Strategies Towards the Synthesis of 4-(3-methyl-but-1-enyl)-3,5,3',4'-tetrahydroxystilbene (Arachidin-1) and Resveratrol Analogues

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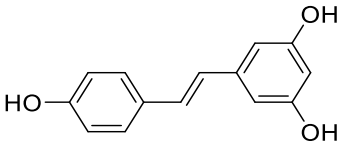
Abstract

Stilbene phytoalexins such as resveratrol, **1**, and the arachidins, including arachidin-1, **2**, are naturally synthesised by peanut (*Arachis hypogaea*) plants[1, 2]. The peanut phytoalexins are polyphenolic compounds consisting of a stilbene backbone, with a number of derivatives also possessing a prenyl moiety [3].



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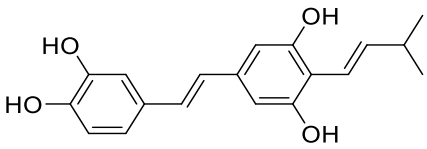

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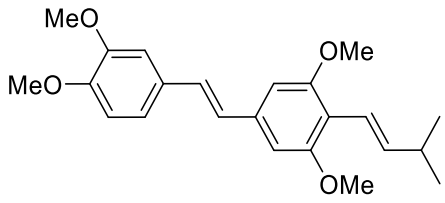
These distinctive phytoalexins have gained attention, as they exhibit various biological activities, for instance arachidin-1, **2**, has been reported to be more potent than resveratrol, **1**, in the inhibition of lipopolysaccharide-induced expression of cyclooxygenase-2 (COX-2) and COX-2 mRNA, *in vitro* at doses that were low in cytotoxicity[3-5]. Additionally the various arachidins have recently been shown to exhibit their anti-inflammatory properties, through the inhibition of a number of inflammatory mediator pathways [3].

In this work, various routes into the synthesis of arachidin-1, **2**, are described, *via* use of the Horner-Wadsworth-Emmons (HWE) reaction. Three different methodologies were explored, the first approach involving silyl ether (TIPS or TBDMS) protected benzaldehydes, proved unsuccessful due to cleavage of the silyl ether protecting groups, in basic and/or acidic conditions. This led to an alternative approach, whereby formation of the stilbene backbone proceeded *via* the regioselective demethylation of an acetal in the presence of sodium metal, subsequent electrophilic substitution using

iodomethane and finally acetal hydrolysis of the acetal, gave the isolated aldehyde in moderate yield (52 %). Coupling of the aldehyde with the substituted benzylphosphonate, *via* the HWE reaction gave the desired *trans*-stilbene in good yield (86 %), however incorporation of the prenyl side chain proved to be challenging *via* the Wohl-Ziegler bromination.

Further adaptation of the aforementioned route, whereby alkylation using diethyl iodomethylphosphonate, enabled the incorporation of the prenyl moiety and the subsequent construction of the *trans*-stilbene backbone, gave the 4-(3-methyl-but-1-enyl)-3,5,3',4'-tetramethoxystilbene, **3**, albeit in poor yield (47 %). The final step involving demethylation using BBr_3 gave arachidin-1, **2**, also in poor yield (30 %), nevertheless this approach has been proved to be a successful route for the total synthesis of arachidin-1, **2**, however optimised studies are required in order to obtain the desired compound in quantitative yields.



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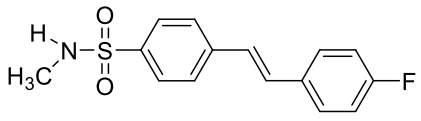
Synthetic analogues of resveratrol, **1**, are also known for their biological activities, including anti-inflammatory and chemopreventative properties. Recently, the anti-proliferative activity of a number of stilbenesulfonamides, against the National Cancer Institute's 60 (NCI-60) human tumour cell line has been reported [6].

Furthermore, the anti-inflammatory effects of novel heterocyclic methylsulfone and sulfonamide analogues, *via* inhibition of the COX-2 protein have also been published[7], however both synthetic routes described require a total of six or seven

steps, from the sulfanilamide and are limited to the synthesis of primary sulfonamides (SO_2NH_2).

In this work, an efficient three step synthesis has been designed and successfully implemented, proceeding *via* chlorosulfonation of diethyl benzylphosphonate, to form the sulfonyl chloride intermediate. Aminolysis of the sulfonyl chloride intermediate was then performed, using a range of primary, secondary and cyclic alkyl amines, as well as aromatic amines; including ammonia, dimethylamine, morpholine and diphenylamine. Finally, formation of the stilbene backbone with various substituted aldehydes, *via* the HWE reaction offered a short, versatile and alternative route to the synthesis of novel primary, secondary and tertiary *trans*-stilbene benzenesulfonamides and heterocyclic analogues, in yields of 42 – 100 %.

The activity of a selection of the synthesised stilbene benzenesulfonamides was evaluated against the human lung adenocarcinoma epithelial cell line (A549). Amongst the compounds tested, analysis of the data showed that the novel analogue, **4**, was found to be the most potent compound, with a GI_{50} of 0.1 μM. Comparison with the previously published data found analogue, **4**, to be approximately 500-fold more potent than the lead compound resveratrol, **1**, (GI_{50} = 51.64 μM) and approximately twice as potent than 5-fluorouracil (GI_{50} = 0.189μM), a chemotherapy drug used to treat various forms of cancer [8].



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Overall, these results demonstrate that the total synthesis of *trans*-arachidin-1, **2**, can be achieved *via* a five step methodology. A versatile route to the synthesis of novel

stilbene benzenesulfonamides has also been successfully achieved, amongst the compounds synthesised one appears to show promising anticancer activity, and warrants further investigation (i.e. *in vitro* studies using other cancer cell lines, and the synthesis of additional compounds using analogue, **4**, as a lead compound).

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Abbreviations

δ	Chemical shift
Ac	Acetyl
AIBN	Azobisisobutyronitrile
Ar	Aromatic
ArH	Aromatic proton
ArC	Aromatic carbon
ATR	Attenuated total reflectance
b.p.	Boiling point
$CDCl_3$	Deuterochloroform (chloroform-*d*)
$ClSO_3H$	Chlorosulfonic acid
CD_3CN	Acetonitrile-d_3
COX	Cyclooxygenase
D_2O	Water-d_2
DMG	Dimethylglyoxime
d	Doublet
dd	Doublet of doublets
dq	Doublet of quartets
dsep	Doublet of septets
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO-d_6	Dimethyl sulfoxide-d_6
EtOAc	Ethyl acetate

EtOH	Ethanol
$EtN(i\text{-}Pr)_2$	Diisopropylethylamine
Equiv.	Equivalent
FGI	Functional group interconversion
GI_{50}	The concentration of a compound required to inhibit cell growth by 50 %.
IC_{50}	The concentration of a compound required to achieve half maximal inhibition.
IC_{100}	The lowest concentration of a compound required to achieve complete inhibition of cell growth
IR	Infrared
J	Coupling constant
Km	Michaelis Menten constant; substrate concentration that gives half maximal velocity of an enzymatic reaction.
lit.	Literature
m	Multiplet
mRNA	messenger RNA
$MgSO_4$	Magnesium sulfate
m.p.	Melting point
MS	Mass spectrometry
m/z	Mass to charge ratio
NAD^+	Nicotinamide adenine dinucleotide
N_2	Nitrogen
NF-κB	Nuclear factor kappa b
NMR	Nuclear magnetic resonance
OMe	Methoxy
Pd	palladium

PGE_2	Prostaglandin E_2
ppm	Parts per million (chemical shift δ)
R_f	Retention factor
RT	Room temperature
s	Singlet
sep	Septet
SI	Selectivity index
Str	Stretch
t	Triplet
*t*BuOK/KOtBu	Potassium-*tert*-butoxide
*t*BuOH	*tert*-butanol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UV	Ultra violet
$ZnBr_2$	Zinc bromide

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Chapter One

1. Introduction

1.1 Stilbenes

The stilbene (1,2-diphenylethylene) structure, comprises two phenyl rings linked together by an ethylene linkage (Figure 1.1). Stilbenes exist in two geometric forms; the stable *trans*-stilbene, **5**, (*E*-stilbene) and the less stable *cis*-stilbene, **6**, (*Z*-stilbene). The *cis*-isomer is considered less stable, due to steric interactions which force the aromatic rings out-of-plane, and as a result conjugation is lost [9].

5 **6**

Figure 1.1 Stilbenes

A number of stilbene derivatives, also known as stilbenoids are present in nature and act as phytoalexins. Phytoalexins are low molecular weight antimicrobial compounds that are synthesised and accumulate in plants, following exposure to fungal attack, excessive ultraviolet light or plant stress [10, 11]. Although the mechanism of action to exogenous invasion is unclear, it has been suggested that these phytoalexins may display antimicrobial activity, by means of disrupting the cellular metabolism of the microorganism [10, 11].

1.2 Peanut stilbenes

A number of stilbene phytoalexins are known to be produced by the peanut plant, *Arachis hypogaea* a species of the legume family (*Legumino Sae*). These phytoalexins, which have been characterised and reported within the literature, are predominately produced by fungally-challenged peanuts (Figure 1.2) and are present as *trans*-isomers [1-3, 12-14], with the majority possessing a prenyl moiety on the stilbene backbone, which is suggested to increase the compound's bioactivity [15].

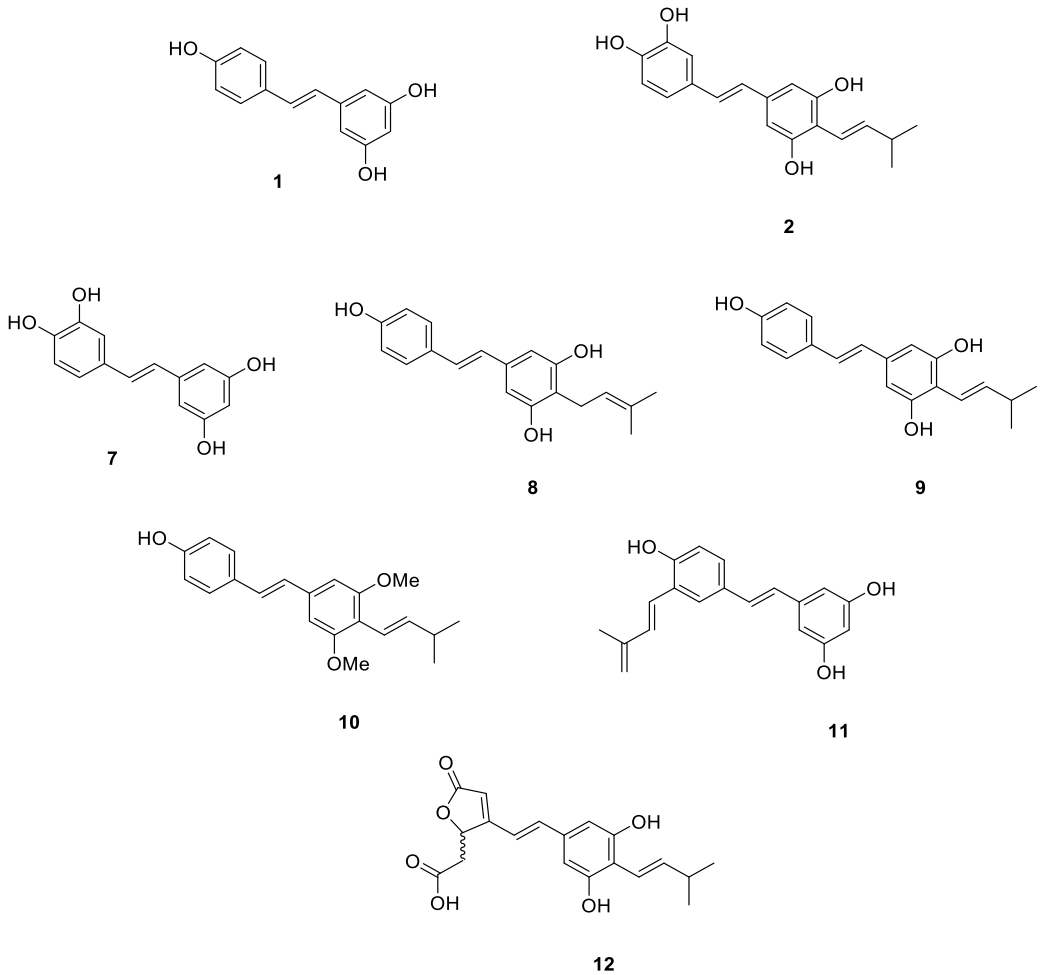


Figure 1.2 Structure of known stilbene phytoalexins from peanut seed; *trans*-resveratrol (1), *trans*-arachidin-1 (2), *trans*-piceatannol (7), *trans*-arachidin-2 (8), *trans*-arachidin-3 (9), *trans*-mucilagin A (10), *trans*-IPD (11) and *trans*-SB-1 (12)

Additionally, other novel phytoalexins (Figure 1.3) have been characterised by Sobolev *et al.,* [1, 16] and by Liu and co-workers [17].

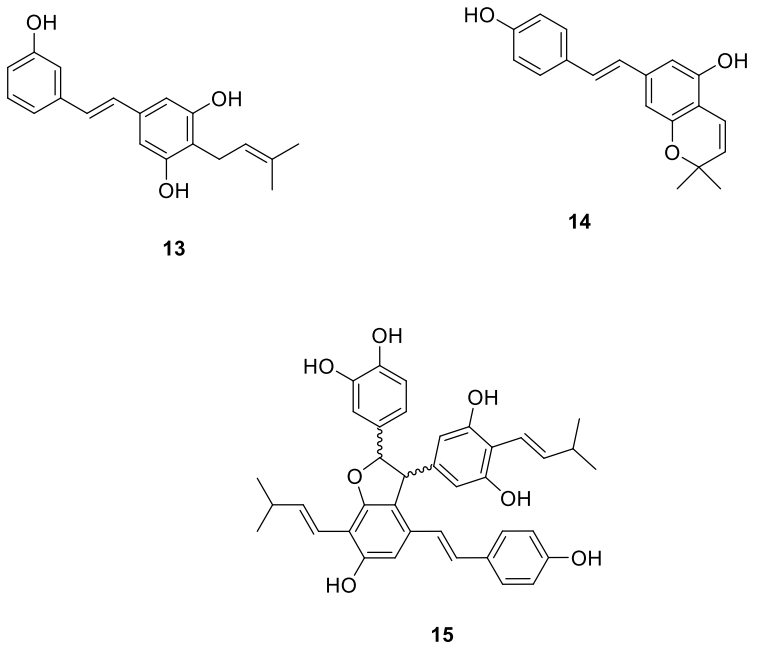


Figure 1.3 Structures of known stilbene phytoalexins from peanut seeds: chiricanine A (13), arahypin-5 (14) and arahypin-6 (15).

These distinctive phytoalexins are currently attracting considerable attention, due to the various biological and therapeutic properties including; antifungal [18], antibacterial [19], cardioprotective[14], neuroprotective[20], phytoestrogenic[21], anti-inflammatory[22], antioxidative [3], and anticancer activity [3, 4, 23], as well as the benefit of being available from a dietary source.

Stilbene phytoalexins are inexpensively extracted from plants, however they are seldom pure. Within the literature, mixtures of stilbenoids are commonly identified *via* spectral analysis (MS, NMR, and HPLC-MS), nonetheless despite the various

extraction methods which have been reported in the literature [1-3, 12-14], stilbenes are usually isolated in minute quantities (μg) [9, 24].

Because of this, the synthesis of known prenylated peanut phytoalexins such as arachidin-1, **2**, and SB-1, **12**, are required, in order to obtain pure samples of these compounds, in sufficient yields to aid with their characterisation. Furthermore this will enable studies to be performed with regards to the biological and therapeutic properties displayed by these compounds.

In this chapter, a brief overview into the biological properties displayed by peanut phytoalexins will be described, next coupling methods used in the formation of the carbon-carbon double bond (C=C), will be presented. Finally a background into benzenesulfonamides will be discussed later in this chapter, these compounds are analogues of resveratrol, **1**, which have been reported to display promising biological activity.

1.3 Biological activity of peanut stilbenoids

1.3.1 Anti-inflammatory and cardioprotective activity

Resveratrol, **1**, exists in its two geometric isomers; *cis*- and *trans*-resveratrol, although the mechanism of action is still unclear, *trans*-resveratrol, **1**, is suggested to be the isomer that exhibits the optimum bioactivity [13].

The ability of both *trans*-resveratrol, **1**, and *trans*-arachidin-1, **2**, to exhibit anti-inflammatory activity, has been suggested to be linked to their capacity to supress cyclooxygenase-2 (COX-2) mRNA expression [4]. This results in reduced levels of the

COX-2 enzyme, which are known to increase during an inflammatory process and consequently leads to an increase in pro-inflammatory prostaglandins (PG) [25, 26].

The effect displayed by these peanut stilbenes on the synthesis of the COX isoenzymes (COX-1 and COX-2), have also been suggested to be linked with their cardioprotective effects[27-29]. In particular, both resveratrol, **1**, [30] and piceatannol, **7**, [31, 32] appear to inihibit COX in the platelets, which leads to the blocking of thromboxane synthesis, and results in a reduced risk of thrombosis [33].

In 1992, Siemann and Creasy [34] published their findings of resveratrol, **1**, in wine (< 2.861 μmol/L), this discovery offered an explanation to the infamous "French Paradox". The French Paradox was an observation made by the scientist Serge Renaud, his justification was that low rates of mortality caused by coronary heart disease in France, was due to the moderate consumption of red wine. Despite the relatively high levels of saturated fat and smoking, as part of the French lifestyle and so implying the consumption of wine may offer additional protection from cardiovascular disease[35-37].

1.3.2 Antioxidative activity

Both resveratrol, **1**, [38] and piceatannol, **7**, [39, 40], are additionally known for their antioxidative activity, and it is suggested that the anti-inflammatory and antioxidative properties displayed by resveratrol, **1**, may also assist in explaining the neuroprotective effects displayed by resveratrol, **1** [41]. Furthermore the prenyl stilbenes; arachidin-1, **2**, arachidin-2, **8**, and arachidin-3, **9**, have been reported also exhibit potent antioxidative activity, and due to the presence of the 3'-OH moiety on

the stilbene backbone, arachidin-1, **2**, was found to display greater activity compared to both arachidin-2, **8**, and arachidin-3, **9** [42].

1.3.3 Anti-ageing activity

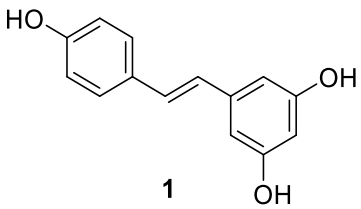
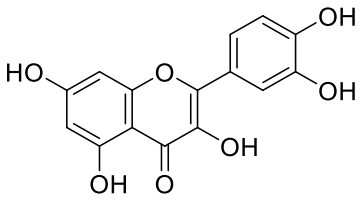
Resveratrol has also been identified as one of the first small molecule activators of SIRT1, an enzyme reported to imitate the effects of calorie restriction *in vivo*, and an important factor in slowing down the rate of ageing, as well as preventing age-related diseases linked to causes of mortality; such as type 2 diabetes, heart disease, cancer and neurodegenerative diseases[43-45].

Howitz *et al.,* [44] discovered resveratrol, **1**, to be the most potent agent, in extending the lifespan of mammalian cells, when compared to other polyphenols including quercetin (3,5,7,3',4'-pentahydroxyflavone), **16**. This peanut phytoalexin was found to be effective in stimulating the activity of SIRT1 up to 10 fold, as a result of decreasing the Km of both nicotinamide adenine dinucleotide (NAD^+) and peptide substrate (Table 1.1).

Moreover when the effects of resveratrol, **1**, on the protein Sir2 was examined, *in vivo* using the single-celled baker's yeast, *S. cerevisiae*, this stilbene was found to prolong the lifespan of the yeast by 70 % [44].

The prolonging of lifespan following treatment with resveratrol, **1**, has also been observed in a concentration dependent manner with *Drosophila* [46], in addition to multi-cellular organisms such as the short-lived vertebrate *Nothobranchius furzeri*, a fish which when in captivity is known to survive for a maximum period of 3 weeks. Nonetheless, despite the promising *in vivo* activity, the mechanism with regards to the longevity effect displayed by resveratrol, **1**, in addition to its correlation with diet restriction is not known[45, 47].

Table 1.1 Stimulation of SIRTI catalytic rate by plant polyphenols [44]

Compound (100 μM)	Ratio to control (mean ± s.e)	Structure
Resveratrol	13.4 ± 1.0	 **1**
Quercetin	4.59 ± 0.47	 **16**

As a potent SIRT1 activator resveratrol, **1**, has been coined to exhibit therapeutic potential in treating type 2 diabetes. An *in vivo* study on mouse models with type 2 diabetes found resveratrol, **1**, to increase mitochondrial activity and insulin sensitivity [48, 49]. However, due to some of the limitations displayed by resveratrol, **1**, including; poor bioavailability and solubility, analogues of resveratrol which display efficacy in prolonging the lifespan eukaryotes are still required [50].

1.3.4 Antimicrobial activity

Studies have also found resveratrol, **1**, to display promising antifungal activity in spermatophytes [51, 52], however the fungicidal effects of this peanut phytoalexin in humans are still scarcely known [2, 3, 51, 53, 54].

A recent report by Jung *et al.,* compared the fungicidal effects of resveratrol, **1**, against amphotericin B, an efficacious antifungal drug used in the treatment of systematic fungal infections, which is associated with severe adverse reactions, e.g. rupturing of red blood cells (haemolysis). When examined against known human infectious fungi; particularly *Candida albicans, Saccharomyces cerevisiae* and *Trichosporon beigelii*, resveratrol, **1**, at doses of 10-20 μg/mL, was found to solely initiate antifungal activity. Additional *in vitro* studies found resveratrol, **1**, to be as potent as amphotericin B, in inhibiting the growth of the fungus *Candida albicans* (Table 1.2).

Table 1.2 Antifungal activities of resveratrol against various fungi [54]

	Minimum Inhibitory Concentration (μg/mL)		
	C. albicans	*S. cerevisiae*	*T. beigelii*
Resveratrol	20	10-20	10
Amphotericin B	5	10	5-10

Furthermore, the study by Jung *et al.,* [54] into the effects of resveratrol, **1**, on human erythrocytes demonstrated the non-haemolytic activity displayed by resveratrol, **1**, against red blood cells. This means that the treatment of systematic fungal infections with resveratrol, **1**, could offer an advantage (over existing antifungal drugs, i.e.

amphotericin B) of reducing the chances of dangerous side effect, thus improving patient compliance.

The administration of current antiviral drugs including; acyclovir, famciclovir and valaciclovir in the treatment of viral infections, are often administered with a corticosteroid [55], which acts as both an anti-inflammatory agent and analgesic to treat the symptoms of pain and inflammation [56, 57], however this may be unnecessary with the application of resveratrol, **1**.

A number of *in vitro* and *in vivo* studies [65 – 67] have detailed the antiviral properties displayed by resveratrol, **1**, frequently reporting this natural stilbene, to be as potent as the various antiviral drugs currently on the market. Furthermore due to the anti-inflammatory effects displayed by resveratrol, **1**, the addition of corticosteroids would no longer be required.

As an antiviral agent, resveratrol, **1**, has been reported to display activity against the herpes simplex virus (*Herpesviridae)* family [58, 59], including the herpes simplex virus-1 (HSV-1), herpes simplex virus 2 (HSV-2) [58, 59], varicella zoster virus (VZV) [57] and human cytomegalovirus (HCMV) [60].

The herpes simplex virus is known to affect an estimated 95 million of the population worldwide [61], although a cure has not been found, medication can be applied in order to reduce the event of spreading. The anti-HSV activity of resveratrol, **1**, by means of *in vitro* and *in vivo* models, have been extensively studied by Docherty *et al*.,[59, 62]. For instance resveratrol, **1**, was found to reduce the cellular growth of mice cells at S-G_2-M phases and inhibit the production of the infected cell protein (ICP-47), an early protein of HSV. When compared to piceatannol, **7**, this stilbenoid was ineffective,

which suggests that in stilbene derived compounds, a specific chemical structure is crucial in the inhibition of HSV replication [58].

Other studies have demonstrated the effectiveness of resveratrol, **1**, as an anti-HSV drug by means of an *in vivo* model. The comparison of the dose dependent resveratrol cream (12.5 % or 25 %) with 5 % acyclovir ointment (Zovirax™) and 10 % docosanol cream (Abreva™) on hairless *SKH1* mice, infected with HSV-1 found this natural stilbene to significantly inhibit the development of HSV-1 induced skin lesions, particularly when compared to 5 % acyclovir ointment Zovirax™ (p = 0.0001), with no signs of dermal toxicity after the application of five times a day for 5 days [59]. Furthermore, when evaluating the route of drug administration, the topical administration of resveratrol, **1**, was found to be an effective route in inhibiting viral replication [63].

Chicken pox (varicella) and shingles (herpes zoster) are signs of primary infection by the varicella-zoster virus (VZV). This virus is transmitted among humans *via* respiratory droplets and direct skin contact, with sufferers often showing signs of a fever and vesicular rash. Subsequent to an infection, the VZV is known to lay dormant within the dorsal root, cranial and autonomic ganglia, with recurring viral infections resulting in shingles. An *in vitro* study by Docherty and co-workers in 2006, examining the effects of non-toxic doses of resveratrol, **1**, (219 μM) on human diploid lung cells (MRC-5) infected with VZV cells, reported resveratrol, **1**, to inhibit the replication of the varicella-zoster virus *via* a dose-dependent, time dependent and reversible approach, when applied 30 h after the viral infection. Resveratrol, **1**, was also reported to operate by not averting the VZV attachment or causing inactivation of the virus, but in a reversible manner, when observed *via* western blot and real-time PCR analysis. The analysis found resveratrol, **1**, to play a significant role in limiting

the synthesis of the IE62 protein, an essential immediate early gene transactivating protein, by reducing the levels of mRNA [57].

Resveratrol, **1**, has also been reported to display potent and selective antiviral activity against HCMV, by inhibiting viral replication when examined on human embryonic lung fibroblasts, limiting the appearance of the immediate-early and late HCMV proteins. With the suggested mode of action proceeding *via* inhibiting the virus-induced activation of the epidermal growth factor receptor (EGFR), and as a result preventing entry into the HCMV virus. As well as inhibiting phosphatidylinositol-3-kinase signal transduction, in addition to the NF-κB and Sp1 transcription factor activation, following an infection [60].

Several antiviral drugs have also been designed to treat the influenza virus, nonetheless many have been found to be ineffective. Resveratrol, **1**, has been reported to effectively inhibit the reproduction of the influenza virus *in vitro*, this stilbene was found to effectively increase the survival of the influenza infected mice, by decreasing pulmonary viral titres [64].

Furthermore resveratrol, **1**, has been shown as non-toxic, in addition to displaying antiviral and anti-inflammatory activity, albeit dependent on the nature of the virus, time of administration, concentration and frequency of treatments per day, therefore this compound encompasses the pharmacological properties desired in a novel drug for the treatment of viral infections. Although the mechanism of action displayed by resveratrol, **1**, is not fully understood, this stilbenoid is known to have an effect on a spectrum of viruses. Reports have also suggested resveratrol, **1**, to selectively target the cell instead of acting directly on the virus, as part of its mechanism to prevent viral replication[57, 64, 65], however this warrants further investigation.

Likewise, the search for an antimicrobial drug of which combines as an anti-inflammatory agent, has attracted great interest. The antifungal and antiviral activity of resveratrol, **1**, [18, 62] as well as the desirable anti-inflammatory property has led to the evaluation of this compound as a potential antibacterial agent, in the treatment of human skin conditions. Initial microbiology studies have identified resveratrol, **1**, as an antimicrobial agent, albeit with selective activity towards Gram negative bacteria.

In 2001, an *in vitro* model examining the antimicrobial activity of resveratrol, **1**, against *Neisseria meningitidis* (meningitis) and *Neisseria gonorrhoeae* (gonorrhoea) was performed by Docherty *et al*., whereby the administration of resveratrol, **1**, was found to selectively inhibit the activity of the Gram-negative bacteria (Table 1.3), however resveratrol, **1**, did not show efficacy against the Gram-positive bacteria examined [66]. The results from other *in vitro* studies, investigating the growth of Gram-positive and -negative bacteria in the presence of resveratrol, **1**, were found to also be consistent with the study performed by Docherty and co-workers [67].

Table 1.3 ICs of resveratrol against various bacteria [66]

Microorganism	IC_{50} (mg/L)	IC_{100} (mg/L)
N. gonorrhoeae	25	75
N. meningitidis	100	125
E. coli	> 200	> 200
S. aureus	> 200	> 200
S. pyogenes	> 200	> 200
P. aeruginosa	> 200	> 200
C. albicans	> 200	> 200

Conversely, the study by Chan *et al.,* in 2002 [68], reported the antibacterial effect of resveratrol, **1**, on a number of Gram-positive bacteria, commonly known to cause various human skin conditions; including *S. aureus* and *Streptococcus* group D*,* known to cause pimples, folliculitis and boils (furuncles), as well as the examination of Gram-negative bacteria; *Pseudomonas aeruginosa* commonly found in water, skin flora and soil and common dermatophytes including *tinea pedis* (athlete's foot) and *tinea corporis* (ringworm). In the study by Chan and co-workers, the use of trypticase soy agar (TSA) plates was reported, a basic medium suitable for culturing various microorganisms. Resveratrol, **1**, at a dose of 171 μg/mL in 1.7 % DMSO, was reported to display efficacy in inhibiting the growth of the Gram-positive bacterium, *S. aureus,* by up to 90 %. However, the application of resveratrol, **1**, at higher doses 342 μg/mL in 3.3 % DMSO was found to show similar results against the Gram-negative bacterium *P. aeruginosa*, with inhibition of up to 50 % against dermatophytes in the presence of 5 % DMSO.

With regards to the activity displayed by resveratrol, **1**, compared to benzoyl peroxide and erythromycin, compounds both commonly used in the formulation of treatments for skin diseases, the performance of this stilbene remains promising [69].

The antimicrobial activity of resveratrol, **1**, is not solely seen with *trans*-resveratrol, **1**, both geometric isomers of resveratrol have been reported to exhibit antimicrobial activity against *E. coli*, *Sarcina lutea*, *Bacillus subtilis* and *Staphylococcus sp.* However, the *trans*-isomer was found to display greater antimicrobial activity in comparison to the *cis* isomer (Table 1.4).

Table 1.4 Diameters of inhibition zone for the resveratrol extracts

Bacterium	Ethanolic extract of *trans*-resveratrol (mm)	Ethanolic extract of *cis*-resveratrol (mm)
Escherichia coli	13.7 ± 1.86	11.6 ± 1.90
Bacillus subtilis	15.0 ± 2.37	10.4 ± 1.77
Staphylococcus sp.	15.8 ± 1.40	11.2 ± 0.9
Sarcina lutea	16.2 ± 1.40	10.0 ± 1.22

In this study *trans*-resveratrol, **1**, was reported to demonstrate significant efficacy against Gram-positive bacteria and limited activity against Gram-negative bacteria. The observations reported may have been as a result of the variation in cell wall structure between the microorganisms examined, as the structure of the cell wall of a Gram-negative bacterium comprises of liposaccharide chains, therefore providing structure and protection from xenobiotics [70].

Studies into the mode of action by which resveratrol, **1**, displays its antibacterial activity against bacterial pathogens is not fully understood, although it has been suggested that the selectivity displayed by resveratrol, **1**, is possibly due to the microorganisms possessing a binding site, which the stilbene compound can easily bind to. Furthermore it is also thought that the antimicrobial activity displayed by resveratrol, **1**, is due to the compound's solubility resveratrol, **1**, being lipophilic is insoluble in water therefore when dissolved in DMSO, instead of ethanol has been shown to improve the compounds performance.

The selection of agar in the study is also crucial in obtaining optimum results with the stilbene, therefore what may be required is an evaluation of the inhibitory activity displayed by resveratrol, **1**, using a medium which is not selective towards the

growth of one colony of organisms. For instance, the use of the Luria-Bertani (LB) agar, although not suitable for organisms such as *Neisseria,* it is a common medium used in microbiology studies and does not favour the growth of one microorganism over another.

1.3.5 Anti-cancer activity

The anti-cancer properties of resveratrol, **1**, including the inhibition of cell proliferation as well as the ability to induce apoptosis, has been demonstrated *in vitro*, against various human cancer cell lines such as; colon, breast, glioma and prostate cancers[23, 71]. Additionally, the arachidins have been reported to exhibit anti-cancer activity, by inducing apoptosis in human leukaemia (HL-60) cancer cells [72], although arachidin-1, **2**, has been found to exhibit greater activity compared to its analogues (**8** and **9**).

Furthermore when examined using mouse macrophages arachidin-1, **2**, was found to display similar or even lower levels of toxicity than resveratrol **1**, which suggests that the reduced levels of toxicity displayed by arachidin-1, **2**, could give it a greater advantage over resveratrol, **1**, as a drug. As one of the clinical challenges with using resveratrol, **1**, was its ability to reduce the growth of cycling normal human peripheral blood lymphocytes, at concentrations similar to that required to inhibit most leukaemia cells [4, 5].

1.4 Pharmacokinetics of resveratrol

Although the therapeutic properties displayed by resveratrol, **1**, are promising, the quantity required to exert these therapeutic effects can often be higher than the amount of resveratrol, **1**, actually measured in human plasma, following oral administration. This is due to the rapid metabolism of resveratrol, **1**, in the liver into its glucuronide and sulphate conjugates, which consequently reduces its bioavailability and as a drug, prevents this natural stilbene from being effective. However, the potential of increasing the bioavailability of resveratrol, **1**, has been reported by De Santi and co-workers, with the use of quercetin, **16**, a flavonoid found in wine, fruits and vegetables, and a potent inhibitor of important drug-metabolising enzymes including Cytochrome P_{450} 3A4 (CYP3A4) and Cytochrome P_{450} 2C9 (CYP2C9)[73].

Previous studies have examined the bioavailability of *trans*-resveratrol, **1**, and the determination of its levels in blood plasma, however very little is known about its distribution, mainly due to the limited availability of validated *in vitro* and *in vivo* methods, which are needed to correctly determine the concentrations of resveratrol, **1**, and its conjugates distributed within the body [23].

An *in vivo* study carried out by Emilia Juan *et al.*, detailed the development of a selective extraction process, used for the determination and quantification of *trans*-resveratrol, **1**, and its conjugates in rat kidney, lung, liver, testis and brain tissues. When administered with 15 mg/kg of pure resveratrol, **1**, the natural compound was detected in the kidneys, liver and lungs, generally organs of which large volumes of blood are applied to. However lower concentrations of resveratrol, **1**, and its metabolites were found in organs with specific barriers naturally designed to prevent xenobiotics from entering. The kidneys were reported to contain considerable

concentrations of pure resveratrol, **1**, and its glucuronide conjugate compared to the other organs. The hydrophilic nature of the sulphate conjugate, meant that it was easily removed from the kidneys, which suggest the possible elimination of *trans*-resveratrol, **1**, *via* renal excretion [74].

As seen from a number of *in vivo* metabolic studies, both Phase I and Phase II reactions on resveratrol, **1**, affect its ability to act as a potential drug, despite it being highly absorbed[75, 76]. It is therefore unclear whether the effects of resveratrol, **1**, observed in cell culture and animal model studies will be replicated in clinical human studies. Despite this, cytotoxicity testing on animal models has shown *trans*-resveratrol, **1**, as a drug to be safe [77], a study in which Sprague-Dawley rats were administered with 20 mg/kg of resveratrol, **1**, for 28 days, a level 1000 times over the amount that may be consumed by a person, drinking one glass of red wine a day verified the compound's non-toxicity [13].

Resveratrol, **1**, is now available within the commercial market as a dietary supplement, sold in capsule, pill and powder form. Although within the literature, the biological and therapeutic properties displayed by resveratrol, **1**, are well known, very little is known about the remaining novel peanut phytoalexins, due to the quantities obtained (μg) when extracted from peanut plants. Therefore strategies towards the total synthesis of these novel compounds are still required, in order to determine if these natural compounds display similar or increased activity compared to resveratrol **1**.

1.5 Structure-Activity-Relationship

The Structure-Activity Relationship (SAR) of a lead compound is examined, in order to determine the relationship between its molecular structure, and the biological activity it exhibits as drug. Knowledge based on the SAR can then be used to perform modifications on the lead compound, in order to improve the pharmacological activity.

Characteristics that influence the SAR of a drug include; size, shape, the presence of functional groups, stereochemistry, reactivity, resonance, electronic effects and so on. Additionally Quantitative Structure Activity Relationship models (QSAR) are often applied, to mathematically characterise the correlation between a lead compound and its biological activity [78, 79].

Resveratrol, **1**, is known as an antioxidant, antimicrobial and cancer chemopreventative agent, however the relationship between its structure and biological activity has not been extensively explored. Although studies have highlighted characteristics, including the stereoisomerism, stilbene skeleton and the positioning of hydroxyl groups, to play an important role in pharmacological activity observed[3, 9].

Lipid peroxidation is a quintessential mechanism which leads to cell and tissue damage, and as a result causes a range of diseases. The potent antioxidative activity displayed by resveratrol, **1**, has been reported to reduce lipid peroxidation, by the scavenging of free radicals *in vitro.* The 4'-OH group is believed to be crucial for the radical scavenging activities displayed by resveratrol, **1**, furthermore the presence of

the 3-OH and 5-OH groups were also found to be equally important, as they offered additional resonance stability for the stilbene [80].

With regards to the role of resveratrol, **1**, in activating the protein SIRT1 and prolonging of lifespan, the hydroxyl moieties at the 3- and 5- positions of the aromatic ring, coupled with the *trans*-geometry have been reported to be necessary for its activity [50], with resveratrol, **1**, displaying potent activity towards the SIRT1 protein up to 12 fold, compared to other substituted analogues [44]. Additionally, both the stilbene backbone and the *trans*-configuration have been suggested to be essential for the antiproliferative and DNA polymerase activity displayed by resveratrol, **1** [38].

1.6 Synthesis of stilbenes

1.6.1 Non-catalytic coupling reactions

Various synthetic routes have been reported for the synthesis of peanut phytoalexins and stilbene derivatives, however the most common coupling methods used in the formation of the carbon-carbon double bond (C=C), include the Wittig-Horner [81, 82] and Horner-Wadsworth-Emmons (HWE) reaction[83, 84]. In addition to palladium (Pd) catalysed coupling reactions such as the Heck [85] and Suzuki [86] reaction. However, other commonly known alkene forming reactions; such as the Julia olefination[87, 88], Ramberg-Bäcklund[89, 90], McMurry [91] and Negishi-Stille reaction [92, 93] have not been fully explored for the synthesis of natural stilbenes. Additionally some reactions including the Peterson reaction, to date have not been reported in the construction of stilbene systems, nevertheless with the majority of the aforementioned reactions, the

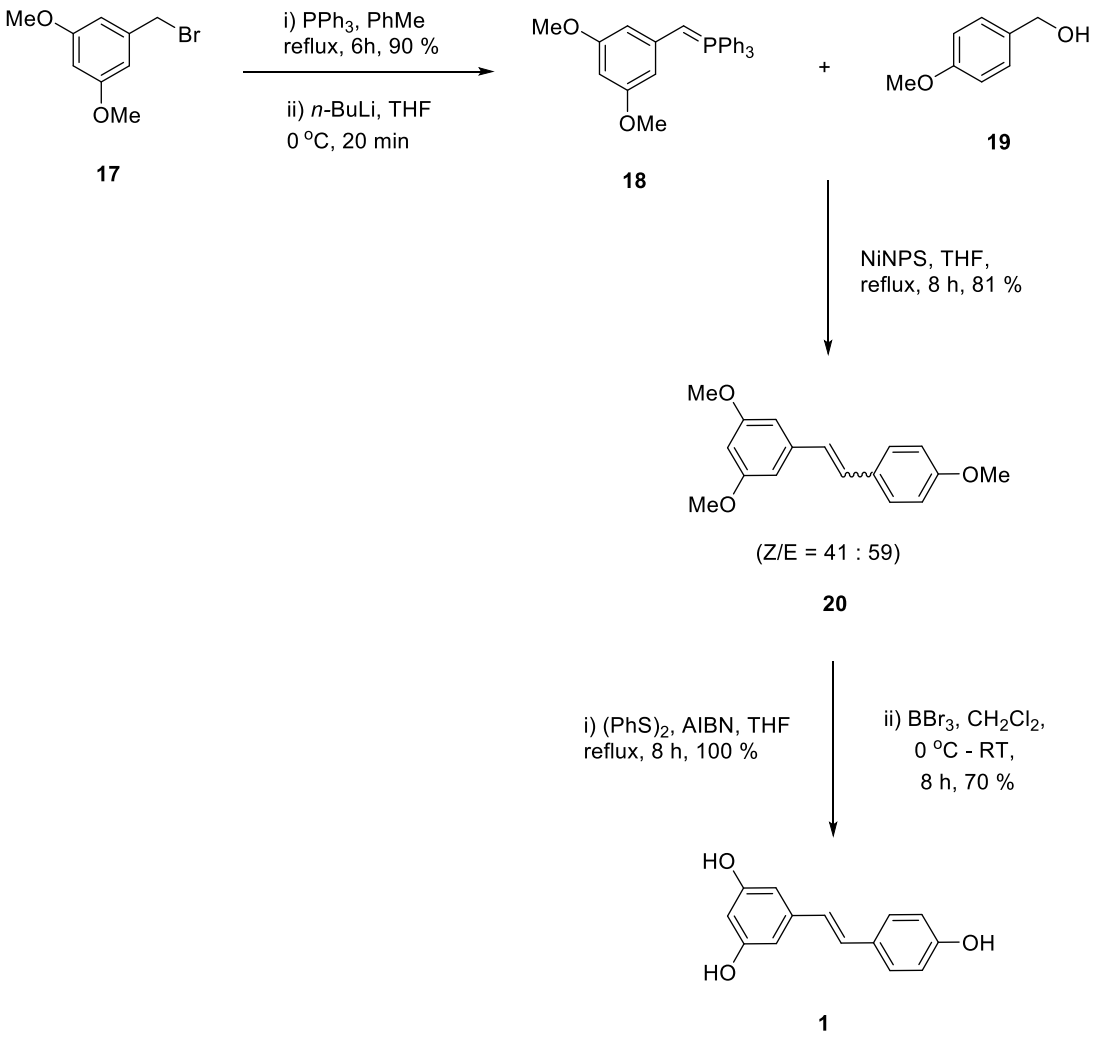
percentage yields obtained are often quite poor due to the number synthetic steps required.

Another challenge with regards to the construction of the C=C bond, is controlling the regio- and stereoselectivity of the reaction, to give the desired *trans*-isomer. The Wittig, also known as the Wittig-Horner type reaction [81], offers a solution to this matter, this traditional coupling approach has been reported in the synthesis of peanut stilbenes including *trans*-resveratrol, **1**, and piceatannol, **7**, in addition to other synthetic analogues [82, 95-102].

This approach has many benefits, due to it being simple, efficient, whilst offering a stereoselective approach to the synthesis of alkenes[103]. Additionally the Wittig is an attractive route compared to other elimination reactions, such as the Julia or Peterson reaction, due to it proceeding in one step[88, 104]. The widespread use of this reaction in organic synthesis has also been attributed to the mild reaction conditions and the ability to proceed without the need of an inert atmosphere or expensive catalysts[9, 81, 103, 105].

Although the Wittig reaction to date is still the primary approach for the formation of stilbenes, this reaction often results in low yields of the desired *trans*-alkene, due to the formation of both *E*/*Z*-alkenes[106]. Additionally, this reaction is limited to substrates possessing a carbonyl moiety and requires a stoichiometric ratio of the reactants used[107].

In 2009 Alonso and co-workers[98], reported a one-pot type Wittig olefination of substituted benzyl alcohols, **19**, and ylide, **18**, in the presence of nickel(0) nanoparticles (NiNPs), in order to synthesise *trans*-resveratrol, **1**, in good yield (70 %) (Scheme 1.1). This study proved that stilbenes could be formed, *via* the Wittig reaction, without the need of a carbonyl substrate.

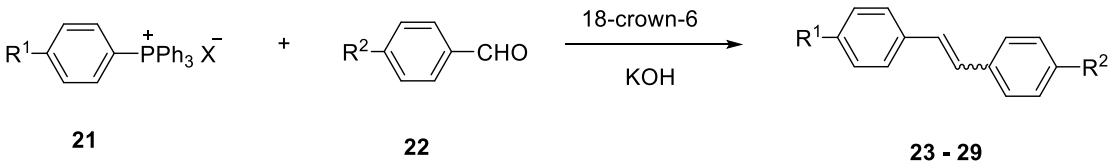


Scheme 1.1 Synthesis of resveratrol *via* Wittig-type olefination in the presence of nickel nanoparticles

Other variations of the Wittig reaction have been reported for the synthesis of both *meta*- and *para*-substituted stilbene derivatives (51 – 93 %), using crown ether, 18-crown-6, potassium hydroxide and a solid-liquid biphasic system (K_2CO_3/PhMe) (Table 1.5). However the stereoselectivity observed in this approach, was found to be comparable with the traditional Wittig reaction, as the selectivity for the *trans*-isomer was believed to be highly dependent on both the substituent present on the phosphonium halide and the reaction condition used. Notably, the solid-liquid

biphasic system comprising of benzyldiphenylchlorophosphonium bromides displayed almost complete *trans*-stereospecificity (*Z*/*E* < 2:98)[108].

Table 1.5 Coupling *via* the Wittig reaction



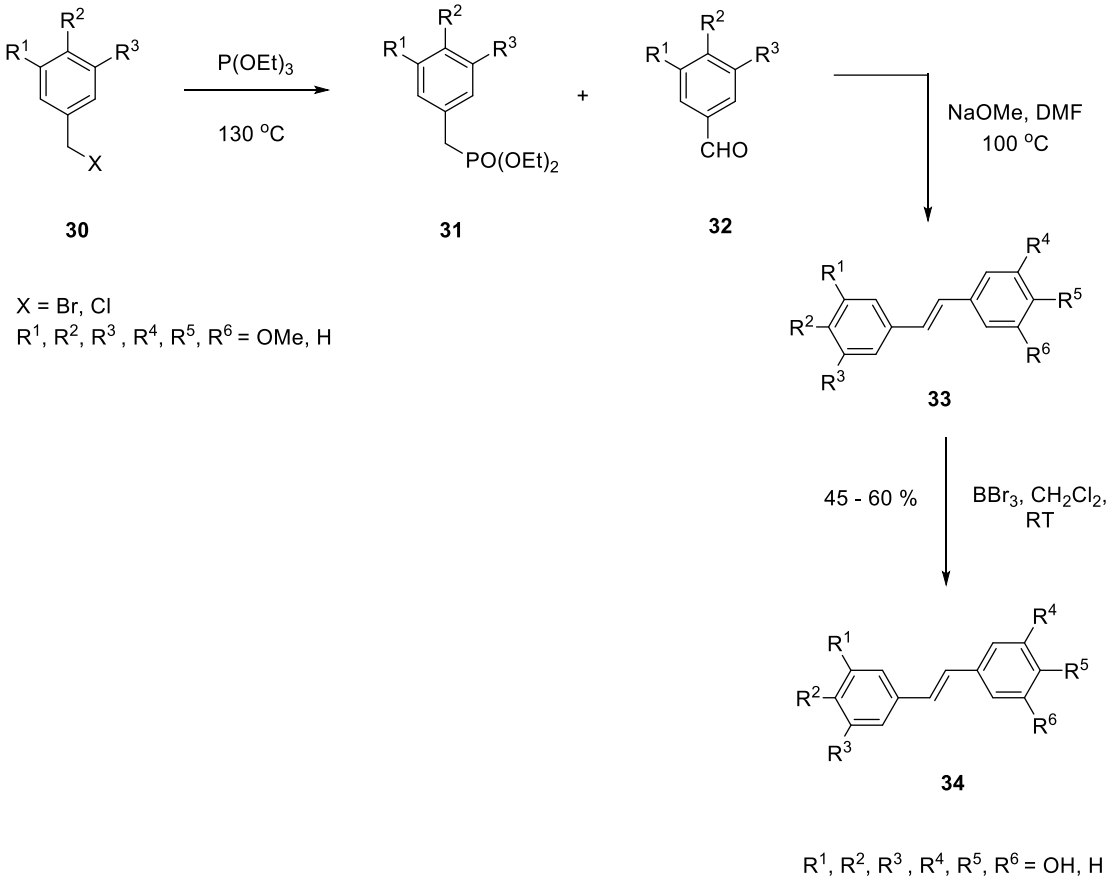
21 **22** **23 - 29**

Compound	R^1	X	R^2	Temperature (°C)	*Z* : *E*[a]
23	*p*-OMe	Cl	H	-70	85 : 15
24	H	Br	*p*-OMe	-70	70 : 30
25	*p*-Me	Cl	H	-70	85 : 15
26	*p*-CF_3	Br	*p*-CF_3	-70	82 : 18
27	*p*-CN	Br	*p*-CN	-70	>98 : <2
28	H	Br	*p*-CF_3	25	4 : 96
29	H	Br	*p*-NO_2	25	1 : 99

[a] Determined by HPLC

Following the discovery of the Wittig reaction in 1954 [81], an alternative and attractive alkene-forming reaction, was first reported by Horner *et al.,* in 1958 [109] and further developed by Wadsworth and Emmons [110].

The HWE reaction is generally limited to the coupling between substituted aldehydes (or ketones) with stabilised phosphonate carbanions. This coupling reaction has proved to be a reliable and versatile route for the synthesis of stilbenes, including many peanut phytoalexins such as resveratrol, **1**, (Scheme 1.2) with high selectivity for the *trans*-isomer [22, 106, 111, 112]. The high selectivity is thought to be due to the phosphonate stabilised carbanions used in the reaction, which thermodynamically favours the construction of the *trans*-isomer over the *cis*-isomer and as a result, affords only the *trans*-alkene [105, 110, 113].



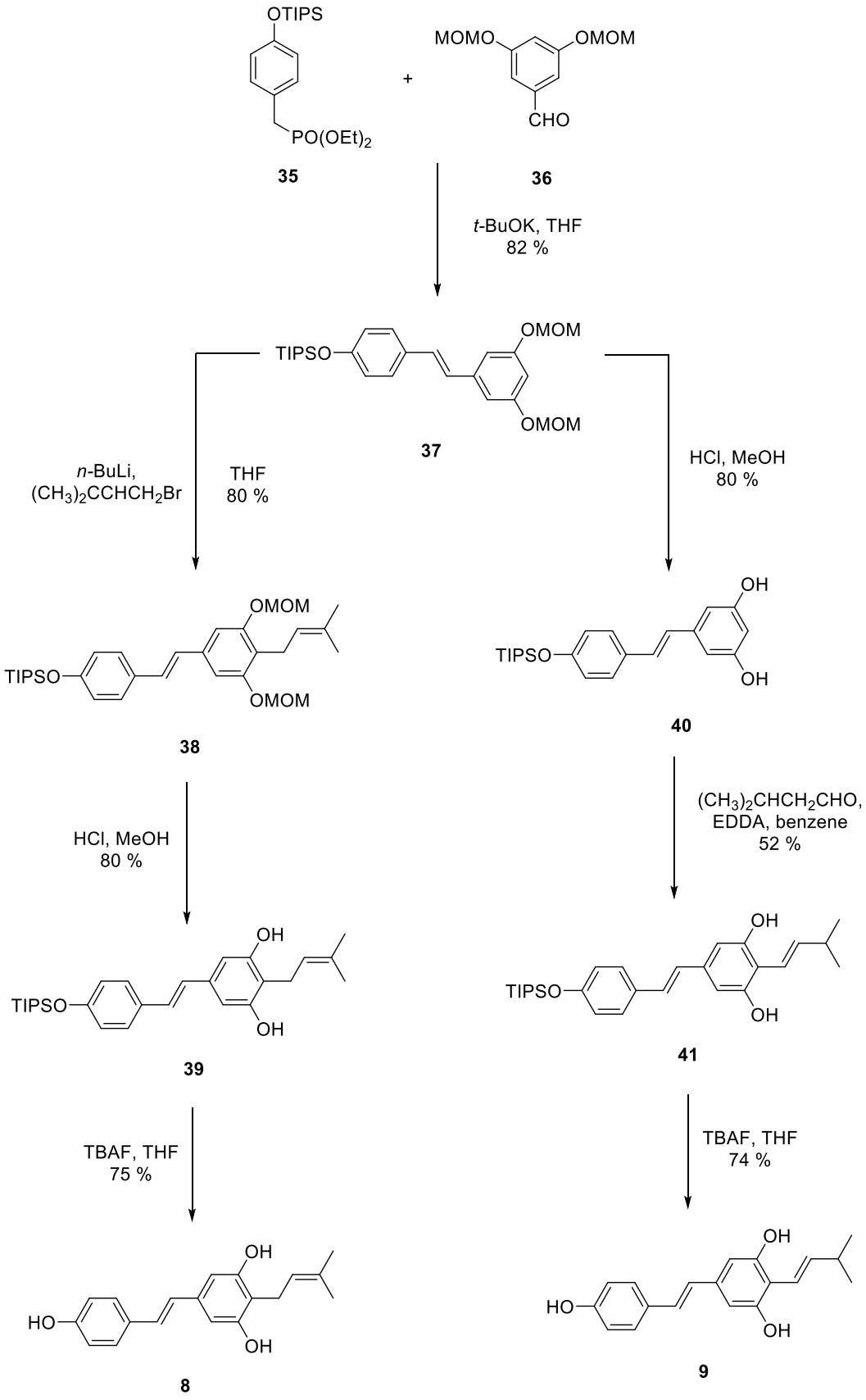
Scheme 1.2 Synthesis of resveratrol and resveratrol analogues *via* the HWE reaction

This reaction has additional advantages, which include the use of mild reaction conditions, and the isolation of the desired *trans*-alkene can be performed by aqueous work up, which enables the easy removal of the product from the water-soluble phosphorus by-product. This gives the HWE reaction a great advantage over the Wittig reaction, as the triphenylphosphine by-product in the Wittig requires separation *via* chromatographic purification [9, 82, 99, 102, 103].

Furthermore, although only limited to compounds possessing a carbonyl moiety, the HWE reaction has been reported to be a reasonable and adaptable method for the coupling of sensitive functional groups, such as furan-2-carboxaldehyde [114, 115].

Within the literature, the reported synthesis of natural prenylated peanut phytoalexins is limited, however the HWE reaction is currently the only coupling reaction, reported in the synthesis of prenylated peanut stilbenes.

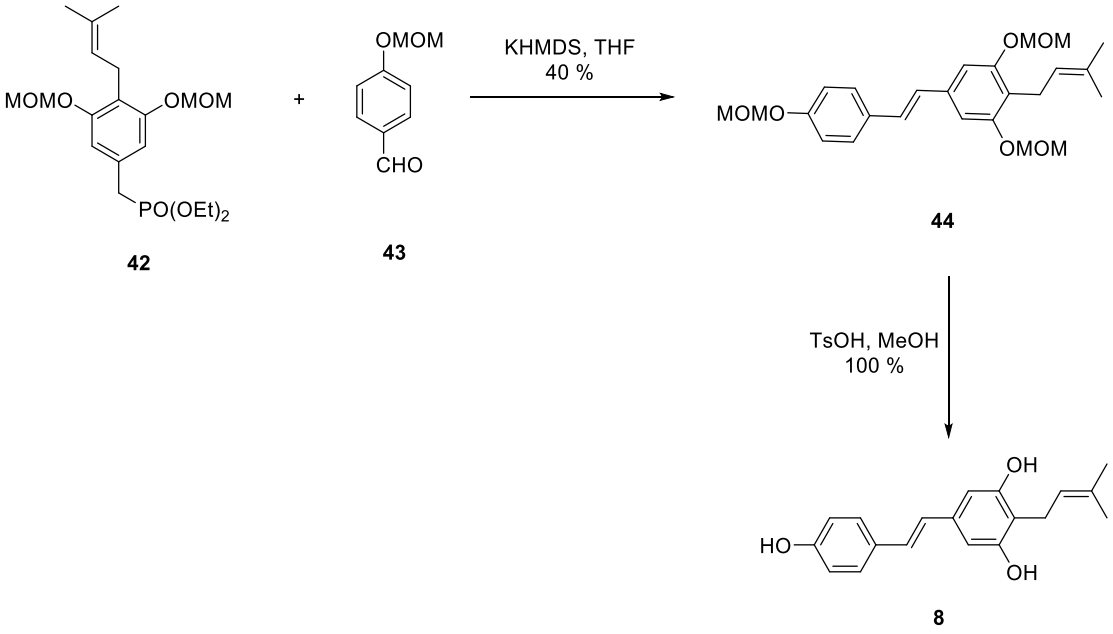
Park and *et al.,*[84] in 2011, reported the synthesis of *trans*-arachidin-2, **8**, and *trans*-arachidin-3, **9**, in good yields, *via* the HWE reaction, whilst using a combination of triisopropylsilyl (TIPS) and methoxymethyl (MOM) protecting groups (Scheme 1.3).



Scheme 1.3 **Synthesis of *trans*-arachidin-2 and *trans*-arachidin-3**

Recently, Hartung and co-workers, in 2014 attempted to synthesise the natural prenylated stilbene Pawhuskins, isolated from purple prairie clovers (*Dalea purpurea*) and at the same time reported an alternative and efficient approach towards the total synthesis of *trans*-arachidin-2, **8**, in quantitative yields, *via* the HWE condensation, with the use of MOM protecting groups (Scheme 1.4) [116].

The HWE coupling has been proved to be an effective route to the synthesis of other peanut phytoalexins, however attempts towards the total synthesis of *trans*-arachidin-1, **2**, to date has not been reported in the literature, therefore it would be of interest to attempt the synthesis of arachidin-1, **2**, *via* this approach.



Scheme 1.4 Synthesis of *trans*-arachidin-2, *via* HWE coupling

Besides the Wittig and HWE coupling reactions, the Julia olefination [88], is an alternative non-catalysed coupling reaction, which has been frequently used for the regioselective synthesis of alkenes. This coupling reaction occurs between a phenyl

sulfone ($PhSO_2$) with either an aldehyde or ketone, in the presence of a powerful reducing agent, such as sodium amalgam [88]. Due to its chemoselectivity towards the sulfone moiety, the reducing agent samarium(II) iodide is suggested to be most favourable for this elimination reaction [117]. This reaction also has its benefits, particularly with regards to the simple preparation of the starting materials, and as a result various substrates, of which poses a $PhSO_2$ moiety, next to the leaving group (carboxylate) can be used.

Although the Julia olefination offers good selectivity for the *trans*-isomer, this reaction is only stereoselective and not stereospecific, furthermore the selectivity has been reported successful, when minimal substitution is present on the coupling substrates [104].

A variation of this coupling reaction by means of the one-pot Julia Olefination, also known as the Julia-Kocienski reaction [118, 119] has been reported, for the synthesis of resveratrol, **1**, and resveratrol analogues (Figure 1.4), with good yields and excellent selectivity (*Z/E* = 1 : 99), when unsubstituted aromatic substrates were used [87].

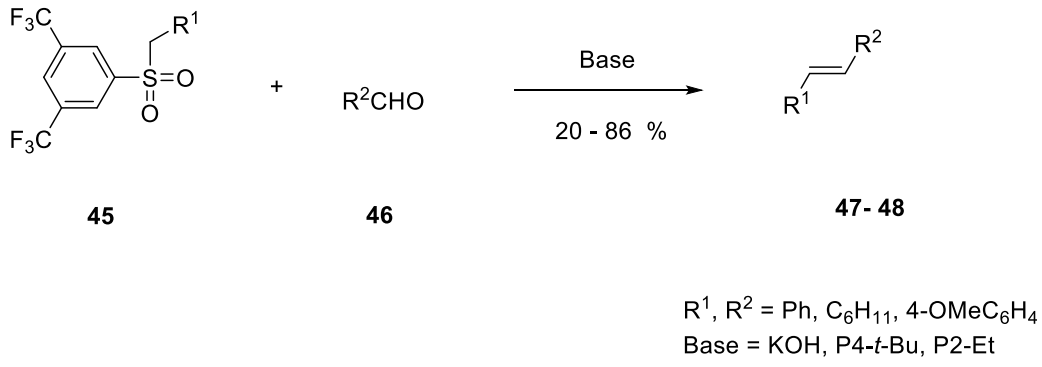
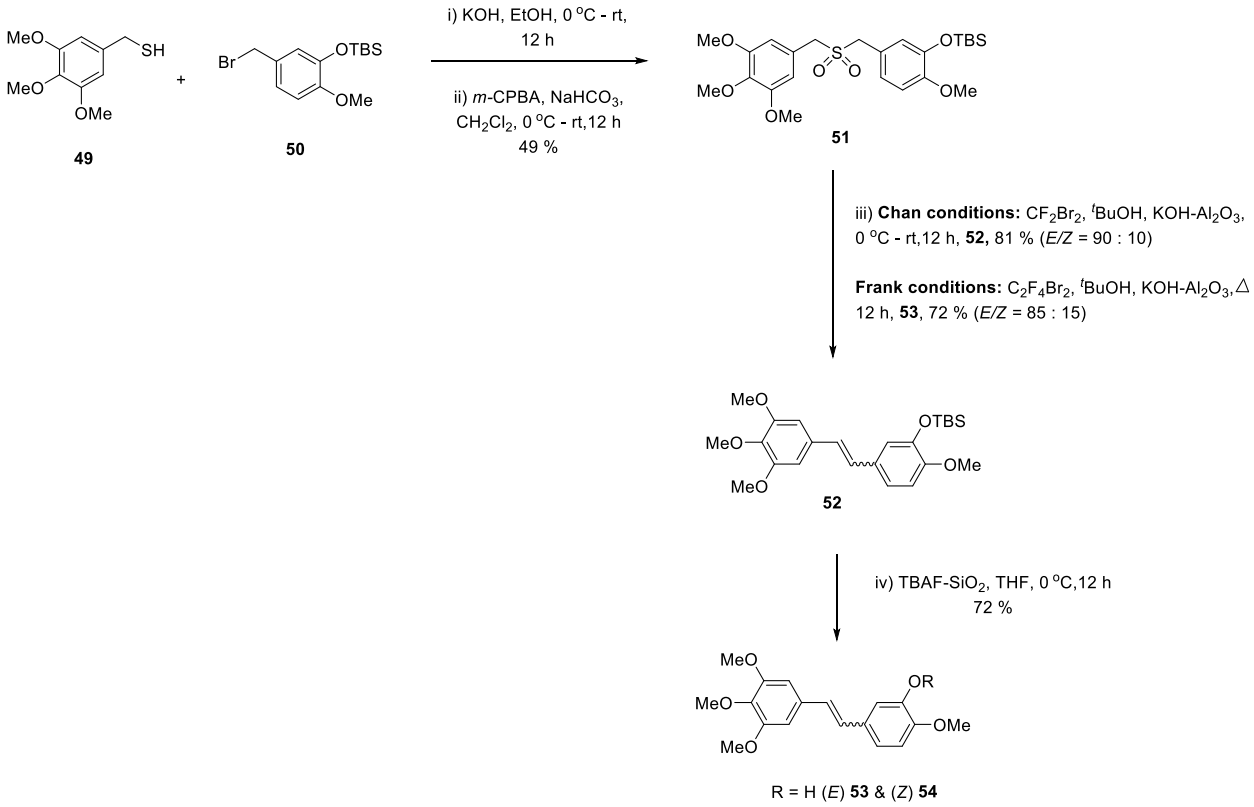


Figure 1.4 **Synthesis of resveratrol analogues, *via* Julia Olefination**

The Ramberg-Bäcklund reaction, discovered by Ludwig Ramberg and Birger Bäcklund in 1940, involves the transformation of α-halosulfones into alkenes, in the presence of a strong base, which is known to favour the formation of *trans*-alkenes [89, 120]. Foot and co-workers, in 2007 [121] reported the use of this coupling reaction, in the synthesis of stilbene analogues, with moderate yields (Scheme 1.5).



Scheme 1.5 Synthesis of stilbene analogues *via* the Ramberg-Bäcklund reaction

This approach has also been reported recently in the literature, as a strategy towards the synthesis of resveratrol, **1** [90]. An advantage of this approach is the use of various substituted α-halosulfones of which are commercially available, although the syntheses of the sulfones are known to be challenging.

A number of modified one-pot syntheses *via* the Ramberg-Bäcklund reaction have been reported, such as the work by Meyers and co-workers, whereby a sulfone is transformed into the *trans*-stilbene, **57**, in quantitative yield, in the presence of carbon tetrachloride and potassium hydroxide (Figure 1.5) [122]. Additionally by Chan *et al.*, whereby the use of potassium hydroxide absorbed unto an aluminium support and dibromodifluoromethane as the halogen source, was reported. This approach, has been shown to allow the transformation of sulfones directly into alkenes (54 – 96 %) [123].

