TOTAL SYNTHESIS OF HYDROXYSTROBILURIN A

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by

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Finally, I would like to thank my brothers Diggory, Giles and Finn, and particularly my parents A-M and Peter, for their love and support, and for always being there for me, especially during this year.

Press on. Nothing in the world can take the place of persistence. Talent will not. Nothing is more common than unsuccessful men with talent. Genius will not. Unrewarded genius is almost a proverb. Education alone will not. The world is full of educated derelicts. Persistence and determination alone are omnipotent.

Calvin Coolidge (1872-1933)

I was burned out from exhaustion, buried in the hail,
Poisoned in the bushes an' blown out on the trail,
Hunted like a crocodile, ravaged in the corn.
"Come in," she said, "I'll give you shelter from the storm."

From 'Shelter from the Storm' by Bob Dylan
from 'Blood on the Tracks' (1975)

Abstract

This thesis describes the first three total syntheses of hydroxystrobilurin A, a member of the strobilurin family of fungicidal natural products which are produced by a variety of fungal species worldwide. Chapter 1 provides an account of the discovery, structure, and biological activity of the strobilurins, describes the total syntheses of strobilurins reported to date, and covers the synthetic and spectroscopic work that has been conducted on the strobilurins by other workers in this department. An overview of the use of palladium-catalysed carbon-carbon bond forming methodologies in syntheses of several natural products and strobilurin analogues is given, followed by a retrosynthetic analysis of hydroxystrobilurin A which delineates two possible strategies for the synthesis of this compound based on the utilisation of such palladium-based chemistry.

Chapter 2 details investigations of these two strategies, with the diene-based route proving more successful than the enyne-based approach. Efficient diene synthesis was achieved *via* Stille coupling, but direct access to hydroxystrobilurin A *via* Stille coupling between a diene alcohol and a β-methoxyacrylate unfortunately proved impossible. The use of hydroxyl-group protection enabled the formation of two triene analogues of hydroxystrobilurin A *via* Stille coupling, and although one of these was found to have isomerised into a non-natural strobilurin triene system, the other possessed the correct stereochemistry and was able to be deprotected to afford a low yield of the natural product. An efficient synthesis of the triene ester analogue of hydroxystrobilurin A was developed, and this compound was reduced to give a low yield of the natural product. Access to the corresponding triene aldehyde was also established, and its reduction to hydroxystrobilurin A was slightly higher yielding, although efforts to improve the efficiency of this process were not successful.

A summary of the above results is given in Chapter 3, followed by a description of several pathways by which future workers may be able to achieve a more efficient synthesis of hydroxystrobilurin A.

Chapter 4 describes preliminary results from the application of the palladium-catalysed carbon-carbon bond-forming techniques described in Chapter 2 to synthetic approaches towards 9-methoxystrobilurins A and K & phomoidrides A and B.

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Abbreviations

2D NMR	two dimensional nuclear magnetic resonance spectroscopy
Ac	acetyl
AcO	acetate
AIBN	2,2'-azobisisobutyronitrile
aq.	aqueous
Ar	aryl
Bn	benzyl
BP	boiling point
br	broad
Bu	butyl
c.	concentrated
calcd.	calculated
cat.	catalytic
Cy	cyclohexyl
d	doublet, day(s)
dba	dibenzylideneacetone
dppf	1,1'-bis(diphenylphosphino)ferrocene
DIBAl-H	diisobutylaluminium hydride
DIPT	diisopropyl tartrate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
δ	chemical shift in parts per million
e	electron
EDCI	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
EI	electron impact
equiv.	equivalent(s)

Et	ethyl
FTF	farnesyl transferase
g	gram(s)
h	hour(s)
HMBC	heteronuclear multiple bond coherence
HMPA	hexamethylphosphoric triamide
HRMS	high resolution mass spectrometry
Hz	hertz
i-Pr	isopropyl
IR	infrared
J	coupling constant
k	kilo
L	litre(s)
LDA	lithium diisopropylamide
m	metre(s), milli, multiplet
m-	*meta*-
M	mega, molar
m-CPBA	*meta*-chloroperbenzoic acid
mol	mole(s)
Me	methyl
min	minute(s)
MOM	methoxymethyl
MP	melting point
MS	mass spectrometry
μ	micro
n-	normal-
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NOE	nuclear Overhauser effect
NMO	*N*-methylmorpholine-*N*-oxide
NMP	1-methyl-2-pyrrolidinone

NMR	nuclear magnetic resonance spectroscopy
OAc	acetate
p-	*para*-
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PMB	*para*-methoxybenzyl
ppm	parts per million
q	quartet
r.t.	room temperature
s	singlet
SQS	squalene synthase
t	triplet
t-	tertiary-
TBHP	*t*-butyl hydroperoxide
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
TFP	tris(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
Tol-BINAP	2,2'-bis[di(*p*-tolyl)phosphino]-1,1'-binaphthyl
TPAP	tetra-*n*-propylammonium perruthenate
V	volt(s)

CHAPTER ONE

Introduction

1.1 Overview

For centuries, man has been aware that there is more to the plants of the world than simply a pretty blossom, pleasant fragrance or delectable flavour. Whether chewing on willow-bark to relieve the pain of an aching tooth, lacing the drink of a troublesome rival with hemlock, or kick-starting another day at the laboratory with a strong coffee, the story of man is intertwined with the utilisation of biologically active natural products made by plants.

However, plants are not the only source of such compounds, with microbes such as bacteria and fungi also producing natural products. Many of these microbial-derived compounds are utilised as antibiotics,* or have served as lead compounds for drug development. Indeed, the use of plant and microbial natural products has been credited with the doubling of average human lifespans in the twentieth century, and nearly 50% of the pharmaceutical industry's most successful products are derived from such molecules.[1]

Nature continually surprises us, yielding new molecules with intriguing structures and often some kind of biological activity. More than half a million natural products are produced by plants,[2] and more undoubtedly await discovery in bacteria and fungi, given that it is estimated that 95% of the total number of fungal species are undescribed, and only 16% of those described have been cultured.[3] Furthermore, some estimates are that between 1000 and 10,000 undiscovered prokaryotes (*i.e.* bacteria, photosynthetic bacteria, and archaebacteria) are present in just one gram of soil.[4]

1.2 The Strobilurin Family and its Relatives

Strobilurin A (**Figure 1.1**) was first isolated in the 1960s in Czechoslovakia by Musílek and co-workers, from a culture of mycelia (the cellular filaments which are the basic structural units

* Any low molecular weight organic natural product made by a microorganism and active in low concentrations against other microorganisms is defined as an antibiotic.

of fungi)[5] from the fruiting body of the basidiomycete[ψ] fungus *Oudemansiella mucida*, collected from a beech tree.[6] At this time, however, it was called mucidin, after the producing organism, and its chemical structure was undetermined. A thorough investigation of its antimicrobial activity by the Czech workers found it had wide-ranging activity against fungi, including *in vitro* activity against a variety of plant fungal pathogens, but no activity against bacteria.[6,7] Successful clinical trials led to its adoption in human and veterinary medicine in the late 1970s under the tradename *Mucidermin Spofa*, as a topical treatment for a number of fungal skin infections.[8]

While a structure for mucidin was proposed by the Czech workers in patents filed in 1974,[9] only the second of these patents contained what was eventually found to be the correct (*E,Z,E*) geometry for the triene system of the molecule, with (*E,E,E*) geometry depicted both in one of the patents and a 1981 paper (**Figure 1.1**).[8d]

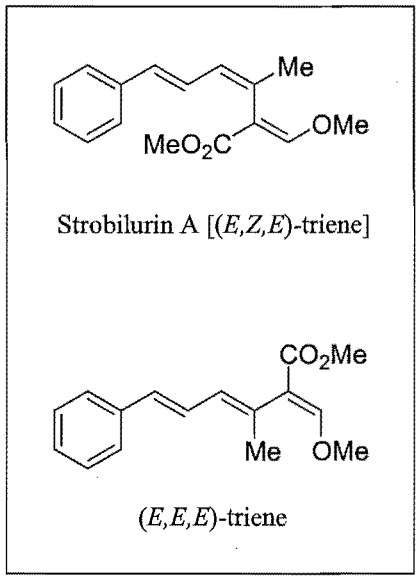


Figure 1.1 The first two strobilurins to be isolated.

Meanwhile, a German research team led by Steglich had in 1977 reported the physical and chemical data of two compounds isolated from another basidiomycete fungus, *Strobiluris*

[ψ] The basidiomycete class of fungi includes mushrooms, toadstools and puffballs.[5]

tenacellus, which often grows on decaying pine cones (*strobilurus* is Latin for pine cone).[10] These natural products displayed powerful antibiosis against a diverse range of fungal species, as well as high cytotoxicity to Ehrlich ascites tumour cells.

The following year, Steglich and co-workers proposed structures for these compounds, which they named strobilurins A and B, after the fungus from which they were isolated (**Figure 1.1**).[11] Although strobilurins A and B had proved to have only weak anti-tumour activity in tests at the National Cancer Institute in the USA, they had shown no acute toxicity in the tumour-bearing mice.[11] At this stage, the Czech group had not published a structure for mucidin, and although Steglich and co-workers noted similarities between mucidin and strobilurin A (identical empirical formula, UV spectrum, and biological activity profile), the fact that the Czech workers had reported an optical activity value for mucidin seemed to preclude the molecules being one and the same. In addition, the German group had also assigned the incorrect (*E,E,E*) geometry to the triene system of strobilurin A (**Figure 1.1**).

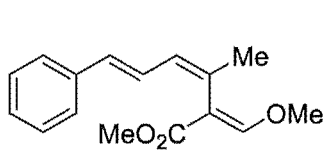
A series of total syntheses of strobilurin A were then undertaken in an attempt to determine the true structure of the natural product. The first synthesis (see page 18, **Figure 1.9**), conducted by Steglich and co-workers, was not particularly helpful, with the stereochemistry of one of the intermediates being wrongly assigned.[12] However, this error was corrected by the authors in a 1984 paper,[13] and the (*E,Z,E*) triene structure of the natural product was confirmed by Beautement and Clough's stereocontrolled synthesis of strobilurin A three years later (see page 19, **Figure 1.10**).[14]

The major factor preventing strobilurin A and mucidin being the same molecule, namely the optical activity reported for mucidin in the Czech group's 1967 patent,[6c] had been withdrawn by these workers in their 1981 publication,[8d] being ascribed to a 'printing error'. A publication four years later by Von Jagow *et al.* eliminated any remaining doubt, proving the structures of mucidin and strobilurin A to be identical by direct spectroscopic comparison.[15]

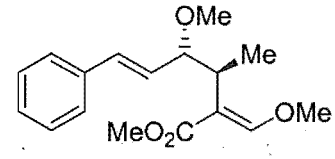
During their investigation, the German researchers had also isolated another compound from *Oudemansiella mucida*, the optically active oudemansin A (**Figure 1.2**).[16] As can be seen, it

also contains the (*E*)-β-methoxyacrylate subunit present in the strobilurins, and this observation, together with the fact that its biological activity profile was found to be very similar to the strobilurins', seemed to indicate that this portion of the molecules was crucial to their activity against fungi, and that both types of molecules were derived from (*E*)-β-methoxyacrylic acid. Given this structural similarity, it would seem possible that the optical activity recorded for strobilurin A might have been a result of the isolate being contaminated with oudemansin A, rather than simply a 'printing error'.

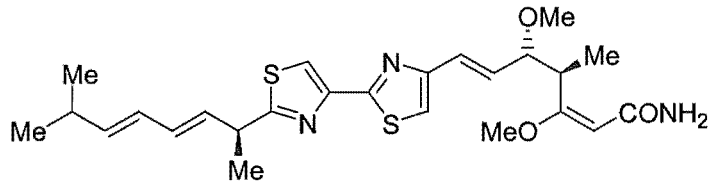
Also depicted in **Figure 1.2** is myxothiazol A, which was described in a 1978 patent,[17] with full details of its physical properties and structure published two years later.[18] It was isolated from the gliding bacterium *Myxococcus fulvus*, and contains a bisthiazole moiety, a 9-carbon isoprenoid chain, and an (*E*)-β-methoxyacrylamide subunit; this latter structure suggests it is another (albeit more modified) derivative of (*E*)-β-methoxyacrylic acid. Like oudemansin A and the strobilurins, myxothiazol A is highly active *in vitro* towards a wide range of fungi, but it also displays activity against some Gram-positive[ħ] bacteria.[18,19]



Strobilurin A



Oudemansin A

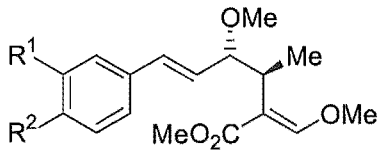


Myxothiazol A

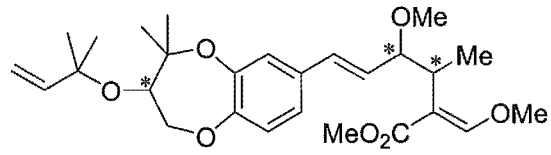
Figure 1.2 Representative examples from three classes of natural products derived from (*E*)-β-methoxyacrylic acid.

[ħ] Gram-positive bacteria possess a peptidoglycan cell wall, which absorbs crystal violet (an iodine dye), thus appearing purple under a light microscope.[5]

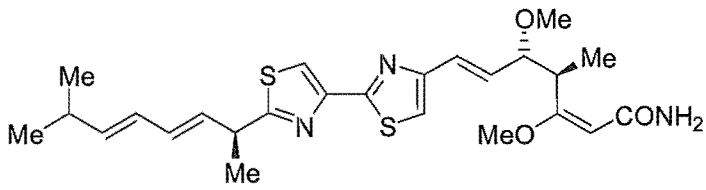
Three more oudemansins have been discovered thus far (**Figure 1.3**), all in fungi which also produce strobilurins,[20] and while only myxothiazol A has been reported in the literature,[18] the 1986 annual report of a German company described the isolation and structural elucidation of a further 23 myxothiazols (**Figure 1.3**).[21]



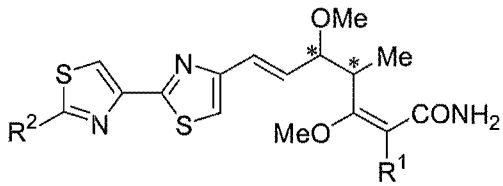
Oudemansin A: $R^1 = R^2 = H$
Oudemansin B: R^1 = OMe, R^2 = Cl
Oudemansin X: R^1 = H, R^2 = OMe



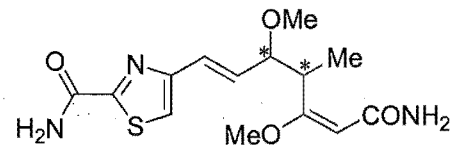
Oudemansin L



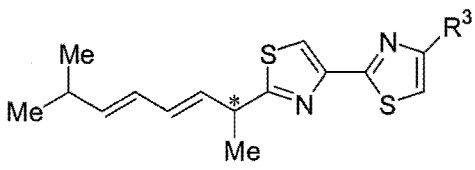
Myxothiazol A



Myxothiazols B to I and K to O (R^1 = H)
Myxothiazols Q, X and Y (R^1 = Me)
[R^2 = 1-hydroxyethyl, acetyl, or branched and oxidised (variously) 9-carbon chain]



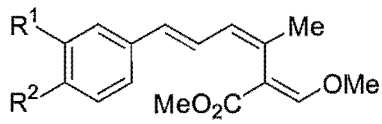
Myxothiazol P



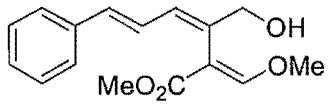
Myxothiazols R to W (R^3 = oxidised 3-, 5-, or 6-carbon chain)

Figure 1.3 The oudemansin and the myxothiazol families (asterisked carbons indicate undetermined stereochemistry).

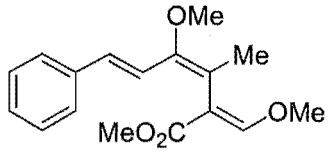
Since the initial reports of strobilurins A and B, a further 12 similar molecules have been discovered.[22] Whilst many of these come from fungi other than *Strobiluris* sp., and have a number of different points and types of substituent variation, all possess an (*E*)-β-methoxyacrylate unit conjugated to an aryl diene system, and are therefore all members of the natural strobilurin family (**Figure 1.4**).



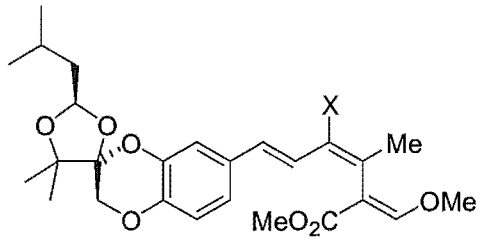
Strobilurin A: $R^1 = R^2 = H$
Strobilurin B: $R^1 = OMe$, $R^2 = Cl$
Strobilurin C: $R^1 = OCH_2CH{=}C(CH_3)_2$, $R^2 = H$
Strobilurin F-1: $R^1 = OH$, $R^2 = H$
Strobilurin F-2: $R^1 = OH$, $R^2 = OCH_2CH{=}C(CH_3)_2$
Strobilurin H $R^1 = H$, $R^2 = OMe$



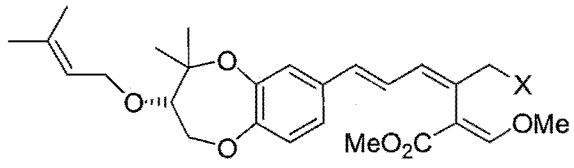
Hydroxystrobilurin A



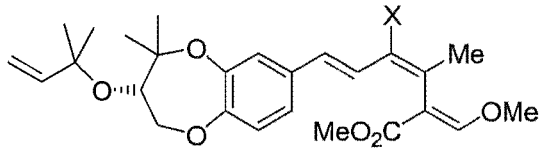
9-Methoxystrobilurin A



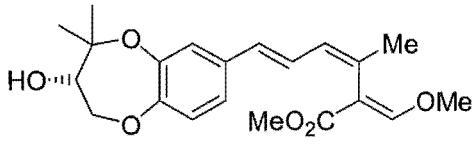
Strobilurin E: X = H
9-Methoxystrobilurin E: X = OMe



Strobilurin D: X = H
Hydroxystrobilurin D: X = OH



Strobilurin K: X = H
9-Methoxystrobilurin K: X = OMe



Strobilurin I

Figure 1.4 The natural strobilurin family.

1.3 Biological Activity of the Strobilurins

Strobilurins (and oudemansins) are now known to be produced by a variety of fungi the world over, in all climate zones,[22] with all except one of these organisms (*Bolinea lutea*, an ascomycete[ψ]) being basidiomycetes.[23] In addition to ensuring high levels of secondary metabolite[†] production by growing fungal cultures on nutrient-rich media in the laboratory, Anke and co-workers also found that the levels of strobilurins produced when the fungi were cultured on wood (their primary natural substrate) were sufficient to inhibit the growth of other fungal species.[24] This demonstrates a survival advantage that strobilurin-generating fungi possess over other fungal species living on the same substrate, and is undoubtedly fundamental to their success in colonising environments worldwide.

The molecular basis of the strobilurins' fungicidal activity was described even before the structure of strobilurin A had been established, with Musílek and co-workers determining that it involves the inhibition of electron transport between cytochromes b and c_1, two enzymes paired in a complex located within the inner membrane of the mitochondria of fungi and other eukaryotes.[25] This complex forms part of the electron transport chain (**Figure 1.5**), a metabolic cascade at the 'business' end of the cellular respiration cycle which generates ATP, the main energy source within cells.[5,26] Steglich's team confirmed these findings, and also noted concomitant inhibition of the synthesis of RNA, DNA and protein, which they presumed was a result of the intracellular deficiency in ATP.[16]

Further investigations by several research groups established that strobilurins A and B, oudemansin A, and myxothiazol A all bind at the same site on cytochrome b (**Figure 1.5**), the ubiquinol oxidation or Q_P centre,[27] and that since each inhibitor can displace another from the site, the binding is reversible.[28] Ubiquinol (the normal substrate) can actually still bind to the Q_P centre on cytochrome b in the presence of an inhibitor, but it is not oxidised to ubiquinone as usual, a phenomenon which has been hypothesised to be due to a slight displacement of

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[ψ] The ascomycete class of fungi includes *Penicillium* sp., yeasts, and truffles.[5]

[†] 'Secondary metabolite' is another term for 'natural product', where 'secondary' refers to the molecule's non-involvement in 'primary' metabolic processes of the organism, such as photosynthesis or respiration.

ubiquinol at the site, resulting from an inhibitor-generated conformational distortion of the enzyme.[29] The suppression of the oxidation of ubiquinol to ubiquinone prevents the flow of electrons from the cytochrome b-c_1 complex to cytochrome c, thus halting ATP generation and consequently cellular respiration.

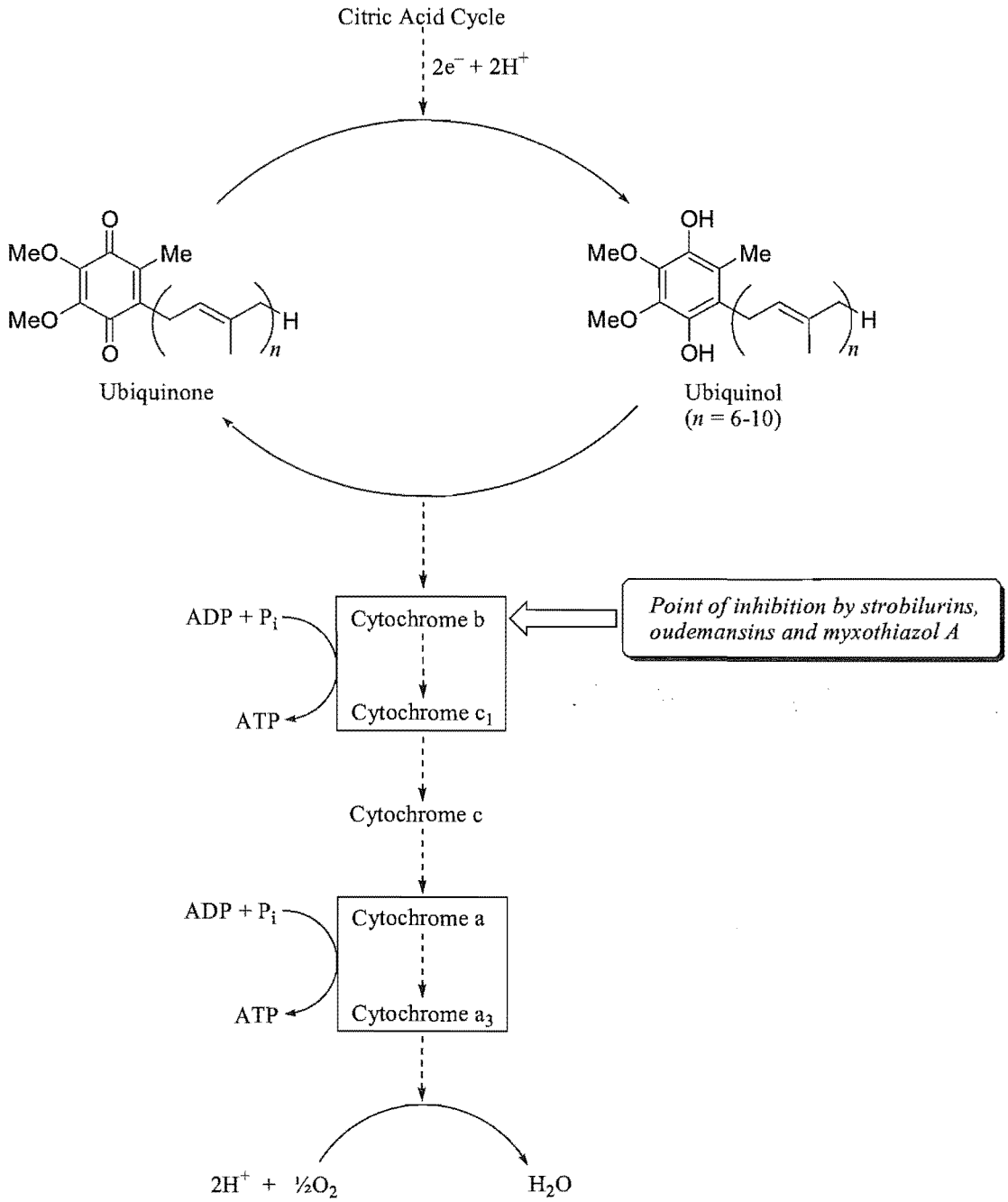
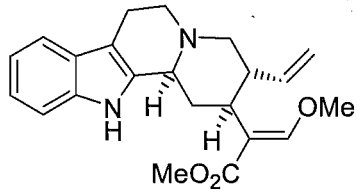


Figure 1.5 The mitochondrial electron transport chain (simplified).[5,30]

As has been noted, the common structural element of the strobilurins, oudemansins and myxothiazol A that is essential to their biological activity is the subunit derived from (*E*)-β-methoxyacrylic acid – an (*E*)-β-methoxyacrylate moiety for the former two and an (*E*)-β-methoxyacrylamide moiety for the latter. Given that this moiety is essential for the molecules' toxicity towards fungi, it is denoted the 'toxophore'.‡ Structure-activity studies of the strobilurins have shown that molecules containing the (*Z*)-isomer of the toxophore are biologically inactive, as are those possessing the non-natural (*E,E,E*)-triene system.[31] Molecular modelling has demonstrated that the natural (*E,Z,E*)-triene conformation results in the (*E*)-β-methoxyacrylate portion adopting a nearly right-angled orientation relative to the phenyl-substituted side chain, imparting a morphology to the molecule which is vastly different compared to that adopted by the (*E,E,E*)-triene, and evidently fundamental to the strobilurins' ability to bind to cytochrome b.[31,12b]

There are other naturally occurring derivatives of (*E*)-β-methoxyacrylic acid. For example, some of the corynanthe alkaloids, such as corynantheine (**Figure 1.6**), contain an (*E*)-β-methoxyacrylate group.[32] However, these molecules do not inhibit mitochondrial respiration or exhibit fungicidal properties, demonstrating that the presence of certain structural features within a molecule is not always indicative of its having a particular biological activity.



Corynantheine

Figure 1.6 Another natural derivative of (*E*)-β-methoxyacrylic acid.

Obviously, a crucial element of the strobilurin-producing fungi's biology must be an immunity to the toxic effects of their own fungicides. Biochemical studies have revealed that

‡ Clough has noted that with strobilurin A being the first of its class to be isolated, the (*E*)-β-methoxyacrylate unit was immediately obvious as the probable toxophore; if strobilurin E (see **Figure 1.4**) had been found first instead, its complex spiroketal moiety might have been wrongly identified as the biologically active portion of the molecule.[47]

this is due to the replacement of a small amino acid (alanine or threonine) at position 127 of the cytochrome b protein by a larger (isoleucine) residue. This mutation is located in the ubiquinol binding site, a region that is highly conserved in species susceptible to strobilurin-type toxins. The presence of the larger isoleucine residue changes the tertiary structure of the binding site such that strobilurins cannot bind at the site, whilst ubiquinol is still able to do so, thus allowing electron transport to continue.[33]

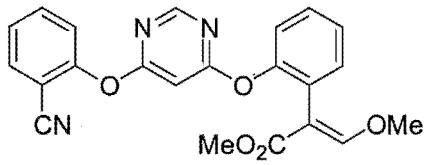
1.4 Strobilurin Analogues as Fungicides

Modern agriculture is dependent upon agrochemicals to control diseases wrought by infectious organisms, which would otherwise destroy crops in the field or post-harvest. Environmental, efficacy and economic concerns continually fuel the search for safer, more pest-specific and cheaper products than those currently in use, and the strobilurin fungicides are a result of this process.

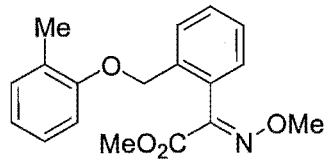
There are now six synthetic strobilurin fungicides known (**Figure 1.7**). Azoxystrobin and kresoxim-methyl were the first on the market, released by Zeneca (now part of Syngenta) and BASF, respectively, in 1996. They were followed three years later by metominostrobin (Shionogi) and trifloxystrobin (Bayer, now part of Novartis), and as of August 2001, pyraclostrobin (BASF) and picoxystrobin (Syngenta) had been announced but were still in development.[34]

Azoxystrobin and picoxystrobin both retain the (*E*)-β-methoxyacrylate toxophore of their natural relatives, while kresoxim-methyl and trifloxystrobin have an (*E*)-β-methoxyacrylamide moiety instead. The methyl ester of the toxophore has been transformed into an amide in metominostrobin, while in pyraclostrobin it is part of a methoxy carbamate. All six compounds have the toxophore directly attached to a phenyl ring, which is itself linked *via* a photostable bridging or spacer group (ranging from an oxygen atom to an oxime group to an oxygenated pyrimidine or pyrazine heterocycle) to a mono- or unsubstituted arene or pyrimidine ring.

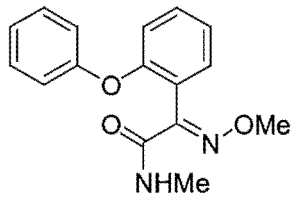
Azoxystrobin, trifloxystrobin, and kresoxim-methyl have all been determined to be safe to birds, mammals, bees, earthworms and beneficial insects,[35] although they, and the new compounds picoxystrobin and pyraclostrobin, are relatively toxic to aquatic invertebrates.[35,36,37] However, more detailed risk assessments of picoxystrobin have shown that the real risks to aquatic life are low in normal-use situations.[36]



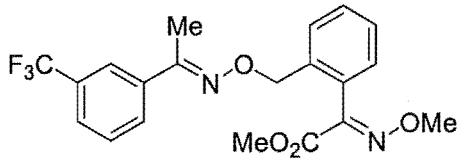
Azoxystrobin [*Zeneca*, **1996**]



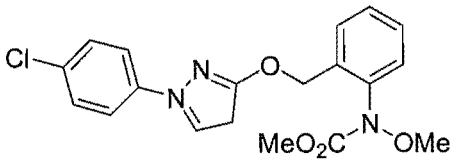
Kresoxim-methyl [*BASF*, **1996**]



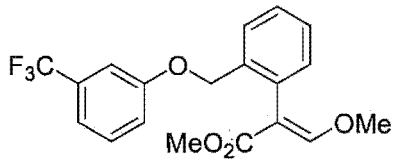
Metominostrobin [*Shionogi*, **1999**]



Trifloxystrobin [*Bayer*, **1999**]



Pyraclostrobin [*BASF*, **unreleased**]



Picoxystrobin [*Syngenta*, **unreleased**]

Figure 1.7 The strobilurin fungicides.

The strobilurin fungicides as a whole are active against a broad range of crop diseases, but azoxystrobin is the only compound which controls fungi from all four classes of plant fungal pathogens,[ψ] which accounts for its financial success (*vide infra*). Its market dominance may be challenged by pyraclostrobin, which has demonstrated similar broad-spectrum activity. As for the rest, metominostrobin was developed exclusively for use on rice, picoxystrobin is a

[ψ] The four classes of plant fungal pathogens are the Basidomycetes and the Ascomycetes (discussed previously), the Deuteromycetes (*e.g.* ringworm, *Aspergillus*), and the Oomycetes (*e.g.* potato blight, downy mildew).

specialist cereal treatment, whilst kresoxim-methyl and trifloxystrobin are generally effective (except against rust diseases and downy mildews).[34]

The combined value of sales of the four strobilurin fungicides on the market in 1999 reached around US$600 million, which represents slightly more than 10% of the global fungicide market. Azoxystrobin sales alone were worth US$415 million, and it is registered for the treatment of a broad spectrum of fungal diseases on 84 different crops in 71 countries, encompassing over 400 crop-disease systems.[34] Interest continues worldwide in strobilurin fungicide research (by 1999, more than 500 patents on strobilurins had been published, from more than 20 countries and research institutions).[38] The primary reasons for this interest are the strobilurins':

- potent fungicidal activity but low toxicity towards plants/animals – efficacy against fungi at levels too low to affect plants/animals;

- novel mode of action – providing an alternative to existing compounds to which some fungi have become resistant;

- relatively simple structure – providing easy starting point for the synthesis of analogues;

- existence as a family of biologically active compounds – showing there is scope for some structural modification without complete loss of activity.

While the isolation and structural elucidation of members of the natural strobilurin family (see **Figure 1.4**) is an ongoing process, strobilurin A's potency towards fungi and unique mode of action were established early on (see sections **1.2** and **1.3**). However, in contrast to its *in vitro* performance, *in vivo* glasshouse testing of strobilurin A proved disappointing, with barely observable activity against two out of six fungal plant pathogens, even when applied at high concentrations.[39] This loss of activity was found to be due to the volatility and photolability of the molecule[33] – not a problem for a fungus living deep within a piece of rotting wood, a light-

free environment where volatility might be useful in distributing the compound to its surroundings, but incompatible with the requirements of an agrochemical fungicide.

Azoxystrobin and kresoxim-methyl (see **Figure 1.7**), the first strobilurin fungicides on the market, were developed contemporaneously by research groups at ICI and BASF, respectively. The story of the process illustrates the benefit which competition can bring to scientific endeavour. Initially, both groups realised that since the less conjugated oudemansin A (see **Figure 1.3**) did not lose a significant amount of bioactivity in glasshouse tests, the conjugated triene system of strobilurin A was the likely cause of the molecule's photolability.[38] Accordingly, they both produced stilbene **1.3** (**Figure 1.8**),[40] in the hope that this compound's aromatic bridge would stabilise its triene system towards light. This strategy was successful in glasshouse trials, but **1.3** was still subject to significant photodegradation in real-life field conditions. This is not unexpected, given that stilbenes are known to undergo (*E*)→(*Z*) photoisomerisation and subsequent facile photocyclisation to dihydrophenanthrenes.[41]

The group at BASF circumvented this problem by synthesising dihydrostilbenes **1.4** (**Figure 1.8**), whose saturated inter-arene bridge made them impervious to intramolecular photochemical isomerisation, and led to their displaying higher activity in field conditions. Consequently, BASF filed patents for **1.3**,[42] as well as for hydrogenated analogues **1.4**,[43] and those containing a sulfur[44] or oxygen atom[45] in the alkyl bridge. However, soon after, workers at BASF were mortified[38] to discover that rival company ICI had already patented a set of very broad and comprehensive general structures for strobilurins containing the (*E*)-β-methoxyacrylate group,[46] which included structures **1.3** and **1.4**.

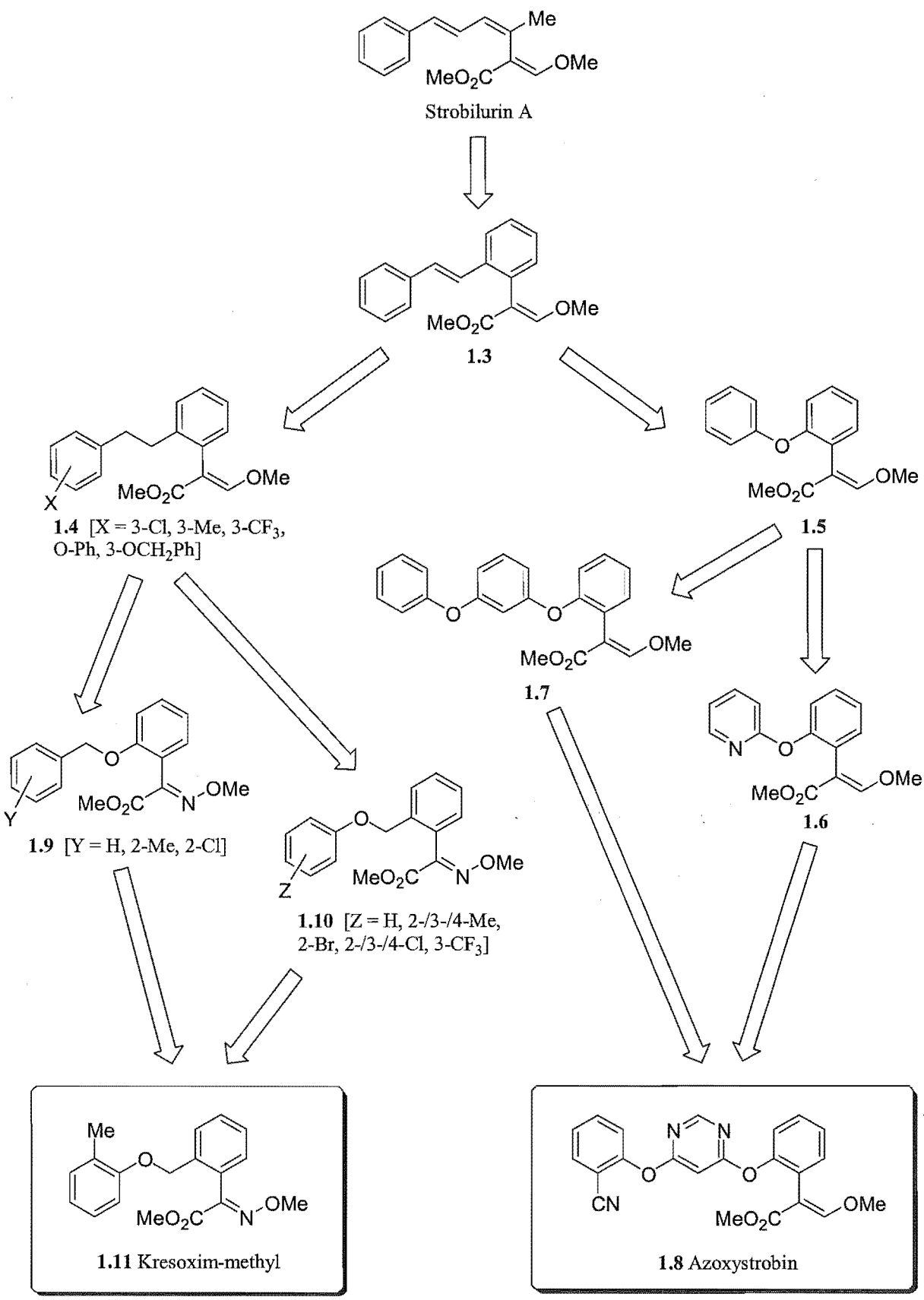


Figure 1.8 Development of the first two strobilurin fungicides.

While researchers at BASF were left pondering their options, work at ICI continued, with the synthesis of diphenyl ether **1.5** (**Figure 1.8**) being an important step forward. In addition to being even more photostable than stilbene **1.3**, ether **1.5** was systemic in plants, meaning it was hydrophilic enough to be transported throughout a plant following application. This is a desirable property for a compound intended for use on plants to possess, as it means fewer applications of the compound are required for treatment of disease. On the other hand, this systemic activity also led to **1.5** displaying some phytotoxicity in sensitive species.[38]

Pyridine derivative **1.6** was a step towards eliminating this undesirable property, although it was still 'probably too mobile',[47] while diether **1.7** had improved fungicidal activity, but no systemic activity, due to the increased hydrophobicity imparted by its phenoxy subtituents.[§] The optimum combination of these factors was realised in 4,6-dioxypyrimidyl-bridged compound **1.8**, which was named azoxystrobin and launched on the German market in February 1996 for use on cereals, under the tradename *Amistar*. It is now also sold as *Quadris*, for use on grapevines, and *Heritage*, for use on turf.[47]

Meanwhile, back at BASF, researchers had regrouped and were persevering in their endeavours, albeit on a different tack. They had decided to convert the enol ether group of the toxophore to an oxime ether. Whilst mindful that an altered toxophore could drastically reduce biological activity, their initial studies of such analogues had suggested that this was not the case, a finding that was consistent with the significant fungicidal activity displayed by the (*E*)-β-methoxyacrylamide-containing myxothiazols (see **Figure 1.3**). The BASF group hurriedly filed a patent for oximes **1.9** in July 1986,[48] which was not a moment too soon: their competitors at ICI filed a patent for these compounds just two days later.[49]

Subsequently, with the help of a very reliable *in vitro* biochemical assay[50] which quantified the inhibitory activity of a given compound to the cytochrome b-c_1 complex more definitively

[§] Systemic activity requires a balance between two opposing physicochemical properties – hydrophobicity, to enable passage through the waxy leaf cuticle into the interior, and hydrophilicity, to allow transport in the aqueous vascular systems of the plant, the xylem and the phloem. Thus, very hydrophobic substances will penetrate the leaf but not undergo systemic transport.[38]

than glasshouse trials (which contain more independent variables, and thus more background 'noise'[51]), the BASF team determined that compounds **1.10** were about ten times more active than their regioisomers **1.9** (**Figure 1.8**). This improved fungicidal efficacy was confirmed in field testing, and with consideration of the dual factors of biological activity and potential ease of synthesis, derivative **1.11** was selected for commercial development. It was released onto the German market under the name kresoxim-methyl in February 1996, a few days before ICI's azoxystrobin.

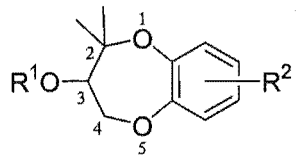
Given that there are natural fungal species resistant (due to mutation)[33] to the actions of molecules which bind to the cytochrome b-c_1 complex, there is the possibility that serious resistance to such inhibitors of mitochondrial respiration will appear. To combat this, the less broad-spectrum strobilurin fungicides are sold as mixtures with one or more other fungicides which have different modes of action. Kresoxim methyl, for example, is combined with the morpholine fungicide fenpropimorph in the product *Brio*, and with the triazole fungicide epoxiconazole in *Allegro*, both of which are treatments for cereals.[38,47]

1.5 Synthetic Work on the Natural Strobilurins

In addition to inspiring the development of a new class of commercial fungicides, the natural strobilurins are novel synthetic targets in their own right. It is important that research towards total syntheses of members of this family of natural products continues, as it may yield both more information on structure-activity relationships and access to useful analogues.

To date, total syntheses have been reported for strobilurin A,[12,13,14] strobilurin B,[52] strobilurin E,[53] 9-methoxystrobilurin A,[54] and 9-methoxystrobilurin K.[55] Some synthetic studies have also been conducted as part of the work which led to the revision of the structures of 9-methoxystrobilurin K, strobilurin D, and hydroxystrobilurin D,[56,57] whilst a recent report has described the influence of aromatic substructure on the anti-fungal activity of various synthetic 9-methoxystrobilurin derivatives.[58] In addition, a thesis by a former member of the author's

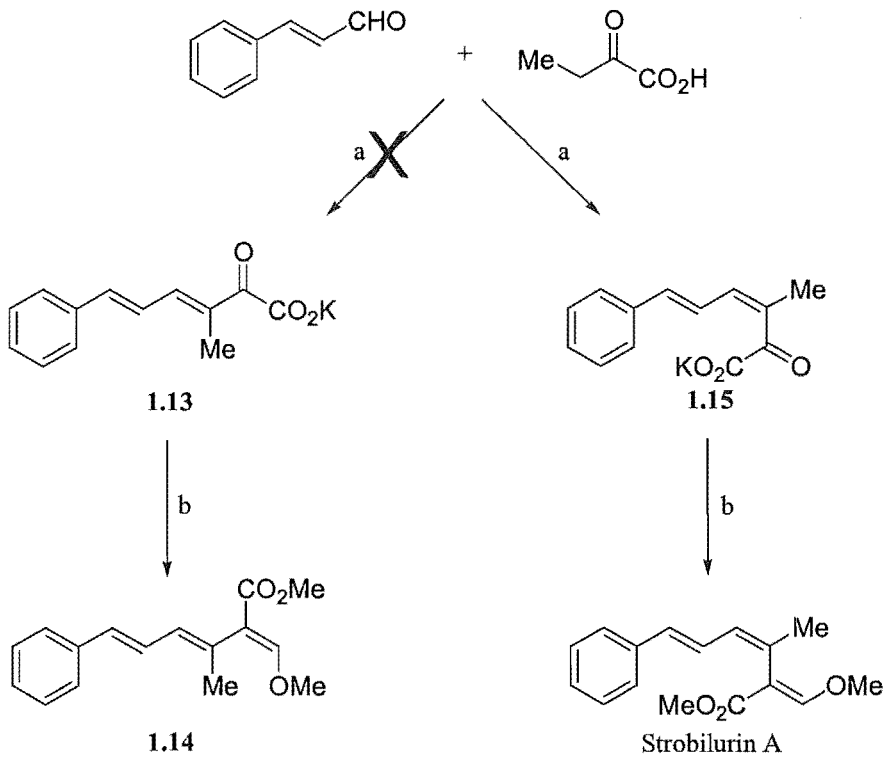
research group (the late Andrew Rea) describes approaches towards the 1,5-benzodioxepin moiety (**1.12**) present in five of the natural strobilurins (**Figure 1.4**).[59]



1.12

1.5.1 Total Syntheses of Strobilurin A

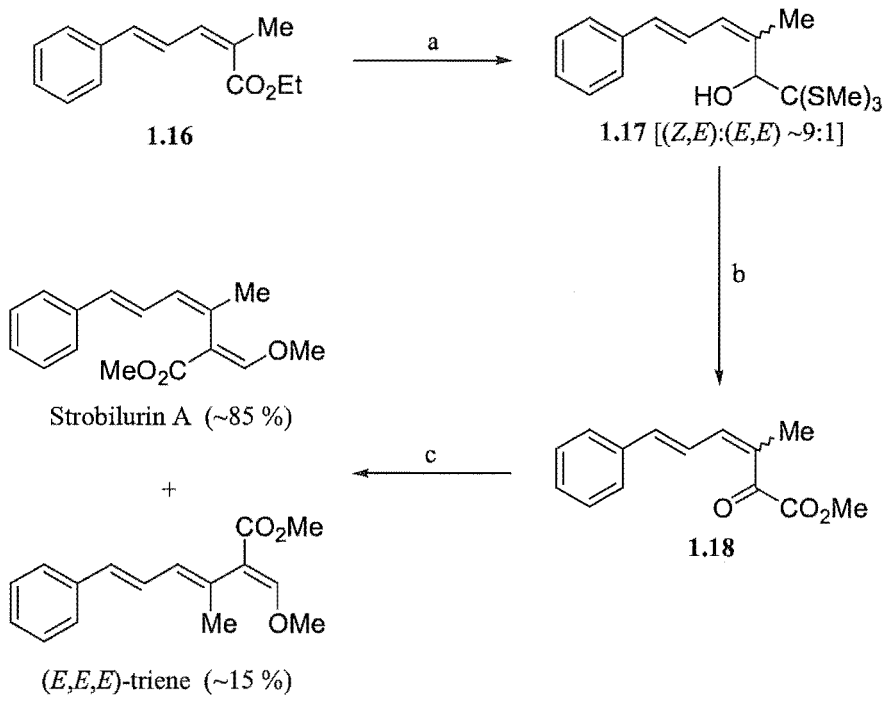
As seen in section **1.2**, syntheses of strobilurin A were an integral part of attempts to confirm the geometry of its triene system. Steglich and co-workers reported the first synthesis (**Figure 1.9**), in which they combined 2-ketobutyric acid and (*E*)-cinnamaldehyde to form what they thought was diene **1.13**, converting this *via* esterification, a Wittig reaction, and photoisomerisation to what they thought to be the natural (*E*,*E*,*E*)-triene (**1.14**).[12] Actually, the diene formed was **1.15**, which, when photoisomerised, gave the correct (*E*,*Z*,*E*)-triene of the natural product, as confirmed in a later paper by the authors.[13]



Reagents: (a) KOH; (b) (i) $SOCl_2$, MeOH; (ii) Ph_3PCH_2OMe, base; (iii) *hv* [reaction conditions and yields not reported].

Figure 1.9 Steglich and co-workers' synthesis of strobilurin A.

Beautement and Clough's synthesis of strobilurin A (**Figure 1.10**)[14] was an improvement on Steglich and co-workers' efforts (although with isomeric mixtures generated at more than one point, their description of the synthesis as 'stereocontrolled' seems rather optimistic). (*Z*,*E*)-Dienoate **1.16** was transformed into (*Z*,*E*)-dienol **1.17**, *via* reduction–oxidation to the corresponding aldehyde, which was then treated with tris(thiomethyl)lithium. Methanolysis of the tris(methylthio) moiety and oxidation of the alcohol afforded a mixture of ketoesters **1.18**, immediate treatment of which with $Ph_3PCHOMe$ under Wittig conditions gave a mixture of strobilurin A and its (*E*,*E*,*E*)-triene isomer, which was separated to give the natural product in 9% overall yield.



Reagents and conditions: (a) (i) $LiAlH_4$, Et_2O, 0 °C, 1 h; (ii) MnO_2, CH_2Cl_2, r.t., 3 h; (iii) $LiC(SMe)_3$, THF, –70 °C; (b) (i) $HgCl_2$, HgO, MeOH/H_2O 12:1, r.t., 15 min ; (ii) MnO_2, CH_2Cl_2, dark, r.t., 10 min; (c) Ph_3PCH_2OMe, base, Et_2O, dark, r.t., 45 min [9 % overall yield (of strobilurin A)].

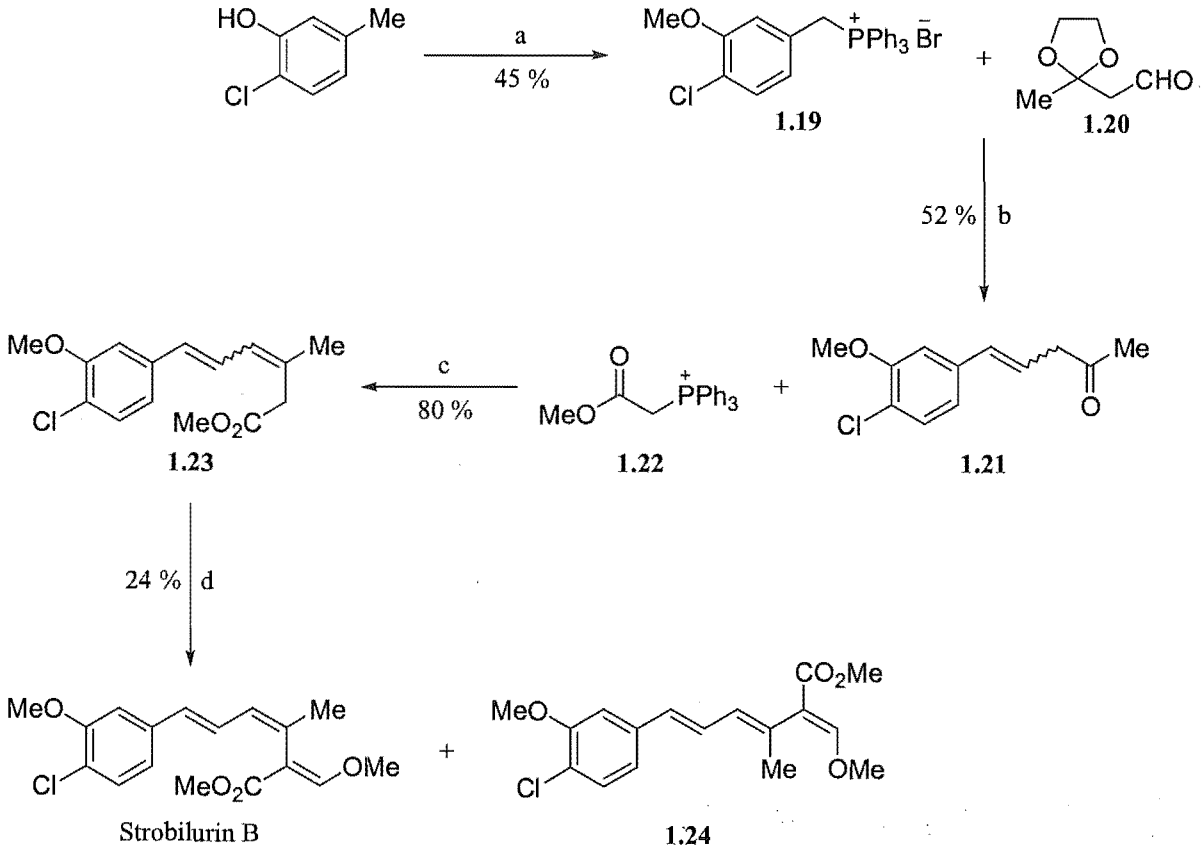
Figure 1.10 Beautement and Clough's synthesis of strobilurin A.

1.5.2 Total Synthesis of Strobilurin B

Strobilurin B was synthesised by Sutter in 1989, again with the use of Wittig methodology to construct the triene system.[52] Phosphonium salt **1.19** was readily prepared in four steps from 2-chloro-5-methylphenol (**Figure 1.11**). Reaction of **1.19** with aldehyde **1.20** generated a 1:1 mixture of (*E*) and (*Z*) isomers of the acetal-containing olefin, which was deprotected to ketone mixture **1.21**, and then reacted with phosphorane **1.22** to give dienoate mixture **1.23**.

Formylation at the α-position of the ester group of **1.23** gave a mixture of enols, which were then O-methylated, and the mixture was separated by column chromatography. Strobilurin B was obtained in 5% overall yield, as was isomeric (*E*,*E*,*E*)-triene **1.24**, together with 5% of other double bond isomers and 10% of unreacted **1.23**. As with Beautement and Clough's

synthesis of strobilurin A (see **Figure 1.10**),[14] the low overall yield of natural product here is due to the poor stereoselectivity which often plagues Wittig techniques, but Sutter welcomed this as a means of obtaining different isomers for comparisons of biological activity.



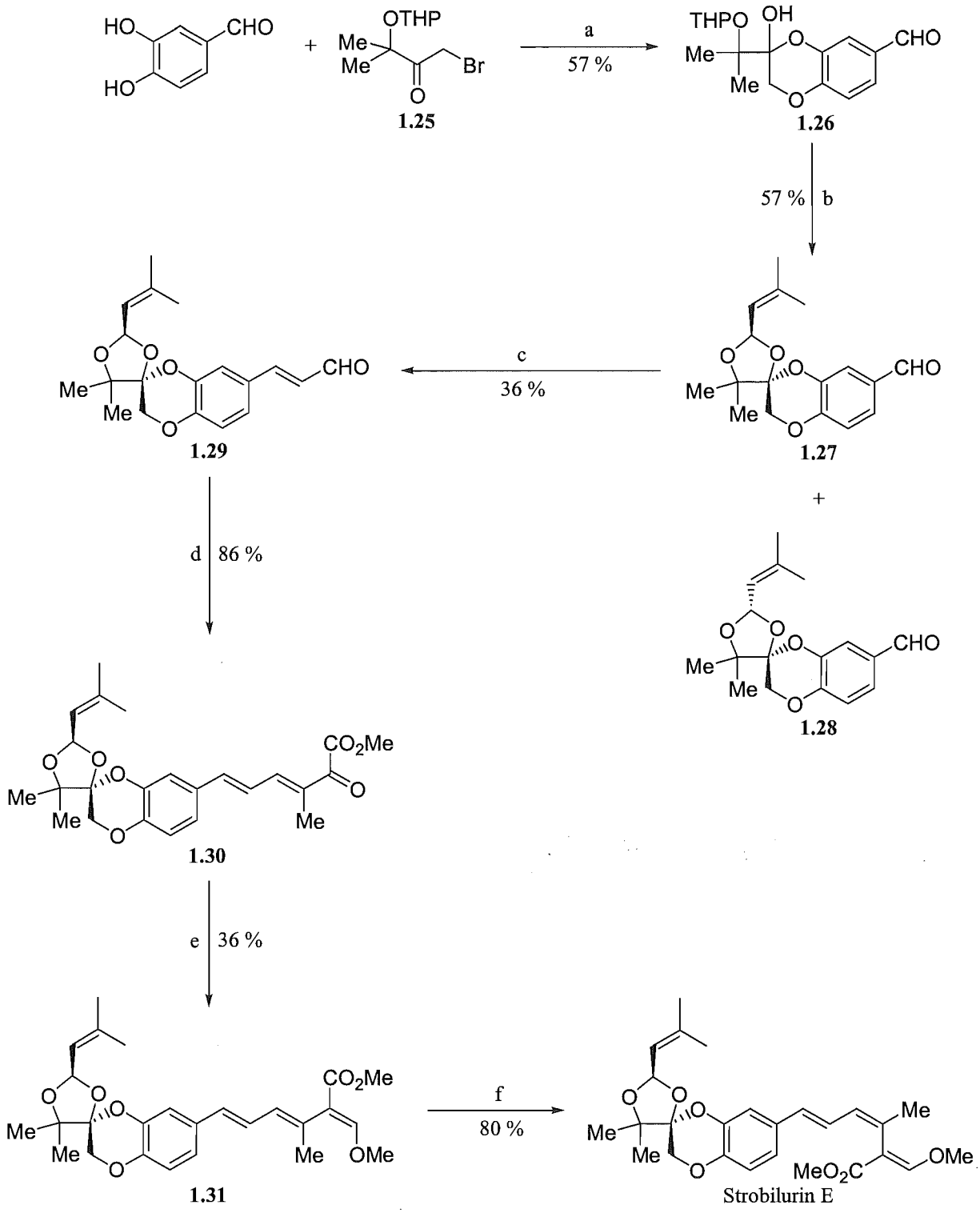
Reagents and conditions: (a) (i) $(MeO)_2SO_2$, K_2CO_3, DMF, r.t.; (ii) NBS, cat. AIBN, CCl_4, reflux; (iii) PPh_3, toluene, reflux; (b) (i) *t*-BuOK, THF, r.t.; (ii) *p*-TSA, acetone/H_2O, 50 °C; (c) base, toluene, reflux; (d) (i) $HCOOCH_3$, NaH, r.t.; (ii) $(MeO)_2SO_2$, K_2CO_3, DMF, r.t. [5 % overall yield (of both products)].

Figure 1.11 Sutter's synthesis of strobilurin B.

1.5.3 Total Synthesis of Strobilurin E

A synthesis of the structurally complex strobilurin E was reported by Steglich and co-workers in 1996 (**Figure 1.12**).[53] The extreme acid sensitivity of the spiroacetal system of strobilurin E demanded that manipulations performed subsequent to the formation of this moiety be free of all traces of acid. As it eventuated, this moiety was formed first in two steps, beginning with the alkylation of 3,4-dihydroxybenzaldehyde with bromoketone **1.25** to afford dioxane **1.26**. Removal of the THP ether of **1.26** followed by immediate reaction of the resulting diol with 3-methylbutenal under acid catalysis gave a 4:3 mixture of desired spiroacetal **1.27** and its diastereoisomer **1.28**.

The next part of the synthesis involved construction of the triene system *via* three consecutive Wittig reactions. First, **1.27** was combined with a two-carbon phosphorane to afford (*E*)-enal **1.29**. Reaction of **1.29** with another ketoester phosphorane afforded (*E*,*E*)-ketoester **1.30**, and finally, treatment of **1.30** with methoxymethylenephosphorane gave (*E*,*E*,*E*)-triene **1.31**. Photoisomerisation of **1.31** gave strobilurin E. Once again, geometrical isomers formed in the non-stereoselective Wittig reactions resulted in a low 3% overall yield.

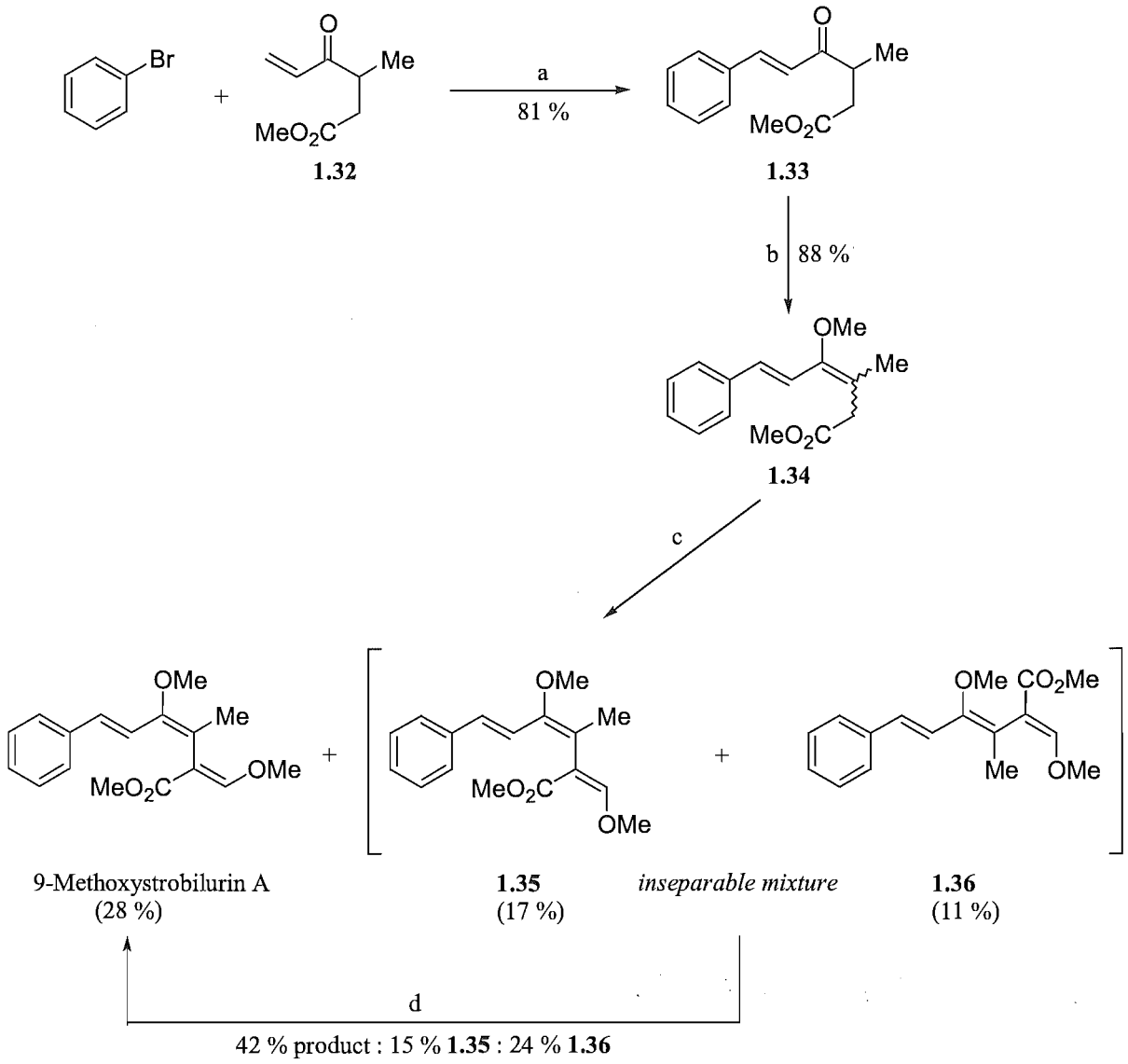


Reagents and conditions: (a) K_2CO_3, acetone, reflux; (b) 3-methylbutenal, cat. pyridinium tosylate, benzene, reflux, 12 h; (c) Ph_3P=CHCHO, benzene, reflux, 30 h; (d) MeC(=PPh_3)$COCO_2Me$, 180 °C, 3 h; (e) Ph_3P=CHOMe, THF, r.t., 15 h; (f) *hv* (> 300 nm), acetone/benzene 10:1, 30 min [3 % overall yield].

Figure 1.12 Steglich and co-workers' synthesis of strobilurin E.

1.5.4 Total Synthesis of 9-Methoxystrobilurin A

A Japanese group headed by Kobayashi reported the synthesis of 9-methoxystrobilurin A in 2000 (**Figure 1.13**).[54] A Heck reaction between bromobenzene and vinyl ketone **1.32** gave enone **1.33**, which was treated with trimethyl orthoformate and catalytic *p*-TsOH to afford the isomeric mixture of methyl enol ethers **1.34**. Formylation of **1.34**, followed by treatment with dimethyl sulfate and potassium carbonate, generated a mixture of 9-methoxystrobilurin A and two geometric isomers. This mixture was subjected to UV irradiation to give the natural product in 28% overall yield, together with an inseparable mixture of two other geometric isomers (**1.35** and **1.36**). This mixture of **1.35** and **1.36** was then irradiated again, isomerising 42% of it into the natural product. Although involving no Wittig techniques, the methodology of this synthesis clearly suffers from similar stereoselectivity problems.

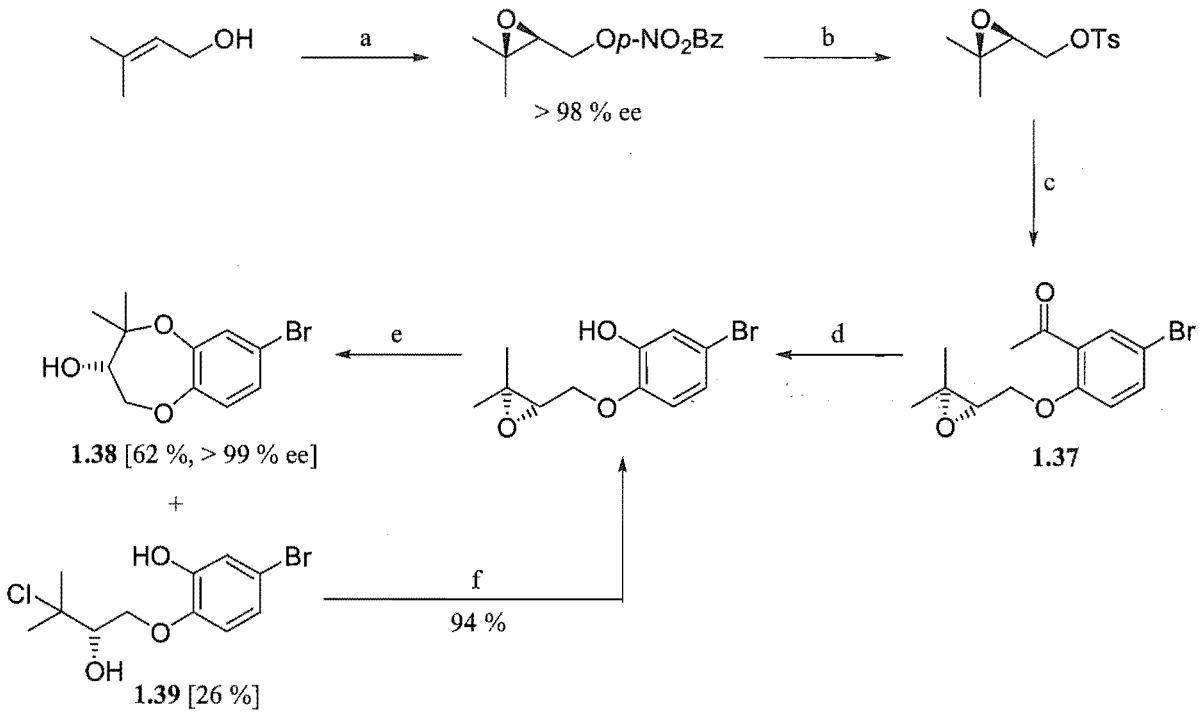


Reagents and conditions: (a) $Pd(OAc)_2$ (20 mol %), PPh_3, NEt_3, 100 °C, 18 h ; (b) $HC(OMe)_3$, *p*-TsOH (10 mol %), MeOH, reflux, 3 h; (c) (i) NaH, HCOOMe; (ii) K_2CO_3, Me_2SO_4; (iii) *hv* (365 nm), acetone/benzene, r.t., 3 h; (d) *hv* (365 nm), acetone/benzene, r.t., 3 h.

Figure 1.13 Kobayashi *et al.*'s synthesis of 9-methoxystrobilurin A.

1.5.5 Total Synthesis of 9-Methoxystrobilurin K

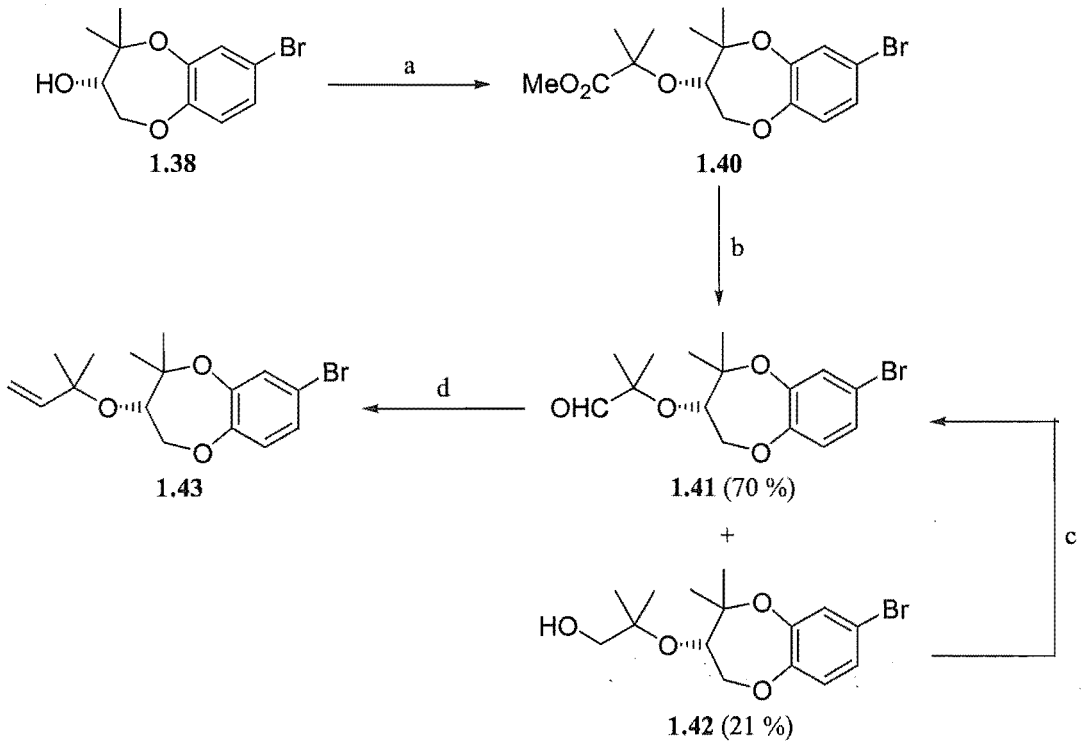
Kobayashi *et al.* have also completed an asymmetric total synthesis of 9-methoxystrobilurin K,[55] with a key feature being efficient construction of the natural product's 1,5-benzodioxepin ring system (**Figure 1.14**). Epoxyphenol **1.37** was prepared in eight steps from isoprenyl alcohol *via* Sharpless asymmetric oxidation, but initial attempts to transform **1.37** into benzodioxepin **1.38** were hampered by the formation of significant amounts of hemiketal product (presumably *via* $SnCl_4$-mediated 1,2-hydride migration within the epoxide of **1.37**, followed by intramolecular cyclisation). However, this undesired process was successfully minimised by conducting the reaction in Et_2O at 0 °C (with minor chlorohydrin product **1.39** being recycled).



Reagents and conditions: (a) (i) TBHP, Ti(*i*-PrO)$_4$, (+)-DIPT, CH_2Cl_2, –40 °C; (ii) *p*-NO_2BzCl, NEt_3, 0 °C; (iii) *recryst. from* Et_2O [75 % over 3 steps]; (b) (i) NaOMe, MeOH, Et_2O, 0 °C; (ii) TsCl, DMAP, CH_2Cl_2, NEt_3, 0 °C; (c) K_2CO_3, 5-bromo-2-hydroxyacetophenone, DMF, r.t. [87 % over 3 steps]; (d) (i) *m*-CPBA, benzene, 60 °C; (ii) DIBAl-H, THF, –78 °C [75 % over 2 steps]; (e) $SnCl_4$, Et_2O, 0 °C; (f) *t*-BuOK, THF, –15 °C.

Figure 1.14 Asymmetric synthesis of 7-bromo-1,5-benzodioxepin-3-ol (**1.38**).

The second section of the synthesis began with a Willamson-type coupling of the sodium alkoxide of **1.38** with methyl 2-bromopropanoate, followed by methylation, to give secondary-tertiary ether-linked α,α-dimethylester **1.40** (**Figure 1.15**). Reduction to aldehyde **1.41** (and oxidation of side-product **1.42** to **1.41**) followed by a Wittig reaction with methyltriphenylphosphorane, afforded 1,5-benzodioxepin **1.43**, containing the full side-chain of this portion of the natural product.

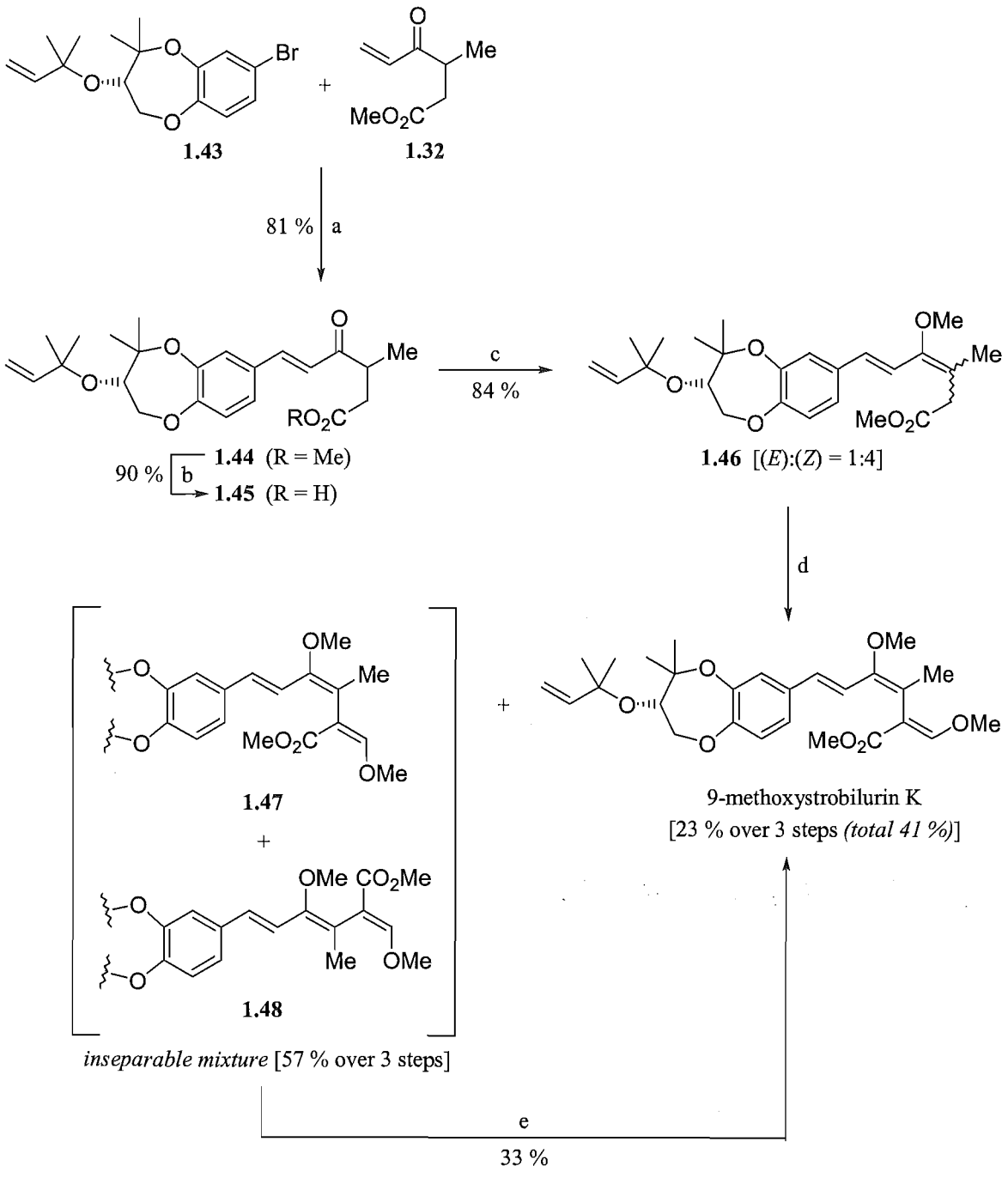


Reagents and conditions: (a) (i) NaH, methyl 2-bromopropanoate, THF, 0 °C; (ii) NaHMDS, MeI, THF, –78 °C [51 % over 2 steps]; (b) DIBAl-H, CH_2Cl_2, –78 °C; (c) $(COCl)_2$, DMSO, NEt_3, –60 °C [96 %]; (d) $Ph_3P{=}CH_2$, DMSO–THF, r.t. [94 %].

Figure 1.15 Construction of C-3 allylic tertiary-secondary ether linkage on 1,5-benzodioxepin.

As in their synthesis of 9-methoxystrobilurin A (see **Figure 1.13**),[54] Kobayashi *et al.* found a Heck reaction – here between **1.43** (instead of bromobenzene) and vinyl ketone **1.32** – an effective beginning to the construction of the strobilurin triene system, forming desired α,β-unsaturated ketone **1.44** (**Figure 1.16**). The acid- and base-sensitivity of the benzodioxepin allylic-tertiary ether linkage of **1.44** necessitated elaboration of this intermediate *via* a stepwise

double methylation. Thus, **1.44** was hydrolysed to the corresponding carboxylic acid **1.45**, treatment of which with *t*-BuOK and dimethyl sulfate, gave methyl enol ether **1.46**. Formylation and dimethyl sulfate treatment of **1.46** afforded a mixture of 9-methoxystrobilurin K and its geometric isomers (**1.47** and **1.48**). Double UV irradiation of this mixture gave 9-methoxystrobilurin K (in a total yield of 41% over 6 steps from **1.43**), together with an inseparable mixture of geometric isomers **1.47** and **1.48**.

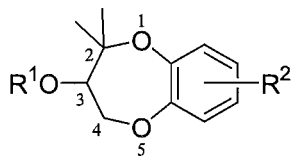


Reagents and conditions: (a) 20 mol % $Pd(OAc)_2$, PPh_3, NEt_3, 100 °C; (b) aq. NaOH–MeOH, r.t. then HCl; (c) *t*-BuOK, DMF, Me_2SO_4, – 45 to –15 °C; (d) (i) NaH, HCO_2Me, r.t.; (ii) K_2CO_3, Me_2SO_4, HCO_2Me, r.t.; (e) *hv* (365 nm).

Figure 1.16 Completion of total synthesis of 9-methoxystrobilurin K.

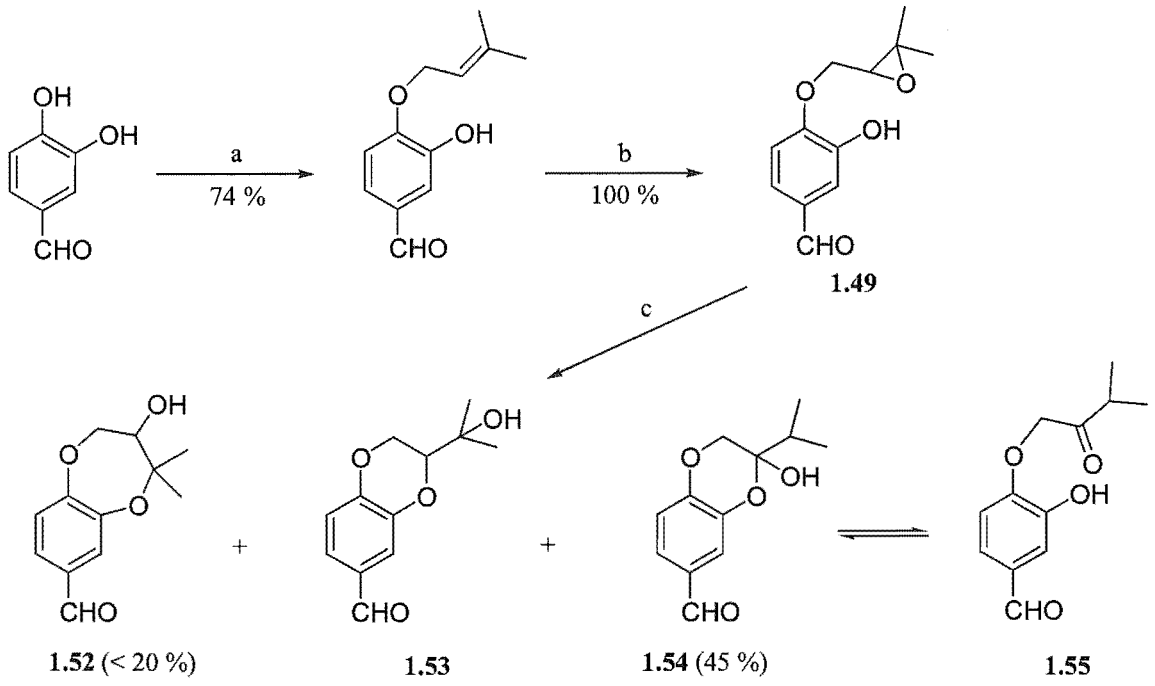
1.5.6 Synthetic Approaches to the 1,5-Benzodioxepin Moiety

In a thesis submitted in 2000,[59] Rea described two synthetic approaches towards the 1,5-benzodioxepin ring system (**1.12**) present in five of the natural strobilurins (see **Figure 1.4**). The first approach was (coincidentally) methodologically identical to that utilised successfully by Kobayashi *et al.* for benzodioxepin construction in their synthesis of 9-methoxystrobilurin K (see **Figure 1.14**),[55] based as it was on attempts to cyclise functionalised aryl epoxides **1.49** and **1.50** into the benzodioxepin system *via* Lewis and Brønsted acid-catalysed rearrangement and intramolecular phenol attack (**Figures 1.17** and **1.18**, respectively). An intramolecular reaction was the key part of the second approach investigated, in which functionalised aryl bromide **1.51** was prepared, but with palladium catalysis being utilised in an attempt to cyclise **1.51** into the benzodioxepin system (**Figure 1.19**).



1.12

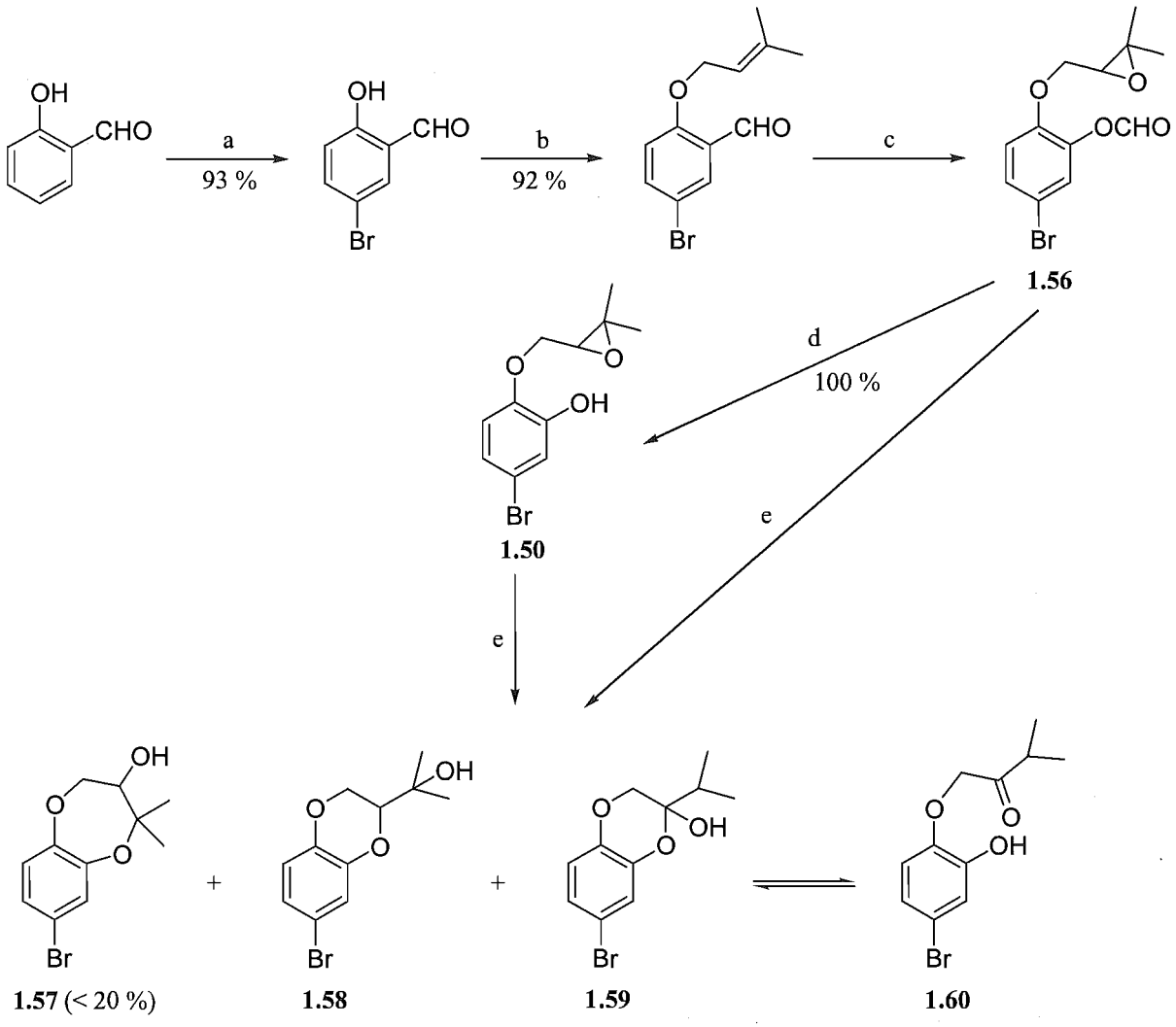
Aryl epoxide **1.49** was prepared in two high yielding steps from 3,4-dihydroxybenzaldehyde (**Figure 1.17**). Many different Lewis and Brønsted acid systems were tried to effect the cyclisation of **1.49** into benzodioxepin **1.52**, but the best results obtained (using $SnCl_4$) were yields of less than 20%. Other products formed in the reaction were isomeric dioxane **1.53** (which was inseparable from **1.52**), and hemiacetal **1.54**, which was the major product and was in equilibrium with its ring-opened isomer **1.55**.



Reagents and conditions: (a) $BrCH_2CH{=}C(CH_3)_2$, K_2CO_3, r.t., 18 h; (b) dimethyldioxirane, –30 °C – r.t., 20 h; (c) $SnCl_4$, THF, r.t., 30 min.

Figure 1.17 Synthesis of aryl epoxide **1.49** and Lewis acid-catalysed cyclisation attempts.

The low yields of **1.52** obtained by cyclisation of **1.49** led to the investigation of another approach, based upon the substitution of a bromine atom for the aldehyde group on the arene ring of the benzodioxepin precursor. Accordingly, aryl epoxide **1.50** was synthesised in an efficient four-step process from salicylaldehyde (**Figure 1.18**). Unfortunately, attempts to cyclise **1.50** (and formate ester **1.56**) into benzodioxepin **1.57** with the use of various Lewis and Brønsted acids mirrored the results obtained with **1.49** (see **Figure 1.17**), with the best yields being less than 20%. The product mixture again included an isomeric dioxane (**1.58**), which was inseparable from **1.57**, and the major product was again an hemiacetal (**1.59**) in equilibrium with its tautomer (**1.60**).



Reagents and conditions: (a) Br_2, $CHCl_3$, 30 °C – reflux, 2 h; (b) $BrCH_2CH{=}C(CH_3)_2$, K_2CO_3, DMF, r.t., 15 h; (c) *m*-CPBA, 0.1 M $Na_2H_2PO_4$, r.t., 16 h; (d) MeOH, reflux, 16 h; (e) $SnCl_4$, CH_2Cl_2, r.t., 24 h.

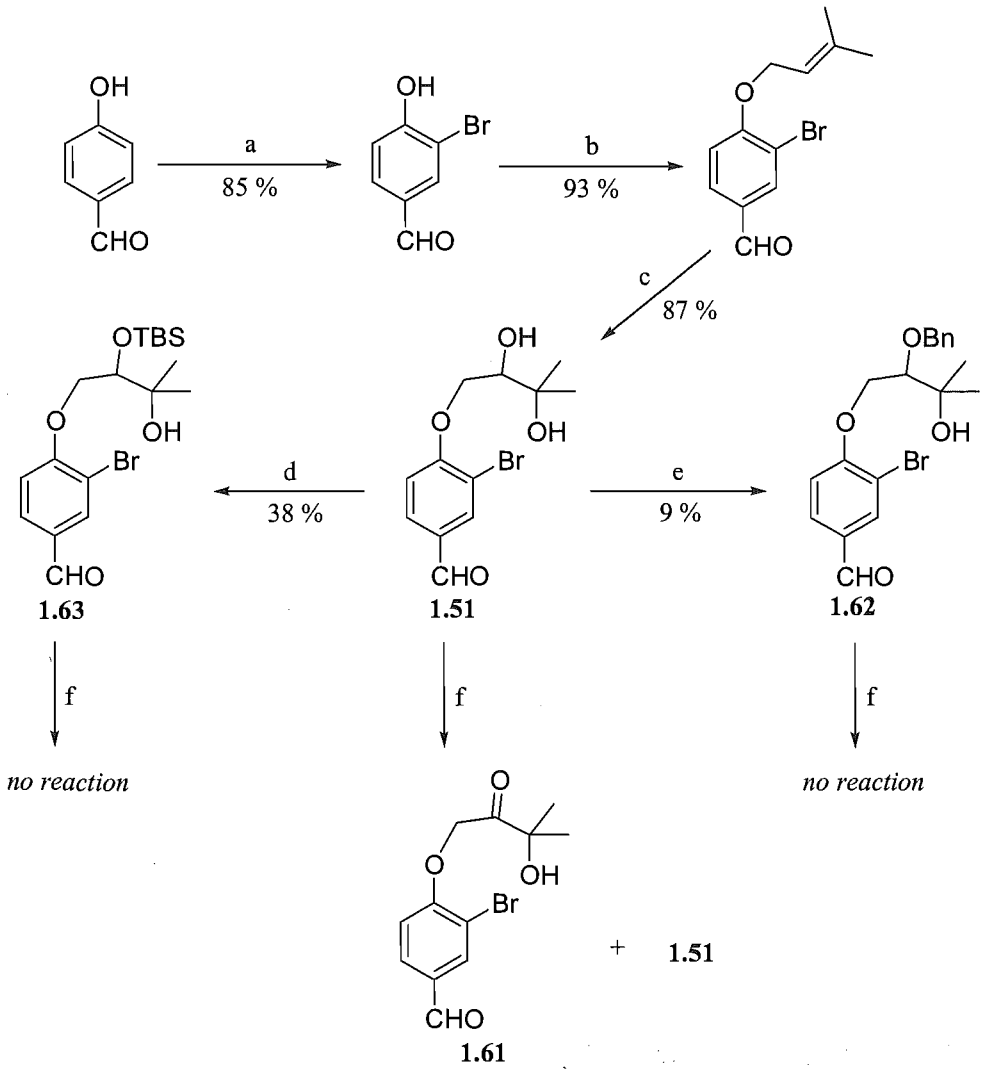
Figure 1.18 Synthesis of aryl epoxide **1.50** and Lewis acid-catalysed cyclisation attempts.

