Development of a dual Fries–Claisen rearrangement strategy

by

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a Doctoral Thesis

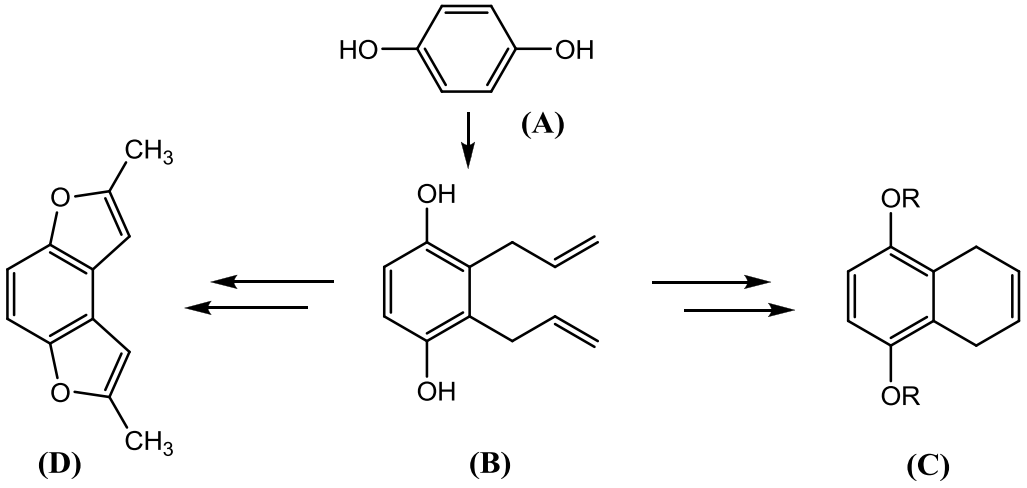
Submitted in partial fulfillment of the requirements for the award of Doctor of Philosophy at Loughborough University

August 2012

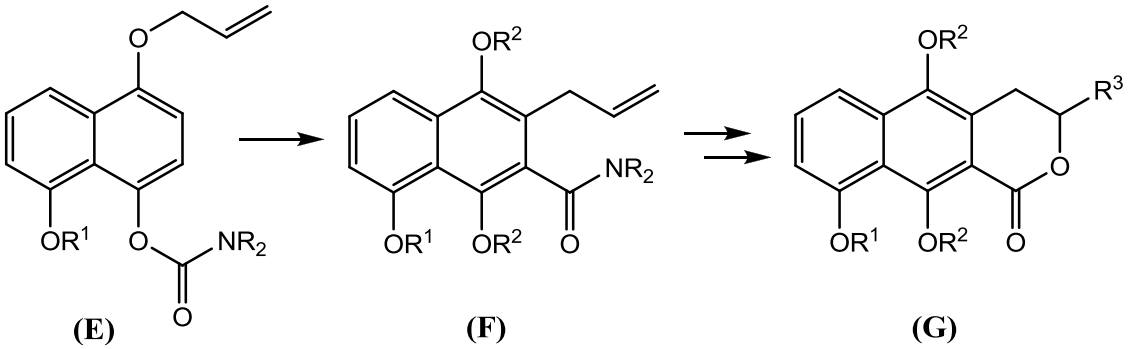
ABSTRACT

Synthetic approaches towards linear fused carbon rings have been developed over the last decades due to their high interest as compounds with potential antibiotic activity and as organic electronics. The application of a novel iterative route towards linear fused carbon ring systems could provide a versatile new mode of access to complex substituted ring systems.

Studies have previously demonstrated the use of an allylation-double Claisen-RCM sequence to build fused carbon rings (**C**).[1] In this thesis we described our work to expand the use of this methodology by developing milder reaction conditions that could be applied to a wider range of compounds. This novel methodology was applied towards the synthesis of benzodifuran compounds (**D**).

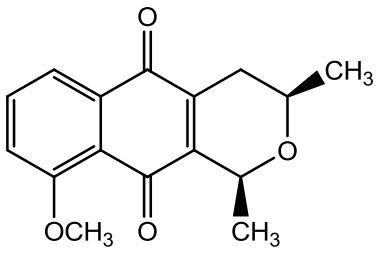


Our work was extended by developing, for the first time, a mixed Fries-Claisen rearrangement strategy which furnishes template (**F**), a key intermediate in the synthesis of pyranonaphthoquinones (**G**).



(E) **(F)** **(G)**

Our work culminated in a new approach to the pyranonaphthoquinone natural products eleutherin (**H**) and isoeleutherin (**I**).



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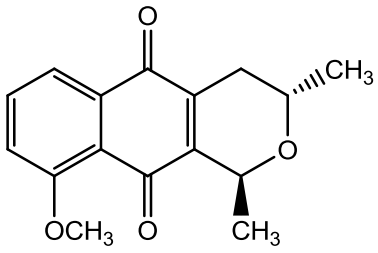

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ACKNOWLEDGEMENTS

Firstly I would like to thank my supervisor Prof. Steve M. Allin for giving me the opportunity to carry out this PhD, and for his continual support, direction and encouragement throught. I would also like to thank Prof. Ray Jones for his guidance and helpful discussions during the course of this project. I appreciate the financial support from both Loughborough University and Charnwood Molecular and I would like to acknowledge all the academic and technical staff for all their assistance.

I would also like to thank all my friends and fellow researchers for all the good times we shared together. Special mention to Acrylate Stanley F.C members with whom I shared memorably experiences and lots of laughs. Tom "don't shoot" Constable, Anish "the princess" Patel, Ben Buckley, Mark Kimber, Jimmy, Rossi, James, Sam, Tom, Andrew and the Spanish squad Fran, Toni and Carlos. Thanks all the "Spaniards" for the unforgettable moments and all the support over the years, sorry not to mention you all but the list would be endless.

To all my friends from Barcelona who haven't given up and still share with me all the banter and the important events wherever we are.

To Cristina, who helped me trough all these years making me smile during the difficult moments. Thanks for all your support, your love and all your patience. Without you next to me I would not have been able to finish this project.

Finally to my family. A mis padres y mi hermano por su incondicional apoyo, todo el cariño mostrado y por estar siempre a mi lado cuando lo he necesitado. Sin vuestra ayuda y vuestros consejos nunca habría llegado a ser la persona que soy.

CONTENTS

ABBREVIATIONS

Ac	acetyl group
Ac_2O	acetic anhydride
AcOH	acetic acid
Ag_2O	silver(I) oxide
aq.	aqueous
b	bending
$BF_3 \cdot Et_2O$	boron trifluoride diethyl etherate
Bn	benzyl group
BnBr	benzyl bromide
BnO_2CCl	benzoyl chloroformate
bp	boiling point
br	broad
CAN	cerium ammonium nitrate
$CDCl_3$	deuterated chloroform
cm^{-1}	wave number
CN	nitrile
Cp_2ZrHCl	zirconocene chloride hydride
d	doublet
DBU	1,8-diazabicycloundec-7-ene
dd	doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMG	direct metalation group
DMPU	*N*,*N'*-dimethyl-*N*,*N'*-propylene urea
DMSO	dimethylsulfoxide
DoM	directed *ortho*-metalation
dt	doublet of triplets
eq.	equivalent(s)
Et	ethyl
Et_2O	diethyl ether
Et_3N	triethylamine
Et_3SiH	triethylsilane
EtOAc	ethyl acetate
EtOH	ethanol

FET	field-effect transistor
g	gram(s)
GP	group protection
h.	hour
hυ	UV radiation
Hz	hertz
i	intense
IBX	2-iodoxybenzoic acid
IR	infrared
LA	Lewis acid
LDA	lithium diisopropylamide
m	multiplet
M	molar
m-CPBA	*meta*-chloroperoxybenzoic acid
md	medium
Me	methyl
Me_3Al	trimethylaluminium
MeI	methyl iodide
MeMgBr	methyl magnesium bromide
MeMgCl	methyl magnesium chloride
MeOH	methanol
MHz	mega hertz
min	minute
mL	millilitre
Mp	melting point
MW	microwave/molecular wire
NBS	*N*-bromosuccinimide
n-BuLi	*n*-butyllithium
$NHMe_2$	dimethylamine
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
o-	*ortho* substituted
ºC	degrees Celsius
OLED	organic light-emitting diode
oop	out of plane
p-	*para* substituted
PAH(s)	polycyclic aromatic hydrocarbon(s)
Pd/C	palladium over carbon
Ph	phenyl
$PhNEt_2$	*N*,*N*-diethylaniline
PhSeCl	phenylselenyl chloride
PhSH	thiophenol
ppm	parts per million

Pr	propyl
psi	pounds per square inch
q	quartet
r.t.	room temperature
RCM	ring closing metathesis
RLi	lithiated reagent
RMgBr	Grignard reagent
s	singlet
sec-BuLi	*sec*-butyllithium
SM	starting material
st	stretching
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Temp.	temperature
TfO	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	tetramethylsilane
TsOH	*para*-toluenesulfonic acid
w	weak
Δ	reflux/heat

CHAPTER ONE: INTRODUCTION

1.1 LINEAR FUSED CARBON RINGS

Polycyclic aromatic hydrocarbons (PAHs) constitute a vast range of organic compounds found in nature from underwater marine organisms[2] to nebulae in outer space.[3] IUPAC defines PAHs as compounds built from two or more benzene rings sharing at least one edge.[4] There are about 10,000 known PAHs[5]. These compounds can be classified in two groups according to their space disposition: linear as tetracene **(1)** or 2D as benzo[α]pyrene **(2)** and coronene **(3)**. PAHs may contain four-, five-, six-, or seven-member rings but those containing five- or six-member rings are the most common. Naphthalene is the simplest example of polycyclic aromatic hydrocarbons.

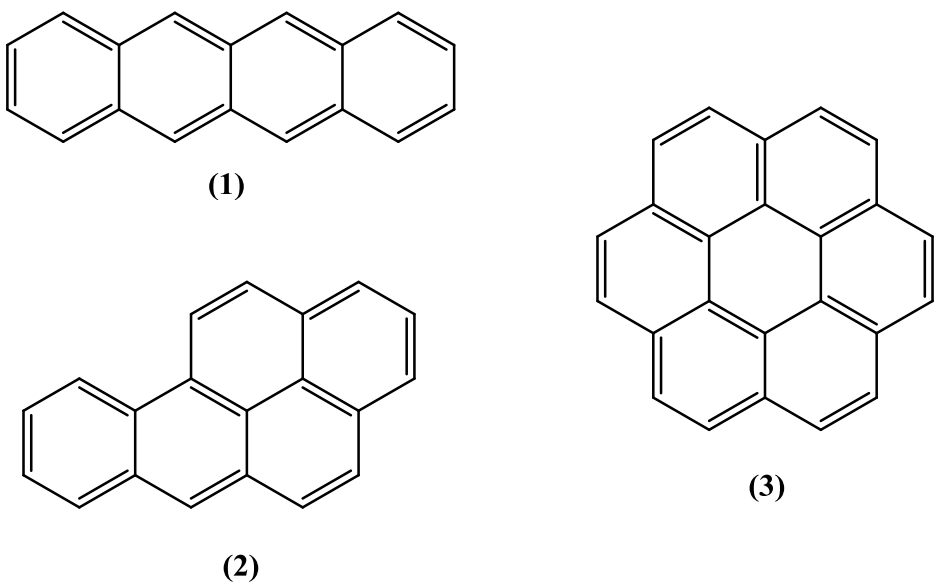
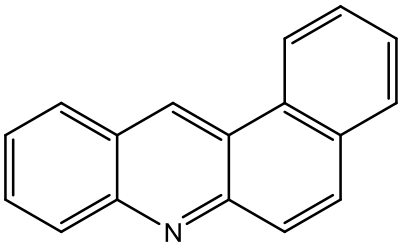


Figure 1: Polycyclic aromatic hydrocarbons

PAHs concern increased significantly at the end of last century due to their high pollution and toxicity rates. Although benzo[α]pyrene **(2)** was the first chemical carcinogen to be discovered PAHs have recently been included in the classification issue reported by the Agency for Toxicity Substances and Disease Registry (ATSDR).[6]

As was previously mentioned PAHs embrace a large amount of compounds. In addition to PAHs that contains only carbon and hydrogen atoms,[7] there are more complex structures containing nitrogen atoms as benz[α]acridine **(4)**, sulfur atoms as pentaceno[2,3-*b*]thiophene **(6)** and oxygen atoms as 2,2-dimethyl-2,3-dihydro-4*H*-benzo[*h*]chromen-4-one **(5)** .[8]



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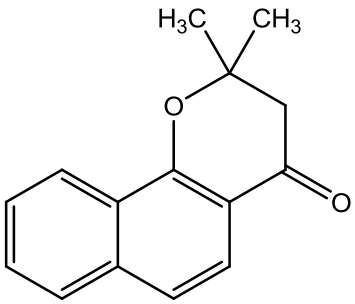

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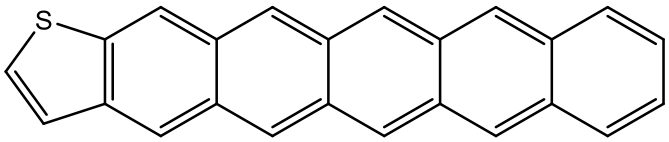

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Figure 2: Heteronuclear polycyclic aromatic hydrocarbons

Over the past few years the interest in PAHs has increased considerably due to their relevance as source of chemical compounds with biological activity, proving interesting results against leukaemia cells and acting as potential DNA intercalators.[9] We have decided to focus our interest in linear fused carbon rings whose structures can be found in some important drugs nowadays.[10]

Linear fused carbon rings can be found as structural motifs in many important areas (pharmaceutical, natural products and materials chemistry). **Figure 3** shows some examples, including tetracycline **(7)**, from the tetracycline antibiotics family, and (*S*)-camptothecin **(8)**. These compounds are of much interest and are widely used in medicinal chemistry.[11,12]

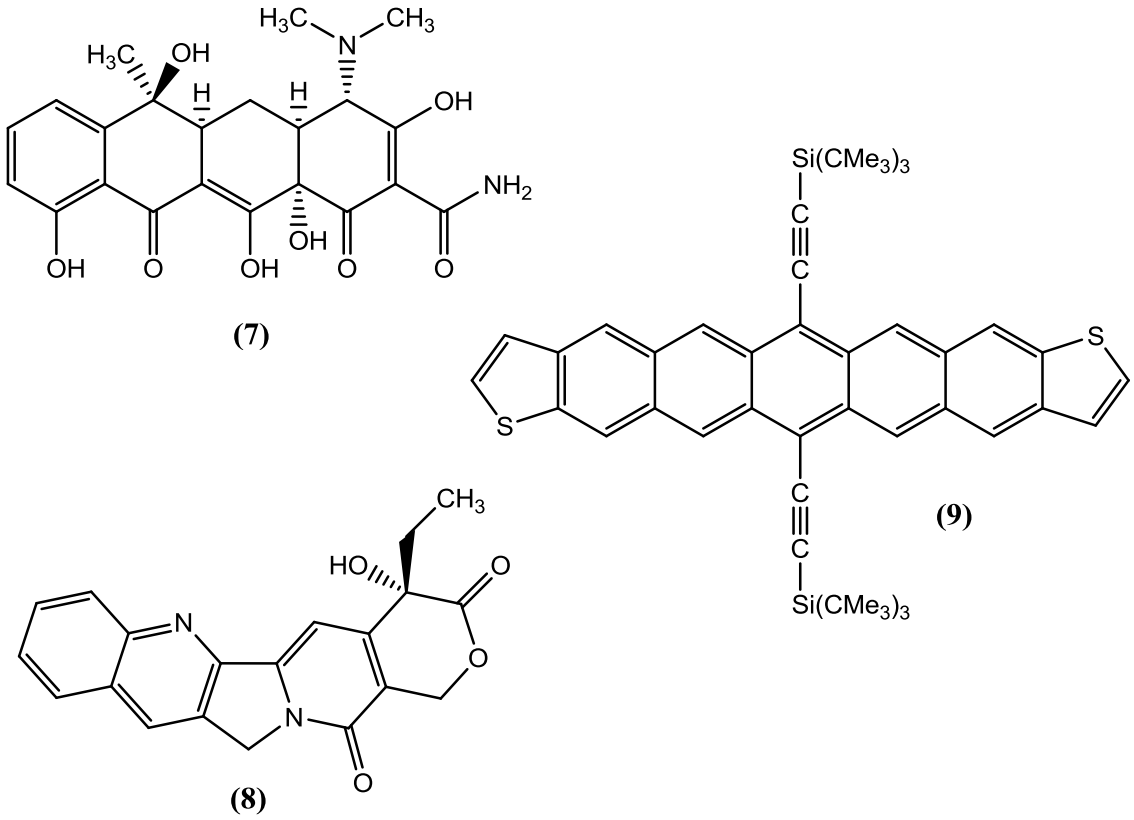


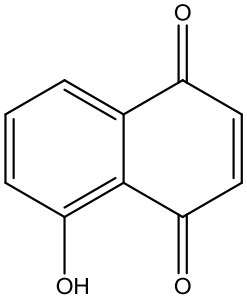
Figure 3: Linear fused carbon rings

Materials chemistry science has recently focused it interest in PAHs and linear fused carbon rings due to their properties as organic conductors in the field of organic electronics.[13] Polycyclic aromatics hydrocarbons and their derivatives **(1**, **6** and **9)** are exploited for their high thin film transistor charge carrier mobility. Linear fused acenes have applications as field-effect transistors (FETs)[14] and organic light-emitting diodes (OLEDs).[15]

Showing typical activity and characteristics of linear fused rings, the juglone series presents a wide range of biological activities including anti-bacterial, anti-cancer and anti-thrombotic activity.[16]

1.2 JUGLONE (5-HYDROXY-1,4-NAPHTHOQUINONE)

Juglone **(10)** is a natural product obtained from the leaves, roots, husk and bark of plants in the *Jugladanceae* family, particularly the black walnut. It has been used for decades as an herbicide, by inhibiting certain enzymes needed for metabolic function, or as a dark orange dye for clothes and inks.



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The juglone skeleton can be found in a great variety of natural compounds such as: rubiginone B1 **(11)** and B2, frydamycin E **(12)**, *γ*–indomycinone **(13)** and mensacarcin **(14)**.

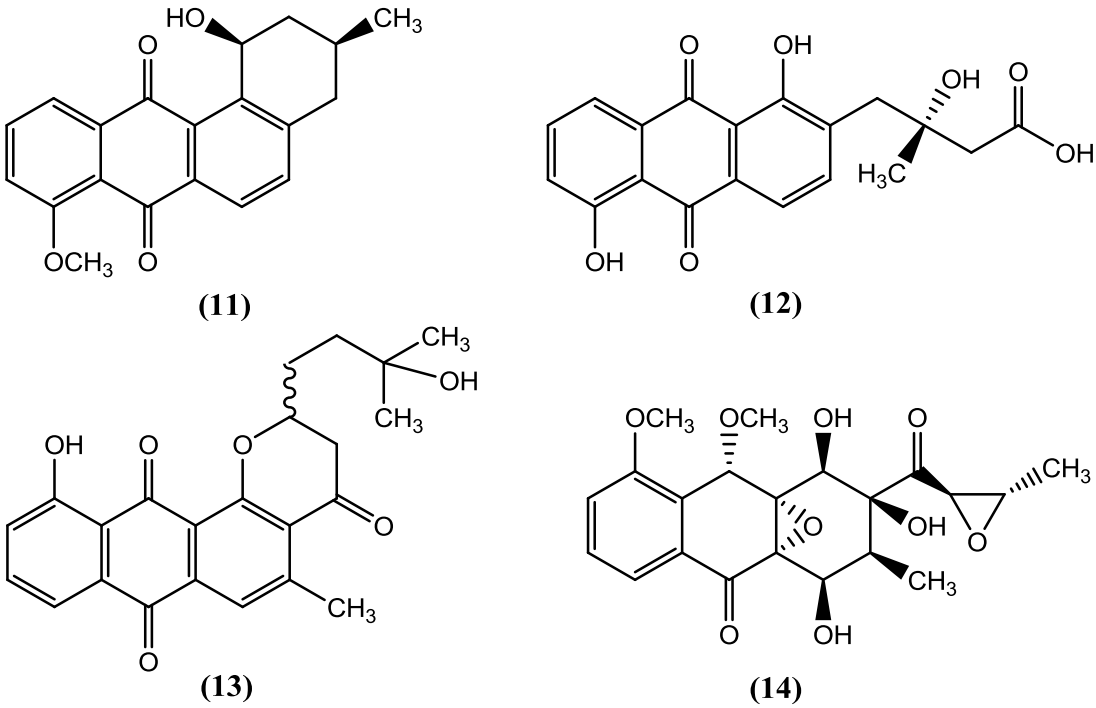


Figure 4: Natural products containing the juglone skeleton

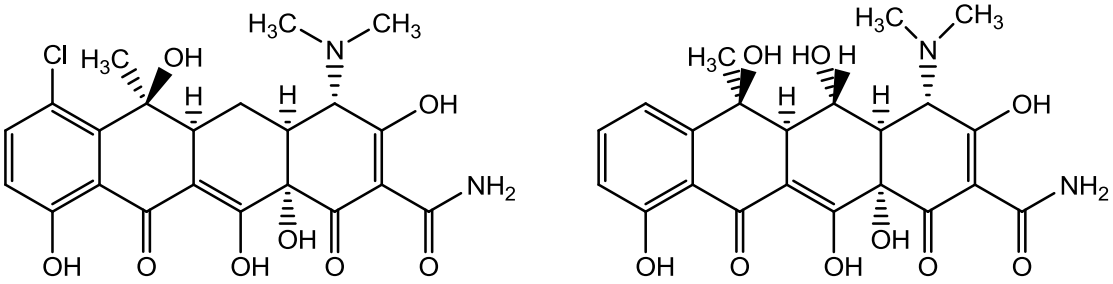
Among the large group of compounds showing biological activity against drug-resistance bacteria with a juglone skeleton in their structure (bisanthraquinones, pyronaphthoquinones) our research was initially focused in the tetracycline antibiotics family.

1.3 TETRACYCLINE ANTIBIOTICS FAMILY

Tetracycline antibiotics are classified as polyketides because of their natural source and the alternating carbonyl and methylene groups in the molecule. Polyketides usually derive from repeated condensation of acetyl coenzyme A and usually the compounds derived from them by further condensations.[17]

Tetracycline compounds were the first major class of therapeutics to earn the distinction of "broad-spectrum antibiotics" and their use in total tons per year is the biggest after penicillins. [18,19] Although tetracyclines are widely used in veterinary and human medicine their overuse has led to widespread bacterial resistance against tetracycline[20] and eventual replacement with more effective antibiotics.

Aureomycin (chlorotetracycline) **(15)** was the first member of the tetracycline family discovered by Duggar in 1948 from a culture of *Streptomyces aureofaciens.*[21] Shortly after other derivatives were subsequently obtained such as terramycin (oxytetracycline) **(16)** and achromycin (tetracycline) **(7)** discovered by Finlay *et al.* in 1950 and Williams *et al*. in 1953 respectively.[22]



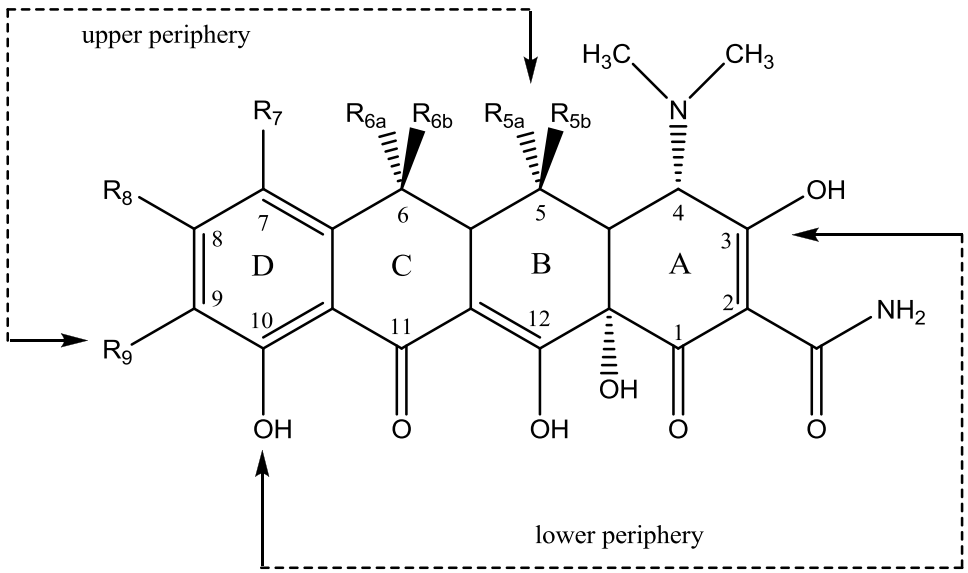
(15) **(16)**

Figure 5: Tetracycline derivatives

Tetracyclines are characterised by a tetracyclic ring structure with a richly substituted ring A and a heavily oxidized periphery that includes a C11, C12 and C11a keto-enol configuration. This general configuration helps bonding to the 30S ribosomal subunit and chelations to divalent cations (Mg^{2+}, Ca^{2+} and Zn^{2+}).[23] Main differences among tetracycline analogues are substitutions at positions in C5, C6 and C7.

Structure-activity relationships based on antibacterial activity subdivide the tetracycline naphthacene ring in two regions **(Figure 6)**. Synthetic modifications on the lower peripheral region reduced both antibiotic and non-antibiotic properties. On the other hand, modifications on the upper peripheral region (most concretely positions C7 to C9 in the D ring) enhance their biological activity.[24]

Replacement of C2 carboxamide moiety with other groups resulted in analogues with inferior antibacterial activity. However, when different substitutions were taken on the amide nitrogen, these analogues showed significant increase in water solubility. Modification of C4 by removal of dimethylamino group also translated in a decrease of antibiotic activity.[25]



		R^{5a}	R^{5b}	R^{6a}	R^{6b}	R^{7}	R^{8}	R^{9}
15	Chlorotetracycline	H	H	CH_3	OH	Cl	H	H
16	Oxytetracycline	OH	H	CH_3	OH	H	H	H
7	Tetracycline	H	H	CH_3	OH	H	H	H
17	Doxycycline	OH	H	CH_3	H	H	H	H
18	Minocycline	H	H	H	H	$N(CH_3)_2$	H	H
19	Sancycline	H	H	H	H	H	H	H
20	Methacycline	OH	H	$=CH_2$		H	H	H

Figure 6: Tetracycline derivatives

Tetracyclines gain access to the bacteria cell by passive diffusion through hydrophilic pores in outer cell membrane and then through inner cytoplasmatic membrane by an energy-dependent active transport.[18,26] Tetracyclines prevent growth of the bacteria by reversible binding to the 30S ribosomal subunit blocking the binding of aminoacyl-tRNA to the acceptor site and inhibiting protein synthesis.[27]

Due to different interactions within the cell "original" tetracyclines are effective against a wide range of bacteria and diseases. As antibiotics they affect both Gram-positive and Gram-negative bacteria, atypical organisms as chlamydiae, myclopasmas and coxiella, and protozoan parasites.[28] Non-antibiotic properties (which are related to their use as metal chelating ionophores) showed good effects against inflammation, proteolysis, angiogenesis, bone metabolism, apoptosis and dermatologic diseases.[29] Tetracyclines low toxicity made them useful for animals and humans although they present minor side-effects as brown teeth, hepatotoxicity and deposition on growing bone.

Unfortunately the indiscriminate use of tetracycline compounds to treat bacterial diseases which affect field crops, food production and veterinary and human medicine has led to the formation of new tetracycline resistance genes.[18,30] Only a small portion of tetracycline is metabolised or absorbed, with most of the dose being released in excreta. The presence of the bioactive compound in nature may promote the development of tetracycline resistance genes. These genes have been found in plasmids and transposons and they are easily spread by conjugal transfer making the use of antibiotics anywhere in the world a source of bacteria resistance genes in other environments.[31] Currently, there are more than 40 known tetracycline resistance genes.[32]

There are two main bacterial resistance mechanisms: Efflux resistance mechanism shows an active efflux of tetracycline out of the cell by insertion of membrane transport protein *tetA* into the bacterial cytoplasmatic membrane, preventing the accumulation of tetracyclines inside the cell and making it inactive. Ribosomal protection resistance mechanism presents a modification on the ribosomal binding site by interaction with protein *tetM* making the binding of tetracycline not possible or distorted and rendering the drug inactive. A third resistance mechanism would involve a modification of tetracycline inside the cell by a chemical reaction but the exact mechanism has not yet been fully elucidated **(Figure 7)**.[33]

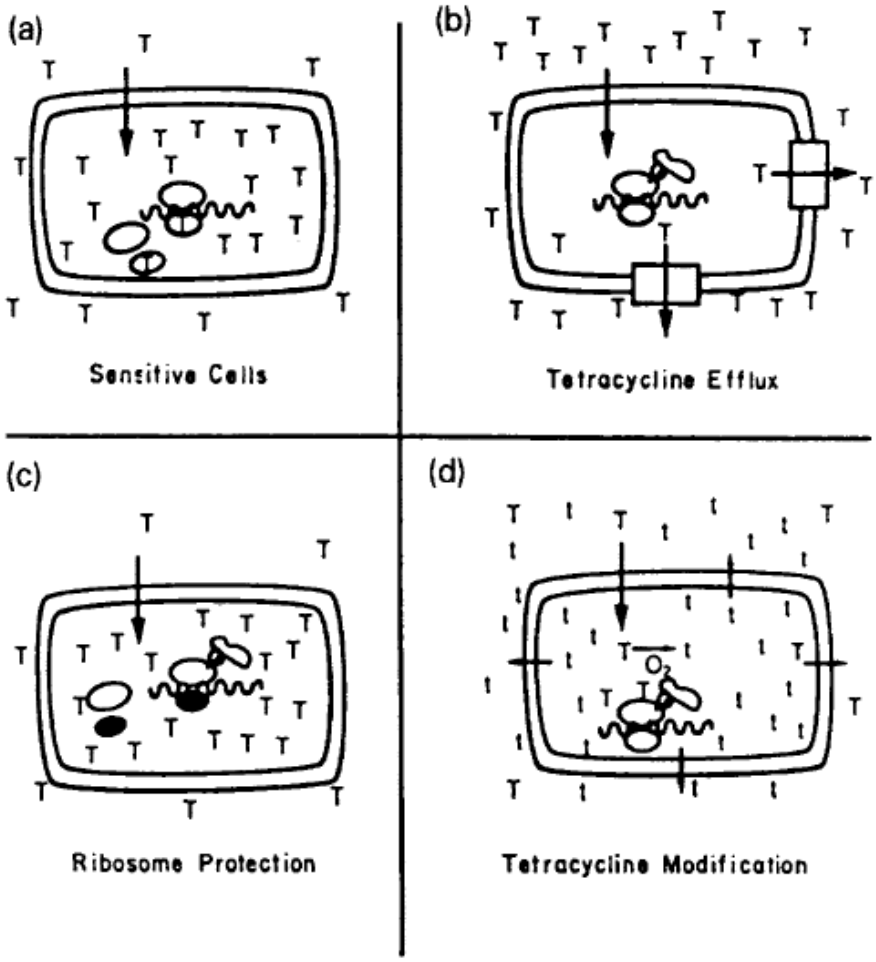
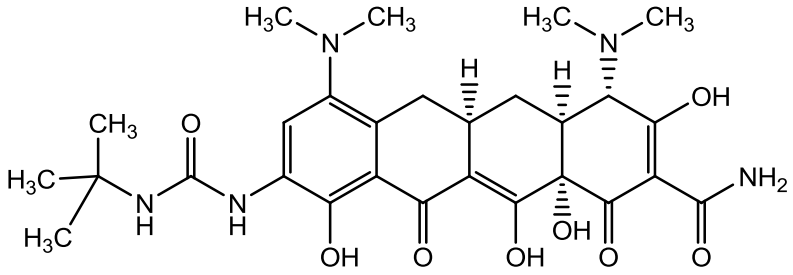


Figure 7: a) Tetracycline penetrates into sensitive bacteria cell reaching high concentrations inside the cell and binding to the 30S ribosomal subunit inhibiting protein synthesis. b) Tetracycline cannot reach a sufficient intracellular concentration due to an increased efflux. c) Ribosome is modified in such a way that tetracycline cannot bind effectively to it. d) Tetracycline is modified inside the cell by an oxygen-requiring chemical reaction rendering it inactive.

The severity of new bacterial resistance created an urgent need to develop new tetracycline derivatives capable of evading these resistance mechanisms. In the 1970s a series of tetracycline derivatives were synthesised. These semisynthetic variants represent the second generation of tetracyclines, being minocycline **(18)** and doxycycline **(17)** the most valuable among them. These analogues are more lipophilic which resulted in more efficient uptake into the cell avoiding efflux resistance mechanism but unfortunately they were ineffective against resistance ribosomal protection mechanism.[34]

To fill the gap left by second generation tetracyclines and finally overcome the ribosomal protection mechanism a third generation of tetracyclines (also called glycylcyclines) have been synthesised recently **(Figure 8)**.[35] The sole successful member at this time is tigecycline **(21)** which presents a C9 modification on the minocycline **(18)** scaffold to avoid both efflux and ribosomal protection mechanisms of resistance. Another third generation derivative is currently under phase II clinical trials, PTK-0796 **(22)**, a broad-spectrum antibiotic.



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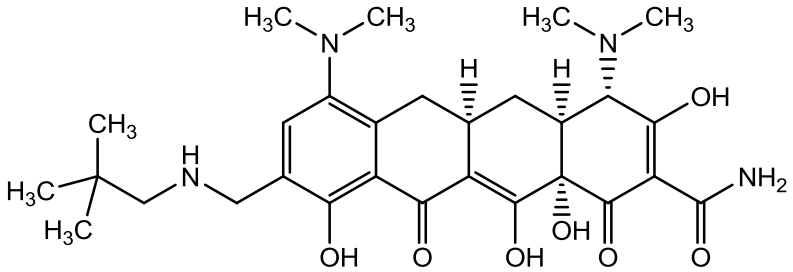

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Figure 8: Glycylcyclines

Different modifications have been introduced into the tetracycline scaffold. Thiatetracyclines and other analogues as chelocardin and anhydrotetracycline are classified as "atypical" tetracyclines due to their action mechanism against microorganisms. Instead of being bacteriostatic[18] these new tetracyclines are bactericidal and they interfere with membrane permeability resulting in cell damage which leads to cell lysis.[36] On interaction with the cell these tetracyclines are preferably trapped in the hydrophobic environment of the cytoplasmatic membrane disrupting its

function. These molecules are of no interest as therapeutic candidates because they cause adverse side effects in humans.[34b]

Lately studies on tetracycline activity confirmed interesting anticancer properties. Oxytetracycline **(16)** and doxytetracycline **(17)** showed inhibitory effect towards human matrix metalloproteinases.[37] These enzymes are involved in the degradation of the extracellular matrix and have implications in inflammatory disorders and cancer. Modification of C4 by other groups leads to depletion of antibiotic activity but improves activity against matrix metalloproteins.

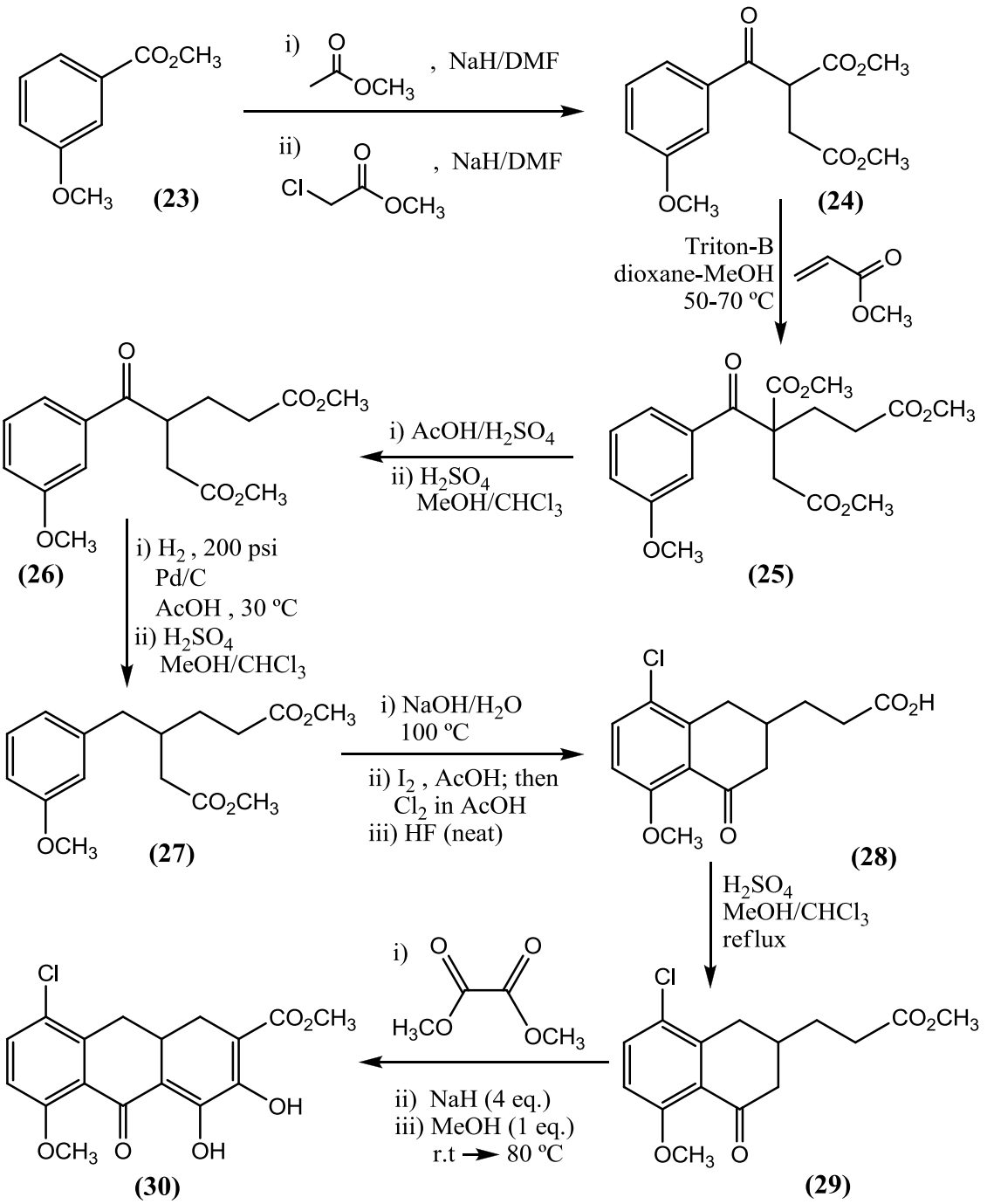
1.3.1 PREVIOUS SYNTHESES OF TETRACYCLINES

The first total synthesis of the tetracycline skeleton was accomplished by Robert B. Woodward and a group at Pfizer.[38] Woodward's synthesis was completely linear and the tetracycline derivative achieved after 18 steps corresponded to sancycline **(19)**, an active antibiotic stable to acid/basic conditions **(Scheme 1)**.

Condensation of *m*-methoxybenzoate **(23)** in *N*,*N*-dimethylformamide in the presence of sodium hydride with methyl acetate and alkylation of the intermediate with methyl chloroacetate gave succinate **(24)**. Michael condensation of the keto diester **(24)** and methyl acrylate in dioxane, with triton B as catalyst, gave the desired keto triester **(25)**. Hydrolysis of the triester **(25)** with a mixture of hot aqueous acetic and sulfuric acids and esterification of the intermediate led to keto diester **(26)**. The carbonyl group of the diester was reduced in acetic acid using 10% palladium on charcoal as catalyst to achieve the diester intermediate which was hydrolysed to the diacid and methylated to yield **(27)** due to purification reasons.

Chlorination of the diacid in glacial acetic acid gave the *para*-substituted diacid. Once the *para*- position was blocked, the cyclodehydration of the chloro acid in liquid

hydrogen fluoride proceeded as expected to afford the desired tetralone **(28)** and was esterified under normal reaction conditions **(29)**. Blocking the *para*- position was a key step to force the condensation onto the more hindered *ortho*- position and esterification of 5-chloro-8-methoxy-1-tetralone-3-proponic acid set the stage for the elaboration of the third ring.



Scheme 1: First synthesis of a tetracycline skeleton natural compound (A)

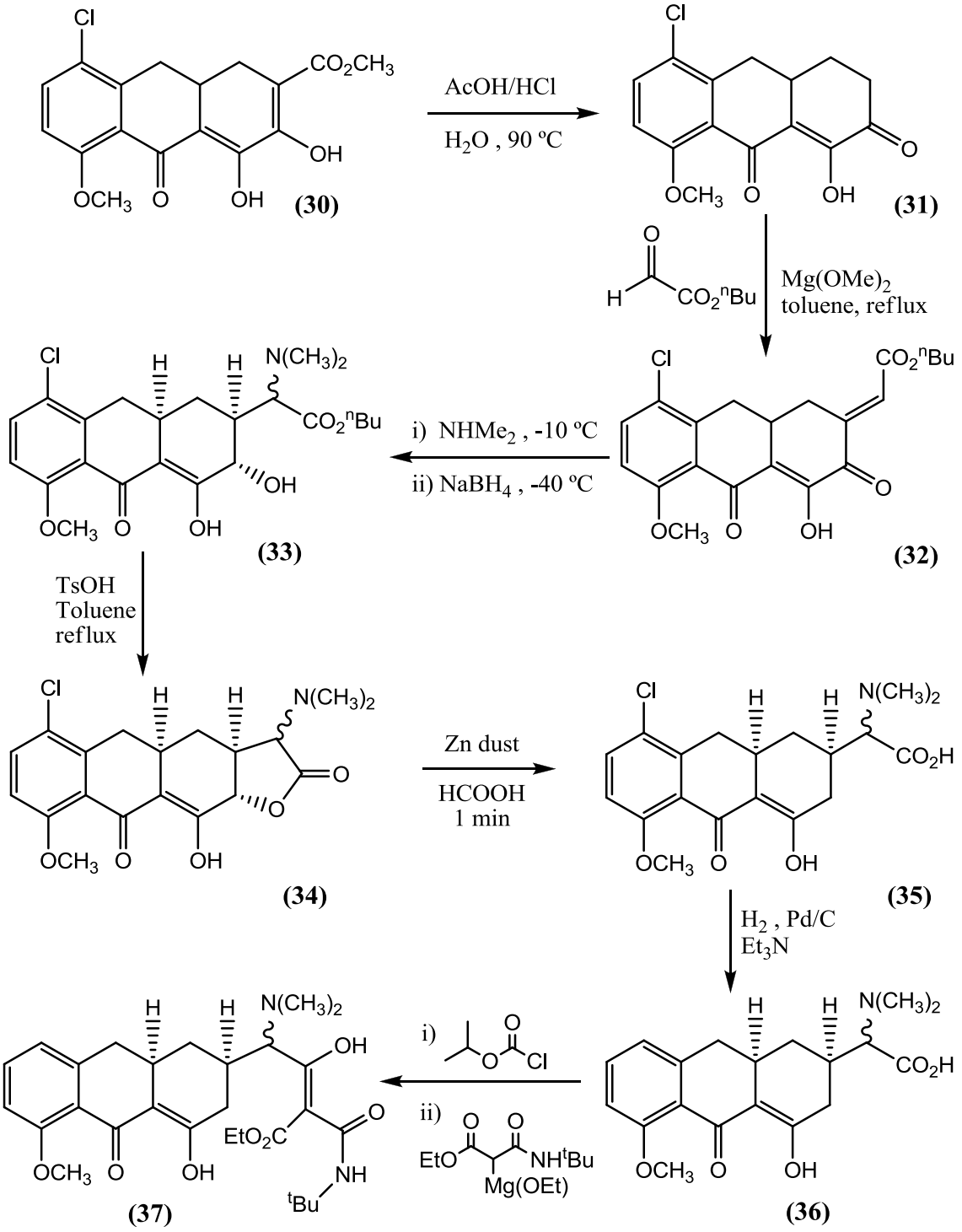
The intermolecular condensation of **(29)** and dimethyl oxalate to achieve the tricyclic ester **(30)** was one of the hardest obstacles Woodward confronted in the synthesis of sancycline **(19)**. The main problem was the intramolecular reaction that could occur due to the constitution of ester **(29)** when treated with sodium hydride in *N*,*N*-dimethylformamide solution. Best conditions to achieve the desired intermolecular condensation between ester **(29)** and dimethyl oxalate were *N*,*N*-dimethylformamide, sodium hydride and methanol.

The tricyclic ester **(30)** was transformed to the hydroanthracene triketone **(31)** **(Scheme 2)** by hot aqueous hydrochloric and acetic acids. This intermediate was chosen previously by Woodward as a key intermediate that will provide the favourable transformations needed for the synthesis of sancycline **(19)**.

Hydroanthracenetrione **(31)** reacted with *n*-butyl glyoxylate in hot toluene with magnesium methoxide as catalyst to achieve the unsaturated ketone **(32)**. Conjugate addition of dimethylamine to **(32)** produced the corresponding Mannich base that was immediately reduced using sodium borohydride to the alcohol to avoid the loss of dimethylamine.

Reflux of the alcohol **(33)** in toluene in the presence of *p*-toluenesulfonic acid gave lactone **(34)**. The product obtained was reduced by zinc dust in formic acid to the dimethylamino acid **(35)**. Catalytic hydrogenation over palladium-charcoal gave the dechloro acid **(36)**.

Synthesis of the acyl malonamate **(37)** was obtained from the reaction between the anhydride obtained from the acid **(36)** and isopropyl chloroformate in the presence of the ethoxymagnesio derivative of *N*-*t*-butyl-malonamate.

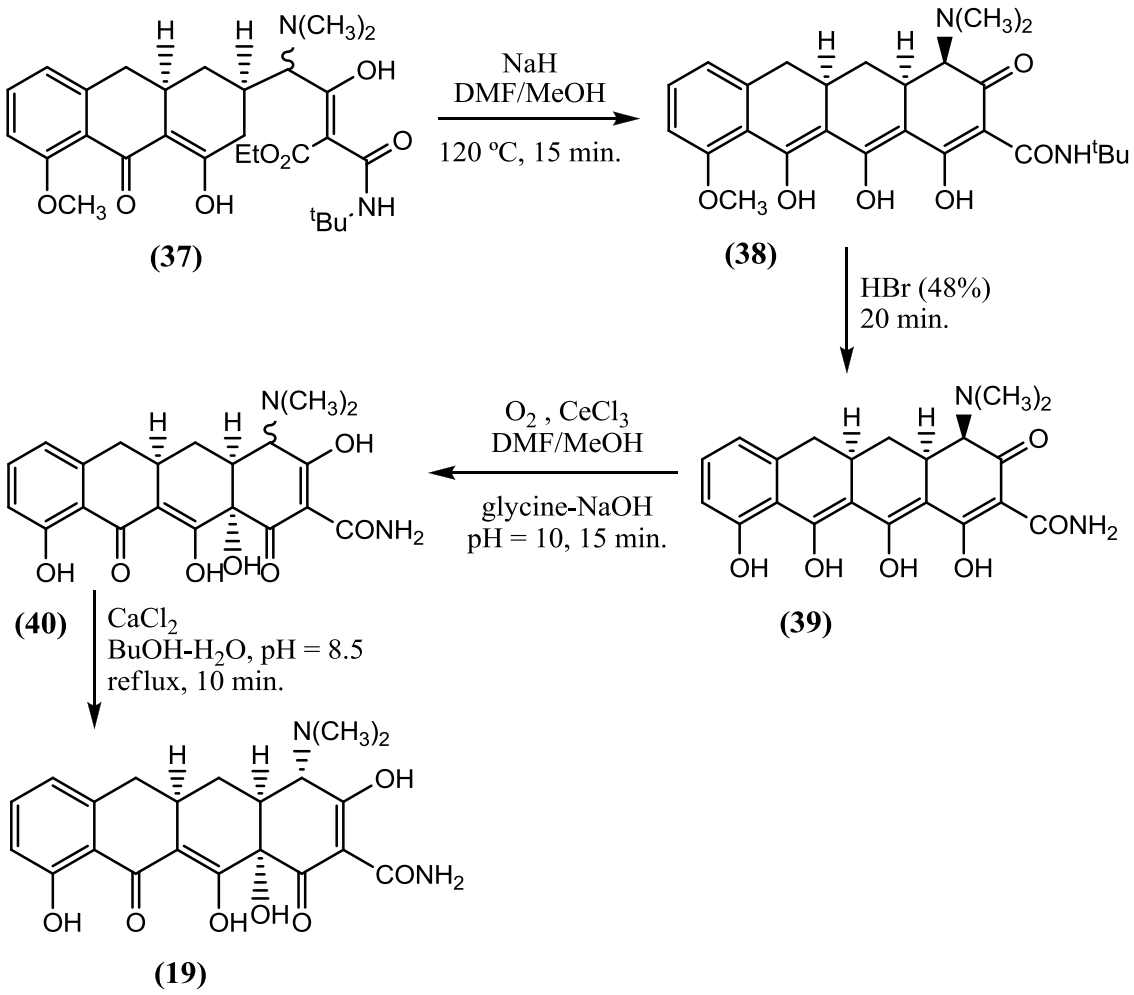


Scheme 2: First synthesis of a tetracycline skeleton natural compound (B)

The synthesis of the acyl malonamate was the master stroke in the synthesis of sancycline **(19)**. The crude acyl malonamate was treated with sodium hydride in *N*,*N*-dimethylformamide in the presence of a small amount of methanol to achieve the

tetracyclic compound **(38)**. Deprotonation of the amide moiety and the two free alcohols by means of sodium hydride generated four enolates. Despite the presence of these four enolates only one of the two plausible intramolecular condensation events was observed. The other intramolecular condensation was not allowed since the enolate double bond cannot rotate to bring the amide into position for cyclisation.

Cleavage of *N*-*t*-butyl and *O*-methyl groups was achieved when **(38)** was heated for 20 minutes with 48% hydrobromic acid. Introduction of the hydroxyl group at C_{12a} was done by carefully oxygenation of **(39)** in the presence of cerous chloride in buffered methanol-dimethylformamide solution to achieve a mixture of diastereomers of 6-demethyl-6-deoxytetracycline **(40)**. Partial epimerization at C4 position was solved by treatment with calcium chloride in buffered butanol-water solution to achieve pure sancycline **(19) (Scheme 3)**.



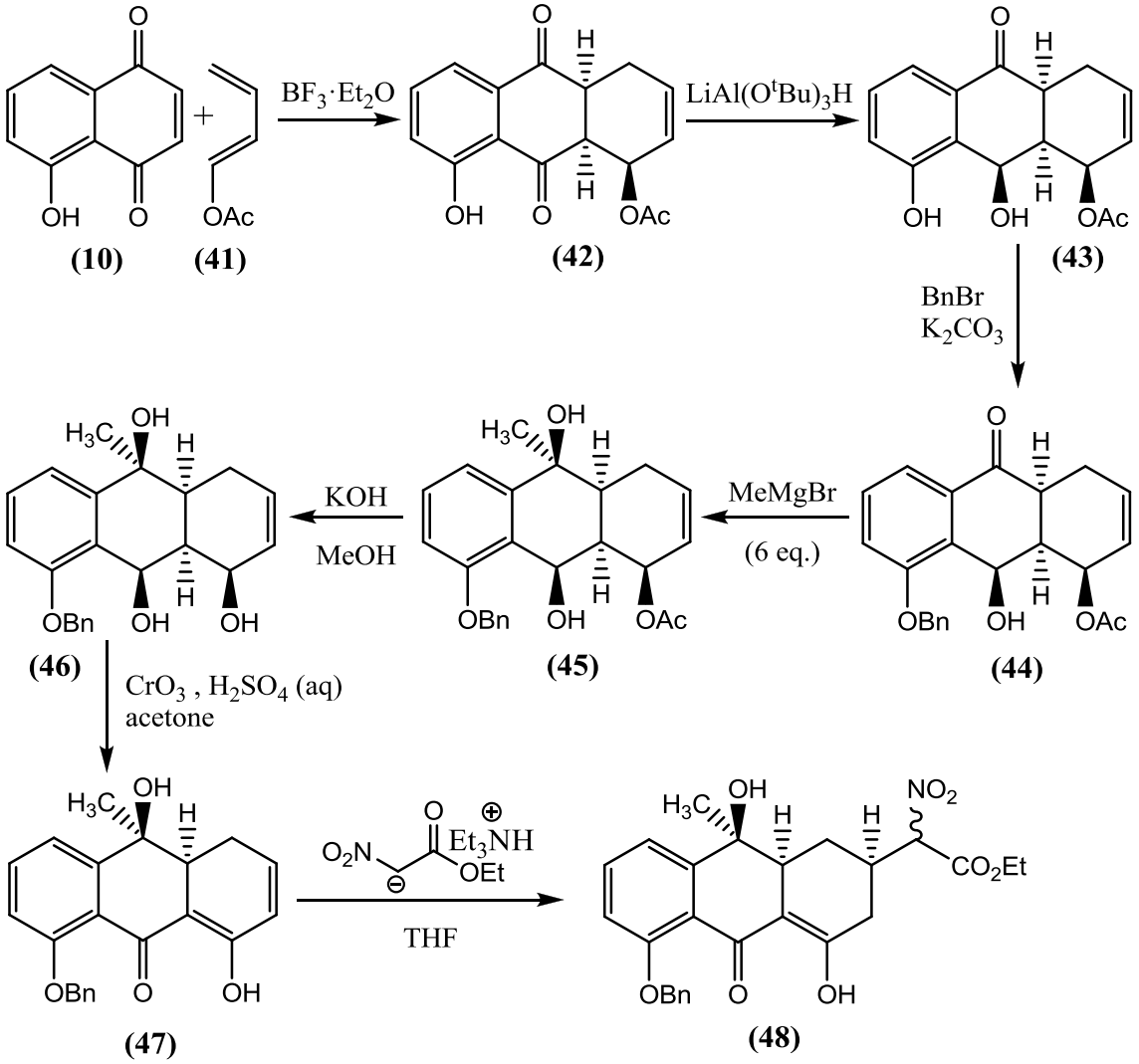
Scheme 3: First synthesis of a tetracycline skeleton natural compound (C)

That was the first synthesis of a tetracycline skeleton containing organic product with full antibiotic activity. However it was not a total synthesis of a tetracycline natural product because substituents at position C_6 were missing.

1.3.2 FIRST SYNTHESIS OF A TETRACYCLINE NATURAL COMPOUND

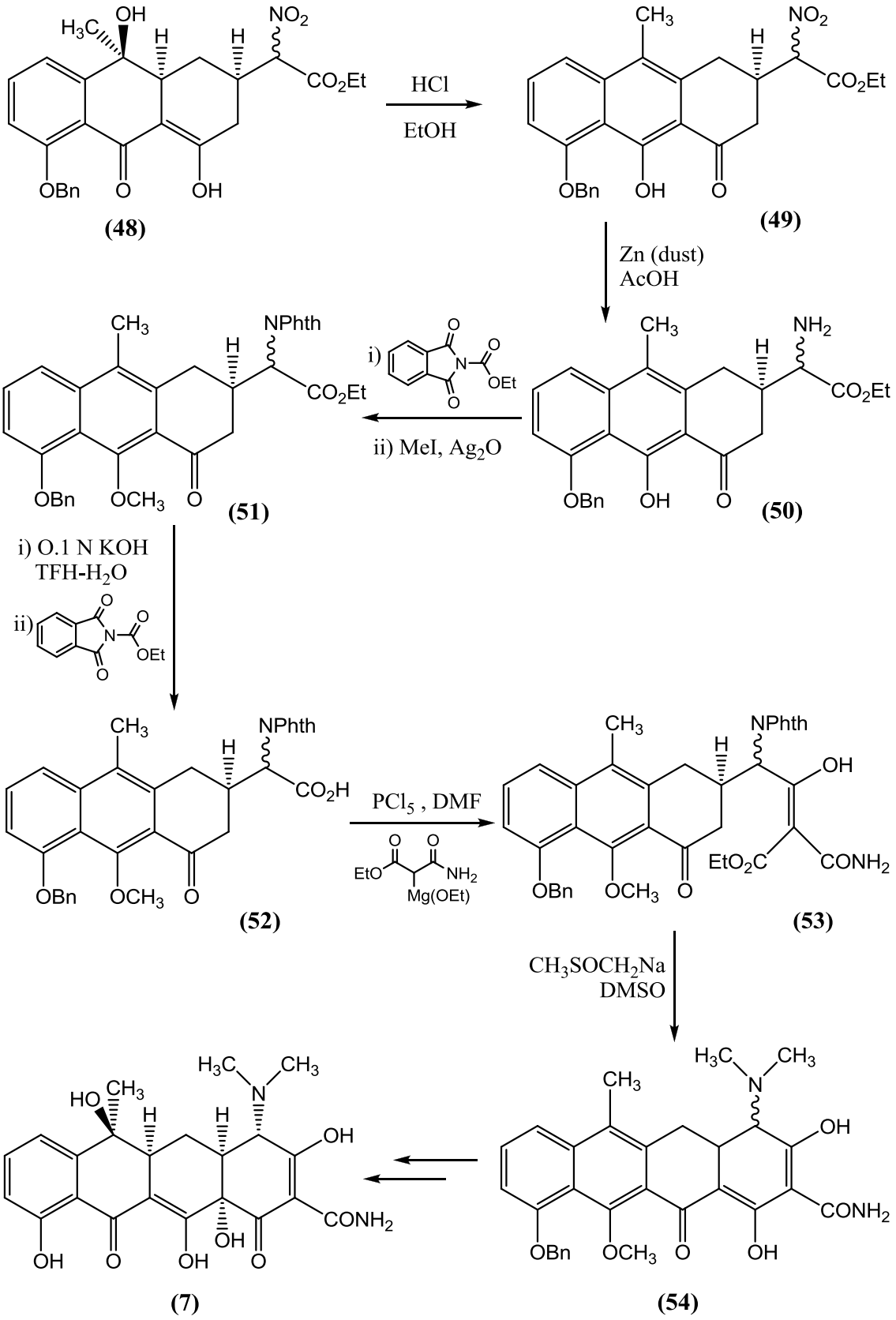
Shemyakin *et al.* **(Scheme 4)** carried out the first synthesis of a tetracycline natural compound.[39] Starting from juglone **(10)** Shemyakin synthesised a tricyclic intermediate that was transformed in the target compound following a similar procedure to the one used by Woodward.[38]

Diels-Alder reaction between juglone **(10)** and diene **(41)** catalyzed with boron trifluoride diethyl etherate led to the tricyclic diketone **(42)**. Regioselective reduction of C9 moiety using lithium tri-*tert*-butoxyaluminium hydride gave alcohol **(43)**. Protection of the phenol moiety using benzyl bromide and potassium carbonate followed by Grignard addition of methyl magnesium bromide yielded dihydroxyanthracene **(45)**. Acetate group was removed using a methanolic solution of potassium hydroxide to achieve compound **(46)** which was oxidised using Jones reagent to yield the tricyclic precursor **(47)**. Condensation of dienediolone **(47)** with the triethylammonium salt of ethyl nitroacetate in tetrahydrofuran gave the C2-epimeric nitroderivative **(48)**. Dehydration of adduct **(48)** with ethanolic hydrochloric acid yielded nitro-compound **(49)**.



Scheme 4: Shemyakin synthesis of sancycline (A)

Nitro-compound **(49) (Scheme 5)** was smoothly reduced to the amino ester **(50)** by zinc dust in acetic acid. Once amino ester **(50)** was synthesised, Shemyakin adopted the Woodward approach to ring A. Direct methylation of amino ester **(50)** was not a valid option due to the lack of reactivity of the dimethylamino acid. For this reason amino ester **(50)** was acylated with carboethoxyphthalamide in tetrahydrofuran and methylated by methyl iodide in the presence of silver(I) oxide to obtain phthaloyl derivative **(51)**. Saponification of this compound using 0.1 N potassium hydroxide in tetrahydrofuran followed by recyclisation of the phthalimido grouping by heating in diglyme at 140 ºC gave the acid **(52)**.



Scheme 5: Shemyakin synthesis of sancycline (B)

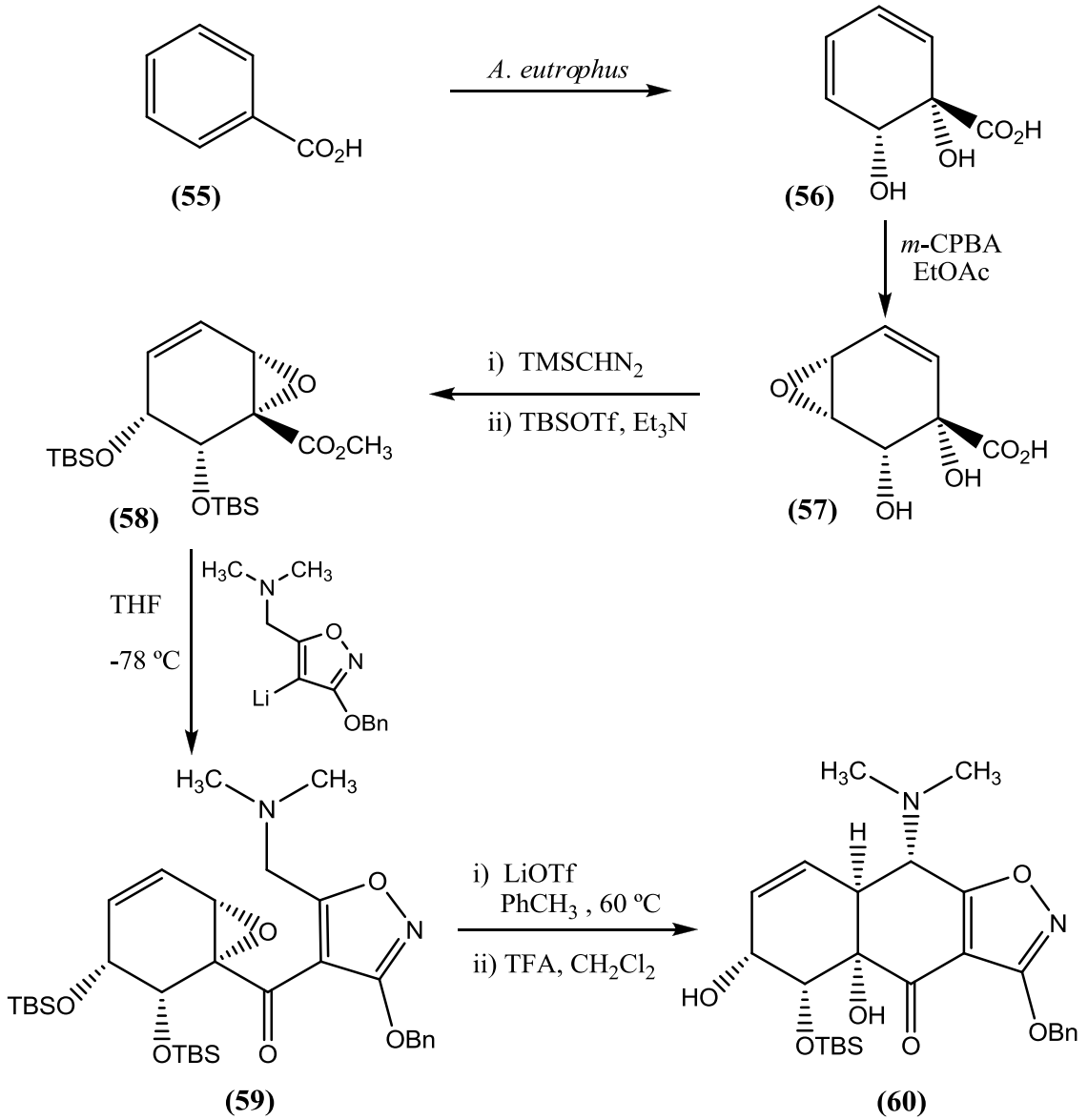
Following the same procedure applied by Woodward *et al.* acid **(52)** was condensed with ethyl ethoxymagnesium malonamate by treatment with phosphorus(V) chloride in *N*,*N*-dimethylformamide to yield the substituted ethyl *N*-phthaloylglycylmalonamate **(53)**. Compound **(53)** was cyclised into the substituted hydronapthacene **(54)** which was hydrolysed and methylated to yield a degradation product from tetracycline which had previously been elaborated into tetracycline **(7)**.[38,40]

Over the years different synthesis towards tetracycline antibiotics have been developed.[41] The most important and versatile was the synthesis developed by Myers *et al.* which used a convergent Michael-Claisen condensation of AB ring precursors with D ring precursors to yield several tetracycline analogues.[42]

1.3.3 MYERS SYNTHESIS OF 6-DEOXYTETRACYCLINE ANTIBIOTICS

Myers *et al.* started the synthesis by introducing the troublesome C12a hydroxyl group in the first step and then proceeded to build the molecule around it **(Scheme 6)**. Microbial dihydroxylation of benzoic acid **(55)** using *Alcaligenes eutrophus* produced the diol **(56)** with >95% enantiomeric excess. Treatment of the diol **(56)** using *meta*-chloroperoxybenzoic acid yielded the α-orientated epoxide **(57)**. Esterification of the acid **(57)** with trimethylsilyldiazomethane, followed by double silylation and concomitant epoxide isomerisation in the presence of *tert*-butyldimethylsilyl triflate afforded epoxide ester **(58)**.

