Studies Towards a Total Synthesis of Colchicine

A Thesis Presented by

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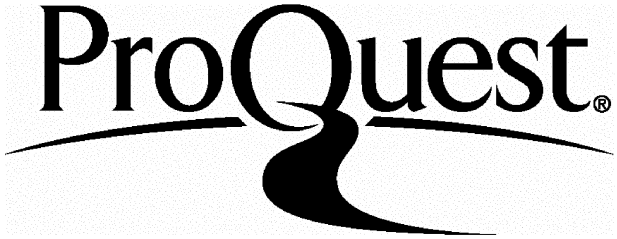

ABSTRACT

This thesis describes a novel strategic approach towards the synthesis of colchicine which involves the use of the transition metal catalysed [5+2] cycloaddition reaction. The thesis is divided into three chapters.

The first introductory chapter presents an overview of colchicine, with particular attention being focused on the isolation, structure, biological properties and biosynthesis of the natural product, together with a thorough account of previous synthetic approaches. Moreover, since the key reaction in our synthetic approach involves the exploitation of the transition metal catalysed [5+2] cycloaddition reaction, a detailed review into the recent developments and uses of this reaction is presented.

In the second chapter, synthetic approaches are described for the preparation of two structurally different alkynyl-vinylcyclopropanes which are required for exploitation of the intramolecular variant of the transition metal mediated [5+2] cycloaddition, this strategy being selected to achieve concomitant formation of both seven-membered rings and also avoiding the problematic methylation of a free tropolone unit. Detailed accounts of the successful synthetic routes to both of these potential cyclisation precursors are presented and discussed. In the event however, formation of the tricyclic skeleton by a variety of metal catalysed [5+2] cycloaddition protocols proved elusive.

The third chapter provides a formal description of the experimental procedures and results obtained.

CONTENTS

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ABBREVIATIONS

Ac	Acetyl
AIBN	α-Azo *iso*-butyronitrile
aq.	Aqueous
Ar	Aromatic
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
b.p.	boiling point
br	broad
Bu	butyl
CBS	Corey-Bakshi-Shibita
CI	Chemical ionisation
cm^{-1}	Wavenumbers
Cp	η^5-Cyclopentadienyl
d	Doublet
DCC	*N,N*-Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
dd	Double doublet
ddd	Double double doublets
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
dec.	decomposes
DIBALH	Di*iso*butylaluminium hydride
DIPEA	Di*iso*propylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dt	Double triplet
Et	Ethyl
Ether	Diethyl ether

FAB	Fast atom bombardment
FT-IR	Fourier transform infra-red
g	Grams
h	Hour
hν	Irradiation of unspecified wavelength
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
HRMS	High resolution mass spectrometry
Im	Imidazole
^{i}Pr	*iso*-Propyl
IR	Infra-red
J	Coupling constant
LDA	Lithium di*iso*propylamide
LHMDS	Lithium hexamethyldisilazane
lit.	Literature value
LRMS	Low resolution mass spectrometry
m	Meta
M	Molar concentration
m	Multiplet
Me	Methyl
min	minutes
ml	Millilitres
mmHg	Millimetres of mercury
mol%	Molar percentage
mol	moles
mmol	millimoles
m.p.	Melting point
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
o	Ortho
p	Para
Pd/C	Palladium on carbon

PE	Petroleum ether
Ph	Phenyl
ppm	Parts per million
py	Pyridine
q	Quartet
R_f	Retention factor
rt	Room temperature
s	Singlet
sat.	Saturated
t	Triplet
TBDMS	*tert*-Butyldimethylsilyl
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDMSOTf	*tert*-Butyldimethylsilyl triflate
tert	Tertiary
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFE	Trifluoroethanol
THF	Tetrahydrofuran
tlc	Thin layer chromatography
TMS	Trimethylsilyl
TMSA	Trimethylsilylacetylene
TMSOTf	Trimethylsilyl triflate
TPAP	Tetra-*N*-propylammonium perruthenate
Ts	*p*-Toluenesulphonyl

CHAPTER ONE

INTRODUCTION

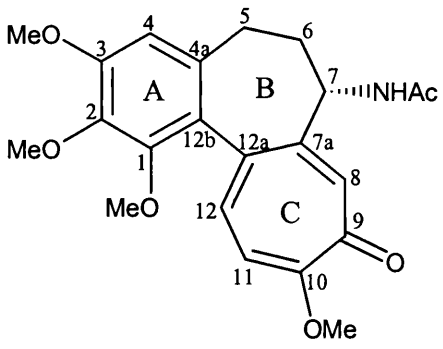
1.0 General Remarks

The present thesis is concerned with synthetic approaches to the synthesis of the natural product, colchicine **1**. The key objective in the synthetic strategy was to employ the transition metal catalysed [5+2] cycloaddition reaction to construct the two seven-membered rings in a single step. Accordingly, the introductory review is divided into two sections. The first part (section 1.1) describes the background to colchicine **1** and the previous synthetic approaches. The second part (section 1.2) consists of a review of the transition metal catalysed [5+2] cycloaddition reaction.

1.1 Colchicine

1.1.1 Isolation

Colchicine **1** has attracted widespread interest over the years due to its potential as an anti-cancer agent. It is the major alkaloid constituent of the autumn crocus, *Colchicum autumnale L.*, otherwise known as the common meadow saffron[1] and is found in all parts of the plant but its concentration is highest within the flowers.[2] The plant can be found in many areas of the Northern Hemisphere, including England and Northern Africa.



1

Figure 1.1

Colchicine **1** was first isolated in 1820 by Pelletier and Caventou,[3] but it was over a hundred years later before the unusual tropolone ring structure embedded within this molecule was predicted by Dewar[4] in 1945, and finally confirmed using X-ray studies by King *et al.*[5] in 1952. For over a decade after the discovery of colchicine **1**, it was believed to be the only active principle of *Colchicum*

autumnale. However, further studies resulted in the discovery of many new alkaloid constituents, with most of the structures now characterised and confirmed by partial synthesis.[6]

1.1.2 Structure

Colchicine **1** is a tricyclic compound with two mutually fused seven-membered rings (Figure 1.1). Ring A is aromatic with three methoxy groups, ring B is seven-membered with an acetamide functionality and ring C is troponoid. The presence of the tropolone ring allows its detection by UV absorption giving a characteristic signal at ~350 nm.

Colchicine **1** contains only one asymmetric centre at *C*-7, the absolute configuration of which was established by Corrodi and Hardegger[7,8] by ozonolysis to *N*-acetyl-L-glutamic acid. Thus it was concluded that natural (-)-colchicine **1** has the *S*-configuration at the stereogenic centre.

Natural (-)-colchicine **1** also possesses an axis of chirality. This is derived from the non-coplanar arrangement of the benzoid A-ring and the troponoidic C-ring. These are twisted at an angle of 53° with respect to one another (Figure 1.2). The acetamide substituent at *C*-7 prefers to adopt an equatorial position, which induces a counter-clockwise helicity in the two aromatic moieties. This is of major importance for understanding the biological properties of colchicine **1** as only the natural enantiomer binds to tubulin.[9]

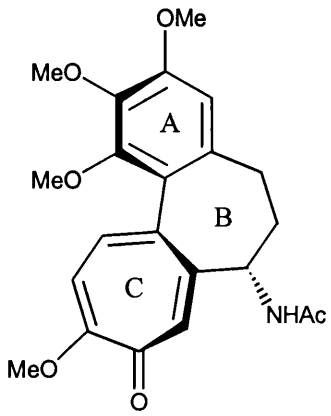
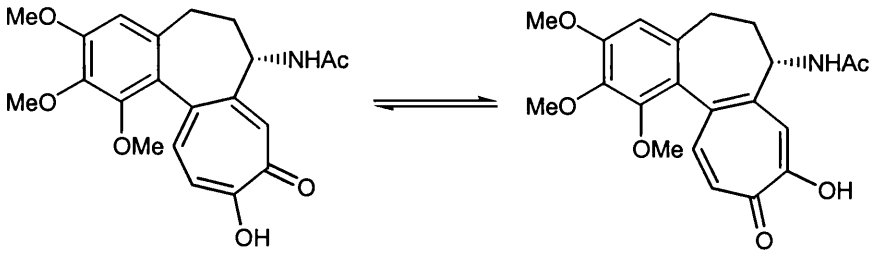


Figure 1.2

The helical configuration was first assigned by Detrich *et al.*[10] to be (*R*) but a few years later, Brossi and co-workers[11] assigned the configuration (*S*), by reference to the *Prelog* rules.[12] This assignment has since been used in the literature, although more recent studies[13] have revealed that an incorrect assignment was in fact made and the correct absolute configuration of natural (-)-colchicine **1** is as originally assigned, (*aR, 7S*).

1.1.3 Structural Analogues

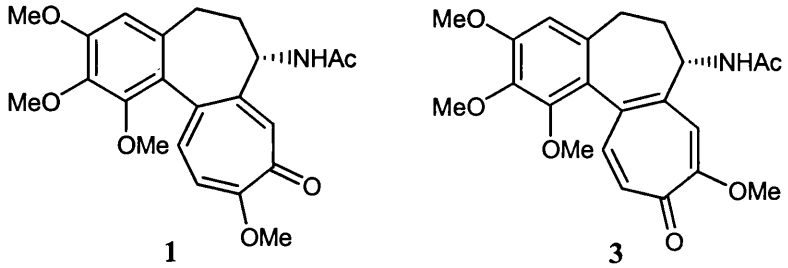
Colchiceine **2** is structurally very similar to colchicine **1**, the only difference being the existence of a free tropolonic ring in colchiceine **2**, as a result, it exists as two rapidly equilibrating tautomeric enol forms (Figure 1.3).



2

Figure 1.3

Colchiceine **2** was first discovered in 1833 by Geiger,[14] however at that time he believed it to be colchicine **1**. It was not until 1857 that Oberlin[15] showed, by mild acid hydrolysis of colchicine **1**, that the same crystalline solid as obtained by Geiger could be formed. This process is reversible and thus colchicine **1** can be re-obtained by methylation of colchiceine **2**, although due to the tautomeric isomerisation that occurs in colchiceine **2**, two isomers are obtained, colchicine **1** and isocolchicine **3** (Figure 1.4).



1 **3**

Figure 1.4

The structural chemistry of colchicine **1** and other related alkaloids has been investigated in great detail but is beyond the scope of this report, however the results are described in several reviews.[1,16,17]

1.1.4 Biological Properties

As early as Egyptian times crude extracts of *Colchicum autumnale* were used as a medical remedy,[18] and since the 16th century it has been used in the treatment of gout. Even now, colchicine **1** is employed extensively for this purpose but the precise mechanism by which it relieves the intense pain is not known. It is believed however, that it involves colchicine's major pharmacological action: its ability to bind to tubulin dimers.

Colchicine **1** is also a potential anti-cancer agent, as it possesses interesting features in arresting cell division during mitosis.[19] Dustin and Lits[20] first noted the specific ability of colchicine **1** to bring the process of cell division to an abrupt halt. This anti-mitotic effect is brought about by small amounts of colchicine **1** binding stoichiometrically to tubulin dimers, thereby preventing the formation of microtubules and consequently spindle formation. In preventing tubulin polymerisation, colchicine **1** has also been shown to inhibit catecholamine secretion from the adrenal medulla,[21] iodine secretion from the thyroid gland[22] and prolactin secretion from pituitary tumour cells in culture.[23]

Colchicine **1** is however, an intensely poisonous substance, which acts by slow absorption into the central nervous system and finally causes death by vasomotor paralysis.[24] Unfortunately, the doses required to induce the anti-mitotic effects are at or near to toxic levels, and as a result, this has prevented it being developed as an anti-cancer agent.

Many attempts have been made to discover more effective and less toxic analogues of colchicine **1**, with particular attention focusing on changes to the methoxy groups of the A and C rings, and the amide functionality of ring B. Colchiceine **2**, *N*-benzyldeacetylcolchiceine **4**, deacetylcolchicine **5** and 3-demethylthiocolchicine **6**, although considerably less toxic, showed only limited antimitotic effects.[25] Deacetyl-*N*-methylcolchicine **7**, on the other hand has not

only proven to be less toxic but has also been used in the treatment of chronic granulocytic leukaemia.[26]

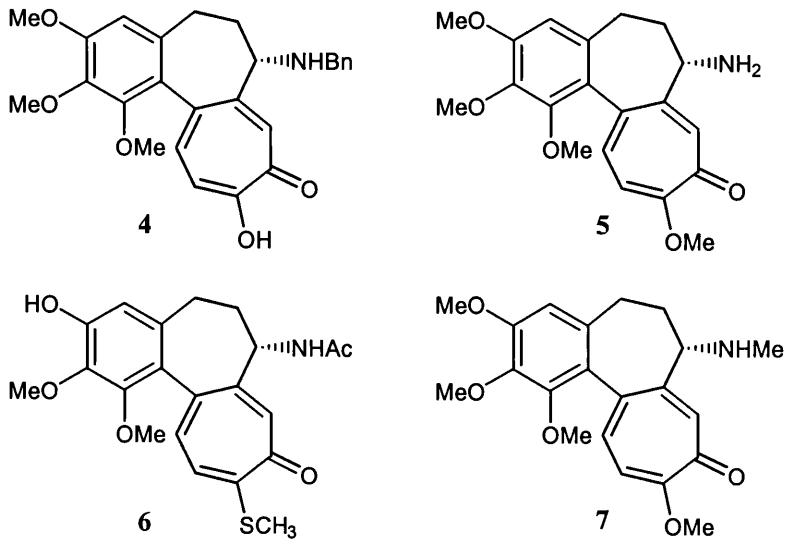


Figure 1.5

In this search for improved colchicine analogues, a number of useful, but often contradictory, qualitative structure-activity relationships have been postulated. Eigsti and Dustin[27] described the following then known requirements for the anti-mitotic activity of colchicine derivatives: 1) at least one methoxy group on ring A; 2) the amino group at *C*-7 should be acylated; 3) presence of a methoxy, alkylamino or alkylthio group on ring C. However, Schindler[28] later showed that the acylamino group at *C*-7 was in fact dispensable, and also noted the critical requirement for the carbonyl moiety of ring C.

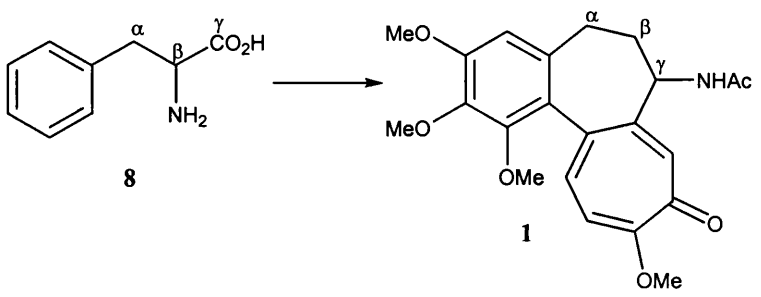
Based on these investigations, Brossi and co-workers carried out extensive structural and biological studies in order to further understand the effect of structural change on tubulin binding and toxicity levels. The structural effects were assessed by measuring the inhibition of tubulin polymerisation and binding of radiolabelled colchicine analogues to tubulin, and they concluded that although no clear relationship between anti-tubulin effect and anti-tumour activity existed, all colchicine analogues found active *in vivo*, did show good anti-tubulin activity.[29]

Unfortunately, no structural analogues of colchicine **1** have thus far provided the desired anti-mitotic effect in unison with the required decrease in toxicity. Although the high toxicity of colchicine **1** has limited its clinical applications, the compound is used extensively in agricultural[30] and biological research.[11]

1.1.5 Biosynthesis

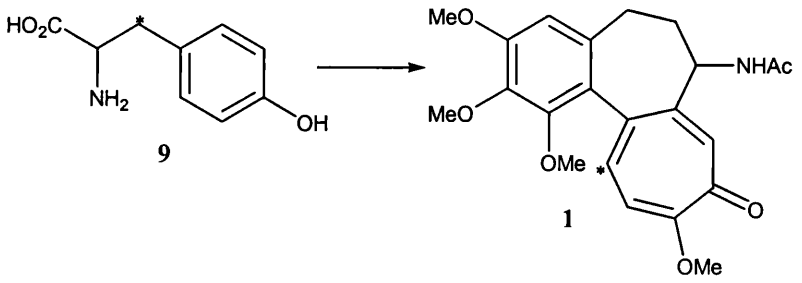
Colchicine **1** possesses many unusual structural features and as a result its mode of biosynthesis has generated a great deal of interest over several decades. For many years it was described as *'the odd man out'* as it appeared to be unrelated to other natural products. However, by studying the biosynthetic pathway used by the *Colchicum* species to build the tropolone natural product Battersby and co-workers[31] discovered that colchicine **1** is actually a substantially modified isoquinolone alkaloid.

Determination of the actual biosynthetic pathway was achieved by tracer experiments initially carried out by Leete[32] and Battersby.[33] These experiments involved feeding ^{14}C-labelled compounds to *Colchicum autumnale* plants and determining if and where the labelled fragments were incorporated into the produced colchicine **1**. For example when [3-^{14}C] phenylalanine **8** was fed to the plant, the labelled carbon was incorporated into colchicine **1**, almost entirely at *C*-5 (Scheme 1.1, *C*-α).[34] Similarly, [2-^{14}C] and [1-^{14}C] phenylalanine **8** were found to label specifically at carbon atoms *C*-6 and *C*-7, respectively (Scheme 1.1, *C*-β and *C*-γ).[33,35]



Scheme 1.1

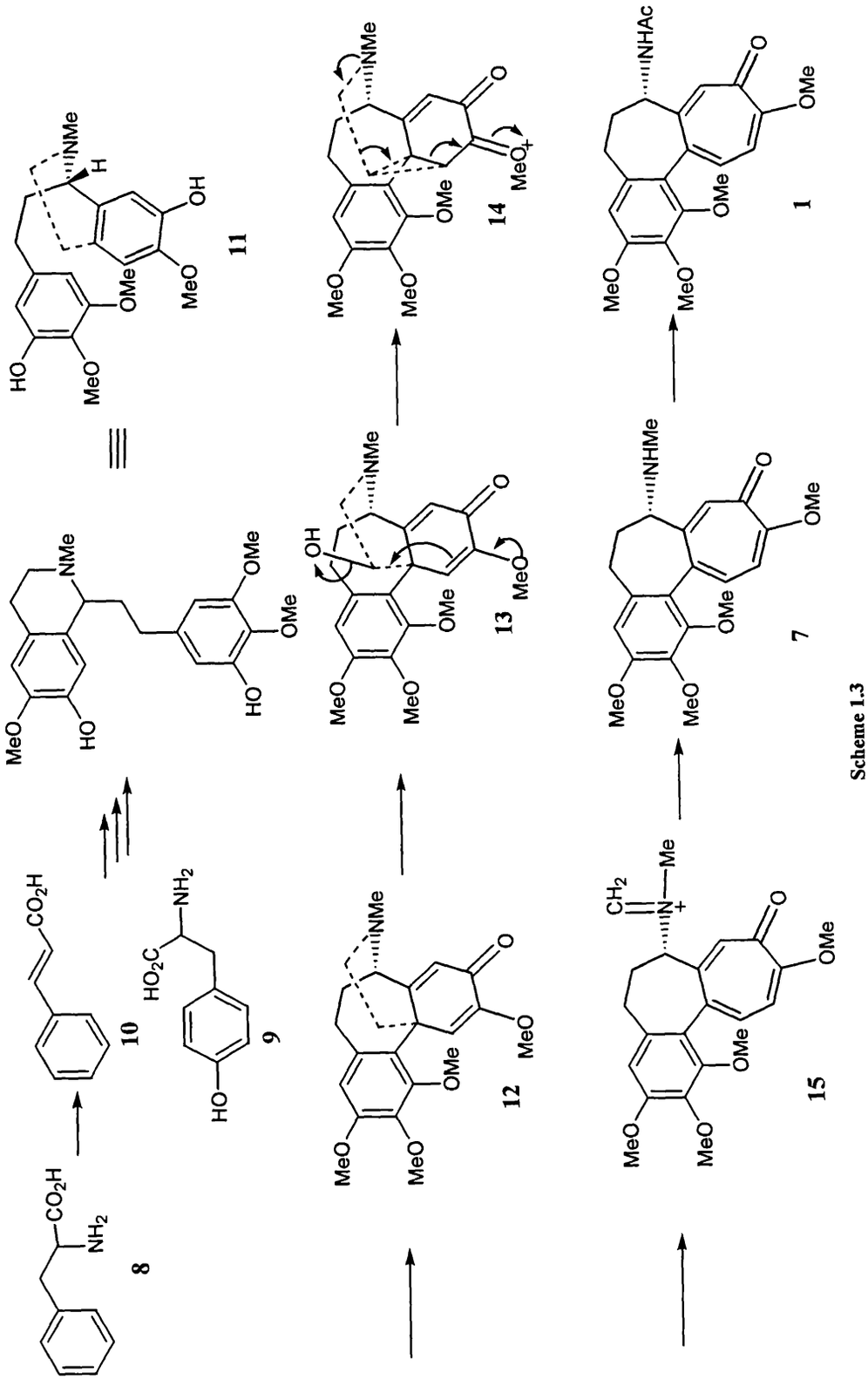
In addition, when [3-^{14}C] tyrosine **9** was fed to the plant, incorporation into colchicine **1** occurred at *C*-12 (Scheme 1.2) showing a specific affiliation to the tropolonic ring.[32,35]



Scheme 1.2

Accordingly, the basic building blocks are cinnamic acid **10** (from phenylalanine **8**) and tyrosine **9**, which together form ring A, carbon atoms *C*-5, *C*-6 and *C*-7 of ring B and *C*-12 of ring C. The tropolone ring is formed in the late stages of the biosynthesis *via* a ring expansion process.

It has been shown that the biosynthetic pathway occurs *via* the tetrahydroisoquinoline alkaloid, (*S*)-autumnaline **11** (Scheme 1.3).[31,36] *Para-para* phenolic oxidative coupling of the two aromatic rings of **11** occurs to produce a new carbon-carbon bond thus forming ring B. This is followed by *O*-methylation to generate a second important intermediate, *O*-methylandrocymbine **12.** Hydroxylation then leads to **13**, which provides a starting point for the ring expansion,[37] which occurs *via* homoallylic assistance from the methoxy group leading to cyclopropane **14**. Electron donation from the nitrogen lone pair then re-opens the cyclopropane ring to give the resulting imine **15**, which is readily hydrolysed thereby affording deacetyl-*N*-methylcolchicine **7**, the precursor to colchicine **1**.



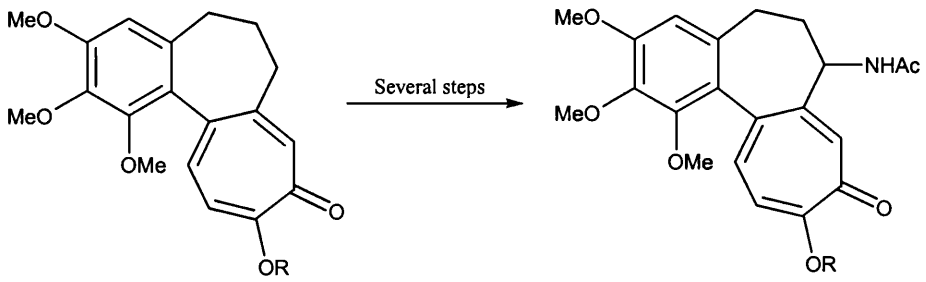
Scheme 1.3

Both ^{14}C-labelled autumnaline **11** and *O*-methylandrocymbine **12** have been employed in tracer experiments, thereby confirming their role as important biosynthetic intermediates.[36]

Although the major features of the biosynthetic pathway were described in the 1960's, Battersby and co-workers continued their research. The use of multiple labelling studies led them to understand in more detail specific parts of the biosynthesis. In particular they have discussed the phenolic oxidative coupling step,[38] the intermediates between *O*-methylandrocymbine **12** and colchicine **1**,[39] and the ring expansion processes.[38,40,41]

1.1.6 Previous Syntheses

For over four decades, colchicine **1** has been the target of an unusually large number of synthetic studies.[42-52] Despite its relatively straightforward appearance, it poses considerable synthetic challenges. The main challenge arises from the lack of methods available for synthesis of the tropolone ring. Most of the previous syntheses have proceeded through the intermediacy of deacetamidocolchicine **16**,[42-47] which can be subsequently converted to colchicine **1** by the introduction of an acetamido group at *C*-7 (Scheme 1.4).



16 (R=Me)
17 (R=H)

1 (R=Me)
2 (R=H)

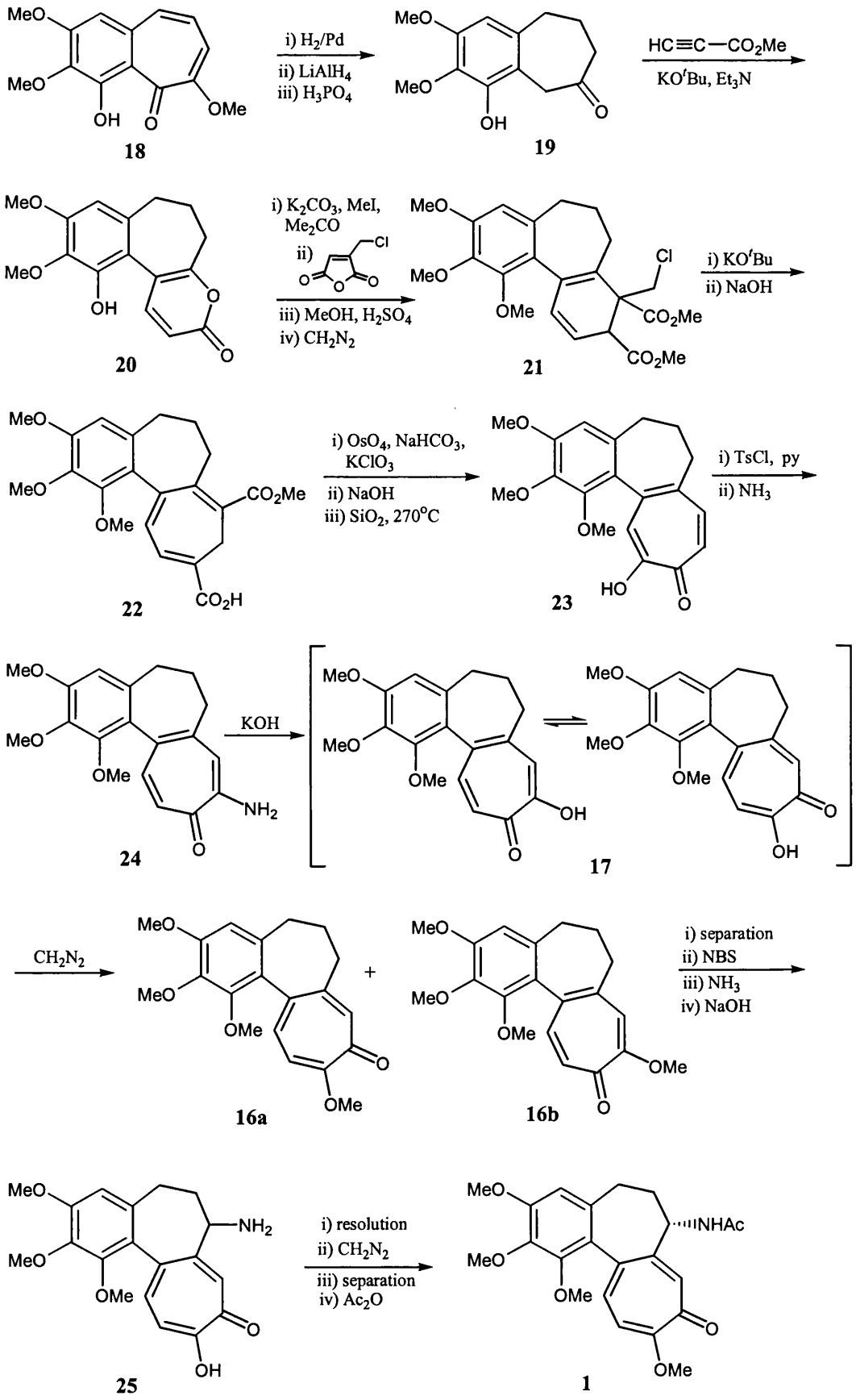
Scheme 1.4

Additionally, the majority of these syntheses[42-50] have proceeded *via* intermediates containing free tropolone ring systems e.g. colchiceine **2** and deacetamidocolchiceine **17**. As previously discussed, free tropolone rings exist as two rapidly interconverting isomers. Thus these syntheses suffer from lack of regiocontrol during the methylation procedures resulting in approximately half of

the material going to waste at a late stage. This situation has been referred to as the "diosphenol problem".