The disappointing yields of benzodioxepins **1.52** and **1.57** obtained *via* Lewis acid-catalysed cyclisations of the corresponding epoxides[ϕ] necessitated a change of tack, and it was decided to attempt benzodioxepin formation *via* palladium-catalysed cyclisation of aryl bromide **1.51**

[ϕ] These poor yields are not unprecedented; Steglich *et al.*'s $La(OTf)_3$-catalysed cyclisation of a similar aryl epoxide (with CH_2Cl_2 as the solvent) also generated the corresponding benzodioxepin in only 20% yield.[57] However, with reference to the successful 1,5-benzodioxepin synthesis developed by Kobayashi *et al.*,[55] it would appear that the use of Et_2O (instead of THF or CH_2Cl_2) as the solvent for the Lewis acid-catalysed aryl epoxide cyclisation reaction would have led to more satisfactory yields of benzodioxepin for both Rea and Steglich *et al.*

(**Figure 1.19**). Buchwald *et al.* have shown that $Pd(OAc)_2$ is capable of catalysing such aryl ether formation processes, under two sets of conditions.[60] Construction of **1.51** proceeded in a facile three-step process from 4-hydroxybenzaldehyde (**Figure 1.19**). However, attempts to cyclise **1.51** into the benzodioxepin system using Buchwald's $Pd(OAc)_2$/Tol-BINAP[†]/K_2CO_3 conditions yielded only a mixture of starting material and ketone **1.61**. Protection of the obviously labile secondary alcohol of **1.51** was then conducted, in an attempt to prevent formation of **1.61**, but neither benzyl (**1.62**) nor *t*-butyldimethylsilyl (**1.63**) derivatives reacted under the cyclisation conditions.

[†] Tol-BINAP = 2,2'-bis[di(*p*-tolyl)phosphino]-1,1'-binaphthyl.

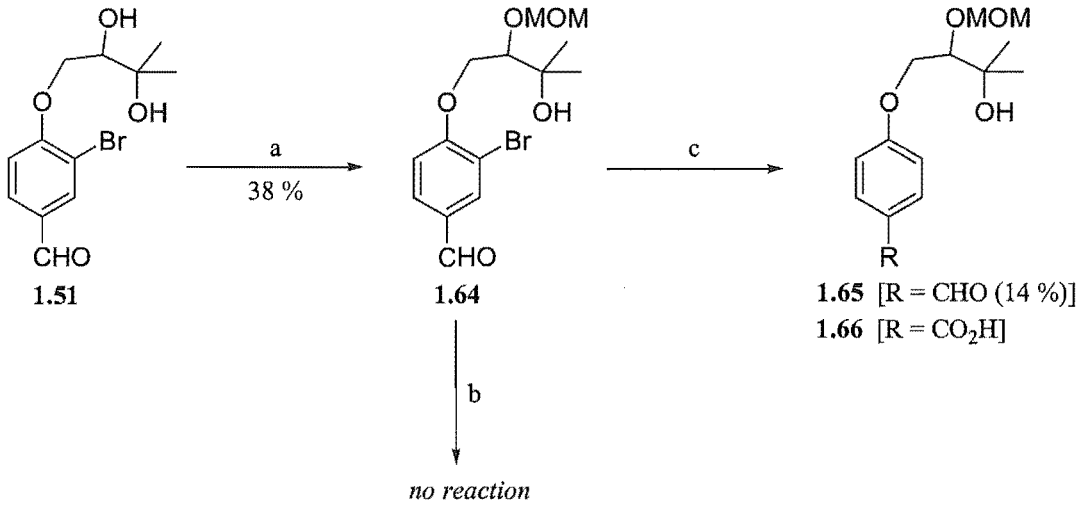


Reagents and conditions: (a) Br_2, $CHCl_3$, 40 °C, 2 h; (b) $BrCH_2CH{=}C(CH_3)_2$, K_2CO_3, r.t., 17 h; (c) OsO_4, NMMO, H_2O/acetone/*t*-BuOH 25:10:2, r.t., 22 h; (d) TBDMSCl, DMAP, imidazole, DMF, r.t., 34 h; (e) BnBr, *t*-BuOK, THF, 14 h; (f) $Pd(OAc)_2$ (5 mol %), Tol-BINAP (6 mol %), K_2CO_3, toluene, 100 °C, 48 h.

Figure 1.19 Synthesis of aryl bromide **1.51** and two protected derivatives, and attempts at cyclisation.

In case the sterically more demanding benzyl and *t*-butyldimethylsilyl groups were responsible for the non-reactivity of **1.62** and **1.63**, bromide **1.51** was protected as MOM ether **1.64**, and attempts were made to cyclise this derivative (**Figure 1.20**). Exposure of **1.64** to $Pd(OAc)_2$/Tol-BINAP/K_2CO_3 gave no reaction, however Buchwald's alternative set of

conditions, $Pd(OAc)_2$/dppf †/*t*-BuONa,[60] gave debrominated products **1.65** and **1.66**. The removal of the bromine atom indicated oxidative insertion of palladium into the C–Br bond was occurring, although clearly the reaction did not proceed beyond this point.

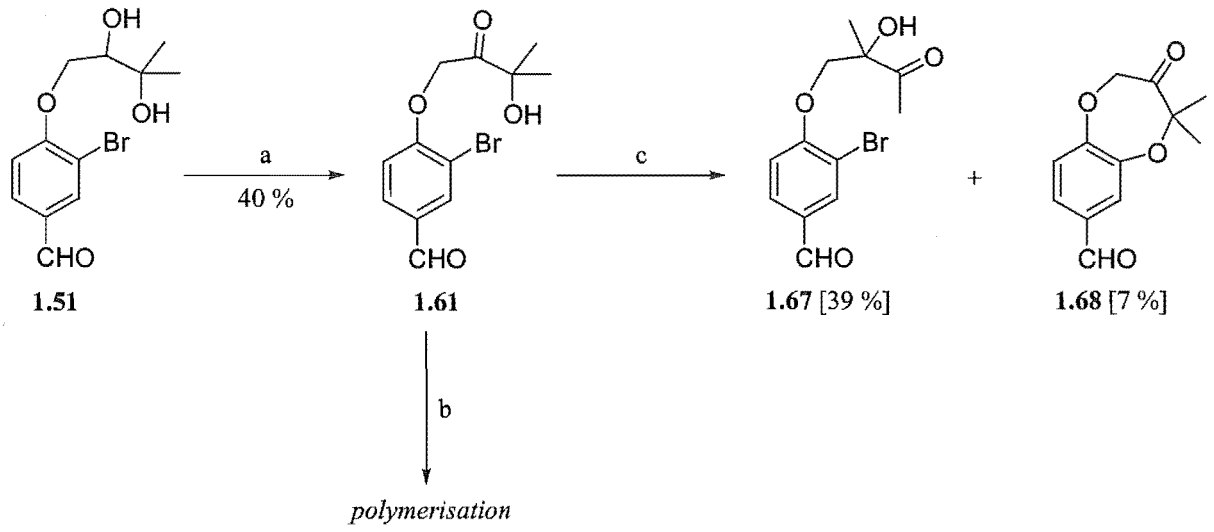


Reagents and conditions: (a) MOMCl, (*i*-Pr)$_2$NEt, CH_2Cl_2, 0 °C – r.t., 14 h;
(b) $Pd(OAc)_2$ (5 mol %)/Tol-BINAP (6 mol %)/K_2CO_3, toluene, 100 °C, 48 h;
(c) $Pd(OAc)_2$ (3 mol %)/dppf (4 mol %)/*t*-BuONa, toluene, 80 °C, 48 h.

Figure 1.20 Synthesis and attempted cyclisation of MOM ether **1.64**.

In a final attempt to obtain the benzodioxepin system *via* palladium catalysis, ketone **1.61** was synthesised *via* TPAP/NMO oxidation (see *Chapter 2*, section **2.2.4.5**) of diol **1.51** (**Figure 1.21**). It was reasoned that the ketone group might function as an even smaller 'protecting' group for the reactive secondary alcohol than MOM, minimising any steric effects which might have inhibited cyclisation of **1.64**. An attempted cyclisation of **1.61** with $Pd(OAc)_2$/dppf/*t*-BuONa produced only polymeric material, however exposure to $Pd(OAc)_2$/Tol-BINAP/K_2CO_3 conditions gave α-ketol **1.67**, and, most pleasingly, benzodioxepin **1.68**. Despite the very low yield of **1.68** (7%), its formation proved that functionalised benzodioxepin rings can be constructed *via* palladium-catalysed aryl ether formation, beckoning further investigations into the viability of this approach.

† dppf = 1,1'-bis(diphenylphosphino)ferrocene.



Reagents and conditions: (a) NMO/TPAP, 4 Å sieves, CH_2Cl_2, r.t., 2 h ;
(b) $Pd(OAc)_2$ (3 mol %)/dppf (4 mol %)/*t*-BuONa, toluene, 80 °C, 24 h;
(c) $Pd(OAc)_2$ (5 mol %)/Tol-BINAP (6 mol %)/K_2CO_3, 100 °C, 24 h.

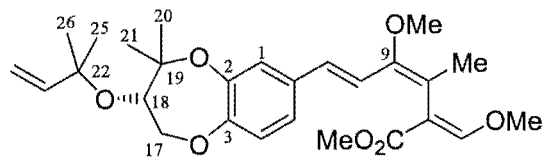
Figure 1.21 Proof of the possibility of benzodioxepin (**1.68**) formation *via* palladium-catalysed cyclisation.

1.5.7 Revision of the Structures of Strobilurins K and D

In a 1994 thesis,[61] Nicholas reported the structure of a new biologically active (*E*)-β-methoxyacrylate-containing natural product isolated from the terrestrial basidiomycete fungus *Favolaschia calocera*. Based on spectroscopic studies, it was assigned the structure **1.68a** (**Figure 1.22**), and was named 9-methoxystrobilurin L. The crucial spectroscopic evidence for **1.68a** was provided by 2-D NMR analyses, and is described below.

An HMBC correlation from diastereotopic protons H-17 to oxygenated aromatic carbon C-3, and an NOE correlation between proton H-1 and the Me-20 and Me-21 protons established the position of one of the isoprene units. This NOE correlation also supported the ether connection between quaternary carbon C-19 and aromatic carbon C-2, leading to the assignment of the dioxepin structure. This assignment was corroborated by NOEs between H-18 and the Me-21, Me-25, and Me-26 protons. An HMBC correlation from proton H-18 to

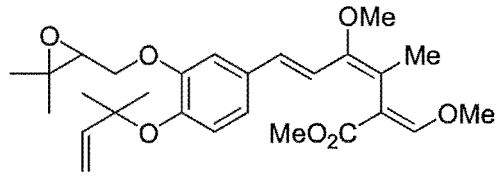
carbon C-22 linked the other isoprene unit to carbon C-18 of the dioxepin ring, *via* an ether bond.



1.68a

Figure 1.22 Nicholas' proposed structure for 9-methoxystrobilurin L.

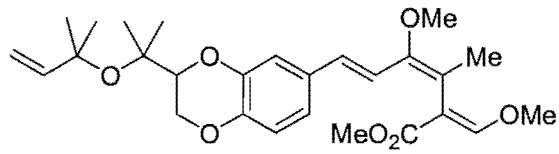
A year later, Steglich *et al.* published details of the isolation of what was apparently another new strobilurin, also from *Favolaschia* sp.[62] Spectroscopic analysis had led them to structure **1.69** (**Figure 1.23**), which they dubbed 9-methoxystrobilurin K.



1.69

Figure 1.23 Steglich *et al.*'s proposed structure for 9-methoxystrobilurin K.

In 1996, Wood *et al.* reported the isolation of a natural product they named 9-methoxystrobilurin L from the basidiomycete fungus *Favolaschia pustulosa*, and proposed it had the structure **1.70** (**Figure 1.24**).[63]



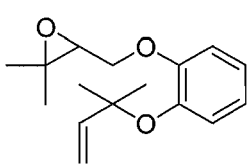
1.70

Figure 1.24 Wood *et al.*'s proposed structure for 9-methoxystrobilurin L.

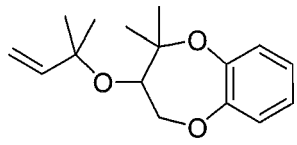
A subsequent investigation by Nicholas *et al.* compared the spectroscopic data for all three compounds (**1.68a**, **1.69**, and **1.70**), and revealed that the *only* significant difference was the H-18 to C-22 HMBC correlation observed by Nicholas – otherwise the data sets were identical.[56] Clearly, this meant two of the three proposed structures were wrong.

The absence of the H-18 to C-22 HMBC correlation in Wood *et al.*'s NMR data, which had been obtained in MeOD, was found to be due to its being obscured by the overlapping T_1 noise ridge of another signal. The fact that this correlation is crucial for the assignment of the ether linkage of **1.68a**, and clearly visible in NMR experiments conducted in $CDCl_3$, but not those carried out in MeOD, is perhaps what led to dioxan-containing structure **1.70** being proposed. However, comparisons of the NMR data (in MeOD) for a synthetic dioxan model compound[64] similar to the dioxan moiety of **1.70** with Wood *et al.*'s data showed significant differences in some key chemical shift values. On the basis of these pieces of information, Wood *et al.*'s proposed structure (**1.70**) could be ruled out, which left either Nicholas' (**1.68a**) or Steglich *et al.*'s (**1.69**) structures as correct.

To corroborate the NMR-based assignment of **1.68a**, Nicholas *et al.* synthesised two model compounds (**Figure 1.25**) for the areas of difference of **1.68a** and **1.69**. It was found that the NMR data of **1.71**, a model for the epoxide structure of **1.69**, were inconsistent with that reported by Steglich *et al.*,[62] most notably the NOE results and the chemical shifts for the supposed epoxide carbons. Conversely, NMR analysis of **1.72**, a model for the benzodioxepin system of **1.68a**, generated data which was consistent with that reported for the natural product in Nicholas' thesis.[61] Together with the key H-18 to C-22 HMBC correlation, which shows the two isoprenyl units are linked, these spectroscopic results enabled Nicholas *et al.* to conclude that 9-methoxystrobilurin K could not possess structure **1.69**, and must be reassigned as **1.68a**. Thus, 9-methoxystrobilurin L (**1.68a**) was the correct structure, and was re-named 9-methoxystrobilurin K.[56] (In addition, Kobayashi *et al.* have recently reported a synthesis of the entire **1.70** structure, noting sufficient differences between its spectroscopic data and those reported for the natural product to support Nicholas *et al.*'s contention that Wood *et al.*'s proposition was incorrect, and that a 1,5-benzodioxepin moiety constituted the most likely structure[65]).



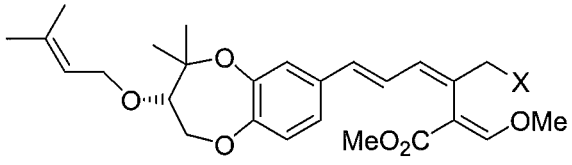
1.71



1.72

Figure 1.25 Model compounds for two possible 9-methoxystrobilurin structures.

In the same paper,[56] Nicholas *et al.* noted that the first reports of strobilurin D[66] and hydroxystrobilurin D[67] had also concluded that the compounds contained epoxide structure **1.71**. Again, a re-examination of the reported chemical shifts for the supposed epoxide carbons supported the presence of a benzodioxepin structure analogous to **1.72**, and led to the natural products being re-assigned the structures depicted below (**Figure 1.26**).



Strobilurin D: X = H

Hydroxystrobilurin D: X = OH

Figure 1.26 Correct structures of hydroxystrobilurin D and strobilurin D.

This was an impressive body of work by Nicholas *et al.*,[56] and in proving that the structures for two distinct but related strobilurins were incorrect, they forced Steglich *et al.* to correct[57] the structures they had originally proposed for strobilurin D,[66] hydroxystrobilurin D,[67] and 9-methoxystrobilurin K.[62]

1.6 Organometallic Chemistry in Natural Products Synthesis

One can see from the strobilurin syntheses described in section **1.4** that notwithstanding some impressive work, such as Steglich *et al.*'s construction of the spiroacetal moiety of strobilurin E (section **1.4.3**), there is scope for improvement, particularly in construction of the (*E*,*Z*,*E*)-triene system. The poor stereoselectivity resulting from Wittig techniques, utilised in all of the total syntheses reported thus far, is often responsible for the generation of isomeric mixtures of trienes, with concomitant low yields of natural product. A potential solution to this problem involves transition metal/organometallic methodologies, as such techniques enable a wide range of synthetic transformations to be conducted, usually with high stereoselectivity, regioselectivity, and functional group tolerance.

1.6.1 Palladium-Catalysed Couplings in Natural Products Synthesis

Palladium has two stable oxidation states, Pd^{2+} (usually written as Pd^{II}) and Pd^{0}, each with its own distinct chemical proclivities, and it is the facility of redox exchange between these two oxidation states that enables various complexes of palladium(II) and (0) to catalyse numerous synthetic transformations. Palladium is expensive, but much less so than other metals used in catalysis, such as rhodium, platinum or osmium, and it is also much less toxic than these other metals, two characteristics that have seen palladium catalysis adopted in at least ten industrial-scale processes.[68] Common examples of palladium catalysts are the air-stable complex dichlorobis(triphenylphosphine)palladium(II) [$Pd(PPh_3)_2Cl_2$] and the air-sensitive complex tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$], although as the actual catalytic species appears to be 'bis(triphenylphosphine)'palladium(0) ['$Pd(PPh_3)_2$'][69] or some *in situ*-generated analogue, they are strictly defined as 'pre-catalysts'.[69]

Three fundamental reactions of such palladium compounds, which have collectively furnished access to an Aladdin's cave of many invaluable organometallic transformations, are oxidative addition, reductive elimination, and transmetallation.[70] Oxidative addition and

reductive elimination are two sides of the same coin – manifestations of the facility with which palladium can shuttle between its two stable oxidation states – and are represented by the equation below (**Figure 1.27**). In oxidative addition, the coordinatively unsaturated complex PdL_2 (Pd^0, d^{10}) reacts with substrate A–B, formally inserting into the A–B bond to form the coordinatively saturated complex A–PdL_2–B (Pd^{II}, d^8). The formal† oxidation of the metal results from the fact that two of its previously non-bonding electrons are now involved in bonding. By analogy, the reverse process is denoted reductive elimination.

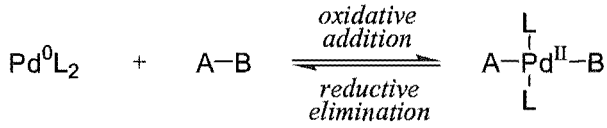


Figure 1.27 Oxidative addition – reductive elimination behaviour of palladium(0) complexes.

Several mechanisms have been determined for oxidative addition, including concerted one-step 'insertions' into A–B by Pd,[71] S_N2 reactions,[72] and electron transfer-radical chain processes,[73] with the mechanism followed dependent on the substrates involved in the reaction [recent research by Casado and Espinet[74] has shown that, in some cases, the overall mechanism is not as simple as depicted above (see section **1.6.1.3**)]. A–B itself can be one of a wide range of compounds, from polar electrophiles [*e.g.* X_2, RX, RC(O)X] to non-polar electrophiles [*e.g.* H_2, RH, RC(O)H] to multiple bonds (where A–B stay connected).

Generally, oxidative addition is facilitated by ligands (L) such as PPh_3 and R^-, which are good σ-donors and thus increase electron density at palladium (*i.e.* they make Pd electron-rich and thus 'happy' to lose electrons *via* oxidation), and impeded by ligands such as CO and alkenes, which are good π-acceptors and thus decrease electron density at palladium (*i.e.* they make Pd electron-poor and thus not 'happy' to lose electrons *via* oxidation). By analogy, these

† 'Formal' is used to emphasise the fact that the oxidation state of transition metals in such complexes, as well as rules for electron counting in ligands and complexes, are formalisms. That is, they are not the 'truth' of the situation, but 'convenient fictions' which contain an element of the truth – constituting a systematic, if not always chemically reasonable way in which to organise an otherwise baffling array of information.

electronic considerations have the opposite effect on the facility of reductive elimination.[ϕ] However, although such trends are noticeable, the role of ligands is not completely understood, and determining the optimum palladium complex for a given process is often a matter of (educated) trial and error.

Transmetallation is the transfer of an R group from an organometallic compound (R–M) to a transition metal (*e.g.* Pd) complex (M'–X), as generalised in the equation below (**Figure 1.28**), where the main group metal (M) is typically zinc, boron, aluminium, zirconium, or tin. Although the electronegativity of M must be less than that of the transition metal (M') for the reaction to proceed, irreversible consumption of R–M' in some subsequent step (*e.g.* reductive elimination – see **Figure 1.29**) can sufficiently perturb the equilibrium to enable the reaction to proceed even if this thermodynamic requirement is not met.

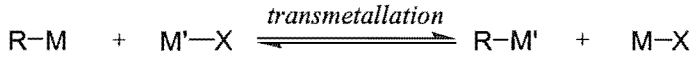


Figure 1.28 General transmetallation reaction.

The utility of these fundamental reactions of palladium compounds is revealed with the realisation that (a) the M'–X of **Figure 1.28** can be the oxidative adduct A–$Pd^{II}L_2$–B of **Figure 1.27**; and that (b) unlike in **Figure 1.27**, the two groups reductively eliminated from the palladium need not be the same two groups that were oxidatively added. It thus follows that an oxidative addition – transmetallation sequence can be used to generate adduct A–$Pd^{II}L_2$–R, and this can then reductively eliminate the new compound A–R (**Figure 1.29**). If A and R are two different organic groups, the net result is a 'cross'-coupling – the formation of a new carbon-carbon bond between two non-identical organic fragments.

[ϕ] In addition to these electronic considerations, it has also been demonstrated that a *cis* arrangement between two groups on the metal is necessary for their reductive elimination [Gillie, A.; Stille, J. K. *J. Am Chem. Soc.* **1980**, *102*, 4933].

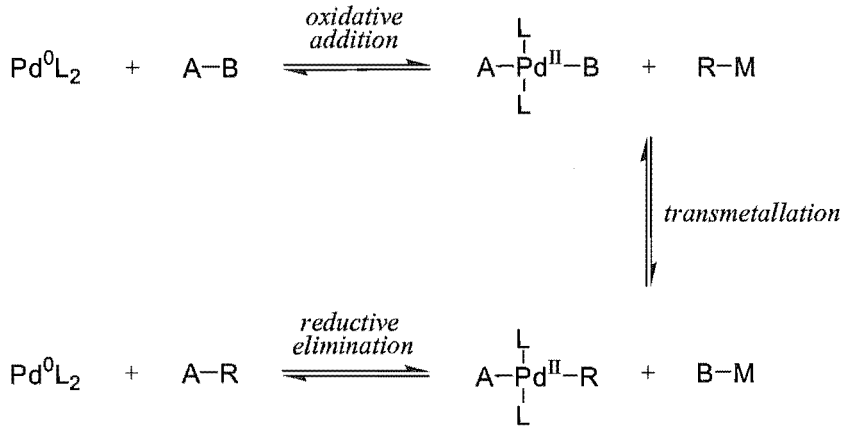


Figure 1.29 Generation of cross-coupled product A–R *via* oxidative addition – transmetallation – reductive elimination sequence.

A more common and convenient way in which such Pd^0-catalysed cross-coupling reactions can be represented is as the catalytic cycle depicted in **Figure 1.30** below. The process enables the union of a vast array of substrates, generally with retention of the stereochemical configurations of both coupling partners – a *sine qua non* for the stereoselective assembly of conjugated systems. The group X is typically a halide or triflate, L commonly PPh_3 or a derivative or analogue thereof, and R an aryl, alkyl, vinyl, or allyl moiety.

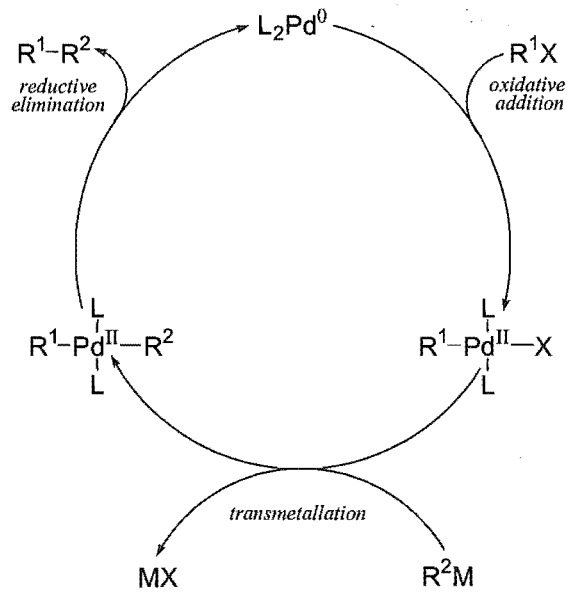


Figure 1.30 General Pd^0-catalysed cross-coupling catalytic cycle.

Three forms of this reaction often employed in natural product syntheses utilise zirconium, boron, or tin as the main group metal (M). In fact, the ubiquity of the latter two metals in such procedures has led to the crossed couplings involving them being commonly known by the name of their original discoverer(s): hence Suzuki-Miyaura couplings utilise organoboron compounds,[75] whilst Stille couplings utilise organotin compounds.[76]

A variety of studies have probed the mechanistics of cross-coupling processes. Negishi *et al.* investigated palladium-catalysed cross-couplings of various (*E*)-1-octenyl metals (Li, Mg, Zn, Cd, Hg, B, Al, Si, Sn, Ti, Zr, Ce) and (*E*)-1-hexenyl iodide, and observed a correlation between the type of metal and the efficiency of the process.[77] They theorised that this meant transmetallation was the rate-determining step of the process, and obtained kinetic data for the palladium-catalysed reaction between an (*E*)-alkenyl zinc chloride and iodobenzene that were consistent with this hypothesis. (It must be noted here that this generalisation does not hold for the Suzuki-Miyaura coupling; Matos and Soderquist have found that the relative rates of each step of this organoboron-based process vary with the nature of the reacting species, and report kinetic studies of certain Suzuki coupling processes in which the organoboron species is not part of the slowest step of the overall reaction[78]). Three extensive NMR-based mechanistic studies (two observing ^{31}P and one ^{19}F) of the Stille coupling reaction concluded that transmetallation was the rate-determining step of this process too[79] – a summary of one of these investigations is given below.

Farina and Krishnan conducted a thorough investigation of the mechanistic basis for the large rate accelerations and higher yields obtained in Stille couplings of a variety of substrates when triphenylarsine ($AsPh_3$) or tris(2-furyl)phosphine (TFP) are utilised as the ligands on palladium [$AsPh_3$ and TFP have a lower donicity (*i.e.* they coordinate more weakly) to Pd^{II} than the more commonly used PPh_3].[79b] The key results were obtained *via* ^{31}P NMR studies of the reaction between phenyl iodide (PhI) and vinyltributylstannane (CH_2=$CHSnBu_3$), catalysed by tris(dibenzylideneacetone)dipalladium(0) [Pd_2dba_3] with PPh_3 or TFP as the ligand.

The oxidative addition reaction between phenyl iodide and Pd_2dba_3/PPh_3 or TFP demonstrated that TFP led to slower rate of oxidative addition than PPh_3. However, since the

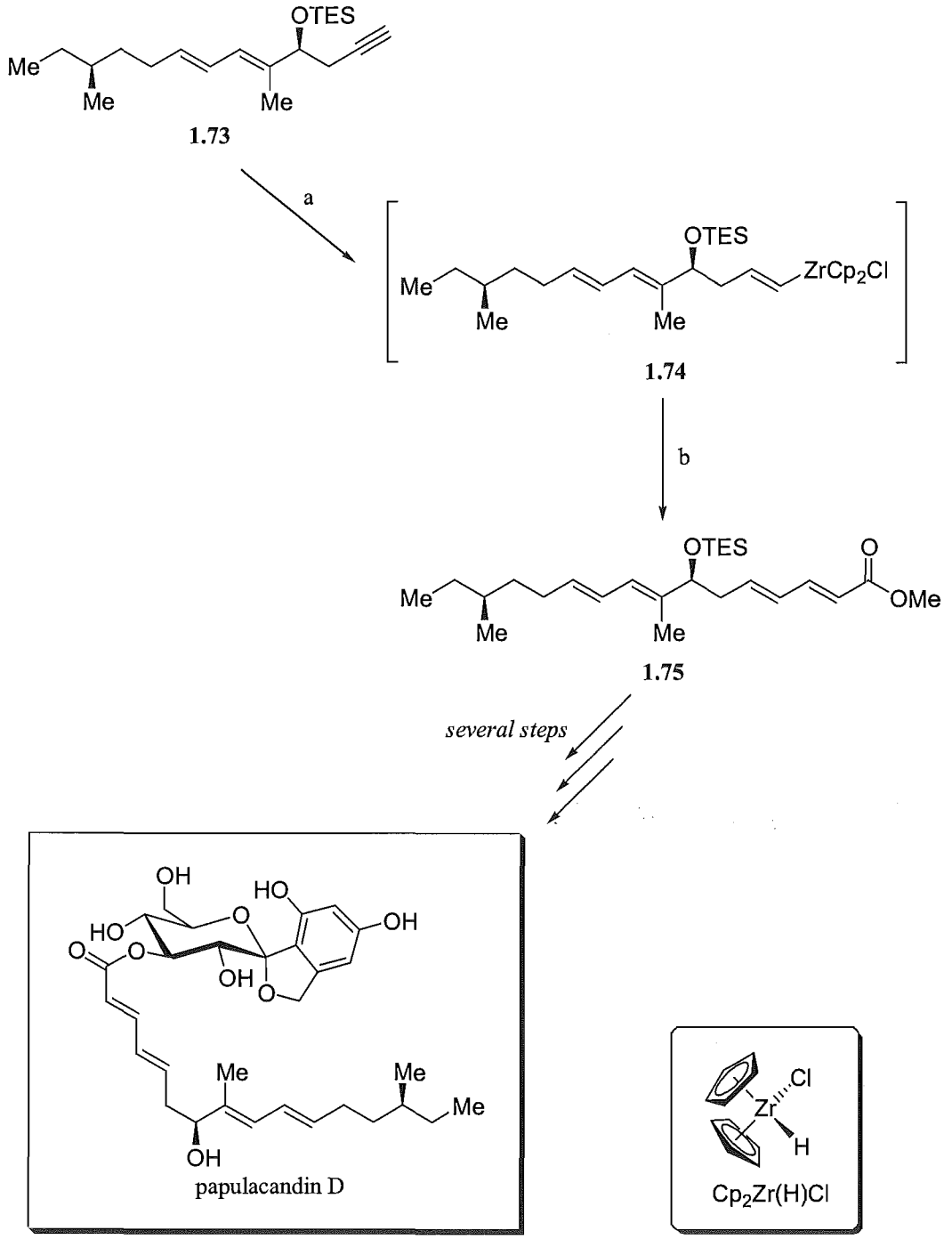
overall rate of reaction (*i.e.* rate of the whole coupling process) with TFP was still faster than with PPh_3, this ruled out the possibility of oxidative addition being the rate-determining step. Addition of vinyltributyltin (CH_2=$CHSnBu_3$) led to the re-formation of $Pd^0(TFP)_2$ but with no visible disappearance of the ^{31}P NMR signal for oxidative adduct $PhPd^{II}(TFP)_2I$, showing that the transmetallation of the latter to $PhPd^{II}(TFP)_2CH$=CH_2 must be the slowest and therefore the rate-determining step *i.e.* as soon as this transmetallation intermediate is formed, it immediately undergoes a much faster reductive elimination reaction to generate the cross-coupled product and regenerate the $Pd^0(TFP)_2$ catalyst, and is thus not visible in ^{31}P NMR (if the converse was true, with fast transmetallation and slow reductive elimination steps, there would obviously be a build-up of the transmetallation intermediate, which would consequently be visible in ^{31}P NMR). Thus, such weakly bonding ligands such as TFP and $AsPh_3$ must facilitate transmetallation – the attack of the nucleophilic R group from Sn – by 'falling off' the Pd^{II} more easily than more strongly binding ligands such as PPh_3. The mechanism of the transmetallation process is meticulously scrutinised in Casado and Espinet's report,[79c] in which they propose a revised catalytic cycle for the Stille coupling which is consistent both with their, Farina and Krishnan's,[79b] and other kinetic data (see section **1.6.1.3**).

Pd-catalysed cross-couplings are particularly useful for the stereoselective construction of the conjugated diene, triene and polyene systems common in natural products, as is illustrated in the next three sections.

1.6.1.1 Alkenyl Zirconocenes

Organozirconium compounds are useful because *trans* alkenyl zirconocenes can be synthesised with complete stereoselectivity and regioselectivity *via* hydrozirconation of the corresponding alkyne with Schwartz's reagent, chlorobis(η^5-cyclopentadienyl)hydridozirconium [$Cp_2Zr(H)Cl$] (see *Chapter 2*, section **2.2.4.1** for a mechanistic discussion).[80] For example, in Barrett *et al.*'s synthesis of the antifungal antibiotic papulacandin D, the hydrozirconation of terminal alkyne **1.73** gave alkenyl zirconocene **1.74**,

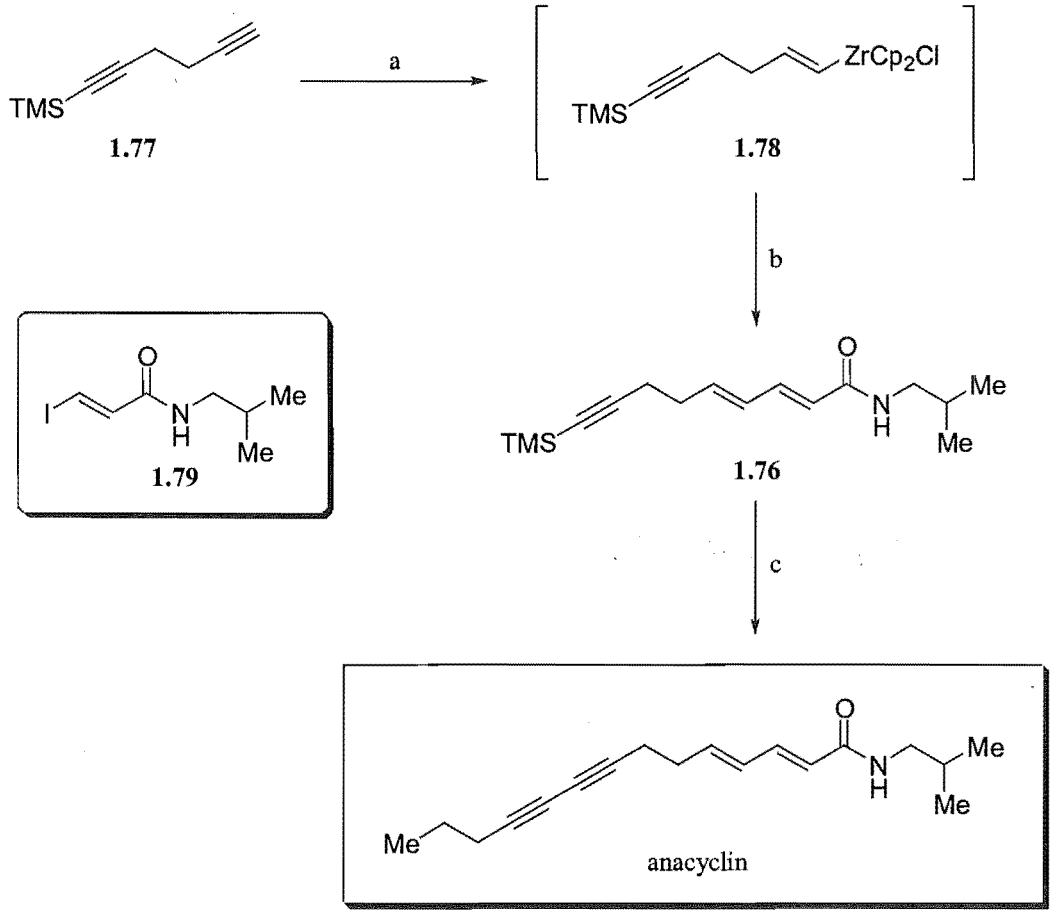
which was coupled *in situ* with methyl (*E*)-3-bromoacrylate, in the presence of pre-reduced $Pd(PPh_3)_2Cl_2$, to afford diene ester **1.75** in 70% yield (**Figure 1.31**).[81]



Reagents and conditions: (a) $Cp_2Zr(H)Cl$, THF, dark, r.t., 45 min; (b) methyl (*E*)-3-bromoacrylate, [$Pd(PPh_3)_2Cl_2$ (10 mol %) + DIBAL-H (20 mol %)], THF, dark, r.t., 15 h [70 % over two steps].

Figure 1.31 Barrett *et al.*'s synthesis of papulacandin D *via* Pd^0-catalysed coupling of an alkenyl zirconocene and a vinyl bromide (TES = triethylsilyl).

Diene **1.76**, a key fragment in Crombie *et al.*'s synthesis of the plant-derived insecticidal natural product anacyclin, was also constructed *via* an alkenyl zirconocene (**Figure 1.32**).[82] Hydrozirconation of diyne **1.77** with Schwartz's reagent[80] afforded alkenyl zirconocene **1.78** (with the non-reduction of the internal triple bond of **1.77** being an apposite demonstration of the chemoselectivity of this hydrometallation), which was coupled *in situ* with vinyl iodide **1.79**, in the presence of pre-reduced $Pd(PPh_3)_2Cl_2$, to give **1.76** in 56% yield. Desilylation of **1.76**, followed by a Cadiot-Chodkiewicz coupling[83] with 1-bromopent-1-yne, afforded anacyclin in 59% yield.



Reagents and conditions: (a) $Cp_2Zr(H)Cl$, benzene, dark, r.t.; (b) **1.79**, cat. [$Pd(PPh_3)_2Cl_2$ + DIBAL-H], THF/benzene [42 % yield over two steps]; (c) (i) $Bu_4N^+F^-$, THF; (ii) 1-bromopent-1-yne, NH_4OH, CuCl, MeOH [59 % yield over two steps].

Figure 1.32 Crombie *et al.*'s synthesis of anacyclin *via* chemoselective hydrozirconation and Pd-catalysed coupling.

1.6.1.2 Alkenyl Boranes

The hydroboration of alkynes, which produces alkenyl boranes, is an extensively studied and well-understood process (see *Chapter 2*, section **2.2.4.1**). However, any type of organoborane holds onto its organic (R) group so tightly that the R group does not possess enough nucleophilicity to transmetallate to palladium (boron is electrophilic, so, in crude terms, it grabs any electrons it can from the R group, precluding their availability for nucleophilic duties), which would seem to rule out the utilisation of organoboranes in palladium-catalysed crossed couplings. Fortunately, the use of anionic bases (often a sodium alkoxide*) circumvents this problem.

The role of the base is outlined in the postulated catalytic cycle for the Suzuki-Miyaura coupling shown below (**Figure 1.33**), and is rationalised as follows. A metathetical displacement of the halide atom (X) from the oxidative addition complex **1.80** by the base ($NaOR^2$) forms alkoxopalladium complex **1.81** (Suzuki *et al.* have demonstrated the intermediacy of such alkoxopalladium complexes in Suzuki-Miyaura couplings[75b]). This complex then undergoes the desired transmetallation reaction with the alkenyl boron species **1.82**, presumably *via* the more nucleophilic, negatively charged alkenyl borate species **1.83** (the negative charge of **1.83** perturbs the previously strong B–alkenyl bond, such that the alkenyl group is free *i.e.* sufficiently nucleophilic to transmetallate to palladium), to produce diorganopalladium complex **1.84**. Finally, reductive elimination from **1.84** affords the cross-coupling product **1.85** and regenerates the palladium(0) catalyst.

* Fluoride can be used instead of hydroxide or alkoxide in the case of base-labile substrates [(a) Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575; (b) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095].

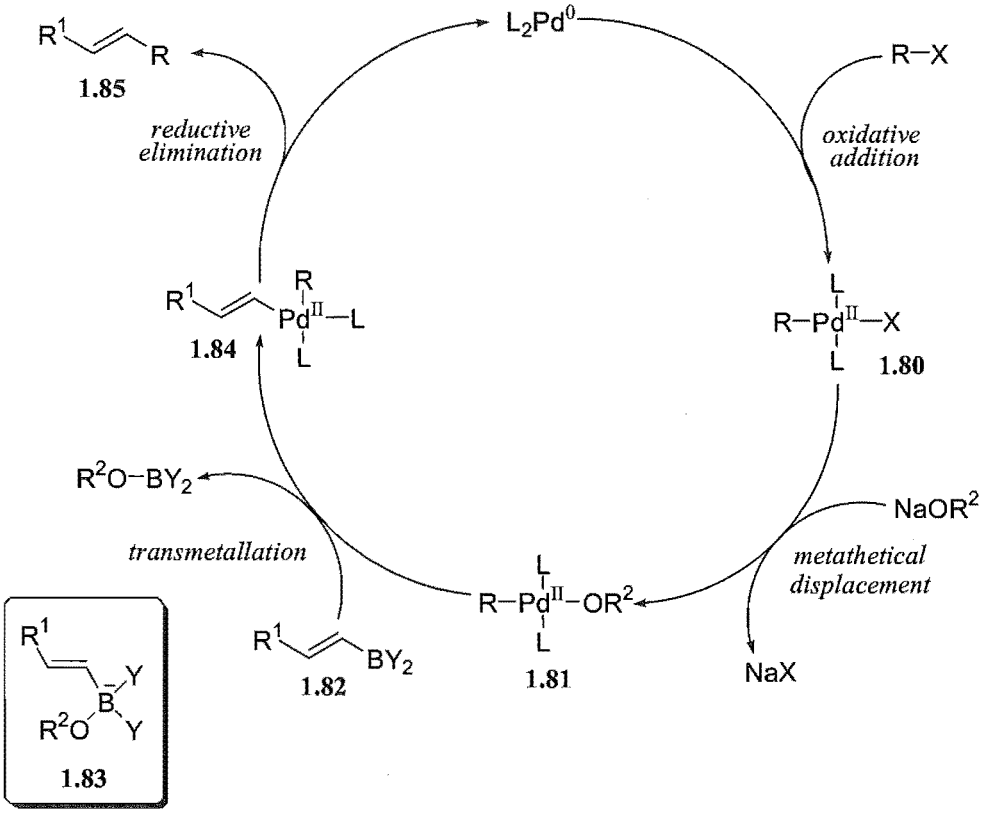
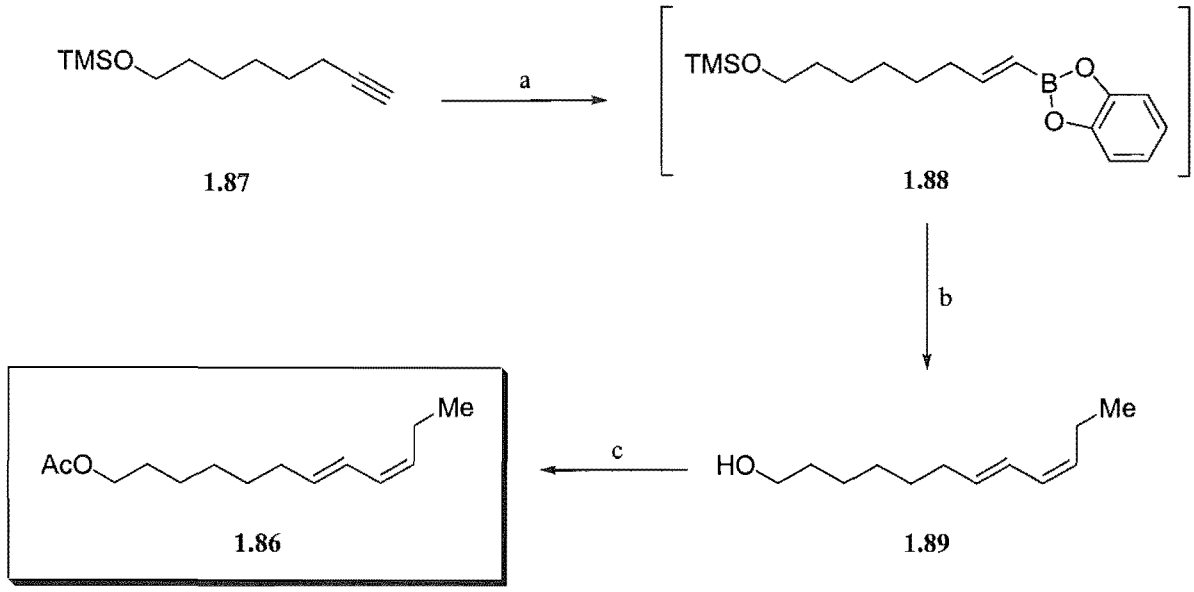


Figure 1.33 Catalytic cycle of the Suzuki-Miyaura coupling.

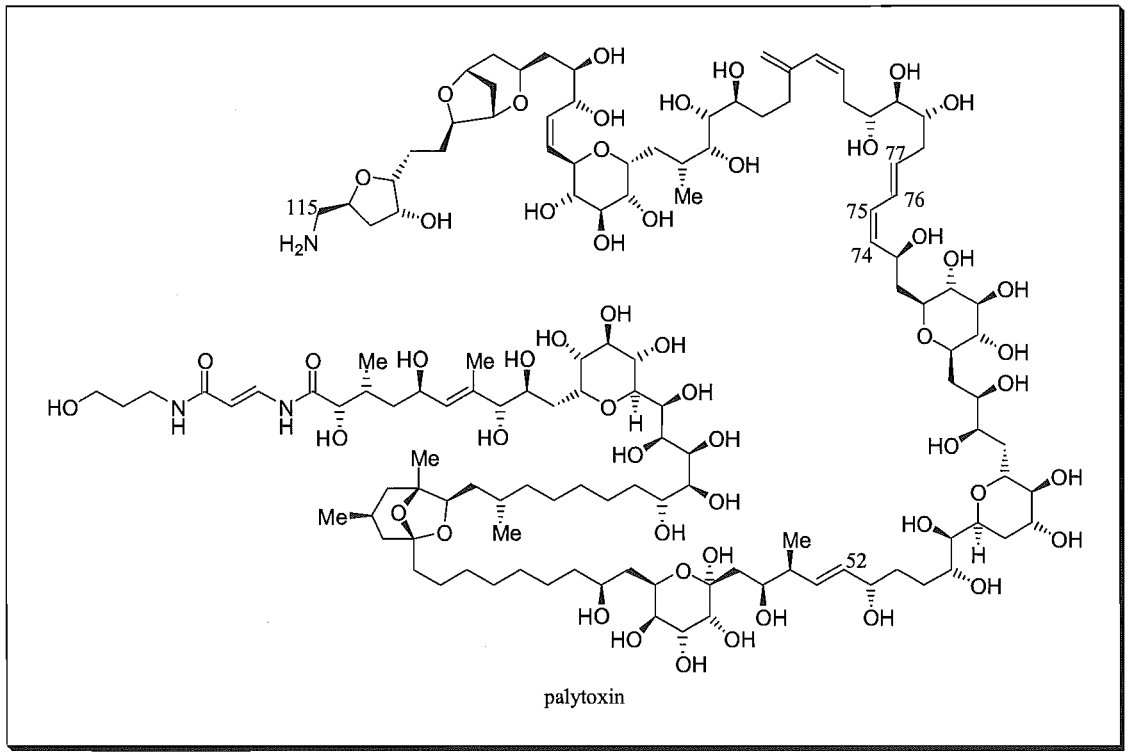
(*E,Z*)-Diene **1.86**, the sex pheromone of the European grapevine moth *Lobesia botrana*, was constructed by Cassani *et al. via* a Suzuki coupling.[84] Alkyne **1.87** was hydroborated with catecholborane[85] (see *Chapter 2*, section **2.2.4.1**) to form alkenyl boronic ester **1.88**, then coupled *in situ* with (*Z*)-1-iodobut-1-ene under Suzuki conditions to afford (*E,Z*)-diene **1.89**. Finally, acetylation of **1.89** gave **1.86** in 62% overall yield (**Figure 1.34**).



Reagents and conditions: (a) catecholborane, THF, 65 °C, 2 h; (b) (*Z*)-1-iodobut-1-ene, $Pd(PPh_3)_4$ (20 mol %), aq. NaOH, hexane, 65 °C, 2 h; (c) Ac_2O, pyridine [62 % yield overall, 99 % isomerically pure].

Figure 1.34 Cassani *et al.*'s synthesis of moth pheromone **1.86** *via* Suzuki-Miyaura coupling.

A modification of standard Suzuki-Miyaura coupling techniques for diene construction was amongst the many useful advancements made by Kishi *et al.* in their synthesis of palytoxin.[86] Produced by soft corals of *Palythoa* sp., this highly toxic and complex molecule presented a formidable challenge to synthetic chemists (*and to the ChemDraw™ skills of the author*).

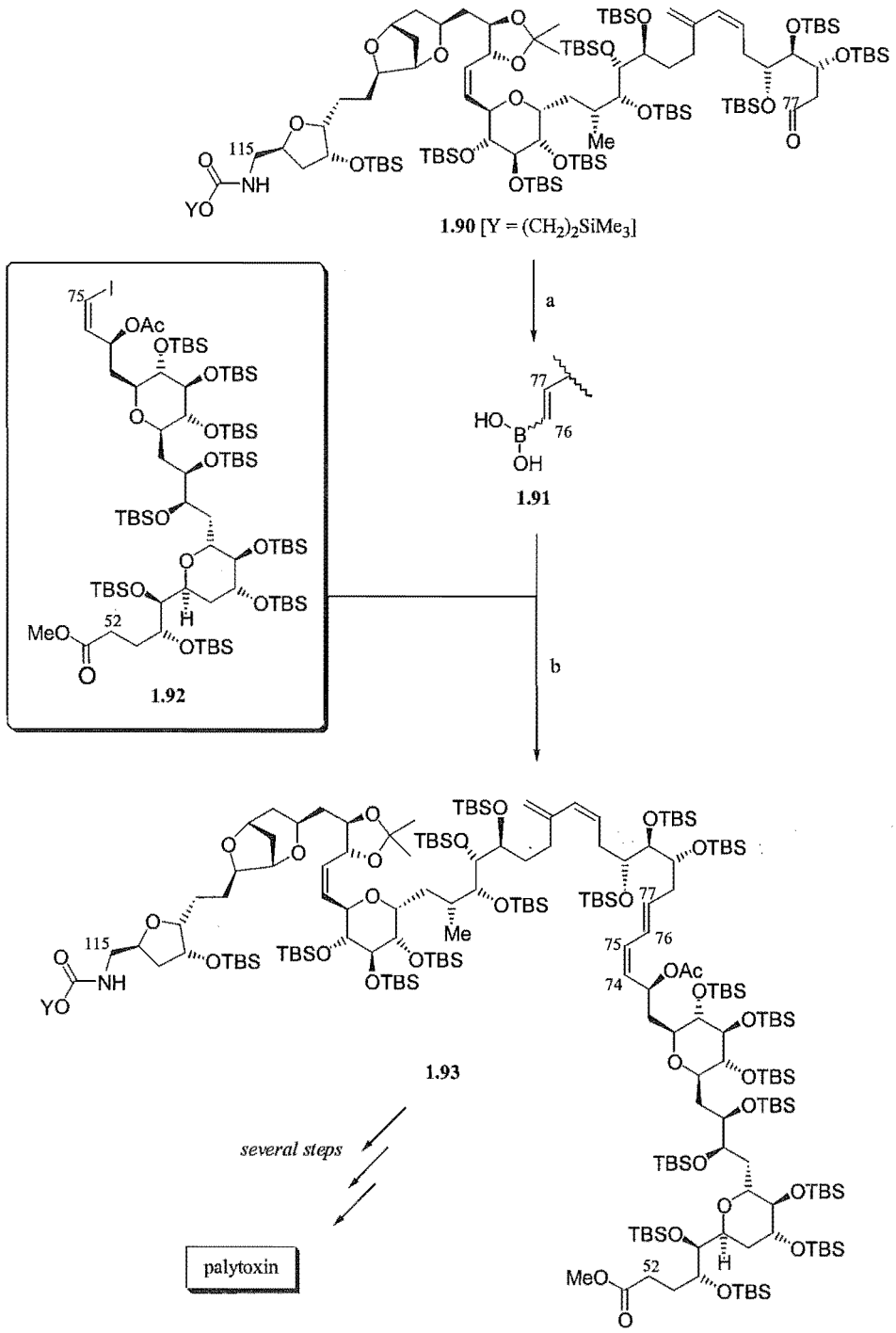


palytoxin

Central to the Kishi group's approach was construction of the C-74 – C-77 (*Z,E*)-diene moiety of palytoxin by coupling a vinyl boronic acid and a vinyl iodide under Suzuki-Miyaura conditions. Initial attempts to access the required boronic acid, *via* hydroboration of the appropriate terminal alkyne with catecholborane, were unsuccessful, with catecholborane preferentially attacking the C-115 carbamate group of the substrate instead. This problem was solved by utilising a different hydroboration method: treatment of aldehyde **1.90** with Matteson's reagent, $LiCH[B(OCH_2CH_2CH_2O)]_2$,[87] gave required (*E*)-vinyl boronic acid **1.91** with 8:1 to 10:1 stereoselectivity (**Figure 1.35**). Without purification, **1.91** was reacted with (*Z*)-vinyl iodide **1.92**, in the presence of thallium hydroxide (TlOH)* and $Pd(PPh_3)_4$, to give the desired (*E,Z*)-diene **1.93** in 70% overall yield from the alcohol precursor of **1.90**. Crucially,

* The investigators had discovered that the efficiency of Suzuki-Miyaura coupling between such large molecules was greatly improved by the use of this base instead of sodium alkoxide.[86a]

1.93 was stereochemically pure despite **1.91** not having been so, as the reaction rate for (*Z*,*Z*)-diene formation was much slower than that for (*Z*,*E*)-diene formation.



Reagents and conditions: (a) (i) $LiCH[B(OCH_2CH_2CH_2O)]_2$–TMEDA, THF, 0 °C; (ii) EtOAc, brine, 1 N HCl; (b) cat. $Pd(PPh_3)_4$, TlOH, THF [70 % overall yield from alcohol precursor to **1.90**].

Figure 1.35 Use of Suzuki-Miyaura coupling for (*Z*,*E*)-diene formation in palytoxin synthesis.

1.6.1.3 Alkenyl Stannanes

Organotin (or organostannane) compounds are easily synthesised by a variety of methods (not just *via* hydrometallation), are relatively stable to both air and moisture, react chemoselectively (such that protection of other functional groups within a given stannane is often unnecessary), whilst possessing enough reactivity to readily transmetallate to palladium. This balance of stability, reactivity, and accessibility is exploited to great effect in the Stille coupling reaction,[76] such that this reaction comprises over half of all current cross-coupling reactions.[88]

As mentioned at the beginning of this section, kinetic studies have shown transmetallation to be the rate-determining step of the Stille coupling cycle.[79] More fundamentally, Casado and Espinet have determined that (in the system they studied) transmetallation involves an *associative* L-for-R^2 substitution on Pd^{II},[79c] as opposed to the *dissociative* I-for-R^2 by mechanism apparently active in the system studied by Farina and Krishnan (and as depicted generally in **Figure 1.30**).[79b] In addition, Casado and Espinet have shown that the oxidative addition of R^1–I to Pd^0L_2 initially gives *cis*-$[R^1Pd^{II}L_2I]$ (**1.94**), followed by isomerisation to the *trans* isomer **1.95**,[74] a discovery which led to their revised mechanism[δ] for the Stille coupling cycle shown below (**Figure 1.36**).[79c] They propose that the associative transmetallation process occurs by an S_E2 (cyclic) mechanism, manifested *via* bridged intermediate $[R^1Pd^{II}L(\mu\text{-}I)(\mu\text{-}R^2)SnBu_3]$ (**1.96**), where the release of L required for the formation of **1.96** accounts for the impeding effect on the reaction caused by addition of excess L. The required *cis* relationship between R^1 and R^2 is fulfilled by **1.96**, which loses $ISnBu_3$ to form the three-coordinate $R^1Pd^I(L)R^2$ complex (**1.97**), which itself then readily eliminates coupling product R^1–R^2 and regains L to re-form the catalytic Pd^0L_2 species.

[δ] Casado and Espinet note that their proposal is not necessarily the only possible mechanism for the Stille coupling, and that other mechanisms may operate alongside or instead of it in reaction systems with highly coordinating solvents, chelating or very bulky ligands [see *Chapter 2*, section **2.2.4.4**, for an example of the oxidative addition of a *stannane* (as opposed to an organohalide or triflate) to a Pd^0–bidentate ligand complex], or in the absence of halide.[79c]

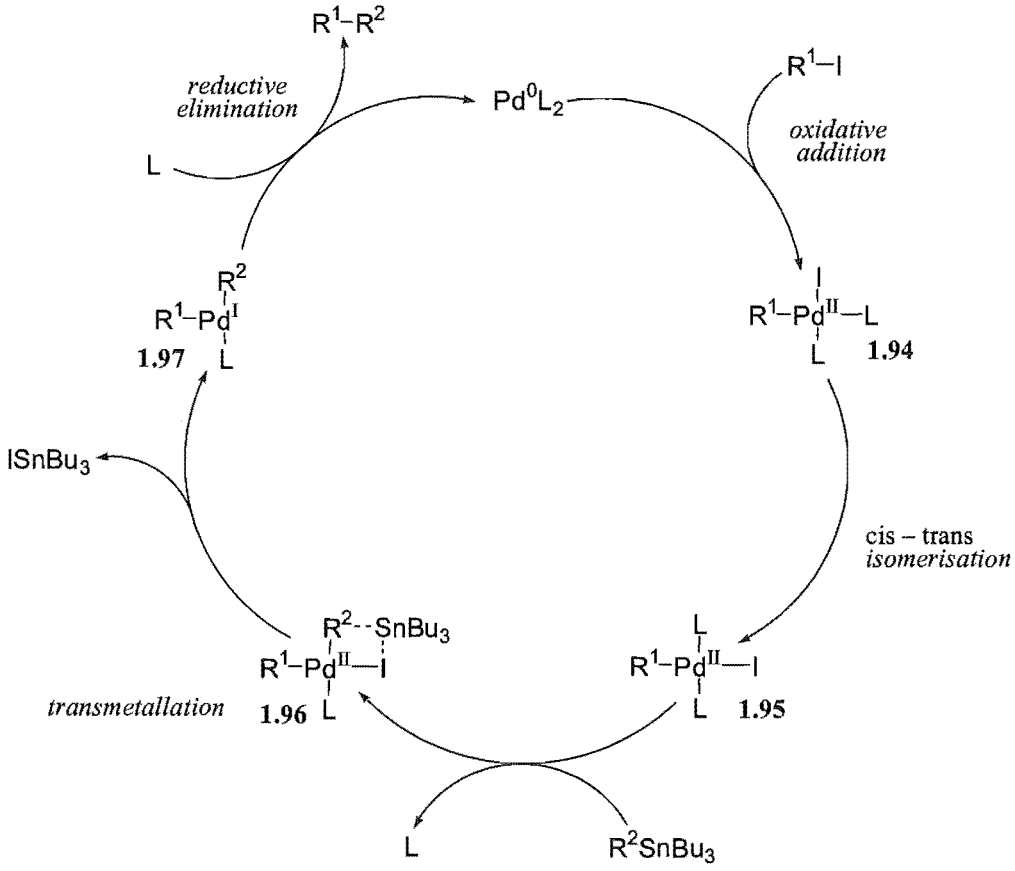
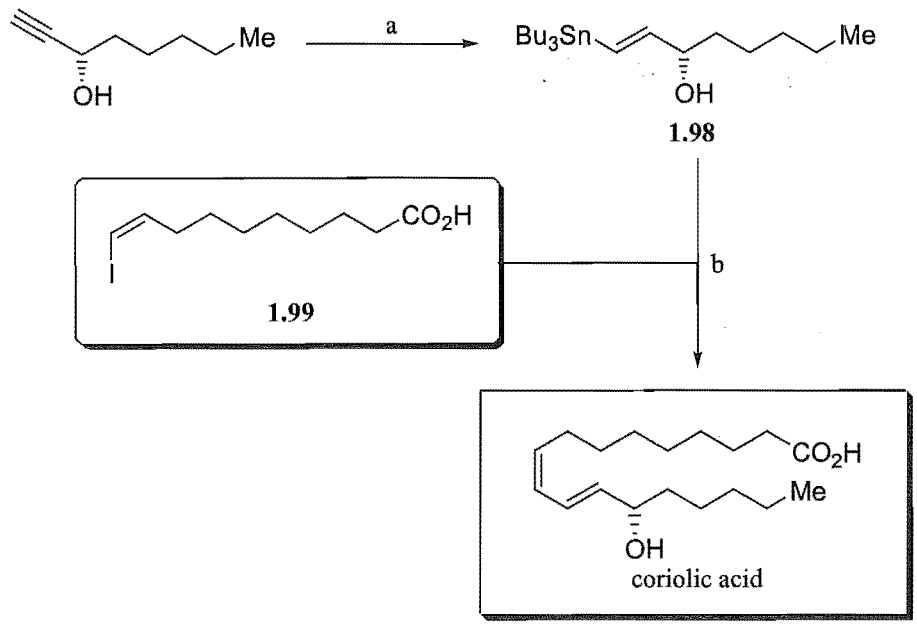


Figure 1.36 Casado and Espinet's revised mechanism for the Stille coupling (L = $AsPh_3$, R^1 = aryl, R^2 = aryl, vinyl).

The inherent toxicity of tin compounds is always a concern, as is the removal and disposal of tin residues. Different non-transferable ('dummy') ligands are sometimes used instead of butyl groups, with the most common being methyl groups, as such trimethyltin derivatives are often more reactive than their tributyltin analogues in Stille coupling methodologies,[89] and generate water-soluble residues which are easily removed from crude product mixtures. However, they are more difficult to synthesise and purify, much more toxic (toxicity being inversely proportional to length of the alkyl chains attached to the tin atom[90]), and undesired transfer (*i.e.* transmetallation) of one of the methyl groups can compete with desired transfer of the R group. Consequently, tributyl tin derivatives are usually preferred, although their non-polarity [and that of the tributyl tin residues they generate in (hydro)stannylations and Stille couplings] can make satisfactory purification of crude product mixtures on silica gel a laborious process (if distillation is not possible). Techniques for the removal of such residues

include C-18 (reverse phase) silica gel chromatography,[91] fluoride washes[76] or additives[92] (to form insoluble Bu_3SnF, which is removable by filtration), fluorous stannane reactants,[93] or acetonitrile–hexane washes (Bu_3SnCl is insoluble in the former but soluble in the latter).[94] Furthermore, in response to concerns about the environmental effects of triorganotin residues, especially in marine environments,[95] Salomon *et al.* have developed a method for the conversion of triorganotin residues into inorganic tin compounds of low toxicity.[96]

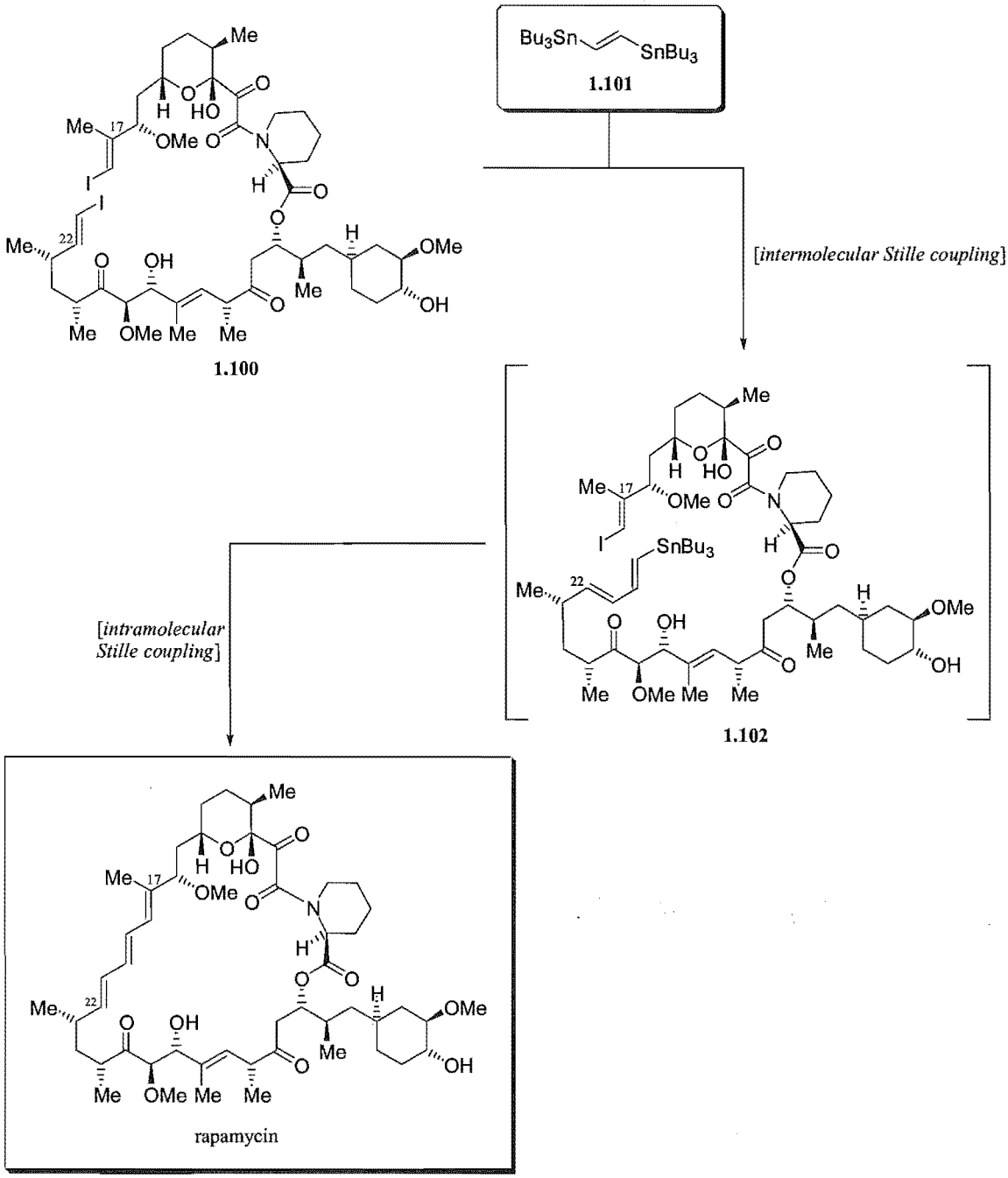
Alkenyl stannanes are often accessed from the corresponding alkyne *via* hydrostannylation (see *Chapter 2*, section **2.2.4.1**), and are commonly utilised in the synthesis of conjugated systems. Stille and Sweet's synthesis of coriolic acid,[97] a member of a family of self-defence substances from rice plants,[98] is one example (**Figure 1.37**). Radical hydrostannylation of (*S*)-1-octyn-3-ol gave vinyl stannane **1.98**, which was coupled with vinyl iodide **1.99** under Stille conditions to give coriolic acid in 76% yield. Noteworthy in this synthesis is the tolerance of free carboxylic acid and hydroxyl moieties, and the mildness of the reaction conditions. In contrast, Chan *et al.*[99] coupled the TBS ether of **1.98** with the methyl ester of **1.99** under Stille conditions, yet only obtained a 60% yield of protected coriolic acid, even after 4 days at 60 °C.



Reagents and conditions: (a) cat. AIBN, Bu_3SnH, 80 °C, 2 h;
(b) $Pd(MeCN)_2Cl_2$ (4 mol %), DMF, r.t., 8 h [76 % yield].

Figure 1.37 Stille and Sweet's synthesis of coriolic acid *via* Stille coupling.

A modified Stille coupling was fundamental to Nicolaou *et al.*'s total synthesis of rapamycin (**Figure 1.38**),[100] a complex macrocyclic antibiotic produced by the bacterium *Streptomyces hygroscopicus* which has also been synthesised by three other groups.[101] In Nicolaou *et al.*'s approach, an elegant tandem intermolecular – intramolecular Stille coupling reaction was used to furnish the molecule's conjugated (*E*,*E*,*E*)-triene moiety in one fell swoop (*as Nicolaou himself might put it*), in the ultimate, macrocyclisation step of the synthesis. Thus, a reaction between fully unprotected bis(vinyl iodide) **1.100** and (*E*)-vinyl stannane **1.101**[102] under Stille conditions introduced the final olefinic moiety, completing the C-17 – C-22 triene system and affording the natural product in 27% yield (together with ~30% unreacted **1.100** and ~30% of an intermediate presumed to be **1.102**, both of which were recycled) (**Figure 1.38**).



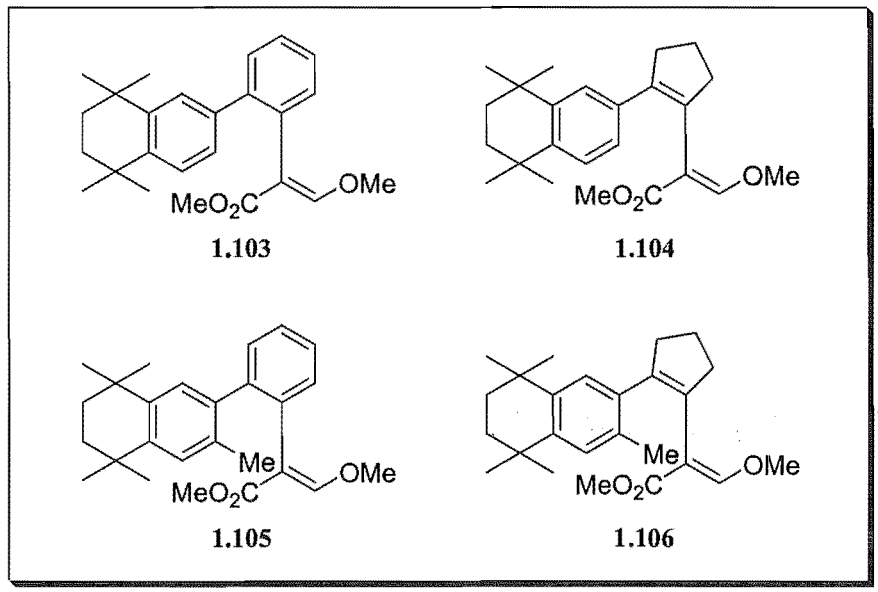
Reagents and conditions: $Pd(MeCN)_2Cl_2$ (20 mol %), $(i\text{-}Pr)_2NEt$, DMF/THF (2:1), r.t. [27 %].

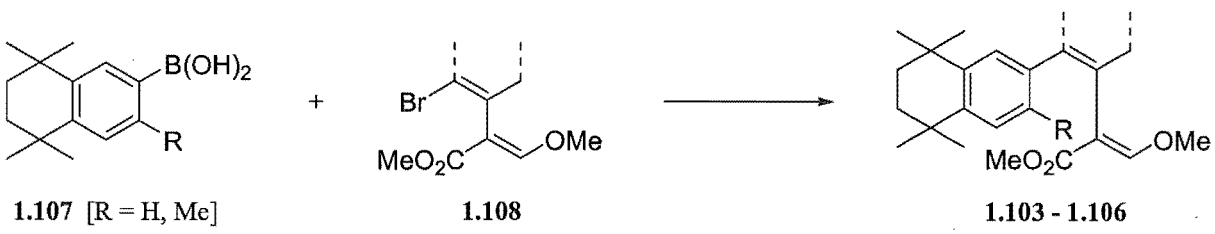
Figure 1.38 Stille coupling-based macrocyclisation in final step of Nicolaou *et al.*'s synthesis of rapamycin.

1.6.1.4 Palladium-Catalysed Couplings in Syntheses of Strobilurin Analogues

In addition to syntheses of the non-natural strobilurin fungicides (see section **1.4**), and some of the natural strobilurins (see section **1.5**), other research groups have applied the palladium-catalysed coupling techniques described in sections **1.6.1.1**, **1.6.1.2**, and **1.6.1.3** to the synthesis of several novel classes of strobilurin analogues.

Yue *et al.* prepared four double-bond locked (*i.e.* photostable) strobilurin analogues (**1.103-1.106**) *via* high-yielding Suzuki couplings between aryl boronic acids **1.107** and α-aryl or α-cyclopentyl (*E*)-β-methoxyacrylates **1.108** (**Figure 1.39**).[103]



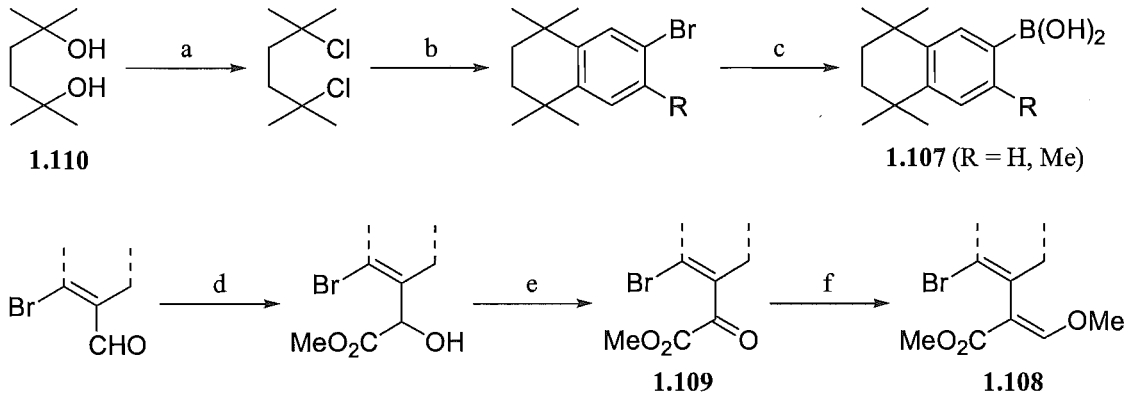


1.107 [R = H, Me] **1.108** **1.103 - 1.106**

Reagents and conditions: $Pd(PPh_3)_4$ (5 mol %), K_3PO_4, dioxane, reflux, 6 h [90-95 %].

Figure 1.39 Yue *et al.*'s synthesis of double-bond locked strobilurin analogues.

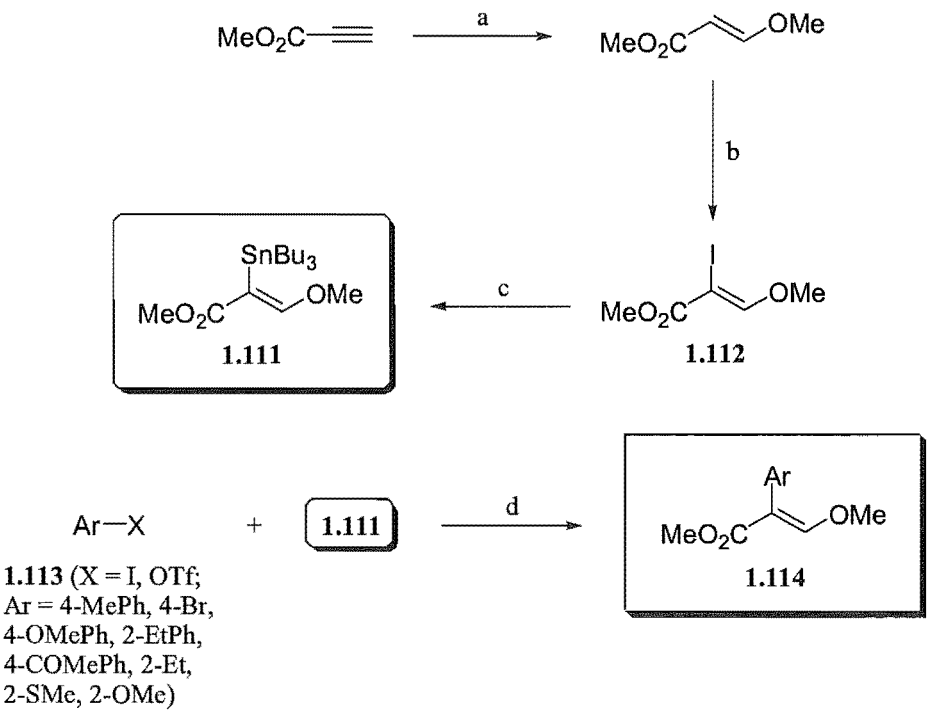
Acrylates **1.108** were constructed *via* α-ketoesters **1.109**, in a stepwise fashion analogous to that used by Beautement and Clough in their synthesis of strobilurin A (see **Figure 1.10**),[14] while boronic acids **1.107** were obtained in three efficient steps from diol **1.110** (**Figure 1.40**).



Reagents and conditions: (a) c. HCl, r.t. [84 %]; (b) bromobenzene *or* 2-bromotoluene, $AlCl_3$, CH_2Cl_2, r.t. [75 % (R = H), 87 % (R = Me)]; (c) (i) *t*-BuLi, –78 °C; (ii) $(i\text{-PrO})_3B$, r.t. then aq. HCl [94 % (R = H), 88 % (R = Me)]; (d) (i) *n*-BuLi, $CH(SMe)_3$, –78 °C; (ii) $HgCl_2$, HgO, aq. MeOH, r.t. [82 % (aryl), 85 % (cyclopentenyl)]; (e) MnO_2, CH_2Cl_2, r.t. [90 % (aryl), 95 % (cyclopentenyl)]; (f) $[Ph_3PCH_2OMe]Cl$, *n*-BuLi, THF, 0 °C [21 % (cyclopentenyl), 34 % (aryl)].

Figure 1.40 Yue *et al.*'s synthesis of Suzuki coupling partners **1.107** and **1.108**.

In another investigation, Hodgson and co-workers incorporated the toxophoric (*E*)-β-methoxyacrylate moiety of the strobilurins directly into analogues,[104] rather than assembling it in a stepwise fashion (a methodology hitherto *de rigueur* in both natural and unnatural strobilurin syntheses). Thus, trisubstituted vinyl stannane **1.111** was prepared in four high-yielding steps from methyl propynoate, with the tributylstannyl group being introduced by treating iodoacrylate **1.112** with bis(tributyltin) under palladium catalysis, based on the methodology developed by Azizian *et al.* (**Figure 1.41**).[105] Stannane **1.111** was then reacted with various aryl iodides and triflates **1.113**, under Farina *et al.*'s modified Stille conditions,[106] to afford stereoisomerically pure (*E*)-α-aryl-β-methoxyacrylates **1.114** in yields ranging from 55 to 92%.



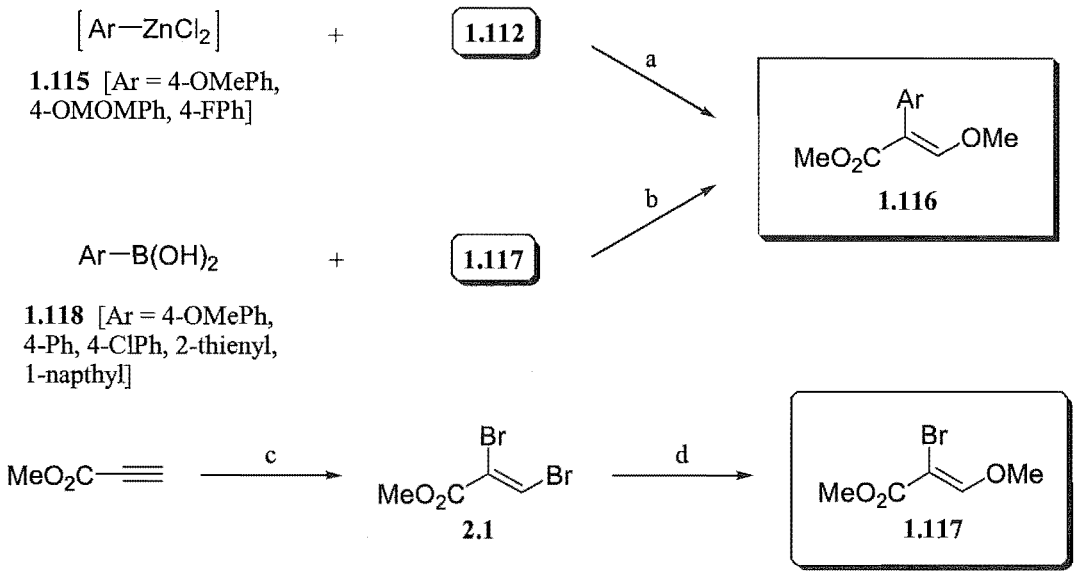
Reagents and conditions: (a) NEt_3, MeOH, Et_2O, r.t., 12 h [90 %]; (b) (i) *N*-iodosuccinimide, AcOH, $CHCl_3$, r.t., 24 h; (ii) NEt_3, CH_2Cl_2, reflux, 3 h [95 %]; (c) $(SnBu_3)_2$, cat. $Pd(PPh_3)_4$, toluene, reflux, 48 h [83 %]; (d) Pd_2dba_3 (8 mol %), $AsPh_3$ (22 mol %), CuI, NMP, 50 °C, 48 h [55-92 %].

Figure 1.41 Hodgson *et al.*'s approach to strobilurin analogues.

Rossi *et al.* extended the methodology of Hodgson *et al.*, utilising iodoacrylate **1.112** in palladium-catalysed couplings with aryl zinc chlorides **1.115**‡ to give stereoisomerically pure (*E*)-α-aryl-β-methoxyacrylates **1.116** in 35-76% yield (**Figure 1.42**).[107] In addition, they synthesised bromoacrylate **1.117**, a less synthetically (and financially – no *N*-iodosuccinimide required) demanding analogue of **1.112**. Although **1.117** was unreactive when combined with 4-methoxyphenyltributylstannane under Farina's Stille conditions,[106] and afforded only poor yields (< 25%) of coupling product with 3,4-dimethoxyphenylzinc chloride, it did couple

‡ Prepared as suspensions in THF by treating solutions of the corresponding arylmagnesium chlorides with dry $ZnCl_2$ at 0 °C.[107]

efficiently with aryl boronic acids **1.118** under Suzuki conditions, giving 50-74% yields of acrylates **1.116**.

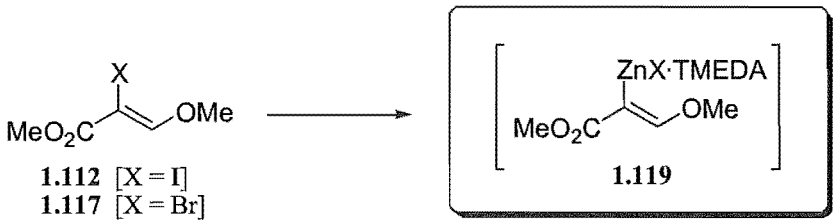


Reagents and conditions: (a) $Pd(PPh_3)_4$ (5 mol %) or $Pd(OAc)_2$ (5 mol %), $AsPh_3$ (10 mol %), THF, r.t., 25-94 h [35-76 %]; (b) $Pd(PPh_3)_4$ (3-5 mol %), K_3PO_4, dioxane, 80 °C, 30-116 h [50-74 %]; (c) Br_2, CCl_4, 70 °C, 1 h; (d) Bu_3SnOMe, $Pd(PPh_3)_4$ (5 mol %), NMP, r.t., 96 h [63 %].

Figure 1.42 Rossi *et al.*'s first approaches to strobilurin analogues.[*]

In a 1998 publication, Rossi *et al.* further developed the utility of organozinc compounds, this time using the acrylate moiety as the organometallic species.[108] Treatment of acrylates **1.112** and **1.117** with an excess of Zn–Ag couple, in a solution of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in THF, afforded stable solutions of TMEDA-complexed organozinc halides **1.119**, compounds which were presumed to adopt a chelate structure such as **1.119a** (**Figure 1.43**).

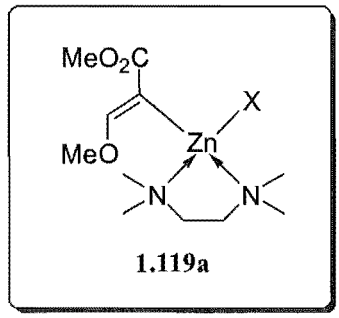
[*] See *Chapter 2* for a similar synthesis of vinyl bromide **2.1** (**Figure 2.2**), and its utilisation in diene synthesis (section **2.2.4.1**, *passim*).



1.112 [X = I]
1.117 [X = Br]

1.119

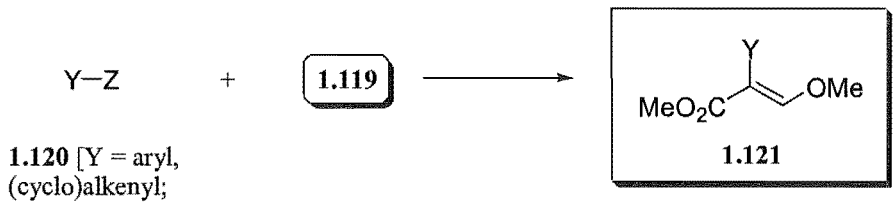
Reagents and conditions: Zn(Ag), TMEDA, TMSCl, THF, 20-70 °C, 7 h [95-98 %].



1.119a

Figure 1.43 Rossi *et al.*'s synthesis of TMEDA-complexed organozinc halides **1.119**.

Reaction of **1.119** with aryl and (cyclo)alkenyl halides or triflates **1.120** afforded α-aryl, α-alkenyl, and α-cyclopentenyl acrylates **1.121** in 20-98% yield (**Figure 1.44**).[108]



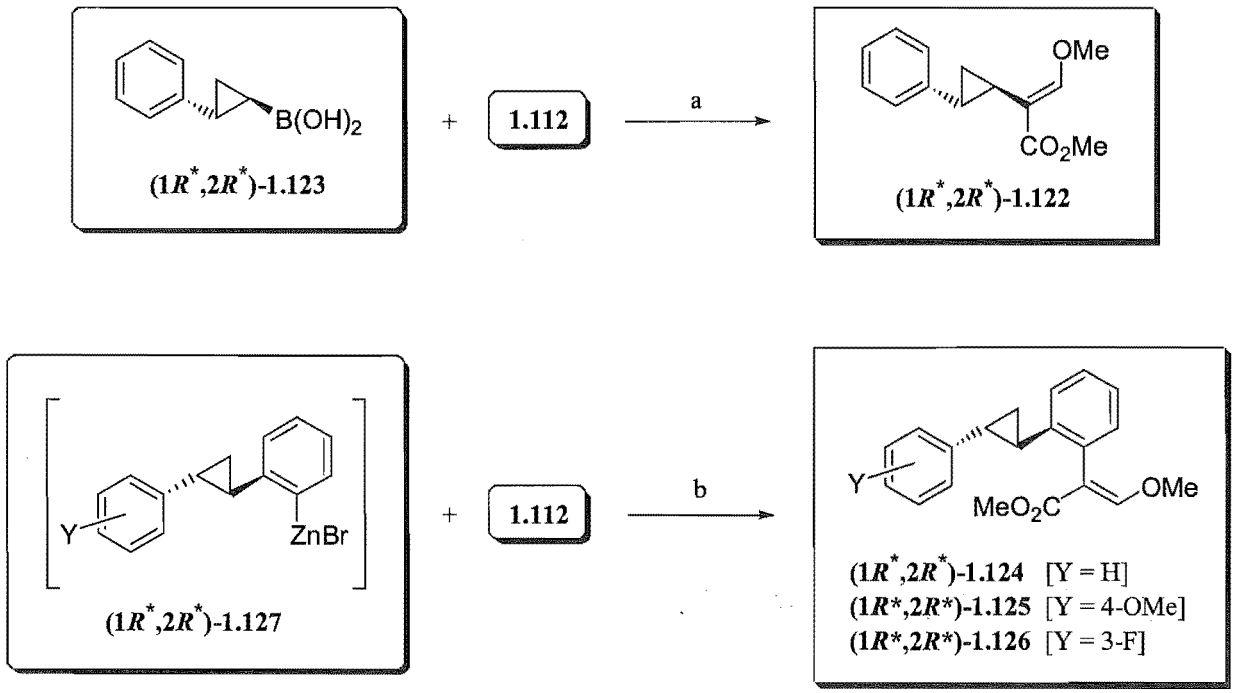
1.120 [Y = aryl, (cyclo)alkenyl; Z = Br, I, OTf]

1.121

Reagents and conditions: $Pd(PPh_3)_4$ (5 mol %), THF, 50-65 °C, 6-50 h [20-98 %].

Figure 1.44 Rossi *et al.*'s organozinc halides **1.119** in synthesis of strobilurin analogues.