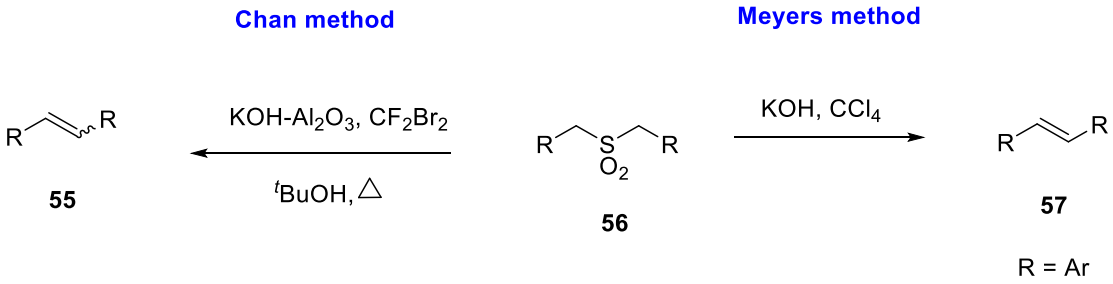
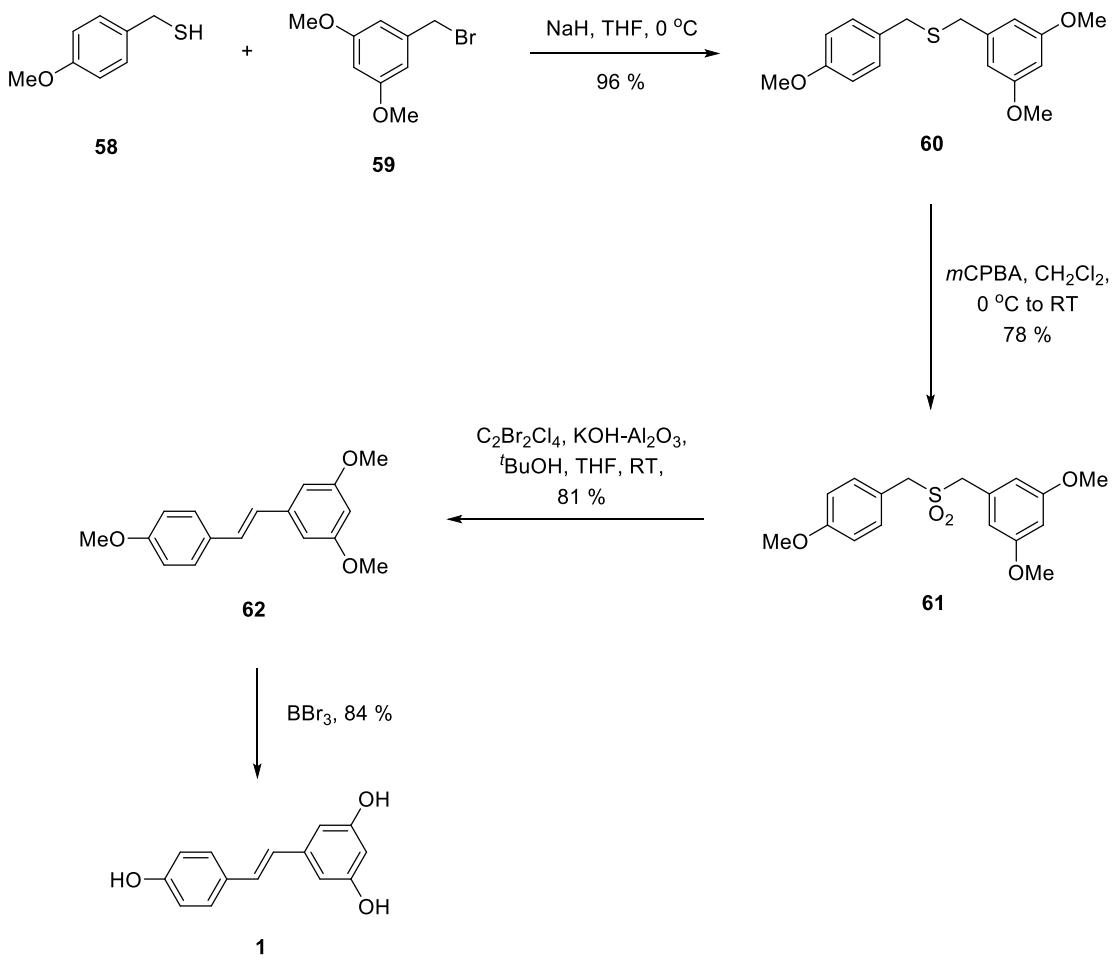


Figure 1.5 **Modified one-pot syntheses *via* the Ramberg-Bäcklund reaction**

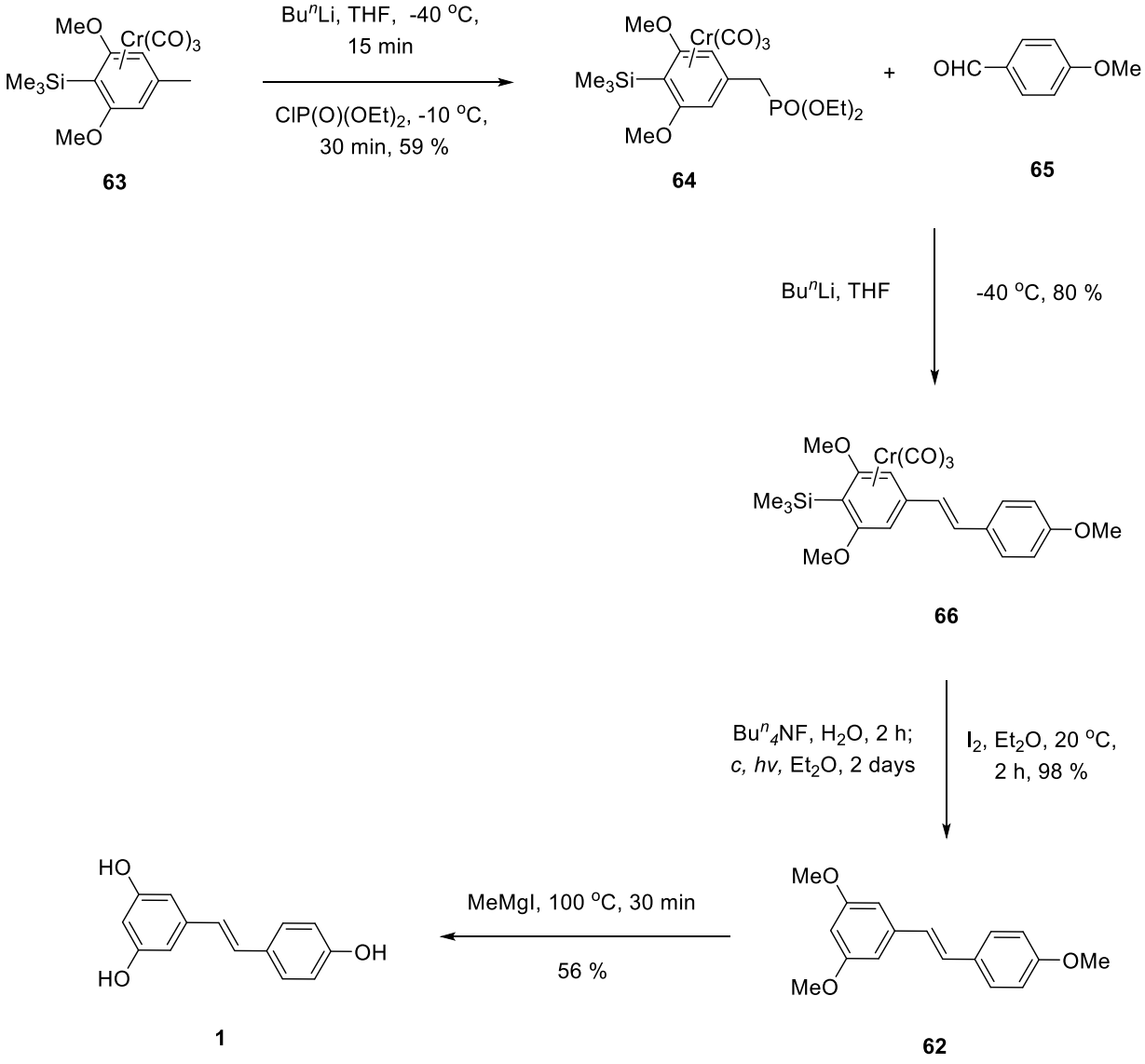
Furthermore, this one-pot Ramberg-Bäcklund approach has been applied towards the total synthesis of *trans*-resveratrol, **1** (Scheme 1.6) [124].



Scheme 1.6 **Synthesis of *trans*-resveratrol *via* the Ramberg-Bäcklund coupling reaction**

The construction of the C=C double bond in stilbenes has also been reported *via* the condensation of an aromatic aldehyde, with a methylarene or phenylacetic acid, this approach is known as the aldol-type condensation [9].

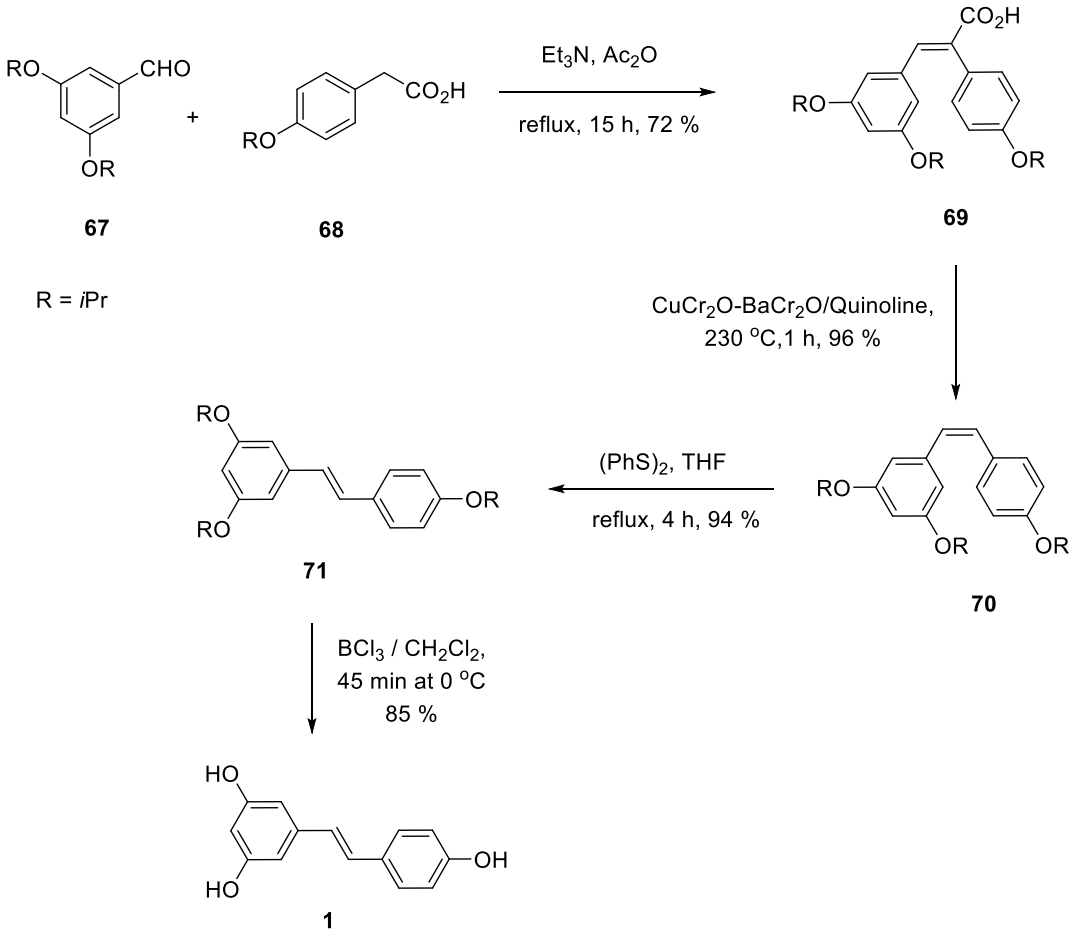
A novel approach to the synthesis of *trans*-resveratrol, **1**, *via* an aldol-type coupling reaction was published studied by Poulnin (Scheme 1.7). The reaction involved the facilitated benzylic deprotonation of an η^6-benzene-$Cr(CO)_3$ analogue, followed by condensation with *para*-anisaldehyde, **65**, in fair yields (56 %) [125].



Scheme 1.7 Synthesis of resveratrol *via* Aldol-type condensation

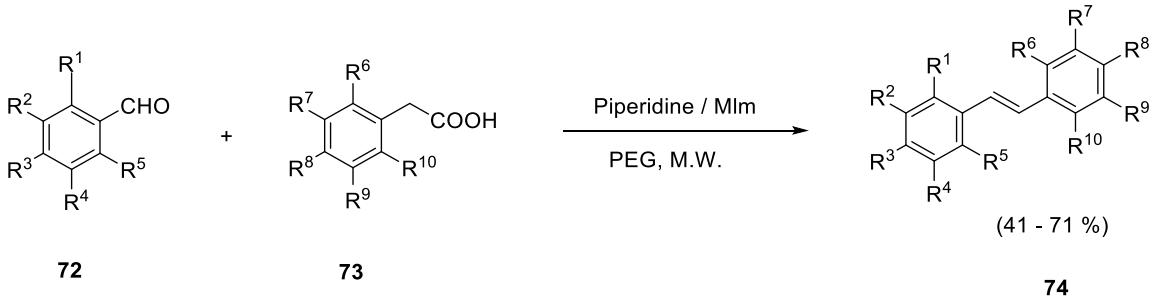
The Perkin reaction [126] is commonly used to form *α,β*-unsaturated carboxylic acids, by the condensation of an aromatic aldehyde and acid anhydride, in the presence of an alkali salt of the acid, however modifications of the Perkin condensation have enabled the synthesis of stilbenes, *via* the coupling of benzaldehydes and phenylacetic acids, to afford stilbenoids, including resveratrol, **1**, [102, 127-130], piceatannol, **7**, [102, 131] and other stilbene analogues, with selectivity for the *trans*-isomer [132, 134].

In 2003 Solladié and co-workers [128] reported the synthesis of resveratrol, **1**, *via* the condensation of 3,5-diisopropoxybenzaldehyde, **67**, with 4-(*tert*-butoxyphenyl)acetic acid, **68**, in the presence of acetic anhydride and triethylamine. The reaction proceeded *via* the subsequent decarboxylation of the acid intermediate, **69**, in the presence of copper chromite, followed by isomerization of the product *via* reflux, using phenyl disulfide in THF, to afford the *trans*-isomer, **71**, in excellent yield. Cleavage of the protecting group in the presence of BCl_3 gave *trans*-resveratrol, **1**, in good yield (85 %) (Scheme 1.8).



Scheme 1.8 **Synthesis of *trans*-resveratrol by the Perkin reaction**

Other research groups have published similar work to this, including the coupling of 3,5-dimethoxyphenylacetic acid with the commercially available 3,5-dihydroxyacetophenone, in the presence of acetic anhydride and triethylamine, to afford stilbenes in good yield [102]. Additionally the work by Sinha *et al.,* [127] offered both a benign and convenient route to the synthesis of resveratrol, **1**, and various stilbenoids, in fair to good yields (41 – 71 %), using the modified Perkin reaction. This reaction involves a one-pot condensation of substituted hydroxybenzaldehydes, **72**, and phenylacetic acids, **73**, in the presence of piperidine-methylimidazole and polyethylene glycol under microwave heating (Figure 1.6). Which in turn prevents the use of toxic quinoline-copper salt reagents in the decarboxylation step of the reaction.



72 **73** **74**

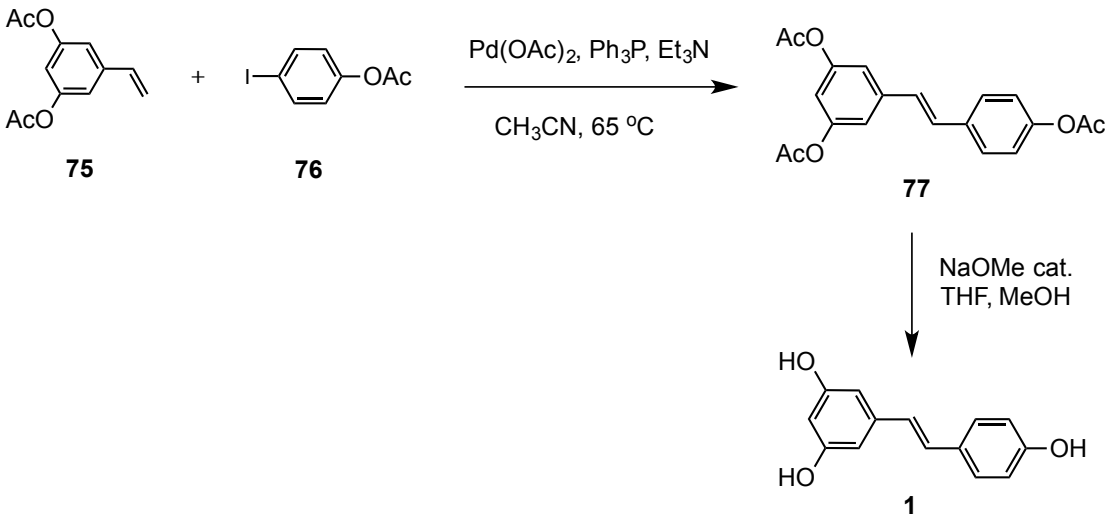
Where at least one of R^1or R^3 or R^5 or R^6 or R^8 or R^{10} = OH
and R^1-R^{10} = H, OMe, OH, Cl, etc

Figure 1.6 Coupling of substituted hydroxybenzaldehydes, using the modified Perkin reaction [127]

1.6.2 Palladium catalysed coupling reactions

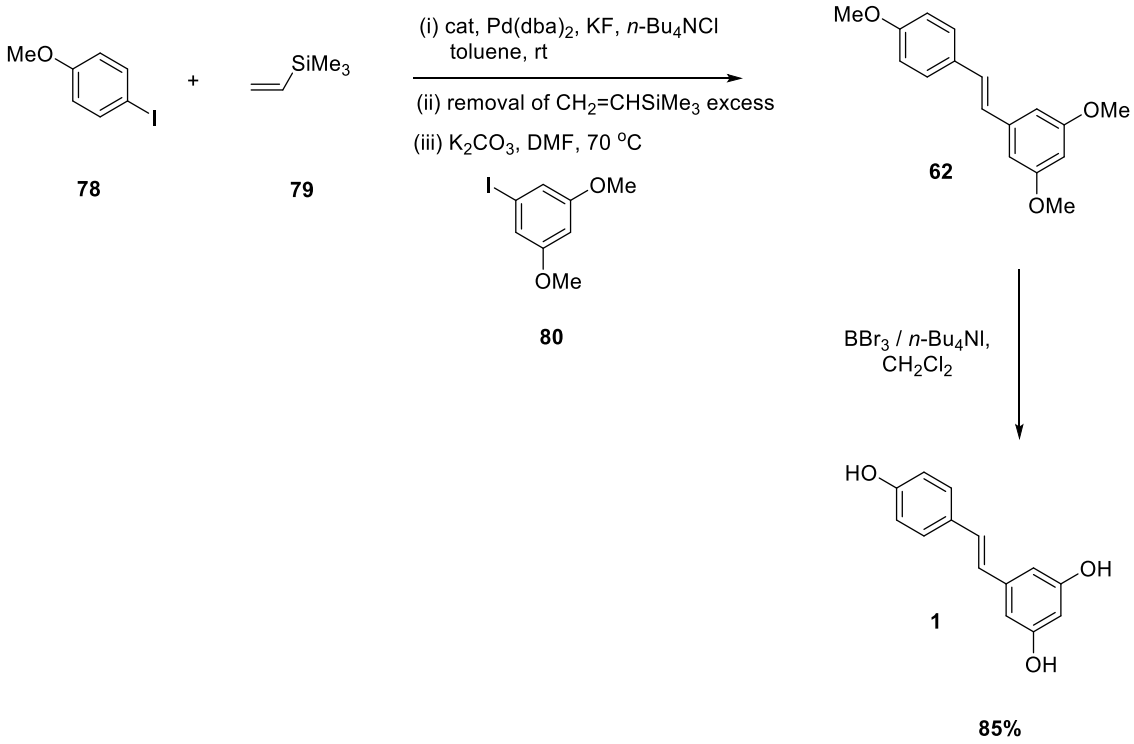
The Heck reaction, also known as Mizoroki-Heck reaction is said to be an ineffective reaction, without the presence of a metal catalyst. This reaction mechanistically involves the coupling of a halide (R-X) *via* nucleophilic addition to an alkene, in the presence of mild bases, such as triethylamine, potassium carbonate or sodium acetate, in addition to a Pd catalyst to form an alkene.

The use of the Heck cross-coupling reaction, in the synthesis of the natural stilbene resveratrol, **1**, is well known. Guiso *et al.,* have demonstrated an efficient synthetic route into the synthesis of resveratrol, **1**, by the coupling of 3,5-diacetoxystyrene, **75**, with the *p*-iodoarene derivative, **76**. The reaction performed in the presence of palladium(II) acetate ($Pd(OAc)_2$), 1 mol % and triphenylphosphine ligands gave solely the *trans*-isomer of resveratrol in excellent yields (99 %) (Scheme 1.9) [135]. Additionally the syntheses of resveratrol, **1**, and other stilbenoids have been reported by the coupling of an aryl halide with a styrene, in good yields [85, 136].



Scheme 1.9 Synthesis of *trans*-resveratrol *via* the Heck coupling reaction in the presence of $Pd(OAc)_2$ catalyst

Another study has reported the one-vessel synthesis of resveratrol, **1**, (Scheme 1.10) *via* a two sequential Heck-type reaction [137]. The synthesis of resveratrol, **1**, in the presence of palladium(0) bis(dibenzylideneacetone) ($Pd(dba)_2$) involved the coupling of the aryl halide (4-methoxyiodobenzene), **78**, with vinyltrimethylsilane, **79**, as the alkene equivalent, to give 4-methoxystyrene, under arylation-desilyation conditions. Subsequent removal of excess vinyl trimethylsilane and arylation of 4-methoxystyrene by 3,5-dimethoxyiodobenzene, **80**, followed by demethylation of *trans*-3,5,4'-trimethoxyresveratrol, **62**, in the presence of boron tribromide / tetra-*n*-butylammonium iodide gave resveratrol, **1**, in good yield (85 %). This synthetic route performed in one-vessel, is efficient and extremely stereo-, regio- and chemo-selective yielding solely the *trans*-isomer.



Scheme 1.10 Synthesis of *trans*-resveratrol, *via* the Heck cross coupling reaction, in the presence of $Pd(dba)_2$ catalyst

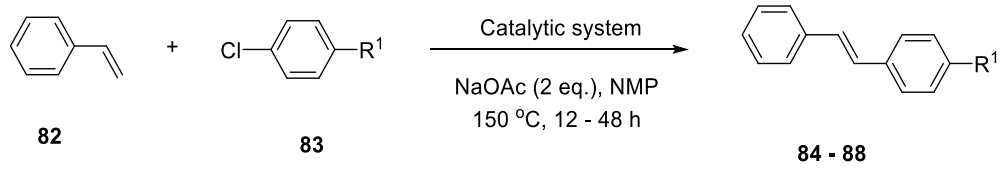
Berthiol *et al.,* [138] have also reported the highly chemo-, regio- and stereoselective synthesis of *trans*-stilbene analogues, *via* the coupling of simple linear alkenes to aryl halides in the presence of a newly developed Pd metal catalyst coordinated to the tedicyp ligand, **81**, (Figure 1.7). This stable catalyst consisting of tetraphosphine ligands was believed to increase catalyst stability due to the ligands close proximity to the metal centre. An increased selectivity for the *trans*-alkenes has been reported to be influenced by a number of factors, first of all by chain length, the longer the alkyl chain, the greater the percentage of the *E*-isomer over the *Z*-isomer. In addition to the choice of halides, as reactions with aryl bromides were reported to be highly selective towards the *trans*-isomer, compared to other halides used [138].

81

Figure 1.7 Structure of *cis, cis, cis*-1,2,3,4-tetrakis(diphenylphospinomethyl) cyclopentane (tedicyp) [138]

Although some limitations of the Heck reaction include the oxidative degradation and side reactions that occur as a result of the phosphine. Furthermore the increased reactivity, selectivity of the reaction and percentage yield are known to be influenced by the type of electrophile used (ArI > ArBr >> ArCl). However studies have found the use of specific catalytic systems, such as palladium(II) acetate, tetraphenylphosphonium chloride (Ph_4PCl/Pd), to increase the activity of these aryl halides (Table 1.6) [139, 140].

Table 1.6 **Synthesis of resveratrol analogues *via* the Heck reaction**



82 **83** **84 - 88**

Compound	R^1	Catalytic system (2 mol %)	DMG (mol %)	Conversion (%)	Selectivity (*trans*:*cis*:1,1-regioisomer)
84	H	$[Pd(MeCN)_2Cl_2]$. 6 Ph_4PCl	12	96	96 : 1 : 3
85	CHO	$Pd(MeCN)_2Cl_2]$. 6 Ph_4PCl[a]	0.6	96	98 : < 1 : 3
86	H	$Pd(OAc)_2$. 6 Ph_4PCl	12	97	97: 1 : 2
87	H	$[Pd(MeCN)_2Cl_2]$.6 Ph_4PCl	-	96	95: 1 : 4
88	H	$[Pd(MeCN)_2Cl_2]$. 6 Ph_4PCl	12	80	97: 1 : 2

[a] 0.1mol %

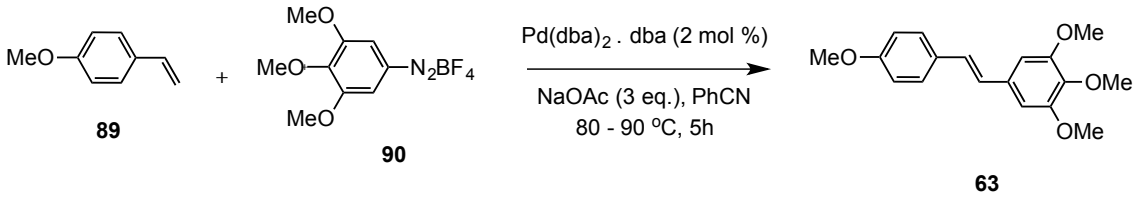
The Heck reaction is considered to be an important reaction in chemistry, with the advantage of being versatile, very efficient and extremely stereoselective, whereby favouring the *trans*-geometric isomer. Palladium is the most popular and widely used metal in homogenous catalysis, as it enables the use of various functional groups in

the starting materials and results in high regio-and chemoselectivity, as a result of selecting the optimum reaction conditions.

Palladium complexes such as Pd(0) and Pd(II), commonly coordinated to triphenylphosphine ligands are frequently used in Heck reactions, however these phosphine ligands in the Pd complexes have been suggested to affect the rate of catalysed reactions [104, 138].

The Heck-Matsuda reactions can be performed using arenediazonium salts, in place of phosphine ligands and a base, though a catalytic loading of the palladium catalyst (1-2 mol %) is required [107]. Nonetheless, the synthetic benefits of using arenediazonium salts have resulted in an increased interest, due the reaction offering high stereo- and regioselectivity. An example of this can be seen with the synthesis of the resveratrol analogue, DMU-212 (3,4,5,4'-tetramethoxystilbene), **63**, in the presence of arenediazonium salt and the catalyst $Pd_2(dba)_2$ [141]. Additionally the use of an arenediazonium salt, with a catalytic loading of 2 mol % $Pd_2(dba)_2 \cdot dba$, gave DMU-212, **63**, in quantitative yield after 20 minutes (Scheme 1.11). However, a lower catalytic loading resulted in longer reaction times, although gave the stilbene in excellent yield (> 90 %).

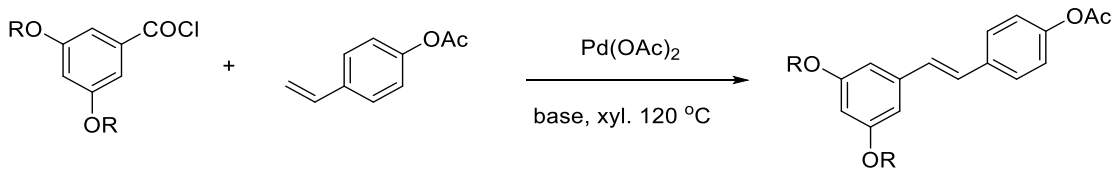
In contrast, the synthesis of resveratrol, **1**, was found to afford moderate yields (< 57 %), in addition to a number of by-products under the same reaction conditions, using 4-methoxystyrene, **89**, and the palladium catalyst ($Pd_2(dba)_2 \cdot dba$). There are many advantages with the use of arenediazonium salts as electrophiles in the Heck reaction, these salts are fast, cost effective, benign, stereoselective and easier to use compared to other traditional protocols.



Scheme 1.11 Synthesis of DMU-212 *via* the Heck-Matsuda coupling reaction

Furthermore, the decarbonylative Heck reactions are proven to be effective in the synthesis of natural stilbenes, although the success of the reaction is also believed to be dependent on the type of base added; where amines including *n*-ethylmorpholine (NEM) and *N,N*-dimethylbenzylamine ($BnNMe_2$), have been reported to be the most effective [142]. Moreover, the versatility of this reaction enables the use of various substituted cyclic alkenes, aryl halides in the formation of *trans*-stilbenes [138, 143]. Alternatively, decarbonylative Heck reactions using chlorides are becoming increasingly popular for the synthesis of stilbenes, specifically resveratrol analogues. This approach has many advantages, such as the reaction being relatively fast, in addition to the various aromatic carboxylic acids which can be used as precursors (Table 1.7) [142].

Table 1.7 Decarbonylative Heck coupling



91 **92** **93 - 98**

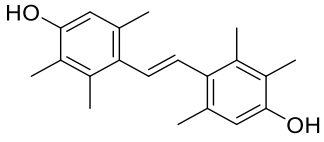
Compound	R	Mol % Pd	Ligand	Base	Time (h)	Yield (%)
93	Me	5	-	NEM	18	75
94	Me	5	-	$BnNMe_2$	18	52
95	Me	5	-	$EtN(i\text{-}Pr)_2$	18	35
96	Ac	1	-	Et_3N	3.5	57
97	Ac	1	-	NEM	3.5	63
98	Ac	1	5	Et_3N	3.5	57

Other reactions such as the Suzuki coupling reaction [86, 144] is an alternative Pd catalysed reaction, which also offers versatility, high selectivity and efficiency. This reaction involves the coupling of a halide with an organoboronic acid (aryl, alkyl, alkenyl or alkynyl) or alternatively with an organoborane or boronate ester or

potassium trifluoroborate substrate, in the presence of a palladium catalyst and a base, such as sodium ethoxide [145, 146].

This reaction has its advantages such as giving both high regio- and stereospecificity, in addition to the easy synthesis of reagents and mild reaction conditions. The Suzuki coupling, as well as the modified Hunsdiecker-Suzuki approach have been reported in the synthesis of resveratrol derivatives[147-149]. However this strategy, to date, has not yet been applied to the synthesis of other peanut stilbenes.

Conversely, the Stille reaction involves the palladium catalysed cross-coupling of organotin compounds (organostannanes) and aryl halide or alkenyl halide or triflate reagents. This approach has its benefits, besides being stereospecific and regioselective, as a variety of electrophiles can be used in this reaction. Furthermore this reaction is known to proceed without the need of a base, which gives the Stille a greater advantage over the Suzuki coupling. Additionally the organostannanes have been suggested to be suitable for use, in the presence of a wide range of functional groups, under mild conditions [92]. However, to date the synthesis of natural peanut stilbenes *via* the Stille reaction has not been reported in the literature, possibly due to the toxicity of the organostannanes [150]. Nonetheless with the hope of forming resveratrol analogues, Kang and co-workers, recently reported the synthesis of the stilbene, 2,3,6,2′,3′,6′-hexamethyl-4,4′-dihydroxy-*trans*-stilbene, **99**, (Figure 1.8) *via* a one-pot Stille–Heck tandem reaction [151].



99

Figure 1.8 2,3,6,2′,3′,6′-hexamethyl-4,4′-dihydroxy-*trans*-stilbene

Similarly only the synthesis of novel *trans*-stilbenes has been reported *via* the Negishi coupling reaction [152, 153]. This reaction involves the cross-coupling of an organozinc reagent and an aryl halide or alkenyl halide or triflate, in the presence of a palladium catalyst. This route is considered stereoselective, versatile with regards to the functional groups present on the organohalide [152, 153], additionally this route is not limited to the formation of biaryls [93].

Kabir *et al.,* in 2007 [154], reported the synthesis of stilbene derivatives, by the coupling of aryl or vinyl iodides with arylzinc reagents, **101**, (Figure 1.9). This versatile approach was found to be advantageous, as various functional groups specifically heteroaromatic compounds could be used, with low catalytic loading, in the absence of a ligand.

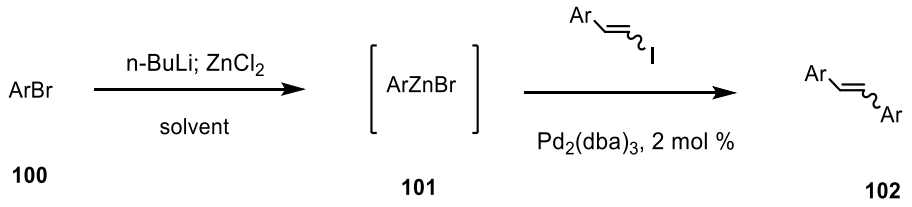
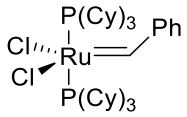


Figure 1.9 Synthesis of stilbene analogues in the presence of arylzinc reagents

1.6.3 Non-palladium catalysed coupling reactions

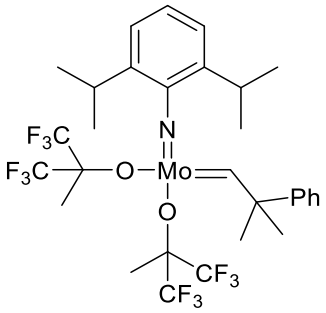
Other well-known alkene forming reactions such as the highly efficient olefin metathesis in the presence of a ruthenium catalyst, **103**, [155] or molybdenum catalyst, **104**, (Figure 1.10) [156], to date have not been fully explored in the synthesis of natural stilbenes.

Grubbs catalyst (1st generation)



103

Schrock catalyst



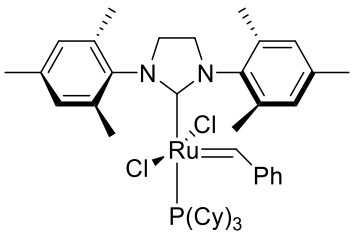
104

Figure 1.10 Structure of ruthenium and molybdenum catalyst

This is primarily due to the complexity in controlling the selectivity and in particular the stereochemistry of the newly formed alkene bond, which often produces a mixture of geometric isomers, as a result of the direct cross coupling of two styrenes, and/or homo-dimerization [157]. Nevertheless, studies reporting the synthesis of stilbenoids *via* olefin cross-metathesis are still somewhat limited [107, 158].

In 2004, Grubbs and co-workers reported their study into the synthesis of stilbenoids, *via* cross metathesis, in the presence of a second generation Grubbs catalyst, **105**, (Figure 1.11), with the use of a range of substituted styrenes [157].

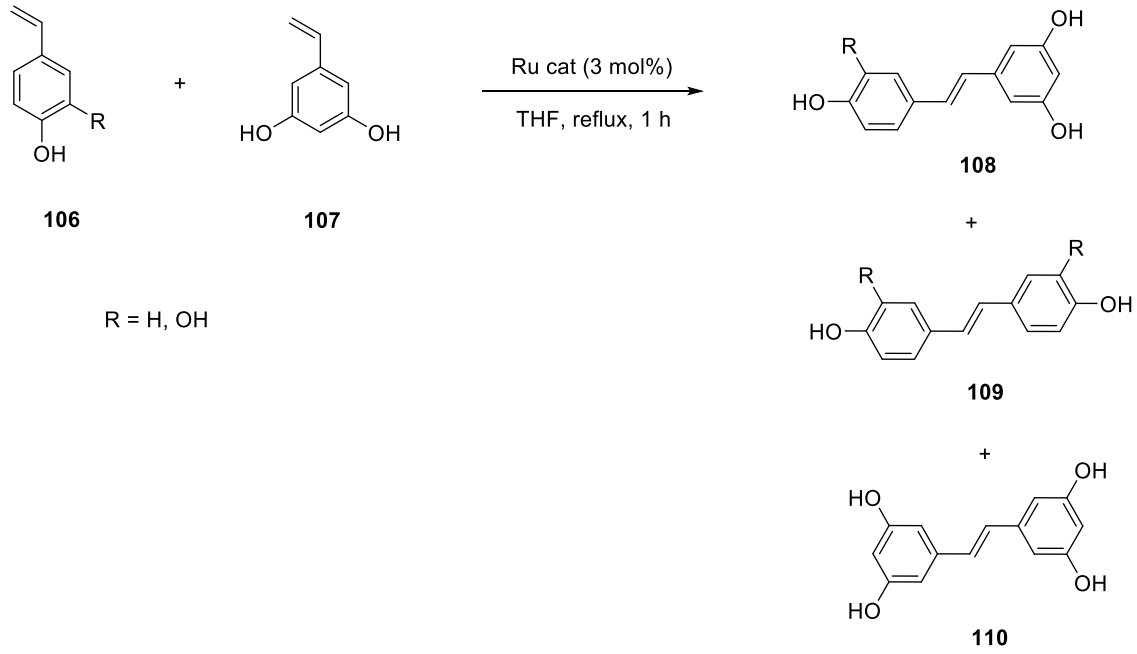
Grubbs catalyst, (2nd generation)



105

Figure 1.11 Structure of second generation Grubbs catalyst

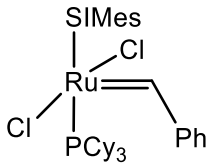
Resveratrol, **1**, was synthesised with high selectivity for the *trans*-isomer (95 %), *via* the cross-metathesis coupling of 3,5-dihydroxystyrene, **107**, with excess 4-hydroxystyrene, **106**, in the presence of the ruthenium-carbene catalytic complex, **105**. Notably, the reaction also gave two other isomers; *trans*-3,3',5,5'-tetrahydroxystilbene, **110**, and *trans*-4,4',dihydroxystilbene, **109**, (Scheme 1.12).



Scheme 1.12 Synthesis of resveratrol *via* cross-metathesis

Additionally Chang and co-workers in 2002, reported the solid-phase cross metathesis using supported styrenyl ethers with styrene derivatives in the presence of the ruthenium carbene catalytic complex (SIMes)(PCy_3)Cl_2Ru=CHPh, **111**, (Figure 1.12). This approach efficiently produced resveratrol, **1**, and other stilbenoid analogues, in good to excellent yields (77 – 98 %), whilst providing 100 % stereoselectivity for the *trans*-isomer. The study demonstrated a benefit of using a solid-phase system for the

cross metathesis for the synthesis of alkenes, as when a solution-phase metathesis was used instead, stereoselectivity was not observed.

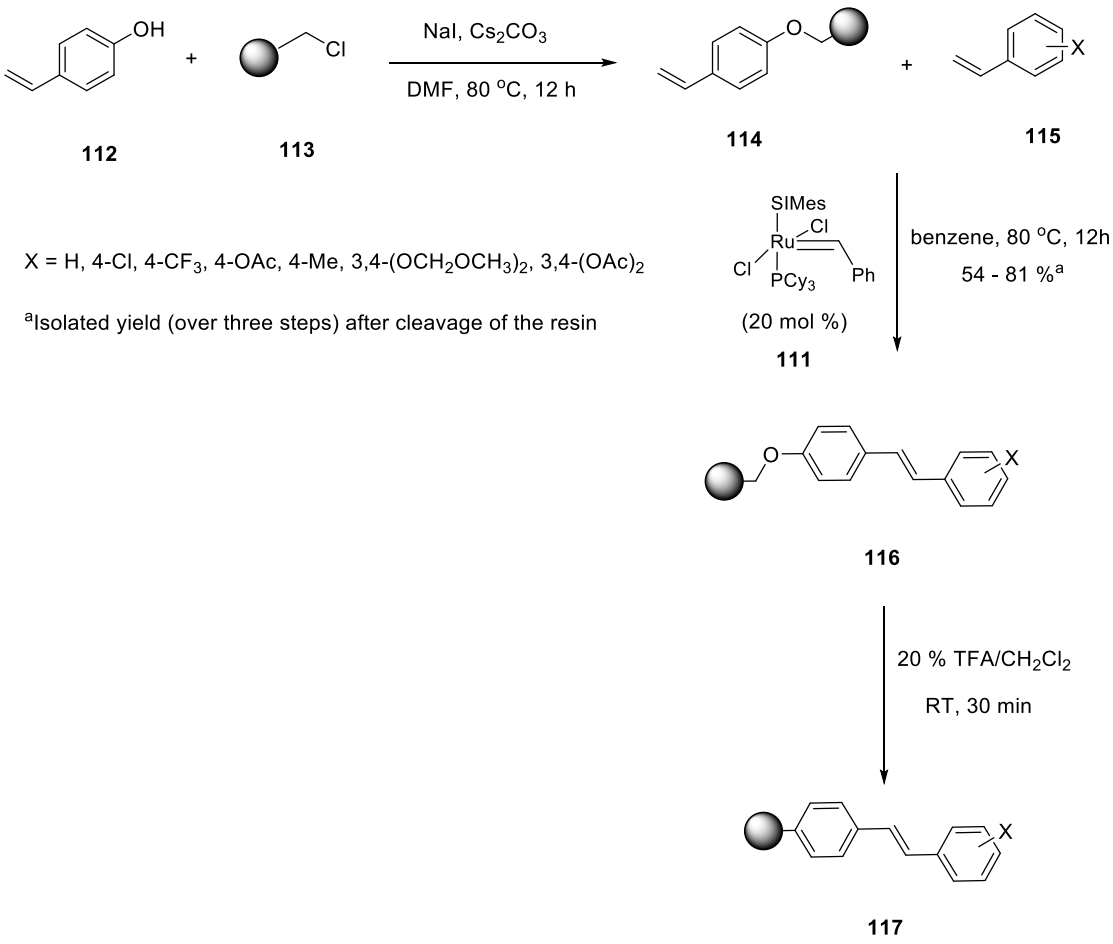


111

Figure 1.12 Structure of ruthenium carbene catalytic complex

Although scarcely reported for the synthesis of natural stilbenes, the solid phase cross metathesis offers a benefit, with regards to easy separation of the product, from the reaction mixture upon completion [159], though the presence of a solid-phase system has been reported to result in slightly slower reaction rates.

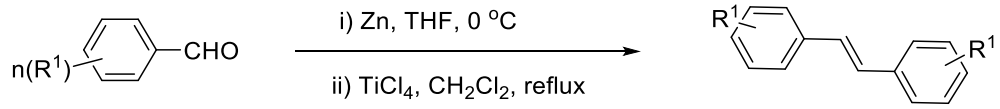
According to Chang and co-workers, the Merrifield resin was found to be most suitable in supporting various styrenyl derivatives in a solution of benzene. The subsequent cleavage and filtration of the resin with trifluoroacetic acid (TFA) in dichloromethane, gave stilbene analogues with complete *trans*-selectivity (Scheme 1.13) [158].



Scheme 1.13 Synthesis of stilbene analogues *via* solid phase cross metathesis

Conversely, the McMurry coupling reaction offers an alternative approach to the synthesis of the C=C bond, *via* the reductive dimerization of two aldehydes or ketones, in the presence of a low-valent titanium catalyst ($TiCl_4$) [91]. This reaction has its disadvantages, as it known to produce geometric isomers, and is limited to the use of molecules possessing a carbonyl (C=O) moiety. Nonetheless the McMurry reaction has been shown to be successful in the synthesis of a number of stilbene derivatives [160-162], in moderate yields (Table 1.8) [163]. However, this approach has not yet been reported in the synthsis of peanut stilbenoids.

Table 1.8 Synthesis of synthetic polyalkoxy- and polysilyoxystilbenes

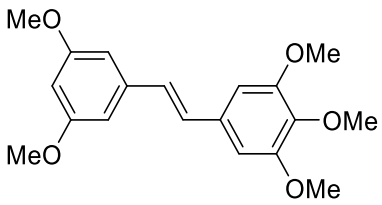


118 **119 - 123**

Compound	Benzaldehyde (R^1)	Stilbene (R^1)	Yield (%)
119	2-Methoxy	2,2'-Dimethoxy	71
120	3-Methoxy	3,3'-Dimethoxy	57
121	3,5-Dimethoxy	3,3', 5,5'-Tetramethoxy	42
122	4-*t*-Butyldimethylsilyloxy	4,4'-di-*t*-Butyldimethylsilyloxy	52
123	3,5-di-*t*-Butyldimethylsilyloxy	3,3',5,5'-Tetra-*t*-butyldimethylsilyloxy	79

1.7 Resveratrol Analogues

Recently within the literature, various resveratrol derivatives have been designed and developed (Pan *et al*., 2009), in the hope of identifying an efficacious anticancer agent. Compounds possessing methoxy moieties around the stilbene scaffold, such as the analogue MR-5, **124** (Figure 1.13), have been extensively researched and found to display increased chemopreventative and/or chemotherapeutic properties, *in vitro*. Moreover these stilbene analogues have been reported to display greater potency compared to resveratrol, **1**[164-167].



124

Figure 1.13 Structure of resveratrol analogue MR5

Several novel sulfonamides have also been reported to exhibit antitumour activity *via* a number of mechanisms, including acting on polo-like kinase (PLK) enzymes; which are involved in mitotic events [168], mitotic cell cycle arrest, apoptosis in the M-phase of cell growth, inhibition of microtubule assembly [169], as well as targeting the G1 phase of the cell cycle in cancer cells [170].

Recently, stilbene benzenesulfonamides, **125**, possessing a primary sulfonamide moiety (SO_2NH_2), have been reported to display promising cancer chemopreventative [164, 171, 172] and anti-inflammatory activity [173]. As a number of studies have reported a link between compounds possessing a sulfonamide moiety and antitumour properties, it has led to the synthesis and study of other novel benzenesulfonamide analogues[169, 170, 174].

1.7.1 Benzenesulfonamides

In 2002, stilbene benzenesulfonamide analogues, **125**, derived from *trans*-resveratrol, **1**, (Figure 1.14) were designed by Yang and co-workers in order to study their activity against the NCI-60 human tumour cell line [6].

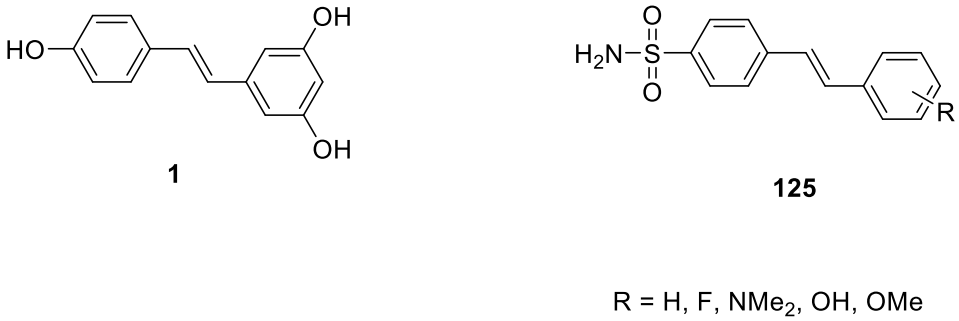


Figure 1.14 ***trans*-stilbene benzenesulfonamide analogues**

Albeit lengthy and requiring a total of 6-7 synthetic steps, the approach developed by Yang *et al.,* enabled the synthesis of seven novel stilbene benzenesulfonamide analogues, **125a – 125g**, (Figure 1.15), possessing a primary sulfonamide moiety (SO_2NH_2).

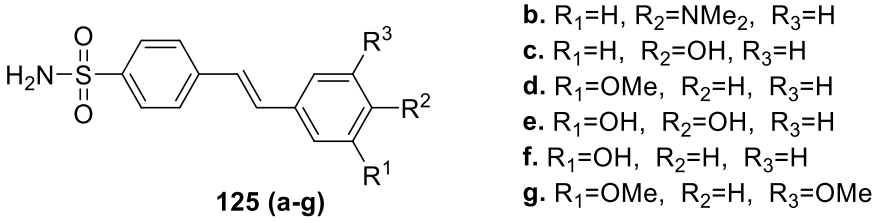
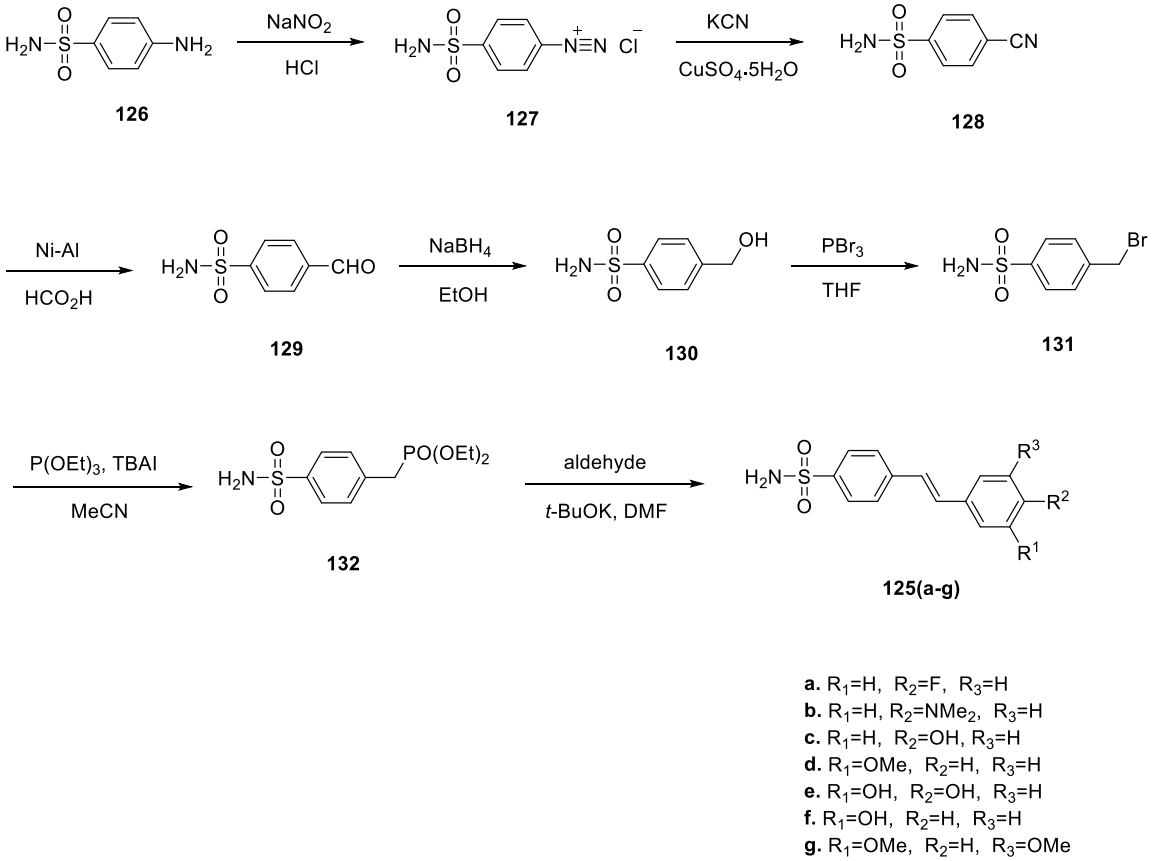


Figure 1.15 **Structure of novel stilbene sulphonamide analogues**

The initial step towards the synthesis of these compounds involved diazotization of the sulphanilamide, **126**, to generate the diazonium salt, **127**, followed by the Sandmeyer reaction in the presence of potassium cyanide/copper sulfate pentahydrate, to generate the benzonitrile, **128**, (53 %). Subsequent Stephen reduction of the benzonitrile with Raney nickel in acid formed benzaldehyde, **129**, (86 %), and

reduction of the aldehyde in the presence of sodium borohydride gave the alcohol, **130**, in good yield (92 %). Treatment with phosphorous tribromide followed by triethyl phosphite formed phosphonate **132**, next Wittig-Horner coupling using the diethyl phosphonium salt with a range of benzaldehydes gave the desired *trans*-stilbene benzenesulfonamides, **125a – 125g** (Scheme 1.14).

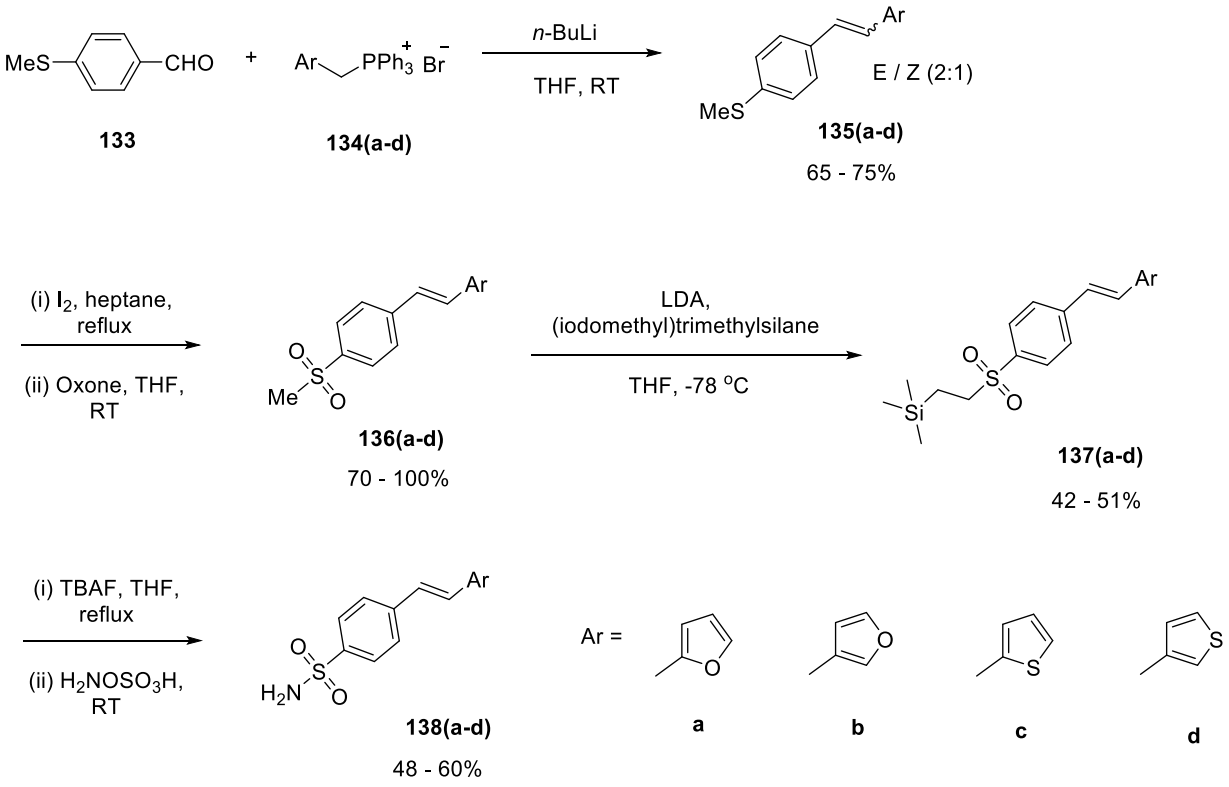


Scheme 1.14 Synthesis of stilbene benzenesulfonamides, *via* the Wittig-Horner coupling reaction

The *in vitro* studies, from the work published by Yang and co-workers, noted that benzenesulfonamides possessing a 4-fluoro, **125a**, or 3-methoxy, **125d**, moiety were found to exhibit significant selective activity against breast; BT-549 (GI_{50} 0.205 μM), and colon; HT-29 (GI_{50} 0.554 μM) tumour cell lines, respectively [6]. Although the

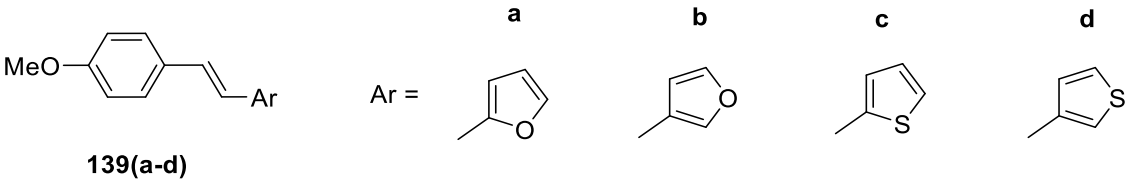
activity of these novel compounds were not compared to the control, the stilbene benzenesulfonamide analogues show promising activity, however their mechanism of action still needs to be understood.

The synthesis of stilbene benzenesulfone and benzenesulfonamide derivatives in the form of styrylheterocycles has also been achieved. The synthetic method reported by Lim *et al.,* details the Wittig reaction to couple the 4-(methylthio)benzaldehyde, **133**, with various phosphonium bromides, **134a** – **134d**. This approach proceeds *via* the oxidation of the 4-methylthio moiety with an aqueous Oxone® solution, to provide the methylsulfone analogues, **136a – 136d**, which can then be converted to the corresponding sulfonamides, **138a – 138d**, in two subsequent steps (Scheme 1.15) [7].



Scheme 1.15 Synthesis of benzenesulfone and benzenesulfonamides analogues, *via* the Wittig reaction

When the benzenesulfone analogues were evaluated for their inhibitory activity against lipopolysaccharide (LPS) stimulated RAW 264.7 murine macrophage cells, these novel compounds were found to result in up to five times reduced potency, compared to the lead compounds, **139(a-d)**, possessing a *para*-OMe moiety (Figure 1.16) [175].



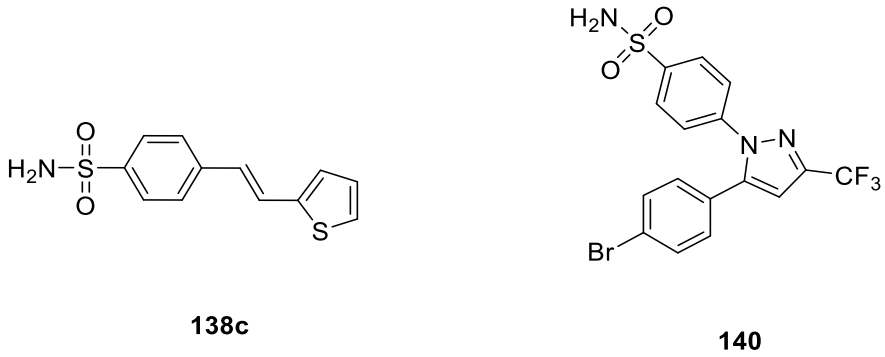
139(a-d)

Figure 1.16 Structure of styrylheterocyclic analogues

Alternatively the benzenesulfonamide analogues, possessing the thiophene functionality, **138c** and **138d**, were reported to be either as equipotent (**138d)**, or found to exhibit a 40-fold greater potency (**138c**), compared to the furan derivatives, **139c** and **139d**, with IC_{50} values of 0.013 μM and 0.44 μM, respectively. Furthermore, benzenesulfonamides possessing a furan moiety, **139a** and **139b**, were found to either display decreased potency (IC_{50} 1.18 μM) or were ineffective (IC_{50} > 50 μM) [173].

In relation to SAR, the presence of a sulfonamide (*p*-SO_2NH_2) or a methylsulfone (*p*-SO_2Me) moiety and the aromatic ring in stilbene benzenesulfonamide analogues, were suggested to be essential in providing the highest efficacy, with regards to selectivity, potency towards COX-2 inhibition, as these pharmacophores have been said to interact with the COX-2 side pocket through tight-binding kinetics [173, 176]. When molecular modelling studies were performed, in order to determine the interaction of the most potent benzenesulfonamide, **138c**, with

the COX-2 protein. The docking study found that the spatial location of the *p*-SO_2NH_2 moiety in compound, **138c**, and the celecoxib analogue (SC-558), **140**, partially overlapped (Figure 1.17). Additionally, the benzenesulfonamide moieties in both groups were superimposed, and were reported to interact with the amino acid residues lining the COX-2 binding site. Furthermore hydrogen bonding was observed between the two oxygen atoms within the SO_2NH_2 moiety and the backbone (N-H) of both His90 and Arg513 (distance = 2.87 Å).



138c **140**

Figure 1.17 Structure of benzenesulfonamide analogue (138c) and SC-558

Additional hydrogen bonding was also observed between the nitrogen atom in the SO_2NH_2 group and the backbone carbonyl in Gln192 (3.72 Å), Phe518 (3.84 Å) / Leu352 (4.12 Å) (Figure 1.18) [7].

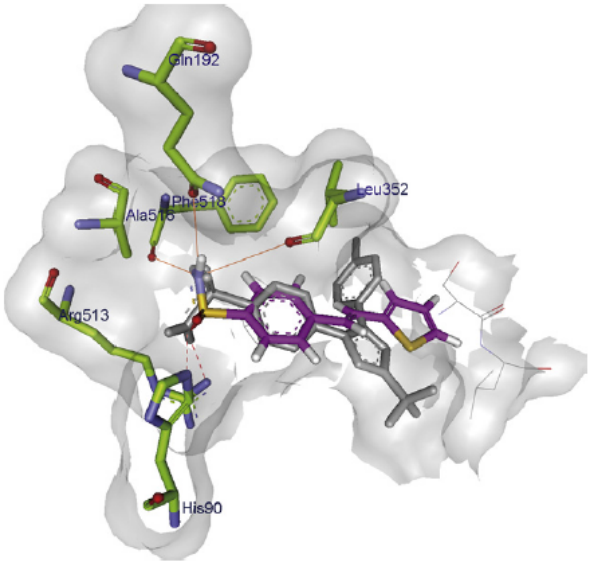


Figure 1.18 Docking model of compound 138c, (shown in purple) and SC-558, 140, (shown in grey) overlaid within the active site of COX-2 (Protein Data Bank code 1CX2). Hydrogen bonds and possible hydrogen bonds indicated by red dashed and orange solid lines, respectively. The key amino acid residues are shown in green [7].

1.7.2 Phenylazobenzenesulfonamides & derivatives

Further studies have discovered a range of phenylazobenzenesulfonamide derivatives, **141**, to display increased potency and selectivity towards the COX-2 protein[177-179].

In order to increase the potency and selectivity, other novel analogues were designed based on the lead compound resveratrol, **1**. These benzenesulfonamides, **141**, comprised of a *para*-sulfonamide functionality, in-place of the *para*-hydroxyl moiety, and the bioisosteric substitution of the central ethylenic linkage with an azo *N,N*-double (N=N) bond (Figure 1.19).

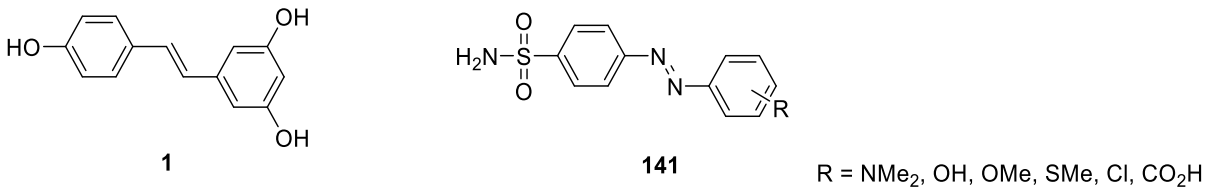
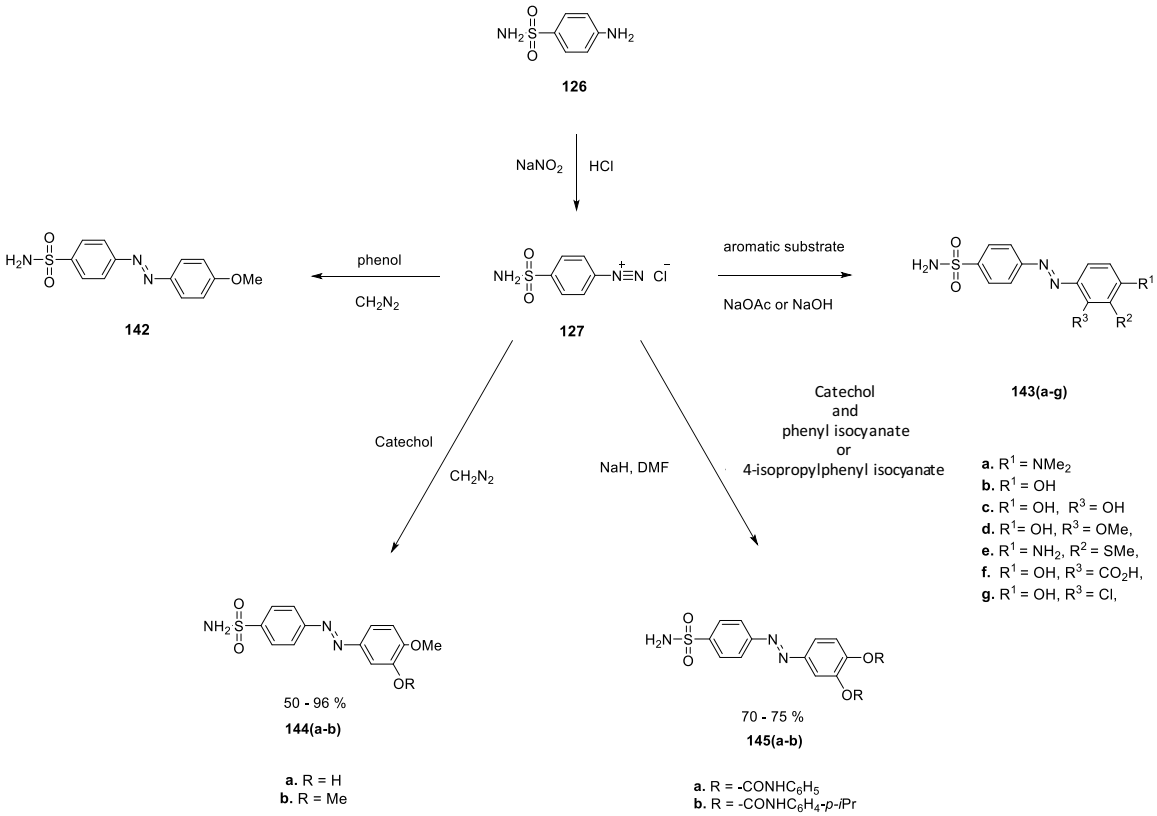


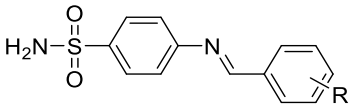
Figure 1.19 Structure of resveratrol and the general structure of phenylazobenzenesulfonamides

The synthesis of these benzenesulfonamide analogues, *via* the coupling of an aryl diazonium salt and various substituted phenols has been reported [180]. However Lin and co-workers, in 2008 successfully developed the synthesis of phenylazobenzenesulfonamides in accordance with the work by Yang *et al.,* [6] *via* diazotization of the sulfanilamide and subsequent coupling of the aryl diazonium salt with various substituted aromatic substrates (Scheme 1.16).

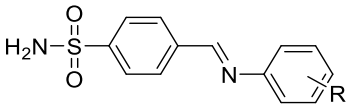


Scheme 1.16 Synthesis of phenylazobenzenesulfonamide analogues

Two years later, the synthesis of 4-benzylideneamino- , 146, and 4-phenyliminomethyl-benzenesulfonamides, 147, (Figure 1.20), constructed by the bioisosteric replacement of the central ethylenic –C=C– bond with a –N=C– or –C=N– double bond were reported [177].



146



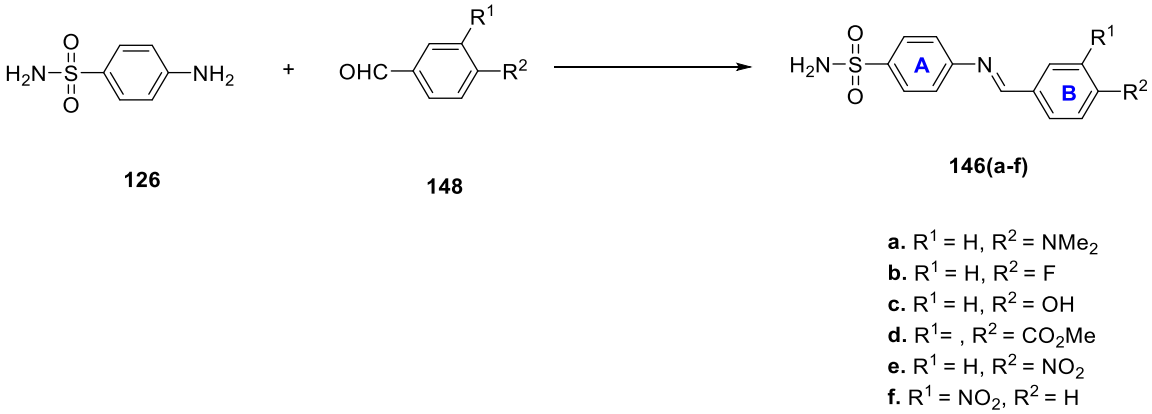
147

R = NMe_2, F, CO_2Me, NO_2, OH

Figure 1.20 Generic structure of 4-benzylideneamino- and 4-phenyliminomethyl-benzenesulfonamides

The various *trans*-4-benzylideneamino benzenesulfonamide derivatives, **146**, (15 – 88 %) were formed by the coupling of a sulfanilamide, **126**, with a substituted or protected benzaldehyde (Scheme 1.17). When these novel benzenesulfonamide analogues were evaluated for their selectivity and potency towards COX-2 inhibition, using a human whole blood (HWB) assay. The electron withdrawing groups (F, NO_2 and CO_2Me), particularly when monosubstituted at the *para*-position to the sulfonamide moiety, were found to display both increased inhibitory activity and selectivity towards the COX-2 enzyme. For instance, benzenesulfonamides; possessing carboxylic (3-CO_2H), **146d**, and hydroxyl (4-OH), **146c**, moieties were reported to exhibit a significant increase in both potency (IC_{50} = 0.74 μM) and increased selective COX-2 inhibitory activity (SI = 114.5), compared to resveratrol, **1**, (SI = 0.1) as well as the nonsteroidal anti-inflammatory drug (NSAID) celecoxib (SI = 78), furthermore compounds comprising of either 3,4,5-trimethoxy or 4-hydroxy-3,5-

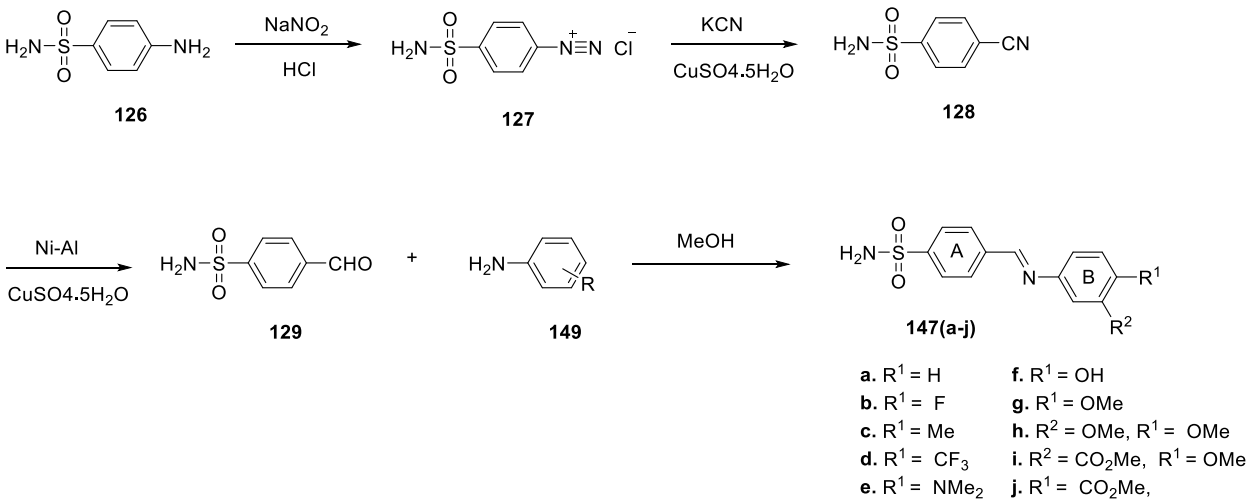
dimethoxy moieties were found display increased selective COX-2 inhibitory activity [181].



Scheme 1.17 Synthesis 4-benzylideneamino benzenesulfonamide derivatives

Conversely, analogues possessing an electron donating groups; such as 4-methyl and 4-methoxy moieties, as well as with the electron withdrawing 4-trifluoromethyl group displayed reduced COX-2 selectivity. Overall, the COX-2 selectivity displayed by these compounds proceeded in the following hierarchy, when the functional groups were position on ring 'B'; 4-F > 4-CO_2Me > 4-NMe_2 > 4-NO_2 > 4-OH > unselective 3-NO_2.