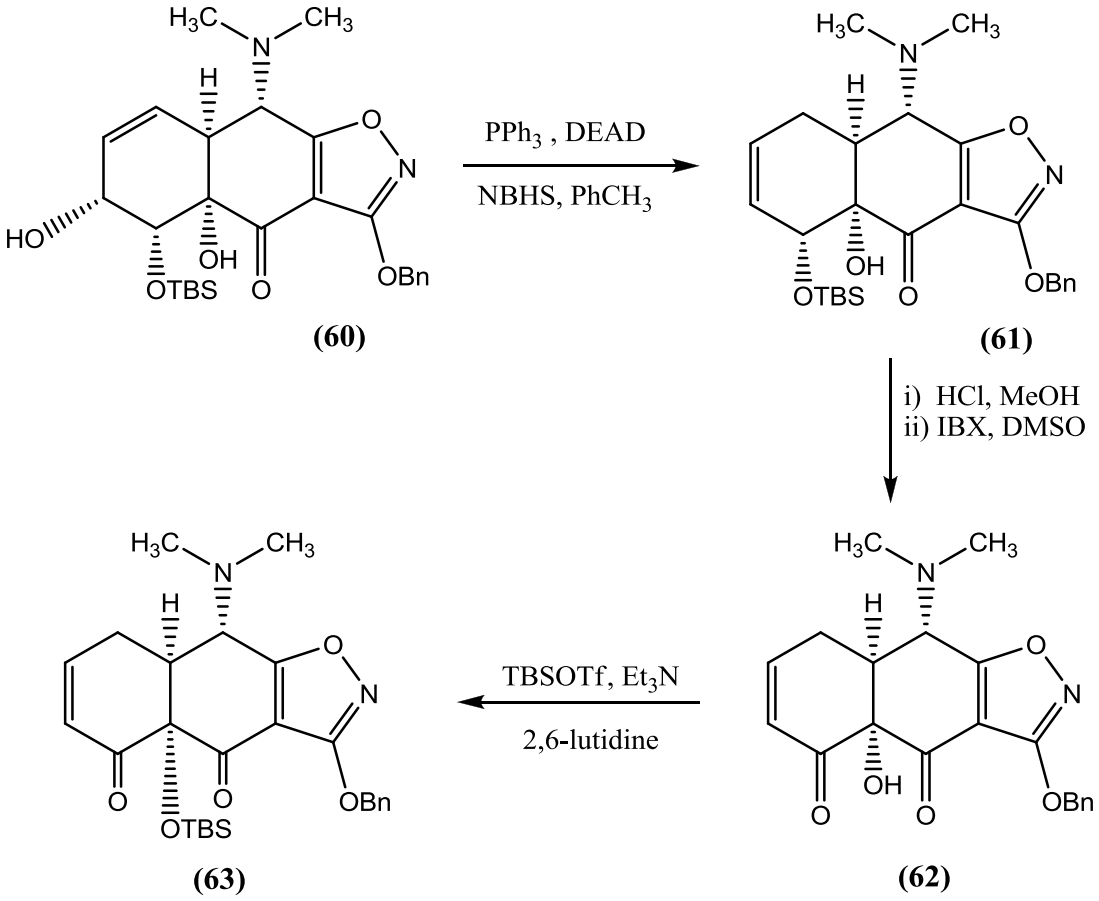
In construction of the A ring the vinylogous carbamic acid function was protected as a 5-benzyloxyisoxazole group. Lithiated 3-benzyloxy-5-dimethylaminomethylisoxazole was added to epoxide ester **(58)** in tetrahydrofuran to achieve ketone **(59)**. Closure of the A ring was achieved after warming ketone **(59)** with lithium triflate in toluene at 60 ºC, followed by selective removal of the allylic silyl ether using trifluoroacetic acid in dichloromethane to yield tricyclic compound **(60)**.



Scheme 6: Myers synthesis of 6-deoxytetracycline antibiotics (A)

Intermediate **(60)** was the product used to prepare the two AB ring precursors **(63)** and **(66)** needed for the convergent Michael-Claisen condensation with the D ring precursors to form the tetracycline analogues (lacking C5 oxygenation or with C5 oxygenation respectively).

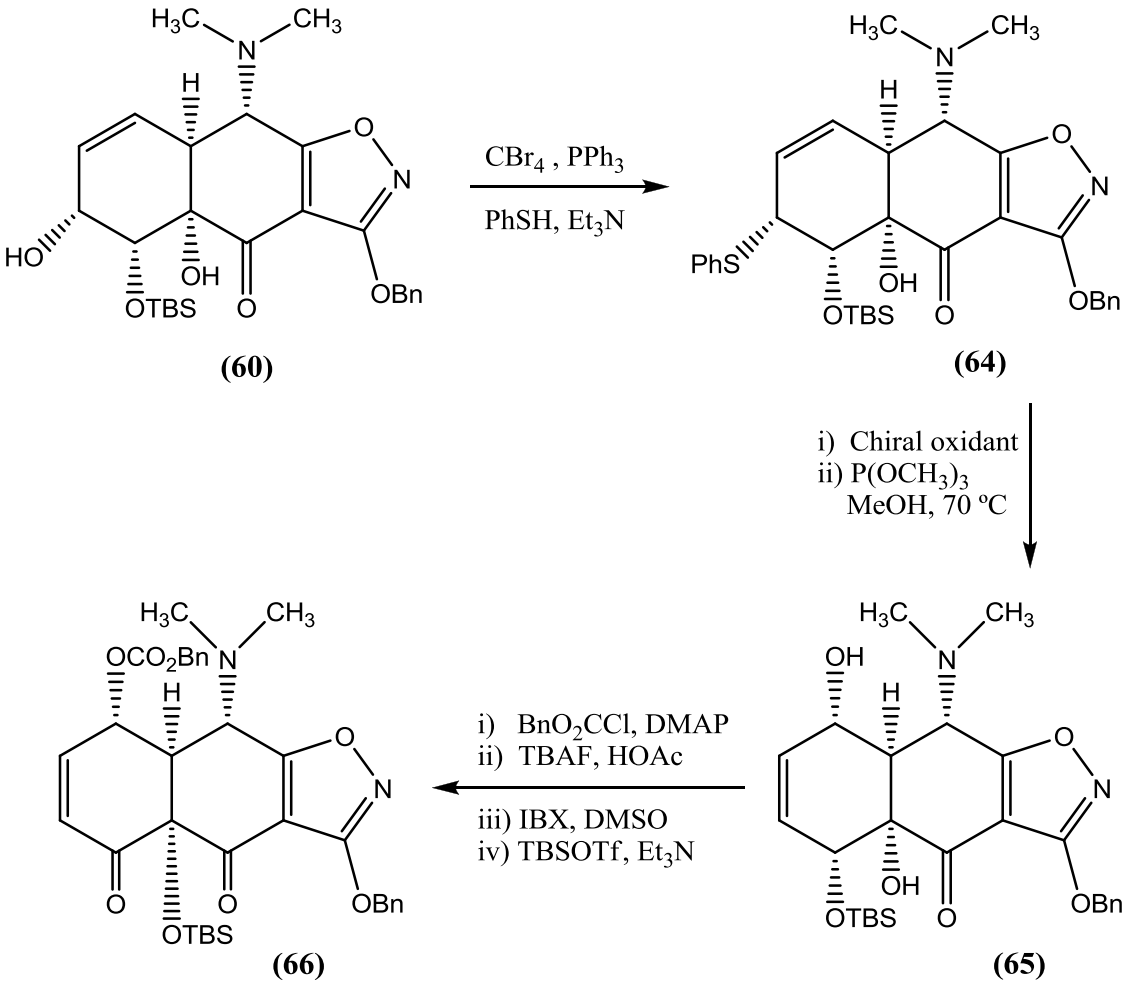
Enone **(63) (Scheme 7)** was synthesised in four steps from precursor **(60)**. Reductive transposition of tricyclic compound **(60)** using triphenylphosphine, diethyl azodicarboxylate and *o*-nitrobenzenesulfonyl hydrazide (NBHS) in toluene led to compound **(61)**. Hydrolysis of the silyl ether protective group using methanolic hydrochloric acid and oxidation of the resulting allylic alcohol by treatment with *o*-iodoxybenzoic acid in dimethylsulfoxide yielded ketone **(62)**. Protection of the remaining tertiary alcohol with *tert*-butyldimethylsilyl trifluoromethanesulfonate in the presence of triethylamine and 2,6-lutidine formed enone **(63)**.



Scheme 7: Myers synthesis of 6-deoxytetracycline antibiotics (B)

Enone **(66) (Scheme 8)** was synthesised in eight steps from precursor **(60)**. Treatment of tricyclic compound **(60)** with carbon tetrabromide, triphenylphosphine and thiophenol in the presence of triethylamine replaced the secondary alcohol with a

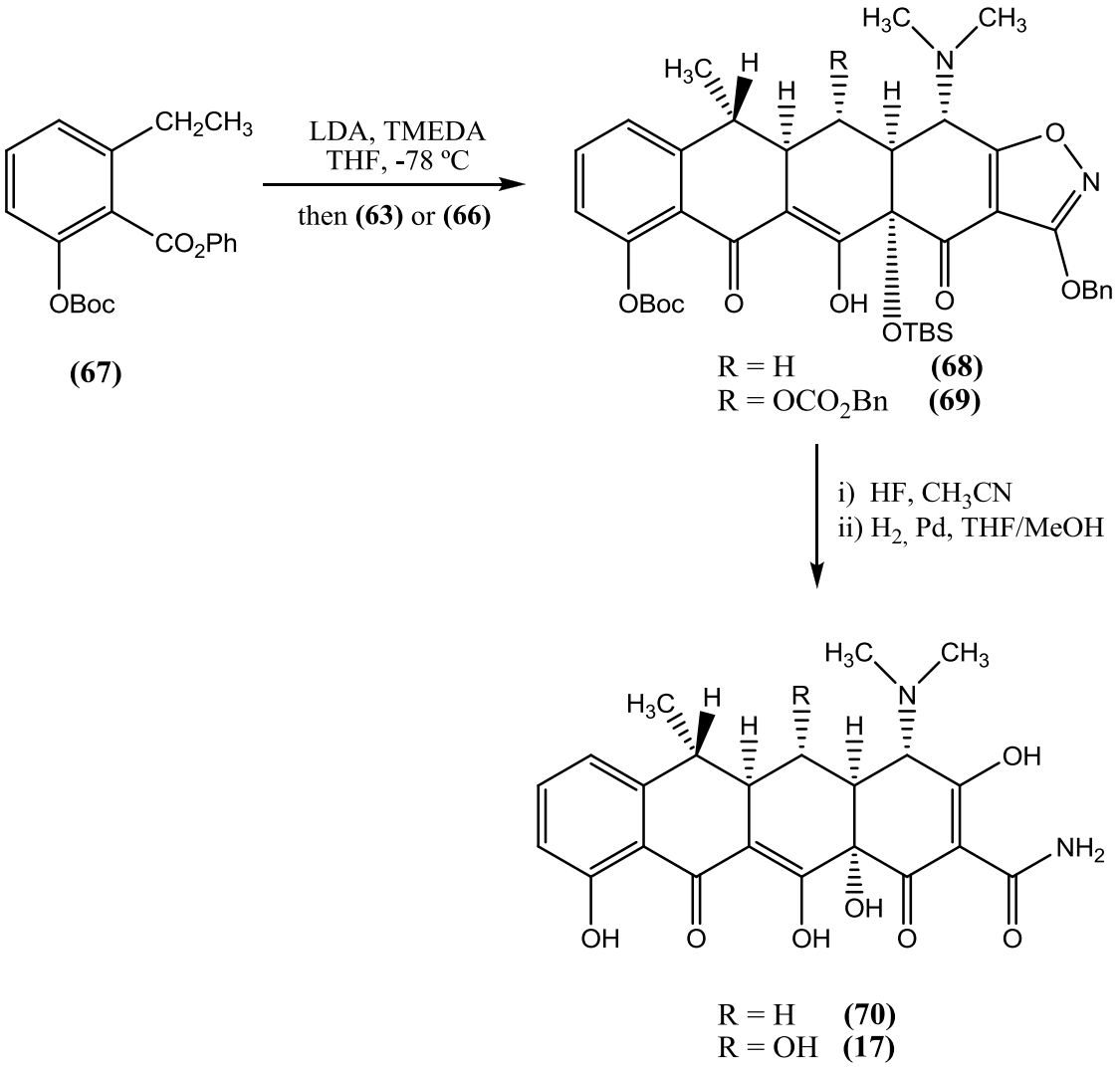
phenylthio group with stereochemical retention **(64)**. Sulfoxidation of thiol derivative **(64)** with (+)-[(8,8-dichlorocamphoryl)sulfonyl]-oxaziridine, a chiral oxidant, and Mislow-Evans rearrangement produced the allylic alcohol **(65)**. Protection of the allylic alcohol using benzoyl chloroformate and 4-dimethylaminopyridine led to an intermediate that was transformed into enone **(66)** following the same procedure applied in the final steps of the synthesis of enone **(63)**.



Scheme 8: Myers synthesis of 6-deoxytetracycline antibiotics (C)

Synthesis of tetracycline derivatives were achieved when enones **(63)** and **(66)** were coupled with a range of different carbanionic D-ring precursors in a Michael-Claisen reaction sequence **(Scheme 9)**. Deprotonation of the D-ring precursor **(67)** with lithium diisopropylamide in the presence of *N,N,N',N'*-tetramethylethylenediamine in tetrahydrofuran at -78 ºC and addition of enones **(63)** and **(66)** led to the corresponding

deoxy- or oxytetracycline compounds **(68)** and **(69)** respectively. Removal of the protective groups using hydrofluoric acid in acetonitrile and catalytic hydrogenation produced (-)-6-deoxytetracycline **(70)** and (-)-doxycycline **(17)**.



Scheme 9: Myers synthesis of 6-deoxytetracycline antibiotics (D)

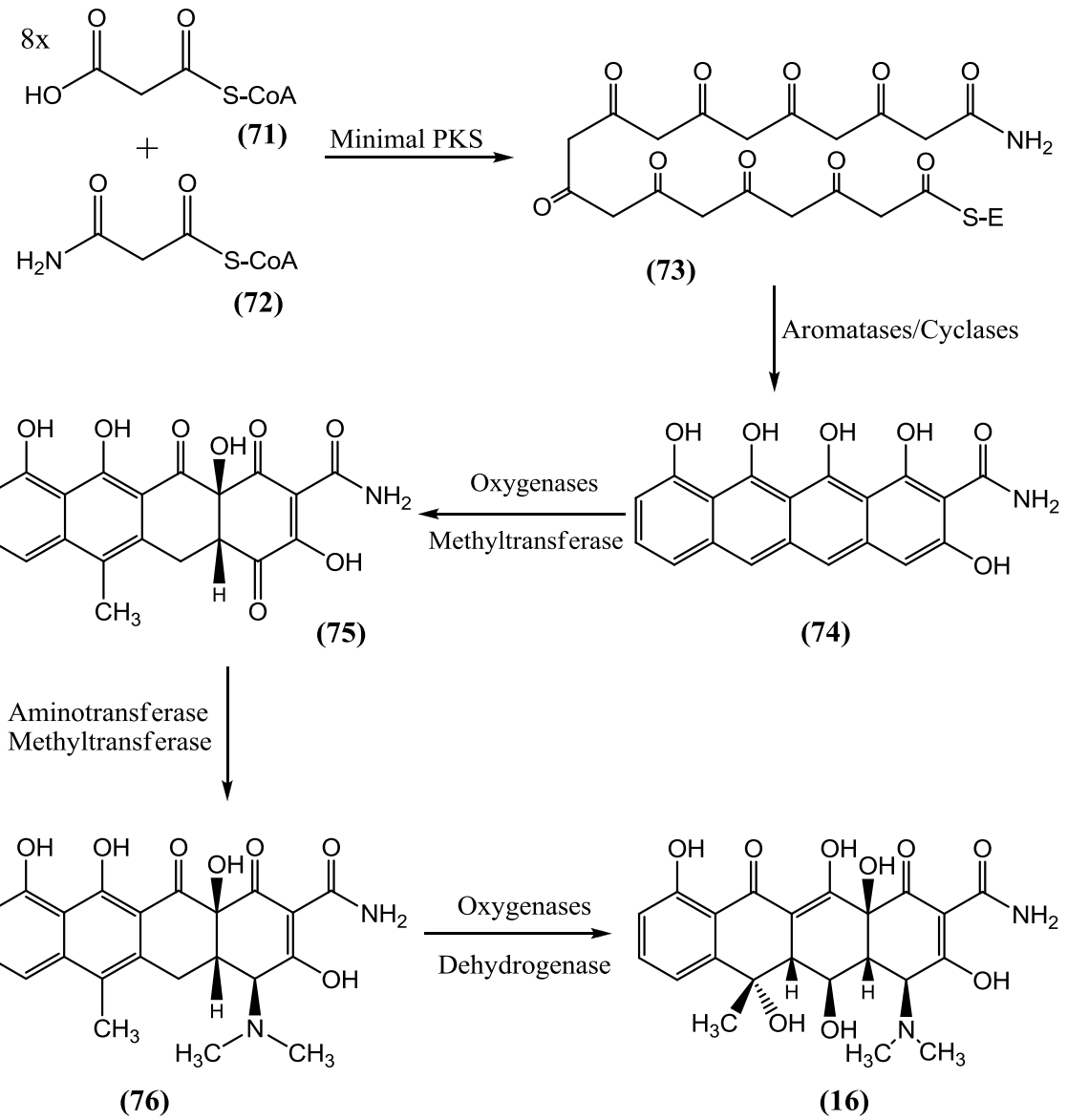
Myers managed to produce a wide range of tetracycline derivatives with reasonable yields in 14 to 18 steps.[42b]

1.3.4 BIOSYNTHETIC PATHWAY

Recent findings on the tetracycline biosynthetic pathway and a more detailed knowledge on the interactions between tetracycline and its molecular targets may allow science to broaden the range of tetracycline derivatives and provide analogues with difficult accessibility by normal synthetic chemistry procedures.

Early knowledge about the biosynthetic pathway identified several key intermediates and gave tetracyclines the denomination of polyketide due to the formation of a poly-β-ketone backbone in the early stages of the biosynthesis.[43] New techniques and thorough studies on the biosynthetic pathways have elucidated the mode of action and the genes needed to carry on the necessary transformations.[44]

The iterative condensation of eight units of malonyl-CoA **(71)** and one unit of malonamyl-CoA **(72)** (responsible of the C2 amide function) using what is known as minimal polyketide synthases (PKS) yielded the poly-β-ketone **(73)**. Addition of a ketoreductase and sequentially cyclisation by different cyclases afforded the pretetramide **(74)**. Oxidation of the pretetramide **(74)** and methylation of C6 using a methyltransferase enzyme generated the 6-methylpretetramid intermediate **(75)**. The C4 dimethylamino group was introduced using aminotransferase and methyltransferase genes to afford the anhydrotetracycline intermediate **(76)**. Oxytetracyline **(16)** was finally synthesised after sequentially oxidation and a reduction **(Scheme 10)**.



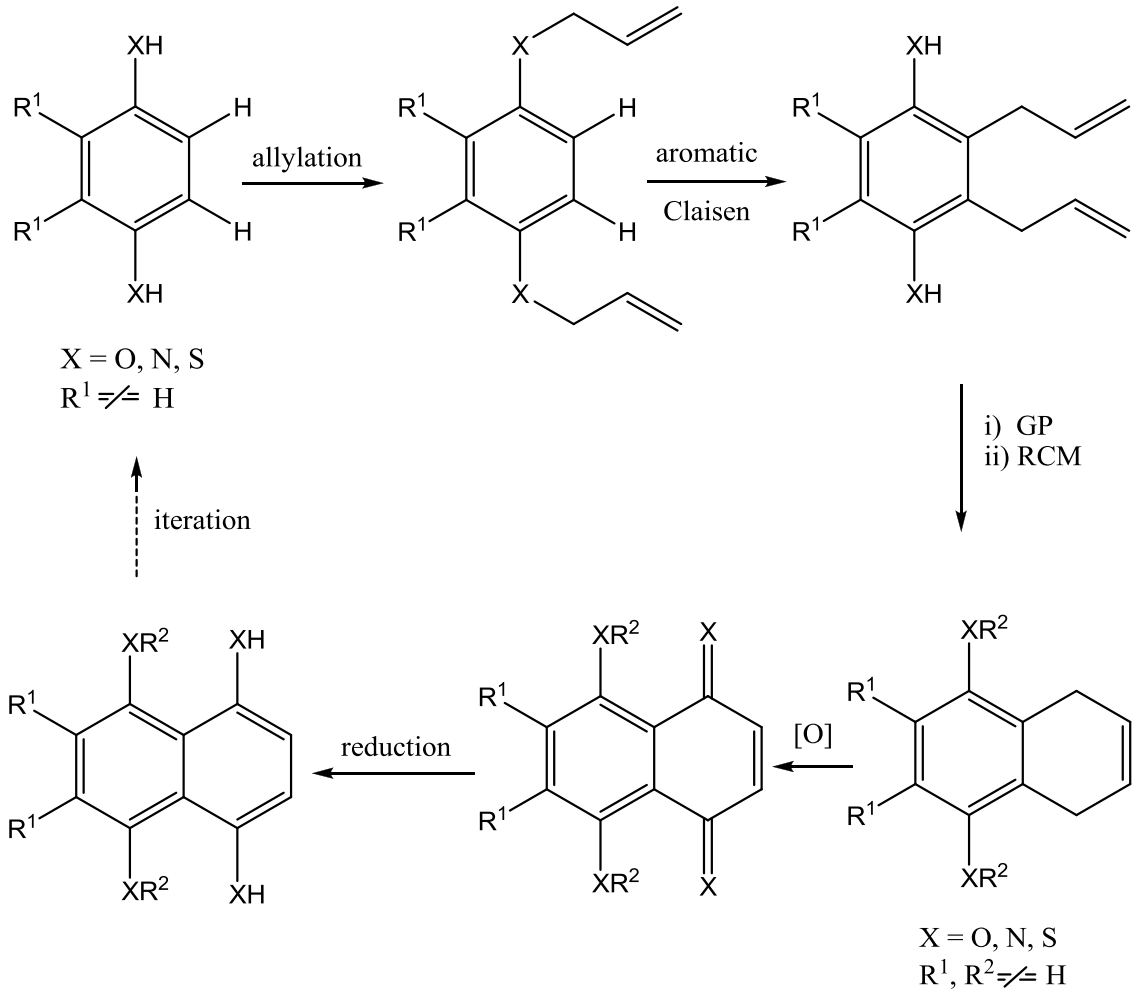
Scheme 10: Biosynthetic pathway towards tetracycline antibiotics

Although several enzymes have been elucidated there are still a large number of new enzymes to be discovered in order to be able to synthesise more complex tetracycline analogues.[45]

Despite all the efforts to achieve tetracycline derivatives there have been little semisynthesis and analogueing, maybe due to their complex chemistry, chemical lability and lack of reactivity of earlier synthetic reagents with the tetracycline scaffold.

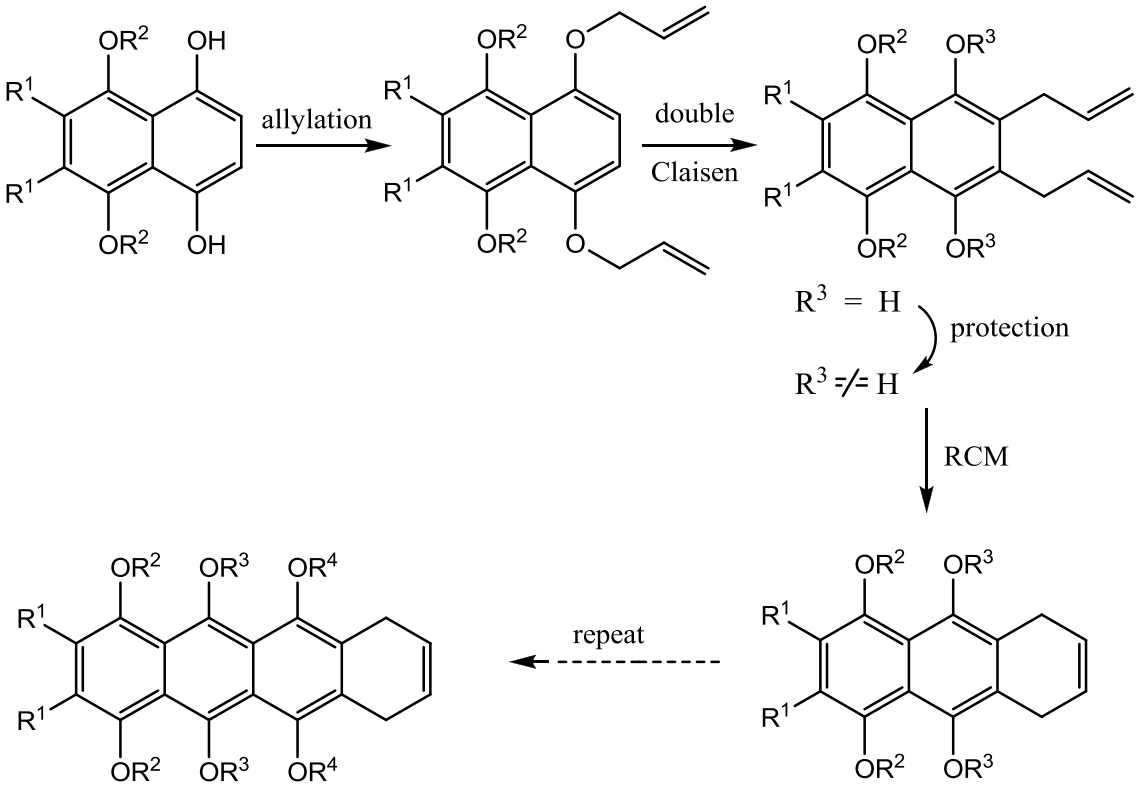
The tetracycline scaffold is a valuable starting point of further drug discovery and tetracyclines are, clinically, much safer than other antibiotics. For these reasons in this thesis a novel iterative protocol has been proposed.

This novel iterative synthetic route towards tetracycline scaffold **(Scheme 11)** is based on the formation of the different rings using three key steps: a double Claisen rearrangement, a ring closing metathesis (RCM) and the oxidation of the ring formed. The use of alternative heteroatoms such as sulfur or nitrogen allows the possibility of applying specific chemistry or heteroatom removal at a later stage.



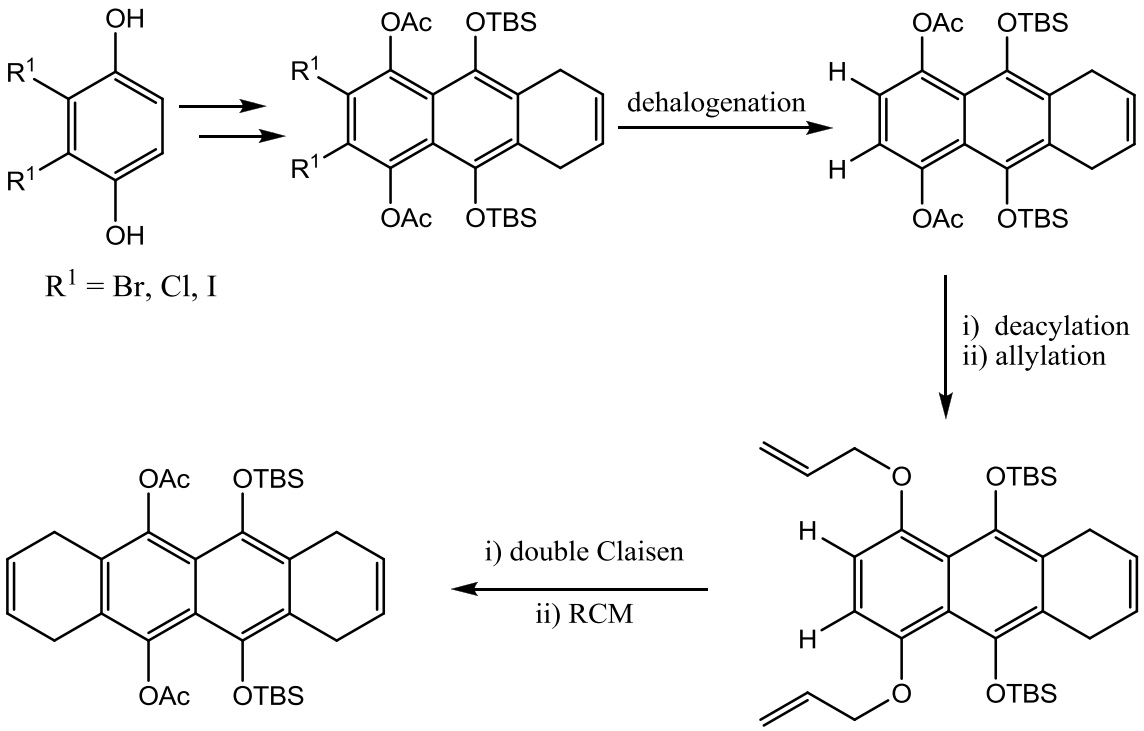
Scheme 11: A new iterative approach to linear fused ring systems

Once the reduced/rearomatised compound is synthesised it can act as a new building block and can be subjected to the same process to add more rings **(Scheme 12)**. This iterative protocol could overcome some of the problems observed in the derivatisation process of the tetracycline scaffold. The use of alternative and complementary protecting groups for the protection of subsequent phenolic groups will allow the deprotection and derivatisation of one specific position to achieve the tetracycline derivatives.



Scheme 12: Iterative route towards tetracycline antibiotics

Another interesting aspect of the iterative route proposed is that, in addition to providing useful reaction sites for further functionalisation, the use of halogenated precursors could allow the construction of new carbon rings in the opposite "direction". As shown in **Scheme 13**, dehalogenation at a later stage will provide new reaction sites to repeat the allylation-double Claisen-ring-closing metathesis procedure and construct new carbon rings.[46]

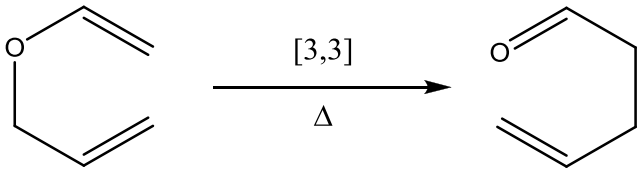


Scheme 13: Multi-directional approach for iterative synthesis

1,2-Dihalogeno-aromatics also provide the opportunity for substitution reactions introducing different groups necessary for more complex tetracyclines such as glycylcyclines and generation of benzyne making possible cycloadditions as a route to add additional ring systems.[47]

1.4 THE CLAISEN REARRANGEMENT

The Claisen rearrangement can be defined as the thermal [3,3]-sigmatropic reorganization of an allyl vinyl ether **(77)** into a γ,δ-unsaturated carbonyl compound **(78)** by a concerted intramolecular process **(Scheme 14)**.[48]

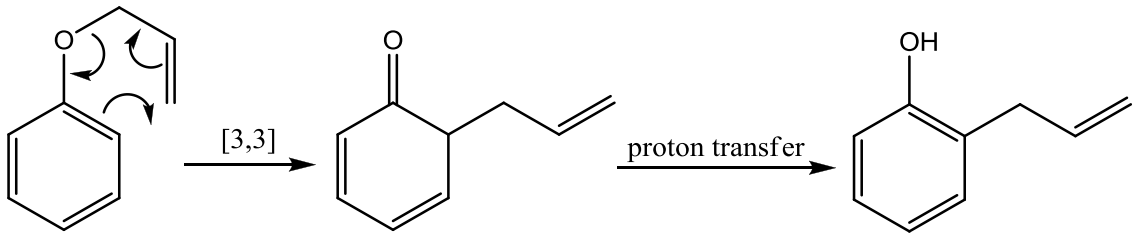


(77) **(78)**

Scheme 14: The Claisen rearrangement

The [3,3]-sigmatropic reaction is a pericyclic reaction wherein the net result is one sigma bond changed to another sigma bond. In this type of rearrangement reaction a substituent moves from one part of a π–bonded system to another part in an intramolecular reaction with simultaneous rearrangement of the π–system.

The aromatic-Claisen rearrangement can be seen as a two step reaction where the first step is the [3,3]-sigmatropic rearrangement and the second step is an ionic proton transfer to regenerate aromaticity **(Scheme 15)**.



Scheme 15: Mechanism of the Claisen rearrangement

The [3,3]-sigmatropic rearrangement can be described using the frontier molecular orbitals involved in the reaction. The requirements for this rearrangement must consider the interactions between the orbitals of the π-system and the migrating fragment **(Figure 10)**. Following the Woodward-Hoffmann rules for sigmatropic

processes, by drawing the orbitals involved **(Figure 9)** in the rearrangement and considering the symmetry of the newly formed orbitals it can be discerned that the [3,3]-sigmatropic rearrangement is allowed.

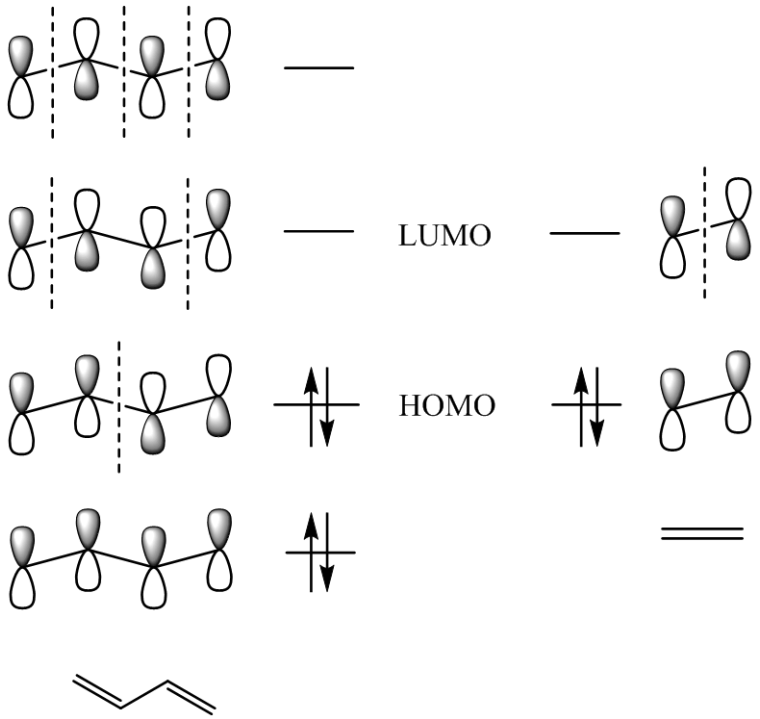


Figure 9: HOMO and LUMO orbitals for a [3,3]-sigmatropic rearrangement. The hexadiene can be studied as an interaction between an ethylene moiety and a butadiene equivalent.[49]

During the transition state the HOMO belonging to the π system of one allyl fragment, which has one node, interacts with the LUMO of the π bond of the other allylic group with the correct symmetry to proceed with the rearrangement and form the new σ bond **(Figure 10)**.

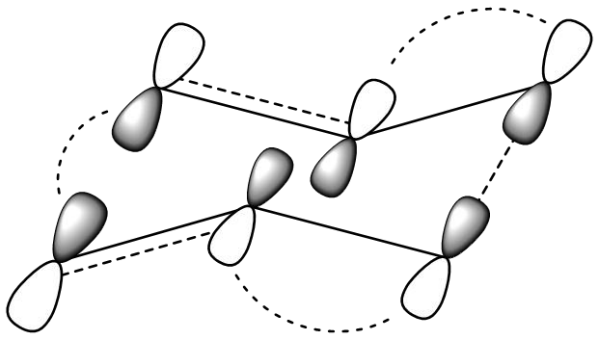
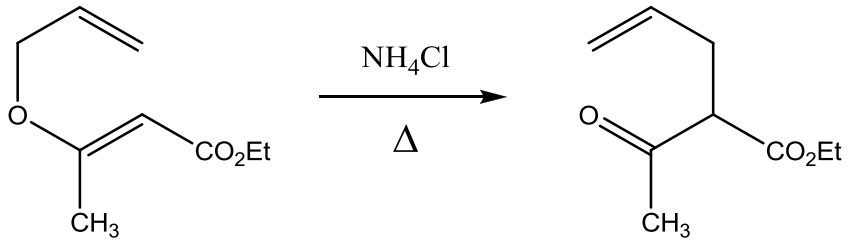


Figure 10: Transition state orbital overlapping in the Claisen rearrangement

Since it was discovered in 1912 by Claisen *et al.* the Claisen rearrangement has been widely used as a synthetic tool by organic chemists due to the easy formation of new carbon-carbon bonds. For this reason the Claisen rearrangement has been subjected continuously to studies to improve yield and reaction conditions.[50]

Originally the Claisen rearrangement was carried out in high temperatures (range for typical reactions is between 150 ºC and 225 ºC) giving the thermal rearrangement. Due to problems such as decomposition of the starting materials and/or final products, long reaction times and competitive side reactions catalytic Claisen rearrangement conditions have been developed to minimize these effects.

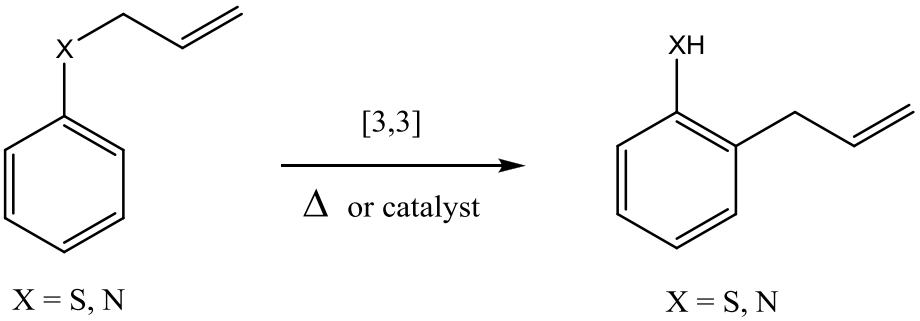
The first report on a catalytic Claisen rearrangement used NH_4Cl as proton donor to increase slightly the rearrangement rate **(Scheme 16)**.[51] Since then numerous substances such as transition-metal complexes, Lewis acids, Brønsted acids, bases, water and also some physical parameters have been developed to catalyze the Claisen rearrangement and accelerate the rate dramatically.[52]



Scheme 16: First catalytic Claisen rearrangement

1.4.1 THIA-CLAISEN AND AZA-CLAISEN REARRANGEMENT

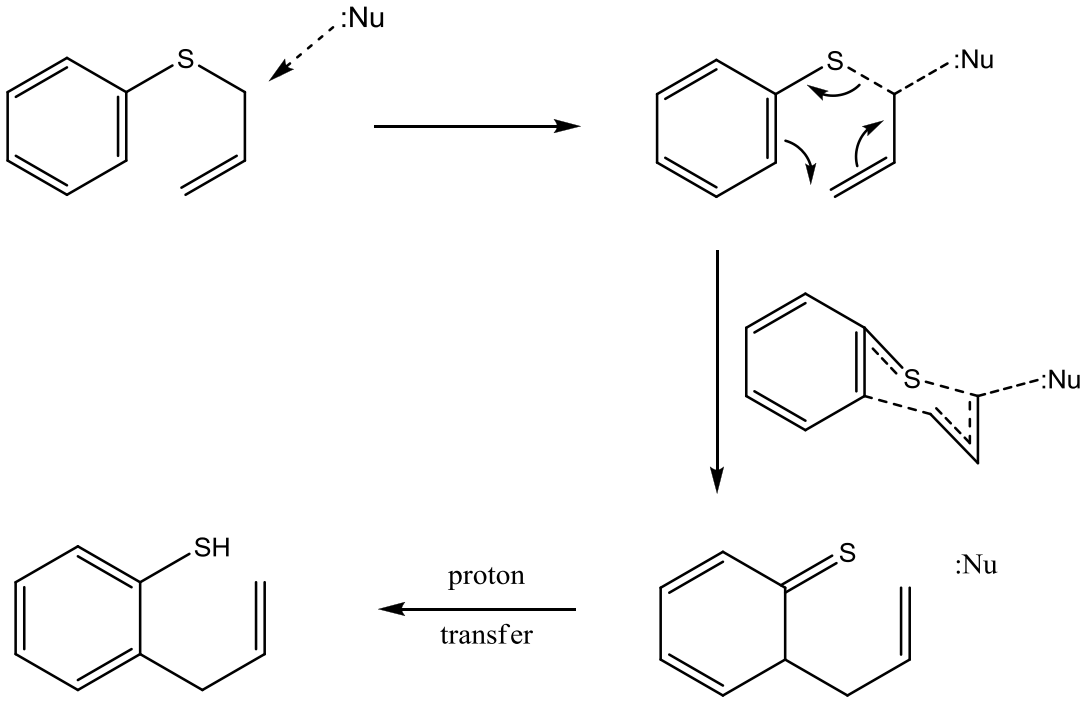
The thio-Claisen rearrangement and the aza-Claisen rearrangement are a variation of the Claisen rearrangement involving, instead of an oxygen atom, sulfur or nitrogen atoms respectively **(Scheme 17)**.[53]



Scheme 17: Hetero-Claisen rearrangement

Thio- and aza-Claisen rearrangements follow the same mechanism as the Claisen rearrangement but to accomplish these reactions and obtain good conversions, factors such as polarity of the solvent and use of a catalyst are very influential.[54,55]

The thio-Claisen rearrangement has been widely studied. The most accepted mechanism involves the formation of a sigma bond in the side chain with a nucleophile (a catalyst or solvent effect) to make the reaction work **(Scheme 18)**.[56]



Scheme 18: Mechanism of the thio-Claisen rearrangement

The nucleophile (Nu) approaches from the rear of the allylic carbon creating a distortion on it and displacing the bonding electrons of C-S in the direction of the sulfur. That distortion is a consequence of the formation of a 2p orbital that allows the molecule to acquire a chair transition state. This state unleashes the organization needed to form the new bonds and releases the Nu. Tautomeric transformation produces the final product. The presence of the Nu is to help the formation of the chair transition state to form the new bonds.

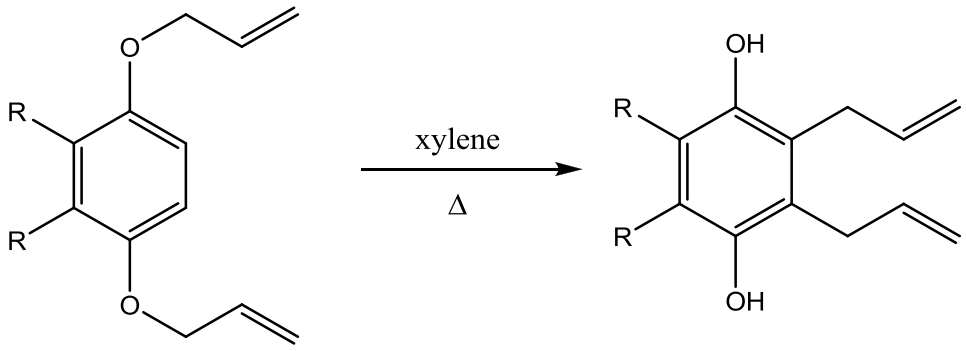
The aza-Claisen rearrangement takes place following a similar mechanism as the one shown in **Scheme 18** but stronger reaction conditions are needed to accomplish the sigmatropic rearrangement. Temperatures range increases from 100 ºC – 150 ºC to 200 ºC - 350 ºC.

The Claisen rearrangement is an important tool for organic chemists because exhibits all the essential properties required by a synthetic procedure: it can be chemo-,

regio-, diastero- and enantioselective, can be performed under mild conditions and affords potentially useful polyfunctionalised molecules. [57]

1.5 DOUBLE CLAISEN REARRANGEMENT

The double Claisen rearrangement involves a double rearrangement of two allyl vinyl ether groups to produce a dicarbonylic compound **(Scheme 19)**. Higher temperatures and longer reaction times are needed to carry out a double Claisen rearrangement.



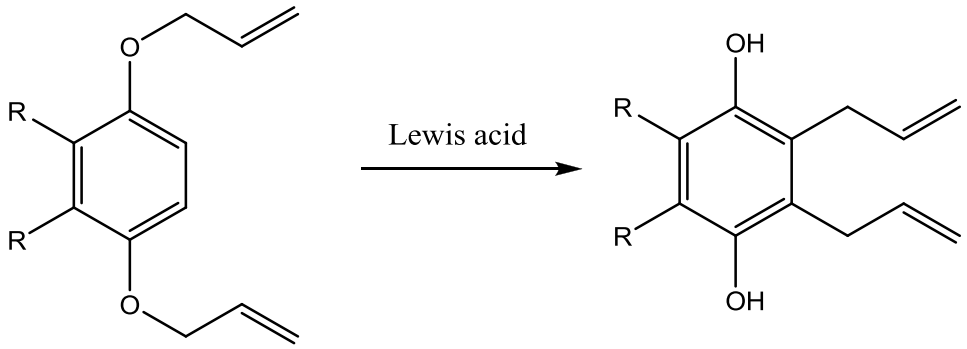
Scheme 19: Double Claisen rearrangement

Hiratani *et al.* achieved a thermal double Claisen rearrangement when searching for chelating agents for transition metal ions, by heating hydroxyquinoline derivatives at 200 ºC.[58] Other thermal double Claisen rearrangements have been carried out but problems with side reactions and decomposition due to the high temperatures needed always came up.[59]

Just a few previous catalytic double Claisen rearrangement reaction conditions have been found. The first additive used for a double Claisen rearrangement was

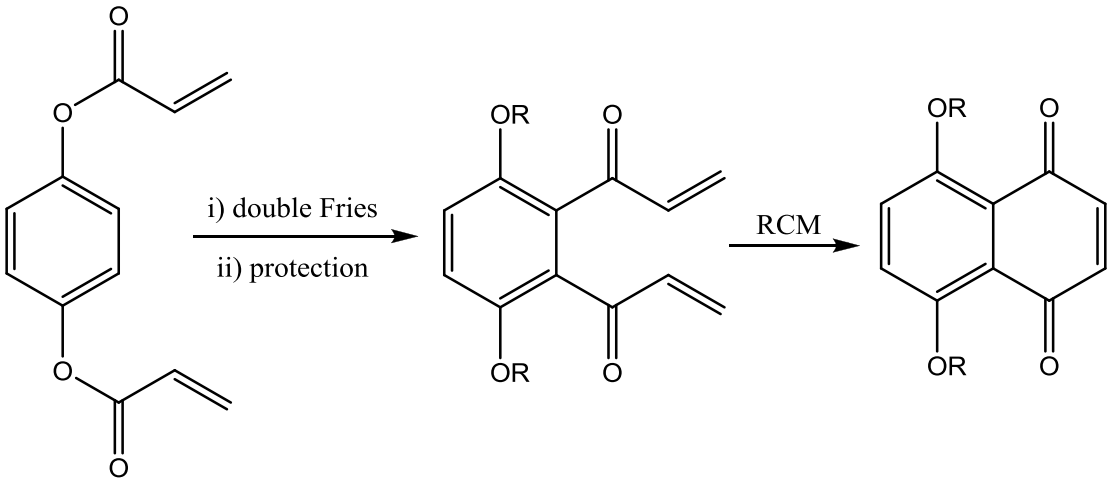
develop by Woodgate in 1981 who added silver/potassium iodide in acetic acid to a mixture of anthraquinones in acetic acid to synthesise anthracyclines. However, Woodgate and Sharghi encountered isomerisation and side chain reaction problems.[60] Nicolaou presented a catalytic microwave mediated double Claisen rearrangement in xylene using triphenylphosphine oxide as catalyst but yield obtained were low.[61]

These reaction conditions make the double Claisen rearrangement harder to perform due to decomposition of the compounds involved in the reaction and a difficult isolation of the final product. In order to develop mild reaction conditions for the double Claisen rearrangement and improve yields our efforts were to be focused in the Lewis acid catalysis that worked well for the Claisen rearrangement **(Scheme 20)**.[62]



Scheme 20: Lewis acid mediated double Claisen rearrangement

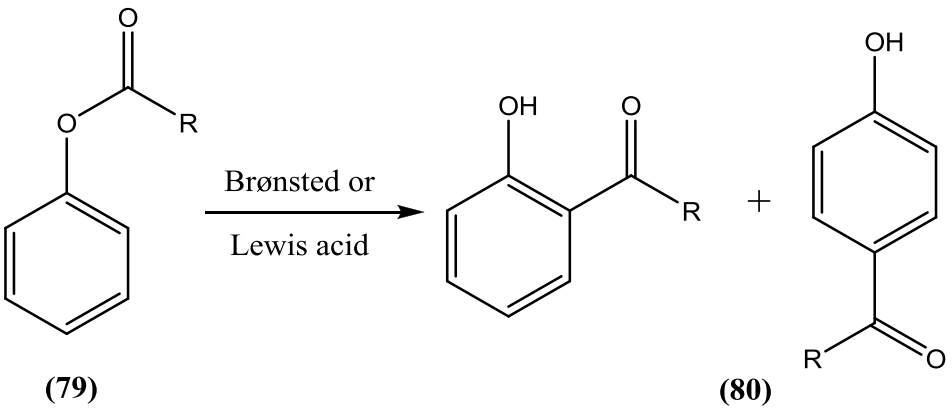
To expand the horizons of the iterative methodology it was thought that other related rearrangements could be useful to accomplish the synthesis of tetracycline antibiotics and related compounds. Among all the possible rearrangements the Fries rearrangement allows to introduce the desired oxygen moiety needed to achieve the target compound in one step **(Scheme 21)**.



Scheme 21: Synthesis of quinone compounds by means of a Fries rearrangement

1.6 THE FRIES REARRANGEMENT

The Fries rearrangement is a chemical transformation in which a phenolic ester **(79)** is converted into the corresponding *o/p*-acyl phenol **(80)** upon heating and Brønsted or Lewis acid catalysis **(Scheme 22)**.



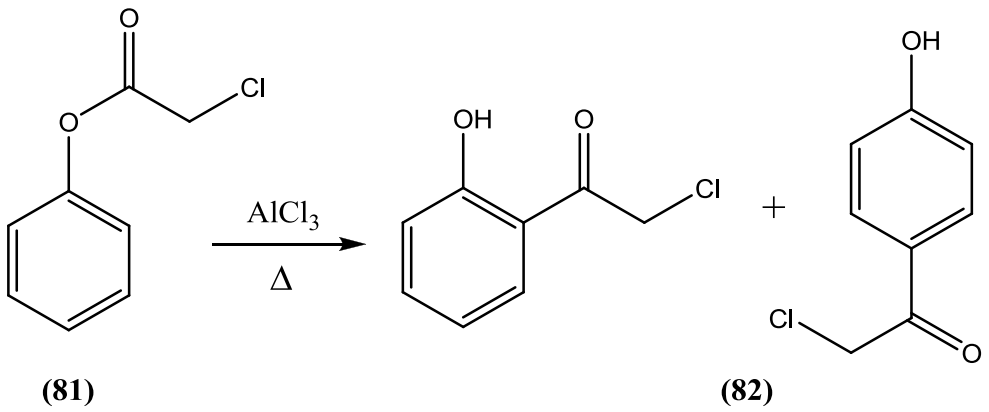
(79) **(80)**

Scheme 22: Fries rearrangement

Although the Fries rearrangement was discovered in 1908, previously Eykmann and Behn showed some of the conditions needed for the transformation.[63] The Fries

rearrangement was developed to avoid the difficulties encountered in preparing certain phenol ketones by the Friedel-Crafts reaction.[64]

K. T. Fries was seeking a methodology to synthesise *o*-chloroacetyl phenols because Friedel-Crafts conditions were not satisfactory and two acetyl groups were introduced into the phenols. By heating phenyl chloroacetate **(81)** with aluminium chloride, Fries observed that a mixture of *o/p*-(chloroacetyl)phenol **(82)** was obtained **(Scheme 23)**.



(81) **(82)**

Scheme 23: Synthesis of chloroacetylphenol

Further studies showed that it was possible to prepare at will either the *ortho*- or the *para*-hydroxy ketone from the same ester by controlling factors such as phenol structure, acyl group nature and temperature.

High temperatures favoured the formation of the *o*-hydroxy ketone while low reaction temperature gave the *p*-hydroxy ketone. Although temperature is the most relevant factor, the nature of the acyl group and phenol structure also play an important role in determining the course of the Fries rearrangement.[65]

The nature of the phenol showed an interesting behaviour. When the phenol is *para*- substituted only the *ortho*- rearrangement product was observed as expected. The presence of a single alkyl group or halogen introduces no difference when the *ortho*- and *para*- positions are available. Carboxyl, benzoyl or nitro groups in a *para*- position relative to the hydroxyl group stops the reaction.

The last factor to consider in a Fries rearrangement is the acyl group involved in the reaction. Even though it is not the most important factor is good to mention that when the other factors are balanced and counteracts each other, the nature of the acyl group will control the course of the reaction. Various acyl groups have been classified in the following order of decreasing rate of rearrangement:

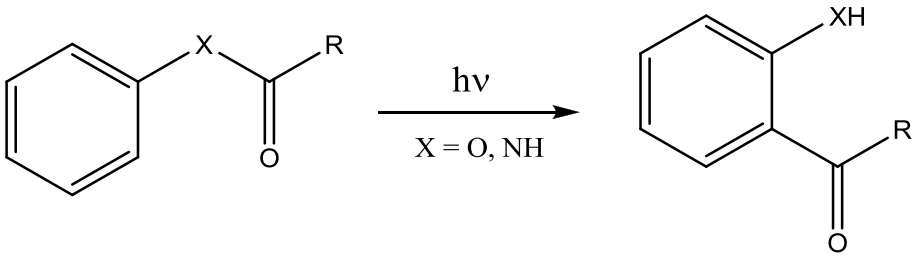
$C_nH_{2n+1}CO$ (n=1…5) > $C_6H_5CH_2CO$ > $C_6H_5CH_2CH_2CO$ > $C_6H_5CH{=}CHCO$ > C_6H_5CO

and bulky acyl groups promote the *ortho*- displacement over *para*- displacement.

Despite an appreciation of all of these factors, and having an established methodology for the Fries rearrangement to refer to, results may vary. Stronger reaction conditions, polysubstituted phenols and fused rings may lead to an elimination of the acyl group.

1.6.1 PHOTO-FRIES REARRANGEMENT

The photo-Fries rearrangement is a variation of the Fries rearrangement that can occur spontaneously. It was discovered in 1960 by Anderson and Reesel when ultraviolet light was irradiated over an alcoholic solution of catechol monoacetate to achieve a mixture of hydroxyacetophenones **(Scheme 24)**.[66]



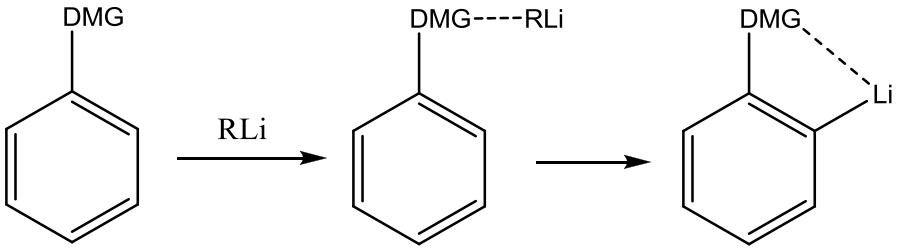
Scheme 24: The photo-Fries rearrangement

Even though yields in photo-Fries rearrangement are slightly lower than classical Fries rearrangement, is well noted that the reaction mechanism of the photo-Fries rearrangement differs from the classical Fries rearrangement allowing the synthesis of new derivatives.

The mechanism of the Fries rearrangement has not been completely elucidated and crossover experiments have shown evidence of both inter- and intramolecular processes.[67] On the other hand, evidence showed that the photo-Fries rearrangement involves a radical pair mechanism.[68]

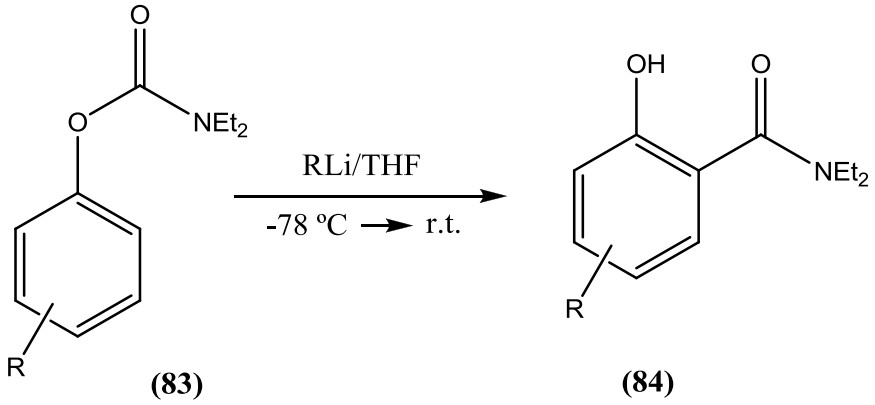
1.6.2 ANIONIC *ORTHO*-FRIES REARRANGEMENT

The anionic Fries rearrangement is also called anionic *ortho*-Fries rearrangement because the reaction specifically leads to *ortho*- position products due to the effect of a direct metalation group (DMG) through the intermediacy of an aryllithium compound **(Scheme 25)**.



Scheme 25: The lithiated intermediate directs the reaction in the *ortho*-position

In the 1980s Snieckus *et al.* described a process involving an *ortho*- metalation reaction of aryl carbamates **(83)** into salicylamides **(84)**. The carbamate was used as a precursor for the *ortho*- rearrangement of the tertiary amide, one of the most powerful *ortho*- directing groups **(Scheme 26)**.[69]



(83) **(84)**

Scheme 26: Synthesis of salicylamides

Standard conditions for metalation of tertiary amides and warming the solution for up to 10-12 hours resulted in the *ortho*-rearranged product only.[70] These results were significant because the anionic *ortho*-Fries rearrangement allowed accommodating hindered acyl groups to be accommodated better than classical Fries rearrangement.

Novel Fries rearrangements have been developed since then: anionic *N*-Fries rearrangement, remote anionic Fries and related rearrangements like the Baker-Venkataram rearrangement.[71]

In this current study we have investigated the development of an innovative mixed Fries-Claisen rearrangement that could provide in relatively few steps a versatile and advanced precursor for the synthesis of compounds with potential biological activity **(Figure 11)**.

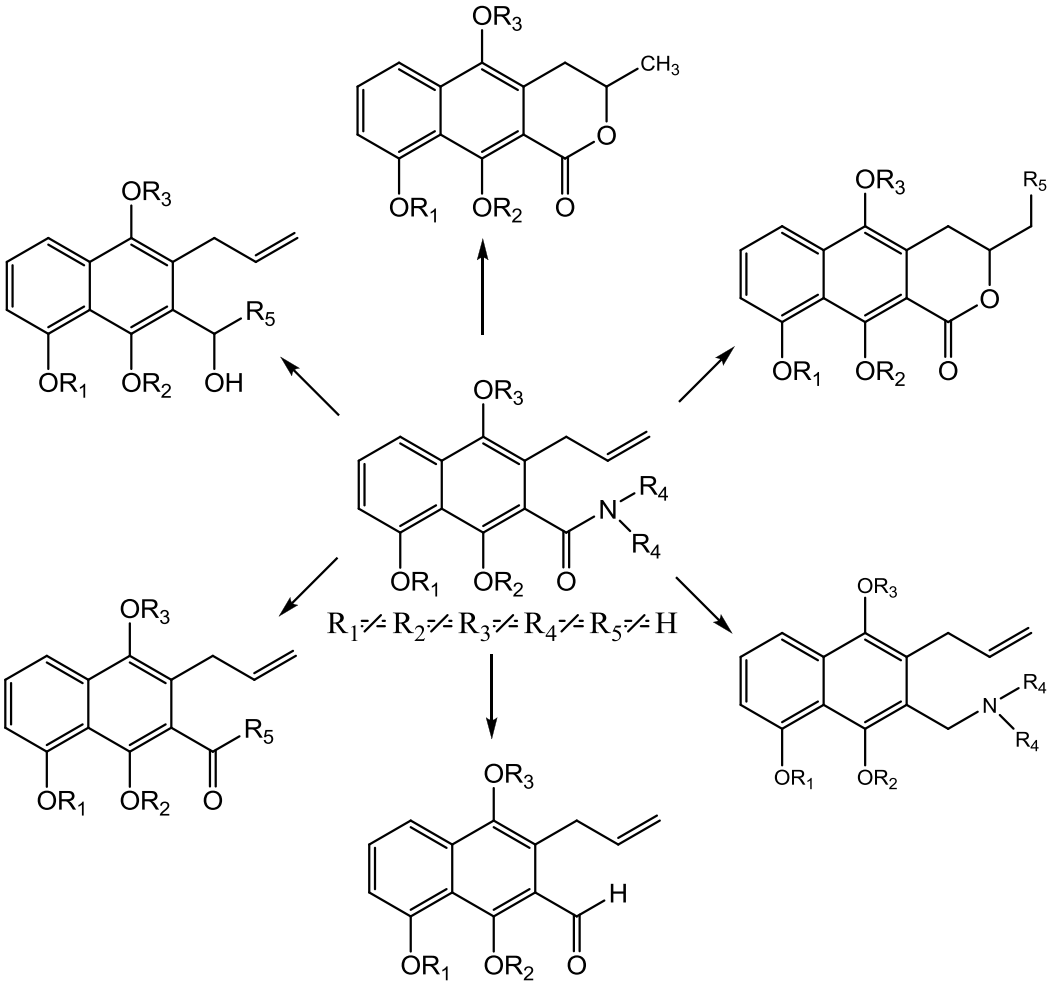


Figure 11: Tandem Fries-Claisen rearranged product as a precursor for compounds with potential antibiotic activity

As shown in **Figure 11**, reduction/substitution of the carbamide moiety to ketone should lead to the formation of new carbon fused rings as an approach towards the synthesis of compounds such as tetracyclines. Lactonisation could provide the pyrano scaffold common in a large number of antibiotics.