Most recently, Rossi *et al.* have synthesised four optically active strobilurin analogues.[109] **(1*R**,2*R**)-1.122**‡ was obtained in 90% yield *via* a Suzuki coupling between iodoacrylate **1.112** and boronic acid **(1*R**,2*R**)-1.123**, whilst **(1*R**,2*R**)-1.124**, **1.125** and **1.126** were formed efficiently *via* couplings between **1.112** and arylcyclopropylzinc bromides **(1*R**,2*R**)-1.127** (**Figure 1.45**). The *trans*-1,2-disubstituted cyclopropane ring in the hydrophobic backbone of these strobilurins restricts their conformation in a manner similar to the arylphenyl or arylcyclopentyl strobilurin analogues of Yue *et al.* (see **Figure 1.39**).[103]

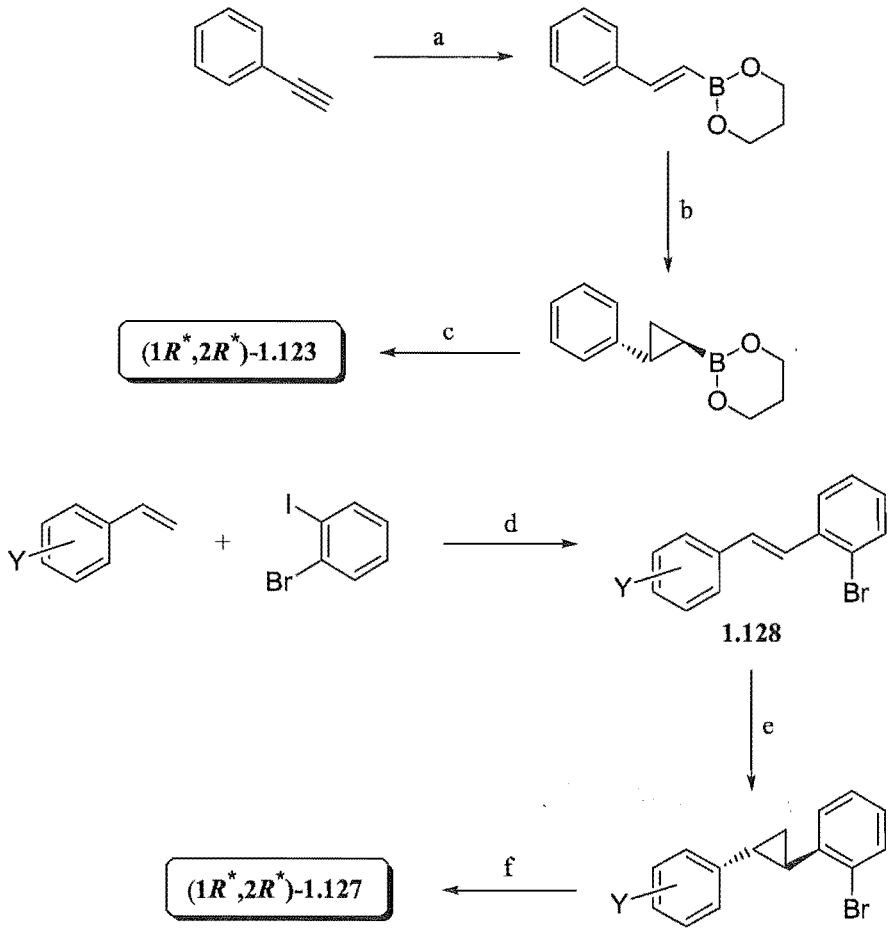


Reagents and conditions: (a) $Pd(PPh_3)_4$ (4 mol %), K_3PO_4, toluene, reflux, 20 h [90 %];
(b) $Pd(PPh_3)_4$ (5 mol %), THF, r.t., 70-96 h [68-80 %].

Figure 1.45 Rossi *et al.*'s synthesis of arylcyclopropyl strobilurins from arylzinc chlorides.

‡ The asterisks in the (**1*R**,2*R****) prefix indicate that the two stereogenic centres have the same ***relative*** configurations [which may or may not (!) be the same as their respective ***absolute*** configurations).

Boronic acid **(1*R**,2*R**)-1.123** was itself synthesised from phenylacetylene in an hydroboration–cyclopropanation–hydrolysis sequence, whilst zinc bromides **(1*R**,2*R**)-1.127** were derived from Heck coupling products **1.128** *via* cyclopropanation, Grignard formation and zincation **(Figure 1.46)**.[109]

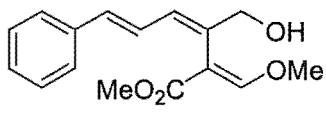


Reagents and conditions: (a) (i) catecholborane, 70 °C, 8 h; (ii) H_2O, r.t., 5 h; (iii) 1,3-propanediol, pentane, r.t., 1.5 h; (iv) distillation [71 % over four steps]; (b) CH_2N_2, $Pd(OAc)_2$ (4 mol %), Et_2O, 0 – 5 °C, 50 min [96 %]; (c) (i) 1.5N KOH, r.t., 80 min; (ii) 2N HCl, 0 °C [93 % over two steps]; (d) $Pd(OAc)_2$ (4 mol %), NEt_3, CH_3CN, reflux, 24 h [71-85 %]; (e) (i) $CF_3CO_2ZnCH_2I$, CH_2Cl_2, r.t., 6-98 h; (ii) H_3O^+ [48-52%]; (f) (i) Mg, THF, reflux, 4 h; (ii) $ZnBr_2$, THF, 0 °C, 15 h.

Figure 1.46 Rossi *et al.'s* synthesis of four arylcyclopropyl zinc chlorides.

1.7 Work Described in this Thesis

The examples in the previous sections fittingly illustrate the fundamental role that palladium-catalysed couplings of organometallic compounds with vinyl halides play in the stereoselective and regioselective syntheses of the conjugated diene and triene systems of natural products and their analogues. This thesis will describe the utilisation of such techniques in a stereoselective approach to hydroxystrobilurin A (**1.129**), which, at the time of writing, constituted both the first known use of Pd-catalysed coupling methodologies to construct the strobilurin triene system, and the first known total syntheses of this natural product.



Hydroxystrobilurin A (**1.129**)

The retrosynthetic analysis below (**Figure 1.47**) outlines the basis of two such palladium-catalysed coupling-based approaches to **1.129**, with the key points being its:

- exploitation of the methodology developed by Hodgson *et al.*[104] and Rossi *et al.*[107] for introduction of the (*E*)-β-methoxyacrylate unit (**C**) in one step;
- flexibility, with the potential for either partner in the coupling reactions required to form the bonds at disconnection points *a*, *b*, or *c* (**Figure 1.47**) to serve as the organometallic species;
- possibility for modification to create potential pathways to other natural strobilurins, such as 9-methoxystrobilurins A and K, by appropriate elaboration of synthons **A** and **B**.

Accordingly, the synthesis of various forms of key fragments **B**, **C**, and **D** will be described, together with explorations of their utility in a palladium-catalysed coupling approach to **1.129** (*Chapter 2*). Preliminary investigations of the application of this methodology to syntheses of 9-methoxystrobilurins A and K (see **Figure 1.4**) and of another (non-strobilurin) natural product will also be described (*Chapter 4*).

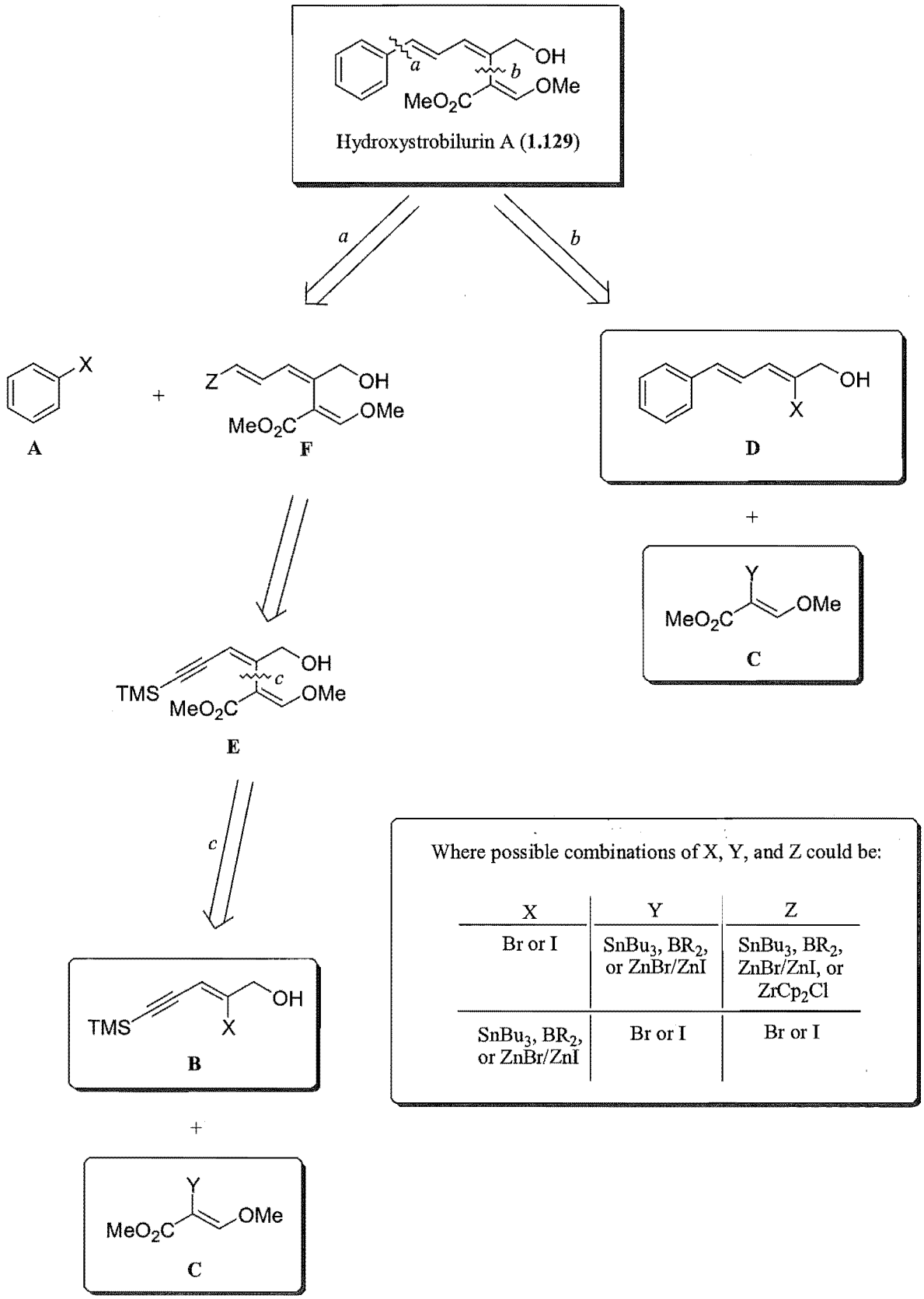


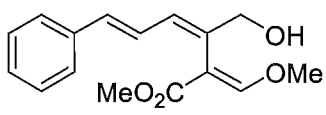
Figure 1.47 Retrosynthetic analysis of hydroxystrobilurin A (**1.129**).

CHAPTER TWO

Total Synthesis of Hydroxystrobilurin A

2.1 Introduction

The isolation, structural elucidation, and biological activity of hydroxystrobilurin A (**1.129**) was reported by Steglich and co-workers in 1995.[110] In addition to typical strobilurin signals, the IR spectrum of **1.129** contained a broad band from 3630 to 3100 cm^{-1}, indicative of the O–H stretching absorption of an hydroxyl group. Signals at δ 4.25 in the ^{1}H NMR spectrum and δ 66.8 in the ^{13}C NMR spectrum confirmed the presence of an hydroxymethylene group, while the rest of the NMR and mass spectral data correlated well with that reported for strobilurin A,[10] 9-methoxystrobilurin A,[111] and hydroxystrobilurin D.[67]



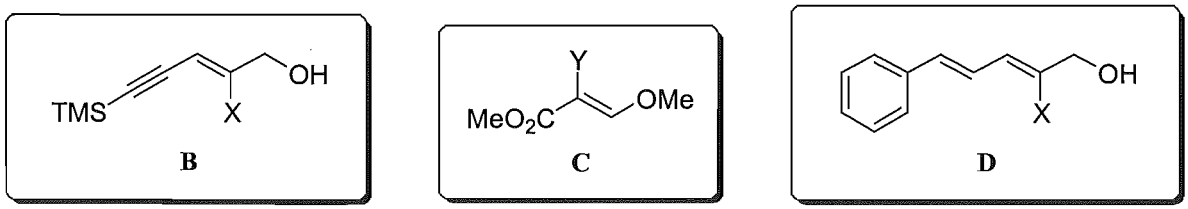
Hydroxystrobilurin A (**1.129**)

The culture of the organism from which it was isolated, a *Pterula* sp. specimen collected from a forest in Germany, also yielded strobilurin A and oudemansin A (see *Chapter 1*, **Figure 1.2**). Hydroxystrobilurin A was observed to have much weaker antifungal activity compared to strobilurin A, with the hydroxyl group of the former compound (being the only difference between the two) evidently the reason for this. This lack of biological activity compared to other members of the strobilurin family may be why hydroxystrobilurin A has not been the target of any syntheses in the literature thus far.

2.2 Synthetic Approaches to Hydroxystrobilurin A

The two primary retrosynthetic disconnections of hydroxystrobilurin A depicted in **Figure 1.47** (see *Chapter 1*), designated *a* and *b*, reveal β-methoxyacrylate **C** and either enyne **B** or diene **D** as key intermediates required for two possible palladium-catalysed coupling approaches to this natural product. The commonality of **C** to both pathways made the synthesis

of various forms of this β-methoxyacrylate a logical point at which to begin synthetic investigations.



2.2.1 Syntheses of β-Methoxyacrylates C

By reference to the work of Hodgson *et al.* (see *Chapter 1*, **Figure 1.41**)[104] and Rossi *et al.* (see *Chapter 1*, **Figure 1.42**),[107] it was apparent that β-methoxyacrylates **1.117**, **1.111**, and **1.112** should be available *via* the following sequence (**Figure 2.1**). Clearly, (*Z*)-dibromide **2.1** was fundamental for access to this pathway.

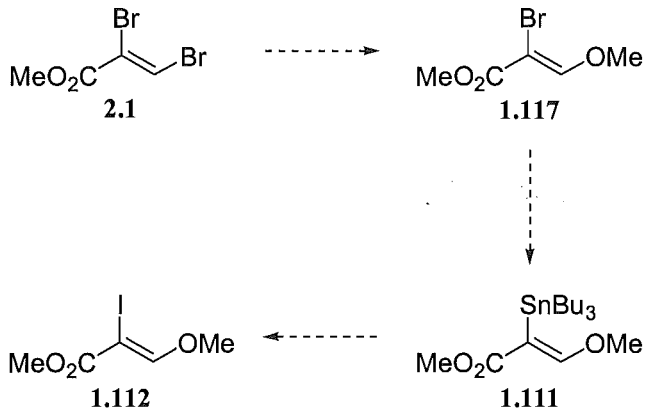
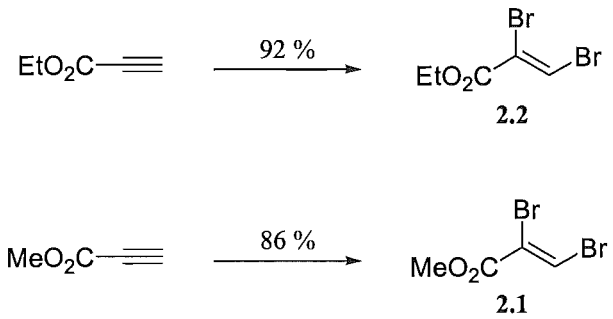


Figure 2.1 Possible synthetic sequence for access to key β-methoxyacrylates.

An *Organic Syntheses* procedure by Myers and Dragovich describes an efficient method for the synthesis of (*Z*)-dibromide **2.2** *via* dibromination of commercially available ethyl propynoate (**Figure 2.2**),[112] a transformation originally reported by Hall and Trippett.[113] Similarly, as mentioned above, Rossi *et al.* have reported that (*Z*)-dibromide **2.1** is analogously accessible from methyl propynoate.[107] With this knowledge, and with reference to the

procedure of Myers and Dragovich,[112] **2.1** was generated in 86% yield from methyl propynoate (**Figure 2.2**).

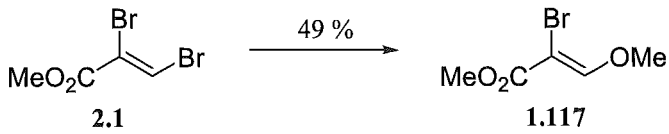


Reagents and conditions: Br_2, CCl_4, 70 °C, 30 min.

Figure 2.2 Synthesis of (*Z*)-dibromide **2.1**, analogous to Myers and Dragovich's synthesis of **2.2**.[†]

Next, **2.1** was converted to β-methoxyacrylate **1.117**, using the conditions of Rossi *et al.* (see *Chapter 1*, **Figure 1.42**).[107] Thus, reaction of **2.1** with tributyltin methoxide (Bu_3SnOMe), under palladium catalysis, afforded **1.117** in a moderate yield (49 %) [**Figure 2.3**], presumably *via* an oxidative addition – transmetallation – reductive elimination sequence analogous to that depicted in **Figure 1.30** (see *Chapter 1*). Interestingly, the chemical shift of the signal representing one of the groups of methoxide protons of **1.117** (δ_H 3.80) differed from the reported value (δ_H 3.60).[107] It is possible this discrepancy was due to a transcription error during the printing of Rossi *et al.*'s original data; however, the rest of their data was consistent with that for **1.117**.

[†] The wholly (*Z*) geometry of **2.1** and **2.2** indicates that, under these conditions, bromine adds to alkynes *via* a free radical mechanism; if the mechanism was electrophilic, significant amounts of the (*E*)-isomer would also be formed.



2.1 **1.117**

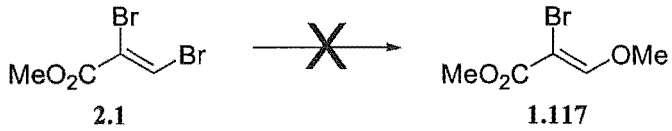
Reagents and conditions: Bu_3SnOMe, $Pd(PPh_3)_2Cl_2$ (5 mol %), NMP, r.t., 3 d.

Figure 2.3 Synthesis of β-methoxyacrylate **1.117**.

Numerous attempts were made to achieve a yield of **1.117** closer to that reported by Rossi *et al.* (63%).[107] Experiments were conducted with a different catalyst [$Pd(PPh_3)_2Cl_2$ instead of $Pd(PPh_3)_4$], and/or a greater excess of Bu_3SnOMe (1.30 equivalents instead of 1.15 equivalents), and/or a longer reaction time (13 days instead of 3 days), and/or on a larger scale (75.0 mmol instead of 4.0 mmol), however none of these modifications had a significant effect upon the efficiency of the process. The presence of small amounts of starting material in the ^1H NMR spectra of some crude reaction mixtures was noted, but did not correlate with the magnitude of the yield obtained. The palladium complexes were freshly prepared and of high purity, as was the starting material, so the possibility remains that, despite increases in the amount of Bu_3SnOMe having no effect on the efficiency of the reaction (*vide supra*), this reagent requires purification immediately prior to being used. Indeed, a more comprehensive publication by the authors does stipulate that freshly distilled Bu_3SnOMe was used (presumably to remove any $Bu_3SnOSnBu_3$ present).[114]

With the separation of **1.117** from tributyltin by-products being a laborious process, it was thought prudent to determine if sodium methoxide/methanol could replace Bu_3SnOMe in the transformation of **2.1** to **1.117**. However, although starting material was consumed, the NMR spectra of the product showed it was not the desired compound.[§] In particular, the ^1H NMR spectrum contained two apparent tertiary alkyl proton doublets instead of the olefinic proton signals of **1.117**, and an extra methoxy group signal (**Figure 2.4**).

[§] This result is consistent with Rossi *et al.*'s finding that sodium alkoxides were unsatisfactory reagents for processes exemplified by the conversion of **2.1** into **1.117**.[114]



2.1 **1.117**

Reagents and conditions: NaOMe/MeOH, 0 °C – r.t., 12 h.

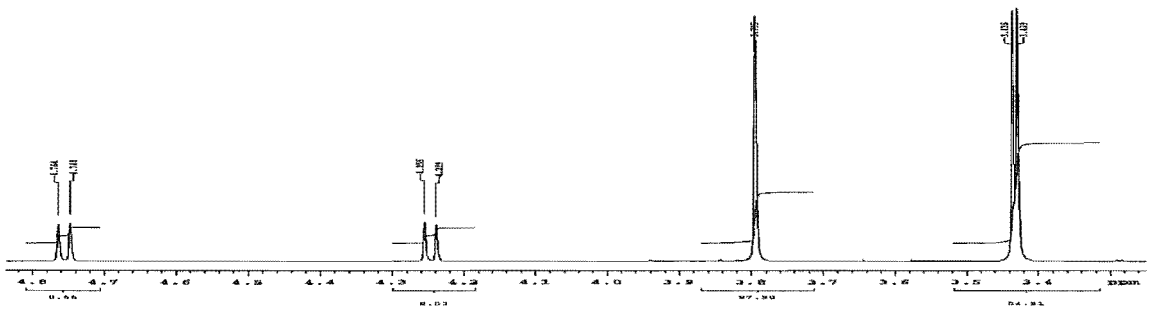
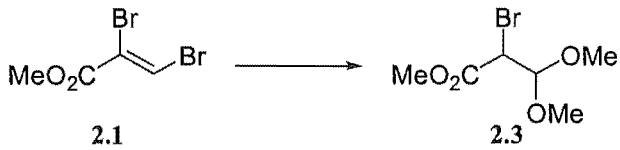


Figure 2.4 500 MHz ^{1}H NMR spectrum of unknown product formed by treatment of **2.1** with NaOMe/MeOH.

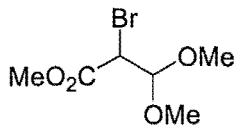
The ^{13}C NMR spectrum of the product indicated a carbonyl group was present, and mass spectroscopy gave an apparent molecular formula of $C_5H_8O_3Br$. These results were consistent with β-acetal propanoate **2.3** (**Figure 2.5**) being the identity of this unexpected product (with loss of methoxide from **2.3** during mass spectral analysis accounting for the observed molecular formula). This proposal is supported by comparison of the proton chemical shifts of proposed structure **2.3** with those reported by Doyle and Trudell for the similar β-acetal **2.4** (**Figure 2.6**).[115]



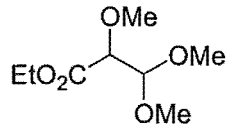
2.1 **2.3**

Reagents and conditions: NaOMe/MeOH, 0 °C – r.t, 12 h.

Figure 2.5 Proposed identity of unexpected product **2.3**.



2.3



2.4

Compound	^{1}H Chemical Shift Values (ppm)
2.3	3.43, 3.44, 3.80, 4.25, 4.76
2.4	1.31, 3.41, 3.44, 3.45, 3.84, 4.26, 4.54.

Figure 2.6 Comparison of ^{1}H NMR data of proposed structure **2.3** with that of related compound **2.4**.

A possible mechanism for the formation of **2.3** is shown in **Figure 2.7**: in the absence of palladium, methoxide may add in a double conjugate addition fashion to **2.1** to give **2.3**.

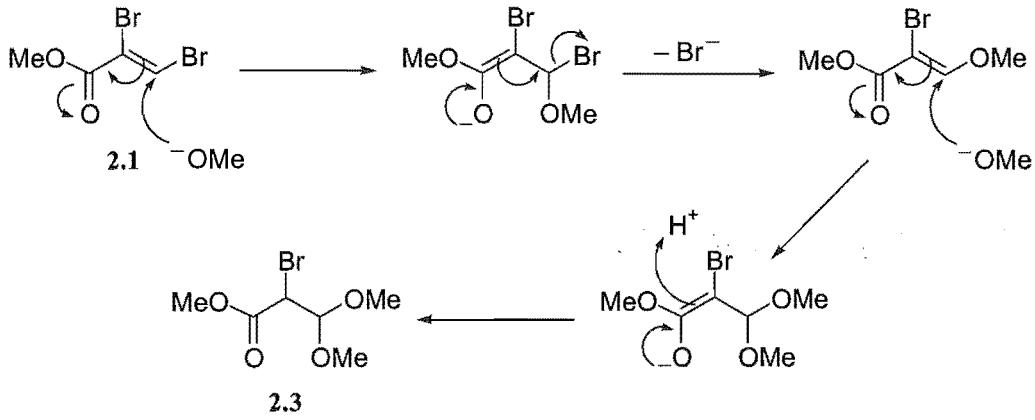
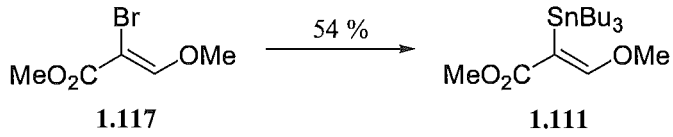


Figure 2.7 Possible mechanism for the formation of **2.3** from **2.1**.

The conversion of bromoacrylate **1.117** into stannylacrylate **1.111** was conducted *via* Hodgson *et al.*'s method.[104] Thus, **1.117** was treated with bis(tributyltin) [$(SnBu_3)_2$] under palladium catalysis to afford a 54% yield of **1.111** (**Figure 2.8**). Hodgson *et al.* mention obtaining similarly moderate yields for this transformation, and found greater success (83% yield) by using iodoacrylate **1.112** instead of **1.117** (see *Chapter 1*, **Figure 1.41**). However, in

this work, the more economical route (avoiding the need for *N*-iodosuccinimide) in **Figure 2.8** was preferred.



1.117 **1.111**

Reagents and conditions: $(SnBu_3)_2$, $Pd(PPh_3)_2Cl_2$ (5 mol %), toluene, dark, reflux, 48 h.

Figure 2.8 Synthesis of stannylacrylate **1.111**.

Hodgson *et al.* were able to confirm the (*Z*) geometry of **1.111** in two ways: by comparison of its $^3J_{Sn-alkenyl\ H}$ values with those for other $SnBu_3$-substituted acrylates and enol ethers of known configuration,[116] and by comparison of its δ_H (=CH) value (7.84) with values calculated from substituent constants for $SnBu_3$ [6.94 (*E*-isomer), 8.17 (*Z*-isomer)] and reported for (*E*)- and (*Z*)-2-(tributylstannyl)-2-butenoates.[116a]

A mechanism for palladium-catalysed processes exemplified by the conversion of **1.117** to **1.111** was proposed by Azizian *et al.*,[105] whereby oxidative addition of $(SnBu_3)_2$ and the RBr to the palladium(II) complex forms an unstable palladium(IV) complex, from which organostannane ($RSnBu_3$) and Bu_3SnBr are reductively eliminated (**Figure 2.9**).

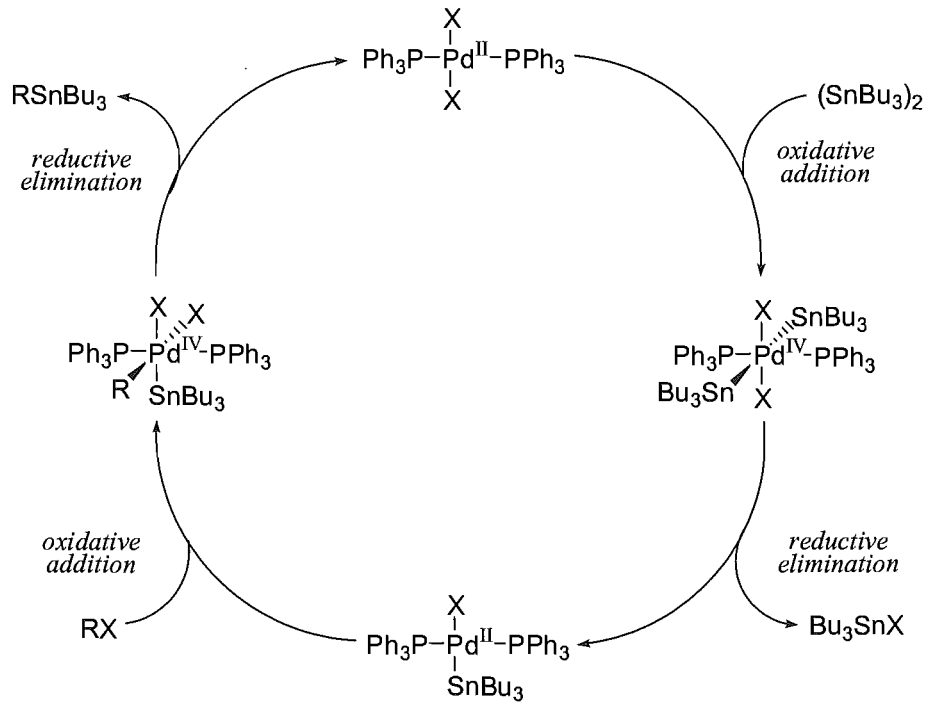
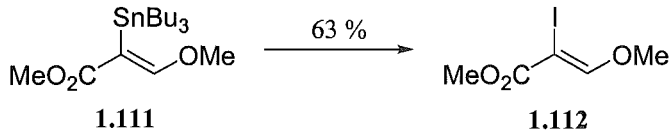


Figure 2.9 Mechanism for Pd-catalysed conversion of RX to $RSnBu_3$ (X = halide).

The final acrylate compound to be synthesised, iodoacrylate **1.112**, was formed by iododestannylation of stannane **1.111** (**Figure 2.10**). The method employed was based on rather sparse experimental details reported by Hodgson *et al.*,[104] and although a good yield (63%) was obtained, with CH_2Cl_2 as the solvent (rather than Et_2O as used by Hodgson *et al.*, which gave lower yields), it was significantly lower than the 95% yield reported by these workers. Only one product and no starting material was visible in both TLC and ^1H NMR analyses of the crude product mixture following the prescribed period of reaction, which seemed to rule out the possibility that failure to go to completion or side product formation was responsible for this relative lack of efficiency. Perhaps, being an iodide (and despite being crystalline), **1.112** was sufficiently volatile to partially evaporate under vacuum?

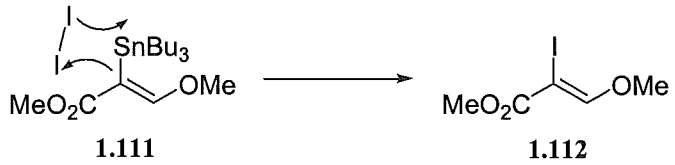


1.111 **1.112**

Reagents and conditions: I_2, CH_2Cl_2, 0 °C, 2 h.

Figure 2.10 Synthesis of iodoacrylate **1.112**.

The (*Z*) geometry of **1.112** is supported by the fact that iododestannylation is known to normally occur with retention of configuration.[117] March and Smith note that although there appears to be no single mechanism by which such halodemetallation processes occur, stereochemical outcomes can often implicate possible mechanisms.[118] In this case, the fact that retention of configuration is observed suggests that this bimolecular electrophilic substitution reaction may proceed *via* an S_Ei mechanism (**Figure 2.11**).[ϕ]



1.111 **1.112**

Figure 2.11 Possible S_Ei mechanism for iododestannylation of **1.111** to **1.112**.

2.2.2 Investigation of Enyne Route

Having gained access to the required group of β-methoxyacrylates **C**, it was decided to begin investigation of the enyne route to hydroxystrobilurin A suggested by the retrosynthesis in **Figure 1.47** (see *Chapter 1*). This required the synthesis of an enyne alcohol **B**, whose reaction with **C** to form ynediene **E** was the initial carbon-carbon bond-forming step in the proposed enyne-based synthesis (**Figure 2.12**). The final two steps would be desilylation of **E**, followed by hydrometallation or hydrometallation and halogenation to triene **F**, and then a coupling of **F** and arene **A** to afford the natural product. Some insight into the potential for adaptation of this approach to a synthesis of 9-methoxystrobilurins A or K might also be provided by exploration of this route (see *Chapter 4*).

[ϕ] Where: S = substitution, $_E$ = electrophilic, i = internal.

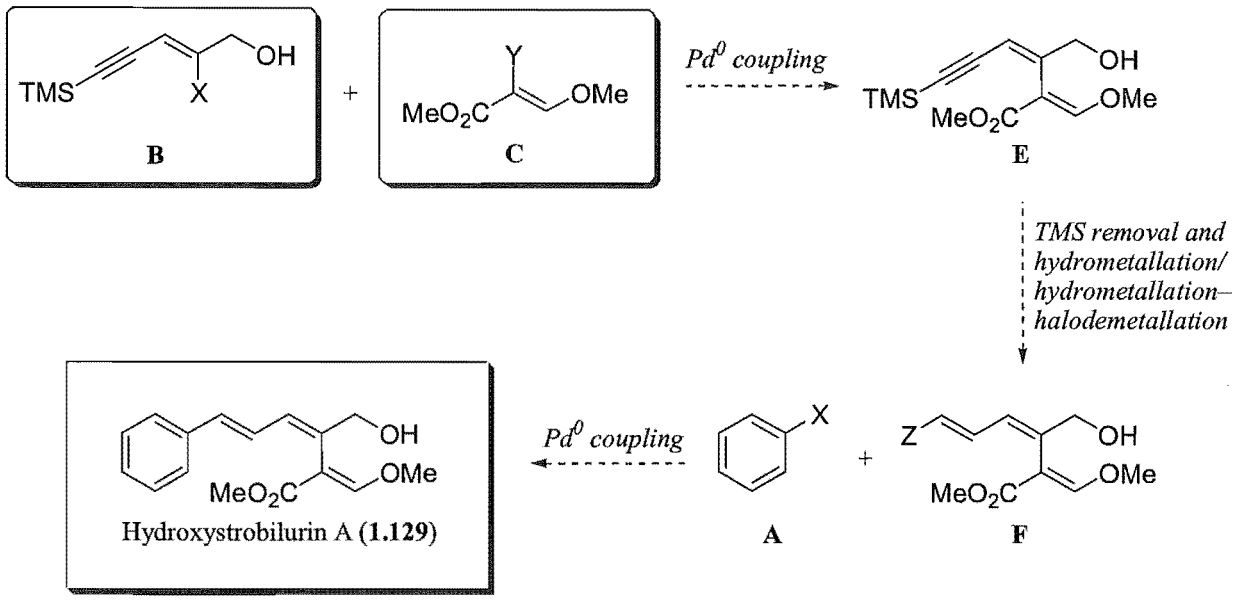
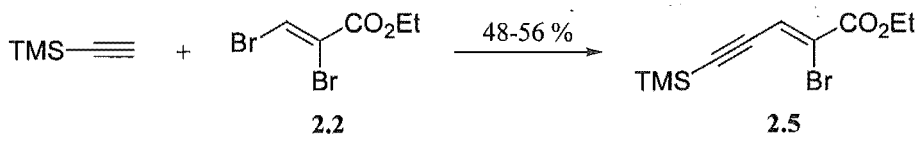


Figure 2.12 Enyne-based approach to hydroxystrobilurin A (where X, Y, and Z are metals or halides).

In devising an approach to enyne **B**, it was noted that Myers and Dragovich, in the same *Organic Syntheses* publication in which they reported the synthesis of dibromide **2.2**, also described a synthesis of enyne ester **2.5**, *via* a Sonogashira coupling[119] between **2.2** and TMS acetylene (**Figure 2.13**).[112]

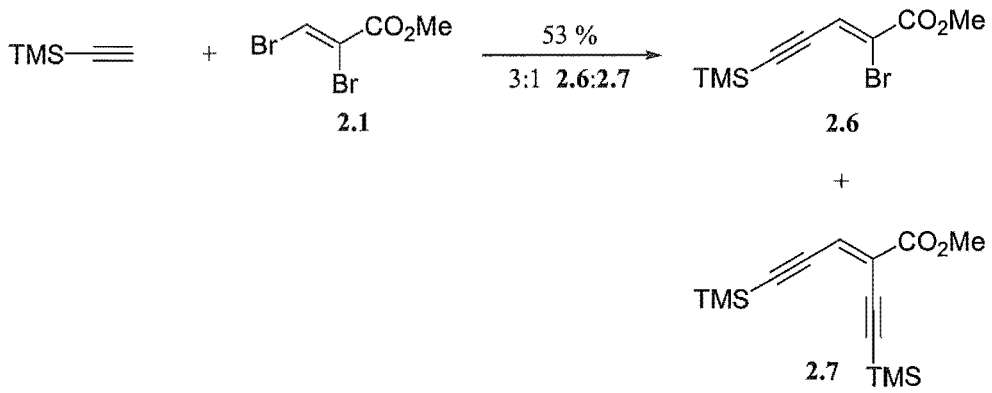


Reagents and conditions: $(i\text{-Pr})_2NEt$, $Pd(PPh_3)_4$ (5 mol %), CuI (20 mol %), DMF, 3-6 h.

Figure 2.13 Myers and Dragovich's synthesis of enyne ester **2.5** *via* Sonogashira coupling.

As expected, the analogous reaction between (trimethylsilyl)acetylene and **2.1** was successful, with a 53% yield of coupling product being formed, although as an inseparable 3:1 mixture of desired enyne ester **2.6** and enediyne ester **2.7** (**Figure 2.14**). Although it was possible that the formation of bis-coupled product **2.7** might be prevented by conducting the reaction for a shorter period of time, this option was not explored, as investigation of the

coupling reaction of **2.6** with a β-methoxyacrylate **C** was the main concern at this time, and it was expected that the absence of a bromine atom in **2.7** would preclude its participation in such a process.



Reagents and conditions: $(i\text{-Pr})_2NEt$, $Pd(PPh_3)_4$ (5 mol %), CuI (20 mol %), DMF, 0 °C, 4 h.

Figure 2.14 Synthesis of enyne ester **2.6** (and enediyne ester **2.7**) *via* Sonogashira coupling.

The mechanism of the Sonogashira coupling is believed to involve the oxidative addition–transmetallation–reductive elimination processes typical to other palladium-catalysed carbon-carbon bond-forming reactions (**Figure 2.15**). (A related procedure, the Stephens-Castro coupling, also generates new sp–sp^2 bonds, but without the use of palladium, and also requires refluxing temperatures and stoichiometric amounts of CuI).[120] The CuI is believed to be required for the formation of an alkynyl copper species, which subsequently undergoes a transmetallation reaction with oxidative addition adduct **2.8**.[121] This mechanism is supported by the observations that the reaction is inhibited by use of an excess of triphenylphosphine [which disfavours breakdown of $Pd(PPh_3)_4$, thus inhibiting the oxidative addition step],[122] and by use of weakly basic amines (which disfavour formation of the alkynyl cuprate).[121,123]

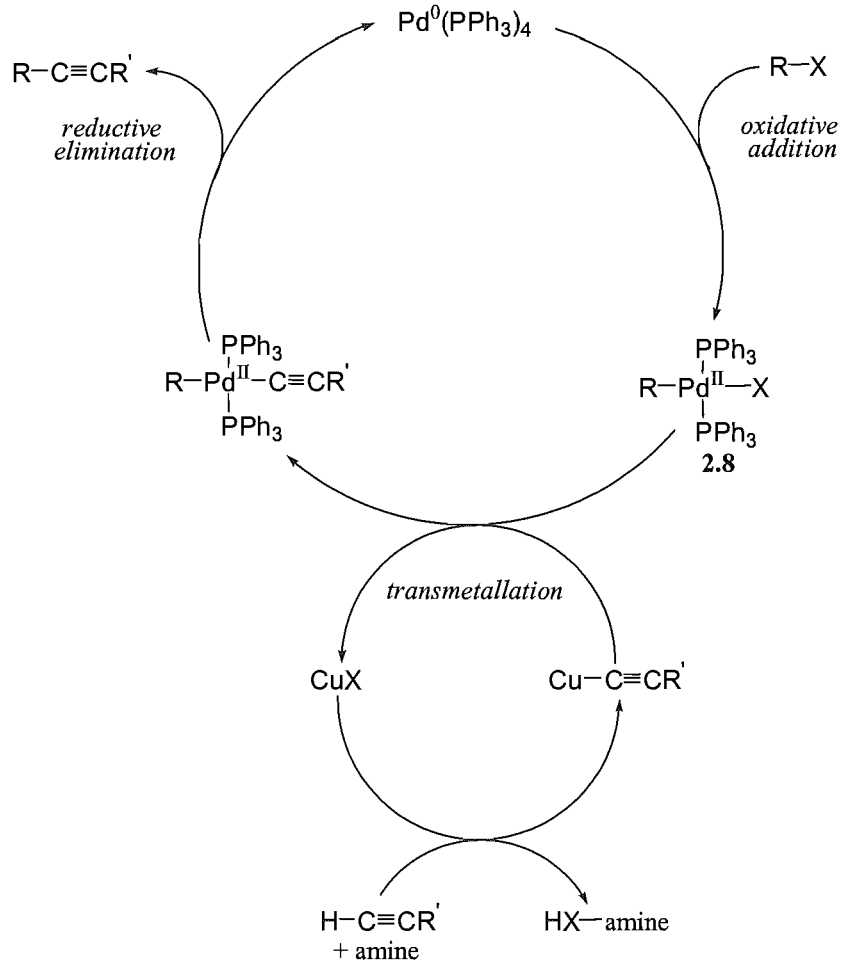
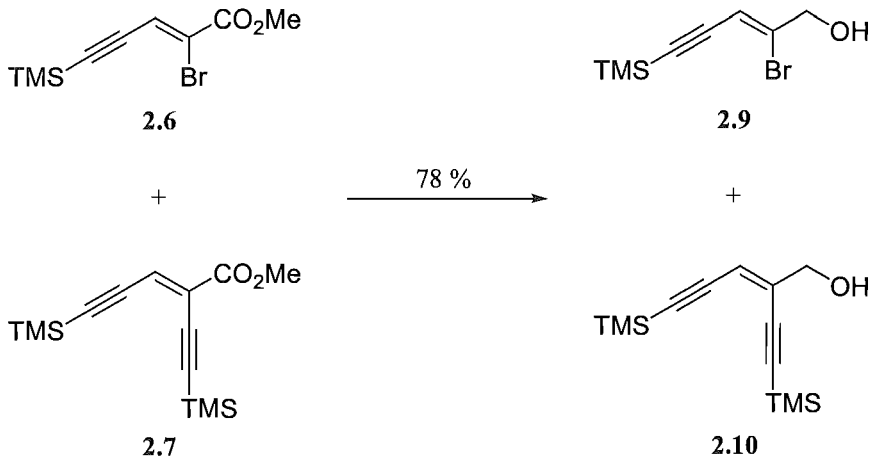


Figure 2.15 Mechanism of the Sonogashira coupling.

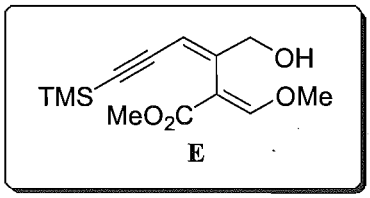
Completion of the synthesis of type **B** enyne alcohol required the reduction of enyne ester **2.6**. Accordingly, treatment of the mixture of **2.6** and **2.7** with DIBAl-H afforded a 78% yield of an inseparable 3:1 mixture of the desired enyne alcohol **2.9** and enediyne alcohol **2.10** (**Figure 2.16**).



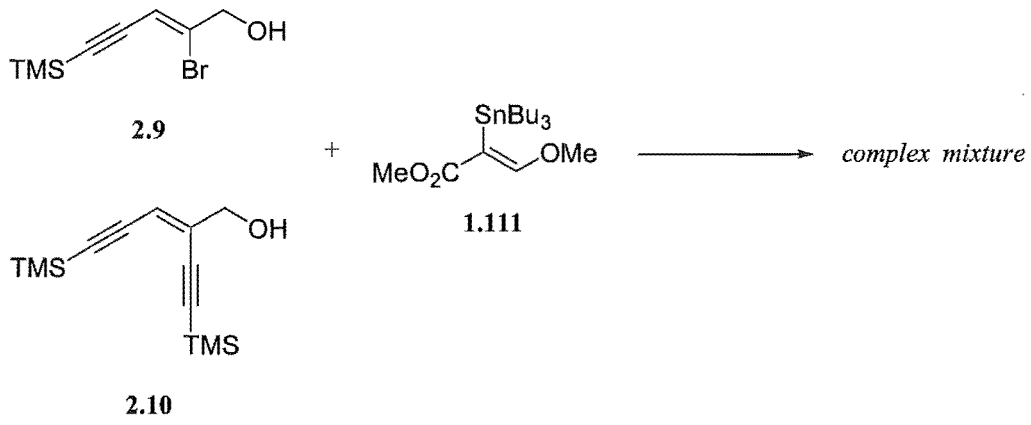
Reagents and conditions: DIBAl-H, Et_2O, –78 – 0 °C, 3.25 h.

Figure 2.16 Reduction of enyne and enediyne esters **2.6** and **2.7** to corresponding alcohols **2.9** and **2.10**.

2.2.3 Attempted Synthesis of Ynediene E



With enyne alcohol **2.9**, a version of synthetic fragment **B** in hand (albeit as an impure 3:1 mixture), it was now possible to attempt a Stille coupling between it and stannane **1.111**, with the aim of forming ynediene **E** (**Figure 2.17**). Unfortunately, although ^1H NMR and TLC analysis of the crude product mixture showed that starting material had been consumed, it also showed that a complex mixture of several compounds had been formed. This result, together with the fact that concurrent exploration of another route was showing more promise, led to investigations into this approach to the natural product being suspended.



Reagents and conditions: $Pd(dppf)Cl_2$ (5 mol %), DMF, dark, 80 °C, 12 h.

Figure 2.17 Attempted Stille coupling of enyne alcohol **2.9** and stannane **1.111**.

2.2.4 Investigation of Diene Route

Parallel with investigation of the enyne-based approach to hydroxystrobilurin A outlined above, efforts were also directed towards the construction of a diene **D** (**Figure 2.18**), a fragment resulting from disconnection of hydroxystrobilurin A at point *b* (see *Chapter 1*, **Figure 1.47**). Access to **D** would enable exploration of the feasibility of its coupling with a β-methoxyacrylate **C** under palladium catalysis, which if successful, would afford **1.129** in an arguably more elegant fashion than *via* the proposed enyne-based route of **Figure 2.12**.

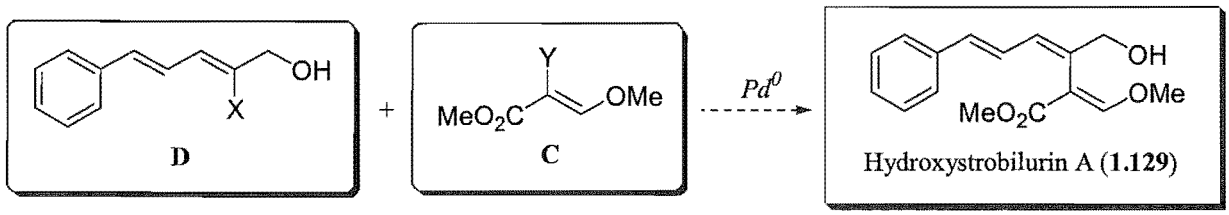


Figure 2.18 Diene-based approach to **1.129** (where X is a metal and Y is a halide, or *vice versa*).

Forseeably, **D** could be produced by reduction of (*Z*,*E*)-diene ester **G**, which might itself derive from a Pd-catalysed coupling between phenylethene **H** and vinyl species **I** (**Figure 2.19**). A good place to start was by using available dibromide **2.1** as **I** (*i.e.* with X = Z = Br), meaning a β-metallo-form of **H** was the required coupling partner.

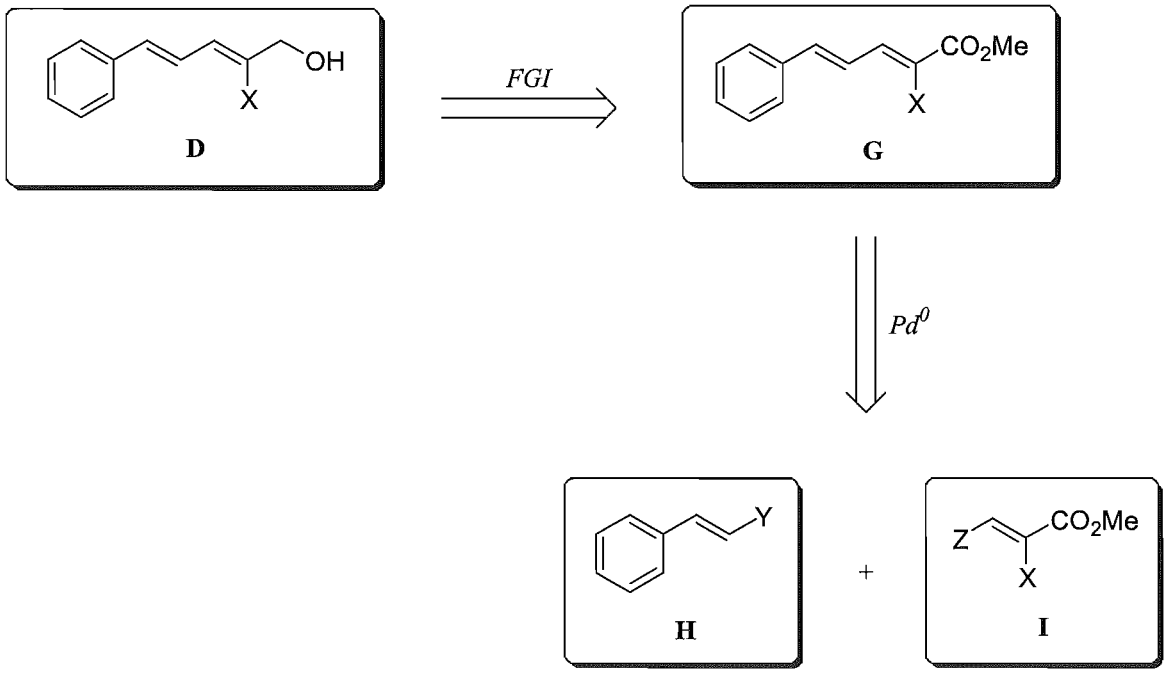


Figure 2.19 Retrosynthetic analysis of diene **D** (where X, Y and Z are metals or halides).

2.2.4.1 Routes to Phenylethene H and Thence to Diene G

2.2.4.1.1 Introduction

A survey of the literature suggested that the most efficient route to an (*E*)-β-metallophenylethene **H** would be *via* hydrometallation of phenylacetylene. In particular, it was apparent that the dual requirements for this transformation – stereoselective *syn* addition of the metal hydride to the triple bond, with regioselective β-metallation – might be fulfilled *via* hydrozirconation, hydroboration or hydrostannylation methodologies (examples of the use of these techniques in natural product syntheses are given in *Chapter 1*, section **1.6.1**). Before they were employed in attempts to synthesise **H**, it was considered important to understand the

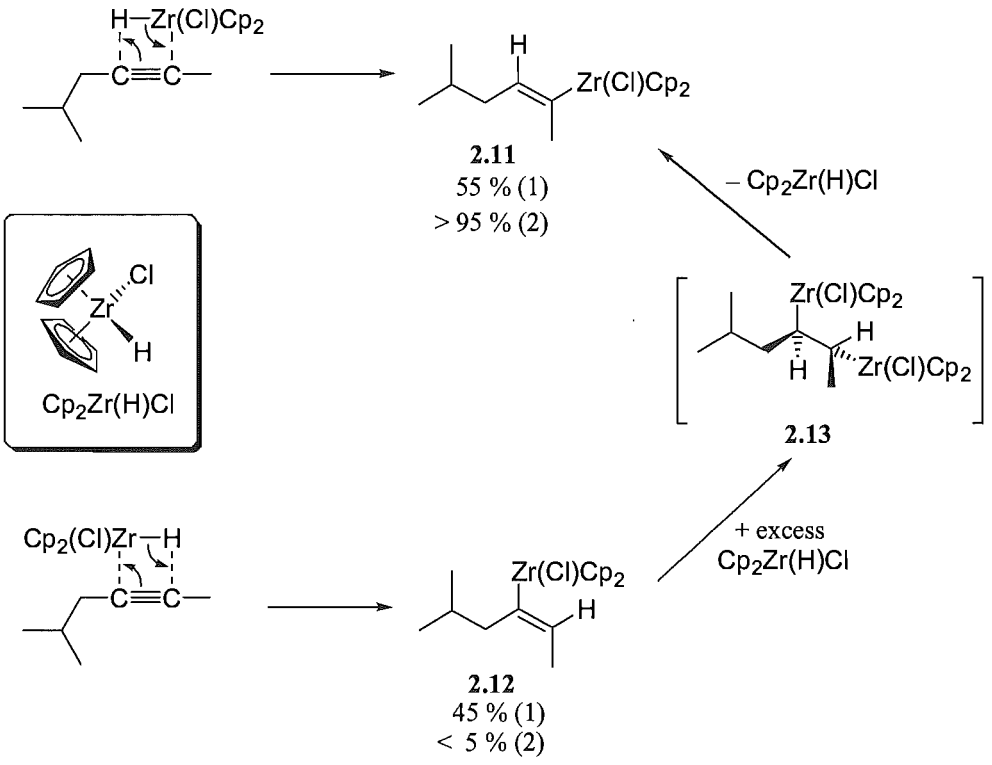
mechanisms and merits of each of these techniques, as such information could provide an indication of the best way forward.

Hydrozirconation[80,124] of terminal alkynes is generally thought to proceed *via* a cyclic four-centre mechanism, with stereoselective *syn* addition of metal hydride [invariably Schwartz's reagent, $Cp_2Zr(H)Cl$] to the least hindered side of the triple bond to afford the (*E*)-β-alkenyl zirconocene (**Figure 2.20**). Steric effects ensure hydrozirconation occurs with 100% regioselective addition of the zirconium moiety to the least hindered alkynyl position *i.e.* to the β-carbon – that which bears the smallest substituent. In the case of hydrozirconation of internal alkynes, where regioisomeric mixtures containing significant quantities of the α-zirconation product may initially be formed, addition of a slight excess of $Cp_2Zr(H)Cl$ leads to a slow isomerisation to a new mixture containing a much greater proportion of the less hindered, β-metallated regioisomer (**Figure 2.20**).

It is presumed that this isomerisation proceeds *via* double addition of Zr–H to the triple bond to form a dizirconoalkyl species, with subsequent *syn* elimination of $Cp_2Zr(H)Cl$ from this species effecting a net isomerisation[Ψ] of the mixture.[124] For example, in **Figure 2.20** below, treatment of 5-methylhex-2-yne with one equivalent of $Cp_2Zr(H)Cl$ yields only a slight excess of the less-hindered product **2.11** (55%) over its more hindered regioisomer **2.12** (45%), but addition of an excess of $Cp_2Zr(H)Cl$ changes the relative amounts of **2.11** and **2.12** to >95% and <5% respectively, presumably *via* dizirconoalkyl intermediate **2.13**.

The so-formed alkenyl zirconocene compounds are air-sensitive, so are either used immediately *in situ* in palladium coupling syntheses (see *Chapter 1*, **Figures 1.31** and **1.32**) or other transmetallation sequences, or may be quenched with iodine to yield the corresponding (*E*)-vinyl iodide.

[Ψ] Since metal hydride addition (hydrometallation) and elimination both proceed in a stereoselective *syn* fashion, this isomerisation process does not result in a loss of stereochemistry about the double bond.



Where (1) *denotes relative % of product from reaction of 1:1 ratio of alkyne and* $Cp_2Zr(H)Cl$*, whilst* (2) *that following addition of excess* $Cp_2Zr(H)Cl$.

Figure 2.20 Mechanism of alkyne hydrozirconation by Schwartz's reagent [$Cp_2Zr(H)Cl$].

Hydroboration[85,125] of alkynes to alkenylboranes also occurs with stereoselective *syn* addition of the metal hydride to the less hindered side of the triple bond, generating (*E*)-alkenylboranes. The process is generally thought to proceed *via* a cyclic four-centre mechanism analogous to that proposed for hydrozirconation (see **Figure 2.20**), except for the fact that the different properties of the various hydroborating reagents available mean significant quantities of the α-metallated alkenyl boron species or the β,β-metallated alkyl diboron species are sometimes formed (with the ratio of β- to α-metallation being somewhat dependent on the substrate). Thus, hydroboration with simple boranes such as diborane (B_2H_6) often yields regioisomeric mixtures (in the case of terminal alkynes),[126] or alkyl diboranes,[127] and even the hindered borane 9-BBN (9-borabicyclo[3.3.1]nonane) [**Figure 2.21**] dihydroborates terminal alkynes to 1,1-diboroalkanes unless a twofold excess of the alkyne is used (although internal alkynes are only monohydroborated by this reagent).[128] Fortunately, efficient monohydroboration can be

achieved with other substituted boranes, such as thexylborane (2,3-dimethyl-2-butylborane),[129] dicyclohexylborane[129] and catecholborane (**Figure 2.21**).[85] Given that the regioselectivity of hydroboration of unsymmetrical alkynes is largely governed by steric effects, the steric bulk of catecholborane has seen it become the reagent of choice for the efficient β-monohydroboration of unsymmetrical alkynes.

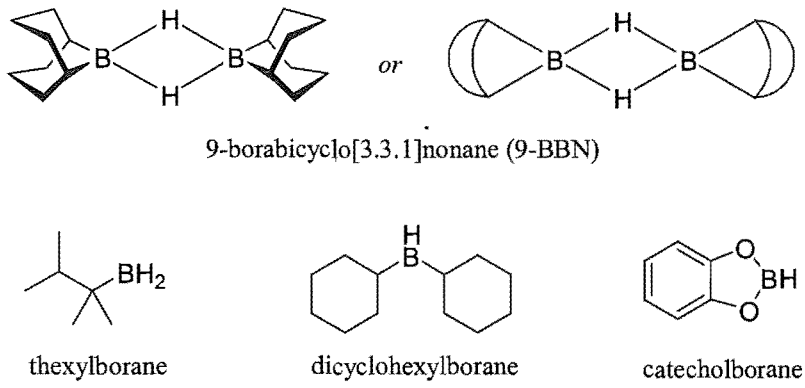
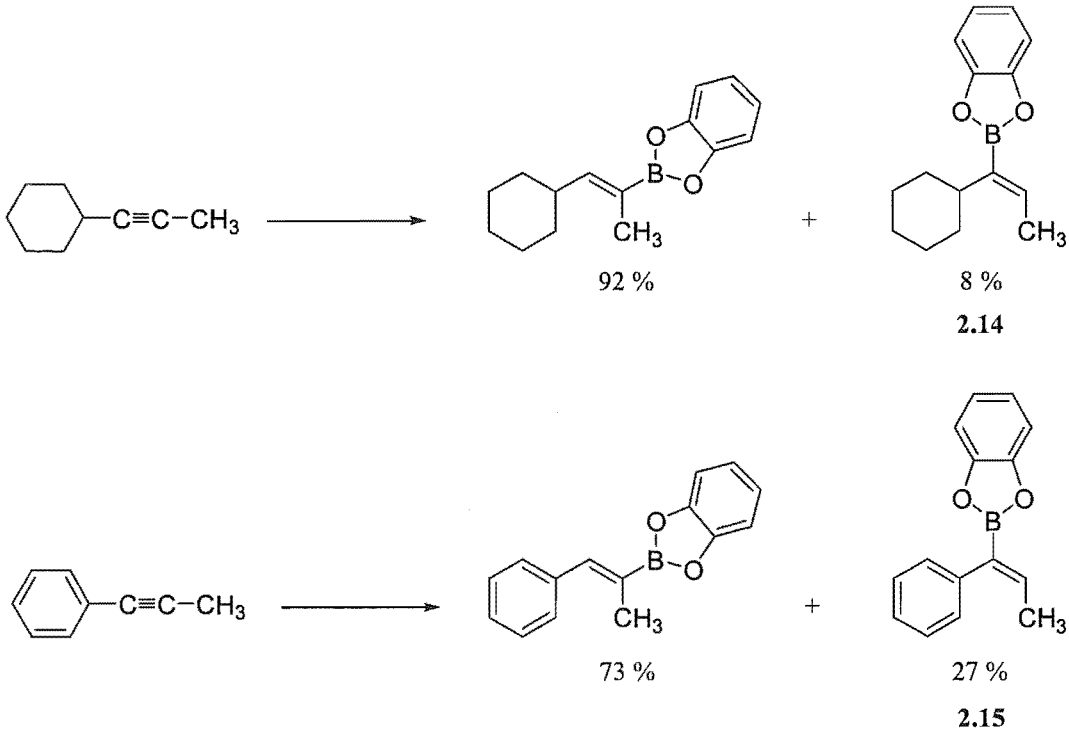


Figure 2.21 Some common hydroborating reagents.

Electronic effects play a minor role in the regioselectivity of hydroboration, but as mentioned above, do sometimes exert an observable influence on the positioning of the boron moiety, and may partially override steric demands. For example, hydroboration of 1-cyclohexylpropyne with catecholborane occurs with 8% attachment of the boron moiety to the more sterically hindered carbon atom, to give α-adduct **2.14** (**Figure 2.22**), whilst treatment of aromatic analogue 1-phenylpropyne yields substantially more of α-adduct **2.15** (27%) – clear evidence of the electronic effect of the phenyl ring.[85b]



Reagents and conditions: catecholborane, 70 °C, 4 h.

Figure 2.22 Steric *versus* electronic effects in hydroboration with catecholborane.

The alkenyl boronate esters formed *via* hydroboration with catecholborane are utilised immediately *in situ* in palladium coupling methodologies (see *Chapter 1*, **Figure 1.34**) or, being more stable than the alkenyl boranes formed by other hydroborating agents (or, indeed, alkenyl zirconocenes), can be purified by distillation before use. Being esters, they can also be easily hydrolysed (by stirring in water at room temperature) to boronic acids, which are usually air-stable[Φ] and crystalline solids,[84,85] thus providing another option for purification or quantification of a given hydroboration product.

Hydrostannylation of alkynes generates alkenyl stannanes, which are stable compounds that can be isolated, purified (although removal of tin residues can be entertaining), and stored. Tributyltin hydride (Bu_3SnH) is the most common stannylation reagent used for the procedure, which can be conducted *via* Lewis acid ($ZrCl_4$, $HfCl_4$) catalysis,[130] transition metal (Pd, Rh,

[Φ] This air-stability of alkenylboronic acids is noteworthy, given that vinyl boronic acid [CH_2=CHB(OH)$_2$] is known to undergo uncontrolled polymerisation upon exposure to air [Matteson, D. D. *J. Am. Chem. Soc.* **1960**, *82*, 4228].

Mo) catalysis,[131] or a free-radical mediated process (AIBN).[132] Lewis acid catalysis proceeds with stereoselective *anti* addition of Bu_3SnH across the triple bond, with regioselective β-addition of the Sn moiety, giving > 95% yields of (*Z*)-β-stannylalkenes **2.16**. The proposed mechanism for this process is shown below (**Figure 2.23**).

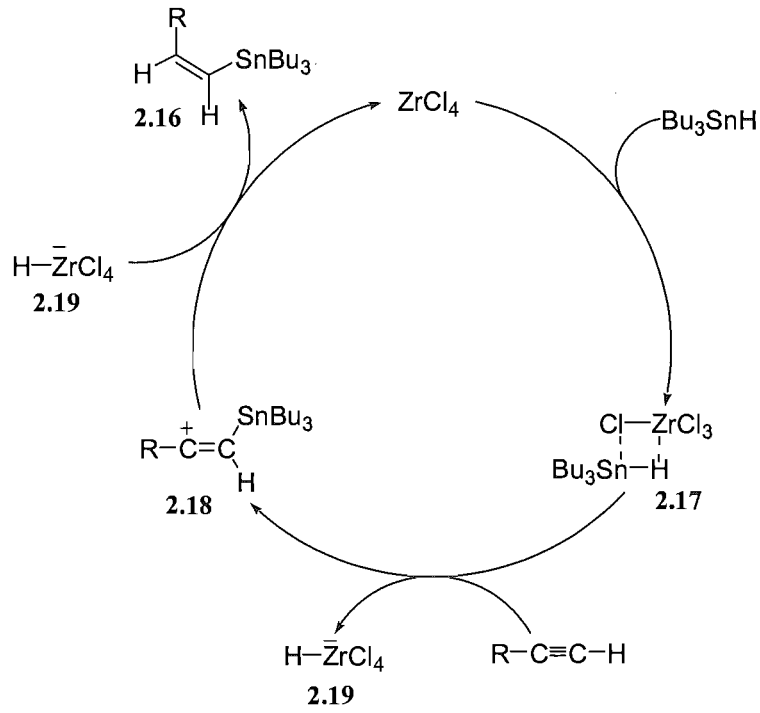


Figure 2.23 Proposed mechanism for Lewis acid-catalysed hydrostannylation of alkynes.

The mechanism postulates bimetallic associative complex **2.17** as the reactive species, with the stannyl moiety of **2.17** adding electrophilically (*i.e.* as Bu_3Sn^+) to the triple bond of the alkyne to generate **2.18**, with concomitant hydride transfer to the zirconium complex to form **2.19**. Ionic species **2.18** and **2.19** then react to form (*Z*)-β-stannylalkenes **2.16**, regenerating $ZrCl_4$ in the process.[130]

In contrast, transition metal-catalysed addition of Bu_3SnH to alkynes occurs *via* stereospecific *syn* addition of Bu_3SnH, as has been shown by use of Bu_3SnD in the $Pd(PPh_3)_4$-catalysed hydrostannylation of phenylacetylene: *syn* addition products **2.20** and **2.21** were formed, but no *anti* addition product **2.22** (**Figure 2.24**).[131b] As can be seen, compared to Lewis

acid catalysis, the regiochemistry of the transition-metal catalysed process is not as clear-cut, with significant quantities of α-stannylated products formed from hydrostannylation of terminal alkynes. The α:β product ratio is dependent on the nature of substitution on the alkyne and on the type of catalyst utilised (with these two factors probably exerting a combination of steric and electronic effects): $Pd(PPh_3)_2Cl_2$[131a] and $Pd(PPh_3)_4$[131b] give mixtures of (*E*)-β- and α-stannylalkenes, while $Mo(\pi\text{-allyl})(CH_3CN)_2(CO)_2Br$,[131a] $Rh(PPh_3)_3Cl$, $Rh(PPh_3)_2(CO)Cl$, and $[RhCl(COD)]_2$ show a preference for α-stannylation.[131c]

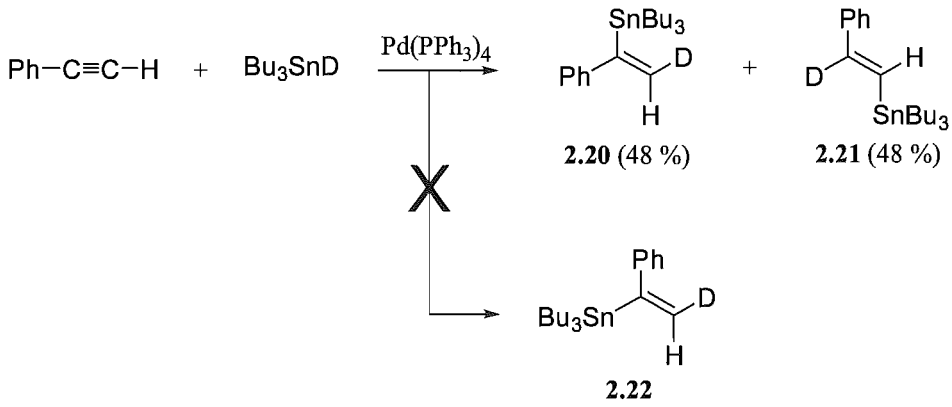


Figure 2.24 Use of deuterium labelling to prove *syn* stereochemistry of Pd-catalysed hydrostannylation.

The catalytic species of the $Pd(PPh_3)_2Cl_2$-mediated process is presumed to be the coordinatively unsaturated palladium(0) complex '$Pd(PPh_3)_2$', formed *via* an *in situ* reduction by Bu_3SnH [analogously, the catalytic molybdenum(0) species is thought to be '$Mo(CO)_2(CH_3CN)_2$'], as shown in the equation below.[131b]

$$Pd^{II}(PPh_3)_2Cl_2 + 2Bu_3SnH \longrightarrow Pd^{0}(PPh_3)_2 + 2Bu_3SnCl + H_2$$

No further proposal has been made as to the mechanism of the process, but that outlined in **Figure 2.25** is plausible. Oxidative addition of $Pd(PPh_3)_2$ to Bu_3SnCl forms palladium(II) complex **2.23**, which could then add *syn* to the alkyne in either of two regio-distinct ways, depending on the relative steric bulk of the Pd and Sn moieties, to form intermediates **2.24** or **2.25**. Bu_3SnH could then add to **2.24** and **2.25** in a *syn* fashion, generating alkyl distannanes

2.27 and **2.26**, respectively (with the steric bulk of the Pd moiety dictating the position of addition of this second stannyl group), from which **2.23** could eliminate to give α-stannylalkene **2.28** or (*E*)-β-stannyl alkene **2.29**.

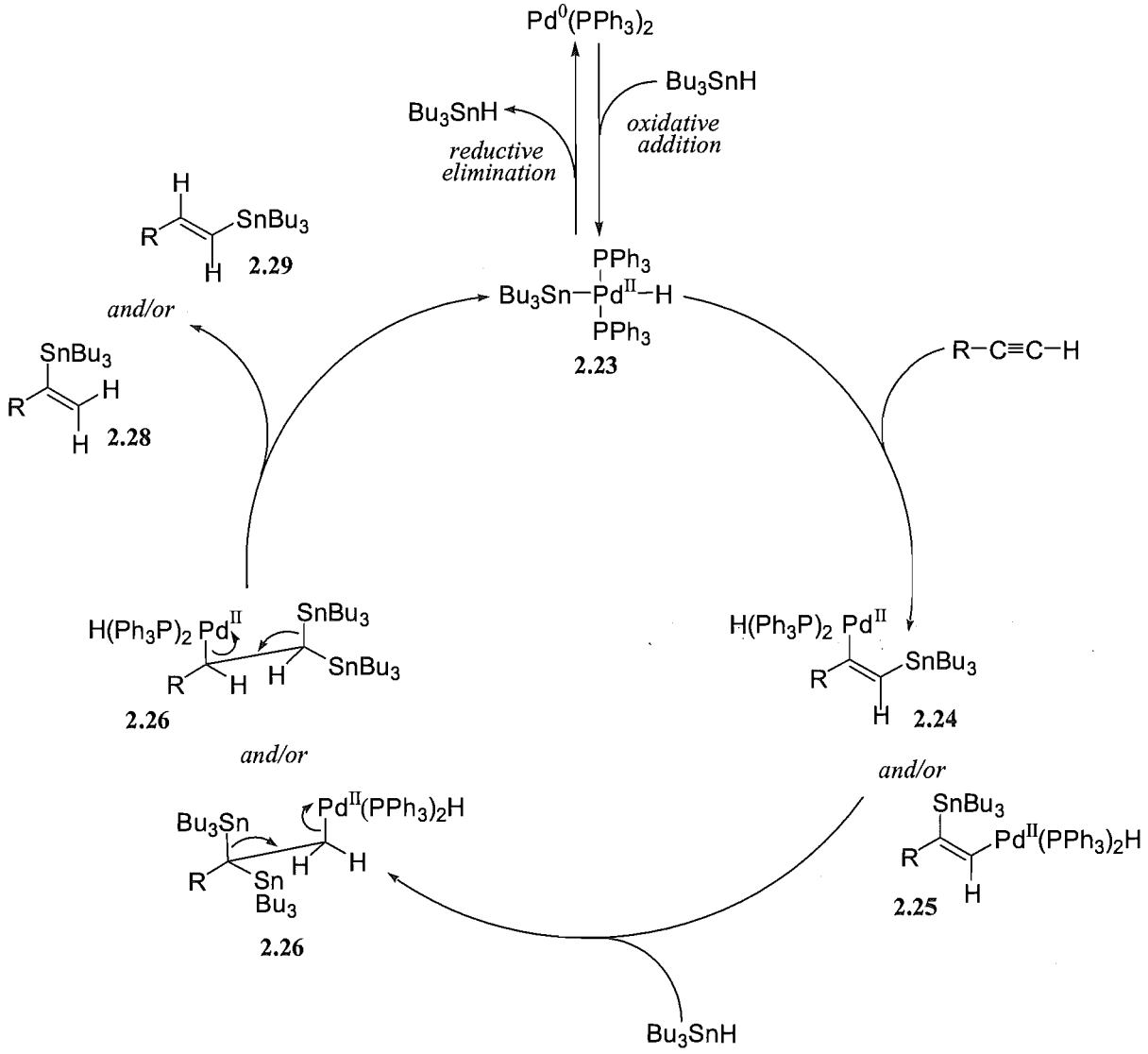


Figure 2.25 Possible mechanism for Pd^0-catalysed hydrostannylation of alkynes.

The free radical-mediated hydrostannylation of alkynes[Φ] is akin to the Lewis acid-catalysed process (see **Figure 2.23**), in that there is net *anti* addition of Bu_3SnH to the triple bond, giving the (*Z*)-stannylalkene product (however, this is only the *first-formed* product: see below).[132] The process begins with the thermal homolysis of radical initiator azobisisobutyronitrile (AIBN), which occurs at moderate temperatures (~ 50 °C) due to the strongly bonded dinitrogen molecule being one of the products, together with two molecules of the tertiary 2-methylpropanenitrilyl radical **2.30** [this scission of one molecule (AIBN) into three molecules also being an entropically favoured process] (**Figure 2.26**).

A hydrogen atom is abstracted from Bu_3SnH by **2.30**, generating a tributyl tin radical, which then attacks the alkyne to form secondary vinyl radical **2.31**. The subsequent reaction of **2.31** with Bu_3SnH (with the latter approaching the less hindered face of **2.31**) affords the *cis* product – (*Z*)-stannylalkene **2.16**. However, reversible addition-elimination of another tributyl tin radical to and from **2.16**, a process that occurs to varying extents depending on the substrate, and particularly with prolonged reaction times or at elevated temperatures, leads to a net isomerisation to the *trans* product – (*E*)-stannylalkene **2.29**.[132b,c] In addition, this hydrostannylation route is regioselective for β-stannylalkene formation from terminal alkynes, *via* secondary radical **2.31**; formation of α-stannylalkenes would require formation of the less stable primary analogue of **2.31**, and thus is not favoured.

[Φ] Leusink *et al.* [*J. Organomet. Chem* **1967**, *9*, 295] have shown that a free-radical mechanism operates in the hydrostannylation of terminal alkynes bearing electron-donating or weakly electron-withdrawing substituents, whilst those possessing strongly electron-withdrawing substituents react *via* an ionic pathway.

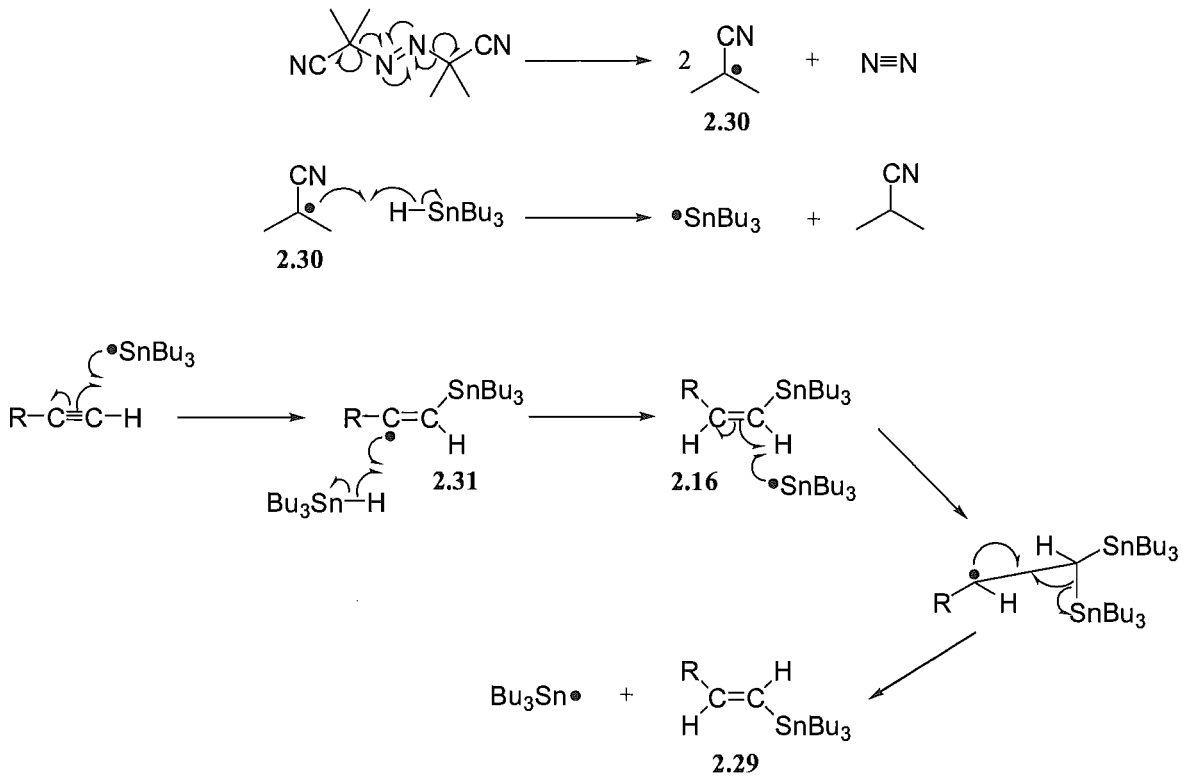
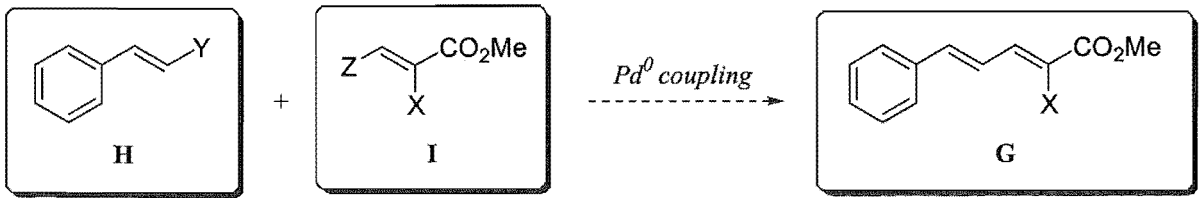


Figure 2.26 Mechanism of free-radical mediated hydrostannylation of terminal alkynes.

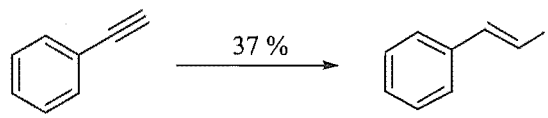
By inspection of the mechanistic bases for the stereoselectivities and regioselectivities obtainable with each of these different methods of alkyne hydrometallation, four possible routes to **H** were revealed: hydrozirconation with Schwartz's reagent, hydroboration with catecholborane, hydrostannylation by palladium catalysis, or hydrostannylation *via* free radical mediation. The Lewis acid-catalysed technique could be rejected, with its complete *anti* hydrostannylation stereoselectivity clearly incompatible with the requirement for an (*E*)-stannyl alkene **H**.

2.2.4.1.2 Investigation of a Hydrozirconation Route to H and thence to G



It was decided to investigate hydrozirconation first, as its complete stereoselectivity for *syn*-hydrometallation and regioselectivity for β-metallation suggested it was the best of the four possible methods for preparation of **H** from phenylacetylene (see previous section for a mechanistic discussion). Moreover, not having to isolate the alkenyl zirconocene **H** should enhance the overall efficiency of the synthesis, enabling the production of a diene **G** from phenylacetylene to be a one-pot process.

Accordingly, Schwartz's reagent was purchased from Boulder Scientific Co.,[‡] and in order to assay its activity, and as a test of methodology, was used for the synthesis of (*E*)-β-iodostyrene **2.32** from phenylacetylene, based on a procedure of Wipf *et al.* (**Figure 2.27**).[80a] Disappointingly, the yield of **2.32** obtained was a mediocre 37%. However, a co-worker in the author's research group obtained a better yield (~ 50%) of a different *trans* vinyl compound *via* an analogous alkyne hydrozirconation route (although by quenching with *N*-bromosuccinimide instead of iodine), and it was therefore decided to use Schwartz's reagent in an attempt to achieve the desired tandem hydrozirconation – Pd-catalysed coupling process.



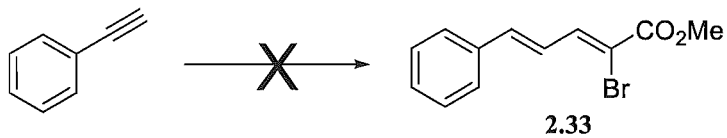
2.32

Reagents and conditions: (i) $Cp_2Zr(H)Cl$, CH_2Cl_2, ~10 °C – r.t., 20 min; (ii) I_2, r.t., 1 h.

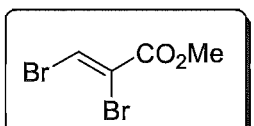
Figure 2.27 Assaying of activity of commercially sourced Schwartz's reagent.

[‡] In a personal communication, Assistant Professor Andrew J. Phillips (then a member of the Wipf group at the University of Pittsburgh) recommended this company as the best source of the reagent, and noted that in their group it was routinely used successfully in hydrozirconation protocols without the need for manipulation in a dry-box.

Thus, phenylacetylene was treated with Schwartz's reagent, followed by addition of $Pd(PPh_3)_2Cl_2$ and vinyl bromide **2.1** (**Figure 2.28**), based on the method of Barrett *et al.* (see *Chapter 1*, **Figure 1.31**).[81] After the reaction mixture had been stirring for approximately 24 h, an aliquot was removed and analysed by ^{1}H NMR spectroscopy. Although the absence of an acetylenic proton signal in the ^{1}H NMR spectrum showed that the phenylacetylene had been consumed, the mixture consisted almost entirely of unreacted **2.1**. Following work-up and purification by column chromatography, a fraction was isolated whose ^{1}H NMR spectrum contained olefinic and aromatic signals, but the quantity of these, and their multiplicity, and the absence of a signal for a methoxy group indicated this was not desired type **G** diene **2.33**. The reaction was repeated with pre-reduced catalyst [*i.e.* $Pd(PPh_3)_2Cl_2$ + DIBAl-H], but to no avail.



2.33

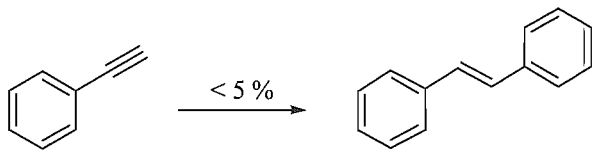


2.1

Reagents and conditions: (i) $Cp_2Zr(H)Cl$, THF, ~10 °C – r.t., 20 min; (ii) **2.1**, $Pd(PPh_3)_2Cl_2$ (5 mol %) or [$Pd(PPh_3)_2Cl_2$ (10 mol %) + DIBAl-H (20 mol %)], r.t., 24 h.

Figure 2.28 Attempted synthesis of diene **2.33** *via* hydrozirconation and Pd-catalysed coupling.

In an effort to shed more light on the viability of the above hydrozirconation – Pd coupling approach, the process was repeated with **2.1** replaced by iodobenzene (**Figure 2.29**). Although the efficacy of the reaction proved similarly disappointing, with only a trace of (*E*)-stilbene being formed, recovery of 49% of the iodobenzene at least confirmed suspicions that it was the hydrozirconation step which was failing. This was supported by a repeat of the iodination assay of **Figure 2.27** affording an even lower yield (12%) of iodostyrene **2.32**.



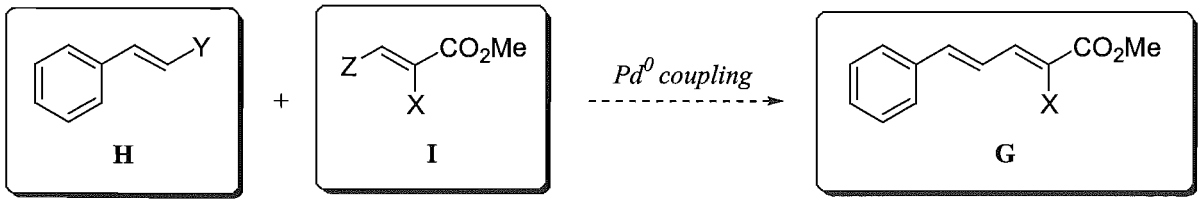
(*E*)-stilbene

Reagents and conditions: (i) $Cp_2Zr(H)Cl$, ~ 10 °C – r.t., 20 min;
(ii) PhI, [$Pd(PPh_3)_2Cl_2$ (10 mol %) + DIBAl-H (20 mol %)], r.t., 24 h.

Figure 2.29 Synthesis of (*E*)-stilbene *via* hydrozirconation and Pd^0-catalysed coupling.

This lack of success with the utilisation of Schwartz's reagent was somewhat puzzling, as it had been purchased from a reputable source (Boulder Chemical Co., USA), manipulated carefully under an inverted funnel-flow of argon (with there apparently being no need for the use of a dry-box, as noted), with glassware that had been rigorously dried prior to use. Perhaps in getting from Boulder, USA to Christchurch, NZ, the reagent had partially degraded?[Ψ] Whatever the problem, and notwithstanding that literature procedures exist for the synthesis of Schwartz's reagent,[133] preliminary results from a concurrent investigation of hydroboration methodologies fuelled a decision to discontinue exploration of hydrozirconation-based routes to diene **G**.

2.2.4.1.3 Investigation of a Hydroboration Route to H and thence to G



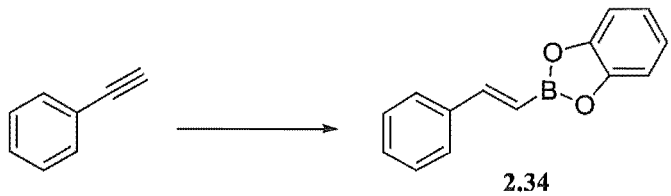
Hydroboration generates alkenyl boron compounds that, like alkenyl zirconocenes, are not isolated but used *in situ*. However, it is also possible to isolate boronic acids *via* hydrolysis of

[Ψ] It has been noted by Lipshutz *et al.* that even with careful handling, the shelf-life of commercially available (Boulder Scientific Co.) Schwartz's reagent is only ~3 months.[133e] The timeframe within which the above experiments were conducted was ~1 month, during which there did appear to have been a decrease in activity of the reagent.

boronate esters, usually of alkenylcatecholboranes (see section **2.2.4.1**).[84,85] As previously mentioned, catecholborane has become the reagent of choice for stereo- and regioselective *syn*-β-hydroboration of alkynes to give (*E*)-β-alkenyl boronic esters. Accordingly, it was decided to use a commercially produced 1 mol L^{-1} solution of catecholborane in THF, and a hydroboration technique based on the procedures of Miyaura and Suzuki[134] and Brown and Gupta.[85a]

In an initial attempt, a solution of phenylacetylene in THF was treated with an equimolar quantity of the above catecholborane solution at 75 °C for 24 h, yielding a material which was determined by ^{1}H NMR spectroscopic analysis to comprise a 2:1 mixture of desired (*E*)-β-phenylethenylboronic ester **2.34** (**Figure 2.30**) and starting material. An effort to purify this crude product *via* chromatography on silica gel yielded only degraded material.

Noting that the literature stated longer reaction times were required when using dilute solutions of hydroboration reagents, the experiment was repeated at 85 °C with no added THF (*in lieu* of a supply of neat catecholborane), in the hope that these conditions would drive the reaction to completion (**Figure 2.30**). This strategy was successful, with no starting material visible in the ^{1}H NMR spectrum of the crude material isolated after 7 h of reaction. However, the yield of this transformation was not determined, and the low, broad melting point [45-60 °C (lit.78 °C)[85a]] of the creamy yellow crystalline product was indicative of a lack of purity.



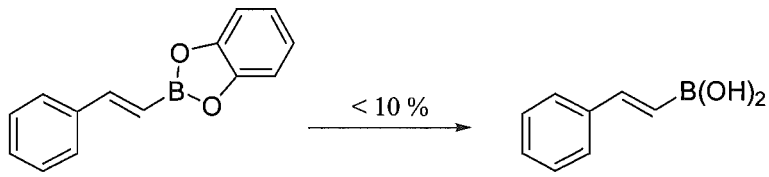
2.34

Reagents and conditions: 1 mol L^{-1} catecholborane, 75 or 85 °C, THF or no solvent, 7 or 24 h.

Solvent	Temperature (°C)	Time (h)	Result
THF	75	24	2:1 **2.34**:SM
none	85	7	All **2.34**, no SM

Figure 2.30 Hydroboration of phenylacetylene with 1 mol L^{-1} catecholborane solution

Given that boronic acids have been demonstrated to couple efficiently in Suzuki coupling methodologies,[84] efforts were made to hydrolyse boronic ester **2.34** to the corresponding acid, *via* the method of Brown and Gupta (**Figure 2.31**).[85a] The boronic acid product (**2.35**) obtained was of high purity [MP 160-162 °C (lit. 163-164 °C)[85a]], but unfortunately only a very small amount was isolated, despite repeated recrystallisation attempts.

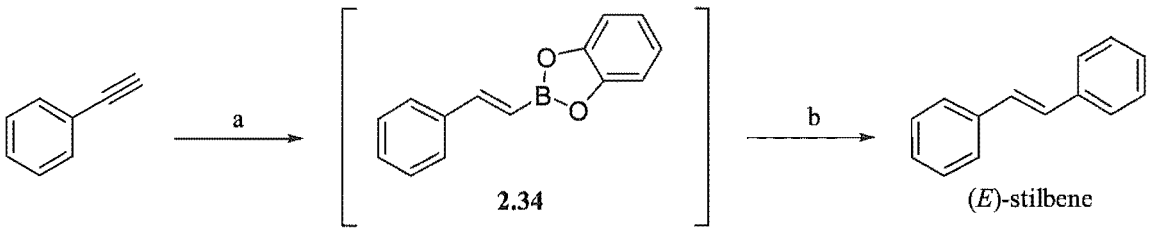


2.34 **2.35**

Reagents and conditions: H_2O, 80 °C, 1 h.

Figure 2.31 Hydrolysis of boronic ester.

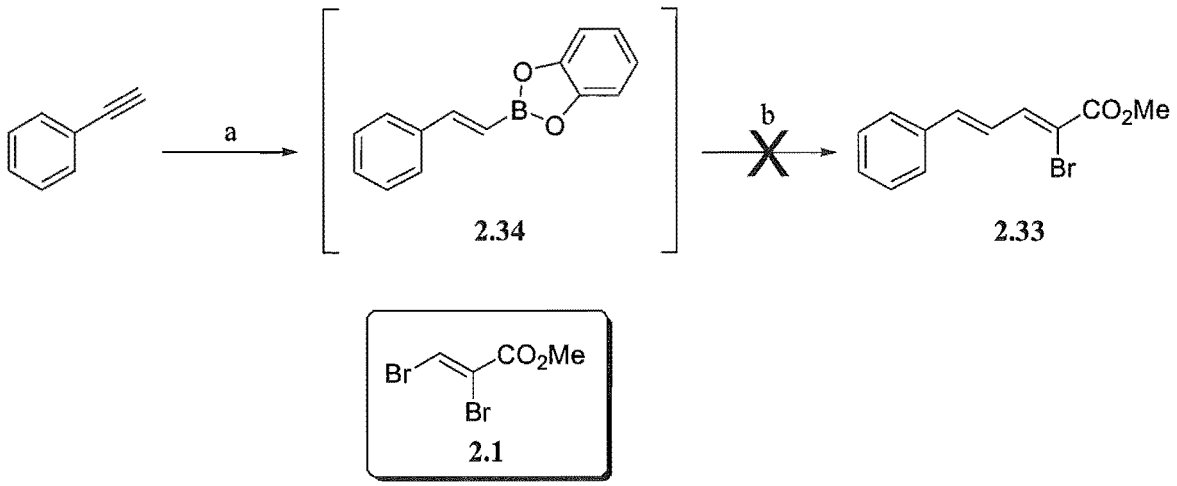
With a route to boronic ester **2.34** established, but with attendant purification difficulties, the logical step was to dispense with isolation and purification of **2.34** and instead investigate its use in a one-pot synthesis of diene ester **2.33**. As with the hydrozirconation investigation (see section **2.2.4.1.2**), a coupling with iodobenzene was conducted first, as a means of determining the efficacy and efficiency of the reaction conditions. Thus, phenylacetylene was treated with a 1 mol L^{-1} solution of catecholborane, and the resultant crude borate ester product (**2.34**) immediately combined with iodobenzene and $Pd(PPh_3)_2Cl_2$ under the cross-coupling conditions of Miyaura and Suzuki (**Figure 2.32**).[134] This procedure afforded a moderate yield (43%) of (*E*)-stilbene.



