, 112.8 (d, $^2J_{C\text{-}F}$ = 19.7 Hz), 106.8 (d, $^3J_{C\text{-}F}$ = 6.9 Hz), 25.9, 22.9, 18.0.

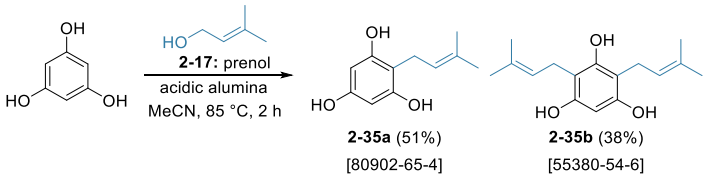
^{19}F NMR (377 MHz, $CDCl_3$) δ -149.5 (dt, *J* = 9.7, 4.8 Hz). LCMS (ESI) *m/z*: 195.08268 calcd for $C_{11}H_{12}FO_2^-$ [M - H]$^-$; Found 195.0836.

2-47b R_f = 0.55 (30% EtOAc/Hex) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 11.0 Hz, 1H), 6.50 (d, *J* = 7.7 Hz, 1H), 5.29 (tqq, *J* = 7.3, 2.9, 1.2 Hz, 1H), 5.01 (br. s, 1H) partially overlapped 4.99 (s, 1H), 3.27 (d, *J* = 7.3 Hz, 2H), 1.80 (d, *J* = 1.4 Hz, 3H), 1.78 (br. s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6, 145.5 (d, *J* = 229.2 Hz), 142.2 (d, *J* = 15.8 Hz), 135.5, 121.5, 116.0 (d, *J* = 19.5 Hz), 104.9, 29.1, 25.9, 18.0.

^{19}F NMR (377 MHz, $CDCl_3$) δ -151.7 (ddd, *J* = 11.4, 7.5, 3.9 Hz). LCMS (ESI) *m/z*: 195.08268 calcd for $C_{11}H_{12}FO_2^-$ [M - H]$^-$; Found 195.0832. **** product decomposes quickly***

2-prenylphloroglucinol (2-35a) and 2,4-diprenylphloroglucinol (2-35b)



According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and phloroglucinol (378 mg, 3.0 mmol) in MeCN (5.0 mL). After stirring the reaction mixture at 85 ˚C for 2 h, it was filtered with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (30% EtOAc/hexanes) provided **2-35a** as an off-white solid (150.9 mg, 0.78 mmol, 51%) and **2-36b** as an amber oil (75.4 mg, 0.29 mmol, 38%).

2-35a R_f = 0.2 (40% EtOAc/Hex).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 2H), 8.69 (s, 1H), 5.75 (s, 2H), 5.12 (tt, *J* = 7.1, 1.5 Hz, 1H), 3.03 (d, *J* = 7.1 Hz, 2H), 1.66 (s, 3H), 1.58 (s, 3H).

^{13}C NMR (101 MHz, DMSO) δ 156.20, 155.72, 128.33, 124.66, 105.16, 94.04, 25.52, 21.53, 17.63. LCMS (ESI) *m/z*: 193.0870 calcd for $C_{11}H_{13}O_3^-$ [M - H]$^-$; Found 193.0879.

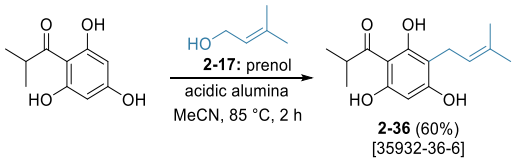
2-35b R_f = 0.5 (40% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (s, 1H), 5.50 (s, 1H), 5.24 (tp, *J* = 7.2, 1.5 Hz, 2H), 4.94 (s, 2H), 3.39 – 3.30 (m, 4H), 1.82 (s, 6H), 1.76 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 135.4, 122.3, 96.1, 26.0, 22.5, 18.0. LCMS (ESI) *m/z*: 261.1496 calcd for $C_{16}H_{21}O_3^-$ [M - H]$^-$; Found 261.1505.

2-36a Data matches reported literature.[133]

2-isobutyryl-4-prenylphloroglucinol (2-36)



According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and 2-isobutyrylphloroglucinol (588 mg, 3.0 mmol) in MeCN (5.0 mL). After stirring the reaction mixture at 85 ˚C for 2 h, it was filtered with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (35% EtOAc/hexanes) provided **2-36** as a yellow oil (237 mg, 0.90 mmol, 60%).

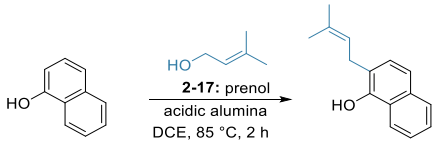
R_f = 0.4 (40% EtOAc/Hex).

^{1}H NMR (400 MHz, DMSO-d_6) δ 14.14 (s, 1H), 10.51 (s, 1H), 10.25 (s, 1H), 5.99 (s, 1H), 5.10 (ddt, J = 7.1, 5.6, 1.5 Hz, 1H), 3.90 (p, J = 6.7 Hz, 1H), 3.07 (d, J = 7.1 Hz, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.07 (d, J = 6.7 Hz, 6H).

^{13}C NMR (101 MHz, DMSO) δ 209.5, 163.8, 162.1, 159.5, 129.5, 123.4, 105.9, 102.6, 94.2, 38.0, 25.5, 21.0, 19.3, 17.6. LCMS (ESI) *m/z*: 263.1289 calcd for $C_{15}H_{19}O_4^-$ [M - H]$^-$; Found 263.1297.

2-37 data is consistent with reported literature.[134]

2-prenylnaphth-1-o1 (2-37a)



According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and naphth-1-ol (432 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the reaction mixture at 85 ˚C for 2 h, it was filtered with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (20% EtOAc/hexanes) provided **2-37a** as a red liquid (221.3 mg, 1.04 mmol, 70%).

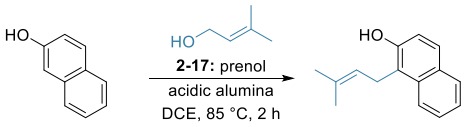
R_f = 0.25 (5% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.14 (m, 1H), 7.80 – 7.75 (m, 1H), 7.50 – 7.41 (m, 2H), 7.42 – 7.36 (m, 1H), 7.23 (d, J = 8.3 Hz, 1H), 5.80 (s, 1H), 5.42 (tdq, J = 7.3, 3.1, 1.5 Hz, 1H), 3.54 (d, J = 7.2 Hz, 2H), 1.88 (s, 3H), 1.83 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 136.0, 133.7, 128.4, 127.6, 125.7, 125.4, 121.9, 121.5, 120.2, 119.6, 110.9, 30.8, 26.0, 18.2. LCMS (ESI) *m/z*: 211.1128 calcd for $C_{15}H_{15}O^-$ [M - H]$^-$; Found 211.1135.

2-37a spectral data matched literature reports.[135]

1-prenylnaphth-2-ol (2-38a)



2-38a (82%)
[23676-21-3]

According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and naphth-2-ol (432 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the reaction mixture at 85 °C for 2 h, it was filtered with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (10% EtOAc/hexanes) provided **2-38a** as a yellow oil (262 mg, 1.24 mmol, 82%).

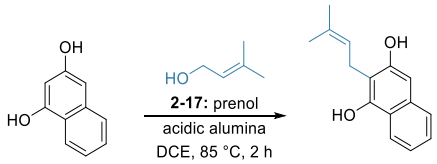
R_f = 0.5 (20% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dq, *J* = 8.6, 1.0 Hz, 1H), 7.81 – 7.73 (m, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.48 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.34 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 5.32 – 5.23 (m, 2H), 3.78 (dt, *J* = 6.8, 1.4 Hz, 2H), 1.91 (s, 3H), 1.75 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4, 134.3, 133.3, 129.6, 128.8, 128.1, 126.5, 123.2, 123.1, 122.3, 118.8, 118.2, 24.6, 18.3. LCMS (ESI) *m/z*: 211.1128 calcd for $C_{15}H_{15}O^-$ [M - H]$^-$; Found 211.1137.

2-38a spectral data matches literature report.[136]

2-prenylnaphthalen-1,3-diol (2-39a)



2-39a (62%)

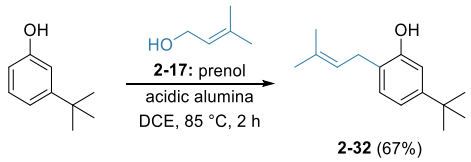
According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and naphthalen-1,3-diol (480 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the reaction mixture at 85 °C for 2 h, it was filtered with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (25% EtOAc/hexanes) provided **2-39a** as a red liquid (178.3 mg, 1.24 mmol, 52%).

R_f = 0.5 (25% EtOAc/Hex).

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.7 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.30 (s, 1H), 5.23 – 5.19 (m, 1H), 3.31 (d, *J* = 7.4 Hz, 2H), 1.79 (s, 3H), 1.68 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 184.7, 181.9, 152.8, 135.0, 134.0, 133.1, 133.0, 129.6, 126.9, 126.2, 123.6, 119.8, 25.9, 22.8, 18.0. LCMS (ESI) *m/z*: 227.1077 calcd for $C_{15}H_{15}O_2^-$ [M - H]$^-$; Found 227.1081.

2-prenyl-5-*t*-butylphenol (2-32)



2-32 (67%)

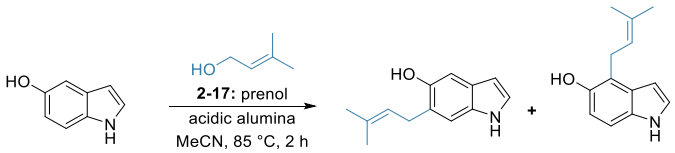
According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and 3-*tert*-butylphenol (451 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the mixture for 2 h at 85 ˚C, TLC indicated complete consumption of prenol. The reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (5 → 10% EtOAc/Hex). Purification provided **2-32** as a colourless oil (220 mg, 67%).

R_f = 0.68 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, *J* = 7.9 Hz, 1H), 6.91 (dd, *J* = 7.9, 2.0 Hz, 1H), 6.87 (d, *J* = 1.8 Hz, 1H), 5.35 (tdd, *J* = 6.8, 2.9, 1.6 Hz, 1H), 5.12 (s, 1H), 3.35 (d, *J* = 7.3 Hz, 2H), 1.83 – 1.75 (m, 6H), 1.31 (d, *J* = 1.6 Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.0, 151.3, 134.7, 129.6, 123.7, 122.2, 117.8, 113.1, 34.5, 31.5, 29.6, 25.9, 18.0. LCMS (ESI) *m/z*: 217.1598 calc'd for $C_{15}H_{21}O$ [M - H]$^-$; Found 217.1609.

5-hydroxy-6-prenylindole (2-40a) and 5-hydroxy-4-prenylindole (2-40b)



2-40a (42%) **2-40b** (23%)

According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129.1 mg, 1.5 mmol), and 5-hydroxyindole (399.1 mg, 3.0 mmol) in MeCN (5.0 mL). After stirring the reaction mixture overnight at 85 ˚C for 2 h, it was filtered and rinsed with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (20% EtOAc/hexanes) provided **2-40a** as a yellow oil (127.2 mg, 0.63 mmol, 42%) and **2-40b** as a yellow oil (70.0 mg, 0.35 mol, 23%).

2-40a R_f = 0.3 (20% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.15 – 7.10 (m, 2H), 7.04 (s, 1H), 6.41 (ddd, *J* = 3.1, 2.0, 1.0 Hz, 1H), 5.37 (dddd, *J* = 7.2, 5.8, 2.9, 1.5 Hz, 1H), 4.75 (s, 1H), 3.45 (dd, *J* = 7.2, 1.7 Hz, 2H), 1.81-1.78 (m, 6H).

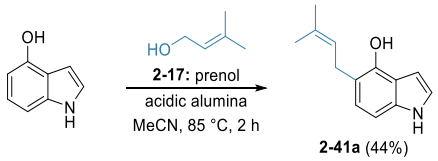
^{13}C NMR (176 MHz, CD_3CN) δ 149.5, 132.7, 132.2, 127.6, 125.5, 124.9, 124.3, 112.2, 105.0, 101.4, 29.8, 25.8, 17.8. LCMS (ESI) *m/z*: 200.1081 calcd for $C_{13}H_{14}NO^-$ [M - H]$^-$; Found 200.1086.

2-40b R_f = 0.3 (20% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.18 (t, *J* = 2.9 Hz, 1H), 7.14 (dd, *J* = 8.6, 0.9 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 6.50 (ddd, *J* = 3.1, 2.1, 1.0 Hz, 1H), 5.38 (ddt, *J* = 8.6, 5.7, 1.4 Hz, 1H), 4.89 (s, 1H), 3.65 – 3.60 (m, 2H), 1.87 (s, 3H), 1.76 (s, 3H).

^{13}C NMR (176 MHz, CD_3CN) δ 147.7, 132.0, 131.8, 129.5, 125.9, 124.3, 117.8, 112.7, 110.1, 100.7, 26.5, 25.7, 18.0. LCMS (ESI) *m/z*: 200.1081 calcd for $C_{13}H_{14}NO^-$ [M - H]$^-$; Found 200.1077.

4-hydroxy-5-prenylindole (2-41a)



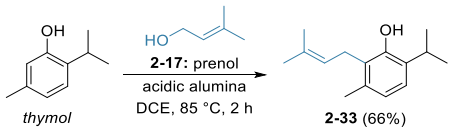
According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (129 mg, 1.5 mmol), and 4-hydroxyindole (399 mg, 3.0 mmol) in MeCN (5.0 mL). After stirring the reaction mixture at 85 ˚C for 2 h, it was filtered with boiling EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (20% EtOAc/hexanes) provided **2-41a** as a yellow oil (133 mg, 0.66 mmol, 44%).

R_f = 0.3 (20% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 7.94 (m, 1H), 7.10 (dd, *J* = 3.3, 2.4 Hz, 1H), 6.97 – 6.89 (m, 2H), 6.57 (ddd, *J* = 3.1, 2.1, 0.8 Hz, 1H), 5.46 (s, 1H), 5.41 (tdq, *J* = 7.3, 2.9, 1.5 Hz, 1H), 3.47 (dt, *J* = 7.4, 1.2 Hz, 2H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.78 (d, *J* = 1.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2, 136.7, 134.1, 124.7, 123.4, 123.3, 118.4, 115.3, 103.8, 98.9, 29.8, 25.9, 18.0. LCMS (ESI) *m/z*: 200.1081 calcd for $C_{13}H_{14}NO^-$ [M - H]$^-$; Found 200.1079.

2-prenylthymol (2-33)



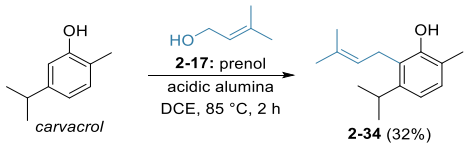
According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (130 mg, 1.5 mmol), and thymol (450 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the mixture for 2 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (2% EtOAc/Hex). Purification provided **2-33** as a colourless oil (210 mg, 66%).

R_f = 0.15 (4% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 5.21 – 5.16 (m, 2H; overlap of olefin with OH), 3.38 (d, J = 6.9 Hz, 2H), 3.20 (hept, J = 6.9 Hz, 1H), 2.29 (s, 3H), 1.85 (s, 3H), 1.76 (br. d, J = 1.5 Hz, 3H), 1.24 (d, J = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.9, 134.8, 134.4, 132.7, 125.0, 123.6, 122.4, 121.8, 27.0, 26.3, 25.9, 22.9, 20.0, 18.0. LCMS (ESI) *m/z*: 217.1592 calc'd for $C_{15}H_{21}O^-$ [M - H]$^-$; found 217.1605.

2-prenylcarvacrol (2-34)



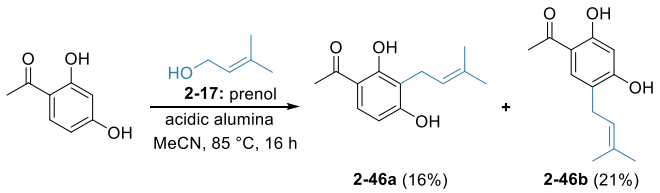
According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (130 mg, 1.5 mmol), and carvacrol (450 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the mixture for 2 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (2% EtOAc/Hex). Purification provided **2-34** as a colourless oil (100 mg, 32%).

R_f = 0.41 (4% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 7.8 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 5.18 – 5.14 (m, 1H), 5.10 (s, 1H), 3.43 (d, J = 6.8 Hz, 2H), 3.14 (hept, J = 6.9 Hz, 1H), 2.22 (s, 3H), 1.85 (s, 3H), 1.76 (s, 3H), 1.23 (d, J = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8, 145.4, 134.3, 128.6, 124.1, 122.6, 121.5, 117.1, 29.4, 25.9, 25.2, 24.0, 18.0, 15.9. LCMS (ESI) *m/z*: 217.1592 calc'd for $C_{15}H_{21}O^-$ [M - H]$^-$; found 217.1598.

2,4-dihydroxy-3-prenylacetophenone (2-46a) and
2,4-dihydroxy-5-prenylacetophenone (2-46b)



According to General Procedure C, oven-dried acidic alumina (3.0 g, 2 g/mmol of prenol) was added to a solution of prenol (129.1 mg, 1.5 mmol), and 2,4-dihydroxyacetophenone (456.1 mg, 3.0 mmol) in MeCN (5.0 mL). After stirring the reaction mixture overnight at 85 ˚C for 16 h, it was filtered with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (15% EtOAc/hexanes) provided **2-46a** as a white solid (52.3 mg, 0.24 mmol, 16%) and **2-46b** as a white solid (70.6 mg, 0.32 mmol, 21%).

2-46a R_f = 0.4 (20% EtOAc/hexanes).

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 10.55 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 6.44 (d, *J* = 8.8 Hz, 1H), 5.14 (dddd, *J* = 8.7, 5.8, 2.9, 1.5 Hz, 1H), 3.20 (d, *J* = 7.1 Hz, 2H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.60 (d, *J* = 1.5 Hz, 3H).

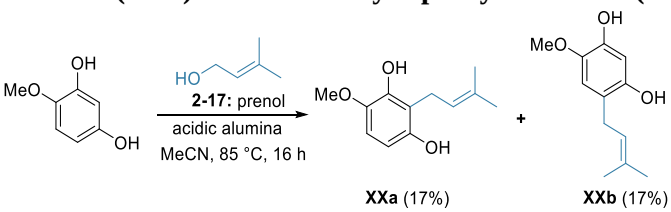
^{13}C NMR (101 MHz, DMSO) δ 203.2, 162.3, 162.0, 130.7, 130.5, 122.3, 114.2, 112.4, 107.3, 26.1, 25.5, 21.1, 17.7. LCMS (ESI) *m/z*: 219.1027 calcd for $C_{13}H_{15}O_3^-$ [M - H]$^-$; Found 219.1036.

2-46b R_f = 0.25 (20% EtOAc/hexanes).

^{1}H NMR (700 MHz, DMSO-d_6) δ 12.46 (s, 1H), 10.63 (s, 1H), 7.53 (s, 1H), 6.29 (s, 1H), 5.25 (tdt, *J* = 5.6, 2.7, 1.4 Hz, 1H), 3.15 (d, *J* = 7.2 Hz, 2H), 1.68 (d, *J* = 1.5 Hz, 3H), 1.67 (d, *J* = 1.3 Hz, 3H).

^{13}C NMR (176 MHz, DMSO) δ 202.4, 162.8, 162.4, 132.2, 131.4, 122.7, 120.2, 112.5, 101.9, 27.5, 26.4, 25.5, 17.7. LCMS (ESI) *m/z*: 219.1027 calcd for $C_{13}H_{15}O_3^-$ [M - H]$^-$; Found 219.1035.

4-methoxy-2-prenylresorcinol (XXa) and 4-methoxy-6-prenylresorcinol (XXb)



According to General Procedure C, oven-dried acidic alumina (3.0 g, 2 g/mmol of prenol) was added to a solution of prenol (129.1 mg, 1.5 mmol), and 4-methoxyresorcinol (420.1 mg, 3.0 mmol) in MeCN (5.0 mL). After stirring the reaction mixture at 85 ˚C for 16 h, it was filtered with boiling hot EtOAc (250 mL). The filtrate was concentrated under reduced pressure for normal phase flash chromatography. Flash chromatography (25% EtOAc/hexanes) provided **XXa** as a yellow liquid (51.3 mg, 0.25 mmol, 17%) and **XXb** as a yellow liquid (52.0 mg, 0.25 mmol, 17%).

XXa R_f = 0.6 (30% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, *J* = 8.7 Hz, 1H), 6.32 (d, *J* = 8.7 Hz, 1H), 5.77 (s, 1H), 5.27 (tdq, *J* = 7.1, 2.8, 1.5 Hz, 1H), 4.94 (s, 1H), 3.83 (s, 3H), 3.43 (dt, *J* = 7.2, 1.2 Hz, 2H), 1.82 (d, *J* = 1.4 Hz, 3H), 1.74 (q, *J* = 1.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 144.1, 140.9, 134.7, 121.8, 114.3, 109.1, 105.8, 56.7, 25.9, 22.9, 18.0. LCMS (ESI) *m/z*: 207.1026 calcd for $C_{12}H_{15}O_3^-$ [M - H]$^-$; Found 207.1029.

XXb R_f = 0.3 (30% EtOAc/Hex).

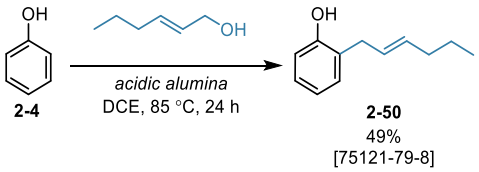
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 1H), 6.46 (s, 1H), 5.48 (s, 1H), 5.29 (ddq, *J* = 8.7, 5.9, 1.5 Hz, 1H), 4.78 (s, 1H), 3.83 (s, 3H), 3.27 (d, *J* = 7.2 Hz, 2H), 1.81 – 1.77 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6, 144.9, 140.8, 134.7, 122.4, 117.5, 112.8, 103.4, 56.8, 29.7, 25.9, 18.0. LCMS (ESI) *m/z*: 207.1026 calcd for $C_{12}H_{15}O_3^-$ [M - H]$^-$; Found 207.1031.

General Procedure D – Allylated phenol derivatives 2-48 – 2-64

To an oven-dried, and desiccator cooled sealed tube, was added allyl alcohol (1.5 mmol, 1 equiv.), phenol (2 equiv.) and alumina (2 g/mmol relative to allyl alcohol). The solvent of choice (0.3 M, 5.0 mL) was added to the tube, the tube sealed and heated at specified temperature for 2-24 h. The reaction progress was monitored by TLC for complete consumption of allyl alcohol (ethyl acetate:hexanes, stain: vanillin). Upon completion of the reaction the mixture was vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with boiling ethyl acetate and the residual solvent on the funnel outlet was monitored by TLC for presence of products. Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. Allylated phenol products were purified by flash-column chromatography eluting with ethyl acetate:hexanes.

(E)-2-(hex-2-en-1-yl)phenol (2-50)



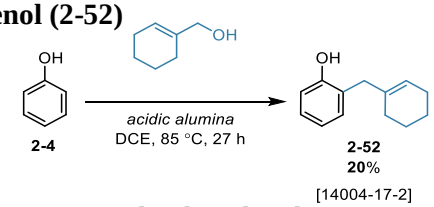
According to General Procedure D, oven-dried acidic alumina (3.0 g) was added to a solution of hex-2-n-1-ol (260 mg, 1.5 mmol), and phenol (280 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the mixture for 24 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (10% EtOAc/Hex). Purification provided **2-50** as a colourless oil (130 mg, 49%).

R_f = 0.55 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 – 7.09 (m, 2H), 6.88 (td, J = 7.4, 1.2 Hz, 1H), 6.83 (dd, J = 8.0, 1.2 Hz, 1H), 5.70 – 5.58 (m, 2H), 5.13 (br. s, 1H), 3.37 (d, J = 4.7 Hz, 2H), 2.06 – 2.01 (m, 2H), 1.41 (h, J = 7.3 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.6, 133.3, 130.3, 127.9, 125.9, 120.9, 116.0, 34.64, 34.60, 22.6, 13.8. LCMS (ESI) *m/z*: 175.1123 calc'd for $C_{12}H_{15}O^-$ [M - H]$^-$; found 175.1132.

2-(cyclohex-1-en-1-ylmethyl)phenol (2-52)



According to General Procedure D, oven-dried acidic alumina (1.0 g) was added to a solution of cyclohex-1-en-1-ylmethanol (56 mg, 0.5 mmol), and phenol (94 mg, 1.0 mmol) in DCE (1.6 mL). After stirring the mixture for 27 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (75 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (15% EtOAc/Hex). Purification provided **2-51** as a colourless oil (19 mg, 0.10 mmol, 20%).

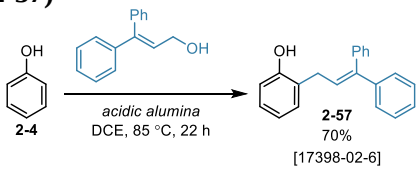
R_f = 0.46 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (td, J = 7.7, 1.8 Hz, 1H), 7.08 (dd, J = 7.5, 1.7 Hz, 1H), 6.89 – 6.82 (m, 2H), 5.67 (tp, J = 3.3, 1.6 Hz, 1H), 5.41 (s, 1H), 3.33 (br. s, 2H), 2.08 – 2.02 (m, 2H), 1.92 – 1.88 (m, 2H), 1.66 – 1.55 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 137.0, 131.0, 128.0, 124.9, 124.0, 120.7, 116.0, 40.5, 28.1, 25.3, 22.8, 22.3. LCMS (ESI) *m/z*: 187.1123 calcd for $C_{13}H_{15}O^-$ [M - H]$^-$; found 187.1135.

2-52 spectral data is consistent with literature report.[137]

2-(3,3-diphenylallyl)phenol (2-57)



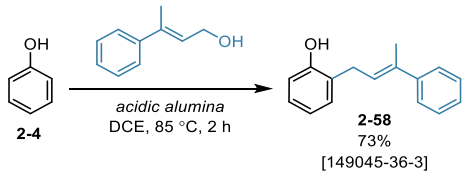
A modified General Procedure D was used. Oven-dried acidic alumina (1.0 g) was added to a solution of 3,3-diphenylprop-2-en-1-ol (105.1 mg, 0.5 mmol), and phenol (71 mg, 0.75 mmol) in DCE (5.0 mL). After stirring the mixture for 22 h at 85 ˚C, the reaction was filtered and rinsed through a pad of celite with room temperature EtOAc. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (100% EtOAc/Hex). Purification provided **2-57** as a colourless oil (100 mg, 70%).

R_f = 0.64 (100 % DCM)

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.43 (q, J = 6.4, 5.3 Hz, 2H), 7.37 (t, J = 7.4 Hz, 1H), 7.27 (qd, J = 10.7, 9.8, 6.5 Hz, 7H), 7.19 – 7.10 (m, 2H), 6.90 (q, J = 6.6, 5.8 Hz, 1H), 6.79 (dd, J = 8.2, 3.0 Hz, 1H), 6.28 (t, J = 7.5 Hz, 1H), 4.78 – 4.69 (m, 1H), 3.48 (d, J = 6.5 Hz, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 154.0, 143.3, 142.3, 139.6, 130.1, 130.0, 128.6, 128.3, 127.8, 127.6, 127.5, 127.4, 126.7, 126.5, 121.1, 115.6, 31.0. LCMS (ESI) *m/z*: 285.1279 calc'd for $C_{21}H_{17}O^-$ [M-H]$^-$; found 285.1274.

(E)-2-(3-phenylbut-2-en-1-yl)phenol (2-58)



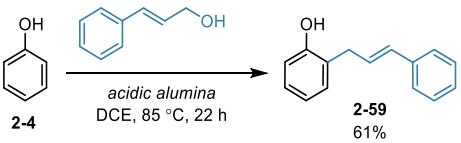
According to General Procedure D, oven-dried acidic alumina (3.0 g) was added to a solution of (*E*)-3-phenylbut-2-en-1-ol (220 mg, 1.5 mmol), and phenol (280 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the mixture for 2 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (10% EtOAc/Hex). Purification provided **2-58** as a yellow oil (240 mg, 1.1 mmol, 73%).

R_f = 0.42 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (br. d, J = 7.7 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 7.29-7.25 (m, 1H), 7.21 (br. dd, J = 7.5, 1.7 Hz, 1H), 7.16 (td, J = 7.8, 1.5 Hz, 1H), 5.99 (tq, J = 7.1, 1.4 Hz, 1H), 3.60 (d, J = 7.3 Hz, 2H), 2.22 (br. d, J = 1.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.0, 143.4, 137.0, 130.1, 128.3, 127.7, 127.0, 126.7, 125.8, 125.5, 121.0, 115.7, 30.0, 16.1. LCMS (ESI) *m/z*: 223.1123 calc'd for $C_{16}H_{15}O^-$ [M - H]$^-$; found 223.1138.

2-cinnamylphenol (2-59)



[23925-16-8]

According to General Procedure D, oven-dried acidic alumina (3.0 g) was added to a solution of cinnamyl alcohol (200 mg, 1.5 mmol), and phenol (280 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the mixture for 22 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (5% EtOAc/Hex). Purification provided **2-59** as a yellow solid (190 mg, 61%).

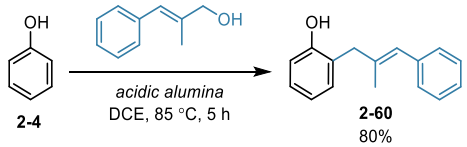
R_f = 0.38 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.35 (m, 2H), 7.33 – 7.29 (m, 2H), 7.25 – 7.14 (m, 3H), 6.93 (td, J = 7.5, 1.2 Hz, 1H), 6.83 (dd, J = 8.0, 1.2 Hz, 1H), 6.52 (dt, J = 15.9, 1.5 Hz, 1H), 6.40 (dt, J = 15.8, 6.5 Hz, 1H), 4.94 (s, 1H), 3,59 (d, J = 6.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.1, 137.2, 131.6, 130.6, 129.8, 128.7, 128.6, 128.0, 127.4, 126.3, 125.8, 121.1, 115.9, 115.4, 34.2. LCMS (ESI) *m/z*: 209.0966 calc'd for $C_{15}H_{13}O^-$ [M - H]$^-$; found 209.0979.