The first total synthesis was reported in 1961 by Eschenmoser[42] (Scheme 1.5). This synthesis began with readily available purpurogallin trimethyl ether **18**, which already possesses the carbon skeleton of the A and B rings of colchicine **1**. A series of selective reduction procedures provided the benzsuberone **19** which subsequently underwent a Michael reaction with methyl propiolate furnishing the pyrone **20**. Methylation of the phenol, and a Diels-Alder cycloaddition with α-chloromaleic anhydride followed by hydrolysis then esterification with diazomethane gave rise to the chlorinated tricycle **21**. Ring expansion was brought about by reaction with potassium *tert*-butoxide followed by selective hydrolysis of the less hindered ester group to form **22**, which contained the full carbocyclic framework of colchicine **1**.

Introduction of the carbonyl and hydroxyl groups at *C*-10 and *C*-11 respectively, was achieved by oxidation with osmic acid then subsequent hydrolysis and decarboxylation of the remaining ester group to give the tropolone **23**, but with the wrong regiochemical disposition of the oxygen atoms for colchicine **1**. Isomerisation was achieved by treatment with *p*-toluenesulfonyl chloride, then ammonia to afford intermediate **24**. Alkaline hydrolysis with potassium hydroxide replaced the amino group with a hydroxyl, furnishing the two tautomeric isomers of deacetamidocolchiceine **17**. Methylation of **17** with diazomethane gave two regioisomers of deacetamidocolchicine **16a** and **16b**. Only one isomer **16b**, had the correct electronic structure for allylic bromination with *N*-bromosuccinimide, which followed by treatment with ammonia and sodium hydroxide yielded the two tautomeric isomers of racemic deacetylcolchiceine **25**. Resolution using D-camphor-10-sulfonic acid, followed by *O*-methylation, separation and finally acetylation gave (-)-colchicine **1**.


MeO
MeO
OH
O
OMe
18
i) H2/Pd
ii) LiAlH4
iii) H3PO4
19
HC≡C—CO2Me
KO'Bu, Et3N
20
i) K2CO3, MeI, Me2CO
ii)
Cl
iii) MeOH, H2SO4
iv) CH2N2
21
i) KO'Bu
ii) NaOH
CO2Me
22
i) OsO4, NaHCO3, KClO3
ii) NaOH
iii) SiO2, 270°C
23
i) TsCl, py
ii) NH3
HO
24
KOH
NH2
17
CH2N2
16a
16b
i) separation
ii) NBS
iii) NH3
iv) NaOH
25
i) resolution
ii) CH2N2
iii) separation
iv) Ac2O
NHAc
1

Scheme 1.5

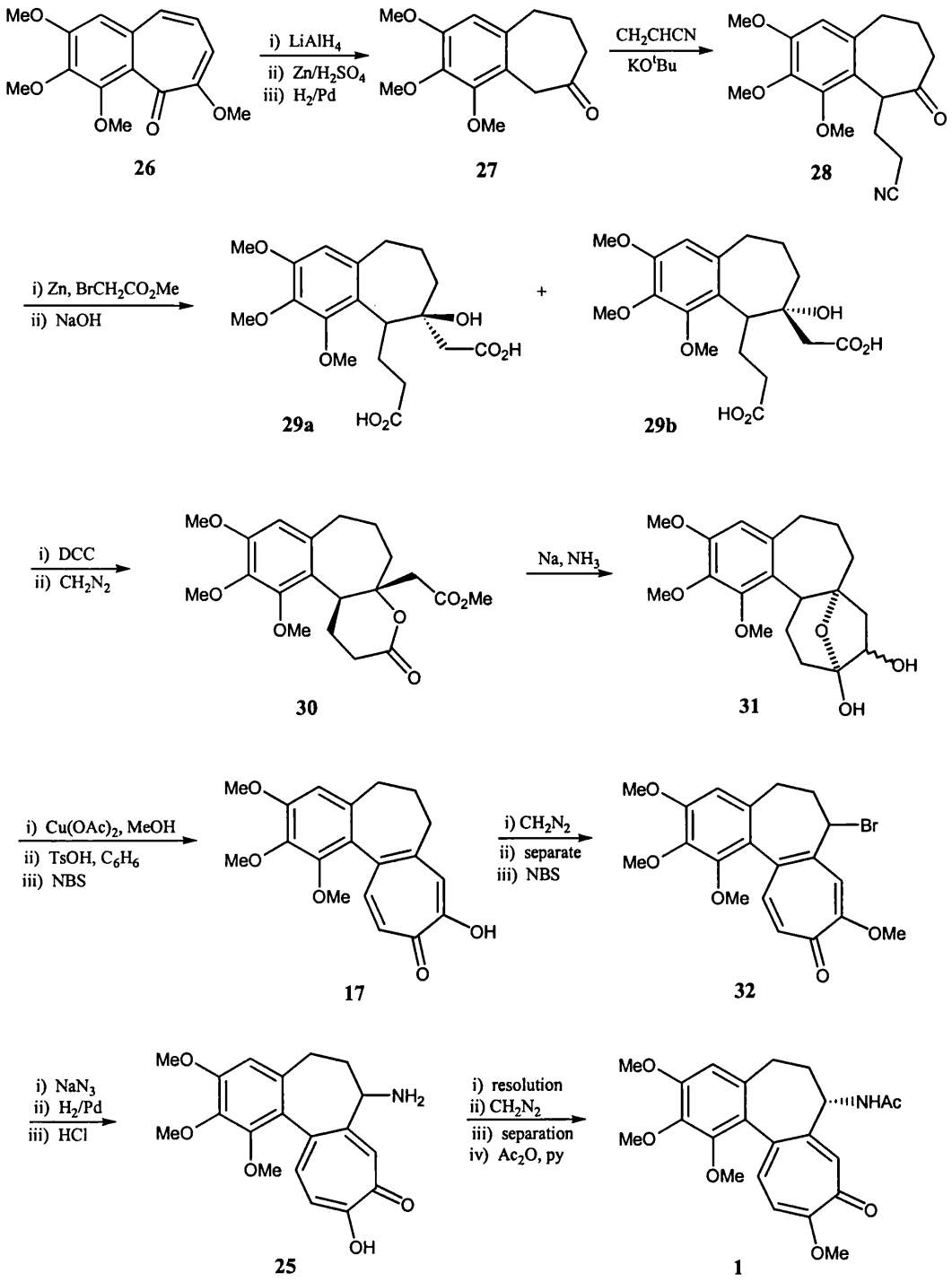
In this synthesis, Eschenmoser elegantly introduces the full carbocyclic framework of colchicine **1** at a very early stage. However, problems were encountered in obtaining the correct tropolone regioisomer, and in introducing the acetamido functionality, as on both occasions the synthesis proceeded *via* the formation of free tropolone systems, thereby requiring tedious separation on two different occasions.

Van Tamelen[43] reported another synthesis which was carried out at the same time as Eschenmoser's and followed a similar synthetic route (Scheme 1.6). A purpurogallin methyl ether **26** was once again employed as the starting material, and was reduced to afford the benzsuberone **27**. Alkylation of the benzsuberone **27** at *C*-10 was carried out by cyanoethylation, catalysed with potassium *tert*-butoxide to give the intermediate **28**. The remaining two carbon atoms were introduced *via* a Reformatsky reaction, and subsequent saponification of the product resulted in two dicarboxylic acid isomers **29a** and **29b**. Cyclisation was carried out on both isomers by reaction with *N,N*-dicyclohexylcarbodiimide and the remaining acid protected as its methyl ester. Two lactones were thus obtained, although unfortunately only the minor isomer **30** had the correct configuration for the next step, as a *trans*-fused arrangement is necessary to achieve a sufficiently close approach by the carbonyl group for formation of the seven-membered ring in **31** to proceed.

An acyloin reaction employing sodium and ammonia was used for the formation of the seven membered ring **31**, which was converted to the free tropolone by oxidation with copper acetate followed by treatment with *p*-toluenesulfonic acid and *N*-bromosuccinimide to give the two tautomeric isomers of deacetamidocolchiceine **17**. The remaining steps then resembled those described in Eschenmoser's synthesis, with the exception that instead of ammonia, an azide ion was used to introduce the nitrogen into the molecule, and the intermediate azide was then converted to the amine **25** by catalytic hydrogenation and subsequent acid hydrolysis.

This sequence employed by van Tamelen offered an advantage over the previous synthesis, in that it provided a more direct access to the tropolone with the correct

disposition of oxygen atoms. However, it still did not manage to avoid the problem of regiocontrol.



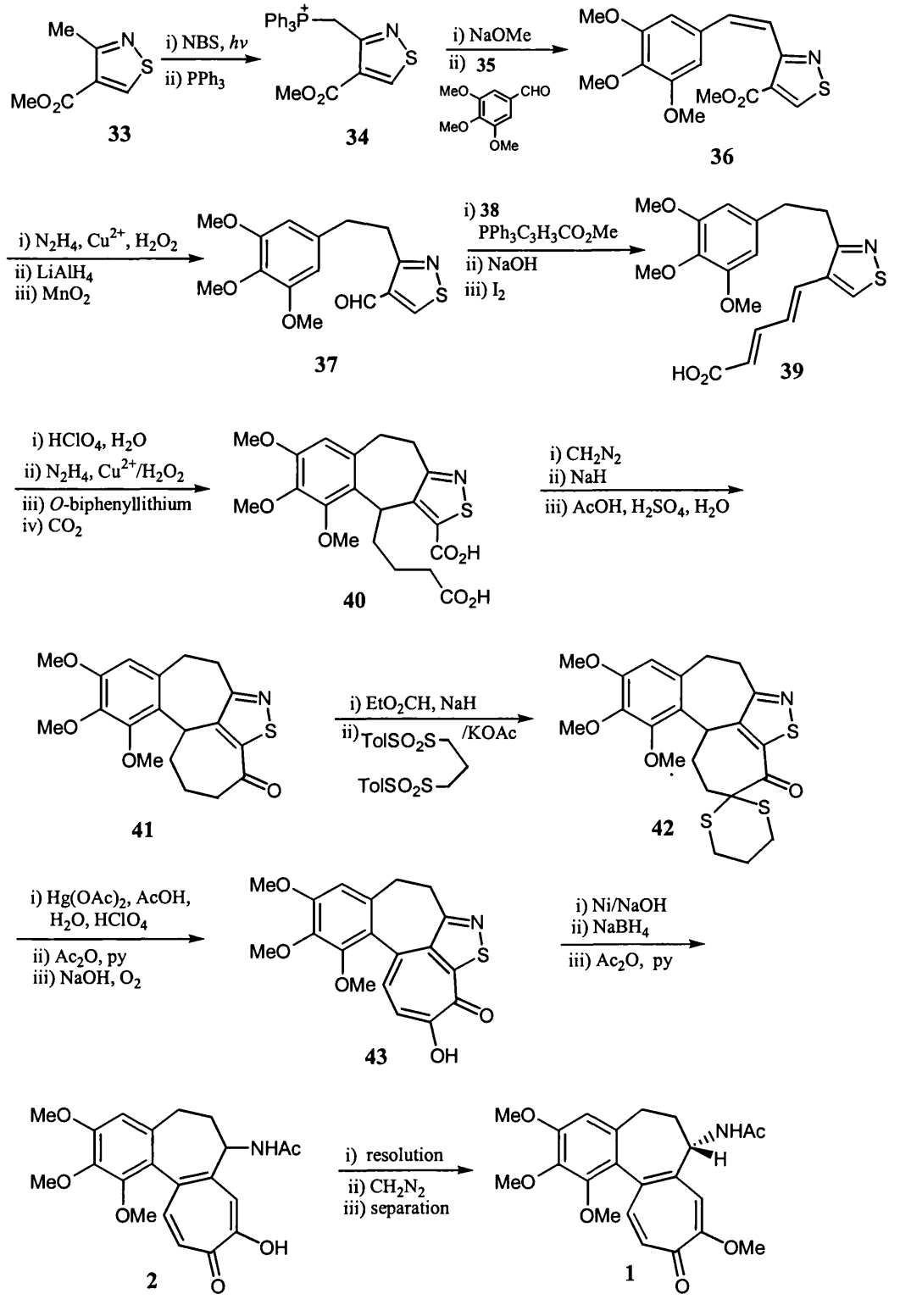
Scheme 1.6

Woodward[49] presented a much more elegant synthesis in 1963 which proved to be a complete departure from all previous syntheses (Scheme 1.7). His approach did not rely on the bromination-ammonolysis reaction for nitrogen insertion but instead, cunningly employed an isothiazole ring **33** in which the nitrogen atom was already present. The nitrogen is masked in the stable isothiazole system until it is released in the final step. In addition, the isothiazole ring **33** also served as a direct platform for the construction of rings B and C.

Reaction of the isothiazole **33** with *N*-bromosuccinimide followed by triphenylphosphine generated the phosphonium salt **34** which was coupled with 3,4,5-trimethoxybenzaldehyde **35** to give the resulting olefin **36**. A series of reduction and oxidation procedures led to the corresponding aldehyde **37**, which was used in a Wittig reaction with ylide **38**. Ester hydrolysis and subsequent iodine catalysed isomerisation of the double bonds gave the acid **39**, as the *trans* isomer. The diacid **40** was formed *via* an acid catalysed cyclisation reaction to form the B ring and subsequent introduction of a second carboxyl group on the thiazole ring was achieved using *O*-biphenyllithium and carbon dioxide. Ring C was constructed by a Dieckmann cyclisation followed by hydrolysis and decarboxylation to yield **41**. The carbon skeleton of colchicine **1** was now in place.

The ketone **41** was converted to the dithioketal **42**, using a new protocol and this product was treated with mercury (II) acetate to enable the formation of the second keto group. Treatment with acetic anhydride in pyridine, and then reaction with base in the presence of oxygen afforded the tropolone **43**. Reductive removal of the sulfur with Raney Nickel, saturation of the carbon-nitrogen double bond with sodium borohydride and finally acetylation of the free amine led to the formation of colchiceine **2**. Finally, methylation of the free tropolone and separation of the two isomers gave (-)-colchicine **1**.

Once again, although Woodward did not solve the issue of regiocontrol in the synthesis of colchicine **1**, he was able to reduce it to one instance.


i) NBS, hv
ii) PPh3
i) NaOMe
ii) 35
33
34
36
i) N2H4, Cu2+, H2O2
ii) LiAlH4
iii) MnO2
i) 38
PPh3C3H3CO2Me
ii) NaOH
iii) I2
37
39
i) HClO4, H2O
ii) N2H4, Cu2+/H2O2
iii) O-biphenyllithium
iv) CO2
i) CH2N2
ii) NaH
iii) AcOH, H2SO4, H2O
40
i) EtO2CH, NaH
ii) TolSO2S /KOAc
TolSO2S
41
42
i) Hg(OAc)2, AcOH,
H2O, HClO4
ii) Ac2O, py
iii) NaOH, O2
i) Ni/NaOH
ii) NaBH4
iii) Ac2O, py
43
i) resolution
ii) CH2N2
iii) separation
2
1

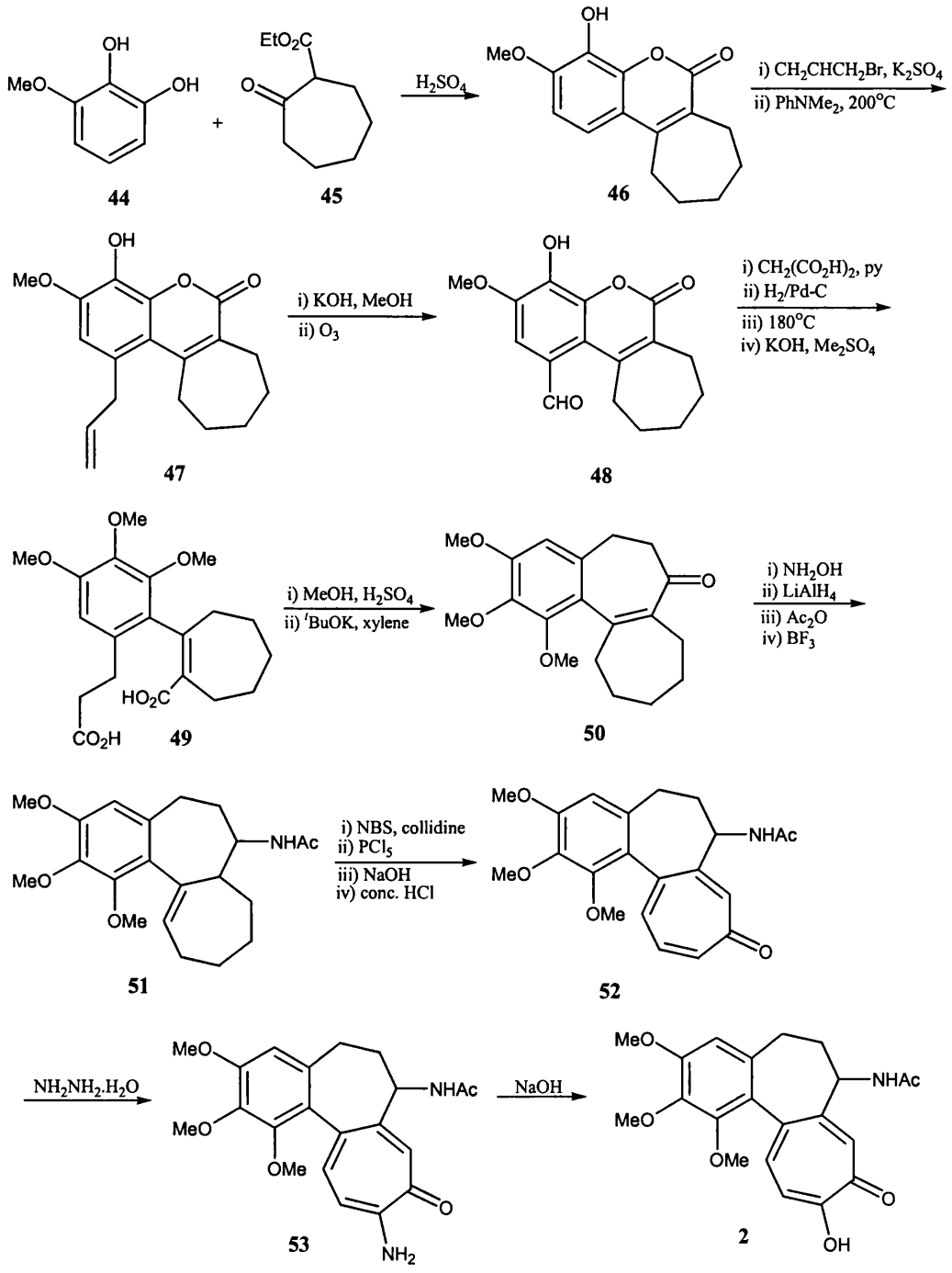
Scheme 1.7

The syntheses discussed so far, have all furnished the tricyclic framework of colchicine **1** *via* sequential construction of ring A, ring B and finally ring C. However, Nakamura and co-workers[48] devised a synthesis in which rings A and C were constructed in the first step.

In the first step of this synthesis (Scheme 1.8), Nakamura introduces the basic carbon framework of the A and C rings *via* Pechmann condensation between methylpyrogallol **44** and ethyl 2-oxocycloheptanecarboxylate **45**. The remaining steps of this route then deal with the construction of ring B, and manipulation of the C ring *via* a tropilidine that is converted to the desired tropolone employing a method developed by Nozoe.[53]

Condensation of methylpyrogallol **44** with ester **45** gave the coumarin **46**. Allylation with propenylbromide enabled a subsequent Cope rearrangement to form **47**, that was subjected to double bond isomerisation and finally ozonolysis to afford the aldehyde **48**. Condensation of **48** with malonic acid, followed by hydrogenation, decarboxylation, and treatment with alkaline dimethyl sulfate provided diacid **49**. Esterification of **49** followed by Dieckmann ring closure of the diester and subsequent decarboxylation, led to the formation of conjugated ketone **50**, containing the constructed B ring. Subsequent reaction with hydroxylamine furnished an oxime that was reduced by lithium aluminium hydride, acetylated and then treated with boron trifluoride to effect double bond isomerisation thereby affording the *N*-acetylated product **51**. Aromatisation was effected by bromination-dehydrobromination procedures employing *N*-bromosuccinimide and collidine respectively. Conversion to the tropolone was achieved using the method of Nozoe,[53] which involved a series of acid and base treatments to afford the tropilidine **52**, followed by reaction with hydrazine to furnish the colchiceinamide **53**. Finally, reaction with base provided colchiceine **2**.

This route and most of the subsequent syntheses proceeded *via* the intermediacy of either colchiceine **2**, or deacetamidocolchicine **16** and consequently relied on the work of Eschenmoser and van Tamelen for formal completion of the total synthesis.

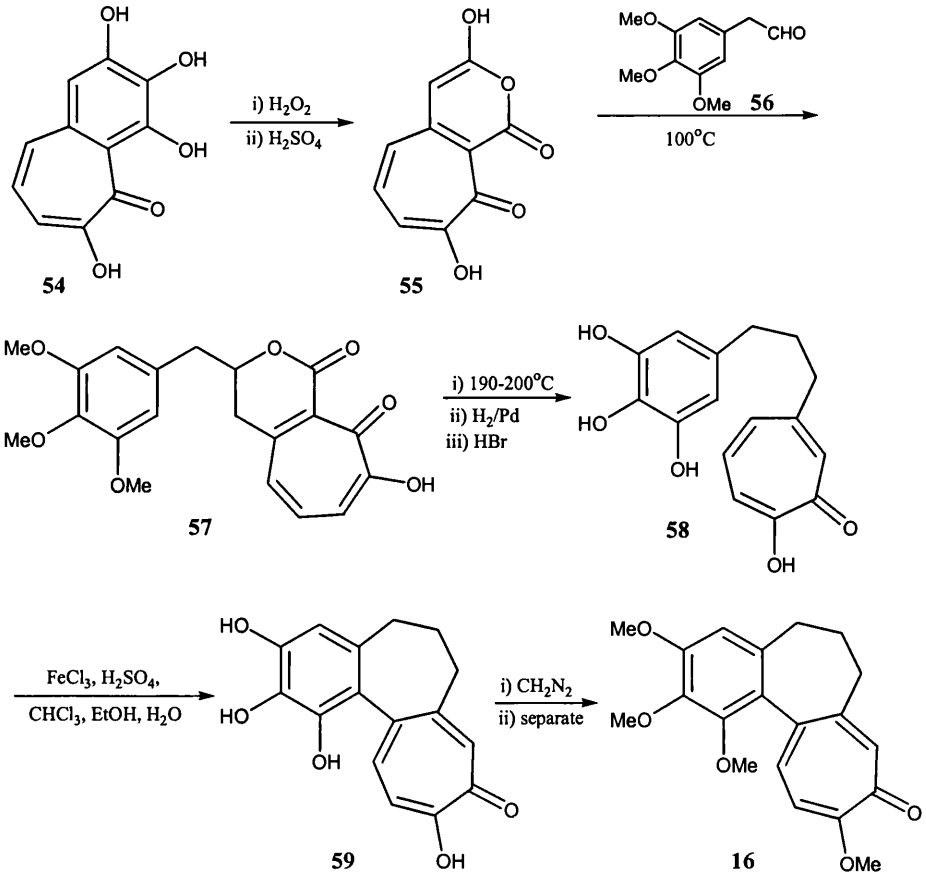


Scheme 1.8

In 1965, Scott[44] described yet another synthesis which began with purpurogallin. However, unlike the earlier syntheses employing this type of starting material, he impressively used it in the construction of ring C (Scheme 1.9). Consequently, this provided a route to colchicine **1** whereby the tropolonic moiety was introduced into the framework in the early stages. What would appear an excellent

method of introducing the tropolonic ring, in fact actually just introduced the problem of regiocontrol into the synthesis in the first instance.

Oxidation and dehydration of the purpurogallin **54**, provided anhydride **55** that underwent a condensation reaction with 3,4,5-trimethoxyphenylacetaldehyde **56** at 100°C. In the course of this reaction, decarboxylation occurred as a result of the influence of the tropolone ring thereby furnishing the lactone **57**. Further pyrolysis resulted in elimination and decarboxylation, which was followed by hydrogenation and demethylation procedures to afford the pyrogallol **58**. The stage was now set to carry out an oxidative coupling reaction with concomitant formation of ring B. The use of ferric chloride and a two-phase mixture of chloroform and acidic ethanol was necessary to ensure none of the product **59** underwent oxidation. Finally, methylation and separation afforded deacetamidocolchicine **16**, subsequent conversion of which to colchicine **1** was achieved as previously described.

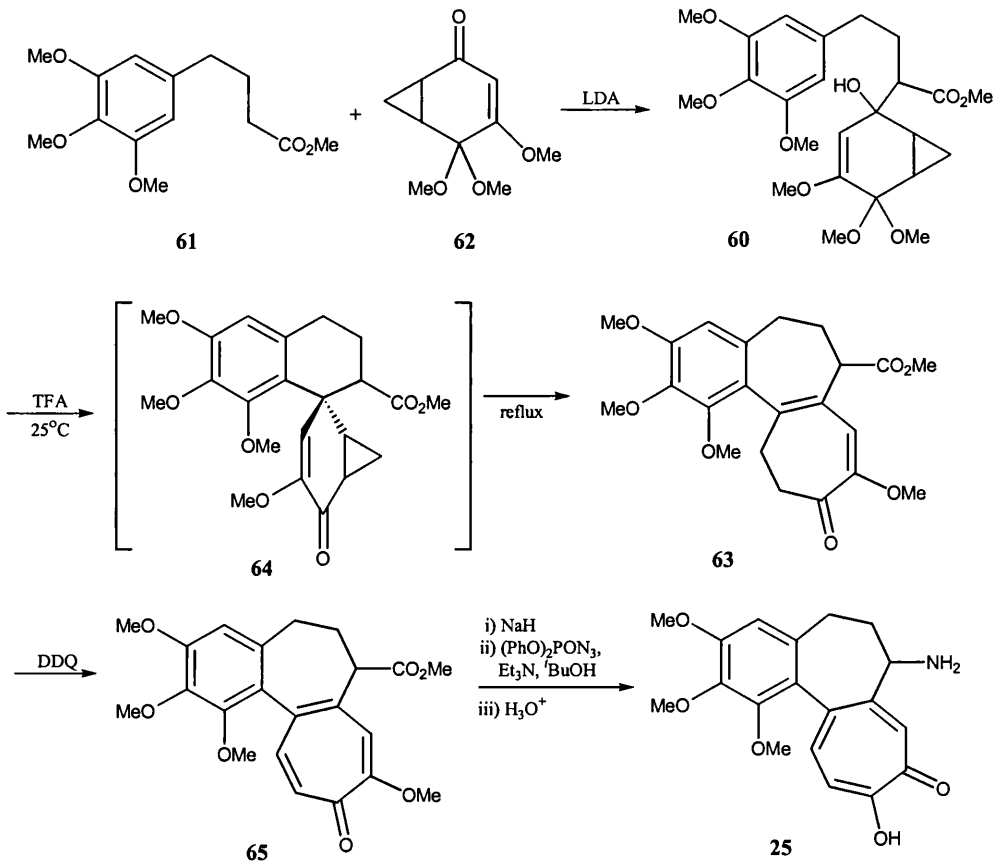


Scheme 1.9

For over a decade, colchicine **1** appeared to have lost its appeal amongst the synthetic fraternity, as there were no further reported syntheses until the 1980's. At this moment in time however, there was a great resurgence of interest.