For example, pyranonaphthoquinones are an interesting class of naturally occurring antibiotic compounds that also display other biological properties such as anti-fungal, anti-viral and anti-cancer activity **(Figure 12)**.[72]

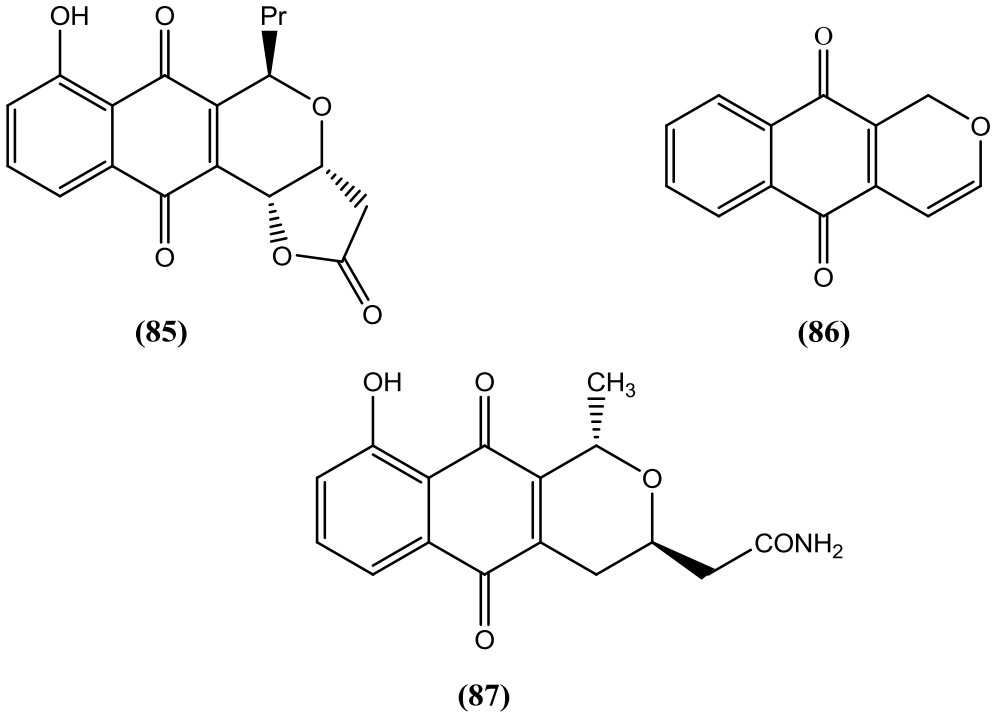
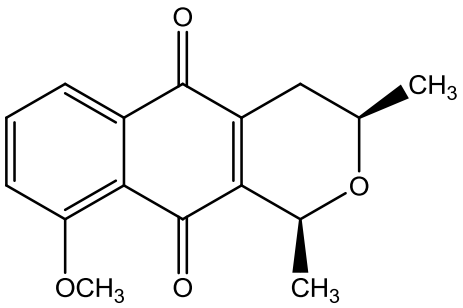


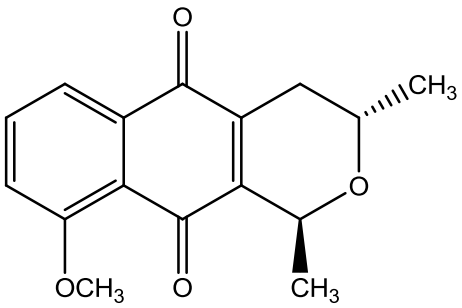
Figure 12: Pyranonaphthoquinones derivatives frenolycin B (85), pentalonging (86) and nanaomycin C (87).

1.7 ELEUTHERIN AND ISOELEUTHERIN

Eleutherin **(88)** and isoeleutherin **(89)** are the simplest examples of naturally occurring naphtho[2,3-*c*]pyran-5,10-quinones. Eleutherin **(88)** was first isolated in 1950 by Schmid *et al.* from the bulbs of *Eleutherin bulbosa* and shortly after, in 1951, Schmid *et al.* isolated isoeleutherin **(89)**, the C3 epimer, from the same bulb extracts.[73,74]



(88)



(89)

Figure 13: Eleutherin (88) and isoeleutherin (89)

Eleutherin **(88)** and isoeleutherin **(89)** present antifungal activity and bactericidal activity against *Pycococus aureus, Streptococcus haemolyticus A,* and *Bacillus subtilis*. Plants from the eleutherin family reported to show inhibitory activity against HIV infection and have been used in ancient medicine to treat heart diseases as angina pectoris.[75]

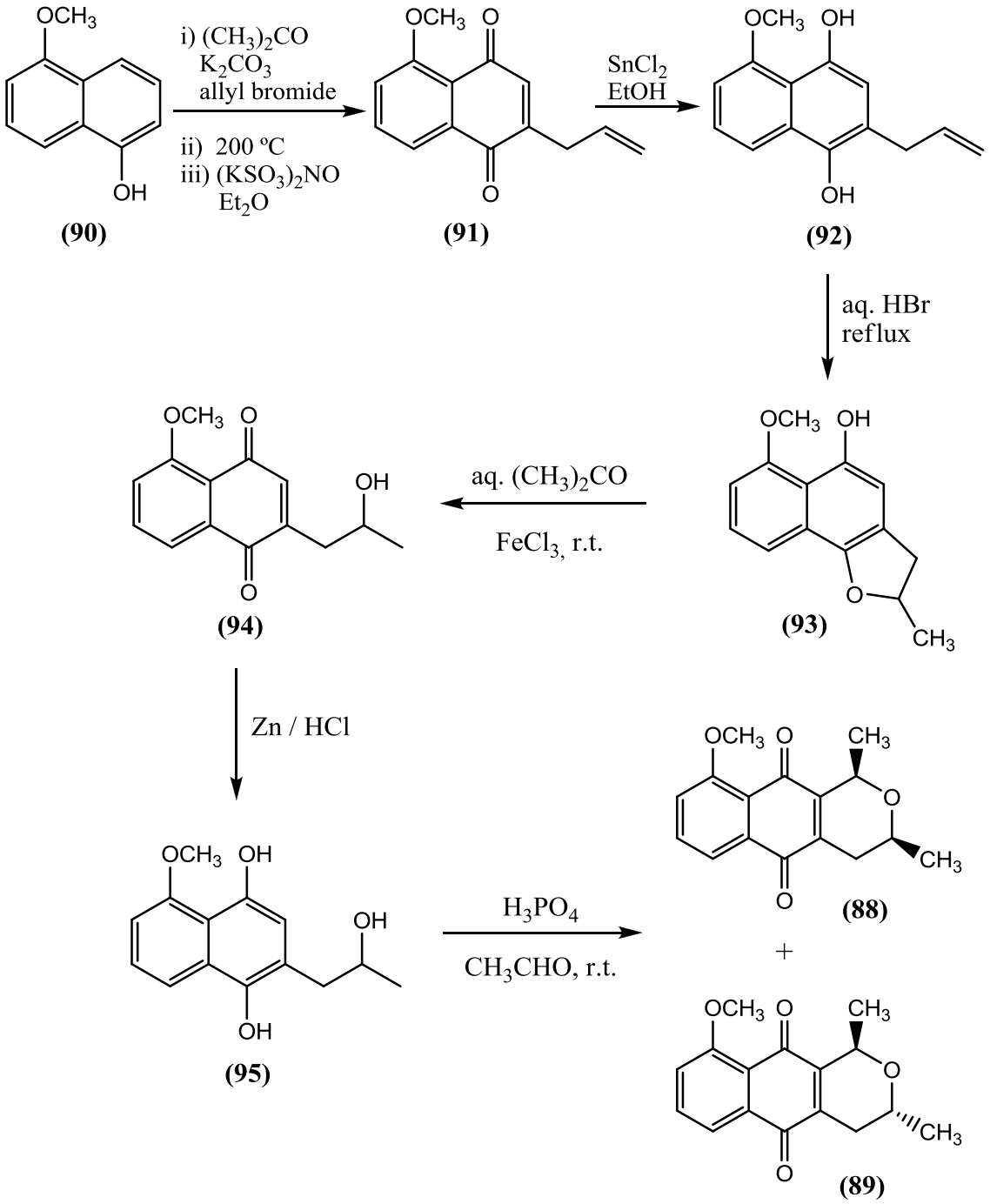
Recent studies developed by Krishnan *et al.* described anti-tumour activity of eleutherin **(88)** through the inhibition of topoisomerase II which is essential in the separation of entangled daughter strands during replication. Due to its important catalytic function topoisomerase II has been a desirable target for anti-cancer drugs because failure of separation/relegation of DNA breaks leads to cell death.[76,77]

During DNA transcription or replication, topoisomerase II initially binds to the DNA chain in a non-covalent way. In the presence of divalent cations, topoisomerase II breaks the DNA strands and is attached covalently to the 5'-phosphate of the DNA. After subsequent ATP binding another strand of DNA passes through the gate and the enzyme reseals the break. ATP hydrolysis releases the DNA and results in enzyme turnover.[78]

If the inhibition affects the covalent intermediate making it more stable and impossible to release topoisomerase II it is called poisoned inhibition. If the inhibition affects any of the steps of the catalytic cycle is called catalytic inhibition. Eleutherin **(88)** belongs to the second class, inhibiting the topoisomerase II-DNA binding in the presence of ATP, inducing the enzyme to religate DNA breaks before dissociating the enzyme from the DNA.[79]

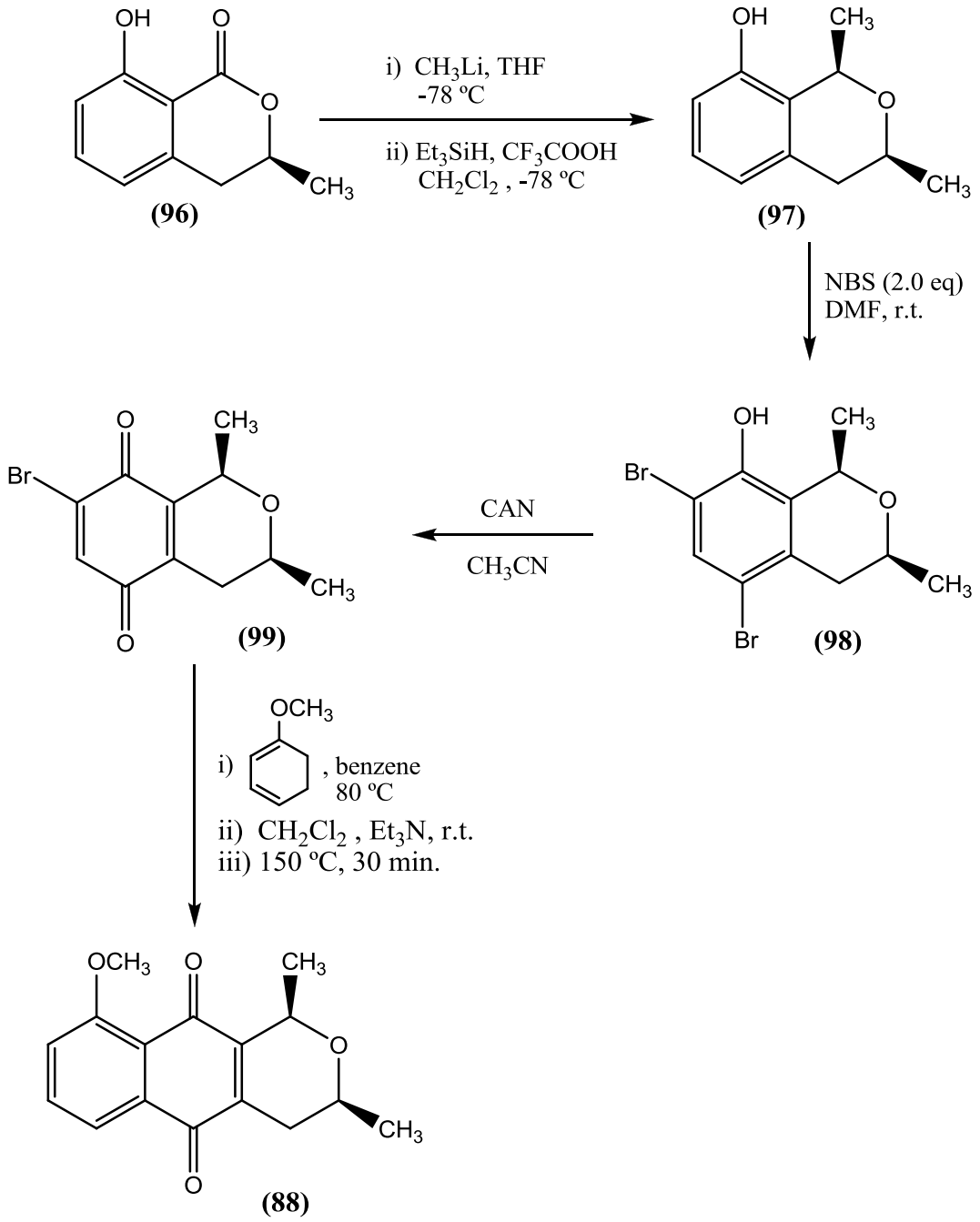
1.7.1 PREVIOUS SYNTHESIS OF ELEUTHERIN AND ISOELEUTHERIN

The synthesis of eleutherin **(88)** and isoeleutherin **(89)** was first reported by Schmid *et al.* in 1958.[80] Allylation of 5-methoxy-1-naphthol **(90)** with allyl bromide in the presence of potassium carbonate with subsequent Claisen rearrangement and oxidation of the rearranged product using potassium nitrososulfonate in diethyl ether yielded allylquinone **(91)**. Reduction of quinone **(91)** by means of stannous chloride to the corresponding hydroquinone **(92)** and subsequent cyclisation with hydrobromic acid produced hydrofuran **(93)**. Reoxidation and ring-opening of hydrofuran **(93)** with iron(III) chloride in aqueous acetone led to hydroxypropylquinone **(94)**. Rearomatisation of the ring using zinc dust in hydrochloric acid afforded hydroquinone **(95)**. Condensation of hydroquinone **(95)** with acetaldehyde in the presence of phosphoric acid produced eleutherin **(88)** and isoeleutherin **(89)** as a separable racemic mixture **(Scheme 27)**.



Scheme 27: Schmid synthesis of racemic eleutherin (88) and isoeleutherin (89)

Over the last years different synthetic routes towards racemic eleutherin **(88)** and analogues have been reported.[81] The first enantioselective synthesis of (+)-eleutherin **(88)** was develop by Donner *et al.* in 2006 starting by Diels-Alder cycloaddition of properly substituted butadienes to benzoquinone **(99)**.[82]

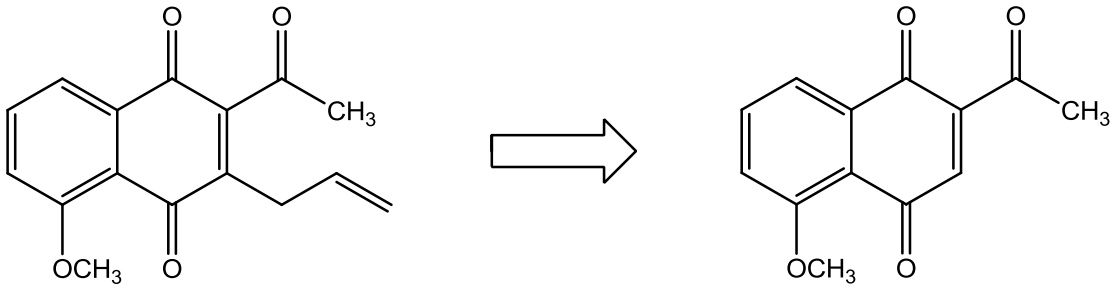


Scheme 28: Donner's synthesis of (+)-eleutherin (88)

Donner and co-workers had previously reported a synthesis for (*S*)-mellein **(96)**.[83] Treatment of (*S*)-mellein **(96)** with methyl lithium in tetrahydrofuran and subsequently stereospecific reduction of the alcohol using trifluoroacetic acid in dichloromethane produced **(97)**. Bromination of benzopyran **(97)** with an excess of *N*-bromosuccinimide in *N*,*N*-dimethylformamide achieved dibromobenzopyran **(98)**,

which was oxidised to the corresponding quinone **(98)** using an aqueous solution of cerium(IV) ammonium nitrate in acetonitrile. Diels-Alder cycloaddition between benzoquinone **(99)** and 1-methoxy-1,3-cyclohexadiene in benzene, followed by pyrolysis yielded (+) eleutherin **(88) (Scheme 28)**. Over the last years a few asymmetric syntheses towards eleutherin **(88)** have been develop involving several steps and yielding mixture of diastereomers.[84]

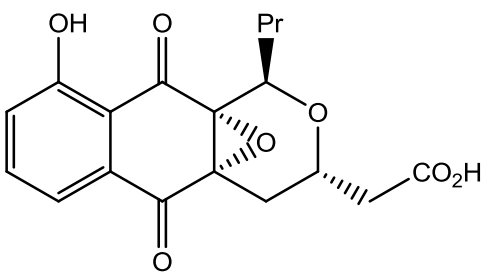
Alkanoylallylnaphthoquinone **(100)** is a good precursor for the synthesis of eleutherin **(88)** but direct allylation of alkanoyl substituted quinones **(101)** showed some problems by conventional methods **(Scheme 29)**.



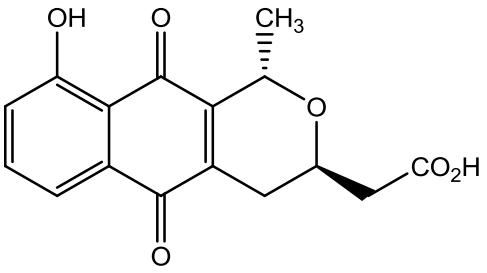
(100) **(101)**

Scheme 29: Alkanoylallyl retrosynthetic analysis

The use of the novel mixed Claisen-Fries rearrangement would allow access to the alkanoylallyl precursor **(100)** and could provide a useful tool for the synthesis of more complex pyranonaphthoquinone derivatives such as frenolicin A **(102)** and nanaomycin A **(103) (Figure 14)**.



(102)

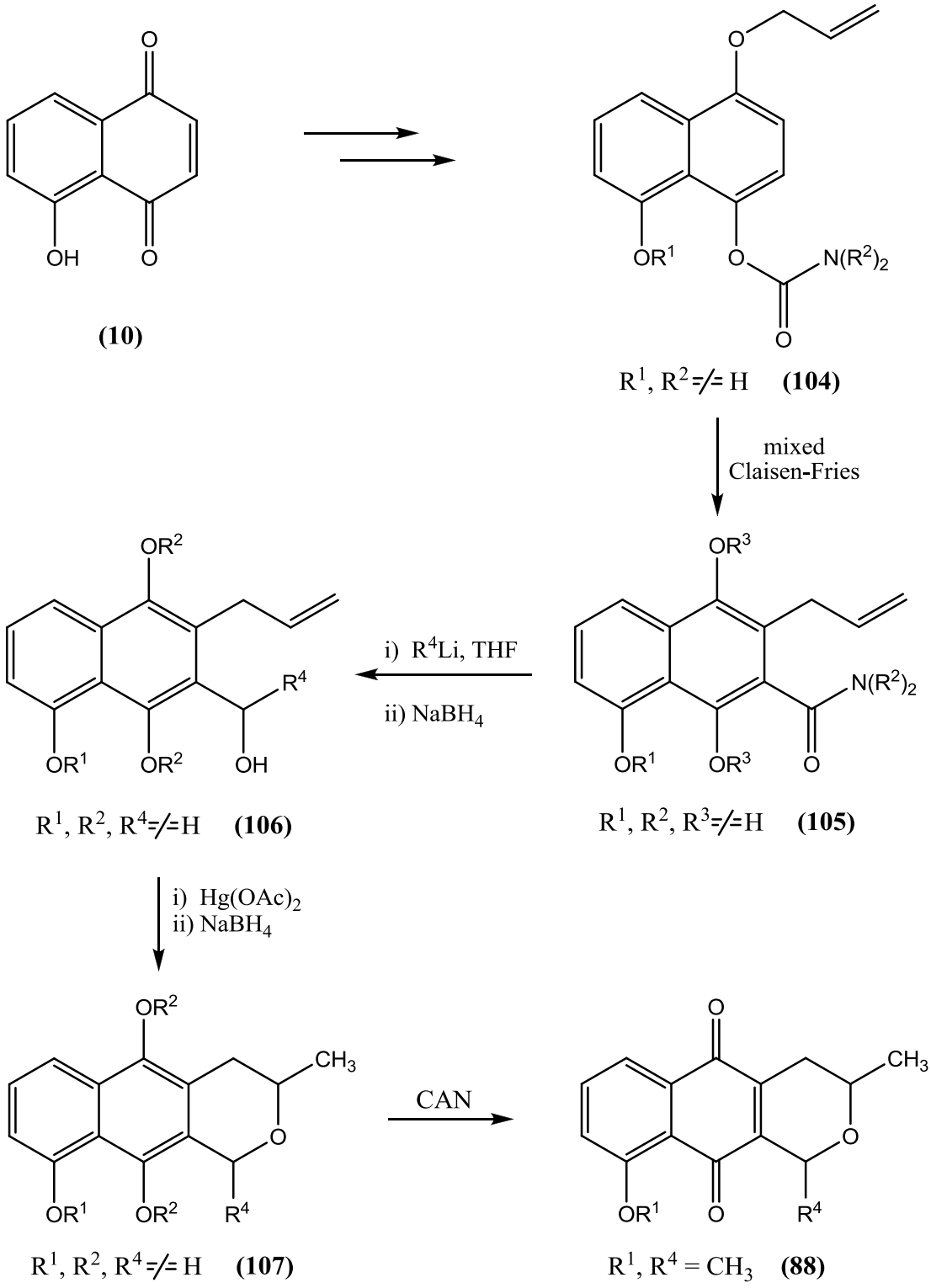


(103)

Figure 14: Pyranonaphthoquinone derivatives

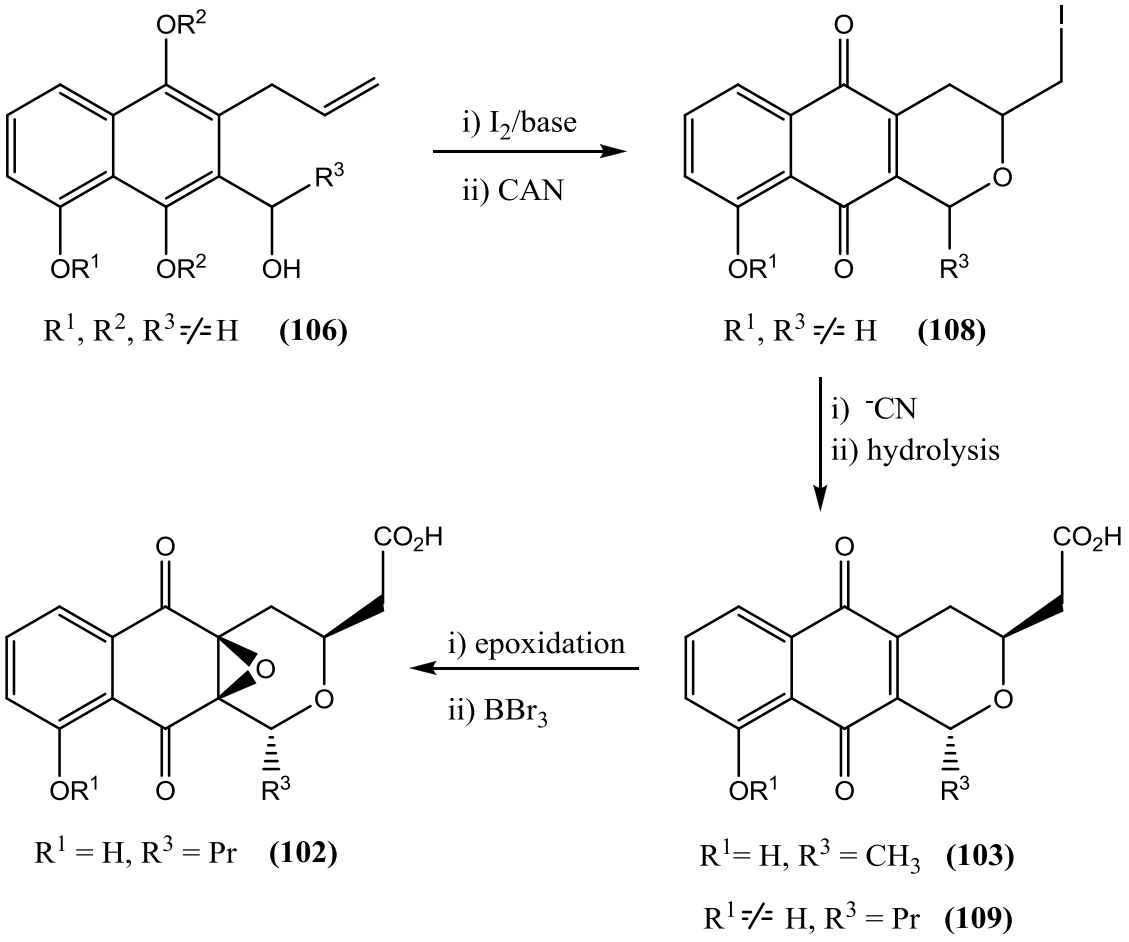
Protection of juglone **(10)**, reduction of the quinone to the corresponding dihydroxy compound, allylation and subsequent introduction of carbamate moiety using standard procedures would yield the Claisen-Fries precursor **(104)**. Claisen rearrangement of compound **(104)**, protection of the free alcohol obtained followed by Fries rearrangement and protection of the new free alcohol moiety would lead to Claisen-Fries rearranged compound **(105)**.

Treatment of compound **(105)** with a lithiated derivative in the presence of sodium borohydride should produce the corresponding alcohol **(106)**. Cyclisation of **(106)** with mercury(II) acetate in the presence of sodium borohydride should yield lactone **(107),** which should undergo oxidative demethylation with cerium(IV) nitrate to obtain eleutherin **(88)** or a naphthoquinone derivative **(Scheme 30)**.



Scheme 30: Synthetic route towards eleutherin and other naphthoquinone compounds

As shown in **Scheme 31**, the use of polysubstituted quinones and different lithiated reagents could provide a wide range of naphthoquinone compounds that could be transformed to more complex natural compounds with antibiotic activity in few steps.



Scheme 31: Proposed synthetic route towards more complex naphthoquinone antibiotics

1.8 FURAN FUSED CARBON RINGS

The furan fused scaffold is commonly present in linear fused carbon rings. It can be found in several natural compounds attached to one side of the linear skeleton. Their biological and pharmacological activities and their physico-chemical properties made

them an important aim in organic and material chemistry.[85] The benzofuran skeleton can be found in furocoumarins or psolarens, well known families of compounds with photochemotherapeutic activity as antiproliferative compounds and, potentially, as fluorescent dyes **(Figure 15)**.[86]

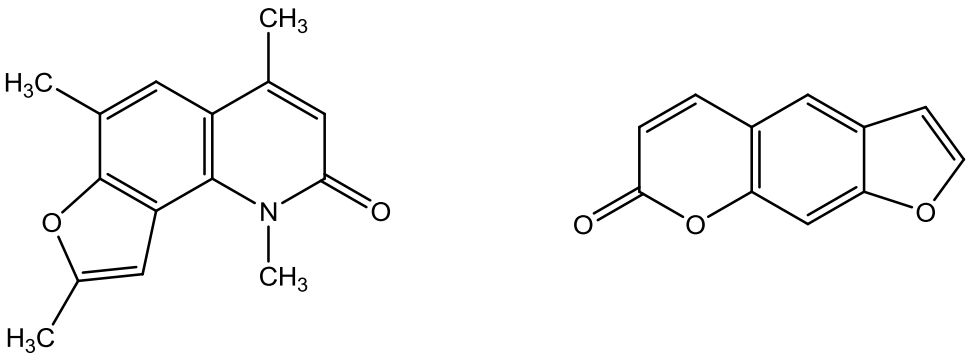


Figure 15: Natural products containing benzofuran scaffold FQ and psolaren

The biological activity of benzofuran derivatives has been widely studied.[87] However their application as organic semiconductors or molecular wires has increased over the last years because they can work as building blocks for molecular electronic devices that can replace silicon in micro-electronic circuits and/or components in solar energy storage systems.[88]

1.8.1 ORGANIC SEMICONDUCTORS

In the quest for suitable materials to be used in devices in electronics and photonics π-conjugated fused rings have interesting and, potentially, technologically important electrical and optical properties.

Organic conjugated molecules and polymers are special candidates because they exhibit a large and ultra-fast nonlinear optical response which means high speed processing, transmission and storage of data.[89] Compared with silicon technology organic molecules are more attractive due to their thermal and chemical stability, versatility and low cost production.

Conjugation length and π electron delocalization length governs the electrical and optical properties of conjugated systems. For these reasons the design of a molecule with optimal charge carrier ability is key in developing an organic field-effect transistor (OFET) or an organic light-emitting diode (OLED).

Acenes family has become a target for organic electronics due to their properties being pentacene the largest member of the family with thin film transistor mobility on par with amorphous silicon.[90] Unfortunately, unsubstituted rings are highly reactive (Diels-Alder reaction with molecular oxygen) which makes them quite unstable for their use in industry.[91] Wudl *et al.* solved this problem by functionalising the rings with bulky groups as tris(trimethylsilyl)silane.[92] The addition of a thiophene fused to the acene ring to improve its stability was firstly introduced by Katz *et al.*[93]

Thiophene derived acenes showed interesting theoretical properties for their use as new materials in organic FETs.[94] Several derivatives from sulfur have been synthesised over the last years searching for the appropriate molecular packing to enhance the π-face interactions. Larger stable linear fused compounds have been achieved (up to seven rings) and different functionalisations have been designed to both improve solubility and enhance cofacial interactions in the solid as shown **Figure 16**.[95]

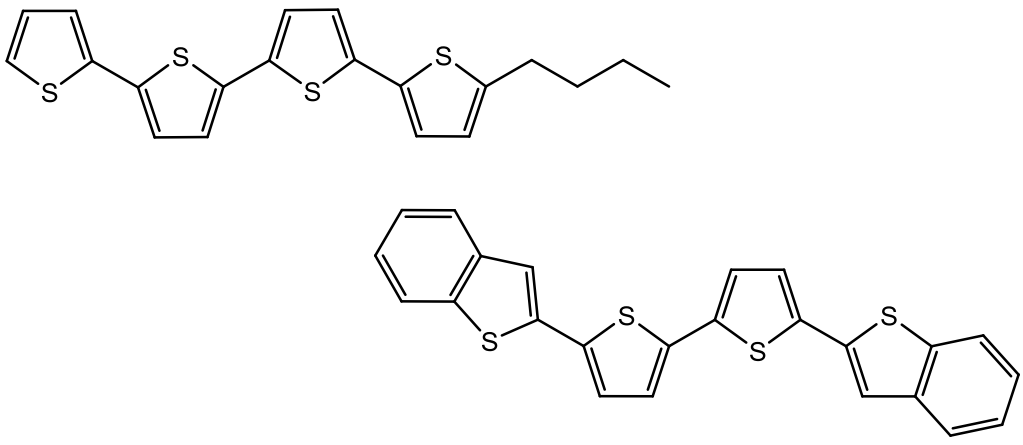


Figure 16: Linear ladder-type π-conjugated polymers

Nowadays organic semiconductors are used as photosensitive materials in information recording processes and are also used in microelectronics. This recently acquired importance demand new and more complex compounds and new synthetic routes that make them available in large scale.

1.8.2 MOLECULAR WIRES

Molecular wires are molecular-scale objects (most common types based on organic molecules) which conduct electrical current and consist of a molecular unit connected to two continuum reservoirs of electrons (usually metallic leads) providing a pathway for the transport of electrons from one reservoir to another.[96] Their conductance properties rely on the transmission probability for an electron to scatter through the molecule. The first molecular wire (MW) system[97] consisted of 1,4-benzene-dithiolate bonded to two gold nanocontacts but recent studies showed structures bonded with other metals as chromium, molybdenum and iron **(Figure 17)**.[98]

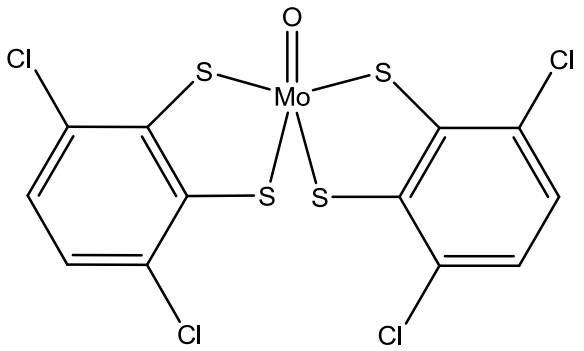
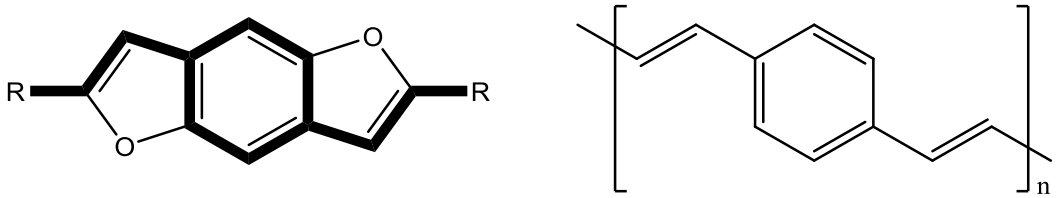


Figure 17: Molybdenum bonded system

In the discovery of new materials that could act as molecular wires benzo[1,2-*b*:4,5-*b*']difurans **(110)** constitute an important class of electroactive chromophores that

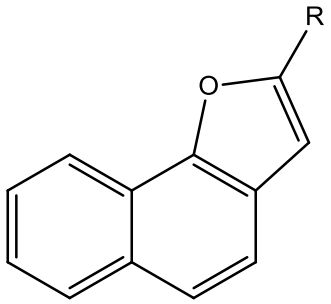
possess close structural similarities to the electroactive moieties used for the construction of polyphenylenevinylene **(111)** and its alkoxy-derivatives **(Figure 18)**.[99]



R =/= H **(110)** **(111)**

Figure 18: Benzodifuran electron conjugation vs. polyphenylenevinylene

Naphthofurans derivatives **(112)** are very interesting due to their structural conformation providing a similar configuration to benzo[1,2-*b*:4,5-*b*']difuran scaffold but with an extra fused ring that improves the delocalization of the electrons, their solubility and makes more accessible the functionalisation of the ring.

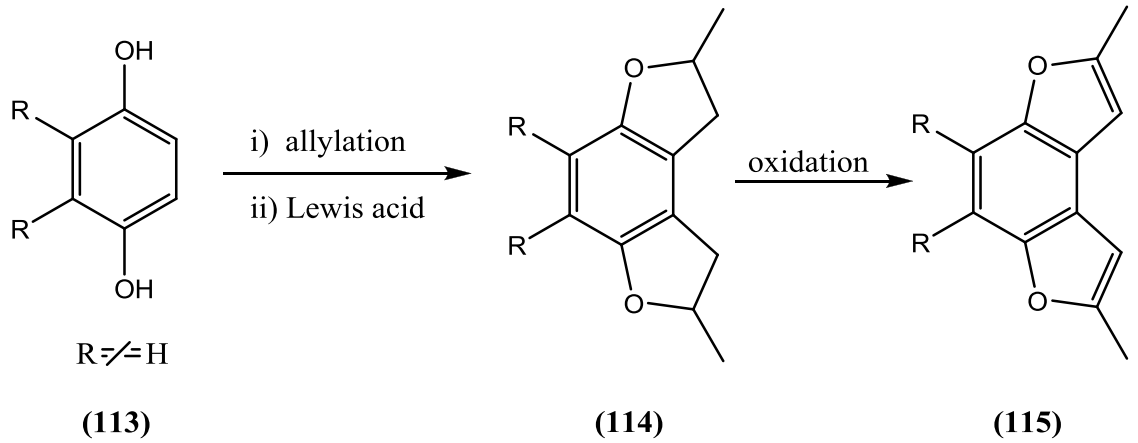


(112)

Figure 19: Naphthofuran scaffold

In the quest for new conditions to improve the aromatic Claisen rearrangement it was observed that some specific Lewis acids could act as catalysts for the formation of dihydrofuran compounds. These dihydrofuran compounds should be easily oxidised to their respective benzofuran derivative.

For these reasons a new synthetic route towards benzodifuran derivatives was proposed. As shown in **Scheme 32**, allylation of dihydroxybenzene **(113)** followed by Lewis acid mediated aromatic Claisen rearrangement would produce dihydrofuran intermediate **(114)**. Oxidation of the dihydrofuran intermediate **(114)** should furnish the corresponding benzodifuran compound **(115)**.[100]



(113) **(114)** **(115)**

Scheme 32: Synthetic proposal towards benzodifuran derivatives

Following the procedure detailed above and changing the different substituents in the benzene ring it is possible to access a wide range of benzodifuran compounds. The different substituents in the ring could be used to improve their solubility, enhanced their facial interactions and link them to other molecules to form a polymeric structure.

1.9 RESEARCH OBJECTIVES

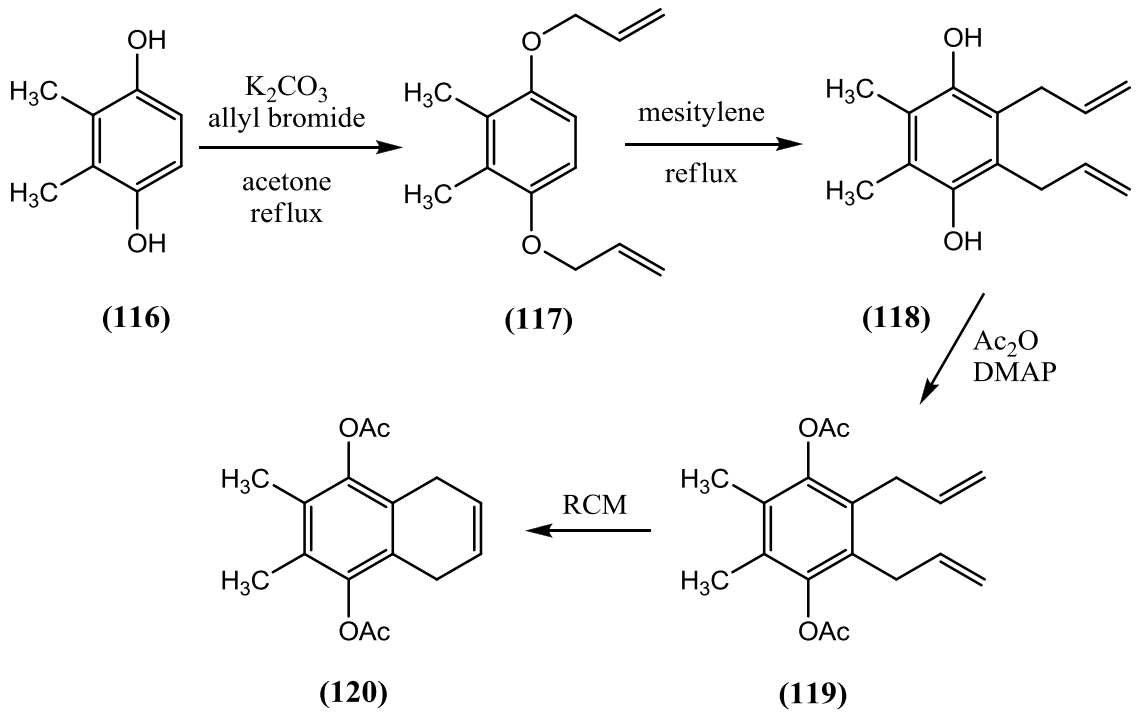
This research project aimed:

- to develop a Lewis acid mediated double Claisen rearrangement.
- to apply this methodology to more complex molecules such as juglone (**10**).
- to evaluate the use of this methodology with sulfur/nitrogen substituted aromatic compounds.
- to expand the horizons of this methodology for the synthesis of benzodifuran compounds.
- to develop a mixed Fries-Claisen rearrangement.
- to apply this methodology towards the synthesis of pyranonaphthoquinone derivatives.

CHAPTER TWO: RESULTS AND DISCUSSIONS

2.1 DOUBLE CLAISEN REARRANGEMENT APPLIED TO HYDROQUINONE AND NAPHTHOQUINONE DERIVATIVES

As mentioned previously the double Claisen rearrangement was our first key step in the quest for a new iterative approach towards linear fused carbon ring derivatives. The double Claisen rearrangement has been previously studied in our research group and by applying the methodology developed by Widenhoefer the desired rearranged target **(118)** was achieved.[101,1] Kotha reported full benzoannulation of quinones using a double Claisen rearrangement followed by a ring-closing metathesis (RCM) to yield compound **(120)**.[102]

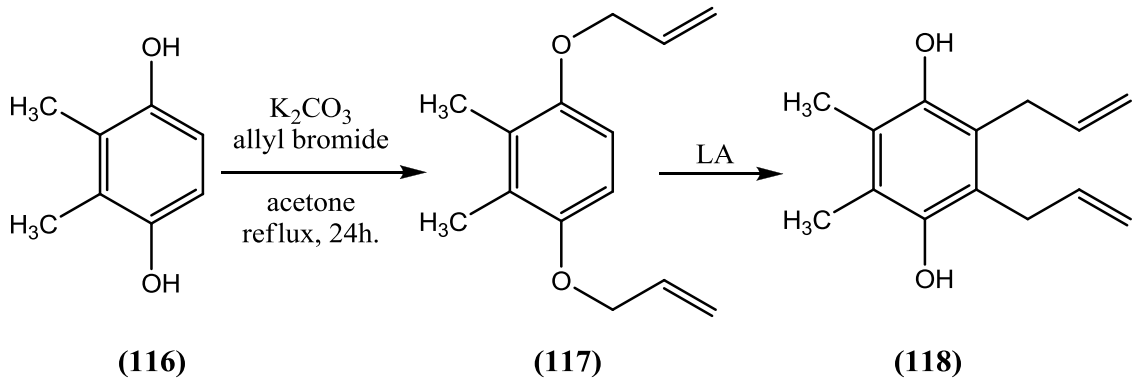


Scheme 33: Synthesis of the new fused ring using Claisen rearrangement and RCM metathesis

Initially, the double Claisen rearrangement was carried out in our research group under thermal conditions **(Scheme 33)**.[1] Unfortunately, the high temperatures needed for carrying it out were too strong for some of the target products leading to thermal degradation and the high-boiling solvents used were really difficult to remove from the

reaction mixture. For these reasons we proposed the development of a new Lewis acid mediated double Claisen rearrangement to find milder reaction conditions.

In order to find the optimum reaction conditions to carry out the double Claisen rearrangement, 2,3-dimethylhydroquinone **(116)** was chosen as starting material. Previous knowledge on the double Claisen rearrangement of 2,3-dimethylhydroquinone **(116)** allowed us to compare the thermal results with those obtained using Lewis acid additives.



(116) **(117)** **(118)**

Scheme 34: Lewis acid mediated double Claisen rearrangement

Double allylation of 2,3-dimethylhydroquinone **(116)** by treatment with potassium carbonate and allyl bromide in refluxing acetone for 24 hours yielded the bisallylated product **(117)** in an 87%, which was used to find the best reaction conditions for the double Claisen rearrangement **(Scheme 34)**. **Table 1** shows the Lewis acids, temperatures, reaction times and solvents that were tried.

Table 1: Mediated Lewis acid double Claisen rearrangement conditions

Entry	Lewis acid	Solvent	Temperature	Time	Product [(b)]	^{1}H NMR ratio	Yield[(a)]
1	-	mesitylene	reflux	24 h.	**118**	Pure	60%
2	-	$PhNEt_2$	MW (100 ºC)	10 min.	**117**	Pure	>95%
3	-	$PhNEt_2$	MW (100 ºC)	1 h.	**117**	Pure	>95%
4	$AlCl_3$	CH_2Cl_2	0 ºC	6 h.	**117**	Pure	>95%
5	BCl_3	CH_2Cl_2	-35 ºC→r.t.	20 h.	mixture	-	-
6	BCl_3	CH_2Cl_2	r.t.	18 h.	**121**	Pure	17%
7	BCl_3	CH_2Cl_2	0 ºC	18 h.	mixture	-	-
8	$BF_3{\cdot}Et_2O$	CH_2Cl_2	-45 ºC→r.t.	24 h.	mixture	-	-
9	$BF_3{\cdot}Et_2O$	CH_2Cl_2	0 ºC	3 h.	**117+118**	1:2	9%
10	$BF_3{\cdot}Et_2O$	CH_2Cl_2	0 ºC	5 h.	**117+118**	1:2	8%
11	$BF_3{\cdot}Et_2O$	CH_2Cl_2	r.t.	16 h.	**121**	-	4%
12	$BF_3{\cdot}Et_2O$	CH_2Cl_2	0 ºC	18 h.	**118**	Pure	65%
13	$BF_3{\cdot}Et_2O$	CH_2Cl_2	0 ºC	18 h.	**118**	Pure	62%
14	$Bi(OTf)_3$	CH_2Cl_2	0 ºC→-20 ºC	18 h.	**117**	Pure	93%
15	$Bi(OTf)_3$	acetonitrile	0 ºC→r.t.	19 h.	mixture	-	-
16	$Bi(OTf)_3$	CH_2Cl_2	0 ºC	18 h.	**117+118**	1:2.5	-
17	$Bi(OTf)_3$	CH_2Cl_2	r.t.	18 h.	**117+121**	1:5	-
18	Me_3Al	CH_2Cl_2	-45 ºC→r.t.	24 h.	**117+118**	1:2.5	-
19	Me_3Al/H_20	CH_2Cl_2	0 ºC	2 h.	**117+118**	2:1	-
20	Me_3Al/H_20	toluene	0 ºC	2 h.	**117**	Pure	68%
21	Me_3Al/H_20	CH_2Cl_2	r.t.	24 h.	**117+121**	2:1	-
22	$TiCl_4$	CH_2Cl_2	0 ºC→r.t.	20 h.	mixture	-	-
23	$TiCl_4$	CH_2Cl_2	0 ºC	17 h.	**121**	Pure	20%
24	$TiCl_4$	CH_2Cl_2	0 ºC	6 h.	**121**	Pure	19%
25	$ZrCl_4$	CH_2Cl_2	-35 ºC→r.t.	18 h.	mixture	-	-
26	$ZrCl_4$	CH_2Cl_2	0 ºC→-20 ºC	18 h.	mixture	-	-
27	$ZrCl_4$	CH_2Cl_2	0 ºC	2 h.	mixture	-	-

(a) Yields for isolated products after flash column chromatography purification
(b) As shown in the ^{1}H NMR spectrum of the crude product

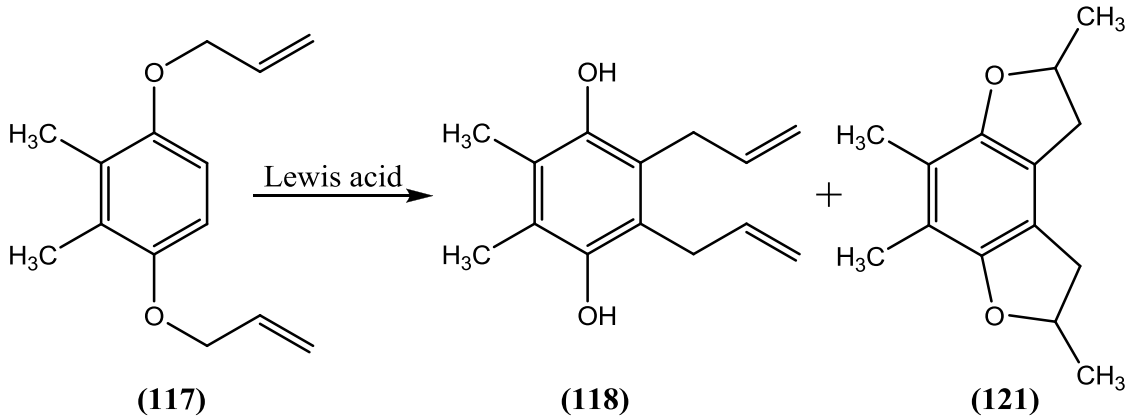
As shown in **Table 1**, optimum conditions to achieve double Claisen rearrangement of 1,4-bis(allyloxy)-2,3-dimethylbenzene **(117)** were boron trifluoride diethyl etherate at 0 ºC in dichloromethane for 18 hours (entries 12 and 13) . Using

these conditions yields were slightly higher (5%) and reactions times were shorter compared to those obtained using thermal conditions (entry 1). When 1,4-bis(allyloxy)-2,3-dimethylbenzene **(117)** was treated with other Lewis acids several results were observed. Treatment at low temperatures usually produced a mixture of starting material **(117)** (entries 4, 14 and 20) or/and Claisen rearranged product **(118)** (entries 9, 10, 18 and 19). When temperature was increased mixtures of decomposition (entries 5, 7, 8, 15, 22, 26 and 27) or/and reaction by-products **(121)** were obtained (entries 17 and 21).

The use of more polar solvents such as toluene (entry 20), acetonitrile (entry 15) and water (entries 19 and 21) did not make any significant difference in the results obtained. Theoretically, polar solvents should accelerate reaction rate however, no difference was observed in the reaction rate or products obtained.[103]

Microwave assisted reaction should lead to the rearranged product **(118)** with similar yields avoiding the problem of long thermal treatment.[104] Unfortunately, after prolonged irradiation no positive results were obtained and only starting material **(117)** was achieved (entries 2 and 3).

Treatment of 1,4-bis(allyloxy)-2,3-dimethylbenzene **(117)** with boron trichloride (entry 6), boron trifluoride diethyl etherate (entry 11) and titanium(IV) chloride (entries 23 and 24) produced an unexpected by-product that was isolated from the reaction mixture. ^{1}H NMR, ^{13}C NMR and IR studies showed that this unexpected by-product, obtained as a major product when bisallylated hydroquinone **(117)** was treated with titanium(IV) chloride at 0 ºC in dichloromethane for 6 hours, corresponded to dihydrofuran compound **(121)**. Some copper and silver catalysts were proven to promote an intramolecular cyclisation in similar compounds.[105] These results were highly satisfactory because only by controlling reaction times and Lewis acid one compound was mainly obtained **(Scheme 35)**.



Scheme 35: Lewis acid mediated Claisen rearrangement and cyclisation

In order to exploit and verify the conditions obtained for the Lewis acid mediated double Claisen rearrangement of 1,4-bis(allyloxy)-2,3-dimethylbenzene **(117)** a battery of compounds was selected as alternative substrates: 2,3-dicyanohydroquinone **(122)**, catechol **(123)**, 2,3-dihydroquinone **(124)** and 2-methylresorcinol **(125) (Figure 20)**.

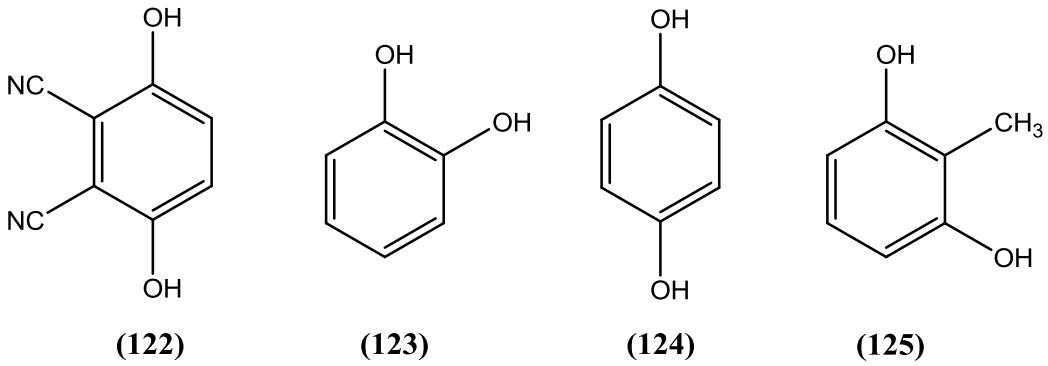
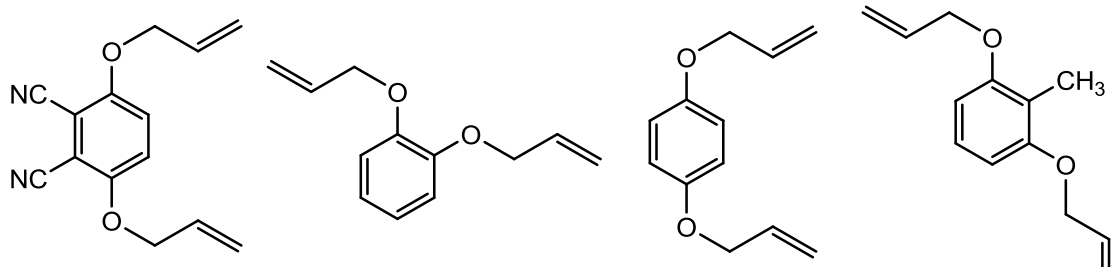


Figure 20: Hydroquinone derivatives

Compounds **(122)**, **(123)**, **(124)** and **(125)** were proposed due to their chemical and structural similarities with 2,3-dimethylhydroquinone **(116).** 2,3-Dicyanohydroquinone **(122)** was selected due to the cyano group present in the molecule that would allow further potential functional group substitutions to achieve

different derivatives with specific chemical properties. 2,3-Hydroquinone **(124)** was chosen because it presents two free *ortho*-position to carry out the Claisen rearrangement making it suitable for an iterative procedure and subsequent right-to-left building orientation. Catechol **(123)** and 2-methylresorcinol **(125)** were the most similar compounds to 2,3-dimethylhydroquinone **(116)** because they have only one reactive position as the other positions are blocked or not accessible to undergo the Claisen rearrangement.

Allylation of compounds **(122)**, **(123)**, **(124)** and **(125)** by means of potassium carbonate and allyl bromide in refluxing acetone for 24 hours produced the corresponding bisallylated derivatives **(126)**, **(127)**, **(128)** and **(129)** in very good yields (>85%) **(Figure 21)**.



(126) **(127)** **(128)** **(129)**

Figure 21: Hydroquinone bisallylated derivatives

Instead of trying all of the Lewis acids, the optimum conditions previously obtained were initially applied. Unfortunately, treatment of bisallylated compounds **(126-129)** with boron trifluoride diethyl etherate at 0 ºC in dichloromethane for 18 hours was not enough to complete the reaction and only starting material was achieved. As a consequence of these results a new set of conditions were tried using alternative Lewis acids and increasing temperatures and reaction times **(Table 2)**.

Table 2: Lewis acid mediated double Claisen conditions

Entry	Compound	Lewis Acid	Solvent	Temperature	Time	Product [(b)]	Yield[(a)]
1	**126**	-	mesitylene	reflux	24 h.	SM	>95%
2	**126**	-	mesitylene	reflux	72 h.	SM	>95%
3	**126**	-	DMF	MW (150 ºC)	1 h.	SM	>95%
4	**126**	-	DMF	MW (180 ºC)	1 h.	SM	>95%
5	**126**	$BF_3{\cdot}Et_2O$	CH_2Cl_2	0 ºC	18 h.	SM	>95%
6	**126**	$BF_3{\cdot}Et_2O$	CH_2Cl_2	r.t.	18 h.	SM	>95%
7	**126**	$BF_3{\cdot}Et_2O$	CH_2Cl_2	reflux	18 h.	SM	>95%
8	**126**	$BF_3{\cdot}Et_2O$	mesitylene	reflux	14 h.	SM	>95%
9	**126**	BCl_3	CH_2Cl_2	r.t.	18 h.	SM	>95%
10	**126**	$TiCl_4$	CH_2Cl_2	r.t.	18 h.	SM	>95%
11	**126**	$TiCl_4$	CH_2Cl_2	reflux	24 h.	SM	>95%
12	**126**	$ZrCl_4$	CH_2Cl_2	r.t.	18 h.	SM	>95%
13	**127**	$BF_3{\cdot}Et_2O$	CH_2Cl_2	0 ºC	18 h.	SM	>95%
14	**127**	BCl_3	CH_2Cl_2	-40 ºC	18 h.	SM	>95%
15	**127**	BCl_3	CH_2Cl_2	r.t.	18 h.	**130**	60%
16	**127**	BCl_3	CH_2Cl_2	reflux	18 h.	mixture	-
17	**127**	$TiCl_4$	CH_2Cl_2	r.t.	18 h.	**131**	42%
18	**127**	$TiCl_4$	CH_2Cl_2	r.t.	6 h.	**131**	66%
19	**127**	$ZrCl_4$	CH_2Cl_2	reflux	16 h.	mixture	-
20	**127**	-	DMF	MW (180 ºC)	1 h.	SM	>95%
21	**128**	-	DMF	MW (180 ºC)	1 h.	SM	>95%
22	**128**	$BF_3{\cdot}Et_2O$	CH_2Cl_2	reflux	18 h.	SM	>95%
23	**128**	BCl_3	CH_2Cl_2	-40 ºC	18 h.	**132**	39%
24	**128**	BCl_3	CH_2Cl_2	r.t.	18 h.	**132**	67%
25	**128**	$TiCl_4$	CH_2Cl_2	r.t.	18 h.	**133**	59%
26	**128**	$TiCl_4$	CH_2Cl_2	r.t.	6 h.	**133**	76%
27	**128**	$ZrCl_4$	CH_2Cl_2	reflux	6 h.	mixture	-
28	**129**	$BF_3{\cdot}Et_2O$	CH_2Cl_2	0 ºC	18 h.	SM	>95%
29	**129**	BCl_3	CH_2Cl_2	r.t.	18 h.	**134**	62%
30	**129**	$TiCl_4$	CH_2Cl_2	r.t.	6 h.	**135**	73%
31	**129**	-	DMF	MW (180 ºC)	1 h.	SM	>95%

(a) Yields for isolated products after flash column chromatography purification
(b) As shown in the ^1H NMR spectrum of the crude product

As shown in **Table 2**, 1,4-bis(allyloxy)-2,3-dicyanobenzene **(126)** did not react under any of the conditions applied although temperatures and reaction times were increased far beyond normal conditions (entries 1-12). This could be explained as an effect of the cyano group (a small π acceptor) on the electronic cloud of the aromatic ring.[106]

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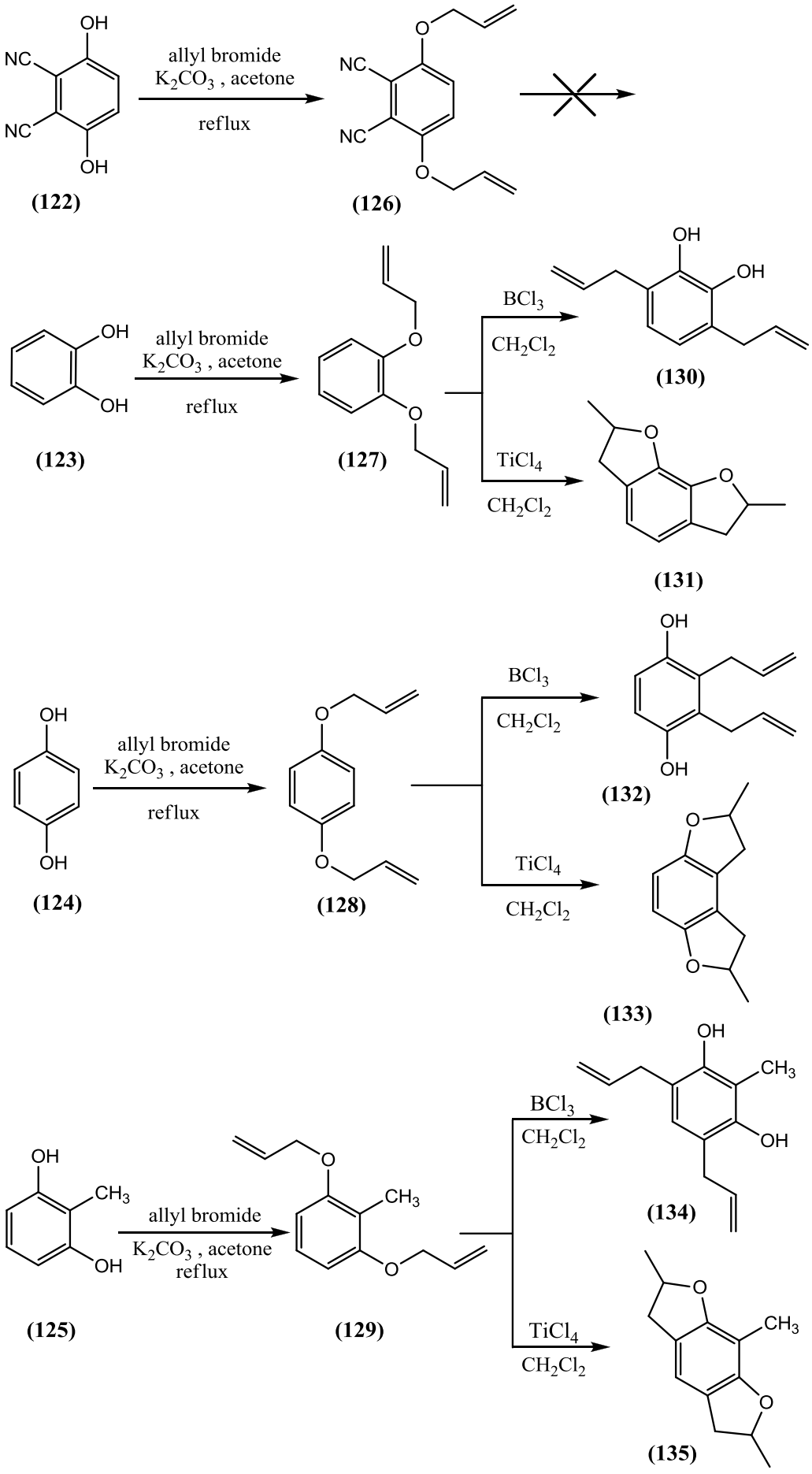
All compounds **(126-129)** were tested under microwave conditions. Although the solvent was changed from *N*,*N*-diethylaniline to *N*,*N*-dimethylformamide (a polar aprotic solvent which absorbs more microwave energy and generates heat energy to increase the reaction rate) and temperatures were increased to 180 ºC no reaction was observed (entries 3, 4, 20, 21 and 31).

Treatment of compounds **(127)**, **(128)** and **(129)** with boron trifluoride diethyl etherate did not yield any of the rearranged product (entries 5-8, 13, 22 and 28) whilst treatment with zirconium(IV) chloride produced a mixture of degradation compounds (entries 19 and 27). The only Lewis acids that reacted with the bisallylated compounds **(127)**, **(128)**, and **(129)** were boron trichloride and titanium(IV) chloride (entries 15, 17, 23-26, 29 and 30) **(Scheme 36)**.



Scheme 36: Lewis acid mediated Claisen rearrangement

As shown in **Scheme 36** and summarised in **Table 3** 1,4-bis(allyloxy)-2,3-dicyanobenzene **(126)** was unreactive under any of the conditions tried. Bisallylated derivatives **(127)**, **(128)**, **(129)** successfully reacted as expected with two of the Lewis acids tried.