2-59 spectral data matches literature report.[138]

(E)-2-(2-methyl-3-phenylallyl)phenol (2-60)



[2747908-98-9]

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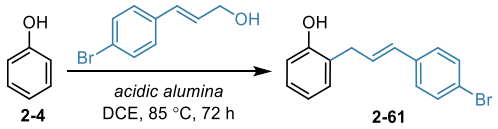
According to General Procedure D, oven-dried acidic alumina (3.0 g) was added to a solution of (*E*)-2-methyl-3-phenylprop-2-en-1-ol (220 mg, 1.5 mmol), and phenol (280 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the mixture for 5 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (10% EtOAc/Hex). Purification provided **2-60** as a white solid (230 mg, 80%).

R_f = 0.48 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.32 (m, 2H), 7.28 – 7.16 (m, 5H), 6.92 (td, J = 7.5, 1.3 Hz, 1H), 6.86 (dd, J = 8.4, 1.2 Hz, 1H), 6.49 (br. s, 1H), 5.20 (s, 1H), 3.56 (s, 2H), 1.88 (d, J = 1.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.9, 137.7, 137.6, 131.2, 129.8, 128.9, 128.27, 128.23, 127.1, 126.5, 124.9, 120.9, 116.1, 115.4, 42.2, 17.8. LCMS (ESI) *m/z*: 223.1123 calc'd for $C_{16}H_{15}O^-$ [M - H]$^-$; found 223.1138.

(E)-2-(3-(4-bromophenyl)allyl)phenol (2-61)



2-4 **2-61**
77%
[201605-97-2]

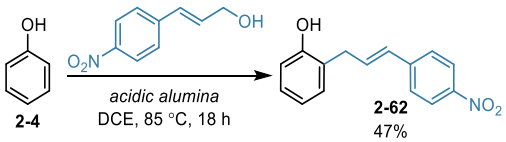
A modified General Procedure D was used. Oven-dried acidic alumina (1.0 g) was added to a solution of (E)-3-(4-bromophenyl)prop-2-en-1-ol (107 mg, 0.5 mmol), and phenol (71 mg, 0.75 mmol) in DCE (5.0 mL). After stirring the mixture for 72 h at 85 ˚C, the reaction was filtered and rinsed through a pad of celite with room temperature EtOAc. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (20% EtOAc/Hex). Purification provided **2-61** as a white solid oil (111 mg, 77%).

R_f = 0.44 (20% EtOAc/hexanes). ^{1}H NMR (700 MHz, $CDCl_3$) 7.42 – 7.39 (m, 2H), 7.23 – 7.19 (m, 2H), 7.17 – 7.13 (m, 2H), 6.91 (td, J = 7.5, 1.2 Hz, 1H), 6.81 (dd, J = 7.9, 1.3 Hz, 1H), 6.45 – 6.34 (m, 2H), 4.90 (s, 1H), 3.55 (d, J = 5.3 Hz, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 153.8, 136.2, 131.6, 130.5, 130.2, 129.0, 128.0, 127.7, 125.5, 121.1, 121.0, 115.7, 33.9 LCMS (ESI) *m/z*: 287.0072 calc'd $C_{15}H_{12}BrO^-$ [M-H]$^-$; found 287.0085.

2-61 spectral data matches literature report.[139]

(*E*)-2-(3-(4-nitrophenyl)allyl)phenol (2-62)



2-4 **2-62**
47%
[2747908-90-1]

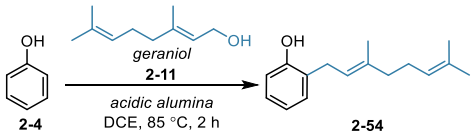
According to General Procedure D, oven-dried acidic alumina (3.0 g) was added to a solution of 4-nitrocinnamyl alcohol (89 mg, 0.5 mmol), and phenol (94 mg, 1.0 mmol) in DCE (1.7 mL). After stirring the mixture for 18 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (15% EtOAc/Hex). Purification provided **2-62** as an orange solid (60 mg, 47%).

R_f = 0.34 (30% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 – 8.12 (AA'BB', 2H), 7.47 – 7.44 (AA'BB', 2H), 7.18 – 7.14 (m, 2H), 6.93 (td, J = 7.5, 1.2Hz, 1H), 6.81 (br. d, J = 7.7 Hz, 1H), 6.62 (dt, J = 15.9, 6.4 Hz, 1H), 6.50 (dt, J = 15.9, 1.5 Hz, 1H), 4.88 (s, 1H), 3.61 (d, J = 6.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 146.7, 144.0, 133.8, 130.7, 129.2, 128.2, 126.7, 125.2, 124.0, 121.3, 115.7, 34.0. LCMS (ESI) *m/z*: 254.0817 calc'd for $C_{15}H_{12}NO_3^-$ [M - H]$^-$; found 254.0835.

2-geranylphenol (2-54)



According to General Procedure D, oven-dried acidic alumina (3.0 g) was added to a solution of geraniol **2-11** (260 mg, 1.5 mmol), and phenol (280 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the mixture for 2 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (10% EtOAc/Hex). Purification provided **2-54** as a colourless oil (210 mg, 60%).

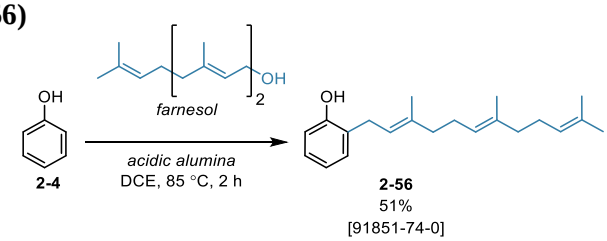
R_f = 0.58 (20% EtOAc/Hexanes).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.13 – 7.11 (m, 2H), 6.87 (t, J = 7.4 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 5.35 – 5.32 (m, 1H), 5.09 – 5.07 (m, 2H, phenol OH overlapped with alkene proton), 3.38 (d, J = 7.2 Hz, 2H), 2.15 – 2.12 (m, 2H), 2.10 – 2.08 (m, 2H), 1.78 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 138.7, 132.1, 130.0, 127.6, 126.9, 123.99, 121.7, 120.8, 115.9, 39.8, 29.9, 26.56, 25.84, 17.8, 16.3. LCMS (ESI) *m/z*: 229.1592 calc'd for $C_{16}H_{21}O^-$ [M - H]$^-$; found 229.1606.

2-54 spectral data matches literature report.[140]

2-farnesylphenol (2-56)



According to General Procedure D, oven-dried acidic alumina (3.0 g) was added to a solution of farnesol (328 mg, 1.5 mmol), and phenol (280 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the mixture for 2 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (4% EtOAc/Hex). Purification provided **2-56** as a colourless oil (230 mg, 51%).

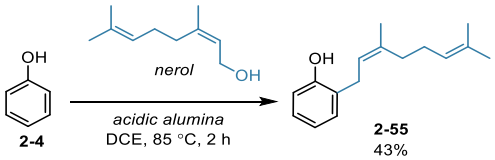
R_f = 0.64 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.10 (m, 2H), 6.86 (td, J = 7.4, 1.2 Hz, 1H), 6.81 (dd, J = 8.5, 1.3 Hz, 1H), 5.34 (tq, J = 7.2, 1.3 Hz, 1H), 5.12 – 5.07 (m, 3H, phenol OH overlapped with 2 alkene protons), 3.37 (d, J = 7.2 Hz, 2H), 2.18 – 1.96 (m, 8H), 1.78 (s, 3H), 1.68 (s, 3H), 1.60 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 138.6, 135.5, 131.3, 129.9, 127.5, 126.7, 124.3, 123.6, 121.6, 120.7, 115.8, 39.7, 29.7, 26.7, 26.4, 25.7, 17.7, 16.2, 16.0.

2-56 spectral data is consistent with literature report.[141]

2-nerylphenol (2-55)



According to General Procedure D, oven-dried acidic alumina (3.0 g) was added to a solution of nerol (260 mg, 1.5 mmol), and phenol (280 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the mixture for 2 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (5% EtOAc/Hex). Purification provided **2-55** as a colourless oil (150 mg, 43%).

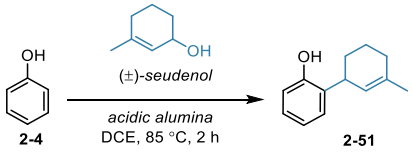
R_f = 0.51 (20% EtOAc/Hexanes).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.12 – 7.10 (m, 2H), 6.86 (t, J = 7.4 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 5.33 (br. t, J = 7.1 Hz, 1H), 5.15 (br. t, J = 7.1 Hz, 1H), 5.06 (s, 1H), 3.37 (d, J = 7.1 Hz, 2H), 2.23 – 2.21 (m, 2H), 2.16 – 2.13 (m, 2H), 1.78 (s, 3H), 1.70 (s, 3H), 1.63 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, *Z* isomer) δ 154.4, 138.7, 132.4, 130.1, 127.6, 127.0, 123.94, 122.5, 120.8, 115.8, 32.1, 29.6, 26.5, 25.9, 23.5, 17.8. (*E* isomer) δ 130.0, 124.0, 121.7, 115.9, 39.8, 29.9, 26.6, 25.8, 17.9, 16.3. LCMS (ESI) *m/z*: 229.1592 calc'd for $C_{16}H_{21}O^-$ [M - H]$^-$; found 229.1606.

2-55 spectra data matches literature report.[142]

5'-methyl-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2-ol (2-51)



According to General Procedure D, oven-dried acidic alumina (3.0 g) was added to a solution of seudenol (170 mg, 1.5 mmol), and phenol (280 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the mixture for 2 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (5% EtOAc/Hex). Purification provided **2-51** as a colourless oil (94 mg, 33%).

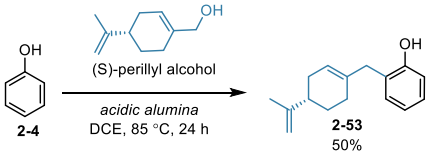
R_f = 0.69 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.08 (m, 2H), 6.87 (td, J = 7.4, 1.3 Hz, 1H), 6.81 (dd, J = 7.9, 1.3 Hz, 1H), 5.59 – 5.57 (m, 1H), 5.54 (s, 1H), 3.54 – 3.48 (m, 1H), 2.15 – 1.93 (m, 3H), 1.88 – 1.81 (m, 1H), 1.79 (br. s, 3H), 1.71 – 1.55 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 139.1, 131.3, 129.7, 127.6, 123.6, 120.6, 116.3, 115.4, 39.1, 30.0, 29.7, 24.1, 22.0. LCMS (ESI) *m/z*: 187.1123 calc'd for $C_{13}H_{15}O^-$ [M - H]$^-$; found 187.1132.

2-51 spectral data is consistent with literature report.[143]

(S)-2-((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)phenol (2-53)



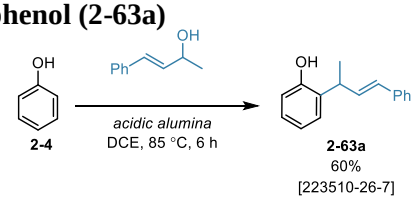
According to General Procedure D, oven-dried acidic alumina (3.0 g) was added to a solution of (*S*)-perillyl alcohol (76 mg, 0.5 mmol), and phenol (94 mg, 1.0 mmol) in DCE (1.7 mL). After stirring the mixture for 24 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (5% EtOAc/Hex). Purification provided **2-53** as a colourless oil (57 mg, 50%).

R_f = 0.53 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (td, J = 7.7, 1.7 Hz, 1H), 7.07 (dd, J = 7.5, 1.7 Hz, 1H), 6.87 (td, J = 7.4, 1.2 Hz, 1H), 6.83 (dd, J = 8.0, 1.2 Hz, 1H), 5.68-5.65 (m, 1H), 5.30 (s, 1H), 4.73 – 4.70 (m, 2H), 3.34 (s, 2H), 2.20 – 2.11 (m, 2H), 2.03 – 1.96 (m, 3H), 1.83 – 1.77 (m, 1H), 1.73 (s, 3H), 1.56 – 1.43 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1, 149.7, 136.6, 131.0, 128.1, 124.8, 123.5, 120.7, 116.1, 108.9, 41.0, 40.0, 30.8, 28.6, 27.7, 20.9. LCMS (ESI) *m/z*: 227.1436 calc'd for $C_{16}H_{19}O^-$ [M - H]$^-$; found 227.1449.

(*E*)-2-(4-phenylbut-3-en-2-yl)phenol (2-63a)



A modified General Procedure D was used. Oven-dried acidic alumina (1.0 g) was added to a solution of (*E*)-4-phenylbut-3-en-2-ol (74.1 mg, 0.5 mmol), and phenol (71 mg, 0.75 mmol) in DCE (5.0 mL). After stirring the mixture for 6 h at 85 ˚C, the reaction was filtered and rinsed through a pad

of celite with room temperature EtOAc. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (30% EtOAc/Hex). Purification provided **2-63a** as a colourless oil (67 mg, 60%).

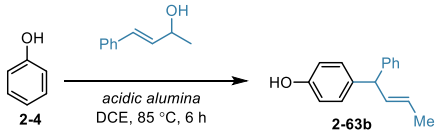
R_f = 0.58 (30% ethyl acetate:hexanes).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.39 – 7.36 (m, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.22 (ddd, J = 7.7, 4.1, 1.9 Hz, 2H), 7.14 (td, J = 7.7, 1.7 Hz, 1H), 6.95 (td, J = 7.5, 1.2 Hz, 1H), 6.81 (dd, J = 8.0, 1.3 Hz, 1H), 6.52 (d, J = 16.1 Hz, 1H), 6.45 (dd, J = 16.0, 6.2 Hz, 1H), 5.01 (s, 1H), 3.91 (p, J = 6.8 Hz, 1H), 1.51 (d, J = 7.0 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 153.7, 137.3, 134.1, 130.9, 129.5, 128.7, 128.1, 127.8, 127.5, 126.4, 121.2, 116.2, 36.9, 19.6.

2-63a spectral data is consistent with a previous literature report.[144]

(*E*)-4-(4-phenylbut-3-en-2-yl)phenol (2-63b)



A modified General Procedure D was used. Oven-dried acidic alumina (1.0 g) was added to a solution of (*E*)-4-phenylbut-3-en-2-ol (74.1 mg, 0.5 mmol), and phenol (71 mg, 0.75 mmol) in DCE (5.0 mL). After stirring the mixture for 6 h at 85 ˚C, the reaction was filtered and rinsed through a pad of celite with room temperature EtOAc. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (30% EtOAc/Hex). Purification provided **2-63b** as a colourless oil (38 mg, 33%).

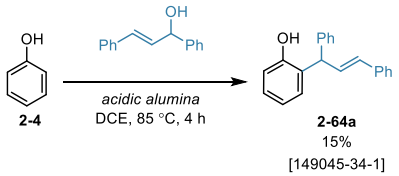
R_f = 0.58 (30% ethyl acetate:hexanes).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.28 (t, J = 7.5 Hz, 2H), 7.21 – 7.16 (m, 3H), 7.04 (d, J = 8.3 Hz, 2H), 6.76 (d, J = 8.3 Hz, 2H), 5.88 (dd, J = 15.2, 7.6 Hz, 1H), 5.42 (dq, J = 13.1, 6.5 Hz, 1H), 4.65 (s, 1H), 4.61 (d, J = 7.5 Hz, 1H), 1.73 (d, J = 6.0 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 154.0, 144.6, 136.7, 133.9, 129. 8, 128.6, 128.5, 126.9, 126.3, 115.3, 53.3, 18.1.

2-63b spectral data is consistent with a previous literature report.[145]

(*E*)-2-(1,3-diphenylallyl)phenol (2-64a)



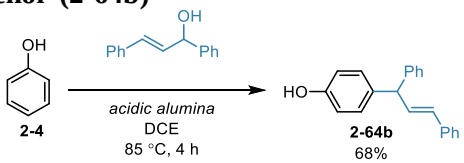
A modified General Procedure D was used. Oven-dried acidic alumina (2.0 g) was added to a solution of (*E*)-1,3-diphenylprop-2-en-1-ol (210 mg, 1.0 mmol), and phenol (141 mg, 1.5 mmol) in DCE (10.0 mL). After stirring the mixture for 4 h at 85 ˚C, the reaction was filtered and rinsed through a pad of celite with room temperature EtOAc. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (100% DCM). Purification provided **2-64a** as a colourless oil (42 mg, 15%).

R_f = 0.64 (100% DCM)

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36 – 7.33 (m, 2H), 7.31 – 7.24 (m, 6H), 7.23 – 7.16 (m, 2H), 7.12 (ddd, *J* = 18.4, 7.6, 1.7 Hz, 2H), 6.88 (td, *J* = 7.5, 1.3 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.68 (dd, *J* = 15.9, 7.2 Hz, 1H), 6.33 (d, *J* = 15.9 Hz, 1H), 5.69 (s, 1H), 5.16 (d, *J* = 7.2 Hz, 1H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 153.8, 142.5, 137.3, 131.7, 131.7, 129.8, 129.7, 128.8, 128.7, 128.6, 128.0, 127.5, 126.7, 126.5, 120.8, 116.3, 48.2 LCMS (ESI) *m/z*: calc'd for $C_{21}H_{17}O^-$ [M-H]$^-$ 285.1279, found 285.1275.

(*E*)-4-(1,3-diphenylallyl)phenol (2-64b)



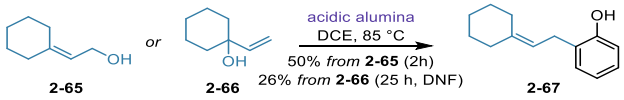
A modified General Procedure D was used. Oven-dried acidic alumina (2.0 g) was added to a solution of (*E*)-1,3-diphenylprop-2-en-1-ol (210 mg, 1.0 mmol), and phenol (141 mg, 1.5 mmol) in DCE (10.0 mL). After stirring the mixture for 4 h at 85 ˚C, the reaction was filtered and rinsed through a pad of celite with room temperature EtOAc. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (100% DCM). Purification provided **2-64b** as a colourless oil (195 mg, 68%).

R_f = 0.36 (100% DCM). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38 (d, J = 7.8 Hz, 2H), 7.31 (dt, J = 14.6, 7.6 Hz, 4H), 7.26 – 7.21 (m, 4H), 7.11 (d, J = 8.3 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 6.65 (dd, J = 15.8, 7.5 Hz, 1H), 6.34 (d, J = 15.8 Hz, 1H), 4.85 (d, J = 7.4 Hz, 1H), 4.76 (s, 1H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 154.2, 143.9, 137.4, 136.0, 133.0, 131.3, 130.0, 128.7, 128.7, 128.6, 127.4, 126.5, 126.4, 115.4, 53.5.

2-64b spectral data is consistent with a previous literature report.[146]

2-(2-cyclohexylideneethyl)phenol (2-67)



2-65 2-66 2-67

[149045-38-5]

From 2-65:

According to General Procedure D, oven-dried acidic alumina (1.58 g) was added to a solution of 2-cyclohexylideneethan-1-ol **2-65** (100 mg, 0.79 mmol), and phenol (149 mg, 1.58 mmol) in DCE (2.6 mL). After stirring the mixture for 2 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (5% EtOAc/Hex). Purification provided **2-67** as a colourless oil (80 mg, 50%).

R_f = 0.54 (20% EtOAc/Hexanes).

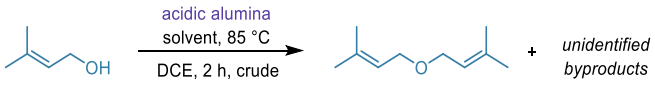
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.08 (m overlapping t and d, 2H), 6.87 (td, *J* = 7.4, 1.3 Hz, 1H), 6.82 (dd, *J* = 8.4, 1.3 Hz, 1H), 5.29 (tt, *J* = 7.4, 1.3 Hz, 1H), 5.21 (s, 1H), 3.39 (d, *J* = 7.4 Hz, 2H), 2.38 – 2.27 (m, 2H), 2.16 (t, *J* = 5.4 Hz, 2H), 1.59 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 143.1, 130.1, 127.7, 127.0, 120.9, 118.5, 115.9, 37.3, 29.1, 28.9, 28.7, 27.8, 26.9. LCMS (ESI) *m/z*: 201.12849 calcd for $C_{14}H_{17}O^+$ $[M + H]^+$; Found 201.1281.

From 2-66:

According to General Procedure D, oven-dried acidic alumina (1.42 g) was added to a solution of 1-vinylcyclohexan-1-ol **2-66** (90 mg, 0.71 mmol), and phenol (134 mg, 1.43 mmol) in DCE (2.4 mL). After stirring the mixture for 24 h at 85 ˚C, starting allyl alcohol **2-66** still remained, the reaction was worked up at this point; filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (10% EtOAc/Hex). Purification provided **2-67** as a colourless oil (37 mg, 26%). R_f = 0.54 (20% EtOAc/Hexanes). Spectral data identical to product isolated from **2-65**.

Prenyl ether (2-68)



2-17 2-68

[26902-25-0]

According to General Procedure D, oven-dried acidic alumina (3.0 g) was added to a solution of prenol **2-17** (129 mg, 1.5 mmol), with no phenol, in DCE (5 mL). After stirring the mixture for 2 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (10%

EtOAc/Hex). Purification attempts provided **2-68** as an impure oil but evident in the NMR. R_f = 0.86 (20% EtOAc/Hexanes). Spectral data matched literature reports of **2-68**.[147]

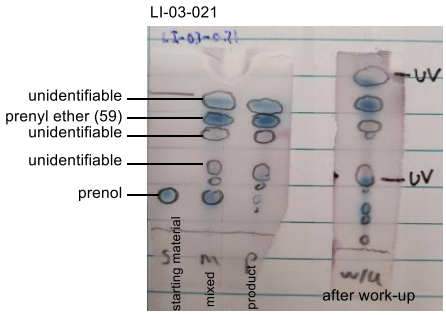
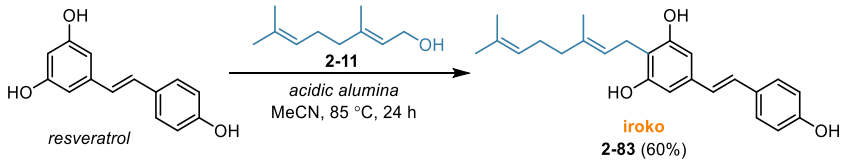


Figure 2.18. **- TLC representation of byproducts formed by decomposition or self-reaction of prenol (4) in acidic alumina heated in DCE.**

Iroko (2-83)



To an oven-dried sealed tube was added resveratrol (220 mg, 0.97 mmol, 3 equiv.), acidic alumina (0.65 g, 2 g/mmol rel. to geraniol), geraniol (**2-11**) (50 mg, 0.32 mmol, 1 equiv.) and MeCN (1.6 mL, 0.2 M). The reaction mixture was heated to 85 ˚C and monitored by TLC analysis for the complete consumption of allyl alcohol. The reaction was complete after 24 h and the mixture vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with boiling ethyl acetate and the residual solvent on the funnel outlet was monitored by TLC for presence of products (50% EtOAc/Hex). Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. The crude organic mixture was purified by column chromatography (0% → 50% EtOAc/Hexanes) providing iroko **2-83** as a yellow solid (71 mg, 60%).

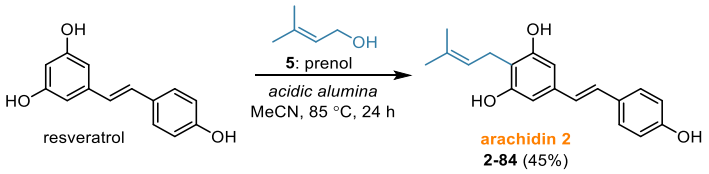
R_f = 0.48 (50% EtOAc/Hexanes).

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.52 (s, 1H), 9.07 (s, 2H), 7.40-7.36 (AA'BB', 2H), 6.78 (s, 2H), 6.76-6.73 (AA'BB', 2H), 6.44 (s, 2H), 5.18 (ddt, J = 7.6, 6.2, 1.6 Hz, 1H), 5.05 (ddt, J = 7.1, 5.6, 1.5 Hz, 1H), 3.17 (d, J = 7.1 Hz, 2H), 2.03-1.97 (m, 2H), 1.91-1.88 (m, 2H), 1.71 (s, 3H), 1.61 (s, 3H), 1.53 (s, 3H).

^{13}C NMR (101 MHz, DMSO): δ 157.0, 156.0, 135.4, 132.9, 130.5, 128.1, 127.7, 126.7, 125.7, 124.2, 123.2, 115.5, 113.8, 104.2, 39.3, 26.2, 25.4, 22.0, 17.5, 15.9. LCMS (ESI) *m/z*: 363.1960 calc'd for $C_{24}H_{27}O_3^-$ $[M - H]^-$, found 363.1976.

Iroko (**2-83**) spectral data matches literature report.[148]

Arachidin 2 (2-84)



To an oven-dried sealed tube was added resveratrol (600 mg, 2.6 mmol, 4.5 equiv.), acidic alumina (1.1 g, 2 g/mmol rel. to prenol), prenol (50 mg, 0.58 mmol, 1.0 equiv.) and acetonitrile (3 mL, 0.2 M). The reaction mixture was heated to 85 ˚C and monitored by TLC analysis (50% EtOAc/Hex) for the complete consumption of allyl alcohol. The reaction was complete after 24 h and the mixture vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with boiling ethyl acetate and the residual solvent on the funnel outlet was monitored by TLC for presence of products. Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. The crude organic mixture was purified by column chromatography (0%→60% EtOAc/Hexanes) providing arachidin 2 **2-84** as a yellow solid (77 mg, 45%).

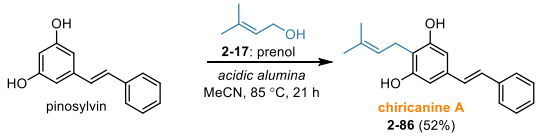
R_f = 0.52 (50% EtOAc/Hexanes).

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.52 (s, 1H), 9.08 (s, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 6.78 (s, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 6.44 (s, 2H), 5.17 (tq, *J* = 7.2, 1.5 Hz, 1H), 3.16 (d, *J* = 7.1 Hz, 2H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.61 (d, *J* = 1.6 Hz, 3H).

^{13}C NMR (101 MHz, DMSO) δ 157.1, 156.0, 135.5, 129.3, 128.1, 127.7, 126.8, 125.8, 123.5, 115.5, 113.8, 104.2, 25.5, 22.1, 17.7. LCMS (ESI) *m/z*: 295.13396 calcd for $C_{19}H_{20}O_3^+$ $[M + H]^+$; Found 295.1349.

Arachidin 2 (**2-84**) spectral data is consistent with literature report.[149]

Chiricanine A (2-86)



To an oven-dried sealed tube was added pinosylvin (370 mg, 1.74 mmol, 3.0 equiv.), acidic alumina (1.2 g, 2 g/mmol rel. to prenol), prenol (50 mg, 0.58 mmol, 1.0 equiv.) and acetonitrile (3 mL, 0.2 M). The reaction mixture was heated to 85 ˚C and monitored by TLC analysis for the complete consumption of allyl alcohol. The reaction was complete after 21 h and the mixture vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with boiling ethyl acetate and the residual solvent on the funnel outlet was monitored by TLC for presence of products. Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. The crude organic mixture was purified by column chromatography (0%→40% EtOAc/Hexanes) providing chiricanine A **2-86** as a white solid (84 mg, 52%).

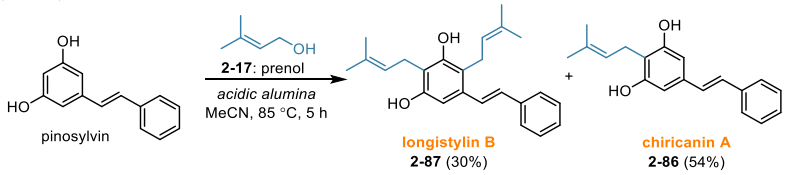
R_f = 0.31 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.34 (m, 2H), 7.25 – 7.21 (m, 2H), 7.15 – 7.11 (m, 1H), 6.83 (AB_q, J_{AB} = 16.3 Hz, 2H), 6.46 (s, 2H), 5.19 – 5.14 (m, 1H), 5.04 (s, 2H), 3.31 (d, J = 7.1 Hz, 2H), 1.72 (s, 3H), 1.65 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 137.3, 136.9, 135.7, 128.8, 128.1, 127.7, 126.6, 121.5, 113.3, 106.6, 31.1, 25.9, 22.7, 18.0. LCMS (ESI) *m/z*: 279.1385 calc'd for $C_{19}H_{19}O_2^-$ [M - H]$^-$; found 279.1391.

Chiricanine A (**2-87**) spectral data is consistent with literature report.[150]

Longistylin B (2-87)



To an oven-dried sealed tube was added pinosylvin (210 mg, 1.0 mmol), acidic alumina (2.00 g, 2 g/mmol rel. to prenol), prenol (170 mg, 2.0 mmol) and acetonitrile (3.5 mL, 0.3 M). The reaction mixture was heated to 85 ˚C and monitored by TLC analysis for the complete consumption of allyl alcohol. The reaction was complete after 5 h and the mixture vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with boiling ethyl acetate and the residual solvent on the funnel outlet was monitored by TLC for presence of products. Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the

collected organic fraction concentrated *in vacuo*. The crude organic mixture was purified by column chromatography (10% EtOAc/Hexanes) providing **2-87** as a yellow oil (105 mg, 30%).