Alternatively the design of 4-phenyliminomethyl-benzenesulfonamide analogues, **147**, proceeded *via* the modified method reported by Yang *et al.,* (Scheme 1.18) [6], in the presence of methanol [177] and the potency and selective inhibitory activities of this series of 4-phenyliminomethyl compounds, **147a – 147j**, were evaluated against both COX-1 and COX-2 isozymes. A reduced selectivity was observed overall, especially with the benzenesulfonamide possessing a 4-*N,N*-dimethylamino, **147e**, moiety (SI = 33.0).



Scheme 1.18 Synthesis of 4-phenyliminomethyl-benzenesulfonamide analogues

Additionally, the recently synthesised novel pyridine acyl sulfonamide analogues, have been found to display enhanced inhibitory activity (IC_{50} = 0.8 μM), when examined *in vitro* on murine macrophage RAW 264.8 cell lines, a number of the analogues exhibited good inhibitory activities against PGE_2 production, with IC_{50} values ranging between 0.15 – 2.8 μM. Furthermore, these benzenesulfonamides were reported to be more potent than celecoxib in inhibiting the growth of melanoma (B-16-F10), liver (HepG2) and breast (MCF-7) cancer cell lines, with no toxicity as a drug compound [179].

Although, the current studies show promising activity, the mechanisms into how these novel benzenesulfonamides exhibit their activity, remains to be reported. However, potential lead parent compounds, of which display increased selectivity towards cancer cell lines, compared to current therapeutic medicines, have been highlighted as either potential drug candidates or lead compounds for further study [138].

Peanut phytoalexins are of great interest due peanuts being a dietary source, of which these bioactive compounds can be administered into the body [182]. Apart from resveratrol, **1**, these natural compounds are currently unavailable within the commercial market and because of this, the use of these natural polyphenols within the pharmaceutical industry remains limited.

Although, the biological properties of *trans*-resveratrol, **1**, has been predominately explored [192 – 194], the biological effects of other prenylated stilbenoids, specifically arachidin-1, **2**, to date has not been extensively explored, especially with regards to the pharmacokinetic properties of this natural compound. Therefore the design and synthesis of natural peanut phytoalexins as well as their analogues are of interest and are essential for further *in vitro* and *in vivo* studies.

The aim of this work was therefore to investigate routes towards the synthesis of arachidin-1, **2**, in order to synthesise an authentic sample of arachidin-1, **2**. An additional aim was to investigate and develop methods towards the synthesis of novel resveratrol analogues, possessing various substituents groups around the aryl rings.

Palladium catalysed reactions have been shown to be efficient in the formation of the stilbene backbone, however with less regioselectivity. Although the literature has proved that the regioselectivity of these catalysed reactions can be controlled, other issues (as discussed in Section 1.6.2) still remain. The formation of the ethylene-linkage *via* traditional methods such the HWE reaction has proved, within the literature to be a favoured and successful approach for the synthesis of natural stilbenes and their derivatives, therefore the use of the HWE reaction will be explored in this research.

1.8 Summary

Stilbene phytoalexins isolated and characterised from the peanut, *Arachis hypogaea*, plant; in particular *trans*-resveratrol, **1**, and *trans*-arachidin-1, **2**, have been found to display an array of promising biological and therapeutic properties. The analogues of resveratrol, in particular stilbene benzenesulfonamides, possessing a primary sulfonamide moiety have been reported to exhibit promising cancer chemopreventative and anti-inflammatory activity compared to resveratrol, **1**. Methodologies into the synthesis of various peanut stilbenoids, specifically resveratrol, **1**, have been established and developed. However, the need for a reliable and stereoselective approach for the synthesis of *trans*-arachidin-1, **2**, and other novel peanut phytoalexins still remains.

Chapter Two

2. Synthesis of Arachidin-1: Part I

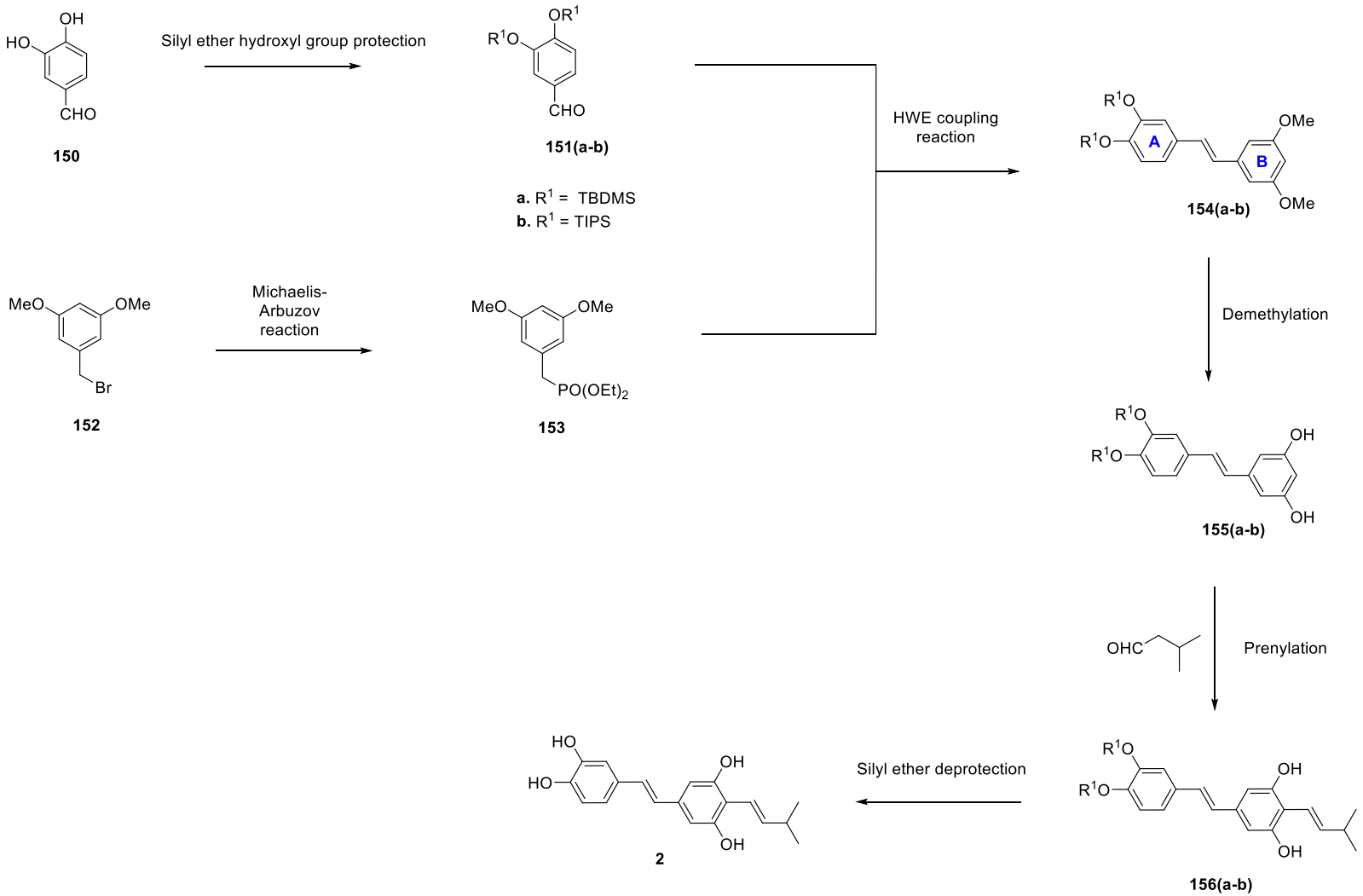
2.1 Strategy for the synthesis of arachidin-1

The first stage of this study was to examine a suitable coupling reaction, which would allow the construction of the *trans*-stilbene backbone. The volume of literature detailing methods for the synthesis of stilbenes and the formation of the C=C double bond is vast [9, 91, 98, 103, 105, 107], however the Horner-Wadsworth-Emmons (HWE) reaction has been shown to be an effective and reliable route for the synthesis of resveratrol, **1**, and its derivatives [9, 22, 106, 111]. As well as natural products, including palmerolide A; a cytotoxin isolated from the antarctic marine tunicate *Synoicum adareanum* [183], with high selectivity for the *trans*-isomer [184].

Additionally, the recent reported synthesis of the naturally occurring peanut prenylated stilbenes, *trans*-arachidin-2, **8**, and *trans*-arachidin-3, **9**, by Park and co-workers [84] has further demonstrated the use of this 'traditional' approach, to be an adaptable method.

Once the reaction conditions for the formation of the stilbene skeleton have been established, it would then enable the study of strategies towards the synthesis of arachidin-1, **2**, to be performed, and give scope to investigate other routes towards the synthesis of novel resveratrol analogues.

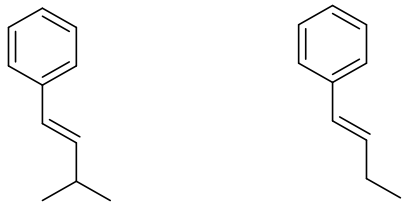
In this chapter the synthetic strategy towards the synthesis of arachidin-1, **2**, is described, the first proposed approach which was adapted from the work reported by Park *et al.,* [84] is outlined, whereby selected silyl ethers were used for the hydroxyl protection of 3,4-dihydroxybenzaldehyde, **150**. The silyl ether selected for this reaction was of importance, as it was necessary for the protecting group to be able to withstand the various basic and/or acidic reactions, the aldehyde would be involved in. Next coupling *via* the HWE reaction with the protected benzaldehyde, **151(a-b)**, and diethyl 3,5-dimethoxybenzylphosphonate, **153**, which was synthesised from the substituted benzyl bromide, **152**, *via* the Michaelis Arbuzov reaction [185] would afford the stilbene backbone. Once the stilbene skeleton was formed, the next step would be demethylation using a strong acid such as boron tribromide, this would then allow for the introduction of the side chain and finally cleavage of the silyl ether protecting groups, to give the target compound, as shown in Scheme 2.1.



Scheme 2.1 **Synthetic strategy into the synthesis of *trans*-arachidin-1**

2.2 Synthesis of branched and un-branched *trans*-alkenes

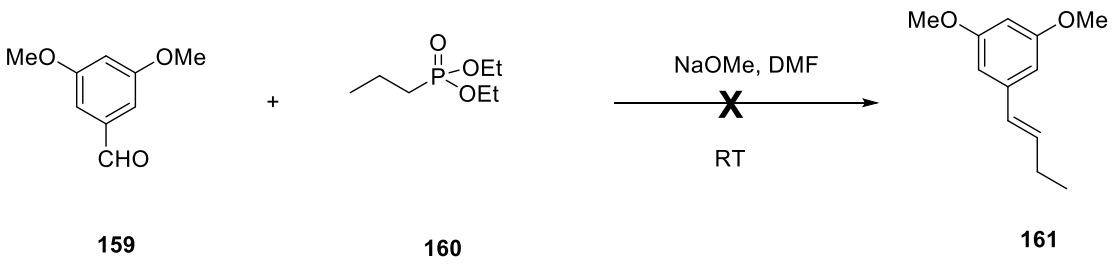
The majority of this work involved coupling to form the *trans*-stilbene backbone, therefore initial studies into the synthesis of *trans*-arachidin-1, **2**, began by performing model reactions in order to examine, with regards to the boundaries of this research, if the HWE reaction, under the chosen reaction conditions would be effective in forming the *trans*-alkene. The study began by exploring the synthesis of branched, **157**, and unbranched, **158**, *trans*-alkenes (Figure 2.1).



157 **158**

Figure 2.1 Structure of branched and unbranched *trans*-alkenes

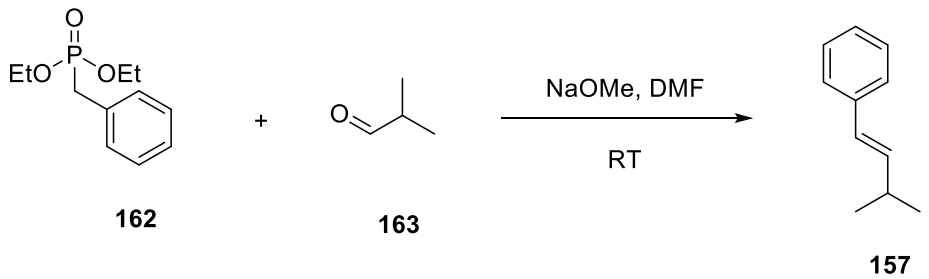
The first model reaction investigated was the coupling of the commercially available 3,5-dimethoxybenzaldehyde, **159**, with diethyl propylphosphonate, **160**, in the presence of sodium methoxide (Scheme 2.2). It was anticipated that the use of this base, would be sufficient to drive the formation of the phosphonate carbanion and the subsequent nucleophilic addition of the carbanion to the aldehyde [103]. Nevertheless, the reaction did not go to completion and failed to result in the desired product, despite the addition of extra sodium methoxide.



159 **160** **161**

Scheme 2.2 Attempted coupling *via* the Horner-Wadsworth-Emmons reaction

Analysis of the reaction mixture (^{1}H NMR) indicated the presence of both starting materials, and it was likely that the lack of stability displayed by the aliphatic phosphonate carbanion, may have been the cause of this unsuccessful reaction [110, 113]. The use of stabilised phosphonate carbanions are known to be essential for the HWE reaction, therefore coupling using diethyl benzylphosphonate, **162**, was attempted (Scheme 2.3). The benzylphosphonate carbanion is known to be stabilised by delocalisation from the aromatic ring, therefore when coupled with 2-methylpropanal, **163**, in the presence of sodium methoxide, this reaction gave a mixture of compounds; the desired compound (*E*)-(3-methylbut-1-en-1-yl)benzene, **157**, (25 %), phosphonate, **162**, (55 %) and aldehyde, **163**, (20 %). Although the reaction did not go to completion, it is possible that longer reaction times may be required in order to obtain higher yields of the alkene.



162 **163** **157**

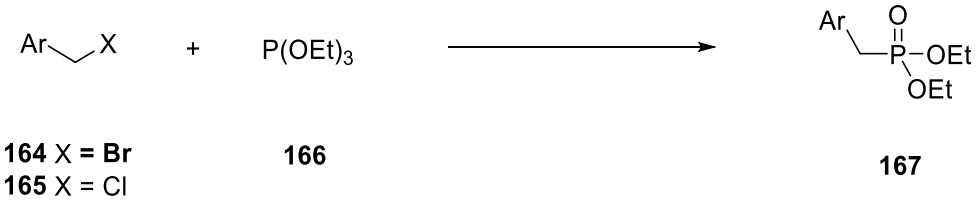
Scheme 2.3 Coupling *via* the Horner-Wadsworth-Emmons reaction using 2-methylpropanal

Nevertheless, formation of the desired C=C bond was evident by characterisation of the ^{1}H NMR spectrum, whereby two doublets at δ 6.00 ppm and δ 6.18 ppm, were observed. Furthermore, the calculated *J* couplings of the two doublets (J_{AB} = 16 Hz and J_{AB} = 15.9 Hz), confirmed the formation of the desired *trans*-alkene, **157**. This therefore proved the traditional HWE reaction, with the use of a stabilised phosphonate, to be a good approach not only for the synthesis of the *trans*-stilbene backbone, but also potentially for the incorporation of the prenyl side-chain.

2.3 Preparation of starting materials

2.3.1 Arbuzov reaction

Several alternative methodologies for the synthesis of diethyl benzylphosphonate (Scheme 2.4), are detailed in the literature, however the traditional and most commonly used method is the Michaelis-Arbuzov reaction [185, 186].



164 X = **Br**
165 X = Cl

166

167

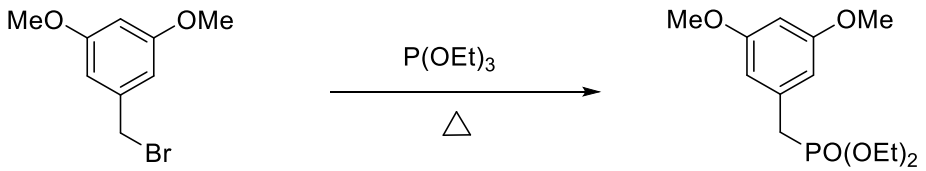
Scheme 2.4 Synthesis of benzylphosphonates

The first method, reported by Michaelis and further developed by Arbuzov, involves nucleophilic attack of the phosphorus atom towards an halide, followed by

dealkylation of the intermediate, *via* a second S_N2 nucleophilic attack to afford the phosphonate ester[187], this substrate is commonly used for coupling reactions such as the HWE reaction [110, 112].

Variations of this rearrangement, are also known; including the Lewis acid-mediated Michaelis-Arbuzov reaction [188], reductive coupling [189], palladium-(0)-catalysed cross-coupling reaction [190, 191], and the conversion of benzyl alcohol to benzylphosphonate, *via* zinc mediated reactions [192]. However the Michaelis-Arbuzov reaction is known to be the most favoured approach due to the excellent yields obtained and the use of inexpensive reagents [185, 186].

In this study, the Arbuzov reaction between 3,5-dimethoxybenzyl bromide, **152**, and triethyl phosphonate (1 equiv.), was performed and gave the desired compound, **153**, in excellent yield (98 %) (Scheme 2.5). Based on optimised reaction conditions performed, this reaction proceeded smoothly when stirring at >130 °C for 24 h. The formation of the new CH_2-P bond was confirmed by ^{1}H NMR, whereby a doublet at δ 3.06 ppm, integrating to two protons (CH_2) was observed on the spectrum.



152 **153**

Scheme 2.5 Michaelis-Arbuzov reaction with triethyl phosphite

Additionally a large $^2J_{PH}$ value was calculated (J = 21.6 Hz), which was characteristic of the geminal coupling between ^{31}P and ^{1}H, therefore confirming the phosphonate, **153**, had been formed.

2.3.2 Hydroxyl group protection

The next step of this methodology was to perform hydroxyl protection on the aldehyde, **150**. Within the literature there were a number of strategies for the protection of the hydroxyl moieties, one approach considered was the conversion of the OH functional groups into their corresponding ethers; for example alkyl, allyl or benzyl ethers. However, allyl ethers and trityl ethers, although stable under basic conditions were very acid-labile, therefore were not an option.

The use of alkyl and benzyl ethers at first were an attractive approach, however as both functional groups were known to be relatively unstable in basic, acidic, and harsh conditions [193], it was likely that cleavage of these protecting groups would occur during the demethylation stage of this methodology (as detailed in Scheme 2.1), in the presence of boron tribromide [194, 195], based on this the alkyl and benzyl ether protecting groups were no longer a viable option

Another option, in relation to the protection of the hydroxyl groups, would be to convert the groups into acetals, such as methoxymethyl ether [194] or benzyloxymethyl ether derivatives. These groups are commonly known to be stable under basic conditions, moreover they are relatively stable under mild acidic conditions. Additionally, as shown by Park and co-workers [84], in the synthesis of peanut prenylated stilbenes, **8-9**, these protecting groups were easy to cleave when incorporated as part of phenols. However, these protecting groups were not selected in this study as they are also known to be unstable during purification *via* column chromatography[193]. Furthermore some acetal reagents are recognized carcinogens, such as methoxymethyl chloride (MOMCl), although an alternative route to the

formation methoxymethyl esters, has been suggested *via* the use of dimethoxymethane [195] and is suggested to be less harmful.

Nevertheless, the conversion of the alcohol, **150**, into silyl ethers, *tert*-butyldimethylsilyl (TBDMS) or triisopropylsilyl (TIPS) group [84, 196], was both attractive and plausible protecting groups to use in this approach, due to the silyl ethers displaying stability in both basic and mild acid conditions, in addition to their selectivity towards primary (1°) alcohols and facile cleavage, in the presence of a fluoride ion or aqueous acid. Furthermore, these inexpensive protective groups have been frequently used as hydroxyl protecting group in the literature[193, 197, 198].

It was therefore decided that protection of 3,4-dihydroxybenzaldehyde, **150**, would be explored using two different silyl ethers (TBDMSCl and TIPSCl) as both protecting groups offered different stabilities in acidic and basic media (Figure 2.2).

The stability of the silyl ether toward acid increases in the following order:

TMS (1) < TES (64) < TBDMS (20,000) < TIPS (700,000) < TBDPS (5,000,000)

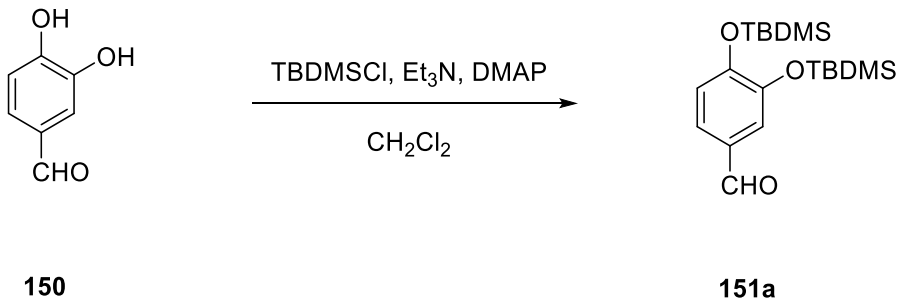
The stability of the silyl ether toward base increases in the following order:

TMS (1) < TES (10-100) < TBDMS ~ TBDPS (20,000) < TIPS (100,000)

Figure 2.2 Stability of common silyl ethers toward acidic/basic media [193]

2.3.2.1 Hydroxyl protection using tert-butyldimethylsilyl chloride

The first hydroxyl group protection was attempted using TBDMSCl (2.2 equiv.), under basic conditions (Scheme 2.6). In accordance with the literature [203], the optimised reaction conditions performed in this work identified the addition of the base DMAP, in excess to be essential in order to accelerate the reaction. Purification *via* flash chromatography, following aqueous work up of the reaction mixture gave the desired TBDMS protected aldehyde, **151a**, in almost quantitative yield 97 %.

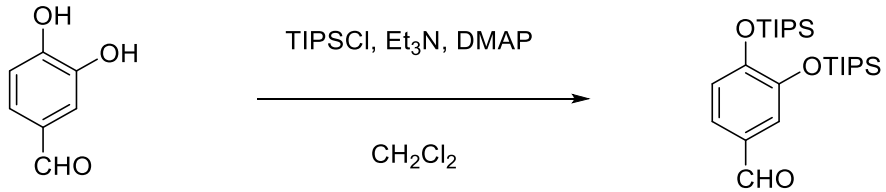


Scheme 2.6 Hydroxyl protection of 3,4-dihydroxybenzaldehyde with TBDMSCl

Characterisation of the silyl protected aldehyde, **151a**, was performed by NMR and MS, from the ^{1}H NMR spectrum singlets at δ 0.00 ppm, integrating to 12 protons (Si-Me) and at δ 0.82 ppm, integrating to 18 protons (6 x Me) were observed, therefore confirming hydroxyl protection with TBDMSCl was successful. Furthermore from the ^{13}C NMR spectrum the carbon nuclei, present within the silyl ether moieties were observed at; δ -3.63 ppm (Si-Me), δ 17.9 ppm (C-*t*-butyl) and δ 25.6 ppm (Me), respectively. Additionally the mass spectral data additionally confirmed the success of the reaction, with a molecular ion peak of *m/z* = 369.

2.3.2.2 Hydroxyl protection using triisopropylsilyl chloride

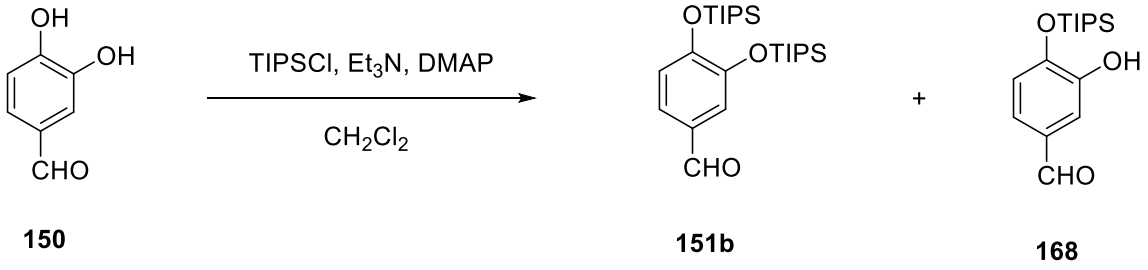
Following the same procedure used for the TBDMSCl reaction, protection of 3,4-dihydroxybenzaldehyde, **150**, was attempted using TIPSCl (Scheme 2.7).



150 **151b**

Scheme 2.7 Hydroxyl protection of 3,4-dihydroxybenzaldehyde with TIPSCl

Characterisation of the product suggested that a mixture of compounds had been made, in this mixture the desired compound, **151b**, with a purity of 86 % was identified, and compound, **168**, which appeared to have only one protected silyl ether moiety (14 %) was also observed *via* ^{1}H NMR analysis (Scheme 2.8). Additionally, formation of the two compounds were observed by mass spectral analysis, whereby molecular ion peaks at *m/z* = 293 ($C_{16}H_{26}O_3Si$) and *m/z* = 450 ($C_{25}H_{46}O_3Si_2$), respectively were seen, therefore indicating the reaction did not to go to completion, and as a result purification proved to be challenging and was repeated a number of times.

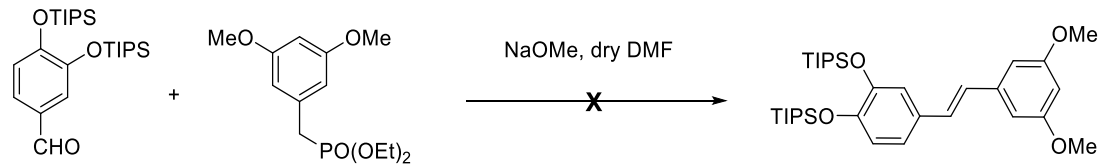


150 **151b** **168**

Scheme 2.8 Attempted synthesis of 3,4-bis((triisopropylsilyl)oxy)benzaldehyde

2.4 Horner-Wadsworth Emmons coupling reaction

The construction of the stilbene was first attempted *via* the HWE reaction, using the TIPS protected aldehyde, **151b**, and the phosphonate, **153**, in the presence of NaOMe (5 equiv) (Scheme 2.9). However the reaction was not successful, this was evident when characterised by both ^{1}H and ^{13}C NMR, as the spectra did not show the presence of the ethylenic linkage. However what was observed were the two starting materials, with the presence of the phosphonate distinctly present in the ^{13}C NMR spectrum.

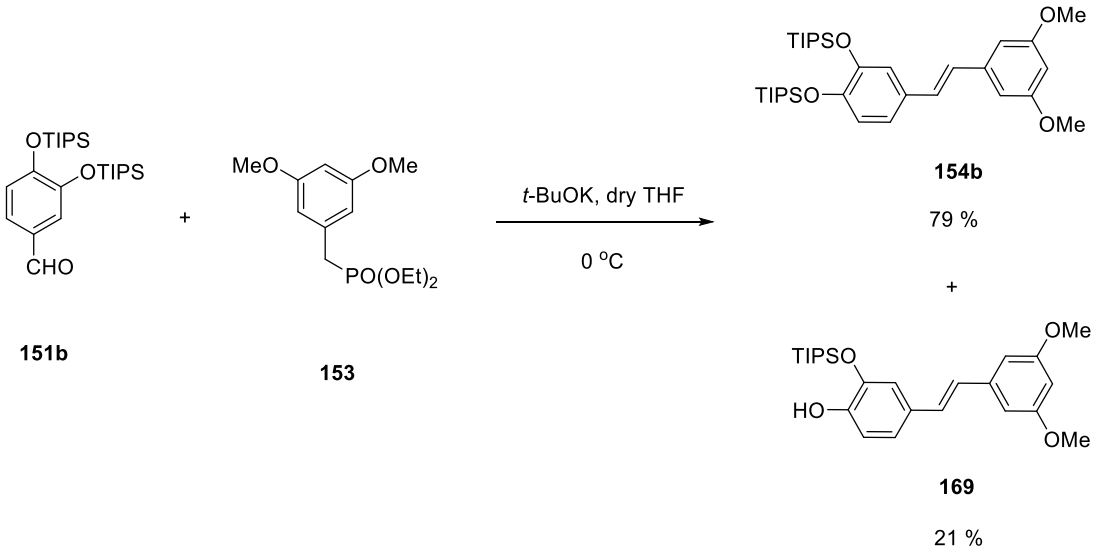


151b **153** **154b**

Scheme 2.9 Attempted synthesis of (*E*)-((4-(3,5-dimethoxystyryl)-1,2-phenylene)bis(oxy))bis(triisopropylsilane)

Next coupling *via* the HWE reaction was attempted again, however this time with the use of potassium *tert*-butoxide (3-4 equiv) and THF, as alternative reagents. Upon immediate addition of the aldehyde, **151a**, to the phosphonate, **153**, a colour change

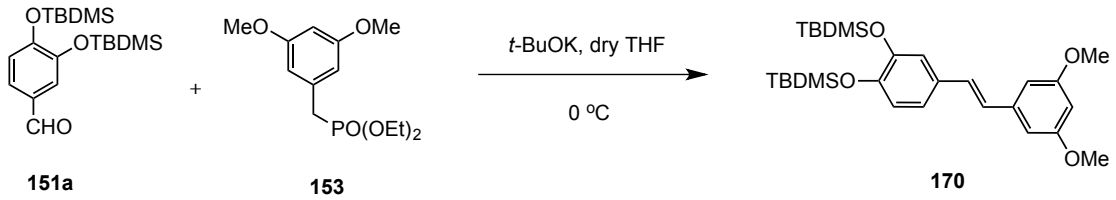
from white to yellow was observed, along with the release of heat energy from the flask, which was indicative that nucleophilic addition as well as the subsequent elimination was occurring. The removal of the phosphate by-product, *via* solvent extraction, gave the *trans*-stilbene in a yield of 79 %, which was similar to the yields reported by Park *et al.,* when MOM (82 %) and TIPS (80 %) protected stilbenes were synthesised in the literature [84]. Although in this work, the results also showed the presence of another stilbene, **169**, when characterised by ^{1}H NMR, and the presence of the two compounds, were additionally confirmed by both mass spectral and TLC analyses, whereby multiple spots were observed. From the mass spectral data the molecular ion peak (*m/z* = 589) of the desired compound, **154b**, was observed, additionally the molecular ion peak of *m/z* = 427 was also identified, which suggests that a stilbene, **169**, possessing the molecular formula of $C_{25}H_{35}O_4Si$ was also formed (Scheme 2.10).



Scheme 2.10 Synthesis of (*E*)-((4-(3,5-dimethoxystyryl)-1,2-phenylene)bis(oxy))bis(triisopropylsilane)

Based on the molecular ion peak value observed, it was possible that cleavage of one TIPS protecting group had occurred. A suggestion as to why one TIPS groups was observed, could be due to the protecting group being unstable in the acidic silica stationary phase, during purification *via* column chromatography. If the acidic stationary phase was the cause of the TIPS protecting group cleaving, an alternative option could be to use a non-silica based stationary phase, however these stationary phases are known to be more expensive.

Next, it was decided upon to investigate and determine, if the TDBMS protected aldehyde would be stable under both basic reaction conditions (HWE coupling) and acidic conditions (purification *via* column chromatography). Following the same procedure as above, coupling of the aldehyde, **151a**, with the diethyl benzylphosphonate, **153**, was examined (Scheme 2.11), the reaction was found to be successful in producing solely the *trans*-alkene. The ^{1}H NMR analysis indicated the presence of two doublets at δ 7.10 and δ 7.23 ppm, respectively, integrating to 2 protons (HC=CH), with *J*-coupling values of 16.5 Hz and 16.8 Hz, respectively, thereby confirming the formation of the ethylene linkage.



Scheme 2.11 Attempted synthesis of stilbene derivative

However, characterisation of the spectrum also suggested that the silyl protecting group had been cleaved, to afford compound, **170** (87 %), attempts were made to separate the mixtures, however due to similar Rf values, this proved to be challenging. Interestingly, cleavage of the TBDMS protecting groups have also been reported in the literature, *via* the Wittig reaction [135].

The successful construction of the stilbene backbone, as suggested by Wadsworth and co-workers [110], involves the phosphoryl-stabilised carbanion attacking the carbonyl, *via* nucleophilic addition, to give the betaine intermediate, which is suggested to be the rate limiting step in the formation of the alkene (Figure 2.3).

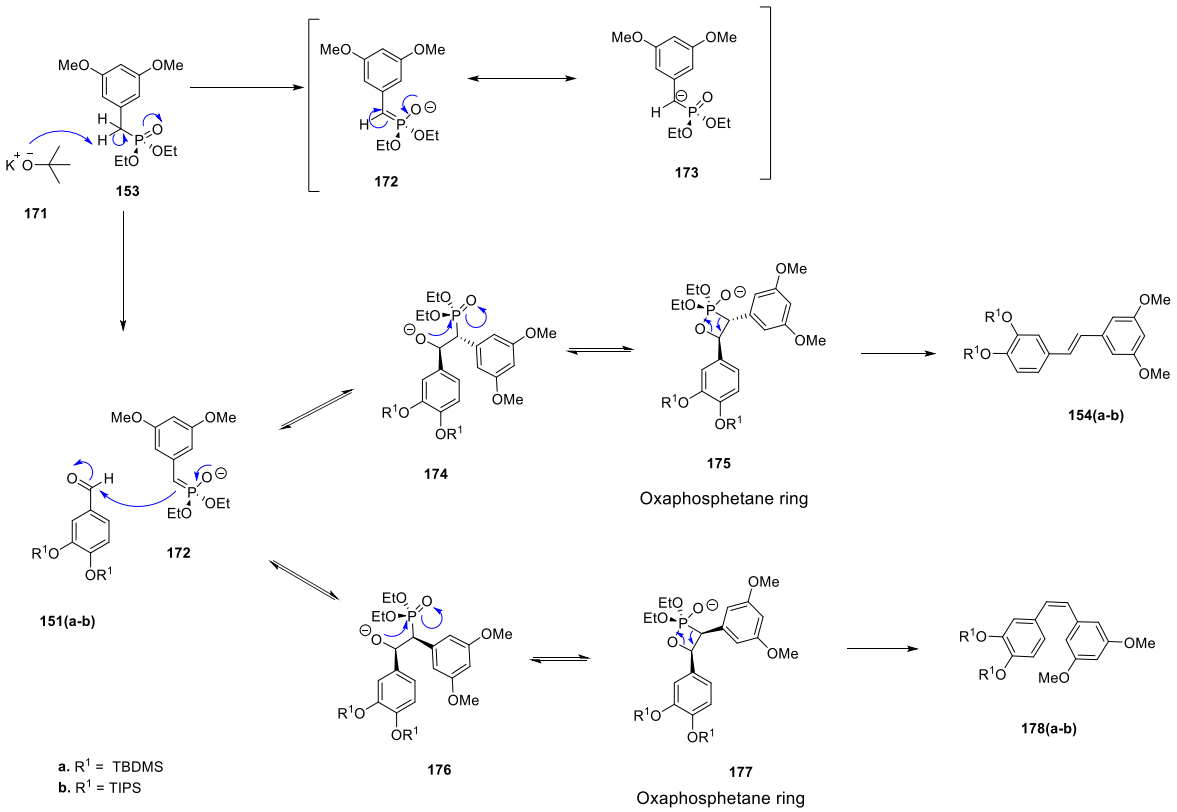


Figure 2.3 Mechanistic approach for the Horner-Wadsworth-Emmons reaction

The carbonyl is thought to approach the C-P bond at a 90° angle, this antiperiplanar approach in relation to steric effect is said to be most favoured (Figure 2.4) [104, 110]. Both the *cis*- and *trans*-oxaphosphetane intermediates are said to lead to stereospecific *syn*-elimination, and result in the formation of both *cis*- and *trans*-alkenes, respectively.

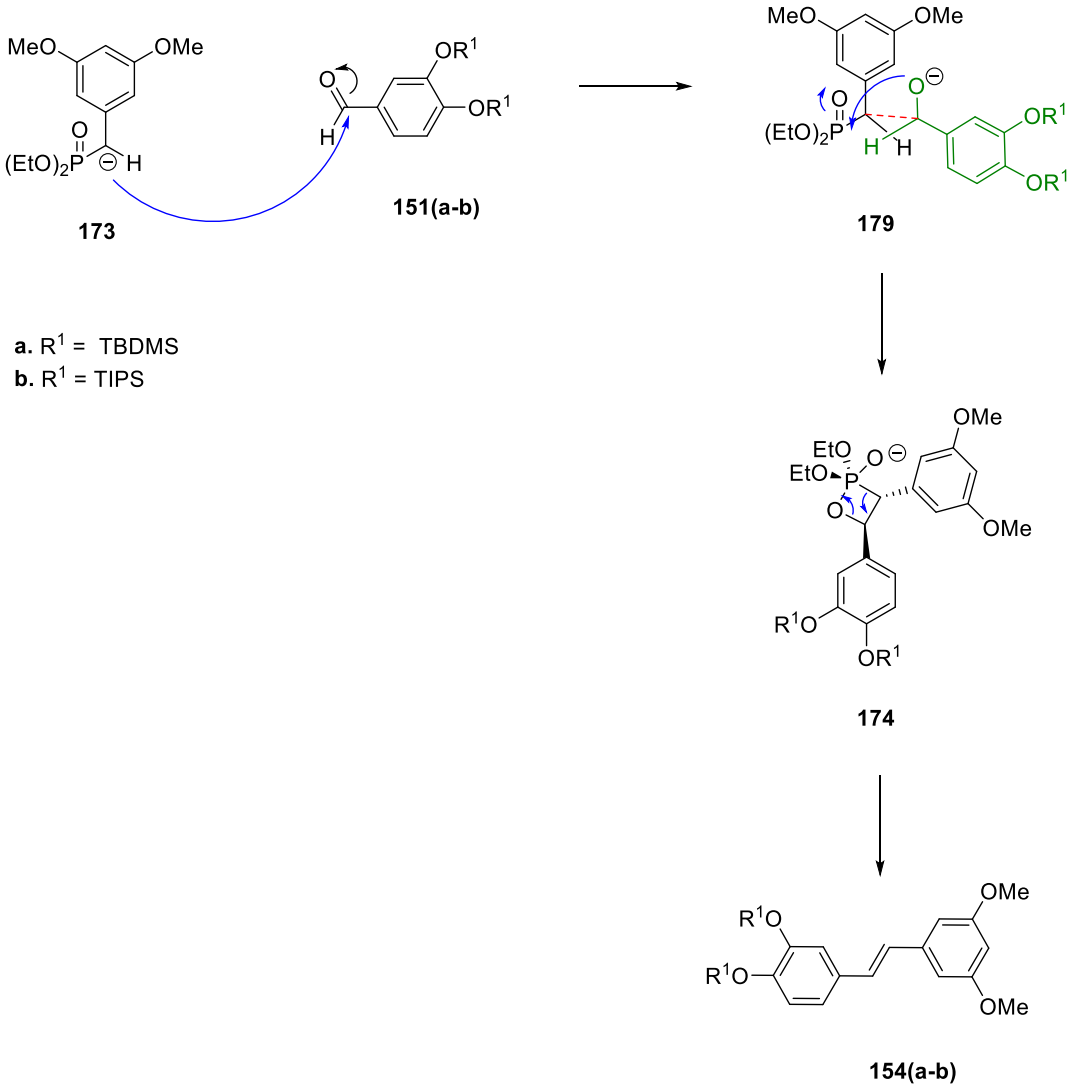
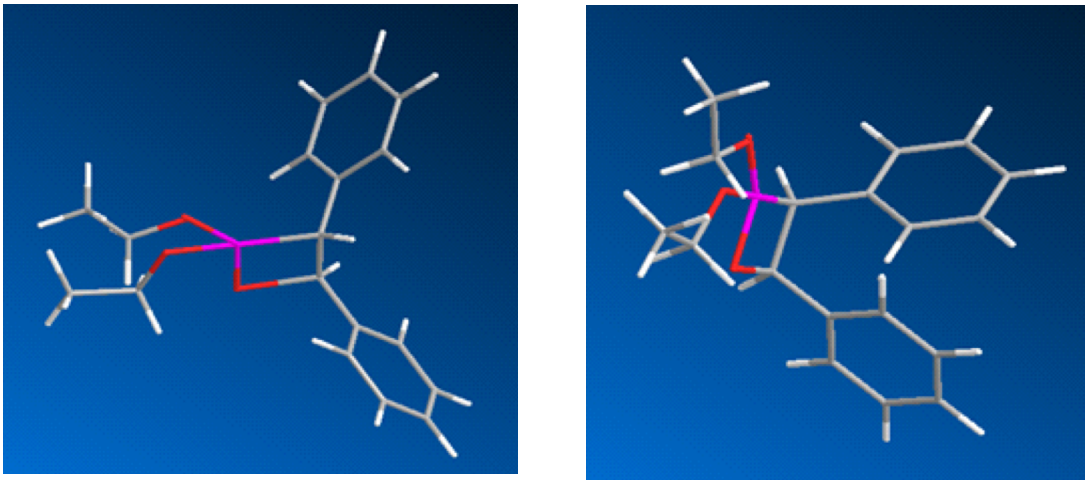


Figure 2.4 **Steric approach between the phosphoryl stabilised carbanion and the carbonyl**

Although this is not fully understood, it is suggested that under kinetic conditions, the product initially formed is the *cis*-oxaphosphetane diastereoisomer, **177**, which consequently affords the *cis*-isomer, **178(a-b)**. However the reversibility of the intermediate affords predominately the *trans*-isomer, **154(a-b)**, under thermodynamic conditions, due to the *trans*-oxaphosphetane, **175**, being more stable. This theory has been supported by both kinetic and spectroscopic studies, of which have shown that the stereochemistry in the HWE reaction can be explained by stereoselectivity in the initial C-C bond formation step, in addition to the reversibility of the two intermediates. It is also suggested that the thermodynamically stable isomer, which leads to the formation of the *trans*-alkene, is due to the bulky aromatic rings of which are positioned on either side of the carbon-carbon bond within the ring (Figure 2.5) [103].



***trans*-oxaphosphetane intermediate** ***cis*-oxaphosphetane intermediate**

Figure 2.5 3D configurations of *trans*- and *cis*-oxaphosphetane intermediates

(Calculated from Cambridgesoft ChemBioDraw Ultra software v.14.0.0.117)

2.5 Summary

The silyl ether protected benzaldehydes, **151a** and **151b**, were synthesized, using either TBDMS or TIPS groups, as hydroxyl-protecting moieties. The 3,4-dihydroxybenzaldehyde, **150**, was most conveniently transformed into the TBDMS or TIPS ether in the presence of DMAP in excess. Furthermore formation of the stilbene skeleton was found to be successful *via* the HWE coupling reaction, however only by coupling of the TIPS protected aldehyde, **151b**, with diethyl benzylphosphonate, **153**, in the presence of *t*-BuOK and THF. According to the literature, the increased steric bulk of the TBDMS group is known to enhance the stability of the protecting group [199], furthermore the chemistry of the HWE reaction has been reported to be suited with this base resistant protecting group [200]. In this study the base used in the HWE coupling reaction, appeared have had an effect on the reactivity of the silyl ether protecting group, TBDMS. Upon purification using silica, the TIPS moiety was found to be susceptible to decomposition during column chromatography and resulted in cleavage from the stilbene scaffold. However, there is a possibility the use of a non-silica based stationary phase, may overcome this issue. Characterization by ^{1}H NMR and mass spectral analysis indicated the presence of the stilbene skeleton, **169**, (21 %), which was found to have one TIPS protecting group.

Chapter Three

3. Synthesis of Arachidin-1: Part II

3.1 Retrosynthetic strategy

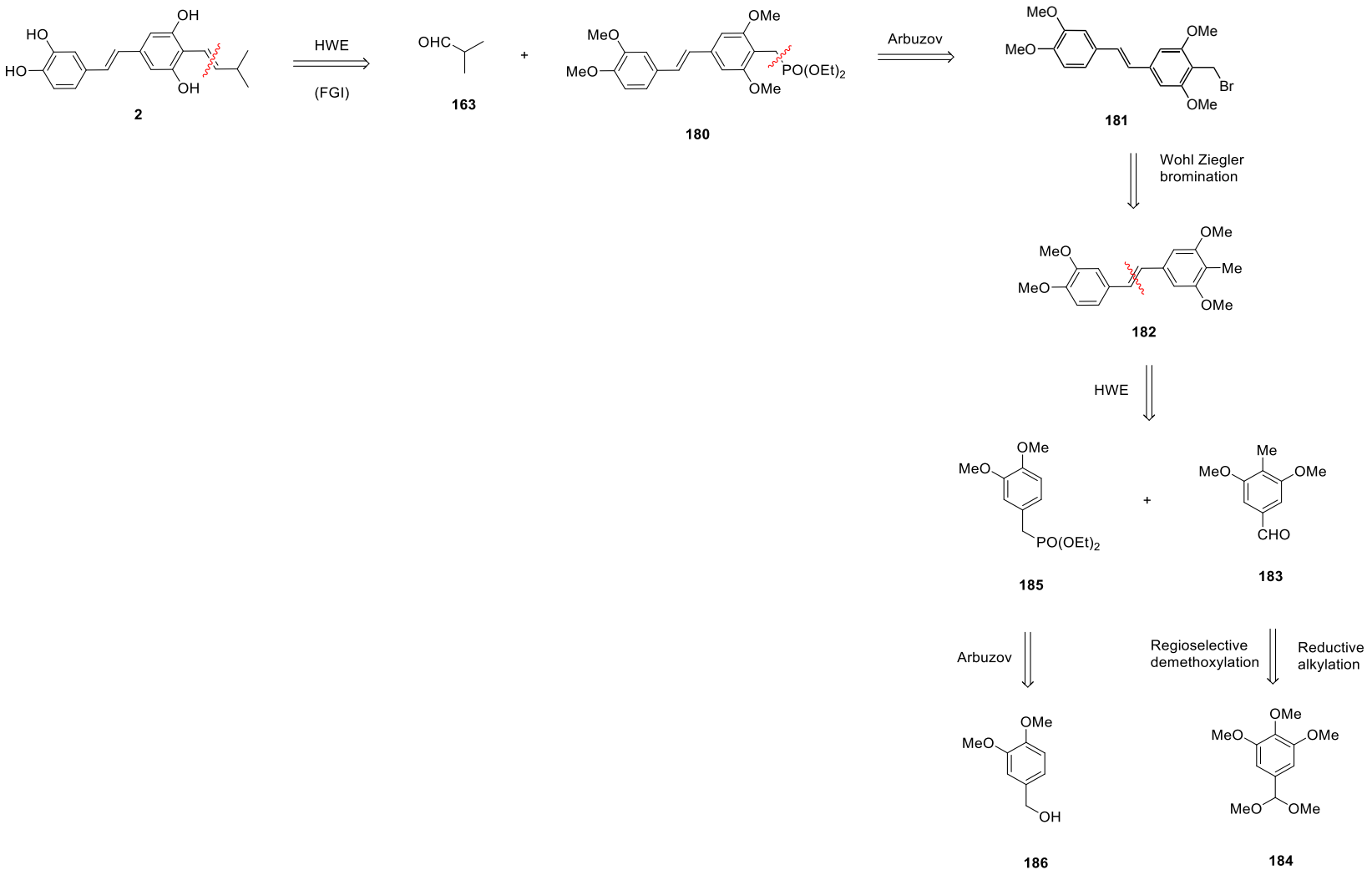
Having attempted the synthesis of arachidin-1, **2**, *via* silyl ether protection, it was decided that an alternative approach, would be to construct the *trans*-stilbene backbone, by the synthesising the substrates; 3,5-dimethoxy-4-methylbenzaldehyde, **183**, and diethyl (3,4-dimethoxybenzyl)phosphonate, **185**, [201, 202] and then coupling the two compounds *via* the Horner-Wadsworth-Emmons (HWE) reaction [103, 110].

The retrosynthetic strategy of this approach is outlined in Scheme 3.1, the starting material 3,4,5-trimethoxybenzaldehyde dimethyl acetal, **184**, was chosen as this compound has been reported to successfully undergo regioselective demethylation, in the presence of an alkali metal. Next subsequent electrophilic substitution of the acetal, **184**, using iodomethane and finally acetal hydrolysis, would give the desired aldehyde, **183**, [201, 202]. The acetal, **184**, used in the study, would also enable the masking of the hydroxyl groups by means of methyl ethers, which are of interest in this approach as these protecting groups have the advantage of being extremely stable in various reaction

conditions, with the option of cleaving *via* a demethylation reaction, in the presence of a strong Lewis acid, at the penultimate stage of the synthetic route [203].

Furthermore, by adapting the procedure described by Azzena and co-workers [201, 202], it would allow for the exploration of electrophilic substitution reactions, using selected alkyl halides, following regioselective demethylation.

Once the stilbene backbone had been formed, it was envisaged that *N*-bromosuccinimide (NBS) could then be used as a brominating agent in the Wohl-Ziegler reaction[204, 205], and the subsequent Michaelis-Arbuzov rearrangement[185, 186] on the brominated stilbene, would afford the phosphonate. Next HWE coupling with 2-methylpropanal, **163**, would allow us to incorporate the side-chain, and finally the demethylation reaction could then be performed, in order to afford arachidin-1, **2**.

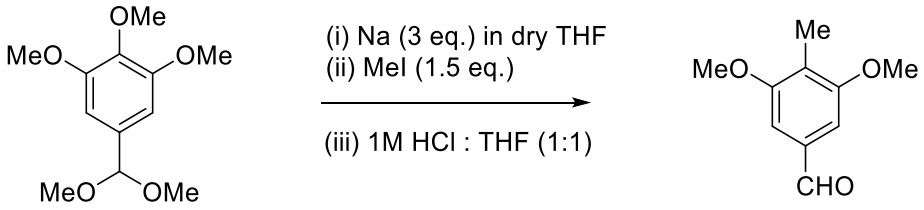


Scheme 3.1 Retrosynthetic strategy for the synthesis of trans-arachidin-1

3.2 Regioselective demethoxylation

The initial step of this approach involved the synthesis of the aldehyde, **183**, (Scheme 3.2), first the 4-methoxy moiety in 3,4,5-trimethoxybenzaldehyde dimethyl acetal, **184**, was regioselectively removed, upon the addition of sodium metal (3 equiv.), this methodology was performed according to the procedure published by Azzena *et al*., [202]. Following the addition of sodium metal, a colour change from yellow to purple was observed in the reaction mixture, therefore indicating the progress of the radical demethoxylation step.

Next, decanting of the reaction mixture, to remove the excess sodium metal was performed, before the reductive alkylation step with iodomethane in excess (~ 1.5 equiv.), which proceeded smoothly. Finally acidic hydrolysis of the crude reaction material, gave the desired benzaldehyde, **183**, with an excellent yield of 92 %. When compared to the literature, the yield obtained was similar to that reported in the literature (> 90 %) [202].



184 **183**

Scheme 3.2 Regioselective demethoxylation of 3,4,5-trimethoxybenzaldehyde dimethyl acetal

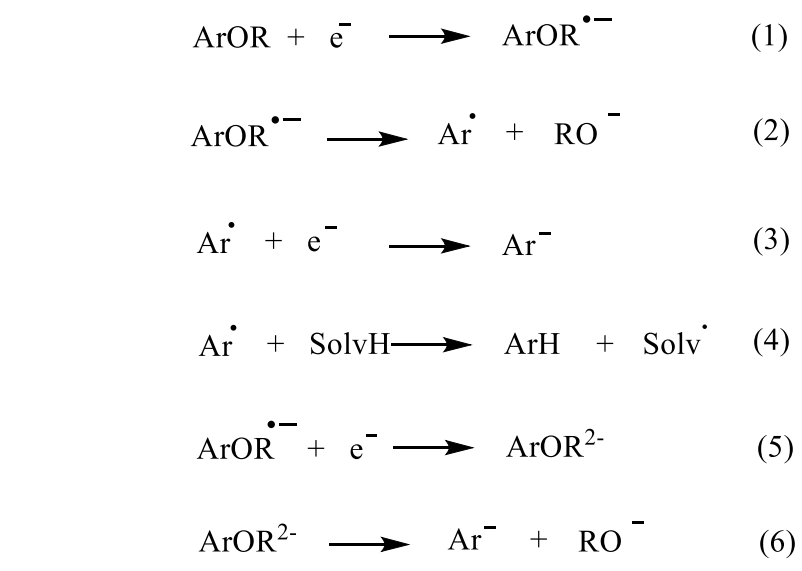
The reaction was repeated, however in the second attempt sodium metal, 30-35 wt. % dispersion in wax, was used instead of the freshly cut sodium, it was envisioned that the increase in surface area of the metal would minimise the challenge of decanting the residual metal from the reaction mixture, prior to the addition of iodomethane. This approach was found to proceed smoothly, without the need of decanting the reaction mixture and gave a high yield of the aldehyde, **183** (82 %). Although the yield obtained with this approach was lower than that reported in the literature, it is possible that the loss of yield may have occurred during the filtration stage of the recrystallization process, as from the analysis (^{1}H NMR) of the precipitate extracted from the mother liquor, the presence of the aldehyde, **183**, along with the what was believed to be an acetal intermediate was observed in the spectrum. When the crude product from the mother liquor was purified again, an additional 6 % yield of the pure product, **183**, was obtained.

The substitution of the methoxy moiety with a hydrogen atom (reductive demethylation) is known to proceed *via* a two-electron-transfer (reductive) process, whereby cleavage of the aryl-oxygen (C-O) bond, present in aryl ethers takes place at the 4-OMe group [206]. Mechanistically two reaction routes have been reported within the literature, and both mechanistic pathways (Equation 3.1), according to Azzena and co-workers [207] are suggested to begin with the formation a radical anion (Equation 3.1; (1)).

The reaction is said to occur *via* cleavage of the radical anion, resulting in the aryl radical being formed (Equation 3.1; (2)), which consequently can be reduced into an aryl anion (Equation 3.1; (3)). Alternatively, a hydrogen atom could be abstracted from the reaction medium (Equation 3.1; (4)) leading to aryl radical decay. The hydrogen atom donors are

suggested to be least likely with the use of THF as the solvent, however, the source of the hydrogen atom is suggested to be from the methoxide ion formed during the reductive cleavage.

The decay of the aryl radical (Equation 3.1; (4)) is thought to compete with the reduction into aryl anions (Equation 3.1; (3)), this is considered to be the stage needed to form the intermediate species, ready for the subsequent electrophilic attack. On the other hand, it is reported that the radical anion is additionally reduced to the dianion, *via* disproportionation (Equation 3.1; (5)), and subsequent cleavage of the aforementioned stage is said to afford the aryl anion (Equation 3.1; (6)). Furthermore studies into the mechanism of reductive demethylation have also found that the nature of the aldehyde protective group, provides a crucial role in the demethylation step of the synthesis [208].



Equation 3.1 The reaction pathway proposed for the cleavage of aryl-O bonds of aryl ethers, *via* reductive electron transfer. [208]

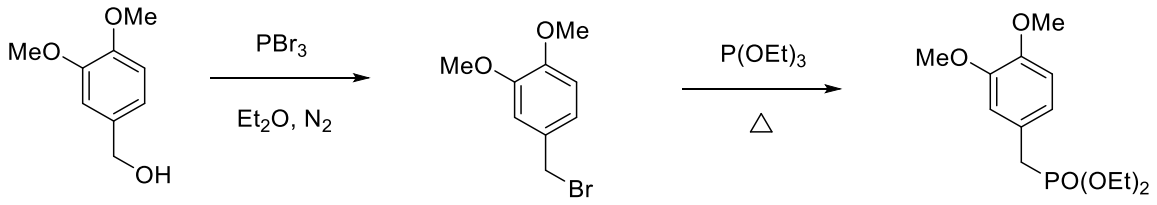
Furthermore, reduction in the presence of an alkali metal in low polarity solvents, such as THF, have been found to result in 100 % regioselective demethoxylation in almost quantitative yields. However, other solvents of lower polarity were found to reduce the reactivity of the substrates, additionally the presence of the dimethyl acetal moiety, *para* to the leaving methoxy group, has been reported to influence the mechanism(s) of the C-O bond cleavage [208]. Azzena *et al*., have suggested that the regioselective cleavage of the aryl-oxygen bond occurs due to the 4-methoxy group, twisting out of plane on the aromatic ring, this twisting is thought to be caused by the two adjacent *ortho*-methoxy groups. Moreover, the reaction is also believed to be influenced, electronically by the two *ortho*-substituents[207, 209].

Under similar conditions to that shown in Scheme 3.2, the regioselective demethoxylation has been previously reported in the literature, using potassium metal as the alkali metal, however for compounds such as 3,4,5-trimethoxybenzaldehye dimethyl acetal **184**, the use of finely cut sodium metal (3 equiv.), was found to be highly successful, with THF being the most suited solvent for the reaction. Moreover the use of potassium metal (3 equiv.) was found to give lower yields, due to the incomplete complete conversion of the acetal. Furthermore, at lower temperatures (-20 °C), the use of the potassium metal gave higher yields, in addition to by-products which according to Azzena *et al*., are believed to be from the Wittig rearrangement of the acetal group, which is induced by reductive electron transfer. The use of lithium metal was also found to result in slow conversion (50 % over 7 days) [169], however the alkylation of the demethoxylated intermediate, with secondary alkyl halides, such as 2-iodopropane has been reported to be unsuccessful,

regardless of extended reaction times [207], based on these findings optimisation studies were not performed for this step of the methodology.

3.3 Formation of the benzylphosphonate

The next step in the synthetic methodology was the nucleophilic substitution (S_N2) reaction of 3,4-dimethoxybenzyl alcohol, using 1.2 equiv. of phosphorus tribromide, in the presence of diethyl ether (Scheme 3.3). The bromo-compound, **187**, was prepared according to the procedure reported by Charlton and co-workers [210] and gave an excellent yield of 93 %, as determined by ^{1}H NMR. Furthermore ^{1}H NMR confirmed the success of the reaction, as a broad singlet which is characteristic of the hydroxyl (O-H) proton environment was no longer observed in the spectrum.



186 **187** **185**

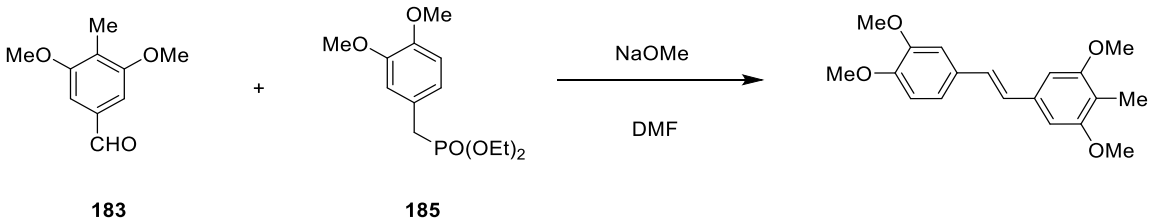
Scheme 3.3 Synthesis of Diethyl (3,4-dimethoxybenzyl)phosphonate

Additionally, the melting product of the crystalline product, **187**, was determined (m.p. 48 ºC - 51 ºC), notably the narrow melting point range obtained was similar to that of the literature 47 - 50 °C [97], therefore indicating that the product was pure. According to

the literature [218], this bromo compound has been reported to be unstable, therefore triethyl phosphite was subsequently added to the crude benzyl bromide, **187**, following full characterisation. The Arbuzov reaction in the presence of triethyl phosphite in excess gave inconsistent yields compared to other Arbuzov reactions performed in this work, with the formation of the desired benzylphosphonate, **185**, obtained in moderate yield (53 %). A possible explanation of the low yield obtained, could be due to the large scale of the reaction (71 g scale), the reaction may have not been given enough time to reach completion, as the presence of the starting material was also observed by ^{1}H NMR. Nevertheless, the formation of the desired phosphonate was confirmed by ^{1}H NMR analysis, with a doublet observed at δ 2.94 ppm, integrating to 2 protons (CH_2-P).

3.4 Coupling *via* HWE

Next the stilbene, **182**, was constructed *via* the HWE reaction, yielding the *trans*-alkene in good yield (86 %), the use of the base (NaOMe) in excess (> 8 equiv) provided the best yields (Scheme 3.4). The synthesis of the stilbene skeleton was performed in a one-pot reaction to reduce the loss of yield, furthermore as suggested by Wadsworth *et al*., [110, 113], preparation of the phosphonate carbanion was carried out, by the addition of the base in DMF at room temperature, to ensure deprotonation of the acidic proton, on the α-carbon adjacent to the phosphorus atom proceeded smoothly.



183 **185**

Scheme 3.4 Synthesis of (*E*)-5-(3,4-dimethoxystyryl)-1,3-dimethoxy-2-methylbenzene

Characterisation by ^{1}H NMR confirmed the formation of the *trans*-isomer, whereby a doublet and a multiplet were observed at δ 6.93 and δ 7.02 ppm, respectively, each integrating to 1 H, with a *J*-coupling value of J_{AB} = 16.2 Hz, which is characteristic of the *trans*-ethylenic linkage (HC=CH). Additionally, from the mass spectral data the molecular ion peak of *m/z* = 315, was observed which confirmed the formation of the stilbene, **182**. The next stage was bromination of the 4-Me moiety, in order to incorporate the prenyl moiety.

3.5 Wohl-Ziegler Bromination

α-Bromination of alkyl, allylic and benzylic compounds, have been reported to proceed using a brominating agent, such as bromine [211, 212], *N*-bromosuccinimide (NBS) [213] or bromotrichloromethane ($CBrCl_3$) [214], in the presence of halogenated solvents such as carbon tetrachloride (CCl_4), dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$) or 1,2-dichloroethane (CH_2ClCH_2Cl), with the reaction proceeding under the irradiation of light and/or with heat.

The Wohl-Ziegler bromination reaction [204, 205], is a benzylic or allylic bromination reaction, commonly performed in the presence a stoichiometric quantity of NBS, as a bromine (Br_2) source, which is generated *in situ*, *via* a rapid reaction. A radical initiator, such as UV or AIBN in minute quantities, is required for the homolytic bond cleavage of Br_2, in addition to a halogenated solvent. Carbon tetrachloride is commonly selected as the halogenated solvent of choice, for use at high temperatures as yields of 30 - 87 % have been reported in the presence of CCl_4, due to the halogenated solvent being inert and having very little capability of undertaking free-radical reactions [213].

Furthermore, though NBS is known to be poorly soluble in CCl_4, the progress of the reaction can be visibly identified by the insoluble succinimide product (Figure 3.1) floating at the surface of the solvent [204].

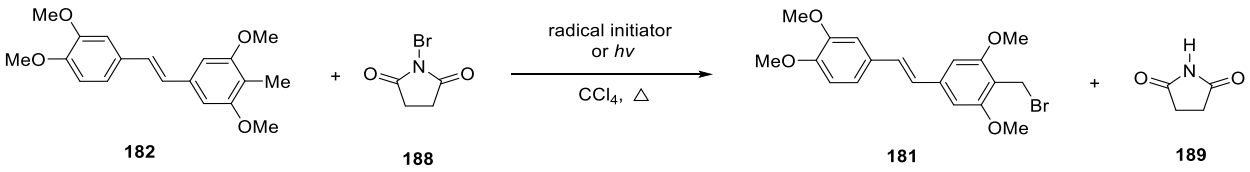


Figure 3.1 Wohl Ziegler Bromination

Although this traditional approach is said to be obsolete [215], the successful preparation of stilbenes *via* the Wohl-Ziegler bromination [204, 205, 213] has been previously reported within the literature [216, 217].

In this study, the radical-initiated bromination of compound, **182**, was performed based on the reaction conditions detailed by Soomro *et al*., [217]; the equivalents of reagents,

effects of irradiation with light, solvent, and temperature effects, were examined (Table 3.1).

First, the Wohl-Ziegler reaction was performed on the stilbene, **182**, in the presence of NBS (Table 3.1; Entry 1), carbon tetrachloride, with the addition of the radical initiators, AIBN and an incandescent light, these conditions gave a very low yield (8 %). However, characterisation by mass spectrometry indicated the presence of the molecular ion peak of *m/z* = 392, and characterisation by ^{1}H NMR, showed the presence of the newly formed CH_2-Br bond, with a peak at δ 4.60 ppm, integrating to 2 H, which is characteristic of the methylene protons, therefore confirming the successful bromination of the 4-Me moiety, within the stilbene skeleton.

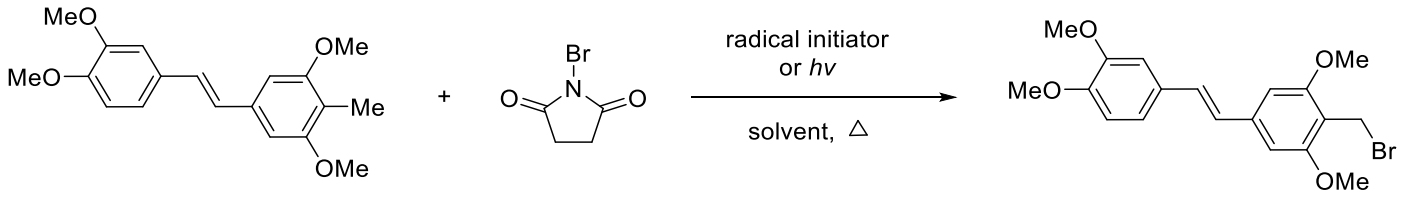
Next, the radical initiated reaction between the stilbene, **182**, NBS, AIBN and carbon tetrachloride, was attempted and in this investigation AIBN was used as the only source of the radical initiator (Table 3.1; Entry 2). This reaction showed an improvement and gave the best yield, albeit still relatively low (19 %), analysis by ^{1}H NMR, indicated the disappearance of the methyl protons at δ 2.10 ppm and the presence of a quartet at δ 4.53 ppm (*J* = 3.2 Hz), which is characteristic of the protons present in a methylene group (CH_2-Br). The presence of the 12 protons present in the four methoxy moieties positioned around the stilbene scaffold, were also observed in their two different proton environments at δ 3.75 ppm and 3.96 ppm, respectively. Although characterisation of the protons within the aromatic region of the spectrum proved exceptionally difficult to perform, due to the noisy baseline, the success of the reaction was confirmed by mass spectrometry, which indicated the presence of a molecular ion peak of *m/z* = 393. In contrast with the literature [229], this reaction indicates the use of an incandescent light is

not required, as the ^{1}H NMR spectrum indicated that the methyl group (Me) had been successfully converted into CH_2-Br, in the presence of the radical initiator (AIBN). However, it is possible that side reactions or decomposition may have occurred, which could offer an explanation to the low yields obtained in this study.

The use of pure water, in the presence of NBS and an incandescent light bulb, has been found to be a benign approach to radical bromination of substituted toluene derivatives[218] and aromatic compounds [219]. The bromination of toluene and xylenes in the presence of bromine and water, under the irradiation of a mercury lamp as the source of light, was additionally reported successful, by Shaw and co-workers [220], furthermore water has been seen to be a suitable alternative solvent, for use radical reactions, compared to the carcinogenic CCl_4 [221].

Unfortunately, the model NBS bromination model reaction, using pure water as an alternative solvent was found to be unsuccessful, with the presence of starting material, **182**, observed by ^{1}H NMR (Table 3.1; Entry 3). It was thought that the temperature the reaction was conducted at 30 $^{\circ}$C, moreover the solubility of NBS in water may be the cause of this reaction been unsuccessful. Nevertheless, as the study had so far shown that the radical initiated NBS bromination, in the presence of CCl_4 was successful, it was decided that the phosphonate could be synthesised *via* the Arbuzov reaction.

Table 3.1 Summary of *N*-Bromosuccinimide bromination reaction conditions



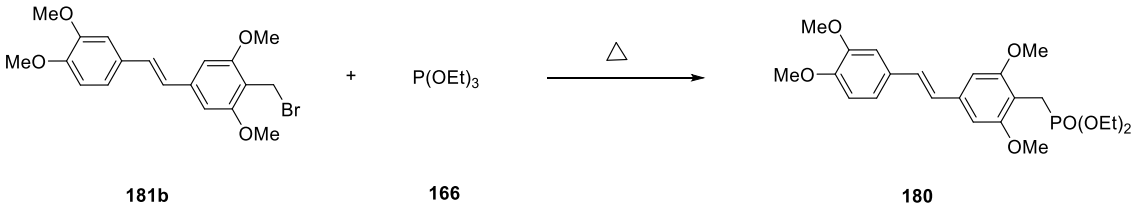
182 **188** **181(a-b)**

Entry	Compound	Solvent	Ratio [stilbene : NBS]	Conditions	% Purity[a]
1	**181a**	CCl_4	1 : 6	78 °C, 24 h, incandescent light, AIBN	19
2	**181b**	CCl_4	1 : 4	78 °C, reflux, 24 h, AIBN	8
3	**-**	H_2O	1 : 1.05	30 °C, 72 h, incandescent light, AIBN	-

[a] Determined by HPLC

3.6 Arbuzov Reaction

Attempts incorporating the phosphonate moiety into the *trans*-stilbene backbone were not successful. The Arbuzov reaction was attempted with the stilbene, **181b**, at a lower temperature (89 °C), in order to avoid decomposition of the product, due to the melting point of the stilbene (98 - 110 ºC) (Scheme 3.5), however characterisation by ^{1}H NMR confirmed the reaction did not go to completion as the presence of both starting materials were detected.