Reagents and conditions: (a) catecholborane, THF, 85 °C, 7 h; (b) PhI, $Pd(PPh_3)_2Cl_2$ (5 mol %), NaOEt, benzene, reflux, 18 h [43 % from PhI, 42 % overall].

Figure 2.32 Synthesis of (*E*)-stilbene *via* hydroboration – Suzuki coupling.

Although the yield of (*E*)-stilbene obtained *via* the above hydroboration – Suzuki coupling approach was not spectacular, it nevertheless demonstrated the potential of the methodology. Consequently, attention was turned to the application of this technique to the synthesis of diene ester **2.33**. An initial attempt to synthesise **2.33** led to consumption of starting material and the generation of at least one conjugated olefinic product, however the absence of a methoxy signal in the ^{1}H NMR spectrum showed no desired product was present (**Figure 2.33**). It was thought probable that the ester moiety was undergoing hydrolysis in the presence of sodium ethoxide and H_2O (during work-up), meaning a milder base would be required for further attempts at this route to **2.33**.

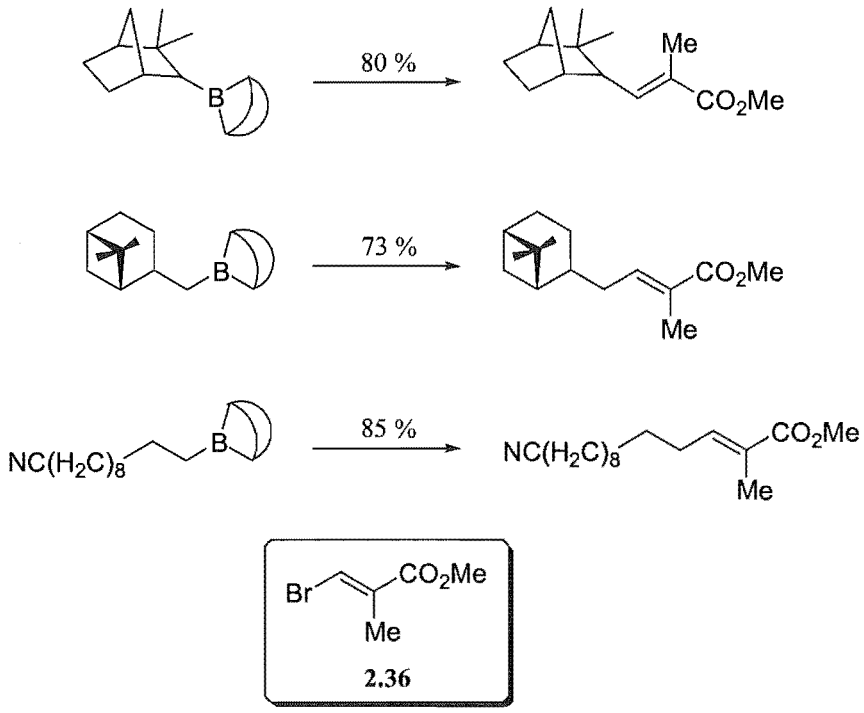


Reagents and conditions: (a) catecholborane, THF, 85 °C, 7 h; (b) **2.1**, $Pd(PPh_3)_2Cl_2$ (5 mol %), NaOEt, benzene, reflux, 18 h.

Figure 2.33 Attempted synthesis of **2.33** under $Pd(PPh_3)_2Cl_2$/NaOEt Suzuki-Miyaura conditions.

Pursuant to this requirement, it was found that Suzuki *et al.* had successfully employed a $Pd(dppf)Cl_2/K_2CO_3$) system in intermolecular crossed couplings between various 9-alkyl-9-BBN compounds and vinyl bromides, including ester-functionalised vinyl bromide **2.36**, as depicted below (**Figure 2.34**).[135] It was hoped that methyl ester of **2.1** would be similarly unscathed by K_2CO_3 under these conditions.‡

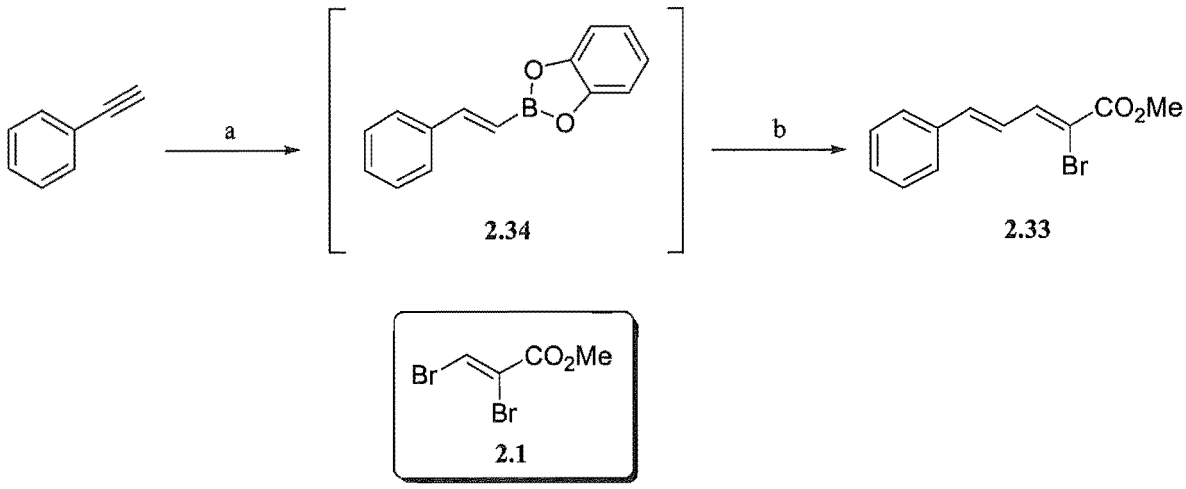
‡ The pK_b values of CO_3^{2-} and EtO^- (in H_2O, but presumably still valid for comparative purposes) are 3.67 and -1.50 respectively [*'CRC Handbook of Chemistry and Physics (82nd edn.)', editor-in-chief Lide, D. R.* (CRC Press LLC, Boca Raton, Florida, USA) **2001**]: thus CO_3^{2-} is a weaker base than EtO^-.



Reagents and conditions: **2.36**, $Pd(dppf)Cl_2$ (3 mol %), K_2CO_3, DMF, 50 °C.

Figure 2.34 Suzuki *et al.*'s cross couplings using K_2CO_3.

Accordingly, phenylacetylene was once again treated with catecholborane to form alkenyl boronic acid **2.34**, and this compound was combined with vinyl bromide **2.1** and $Pd(dppf)Cl_2/K_2CO_3$ under the conditions of Suzuki *et al.* (**Figure 2.35**).[135] Happily, this different reaction system was indeed an improvement, with a quantity of **2.33** being formed; however, the 20% yield (based on ~10% recovered **2.1** starting material) was still disappointing. Attempts were made to improve this result by deoxygenation of reaction mixtures (in case dissolved oxygen was prematurely terminating the catalytic cycle), but this had a negligible effect on the amount of unreacted **2.1** and the overall efficiency of the process.

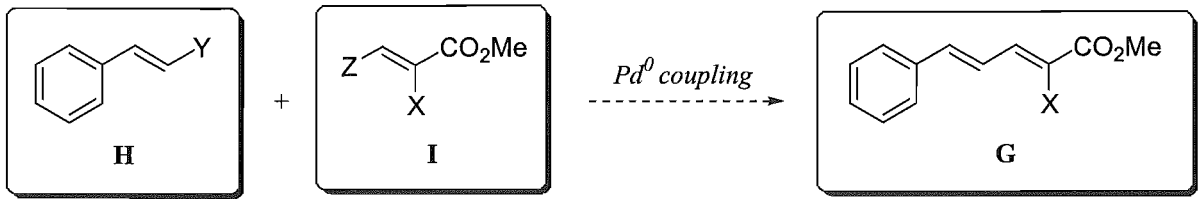


Reagents and conditions: (a) catecholborane, THF, 85 °C, 7 h; (b) **2.1**, $Pd(dppf)Cl_2$ (3 mol %), K_2CO_3, DMF, 50 °C, 12 h [20 % overall].

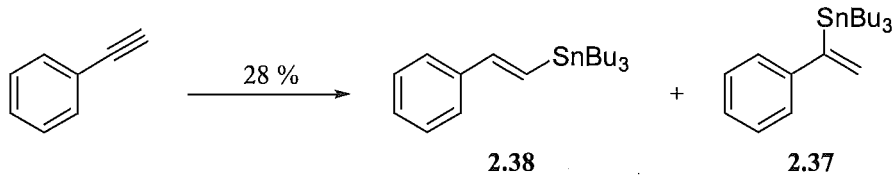
Figure 2.35 Synthesis of **2.33** *via* Suzuki coupling with $Pd(dppf)Cl_2/K_2CO_3$.

Overall, although this hydroboration – Suzuki coupling route did afford some of desired diene ester **2.33**, and was therefore an improvement on the hydrozirconation – Pd-catalysed coupling attempts described earlier (section **2.2.4.1.2**), the overall yield of the process was disappointing. The results suggested that it was the hydroboration step that was the problem, perhaps due to the use of a solution of catecholborane rather than the neat reagent. However, rather than spend more time on this problem, promising preliminary investigations of hydrostannylation and Stille coupling methodologies suggested these might comprise a more fruitful approach to **2.33**, and thus the focus of the synthetic study was shifted to the utilisation of organotin chemistry.

2.2.4.1.4 Investigation of a Hydrostannylation Route to H and thence to G



The two options available for hydrostannylation of phenylacetylene with Bu_3SnH were with a palladium catalyst or *via* free radical mediation (see section **2.2.4.1.1**). The former method was trialled first, phenylacetylene being treated with Bu_3SnH and $Pd(PPh_3)_2Cl_2$ based on the procedure of Zhang *et al.* (**Figure 2.36**).[131a] The predominance of the α-stannylated product **2.37** at the expense of desired (*E*)-β-stannane **2.38** (a result not without precedent, with Zhang *et al.* having obtained such mixtures) and the low overall yield of hydrostannylated products meant this was an unsatisfactory route to **2.38**, and it was hoped that the free-radical mediated process would prove both more stereoselective and efficient.

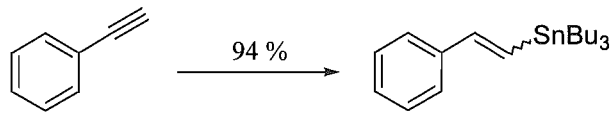


Reagents and conditions: Bu_3SnH, $Pd(PPh_3)_2Cl_2$ (20 mol %), THF, r.t, 45 min [ratio of **2.38** to **2.37** of 1.0:1.6].

Figure 2.36 Pd-catalysed hydrostannylation of phenylacetylene.

A literature search revealed Stille and Labadie had successfully obtained **2.38** by a free-radical hydrostannylation method, so their experimental procedure was used (**Figure 2.37**).[136] Satisfyingly, an excellent yield of (*E*)-β-stannane **2.38** was afforded by this method, although ^1H NMR spectroscopic analysis revealed the presence of a small quantity of (*Z*)-**2.38** [(*E*):(*Z*) ratio of 12.4:1.0], from which (*E*)-**2.38** was unable to be separated by chromatography or distillation. The above (*E*):(*Z*) ratio for **2.38** was the best achieved, despite resulting from a shorter reaction time (19.5 h) than the 24 h prescribed by Stille and Labadie; allowing the

reaction to proceed for the full 24 h, or for 42 h, saw the ratio significantly decrease (see table, **Figure 2.37**). [It is possible that Stille and Labadie might have also observed this phenomenon, but were able to achieve (*E*):(*Z*) separation at their distillation pressure of 0.1 mm Hg, compared to the lowest pressure of 2.2 mm Hg which was available during this work.]



2.38

Reagents and conditions: Bu_3SnH, cat. AIBN, 50 °C, 19.5 h [(*E*):(*Z*) = 12.4:1.0].

Reaction time (h)	(*E*):(*Z*) ratio*
15.3	7.5:1.0
19.5	12.4:1.0
24.0	8.1:1.0
42.0	1.9:1.0

* *Estimated by comparison of integral ratios of olefinic signals in ^1H NMR spectra.*

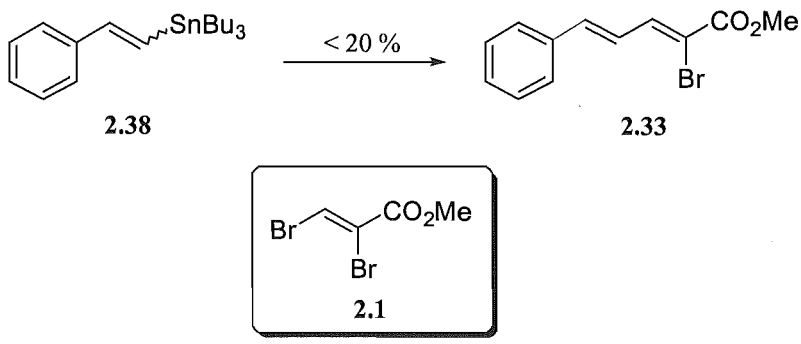
Figure 2.37 Free-radical mediated hydrostannylation of phenylacetylene.

Although a more rigorous mechanistic investigation would be necessary to corroborate these results, they imply that in addition to the first-formed (*Z*)-product of free-radical hydrostannylation of phenylacetylene undergoing a net isomerisation to the (*E*)-product as the reaction progresses, in accordance with the known mechanism (see page 89, **Figure 2.26**),[132] there is also a point at which this process 'switches direction' *i.e.* net isomerisation is from the (*E*)- to the (*Z*)-isomer [although the *chemical* yield of (*E*)- and (*Z*)-**2.38** would need to be obtained to confirm these ^1H NMR yields].

The efficiency of this hydrostannylation procedure and the stability of **2.38** outweighed the potentially negative aspect of an extra step being added to the approach by the necessity for such stannanes to be isolated and purified (unlike alkenyl zirconocenes or boronic esters). Furthermore, it was hoped that the fact that Stille couplings have been successfully utilised in

the latter stages of the construction of the conjugated polyene systems of complex natural products such as rapamycin (see *Chapter 1*, **Figure 1.38**)[100] and calyculin A (see next page)[137] augured well for the next required step of the synthesis – a Stille coupling between **2.38** and vinyl bromide **2.1**.

Accordingly, **2.38** was combined with vinyl bromide **2.1** under Stille conditions (**Figure 2.38**). After overnight reaction, the ^{1}H NMR spectrum of the crude product mixture showed promising olefinic signals and one major methoxy signal, although there were also several other methoxy signals present. Subsequent purification afforded a disappointingly low yield of desired type **G** diene **2.33**.



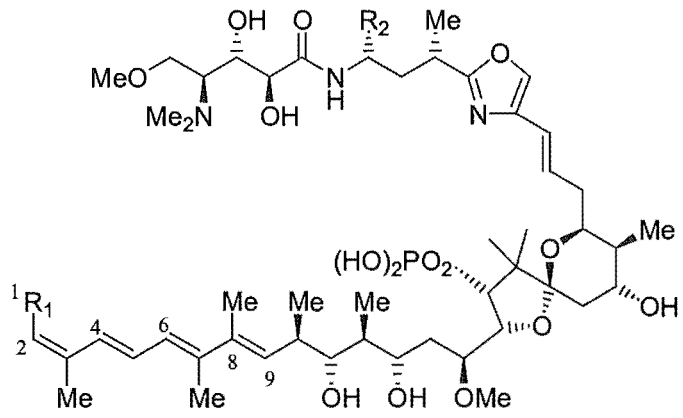
Reagents and conditions: **2.1**, $Pd(PPh_3)_2Cl_2$ (5 mol %), DMF, 80 °C, dark, 12 h.

Figure 2.38 Low yielding Stille coupling route to type **G** diene **2.33**.

Mindful of the sage words of Hegedus,[Ψ] modification of the transmetallation step seemed to be a means by which the efficiency of this Stille coupling might be improved. A germane example of such a tactic is Pihko and Koskinen's synthesis of a key intermediate *en route* to a building block of the conjugated C_1–C_9 tetraene fragment of calyculins A and C and

[Ψ] 'In [cross-coupling reactions], the transmetallation step is almost always the rate limiting step, and when catalytic cycles involving a transmetallation step fail, it is usually this step which needs attention.' [Hegedus, L. in *'Transition Metals in the Synthesis of Complex Organic Molecules', 2nd edn.* (University Science Books, Sausalito, California, USA) **1999**].

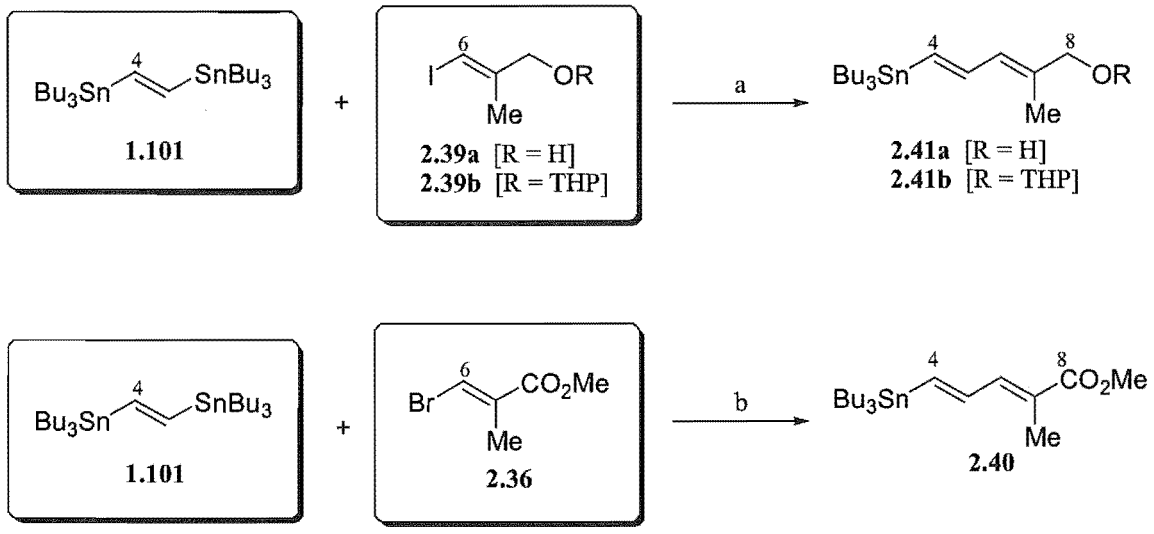
calyculinamide A,[138] cytotoxic compounds isolated from marine sponges *Discodermia calyx*[139] and *Lamellomorpha strongylata* (**Figure 2.39**).[140]



Calyculin A: R_1 = CN, R_2 = H
Calyculin C: R_1 = CN, R_2 = Me
Calyculinamide A: R_1 = $CONH_2$, R_2 = H

Figure 2.39 The calyculins and calyculinamide A.

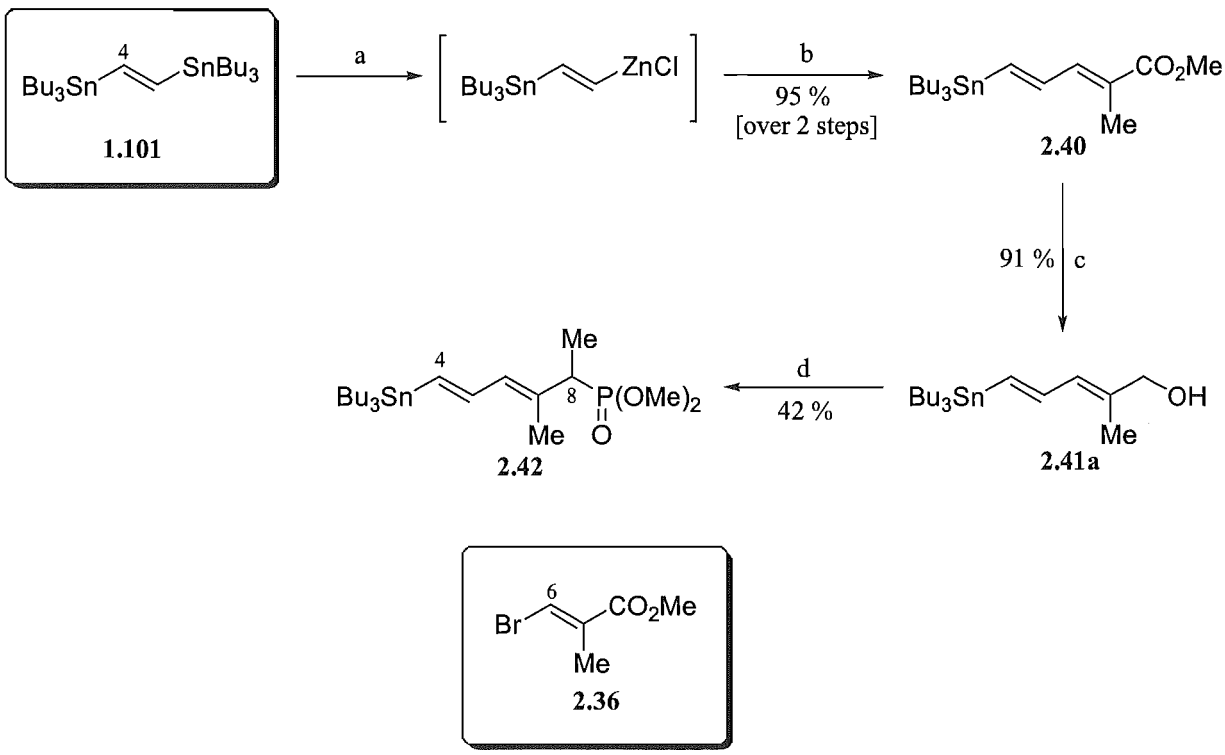
Initially, Pihko and Koskinen persevered with a 'classical' approach to Stille reaction optimisation, trialling various different solvent systems, reaction temperatures, quantities and types of palladium catalyst, and both vinyl bromide **2.36** and vinyl iodides **2.39a** and **b** in attempts to efficiently access dienes **2.40** and **2.41** from distannane **1.101**[102] (**Figure 2.40**) [see *Chapter 1*, **Figure 1.38** for Nicolaou *et al.*'s use of **1.101** in their synthesis of rapamycin]. However, the reaction proved intransigently sluggish, leading to decomposition of starting materials and products, and although the use of $Pd_2dba_3/AsPh_3$ improved the rate and efficiency of the process in some cases, best yields were no greater than 40%.



Reagents and conditions: (a) Pd_2dba_3 (2 mol %), $AsPh_3$ (8 mol %), THF, 50 °C [**2.41a**, 40%]; $Pd(MeCN)_2Cl_2$ (10 mol %), DMF, r.t. [**2.41b**, < 10 %]; (b) Pd_2dba_3 (2 mol %), $AsPh_3$ (16 mol %), THF, 50 °C [< 15 %].

Figure 2.40 Pihko and Koskinen's 'classical' Stille coupling approach to calyculin/calyculinamide tetraene subunit precursors.

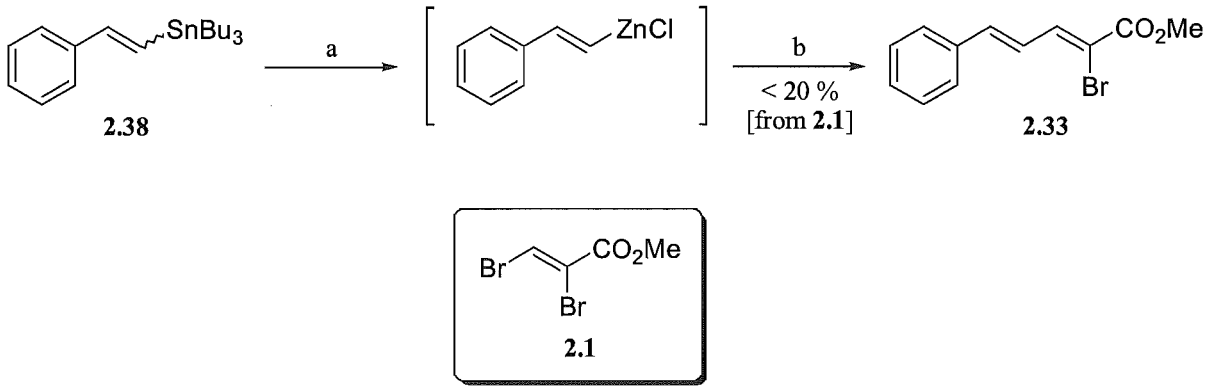
Consequently, the researchers turned to modifying the transmetallation conditions in an attempt to improve the efficiency of the process. And lo and behold, sequential treatment of distannane **1.101** with *n*-butyllithium and $ZnCl_2$, followed by a Pd-catalysed coupling with vinyl bromide **2.36**, afforded an excellent 95% yield of diene ester **2.40** (**Figure 2.41**). This impressive result incorporates three consecutive transmetallations of the vinyl moiety (Sn→Li→Zn→Pd), with an average yield of 78% per step. It is also noteworthy that there was reportedly no trace of the destannylated product which would be formed from reaction at tin rather than at zinc, demonstrating the complete chemoselectivity of the Pd-catalysed coupling. Subsequent reduction of **2.40** gave diene alcohol **2.41a**, which was elaborated to the desired key intermediate, phosphonate **2.42**.



Reagents and conditions: (a) (i) *n*-BuLi, THF, –78 °C, 30 min; (ii) $ZnCl_2$, THF, –78 to –20 °C; (b) **2.36**, cat. $Pd(PPh_3)_4$, 0 °C, 20 min; (c) DIBAL-H, –78 °C; (d) (i) CBr_4, PPh_3, 2,6-lutidine; (ii) $(MeO)_2P(O)Na$; (iii) *n*-BuLi, MeI.

Figure 2.41 Pihko and Koskinen's successful synthesis of a calyculin/calyculinamide tetraene subunit precursor *via* a Sn→Li→Zn→Pd transmetallation.

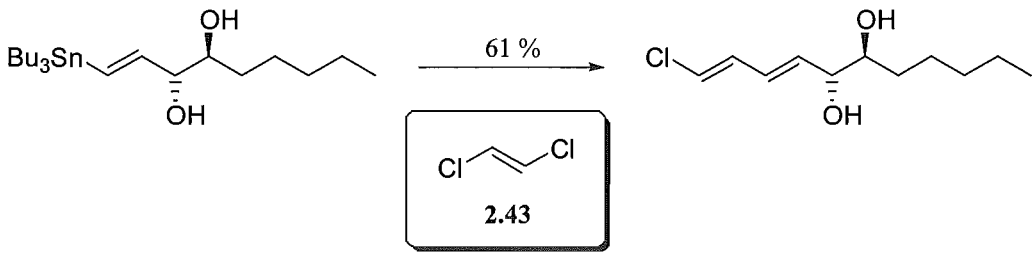
Given the success of Pihko and Koskinen's transmetallation from tin to zinc, a degree of sanguinity accompanied the application of their methodology to the synthesis of **2.33** (**Figure 2.42**). Unfortunately, although ^1H NMR spectroscopic analysis of the crude product mixture formed by this approach showed that starting material had been consumed and that some **2.33** had been formed, there were again several other methoxy signals present, and the yield of desired product was once more disappointing.



Reagents and conditions: (a) (i) *n*-BuLi, THF, –78 °C, 30 min; (ii) $ZnCl_2$, THF, –78 to –20 °C; (b) **2.1**, $Pd(PPh_3)_4$ (5 mol %), 0 °C, THF, 2 h.

Figure 2.42 Low yielding approach to **2.33**, *via* Sn→Zn transmetallation.

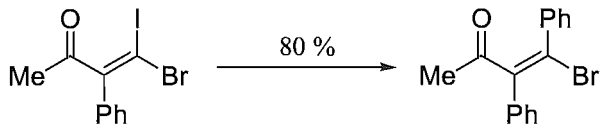
The failure of modification of the transmetallation step to afford efficient access to **2.33** from **2.38** led to the suspicion that it was actually another step in the catalytic cross-coupling cycle that required attention. It is known that for alkenyl halides, the order of reactivity in oxidative addition processes is I > Br > Cl *i.e.* reactivity is inversely proportional to halide electronegativity [the more electron-withdrawing (electronegative) the halogen atom, the more the formation (*via* oxidative addition) of the electron-deficient Pd^{II} complex will be disfavoured]. These reactivity trends are reflected in only activated alkenyl chlorides being reactive under Stille conditions, such as vinyl chloride **2.43** in the diene synthesis below (**Figure 2.43**),[141] in contrast to the ubiquity of a wide range of alkenyl bromides and iodides in Stille couplings.



Reagents and conditions: **2.43**, cat. $Pd(PPh_3)_4$, DMF.

Figure 2.43 Rare example of the use of an alkenyl chloride in a Stille coupling reaction.

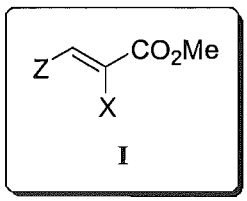
Similarly, a distinction also exists between alkenyl bromides and alkenyl iodides, with the relatively lower reactivity of bromides meaning they only participate in oxidative addition at elevated temperatures, under which conditions they also often undergo (*E*)→(*Z*) isomerisation. Since stereoselectivity is almost invariably a prequisite for a given cross-coupling reaction, an iodide is thus often preferred over the corresponding bromide. A clear example of these halides' relative reactivities is seen below, where the mild reaction temperature leaves the bromide functionality untouched whilst the iodide reacts (**Figure 2.44**).[142]

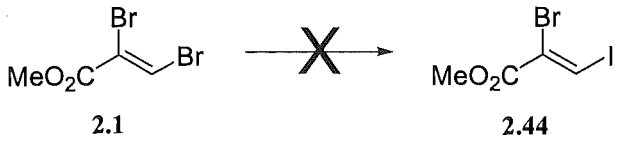


Reagents and conditions: $PhSnMe_3$, cat. $Pd(PPh_3)_2Cl_2$, THF, r.t.

Figure 2.44 Example of the differing reactivities of alkenyl bromides *versus* iodides.

The application of such a tactic to the synthesis of **2.33** required a form of fragment **I** with (at least) substituent Z being iodine; obviously, it would be convenient if such a molecule could be accessed from vinyl bromide **2.1**. However, an initial attempt to generate this desired iodide (**2.44**) *via* the I-for-Br exchange procedure for aromatic bromides reported by Suzuki *et al.*[143] led only to degradation of starting material (**Figure 2.45**).

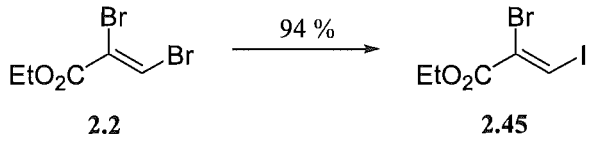




Reagents and conditions: KI, CuI, HMPA, 160 °C, 60 h.

Figure 2.45 Attempt to synthesise iodide **2.44** from bromide **2.1**.

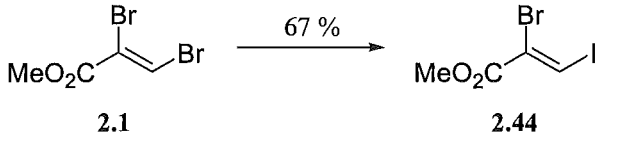
It was subsequently discovered that Caddick *et al.* had reported the use of a Finkelstein reaction[144] to generate vinyl iodide **2.45** from the corresponding bromide **2.2** (**Figure 2.46**).[145] [This halide exchange is an equilibrium process, but is shifted in favour of the production of **2.45** by the precipitation of NaBr (which is insoluble in acetone) out of solution in the reaction mixture].



Reagents and conditions: NaI, acetone, reflux, 72 h.

Figure 2.46 Caddick *et al.*'s synthesis of iodide **2.45** from bromide **2.2**.

As was hoped, analogous treatment of vinyl bromide **2.1** afforded a good yield of vinyl iodide **2.44** (**Figure 2.47**).



Reagents and conditions: NaI, acetone, reflux, 72 h.

Figure 2.47 Synthesis of iodide **2.44** from **2.1**.

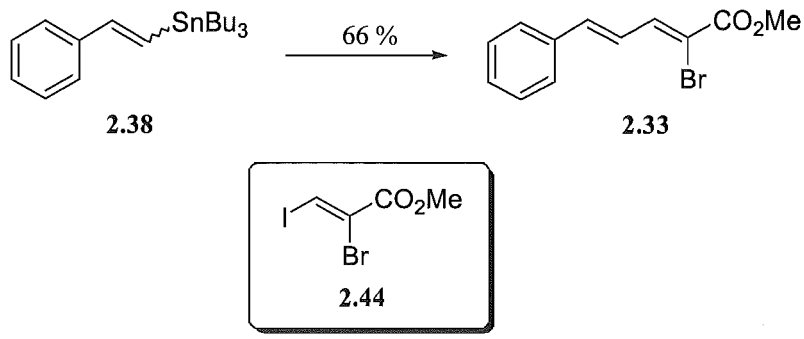
Having established access to vinyl iodide **2.44**, the stage was now set for determining whether it would prove more amenable to oxidative addition with Pd than its largely unreactive bromine analogue (**2.1**). Accordingly, **2.44** was combined with stannane **2.38** under Stille conditions and, satisfyingly, this reaction afforded a much-improved yield (55%) of desired diene **2.33** (**Figure 2.48**) as a bright yellow solid [MP 53-55 °C (lit. 60-61 °C)[146]].♚ This result supported the hypothesis that oxidative addition of Pd into the C–Br bond of **2.1** had been the inefficacious step in previous attempts to synthesise **2.33** *via* stannane **2.38** (*and somewhat restored the author's faith in chemistry*). It also seems likely that this relatively low reactivity of bromide **2.1** might have contributed to the low yield of **2.33** obtained *via* borane **2.34** (see **Figure 2.35**).

Attention was now turned to optimising the coupling reaction between **2.38** and **2.44** by varying the nature of the palladium/ligand catalyst and solvent systems. A total of eight different systems were trialled, including $Pd(PhCN)_2Cl_2/AsPh_3/CuI$,§ but the best results were obtained with $Pd(dppf)Cl_2$, which gave a 66% yield of **2.33** (**Figure 2.48**).

♚ Although this illustrates a discrepancy between the melting point observed for **2.33** and the value reported for this compound by von Auwers and Müller in 1923,[146] the rest of the spectroscopic data for **2.33** were consistent with the structure shown.

§ Farina *et al.* have shown that in Stille couplings utilising both highly polar solvents such as NMP and weakly-coordinating ligands such as $AsPh_3$, the intermediacy of an organocopper species is likely *i.e.* the overall transmetallation process is Sn→Cu→Pd, as in the equation below [Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. *J. Org. Chem.* **1994**, *59*, 5905]. The use of $AsPh_3$ and CuI has proven invaluable for facilitating Stille couplings that are otherwise difficult to achieve, such as those of α-iodoenones [Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919].

$$RSnBu_3 + CuI \overset{NMP}{\rightleftharpoons} RCu + ISnBu_3$$



Reagents and conditions: **2.44**, $Pd(dppf)Cl_2$ (5 mol %), DMF, 80 °C, dark, 12 h.

X	**Catalyst** (5 mol %, except *)	**Solvent**	**Yield**
Br	$Pd(PPh_3)_2Cl_2$	DMF	< 20 %
I	$Pd(PPh_3)_2Cl_2$	DMF	55 %
I	$Pd(PPh_3)_2(OAc)_2$	DMF	48 %
I	$Pd(PhCN)_2Cl_2$, $AsPh_3$, CuI*	NMP	49 %
I	$Pd(AsPh_3)_2Cl_2$	DMF	58 %
I	$Pd(CH_3CN)_2Cl_2$	DMF	54 %
I	$[PdCl(\pi\text{-}C_3H_5)]_2$	DMF	60 %
I	$Pd(PPh_3)_4$	DMF	63 %
I	$Pd(dppf)Cl_2$	DMF	66 %

* 5 mol %/10 mol %/10mol %

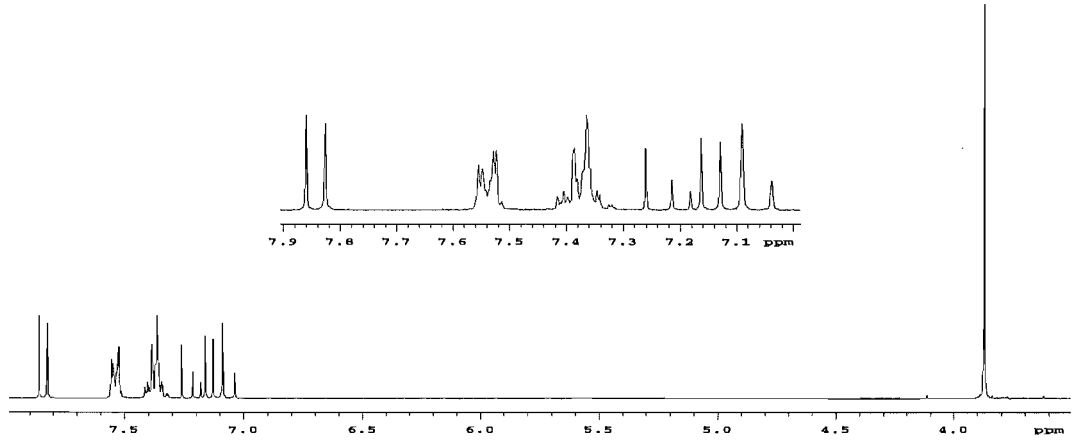


Figure 2.48 Optimised synthesis and 500 MHz ^1H NMR spectrum of type G diene **2.33**.

The fact that the Pd catalyst incorporating a chelating ligand [$Pd(dppf)Cl_2$], rather than a 'soft' ligand [*e.g.* $Pd(PhCN)_2Cl_2/AsPh_3$, $Pd(AsPh_3)_2Cl_2$] afforded the best yield of product was interesting. Although this phenomenon was not investigated further, it could be that steric constraints imposed on the complex's structure by dppf are one of the reasons for its greater activity in this reaction (in contrast to electronic effects which generally dominate in the reactions where catalysts incorporating 'soft' ligands, such as $AsPh_3$, are most effective). Indeed, Hayashi *et al.* observed that the P–Pd–P angle in the X-ray crystallographic structure of $Pd(dppf)Cl_2$ is unusually large, presumably due to the steric effect of the bulky dppf moiety (**Figure 2.49**).[147]

The magnitude of this angle in $Pd(dppf)Cl_2$ may signify the presence of significant strain in the chelate ring, and dissociation of one of the phosphine groups of the dppf moiety from Pd would relieve this strain and thus be an energetically favourable process. Since such a dissociation of one of the phosphine ligands on Pd is required for the associative L-for-R^2 substitution of the rate-determining Sn → Pd transmetallation, according to Casado and Espinet's proposed mechanism for the Stille coupling (see *Chapter 1*, **Figure 1.36**),[79c] this may indicate that this $Pd(dppf)Cl_2$-catalysed Stille coupling reaction also follows this mechanistic pathway, as opposed to one in which transmetallation involves a dissociative I-for-R^2 process (see *Chapter 1*, section **1.6.1.3** and **Figure 1.30**).[Ω]

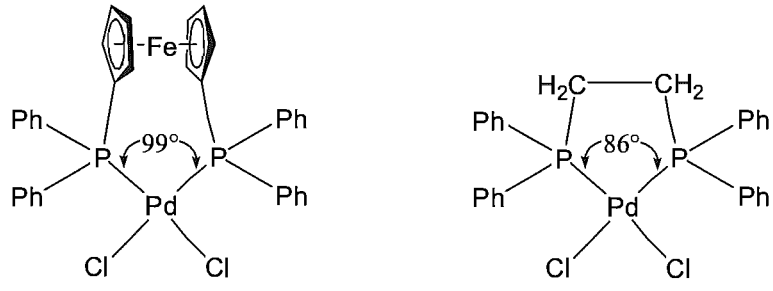
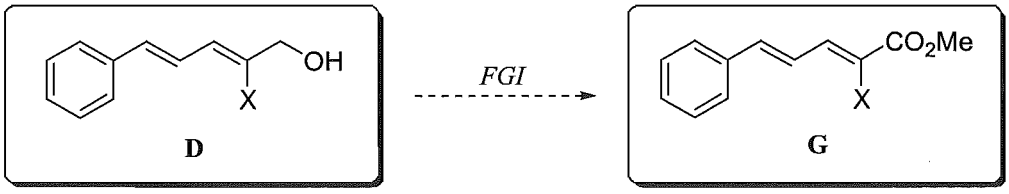


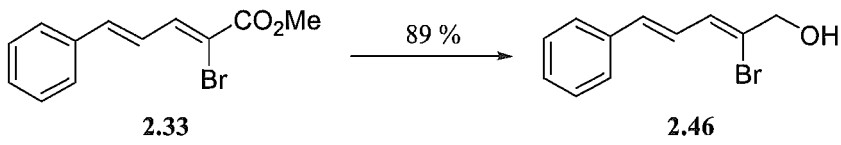
Figure 2.49 Large P–Pd–P angle of $Pd(dppf)Cl_2$ compared to $Pd(dppe)Cl_2$.

[Ω] Furthermore, Hayashi *et al.* observed that in the $Pd(Y)Cl_2$-catalysed cross-coupling of alkyl Grignard and alkylzinc reagents with organic halides, where Y equals one of the bidentate phosphines dppf, dppe [1,2-bis(diphenylphosphino)ethane], dppp [1,3-bis(diphenylphosphino)propane], or dppb [1,4-bis(diphenylphosphino)butane], the selectivity and activity of the catalyst was proportional to the magnitude of its P–Pd–P angle, which was in turn proportional to the size of the phosphine ligand *i.e.* dppf >> dppb ~ dppp >> dppe.[147]

2.2.4.2 Conversion of Diene G to Diene D



With an efficient route to **G**-type diene **2.33** devised, the next task was to reduce its methyl ester group to the corresponding allylic alcohol to yield a type **D** diene. Pleasingly, this functional group interconversion was efficiently achieved by treating **2.33** with DIBAl-H, based on conditions used by Caddick *et al.*,[145] to afford an 89% yield of diene **2.46** (**Figure 2.50**).

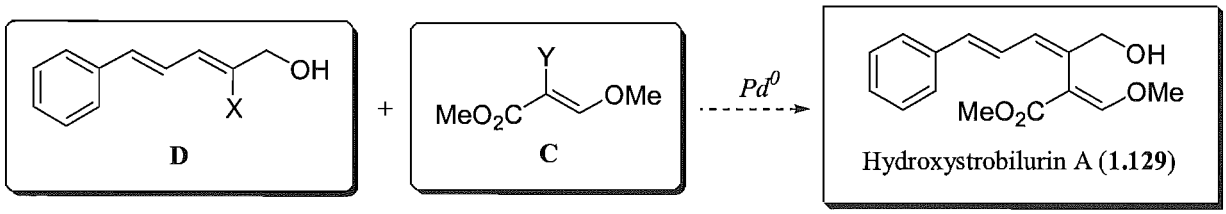


2.33 **2.46**

Reagents and conditions: DIBAl-H, Et_2O, –78 – 0 °C, 3 h.

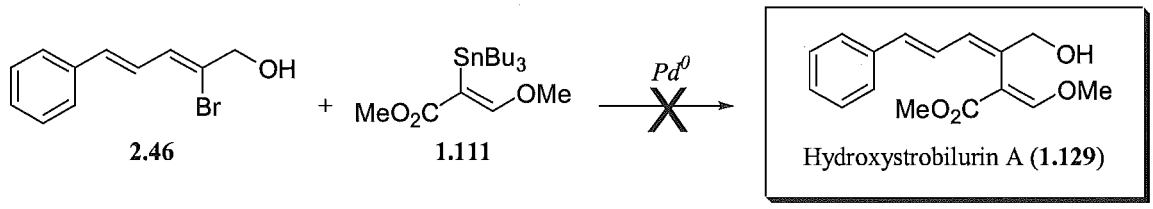
Figure 2.50 Synthesis of diene alcohol **2.46**.

2.2.4.3 Hydroxystrobilurin A From Diene D + β-Methoxyacrylate C?



It was now possible to investigate the viability of a Stille coupling between a diene **D** (**2.46**) and a β-methoxyacrylate **C** (stannane **1.111**) which, if successful, would yield hydroxystrobilurin A. Accordingly, several attempts were made to couple **2.46** and **1.111**, under a variety of different Stille conditions, including the use of Littke and Fu's

$Pd_2dba_3/P(t\text{-}Bu)_3/CsF$ system (**Figure 2.51**).[148] ‡ Disappointingly however, no desired product was afforded by any of these methods, with unreacted or degraded starting reagents being the only materials isolated from reaction mixtures.



Catalyst (mol %)	**Conditions**
$Pd(PPh_3)_2Cl_2$ (5)	NMP, 80 °C
$Pd(PPh_3)_2Cl_2$ (5)	DMF, 80 °C
Pd_2dba_3 (5), $AsPh_3$ (10), CuI	NMP, 50 °C
Pd_2dba_3 (15), $P(t\text{-}Bu)_3$ (60)	NMP, 50 °C
Pd_2dba_3 (15), $P(t\text{-}Bu)_3$ (60), CsF	NMP, 50 °C
Pd_2dba_3 (15), $P(t\text{-}Bu)_3$ (60), CsF	dioxane, 50 °C

Figure 2.51 Summary of unsuccessful attempts to synthesise **1.129** from diene alcohol **2.46** and stannane **1.111**.

It was not clear whether the failure of this Stille coupling was due to the structural or electronic nature of either or both desired coupling partners, however Hodgson *et al.*'s successful utilisation of **1.111** in Stille couplings with a range of different aryl iodides and triflates (see *Chapter 1*, **Figure 1.41**)[104] suggests that this compound was not the problem. Thus, although a usual feature of the Stille technique is its tolerance of unprotected functionality within either coupling partner (see *Chapter 1*, **Figure 1.37**), it seemed that the unprotected hydroxyl group of **2.46** must be somehow inhibiting its reaction with **1.111**.

‡ $P(t\text{-}Bu)_3$ is a sterically-hindered and electron-rich phosphine which, when combined with Pd_2dba_3, catalyses cross-couplings between a wide range of aryl chlorides, even normally unreactive electron-rich and electron-neutral examples [Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3387]. CsF plays a dual role, presumably facilitating the Sn→Pd transmetallation of the Stille process, *via* F^- attaching to the organotin reagent to form a hypervalent, pentacoordinate, more reactive tin species, whilst also assisting in removal of tin residues – the bane of many a synthetic chemist – presumably *via in situ* formation of insoluble Bu_3SnF (as no Bu_3SnCl can be detected in product mixtures).[92]

Investigating methods of protecting this hydroxyl group, and exploring the Stille reactivity of the resultant derivatives, therefore constituted the next area requiring examination.

Even if it turned out to have no effect on the desired Stille coupling process, hydroxyl protection constitutes the first step required to transform **2.46** into the corresponding stannane form of **D**, *en route* to determining if the latter would react with haloacrylates **1.117** or **1.112** (see **Figure 2.1**); such an interchange of the functionalities of desired Stille coupling partners is a technique often employed to facilitate/optimise these reactions.

2.2.4.4 Utilisation of Protected Dienes J *en route* to Hydroxystrobilurin A

The rationale here was simple; convert **2.46** to a protected derivative **J**, determine if **J** was amenable to the desired Stille coupling with **1.111**, and if so, if the resultant triene could be deprotected to give hydroxystrobilurin A (**1.129**) (**Figure 2.52**).

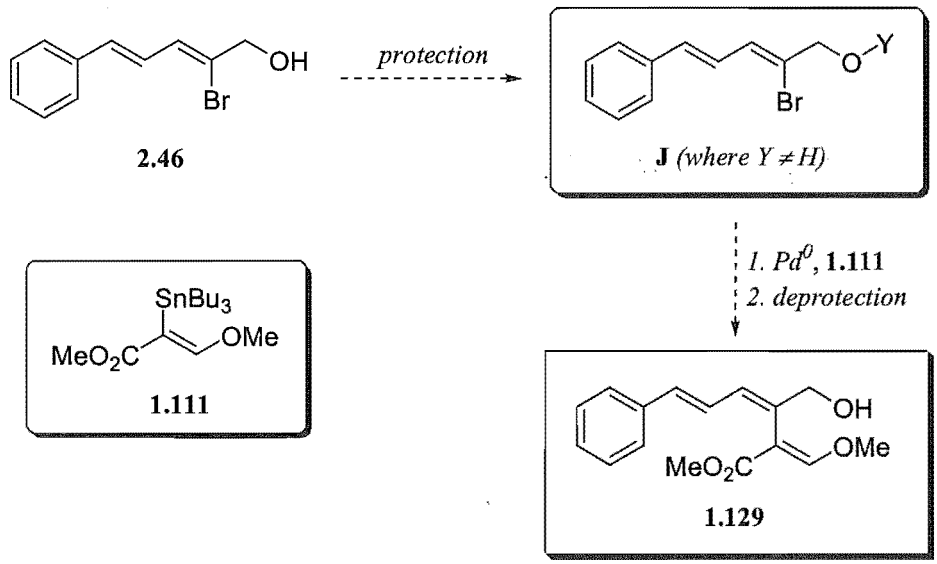
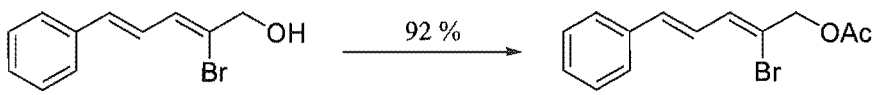


Figure 2.52 General protection – Pd coupling – deprotection scheme.

It was decide to first investigate acetate as a protecting group, as it was thought its presence should impart a different electronic character to the C–Br bond of the diene (compared to the

hydroxyl H of **2.46**) and thus perhaps facilitate the desired Stille coupling with **1.111**. Accordingly, diene acetate **2.47** was efficiently synthesised by treatment of **2.46** with acetic anhydride (Ac_2O) and triethylamine (**Figure 2.53**).



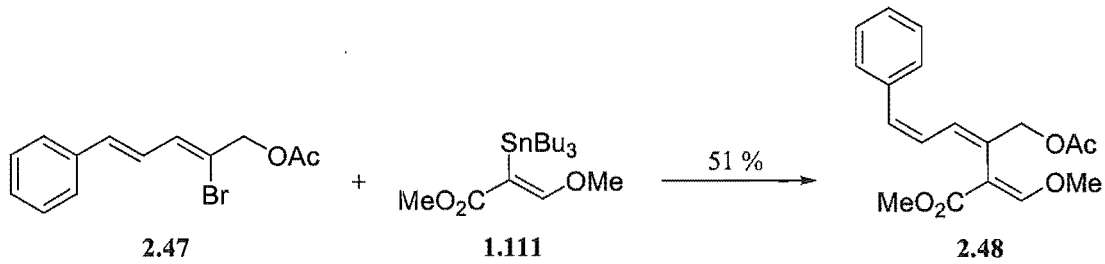
2.46 **2.47** [Ac = C(O)Me]

Reagents and conditions: Ac_2O, NEt_3, DMAP, CH_2Cl_2, 0 °C – r.t., 2 h.

Figure 2.53 Synthesis of diene acetate **2.47**.

Diene acetate **2.47** was duly combined with stannane **1.111** under Stille conditions, and, happily, along with 20% of the diene starting material being recovered, some coupling product (**2.48**) was also obtained (**Figure 2.54**). However, from inspection of the olefinic coupling constants in the ^{1}H NMR spectrum of triene acetate **2.48**, it was clear that the stereochemistry of the diene had not been preserved: the magnitude of the coupling constant for the protons of the double bond immediately adjacent to the phenyl ring (5.6 Hz) was significantly different from that for the same protons in the starting material (15.6 Hz). Indeed, although the latter value was consistent with the expected *trans* $^3J_{HH}$ relationship between these two protons (*trans* coupling constants typically being around 14-16 Hz), the former value was not, rather being consistent with a *cis* $^3J_{HH}$ relationship (*cis* coupling constants typically being around 6-8 Hz). Thus, **2.48** could not possess the desired (*E,E,E*)-triene stereochemistry of the natural product, and was instead tentatively assigned the (*Z,E,E*) structure shown.*

* The reaction was repeated under the same conditions, and again with dppf substituted for $AsPh_3$, and the ^{1}H NMR spectrum of the product obtained in both cases was identical to that in **Figure 2.54**. Thus, the apparent isomerisation was tentatively attributed to the nature of the reagent, as opposed to being due to the reaction conditions (although the observation of non-isomerised triene formation *via* coupling of **1.111** with other dienes was needed to support this hypothesis).



2.47 **1.111** **2.48**

Reagents and conditions: Pd_2dba_3 (10 mol %), $AsPh_3$ (40 mol %), CuI, NMP, 50 °C, dark, 12 h.

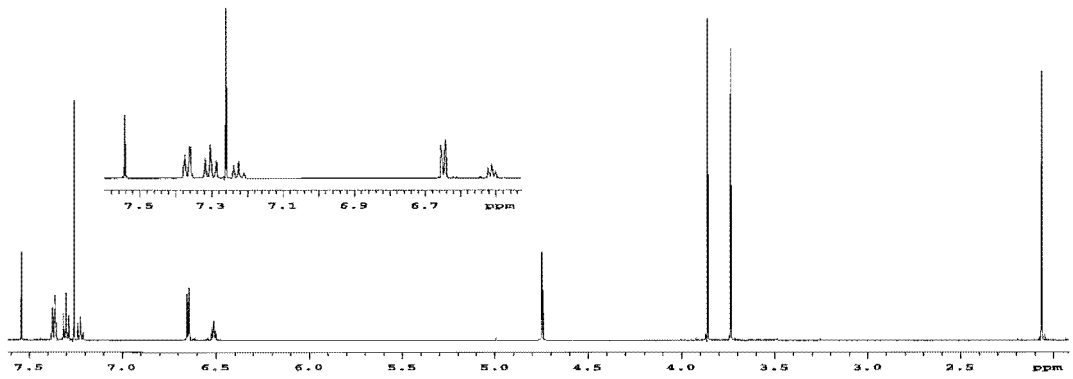


Figure 2.54 Synthesis and 500 MHz ^{1}H NMR spectrum of triene acetate **2.48**.

Unequivocal corroboration of this assignment for the structure of **2.48** would require further spectroscopic studies, conceivably involving NOE experiments to confirm the spatial relationship between protons of the apparent *cis* double bond. However, given that the doublets for two of the olefinic protons are completely coincident (at ~ 6.6 ppm) in its ^{1}H NMR spectrum (see **Figure 2.54**), this would be a difficult exercise, if possible at all.

The occurrence of such double bond isomerisation was interesting, as although the strobilurins are known to undergo such processes if subjected to prolonged UV irradiation, either in the field or in the laboratory (see *Chapter 1*, sections **1.4** and **1.5**), such treatment was not a part of the Stille conditions utilised. It is more likely that this was an example of a Pd-catalysed isomerisation, although the only examples in the literature are of the (*Z*)→(*E*), conversion, rather than the (*E*)→(*Z*) isomerisation observed here.[149] Perhaps, then, the Pd^0-catalysed mechanism in **Figure 2.55** may be a possible manner in which the (*E*)→(*Z*)

isomerisation may proceed,[♣] although whether this would occur prior or subsequent to triene formation is not clear.

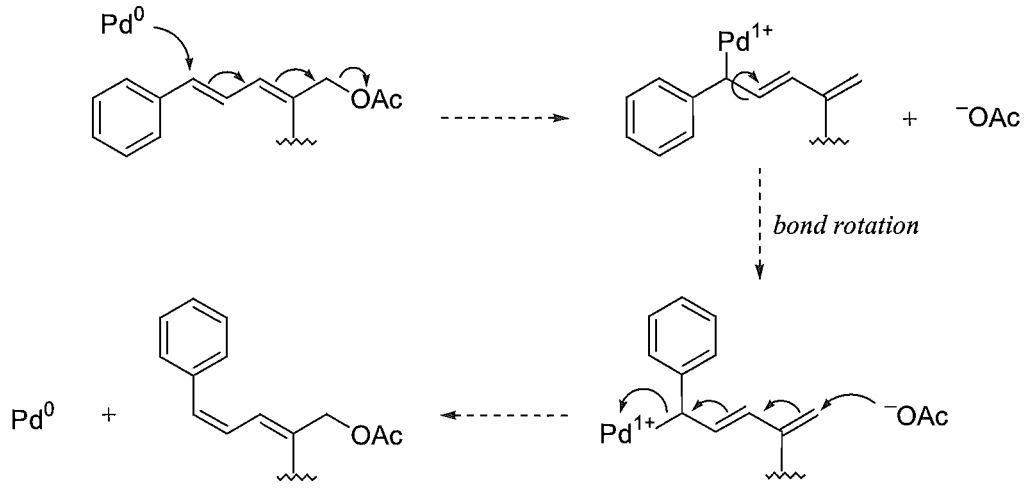
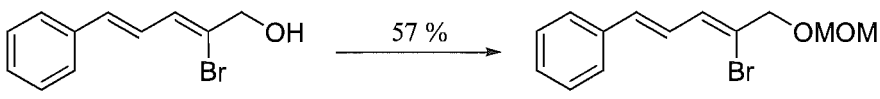


Figure 2.55 Proposed Pd^0-catalysed mechanism for (*E*)→(*Z*) double bond isomerisation.

Despite this unexpected isomerisation *en route* to **2.48**, it was encouraging to have achieved triene formation *via* Stille coupling between a type **J** diene and **1.111** – a result which supported the hypothesis that the hydroxyl group of diene **2.46** was the reason for its non-reactivity under Stille conditions. In the hope that a different type of hydroxyl protection of **2.46** might afford a diene averse to such isomerisation, **2.46** was derivatised to its methoxymethyl (MOM) ether (**2.49**) [**Figure 2.56**].



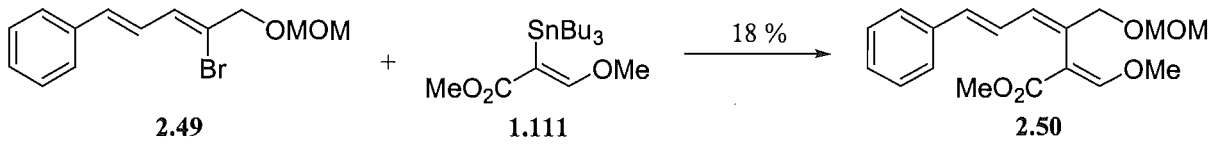
2.46 **2.49** (MOM = CH_2OCH_3)

Reagents and conditions: MOM-Cl, $(i\text{-Pr})_2NEt$, CH_2Cl_2, 0 °C – r.t., 50 h.

Figure 2.56 Synthesis of MOM diene **2.49**.

[♣] Palladium is well-known as a mediator of double-bond isomerisation, *via* the intermediacy of π-allyl palladium complexes [*e.g.* Nakamura, H.; Iwama, H.; Ito, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 10850].

MOM diene **2.49** was reacted with stannane **1.111** under exactly the same Stille conditions as afforded triene acetate **2.48**, but unfortunately only a very low yield (18%) of MOM triene **2.50** was obtained (**Figure 2.57**), with most of **2.49** (~69%) being recovered unreacted. However, it was noted with some relief that the olefinic signals in the ^{1}H NMR spectrum of **2.50** were consistent with the desired (*E,E,E*)-triene geometry shown, as this supported the hypothesis that the apparent isomerisation which occurred during formation of triene acetate **2.48** (see **Figure 2.54**) was a substrate-specific event.



2.49 **1.111** **2.50**

Reagents and conditions: Pd_2dba_3 (10 mol %), $AsPh_3$ (40 mol %), CuI, NMP, dark, 50 °C, 24 h .

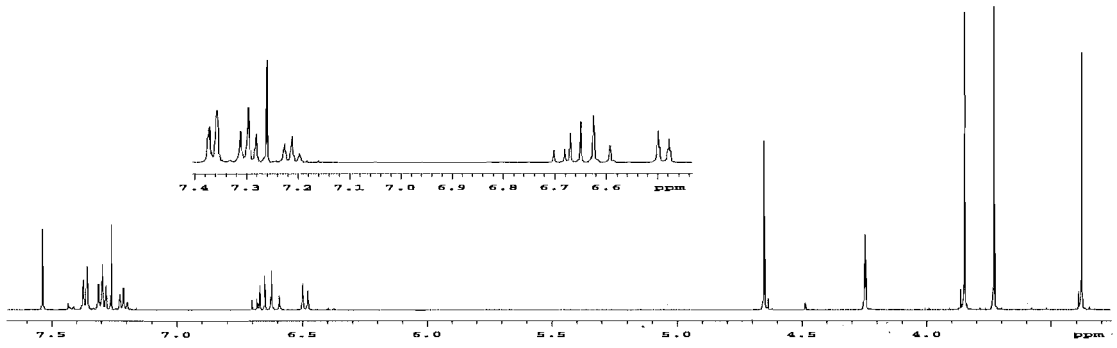


Figure 2.57 Synthesis and 500 MHz ^{1}H NMR spectrum of MOM triene **2.50**.

The low yield obtained from the Stille coupling of **2.49** and **1.111** obviously meant improvement was necessary in order to achieve efficient triene formation. A logical option was to change the nature of substitution on the diene, and to this end the conversion of bromide-substituted MOM diene **2.49** into the corresponding stannane **2.51**, and thence to iodide **2.52**, was necessary (**Figure 2.58**). Access to stannane **2.51** would enable its Stille coupling reactivity with iodide **1.112** (see **Figure 2.10**) to be explored, whilst it was hoped iodide **2.52** might prove as superior to bromide **2.49** in reaction with stannane **1.111** under Stille conditions as iodide **2.44** was to bromide **2.1** in reaction with stannane **2.38** (see **Figures 2.38** and **2.48**).

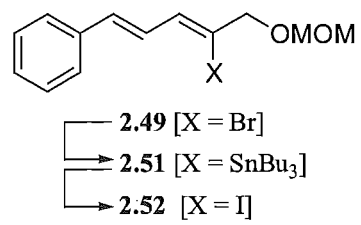
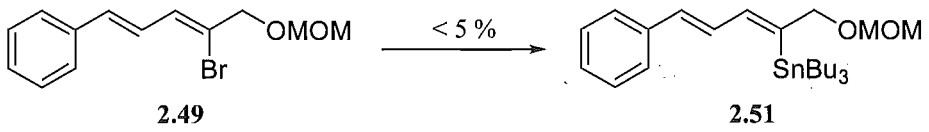


Figure 2.58 Synthetic interconnection between three potential Stille coupling partners.

Initial attempts were made to synthesise stannane **2.51** *via* lithium-halogen exchange, following the method used by Hoye and Chen for the analogous preparation of aryl stannanes (**Figure 2.59**).[150] [ξ] However, despite a deep orange solution forming upon addition of *n*-BuLi, only a trace of desired product was visible in the ^{1}H NMR spectrum of the quenched reaction mixture, with most of the starting material being recovered unreacted. The reaction was repeated with the use of *t*-BuLi instead of *n*-BuLi, but although this more basic alkyllithium generated the rich red colour typical of a conjugated alkenyllithium species, once again much of the starting material was recovered, with only a trace amount of **2.51** being visible in the ^{1}H NMR spectrum of the crude product mixture.



2.49 **2.51**

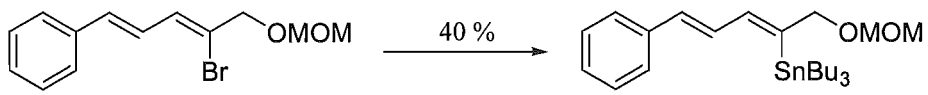
Reagents and conditions: *n*-BuLi or *t*-BuLi (1.0 equiv.), –78 °C – r.t., THF, 20 – 50 min.

Figure 2.59 Attempts to access stannane **2.51** from bromide **2.49** *via* lithium-halogen exchange.

The successful synthesis of stannane **1.111** from bromide **2.1** *via* Pd-catalysed substitution of tin for bromine (see **Figure 2.8**) suggested that this technique might also be fruitful for an alternative route to **2.51** from **2.49**. And indeed, treatment of **2.49** with $(SnBu_3)_2$ under

[ξ] Subsequent to the completion of this area of work concerned with the conversion of bromide **2.49** to stannane **2.51**, it was discovered that specific reaction conditions are necessary for the conversion of vinyl bromides to vinyl stannanes *via* lithium-halogen exchange (distinct from the conditions suitable for the analogous preparation of aryl stannanes): see *Chapter 3*, section **3.2.2**.

palladium catalysis gave a 40% yield of stannane **2.51** (**Figure 2.60**). However, ^{1}H NMR analyses showed that a small amount (~10%) of starting material consistently remained in crude product mixtures, despite attempts to drive the reaction to completion (and hopefully increase yields) by use of longer reaction times and greater amounts of $(SnBu_3)_2$. Thus, investigations towards a more efficient route to **2.51** were instigated.

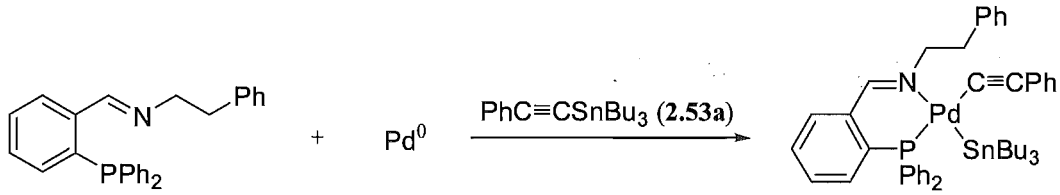


2.49 **2.51**

Reagents and conditions: $(SnBu_3)_2$, $Pd(PPh_3)_2Cl_2$ (5 mol %), toluene, reflux, dark, 48 h.

Figure 2.60 Pd-catalysed synthesis of stannane **2.51** from bromide **2.49**.

Shirakawa *et al.* found that phenylethynylstannane **2.53a** oxidatively adds to a Pd^0 complex coordinated with the bidentate iminophosphine **2.54a** to give the Pd^{II} complex **2.55a** (**Figure 2.61**), a reaction which they utilised for the cross-coupling of **2.53a** with aryl iodides.[151]

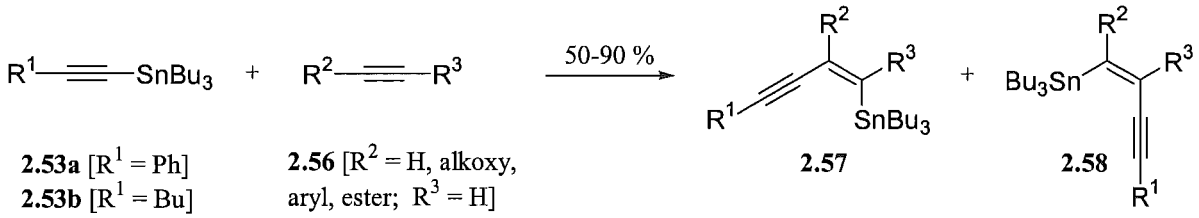


2.54a **2.55a**

Figure 2.61 Shirakawa *et al.*'s oxidative addition of an alkynylstannane to a Pd^0–iminophosphine chelate.

Subsequently, Shirakawa *et al.* discovered that a range of type **2.55** palladium complexes formed from Pd^0, iminophosphines **2.54**, and alkynyl stannanes **2.53** would react with alkynes **2.56** to afford conjugated (*Z*)-(stannyl)enynes **2.57** and **2.58** (**Figure 2.62**).[152] This reaction is a stereoselective *syn* alkynylstannylation of **2.56** by **2.53**, and is the first example of carbometallation proceeding *via* oxidative addition of a C–M bond to a transition metal

complex. Yields, regioselectivities, and reaction rates for the alkynylstannylation process were all increased by the use of iminophosphines bearing more bulky imino moieties (*e.g.* **2.54b** formed a better catalyst with Pd^0 than did **2.54a**), with these iminophosphines **2.54** being prepared by condensation of 2-(diphenylphosphino)benzaldehyde with the appropriate amine (**Figure 2.62**).



Reagents and conditions: $[PdCl(\pi\text{-}C_3H_5)]_2$ (16 mol %), **2.54a-e** (8.2 mol %), THF, 50 °C, 2-96 h.

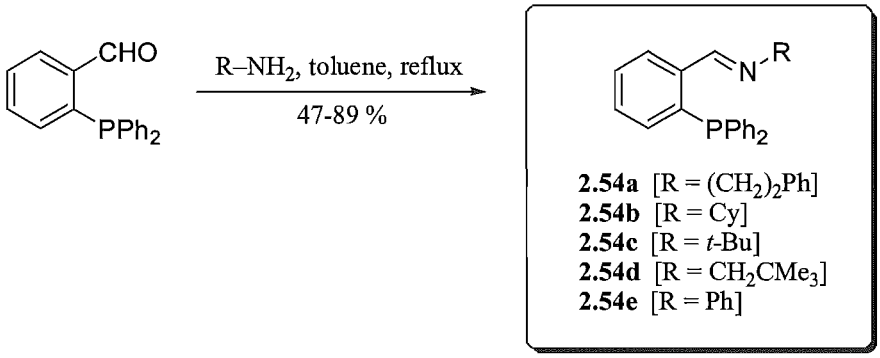
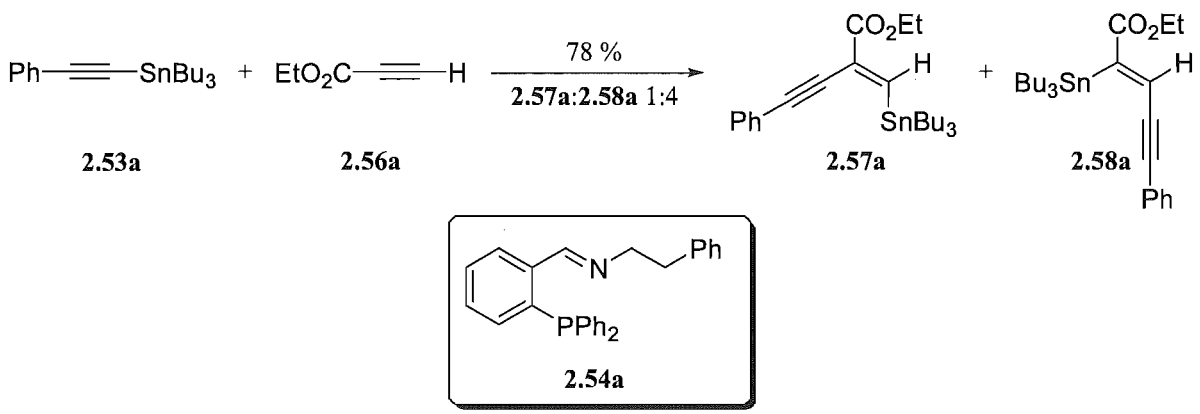


Figure 2.62 Shirakawa *et al.*'s Pd^0–iminophosphine-catalysed alkynylstannylation.

The specific example from this work relevant to the synthesis of stannane **2.51** was the $[PdCl(\pi\text{-}C_3H_5)]_2$/**2.54e**-catalysed reaction between **2.53a** and ethyl propynoate (**2.56a**), which gave a 78% yield of enynes **2.57a** and **2.58a**, in a regioisomeric ratio of 1:4 (**Figure 2.63**).



Reagents and conditions: $[PdCl(\pi\text{-}C_3H_5)]_2$ (16 mol %), **2.54a** (8.2 mol %), THF, 50 °C, 3 h.

Figure 2.63 Potentially useful alkynylstannylation reaction (see below).

It seemed not unreasonable to presume that methyl propynoate (**2.56b**) might successfully replace **2.56a** in this process, which would give access to enynes **2.57b** and **2.58b**, conceivably with a similar degree of regioselectivity (**Figure 2.64**). Reduction of the ester moiety of **2.58b** should afford alcohol **2.59**, which could be protected to give enyne stannane **2.60**. Finally, **2.60** might be able to be stereoselectively reduced to diene stannane **2.51**, concluding a more efficient route to this product than that shown in **Figure 2.60**.

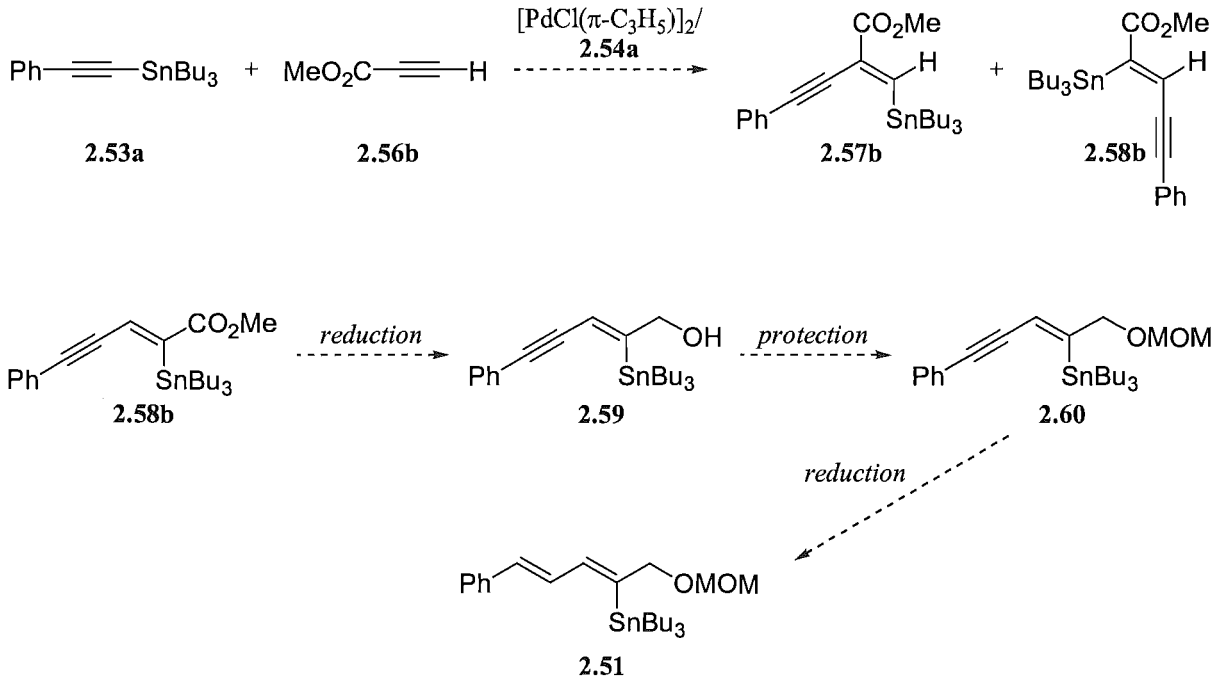
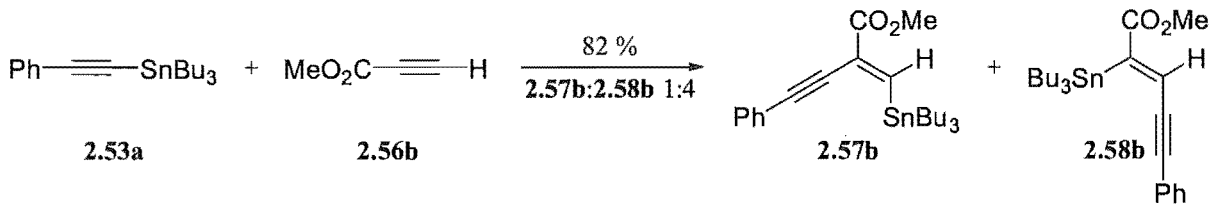


Figure 2.64 Potential for utilisation of alkynylstannylation product **2.58b** in an approach to stannane **2.51**.

Accordingly, imine **2.54a** was prepared according to Shirakawa *et al.*'s procedure (see **Figure 2.62**).[151] Crystallisation of the oily product proved extremely difficult, and it was the luck of the (one quarter) Irish that a satisfactory quantity of solid material [67%, MP 71-74 °C (lit. 87-89 °C)[151]] was able to be obtained (only one of many subsequent attempts at this crystallisation proved fruitful). Happily, however, the desired reaction between **2.53a** and methyl propynoate (**2.56b**) was a success, affording an 82% yield of regioisomers **2.57b** and **2.58b**, in a ratio of 1:4 (**Figure 2.65**).



2.53a **2.56b** **2.57b** **2.58b**

Reagents and conditions: $[PdCl(\pi\text{-}C_3H_5)]_2$/**2.54a**, THF, 50 °C, 3 h.

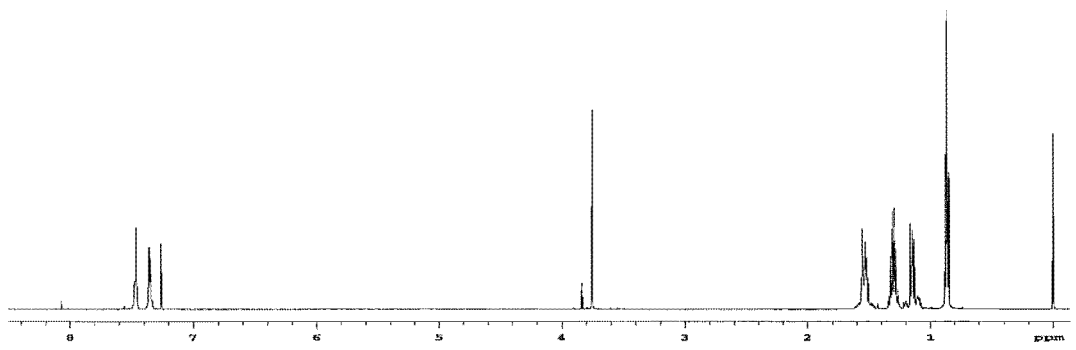


Figure 2.65 Synthesis and 500 MHz ^{1}H NMR spectrum of regioisomeric enynes **2.57b** and **2.58b**.

A mechanism for this process was proposed by Shirakawa *et al.* (**Figure 2.66**).[151,152] The first step is oxidative addition of the alkynylstannane (in this case **2.53a**) to a complex of **2.54** (represented schematically as a simple bidentate N–P moiety) and Pd^0, giving a Pd^{II} complex **2.55** (as discussed previously – see **Figure 2.61**). An alkyne (in this case **2.56b**) can then insert into the C–Pd bond in two regiodistinct ways, to produce carbopalladated intermediates **2.61** and **2.62**. Since **2.56b** is an electron-deficient alkyne, the electronic requirements of these intermediates will dominate over demands for the minimisation of steric interactions in their structures, and thus electronically favoured intermediate **2.61** will dominate over sterically intermediate favoured intermediate **2.62**.[φ] Thus, reductive elimination will afford a product mixture in which enyne **2.58b** will be more prevalent than its regioisomer **2.57b**, as observed (see **Figure 2.65**).

[φ] Conversely, in the reactions of more bulky aryl alkynes, steric factors dominate over electronic demands, and thus the carbopalladation intermediate which minimises steric interactions is favoured, leading to a mixture of regioisomers of an inversely proportional ratio (to that which would be produced by the domination of electronic demands).

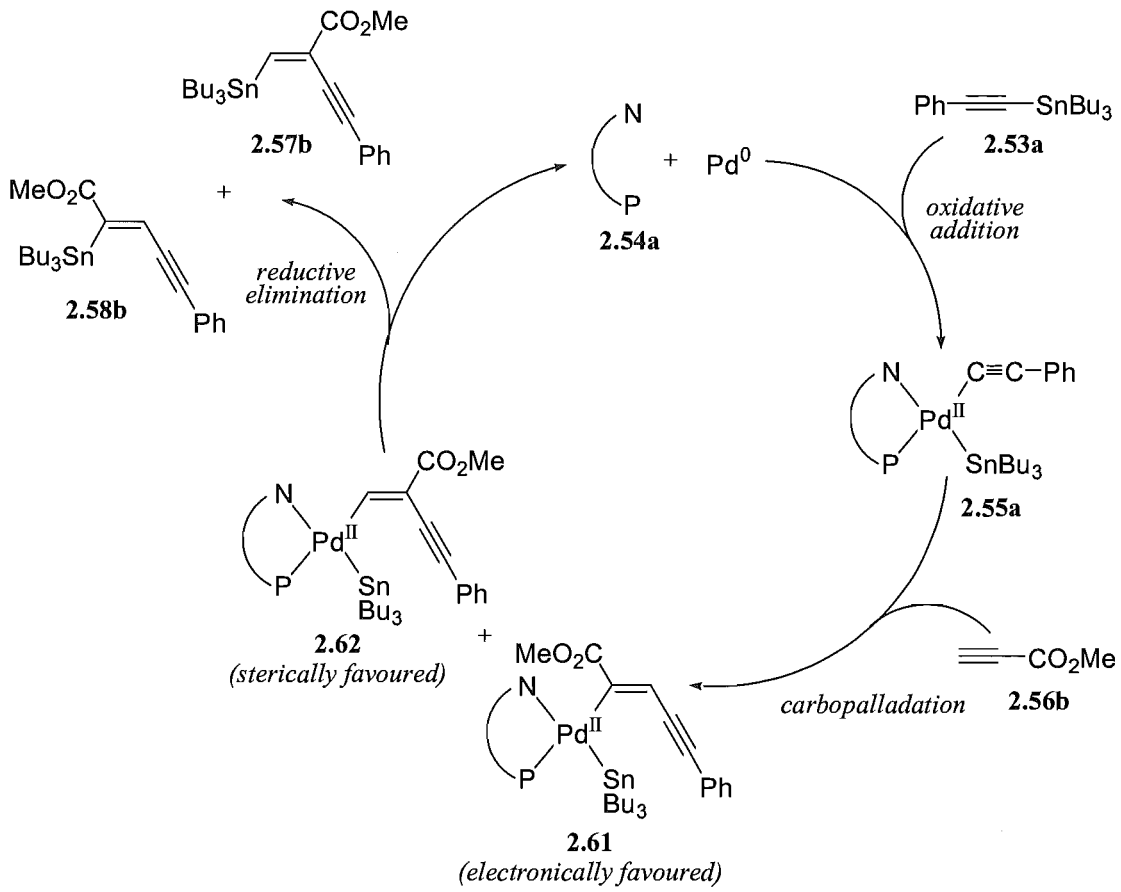
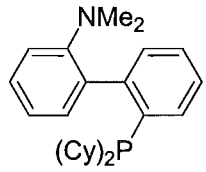


Figure 2.66 Shirakawa *et al*'s proposed mechanism for alkynylstannylation.

Imine ligand **2.54e** (see **Figure 2.62**) had also been used successfully by Shirakawa *et al.*, affording a 71% yield of enynes **2.57a** and **2.58a** from the reaction of **2.53a** and **2.56a**, with the 1:13 ratio of **2.57a** to **2.58a** being considerably better than the 1:4 ratio achieved with imine **2.54a** (**Figure 2.63**)].[152] Accordingly, **2.54e** was prepared, but unfortunately this imine proved even more averse to recrystallisation than **2.54a**, and so was not able to be utilised in any alkynylstannylation reaction.

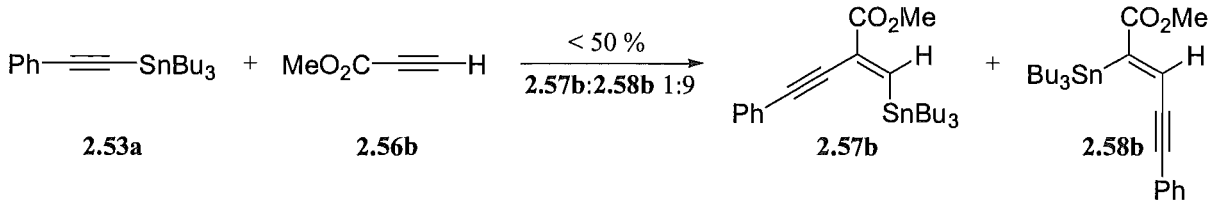
Whilst searching for an easily recrystallisable or naturally crystalline alternative to imines **2.54a** and **e**, it was found that the bidentate compound 2-(dicyclohexylphosphino)-2'-(*N*,*N*-dimethylamino)biphenyl (**2.63**), one of a family of biphenyl compounds which Buchwald *et al.* have used to form highly active complexes with $Pd(OAc)_2$ that catalyse room-temperature Suzuki couplings of aryl halides,[153] was a commercially available crystalline solid. It was

recognised that the N and P atoms of **2.63** might function as an *amino*phosphine moiety and chelate with Pd^0 in an analogous manner to the N and P atoms of *imino*phosphines **2.54a-e**, perhaps enabling a Pd^0-**2.63** complex to also function as a catalyst for the alkynylstannylation process.



2.63

Thus, following the purchase of a quantity of **2.63**, **2.53a** was combined with **2.56b** under the conditions used previously (see **Figure 2.65**), except with replacement of **2.54e** with **2.63** (**Figure 2.67**). ^{1}H NMR spectroscopic analysis of the crude product mixture showed that starting materials had been consumed, and that there appeared to be some desired product present, as well as several side products. But most interestingly, integrals for the methoxy signals showed that the ratio of **2.57b** to **2.58b** was 1:9, considerably better than the 1:4 ratio obtained with imine ligand **2.54a** (see **Figure 2.65**). Given the steric bulk of **2.63**, this result further illustrated the dominance of electronic over steric demands in alkynylstannylations of electron-deficient alkynes such as **2.56b**, in accordance with the observations of Shirakawa *et al.*[152] However, following initial chromatographic purification attempts, it was clear that the yield of enynes **2.57b** and **2.58b** from this Pd^0/**2.63**-catalysed alkynylstannylation reaction (<50%) was inferior to that obtained with **2.54a** (82%), so investigations in this area were discontinued (although it may be an interesting exercise for future workers to explore the optimisation of this reaction).



2.53a **2.56b** **2.57b** **2.58b**

Reagents and conditions: $[PdCl(\pi\text{-}C_3H_5)]_2$/**2.63**, THF, 50 °C, 3 h.

Figure 2.67 Use of biphenyl ligand **2.63** in Shirakawa-style enyne synthesis.

Notwithstanding the facility with which this alkynylstannylation generates enynes, it was recognised that an even more useful result would be if $[PdCl(\pi\text{-}C_3H_5)]_2$/**2.54a** or **2.63** catalysed the *alkenyl*stannylation of **2.53b** by phenylethenylstannane **2.38**, as this would enable immediate access to diene stannane **2.64**, a stannyl analogue of diene **2.33** (**Figure 2.68**). Stannane **2.64** should then be able to be converted to stannane **2.51**, or could perhaps be more directly utilised as a Stille coupling partner with iodide **1.112**, to give triene ester **2.65**.

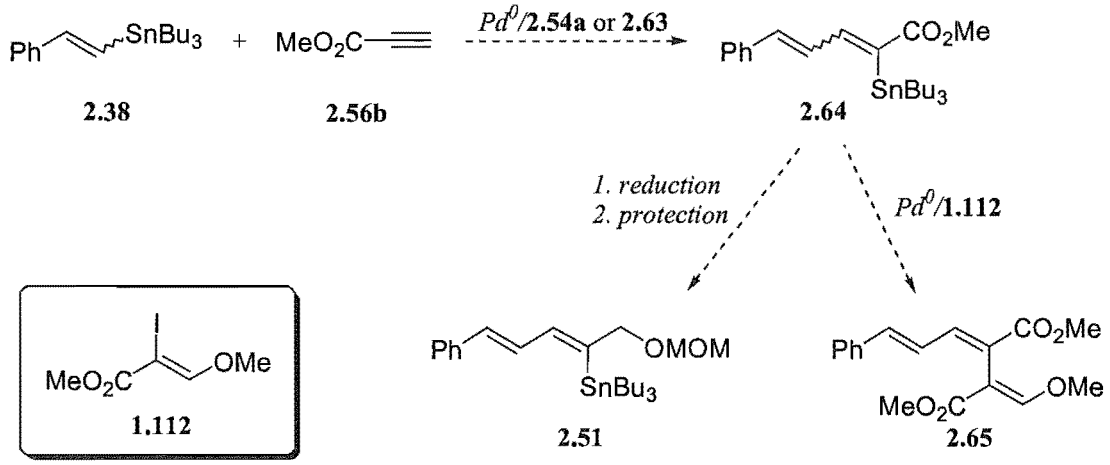
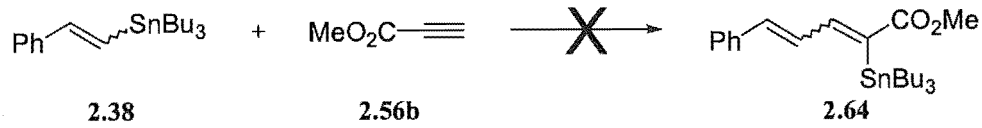


Figure 2.68 Potential alkenylstannylation route to useful stannane **2.64**.

Accordingly, a mixture of **2.38** and **2.56b** was treated with $[PdCl(\pi\text{-}C_3H_5)]_2$/**2.54a** or **2.63** under the same conditions that generated enynes **2.57b** and **2.58b**, except that reaction mixtures were stirred for 12 h instead of 3 h. Disappointingly, ^{1}H NMR spectroscopic analysis of reaction mixtures showed only unreacted **2.38** and small amounts of several unidentified methoxylated side products to be present, with no conjugated olefinic signals visible (**Figure 2.69**). The procedure was repeated with toluene as a solvent instead of THF, but was similarly unsuccessful. At this point, it was clear that alkenylstannylation was not possible under Shirakawa conditions, so this approach to **2.64** was abandoned.

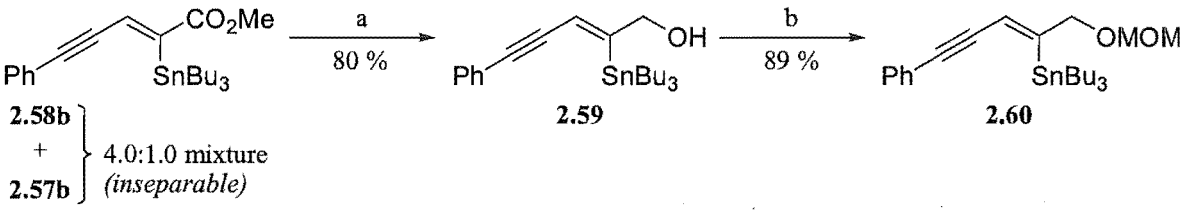


2.38 **2.56b** **2.64**

Reagents and conditions: $[PdCl(\pi\text{-}C_3H_5)]_2$/**2.54a** *or* **2.63**, THF *or* toluene, 50 °C, 12 h.