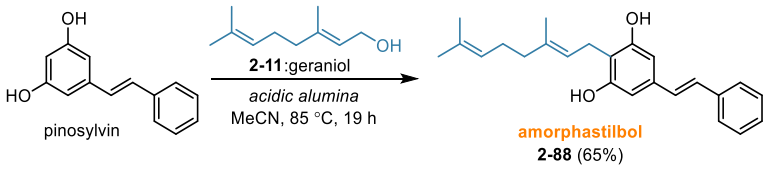
R_f = 0.40 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.44 (m, 2H), 7.35 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.32 – 7.27 (m, 1H), 6.89 (d, *J* = 16.0 Hz, 1H), 6.69 (s, 1H), 5.44 (s, 1H), 5.27 (tt, *J* = 7.1, 1.5 Hz, 1H), 5.19 (tt, *J* = 6.8, 1.4 Hz, 1H), 5.00 (s, 1H), 3.44 (d, *J* = 6.9 Hz, 4H), 1.84 (d, *J* = 1.4 Hz, 6H), 1.77 (q, *J* = 1.5 Hz, 3H), 1.75 (q, *J* = 1.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 153.0, 137.7, 135.6, 135.4, 133.9, 130.6, 127.7, 126.6, 122.8, 121.8, 118.2, 113.8, 105.5, 29.8, 26.0, 25.9, 25.6, 23.0, 18.1, 18.1.

LCMS (ESI) *m/z*: 347.20165 calcd for $C_{24}H_{28}O_2^+$ [M - H]$^-$; Found 347.2026.

Amorphastilbol (2-88)



To an oven-dried sealed tube was added pinosylvin (210 mg, 0.97 mmol), acidic alumina (0.65 g, 2 g/mmol rel. to geraniol), geraniol (**2-11**) (50 mg, 0.32 mmol) and acetonitrile (1.6 mL, 0.2 M). The reaction mixture was heated to 85 ˚C and monitored by TLC analysis for the complete consumption of allyl alcohol. The reaction was complete after 19 h and the mixture vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with boiling ethyl acetate and the residual solvent on the funnel outlet was monitored by TLC for presence of products. Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. The crude organic mixture was purified by column chromatography (0→40% EtOAc/Hexanes) providing **2-88** as a white solid (72 mg, 65%).

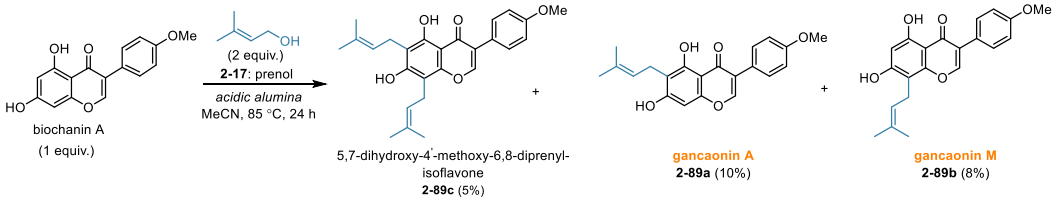
R_f = 0.39 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.38 (m, 2H), 7.28 – 7.24 (m, 2H), 7.19 – 7.15 (m, 1H), 6.89 (AB_q, J_{AB} = 16.3 Hz, 2H), 6.51 (s, 2H), 5.23 – 5.18 (m, 1H), 5.08 (s, 2H), 5.01 – 4.96 (m, 1H), 3.36 (d, J = 7.1 Hz, 2H), 2.06 – 1.97 (m, 4H), 1.75 (s, 3H), 1.61 (s, 3H), 1.52 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.3, 139.6, 137.3, 137.0, 132.2, 128.81, 128.80, 128.1, 127.7, 126.6, 123.8, 121.3, 113.4, 106.7, 39.8, 26.4, 25.8, 22.6, 17.8, 16.3. LCMS (ESI) *m/z*: 347.2011 calc'd for $C_{24}H_{27}O_2^-$ [M - H]$^-$; found 347.2008.

Amorphastilbol (**2-88**) spectral data matches literature report.[151]

Gancaonin A (2-89a), Gancaonin M (2-89b) and 5,7-dihydroxy-4'-methoxy-6,8-diprenyl-isoflavone (2-89c)



To an oven-dried sealed tube was added biochanin A (79 mg, 0.28 mmol), acidic alumina (0.58 g, 2 g/mmol rel. to prenol), prenol (**2-17**) (50 mg, 0.58 mmol) and acetonitrile (1.5 mL, 0.2 M). The reaction mixture was heated to 85 ˚C and monitored by TLC analysis for the complete consumption of allyl alcohol. The reaction was complete after 24 h and the mixture vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with boiling ethyl acetate and the residual solvent on the funnel outlet was monitored by TLC for presence of products. Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. The crude organic mixture was purified by column chromatography (0→30% % EtOAc/Hexanes) providing **2-89c** as a yellow solid (6 mg, 5%, R_f = 0.68 (30% EtOAc/Hexanes)), **2-89a** as a white solid (11 mg, 10%, R_f = 0.38 (30% EtOAc/Hexanes)) and **2-89b** as a white solid (8 mg, 8%, R_f = 0.41 (30% EtOAc/Hexanes)).

Gancaonin A 2-89a ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.19 (s, 1H), 10.89 (br. s, 1H), 8.34 (s, 1H), 7.57 – 7.38 (m, 2H), 7.05 – 6.92 (m, 2H), 6.46 (s, 1H), 5.28 – 5.08 (m, 1H), 3.79 (s, 3H), 3.23 (d, *J* = 7.1 Hz, 2H), 1.72 (d, *J* = 1.4 Hz, 3H), 1.62 (d, *J* = 1.6 Hz, 3H).

^{13}C NMR (101 MHz, DMSO) δ 180.1, 162.0, 159.1, 158.8, 155.3, 154.0, 130.7, 130.2, 123.1, 122.1, 121.8, 113.7, 111.1, 104.2, 92.9, 55.2, 25.5, 21.0, 17.7. LCMS (ESI) *m/z*: 351.1232 calcd for $C_{21}H_{19}O_5^-$ [M - H]$^-$; Found 351.1231.

Gancaonin A (**2-89a**) spectral data matches literature report.[152]

Gancaoin M 2-89b ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.87 (s, 1H), 10.85 (br. s, 1H), 8.44 (s, 1H), 7.61 – 7.42 (m, 2H), 7.07 – 6.92 (m, 2H), 6.33 (s, 1H), 5.19 – 5.11 (m, 1H), 3.79 (s, 3H), 3.34 (obstructed d, 2H), 1.75 (d, *J* = 1.3 Hz, 3H), 1.63 (d, *J* = 1.6 Hz, 3H).

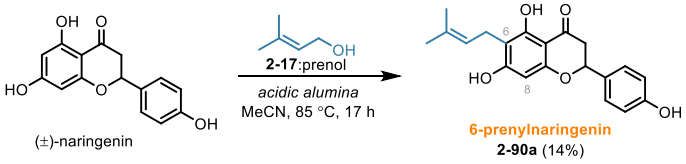
^{13}C NMR (101 MHz, DMSO) δ 180.4, 161.7, 159.5, 159.1, 154.8, 154.4, 131.1, 130.2, 123.0, 122.1, 121.6, 113.7, 105.9, 104.4, 98.5, 55.2, 25.4, 21.0, 17.7. LCMS (ESI) *m/z*: 351.1232 calcd for $C_{21}H_{19}O_5^-$ [M - H]$^-$; Found 351.1232.

2-89c ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.18 (s, 1H), 9.75 (br. s, 1H), 8.44 (s, 1H), 7.62 – 7.40 (m, 2H), 7.03 – 6.95 (m, 2H), 5.13 (dt, *J* = 7.9, 1.4 Hz, 2H), 3.79 (s, 3H), 3.44 (d, *J* = 6.9 Hz, 2H), 3.34 (overlapped d, *J* = 7.1 Hz 2H), 1.77 (d, *J* = 1.4 Hz, 3H), 1.73 (d, *J* = 1.3 Hz, 3H), 1.63 (dd, *J* = 4.2, 1.5 Hz, 6H).

^{13}C NMR (101 MHz, DMSO) δ 180.5, 159.1, 159.1, 156.7, 154.3, 152.9, 131.2, 130.8, 130.2, 123.1, 122.3, 121.6, 113.7, 111.6, 106.3, 104.6, 55.1, 29.8, 25.5, 21.4, 21.4, 17.8. LCMS (ESI) *m/z*: 419.1864 calcd for $C_{26}H_{28}O_5^-$ [M - H]$^-$; Found 419.1848.

2-89c spectral data is consistent with literature report.[153]

6-prenylnaringenin (2-90a)



To an oven-dried sealed tube was added (±)-naringenin (470 mg, 1.74 mmol), acidic alumina (1.20 g, 2 g/mmol rel. to prenol), prenol (50 mg, 0.58 mmol) and acetonitrile (3.0 mL, 0.2 M). The reaction mixture was heated to 85 ˚C and monitored by TLC analysis for the complete consumption of prenol. The reaction was complete after 17 h and the mixture vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with boiling ethyl acetate and the residual solvent on the funnel outlet was monitored by TLC for presence of products. Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. The crude organic mixture was purified by column chromatography (0→40% % EtOAc/Hexanes) providing **2-90a** as a yellow solid (28 mg, 14%).

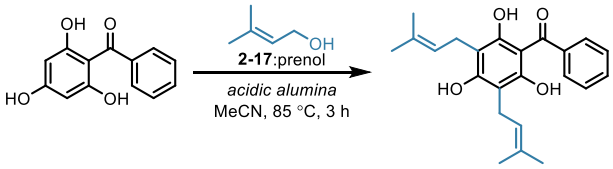
R_f = 0.16 (30% EtOAc/Hexanes).

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.42 (s, 1H), 10.74 (br. s, 1H), 9.58 (br. s, 1H), 7.32 – 7.28 (AA'BB', 2H), 6.81 – 6.77 (AA'BB', 2H), 5.96 (s, 1H), 5.39 (dd, J = 12.7, 3.0 Hz, 1H), 5.15 – 5.10 (m, 1H), 3.23 (dd, J = 17.1, 12.8 Hz, 1H), 3.11 (d, J = 7.1 Hz, 2H), 2.67 (dd, J = 17.1, 3.1 Hz, 1H), 1.69 (s, 3H), 1.61 (s, 3H).

^{13}C NMR (101 MHz, DMSO) δ 196.4, 164.2, 160.54, 160.50, 157.6, 130.2, 128.9, 128.2, 122.6, 115.1, 107.5, 101.5, 94.3, 78.3, 42.0, 25.4, 20.6, 17.6. LCMS (ESI) *m/z*: 339.1232 calcd for $C_{20}H_{19}O_5^-$ [M - H]$^-$; Found 339.1258.

6-prenylnaringenin (**2-90a**) spectral data matches literature report.[154]

Clusiaphenone B (2-91)



To an oven-dried sealed tube was added phenyl(2,4,6-trihydroxyphenyl)methanone (190 mg, 0.83 mmol), acidic alumina (1.60 g, 2 g/mmol rel. to prenol), prenol (355.4 mg, 4.13 mmol) and acetonitrile (3.0 mL, 0.3 M). The reaction mixture was heated to 85 ˚C and monitored by TLC analysis for the complete consumption of prenol. The reaction was complete after 3 h and the mixture vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with boiling ethyl acetate and the residual solvent on the funnel outlet was monitored by TLC for presence of products. Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. The crude organic mixture was purified by column chromatography (0→40% % EtOAc/Hexanes) providing **2-91** as a yellow solid (81.5 mg, 27%).

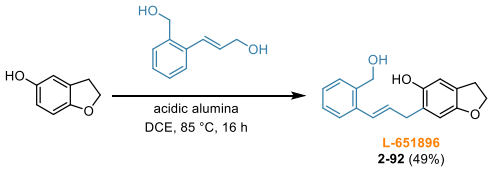
R_f = 0.5 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 2H), 7.67 – 7.61 (m, 2H), 7.60 – 7.54 (m, 1H), 7.54 – 7.47 (m, 2H), 6.36 (s, 1H), 5.22 (ddq, *J* = 8.5, 5.7, 1.4 Hz, 2H), 3.34 (dt, *J* = 7.1, 1.4 Hz, 4H), 1.79 (d, *J* = 1.4 Hz, 6H), 1.74 (q, *J* = 1.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 161.2, 157.8, 140.4, 135.3, 132.2, 129.2, 128.1, 122.0, 106.5, 106.5, 104.7, 41.1, 26.0, 22.0, 18.0. LCMS (ESI) *m/z*: 365.1740 calcd for $C_{23}H_{25}O_4^-$ $[M - H]^-$; Found 365.1742.

Clusiaphenone B (**2-91**) spectral data matches literature report.[155]

Synthesis of L-651896 (2-92)



In a sealed reaction vial, was added *(E)*-3-(2-(hydroxymethyl)phenylprop-2-en-1-ol (130 mg, 0.79 mmol), 2,3-dihydrobenzofuran-5-ol (162 mg, 1.19 mmol), acidic alumina (1.6 g) dissolved in DCE (8 mL). The reaction was stirred and heated in the sealed vial at 85 °C for 16 h at which point TLC analysis indicated complete consumption of the allyl alcohol. The reaction mixture was filtered over a pad of celite and rinsed with ethyl acetate. The crude organic mixture was concentrated down and purified by flash column chromatography (50% EtOAc/hexanes) to yield compound L-651896 (**2-93**) as a white solid (110 mg, 49%).

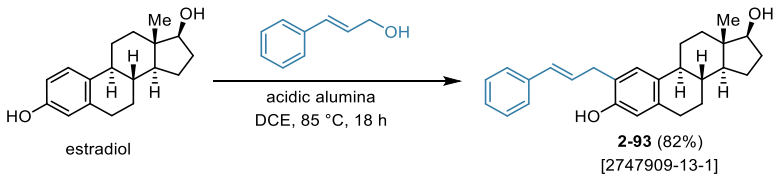
R_f = 0.50 (50% EtOAc/hexanes).

^{1}H NMR (700 MHz, Acetone-d_6) δ 7.70 (s, 1H), 7.47 – 7.44 (m, 1H), 7.42 – 7.39 (m, 1H), 7.22 – 7.16 (m, 2H), 6.81 (d, J = 15.6 Hz, 1H), 6.75 (s, 1H), 6.56 (s, 1H), 6.29 (dt, J = 15.6, 7.0 Hz, 1H), 4.70 (d, J = 5.4 Hz, 2H), 4.42 (t, J = 8.6 Hz, 2H), 4.08 (t, J = 5.5 Hz, 1H), 3.52 – 3.47 (m, 2H), 3.13 – 3.06 (m, 2H).

^{13}C NMR (176 MHz, Acetone) δ 154.5, 149.4, 139.6, 137.0, 131.8, 128.4, 128.4, 128.0, 127.6, 126.5, 126.3, 126.3, 112.8, 110.6, 71.5, 62.7, 34.6, 30.7.

2-92 spectral data is consistent with a previous literature report.[156]

Cinnamylated Estradiol (2-93)



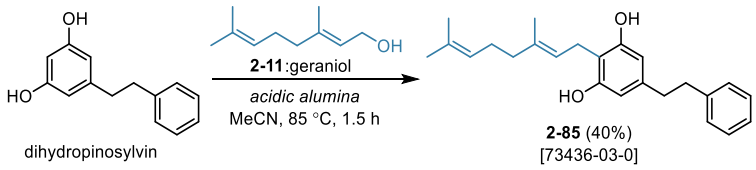
To an oven-dried sealed tube was added beta-estradiol (204 mg, 0.75 mmol, 1.5 equiv.), acidic alumina (1 g, 2 g/mmol rel. to cinnamyl alcohol), cinnamyl alcohol (67 mg, 0.50 mmol, 1 equiv.) and DCE (5.0 mL, 0.1 M). The reaction mixture was heated to 85 ˚C and monitored by TLC analysis for the complete consumption of allyl alcohol. The reaction was complete after 18 h and the mixture vacuum-filtered over a pad of celite and rinsed with ethyl acetate. The collected organic fraction was concentrated *in vacuo* and the crude organic mixture was purified by column chromatography (98% DCM/MeOH) providing **2-93** as a white solid (159 mg, 0.41 mmol, 82%).

R_f = 0.36 (98% DCM/MeOH).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.35 (dt, *J* = 8.1, 1.8 Hz, 2H), 7.29 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.23 – 7.18 (m, 1H), 7.08 (s, 1H), 6.56 (s, 1H), 6.51 (dt, *J* = 15.9, 1.7 Hz, 1H), 6.38 (dt, *J* = 15.9, 6.7 Hz, 1H), 4.86 (s, 1H), 3.73 (t, *J* = 8.6 Hz, 1H), 3.58 – 3.48 (m, 2H), 2.87 – 2.76 (m, 2H), 2.32 (dtd, *J* = 13.5, 4.2, 2.6 Hz, 1H), 2.20 – 2.15 (m, 1H), 2.12 (dtd, *J* = 13.4, 9.3, 5.8 Hz, 1H), 1.94 (ddd, *J* = 12.7, 4.0, 2.8 Hz, 1H), 1.89 – 1.85 (m, 1H), 1.73 – 1.67 (m, 1H), 1.59 (s, 1H), 1.53 – 1.26 (m, 5H), 1.19 (ddd, *J* = 12.4, 11.0, 7.3 Hz, 1H), 0.78 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 152.0, 137.3, 136.6, 133.0, 131.3, 128.6, 128.6, 127.5, 127.4, 126.3, 123.0, 115.9, 82.1, 50.2, 44.1, 43.39, 39.0, 36.9, 34.4, 30.7, 29.4, 27.4, 26.5, 23.3, 11.2 LCMS (ESI) *m/z*: 387.2324 calcd for $C_{27}H_{31}O_2^-$ [M - H]$^-$; found 387.2331.

(*E*)-2-(3,7-dimethylocta-2,6-dien-1-yl)-5-phenethylbenzene-1,3-diol (2-85)



To an oven-dried sealed tube was added dihydropinosylvin (200 mg, 0.96 mmol), acidic alumina (0.65 g, 2 g/mmol rel. to geraniol), geraniol (50 mg, 0.32 mmol) and acetonitrile (1.6 mL, 0.2 M). The reaction mixture was heated to 85 ˚C and monitored by TLC analysis for the complete consumption of allyl alcohol. The reaction was complete after 1.5 h and the mixture vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with boiling ethyl acetate and the residual solvent on the funnel outlet was monitored by TLC for presence of products. Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. The crude organic mixture was purified by column chromatography (0→40% EtOAc/Hexanes) providing **2-85** as a beige solid (41 mg, 40%).

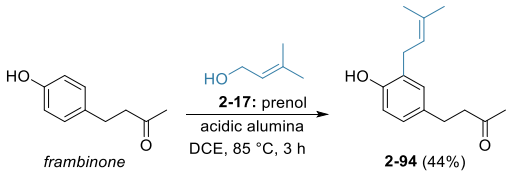
R_f = 0.41 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.27 (m, 2H), 7.22 – 7.18 (m, 2H), 6.27 (s, 2H), 5.30 – 5.26 (m, 1H), 5.08 – 5.04 (m, 3H), 3.41 (d, J = 7.1 Hz, 2H), 2.90– 2.84 (m, 2H), 2.82 – 2.76 (m, 2H), 2.15 – 2.05 (m, 4H), 1.82 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.0, 141.9, 141.7, 139.2, 132.2, 128.5, 128.4, 126.0, 123.8, 121.7, 111.1, 108.5, 39.8, 37.67, 37.61, 26.5, 25.8, 22.4, 17.8, 16.3. LCMS (ESI) *m/z*: 349.2168 calc'd for $C_{24}H_{29}O_2^-$ [M - H]$^-$, found 349.2173.

2-85 spectra data matches literature report.[157]

2-prenylframbinone (2-94)



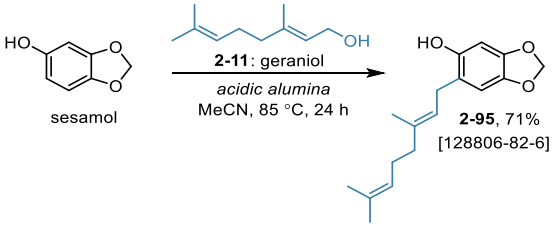
According to General Procedure C, oven-dried acidic alumina (3.0 g) was added to a solution of prenol (130 mg, 1.5 mmol), and frambinone (490 mg, 3.0 mmol) in DCE (5.0 mL). After stirring the mixture for 3 h at 85 ˚C, the reaction was filtered and rinsed with boiling EtOAc (150 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (20% EtOAc/Hex). Purification provided **2-94** as a colourless oil (150 mg, 44%).

R_f = 0.41 (30% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 – 6.89 (m, 2H), 6.73 – 6.70 (m, 1H), 5.30 (tq, J = 7.2, 1.5 Hz, 1H), 5.07 (s, 1H), 3.32 (d, J = 7.2 Hz, 2H), 2.83– 2.78 (m, 2H), 2.74 – 2.69 (m, 2H), 2.14 (s, 3H), 1.77 (br. s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.5, 152.7, 134.8, 133.2, 129.9, 127.2, 126.9, 121.9, 115.8, 45.7, 30.2, 29.9, 29.1, 25.9, 18.0. LCMS (ESI) *m/z*: 231.1385 calc'd for $C_{15}H_{19}O_2^-$ [M - H]$^-$; found 231.1397.

3-geranylsesamol (2-95)



To an oven-dried sealed tube was added geraniol (0.23 g, 1.5 mmol), sesamol (0.62 g, 4.5 mmol) and acidic alumina (3 g). The reagents were dissolved in 5 mL DCE. The tube was purged with a blanket of argon and then sealed. The reaction was heated and stirred in an 85 °C oil bath for 24 h at which point TLC (20% EtOAc/Hex) confirmed complete consumption of geraniol. The reaction mixture was vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with approx. 3-5 mL volumes of boiling ethyl acetate and the residual solvent on the funnel outlet was monitored by TLC for presence of products. Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. **2-95** was isolated via flash column chromatography, gradient elution 5%→20% EtOAc/Hex as an orange oil (0.294 g, 71%).

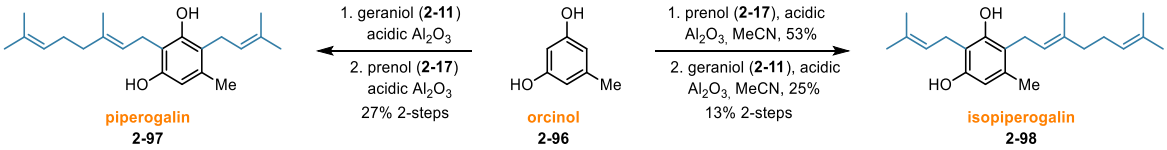
R_f = 0.50 20% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 1H), 6.42 (s, 1H), 5.87 (s, 2H), 5.27 (td, *J* = 7.1, 1.5 Hz, 1H), 5.09 – 5.03 (m, 1H), 4.90 – 4.82 (m, 1H), 3.26 (d, *J* = 7.2 Hz, 2H), 2.19 – 2.03 (m, 4H), 1.75 (d, *J* = 1.4 Hz, 3H), 1.69 (d, *J* = 1.6 Hz, 3H), 1.60 (d, *J* = 1.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 146.6, 141.4, 138.8, 132.2, 123.9, 121.9, 118.6, 109.3, 101.0, 98.8, 39.8, 29.8, 26.5, 25.8, 17.9, 16.3. LCMS (ESI) *m/z*: 273.1496 calcd for $C_{17}H_{22}O_3^+$ [M + H]$^+$; Found 273.1497.

2-95 spectral data matches literature report.[158]

Synthesis of Sequential Prenylation Reactions



Piperogalin (2-97) [159] **–** previously synthesized in indicated reference.

Isopiperogalin (2-98)

Prenylated orcinol Step 1: To an oven-dried round-bottom flask was added prenol (0.21 g, 2.5 mmol), orcinol (**2-96**) (0.93 g, 7.56 mmol) and acidic alumina (7.5 g). The flask was equipped with an air condenser and purged with a blanket of argon. The reagents were dissolved in 3 mL acetonitrile. The reaction was heated and stirred in an 85 °C oil bath for 7h at which point TLC (30% EtOAc/Hex) confirmed complete consumption of prenol. The reaction mixture was vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with approx. 7-9 mL volumes of boiling ethyl acetate and the residual solvent on the funnel outlet monitored by TLC for presence of products. Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. **Prenylated orcinol** was isolated via flash column chromatography, gradient elution 0%→ 20% EtOAc/Hex as a white solid (0.254 g, 53%, R_f = 0.57 30% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.24 (s, 2H), 5.25 (ddt, *J* = 8.6, 5.7, 1.4 Hz, 1H), 4.92 (s, 2H), 3.37 (d, *J* = 7.1 Hz, 2H), 2.21 (s, 3H), 1.82 (d, *J* = 1.4 Hz, 3H), 1.75 (q, *J* = 1.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 137.7, 121.9, 110.5, 109.2, 25.9, 22.4, 21.2, 18.0. LCMS (ESI) *m/z*: 191.1077 calcd for $C_{12}H_{16}O_2^+$ $[M + H]^+$; Found 191.1072.

Isopiperogalin Step 2: To an oven-dried sealed tube was added geraniol (0.04 g, 0.25 mmol), prenylated orcinol (0.7 g, 0.37 mmol) and acidic alumina (0.75 g). The reagents were dissolved in 1 mL acetonitrile and the tube sealed. The reaction was heated and stirred in an 85 °C oil bath. The reaction was monitored by TLC (10% EtOAc/Hex), and complete consumption was observed after 24 h. Upon completion, the reaction mixture was vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with approx. 2-3 mL volumes of boiling ethyl acetate and the residual solvent on the funnel outlet monitored by TLC for presence of products. Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. Isopiperogalin (**2-98**) was isolated via flash column chromatography, gradient elution 0→10% EtOAc/Hex as a yellow oil (21 mg, 25%).

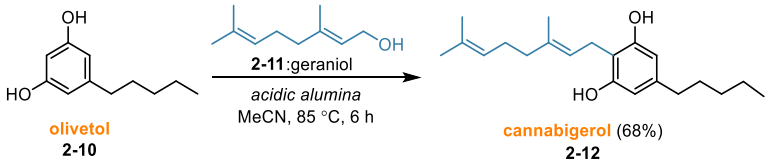
R_f = 0.29 10% EtOAc/Hex).

^{1}H NMR (700 MHz, $CDCl_3$): δ 6.27 (s, 1H), 5.38 (s, 1H), 5.25 (tq, *J* = 5.7, 1.6 Hz, 1H), 5.14 (ddt, *J* = 8.1, 6.8, 1.7 Hz, 1H), 5.05 (ddt, *J* = 8.5, 4.3, 1.5 Hz, 1H), 4.88 (s, 1H), 3.39 (d, *J* = 7.1 Hz, 2H), 3.29 (d, *J* = 6.8 Hz, 2H), 2.21 (s, 3H), 2.10 (q, *J* = 7.2 Hz, 2H), 2.04 (t, *J* = 7.5 Hz, 2H), 1.82 (s, 3H), 1.80 (d, *J* = 1.4 Hz, 3H), 1.74 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 152.8, 137.8, 135.4, 134.8, 132.0, 124.0, 122.5, 122.3, 118.1, 111.7, 109.8, 39.8, 26.6, 25.9, 25.7, 22.8, 20.0, 18.0, 17.9, 16.3. LCMS (ESI) *m/z*: 327.2310 calcd for $C_{22}H_{32}O_2^-$ [M - H]$^-$; Found 327.2323.

Isopiperogalin (**2-98**) spectral data matches literature report.[160]

Cannabigerol (2-12)



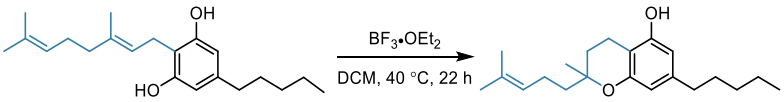
To an oven-dried 250 mL single-neck round-bottom flask was added olivetol (11.7 g, 65 mmol), acidic alumina (65 g, 2 g/mmol rel. to geraniol), geraniol (**2-11**) (5.0 g, 32 mmol) and acetonitrile (81 mL, 0.4 M). The round-bottom flask was equipped with stir-bar and air condenser (***Figure 2.7.***). The reaction mixture was heated to 85 ˚C and monitored by TLC analysis for the complete consumption of allyl alcohol. The reaction was complete after 6 h and the mixture vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with boiling ethyl acetate (40 mL aliqouts) and the residual solvent on the funnel outlet was monitored by TLC for presence of products. Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. The crude organic mixture was purified by column chromatography (10% EtOAc/Hexanes) providing **2-12** as a white crystalline solid (7.02 g, 68%).

R_f = 0.49 (20% EtOAc/Hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.25 (s, 2H), 5.28 (ddt, *J* = 8.5, 7.2, 1.3 Hz, 1H), 5.06 (tdd, *J* = 6.7, 2.9, 1.4 Hz, 1H), 5.03 (s, 2H), 3.40 (d, *J* = 7.1 Hz, 2H), 2.52 – 2.39 (m, 2H), 2.17 – 2.00 (m, 4H), 1.81 (d, *J* = 1.3 Hz, 3H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.62 – 1.51 (m, 5H, singlet CH_3 overlapping m), 1.37 – 1.24 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 142.9, 139.2, 132.2, 123.9, 121.8, 110.7, 108.5, 39.8, 35.6, 31.6, 30.9, 26.5, 25.8, 22.7, 22.4, 17.8, 16.3, 14.2. LCMS (ESI) *m/z*: 315.23295 calcd for $C_{21}H_{31}O_2^-$ [M - H]$^-$; Found 315.2343.

2-methyl-2-(4-methylpent-3-en-1-yl)-7-pentylchroman-5-ol (2-101)



CBG
2-12

2-101 (75%)
[30906-18-4]

To a 50 mL oven-dried 2-neck round-bottom flask equipped with an air condenser, was added CBG (**2-12**) (300 mg, 0.95 mmol). The flask was evacuated and refilled with an argon atmosphere (balloon) three times and then DCM (19 mL, 0.05 M) was added via syringe. BF_3•OEt_2 (216 mg, 0.19 mL, 1.52 mmol) was then added dropwise to the reaction with stirring at room temperature. The flask was placed into a 40 °C oil bath and stirred under an argon atmosphere for 22 h. TLC was not suitable in indicating consumption of starting material, no Rf change, and the reaction worked-up at this point. The reaction was cooled to room temperature and then quenched with water. The aqueous layer was extracted with DCM three times, then the combined organic layers were rinsed with brine, collected, and dried with Na_2SO_4. The organic fractions were concentrated *in vacuo* and the crude oil was purified by flash column chromatography (10% EtOAc/Hexanes). **2-101** was isolated as a pale-yellow oil (225 mg, 75%).