Thus, in 1981 Evans[50] explored the possibility of constructing the tropolonic C ring of colchicine **1** by utilising cyclopropanated quinone monoketals. The use of this elegant methodology provided a route to achieving simultaneous cyclisation and ring expansion, furnishing rings B and C in a single operation (Scheme 1.10).

Construction of the essential vinylogous hemiketal **60**, was easily achieved through an aldol-like reaction between ester **61** and cyclopropanated quinone monoketal **62**. Hydrolysis of the hemiketal **60** in refluxing trifluoroacetic acid facilitated the simultaneous cyclisation and ring expansion furnishing the deacetamidoisocolchicine derivative **63** in an excellent 92% yield. Interestingly, when the reaction was carried out at room temperature it was possible to isolate the spirocyclised product **64**, and elevated temperatures were required to carry out the ring expansion process, suggesting that this complex transformation proceeded *via* initial cyclisation followed by ring expansion. Oxidation with DDQ to afford **65**, followed by a series of standard procedures, provided the desired natural product.



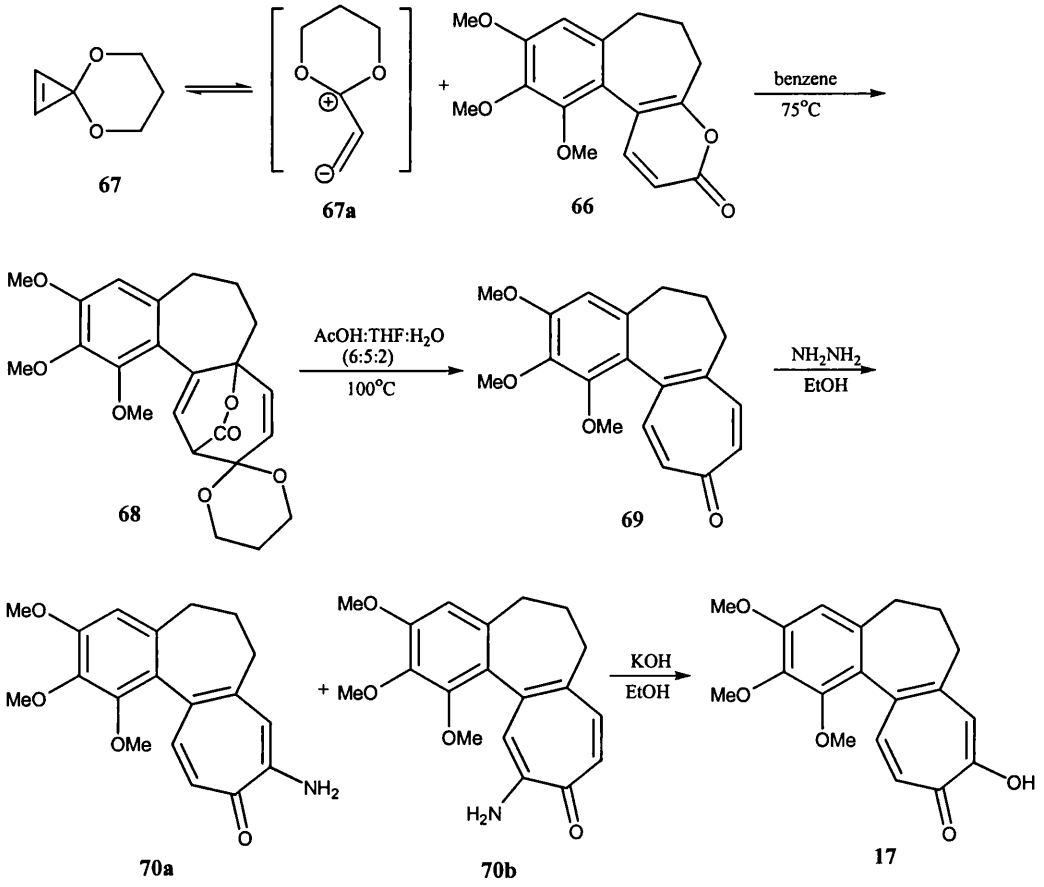
Scheme 1.10

This magnificent reaction constructed the full carbocyclic framework of colchicine **1** in a single step, but unfortunately once again did not manage to avoid the intermediacy of a free tropolone derivative.

Some five years later, Boger and Brotherton[47] described the first application of Diels-Alder chemistry to the synthesis of colchicine **1**. Their approach was based on the idea that a thermal [3+4] cycloaddition of a cyclopropane ketal and a pyrone could be employed to facilitate the formation of ring C (Scheme 1.11).

Utilising Eschenmoser's pyrone **66** which already had rings A and B intact, they performed a [3+4] cycloaddition in the presence of cyclopropane ketal **67**, which at 75°C exists in equilibrium with the delocalised singlet vinylcarbene **67a** furnishing the adduct **68** in an encouraging 73% yield. Fortunately, the competing [4+2] cycloaddition was in fact an unfavourable process as a result of adverse steric interactions hindering the transition state of this reaction.

With all three rings intact, mild aqueous acidic treatment of **68** led to sequential ketal hydrolysis followed by thermal decarboxylation in a single step to provide the tropone **69**. Conversion to the desired tropolone required the introduction of an additional hydroxyl group into ring C, which was achieved by prior introduction of an amine functionality by reaction with hydrazine. Unfortunately, reaction occurred at both carbon positions adjacent to the tropone carbon, providing a 1:1 mixture of regioisomers **70a** and **70b**. Only one isomer **70a**, had the correct regiochemistry required for the conversion to deacetamidocolchiceine **17**. Once again, further progression to colchicine **1** followed the methods described by Eschenmoser and van Tamelen.



Scheme 1.11

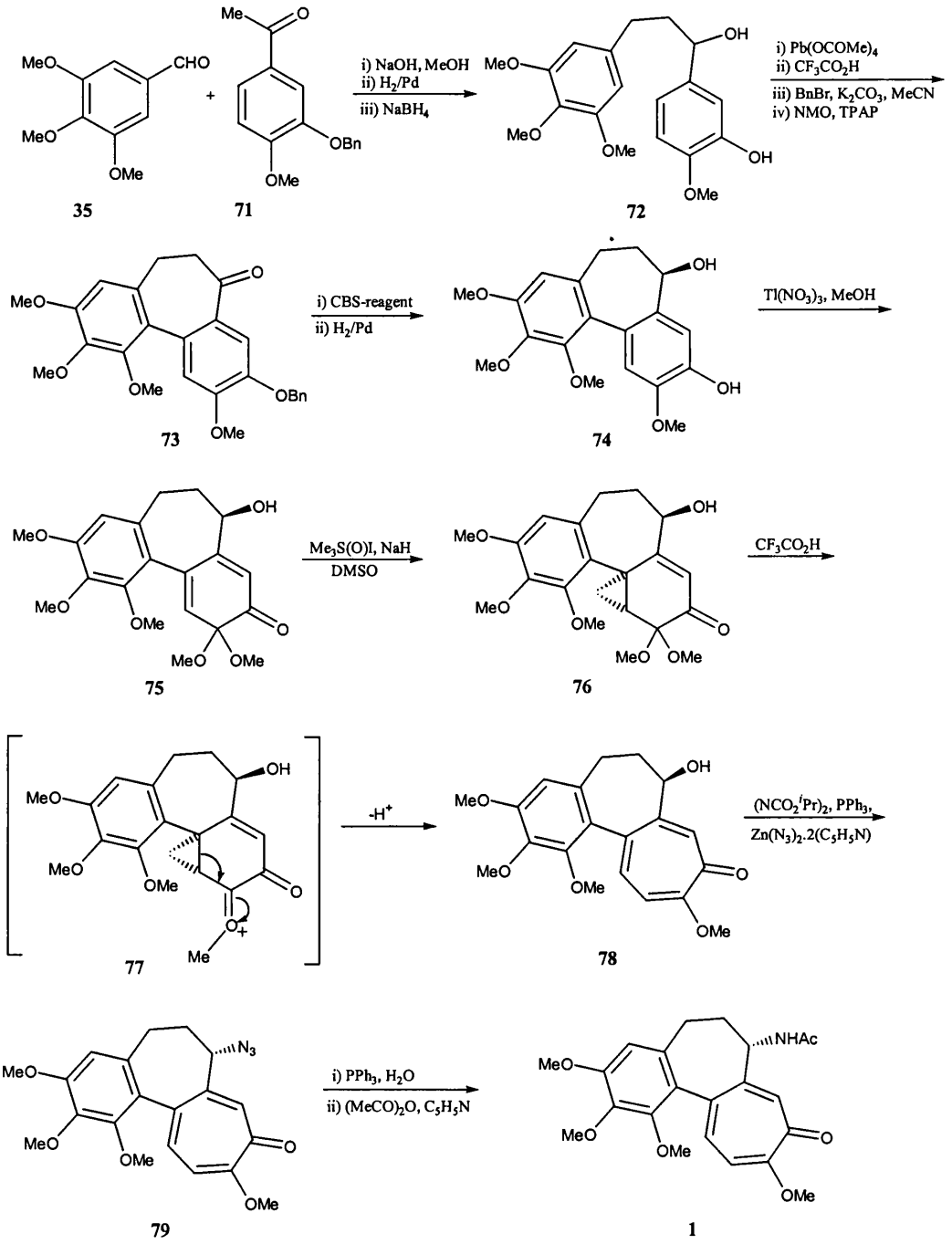
This synthesis manages to elegantly apply the [3+4] cycloaddition reaction to the synthesis of tropones, however, the conversion of these to their tropolone relatives is not so sophisticated. Not only does the synthesis proceed *via* the intermediacy of deacetamidocolchiceine **17** as the majority of previous syntheses do, but it has

the additional drawback that during the oxidation sequence of **69** to **17**, an additional regioisomer is also produced.

As we have seen, all of the previous syntheses discussed have presented some problems of regiocontrol, especially in relation to the tautomeric diosphenol problem. In addition, the chiral nature of the acetamide functionality has not been addressed in any way other than through resolution.

It was not until 1992 when Banwell[51] finally reported the first fully regiocontrolled synthesis of colchicine **1** (Scheme 1.12). His approach was based on the known biosynthetic pathway. In particular he attempted to mimic in the laboratory the later stages of the biosynthesis, which involve the formation of the troponolic C ring *via* a ring expansion process (section 1.1.5).

3,4,5-Trimethoxybenzaldehyde **35** and acetophenone **71** were used as starting materials and were readily transformed to the 1,3-diarylpropanol **72** *via* a crossed-aldol reaction. Ring B was formed using an oxidative coupling protocol developed by Umezawa.[54] The resulting ketone **73** was subjected to enantioselective reduction with stoichiometric quantities of CBS-reagent, followed by debenzylation to afford phenol **74**. Taylor-Mckillop[55] oxidation was performed on phenol **74** to afford the cyclohexadienone **75**. Nucleophilic cyclopropanation with dimethylsulfoxonium methylide led to formation of the key intermediate, σ-homo-*O*-benzoquinone mono-acetal **76**, reaction of which with trifluoroacetic acid resulted in biomimetic ring expansion to give the troponoid **78**. Mitsunobu chemistry then afforded the azido-compound **79**, and reduction and subsequent acetylation led to colchicine **1** with greater than 81% enantioselective excess.



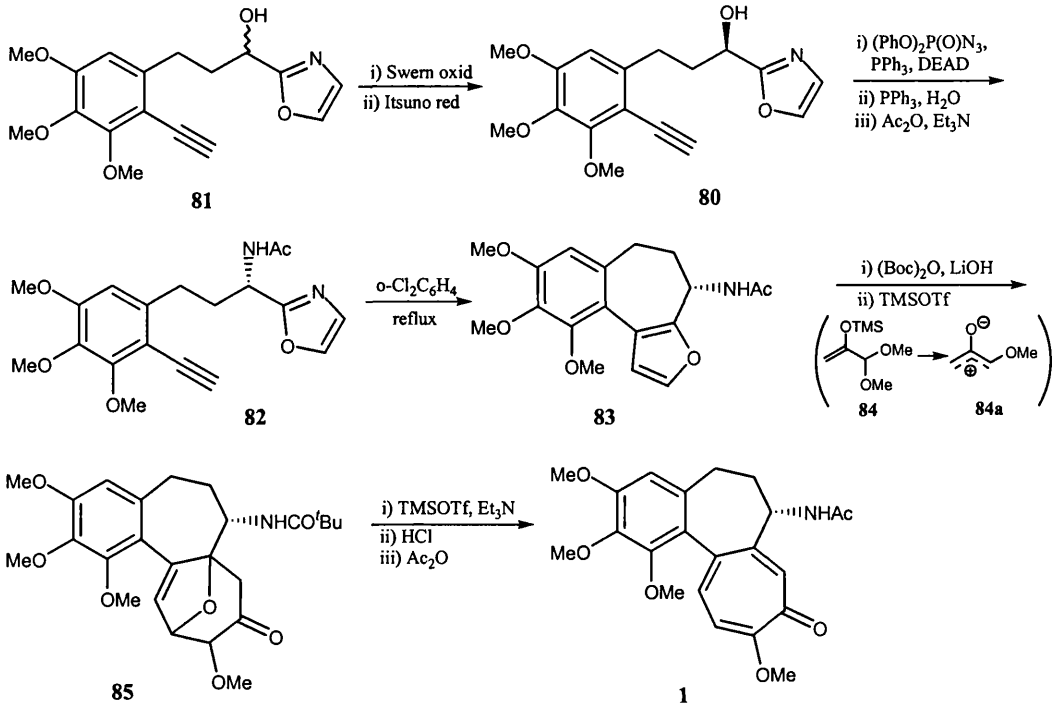
Scheme 1.12

In his outstanding effort which avoided the occurrence of a free tropolone ring system such as that found in deacetamidocolchiceine **17** or colchiceine **2**, Banwell has superbly managed to provide the first regiocontrolled synthesis of colchicine **1**.

The only other regiochemical synthesis of colchicine **1** was described some years later. Cha and co-workers[52] also managed to avoid the intermediacy of any colchiceine derivatives by employing a [4+3] cycloaddition reaction of an α-alkoxy substituted oxyallyl cation and a furan to facilitate the formation of the tropolonic C ring (Scheme 1.13). The same group also managed to install the *C*-7 acetamide functionality in an ingenious manner *via* a chiral alcohol, which was introduced prior to cyclisation.

Preparation of the (*R*)-alcohol **80** was achieved by Swern oxidation of the racemate **81**, followed by chiral reduction employing Itsuno's method[56] in 85-90% ee. Subsequent conversion to the (*S*)-amide **82** was achieved through a sequence incorporating a Mitsunobu reaction. A thermolysis reaction of **82**, furnished the desired furan **83** for the key [4+3] cycloaddition. However, prior conversion of the acetamide to the *tert*-butyl counterpart proved necessary in order to prevent formation of the undesired regioisomer. The [4+3] cycloaddition of furan with trimethylsilylenol ether **84** was achieved in the presence of trimethylsilyl triflate, (required to perform the *in situ* generation of the allyl cation **84a**), providing the cycloadduct **85** as a single regioisomer. Finally, double elimination of the oxa-bridge was achieved with excess trimethylsilyl triflate and triethylamine, and the *N*-acetyl group was introduced to complete the synthesis.

The selection of this cycloaddition reaction provided a direct route to obtaining the tropolonic C ring with correct regiochemistry, thereby avoiding the formation of any free tropolone intermediates. Additionally, by introducing a chiral centre at the early stages of the synthesis, this group managed to obtain colchicine **1** in approximately 90% ee, a substantial improvement on that achieved by Banwell.



Scheme 1.13

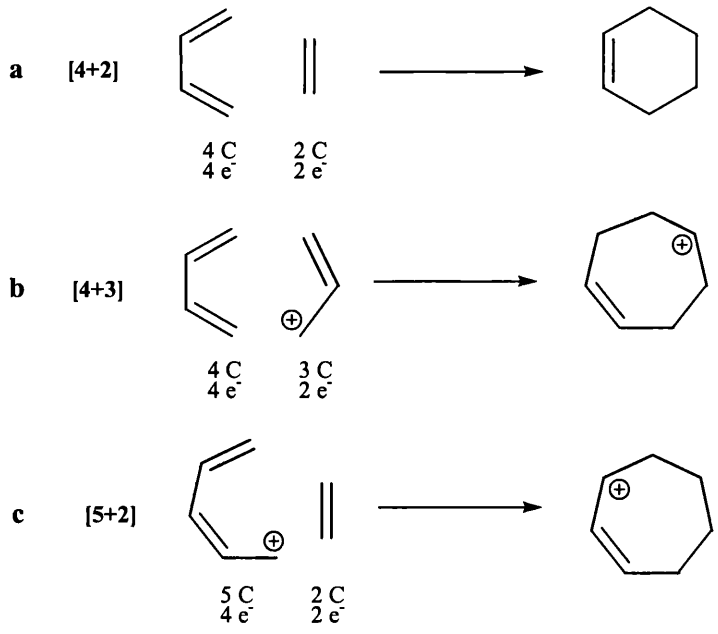
The foregoing review has hopefully highlighted that colchicine **1** has remained as a jewel in the crown of organic synthesis, and that it is only within the last decade that satisfactory solutions to the problems of regioselectivity and enantioselectivity have emerged. Our own objective was to forge a synthesis of colchicine **1** in which both of these issues were also addressed and in a manner which led to simultaneous formation of both seven-membered rings in a single step. Since the key step involved exploitation of the transition metal catalysed [5+2] cycloaddition reaction, it is therefore appropriate at this stage to provide an introductory review on the recent developments and highlights in this area.

1.2 Transition Metal Catalysed [5+2] Cycloaddition Reaction

1.2.1 Background

Cycloaddition reactions are extremely powerful tools in organic synthesis as they enable the formation of complex products from fundamental building blocks in a single synthetic operation. The most famous reaction is of course the Diels-Alder reaction, which has been used extensively for the synthesis of six-membered rings (Scheme 1.14a). However, cycloaddition methods for the synthesis of seven-membered rings are extremely limited. This has provided a major problem for synthesis, as targets containing seven-membered rings are frequently encountered, and many of these targets are also biochemically and medicinally significant.

Previous strategies have been largely limited to two isoelectronic variants of the Diels-Alder cycloaddition (Scheme 1.14). All of these can of course be formally considered as $\pi_{4s} + \pi_{2s}$ cycloadditions in terms of Frontier Orbital Theory.

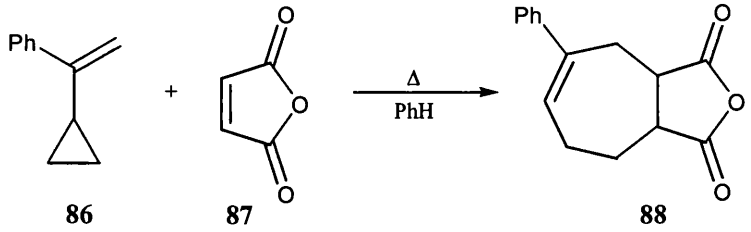


Scheme 1.14

In the first of these, the Diels-Alder dienophile is replaced by an allyl cation (two π-electrons, three carbons). Reaction of the allyl cation with a suitable diene allows the formation of a seven-membered ring *via* a [4+3] cycloaddition reaction (Scheme 1.14b).[57] In the second variant, a pentadienyl cation (four π-electrons,

five carbons) is used in place of the diene thereby providing a route for the synthesis of seven-membered rings through a [5+2] cycloaddition (Scheme 1.14c).[58] However, both these cases involve the often problematic generation of ionic or zwitterionic reactive intermediates.

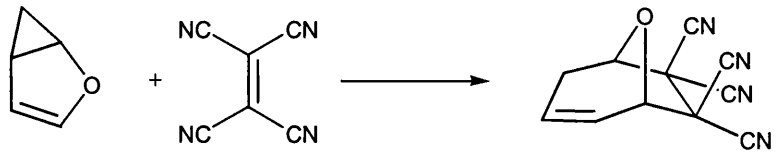
The recognition that vinylcyclopropanes have diene-like properties has stimulated a great deal of interest in the development of a homologue of the Diels-Alder reaction for seven-membered ring synthesis involving the cycloaddition of vinylcyclopropanes with π-systems. In 1959 Sarel and Breuer[59] reported the [5+2] cycloaddition of a vinylcyclopropane **86** and maleic anhydride **87** to form the seven-membered ring **88** (Scheme 1.15). However, efforts to reproduce this reaction in other labs have proved unsuccessful and it has not been applied to other simple vinylcyclopropanes.[60,61]



86 **87** **88**

Scheme 1.15

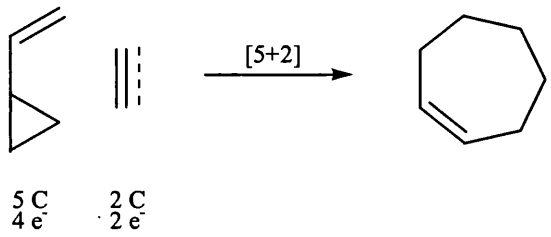
In contrast, bicyclic vinylcyclopropanes have been shown to react with activated alkenes and alkynes to produce seven-membered rings. For example, Herges and Ugi[62] discussed the concerted reactions of homofurans such as **89** with activated π-systems such as tetracyanoethylene **90**, to afford complex cyclic products such as **91** (Scheme 1.16). However, these reactions are limited to bicyclic vinylcyclopropanes which are activated both by the heteroatom substitution and by release of strain.



89 90 91

Scheme 1.16

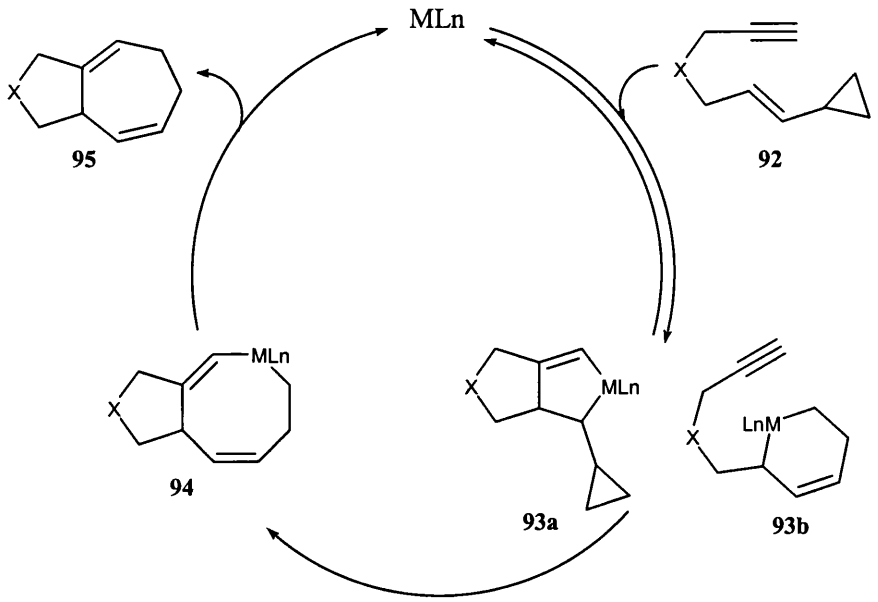
In 1995, following their studies on transition metal catalysed [4+4] and [4+2] cycloadditions,[63,64] Wender and co-workers reported the long sought after transition metal catalysed [5+2] cycloaddition reaction of vinylcyclopropanes with alkynes,[65] and the group have subsequently extended it to alkenes[66,67] and allenes[68] (Scheme 1.17). This approach was based on the idea that the metal mediated opening of a vinylcyclopropane would provide a 5-carbon homologue of the Diels-Alder diene to effect a [5+2] cycloaddition reaction in the presence of a suitable dienophile.



Scheme 1.17

1.2.2 Mechanistic Approach

Wender based his investigations on the difficulties encountered in previous attempts to effect a [5+2] cycloaddition with vinylcyclopropanes under conventional conditions, coupled with the observation that various transition metals are capable of cleaving cyclopropanes.[69] The design was based on the mechanistic hypothesis outlined for an intramolecular variant in Scheme 1.18.



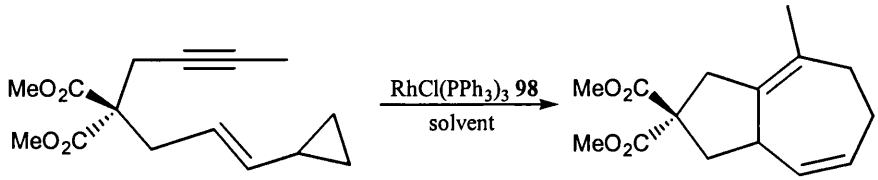
Scheme 1.18

According to this sequence, oxidative addition of the metal catalyst to substrate **92** would lead to the formation of metallacyclopentene **93a**. Due to the close proximity of the carbon-metal bond to the cyclopropane, the metallacycle **93a** would be expected to undergo strain driven ring expansion to provide the eight-membered metallacycle **94**. Finally, reductive elimination would lead to the formation of the seven-membered cycloadduct **95** with regeneration of the metal catalyst. An alternative mechanistic scenario might involve coordination of the metal catalyst to the vinylcyclopropane **92** followed by rearrangement to produce metallacycle **93b**. Coordination of the alkyne with the metal centre followed by subsequent carbon-carbon bond formation then provides an alternative pathway to **94**.

1.2.3 Alkyne Reactions

1.2.3.1 Wilkinson's Catalyst

Wender[65] reported the viability of this process in the form of the first metal catalysed [5+2] cycloaddition between unactivated vinylcyclopropanes and tethered alkynes (Scheme 1.19).



96 97

Scheme 1.19

Early work involved reaction of the alkynyl-vinylcyclopropane **96** with Wilkinson's catalyst, $[RhCl(PPh_3)_3]$ **98** in toluene at reflux for several days, providing the desired cycloadduct **97** in an excellent 84 % yield (Table 1.1, entry 1). An increase in solvent polarity led to an increase in reaction rate (Table 1.1, entry 2), presumably due to facilitated ligand dissociation. Further rate acceleration was achieved by the addition of silver (I) triflate, which precipitates silver chloride and thereby irreversibly forms a cationic rhodium (I) species. The rate acceleration achieved on addition of silver (I) triflate and the use of a polar solvent might suggest that the active precursor in the catalytic pathway is in fact the cationic rhodium (I) species, $Rh^+(PPh_3)_3$.

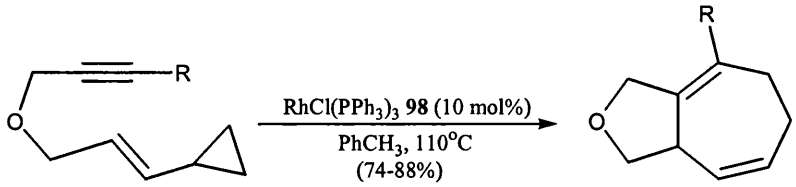
Entry	Solvent	Additive	Temp (°C)	Time (h)	Yield (%)
1	$PhCH_3$	None	110	48	84
2	CF_3CH_2OH	None	55	19	90-95
3	$PhCH_3$	AgOTf	110	0.3	83

Table 1.1

Further studies[65] have established the general applicability of this rhodium (I) catalysed [5+2] cycloaddition reaction to internal, terminal, electron rich, electron poor and conjugated alkynes, thereby allowing the flexible and efficient synthesis of a variety of seven-membered rings. Thus, the reaction has been shown to be completely insensitive to steric and electronic factors with a whole range of alkyne substituents being tolerated.