Figure 2.69 Attempted alkenylstannylation route to stannane **2.64**.

Returning to the enyne approach to stannane **2.51** (see **Figure 2.64**, page 122), the next task was to reduce ester functionalities of enynes **2.57b** and **2.58b**, and it was hoped that the two enyne alcohols produced might be of sufficiently different polarity to enable separation. Happily, this proved to be the case, with enyne alcohol **2.59** (**Figure 2.70**) easily separable from its regioisomer by the use of standard flash chromatography techniques. Subsequent treatment of **2.59** with MOM-Cl afforded an excellent yield of enyne MOM ether **2.60**.



2.58b + **2.57b** 4.0:1.0 mixture *(inseparable)*

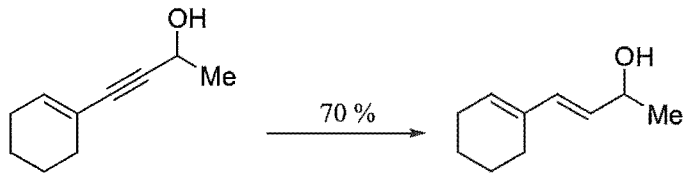
2.59 **2.60**

Reagents and conditions: (a) DIBAl-H, Et_2O, –78 – 0 °C, 3 h; (b) MOM-Cl, $(i\text{-}Pr)_2NEt$, 0 °C – r.t., 48 h.

Figure 2.70 Synthesis of enyne MOM ether **2.60** *via* enyne alcohol **2.59**.

Now it was time to determine if the triple bond of **2.60** could be selectively reduced – both stereoselectively [to give the (*E*)-alkene] and chemoselectively [leaving the double bond of the enyne untouched] – to complete the alternative route to diene stannane **2.51** outlined in **Figure 2.64**. A search of the literature revealed two papers which suggested that the appropriate hydride addition reagent would be $LiAlH_4$. In the first, Chanley and Sobotka used $LiAlH_4$ for the selective reduction of the triple bond of enyne **2.66** to diene **2.67** (**Figure 2.71**).[154] Although they do not specify the stereochemistry of the reaction or of **2.67** itself, the second

study (see below) attests to the fact that the addition of hydride to **2.66** must occur in an *anti* fashion, to give the (*E*)-alkene **2.67** as shown.

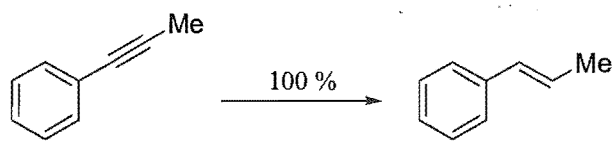


2.66 **2.67**

Reagents and conditions: $LiAlH_4$, Et_2O, reflux, 3 h.

Figure 2.71 Chanley and Sobotka's stereoselective and chemoselective enyne reduction.

Magoon and Slaugh detail the use of $LiAlH_4$ for the 100 % stereoselective reduction of a number of internal alkynes to (*E*)-alkenes, exemplified by the reduction of 1-phenyl-1-propyne (**2.68**) to 1-phenyl-1-propene (**2.69**) [**Figure 2.72**].[155] The utilisation of the ethereal solvent THF was found to be critical to the stereochemistry and efficacy of the process; when toluene was used instead, the major products were the corresponding (*Z*) alkene (resulting from *syn* addition of hydride to the alkyne) and the fully saturated alkane.



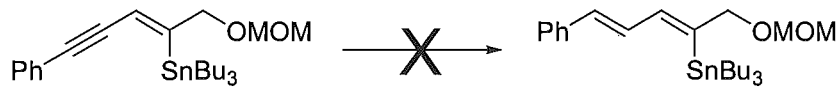
2.68 **2.69**

Reagents and conditions: $LiAlH_4$, THF, reflux, 13 h.

Figure 2.72 One of Magoon and Slaugh's stereoselective alkyne reductions.[†]

[†] The fact that such alkyne substrates may be successfully reduced with $LiAlH_4$ seems to disprove the statement that '$LiAlH_4$ is only effective [at reducing alkynes to alkenes] when the alkyne has a hydroxyl group in the α-position' [Norman, R. O. C.; Coxon, J. M. *'Principles of Organic Synthesis' (3rd edn.)* **1993** (Blackie Academic & Professional, Chapman & Hall, Glasgow, UK), 640].

Thus it was with reference to the successful reductions discussed above that an analogous reduction of enyne **2.60** was attempted. TLC analysis of the crude reaction mixture appeared to show that starting material had been consumed, but although the ^{1}H NMR spectrum contained some olefinic signals, the number of these, and the very small integral values for the several MOM group signals also present suggested that starting material had been deprotected and/or degraded by the conditions used (**Figure 2.73**). The material obtained from column chromatography of this crude mixture seemed to confirm these suspicions, with small amounts of many different unidentified compounds being isolated. Although not constituting a full investigation of the viability of this reduction, this initial lack of success led to a decision to suspend this area of investigation, and return to it later if the alternative 'all-diene' route already underway proved ultimately unsuccessful.



2.60 **2.51**

Reagents and conditions: $LiAlH_4$, THF, reflux, 13 h.

Figure 2.73 Attempt to access stannane **2.51** by reduction of enyne **2.60**.

The key question now was whether stannane **2.51** would serve as a more efficient precursor to MOM triene **2.50** than its bromine analogue **2.49** (see **Figure 2.57**). In addition, with sufficient quantities of both bromide **1.117** and iodide **1.112** available, it should be possible to compare the reactivity of these two acrylates with **2.51** under Stille conditions (**Figure 2.74**).

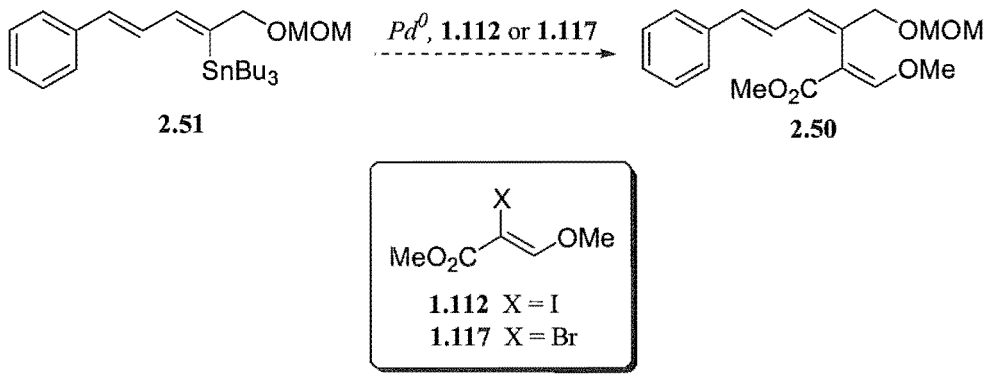
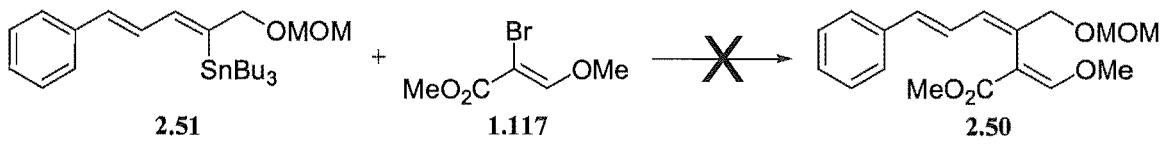


Figure 2.74 Potential Stille coupling route to MOM triene **2.50** *via* stannane **2.51**.

In a first attempt to form triene **2.50**, stannane **2.51** was combined with bromide **1.117** in the presence of catalytic $Pd(dppf)Cl_2$ (**Figure 2.75**). The reaction mixture was followed by TLC, and with no change evident after 12 h stirring at room temperature, was heated to 50 °C and maintained at this temperature for 12 h. After this time, TLC analysis showed that in addition to starting material, there was also a new compound present. Unfortunately, ^1H NMR spectroscopic analysis of the fractions obtained from chromatographic purification of the crude product mixture showed that no coupling product was present. The products appeared to be various isomers derived from homocoupling of **2.51**, with virtually all of the quantity of **1.117** originally added to the reaction mixture being recovered.



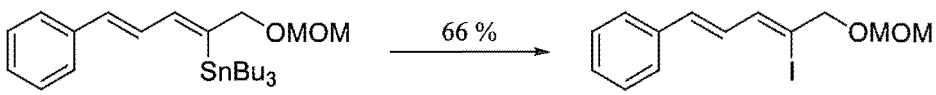
Reagents and conditions: $Pd(dppf)Cl_2$ (5 mol %), DMF, r.t. – 50 °C, dark, 24 h.

Figure 2.75 First attempt to form MOM triene **2.50** *via* stannane **2.51**.

Following this initial attempt, the above reaction was repeated under the same conditions, but with bromide **1.117** replaced by iodide **1.112**. TLC analysis of the reaction mixture after

12 h stirring at 50 °C showed only starting materials were present, so the reaction temperature was increased to ~100 °C and the mixture stirred for a further 24 h. After this time the reaction mixture was still unchanged according to TLC analysis, so was stirred for a further 96 h, leading to consumption of the limiting reagent (**1.112**). A ^{1}H NMR spectrum of the isolated crude material showed that together with some unreacted **2.51**, there were some interesting new signals. However, column chromatography afforded fractions containing only unreacted **2.51** and what appeared to be another mixture of isomers of homocoupled **2.51**. Taken together with the failure of **2.51** to couple with **1.117** (see **Figure 2.75**), this result seemed to demonstrate that stannane **2.51** was unreactive with acrylates **1.112** and **1.117** under Stille conditions. [*However, see page 132 for a re-appraisal of the success of this attempted coupling of* **2.51** *and* **1.112**].

Given the apparent non-reactivity of **2.51**, the next option in the synthetic plan (based on the interconnection depicted in **Figure 2.58**) was to determine if its iodo-analogue **2.52** might couple with stannane **1.111** under Stille conditions to give MOM triene **2.50**. Thus, **2.51** needed to be iododestannylated, a process which had successfully been utilised for the synthesis of iodide **1.112** from stannane **1.111** (see **Figure 2.10**). Treatment of **2.51** using these conditions did afford some product, but in a mediocre 45% yield. However, the efficiency of the process was improved by the use of Et_2O instead of CH_2Cl_2 (as *per* Rousset *et al.*[156]), giving a 66% yield of iodide **2.52** (**Figure 2.76**).



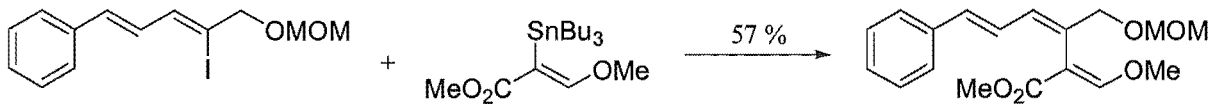
2.51 **2.52**

Reagents and conditions: I_2, Et_2O, 0 °C, 1 h.

Figure 2.76 Synthesis of iodide **2.52** by iododestannylation of **2.51**.

Iodide **2.52** was duly combined with stannane **1.111** under Stille conditions, and, pleasingly, produced a good yield (57%) of MOM triene **2.50**. ^{1}H NMR spectroscopic analysis of **2.50**

showed it possessed the desired (*E*,*E*,*E*) stereochemistry, and that it contained 9% of another unidentified triene isomer, from which it was inseparable by column chromatography. This result was further support for the hypothesis that the double bond isomerisation which apparently occurred during the formation of **2.48** was an adventitious event and, compared with the 18% yield of **2.50** obtained from bromide **2.49** (see **Figure 2.57**), was further evidence for the higher reactivity of alkenyl iodides over alkenyl bromides in cross-coupling processes (*c.f.* **Figures 2.38** and **2.48**).

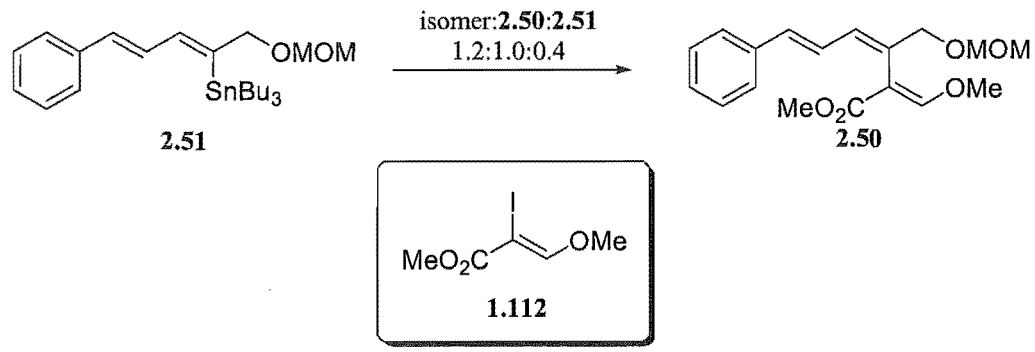


2.52 **1.111** **2.50** [91:9 mixture with unidentified triene isomer]

Reagents and conditions: Pd_2dba_3 (10 mol %), $AsPh_3$ (40 mol %), CuI, NMP, dark, 50 °C, 24 h.

Figure 2.77 Synthesis of MOM triene **2.50** from iodide **2.52**.

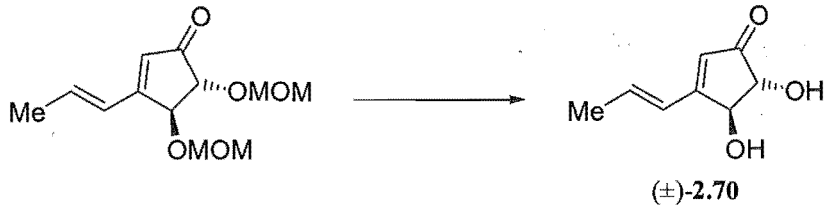
As part of routine double-checking of the several previous and apparently unsuccessful attempts to form **2.50**, the ^{1}H NMR spectrum of **2.50** was compared with the ^{1}H NMR spectrum of the crude reaction mixture from the attempted Stille coupling between **2.51** and **1.112** (*see page 131*). This revealed that there actually had been some **2.50** formed by the latter route, although there was another unidentified major product also present (presumably a double bond isomer), together with some stannane starting material (**2.51**); the respective ratios of these three components, as estimated from integration of benzylic proton signals, was approximately 1.0:1.2:0.4 (**Figure 2.78**). Although an actual value for the yield of **2.50** from this reaction was not determined, that such a mixture was generated suggests that it was a less efficient route for MOM triene formation.



Reagents and conditions: **1.112**, $Pd(dppf)Cl_2$, DMF, r.t. – 50 – 100 °C, dark, 132 h.

Figure 2.78 A less successful Stille coupling route to MOM triene **2.50**.

The time to investigate the pivotal step of this hydroxyl-protected diene route to hydroxystrobilurin A was now here: could the MOM group be removed to furnish the natural product? The first method of MOM hydrolysis tried was based on the technique utilised by Auerbach and Weinreb in the ultimate step of their synthesis of racemic terrein (**2.70**), the (+)-form of which is a metabolite of *Aspergillus terreus* (**Figure 2.79**).[157]

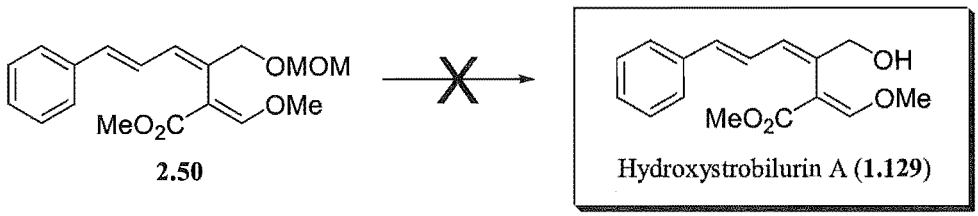


Reagents and conditions: cat. c.HCl, MeOH, 62 °C, 15 min [no yield reported].

Figure 2.79 Auerbach and Weinreb's method of MOM ether hydrolysis.

Although no yield was reported for the MOM hydrolysis described above, it was a simple procedure and therefore a logical place to start. Thus, a sample of **2.50** was dissolved in dry MeOH and treated with a catalytic amount of concentrated HCl. However, despite stirring for 15 h at 51 °C (this lower temperature being used to minimise the possibility of acid-catalysed

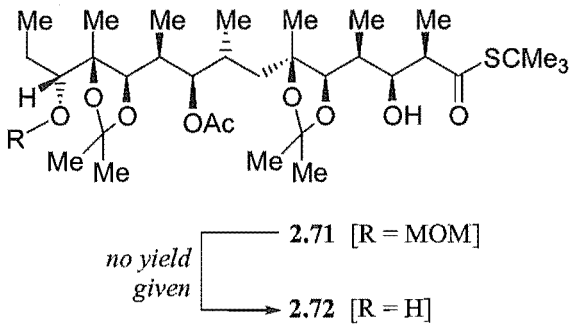
hydrolysis of the enol ether or acrylate ester of **2.50**), only unreacted starting material was recovered from the reaction mixture (**Figure 2.80**).



Reagents and conditions: cat. c.HCl, MeOH, 51 °C, 15 h.

Figure 2.80 Attempt to hydrolyse MOM ether of triene **2.50**.

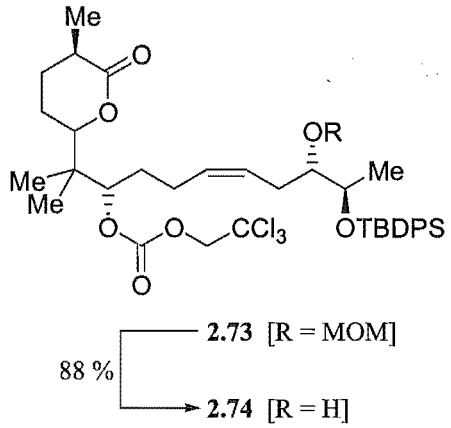
Although the possibility existed of increasing the reaction temperature to determine if this MOM hydrolysis method of Auerbach and Weinreb[157] could be successfully applied to the conversion of **2.50** to **1.129**, it was deemed more appropriate to first investigate another, milder method *i.e.* one more explicitly tolerant of the presence of acid-sensitive functionalities such as esters than the method of **Figure 2.79**. Apropos this concern, Woodward *et al.* found *in situ*-generated TMSBr effective for the hydrolysis of the MOM ether of **2.71** to give **2.72** (**Figure 2.81**),[158] as part of work which culminated in their asymmetric total synthesis of the macrocyclic antibiotic erythromycin, a compound produced by a strain of *Streptomyces erythreus*.[159] The mildness and selectivity of Woodward *et al.*'s method is demonstrated by the fact that the hydrolysis was conducted in the presence of two diol-protecting acetonide groups, moieties which are typically cleaved by aqueous acid.



Reagents and conditions: TMSCl, NEt_4Br, CH_2Cl_2, 0 °C.

Figure 2.81 Woodward *et al.*'s hydrolysis of the MOM ether of **2.71**.

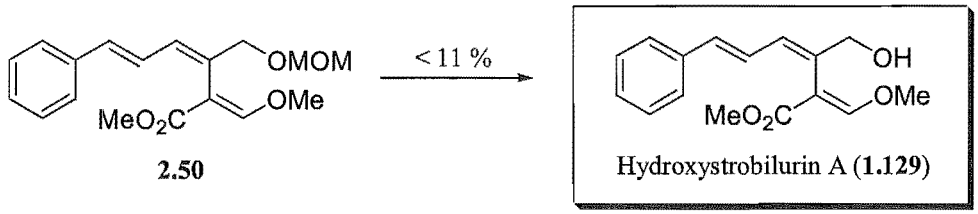
Finding these conditions of Woodward *et al.* to only partially cleave MOM ethers in their compounds, Hanessian *et al.* extended the methodology by utilising pre-formed TMSBr to effect the hydrolysis, as illustrated by the conversion of **2.73** to **2.74** (**Figure 2.82**).[160] As can be seen, TMSBr is inert towards TBDPS ethers, and Hanessian *et al.* also determined that it did not react with esters, amides, or methyl and benzyl ethers.



Reagents and conditions: TMSBr, CH_2Cl_2,
4 Å sieves, –30 – 0 °C, 25 min.

Figure 2.82 Example of MOM hydrolysis performed by Hanessian *et al.*

With the above result in mind, it was with a degree of sanguinity that hydrolysis of the MOM ether of **2.50** was attempted *via* the conditions of Hanessian *et al.* (**Figure 2.83**).[160] ^{1}H NMR spectroscopic analysis of the crude mixture obtained from this reaction showed that although the MOM ether had been removed, the product mixture comprised four different alcohol products. Moreover, the signal representing the allylic protons of **1.129** (as identified by reference to the ^{1}H NMR data for the natural sample of **1.129** isolated and characterised by Steglich *et al.*[110]) indicated it was a minor component of this mixture: the ratio of its integral to that of the largest allylic proton signal was 1.0:4.5. Unsurprisingly, then, subsequent purification of the crude mixture afforded a low yield (< 11%) of hydroxystrobilurin A.



Reagents and conditions: TMSBr, 4 Å sieves, CH_2Cl_2, –30 – 0 °C, 9 h.

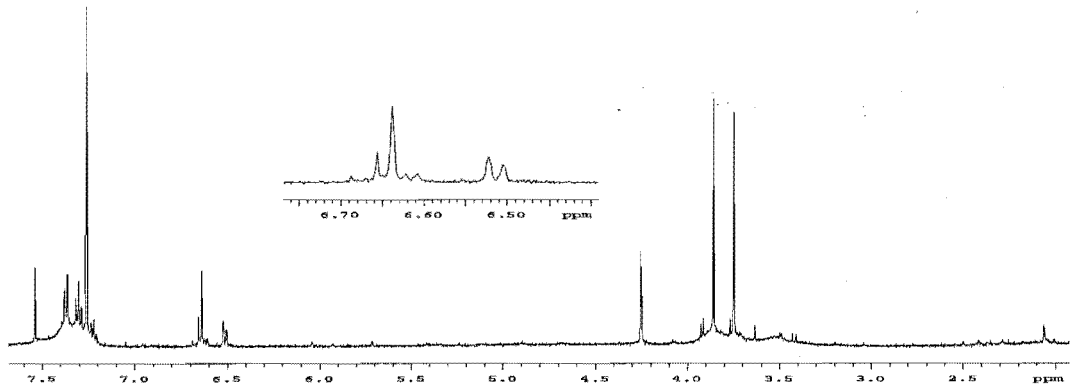


Figure 2.83 Synthesis and 500 MHz ^{1}H NMR spectrum of hydroxystrobilurin A (**1.129**) derived from deprotection of MOM triene **2.50**.

Hanessian *et al.* do not explicitly detail a mechanism for MOM hydrolysis by TMSBr, but note that there is precedent for the formation of oxonium ions in the presence of silicon-containing oxygenophiles,[161] and suggest that the process may thus proceed *via* the

intermediacy of an oxonium ion species. In view of this, the mechanistic pathway depicted in **Figure 2.84** may be representative of the hydrolysis process.

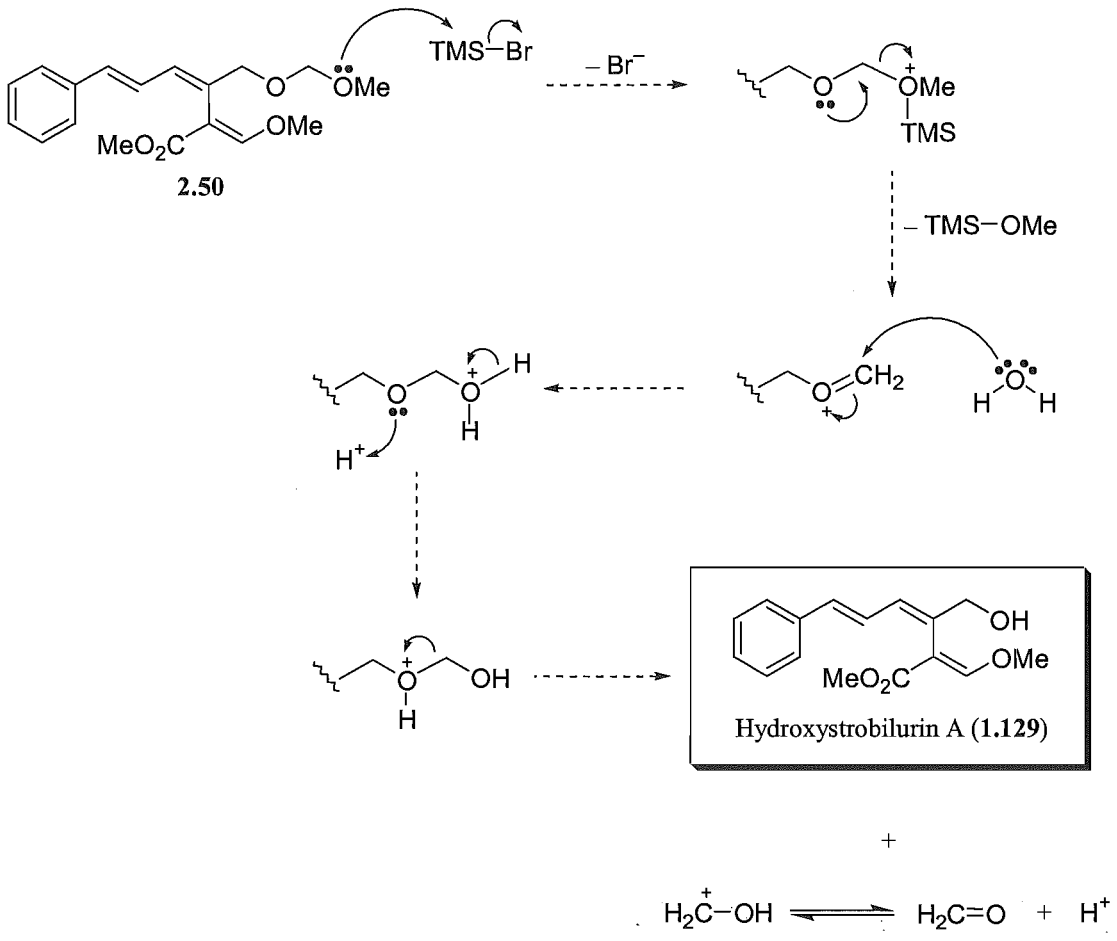


Figure 2.84 Possible mechanism of TMSBr-mediated MOM ether hydrolysis (where H_2O is utilised in reaction work-up procedure).

Unfortunately, an attempt to improve the efficiency of **2.50** deprotection was unsuccessful: a doubling of the scale of the reaction served only to decrease the ratio of **1.129** to the major side product allylic proton signal (in the ^{1}H NMR spectrum of the crude reaction mixture) to 1.0:16.0. Overall, the fact that ^{1}H NMR spectroscopic analysis showed the absence of the MOM ether moiety from product mixtures, and that there was only small amount of **1.129** present, suggested that an isomerisation of **1.129** was occurring subsequent to its formation from **2.50**.

At this stage, in addition to being unable to efficiently convert **2.50** into the natural product, supplies of this key triene intermediate had been exhausted. Thus, it was decided to take a step sideways, and see if iodide **2.52** was amenable to deprotection, and, if so, whether the resulting free-hydroxyl diene iodide (**2.75**) might be active as a Stille coupling partner with stannane **1.111** (**Figure 2.85**). Should access to **1.129** *via* iodide **2.75** prove possible, this would fit the observed trend of alkenyl iodides being more reactive than alkenyl bromides (see **Figures 2.38** & **2.48**, and **2.54** & **2.74**); if not, this would be further evidence that the hydroxyl group of this type of diene was responsible for inhibiting the desired Stille coupling process.

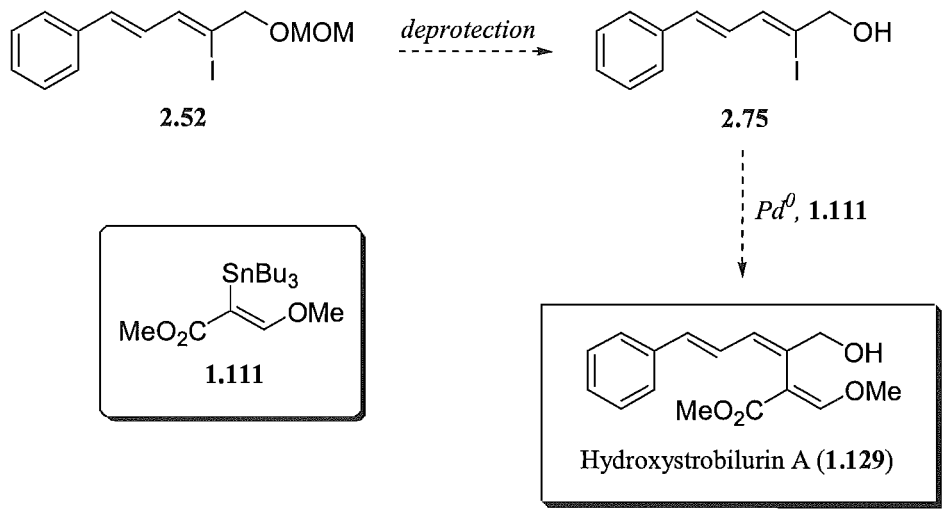
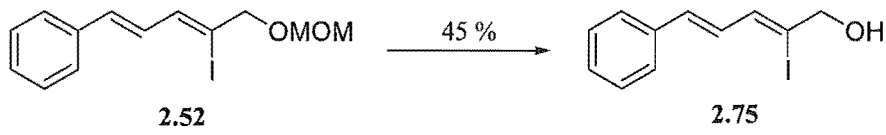


Figure 2.85 Proposed route to **1.129** *via* iodide **2.75**.

Accordingly, **2.52** was treated with TMSBr under identical conditions as were used for the deprotection of **2.50**, and the MOM group of **2.52** was duly removed (**Figure 2.86**). Some decomposition of the crude **2.75** occurred during its purification by flash chromatography, which was perhaps a reason for the less than spectacular yield (45%) of product ultimately obtained. Moreover, despite protection from light and storage under argon, the sample of purified **2.75** darkened from an initial pale yellow to a greenish-black colour overnight, and several new spots were visible in TLC analysis, indicating the material was continuing to decompose. This marked instability of **2.75** precluded its further characterisation (however, the absence of the MOM group from **2.75** was confirmed by inspection of its ^{1}H NMR spectrum,

and the chemical shifts and multiplicity of signals observed therein were consistent with those already observed for these diene systems), and meant that any investigations of its Stille coupling utility would be best conducted with crude **2.75**, without attempting purification.



2.52 **2.75**

Reagents and conditions: TMSBr, 4 Å sieves, CH_2Cl_2, –30 – 0 °C, 9 h.

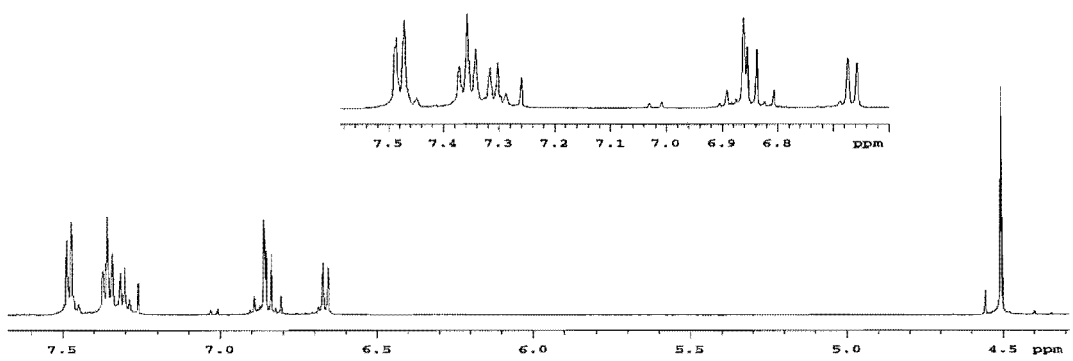
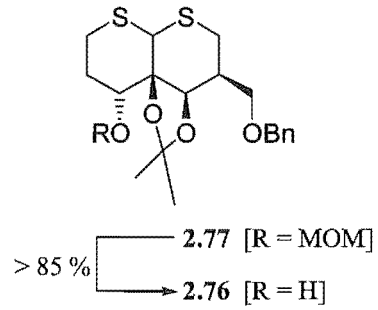


Figure 2.86 Synthesis and 500 MHz ^{1}H NMR spectrum of iodide **2.75**.

In an effort to achieve a more efficient synthesis of **2.75** from **2.52**, a different method of MOM ether hydrolysis was investigated. To this end, it was noted that in the first of their triptych of publications on the asymmetric total synthesis of erythromycin, Woodward *et al.* had utilised trifluoroacetic acid to generate dithiadecalin **2.76** from its MOM analogue **2.77** (**Figure 2.87**).[162] This technique seemed a possibility, especially given that the acetonide moiety of **2.77** was unscathed by the treatment.

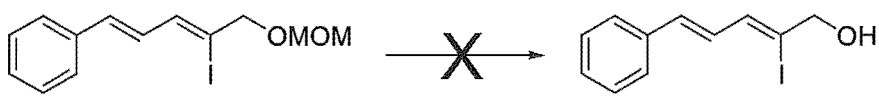


Reagents and conditions: CF_3COOH, CH_2Cl_2, r.t.

Figure 2.87 Woodward *et al.*'s hydrolysis of the MOM ether of **2.77**.

Thus, **2.52** was treated with 1 equivalent of CF_3COOH, initially at 0 °C for 4 h (a lack of experimental detail in Woodward *et al.*'s paper[162] meant common sense had to be used to devise a procedure). TLC analysis after this time showed only starting material to be present, so the reaction mixture was allowed to warm to room temperature overnight. With no product visible by TLC analysis after this time, another equivalent of CF_3COOH was added. After another 7 h stirring at room temperature, there was still no change, so a third equivalent of CF_3COOH was added and the mixture stirred for a further 5 days.

After this time, although some starting material remained, there was also a new spot visible in the TLC at a similar R_f to that which had been previously observed for desired product **2.75**. Unfortunately, ^1H NMR spectroscopic analysis of the crude product mixture showed it contained only starting material and some other unidentified side-products, with the absence of any desired product **2.75** (**Figure 2.88**). Whilst it was realised that the reaction might be facilitated by heating, this possibility was left to be investigated at a later date, should **2.75** prove successful in the desired Stille coupling reaction with **1.111**.

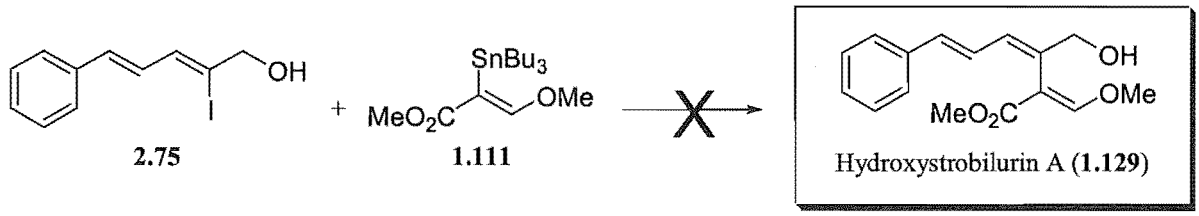


2.52 **2.75**

Reagents and conditions: CF_3COOH, CH_2Cl_2, r.t., 6 d.

Figure 2.88 Attempt to hydrolyse MOM ether of **2.52**.

A fresh sample of diene iodide **2.75** was prepared from **2.52**, as before (see **Figure 2.86**), and a sample of the crude product mixture checked by ^{1}H NMR spectroscopic analysis. Apart from a few solvent signals, the ^{1}H NMR spectrum of this crude **2.75** was very clean, and so was combined with stannane **1.111** under Stille conditions (**Figure 2.89**). After overnight reaction, a white solid was visible in the reaction flask, and the possibility that this was Bu_3SnI, indicating that the desired coupling had taken place, was entertained for a few hopeful minutes. Unfortunately however, although the ^{1}H NMR spectrum of the crude product mixture showed that both starting materials had been consumed, comparison with ^{1}H NMR spectrum of the sample of synthetic **1.129** prepared from MOM triene **2.50** (see **Figure 2.83**) showed that none of this desired product had been formed.



Reagents and conditions: Pd_2dba_3 (10 mol %), $AsPh_3$ (40 mol %), CuI, NMP, dark, 50 °C, 24 h.

Figure 2.89 Attempt to synthesise hydroxystrobilurin A (**1.129**) from **2.75**.

Although disappointing, the failure of iodide **2.75** to couple with **1.111** was akin to the unreactivity of its bromine analogue **2.46** with **1.111** under analogous conditions (see **Figure 2.51**), and demonstrated that failure of the oxidative addition step of the desired Stille coupling process was not the problem. Together with the fact that MOM bromide **2.49**, MOM iodide **2.52**, and acetate **2.47** *did* couple with **1.111** under Stille conditions (see **Figures 2.57**, **2.77** and **2.54**), this result lent further support to the hypothesis that the free hydroxyl group of **2.46** and **2.75** was somehow preventing their reaction with **1.111**.

At this stage of the investigation, it was clear that the protected-hydroxyl group approach to the natural product was not as successful as had been hoped, with an apparent double-bond isomerisation during the formation of triene acetate **2.48** (see **Figure 2.54**), and the

deprotection of MOM triene **2.50** affording a very low yield of hydroxystrobilurin A (see **Figure 2.83**). Thus, although other hydroxyl group protection methodologies remained to be explored, it was decided to instead develop an alternative 'protection' paradigm for this troublesome moiety.

2.2.4.5 A Diene Approach *via* Functional Group Interconversion

The basis of this approach is depicted in **Figure 2.90** below: dienes **K**, where –C(O)Y is an ester or aldehyde functionality, might couple with stannane **1.111** under Stille conditions to give trienes **L**, which may be able to be reduced to the natural product.

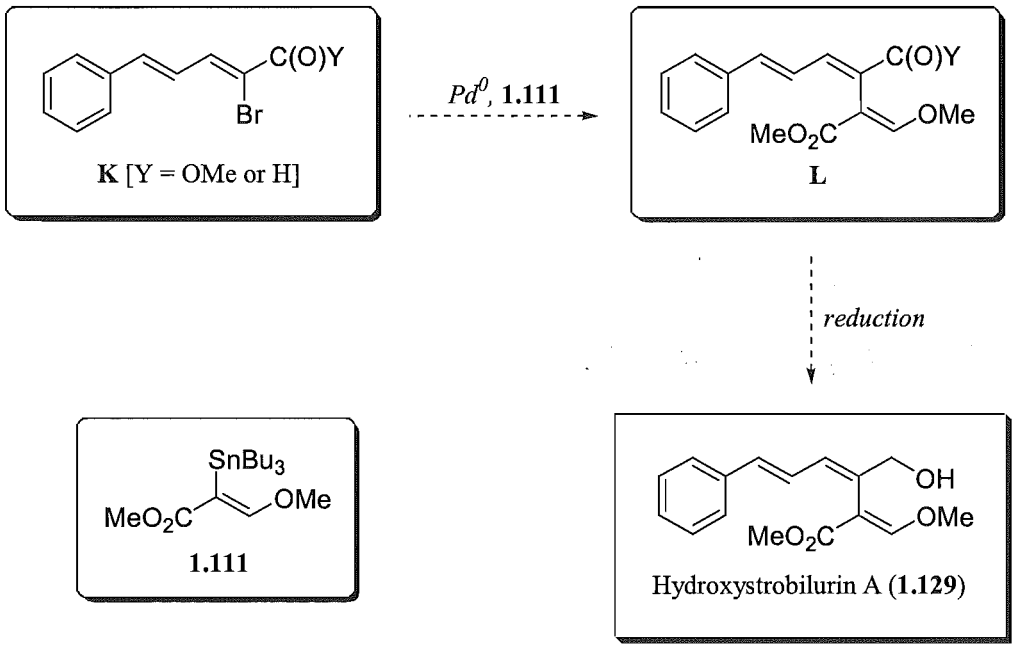
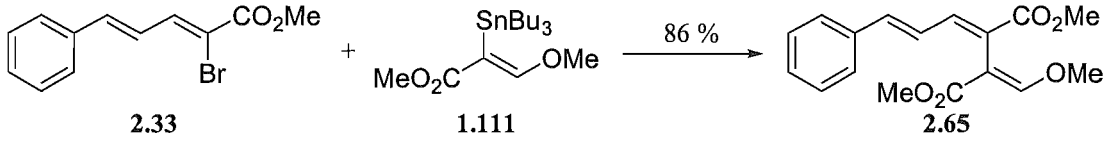


Figure 2.90 Potential functional group interconversion-based diene approach to hydroxystrobilurin A.

With an efficient synthesis of **2.33**, the ester (Y = OMe) form of diene **K** having already been devised (see **Figure 2.48**), some headway had already been made into exploring this approach. Direct reduction of ester **2.33** to the corresponding Y = H (*i.e.* aldehyde) form of **K**

was expected to be as challenging as it was preferable, and as such there existed the alternative route *via* oxidation of alcohol **2.46**. With respect to the carbon-carbon bond-forming step of the approach, previous experience suggested that the absence of an hydroxyl group from dienes **K** means that they should couple with **1.111** to give trienes **L**. In contrast, the ultimate transformation of this approach – selective reduction of the ester or aldehyde moiety of **L** in the presence of the acrylate ester to give **1.129** – could prove challenging.

An appropriate place to start was with the cross-coupling of ester **2.33** and stannane **1.111**, and pleasingly, this reaction afforded an excellent 86% yield of type **L** triene ester **2.65**, with the $^3J_{HH}$ coupling constants observed in the ^{1}H NMR spectrum of compound being consistent with the desired (*E,E,E*) triene geometry shown (**Figure 2.91**).



2.33 **1.111** **2.65**

Reagents and conditions: Pd_2dba_3 (10 mol %), $AsPh_3$ (40 mol %), CuI, NMP, dark, 50 °C, 12 h.

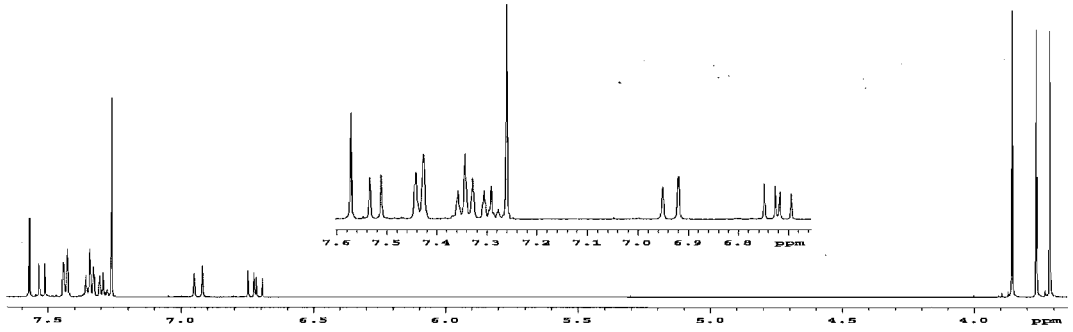


Figure 2.91 Synthesis and 500 MHz ^{1}H NMR spectrum of triene ester **2.65**.

With the DIBAl-H having proven effective for the reduction of ester **2.33** to alcohol **2.46** (see **Figure 2.50**), this reagent was the logical choice for the all-important next step: reduction of triene ester **2.65** to hydroxystrobilurin A. Clearly, it was a possibility that either (or both) of the α,β-unsaturated esters might be reduced by DIBAl-H. However, it was thought that the

structure of **2.65** might impart some chemoselectivity to the reduction process, in that the resonance stabilisation enjoyed by the vinylogous ester of **2.65** (**Figure 2.92**) might render it relatively less prone to reduction, by making it less electrophilic than the non-vinylogous ester, thus directing the reduction to occur at the latter functionality, as desired (also, reduction of the vinylogous ester would destroy this resonance stabilisation, which would be unfavourable).

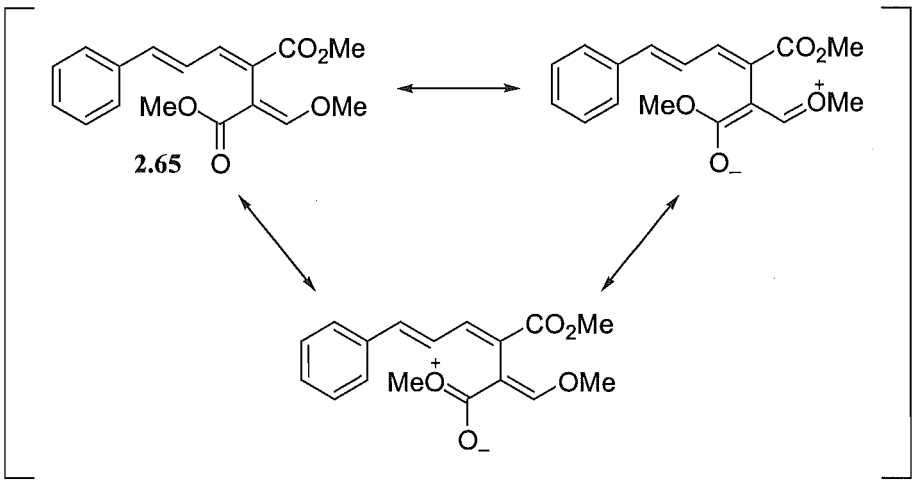
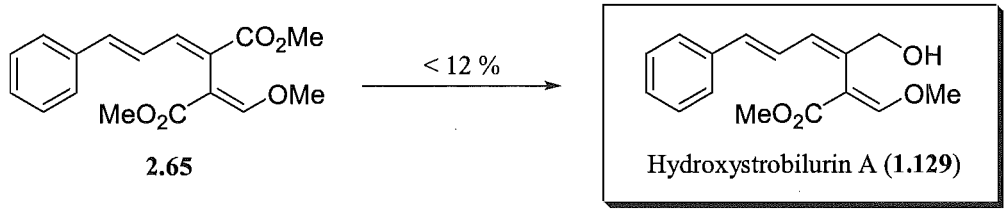


Figure 2.92 Resonance stabilisation of vinylogous ester of **2.65**.

Accordingly, seven attempts were made at the reduction of **2.65** to **1.129** (**Figure 2.93**) below, with the type of solvent utilised having a pronounced effect on the efficacy of the process: reactions conducted in Et_2O yielded only traces of **1.129**, no matter whether they were conducted entirely at –78 °C or allowed to warm to 0 °C. Similarly, an experiment with THF (a more polar ethereal solvent) was also fruitless, as were the first two experiments using CH_2Cl_2, even when permitted to warm to room temperature. A tenfold increase in the amount of DIBAl-H used led to complete consumption of starting material, but (perhaps unsurprisingly) yielded a mixture of over-reduced products devoid of **1.129**. Clearly, reduction of either ester of **2.65**, let alone selective reduction of the non-vinylogous moiety, was a non-trivial undertaking.

Finally, an experiment utilising the conditions employed for the routinely successful reduction of ester **2.33** to alcohol **2.46** (see **Figure 2.50**), except with the use of CH_2Cl_2 instead

of Et_2O, did afford a low yield (< 12%) of the natural product (**Figure 2.93**). Although this yield of **1.129** was virtually the same as that obtained *via* deprotection of MOM triene **2.50** (see **Figure 2.83**), it was hoped this did not demonstrate a general disinclination of such trienes to efficient conversion to hydroxystrobilurin A, nor augur ill of the alternative approach to **1.129** *via* the aldehyde form of triene **L**. Indeed, it was hoped that the typical situation of aldehydes being more reactive than esters would be manifest in reactions of an aldehyde **L** with a hydride reducing agent.



2.65

Hydroxystrobilurin A (**1.129**)

Reagents and conditions: DIBAl-H, CH_2Cl_2, –78 – 0 °C, 3 h.

DIBAl-H Equivalents	Solvent	Reaction Conditions	Yield of 1.129
1.0	Et_2O	–78 °C, 5 h	trace
1.0	Et_2O	–78 – 0 °C, 3 h	trace
1.0	THF	–78 °C, 12 h	trace
1.0	CH_2Cl_2	–78 °C, 9 h	trace
1.0	CH_2Cl_2	–78 °C – r.t., 72 h	trace
10.0	CH_2Cl_2	–78 – 0 °C, 12 h	trace
2.2	CH_2Cl_2	–78 – 0 °C, 3 h	< 12 %

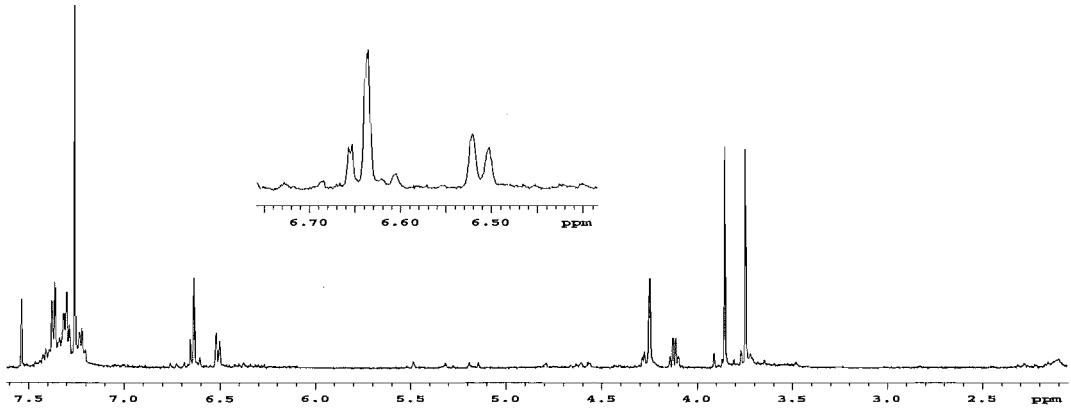


Figure 2.93 Summary of attempts to reduce **2.65** to **1.129**, with 500 MHz ^{1}H NMR spectrum of product from sole successful experiment.

The key question now was whether an aldehyde form of diene **K** (**2.78**) could be accessed directly from diene ester **2.33**, or whether it would be necessary to obtain **2.78** *via* oxidation of diene alcohol **2.46** (**Figure 2.94**)

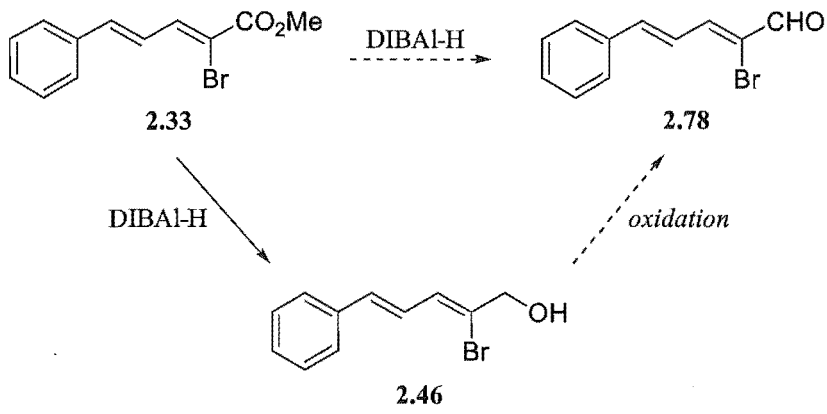
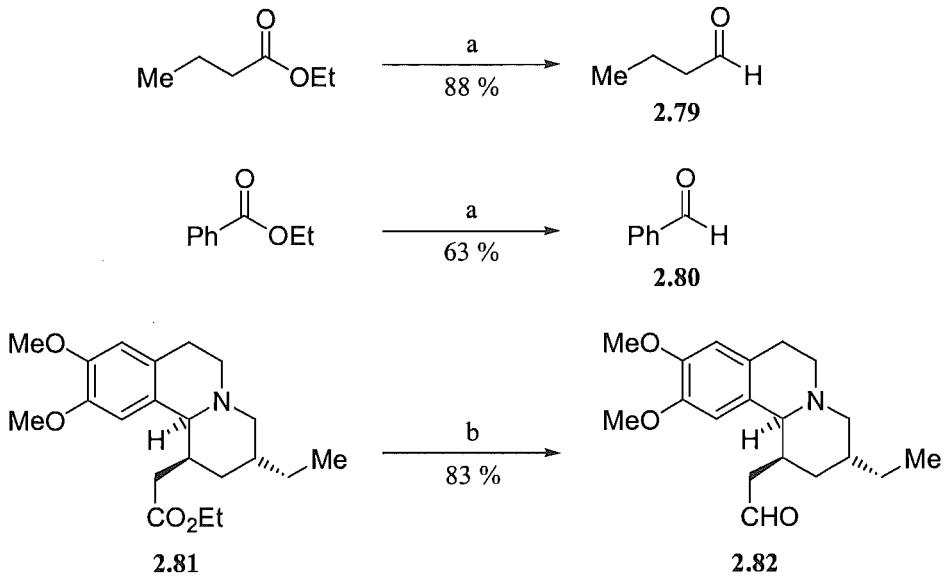


Figure 2.94 Two possible routes to diene aldehyde **2.78**.

To this end, Zakharkin and Khorlina have reported good yields of various aliphatic and aromatic aldehydes by treatment of the corresponding esters with DIBAl-H at –70 °C, as exemplified by the syntheses of **2.79** and **2.80** (**Figure 2.95**).[163] A marked solvent effect was observed in the transformations, with yields from reactions using toluene or hexane exceeding those conducted in ether by 10-15%.[ϒ] Also depicted in **Figure 2.95** is Szántay *et al.*'s application of this methodology to the reduction of ester **2.81** to aldehyde **2.82**, part of their total synthesis of a plant alkaloid.[164]

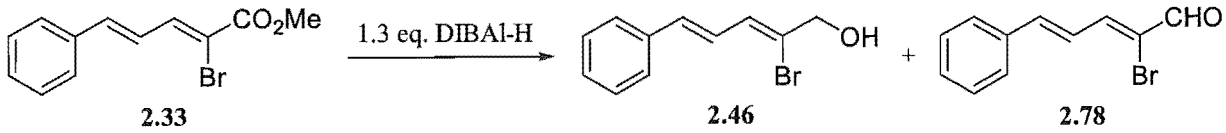
[ϒ] This observation is consistent with what is known about the role of the solvent in the mechanism of reduction of esters by DIBAl-H. Polar solvents (*e.g.* Et_2O) can coordinate to the Al atom in the first-formed tetrahedral intermediate of the reduction process, causing the breakdown of this intermediate to an aldehyde, which is then further reduced by DIBAl-H to a primary alcohol. However, when stabilised by both low temperature and a non-polar solvent (*e.g.* toluene), this tetrahedral intermediate persists, and addition of excess H_2O breaks it down to release the aldehyde, and prevents further oxidation of this product by quenching any remaining DIBAl-H.



Reagents and conditions: (a) DIBAl-H, –70 °C, toluene or hexane, 1 h;
(b) DIBAl-H, toluene, –60 °C, 2 h.

Figure 2.95 Zakharkin and Khorlina's and Szántay *et al.*'s syntheses of aldehydes *via* DIBAl-H reduction of the corresponding esters.

Thus, based on the experimental details of Szántay *et al.*,[164] but at the lower reaction temperature used by Zakharkin and Khorlina,[163] ester **2.33** was treated with DIBAl-H (**Figure 2.96**). Unfortunately, ^{1}H NMR spectroscopic analysis showed that the crude product mixture consisted largely of unreacted starting material, together with a very small amount of alcohol **2.46**, and only a trace of desired aldehyde product **2.78**. In an effort to obtain a better yield of **2.78**, the experiment was repeated at the lower temperature of ~ –105 °C, which necessitated a change of solvent from toluene to Et_2O [as MP (toluene) = –95 °C, whilst MP (Et_2O) = –116 °C]. However, the amount of **2.78** formed by this method was still tiny.



2.33 **2.46** **2.78**

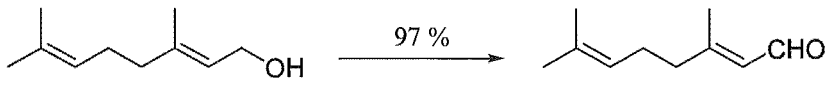
Solvent	Reaction conditions	Ratio of 2.33:2.46:2.78*
toluene	–70 °C, 1.5 h	264:38:1
Et_2O	–105 °C, 3.0 h	37:8:1

* *Determined by comparison of ^{1}H NMR integral ratios of allyl, methoxy, and aldehyde proton signals.*

Figure 2.96 Attempted reduction of **2.33** to **2.78**.

This inability to access **2.78** directly from **2.33** was disappointing but not altogether unexpected. Despite the successes of Zakharkin and Khorlina[163] and Szántay *et al.*,[164] literature syntheses often incorporate the less direct aldehyde synthesis consisting of reduction of the ester to the alcohol, followed by oxidation to the aldehyde. Thus, turning attention to this approach, it was necessary to find a reagent to oxidise alcohol **2.46** to aldehyde **2.78**.

The first oxidant applied to this transformation was the 'classical' and inexpensive stoichiometric oxidising agent manganese dioxide (MnO_2).[165] Corey *et al.*'s geranial synthesis is illustrative of the efficacy with which allylic alcohols can be converted to their corresponding α,β-unsaturated aldehydes with this reagent (**Figure 2.97**).[166]

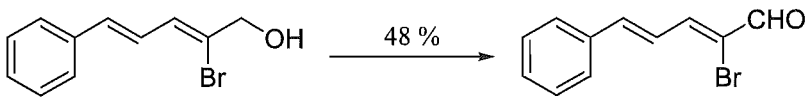


geraniol geranial

Reagents and conditions: MnO_2, hexane, 0 °C, 30 min.

Figure 2.97 Example of oxidation of an allylic alcohol to an aldehyde using MnO_2.

Oxidatively active† MnO_2 was easily prepared by pyrolysis of manganese carbonate ($MnCO_3$), as *per* the procedure of Harfenist *et al.*,[167] and treatment of **2.46** with this MnO_2, using the conditions of Corey *et al.*,[166] afforded a 48% yield of desired aldehyde product **2.78** (**Figure 2.98**). Although no unreacted starting material was recovered from this reaction, it was hoped that a more efficient conversion of **2.46** to **2.78** might be possible with a different oxidant.



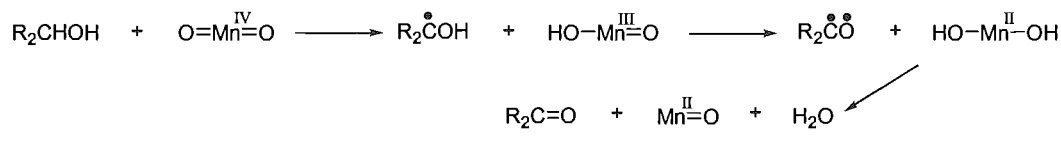
2.46 **2.78**

Reagents and conditions: MnO_2, CH_2Cl_2, r.t., 48 h.

Figure 2.98 Oxidation of alcohol **2.46** to aldehyde **2.78** with MnO_2.

Chromium, a neighbour of manganese in the transition metal series of the periodic table, is the crucial component of the some of most widely used stoichiometric oxidising agents in organic chemistry (*see reference in footnote on page 150*). Among the most common of these are those which utilise Cr^{VI}, such as pyridinium chlorochromate (PCC) [**2.83**], pyridinium dichromate (PDC) [**2.84**], and dipyridine chromium trioxide [**2.85**] (**Figure 2.99**). From an inspection of the literature, **2.85** appeared to be the most suitable of these three oxidants for effecting the desired **2.46** to **2.78** transformation, as both **2.83** and **2.84** have been known to cause (*E*)→ (*Z*) isomerisation during oxidation of allylic alcohols.[168]

† Active manganese dioxide is a non-stoichiometric material (*i.e.* MnO_x, with $1.93 < x < 2.00$) whose structure is dependent on the method of preparation. The necessity for excess water to be removed from MnO_2 for its activation is rationalised in terms of vacant polar sites on the oxide surface being required for adsorption of the organic substrate prior to oxidation. However, a certain amount of water is present in the oxidatively active compound, as has been shown by various structural studies, and a 'locked, water-associated chain' has been proposed for the structure of activated MnO_2 [Fatiadi, A. J. *J. Chem. Soc.* **1971**, *B(5)*, 889]. The actual oxidation mechanism is not fully understood, but there is evidence for the existence of a free radical pathway (such as that shown below) in the oxidation of alcohols [Pratt, E. F.; van de Castle, J. F. *J. Org. Chem.* **1961**, *26*, 2973].



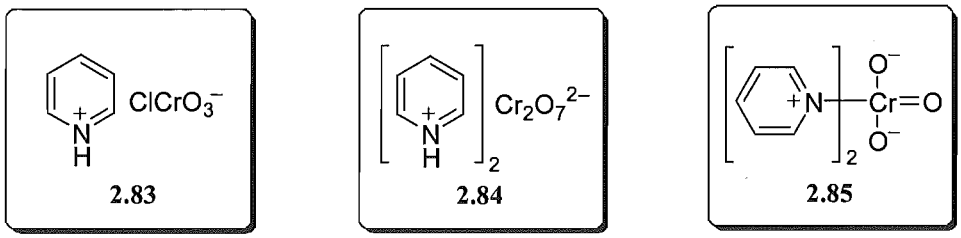
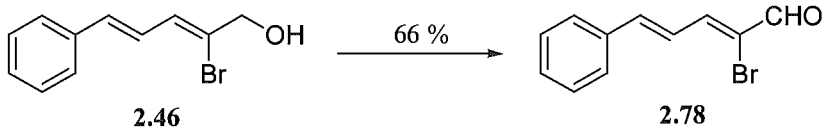


Figure 2.99 Three common Cr^{VI} oxidising agents.

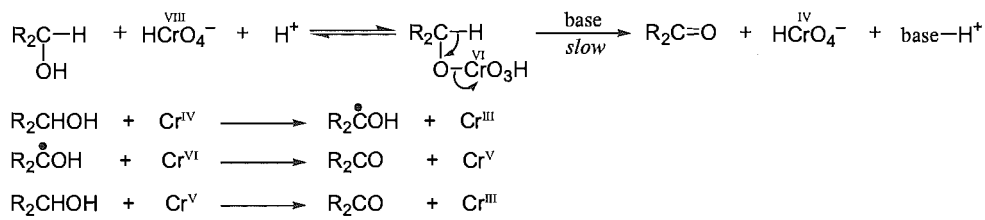
Several different methods exist for the utilisation of **2.85** in oxidative transformations, distinguished by how the reagent is prepared.[169] As it happened, Ratcliffe and Rodehorst's method[169d] for *in situ* preparation of **2.85** was gainfully employed for the oxidation of **2.46** to **2.78** (**Figure 2.100**). The 66% yield of **2.78** thus obtained (again with no starting material being recovered) was a distinct improvement on the 48% yield obtained with MnO_2 (see **Figure 2.98**), but it was still hoped that another oxidant might further improve the efficiency of this process.



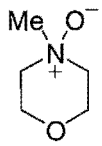
Reagents and conditions: **2.85**, CH_2Cl_2, r.t., 24 h.

Figure 2.100 Oxidation of alcohol **2.46** to aldehyde **2.78** with **2.85**.‡

‡ The literature is devoid of studies specifically concerning the mechanism of oxidation of alcohols by **2.85**, in contrast to the many studies on mechanistics of chromic acid (*i.e.* chromium trioxide in aqueous media) oxidation [Cainelli, G.; Cardello, G. *'Chromium Oxidations in Organic Chemistry'* (Springer-Verlag, Berlin, Heidelberg) **1984**, *and references therein*]. The generally accepted mechanism for chromic acid oxidation is that proposed by Westheimer *et al.* [Holloway, F.; Cohen, M.; Westheimer, F. *J. Am. Chem. Soc.* **1951**, *73*, 65], who showed that the second step – hydrolysis of the chromate ester – was rate-determining. Also of note is the involvement of intermediate valencies of chromium as well as Cr^{VI}. However, the presence of H^+ in this pathway would seem to preclude its constituting a possible mechanism for the oxidation of alcohols by the non-acidic **2.85** species.



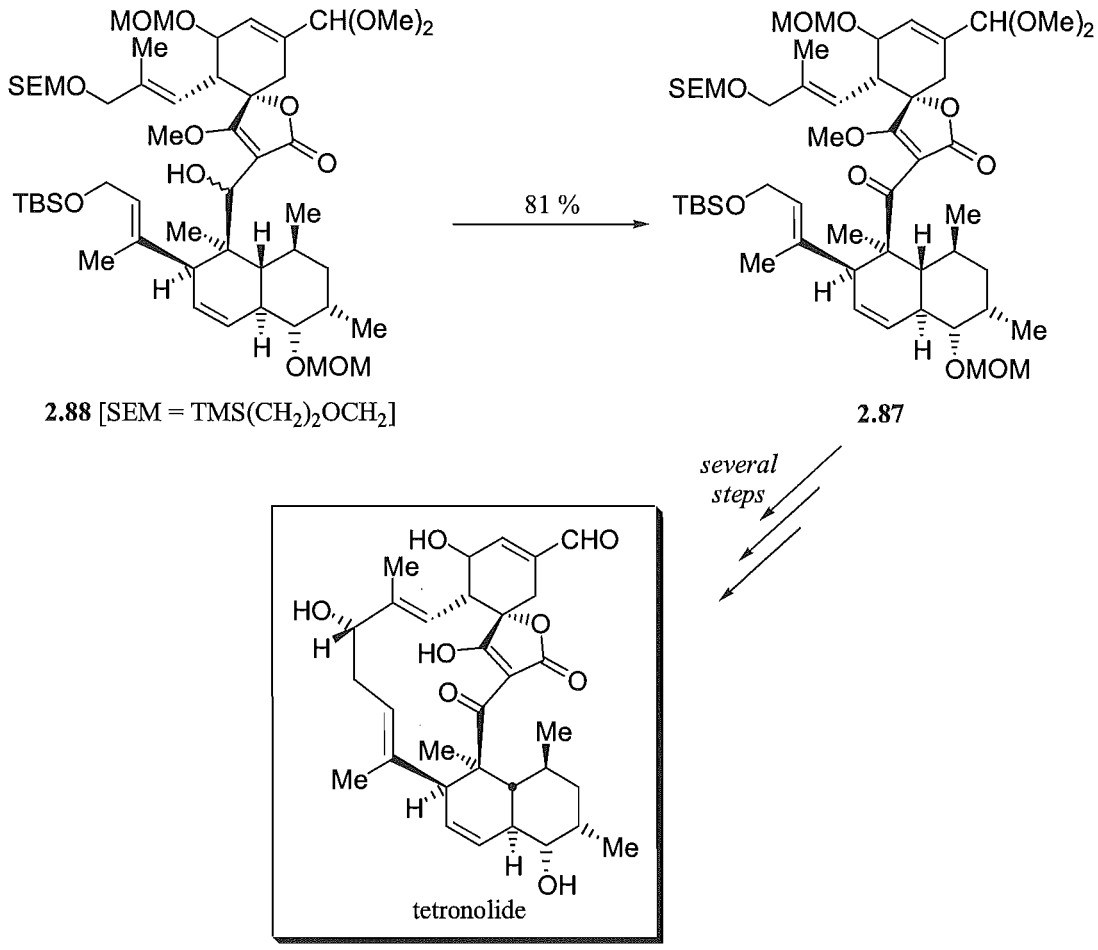
Notwithstanding the efficacy of stoichiometric oxidising agents such as MnO_2[165] and the Cr^{VI}/pyridine family, activated DMSO reagents,[170] and the Dess-Martin periodinane,[171] current demands are for more efficient oxidants which do not generate toxic by-products. Such a requirement is met by the catalytic tetra-*n*-propylammonium perruthenate (TPAP) [$Pr_4N^+RuO_4^-$]/*N*-methylmorpholine-*N*-oxide (NMO) [**2.86**] oxidant system developed by Ley *et al.*,[172] in which TPAP, the oxidising agent proper, is rendered catalytic by the presence of a stoichiometric amount of NMO, which acts as a co-oxidant (*i.e.* it re-oxidises the reduced form of TPAP, thereby enabling continued substrate oxidation).



2.86

Other advantages of the TPAP/NMO oxidation system is that reactions generally proceed at room temperature, are usually complete within five minutes to one hour, are amenable to scale-up, and that work-up of reaction mixtures is simple. Furthermore, the system has proven effective when other oxidation methods have been ineffective or failed entirely and, crucially, is tolerant of a wide range of functionality. Takeda *et al.*'s synthesis of ketone **2.87** from alcohol **2.88** (*en route* to a synthesis of tetronolide, the aglycon[ϒ] of the tetrocarcin family of antitumour antibiotics isolated from *Micromonospora chalcea*[173]) aptly illustrates both of these properties (**Figure 2.101**).[174]

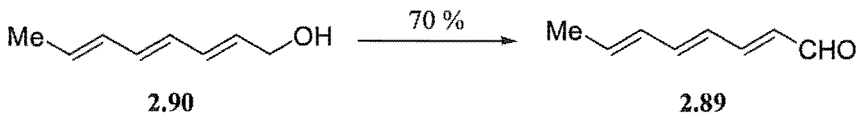
ϒ 'Aglycon' is the term for the residue formed by replacing the glycosyl group (*i.e.* carbohydrate portion) of a glycoside (carbohydrates in which the anomeric OH group has been replaced by –XR, where may be X = O, N, S, Se) with a hydrogen atom. In other words, the non-sugar bit of a glycoside plus a hydrogen atom.



Reagents and conditions: TPAP/NMO, 4 Å sieves, CH_3CN, 5 h [*DMSO/TFA, MnO_2, PCC all failed*].

Figure 2.101 Takeda *et al.*'s use of TPAP/NMO oxidation system in a complex natural product synthesis (in which other oxidants failed).

As the above example shows, allylic alcohols are suitable substrates for the TPAP/NMO system. A further example – one more structurally relevant to the desired conversion of **2.46** to **2.78** – is Ley *et al.*'s synthesis of the conjugated triene aldehyde **2.89** from allylic alcohol **2.90** (**Figure 2.102**).[175]



2.90 **2.89**

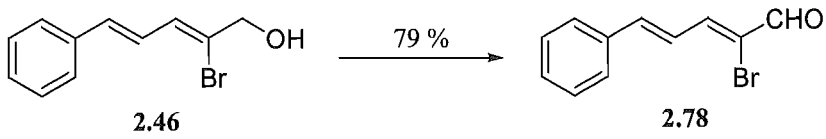
Reagents and conditions: TPAP/NMO, 4 Å sieves, CH_3CN, r.t., 1.5 h.

Figure 2.102 Ley *et al.*'s oxidation of a triene alcohol with TPAP/NMO.

Cognisant of the impressive array of properties of the TPAP/NMO oxidation system as outlined above, it was with some hope that it was utilised for the oxidation of **2.46**. Satisfyingly, treatment of **2.46** with TPAP/NMO in CH_2Cl_2 over powdered 4Å molecular sieves[ϕ] gave aldehyde **2.78** in 79% yield (based on 15% recovered starting material) [**Figure 2.103**]. Similar failures of TPAP/NMO oxidations to go to completion were noted by Ley *et al.*, who solved the problem with the use of CH_3CN – either in place of or as a co-solvent with CH_2Cl_2.[172] However, conducting the TPAP/NMO oxidation of **2.46** in CH_3CN instead of CH_2Cl_2 gave a lower yield of **2.78** (68%), even with the smaller amount of starting material recovered (6%) taken into account.

[ϕ] Ley *et al.* found that the efficiency and rate of TPAP/NMO oxidations was significantly increased by the use of molecular sieves, particularly if they were ground into a fine powder before use [Griffith, W. P.; Ley, S. V.; Whitcombe, G.P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625]. Indirect evidence as to how the water-scavenging ability of these sieves enhances the efficacy of the oxidation system is as follows. Firstly, the oxidation of primary alcohols with TPAP/NMO in non-aqueous solvents affords aldehydes rather than carboxylic acids. Given that the latter are known to form from the former *via* aldehyde hydrates [Sayer, J. M. *J. Org. Chem.* **1975**, *40*, 2545, *and references therein*], it may be that sieves prevent such aldehyde hydration and consequent over-oxidation to carboxylic acids from occurring. Secondly, a study of the kinetics of the stoichiometric reaction of TPAP with propan-2-ol in CH_2Cl_2 found that the reaction was strongly autocatalytic (*i.e.* rate is initially slow, accelerates as the reaction proceeds, then decreases near the end of the reaction), and that this autocatalysis was retarded by small amounts of water [Lee, D. G.; Wang, Z.; Chandler, W. D. *J. Org. Chem.* **1992**, *57*, 3276]. Lee *et al.* proposed that the autocatalysis was mediated by colloidal RuO_2 particles (formed *via* the equation below) and that the binding of water molecules to these particles reduced the number of sites available to $[RuO_4]^-$, hence slowing the reaction. Assuming that NMO/catalytic TPAP oxidations also proceed *via* this or an analogous mechanism, the removal of water – both that released upon dissolution of the NMO and that produced during the reaction – is thus similarly desirable.

$$[RuO_4]^- + nRuO_2 \longrightarrow [RuO_4.nRuO_2]^-$$



2.46 **2.78**

Reagents and conditions: TPAP/NMO, 4 Å sieves, CH_2Cl_2, r.t., 24 h.

Figure 2.103 Oxidation of alcohol **2.46** to aldehyde **2.78** with TPAP/NMO.

The mechanism of such oxidations by the TPAP/NMO system is not clear, although Ley *et al.* have proposed a reaction sequence for $[RuO_4]^-$ in non-aqueous solution (**Figure 2.104**).[172] The sequence is a two-electron process and is thus akin to the chromate ester formation step in the mechanism of alcohol oxidation by chromic acid (*see footnote on page 151*).

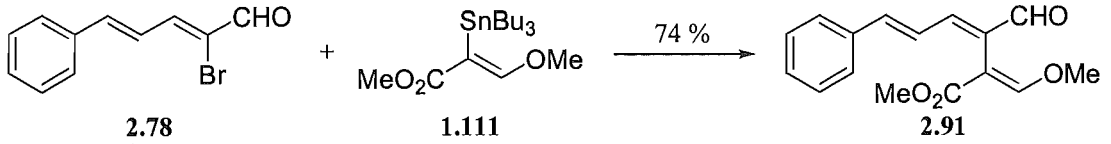
$$Ru^{VII} + 2e^- \longrightarrow Ru^{V}$$

$$2Ru^{V} \longrightarrow Ru^{VI} + Ru^{IV}$$

$$Ru^{VI} + 2e^- \longrightarrow Ru^{IV}$$

Figure 2.104 Ley *et al.*'s proposed reaction sequence for the ruthenium of TPAP during alcohol oxidation.

With an efficient approach to **2.78** having been devised, investigating triene formation *via* Stille coupling was once again the order of the day. Accordingly, **2.78** was reacted with stannane **1.111** under several Stille conditions, with the best result being a very good yield (74%) of type **L** triene aldehyde **2.91** (**Figure 2.105**).



2.78 **1.111** **2.91**

Reagents and conditions: Pd_2dba_3 (10 mol %), $AsPh_3$ (40 mol %), CuI, NMP, dark, 50 °C, 12 h.

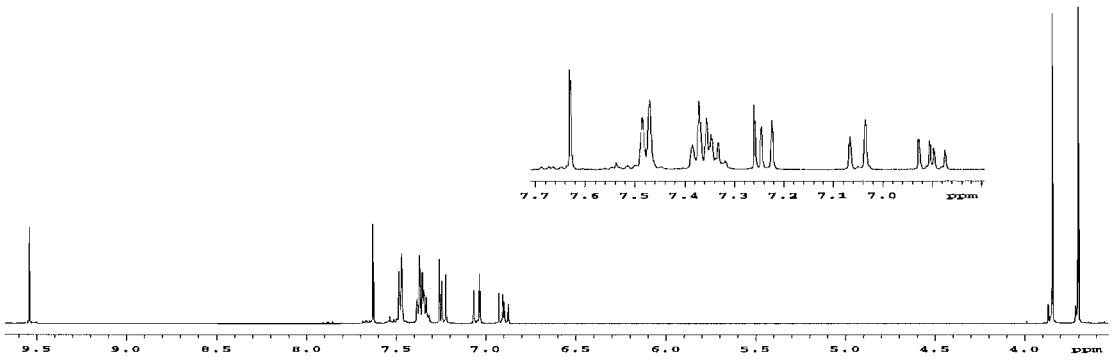
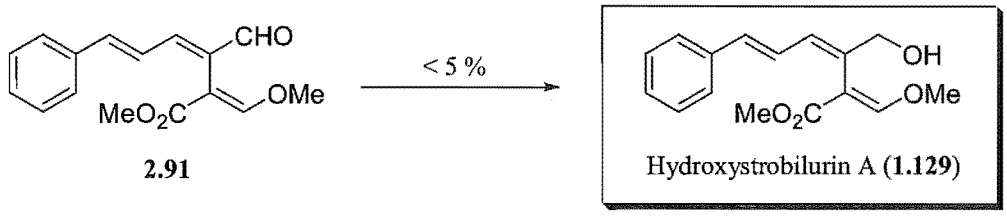


Figure 2.105 Synthesis and 500 MHz ^{1}H NMR spectrum of triene aldehyde **2.91**.

And so to the pivotal final step of this second functional group interconversion-based route to hydroxystrobilurin A (**1.129**): attempted selective reduction of the aldehyde moiety of triene **2.91**. Notwithstanding that the conversion of triene ester **2.65** to **1.129** with DIBAl-H had been of very limited success (see **Figure 2.93**), it was thought that the aldehyde moiety of **2.91** could prove more reactive with DIBAl-H than did the ester functionality of **2.65**.

Accordingly, **2.91** was treated with (initially just one equivalent) of DIBAl-H, and the reaction mixture left stirring for 12 h at room temperature (**Figure 2.106**). After this time, analysis of a sample of the reaction mixture by ^{1}H NMR showed that there was a 1.5:1.0 ratio of starting material to desired product (**1.129**) present, together with smaller amounts of other unidentified products. In an attempt drive the reaction to completion, the reaction mixture was re-cooled to –78 °C, another equivalent of DIBAl-H was added, and this new reaction mixture was allowed to warm to room temperature over 24 h. ^{1}H NMR spectroscopic analysis of the crude material obtained from this reaction showed that although all of the starting material had been consumed subsequent to the addition of extra DIBAl-H, this had unfortunately also led to

a concomitant increase in the number and size of unidentified by-product signals, rather than the formation of more of hydroxystrobilurin A. Consequently, only a tiny amount (< 5%) of the natural product was obtained after purification of this crude mixture.



2.91

Hydroxystrobilurin A (**1.129**)

Reagents and conditions: DIBAl-H (2 eq.), CH_2Cl_2, –78 °C – r.t., 36 h.

Figure 2.106 Attempt to reduce **2.91** to hydroxystrobilurin A with DIBAl-H.

Of the remaining hydride reducing agents used in organic synthesis, the two most common are $LiAlH_4$ and $NaBH_4$. The latter is preferred for the reduction of aldehydes and ketones due to its intrinsically lower reactivity *i.e.* $NaBH_4$ reduces fewer functional groups than does $LiAlH_4$.[ξ] In particular, $NaBH_4$ only reduces ester moieties very slowly, and chemoselectively reduces less stable carbonyl groups. Given the fact that the ester moiety of **2.91** is resonance-stabilised, this suggested that $NaBH_4$ might reduce **2.91** to **1.129** without the generation of side products. (An approximate representation[†] of the mechanism of aldehyde reduction by $NaBH_4$ is shown in **Figure 2.107**).

[ξ] $LiAlH_4$ reduces esters, acids, nitriles, amides, aldehydes and ketones; $NaBH_4$ reduces acid chlorides, imines, aldehydes, ketones (and esters, but very slowly).

[†] Further mechanistic details include the likelihood of reaction between the methanol solvent and $NaBH_4$ to form various methoxyborohydrides $NaBH_{4-n}(OR)_n$ (where n = 1, 2 or 3) [(a) Loupy, A.; Seyden-Penne, J. *Tetrahedron* **1980**, *36*, 1937; (b) Wigfield, D. C.; Gowland, F. W. *Tetrahedron Lett.* **1979**, 2209], which may then act as the actual reducing species; and the possibility that the sodium cation is involved in some kind of coordination to the carbonyl oxygen.

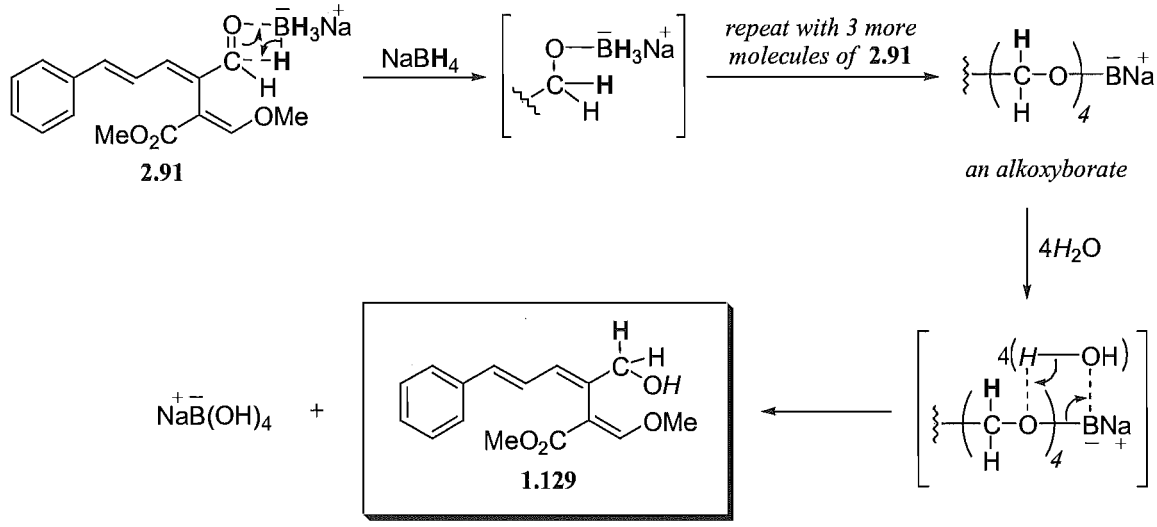
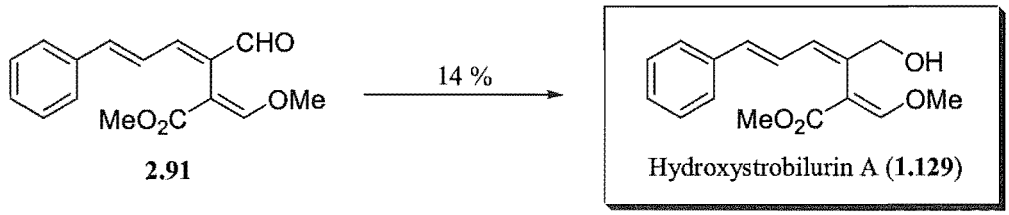


Figure 2.107 Key aspects of the mechanism of aldehyde reduction by $NaBH_4$ (the two hydrogens added to **2.91** in the reduction are highlighted to show their different sources).

Thus, a number of experiments were conducted in which a solution of **2.91** in dry MeOH was treated with a quantity of $NaBH_4$, with the best result obtained by the use of 0.5 equivalents of $NaBH_4$ (**Figure 2.108**). The integral ratio of olefinic starting material signals to those of desired product (**1.129**) in the ^1H NMR spectrum of the crude product mixture of this reaction was ~1.8:1.0, and a 14% yield of hydroxystrobilurin A (based on 32% recovered **2.91**) was obtained following purification.

Given that such a significant amount of **2.91** was recovered from this first reaction, further experiments were conducted with greater molar ratios of $NaBH_4$ in an attempt to achieve a more efficient conversion of **2.91** into **1.129**. ^1H NMR spectroscopic analysis of the crude reaction mixture resulting from treatment of **2.91** with 1.0 equivalents of $NaBH_4$ did show an improvement in the ratio of **2.91** to **1.129** (~1.1:1.0), but the spectrum also contained many more and larger signals for unidentified side products; although an accurate yield was not obtained, such an increase in side product formation indicated it was clearly less successful. Finally, use of 2.0 equivalents of $NaBH_4$ led to complete consumption of **2.91**, but without any **1.129** being formed, with the signals for unidentified side products being even larger and more numerous than before.



2.91

Hydroxystrobilurin A (**1.129**)

Reagents and conditions: $NaBH_4$ (0.5 equiv.), MeOH, 0 °C – r.t., 36 h.

$NaBH_4$ equivalents	Reaction time (h)	1.129:2.91 ratio[a]	Yield
0.5	36	1.0:1.8	14 %
1.0	12	1.0:1.1	*not isolated*
2.0	72	–[b]	*trace*

[a] *Estimated by comparison of integral ratios of olefinic proton signals in ^1H NMR spectra of crude product mixtures.*

[b] *No* **2.91** *present in ^1H NMR spectrum of crude product mixture.*

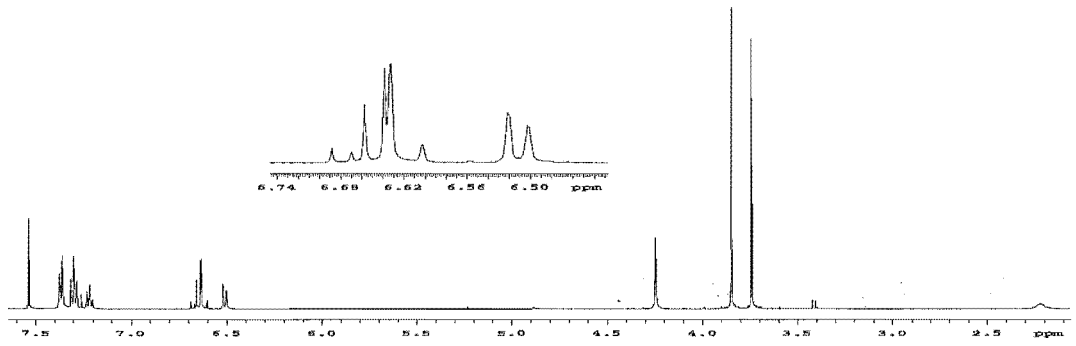


Figure 2.108 Summary of attempts to reduce **2.91** to hydroxystrobilurin A, and 500 MHz ^1H NMR spectrum of product obtained from the most successful experiment.

Although the side products generated in these reactions were not positively identified, their chemical shifts in the ^1H NMR spectra were suggestive of the allylic protons of an α,β-saturated alcohol group (*i.e.* $RCH_2CH_2C\mathbf{H_2}OH$), whilst the size of their signals increased in proportion to the amount of hydride used in the experiment. These observations, together with the fact that it is not unusual for $NaBH_4$ to afford 1,4- (*i.e.* conjugate) addition products when reacting with α,β-unsaturated aldehydes or ketones, suggested that $NaBH_4$ was not reacting solely in the desired 1,2-addition fashion with the aldehyde carbonyl group of **2.91**, and that it was also participating in 1,4-addition.

A possible mechanistic rationale for the mixed 1,2-/1,4-addition process is shown in **Figure 2.109** below: conjugate (1,4-) addition of hydride to **2.91** would give α,β-saturated aldehyde **2.92** which, given there was no aldehyde proton signal other than for starting material observed in the ^{1}H NMR spectra of crude reaction mixtures, probably reacts further – *this* time in a 1,2- fashion – to give α,β-saturated alcohol **2.93**. This may also suffer conjugate addition of hydride to its acrylate moiety to give **2.94** (further 1,2-addition to the carbonyl group is unlikely, given the sluggish rate at which $NaBH_4$ reacts with esters), whose two stereocentres may be a reason for the plenitude of side product signals observed in the ^{1}H NMR spectra.

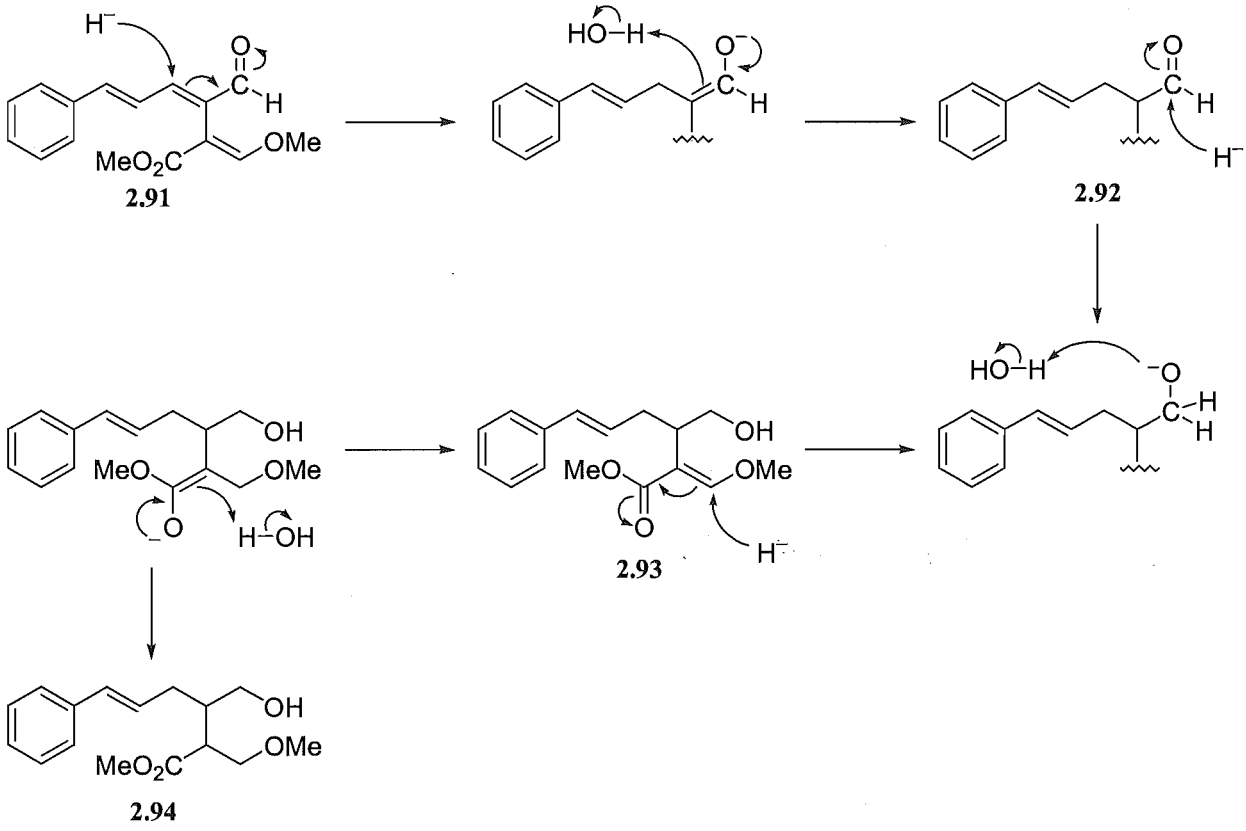
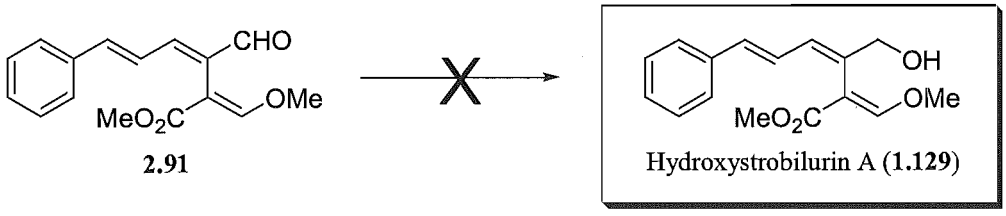


Figure 2.109 Formation of α,β-saturated alcohols **2.93** and **2.94** *via* 1,4- (conjugate) and 1,2- (direct) addition of hydride (from $NaBH_4$) to **2.91**.