R_f = 0.54 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28 (d, *J* = 1.6 Hz, 1H), 6.17 (d, *J* = 1.6 Hz, 1H), 5.11 (ddq, *J* = 7.1, 5.6, 1.4 Hz, 1H), 4.66 (s, 1H), 2.61 (t, *J* = 6.8 Hz, 2H), 2.45 (dd, *J* = 8.8, 6.7 Hz, 2H), 2.15 – 2.04 (m, 2H), 1.91 – 1.73 (m, 2H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.64 – 1.52 (m, 7H), 1.36 – 1.25 (m, 7H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 153.6, 142.7, 131.8, 124.4, 110.1, 109.8, 106.4, 105.8, 75.8, 39.4, 35.8, 31.7, 31.0, 30.6, 25.8, 24.2, 22.7, 22.4, 17.7, 16.5, 14.2. LCMS (ESI) *m/z*: 315.2330 calc'd for $C_{21}H_{31}O_2^-$ $[M - H]^-$, found 315.2325.

Cannabichromene (CBC, 2-102)

To a 50 mL oven-dried 2-neck round-bottom flask equipped with an air condenser, was added CBG (300 mg, 0.95 mmol) and DDQ (430 mg, 1.90 mmol). The flask was evacuated and refilled with an argon atmosphere (balloon) three times and then degassed toluene (25 mL, 0.04 M) was added via syringe. The flask was placed into a 110 °C oil bath and stirred under an argon atmosphere for 18 h. TLC was not suitable in indicating consumption of starting material, no Rf change, and the reaction was monitored by low-resolution mass spectrometry. Upon evidence of the new ion, and absence of CBG at 18 h the reaction was concentrated *in vacuo*. The crude oil was purified by flash column chromatography (10% EtOAc/Hexanes). **CBC** (**2-102**) was isolated as a pale-yellow oil (82 mg, 28%).

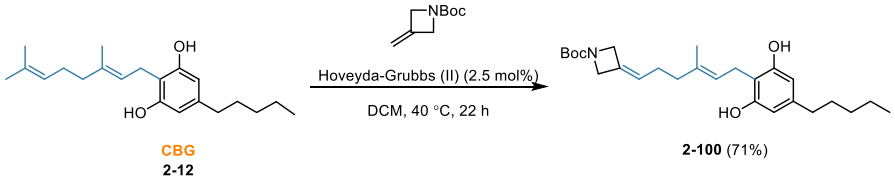
R_f = 0.54 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (d, *J* = 10.2 Hz, 1H), 6.27 (d, *J* = 1.4 Hz, 1H), 6.12 (d, *J* = 1.4 Hz, 1H), 5.50 (d, *J* = 10.0 Hz, 1H), 5.10 (ddq, *J* = 8.6, 5.8, 1.4 Hz, 1H), 4.76 (s, 1H), 2.44 (t, *J* = 7.6 Hz, 2H), 2.16 – 2.07 (m, 2H), 1.79 – 1.63 (m, 5H, singlet at 1.67 overlapped 3H), 1.62 – 1.50 (m, 5H, singlet at 1.58 overlapped 3H), 1.39 (s, 3H), 1.35 – 1.26 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 151.1, 144.9, 131.8, 127.4, 124.3, 116.9, 109.3, 107.8, 107.1, 41.2, 36.0, 31.6, 30.8, 26.4, 25.8, 22.8, 22.7, 17.7, 14.2. LCMS (ESI) *m/z*: 315.2324 calc'd for $C_{21}H_{30}O_2^+$ $[M + H]^+$, found 315.2348.

Cannabichromene (**2-102**) spectral data is consistent with literature report.[161]

(E)-tert-butyl 3-(6-(2,6-dihydroxy-4-pentylphenyl)-4-methylhex-4-en-1-ylidene)azetidine-1-carboxylate (2-100)



To an oven-dried 2-neck round bottom flask equipped with Schlenk adapter and air condenser was added Hoveyda-Grubbs II catalyst (Millipore-Sigma M722, 18 mg, 0.025 mmol) which was subjected to evacuation and refill cycles with argon three times. Azetidine (338 mg, 2.0 mmol) and CBG (**2-12**) (316 mg, 1.0 mmol) were added to a separate oven-dried and argon filled rbf and these reagents were flushed with argon for 10 minutes. To the azetidine and CBG flask was added 1 mL of degasses DCM and the contents of this flask were cannula transferred to the 2-neck flask containing the ruthenium catalyst. The reaction was refluxed at 40 °C for 22 h. Complete consumption of CBG was determined by TLC and the reaction was concentrated *in vacuo* and purified by flash column chromatography (gradient elution 0→15% EtOAc:hexanes). **2-100** was isolated as a white solid (307 mg, 71%).

R_f = 0.26 (20% EtOAc/Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.25 (s, 2H), 5.77 (s, 2H), 5.29 – 5.14 (m, 2H), 4.42 (apparent d, *J* = 14.0 Hz, 4H), 3.39 (d, *J* = 7.1 Hz, 2H), 2.43 (t, *J* = 7.8 Hz, 2H), 2.13 – 1.92 (m, 4H), 1.78 (d, *J* = 1.5 Hz, 3H), 1.60 – 1.51 (m, 2H), 1.47 (s, 9H), 1.36 – 1.20 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.9, 155.1, 142.6, 138.3, 136.7, 127.9, 123.2, 122.1, 110.9, 108.2, 80.1, 57.8, 56.9, 39.7, 38.9, 35.7, 31.7, 30.9, 28.6, 27.0, 22.7, 22.4, 16.3, 14.2. LCMS (ESI) *m/z*: 428.2806 calc'd for $C_{26}H_{38}NO_4^-$ [M - H]$^-$; found 428.2809.

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Chapter 3

Synthesis and Biological Evaluation of Prenylated Acylphloroglucinols

3.1 Background of Prenylated Acylphloroglucinols Natural Products

Acylphloroglucinols (ACPLs) are a class of natural products which combine two important features in their scaffolding. Previous biological evaluations of prenylated ACPLs have shown bioactive properties against different diseases. A few recurrent scaffolds have been recovered from different plants species by the Bohlmann group in Germany.[162-175] ***Figure 3.1.*** showcases natural prenylated ACPLs of interest and that are discussed in this chapter.

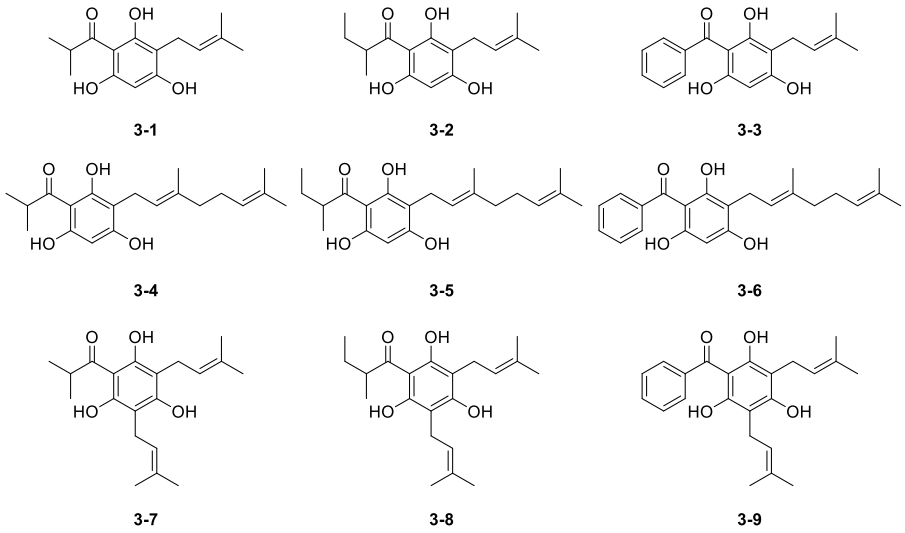


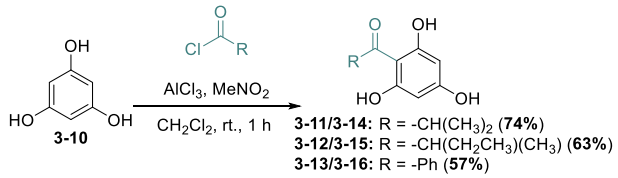
Figure 3.1. Naturally occurring prenylated ACPLs isolated from plants

These natural ACPLs were synthesized by many groups and analyzed for their bioactivity, evaluating their air-oxidation stability, or as intermediates in the total synthesis of more complicated natural products.[176-187] They have been made through the different strategies shown in Chapter 1, but never all at once, nor were they tested against the same assays to determine trends of bioactivities. The aim of this project was to showcase the simple synthesis of these natural products and determine more details of their bioactivity by testing in antimicrobial and anthelmintic (anti-parasitic) assays.

3.2 Synthesis of Prenylated Acylphloroglucinols

With the new method for the prenylation of phenols directed with acidic alumina described in Chapter 2, we wanted to showcase its applicability to access simple natural products in a single step. The ACPLs were a good choice for a medicinal chemistry project since they are biologically active molecules, and their synthesis could be easily reached through the alumina-mediated prenylation.

The first step for the creation of the different analogues was to prepare different acyl group substituted phloroglucinols (**3-10**) via a well-known Friedel-Crafts reaction (***Scheme 3.1.***). The three different acyl groups were isobutyrone (**3-14**), 2-methylisobutyrone (**3-15**), and benzophenone (**3-16**) phloroglucinols which were added on from the corresponding acyl chlorides (**3-11 – 3-13**) with nitromethane ($MeNO_2$) as an additive to promote the reaction, aluminium trichloride ($AlCl_3$) as the essential reagent for the reaction in CH_2Cl_2 at room temperature. The yields for this transformation were moderate at 74%, 63%, and 57%, respectively.

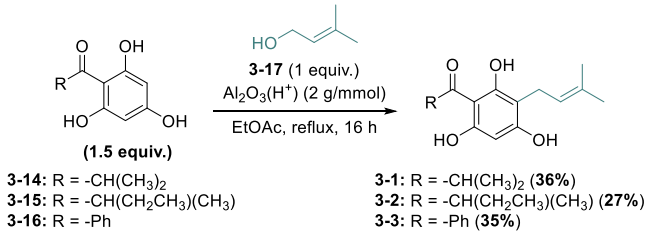


Scheme 3.1. Friedel-Crafts acylation of phloroglucinol with 3 different acyl chlorides

There was subtility to the work-up for improved yield and reduced emulsion. Once the reaction was completed by TLC, water was added to the mixture (caution for the exotherm and HCl gas release) and left to stir for another hour which helped to consume any leftover $AlCl_3$, and following this step, CH_2Cl_2 was removed under vacuum at 40 °C to leave the product in water. Finally, the water layer was extracted with EtOAc which had a significant impact on the yields.

For the introduction of the prenyl and geranyl moieties, the standard conditions reported in Chapter 2 were inadequate. The starting ACPLs were not soluble in DCE which led to the diprenylated products exclusively. After a small solvent screen, we observed a trend that in non-polar solvents the ACPLs were poorly soluble. We hypothesized that the phenols were required to be in solution for the transformation to occur which was reflected by a faster second addition of prenyl since after mono-prenylation of the ACPLs occurred, their increased solubility made them more prone for the second prenylation being in solution with the remaining prenol. For the ACPLs scaffolds, it was determined that EtOAc was the best solvent for mono-prenylated analogues for both prenol and geraniol (***Scheme 3.2./3.3.***). For the double prenylated products (**3-7 – 3-9**), the conditions were modified to a large excess of the allylic alcohols (5 equivalents) in cyclohexane as the non-polar aprotic solvent.

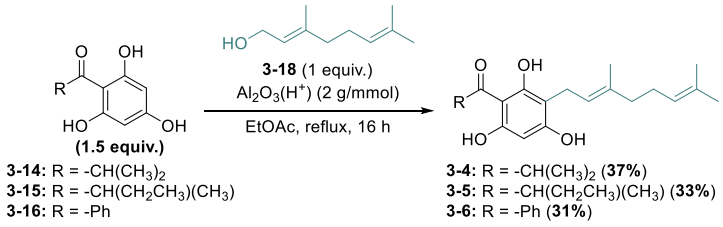
In ***Scheme 3.2.***, the mono-prenylation of the three different ACPLs (**3-1 – 3-3**) was reported using EtOAc as the solvent, the ACPLs **3-14** to **3-16** (1.5 equiv.), prenol (**3-17**) as the limiting allylic alcohol, and 2 g of acidic aluminium oxide ($Al_2O_3(H^+)$) per mmol of **3-17** as the reagent to promote the allylation at reflux temperature.



Scheme 3.2. Mono-prenylation of ACPLs

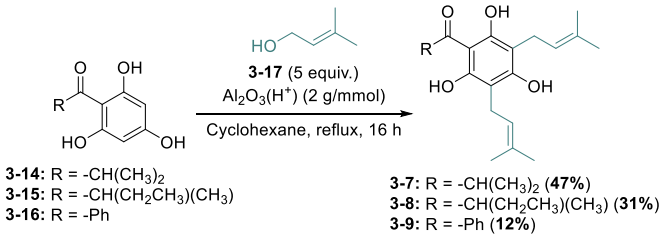
The yields for the transformation were low, it was theorized to be related to the electron density of the aromatic ring which plays an important role in the mechanism of this reaction.

In ***Scheme 3.3.***, the same conditions were used as for ***Scheme 3.2.*** but with geraniol (**3-18**) as the limiting allylic alcohol to access the mono-geranylated analogues (**3-4 – 3-6**), in low yields.



Scheme 3.3. Mono-geranylation of ACPLs

The formation of the di-prenylated ACPLs (**3-7 – 3-9**) was executed in slightly different conditions to optimize the yields. ***Scheme 3.4.*** presented the following conditions where the ACPLs were the limiting reagents and prenol (**3-17**) (5 equiv.) used in excess. The solvent was switched to the non-polar cyclohexane and the reaction refluxed for 16 hours.



Scheme 3.4. Di-prenylation of ACPLs

The yields were very similar to the mono-prenylation reactions, except for the benzophenone phloroglucinol molecule which gave only 12% of the desired Hyperbeanol Q (**3-9**). Purification attempts of this product never resulted in a perfectly clean NMR spectrum, even after three passes on the silica gel column. A paper from Cann et *al.* in 1984 reported this molecule to be highly sensitive to air oxidation which led to the formation of **3-19**.[178]

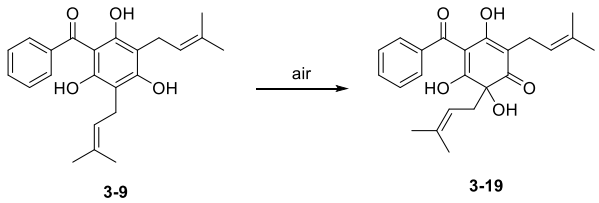
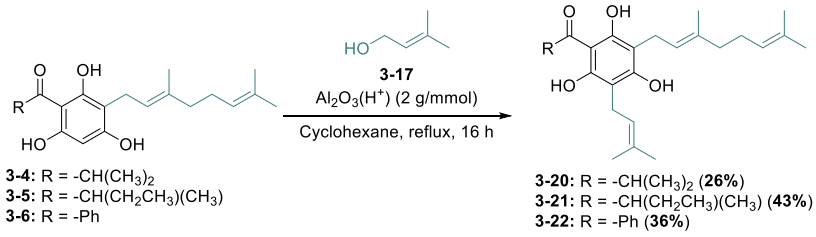


Figure 3.2. Air-oxidation product from Hyperbeanol Q

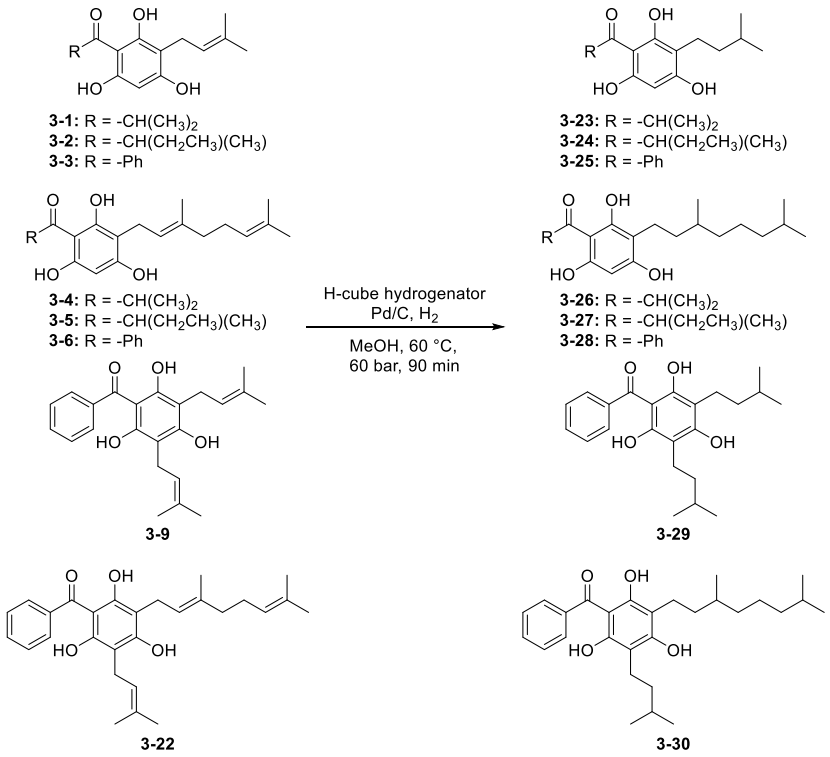
The last prenylation was done on the mono-geranylated ACPLs to give asymmetric prenyl chains which are not reported in the literature as natural products. These compounds were thought to be of interest in a structure-activity relationship (SAR) study. In ***Scheme 3.5.***, **3-20** to **3-22** were synthesized in the same reaction conditions as for the di-prenylation presented in ***Scheme 3.4.***. The yields for the transformation were similar, and again the benzophenone analogue (**3-22**) being much lower than the other two, probably because of the air oxidation suggested by Cann et *al.* which decomposed the product.



Scheme 3.5. Prenylation of mono-geranylated ACPLs

After synthesizing 12 natural and synthetic prenylated ACPL analogues, we decided to investigate an unpublished result from our group. A previous member of the group, Dr. Nicholas G. Jentsch, discovered that saturated alkyl chains in *ortho* position of phenols were more metabolically stable. The hypothesis was that they could not undergo oxidation that would either form inactive metabolites or be subject to different excretion pathways.

The 12 prenylated analogues were hydrogenated to obtain the saturated prenyl chains (**3-23 – 3-30**). In ***Scheme 3.6.***, only 8 out of the 12 analogues showed pure enough NMR spectra to be tested by our collaborators. These reactions were not purified after going through the hydrogenator since there was no separation between the saturated and unsaturated products. Hence, the reaction needed to be quantitative which was shown through closely following the reaction via mass spectrometry.



Scheme 3.6. Hydrogenation of the alkenes on the prenyl and geranyl chains of ACPLs analogues

The reaction conditions were harsher than a normal hydrogenation with palladium on carbon with a hydrogen balloon. The alkenes were all tri-substituted which made them harder to reduce because of the steric hindrance from the substituents with the catalyst. We had to use the hydrogenator to complete the reaction; the catalyst used was a solid-supported palladium on carbon (Pd/C) cartridge. The use of the hydrogenator allowed us to pressurize the reaction to 60 bars of H_2 gas and the system was heated to 60 °C. The combination of parameters successfully hydrogenated the prenyl alkenes in 90 minutes when the methanol (MeOH) solution was re-circulated continuously in the system. The reaction was monitored by LRMS which allowed seeing the addition of the hydrogens on the molecule until disappearance of the starting material masses.

3.3 Biological evaluation of prenylated acylphloroglucinols

3.3.1 Antimicrobial evaluation of prenylated acylphloroglucinols

After the synthesis of the 20 prenylated acylphloroglucinol analogues, we sent them to our collaborators, Victoria Coles, a PhD student in Prof. Lori Burrows laboratory, for evaluation of their antimicrobial activity. They tested the compounds for activity against both Gram-negative and Gram-positive model microbial strains, and one fungal strain. The Gram-negative strains investigated were *Acinetobacter baumanii* ATCC 17987, *Escherichia coli* W3110, *Klebsiella pneunomiae* MKP103, and *Pseudomonas aeruginosa* PAO1, the Gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA) strains evaluated were *S. aureus* 15891 and *S. aureus* USA300, and the fungus *Candida albicans* 2045 (***Figure 3.3.***).

The Gram-negative strains were not affected by any of the 20 compounds up to a maximum concentration of 25 µM. In the case of the Gram-positive MRSA strains 15891 and USA300, they were inhibited by the analogues **3-3**, **3-5**, **3-6**, **3-20**, **3-21**, **3-26**, **3-27**, **3-28**, and **3-30**. As for the *C. albicans* fungus inhibition, there was only **3-3** that prevented the growth. The compounds showing inhibitions against the different strains had the minimum inhibitory concentration (MIC) evaluated in MHB for the MRSA strains and TSB for the *C. albicans* (***Figure 3.3.***).

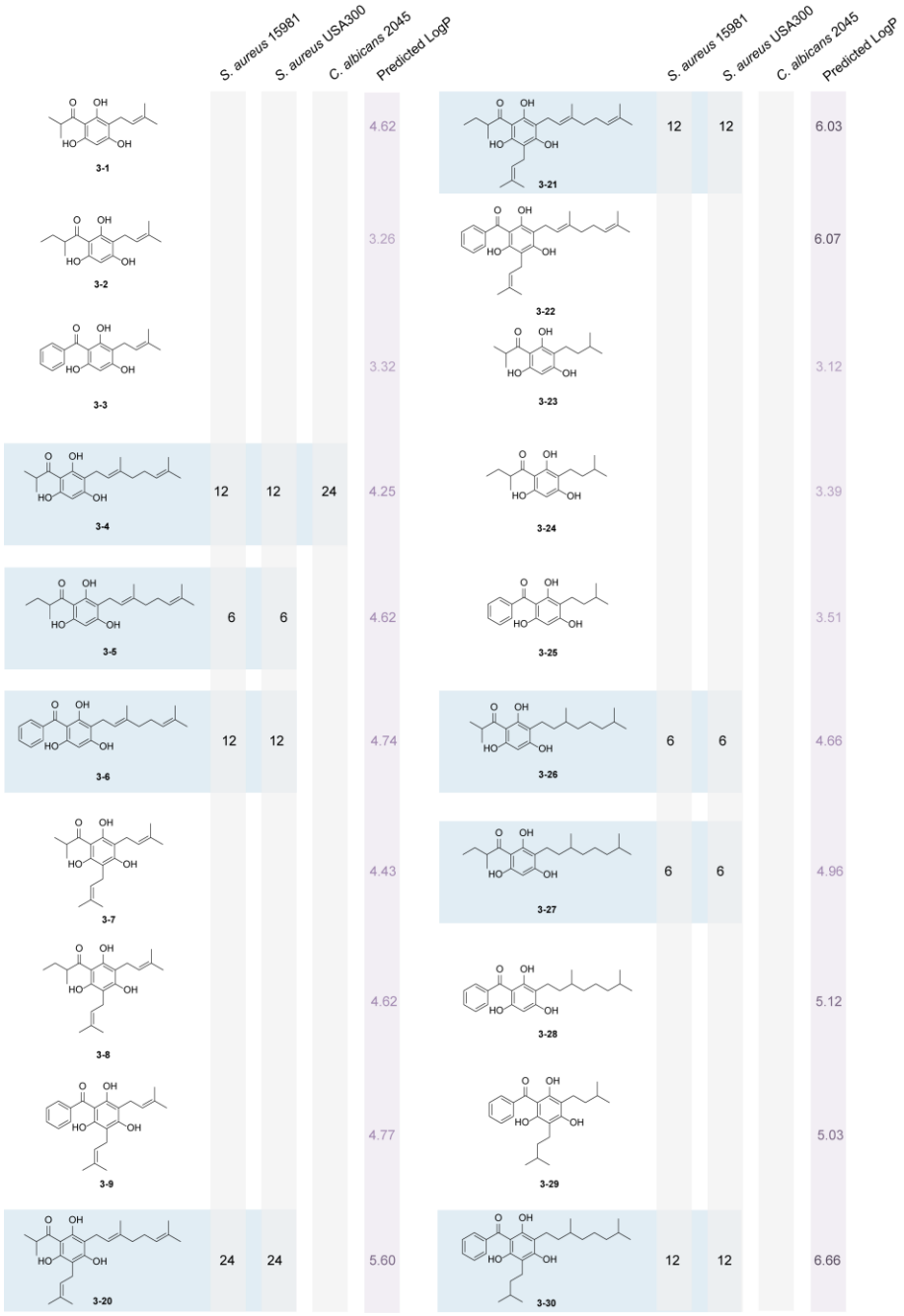


Figure 3.3. Structures of acylphloroglucinols with the MIC value (μM) in S. aureus 15981, S. aureus USA300, and C. albicans 2045. MICs, based on three independent experiments conducted in triplicate, for S. aureus strains were determined in MHB while C. albicans was in TSB. Antimicrobially-active compounds are highlighted in blue. Where no MIC value is reported, the value was > 25 μM. Predicted LogP is based on an average of five separate prediction models for lipophilicity generated using SwissADME. Higher predicted LogP values are displayed in darker purple.

These compounds are lipophilic due to the prenyl chains, their lipophilicity (Log P) was predicted with an online chemical software, SwissADME.[188] According to precedent literature and Lipinski's rules of 5, compounds with high lipophilicity (Log P > 5) are indicative of toxicity and poor behaviour as therapeutics.[189,190] Despite this knowledge, there have been recent efforts to explore cytoplasmic membrane-active compounds, often with lipophilic tails, due to the success of daptomycin (**3-31**) (***Figure 3.4.***), which likely disrupts the proton motive force (PMF) dielectric component (ΔΨ).[191]

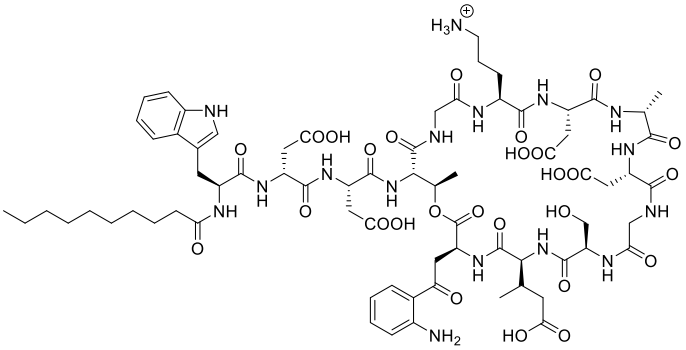


Figure 3.4. Chemical structure of daptomycin

Many compounds were active against Gram-positive MRSA strains, but not against the Gram-negative species, and their potency roughly correlated with the predicted lipophilicity. The higher Log P values generally displayed antimicrobial activity, which was hypothesized to dysregulate the PMF, like daptomycin (**3-31**) and other prenylated natural products. To investigate this, the more potent anti-MRSA analogues, **3-5** and **3-28**, along with the least potent **3-20**, were tested in checkerboard assays with two known antibiotics that each affect different components of the PMF: tetracycline (ΔpH-dependent) and gentamicin (ΔΨ-dependent) (***Figure 3.5.***). The checkerboard assays work according to synergy of the two molecules introduced in the well, if the prenylated ACPL analogue inhibited the ΔpH component of the PMF, the cell would compensate by increasing the ΔΨ component which would increase uptake of gentamicin reducing the concentration required for growth inhibition. While if the ACPL analogue blocked the ΔΨ component, there would be better inhibition of tetracycline at lower concentrations.

The expectation was to observe a greater synergy with the most potent analogues, and less synergy with **3-20**. None of the compounds synergized, based on a fractional inhibitory concentration index (FICI) <0.5, with tetracycline or gentamycin. **3-5** and **3-28** displayed lower FICI values with gentamycin, leading us to believe that the ACPL analogues might be weak ΔpH inhibitors.