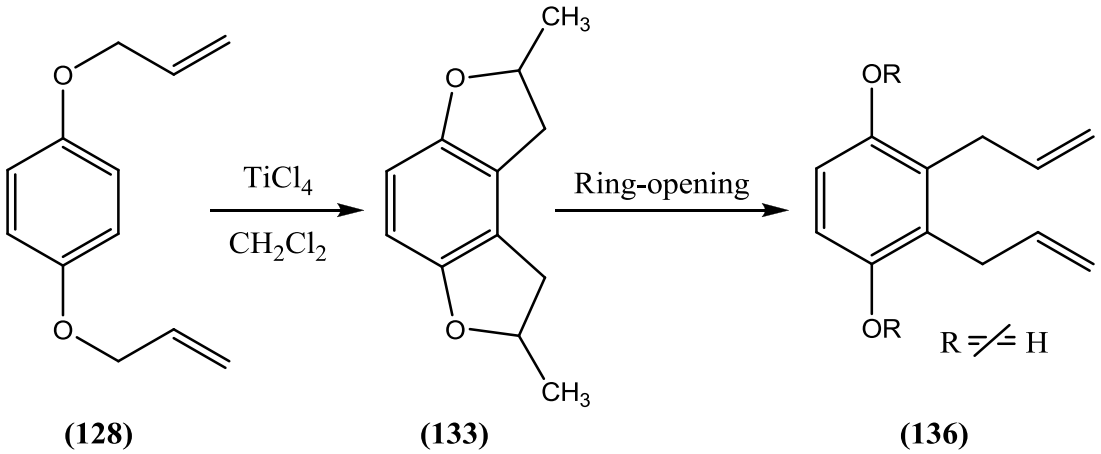
Table 3: Conditions to carry out the Lewis acid mediated Claisen rearrangement

Conditions / Compound	BCl_3 (r.t.)	$TiCl_4$ (r.t.)
126	SM	SM
127	**130** (60% yield)	**131** (66% yield)
128	**132** (67% yield)	**133** (76% yield)
129	**134** (62% yield)	**135** (73% yield)

As noted in **Table 3**, best conditions to achieve the Lewis acid mediated double Claisen rearrangement for compounds **(127)**, **(128)** and **(129)** were boron trichloride in dichloromethane at room temperature for 18 hours. Yields were very similar to the ones obtained for 1,4-bis(allyloxy)-2,3-dimethylbenzene **(117)**.

In order to obtain the dihydrofuran compounds **(131)**, **(133)** and **(135)** bisallylated derivatives **(127)**, **(128)** and **(129)** were treated with titanium(IV) chloride in the presence of dichloromethane at room temperature for 6 hours. Compounds **(131)**, **(133)** and **(135)** were obtained as a mixture of inseparable diastereomers. The diasteromeric ratios of **(131)**, **(133)** and **(135)** were assigned using ^{1}H NMR analysis being (14:1), (3:1) and (12:1) respectively. As shown in **Table 3** yields were from moderate to good (65%-75%) and it is good to notice that dihydrofuran compound yields were always higher than the ones obtained for the simple double Claisen rearrangement.

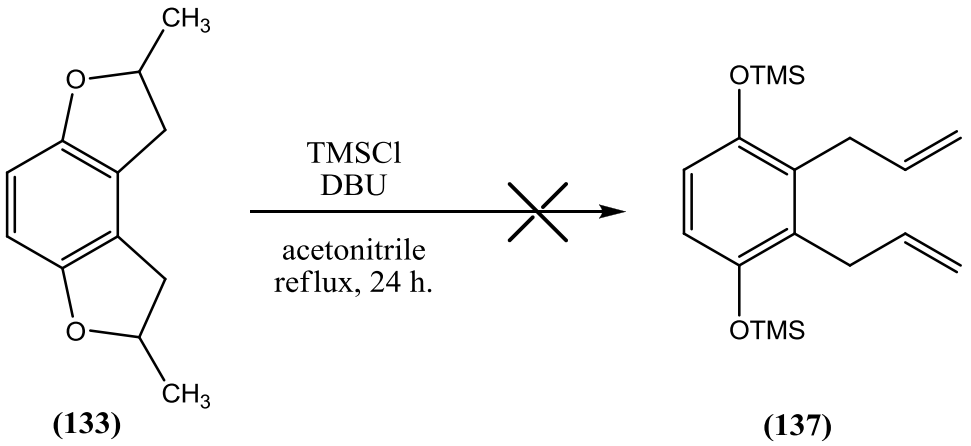
Once the conditions for the Lewis acid mediated double Claisen rearrangement were well defined, a ring-opening/protection methodology was proposed to obtain the protected alcohol needed for the next synthetic step. Prior results confirmed that cyclisation using titanium(IV) chloride led to higher than yields than double Claisen rearrangement making this one step methodology more suitable for obtaining the ring-closing metathesis precursor **(136)**. Vogel *et al.* carried out the dihydrofuran ring opening and subsequent protection of the free alcohol moiety in one step as outlined in **Scheme 37** using triethylamine and trimethylsilyl trifluoromethanesulfonate.[107]



(128) **(133)** **(136)**

Scheme 37: Ring-opening procedure to achieve bisallylated compounds

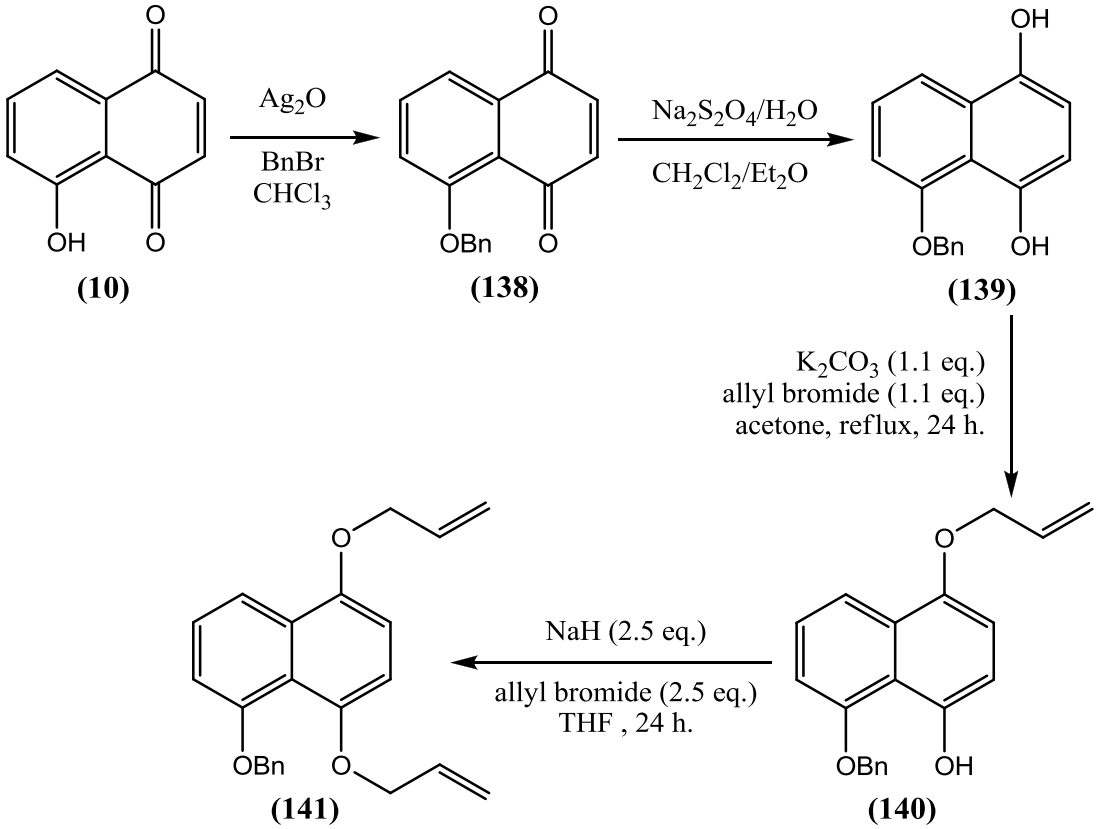
Using a similar approach, dihydrofuran compound **(133)** was treated with 3.0 equivalents of trimethylsilyl chloride in acetonitrile in the presence of a strong base such as 1,8-diazabicycloundec-7-ene (DBU) under reflux for 24 hours. Unfortunately, only starting material was recovered **(Scheme 38)**.



(133) **(137)**

Scheme 38: Attempted ring-opening reaction

Following with the investigation it was decided to apply the reaction conditions obtained to more functionalised compounds. It was proposed using as starting material juglone **(10)**, a suitable CD ring core generally used in previous synthesis towards tetracycline antibiotics **(Scheme 39)**.[108]



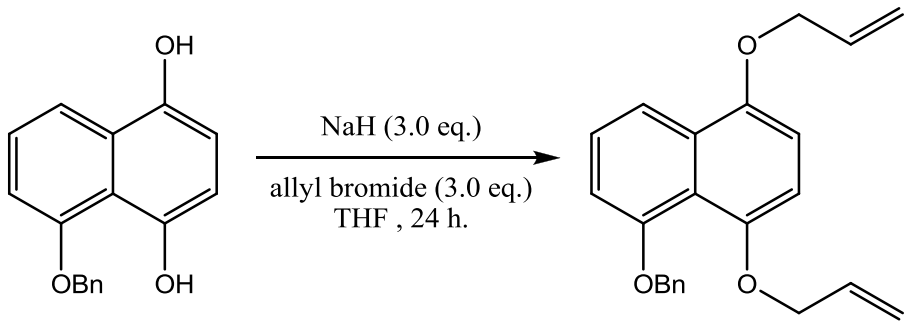
(10) **(138)** **(139)** **(140)** **(141)**

Scheme 39: Synthesis of 1,4-bis(allyloxy)-5-(benzyloxy)naphthalene (141)

Treatment of juglone **(10)** with 3.0 equivalent of silver(I) oxide and 3.0 equivalents of benzyl bromide in chloroform for 72 hours yielded *O*-benzylated compound **(138)** in 94% yield.[109] Reduction of quinone **(138)** to its corresponding hydroquinone **(139)** was achieved in 95% yield using a mixture of aqueous solution of sodium dithionite (8.5 equivalents) in the presence of dichloromethane.

Selective mono-allylation of naphthohydroquinone **(139)** was afforded cleanly in 82% yield using equivalents of potassium carbonate and allyl bromide in refluxing acetone for 24 hours. A stronger base like sodium hydride was needed to deprotonate the most hindered alcohol moiety. Allylation of **(140)** by treatment with sodium hydride and allyl bromide in tetrahydrofuran yielded bisallylated naphthohydroquinone **(141)** in 73% after purification.

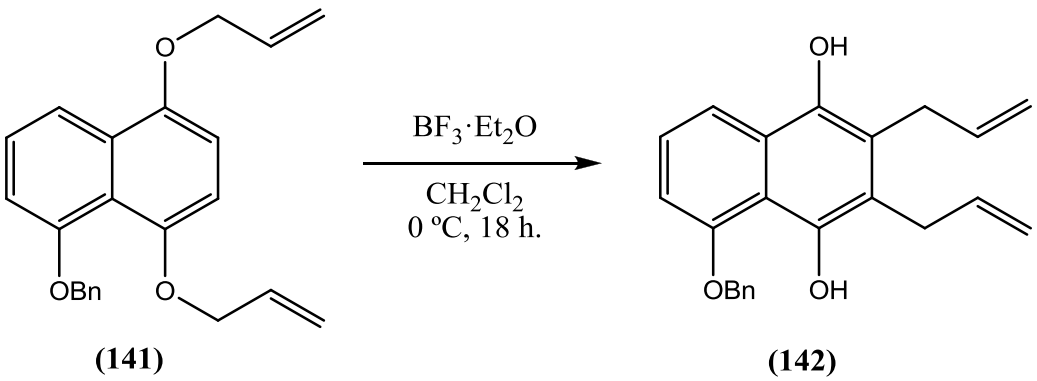
Direct double allylation of naphthohydroquinone **(139)** can be carried out using excess of sodium hydride (3.0 equivalents) and allyl bromide in tetrahydrofuran for 24 hours to obtain **(141)** in 66% yield **(Scheme 40)**.



(139) **(141)**

Scheme 40: 1 step double allylation reaction

With key intermediate **(141)** obtained in 60% overall yield after four steps it was decided to apply the conditions obtained initially for the Lewis acid mediated double Claisen rearrangement **(Scheme 41)**.



(141) **(142)**

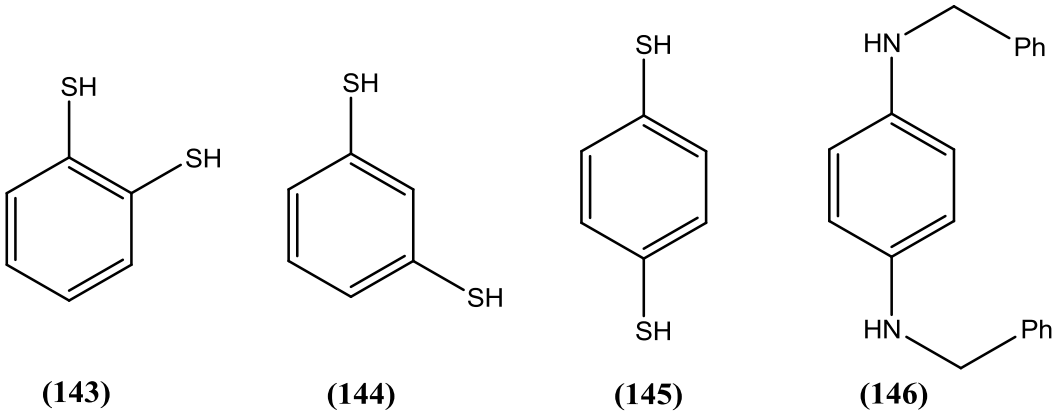
Scheme 41: Lewis acid mediated double Claisen rearrangement of (141)

The ^1H NMR crude spectrum showed that when bisallylated naphthohydroquinone **(141)** was treated with boron trifluoride diethyl etherate in dichloromethane at 0 ºC for 18 hours the rearranged product **(142)** was obtained. However, the reaction mixture showed other impurities and the crude yield was very low (40%). When the rearrangement was carried out under thermal conditions results were very similar. In the view of the results obtained other reagents should be investigated to afford target **(142)** purer and with better yields.

With an established procedure in place to carry out the Lewis acid mediated double Claisen rearrangement for hydroquinone derivatives it was decided to investigate the applications of this methodology to carry out double thio- and aza-Claisen rearrangements.

2.2 DOUBLE THIO- AND AZA-CLAISEN REARRANGEMENTS

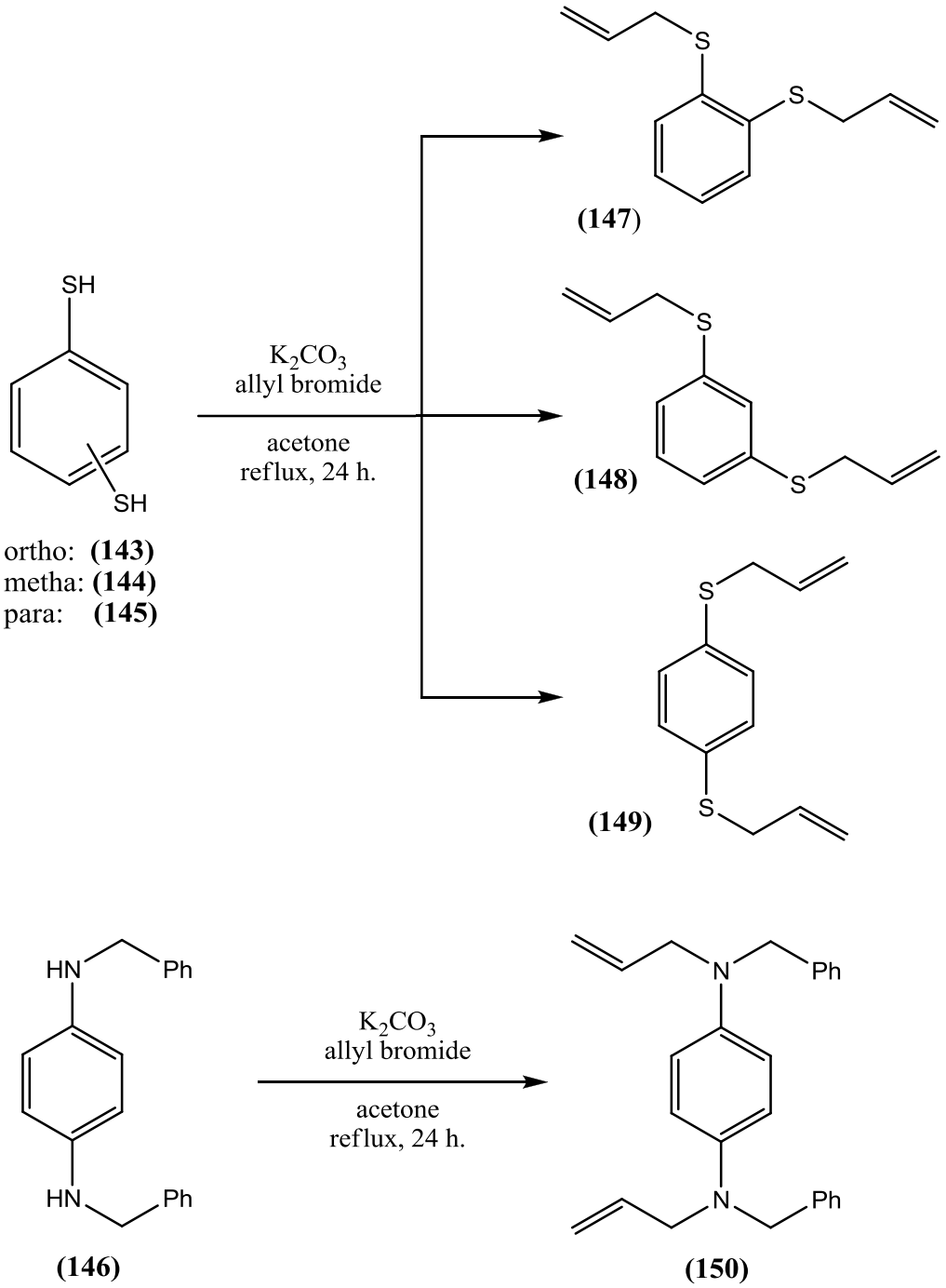
In the pursuit of a synthetic methodology towards fused carbon rings with different heteroatoms to afford more complex compounds, thio- and aza-Claisen rearrangements arise as an interesting tool. For this reason benzene-1,2-dithiol **(143)**, benzene-1,3-dithiol **(144)**, benzene-1,4-dithiol **(145)** and *N,N'*-dibenzylbenzene-1,4-diamine **(146)** were chosen for study **(Figure 22)**.



(143) **(144)** **(145)** **(146)**

Figure 22: Benzenedithiol and benzenediamine derivatives

Typical allylation conditions were applied to **(143)**, **(144)**, **(145)** and **(146)** to yield the corresponding bisallylated compounds **(147)**, **(148)**, **(149)** and **(150)** with a 87%, 89%, 93% and 83% yield respectively **(Scheme 42)**.



Scheme 42: Bisallylated benzenedithiols and benzenediamine

Treatment of bisallylated compounds **(147-150)** with boron trifluoride diethyl etherate in dichloromethane at 0 ºC for 18 hours showed no positive results and only starting material was recovered (entries 1, 7, 17 and 20). For this reason a new battery of conditions were applied **(Table 4)**.

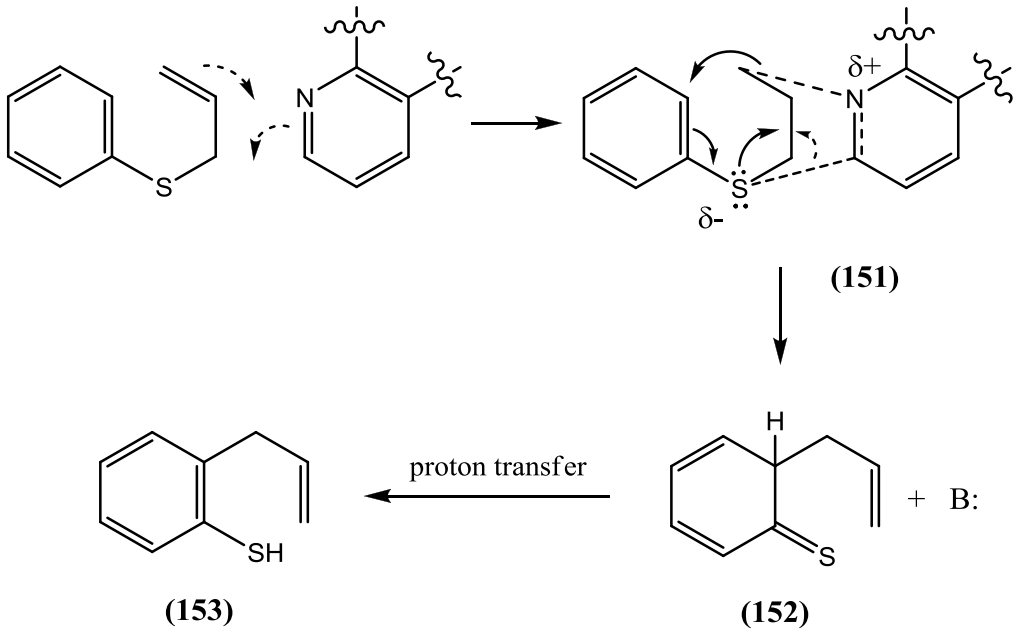
Table 4: Lewis acid mediated double thio- and aza-Claisen rearrangement

Entry	Compound	Lewis Acid	Solvent	Temperature	Time	Product [(b)]	Yield[(a)]
1	**150**	$BF_3{\cdot}Et_2O$	CH_2Cl_2	0 ºC	18 h.	SM	93%
2	**150**	$TiCl_4$	CH_2Cl_2	r.t.	6 h.	SM	92%
3	**150**	BCl_3	CH_2Cl_2	r.t.	24 h.	SM	89%
4	**150**	-	$PhEt_2N$	MW(180 ºC)	1 h.	SM	78%
5	**150**	-	mesitylene	reflux	48 h.	SM	90%
6	**150**	$BF_3{\cdot}Et_2O$	xylenes	reflux	24 h.	SM	87%
7	**147**	$BF_3{\cdot}Et_2O$	CH_2Cl_2	0 ºC	18 h.	SM	88%
8	**147**	-	mesitylene	reflux	48 h.	SM	89%
9	**147**	-	toluene	r.t.	24 h.	SM	90%
10	**147**	-	toluene	reflux	24 h.	SM	89%
11	**147**	-	quinoline	reflux	24 h.	SM	94%
12	**147**	-	quinoline	reflux	72 h.	SM	85%
13	**147**	BCl_3	CH_2Cl_2	reflux	18 h.	SM	88%
14	**147**	$TiCl_4$	CH_2Cl_2	reflux	6 h.	SM	84%
15	**147**	$TiCl_4$	acetonitrile	r.t	24 h.	SM	90%
16	**147**	$TiCl_4$	CH_2Cl_2	reflux	24 h.	SM	86%
17	**148**	$BF_3{\cdot}Et_2O$	CH_2Cl_2	0 ºC	18 h.	SM	91%
18	**148**	-	mesitylene	reflux	48 h.	SM	89%
19	**148**	BCl_3	CH_2Cl_2	reflux	72 h.	SM	92%
20	**149**	$BF_3{\cdot}Et_2O$	CH_2Cl_2	0 ºC	18 h.	SM	89%
21	**149**	$TiCl_4$	quinoline	reflux	72 h.	SM	93%

(a) Yields for isolated products after flash column chromatography purification
(b) As shown in the ^1H NMR spectrum of the crude product

The solvent was changed from mesitylene to quinoline, an amine base solvent, to avoid irreversible propenylization of the substrate (entries 11, 12 and 21).[110] As shown in **Scheme 43**, the heterocyclic amine delocalised the electronic cloud in the allylic thiophenyl ether configuration **(151).** The six membered ring intermediate **(151)** rearranged to form **(152)** which led to the *o*-allylthiophenol **(153)** after tautomerisation. Reaction times were increased to obtain the rearranged derivatives. However, only starting material was recovered from the reaction mixture when it was applied to

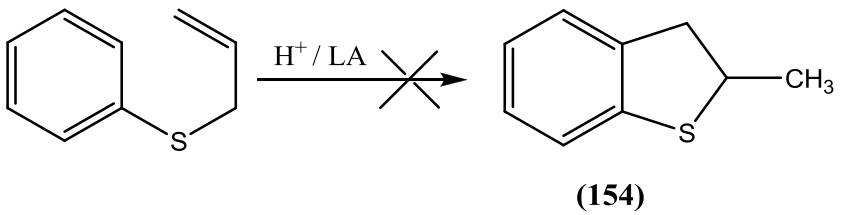
compounds **147-150**. The use of polar solvents did not make any difference to the results obtained.



Scheme 43: Formation of the stabilised intermediate (151)

It has been reported that acid catalysis of the thio-Claisen rearrangement could easily produce dihydrobenzothiophene derivatives **(154)** by cyclisation. The use of Lewis acid catalysis has not been reported and only some palladium and nickel complexes have been used to catalyse the thio-Claisen rearrangement.[111] When Lewis acids were applied to compounds **(147-150)** no rearrangement was observed.

It is worth noting that neither of the by-products detailed by other researchers (**Scheme 44**, **154**) nor even traces of single rearranged product were obtained.[112] Only starting material was recovered from the reaction mixture in our reactions.

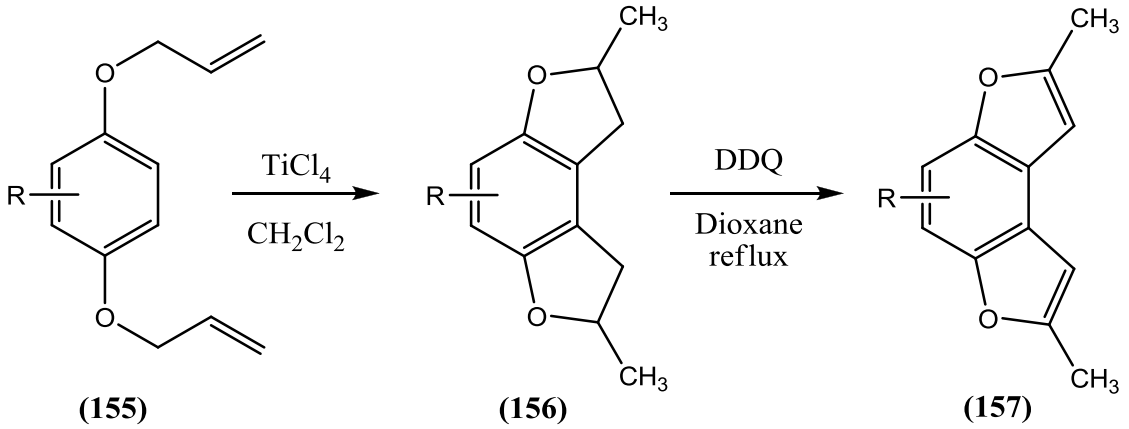


Scheme 44: Potential formation of dihydrobenzothiophene by-product (154)

It is known that thio- and aza-Claisen rearrangements need stronger conditions than Claisen rearrangement but as **Table 4** shows none of the conditions applied promoted the reaction.[113]

2.3 SYNTHESIS OF BENZODIFURANS

The structure of benzodifurans leads them to have interesting electronic properties and an ability to act as organic semiconductors.[89,99] Using the knowledge acquired during the development of our new conditions for a Lewis acid mediated double Claisen rearrangement, a novel synthetic route towards benzodifuran compounds was proposed **(Scheme 45)**.



Scheme 45: Oxidation proposal for the synthesis of benzodifuran compounds

The conditions from **Table 3** were applied to bisallylated compounds **(155)** yielding dihydrofuran precursors **(156).** Subsequent oxidation using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane was expected to produce the corresponding benzofuran derivatives **(157)**.[114]

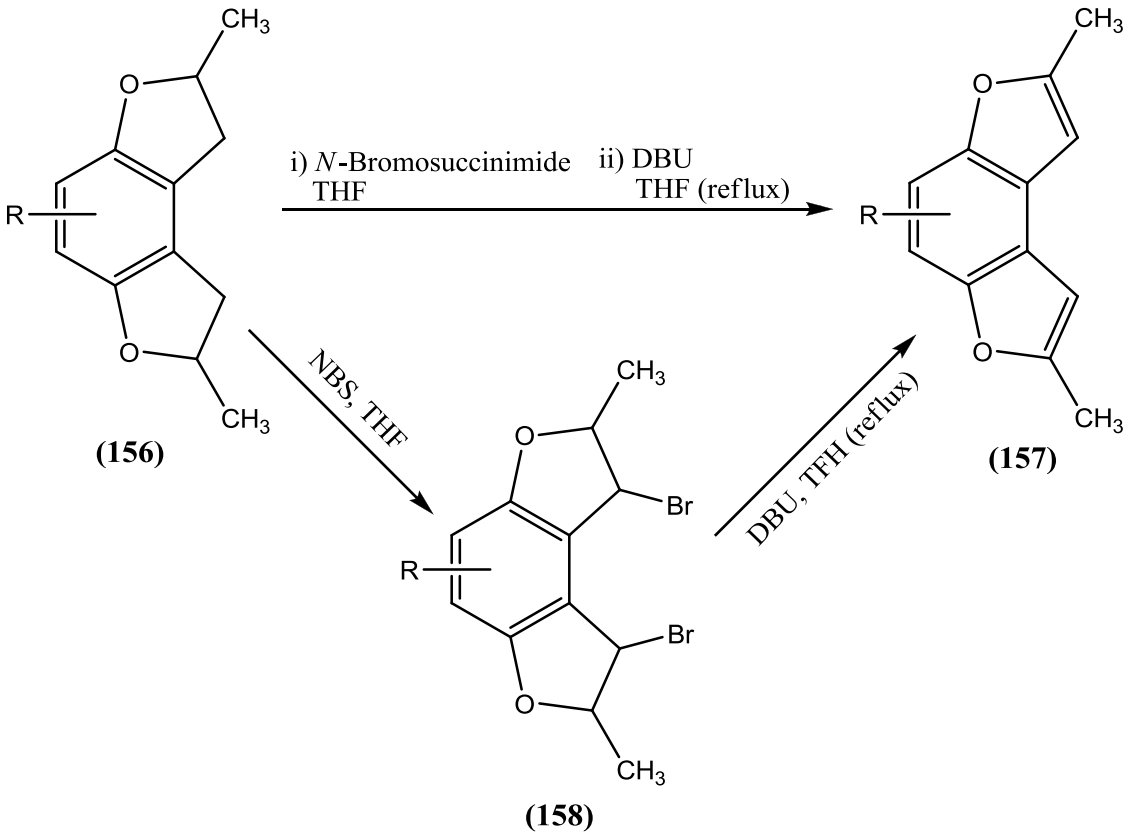
Table 5: Oxidation conditions attempted to yield benzodifuran compounds

Compound	Solvent	Time	Oxidation agent	Temperature	Product [(a)]
135	dioxane	4 h.	DDQ (3.0 eq.)	reflux	complex mixture
135	dioxane	24 h.	DDQ (3.0 eq.)	reflux	complex mixture
133	dioxane	24 h.	DDQ (4.0 eq.)	reflux	complex mixture
133	toluene	48 h.	DDQ (3.0 eq.)	reflux	complex mixture
135	toluene	72 h.	DDQ (3.0 eq.)	reflux	complex mixture
131	toluene	72 h.	DDQ (4.0 eq.)	reflux	complex mixture
133	DMF	4 h.	DDQ (3.0 eq.)	reflux	complex mixture

(a) As shown in the ^{1}H NMR spectrum of the crude product

Unfortunately, as shown in **Table 5**, all results were unsuccessful and no starting material or expected products were obtained after reaction. No peaks corresponding to final products were observed by analysis of the crude reaction mixture by ^{1}H NMR. An excess of DDQ and the formation of intractable reaction by-products in the reaction mixture made isolation and purification of any single product impossible.

For these reasons, and keeping the idea of an oxidation procedure, new conditions were proposed to oxidise benzodihydrofuran compounds **(156)** to their corresponding benzodifuran derivatives **(157)**. Dihydrofuran side-chain bromination by means of *N*-bromosuccinimide in the presence of tetrahydrofuran and subsequent elimination using a strong base such as 1,8-diazabicycloundec-7-ene (DBU) could lead to benzodifuran **(157) (Scheme 46)**.[115]



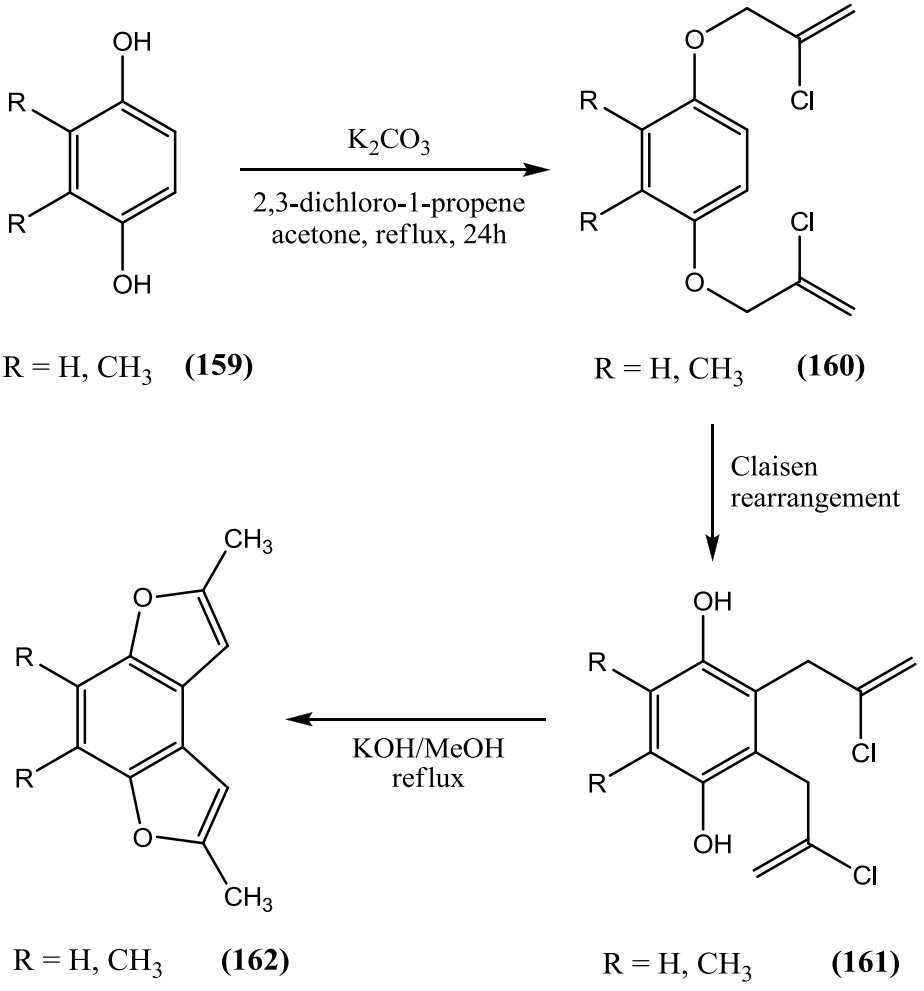
Scheme 46: Generation of benzofuran targets

Benzodihydrofurans **(133)** and **(135)** were reacted with 3.0 equivalents of *N*-bromosuccinimide in tetrahydrofuran for 4 hours at room temperature. After removing the solvent a solution of 1,8-diazabicycloundec-7-ene in tetrahydrofuran was added and the reaction mixture was heated to reflux for 18 hours. After column chromatography purification over silica gel using a mixture of petrol/ethyl acetate as eluent a 9% of an unknown mixture was recovered. Attempts to isolate the bromo derivative **(158)** after reaction with *N*-bromosuccinimide in tetrahydrofuran were also unproductive and no peaks of the expected compound were observed in the ^{1}H NMR spectrum.

Due to all the problems observed in the oxidation procedure a change in the approach to benzodifuran compounds using double Claisen rearrangement was proposed **(Scheme 47)**. Instead of using unsubstituted allyl groups, 2-chloro substituted

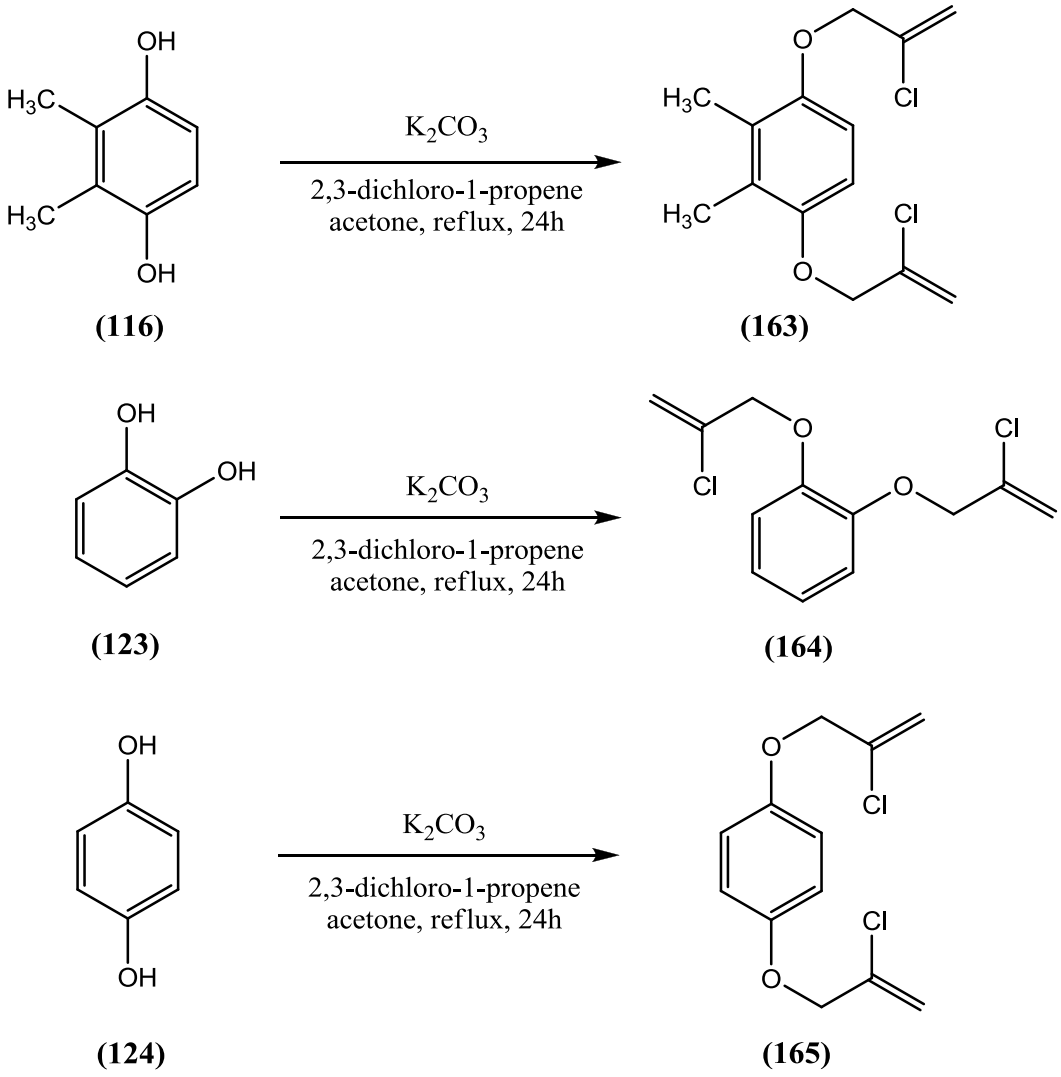
propenes were used in order to carry out the elimination/cyclisation towards the benzodifuran derivatives[116].

Allylation of hydroquinone **(159)** by treatment with potassium carbonate and 2,3-dichloro-1-propene in refluxing acetone for 24 hours could produce chloro derivative **(160)**. Double Claisen rearrangement of chloro-hydroquinone **(160)** could lead to diol **(161)** which should undergo intramolecular cyclisation and dechlorination to yield **(162)** in the presence of methanolic potassium hydroxide at reflux **(Scheme 47)**.



Scheme 47: Elimination/cyclisation synthetic route towards benzofuran derivatives

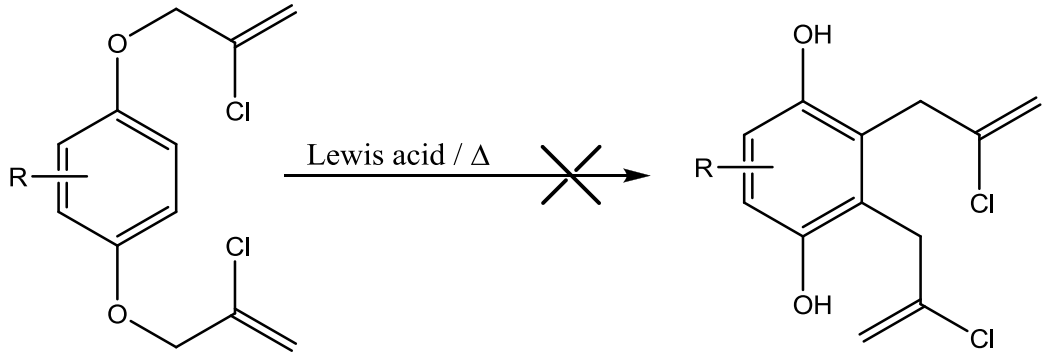
A new battery of chloro-compounds was synthesised **(Scheme 48)** in order to explore the reaction conditions required to achieve the double Claisen rearrangement and subsequent chemistry. Compounds **(116)**, **(123)** and **(124)** were refluxed in acetone for 24 hours in the presence of potassium carbonate and 2,3-dichloro-1-propene to yield compounds **(163)**, **(164)** and **(165)** in a 52%, 45% and 56% yield respectively.



Scheme 48: Synthesis of substituted 2-chloropropenehydroquinones

The original conditions used for the rearrangement of 1,4-bis(allyloxy)-2,3-dimethylbenzene **(117)** were applied to compound **(163)**, but after 18 hours only starting

material was recovered (Table 6, entry 1). For this reason alternative conditions were attempted for rearrangement of compound **(165)** (**Table 6)**.



Scheme 49: Attempted rearrangement of substituted 2-chloropropenehydroquinones

Table 6: Rearrangement conditions for (165)

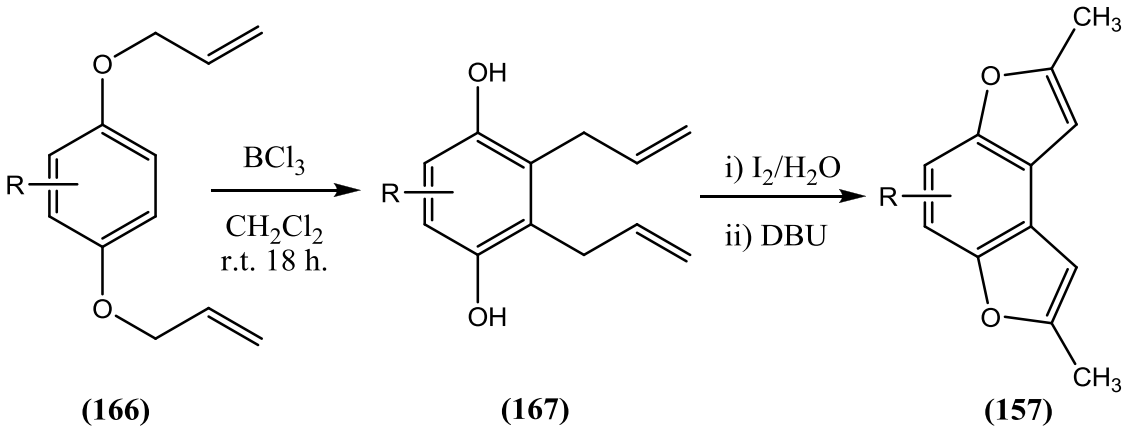
Entry	Compound	Lewis Acid	Solvent	Temp.	Time	Product[(b)]	Yield[(a)]
1	**163**	$BF_3 \cdot Et_2O$	CH_2Cl_2	0 ºC	18 h.	SM	95%
2	**165**	-	mesitylene	reflux	24 h.	SM	>95%
3	**165**	-	DMF/H_2O	reflux	24 h.	SM	>95%
4	**165**	-	DMF/H_2O	reflux	48 h.	SM	>95%
5	**165**	$TiCl_4$	CH_2Cl_2	r.t.	6 h.	SM	>95%
6	**165**	BCl_3	CH_2Cl_2	r.t.	18 h.	SM	>95%
7	**165**	BCl_3	CH_2Cl_2	reflux	24 h.	SM	>95%
8	**165**	BCl_3	CH_2Cl_2	reflux	48 h.	SM	>95%

(a) Yields for isolated products after flash column chromatography purification
(b) As shown in the ^1H NMR spectrum of the crude product

As shown in **Table 6** when the reaction mixture was heated in refluxing mesitylene (entry 2) or polar solvents (entries 3 and 4) no reaction was observed **(Scheme 49)**. Addition of Lewis acids to the reaction mixture under heat did not yield any of the expected products either (entries 5-8). The presence of a chloro substituent in the aliphatic chain has been studied previously by Carpenter *et al*. Predictions obtained applying a Hückel molecular orbital (HMO) model for a π donor such as chloro showed

a significant increase in $\Delta H^{\neq}$ which would imply an increase of the energy needed to carry out the rearrangement.[117] That could explain why no rearranged product was achieved.

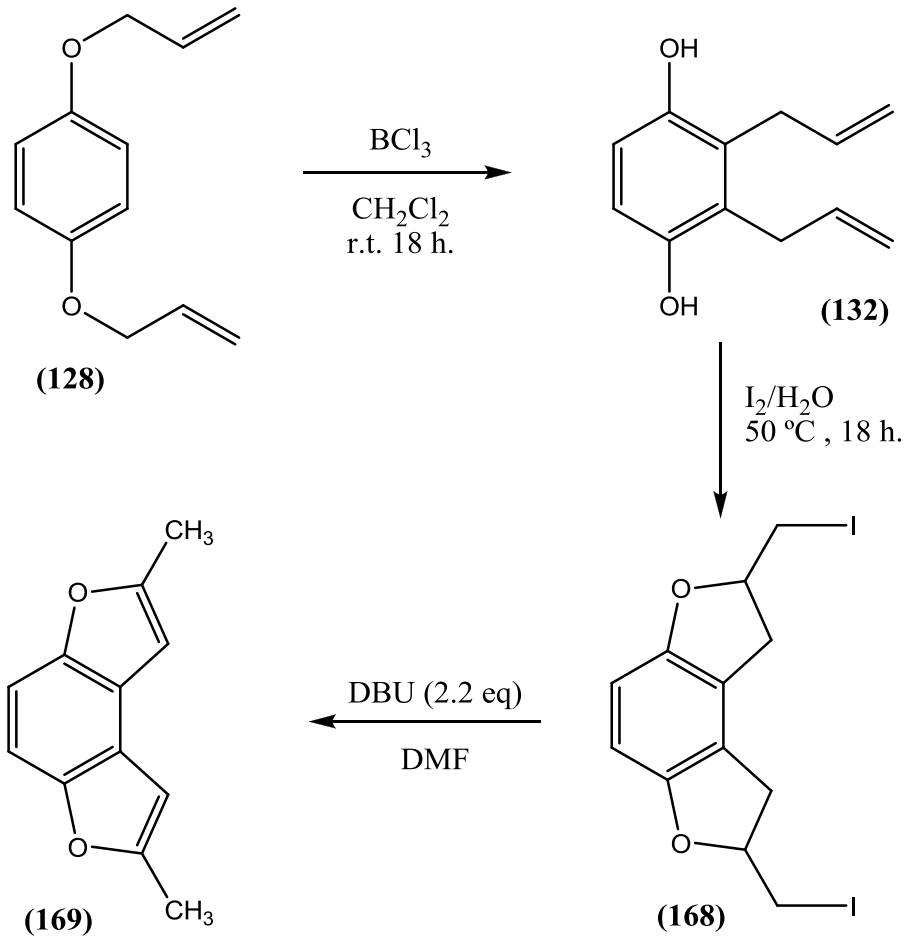
As the synthetic pathways from benzodihydrofurans **(156)** or chloro-substituted bisallylated compounds **(163-165)** to achieve the benzodifuran compounds **(157)** were not successful a new synthetic route was planned. Claisen rearrangement of bisallylated hydroquinones **(166)** would produce hydroquinones **(167)**. Iodocyclisation of hydroquinones **(167)** by treatment with iodine in water and subsequent elimination using a base would lead to benzodifuran derivatives **(157) (Scheme 50)**.[118]



(166) **(167)** **(157)**

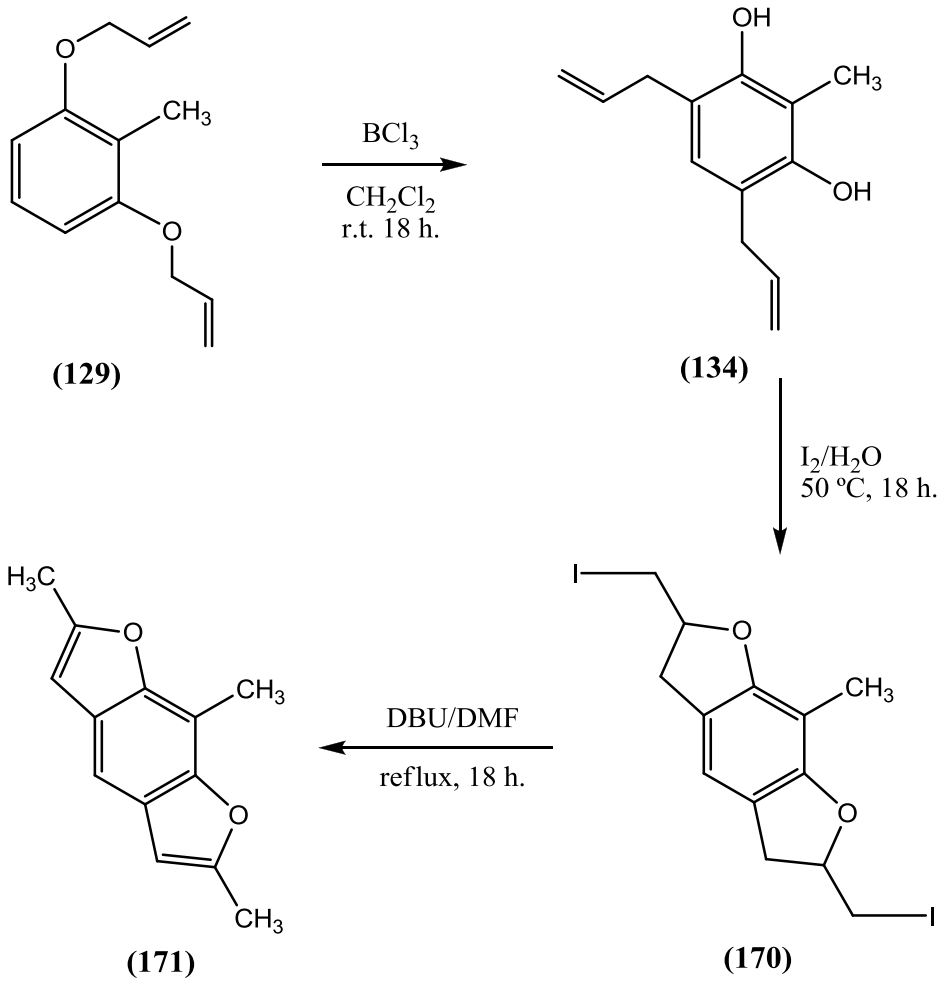
Scheme 50: Iodocyclisation/elimination synthesis of benzodifuran compounds (157)

The first step was carried out on substrate **(128)** using the optimum conditions developed previously for the Lewis acid mediated double Claisen rearrangement **(Table 3)**. Rearranged compound **(132)** was reacted with an excess of iodine (2.5 eq.) and water and heated to 50 ºC for 18 hours to achieve dihydrobenzodifuran **(168)** in 65% yield after intramolecular cyclisation. Elimination of iodine moiety **(168)** in refluxing dimethylformamide in the presence of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) led to the desired benzodifuran compound **(169)** in 73% yield after purification **(Scheme 51)**.



Scheme 51: Synthesis of 2,7-dimethylbenzofuro[5,4-*b*]furan (169)

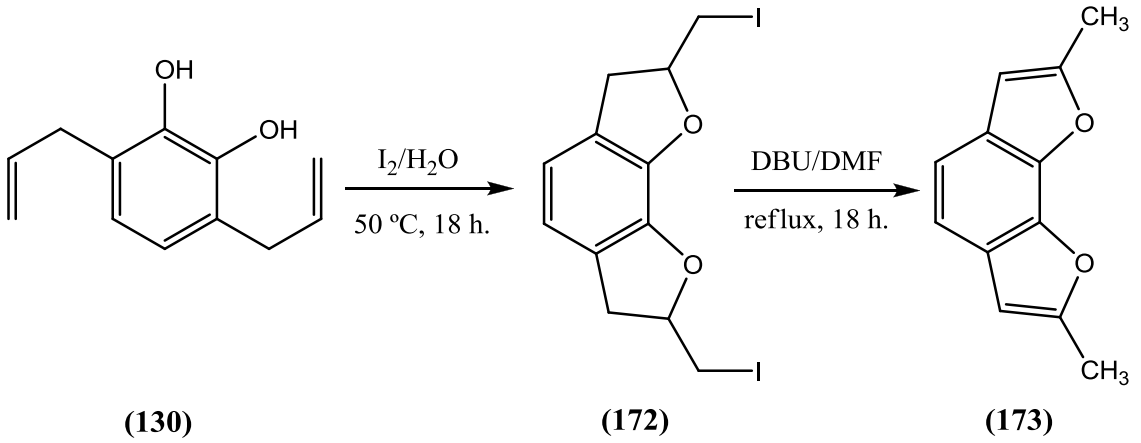
The same procedure was applied to 1,3-bis(allyloxy)-2-methylbenzene **(129)** to afford benzodifuran **(171)** in 45 % overall yield. Both dihydrobenzodifuran derivatives **(168)** and **(170)** were isolated as a mixture of inseparable diastereomers (1:1) and purified to remove all the excess of iodine but further research proved that one pot reaction was equally as successful and no isolation of the iodolactone derivative was needed **(Scheme 52)**.



(129) (134) (171) (170)

Scheme 52: One-pot iodocyclisation/elimination procedure

When reaction conditions were applied to catechol **(123)** yields dropped drastically. Dihydrobenzodifuran derivative **(172)** was isolated in 29% yield as a mixture of diastereomers (1:1) and subsequent elimination produced benzodifuran **(173)** in 35% yield **(Scheme 53)**.



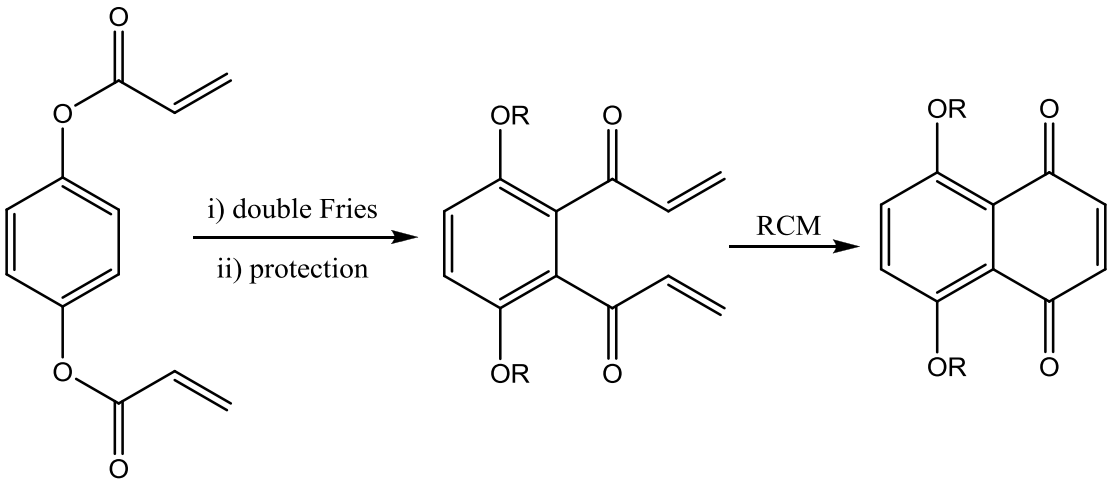
(130) **(172)** **(173)**

Scheme 53: Synthesis of 2,7-dimethylbenzofuro[7,6-*b*]furan (173)

The direct conversion of bisallylated compounds **(128-130)** to their corresponding benzodifuran compounds **(168-172)** was successfully achieved by applying the iodocyclisation/elimination methodology **(Scheme 50)**. It can be concluded that a feasible procedure for the synthesis of benzodifuran derivatives has been developed.

2.4 DOUBLE FRIES REARRANGEMENT

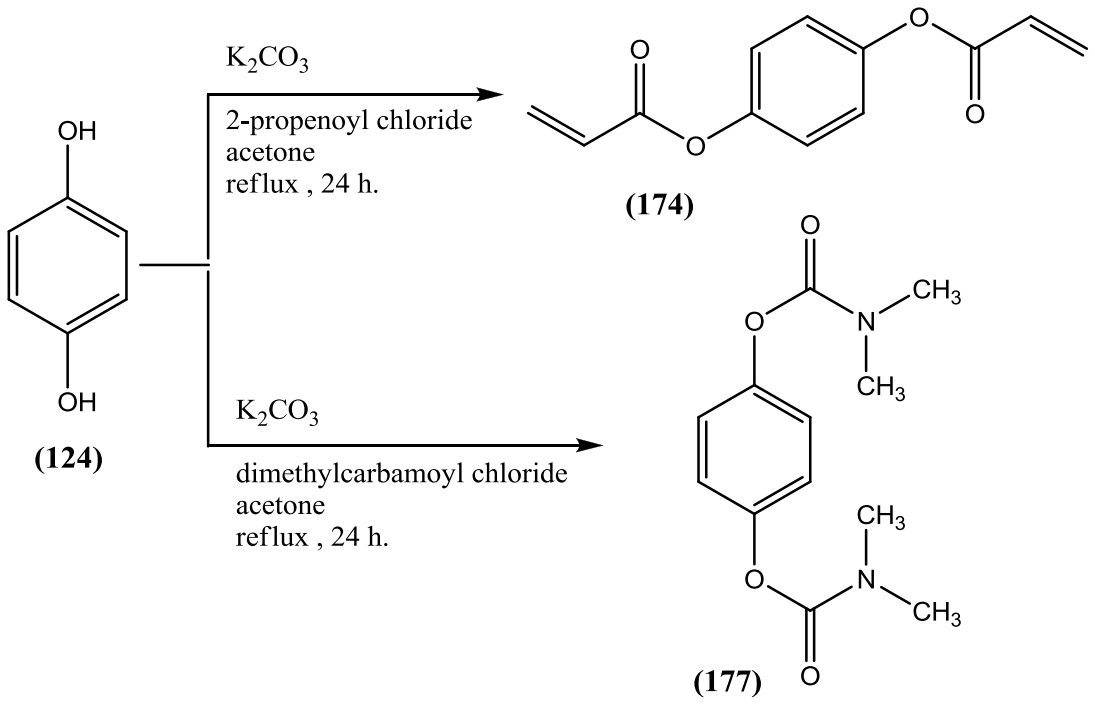
As mentioned previously, our proposed iterative methodology towards linear fused carbon rings consisted mainly of three steps: a double Claisen rearrangement, ring-closing metathesis and oxidation/rearomatisation. The use of a double Fries rearrangement would short the synthetic route avoiding the potentially problematic benzylic oxidation **(Scheme 54)**.



(174) **(175)** **(176)**

Scheme 54: Proposed tandem double Fries rearrangement-RCM synthesis of new fused rings

Up to date no double Fries rearrangement applied to the same ring has been reported. For this reason, single Fries rearrangement condition were extrapolated and applied to 1,4-phenylene diacrylate **(174)** and 1,4-phenylene bis(dimethylcarbamate) **(177)**.[119] Hydroxyquinone **(124)** was acylated by treatment with 2.5 equivalents of potassium carbonate in refluxing acetone for 24 hours in the presence of 2.5 equivalents of 2-propenoyl chloride and dimethylcarbamoyl chloride to achieve compounds **(174)** and **(177)** in 81% and 89% yield respectively **(Scheme 55)**.



Scheme 55: Synthesis of bisacylated derivatives

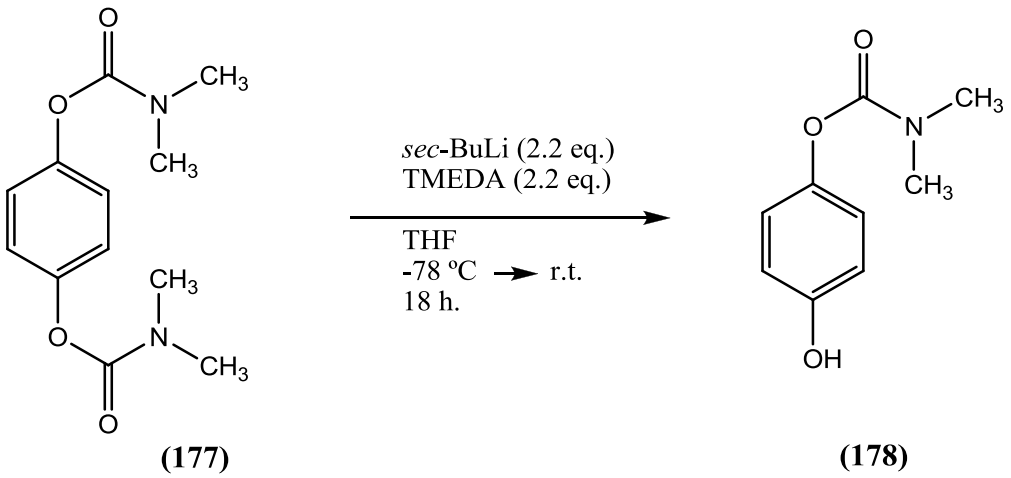
The conversion of bisacylated compounds **(174)** and **(177)** to their corresponding doubly rearranged products by modification of the conditions achieved by Snieckus was attempted **(Table 7)**. Snieckus carried out single Fries rearrangement using 1.1 equivalents of *sec*-butyllithium and *N,N,N',N'*-tetramethylethylenediamine in THF at -78 ºC and the resulting lithiated species were warmed up to room temperature over 10-12 hours.[120]

Table 7: Attempted double Fries rearrangement conditions

Entry	Compound	Base	Additive	Equival.	Time	Temperature	Product [(b)]	Yield[(a)]
1	**174**	*sec*-BuLi	TMEDA	2.2	18 h.	-78 ºC→r.t.	SM	>95%
2	**174**	*sec*-BuLi	TMEDA	6.0	18 h.	-78 ºC→r.t.	degradation	-
3	**174**	LDA	-	2.2	18 h.	-78 ºC→r.t.	SM	>95%
4	**177**	*sec*-BuLi	TMEDA	2.2	18 h.	-78 ºC→r.t.	**178**	74%
5	**177**	*sec*-BuLi	TMEDA	6.0	18 h.	-78 ºC→r.t.	degradation	-
6	**177**	LDA	-	2.2	18 h.	0 ºC→r.t.	**177**	>95%

(a) Yields for isolated products after flash column chromatography purification
(b) As shown in the ^{1}H NMR spectrum of the crude product

Our first thoughts were to double the equivalents of base and additive used by Snieckus in the single Fries rearrangement. As shown in **Table 7**, treatment of **(174)** and **(177)** with 2.2 equivalents of *sec*-butyllithium and *N,N,N',N'*-tetramethylethylenediamine in tetrahydrofuran at -78 ºC and heated to room temperature over 18 hours produced only starting material **(174)** and deacylation compound **(178)** **(Scheme 56)** respectively (entries 1 and 4). Adding extra excess (6.0 equivalents) of *sec*-butyllithium and TMEDA to 1,4-phenylene diacrylate **(174)** and 1,4-phenylene bis(dimethylcarbamate) **(177)** yielded a mixture deacylation and side reactions compounds (entries 2 and 5). When bisacylated compounds **(174)** and **(177)** were treated with 2.2 equivalents of lithium diisopropylamine in tetrahydrofuran at 0 ºC and heated to room temperature over 18 hours only starting material was recovered from the reaction mixture (entries 3 and 6).