Reaction of the alkynyl-vinylcyclopropanes **99** proceeded in the presence of 10 mol% $RhCl(PPh_3)_3$ **98** in refluxing toluene to give the desired bicyclic products **100** typically in 74-88% yield, regardless of whether the alkyne substituent is a

hydrogen atom or the much bulkier TMS group, or whether an electron withdrawing, electron donating or conjugating group is employed (Scheme 1.20).



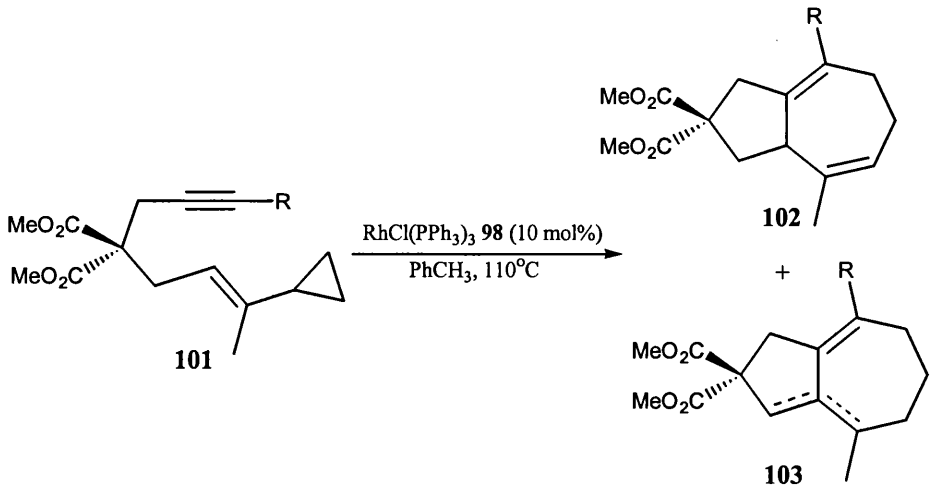
99
(R = Me, TMS, CO_2Me, Ph, H)

100

Scheme 1.20

Also, a variety of functional groups can be incorporated into the linking chain between the alkyne and vinylcyclopropane moieties. In particular Wender has incorporated diester, monoester, dimethyl, ether, siloxane and sulfonamide moieties into his diverse systems.

The effect of substitution at the olefinic position has also been investigated, and it has been found that in general substitution at this position has little effect on the efficiency of the cycloaddition reaction (Scheme 1.21). However, in some cases, further positional isomerisation of the double bond in the initial product has been observed, resulting in the formation of additional isomers.



Scheme 1.21

This problematic isomerisation is highly dependent upon the nature of the alkyne substituent (Table 1.2). For example, when a terminal alkyne or one bearing an

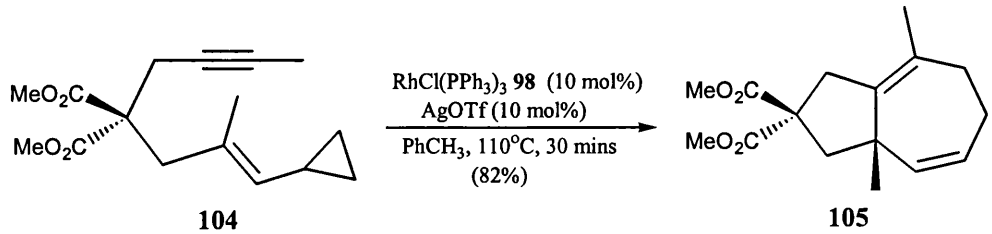
electron withdrawing substituent (Table 1.2, entries 3 and 4) is employed in the cycloaddition reaction, the desired cycloadduct **102** is obtained in an excellent yield as the sole product. However, cycloaddition of yne-vinylcyclopropane **101** bearing a methyl substituent has been shown to give the isomerisation product **103** along with the expected product **102** (Table 1.2, entry 1). It was also shown in this case, that incorporation of silver (I) triflate into the reaction decreases the ratio of desired product (Table 1.2, entry 2). Finally, a bulky substituent such as TMS provided only the isomerisation product (Table 1.2, entry 5).

Entry	R	Time (h)	Yield (%)	Product ratio (102:103)
1	Me	48	89	3.5:1
2[a]	Me	2.5	92	1:2
3	H	48	82	1:0
4	CO_2Me	16	81	1:0
5	TMS	168	71	0:1

[a] 10 mol% AgOTf employed in reaction

Table 1.2

Interestingly, the cycloaddition has been shown to proceed much more efficiently with geminal dialkyl substitution of the alkene, requiring much shorter reaction times with no formation of the isomerisation by-product (Scheme 1.22). However, no explanation is provided for this phenomenon.



104 **105**

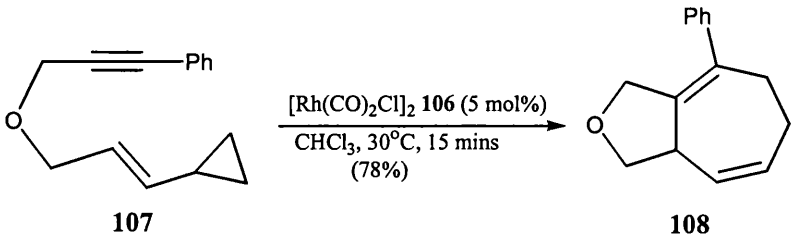
Scheme 1.22

1.2.3.2 $[Rh(CO)_2Cl]_2$ Catalyst

Through his initial investigations into the transition metal catalysed [5+2] cycloaddition reaction of alkynes and vinylcyclopropanes, Wender has clearly demonstrated the applicability of the reaction to a wide variety of precursors. Nevertheless, as we have seen above a few problematic cases have surfaced with the main problem being the secondary isomerisation which occurred when substituted olefins were employed. In addition to this, the high reaction temperatures required could pose problems for more fragile substrates.

As a result, further studies led to the development of a new catalyst for the cycloaddition reactions. In his search for a more reactive catalyst, Wender discovered that $[Rh(CO)_2Cl]_2$ **106** was also successful in facilitating the [5+2] cycloaddition reactions, but more interestingly, it was impressively effective in many of the previously problematic cases.[70]

The use of $[Rh(CO)_2Cl]_2$ **106** in place of Wilkinson's catalyst **98** enables the cycloaddition to proceed under much milder conditions and with shorter reaction times. In addition, lower catalyst loadings can be employed and there is no requirement for the activation by silver (I) triflate. This is illustrated in the following example (Scheme 1.23), in which yne-vinylcyclopropane **107** was stirred with 5 mol% Rh(I)-catalyst **106** in chloroform at 30°C to give the desired cycloadduct **108** after only 15 minutes in an impressive 78% yield. As with Wilkinson's catalyst **98**, comparable results were obtained for a wide range of alkyne substituents.[70]

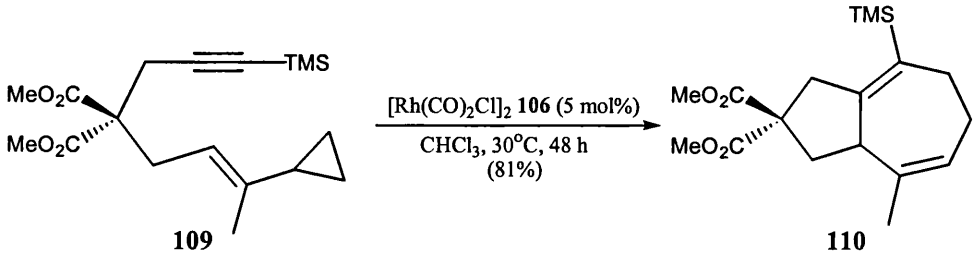


107 **108**

Scheme 1.23

Another advantage of this highly reactive catalyst is that when employed in reactions involving substituted olefins, the reaction proceeds efficiently furnishing

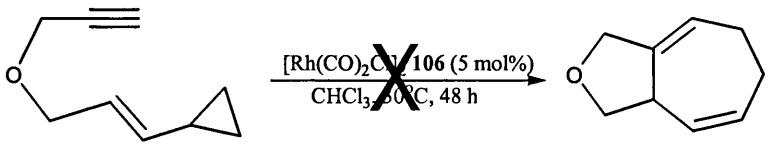
the desired cycloadduct without secondary isomerisation of the product alkene, a problem previously encountered with Wilkinson's catalyst **98**. This is illustrated by the reaction of the methyl substituted vinylcyclopropane **109** with $[Rh(CO)_2Cl]_2$ **106**, which furnished the desired seven-membered ring **110** in an excellent 81% yield (Scheme 1.24, cf. Scheme 1.21, Table 1.2, entry 5).



109 **110**

Scheme 1.24

Although $[Rh(CO)_2Cl]_2$ **106** has been shown to be a general and useful catalyst for the intramolecular cycloaddition of alkynyl-vinylcyclopropanes, it does however pose a major drawback in that, when employed in reactions involving terminal alkynes, no cycloaddition is observed. This is demonstrated in the following reaction of terminal alkyne-vinylcyclopropane **111** (Scheme 1.25).



111 **112**

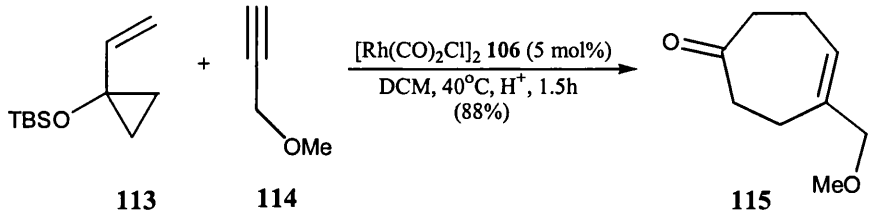
Scheme 1.25

This change in reactivity may be attributed to the highly electron-deficient nature of the rhodium, which may lead to insertion into the terminal alkyne C-H bond, thus altering the course of reaction. It is noteworthy, that when this reaction was repeated applying the standard Wilkinson's catalyst conditions, the desired cycloadduct **112** was obtained in 50% yield, with the low yield being attributed to the volatility of the starting material **111**.

1.2.3.3 Intermolecular Reactions

Given the success of the intramolecular [5+2] cycloaddition reactions and the ready availability of alkynes, Wender hoped to extend the scope of the reaction to intermolecular systems. However, early investigations with Wilkinson's catalyst **98** resulted in failure, even when conditions were employed for which the corresponding intramolecular reaction worked well.[71]

However, Wender subsequently reported that the intermolecular [5+2] cycloaddition between an alkyne and a vinylcyclopropane may be achieved in high yield, in the presence of $[Rh(CO)_2Cl]_2$ **106** at temperatures just above room temperature.[71,72] For example, reaction of vinylcyclopropane **113** and alkyne **114** in the presence of 5 mol% Rh(I)-catalyst **106** in chloroform at 40°C furnished after acidic hydrolysis of the initial silylenol ether product, cycloheptanone **115** in 88% yield (Scheme 1.26).

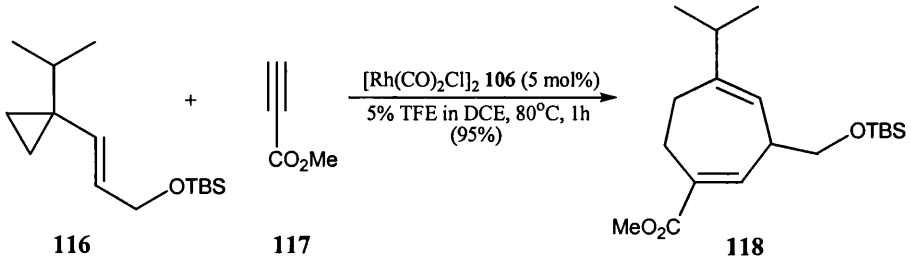


113 **114** **115**

Scheme 1.26

Similar results were obtained for a whole range of alkynes, such as those bearing alkyl, ester, hydroxy and silicon functionalities, providing a convenient route to a huge variety of substituted silylenol ether cycloadducts or their corresponding cycloheptanones.[71]

More recently, Wender has applied this methodology to new systems posing regiochemical issues.[73] For example, reaction of the alkyl substituted vinylcyclopropane **116** with alkyne **117** in the presence of 5 mol% $[Rh(CO)_2Cl]_2$ **106** furnished the seven-membered carbocycle **118** as a single regioisomer in an excellent 95% yield (Scheme 1.27). The use of trifluoroethanol (TFE) as co-solvent was found to increase reaction rate and yield.

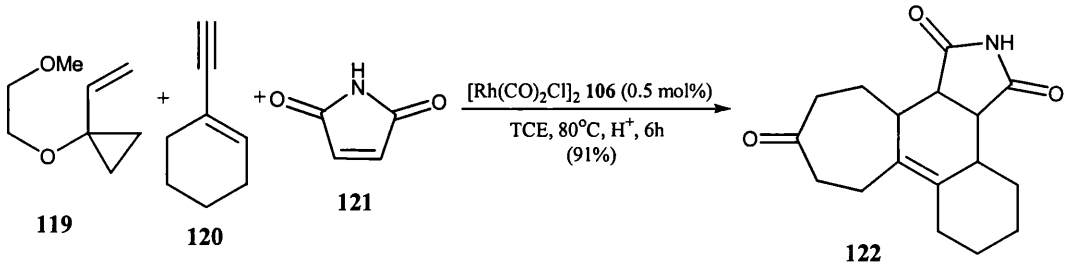


116 117 118

Scheme 1.27

This remarkable result is brought about by the preference for the alkynyl substituent to adopt a position away from the olefinic substituent of the vinylcyclopropane, thereby minimising steric effects.

The excellent functional group tolerance and chemoselectivity of the intermolecular [5+2] cycloaddition for alkynes and vinylcyclopropanes has led to its application in new multicomponent processes, involving serial [5+2]/[4+2] cycloadditions.[74] The following example is illustrative of these serial cycloaddition reactions (Scheme 1.28). A [5+2] cycloaddition of the vinylcyclopropane **119** with alkyne **120** facilitated the formation of a diene, which subsequently underwent a [4+2] cycloaddition with dienophile **121** affording the tetracyclic system **122** in an excellent 91% yield.



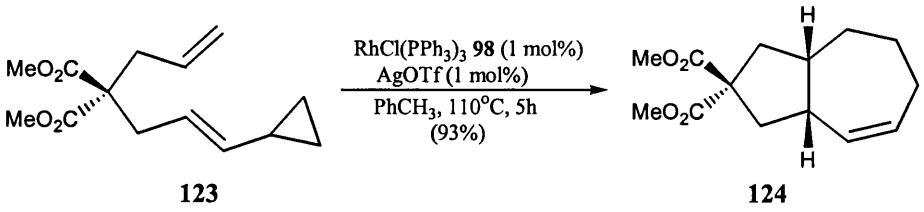
119 120 121 122

Scheme 1.28

These multicomponent reactions have been extended to incorporate a range of enynes and dienophiles, and provide an efficient route to functionalised polycyclic compounds, which could serve as flexible building blocks for complex molecule syntheses, combinatorial libraries and medicinal targets.[74]

1.2.4 Alkene Reactions

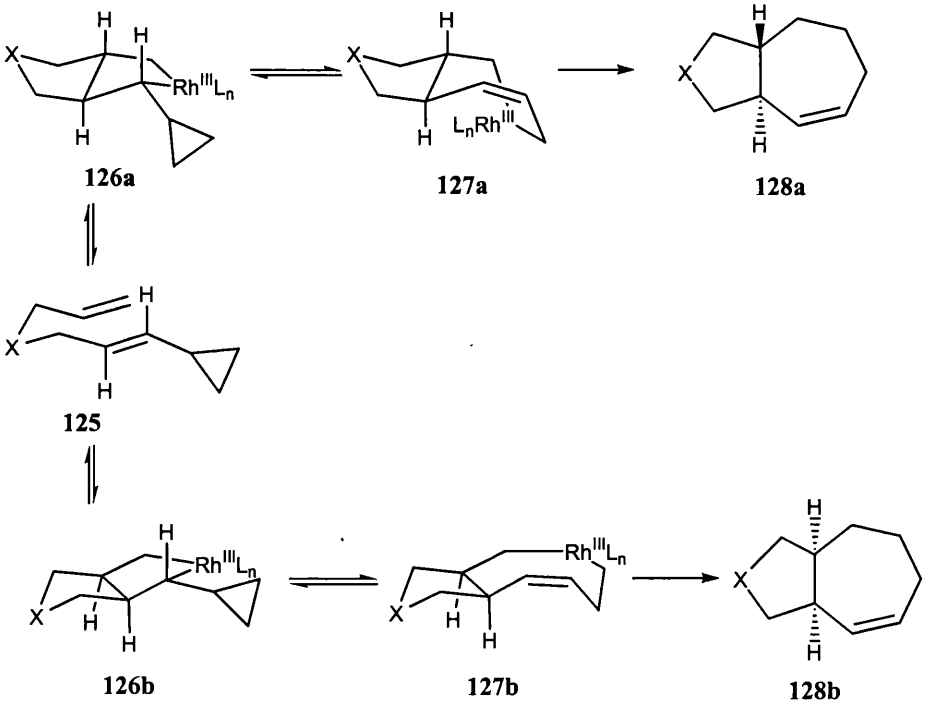
More recently, the [5+2] cycloaddition reaction has been extended to alkenes, and once again the reactions proceed with remarkable efficiency and selectivity under the same conditions as described for alkynes.[66,67] Thus, for example, the cycloaddition of alkenyl-vinylcyclopropane **123** in the presence of 1 mol% $RhCl(PPh_3)_3$ **98** and silver (I) triflate provided the desired cycloadduct **124** in an excellent 93% yield as a single diastereoisomer (Scheme 1.29).



123 **124**

Scheme 1.29

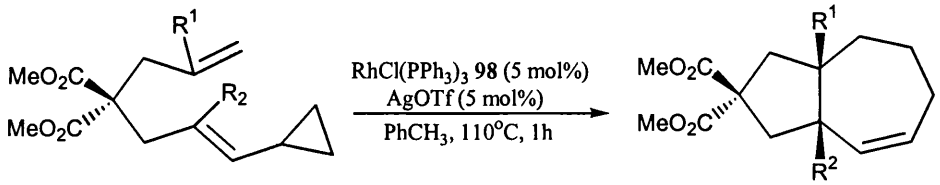
From a mechanistic standpoint, it is interesting to consider that these reactions proceed to give only a single diastereoisomer, as the reaction between an alkene and vinylcyclopropane could, in principle, result in the formation of two diastereomeric products **128a** and **128b** (Scheme 1.30).



Scheme 1.30

The stereochemistry of these cycloadducts is considered to arise during the initial cyclometallation process leading either to **126a** or to **126b** and is fixed by the turnover of these intermediates to products. The formation of **128b** thus reflects a kinetic preference for the reaction *via* the *cis*-fused intermediates **126b** and **127b**, relative to their *trans*-fused counterparts, **126a** and **127a**.

Investigation into substitution on either of the two alkene components as indicated in the following example (Scheme 1.31) suggested that this methodology could be applied to the synthesis of bicyclic targets containing quaternary centres. Both methyl substituted vinylcyclopropanes **129a** and **129b** reacted rapidly with excellent efficiency to afford exclusively the *cis*-fused products, **130a** (R^1=H, R^2=Me) and **130b** (R^1=Me, R^2=H), respectively.

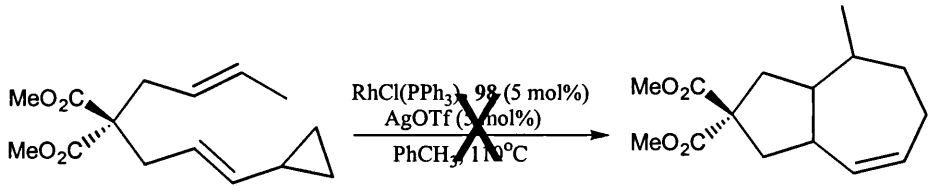


129a-c **130a-c**

a) R^1=H, R^2=Me (92%), b) R^1=Me, R^2=H (94%), c) R^1=R^2=Me (0%)

Scheme 1.31

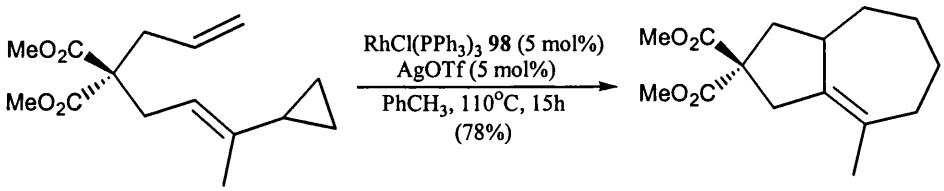
However, this point marks the furthest point of advance in terms of substituted alkenes in these reactions, since thus far, it has not been possible to achieve the cycloaddition of substrates such as **129c** which would lead to cycloadducts bearing two angular methyl groups such as **130c** (R^1=R^2=Me). Likewise, substrates bearing methyl groups at the alkene terminus do not undergo efficient cycloaddition, for example, the attempted cycloaddition of methyl-substituted alkene **131** afforded none of the desired cycloadduct **132** (Scheme 1.32). This prevents the applicability of the reaction to 1,2-disubstituted alkenes and thereby poses a major synthetic limitation since it precludes synthetic access to the carbocyclic cores of some of the largest natural product families.



131 132

Scheme 1.32

Finally, substitution at the olefinic position of the vinylcyclopropane provides the same problem as was encountered previously for alkynyl-vinylcyclopropanes, and as a result the secondary isomerisation product is obtained. This is observed in the reaction of alkenyl-vinylcyclopropane **133** with 5 mol% Rh-catalyst and silver (I) triflate which provided the cycloadduct **134** as the sole product in 78% yield (Scheme 1.33).

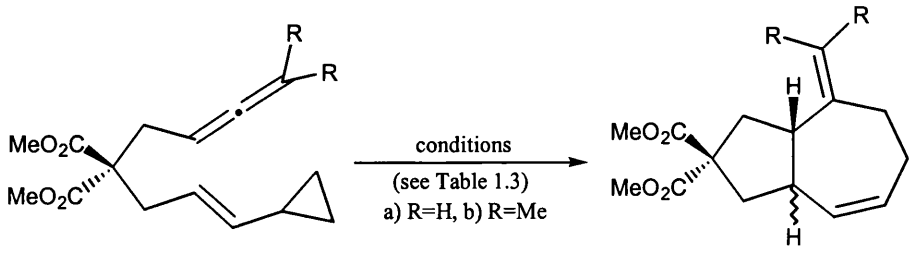


133 134

Scheme 1.33

1.2.5 Allene Reactions

In completing the series of suitable 2π-components for the [5+2] cycloaddition reaction, Wender[68] has also investigated the use of allenes. The scope of this reaction has been explored with a complete set of mono-, di- and trisubstituted allenes. Reaction of allenyl-vinylcyclopropane **135** with rhodium (I) catalyst provided the desired cycloadduct **136** (Scheme 1.34).



135a-b 136a-b

Scheme 1.34

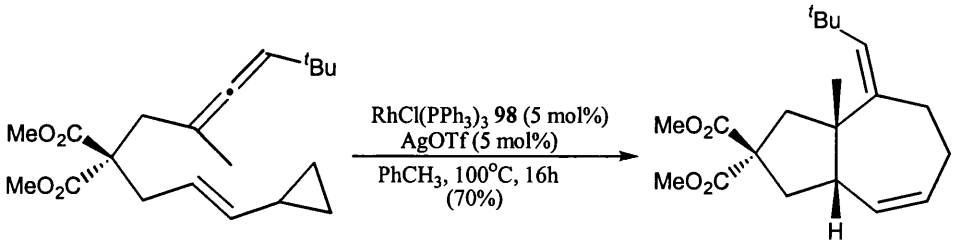
In varying the catalytic system, Wender demonstrated that it was possible to control the ring fusion selectivity (Table 1.3). For example, when the terminal allene **135a** was subjected to Wilkinson's catalyst **98** (entry 1), the reaction proceeded to give the cycloadduct **136a** with *cis/trans* junction mixture in a 1.1:1.0 ratio. Conversely, substitution of Wilkinson's catalyst **98** with $[Rh(CO)_2Cl]_2$ **106**, improved the selectivity enormously with the *cis/trans* ratio increasing in favour of the *cis* diastereoisomer to >20:1 (entry 2).

Entry	R	Catalyst	Solvent/ Temp (°C)	Time (h)	*cis:trans* ratio (yield)
1	H	5mol% $[RhCl(PPh_3)_3]$ and AgOTf	$PhCH_3$/110	10	1.1:1 (68%)
2	H	5mol% $[Rh(CO)_2Cl]_2$	DCE/90	3.5	>20:1 (83%)
3	Me	5mol% $[RhCl(PPh_3)_3]$ and AgOTf	$PhCH_3$/110	1	2:1 (92%)
4	Me	10mol% $[Rh(CO)_2Cl]_2$	$PhCH_3$/110	0.75	10:1 (90%)

Table 1.3

Unlike the alkene counterparts, substitution at the allene terminus did not hinder the cycloaddition reaction. In fact, when the dimethyl allene **135b** was subjected to reaction with either of the rhodium (I) catalysts the cycloaddition proceeded efficiently to furnish the bicyclic diene **136b** (Table 1.3, entries 3 and 4). Once again, the reaction selectivity was controlled by the catalytic system, with $[Rh(CO)_2Cl]_2$ **106**, showing a greater preference for formation of the *cis*-fused diastereoisomer.

Incorporation of 1,3-disubstituted allenes into the cycloaddition reaction has also proven to be a spectacular success.[68] On exposure of the 1,3-disubstituted allene **137** to Wilkinson's catalyst **98**, the desired cycloaddition occurred furnishing the cycloadduct **138** solely as the *cis*-fused isomer in an encouraging 70% yield (Scheme 1.35).

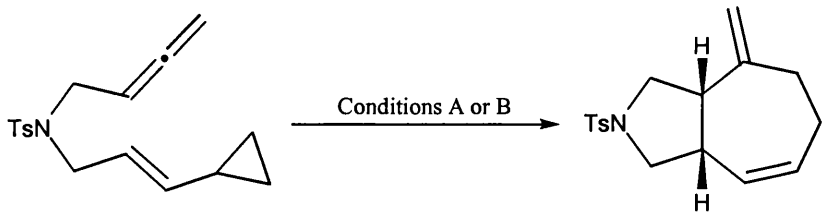


137 **138**

Scheme 1.35

Furthermore, reduction of, or addition to the resultant exocyclic alkene provides an achievable route to a variety of functionalised products, which could not otherwise be obtained through the corresponding cycloaddition of substituted alkenes.

Finally, in an elegant application of this methodology to the synthesis of heterocyclic products, Wender has shown that a substrate incorporating a nitrogen tether may also undergo cyclisation in the presence of a rhodium (I) catalyst.[68] Thus, reaction of allene **139** with either Wilkinson's catalyst **98** or $[Rh(CO)_2Cl]_2$ **106**, led to the heterocyclic product **140** as a single diastereoisomer in excellent yield (Scheme 1.36).