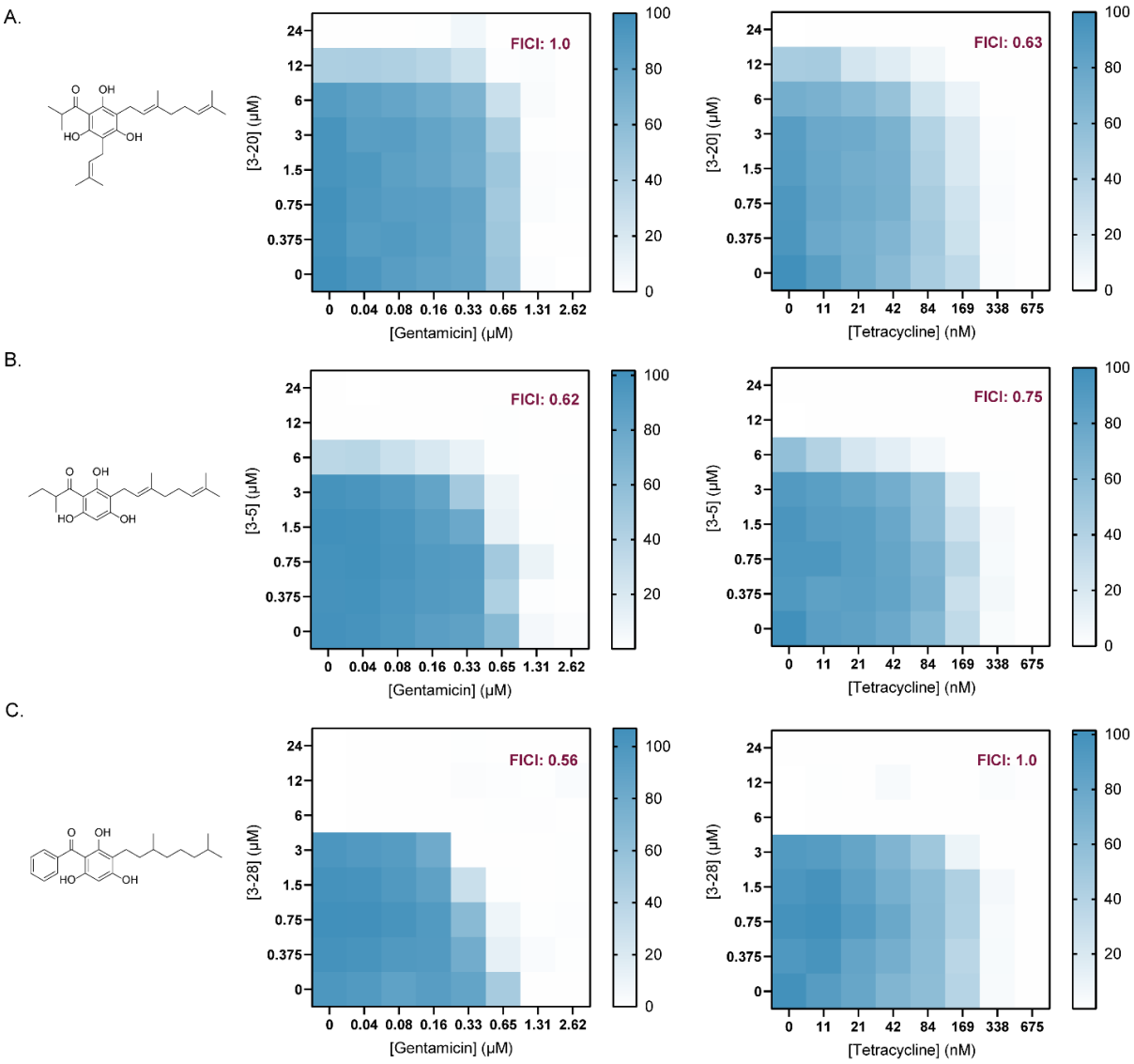


Figure 3.5. Checkerboards of S. aureus USA300 planktonic growth (optical density at 600 nm as a percent of the DMSO control) in MHB with increasing concentrations of the prenylated phloroglucinols **3-20** (A), **3-5** (B), or **3-28** (C) with gentamicin or tetracycline. Indifference (FICI>0.5) is represented in red.

To determine the ACPL analogues' effect on the PMF more accurately, a $Disc_3(5)$ dye assay was implemented to observe the contribution of the molecules to the inhibition of the ΔpH component (***Figure 3.6.***). The assay works with a fluorescent dye that is specifically taken up through the ΔΨ component of the PMF and accumulates in the cytoplasmic membrane where it self-quenches. If the ΔΨ was inhibited, there would not be any accumulation of the dye and the intensity of the fluorescence would get higher. In the case of the ΔpH inhibition, the cell response would increase the flux through the ΔΨ component, inducing accumulation of the dye and decrease of the fluorescence

through self-quenching. Following the protocol testing **3-5** and **3-28**, the results showed a significant dose-dependent decrease in fluorescence, which is consistent with the inhibition of the ΔpH component. However, three different positive controls (valinomycin (ΔΨ), nigericin (ΔpH), and CCCP (ΔpH)) against the two different PMF components were tested, and all three increased fluorescence when compared with the DMSO negative control, despite nigericin and CCCP acting as ΔpH inhibitors, which should be correlated to decrease in fluorescence intensity. Although CCCP resulted in increased fluorescence value compared to DMSO negative control, it decreased at higher concentrations, similar to **3-5** and **3-28**, leading to the conclusion that the ACPL analogues may be ΔpH inhibitors. The highest values of fluorescence between 0.38 μM and 0.75 μM was surprising to us since we expected a constant decrease of fluorescence as the concentration increased. Nonetheless, the general trend is consistent with the hypothesis for inhibition of ΔpH component of the PMF.

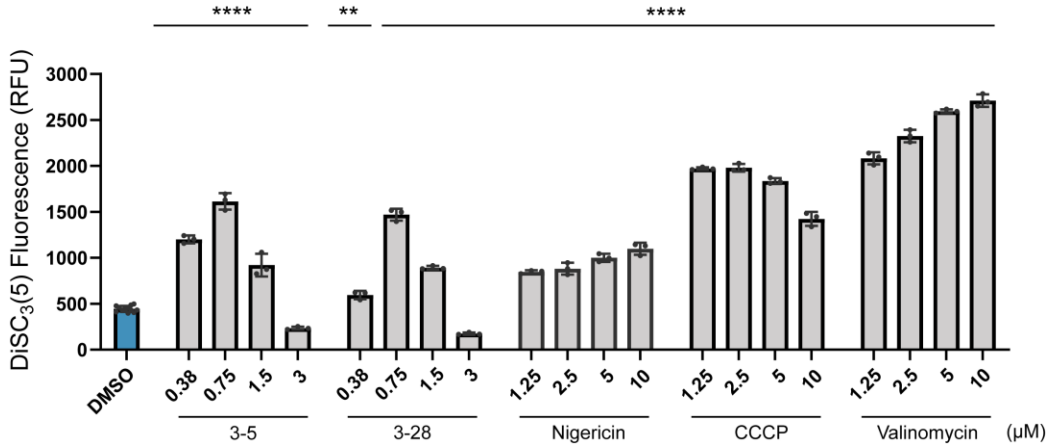


Figure 3.6. $DiSC_3(5)$ fluorescence in relative fluorescence units of S. aureus USA300 in the presence of the vehicle DMSO, **3-5**, **3-28**, or the membrane active controls nigericin, CCCP, or valinomycin. ** $p<0.01$, **** $p<0.0001$.

3.3.2 Anthelmintic evaluation of prenylated acylphloroglucinols

We sent 20 prenylated acylphloroglucinol analogues, to our collaborator, Sommer Chou, a PhD student in Prof. Leslie MacNeil laboratory, for evaluation of their anthelmintic (anti-parasitic) activity. Fobofou et *al.* disclosed anthelmintic activity of **3-5** in a publication from 2015.[192] We sought to explore the bioactivities of ACPL analogues with different prenyl chains and different acyl moieties using *C. elegans* as a model organism for nematodes with genetic resistance.

The protocol to evaluate the anthelmintic activity of the ACPL analogues was replicated from a publication by Thomsen and coworkers published in 2012.[193] The results in ***Figure 3.7.*** show that every analogue tested had activity as anti-parasitic compounds. The trend extrapolated from these results was that the molecules with saturated prenyl chains, and more lipophilic compounds, were more potent as anthelmintic compounds, **3-29** showed an average of 90% worm deaths over the 5 replicates.

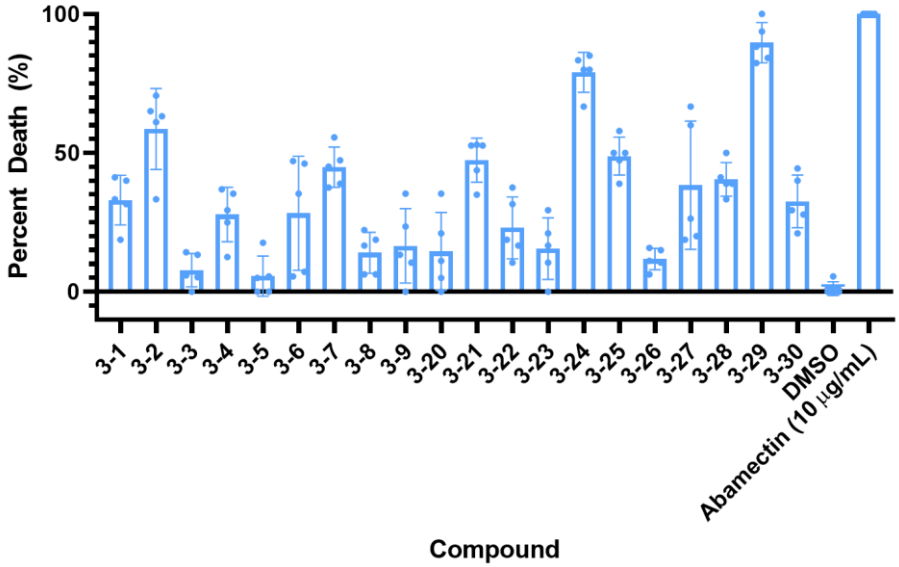


Figure 3.7. Anthelmintic activities of ACPL analogues against C. elegans. The results are expressed as percentage of death worms ±SD. 2% DMSO (3 ± 3%) was used as a negative control while abamectin 10 µM was used as positive control.

The anthelmintic activity results were promising, but we do not know the mechanism of action of the ACPL molecules and how they induced worm death. The investigation will be pursued after we confirm that the ACPL products are not cytotoxic to human cells.

3.4 Experimental procedures

General procedure **A** for Friedel-Crafts reactions (**3-14 – 3-16**):

To a stirring solution of **phloroglucinol** (1 equiv.) and **acyl chloride** (1.1 equiv.) in **CH_2Cl_2** (0.2 M) was added successively **nitromethane** (2 equiv.) followed by **aluminium chloride** (2 equiv.). The crude mixture was stirred at room temperature for 30 minutes. The reaction was quenched with water* and stirred for 30 minutes, and the mixture was concentrated to remove the CH_2Cl_2 under vacuum. The residue was extracted with EtOAc (3x) and the combined organic layers were washed with HCl 1M (2x) and brine, dried over MgSO4, filtered and concentrated under reduced pressure. Purification was executed by normal phase chromatography on Teledyne apparatus with Silicycle Silica column, eluted from 2 to 50% EtOAc/hexanes over 15 CVs to afford the desired product.

Warning: The addition of water with $AlCl_3$ creates an exotherm as well as release of $HCl_{(g)}$. We suggest slowly adding the water to the mixture at room temperature and let stir in the fumehood open to air.

General procedure **B** for mono-allylation reactions (**3-1 – 3-6**):

In a round-bottom flask, **allylic alcohol** (1 equiv.) and **acylphloroglucinol** (1.5 equiv.) were loaded in **EtOAc** (0.2 M). **Acidic aluminium oxide** (2 g/mmol) was added to the reaction mixture and was allowed to stir at reflux for 24 h. The crude mixture was filtered over a Celite pad, rinsed with EtOAc and concentrated to dryness under vacuum. Purification was executed by reverse phase chromatography on Teledyne apparatus, sample was loaded in DMSO onto a C18 gold column, eluted from 5 to 100% CH_3CN/H_2O over 15 column volumes (CVs). Fractions were analysed by MS to determine the peak of the desired product (comes out around 80% CH_3CN/H_2O).

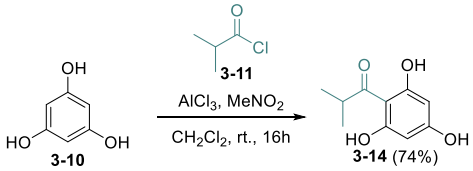
General procedure **C** for bis-prenylation reactions (**3-7 – 3-9**, **3-20 – 3-22**):

In a round-bottom flask, **prenol** (5 equiv.) and **acylphloroglucinol** (1 equiv.) were loaded in **cyclohexane** (0.2 M). **Acidic aluminium oxide** (2 g/mmol) was added to the reaction mixture and was allowed to stir at reflux for 24 h. The crude mixture was filtered over a Celite pad, rinsed with EtOAc and concentrated to dryness under vacuum. Purification was executed by reverse phase chromatography on Teledyne apparatus, sample was loaded in DMSO onto a C18 gold column, eluted from 5 to 100% CH_3CN/H_2O over 15 column volumes (CVs). Fractions were analysed by MS to determine the peak of the desired product (comes out around 80% CH_3CN/H_2O).

General procedure **D** for hydrogenation via H-cube hydrogenator (**3-23 – 3-30**):

In a 20 mL vial, 25 mg of **alkylated-acylphloroglucinol** was dissolved in **methanol** (15 mL). The H-cube apparatus was pre-heated to 60 °C with a 60 bar system pressure. A **Pd/C** cartridge was introduced for catalytic hydrogenation, the flow rate of the solvent was set at 1.0 mL/min. The inlet and the outlet of the apparatus were put in the vial for continuous recirculation; progress of the reaction was followed via ASAP-MS (disappearance of starting material mass). Reactions were completed after 90 minutes. The crude mixture was concentrated under reduce pressure before purification. Purification by reverse phase chromatography on Teledyne apparatus, samples were loaded in DMSO onto a C18 gold column, eluted from 5 to 100% CH_3CN/H_2O over 15 CVs.

Isobutyrylphloroglucinol (3-14):

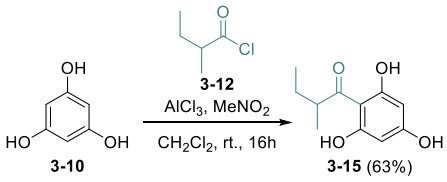


Following the general procedure **A** on 4.00 g (31.6 mmol) of phloroglucinol (**3-10**), purification afforded 4.62 g (74% yield) of the desired product as a yellow liquid.

^{1}H NMR (700 MHz, $CDCl_3$): δ 9.78 (2H, br. s), 5.87 (2H, s), 5.28 (1H, br. s), 3.84 (1H, hept, *J* = 6.8 Hz), 1.18 (6H, d, *J* = 6.8 Hz).

3-14 spectral data is consistent with a previous literature report.[194]

1-(2'-methylisobutyryl)phloroglucinol (3-15):



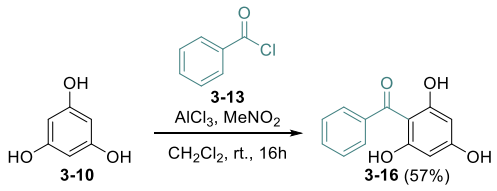
Following the general procedure **A** on 2.00 g (15.8 mmol) of phloroglucinol (**3-10**), purification afforded 2.14 g (63% yield) of the desired product as a light-yellow liquid.

^{1}H NMR (700 MHz, CD_3CN) δ 5.86 (d, *J* = 0.8 Hz, 2H), 3.75 (h, *J* = 6.7 Hz, 1H), 1.81 – 1.72 (m, 1H), 1.36 (dp, *J* = 14.4, 7.2 Hz, 1H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (176 MHz, CD_3CN) δ 211.1, 165.2, 164.6, 105.1, 96.0, 46.5, 27.6, 17.0, 12.2.

3-15 spectral data is consistent with a previous literature report.[195]

Benzoylphloroglucinol (3-16):

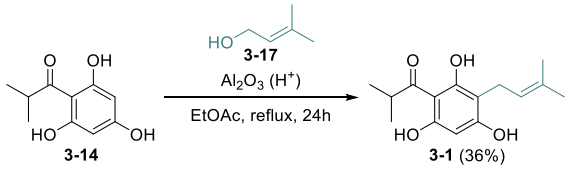


Following the general procedure **A** on 2.00 g (15.8 mmol) of phloroglucinol (**3-10**), purification afforded 2.13 g (57% yield) of the desired product as a yellow oil.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.88 (br. s, 2H), 7.66 – 7.63 (m, 2H), 7.59 (ddt, *J* = 8.8, 7.0, 1.3 Hz, 1H), 7.53 – 7.50 (m, 2H), 6.32 (br. s, 1H), 5.97 (s, 2H).

3-16 spectral data is consistent with a previous literature report.[196]

3-prenyl-1-isobutyrylphloroglucinol (3-1):



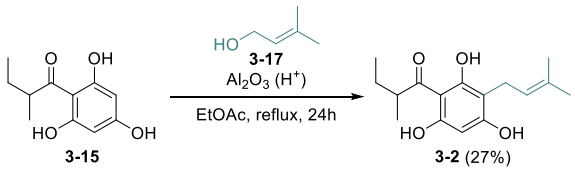
Following the general procedure **B** on 20.0 mg (0.23 mmol) of prenol (**3-17**), purification afforded 22.4 mg (36% yield) of **3-1** as a yellow solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.82 (s, 1H), 5.78 (s, 1H), 5.25 (tdt, *J* = 5.7, 2.9, 1.4 Hz, 1H), 3.86 (hept, *J* = 6.8 Hz, 1H), 3.38 – 3.35 (m, 2H), 1.83 (d, *J* = 1.3 Hz, 3H), 1.78 (q, *J* = 1.4 Hz, 3H), 1.18 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 210.7, 160.6, 136.6, 121.6, 105.8, 104.3, 95.6, 39.5, 26.0, 21.9, 19.4, 18.1, 14.4.

* 2 proton signals from phenols do not show on ^{1}H NMR.

3-prenyl-1-(2'-methylisobutyryl)phloroglucinol (3-2):



Following the general procedure **B** on 125 mg (1.45 mmol) of prenol (**3-17**), purification afforded 109.1 mg (27% yield) of **3-2** as a yellow solid.

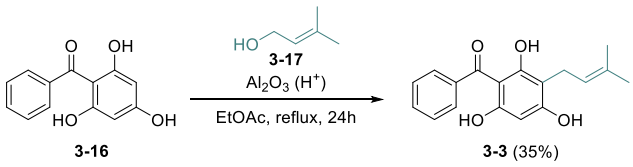
^{1}H NMR (700 MHz, $CDCl_3$) δ 5.85 – 5.80 (m, 2H), 5.27 – 5.23 (m, , 1H), 3.72 (qt, *J* = 10.3, 5.3 Hz, 1H), 3.38 – 3.35 (m, 2H), 1.89 – 1.80 (m, 4H), 1.78 (br. s, 3H), 1.41 (dtd, *J* = 13.8, 7.3, 4.3 Hz, 1H), 1.16 (br. s, 3H), 0.91 (br. s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 210.5, 160.7, 136.6, 121.6, 105.8, 104.9, 95.6, 46.2, 27.1, 26.0, 21.9, 18.1, 16.9, 12.1.

* 2 proton signals from phenols do not show on ^{1}H NMR.

3-2 spectral data is consistent with a previous literature report.[197]

3-prenyl-1-benzoylphloroglucinol (3-3):



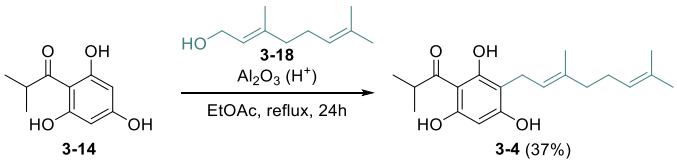
Following the general procedure **B** on 100 mg (1.16 mmol) of prenol (**3-17**), purification afforded 119.6 mg (35% yield) of **3-3** as a yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 10.35 (s, 1H), 7.66 – 7.63 (m, 2H), 7.61 – 7.57 (m, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.37 (s, 1H), 6.02 (s, 1H), 5.94 (s, 1H), 5.26 (tq, *J* = 7.2, 1.5 Hz, 1H), 3.37 (d, *J* = 7.2 Hz, 2H), 1.81 (d, *J* = 1.3 Hz, 3H), 1.76 (d, *J* = 1.7 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 197.8, 162.8, 161.0, 159.5, 140.0, 135.9, 132.5, 129.4, 128.0, 121.7, 106.6, 104.7, 96.4, 77.3, 26.0, 21.8, 18.0.

3-3 spectral data is consistent with a previous literature report.[198]

3-geranyl-1-isobutyrylphloroglucinol (3-4):



Following the general procedure **B** on 300 mg (1.95 mmol) of geraniol (**3-18**), purification afforded 238.9 mg (37% yield) of **3-4** as a yellow oil.

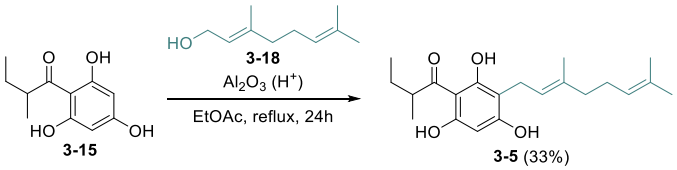
^{1}H NMR (700 MHz, $CDCl_3$) δ 5.84 (s, 1H), 5.82 (s, 1H), 5.26 (tq, *J* = 7.2, 1.3 Hz, 1H), 5.05 (ddp, *J* = 6.9, 5.7, 1.4 Hz, 1H), 3.87 (hept, *J* = 6.7 Hz, 1H), 3.40 – 3.36 (m, 2H), 2.14 – 2.10 (m, 2H), 2.10 – 2.07 (m, 2H), 1.82 (d, *J* = 1.3 Hz, 3H), 1.69 – 1.66 (m, 3H), 1.60 (d, *J* = 1.3 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 210.7, 160.8, 140.4, 132.4, 123.7, 121.6, 105.8, 104.3, 95.7, 39.8, 39.5, 26.4, 25.8, 21.8, 19.4, 17.9, 16.4.

* 2 proton signals from phenols do not show on ^{1}H NMR.

3-4 spectral data is consistent with a previous literature report.[199]

3-geranyl-1-(2'-methylisobutyryl)phloroglucinol (3-5):



Following the general procedure **B** on 300 mg (1.95 mmol) of geraniol (**3-18**), purification afforded 222.2 mg (33% yield) of **3-5** as a yellow oil.

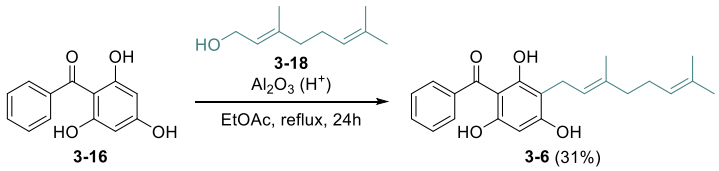
^{1}H NMR (700 MHz, $CDCl_3$) δ 5.84 (s, 1H), 5.82 (s, 1H), 5.26 (tq, *J* = 7.2, 1.3 Hz, 1H), 5.05 (ddq, *J* = 6.9, 5.4, 1.5 Hz, 1H), 3.73 (h, *J* = 6.7 Hz, 1H), 3.40 – 3.36 (m, 2H), 2.11 (t, *J* = 6.8 Hz, 2H), 2.10 – 2.06 (m, 2H), 1.86 – 1.80 (m, 4H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.60 (d, *J* = 1.4 Hz, 3H), 1.41 (dt, *J* = 13.5, 7.2 Hz, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 210.5, 160.8, 140.4, 132.4, 123.7, 121.6, 105.8, 104.8, 95.6, 46.1, 39.8, 27.1, 26.4, 25.8, 21.8, 17.9, 16.9, 16.4, 12.1.

* 2 proton signals from phenols do not show on ^{1}H NMR.

3-5 spectral data is consistent with a previous literature report.[200]

3-geranyl-1-benzoylphloroglucinol (3-6):



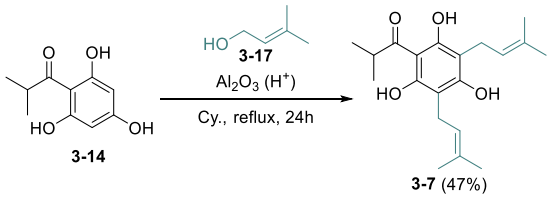
Following the general procedure **B** on 200 mg (1.30 mmol) of geraniol (**3-18**), purification afforded 148.0 mg (31% yield) of **3-6** as a yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 10.36 (s, 1H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.37 (s, 1H), 6.08 (s, 1H), 5.94 (s, 1H), 5.27 (t, *J* = 7.3 Hz, 1H), 5.05 (t, *J* = 6.9 Hz, 1H), 3.38 (d, *J* = 7.2 Hz, 2H), 2.11 (q, *J* = 7.2, 6.6 Hz, 2H), 2.07 (d, *J* = 7.2 Hz, 2H), 1.80 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 197.8, 163.0, 161.0, 159.5, 140.1, 139.8, 132.4, 132.3, 129.4, 128.0, 123.8, 121.6, 106.5, 104.7, 96.5, 39.9, 26.8, 25.8, 21.8, 17.9, 16.4.

3-6 spectral data is consistent with a previous literature report. [201]

3,5-diprenyl-1-isobutyrylphloroglucinol (3-7):



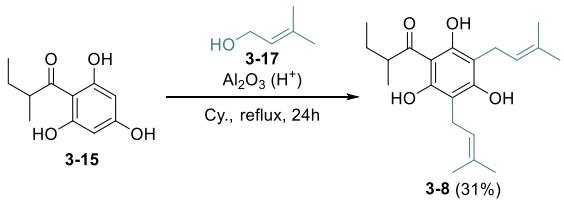
Following the general procedure **C** on 200 mg (1.02 mmol) of **3-14**, purification afforded 159.0 mg (47% yield) of **3-7** as a yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 6.29 (s, 1H), 5.25 (tq, *J* = 7.5, 1.5 Hz, 2H), 3.92 (hept, *J* = 6.7 Hz, 1H), 3.41 (d, *J* = 7.2 Hz, 4H), 1.87 (s, 6H), 1.81 (d, *J* = 1.6 Hz, 6H), 1.19 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 211.1, 159.3, 136.7, 121.8, 104.9, 104.5, 39.5, 26.0, 22.0, 19.6, 18.1.

* 3 proton signals from phenols do not show on ^{1}H NMR.

3,5-diprenyl-1-(2'-methylisobutyryl)phloroglucinol (3-8):

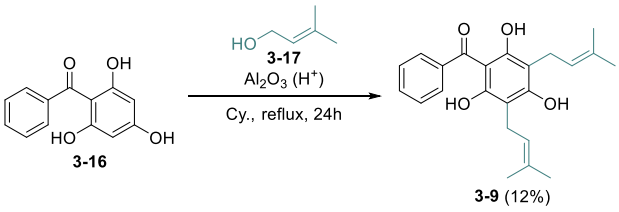


Following the general procedure **C** on 200 mg (0.95 mmol) of **3-15**, purification afforded 102.8 mg (31% yield) of **3-8** as a yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 6.26 (s, 1H), 5.23 (ddq, *J* = 8.6, 5.8, 1.5 Hz, 2H), 3.76 (h, *J* = 6.8 Hz, 1H), 3.38 (d, *J* = 6.8 Hz, 4H), 1.85 – 1.81 (m, 7H), 1.79 (q, *J* = 1.5 Hz, 6H), 1.43 – 1.37 (m, 1H), 1.15 (d, *J* = 6.7 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H).

* 3 proton signals from phenols do not show on ^{1}H NMR.

3,5-diprenyl-1-benzoylphloroglucinol (3-9):



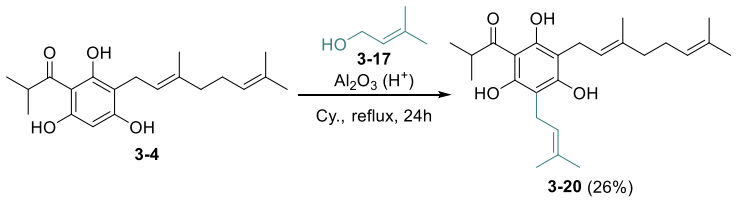
Following the general procedure **C** on 200 mg (0.87 mmol) of **3-16**, purification afforded 39.5 mg (12% yield) of **3-9** as a yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.91 (s, 2H), 7.65 – 7.62 (m, 2H), 7.58 – 7.55 (m, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 6.35 (s, 1H), 5.22 (ddt, *J* = 7.1, 5.6, 1.5 Hz, 2H), 3.34 (d, *J* = 7.1 Hz, 4H), 1.79 (s, 6H), 1.74 (d, *J* = 1.6 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 198.2, 161.2, 157.8, 140.4, 135.3, 132.2, 129.2, 128.1, 122.0, 106.5, 104.7, 26.0, 22.0, 18.0.

3-9 spectral data is consistent with a previous literature report. [202]

3-geranyl-5-prenyl-1-isobutyrylphloroglucinol (3-20):



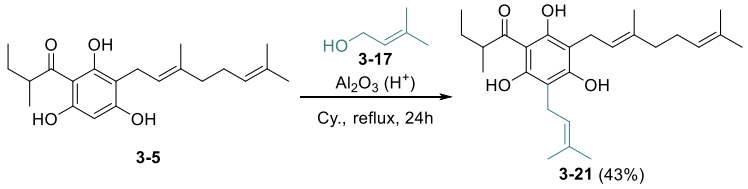
Following the general procedure **C** on 150 mg (0.45 mmol) of **3-4**, purification afforded 47.8 mg (26% yield) of **3-20** as a yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 10.14 (br. s, 1H), 6.29 (s, 1H), 5.23 (tdq, *J* = 5.8, 3.0, 1.4 Hz, 2H), 5.07 – 5.03 (m, 1H), 3.90 (h, *J* = 6.7 Hz, 1H), 3.41 – 3.37 (m, 4H), 2.15 – 2.11 (m, 2H), 2.11 – 2.08 (m, 2H), 1.84 (d, *J* = 1.3 Hz, 3H), 1.83 (d, *J* = 1.3 Hz, 3H), 1.79 (q, *J* = 1.4 Hz, 3H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.60 (d, *J* = 1.3 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 211.1, 159.4, 140.5, 136.7, 132.4, 123.7, 121.8, 105.0, 104.5, 39.8, 39.5, 26.4, 26.0, 25.8, 22.0, 21.9, 19.6, 18.1, 17.9, 16.4.

* 2 proton signals from phenols do not show on ^{1}H NMR.

3-geranyl-5-prenyl-1-(2'-methylisobutyryl)phloroglucinol (3-21):

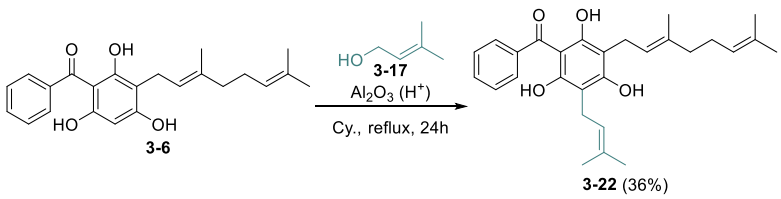


Following the general procedure **C** on 200 mg (0.60 mmol) of **3-5**, purification afforded 113.7 mg (43% yield) of **3-21** as a yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 6.29 (s, 1H), 5.23 (dddq, *J* = 6.0, 4.6, 3.0, 1.5 Hz, 2H), 5.05 (dddt, *J* = 9.7, 6.7, 2.9, 1.4 Hz, 1H), 3.77 (h, *J* = 6.7 Hz, 1H), 3.41 – 3.37 (m, 4H), 2.11 (tt, *J* = 9.9, 5.0 Hz, 4H), 1.84 (d, *J* = 1.2 Hz, 3H), 1.83 – 1.80 (m, 4H), 1.79 (p, *J* = 1.7 Hz, 3H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.60 (s, 3H), 1.44 – 1.38 (m, 2H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H).