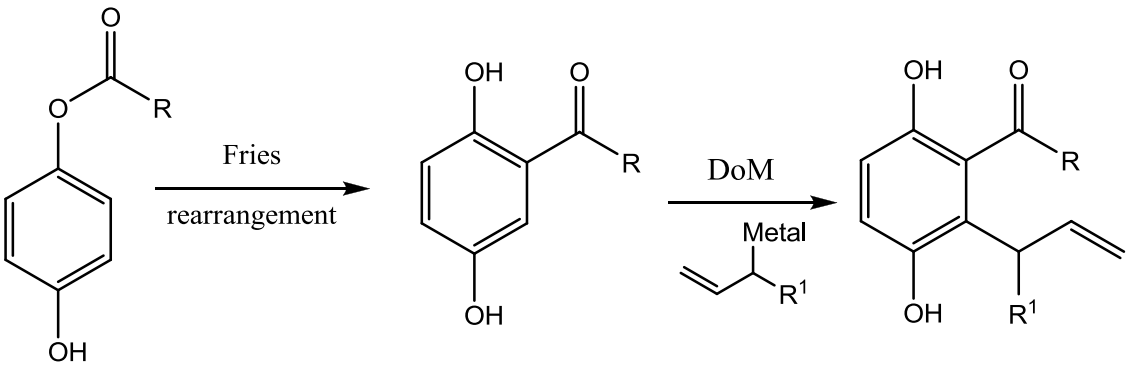
(177) **(178)**

Scheme 56: Deacylation reaction

In the light of the results obtained it was concluded that double Fries rearrangement is disfavoured because of inevitable ring deactivation and the harsh reaction conditions resulted in mono-deacylation or degradation compounds. This is perhaps reflected by the lack of evidence of double Fries rearrangements in the literature.

2.5 MIXED FRIES-CLAISEN REARRANGEMENT

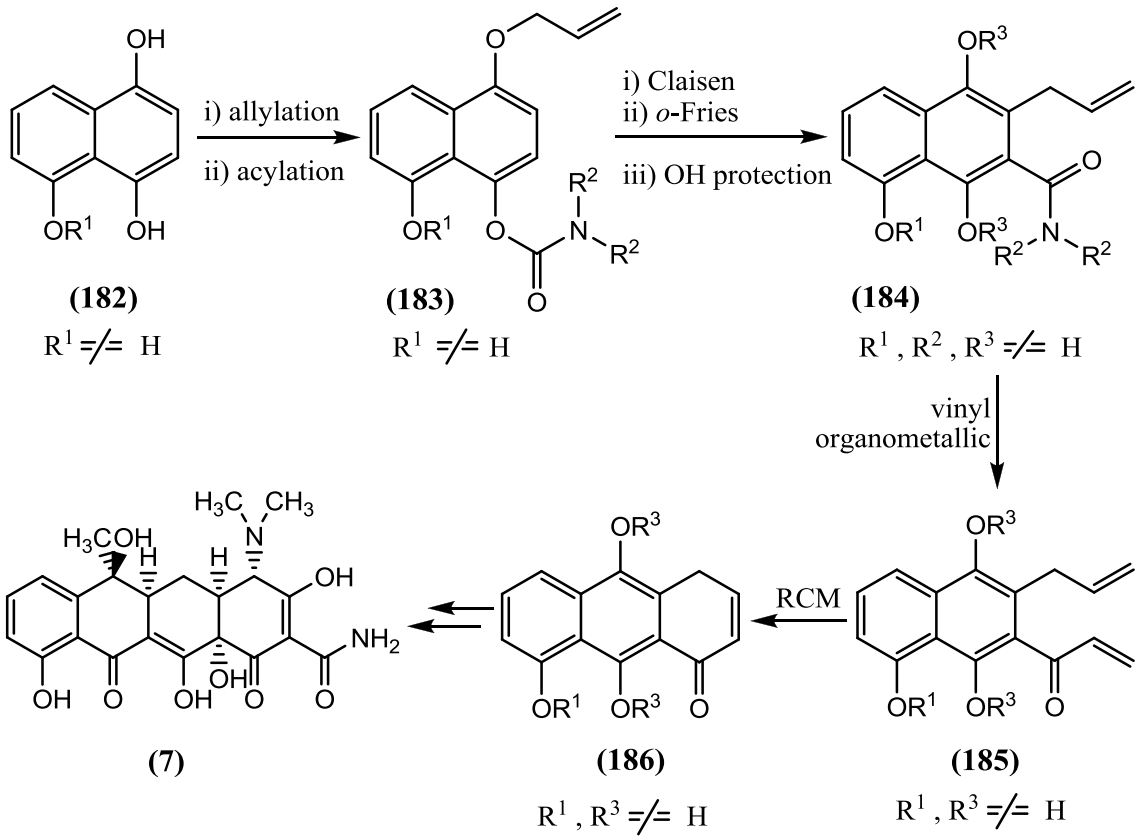
Failing to achieve the double Fries rearrangement, our efforts were then focused into the development of a novel tandem Fries-Claisen reaction. To date, previous synthesis of allyl-hydroxyphenyl ketone derivatives **(181)** have involved a Fries rearrangement and subsequent directed *ortho* metalation (DoM) **(Scheme 57)**.[121]



R =/= H **(179)** **(180)** **(181)**

Scheme 57: Fries-DoM mediated synthesis of allyl-enones

Although a mixed Fries-Claisen rearrangement is not a formal iterative route its advantages make this novel route very promising **(Scheme 58)**. The use of the knowledge previously acquired on juglone **(10)** to proceed with a selective mono-allylation on hydroquinone **(182)** would allow acylation onto the required position, **(183)**. Tandem Fries-Claisen rearrangement and subsequent protection would produce rearranged compound **(184)**. Displacement of the amide moiety with vinyl organometallic reagents could afford enone **(185)** which could undergo RCM to yield tricyclic compound **(186)**. Transformation of **(186)** into tetracycline **(7)** has been reported in previous synthesis.

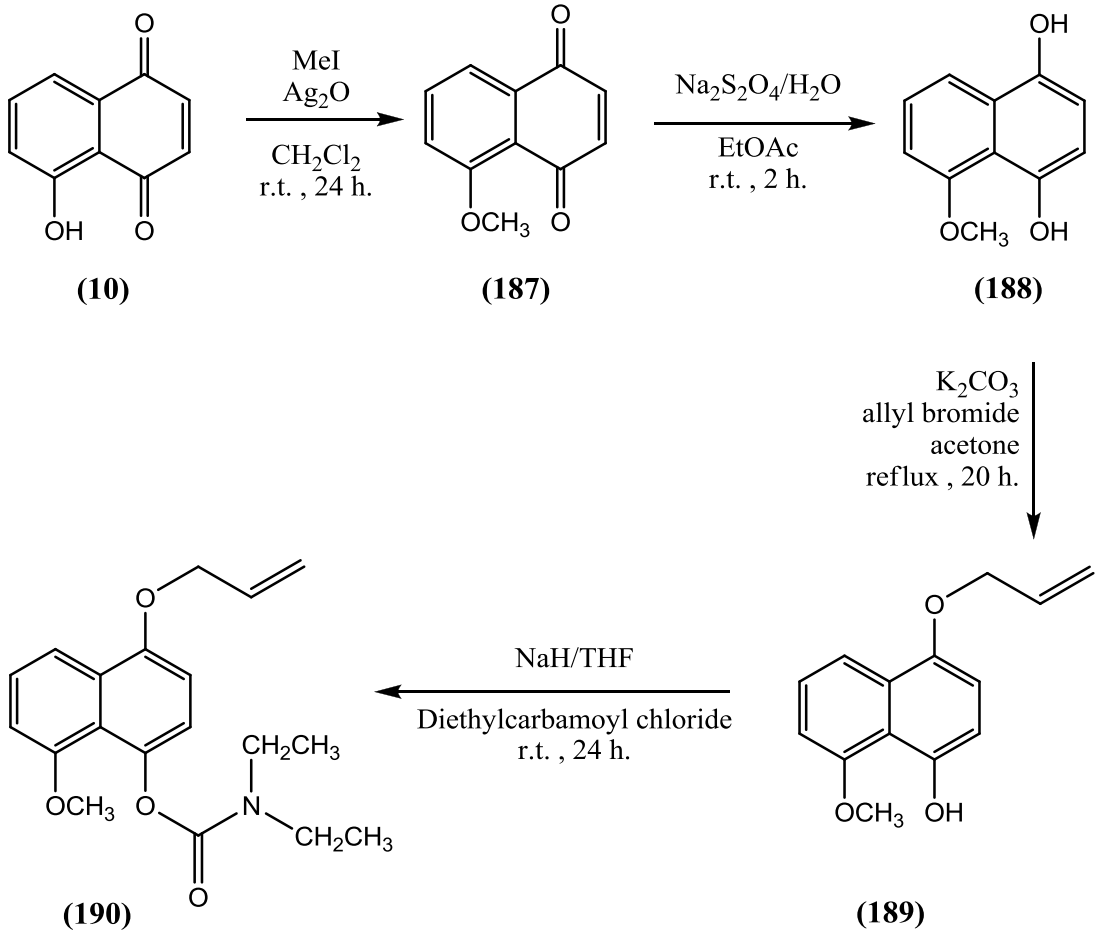


Scheme 58: Proposed mixed Fries-Claisen route towards tetracycline antibiotics

The Fries-Claisen precursor **(Scheme 59)** was synthesised following the same procedure used for the synthesis of the bisallylated juglone derivative **(141)**. Benzyl protection was substituted for a more ready available methyl protection by adding 2.0 equivalents of methyl iodide in the presence of 1.5 equivalent of silver(I) oxide to a stirred solution of juglone **(10)** in dichloromethane. Recrystallisation of the solid in ethanol gave the methyl protected compound **(187)** in 85% yield.

Methyl protected juglone **(187)** was reduced to its hydroquinone analogue **(188)** using an aqueous solution of sodium dithionite (8.5 equivalents) in the presence of ethyl acetate. Addition of the allyl moiety needed for the Claisen rearrangement was carried out using 1.1 equivalents of potassium carbonate and 1.1 equivalents of allyl bromide in refluxing acetone for 24 hours. The overall yield for the two steps was 88%.

A carboxamide moiety was added when 4-(allyloxy)-8-(methoxy)naphthalen-1-ol **(189)** was deprotonated using sodium hydride in tetrahydrofuran and reacted with diethylcarbamoyl chloride at room temperature for 24 hours to afford the Fries-Claisen precursor **(190)** in 82% yield.



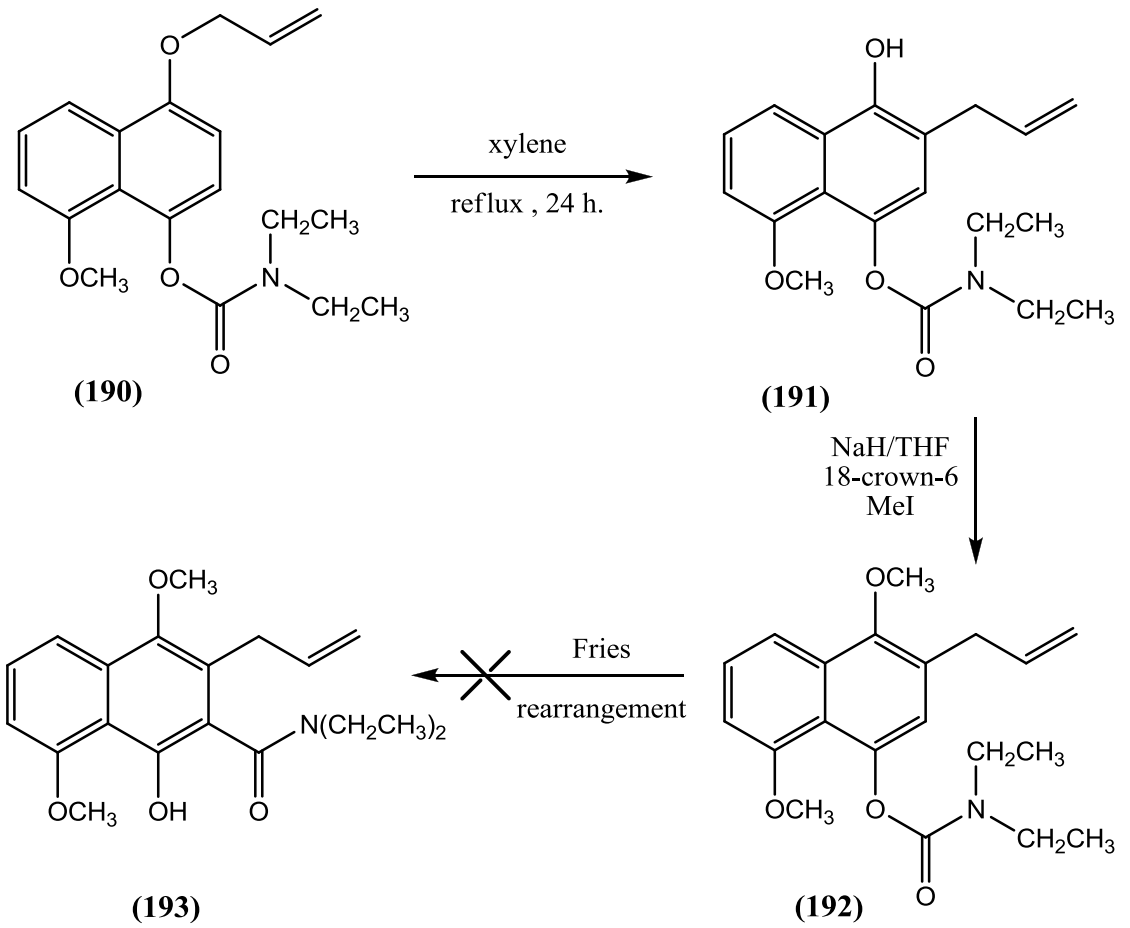
Scheme 59: Synthesis of 4-(allyloxy)-8-methoxynaphthalen-1-yl diethylcarbamate (184)

With an efficient methodology now stabilised for the synthesis of the Fries-Claisen precursor **(190)**, our efforts were focused on finding suitable conditions to carry out both rearrangements. A mixed Fries-Claisen rearrangement has not been performed previously and for this reason it was decided to start with a thermal Claisen rearrangement and to then subsequently proceed with the Fries rearrangement.

Thermal Claisen rearrangement was performed using xylenes as solvent to obtain the Claisen rearranged product **(191)** in 83% yield. Reaction times were maintained at 24 hours. Solvent was changed to xylenes due to its lower boiling point (139 ºC *versus* mesitylene 164 ºC) making purification of the reaction crude product easier.

Although the reaction temperature was lower, the Claisen rearrangement ratio was higher than expected from previous results **(Table 1)**. This could be explained as a consequence of the carboxamide moiety present in the carbon ring. The carboxamide group could act as an electron donating group activating the ring which will accelerate the reaction rate favouring the formation of the Claisen rearranged product.

Free hydroxyl group **(191)** was protected as its methyl derivative **(192)** in 65% yield by treatment with 2.5 equivalents of methyl iodide in the presence of 2.5 equivalents of sodium hydride in tetrahydrofuran. Alcohol protection proceeded with lower yields than expected and for this reason 18-crown-6 was added to the reaction mixture. 18-Crown-6 successfully coordinated the free sodium cation leaving the hydroxyl group more accessible and, therefore, increasing the yield to 78% **(Scheme 60)**.



Scheme 60: Attempted Claisen-Fries rearrangement

In order to carry out the Fries rearrangement of compound **(193)** the conditions developed by Snieckus were tested.[120] The methyl protected Claisen product **(192)** was dissolved in tetrahydrofuran, cooled to -78 ºC and then *N,N,N',N'*-tetramethylethylenediamine was added. A solution of *sec*-butyllithium in tetrahydrofuran was added by cannula over and the reaction mixture was stirred for 2 hours at -78 ºC and then warmed to room temperature over 2 hours. Unfortunately, these conditions did not afford the rearranged product **(193)** (Table 8, entry 1). For this reason, alternative reaction conditions were investigated **(Table 8)**.

Table 8: Attempted Fries rearrangement conditions

Entry	Base	Additive	Equival.	Solvent	Time	Temp.	Product [(b)]	Yield[(a)]
1	*sec*-BuLi	TMEDA	1.1	THF	18 h.	-78 ºC→r.t.	SM	>95%
2	*sec*-BuLi	TMEDA	1.1	THF	18 h.	r.t.	SM	75%
3	LDA	-	3.0	THF	18 h.	-78 ºC→r.t.	SM	>95%
4	LDA	-	3.0	THF	18 h.	r.t.→reflux	SM	>95%

(a) Yields for isolated products after flash column chromatography purification
(b) As shown in the ^{1}H NMR spectrum of the crude product

As shown in **Table 8**, all the efforts to carry out the Fries rearrangement on compound **(192)** failed. Heating the mixture at room temperature did not yield any of the expected rearranged product and some of the starting material was lost in the reaction, probably as decomposition products (entry 2). *sec*-Butyllithium was replaced by lithium diisopropylamide (LDA) since these reaction conditions allowed heating the mixture to reflux temperature in an effort to force the reaction towards the rearranged product (entries 3 and 4). However, only starting material was recovered from the reaction mixture in these cases.

It was concluded that, because of the colour change observed in the reaction mixture, a naphthyl carbanion maybe formed and that the reaction could not be completed because the reaction site was too sterically crowded for the delivery of the acyl group **(Figure 23)**.

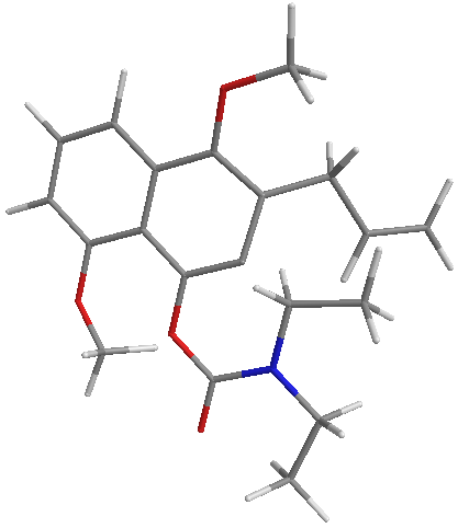
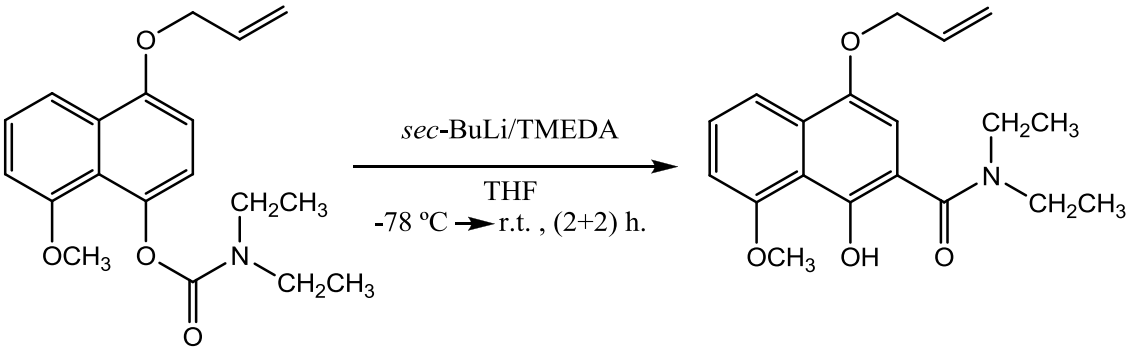


Figure 23: 3D view showing the sterically crowded position C8

In order to avoid steric hindrance it was decided to carry out the Fries rearrangement prior to the Claisen rearrangement. By performing the Fries rearrangement at an earlier stage the conditions developed by Snieckus became more relevant because there were two available positions which could undergo Fries rearrangement. Anionic *ortho*-Fries rearrangement promotes the rearrangement to proceed in the desired position avoiding undesired by-products that could affect the later Claisen rearrangement **(Scheme 61)**.



(190) **(194)**

Scheme 61: Fries rearrangement of diethylcarbamate (190)

Treatment of diethylcarbamate **(190)** with 1.1 equivalents of *sec*-butyllithium and TMEDA in tetrahydrofuran at -78 ºC for 2 hours followed by warming to room temperature over 2 hours afforded the Fries rearranged product **(194)** in a poor 12% yield (Table 9, entry 1). Freshly distilled *N,N,N',N'*-tetramethylethylenediamine and tetrahydrofuran were used in the reaction. In order to force the reaction and increase the yield of rearranged product several conditions were then tried **(Table 9)**.

Table 9: Fries rearrangement conditions for diethylcarbamate (190)

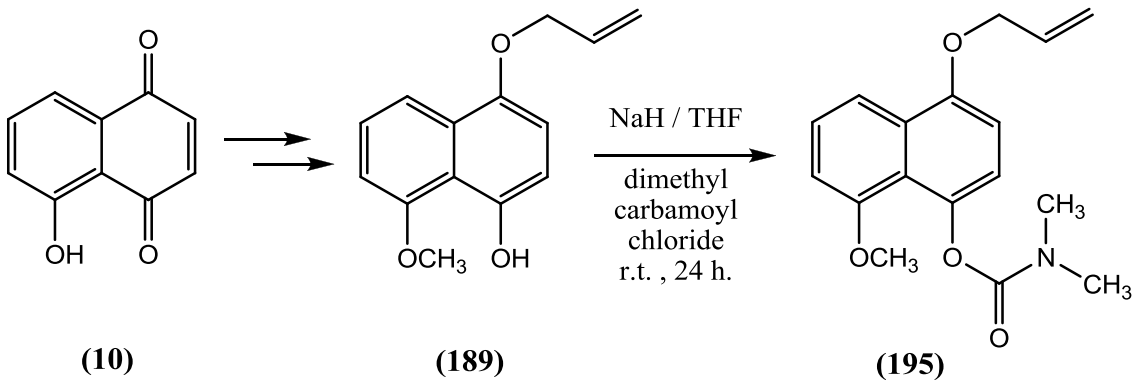
Entry	Base	Additive	Equivalents	Temperature	Time	Product[(b)]	Yield[(a)]
1	*sec*-BuLi	TMEDA	1.1	-78 ºC→r.t.	(2+2) h.	**194**	12%
2	*sec*-BuLi	TMEDA	1.5	-78 ºC→r.t.	(2+18) h.	**194**	10%
3	*sec*-BuLi	TMEDA	1.1	r.t.	24 h.	SM	>95%
4	*sec*-BuLi	TMEDA	1.1 + 1.0	-78 ºC→r.t.	(2+24) h.	**194**	8%
5	LDA	-	3.0	-78 ºC→reflux	(2+2) h.	SM	>95%
6	LDA	-	3.0 + 2.0	-78 ºC→reflux	(2+18) h.	SM	>95%

(a) Yields for isolated products after flash column chromatography purification
(b) As shown in the ^{1}H NMR spectrum of the crude product

As shown in **Table 9**, no significant differences were found when diethylcarbamate **(190)** was treated with extra excess of *sec*-butyllithium and TMEDA (entries 2, 3 and 4). Reaction of diethylcarbamate **(190)** with lithium diisopropylamide in tetrahydrofuran at reflux delivered starting material (entries 5 and 6). Although the reaction mixture was heated to reflux temperature treatment with LDA avoided the formation of the decomposition compounds as previously observed (Table 8, entries 3 and 4).

The reaction mixture colour changed when the base was added suggesting that the carbanion was formed. With the meta position free it was thought that migration of diethylcarbamate was unfavoured due to congestion within the lithium coordination sphere increasing the energy needed to carry out the rearrangement. In the light of the results obtained it was decided to change to dimethylcarbamate instead of diethylcarbamate in order to minimise sterical hindrance and increase the reaction rate.[122]

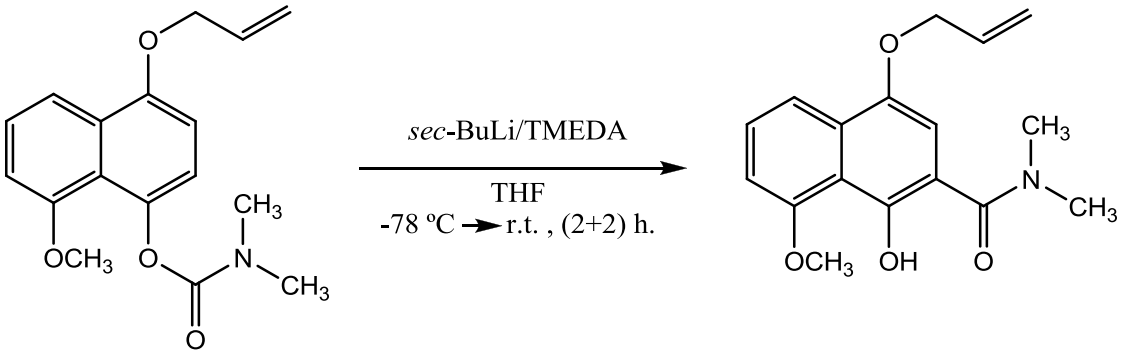
Following the same procedure used for the synthesis of 4-(allyloxy)-8-methoxynaphthalen-1-yl diethylcarbamate **(190)** but exchanging diethylcarbamoyl chloride for dimethylcarbamoyl chloride, afforded 4-(allyloxy)-8-methoxynaphthalen-1-yl dimethylcarbamate **(195)** in 88% yield **(Scheme 62)**.



(10) **(189)** **(195)**

Scheme 62: Synthesis of dimethylcarbamate (189)

The first attempt to carry out the Fries rearrangement was under Snieckus conditions.[120] Dropwise addition of 1.1 equivalents of *sec*-butyllithium, at -78 ºC, to a solution of 4-(allyloxy)-8-methoxynaphthalen-1-yl dimethylcarbamate **(195)** in tetrahydrofuran in the presence of 1.1 equivalents of *N,N,N',N'*-tetramethylethylendiamine for 2 hours and subsequent heating to room temperature over 2 hours led to the Fries rearranged compound **(196)** in 45% yield **(Scheme 63)**.



(195) **(196)**

Scheme 63: Fries rearrangement of dimethylcarbamate (196)

All reagents and solvents were freshly distilled and *sec*-butyllithium was titrated before being used in the reaction. Although all the conditions were controlled, reproducibility was difficult to achieve making yields vary from 20% to 60%. For this

reason alternative reaction conditions to carry out the *ortho*-Fries rearrangement were investigated **(Table 10)**.

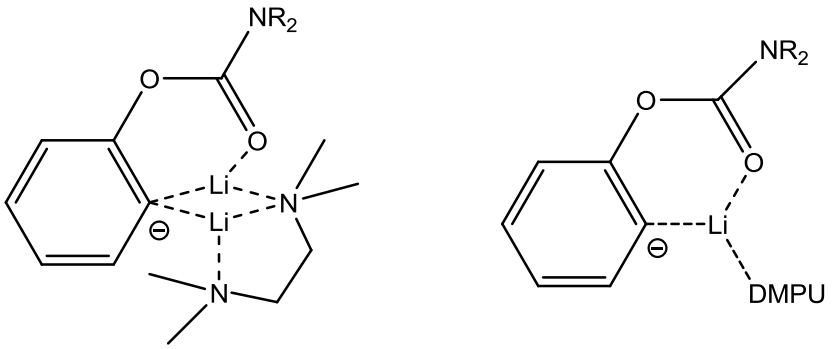
Table 10: Fries rearrangement conditions for dimethylcarbamate (195)

Entry	Base	Additive	Solvent	Eq.	Temperat.	Time	Product[(b)]	Yield[(a)]
1	*sec*-BuLi	TMEDA	THF	1.1	-78 ºC→r.t.	(2+2) h.	**196**	58%
2	*sec*-BuLi	TMEDA	THF	1.1	-78 ºC→r.t.	(2+18) h.	**196**	46%
3	*sec*-BuLi	TMEDA	THF	1.5	-78 ºC→r.t.	(2+18) h.	**196**	34%
4	*sec*-BuLi	TMEDA	THF	1.1+1.1	-78 ºC→r.t.	(2+2+18) h.	**196**	40%
5	*sec*-BuLi	TMEDA	THF	1.1	r.t.	4 h.	**196**	28%
6	*sec*-BuLi	TMEDA	THF	1.1	r.t.	18 h.	**196**	21%
7	*sec*-BuLi	TMEDA	THF	1.1	r.t.	72 h.	**196**	24%
8	*sec*-BuLi	DMPU/THF (1:9)	THF	1.1	-78 ºC→r.t.	(2+2) h.	**196**	30%
9	sec-BuLi	-	DME	1.1	-78 ºC→r.t.	(2+2) h.	SM	92%
10	LDA	DMPU/THF (1:9)	THF	1.1	-78 ºC→r.t.	(2+2) h.	SM	96%
11	LDA	-	DME	1.1	-78 ºC→r.t.	(2+2) h	SM	90%

(a) Yields for isolated products after flash column chromatography purification
(b) As shown in the ^{1}H NMR spectrum of the crude product

As shown in **Table 10,** when **(195)** was treated with extra equivalents of *sec*-butyllithium (entries 3 and 4) and/or during longer reaction times (entry 2) it rearranged as expected, although yields were a bit lower. Higher temperatures did not increase the reaction yield (entries 5-7).

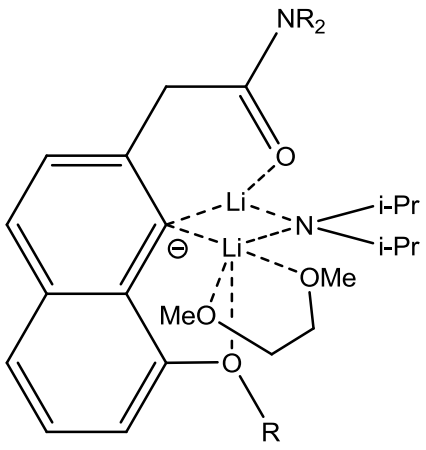
N,*N'*-Dimethyl-*N*,*N'*-propylene urea (DMPU) was used instead of TMEDA in order to try to increase the rearrangement reaction rate (entries 8 and 10). TMEDA coordinates with the lithiated intermediate forming a dimeric structure **(197)** whilst DMPU coordinates with the lithiated intermediate forming a monomeric structure **(198)**. Although the monomeric structure **(198)** leaves the bonding site more accessible for the migration of the acyl group no improvement on the yield reaction was observed (entry 8) **(Figure 24)**.[123]



(197) **(198)**

Figure 24: Dimeric and monomeric coordinated lithiated species

1,2-Dimethoxyethane (DME) coordinates in a similar way to **(197)**. DME forms a chelate in the transition state with the neighbouring methoxy group decreasing slightly the transition state energy **(Figure 25, 199)**. However, the decrease on the transition state energy was not significant to promote the rearrangement (entry 11).[123b]



(199)

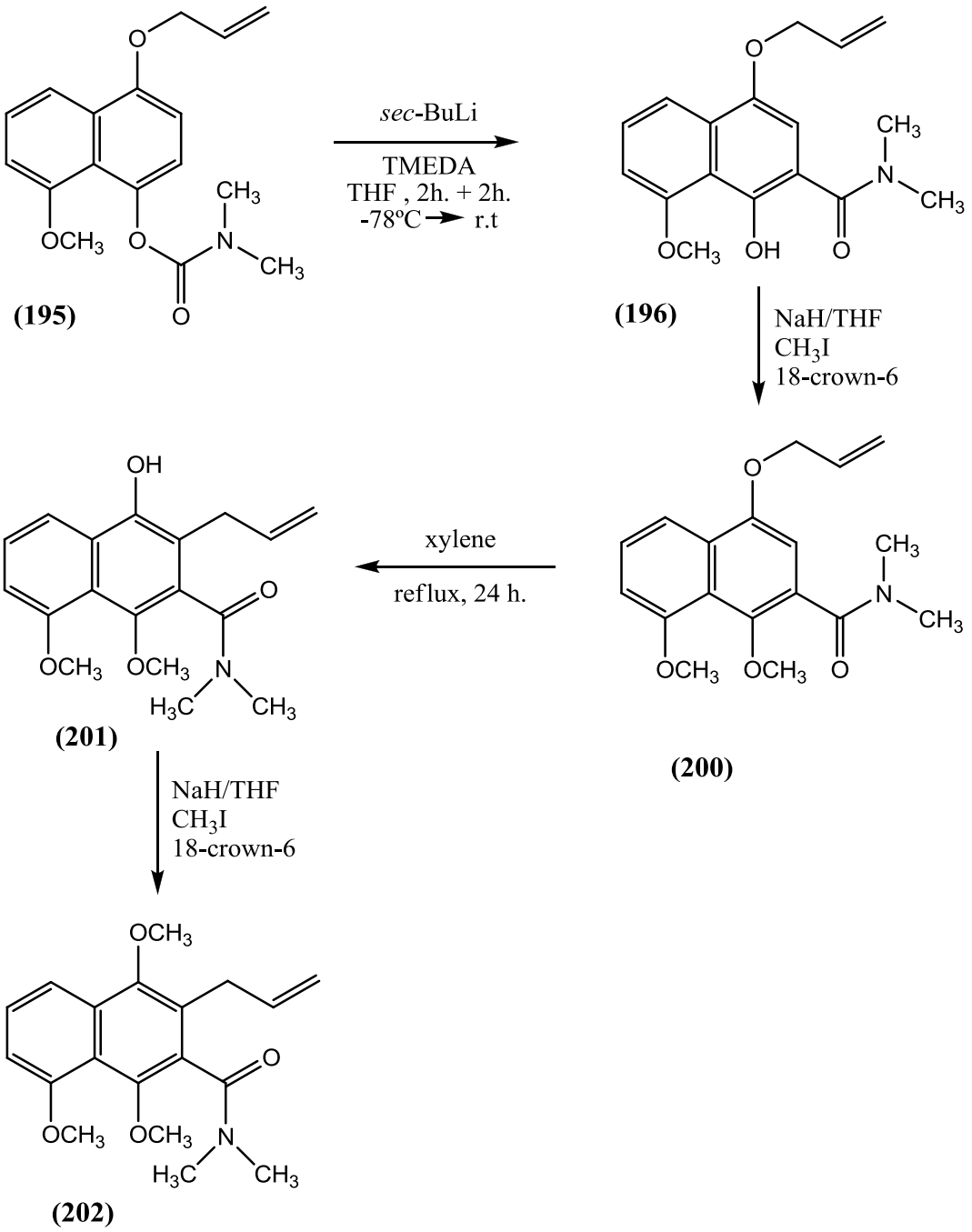
Figure 25: Chelated intermediate formed by DME in LDA

In the light of the results obtained it was decided to continue and accept that optimum conditions for the Fries rearrangement were 1.1 equivalents of *sec*-butyllithium and *N,N,N',N'*-tetramethylethylenediamine at -78 ºC for 2 hours and heated to room temperature over 2 hours.

Before proceeding with the Claisen rearrangement step, protection of the free hydroxyl group was performed. Treatment of **(196)** with 2.5 equivalents of sodium hydride and 2.5 equivalents of methyl iodide in tetrahydrofuran with a catalytic amount of 18-crown-6 afforded dimethylcarbamide **(200)** in 95% yield. Some problems were experienced during the isolation and purification process of the protected compound **(200)**. 18-Crown-6 decomposed after reaction and its removal from the reaction mixture by flash column chromatography was unsuccessful. When **(200)** was dissolved in dichloromethane, mixed with charcoal and filtered through Celite®, purification was not fully completed. Purification of **(200)** was carried out by washing the crude with hexane, with some loss of product yield from 95% to 83%.

Refluxing compound **(200)** in xylenes for 24 hours led to the Claisen rearranged compound **(201)** in 95% yield. Protection of the new free hydroxyl group was carried out using standard conditions to achieve compound **(202)** in 88% yield after hexane wash **(Scheme 64)**.

When the Claisen rearrangement was carried out using Lewis acids such as boron trichloride or titanium(IV) chloride in dichloromethane for 18 hours at room temperature decomposition products were observed due to partially removal of the methyl protecting group and isomerisation of the double bond.

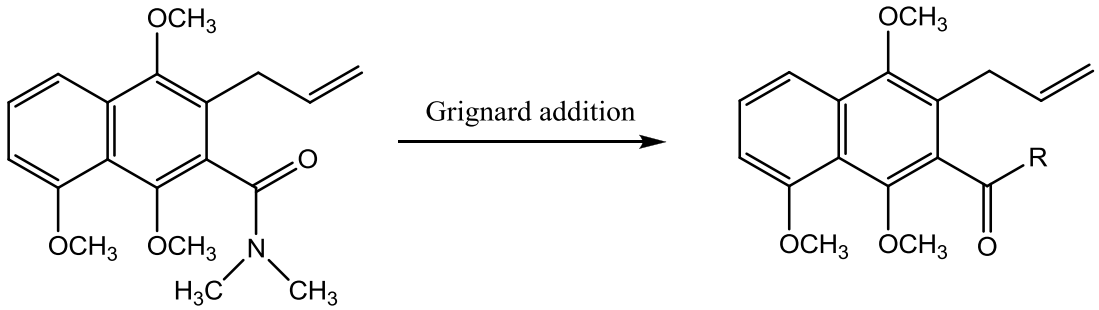


Scheme 64: Mixed Fries-Claisen rearrangement

As previously mentioned, a mixed Fries-Claisen rearrangement could provide advanced precursors for compounds with potential biological activity **(Figure 11)**. With a feasible synthetic methodology towards the Fries-Claisen product **(202)** now available it was decided to apply this synthetic route to access benzannelated targets **(Scheme 58)**.

2.6 GRIGNARD ADDITION TO AMIDE MOIETY

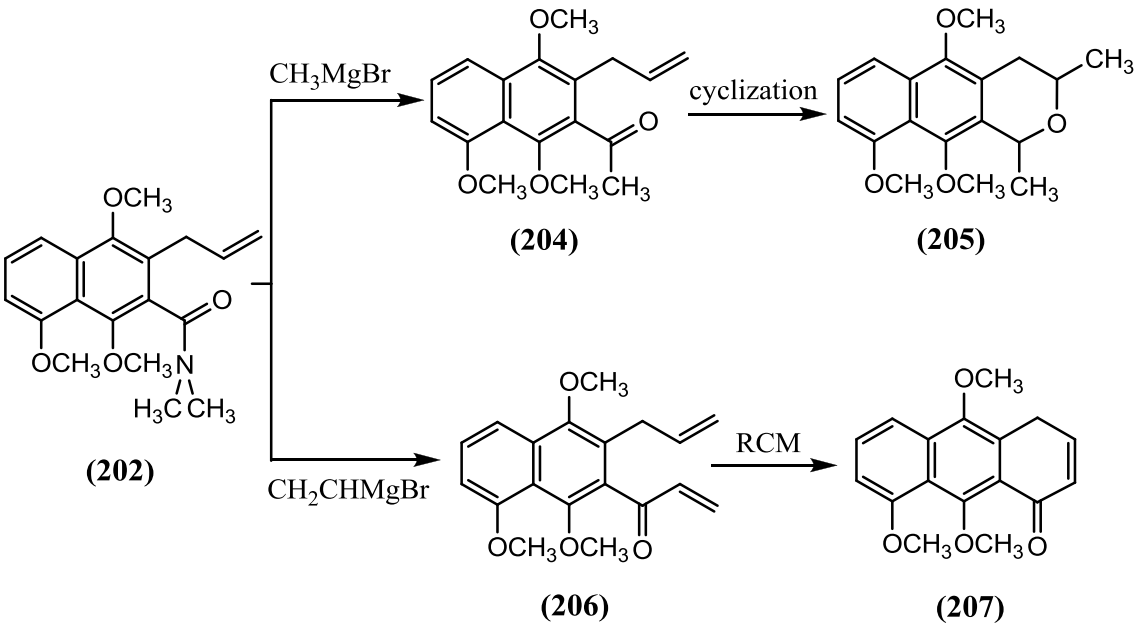
Our first aim was to attempt the displacement of the amide moiety using Grignard reagents. Addition of a Grignard reagent to the carbamide moiety would allow us to reach a wide range of substituted ketone products **(203) (Scheme 65)**.[124] These ketones could be suitable for further functionalisation and build up more rings adjacent to the original scaffold.



(202) **(203)** R ≠ H

Scheme 65: Proposed Grignard addition

Methylmagnesium chloride and vinylmagnesium bromide were chosen due to their suitable characteristics for future substitutions. Addition of methylmagnesium chloride to carbamide **(202)** could lead to methyl ketone **(204)** which could cyclise to lactone **(205)** an advanced precursor of eleutherin **(88) (Scheme 66)**. Addition of vinylmagnesium bromide could lead to **(206)**. Subsequent cyclisation by ring-closing metathesis (RCM) could yield tricyclic ketone **(207)** which could be converted to tetracycline **(7)** using known methodologies **(Scheme 66)**.



Scheme 66: Proposed synthesis of tricyclic derivatives *via* Grignard addition

In order to avoid over-reaction by double addition of the Grignard reagent to the amide yielding the alcohol, the reaction was initially tried adding only 1.1 equivalents of Grignard reagent at low temperature to achieve the corresponding ketones **(204, 206)** (**Table 11**, entries 1 and 6). Unfortunately, no addition was observed and only starting material was recovered from the reaction mixture. For this reason stronger conditions were proposed **(Table 11)**.

Table 11: Grignard's addition to carbamide (202)

Entry	Grignard	Solvent	Equival.	Temperature	Time	Product [(a)]
1	CH_3MgCl	THF	1.1	0 ºC→r.t.	30 min.+ 4 h.	SM
2	CH_3MgCl	THF	1.1	0 ºC→r.t.	30 min. + 18 h.	SM
3	CH_3MgCl	THF	1.1	Reflux	18 h.	SM
4	CH_3MgCl	THF	3.0	0 ºC→r.t.	(2+4) h.	SM
5	CH_3MgCl	THF	3.0	Reflux	18 h.	SM
6	$CH_2CHMgBr$	THF	1.1	0 ºC→r.t.	30 min.+ 4 h.	SM
7	$CH_2CHMgBr$	THF	1.1	Reflux	18 h.	SM
8	CH_3Li	THF	1.1	0 ºC→r.t.	30 min.+ 4 h.	SM

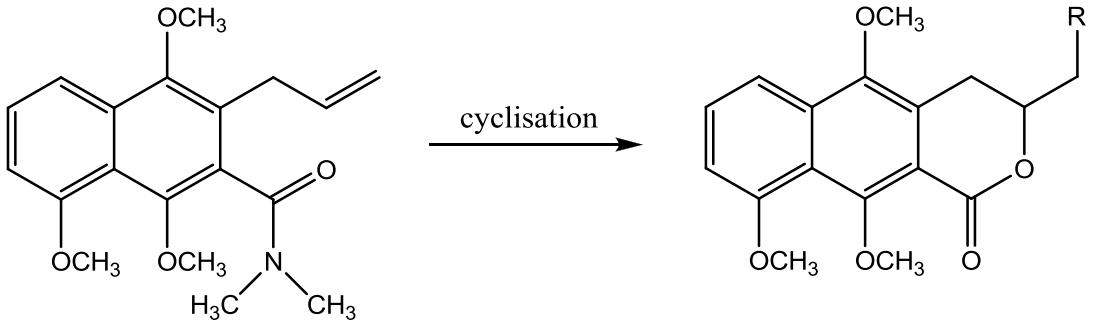
(a) As shown in the ^1H NMR spectrum of the crude product

As shown in **Table 11**, longer reaction times or heating the mixture to reflux made no difference (entries 2 and 3). Addition of more equivalents of methylmagnesium chloride (entries 4 and 5) or using an alternative reagent such as methyllithium (entry 8) led to the same results as previous entries. Although the carbamide moiety should have reacted and led to the corresponding substituted ketone, all these efforts were ineffective and only starting material was recovered after purification.

Failure to convert carbamide **(202)** into ketone **(203)** led us to investigate other possible synthetic routes to achieve the tricyclic lactone and its derivatives **(208)**. Our first attempt was following a cyclisation procedure similar to the one employed for the synthesis of halohydrins.[125]

2.7 SIDE CHAIN RING CYCLISATION

Cyclisation of the Fries-Claisen rearranged compound **(202)** was still a primary objective. For this reason a new pathway for ring formation/cyclisation was proposed **(Scheme 67)**.[126]

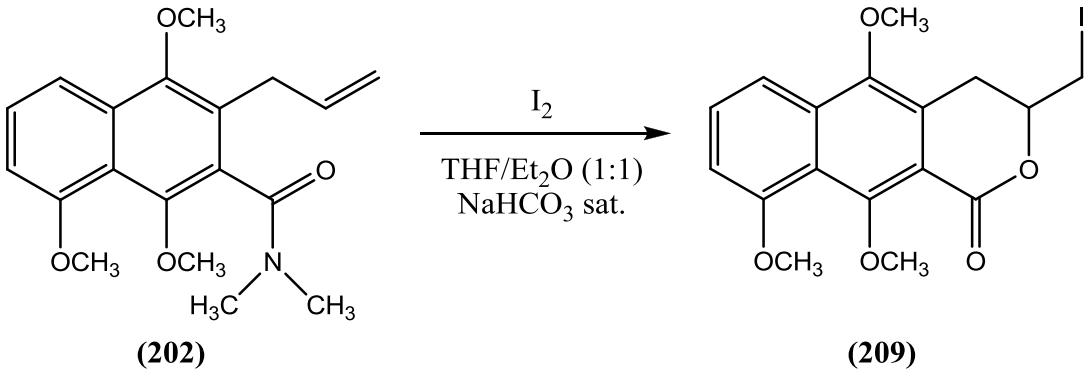


(202) **(208)**

Scheme 67: Proposed cyclisation towards lactone derivatives (208)

2.7.1 IODOLACTONIZATION

The cyclisation procedure used for the synthesis of the benzodihydrofuran compounds **(Scheme 50)** was extrapolated for the Fries-Claisen rearranged compound **(202)** in order to proceed with the cyclisation. Treatment of allylnaphthamide **(202)** with iodine in the presence of a base such as sodium hydrogen carbonate could yield iodolactam **(209) (Scheme 68)**.



(202) **(209)**

Scheme 68: Iodolactonization reaction

On applying the conditions developed by Lutz *et al.*, allylnaphthamide **(202)** was dissolved in a mixture of tetrahydrofuran and diethyl ether (1:1), treated with saturated aqueous sodium hydrogencarbonate solution at 0 ºC and subsequent addition of 4.0 equivalents of iodine. However, after 18 hours at 0 ºC only starting material and iodine were recovered from the reaction mixture (**Table 12**, entry 1).[127]

As this cyclisation reaction was demonstrated to work with similar compounds **(Scheme 50)**, it was decided to try alternative reaction conditions in order to proceed with the cyclisation of allylnaphthamide **(202) (Table 12)**.

Table 12: Iodolactonization of carbamide (202)

Entry	Iodine	Solvent	Base	Temperature	Time	Product [(b)]	Yield[(a)]
1	4.0 eq.	THF/Et_2O	$NaHCO_3$	0 ºC	18 h.	SM	>95%
2	4.0 eq.	THF/Et_2O	$NaHCO_3$	r.t.	20 h.	SM	>95%
3	6.5 eq.	THF/Et_2O	$NaHCO_3$	r.t.	48 h.	SM	>95%
4	15 eq.	THF/Et_2O	$NaHCO_3$	r.t.	24 h.	**209**	32%
5	6.5 eq.	THF/Et_2O	$NaHCO_3$	reflux	18 h.	**209**	60%
6	6.5 eq.	THF/Et_2O	$NaHCO_3$	reflux	48 h.	**209**	58%

(a) Yields for isolated products after flash column chromatography purification
(b) As shown in the ^1H NMR spectrum of the crude product

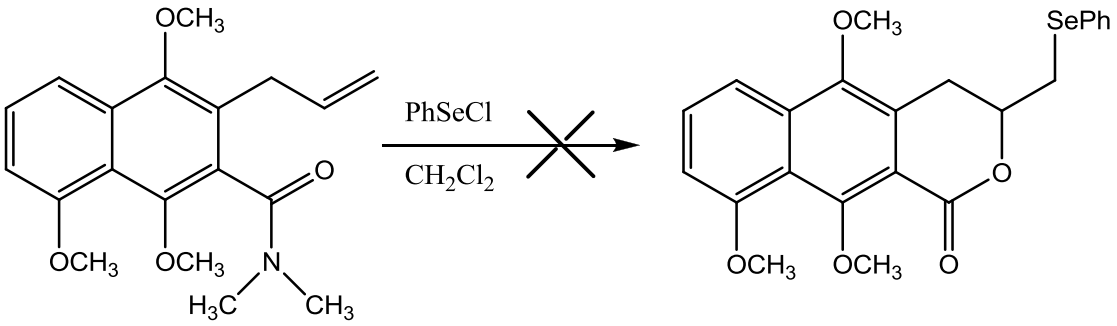
As shown in **Table 12**, when the reaction was carried out at low temperatures no reaction was observed (entries 1, 2 and 3) unless a high excess of iodine was added (entry 4). Although entry 4 produced iodolactone **(209)**, the reaction mixture was very messy and removal of the excess iodine from the reaction mixture needed lots of extra washes. Heat was needed for the reaction to proceed as shown in entries 5 and 6. Best conversions to iodolactone **(209)** were obtained when allylnaphthamide **(202)** was dissolved in a mixture of tetrahydrofuran and diethyl ether (1:1), treated with saturated aqueous sodium hydrogencarbonate solution and 6.5 equivalents of iodine and heated to reflux for 18 hours (entry 5).

When the mixture was heated at reflux for 48 hours the reaction yield did not improve (entry 6). Instead of recovering starting material after column chromatography purification only cyclisation and degradation compounds were obtained.

2.7.2 PHENYLSELENOLACTONIZATION

In order to broaden the limits of the reaction it was decided to try the cyclisation procedure using a selenenyl chloride. Phenylselenolactonizations conditions developed by Nicolaou *et al.* were applied to allylnaphthamide **(202)**.[128] However, when **(202)** was

treated with 1.1 equivalents of phenylselenyl chloride in dichloromethane at room temperature for 24 hours only starting material was recovered **(Scheme 69)**.



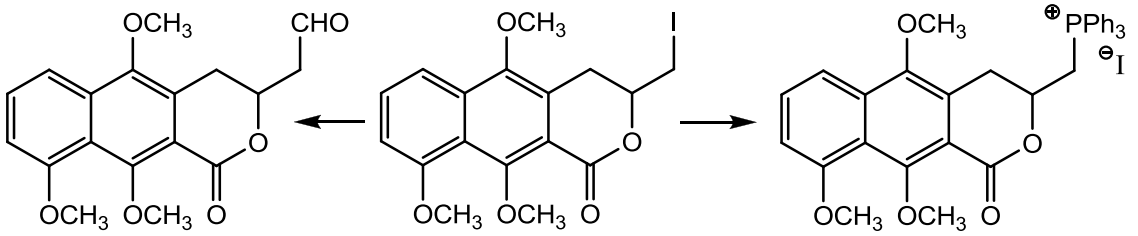
(202) **(210)**

Scheme 69: Phenylselenolactonization attempt

Initially it was thought that the reaction conditions were not strong enough (as happened with the iodolactonization reaction). For this reason the reaction was heated to reflux for 24 hours but no reaction was observed. Checking the reaction conditions obtained in **Table 12** showed that the presence of the base played an important role promoting the hydrolysis of the amide to the corresponding acid needed to proceed with the cyclisation step. For this reason saturated aqueous sodium hydrogen carbonate solution was added into the reaction mixture. Unfortunately, only starting material was recovered after purification.

2.8 FORMATION OF A WITTIG REAGENT

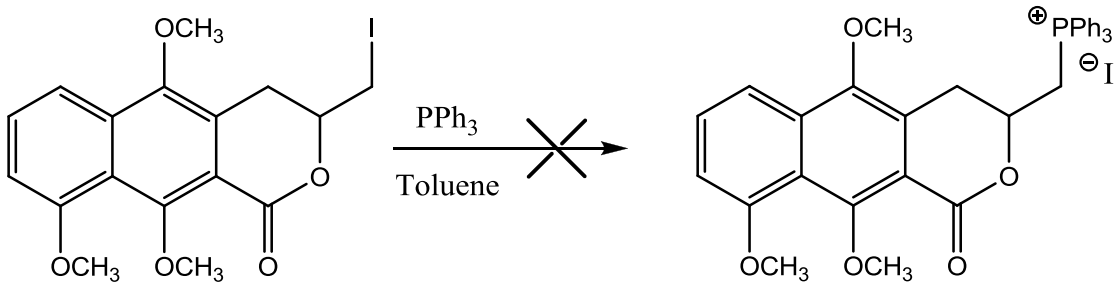
Iodomethylisochromenone **(209)** could be a good precursor for more complex pyranonaphthoquinones with potential antibiotic properties such as anti-fungal, anti-viral, and anti-cancer activity.[72] Functionalisation at the iodine moiety was an important step in order to make the compound suitable for coupling with other structures **(Scheme 70)**.



(212) **(209)** **(211)**

Scheme 70: Possible iodolactone derivatives

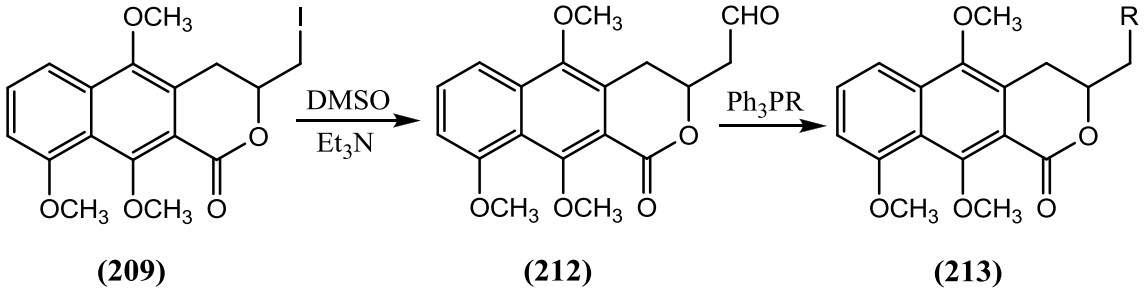
Our first attempt was transforming the iodolactone into a triphenylphosphonium salt **(211)** suitable for a Wittig reaction. Treatment of iodolactone **(209)** with 3.0 equivalents of triphenylphosphine in toluene at room temperature for 18 hours was unproductive. Only starting material and unreacted triphenylphosphine were recovered after purification. Heat was applied to the reaction mixture but after 18 hours at reflux no reaction was observed **(Scheme 71)**.



(209) **(211)**

Scheme 71: Attempted synthesis of triphenylphosphonium salt (211)

Failing to achieve the synthesis of the triphenylphosphonium salt **(211)** it was decided to try the coupling reaction the other way round. Instead of preparing the phosphonium ylide and coupling it to an aldehyde, it was decided to synthesise the aldehyde **(212)** and execute the Wittig reaction with different phosphonium ylides. This methodology could produce advanced precursors for natural compounds with potential antibiotic activity **(213) (Scheme 72)**.

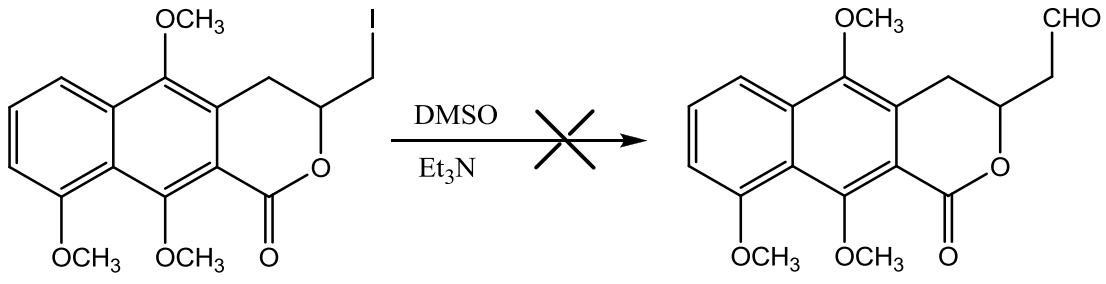


(209) **(212)** **(213)**

Scheme 72: Aldehyde formation and coupling synthetic pathway

Kornblum oxidation is a known methodology that converts halides to the corresponding aldehydes.[129] Iodolactone **(209)** was heated to reflux in dimethylsulfoxide for 18 hours and then triethylamine was added. The reaction mixture was stirred at reflux 18 more hours. Unfortunately, no reaction was observed and after work-up only starting material was recovered.

The use of additives such as silver salts has been demonstrated to improve the reaction yields and make reactions proceed under milder conditions.[130] For these reasons 1.0 equivalents of silver tetrafluoroborate were added to a solution of iodolactone **(209)** in dimethylsulfoxide and the reaction mixture was heated to reflux for 18 hours. Triethylamine was added and the heating was prolonged for 18 hours. However, after purification only starting material was recovered (72%) **(Scheme 73)**.



(209) **(212)**

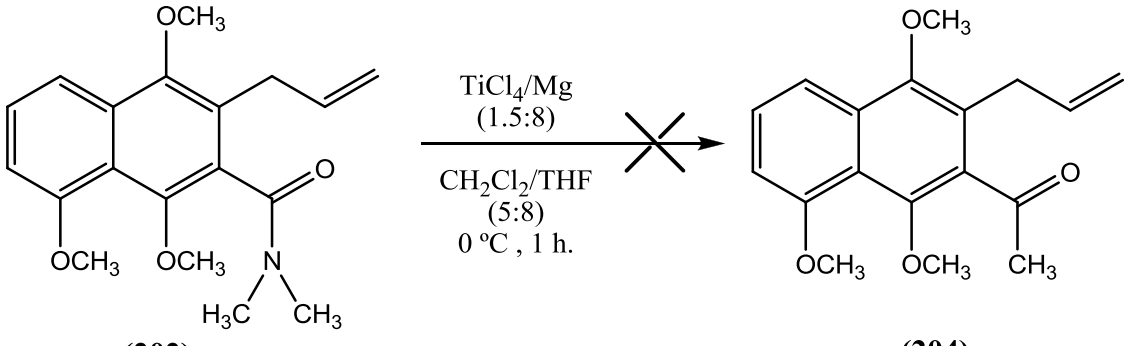
Scheme 73: Failed conversion to aldehyde (212)

With no positive results on the conversion of iodolactone **(209)** into a suitable derivative for coupling reactions, the efforts were focused on a reduction/cyclisation procedure for the synthesis of advanced pyranonaphthoquinone precursors.

2.9 AMIDE REDUCTION TO METHYL KETONE

As mentioned previously **(Scheme 66)**, addition of methylmagnesium chloride to carbamide **(202)** had a special interest because it would have led, after subsequent cyclisation and oxidative demethylation, to eleutherin **(88)**.

Although it was not possible to carry out the Grignard addition, other pathways to synthesise the methyl ketone **(204)** were proposed. Yan *et al.* reported a successful conversion of amides to their corresponding methyl ketones by direct coupling with dichloromethane promoted by a $TiCl_4$/Mg/THF-system **(Scheme 74)**.[131]

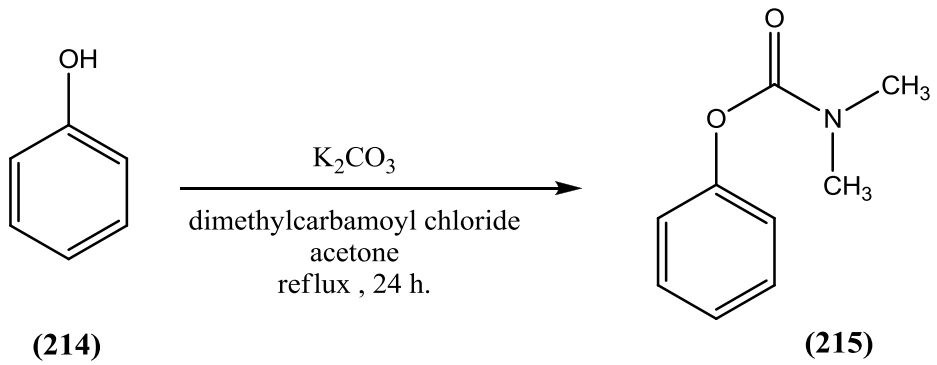


(202) **(204)**

Scheme 74: Proposed dichloromethane coupling for the synthesis of methyl ketones

Allylnaphthamide **(202)** was dissolved in a mixture of dichloromethane and tetrahydrofuran (5:8) in the presence of titanium(IV) chloride and magnesium (1.5:8) at 0 ºC for 1 hour **(Scheme 74)**. However, after filtration/purification through silica only starting material was recovered.

In order to find the suitable conditions to carry out the reduction of carbamide to ketone an accessible compound with similar functionality **(215)** was synthesised for this purpose. Acylation of phenol **(214)** by treatment with 2.0 equivalents of potassium carbonate and 2.0 equivalents of dimethylcarbamoyl chloride in the presence of potassium carbonate in refluxing acetone for 24 hours afforded phenyl dimethylcarbamate **(215)** in 93% yield **(Scheme 75)**.



(214) **(215)**

Scheme 75: Synthesis of phenyl dimethylcarbamate (215)

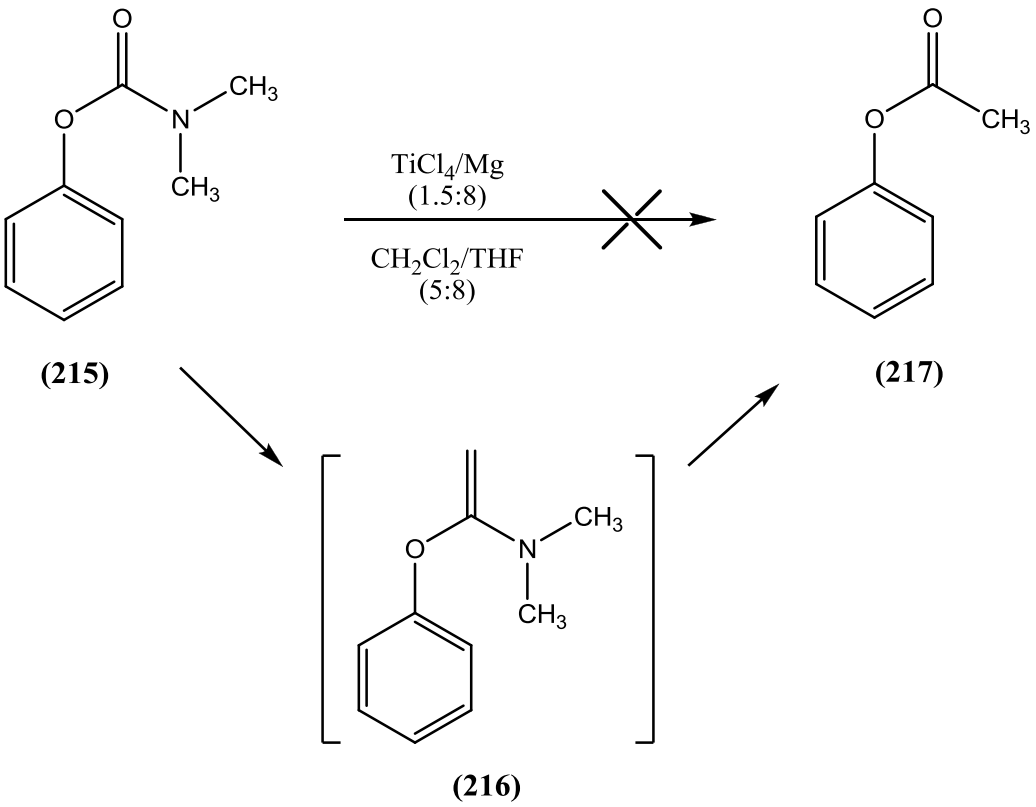
As shown in **Table 13**, carbamate **(215)** was reacted using fixed proportions of titanium(IV) chloride and magnesium (1.5:8) and tetrahydrofuran and dichloromethane (5:8) to form the optimum $TiCl_4/Mg/CH_2Cl_2$-system.[131] Reaction times and temperatures were changed in order to find the reaction conditions needed to afford methyl ketone **(217)**.