139 **140**

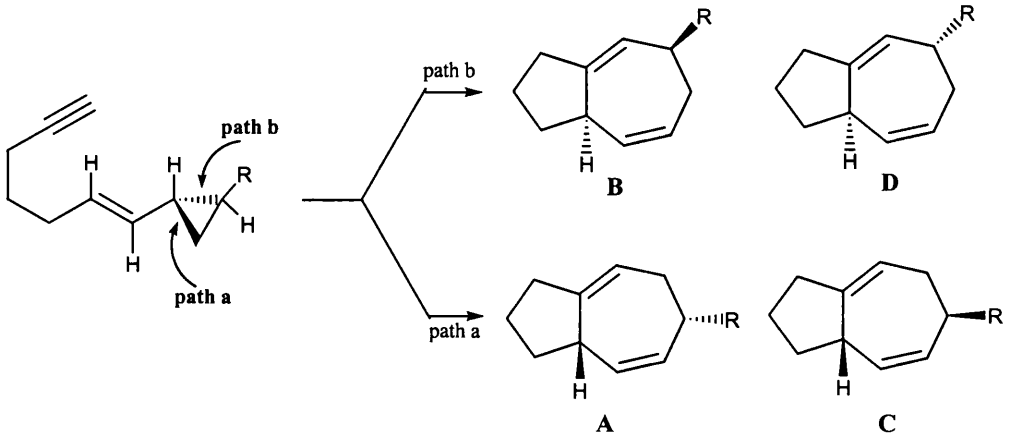
A = $RhCl(PPh_3)_3$ **98** (5 mol%), AgOTf (5 mol%), $PhCH_3$, 100°C, 30min (85%)
B = $[Rh(CO)_2Cl]_2$ **106** (5 mol%), $PhCH_3$, 100°C, 45min (90%)

Scheme 1.36

1.2.6 1,2-Disubstituted Vinylcyclopropanes

Thus far, in his studies of the [5+2] cycloaddition reaction, Wender had only considered systems with monosubstitued cyclopropanes. However, the introduction of a second cyclopropyl substituent would present a bifurcation of the reaction pathway, potentially leading to a diastereomeric mixture of

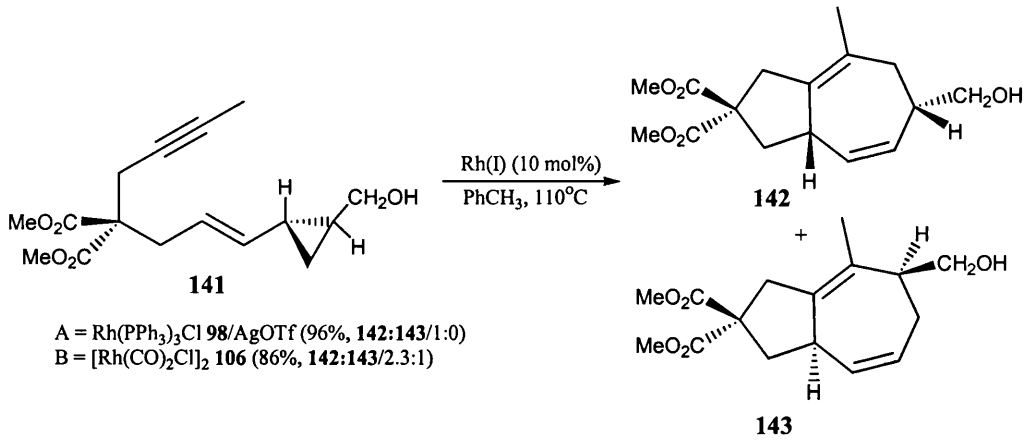
regioisomers and a total of four possible products (Scheme 1.37). Cleavage of either of the two cyclopropyl bonds would result in the formation of two possible regioisomers (A and B), and as both of these cleavages could proceed with retention or loss of configuration, each regioisomer would present two possible stereoisomers (B/D and A/C).



Scheme 1.37

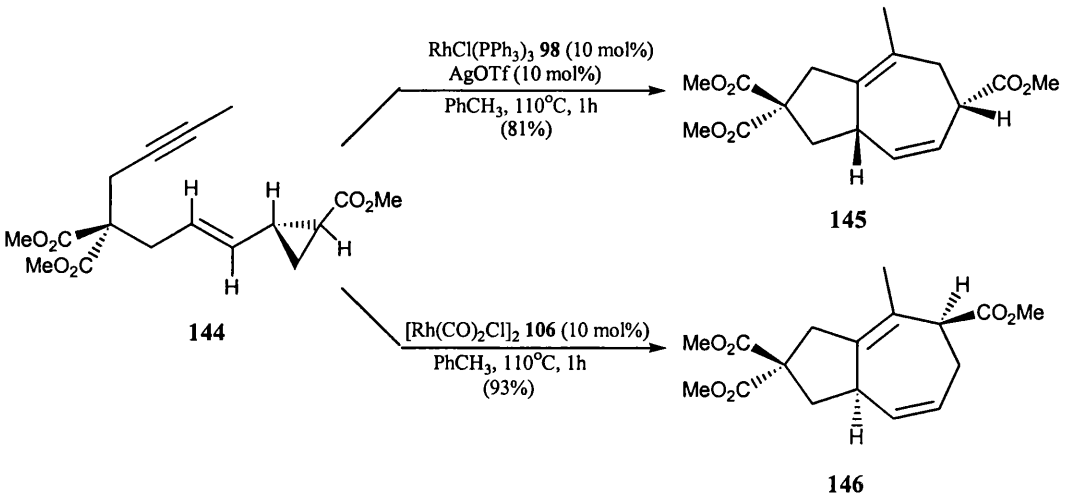
Thus, in introducing 1,2-disubstitution into vinylcyclopropanes, Wender has introduced a whole variety of new questions concerning regio- and stereoselectivity. However, he has demonstrated that these reactions are in fact much simpler in practice than might at first be anticipated.[75,76]

Reaction of the *trans*-disubstituted cyclopropane **141** with Wilkinson's catalyst **98** and silver (I) triflate resulted in cleavage of the least substituted cyclopropyl bond thereby affording cycloadduct **142** as a single regio- and diastereoisomer in a pleasingly high 80% yield (Scheme 1.38, conditions A). Wender has investigated a whole series of compounds, incorporating differing steric, electronic and coordinative characteristics. Through these studies, he has concluded that when Wilkinson's catalyst **98** is employed in these reactions, cleavage of the least substituted cyclopropyl bond is favoured in all cases, irrespective of the nature of the substituent.



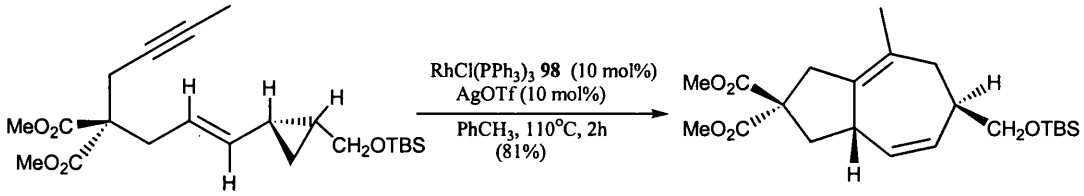
Scheme 1.38

Conversely, when the reactions are carried out in the presence of $[Rh(CO)_2Cl]_2$ **106**, the results obtained are not so straightforward. For example, reaction of yne-vinylcyclopropane **141** in the presence of 10 mol% $[Rh(CO)_2Cl]_2$ **106** proceeded to afford the two regioisomeric cycloadducts **142** and **143** in a 2.3:1 ratio (Scheme 1.38, conditions B). Generally, use of the dimeric rhodium catalyst results in a mixture of regioisomers, but in most instances the reaction still favours cleavage of the least substituted bond. The exception to this case is when cyclopropanes are used which bear an electron-withdrawing substituent. Interestingly, in this case the selectivity is reversed, and the more highly substituted bond is cleaved. Thus it is possible with *trans*-substituted cyclopropanes such as **144**, to alter the regioselectivity of cleavage merely by changing the catalyst (Scheme 1.39).



Scheme 1.39

When *cis*-substituted cyclopropanes are employed in these reactions the regioselectivity observed is complementary to that obtained for *trans*-substituted cyclopropanes, on the other hand however, the stereoselectivity is reversed. For example the reaction of *cis*-cyclopropane **147** proceeds in the presence of 10 mol% $RhCl(PPh_3)_3$ **98** and silver (I) triflate with cleavage of the least substituted bond to afford the cycloadduct **148** in 81% yield (Scheme 1.40). Thus, the *cis* or *trans* configuration of the cyclopropyl substituents directly determines the diastereomeric nature of the cycloadduct.



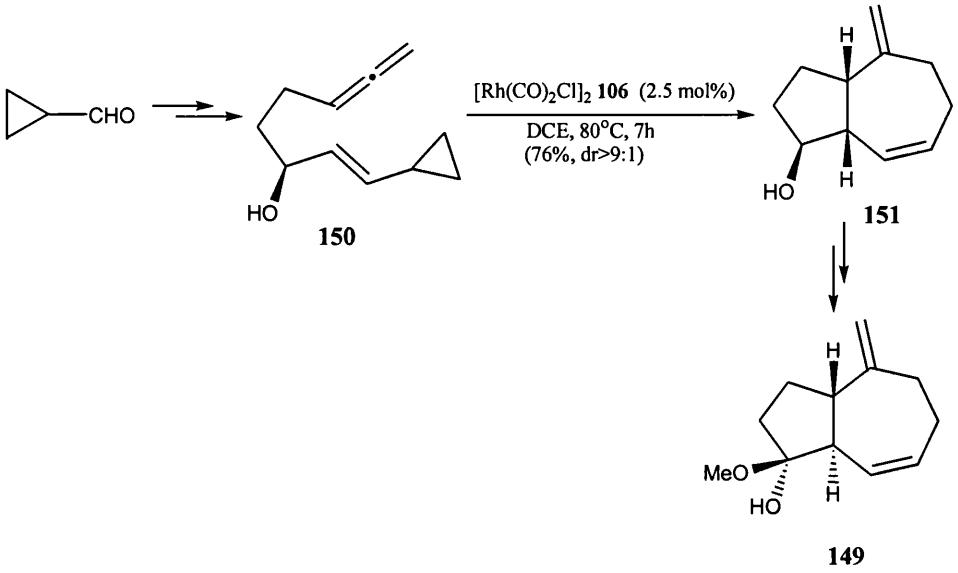
147 **148**

Scheme 1.40

By this investigation, Wender has therefore provided routes for the obtention of all four regioisomeric and diastereomeric cycloadducts detailed in Scheme 1.37, through varying the nature of the substituent, the type of catalyst or the *cis/trans* relationship of the cyclopropyl substituents. Clearly, these control elements are of enormous value in driving towards a Diels-Alder like reaction for seven-membered rings.

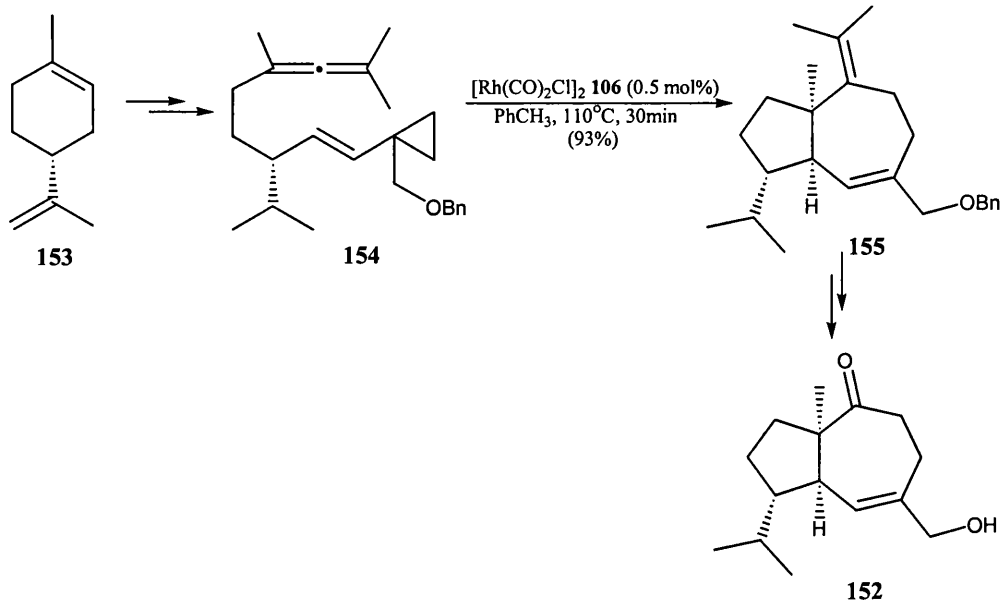
1.2.7 Application to Total Synthesis

In testing this new cycloaddition within the context of total synthesis, Wender has demonstrated that it is indeed a robust process. For example, the total synthesis of (+)-dictamnol[77] **149** was readily achieved in only 6 steps and 9% overall yield through a rhodium (I)-catalysed cycloaddition of an allenyl-vinylcyclopropane **150** which gave the cycloadduct **151** in 76% yield (Scheme 1.41).



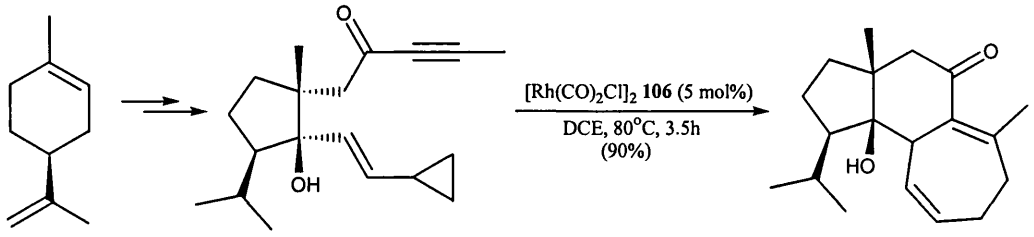
Scheme 1.41

Similarly, a total synthesis of (+)-aphanamol[78] **152** was realised in only 10 steps and 14% overall yield from (*R*)-limonene **153** through a rhodium (I)-catalysed intramolecular [5+2] cycloaddition of the allenyl-vinylcyclopropane **154**. This route facilitated access to cycloadduct **155** in 93% yield with complete chemo-, regio- and diastereoselectivity (Scheme 1.42).



Scheme 1.42

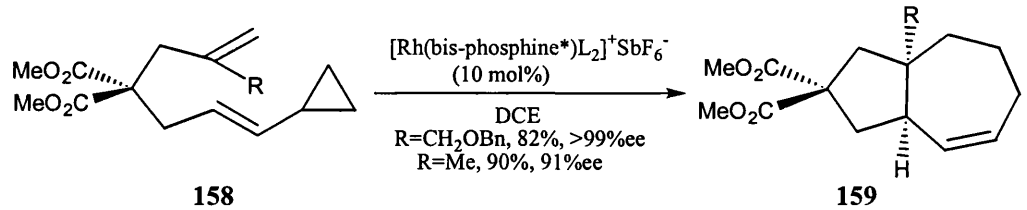
More recently, Wender has described a concise asymmetric synthesis of the tricyclic core of nerve growth factor-inducing cyathane diterpenes.[79] This achievement was made through the rhodium (I)-catalysed cycloaddition of ynone-vinylcyclopropane **156** furnishing the cyathane core **157** in 90% yield and >95% selectivity, thereby, providing an efficient route to cyathane diterpenes in 14 steps and an overall 13% yield (Scheme 1.43).



156 **157**

Scheme 1.43

The above examples elegantly illustrate how pre-existing chirality in a substrate may be used in conjunction with the [5+2] cycloaddition as a route to achieving asymmetric synthesis. Conversely, when no pre-existing chirality is present, Wender has also shown that the process may be rendered asymmetric by the use of an asymmetric catalyst.[80] For example, reaction of vinylcyclopropanes such as **158** in the presence of asymmetric bidentate phosphine ligands have been found to facilitate [5+2] cycloaddition reactions as well as inducing good to excellent enantioselectivity (91-99% ee) in the resultant cycloadduct **159** (Scheme 1.44).



158 **159**

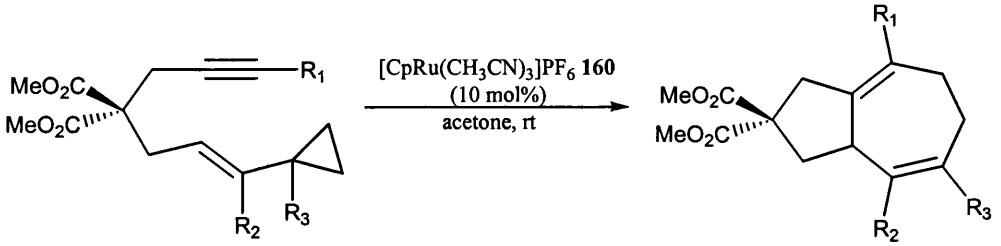
Scheme 1.44

1.2.8 [CpRu(CH3CN)3]PF6 Catalyst

The success of the Rh(I)-catalysed [5+2] cycloaddition pioneered by the Wender group has also stimulated interest in the development of an alternative catalyst system. In his search for atom economy in organic synthesis involving the ruthenium complex, $[CpRu(CH_3CN)_3]PF_6$ **160**, Trost and co-workers have

accordingly discovered the ability of this catalyst to catalyse the intramolecular [5+2] cycloaddition of alkynyl-vinylcyclopropanes.[81]

Trost demonstrated the ease with which these reactions proceed in the presence of 10 mol% Ru(II)-catalyst **160** in acetone at room temperature (Scheme 1.45). For example, when alkynyl-vinylcyclopropane **161a** was employed, cycloaddition proceeded to give the cycloadduct **162a** in an excellent 83% yield



161a-d

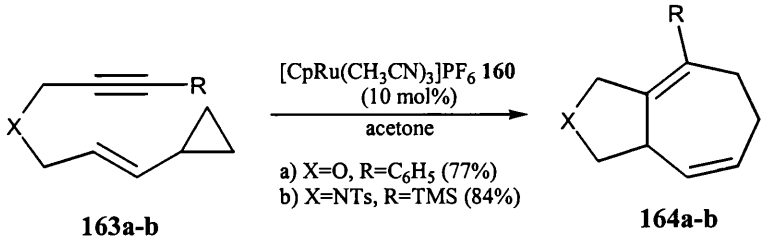
a) R_1=H, R_2=H, R_3=H (83%)
b) R_1=C_6H_5, R_2=H, R_3=H (82%)
c) R_1=CH_3, R_2=CH_3, R_3=H (87%)
d) R_1=CH_3, R_2=H, R_3=CH_3 (75%)

162a-d

Scheme 1.45

A study of the scope of this catalyst also revealed a tolerance for substitution at the alkyne, alkene and cyclopropyl positions (Scheme 1.45, a-d). When vinylcyclopropanes with substitution at R_2 are used (Scheme 1.45, c), none of the secondary isomerisation that was so problematic in reactions with Wilkinson's catalyst **98** was encountered.

As with the previous catalyst systems, this new methodology allows for the incorporation of ethers and sulfonamido groups, thereby providing access to a range of biologically interesting molecules as exemplified by the reactions of either **163a** or **163b** in the presence of 10 mol% $[CpRu(CH_3CN)_3]PF_6$ catalyst **160** in acetone to furnish the cycloadducts **164a** and **164b** in 77% and 84% respectively (Scheme 1.46).

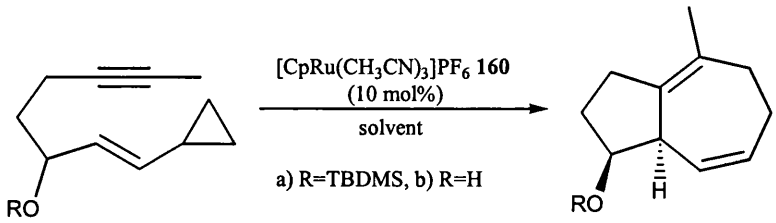


163a-b **164a-b**

Scheme 1.46

The extraordinary reactivity of the $[CpRu(CH_3CN)_3]PF_6$ catalyst **160** may be attributed to the extremely labile nature of the acetonitrile ligands in the presence of acetone or DMF, which facilitates the formation of the reactive species, $[CpRu]^+$. Although Trost suggests that the ruthenium and rhodium catalysed reactions must proceed through different mechanisms, both authors do in fact postulate very similar mechanistic pathways (Scheme 1.18).[65,81]

The cationic Ru(II)-catalyst **160** may also act as a Lewis acid and consequently, Trost felt that it was necessary to investigate its applicability to substrates bearing a potential leaving group at the allylic position.[81] In the event both free and protected allylic alcohols were tolerated, furnishing the desired cycloadducts with no depreciation in yield (Scheme 1.47, Table 1.4).



165a-b **166a-b**

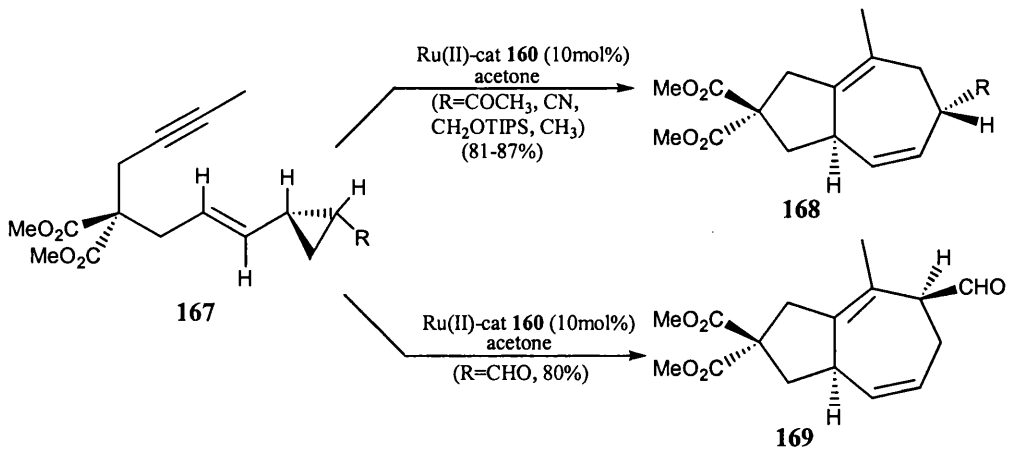
Scheme 1.47

Entry	R	Solvent	Yield (%)	Diastereomeric ratio (*trans/cis*)
1	TBDMS	acetone	92	3.1:1
2	TBDMS	DMF	73	5.1:1
3	H	DMF	70	1.5:1

Table 1.4

Reaction of the protected alcohol **165a** indicates a small preference for formation of the *trans* isomer **166a** (Table 1.4, entry 1), and on changing the solvent from acetone to DMF, the diastereoselectivity is improved from 3.1:1 to 5.1:1 (Table 1.4, entry 2). Unfortunately, a diminished diastereoselectivity of 1.5:1 was noted when the free allylic alcohol **165b** was employed suggesting that the observed diastereoselectivity may be a result of steric factors (Table 1.4, entry 3).

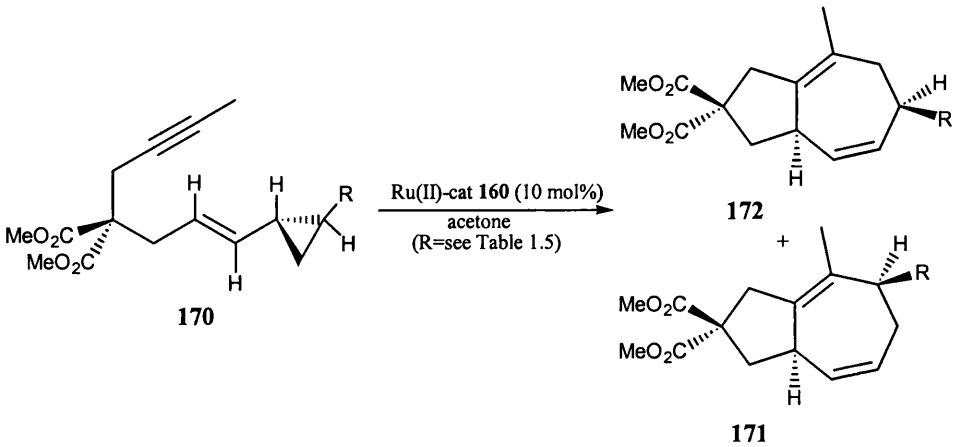
In order to further explore the scope of the Ru(II)-catalyst **160** in these reactions, Trost then undertook an intensive study of 1,2-disubstituted cyclopropanes, paying particular attention to the observed regioselectivity.[82] Employment of $[CpRu(CH_3CN)_3]PF_6$ **160** in the reaction of the *cis*-disubstituted cyclopropanes **167**, for a range of substituents showed an almost exclusive preference for cleavage of the less hindered cyclopropyl bond providing cycloadduct **168** (Scheme 1.48). The only exception to this case was observed when an aldehyde substituent was incorporated, whereby migration of the more substituted bond of **167** provided the alternative regioisomer **169** (Scheme 1.48). Curiously, incorporation of the aldehyde substituent not only affected the regioselectivity but also provided the opposite diastereoisomer.



Scheme 1.48

Contrastingly, the regioselectivity observed for the *trans*-disubstituted cyclopropanes was not so straightforward (Scheme 1.49). Remarkably, the *trans*-aldehyde substrate **170** reacted favouring the same regioselectivity to that obtained for the *cis*-counterpart (Table 1.5, entry 1). However, here the similarity ended, with subsequent substrates indicating little or no preferred regioselectivity,

for example ester and cyano substrates displayed only a small preference for migration of the more substituted bond to give **171** (Table 1.5, entries 2 and 3), whereas ketone and silyloxy substrates showed a small bias for cleavage at the less hindered bond to afford cycloadduct **172** (Table 1.5, entries 5 and 6).



Scheme 1.49

Entry	R	Yield (%)	Diastereomeric ratio (172:171)
1	CHO	83	1:12
2	CO_2CH_3	90	1:2
3	CN	87	1:1.9
4	SO_2Ph	78	1:1
5	$COCH_3$	83	1.5:1
6	CH_2OTIPS	81	3:1

Table 1.5

Although regiocontrol appears absent for *trans*-substrates, Trost emphasises that these reactions are however highly stereoselective resulting in the formation of only one diastereoisomer, the only exception being noted for the *cis*-aldehyde **169**. Whereas steric effects dominate the regioselectivity of *cis*-cyclopropyl substrates, the bond energy of the cleaving bond appears to be more important for the *trans*-substrates.

Trost also attempted to apply his Ru(II)-catalyst **160** to the intramolecular cycloaddition of an alkene and vinylcyclopropane, but unfortunately $[CpRu(CH_3CN)_3]PF_6$ **160** proved to be completely unreactive as a catalyst with this functional group combination.[83]

1.2.9 Concluding Remarks

The investigations carried out by Wender and Trost have provided a thorough insight into the scope of the transition metal catalysed [5+2] cycloaddition reaction. In fact, the three proposed catalyst systems each provide different opportunities to realise these cycloaddition reactions. Problems arising from the use of a particular catalyst may be absent on selection of one of the alternatives. For example, secondary isomerisation of substituted olefins was a major problem for Wilkinson's catalyst **98**, but was not observed when either $[Rh(CO)_2Cl]_2$ **106** or $[CpRu(CH_3CN)_3]PF_6$ **160** was employed. In addition, $[Rh(CO)_2Cl]_2$ **106** does not catalyse reactions incorporating terminal alkynes, but no problems are observed with Wilkinson's catalyst **98** or $[CpRu(CH_3CN)_3]PF_6$ **160**.

A particular point of interest was the ability to control the regioselectivity of 1,2-disubstituted cyclopropanes by selection of the appropriate catalyst. Wilkinson's catalyst **98** demonstrated the most consistent regio- and stereocontrol, as in all cases, preference for cleavage of the less hindered cyclopropyl bond was observed. In addition, the diastereoselectivity of these reactions was directly related to the *cis* or *trans* configuration of the cyclopropyl substitution, regardless of the nature of the substituents. The only drawback to using this catalyst was the requirement for relatively harsh reaction conditions.

The $[Rh(CO)_2Cl]_2$ **106** catalyst offered a route to achieving cleavage of the more hindered cyclopropyl bond, however, this selectivity was only observed for cyclopropanes bearing electron withdrawing groups. Otherwise the resulting regio- and stereoselectivity was analogous to that of Wilkinson's catalyst **98**, although mixtures were frequently obtained.