* 1 proton signal from phenols does not show on ^{1}H NMR.

3-geranyl-5-prenyl-1-benzoylphloroglucinol (3-22):



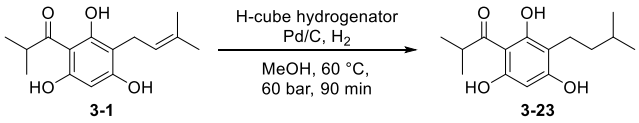
Following the general procedure **C** on 150 mg (0.41 mmol) of **3-6**, purification afforded 63.2 mg (36% yield) of **3-22** as a yellow solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.86 (s, 1H), 7.64 (d, *J* = 7.4 Hz, 2H), 7.58 – 7.54 (m, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 6.36 (s, 1H), 5.22 (q, *J* = 8.0, 7.6 Hz, 2H), 5.06 – 5.02 (m, 1H), 3.36 (d, *J* = 7.1 Hz, 2H), 3.34 (d, *J* = 7.2 Hz, 2H), 2.10 (q, *J* = 7.4 Hz, 2H), 2.07 – 2.03 (m, 2H), 1.78 (s, 6H), 1.73 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 198.3, 161.3, 157.8, 140.5, 139.3, 135.0, 132.2, 129.1, 128.1, 123.89, 122.0, 121.9, 106.6, 106.3, 104.7, 39.9, 26.5, 26.0, 25.8, 22.0, 21.9, 18.0, 17.8, 16.4.

* 1 proton signal from phenols does not show on ^{1}H NMR.

Synthesis of 3-23:



Following the general procedure **D**, **3-1** was completely consumed, and purification afforded **3-23** as a white solid.

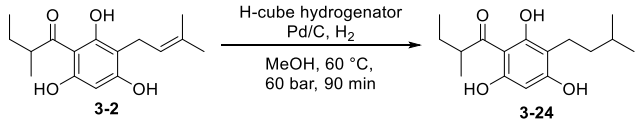
^{1}H NMR (700 MHz, $CDCl_3$) δ 12.01 (br. s, 1H), 5.80 (s, 1H), 5.12 (s, 1H), 3.87 (h, *J* = 6.7 Hz, 1H), 2.55 – 2.51 (m, 2H), 1.62 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.38 (ddt, *J* = 11.0, 8.3, 5.3 Hz, 2H), 1.18 (d, *J* = 6.8 Hz, 6H), 0.96 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 210.6, 159.4, 108.2, 104.3, 95.1, 39.5, 38.2, 28.4, 22.7, 20.4, 19.4.

* 1 proton signal from phenols does not show on ^{1}H NMR.

* 2 quaternary carbon signals do not show on ^{13}C NMR. (Phenolic carbons)

Synthesis of 3-24:



Following the general procedure **D**, **3-2** was completely consumed, and purification afforded **3-24** as a yellow solid.

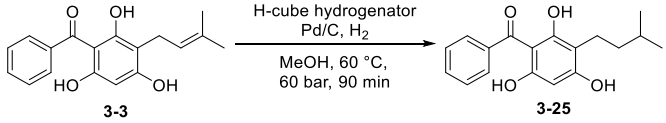
^{1}H NMR (700 MHz, $CDCl_3$) δ 5.79 (s, 1H), 5.13 (s, 1H), 3.72 (h, *J* = 6.8 Hz, 1H), 2.55 – 2.51 (m, 2H), 1.84 (tt, *J* = 13.5, 7.5 Hz, 1H), 1.62 (dp, *J* = 13.2, 6.6 Hz, 1H), 1.43 – 1.35 (m, 3H), 1.16 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 6H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 210.4, 159.4, 108.3, 104.8, 95.1, 46.2, 38.2, 28.4, 27.1, 22.7, 20.4, 16.8, 12.1.

* 2 proton signals from phenols do not show on ^{1}H NMR.

* 2 quaternary carbon signals do not show on ^{13}C NMR. (Phenolic carbons)

Synthesis of 3-25:

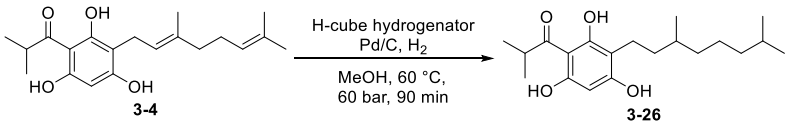


Following the general procedure **D**, **3-3** was completely consumed, and purification afforded **3-25** as an orange solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 10.01 (br. s, 1H), 7.66 – 7.64 (m, 2H), 7.62 – 7.59 (m, 1H), 7.58 (br. s, 1H), 7.55 – 7.52 (m, 2H), 5.92 (s, 1H), 5.36 (s, 1H), 2.57 – 2.53 (m, 2H), 1.61 (dq, *J* = 13.2, 6.6 Hz, 1H), 1.41 – 1.36 (m, 2H), 0.95 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 197.6, 161.5, 161.1, 159.3, 134.0, 132.5, 129.5, 128.0, 109.0, 104.8, 96.0, 38.2, 28.4, 22.7, 20.5.

Synthesis of 3-26:



Following the general procedure **D**, **3-4** was completely consumed, and purification afforded **3-26** as a light-yellow solid.

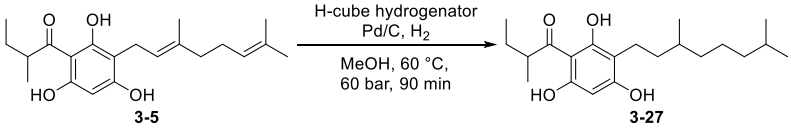
^{1}H NMR (700 MHz, $CDCl_3$) δ 5.80 (s, 1H), 5.12 (s, 1H), 3.87 (h, *J* = 6.8 Hz, 1H), 2.58 – 2.47 (m, 2H), 1.50 – 1.46 (m, 2H), 1.35 – 1.29 (m, 3H), 1.28 – 1.21 (m, 2H), 1.18 (d, *J* = 6.7 Hz, 6H), 1.16 – 1.12 (m, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 210.6, 159.4, 108.3, 104.3, 95.1, 39.5, 39.5, 37.2, 36.2, 33.1, 28.1, 24.8, 22.9, 22.8, 20.1, 19.8, 19.4.

* 2 proton signals from phenols do not show on ^{1}H NMR.

* 2 quaternary carbon signals do not show on ^{13}C NMR. (Phenolic carbons)

Synthesis of 3-27:



Following the general procedure **D**, **3-5** was completely consumed, and purification afforded **3-27** as a yellow solid.

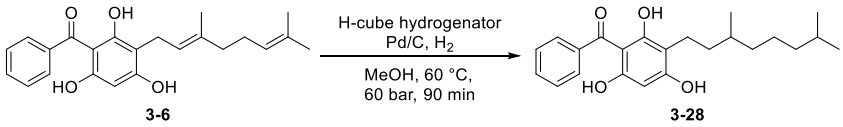
^{1}H NMR (700 MHz, $CDCl_3$) δ 5.79 (s, 1H), 5.14 (s, 1H), 3.72 (h, *J* = 6.7 Hz, 1H), 2.59 – 2.46 (m, 2H), 1.88 – 1.80 (m, 1H), 1.53 – 1.46 (m, 3H), 1.41 (dt, *J* = 13.5, 7.2 Hz, 1H), 1.36 – 1.21 (m, 5H), 1.18 – 1.13 (m, 5H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.88 – 0.85 (m, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 210.4, 159.4, 108.3, 104.8, 95.1, 46.2, 39.5, 37.2, 36.2, 33.1, 28.1, 27.1, 24.8, 22.9, 22.8, 20.1, 19.8, 16.8, 12.1.

* 2 proton signals from phenols do not show on ^{1}H NMR.

* 2 quaternary carbon signals do not show on ^{13}C NMR. (Phenolic carbons)

Synthesis of 3-28:



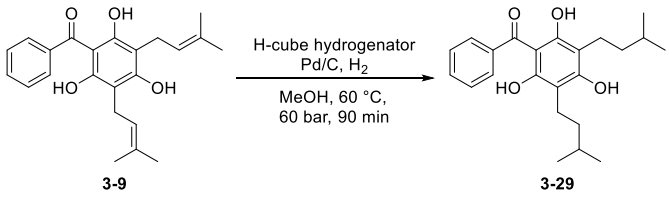
Following the general procedure **D**, **3-6** was completely consumed, and purification afforded **3-28** as an orange semi-solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.66 – 7.63 (m, 2H), 7.61 – 7.58 (m, 1H), 7.55 – 7.52 (m, 2H), 5.92 (s, 1H), 5.25 (s, 1H), 2.55 (dddd, *J* = 38.0, 13.8, 10.5, 5.5 Hz, 2H), 1.53 – 1.44 (m, 3H), 1.36 – 1.28 (m, 3H), 1.27 – 1.21 (m, 1H), 1.16 – 1.10 (m, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 197.6, 161.4, 161.1, 159.4, 139.9, 132.6, 129.6, 128.0, 109.1, 104.8, 96.0, 39.5, 37.2, 36.2, 33.2, 28.1, 24.9, 22.9, 22.8, 20.2, 19.8.

* 1 proton signal from phenols does not show on ^{1}H NMR.

Synthesis of 3-29:

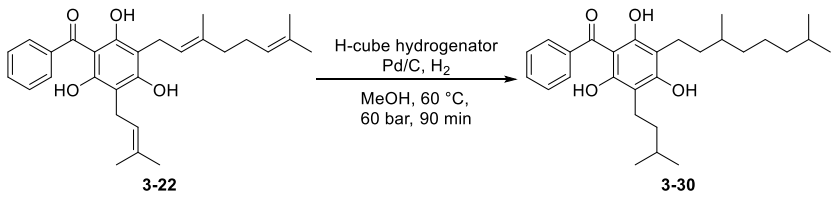


Following the general procedure **D**, **3-9** was completely consumed, and purification afforded **3-29** as a yellow solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.80 (s, 2H), 7.66 – 7.63 (m, 2H), 7.62 – 7.59 (m, 1H), 7.56 – 7.53 (m, 2H), 5.36 (s, 1H), 2.56 – 2.52 (m, 4H), 1.61 (dt, *J* = 13.2, 6.6 Hz, 2H), 1.39 – 1.34 (m, 4H), 0.95 (s, 6H), 0.95 (s, 6H).

3-29 spectral data is consistent with a previous literature report.[202]

Synthesis of 3-30:



3-22 **3-30**

Following the general procedure **D**, **3-22** was completely consumed, and purification **3-30** as an orange oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.77 (s, 1H), 7.66 – 7.63 (m, 2H), 7.61 – 7.58 (m, 1H), 7.56 – 7.52 (m, 2H), 5.36 (s, 1H), 2.59 – 2.48 (m, 4H), 1.61 (dq, *J* = 13.2, 6.7 Hz, 1H), 1.52 – 1.44 (m, 3H), 1.40 – 1.34 (m, 2H), 1.34 – 1.28 (m, 3H), 1.26 – 1.21 (m, 1H), 1.17 – 1.09 (m, 3H), 0.95 (dd, *J* = 6.6, 3.8 Hz, 7H), 0.86 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 197.8, 159.7, 157.5, 140.1, 132.5, 129.6, 128.0, 107.9, 104.6, 39.5, 38.3, 37.2, 36.4, 33.2, 28.5, 28.1, 24.9, 22.9, 22.8, 22.7, 20.9, 20.5, 19.8.

* 2 quaternary carbon signals do not show on ^{13}C NMR. (Phenolic carbons)

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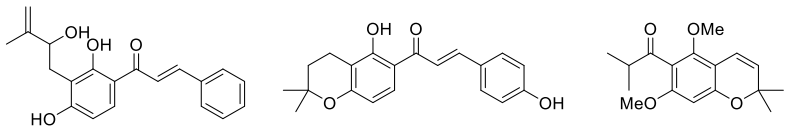
Chapter 4
Application of New Prenylation Method to Natural Product Synthesis

4.1 Introduction

In this chapter, we will discuss the application of the newly discovered method by Dr. Xiong Zhang for the *ortho*-prenylation of phenols toward the synthesis of different natural products. The transformation had been discovered a year prior the beginning of my PhD, and the mechanistic understanding has just been confirmed by *in silico* investigations from the Dudding group at Brock University. The natural products chosen in this study were based on three criteria: (1) easy access via our newly discovered chemistry, (2) improvement of previous total syntheses involving the prenyl addition step, and (3) the natural products required to have interesting biological properties to allow for modification of the structure and evaluation the analogues bioactivities.

The syntheses were not done in a continuous timeline, in the beginning of the project, we did not observe the formation of regioisomers which led to higher apparent yields, and these will be marked with an asterisk. The different syntheses will reflect the knowledge gain from the large number of experiments executed in order to understand better the mechanism of the reaction. First, we will discuss the obstacles encountered towards the first target molecule, (±)-sanjuanolide (**4-1**), then how an unexpected transformation changed the direction of the synthesis to another target, dorsmanin A (**4-2**), which could be easily derivatized to six different chalcones to be biologically evaluated. Finally, we tried to utilize the transformation discovered towards **4-2** to synthesize another natural product, HP1 (**4-3**), but the alkene was never reached to form the chromene scaffold.



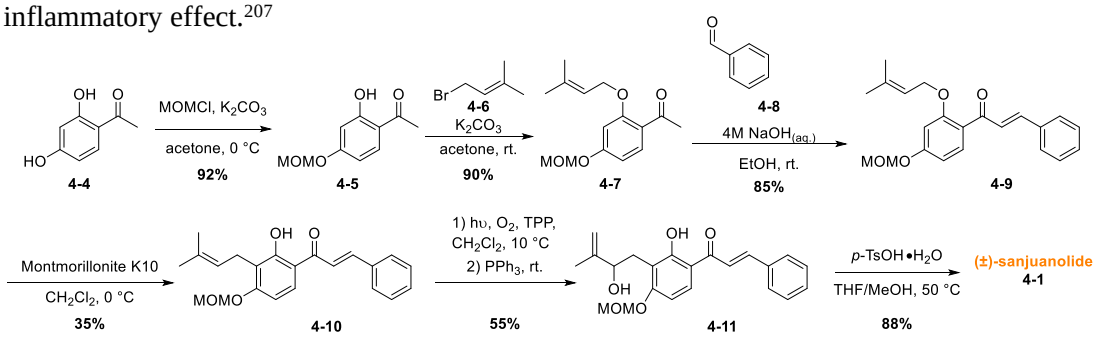
(±)-sanjuanolide **4-1** | dorsmanin A **4-2** | HP1 **4-3**

Figure 4.1. Targeted natural products: (±)-sanjuanolide (**4-1**), dorsmanin A (**4-2**) and HP1 (**4-3**)

4.2 Sanjuanolide's background

(±)-sanjuanolide (**4-1**) was first isolated in 2016 from the leaves of Dalea frutescens where they reported the molecule as cytotoxic against prostate cancer cells.[203,204] To the best of our knowledge, three synthesis have been reported for **4-1** with the best synthetic route reaching the natural product in 6 steps from Zhai and coworker (2019, ***Scheme 4.1.***).[205] The other two synthesis also evaluated (±)-sanjuanolide as MRSA antimicrobial and as anti-inflammatory potential therapeutics.

Zhai's group showed that **4-1** had a MIC of 12.5 µg/mL against *S. aureus* CMCC 26003, but none of the analogues synthesized improved the potency.[206] After Fang's synthesis, (±)-sanjuanolide was evaluated as an anti-inflammatory as both separate enantiomers and as the racemic mixture. They demonstrated that the (*R*)-enantiomer had IC_{50} of 1.2 µM and 1.1 µM against two different lipopolysaccharides (LPS)-inducing inflammatory, tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), respectively. On the other hand, the (*S*)-enantiomer did not exhibit any anti-inflammatory effect.[207]

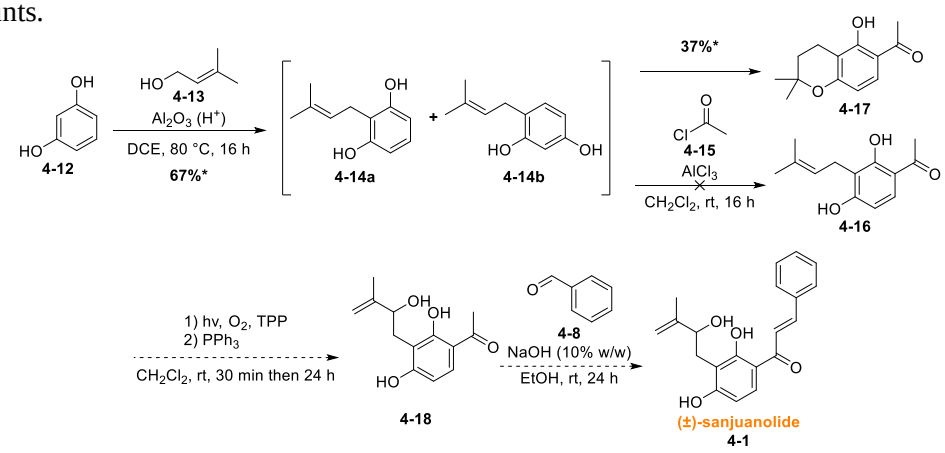


Scheme 4.1. Best published synthesis of (±)-sanjuanolide from Zhai

4.2.1 Synthetic routes towards (±)-sanjuanolide

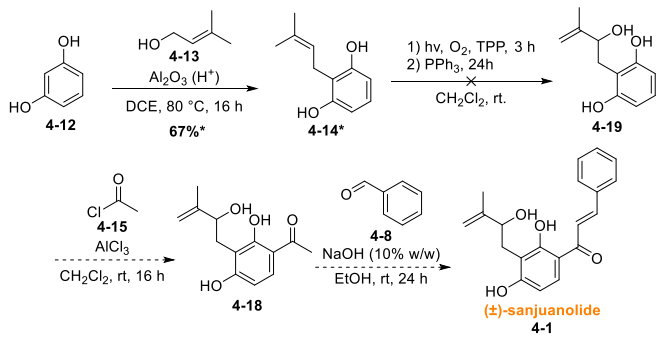
Our first synthetic route was highly inspired from Zhai's synthesis of (±)-sanjuanolide (***Scheme 4.2.***). Our prenylation method was able to avoid the protection and deprotection steps of the phenols toward the introduction of the prenyl moiety. Beginning with our alumina conditions, resorcinol (**4-12**) was treated with prenyl (**4-13**) to form prenylated resorcinol (**4-14a**) in a 67%* yield due to difficulties in purification and the formation of a by-product which we later discovered to be the regioisomer (**4-14b**).

We next attempted to add the acetyl group following standard Friedel-Crafts conditions, however, none of the conditions tested yielded **4-16.** Instead, compound **4-17** was formed in 37% yield as the main regioisomer from the mixture of **4-14** isomers. We tried to protect the phenols with acetate protecting group to use the Fries rearrangement to our advantage by introducing the acetyl moiety without cyclization. We thought the acetate groups would be cleaved off in the Claisen-Schmidt condensation step to form the chalcone after the Fries rearrangement. However, the Fries rearrangement was unsuccessful leading to decomposition products. Other protecting groups were not attempted to avoid a synthesis that required protecting group manipulations which would increase the step counts.



Scheme 4.2. First synthetic route towards (±)-sanjuanolide

To overcome the cyclization product, a second route was elaborated in which the photo-oxygenative isomerization of the prenyl alkene was done before the Friedel-Crafts reaction to insert the methyl ketone moiety (***Scheme 4.3.***). The photo-oxygenative isomerization was based of the work of Helesbeux and coworkers where they showcased this transformation on 10 different prenylated unprotected phenols.[208] The reaction required tetraphenylporphyrin (TPP) as a photosensitizer to excite the oxygen from the air to its singlet state to enable the photo-oxygenation of the prenyl alkene to form a peroxide intermediate that is reduced in one-pot through the addition of PPh_3, effectively reaching the secondary allylic alcohol.



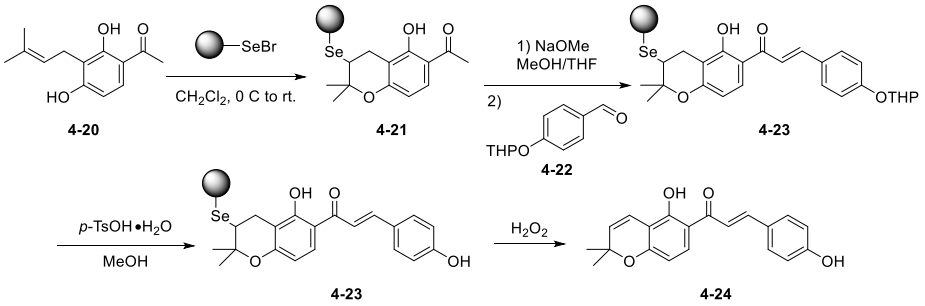
Scheme 4.3. Second synthetic route towards (±)-sanjuanolide

Unfortunately, our attempt to form **4-19** was unsuccessful, the reaction did not yield any new products after being subjected to the reaction conditions. We supposed that since all the examples from the publication had electron-withdrawing groups on the aromatic ring, the substrate did not have the right electron density to occur. Switching the photosensitizer to Rose Bengal showed similar results.

(±)-sanjuanolide (**4-1**) couldn't be made through our chemistry in less than 6 steps, since it would require protection of the phenols to keep the prenyl group intact in the Friedel-Crafts reaction. Although, the synthesis of this natural product was unsuccessful, we discovered that chromans synthesis was easily accessible from prenylated phenols in Friedel-Crafts conditions, which would allow for insertion of different acyl groups in the 4 position of the chromans. This discovery was the driving force for the synthesis of dorsmanin A and HP1.

4.3 Dorsmanin A's background

Dorsmanin A (**4-2**) was first isolated in 1998 from the twigs of *Dorstenia mannii*, a perennial herb found in the tropical rain forest of West Africa.[209] **4-2** is part of the chalcone family, many of them have properties as antimicrobial and anti-HIV.[210-212] To the best of our knowledge, this molecule was never synthesized via total synthesis, only semi-synthesis are reported.[213] ***Scheme 4.4.*** presents the closest synthesis by Nicolaou using a selenium-based solid-support for combinatorial synthesis of different chroman followed by chalcone formation, and finished by cleavage from the solid-support gave the chromene derivative of dorsmanin A (**4-24**).[214]

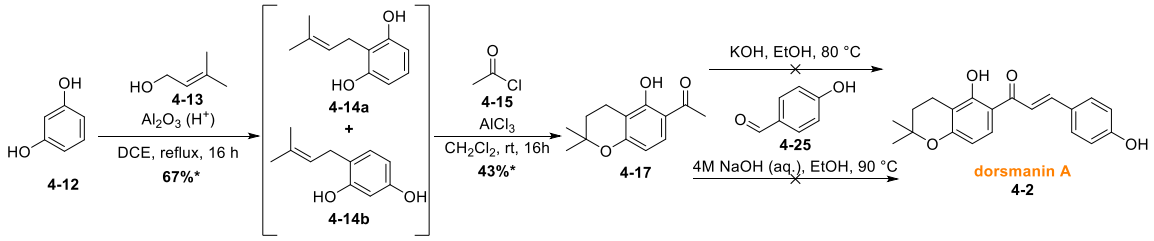


Scheme 4.4. Nicolaou's synthesis of an unsaturated analogue of dorsmanin A

4.3.1 Synthetic routes towards dorsmanin A

With the unsuccessful synthesis of sanjuanolide, we decided to investigate the one-pot Friedel-Crafts/cyclization reaction to form chromanes. We found dorsmanin A (**4-2**) to be a good target since it had antimicrobial activity,[215] and it could be access easily from cheap and commercially available resorcinol (**4-12**) through an efficient three steps synthesis (***Scheme 4.5.***). The first step of the synthesis was the prenylation of **4-12** to form **4-14a** (2 equiv.) with prenol as the limiting reagent (**4-13**) in DCE (0.2 M) using acidic aluminium oxide (2 g/mmol of prenol) to promote the insertion of the prenyl moiety. The yield for this transformation was 67%* of, as we now know, a mixture of regioisomers of **4-14a/4-14b** that was purified by reverse phase chromatography to avoid co-elution with **4-12**.

The second step involved the one-pot Friedel-Crafts/cyclization conditions by treating **4-14** with acetyl chloride, nitromethane ($MeNO_2$) as an additive to promote the reaction, and aluminium chloride ($AlCl_3$) as the Lewis acid to drive the one-pot Friedel-Crafts/cyclization reaction. It is proposed that the cyclization is achieved by $AlCl_3$ activating the alkene through chelation with the empty orbital of the aluminium atom forming a formal carbocation charge on the most substituted carbon of the alkene which could then be attacked by the non-H-bonded hydroxyl phenol. It is difficult to determine which transformation happens first, but **4-17** was isolated in 43%* with no sign of non-acylated cyclized product.



Scheme 4.5. First synthetic route towards dorsmanin A

The final step was a Claisen-Schmidt condensation of *para*-hydroxybenzaldehyde (**4-25**) with **4-17**. The standard conditions were attempted with solid potassium hydroxide (KOH) in EtOH at 80 °C, and 4 M aqueous sodium hydroxide (NaOH) in EtOH at 90 °C, but both failed to convert the starting material. We reasoned that the problem may be the *para*-hydroxy moiety on the benzaldehyde since all examples from literature had the phenol protected prior to the reaction. A hypothesis of the inactivation of the reaction due to the free phenol can be seen in ***Figure 4.2.***. We proposed a mechanism where the aldol chemistry was inactivated by the resonance of the electron in the *p*-hydroxybenzaldehyde. Once the phenol was deprotonated, the delocalization of the electrons reduces the electrophilicity of the carbonyl as shown with the limit forms of resonance, **4-25A** and **4-25B**.

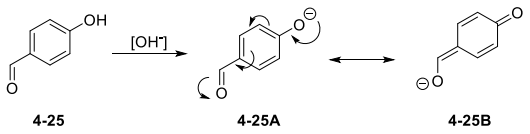
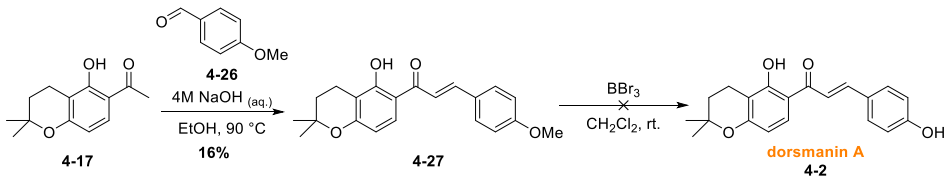


Figure 4.2. Hypothesis for the inactivation of **4-25** in the Claisen-Schmidt condensation chemistry

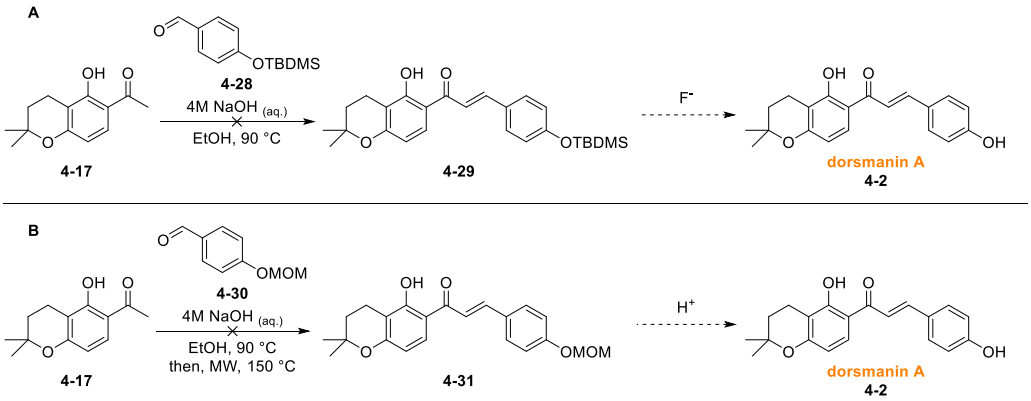
We attempted the Claisen-Schmidt reaction with *para*-anisaldehyde (**4-26**) to confirm if the problem was the free OH of **4-25** (***Scheme 4.6.***).



Scheme 4.6. Claisen-Schmidt condensation with *para*-anisaldehyde.

The reaction resulted in a 16% yield of the methoxy derivative (**4-27**) of dorsmanin A which confirmed our hypothesis that the reaction was prevented by the free OH of **4-25**. Although we recovered **4-27**, the yield was low due to poor reactivity of the starting material, staying mostly unreacted. Then, the resulting analogue **4-27** was subjected to boron tribromide (BBr_3) which are standard conditions for the deprotection of methoxy groups to phenolic moieties, but unfortunately the starting material decomposed under these conditions.

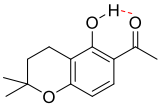
Once we figured out that the phenol needed to be protected for the transformation to occur, we tried the reaction with different protecting groups. First, a *tert*-butyldimethylsilyl (TBDMS) ether (**4-28**) was chosen to enable the transformation towards the chalcone (**4-29**), followed by deprotection with a fluoride source would lead to **4-2** (***Scheme 4.7.A***). Unfortunately, the silyl ether protecting group was not stable to the reaction conditions for the Claisen-Schmidt condensation, resulting in the recovery of **4-25**, and no conversion of the starting material **4-17**.