Table 13: Reduction of carbamate (215)

Entry	Reagents	Solvent	Time	Temperature	Product [(b)]	Yield [(a)]
1	$TiCl_4$/Mg	CH_2Cl_2/THF	1 h.	0 ºC	SM	91%
2	$TiCl_4$/Mg	CH_2Cl_2/THF	2 h.	0 ºC→r.t	SM	89%
3	$TiCl_4$/Mg	CH_2Cl_2/THF	2 h.	r.t.	SM	97%
4	$TiCl_4$/Mg	CH_2Cl_2/THF	18 h.	r.t.	SM	93%
5	$TiCl_4$/Mg	CH_2Cl_2/THF	(1+18) h.	0 ºC→r.t→reflux	SM	75%

(a) Yields for isolated products after flash column chromatography purification
(b) As shown in the ^{1}H NMR spectrum of the crude product

Unfortunately, when compound **(215)** was reacted under any of the reaction conditions shown in **Table 13** all attempts failed to produce any of the phenol ester **(217)**. Heating the reaction mixture to room temperature yielded only starting material (entries 2, 3 and 4). When the mixture was heated to reflux no methylation was observed and the yield decreased due to degradation products observed in the reaction mixture (entry 5) **(Scheme 76)**.

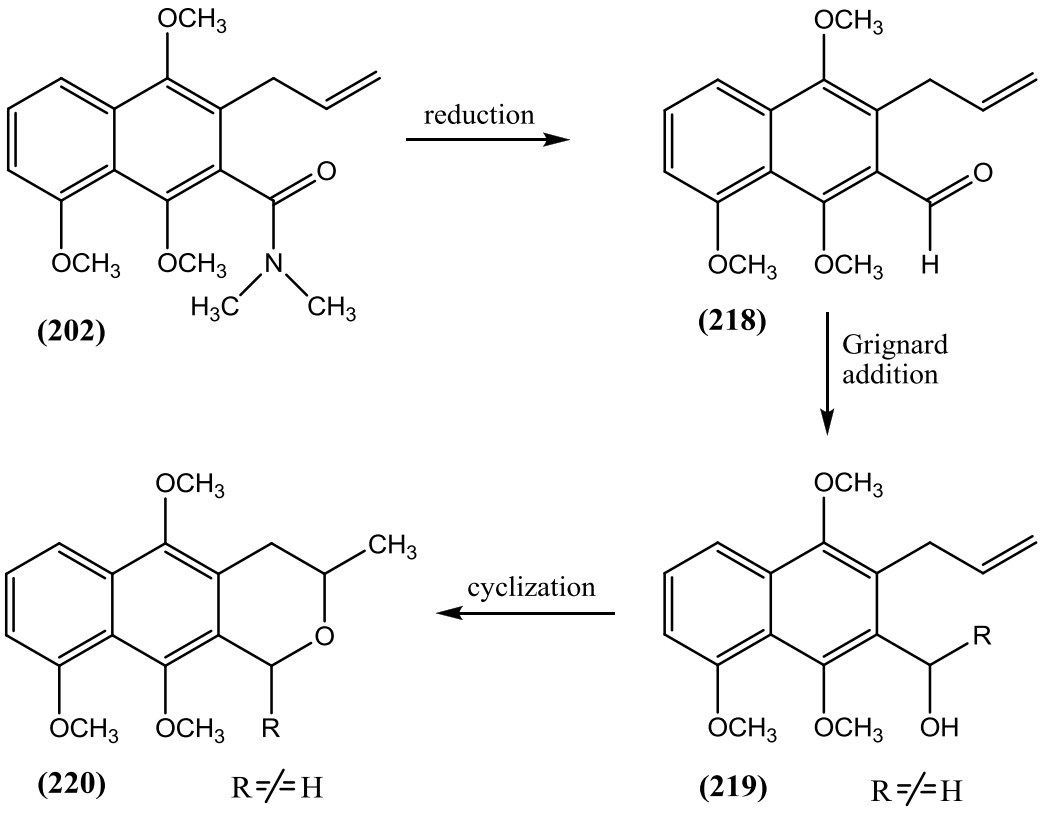


Scheme 76: Attempted carbonyl-methylenation

Treatment of carbamate **(215)** with the $TiCl_4/Mg/CH_2Cl_2$-system should have lead to the corresponding enamine intermediate **(216)** through a Wittig type reaction mechanism, which should have reacted easily with water to give methyl ketone **(217)**. However, no traces of methylenation product **(217)** nor alkene intermediate **(216)** were observed.[131]

2.10 AMIDE REDUCTION TO ALDEHYDE

As a consequence of the problems found to displace the amide using Grignard reagents or similar compounds it was decided to convert the amide **(202)** into an aldehyde, which is supposed to be more reactive. Addition of a Grignard reagent to aldehyde **(218)** and subsequent cyclisation of the free hydroxyl group **(219)** could lead to advanced precursors of naphthoquinone derivatives **(220) (Scheme 77)**.[132]

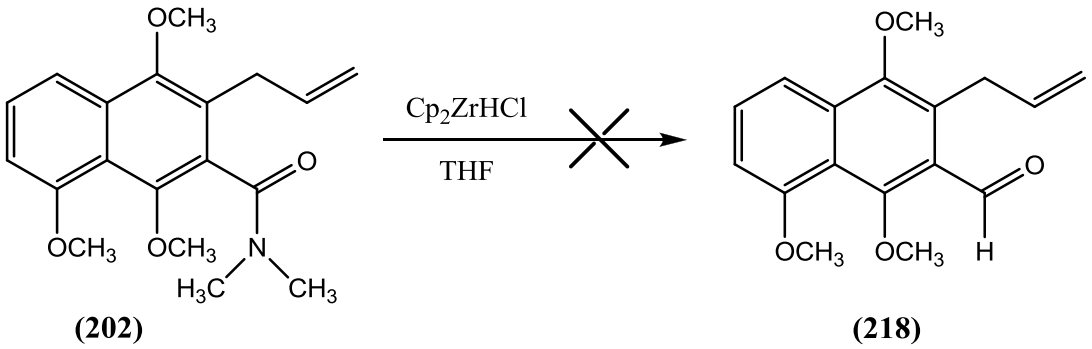


Scheme 77: Proposed synthetic route towards pyranonaphthoquinone derivatives

The first step to accomplish the synthesis of lactone **(220)** was the reduction of carbamide **(202)** to aldehyde **(218)**. Although problems with over-reaction leading to the corresponding alcohol could be expected, mild reaction conditions have been developed over the last few years to carry out the reduction specifically to the aldehyde.[133]

Georg *et al.* reported the hydrozirconation of tertiary amides to aldehydes using Schwartz's reagent (Cp_2ZrHCl) under mild conditions.[134,135] Schwartz's reagent was synthesised by reaction of titanocene dichloride with 2.0 equivalents of lithium aluminium hydride in tetrahydrofuran at room temperature for 1 hour. This compound is very sensitive to light, heat and air and for these reasons it was kept as a 0.5 M solution in tetrahydrofuran at 4 ºC.[135b]

Treatment of carbamide **(202)** with 1.2 equivalents of bis(cyclopentadienyl)zirconium chloride hydride in tetrahydrofuran at room temperature for 30 minutes until the solution colour faded. Silica was added and the reaction mixture was filtered. Unfortunately, only starting material was recovered. Treatment of carbamide **(202)** with 2.0 equivalents of bis(cyclopentadienyl)zirconium chloride hydride under an inert atmosphere and stirring for 90 minutes failed to yield the expected aldehyde **(218) (Scheme 77)**.



(202) **(218)**

Scheme 78: Attempted reduction of (202) using Schwartz's reagent

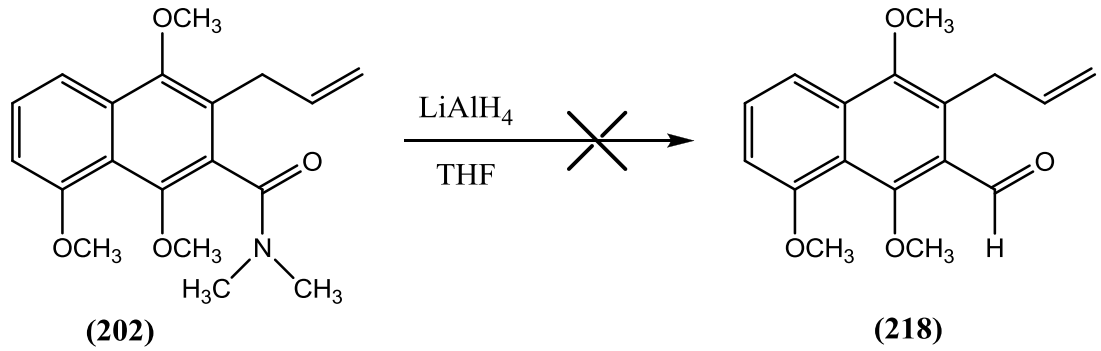
When the reaction takes place, the zirconium reagent is incorporated to form a stable complex structure which would be hydrolysed with water to yield the corresponding aldehyde. It was concluded that coupling of the zirconium with the oxygen atom proceeded as expected because the original orange colour of the zirconium complex faded after 30 minutes. However, probably due to interactions with other vicinal oxygen atoms, cleave of amide moiety was not achieved and the complex was destroyed in the work-up.

In the view of the results obtained by treatment with soft reducing reagents it was decided to use stronger reducing agents. Various studies showed the possibility of carrying out the reduction of tertiary amides to aldehydes using a source of hydride by controlling reaction conditions to avoid over-reaction. Most of these reactions are carried out at low temperature.[136]

Diisobutylaluminium hydride exists as a bridged dimer in solution and it becomes a reducing agent after it forms a complex with the oxygen atom. At low temperatures a tetrahedral intermediate is formed which would lead to the aldehyde after aqueous work-up. For this reason carbamide **(202)** was reacted with diisobutylaluminium hydride in tetrahydrofuran at 0 ºC for 1 hour and sulfuric acid was added to the reaction mixture at 0 ºC controlling that temperature did not raise over 5 ºC. Unfortunately, only starting material was recovered after purification.

The tetrahedral intermediate for amides is quite stable and could withstand stronger reaction conditions. Typical amide reduction using lithium aluminium hydride and quenching the reaction at low temperatures in acid should lead to the corresponding aldehyde.[137] When carbamide **(202)** was treated with 3.0 equivalents of lithium aluminium hydride in tetrahydrofuran at -78 ºC for 30 minutes and the mixture was quenched with hydrochloric acid (6M) no evidence of reaction was observed. In a final attempt to force the reaction and obtain the reduction of **(202)** 3.0 equivalents of lithium

aluminium hydride were added at 0 ºC for 2 hours. The reaction was quenched with hydrochloric acid (6M) but no satisfactory results were achieved **(Scheme 79)**.

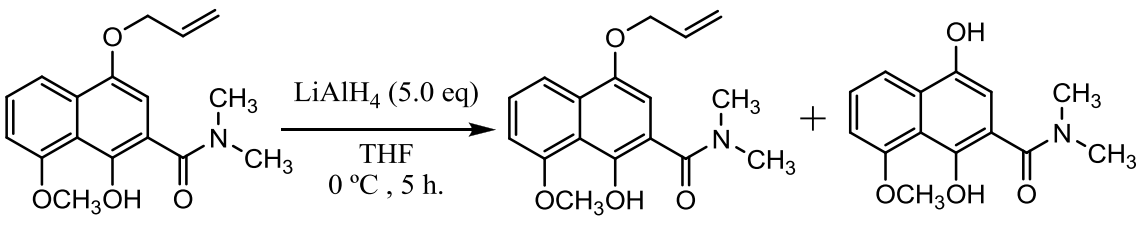


(202) **(218)**

Scheme 79: Failed reduction of tertiary amide (202) to aldehyde (218)

Previous results seemed to be pointing at the same direction. After all the efforts and different reaction conditions applied to carbamide **(202)** the molecule showed no response and stayed unreactive. For this reasons it was decided to try stronger conditions on a previous molecule and verify the results obtained.

Hydroxynaphthamide **(196)** was treated with 5.0 equivalents of lithium aluminium hydride in tetrahydrofuran at 0 ºC. The mixture was heated to room temperature and reacted for 5 hours. After work-up and purification only starting material and the degradation compound **(221)**, obtained by cleavage of the allyl moiety, were recovered from the reaction mixture **(Scheme 80)**.



(196) **(196)** **(221)**

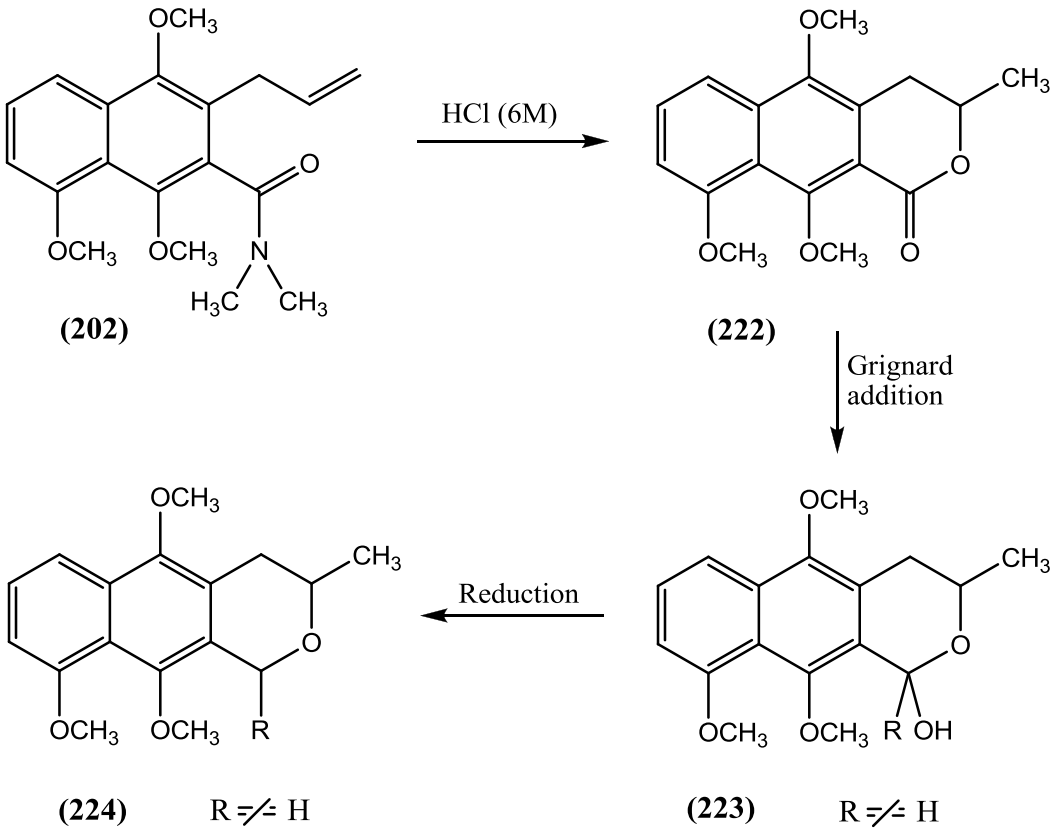
Scheme 80: Reduction of carbamide (196) with $LiAlH_4$

In view of the results obtained it was concluded that both allylnaphthamide derivatives **(196** and **202)** were too stable to undergo substitution reactions and displace the carbamide moiety. Although amide carbon-oxygen bond should be weaker than normal carbon-oxygen bonds, due to its vicinal nitrogen atom, no reduction of the amide was observed to achieve the corresponding aldehyde and/or tertiary amine.

The only reaction observed was hydrolysis of carbamide **(202)** in sodium carbonate and iodolactonization using iodine and aqueous sodium hydrogencarbonate in a mixture of tetrahydrofuran and diethyl ether (1:1) at reflux **(Scheme 68)**. However, no further substitutions could be carried out and iodolactone **(209)** remained inactive. For these reasons a new cyclisation process was proposed in order to achieve advanced pyranonaphthoquinones precursors.

2.11 ACIDIC CYCLISATION TOWARDS LACTONE SCAFFOLD

Our final approach to the synthesis of eleutherin **(88)** and other related pyronaphthoquinones consisted on an acidic cyclisation to yield isochromenone **(222)**.[138] Grignard addition to the ketone moiety and subsequent reduction of the free hydroxyl group obtained **(223)** would lead to pyranonaphthoquinone precursor **(224)**.[132,139] As shown in **Scheme 81** the use of different Grignard reagents could lead to several derivatives with potential antibiotic properties.



Scheme 81: Proposed synthetic route towards pyranonaphthoquinone derivatives

Initially, allylnaphthamide **(202)** was reacted in refluxing aqueous hydrochloric acid for 48 hours. After purification most of the compound was consumed and decomposed yielding only a 30% yield of demethylated isochromenone **(226)** (**Table 14**, entry 5). For this reason milder reaction conditions were investigated to find the most favourable conditions to proceed with the transformation **(Table 14)**.

Table 14: Acidic cyclisation of carbamate (202)

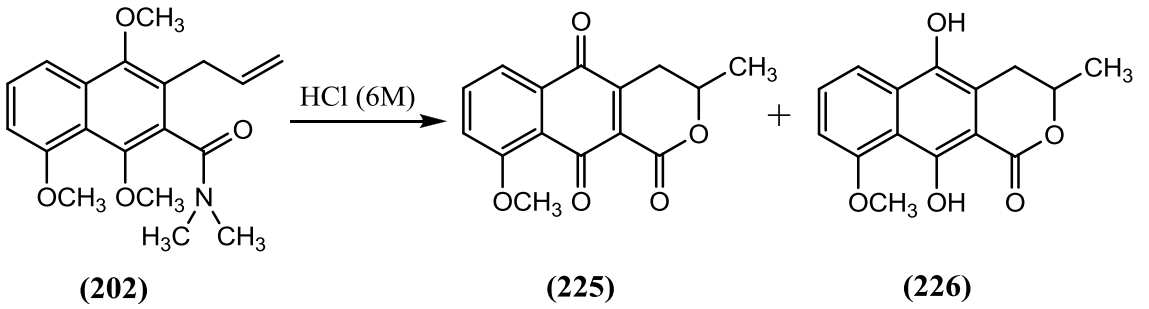
Entry	Acid	Solvent	Time	**202**	**225**	**226**	**Degradation**
1	HCl (6M)	H_2O	6 h.	92%	-	-	-
2	HCl (6M)	H_2O	12 h.	60%	15%	-	20%
3	HCl (6M)	H_2O	18 h.	-	50%	13%	30%
4	HCl (6M)	H_2O	24 h.	-	10%	15%	55%
5	HCl (6M)	H_2O	48 h.	-	-	30%	65%
6	HCl (6M)	Et_2O/THF	18 h.	98%	-	-	-

(a) Yields for isolated products after flash column chromatography purification

As shown in **Table 14** when carbamide **(202)** was heated for 6 hours (entry 1) no reaction was observed and only starting material was recovered. Screening a range of reaction times between 6 hours and 48 hours it was observed that optimum conditions to achieve cyclisation were treatment of carbamide **(202)** with refluxing aqueous hydrochloric acid (6M) for 18 hours (entry 3) **(Scheme 82)**.

The solvent was changed from water to a mixture of diethyl ether and tetrahydrofuran (1:1) to improve solubility of carbamide **(202)** and soften the reaction conditions (entry 6). Unfortunately, although the entire compound was in solution, after purification only starting material was obtained maybe due to the lower boiling point of tetrahydrofuran (66 ºC).

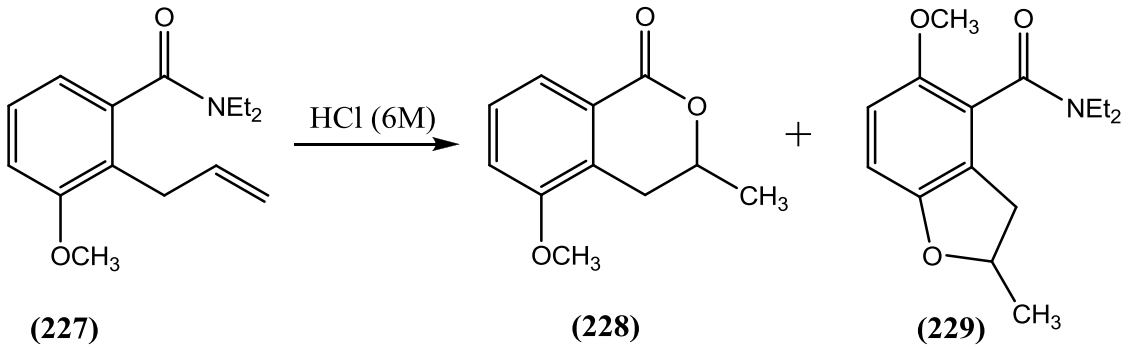
When the reaction time was prolonged to over 18 hours the proportion of degradation and demethylated compounds increased (entries 5 and 6). It is very significant to highlight the increase in degradation compounds *versus* demethylated product. These results showed that longer reaction times encouraged the compound to decompose.



(202) **(225)** **(226)**

Scheme 82: Acidic cyclisation of allylnaphthamide (202)

Snieckus *et al.* mentioned the formation of a benzodihydrofuran compound when a similar carbamide was treated with aqueous hydrochloric acid **(Scheme 83)**. However, when these conditions were applied to our compounds, ^{1}H NMR analysis showed no peaks corresponding to the formation of the benzodihydrofuran derivative.[140]



(227) **(228)** **(229)**

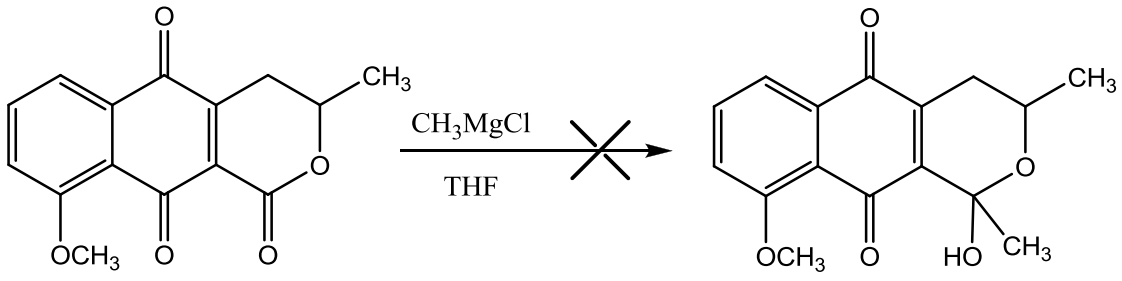
Scheme 83: Formation of the benzodihydrofuran (229) under acidic conditions

As happened previously with sodium carbonate during the iodolactonization process, refluxing acid was able to hydrolyse the amide and transform it into a carboxylic acid which cyclised to yield the desired lactone **(225)**.

2.11.1 GRIGNARD ADDITION TO LACTONE

Once lactone **(225)** was successfully prepared, Grignard addition to the ketone moiety to achieve the corresponding alcohol **(230)** was attempted. Following a similar procedure to the one used for the displacement of the amide moiety **(Scheme 65)**, lactone **(225)** was treated with methyl magnesium chloride in tetrahydrofuran at low temperature **(Scheme 84)**.[124]

Addition of 1.0 equivalents of methylmagnesium chloride to lactone **(225)** in tetrahydrofuran at -78 ºC and stirring at room temperature for 24 hours resulted in no reaction and only starting material was recovered. When 3.0 equivalents of methylmagnesium chloride in tetrahydrofuran were added at 0 ºC and the reaction mixture was stirred at room temperature for 24 hours the same results were obtained. Changing methylmagnesium chloride to methylmagnesium bromide made no difference. Treatment of isochromenone **(225)** with 3.0 equivalents of methyllithium in tetrahydrofuran at room temperature for 18 hours gave a very messy crude ^{1}H NMR spectrum. No peaks corresponding to the desired compound were observed making.



(225) **(230)**

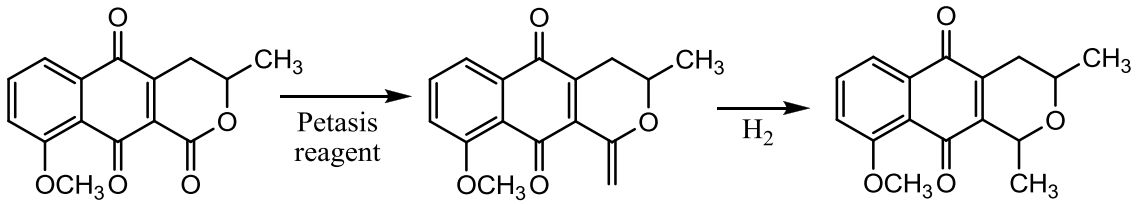
Scheme 84: Attempted Grignard addition

It was decided to try the addition/reduction steps in situ. Lactone **(225)** was treated with 10 equivalents of methyllithium in the presence of tetrahydrofuran at -78 ºC and then reacted at room temperature for 24 hours. Solvent was removed under reduced

pressure and the crude reaction mixture was redissolved in dichloromethane. 15 equivalents of triethylsilane and 4.4 equivalents of boron trifluoride diethyl etherate were added at room temperature and stirred for 8 hours. However, only a black oily mixture of degradation compounds was isolated after work-up.

2.11.2 REDUCTION TO ALKENE VIA TEBBE REACTION

The failure to accomplish Grignard addition to lactone **(225)** led us to decide to try another pathway towards eleutherin **(88)**. Reduction of the ester/lactone moiety using the Petasis reagent would lead to alkene **(231)** which could be hydrogenated to achieve eleutherin **(88) (Scheme 85)**. [141]



(225) **(231)** **(88)**

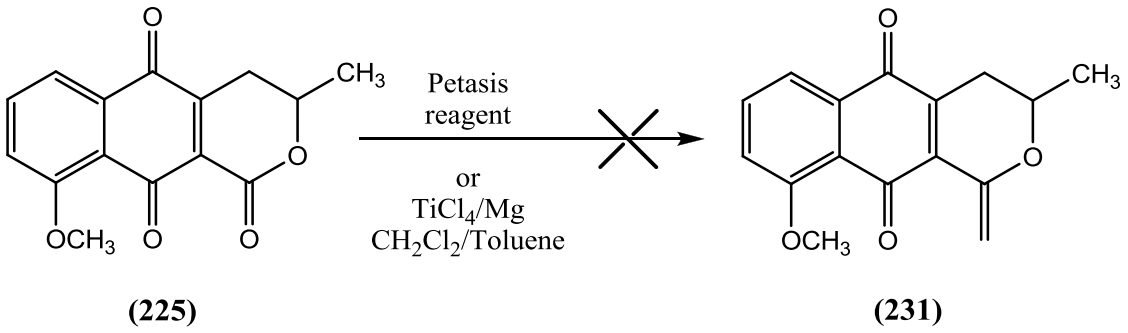
Scheme 85: Methylenation/hydrogenation pathway towards eleutherin (88)

The Petasis reagent or dimethyltitanocene was synthesised by reaction of titanocene dichloride with 2.0 equivalents of methyllithium in toluene at 0 ºC. This compound is very unstable and for this reason it was synthesised as a 0.3 M solution in toluene and kept at 4 ºC.

A solution of lactone **(225)** in toluene was reacted with the Petasis reagent and heated to reflux until the solution colour changed (approximately 30 minutes). After work-up a complex mixture of compounds was obtained none of them corresponding

with the expected alkene **(231)**. Longer reaction time made no difference and the same results were obtained after heating the reaction at reflux for 90 minutes.

Conversion of lactone **(225)** into alkene **(231)** was attempted using methylenation conditions applied previously for the reduction of amide **(202)** to ketone **(204)**.[142] Lactone **(225)** was dissolved in a mixture of dry dichloromethane and tetrahydrofuran (5:8) and added dropwise to a suspension consisting of magnesium and titanium(IV) chloride (1:4) and reacted at 0 ºC for 1 hour. However, these conditions proved to be inefficient and a complex mixture with no trace of the desired alkene was obtained **(Scheme 86)**.



(225) **(231)**

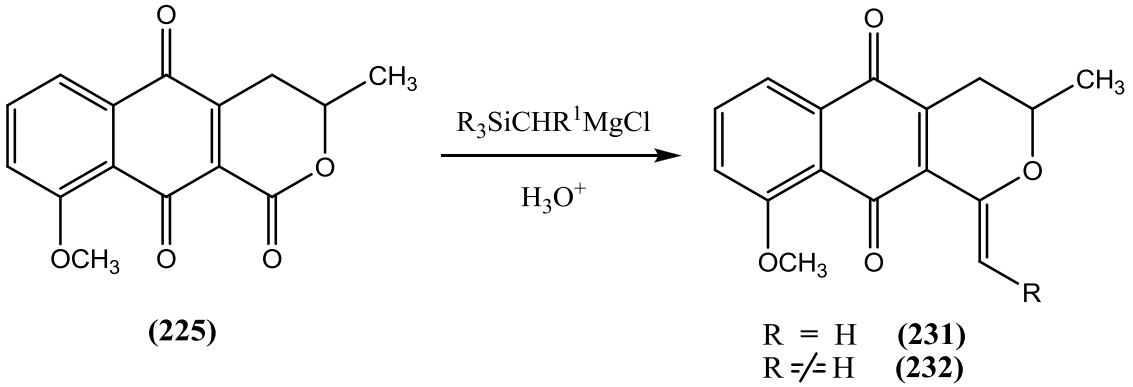
Scheme 86: Attempted reduction of (225) to alkene (231)

Although reduction of **(225)** using the Petasis reagent did not work as expected, alkene **(231)** and its related compounds were very interesting intermediates to investigate due to their possible use as advanced pyranonaphthoquinone precursors.

2.11.3 PETERSON'S OLEFINATION

Peterson olefination allows the preparation of alkenes from α–silylcarbanions. The reaction goes through a β–hydroxysilane intermediate which eliminates under acid or basic conditions to yield the corresponding alkene **(Scheme 87)**.[143] The Peterson olefination was chosen as an alternative to the Tebbe reaction because it could lead to

alkene **(231)** and other related pyranonaphthoquinone derivatives, which would follow the same synthetic pathway towards eleutherin precursor **(205)** as shown in **Scheme 85**.

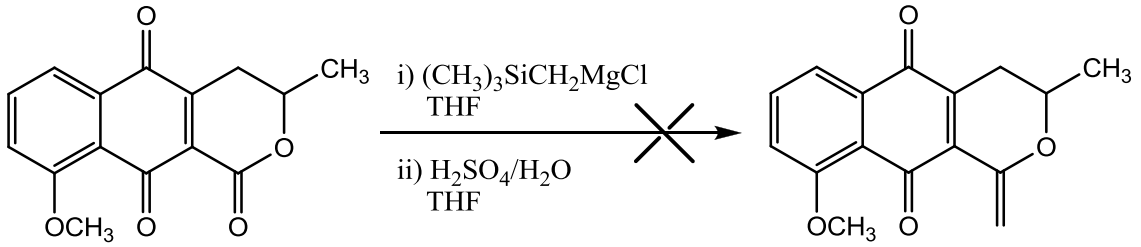


(225)

R = H **(231)**
R ≠ H **(232)**

Scheme 87: Peterson's olefination

In order to achieve alkene **(231)**, lactone **(225)** was treated with 2.0 equivalents of trimethylsilylmethylmagnesium chloride in the presence of tetrahydrofuran at room temperature for 24 hours. After 24 hours aqueous sulfuric acid (2M) was added and the mixture was stirred at room temperature another 24 hours. ^{1}H NMR showed no peaks corresponding to the desired alkene although it showed traces of deprotected compound **(226)**, starting material **(225)** and unknown products **(Scheme 88)**.



(225) **(231)**

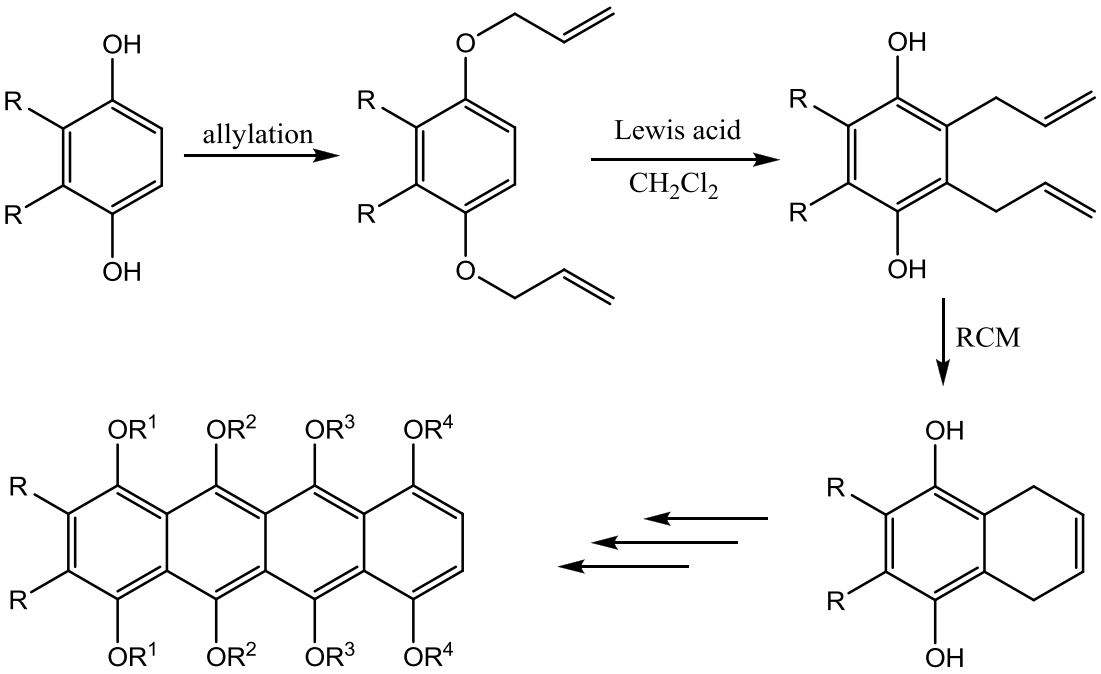
Scheme 88: Attempted reduction of lactone (225) using Peterson's olefination

CHAPTER THREE:

CONCLUSIONS AND FUTURE WORK

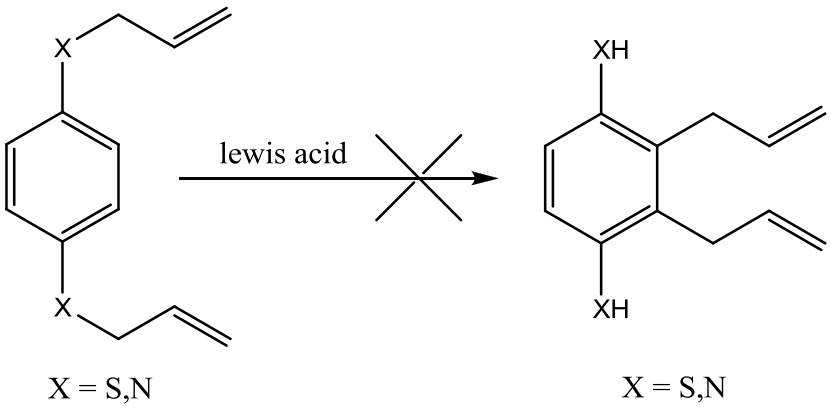
3.1 CONCLUSIONS

We have developed a new Lewis acid mediated double Claisen rearrangement methodology suitable for the synthesis of hydroquinone derivatives. The use of this methodology could be potentially applied to more complex compounds towards the synthesis of compounds with potential antibiotic activity.



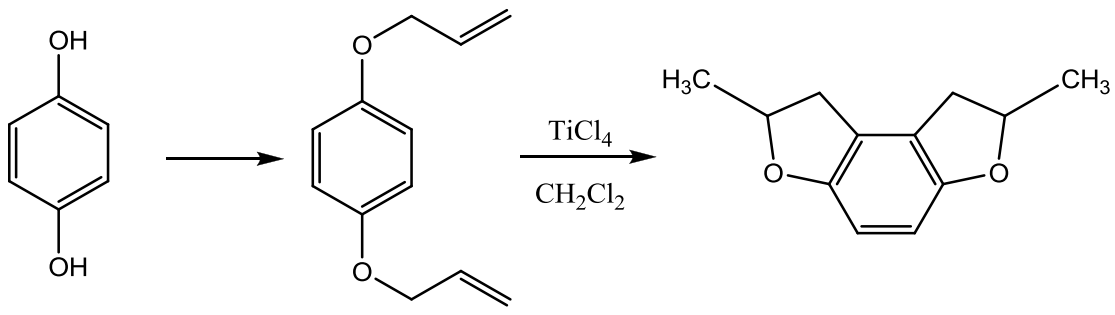
Scheme 89: Novel iterative route towards fused carbon rings

Unfortunately, the Lewis acid mediated double Claisen rearrangement methodology could not be transferred to their sulfur/nitrogen equivalents as they remained unreactive.



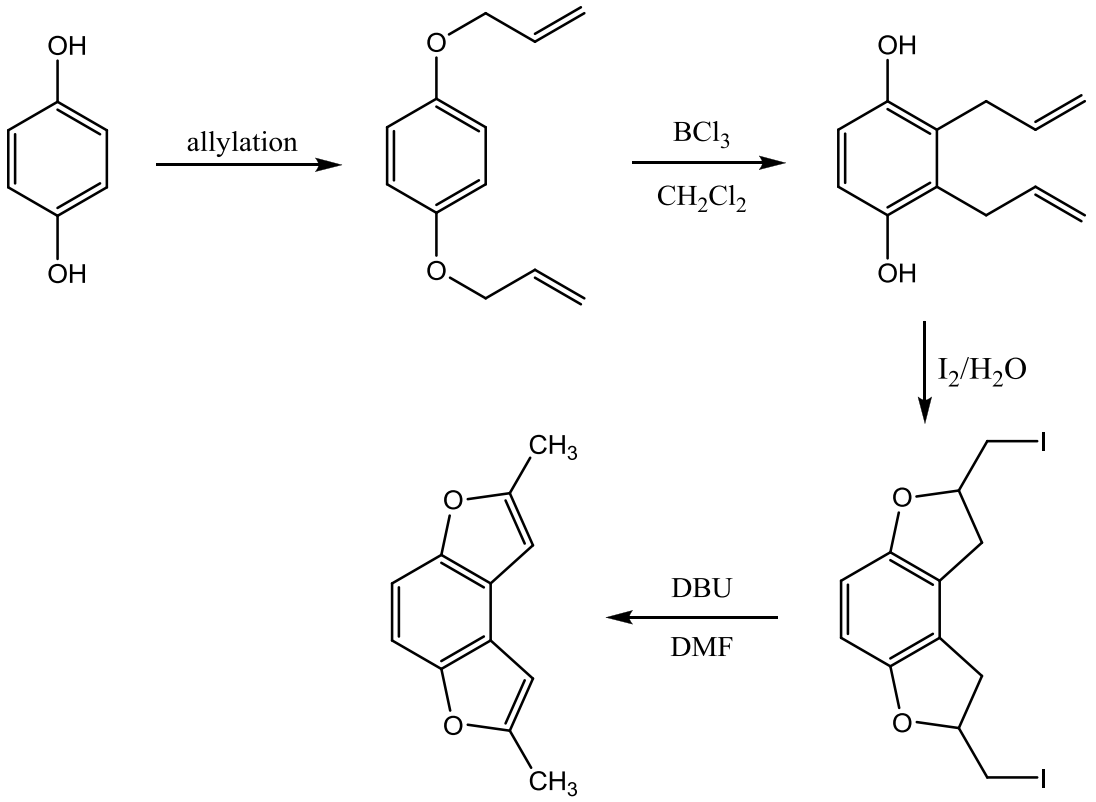
Scheme 90: Attempted double thio/aza-Claisen rearrangement

We have shown the versatility of our methodology by preparing benzodihydrofuran compounds by applying alternative Lewis acids to mediate the reaction.



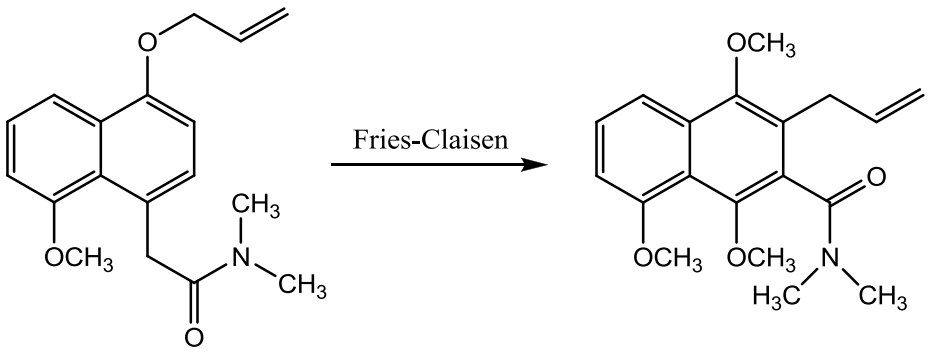
Scheme 91: Synthesis of benzodihydroxyfuran compounds

We have also extended the limits of the Lewis acid mediated double Claisen rearrangement protocol and have applied it to the synthesis of benzodifuran compounds. These compounds have potential interest as components of molecular wires due to their interesting electrical properties.



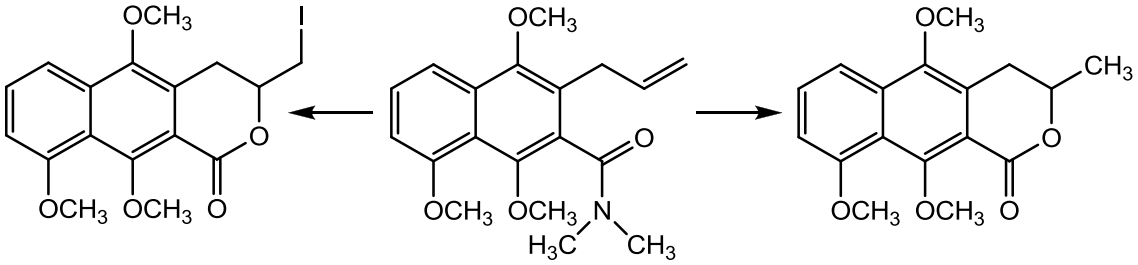
Scheme 92: Synthesis of benzodifuran compounds

We have developed, for the first time, a procedure to carry out a mixed Fries-Claisen rearrangement.



Scheme 93: Mixed Fries-Claisen rearrangement

The potential of this novel methodology has been demonstrated through the synthesis of the pyranonaphthoquinone scaffold, an advanced precursor for eleutherin **(88)** and other pyranonaphthoquinone derivatives such as nanaomycin A **(103)**.

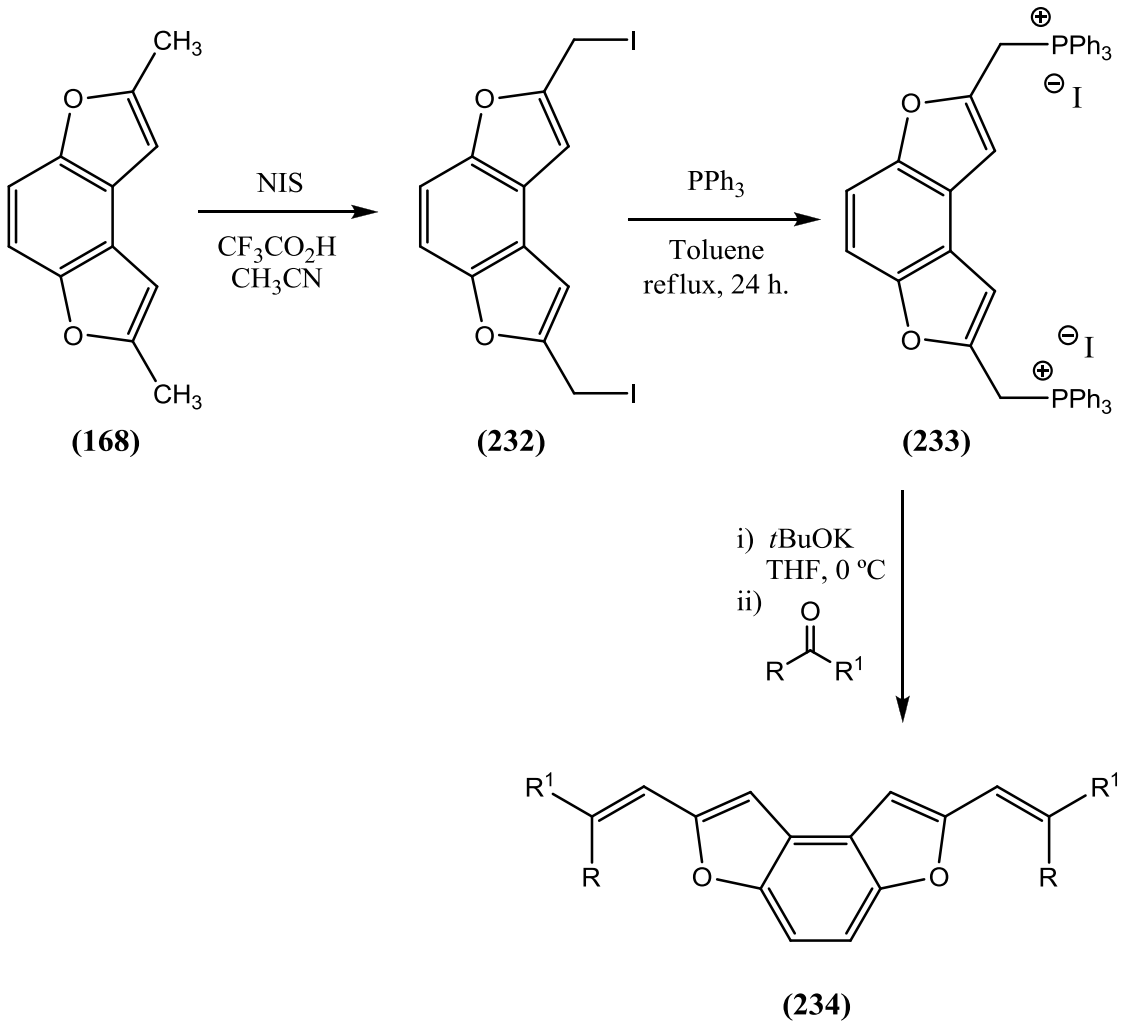


Scheme 94: Mixed Fries-Claisen rearranged product as a precursor for pyranonaphthoquinones

3.2 FUTURE WORK

3.2.1 MOLECULAR WIRES

The functionalisation of benzodifuran compounds could allow coupling with similar structures in a polymeric scaffold increasing the electron delocalization and the conjugation giving access to new compounds with optimal charge carrier ability. In our quest for compounds with structural similarities to polyphenylenevinylene **(111)** we managed to synthesise a range of compounds which could be used as advanced precursors for more complex conjugated molecules. Benzodifuran compounds **(168-170)** could be easily functionalised and coupled with other structures to improve their electrical properties **(Scheme 94)**.



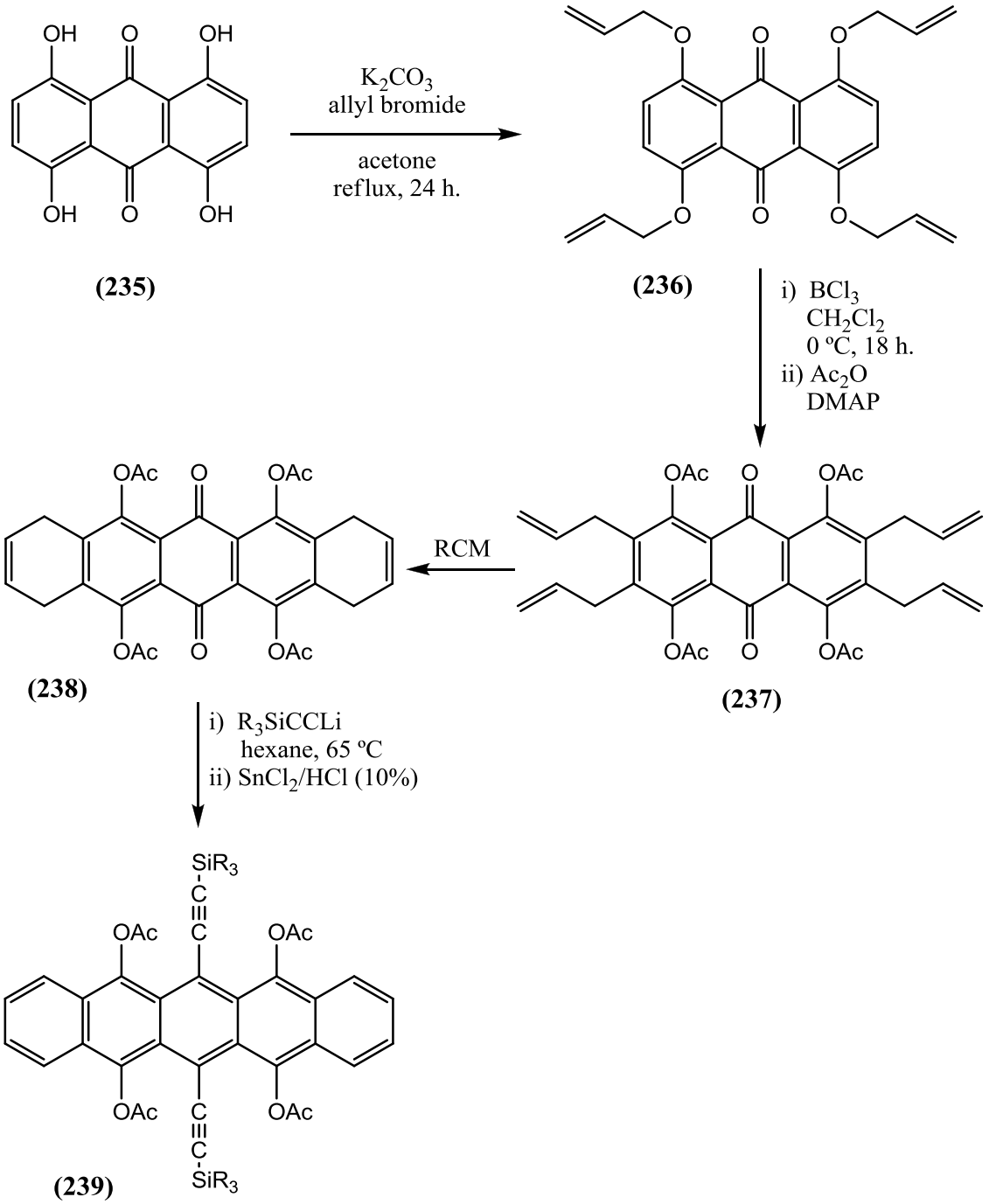
Scheme 95: Potential route towards more complex benzodifuran compounds (234)

Iodination of 2,7-dimethylbenzofuro[5,4-*b*]furan **(168)** with *N*-iodosuccinimide and a catalytic amount of trifluoroacetic acid in the presence of acetonitrile could lead to iodinated compound **(232)**.[144] Treatment of **(232)** with triphenylphosphine in toluene could yield triphenylphosphonium salt **(233)** which could undergo Wittig reaction with ketones or aldehydes to yield highly-conjugated compounds **(234)**.

3.2.2 LINEAR FUSED CARBON RINGS:

By applying the double Claisen methodology we can envisage a versatile way to access functionalised pentacene rings **(Scheme 95)**. As mentioned previously, unsubstituted pentacenes are very unstable and react easily with oxygen.

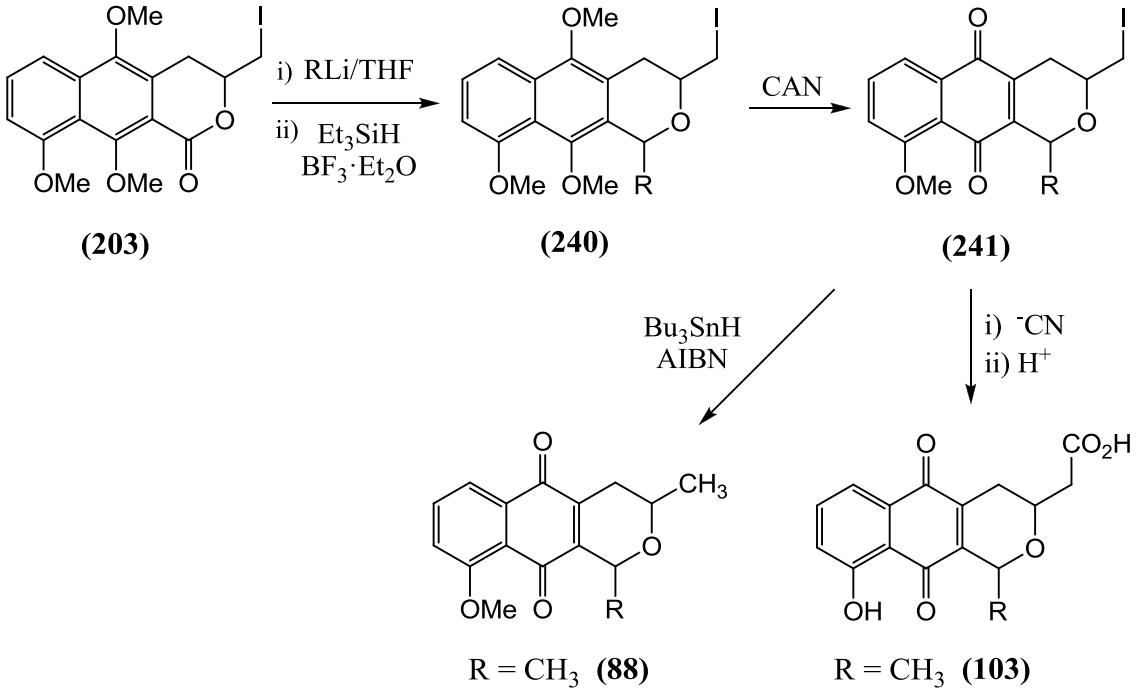
Allylation of 1,4,5,8-tetrahydroxyanthra-9,10-quinone **(235)** by means of potassium carbonate and allyl bromide could produce tetraallylated anthraquinone **(236)** which could undergo Claisen rearrangement under the conditions developed previously **(Table 3)** to yield **(237)**. Protection of the free hydroxyl groups and subsequent cyclisation by RCM could lead to protected pentacene **(238)**. Addition of trialkylsilyllithiated compounds followed by deoxygenation with stannous chloride could yield the desired substituted acene **(239)**.



Scheme 96: Potential route towards highly functionalised fused carbon rings

3.2.3 PYRANONAPHTHOQUINONE DERIVATIVES:

Addition of lithiated compounds to iodolactone **(203)** and elimination of the free hydroxyl group obtained could furnish iodopyran **(240)**. Oxidative demethylation using CAN could yield quinone **(241)** which could act as a building block for more complex structures. Nucleophilic substitution with cyanide and subsequent hydrolysis could yield nanaomycin **(103)** whilst radical elimination of the iodo moiety with tributyltin hydride and azobisisobutyronitrile could yield to racemic eleutherin **(88)**.



Scheme 97: Potential route towards more complex pyranonaphthoquinone derivatives

Later studies in our research group demonstrated the utility of this methodology for the synthesis of eleutherin **(88)** following a similar procedure. Dehalogenation using tributyltin hydride achieved the corresponding methyl-lactone. Addition of methyllithium, removal of the hydroxyl group with triethylsilane and oxidative demethylation using CAN produced eleutherin **(88)**.[145]

CHAPTER 4: EXPERIMENTAL

4.1 GENERAL INFORMATION

Commercial dry solvents were used in all reactions except for light petroleum and ethyl acetate which were distilled before, dichloromethane which was distilled from CaH_2 and tetrahydrofuran which was distilled from sodium. Light petroleum refers to the fractions with a boiling point between 40-60 ºC. Organolithium solutions were titrated against diphenylacetic acid before use. Purification of compounds was carried using flash column chromatography over silica gel or by recrystallisation.

Anhydrous reactions were carried out in oven-dried glassware and under an atmosphere of nitrogen or argon.

Melting points were determined on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance.

Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer on NaCl plates and a Perkin-Elmer Spectrum 65 FT-IR spectrometer on NaCl plates in the range of 600-3800 cm^{-1} following a standard background correction.

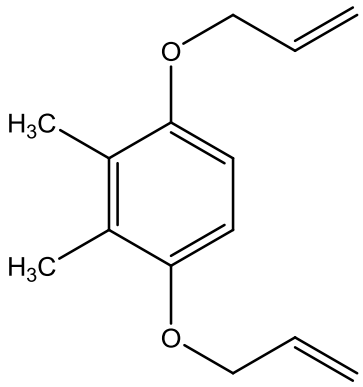
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DPX-400 spectrometer as solutions in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR spectra and $CDCl_3$ standard for ^{13}C NMR spectra unless otherwise specified. Chemical shifts are given in parts per million (ppm). Multiplicity is denoted as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), multiplet (m) or broad (br). Coupling constant (*J*) values are given in hertz (Hz).

High-resolution mass spectrometry was carried out on a Thermo Exactive (Orbi) instrument, where the spectra was recorded in positive ion mode using electrospray ionisation (ES) from methanol or methanol/acid acetic (1% v/v) solution.

Thin layer chromatography using silica gel absorbent was carried out with aluminium backed plates coated with silica gel (Merck Kieselgel 60 F_{254}). Silica gel (Merck Kieselgel 60 H silica) was used for column chromatography, a standard purification procedure, unless otherwise specified.

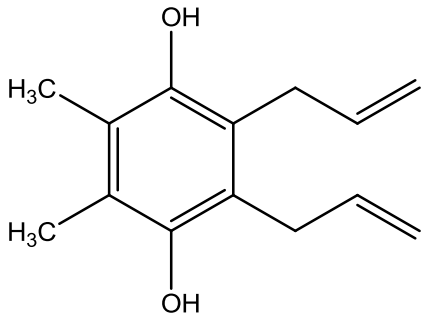
4.2 HYDROXYQUINONE DERIVATIVES

1,4-Bis(allyloxy)-2,3-dimethylbenzene (117)



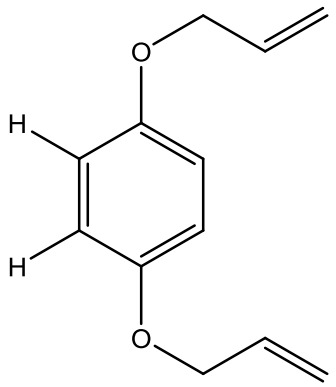
Potassium carbonate (7.5 g, 0.055 mol) and allyl bromide (4.7 mL, 0.055 mol) were added to a stirred solution of 2,3-dimethylhydroquinone (3.0 g, 0.022 mol) in 20 ml of freshly distilled acetone. The mixture was heated at reflux for 24 hours and then filtered. Ethyl acetate (50 mL) was added to the solution and acetone was removed under reduced pressure. The mixture was transferred to a separation funnel and water (100 mL) was added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with water, 1M aqueous NaOH (3x50 mL) and water (1x100 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure to obtain an orange oil. This crude oil was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a white solid (4.17 g, 87% yield); Mp 66 ºC – 68 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3017.6 (CH, st, i), 2920.4 (CH_2 st, i), 2858.3 (CH_3 st, i), 1647.7 (C=C st, md), 1455.8 (CH_2 b, md), 1359.0 (CH_3 b, w), 1254.2 (C-O-C st, md), 995.4 ($CH=CH_2$ oop, w), 788.6 (CH_{ar} b, w); δ_H (400 MHz, $CDCl_3$): 2.258 (6H, s, 2 x C*H*$_3$), 4.52 (4H, dt, *J* 1.6, 5.2 Hz, 2 x OC*H*$_2$CHCH$_2$), 5.31 (2H, dq, *J* 1.6, 10.4 Hz, OCH$_2$CHC*H*$_2$), 5.47 (2H, dq, *J* 1.6, 15.6 Hz, OCH$_2$CHC*H*$_2$), 6.12–6.17 (2H, m, 2 x OCH$_2$C*H*CH$_2$), 6.69 (2H, s, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 12.3 (CH_3), 69.8 (CH_2), 109.6 (CH), 116.7 (CH_2), 127.2 (C), 134.0 (CH), 151.1 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{14}H_{18}NaO_2$ 218.1307, found 218.1306 (+2.02 ppm).

2,3-diallyl-5,6-dimethylbenzene-1,4-diol (118)



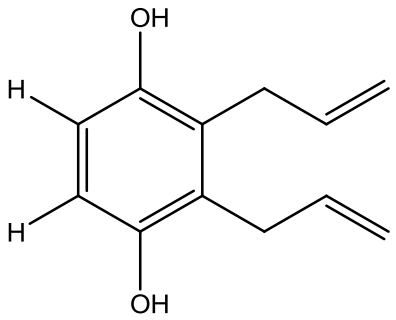
Boron triflouride diethyl etherate (0.5 mL, 0.003 mol) was added dropwise to a solution of 1,2-bis(allyloxy)benzene (0.25 g, 0.001 mol) in 10 mL of anhydrous dichloromethane under N_2 atmosphere at 0 ºC. The solution was stirred at 0 ºC for 18 hours and then water (25 mL) was slowly added. The mixture was transferred to a separation funnel. The two layers were separated and the aqueous layer was extracted with dichloromethane (3x20 mL). The combined organic layers were washed with water (1x100 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a brown solid which was filter-washed with cold hexane (50 ml) (0.16 g, 64 % yield); Mp 93 ºC - 96 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3339.4 (OH st, br), 3154 (CH st, md), 3983.2 (CH_2 st, md), 2980.7 (CH_3 st, md), 1634.6 (C=C st, w), 1480.2 (CH_2 b, w), 1242.1 (C-O-C), 995.1-909.6 ($CH=CH_2$ oop, w), 677.9 (CH_{ar} oop, i); δ_H (400 MHz, $CDCl_3$): 2.04 (6H, s, 2 x ArCH_3), 3.31 (4H, dt, *J* 1.4, 5.2 Hz, 2 x ArCH_2CHCH_2), 4.55 (2H, s, 2 x ArO*H*), 4.99 (2H, dq, *J* 1.8, 10.2 Hz, OCH_2CHCH_2), 5.13 (2H, dq, *J* 1.8, 16.4 Hz, OCH_2CHCH_2), 5.84-5.62 (2H, m, 2 x $ArCH_2CHCH_2$); δ_C (100 MHz, $CDCl_3$): 11.6 (CH_3), 31.1 (CH_2), 115.3 (CH_2), 125.3 (C), 132.7 (C), 138.1 (CH), 148.8 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{14}H_{18}NaO_2$ 241.2813, found 241.2812 (+1.12 ppm).