$[CpRu(CH_3CN)_3]PF_6$ **160** indicated an exclusive preference for cleavage of the less hindered cyclopropyl bond for *cis*-substituted cyclopropanes. However, very

little, or often, no regiocontrol whatsoever was observed for the *trans*-substituted compounds, although a small bias for cleavage of the more hindered bond was observed for electron withdrawing substituents.

In conclusion, although Wilkinson's catalyst **98** appears to offer a broader scope of reactivity, the $[Rh(CO)_2Cl]_2$ **106** and $[CpRu(CH_3CN)_3]PF_6$ **160** catalysts are efficient in overcoming many of the problematic cases which have been encountered, in addition to providing the opportunity for much milder reaction conditions.

CHAPTER TWO

RESULTS AND DISCUSSION

2.1 Aims and Objectives

As we have seen, considerable effort has been focused on the synthesis of colchicine **1** over the past 40 years, and even now it remains a challenging target in the eyes of the synthetic chemist. Apart from the more recent work described by Banwell[51] in 1992 and Cha[52] in 1998, all of the previous syntheses have suffered from a lack of regiocontrol as they have proceeded through the intermediacy of a free tropolone derivative, thereby suffering from the inevitable loss of yield on separating the methylation products (the "diosphenol problem"). Moreover, there have been no reported syntheses in which the acetamido function at *C*-7 has been introduced in a totally enantiospecific manner, although of course the route reported by Cha[52] (90% ee) would be a considerable challenge to surpass.

Thus, a synthesis of colchicine **1** that will address these problems of regio- and enantioselectivity remains a highly attractive goal. We hoped to develop such a synthesis of colchicine **1** by employing three basic strategies. First of all, we hoped to obtain a method for formation of the tropolonic methyl ether which does not occur *via* methylation of a free tropolone. Secondly, by forming both rings B and C together in a single step we hoped that the overall number of steps required could be reduced, together with providing opportunities for introduction of different functionalities into the molecule. Finally, we wished to introduce the acetamido functionality at *C*-7 by an asymmetric step.

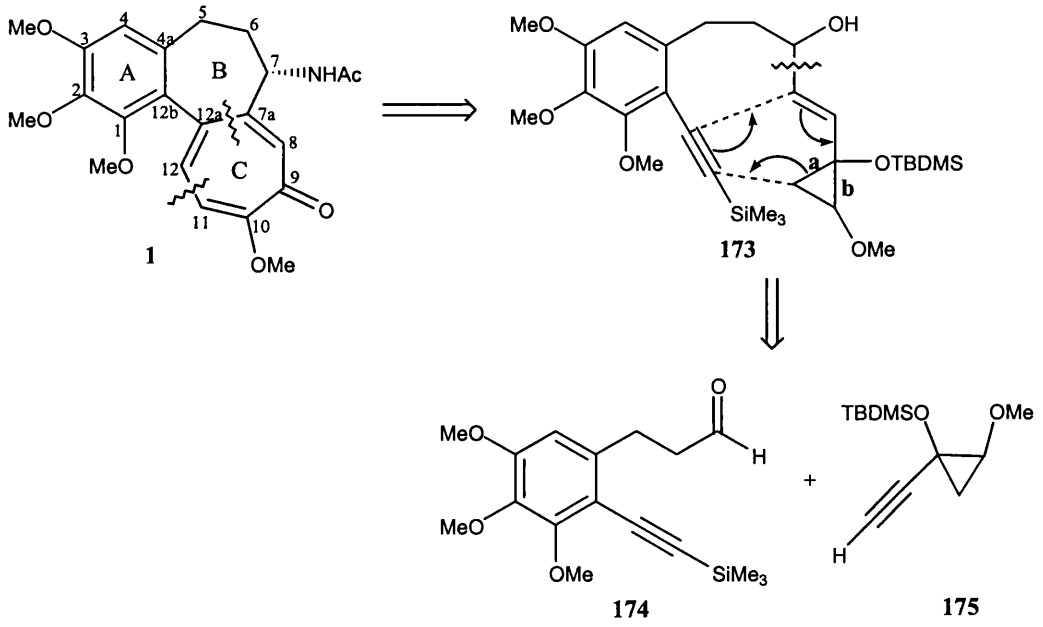
In pursuit of the above objectives, the transition metal catalysed [5+2] cycloaddition reaction appealed to us as an extremely plausible, albeit somewhat challenging, ambition.

2.2 Retrosynthetic Analysis in the Proposed [5+2] Cycloaddition Route for the Synthesis of Colchicine

Colchicine **1** consists of two seven-membered rings, and consequently, the metal mediated [5+2] cycloaddition may serve as a powerful tool in achieving a successful synthetic route to this molecule *via* simultaneous construction of these

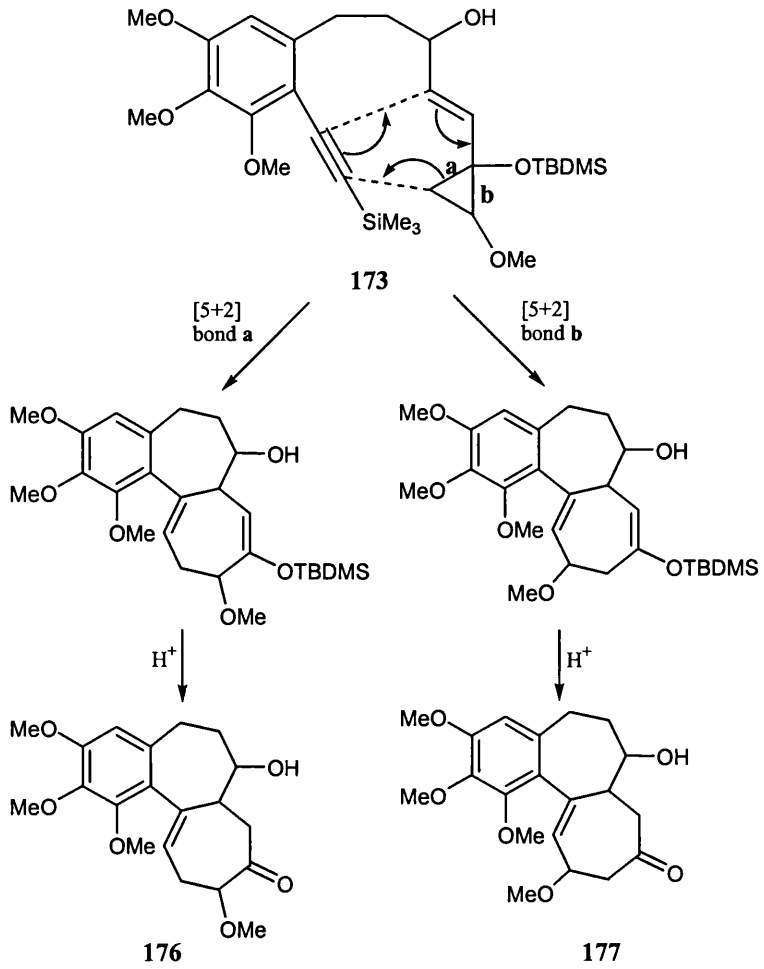
two rings. To the best of our knowledge, this method has not been previously applied to such a highly oxygenated molecule.

The following highly convergent retrosynthetic analysis of colchicine **1** was accordingly envisaged (Scheme 2.1). It was proposed that cleavage of bond (7a-12a) and bond (11-12) would provide the alkynyl-vinylcyclopropane **173**, which we hoped would be a suitable candidate for the [5+2] cycloaddition reaction developed by Wender.[65] Thus the alkyne moiety would provide the 2π-component and the vinylcyclopropane the 5π-component for the target reaction. Further disconnection of the allylic alcohol **173** provides the aldehyde **174** and the alkynylcyclopropane **175**, which were accordingly the chosen target building blocks for the synthesis.



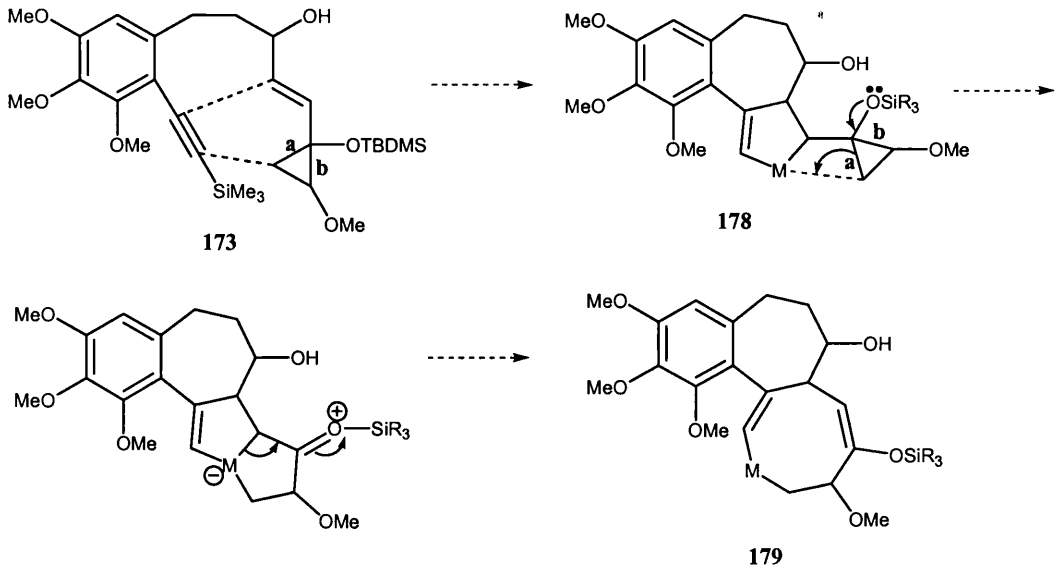
Scheme 2.1

Nevertheless, this approach presented an important regiochemical question as to whether bond **a** or bond **b** of the cyclopropyl ring would break in the cycloaddition reaction. Cleavage of bond **a** would lead to the desired colchicine structure **176**, but cleavage of bond **b** would result in the formation of an undesired regioisomeric colchicine skeleton **177** (Scheme 2.2).



Scheme 2.2

Unfortunately, at the outset of our own study, insufficient work had been published on such substitution patterns around the cyclopropane to allow any clear predictions to be made. We reasoned however, as implied in Scheme 2.3, that electron release from the silyloxy group should be dominant in favouring the ring expansion of the metallocyclopentene **178** to the eight-membered ring **179**, and that, of the two possible modes of cleavage, the least substituted but less electron rich, bond **a** might be simply favoured on steric grounds. It was from this optimistic view that we therefore embarked on the daring strategy of carrying out the key step towards the end of the synthesis.

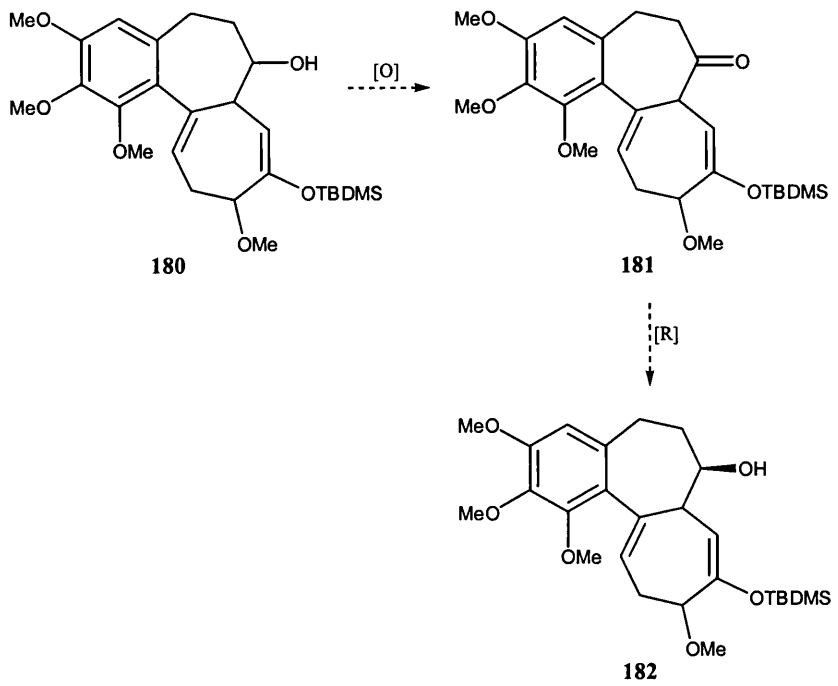


Scheme 2.3

2.3 Incorporation of the Chiral Centre at *C*-7

Our secondary objective was to introduce the acetamido functionality at *C*-7 in an enantioselective fashion, which we hoped to achieve *via* the nucleophilic displacement of an oxygen-based leaving group using the Mitsunobu reaction.[84] This of course demanded the pre-existence of a chiral alcohol at *C*-7, possessing the opposite absolute configuration to that required in the target molecule.

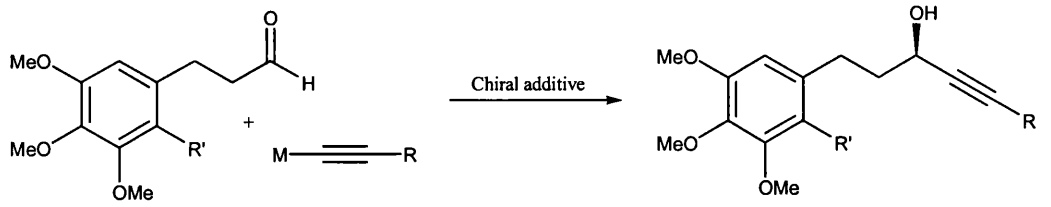
Two strategies were thus proposed for formation of a suitable (*R*)-alcohol, the first of which involved a series of oxidation and reduction procedures as described in the synthesis of Banwell.[51] Thus, it was hoped that oxidation of the racemic alcohol **180** would provide the ketone **181**, which could then undergo an enantioselective reduction in the presence of a chiral reducing agent to furnish the (*R*)-alcohol **182** (Scheme 2.4). In particular, Corey has shown that oxazaborolidine derivatives are excellent catalysts for borane reductions of a variety of achiral ketones to chiral secondary alcohols with 84-99% enantiomeric excess.[85,86]



Scheme 2.4

The second and more attractive strategy involved construction of the chiral alcohol prior to the cyclisation step. This could be achieved by nucleophilic addition of a metalated acetylene **183** to an aldehyde **184** in the presence of a chiral additive with formation of a chiral propargylic alcohol **185** (Scheme 2.5). This approach provided a substantial synthetic advantage over the previous method, as it would enable formation of a desired carbon-carbon bond with concomitant generation of the stereogenic centre in a single transformation. However, although many of the current methods for such an operation are far from ideal and suffer from limited scope and moderate enantioselectivity,[87,88,89] Corey[90] has reported that the oxazaborolidine catalysed enantioselective addition of alkynylboranes to aldehydes occurs in high yields and with excellent ee's. Furthermore, Carreira[91,92,93] has recently described new methodology involving the addition of zinc acetylides to aldehydes in the presence of optically active amino alcohols which furnishes secondary alcohols in up to 99% ee.

Thus, several methods were therefore available for obtaining a suitable (*R*)-alcohol, which would allow subsequent introduction of the (*S*)-acetamido group.

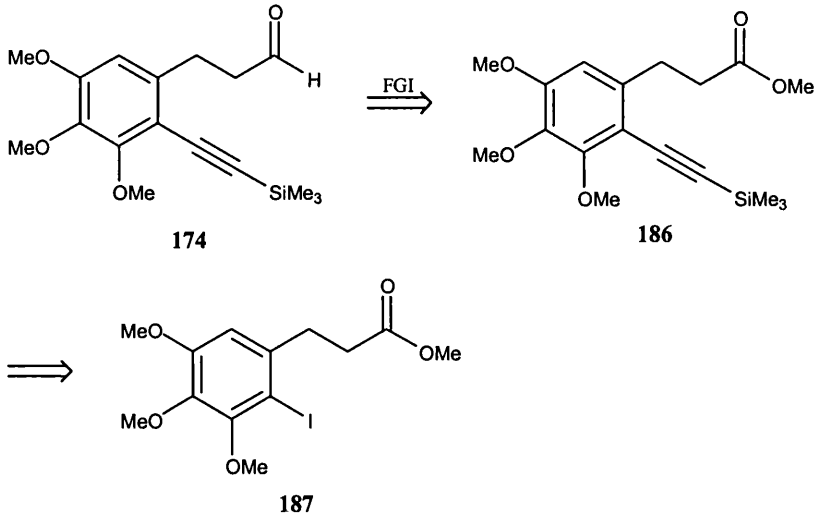


184 183 185

Scheme 2.5

2.4 The Synthesis of Aldehyde (174)

Our initial attention was focused on obtaining the aldehyde **174**, this was envisaged in retrosynthetic terms as a simple three stage operation featuring reduction of the ester **186**, and a palladium catalysed alkynylation disconnection (Scheme 2.6).

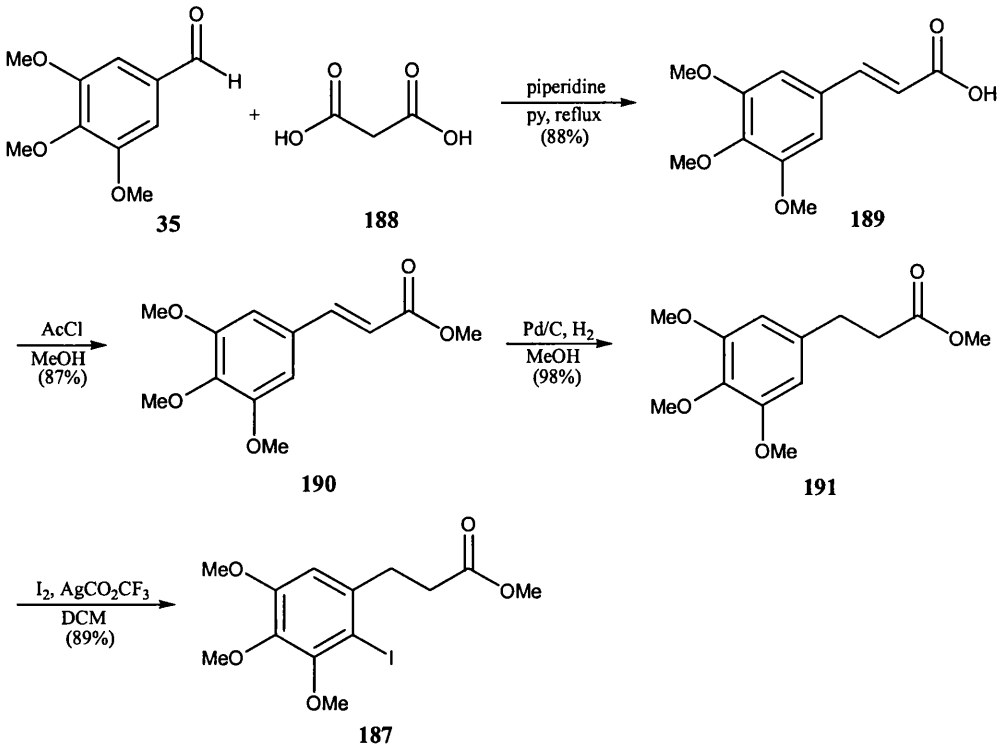


174 186 187

Scheme 2.6

The starting material for the synthesis of the aryl iodide **187**, was the readily available 3,4,5-trimethoxybenzaldehyde **35**, which was employed in a Knoevenagel condensation with malonic acid **188** as described by Koo *et al.*[94] and furnished the cinnamic acid **189** in an isolated yield of 88% as the (*E*)-isomer exclusively. Subsequent elaboration to the methyl ester was achieved by treatment with a methanolic solution of hydrogen chloride, produced by addition of acetyl chloride to methanol, to afford **190** in 87% yield. Hydrogenation of **190** over 10% palladium on carbon provided the saturated ester **191** in almost quantitative yield, and subsequent monoiodination of the aromatic ring with elemental iodine and

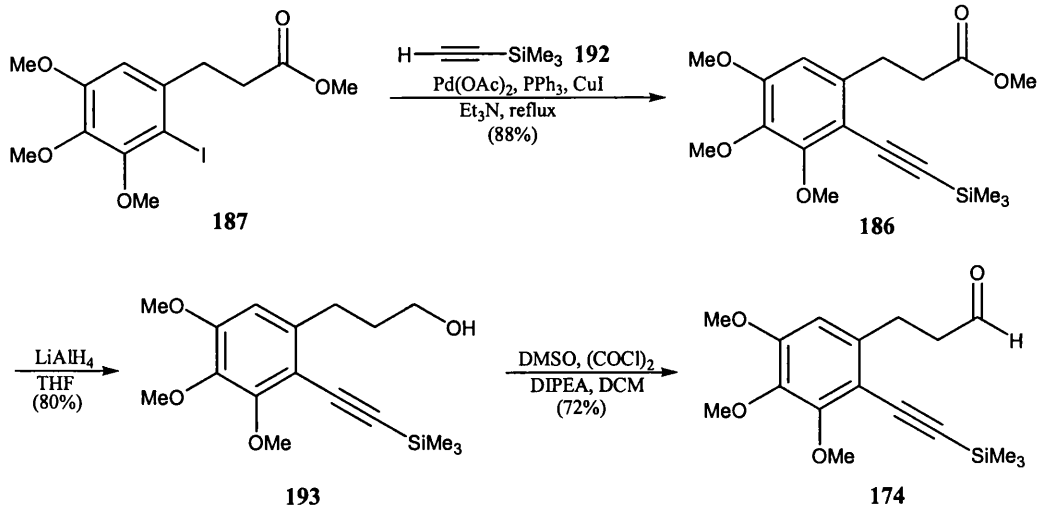
silver trifluoroacetate[95] afforded the desired aryl iodide **187** in 89% yield (Scheme 2.7).



Scheme 2.7

This approach enabled the synthesis of **187** to be achieved in multigram quantities with an excellent overall yield of 67%, utilising cheap, readily available starting materials and requiring no chromatography until the final step.

As proposed in the retrosynthetic analysis, we then hoped to introduce the alkyne moiety *via* a palladium catalysed coupling reaction of the aryl iodide **187** and trimethylsilylacetylene **192**. The Sonogashira coupling protocol[96] was employed using palladium (II) acetate, copper (I) iodide, triphenylphosphine and triethylamine, which furnished the acetylenic compound **186** in an excellent 88% yield. The selection of this procedure enables the generation of the active palladium (0) catalyst *in situ* from the palladium (II) acetate by reduction and coordination with triphenylphosphine (Scheme 2.8).

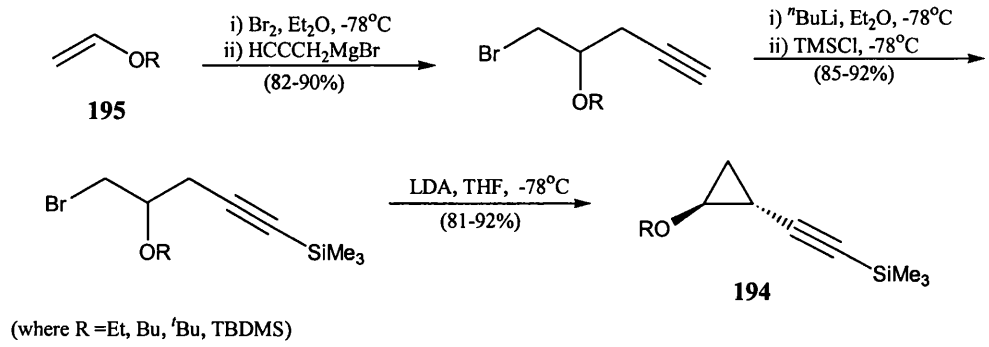


Scheme 2.8

It was anticipated that the aldehyde **174** could be obtained directly *via* reduction of the ester **186** with diisobutylaluminium hydride, however attempts to achieve this operation were unsuccessful, the reaction proceeded too far and as a result over reduction led to the alcohol **193**. Consequently, the ester **186** was first reduced with lithium aluminium hydride, which resulted in clean conversion to alcohol **193**, followed by a Swern oxidation reaction[97] to furnish the target aldehyde **174** in a 58% yield over the two steps (Scheme 2.8).

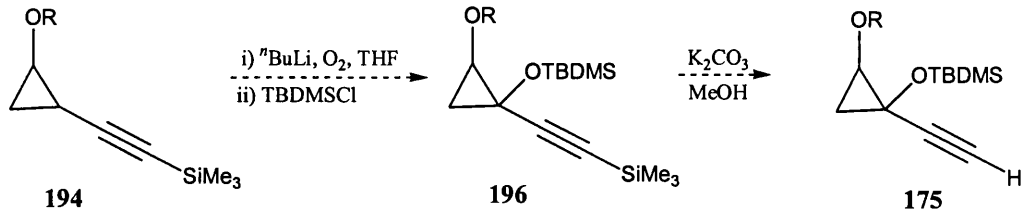
2.5 The Synthesis of Alkynylcyclopropane (175)

Concentrating now on the synthesis of the alkynylcyclopropane **175**, our attention was directed towards the literature in search for potential opportunities. In the first instance, we were particularly attracted by the excellent methodology for the synthesis of 1,2-(*bis*-oxy)-cyclopropanes which had been reported by de Meijere.[98] According to his procedure, 2-alkoxyethynylcyclopropanes **194** can be synthesised stereoselectively and in excellent yield over three steps from alkyl vinyl ethers **195** (Scheme 2.9).



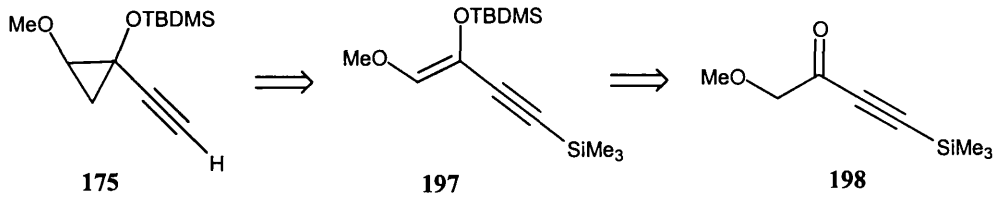
Scheme 2.9

It was anticipated that subsequent reaction of the lithiated cyclopropane of **194** with molecular oxygen, followed by *tert*-butyldimethylsilyl chloride would furnish **196**. Finally, cleavage of the trimethylsilyl group should provide the target alkynylcyclopropane **175** (R = Me) (Scheme 2.10).



Scheme 2.10

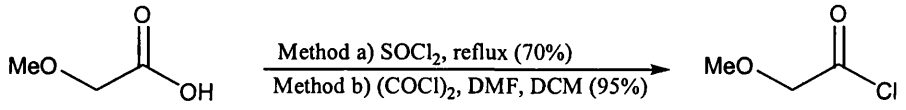
Unfortunately, this procedure could not be attempted, as the required alkyl vinyl ether in our case was methyl vinyl ether **195** (R = Me), a gas which was not readily available. An alternative strategy was therefore required, and the simple route involving cyclopropanation of an appropriate silylenol ether such as **197** was selected (Scheme 2.11). This in turn required the preparation of the acetylenic ketone **198**, which in the event proved to be a somewhat challenging objective.