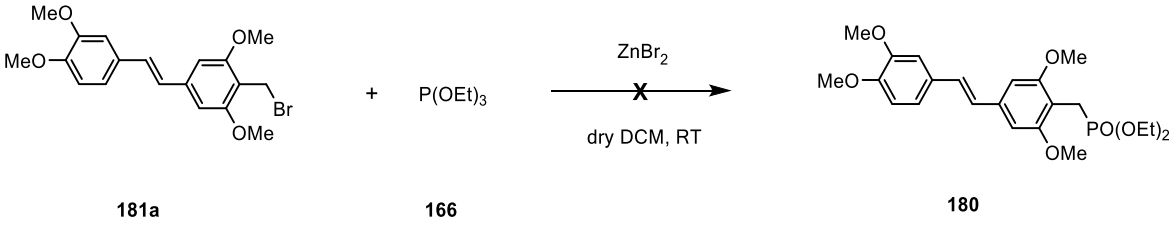
181b **166** **180**

Scheme 3.5 Attempted synthesis of diethyl (*E*)-(4-(3,4-dimethoxystyryl)-2,6-dimethoxybenzyl)phosphonate

Within the stilbene skeleton, the presence of the methylene (CH_2-Br) protons (δ 4.59 ppm) were observed, moreover the CH_2-P bond usually observed at ~ δ 3.00 ppm and large *J*-coupling value ($J_{P\text{-}H}$ ~ 21 Hz) was not detected. Characterisation by mass spectrometry indicated the presence of molecular ion peaks of *m/z* = 393 (^{79}Br) and *m/z* = 394 (^{80}Br), respectively, which are characteristic of the brominated stilbene, **181b**. Therefore suggesting the temperature used in the reaction was not high enough to activate the reaction.

Since the traditional Michaelis–Arbuzov rearrangement was unsuccessful, an adapted Arbuzov reaction reported by Rajeshwaran *et al.,* [188], was attempted whereby the Lewis acid zinc bromide ($ZnBr_2$), was used as a catalyst in order to lower the

temperature needed for the reaction (Scheme 3.6). Characterisation by ^{1}H NMR indicated only the presence of the starting material, **181a**, furthermore the molecular ion peak of the desired product was not observed following analysis by mass spectrometry.



181a **166** **180**

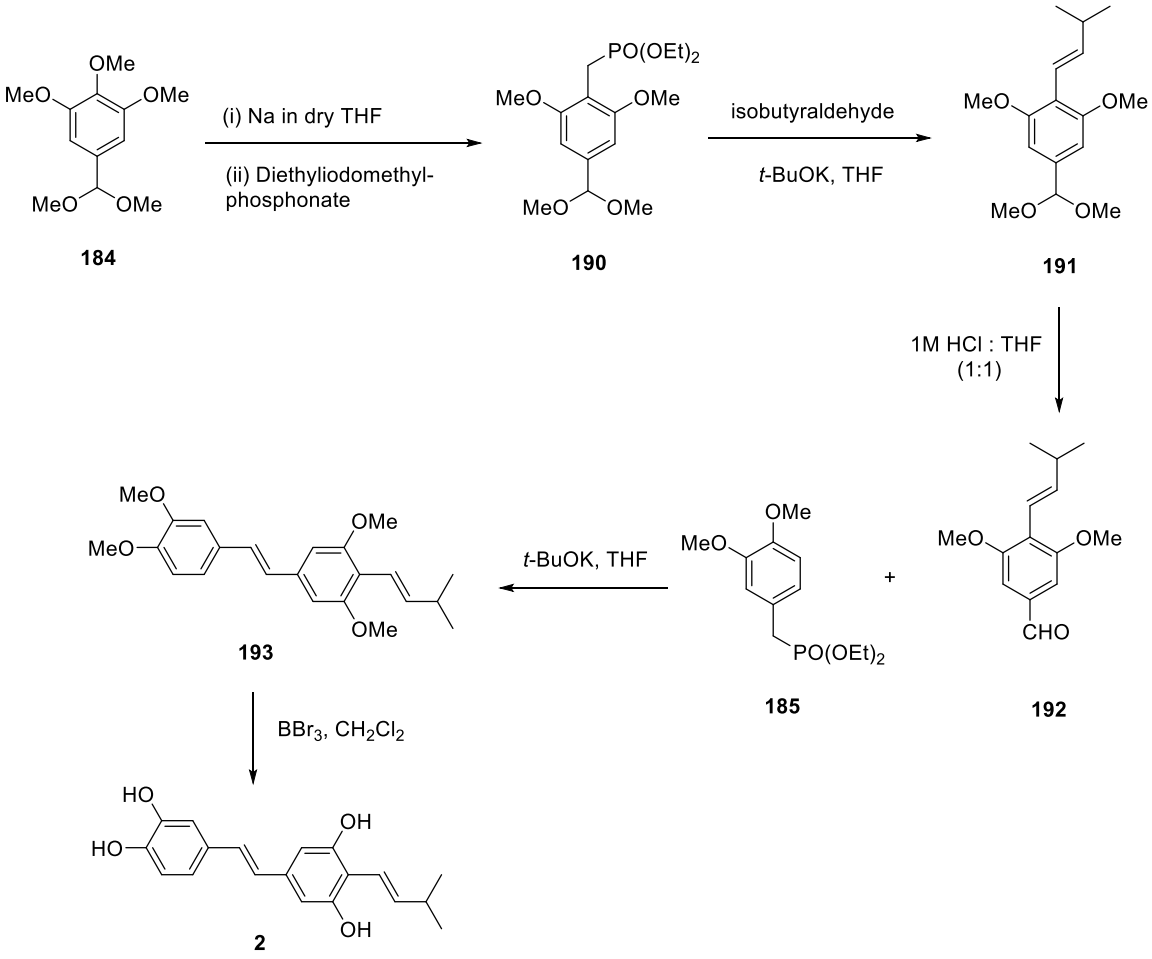
Scheme 3.6 Attempted synthesis of diethyl (E)-(4-(3,4-dimethoxystyryl)-2,6-dimethoxybenzyl)phosphonate in the presence of the Lewis acid catalyst, zinc bromide

It can be argued that an increased equivalent of the Lewis acid could have been used in the reaction, however the failure of the reaction could also be due to the approach of the large triethyl phosphite group, therefore contributing to steric effects and preventing the reaction from proceeding.

3.7 Strategy for the synthesis of arachidin-1: Part III

Having unsuccessfully attempted the synthesis of arachidin-1, **2**, *via* the classical Wohl Ziegler bromination reaction [205, 213], it was thought that the scope of the regioselective demethoxylation of 3,4,5-trimethoxybenzaldehyde dimethyl acetal, **184**, could be investigated further. Therefore with this assumption, an alternative strategy towards the total synthesis of arachidin-1, **2**, was devised, as shown in Scheme 3.7

which additionally provided the advantage of avoiding the previously required NBS brominating step.

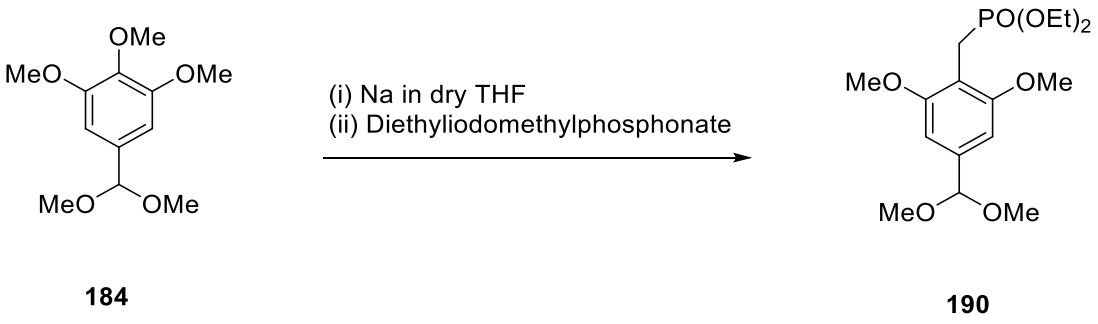


Scheme 3.7 Synthetic strategy for the total synthesis of *trans*-arachidin-1

3.7.1 Regioselective reductive electrophilic substitution with diethyl(iodomethyl)phosphonate

The studies by Azzena *et al.*,[202, 222] have shown the approach, *via* the regioselective demethoxylation of 3,4,5-trimethoxybenzaldehyde dimethyl acetal, **184**, to be an advantageous route to incorporate various alkyl moieties, including methyl, ethyl and butyl groups, into the 4-position of a substituted benzaldehyde using primary alkyl halides [202].

Although it has not been previously reported in the literature, it was envisaged that alkylation with diethyl iodomethylphosphonate, as the electrophilic reagent could conveniently introduce a diethyl phosphonate moiety at the 4-position of the acetal, **184**, (Scheme 3.8).



184 **190**

Scheme 3.8 Regioselective reductive alkylation of 3,4,5-trimethoxybenzaldehyde dimethylacetal using diethyl(iodomethyl)phosphonate

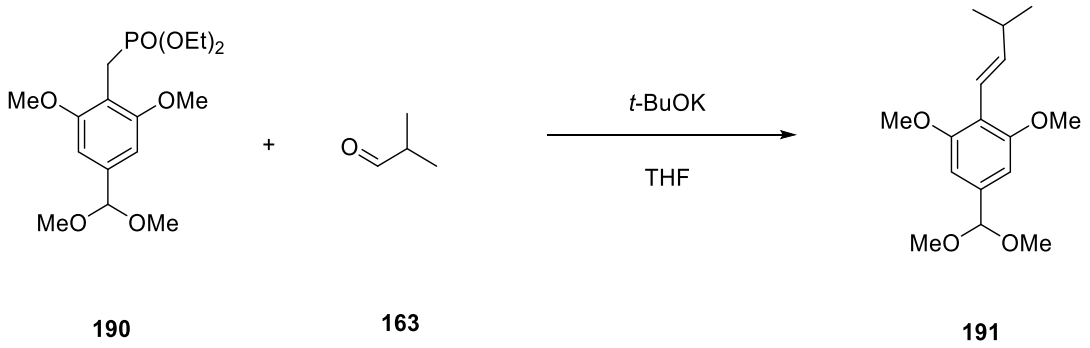
This reaction was attempted in a small scale, with the aim of optimising the reaction once the methodology had been proven successful. Following the regioselective demethylation of the acetal, **184**, in the presence of sodium metal, *via* a two-electron-transfer step of the 4-OMe group, alkylation of the intermediate proceeded by the

addition of the primary alkyl halide diethyl, iodomethylphosphonate (1.5 equiv.) at a low temperature (0 °C), work up gave the alkylated crude acetal product, **190**, in good yield (86 %). Characterisation by the mass spectral analysis, was found to be valuable, as the mass corresponding to the molecular ion (*m/z* = 361) of the desired compound, **190**, was observed. Furthermore, formation of the phosphonate, **190**, was also confirmed by ^{1}H NMR, although the presence of the acetal, **184**, (14 %), was also detected, it is possible that longer reaction times may be required, or optimisation of the reagents may be needed, in order to obtain higher yields.

3.7.2 Prenylation *via* HWE coupling

Once the phosphonate, **190**, was formed, two possible routes were considered for the next step in the methodology, the first option was deprotection of the acetal, **190**, to afford the aldehyde, and subsequent HWE coupling to first form the 3-methylbut-1-enyl side construct the stilbene backbone.

Alternatively, the second option was to incorporate the side chain first, followed by the deprotection of the acetal, **191**, to give the aldehyde, **192**. However it was assumed that should the aldehyde be formed first, isomerisation would occur in the presence of the base during the HWE coupling reaction. Since acetals are known to be stable in the presence of nucleophiles and bases at room temperature [203], it was decided the next step of this methodology would be to incorporate the 3-methylbut-1-enyl moiety (Scheme 3.9).



190 **163** **191**

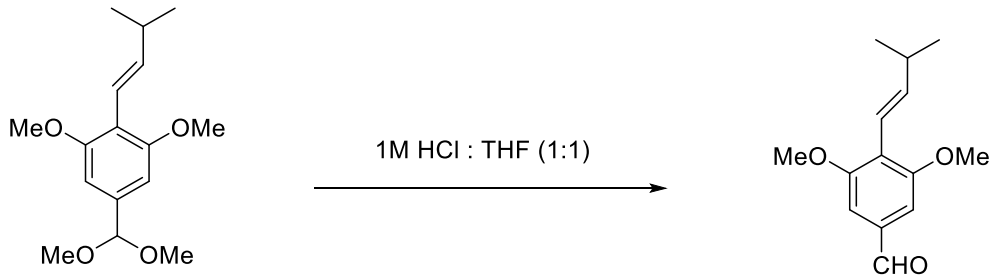
Scheme 3.9 Coupling of diethyl (4-(dimethoxymethyl)-2,6-dimethoxybenzyl)phosphonate with 2-methylpropanal

Treatment of the acetal, **190**, with 2-methylpropanal, **163**, in the presence of *t*-BuOK and THF as the solvent, proceed smoothly to give the desired prenylated acetal, **191**, in good yield (71 %). Formation of the *trans*-alkene moiety was confirmed by ^{1}H NMR, following the success of the reaction, acetal hydrolysis was immediately performed.

3.7.3 Acetal hydrolysis

There were various methods reported for the deprotection of acetals [223, 224], however cleavage of the acetal, **191**, was performed according to the work published by Azzena and co-workers [202], *via* acid catalysed hydrolysis [203]. The acetal hydrolysis proceed by stirring the acetal, **191**, with a solvent system comprising of aqueous hydrochloric acid and tetrahydrofuran in a 1:1 ratio (Scheme 3.10). This approach gave the desired (*E*)-3,5-dimethoxy-4-(3-methylbut-1-en-1-yl)benzaldehyde, **192**, in moderate yield (52 %). Characteristic bands arising from the aldehyde, carbonyl stretch (C=O) were observed from the IR spectrum, with the C=O bands located at

1706 cm^{-1}, furthermore characterisation by mass spectrometry indicated the desired product, **192**, (MW = 234 $gmol^{-1}$), was successfully made as the presence of a molecular ion peak of *m/z* 233 was also observed.



191 **192**

Scheme 3.10 Acid catalysed hydrolysis of the dimethyl acetal

The acetal hydrolysis is known to proceed first by protonation of a methoxy (OMe) moiety, with the acid (HCl), leading to the subsequent loss of methanol, and affording the oxonium ion as the cationic intermediate. Next, the nucleophilic attack towards the electrophilic cation, *via* 1,2-addition results in the formation of the protonated hemiacetal, followed by proton transfer to the adjacent OMe group, leading to the loss of a second alcohol, *via* 1,2-elimination. Lastly deprotonation of the protonated aldehyde to affords the aldehyde (Figure 3.2) [225].

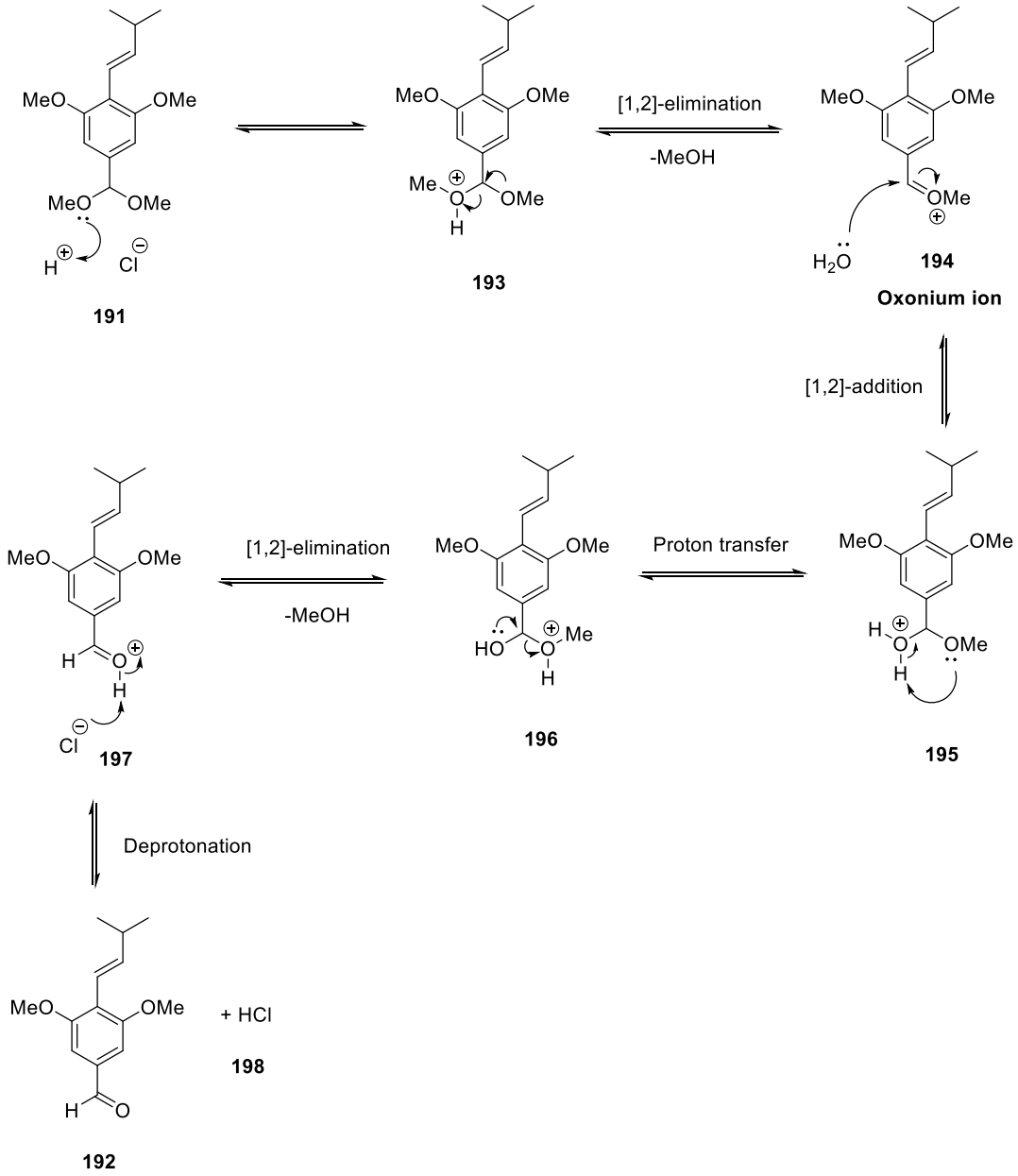
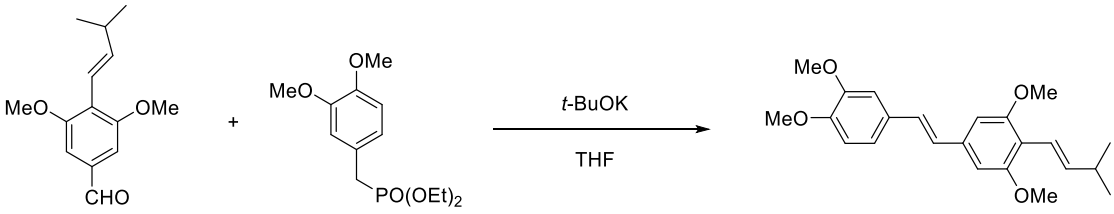


Figure 3.2 Acid catalysed hydrolysis mechanism of (*E*)-5-(dimethoxymethyl)-1,3-dimethoxy-2-(3-methylbut-1-en-1-yl)benzene

3.7.4 Formation of the stilbene *via* HWE coupling

Coupling using 1 equiv. of the previously synthesised 3,4-dimethoxy benzylphosphonate, **185**, with the newly formed aldehyde, **192**, (1 equiv.), in the presence of *t*-BuOK and THF, successfully formed the crude *trans*-alkene in moderate yield (30 %) (Scheme 3.11). Characterisation by mass spectrometry indicated the reaction did not go to entire completion, as the presence of benzylphosphonate, **185**, was also observed on the spectrum (*m/z* = 287), in addition to the molecular ion peak of the desired product, **3**, (*m/z* = 367), however optimised studies are still required in order to obtain higher yields.



192 **185** **3**

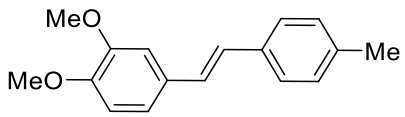
Scheme 3.11 Horner-Wadsworth-Emmons condensation of 3,4-dimethoxy benzylphosphonate and substituted benzaldehyde.

3.7.5 Demethylation model reactions

The use of ethers as protective groups for phenols, have the advantage of being extremely stable in various reaction conditions, with the option of facile cleavage *via* demethylation [203]. This type of reaction is known to proceed using harsh reagents and/or reaction conditions, such as the use of the reagent boron tribromide (BBr_3), in the presence of dichloromethane, at extremely low temperatures [226]. Additionally the

use of pyridine hydrochloride (Py.HCl) at high temperatures [227, 228], is a well-known approach. Alternatively, milder reaction conditions using an aluminium halide-thiol system, have been reported in the literature for the demethylation of methyl ethers of alcohols and phenols [229]. Furthermore methyl ethers are also known to be cleaved in the presence of iodotrimethylsilane (TMSI) [230-232], $AlCl_3$ [233] and $BeCl_2$ [234]. Additionally, sodium thioethoxide in the presence of *N*,*N*-dimethylformamide has also been reported by Feutrill and Mirrington as a powerful reagent, for the cleaving of aryl methyl ethers[235].

With a number of the possible demethylation reagents being expensive to purchase, it was decided to perform model demethylation studies, using the readily available and inexpensive Py.HCl, in addition to boron tribromide (BBr_3), and TMSI. A pure sample of the stilbene, *trans*-3,4-dimethoxy-4'-methylstilbene, **199**, as shown in Figure 3.3, was used, as this stilbene being similar in structure to our target product, **2**, was simple to construct on a large scale. These studies were considered advantageous as it would enable us to determine the most suited reaction conditions and reagent(s), needed for the cleavage of the aryl ethers present around compound, **199**, to be performed.



199

Figure 3.3 Structure of *trans*-3,4-dimethoxy-4'-methylstilbene

Demethylation reactions using the Lewis acid BBr_3 is a reliable and commonly used method within the literature [226], for the cleavage of OMe moieties.

In this work, the established cleavage of methyl aryl ethers using the Lewis acid, boron tribromide was attempted first, this approach led to C-O bond cleavage, to give an alkyl bromide in addition to an alkoxyborane, which affords an alcohol following aqueous workup (Figure 3.4). As a result of this complexation, it is suggested that one mole of BBr_3 should be used for each heteroatom present within the molecule. Within the stilbene backbone, **199**, there were two ethereal oxygens, therefore the use of 4 equiv. of BBr_3 was decided upon.

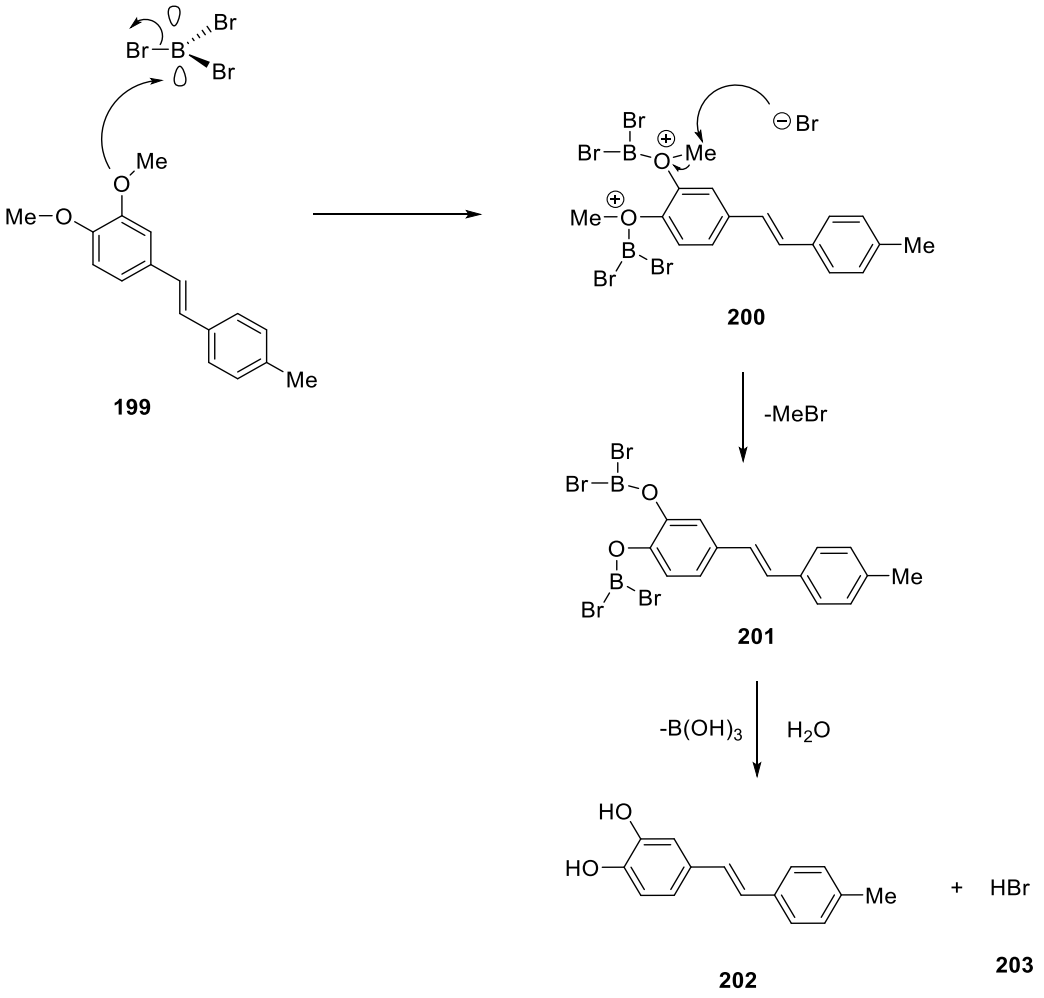
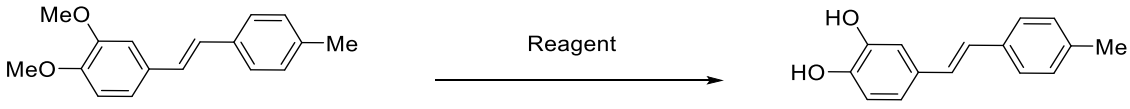


Figure 3.4 Demethylation mechanism using boron tribromide

Within the literature, demethylation reactions using BBr_3 have been reported to proceed at temperatures at or below room temperature, with the use solid CO_2 (-70 °C) or liquid nitrogen (-196 °C), to achieve the temperatures required for the reaction [226]. However, due to the resources available, examining the reaction at temperatures lower than -20 °C was not possible. Nevertheless, when stirring at a temperature of -20 °C, the crude product was obtained after 4 h, following solvent extraction and trituration the desired product, **202a**, was isolated in low yield (44 %).

Table 3.2 Summary of model demethylation reaction conditions



199 **202(a-b)**

Entry	Compound	reagent	Ratio [stilbene : reagent]	Conditions	% Purity[a]
1	**202a**	BBr_3	1 : 4	-20 °C / 4 h	44
2	**-**	Py.HCl	1 : (>10)	> 180 °C / 3 h	-
3	**202b**	Py.HCl	1 : (>10)	141 °C / 1 h	38
4	**-**	TMSI	1 : 2.5	30 °C / 72 h / DCM	-

[a] Determined by ^{1}H NMR

Characterisation by IR analysis indicated a broad peak at υ 3344 cm^{-1}, which is characteristic of the hydroxyl moiety (OH). Furthermore, the protons from the methoxy moieties (OMe) were not observed on the ^{1}H NMR spectrum, therefore signifying the success of the reaction. However, what was observed was a broad

singlet integrating to 2 protons at δ 5.32 ppm, which is characteristic of the OH proton environment. The disappearance of the broad singlet was also observed when a D_2O exchange was performed on the NMR sample. The molecular ion peak of the desired product (*m/z* = 225) was also observed by mass spectrometry, therefore confirming OMe cleavage.

Alternative demethylation methods were additionally explored (Table 3.2), next in the presence of molten pyridine hydrochloride at elevated temperatures of 141 – 200 °C[236]. This reagent has also been reported in the literature, for the demethylation of methyl aryl ethers under solvent free conditions, *via* microwave heating [227]. However, in this study the small scale model demethylation reactions with Py.HCl in excess (> 180 °C) were unsuccessful, as characterisation by ^{1}H NMR showed that decomposition had occurred, therefore suggesting the high temperature required to keep the reagent molten could have disrupted the integrity of the structure. Furthermore due to the raised temperature, the reaction mixture turned into a dark tar-like solid, therefore making it challenging to extract. As a result, the reaction was heated for no longer than 1 h at 141 °C, with intermittent monitoring by TLC (Table 3.2; Entry 3).

Characterisation of the product, by ^{1}H NMR data suggested cleavage of the methyl moieties had been successful, as the proton environments characteristic of the phenolic (OH) protons at δ 5.12 ppm (2 H) were observed. Furthermore characterisation by mass spectrometry also confirmed cleavage, as a molecular ion peak of *m/z* = 226 was observed. Although demethylation using pyridine hydrochloride was successful in the model reaction, the ^{1}H NMR also confirmed the presence of a mixture of compounds; the desired product, **202c**, (38 %), but also the

presence of the starting material, **199**, (18 %), and residual solvent ethyl acetate (44%). Furthermore the issues with regards to using elevated temperatures, and maintaining the temperature within the reaction flask, in order to prevent the salt from returning back to its crystalline state, made this method an unattractive one to use.

Next, the demethylation was explored using TMSI (2.5 equiv.), this specific molar equivalent was chosen as according to the work by Tamura and co-workers (245), the cleavage of aryl ethers was found to be successful when this ratio was used. This model study therefore proceeded with 1 equiv. of the stilbene, **199**, and TMS-iodide (2.5 equiv.), dissolved in DCM (Table 3.2; Entry 4). In accordance with the literature the demethylation reaction using TMSI was found to proceed slowly [232, 237], as monitoring by TLC over 72 h did show the slow progress of the reaction. Characterisation of the dark brown oil, by ^{1}H NMR indicated the presence of a mixture of compounds comprising of both OH and OMe groups, around the stilbene backbone, as the proton environments at δ 3.89 ppm and 3.93 ppm, which are characteristic of the methoxy moieties were observed, therefore suggesting the compounds present were those shown in Figure 3.5. The mixture of products also resulted in difficulties in separating the desired product.

202c **204**

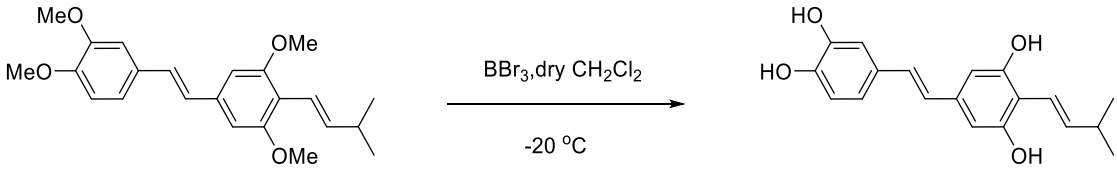
Figure 3.5 Structure of (E)-2-methoxy-4-(4-methylstyryl)phenol and (E)-2-methoxy-5-(4-methylstyryl)phenol

Although TMSI is known to be an effective reagent in the regioselective mono *ortho*-demethylation of less accessible methoxy moieties, the failure of the reaction was likely due to TMSI being a less reactive reagent, compared to alternative demethylating reactions using reagents such as BBr_3 [232], it was therefore decided to explore the use of the reagent BBr_3 in our next stage of study.

3.7.6 Demethylation of 5-((*E*)-3,4-dimethoxystyryl)-1,3-dimethoxy-2-((*E*)-3-methylbut-1-en-1-yl)benzene

The demethylation reaction, in the presence of milder reagents such as BBr_3 has been reported to react faster compared to alternative reagents such as TMSI [232, 237]. Based on this model study the Lewis acid, BBr_3 was the only reagent to successfully cleave the aryl methyl ethers with good yield, compared to the other two reagents examined. The choice of using BBr_3 was also decided on, based on the rationale that the reaction conditions could be controlled easily, in comparison to demethylation reactions using Py.HCl.

Using identical reaction conditions as the model study, whereby 5 equiv. of BBr_3 and the stilbene, **3**, (1 equiv.) were stirred at -20 °C, gave the crude in low yield (47 %) (Scheme 3.12). Analysis by mass spectrometry indicated the desired compound, **2**, had been successfully synthesised, as a molecular ion peak of (*m/z* = 312) was observed, however optimised studies are still required in order to obtain arachidin-1, **2**, in quantitative yields.



3 2

Scheme 3.12 Demethylation using boron tribromide

3.8 Summary

The synthesis of arachidin-1, **2**, was explored first *via* the Wohl Ziegler bromination of the synthesised stilbene (*E*)-5-(3,4-dimethoxystyryl)-1,3-dimethoxy-2-methylbenzene, **182**, using NBS as the brominating source. A range of conditions were attempted, including the use of the benign solvent, water which was found to be unsuccessful. In order to synthesise the target compound, an alternative route was envisaged, by means of the regioselective demethoxylation of 3,4,5-trimethoxybenzaldehyde dimethyl acetal, **184**, and subsequent alkylation with diethyl iodomethylphosphonate. This reaction proved successful, which enabled the incorporation of the side chain *via* the classic HWE reaction, in the presence of 2-methylpropanal, **163**. Following acetal hydrolysis of the dimethyl acetal, **191**, the stilbene backbone was successfully constructed, once again using the HWE coupling reaction between the aldehyde, **192**, and 3,4-dimethoxy benzylphosphonate, **185**. The small scale model demethylation reactions found boron tribromide to be the most suited reagent for the cleavage of the methyl ethers, and when demethylation was performed on the stilbene, **3**, analysis by mass spectrometry indicated that the reaction was successful, and confirmed the formation of the target compound, arachidin-1, **2**.

Chapter Four

4. Synthesis of resveratrol analogues: Part I

4.1 Strategies to the synthesis of resveratrol analogues – Part I

An additional aim of this work, was to investigate and develop methods towards the synthesis of novel resveratrol analogues. Although various potential analogues could have been made, derivatives possessing methoxy or sulfonamide moieties were of interest, as according to the literature the presence of these functional groups have been found *in vitro,* to display comparable or increased chemopreventative and/or chemotherapeutic properties, compared to resveratrol, **1**, [164-167].

Notably, the polymethoxy analogues of resveratrol whereby the hydroxyl groups have been replaced with polymethoxy moieties around the stilbene scaffold, are of interest as these compounds have been reported to offer increased lipophilicity in addition to exhibiting anticancer activity. For instance, both natural and synthetic analogues of resveratrol; including MR-3, **205**, MR-5, **124**, DMU-212, **63**, and Combretastatin A-4, **206**, (Figure 4.1) have been reported to prevent cancer growth in several cancer cell lines[167, 238-243].

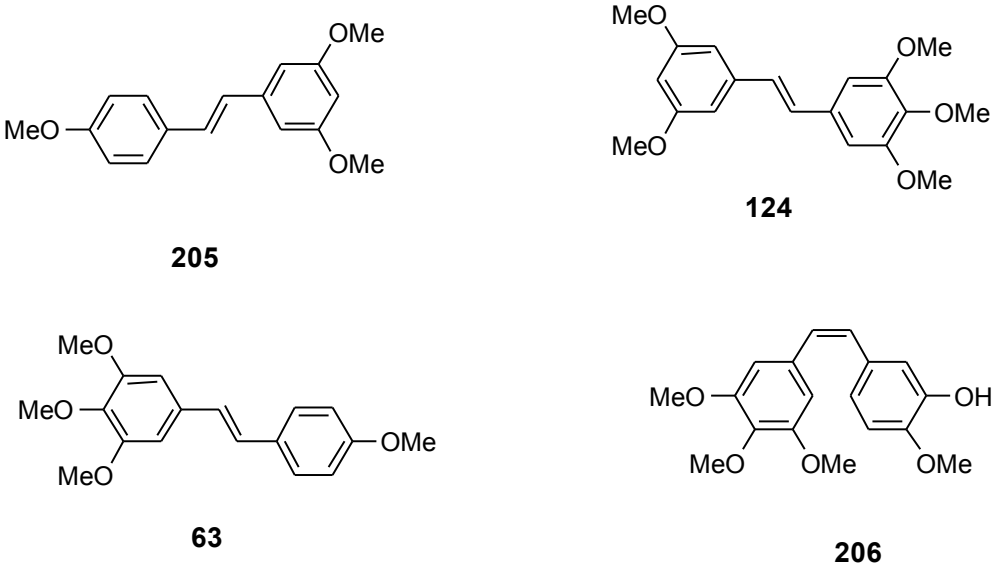


Figure 4.1 Chemical structure of methoxy analogues of resveratrol

The stilbene, MR-5, **124**, has been found to display increased anti-proliferative effects, compared to both resveratrol, **1**, and its methoxy derivatives [166]. Further studies have suggested that not only does the presence of additional methoxy moieties increase the compound's activity towards apoptosis, but importantly the presence of the 3,4,5- trimethoxy substitutions, the *trans*-stilbene backbone, and the presence of a 4'-OMe moiety on the stilbene backbone have been suggested to be essential for retaining the anticancer activity of these analogues [166, 244].

The construction of synthetic polymethoxy stilbenes in the form of MR-5, **124**, [245-247] and related analogues [240] have been described in the literature, however the synthesis of polymethoxy analogues of resveratrol, possessing either an aliphatic side chain or a prenyl moiety, to our knowledge has not yet been explored.

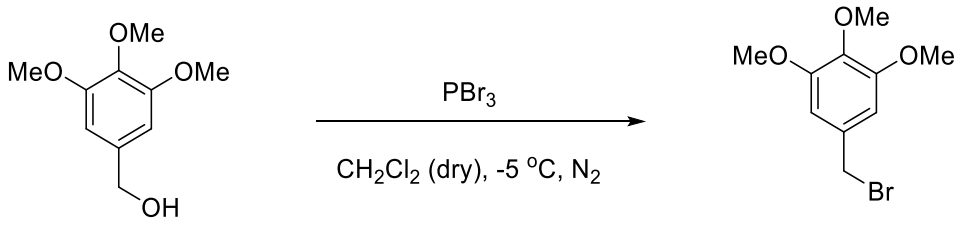
In this chapter, the aim of this phase of work was to synthesise resveratrol analogues, by incorporating a side chain into the polymethoxy-stilbene backbone, with the aim of improving the anti-cancer properties. The Horner-Wadsworth-Emmons (HWE)

reaction has been proved to be a simple and versatile reaction in the formation of the stilbene backbone, therefore this coupling reaction was used to construct the *trans*-stilbene backbone, using diethyl 3,4,5-trimethoxybenzylphosphonate, **209**, and 3,5-dimethoxybenzaldehyde **211**. Next the regioselective formylation using the Lewis acid ($TiCl_4$), as detailed by Garcia *et al.,* [248], would allow the addition of a formyl moiety unto the stilbene skeleton and finally enable the incorporation of the side chain *via* a non-catalytic coupling reaction, would afford the target compound.

4.2 Synthesis of diethyl 3,4,5-trimethoxybenzylphosphonate

The first stage of the synthesis was the formation of 5-(bromomethyl)-1,2,3-trimethoxybenzene, **208**, the synthetic procedures available for the preparation of alkyl halides from alcohols are vast. However most methods detailed in the literature involve the conversion of an alcohol into the corresponding halide, in the presence of reagents; such as phosphorus halides [210, 249], triphenylphosphine [250, 251], 2,4,6-trichloro[1,3,5]triazine in *N*,*N*-dimethyl formamide, [252], or thionyl chloride [253]. Other examples within the literature report the use of thiols, as possible alternative precursors to alcohols [254], although these reagents facilitate the direct conversion of alcohols to alkyl halides, the reaction conditions employed for some of these methods can be quite extreme. It was therefore decided that the substituted benzyl bromide would be prepared using phosphorus tribromide, to convert the primary alcohol, 3,4,5-trimethoxybenzyl alcohol, **205**, into 5-(bromomethyl)-1,2,3-trimethoxybenzene, **208**. Under the reaction conditions, shown in Scheme 4.1, the formation of the phosphorus ester and subsequent nucleophilic substitution (S_N2) proceeded smoothly, to afford the

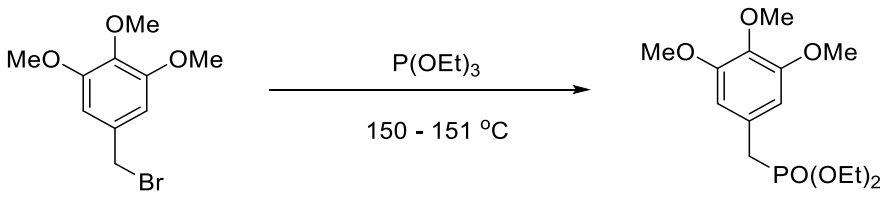
desired compound, **208**, with an isolated yield of 97 %. Due to the lack of stability displayed by the benzyl bromide, **208**, [210] the product was immediately used for the subsequent Michaelis-Arbuzov reaction, following full characterisation.



207 **208**

Scheme 4.1 Synthesis of 5-(bromomethyl)-1,2,3-trimethoxybenzene

Having formed the benzyl bromide, **208**, the conversion into the phosphonate was attempted, using the traditional Michaelis-Arbuzov reaction (198, 201). The preparation of the benzylphosphonate, **209**, from 5-(bromomethyl)-1,2,3-trimethoxybenzene, **208**, (Scheme 4.2) also proceeded smoothly with a high % purity obtained (90 %). However, it is thought that due to the large scale of the reaction (39 g), had sufficient time been given to the reaction, quantitative yields would have been obtained from the reaction, as the presence of triethyl phosphite (10 %) was also detected by ^{1}H NMR.



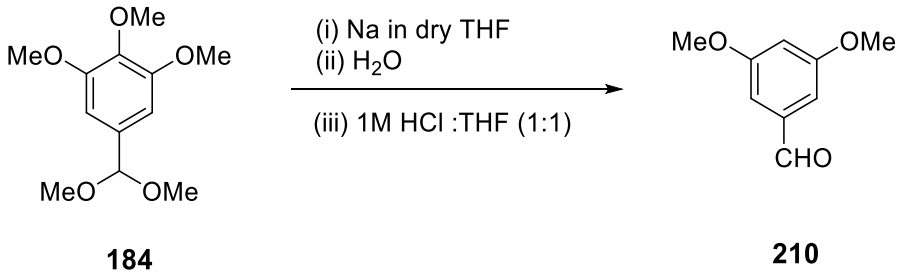
208 **209**

Scheme 4.2 Synthesis of diethyl 3,4,5-trimethoxybenzylphosphonate

The formation of the new CH_2-P bond was confirmed by ^{1}H NMR, whereby a doublet was observed at δ 2.70 ppm, integrating to two protons (CH_2). Additionally a large $^2J_{PH}$ value was calculated (J = 21.4 Hz), which was characteristic of the geminal coupling between ^{31}P and ^{1}H. Furthermore, based on the mass spectral data the molecular ion peak (m/z = 319) of the desired compound, **209**, was also observed. As the results proved the formation of the phosphonate, **209**, was successful, the next step of the methodology was to synthesise the aldehyde, **210**, which would also be used for the HWE coupling.

4.3 Synthesis of 3,5-dimethoxybenzaldehyde

Next the benzaldehyde, **210**, was synthesised from 3,4,5-trimethoxybenzaldehyde dimethyl acetal, **184**. The previous work by Azzena and co-workers [202], offered a route to the highly regioselective demethoxylation of the acetal, **184**, *via* cleavage of the aromatic C-O bond present in the methoxy group, by electron transfer in the presence of sodium metal [222]. As detailed in Section 3.2, amendments to the procedure were made, these included the type of sodium used, for instance sodium metal pellets were replaced by sodium, 30-35 wt % dispersion in wax, in order to increase the surface area of the metal, therefore avoiding the problems of residual metal within the reaction mixture, due to the metal being used in excess and the need to decant the mixture into a clean vessel, before performing acetal hydrolysis (Scheme 4.3).



184 **210**

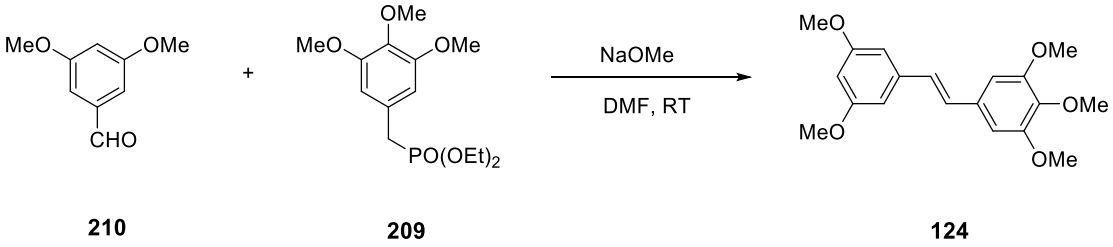
Scheme 4.3 Synthesis of 3,5-dimethoxybenzaldehyde

Characterisation of the isolated product (100 %), were consistent with the literature [202], and formation of the aldehyde, **210**, was confirmed by ^{1}H NMR, whereby a singlet at δ 9.80 ppm, integrating to one proton was observed, which was characteristic of the aldehyde (CHO) moiety. Additionally, two identical singlets at δ 3.74 ppm and δ 3.75 ppm, were observed each peak integrating to three protons, therefore confirming the presence of the two OMe moieties. More importantly multiplets at δ 6.60 ppm, integrating to one proton and at δ 6.91 ppm, of which integrated to two protons were also observed, indicating the presence of three protons around the aromatic ring, and confirming that the regioselective demethoxylation of the 4-OMe group had successfully taken place.

4.4 Coupling of aldehyde with diethyl benzylphosphonate

Next coupling of the aldehyde with the phosphonate to form the desired *trans*-stilbene, **124**, the HWE reaction conditions, previously employed in Chapter 2 were used in this methodology to give the crude product, **124**, in a high yield (72 %), however following recrystallization and characterisation by ^{1}H NMR the yield of the

trans-stilbene, **124**, was reduced to 39 % (Scheme 4.4). When compared to the literature [149], the yield of the pure product obtained in this work was considerably lower than that reported in the literature (88 %), although the methodology described in the literature was different. However, the reduction in yield was possibly due to the less polar solvent (ethanol) used in the purification process, it can therefore be concluded that the use of a more polar solvent, namely methanol would have given a higher % yield.



210 **209** **124**

Scheme 4.4 Synthesis of 3',5',3,4,5-pentamethoxy stilbene

Nonetheless, subsequent optimisation of reactions were performed, whereby the inexpensive 3,5-dimethoxybenzaldehyde, **210**, was purchased and used for the HWE reaction, on a large scale. Recrystallization of the isolated product using methanol gave the *trans*-stilbene, **124**, in excellent yield (89 %), the pure product was found to have a similar melting point value (132 – 136 °C) to that of the literature (135 ºC) [249, 301].

4.5 Formylation of substituted *trans*-stilbene

In order to incorporate a side-chain into the stilbene scaffold, it was envisaged that a formylation reaction would allow us to introduce a formyl group (-CHO) into the pentamethoxy-stilbene backbone, **124**, (Figure 4.2). The literature provides a number of ways to perform aromatic formylation reactions, *via* electrophilic aromatic substitution; these include Rieche formylation, in the presence of dichloromethyl methyl ether [255], Vilsmeier-Haack reaction using the electrophilic chloroiminium salt [256, 257], the Reimer-Tiemann reaction [258, 259], using the electrophilic chloroiminium salt and the use of hexamethylenetetramine in the Duff reaction [260, 261]. The formylation of aromatic compounds has also been reported *via* the Sommelet reaction [262] the Gattermann [263-265] and Gattermann-Koch approach [266], however, these methods are known to afford low yields, and often require harsh reaction conditions. On the other hand, the Rieche formylation presented itself as an attractive route, as within the literature it is commonly used with sterically hindered compounds [248, 267], and therefore was considered to be an plausible reaction to use with the sterically hindered polymethoxy-stilbene substrate, **212**.

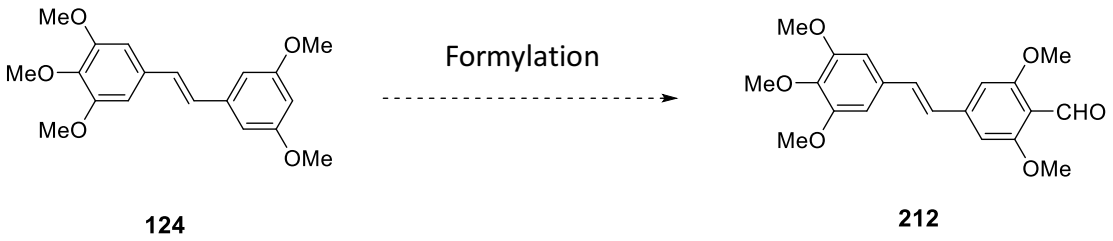
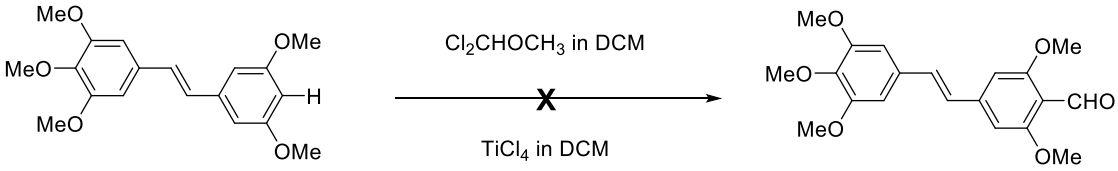


Figure 4.2 Proposed formylation of 3',5',3,4,5-pentamethoxy stilbene

The reaction was performed using dichloromethyl methyl ether (1.4 equiv.), in the presence of 6 equiv. of the Lewis acid, titanium(IV) chloride (Scheme 4.5). The reaction temperature was kept as low as possible during the addition, as studies have indicated at higher temperatures (> 0 °C), the yield obtained can often be low, as a result of side reactions occurring simultaneously with the formylation reaction, whereby the dichloromethyl methyl ether is decomposed [268].



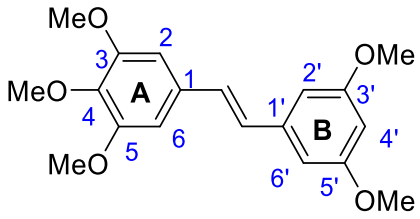
124 **212**

Scheme 4.5 Attempted formylation of 3',5',3,4,5-pentamethoxy stilbene

Characterisation by ^{1}H NMR indicated the desired product was not obtained, surprisingly analysis of the ^{1}H NMR spectrum suggested that whilst formylation at the *ortho* position (between the 3', 5'-dimethoxy groups) did not occur, di-formylation however had taken place. Additionally, the mass spectral analysis indicated the presence of a molecular ion peak of *m/z* = 387, which suggests that the compound made was a 3,4,5,3',5'-pentamethoxystilbene, **213**, possessing two aldehyde moieties within its structure, and had a molecular weight of 386 gmol^{-1}.

On the ^{1}H NMR spectrum two singlets; at δ 10.43 ppm and 10.52 ppm, were also observed which were characteristic of aldehyde protons, thereby indicating the presence of two CHO groups on the aryl ring. The shielded peak (δ 10.43 ppm), due to the three OMe moieties, indicated that the aldehyde may be positioned on ring 'A' of

the stilbene skeleton (Figure 4.3). Once one formyl group had substituted in the aromatic ring, it was unlikely that further substitution would occur on the same ring as electronically, it would be deactivated, therefore not allowing further substitutions in that ring [267].



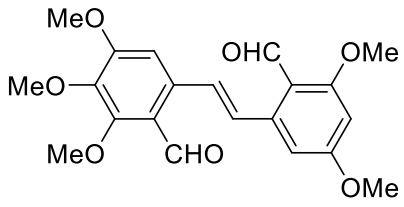
124

Figure 4.3 Annotated structure of 3',5',3,4,5-pentamethoxy stilbene

Looking at the OMe peaks on the ^{1}H NMR spectrum, five singlets within the region of δ 3.89 ppm - δ 4.03 ppm, were observed therefore suggesting the five methoxy groups around the stilbene skeleton were in different environments. Similarly, this was also observed on the ^{13}C NMR spectrum, whereby three peaks at δ ~ 55 ppm and two peaks at ~ 61 ppm, respectively were identified. If formylation had occurred at the desired position (position 4'), as electronically the *meta*-methoxy groups adjacent to the 4'-position is believed to activate the 4'-H (Figure 4.3), making it more reactive for electrophilic aromatic substitution to occur, we would therefore have seen the symmetry within the molecule remain, with the three peaks on the spectrum representing the methoxy groups.

The two protons present in the alkene linkage between the two aromatic rings, are characteristically observed in the ^{1}H NMR spectrum as two doublets, however what

was observed was one peak, integrated to two protons which appeared to be coupling, thereby suggesting the alkene protons were possibly in indistinguishable chemical environments. Following an expansion of the spectrum, doublet of doublets with a *J*-coupling of J = 16.0 Hz, were observed which are characteristic of coupling constant for *trans*-alkenes. This peak was observed downfield at δ 7.9 ppm, therefore suggesting that the product synthesised was likely to be 2,2'-diformyl-3,4,5,3',5'-pentamethoxystilbene, **213**, (Figure 4.4). However, further structure determination techniques by 2D NMR (NOESY), in the future will be performed in order to determine the positions of the formyl groups within the stilbene backbone.



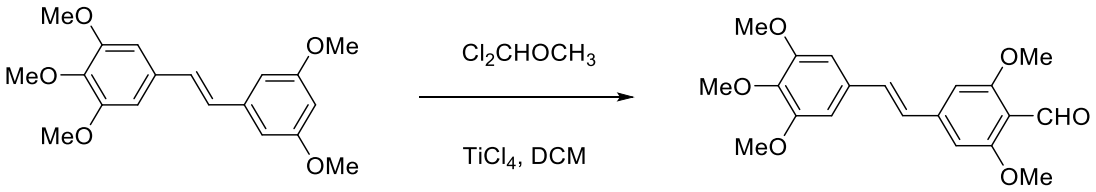
213

Figure 4.4 Chemical structure of di-formyl stilbene

Cresp and co-workers reported the formation of two products, when titanium(IV) chloride ($TiCl_4$) and dichloromethyl methyl ether were reacted with phenols, resulting in a major and minor product, in the presence of both hydroxyl- and methoxy-rich aromatic compounds [269]. Similarly, Yakubov and co-workers also reported the occurrence of di-formylation, *via* the Rieche formylation, when using Lewis acids including $TiCl_4$ and $AlCl_3$, respectively, with dichloromethyl methyl ether, in the presence of sterically hindered arenes, such as mesitylene and durene [267].

Further studies were performed in order to optimise the reaction conditions and the equivalent of $TiCl_4$ used, in order to successfully incorporate an aldehyde moiety into the stilbene backbone (Table 4.1). Notably, the Lewis acid in excess (6 equiv.), in addition to the reaction proceeding at very a low temperatures (-10 to -15 °C) for a duration of 2 h, gave the desired formyl compound, **212a**, in moderate yield (50 %). The Lewis acid, $TiCl_4$ was chosen in excess of 6 equivalents, so that the metal halide could coordinate with the neighbouring methoxy groups positioned at 3,4,5- of the stilbene, **124**, and the reaction time was kept to a minimum to prevent other side reactions from occurring. This approach was found to be ideal, however further work towards optimising the formylation reaction is required, in order to improve the % yield.

Table 4.1 The formylation reaction of *trans*-pentamethoxy stilbene with titanium tetrachloride



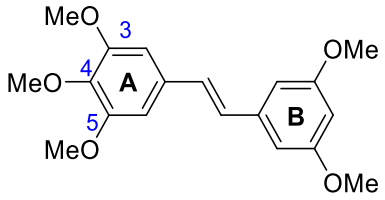
124 **212a**

Entry	Compound	Equivalents of $TiCl_4$	Temperature (ºC)	Time (h)	Yield [a] (%)
1	**212a**	6	-15 to -10	2	50
2	-	6	-10 to RT	8	-
3	-	5	-10 to -5	3	-

[a] Determined by ^{1}H NMR

On the other hand when 6 equiv. of the Lewis acid was used at a temperature range of -10 to RT, the reaction was unsuccessful. It is possible that the length of the reaction time (8 h) and the temperature of the reaction mixture for that length of time, may have led to decomposition (Table 4.1), as the product obtained could not be identified by NMR, nor by mass spectral analysis. Additionally, when 5 equiv. of $TiCl_4$ was used, only the presence of the starting material, **124**, was detected by ^1H NMR, therefore suggesting that more than 5 equiv. of the Lewis acid is required in the formylation reaction with the stilbene, **124**.

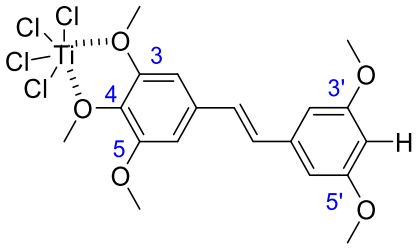
The findings from the optimisation studies, are in line with the work developed by Garcia *et al.,* whereby it has been reported that the *ortho*-formylation of polysubstituted aromatic compounds, in the presence of dichloromethyl methyl ether and $TiCl_4$ can regioselectively occur, affording high yields and most importantly without the event of di-formylation taking place [248]. According to Garcia *et al.,* the high regioselectively of this reaction is suggested to be due to the metal halide coordinating with each heteroatom present on the stilbene skeleton. A number of studies have also supported the rationale behind the use of the Lewis acid in excess, in order to ensure the coordination with the heteroatom. This would therefore hinder substitution at ring 'A' (Figure 4.5) and increase the electrophilicity of the dichloromethyl methyl ether, as well as allow electrophilic aromatic substitution to take place, resulting in the formation of the formyl moiety at the vacant *ortho*-position on ring 'B' [248].



124

Figure 4.5 Structure of 3',5',3,4,5-pentamethoxy stilbene

This same theory could offer an explanation, to why addition of the formyl group did not occur, at position 4'- on the stilbene backbone. It is possible, that because of the excess $TiCl_4$ (6 equiv) used, there was an increased chance of $TiCl_4$ binding to more than one methoxy functional group, therefore hindering substitution. This is illustrated in Figure 4.6, which shows the structure of compound, **214**, and the binding of $TiCl_4$ to more than one methoxy moiety, thereby hindering electrophilic aromatic substitution on position 4' [270].

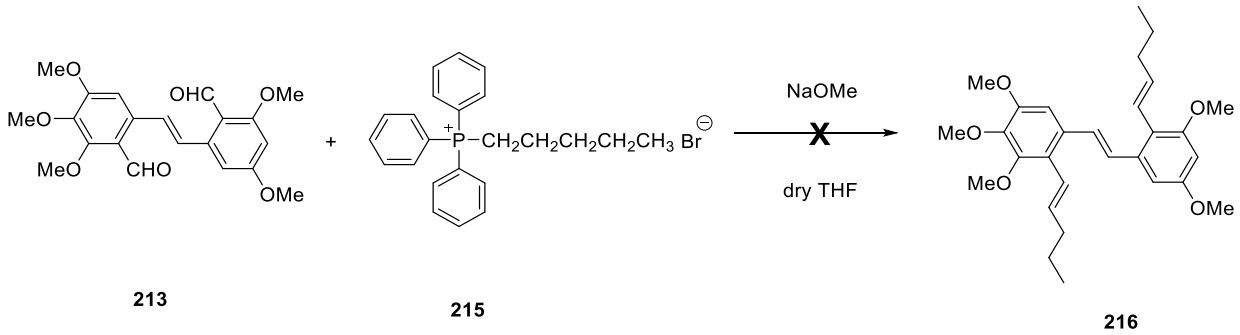


214

Figure 4.6 Coordination of the Lewis acid, $TiCl_4$, with methoxy moiety

4.6 Coupling reaction

The formation of compound, **213**, presented an opportunity to perform a coupling reaction, in order to determine if a side chain could be incorporated unto the stilbene backbone (Scheme 4.6).

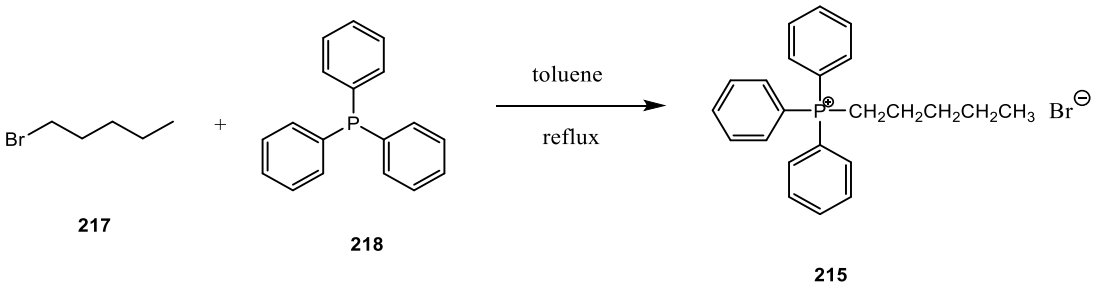


Scheme 4.6 Attempted synthesis of stilbene derivative *via* the Wittig reaction

As detailed in Chapter 2, the HWE reaction with an aliphatic phosphonate was found to be unsuccessful, therefore the Wittig reaction was chosen as an alternative method for the formation of the carbon-carbon double (C=C) bond. The utilisation of a phosphonium ylide was considered to be favourable, although it has been reported that the use non-stabilised ylides, kinetically would result in the formation of the less stable *cis*-alkene, Maryanoff *et al.,* additionally stated that the use of aromatic aldehydes in the presence of non-stabilised ylides, may result in the formation of *trans*-alkenes, in the presence of a strong base [103].

The first step in the reaction was to form a phosphonium salt, which could then be deprotonated to form the ylide. Treatment of triphenylphosphine with the alkyl halide, 1-bromopentane, under reflux in the presence of toluene, gave the desired alkyltriphenylphosphonium salt (Scheme 4.7), albeit in low yield (26 %). Nonetheless,

formation of the desired product, **215**, was confirmed by mass spectral analysis, as the presence of a molecular ion peak of *m/z* = 332 was observed.



217 **218** **215**

Scheme 4.7 Synthesis of pentyltriphenylphosphonium salt

Next, coupling with the diformylstilbene, **217**, was attempted in the presence of sodium methoxide, in order to form the phosphonium ylide, *via* deprotonation of the α-carbon in the alkyltriphenylphosphonium salt. However, the desired product was not detected by ^{1}H NMR, what was observed were the starting materials. It is possible the ylide may have been too bulky to couple with the aldehyde moieties, on the other hand the base used may have also played a crucial part in the unsuccessful deprotonation of the α-carbon positioned on the phosphonium salt.

After searching the literature, the work by McNulty and Das [96], offers an alternative and benign approach to the synthesis of *trans*-alkenes, with high stereocontrol *via* the Wittig reaction. The use of these reported semi-stabilised ylides, derived from trialkyl benzylphosphonium salts and sodium hydroxide, in the presence of water, albeit with limited applicability as only small alkyl functionalities (trimethyl and triethylphosphosphine oxides) are highly soluble in water. This alternative route is an approach to explore, as the synthesis of *trans*-stilbenes, including DMU-212, **63**, have already been successfully attempted *via* this approach.

4.7 Summary

The polymethoxy stilbene backbone, **124**, was synthesized using diethyl 3,4,5-trimethoxybenzylphosphonate, **209**, and the commercially available 3,5-dimethoxybenzaldehyde, **211**, *via* the HWE reaction, under mild reaction conditions. Formation of the substituted benzylphosphonate, **209**, proceeded smoothly *via* the S_N2 reaction between triethyl phosphite and 3,4,5-trimethoxybenzyl bromide, **208**. Coupling of the phosphonate, **209**, with the benzaldehyde, **211**, gave the desired stilbene in excellent yield (89%), when the commercially available aldehyde, **211**, was used. Attempts of the formylation reaction with the substituted stilbene, using dichloromethyl methyl ether and various molar equivalents of titanium(IV) chloride and reaction temperatures were unsuccessful, as di-formylation on the stilbene skeleton was believed to have occurred, in accordance with the observations by Yakubov *et al*., [267] and Cresp *et al.,* [269].

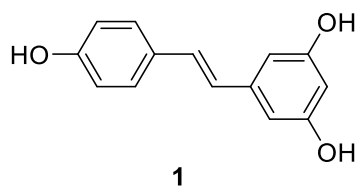
Attempts to incorporate a side chain into the diformylstilbene, **213**, *via* the HWE reaction, under mild conditions were made however the use of an unstabilized phosphonate appeared to be unsuccessful under these reaction conditions. The Wittig reaction was subsequently attempted using a triphenyl-derived phosphonium ylide, which was prepared by heating 1-bromopentane, **217**, with triphenylphosphine, **218**, under reflux, albeit in poor yield (26 %). Coupling of the alkyltriphenylphosphonium salt, **215**, with the aldehyde, **213**, *via* the Wittig reaction was also found to be unsuccessful.

Chapter Five

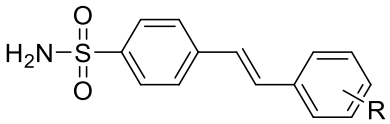
5. Synthesis of resveratrol analogues: Part II

5.1 Strategies to the synthesis of resveratrol analogues – Part II

Resveratrol, **1**, has been reported to induce apoptosis in a number of cancer cell lines, including the human pancreatic [271], and lung cancer cell lines [165]. Furthermore, as detailed in Chapter 1, various resveratrol analogues have been extensively studied within the literature, in order to find a potential cancer chemopreventative and/or cancer chemotherapeutic agent [166]. In 2002, Yang and co-workers [6] reported the synthesis of novel stilbenesulfonamide analogues possessing a primary sulfonamide (SO_2NH_2) moiety, in place of the 4'-OH moiety in *trans*-resveratrol, **1**, (Figure 5.1), even though the published methodology towards the synthesis of stilbene benzenesulfonamides was long (7-8 steps), and limited to the synthesis of primary sulfonamides, these compounds were found to display both increased activity against several cancer cell lines, when compared to resveratrol, **1**.



1



125

R = H, F, NMe_2, OH, OMe

Figure 5.1 Structure of resveratrol and *trans*-stilbene benzenesulfonamides

The sulfonamide functional group (SO_2NH_2) has been widely reported in the literature, and suggested to be implicated in the potent antitumour activity of a number of anticancer drugs such as the compound E7010, which is currently in clinical trials as an anticancer drug [164, 169-171, 174].

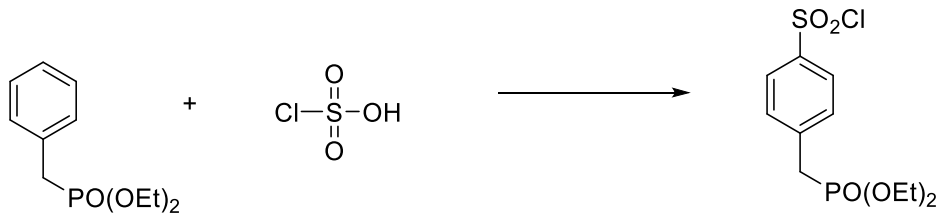
The discoveries from these studies indicates a need for further examination of novel stilbenesulfonamides, in order to enhance their selectivity and activity towards various cancer cell lines. In this chapter, the aim of this phase of work was to design and develop a versatile methodology, which would enable the synthesis of novel *trans*-resveratrol analogues, in the form of stilbene benzenesulfonamides, **125**.

A three step methodology towards the synthesis of stilbenesulfonamides, *via* the HWE reaction has been designed, it was believed that this approach would enable the synthesis of stilbene benzenesulfonamide analogues of which comprised of primary, secondary and tertiary sulfonamide moieties.

5.2 Strategy towards stilbenesulfonamide synthesis

A number of routes into the synthesis stilbenesulfonamides were explored, within the literature, however the possibility of forming various sulfonamides, by reacting a sulfonyl chloride moiety with an amine [272] was of great interest. For this reason chlorosulfonic acid was identified as a suitable sulfonating species, which could be used to synthesise an arylsulfonyl chloride intermediate.

According to the literature, the chlorosulfonation of *trans*-stilbene (1,2-diphenylethene), **5**, was considered unsuccessful, and would not afford identifiable products, due to the stability of the substrate [272]. After searching the literature, it was discovered that Hoffmann and co-workers [273] reported that an aryl sulfonyl chloride intermediate could be formed prior to coupling, by reacting excess chlorosulfonic acid, **219**, with diethyl benzylphosphonate, **162**, (Scheme 5.1).