By inspection of the literature, it was found that Luche had developed a facile procedure for highly selective 1,2-reductions of α,β-unsaturated ketones with $NaBH_4$, by the use of equimolar amounts of cerium(III) chloride heptahydrate ($CeCl_3.7H_2O$).[176] In the hope of achieving similar 1,2-selectivity, **2.91** was treated with $NaBH_4$ and $CeCl_3.7H_2O$ according to Luche's procedure

(**Figure 2.110**). And indeed, signals presumed to represent 1,4-addition products (in the ^{1}H NMR spectra of the crude product mixtures from reactions of $NaBH_4$ alone with **2.91**) were absent from the ^{1}H NMR spectrum of the crude product mixture of this reaction, suggesting that Ce^{3+} was performing its desired role. However, in addition to a small amount of unreacted **2.91**, there were also several new signals present in the olefinic and allylic proton regions of the spectrum. Most pertinently, only trace amounts of desired product **1.129** were present in the ^{1}H NMR spectra of purified material from this reaction, with the remainder being a mixture of unreacted **2.91** and several unidentified products.



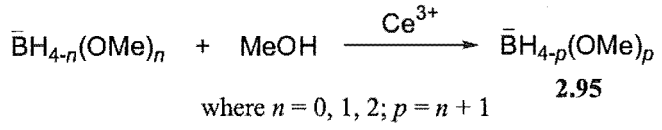
Reagents and conditions: $NaBH_4$ (1.0 equiv.), $CeCl_3.7H_2O$ (1.0 equiv), MeOH, r.t., 2 h.

Figure 2.110 Attempt to selectively reduce **2.91** with $NaBH_4/CeCl_3.7H_2O$.

Why only trace amounts of hydroxystrobilurin A were formed *via* the above process was not clear, although studies on the mechanism of action of Ce^{3+} in the reduction process do provide a possible explanation. Gemal and Luche propose that Ce^{3+} plays two roles, the first being catalysing the methanolysis of the borohydride anion to methoxyborohydrides **2.95** (**Figure 2.111**).[177] According to hard-soft acid-base theory criteria, **2.95** are 'harder' bases than BH_4^-, thus they should react better at the 'hard' site of the α,β-unsaturated carbonyl system (*i.e.* the carbonyl carbon), as desired. The second function of Ce^{3+} is proposed to be activation of the carbonyl group, with empirical evidence from Gemal and Luche's work supporting an *indirect* coordination of Ce^{3+} to this group, *via* a hydrogen-bonding interaction to the carbonyl oxygen intermediated by a methanol molecule (*i.e.* solvent complexation).[177]

However, a recent spectrometric investigation by Asakura *et al.* supports the existence of a *direct* interaction between Ce^{3+} and the carbonyl oxygen, which they propose is responsible for

the enhanced 1,2-reduction selectivity imparted by $CeCl_3.7H_2O$ (**Figure 2.111**).[178] Perhaps, then, subsequent to the reduction of the aldehyde moiety of **2.91**, Ce^{3+} coordinates to the acrylate carbonyl oxygen atom and facilitates some kind of intramolecular reaction, transforming the desired hydroxystrobilurin A product into a new compound.



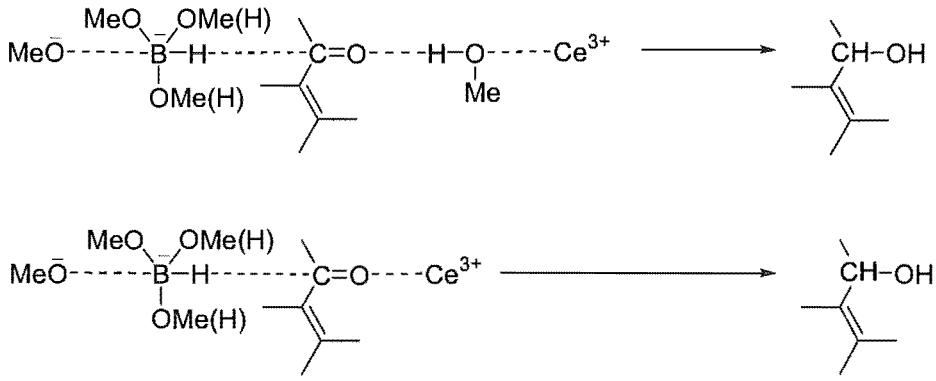


Figure 2.111 Proposed dual role of Ce^{3+} in facilitation of 1,2-reduction: methanolysis of BH_4^-, and indirect or direct coordination to aldehyde carbonyl oxygen.

Clearly, efficient selective reduction of the aldehyde functionality of **2.91** was not as simple an undertaking as was originally hoped. Moreover, the fact that a search of the literature for examples of selective reductions of aldehydes structurally analogous to **2.91** was fruitless is perhaps a further indication of the difficulty inherent to this transformation.

2.3 Summary

Efficiency-wise, the formation of hydroxystrobilurin A (**1.129**) by reduction of triene aldehyde **2.91** was only slightly higher yielding than *via* reduction of triene ester **2.65**, so the ultimate steps of both of the functional group interconversion-based routes to **1.129** proved little better than the formation of **1.129** by deprotection of MOM triene **2.50** (**Figure 2.112**). However, notwithstanding this, and similarly low overall yields, all three routes constituted total syntheses of **1.129**, with most of the Pd-catalysed carbon-carbon bond forming reactions fundamental to the syntheses being efficient. Much information has been garnered on the proclivities of the strobilurin triene system, and in the next chapter these results are summarised, and their implications and indications for future studies towards an improved total synthesis of **1.129** are discussed.

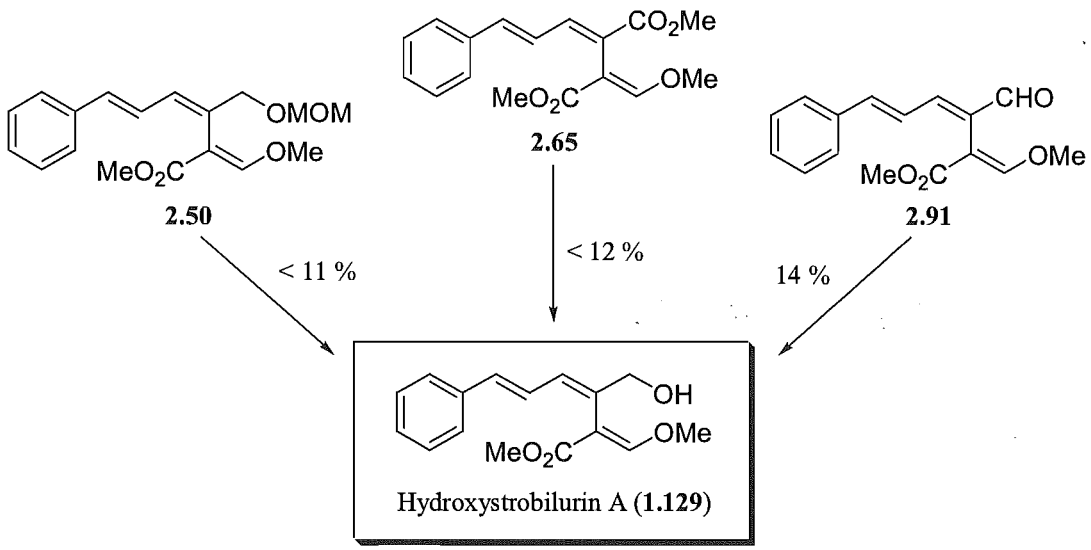
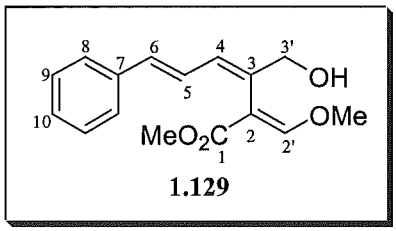


Figure 2.112 Comparison of efficiency of three routes to **1.129**.

2.4 Properties of Hydroxystrobilurin A

The spectroscopic data of the synthetic hydroxystrobilurin A (**1.129**) prepared as described above provided was in good agreement with those reported for the natural material by Steglich *et al.*[110] A comparison of infrared and mass spectroscopic data is given below (**Figure 2.113**).



1.129

	IR & MS DATA FOR HYDROXYSTROBILURIN A	
	Natural	**Synthetic (1.129)**
IR (cm^{-1})	3630~3100, 1705, 1625 (KBr)	3445, 1699, 1622 (film)
M^+	274.1214 (EI)	274.1205 (EI)

Figure 2.113 Infrared and mass spectroscopic data for hydroxystrobilurin A (**1.129**).

Both the ^1H and ^{13}C NMR data of synthetic hydroxystrobilurin A are consistent with that reported for the natural material, as can be seen in **Figure 2.114**. The sole distinguishing feature of the data of the synthetic compound is the presence of a ^1H chemical shift for the –OH moiety, which was possibly due to the higher field strength at which these data were collected.

	NMR DATA FOR HYDROXYSTROBILURIN A	
	Natural	**Synthetic (1.129)**
^{1}H	δ (300 MHz, $CDCl_3$)	δ (500 MHz, $CDCl_3$)
	7.54 [s, 1H, H-2']	7.54 [s, 1H]
	7.37 [d, 2H, J = 7.3 Hz, H-8]	7.35 [d, 2H, J = 7.3 Hz]
	7.30 [dd, 2H, J = 7.3 Hz, H-9]	7.30 [dd, 2H, J = 7.3 Hz]
	7.22 [dd, 1H, J = 7.3 Hz, H-10]	7.22 [dd, 1H, J = 7.3 Hz]
	6.66 [dd, 1H, J = 15.3, 9.3 Hz, H-5]	6.66 [dd, 1H, J = 15.4, 9.3 Hz]
	6.62 [d, 1H, J = 15.3 Hz, H-6]	6.62 [d, 1H, J = 15.4 Hz]
	6.51 [d, 1H, J = 9.3 Hz, H-4]	6.51 [d, 1H, J = 9.3 Hz]
	4.25 [s, 2H, H-3']	4.25 [s, 2H]
	3.85 [s, 3H, 2'-OMe]	3.85 [s, 3H]
	3.75 [s, 3H, 1-OMe]	3.74 [s, 3H]
		2.22 [br s, 1H, OH]
^{13}C	δ (75.5 MHz, $CDCl_3$)	δ (126 MHz, $CDCl_3$)
	168.1 [C-1]	168.1
	160.4 [C-2']	160.4
	137.4 [C-3]	137.3
	134.0 [C-6]	134.0
	133.6 [C-7]	133.6
	130.9 [C-4]	130.8
	128.5 [C-9]	128.5
	127.7 [C-10]	127.6
	126.5 [C-8]	126.5
	125.6 [C-5]	125.6
	107.8 [C-2]	107.8
	66.8 [C-3']	66.6
	62.0 [2'-OMe]	62.0
	51.8 [1-OMe]	51.8

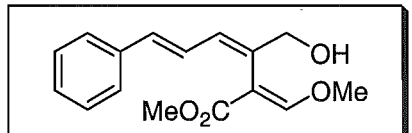
Figure 2.114 ^{1}H and ^{13}C NMR data of natural and synthetic hydroxystrobilurin A.

CHAPTER THREE

Hydroxystrobilurin A Synthesis Summary and Future Studies

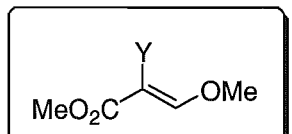
3.1 Summary

The work described in this thesis has culminated in three low-yielding syntheses of hydroxystrobilurin A (**1.129**), a member of the strobilurin family of fungal natural products. Palladium catalysis played a key role in the syntheses, both in the production of intermediates and in the formation of the carbon-carbon bonds of the strobilurin triene system. Generally, the Stille reaction was successfully employed for efficient diene and triene synthesis (although with some notable exceptions) and to the best of this author's knowledge, this constitutes the first example of the use of palladium-catalysed carbon-carbon bond formation techniques for the formation of the triene system of the strobilurins. The next chapter describes preliminary investigations on the application of this methodology to a synthesis of 9-methoxystrobilurins A and K, and another, non-strobilurin natural product.



Hydroxystrobilurin A (**1.129**)

The initial requirement was to establish access to β-methoxyacrylates **C**, which were triene precursors in both of the proposed routes to **1.129**. This was achieved with reasonable overall efficiency from the readily available alkyne methyl propynoate, to give bromide **1.117**, stannane **1.111** and iodide **1.112** (**Figure 3.1**). An attempt was made to convert dibromide **2.1** to **1.117** with NaOMe instead of Bu_3SnOMe, but this afforded only acetal **2.3** (presumably *via* double conjugate addition of methoxide).



C

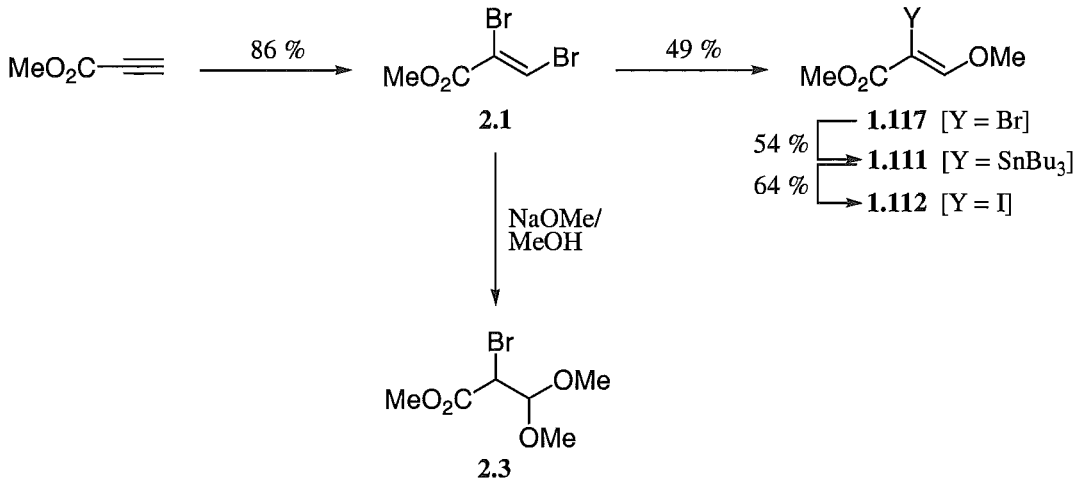


Figure 3.1 Preparation of β-methoxyacrylates, and unexpected formation of **2.3** from **2.1**.

Next, exploration of the first route to **1.129** was begun, an approach whose success was predicated upon the formation of ynediene **E** *via* a cross coupling between an enyne **B** and a β-methoxyacrylate **C**. To this end, an efficient two-step process from commercially available TMS acetylene, comprising a Sonogashira coupling with vinyl bromide **2.1** followed by ester reduction, gave type **B** enyne alcohol **2.9** (**Figure 3.2**). However, an attempt to synthesise ynediene **E** *via* a Stille coupling between **2.9** and stannane **1.111** yielded a complex mixture. Notwithstanding that other coupling options existed, preliminary investigations on an alternative approach to **1.129** were showing more promise, and the focus was shifted away from this enyne-based approach.

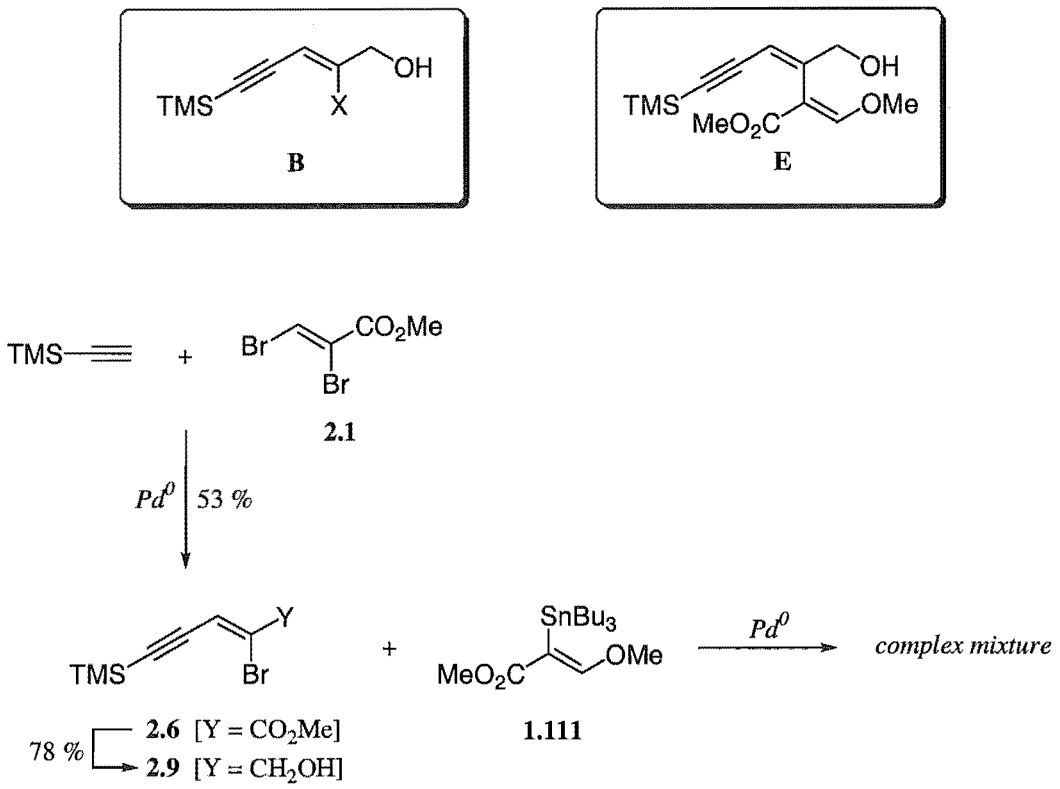


Figure 3.2 Investigation of enyne-based approach (where X = metal or Br, I).

The alternative approach also had the potential to be a rapid route to the natural product, but was based on diene rather than enyne formation, with the aim of forming **1.129** directly, *via* a crossed coupling between a diene **D** and a β-methoxyacrylate **C** (**Figure 3.3**). It was reasoned that diene **D** should be available *via* a functional group interconversion from diene **G**, a fragment which was itself likely to be accessible *via* a cross-coupling between phenylethene **H** and vinyl species **I**.

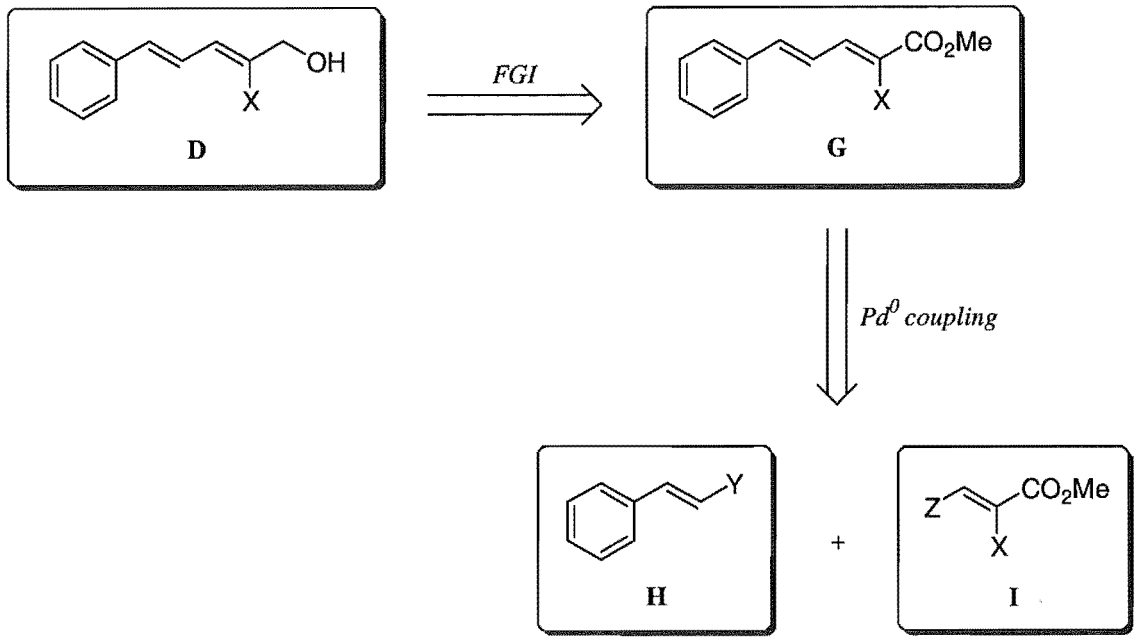


Figure 3.3 Retrosynthetic basis of diene approach (where X, Y, Z = metal or Br, I).

Initially, hydrozirconation or hydroboration of phenylacetylene to give **H**, followed by immediate Pd-catalysed coupling with the already available type **I** bromide **2.1**, beckoned as potential 'one-pot' routes to the bromide form of **G** (**2.33**). Unfortunately however, the hydrozirconation-based pathway afforded no **2.33**, whilst only low yields were obtained *via* the hydroboration route (**Figure 3.4**). These results, together with the fact that low yields of cross-couplied product were obtained even when iodobenzene was used instead of **2.1** (a result which suggested hydrozirconation/hydroboration of phenylacetylene was not proceeding efficiently), necessitated the investigation of an alternative, hydrostannylation-based approach to **2.33**.

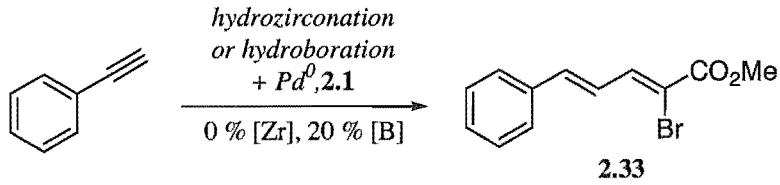


Figure 3.4 Hydrozirconation- and hydroboration-based routes to type **G** diene **2.33**.

Pleasingly, hydrostannylation of phenylacetylene did prove effective (with the free-radical-mediated process being superior to that catalysed by Pd), however subsequent Stille couplings between thus-formed stannane **2.38** and bromide **2.1** afforded poor yields of **2.33**, and transmetallation from tin to zinc did nothing to improve this state of affairs (**Figure 3.5**). Fortunately, **2.1** was easily converted to its β-iodo-analogue **2.44**, which coupled efficiently with **2.38** under Stille conditions (**Figure 3.5**). This result showed that the oxidative addition step of the cross-coupling process had been of low efficiency with vinyl bromide **2.1**, but was very efficient with vinyl iodide **2.44**, an observation that was consistent with literature precedent.[142] Furthermore, it seems likely that in addition to the inefficiency of hydroboration, this lower reactivity of **2.1** had been responsible for the low yields of **2.33** obtained *via* the previously described route (see **Figure 3.4**).

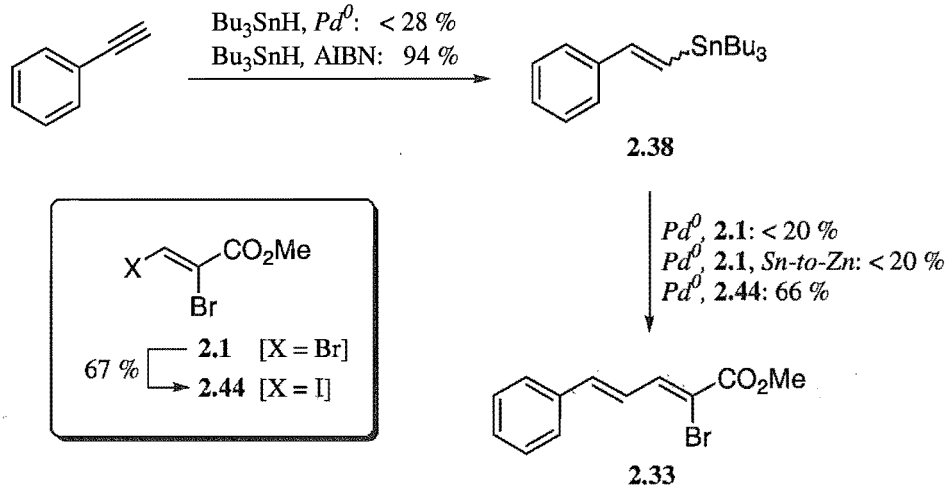


Figure 3.5 Ultimately successful hydrostannylation-based route to **2.33**.

Reduction of diene ester **2.33** to diene alcohol **2.46** proceeded without incident, and a wide range of different Stille conditions were then investigated in attempts to bring this bromine form of **D** into reaction with stannane **1.111** to afford the natural product. Unfortunately, these efforts were to no avail, with **2.46** proving unreactive with **1.111** (**Figure 3.6**).

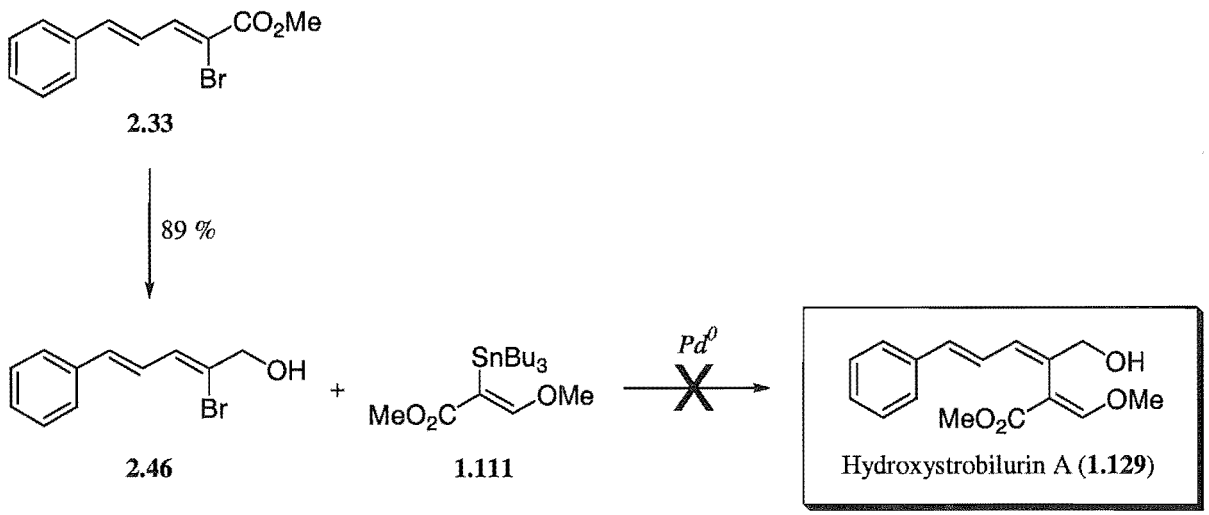


Figure 3.6 Reduction of ester **2.33** to alcohol **2.46**, and attempted formation of the natural product by Stille coupling.

With **1.111** having been successfully employed in Stille coupling regimes by other workers,[104] the problem seemed to be **2.46**, and an obvious option was to protect this molecule's free hydroxyl group, determine if this protected derivative was reactive with **1.111** under Stille conditions, and, if so, whether a deprotection of the resultant triene could be effected to give the natural product.

Thus, diene alcohol **2.46** was derivatised to diene acetate **2.47**, and, gratifyingly, gave moderate yields of triene **2.48** when combined with **1.111** under Stille conditions, confirming that the free hydroxyl group of **2.46** had been responsible for its unreactivity (**Figure 3.7**). Unexpectedly however, the ^{1}H NMR spectrum of triene **2.48** indicated it did not possess the desired (*E,E,E*) stereochemistry, instead apparently having the (*Z,E,E*) geometry shown. A Pd^0-catalysed mechanism was proposed as a possible means by which this double-bond isomerisation might occur, either prior or subsequent to triene formation.

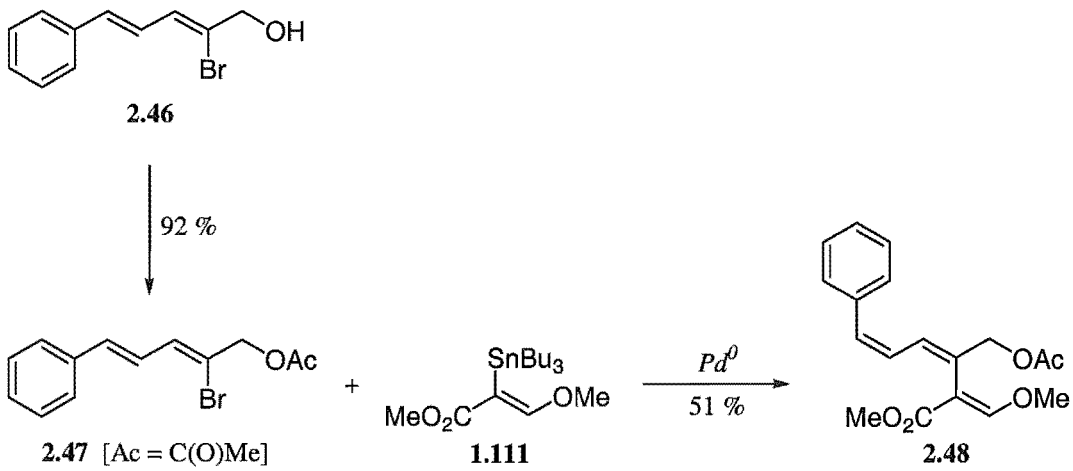


Figure 3.7 Derivatisation of alcohol **2.46** to acetate **2.47**, and formation of (unexpectedly) isomerised triene acetate **2.48**.

Due to the apparent isomerisation during formation of triene acetate **2.48**, as well the fact that 20% of the starting material (**2.47**) was recovered from the crude product mixture, another type of hydroxyl protection was investigated. Thus, **2.46** was successfully derivatised to MOM ether **2.49**, but the subsequent Stille coupling of **2.49** with stannane **1.111** resulted in a disappointingly low yield of triene **2.50** (**Figure 3.8**). Nevertheless, it was noted with some relief that the olefinic coupling constants in the ^{1}H NMR spectrum of **2.50** were consistent with its possessing the desired (*E,E,E*) geometry, supporting the contention that the apparent isomerisation during the formation of **2.48** was a consequence of the structure of this particular triene (or its diene precursor **2.47**), as opposed to being due the Stille coupling conditions themselves.

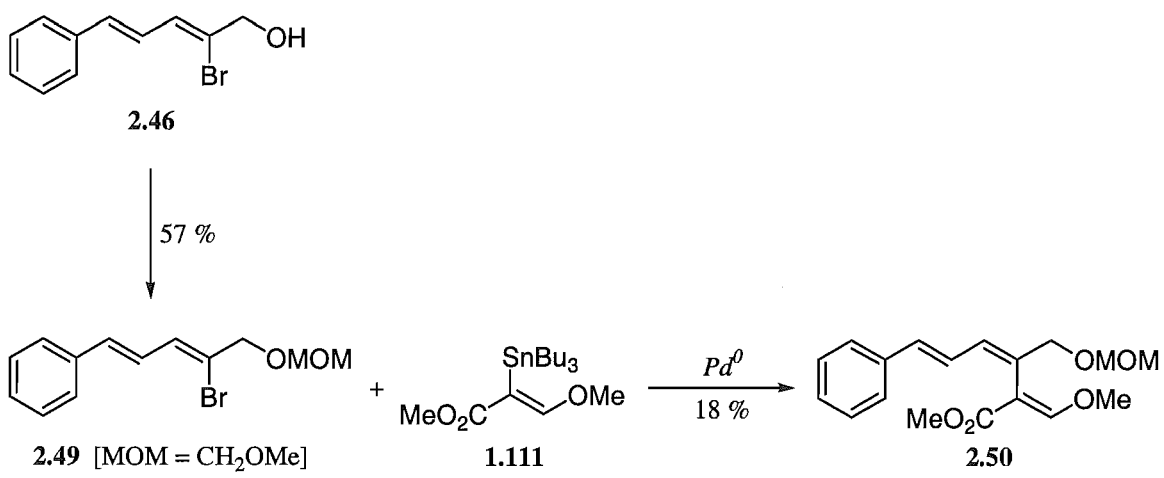


Figure 3.8 Derivatisation of alcohol **2.46** to MOM ether **2.49**, and inefficient formation of MOM triene **2.50**.

Of the several techniques investigated for the synthesis of the (hopefully more reactive) stannyl analogue of **2.49**, only Pd-catalysed stannylation gave reasonable yields of stannane **2.51** (**Figure 3.9**). Halogen-metal exchange treatment of **2.49** (*n*- or *t*-BuLi, Bu_3SnCl, –78 °C – r.t.) afforded only trace amounts of **2.51**, and enyne stannane **2.60**, which was obtained in three efficient steps from phenylethynylstannane (**2.53a**) and methyl propynoate (**2.56b**) [diene stannane **2.64** being unaccessible under these conditions], could not be reduced to **2.51**.

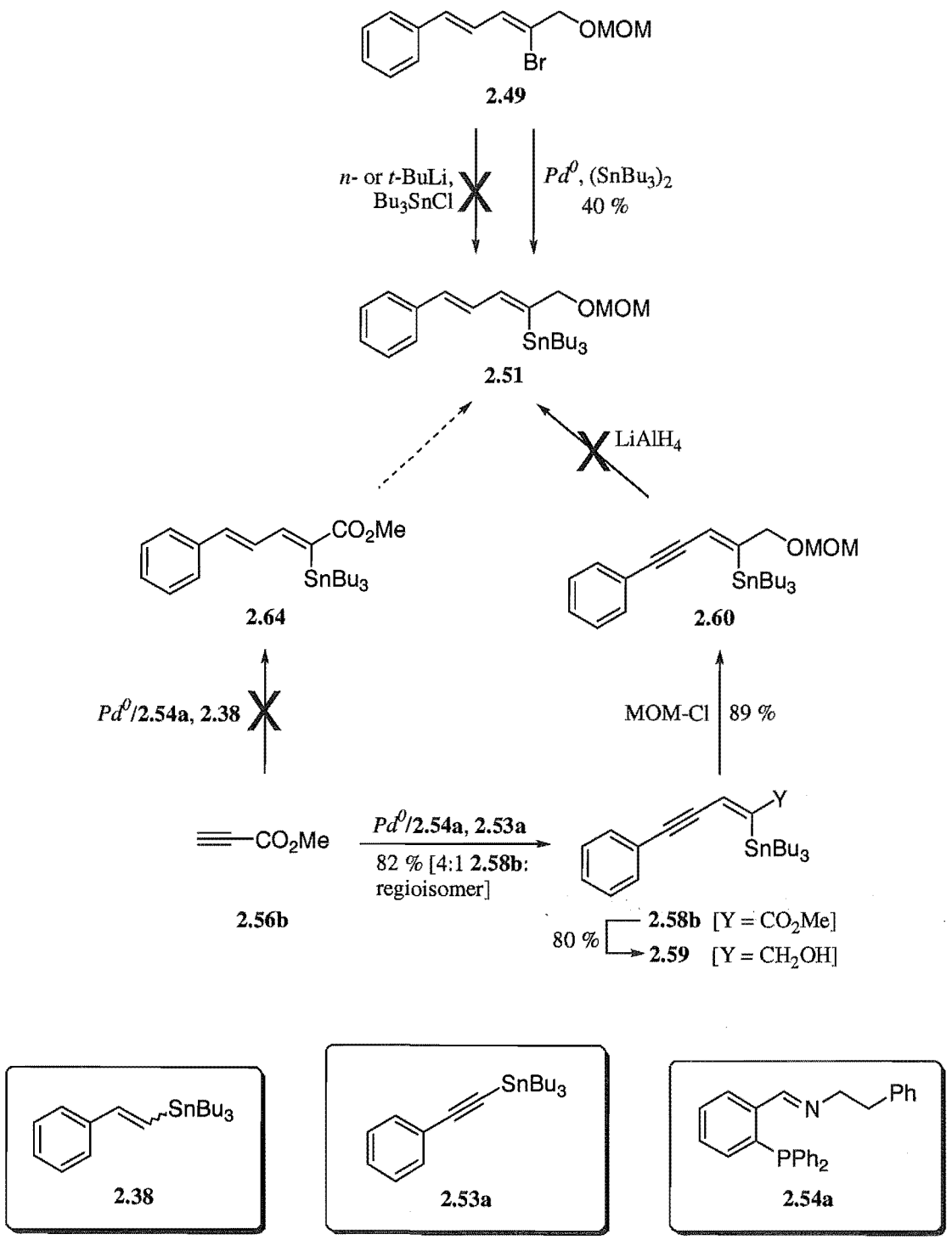


Figure 3.9 Summary of various routes investigated for synthesis of diene stannane **2.51**.

Access to diene **2.51** enabled its Stille coupling activity to be explored. Disappointingly, no cross-coupling occurred between **2.51** and bromide **1.117**, and although some triene **2.50** seemed to be formed from the reaction of **2.51** with iodoacrylate **1.112**, the crude material also contained significant amounts of unreacted **2.51**, and another unidentified compound (**Figure 3.10**). That only a modicum of Stille reactivity had been observed between bromide **2.49** and bromide **1.117** hinted that oxidative addition efficiency was also critical to the success of this coupling, and with this in mind, **2.51** was converted to iodide **2.52**. And indeed, **2.52** was a more reactive substrate, affording a good yield of triene **2.50** when combined with **1.111** under Stille conditions (*c.f.* **Figure 3.5**).

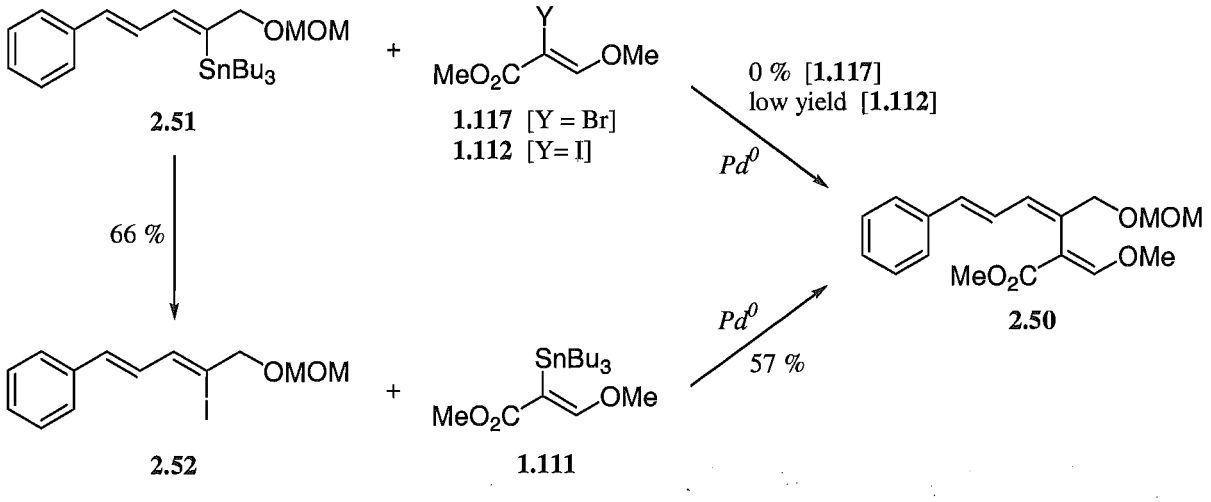


Figure 3.10 Ultimately efficient synthesis of MOM triene **2.50**.

Deprotection of **2.50** to give the natural product (**1.129**) was initially attempted with catalytic aqueous acid, but this was unsuccessful. However, a low yield of **1.129** was afforded with the use of TMSBr as the cleavage agent, although attempts to improve the efficiency of this crucial transformation by scaling up the reaction were unsuccessful, due to apparent triene isomerisation becoming concomitant with deprotection (**Figure 3.11**). Thus, iodide **2.52** was deprotected to free-hydroxyl iodide **2.75** with TMSBr (CF_3COOH having proven inefficacious), and this diene was combined with stannane **1.111** under Stille conditions. However, like its bromide analogue (**2.46**), iodide **2.75** was completely unreactive with **1.111**.

These results contrasted with iodide **2.52** being found to be more reactive under Stille conditions than its bromide analogue **2.49** (see **Figures 3.8** and **3.10**), and suggested that the fact that neither bromide **2.46** nor iodide **2.75** underwent cross-coupling with **1.111** could not be attributed to failure of the oxidative addition step; rather (as previously postulated), the reaction appeared to be inhibited by the hydroxyl group of **2.46** or **2.75**.

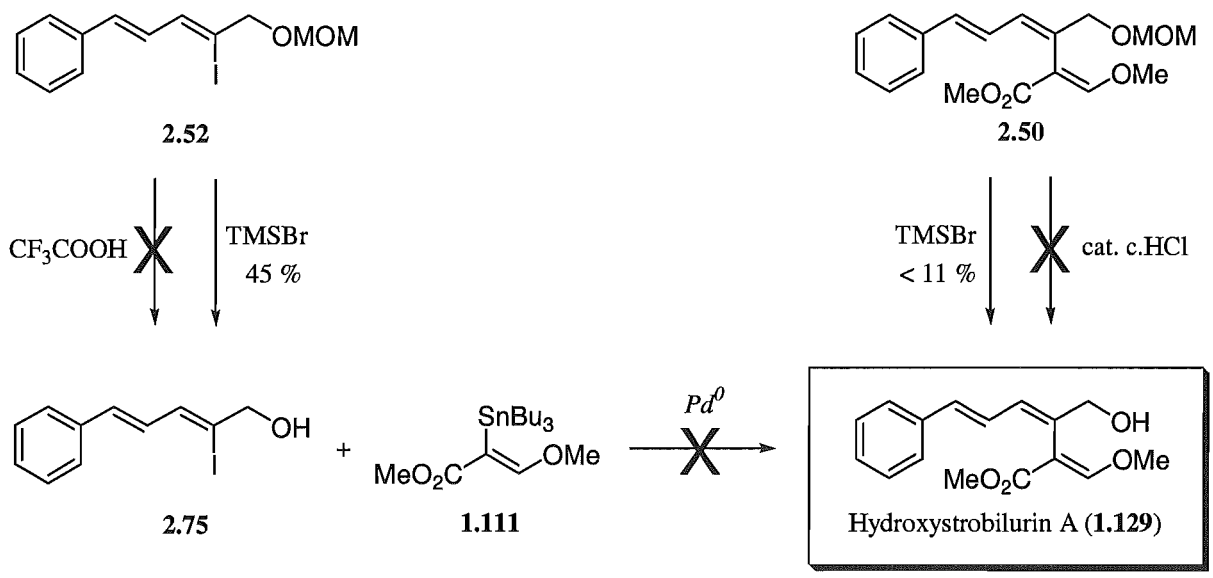


Figure 3.11 Final gambit of hydroxyl-protection approach, with low-yielding ultimate step to hydroxystrobilurin A.

The final routes to **1.129** investigated were based on a functional group interconversion approach, whereby it was hoped the natural product might be furnished by selective reduction of a triene ester or triene aldehyde precursor. Thus, diene ester **2.33** efficiently coupled with stannane **1.111** under Stille conditions to give triene ester **2.65**, but attempted selective reduction the non-vinylogous ester of **2.65** gave a complex mixture apparently consisting mostly of over-reduced products, and thus only a low yield of **1.129** (**Figure 3.12**).

The DIBAl-H reduction of **2.33** was unable to be halted at the diene aldehyde (**2.78**) stage, but a good yield of **2.78** was obtained by oxidation of diene alcohol **2.46**. Aldehyde **2.78** duly proved an effective Stille coupling partner with **1.111**, giving triene aldehyde **2.91**, but disappointingly, attempted selective reduction of the aldehyde functionality of **2.91** with

$NaBH_4$ also afforded only a low yield of hydroxystrobilurin A (**Figure 3.12**), with apparent conjugate (1,4-) addition of hydride competing with (and at greater concentrations of hydride, replacing) the desired direct (1,2-) addition process. Use of $CeCl_3$ with $NaBH_4$ did decrease the prevalence of this apparent conjugate addition process, but rather than leading to a concomitant increase in the yield of direct reduction product **1.129** – only trace amounts of which were formed by this treatment – new side products were formed instead.

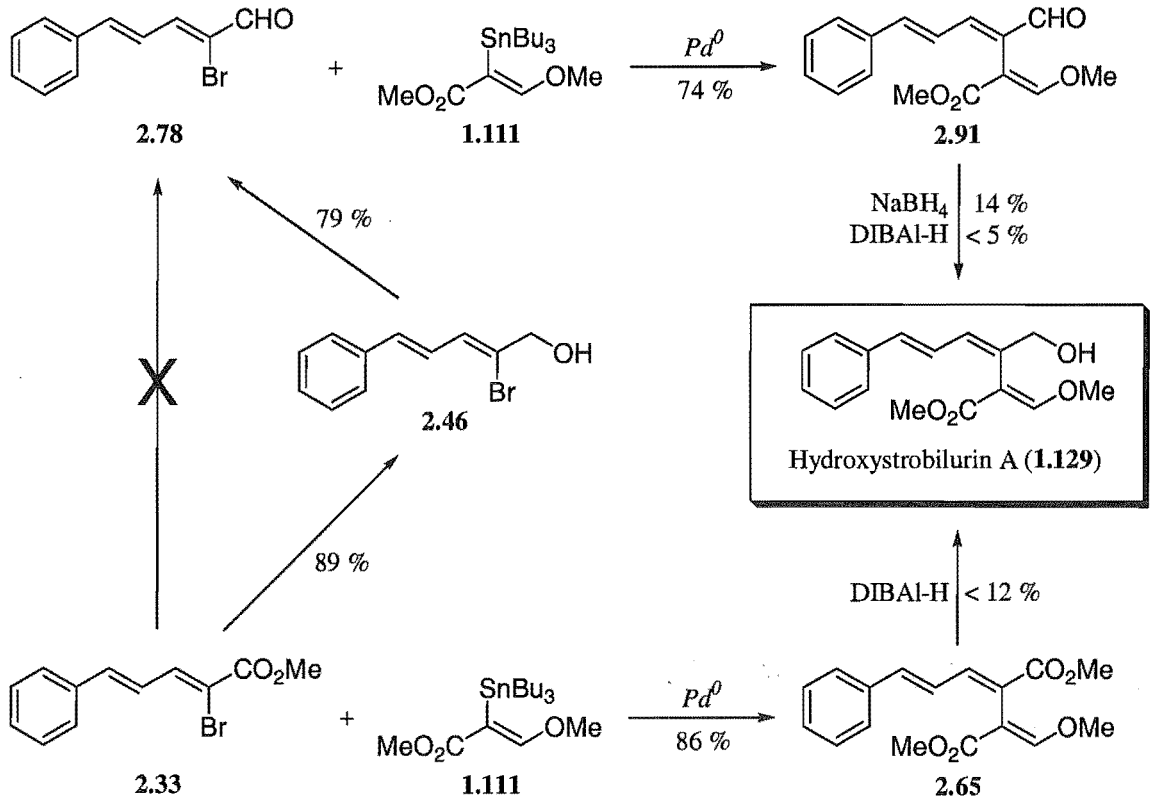


Figure 3.12 Summary of two pathways of functional group-interconversion approach, both with low-yielding ultimate steps to give the natural product.

A comparison of all the triene formation reactions attempted in this Stille coupling-based approach to hydroxystrobilurin A (**1.129**) whose efficacy has been established is given in **Figure 3.13** (all reactions having been conducted using the same catalyst/solvent/temperature system *i.e.* Pd_2dba_3, $AsPh_3$,CuI/NMP/50 °C). Of note is the complete non-reactivity of free-hydroxyl-containing dienes **2.46** and **2.75**, which is in marked contrast to the fair to good reactivity of protected-hydroxyl dienes **2.47**, **2.49**, **2.51**, and **2.52**, and the excellent reactivity of

oxidised-hydroxyl dienes **2.33** and **2.78**. No mechanistic studies of these Stille couplings were undertaken, and apart from the greater yield of triene formation from iodide **2.52** compared to bromide **2.49** being clearly attributable to electronic differences (*i.e.* alkenyl iodides undergoing oxidative addition more readily than alkenyl bromides), it is difficult to rationalise these results.

However, it can be said that the results suggest that the oxidative addition step was not that which was failing in the case of the reactions involving dienes **2.46** and **2.75**. Mechanistically, one might expect inductive donation of electron density by the $-CH_2OH$ moiety of **2.46** and **2.75** to stabilise the electron-deficient Pd^{II} species formed by oxidative addition, and inductive withdrawal of electron density by the –C(O)R moieties of dienes **2.33** and **2.78** to have a destabilising effect, and yet **2.33** and **2.78** are reactive whilst **2.46** and **2.75** are not.

This leaves the possibility that the non-reactivity of **2.46** and **2.75** is due to their inhibition of the transmetallation and/or reductive elimination steps of the Stille coupling process. Given the known rate-determining nature of transmetallation in cross-coupling processes, this step seems more likely to be that which is being adversely affected, but it is not possible to propose any mechanistic explanation(s) for these results without additional data, such as may be generated by further exploration of this synthetic system according to the suggestions in sections **3.2.2** and **3.2.3**.

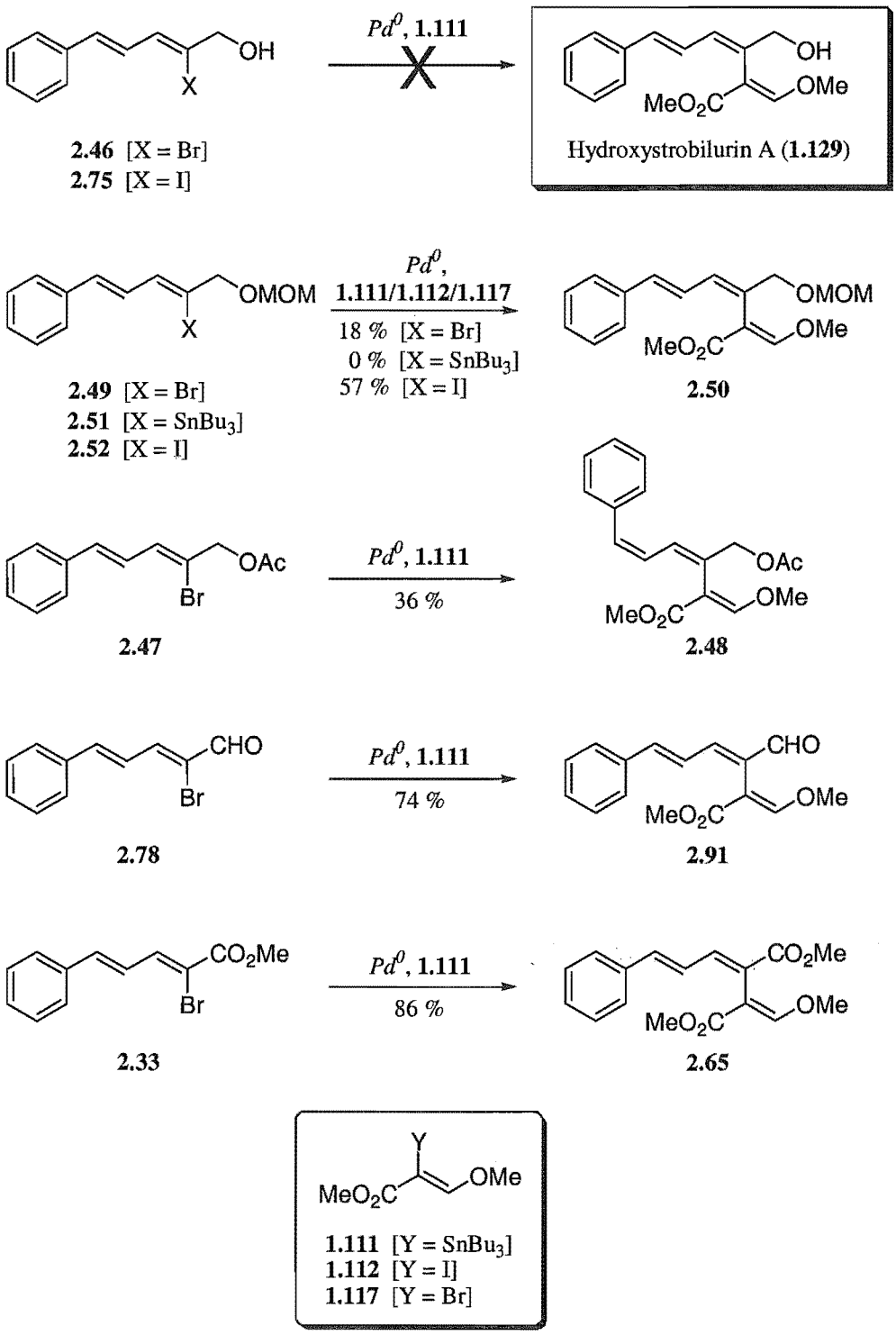


Figure 3.13 Comparison of efficiency of attempted triene formation reactions.

To the best of this author's knowledge, the syntheses described in this thesis constitute both the first three total syntheses of hydroxystrobilurin A (**1.129**), and the first example of the use of Pd-catalysed carbon-carbon bond forming methodology (in this case the Stille coupling) for efficient, stereoselective construction of the strobilurin triene system (see **Figures 3.5** and **3.13**). The total number of synthetic steps from the two commercially available starting materials (phenylacetylene and methyl propynoate) ranged from eight to twelve (**Figure 3.14**).

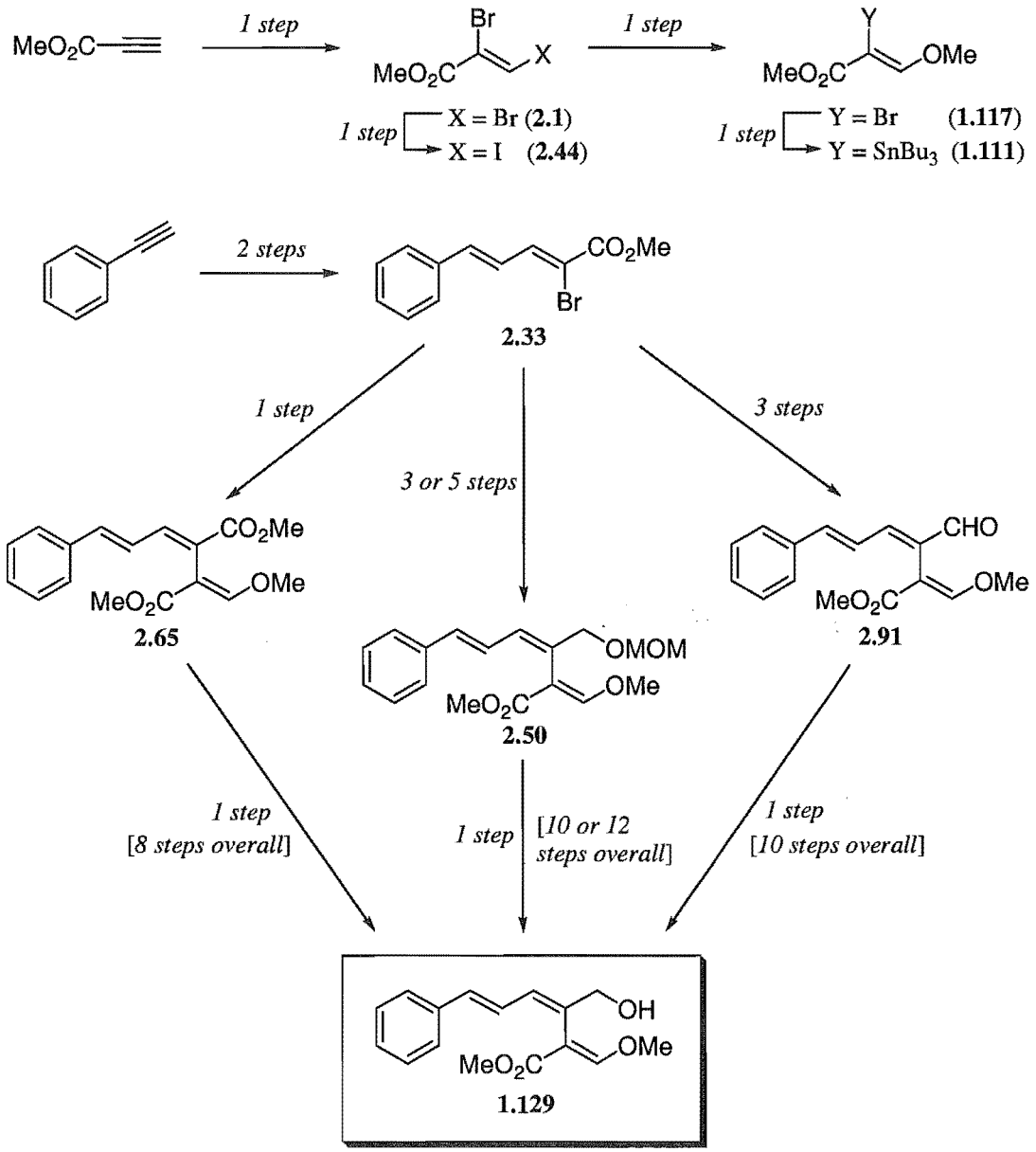


Figure 3.14 Three total syntheses of hydroxystrobilurin A (**1.129**).

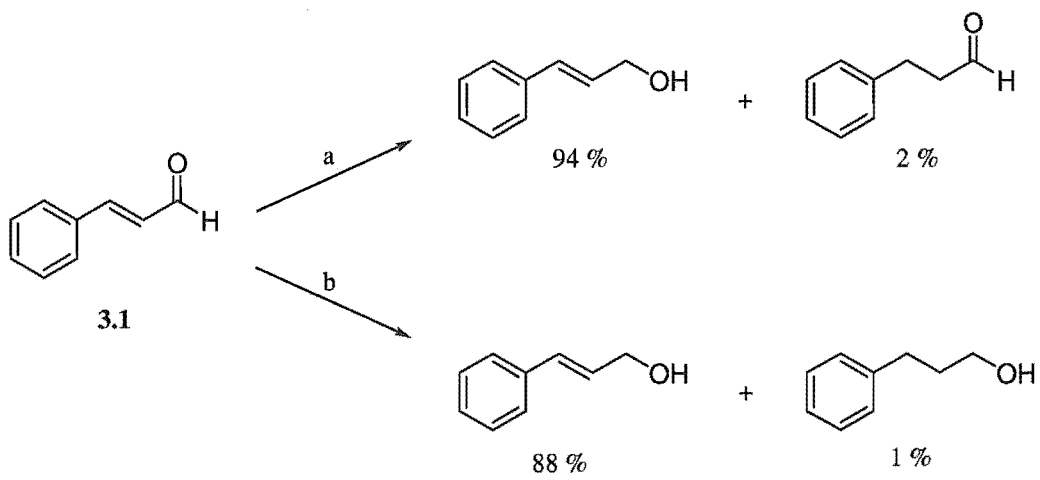
3.2 Future Studies

As can be seen from the previous section, the failure or mediocre yields of several of the reactions investigated *en route* to hydroxystrobilurin A detracted from the overall efficiency of the three total syntheses of this natural product. However, a number of possibilities remain to be investigated, both in the area of reaction optimisation and in the development of new Stille coupling-based approaches, and these will be outlined in this section.

3.2.1 Other Methods for Direction of Aldehyde Reduction

In light of side-product formation occurring when $CeCl_3$ was used with $NaBH_4$ in an attempt to direct the reduction of triene aldehyde **2.91** see *Chapter 2*, page 160, **Figure 2.110**), it would be useful to find another means by which to achieve this pivotal transformation (one which arguably has greater potential for success than the selective reduction of triene ester **2.65**). As such, the chemoselective hydrogenation methodologies of Noyori *et al.*[179] or Chen *et al.*[180] – which utilise H_2 and catalytic amounts of (non-lanthanide) metal–phosphine complexes to direct the 1,2-reduction process – seem worthy of investigation.

Noyori *et al.*'s system is a ternary, ruthenium-based catalyst, comprising a dichlorotris(triphenylphosphine) complex of Ru^{II}, 1,2-diaminoethane, and KOH [$Ru(PPh_3)_3Cl_2$–$H_2N(CH_2)_2NH_2$–KOH] which is active at very low catalytic loadings [substrate:catalyst molar ratios of 500 or 10000:1], ambient temperature, and with 1-8 atm of H_2, and affords >95% yields of unsaturated alcohols from the corresponding aldehydes and ketones (with generally only trace amounts of over-reduced products formed), as exemplified by the reduction of **3.1** (**Figure 3.15**).[179] Chen *et al.*'s dialkylarylphosphine-stabilised copper(I) hydride catalyst, $[(Ph_3P)CuH]_6$, is also active at ambient temperatures and with similar pressures of H_2, and although it functions more slowly and is required in higher molar ratios than Noyori *et al.*'s Ru^{II} catalyst, it is comparatively inexpensive, and is slightly more regioselective for 1,2-reduction (**Figure 3.15**).[180]



Reagents and conditions: (a) $Ru(PPh_3)_3Cl_2$–$H_2N(CH_2)_2NH_2$–KOH [0.2:0.2:0.4 mol %], H_2 [4 atm], 2-propanol–toluene [6:1], r.t., 0.5 h; (b) $[(Ph_3P)CuH]_6$ [0.83 mol % = 5 mol % Cu], $PhP(CH_2)_4$ [6 eq. wrt Cu], *t*-BuOH [40 eq. wrt Cu], H_2 [5 atm], benzene, r.t., 18 h.

Figure 3.15 Comparison of efficiency and efficacy of 1,2-reduction of an α,β-unsaturated aldehyde *via* Noyori *et al.*'s (Ru^{II}) and Chen *et al.*'s (Cu^{I}) catalytic hydrogenation methods.

Aside from the single-step optimisation possibility described above, there are several other interrelated diene-based pathways which may warrant exploration by future workers, and these are described in the next section, together with some methodologically similar enyne-based approaches to the natural product. As a consequence of the success and familiarity with Stille coupling techniques gained during the work described in this thesis, most of the carbon-carbon bond-formation of these pathways is *via* the reaction of vinyl tin compounds with vinyl halides, except where (indicated) the former may be replaceable with phenylzinc chloride, phenylboronic acid, or Rossi *et al.*'s zinc acrylates.[107]

3.2.2 Future Diene-Based Strategies

Undoubtedly the most disappointing result was the inability to access hydroxystrobilurin A directly *via* a Stille coupling between dienes **2.46** or **2.75** and acrylates **1.111** or **1.117**, respectively. However, several variations of this approach remain to be explored. First, either the trimethyl analogue (**3.2**) of **1.111** (trimethyltin compounds are often more reactive than

their tributyltin analogues, and **3.2** should be accessible in an analogous fashion to **1.111** from **1.117** – see *Chapter 2*, **Figure 2.8**), or the acrylate-derived organozinc halides **1.119** developed and used by Rossi *et al.* for syntheses of strobilurin analogues (see *Chapter 1*, **Figures 1.43** and **1.44**)[108] may prove reactive with **2.46** or **2.75** (**Figure 3.16**).

Second, an interchange of tin and halide vinyl substituents of the potential Stille coupling partners may result in precursors which cross-couple to form the natural product: *i.e.* diene stannane **3.3**, which should be available *via* metal-halogen exchange from **2.46** (a process necessarily conducted using *t*-BuLi at temperatures below –110 °C,[181] most conveniently in the ternary Trapp solvent system[182] ‡), or *via* reduction of enyne stannane **3.4**, may couple with acrylates **1.112** or **1.117** under Stille conditions (**Figure 3.16**). Or, **3.3** could be iododestannylated to **2.75**, and this iodide combined with stannane **3.2** under Stille conditions (**2.75** having proven unreactive with stannane **1.111** – see *Chapter 2*, **Figure 2.89**). Facilitation and/or further enhancement of potential Stille coupling routes to **1.129** from **2.46**, **3.3**, or **2.75** may also be realised with use of the phosphonium salt $Ph_2PO_2NBu_4$ as a tin scavenger (*i.e.* the phosphonium anion complexes with tin, leading to the precipitation of $Ph_2PO_2SnR_3$ out of solution), a technique described by Liebeskind *et al.*[183] An excellent example of the utilisation of the transposition of Stille coupling partner functionality, the increased reactivity of trimethyltin compounds, and $Ph_2PO_2NBu_4$ for the facilitation and optimisation of Stille couplings is seen in Smith and Ott's syntheses of the polyene natural products (–)-macrolactins A and E, and macrolactinic acid.[89b]

‡ That these specific conditions were not employed during treatment of diene bromide **2.46** with *t*-BuLi/Bu_3SnCl (see *Chapter 2*, **Figure 2.59**) is probably why this attempted metal-halogen exchange afforded only trace amounts of desired diene stannane **2.49**.

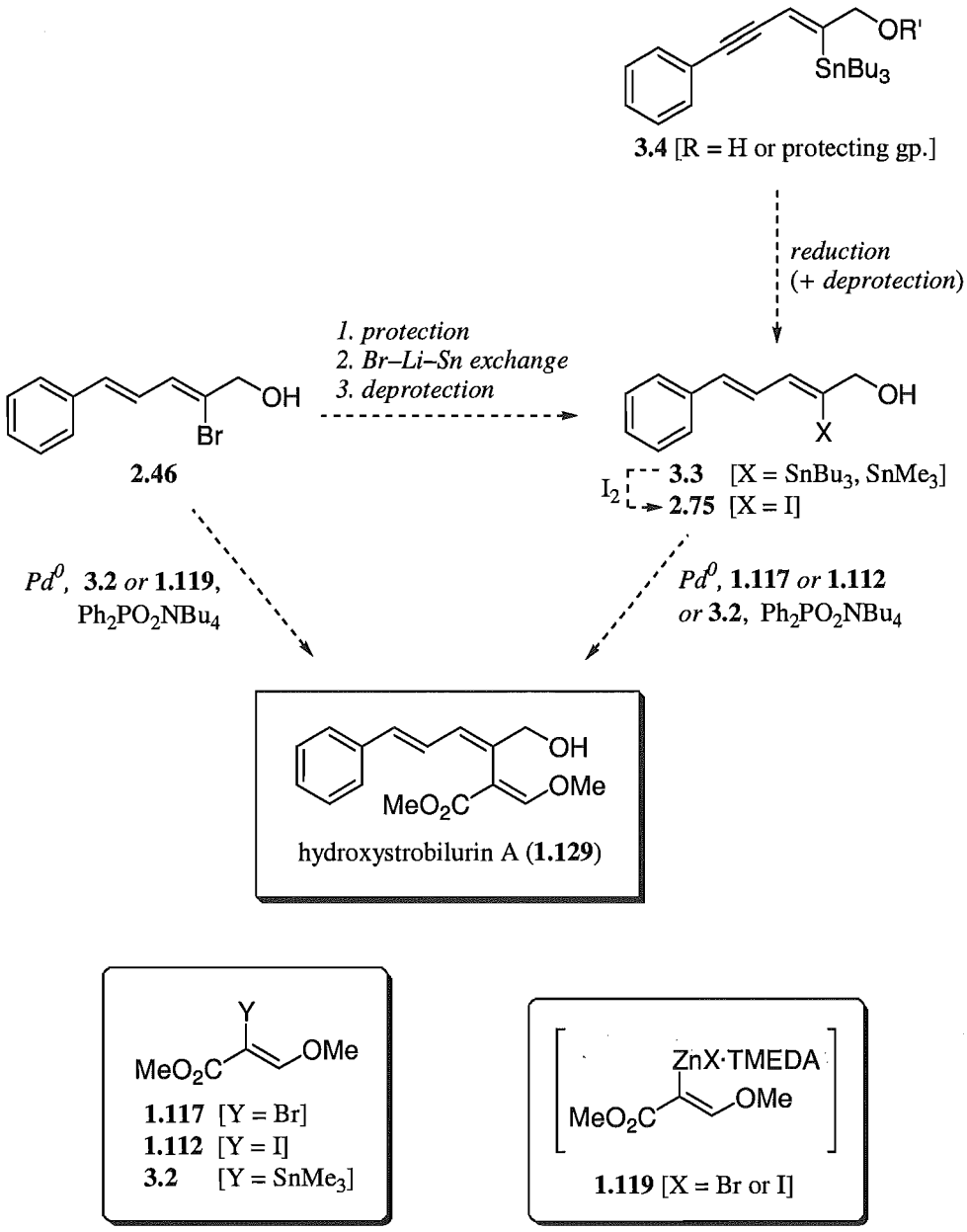


Figure 3.16 Possible routes to hydroxystrobilurin A *via* diene alcohol **2.46**, **2.75**, or **3.3**.

Another variation on the functional group-interconversion diene approach to **1.129**, but with the potential to be more efficient than the two examples of such a route already investigated (*i.e.* reduction of triene ester **2.65** or triene aldehyde **2.91** – see *Chapter 2*, **Figures 2.93** and **2.108**), could proceed *via* diene acid **3.5** (**Figure 3.17**). Hydrolysis of ester **2.33** should afford required **3.5**, which may couple with stannane **1.111** or **3.2** or a zinc halide **1.119** under Stille

conditions to give triene acid **3.6**. The final step – reduction of **3.6** to **1.129** – is that which could impart greater efficiency to this approach, as Brown *et al.*'s BH_3–THF reagent is virtually quantitatively selective for the reduction of acids in the presence of esters.[184]

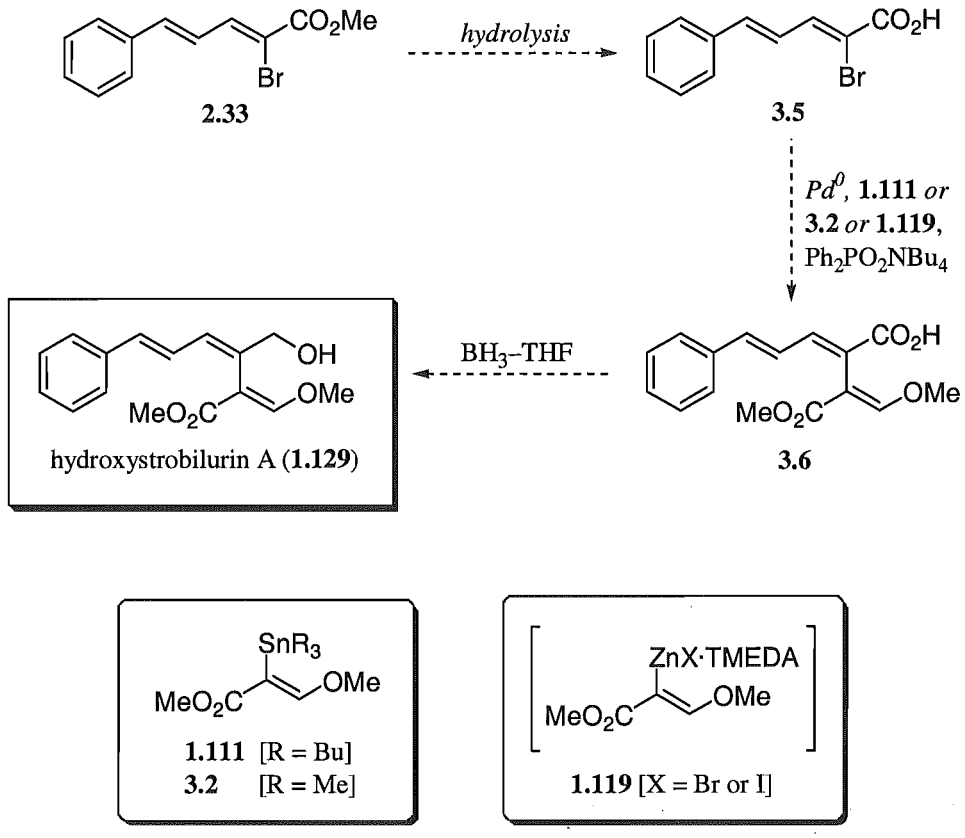


Figure 3.17 Possible route to hydroxystrobilurin A *via* diene acid **3.6**.

A different mode of diene formation may be possible *via* a structurally faithful application of the methods of the Sn→Li→Zn→Pd transmetallation technique of Pihko and Koskinen (see *Chapter 2*, **Figure 2.41**):[138] the mediocre yield of diene **2.33** obtained by application of this technique (see *Chapter 2*, **Figure 2.42**) may have been due to use of stannane **2.38** rather than distannane **1.101**.[102] Thus, reaction of **1.101** or its methyl analogue **3.7**[185] with iodide **2.44**, followed by ester reduction, may afford diene **3.8**, combination of which with stannane **1.111** or **3.2** or a zinc acrylate **1.119** under Stille conditions could yield triene alcohol **3.9** (**Figure 3.18**). A Stille coupling between **3.9** and iodobenzene (PhI) could then form the natural

product **1.129**. Alternatively, iododestannylation of **3.9** to iodide **3.10**, followed by Stille coupling of **3.10** with phenylstannane **3.11**[186] or **3.12**,[187] or coupling with phenylboronic acid (**3.13**) or phenylzinc chloride (**3.14**) under Rossi *et al.*'s conditions (see *Chapter 1*, **Figure 1.45**)[107] may give **1.129**.

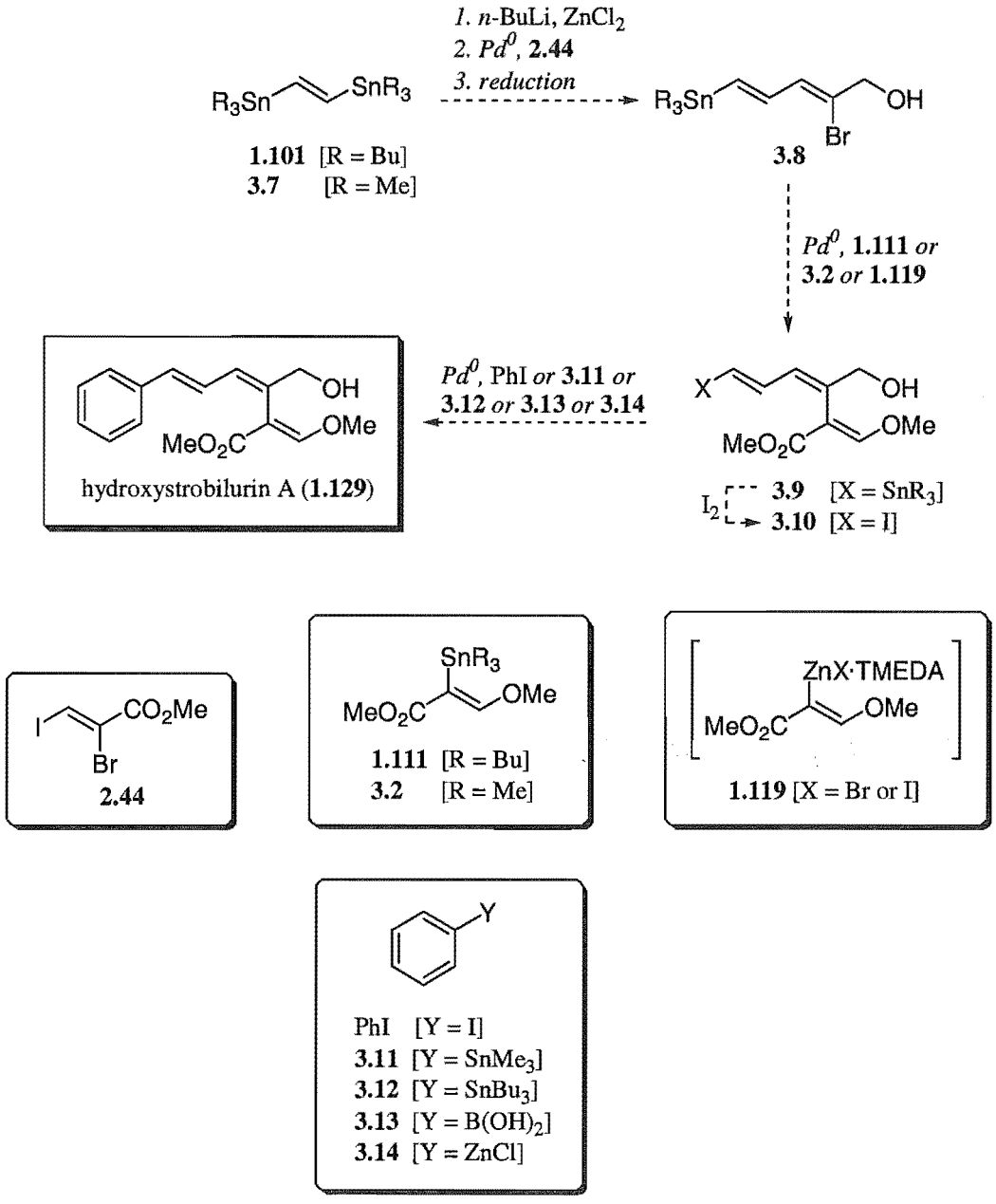


Figure 3.18 Possible route to hydroxystrobilurin A from distannane **1.101** or **3.7**.

An interchange of substituents of the initial Stille coupling partners in the above route is the basis for a final potential diene-based approach. Thus, diiodide **3.15**,[188] which should be accessible by iododestannylation of **1.101** or **3.7**, may couple with Mitchell *et al.*'s distannane **3.16**[185] under Stille conditions to give diene **3.17** (**Figure 3.19**). This could then be elaborated to the natural product, as before.

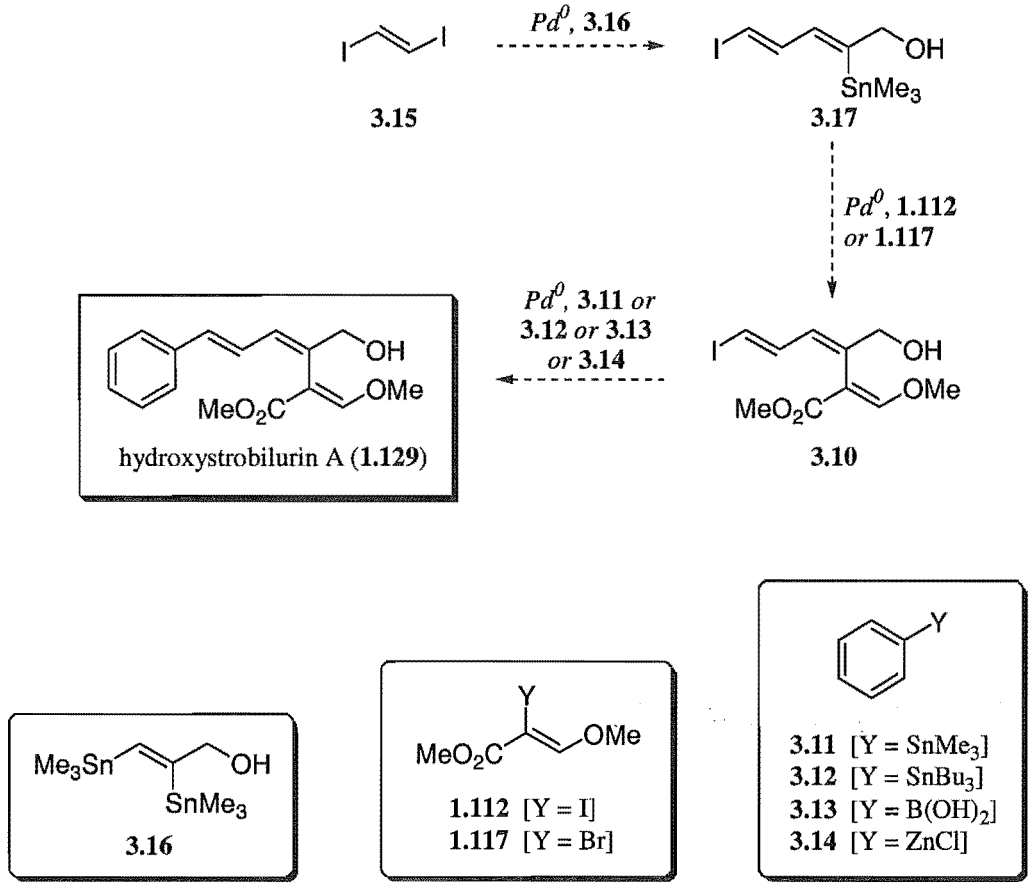


Figure 3.19 Possible route to hydroxystrobilurin A from diiodide **3.15**.

3.2.3 Future Enyne-Based Strategies

The two potential enyne-based approaches to the natural product outlined in **Figure 3.20** below start from two different trimethylsilyl(trialkylstannyl)acetylenes and initially use two different carbon-carbon bond-forming processes, but thereafter utilise the same cross-coupling methodologies as in the diene-based approaches already described. Thus,

trimethylsilyl(tributylstannyl)acetylene (**3.18**)[189] or its trimethylstannyl analogue **3.19**[190] may react with methyl propynoate under Shirakawa *et al.*'s Pd^0–iminophosphine catalysis (see *Chapter2*, **Figure 2.62**)[152] to give enyne esters **3.20**, whilst it has already been established that a Sonogashira coupling[119] between (trimethylsilyl)acetylene and vinyl bromide **2.1** is a viable route to enyne ester **2.6** (see *Chapter 2*, **Figure 2.14**).

Enyne esters **3.20** and **2.6** could be directly hydrolysed to enyne acids **3.21** and **3.22**, respectively, or **3.20** could first be iododestannylated to **3.23**, which may be hydrolysed to enyne acid **3.24**. Combination of one of these enyne acids with the appropriately functionalised acrylate derivative (**1.111**, **1.112**, **1.117**, **3.2** or **1.119**) under palladium catalysis may afford ynediene acid **3.25**. Desilylation of **3.25** will unmask the acetylene, which may then be hydrostannylated to give the (*E*,*E*,*E*)-triene stannane [or hydrostannylated and then iododestannylated to give the (*E*,*E*,*E*)-triene iodide], whose reaction with iodobenzene (PhI), under Stille conditions [or with **3.11** or **3.12** under Stille conditions, or **3.13** or **3.14** under Rossi *et al.*'s conditions],[107] should give triene acid **3.6** (*c.f.* **Figure 3.17**). Finally, treatment of **3.6** with carboxylic acid-specific reductant BH_3–THF,[184] as before, may afford the natural product.

Alternatively, enyne ester **2.6** can be reduced to enyne alcohol **2.9** (see *Chapter 2*, **Figure 2.16**), and enyne esters **3.20** should be able to be reduced to enyne alcohol **3.26** (or first iododestannylated to **3.23**, and then reduced to enyne alcohol **3.27**) [**Figure 3.20**]. Combination of one of these enyne alcohols with the appropriately functionalised acrylate derivative (**1.111**, **1.112**, **1.117**, **3.2** or **1.119**) under palladium catalysis may afford ynediene alcohol **E** (whose formation thus has been only partly explored – see *Chapter 2*, **Figure 2.17**). Desilylation of **E**, then hydrostannylation [or hydrostannylation, then iododestannylation], followed by Pd^0-catalysed coupling of the resultant (*E*,*E*,*E*)-triene stannane with PhI [or of the resultant (*E*,*E*,*E*)-triene iodide with **3.11**, **3.12**, **3.13** or **3.14**], should give **1.129**.

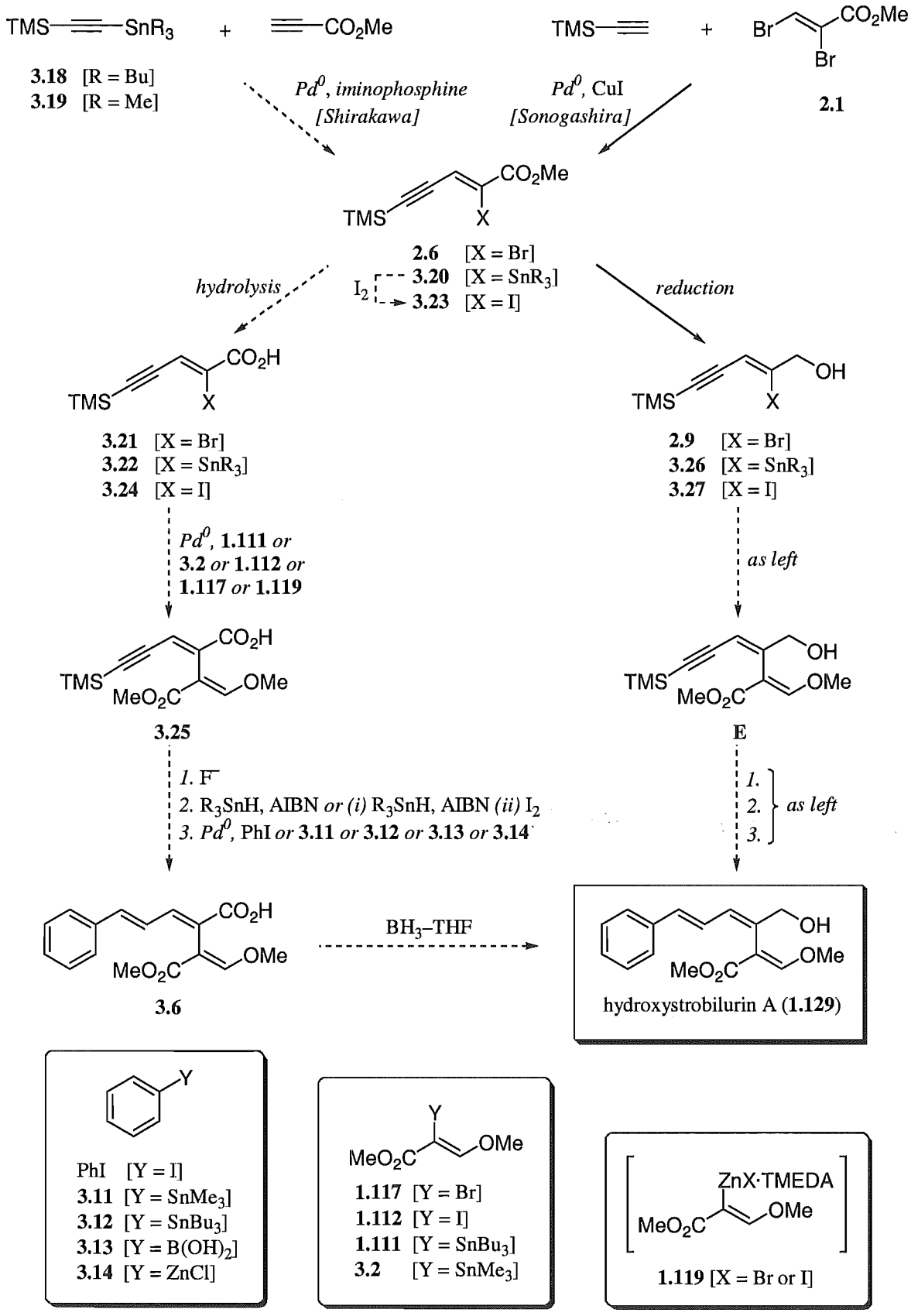


Figure 3.20 Enyne-based approaches to hydroxystrobilurin A.

3.3 Replace Tin with Indium?

As the approaches outlined in the previous two sections illustrate, the possibilities for future improved Pd coupling-based syntheses of hydroxystrobilurin A are many. In addition to exploitation of these techniques, and in light of the advent of the 'green chemistry' paradigm,[191] which emphasises the desirability of striving for greater efficiency in synthesis and the minimisation of (especially toxic) side product formation and the use of toxic reagents (such as the organometallic derivatives of tin), a technique developed by Pérez *et al.* for the synthesis and utilisation of indium organometallics may be of use.[192] Although this methodology is not discussed in any detail here, suffice it to say the fact that Group 13 element indium shares some of the chemical characteristics of Group 14 element tin, whilst forming organometallic compounds of (apparent) low toxicity,[193] and – perhaps most appealingly to the synthetic chemist – that triorganoindium compounds transfer *all three* of their organic groups in high-yielding Pd- or Ni-catalysed cross-coupling reactions with organic electrophiles (as in the equation below), makes this new carbon-carbon bond-formation technique worthy of investigation.

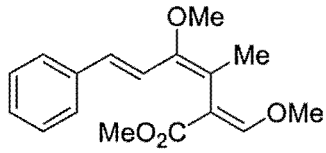
$$R_3In + 3R'\text{–}X \xrightarrow[THF]{\text{Pd or Ni catalyst}} 3R'\text{–}R$$

CHAPTER FOUR

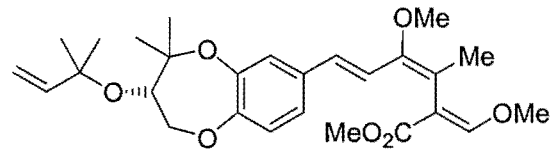
Synthetic Investigations of the 9-Methoxystrobilurins & the Phomoidrides

4.1 Introduction

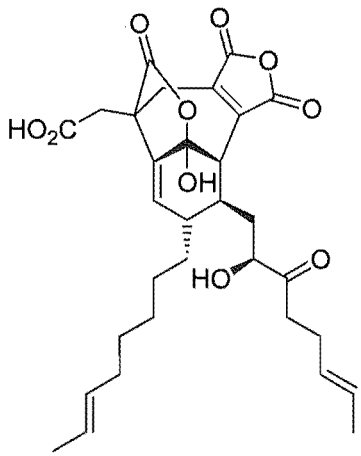
The Pd coupling-based methodologies utilised for efficient carbon-carbon bond formation in the approaches to hydroxystrobilurin A described in Chapter 2 are also fundamental to potential synthetic approaches towards four other fungal-derived natural products shown in **Figure 4.1** below: 9-methoxystrobilurins A (**4.1**) and K (**4.2**),[62] and phomoidrides[a] A (**4.3**) and B (**4.4**) [**4.3** and **4.4** are also known by their original registry designations, CP-225,917 and CP-263,114].[194] This chapter will describe these approaches, the results garnered from preliminary explorations of their feasibility, and implications and indications for future research.