175 197 198

Scheme 2.11

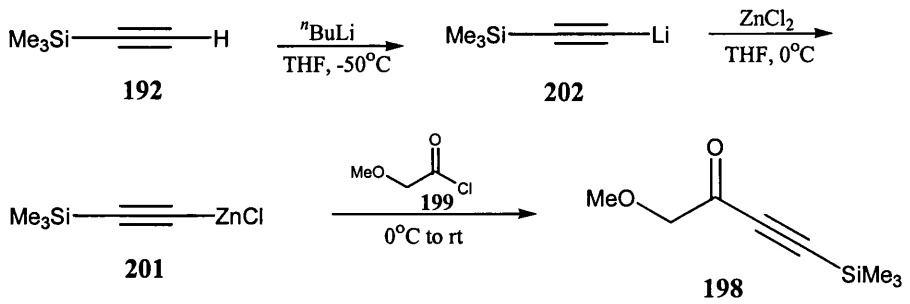
The starting material for our investigations was methoxyacetyl chloride **199**, the preparation of which was reliably achieved under standard conditions from methoxyacetic acid **200**. Initially the reaction of the acid **200** in refluxing thionyl chloride furnished the corresponding acid chloride **199** in 70% yield, but the boiling points of the acid chloride **199** and thionyl chloride were relatively close and therefore separation proved difficult. Selection of the oxalyl chloride/DMF protocol however afforded the same product **199** in a much improved 95% yield (Scheme 2.12).



200 **199**

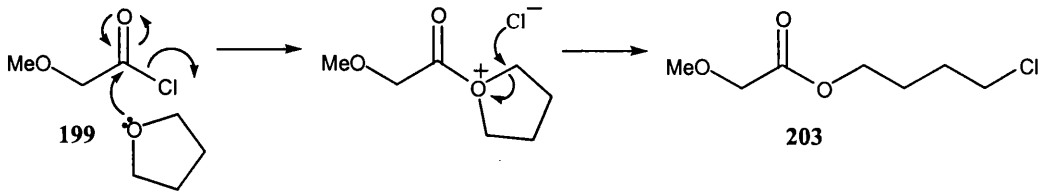
Scheme 2.12

Our initial approach involved the reaction of acid chloride **199** with a solution of alkynylzinc chloride **201** in THF to afford the desired acetylenic ketone **198** (Scheme 2.13). Preparation of the alkynyllithium species **202** was readily achieved by treatment of trimethylsilylacetylene **192** with *n*-butyllithium in THF at -50°C. Subsequent reaction with an equivalent amount of freshly fused zinc chloride at 0°C led to the alkynylzinc chloride **201**, which underwent reaction with the acid chloride **199** to afford the desired acetylenic ketone **198** in a disappointing 30% yield.



Scheme 2.13

A second product **203** was obtained in a 2:1 ratio with the ketone **198**, and was identified to be the ester resulting from reaction of THF with methoxyacetyl chloride **199** (Scheme 2.14). This explained the low yield of ketone **198**, as the side-reaction was consuming vital starting material. Negishi and co-workers[99] had previously noted the formation of such chloro compounds, however, they suggested that it was not a serious problem in any of their experiments, but none of the acid chlorides investigated in their studies possessed α-protons. In our case, the reaction of methoxyacetyl chloride **199** with THF was more dominant than the desired reaction with the alkynylzinc reagent **201**.



Scheme 2.14

Attempts were made to prevent this major side-reaction from occurring (Table 2.1). One equivalent of zinc chloride and *n*-butyllithium, 1.1 equivalents of trimethylsilylacetylene **192**, and 1.2 equivalents of methoxyacetyl chloride **199** were used in each reaction. The ratio of ketone **198** to ester **203** was calculated using ^{1}H NMR by measurement of the relative intensities of the CH_2OMe integrals.

Entry	$Pd(PPh_3)_4$ (mol%)	Ratio 198:203	Yield (%) 198
1	-	1:2	30
2	-	3:4	24
3	0.4	2:1	22

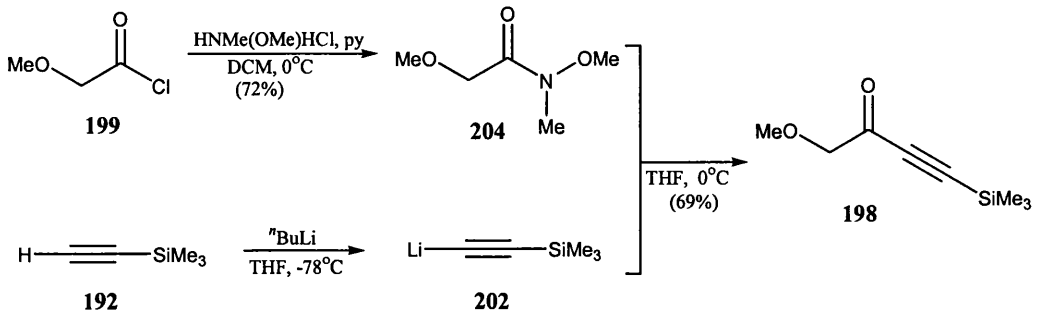
Table 2.1

Firstly, the reaction temperature was considered, and the reaction was repeated but this time controlling temperatures and addition rates much more carefully. This provided the ketone **198** and ester **203** in a 3:4 ratio (Table 2.1, entry 2), thereby slightly increasing the ratio of desired ketone. However, ketone **198** was isolated in a lower yield, but this was probably due to the reaction being performed on an even smaller scale.

Palladium tetrakis(triphenylphosphine) has been shown to promote reactions of this type which are otherwise unreactive by activating the carbonyl bond for attack by the acetylide.[99,100] Consequently, a small amount of $Pd(PPh_3)_4$ was employed in the reaction (Table 2.1, entry 3). This resulted in an increase in reaction rate with the reaction being complete within 2 hours, as opposed to the previous examples where it had to be left overnight. Although the rate acceleration led to an increase in ratio of the products in favour of the desired ketone **198**, once again there was no increase in the isolated yield.

Thus, it was decided that an alternative route should be employed for the synthesis of ketone **198**. It has been reported that *N*-methoxy-*N*-methylamides combine cleanly with both Grignard reagents and organolithium species in THF to form ketones, without the formation of tertiary alcohols, even in the presence of a large excess of the organometallic reagent.[101] Accordingly, *N*-methoxy-*N*-methylamide **204** was prepared in 72% yield by treatment of methoxyacetyl chloride **199** with *N,O*-dimethylhydroxylamine hydrochloride in the presence of pyridine at 0°C. Subsequent preparation of the lithiated species **202** was achieved by reaction of trimethylsilylacetylene **192** with *n*-butyllithium at -78°C, thereby permitting

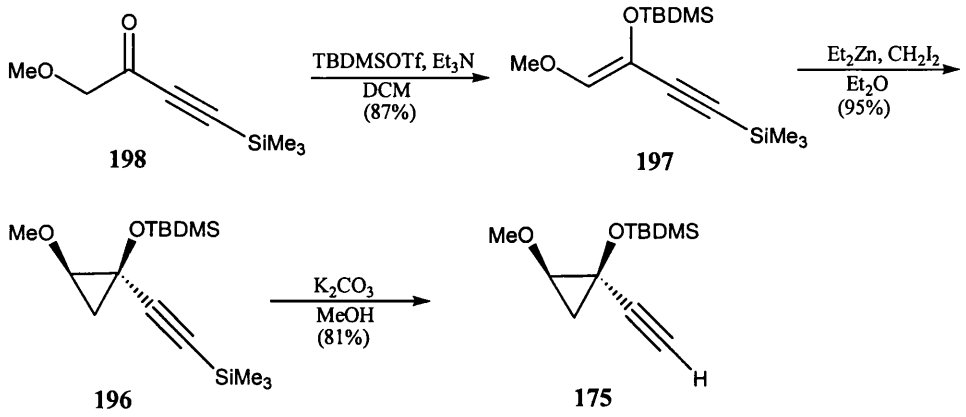
addition to the *N*-methoxy-*N*-methylamide **204** to afford the acetylenic ketone **198** (Scheme 2.15).



Scheme 2.15

Using this methodology as described by Weinreb,[101] the desired ketone **198** was obtained in an overall 50% yield from the acid chloride **199**. This was not an excellent yield, but was a considerable improvement on the previous method.

With a preparative route to the acetylenic ketone **198** in hand, we were ready to proceed with the synthetic route to alkynylcyclopropane **175** (Scheme 2.16). Elaboration to the silylenol ether **197** was readily achieved by treatment with *tert*-butyldimethylsilyl triflate in the presence of triethylamine, affording the desired product as a single stereoisomer in 87% yield, although the stereochemistry of the isomer was not assigned at this stage. The *tert*-butyldimethylsilyl group was selected in the hope that the trimethylsilyl group at the acetylenic terminus could be selectively removed at a later stage without affecting the silylenol ether moiety. Conversion to the cyclopropane **196** was then readily achieved *via* a modified Simmons-Smith cyclopropanation. The necessary zinc carbenoid was generated from diethylzinc and diiodomethane under standard Furukawa conditions.[102] The addition of this carbenoid to silylenol ether **197** produced the required cyclopropane **196** in excellent yield, although the reaction was quite slow due to the considerable steric hindrance around the double bond. Finally, selective desilylation at the alkyne terminus of the cyclopropane **196** was achieved by treatment with anhydrous potassium carbonate to afford the target alkynylcyclopropane **175** in 81% yield as a single diastereoisomer.



Scheme 2.16

The relative stereochemistry of **175** was assigned through nOe measurements (see Appendix, Figure 1 and Figure 2). Irradiation of the methoxy signal resulted in an enhancement of the *gem*-cyclopropyl proton, the *trans*-cyclopropyl proton and the *tert*-butyldimethylsilyl signals, whereas, irradiation of the –C*H* signal produced an enhancement of the adjacent methoxy moiety, the *cis*-cyclopropyl proton and the terminal acetylenic proton (Figure 2.1).

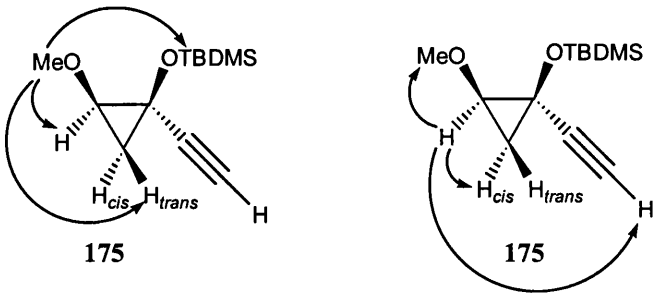
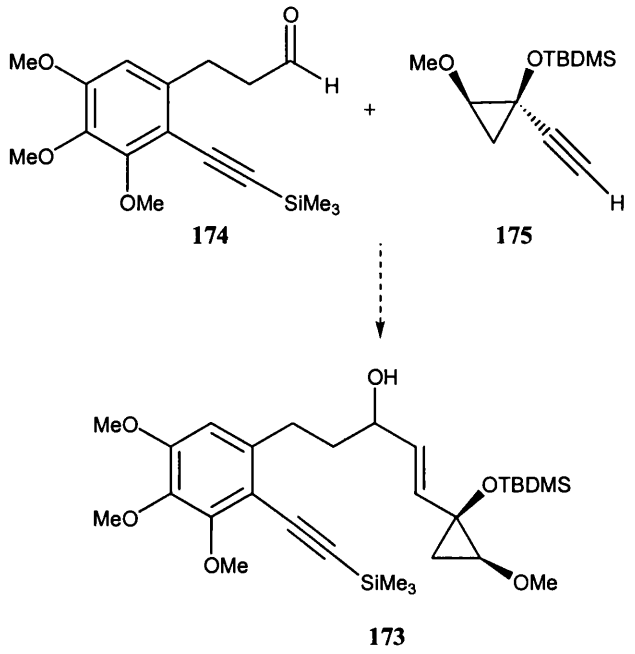


Figure 2.1

Unfortunately, the cyclopropane **175** proved to be a highly labile intermediate, and consequently, could only be synthesised on a relatively small scale. The resulting decomposition may possibly be attributed to the greater ease of protonation of the acetylenic group on removal of the silyl protection.

2.6 Coupling of Aldehyde (174) and Alkynylcyclopropane (175)

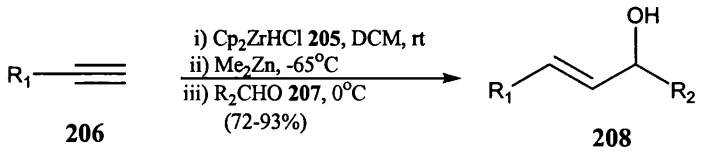
With the aldehyde **174** and the alkynylcyclopropane **175** building blocks in hand, our attention was then directed towards achieving the desired coupling of these two key fragments to provide the target alkynyl-vinylcyclopropane **173** which contained all of the necessary carbon atoms for the colchicine framework (Scheme 2.17).



Scheme 2.17

At this stage our attention was once again drawn to the literature in the search for a method that would furnish an allylic alcohol directly from the coupling of an aldehyde and an alkyne. Accordingly, it has been reported that the hydrozirconation of alkynes with Schwartz's reagent, (Cp_2ZrHCl) **205**, allows the convenient preparation of a wide range of functionalised organozirconocenes.[103] Furthermore, the addition of these organozirconocene complexes to aldehydes could provide a pathway for the desired carbon-carbon bond formation. However, the organozironocene complexes are relatively unreactive towards organic electrophiles as a result of the bulky cyclopentadienyl groups preventing attack, and therefore catalysis or transmetallation procedures are often required.[104-109]

In 1994, Wipf[109] reported elegant methodology for achieving this desired carbon-carbon bond formation *via* a zirconium-zinc transmetallation process. Initial hydrozirconation of alkyne **206** with Schwartz's reagent **205**, followed by transmetallation with dimethylzinc furnished the desired zinc reagent, and subsequent reaction with the aldehyde **207** furnished the (*E*)-allylic alcohol **208** in high yield for a range of simple substrates (Scheme 2.18).



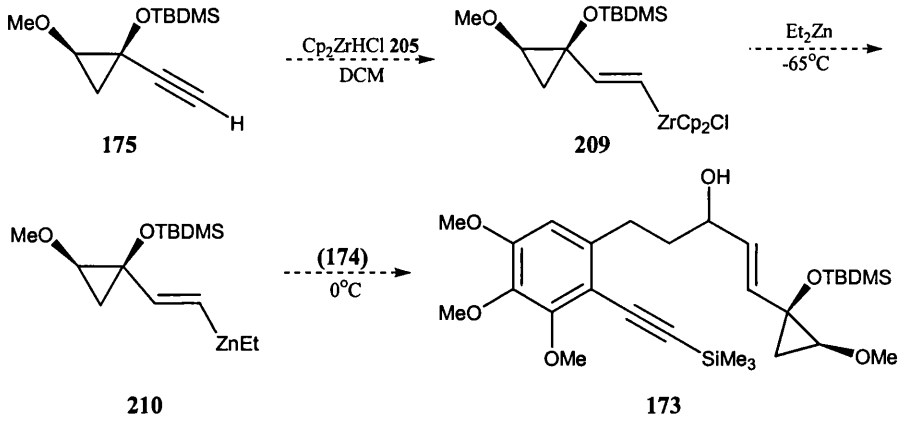
206 **208**

(R_1 = C_4H_9, $CH_2CH_2OTBDPS$, $CH_2CH_2CO_2CH_2Ph$)
(R_2 = Ph, n-C_5H_{11}, CHCHPh, $C(CH_3)_3$)

Scheme 2.18

Moreover, further work by Wipf,[110] then led to the development of a catalytic asymmetric protocol in the presence of amino thiol chiral agents, thereby providing an attractive route to chiral allylic alcohols in excellent ee's. This excellent methodology was highly attractive to us for the synthesis of our precursor **173**, as it would enable not only the formation of the allylic alcohol, but also achieve concomitant introduction of the desired chirality.

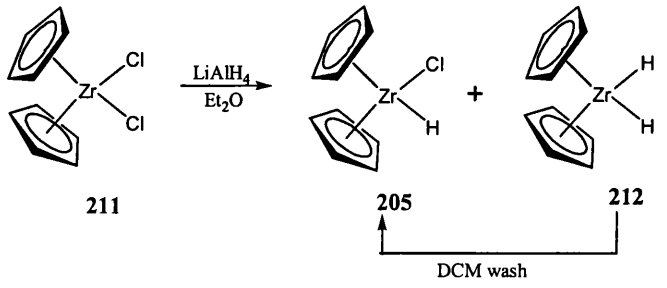
To achieve the desired coupling between aldehyde **174** and alkynylcyclopropane **175**, we therefore hoped to apply this methodology to our system, albeit that it had not been previously applied to a highly functionalised substrate such as **175**. Nevertheless, we anticipated that the initial hydrozirconation of alkynylcyclopropane **175** with Schwartz's reagent **205** would form the relatively unreactive alkenylzirconocene **209**, and that this could be followed by transmetallation with diethylzinc to the potentially more reactive organozinc species **210**. Finally, subsequent addition of aldehyde **174** to the organozinc species **210**, would hopefully lead to formation of the target allylic alcohol **173** (Scheme 2.19).



Scheme 2.19

However, as both the starting aldehyde **174** and the alkynylcyclopropane **175** fragments were rather precious, we chose to commence our investigations by carrying out some model studies employing commercially available reagents.

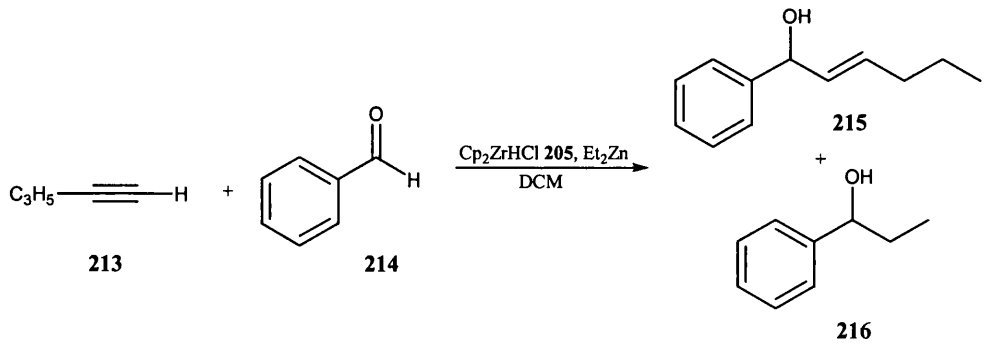
In addition, although Schwartz's reagent **205** is commercially available, it is often of poor quality with the majority of workers preferring to generate their own reagent. Consequently, Schwartz's reagent **205** was prepared according to the procedure of Buchwald and co-workers from *bis*(cyclopentadienyl)zirconium dichloride **211** (Scheme 2.20).[111,112] Thus, reduction of zirconocene dichloride **211** was achieved using a filtered solution of lithium aluminium hydride in ether to give a mixture of Schwartz's reagent **205** and the zirconocene dihydride **212**. The formation of this latter product as a result of over reduction did not however pose any problems since it was readily converted back to Schwartz's reagent **205** by washing with DCM. This allowed the preparation of Schwartz's reagent **205** in 70% yield contaminated by only 6% of the zirconocene dihydride **212**.



Scheme 2.20

Other methods are available for the preparation of Schwartz's reagent **205**,[113,114] although the chosen method is the most efficient as it circumvents the need for expensive reducing agents, and the use of a filtered lithium aluminium hydride solution substantially simplifies the product isolation. Furthermore, preparation of Schwartz's reagent **205** in this manner has the additional advantage that as there are no salt impurities, the end point of the hydrozirconation reaction is signalled when the heterogeneous reaction mixture turns clear.

Thereafter, the zirconocene-zinc transmetallation coupling reaction was attempted using 1-pentyne **213** and benzaldehyde **214** as simple partners (Scheme 2.21). In the event, upon transmetallation of the organozirconocene with diethylzinc, alkene transfer to the aldehyde **214** was found to compete with the undesired alkylation, and thus the (*E*)-allylic alcohol **215** and the secondary alcohol **216** were obtained as an inseparable mixture. Attempts to increase the ratio of allylic alcohol **215** were made by altering the number of equivalents of reagents (Table 2.2).



213 **214** **215** **216**

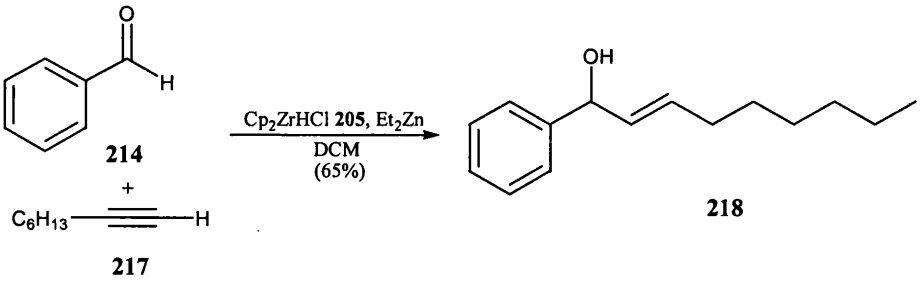
Scheme 2.21

Entry	Alkyne (eq.)	Schwartz's reagent (eq.)	Diethylzinc (eq.)	Ratio 215:216	Yield (%) 215+216
1	1.15	1.15	1.15	2:1	65
2	1.1	1	1	1:1	65
3	1.2	1	1.1	1:1	51
4	1.65	1	1.5	3:1	53

Table 2.2

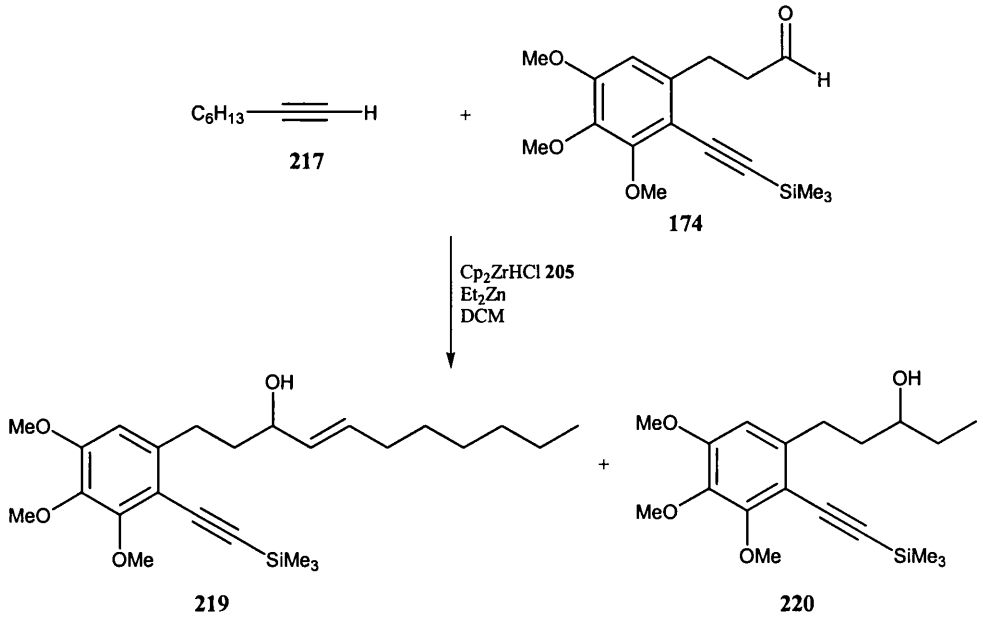
The product ratios were calculated using ^{1}H NMR by measurement of the relative intensities of the protons α to the hydroxyl groups. An increase in the percentage of allylic alcohol **215** was observed as more organozinc species was made available (Table 2.2, entries 1 and 4).

This reaction was also studied using 1-octyne **217** as the alkyne fragment. Curiously, in this case no competing alkylation occurred and as a result the (*E*)-allylic alcohol **218** was isolated as the sole product in 65% yield (Scheme 2.22). This improved reactivity of 1-octyne **217** over 1-pentyne **213** could only be attributed to increased steric bulk as a result of the greater size difference between the ethylzinc moiety and the octenylzinc moiety compared to pentenylzinc. This provided us with some hope for the success of the coupling reaction between our target aldehyde **174** and the alkynylcyclopropane **175**, as the alkynylcyclopropane **175** is also a relatively bulky substrate.



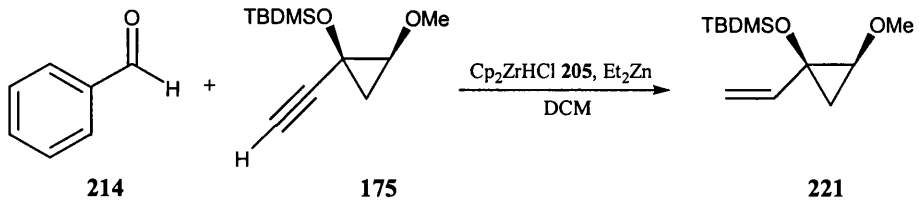
Scheme 2.22

Encouraged by the results obtained in these model studies, we were then ready to incorporate our aldehyde **174** into the reaction, whilst continuing to use 1-octyne **217** as the alkyne component. Addition of aldehyde **174** to the organozinc species of 1-octyne **217** led to the formation of the (*E*)-allylic alcohol **219** and also to the undesired secondary alcohol **220** in a 3:1 ratio (Scheme 2.23). Fortunately, on this occasion it was possible to separate the two compounds and therefore the allylic alcohol **219** was isolated in 52% yield by column chromatography.



Scheme 2.23

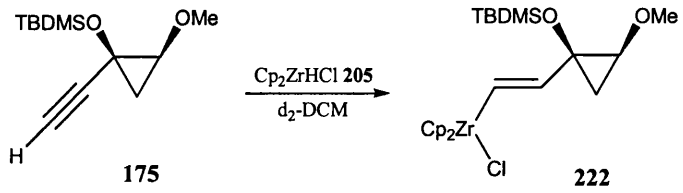
Satisfied with the results obtained in the model studies thus far, we were ready to attempt the much more ambitious reaction of the alkynylcyclopropane **175** with benzaldehyde **214**, before finally incorporating the two key fragments into the hydrozirconation reaction. However, when the alkynylcyclopropane **175** was employed in the reaction, it appeared that no coupling was occurring. Instead, ^{1}H NMR analysis suggested that the alkyne moiety was in fact reduced to alkene **221** and benzaldehyde **214** remained unreacted (Scheme 2.24).



Scheme 2.24

This result suggested that the hydrozirconation procedure was occurring successfully and that any problem with the reaction lay in the subsequent steps. However, we undertook an NMR investigation of the hydrozirconation step to confirm that this crucial transformation was indeed occurring successfully. When Schwartz's reagent **205** was added to a solution of alkynylcyclopropane **175** in deuterated DCM, subsequent NMR analysis indicated that the hydrozirconation

had proceeded successfully with formation of the alkenylzirconocene compound **222** (Scheme 2.25).

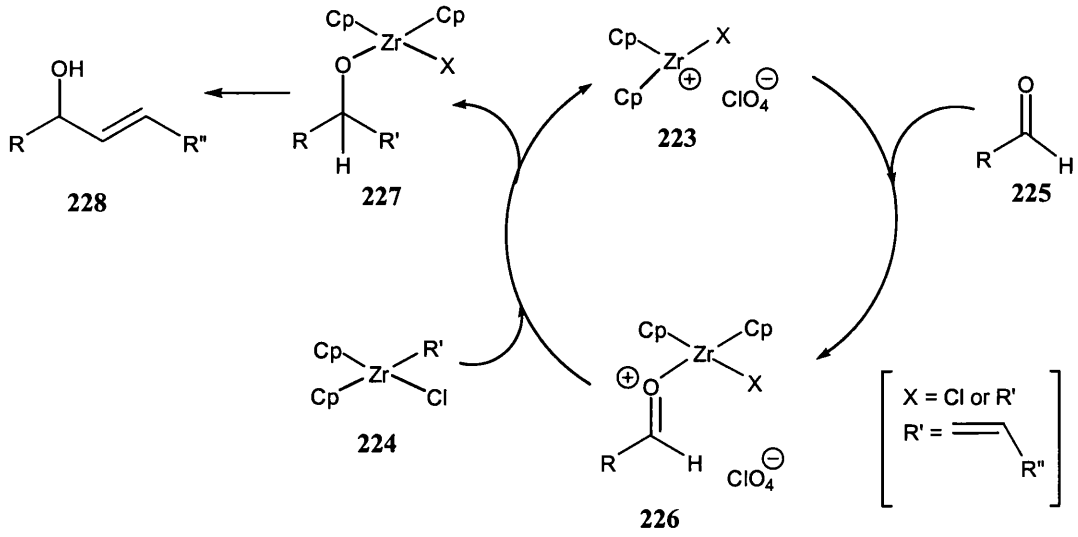


Scheme 2.25

Unfortunately however, further attempts to achieve transmetallation and coupling operations were without success and consequently, the zirconocene-zinc transmetallation procedure was not further applied to our system.