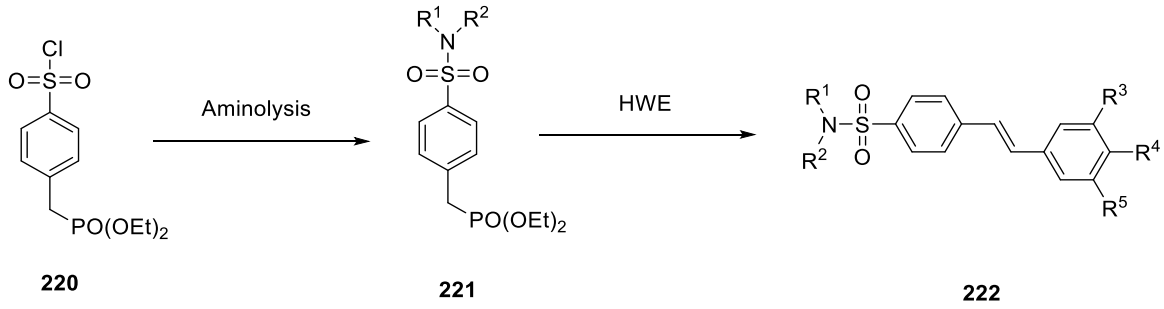


162 **219** **220**

Scheme 5.1 Chlorosulfonation of diethyl benzylphosphonate

The preparation of the sulfonyl chloride intermediate, **220**, would then allow for the subsequent aminolysis reaction to proceed, as it was expected that *via* this approach the

sulfonamide moiety, at the 4'-position of the stilbene skeleton could be varied using a wide range of amines. Finally, coupling *via* the HWE reaction would form the stilbene backbone (Figure 5.2), therefore providing an alternative and concise route for the synthesis of stilbene benzenesulfonamides, **222**.



220 **221** **222**

R^1, R^2 = H, alkyl, aryl, $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$
R^3 = H, OMe
R^4 = H, OMe, F, NMe_2
R^5 = H, OMe

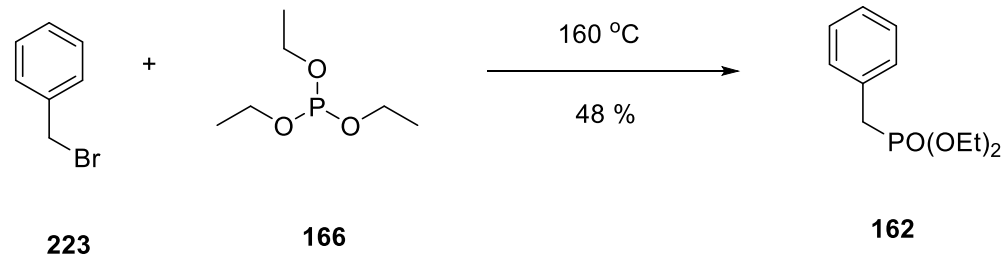
Figure 5.2 Approach to the synthesis of stilbene sulfonamides

The use of this methodology, as detailed in Figure 5.2, would first of all allow the use of various substituted benzaldehydes; possessing electron-withdrawing or electron-donating groups. Second of all, it would enable the use of various amines, to produce a range of sulfonamide moieties. Additionally in developing this work, the methodology would enable an inexpensive, direct and versatile route towards the synthesis *trans*-stilbene benzenesulfonamide analogues, in addition to other novel analogues, reported in the literature [164, 173].

The choice of analogues synthesised in this study were primarily limited to aldehydes possessing the most attractive functionalities, based on previous literature [164, 173], as it was envisioned that additional analogues would be made, following the biological studies which would be performed on these compounds.

5.2.1 Synthesis of diethyl benzylphosphonate

The first step, was the synthesis of the diethyl benzylphosphonate, **162**, *via* the Michaelis Arbuzov reaction [187], with the use of benzyl bromide, **223**, and triethyl phosphite, **166**, (Scheme 5.2). This S_N2 reaction proceeded smoothly for 48 h, to give the diethyl benzylphosphonate, **162**, in moderate yield (48 %). No further purification was performed, as a high % purity (96 %), was calculated *via* ^{1}H NMR analysis.



223 **166** **162**

Scheme 5.2 Synthesis of diethyl benzylphosphonate *via* the Michaelis-Arbuzov reaction

IR characterisation indicated the important P=O peak at approximately υ 1250 cm^{-1}, furthermore characterisation by ^{1}H NMR displayed a doublet with a large two-bond coupling constant at δ 3.09 ppm ($^2J_{P\text{-}H}$ = 21.9 Hz), which was indicative of the phosphorus coupling with a proton nuclei positioned on the α-carbon. The protons present

in the P-CH_2 bond, on a ^{1}H NMR spectrum should show as a doublet in a ratio of 1:1 [274], however a roofing effect was observed in the spectrum obtained. An explanation may be due to the presence of low level impurities underneath the peaks located at δ 3.09 ppm, because of this a deuterium oxide (D_2O) shake was performed on the sample, to see if the effect of a different solvent would alter the nature of the peak, nevertheless the data showed minimal changes at this particular chemical shift. Additionally, doublet of quartets [275], which appear to overlap on the ^{1}H NMR spectrum were observed, and were believed to be attributed to the protons present in the O-CH_2 moiety of compound, **162**, being diastereotopic. As a result, the protons were observed in inequivalent chemical environments on the proton NMR spectrum [274].

Although the phosphonate, **162**, was synthesised in moderate yields, it was decided that the synthesis of the phosphonate, **162**, was not necessary as the substrate could be inexpensively purchased. Furthermore, by starting the synthetic methodology from the commercially available diethyl benzylphosphonate, **162**, it would enable the total reaction sequence to be reduced to three steps.

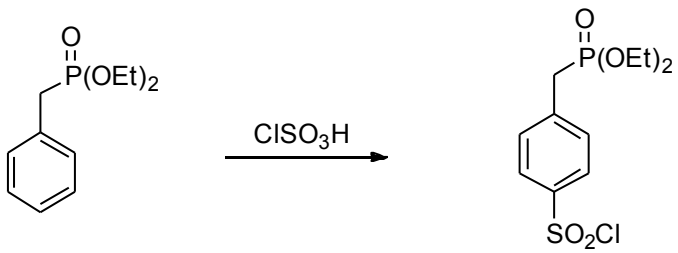
5.2.2 Synthesis of diethyl 4-(chlorosulfonyl)benzylphosphonate

The next step was to prepare the aryl sulfonyl chloride, the formation of this synthetic intermediate has been reported, *via* various methodologies including chlorosulfonation using chlorosulfonic acid, **219** [276], alternatively by direct oxidation of thiol analogues, in the presence of hydrogen peroxide (H_2O_2) and the Lewis acid titanium tetrachloride [277, 278], or with sulfonic acids in the presence of the chlorinating agent; 2,4,6-trichloro-1,3,5-

triazine [279]. Within the literature, chlorosulfonic acid, **219**, has been shown to be a versatile reagent in the chlorosulfonation of various organic compounds [273], therefore this acid was chosen as the sulfonating species. Furthermore, the formation of the sulfonyl chloride, when involving aromatic and hetero-aromatic substrates, was suggested to be successful with chlorosulfonic acid, **219**, in excess [280], which was of great advantage, as a substituted aromatic substrate would be used in this methodology.

According to the literature, it has been suggested that the presence of the chlorosulfonic acid, **219**, in excess drives the reaction to completion, thereby converting the sulfonic acid reaction intermediate into the sulfonyl chloride, **220** [276]. Chlorosulfonic acid reactions, between the substrate and acid, have also been reported to be successful in the presence of a solvent, such as dichloromethane and thionyl chloride [273].

Therefore, the first attempt in forming the sulfonyl chloride intermediate, **220**, proceeded by reacting diethyl benzylphosphonate, **162**, with chlorosulfonic acid, **219**, in excess [281], this approach was found to be successful and gave the sulfonyl chloride, **220**, in good yield (82 %) (Scheme 5.3).

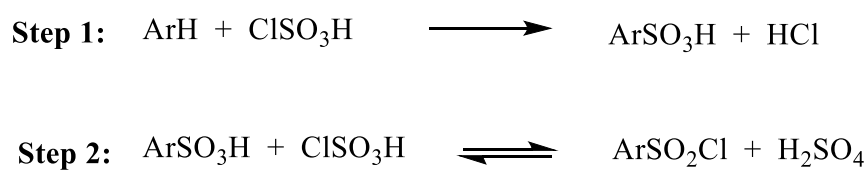


162 **220**

Scheme 5.3 Chlorosulfonation of diethyl benzylphosphonate

The structural assignment by IR spectral analysis featured two distinguishable peaks, characteristic of the sulfonyl chloride (S=O) bond present at υ = 1173 cm^{-1} and 1369 cm^{-1}, respectively. Additionally, the presence of the phosphonate moiety was also observed at υ = 1246 cm^{-1} (P=O *str*). Formation of the sulfonyl chloride intermediate was also confirmed by ^{1}H NMR, whereby of the presence of two doublets, with chemical shifts at δ 7.49 ppm and δ 7.90 ppm, were observed indicating the presence of a 1,4-disubstituted aromatic system.

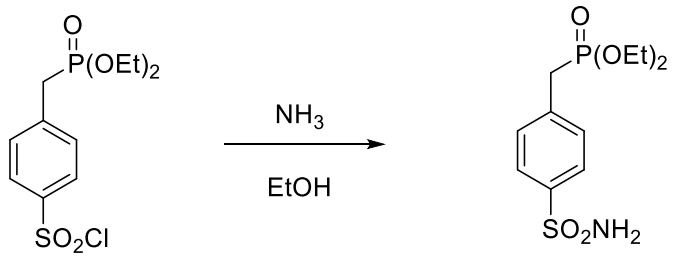
As the chlorination step in the chlorosulfonation reaction was a reversible step (Equation 5.1) [276], the optimised reaction conditions, with chlorosulfonic acid : substrate in a ratio of (10 : 1) was used in order to ensure the completion of the reaction in high yields. Furthermore, the initial slow addition of the substrate, **162**, to the excess chlorosulfonic acid, **219**, at temperatures of less than 0 °C was found to be successful in order to minimise unwanted side reactions, such as di-sulfonation as well as the production of arylsulfonic acid.



Equation 5.1 Two-step process of chlorosulfonation with an aromatic substrate

5.2.3 Synthesis of diethyl 4-sulfamoylbenzylphosphonate

Having successfully formed the sulfonyl chloride intermediate, **220**, the aminolysis reaction using various amines was explored. One of the most important aspects to demonstrate, was that the primary sulfonamide moiety (SO_2NH_2) could be formed with this approach. Therefore the aminolysis reaction was initially attempted using excess ammonia solution (in 2 M ethanol), as the source of ammonia, with diethyl 4-(chlorosulfonyl)benzylphosphonate, **220**, (Scheme 5.4). This reaction was found to proceed smoothly, affording the desired primary sulfonamide, **221a**, in excellent yield (90 %).



220 **221a**

Scheme 5.4 Synthesis of sulfonamide *via*, aminolysis using ammonia

Formation of the desired sulfonamide was confirmed by IR analysis, whereby the characteristic bands arising from the primary sulfonamide stretch were observed, with the S=O bands located at υ 1156 cm^{-1} and 1337 cm^{-1}, respectively. More importantly N-H bands were identified in the form of two broad peaks (υ 3200 cm^{-1} and 3298 cm^{-1}),

which are characteristic of primary amines. Furthermore, the presence of the phosphonate ester was also observed, with peaks characteristic of the P=O bond at approximately υ 1234 cm^{-1} identified, thereby confirming the phosphonate moiety was still present. Additionally, following characterisation by ^{1}H NMR, the presence of the sulfonamide moiety was confirmed at δ 4.99 ppm, and to identify the exchangeable protons present in the sulfonamide moiety, a D_2O exchange was performed whereby the disappearance of the N-H signal, with the appearance of a DOH peak was observed as expected. As the rapid proton exchange seen with the sulfonamide, meant that coupling could not be observed with the protons bonded to the nitrogen atom and neighbouring nuclei [282]. Furthermore, the $J_{H\text{-}H}$ coupling values (J = 8.2 Hz) calculated, were indicative of the interaction between the protons present in the aromatic ring, that were *ortho* to one another.

The mechanistically the amine acts as a nucleophile, and aminolysis is believed to proceed *via* rapid nucleophilic attack of the amine, on the electrophilic sulfonyl centre to produce the sulfonamide [283] *via* a bimolecular S_N2-type mechanism, with a linear bipyramidal transition state being formed (Figure 5.3) [273].

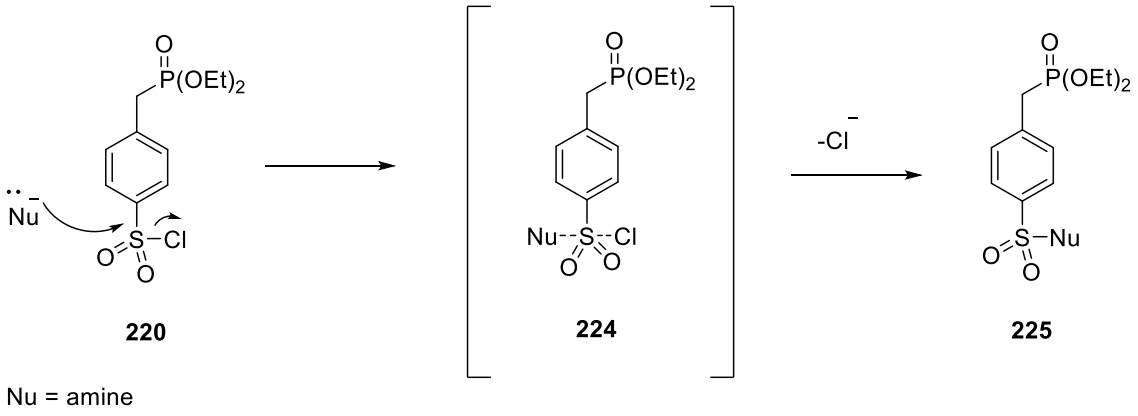


Figure 5.3 **S_N2 mechanism for the aminolysis reaction with aryl-sulfonyl chlorides and amines**

5.2.3.1 Examining the scope of the reaction: amine screening

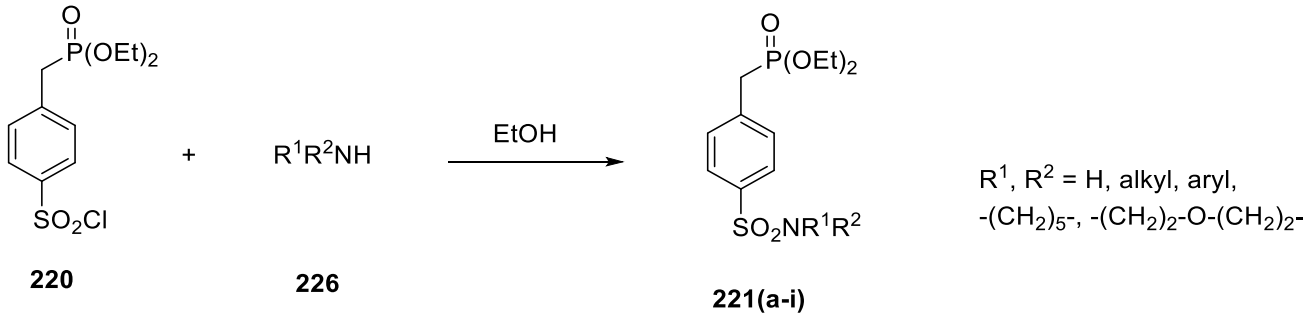
Following the success of forming the primary sulfonamide with ammonia, it was of interest to explore the scope of this methodology by screening various amines with the diethyl 4-(chlorosulfonyl)benzylphosphonate, **220**, intermediate, in order to determine if the aminolysis reaction would be successful.

In order to examine the versatility and flexibility of this methodology, the amines used in the screening were selected to ensure they represented a range of primary, secondary and cyclic alkyl amines, as well as aromatic amines. Therefore the amines studied included; methylamine, ethylamine, amylamine, dimethylamine, dipropylamine, piperidine, morpholine and diphenylamine (Table 5.1).

The use of primary, secondary and cyclic alkyl amines gave the desired products in moderate to high yields and as expected, the nucleophilicity of the amine was found to influence the rate of reaction. For instance reactions with primary amines (Table 5.1; Entries 1 - 4), and cyclic aliphatic amines (Table 5.1; Entries 7 and 8), although gave moderate to high yields, the reaction time was found to be between 12 – 48 h.

On the other hand, the reaction with diphenylamine (Table 5.1; Entry 9), a relatively weak and large nucleophile, was also effective however a longer reaction time of five days was required. Nonetheless, the promising results observed with the sulfonyl chloride intermediate, **220**, and possible use of diverse amines, suggests that this novel approach offers an alternative approach towards the synthesis of a wide range of sulfonamide analogues.

Table 5.1 **Summary for the addition-elimination reaction of amines**



220 **226** **221(a-i)**

Entry	Compound	Amine	Condition	% Purity[a] (% Yield)
1	**221a**	ammonia	RT / 12 h	90
2	**221b**	methylamine	RT / 24 h	100 (57)
3	**221c**	ethylamine	RT / 48 h	96 (61)
4	**221d**	amylamine	RT / 48 h	60
5	**221e**	dimethylamine	RT / 48 h	98 (68)
6	**221f**	dipropylamine	RT / 48 h	81
7	**221g**	piperidine	RT / 48 h	88
8	**221h**	morpholine	RT / 48 h	82
9	**221i**	diphenylamine	RT / 5 d	83

[a] Determined by ^{1}H NMR

5.2.4 Synthesis of (*E*)-4-(3,4-dimethoxystyryl)benzenesulfonamide

The work presented in Chapters 2 to 4, demonstrates the versatility of using the HWE condensation reaction in forming the stilbene skeleton, with high selectivity for the *trans*-alkene. In this chapter the same coupling reaction was examined for the synthesis of novel stilbenesulfonamides, as the versatile nature of this approach would additionally allow the exploration of various heterocyclic aldehydes, in the synthesis of the stilbenesulfonamide analogues [9]. Furthermore, the mild reaction conditions employed would be ideal for the synthesis of stilbenesulfonamides on a larger scale.

The general reaction involved the coupling of the substituted phosphonate (1 equiv), with a benzaldehyde (1 equiv), in the presence of a base (NaOMe or *t*-BuOK) and a solvent (DMF or THF) at room temperature. The aldehydes selected for this study (Figure 5.4), were not chosen based on the Hansch method or the Topliss scheme [79, 284], as examining the versatility of this three step methodology was of primary interest. Therefore a variety of aldehydes, possessing the most attractive substitutions on the ring were selected based on the literature, specifically the work by Yang and co-workers (6), whereby substituents possessing the electron-withdrawing group, namely fluorine (F), in addition to substituents comprising of electron-donating groups such as dimethylamino (NMe_2) and methoxy (OMe) moieties, were reported to display significant anti-cancer activity against a number of cancer cell lines, when examined *in vitro* against the NCI-60 human tumour cell line.

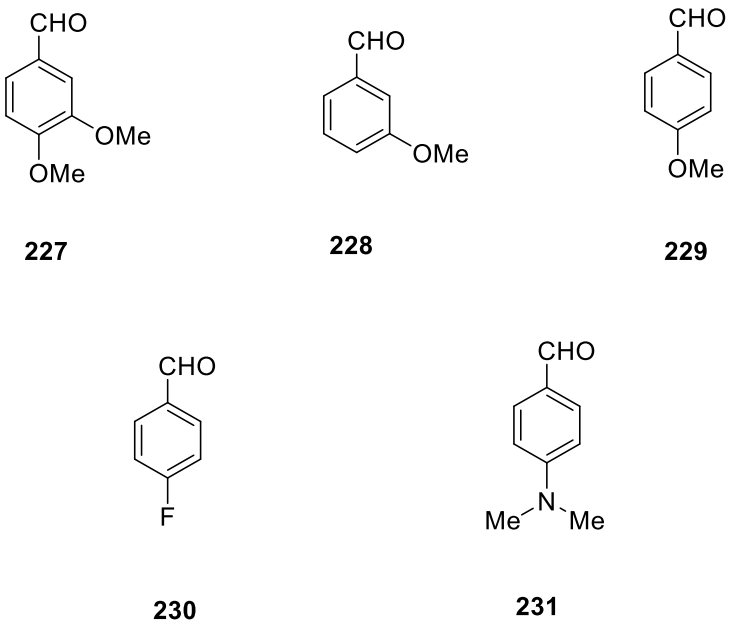


Figure 5.4 Benzaldehydes selected for HWE coupling

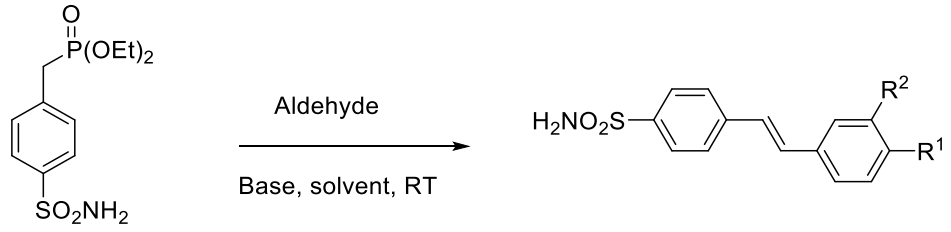
The stilbenesulfonamide comprising of the 4-fluoro moiety, was of great interest as this analogue was found to display efficacious growth inhibitory activity (GI_{50} 8.93), towards the non-small cell lung cancer cell line (A549). A cell line which would be used in this study to examine the biological activity of the novel stilbene benzenesulfonamides synthesised, therefore it was of interest to synthesise a range of analogues, using the various secondary and tertiary benzenesulfonamides available from the library.

The first coupling reaction was explored using the primary sulfonamide, **221a**, with various aldehydes, in a 1:1 ratio (Table 5.2), the reaction proceeded smoothly with over 5 equiv. of the base (NaOMe) and DMF as the solvent. Compared to the six step methodology described by Yang *et al.,* [6], this three step methodology proved to be successful, when it came to constructing the same analogues (**125a**, **125b**, **125c** and **125g**), reported by Yang and co-workers [6]. Unfortunately, direct comparisons of the %

yields could not be made, as the yields of the stilbenesulfonamide analogues were not stated in the literature.

Nevertheless characterisation by ^{1}H NMR spectra, confirmed that these stilbene analogues, all featured an important pair of doublets, corresponding to the alkene protons in a *trans*-configuration at δ ~7.1 ppm and δ ~7.0 ppm. Furthermore the calculated *J*-coupling values (J = 16 - 17 Hz), were distinctly characteristic of the proton coupling interactions occurring in a *trans*-alkene bond. Based on the ^{1}H NMR data, the addition of sodium methoxide in excess (> 5 equiv) resulted in a percentage purity between 77 – 98 %, although the reaction involving 4-dimethylaminobenzaldehyde, **231**, was found to give the lowest % yield, with the stilbene, **231**, obtained in a moderate yield of 77 % (Table 5.2; Entry 4). The low yield was thought to be due to the phosphonate being added to the reaction mixture in excess, which explains why the presence of the starting material, **221a**, (23 %) was also observed by ^{1}H NMR.

Table 5.2 Stilbenesulfonamides *via* HWE condensation reactions using diethyl 4-sulfamoylbenzylphosphonate



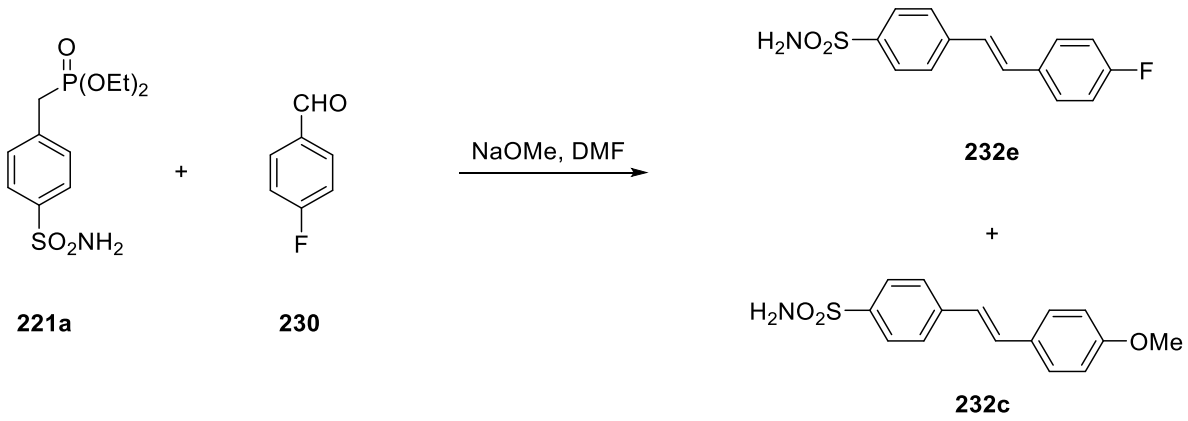
221a **232 (a- d)**

Entry	Compound	R^1	R^2	Conditions	% Purity[a] (%Yield)
1	**232a**	OMe	OMe	NaOMe, DMF	96 (15)
2	**232b**	H	OMe	NaOMe, DMF	88
3	**232c**	OMe	H	NaOMe, DMF	98 (7)
4	**232d**	NMe_2	H	NaOMe, DMF	77

[a] Determined by ^{1}H NMR

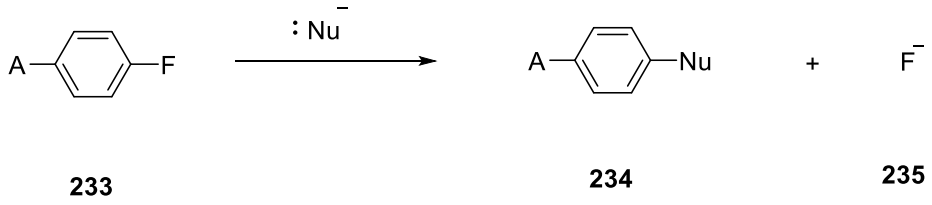
Coupling with 4-fluorobenzaldehyde, **230**, in the presence of sodium methoxide (> 5 equiv.), gave a mixture of two compounds (Scheme 5.5), characterisation by ^{1}H NMR displayed a distinguishable peak at δ 3.83 ppm, indicating the presence of a methoxy group, additionally the spectrum featured the important pair of doublets corresponding to the alkene (HC=CH) protons at δ 6.97 ppm and δ 7.17 ppm, respectively. Furthermore the calculated *J*-coupling (*J* = 16.4 Hz), distinctly characteristic of the hydrogen coupling interactions occurring in a *trans*-alkene bond

was calculated, therefore confirming the *trans*-stilbene skeleton had been formed. Additionally, the nuclear spin from ^{19}F was observed, due to the strong coupling of the fluorine nuclei with the protons, leading to extra splitting in the ^{1}H NMR spectrum [282].



Scheme 5.5 Coupling *via* the Horner-Wadsworth-Emmons reaction using sodium methoxide

Based on this characterisation it was likely that the product synthesised, comprised of a mixture of compounds possessing a 4-MeO or a 4-fluoro moiety, within the stilbene structure. To confirm this, characterisation by LCMS was performed on the mixture, the molecular ion peaks of *m/z* = 275 ($C_{14}H_{12}FNO_2S$ requires 277) and *m/z* = 288 ($C_{15}H_{15}NO_3S$ requires 289), were observed. Additionally calculation of the % purity, by ^{1}H NMR identified the presence of compounds **232e** and **232c** in a 4:1 ratio, which suggests that displacement of the *para*-fluoro moiety on the benzaldehyde, **230**, had occurred with the nucleophile (MeO) from the base (NaOMe), *via* nucleophilic aromatic substitution (S_NAr) (Figure 5.5) [285].



233 **234** **235**

A = CHO or electron-withdrawing group
Nu = OMe

Figure 5.5 Nucleophilic aromatic substitution (S_NAr) reaction

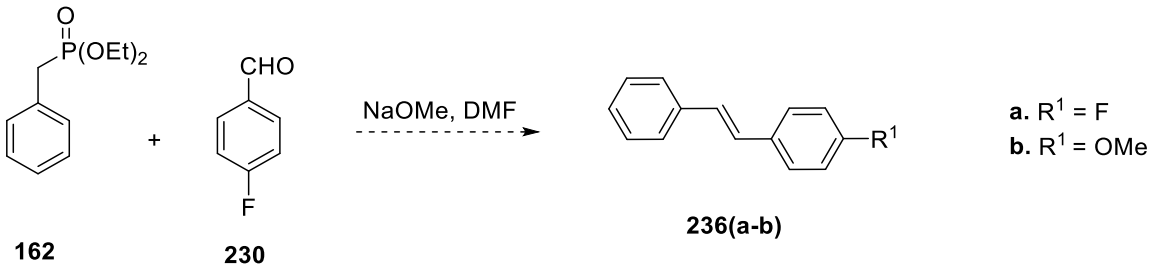
To rule out any postulation of the incorrect aldehyde, **230**, being used the experiment was repeated, nonetheless the presence of the methoxy moiety was observed again on the spectrum. Furthermore comparison of the ^{1}H NMR spectrum of the starting material, **230**, with the stilbene, **232e**, was performed as it was thought that the starting material might have some impurities, however the spectral data only confirmed the presence of 4-fluorobenzaldehyde **230**.

Based on this discovery, further studies were carried out to investigate the influence of NaOMe, in the coupling between 4-fluorobenzaldehyde, **230**, and diethyl 4-sulfamoylbenzylphosphonate, **221a**, in order to determine first of all, if the HWE reaction was occurring prior to the S_NAr, on the fluorine atom. Secondly, to determine the influence of the *para*-sulfonamide moiety, as an electron withdrawing group, and the effect it had on the addition-elimination mechanism.

To examine this, coupling reactions were performed with diethyl benzylphosphonate, **162**, and 4-fluorobenzaldehyde, **230**, in the presence of sodium methoxide at 1, 5 and 10 equivalents, respectively (Table 5.3). The various molar equivalents of the base were used in order to determine at which molar equivalent, nucleophilic aromatic substitution would occur. The first study, using NaOMe (1 equiv.), was found to

produce the 4-fluorostilbenesulfonamide, **236a**, in quantitative yield (Entry 1). However, characterisation by ^{1}H NMR of the subsequent reactions (5 and 10 equiv of NaOMe), indicated the presence of the methoxy moiety, with a distinguishable singlet peak at δ ~ 3.8 ppm observed in the spectra, in addition to strong coupling of the fluorine nuclei, with the protons.

Table 5.3 Synthesis of (*E*)-1-fluoro-4-styrylbenzene *via* the Horner-Wadsworth-Emmons reaction



162 **230** **236(a-b)**

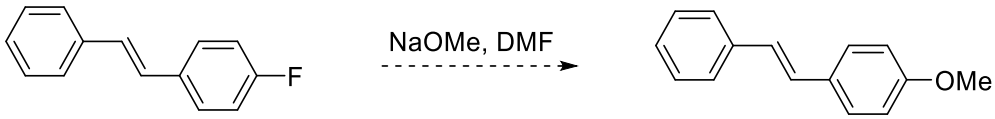
Entry	Compound	Equiv of NaOMe	% Purity[a] [Fluoro : OMe]
1	**236a**	1	> 99 : <1
2	**236b**	5	80 : 20
3	**236c**	10	53 : 47

[a] Determined by ^{1}H NMR

The addition of NaOMe (5 equiv.), gave the desired compound, **236a**, (80 %) and analogue, **236b**, (20 %) (Table 5.4; Entry 2), whereas the addition of NaOMe (10 equiv), considerably increased the yield of the 4-methoxy-stilbenebenzenesulfonamide analogue, **236b**, up to 47 % (Table 5.4; Entry 3).

Next, a reaction using a pure sample of the synthetic stilbene; (E)-1-fluoro-4-styrylbenzene, **236a**, and NaOMe (5 equiv), was carried out in order to determine if S_NAr would occur in the absence of the electron withdrawing group (SO_2NH_2). Aromatic substitution was believed to occur, with up to 8 times as much of the 4-fluoro analogue, **236a**, identified on the NMR spectrum, compared to the methoxy equivalent, **236b**, (Table 5.4; Entry 1). This result confirmed that the presence of the sulfonamide moiety on the stilbene backbone was not important, and did not have an influence on the S_NAr reaction observed.

Table 5.4 Attempted synthesis of (*E*)-1-methoxy-4-styrylbenzene



236a **236b**

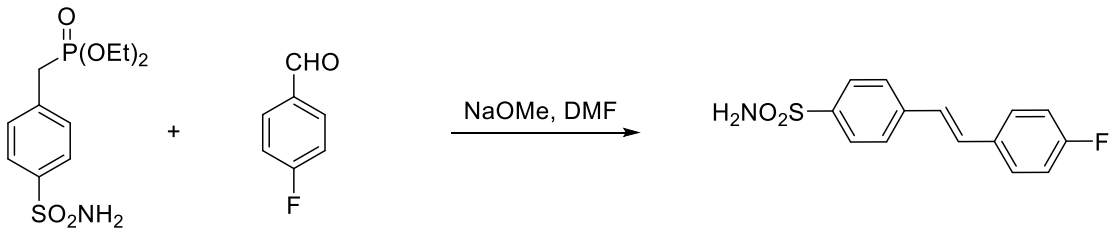
Entry	Equiv of NaOMe	% Purity[a] [Fluoro : OMe]
1	5	82 : 18

[a] Determined by ^1H NMR

Next coupling with the primary sulfonamide, **221a**, with 4-fluorobenzaldehyde, **230**, was performed, in order to determine at what equivalent of the base S_NAr began to occur. As expected substitution did not occur when 1 equiv. of NaOMe was used, and

under this reaction condition the condensation reaction proceeded smoothly, to afford the desired stilbene, **232e**, in excellent yield 98 % (Table 5.5; Entry 1). Notably, in contrast with the previous reactions, when > 5 equiv. of NaOMe was used the stilbene, **232e**, was identified as the major product (95 %) on the ^{1}H NMR spectrum, additionally a minimal amount of compound, **232c** (5 %), was detected.

Table 5.5 Synthesis of (*E*)-4-(4-fluorostyryl)benzenesulfonamide *via* the Horner-Wadsworth-Emmons reaction



221a **230** **232e**

Entry	Equiv of NaOMe	% Purity[a] (% Yield)
1	1	98 (77)
2	5	95 (83)

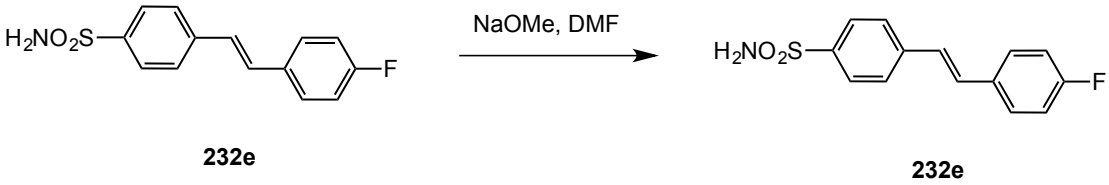
[a] Determined by ^{1}H NMR

Finally, to examine the effect of the presence of sulfonamide moiety on the stilbene backbone, NaOMe (1 and 5 equiv, respectively) was added to a pure sample of the stilbene sulfonamide, **232e**, and stirred in the presence of DMF at room temperature, however substitution did not occur, with both equivalents of the base (Table 5.6).

.

These results suggest that substitution of the fluorine atom with the methoxy moiety only occurs during the HWE reaction when the NaOMe is present in excess (> 5 equiv.).

Table 5.6 Coupling *via* the Horner-Wadsworth-Emmons reaction using sodium methoxide



232e **232e**

Entry	Equiv of NaOMe	% Purity[a] (% Yield)
1	1	100 (57)
2	5	98 (64)

[a] Determined by ^{1}H NMR

This assumption was proved by the subsequent reactions performed on the remaining sulfonamide analogues (**221b – 221i**), whereby S_NAr was believed to occur prior to the formation of the stilbene backbone, thereby giving a mixture of products (Figure 5.6). However, it would be advantageous to perform in-depth NMR studies, and observe the kinetics of the reaction, in order to prove this hypothesis and consequently determine the rate at which the simultaneous reactions (S_NAr and HWE coupling) are occurring.

As an alternative approach the reaction between 4-fluorobenzaldehyde, **230**, and the primary sulfonamide benzenesulfonamide, **221a**, was performed in the presence of

t-BuOK (~ 2 equiv) and THF, this approach was found to proceed smoothly (Figure 5.6), affording the desired stilbenesulfonamide, **232e**, in quantitative yield.

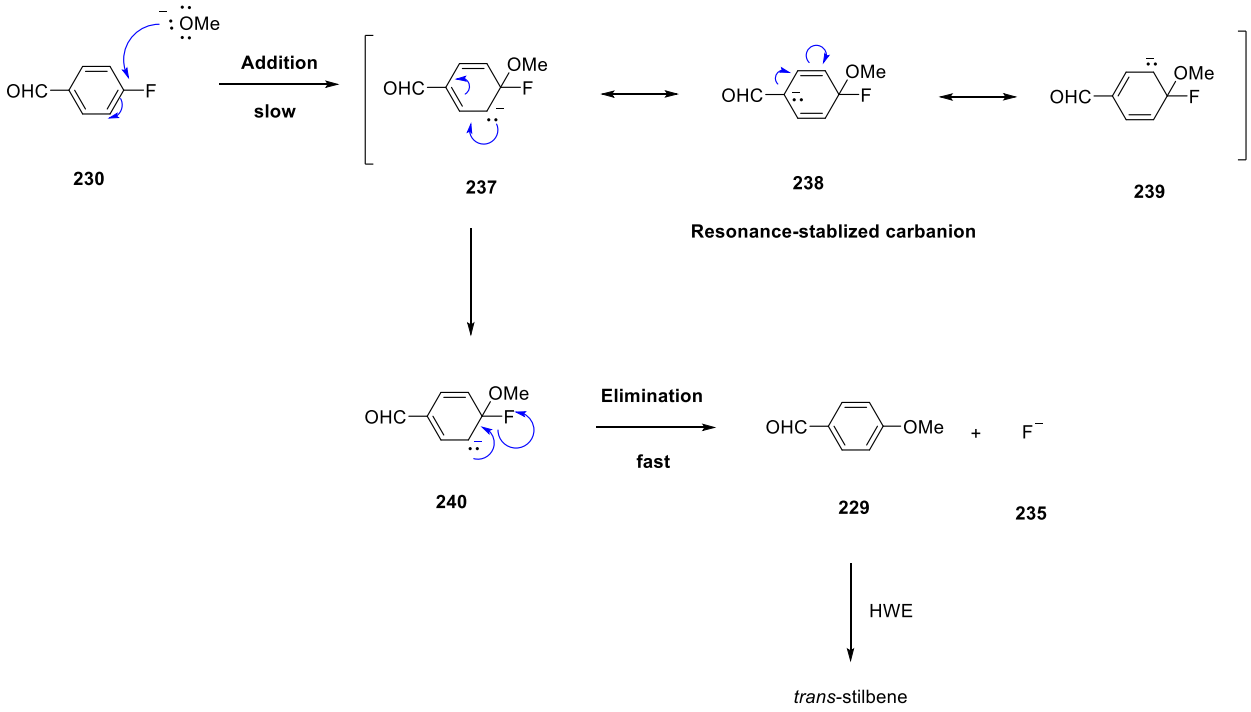


Figure 5.6 **S_NAr Mechanistic in the formation of stilbene sulfonamide analogues**

Next the coupling with various heterocyclic aldehydes were explored (Figure 5.7), these compounds were of interest as the synthesis of novel COX-2 inhibitors, in the form of stilbene benzenesulfone and benzenesulfonamide derived styrylheterocycles have also been achieved in 4 - 6 steps, by Lim and co-workers [7] .

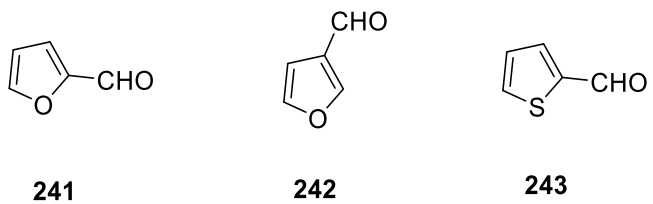
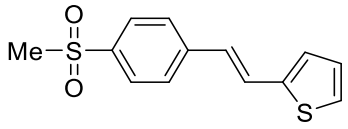


Figure 5.7 **Heterocyclic aldehydes selected**

These analogues, specifically possessing the thiophene functionality (compound **138c**), were reported to show up to 40-fold potency, compared to the lead compound, **244**, (Figure 5.8) [173]. It was therefore of interest to examine if the six step methodology, described in the literature, could be improved using the three step approach developed in this study, in order to synthesise both the compounds reported by Lim *et al.,* in addition to other novel benzenesulfonamide derived styrylheterocycles for biological screening.

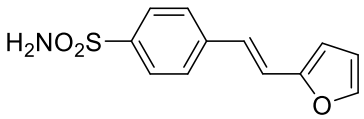
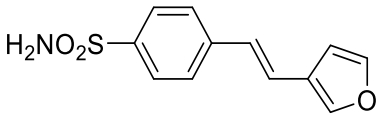
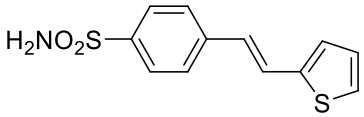


244

Figure 5.8 Benzenesulfone analogue

Following the procedure described in Section 5.2.4, the HWE reaction proceeded in the presence of NaOMe (~5 equiv) and DMF, upon occasion when issues with solubility were observed, THF was used as an alternative solvent and was found to display increased solubility with the heterocyclic aldehydes, compared to DMF (Table 5.7). Notably, the stilbenesulfonamide analogues **245**, **246** and **247** synthesised from this three step approach were isolated in higher yields (96 – 100 %), compared to the literature (48 – 60 %) [173].

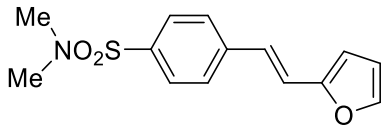
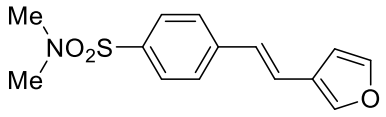
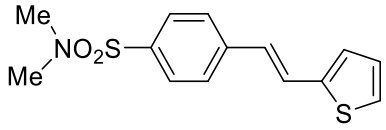
Table 5.7 Benzenesulfonamide derived styrylheterocycles formed *via* the HWE reaction using diethyl 4-sulfamoylbenzylphosphonate

Entry	Compound	Structure	Base/Solvent	% Purity[a] (% Yield)
1	**245**		NaOMe, DMF	100 (30)
2	**246**		NaOMe, THF	98 (94)
3	**247**		NaOMe, DMF	96 (49)

[a] Determined by ^{1}H NMR

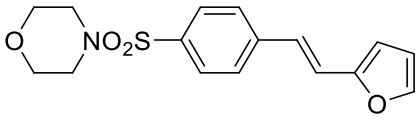
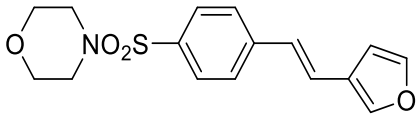
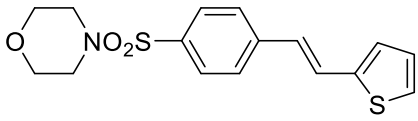
Following the success of the HWE coupling reaction with the various heterocyclic aldehydes, the synthesis of other novel benzenesulfonamides were explored, using the sulfonamide analogues **221e** and **221h**. The novel compounds synthesised with diethyl 4-(*N*,*N*-dimethylsulfamoyl)benzylphosphonate, **221e**, gave excellent yields with 100 % purity (Table 5.8). However, the % yields were not comparable when the cyclic sulfonamide analogue, **221h**, was used, as a moderate yield of 49 % was obtained (Table 5.9).

Table 5.8 Benzenesulfonamide derived styrylheterocycles formed *via* the HWE reaction using diethyl 4-(*N*, *N*-dimethylsulfamoyl)benzylphosphonate

Entry	Compound	Structure	Base/Solvent	% Purity[a] (%Yield)
1	**248**		NaOMe, THF	100 (59)
2	**249**		NaOMe, THF	98 (100)
3	**250**		NaOMe, DMF	93

[a] Determined by ^{1}H NMR

Table 5.9 Benzenesulfonamide derived styrylheterocycles formed *via* the HWE reaction using diethyl 4-(morpholinosulfonyl)benzylphosphonate

Entry	Compound	Structure	Base/Solvent	% Purity[a]
1	**251**		NaOMe, DMF	50
2	**252**		NaOMe, DMF	86
3	**253**		NaOMe, DMF	49

[a] Determined by ^{1}H NMR

Next the versatility of this methodology was explored using the remaining novel benzenesulfonamide analogues synthesised in this chapter (Figure 5.9). The secondary sulfonamide analogues, **221b** - **221h**, were additionally coupled with the selected benzaldehydes (Figure 5.4), under the same reaction conditions described earlier in this chapter (Section 5.2.4).

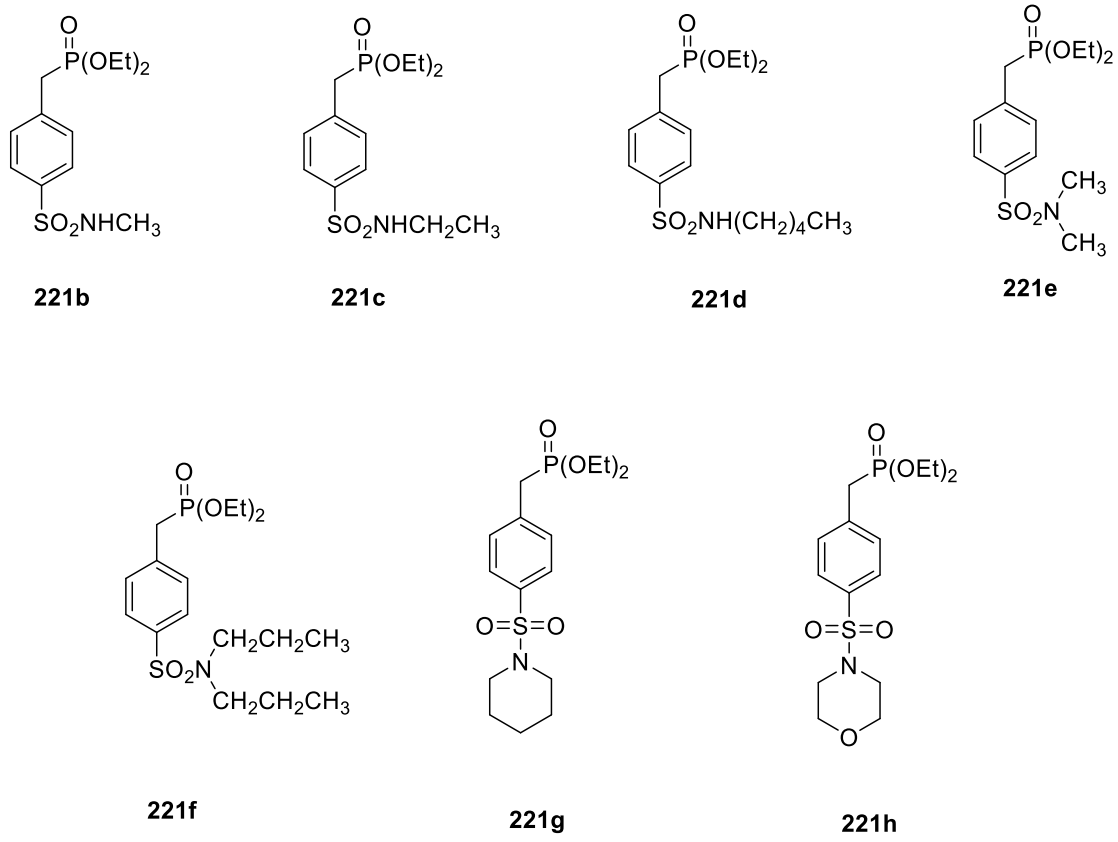


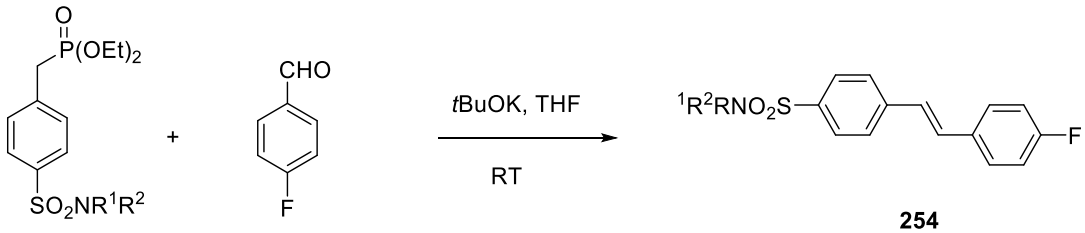
Figure 5.9 Structure of benzenesulfonamide analogues used in HWE coupling reactions

Compared to the primary sulfonamide, coupling with sulfonamide analogues **221b**, **221c** and **221d**, gave moderate to excellent yields (61 – 100 %), with the minimal yield obtained from the coupling between the secondary sulfonamide, **221b**, and 3-methoxybenzaldehyde **228**. Notably, the isolated yields from the coupling between

the tertiary sulfonamide, **221f**, and the various aldehydes were high (92 – 100 %). On the other hand coupling with tertiary cyclic sulfonamides, **221g** and **221h**, overall gave the stilbene benzenesulfonamides in moderate % yields (59 – 77 %), this was especially the case when a stoichiometric ratio of the sulfonamide and aldehyde (1:1) was used, in the presence of NaOMe (> 6 equiv.). However when the stoichiometric ratio was increased, with the addition of the sulfonamide in excess (> 1.2 equiv.), the % yields also increased. Additionally, when *t*-BuOK (~2 equiv.) was used as an alternative base, overall excellent % yields (92 – 98 %) were obtained (Table 5.10).

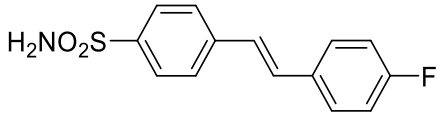
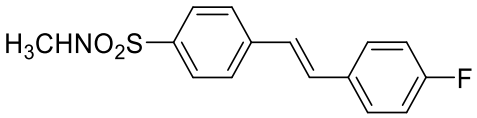
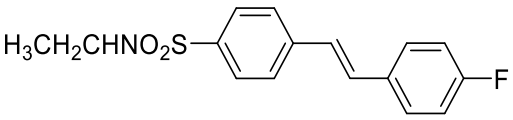
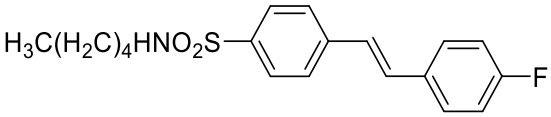
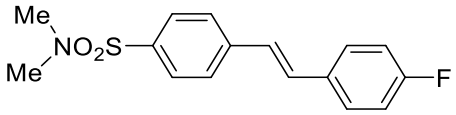
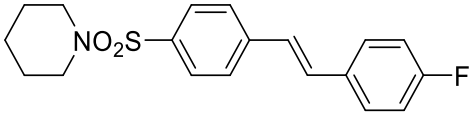
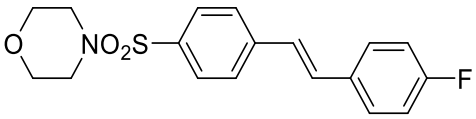
Finally, the HWE coupling of 1°, 2° and 3° benzenesulfonamide analogues with 4-fluorobenzaldehyde, **230b**, was examined, and as expected when NaOMe was used a mixture of compounds were observed, due to S_NAr taking place in the reaction. However, when *t*-BuOK (~ 2 equiv) was used as an alternative base, in the presence of THF the desired product was obtained. The yields obtained from the latter reaction gave almost quantitative yields (> 92 %), the high yields were observed with the majority of stilbenesulfonamides, apart from compound, **225**, which gave an isolated yield of 66 % (Table 5.10). The lower yield obtained was likely due to the low equiv. of base used in the reaction compared to the other analogues, as the presence of the starting materials were also observed on the ^{1}H NMR. It can therefore be postulated that if the same equivalent of base was used, complete conversion of the starting materials would have been observed.

Table 5.10 Synthesis of stilbenesulfonamides *via* HWE condensation reactions with 4-fluorobenzaldehyde



221 **230** **254**

R^1, R^2 = alkyl, aryl, -$(CH_2)_5$-, -$(CH_2)_2$-O-$(CH_2)_2$-

Entry	Compound	Structure	% Purity[a] (% Yield)
1	**232e**		100 (65)
2	**255**		66
3	**256**		98 (39)
4	**257**		100 (34)
5	**258**		98 (40)
6	**259**		92
7	**260**		98 (54)

[a] Determined by ^{1}H NMR

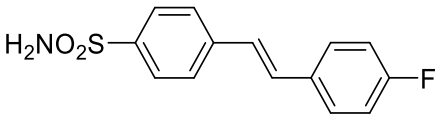
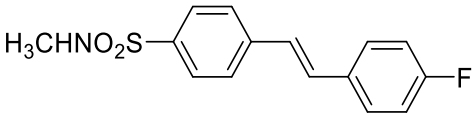
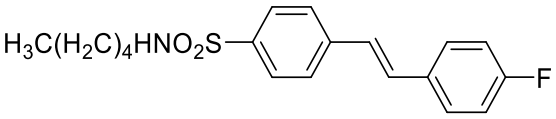
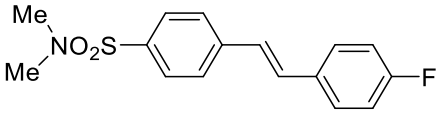
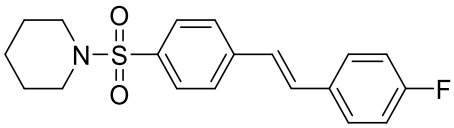
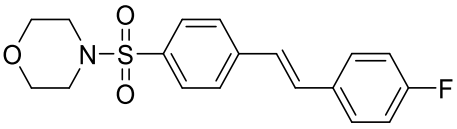
5.3 Biological testing of analogues

Lung cancer is said to be the second leading cause of tumour-related deaths, with a 5 % survival rate, despite only accounting for approximately 20 % of cancer diagnosis. In the UK, the non-small cell lung cancer has been reported to account for 87 % of lung cancers, with the adenocarcinoma being the most common type of primary lung cancer diagnosed [170]. For this reason, the non-small cell lung carcinoma cell line, A549 was selected for this study, to assess the antitumour activity of the test compounds selected as per Section 5.3.1.

5.3.1 Stilbenesulfonamide analogue selection

The present study involved the selection of six compounds from the library of analogues synthesised (Table 5.11). These compounds were investigated *in vitro* for their potential activity, with the objective of examining with regards to the SAR, the efficacy of the various sulfonamide moieties, compared to the lead compound resveratrol, **1**, as well as other compounds within the literature.

Table 5.11 **Stilbenesulfonamide analogues selected for cytotoxicity studies.**

Compound	Structure	CLogP [a]
232e		3.14
255		3.75
257		5.87
258		4.17
259		5.37
260		4.12

[a] Calculated LogP (CLogP) obtained from Cambridgesoft ChemBioDraw Ultra software v.14.0.0.117.

The study by Yang *et al.,* [6] identified the stilbene benzenesulfonamide analogue comprising of a fluorine moiety, **125a**, to be the most selective towards the A459 cell line. To ensure consistency with our study, compounds of which possessed a 4-fluoro moiety on the aromatic ring were also chosen, as it would allow for the effects of the various sulfonamide moieties to be examined, with regards to the inhibition of cell proliferation and also allow for comparisons with the stilbene benzenesulfonamide analogue, **125a** to be made. Furthermore, the bioisosteric replacement of a hydrogen atom with a fluorine atom was also considered advantageous, as this would aid in improving the pharmacokinetic properties of resveratrol, **1**, specifically with regards increasing the bioavailability of the lead compound.

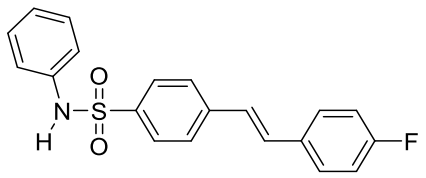
Within the literature, studies have reported the presence of the sulfonamide (*p*-SO_2NH_2) moiety and aromatic ring, to be essential in providing the highest efficacy with regards to its anticancer properties. Moreover, the sulfonamide moiety, *para*-substituted on the aromatic ring is believed to be preferred [173, 176], as additional substitution on the aromatic ring is thought to sterically reduce the activity of the compound, due to the presence of a bulky side chain which may hinder the protein interaction [286]. Based on these assumptions, analogue **255** and **257** (Table 5.11), were selected in order to determine the steric effects displayed by these secondary (2°) sulfonamide analogues.

The stilbenesulfonamide, **257**, in particular was selected based on the work by Huang and co-workers, as the amylamine functional group was reported to be involved in a number of anticancer mechanisms, including DNA alkylation [287], and was therefore of interest particularly with regards to SAR, and determining if an increase in lipophilicity (CLogP 5.87), would lead to an increase in activity. Although it was also likely that this compound may be too lipophilic, and as a drug, may result in decreased

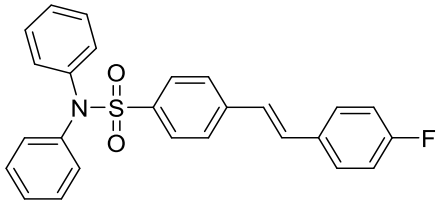
permeability and in low oral absorption [288].

The rationale behind the selection of the tertiary (3°) sulfonamide analogue, possessing the *N*,*N*-dimethylsulfamoyl moiety, **258**, was not only to determine the steric effects displayed by this analogue, but also to explore the influence of protein interactions. As this derivative lacks the hydrogen atoms on the sulfonamide nitrogen, it was thought the absence of hydrogen would signify a reduced number of hydrogen bond donors (HBD) for protein interactions, and as a result reduce its efficacy.

Finally, the cyclic sulfonamides, **259** and **260**, were selected to examine the steric influences displayed by the presence of the morpholine and piperidine functional groups, respectively. Additionally, examining the effects of an aromatic sulfonamide, such as the *N*-phenylsulfamoyl, **261**, or *N*,*N*-diphenylsulfamoyl, **263**, derivative (Figure 5.10) would have been of great interest in this study, as the presence of an additional aromatic group would have given an insight into the electronic effects arising from electron rich groups, in relation to their efficacy towards the cancer cell line. However, it was also possible that the presence of an additional aromatic group, would have decreased the compound's efficacy, as a result of the electron localisation effects [289]. Nevertheless neither analogues were available from the library of compounds synthesised at the time the study took place, so were not examined in this preliminary study.



261



262

Figure 5.10 Structure of *N-phenyl* stilbenesulfonamide analogues

The biological testing of the analogues were performed at the University of Hertfordshire, compounds which did not have a % purity of > 98 % when synthesised, were recrystallised to ensure that the purity of the compounds used in this study were over 98 %. Furthermore the use of a reference anticancer drug and a pure sample of resveratrol, **1**, were omitted from this study, although it would have been of advantage to use either compounds as a reference, this was not considered a major issue at this stage of the preliminary study, as direct comparisons of cytotoxicity data could still made by referring to the literature, albeit the experimental conditions are known to vary.

5.3.2 Growth inhibition of A549 cell line

The anti-cancer activity of the six novel stilbenesulfonamides were examined with regards to their antiproliferative activity against the A549 cancer cell line, *via* the use of two common cell proliferation assays; trypan blue dye-exclusion and Sulforhodamine B protein (SRB) assay, the methods used are described in Appendix II. Trypan blue is a stain commonly used in dye exclusion methods in order to assess cell viability, this procedure was based on the staining of non-viable (dead) cells with compromised membrane integrity, whilst viable (living) cells were unaffected and therefore were not stained by the dye [290]. The SRB assay was also performed in order to determine both growth inhibition as well as cytotoxicity, this assay was based on the quantification of cellular protein content in order to determine cell density [291].

5.3.2.1 Trypan Blue dye exclusion growth assay

To determine the effect of the selected compounds (Table 5.11) on cell population growth, the A549 cancer cells were treated with two doses of each stilbene benzenesulfonamide analogue at concentrations of 50 µM and 5 µM, as presented in Figure 5.11 and Figure 5.12, respectively. The number of non-viable cells, which were stained with the trypan blue dye, were then counted under the light-microscope at 24, 48, 72 and 96 h. Analysis of the data from the trypan blue assays clearly indicated that analogue, **232e**, at a concentration of 50 µM significantly reduced A549 cell growth ($p < 0.05$) compared to the control (1 % DMSO), in a time and dose dependent manner. Additionally compound, **255**, at the same concentration (50 µM) was found to significantly decrease A549 cell growth at 24, 48 and 72 h ($p < 0.05$) (Figure 5.11).

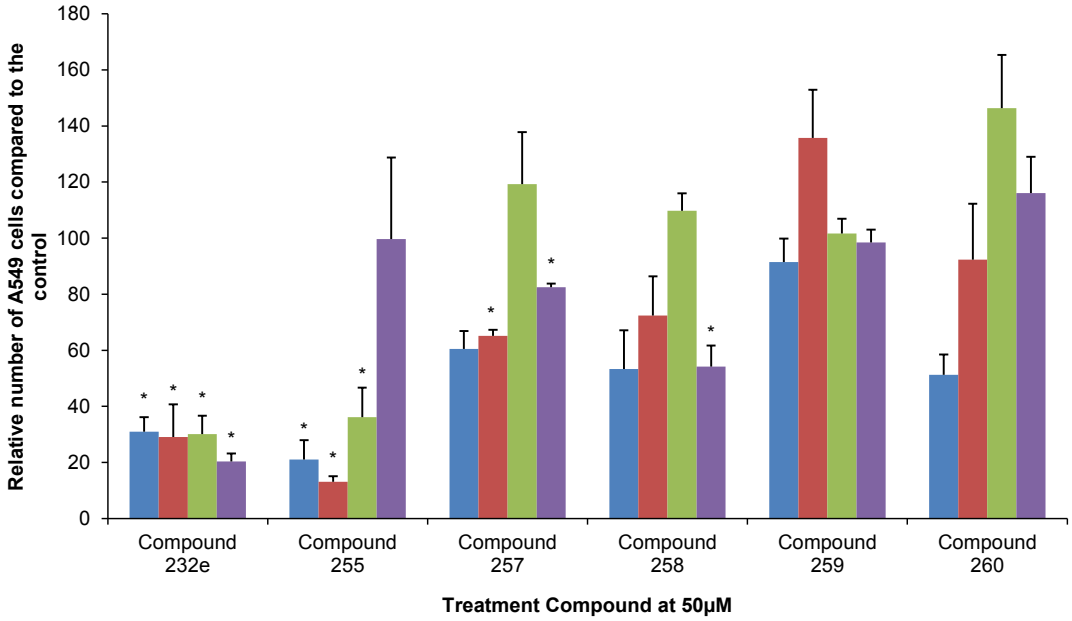


Figure 5.11 Dose and Time dependent responses of A549 of stilbenesulfonamide analogues (50µM)

Relative number of A549 cells counted at 24, 48, 72, and 96 h, after treatment with compounds **232e**, **255**, **257**, **258**, **259** and **260**, relative to the control 1 % DMSO. Blue bars indicate 24 h incubation, red bars indicate 48 h incubation, green bars indicate 72 h incubation, and purple bars indicate 96 h incubation. * = $p < 0.05$. Bars display number of cells relative to vehicle control. Data shown as mean + s.d. n = 6 wells

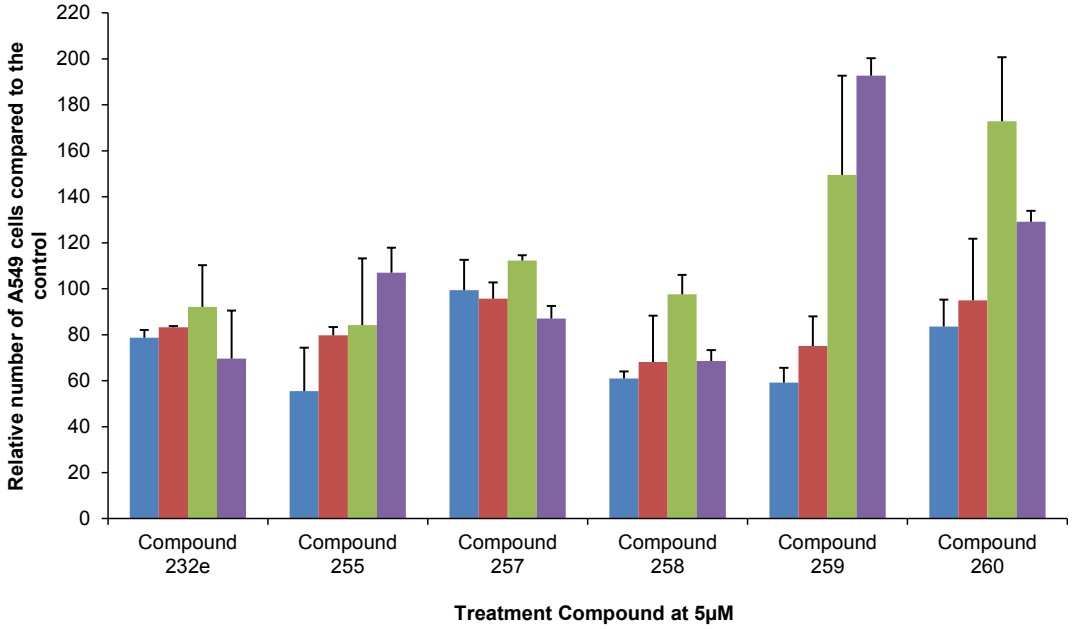


Figure 5.12 Dose and Time dependent responses of A549 of stilbenesulfonamide analogues (5 μM)

Relative number of A549 cells counted at 24, 48, 72, and 96 h, after treatment with compounds **232e**, **255**, **257**, **258**, **259** and **260**, relative to the control 1 % DMSO. Blue bars indicate 24 h incubation, red bars indicate 48 h incubation, green bars indicate 72 h incubation, and purple bars indicate 96 h incubation. * = $p < 0.05$. Bars display number of cells relative to vehicle control. Data shown as mean + s.d. n = 6 wells

Compounds **257** and **258**, at 50 μM also appeared to be effective at reducing A549 cell growth, however the effect displayed by these compounds were only observed at specific times, for instance compound, **257**, was found to only significantly reduce cell growth ($p < 0.05$) at 48 and 96 h (compared to the control), but not at 72 h. The reasons behind these findings are not clear; it is possible that the variations observed here were a result of different opinions as to what was considered viable and non-viable. Though attempts were made to standardise the cell counting technique, ensuring that only viable cells were counted when the distinct colour of the blue dye was not observed, it should be considered that the trypan blue assay is a subjective procedure, which relies on the subtle colour changes between the cells displayed

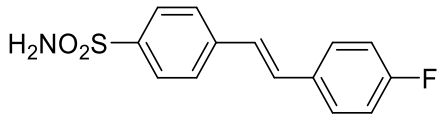
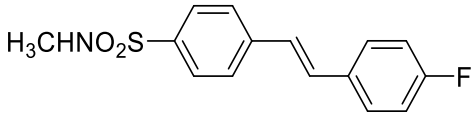
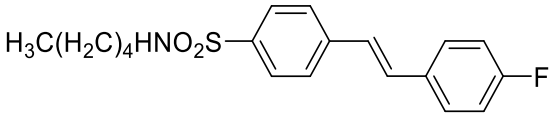
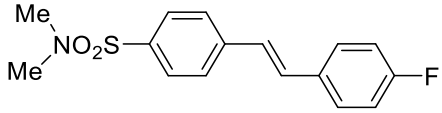
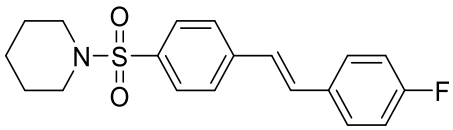
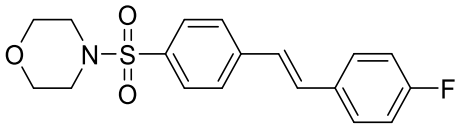
under a light microscope [292].

Furthermore, no significant effects were observed following the treatments with **259** and **260**, at concentration of both 50 and 5 μM. When considering the effect of the other compounds (**232e**, **255**, **257**, and **258**) at a concentration of 5 μM, it appeared that as a general trend, that the stilbenesulfonamide analogues did not have a significant effect on cell growth (Figure 5.12).

5.3.2.2 SRB Assay

Next, the cytotoxicity of the selected stilbenesulfonamide analogues (**232e**, **255**, **257**, **258**, **259** and **260**) against the A549 cancer cell line was determined using the SRB assay, according to the National Cancer Institute's methodology [8]. The cells were treated at a range of concentrations of the test compounds from 0 to 500μM, for 48 h and examined for cellular protein content, in order to calculate the molar concentration of each compound resulting in 50 % cell growth inhibition (GI_{50}). Table 5.12 summarised the GI_{50} values for each compound tested, and has been ranked from the most to the least potent as follows: **255** > **232e** > **257** > **260**, with compound **258** and **259** displaying no cytotoxic activity. Notably, compound, **255** (GI_{50} 0.1 μM), was found to be the most effective in reducing the cell protein content, when compared to the other analogues examined in this study. The second most potent compound was **232e (**GI_{50} 10.4 μM), whereby the GI_{50} measured, was found to be similar to that reported in the study by Yang *et al.,* (GI_{50} 8.9 μM) [6] (Table 5.12).