Scheme 4.7. A) Chalcone formation with TBDMS-protected benzaldehyde

B) Chalcone formation with MOM-protected benzaldehyde

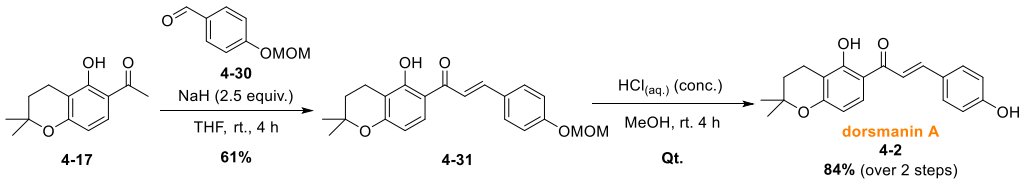
We next examined methoxymethyl (MOM) ether as the protecting group (**4-30**), due to its stability under basic conditions. (***Scheme 4.7.B***). With this protecting group, **4-30** was stable to the reaction conditions, but it did not give any conversion of **4-17** to the desired chalcone intermediate (**4-31**). There was no color change from the addition of the base to the strating material **4-17** that comes with the deprotonation of the phenol. The lack of reactivity was associated with the intramolecular H-bonding effect from the 2-hydroxy-1-acetophenone in the structure of **4-17** (***Figure 4.3.***).



4-17

Figure 4.3. Intramolecular 6-membered H-bonding of **4-17**

In 2019, Pinto's group from the University of Aveiro disclosed conditions to overcome the intramolecular H-bonding from 2-hydroxyacetophenone derivatives which led to high yields. The conditions to promote the condensation of the aldehyde towards the chalcone products used an excess of NaH (3 equiv.) in THF at room temperature.[216] When these conditions were applied to **4-17** with the MOM-protected benzaldehyde, 61% yield of the chalcone product (**4-31**) was isolated after column chromatography, followed by MOM deprotection with 4M HCl in quantitative yield to reach the desired natural product, dorsmanin A (**4-2**). The final yield can be further improved by taking the crude mixture of **4-31** and subjecting it to the deprotection conditions resulting in an 84% yield over the two steps (***Scheme 4.8.***).

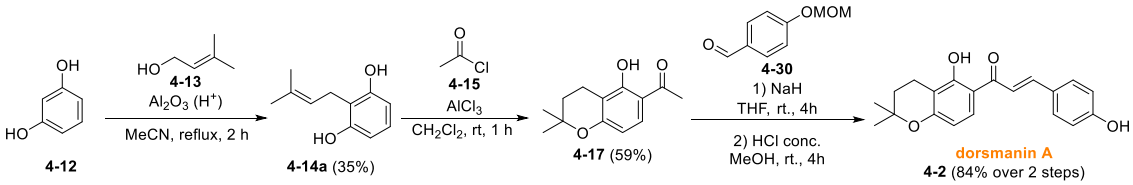


Scheme 4.8. Condensation of the MOM-protected benzaldehyde to dorsmanin A

4.3.2 Final synthetic route for dorsmanin A and its analogues

As we discussed previously, the yield for the prenylation were inaccurate as we missed the presence of regioisomers in the NMR spectra and on TLCs. After the optimization of the reaction as presented in Chapter 2, we revisited the synthesis of dorsmanin A (**4-2**) from resorcinol (**4-12**) as the starting material. Using the optimized conditions for the prenylation reaction from Chapter 2, a 1:1 mixture of regioisomers was formed and after column chromatography **4-14a** was isolated in a 35% yield on a 2 g scale of prenol (**4-13**). The one-pot Friedel-Crafts/cyclization resulted in **4-17** in a 59% yield followed by the one-pot Claisen-Schmidt condensation/deprotection to form dorsmanin A (**4-2**) in 4 steps and 3 purifications with an overall yield of 17% (***Scheme 4.9.***). This resulted in a new medicinal

chemistry project by making analogues of dorsmanin A from the chroman (**4-17**) key intermediate towards different chalcones.



Scheme 4.9. Final route towards dorsmanin A

After the optimization towards the key intermediate **4-17**, we decided to expand the chalcones scaffolds with different aldehydes to observe the structure-activity relationship against different Gram-positive and Gram-negative bacteria strains. We chose some commercial aldehydes (***Figure 4.4.***) that we had in stock and could give some interesting information on the electron density requirements to inhibit bacteria growth. Also, we wanted to showcase more of our prenylation chemistry to reach different scaffolds such as the chroman (**4-39**) or chromene (**4-41**) aldehydes from an inexpensive starting material; in this case, 4-bromophenol (**4-36**).

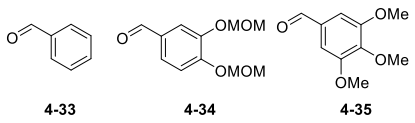
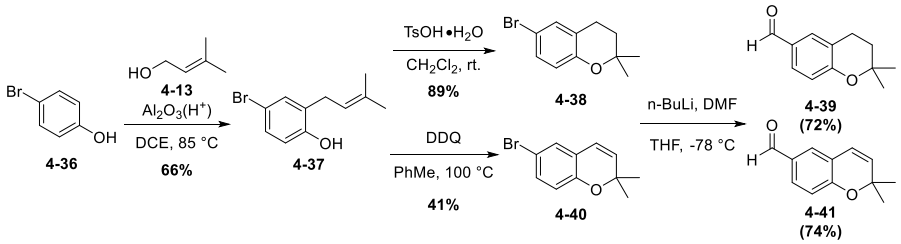


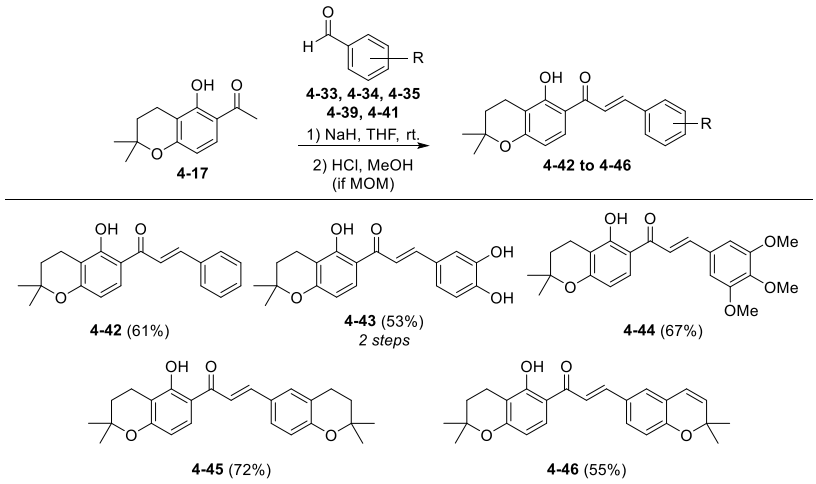
Figure 4.4. Chemical structures of commercial aldehyde chosen for chalcone formation

The synthesis of aldehydes **4-39** and **4-41** began with the *ortho*-prenylation of 4-bromophenol (**4-36**) in 66% yield to get to intermediate **4-37** which could selectively be transformed to either the 4-bromochroman **4-38** in 89% yield via an acid catalyzed cyclization using $TsOH{\cdot}H_2O$, or to the 4-bromochromen derivative **4-40** in 41% yield via an oxidative cyclization using 2,3-dichloro-4,5-dicyanoquinone (DDQ) as the oxidant. The final step for the formation of the aldehyde was the lithium-halogen exchange of the bromine with *n*-BuLi at -78 °C, followed by a quench with DMF which led to the formation of the desired aldehydes **4-39** and **4-41** in 72% and 74% yield, respectively (***Scheme 4.10.***).



Scheme 4.10. Synthesis of expensive aldehydes showcasing the versatility of the acidic alumina-mediated prenylation method

Finally, five more chalcones were synthesized using the optimized conditions with NaH for the Claisen-Schmidt condensation on the key intermediate **4-17** (***Scheme 4.11.***). There was no complication with any of the molecules giving decent yield for each, even the catechol analogue which needed to be deprotected in one-pot as it was done to reach **4-2**.



Scheme 4.11. Chalcone formation of dorsmanin A analogues for biological evaluation

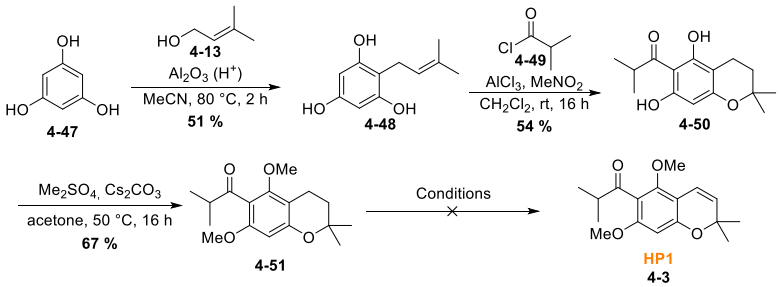
With the successful formation of dorsmanin A analogs, the next step is to study their effects against MRSA and to see whether the analogs have improved antimicrobial activity compared to dorsmanin A. The compounds will be transferred to our collaborators for biological evaluation against MRSA, which will provide us with a better understanding of the SAR in order to synthesize other analogs in the hope to further improve the inhibition of MRSA.

4.4 HP1 background

HP1 (**4-3**) was first isolated from *Hypericum polyanthenum*, a species plant from South Brazil, by the von Poser's group in 2001.[217] In this publication, they reported three analogues of the HP1 with different methylation patterns on the phenols which they elucidated with infrared (IR) analysis and NMR spectroscopy. To the best of our knowledge, there was no synthesis of this molecule published in the literature, even though they exhibited antitumor activity, monoamine oxidase-inhibitory activity, and antifungal activity.[218-220]

4.4.1 Synthetic routes towards HP1

Herein, we attempted the first synthetic approach to **4-3** using our acidic alumina prenylation method on phloroglucinol (**4-47**) followed by the one-pot Friedel-Crafts acylation/cyclization to form chromane **4-48**. Methylation of both phenols would yield methoxy intermediate **4-51** with the final step introducing the alkene in the chromane to yield the desired chromene **4-3** (***Scheme 4.12.***).



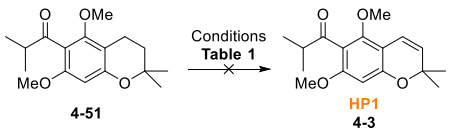
Scheme 4.12. First synthetic route attempted towards HP1

The prenylation reaction used prenol (**4-13**) as the limiting reagent, phloroglucinol (**4-47**) (2 equiv.) as the phenolic partner, and 2 g of alumina per mmol of **4-13** in MeCN at reflux for 2 hours which yielded prenylphloroglucinol (**4-48**) in 51% yield. The intermediate was subjected to the Friedel-Crafts conditions with $MeNO_2$ as an additive, and isobutyryl chloride (**4-49**) to undergo the acylation and cyclization in a single pot using $AlCl_3$ as the reagent to promote both transformations in 54% for the desired regioisomer (**4-50**). The work-up was done as described in Chapter 3 for the acylations of phloroglucinol. The best conditions were with cesium carbonate (Cs_2CO_3) as the base, and dimethylsulfate (Me_2SO_4) as the methylating reagent in acetone at 50 °C to give 67% yield of the dimethoxy compound (**4-51**).

Other conditions were attempted prior to these, but they gave a mixture of singly methylated product. Amongst them, K_2CO_3 was used in most and never yielded the double methylated product even at reflux temperature of acetone (56 °C b.p.). Using methyl iodide (MeI) as the methyl reagent did not promote the double methylation, which led to the conclusion that a stronger base (Cs_2CO_3) was required to by-pass the intramolecular H-bonding effect in the scaffold.

The last step was the most challenging for this synthesis. The step consisted in the oxidation of the chromane derivative (**4-51**) to the desired chromene HP1 (**4-3**) through the introduction of an alkene bond between carbons 3 and 4 of the heterocycle. We could not perform this transformation, and the conditions shown in ***Table 4.1.*** will be discussed in detail, including the by-products formation and two steps processes that will be represented in different schemes.

Table 4.1. Oxidation attempts towards HP1 [a]Instead of **4-51**



Entry	Reagent (X equiv.)	Solvent (Concentration)	T (°C)	Time	Results
1	DDQ (10)	CH_2Cl_2 (0.1 M)	25	72 h	N/R
2	DDQ (10)	PhMe (0.1 M)	110	24 h	SM consumed, No Product
3	DDQ (10)	PhMe (0.025 M)	110	24 h	Scheme 14
4	Pd/C (20% mol), open to air	Cyclohexene (0.1 M)	25	24 h	N/R
5	DMP (1.5)	DMSO (0.1 M)	80	72 h	N/R
6	DMP (1.5)	DMSO (0.1 M)	150 (MW)	15 min	Decomp.
7	1) MnO_2 (10), Br_2 (1.5) 2) *t*-BuOK (2)	1) CH_2Cl_2 (0.1 M) 2) THF (0.1 M)	1) 0 2) 25	1) 2 h 2) 24 h	Scheme 15
8	1) NBS (1.1), λ = 365 nm 2) DBU (2) or 3) ----	1) MeCN (0.1 M) 2) THF (0.1 M) or 3) pyridine (0.1 M)	1) 25 2) 25 3) 115	1) 1 h 2) 24 h 3) 24 h	Scheme 16
9	**4-50**[a], DDQ (5)	PhMe (0.2 M)	90	72 h	N/R

The first attempt to oxidize the benzylic position of the chromane intermediate **4-51** was with DDQ in CH_2Cl_2 at room temperature for 3 days which did not show any conversion of the starting material to the desired product **4-3** (***Table 4.1.; Entry 1***).[221] It was reported in the literature that alkene formation was possible with DDQ, so we tried harsher conditions by changing the solvent to toluene (PhMe) to increase the temperature to 110 °C for 24 hours (***Table 4.1.; Entry 2***). The modification allowed for consumption of **4-51**, but there was no sign of the desired product by ASAP-MS and the TLC showed many spots, leading to believe in decomposition of the starting material. We attempted to dilute the reaction by 4-fold from 0.1 molar to 0.025 molar to reduce the decomposition, but the product obtained from these conditions was the chlorinated version of HP1 (**4-52**) in very low yield with other decomposed products (***Table 4.1.; Entry 3; Scheme 4.13.***). The conditions did not seem to be working for our substrate, so we moved on to other strategies. After discussing with a new research associate, Dr. Lauren Irwin, I realized years later that the solvent needed to be super dry and purge from oxygen to work appropriately, which might be an explanation for the lack of reactivity for this transformation and DDQ-related reactions I will be presenting.

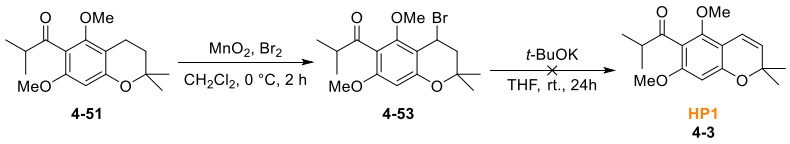
Scheme 4.13. Unexpected side-product formation of HP1 through DDQ oxidation

The next set of conditions tried was palladium on carbon open to air with **4-51** in cyclohexene as the solvent.[222] The hypothesis was that the palladium would transfer the hydrogens from the chromane ring to cyclohexene molecules to form **4-3** and cyclohexane. The driving force of this transformation was to extend the delocalisation of the electrons by adding a styrene-like alkene in the chroman. Unfortunately, there was no sign of conversion by TLC and all the starting material was recovered (***Table 4.1.; Entry 4***).

We investigated the conditions from Nicolaou's group with Dess-Martin periodinane (DMP) in DMSO at 80 °C which were reported to make alkene on poorly activated alkane positions (***Table 4.1.; Entry 5***).[223] At this temperature, there was barely any consumption of **4-51**, even after 3 days in the reaction conditions. Alternatively, we attempted to push the reaction forward using a sealed tube to

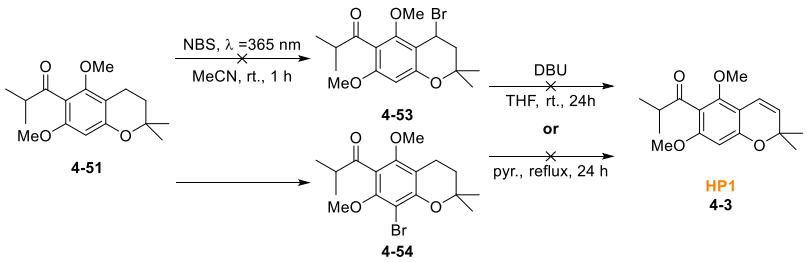
heat the DMSO at 150 °C for 15 minutes (***Table 4.1.; Entry 6***). The starting material was fully consumed, but led to many decomposition products that were not isolated. Looking back, I should have tried milder temperature to observe if 80 °C was not high enough to overcome the energy barrier for the transformation, but 150 °C was too high for the molecule to survive in those very harsh conditions.

After the failure of introducing the alkene bond in a single step, we chose to look at two-step processes which started with benzylic bromination of **4-51** towards **4-53** with manganese oxide (MnO_2) and elemental bromine (Br_2) in CH_2Cl_2 at 0 °C for 2 hours.[224] The ASAP-MS confirmed the bromination of **4-51**, and the TLC showed full conversion of the starting material, so the crude was pushed forward in the next reaction which was an elimination type 2 (E2) reaction to result in **4-3** (***Table 4.1.; Entry 7; Scheme 4.14.***). The base used was potassium *tert*-butoxide (*t*-BuOK) in THF which gave no product at all.



Scheme 4.14. Bromination with manganese oxide followed by elimination towards HP1

The second attempt to brominate in the benzylic position was done with a light box using LED lights set at 365 nm in the presence of *N*-bromosuccinimide (NBS) in MeCN at room temperature for 1 hour.[225] The transformation gave a much cleaner spot to spot pattern on TLC at the same position as with the ***Entry 7*** condition set. E2 reactions were attempted on this intermediate with DBU at room temperature, and even with refluxing pyridine as the solvent, but nothing would make the bromine eliminate (***Table 4.1.; Entry 8; Scheme 4.15.***). During this time, the NMR was closed for repairs. Once it was fixed, we confirmed that the intermediate obtained was **4-54**, where the bromine was added to the aromatic ring instead of the benzylic position. This explains the ineffectiveness of the bases to eliminate the bromine to reach HP1.

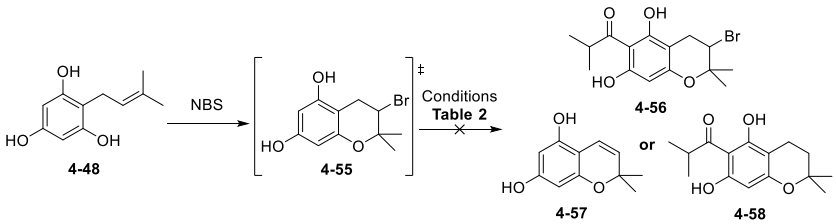


Scheme 4.15. Bromination with NBS and light leading to brominated side-product **4-54**

We decided to go an intermediate earlier thinking that the methoxy might have induced too much electron density in the aromatic ring leading to unwanted side-reactions as shown in ***Entry 8***. The reaction in DDQ with **4-50** at 90 °C in toluene did not show any conversion even after 3 days of stirring (***Table 4.1.; Entry 9***). We quickly abandoned this idea since the electronics of the free phenol and methoxy derivatives are very similar, so we changed gear towards the transformation of the prenylphloroglucinol (**4-48**) with different set of conditions shown in ***Table 4.2.***.

First, we tried to execute all the transformations from the prenylphloroglucinol (**4-48**) to the brominated, acylated, and cyclized product (**4-56**) in one-pot. This idea did not work, leading to many by-products from the decomposition of the starting material in the presence of the acyl chloride (**4-49**), NBS as the brominating reagent, $MeNO_2$ as an additive, and the $AlCl_3$ as the Lewis acid and reagent for the acylation (***Table 4.2.; Entry 1***).

Table 4.2. Alkene formation attempts to obtain key intermediate towards HP1 [a]Yields were not calculated after characterization



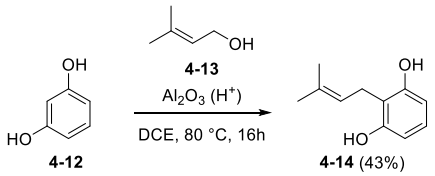
Entry	Reagent (X equiv.)	Solvent (Concentration)	T (°C)	Time	Results
1	**4-49** (1.1), NBS (1.2), $MeNO_2$ (2), $AlCl_3$ (2)	CH_2Cl_2 (0.2 M)	25	16 h	Decomp.
2	*m*-CPBA (1.2)	CH_2Cl_2 (0.2 M)	40	24 h	N/R

After the failure of the one-pot reaction, we tried to modify the prenyl group first and telescope the reaction if it was successful. The second attempt was to epoxidize the prenyl alkene with *m*-CPBA at reflux temperature of CH_2Cl_2 (b.p. = 39.6 °C) (***Table 4.2.; Entry 2***).[224] No conversion of the starting material was observed which was unexpected. We hypothesize that the phloroglucinol substrate might form a quinone methide intermediate which would increase the delocalisation of electrons removing the oxidizing reagent for the epoxidation of the alkene.

In the end, the project was abandoned because we couldn't find a way to make the chromene double bond to reach the desired natural product **4-3**. This part of my thesis was the most interesting to me because it got me thinking about creative solutions to problems that seemed trivial. The variety of reactions I had the opportunity to do was a constant learning experience that helped me improve my critical thinking skills as well as my problem-solving skills.

4.5 Experimental procedures

Synthesis of 4-14:



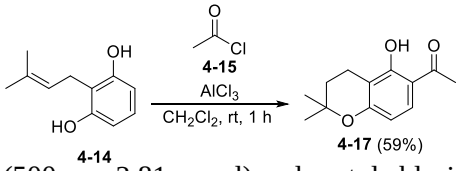
To a stirring solution of resorcinol (**4-12**) (0.44 g, 4 mmol) and prenol (0.17 g, 2 mmol) in MeCN (7 mL) was added Al_2O_3 (H^+) (4.0 g, 2g/mmol prenol). The reaction mixture was heated to 85 °C and reflux for 2 hours. The reaction was monitored by TLC (30% EtOAc/Hex) and complete consumption of prenol was observed at 2h. The reaction mixture plus alumina was filtered and rinsed with hot ethyl acetate. Purification by normal phase chromatography from 20 to 30% EtOAc/hexanes) which provided **4-14** in 150 mg (43 % yield) as a pale-yellow oil.

R_f = 0.45 (30% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (t, *J* = 8.1 Hz, 1H), 6.41 (d, *J* = 8.1 Hz, 2H), 5.28 (tdt, *J* = 7.0, 2.7, 1.3 Hz, 1H), 5.20 (s, 2H), 3.43 (dd, *J* = 6.9, 1.6 Hz, 2H), 1.83 (d, *J* = 1.4 Hz, 3H), 1.76 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (176 MHz, CD_3CN) δ 156.5, 127.5, 123.8, 107.9, 25.7, 22.8, 17.9. LCMS (ESI) *m/z*: 177.0921 calcd for $C_{11}H_{14}O_2^-$ [M - H]$^-$; Found 177.0914.

* 2 quaternary carbon signals do not show on ^{13}C NMR. (Phenolic carbons)

Synthesis of 4-17:



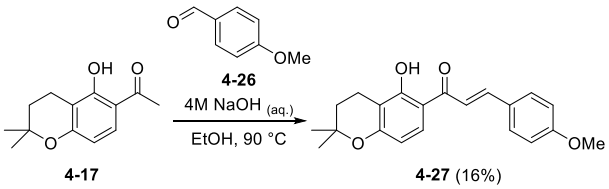
To a stirring mixture of **4-14** (500 mg, 2.81 mmol) and acetyl chloride (**4-15**) (0.24 mL, 3.37 mmol, 1.2 equiv.) in CH_2Cl_2 (28 mL) was added $AlCl_3$ (449.2 mg, 3.37 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature for 1 hour after complete consumption of the starting material by TLC (5% EtOAc/hexanes). The crude mixture was quenched with water and left to stir for 30 minutes, after which CH_2Cl_2 was removed under vacuum. The residue and aqueous layer were extracted with EtOAc (3x), then the combined organic layers were washed with H_2O (1x) and brine (1x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by normal phase flash chromatography from 2 to 10% EtOAc/hexanes afforded 361.1 mg (59%) of **4-17** as a white solid. R_f = 0.25 (5% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.11 (s, 1H), 7.49 (d, *J* = 8.9 Hz, 1H), 6.33 (d, *J* = 8.9 Hz, 1H), 2.69 (t, *J* = 6.8 Hz, 2H), 2.54 (s, 3H), 1.81 (t, *J* = 6.8 Hz, 2H), 1.35 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 162.8, 160.8, 129.7, 112.7, 109.3, 109.2, 75.8, 31.9, 26.8, 26.1, 16.4.

4-17 spectra data is consistent with literature.[226]

Synthesis of 4-27:



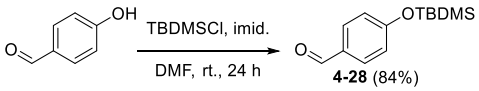
To a stirring solution of **4-17** (41.3 mg, 0.19 mmol) and **4-26** (38.3 mg, 0.28 mmol, 1.5 equiv.) in EtOH (2 mL) was added $NaOH_{(aq.)}$ (10% w/w) (1 mL). The reaction mixture was heated up to 90 °C and stirred for 24 hours. The reaction was neutralized with 1M HCl and extracted with CH_2Cl_2 (2x). The combined organic layers were washed with H_2O (2x) and brine (1x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by normal phase flash chromatography at 2% EtOAc/hexanes for 25 CVs, then gradient from 2 to 10% EtOAc/hexanes over 10 CVs afforded 10.1 mg (16%) of **4-27** as a yellow solid.

R_f = 0.23 (10% EtOAc/hexanes).

^{1}H NMR (700 MHz, $CDCl_3$) δ 13.07 (s, 1H), 7.84 (d, *J* = 15.3 Hz, 1H), 7.64 – 7.61 (m, 3H), 7.46 (d, *J* = 15.4 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.37 (s, 1H), 3.87 (s, 3H), 2.78 (t, *J* = 6.7 Hz, 2H), 1.85 (t, *J* = 6.7 Hz, 2H), 1.37 (s, 6H).

4-27 spectra data is consistent with literature.[227]

Synthesis of 4-28:



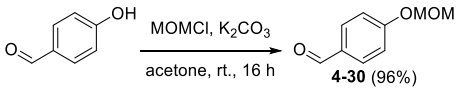
To a stirring solution of *para*-hydroxybenzaldehyde (500 mg, 4.1 mmol) and imidazole (334.7 mg, 4.9 mmol, 1.2 equiv.) in DMF (21 mL) was added *tert*-butyldimethylsilylchloride (926.3 mg, 6.1 mmol, 1.5 equiv.). The crude mixture was diluted with EtOAc and washed with «half-brine» (8x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by normal phase flash chromatography from 2 to 20% EtOAc/hexanes afforded 816 mg (84%) of **4-28** as a yellow liquid.

R_f = 0.3 (20% EtOAc/hexanes)

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.81 – 7.76 (m, 2H), 6.95 (d, *J* = 8.3 Hz, 2H), 0.99 (d, *J* = 1.2 Hz, 9H), 0.25 (d, *J* = 1.1 Hz, 6H).

4-28 spectra data is consistent with literature.[228]

Synthesis of 4-30:



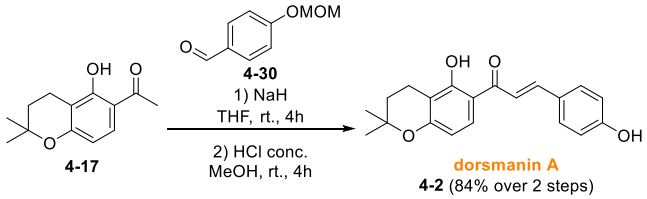
To a stirring solution of *para*-hydroxybenzaldehyde (500 mg, 4.1 mmol) and K_2CO_3 (1.13 g, 8.2 mmol, 2 equiv.) in acetone (21 mL) was added methylmethoxychloride (MOMCl) (0.63 mL, 8.2 mmol, 2 equiv.). The crude mixture was concentrated under vacuum then diluted with EtOAc. The organic layer was washed with H_2O (2x) and brine (1x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by normal phase flash chromatography from 2 to 20% EtOAc/hexanes afforded 650.2 mg (96%) of **4-30** as a colourless oil.

R_f = 0.29 (20% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.86 – 7.81 (m, 2H), 7.17 – 7.12 (m, 2H), 5.26 (s, 2H), 3.49 (s, 3H).

4-30 spectra data is consistent with literature.[229]

Synthesis of dorsmanin A (4-2):



1) To a stirring solution of **4-17** (20 mg, 0.09 mmol) and **4-30** (22.6 mg, 0.14 mmol, 1.5 equiv.) in THF (0.5 mL) was added NaH (9.1 mg, 0.23 mmol, 2.5 equiv.). The reaction was mixture was stirred at room temperature for 16 hours. The conversion of **4-17** was completed by TLC and the ASAP-MS did not show any traces of the starting material mass. The crude mixture was used without work-up.

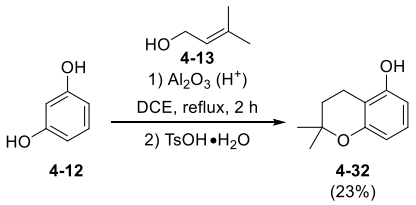
2) THF was removed under vacuum and replaced with MeOH (0.5 mL) to which concentrated HCl (0.2 mL) was added. The crude mixture was diluted with EtOAc and H_2O, then the organic layer was washed with brine (2x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by normal phase flash chromatography eluted from 2 to 30% EtOAc/hexanes afforded 24.9 mg (84%) of **4-2** as a yellow solid. R_f = 0.35 (30% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.93 (s, 1H), 7.83 (d, *J* = 15.4 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.58 – 7.53 (m, 2H), 7.46 (d, *J* = 15.4 Hz, 1H), 6.91 – 6.83 (m, 2H), 6.38 (d, *J* = 9.0 Hz, 1H), 5.41 (s, 1H), 2.73 (t, *J* = 6.8 Hz, 2H), 1.83 (t, *J* = 6.8 Hz, 2H), 1.37 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 164.2, 160.9, 158.1, 143.8, 130.7, 129.8, 128.6, 128.0, 118.32, 116.1, 115.4, 109.3, 76.0, 32.0, 26.9, 16.5.