1,4-Bis(allyloxy)benzene (128)



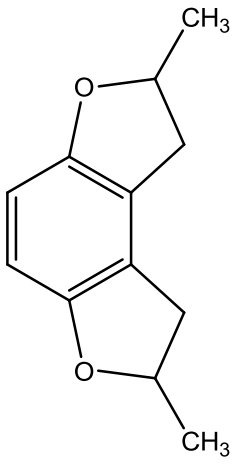
Potassium carbonate (15.6 g, 0.11 mol) was added to a stirred solution of 1,4-hydroquinone (5.0 g, 0.045 mol) in 50 mL of freshly distilled acetone. After 5 minutes of vigorous stirring allyl bromide (9.8 mL, 0.11 mol) was added and the mixture was heated at reflux for 24 hours. After 24 hours the mixture was cooled down at room temperature, diethyl ether (75 mL) was added and the solution was filtered. Acetone was removed under reduced pressure and the solution was transferred to a separation funnel. The mixture was transferred to a separation funnel and water (100 mL) was added. The two layers were separated and the aqueous layer was extracted with diethyl ether (3x75 mL). The combined organic layers were washed with water (1x100 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a white solid (8.00 g, 93% yield); Mp 33 ºC - 34 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3082.1 (CH st, md), 2984.8 (CH_2 st, md), 2910.0 (CH3 st, i), 1640.6 (C=C st, w), 1455.9 (CH_2 b, md), 1253.3 and 1019.6 (C-O-C st, md), 826.5 (CHar. oop, md) ; δ_H (400 MHz, $CDCl_3$): 4.51 (4H, dt, *J* 1.6, 5.2 Hz, 2 x OC*H*$_2$CHCH$_2$), 5.30 (2H, dq, *J* 1.6, 12.0 Hz, OCH$_2$CHC*H*$_2$), 5.43 (2H, dq, *J* 1.6, 17.2 Hz, OCH$_2$CHC*H*$_2$), 6.04-6.12 (2H, m, 2 x OCH$_2$C*H*CH$_2$), 6.88 (4H, s, 4 x Ar*H*). δ_C (100 MHz, $CDCl_3$): 69.6 (CH_2), 115.7 (CH), 116.0 (CH), 117.1 (CH_2), 133.4 (CH), 152.9 (C); FTMS (ES) (M+Na) calculated for $C_{12}H_{14}NaO_2$ 213.0891, found 213.0891 (+0.84 ppm).

2,3-diallylbenzene-1,4-diol (132)



A 1.0 M solution of boron trichloride in dichloromethane (15.8 mL, 0.016 mol) was added dropwise to a solution of 1,4-bis(allyloxy)benzene (1.0 g, 0.0053 mol) in 50 mL of anhydrous dichloromethane under N_2 atmosphere. The solution was stirred at room temperature for 24 hours and then water (50 mL) was added slowly. The mixture was transferred to a separation funnel. The two layers were separated and the aqueous layer was extracted with dichloromethane (3x50 mL). The combined organic layers were washed with water (1x100 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a white solid (0.75 g, 75% yield); Mp: 123 ºC - 125 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3435.5 (OH st, md), 2908.3 (CH st, i), 1663.5 (C=C st, w), 1436.6 (CH_2 b, md), 1209.9 and 1027.7 (C-O-C st, w), 823.6 (CHar. oop, md); δ_H (400 MHz, DMSO): 3.20 (4H, dt, *J* 1.4, 5.4 Hz, 2 x ArCH_2CHCH_2), 5.03 (2H, dq, *J* 1.6, 10.2 Hz, OCH_2CHCH_2), 5.17 (2H, dq, *J* 1.6, 17.0 Hz, OCH_2CHCH_2), 5.90-5.94 (2H, m, 2 x $ArCH_2CHCH_2$), 6.50 (2H, s, 2 x Ar*H*), 8.54 (2H, s, 2 x ArO*H*); δ_C (100 MHz, DMSO): 33.5 (CH_2), 115.3 (CH_2), 116.0 (CH), 124.0 (C), 137.4 (CH), 147.1 (C); FTMS (ES) (M+Na) calculated for $C_{12}H_{14}NaO_2$ 213.0891, found 213.0892 (-1.84 ppm).

2,6-Dimethyl-2,3,6,7-tetrahydrobenzofuro[5,6-*b*]furan (133)

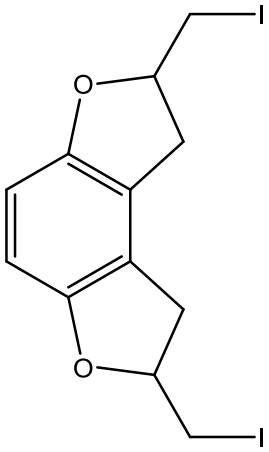


A 1.0 M solution of titanium tetrachloride in dichloromethane (15.8 mL, 0.016 mol) was added dropwise at room temperature to a solution of 1,4-bis(allyloxy)benzene (1.0 g, 0.005 mol) in 45 mL of anhydrous dichloromethane under N_2 atmosphere. The dark solution was stirred for 6 hours at room temperature. The mixture was filtered through a pad of Celite® and washed with 50 mL of dichloromethane. The solvent was removed under reduced pressure. The crude oil achieved was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a mixture of inseparable diastereomers as a dark brown oil (0.76 g, 76% yield). υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 2973.6 (CH st, i), 2928.4 (CH st, i), 2872.7 (CH st, md), 1608.6 (C=C, st, w), 1406.2 (CH_2 b, i), 1428.1 (CH_3 b, i), 1379.2 (CH_3 b, md), 1264.5 and 1024.5 (C-O-C b, i), 863.5 (CHar. oop, w); FTMS (ES) ($M+Na^+$) calculated for $C_{12}H_{14}NaO_2$ 213.0891, found 213.0891 (+1.00 ppm).

Diastereomer 1: δ_H (400 MHz, $CDCl_3$): 1.46 (6H, d, *J* 6.4 Hz, 2 x $ArCH_2CHCH_3$), 2.87-2.93 (4H, m, $ArCH_2CHCH_3$), 4.22-4.29 (2H, m, 2 x $ArCH_2CHCH_3$), 6.52 (2H, s, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 24.9 (CH_3), 41.0 (CH_2), 58.6 (CH), 118.7 (CH), 126.7 (C), 153.6 (C).

Diastereomer 2: δ_H (400 MHz, $CDCl_3$): 1.35 (6H, d, *J* 6.4 Hz, 2 x $ArCH_2CHCH_3$), 2.70 (2H, q, *J* 4.4 Hz, $ArCH_2CHCH_3$), 3.17 (2 x 1H, dd, *J* 8.8, 15.6 Hz, $ArCH_2CHCH_3$), 4.78-4.84 (2H, m, 2 x $ArCH_2CHCH_3$), 6.45 (2H, s, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 21.6 (CH_3), 37.4 (CH_2), 79.7 (CH), 112.9 (CH), 124.3 (C), 147.4 (C).

2,7-bis(iodomethyl)-1,2,7,8-tetrahydrobenzofuro[5,4-*b*]furan (168)

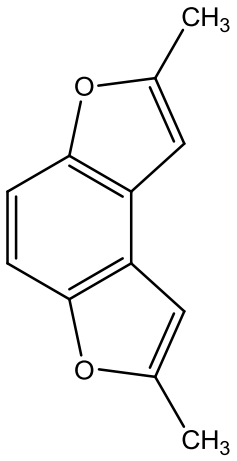


2,3-Diallylbenzene-1,4-diol (1.0 g, 0.005 mol) was stirred in 50 mL of water vigorously (no solution observed). Iodine (3.4 g, 0.013 mol) was added and the mixture was heated at 50 ºC for 18 hours (colour changed to orange). After 18 hours ethyl acetate (50 mL) was added and the mixture was transferred to a separation funnel. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with saturated sodium thiosulfate aqueous solution (2x25 mL) and water (1x50 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a mixture of diastereomers as a yellow solid (1.5 g, 65% yield); Mp: 157 ºC - 159 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3154.8 (CH st, md), 2961.8 (CH st, i), 2898.4 (CH st, md), 1609.2 (C=C st, w), 1459.0 (CH_2 b, md), 1450.1 (CH_3 b, md), 1381.3 (CH_3 b, w), 1238.8 and 1096.0 (C-O-C st, md), 911.0 (CHar. oop, w), 650.8 (C-I st, i); FTMS (ES) ($M+Na^+$) calculated for $C_{12}H_{12}I_2NaO_2$ 464.8824, found 464.8823 (+1.93 ppm).

Diastereomer 1: δ_H (400 MHz, $CDCl_3$): 2.93-2.99 (4H, m, 2 x ArCH_2CHCH_2I), 3.38-3.43 (4H, m, 2 x ArCH_2CHCH_2I), 4.82-4.90 (2H, m, 2 x ArCH_2C*H*CH_2I), 6.52 (2H, s, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 9.0 (CH_2), 36.4 (CH_2), 82.0 (CH), 107.12 (CH), 125.1 (C), 154.0 (C).

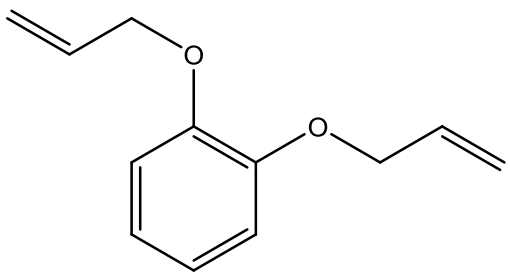
Diastereomer 2: δ_H (400 MHz, $CDCl_3$): 2.93-2.99 (4H, m, 2 x ArCH_2CHCH_2I), 3.38-3.43 (4H, m, 2 x ArCH_2CHCH_2I), 4.82-4.90 (2H, m, 2 x ArCH_2C*H*CH_2I), 6.58 (2H, s, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 8.9 (CH_2), 35.2 (CH_2), 81.8 (CH), 106.1 (CH), 122.5 (C), 153.5 (C).

2,7-dimethylbenzofuro[5,4-*b*]furan (169)



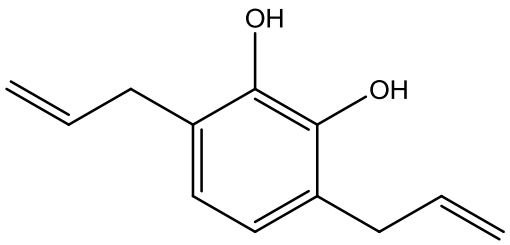
2,7-Bis(iodomethyl)-1,2,7,8-tetrahydrobenzofuro[5,4-*b*]furan (0.100 g, 0.00023 mol) was dissolved in dimethylformamide (5 mL) at room temperature. 1,8-Diazabicyclo[5.4.0] undec-7-ene (0.1 mL, 0.0005 mol) was added and the mixture was stirred at reflux for 18 hours. After 18 hours the mixture was cooled to room temperature and water (15 mL) and ethyl acetate (15 mL) were added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x15 mL). The combined organic layers were washed with water (1x20 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a brown oil (0.03 g, 73% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3155.0 (CH st, w), 2926.8 (CH st, i), 2855.4 (CH st, md), 1615.8 (C=C st, md), 1366.8 (CH_3 b, md), 1262.3 and 1045.7 (C-O-C st, md), 851.2 (CHar. oop, w); δ_H (400 MHz, $CDCl_3$): 2.45 (6H, s, 2 x ArCHCCH_3), 6.38 (2H, s, 2 x ArC*H*CCH_3), 7.40 (2H, s, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 14.3 (CH_3), 100.5 (CH), 102.7 (CH), 126.0 (C), 151.7 (C), 155.5 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{12}H_{10}NaO_2$ 209.0578, found 209.0578 (+0.42 ppm).

1,2-Bis(allyloxy)benzene (126)



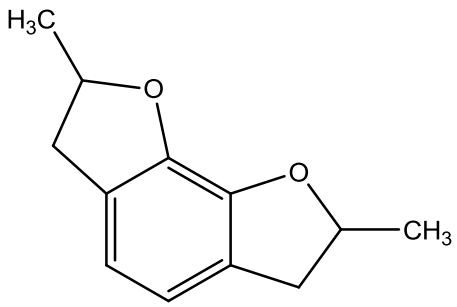
Potassium carbonate (15.6 g, 0.113 mol) was added to a stirred solution of catechol (5.0 g, 0.045 mol) in 50 mL of freshly distilled acetone. After 5 minutes of vigorous stirring allyl bromide (9.8 mL, 0.113 mol) was added and the mixture was heated at reflux for 24 hours. After 24 hours the mixture was cooled down at room temperature, ethyl acetate (75 mL) was added and the solution was filtered. Acetone was removed under reduced pressure and the solution was transferred to a separation funnel. The mixture was transferred to a separation funnel and water (100 mL) was added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x75 mL). The combined organic layers were washed with water (1x100 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a orange oil (8.60 g, 87% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3016.8 (CH st, md), 2863.4 (CH st, w), 1647.2 (C=C st, i), 1452.8 (CH_2 b, md), 1253.9 and 1019.3 (C-O-C st, i), 996.5 and 925.6 ($CH=CH_2$ oop, md); δ_H (400 MHz, $CDCl_3$): 4.64 (4H, dt, *J* 1.6, 5.2 Hz, 2 x OCH_2CHCH_2), 5.31 (2H, dq, *J* 1.6, 10.4 Hz, OCH_2CHCH_2), 5.46 (2H, dq, *J* 1.6, 17.2 Hz, OCH_2CHCH_2), 6.10-6.09-6.17 (2H, m, 2 x OCH_2CHCH_2), 6.95 (4H, s, 4 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 69.9 (CH_2), 114.1 (CH), 117.8 (CH_2), 121.6 (CH), 133.4 (CH), 148.7 (C); FTMS (ES) (M+Na) calculated for $C_{12}H_{14}NaO_2$ 213.0891, found 213.0893 (-2.84 ppm).

3,6-diallylbenzene-1,2-diol (130)



A 1.0 M solution of boron trichloride in dichloromethane (15.8 mL, 0.016 mol) was added dropwise to a solution of 1,2-bis(allyloxy)benzene (1.0 g, 0.0053 mol) in 50 mL of anhydrous dichloromethane under N_2 atmosphere. The solution was stirred at room temperature for 24 hours and then water (50 mL) was added slowly. The mixture was transferred to a separation funnel. The two layers were separated and the aqueous layer was extracted with dichloromethane (3x50 mL). The combined organic layers were washed with water (1x100 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude oil was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a brown oil (0.69 g, 69% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3420.7 (OH st, i), 1653.3 (C=C st, i), 1437.7 (CH_2 b, md), 1207.1 and 1025.9 (C-O-C st, md), 825.1 (CHar. oop, md); δ_H (400 MHz, $CDCl_3$): 3.19 (4H, dt, *J* 1.6, 6.4 Hz, 2 x Ar*C*H_2CHCH_2), 4.91 (2H, dq, *J* 2.0, 17.0 Hz, ArCH_2CHCH_2), 4.96 (2H, dq, *J* 2.0, 10.2 Hz, ArCH_2CHCH_2), 5.81-5.89 (2H, m, 2 x ArCH_2C*H*CH_2), 6.66 (2H, s, 2 x Ar*H*), 7.19 (2H, s, 2 x ArO*H*); δ_C (100 MHz, $CDCl_3$): 36.4 (CH_2), 115.6 (CH_2), 116.7 (CH), 130.6 (C), 137.3 (CH), 141.8 (C); FTMS (ES) (M+Na) calculated for $C_{12}H_{14}NaO_2$ 213.0891, found 213.0893 (-3.04 ppm).

2,7-Dimethyl-2,3,6,7-tetrahydrobenzofuro[7,6-*b*]furan (131)

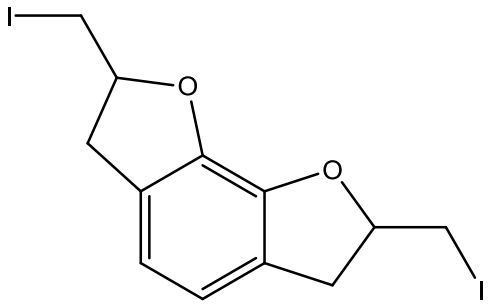


A 1.0 M solution of titanium tetrachloride in dichloromethane (15.8 mL, 0.016 mol) was added dropwise at room temperature to a solution of 1,2-bis(allyloxy)benzene (1.0 g, 0.005 mol) in 45 mL of anhydrous dichloromethane under N_2 atmosphere. The dark solution was stirred for 6 hours at room temperature. The mixture was filtered through a pad of Celite® and washed with 50 mL of dichloromethane. The solvent was removed under reduced pressure. The crude oil achieved was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a mixture of diastereomers as a dark brown oil (0.66 g, 66% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 2975.3 (CH st, i), 2926.6 (CH st, md), 1625.2 (C=C st, md), 1455.5 (CH_2 b, i), 1378.2 (CH_3 b, md), 1262.2 and 1012.7 (C-O-C st, md), 844.3 (CHar. oop, w); FTMS (ES) (M+Na) calculated for $C_{12}H_{14}NaO_2$ 213.0891, found 213.0891 (+0.93 ppm).

Diastereomer 1: δ_H (400 MHz, $CDCl_3$): 1.45 (6H, d, *J* 2.4 Hz, 2 x ArOCHC*H*$_3$), 2.95-2.99 (4H, m, 2 x ArC*H*$_2$CHCH$_3$), 4.29-4.31 (2H, m, 2 x ArOC*H*CH$_3$), 6.59 (2H, s, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 25.0 (CH_3), 41.1 (CH_2), 59.2 (CH), 123.7 (CH), 127.2 (C), 146.0 (C).

Diastereomer 2: δ_H (400 MHz, $CDCl_3$): 1.43 (6H, d, *J* 2.4 Hz, 2 x ArOCHC*H*$_3$), 2.95-2.99 (4H, m, 2 x ArC*H*$_2$CHCH$_3$), 4.29-4.31 (2H, m, 2 x ArOC*H*CH$_3$), 6.58 (2H, s, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 24.9 (CH_3), 41.0 (CH_2), 58.3 (CH), 122.7 (CH), 126.7 (C), 138.9 (C).

2,7-Bis(iodomethyl)-2,3,6,7-tetrahydrobenzofuro[7,6-*b*]furan (172)

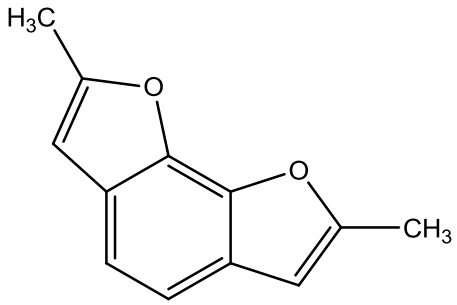


3,6-Diallylbenzene-1,2-diol (1.0 g, 0.005 mol) was stirred in 50 mL of water vigorously (no solution observed). Iodine (3.4 g, 0.013 mol) was added and the mixture was heated at 50 ºC for 18 hours (colour changed to orange). After 18 hours ethyl acetate (50 mL) was added and the mixture was transferred to a separation funnel. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with saturated sodium thiosulfate aqueous solution (2x25 mL) and water (1x50 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a mixture of diastereomers as a brown oil (0.7 g, 29% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3144.5 (CH st, md), 2961.8 (CH st, i), 1684.7 (C=C st, w), 1468.3 (CH_2 b, md), 1248.8 (C-O-C st, i), 667.9 (C-I st, md); FTMS (ES) ($M+Na^+$) calculated for $C_{12}H_{12}I_2NaO_2$ 464.8824, found 464.8822 (+3.00 ppm).

Diastereomer 1: δ_H (400 MHz, $CDCl_3$): 2.99-3.05 (4H, m, 2 x ArCH_2CHCH_2I), 3.40-3.49 (4H, m, 2 x ArCH_2CHCH_2I), 4.87-4.94 (2H, m, 2 x ArCH_2C*H*CH_2I), 6.62 (2H, s, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 9.2 (CH_2), 36.6 (CH_2), 83.7 (CH), 120.1 (CH), 124.0 (C), 148.1 (C).

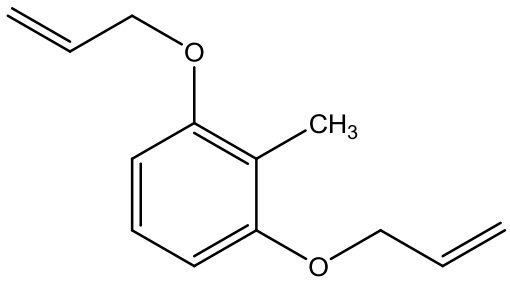
Diastereomer 2: δ_H (400 MHz, $CDCl_3$): 2.99-3.05 (4H, m, 2 x ArCH_2CHCH_2I), 3.40-3.49 (4H, m, 2 x ArCH_2CHCH_2I), 4.87-4.94 (2H, m, 2 x ArCH_2C*H*CH_2I), 6.70 (2H, s, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 8.9 (CH_2), 34.9 (CH_2), 81.2 (CH), 119.4 (CH), 123.6 (C), 147.7 (C).

2,7-Dimethylbenzofuro[7,6-*b*]furan (173)



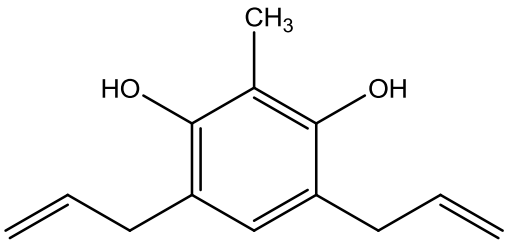
2,7-Bis(iodomethyl)-2,3,6,7-tetrahydrobenzofuro[7,6-*b*]furan (0.100 g, 0.0002 mol) was dissolved in dimethylformamide (5 mL) at room temperature. 1,8-Diazabicyclo[5.4.0] undec-7-ene (0.1 mL, 0.0005 mol) was added and the mixture was stirred at reflux for 18 hours. After 18 hours the mixture was cooled to room temperature and water (15 mL) and ethyl acetate (15 mL) were added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x15 mL). The combined organic layers were washed with water (1x20 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude oil was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain (0.03 g, 73% yield) a brown oil; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3150.0 (CH st, md), 2936.8 (CH st, i), 1612.8 (C=C st, md), 1368.8 (CH_3 b, md), 1261.7 (C-O-C st, md), 848.2 (CHar. oop, w); δ_H (400 MHz, $CDCl_3$): 2.43 (6H, s, 2 x ArCHCC*H*$_3$), 6.37 (2H, s, ArC*H*CCH$_3$), 7.24 (2H, s, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 14.3 (CH_3), 101.6 (CH), 103.9 (CH), 125.8 (C), 151.0 (C), 155.8 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{12}H_{10}NaO_2$ 209.0578, found 209.0578 (-0.99 ppm).

1,3-Bis(allyloxy)-2-methylbenzene (129)



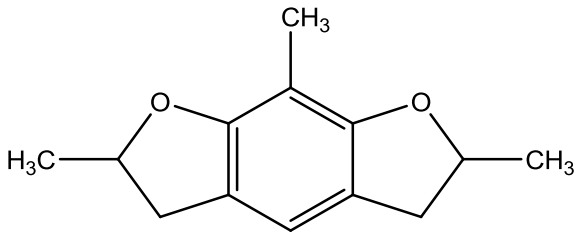
Potassium carbonate (13.9 g, 0.101 mol) was added to a stirred solution of 2-methylresorcinol (5.0 g, 0.041 mol) in 50 mL of freshly distilled acetone. After 5 minutes of vigorous stirring allyl bromide (8.7 mL, 0.101 mol) was added and the mixture was heated at reflux for 24 hours. After 24 hours the mixture was cooled down at room temperature, diethyl ether (75 mL) was added and the solution was filtered. Acetone was removed under reduced pressure and the solution was transferred to a separation funnel. The mixture was transferred to a separation funnel and water (100 mL) was added. The two layers were separated and the aqueous layer was extracted with diethyl ether (3x75 mL). The combined organic layers were washed with water (1x100 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a yellow oil (7.15 g, 87% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3016.8 (CH st, md), 2919.4 (CH st, i), 2862.3 (CH st, md), 1647.1 (C=C st, w), 1472.3 (CH_2 b, md), 1369.1 (CH_3 b, w), 1252.1 and 1011.9 (C-O-C st, md), 993.7 and 922.9 (CH=CH_2 oop, md); δ_H (400 MHz, $CDCl_3$): 2.28 (3H, s, ArC*H*$_3$), 4.60 (4H, dt, *J* 1.6, 5.2 Hz, 2 x ArC*H*$_2$CHCH$_2$), 5.35 (2H, dq, *J* 1.6, 10.8 Hz, ArCH$_2$CHC*H*$_2$), 5.52 (2H, dq, *J* 1.6, 17.2 Hz, ArCH$_2$CHC*H*$_2$), 6.11-6.17 (2H, m, 2 x ArCH$_2$C*H*CH$_2$), 6.60 (2H, d, *J* 8.4 Hz, 2 x Ar*H*), 7.15 (1H, t, *J* 8.0 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$): 8.5 (CH_3), 69.5 (CH_2), 104.7 (CH), 115.4 (C), 116.9 (CH_2), 125.4 (CH), 133.3 (CH), 159.9 (C); FTMS (ES) (M+Na) calculated for $C_{13}H_{16}NaO_2$ 227.1048, found 227.1050 (-3.04 ppm).

4,6-Diallyl-2-methylbenzene-1,3-diol (134)



A 1.0 M solution of boron trichloride (14.8 mL, 0.015 mol) was added dropwise to a solution of 1,3-bis(allyloxy)-2-methylbenzene (1.0 g, 0.0049 mol) in 50 mL of anhydrous dichloromethane under N_2 atmosphere. The solution was stirred at room temperature for 24 hours and then water (50 mL) was added slowly. The mixture was transferred to a separation funnel. The two layers were separated and the aqueous layer was extracted with dichloromethane (3x50 mL). The combined organic layers were washed with water (1x100 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain an orange solid (0.72 g, 72% yield); Mp: 52 ºC - 54 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3504.9 (OH st, i), 3054.4 (CH st, md), 2984.3 (CH st, md), 2853.2 (CH st, md), 1677.1 (C=C st, w), 1637.3 (C=C st, w), 1616.8 (C=C st, w), 1431.8 (CH_2 b, md), 1388.5 (CH_3 b, md), 1265.9 and 1060.6 (C-O-C st, md), 926.2 (C=CH oop, w); δ_H (400 MHz, $CDCl_3$): 2.170 (3H, s, $ArCH_3$), 3.36 (4H, dt, *J* 1.2, 6.4 Hz, 2 x $ArCH_2CHCH_2$), 4.99 (2H, s, 2 x ArO*H*), 5.16 (2H, dq, *J* 2.0, 10.6 Hz, 2 x $ArCH_2CHCH_2$), 5.21 (2H, dq, J 2.0, 17.2 Hz, 2 x $ArCH_2CHCH_2$), 5.97-6.06 (2H, m, 2 x $ArCH_2CHCH_2$), 6.71 (1H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$): 8.4 (CH_3), 35.4 (CH_2), 111.4 (C), 116.4 (CH_2), 116.5 (C), 128.3 (CH), 137.0 (CH), 152.0 (C); FTMS (ES) (M+Na) calculated for $C_{13}H_{16}NaO_2$ 227.1049, found 227.1048 (-2.41 ppm).

2,6,8-Trimethyl-2,3,5,6-tetrahydrobenzofuro[6,5-*b*]furan (135)

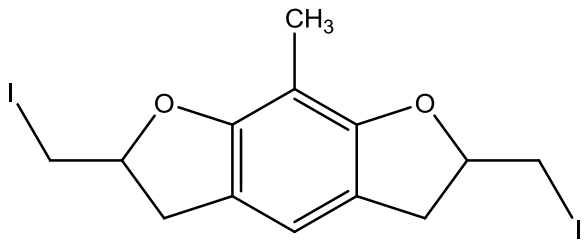


A 1.0 M solution of titanium tetrachloride in dichloromethane (14.7 mL, 0.015 mol) was added dropwise at room temperature to a solution of 1,3-bis(allyloxy)-2-methylbenzene (1.0 g, 0.0045 mol) in 45 mL of anhydrous dichloromethane under N_2 atmosphere. The dark solution was stirred for 6 hours at room temperature. The mixture was filtered through a pad of Celite® and washed with 50 mL of dichloromethane. The solvent was removed under reduced pressure. The crude oil achieved was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a mixture of diastereomers as a red-orange oil (0.73 g, 73% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 2976.0 (CH st, md), 2927.6 (CH st, i), 2867.0 (CH st, md), 1612.9 (C=C st, md), 1446.5 (CH_2 b, md), 1378.5 (CH_3 b, md), 1276.8 and 1010.4 (C-O-C st, md), 847.8 (CHar. oop, w); FTMS (ES) (M+Na) calculated for $C_{13}H_{16}NaO_2$ 227.1047, found 227.1048 (+1.14 ppm).

Diastereomer 1: δ_H (400 MHz, $CDCl_3$): 1.46 (6H, d, *J* 6.0 Hz, 2 x ArOCHC*H*$_3$), 2.08 (3H, s, ArC*H*$_3$), 2.86-2.93 (4H, m, 2 x ArC*H*$_2$CHCH$_3$), 4.20-4.26 (2H, m, 2 x ArOC*H*CH$_3$), 6.66 (1H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$): 8.7 (CH_3), 24.8 (CH_3), 41.2 (CH_2), 59.0 (CH), 110.7 (C), 116.4 (C), 131.1 (CH), 151.6 (C).

Diastereomer 2: δ_H (400 MHz, $CDCl_3$): 1.38 (6H, d, *J* 6.0 Hz, 2 x ArOCHC*H*$_3$), 2.06 (3H, s, ArC*H*$_3$), 2.86-2.93 (4H, m, 2 x ArC*H*$_2$CHCH$_3$), 4.20-4.26 (2H, m, 2 x ArOC*H*CH$_3$), 6.57 (1H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$): 8.7 (CH_3), 22.3 (CH_3), 41.1 (CH_2), 56.5 (CH), 110.6 (C), 116.4 (C), 131.0 (CH), 153.0 (C).

2,6-Bis(iodomethyl)-8-methyl-2,3,5,6-tetrahydrobenzofuro[6,5-*b*]furan (170)

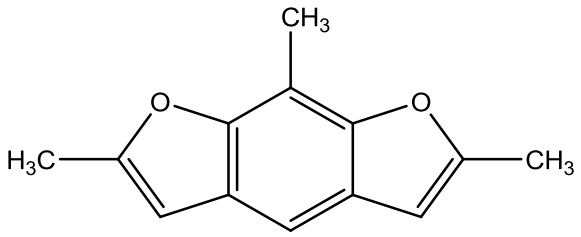


4,6-Diallyl-2-methylbenzene-1,3-diol (0.25 g, 0.0012 mol) was stirred in 20 mL of water vigorously (no solution observed). Iodine (0.761 g, 0.003 mol) was added and the mixture was heated at 50ºC for 18 hours. After 18 hours ethyl acetate (25 mL) was added and the mixture was transferred to a separation funnel. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x25 mL). The combined organic layers were washed with saturated sodium thiosulfate aqueous solution (2x25 mL) and water (1x50 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude oil achieved was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a mixture of diastereomers as a yellow solid (0.36 g, 65% yield); Mp: 175 ºC – 177 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3134.5 (CH st, md), 2958.8 (CH st, i), 2745.9 (CH st, md), 1693.1 (C=C st, w), 1448.9 (CH_2 b, md), 1383.4 (CH_3 b, md), 1237.7 and 1046.0 (C-O-C st, i), 865.2 (CHar. oop, md), 651.3 (C-I, st, md); FTMS (ES) (M+) calculated for $C_{13}H_{14}IO_2$ 455.9083, found 455.9085 (+2.71 ppm).

Diastereomer 1: δ_H (400 MHz, $CDCl_3$): 2.62 (3H, s, ArC*H*$_3$), 2.91-2.99 (4H, m, 2 x ArC*H*$_2$CHCH$_2$I), 3.39-3.46 (4H, m, 2 x ArCH$_2$CHC*H*$_2$I), 4.85-4.88 (2H, m, 2 x ArCH$_2$C*H*CH$_2$I), 7.14 (1H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$): 9.3 (CH_2), 10.2 (CH_3), 35.2 (CH_2), 81.9 (CH), 126.9 (CH), 117.5 (C), 125.4 (C), 155.1 (C).

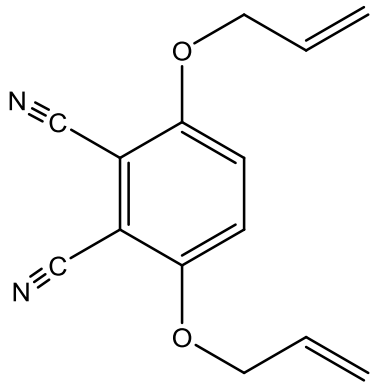
Diastereomer 2: δ_H (400 MHz, $CDCl_3$): 2.61 (3H, s, ArC*H*$_3$), 2.91-2.99 (4H, m, 2 x ArC*H*$_2$CHCH$_2$I), 3.39-3.46 (4H, m, 2 x ArCH$_2$CHC*H*$_2$I), 4.85-4.88 (2H, m, 2 x ArCH$_2$C*H*CH$_2$I), 6.91 (1H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$): 9.1 (CH_2), 10.1 (CH_3), 33.6 (CH_2), 81.9 (CH), 116.8 (C), 122.3 (CH), 125.4 (C), 156.0 (C).

2,6,8-Trimethylbenzofuro[6,5-*b*]furan (171)



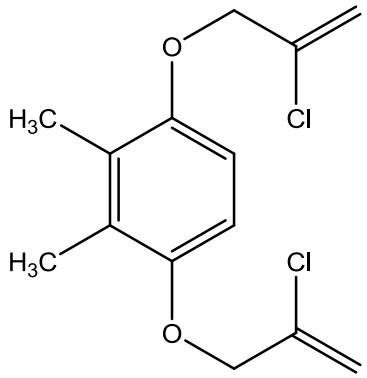
2,6-Bis(iodomethyl)-8-methyl-2,3,5,6-tetrahydrobenzofuro[6,5-*b*]furan (0.600 g, 0.0014 mol) was dissolved in dimethylformamide (10 mL) at room temperature. 1,8-diazabicyclo[5.4.0] undec-7-ene (0.45 mL, 0.003 mol) was added and the mixture was stirred at reflux for 18 hours. After 18 hours the mixture was cooled to room temperature and water (15 mL) and ethyl acetate (15 mL) were added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x15 mL). The combined organic layers were washed with water (1x20 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a brown oil (0.17 g, 70% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 2924.7 (CH st, md), 2856.0 (CH st, md), 1676.8 (C=C st, w), 1615.2 (C=C st, w), 1386.8 (CH3 b, md) 1278.1 and 1099.1 (C-O-C st, md), 939.1 (CHar.oop, md); δ_H (400 MHz, $CDCl_3$): 2.39 (6H, s, 2 x ArCHCC*H*$_3$), 2.61 (3H, s, ArC*H*$_3$), 6.33 (2H, s, 2 x ArC*H*CCH$_3$), 7.23 (1H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$): 8.7 (CH_3), 14.2 (CH_3), 102.3 (CH), 103.4 (C), 106.4 (CH), 125.8 (C), 151.7 (C), 154.4 (C); FTMS (ES) (M+Na) calculated for $C_{13}H_{12}NaO_2$ 223.0735, found 223.0736 (-1.21 ppm).

1,4-Bis(allyloxy)-2,3-dicyanobenzene (122)



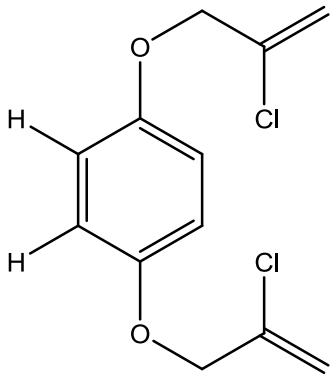
Potassium carbonate (5.4 g, 0.040 mol) was added to a stirred solution of 1,4-dicyanohydroquinone (2.5 g, 0.016 mol) in 50 mL of freshly distilled acetone. After 5 minutes of vigorous stirring allyl bromide (3.5 mL, 0.040 mol) was added and the mixture was heated at reflux for 24 hours. After 24 hours the mixture was cooled down at room temperature, ethyl acetate (50 mL) was added and the solution was filtered. Acetone was removed under reduced pressure and the solution was transferred to a separation funnel. The mixture was transferred to a separation funnel and water (100 mL) was added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with water (1x100 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a white solid (2.65 g, 71% yield); Mp: 170 ºC - 171 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3045.0 (CH st, md), 2910.3 (CH st, md), 2250.5 (C≡N st, i), 1658.4 (C=C st, w), 1460.4 (CH_2 b, md), 1281.4 (C-0-C st, md), 826.1 (CHar. oop, w); δ_H (400 MHz, $CDCl_3$): 4.59 (4H, dt, *J* 1.6, 5.2 Hz, 2 x O*C*H_2CHCH_2), 5.29 (2H, dq, *J* 1.6, 17.6 Hz, OCH_2CHCH_2), 5.38 (2H, dq, *J* 1.6, 10.6 Hz, OCH_2CHCH_2), 5.91-5.97 (2H, m, 2 x OCH_2C*H*CH_2), 7.106 (2H, s, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 70.6 (CH_2), 105.6 (C), 113.0 (C), 118.9 (CH_2), 119.0 (CH), 131.4 (CH), 154.8 (C); FTMS (ES) (M+Na) calculated for $C_{14}H_{12}N_2O_2$ 240.0899, found 240.0901 (-2,23 ppm).

1,4-Bis(2-chloroallyloxy)-2,3-dimethylbenzene (163)



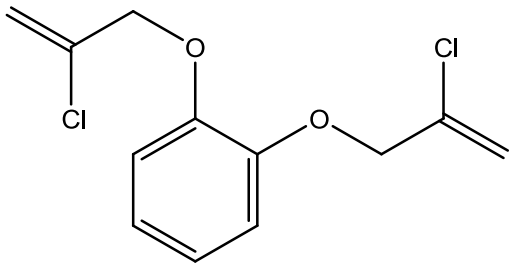
Potassium carbonate (7.95 g, 0.057 mol) was added to a stirred solution of 2,3-dimethylhydroquinone (3.0 g, 0.022 mol) in 50 mL of freshly distilled acetone. After 5 minutes of vigorous stirring 2,3-dichloropropene (5.25 mL, 0.057 mol) was added and the mixture was heated at reflux for 24 hours. After 24 hours the mixture was cooled down at room temperature, diethyl ether (25 mL) was added and the solution was filtered. Acetone was removed under reduced pressure and the solution was transferred to a separation funnel. The mixture was transferred to a separation funnel and water (50 mL) was added. The two layers were separated and the aqueous layer was extracted with diethyl ether (3x25 mL). The combined organic layers were washed with 1M sodium hydroxide solution (1x25 mL) and water (1x25 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a yellow oil (2.6 g, 42% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3016.3 (CH st, md), 2927.1 (CH st, md), 1642.1 (C=C st, w), 1482.8 (CH_2 b, md), 1383.4 (CH_3 b, md), 1260.4 and 1100.0 (C-O-C st, md), 908.5 (CHar. oop, w), 735.5 (C-Cl st, md); δ_H (400 MHz, $CDCl_3$): 2.14 (6H, s, 2 x ArCH_3), 4.43 (4H, t, *J* 1.6 Hz, 2 x OCH_2CClCH_2), 5.35 (2H, dd, *J* 1.6, 3.2 Hz, OCH_2CClCH_2), 4.50 (2H, dd, *J* 1.2, 3.2 Hz, OCH_2CClCH_2), 6.51 (2H, s, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 31.0 (CH_3), 71.5 (CH_2), 110.8 (CH), 113.3 (CH_2), 124.3 (C), 137.0 (C), 150.1 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{14}H_{16}{}^{35}Cl_2NaO_2$ 309.0425, found 309.0424 (+1.55 ppm).

1,4-Bis(2-chloroallyloxy)benzene (165)



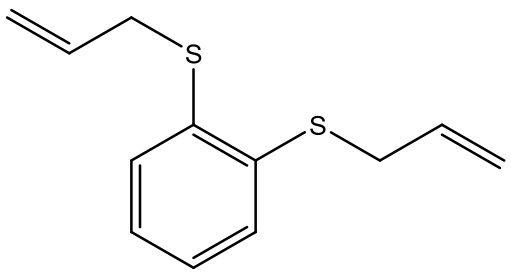
Potassium carbonate (7.95 g, 0.057 mol) was added to a stirred solution of 1,4-hydroquinone (2.5 g, 0.023 mol) in 50 mL of freshly distilled acetone. After 5 minutes of vigorous stirring 2,3-dichloropropene (5.25 mL, 0.057 mol) was added and the mixture was heated at reflux for 24 hours. After 24 hours the mixture was cooled down at room temperature, diethyl ether (25 mL) was added and the solution was filtered. Acetone was removed under reduced pressure and the solution was transferred to a separation funnel. The mixture was transferred to a separation funnel and water (50 mL) was added. The two layers were separated and the aqueous layer was extracted with diethyl ether (3x25 mL). The combined organic layers were washed with 1M sodium hydroxide solution (1x25 mL) and water (1x25 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a grey solid (2.9 g, 48% yield); Mp: 153 ºC – 155 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3155.0 (CH st, md), 2926.8 (CH st, i), 1640.4 (C=C st, w), 1457.5 (CH_2 b, md), 1214.8 and 1053.2 (C-O-C st, md), 909.0 (CHar. oop, w), 735.0 (C-Cl st, md); δ_H (400 MHz, $CDCl_3$): 4.53 (4H, t, *J* 1.8 Hz, 2 x OC*H*$_2$CClCH$_2$), 5.43 (2H, dd, *J* 1.6, 3.2, Hz, OCH$_2$CClC*H*$_2$), 5.54 (2H, dd, *J* 1.2, 3.2 Hz, OCH$_2$CClC*H*$_2$), 6.87 (4H, s, 4 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 70.9 (CH_2), 113.7 (CH_2), 116.2 (CH), 136.5 (C), 152.7 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{12}H_{12}{}^{35}Cl_2NaO_2$ 281.0112, found 281.0113 (-1.78 ppm).

1,2-Bis(2-chloroallyloxy)benzene (164)



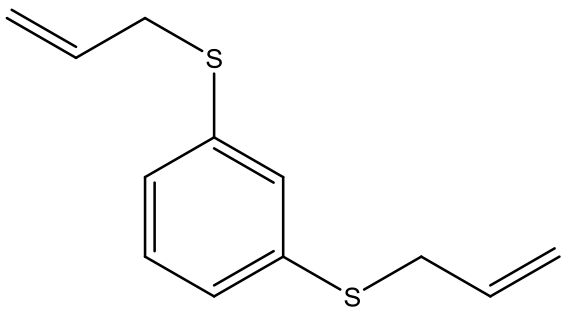
Potassium carbonate (7.95 g, 0.057 mol) was added to a stirred solution of catechol (2.5 g, 0.023 mol) in 50 mL of freshly distilled acetone. After 5 minutes of vigorous stirring 2,3-dichloropropene (5.25 mL, 0.057 mol) was added and the mixture was heated at reflux for 24 hours. After 24 hours the mixture was cooled down at room temperature, diethyl ether (25 mL) was added and the solution was filtered. Acetone was removed under reduced pressure and the solution was transferred to a separation funnel. The mixture was transferred to a separation funnel and water (50 mL) was added. The two layers were separated and the aqueous layer was extracted with diethyl ether (3x25 mL). The combined organic layers were washed with 1M sodium hydroxide solution (1x25 mL) and water (1x25 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a grey solid (2.4 g, 39% yield); Mp: 167 ºC - 169 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3135.6 (CH st, md), 2929.0 (CH st, md), 1648.4 (C=C st, w), 1459.5 (CH_2 b, md), 1218.8 and 1049.3 (C-O-C st, md), 911.0 (CHar. oop, md), 737.0 (C-Cl st, md); δ_H (400 MHz, $CDCl_3$): 4.54 (4H, t, *J* 1.8 Hz, 2 x OC*H*$_2$CClCH$_2$), 5.39 (2H, dd, *J* 1.6, 3.2, Hz, OCH$_2$CClC*H*$_2$), 5.41 (2H, dd, *J* 1.2, 3.2 Hz, OCH$_2$CClC*H*$_2$), 6.90 (4H, s, 4 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 71.2 (CH_2), 114.7 (CH_2), 116.9 (CH), 119.8 (CH), 135.8 (C), 144.7 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{12}H_{12}{}^{35}Cl_2NaO_2$ 281.0112, found 281.0112 (-0.98 ppm).

1,2-Bis(allylthio)benzene (147)



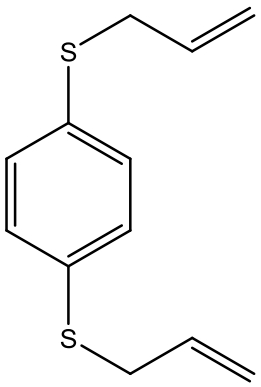
Potassium carbonate (1.21 g, 0.009 mol) was added to a stirred solution of benzene-1,2-dithiol (0.500 g, 0.0035 mol) in 10 mL of freshly distilled acetone. After 5 minutes of vigorous stirring allyl bromide (0.8 mL, 0.009 mol) was added and the mixture was heated at reflux for 24 hours. After 24 hours the mixture was cooled down at room temperature, diethyl ether (15 mL) was added and the solution was filtered. Acetone was removed under reduced pressure and the solution was transferred to a separation funnel. The mixture was transferred to a separation funnel and water (20 mL) was added. The two layers were separated and the aqueous layer was extracted with diethyl ether (3x15 mL). The combined organic layers were washed with 1M sodium hydroxide solution (1x20 mL) and water (1x20 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a yellow oil (0.684 g, 87% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3007.8 (CH st, md), 2976.3 (CH st, md), 1637.3 (C=C st, w), 1476.0 (CH_2 b, md), 922.3 ($CH=CH_2$ oop, w), 730.8 (CHar. oop, w); δ_H (400 MHz, $CDCl_3$): 3.59 (4H, dt, *J* 1.2, 6.8 Hz, 2 x S*C*H_2CHCH_2). 5.11 (2H, dq, *J* 1.2, 10 Hz, SCH_2CHCH_2), 5.19 (2H, dq, *J* 2.05, 16.0 Hz, SCH_2CHCH_2), 5.88-5.96 (2H, m, 2 x SCH_2CHCH_2), 7.17-7.20 (2H, m, 2 x Ar*H*), 7.35-7.37 (2H, m, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 36.5 (CH_2), 118.0 (CH_2), 126.5 (CH), 129.8 (CH), 134.1 (CH), 139.7 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{12}H_{14}NaS_2$ 245.0435, found 245.0435 (+0.79 ppm).

1,3-Bis(allylthio)benzene (148)



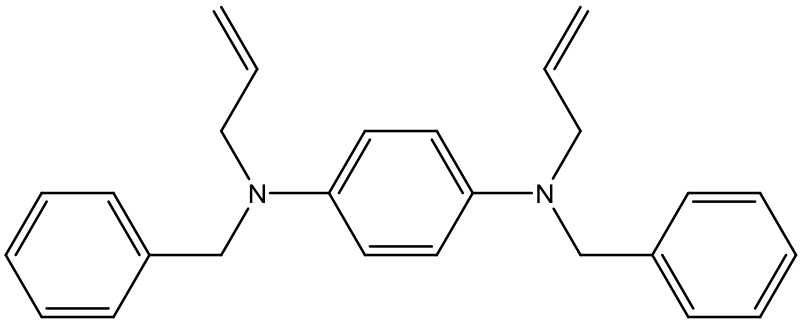
Potassium carbonate (1.21 g, 0.009 mol) was added to a stirred solution of benzene-1,3-dithiol (0.500 g, 0.0035 mol) in 10 mL of freshly distilled acetone. After 5 minutes of vigorous stirring allyl bromide (0.8 mL, 0.009 mol) was added and the mixture was heated at reflux for 24 hours. After 24 hours the mixture was cooled down at room temperature, diethyl ether (15 mL) was added and the solution was filtered. Acetone was removed under reduced pressure and the solution was transferred to a separation funnel. The mixture was transferred to a separation funnel and water (20 mL) was added. The two layers were separated and the aqueous layer was extracted with diethyl ether (3x15 mL). The combined organic layers were washed with 1M sodium hydroxide solution (1x20 mL) and water (1x20 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a yellow oil (0.700 g, 89% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3085.5 (CH st, md), 2982.0 (CH st, md), 1636.8 (C=C st, w), 1463.7 (CH_2 b, md), 988.4 and 907.9 ($CH=CH_2$ oop, md), 733.7 (CHar. oop, w), 650.5 (C-S st, w); δ_H (400 MHz, $CDCl_3$): 3.53 (4H, dt, *J* 1.2, 6.8 Hz, 2 x SCH_2CHCH_2), 5.08 (2H, dq, *J* 1.2, 10.8 Hz, SCH_2CHCH_2), 5.14 (2H, dq, *J* 1.2, 16.8 Hz, SCH_2CHCH_2), 5.85-5.95 (2H, m, 2 x SCH_2CHCH_2), 7.12-7.16 (2H, m, 2 x Ar*H*), 7.24 (1H, s, Ar*H*), 7.29 (1H, t, *J* 1.6 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$): 37.0 (CH_2), 118.0 (CH_2), 127.5 (CH), 129.2 (CH), 130.2 (CH), 133.3 (CH), 136.7 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{12}H_{14}NaS_2$ 245.0435, found 245.0433 (+2.29 ppm).

1,4-Bis(allylthio)benzene (149)



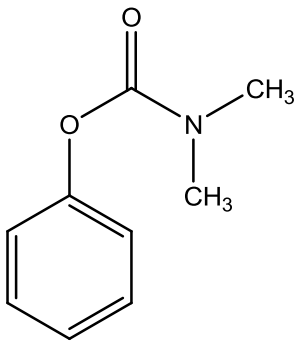
Potassium carbonate (1.21 g, 0.009 mol) was added to a stirred solution of benzene-1,4-dithiol (0.500 g, 0.0035 mol) in 10 mL of freshly distilled acetone. After 5 minutes of vigorous stirring allyl bromide (0.8 mL, 0.009 mol) was added and the mixture was heated at reflux for 24 hours. After 24 hours the mixture was cooled down at room temperature, diethyl ether (15 mL) was added and the solution was filtered. Acetone was removed under reduced pressure and the solution was transferred to a separation funnel. The mixture was transferred to a separation funnel and water (20 mL) was added. The two layers were separated and the aqueous layer was extracted with diethyl ether (3x15 mL). The combined organic layers were washed with 1M sodium hydroxide solution (1x20 mL) and water (1x20 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a yellow oil (0.735 g, 93% yield). υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3083.5 (CH st, md), 2919.4 (CH st, i), 1636.4 (C=C st, md), 1478.5 (CH_2 b, md), 989.0 and 922.7 (CH=CH_2 oop, w), 704.8 (C-S st, w); δ_H (400 MHz, $CDCl_3$): 3.54 (4H, dt, *J* 1.2, 6.8 Hz, 2 x S*C*H_2CHCH_2), 5.08 (2H, dq, *J* 1.6, 10.0 Hz, SCH_2CHCH_2), 5.14 (2H, *J* 1.6, 17.0 Hz, SCH_2CHCH_2), 5.84-5.94 (2H, m, 2 x SCH_2CHCH_2), 7.28 (4H, s, 4 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 37.05 (CH_2), 118.00 (CH_2), 130.38 (CH), 133.47 (CH), 134.94 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{12}H_{14}NaS_2$ 245.0435, found 245.0437 (-3.22 ppm).

_N,N_-Diallyl-_N.N_-diphenylbenzene-1,4-diamine (150)



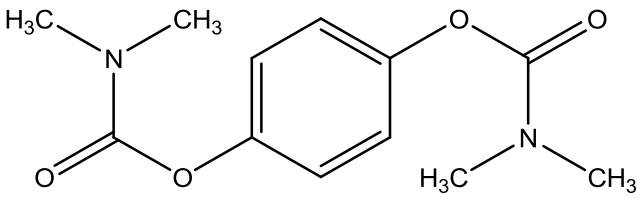
Potassium carbonate (1.45 g, 0.01 mol) was added to a stirred solution of *N,N*-diphenyl-1,4-diamine (1.50 g, 0.0052 mol) in 20 mL of freshly distilled acetone. After 5 minutes of vigorous stirring allyl bromide (0.9 mL, 0.01 mol) was added and the mixture was heated at reflux for 24 hours. After 24 hours the mixture was cooled down at room temperature, diethyl ether (20mL) was added and the solution was filtered. Acetone was removed under reduced pressure and the solution was transferred to a separation funnel. The mixture was transferred to a separation funnel and water (25 mL) was added. The two layers were separated and the aqueous layer was extracted with diethyl ether (3x20 mL). The combined organic layers were washed with 1M sodium hydroxide solution (1x25 mL) and water (1x25 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a grey solid (1.58 g, 83% yield); Mp: 169 ºC – 171.0 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3085.8 (CH st, md), 2981.3 (CH st, i), 2854.2 (CH_{NH_2} st, md), 1642.3 (C=C st, md), 1494.9 (CH_2 b, md), 1358.2 (C-N $_{aryl}$ st, w), 1296.9, 1232.0, 1028.0 (C-N $_{alkyl}$ st, w), 907.6 ($CH=CH_2$ oop, md); δ_H (400 MHz, $CDCl_3$): 3.88 (4H, dt, J 1.6, 5.2 Hz, 2 x NCH_2CHCH_2), 4.41 (4H, s, 2 x $ArCH_2C_6H_5$), 5.12 (2H, dq, *J* 1.6, 10.8 Hz, 2 x NCH_2CHCH_2), 5.21 (2H, dq, *J* 1.6, 17.2 Hz, 2 x NCH_2CHCH_2), 5.82-5.90 (2H, m, 2 x NCH_2CHCH_2), 6.68 (4H, s, 4 x Ar*H*), 7.20-7.30 (10H, m 2 x $ArCH_2C_6H_5$); δ_C (100 MHz, DCl_3): 53.8 (CH_2), 54.91 (CH_2), 114.8 (CH), 116.3 (CH_2), 126.6 (CH), 127.0 (CH), 128.4 (CH), 134.6 (CH), 139.7 (C), 141.5 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{26}H_{28}N_2Na$ 391.2150, found 391.2151(-1.39 ppm).

Phenyl dimethylcarbamate (215)



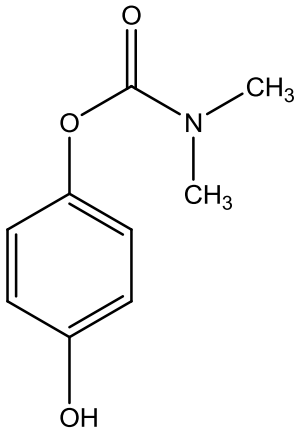
Potassium carbonate (4.70 g, 0.034 mol) was added to a stirred solution of phenol (1.50 g, 0.016 mol) in 50 mL of freshly distilled acetone. After 5 minutes of vigorous stirring dimethylcarbamoyl chloride (2.3 mL, 0.022 mol) was added and the mixture was heated at reflux for 24 hours. After 24 hours the mixture was cooled down at room temperature, ethyl acetate (40mL) was added and the solution was filtered. Acetone was removed under reduced pressure and the solution was transferred to a separation funnel. The mixture was transferred to a separation funnel and water (50 mL) was added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x30 mL). The combined organic layers were washed with 1M sodium hydroxide solution (1x30 mL) and water (1x30 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a white solid (2.48 g, 93% yield); Mp: 38 ºC - 40 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3054.6 (CH st, md), 2941.1 (CH st, i), 1719.8 (C=O st, i), 1594.2 (C=C st, md), 1391.1 (CH_3 b, md), 1265.8 (C-O-C st, md), 1209.0 (C-N $_{aryl}$ st, w), 1025.3 (C-O-C st, md), 740.0 (CHar. oop, md); δ_H (400 MHz, $CDCl_3$): 3.00 (3H, s, N(CH_3)$_2$), 3.09 (3H, s, N(CH_3)$_2$), 7.11 (2H, d, *J* 7.6 Hz, 2 x Ar*H*), 7.18 (1H, d, *J* 7.2 Hz, Ar*H*), 7.35 (2H, t, *J* 6.4 Hz, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 36.4 (CH_3), 36.7 (CH_3), 121.8 (CH), 125.1 (CH), 129.2 (CH), 151.6 (C), 154.9 (C); FTMS (ES) ($M+Na^+$) calculated for $C_9H_{11}NNaO_2$ 188.0687, found 188.0688 (-1.41 ppm).

1,4-Phenylene bis(dimethylcarbamate) (177)



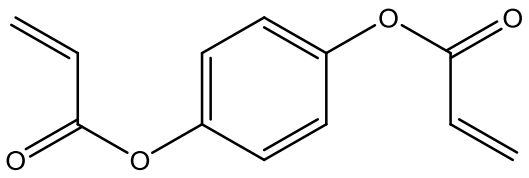
Potassium carbonate (7.80 g, 0.057 mol) was added to a stirred solution of 1,4-hydroquinone (2.50 g, 0.023 mol) in 40 mL of freshly distilled acetone. After 5 minutes of vigorous stirring dimethylcarbamoyl chloride (5.2 mL, 0.057 mol) was added and the mixture was heated at reflux for 24 hours. After 24 hours the mixture was cooled down at room temperature, ethyl acetate (40mL) was added and the solution was filtered. Acetone was removed under reduced pressure and the solution was transferred to a separation funnel. The mixture was transferred to a separation funnel and water (50 mL) was added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x30 mL). The combined organic layers were washed with 1M sodium hydroxide solution (1x30 mL) and water (1x30 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a beige solid (5.12 g, 89% yield); Mp: 129 ºC - 131 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3055.4 (CH st, i), 2939.1 (CH st, i), 1720.9 (C=O st, i), 1618.5 (C=C st, md), 1444.0 and 1388.8 (CH_3 b, md), 1266.0 (C-O-C st, md), 1232.1 (C-N st, md), 1015.6 (C-O-C st, md), 846.5 (CHar. oop, md); δ_H (400 MHz, $CDCl_3$): 3.00 (6H, s, $OCN(CH_3)_2$), 3.08 (6H, s, $OCN(CH_3)_2$), 7.09 (4H, s, 4 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 36.4 (CH_3), 36.7 (CH_3), 122.3 (CH), 148.5 (C), 154.8 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{12}H_{16}N_2NaO_4$ 275.1008, found 275.1010 (-2.68 ppm).

4-Hydroxyphenyl dimethylcarbamate (178)



A 1.4M solution of *sec*-butyllithium (3.3 mL, 0.004 mol) was added dropwise to a solution of *N,N,N',N'*-tetramethylethylenediamine (0.65 mL, 0.004 mol) in dry tetrahydrofuran (35 mL) under N_2 atmosphere. The mixture was cooled to -78 ºC and a solution of 4-(allyloxy)-8-methoxynaphthalen-1-yl dimethylcarbamate (0.5 g, 0.002 mol) in dry tetrahydrofuran (15 mL) was cannulated in a constant flow keeping temperature low. The solution was stirred for 2 hours at -78 ºC, heated to room temperature and stirring was prolonged 2 hours at this temperature. The reaction was quenched with a saturated aqueous ammonium chloride solution (50 mL) and the mixture was transferred into a separation funnel. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x75 mL). The combined organic layers were washed with water (1x75 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using a mixture of petrol/EtOAc (2:3) as eluent to obtain a yellow solid (0.37g, 74% yield); Mp: 157 ºC – 159 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3368.3 (OH st, i), 3054.3 (CH st, md), 2986.9 (CH st, i), 1697.2 (C=C st, md), 1601.3 (C=C st, w), 1440.0 and 1396.6 (CH_3 b, md), 1265.7 (C-O-C st, md), 1203.3 (C-N st, md), 1019.8 (C-O-C st, md), 868.2 (CHar. oop, w); δ_H (400 MHz, DMSO): 2.88 (3H, s, N(C*H*$_3$)$_2$), 3.01 (3H, s, N(C*H*$_3$)$_2$), 6.72 (2H, d, *J* 4.4 Hz, 2 x Ar*H*), 6.88 (2H, d, *J* 4.4 Hz, 2 x Ar*H*), 9.34 (1H, s, O*H*); δ_C (100 MHz, DMSO): 36.0 (CH_3), 36.2 (CH_3), 115.3 (CH), 122.6 (CH), 143.5 (C), 154.4 (C), 154.5 (C); FTMS (ES) ($M+Na^+$) calculated for $C_9H_{11}NNaO_3$ 204.0637, found 204.0636 (+1.01 ppm).

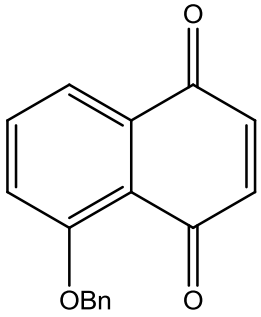
1,4-Phenylene diacrylate (174)



Potassium carbonate (7.80 g, 0.057 mol) was added to a stirred solution of 1,4-hydroquinone (2.50 g, 0.023 mol) in 40 mL of freshly distilled acetone. After 5 minutes of vigorous stirring 2-propenoyl chloride (4.6 mL, 0.057 mol) was added and the mixture was heated at reflux for 24 hours. After 24 hours the mixture was cooled down at room temperature, ethyl acetate (40mL) was added and the solution was filtered. Acetone was removed under reduced pressure and the solution was transferred to a separation funnel. The mixture was transferred to a separation funnel and water (50 mL) was added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x30 mL). The combined organic layers were washed with 1M sodium hydroxide solution (1x30 mL) and water (1x30 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by recrystallisation using a mixture of hexane/dichloromethane to obtain a white solid (4.0 g, 81% yield); Mp: 72 ºC – 73 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3054.8 (CH st, i), 2987.2 (CH st, i), 1744.72 (C=O st, i), 1636.0 (C=C st, w), 1624.5 (C=C st, i), 1404.6 (CH_2 b, md), 1295.9 (C-C(O)-C st, md), 1265.9 and 1016.9 (C-O st, i), 984.1 and 911.8 (CH=CH_2 oop, md), 896.2 (CHar. oop, w); δ_H (400 MHz, $CDCl_3$): 6.01 (2H, dd, *J* 1.2, 10.4 Hz, 2 x ArOCOCHC*H*$_2$), 6.31 (2H, dd, *J* 10.4, 17.2 Hz, 2 x ArOCOC*H*CH_2), 6.60 (2H, dd, *J* 1.2, 17.2 Hz, 2 x ArOCOCHC*H*$_2$), 7.16 (4H, d, *J* 0.8 Hz, 4 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 122.3 (CH), 122.4 (CH), 128.0 (CH), 132.8 (CH_2), 148.0 (C), 164.4 (C); FTMS (ES) (M+) calculated for $C_{12}H_{10}O_4$ 218.0579, found 218.0577 (+2.62 ppm).

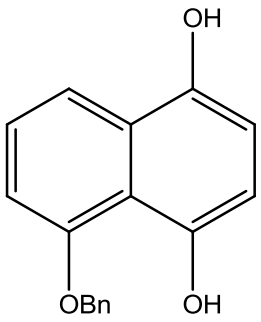
4.3 5-HYDROXY-1,4-NAPHTHOQUINONE DERIVATIVES

5-Benzyloxy-1,4-benzoquinone (138)



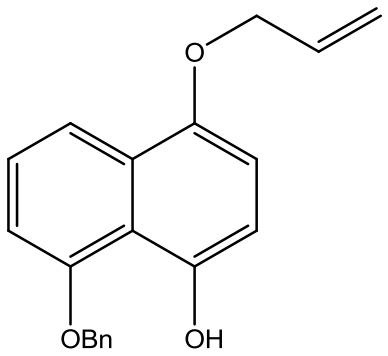
5-Hydroxy-1,4-benzoquinone (2.5 g, 0.014 mol) was dissolved in freshly distilled chloroform (100 mL) under N_2 atmosphere. The orange solution was stirred vigorously for 5 minutes, silver(I) oxide (10.0 g, 0.043 mol) was added and stirring was continued for 5 minutes more. Benzyl bromide (4.80 mL, 0.042 mol) was added and the mixture was stirred for 72 hours at room temperature. The mixture was filtered through a pad of Celite® and washed with 50 mL of ethyl acetate. The solvent was removed under reduced pressure to achieve an orange solid. The crude was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a dark yellow solid (3.43 g, 94% yield); Mp: 131 ºC – 134 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3068.3 (CH st, md), 2927.9 (CH st, i), 1794.0 (C=O st, i), 1661.2 (C=C st, w), 1614.9 (C=C st, w), 1468.2 (CH_2 b, md), 1254.7 and 1020.9 (C-O st, md), 732.8 (CHar. oop, w); δ_H (400 MHz, $CDCl_3$): 5.38 (2H, s, $OCH_2C_6H_5$), 6.87 (2H, s, 2 x Ar*H*), 7.31-7.36 (2H, m, Ar*H* + $OCH_2C_6H_5$), 7.41 (2H, t, *J* 8.0 Hz, $OCH_2C_6H_5$), 7.57 (2H, d, *J* 7.2 Hz, $OCH_2C_6H_5$), 7.62 (1H, t, *J* 8.4 Hz, Ar*H*), 7.73 (1H, dd, *J* 1.2, 8.2 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$): 70.9 (CH_2), 119.5 (CH), 120.2 (C), 126.7 (CH), 128.0 (CH), 128.4 (CH), 128.9 (CH), 134.1 (C), 134.8 (CH), 136.0 (C), 140.9 (CH), 158.5 (C), 184.1 (C), 185.2 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{17}H_{12}NaO_3$ 287.0684, found 287.0686 (-3.01 ppm).