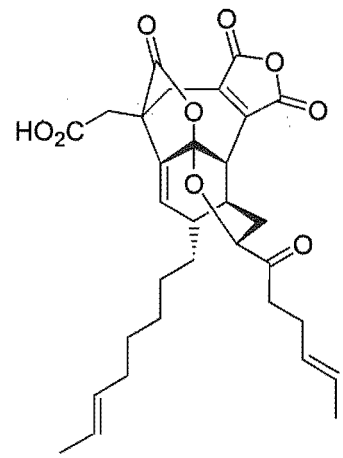
9-methoxystrobilurin A (**4.1**)



9-methoxystrobilurin K (**4.2**)



phomoidride A [CP-225,917] (**4.3**)



phomoidride B [CP-263,114] (**4.4**)

Figure 4.1 The 9-methoxystrobilurins and the phomoidrides: fungal natural products.

[a] This name derives from the fact that the molecules contain anhydride functionalities, and that the producing organism displayed the characteristics of *Phoma* sp. [Hepworth, D. *Chem. Ind. (London)* **2000**, *2*, 59].

4.2 Potential Approaches to 9-Methoxystrobilurins A and K

4.2.1 Introduction

The isolation of 9-methoxystrobilurins A (**4.1**) and K (**4.2**) from a fungus of *Favolaschia* sp. was reported by Anke and Steglich *et al.* in 1995.[62] In addition to exhibiting anti-fungal activity typical of the strobilurins, **4.1** and **4.2** both demonstrated potent cytostasis towards human-derived tumour cell lines without significant associated cytotoxicity, a property seemingly due to their unique structural features. The structure originally proposed for 9-methoxystrobilurin K by Anke and Steglich *et al.*'s was shown by Nicholas and Blunt *et al.* to be inconsistent with the spectroscopic data, who proposed the benzodioxepin-containing structure (**4.2**) instead.[56] The veracity of **4.2** was confirmed by a re-investigation by Anke and Steglich *et al.* (see *Chapter 1*, section **1.5.7** for a full discussion of this and a related structural re-assignment).[57]

Methoxy substitution at C-9 distinguishes the triene system common to **4.1** and **4.2** from that of other strobilurins, such as hydroxystrobilurin A, increasing the complexity of the challenge these molecules present to the synthetic chemist. During the period in which the work described in this thesis was completed, total syntheses of **4.1**[54] and **4.2**[55] were reported by Kobayashi *et al.* (see *Chapter 1*, sections **1.5.4** and **1.5.5**), but the approach these workers used for formation of the triene system generated mixtures of geometric isomers that were only partly separable, and thus there is scope for a more stereoselective synthesis of these molecules.

4.2.2 Synthetic Rationale, Initial Results, and Future Work

A retrosynthetic analysis of **4.1** and **4.2** (with both molecules represented as generalised structure **4.5**) which incorporates such stereoselectivity requirements is depicted in **Figure 4.2**. Disconnection of **4.5** at *a* reveals that it could be derived from reaction of stannane **1.111** or **3.2**, iodide **1.112**, bromide **1.117** or organozinc acrylates **1.119**[108] with an appropriately

functionalised form of diene **4.6** under Pd catalysis. The synthesis of **1.111** and **1.112** has been previously described (see *Chapter 2*, **Figures 2.8** and **2.10**), **1.119** should be available by the procedure of Rossi *et al.* (see *Chapter 1*, **Figure 1.43**),[108] whilst **4.6** could be accessible by reduction of enyne **4.7** (Ar is defined as a phenyl group in **4.6** and **4.7** as the benzodioxepin version of **4.7** may be unstable to alkyne-reducing conditions).[**]

Alternatively, disconnection of **4.5** at *b* reveals it could be also be derived from reaction of an aryl compound **4.8** with an appropriately functionalised form of triene **4.9** under Pd catalysis; where Ar is a phenyl group, **4.8** could be represented by iodobenzene or benzene derivatives **3.11-3.14**,[107] whilst the benzodioxepin versions of **4.8** could be Kobayashi *et al.*'s bromide **1.43** itself, or an I/SnR_3 analogue produced by modification of their synthesis of **1.43** (see *Chapter 1*, **Figure 1.15**).[55] Triene **4.9** should be available from ynediene **4.10** *via* desilylation and hydrostannylation (followed by iododestannylation, if required), disconnection of which at *c* shows that it could derived from a Pd-catalysed reaction between **1.111**, **3.2**, **1.112**, **1.117**, or **1.119** and an appropriately functionalised form of enyne **4.11**.

[**] It is possible that the methoxy group, being α to the alkyne, will facilitate the reduction of this triple bond by $LiAlH_4$ in an analogous manner to which α-hydroxy groups on alkynes are known to do.

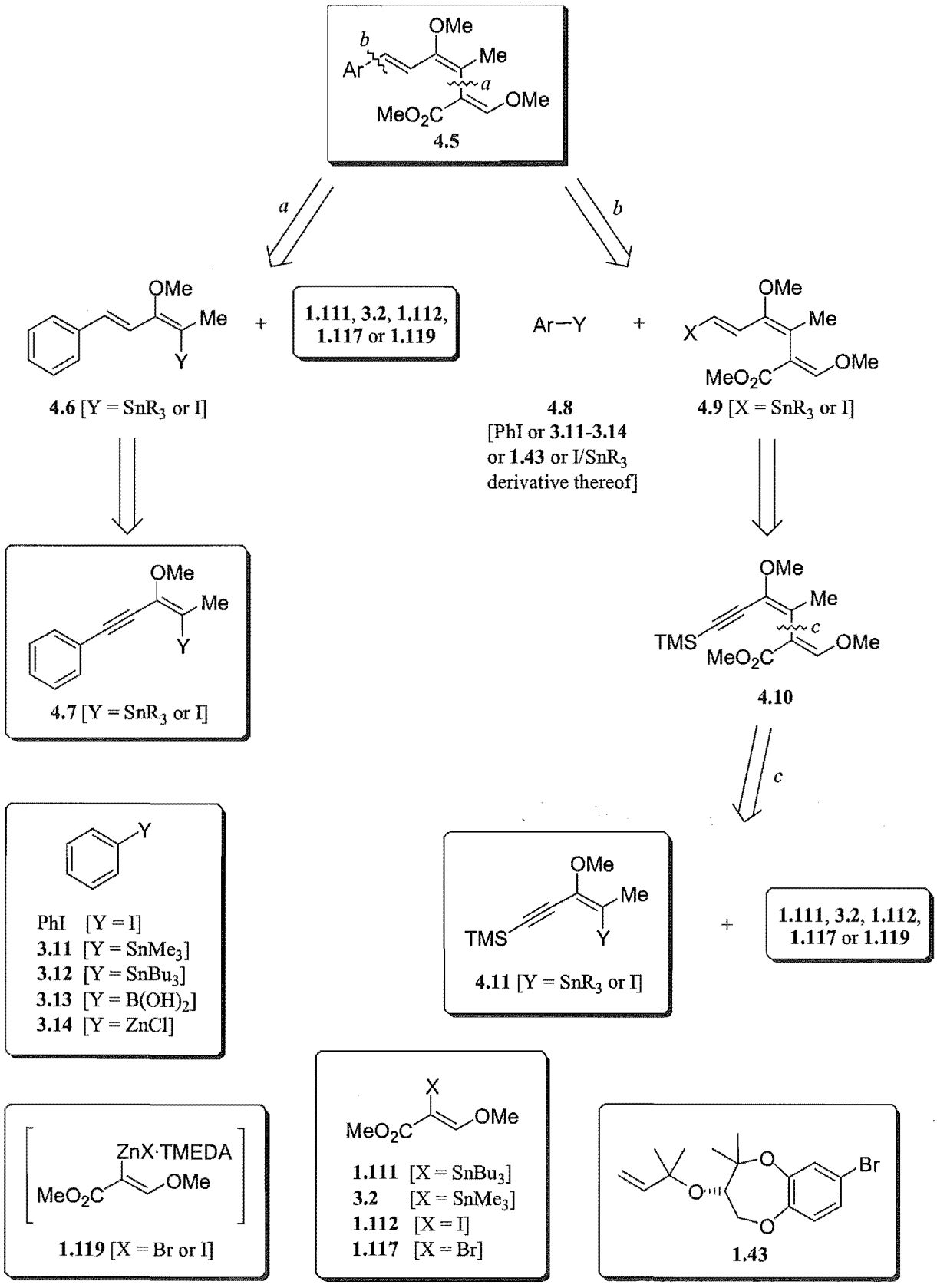
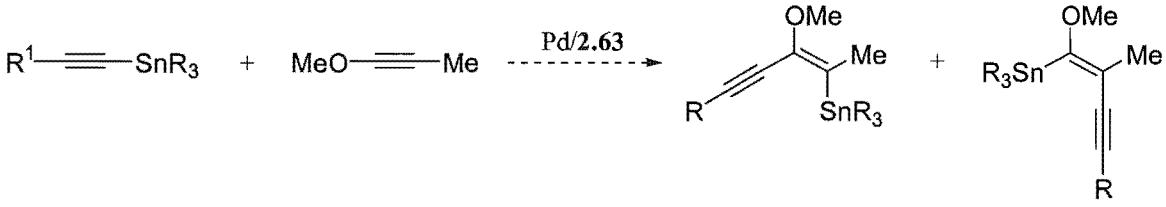
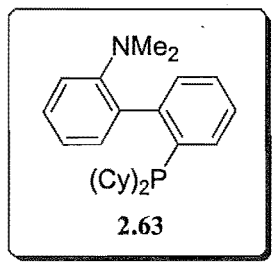


Figure 4.2 Retrosynthetic analysis of 9-methoxystrobilurins A and K (generalised as **4.5**).

There is an obvious analogy between the enynes **4.7** and **4.11**, and thus it is unsurprising that both may be accessible *via* the same methodology: a Shirakawa-type alkynylstannylation of an alkyne (see *Chapter 2*, **Figure 2.62**),[152] a technique which was successfully employed for enyne formation during investigations towards the synthesis of hydroxystrobilurin A (see *Chapter 2*, **Figures 2.65** and **2.67**). Thus, reaction of stannane **2.53a** or **4.12**, or stannane **3.18**[189] or **3.19**[189] with methoxypropyne (**4.13**)[195] under Shirakawa conditions may yield enynes **4.7** and **4.11** respectively (**Figure 4.3**). Their corresponding regioisomers (**4.14** and **4.15**) could also be formed, but given the marked regioselectivity demonstrated by biphenyl ligand **2.63** for formation of the electronically favoured alkynylstannylation product of such reactions (see *Chapter 2*, **Figure 2.67**) – which in this case will be **4.7** and **4.11** – it is likely that **4.14** and **4.15** will be minor products.



2.53a [R^1 = Ph, R = Bu] **4.13** **4.7** [R = Ph] **4.14** [R = Ph]
4.12 [R^1 = Ph, R = Me] **4.11** [R = TMS] **4.15** [R = TMS]
3.18 [R^1 = TMS, R = Bu]
3.19 [R^1 = TMS, R = Me]



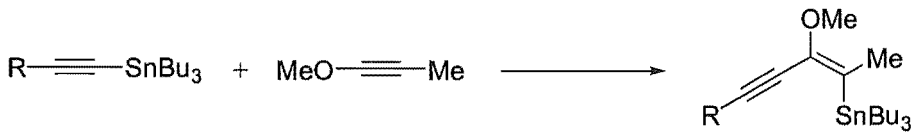
2.63

Figure 4.3 Possible Shirakawa-style synthesis of enynes **4.7** and **4.11**.

Accordingly, methoxypropyne (**4.13**)[ψ] was reacted with stannane **2.53a**, and with stannane **3.18**, under π-allylpalladium chloride dimer/**2.63** catalysis (**Figure 4.4**). The ^{1}H NMR spectra of these crude mixtures contained (in addition to some starting material) only one major

[ψ] Prepared from propanal (as described by Nooi and Arens[195]) by Andrew Muscroft-Taylor.

product,† as demonstrated by the presence of only one methoxy group signal and one methyl group signal, related by a 1:1 integral ratio (**Figure 4.4**). Moreover, apparent $^{3}J(^{119/117}\text{Sn-H})$ coupling between the methyl group protons and the tin atom – manifested as satellite peaks ~21.6 Hz either side of the methyl group singlets in each spectrum – suggested that in both cases the product was the desired enyne **4.7** or **4.11**. However, attempts at purification of these crude mixtures by flash chromatography (both on silica gel and alumina) and by distillation led to degradation of products.



2.53a [R = Ph] **4.13** **4.7** [R = Ph]
3.18 [R = TMS] **4.11** [R = TMS]

Reagents and conditions: $[PdCl(\pi\text{-}C_3H_5)]_2$ [2.4 mol %], **2.63** [4.8 mol %] , THF, 50 °C, 3 h [yields not calculated].

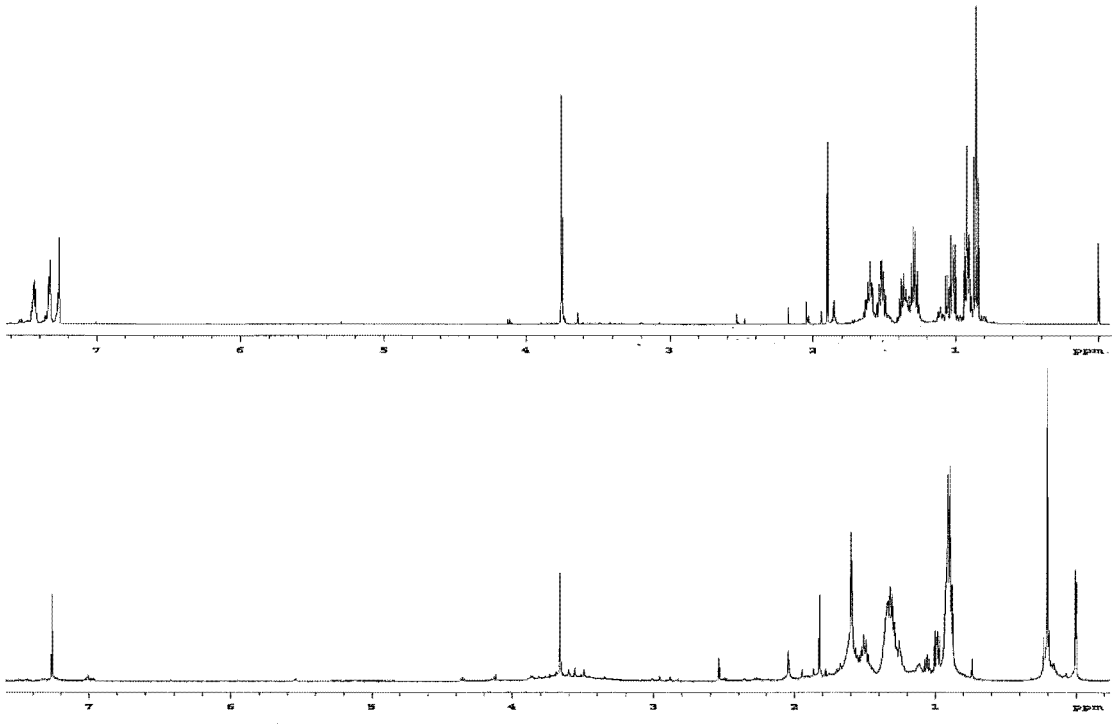
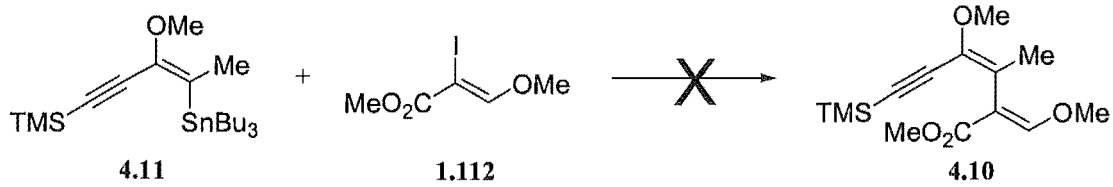


Figure 4.4 Synthesis and 500 MHz ^{1}H NMR spectra of enynes **4.7** (top) and **4.11** (bottom).

† This marked regioselectivity may be due to the formation of **4.7** and **4.11** being sterically as well as electronically favoured, an hypothesis which could be confirmed by determining if the use of the less sterically bulky 2–NH_2 analogue of 2'-$N(CH_3)_2$ biphenyl ligand **2.63** in these reactions would result in less regioselective product mixtures. In light of the observation by Shirakawa *et al.* of a positive correlation between steric bulk of the imine group and regioselectivity in the alkynylstannylation of some substrates, this may well prove to be the case.[152]

The molecular formula for **4.11** as determined by mass spectroscopy, $C_{17}H_{33}O^{28}Si^{120}Sn$, was further support for its having been formed. However, an attempt to form desired ynediene **4.10** by reaction of a sample of crude **4.11** and iodide **1.112** under Stille conditions was not successful, affording only a mixture of unreacted **1.112** and an unidentified side product (**Figure 4.5**). Whilst this result was disappointing, the fact that it may have been due to the impurity of **4.11**, and that it is possible that trimethyltin or iodo-analogues of **4.11** (see **Figure 4.2**) may prove efficient Pd-catalysed coupling partners, leaves room for hope that future work on this key reaction will prove fruitful.



4.11 **1.112** **4.10**

Reagents and conditions: Pd_2dba_3 [10 mol %], $AsPh_3$ [40 mol %], CuI, NMP, 50 °C, dark, 12 h.

Figure 4.5 Attempt to form ynediene **4.10**.

As can be seen, although the true potential of the possible routes to 9-methoxystrobilurins A and K based on the outlined retrosyntheses in **Figure 4.2** remains to be established, preliminary results suggest that Shirakawa *et al.*'s alkyne alkynylstannylation methodology[152] is a practical route to stannyl versions of enynes **4.7** and **4.11**. Consequently, the first priorities for future research must be to optimise the synthesis of these enynes, prior to a full exploration of their potential utility in the formation of ynediene **4.10** and diene **4.6**.

Finally, a retrosynthetic disconnection of **4.1** and **4.2** not outlined in **Figure 4.2**, but which given the availability of **4.13** may also be worth investigating, is shown in **Figure 4.6** (with generalised structure **4.5** again representing both **4.1** and **4.2**). Disconnection at *a* and *c* in **4.5** unmasks three fragments, which may be able to be joined *via* Pd-catalysed coupling techniques. Iodide **4.16** should be available by iododestannylation of the corresponding stannane – either phenylethenylstannane **2.38** (see *Chapter 2*, **Figure 2.37**), if attempting to synthesise

9-methoxystrobilurin A (**4.1**), or benzodioxepin ethenylstannane **4.17**, if attempting to synthesise 9-methoxystrobilurin K (where **4.17** should be available by coupling Kobayashi *et al.*'s benzodioxepin **1.43**[55] with distannane **1.101**[102] under Stille conditions). Distannane **4.18** although unknown in the literature, may be accessible by treatment of **4.13** with $(SnMe_3)_2$ under Pd catalysis, according to the procedure described by Mitchell *et al.* for the formation of (*Z*)-distannylalkenes from alkynes.[185] ξ

ξ The use of $(SnMe_3)_2$ for such distannylations appears essential, with Mitchell *et al.* noting that the reaction of $(SnBu_3)_2$ with alkynes was not quantitative.[185] In addition, although they observed that non-terminal alkynes such as TMS- and *t*-butylacetylene were not reactive, they found that 1,4-diphenylbutadiyne and 1,2-di(methoxymethyl)acetylene were, so it is not unreasonable to hope that **4.13** might serve as a precursor to **4.18**.

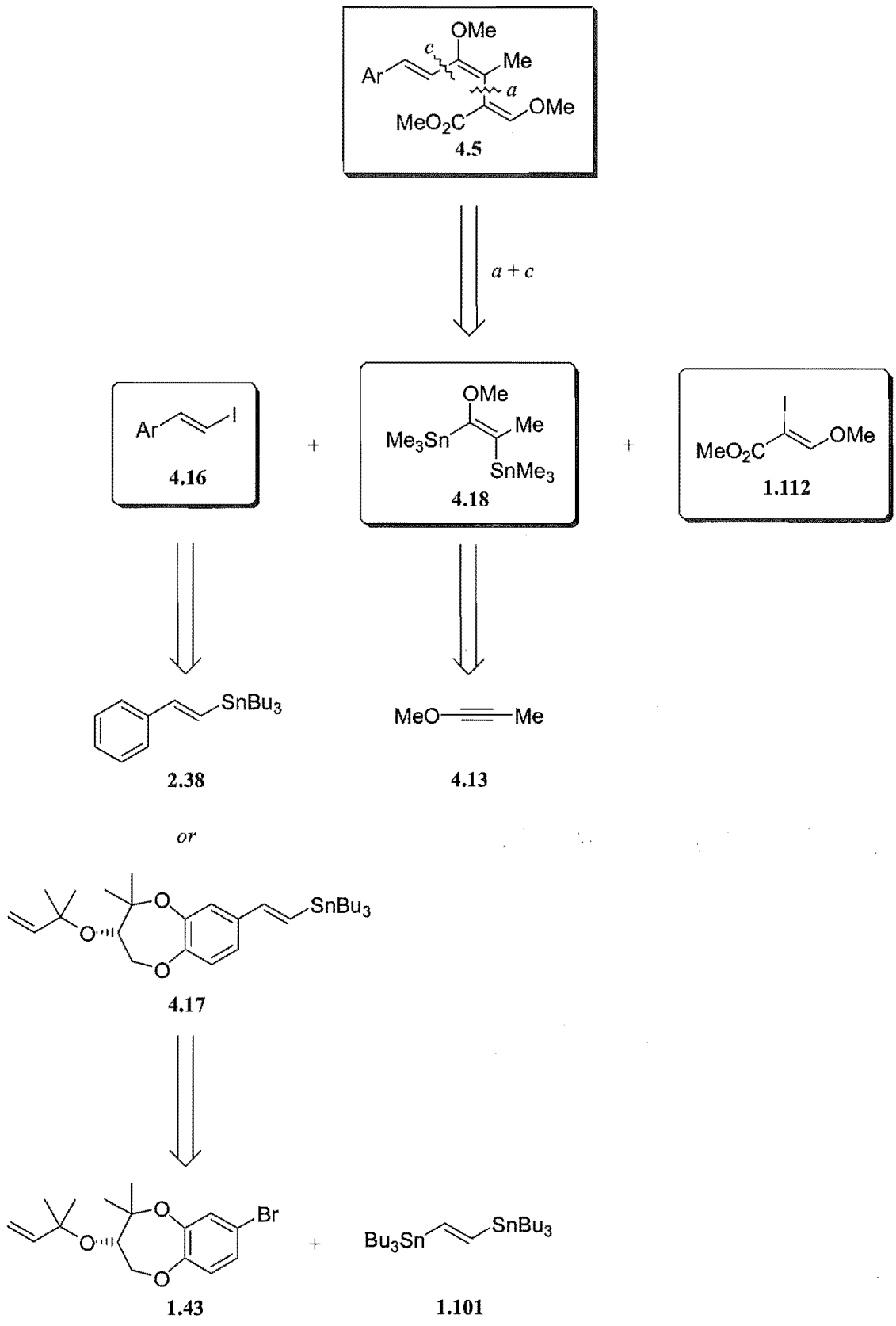
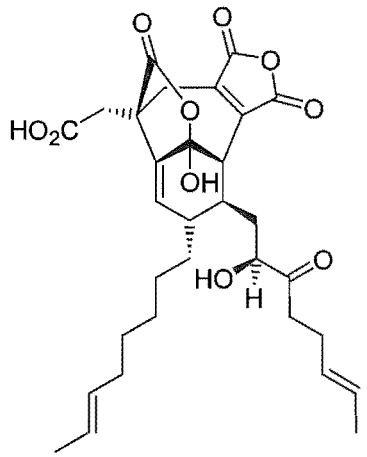


Figure 4.6 Another retrosynthetic analysis of 9-methoxystrobilurins A and K.

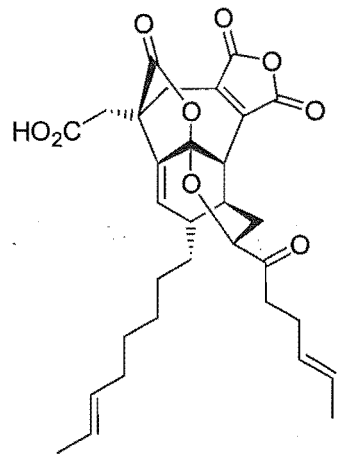
4.3 Potential Approaches to the Phomoidrides A and B

4.3.1 Introduction

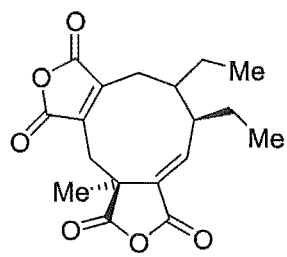
In 1997, workers at Pfizer reported the structural elucidation and biological properties of CP-225,917 (**4.3**) and CP-263,114 (**4.4**), two natural products which they had isolated from a fungus apparently of *Phoma* sp. collected from juniper twigs in Texas, USA (**Figure 4.7**).[194] These molecules have since been named phomoidrides A (**4.3**) and B (**4.4**) [see *page 191*]. The nine-membered ring core and peripheral anhydride functionality of these compounds identified them as members of the nonadride class of natural products,[196] exemplified by the prototypical nonadride glaucanic acid (**4.19**).[197] Furthermore, biomimetic studies by several groups attest to the existence of a common biosynthetic pathway for **4.3**, **4.4** and **4.19**, based upon dimerisation of an anhydride precursor.[198]



(+)-phomoidride A [CP-225,917] (**4.3**)



(–)-phomoidride B [CP-263,114] (**4.4**)



glaucanic acid (**4.19**)

Figure 4.7 The phomoidrides and glaucanic acid: representative nonadride natural products.

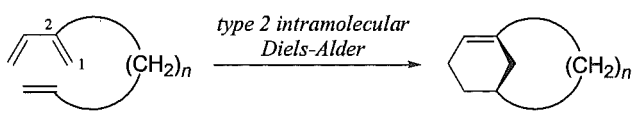
With their dense, highly substituted polycyclic structures, incorporating an anti-Bredt bridgehead olefin and six stereocentres, and their potentially therapeutically useful inhibition of the enzymes squalene synthase (SQS)[4] and farnesyl tranferase (FTF),[4] **4.3** and **4.4** garnered the attention of chemists worldwide, and became the target of intense synthetic efforts in many research institutions. Two different total syntheses of **4.3** and **4.4** were recently reported by Nicolaou *et al.*[199] and Danishefsky *et al.*,[200] while Shair *et al.* and Fukuyama *et al.* have synthesised **4.4** alone.[201] In addition, several groups have constructed models of the molecules' bicyclic core.[202]

Of relevance to this discussion are the syntheses of **4.3** and **4.4** by Nicolaou *et al.*[199] and **4.4** by Fukuyama *et al.*,[201b] as both utilise a type 2 intramolecular Diels-Alder reaction[m] for the crucial step in which the bicyclic phomoidride core is formed. Such a reaction is also fundamental to the approach to **4.3** under investigation in the author's research group, as will be described. (This intramolecular cycloaddition methodology has proven invaluable in syntheses of other strained bridgehead bicycles, as exemplified by the studies of Shea *et al.*,[203] and has been used as a means of direct entry into the taxane[204] and esperamicin[205] ring systems). Thus, Nicolaou *et al.* treated triene **4.20** with catalytic **4.21** to form bicycle **4.22** in high yield and diastereomeric excess, then elaborated this intermediate into **4.3** (and thence to **4.4**),[199b]

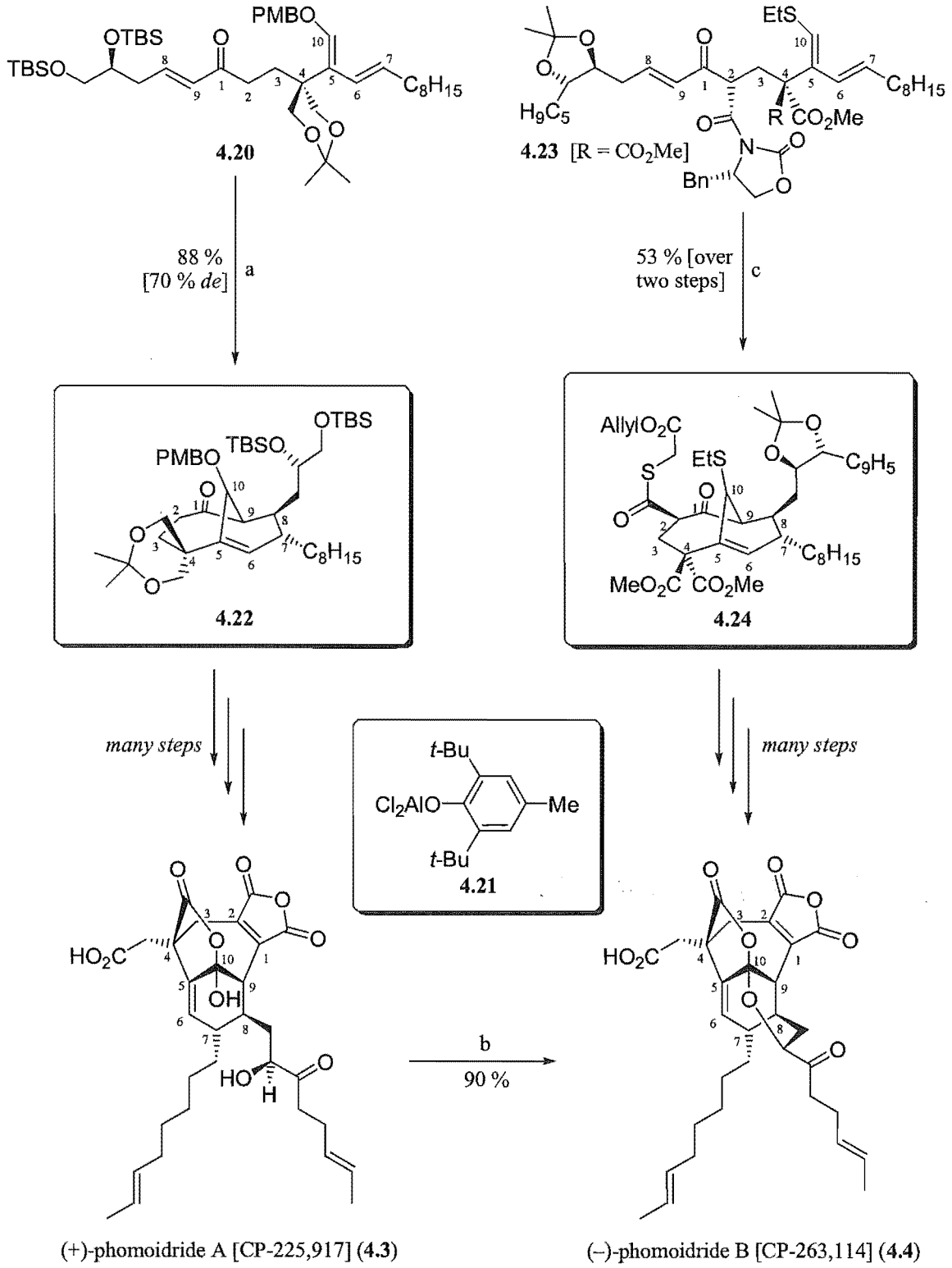
[4] SQS catalyses the first committed step on the pathway to cholesterol biosynthesis, thus a pharmaceutical inhibitor of this enzyme could potentially lower cholesterol levels in those at risk of atherosclerosis and associated pathologies without affecting the production of biomolecules earlier in the pathway. Another class of fungal-derived SQS inhibitors, the zaragozic acids (zaragozic acid A having been, interestingly, a co-isolate of the phomidrides[194]) is also currently a target for synthetic chemists, and has piqued the interest of the pharmaceutical industry [(a) Sato, H.; Nakamura, N.; Watanabe, N.; Hashimoto, S. *Synlett* **1997**, 451; (b) Armstrong, A.; Jones, L. H.; Barsanti, P. A. *Tetrahedron Lett.* **1998**, *39*, 3337].

[4] FTF is responsible for the post-translational modification of proteins. Given that a mutant form of the Ras protein, one of its more important substrates, is implicated in over 30% of human cancers (with mutant Ras enabling the unregulated cell division which leads to tumour formation), a pharmaceutical inhibitor of FTF would be a significant addition to our armamentarium against cancer [(a) Nadin, A.; Nicolaou, K. C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1622; (b) Scheffzek, K.; Ahmadian, M. R.; Kabsch, W.; Wiesmüller, L.; Lautwein, A.; Schmitz, F.; Wittinghoffer, A. *Science* **1997**, *277*, 333; (c) Egan, S. E.; Weinberg, R. A. *Nature* **1993**, *365*, 781; (d) Rawls, R. L. *Chem. & Eng. News* **1998**, *April 20*, 67].

[m] The substrate of a type 2 intramolecular Diels-Alder reaction consists of a dienophile tethered to the 2-position of a diene (rather than to the 1-position).



whilst Fukuyama *et al.* treated triene **4.23** with $ZnCl_2$–Et_2O and catalytic pyridine and converted the thus-formed crude bicyclic product to thioester **4.24**, which was elaborated into **4.4** (**Figure 4.8**).[201b]



Reagents and conditions: (a) **4.21** (20 mol %), toluene, –80 °C, 1 h; (b) CH_3SO_3H, $CDCl_3$, r.t., 36 h; (c) (i) $ZnCl_2.OEt_2$, pyridine (14 mol %), CH_2Cl_2, r.t., 1 h; (ii) allyl thioglycolate, LHMDS, Et_2O, 0 °C, 3 h.

Figure 4.8 Nicolaou *et al.*'s synthesis of **4.3** and **4.4** and Fukuyama *et al.*'s of **4.4**, both *via* a type 2 intramolecular Diels-Alder reaction.

4.3.2 Synthetic Strategy

As mentioned, the route to **4.3** being investigated in the author's research group is also based upon the use of a type 2 intramolecular Diels-Alder reaction, with which it was envisaged that the nonadride core and most of the stereocentres of **4.3** might be formed in one step (as confirmed by the work of Nicolaou *et al.*[199] and Fukuyama *et al.*[201b] – see **Figure 4.8**). A retrosynthetic analysis of the approach is shown in **Figure 4.9**, wherein it can been seen that the β-acid and lactone at C-4 is abbreviated as a malonate moiety, so as to minimise the possibility of diastereoisomers being generated in the formation of Diels-Alder adduct **4.25**. Diels-Alder precursor triene **4.26** may be generated by reaction between diene **4.27** and dienophile **4.28**: these molecules should combine to give **4.26** *via* formation of its C-2 – C-3 bond (when Y = H and Z = CH_2Br) or its C-3 – C-4 bond (when Y = CH_2Br and Z = CuCNBr, or Y = CH_2MX and Z = I).

The inclusion of the maleic anhydride moiety in Diels-Alder precursor **4.26** illustrates a key difference in this proposed approach compared to the syntheses of Nicolaou *et al.*[199] and Fukuyama *et al.*,[201b] whose introduction of this moiety *after* the formation of their respective Diels-Alder adducts (see **Figure 4.8**) proved a formidable undertaking. In Nicolaou *et al.*'s case, the failure of conventional strategies to enable elaboration of the C-1 ketone of an earlier equivalent of **4.22** into the requisite maleic anhydride functionality (a result which was attributed to 'excessive steric screening') necessitated the development of a novel means of forming this moiety.[199c]

Work conducted towards the synthesis of **4.27** and **4.28** is detailed in the following sections.

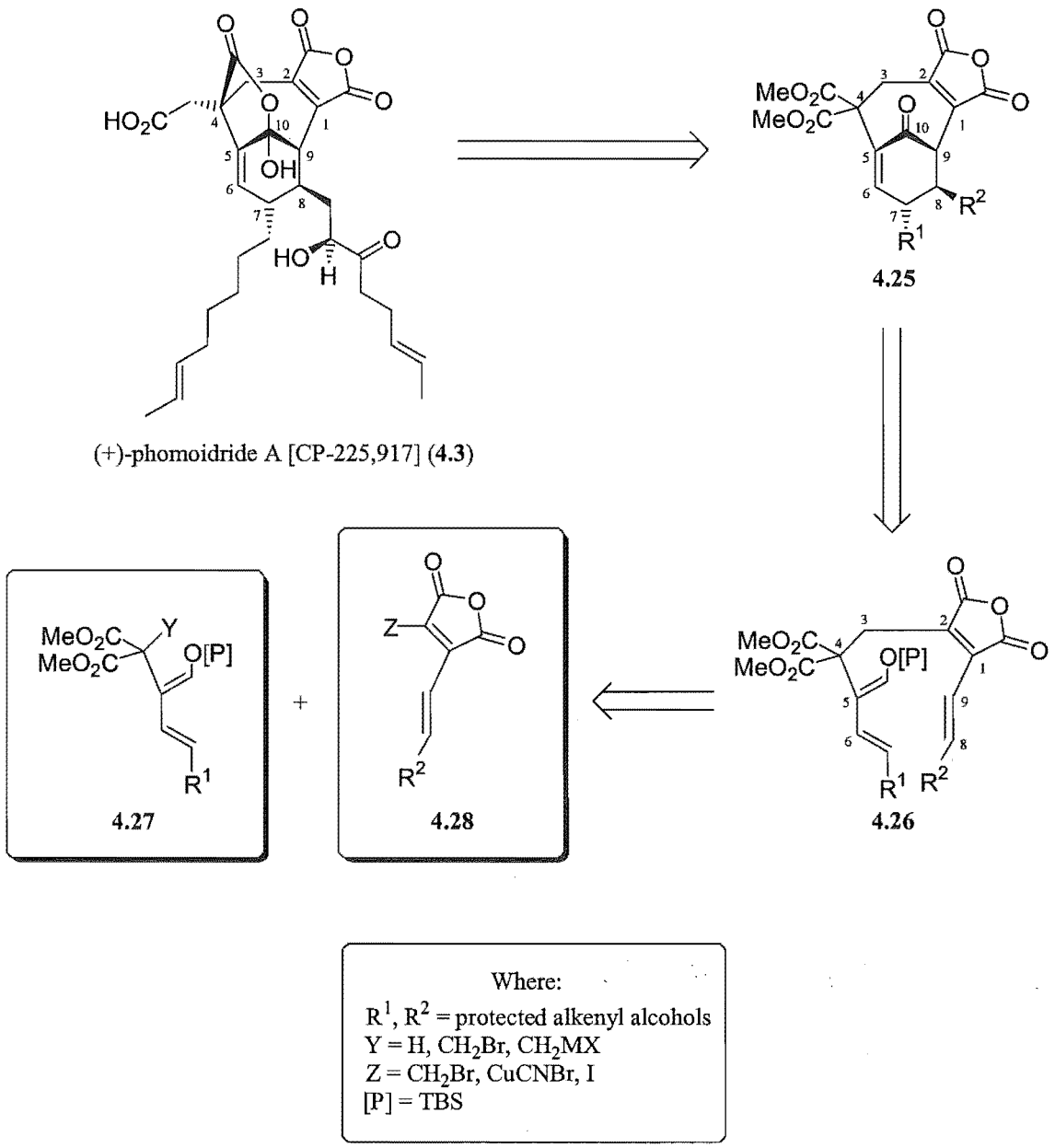
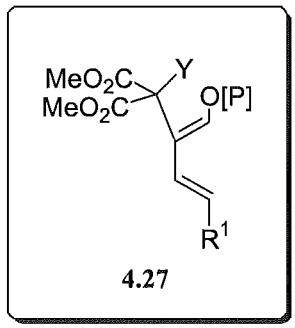


Figure 4.9 A retrosynthesis of **4.3**, based on the use of a type 2 intramolecular Diels-Alder reaction to form the nonadride core of the natural product.

4.3.3 Approaches to Diene 4.27

Investigations toward a synthesis of a diene **4.27** where Y = H are described in this section.

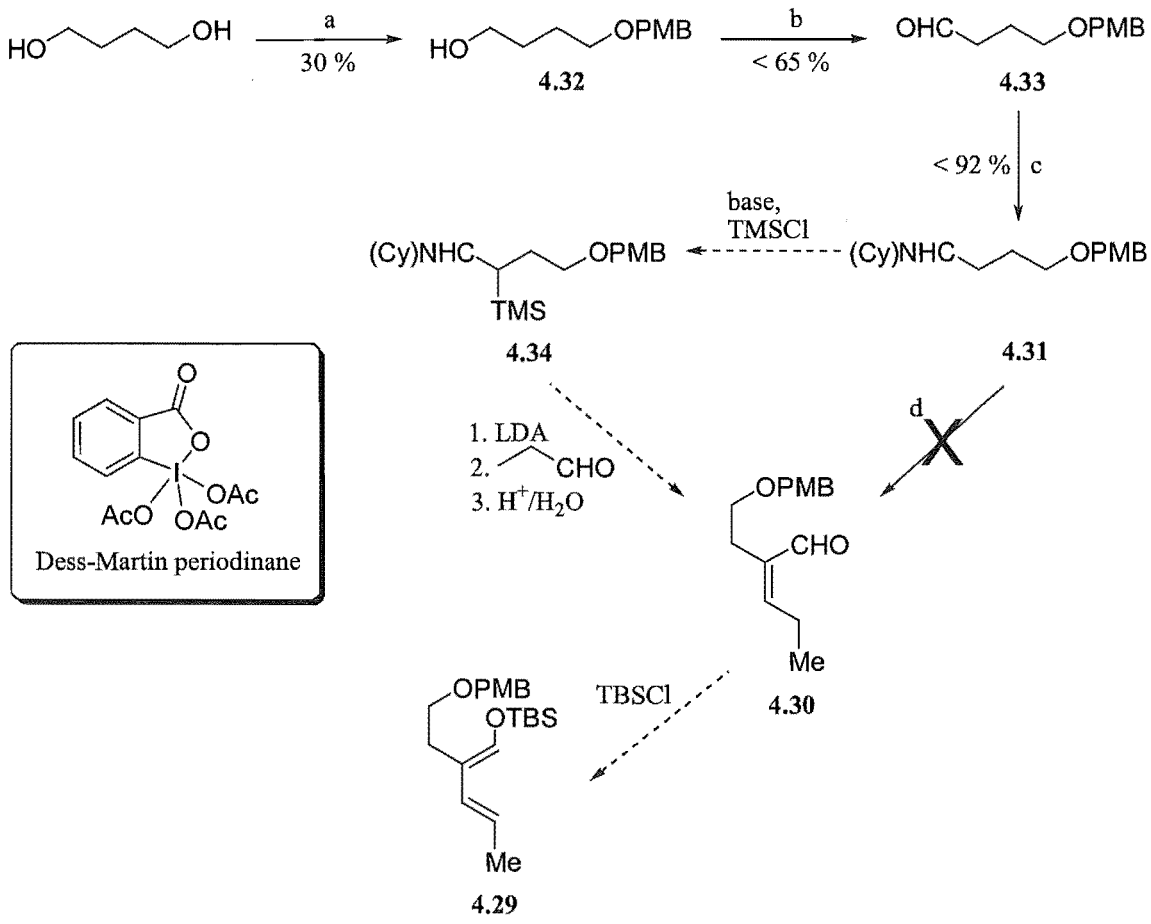


4.27

4.3.3.1 Aldehyde Approach

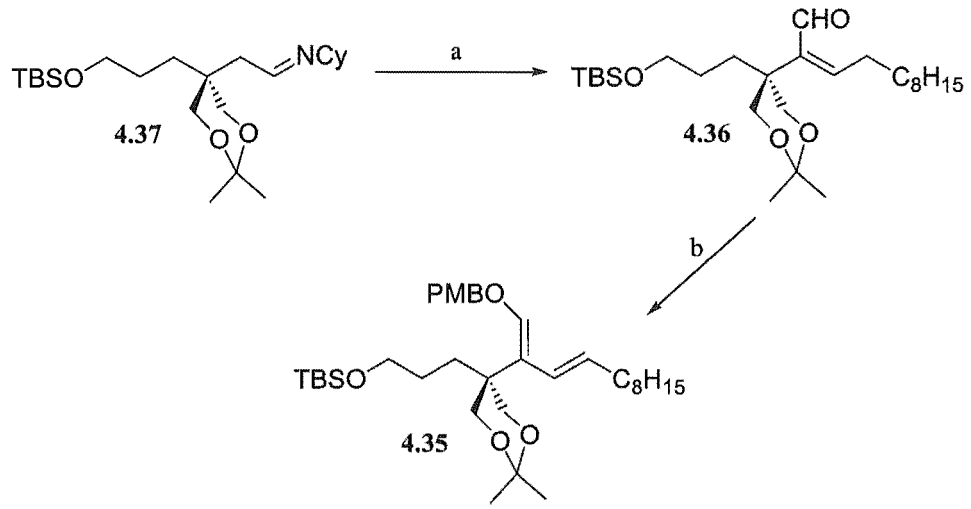
Diene **4.29**, a model for diene **4.27** in which the C-4 malonate functionality is omitted, was the target of this first approach, whereby it was proposed to form required precursor α,β-unsaturated aldehyde **4.30** *via* a directed aldol reaction[206] between imine **4.31** and propanal (**Figure 4.10**). Preliminary investigations of this approach were conducted as follows, beginning with the monoprotection of 1,4-butanediol with PMB-Br to give alcohol **4.32**, which was then oxidised to aldehyde **4.33** with the Dess-Martin periodinane.[171] The procedure of Skita and Wulff[207] was employed to transform **4.33** into imine **4.31**, but this compound proved unreactive with propanal under the conditions utilised.

The application of a technique reported by Corey *et al.* for the facilitation of such aldol reactions[208] – which would in this case comprise the reaction of TMS derivative **4.34** with propanal – was due to be the next area of exploration, but at this point Nicolaou *et al.* published the first report of their work on the phomoidrides, in which they detailed the synthesis of diene **4.35** from an α,β-unsaturated aldehyde **4.36** (**Figure 4.11**), which was itself formed *via* a directed aldol reaction between imine **4.37** and an aldehyde.[199d] As a consequence, work on the approach outlined in **Figure 4.10** was abandoned.



Reagents and conditions: (a) PMB-Br, NaH, DMF, –15 °C – r.t., 12 h; (b) Dess-Martin periodinane, CH_2Cl_2, r.t., 12 h; (c) cyclohexylamine, 0 °C – r.t, 12 h; (d) (i) propanal, LDA, –75 °C – r.t or 0 °C – r.t., THF, 12 h; (ii) oxalic acid, H_2O.

Figure 4.10 An approach to a model for type **4.27** diene **4.29** *via* α,β-unsaturated aldehyde **4.30**.



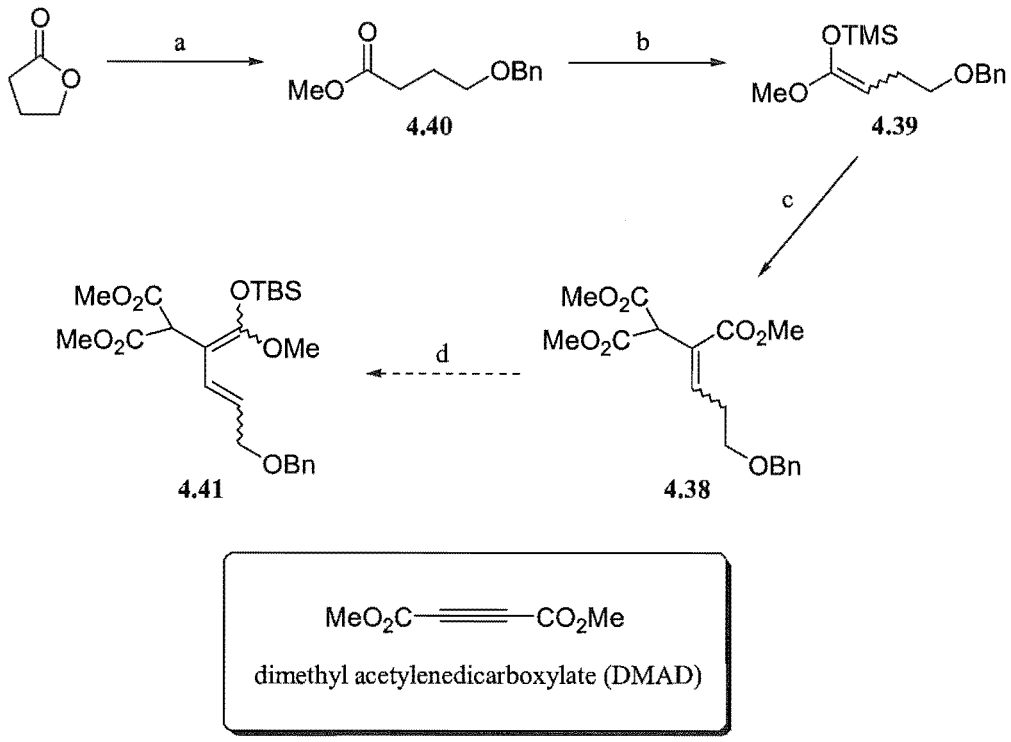
Reagents and conditions: (a) (i) LDA, Et_2O, –20 °C, 1 h; (ii) $C_9H_{17}CHO$ in Et_2O, –78 to –30 °C, 12 h; (iii) oxalic acid, H_2O, 0 °C, 4 h [60 % overall from aldehyde precursor to **4.37**]; (b) KH, PMBCl, DME:HMPA (5:2), 0 °C, 4 h [78 %, (*E,E,Z*):(*E,E,E*) ~ 10:1].

Figure 4.11 Nicolaou *et al.*'s synthesis of diene **4.35** *via* α,β-unsaturated aldehyde **4.37**.

4.3.3.2 Ester Approach

Preliminary investigations were conducted on a route to a type **4.27** diene (where Y= H) also based upon the formation of an α,β-unsaturated carbonyl compound, but which in this case was ester **4.38**, which incorporates a C-4 malonate moiety, and was to be formed *via* a cycloaddition reaction between silyl ketene acetal **4.39** and dimethyl acetylenedicarboxylate (DMAD) [**Figure 4.12**]. To begin, base-mediated ring-opening and protection of γ-butyrolactone using the procedure of Leahy *et al.*,[209] followed by Fischer esterification, gave ester **4.40**. Treatment of **4.40** with LDA and TMSCl under the conditions of Ainsworth *et al.*[210] gave silyl ketene acetal **4.39**, which underwent the desired [2 + 2] cycloaddition–retro-cycloaddition reaction with DMAD under the conditions of Mitani *et al.*[211] to afford α,β-unsaturated ester **4.38**. (The efficiency of this key transformation obviously requires improvement, and interestingly, preliminary investigations appear to show that the omission of $ZrCl_4$ and the use of toluene instead of CCl_4, rather than having a deleterious effect upon the process, actually results in higher yields of **4.38**).

Treatment of **4.38** with LDA and TBSCl should afford type **4.27** diene **4.41**, however exploration of this transformation (and work on the optimisation of the other reactions comprising this approach) was suspended whilst investigations toward required dienophile **4.28** were conducted.

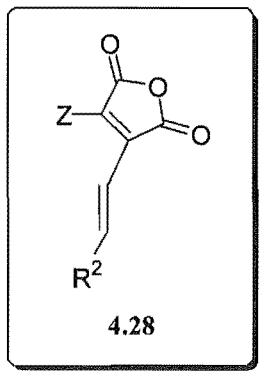


Reagents and conditions: (a) (i) BnBr, KOH, toluene, reflux 3 d then stand at r.t. 1 d; (ii) MeOH, cat. c.H_2SO_4, reflux [< 15 % over 2 steps]; (b) (i) LDA, –78 °C, 0.5 h; (ii) TMSCl, –78 °C – r.t. then r.t. 0.5 h [< 80 %, 1.3:1.0 **4.39**:SM]; (c) DMAD, $ZrCl_4$, CCl_4, reflux, 12 h [10 %]; (d) LDA, TBSCl.

Figure 4.12 An approach to type **4.27** diene **4.41** *via* α,β-unsaturated ester **4.38**.

4.3.4 Approaches to Dienophile 4.28

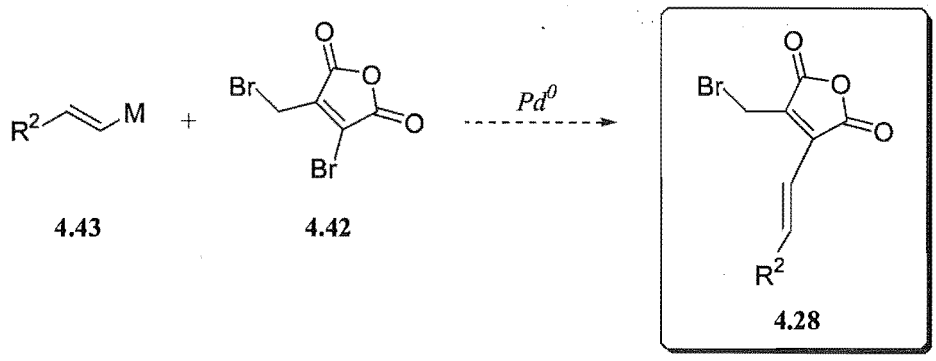
Investigations toward a synthesis of dienophile **4.28** where Z = CH_2Br are described in this section.



4.28

4.3.4.1 Anhydride Approach

This route required access to 1-bromomethyl-2-bromomaleic anhydride (**4.42**), which was to be used as a Pd-catalysed coupling partner for vinyl metal species **4.43** to form dienophile **4.28** (**Figure 4.13**). Accordingly, several routes towards **4.42** were investigated.



4.43 **4.42** **4.28**

Figure 4.13 Proposed synthesis of dienophile **4.28** from **4.42** and **4.43** (where M = BR_2, SnR_3 *etc.*).

Initially, an attempt was made to form bromomethyl maleic anhydride (**4.44**), a potential precursor to **4.42**, by irradiating a mixture of methyl maleic anhydride (**4.45**) and NBS, but this

was not successful (**Figure 4.14**). Subsequently, it was found that Eschenmoser *et al.* had also reported the failure of this reaction.[212] Next, an effort was made to prepare methylene maleic anhydride (**4.46**) by pyrolysis of citric acid (**4.47**) under the conditions of Shriner *et al.*,[213] as Nokami *et al.* have reported a method for the conversion of **4.46** to **4.44** by reaction with bromine and triethylamine.[214] However, despite many attempts to optimise the procedure, **4.45** was consistently the major product obtained, with only very small amounts of **4.46** being formed. Finally, **4.45** was subjected to the conditions of Nokami *et al.*[214] in the hope of forming 1-bromo-2-methylmaleic anhydride (**4.48**), but this too was unsuccessful, affording only degraded starting material.

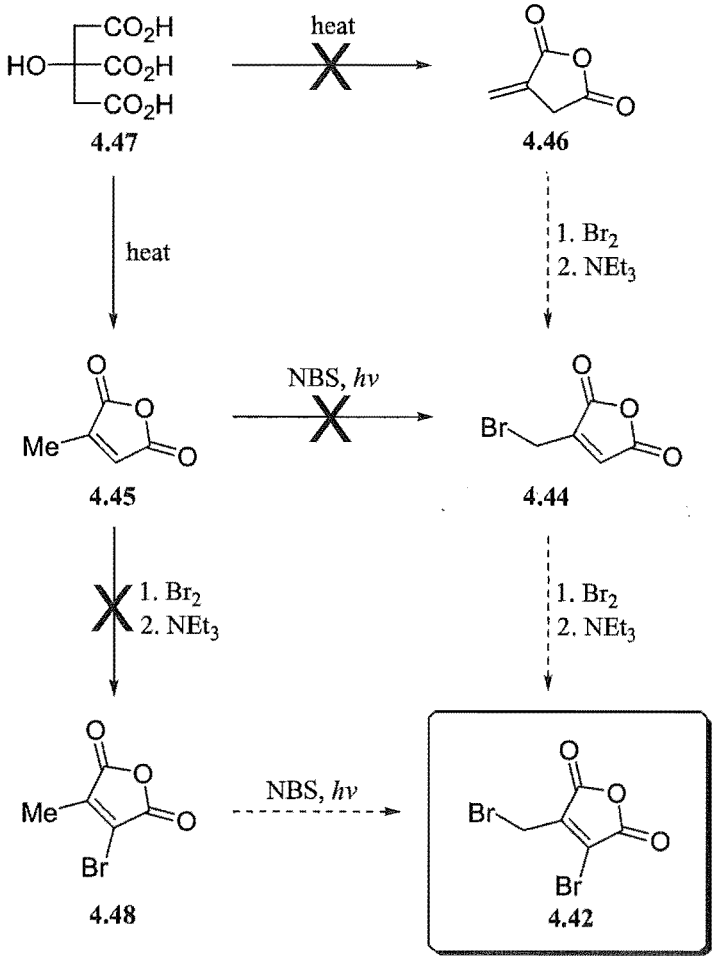
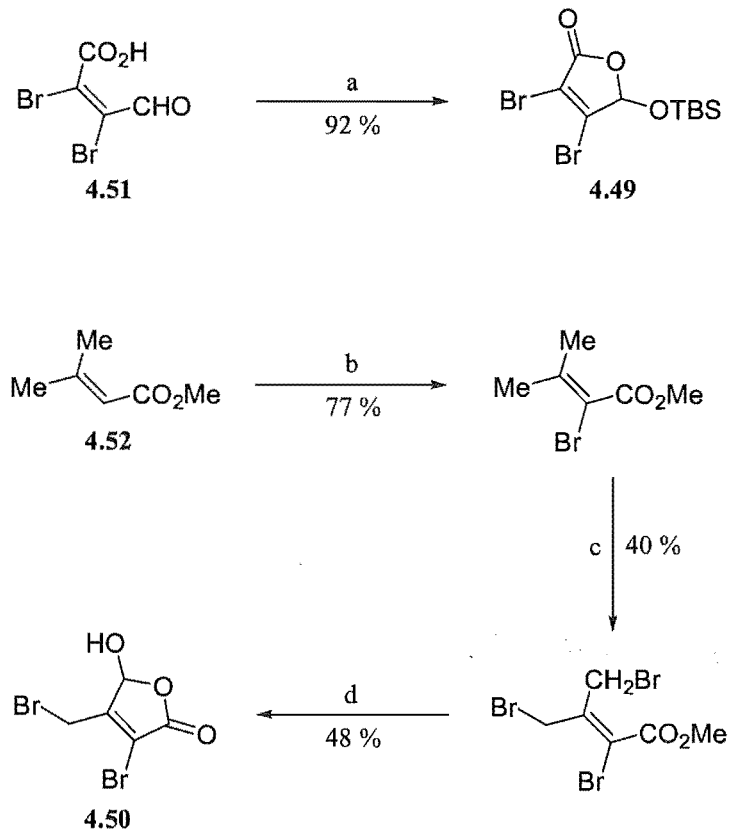


Figure 4.14 Attempted synthesis of dienophile precursor **4.42**.

Although the failure of the reactions in **Figure 4.14** was disappointing, useful developments have occurred in the time since this work was conducted. Firstly, **4.46** is now commercially available, so it should be possible to investigate its further conversion to **4.45** using the conditions of Nokami *et al.*[214] Secondly, syntheses of TBS ether **4.49** and alcohol **4.50** have been reported: Sukilowski *et al.* synthesised **4.49** in one step from mucobromic acid (**4.51**),[198b,c] whilst Lloveras *et al.* synthesised **4.50** in four steps from acrylate **4.52** (**Figure 4.15**).[215]



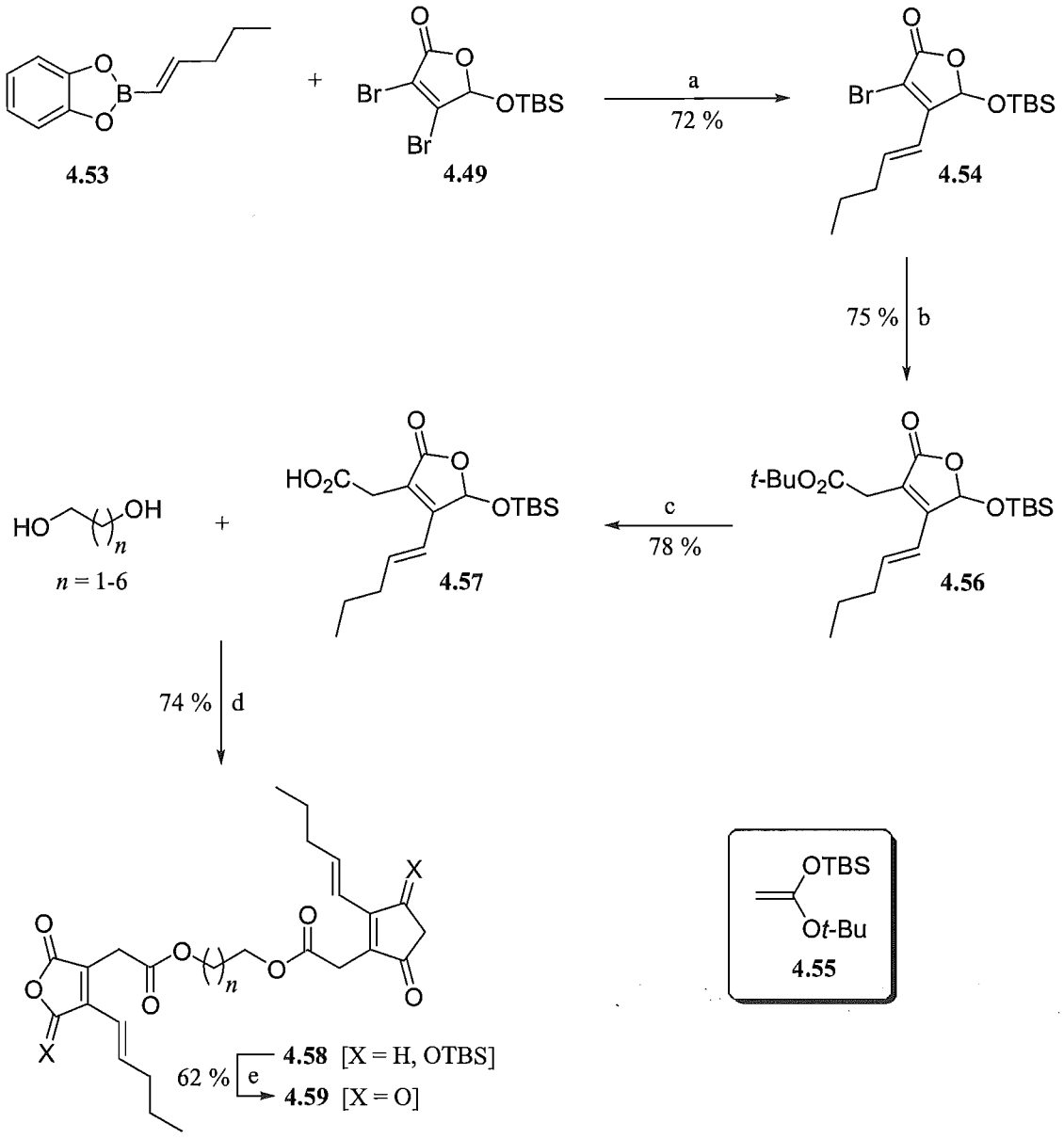
Reagents and conditions: (a) TBSCl, $(i\text{-Pr})_2NEt$, DMF, 0 °C, 5 min; (b) (i) Br_2, CCl_4, r.t., 1 h; (ii) NEt_3, CH_2Cl_2, 0 °C – r.t., 16 h; (c) NBS, CCl_4, *hν*, 3.6 d; (d) 48 % HBr, reflux, 8 h.

Figure 4.15 Potentially useful anhydrides synthesised by Sukilowski *et al.* (**4.49**) and Lloveras *et al.* (**4.50**).

Oxidation of **4.50** to dienophile precursor **4.42** should be a facile process, but of even greater import is that Sukilowski *et al.* found **4.49** to be reactive with boronic ester **4.53** under Suzuki-

Miyaura coupling conditions, yielding **4.54**, an –OTBS analogue of dienophile **4.28** (**Figure 4.16**).[198b] A Pd-catalysed coupling between **4.54** and silyl ketene acetal **4.55** gave **4.56**, which was hydrolysed to acid **4.57**. EDCI-mediated[~] condensation of **4.57** with an equimolar mixture of 1,*n*-diols gave a collection of bisesters **4.58**, which were desilylated and oxidised to afford bisanhydrides **4.59**. This Suzuki-Miyaura coupling reactivity of **4.49**, and the facility with which **4.58** was converted to **4.59**, suggests that future workers should be able to achieve a synthesis of dienophile **4.28** from **4.49** and **4.43**.

[~] EDCI – 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride – is a coupling reagent which facilitates the formation of amide bonds [Desai, M. C.; Stramiello, L. M. S. *Tetrahedron Lett.* **1993**, *34*, 7685].

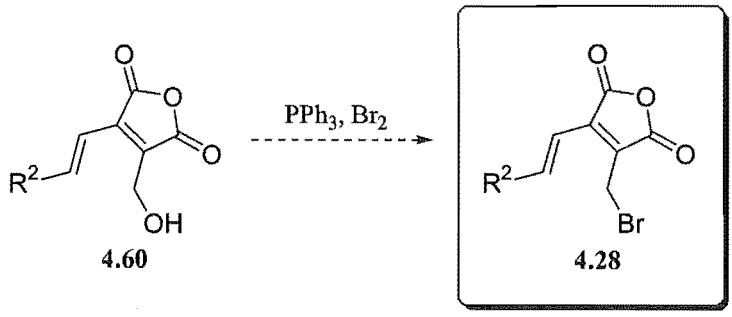


Reagents and conditions: (a) cat. $Pd(PPh_3)_2Cl_2$, aq. KOAc (16 mol %), benzene, reflux, 20 h; (b) **4.55**, $Pd(Tol_3P)_2Cl_2$ (8.6 mol %), KOAc, THF, reflux, 24 h; (c) CF_3COOH, CH_2Cl_2, r.t., 1 h; (d) DMAP, EDCI, THF, r.t., 6 h; (e) (i) 60 % HF in pyridine, THF, r.t., 24 h; (ii) PCC, powdered 4 Å sieves, CH_2Cl_2, r.t., 8 h.

Figure 4.16 Sukilowski *et al.*'s use of **4.49** in Pd-catalysed couplings *en route* to bisanhydrides **4.59**.

4.3.4.2 Furan Approach

Preliminary investigations into another potential route to dienophile **4.28** were conducted by a former co-worker in the author's research group (Anna Fitzgerald).[216] This approach targets the formation of anhydride **4.60**, which should be transformed into **4.28** upon treatment with PPh_3/Br_2 (**Figure 4.17**).[217]



4.60 **4.28**

Figure 4.17 Possible method for conversion of **4.60** to dienophile **4.28**.

The approach to **4.60** was initiated with the reduction of commercially available 3-furoic acid to alcohol **4.61** (**Figure 4.18**). Protection of **4.61** gave TBS ether **4.62**, and lithiation of **4.62** in the presence of HMPA (both reactions being based on procedures of Keay and Bontront[218] and Danishefsky *et al.*[200b]) yielded silane **4.63** (*via* lithiation at C-2 followed by 1,4 O→ C silyl migration). Stannylation of **4.63** afforded **4.64**, which was then iododestannylated to give iodide **4.65**. Time constraints meant that Fitzgerald was not able to optimise the synthesis of or fully characterise these intermediates, nor investigate the reactivity of **4.65** in Danishefsky *et al.*'s photo-oxidation + oxidation conditions[200b] or in Pd-catalysed coupling conditions, thus these must be priorities for future investigation of this promising approach to dienophile **4.28** precursor **4.60**.

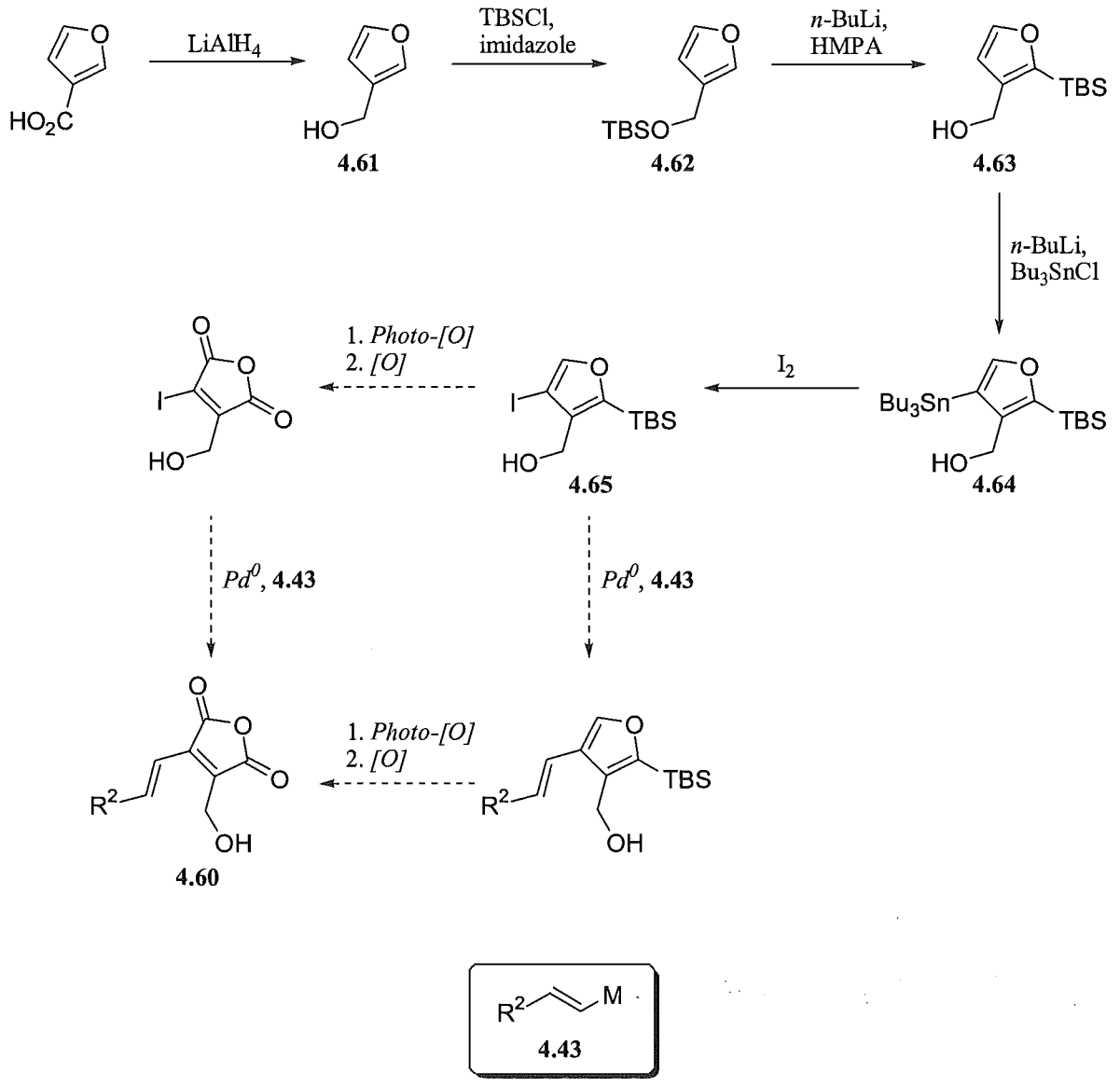


Figure 4.18 Furan-based approach to dienophile precursor anhydride **4.60** (where M = BR_2, SnR_3 *etc.*).

4.3.4.3 Diester Approach

In addition to the anhydride- and furan-based approaches to dienophile **4.28** described in the previous two sections, an alternative paradigm was also explored, in which diester **4.66** – which should be easily transformable into its cyclic analogue **4.28** under acidic conditions – was the target (**Figure 4.19**).

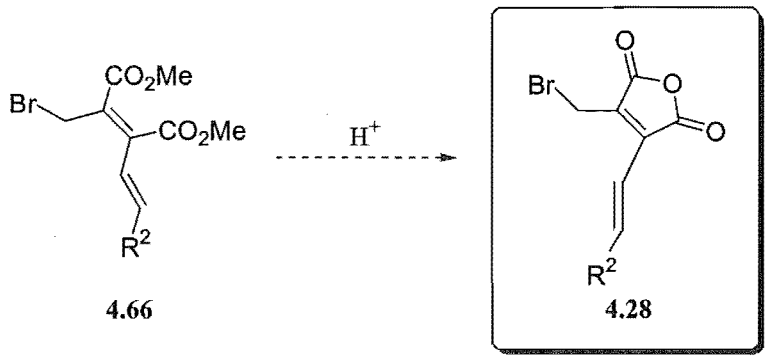
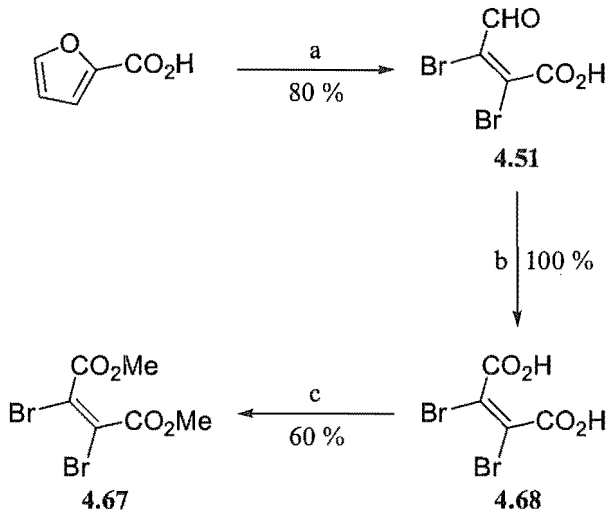


Figure 4.19 Possible method for conversion of **4.66** to dienophile **4.28**.

The main approach to **4.66** investigated utilised Stille coupling chemistry, with (*Z*)-dibromodiester **4.67** being one of the required coupling partners. This reactant was prepared stereoselectively† in a three-step process *via* known compounds, beginning with the use of Allen and Spangler's method for the bromination of 2-furoic acid to form mucobromic acid (**4.51**) [**Figure 4.20**].[219] Oxidation of **4.51** according to the procedure of Salmony and Simonis gave dibromomaleic acid **4.68**,[220] which was then converted into **4.67** *via* the acid chloride.

† (*Z*)-Dibromoester **4.67** has been prepared as a ~1:1 mixture with its (*E*)-isomer [Kloster-Jensen, E. *Acta. Chem. Scand.* **1963**, *17*, 1866]. The (*E*)-isomer has also been prepared alone [Lutz, R. *J. Am. Chem. Soc.* **1930**, *52*, 3405].



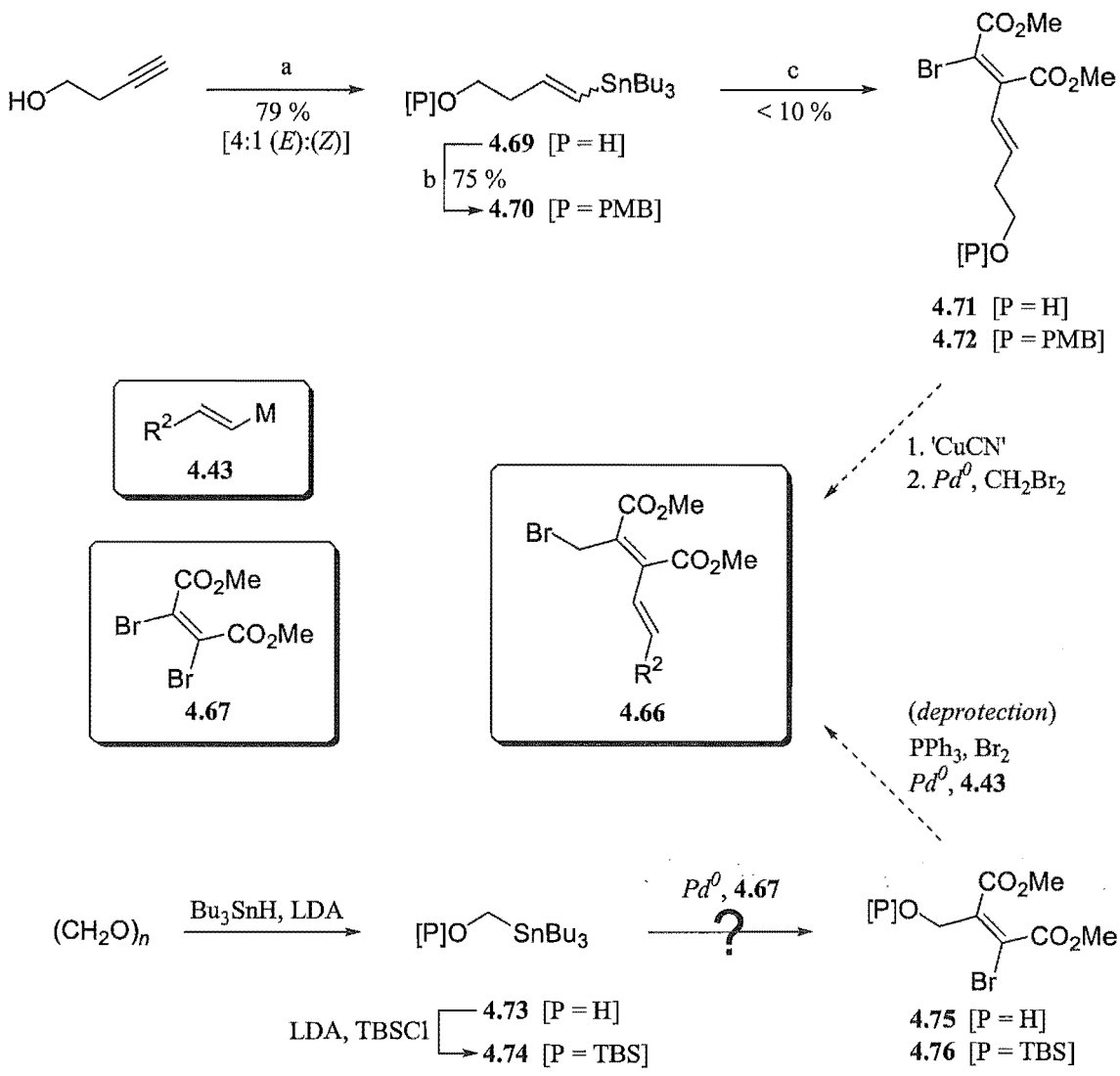
Reagents and conditions: (a) Br_2, H_2O, reflux, 1 h; (b) HNO_3, stand, r.t., 5.5 d; (c) $SOCl_2$, MeOH, reflux, 5.5 h.

Figure 4.20 Synthesis of (*Z*)-dibromodiester **4.67** from 2-furoic acid.

With **4.67** in hand, preliminary explorations of its reactivity in Pd-catalysed coupling-based approaches to diester **4.66** were conducted (**Figure 4.21**). Stannane **4.69**, prepared from 3-butyn-1-ol by the procedure of Pilli *et al.*,[221] and its protected derivative **4.70** were each combined with **4.67** under Stille conditions, but these experiments produced only very low yields of desired products **4.71** and **4.72**. An analogous approach from the 'other end', whereby Fitzgerald attempted to couple stannane **4.73** or its protected derivative **4.74** (prepared from paraformaldehyde, as reported by Majeed *et al.*[222]) with **4.67** to form **4.75** or **4.76**, was of indeterminate success.[216]

In light of the success enjoyed by Sukilowski *et al.* in their utilisation of anhydride **4.49** in Suzuki-Miyaura coupling conditions (see **Figure 4.16**),[198b] the lack of/low Stille coupling reactivity of **4.67** as depicted in **Figure 4.21** may indicate that a diester is not an appropriate coupling partner under such conditions, and/or that Stille conditions themselves are unsuitable. The validity of the former hypothesis should be confirmed (or otherwise) by further exploration of the furan approach (see **Figure 4.18**), whilst the latter possibility could be investigated by

determining the reactivity of the catecholboronic ester analogues of stannanes **4.69**, **4.70**, **4.73** and **4.74** with **4.67** under Suzuki-Miyaura conditions.



Reagents and conditions: (a) Bu_3SnH, AIBN, 95 °C, 16 h; (b) PMB-Br, NaH, THF, 0 °C – r.t., 20 h; (c) **4.67**, Pd_2dba_3 (10 mol %), $AsPh_3$ (40 mol %), CuI, NMP, dark, 50 °C, 20 h.

Figure 4.21 Two Stille coupling-based approaches to dienophile precursor **4.66** (where M = SnR_3, BR_2 *etc.*).

In light of the increased Stille-coupling reactivity of the β-iodo-monoester analogue of **4.67** (*i.e.* **2.44**) compared to its β-bromo-analogue **2.1** (see *Chapter 2*, **Figures 2.38** and **2.48**), an

attempt was made to transhalogenate **4.67** to its diiodo-analogue **4.77** under the conditions used to convert **2.1** to **2.44** (see *Chapter 2*, **Figure 2.47**), but this gave only a complex mixture of products from which no **4.77** could be extracted (**Figure 4.22**). Nevertheless, it would be prudent for future workers to conduct a fuller investigation of the viability of this transformation. In addition, given the desirability of exploring all possible combinations of functionality in desired Stille coupling partners, it would be worth determining if the stannyl analogue of **4.67** (*i.e.* **4.78**) could be obtained by treatment of DMAD with $(SnMe_3)_2$ under Pd catalysis, according to the conditions of Mitchell *et al.* (**Figure 4.22**).[185] If so, distannane **4.78** could prove superior to **4.67** in a route to **4.66** analogous to that in **Figure 4.21**, and/or may enable access to diiodide **4.77**.

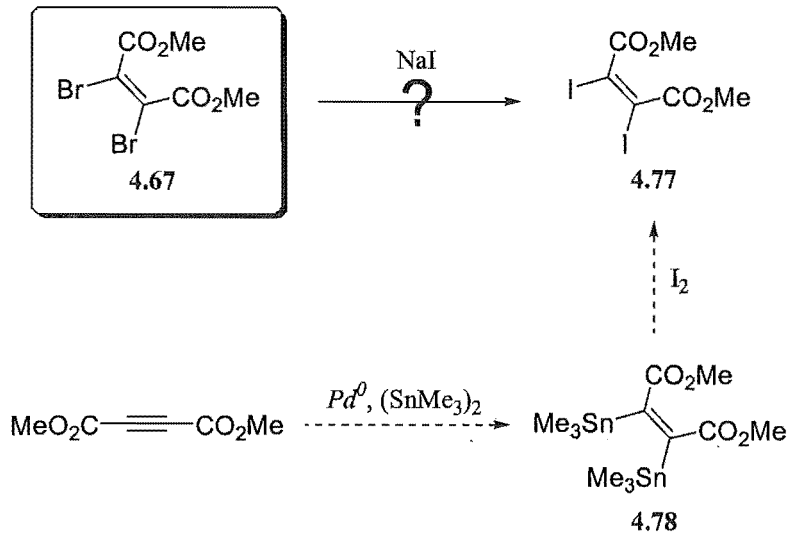
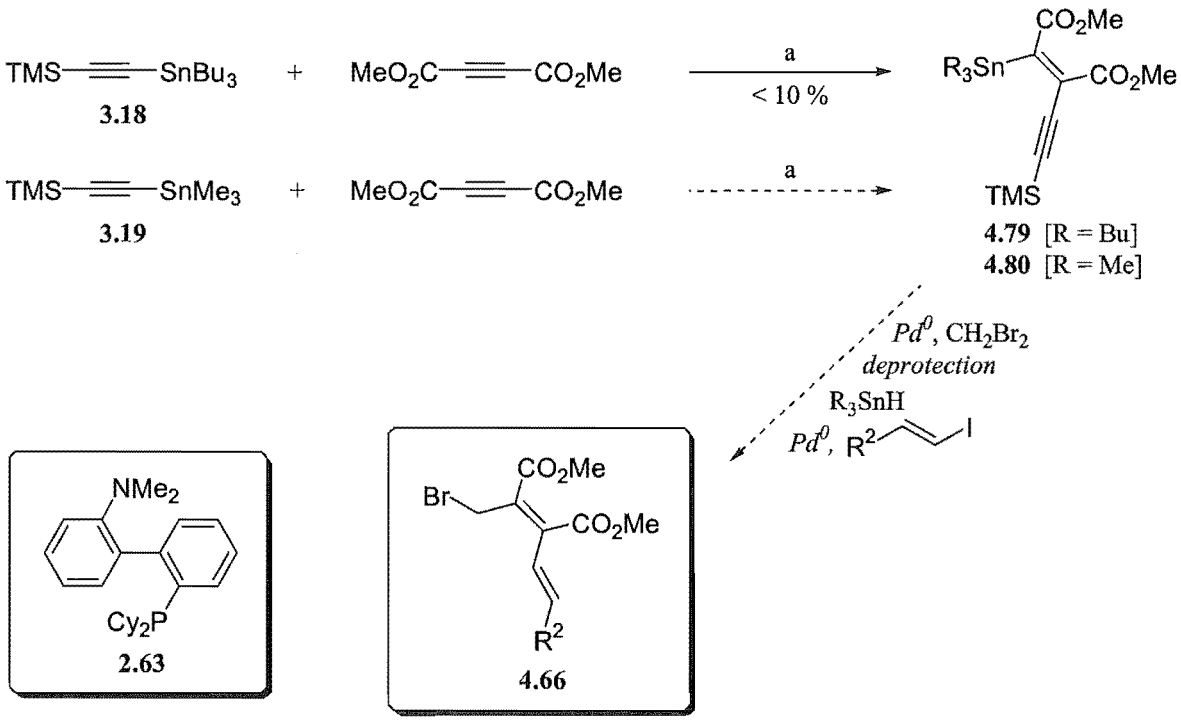


Figure 4.22 Possible routes to iodo- and stannyl analogues of dibromide **4.67**.

Finally, the key reaction of an alternative route to **4.66** which does not require the use of diester **4.67** was also investigated, with DMAD being combined with stannane **3.18**[189] under Shirakawa conditions (see *Chapter 2*, **Figure 2.62**) [**Figure 4.23**].[152] Although this afforded only a very low yield of desired enyne **4.79**, the reaction conditions were not optimised, nor was the potential of stannane **3.19**[190] as a precursor to enyne **4.80** determined. It is thus worth persevering with exploration of this alkynylstannylation-based approach to **4.66**, which may prove an invaluable alternative to the Stille-coupling based approaches depicted in **Figure 4.21**.



Reagents and conditions: $[PdCl(\pi\text{-}C_3H_5)]_2$ (4 mol %), **2.63** (4 mol %), THF, 50 °C, 12 h.

Figure 4.23 Shirakawa alkynylstannylation-based approach to dienophile precursor **4.66**.

4.4 Summary

It is to be hoped that the reader may see that notwithstanding some failed reactions [*and the frustration/honour of being 'trumped' by Nicolaou et al.*], the chemistry described in this chapter retains sufficient promise so as to warrant continued research towards Pd coupling-based syntheses of the 9-methoxystrobilurins and the phomoidrides.

CHAPTER FIVE

Experimental

5.1 General Experimental

Reagents and Solvents

Reagents and solvents were purified according to well-established procedures.[223] Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled from sodium benzophenone ketyl immediately prior to use. Toluene, dichloromethane (CH_2Cl_2), triethylamine (NEt_3) and *N*,*N*-diisopropyl-*N*-ethylamine (Hünig's base) were freshly distilled from calcium hydride immediately prior to use. Carbon tetrachloride (CCl_4) was distilled from phosphorus pentoxide and stored under nitrogen or argon over freshly activated 4 Å molecular sieves. Acetone was dried over freshly activated 4 Å molecular sieves for 24 h, then distilled and stored under nitrogen or argon. *N*,*N*-Dimethylformamide (DMF) was dried by standing over two batches of freshly activated 4 Å molecular sieves for 24 h each, before being stored under nitrogen or argon over a third batch of freshly activated 4 Å molecular sieves (residual dimethylamine was removed by evacuating the solvent at ~2.2 mm Hg for at least 10 minutes immediately prior to use). Methanol was distilled from $Mg(OMe)_2$ and stored under nitrogen or argon. Dry 1-methyl-2-pyrrolidinone (NMP) was purchased from Aldrich, stored under nitrogen or argon, and used without further purification. Petroleum ether used consisted of the fraction with a boiling range of 50-70 °C.

Solutions of *n*- and *t*-butyllithium (BuLi) in hexanes were titrated in diethyl ether with *s*-butanol, using 1,10-phenanthroline as the indicator.[224] Acetic anhydride was distilled from phosphorous pentoxide. Copper(I) iodide (CuI) was purified by refluxing in dichloromethane in a Soxhlet apparatus for 24 h, and then stored in the dark under nitrogen or argon. Trimethylsilyl chloride (TMSCl) was distilled from calcium hydride and stored under nitrogen or argon over freshly activated 4 Å molecular sieves. Cyclohexylamine was distilled from Na, and stored over Na under nitrogen or argon.

4-Methoxybenzyl bromide (PMB-Br) was prepared immediately prior to use by shaking a solution of 4-methoxybenzyl alcohol in Et_2O (10 mL of Et_2O per g of alcohol) with an equal

volume of hydrobromic acid (HBr). Chloromethyl methyl ether (MOM-Cl) was prepared according to the literature procedure[225] and stored in the freezer. $Pd(PPh_3)_2Cl_2$,[226] $Pd(PPh_3)_4$,[227] $Pd(dppf)Cl_2$,[228] $Pd(CH_3CN)_2Cl_2$,[229] and $Pd(PhCN)_2Cl_2$[230] were prepared according to literature methods; $Pd(PPh_3)_4$ was stable for several months if stored in the dark in the freezer under nitrogen or argon. $Pd(AsPh_3)_2Cl_2$ was prepared in analogous manner to $Pd(PPh_3)_2Cl_2$.[226] 2,2'-Azobisisobutyronitrile (AIBN) was prepared according to literature methods.[231] Methoxypropyne (**4.13**) was prepared as described by Nooi and Arens.[195] Trimethylsilyl(ethynyl)stannane (**3.18**) was prepared according to the procedure of Logue and Teng.[189] Lithium diisopropylamide (LDA) was prepared *in situ* according to the procedure of House *et al.*,[232] as described by Leonard *et al.*[233] The Dess-Martin periodinane was prepared by the methods of Ireland and Liu[171b] & Dess and Martin.[171c]

Unless otherwise stated, all reactions were performed in oven- or flame-dried glassware under an atmosphere of nitrogen or argon, and reaction temperatures refer to the external bath temperature. All organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered to remove solids prior to removal of solvents under reduced pressure on a Büchi rotary evaporator. When necessary, a high-vacuum pump (~2.2 mmHg) was used to remove the last traces of solvent from purified compounds.