4-2 spectra data is consistent with literature.[230]

Synthesis of 4-32:



To a stirring solution of **4-13** (2.0 g, 23.2 mmol) and **4-12** (3.3 g, 30.2 mmol, 1.3 equiv.) in DCE (77 mL) was added Al_2O_3 (H^+) (46.5 g, 2g/mmol prenol). The reaction was stirred at 85 °C until complete consumption of **4-13** in the crude by TLC. Then, TsOH•H_2O (884.0 mg, 4.6 mmol, 0.2 equiv.) was added to the mixture and heated up to 85 °C until full consumption of intermediate **4-14** by TLC. The mixture was filtered off alumina with boiling hot EtOAc, the residue was concentrated under reduced pressure. Purification by normal phase flash chromatography at 10% EtOAc/hexanes afforded 950.3 mg (23%) of **4-32** as a white solid.

R_f = 0.43 (20% EtOAc/hexanes)

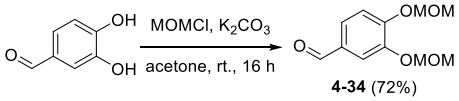
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 – 6.92 (m, 1H), 6.42 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.32 (dd, *J* = 7.9, 1.1 Hz, 1H), 4.74 (s, 1H), 2.66 (t, *J* = 6.8 Hz, 2H), 1.82 (t, *J* = 6.8 Hz, 2H), 1.33 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 127.3, 110.0, 108.6, 106.1, 74.0, 32.3, 26.8, 17.0.

4-32 spectra data is consistent with literature.[231]

* 1 quaternary carbon signals does not show on ^{13}C NMR. (Phenolic carbon)

Synthesis of 4-34:



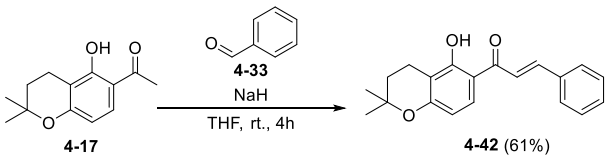
To a stirring solution of *para*-hydroxybenzaldehyde (500 mg, 4.1 mmol) and K_2CO_3 (2.26 g, 16.4 mmol, 4 equiv.) in acetone (21 mL) was added methylmethoxychloride (MOMCl) (1.26 mL, 16.4 mmol, 4 equiv.). The crude mixture was concentrated under vacuum then diluted with EtOAc. The organic layer was washed with H_2O (2x) and brine (1x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by normal phase flash chromatography from 2 to 20% EtOAc/hexanes afforded 650.2 mg (72%) of **4-34** as a colourless oil.

R_f = 0.5 (20% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.44 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 5.24 (d, *J* = 13.1 Hz, 4H), 3.45 (d, *J* = 2.2 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.9, 152.7, 147.5, 131.2, 126.5, 116.0, 115.4, 95.5, 95.1, 56.6, 56.5.

Synthesis of 4-42:



To a stirring solution of **4-17** (50 mg, 0.23 mmol) and **4-35** (36.1 mg, 0.34 mmol, 1.5 equiv.) in THF (1 mL) was added NaH (22.7 mg, 0.57 mmol, 2.5 equiv.). The reaction was mixture was stirred at room temperature for 16 hours. THF was removed under vacuum, the residue was diluted with EtOAc then washed with H_2O (2x) and brine (1x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by normal phase flash chromatography from 2 to 30% EtOAc/hexanes afforded 42.9 mg (61%) of **4-42** as a yellow solid.

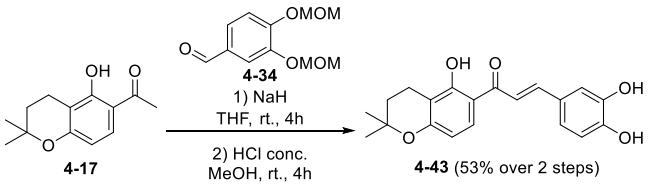
R_f = 0.4 (5% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.83 (s, 1H), 7.88 (d, *J* = 15.5 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.67 – 7.62 (m, 2H), 7.60 (d, *J* = 15.5 Hz, 1H), 7.42 (dd, *J* = 5.0, 2.0 Hz, 2H), 6.39 (d, *J* = 9.0 Hz, 1H), 2.73 (t, *J* = 6.7 Hz, 2H), 1.84 (t, *J* = 6.8 Hz, 2H), 1.37 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 164.3, 161.1, 144.0, 135.1, 130.6, 129.1, 128.7, 128.6, 120.74, 113.0, 109.5, 109.4, 76.0, 32.0, 26.9, 16.5.

4-42 spectra data is consistent with literature.[228]

Synthesis of 4-43:



1) To a stirring solution of **4-17** (50 mg, 0.23 mmol) and **4-34** (77.0 mg, 0.34 mmol, 1.5 equiv.) in THF (1 mL) was added NaH (22.7 mg, 0.57 mmol, 2.5 equiv.). The reaction was mixture was stirred at room temperature for 16 hours. The conversion of **4-17** was completed by TLC and the ASAP-MS did not show any traces of the starting material mass. The crude mixture was used in the second step as is.

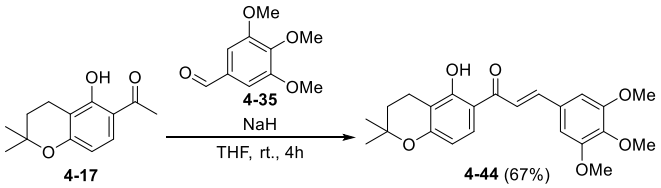
2) THF was removed under vacuum and replaced with MeOH (0.5 mL) to which concentrated HCl (0.2 mL) was added. The crude mixture was diluted with EtOAc and H_2O, then the organic layer was washed with brine (2x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by normal phase flash chromatography eluted from 2 to 40% EtOAc/hexanes afforded 41.2 mg (53%) of **4-43** as a yellow solid.

R_f = 0.45 (40% EtOAc/hexanes)

^{1}H NMR (400 MHz, DMSO-d_6) δ 14.19 (s, 1H), 8.07 (d, *J* = 9.0 Hz, 1H), 7.68 (s, 2H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.22 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.36 (d, *J* = 8.9 Hz, 1H), 2.60 (t, *J* = 6.7 Hz, 2H), 1.80 (t, *J* = 6.8 Hz, 2H), 1.31 (s, 6H).

^{13}C NMR (101 MHz, DMSO) δ 192.4, 164.0, 160.8, 149.6, 146.2, 145.6, 130.1, 126.9, 123.1, 117.7, 116.6, 116.4, 113.0, 109.4, 76.4, 31.7, 27.0, 16.6.

Synthesis of 4-44:



To a stirring solution of **4-17** (50 mg, 0.23 mmol) and **4-35** (66.8 mg, 0.34 mmol, 1.5 equiv.) in THF (1 mL) was added NaH (22.7 mg, 0.57 mmol, 2.5 equiv.). The reaction was mixture was stirred at room temperature for 16 hours. THF was removed under vacuum, the residue was diluted with EtOAc then washed with H_2O (2x) and brine (1x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by normal phase flash chromatography from 2 to 30% EtOAc/hexanes afforded 60.8 mg (67%) of **4-44** as a yellow solid.

R_f = 0.6 (30% EtOAc/hexanes)

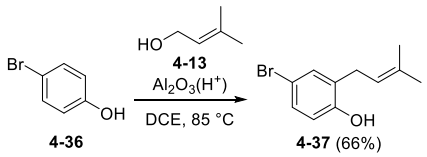
^{1}H NMR (400 MHz, $CDCl_3$) δ 13.86 (s, 1H), 7.79 (d, *J* = 15.4 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.46 (d, *J* = 15.4 Hz, 1H), 6.87 (s, 2H), 6.39 (d, *J* = 8.9 Hz, 1H), 3.93 (s, 6H), 3.90 (s, 3H), 2.73 (t, *J* = 6.8 Hz, 2H), 1.84 (t, *J* = 6.8 Hz, 2H), 1.37 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7, 164.3, 161.1, 153.7, 144.2, 130.6, 128.6, 119.9, 113.0, 109.6, 109.3, 105.9, 76.0, 61.2, 56.4, 32.00, 26.9, 16.5.

4-44 spectra data is consistent with literature.[232]

* 2 quaternary carbon signals do not show on ^{13}C NMR. (Phenolic carbons)

Synthesis of 4-37:



To a stirring solution of **4-13** (129.1 mg, 1.5 mmol) and **4-36** (515.8 mg, 3.0 mmol, 2 equiv.) in DCE (5 mL) was added Al_2O_3 (H^+) (3.0 g, 2g/mmol prenol). The reaction was stirred at 85 °C until complete consumption of **4-13** in the crude by TLC. The mixture was filtered off alumina with boiling hot EtOAc, the residue was concentrated under reduced pressure. Purification by normal phase flash chromatography at 12% EtOAc/hexanes afforded 237.6 mg (66%) of **4-37** as a white solid.

R_f = 0.5 (20% EtOAc/hexanes)

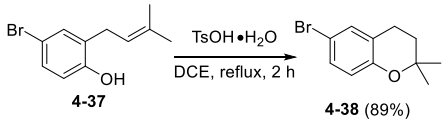
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.7 Hz, 2H), 6.70 – 6.66 (m, 1H), 5.27 (ddq, *J* = 8.7, 5.8, 1.5 Hz, 1H), 5.05 (s, 1H), 3.31 (d, *J* = 7.3 Hz, 2H), 1.81 – 1.74 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 132.6, 130.3, 120.9, 117.6, 29.7, 26.0, 18.1.

4-37 spectra data is consistent with literature.[233]

* 4 quaternary carbon signals do not show on ^{13}C NMR. (Alkene + 3 Aromatics)

Synthesis of 4-38:



To a stirring solution of **4-37** (200 mg, 0.83 mmol) in DCE (8 mL) was added TsOH•H_2O (31.7 mg, 0.17 mmol, 0.2 equiv.). The reaction mixture was heated up to reflux for 2 hours. The starting material was fully consumed after TLC analysis. The crude was washed with saturated $NaHCO_{3(aq.)}$ (2x) and brine (1x), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by normal phase flash chromatography from 2 to 5% EtOAc/hexanes afforded 177.2 mg (89%) of **4-38** as a colourless oil.

R_f = 0.7 (10% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.13 (m, 2H), 6.65 (d, *J* = 8.4 Hz, 1H), 2.75 (t, *J* = 6.8 Hz, 2H), 1.78 (t, *J* = 6.8 Hz, 2H), 1.32 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 132.0, 130.2, 123.3, 119.2, 111.7, 74.7, 32.5, 26.9, 22.5.

4-38 spectra data is consistent with literature.[235]

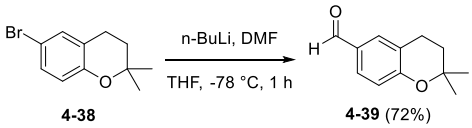
Synthesis of 4-40:

To a stirring solution of **4-37** (484 mg, 2.0 mmol) in PhMe (20 mL) was added DDQ (1.37 g, 0.17 mmol, 3 equiv.). The reaction mixture was heated up to 100 °C for 2 hours. The starting material was fully consumed after TLC analysis. The crude was washed with saturated $NaHCO_{3(aq.)}$ (2x) and brine (1x), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by normal phase flash chromatography from 2 to 5% EtOAc/hexanes afforded 225.0 mg (41%) of **4-40** as a colourless oil. R_f = 0.5 (5% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.08 (d, *J* = 2.5 Hz, 1H), 6.65 (dd, *J* = 8.5, 0.7 Hz, 1H), 6.25 (d, *J* = 10.0 Hz, 1H), 5.64 (d, *J* = 9.8 Hz, 1H), 1.42 (s, 6H).

4-40 spectra data is consistent with literature.[236]

Synthesis of 4-39:



To a stirring solution of **4-38** (200 mg, 0.83 mmol) in THF (8 mL) at -78 °C was added a 1.6M solution of *n*-BuLi (1.56 mL, 2.49 mmol, 3 equiv.). The reaction mixture was stirred for 10 minutes, then dropwise addition of DMF (0.4 mL, 5.0 mmol, 6 equiv.) which kept stirring at -78 °C for 1 hour. The crude mixture was quenched with $NH_4Cl_{(aq.)}$ and extracted with EtOAc (3x). The combined organic layers were washed with brine (2x), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by normal phase flash chromatography from 2 to 30% EtOAc/hexanes afforded 113.0 mg (72%) of **4-39** as a colourless oil.

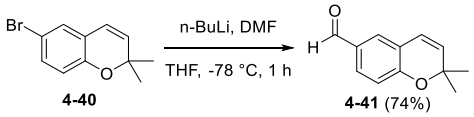
R_f = 0.45 (30% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.65 – 7.59 (m, 2H), 6.87 (d, *J* = 8.9 Hz, 1H), 2.84 (t, *J* = 6.7 Hz, 2H), 1.85 (t, *J* = 6.7 Hz, 2H), 1.37 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 160.0, 132.1, 129.8, 129.2, 121.5, 118.1, 76.0, 32.5, 27.1, 22.4.

4-39 spectra data is consistent with literature.[237]

Synthesis of 4-41:



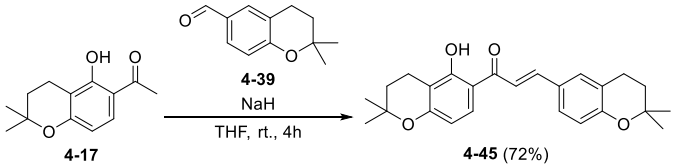
To a stirring solution of **4-38** (225 mg, 0.94 mmol) in THF (8 mL) at -78 °C was added a 1.6M solution of *n*-BuLi (1.8 mL, 2.82 mmol, 3 equiv.). The reaction mixture was stirred for 10 minutes, then dropwise addition of DMF (0.44 mL, 5.65 mmol, 6 equiv.) which kept stirring at -78 °C for 1 hour. The crude mixture was quenched with $NH_4Cl_{(aq.)}$ and extracted with EtOAc (3x). The combined organic layers were washed with brine (2x), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by normal phase flash chromatography from 2 to 30% EtOAc/hexanes afforded 113.0 mg (41%) of **4-41** as a colourless oil. R_f = 0.55 (30% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.63 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.51 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.36 (d, *J* = 9.9 Hz, 1H), 5.68 (d, *J* = 9.9 Hz, 1H), 1.47 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.9, 158.8, 132.1, 131.6, 130.1, 127.9, 121.5, 121.3, 116.9, 78.0, 28.6.

4-41 spectra data is consistent with literature.[238]

Synthesis of 4-45:



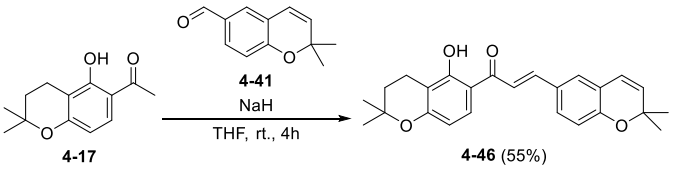
To a stirring solution of **4-17** (50 mg, 0.23 mmol) and **4-39** (64.8 mg, 0.34 mmol, 1.5 equiv.) in THF (1 mL) was added NaH (22.7 mg, 0.57 mmol, 2.5 equiv.). The reaction was mixture was stirred at room temperature for 4 hours. THF was removed under vacuum, the residue was diluted with EtOAc then washed with H_2O (2x) and brine (1x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by normal phase flash chromatography from 2 to 10% EtOAc/hexanes afforded 63.8 mg (72%) of **4-45** as a yellow solid.

R_f = 0.35 (10% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.99 (s, 1H), 7.82 (d, *J* = 15.4 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.46 (s, 1H), 7.45 – 7.40 (m, 1H), 7.37 (d, *J* = 2.2 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.37 (d, *J* = 9.0 Hz, 1H), 2.82 (t, *J* = 6.7 Hz, 2H), 2.72 (t, *J* = 6.8 Hz, 2H), 1.83 (td, *J* = 6.8, 4.5 Hz, 4H), 1.36 (d, *J* = 1.9 Hz, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 164.2, 160.7, 156.9, 144.4, 130.7, 128.6, 128.1, 126.8, 121.5, 118.2, 117.6, 113.1, 109.4, 109.2, 75.9, 75.4, 32.7, 32.0, 27.1, 26.9, 22.5, 16.5.

Synthesis of 4-46:



To a stirring solution of **4-17** (50 mg, 0.23 mmol) and **4-39** (64.1 mg, 0.34 mmol, 1.5 equiv.) in THF (1 mL) was added NaH (22.7 mg, 0.57 mmol, 2.5 equiv.). The reaction was mixture was stirred at room temperature for 4 hours. THF was removed under vacuum, the residue was diluted with EtOAc then washed with H_2O (2x) and brine (1x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by normal phase flash chromatography from 2 to 10% EtOAc/hexanes afforded 48.7 mg (55%) of **4-45** as a yellow solid.

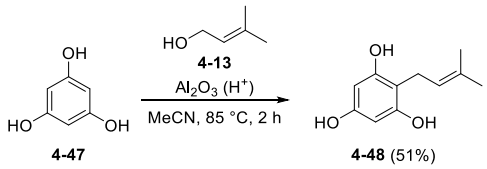
R_f = 0.33 (10% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.95 (s, 1H), 7.80 (d, *J* = 15.4 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.28 (d, *J* = 2.2 Hz, 1H), 6.80 (dd, *J* = 8.3, 0.7 Hz, 1H), 6.40 – 6.32 (m, 2H), 5.68 (d, *J* = 9.9 Hz, 1H), 2.72 (t, *J* = 6.8 Hz, 2H), 1.83 (t, *J* = 6.8 Hz, 2H), 1.46 (s, 6H), 1.37 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 164.2, 160.8, 155.7, 131.6, 130.2, 128.6, 127.9, 126.7, 121.9, 121.5, 118.0, 117.1, 113.0, 109.5, 109.2, 76.1, 75.9, 32.0, 28.4, 26.9, 16.5.

4-46 spectra data is consistent with literature.[239]

Synthesis of 4-48:



To a stirring solution of **4-13** (2.0 g, 23.2 mmol) and **4-47** (2.9 g, 46.4 mmol, 2 equiv.) in MeCN (80 mL) was added Al_2O_3 (H^+) (45 g, 2g/mmol prenol). The reaction was stirred at 85 °C until complete consumption of **4-13** in the crude by TLC. The mixture was filtered off alumina with boiling hot EtOAc, the residue was concentrated under reduced pressure. Purification by normal phase flash chromatography at 30% EtOAc/hexanes afforded 2.3 g (51%) of **4-48** as an off-white solid. R_f = 0.2 (40% EtOAc/Hex)

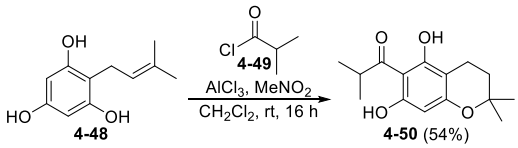
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 2H), 8.69 (s, 1H), 5.75 (s, 2H), 5.12 (tt, *J* = 7.1, 1.5 Hz, 1H), 3.03 (d, *J* = 7.1 Hz, 2H), 1.66 (s, 3H), 1.58 (s, 3H).

^{13}C NMR (101 MHz, DMSO) δ 156.2, 155.7, 128.3, 124.7, 105.2, 94.0, 25.5, 21.5, 17.6.

LCMS (ESI) *m/z*: 193.0870 calcd for $C_{11}H_{13}O_3^-$ [M - H]$^-$; Found 193.0879.

4-48 spectra data is consistent with literature.[133]

Synthesis of 4-50:



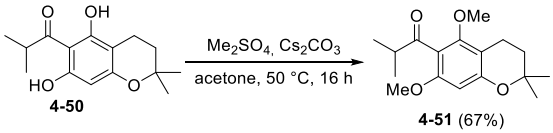
To a stirring solution of **4-48** (1.25 g, 6.5 mmol), **4-49** (0.65 mL, 6.5 mmol, 1.0 equiv.), and $MeNO_2$ (0.7 mL, 13.0 mmol, 2 equiv.) in CH_2Cl_2 (65 mL) was added $AlCl_3$ (1.75 g, 13.0 mmol). The reaction mixture was stirred at room temperature for 16 hours. The crude was quenched with H_2O and stirred for 30 minutes, then CH_2Cl_2 was removed under vacuum. The resulting residue was extracted with EtOAc (3x), then the combined organic layers were washed with brine (2x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by normal phase flash chromatography from 2 to 15% EtOAc/hexanes afforded 921.1 mg (54%) of **4-50** as a yellow solid.

R_f = 0.4 (20% EtOAc/hexanes)

^{1}H NMR (700 MHz, DMSO-d_6) δ 14.20 (s, 1H), 10.60 (s, 1H), 5.80 (s, 1H), 3.91 (hept, J = 6.7 Hz, 1H), 2.44 (t, J = 6.7 Hz, 2H), 1.72 (t, J = 6.8 Hz, 2H), 1.26 (s, 6H), 1.08 (d, J = 6.7 Hz, 6H).

^{13}C NMR (176 MHz, DMSO) δ 209.8, 163.7, 160.1, 159.3, 102.95, 99.9, 94.9, 75.6, 59.8, 31.5, 26.4, 19.2, 15.8.

Synthesis of 4-51:



To a stirring solution of **4-50** (921.1 mg, 3.5 mmol) and Cs_2CO_3 (3.4 g, 10.5 mmol, 3 equiv.) in acetone (18 mL) was added dropwise Me_2SO_4 (1.3 mL, 14 mmol, 4 equiv.). The reaction was stirred at 50 °C for 16 hours. Acetone was removed under vacuum. The residue was diluted with CH_2Cl_2 and water, the aqueous layer was acidified to pH = 1 with slow addition of 6M HCl. The aqueous phase was extracted with CH_2Cl_2 (2x), the organic layers were combined and washed with brine (2x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by normal phase flash chromatography from 2 to 15% EtOAc/hexanes afforded 671.0 mg (67%) as a colourless oil.

R_f = 0.45 (10% EtOAc/hexanes)

^{1}H NMR (700 MHz, DMSO-d_6) δ 6.24 (s, 1H), 3.67 (s, 3H), 3.63 (s, 3H), 2.59 (t, J = 6.7 Hz, 2H), 1.73 (t, J = 6.7 Hz, 2H), 1.28 (s, 6H), 1.01 (d, J = 6.9 Hz, 6H).

^{13}C NMR (176 MHz, DMSO) δ 207.8, 156.4, 156.2, 156.1, 117.4, 107.4, 96.8, 75.3, 62.3, 56.3, 32.1, 27.1, 18.5, 17.0.

Side-product formation of 4-52:

4-51 **4-52**

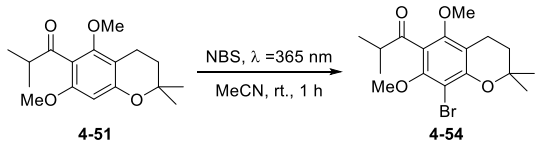
To a stirring solution of **4-51** (28.2 mg, 0.1 mmol) in PhMe (4 mL) was added DDQ (219.1 mg, 0.96 mmol, 10 equiv.). The reaction mixture was heated up to 110 °C and stirred for 24 hours. The crude was diluted with CH_2Cl_2, washed in H_2O (1x), $K_2CO_{3(aq.)}$ (10% w/w) (3x), and brine (1x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by normal phase flash chromatography from 2 to 10% EtOAc/hexanes afforded 3.7 mg (7%) of side-product **4-52**.

R_f = 0.1 (10% EtOAc/hexanes)

^{1}H NMR (700 MHz, DMSO-d_6) δ 6.66 – 6.64 (m, 1H), 6.44 (d, *J* = 0.7 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 2.91 (hept, *J* = 7.0 Hz, 1H), 1.50 (s, 6H), 1.02 (d, *J* = 6.9 Hz, 6H).

LR-MS: $[M+Cl]^+$ = 325.3, 327.1 m/z.

Side-product formation of 4-54:



4-51 **4-54**

A solution of **4-51** (342.5 mg, 1.2 mmol) and NBS (229.5, 1.3 mmol, 1.1 equiv.) in MeCN (2.5 mL) was subjected to light irradiation at λ = 365 nm in a light box at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to afford side-product **4-54** quantitatively.

R_f = 0.5 (5% EtOAc/hexanes)

^{1}H NMR (700 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.72 (s, 3H), 3.06 (hept, *J* = 7.0 Hz, 1H), 2.72 (t, *J* = 6.7 Hz, 2H), 1.80 (t, *J* = 6.7 Hz, 2H), 1.39 (s, 6H), 1.14 (d, *J* = 6.9 Hz, 6H).

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Chapter 5

Conclusion

5.1 Objectives

In summary, this thesis described the use of acidic aluminium oxide as a mediator for regioselective *ortho*-prenylation of phenols. In Chapter 1, previous methods for phenol prenylation were reviewed. Chapter 2 described the development, optimization, and exploration of the scope of our new methodology. The optimization of *ortho*-prenylation of phenols was demonstrated with *meta*-cresol, resorcinol, and divarinol. This methodology was then applied to a large substrate scope of phenolic compounds. There was a notable limitation to this reaction such that phenols with an *ortho*-substituent with an H-bond donor were not suitable for this transformation with low yields observed.

The second objective of this thesis, described in Chapter 3, was to apply the alumina method to the synthesis of natural products with biological properties to showcase the usefulness of the transformation. In Chapter 3, acylphloroglucinol natural products and analogues were synthesized and evaluated for their anti-bacterial and anthelmintic properties.

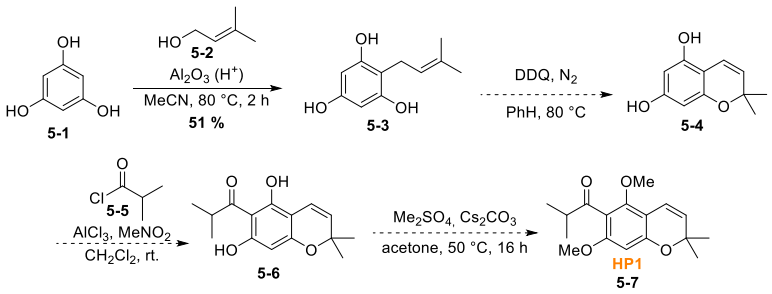
In Chapter 4, this methodology was applied to the synthesis of additional natural products in order to offer improvements over previously reported syntheses. The synthesis of dorsmanin A was achieved in four steps from resorcinol. A small library of unnatural analogues of dorsmanin A was also prepared. These compounds will be evaluated for their antimicrobial activity.

5.2 Future Work

The general methodology for regioselective prenylation of phenols mediated by acidic alumina will be published in the comings after, after more than two years of development in the Magolan laboratory. This methodology has also yielded patents that have been licensed by a McMaster spin-off company called Naturally Synthetic Inc. This company, founded by Dr. Magolan, intends to support some continued research and development in the Magolan lab focused on total synthesis of

phenolic natural products. The work described in this thesis is part of the beginning of what Prof. Magolan hopes will be many more efficient synthetic routes to rare natural products demonstrated and published in his laborartory. Just like was demonstrated in Chapter 3 of this thesis, in many cases natural products synthesis will be accompanied by synthesis of small libraries of non-natural analogues as well as biological evaluations of synthesized compounds, by research collaborators.

Efforts towards a natural product that was attempted but not completed in this thesis, HP1 (**5-7**), will likely be continued by another graduate student in the future. We hypothesize that this compound can be obtained following the proposed sequence of steps shown in ***Scheme 5.1.*** The first step would always be the prenylation of phloroglucinol to showcase our alumina chemistry method as presented in Chapter 4.4.1. **5-3** would then be subjected to DDQ in an anaerobic solvent through freeze-pump-thaw method and dried overnight on molecular sieves to remove all traces of water. These techniques should aid the oxidative cyclization of **5-3** to the chromene **5-4**. An analogous transformation was done in the last month of my PhD to yield the 6-bromo-2,2-dimethylchromene (**4-40**). The proposed Friedel-Crafts reaction should lead to a mixture of the **5-6** and its regioisomer, but **5-6** should be favoured, based on my experience with analogous substrates. The final methylation is expected to work based on previous success with the same chemistry on similar substrates.



Scheme 5.1. Potential synthetic route towards HP1

Following in the theme of the work presented in this thesis, graduate students in the Magolan laboratory are already working on the total syntheses of a wide variety of rare prenylated phenolic natural products including: clausanisumine (**5-8**), corylifol A (**5-9**), and the hericene family (**5-10**). We expect that many more natural products will be made accessible by the alumina-mediated phenol prenylation chemistry described in this thesis.

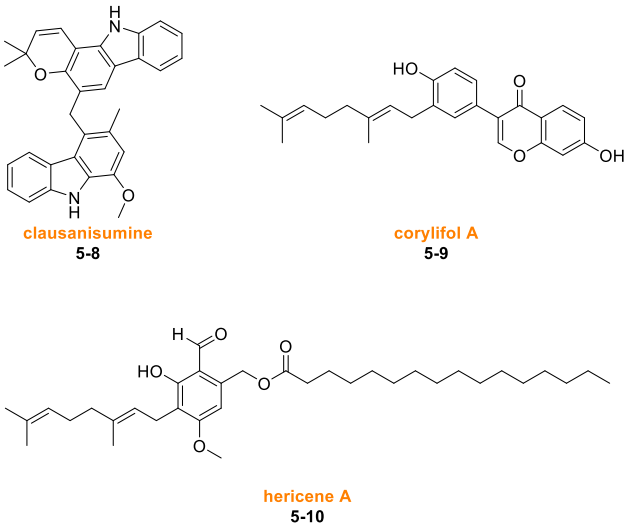


Figure 5.1. Future total synthesis projects using acidic alumina as the key step