Table 5.12 Cytotoxicity of *trans*-stilbenesulfonamide analogues from Sulforhodamine B assay

Compound	Structure	Cytotoxicity (GI_{50} μM)[a]
232e		8.9[b] 10.4
255		0.1
257		220
258		-
259		-
260		>500

[a] The GI_{50} values are the concentrations relating to 50 % growth inhibition.
[b] Data reported by Yang and co-workers (6).

The results from the SRB assay seem to be in accordance with the trypan blue assay data (Section 5.3.2.1), as both assays showed that the compounds with the best antitumour activity were **232e** and **255**. However, based on the high potency (GI_{50}) calculated for compound **255** (GI_{50} 0.1 μM) from the SRB assay, an even greater inhibition of cell population growth would have been expected, during the study

performed using the trypan blue assay (Section 5.3.2.1), when compared to the other compounds tested. The reasons for these differences are unclear and require further investigation.

Nevertheless, both analogues, **232e** and **255**, were found to exhibit increased antiproliferative effects when compared to the lead compound, resveratrol **1**. Although for comparative purposes care must be taken when results come from different *in vitro* studies, the results from the SRB assay performed using resveratrol, **1**, as detailed from the NCI Developmental Therapeutics Programme database[8], reported resveratrol, **1**, to have a GI_{50} of 51.64 μM. By comparison, this means that resveratrol is ca. 500-fold less potent than the analogue, **255**, (GI_{50} 0.1 μM). Furthermore, compound, **255**, (GI_{50} 0.1 μM) was also found to be more potent, compared to 5-fluorouracil (GI_{50} 0.189μM) [8], a synthetic compound used to treat various forms of cancer.

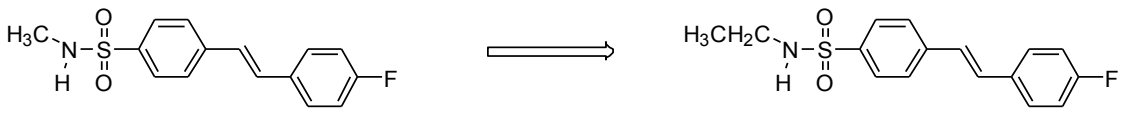
5.3.3 Structure-Activity-Relationship

The SAR of benzenesulfonamide analogues, possessing various functional groups on the sulfonamide nitrogen have been explored extensively [293, 294], based on the cell viability data in this study, it is not surprising that compound, **232e**, displayed increased activity against the A549 cancer cell line, as the presence of the sulfonamide (SO_2NH_2) moiety is known within the literature, to be essential in providing the highest efficacy, in relation to anticancer properties [169, 170, 174]. Furthermore, the promising results observed with compound, **255**, indicates that the presence of a HBD atom on the sulfonamide moiety and minimal steric effects on the sulfonamide nitrogen, may be important for activity.

On the other hand, both the increased hydrophobic (π) and steric effects displayed by compounds **257**, **258**, **259** and **260**, were found to decrease their activity, which suggest that the presence of steric and hydrophobic interactions are not important for activity.

Remarkably, compound **257**, which also possesses a HBD atom in the sulfonamide moiety was found to display decreased activity, based on this finding it is possible that the longer alkyl chain may have moved the hydrogen bonding ability within the sulfonamide moiety in compound, **257**, further away from the target binding pocket it was interacting with. It is also possible that the chain extension, resulting from the long alkyl chain may have changed the distances of the pharmacophore points in compound, **257** and led to a decrease in activity, however this warrants further investigation.

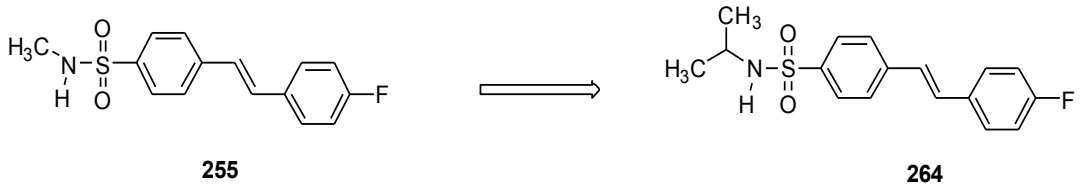
Based on the growth inhibition studies, it possible that the presence of a HBD and minimal steric hindrance are essential for activity, it would be of interest to explore the steric and hydrophobic influences displayed by the stilbenesulfonamide made from ethylamine, **256**, (Figure 5.13) whereby an additional carbon chain is added to the sulfonamide nitrogen, in order to determine at what alkyl chain length efficacy and potency decreases.



255 **256**

Figure 5.13 Structure of stilbenesulfonamide analogues to be considered for further study

Additionally, it would also be of interest to determine the importance of the presence of the methyl group on the sulfonamide nitrogen in compound, **255**, as the growth inhibition studies found compound, **258**, of which comprised of two methyl groups, each positioned on the sulfonamide nitrogen, to have minimal effect on decreasing A549 cell growth. Therefore, by constructing the stilbenesulfonamide, **264**, shown in Figure 5.14, the presence of the isopropyl moiety on the sulfonamide nitrogen would allow us to explore the steric effects of this group, whilst the hydrogen bonding ability of the sulfonamide is maintained, and to see if an increase or decrease in activity is observed with compound **264**.



255 **264**

Figure 5.14 Structure of stilbenesulfonamide analogues to be considered for further study

The presence of the fluorine atom on the aromatic ring, meant that a good level of solubility was obtained with the compounds examined. However as the main focus of the preliminary study was to solely examine the influence of the groups on the sulfonamide moiety, conclusions with regards to the SAR of the functional group positioned on the other aromatic ring cannot be fully drawn, but does warrant further investigation.

5.4 Summary

An alternative approach to the synthesis of *trans*-stilbenesulfonamides is presented, *via* the coupling of 1,4-disubstituted benzylphosphonate analogue, by means of the HWE reaction. The 1,4-disubstituted benzylphosphonate, **220**, was prepared *via* chlorosulfonation of the inexpensive and commercially available diethyl benzylphosphonate, **162**, using chlorosulfonic acid, **219**. Subsequent aminolysis of the sulfonyl chloride intermediate, **220**, with various amines successfully afforded the desired primary, secondary, tertiary heterocyclic stilbenesulfonamide analogues, **221a-221i**. Various aldehydes, including heterocyclic aldehydes were found to couple with substituted 1,4-disubstituted benzylphosphonate analogues, **221a-221i**, *via* the HWE reaction, affording the desired products in moderate to high yields. Alternatively, the condensation of 4-fluorobenzaldehyde, **230**, with the 1,4-disubstituted benzylphosphonate, **221a**, was found to be successful in the presence of potassium-*tert*-butoxide, as the base. In developing the work, this approach has also enabled an inexpensive, short and versatile synthetic route for the synthesis of a number of *trans*-stilbenesulfonamide analogues, previously reported in the literature. The growth inhibition studies performed found compound, **255**, (GI_{50} 0.1 μM) to be increasingly more potent, compared to resveratrol, **1**, (GI_{50} 51.64 μM) and other current chemotherapeutic drugs in the market, such as 5-fluorouracil (GI_{50} = 0.189μM), however further studies are required in order to understand the mechanism of action.

6. Conclusions and Future Work

6.1 Conclusions

The aim of this thesis was to investigate various routes towards the synthesis of *trans*-arachidin-1, **2**, in addition to resveratrol analogues. We have demonstrated for the first time a new methodology for the synthesis of arachidin-1, **2**, and resveratrol analogues, in the form of stilbene benzenesulfonamides, *via* the HWE reaction. This alkene forming reaction was found to be a favourable approach in the construction of the *trans*-stilbene, whilst affording 100 % *E*-selectivity.

In the approach designed for the synthesis of arachidin-1, **2**, incorporation of the prenyl side chain was addressed by examining the regioselective demethoxylation reaction with the acetal, **184**, whereby the use of iodomethylphosphonate at the alkylation step of the reaction, enabled the formation of the desired phosphonate, **190**, in good yield (86 %). This approach was found to be successful and enabled the construction of the 3-methylbut-1-enyl moiety in good yield (71 %), followed by the synthesis of the stilbene backbone, **3**, *via* the HWE reaction. The final step involving demethylation using BBr_3 gave arachidin-1, **2**, albeit in poor yield (30 %), however optimised studies are required in order to obtain the desired compound in quantitative yields.

Other methodologies designed for the synthesis of arachisin-1,**2**, were not successful, for instance the approach based on the methodology reported by Park and co-workers [84], involving the coupling of a silyl ether protected benzaldehyde, **151b**, with the phosphonate, **153**, *via* the HWE reaction highlighted problems, for instance

early cleavage of the silyl ether protecting groups was observed, which meant that this approach could not be explored further. However, this might have been prevented by the use of a non-silica based stationary phase, during purification *via* column chromatography.

To overcome this drawback an alternative methodology was designed, this approach proceeded by the regioselective demethoxylation of the 3,4,5-trimethoxybenzaldehyde dimethyl acetal, **184**, followed by alkylation with methyl iodide, and acetal hydrolysis to give the desired benzaldehyde, **183**. The subsequent HWE coupling of the aldehyde, **183**, with 3,4-dimethoxy benzylphosphonate, **185**, gave the *trans*-stilbene in good yield (86 %). Next the Wohl Ziegler bromination of the stilbene, **182**, although bromination, using NBS was found to be successful, an interesting observation was that the presence of both the radical initiator (AIBN) and incandescent light was not required for the required to proceed successfully. Nevertheless the main disadvantage of this reaction was the need of a toxic solvent, carbon tetrachloride, in large quantities, additionally this approach could not be taken further as a result of steric issues, which meant that the formation of the phosphonate was unsuccessful.

Next a study into the synthesis of resveratrol analogues was performed, the formation of *trans*-5-(3,5-dimethoxystyryl)-1,2,3-trimethoxybenzene, **124**, was successfully achieved *via* the HWE reaction, albeit in poor yield (39 %), furthermore formylation of the substituted stilbene, using dichloromethyl methyl ether and titanium(IV) chloride, was found to be unsuccessful. After studies were carried out to optimise these conditions, the experimental data suggested that at an elevated temperature of above -10 °C, di-formylation on the stilbene skeleton occurs, specifically when the Lewis acid is used in excess (> 6 equiv.).

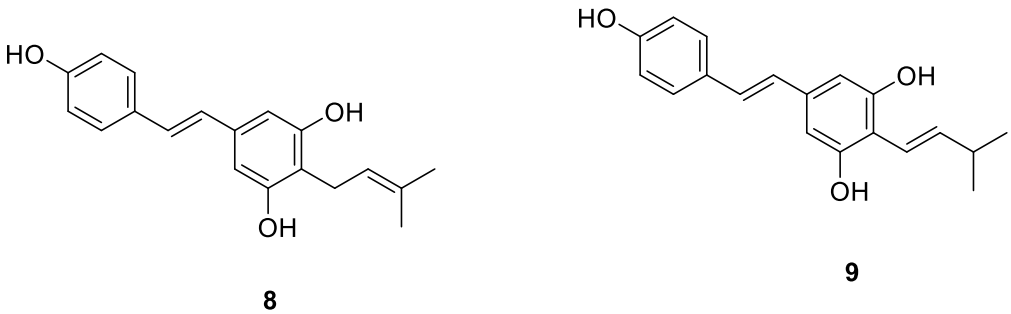
Nonetheless studies into the synthesis of resveratrol analogues in the form of *trans*-stilbene benzenesulfonamides was successfully demonstrated in Chapter 5, this novel and versatile methodology enabled the conversion of various primary, secondary and cyclic alkyl amines, as well as aromatic amines into a range of benzenesulfonamide analogues, in good to excellent yields (60 – 100%), the design of this methodology also enabled a scale up of at least a 15 g scale. Construction of the stilbene backbone *via* the HWE coupling reaction, enabled the formation of a library of stilbene benzenesulfonamide analogues, using various substituted aldehydes in addition heterocyclic aldehydes, in moderate to high yields (42 – 100 %), with excellent *E*-selectivity. Although this approach offers the scope of structural variety, the compounds synthesised in this phase of work, did not represent this extensively.

The A459 growth inhibition studies performed on the selected six stilbene benzenesulfonamide compounds, demonstrates that with regards to SAR the alkyl substitutions on the sulfonamide nitrogen, has an effect of the cytotoxic activity of these novel compounds. With the stilbene benzenesulfonamide, **255**, made from methylamine, exhibiting increased antiproliferative activity compared to the parent compound resveratrol, **1**, (approximately 500-fold) and other cancer chemotherapeutic drugs currently on the market. This analogue will be used as a lead compound, along with the ammonia derivative, **232e**, in subsequent antiproliferative studies.

6.2 Future Work

Synthesis of arachidin-1

The results from this work, offers a promising approach to the total synthesis of the natural stilbene phytoalexin arachidin-1, **2**, by means of coupling the synthesised (*E*)-3,5-dimethoxy-4-(3-methylbut-1-en-1-yl)benzaldehyde, **192**, and diethyl (3,4-dimethoxybenzyl)phosphonate, **185**, *via* the HWE reaction. Although the present work has shown the success of this methodology on a small scale, the next step of this work is to synthesise arachidin-1, **2**, using the methodology described in Chapter 3; part II, on a larger scale. In order to fully characterise the reaction intermediates, as well as constructing this peanut phytoalexin in quantitative yield and with increased purity. It would also be desirable to extend this methodology to the synthesis of other peanut phytoalexins, therefore a second aspect of the future work would be to synthesise stilbenes including arachidin-2, **8**, and arachidin-3, **9**, (Figure 6.1) which belong to the arachidin family.



8 **9**

Figure 6.1 Structure of known stilbene phytoalexins *trans*-arachidin-2 (8) and *trans*-arachidin-3 (9)

Synthesis of resveratrol analogues

A successful methodology has been developed for the synthesis of stilbene benzenesulfonamides, by the coupling of diethyl 4-sulfamoylbenzylphosphonate, **221a**, with various benzaldehydes, *via* the HWE condensation reaction. The reaction conditions developed have been found to be applicable to a diverse range of primary, secondary and cyclic alkyl amines, as well as aromatic amines and as a result, this approach has enabled the synthesis of a library of novel stilbene benzenesulfonamides, however one aspect of the future work will be to fully characterize these novel compounds using other analytical techniques including elemental analysis, in order to determine the elemental composition of each analogue and x-ray crystallography, in order to identify the arrangement of atoms in three dimensional space.

The present work has also shown the versatility of this reaction, furthermore based on the biological studies performed some interesting findings have emerged. Both stilbenesulfonamides made from ammonia and methylamine have displayed potent anti-proliferative activity, by decreasing protein density in the SRB study. However, these results were obtained from preliminary studies, therefore there is much work to be done in examining the activity of these compounds.

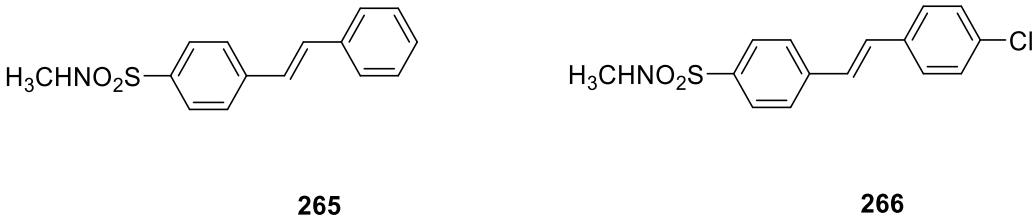
As a result the first aspect of the future work would be to investigate and extend the work further by examining structural modifications of the stilbene benzenesulfonamide analogues, by considering a non-mathematical utilization of the Hansch approach to drug design, as recommended by Topliss [79, 284], as they represent a range of hydrophobic (π) properties, steric properties and electronic (σ) properties.

By using the Topliss scheme, it would provide a further understanding of the structure

activity relationship of these novel compounds, *via* an optimization process in order to determine which substituents on the aromatic ring will lead to increased potency with regards to anti-cancer activity.

In terms of the study performed by Yang *et al.,* [6], it is not clear if the benzenesulfonamide analogues were selected based on a quantitative structure-activity relationship approach, nevertheless Yang and co-workers reported compound, **125a**, to be the most efficacious against the A549 cell line. Interestingly, the results from the growth inhibition studies discussed in Section 5.3.2, indicated an overall increase in activity, as the hydrophobicity of the functional group on the sulfonamide nitrogen increased, specifically from a hydrogen to a methyl group, with the novel analogue compound, **255**, found to be increasingly potent. It would therefore be of interest to use compound, **255**, as a lead compound and optimise the substituents on the non-sulfonamide aromatic ring, using the Topliss scheme in order to enhance the potency.

Therefore synthesising and investigating the activity of the unsubstituted stilbenesulfonamide, **265**, in addition to an analogue possessing a hydrophobic and electron withdrawing 4-chloro moiety, **266**, (Figure 6.2), would enable the potencies of these analogues to be compared, with both analogue, **255**, and resveratrol, **1**. In order to determine if the compound possessing the 4-chloro moiety will display equal, less or increased activity compared to the unsubstituted stilbenesulfonamide analogue, **266**. Furthermore, this would help to determine which substituted aldehyde to select next, based on the Topliss scheme [295] when synthesising new stilbenesulfonamide analogues.



265 **266**

Figure 6.2 Structures of stilbenesulfonamide analogues to be examined for biological activity

Once the optimum substituent on the non sulfonamide aromatic ring, has been identified enhancing the groups on the sulfonamide nitrogen would be of interest, as previously mentioned in Section 5.3.3, it would give us an understanding of the steric, and hydrophobic influences displayed by compounds, **264** and **256**, (Figure 6.3), compared to compound **255**.

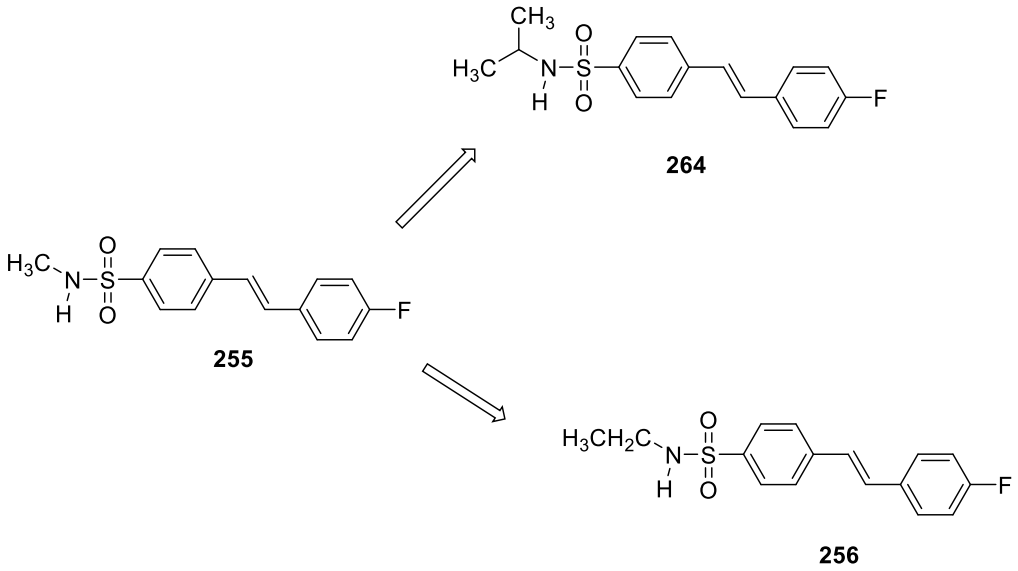


Figure 6.3 Structure of stilbenesulfonamides to be considered for future work

In terms of examining the biological activity of the novel stilbene benzenesulfonamides, although the assays performed in this preliminary study show

interesting results, in order to understand the activity of these compounds, the next aspect of the future work, would be to perform additional studies, using MTS, LDH assays in order to determine the mechanism of cell death displayed by these novel compounds. Additionally performing studies including flow cytometry to measure annexin V and PI in order to determine early-phase apoptosis and/or cell necrosis.

One main limitation of this preliminary *in vitro* study, was that the activity of these novel analogues were only examined using one cancer cell line (A549). In order to determine the potential anticancer activity and gain a better understanding into the efficacy displayed by these novel stilbene benzenesulfonamides, the activity of these compounds against the breast cancer carcinoma (IGROV-1) would be of interest to investigate next, as a number of the stilbenesulfonamide analogues synthesised by Yang *et al.*, have also been reported to be highly selective against this cancer cell line[6]. Furthermore, toxicity studies will need to be performed *in vitro*, in order to determine if these novel stilbene benzenesulfonamide analogues are only selective towards cancer cells and not normal mammalian cells.

Within the literature resveratrol, **1**, has been reported to exhibit fungicidal effects against known human infectious fungi, particularly *Saccharomyces cerevisiae* whilst displaying similar potency to amphotericin B [54]. It would therefore be of interest as future work to examine the antifungal activity of the stilbene benzenesulfonamides against the single-celled eukaryote, *Saccharomyces cerevisiae*.

Finally, the synthesis of stilbene benzenesulfone derivatives in the form of styrylheterocycles, **136(a-d)**, *via* the Wittig coupling reaction, has been published by Lim *et al.,* [173] with moderate to high yields (70 – 100 %). These analogues are of

biological interest, as they have been shown to display high selectivity and potency towards the COX-2 protein, therefore another direction would be to explore the scope of the three step methodology designed in Chapter 5, and determine whether, this approach could be adapted and extended to the synthesis of a methylsulfone (*p*-SO_2Me) moiety, in order to form stilbene benzenesulfone analogues, with various functional groups, in order to explore their selectivity towards COX-2 inhibition further (Figure 6.4).

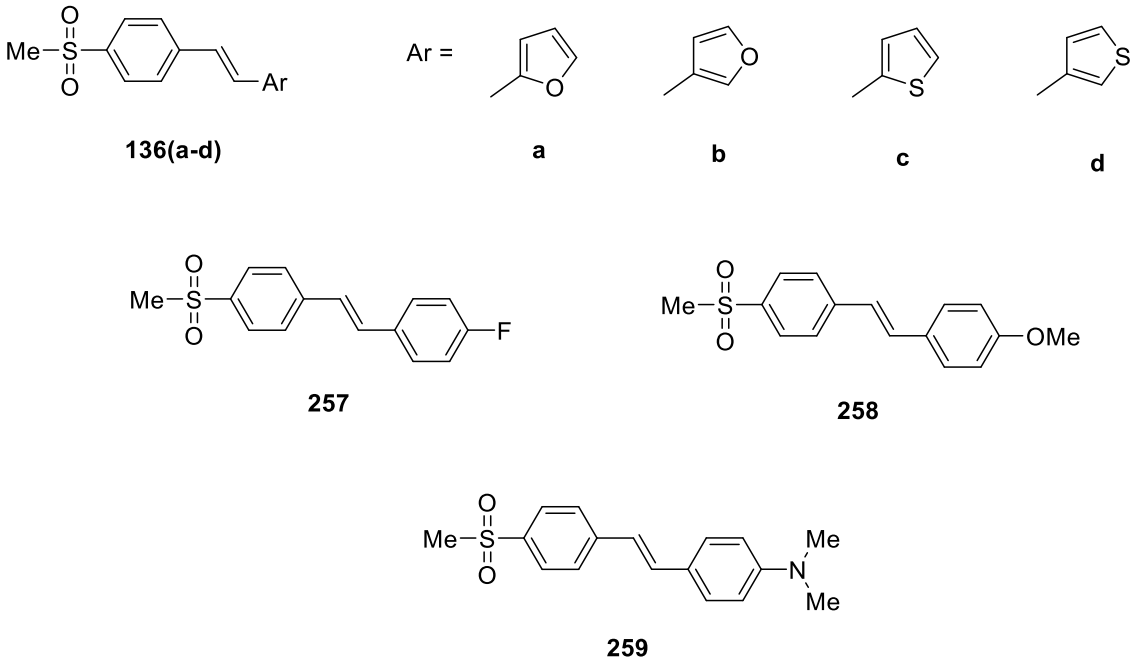


Figure 6.4 Structure of stilbenebenzenesulfone analogues to be considered for future work

Chapter Seven: Experimental

7. General Experimental Details

Reaction Conditions

All moisture or oxygen sensitive reactions were performed under an atmosphere of nitrogen, using oven dried glassware, syringes and needles. All transfers were carried out using glass or plastic syringes. Stirring was by internal magnetic stirrer unless otherwise stated. The organic phases were dried with anhydrous magnesium sulfate or sodium sulfate. All reactions were monitored by TLC.

Solvents

Tetrahydrofuran, dichloromethane and chloroform were dried over molecular sieves (4Å). All other solvents were used as supplied from commercial sources.

Reagents and Materials

The materials and commercial available reagents were used as supplied unless stated otherwise.

Chromatography

Thin layer chromatography analysis was carried out using POLYGRAM® SIL G/UV_{254} silica gel with fluorescent plates (Macherey-Nagel); thickness of layer 0.20 mm. Visualisation by exposure to ultraviolet light (λ = 254 nm / 365 nm) and/or by staining with iodine vapour. Flash column chromatography was carried out using Merck silica gel 60 (230- 400 mesh). Samples were applied in a concentrated form; using an appropriate solvent.

Physical and analytical measurements

Melting points were determined using a Griffin melting point apparatus and are uncorrected. Infrared spectra were recorded using either a Perkin Elmer FT-IR/FIR Spectrometer Frontier, with samples prepared as thin films on the universal ATR sampling accessory, or on a Varian FT-IR 800 Scimter series, with samples prepared as thin films between either NaCl plates or ATR sampling accessory, or on KBr discs. ^{1}H NMR and ^{13}C NMR spectra were recorded on one of the following spectrometers: a Bruker AM360, operating at 150 MHz, 300 MHz, 500 MHz and 600 MHz and JEOL ECA, operating at 400 MHz and 600 MHz for proton (^{1}H) and at 100 MHz and 150 MHz for carbon (^{13}C). NMR measurements were recorded in either chloroform-d ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6) as solvent, unless otherwise stated. For the identification of exchangeable protons, deuterium oxide (D_2O) was used. The chemical shift values (δ_H and δ_C) are quoted as parts per million (ppm) relative to the internal standard tetramethylsilane (TMS) and/or the residual proton solvent peak for ^{1}H NMR spectra, and from the solvent peaks for ^{13}C NMR, using values obtained from literature [296]. The multiplicity of a ^{1}H NMR signal is designated by the following

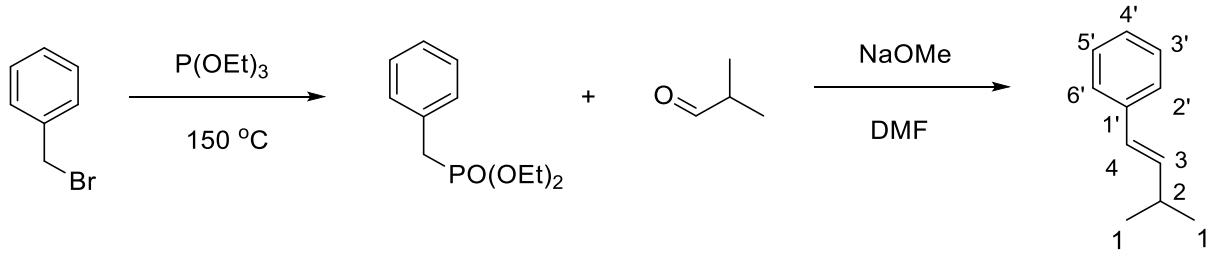
abbreviation: s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, dd = doublet of doublets, dq = doublet of quartets, dsep = doublet of septets, m = multiplet and br = broad signal. Multiplets are reported as the mean chemical shift at which they appear. The coupling constants (*J* values) are reported to one decimal place with values in hertz (Hz). ^{1}H NMR spectra are reported in the form δ_H (integration, multiplicity, coupling constants, assignment). ^{13}C NMR data are recorded in the form δ_C (assignment). Low-resolution mass spectra, with electrospray ionisation (ESI) were recorded on a Varian system with 2 x 210 LC pumps, a 400 auto sampler and a 1200L mass spectrometer.

Characterisation

The structures of compounds synthesised within this experimental chapter were analysed and characterised on the basis of, but are not limited to, the following spectral data; IR, ^{1}H NMR, ^{13}C NMR and low-resolution mass spectra (ESI). In many instances assignment of ^{13}C NMR signals were supported by DEPT experiments. The purity of the compounds was determined by NMR analysis, this technique was used to confirm the compounds synthesised were ≥ 95 % pure. General structural annotations for compounds characterised by ^{1}H and ^{13}C NMR analysis, can be seen in Appendix I. Wherever it was not possible to fully characterise a compound, by obtaining all required data, reasons for this have been specified in the main section of the thesis.

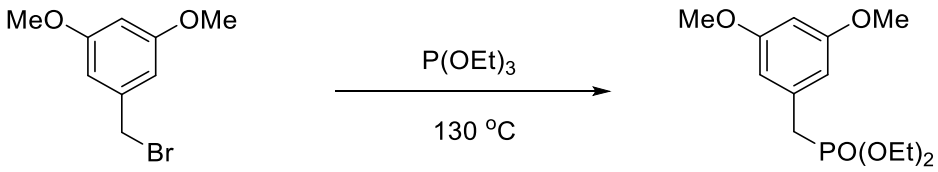
7.1 Experimental for Chapter 2

(E)-(3-methylbut-1-en-1-yl)benzene (157)



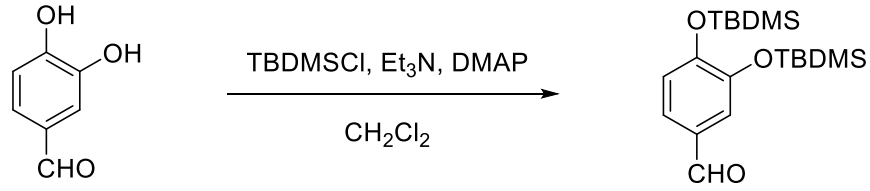
Triethyl phosphite (7.2 g, 44 mmol) and benzyl bromide (5.04 g, 29 mmol) were heated at 150 ºC, whilst stirring under a N_2 atmosphere. Once the reaction was complete, 20 h, as indicated by TLC [3:1 DCM/cyclohexane], the mixture was cooled to room temperature; anhydrous DMF (150 mL). Sodium methoxide (20.99 g, 389 mmol) was added and the resulting mixture was stirred for 30 min, followed by the addition of 2-methylpropanal. (1.98 g, 27 mmol). Upon completion of the reaction (24 h), the mixture was poured into ice-cold water; the precipitate was filtered off and dried, to give the title product as an orange solid 3.23 g. R_f 0.90 [3:1 DCM/cyclohexane]; υ_{max} (neat)/cm^{-1} 1466, 1620 (C=C), 2977, 3263 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 1.04 (6H, d, J = 6 Hz, CH_3), 6.18 (1H, d, J_{AB} = 16 Hz, *trans*-HC=CH), 6.33 (1H, d, J_{AB} = 15.9 Hz, *trans*-HC=CH), 2.45 (1H, sep, J = 6 Hz, CH), 7.37-7.20 (5H, m, ArH); δ_C (100 MHz; $CDCl_3$) 22.5, 23.3 (2 x C_1), 36.6 (C_2), 126.6 ($C_{4'}$), 126.8 (C_4), 127.7 ($C_{3'}$ & $C_{5'}$), 128.5 ($C_{3'}$ & C_6'), 137.4 ($C_{1'}$), 138.1 (C_3). % purity determined by ^{1}H NMR (compound, **157**, (25 %), compound, **162**, (55 %), compound, **163**, (20 %)).

Diethyl 3,5-dimethoxybenzylphosphonate (153)



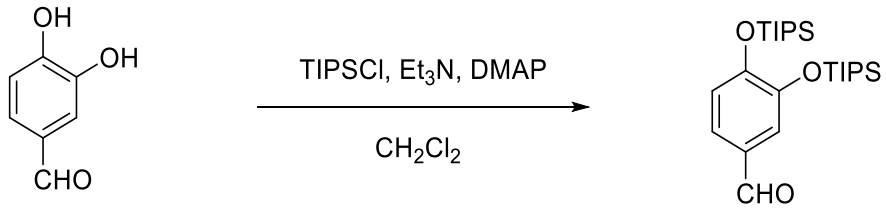
Triethyl phosphite (1.55 g, 9.3 mmol) was added to 3,5-dimethoxybenzyl bromide (1.43 g, 6.2 mmol). Following the addition, the resulting mixture was heated at 130 °C, whilst stirring for 24 h under N_2. Once the reaction was complete, as indicated by TLC [3:1 DCM/cyclohexane], the reaction mixture was left to cool to room temperature, to give the desired product (1.98 g, 100 %) as an orange oil; R_f 0.22 [3:1 DCM/cyclohexane]; υ_{max} (film)/cm^{-1} 1020 (C-O), 1248 (P=O), 1600 (C=C), 2842, 2905, 2941, 2987 (C-H and =CH-), 3443 (H_2O); δ_H (400 MHz; $CDCl_3$) 1.22 (6H, dt, *J* = 7.2 Hz, C-CH_3), 3.06 (2H, d, *J* = 21.6 Hz, CH_2-P), 3.73 (6H, s, OMe), 3.98 (4H, m, O-CH_2-C), 6.30 (1H, br, *J* = 6.1 Hz, ArH_4), 6.41 (2H, br, *J* = 2.4 Hz, $ArH_{3\ \&\ 5}$); δ_C (100 MHz; $CDCl_3$) 16.2, 16.4 (CH_2-$\underline{C}H_3$), 33.3, 34.7 (CH_2-P), 55.3 (OMe), 62.1, 62.2 (O-CH_2-C), 99.1 (C_1), 107.8, 107.9 (C_2 & C_6), 133.6, 133.7 (C_1), 160.7 (C_3 & C_5); LCMS (ESI) found *m/z* $[M+H]^+$: 289, $C_{13}H_{21}O_5P$ requires 288.11.

3,4-bis((tert-butyldimethylsilyl)oxy)benzaldehyde (151a)



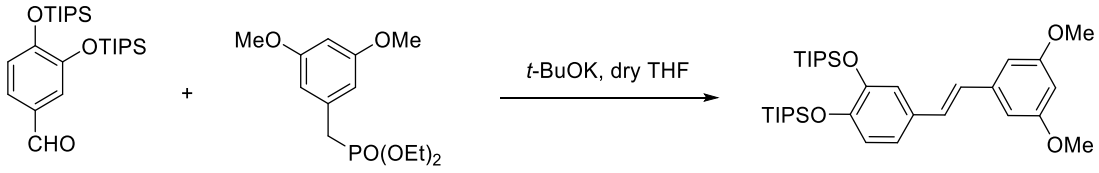
To a stirred solution of 3,4-dihydroxybenzaldehyde (6.16 g, 44 mmol) in anhydrous DCM (120 mL), cooled to the required temperature (0 °C), triethylamine (9.43 g, 93 mmol) was added, followed by DMAP (1.08 g, 8.8 mmol), in anhydrous DCM (80 mL). Following the addition, the resulting mixture was stirred at 0 °C for 10 min. *tert*-Butyldimethylsilyl chloride (14.1 g, 94 mmol) was added, and the resulting mixture warmed to room temperature and stirred for 18 h. Water (100 mL) was added to the reaction mixture, the mixture was extracted with dichloromethane (3 x 100 mL); the organic phases were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The crude product was purified by flash chromatography using DCM, to afford the title product, **151a**, (16.06 g, 98 %), as a pale yellow oil; R_f 0.59 [DCM]; υ_{max} (film)/cm^{-1} 1590 (C=C), 1682 (C=O), 2856, 2936, 2959 (C-H and =CH-); δ_H (600 MHz; $CDCl_3$) 0.00 (12H, s, Si-CH_3), 0.82 (18H, s, C-CH_3), 6.90 (1H, d, *J* = 8.2 Hz, ArH_5), 7.33 (1H, s, ArH_2), 7.37 (1H, d, *J* = 7.8 Hz, ArH_6), 9.75 (1H, s, CHO); δ_C (150 MHz; $CDCl_3$) -3.63 (Si-CH_3), 17.9 (<u>C</u>-$(CH_3)_3$), 25.6 (C-(<u>C</u>$H_3)_3$), 108.9 (C_2), 110.3 (C_5), 126.8 (C_6), 130.0 (C_1), 149.5 (C_3) 154.4 (C_4), 190.9 (CHO); LCMS (ESI) found *m/z* $[M+3]^+$: 369, $C_{19}H_{34}O_3Si_2$ requires 366.20.

3,4-bis((triisopropylsilyl)oxy)benzaldehyde (151b)



To a stirred solution of 3,4-dihydroxybenzaldehyde (5.00 g, 36 mmol) in anhydrous DCM (120 mL), cooled to the required temperature (0 °C), triethylamine (7.69 g, 79 mmol) was added, followed by DMAP (0.88 g, 7.2 mmol), in anhydrous DCM (100 mL). Following the addition, the resulting mixture was stirred at 0 °C for 10 min. Triisopropylsilyl chloride (14.6 g, 76 mmol) was added drop wise, and the resulting mixture warmed to room temperature and stirred for 18 h. Water (100 mL) was added to the reaction mixture, the mixture was extracted with dichloromethane (3 x 100 mL); the organic phases were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*, to give the crude compound (15.67 g, 96 %). Purification by flash column chromatography [DCM], gave the title compound, **151b**, (14.72 g, 90 %), as a yellow oil; R_f 0.62 [1:2 DCM/cyclohexane]; υ_{max} (film)/cm^{-1} 1593 (C=C), 1702 (C=O), 2729, 2865, 2892, 2942 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 1.11 (36H, m, C-CH_3), 1.32 (6H, sep, J = 2.5 Hz, Si-CH), 6.92 (1H, d, J = 8.1 Hz, $ArH_{5'}$), 7.30 (1H, dd, ^4J = 2.1 Hz, J = 6.1 Hz, ArH_2), 7.35 (1H, d, J = 2.0 Hz, ArH_6), 9.77 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 17.9 (CH-$\underline{C}H_3$), 26.9 (Si-CH), 118.9 (C_2), 119.6 (C_5), 125.2 (C_6), 130.3 (C_1), 147.8 (C_3) 153.4 (C_4), 190.7 (CHO); LCMS (ESI) found *m/z* $[M-H]^-$: 293, $C_{16}H_{25}O_3Si$ requires 293.16; 450, $C_{25}H_{46}O_3Si_2$ requires 450.30. % purity determined by ^1H NMR (compound, **151b**, (86 %), compound, **150**, (14 %)).

(*E*)-((4-(3,5-dimethoxystyryl)-1,2-phenylene)bis(oxy))bis(triisopropylsilane) (154b)



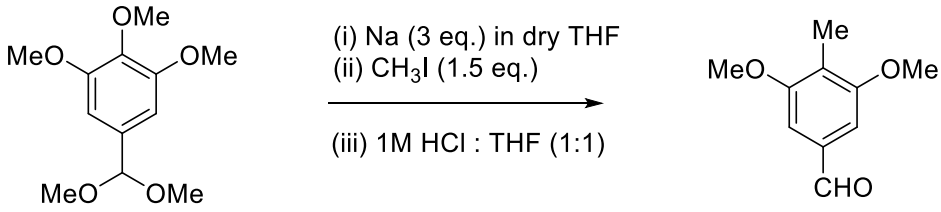
To a solution of diethyl 3,5-dimethoxybenzylphosphonate (7.40 g, 25 mmol) and 3,4-bis((triisopropylsilyl)oxy)benzaldehyde (11 g, 24 mmol) in dry THF (100 mL) at 0 ºC, under N_2 atmosphere. Potassium-*tert*-butoxide (8.29 g, 113 mmol) was added, then the reaction was stirred for 18 h at room temperature, under N_2 atmosphere. The reaction was monitored by TLC [DCM]. Once the reaction was complete, as indicated by TLC, the reaction was quenched by the addition of water (50 mL) and the reaction mixture was extracted with ethyl acetate (3 x 100 mL), the organic phases were combined, washed with saturated NH_4Cl solution (50 mL), followed by water (50 mL), then brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the impure product (8.04 g, 56 %) as an orange oil. Purification by column chromatography on silica gel [1:10 cyclohexane/EtOAc], gave the product as a pale yellow oil (3.84 g, 27 %); R_f 0.10, 0.65, 0.73, 0.81, 0.93 [DCM]; υ_{max} (film)/cm^{-1} 1593 (C=C), 2869, 2892, 2947 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 1.13 (36H, m, C-CH_3), 1.31 (6H, sep, J = 8.0 Hz, Si-CH), 3.82 (6H, s, OMe), 6.36 (1H, d, J = 2.0 Hz, ArH_4), 6.63 (2H, d, J = 1.0 Hz, $ArH_{2',5'}$), 6.80 (1H, m, ArH_2), 6.79 (1H, m, *trans*-HC=CH), 6.94 (1H, d, J_{AB} = 16.3 Hz, *trans*-HC=CH), 6.96 (1H, dd, ^4J = 1.8 Hz, J = 5.2 Hz, $ArH_{6'}$), 6.98 (1H, s, ArH_6 - overlapping); δ_C (100 MHz; $CDCl_3$) 12.0, 12.3, (CH_3), 17.7, 18.0 (Si-CH), 55.3 (OMe), 99.6 (C_4), 104.4 (C_2 & C_6), 117.5 ($C_{2'}$), 117.7 ($C_{5'}$), 124.0 ($C_{6'}$), 127.1, 127.3 ($C_{7'}$ & C_7), 129.8 ($C_{1'}$), 142.8 ($_{C1}$), 147.1 ($C_{4'}$) 147.2

($C_{3'}$), 160.9, 161.0 (C_3 & C_5); LCMS (ESI) found *m/z* $[M+H]^+$: 427, $C_{25}H_{35}O_4Si$ requires 427.23, 589, $C_{34}H_{58}O_4Si_2$ requires 584.37.

% purity determined by ^1H NMR (compound, **154b**, (79 %), compound, **169**, (21 %)).

7.2 Experimental for Chapter 3

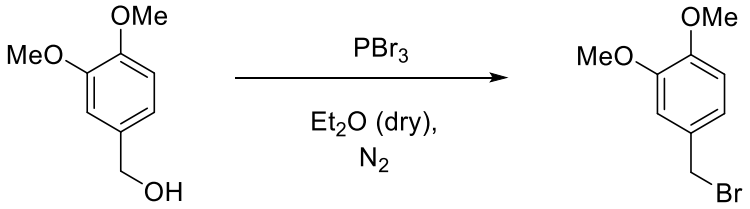
3,5-dimethoxy-4-methylbenzaldehyde (183)



A solution of 3,4,5-trimethoxybenzaldehyde dimethyl acetal (12.07 g, 50 mmol) in anhydrous THF (180 mL), was added dropwise, to a stirring mixture of sodium, 30-35 wt % dispersion in paraffin, (9.88 g, 429 mmol) in anhydrous THF (60 mL) cooled to 1 ºC, under an atmosphere of N_2. The resulting mixture was stirred for 26 h under an atmosphere of N_2, at room temperature. Once the reaction was complete, as indicated, by TLC [3:1 DCM/cyclohexane], the mixture was cooled to 0 ºC, followed by the dropwise addition of iodomethane (7 mL). The resulting mixture was stirred at room temperature, under an atmosphere of N_2 for 24 h. Once the reaction complete, the mixture was added dropwise to water (120 mL) and extracted with ether (2 x 200 mL), the organic phases were collected and washed with water (120 mL), and the organic phase was separated and dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude acetal. The crude solid was dissolved in a solution of 1M hydrochloric acid (200 mL) in THF (200 mL); (1:1) and stirred at room temperature for three days, after which the mixture was extracted with diethyl ether (3 x 120 mL), The organic phases were then combined and washed with water (2 x 120 mL), the organic phase was separated and dried with $MgSO_4$, filtered and concentrated *in vacuo*. Recrystallization (propan-1-ol) gave the title compound, **183** (yield: 8.24 g, 92 %) as a yellow solid; R_f

0.59 [3:1 DCM/cyclohexane]; m.p. 86 ºC - 88 ºC (lit m.p. 89 - 90 °C [297]); υ_{max} (neat)/cm^{-1} 1126, 1239 (C-O), 1391 (CH_3), 1462, 1588 (C=C), 1684 (C=O), 2751, 2797, 2847, 2931, 2973, 3015, 3066, 3112 (C-H and =CH-); δ_H (100 MHz; $CDCl_3$) 2.10 (3H, s, C-CH_3), 3.88 (6H, s, OMe), 6.98 (2H, s, $ArH_{2\ \&\ 6}$), 9.84 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 8.9 (CH_3), 55.8 (OMe), 104.6 (C_3 & C_5), 122.4 (C_1), 135.1 (C_4), 158.6 (C_2 & C_6), 191.9 (CHO); LCMS (ESI) found *m/z* $[M-H]^-$: 180, $C_{10}H_{12}O_3$ requires 180. The data was consistent with literature values [201, 202].

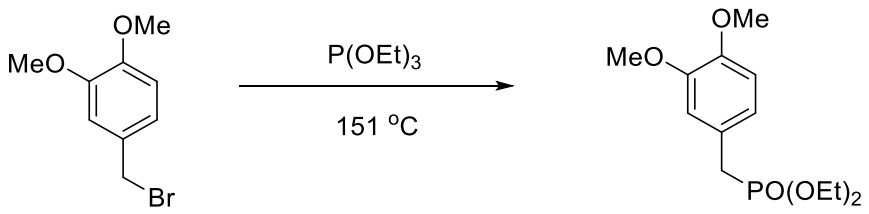
4-(Bromomethyl)-1,2-dimethoxybenzene (187)



Phosphorus tribromide (90 g, 335 mmol), dissolved in anhydrous diethyl ether (160 mL) was slowly added to a stirred solution of 3,4-dimethoxybenzyl alcohol (47 g, 280 mmol) in anhydrous diethyl ether (410 mL), at room temperature, under an atmosphere of N_2, then the reaction was stirred for 22 h. Following the completion of the reaction, as indicated by TLC [DCM], the reaction mixture was poured into ice cold water (500 mL) and the mixture was neutralised by the addition of sodium hydrogen carbonate. The reaction mixture was extracted with dichloromethane (3 x 200 mL), The organic phases were then combined and dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 4-(bromomethyl)-1,2-dimethoxybenzene, (yield: 65 g, 101 %), as white crystals; R_f 0.22 [DCM]; m.p. 48 ºC - 51 ºC (lit m.p. 47 - 50 °C [97]); υ_{max} (KBr)/cm^{-1} 1035 (C-O), 1420 (CH_3), 1607, 1523 (C=C), 2839, 2910, 2952, 3005,

3014 (C-H and =CH-); δ_H (75 MHz; $CDCl_3$) 3.73 (3H, s, OMe), 3.75 (3H, s, OMe), 4.49 (2H, s, CH_2), 6.78 (1H, d, *J* = 9 Hz, ArH_3), 6.93 (2H, m, *J* = 9 Hz, $ArH_{2\ \&\ 6}$); δ_C (100 MHz; $CDCl_3$) 34.5 (CH_2-Br), 55.7, 55.8 (2 x OMe), 111.1 (C_3), 112.1 (C_6), 120 (C_2), 130.8 (C_1), 148.6 (C_5), 149.2 (C_4); LCMS (ESI) found *m/z* $[M + H]^+$: 230 (^{79}Br), $C_9H_{11}BrO_2$ requires 229. The data was consistent with literature values [218]. % purity determined by ^{1}H NMR (compound, **187**, (93 %), compound, **186**, (7 %)).

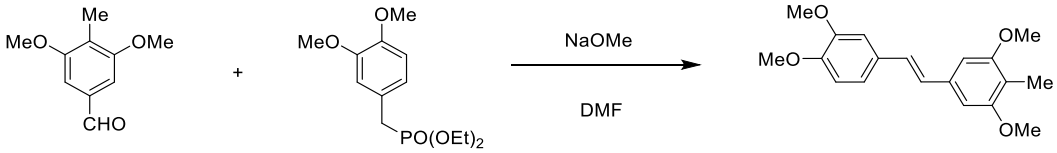
Diethyl (3,4-dimethoxybenzyl)phosphonate (185)



Triethyl phosphite (77 g, 0.46 mol) was added to 3,4-dimethoxybenzyl bromide (71 g, 0.31 mol), then the resulting solution was heated at 151 °C, under an atmosphere of N_2, for 24 h. The desired product was obtained upon cooling to room temperature (yield: 50.60 g, 57 %) as colourless oil. No further work up or additional purification was performed. R_f 0.08 [2:1 DCM/cyclohexane]; υ_{max} (neat)/cm^{-1} 1249 (P=O), 2832, 2907, 2937, 2978 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 1.16 (6H, t, *J* = 4.1 Hz, C-CH_3), 2.94 (2H, d, *J* = 21.1 Hz, CH_2-P), 3.73 (3H, s, OMe), 3.75 (3H, s, OMe), 3.92 (4H, m, *J* = 5.4 Hz, O-CH_2-C), 6.78 (1H, d, *J* = 9 Hz, ArH_3), 6.94 (2H, m, *J* = 9 Hz, $ArH_{2\ \&\ 6}$); δ_C (100 MHz; $CDCl_3$) 16.4 (2 x CH_3), 32.4, 33.8 (CH_2-P), 55.8 (2 x OMe), 62.7, 62.0 (2 x OCH_2), 111.1 (C_3), 112.8 (C_6), 121.8 (C_2), 123.7 (C_4) 147.9 (C_5), 148.8 (C_4); LCMS (ESI) found *m/z* $[M + H]^+$: 289, $C_{13}H_{21}O_5P$ requires 288. % purity

determined by ^{1}H NMR (compound, **185**, (48 %), triethyl phosphite (52 %)). The data was consistent with literature values [201, 202].

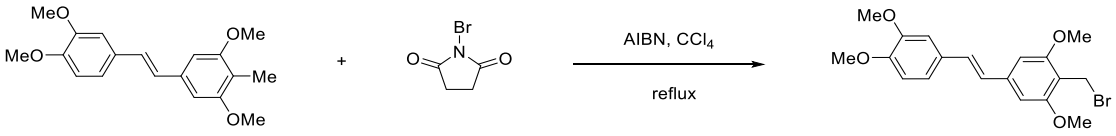
(*E*)-5-(3,4-dimethoxystyryl)-1,3-dimethoxy-2-methylbenzene (182)



To a stirred mixture of the diethyl (3,4-dimethoxybenzyl)phosphonate (50.60 g, 0.17 mmol) in anhydrous DMF (210 mL) at room temperature, under an atmosphere of N_2, sodium methoxide (9.1 g, 0.16 mol) was added. The reaction was stirred for 30 min, then 3,5-dimethoxy-4-methylbenzaldehyde (20.24 g, 0.11 mmol) in anhydrous DMF (50 mL) was added to the stirred mixture and the reaction mixture was left to stir at room temperature. The reaction was monitored by TLC [3:1 DCM/cyclohexane]. Once the reaction was complete, as indicated by TLC, the reaction was quenched by the addition of ice and stirred. The precipitate was filtered off, washed with cold water and air dried to give the crude product; (*E*)-5-(3,4-dimethoxystyryl)-1,3-dimethoxy-2-methylbenzene (yield: 12.29 g, 35 %), as a pale yellow solid. R_f 0.48 [3:1 DCM/cyclohexane]; m.p. 147 ºC - 159 ºC; υ_{max} (KBr)/cm^{-1} 1143 (C-O), 1420 (CH_3), 1462, 1511, 1584 (C=C), 2849, 2917, 2956, 2994, 3002 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 2.10 (3H, s, CH_3), 3.87 (6H, s, OMe), 3.89 (3H, s, OMe), 3.94 (3H, s, OMe), 6.68 (2H, s, $ArH_{2\ \&\ 6}$), 6.86 (1H, d, J = 12 Hz, $ArH_{5'}$), 6.93 (1H, d, J_{AB} = 16.2 Hz, *trans*-HC=CH), 7.02 (1H, m, *trans*-HC=CH), 6.97 (1H, m, $ArH_{2'}$), 7.27 (1H, d, J = 6 Hz, $ArH_{6'}$); δ_C (100 MHz; $CDCl_3$) 8.93 (CH_3), 55.8, 55.9 (OMe), 101.8 (C_2 & C_6), 108.7 ($C_{2'}$), 111.3 ($C_{5'}$), 114.2 (C_4), 119.8 ($C_{6'}$), 127.4, 127.7 (C_7 & $C_{7'}$), 130.5 ($C_{1'}$),

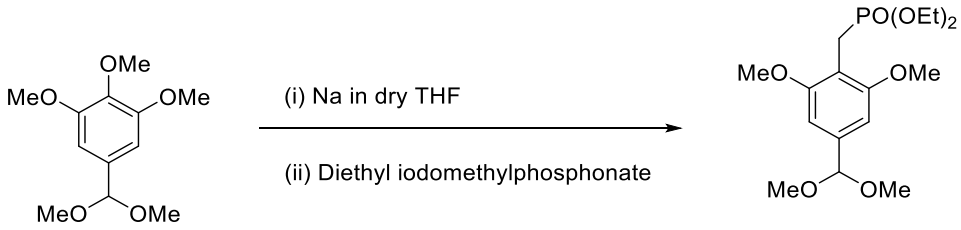
136.0 (C_1), 148.9 ($C_{4'}$), 149.2 ($C_{3'}$), 158.5 (C_3 & C_5); LCMS (ESI) found *m/z* $[M + H]^+$: 315, $C_{19}H_{22}O_4$ requires 314. % purity determined by ^1H NMR (compound, **182**, (86 %), compound, **183**, (14 %)).

Attempted Synthesis of (*E*)-2-(bromomethyl)-5-(3,4-dimethoxystyryl)-1,3-dimethoxybenzene (181b)



To the crude (*E*)-5-(3,4-dimethoxystyryl)-1,3-dimethoxy-2-methylbenzene (0.92 g, 2.9 mmol) dissolved in carbon tetrachloride (70 mL), N-bromosuccinimide (2.08 g, 12 mmol) followed by 2,2′-azobis(2-methylpropionitrile) (0.032 mg, 1.9 x 10^{-5} mmol) was added, then the mixture was heated under reflux at 78 °C, whilst stirring for 24 h. The reaction was monitored by TLC [3:1 DCM/cyclohexane], once the reaction was complete, the mixture was cooled and filtered using a sintered funnel, to collect the succinimide solid. The organic solvent was washed with water (3 x 100 mL) dried (Na_2SO_4), filtered and concentrated *in vacuo*. Petroleum ether, 40 – 60 % (50 mL) was added and the precipitate was filtered under vacuum, to afford a beige solid. Yield: 0.22 g, 19 %; R_f 0.55 [2:1 EtOAc/cyclohexane]; m.p. 98 - 110 ºC; υ_{max} (neat)/cm^{-1} 1167 (C-O), 1514, 1589 (C=C), 2843, 2948, 3014 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 3.88 (6H, s, OMe), 3.90 (3H, s, OMe), 3.93 (3H, s, OMe), 4.58 (2H, q, *J* = 3.12 Hz, CH_2-Br), 6.85 (2H, s, $ArH_{2\ \&\ 6}$), 6.89 (1H, m, *trans*-HC=CH), 6.92 (1H, m, $ArH_{5'}$), 6.99 (1H, d, J_{AB} = 16.0 Hz, *trans*-HC=CH), 7.32 (1H, m, $ArH_{2'}$), 7.53 (1H, m, $ArH_{6'}$); LCMS (ESI) found *m/z* $[M+H]^+$: 393, $C_{19}H_{21}BrO_4$ requires 392.

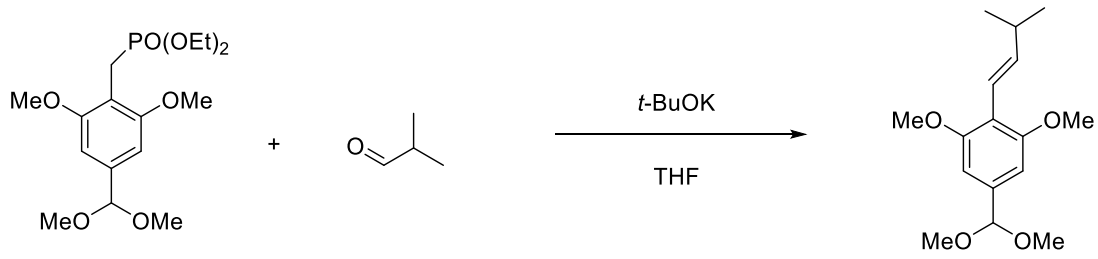
Diethyl (4-(dimethoxymethyl)-2,6-dimethoxybenzyl)phosphonate (190)



A solution of 3,4,5-trimethoxybenzaldehyde dimethyl acetal (3.23 g, 13 mmol) in anhydrous THF (30 mL), was added dropwise, to a stirring mixture of sodium, 30-35 wt % dispersion in paraffin (2.8 g, 121 mmol) in anhydrous THF (110 mL) cooled to 0 ºC, under an atmosphere of N_2. The resulting mixture was stirred for 24 h under an atmosphere of N_2, at room temperature. Once the reaction complete, as indicated by TLC [3:1 DCM/cyclohexane], the mixture was cooled to 0 ºC and diethyl iodomethylphosphonate (5.0 g, 18 mmol) was added drop wise. The resulting mixture was stirred at room temperature, under N_2 for 24 h. The reaction was quenched by the addition of water (20 mL) and extracted with ether (3 x 30 mL), the organic phases were collected and washed with water (20 mL), and then brine (20 mL), and the organic phases were collected, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude acetal, as a fluffy orange solid. The crude acetal was immediately used for the next reaction. Yield: 6.92 g. R_f 0.06 [3:1 DCM/cyclohexane]; υ_{max} (neat)/cm^{-1} 1118, 1204 (C-O), 1462, 1595 (C=C), 2847, 2915, 2953 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 1.24 (6H, t - broad, C-CH_3), 3.32 (2H, d - broad, CH_2-P), 3.47 (6H, m - broad, OMe), 3.84 (6H, m - broad, OMe), 3.95 (4H, m, O-CH_2-C), 6.38 (1H, s, CH), 6.50 (2H, s - broad, $ArH_{2\ \&\ 6}$); LCMS (ESI) found *m/z* = 361, $C_{16}H_{27}O_7P$ requires 362. Broad peak signals were observed in the NMR spectrum, therefore the

product could not be fully characterised by NMR analysis. % purity determined by ^{1}H NMR (compound, **190**, (86 %), compound, **184**, (14 %)).

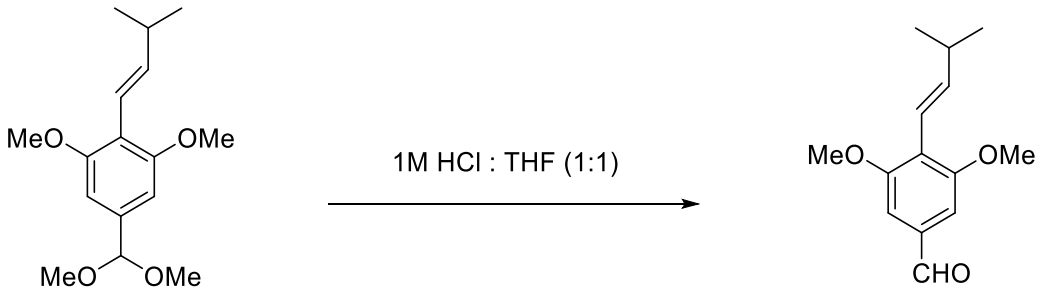
(*E*)-5-(dimethoxymethyl)-1,3-dimethoxy-2-(3-methylbut-1-en-1-yl)benzene (191)



Crude diethyl (4-(dimethoxymethyl)-2,6-dimethoxybenzyl)phosphonate (6.70 g, 18 mmol) was stirred in anhydrous THF (30 mL) at room temperature, under an atmosphere of N_2. *t*-BuOK (8.61 g, 77 mmol) was added and the resulting mixture was stirred for 15 min; 2-methylpropanal (1.58 g, 22 mmol) was added to the stirred mixture and left to stir at room temperature. The reaction was monitored by TLC [3:1 DCM/cyclohexane], once the reaction was complete, the reaction was quenched by the addition of ice and the resulting mixture was extracted with ether (3 x 150 mL), the organic phases were collected and washed with water (50 mL), then brine (50 mL). The organic phases were collected, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford an orange solid. The crude product, was immediately used for the next reaction. Yield: 8.14 g, 157 %. R_f 0.16 [3:1 DCM/cyclohexane]; υ_{max} (neat)/cm^{-1} 1119, 1204 (C-O), 1462, 1596 (C=C), 2848, 2915, 2956 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 0.94 (6H, d, J = 6.7 Hz, C-$(CH_3)_2$), 1.92 (1H, dsep, C<u>H</u>-$(CH_3)_2$), 3.46 (6H, s, OMe), 3.78 (6H, s, OMe), 6.35 (1H, dd, J = 16.0 Hz, J = 2.3 Hz, *trans*-C<u>H</u>=CH), 6.52 (1H, d, J_{AB} = 15.9 Hz, *trans*-CH=C<u>H</u>), 6.67 (2H, d, J = 2.2 Hz, ArH_2 &

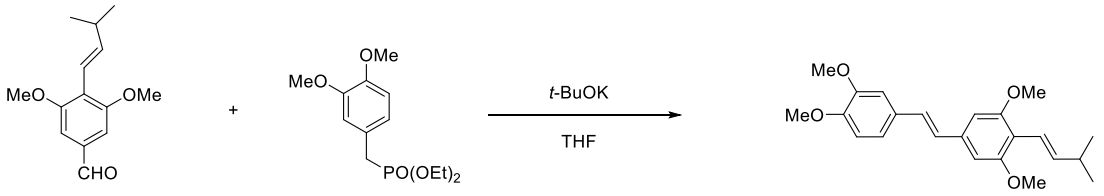
$_6$), 6.75 (1H, s, CH); LCMS (ESI) found *m/z* $[M-H]^-$: 279, $C_{16}H_{24}O_4$ requires 280. % purity determined by ^{1}H NMR (compound, **190**, (71 %), compound, **191**, (29 %)).

(*E*)-3,5-dimethoxy-4-(3-methylbut-1-en-1-yl)benzaldehyde (192)



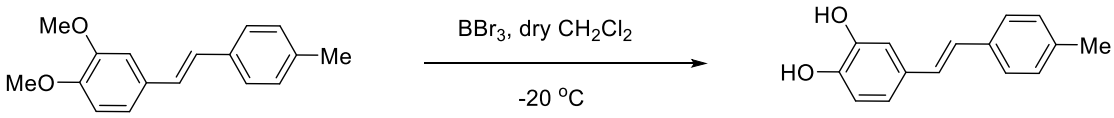
The crude acetal (8.04 g, 29 mmol) was dissolved in a solution of 1M HCl : THF (75 mL : 75 mL) and stirred at room temperature for 48 h, after which the mixture was extracted with diethyl ether (3 x 150 mL), the organic phases were then combined and washed with water (50 mL), the organic phase were collected, dried ($MgSO_4$), filtered and concentrated *in vacuo*, to give the crude yellow fluffy solid. The crude product, was immediately used for the next reaction. Yield: 6.56 g, 98 %. R_f 0.36 [3:1 DCM/cyclohexane]; υ_{max} (neat)/cm^{-1} 1072 (C-O), 1472 (C=C), 1706 (C=O), 2848, 2915, 2956 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 0.96 (6H, d, *J* = 6.9 Hz, C-$(CH_3)_2$), 1.91 (1H, dsep, *J* = 4.0 Hz, C<u>H</u>-$(CH_3)_2$), 3.77 (6H, s, OMe), 6.47 (1H, dd, J_{AB} = 16.0 Hz, J_{AB} = 2.4 Hz, *trans*-C<u>H</u>=CH), 6.54 (1H, d, J_{AB} =15.9 Hz, *trans*-CH=C<u>H</u>), 6.66 (2H, d, *J* = 2.2 Hz, $ArH_{2\ \&\ 6}$), 9.82 (1H, s, CHO); LCMS (ESI) found *m/z* $[M-H]^-$: 233, $C_{14}H_{18}O_3$ requires 234. % purity determined by ^{1}H NMR (compound, **192**, (52 %), compound, **191**, (48 %)).

5-((*E*)-3,4-dimethoxystyryl)-1,3-dimethoxy-2-((*E*)-3-methylbut-1-en-1-yl)benzene (3)



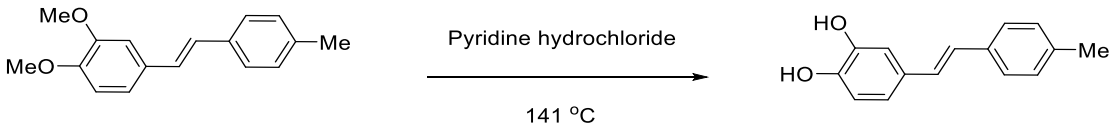
To a stirred mixture of the benzylphosphonate (5.23 g, 18 mmol) in THF (40 mL) at room temperature, *t*-BuOK (6.02 g, 54 mmol) was added and the resulting mixture was stirred. (*E*)-3,5-Dimethoxy-4-(3-methylbut-1-en-1-yl)benzaldehyde (6.53 g, 18 mmol) was added and the reaction mixture was left to stir at room temperature. The reaction was monitored by TLC [3:1 dichloromethane/cyclohexane]. Once the reaction was complete (24 h), the reaction was quenched by the addition of water (50 mL) and extracted with ether (3 x 100 mL); the organic phases were collected and washed with water (50 mL), and the organic phase was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the product, as a golden yellow oil (yield: 3.09 g, 30 %). Trituration of the crude product [diethyl ether/cyclohexane], gave the titled product, **3**, as an orange solid. Yield 30 %; R_f 0.67 [3:1 DCM/cyclohexane]; m.p. 78 - 89 ºC; υ_{max} (neat)/cm^{-1} 1205 (C-O), 1377, 1515 (CH_3), 1462, 1597 (C=C), 2848, 2915, 2955 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 0.95 (6H, d, J = 6.8 Hz, C-$(CH_3)_2$), 1.92 (1H, dsep, C<u>H</u>-$(CH_3)_2$), 3.77 (3H, s, OMe), 3.79 (3H, s, OMe), 3.87 (6H, s, OMe), 6.47 (1H, d, J_{AB} = 16.0 Hz, *trans*-C<u>H</u>=CH), 6.55 (1H, d, J_{AB} = 16.0 Hz, *trans*-CH=C<u>H</u>), 6.67 (2H, d, J = 2.4 Hz, $ArH_{2\ \&\ 6}$), 6.79 (1H, d, J_{AB} = 16.0 Hz, *trans*-<u>H</u>C=CH $_{stilbene}$), 6.85 (1H, m, *trans*-HC=C<u>H</u> $_{stilbene}$), 6.82 (1H, m, $ArH_{6'}$ - overlapping), 6.89 (1H, d, J = 2.5 Hz, $ArH_{2'}$), 6.98 (1H, m, $ArH_{6'}$); LCMS (ESI) found *m/z* $[M-H]^-$: 367, $C_{23}H_{28}O_4$ requires 368.

Model reaction: Demethylation with boron tribromide (202a)



To a solution of (*E*)-1,2-dimethoxy-4-(4-methylstyryl)benzene (0.5 g, 1.9 mmol) dissolved in dry DCM (45 mL), cooled to -20 ºC, whilst stirring under an atmosphere of N_2, boron tribromide (1.97 g, 7.9 mmol) was added dropwise. Following the addition, the round bottom flask was allowed to warm up to room temperature, whilst stirring. Once the reaction was complete (4 h), as indicated by TLC [1:2 EtOAc/DCM], the reaction mixture was added dropwise into a saturated solution of $NaHCO_3$ (40 mL), whilst stirring, then the DCM solvent was removed. The resulting aqueous solution was extracted with ethyl acetate (3 x 100 mL), the organic phases were collected, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Yield of crude product: 0.34 g, 76 %, as a yellow oily solid. Trituration of the crude product [diethyl ether / cyclohexane], gave the pure product (0.20 g, 44 %), as a pale yellow solid. R_f 0.75 [1:5 EtOAc/DCM]; m.p. 140 °C – 143 °C; υ_{max} (neat)/cm^{-1} 1439, 1516, 1597 (C=C), 2855, 2913, 3023 (C-H and =CH-), 3344 (OH); δ_H (400 MHz; $CDCl_3$) 2.34 (3H, s, CH_3), 4.82 (2H, s - broad, OH), 6.83 (1H, d, *J* 8.0 Hz, $ArH_{5'}$), 6.89 (1H, d, J_{AB} = 16.0 Hz, *trans*-HC=CH), 6.94 (1H, d, J_{AB} = 16.0 Hz, *trans*- HC=CH), 6.94 (1H, dd, *J* = 2.3 Hz, *J* = 8.0 Hz, $ArH_{6'}$), 7.05 (1H, d, *J* = 2.0 Hz, $ArH_{2'}$), 7.14 (2H, d, *J* = 8.0 Hz, $ArH_{3\ \&\ 5}$), 7.36 (2H, d, *J* = 8.0 Hz, $ArH_{2\ \&\ 6}$); δ_C (100 MHz; $CDCl_3$) 21.0 (CH_3), 116.1 ($C_{2'}$), 119.5 ($C_{5'}$), 125.0 ($C_{6'}$), 132.8 (C_7 & $C_{7'}$), 133.8, 133.9 (C_2 & C_6), 136.7 (C_3 & C_5), 139.2 (C_1), 143.4 (C_1), 146.5 (C_4), 154.10 ($C_{3'}$), 154.63 ($C_{4'}$); LCMS (ESI) found *m/z* $[M-H]^-$: 225, $C_{15}H_{14}O_2$ requires 226.