Chromatography and Small-Scale Distillation

Analytical thin-layer chromatography (TLC) was conducted on aluminium-backed Merck Kieselgel $KG60F_{254}$ silica plates or Fluka aluminium-backed alumina type H plates. The developed TLC plates were visualised under short- or long-wave ultraviolet (UV) light, and/or by staining in a potassium permanganate or a phosphomolybdic acid (PMA) dip.[234]

Flash chromatography was performed on Merck Silica 60 (40-63 μm) or Laporte Alumina, Grade H (100-200 mesh), according to the guidelines of Still and co-workers,[235] as described by Leonard *et al.*[236]

Small-scale (bulb-to-bulb) distillation was performed under low or high vacuum in a Büchi Kugelrohr apparatus, according to the guidelines of Leonard *et al.*[237]

Physical and Spectroscopic Techniques

Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected.

^{1}H NMR spectra were obtained on either a Varian Unity 300 or a Varian Inova 500 spectrometer, operating at 300 MHz and 500 MHz respectively, typically with a delay (d_1) of 5 s. ^{13}C NMR spectra were obtained on a Varian XL 300 or a Varian Unity spectrometer, operating at 75 MHz, or a Varian Inova 500 spectrometer, operating at 126 MHz, typically with a delay (d_1) of 2-3 s. Chemical shifts are reported in parts per million (ppm) on the δ scale, and are referenced to residual $\mathbf{C}HCl_3$ at δ_H 7.260 and $\mathbf{C}DCl_3$ at δ_C 77.0.

Infrared spectra (IR) were obtained on a Shimadzu FTIR-8201 PC spectrometer. Spectra of solids were obtained from KBr plates or by the diffuse reflectance method, whilst spectra of oils, gums or resins were obtained from thin films between KBr plates. Values are reported in wavenumbers (cm^{-1}).

High-resolution mass spectrometry (HRMS) was conducted on a Kratos MS80RFA mass spectrometer operating in electron ionisation (EI) mode at 70 eV and at 4 kV accelerating potential.

5.2 Nomenclature

The nomenclature system used in this thesis is in accordance with IUPAC recommendations, as detailed by Fox and Powell.[238]

5.3 Experiments Described in Chapter 2

Methyl (*Z*)-2,3-dibromopropenoate 2.1

2.1

Methyl propynoate (10.56 g, 125.94 mmol) was added to dry CCl_4 (103 mL) in a three-necked flask equipped with an intra-flask thermometer and a dropping funnel, and the solution was heated slowly to 70 °C. Bromine (6.59 mL, 159.80 mmol) was added dropwise to the heated solution, with the reaction temperature maintained as close as possible to 70 °C throughout the addition, and the resultant deep orange solution was stirred at this temperature for 30 min. After this time, the reaction mixture was cooled to room temperature, and solvent and excess bromine were removed under reduced pressure. The residue was re-dissolved in Et_2O and washed with saturated aqueous $Na_2S_2O_3$ solution. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 5% EtOAc:petroleum ether, to yield bromide **2.1** as a pale yellow liquid (26.38 g, 86%).

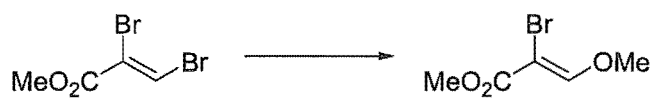
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.86 [s, 3H, CH_3], 8.24 [s, 1H, CH].

^{13}C NMR (75 MHz, $CDCl_3$): δ 53.6, 122.0, 126.7, 161.1.

IR (film): 1736 cm^{-1}.

HRMS: Calcd. for $C_4H_4O_2{}^{79}Br_2$ (M^+) 241.8578, found 241.8578.

Methyl (*Z*)-2-bromo-3-methoxypropenoate 1.117



2.1 **1.117**

Bromide **2.1** (6.80 g, 27.88 mmol) was dissolved in dry NMP (28 mL) and the stirred solution deoxygenated by five flush-evacuate cycles. $Pd(PPh_3)_2Cl_2$ (0.978 g, 1.39 mmol) was added and the mixture deoxygenated again as before. Tributyltin methoxide (10.44 mL, 36.24 mmol) was added *via* syringe and the mixture was once again deoxygenated, then stirred in the dark at room temperature for 96 h. After this time, the reaction mixture was diluted with H_2O, and extracted with Et_2O (x 4). The combined organic extracts were stirred with saturated aqueous KF solution in the dark for 2 h, and then separated. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 15% EtOAc:petroleum ether, to give bromide **1.117** as a yellow oil which solidified upon standing to a cream solid (2.68 g, 49%).

MP: 30-34 °C (lit. 31-32 °C).[114]

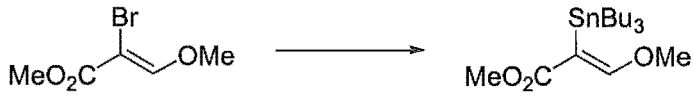
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.80 [s, 3H, $\mathbf{H_3}CO_2C$], 3.98 [s, 3H, $OC\mathbf{H_3}$], 7.78 [s, 1H, C**H**].

^{13}C NMR (75 MHz, $CDCl_3$): δ 51.9, 61.8, 90.6, 159.3, 163.0

IR (film): 1632, 1720 cm^{-1}.

HRMS: Calcd. for $C_5H_7O_3{}^{79}Br$ (M^+) 193.9579, found 193.9579.

Methyl (*Z*)-2-(tributylstannyl)-3-methoxypropenoate 1.111



1.117 **1.111**

$Pd(PPh_3)_2Cl_2$ (26 mg, 0.04 mmol) was added to stirred solution of bromide **1.117** (145 mg, 0.75 mmol) in dry toluene (12 mL) and the mixture was deoxygenated by five flush-evacuate cycles. Bis(tributyl)tin (0.450 mL, 0.89 mmol) was added *via* syringe, and the mixture was deoxygenated again as before, then stirred at reflux in the dark for 48 h. After this time, the reaction mixture was cooled to room temperature, diluted with H_2O, extracted with Et_2O (x 4), and the combined organic extracts were stirred in the dark with saturated aqueous KF solution for 2 h. After this time, the organic layer was separated and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with

5% EtOAc:petroleum ether, to give stannane **1.111** as a colourless viscous oil (164 mg, 54%). Due to the lack of NMR and HRMS data in the literature for this known compound,[104] it was fully characterised.

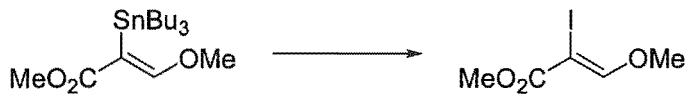
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 [t, J = 7.3 Hz, 9H, $Sn(C_3H_6\mathbf{CH_3})_3$], 0.97 [m, 6H, $Sn(C_2H_4\mathbf{CH_2}CH_3)_3$], 1.30 [m, 6H, $Sn(CH_2\mathbf{CH_2}C_2H_5)_3$], 1.48 [m, $Sn(\mathbf{CH_2}C_3H_7)_3$], 3.67 [s, 3H, $\mathbf{H_3}CO_2C$], 3.75 [s, 3H, $OC\mathbf{H_3}$], 7.81 [s, 1H, C**H**].

^{13}C NMR (75 MHz, $CDCl_3$): δ 10.8, 13.6, 27.1, 28.9, 50.9, 60.3, 107.2, 169.6, 172.1.

IR (film): 1605, 1693 cm^{-1}.

HRMS: Calcd. for $C_{13}H_{25}O_3{}^{120}Sn$ (M^+ – Bu) 349.0825, found 349.0826.

Methyl (*Z*)-2-iodo-3-methoxypropenoate 1.112



1.111 **1.112**

Iodine (128 mg, 0.51 mmol) was added to a stirred solution of stannane **1.111** (186 mg, 0.46 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C, and the mixture was stirred at this temperature for 2 h. After this time, the reaction mixture was diluted with H_2O, and extracted with CH_2Cl_2 (x 3). The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ solution, and solvent was removed under reduced pressure. The crude residue was re-dissolved in Et_2O, stirred with saturated aqueous KF solution in the dark for 2 h, and then separated. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 15% EtOAc:petroleum ether, to give iodide **1.112** as a cream-white solid (70 mg, 63%).

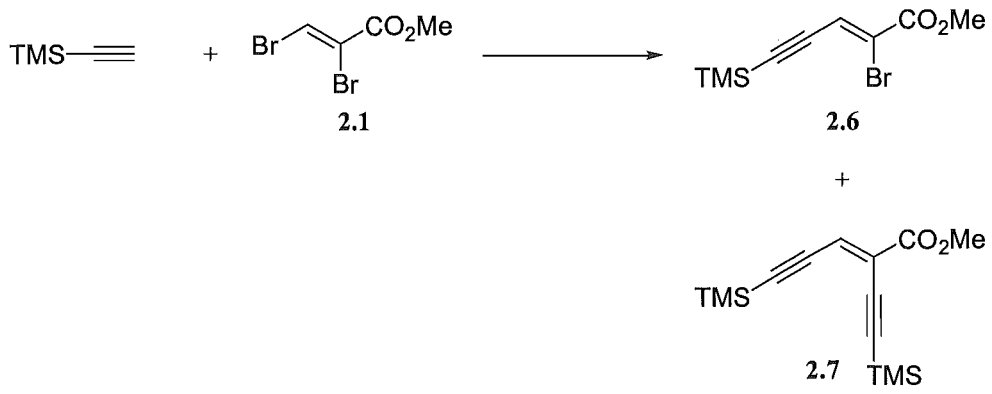
MP: 59-61 °C (lit. 66-67 °C).[104]

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.77 [s, 3H, $\mathbf{H_3}CO_2C$], 3.99 [s, 3H, $OC\mathbf{H_3}$], 7.67 [s, 1H, C**H**].

^{13}C NMR (75 MHz, $CDCl_3$): δ 52.7, 61.9, 64.8, 164.1, 164.2.

HRMS: Calcd. for $C_5H_7O_3{}^{127}I$ (M^+) 241.9439, found 241.9440.

Methyl (*Z*)-2-bromo-5-(trimethylsilyl)pent-2-en-4-ynoate 2.6 and methyl (*E*)-2-(trimethylsilylethynyl)-5-(trimethylsilyl)pent-2-en-4-ynoate 2.7



Bromide **2.1** (1.00 mL, 9.08 mmol) was dissolved in DMF (16 mL), and the solution was deoxygenated by five flush-evacuate cycles and then cooled to 0 °C. (Trimethylsilyl)acetylene (2.19 mL, 15.47 mmol) and *N*,*N*-diisopropylethylamine (2.69 mL, 15.47 mmol) were added sequentially *via* syringe, and the solution deoxygenated again. CuI (364 mg, 1.82 mmol) and $Pd(PPh_3)_4$ (524 mg, 0.45 mmol) were added sequentially, the mixture was deoxygenated once again, and then stirred for 4 hours at 0 °C. After this time, the reaction mixture was poured into a solution of Na_4EDTA (490 mg) in H_2O (40 mL) and saturated aqueous NH_4Cl solution (10 mL). The resulting brown suspension was extracted with 50% EtOAc:petroleum ether (x 4) and washed with H_2O. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 5% acetone:petroleum ether, to give an inseparable mixture of esters **2.6** and **2.7** as a light green oil (1.67 g). By comparison of the integrals for the olefinic protons in the ^1H NMR spectrum of this mixture, the ratio of **2.6** to **2.7** was estimated as being 3:1, equating to a 53% yield of **2.6**. This mixture was used without attempts at separation.

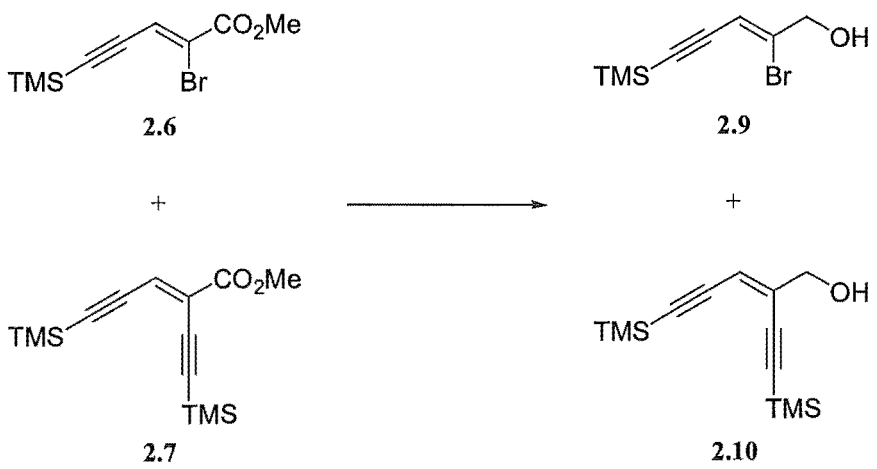
^1H NMR (500 MHz, $CDCl_3$): δ 0.24 [s, 27H, $Si(CH_3)_3$], 3.81 [s, 3H, CO_2CH_3 (**2.7**)], 3.85 [s, 3H, CO_2CH_3 (**2.6**)], 6.95 [s, 1H, C=CH (**2.7**)], 7.29 [s, 1H, C=CH (**2.6**)].

^{13}C NMR (75 MHz, $CDCl_3$): δ -0.7, -0.5, -0.4, 52.5, 53.3, 98.4, 100.3, 101.1, 105.2, 112.0, 123.88, 123.93, 125.2, 127.9, 162.1, 163.9.

IR (film): 1724, 1735 cm^{-1}.

HRMS: Calcd. for $C_9H_{13}O_2{}^{79}Br^{28}Si$ (M^+) 259.9868, found 258.9868.
Calcd. for $C_{14}H_{22}O_2{}^{28}Si_2$ (M^+) 278.1158, found 278.1158.

(*Z*)-2-Bromo-5-(trimethylsilyl)pent-2-en-4-yn-1-ol 2.9 and
(*E*)-2-(trimethylsilylethynyl)-5-(trimethylsilyl)pent-2-en-4-yn-1-ol 2.10



Neat DIBAl-H (0.773 mL, 4.34 mmol) was added dropwise *via* syringe to a stirred solution of esters **2.6** and **2.7** (519 mg, 1.67 mmol of **2.7**) in dry Et_2O (6 mL) at –78 °C, and the mixture was stirred at this temperature for 15 min, then at 0 °C for 3 h. After this time, the reaction mixture was quenched with saturated aqueous sodium tartrate solution, and the resulting gelatinous slurry stirred vigorously at room temperature for 1 h, and then extracted with Et_2O (x 4). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with eluting with 15% EtOAc:petroleum ether, to give an inseparable mixture of alcohols **2.9** and **2.10** as a pale yellow oil (362 mg). By comparison of the integrals for the olefinic protons in the ^{1}H NMR spectrum of this mixture, the ratio of **2.9** to **2.10** was estimated as being 3:1, equating to a 75% yield of **2.9**. This mixture was used without attempts at separation.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.22 [s, 9H, $Si(CH_3)_3$]), 1.70 [t, J = 6.1 Hz, 1H, CH_2OH (**2.10**)], 1.98 [t, J = 6.7 Hz, 1H, CH_2OH (**2.9**)], 4.18 [d, J = 6.1 Hz, 2H, CH_2OH (**2.10**)], 4.32 [d, J = 6.7 Hz,. 2H, CH_2OH (**2.9**)], 5.99 [s, 1H, C=CH (**2.10**)], 6.31 [s, 1H, C=CH (**2.9**)].

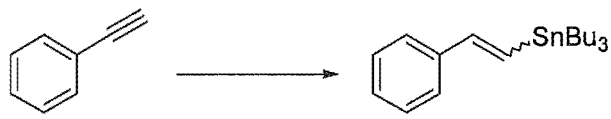
^{13}C NMR (75 MHz, $CDCl_3$): δ -0.3, -0.10, -0.07, 64.4, 67.3, 100.7, 100.8, 101.90, 101.95, 102.5, 104.1, 110.4, 115.1, 135.2, 137.4.

IR (film): 3352 cm^{-1}.

HRMS: Calcd. for $C_8H_{13}O^{79}Br^{28}Si$ (M^+) 231.9919, found 231.9911.

Calcd. for $C_{13}H_{22}O^{28}Si_2$ (M^+) 250.1209, found 250.1209.

(*E*/*Z*)-1-(Tributylstannyl)-2-phenylethene 2.38



2.38

A stirred mixture of phenylethyne (3.81 mL, 34.65 mmol), tributyltin hydride (9.82 mL, 36.49 mmol) and AIBN (0.022 g, 0.14 mmol) was heated slowly over 1 h to 50 °C, and maintained at this temperature for 19 h. After this time, the reaction mixture was cooled to room temperature and diluted with EtOAc. The mixture was filtered to remove a white precipitate, and the solvent was removed under reduced pressure. The crude residue was purified by bulb-to-bulb distillation to give stannane **2.38** as a pale yellow liquid (12.75 g, 94%). By comparison of the integrals for the olefinic protons in the ^{1}H NMR spectrum of **2.38**, the (*E*):(*Z*) ratio was estimated as being 12.4:1.0. This mixture was used without attempts at separation.

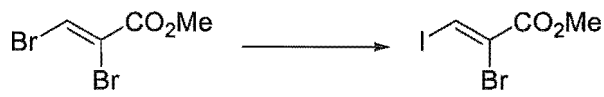
BP: 180 °C @ 2.2 mmHg (lit. 134 °C @ 0.1 mmHg).[136]

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 [t, J = 7.3 Hz, 9H, $Sn(C_3H_6CH_3)_3$], 0.98 [m, 6H, $Sn(C_2H_4CH_2CH_3)_3$], 1.35 [m, 6H, $Sn(CH_2CH_2C_2H_5)_3$], 1.55 [m, 6H, $Sn(CH_2C_3H_7)_3$], 6.87 [s, 2H, C**H**=C**H**], 7.24 [t, J = 7.5 Hz, 1H, Ar**H**], 7.32 [dd, J = 7.8, 7.5, 2H, Ar**H**], 7.42 [d, J = 7.8 Hz, 2H, Ar**H**].

^{13}C NMR (75 MHz, $CDCl_3$): δ 9.5, 13.7, 27.3, 29.2, 125.9, 127.4, 128.3, 129.0, 138.8, 146.7.

HRMS: Calcd. for $C_{16}H_{25}{}^{120}Sn$ (M^+ – Bu) 337.0977, found 337.0978.

Methyl (*Z*)-2-bromo-3-iodopropenoate 2.44



2.1 **2.44**

Sodium iodide (15.93 g, 106.26 mmol) was added to a stirred solution of bromide **2.1** (11.05 g, 45.32 mmol) in dry acetone (75 mL), and the resulting dark orange suspension was stirred at reflux for 72 h. After this time, the reaction mixture was cooled to room temperature, solvent was removed under reduced pressure, and the residue was re-suspended in EtOAc and filtered to remove solids. The clear filtrate was washed with saturated aqueous $Na_2S_2O_3$ solution, and the aqueous washings were re-extracted with EtOAc (x 3). The solvent was removed from the combined organic extracts under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 5% EtOAc:petroleum ether, to give iodide **2.44** as a pale yellow, pleasant-smelling oil (8.87 g, 67%).

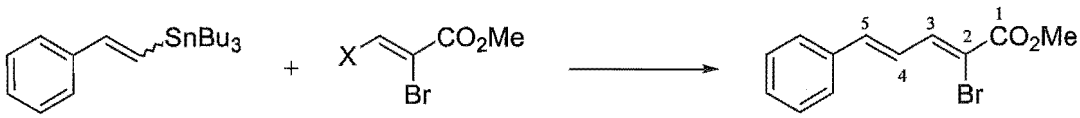
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.84 [s, 3H, CH_3], 8.77 [s, 1H, CH].

^{13}C NMR (75 MHz, $CDCl_3$): δ 53.6, 103.3, 128.2, 160.2.

IR (film): 1732 cm^{-1}.

HRMS: Calcd. for $C_4H_4O_2{}^{79}Br^{127}I$ (M^+) 289.8438, found 289.8439.

Methyl (2*Z*,4*E*)-2-bromo-5-phenylpenta-2,4-dienoate 2.33



2.38 **2.1** [X= Br] **2.44** [X = I] **2.33**

The table below summarises the reagent, catalyst and solvent combinations investigated in the optimisation of this procedure. Reactions were conducted at 80 °C for 12 h using 5 mol % of catalyst, unless otherwise indicated.

X	Catalyst	Solvent	Yield
Br	$Pd(PPh_3)_2Cl_2$	DMF	< 20 %
I	$Pd(PPh_3)_2Cl_2$	DMF	55 %
I	$Pd(PPh_3)_2(OAc)_2$	DMF	48 %
I	$Pd(PhCN)_2Cl_2/AsPh_3/CuI$*	NMP	49 %
I	$Pd(AsPh_3)_2Cl_2$	DMF	58 %
I	$Pd(CH_3CN)_2Cl_2$	DMF	54 %
I	$[PdCl(\pi\text{-}C_3H_5)]_2$	DMF	60 %
I	$Pd(PPh_3)_4$	DMF	63 %
I	$Pd(dppf)Cl_2$	DMF	66 %

* 5 mol %/10 mol %/10mol %

A typical procedure was as follows:

A solution of $Pd(dppf)Cl_2$ (0.945 g, 1.29 mmol) in dry DMF (35 mL) and a solution of stannane **2.38** (10.16 g, 25.85 mmol) in dry DMF (30 mL) were added sequentially *via* cannula to a stirred solution of iodide **2.44** (7.14 g, 24.55 mmol) in dry DMF (25 mL). The reaction mixture was deoxygenated by four freeze-evacuate-thaw cycles, and then stirred at 80 °C in the dark for 12 h. After this time, the reaction mixture was cooled to room temperature, and stirred with saturated aqueous KF solution in the dark for 3 h. The layers were separated, and the aqueous layer was re-extracted with EtOAc (x 2). Solvent was removed from the combined organic extracts under reduced pressure, and the crude residue was loaded onto a short silica gel column and flushed with petroleum ether to remove the bulk of the non-polar tin by-products present. The product was recovered by flushing the column with EtOAc, which was then removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 5% EtOAc:petroleum ether, to give diene ester **2.33** as a bright yellow solid (4.34 g, 66%).

MP: 53-55 °C (lit. 60-61 °C).[146b]

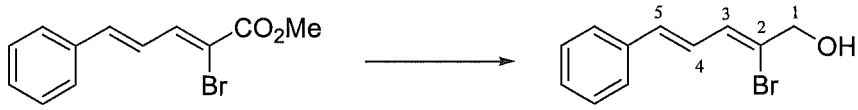
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.87 [s, 3H, 1-OC**H**$_3$], 7.06 [d, J = 15.6 Hz, 1H, H-5], 7.17 [dd, J = 15.6, 10.3 Hz, 1H, H-4], 7.34-7.40 [m, 3H, Ar**H**], 7.53 [d, J = 7.3 Hz, 2H, Ar**H**], 7.84 [d, J = 10.3 Hz, 1H, H-3].

^{13}C NMR (75 MHz, $CDCl_3$): δ 53.2, 113.5, 125.0, 127.4, 128.7, 129.5, 135.7, 141.4, 142.8, 163.3.

IR (KBr): 1707 cm^{-1}.

HRMS: Calcd. for $C_{12}H_{11}O_2{}^{79}Br$ 265.9942 (M^+), found 265.9942.

(2*Z*,4*E*)-2-Bromo-5-phenylpenta-2,4-dien-1-ol 2.46



2.33 **2.46**

Neat DIBAl-H (1.87 mL, 10.50 mmol) was added dropwise *via* syringe to a stirred solution of ester **2.33** (1.28 g, 4.81 mmol) in dry Et_2O (15 mL) at –78 °C, and the reaction mixture was stirred at this temperature for 15 min, then at 0 °C for 3 h. After this time, the reaction mixture was quenched at 0 °C with saturated aqueous sodium tartrate solution, and the resulting gelatinous slurry was stirred vigorously at room temperature for 1 h and then extracted with Et_2O (x 4). Solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 20% EtOAc:petroleum ether, to give alcohol **2.46** as a cream solid (1.03 g, 89%).

MP: 75-77 °C.

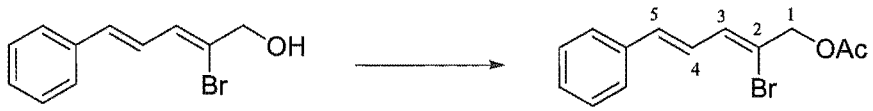
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.99 [t, J = 6.6 Hz, 1H, 1-O**H**], 4.38 [d, J = 6.6 Hz, 2H, H-1], 6.752 [d, J = 9.8 Hz, 1H, H-3], 6.754 [d, J = 15.9 Hz, 1H, H-5], 7.04 [dd, J = 15.9, 9.8 Hz, 1H, H-4], 7.28 [t, J = 7.6 Hz, 1H, Ar**H**], 7.35 [dd, J = 7.6, 7.3 Hz, 2H, Ar**H**], 7.49 [d, J = 7.3 Hz, 2H, Ar**H**].

^{13}C NMR (75 MHz, $CDCl_3$): δ 68.4, 125.2, 126.7, 127.1, 128.3, 128.4, 128.7, 136.2, 136.6.

IR (KBr): 3255 cm^{-1}.

HRMS: Calcd. for $C_{11}H_{11}O^{79}Br$ 237.9993, found 237.9993.

(2*Z*,4*E*)-1-Acetoxy-2-bromo-5-phenylpenta-2,4-diene 2.47



2.46 **2.47**

Triethylamine (16 μL, 1.11 mmol) and acetic anhydride (10 μL, 1.02 mmol) were added sequentially *via* syringe to a stirred solution of alcohol **2.46** (221 mg, 0.92 mmol) and 4-(dimethylamino)pyridine (23 mg, 0.19 mmol) in dry CH_2Cl_2 (1.5 mL) at 0 °C, and the mixture was allowed to warm to room temperature over 2 h. After this time, the reaction mixture was diluted with H_2O, the organic layer separated, and the aqueous layer extracted with $CHCl_2$ (x 2). The combined organic extracts were then washed with saturated aqueous NH_4Cl solution. Solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 5% EtOAc:petroleum ether, to give acetate **2.47** as a pale cream solid (296 mg, 92%).

MP: 68-69 °C.

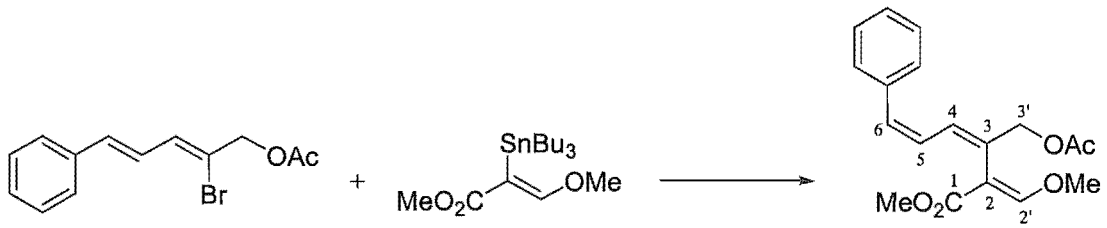
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.14 [s, 3H, 1-OC(O)C**H**$_3$], 4.86 [s, 2H, H-1], 6.75 [d, J = 9.8 Hz, 1H, H-3], 6.79 [d, J = 15.8 Hz, 1H, H-5], 7.02 [dd, J = 15.8, 9.8 Hz, 1H, H-4], 7.29 [t, J = 7.1 Hz, 1H, Ar**H**], 7.35 [dd, J = 7.6, 7.1 Hz, 2H, Ar**H**], 7.47 [d, J = 7.6 Hz, 2H, Ar**H**].

^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 68.9, 120.6, 125.0, 126.8, 128.4, 128.6, 131.9, 136.4, 137.2, 170.2.

IR (KBr): 1729 cm^{-1}.

HRMS: Calcd. for $C_{13}H_{13}O_2{}^{79}Br$ (M^+) 280.0099, found 280.0099.

Methyl (3*E*,5*Z*,*E*)-2-(methoxymethylene)-3-(acetoxymethyl)-6-phenylhexa-3,5-dienoate 2.48



2.47 **1.111** **2.48**

$Pd_2(dba)_3$ (43 mg, 0.05 mmol), $AsPh_3$ (58 mg, 0.19 mmol), CuI (90 mg, 0.47 mmol), were added sequentially to a stirred solution of bromide **2.47** (132 mg, 0.47 mmol) in dry NMP (1 mL). A solution of stannane **1.111** (287 mg, 0.71 mmol) in dry NMP (1 mL) was then added *via* cannula. The reaction mixture was deoxygenated by six freeze-evacuate-thaw cycles, and then stirred at 50 °C in the dark for 12 h. After this time, the reaction mixture was cooled to room temperature, diluted with H_2O, and extracted with EtOAc (x 4). Solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 25% EtOAc:petroleum ether, to give starting material (**2.47**, 47 mg), and triene **2.48** as a pale yellow gum (49 mg, 51% based on recovered **2.47**).

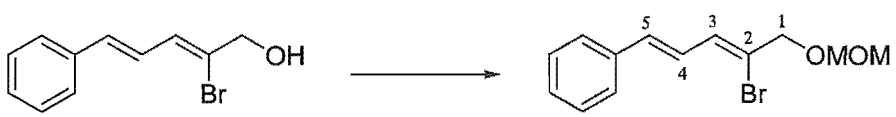
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.07 [s, 3H, 3'-OC(O)C**H**$_3$], 3.74 [s, 3H, 1-OC**H**$_3$], 3.86 [s, 3H, 2'-OC**H**$_3$], 4.47 [s, 2H, H-3'], 6.51 [dd, J = 5.6, 4.9 Hz, 1H, H-5], 6.647 [d, J = 4.9 Hz, 1H, H-4], 6.648 [d, J = 5.6 Hz, 1H, H-6), 7.24, [dd, J = 7.1 Hz, 7.1 Hz, 1H, Ar**H**], 7.32 [dd, J = 8.1, 7.1 Hz, 2H, Ar**H**], 7.37 [d, J = 8.1 Hz, 2H, Ar**H**], 7.54 [s, 1H, H-2'].

^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 51.7, 62.1, 67.0, 106.9, 125.3, 126.6, 127.8, 128.55, 128.62, 132.1, 134.6, 137.2, 160.8, 167.5, 170.7.

IR (film): 1626, 1705, 1738 cm^{-1}.

HRMS: Calcd. for $C_{18}H_{20}O_5$ (M^+) 316.1311, found 316.1311.

(2*Z*,4*E*)-1-(Methoxymethoxy)-2-bromo-5-phenylpenta-2,4-diene 2.49



2.46 **2.49**

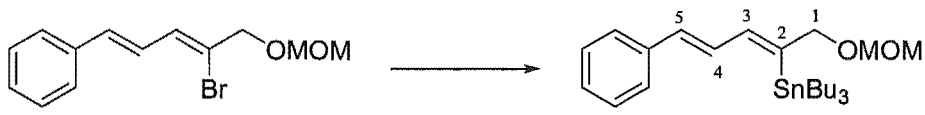
N,N-Diisopropylethylamine (1.93 mL, 11.10 mmol) and chloromethyl methyl ether (0.68 mL, 8.88 mmol) were added sequentially *via* syringe to a stirred solution of alcohol **2.46** (1.062 g, 4.44 mmol) in CH_2Cl_2 (50 mL) at 0 °C, and the mixture was allowed to warm to room temperature over 96 h. After this time, the reaction mixture was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with EtOAc (x 4). Solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 20% EtOAc:petroleum ether, to give MOM ether **2.49** as an amber oil (1.26 g, 100%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.42 [s, 3H, 1-OCH_2OCH_3], 4.34 [s, 2H, H-1], 4.70 [s, 2H, 1-OCH_2OCH_3], 6.750 [d, J = 10.3 Hz, 1H, H-3], 6.754 [d, J = 15.9 Hz, 1H, H-5], 7.06 [dd, J = 15.9, 10.3 Hz, 1H, H-4], 7.28 [t, J = 7.6 Hz, 1H, Ar**H**], 7.34 [dd J = 7.6, 7.3 Hz, 2H, Ar**H**], 7.47 [d, J = 7.3 Hz, 2H, Ar**H**].

^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5, 71.9, 95.1, 123.5, 125.2, 126.7, 128.2, 128.6, 130.2, 136.3, 136.5.

HRMS: Calcd. for $C_{13}H_{15}O_2{}^{79}Br$ (M^+) 282.0256, found 282.0253.

(2*Z*,4*E*)-1-(Methoxymethoxy)-2-(tributylstannyl)-5-phenylpenta-2,4-diene 2.51



2.46 **2.51**

$Pd(PPh_3)_2Cl_2$ (0.390 g, 0.56 mmol) was added to a solution of bromide **2.46** (3.14 g, 11.10 mmol) in dry toluene (63 mL), and the mixture was deoxygenated by five flush-evacuate cycles. Bis(tributyl)tin (4.70 mL, 0.83 mmol) was added *via* syringe, and the mixture was deoxygenated again, and then stirred at reflux in the dark for 72 h. After this time, the reaction mixture was cooled to room temperature, diluted with H_2O, and extracted with Et_2O (x 4). The combined organic extracts were stirred with saturated aqueous KF solution in the dark for 24 h, and then separated. Et_2O was removed under reduced pressure, and toluene was removed

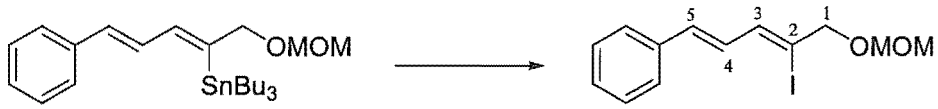
azeotropically with MeOH under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with 5% EtOAc:petroleum ether, to give stannane **2.51** as a yellow oil (1.84 g, 40%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 [t, J = 7.3 Hz, 9H, $Sn(C_2H_6\mathbf{CH_3})_3$], 1.05 [m, 6H, $Sn)C_2H_4\mathbf{CH_2}CH_3)_3$], 1.34 [m, 6H, $Sn(CH_2\mathbf{CH_2}C_2H_5)_3$], 1.54 [m, 6H, $Sn(\mathbf{CH_2}C_3H_7)_3$], 3.39 [s, 3H, 1-$OCH_2OC\mathbf{H_3}$], 4.27 [s, 2H, H-1], 4.64 [s, 2H, 1-$OC\mathbf{H_2}OCH_3$], 6.56 [d, J = 15.6 Hz, 1H, H-5], 6.78 [dd, J = 15.6, 10.7 Hz, 1H, H-4], 7.01 [d, J = 10.7 Hz, 1H, H-3], 7.23 [t, J = 7.2 Hz, 1H, Ar**H**], 7.32 [dd, J = 7.8, 7.2 Hz, 2H, Ar**H**], 7.36 [d, J = 7.8 Hz, 2H, Ar**H**].

^{13}C NMR (75 MHz, $CDCl_3$): δ 10.7, 13.6, 27.3, 29.1, 55.3, 74.4, 95.3, 126.2, 127.4, 128.6, 129.6, 133.6, 137.4, 140.9, 147.9.

HRMS: Calcd. for $C_{25}H_{42}O_2{}^{120}Sn$ (M^+ – Bu) 437.1502, found 437.1503.

(2*Z*,4*E*)-1-(Methoxymethoxy)-2-iodo-5-phenylpenta-2,4-diene 2.52



2.51 **2.52**

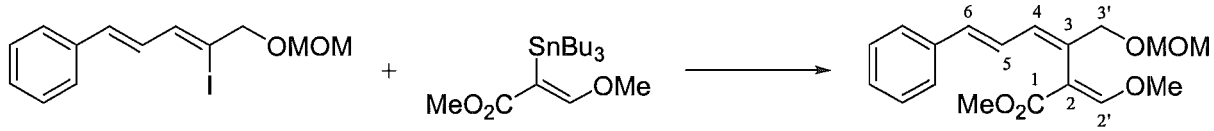
A solution of iodine (61 mg, 0.24 mmol) in dry Et_2O (2 mL) was added *via* cannula to a stirred solution of stannane **2.51** (101 mg, 0.21 mmol) in dry Et_2O (2 mL) at 0 °C, and the mixture was stirred at this temperature for 1 h. After this time, the reaction mixture was diluted with Et_2O and washed with saturated aqueous $Na_2S_2O_3$ solution Solvent was removed under reduced pressure, and the residue was purified by flash chromatography on alumina, eluting with 5% EtOAc:petroleum ether, to give iodide **2.52** as viscous pale orange oil (45 mg, 66%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.43 [s, 3H, 1-$OCH_2OC\mathbf{H_3}$], 4.36 [s, 2H, H-1], 4.70 [s, 2H, 1-$OC\mathbf{H_2}OCH_3$], 6.67 [d, J = 9.8 Hz, 1H, H-3], 6.81 [d, J = 15.6 Hz, 1H, H-5,], 6.93 [dd, J = 15.6, 9.8 Hz, 1H, H-4], 7.28 [t, J = 7.3 Hz, 1H, Ar**H**], 7.35 [dd, J = 7.8, 7.3 Hz, 2H, Ar**H**], 7.47 [d, J = 7.8 Hz, 2H, Ar**H**].

^{13}C NMR (75 MHz, $CDCl_3$): δ 55.6, 75.1, 94.9, 103.7, 126.8, 128.3, 128.6, 129.6, 135.7, 136.5, 137.0.

HRMS: Calcd. for $C_{13}H_{15}O_2{}^{127}I$ (M^+) 330.0116, found 330.0117.

Methyl (3*E*,5*E*,*E*)-2-(methoxymethylene)-3-(methoxymethoxymethyl)-6-phenylhexa-3,5-dienoate 2.50



2.52 **1.111** **2.50**

$Pd_2(dba)_3$ (37 mg, 0.04 mmol), $AsPh_3$ (49 mg, 0.16 mmol) and CuI (76 mg, 0.40 mmol) were added sequentially to a stirred solution of iodide **2.52** (132 mg, 0.40 mmol) in dry NMP (2 mL). A solution of stannane **1.111** (243 mg, 0.60 mmol) in dry NMP (2 mL) was then added *via* cannula. The reaction mixture was deoxygenated by six freeze-evacuate-thaw cycles, and then stirred at 50 °C in the dark for 12 h. After this time, the reaction mixture was cooled to room temperature, diluted with H_2O, and extracted with EtOAc (x 4). Solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 35% EtOAc:petroleum ether, to give triene **2.50** as a viscous yellow oil (73 mg, 57%).

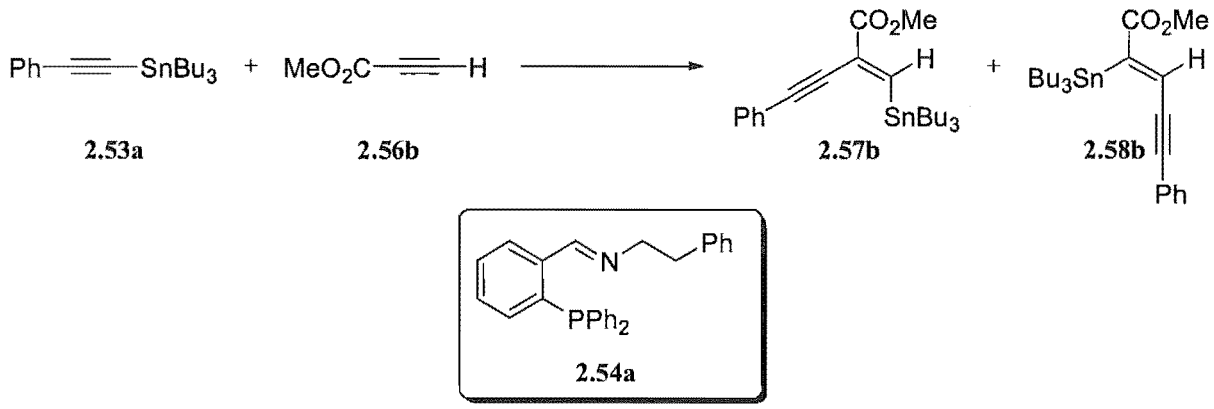
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.38 [s, 3H, 3'-OCH_2OCH_3], 3.73 [s, 3H, 1-OCH_3], 3.85 [s, 3H, 2'-OCH_3], 4.25 [s, 2H, H-3'], 4.65 [s, 2H, 3'-OCH_2OCH_3], 6.49 [d, J = 10.3 Hz, 1H, H-4], 6.61 [d, J = 15.6 Hz, 1H, H-6], 6.68 [dd, J = 15.6, 10.3 Hz, 1H, H-5], 7.21 [t, J = 7.3 Hz, 1H, Ar**H**], 7.30 [dd, J = 7.3, 7.3 Hz, 2H, Ar**H**], 7.37 [d, J = 7.3 Hz, 2H, Ar**H**], 7.54 [s, 1H, H-2'].

^{13}C NMR (75 MHz, $CDCl_3$): δ 51.5, 55.2, 61.9, 69.5, 95.1, 107.4, 125.7, 126.4, 127.5, 128.5, 130.8, 130.9, 133.6, 137.4, 160.4, 167.6.

IR (film): 1626, 1709 cm^{-1}.

HRMS: Calcd. for $C_{18}H_{22}O_5$ (M^+) 318.1467, found 318.1467.

Methyl (*Z*)-2-(tributylstannyl)-5-phenylpent-2-en-4-ynoate 2.57b and methyl (*E*)-2-(phenylethynyl)-3-(tributylstannyl)propenoate 2.58b



Methyl propynoate (**2.56b**) [4.81 mL, 54.01 mmol] was added *via* syringe to solution of *N*-(2-diphenylphosphinobenzylidene)-2-phenylethylamine (**2.54a**) [0.340 g, 0.86 mmol] and π-allylpalladium chloride dimer (0.158 g, 0.43 mmol) in dry THF (196 mL), and the resulting solution was deoxygenated by four freeze-evacuate-thaw cycles. Tributyl(phenylethynyl)tin (**2.53a**) [6.31 mL, 18.0 mmol] was added *via* syringe, and the mixture was stirred at 50 °C for 3 h. After this time, solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 5% EtOAc:petroleum ether, to give an inseparable mixture of regioisomeric enyne esters **2.57b** and **2.58b** as a yellow-orange oil (7.00 g, 82%). By comparison of the integrals for the olefinic protons in the ^{1}H NMR spectrum of this mixture, the ratio of **2.57b** to **2.58b** was estimated as being 1:4. This mixture was used without attempts at separation.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 [m, 9H, $Sn(C_3H_6\mathbf{CH_3})_3$], 1.15 [m, 6H, $Sn(C_2H_4\mathbf{CH_2}CH_3)_3$], 1.31 [m, 6H, $Sn(CH_2\mathbf{CH_2}C_2H_5)_3$], 1.52 [m, 6H, $Sn(\mathbf{CH_2}C_3H_7)_3$], 3.76 [s, 3H, $CO_2\mathbf{CH_3}$ (**2.58b**)], 3.83 [s, 3H, $CO_2\mathbf{CH_3}$ (**2.57b**)], 7.33-7.36 [m, 3H, Ar**H**], 7.46-7.48 [m, 3H, Ar**H** and C**H**=C (**2.58b**)], 8.07 [s, 1H, C**H**=C (**2.57b**)].

^{13}C NMR (75Hz, $CDCl_3$): δ 11.2, 13.6, 27.2, 29.0, 51.8, 52.5, 88.9, 97.8, 122.6, 122.8, 128.2, 128.3, 128.4, 128.9, 131.5, 131.6, 133.5, 149.6, 159.8, 164.0, 171.2.

IR: 1707 cm^{-1}.

HRMS: Calcd. for $C_{20}H_{27}O_2{}^{120}Sn$ (M^+ – Bu) 419.1032, found 419.1033.

(*Z*)-2-(Tributylstannyl)-5-phenylpent-2-en-4-yn-1-ol 2.59

2.58b **2.59**

Neat DIBAl-H (3.33 mL, 18.71 mmol) was added dropwise to a stirred solution of esters **2.57b** and **2.58b** (4.07 g, 6.85 mmol of **2.58b**) in dry Et_2O (25 mL) at –78 °C, and the reaction mixture was stirred at this temperature for 15 min, then at 0 °C for 3 h. After this time, the reaction mixture was quenched by addition of saturated aqueous sodium tartrate solution. The resulting gelatinous slurry was stirred vigorously at room temperature for 1 h and then extracted with Et_2O (x 4). Solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 10% EtOAc:petroleum ether, to give **2.59** as an amber oil (2.71 g, 88%).

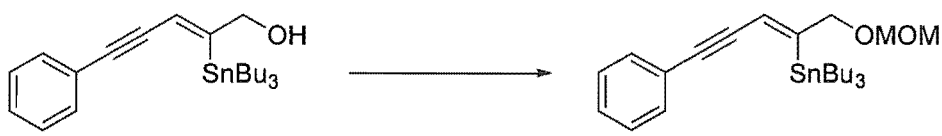
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 [t, J = 7.3 Hz, 9H, $Sn(C_3H_6\mathbf{CH_3})_3$], 1.01 [m, 6H, $Sn(C_2H_4\mathbf{CH_2}CH_3)_3$], 1.31 [m, 6H, $Sn(CH_2\mathbf{CH_2}C_2H_5)_3$], 1.42 [br s, 1H, $CH_2\mathbf{OH}$], 1.54 [m, 6H, $Sn(\mathbf{CH_2}C_3H_7)_3$], 4.37 [s, 2H, $\mathbf{CH_2}OH$], 6.56 [s, 1H, C**H**=C], 7.30-7.34 [m, 3H, Ar**H**], 7.41-7.43 [m, 2H, Ar**H**].

^{13}C NMR (75 MHz, $CDCl_3$): δ 10.1, 13.6, 27.3, 29.2, 69.2, 89.8, 90.2, 117.9, 123.5, 127.9, 128.2, 131.2, 161.9.

IR (film): 3300 cm^{-1}.

HRMS: Calcd. for $C_{19}H_{27}O^{120}Sn$ (M^+ – Bu) 391.1083, found 391.1084.

(*Z*)-1-(Methoxymethoxy)-2-(tributylstannyl)-5-phenylpent-2-en-4-yne 2.60



2.59 **2.60**

N,N-Diisopropylethylamine (0.99 mL, 5.70 mmol) and chloromethyl methyl ether (0.35 mL, 4.56 mmol) were added sequentially *via* syringe to a stirred solution of alcohol **2.59** (1.02 g, 2.28 mmol) in CH_2Cl_2 (23 mL) at 0 °C, and the mixture was allowed to warm to room temperature over 96 h. After this time, the mixture was cooled to 0 °C, quenched by addition of saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc (x 4). Solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel, eluting with 2% EtOAc:petroleum ether, to give MOM ether **2.60** as a yellow oil (0.993 g, 89%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 [t. J = 7.3 Hz, 9H, $Sn(C_3H_6\mathbf{CH_3})_3$], 1.09 [m, 6H, $Sn(C_2H_4\mathbf{CH_2}CH_3)_3$], 1.30 [m, 6H, $Sn(CH_2\mathbf{CH_2}C_2H_5)_3$], 1.54 [m, 6H, $Sn(\mathbf{CH_2}C_3H_7)_3$], 3.39 [s, 3H, $CH_2OCH_2O\mathbf{CH_3}$], 4.27 [s, 2H, $\mathbf{CH_2}OCH_2OCH_3$], 4.65 [s, 2H, $CH_2O\mathbf{CH_2}OCH_3$], 6.57 [s, 1H, **CH**=C], 7.28-7.33 [m, 3H, Ar**H**], 7.40-7.42 [m, 2H, Ar**H**].
^{13}C NMR (75 MHz, $CDCl_3$): δ 10.5, 13.7, 27.3, 29.1, 55.3, 73.3, 89.8, 90.1, 95.5, 119.4, 123.6, 127.9, 128.2, 131.3, 158.9.
HRMS: Calcd. for $C_{13}H_{31}O_2{}^{120}Sn$ (M^+ – Bu) 435.1345, found 435.1346.

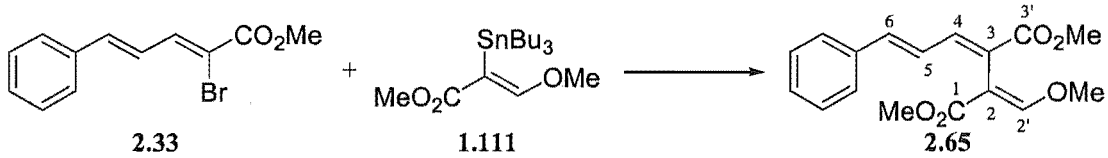
(2*Z*,4*E*)-2-Iodo-5-phenylpenta-2,4-dien-1-ol 2.75

2.52 **2.75**

Trimethylsilyl bromide (46 μL, 0.35 mmol) was added *via* syringe to a stirred solution of MOM ether **2.52** (29 mg, 0.09 mmol) in dry CH_2Cl_2 (2 mL) over 4 Å molecular sieves at –30 °C. The mixture was stirred at this temperature for 1 h, and then at 0 °C for 12 h. After this time, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with Et_2O (x 3). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 2% EtOAc:petroleum ether, to give alcohol **2.75** as a pale yellow oil (11 mg, 46%) which decomposed within hours.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.51 [s, 2H, H-1], 6.67 [d, J = 8.3 Hz, 1H, H-3], 6.85 [m, 2H, H-4 and H-5], 7.30 [t, J = 7.1 Hz, 1H, Ar**H**], 7.36 [dd, J = 7.3, 7.1 Hz, 2H, Ar**H**], 7.49 [d, J = 7.3 Hz, 2H, Ar**H**].

Methyl (3*E*,5*E*,*E*)-2-(methoxymethylene)-3-(methoxycarbonyl)-6-phenylhexa-3,5-dienoate 2.65



2.33 **1.111** **2.65**

$Pd_2(dba)_3$ (125 mg, 0.14 mmol), $AsPh_3$ (167 mg, 0.55 mmol) and CuI (260 mg, 1.37 mmol), were added sequentially to a stirred solution of bromide **2.33** (365 mg, 1.37 mmol) in dry NMP (4 mL). A solution of stannane **1.111** (831 mg, 2.05 mmol) in dry NMP (4 mL) was then added *via* cannula. The mixture was deoxygenated by six freeze-evacuate-thaw cycles and then stirred at 50 °C in the dark for 12 h. After this time, the reaction mixture was cooled to room temperature, diluted with H_2O, and extracted with EtOAc (x 4). Solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 25% EtOAc:petroleum ether, to give triene **2.65** as a resinous yellow oil (355 mg, 86%).

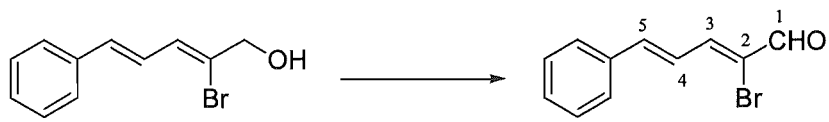
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.72 [s, 3H, 3'-OC**H**$_3$], 3.76 [s, 3H, 1-OC**H**$_3$], 3.86 [s, 3H, 2'-OC**H**$_3$], 6.72 [dd, J = 11.0, 15.6 Hz, 1H, H-5], 6.93 [d, J = 15.6 Hz, 1H, H-6], 7.29 [t, J = 7.3 Hz, 1H, Ar**H**], 7.34 [dd, J = 7.3, 7.3 Hz, 2H, Ar**H**], 7.43 [d, J = 7.3 Hz, 2H, Ar**H**], 7.52 [d, J = 11.0 Hz, 1H, H-4], 7.57 [s, 1H, H-2'].

^{13}C NMR (75 MHz, $CDCl_3$): δ 51.6, 51.9, 61.9, 105.5, 123.5, 124.9, 127.1, 128.6, 128.8, 136.3, 140.3, 141.5, 160.3, 167.2, 167.5.

IR (film): 1620, 1713 cm^{-1}.

HRMS: Calcd. for $C_{17}H_{18}O_5$ (M^+) 302.1154, found 302.1154.

(2*Z*,4*E*)-2-Bromo-5-phenylpenta-2,4-dienal 2.78



2.46 **2.78**

Tetra-*n*-propylammonium perruthenate (67 mg, 0.19 mmol) was added to a stirred suspension of alcohol **2.46** (894 mg, 3.74 mmol), *N*-methylmorpholine-*N*-oxide (657 mg, 5.61 mmol) and powdered 4 Å molecular sieves (1.87 g) in dry CH_2Cl_2 (8 mL). The resulting dark green suspension was stirred vigorously at room temperature for 12 h. After this time, the solvent was removed under reduced pressure, and the organic residue was re-suspended in EtOAc and filtered through a plug of silica gel to remove solids. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 15% EtOAc:petroleum ether, to give starting material (**2.46**, 133 mg), and aldehyde **2.78** as a canary yellow solid (593 mg, 79% based on consumed **2.46**).

MP: 89-90 °C.

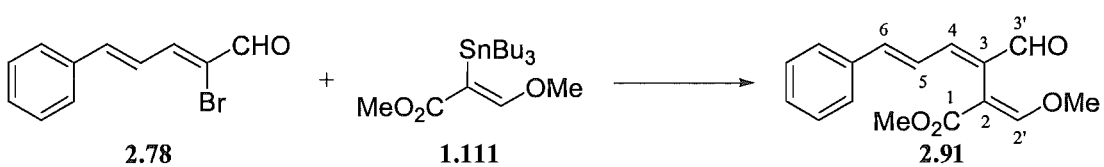
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 [d, J = 15.6 Hz, 1H, H-5], 7.37 [dd, J = 15.6, 10.5 Hz, 1H, H-4], 7.42 [m, 3H, Ar**H**], 7.59 [d, J = 7.3 Hz, 1H, Ar**H**], 7.61 [d, J = 10.5 Hz, 1H, H-3], 9.30 [s, 1H, H-1].

^{13}C NMR (75 MHz, $CDCl_3$): δ 124.3, 125.4, 127.8, 128.9, 130.2, 135.2, 145.1, 148.9, 185.7.

IR (KBr): 1686 cm^{-1}.

HRMS: Calcd. for $C_{11}H_9O^{79}Br$ (M^+) 235.9837, found 235.9834.

(3*E*,5*E*,*E*)-2-(Methoxymethylene)-3-formyl-6-phenylhexa-3,5-dienoate 2.91

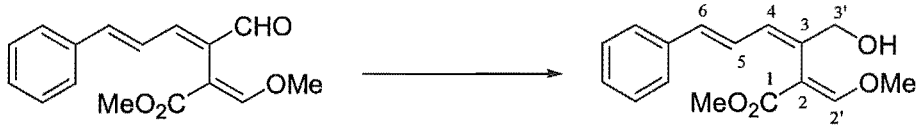


2.78 **1.111** **2.91**

$Pd_2(dba)_3$ (79 mg, 0.09 mmol), $AsPh_3$ (106 mg, 0.35 mmol) and CuI (165 mg, 0.87 mmol) were added sequentially to a stirred solution of bromide **2.78** (206 mg, 0.87 mmol) in dry NMP (2 mL). A solution of stannane **1.111** (527 mg, 1.30 mmol) in dry NMP (2 mL) was then added *via* cannula. The reaction mixture was deoxygenated by six freeze-evacuate-thaw cycles, and stirred at 50 °C in the dark for 12 h. After this time, the reaction mixture was cooled to room temperature, diluted with H_2O, and extracted with Et_2O (x 4). Solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 30% EtOAc:petroleum ether, to give triene **2.91** as a bright yellow gum (174 mg, 74%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.70 [s, 3H, 1-OC**H**$_3$], 3.85 [s, 3H, 2'-OC**H**$_3$], 6.90 [dd, J = 15.6, 11.2 Hz, 1H, H-5], 7.05 [d, J = 15.6 Hz, 1H, H-6], 7.23 [d, J = 11.2 Hz, 1H, H-4], 7.32-7.39 [m, 3H, Ar**H**], 7.48 [d, J = 7.3 Hz, 2H, Ar**H**], 7.63 [s, 1H, H-2'], 9.54 [s, 1H, H-3'].
^{13}C NMR (75 MHz, $CDCl_3$): δ 51.2, 61.7, 103.0, 124.3, 127.2, 128.5, 129.2, 133.6, 135.6, 142.0, 149.8, 161.0, 166.5, 191.8.
IR (film): 1678, 1709 cm^{-1}.
HRMS: Calcd. for $C_{16}H_{16}O_4$ (M^+) 272.1049, found 272.1049.

(3*E*,5*E*,*E*)-2-(Methoxymethylene)-3-(hydroxymethyl)-6-phenylhexa-3,5-dienoate Hydroxystrobilurin A (1.129)



2.91 **1.129**

$NaBH_4$ (7 mg, 0.18 mmol) was added to a stirred solution of aldehyde **2.91** (97 mg, 0.36 mmol) in dry MeOH (3 mL) at 0 °C, and the reaction mixture was allowed to warm to room temperature in the dark over 36 h. After this time, most of the MeOH was removed under high vacuum, and the remaining solution was diluted with H_2O and extracted with EtOAc (x 4). Solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 50% EtOAc:cyclohexane, to give starting material

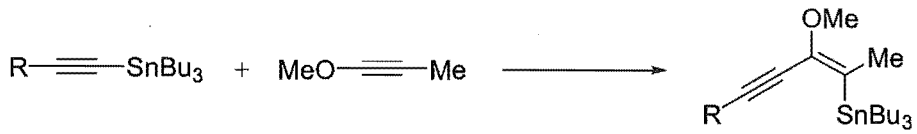
(**2.91**, 32 mg), and hydroxystrobilurin A (**1.129**) as yellow-green resin (9 mg, 14% based on recovered **2.91**).

	IR & MS DATA FOR HYDROXYSTROBILURIN A	
	Natural	**Synthetic (1.129)**
IR (cm^{-1})	3630~3100, 1705, 1625 (KBr)	3445, 1699, 1622 (film)
M^+	274.1214 (EI)	274.1205 (EI)

	NMR DATA FOR HYDROXYSTROBILURIN A	
	Natural	**Synthetic (1.129)**
^1H	δ (300 MHz, $CDCl_3$) 7.54 [s, 1H, H-2'] 7.37 [d, 2H, *J* = 7.3 Hz, H-8] 7.30 [dd, 2H, *J* = 7.3 Hz, H-9] 7.22 [dd, 1H, *J* = 7.3 Hz, H-10] 6.66 [dd, 1H, *J* = 15.3, 9.3 Hz, H-5] 6.62 [d, 1H, *J* = 15.3 Hz, H-6] 6.51 [d, 1H, *J* = 9.3 Hz, H-4] 4.25 [s, 2H, H-3'] 3.85 [s, 3H, 2'-OMe] 3.75 [s, 3H, 1-OMe]	δ (500 MHz, $CDCl_3$) 7.54 [s, 1H] 7.35 [d, 2H, *J* = 7.3 Hz] 7.30 [dd, 2H, *J* = 7.3 Hz] 7.22 [dd, 1H, *J* = 7.3 Hz] 6.66 [dd, 1H, *J* = 15.4, 9.3 Hz] 6.62 [d, 1H, *J* = 15.4 Hz] 6.51 [d, 1H, *J* = 9.3 Hz] 4.25 [s, 2H] 3.85 [s, 3H] 3.74 [s, 3H] **2.22 [br s, 1H, OH]**
^{13}C	δ (75.5 MHz, $CDCl_3$) 168.1 [C-1] 160.4 [C-2'] 137.4 [C-3] 134.0 [C-6] 133.6 [C-7] 130.9 [C-4] 128.5 [C-9] 127.7 [C-10] 126.5 [C-8] 125.6 [C-5] 107.8 [C-2] 66.8 [C-3'] 62.0 [2'-OMe] 51.8 [1-OMe]	δ (126 MHz, $CDCl_3$) 168.1 160.4 137.3 134.0 133.6 130.8 128.5 127.6 126.5 125.6 107.8 66.6 62.0 51.8

5.4 Experiments Described in Chapter 4

(*Z*)-2-(Tributylstannyl)-5-phenylpent-2-en-4-yne 4.7
(*Z*)-2-(Tributylstannyl)-5-(trimethylsilyl)pent-2-en-4-yne 4.11



2.53a [R = Ph] **4.13** **4.7** [R = Ph]
3.18 [R = TMS] **4.11** [R = TMS]

General procedure:

To solution of 2-(dicyclohexylphosphino)-2'-(*N*,*N*-dimethylamino)biphenyl (**2.63**) [4.8 mol %] and π-allylpalladium chloride dimer [2.4 mol%] in cold dry THF was added *via* cannula a solution of methoxypropyne (**4.13**) [3 equiv.] in cold dry THF, followed by either phenylethynylstannane **2.53a** [1 equiv.] *via* syringe or a solution of trimethylsilylethynylstannane **3.18** [1 equiv.] in cold dry THF *via cannula*, and the resulting mixture was stirred at 50 °C for 3 h. After this time, solvent was removed under reduced pressure, and a sample of the crude **4.7** or **4.11** was examined by ^{1}H NMR.

^{1}H NMR (500 MHz, $CDCl_3$) [**4.7**]: δ 0.84-1.65 [m, $Sn(C_4\mathbf{H}_9)_3$], 1.90 [s, $\mathbf{CH}_3$, $^3J_{Sn\text{-}H}$ ~ 21.6 Hz], 3.75 [s, $OC\mathbf{H}_3$], 7.26-7.28 [m, Ar**H**], 7.32-7.34 [m, Ar**H**], 7.42-7.46 [m, Ar**H**].

^{1}H NMR (500 MHz, $CDCl_3$) [**4.11**]: δ 0.20 [s, $Si(C\mathbf{H}_3)_3$], 0.88-1.68 [m, $Sn(C_4\mathbf{H}_9)_3$], 1.82 [s, $\mathbf{CH}_3$, $^3J_{Sn\text{-}H}$ ~ 21.6 Hz], 3.66 [s, $OC\mathbf{H}_3$].

4-(4-methoxybenzyl)oxybutan-1-ol 4.32

4.32

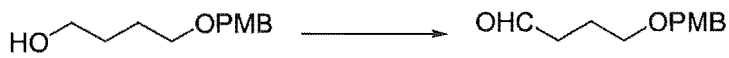
To a solution of 1,4-butanediol (7.00 g, 77.7 mmol) in dry DMF (35 mL) at –15 °C was added *via cannula* a solution of NaH (80% suspension in oil, 2.48 g, 85.5 mmol) in dry DMF

(35 mL), and the mixture was stirred at this temperature for 0.5 h. A solution of PMB-Br (14.6 g, 73.0 mmol) in dry DMF (21 mL) was added, and the reaction mixture was stirred for a further 0.5 h at –15 °C, and then allowed to warm to room temperature over 12 h. After this time, the reaction mixture was quenched by pouring into ice-H_2O, and extracted with Et_2O (x 3). Solvent was removed under reduced pressure, and the residue was purified by bulb-to-bulb distillation to give alcohol **4.32** as colourless oil (5.58 g, 30%). The ^{1}H NMR data for this compound was in agreement with that reported by Onoda *et al.*[239]

BP: ~250 °C @ 2.2 mmHg.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66-1.70 [m, 4H, H-2 and H-3], 2.50 [br s, 1H, **OH**], 3.51 [m, 2H, H-4], 3.64 [m, 2H, H-1], 3.80 [s, 3H, OCH_2ArOCH_3], 4.45 [s, 2H, OCH_2ArOCH_3], 6.88 [d, 2H, J = 8.5 Hz, Ar**H**], 7.26 [d, 2H, J = 8.5 Hz, Ar**H**].

4-(4-Methoxybenzyl)oxybutanal 4.33

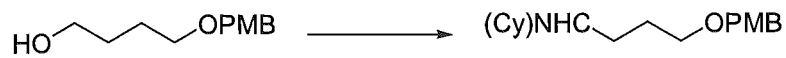


4.32 **4.33**

To a solution of Dess-Martin periodinane (3.03 g, 7.10 mmol) in dry CH_2Cl_2 (15 mL) was added *via cannula* a solution of alcohol **4.32** (1.00 g, 4.73 mmol) in dry CH_2Cl_2 (10 mL), and the reaction mixture was stirred at room temperature for 12 h. After this time, the reaction mixture was diluted with Et_2O, and poured into a solution of $Na_2S_2O_3$ (50 mmol) in $NaHCO_3$ (20 mL), and stirred until the solid dissolved. The organic layer was separated, the aqueous layer was extracted with Et_2O (x 3), and solvent was removed under reduced pressure to give aldehyde **4.33** as a pale yellow oil (0.640 g, 65%). Comparison of the integral ratios for the H-2 signals in the ^{1}H NMR spectrum of this compound indicated that it comprised a ~1.0:1.0 mixture of **4.33** and starting material, and it was used without purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85-2.00 [m, 2H, H-3], 2.50-2.60 [m, 2H, H-2], 3.46-3.52 [m, 2H, H-4], 3.80 [s, 3H, OCH_2ArOCH_3], 4.42 [s, 2H, OCH_2ArOCH_3], 6.88 [d, 2H, J = 8.5 Hz, Ar**H**], 7.26 [d, 2H, J = 8.5 Hz, Ar**H**], 9.75 [s, 1H, **CHO**].

4-(4-Methoxybenzyl)oxy-1-cyclohexyliminobutane 4.31



4.33 **4.31**

Aldehyde **4.33** (0.114 g, 0.545 mmol) was dissolved in dry cyclohexylamine (0.133 g, 1.34 mmol) at 0 °C, and the reaction mixture was allowed to warm to room temperature overnight. After this time, the reaction mixture was diluted with Et_2O, and solvent was removed under reduced pressure to give crude imine **4.31** as a deep orange oil (0.145 g, 92%). ^{1}H NMR analysis indicated that this product contained small amounts of starting material and an unidentified side product, and it was used without purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00-1.90 [m, 11H, $\mathbf{H}_{11}C_6N$=CH], 2.27-2.33 [m, 2H, H-3], 2.58-2.66 [m, 2H, H-2], 3.45-3.51 [m, 2H, H-4], 3.80 [s, 3H, $OCH_2ArOC\mathbf{H}_3$], 4.43 [s, 2H, $OC\mathbf{H}_2ArOCH_3$], 6.87 [d, 2H, J = 8.5 Hz, Ar**H**], 7.25 [d, 2H, J = 8.5 Hz, Ar**H**], 7.66-7.68 [m, 1H, $\mathbf{H}_{11}C_6N$=C**H**].

Methyl 4-(benzyloxy)butanoate 4.40

4.40

To a mechanically stirred solution of γ-butyrolactone (15.0 mL, 0.195 mol) and benzyl bromide (83.0 mL, 0.700 mol) in dry toluene (300 mL) in a three-necked round-bottom flask was added crushed potassium hydroxide (50.4 g, 0.884 mol). The resulting mixture was refluxed for 3 d, and then cooled to room temperature and allowed to stand for 1 d. After this time, the mixture was treated with Et_2O (1 x 300 mL) and H_2O (1 x 200 mL), and the organic layer was separated. The aqueous phase was extracted with Et_2O (x 3), and the combined

organic extracts were used as described below. The aqueous phase was cooled to 0 °C and slowly acidified with 3 mol L^{-1} H_2SO_4. The acidic wash was extracted with Et_2O (x 3), and solvent was removed under reduced pressure to give a first batch of crude 4-(benzyloxy)butanoic acid as a colourless oil (26.8 g).

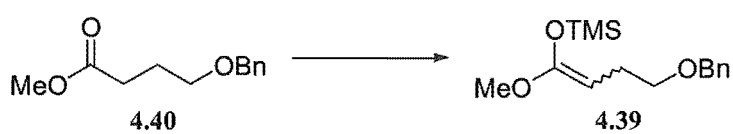
To the organic extracts from above was added H_2O (80 mL) and crushed potassium hydroxide (28.8 g, 0.500 mol), and the mixture was refluxed for 1 d. After this time, the reaction mixture was diluted with H_2O and extracted with Et_2O (x 3). The aqueous phase was cooled and acidified as above, and extracted with Et_2O (x 3). The organic extracts were combined, and solvent was removed under reduced pressure to give a second batch of crude 4-(benzyloxy)butanoic acid as a colourless oil (2.01 g). The two batches of crude 4-(benzyloxy)butanoic acid were combined (28.80 g, 76%), a sample was analysed by ^{1}H NMR spectroscopy (generating data which compared well with that reported for this compound by Leahy *et al.*[209]), and this material was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96 [m, 2H], 2.48 [m, 2H], 3.53 [m. 2H], 4.50 [s, 2H], 7.20-7.40 [m, 5H].

To a solution of crude 4-(benzyloxy)butanoic acid (1.80 g, 9.24 mmol) in dry MeOH (20 mL) was added two drops of concentrated H_2SO_4, and the mixture was refluxed for 12 h. After this time, the reaction mixture was cooled to room temperature, neutralised with saturated aqueous $NaHCO_3$ solution, diluted with H_2O, and extracted with EtOAc (x 3). Solvent was removed under reduced pressure, and the crude residue was purified by flash chromatography on silica gel, eluting with 40% EtOAc:petroleum ether, to give ester **4.40** as a colourless oil (0.385 g, 20%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92-1.96 [m, 2H, H-3], 2.41-2.46 [m, 2H, H-2], 3.48-3.53 [m, 2H, H-4], 3.65 [s, 1H, **H_3**CO], 4.49 [s, 2H, OC**H_2**Ar], 7.20-7.40 [m, 5H, Ar**H**].

Methyl (*Z*)/(*E*) 1-(trimethylsilyloxy)-4-(benzyloxy)but-1-eneoate 4.39

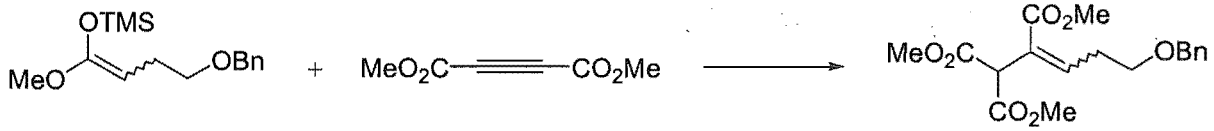


4.40 **4.39**

A solution of ester **4.40** (2.25 mg, 10.82 mmol) in dry THF (10 mL) was added dropwise to a solution of LDA (10.82 mmol) in THF at 0 °C, and the mixture was stirred at this temperature for 0.5 h. After this time, TMSCl (4.76 mL, 37.87 mmol) was added dropwise, and the mixture was allowed to warm to room temperature over 0.5 h. After this time, diisopropylamine (0.758 mL, 5.41 mmol) was added, and the mixture stirred for a further 0.25 h. After this time, the mixture was filtered, and solvent was removed from the filtrate under reduced pressure to give silyl ketene acetal **4.39** as a colourless oil (3.37 g, 80%). Comparison of the integral ratios for H-3 in the ^{1}H NMR spectrum of this compound indicated it comprised a ~1.3:1.0 mixture of **4.39** and starting material, and it was used without purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24-2.31 [m, 2H, H-3], 3.39-3.42 [m, 2H, H-4], 3.46-3.52 [m, 1H, H-2], 3.65 [s, 3H, **H**$_3$CO], 4.49-4.51 [m, 2H, OC**H**$_2$Ar], 7.20-7.30 [m, 5H, Ar**H**].

Methyl (*Z*)/(*E*)-2,3-di(methoxycarbonyl)-6-(benzyloxy)hex-3-eneoate 4.38



4.39 **4.38**

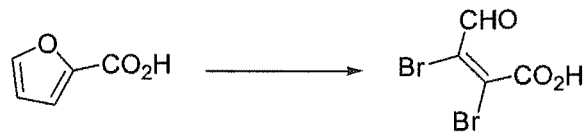
To a stirred solution of silyl ketene acetal **4.39** (340 mg, 1.21 mmol) and dimethyl acetylenedicarboxylate (74 μL, 0.61 mmol) in dry CCl_4 (1.5 mL) at 0 °C was added $ZrCl_4$ (14 mg, 0.61 mmol), and the resulting solution was refluxed for 12 h. After this time, the reaction mixture was cooled to room temperature, diluted with H_2O, and extracted with Et_2O (x 3). Solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 25% EtOAc:petroleum ether, to give ester **4.38** as a yellow oil (42 mg, 10%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.92 [dd, J = 13.2, 6.5 Hz, H-5], 3.59 [t, J = 6.5 Hz, H-6], 3.75 [s, 9H, CO_2CH_3], 4.47 [s, 1H, H-2], 4.52 [s, 2H, H-6], 6.32 [t, J = 6.7 Hz, H-4], 7.20-7.40 [m, 5H, ArH].

^{13}C NMR (75 MHz, $CDCl_3$): δ 30.4, 51.8, 52.7, 55.4, 68.7, 72.6, 72.9, 125.7, 127.5, 128.2, 128.3, 138.2, 145.1, 166.0, 168.2.

HRMS: Calcd. for $C_{17}H_{19}O_6$ ($M^+ - OCH_3$) 319.1182, found 319.1182.

Mucobromic acid 4.51



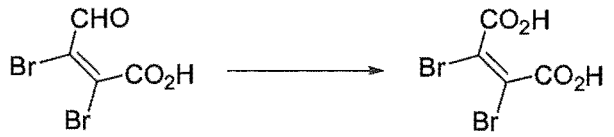
4.51

Mucobromic acid (**4.51**) was prepared from 2-furoic acid by the literature method reported by Allen and Spangler.[219]

Yield: white solid, 80%.

MP: 120-121 °C (lit. 122-124 °C).[219]

(*Z*)-2,3-Dibromo-but-2-enedioic acid 4.68



4.51 **4.68**

Diacid **4.68** was prepared from **4.51** by the literature method reported by Salmony and Simonis.[220]

Yield: white solid, 100%.

MP: 124 °C (lit. 123-124 °C).[220]

Dimethyl (*Z*)-2,3-dibromo-but-2-enedioate 4.67

4.68 **4.67**

Dry MeOH (28 mL) was added *via* syringe to a slurry of acid **4.68** (11.77 g, 42.98 mmol) in thionyl chloride (13 mL). The resulting pale yellow solution was refluxed for 12 h (with a reflux condenser fitted with a $CaCl_2$ drying tube). After this time, the reaction mixture was cooled to room temperature, and solvent and excess thionyl chloride were removed under reduced pressure. The residue was re-dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution. Solvent was removed under reduced pressure, and the crude residue was purified by bulb-to-bulb distillation to give diester **4.67** as a pale yellow oil (7.76 g, 60%). Due to the lack of physical and spectroscopic data in the literature for this known compound,[240] it was fully characterised.

BP: 160-165 °C @ 2.2 mmHg.

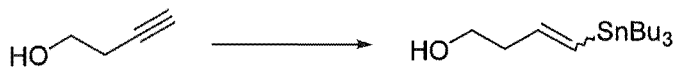
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.86.

^{13}C NMR (75 MHz, $CDCl_3$): δ 53.8, 124.9, 162.5.

IR (film): 1740 cm^{-1}.

HRMS: Calcd. for $C_6H_6O_4{}^{79}Br_2$ (M^+) 299.8633, found 299.8633.

***E/Z*-4-(Tributylstannyl)but-3-en-1-ol 4.69**



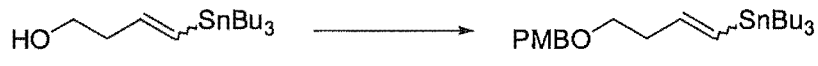
4.69

A mixture of 3-butyn-1-ol (1.26 mL, 16.70 mmol), tributyltin hydride (6.73 mL, 25.00 mmol), and AIBN (85 mg, 0.52 mmol) was stirred at 95 °C for 16 h. After this time, the reaction mixture was cooled to room temperature, and purified by flash chromatography on silica gel, eluting with 5% EtOAc:pentane, to give stannane **4.69** as a pale yellow oil (4.78 g, 79%). By comparison of the integrals for the olefinic protons in the ^{1}H NMR spectrum of **4.69**, the (*E*):(*Z*) ratio was found to be ~4:1, and this mixture was used without attempts at separation. The ^{1}H NMR data for (*E*)-**4.69** was in good agreement with that reported by Pilli *et al.* (who did not report mass spectral data for this compound).[221]

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 [m, 15H, $Sn(C_2H_4C\mathbf{H_2}C\mathbf{H_3})_3$], 1.30 [m, 6H, $Sn(CH_2C\mathbf{H_2}C_2H_5)_3$], 1.49 [m, 6H, $Sn(C\mathbf{H_2}C_3H_7)_3$], 2.32 [m, 2H, $HOCH_2C\mathbf{H_2}$ (*Z*-isomer)], 2.42 [m, 2H, $HOCH_2C\mathbf{H_2}$ (*E*-isomer)], 3.68 [m, 2H, $HOC\mathbf{H_2}$], 5.93 [dt, J = 19.0, 6.3 Hz, C**H**=CHSn (*E*-isomer)], 6.01 [d, J = 12.7 Hz, 1H, CH=C**H**Sn (*Z*-isomer)], 6.06 [d, J = 19.0 Hz, CH=C**H**Sn (*E*-isomer)], 6.51 [dt, J = 12.7, 6.8 Hz, 1H, C**H**=CHSn (*Z*-isomer)].

HRMS: Calcd. for $C_{12}H_{25}O^{120}Sn$ (M^+ – Bu) 305.0941, found 305.0942.

E/Z-1-(Tributylstannyl)-4-(methoxybenzyl)oxybut-1-ene 4.70



4.69 **4.70**

A solution of PMB-Br (291 mg, 1.45 mmol) in dry THF (3 mL) was added *via* cannula to a stirred solution of stannane **4.69** (475 mg, 1.32 mmol) in dry THF (3 mL). The mixture was cooled to 0 °C, and NaH (74 mg of 60% dispersion in hexanes, 1.84 mmol) was added. After stirring for 5 min at 0 °C, the mixture was allowed to warm to room temperature and stirred for 20 h. After this time, the reaction mixture was diluted with H_2O and extracted with EtOAc (x 4). Solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 2% EtOAc:petroleum ether, to give stannane **4.70** as a colourless oil (472 mg, 75%). By comparison of the integrals for the olefinic protons in the ^{1}H NMR spectrum of **4.70**, the (*E*):(*Z*) ratio was found to be ~4:1. This mixture was used without attempts at separation.

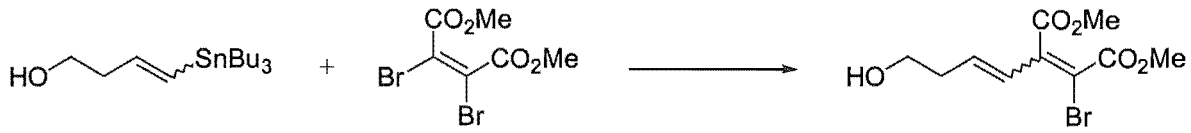
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 [m, 15H, $Sn((CH_2)_2C\mathbf{H_2}C\mathbf{H_3})_3$], 1.30 [m, 6H, $Sn(CH_2C\mathbf{H_2}C_2H_5)_3$], 1.49 [m, 6H, $Sn(C\mathbf{H_2}C_3H_7)_3$], 2.35 [m, 2H, $ArCH_2OCH_2C\mathbf{H_2}$ (*Z*-isomer)], 2.45 [m, 2H, $ArCH_2OCH_2C\mathbf{H_2}$ (*E*-isomer)], 3.47 [t, J = 7.0 Hz, 2H, $ArCH_2OC\mathbf{H_2}CH_2$ (*Z*-isomer)], 3.49 [t, J = 7.0 Hz, 2H, $ArCH_2OC\mathbf{H_2}CH_2$ (*E* isomer)], 3.80 [s, 3H, $\mathbf{H_3}COAr$], 4.45 [s, 2H, $ArC\mathbf{H_2}OCH_2CH_2$], 5.98 [m, 3H, CH=C**H**Sn (*E*- and *Z*-isomers) and C**H**=CHSn (*E*-

isomer)], 6.52 [dt, J = 12.2, 7.3 Hz, 1H, C**H**=CHSn (*Z*-isomer)], 6.87 [m, 2H, Ar**H**], 7.26 [m, 2H, Ar**H**].

^{13}C NMR (75 MHz, $CDCl_3$): δ 9.4, 13.7, 27.3, 29.1, 38.2, 55.2, 69.4, 69.7, 72.5, 72.6, 113.7, 129.2, 129.9, 130.62, 130.65, 144.7, 145.4, 159.1.

HRMS: Calcd. for $C_{20}H_{33}O_2{}^{120}Sn$ (M^+ – Bu) 425.1502, found 425.1503.

Methyl (2*E*, 4*E*)-2-bromo-3-methoxycarbonyl-7-hydroxyhepta-2,4-dienoate and Methyl (2*E*, 4*Z*)-2-bromo-3-methoxycarbonyl-7-hydroxyhepta-2,4-dienoate 4.71



4.69 **4.67** **4.71**

Pd_2dba_3 (22 mg, 0.02 mmol), $AsPh_3$ (29 mg, 0.10 mmol) and CuI (45 mg, 0.24 mmol) were added sequentially to a stirred solution of bromide **4.67** (72 mg, 0.24 mmol) in dry NMP (2 mL). A solution of stannane **4.69** (129 mg, 0.36 mmol) in dry NMP (2 mL) was then added *via* cannula. The mixture was deoxygenated by four freeze-pump-evacuate cycles and stirred at 80 °C in the dark for 20 h. After this time, the reaction mixture was cooled to room temperature, diluted with H_2O, and extracted with EtOAc (x 4). Solvent was removed under reduced pressure, and the residue (which ^{1}H NMR analysis showed was a complex mixture of several products) was purified by flash chromatography on silica gel, eluting with 50% EtOAc:petroleum ether, to give **4.71** as a pale yellow viscous oil (6 mg, 9%). By comparison of the integrals for the olefinic protons in the ^{1}H NMR spectrum of **4.71**, the (*E*):(*Z*) ratio was found to be ~4:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34 [m, $HOCH_2C\mathbf{H}_2$ (*Z*-isomer)], 2.50 [m, 2H, $HOCH_2C\mathbf{H}_2$, (*E*-isomer)], 3.70 [t, J = 6.3 Hz, 2H, $HOC\mathbf{H}_2CH_2$ (*Z* isomer)], 3.76 [t, J = 6.3 Hz, 2H, $HOC\mathbf{H}_2CH_2$ (*E* isomer)], 3.80 [s, 3H, $BrC{=}CCO_2C\mathbf{H}_3$ (*Z* isomer)], 3.82 [s, 3H, $BrC{=}CCO_2C\mathbf{H}_3$ (*E* isomer)], 3.87 [s, 3H, $BrCCO_2C\mathbf{H}_3$ (*Z* isomer)], 3.88 [s, 3H, $BrCCO_2C\mathbf{H}_3$ (*E* isomer)], 5.98 [dt, J = 11.2, 7.6 Hz, 1H, $CH_2C\mathbf{H}$=CH (*Z* isomer)], 6.17 [dt, J = 15.6, 7.3 Hz,

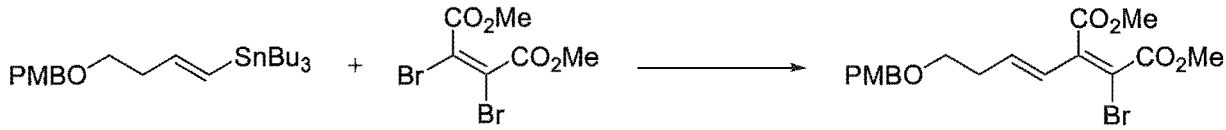
1H, CH_2CH=CH (*E* isomer)], 6.24 [d, J = 11.2 Hz, 1H, CH_2CH=C**H** (*Z* isomer)], 6.67 [d, J = 15.6 Hz, 1H, CH_2CH=C**H** (*E* isomer)].

^{13}C NMR (75 MHz, $CDCl_3$): δ 36.9, 53.0, 53.7, 61.1, 112.8, 128.7, 133.5, 141.1, 144.2, 162.8, 166.9.

IR (film): 1720, 1736, 3413, 3470 cm^{-1}.

HRMS: Unobtainable at time of writing due to coincidence of major fragment ion with that of reference compound.

Methyl (2*E*, 4*E*)-2-bromo-3-methoxycarbonyl-7-[4-(methoxybenzyl)oxy]hepta-2,4-dienoate 4.72



4.70 **4.67** **4.72**

Pd_2dba_3 (9 mg, 0.01 mmol), $AsPh_3$ (29 mg, 0.01 mmol) and CuI (19 mg, 0.10 mmol) were added sequentially to a stirred solution of bromide **4.67** (30 mg, 0.10 mmol) in dry NMP (2 mL). A solution of stannane **4.70** (71 mg, 0.15 mmol) in dry NMP (2 mL) was then added *via* cannula. The mixture was deoxygenated by four freeze-pump-evacuate cycles and then stirred at 80 °C in the dark for 40 h. After this time, the reaction mixture was cooled to room temperature, diluted with H_2O, and extracted with EtOAc (x 4). Solvent was removed under reduced pressure, and the residue (which ^{1}H NMR analysis showed was a complex mixture of several products) was purified by flash chromatography on silica gel, eluting with 25% EtOAc:petroleum ether, to give (*E*)-**4.72** as a pale yellow viscous oil (3 mg, 7%).

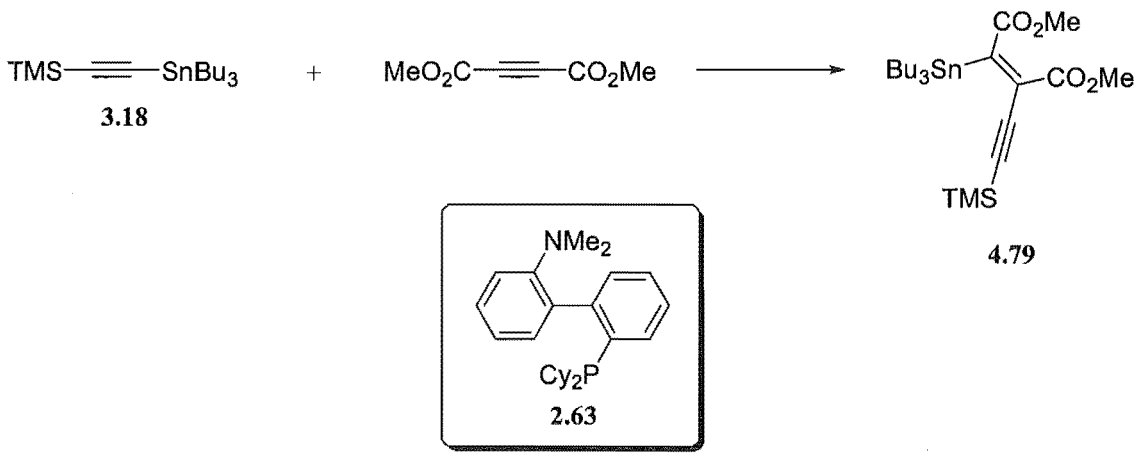
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.53 [m, $ArCH_2OCH_2CH_2$], 3.55 [t, J = 6.5 Hz, 2H, $ArCH_2OCH_2CH_2$], 3.80 [s, 3H, H_3COAr], 3.83 [s, 3H, $BrC{=}CCO_2CH_3$], 3.88 [s, 3H, $BrCCO_2CH_3$], 4.45 [s, 2H, $ArCH_2OCH_2CH_2$], 6.19 [dt, J = 16.1, 6.8 Hz, 1H, CH_2CH=CH], 6.65 [d, J = 16.1 Hz, 1H, CH_2CH=C**H**], 6.88 [m, 2H, Ar**H**], 7.24 [m, 2H, Ar**H**].

^{13}C NMR (75 MHz, $CDCl_3$): δ 34.1, 52.9, 53.6, 55.3, 68.1, 72.7, 113.8, 128.1, 129.3, 130.1, 132.8, 141.8, 142.3, 144.6, 159.2, 166.9.

IR (film): 1717, 1738 cm^{-1}.

HRMS: Calcd. for $C_{18}H_{21}O_6{}^{79}Br$ (M^+) 412.0521, found 412.0522.

Methyl (2*E*)-2-(tributylstannyl)-3-methoxycarbonyl-5-(trimethylsilyl)pent-2-en-4-ynoate 4.79



Dimethyl acetylenedicarboxylate (0.099 mL, 0.81 mmol) was added *via* syringe to a solution of 2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl (**2.63**) [5 mg, 0.01 mmol], and π-allylpalladium chloride dimer (2 mg, 0.01 mmol) in dry THF (3 mL), and the resulting solution was deoxygenated by four freeze-evacuate cycles. Tributyl(trimethylsilylethynyl)tin (**3.18**) [104 mg, 0.27 mmol] was then added *via* syringe, and the mixture was stirred at 50 °C for 12 h. After this time, the solvent was removed under reduced pressure, and the residue (which ^{1}H NMR analysis showed was a complex mixture of several products) was purified by flash chromatography on silica gel, eluting with 5% EtOAc:petroleum ether, to give enyne **4.79** as a yellow oil (7 mg, 5%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.23 [s, 9H, $Si(\mathbf{CH_3})_3$], 0.90 [t, J = 7.3 Hz, 9H, $Sn(C_3H_6\mathbf{CH_3})_3$], 1.15 [m, 6H, $Sn(C_2H_4\mathbf{CH_2}CH_3)_3$], 1.32 [m, 6H, $Sn(CH_2\mathbf{CH_2}C_2H_5)_3$], 1.52 [m, 6H, $Sn(\mathbf{CH_2}C_3H_7)_3$], 3.76 [s, 6H, $\mathbf{H_3}CO_2C(R)C{=}C(Sn)CO_2\mathbf{CH_3}$].

^{13}C NMR (75 MHz, $CDCl_3$): δ -0.4, 11.0, 13.6, 27.2, 28.7, 51.6, 52.7, 99.0, 101.7, 124.9, 162.6, 164.4, 171.9.

IR (film): 1717, 1734 cm^{-1}.

HRMS: Calcd. for $C_{19}H_{33}O_4{}^{28}Si^{120}Sn$ (M^+ – Bu) 473.1169, found 473.1170.

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