5-(Benzyloxy)naphthalene-1,4-diol (139)



To a solution of 5-benzyloxy-1,4-benzoquinone (1.0 g, 0.004 mol) in 60 mL of dichloromethane/diethyl ether (1:3) was added a freshly prepared solution of sodium dithionite (5.5 g, 0.031 mol) in water (30 mL). The mixture was stirred at room temperature for 2 hours. Diethyl ether (45 mL) and water (45 mL) were added and the solution was transferred into a separation funnel. The two layers were separated and the aqueous layer was extracted with diethyl ether (3x75 mL). The combined organic layers were washed with 1M sodium hydroxide solution (1x75 mL) and water (3x75 mL), dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure to obtain a brown solid (1.02 g, 95% yield); Mp: 172 ºC – 174 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3341.3 (OH st, i), 3155.1 (CH st, i), 2900.0 (CH st, i), 1637.3 (C=C st, w), 1607.9 (C=C st, w), 1469.8 (CH_2 b, md), 1261.9 and 1036.9 (C-O-C st, md), 732.8 (CHar. oop, md); δ_H (400 MHz, $CDCl_3$): 4.89 (1H, s, O*H*), 5.30 (2H, s, OC*H*$_2$C$_6$H$_5$), 6.68 (1H, d, *J* 8.4 Hz, Ar*H*), 6.76 (1H, d, *J* 8.0 Hz, Ar*H*), 6.92 (1H, d, *J* 7.6 Hz, Ar*H*), 7.33 (1H, t, *J* 8.4 Hz, Ar*H*), 7.38-7.50 (5H, m, OCH$_2$C$_6$*H*$_5$), 7.77 (1H, d, *J* 7.6 Hz, Ar*H*), 9.02 (1H, s, O*H*); δ_C (100 MHz, $CDCl_3$): 71.7 (CH_2), 106.1 (CH), 109.4 (CH), 110.8 (CH), 115.2 (C), 115.7 (C), 115.9 (CH), 125.2 (CH), 126.8 (C), 128.0 (CH), 128.8 (CH), 129.0 (CH), 135.2 (C), 143.7 (C), 148.3 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{17}H_{14}NaO_3$ 289.0841, found 289.0842 (-1.26 ppm).

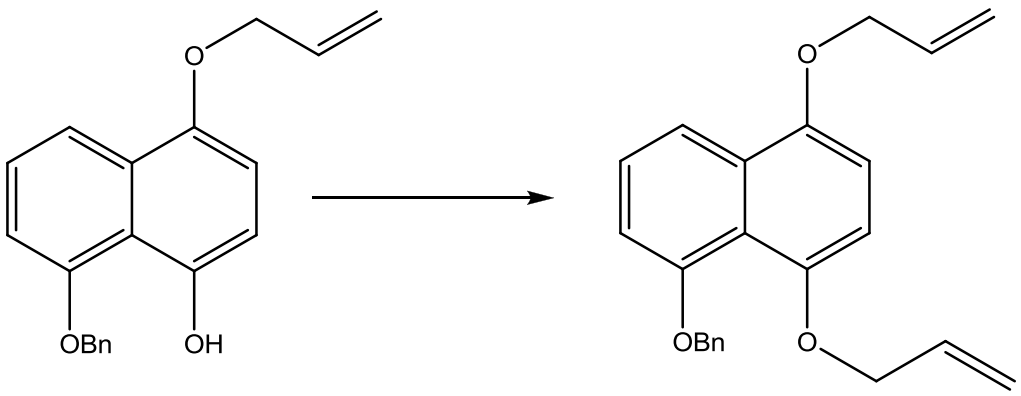
4-(Allyloxy)-8-(benzyloxy)naphthalen-1-ol (140)



Potassium carbonate (1.71 g, 0.012 mol) and allyl bromide (1.1 mL, 0.012 mol) were added to a stirred solution of 5-(benzyloxy)naphthalene-1,4-diol (3.0 g, 0.011 mol) in 50 mL of acetone. The mixture was heated at reflux for 24 hours and then filtered. Ethyl acetate (50 mL) was added to the solution and acetone was removed under reduced pressure. The mixture was transferred to a separation funnel and water (100 mL) was added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with water (1x50 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure to obtain a brown solid (0.188 g, 82% yield); Mp: 95 ºC - 97 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3418.5 (OH st, i), 3054.2 (CH st, md), 2986.4 (CH st, i), 2880.2 (CH $_{OCH_2}$ st, md), 1659.3 (C=C st, w), 1632.6 (C=C st, w), 1609.3 (C=C st, w), 1456.1 (CH_2 b, md), 1265.7 (C-O-C st, i), 1233.7 (C-OH b, md), 1028.0 (C-O-C st, i), 996.3 and 907.1 (CH=CH_2 oop, w), 738.8 (CHar. oop, w); δ_H (400 MHz, $CDCl_3$): 4.61 (2H, dt, *J* 1.6, 5.2 Hz, OC*H*$_2$CHCH$_2$), 5.29 (1H, dq, *J* 1.2, 10.4 Hz, 1 x OCH$_2$CHC*H*$_2$), 5.27 (2H, s, OC*H*$_2$C$_6$H$_5$), 5.47 (1H, dq, *J* 1.2, 17.2 Hz, 1 x OCH$_2$CHC*H*$_2$), 6.07-6.17 (1H, m, OCH$_2$C*H*CH$_2$), 6.71 (1H, d, *J* 7.2 Hz, Ar*H*), 6.79 (1H, d, *J* 6.4, ArH), 6.89 (1H, d, *J* 8.0 Hz, Ar*H*), 7.28-7.47 (6H, m, OCH$_2$C$_6$*H*$_5$ + Ar*H*), 7.91 (1H, d, *J* 8.2 Hz, Ar*H*), 9.00 (1H, s, ArO*H*); δ_C (100 MHz, $CDCl_3$): 69.8 (CH_2), 71.7 (CH_2), 106.3 (CH), 108.2 (CH), 109.2 (CH), 115.8 (C), 116.3 (CH), 117.2 (CH_2), 125.2 (CH), 127.6 (CH), 128.0 (CH), 128.3 (CH), 128.8 (CH), 129.0 (CH), 133.7 (CH), 135.3 (C), 138.3 (C), 147.1 (C), 148.2 (C), 155.2 (C); FTMS (ES) (M+Na^+) calculated for $C_{20}H_{18}NaO_3$ 329.1154, found 329.1154 (-0.78 ppm).

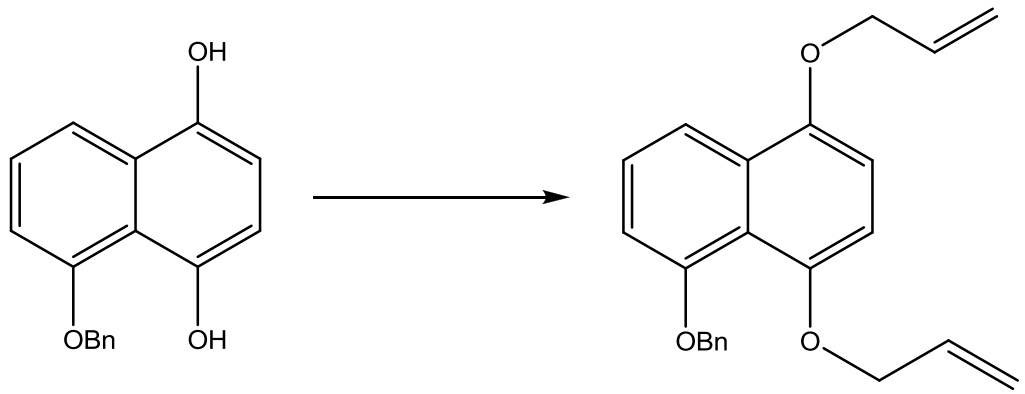
1,4-Bis(allyloxy)-5-(benzyloxy)naphthalene (141)

- Method A)



Sodium hydride (0.33 g, 0.0082 mol) was added to a solution of 4-(allyloxy)-8-(benzyloxy)naphthalen-1-ol (1.0 g, 0.0.0033 mol) in 50 mL of anhydrous tetrahydrofuran under N_2 atmosphere and the mixture was stirred at room temperature for 30 minutes. Allyl bromide (0.7 mL, 0.0082 mol) was added slowly and the mixture was stirred for another 2 hours at room temperature. The solution was cooled down at 0ºC and 75 mL of saturated ammonium chloride solution were added slowly. The mixture was transferred to a separation funnel. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with water (1x50 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a red solid (0.145 g, 73% yield).

- Method B)

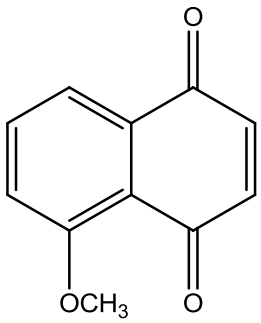


Sodium hydride (0.075 g, 0.002 mol) was added slowly to a solution of 5-(benzyloxy)naphthalene-1,4-diol (0.2 g, 0.0007 mmol) in 10mL of anhydrous tetrahydrofuran under N_2 atmosphere and the mixture was stirred at room temperature for 1 hour. Allyl bromide (0.2 mL, 0.002 mmol) was added slowly and the mixture was stirred for 24 hours at room temperature. The solution was cooled down at 0 ºC and 15 mL of saturated ammonium chloride solution were added slowly. The mixture was transferred to a separation funnel. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x15 mL). The combined organic layers were washed with water (1x15 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a red solid (0.173 g, 66% yield).

Mp: 86 ºC - 88 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3068.5 (CH st, i), 2926.9 (CH st, i), 2857.4 (CH $_{OCH_2}$ st, md), 1697.2 (C=C st, w), 1648.7 (C=C st, w), 1412.8 (CH_2 b, md), 1273.3 and 1028.6 (C-O-C st, md), 995.8 and 907.0 (CH=CH_2 oop, md), 731.9 (CHar. oop, w); δ_H (400 MHz, $CDCl_3$): 4.53 (2H, dt, *J* 1.2, 6.4 Hz, ArOC*H*$_2$CHCH_2), 4.65 (2H, dt, *J* 1.6, 5.2 Hz, ArOC*H*$_2$CHCH_2), 5.13 (1H, dq, *J* 1.2, 10.4 Hz, ArOCH_2CHC*H*$_2$), 5.20 (2H, s, ArOC*H*$_2$C$_6$H$_5$), 5.30 (1H, dq, *J* 1.2, 16.4.2 Hz, ArOCH_2CHC*H*$_2$), 5.34 (1H, dq, *J* 1.6, 7.6 Hz, ArOCH_2CHC*H*$_2$), 5.52 (1H, dq, *J* 1.6, 17.2 Hz, ArOCH_2CHC*H*$_2$), 5.93-6.02 (1H, m ArOCH_2C*H*CH_2), 6.13-6.19 (1H, m ArOCH_2C*H*CH_2), 6.75 (1H, dd, *J* 8.4, 14.0 Hz, Ar*H*), 6.97 (1H, d, *J* 7.2 Hz, Ar*H*), 7.28-7.42 (5H, m, ArOCH_2C$_6$*H*$_5$), 7.75 (2H, d, *J*

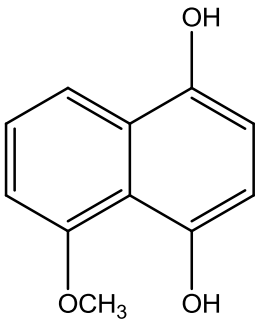
6.8 Hz, 2 x Ar*H*), 7.93 (1H, d, *J* 7.6 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$): 69.5 (CH_2), 71.9 (CH_2), 72.1 (CH_2), 105.9 (CH), 109.1 (CH), 109.3 (CH), 115.2 (CH), 117.1 (CH_2), 117.2 (CH_2), 119.4 (C), 125.8 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 129.2 (C), 133.6 (CH), 134.1 (CH), 137.3 (C), 148.8 (C), 149.9 (C), 155.8 (C); FTMS (ES) (M+Na) calculated for $C_{23}H_{22}NaO_3$ 369.1467, found 369.1468 (-1.44 ppm).

5-Methoxy-1,4-benzoquinone (187)



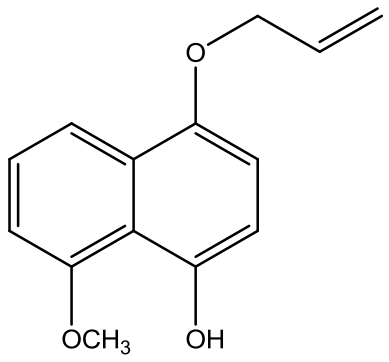
5-Hydroxy-1,4-benzoquinone (5.0 g, 0.029 mol) was dissolved in freshly distilled dichloromethane (100 mL) under N_2 atmosphere. The orange solution was stirred vigorously for 5 minutes, silver(I) oxide (10.0 g, 0.043 mol) was added and stirring was continued for 5 minutes more. Methyl iodide (3.61 mL, 0.058 mol) was added and the mixture was stirred for 20 hours at room temperature. The mixture was filtered through a pad of Celite® and washed with 50 mL of ethyl acetate. The solvent was removed under reduced pressure to achieve an orange solid. Recrystallisation from ethanol gave the desired compound as an orange solid (4.6 g, 89% yield); Mp: 176 ºC – 178 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3028.4 (CH st, md), 2921.3 (CH st, i), 1795.5 (C=O st, i), 1678.6 (C=C st, md), 1614.1 (C=C st, w), 1450.1 and 1353.9 (CH_3 b, md), 1254.7, and 1020.9 (C-O-C st, i), 851.7 (CHar. oop, w); δ_H (400 MHz, $CDCl_3$): 4.01 (3H, s, OC*H*$_3$), 6.87 (1H, d, *J* 4.0 Hz, Ar*H*), 7.32 (2H, d, *J* 7.2 Hz, 2 x Ar*H*), 7.71-7.72 (2H, m, 2 x Ar*H*); δ_C (100 MHz, $CDCl_3$): 56.5 (CH_3), 118.0 (CH), 119.2 (CH), 119.8 (C), 134.1 (C), 135.0 (CH), 136.2 (CH), 140.9 (CH), 159.7 (C), 184.3 (C), 185.2 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{11}H_8NaO_3$ 211.0371, found 211.0370 (+1.38 ppm).

5-(Methoxy)naphthalene-1,4-diol (188)



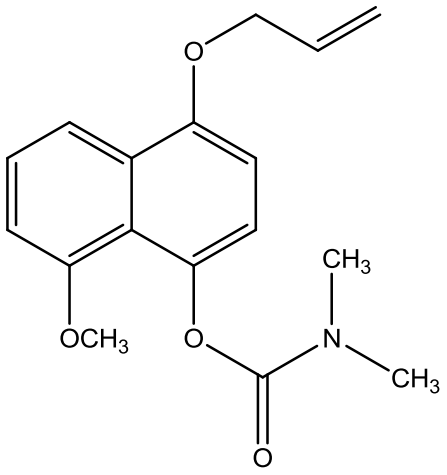
To a solution of 5-methoxy-1,4-benzoquinone (4.5 g, 0.024 mol) in ethyl acetate (150 mL) was added a freshly prepared solution of sodium dithionite (35.4 g, 0.21 mol) in water (250 mL). The mixture was stirred at room temperature for 2 hours and transferred into a separation funnel. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x75 mL). The combined organic layers were washed with 1M sodium hydroxide solution (1x75 mL) and water (3x75 mL), dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure to obtain a brown solid (4.50 g, 100% yield); Mp: 191 ºC – 193 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3404.4 (OH st, i), 3054.6 (CH st, i), 2986.8 (CH st, i), 1661.9 (C=C st, md), 1616.1 (C=C st, w), 1335.6 (CH_3 b, md), 1265.8 (C-OH st, md), 896.7 (CHar. oop, w); δ_H (400 MHz, $CDCl_3$): 4.06 (3H, s, ArOC*H*$_3$), 4.87 (1H, s, ArO*H*), 6.68 (1H, d, *J* 12.0 Hz, Ar*H*), 6.77 (1H, d, *J* 8.0 Hz, Ar*H*), 6.84 (1H, d, *J* 7.6 Hz, Ar*H*), 7.35 (1H, t, *J* 8.4 Hz, Ar*H*), 7.76 (1H, d, *J* 8.0 Hz, Ar*H*), 8.97 (1H, s, ArO*H*); δ_C (100 MHz, $CDCl_3$): 56.1 (CH_3), 104.7 (CH), 109.3 (CH), 110.8 (CH), 115.5 (CH), 119.2 (C), 125.2 (CH), 126.7 (C), 143.7 (C), 148.3 (C), 156.0 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{11}H_{10}NaO_3$ 213.0528, found 213.0530 (-3.41 ppm).

4-(Allyloxy)-8-(methoxy)naphtalen-1-ol (189)



Potassium carbonate (3.6 g, 0.026 mol) and allyl bromide (2.25 mL, 0.026 mol) were added to a stirred solution of 5-(methoxy)naphthalene-1,4-diol (4.5 g, 0.024 mol) in 100 mL of acetone. The mixture was heated to reflux for 20 hours and then filtered. Ethyl acetate (100 mL) was added to the solution and acetone was removed under reduced pressure. The mixture was transferred to a separation funnel and water (150 mL) was added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x75 mL). The combined organic layers were washed with water (1x100 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure to obtain a brown solid (4.73 g, 87% yield); Mp: 92 ºC – 93 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3418.5 (OH st, i), 3054.1 (CH st, md), 2984.1 (CH st, i), 2943.4 (CH st, i), 1632.2 (C=C st, w), 1610.9 (C=C st, md), 1465.2 (CH_2 b, i), 1434.9 and 1372.4 (CH_3 b, md), 1265.5 (C-O-C st, i), 1233.6 (C-OH st, md), 1062.6 (C-O-C st, md), 738.3 (CHar. oop, w); δ_H (400 MHz, $CDCl_3$): 4.03 (s, 3H, OC*H*$_3$), 4.61 (2H, dt, *J* 1.6, 5.4 Hz, OC*H*$_2$CHCH$_2$), 5.29 (1H, dq, *J* 1.6, 10.4 Hz, 1 x OCH$_2$CHC*H*$_2$), 5.47 (1H, dq, *J* 1.6, 17.2 Hz, 1 x OCH$_2$CHC*H*$_2$), 6.09-6.17 (1H, m, OCH$_2$C*H*CH$_2$), 6.74-6.79 (2H, m, Ar*H*), 6.82 (1H, d, *J* 7.6 Hz, Ar*H*), 7.32 (1H, t, *J* 8 Hz, Ar*H*), 7.89 (1H, d, *J* 9.2Hz, Ar*H*), 8.96 (1H, s, O*H*); δ_C (100 MHz, $CDCl_3$): 56.1 (CH_3), 69.8 (CH_2), 104.9 (CH), 108.2 (CH), 109.1 (CH), 115.6 (C), 116.1 (CH), 117.2 (CH_2), 125.2 (CH), 128.2 (C), 133.7 (CH), 147.0 (C), 148.2 (C), 156.0 (C); FTMS (ES) (M+Na^+) calculated for $C_{14}H_{14}NaO_3$ 253.0841, found 253.0840 (+1.30 ppm).

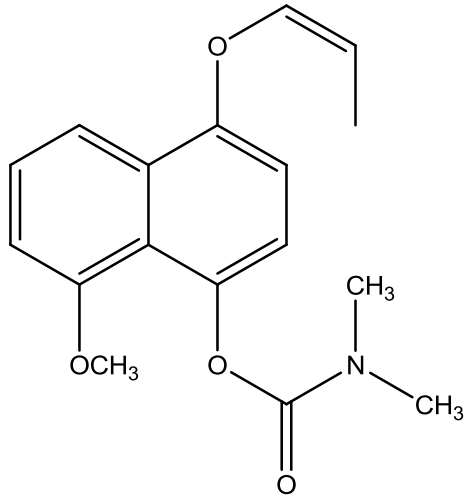
4-(Allyloxy)-8-methoxynaphthalen-1-yl dimethylcarbamate (195)



Sodium hydride (1.41 g, 0.035 mol) was added to a solution of 4-(allyloxy)-8-(methoxy)naphtalen-1-ol (3.25 g, 0.014 mol) in tetrahydrofuran (100 mL) under N_2 atmosphere and the mixture was stirred at room temperature for 2 hours. Dimethylcarbamoyl chloride (2.60 mL, 0.028 mol) was added slowly and stirring was prolonged for 20 hours. The reaction was quenched with a saturated aqueous ammonium chloride solution (150 mL) and the mixture was transferred into a separation funnel. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x75 mL). The combined organic layers were washed with water (1x75 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure to achieve a brown solid. The solid was purified using flash column chromatography over silica gel using a mixture of petrol/EtOAc (1:1) as eluent obtaining an orange oil (3.74 g, 88% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3054.4 (CH st, md), 2986.7 (CH st, md), 2938.9 (CH st, md), 2837.0 (CH $_{OCH_3}$ st, w), 1603.8 (C=C st, w), 1464.9 (CH_2 b, md), 1439.9 and 1377.2 (CH_3 b, md), 1265.8 (C-O-C st, i), 1193.7 (C-N st, md), 1040.3 (C-O-C st, md); δ_H (400 MHz, $CDCl_3$): 3.05 (3H, s, N(CH_3)$_2$), 3.18 (3H, s, N(CH_3)$_2$), 3.86 (3H, s, OCH_3), 4.67 (2H, dt, *J* 1.2, 5.2 Hz, OCH_2CHCH$_2$), 5.34 (1H, dq, *J* 1.4, 17.6 Hz, OCH$_2$CHCH_2), 5.42 (1H, dq, *J* 1.4, 10.4 Hz, OCH$_2$CHCH_2), 6.10-6.19 (1H, m, OCH$_2$C*H*CH$_2$), 6.75 (1H, d, *J* 8 Hz, Ar*H*), 6.84 (1H, d, *J* 7.6 Hz, Ar*H*), 6.98 (1H, d, *J* 8Hz, Ar*H*), 7.34 (1H, t, *J* 8.2 Hz, Ar*H*), 7.90 (1H, d, *J* 8.4 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$): 36.4 (CH_3), 36.8 (CH_3), 55.7 (CH_3), 69.7 (CH_2), 105.4 (CH), 106.7 (CH), 114.9 (CH), 117.4 (CH_2), 119.1 (CH), 120.3 (C), 125.6

(CH), 128.6 (C), 133.3 (CH), 140.8 (C), 151.8 (C), 155.4 (C), 156.1 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{17}H_{19}NNaO_4$ 324.1212, found 324.1212 (+0.72 ppm).

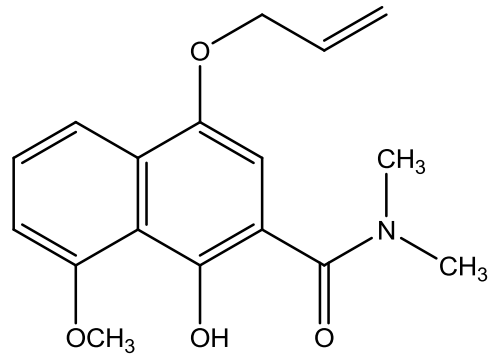
(Z)-8-methoxy-4-(prop-1-enyloxy)naphthalen-1-yl dimethylcarbamate



A 1.0 M solution of boron trichloride in dichloromethane (5.0 mL, 0.005 mol) was added dropwise at room temperature to a solution of 4-(allyloxy)-8-methoxynaphthalen-1-yl dimethylcarbamate (0.5 g, 0.0017 mol) in 45 mL of anhydrous dichloromethane under N_2 atmosphere. The dark solution was stirred for 18 hours at room temperature. The mixture was filtered through a pad of Celite® and washed with 50 mL of dichloromethane. The solvent was removed under reduced pressure. The crude oil achieved was purified by flash column chromatography over silica gel using petrol/EtOAc (in increasing %) as eluent to obtain a brown solid (0.22 g, 44% yield); Mp: 127 ºC – 129 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3022.8 (CH st, md), 2966.7 (CH st, i), 1720.8 (C=O st, i), 1633.8 (C=C st, w), 1410.2 and 1384.1 (CH_3 b, md), 1266.8 (C-O-C st, i), 1197.7 (C-N st, w), 1043.1 (C-O-C st, md), 900.1 (CH=CH oop, w), 778.2 (CHar. oop, w); δ_H (400 MHz, $CDCl_3$): 1.80 (3H, d, *J* 8.2 Hz, ArOCHC*H*$_3$), 3.05 (3H, s, CON(C*H*$_3$)$_2$), 3.18 (3H, s, CON(C*H*$_3$)$_2$), 3.87 (3H, s, ArOC*H*$_3$), 4.88-4.99 (1H, m, ArOC*H*CHCH$_3$), 6.43 (1H, dq, *J* 6.4, 1.6 Hz, ArOCHC*H*CH$_3$), 6.85 (1H, d, *J* 7.6 Hz, Ar*H*), 6.90 (1H, d, *J* 8.0 Hz, Ar*H*), 7.00 (1H, d, J 8.0 Hz, Ar*H*), 7.38 (1H, t, *J* 8.4 Hz, Ar*H*), 7.88 (1H, d, *J* 7.6 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$): 12.3 (CH_3), 36.4 (CH_3), 36.8 (CH_3), 55.7 (CH_3), 106.7 (CH), 107.8 (CH), 108.7 (CH), 114.7 (CH), 119.1 (CH), 120.3

(C), 126.0 (CH), 128.5 (C), 141.3 (CH), 142.1 (C), 150.8 (C), 155.4 (C), 156.0 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{17}H_{19}NaNO_3$ 324.1212, found 324.1211(+1.18 ppm).

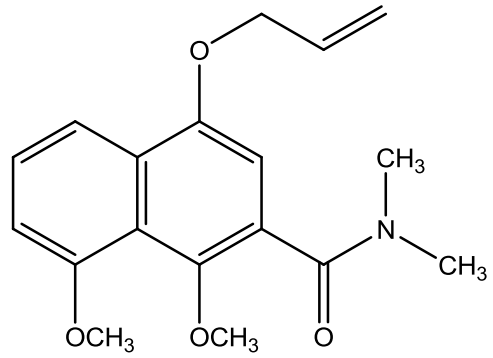
4-(Allyloxy)-1-hydroxy-8-methoxy-*N*,*N*-dimethyl-2-naphthamide (196)



A 1.4M solution of *sec*-butyllithium (4.4 mL, 0.0055 mol) was added dropwise to a solution of *N,N,N',N'*-tetramethylethylenediamine (0.83 mL, 0.0055 mol) in dry tetrahydrofuran (125 mL) under N_2 atmosphere. The mixture was cooled to -78 ºC and a solution of 4-(allyloxy)-8-methoxynaphthalen-1-yl dimethylcarbamate (1.5 g, 0.005 mol) in dry tetrahydrofuran (50 mL) was cannulated in a constant flow keeping temperature low. The solution was stirred for 2 hours at -78 ºC, heated to room temperature and stirring was prolonged 2 hours at this temperature. The reaction was quenched with a saturated aqueous ammonium chloride solution (150 mL) and the mixture was transferred into a separation funnel. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x75 mL). The combined organic layers were washed with water (1x75 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using a mixture of petrol/EtOAc (2:3) as eluent to obtain a yellow oil (0.68 g, 45% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3400.0 (OH st, i), 2955.1 (CH st, md), 2927.7 (CH st, md), 2853.7 (CH_{OCH_3} st, md), 1639.4 (C=O st, i), 1458.2 (CH_2 b, md), 1446.8 and 1391.0 (CH_3 b, md), 1261.7 and 1068.8 (C-O-C st, i), 993.6 and 918.6 ($CH=CH_2$ oop, md), 736.2 (CHar. oop, md); δ_H (400 MHz, $CDCl_3$): 3.03 (6H, br, $CN(CH_3)_2$), 3.98 (3H, s, OCH_3), 4.57 (2H, dt, *J* 1.2, 5.2 Hz,

O*CH*$_2$CHCH$_2$), 5.24 (1H, dd, *J* 1.6, 10.4 Hz, OCH$_2$CHC*H*$_2$), 5.41 (1H, dd, *J* 1.6, 17.2 Hz, OCH$_2$CHC*H*$_2$), 6.00-6.10 (1H, m, OCH$_2$C*H*CH$_2$), 6.68 (1H, s, Ar*H*), 6.81 (1H, d, *J* 8.0 Hz, Ar*H*), 7.31 (1H, t, *J* 8.0 Hz, Ar*H*), 7.83 (1H, d, *J* 8.0 Hz, Ar*H*), 9.27 (1H, s, ArO*H*); δ_C (100 MHz, $CDCl_3$): 31.1 (CH_3), 56.1 (CH_3), 56.3 (CH_3), 69.6 (CH_2), 105.8 (CH), 106.3 (CH), 114.9 (CH), 117.1 (C), 117.4 (CH_2), 126.5 (C), 126.9 (CH), 128.7 (C), 133.4 (CH), 144.1 (C), 147.1 (C), 156.4 (C), 169.7 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{17}H_{19}NNaO_4$ 324.1212, found 324.1214 (-3.42 ppm).

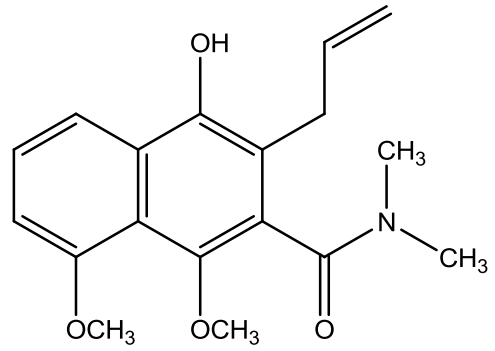
4-(Allyloxy)-1,8-dimethoxy-*N*,*N*-dimethyl-2-naphthamide (200)



4-(Allyloxy)-1-hydroxy-8-methoxy-*N*,*N*-dimethyl-2-naphthamide (1.0 g, 0.003 mol) was dissolved in dry tetrahydrofuran (50 mL) under N_2 atmosphere. The solution was vigorously stirred, sodium hydride 60% dispersion in mineral oil (0.3 g, 0.007 mol) and 18-crown-6 (0.01g, 0.0003 mol) were added slowly. The mixture was stirred for 2 hours, methyl iodide (0.42 mL, 0.007 mol) was added and stirring was prolonged for 24 hours. The reaction was quenched with a saturated aqueous ammonium chloride solution (100 mL) and the mixture was transferred into a separation funnel. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with water (1x100 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The oil was dissolved in ethyl acetate (25 mL), active charcoal was added while heating the solution and the mixture was filtered through a pad of Celite® to obtain an orange oil (1.0 g, 95% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 2931.7 (CH st, md), 2823.7 (CH st, md), 1648.9 (C=O st, i), 1600.2 (C=C st, w), 1450.1 (CH_2 b, md), 1448.1 and 1385.5 (CH_3 b, md), 1262.1 and 1068.6 (C-O-C st, w), 977.7 and 906.9

(CH=CH_2 oop, w), 780.4 (CHar. oop, md); δ_H (400 MHz, $CDCl_3$): 3.00 (3H, s, $CN(CH_3)_2$), 3.09 (3H, s, $CN(CH_3)_2$), 3.82 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.61 (2H, dt, *J* 1.2, 5.4 Hz, OCH_2CHCH_2), 5.21 (1H, dd, *J* 1.6, 10.2 Hz, OCH_2CHCH_2), 5.36 (1H, dd, *J* 1.6, 17.4 Hz, OCH_2CHCH_2), 6.02-6.14 (1H, m, OCH_2CHCH_2), 6.68 (1H, s, Ar*H*), 6.81 (1H, d, *J* 8.2 Hz, Ar*H*), 7.31 (1H, t, *J* 8.0 Hz, Ar*H*), 7.83 (1H, d, *J* 8.2 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$): 33.4 (CH_2), 56.1 (CH_3), 56.3 (CH_3), 63.1 (CH_3), 66.2 (CH_3), 106.1 (CH), 106.7 (CH), 115.2 (C); 116.5 (CH), 117.2 (C), 117.9 (CH_2), 118.2 (C), 126.7 (CH), 133.7 (CH), 144.2 (C), 147.2 (C), 156.4 (C), 169.5 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{18}H_{21}NNaO_4$ 338.1368, found 338.1637 (+2.01 ppm).

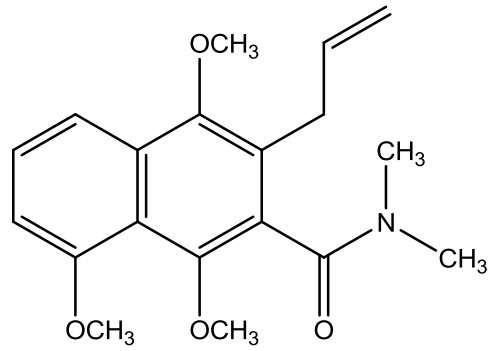
3-Allyl-4-hydroxy-1,8-dimethoxy-*N*,*N*-dimethyl-2-naphthamide (201)



4-(Allyloxy)-1,8-dimethoxy-*N*,*N*-dimethyl-2-naphthamide (1.0 g, 0.003 mol) was dissolved in xylene (10 mL) and the solution was heated to reflux for 24 hours. Solvent was removed under reduced pressure to achieve a grey solid. The solid was purified by flash column chromatography over silica gel using EtOAc as eluent to obtain a grey solid (1.0 g, 95% yield); Mp: 194 ºC – 196 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3308.9 (OH, st, i), 3038.5 (CH st, md), 2978.2 (CH st, md), 2834.1 (CH st, md), 1638.8 (C=O st, i), 1464.2 (CH_2 b, md), 1408.3 and 1369.9 (CH_3 b, md), 1268.2 and 1072.1 (C-O-C st, md), 778.3 (CHar. oop, md); δ_H (400 MHz, $CDCl_3$): 2.80 (3H, s, $CNCH_3$), 3.15 (3H, s, $CNCH_3$), 3.20 (1H, dt, *J* 1.6, 16.0 Hz, $ArCH_2CHCH_2$), 3.36 (1H, dt, *J* 1.5, 16.0 Hz, $ArCH_2CHCH_2$), 3.84 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 5.08 (1H, dq, *J* 1.2, 10.4 Hz, $ArCH_2CHCH_2$), 5.12 (1H, dq, *J* 1.2, 17.2 Hz, $ArCH_2CHCH_2$), 5.87-5.94 (1H, m, $ArCH_2CHCH_2$), 6.38 (1H, s, ArO*H*), 6.84 (1H, d, *J* 7.5 Hz, Ar*H*), 7.35 (1H, t, *J* 8.0 Hz, Ar*H*), 7.78 (1H, d, *J* 7.5 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$): 32.3 (CH_2), 34.5 (CH_3), 38.4

(CH_3), 56.1 (CH_3), 63.5 (CH_3), 106.1 (CH), 114.7 (CH), 116.4 (CH_2), 116.7 (C), 119.3 (C), 126.1 (CH), 128.6 (C), 128.8 (C), 135.6 (CH), 145.5 (C), 146.9 (C), 156.0 (C), 169.2 (C); ; FTMS (ES) ($M+Na^+$) calculated for $C_{18}H_{21}NNaO_4$ 338.1368, found 338.1636 (+3.92 ppm).

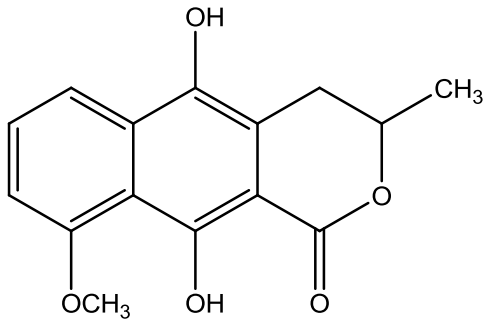
3-Allyl-1,4,8-trimethoxy-*N*,*N*-dimethyl-2-naphthamide (202)



3-Allyl-4-hydroxy-1,8-dimethoxy-*N*,*N*-dimethyl-2-naphthamide (1.0 g, 0.003 mol) was dissolved in dry tetrahydrofuran (50 mL) under N_2 atmosphere. The solution was vigorously stirred, sodium hydride 60% dispersion in mineral oil (0.3 g, 0.007 mol) and 18-crown-6 (0.01g, 0.0003 mol) were added slowly. The mixture was stirred for 2 hours, methyl iodide (0.45 mL, 0.007 mol) was added and stirring was prolonged for 24 hours. The reaction was quenched with a saturated aqueous ammonium chloride solution (100 mL) and the mixture was transferred into a separation funnel. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with water (1x100 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The oil was dissolved in ethyl acetate (25 mL), active charcoal was added while heating the solution and the mixture was filtered through a pad of Celite® to obtain an orange oil (0.90 g, 88% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3054.6 (CH st, md), 2986.9 (CH st, i), 2841.9 (CH st, md), 2815.6 (CH_{OCH_3} st, md), 1629.7 (C=O st, i), 1497.1 (CH_2 b, md), 1388.2 (CH_3 b, md), 1265.6 and 1070.4 (C-O-C st, md), 906.1 ($CH=CH_2$ oop, w), 739.3 (CHar. oop, w); δ_H (400 MHz, $CDCl_3$): 2.78 (3H, s, $CN(CH_3)_2$), 3.13 (3H, s, $CN(CH_3)_2$), 3.48 (1H, dt, *J* 1.5, 16.0 Hz, $ArCH_2CHCH_2$), 3.62 (1H, dt, *J* 1.5, 16.8 Hz, $ArCH_2CHCH_2$), 3.85 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.01

(3H, s, OC*H*$_3$), 4.99 (1H, dq, *J* 1.8, 10.4 Hz, ArCH$_2$CHC*H*$_2$), 5.07 (1H, dq, *J* 1.8, 17.4 Hz, ArCH$_2$CHC*H*$_2$), 5.89-6.00 (1H, m, ArCH$_2$C*H*CH$_2$), 6.88 (1H, d, *J* 7.5 Hz, Ar*H*), 7.43 (1H, t, *J* 8.0 Hz, Ar*H*), 7.68 (1H, d, *J* 7.5 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$): 31.8 (CH_2), 34.4 (CH_3), 38.4 (CH_3), 56.1 (CH_3), 62.1 (CH_3), 63.4 (CH_3), 106.0 (CH), 114.9 (CH), 115.5 (CH_2), 119.7 (C), 126.3 (C), 126.9 (CH), 129.5 (C), 131.4 (C), 136.3 (CH), 148.5 (C), 150.7 (C), 156.5 (C), 168.6 (C); FTMS (ES) (M+) calculated for $C_{19}H_{23}NO_4$ 329.1627, found 329.1629 (-2.99 ppm).

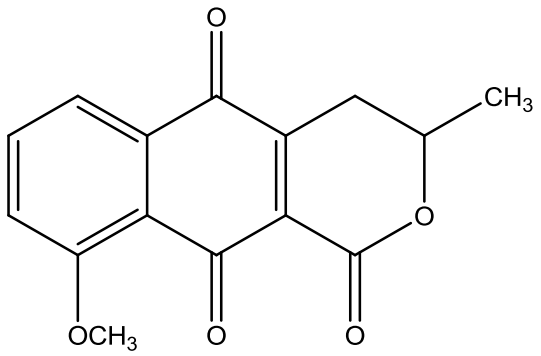
5,10-Dihydroxy-9-methoxy-3-methyl-3,4-dihydro-1*H*-benzo[*g*]isochromen-1-one (225)



3-Allyl-1,4,8-trimethoxy-*N*,*N*-dimethyl-2-naphthamide (1.0 g, 0.003 mol) was stirred in an aqueous hydrochloric acid (6M) solution (15 mL) and the mixture was heated to reflux for 18 hours. Water (50 mL) and dichloromethane (50 mL) were added and the mixture was transferred to a separation funnel. The two layers were separated and the aqueous layer was extracted with dichloromethane (3x50 mL). The combined organic layers were washed with water (1x25 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by flash column chromatography over silica gel using a mixture of petrol/EtOAc (2:3) to obtain a dark green oil (0.11 g, 13% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3409.7 (OH st, i), 3054.7 (CH st, i), 2986.9 (CH st, md), 2937.6 (CH st, w), 2845.9 (CH $_{OCH_3}$ st, w), 1660.7 (C=O st, i), 1637.2 (C=C st, md), 1609.2 (C=C st, w), 1452.7 (CH_2 b, md), 1421.9 and 1379.4 (CH_3 b, md), 1265.8 (C-O-C st, i), 1241.0 (C-O st, md), 1026.3 (C-O-C st, md), 739.1 (CHar. oop, md); δ_H (400 MHz, $CDCl_3$): 1.58 (3H, d, *J* 6.4 Hz, ArCH$_2$CHC*H*$_3$), 2.83 (1H, dd, *J* 10.8, 16.4 Hz, ArC*H*$_2$CHCH$_3$),

3.33 (1H, dd, *J* 3.2, 16.0 Hz, ArC*H*$_2$CHCH$_3$), 3.81 (3H, s, ArOC*H*$_3$), 4.70-4.75 (1H, m, ArCH$_2$C*H*CH$_3$), 6.92 (1H, dd, *J* 1.2, 8.0 Hz, Ar*H*), 7.48-7.57 (2H, m, 2 x Ar*H*), 9.54 (1H, s, ArO*H*), 13.64 (1H, s, ArO*H*); δ_C (100 MHz, $CDCl_3$): 20.9 (CH_3), 28.9 (CH_2), 61.4 (CH_3), 76.5 (CH), 100.0 (C), 111.8 (CH), 112.8 (CH), 113.6 (C), 122.2 (C), 132.3 (CH), 134.1 (C), 144.1 (C), 157.6 (C), 159.4 (C), 171.4 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{15}H_{14}NaO_5$ 297.0739, found 297.0738 (+1.29 ppm).

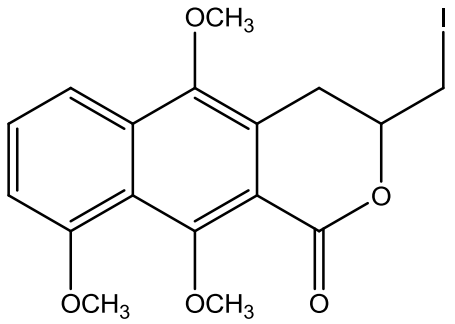
9-methoxy-3-methyl-3,4-dihydro-1H-benzo[*g*]isochromene-1,5,10-trione (225)



3-allyl-1,4,8-trimethoxy-*N*,*N*-dimethyl-2-naphthamide (1.0 g, 0.003 mol) was stirred in a 6M aqueous solution of chlorhydric acid (15 mL) and the mixture was heated to reflux for 18 hours. Water (50 mL) and dichloromethane (50 mL) were added and the mixture was transferred to a separation funnel. The two layers were separated and the aqueous layer was extracted with dichloromethane (3x50 mL). The combined organic layers were washed with water (1x25 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by flash column chromatography over silica gel using a mixture of petrol/EtOAc (2:3) to obtain a dark green oil (0.45 g, 50% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 2917.9 (CH st, i), 2849.0 (CH st, md), 1636.3 (C=O st, i), 1451.9 and 1379.0 (CH_3 b, i), 1240.7 and 1027.4 (C-O-C st, md), 757.9 (CHar. oop, w) ; δ_H (400 MHz, $CDCl_3$): 1.46 (3H, d, *J* 6.4 Hz, OCHC*H*$_3$), 2.85 (1H, dd, *J* 11.2, 16.4 Hz, 1 x OCHC*H*$_2$), 3.34 (1H, dd, *J* 2.4, 16.4 Hz, 1 x OCHC*H*$_2$), 3.81 (3H, s, ArOC*H*$_3$), 4.69-4.74 (1H, m, OC*H*CH$_3$), 6.94 (1H, d, *J* 7.6 Hz, Ar*H*), 7.50-7.61 (2H, m, 2 x Ar*H*) ; δ_C (100 MHz, $CDCl_3$): 20.9 (CH_3), 29.7

(CH_2), 61.4 (CH_3), 76.5 (CH), 100.0 (C), 111.9 (CH), 112.8 (CH), 113.4 (C), 122.1 (C), 132.3 (CH), 134.0 (C), 145.5 (C), 157.6 (C), 159.1 (C), 180.8 (C).

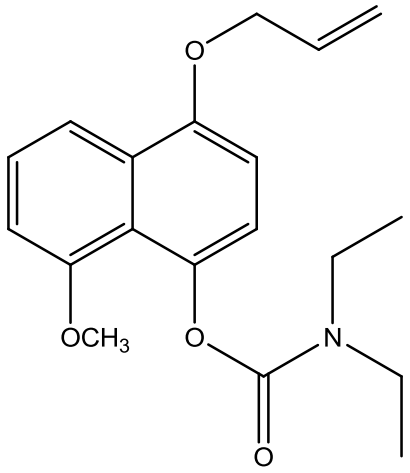
3-(Iodomethyl)-8,9,10-trimethoxy-3,4-dihydroanthracen-1(2*H*)-one (209)



To a solution of 3-allyl-1,4,8-trimethoxy-*N*,*N*-dimethyl-2-naphthamide (0.50 g, 0.0015 mol) in a mixture of tetrahydrofuran and diethyl ether (15 mL, 1:1) was added a saturated aqueous sodium carbonate solution (15 mL). After 5 minutes of vigorous stirring iodine (2.47 g, 0.0097 mol) was added and stirring was prolonged for 18 hours at reflux. Diethyl ether (25 mL) and water were added and the mixture was transferred to a separation funnel. The two layers were separated and the aqueous layer was washed with diethyl ether (3x25 mL). The combined organic layers were washed with water (1x25 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by flash column chromatography over silica gel using a mixture of petrol/EtOAc (1:1) to obtain a yellow solid (0.38 g, 60% yield); Mp: 210 ºC – 213 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3044.8 (CH st, i), 2987.6 (CH st, i), 2947.7 (CH st, md), 2843.1 (CH_{OCH_3} st, w), 1760.8 (C=O st, i), 1647.2 (C=C st, md), 1452.2 (CH_2 b, md), 1421.3 and 1358.4 (CH_3 b, md), 1264.8 and 1020.3 (C-O-C st, i), 759.1 (CHar. oop, md); δ_H (400 MHz, $CDCl_3$): 2.99 (1H, dd, *J* 2.1, 12.8 Hz, OCHC*H*$_2$), 3.45 (1H, dd, *J* 7.2, 10.4 Hz, OCHC*H*$_2$), 3.51 (1H, dd, *J* 4.8, 8.4 Hz, ArCHC*H*$_2$I), 3.56 (1H, dd, *J* 2.0, 12.8 Hz, ArC*H*CH$_2$I), 3.89 (3H, s, OC*H*$_3$), 3.98 (3H, s, OC*H*$_3$), 4.02 (3H, s, OC*H*$_3$), 4.41-4.43 (1H, m, OC*H*CH$_2$I), 6.93 (1H, d, *J* 8.0 Hz, Ar*H*), 7.69 (1H, d, *J* 7.6 Hz, Ar*H*), 7.57 (1H, t, *J* 7.6 Hz, Ar*H*); δ_C (100 MHz,

$CDCl_3$): 27.0 (CH_2), 34.7 (CH_3), 37.0 (CH_2), 39.3 (CH_3), 66.4 (CH_3), 80.4 (CH), 110.6 (CH), 112.9 (CH), 117.0 (C), 117.9 (C), 122.2 (C), 122.9 (C), 127.9 (CH), 145.4 (C), 152.4 (C), 154.3 (C), 167.1 (C); FTMS (ES) (M+) calculated for $C_{17}H_{17}IO_5$ 428.0121, found 428.0121 (+0.59 ppm).

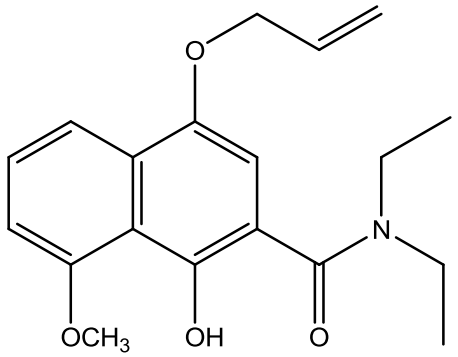
4-(Allyloxy)-8-methoxynaphthalen-1-yl diethylcarbamate (190)



Sodium hydride (1.91 g, 0.05 mol) was added to a solution of 4-(allyloxy)-8-(methoxy)naphtalen-1-ol (5.5 g, 0.024 mol) in tetrahydrofuran (70 mL) under N_2 atmosphere and the mixture was stirred at room temperature for 2 hours. Diethylcarbamoyl chloride (6.0 mL, 0.05 mol) was added slowly and stirring was prolonged for 18 hours. The reaction was quenched with saturated aqueous ammonium chloride (100 mL) and the mixture was transferred into a separation funnel. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x75 mL). The combined organic layers were washed with water (1x75 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure to achieve a brown solid. The solid was purified using flash column chromatography over silica gel using a mixture of petrol/EtOAc (1:1) as eluent obtaining an orange oil (6.45 g, 82% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 2979.6 (CH st, md), 2934.0 (CH st, md), 1701.9 (C=O st, i), 1603.2 (C=C st, w), 1465.0 (CH_2 st, md), 1411.1 and 1380.4 (CH_3 b, md), 1267.0 and 1070.2 (C-O-C st, i), 991.2 and 907.4 ($CH=CH_2$ oop, md), 733.3 (CHar. oop, md); δ_H (400 MHz, $CDCl_3$): 1.23 (3H, t, *J* 7.2 Hz, $N(CH_2C\mathit{H}_3)_2$), 1.32 (3H, t, *J* 7.2 Hz, $N(CH_2C\mathit{H}_3)_2$), 3.42 (2H, q, *J* 14.0 Hz, $N(C\mathit{H}_2CH_3)_2$), 3.55 (2H, q, *J* 7.2 Hz,

N(CH_2CH_3)$_2$), 3.87 (3H, s, ArOCH_3), 4.68 (2H, dt, *J* 1.6, 5.2 Hz, ArOCH_2CHCH$_2$), 5.32 (1H, dq, *J* 1.6, 10.8 Hz, ArOCH$_2$CHCH_2), 5.50 (1H, dq, *J* 1.6, 17.2 Hz, ArOCH$_2$CHCH_2), 6.11-6.19 (1H, m, ArOCH$_2$C*H*CH$_2$), 6.76 (1H, d, *J* 8.0 Hz, Ar*H*), 6.86 (1H, d, *J* 9.6 Hz, Ar*H*), 6.99 (1H, d, *J* 8.4 Hz, Ar*H*), 7.36 (1H, t, *J* 8.0 Hz, Ar*H*), 7.91 (1H, dd, *J* 0.8, 8.0 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$): 14.0 (CH_3), 14.1 (CH_3), 41.6 (CH_2), 42.0 (CH_2), 55.5 (CH_3), 69.3 (CH_2), 105.3 (CH), 106.4 (CH), 114.8 (CH), 117.4 (CH_2), 119.1 (CH), 120.4 (C), 125.6 (CH), 128.5 (C), 133.3 (CH), 140.8 (C), 151.8 (C), 155.4 (C), 155.5 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{19}H_{23}NNaO_4$ 352.1525, found 352.1527 (-3.08 ppm).

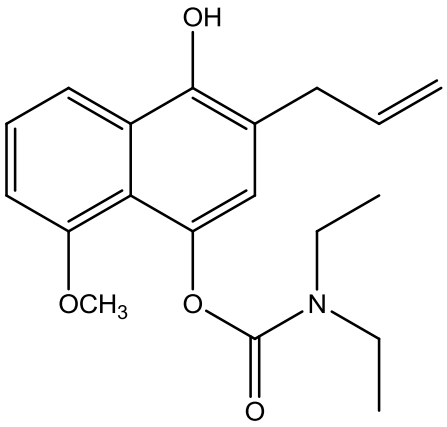
4-(Allyloxy)-1-hydroxy-8-methoxy-*N*,*N*-diethyl-2-naphthamide (194)



A 1.4M solution of *sec*-butyllithium (1.2 mL, 0.002 mol) was added dropwise to a solution of *N,N,N',N'*-tetramethylethylenediamine (0.2 mL, 0.002 mol) in dry tetrahydrofuran (25 mL) under N_2 atmosphere. The mixture was cooled to -78 ºC and a solution of 4-(allyloxy)-8-methoxynaphthalen-1-yl diethylcarbamate (0.5 g, 0.001 mol) in dry tetrahydrofuran (25 mL) was cannulated in a constant flow keeping temperature low. The solution was stirred for 2 hours at -78 ºC, heated to room temperature and stirring was prolonged 2 hours at this temperature. The reaction was quenched with a saturated aqueous ammonium chloride solution (50 mL) and the mixture was transferred into a separation funnel. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x75 mL). The combined organic layers were washed with water (1x75 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was

removed under reduced pressure. The crude was purified by flash column chromatography over silica gel using a mixture of petrol/EtOAc (2:3) as eluent to obtain a orange oil (0.06g, 12% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3459.8 (OH st, i), 3001.2 (CH st, i), 2944.1 (CH st, md), 1704.8 (C=O st, i), 1466.1 (CH_2 b, md), 1414.9 and 1377.2 (CH_3 b, w), 1257.1 and 1072.1 (C-O-C st, i), 988.4 and 901.8 ($CH=CH_2$ oop, md), 733.3 (CHar. oop, md) δ_H (400 MHz, $CDCl_3$): 1.29 (3H, t, *J* 7.2 Hz, $N(CH_2C\mathit{H}_3)_2$), 1.31 (3H, t, *J* 7.2 Hz, $N(CH_2C\mathit{H}_3)_2$), 3.44 (2H, q, *J* 7.2 Hz, $N(C\mathit{H}_2CH_3)_2$), 3.55 (2H, q, *J* 7.2 Hz, $N(C\mathit{H}_2CH_3)_2$), 3.91 (3H, s, $ArOC\mathit{H}_3$), 4.70 (2H, dt, *J* 1.6, 5.2 Hz, $ArOC\mathit{H}_2CHCH_2$), 5.31 (1H, dq, *J* 1.6, 10.8 Hz, $ArOCH_2CHC\mathit{H}_2$), 5.52 (1H, dq, *J* 1.6, 17.2 Hz, $ArOCH_2CHC\mathit{H}_2$), 5.99-6.01 (1H, m, $ArOCH_2C\mathit{H}CH_2$), 6.88 (1H, d, *J* 9.6 Hz, Ar*H*), 7.03 (1H, d, *J* 8.4 Hz, Ar*H*), 7.34 (1H, t, *J* 8.0 Hz, Ar*H*), 7.92 (1H, dd, *J* 0.8, 8.0 Hz, Ar*H*), 9.27 (1H, s, ArO*H*); δ_C (100 MHz, $CDCl_3$): 12.8 (CH_3), 13.0 (CH_3), 42.5 (CH_2), 43.0 (CH_2), 55.7 (CH_3), 69.9 (CH_2), 104.0 (CH), 115.1 (CH), 115.9 (CH), 117.5 (CH_2), 119.2 (CH), 120.5 (C), 126.2 (CH), 128.1 (C), 140.6 (C), 151.0 (C), 155.2 (C), 155.4 (C), 165.1 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{19}H_{23}NNaO_4$ 352.1525, found 352.1526 (-1.33 ppm).

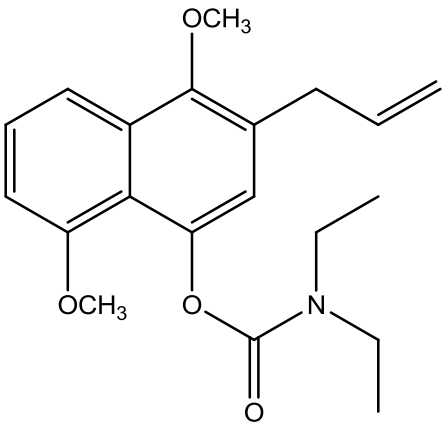
3-Allyl-4-hydroxy-8-methoxynaphthalen-1-yl diethylcarbamate (191)



4-(Allyloxy)-8-methoxynaphthalen-1-yl diethylcarbamate (2.0 g, 0.006 mol) was dissolved in xylene (10 mL) and the solution was heated to reflux for 24 hours. Solvent was removed under reduced pressure to achieve a gray solid. The solid was purified by flash column chromatography over silica gel using EtOAc as eluent to obtain a grey

solid (1.6 g, 83% yield); Mp: 117 ºC - 119 ºC; υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 3304.6 (OH st, md), 2979.7 (CH st, md), 2936.2 (CH st, md), 1692.8 (C=O st, i), 1632.9 (C=C st, w), 1606.7 (C=C st, md), 1464.0 (CH_2 b, md), 1414.0 and 1386.8 (CH_3 b, md), 1275.7 and 1066.5 (C-O-C st, i), 733.3 (CHar. oop, md); δ_H (400 MHz, $CDCl_3$): 1.29 (3H, t, *J* 7.2 Hz, $N(CH_2CH_3)_2$), 1.32 (3H, t, *J* 7.2 Hz, $N(CH_2CH_3)_2$), 3.11 (2H, t, *J* 1.2, 6.4 Hz, $ArOCH_2CHCH_2$), 3.46 (2H, q, *J* 7.2 Hz, $N(CH_2CH_3)_2$) 3.54 (2H, q, *J* 7.2 Hz, $N(CH_2CH_3)_2$), 3.86 (3H, s, $ArOCH_3$), 5.01-5.12 (2H, m, $ArOCH_2CHCH_2$), 5.81-5.90 (1H, m, $ArOCH_2CHCH_2$), 6.50 (1H, br, ArOH), 6.73 (1H, d, *J* 7.6 Hz, ArH), 7.07 (1H, s, ArH), 7.18 (1H, t, *J* 7.6 Hz, ArH), 7.58 (1H, d, *J* 7.6 Hz, ArH).; δ_C (100 MHz, $CDCl_3$): 13.6 (CH_3), 14.0 (CH_3), 34.5 (CH_2), 41.7 (CH_2), 42.1 (CH_2), 55.5 (CH_3), 105.3 (CH), 114.8 (CH), 116.3 (CH_2), 118.9 (C), 119.9 (C), 121.5 (CH), 125.1 (CH), 128.1 (C), 128.9 (CH), 139.7 (C), 147.0 (C), 155.2 (C), 155.9 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{19}H_{23}NNaO_4$ 352.1525, found 352.1527 (-2.91 ppm).

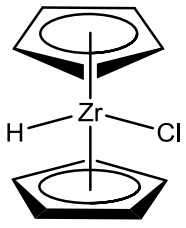
3-Allyl-4,8-dimethoxynaphthalen-1-yl diethylcarbamate (192)



3-Allyl-4-hydroxy-8-methoxynaphthalen-1-yl diethylcarbamate (1.0 g, 0.003 mol) was dissolved in dry tetrahydrofuran (75 mL) under N_2 atmosphere. The solution was vigorously stirred and sodium hydride 60% dispersion in mineral oil (0.31 g, 0.008 mol) and 18-crown-6 (0.08g, 0.0003 mol) were added slowly. The mixture was stirred for 2 hours, methyl iodide (0.5 mL, 0.008mol) was added and stirring was prolonged for 24 hours. The reaction was quenched with a saturated aqueous ammonium chloride solution (100 mL) and the mixture was transferred into a separation funnel. The two

layers were separated and the aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with water (1x100 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The oil was dissolved in ethyl acetate (25 mL), active charcoal was added while heating the solution and the mixture was filtered through a pad of Celite® to obtain a brown oil (0.8 g, 78% yield); υ_{max} (thin film, CH_2Cl_2)/cm^{-1}: 2979.3 (CH st, md), 2935.5 (CH st, md), 2843.1 (CH $_{OCH_3}$ st, w), 1701.7 (C=O st, i), 1627.9 (C=C st, w), 1605.9 (C=C st, w), 1473.9 (CH_2 b, md), 1426.6 and 1379.4 (CH_3 b, md), 1274.0 (C-O-C st, i), 1222.4 (C-N st, w), 1067.5 (C-O-C st, md), 733.2 (CHar. oop, md); δ_H (400 MHz, $CDCl_3$): 1.23 (3H, t, *J* 7.2 Hz, $N(CH_2C\mathit{H}_3)_2$), 1.32 (3H, t, *J* 7.2 Hz, $N(CH_2C\mathit{H}_3)_2$), 3.41 (2H, q, *J* 6.8 Hz, $N(C\mathit{H}_2CH_3)_2$), 3.50-3.56 (4H, m, $ArOC\mathit{H}_2CHCH_2$ and $N(C\mathit{H}_2CH_3)_2$), 3.86 (6H, s, $ArOCH_3$ and $ArOCH_3$), 5.09-5.14 (2H, m, $ArOCH_2CHC\mathit{H}_2$), 5.98-6.02 (1H, m, $ArOCH_2C\mathit{H}CH_2$), 6.79 (1H, d, *J* 8.0 Hz, Ar*H*), 6.94 (1H, s, Ar*H*), 7.37 (1H, t, *J* 8.4 Hz, Ar*H*), 7.67 (1H, d, *J* 8.4, Ar*H*); δ_C (100 MHz, $CDCl_3$): 13.5 (CH_3), 14.0 (CH_3), 33.6 (CH_2), 41.6 (CH_2), 42.0 (CH_2), 55.5 (CH_3), 62.0 (CH_3), 105.46 (CH), 114.8 (CH), 116.3 (CH_2), 119.6 (C), 121.4 (CH), 126.3 (CH), 128.5 (C), 131.2 (C), 136.6 (CH), 143.4 (C), 150.8 (C), 155.2 (C), 155.9 (C); FTMS (ES) ($M+Na^+$) calculated for $C_{20}H_{25}NNaO_4$ 366.1681, found 366.1860 (+1.44 ppm).

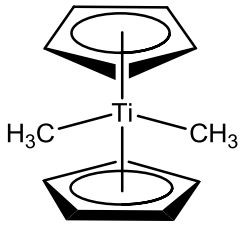
Bis(cyclopentadienyl)zirconium chloride hydride



Lithium aluminium hydride (0.5 g, 0.013 mol) was added dropwise to a solution of bis(cyclopentadienyl)zirconium(IV) dichloride (0.5 g, 0.02 mol) in dry tetrahydrofuran (25 mL). The reaction mixture was stirred at room temperature for 24 hours until colour changed to orange. The reaction was quenched with a saturated aqueous ammonium chloride solution (25 mL), diethyl ether was added (25 mL) and the mixture was

transferred into a separation funnel. The two layers were separated and the organic layer was concentrated under reduced pressure to a final volume of 15 mL (3.0 M solution in diethyl ether).

Dimethyl titanocene



A 3.0 M solution of methyllitium in diethyl ether (2.7 mL, 0.004 mol) was added to a solution of bis(cyclopentadienyl)titanium(IV) dichloride (0.5 g, 0.02 mol) in 10 mL of dry toluene at 0 ºC. After 1 hour stirring at 0 ºC the solution colour changed to bright red indicating that the reaction was completed. The reaction mixture was washed with 25 mL of saturated ammonium chloride solution and the organic layer was concentrated to 15 mL (3.0 M solution in toluene).

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