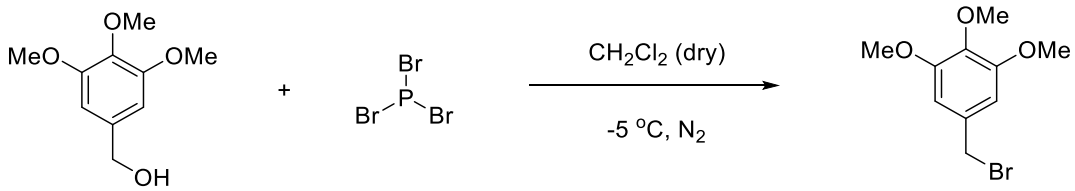
Model reaction: Attempted demethylation with pyridine hydrochloride (202b)



(*E*)-1,2-Dimethoxy-4-(4-methylstyryl)benzene (0.74 g, 2.9 mmol) and excess molten pyridine hydrochloride (5.42 g, 47 mmol) were mixed and heated (141 ºC), whilst stirring for 1 h. Once the reaction was complete, as indicated by TLC [2:1 DCM/cyclohexane], the reaction mixture was poured into 2N HCl (50 mL) and the resulting mixture was extracted with ethyl acetate (3 x 100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the impure product. Purification by trituration with ether : cyclohexane (3:1), gave the pure product (0.17 g, 26 %), as a deep orange solid. R_f 0.08 [3:1 DCM/cyclohexane]; υ_{max} (neat)/cm^{-1} 1515, 1601 (C=C), 2856, 2911, 3025 (C-H and =CH-), 3405 (OH); δ_H (600 MHz; $CDCl_3$) 2.33 (3H, s, CH_3), 5.12 (2H, s, OH), 6.82 (1H, d, *J* = 8.2 Hz, $ArH_{5'}$), 6.90 (1H, m, *trans*-HC=CH), 6.94 (1H, m, *trans*-HC=CH), 9.40 (1H, dd, *J* = 2.4 Hz, *J* = 7.8 Hz, $ArH_{6'}$), 7.04 (1H, d, *J* = 2.0 Hz, $ArH_{2'}$), 7.12 (2H, d, *J* = 7.8 Hz, $ArH_{3\ \&\ 5}$), 7.35 (2H, d, *J* = 7.8 Hz, $ArH_{2\ \&\ 6}$); δ_C (100 MHz; $CDCl_3$) 21.2 (CH_3), 112.8 ($C_{2'}$), 115.5 ($C_{5'}$), 120.0 ($C_{6'}$), 126.2 (C_7 & $C_{7'}$), 127.0 (C_2 & C_6), 129.3 (C_3 & C_5), 131.3 ($C_{1'}$), 134.6 (C_1), 137.1 (C_4) 143.1 ($C_{3'}$), 143.5 ($C_{4'}$); LCMS (ESI) found *m/z* $[M-H]^-$: 225, $C_{15}H_{14}O_2$ requires 226. % purity determined by ^1H NMR (compound, **202b**, (38 %), ethyl acetate (44 %), compound, **199**, (18 %)).

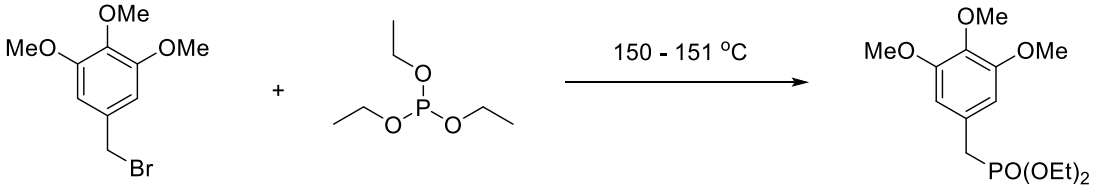
7.3 Experimental for Chapter 4

5-(Bromomethyl)-1,2,3-trimethoxybenzene (208)



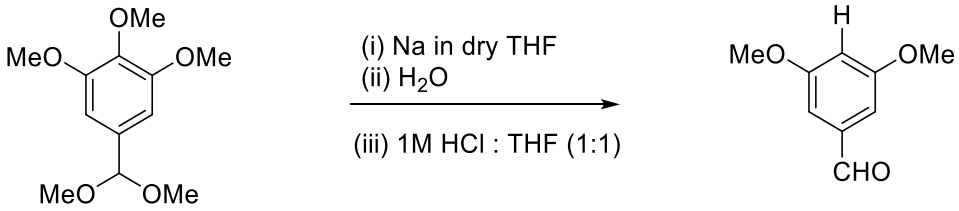
To a solution of 3,4,5-trimethoxybenzyl alcohol (37 g, 187 mmol) in anhydrous dichloromethane (535 mL), cooled to -5 °C, whilst stirring, phosphorus tribromide (35 g, 144 mmol) was added dropwise and the resulting mixture was stirred for 4 h at -5 °C. Once the reaction was complete, as indicated by TLC [3:1 DCM/cyclohexane], the reaction mixture was added slowly to ice whilst stirring and neutralised with sodium hydrogen carbonate. The mixture was extracted with dichloromethane (3 x 120 mL); the organic phases were combined and dried (Na_2SO_4) filtered and concentrated *in vacuo* to afford the crude title compound, **208**, (yield: 38.60 g), as a pale pink solid; R_f 0.24 [3:1 DCM/cyclohexane]; υ_{max} (neat)/cm^{-1} 668 (C-Br), 1125 (C-O), 1469, 1592 (C=C), 22836, 2940, 2969, 2994, 3077 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 3.79 (3H, s, OMe), 3.81 (6H, s, OMe), 4.41 (2H, s, CH_2), 6.57 (2H, s, $ArH_{2\ \&\ 6}$); δ_C (100 MHz; $CDCl_3$) 34.5 (CH_2), 56.1 (2 x OMe - *meta*), 60.9 (OMe), 106.1 (C_2 & C_6), 133.2 (C_1), 138.0 (C_4), 153.3 (C_3 & C_5). LCMS (ESI) found *m/z* $[M-H]^-$: 259, $C_{10}H_{13}BrO_3$ requires 260.00.

Diethyl 3,4,5-trimethoxybenzylphosphonate (209)



The diethyl benzylphosphonate derivative was prepared according to the procedure reported by Azzena *et al.,* [222]. Triethyl phosphite (37.46 g, 225 mmol) and 5-(bromomethyl)-1,2,3-trimethoxybenzene (38.60 g, 148 mmol), were heated under reflux at 151 °C under an atmosphere of N_2, for 24 h. Following completion, as indicated by TLC [3:1 DCM/cyclohexane], the reaction mixture was left to cool to room temperature, yielding the desired product (yield: 61.16 g, 130 %), as a pale yellow viscous oil; R_f 0.09 [3:1 DCM/cyclohexane]; υ_{max} (neat)/cm^{-1} 1247 (P=O), 1462, 1590 (C=C), 2839, 2913, 2940, 2986 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 0.89 (6H, t, J = 7.0 Hz, C-CH_3), 2.70 (2H, d, J = 21.4 Hz, CH_2-P), 3.42 (3H, s, OMe), 3.46 (6H, s, OMe), 3.66 (4H, dq, J = 7.0 Hz, O-CH_2), 6.18 (2H, d, J = 2.5 Hz, $ArH_{2\ \&\ 6}$); δ_C (100 MHz; $CDCl_3$) 16.0, 16.1 (2 x CH_3), 32.7, 34.1 (CH_2-P), 55.7 (2 x OMe - *meta*), 60.3 (OMe), 61.7, 61.8 (2 x O-CH_2), 106.6, 106.7 (C_2 & C_6), 126.8 (C_1), 136.7 (C_4), 152.8 (C_3 & C_5); LCMS (ESI) found *m/z* $[M + H]^+$: 319, $C_{14}H_{23}O_6P$ requires 318. % purity determined by ^1H NMR (compound, **208**, (90 %), triethyl phosphite (10 %)).

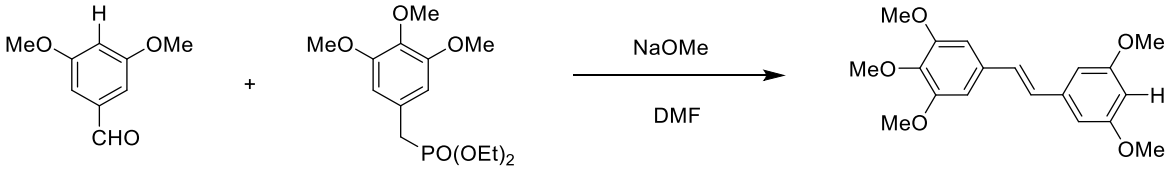
3,5-dimethoxybenzaldehyde (211)



To a solution of anhydrous tetrahydrofuran (360 mL) and sodium metal, 30-35 wt. % dispersion in wax (5.79 g, 84 mmol), cooled to -5 °C, 3,4,5-trimethoxybenzylaldehyde dimethyl acetal (26.17 g, 108 mmol) dissolved in anhydrous tetrahydrofuran (144 mL) was added drop wise, under an atmosphere of N_2, and the resulting mixture was stirred for 3 days at room temperature. Once the reaction was complete, as indicated by TLC, the reaction mixture was quenched by the dropwise addition of water (480 mL). The mixture was extracted with diethyl ether (3 x 360 mL); the organic phases were combined and washed with brine, then dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude acetal. The crude acetal (29.2 g) was dissolved in THF (395 mL): 1M HCl (395 mL), the reaction mixture was stirred for 48 h at room temperature. Once the reaction was complete, as indicated by TLC, the reaction mixture was extracted with diethyl ether (4 x 360 mL); the organic phases were combined and washed with water (4 x 360 mL), then brine (20 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the afford the title compound, **211**, (yield: 18.02 g, 100 %), as a yellow solid; m.p. 45 - 48 ºC (Lit. m.p. 46 – 48 ºC [202]); R_f 0.74 [3:1 DCM/cyclohexane]; υ_{max} (KBr)/cm^{-1} 1129, 1234 (C-O), 1463, 1592 (C=C), 1695 (C=O), 2755, 2850 (CHO), 2921, 3010, 3092 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 3.74 (3H, s, OMe), 3.75 (3H, s, OMe), 6.60 (1H, m, ArH_4), 6.91 (2H, m, ArH_2 & $_6$), 9.80 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 55.5

(OMe), 107.0 (C_2 & C_6), 138.4 (C_1 & C_4), 139.4 (C_3 & C_5), 191.8 (CHO); LCMS (ESI) found *m/z* $[M-H]^-$: 165, $C_9H_{10}O_3$ requires 166. The data was consistent with literature values [202].

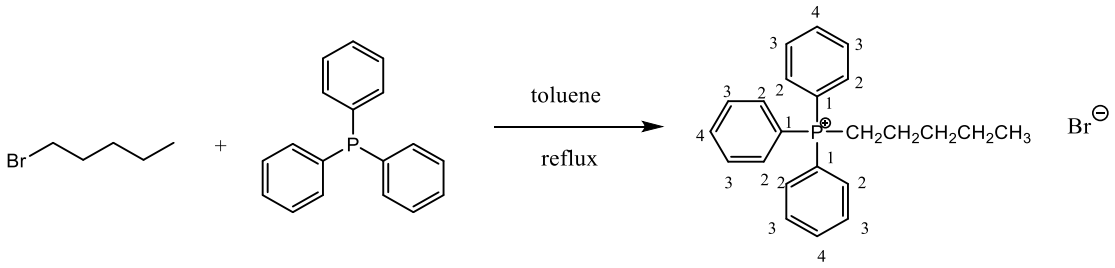
(*E*)-5-(3,5-dimethoxystyryl)-1,2,3-trimethoxybenzene (124)



To a stirred mixture of 3,5-dimethoxybenzaldehyde (18.02 g, 108 mmol) in DMF (270 mL) at room temperature, under N_2, diethyl (3,4,5-trimethoxybenzyl)phosphonate (33.06 g, 104 mmol), followed by sodium methoxide (28.5 g, 528 mmol) was added. The reaction was stirred at room temperature, under an atmosphere of N_2. Once the reaction was complete, as indicated by TLC [3:1 DCM/cyclohexane], the reaction was quenched by the addition of ice and stirred. The precipitate formed was filtered off, washed with cold water and air dried to give the impure product as a pale brown solid (72 %). Purification by recrystallization (ethanol) afforded the desired product, **124**, as a white crystals. Yield: 13.39 g, 39 %; m.p. 128 - 132 ºC (Lit. m.p. 135 ºC [298]; R_f 0.27 [3:1 DCM/cyclohexane]; υ_{max} (KBr)/cm^{-1} 1511, 1589 (C=C), 2835, 2849, 2918, 2976, 3005, 3034 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 3.85 (6H, s, OMe), 3.89 (3H, s, OMe), 3.93 (6H, s, OMe), 6.41 (1H, t, *J* = 2.2 Hz, ArH_4), 6.68 (2H, d, *J* = 2.2 Hz, $ArH_{2\&\ 6}$), 6.75 (2H, s, $ArH_{2'\ \&\ 6'}$), 6.95 (1H, d, J_{AB} = 16.1 Hz, *trans*-HC=CH), 7.03 (1H, d, J_{AB} = 16.5 Hz, *trans*-HC=CH); δ_C (75 MHz; $CDCl_3$) 55.4, 56.2, 61.0 (OMe), 100.0 (C_4), 103.7 ($C_{2'}$ & $C_{6'}$), 104.5 (C_2 & C_6), 128.2, 129.2 (C_7 & $C_{7'}$), 132.9 ($C_{1'}$),

138.1 ($C_{4'}$), 139.3 ($C_{6''}$), 153.4 ($C_{3'}$ & $C_{6'}$), 161.0 (C_3 & C_5); LCMS (ESI) found *m/z* $[M + H]^+$: 331, $C_{19}H_{22}O_5$ requires 330.

Pentyltriphenylphosphonium bromide (215)

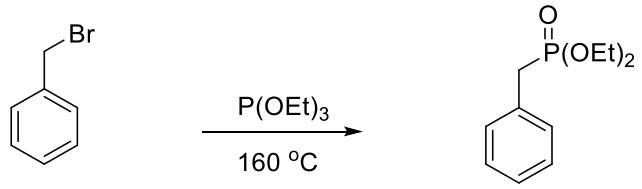


To a stirred solution of 1-bromopentane (9.99 g, 66 mmol) in toluene (50 mL), triphenylphosphine (4.32 g, 16 mmol), was added, the mixture was refluxed 18 h. Following completion, as indicated by TLC [3:1 cyclohexane/DCM], the reaction mixture was left to cool to room temperature and the mixture was poured into ice, filtered and washed with cold diethyl ether, to afford the crude product as a white solid. Yield: 1.42 g, 21 %; R_f 0.08 [3:1 cyclohexane/DCM]; m.p. 150 - 153 °C (Lit m.p. 167 – 168 °C [299]); υ_{max} (KBr)/cm^{-1} 1436, 1585 (C=C), 2793, 2859, 2956, 3055 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 0.69 (3H, t, *J* = 7.3 Hz, C-CH_3), 1.18 (2H, q, *J* = 7.2 Hz, CH_2), 1.51 (4H, m, CH_2), 3.57 (2H, t, *J* = 3.3 Hz, CH_2-P), 7.61 (6H, m, ArH_2), 7.71 (9H, m, $ArH_{4\ \&\ 3}$); δ_C (100 MHz; $CDCl_3$) 13.6 (CH_3), 22.1, 22.5, 23.0 (CH_2), 32.3, 32.4 (CH_2-P), 130.5, 130.6 (C_1), 133.5, 133.6 (C_3 & C_2), 135.1 (C_1); LCMS (ESI) found *m/z* [M-H]: 332 $C_{23}H_{26}P^+$ requires 333.

The data was consistent with literature values [105].

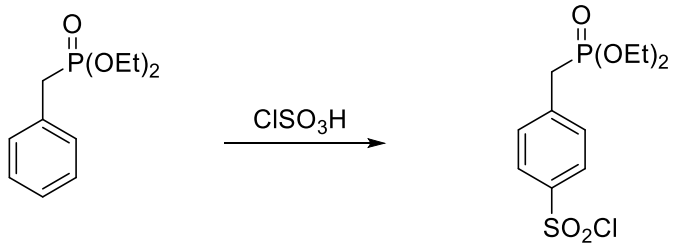
7.4 Experimental for Chapter 5

Diethyl benzylphosphonate (162)



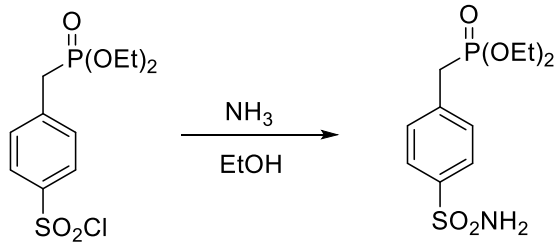
Triethyl phosphite (210 g, 1.26 mol) and benzyl bromide (179 g, 1.05 mol), were heated at 160 °C, under an atmosphere of N_2, for 48 h. The reaction was monitored by TLC [2:1 EtOAc/cyclohexane]. Following completion, as indicated by TLC, the reaction mixture was left to cool to room temperature affording the desired product (yield: 116.5 g, 48 %) as pale yellow oil; R_f 0.45 [2:1 EtOAc/cyclohexane]; υ_{max} (NaCl)/cm^{-1} 1250 (P=O), 2908, 2933, 2982, 3034, 3063, 3090 (C-H and =CH-); δ_H (600 MHz; $CDCl_3$) 1.16 (6H, t, *J* = 7.3 Hz, C-CH_3), 3.09 (2H, d, *J* = 21.9 Hz, CH_2-P), 3.95 (4H, m, O-CH_2-C), 7.18 - 7.24 (5H, m, ArH); δ_C (100 MHz; $CDCl_3$) 16.74 (2 x CH_3), 33.1, 34.5 (CH_2-P), 62.1, 62.2 (2 x O-CH_2), 126.9 (C_1), 128.5 (C_3 & C_5), 129.8 (C_2 & C_6), 131.6, 131.7 (C_4); LCMS (ESI) found *m/z* $[M + H]^+$: 229, $C_{11}H_{17}O_3P$ requires 228.

Diethyl 4-(chlorosulfonyl)benzylphosphonate (220)



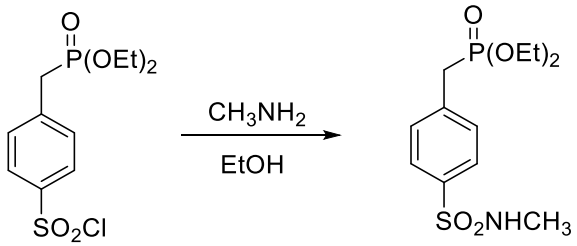
Diethyl 4-(chlorosulfonyl)benzylphosphonate was prepared according to the procedure reported by Herweh [275]. Chlorosulfonic acid (152 g, 1.31 mol) was cooled to 0 °C. Diethyl benzylphosphonate (30 g, 131 mmol) was added dropwise and the resulting mixture was stirred for 24 h at room temperature. Once the reaction was complete, as indicated by TLC [4:1 EtOAc/cyclohexane], the reaction mixture was added slowly to ice whilst stirring. The mixture was extracted with dichloromethane (4 x 150 mL); the organic phases were combined and washed with 10 % aqueous sodium hydrogen carbonate solution (3 x 50 mL). The organic phases were then combined and washed with brine (50 mL), the organic phase was separated and dried (Na_2SO_4), filtered and concentrated *in vacuo* (yield: 38.83 g, 90 %), to give the product as a viscous pale yellow oil; R_f 0.22 [4:1 EtOAc/cyclohexane]; υ_{max} (NaCl)/cm^{-1} 1246 (P=O), 1173, 1369 (S=O), 1592 (C=C), 2911, 2932, 2984, 3051, 3091 (C-H and =CH-); δ_H (600 MHz; $CDCl_3$) 1.21 (6H, t, *J* = 7.3 Hz, C-CH_3), 3.20 (2H, d, *J* = 22.0 Hz, CH_2-P), 4.01 (4H, m, OCH_2-C), 7.49 (2H, dd, *J* = 8.2 Hz, *J* = 2.0 Hz, $ArH_{3\ \&\ 5}$), 7.90 (2H, d, *J* = 8.2 Hz, $ArH_{2\ \&\ 6}$); δ_C (150 MHz; $CDCl_3$) 16.2 (2 x CH_3), 33.2, 34.1 (CH_2-P), 62.3 (2 x O-CH_2), 126.9 (C_2 & C_6), 130.8 (C_3 & C_5), 140.5 (C_4), 142.6 (C_1); LCMS (ESI) found *m/z* $[M + H]^+$: 327 (^{35}Cl), 329 (^{37}Cl), 328 (^{35}Cl and ^{13}C), $C_{11}H_{16}ClO_5PS$ requires 326. % purity determined by ^1H NMR (compound, **220**, (82 %), compound, **162**, (18%)).

Diethyl 4-sulfamoylbenzylphosphonate (221a)



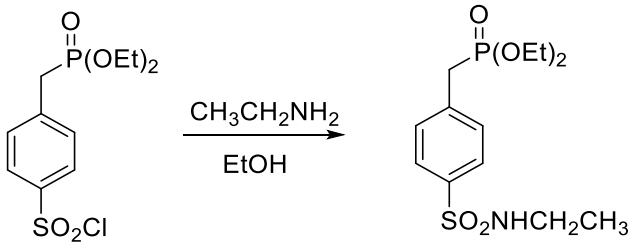
Method A: A solution of ammonia solution in 2M EtOH (16 mL) in ethanol (20 mL), was added slowly to a stirred solution of diethyl 4-(chlorosulfonyl)benzylphosphonate (18.28 g, 56 mmol), cooled to the required temperature (< 10 ºC). Following the addition, the resulting mixture was stirred at room temperature. Once the reaction was complete, as indicated by TLC [1:4 cyclohexane/EtOAc], the mixture was poured into a minimal amount of ice and filtered to afford a solid product (yield: 13.41 g, 78 %) as a white solid. R_f 0.16 [EtOAc]; m.p. 145-149 °C; υ_{max} (NaCl)/cm^{-1} 1234 (P=O), 1156, 1337 (S=O), 1604 (C=C), 2921, 2995, 3058, 3141 (C-H and =CH-), 3200, 3298 (N-H); δ_H (600 MHz; $CDCl_3$) 1.25 (6H, t, *J* = 7.8 Hz, C-CH_3), 3.19 (2H, d, *J* = 22.0 Hz, CH_2-P), 4.03 (4H, m, OCH_2), 4.99 (2H, s, NH_2), 7.42 (2H, dd, *J* = 8.2 Hz, *J* = 1.9 Hz, ArH $_{3\ \&\ 5}$), 7.85 (2H, d, *J* = 8.2 Hz, ArH $_{2\ \&\ 6}$); δ_C (150 MHz; $CDCl_3$) 16.3 (2 x CH_3), 33.2, 34.1 (CH_2-P), 62.4 (2 x O-CH_2), 126.6 (C_2 & C_6), 129.2 (C_3 & C_5), 130.4 (C_4), 137.0 (C_1); LCMS (ESI) found *m/z* $[M-H]^-$: 305, $[M+H]^+$: 308, $C_{11}H_{18}NO_5PS$ requires 307. % purity determined by ^{1}H NMR (compound, **221a**, (90 %), compound, **220**,(10%)).

Diethyl 4-(*N*-methylsulfamoyl)benzylphosphonate (221b)



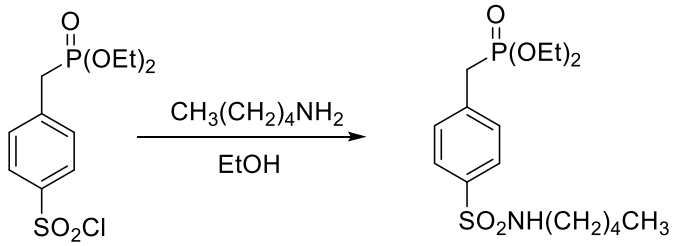
According to method A; the reaction with diethyl 4-(chlorosulfonyl)benzylphosphonate (4.04 g, 12 mmol) and methylamine solution 40 wt % in H_2O (2.4 mL) gave the desired product, **221b** (yield: 2.25 g, 57 %) as a white solid; R_f 0.11 [1:4 cyclohexane/EtOAc]; m.p. 112-115 °C; υ_{max} (NaCl)/cm^{-1} 1242 (P=O), 1159, 1311 (S=O), 2866, 2910, 2989, 3097 (C-H and =CH-), 3313 (N-H); δ_H (600 MHz; $CDCl_3$) 1.23 (6H, t, *J* = 7.8 Hz, C-CH_3), 2.62 (3H, d, *J* = 5.5 Hz, N-CH_3), 3.19 (2H, d, *J* = 22.4 Hz, CH_2-P), 4.02 (4H, m, O-CH_2), 4.68 (1H, q, *J* = 5.0 Hz, N-H), 7.43 (2H, dd, *J* = 8.2 Hz, *J* = 1.9 Hz, ArH $_{3\ \&\ 5}$), 7.78 (2H, d, *J* = 8.2 Hz, ArH $_{2\ \&\ 6}$); δ_C (150 MHz; $CDCl_3$) 16.3 (2 x CH_3), 29.1 (N-CH_3), 33.4, 34.3 (CH_2-P), 62.4 (2 x O-CH_2), 127.4 (C_2 & C_6), 130.5 (C_3 & C_5), 137.2 (C_4), 137.6 (C_1); LCMS (ESI) found *m/z* $[M-H]^-$: 320, $[M+H]^+$: 322, $C_{12}H_{20}NO_5PS$ requires 321.

Diethyl 4-(*N*-ethylsulfamoyl)benzylphosphonate (221c)



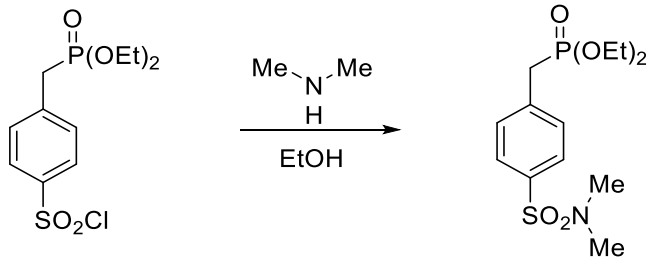
According to method A; the reaction with diethyl 4-(chlorosulfonyl)benzylphosphonate (4.27 g, 13 mmol) and ethylamine solution 40 wt % in H_2O (1.5 mL) gave the desired product, **221c** (yield: 2.69 g, 61 %) as a white solid; R_f 0.13 [1:4 cyclohexane/EtOAc]; m.p. 129-132 °C; υ_{max} (film)/cm^{-1} 1233 (P=O), 1159, 1311 (S=O), 2885, 2984, 3097 (C-H and =CH-); δ_H (600 MHz; $CDCl_3$) 1.07 (3H, t, *J* = 7.2 Hz, N-C-CH_3), 1.23 (6H, t, *J* = 7.2 Hz, O-C-CH_3), 2.96 (2H, m, N-CH_2), 3.18 (2H, d, *J* = 22.0 Hz, CH_2-P), 4.00- 4.03 (4H, m, O-CH_2), 4.59 (1H, t, N-H), 7.42 (2H, dd, *J* = 8.2 Hz, *J* = 2.8 Hz, $ArH_{3\ \&\ 5}$), 7.80 (2H, d, *J* = 8.2 Hz, $ArH_{2\ \&\ 6}$); δ_C (150 MHz; $CDCl_3$) 15.2 (N-C-$\underline{C}H_3$), 16.3 (2 x CH_3), 33.3, 34.2 (CH_2-P), 38.2 (N-CH_2), 62.3 (2 x O-CH_2), 127.2 (C_2 & C_6), 130.4 (C_3 & C_5), 137.1 (C_4), 138.6 (C_1); LCMS (ESI) found *m/z* $[M-H]^-$: 334, $C_{13}H_{22}NO_5PS$ requires 335.

Diethyl 4-(*N*-pentylsulfamoyl)benzylphosphonate (221d)



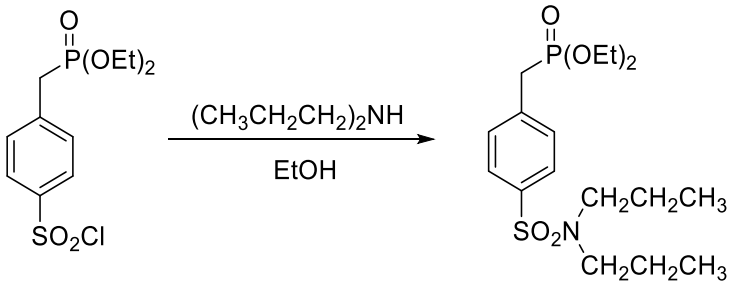
Method B: A solution of amylamine (19 mL) in ethanol (20 mL), was added slowly to a stirred solution of diethyl 4-(chlorosulfonyl)benzylphosphonate (24.3 g, 75 mmol), cooled to the required temperature (< 10 ºC). Following the addition, the resulting mixture was stirred at room temperature. Once the reaction was complete, as indicated by TLC [1:4 cyclohexane/EtOAc], the mixture was poured into a minimal amount of ice and stirred. When a solid precipitate was not formed, during aqueous work up, the mixture was extracted with dichloromethane (3 x 50 - 100 mL); the organic phases were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*, to afford the product (yield: 27.62 g) as a golden yellow oil; R_f 0.71[EtOAc]; υ_{max} (NaCl)/cm^{-1} 1230 (P=O), 1160, 1330 (S=O), 2859, 2929, 2963, 3154 (C-H and =CH-), 3276 (N-H); δ_H (600 MHz; $CDCl_3$) 0.76 (3H, t, *J* = 7.2 Hz, C-CH_3), 1.16 - 1.20 (6H, m, O-C-CH_3), 1.26 - 1.39 (6H, m, C-CH_2), 2.83 (2H, t, *J* = 7.2 Hz, N-CH_2-C), 3.17 (2H, d, *J* = 22.2 Hz, CH_2-P), 3.96-4.06 (4H, m, O-CH_2), 5.38 (1H, s, NH), 7.38 (2H, dd, *J* = 8.4 Hz, *J* = 2.4 Hz, $ArH_{3\ \&\ 5}$), 7.75 (2H, d, *J* = 9 Hz, $ArH_{2\ \&\ 6}$); δ_C (150 MHz; $CDCl_3$) 13.8 ($CH_{3\ sulfonamide}$), 16.3 ($CH_{3\ phosphonate}$), 22.0 ($\underline{C}H_2$-CH_3), 28.6, 29.1 (2 x CH_2), 32.7, 34.0 (CH_2-P), 43.1 (N-CH_2), 62.4 (2 x O-CH_2), 127.1 (C_2 & C_6), 130.2 (C_3 & C_5), 136.4 (C_4), 138.9 (C_1); LCMS (ESI) found *m/z* $[M + H]^+$: 378, $C_{16}H_{28}NO_5PS$ requires 377. % purity determined by ^1H NMR (compound, **221d**, (60 %), compound, **220**,(40%)).

Diethyl 4-(*N*,*N*-dimethylsulfamoyl)benzylphosphonate (221e)



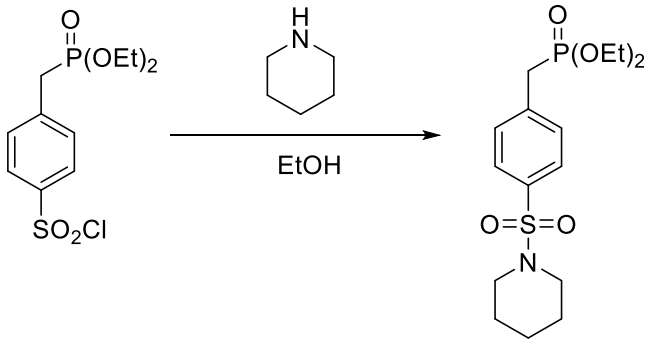
According to method A; the reaction with diethyl 4-(chlorosulfonyl)benzylphosphonate (6.1 g, 19 mmol) and dimethylamine (5 mL) gave the titled product, **221e** (yield: 4.18 g, 68 %) as a white solid; R_f 0.17 [1:3 cyclohexane/EtOAc]; m.p. 129 – 133 °C; υ_{max} (NaCl)/cm^{-1} 1257 (P=O), 1163, 1338 (S=O), 2915, 2982, 3028, 3090 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 1.20 (6H, t, *J* = 7.0 Hz, C-CH_3), 2.65 (6H, s, N-CH_3), 3.17 (2H, d, *J* = 22.1 Hz, CH_2-P), 4.00 (4H, m, O-CH_2), 7.44 (2H, dd, *J* = 8.5 Hz, *J* = 2.5 Hz, ArH $_{3\ \&\ 5}$), 7.67 (2H, d, *J* = 7.7 Hz, ArH $_{2\ \&\ 6}$); δ_C (100 MHz; $CDCl_3$) 16.4 ($CH_{3\ phosphonate}$), 33.1, 34.5 (CH_2-P), 33.1, 34.5 (N-CH_3), 62.3, 62.4 ($\underline{C}H_2$-CH_3), 128.0 (C_2 & C_6), 130.4 (C_3 & C_5), 134.0 (C_4), 137.4 (C_1); LCMS (ESI) found *m/z* $[M + H]^+$: 336, $C_{13}H_{22}NO_5PS$ requires 335.

Diethyl 4-(*N*,*N*-dipropylsulfamoyl)benzylphosphonate (221f)



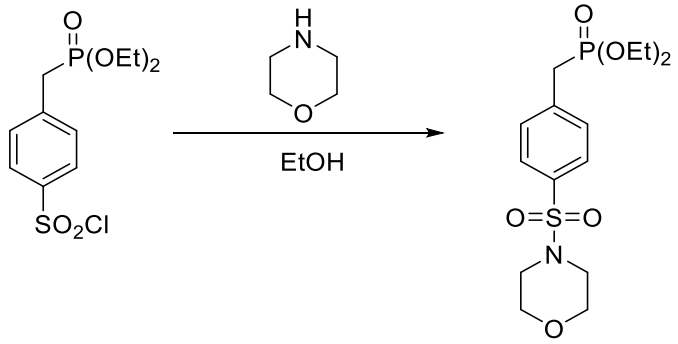
According to method B; the reaction with diethyl 4-(chlorosulfonyl)benzylphosphonate (3.14 g, 9.6 mmol) and dipropylamine (15 mL) gave the product (yield: 1.79 g, 48 %) as an orange oil; R_f 0.5 [3:1 cyclohexane/EtOAc]; υ_{max} (film)/cm^{-1} 1253 (P=O), 1160, 1336 (S=O), 1600 (C=C), 2884, 2930, 2977 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 0.80 (6H, t, *J* = 7.4 Hz, $CH_{3\ sulfonamide}$), 1.18 (6H, t, *J* = 6.9 Hz, $CH_{3\ phosphonate}$), 1.49 (4H, q, *J* = 7.6 Hz, $C\underline{H}_2$-CH_3), 3.01 (4H, t, *J* = 7.5 Hz, N-CH_2), 3.14 (2H, d, *J* = 22.0 Hz, P-CH_2), 3.99 - 3.95 (4H, m, O-CH_2), 7.41 (2H, dd, *J* = 8.1 Hz, *J* = 1.8 Hz, $ArH_{3\&\ 5}$), 7.69 (2H, d, *J* = 8.2 Hz, $ArH_{2\ \&\ 6}$); δ_C (100 MHz; $CDCl_3$) 11.2 ($CH_{3\ sulfonamide}$), 16.1, 16.4 ($CH_{3\ phosphonate}$), 22.0 ($\underline{C}H_2$-CH_3), 33.1, 34.5 (CH_2-P), 50.0 (N-CH_2), 62.4 (O-CH_2), 127.2 (C_2 & C_6), 130.4 (C_3 & C_5), 136.6 (C_4), 138.8 (C_1); LCMS (ESI) found *m/z* $[M + H]^+$: 392, $C_{17}H_{30}NO_5PS$ requires 391. % purity determined by ^1H NMR (compound, **221f**, (81 %), compound, **220**, (19 %)).

Diethyl 4-(piperidine-1-ylsulfonyl)benzylphosphonate (221g)



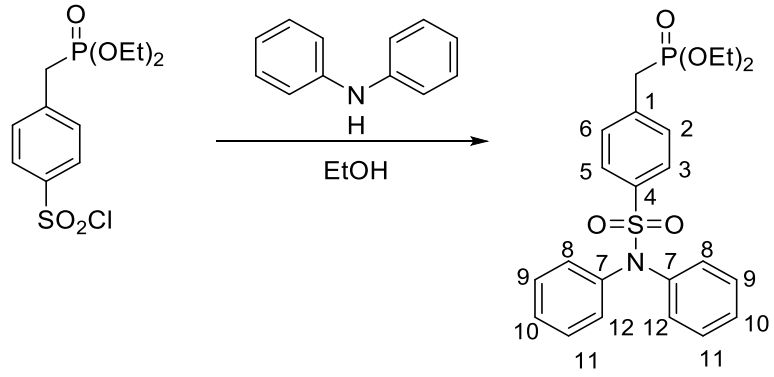
According to method B; the reaction with diethyl 4-(chlorosulfonyl)benzylphosphonate (6 g, 18 mmol) and piperidine (3.8 mL) gave the product (yield: 5.57 g, 81 %) as pale yellow/colourless needles; R_f 0.25 [DCM]; υ_{max} (film)/cm^{-1} 1257 (P=O), 1163, 1338 (S=O), 2915, 2982, 3028, 3090 (C- and =CH-); δ_H (600 MHz; $CDCl_3$) 1.22 (6H, dt, *J* = 3 Hz, C-CH_3), 2.67 (6H, s, N-CH_2), 3.19 (2H, d, *J* = 22.2 Hz, P-CH_2), 4.00 (4H, m, OCH_2), 7.45 (2H, dd, *J* = 8.4 Hz, *J* = 2.4 Hz, $ArH_{3\ \&\ 5}$), 7.67 (2H, d, *J* = 8.2, $ArH_{2\ \&\ 6}$); δ_C (100 MHz; DMSO-d_6) 16.7 (2 x CH_3), 23.4, 25.1 (2 x $CH_{2\ sulfonamide}$), 32.1 (CH_2-P), 47.1 (N-CH_2), 62.1 (2 x O-CH_2), 127.9 (C_2 & C_6), 131.2 (C_3 & C_5), 134.2 (C_4), 138.6 (C_1); LCMS (ESI) found *m/z* $[M + H]^+$: 376, $C_{16}H_{26}NO_5PS$ requires 375. % purity determined by ^1H NMR (compound, **221g**, (88 %), compound, **220**, (12 %).

Diethyl 4-(morpholinosulfonyl)benzylphosphonate (221h)



According to method B; the reaction with diethyl 4-(chlorosulfonyl)benzylphosphonate (24 g, 74 mmol) and morpholine (14 mL) gave the product (yield: 21.41 g, 88 %) as opaque/colourless oil; R_f 0.40 [EtOAc]; υ_{max} (film)/cm^{-1} 1243 (P=O), 1160, 1347 (S=O), 2868, 2907, 2929, 2989, 3094 (C-H and =CH-); δ_H (600 MHz; $CDCl_3$) 1.20 (6H, t, *J* = 7.0 Hz, C-CH_3), 2.86 - 2.96 (4H, m, N-CH_2), 3.16 (2H, d, *J* = 22.2 Hz, P-CH_2), 4.00-4.01 (4H, m, OCH_2), 7.45 (2H, dd, *J* = 8.4 Hz, *J* = 2.5 Hz, ArH $_{3\ \&5}$), 7.66 (2H, d, *J* = 8.4 Hz, ArH $_{2\ \&\ 6}$); δ_C (100 MHz; $CDCl_3$) 16.4 (2 x CH_3), 33.2, 34.6 (CH_2-P), 46.0 (N-CH_2), 62.4 (O-$CH_{2-\ phosphonate}$), 66.1 (O-$CH_{2-\ morpholine}$), 128.1 (C_2 & C_6), 130.6 (C_3 & C_5), 133.7 (C_4), 137.9 (C_1); LCMS (ESI) found *m/z* $[M + H]^+$: 378, $C_{15}H_{24}NO_6PS$ requires 377. % purity determined by ^{1}H NMR (compound, **221h**, (82 %), compound, **220**, (18 %)).

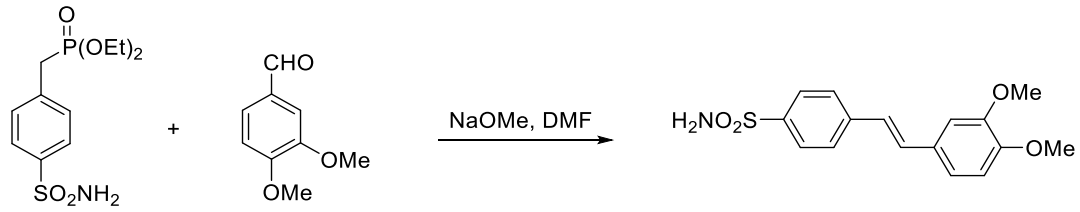
Diethyl 4-(*N*,*N*-diphenylsulfamoyl)benzylphosphonate (221i)



According to method B; the reaction with diethyl 4-(chlorosulfonyl)benzylphosphonate (6.04 g, 19 mmol) and diphenylamine (5 mL) gave the product (yield: 7.79 g, 92 %) as a green oil; R_f 0.87 [3:1 cyclohexane/EtOAc]; υ_{max} (film)/cm^{-1} 1244 (P=O), 1175, 1312 (S=O), 2911, 2941, 2980, 3044, 3132, 3205, 3308 3386, (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 1.16 (6H, t, *J* = 7.5 Hz, C-CH_3), 3.43 (2H, d, *J* = 22.2 Hz, P-CH_2), 3.95-3.97 (4H, m, OCH_2), 6.83 (6H, t, *J* = 7.3 Hz, ArH), 7.08 (2H, d, ArH $_{10}$), 7.22 (4H, t, ArH $_{7,9,\ 11\ \&\ 12}$), 7.58 (2H, dd, *J* = 8.4 Hz, *J* = 2.4 Hz, ArH $_{2\ \&\ 6}$), 7.86 (2H, d, *J* = 7.8 Hz, ArH $_{3\ \&\ 5}$); δ_C (100 MHz; DMSO-d_6) 16.7 (2 x CH_3), 31.0, 31.9 (CH_2-P), 62.1 (2 x O-CH), 117.2 (C_8 & C_{12}), 120.1 (C_{10}), 128.0 (C_3 & C_5), 129.7 (C_{10}), 131.6 (C_2 & C_6, C_9 & C_{11}), 132.4 (C_1), 140.0 (C_4), 140.9 (C_7); LCMS (ESI) found *m/z* $[M+H]^+$: 460, $C_{23}H_{26}NO_5PS$ requires 459.

% purity determined by ^{1}H NMR (compound, **221i**, (83 %), compound, **220**, (17 %)).

(*E*)-4-(3,4-dimethoxystyryl)benzenesulfonamide (232a)

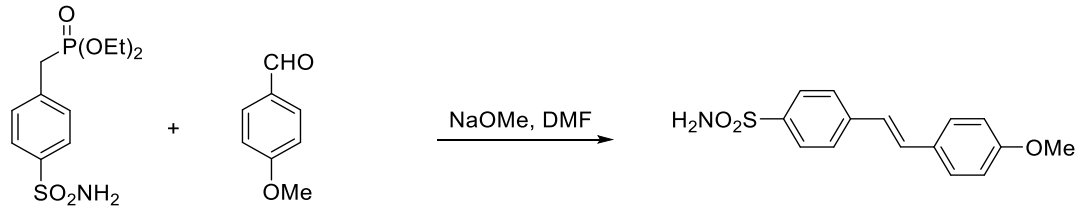


Method C:

To a stirred mixture of diethyl 4-sulfamoylbenzylphosphonate (2.00 g, 6.5 mmol) in DMF (10 mL) at room temperature, under N_2 atmosphere, sodium methoxide (5.27 g, 97 mmol) was added. The reaction was stirred for 30 min and 3,4-dimethoxybenzaldeyde (1.06 g, 6.4 mmol) dissolved in DMF (10 mL) was added to the stirred mixture and the reaction mixture was left to stir at room temperature. The reaction was monitored by TLC [1:4 cyclohexane/EtOAc]. Once the reaction was complete, as indicated by TLC, the reaction was quenched by the addition of ice, filtered, washed with cold water and air dried to give the impure product as a golden yellow solid. Purification by recrystallization (absolute ethanol 99%) gave the titled product, **232a**, as a pale yellow solid (yield: 0.31 g, 15 %); R_f 0.86 [EtOAc]; m.p. 221 - 227 °C; υ_{max} (film)/cm^{-1} 1156, 1329 (S=O), 1516, 1591 (C=C), 2839, 2945, 2972, 3004 (C-H and =CH), 3250, 3340 (N-H); δ_H (400 MHz; DMSO-d_6) 3.80 (6H, s, OMe), 6.98 (1H, d, J = 8.4 Hz, ArH $_5$), 7.14 (1H, dd, J = 8.4 Hz, J = 1.9 Hz, ArH $_6$), 7.22 (1H, d, J_{AB} = 16.4 Hz, *trans*-HC=CH), 7.29 (1H, d, J = 1.8 Hz, ArH $_2$), 7.34 (1H, d, J_{AB} = 16.0 Hz, *trans*-HC=CH), 7.32 (2H, s, NH_2), 7.59 (2H, d, J = 8.6 Hz, ArH $_{3'\ \&\ 2'}$), 7.79 (2H, d, J = 8.5 Hz, ArH $_{5'\ \&\ 6'}$); δ_C (150 MHz; DMSO-d_6) 56.0, 56.6 (OMe), 109.9 (C_2), 112.3 (C_5), 121.1 (C_6), 125.3 ($C_{2'}$ & $C_{6'}$), 126.6 ($C_{3'}$ & $C_{5'}$), 126.8 (C_7 &

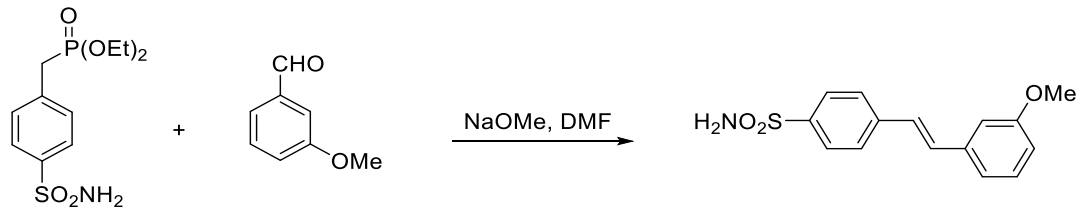
$C_{7'}$), 131.7 (C_1), 141.5 ($C_{1'}$), 142.8 ($C_{4'}$), 149.5 (C_4), 149.7 (C_3); LCMS (ESI) found *m/z* $[M-H]^-$: 318, $C_{18}H_{17}NO_4S$ requires 319.

(*E*)-4-(4-methoxystyryl)benzenesulfonamide (232b)



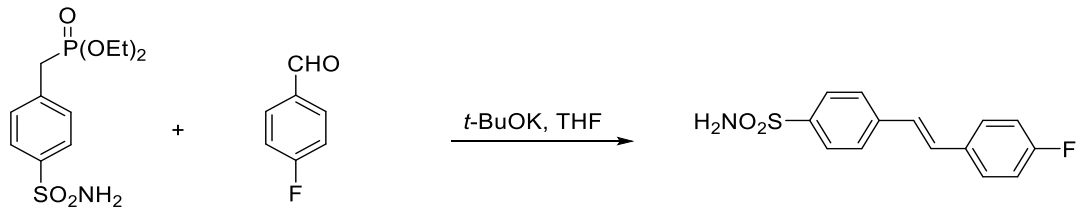
According to method C; the reaction with diethyl 4-sulfamoylbenzylphosphonate (0.99 g, 3.2 mmol) and 4-methoxybenzaldeyde (0.44 g, 3.2 mmol) provided the impure product as a beige solid (yield: 0.34 g, 36 %). Purification by recrystallization (diethyl ether) gave the desired product as a beige solid (yield: 0.31 g, 33 %); R_f 0.78 [1:3 cyclohexane/EtOAc]; m.p. 259 - 262 °C; υ_{max} (film)/cm^{-1} 1164, 1308 (S=O), 1513, 1592 (C=C), 2946, 2983, 3020, 3062 (C-H and =CH-), 3262, 3351 (N-H); δ_H (400 MHz; DMSO-d_6) 3.37 (2H, s, NH_2), 3.78 (3H, s, OMe), 6.97 (2H, d, *J* 8.8 Hz, ArH $_{11\ \&\ 13}$), 7.17 (1H, d, J_{AB} = 16.4 Hz, *trans*-HC=CH), 7.36 (1H, d, J_{AB} = 16.4 Hz, *trans*-HC=C<u>H</u>), 7.58 (2H, d, *J* = 8.8 Hz, ArH $_{10\ \&\ 14}$), 7.73 (2H, d, *J* = 8.5 Hz, ArH $_{2\ \&\ 3}$), 7.79 (2H, d, *J* = 8.5 Hz, ArH $_{5\ \&\ 6}$); δ_C (150 MHz; DMSO-d_6) 55.7 (OMe), 114.8 (C_{11} & C_{13}), 125.1 (C_3 & C_5), 126.6 (C_2 & C_6), 126.8 (C_7 & C_8), 128.7 (C_9), 131.3 (C_{10} & C_{14}), 141.4 (C_4), 142.3 (C_1), 159.9 (C_{12}); LCMS (ESI) found *m/z* $[M-H]^-$: 288 $C_{15}H_{15}NO_3S$ requires 289. % purity determined by ^1H NMR (compound, **232b**, (88 %), compound, **228**, (12 %)).

(*E*)-4-(3-methoxystyryl)benzenesulfonamide (232c)



According to method C; the reaction with diethyl 4-sulfamoylbenzylphosphonate (2.00 g, 6.5 mmol) and 3-methoxybenzaldeyde (0.89 g, 6.6 mmol) provided the impure product as a brown solid. Purification by recrystallization (absolute ethanol 99 %) gave the titled product, **232c**, as a beige solid (yield: 0.14 g, 7 %); R_f 0.88 [EtOAc]; m.p. 149 - 151 °C; υ_{max} (film)/cm^{-1} 1156, 1321 (S=O), 1577, 1608 (C=C), 2842, 2950, 2976, 3020, 3072 (C-H and =CH-), 3237, 3320 (N-H); δ_H (600 MHz; $CDCl_3$) 3.84 (3H, s, OMe), 4.74 (2H, s, NH_2), 6.86 (1H, dd, J = 8.2 Hz, J = 1.2 Hz, ArH $_4$), 7.04 (1H, broad, ArH $_6$), 7.05 (1H, d, J_{AB} = 16.5 Hz, HC=CH), 7.11 (2H, d, J = 7.8 Hz, ArH $_2$), 7.18 (1H, d, J_{AB} = 16.5 Hz, HC=CH), 7.28 (1H, t, J = 7.8 Hz, ArH $_5$), 7.61 (2H, d, J = 8.7 Hz, ArH $_{3' \& 2'}$), 7.88 (2H, d, J = 8.2 Hz, ArH $_{5' \& 6'}$); δ_C (100 MHz; $CDCl_3$) 55.3 (OMe), 112.1 (C_2), 114.1 (C_4), 119.5 (C_6), 126.7 ($C_{3'}$, $C_{5'}$, $C_{2'}$, & $C_{6'}$), 126.9 (C_7 & $C_{7'}$), 129.8 (C_5), 132.0 (C_1), 138.0 ($C_{1'}$), 141.8 ($C_{4'}$), 159.9 (C_3); LCMS (ESI) found *m/z* $[M-H]^-$: 287, $C_{15}H_{15}NO_3S$ requires 289.

(*E*)-4-(4-fluorostyryl)benzenesulfonamide (232e)

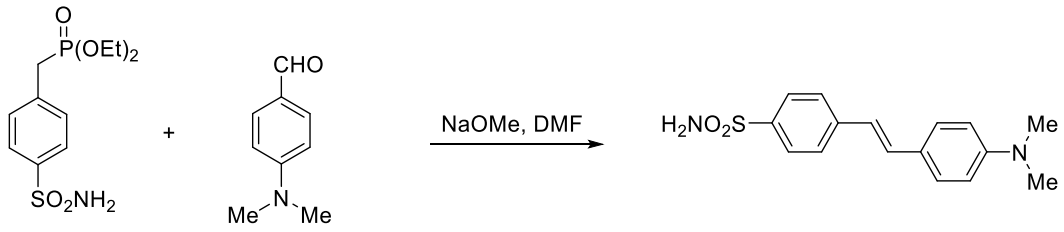


Method F:

To a stirred mixture of diethyl 4-sulfamoylbenzylphosphonate (1.00 g, 3.3 mmol) in THF (18 mL) at room temperature, under N_2, potassium *tert*-butoxide (0.73 g, 6.5 mmol) was added. The reaction was stirred for 5 minutes and 4-fluorobenzaldehyde (0.43 g, 3.5 mmol) was added to the stirred mixture and the reaction mixture was left to stir at room temperature for 4 h. Once the reaction was complete, as indicated by TLC [3:1 EtOAc/cyclohexane], the reaction was quenched by the addition of ice, filtered, washed with cold water and air dried. When a solid precipitate was not formed, the reaction mixture was extracted with DCM (3 x 50 mL), the organic phases were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the product as a white solid (yield: 0.59 g, 65 %). Purification by washing (diethyl ether and cyclohexane) afforded the titled product, **232e**, as a white solid (yield: 0.46 g, 51 %); R_f 0.84 [1:3 cyclohexane/EtOAc]; m.p. 189 - 194 °C; υ_{max} (film)/cm^{-1} 1163, 1324 (S=O), 1512, 1590 (C=C), 3018, 3049, 3067 (C-H and =CH-), 3268, 3367 (N-H); δ_H (600 MHz; $CDCl_3$) 4.78 (2H, s, NH_2), 7.07 (2H, t, J = 8.5 Hz, ArH $_{3\ \&\ 5}$), 7.02 (1H, d, J_{AB}= 16.1 Hz, *trans*-HC=CH), 7.17 (1H, d, J_{AB} = 16.4 Hz, *trans*-HC=CH), 7.50 (2H, q, J = 8.8 Hz, ArH $_{2\ \&\ 6}$), 7.61 (2H, d, J = 8.3 Hz, ArH $_{3'\ \&\ 2'}$), 7.89 (2H, d, J = 8.4 Hz, ArH $_{5'\ \&\ 6'}$); δ_C (150 MHz; DMSO-d_6) 116.1, 116.3 (C_3 & C_5), 126.7 ($C_{2'}$ & $C_{6'}$), 127.2 ($C_{3'}$ & $C_{5'}$), 129.2, 129.3 (C_7 & $C_{7'}$), 130.4 (C_2 & C_6), 133.7 (C_1), 140.9 ($C_{1'}$), 143.2

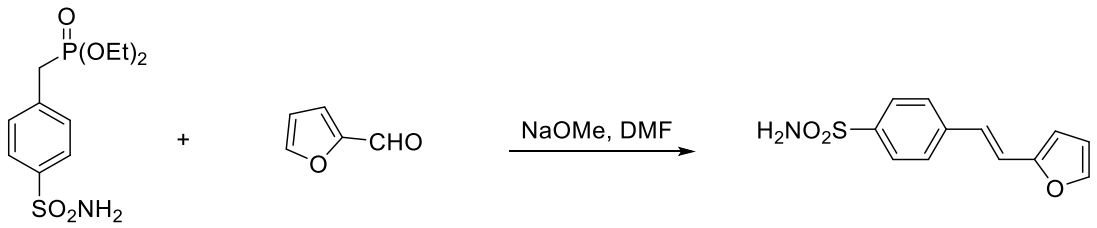
($C_{4'}$), 161.3, 163.7 (C_4); LCMS (ESI) found *m/z* $[M-H]^-$: 276, $C_{14}H_{12}FO_2S$ requires 277.

(*E*)-4-(4-(dimethylamino)styryl)benzenesulfonamide (232d)



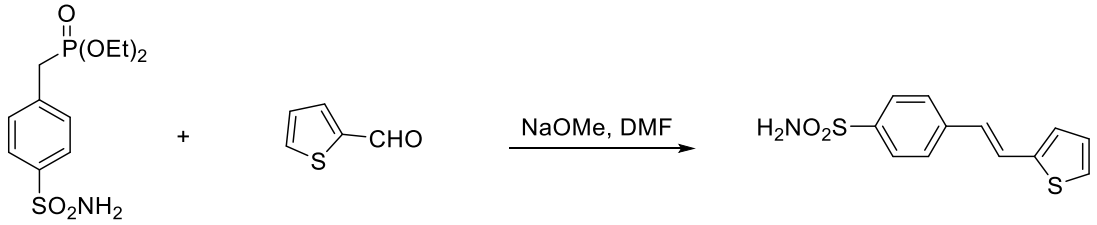
According to method C; the reaction with diethyl 4-sulfamoylbenzylphosphonate (0.76 g, 2.5 mmol) and 4-(dimethylamino)benzaldehyde (0.35 g, 2.3 mmol) provided the impure product as a bright yellow solid (yield: 0.61 g, 86 %). Purification by recrystallization (diethyl ether) afforded the desired product as an orange solid (yield: 0.2 g, 28 %); R_f 0.83 [1:3 cyclohexane/EtOAc]; m.p. 254 °C - decomposed; υ_{max} (film)/cm^{-1} 1154, 1303 (S=O), 1592 (C=C), 2811, 2909, 2992, 3076 (C-H and =CH-), 3253, 3351 (N-H); δ_H (400 MHz; DMSO-d_6) 2.94 (6H, s, N-CH_3), 6.73 (2H, d, *J* = 8.7 Hz, ArH $_{11\ \&\ 13}$), 7.03 (1H, d, J_{AB} = 16.4 Hz, *trans*-HC=C<u>H</u>), 7.29 (1H, m, *trans*-<u>H</u>C=CH), 7.31 (1H, s, NH_2), 7.47 (2H, d, *J* = 8.6 Hz, ArH $_{2\ \&\ 6}$), 7.68 (2H, d, *J* = 8.4 Hz, ArH $_{3'\&2'}$), 7.75 (2H, d, *J* = 8.4 Hz, ArH $_{6'\&\ 5'}$); δ_C (100 MHz; DMSO-d_6) 40.2 (N-CH_3), 112.7 (C_3 & C_5), 122.4 (C_1), 126.4 (C_2 & C_6), 126.6 ($C_{2'}$ & $C_{6'}$), 128.5 ($C_{3'}$ & $C_{5'}$) 132.0 (C_7 & $C_{7'}$), 143.1 ($C_{1'}$), 142.1 ($C_{4'}$), 150.9 (C_4); LCMS (ESI) found *m/z* $[M-H]^-$: 301, $C_{16}H_{18}N_2O_2S$ requires 302. % purity determined by ^{1}H NMR (compound, **232d**, (77 %), compound, **231**, (23 %)).

(*E*)-4-(2-(furan-2-yl)vinyl)benzenesulfonamide (245)



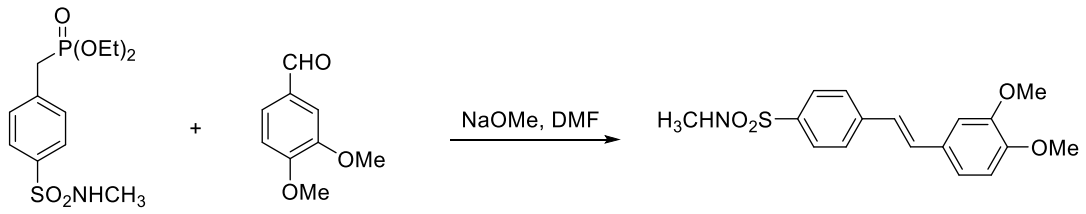
To a stirred mixture of diethyl 4-sulfamoylbenzylphosphonate (1.02 g, 3.3 mmol.) in DMF (16 mL) at room temperature, under an atmosphere of N_2, sodium methoxide (7.55 g, 139 mmol) was added. The reaction was stirred for 30 min then furan-2-carboxaldehyde (0.31 g, 3.2 mmol) was added to the stirred mixture and the reaction mixture was left to stir at room temperature. The reaction was monitored by TLC [1:3 cyclohexane/EtOAc]. Once the reaction was complete, as indicated by TLC, the reaction was quenched by the addition of ice, filtered, washed with cold water and air dried to give the impure product as a pale yellow solid (yield: 0.24 g, 30 %). Purification by recrystallization (diethyl ether) gave the titled product, **245**, as a pale yellow solid (yield: 0.17 g, 21 %); R_f 0.75 [3:1 EtOAc/cyclohexane]; m.p. 234 - 236 °C; υ_{max} (film)/cm^{-1} 1159, 1294 (S=O), 1536 (C=C), 2871, 3067, 3155 (C-H and =CH), 3253, 3346 (N-H); δ_H (400 MHz; DMSO-*d*$_6$) 6.58 (1H, dd, *J* = 3.0 Hz, =CH $_3$), 6.64 (1H, d, *J* = 3.2 Hz, =CH $_2$), 7.04 (1H, d, J_{AB} = 16.4 Hz, *trans*-HC=CH), 7.28 (1H, d, J_{AB} = 16.3 Hz, *trans*-HC=CH), 7.34 (2H, s, NH_2), 7.73 (1H, m, =CH $_4$), 7.76 (4H, q, *J* = 9.0 Hz, ArH $_{3'\&\ 2'}$, ArH $_{5\ \&\ 6}$); δ_C (100 MHz; DMSO-*d*$_6$) 111.4 (C_2), 112.8 (C_3), 119 (C_5), 125.1 (C_7), 126.7 ($C_{2'}$ & $C_{6'}$), 127.0 ($C_{3'}$ & $C_{5'}$), 140.6 ($C_{1'}$), 142.7 ($C_{4'}$), 144.1 (C_4), 152.7 (C_1); LCMS (ESI) found *m/z* [M-H]$^-$: 248, $C_{12}H_{12}NO_3S$ requires 249.

(*E*)-4-(2-(thiophen-2-yl)vinyl)benzenesulfonamide (247)



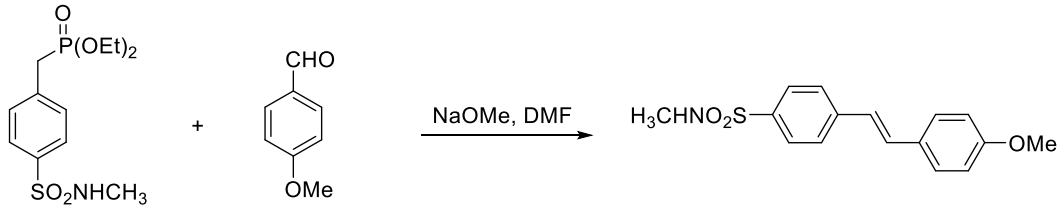
To a stirred mixture of diethyl 4-sulfamoylbenzylphosphonate (1.04 g, 3.4 mmol.) in DMF (16 mL) at room temperature, under an atmosphere of N_2, sodium methoxide (6.25 g, 116 mmol) was added. The reaction was stirred for 30 min, 2-thiophenecarboxaldehyde (0.33 g, 2.9 mmol) was added to the stirred mixture and the reaction mixture was left to stir at room temperature under an atmosphere of N_2. The reaction was monitored by TLC [1:3 cyclohexane/EtOAc]. Once the reaction was complete, as indicated by TLC, the reaction was quenched by the addition of ice, filtered, washed with cold water and air dried to give the titled product, **247**, as a golden yellow solid (yield: 0.38 g, 49 %). Purification not performed, as the compound was considered to be of adequate purity, following analysis by ^{1}H NMR. R_f 0.87 [3:1 EtOAc/cyclohexane]; m.p. 254 – 259 °C; υ_{max} (film)/cm^{-1} 1160, 1289 (S=O), 1596 (C=C), 3013, 3069, 3102 (C-H and =CH), 3263, 3348 (N-H); δ_H (400 MHz; DMSO-d_6) 7.01 (1H, d, J_{AB} = 16.3 Hz, *trans*-HC=CH), 7.09 (1H, t, J = 3.5 Hz, =CH $_3$), 7.28 (1H, d, =CH $_2$ overlapping), 7.32 (2H, s, NH_2 - overlapping), 7.53 (1H, d, J = 4.6 Hz, =CH $_4$), 7.61 (1H, d, J_{AB} = 16.1 Hz, *trans*-HC=CH), 7.76 (4H, d, J = 9.9 Hz, ArH$_{3', \& 2'}$, ArH $_{6' \& 5'}$); δ_C (100 MHz; DMSO-d_6) 125.0 ($C_{2'}$& $C_{6'}$), 126.6 ($C_{3'}$ & $C_{5'}$), 126.8 (C_3), 127.0 (C_2), 128.3 (C_7 & C_4), 128.6 (C_7), 140.6 ($C_{1'}$), 142.3 (C_1), 143.1 ($C_{4'}$); LCMS (ESI) found *m/z* $[M-H]^-$: 265, $C_{12}H_{11}NO_2S_2$ requires 265.

(*E*)-4-(3,4-dimethoxystyryl)-*N*-methylbenzenesulfonamide (260)



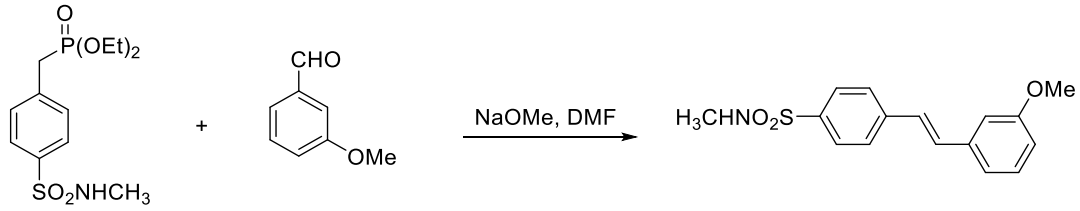
According to method C; the reaction with diethyl 4-(N-methylsulfamoyl)benzylphosphonate (1.43 g, 4.5 mmol) and 3,4-dimethoxybenzaldeyde (0.76 g, 4.6 mmol) provided the product as a cream solid (yield: 0.95 g, 64 %); Purification by recrystallization (absolute ethanol) gave the desired product as a fluffy cream solid (yield: 0.53 g, 36 %); R_f 0.52 [2:1 EtOAc/cyclohexane]; m.p. 164 - 169 °C; υ_{max} (film)/cm^{-1} 1138, 1318 (S=O), 1517, 1591 (C=C), 2845, 2942, 2965, 3007, 3081 (C-H and =CH-), 3271 (N-H); δ_H (400 MHz; $CDCl_3$) 2.65 (3H, d, J = 5.2 Hz, N-CH_3), 3.86 (3H, s, OMe), 3.92 (3H, s, OMe), 4.71 (1H, q, J = 5.2 Hz, N-H), 6.85 (1H, d, J = 8.8 Hz, ArH $_5$), 6.96 (1H, d, J_{AB} = 16.2 Hz, *trans*-HC=CH), 7.05 (1H, d, J = 6.4 Hz, ArH $_6$), 7.06 (1H, d, J = 6.6 Hz, ArH $_2$), 7.14 (1H, d, J_{AB} = 16.2 Hz, *trans*-HC=CH), 7.58 (2H, d, J = 8.5 Hz, ArH $_{3'\ \&\ 2'}$), 7.80 (2H, d, J = 8.4 Hz, ArH $_{5'\&\ 6'}$); δ_C (100 MHz; $CDCl_3$) 29.3 (N-CH_3), 56.0 (2 x OMe), 108.9 (C_2), 111.2 (C_5), 120.7 (C_6), 126.6 ($C_{2'}$ & $C_{6'}$), 127.8 ($C_{3'}$ & $C_{5'}$), 129.5 (C_7 & $C_{7'}$), 131.9 (C_1), 136.6 ($C_{1'}$), 142.1 ($C_{4'}$), 149.2 (C_4), 149.6 (C_3); LCMS (ESI) found *m/z* $[M-H]^-$: 332, $C_{17}H_{19}NO_4S$ requires 333. % purity determined by ^1H NMR (compound, **260**, (90 %), ethyl acetate (10 %)).

(*E*)-4-(4-methoxystyryl)-*N*-methylbenzenesulfonamide (261)



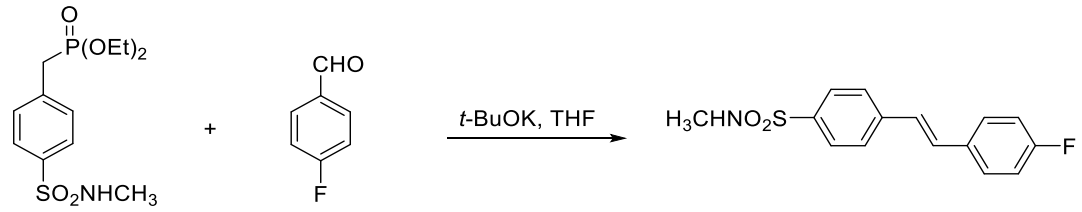
According to method C; the reaction with diethyl 4-(*N*-methylsulfamoyl)benzylphosphonate (1.45 g, 4.5 mmol) and *p*-anisaldehyde (0.61 g, 4.5 mmol) provided the product as an orange solid (yield: 1.21 g, 88 %). Purification by recrystallization (absolute ethanol) gave the desired product as a fluffy pale orange solid (yield: 0.57 g, 42 %); R_f 0.59 [3:1 EtOAc/cyclohexane]; m.p. 203 - 208 °C; υ_{max} (film)/cm^{-1} 1154, 1317 (S=O), 1517, 1592 (C=C), 2843, 2909, 2955, 2983, 3020 (C-H and =CH-), 3281 (N-H); δ_H (400 MHz; $CDCl_3$) 2.67 (3H, d, N-CH_3), 3.83 (3H, s, OMe), 4.32 (1H, q, *J* = 5.4 Hz, N-H), 6.91 (2H, d, *J* = 8.8 Hz, ArH $_{3\ \&\ 5}$), 6.97 (1H, d, J_{AB} = 16.3 Hz, *trans*-HC=CH), 7.17 (1H, d, J_{AB}= 16.3 Hz, *trans*-HC=CH), 7.47 (2H, d, *J* = 8.7 Hz, ArH $_{2\ \&\ 6}$), 7.59 (2H, d, *J* = 8.5 Hz, ArH $_{3'\ \&\ 2'}$), 7.80 (2H, d, *J* = 8.5 Hz, ArH $_{6'\ \&\ 5'}$); δ_C (100 MHz; $CDCl_3$) 31.8 (N-CH_3), 57.9 (OMe), 116.8 (C_3 & C_5), 129.1 ($C_{2'}$ & $C_{6'}$), 130.2 ($C_{3'}$ & $C_{5'}$), 130.2 (C_7 & $C_{7'}$), 130.7 (C_1), 134.2 (C_2 & C_6), 139.0 ($C_{1'}$), 144.8 ($C_{4'}$), 162.5 (C_4); LCMS (ESI) found *m/z* $[M-H]^-$: 302, $C_{16}H_{17}NO_3S$ requires 303. % purity determined by ^{1}H NMR (compound, **261**, (61 %), ethanol (39 %)).

(*E*)-4-(3-methoxystyryl)-*N*-methylbenzenesulfonamide (262)



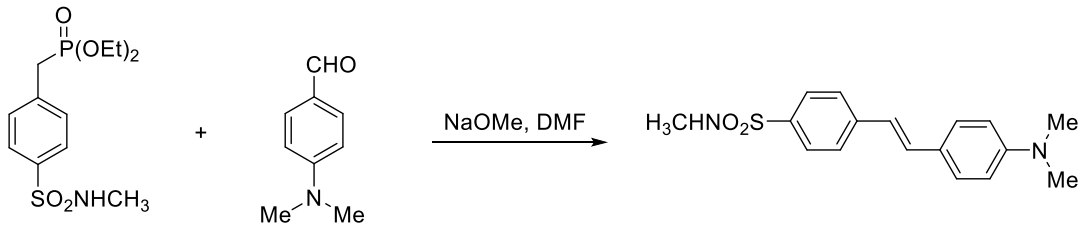
According to method C; the reaction with diethyl 4-(*N*-methylsulfamoyl)benzylphosphonate (1.80 g, 5.6 mmol) and 3-methoxybenzaldehyde (0.76 g, 5.9 mmol) provided the product as a yellow solid. Purification by recrystallization (absolute ethanol 99 %) gave the titled product, **262**, as a pale yellow solid (yield: 0.09 g, 5 %); R_f 0.82 [EtOAc]; m.p. 85 - 89 °C; υ_{max} (film)/cm^{-1} 1160, 1312 (S=O), 1582 (C=C), 2937, 2963, 3011, 3024, (C-H and =CH-), 3263 (N-H); δ_H (600 MHz; $CDCl_3$) 2.67 (3H, d, J = 5.4 Hz, N-CH_3), 3.84 (3H, s, OMe), 4.28 (1H, q, J = 5.2, N-H), 6.86 (1H, m, ArH $_4$), 7.05 (1H, d, J = 7.3 Hz, ArH $_6$), 7.08 (1H, d, J_{AB} = 16.5 Hz, *trans*-HC=CH), 7.12 (1H, d, J = 7.3 Hz, ArH $_2$), 7.17 (1H, d, J_{AB} = 16.0 Hz, *trans*-HC=CH), 7.29 (1H, t, J = 8.2 Hz, ArH $_5$), 7.61 (2H, d, J = 8.7 Hz, ArH $_{3' \& 2'}$) 7.82 (2H, d, J = 9 Hz, ArH $_{5' \& 6'}$); δ_C (150 MHz; $CDCl_3$ and DMSO-d_6) 27.9 (N-CH_3), 54.4 (OMe), 111.1 (C_2), 113.2 (C_4), 118.6 (C_6), 125.9 ($C_{3'}$, $C_{5'}$), 126.3 ($C_{2'}$, & $C_{6'}$), 126.6 (C_7 & $C_{7'}$), 128.9 (C_5), 130.6 (C_1), 137.0 ($C_{1'}$), 140.2 ($C_{4'}$), 158.9 (C_3); LCMS (ESI) found *m/z* $[M-H]^-$: 301, $C_{16}H_{17}NO_3S$ requires 303.

(*E*)-4-(4-fluorostyryl)-*N*-methylbenzenesulfonamide (255)



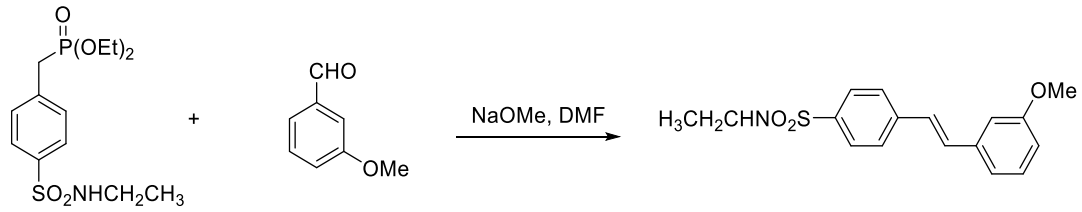
According to method F; the reaction with diethyl 4-(*N*-methylsulfamoyl)benzylphosphonate (1.00 g, 3.1 mmol) and 4-fluorobenzaldehyde (0.39 g, 3.1 mmol) provided the product as a pale cream solid (yield: 0.90 g, 99 %). Purification by washing (diethyl ether and cyclohexane) afforded the desired product as a white crystalline solid (yield: 0.62 g, 68 %); R_f 0.75 [3:1 EtOAc/cyclohexane]; m.p. 163 - 167 °C; υ_{max} (film)/cm^{-1} 1152, 1314 (S=O), 1512, 1590 (C=C), 2830, 3023, 3049, 3075 (C-H and =CH-), 3273 (N-H); δ_H (400 MHz; $CDCl_3$) 2.68 (3H, d, J = 5.4 Hz, CH_3), 4.42 (1H, q, J = 5.4 Hz, N-H), 7.02 (1H, m, *trans*-HC=CH), 7.07 (2H, t, J = 8.6 Hz, ArH $_{3\ \&\ 5}$), 7.17 (1H, d, J_{AB} = 16.4 Hz, *trans*-HC=CH), 7.50 (2H, q, J = 8.7 Hz, ArH $_{2\ \&\ 6}$), 7.61 (2H, d, J = 8.6 Hz, ArH $_{3'\ \&\ 2'}$), 7.83 (2H, d, J = 8.5 Hz, ArH $_{6'\ \&\ 5'}$); δ_C (100 MHz; $CDCl_3$) 29.4 (N-CH_3), 115.8, 116.0 (C_3 & C_5), 126.5, 126.9 ($C_{2'}$ & $C_{6'}$), 127.8 ($C_{3'}$ & $C_{5'}$) 128.5 (C_7 & $C_{7'}$), 130.9 (C_2 & C_6), 132.7 (C_1), 137.2 ($C_{1'}$), 141.7 ($C_{4'}$), 161.4, 164.1 (C_4); LCMS (ESI) found *m/z* $[M-H]^-$: 290, $C_{15}H_{14}FNO_2S$ requires 291. % purity determined by ^{1}H NMR (compound, **255**, (66 %), diethyl ether (34 %)).

(*E*)-4-(4-(dimethylamino)styryl)-*N*-methylbenzenesulfonamide (263)



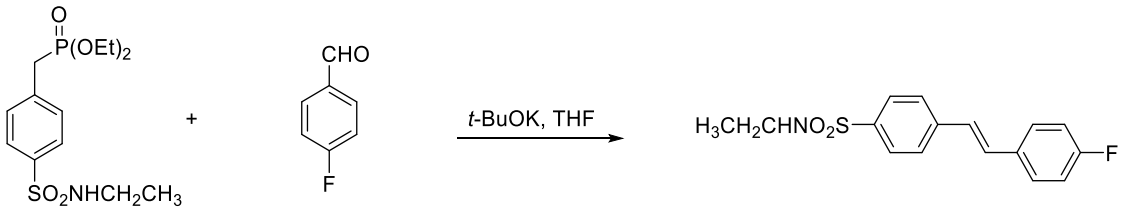
According to method C; the reaction with diethyl 4-(*N*-methylsulfamoyl)benzylphosphonate (1.03 g, 3.2 mmol) and 4-(dimethylamino)benzaldehyde (0.50 g, 3.4 mmol) provided the product as a fluorescent yellow solid (yield: 0.6 g, 59 %). Purification by recrystallization (diethyl ether) afforded the desired product as a fluorescent yellow solid (yield: 0.49 g, 48 %); R_f 0.90 [3:1 EtOAc/cyclohexane]; m.p. 131 - 134 °C; υ_{max} (film)/cm^{-1}1145, 1294 (S=O), 2815, 2862, 2895, 2950, 2983, 3025 (C-H and =CH-), 3262 (N-H); δ_H (400 MHz; DMSO-d_6) 2.41 (3H, s, N-CH_3), 2.95 (6H, s, N-CH_3), 6.73 (2H, d, J = 8.8 Hz, ArH $_{3\ \&\ 5}$), 7.04 (1H, d, J_{AB} = 16.3 Hz, *trans*-HC=CH), 7.30 (2H, d, J_{AB} = 16.3 Hz, J = 16.3 Hz, *trans*-HC=CH), 7.47 (2H, d, J = 8.8 Hz, ArH $_{2\ \&\ 6}$), 7.69 (4H, d, ArH $_{3'\ \&\ 2'}$ & ArH $_{6'\ \&\ 5'}$), 7.71 (1H, s, NH_2 - overlap); δ_C (100 MHz; DMSO-d_6) 29.2 (NH-CH_3), 40.3, 40.4 (N-CH_3), 112.5, 112.6 (C_3 & C_5), 122.2 (C_1), 126.6 (C_2 & C_6), 126.8 ($C_{2'}$ & $C_{6'}$), 127.6 ($C_{3'}$ & $C_{5'}$) 128.6 (C_7 & $C_{7'}$), 132.4 ($C_{1'}$), 141.0 ($C_{4'}$), 150.5 (C_4); LCMS (ESI) found *m/z* $[M + H]^+$: 317, $C_{17}H_{20}N_2O_2S$ requires 316. % purity determined by ^{1}H NMR (compound, **263**, (90 %), compound, **221b**, (10 %)).

(*E*)-*N*-Ethyl-4-(3-methoxystyryl)benzenesulfonamide (264)



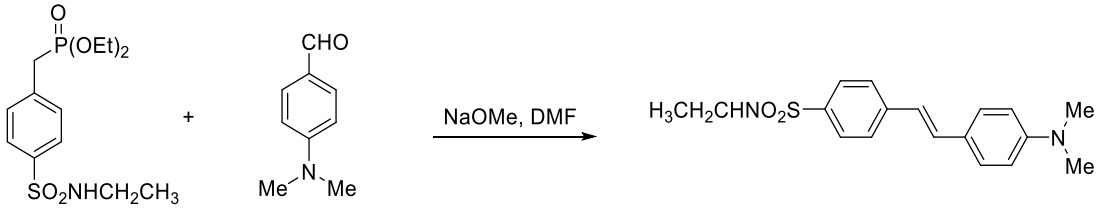
According to method C; the reaction with diethyl 4-(*N*-ethylsulfamoyl)benzylphosphonate (0.54 g, 1.6 mmol) and *m*-anisaldehyde (0.22 g, 1.6 mmol) gave the product as a golden yellow solid (yield: 0.059 g, 12 %). Purification by recrystallization (diethyl ether) afforded the titled product as a pale yellow solid (yield: 0.05 g, 10 %). R_f 0.92 [3:1 EtOAc/cyclohexane]; m.p. 92 - 96 °C; υ_{max} (film)/cm^{-1} 1156, 1316 (S=O), 1582 (C=C), 2842, 2948, 2989 (C-H and =CH-), 3269 (N-H); δ_H (400 MHz; $CDCl_3$) 1.10 (3H, t, J = 5.2 Hz, N-CH_3), 3.03 (3H, q, J = 6.0 Hz, C$\underline{H}_2$-CH_3), 3.84 (3H, s, OMe), 4.55 (1H, t, N-H), 6.86 (1H, dd, J = 8.2 Hz, J = 2.3 Hz, ArH $_4$), 7.05 (1H, d, J = 1.2 Hz, ArH $_6$), 7.09 (1H, d, J_{AB} = 16.4 Hz, *trans*-$\underline{H}$C=CH), 7.18 (1H, d, J_{AB} = 16.3 Hz, *trans*-HC=C$\underline{H}$), 7.13 (1H, s, ArH $_2$), 7.29 (1H, t, J = 7.8 Hz, ArH $_5$), 7.60 (2H, d, J = 8.6 Hz, ArH $_{3'\ \&\ 2'}$), 7.83 (2H, d, J = 8.5 Hz, ArH $_{5'\&\ 6'}$); δ_C (100 MHz; $CDCl_3$) 15.2 (CH_3), 38.3 (NH-CH_2), 55.3 (OMe), 112.2 (C_2), 114.2 (C_4), 119.6 (C_6), 126.9 ($C_{3'}$, $C_{5'}$), 127.1 ($C_{2'}$, & $C_{6'}$), 127.6 (C_7 & $C_{7'}$), 129.9 (C_5), 132.0 (C_1), 137.9 ($C_{1'}$), 138.4 ($C_{4'}$), 160.0 (C_3); LCMS (ESI) found *m/z* $[M-H]^-$: 316, $C_{17}H_{19}NO_3S$ requires 317. % purity determined by ^{1}H NMR (compound, **264**, (83 %), diethyl ether (17 %)).

(*E*)-*N*-Ethyl-4-(4-fluorostyryl)benzenesulfonamide (256)



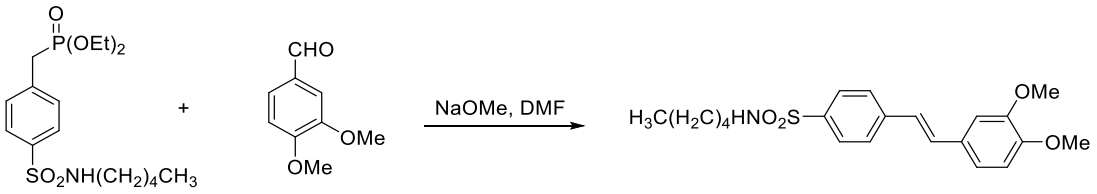
According to method F; the reaction with diethyl 4-(*N*-ethylsulfamoyl)benzylphosphonate (0.85 g, 2.5 mmol) and 4-fluorobenzaldehyde (0.31 g, 2.5 mmol) gave the product as a white solid (yield: 0.60 g, 78 %). Purification by washing (diethyl ether and cyclohexane) afforded the desired product as a white crystalline solid (yield: 0.30 g, 39 %); R_f 0.84 [3:1 EtOAc/cyclohexane]; m.p. 149 - 153 °C; υ_{max} (film)/cm^{-1} 1158, 1319 (S=O), 1507, 1595 (C=C), 2882, 2945, 2997, 3059 (C-H and =CH-), 3299 (N-H); δ_H (400 MHz; $CDCl_3$) 1.10 (3H, t, J = 7.2 Hz, CH_3), 3.02 (2H, q, J = 6.1 Hz, CH_2), 4.67 (1H, t, J = 5.9 Hz, N-H), 7.01 (1H, d, J_{AB} = 16.5 Hz, *trans*-HC=CH), 7.06 (2H, t, J = 8.6 Hz, ArH $_{3\ \&\ 5}$), 7.16 (1H, d, J_{AB} = 16.2 Hz, *trans*-HC=CH), 7.49 (2H, d, J = 8.8 Hz, ArH $_{2\ \&\ 6}$), 7.60 (2H, d, J = 8.6 Hz, ArH $_{3'\ \&\ 2'}$), 7.84 (2H, d, J = 8.3 Hz, ArH $_{6'\ \&\ 5'}$); δ_C (100 MHz; $CDCl_3$) 15.1 (CH_2-CH_3), 38.3 (CH_2), 115.8, 116.0 (C_3 & C_5), 126.6, 126.9 ($C_{2'}$ & $C_{6'}$), 127.6 ($C_{3'}$ & $C_{5'}$), 128.5 (C_7 & $C_{7'}$), 130.8 (C_2 & C_6), 132.7 (C_1), 138.4 ($C_{1'}$), 141.6 ($C_{4'}$), 161.6 (C_4); LCMS (ESI) found *m/z* $[M-H]^-$: 304, $C_{16}H_{16}FNO_2S$ requires 305.

(*E*)-4-(4-(Dimethylamino)styryl)-*N*-ethylbenzenesulfonamide (265)



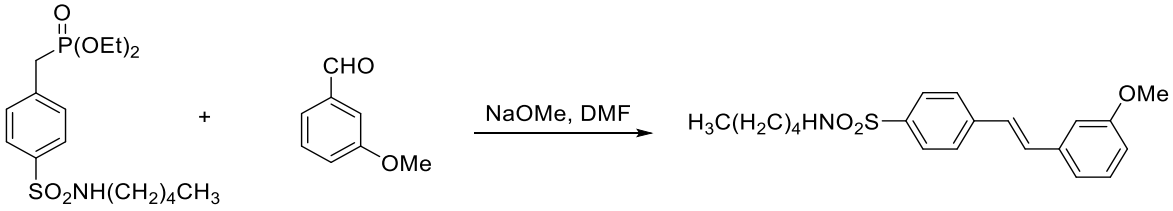
According to method C; the reaction with diethyl 4-(*N*-ethylsulfamoyl)benzylphosphonate (0.60 g, 1.8 mmol) and 4-(dimethylamino)benzaldehyde (0.30 g, 2.0 mmol) gave the product as a brown solid (yield: 0.15 g, 25 %). Purification by recrystallization (ethanol) afforded the desired product as a light brown solid (yield: 0.09 g, 15 %); R_f 0.91 [3:1 EtOAc/cyclohexane]; m.p. 207 - 210 °C; υ_{max} (film)/cm^{-1} 1155, 1312 (S=O), 1602 (C=C), 2816, 2885, 2945, 2987, 3028 (C-H and =CH-), 3291 (N-H); δ_H (400 MHz; $CDCl_3$) 1.10 (3H, t, J = 7.2 Hz, $CH_{3\ sulfonamide}$), 3.01 (6H, s, N-CH_3), 4.51 (2H, t, J = 6.0 Hz, N-CH_2), 6.70 (2H, d, J = 8.8 Hz, Ar$H_{3\ \&\ 5}$), 6.89 (1H, d, J_{AB} = 16.2 Hz, *trans*-HC=CH), 7.14 (1H, d, J_{AB} = 16.2 Hz, *trans*-HC=CH), 7.41 (2H, d, J = 8.6 Hz, Ar$H_{2\ \&\ 6}$), 7.55 (2H, d, J = 8.4 Hz, Ar$H_{3'\ \&\ 2'}$), 7.84 (2H, d, J = 8.3 Hz, Ar$H_{5'\ \&\ 6'}$); δ_C (100 MHz; $CDCl_3$) 15.1 (CH_2-CH_3), 38.3 (N-CH_2), 40.2 (N-CH_3), 112.3 (C_3 & C_5), 122.1 (C_1), 124.6 (C_2 & C_6), 126.2 ($C_{2'}$ & $C_{6'}$), 127.5 ($C_{3'}$ & $C_{5'}$), 128.2 (C_7 & $C_{7'}$), 137.0 ($C_{1'}$), 142.8 ($C_{4'}$), 150.7 (C_4); LCMS (ESI) found *m/z* $[M-H]^-$: 331, $C_{18}H_{22}N_2O_2S$ requires 330.

(*E*)-4-(3,4-Dimethoxystyryl)-*N*-pentylbenzenesulfonamide (266)



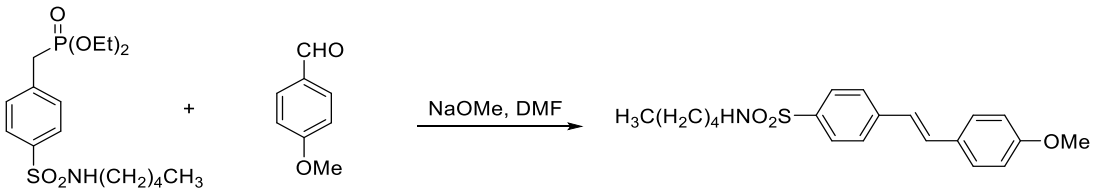
According to method C; the reaction with diethyl 4-(*N*-pentylsulfamoyl)benzylphosphonate (1.10 g, 2.9 mmol) and 3,4-dimethoxybenzaldehyde (0.47 g, 2.8 mmol) gave the product as an orange oil (yield: 0.87 g, 77 %); R_f 0.90 [2:1 EtOAc/cyclohexane]; υ_{max} (film)/cm^{-1} 1160, 1330 (S=O), 1519, 1529 (C=C), 2847, 2863, 2932, 2952, 3069 (C-H and =CH-), 3255 (N-H); δ_H (400 MHz; DMSO-d_6) 0.79 (3H, t, J = 6.7 Hz, C-CH_3), 1.18 (4H, m, C-CH_2), 1.35 (2H, m, C-CH_2), 2.72 (2H, q, J = 6.6 Hz, N-CH_2), 3.78 (3H, s, OMe), 3.82 (3H, s, OMe), 4.32 (1H, t, J = 5.6 Hz, NH_2), 6.87 (2H, d, J = 8.5 Hz, ArH $_{5\ \&\ 6}$), 6.97 (1H, d, J_{AB} = 16.2 Hz, *trans*-HC=CH), 7.07 (1H, m, ArH $_2$), 7.15 (1H, d, J_{AB} = 16.4 Hz, *trans*-HC=CH), 7.75 (2H, d, J = 8.4 Hz ArH $_{3'\ \&\ 2'}$); 7.59 (2H, d, J = 8.6 Hz, ArH $_{5'\ \&\ 6'}$), δ_C (100 MHz; $CDCl_3$) 13.9 (CH_3), 22.2 (CH_2-CH_3), 28.7, 29.4 (2 x CH_2), 43.3 (NH-CH_2), 56.0 (OMe), 109.0 (C_2), 111.3 (C_5), 120.6 (C_6), 126.6 ($C_{2'}$ & $C_{6'}$), 127.6 ($C_{3'}$ & $C_{5'}$), 132.2 (C_7 & $C_{7'}$), 131.9 (C_1), 136.6 ($C_{1'}$), 142.1 ($C_{4'}$), 149.2 (C_4), 149.6 (C_3); LCMS (ESI) found *m/z* $[M-H]^-$: 388, $C_{21}H_{27}NO_4S$ requires 389.

(*E*)-4-(3-Mmethoxystyryl)-*N*-pentylbenzenesulfonamide (267)



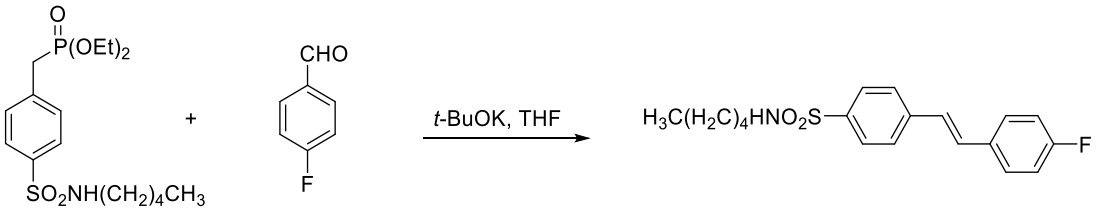
According to method C; the reaction with diethyl 4-(*N*-pentylsulfamoyl)benzylphosphonate (1.10 g, 2.9 mmol) and *m*-anisaldehyde (0.45 g, 3.3 mmol) afforded the product as an orange oil, purification not performed (yield: 0.87 g, 83 %); R_f 0.89 [3:1 EtOAc/cyclohexane]; υ_{max} (film)/cm^{-1} 1152, 1320 (S=O), 1516 (C=C), 2866, 2938, 2966 (C-H and =CH-), 3270 (N-H); δ_H (400 MHz; $CDCl_3$) 0.79 (3H, t, *J* = 6.8 Hz, CH_3), 1.15 (4H, m, C-CH_2), 1.40 (2H, m, C-CH_2), 2.86 (2H, q, *J* = 6.6 Hz, N-CH_2), 3.78 (3H, s, OMe), 5.76 (2H, t, *J* = 6.0 Hz, N-H), 6.79 (1H, dd, *J* = 5.7 Hz, *J* = 1.8 Hz, ArH $_6$), 7.00 (1H, d, J_{AB} = 16.3 Hz, *trans*-HC=CH), 7.07 (1H, m, *trans*-HC=CH), 7.05 (2H, m, *J* = 7.9 Hz ArH $_2$), 7.23 (1H, t, *J* = 7.9 Hz, ArH $_{13}$), 7.54 (2H, d, *J* = 8.3 Hz, ArH $_{3'\&\ 2'}$), 7.82 (2H, d, *J* = 8.4 Hz, ArH $_{5'\ \&\ 6'}$); δ_C (100 MHz; DMSO-d_6) 14.3 (CH_3), 22.1 (CH_2-CH_3), 28.7, 29.2 (CH_2-CH_2), 43.3 (N-CH_2), 55.6 (OMe), 112.3 (C_2), 114.6 (C_4), 120.0 (C_6), 127.4 ($C_{3'}$, $C_{5'}$), 127.5 ($C_{2'}$, & $C_{6'}$), 130.3 (C_7 & $C_{7'}$), 131.8 (C_5), 138.5 (C_1), 139.6 ($C_{1'}$), 141.4 ($C_{4'}$), 160.1 (C_3); LCMS (ESI) found *m/z* $[M-H]^-$: 358, $C_{20}H_{25}NO_3S$ requires 359. % purity determined by ^1H NMR (compound, **267**, (86 %), compound, **221d**, (8 %), compound, **228**, (6 %)).

(*E*)-4-(4-Methoxystyryl)-*N*-pentylbenzenesulfonamide (268)



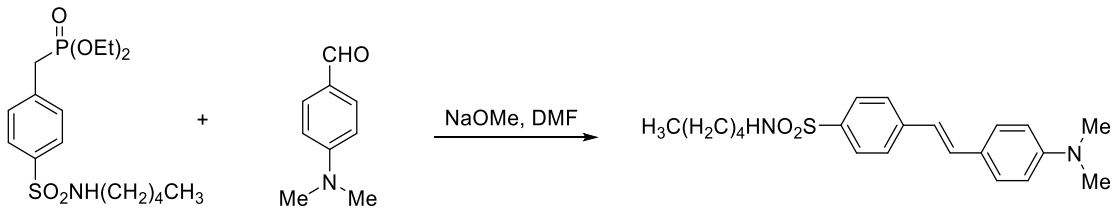
According to method C; the reaction with diethyl 4-(*N*-pentylsulfamoyl)benzylphosphonate (2.08 g, 5.5 mmol) and *p*-anisaldehyde (yield: 0.78 g, 5.7 mmol) afforded the product as an orange solid. Purification by recrystallization (diethyl ether) gave the desired product as an orange solid (yield: 0.28 g, 14 %); R_f 0.93 [3:1 EtOAc/cyclohexane]; m.p. 154 - 155 °C; υ_{max} (film)/cm^{-1} 1148, 1325 (S=O), 1592 (C=C), 2858, 2940, 2966, 3017 (C-H and =CH-), 3272 (N-H); δ_H (400 MHz; DMSO-d_6) 0.79 (3H, m, C-CH_3), 1.18 (4H, m, C-CH_2), 1.35 (2H, q, J = 6.0 Hz, C-CH_2), 2.72 (2H, q, J = 6.5 Hz, N-CH_2), 3.78 (3H, s, OMe), 6.97 (2H, d, J = 8.5 Hz, $ArH_{3\ \&\ 5}$), 7.17 (1H, d, J_{AB} = 16.4 Hz, *trans*-HC=CH), 7.36 (1H, d, J_{AB} = 16.4 Hz, *trans*-HC=CH), 7.53 (1H, s, NH), 7.58 (2H, d, J = 8.3 Hz, $ArH_{2\ \&\ 6}$), 7.74 (4H, s, $ArH_{3'\ \&\ 2'}$ & $ArH_{6'\ \&\ 5'}$); δ_C (100 MHz; $CDCl_3$) 13.9 (CH_3), 22.2 (CH_2-CH_3), 28.7, 29.3 (CH_2-CH_2), 43.3 (N-CH_2), 55.4 (OMe), 114.3 (C_3 & C_5), 124.6 ($C_{2'}$ & $C_{6'}$), 126.6 ($C_{3'}$ & $C_{5'}$), 128.2 (C_7 & $C_{7'}$), 129.3 (C_1), 129.3 (C_2 & C_6), 137.9 ($C_{1'}$), 142.1 ($C_{4'}$), 160.0 (C_4); LCMS (ESI) found *m/z* $[M-H]^-$: 358, $C_{20}H_{25}NO_3S$ requires 359. % purity determined by ^1H NMR (compound, **268**, (92 %), compound, **221d**, (8 %), compound, **229**, (6 %)).

(*E*)-4-(4-Fluorostyryl)-*N*-pentylbenzenesulfonamide (257)



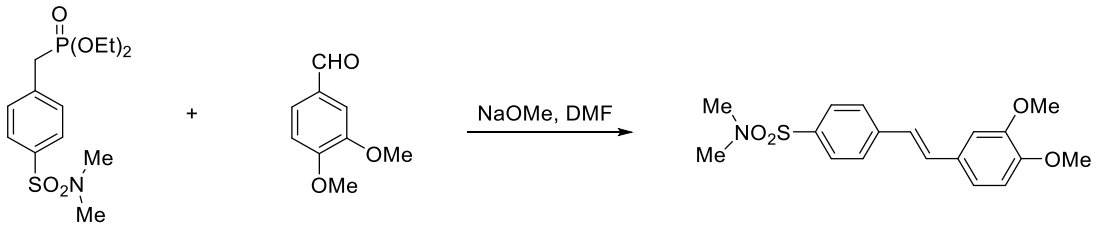
According to method F; the reaction with diethyl 4-(*N*-pentylsulfamoyl)benzylphosphonate (1.6 g, 4.2 mmol) and 4-fluorobenzaldehyde (0.53 g, 4.3 mmol) gave the product as an orange crystalline solid. Purification by washing (diethyl ether and cyclohexane) afforded the desired product as a white crystalline solid (yield: 0.5 g, 34 %); R_f 0.95 [3:1 EtOAc/cyclohexane]; m.p. 133 - 135 °C; υ_{max} (film)/cm^{-1} 1158, 1324 (S=O), 1512, 1590 (C=C), 2866, 2934, 2960, 3023, 3059 (C-H and =CH-), 3278 (N-H); δ_H (400 MHz; $CDCl_3$) 0.83 (3H, t, *J* = 6.2 Hz, CH_3), 1.23 (2H, q, *J* = 7.2 Hz, C$\underline{H}_2$-CH_3), 1.47 (2H, q, *J* = 7.0 Hz, N-CH_2-C$\underline{H}_2$), 2.96 (2H, q, *J* = 6.8 Hz, N-C$\underline{H}_2$-CH_2), 4.59 (1H, t, *J* = 6.0 Hz, N-H), 7.01 (1H, d, J_{AB} = 16.4 Hz, $\underline{H}$C=CH), 7.06 (2H, m, ArH $_{3\ \&\ 5}$), 7.16 (1H, m, HC=C$\underline{H}$), 7.49 (2H, q, *J* = 5.4 Hz, ArH $_{2\ \&\ 6}$), 7.59 (2H, d, *J* = 8.6 Hz, ArH $_{3'\ \&\ 6'}$), 7.83 (2H, d, *J* = 8.3 Hz, ArH $_{5'\ \&\ 6'}$); δ_C (100 MHz; $CDCl_3$) 13.9 (CH_3), 22.2 ($\underline{C}H_2$-CH_3), 28.7, 29.3 (CH_2-CH_2), 43.3 (N-CH_2), 115.8, 116.0 (C_3 & C_5), 126.5, 126.8 ($C_{2'}$ & $C_{6'}$), 127.6 ($C_{3'}$ & $C_{5'}$), 128.4, 128.5 (C_7 & $C_{7'}$), 130.8 (C_2 & C_6), 132.7 (C_1), 138.4 ($C_{1'}$), 141.5 ($C_{4'}$), 161.6 (C_4); LCMS (ESI) found *m/z* $[M-H]^-$: 346, $C_{19}H_{22}FNO_2S$ requires 347.

(*E*)-4-(4-(Dimethylamino)styryl)-*N*-pentylbenzenesulfonamide (269)



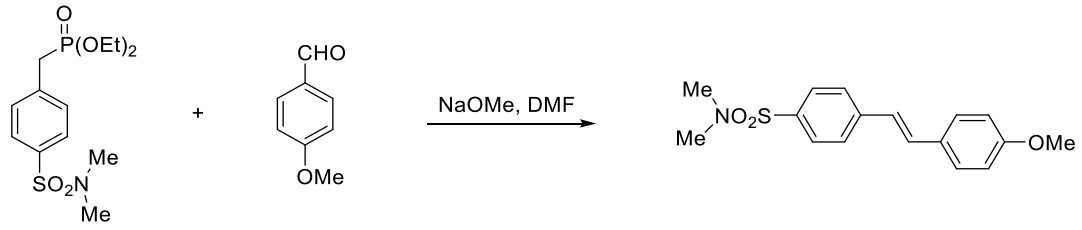
According to method C; the reaction with diethyl 4-(*N*-pentylsulfamoyl)benzylphosphonate (2.02 g, 5.4 mmol) and 4-(dimethylamino)benzaldehyde (0.88 g, 5.9 mmol) gave the product as a waxy orange solid (yield: 0.43 g, 20 %). Purification by recrystallization (diethyl ether) afforded the desired product as a dark orange solid (yield: 0.22 g, 11 %); R_f 0.93 [3:1 EtOAc/cyclohexane]; m.p. 165 - 240 °C; υ_{max} (film)/cm^{-1} 1153, 1317 (S=O), 1593 (C=C), 2802, 2862, 2931, 2961, 3030 (C-H and =CH-), 3268 (N-H); δ_H (400 MHz; DMSO-d_6) 0.79 (3H, t, J = 6.6 Hz, C-CH_3), 1.86 (4H, m, C-CH_2), 1.35 (2H, q, J = 6.7 Hz, C-CH_2), 2.72 (2H, q, J = 7.0 Hz, N-CH_2), 2.94 (6H, s, N-CH_3), 3.36 (1H, s, NH – overlapping with H_2O peak), 6.72 (2H, d, J = 8.8 Hz, ArH $_{3\ \&\ 5}$), 7.03 (1H, d, J_{AB} = 16.4 Hz, *trans*-HC=CH), 7.29 (1H, d, J_{AB} = 16.4 Hz, *trans*-HC=CH), 7.46 (2H, d, J = 8.7 Hz, ArH $_{2\ \&\ 6}$), 7.71 (4H, s, ArH $_{3'\ \&\ 2'}$ & ArH $_{5'\&\ 6'}$); δ_C (100 MHz; DMSO-d_6) 14.3 (CH_3), 22.2 (CH_2), 28.7, 29.1 (CH_2), 40.02 (N-CH_3), 43.0 (NH-CH_2), 112.6 (C_3 & C_5), 122.3 (C_1), 127.4 (C_2 & C_6), 127.4 ($C_{2'}$ & $C_{6'}$) 128.6 ($C_{3'}$ & $C_{5'}$), 132.3 (C_7 & $C_{7'}$), 138.4 ($C_{1'}$), 142.4 ($C_{4'}$), 150.9 (C_4); LCMS (ESI) found *m/z* $[M-H]^-$: 371, $C_{21}H_{28}N_2O_2S$ requires 372.

(*E*)-4-(3,5-Dimethoxystyryl)-*N*,*N*-dimethylbenzenesulfonamide (270)



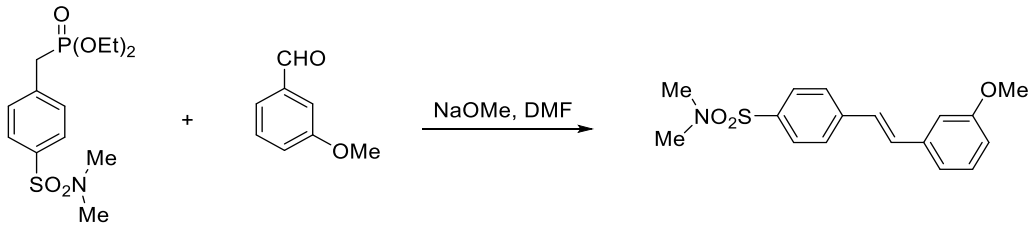
According to method C; the reaction with diethyl 4-(*N,N*-dimethylsulfamoyl)benzylphosphonate (2.02 g, 6.0 mmol) and 3,4-dimethoxybenzaldehyde (1.00 g, 6.0 mmol) afforded the titled product, **270**, as a golden solid (yield: 1.95 g, 93 %). Purification by recrystallization (diethyl ether) afforded the product as a pale golden solid (yield: 1.69 g, 81 %); R_f 0.78 [2:1 EtOAc/cyclohexane]; m.p. 154 - 158 °C; υ_{max} (film)/cm^{-1} 1155, 1335 (S=O), 1589 (C=C), 2848, 2881, 2913, 2936 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 2.71 (6H, d, *J* 5.7 Hz, N-CH_3), 3.90 (3H, s, OMe), 3.94 (3H, s, OMe), 6.86 (1H, d, *J* = 7.8 Hz, ArH $_5$), 6.97 (1H, d, J_{AB}= 16.2 Hz, *trans*-HC=CH), 7.07 (2H, m, ArH $_{2\ \&\ 6}$), 7.16 (1H, d, J_{AB} = 16.2 Hz, *trans*-HC=CH), 7.61 (2H, d, *J* = 8.2 Hz, ArH $_{3'\ \&\ 2'}$), 7.73 (2H, d, *J* = 8.4 Hz, ArH $_{5'\ \&\ 6'}$); δ_C (100 MHz; $CDCl_3$) 38.0 (N-CH_3), 56.0 (OMe), 109.0 (C_2), 111.3 (C_5), 120.7 (C_6), 124.8 ($C_{2'}$ & $C_{6'}$), 126.5 ($C_{3'}$& $C_{5'}$), 128.3 (C_7 & $C_{7'}$), 132.0 (C_1), 133.4 ($C_{1'}$), 142.1 ($C_{4'}$), 149.3 (C_4), 149.7 (C_3); LCMS (ESI) found *m/z* $[M+H]^+$: 348, $C_{18}H_{21}NO_4S$ requires 347.

(*E*)-4-(4-Methoxystyryl)-*N*,*N*-dimethylbenzenesulfonamide (271)



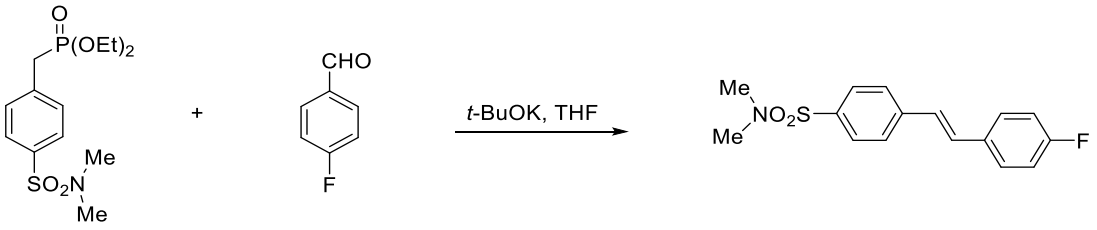
According to method C; the reaction with diethyl 4-(*N*,*N*-dimethylsulfamoyl)benzylphosphonate (2.0 g, 6.0 mmol) and *p*-anisaldehyde (0.81 g, 6.0 mmol) gave the crude product as a pale yellow solid (yield: 2.77 g, 146 %). Purification by recrystallization (diethyl ether) afforded the titled product, **271**, as a pale yellow solid (yield: 1.64 g, 87 %); R_f 0.89 [3:1 EtOAc/cyclohexane]; m.p. 210 - 216 °C; υ_{max} (film)/cm^{-1} 1155, 1335 (S=O), 1515, 1593 (C=C), 2839, 2945, 2973, 3028 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 2.71 (6H, s, N-CH_3), 3.83 (3H, s, OMe), 6.91 (2H, d, J = 8.8 Hz, ArH $_5$), 6.97 (1H, d, J_{AB} = 16.3 Hz, *trans*-HC=CH), 7.17 (1H, d, J_{AB} = 16.4 Hz, *trans*-HC=CH), 7.47 (2H, d, J = 8.5 Hz, ArH $_{2\ \&\ 6}$), 7.60 (2H, d, J = 8.2 Hz, ArH $_{3'\ \&\ 2'}$), 7.72 (2H, d, J = 8.4 Hz, ArH$_{5'\ \&\ 6'}$); δ_C (100 MHz; $CDCl_3$) 38.0 (N-CH_3), 55.4 (OMe), 112.6 (C_3 & C_5), 124.6 (C_1), 126.5 (C_2 & C_6), 128.2 ($C_{2'}$ & $C_{6'}$), 129.3 ($C_{3'}$ & $C_{5'}$), 131.7 (C_7 & $C_{7'}$), 133.4 ($C_{1'}$), 142.2 ($C_{4'}$), 160.8 (C_4); LCMS (ESI) found *m/z* $[M+H]^+$: 317, $C_{17}H_{19}NO_3S$ requires 317. % purity determined by ^{1}H NMR (compound, **271**, (92 %), compound, **221e**, (8 %)).

(*E*)-4-(3-Methoxystyryl)-*N*,*N*-dimethylbenzenesulfonamide (272)



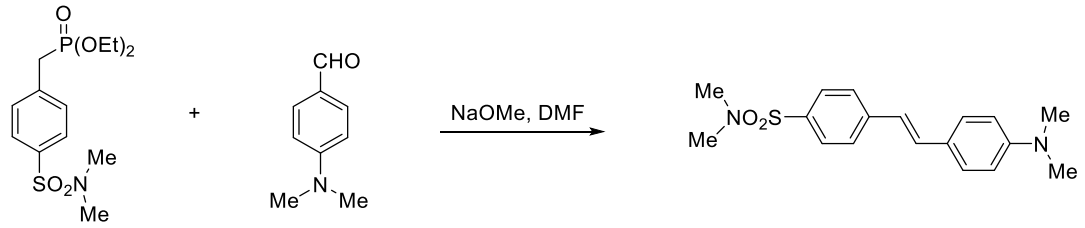
According to method C; the reaction with diethyl 4-(*N,N*-dimethylsulfamoyl)benzylphosphonate (2.08 g, 6.2 mmol) and 3-methoxybenzaldehyde (0.82 g, 6.0 mmol) gave the impure product as beige solid (yield: 1.65 g, 84 %). Purification by recrystallization (absolute ethanol) afforded the titled product, **272**, as a pale beige solid (yield: 1.26 g, 64 %); R_f 0.78 [EtOAc]; m.p. 131 - 135 °C; υ_{max} (KBr)/cm^{-1} 1047, 1256 (C-O), 1582 (C=C), 1156.2, 1330 (S=O), 2807, 2837, 2889, 2933, 2959, 3007, 3059 cm^{-1} (C-H and =CH-); δ_H (600 MHz; $CDCl_3$) 2.70 (6H, s, N-CH_3), 3.84 (3H, s, OMe), 6.85 (1H, dd, J = 8.2 Hz, J = 1.5 Hz, ArH_4), 7.05 (1H, m, ArH_6), 7.10 (1H, d, J_{AB} = 16.5 Hz, *trans*-HC=CH), 7.12 (1H, d, J = 9.1 Hz, ArH_2), 7.18 (1H, m, *trans*-HC=CH), 7.28 (1H, t, J = 8.2, ArH_5), 7.63 (2H, d, J = 8.2 Hz, $ArH_{3'\&\ 2'}$), 7.74 (2H, d, J = 8.2 Hz, $ArH_{5'\ \&\ 6'}$); δ_C (100 MHz; $CDCl_3$) 38.0 (N-CH_3), 55.3 (OMe), 112.2 (C_2), 114.2 (C_4), 119.6 (C_6), 126.9, 127.1, ($C_{3'}$, $C_{5'}$), 127.2 ($C_{2'}$, & $C_{6'}$), 128.2 (C_7 & $C_{7'}$), 132.9 (C_5), 133.9 (C_1), 137.9 ($C_{1'}$), 141.7 ($C_{4'}$), 160.0 (C_3); LCMS (ESI) found *m/z* $[M+H]^+$: 318, $C_{17}H_{19}NO_3S$ requires 317.

(*E*)-4-(4-Fluorostyryl)-*N*,*N*-dimethylbenzenesulfonamide (258)



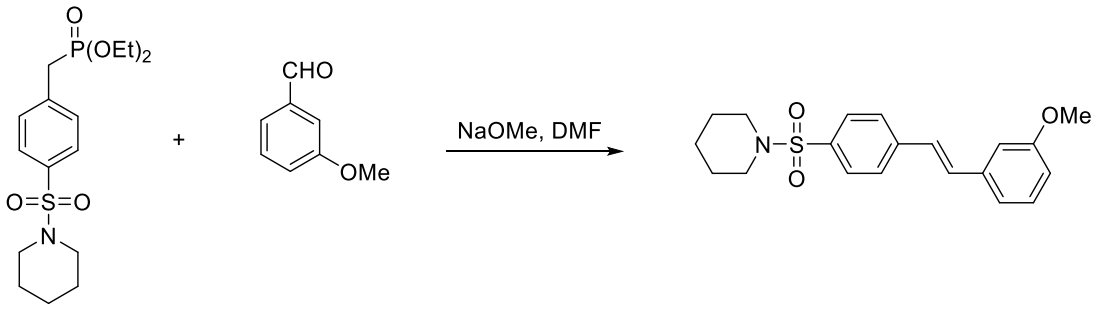
According to the method F; the reaction with diethyl 4-(*N,N*-dimethylsulfamoyl)benzylphosphonate (1.06 g, 3.1 mmol) and 4-fluorobenzaldehyde (0.39 g, 3.1 mmol) afforded the product as beige solid (yield: 0.58 g, 60 %). Purification by washing (diethyl ether and cyclohexane) afforded the desired product as a pale cream solid (yield: 0.39 g, 40 %); R_f 0.84 [2:1 EtOAc/cyclohexane]; m.p. 193 - 197 °C; υ_{max} (film)/cm^{-1} 1158, 1329 (S=O), 1512, 1595 (C=C), 2814, 2872, 2976, 3085 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 2.72 (6H, t, J = 5.1 Hz, CH_3), 7.02 (1H, d, J_{AB} = 16.2 Hz, *trans*-HC=CH),7.06 (2H, m, $ArH_{3\ \&\ 5}$), 7.17 (1H, m, *trans*-HC=CH), 7.49 (2H, dd, J = 5.4 Hz, $ArH_{2\ \&\ 6}$), 7.62 (2H, d, J = 8.3 Hz, $ArH_{3'\ \&\ 6'}$), 7.74 (2H, d, J = 8.2 Hz, $ArH_{5'\ \&\ 6}$); δ_C (100 MHz; $CDCl_3$) 38.0 ($N\text{-}CH_3$), 115.8, 116.0 (C_3 & C_5), 126.6, 126.7 ($C_{2'}$ & $C_{6'}$), 127.2 ($C_{3'}$ & $C_{5'}$), 128.3, 128.5 (C_7 & $C_{7'}$), 130.9 (C_2 & C_6), 132.7 (C_1), 134.0 ($C_{1'}$), 141.7 ($C_{4'}$), 161.6 (C_4); LCMS (ESI) found *m/z* $[M+H]^+$: 306, $C_{16}H_{16}FNO_2S$ requires 305.

(*E*)-4-(4-(Dimethylamino)styryl)-*N*,*N*-dimethylbenzenesulfonamide (273)



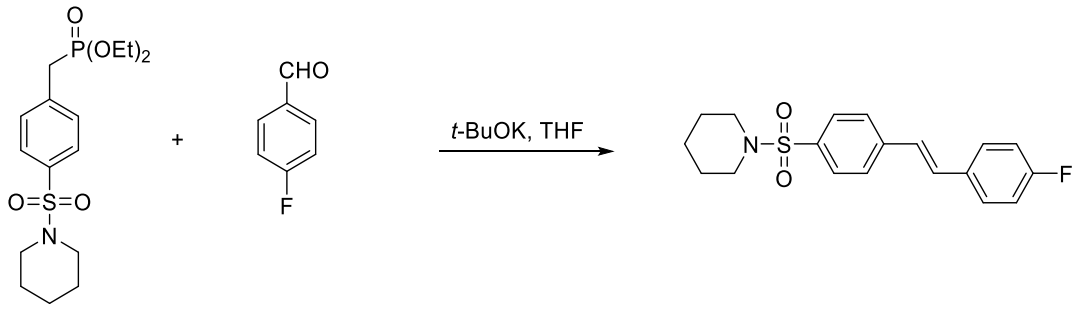
According to method C; the reaction with diethyl 4-(*N*,*N*-dimethylsulfamoyl)benzylphosphonate (2.01 g, 6.0 mmol) and 4-(dimethylamino)benzaldehyde (0.89 g, 6.0 mmol) afforded the impure product as a golden yellow solid (yield: 1.56 g, 79 %). Purification by recrystallization (diethyl ether) afforded the titled product, **273**, as a golden yellow solid (yield: 1.19 g, 60 %); R_f 0.97 [EtOAc]; m.p. 210 - 215 °C; υ_{max} (film)/cm^{-1} 1157, 1331 (S=O), 1588 (C=C), 2809, 2914, 3024 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 2.71 (6H, s, CH_3), 2.99 (6H, s, CH_3), 6.50 (2H, d, J = 8.4 Hz, ArH $_{3\ \&\ 5}$), 6.90 (1H, d, J_{AB} = 16.3 Hz, *trans*-HC=CH), 7.15 (1H, d, J_{AB} = 16.2 Hz, *trans*-HC=CH), 7.42 (2H, d, J = 8.4 Hz, ArH $_{2\ \&\ 6}$), 7.57 (2H, d, J = 8.2 Hz, ArH $_{3'\ \&\ 2'}$), 7.79 (2H, d, J = 7.9 Hz, ArH $_{5'\&\ 6'}$); δ_C (100 MHz; $CDCl_3$) 38.0 (N-CH_3), 40.4 (N-CH_3), 112.3 (C_3 & C_5), 122.1 (C_1), 124.6 (C_2 & C_6), 126.1 ($C_{2'}$ & $C_{6'}$), 128.2 ($C_{3'}$ & $C_{5'}$), 128.3 (C_7 & $C_{7'}$), 132.5 ($C_{1'}$), 142.9 ($C_{4'}$), 150.7 (C_4); LCMS (ESI) found *m/z* $[M+H]^+$: 331, $C_{18}H_{22}N_2O_2S$ requires 330.

(*E*)-1-((4-(3-Methoxystyryl)phenyl)sulfonyl)piperidine (274)



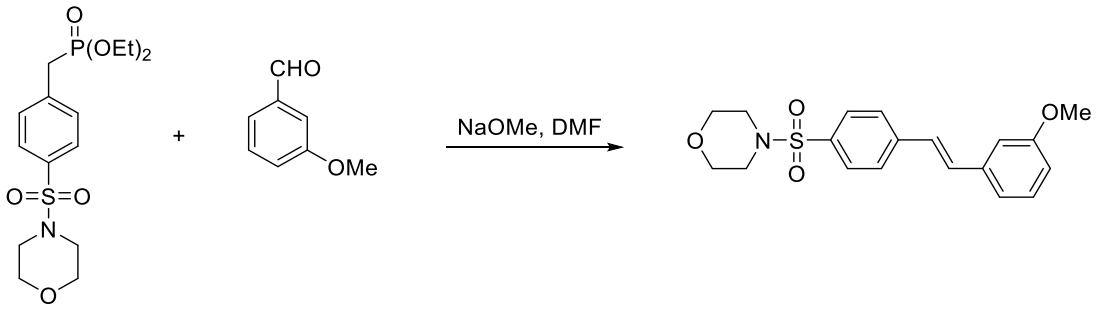
According to method C; the reaction with diethyl 4-(piperidine-1-ylsulfonyl)benzylphosphonate (1.54 g, 4.1 mmol) and *m*-anisaldehyde (0.55 g, 4.1 mmol) gave the product as a brown solid (yield: 0.87 g, 59 %). Purification by recrystallization (diethyl ether) afforded the desired product as a pale orange solid (yield: 0.47 g, 32 %); R_f 0.86 [3:1 EtOAc/cyclohexane]; m.p. 144 - 146 °C, υ_{max} (film)/cm^{-1} 1157, 1325 (S=O), 1580 (C=C), 2862, 2948, 3005 (C-H and =CH-); δ_H (400 MHz; DMSO-d_6) 1.35 (2H, m, C-CH_2), 1.52 (4H, m, C-CH_2), 2.89 (4H, t, J = 5.3 Hz, N-CH_2), 3.80 (3H, s, OMe), 6.90 (1H, dd, J = 8.3 Hz, J = 2.4 Hz, ArH $_4$), 7.22 (2H, d, J = 7.8 Hz, ArH $_6$), 7.23 (1H, s, ArH $_2$), 7.32 (1H, t, J = 8.2 Hz, ArH $_5$), 7.38 (1H, d, J_{AB} = 16.5 Hz, *trans*-HC=CH, 7.43 (1H, d, J_{AB} = 16.5 Hz, *trans*-HC=CH), 7.70 (2H, d, J = 8.4 Hz, ArH $_{3' \& 2'}$), 7.83 (2H, d, J = 8.4 Hz, ArH $_{5' \& 6'}$); δ_C (100 MHz; DMSO-d_6) 23.4, 25.2 (3 x CH_2), 47.1 (N-CH_2), 55.6 (OMe), 112.5 (C_2), 114.71 (C_4), 120.1 (C_6), 127.5 ($C_{3'}$, $C_{5'}$), 128.4 ($C_{2'}$, & $C_{6'}$), 130.3 (C_7 & $C_{7'}$), 132.3 (C_5), 134.5 (C_1), 138.4 ($C_{1'}$), 142.1 ($C_{4'}$), 160.1 (C_3); LCMS (ESI) found *m/z* [M + H]$^+$: 358, $C_{20}H_{23}NO_3S$ requires 357. % purity determined by ^{1}H NMR (compound, **274**, (94 %), diethyl ether (6 %)).

(*E*)-1-((4-(4-Fluorostyryl)phenyl)sulfonyl)piperidine (259)



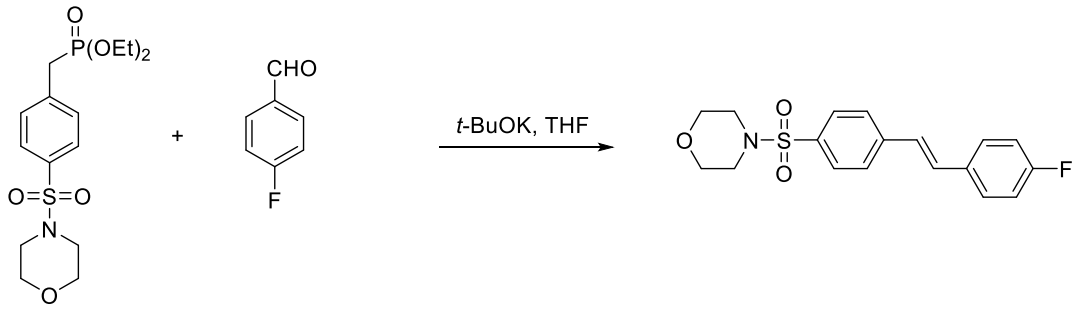
According to method F; the reaction with diethyl 4-(piperidine-1-ylsulfonyl)benzylphosphonate (1.51 g, 4.0 mmol) and 4-fluorobenzaldehyde (0.46 g, 3.7 mmol) gave the product as a beige solid (yield: 0.95 g, 68 %). Purification by recrystallization (diethyl ether and cyclohexane) afforded the product as a light brown solid (yield: 0.71 g, 51 %); R_f 0.86 [3:1 EtOAc/cyclohexane]; m.p. 208 - 213 °C; υ_{max} (film)/cm^{-1} 1158, 1340 (S=O), 1512, 1590 (C=C), 2846, 2934, 2960, 2991, 3023, 3080 (C-H and =CH-); δ_H (400 MHz; DMSO-d_6) 1.35 (2H, m, C-CH_2), 1.53 (4H, m, C-CH_2), 2.88 (4H, t, J = 5.8 Hz, N-CH_2), 6.97 (2H, d, J = 8.4 Hz, ArH $_{3\ \&\ 5}$), 7.20 (1H, d, J_{AB} = 16.5 Hz, *trans*-HC=CH), 7.60 (1H, d, J_{AB} = 16.5 Hz, *trans*-HC=CH), 7.60 (2H, d, J = 8.5 Hz, ArH $_{2\ \&\ 6}$), 7.68 (2H, d, J = 8.1 Hz, ArH $_{3'\ \&\ 2'}$), 7.79 (2H, d, J = 8.1 Hz, ArH $_{5'\ \&\ 6'}$); δ_C (100 MHz; DMSO-d_6) 23.4, 25.2 (3 x CH_2), 47.1 (N-CH_2), 114.8, 115.2 (C_3 & C_5), 127.1 ($C_{2'}$ & $C_{6'}$), 128.4 ($C_{3'}$ & $C_{5'}$), 128.9 (C_7 & $C_{7'}$), 129.6 (C_2 & C_6), 132.1 (C_1), 142.5 ($C_{1'}$ & $C_{4'}$), 160.1 (C_4); LCMS (ESI) found *m/z* $[M + H]^+$: 346, $C_{19}H_{20}FNO_2S$ requires 345. % purity determined by ^{1}H NMR (compound, **259**, (92 %), compound, **221g**, (8 %)).

(*E*)-4-((4-(3-Methoxystyryl)phenyl)sulfonyl)morpholine (275)



According to method C; the reaction with diethyl 4-(morpholinosulfonyl)benzylphosphonate (1.0 g, 2.6 mmol) and *m*-anisaldehyde (0.36 g, 2.6 mmol) gave the impure product as white solid (yield: 0.67 g, 70 %). Purification by recrystallization (ethanol) afforded the desired product as a fine white solid (yield: 0.33 g, 35 %); R_f 0.64 [DCM]; m.p. 163 - 165 ˚C; υ_{max} (film)/cm^{-1} 1164, 1327 (S=O), 1592 (C=C), 2857, 2932, 3002 (C-H and =CH-); δ_H (600 MHz; $CDCl_3$) 3.01 (4H, t, *J* = 4.8 Hz, , N-CH_2), 3.73 (4H, t, *J* = 3.6 Hz, O-CH_2), 3.84 (3H, s, OMe), 6.85 (1H, dd, *J* = 8.4 Hz, *J* = 2.4 Hz, ArH $_4$), 7.05 (1H, m, ArH $_6$), 7.09 (1H, d, J_{AB} = 15.6 Hz, *trans*-HC=CH), 7.12 (1H, d, *J* = 8.4 Hz, ArH_2), 7.19 (1H, d, J_{AB} = 16.2 Hz, *trans*-HC=CH), 7.29 (1H, t, *J* = 7.8 Hz, ArH $_5$), 7.63 (2H, d, *J* = 8.4 Hz, ArH $_{3' \& 2'}$), 7.71 (2H, d, *J* = 8.4 Hz, ArH $_{5' \& 6'}$); δ_C (150 MHz; $CDCl_3$) 46.0 (N-CH_2), 55.3 (OMe), 66.1 (O-CH_2), 112.1 (C_2), 114.1 (C_4), 119.5 (C_6), 126.7 ($C_{3'}$, $C_{5'}$), 126.8 ($C_{2'}$ & $C_{6'}$), 128.3 (C_7 & $C_{7'}$), 130.0 (C_5), 132.3 (C_1), 139.8 ($C_{1'}$), 141.3 ($C_{4'}$), 159.8 (C_3); LCMS (ESI) found *m/z* $[M + H]^+$: 360, $C_{19}H_{21}NO_4S$ requires 359. % purity determined by ^{1}H NMR (compound, **275**, (77 %), compound, **221h**, (23 %)).

(*E*)-4-((4-(4-Fluorostyryl)phenyl)sulfonyl)morpholine (260)



According to method F; the reaction with diethyl 4-(morpholinosulfonyl)benzylphosphonate (1.58 g, 4.2 mmol) and 4-fluorobenzaldehyde (0.52 g, 4.2 mmol) afforded the impure product as white solid (yield: 1.39 g, 96 %). Purification by washing (diethyl ether and cyclohexane) afforded the desired product as a pale cream solid (yield: 0.79 g, 54 %); R_f 0.92 [3:1 EtOAc/cyclohexane]; m.p. 210 - 215 °C; υ_{max} (film)/cm^{-1} 1163, 1350 (S=O), 1507, 1595 (C=C), 2866, 2898, 2934, 2971, 3070 (C-H and =CH-); δ_H (400 MHz; $CDCl_3$) 3.00 (4H, t, *J* = 4.5 Hz, N-CH_2), 3.73 (4H, t, *J* = 4.7 Hz, O-CH_2), 7.02 (1H, m, *trans*-HC=CH), 7.06 (2H, t, *J* = 8.7 Hz, ArH $_{3\ \&\ 5}$), 7.18 (1H, d, J_{AB} = 16.3 Hz, *trans*-HC=CH), 7.50 (2H, d, *J* = 5.4 Hz, ArH $_{2\ \&\ 6}$), 7.62 (2H, d, *J* = 8.6 Hz, ArH $_{3'\ \&\ 2'}$), 7.71 (2H, d, *J* = 8.4 Hz, ArH $_{6'\&\ 5'}$); δ_C (100 MHz; $CDCl_3$) 46.0 (N-CH_2), 66.1 (O-CH_2), 115.8, 116.0 (C_3 & C_5), 126.4, 126.8 ($C_{2'}$ & $C_{6'}$), 128.4 ($C_{3'}$ & $C_{5'}$), 128.5, 128.6 (C_7 & $C_{7'}$), 131.2 (C_2 & C_6), 132.6 (C_1), 133.5 ($C_{1'}$), 142.1 ($C_{4'}$), 161.7 (C_4); LCMS (ESI) found *m/z* $[M+H]^+$: 348, $C_{18}H_{18}FNO_3S$ requires 347

8. References

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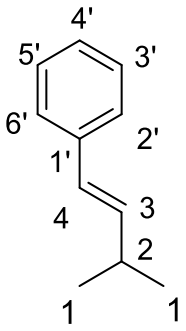
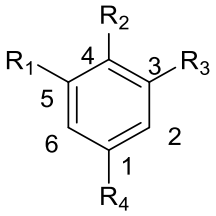
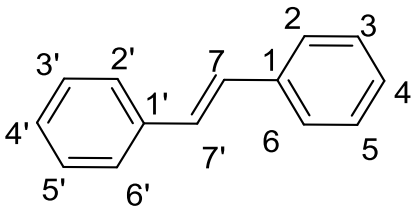
Appendix

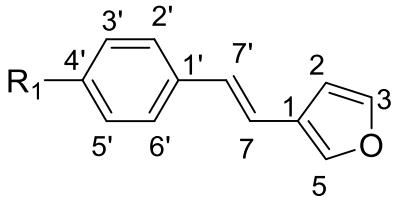
Appendix I



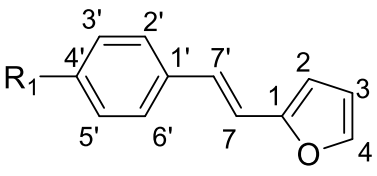


R_1, R_3 = H, OMe
R_2 = H, OMe, SO_2Cl, sulfonamide derivative
R_3 = CHO, CH_2Br, $CH_2PO(OEt)_2$

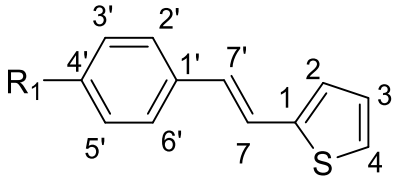




R_1 = Sulfonamide derivative



R_1 = Sulfonamide derivative



R_1 = Sulfonamide derivative

Appendix A1 The annotated reference for general compounds characterised by ^{1}H and ^{13}C NMR analysis

Appendix II

Appendix A2 List of reagents, assay kits used for biological testing

Reagent	Company	Serial Number	Concentration
A549 cell line	University of Nottingham	-	-
Dulbecco's Modified Eagle Medium (DMEM)	Gibco® Life Technologies	31885-023	1x (w/v)
Penicillin/Streptomycin	Sigma	PO781	10,000 units/mL (w/v)/10 mg/mL (w/v)
L-glutamine	Gibco® Life Technologies	25030-024	200 mM
Dulbecco's phosphate buffered saline (DPBS/PBS) Diluted to X1 in deionized water to make PBS	Gibco® Life Technologies	14200-067	10x (w/v)
Trypsin/EDTA	Sigma	T4174	0.5 % (w/v) / 0.5 % (w/v)
Trypan Blue	Sigma (Life Science)	T8154	0.4 % (w/v)
Cell Titer 96 Aqueous One Solution Cell Proliferation Assay	ProMega	G3580	-
Dimethyl sulfoxide	Sigma	D2650	Neat
Foetal Bovine Serum (FBS)	Gibco	10500-064	-
Trichloroacetic acid	European Pharmacopeia	1092501	Neat
Sulforhodamine B	Sigma	230162-5G	-

Cell culture

The non-small cell lung carcinoma cancer cell line, A549 was grown in the Dulbecco's Modified Eagle medium, supplemented with 10% heat-inactivated fetal bovine serum, 100 u/mL penicillin, 100 μg/ml streptomycin and 2 mM (w/v) L-glutamine solution.

Trypan blue dye exclusion growth assay

The A549 cells were plated out into 96-well plates and incubated at 37 °C overnight to allow for cell attachment. Each stilbene benzenesulfonamide analogue was then dissolved in dimethyl sulfoxide (DMSO), mixed with fresh medium and added to each plate at the desired concentration (5.0 and 50 μM). The final DMSO concentration in all cultures was 1.0 % v/v. This concentration of DMSO did not alter cell-growth when compared with the vehicle free medium (no drug).

Following each of the selected treatment period (24, 48, 72 and 96 h), the cells were harvested by trypsinization and centrifuged. The cell pellet was resuspended in 2 mL of fresh media and the cells were stained with trypan blue dye. The number of non-viable (dead) and viable cells was counted using a haemocytometer. Growth inhibition by the stilbene benzenesulfonamide analogues was expressed as a percentage of the control (cells treated with the vehicle).

Sulforhodamine B assay (SRB)

Cells (A549) were plated out in 96-well plates on day 0 and then treated on day 1 with concentrations of each tested compound at 0 to 500 μM (dissolved in DMSO and fresh media as described above) for 48 h.

At completion of the experiment, the cells were fixed by adding trichloroacetic acid to a final concentration of 5 % (v/v). After 1 h at 4 °C, plates were washed four times with deionised water, dried, and stained for 30 min with 50 μL sulforhodamine B in PBS (0.4 %, w/v). Following three wash steps with 1 % acetic acid, 150 μL Tris (10 mM/L) was added to dissolve the staining. The plates were then read at 492 nm using a spectrophotometer. After correction for medium-only and no-drug controls, the GI_{50} values were calculated from the growth inhibition curves generated by fitting sigmoidal curves to the data using nonlinear least square regression analysis.

Statistical analysis

Descriptive statistics were performed using Microsoft Excel 2010, including Q-tests for outliers. Tests for normality were performed using Shapiro-Wilks test, and tests for significance were carried out using One-Way ANOVA and Tukey or Games-Howell post-hoc tests, using IBM SPSS Statistics 22. The chosen level of significance was $p < 0.05$.