Another possible approach towards achieving the desired reaction would be to employ "catalytic" methods to enhance the reactivity of the organozirconocene. In particular, Suzuki and co-workers[107,108] have shown that silver (I) salts such as $AgClO_4$ catalyse the addition of organozirconocenes to aldehydes.

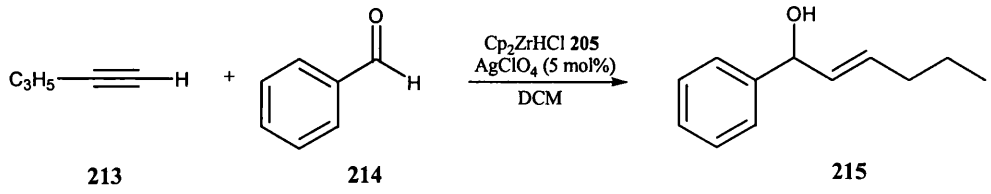
The activity of $AgClO_4$ in these reactions can be explained by considering the following catalytic cycle (Scheme 2.26). The cationic zirconocene species **223** generated by the action of the silver (I) salt on the alkenyl organozirconocene **224**, is capable of activating the carbonyl group of an aldehyde **225**, to afford the activated species **226**. This encourages the transfer of the R' group from another molecule of **224** with formation of **227**, thereby providing the (*E*)-allylic alcohol **228**. Irrespective as to whether the transfer is intra- or intermolecular in nature, the cationic complex **223** is regenerated, so that a catalytic amount of silver salt suffices for the overall rate enhancement.



Scheme 2.26

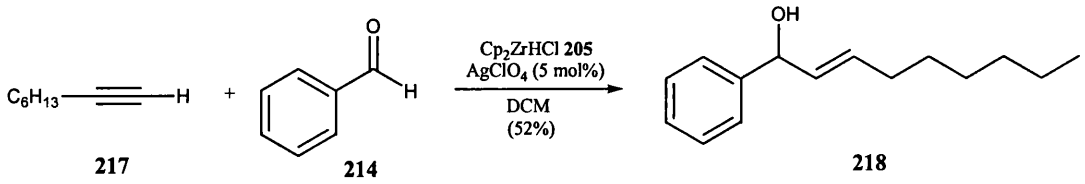
As we remained certain that the hydrozirconation of alkynylcyclopropane **175** was occurring successfully, and that the problem with the coupling reaction lay in the subsequent transmetallation with diethylzinc, we were accordingly optimistic about the silver (I)-catalysed method.

As in our earlier model studies, work commenced with the reaction of benzaldehyde **214** and 1-pentyne **213**. The hydrozirconation of 1-pentyne **213** was performed in the usual manner by reaction with Schwartz's reagent **205**, followed by addition of the aldehyde **214** as a solution in DCM, and finally 5 mol% $AgClO_4$ was added in a single portion (Scheme 2.27). Unfortunately, this reaction would not proceed to completion, even on the addition of further catalyst, or when allowed to react for longer periods of time. Unreacted benzaldehyde **214** was always recovered in addition to the desired allylic alcohol **215**.



Scheme 2.27

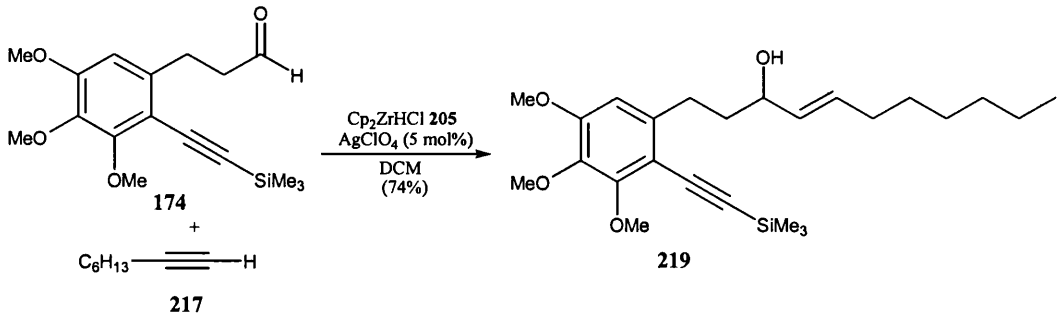
Conversely, when 1-octyne **217** was employed, the reaction proceeded cleanly to afford the expected allylic alcohol **218** as the sole product in 52% yield (Scheme 2.28). This reaction proceeded almost instantaneously on addition of the silver catalyst, in fact the success of reaction could be predicted merely by inspection, since on addition of the catalyst, the solution immediately turned from colourless to brown.



217 **214** **218**

Scheme 2.28

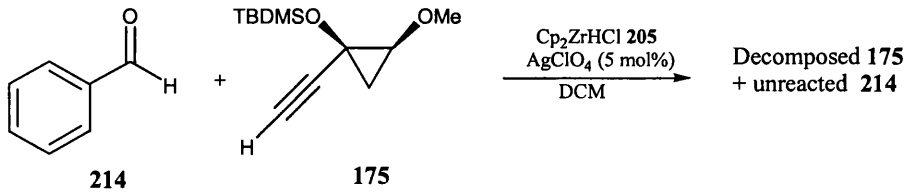
The reaction of the key aldehyde **174** with 1-octyne **217** proved to be even more rewarding. In fact, on addition of 5 mol% $AgClO_4$, the desired (*E*)-allylic alcohol **219** was obtained as the sole product in an excellent 74% yield (Scheme 2.29).



174 + **217** → **219**

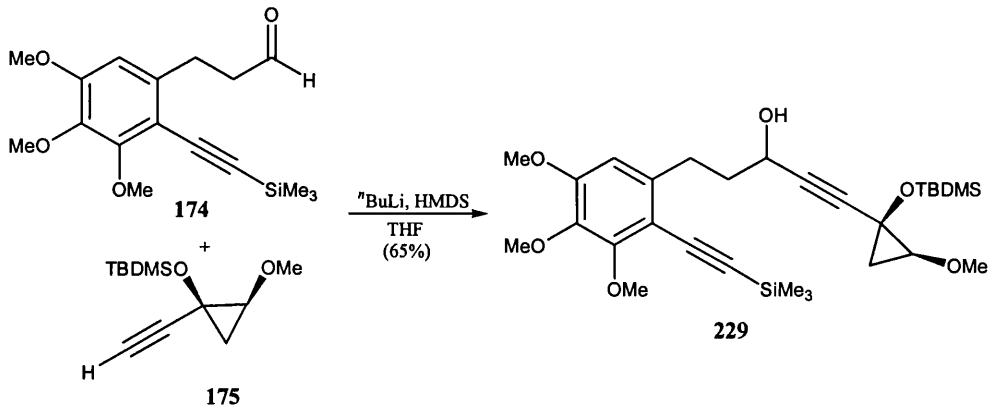
Scheme 2.29

The success of this reaction represented a significant advantage over the transmetallation route, as it provided a route to allylic alcohol **219** which avoided the competing alkylation reaction. Moreover, reactions were carried out at room temperature and circumvented the need for the air sensitive and pyrophoric diethylzinc reagent. Unfortunately however, once again, use of the alkynylcyclopropane **175** did not lead to the desired coupling reaction, and indeed the use of $AgClO_4$ resulted in complete decomposition of the alkynyl fragment **175** almost certainly *via* ring opening of the cyclopropane ring (Scheme 2.30).



Scheme 2.30

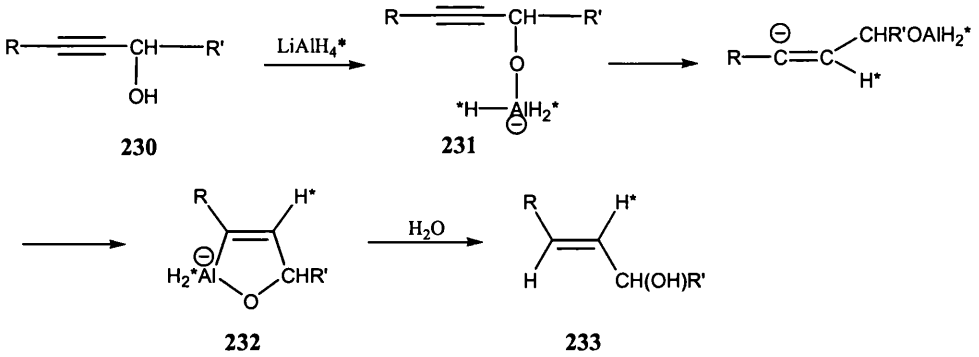
Much time and effort was invested into achieving the coupling reaction between aldehyde **174** and alkynylcyclopropane **175** without any evidence whatsoever for success. At this stage, since we were keen to achieve the synthesis of the key cyclisation precursor **173**, it was consequently decided to proceed with a more traditional and perhaps less elegant methodology. Thus, reaction of alkynylcyclopropane **175** with lithium hexamethyldisilazane in THF facilitated the coupling to the aldehyde **174**, thereby furnishing the racemic propargylic alcohol **229** in 65% yield (Scheme 2.31).



Scheme 2.31

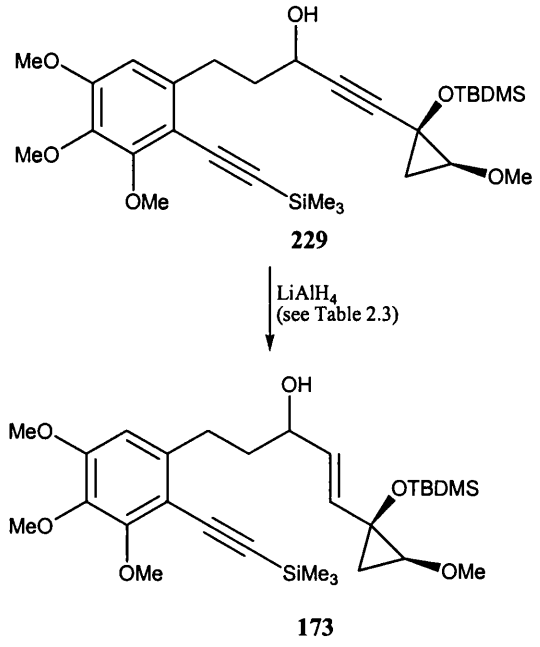
A variety of reductive methods were, in principle, available for elaboration of the propargylic alcohol **229** to allylic alcohol **173**. In fact, it was possible to control the stereoselectivity of the resultant olefin by the nature of the reducing agent. At this stage, because it was not apparent which regioselectivity was required for our alkynyl-vinylcyclopropane **173**, we therefore investigated controlled methods for the synthesis of both the (*E*)- and the (*Z*)-allylic alcohols.

The lithium aluminium hydride reduction of propargylic alcohols has been shown to furnish the corresponding allylic alcohols, and the ease of reduction of C≡C to C=C is facilitated by the neighbouring hydroxyl group.[115,116] In general, reductions of this type afford (*E*)-allylic alcohols, which can be explained by the mechanistic pathway shown in Scheme 2.32. Reduction proceeds *via* initial coordination of the aluminium species to the oxygen of allylic alcohol **230**, followed by specific hydride transfer from aluminium to the adjacent carbon of the acetylene **231**. This then leads to formation of the 5-membered organoaluminium cycle **232** and finally, hydrolysis occurs with retention of the *trans*-geometry to afford the (*E*)-allylic alcohol **233**.



Scheme 2.32

Initially, reaction with propargylic alcohol **229** was carried out employing 1.3 equivalents of lithium aluminium hydride in THF at reflux for 24 hours. These conditions provided the desired allylic alcohol **173** exclusively as the (*E*)-isomer, but in a disappointing 28% yield (Scheme 2.33, Table 2.3, entry 1).



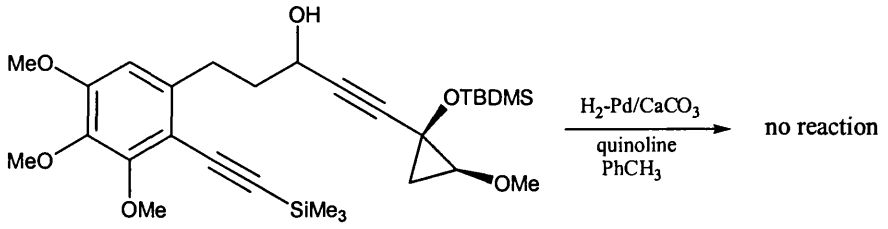
Scheme 2.33

It was thought that the high reaction temperature employed might result in decomposition at some stage thereby explaining the low yield, and the use of diethyl ether provided the opportunity for a reduction in temperature. Consequently, the reaction was repeated in ether at reflux, but unfortunately with no increase in isolated yield (Table 2.3, entry 3). In fact, it was realised that the reaction could be performed even at ambient temperature to afford the allylic alcohol **173** with an improved yield of 43% (Table 2.3, entry 4). The reaction was not affected by use of a smaller excess of lithium aluminium hydride reagent (Table 2.3, cf. entries 1, 2 and 4, 5).

Entry	$LiAlH_4$ (eq.)	Solvent	Reaction Temperature	Yield (%)
1	1.3	THF	reflux	28
2	1.1	THF	reflux	26
3	1.3	ether	reflux	25
4	1.3	ether	rt	43
5	1.1	ether	rt	43

Table 2.3

The alternative alkene stereochemistry is available through selection of Lindlar's catalyst which is used for the selective conversion of alkynes to (*Z*)-alkenes by delivering both hydrogen atoms simultaneously in a *syn*-manner.[117] Thus, in an attempt to obtain the (*Z*)-allylic alcohol **173**, a solution of propargylic alcohol **229** in toluene was subjected to hydrogenation at atmospheric pressure in the presence of Lindlar's catalyst and quinoline. However, no reaction occurred and unreacted propargylic alcohol **229** was recovered (Scheme 2.34).



229

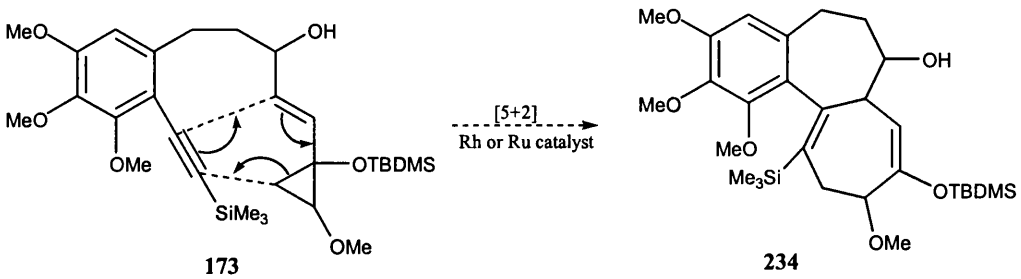
Scheme 2.34

Since examination of molecular models indicated that the (*E*)-vinylcyclopropane **173** could serve as a precursor for the [5+2] cycloaddition reaction, it was decided to continue our approach with this substrate.

2.7 Cycloaddition Studies on Precursor (173)

2.7.1 Wilkinson's Catalyst in the [5+2] Cycloaddition Reaction

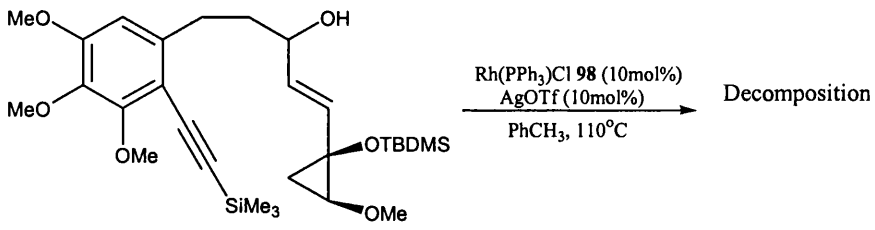
With the valuable alkynyl-vinylcyclopropane **173** in hand we were now ready to begin the key cyclisation studies. As previously discussed, it was hoped that the [5+2] cycloaddition of alkynyl-vinylcyclopropane **173** would occur in the presence of either a ruthenium (II) or rhodium (I)-catalyst to bring about the desired simultaneous formation of both seven-membered rings (Scheme 2.35). Additionally, as if we had not already set ourselves an ambitious enough target, it was also our hope that this reaction would proceed with the desired regioselectivity involving exclusive cleavage of the less substituted cyclopropyl bond to give **234**.



173 234

Scheme 2.35

Wender[75] has shown that Wilkinson's catalyst **98** can be employed in these cycloaddition reactions to facilitate the cyclisation in a regioselective fashion *via* cleavage of the least substituted cyclopropyl bond. Hence, alkynyl-vinylcyclopropane **173** was subjected to 10 mol% Wilkinson's catalyst **98** in the presence of silver triflate co-catalyst in toluene at reflux. However under these relatively harsh conditions complete decomposition of the starting material occurred and no evidence was obtained for formation of the desired tricyclic skeleton (Scheme 2.36).



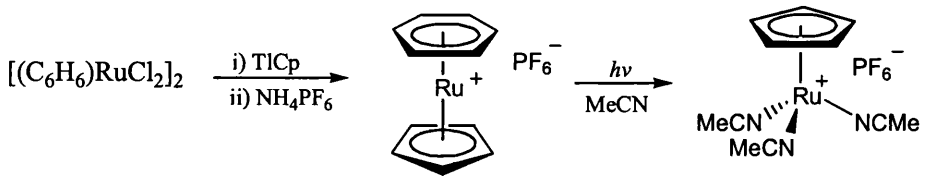
173

Scheme 2.36

As a consequence of the evident instability of **173** at these high temperatures, we then decided to attempt the reaction using the $[CpRu(CH_3CN)_3]PF_6$ **160** catalyst developed by Trost.[81] It was anticipated that the use of this catalyst would enable the reaction to be carried out at room temperature in acetone as solvent. Unfortunately, unlike Wilkinson's catalyst **98** the cationic ruthenium catalyst, $[CpRu(CH_3CN)_3]PF_6$ **160**, widely employed by Trost in his [5+2] cycloaddition studies, is not commercially available, and in consequence had to be synthesised.

2.7.2 Synthesis of $[CpRu(CH_3CN)_3]PF_6$

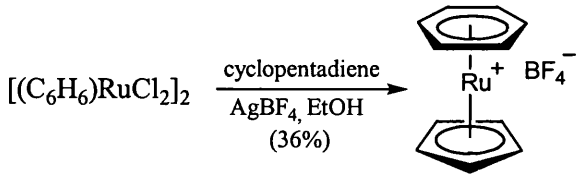
Gill and Mann[118] reported a synthesis of $[CpRu(CH_3CN)_3]PF_6$ **160** in 1982, starting from readily available $[(C_6H_6)RuCl_2]_2$ **235** (Scheme 2.37). Introduction of the cyclopentadienyl ligand was achieved by reaction with thallium cyclopentadienide,[119] and the hexafluorophosphate salt was then precipitated by treatment with aqueous ammonium hexafluorophosphate. Photolysis of the resultant salt **236** in acetonitrile solvent then furnished the desired cyclopentadienyl ruthenium species **160**.



235 **236** **160**

Scheme 2.37

Although this synthesis appears relatively straightforward, the use of stoichiometric thallium salts was extremely unattractive to us due to the toxic nature of thallium. We therefore considered an alternative approach which would involve substitution of thallium with a much safer alternative, such as silver. Furthermore, in 1986 Suzuki and co-workers[120] reported the synthesis of $[CpRu(C_6H_6)]BF_4$ **237** from $[(C_6H_6)RuCl_2]_2$ **235** by reaction with cyclopentadiene and silver tetrafluoroborate (Scheme 2.38).



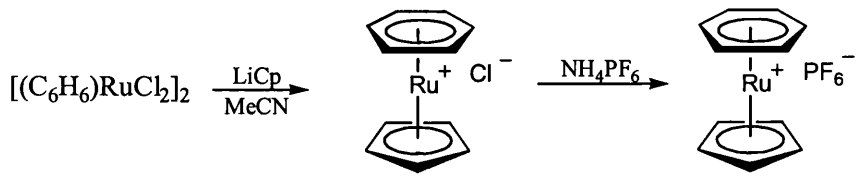
235 **237**

Scheme 2.38

It was anticipated that substitution of silver tetrafluoroborate with the hexafluorophosphate salt would afford the desired ruthenium species **236**.

However, although we were able to isolate **237** in a 27% yield, the corresponding reaction utilising silver hexafluorophosphate led to **236** in an extremely poor 3% yield.

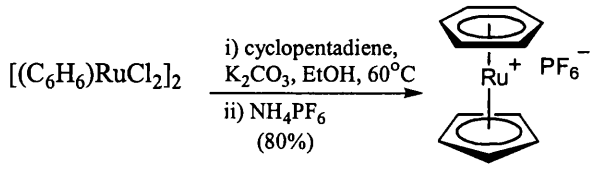
In the search for yet another alternative, it was hoped that lithium cyclopentadienide would react in a similar manner to its thallium counterpart. Thus lithium cyclopentadienide was synthesised according to the procedure of Brandsma by reaction of *n*-butyllithium with freshly cracked cyclopentadiene.[121] Subsequent reaction of $[(C_6H_6)RuCl_2]_2$ **235** with lithium cyclopentadienide in acetonitrile furnished the ruthenium species **238** which was treated with aqueous ammonium hexafluorophosphate to furnish the desired $[CpRu(C_6H_6)]PF_6$ **236** in an overall 61% yield (Scheme 2.39).



235 **238** **236**

Scheme 2.39

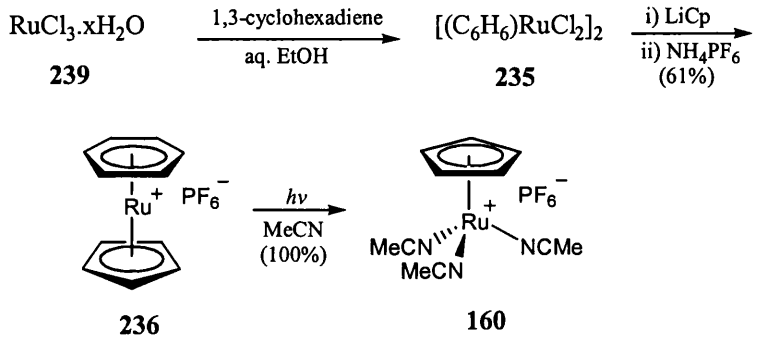
Henceforth, this method was utilised in our synthesis as an alternative approach to that described by Gill and Mann.[118] However, much more recently, Trost[122] has finally reported a convenient synthetic route to obtaining $[CpRu(CH_3CN)_3]PF_6$ **160**. In this synthesis, Trost isolated the desired ruthenium species **236** by utilising cyclopentadiene and potassium carbonate as opposed to thallium cyclopentadienide (Scheme 2.40). Unfortunately, this procedure was not reported until some time after our own investigations.



235 **236**

Scheme 2.40

With a route to obtaining the desired cyclopentadienyl species in hand, the synthesis of $[CpRu(CH_3CN)_3]PF_6$ **160** was completed in accordance with literature procedure.[118] The overall sequence which we used can therefore be summarised as follows. Preparation of $[(C_6H_6)RuCl_2]_2$ **235** was achieved by reaction of ruthenium chloride **239** and 1,3-cyclohexadiene in aqueous ethanol.[123] Subsequent reaction with lithium cyclopentadienide and ammonium hexafluorophosphate then provided a tan coloured solid which was dissolved in acetone and filtered through a pad of alumina to afford $[CpRu(C_6H_6)]PF_6$ **236** as a white crystalline solid. Finally, $[CpRu(C_6H_6)]PF_6$ **236** was dissolved in acetonitrile and irradiated with the power of a 450-W Hanovia medium pressure mercury lamp for 6 hours, thereby facilitating the exchange of the benzene ligand with three acetonitrile ligands and thus affording $[CpRu(CH_3CN)_3]PF_6$ **160** quantitatively as a brown solid (Scheme 2.41).

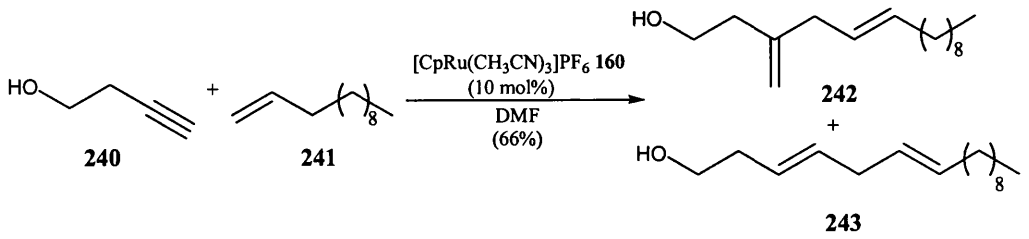


Scheme 2.41

The $[CpRu(CH_3CN)_3]PF_6$ **160** thus obtained was spectroscopically pure in terms of comparison with the literature data.[118] However, having never synthesised such a compound before, we elected to employ the catalyst in a literature reaction to confirm its reactivity. After a search for a simple procedure employing commercially available starting materials, we decided to perform the ruthenium-catalysed addition of a terminal alkyne to an alkene as described by Trost.[124]

Trost has shown that these addition reactions proceed in the presence of ruthenium catalysts to give the resulting branched and linear products. Consequently, reaction of but-3-yn-1-ol **240** and 1-dodecene **241** in the presence

of 10 mol% $[CpRu(CH_3CN)_3]PF_6$ **160** in DMF at room temperature furnished the branched and linear alcohols **242** and **243** in a 7.3:1 ratio as an inseparable mixture in 66% overall yield (Scheme 2.42). Since the results obtained were in excellent agreement with those reported by Trost,[124] we were satisfied that our catalyst had been correctly prepared.

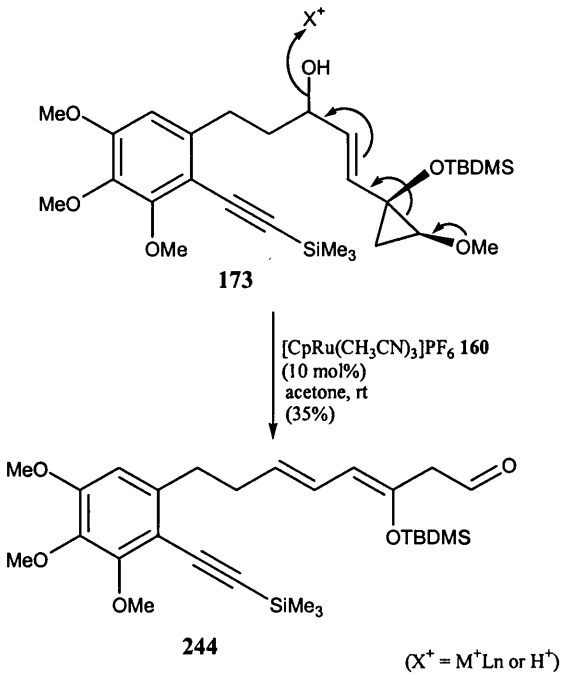


Scheme 2.42

2.7.3 $[CpRu(CH_3CN)_3]PF_6$ in the [5+2] Cycloaddition Reaction

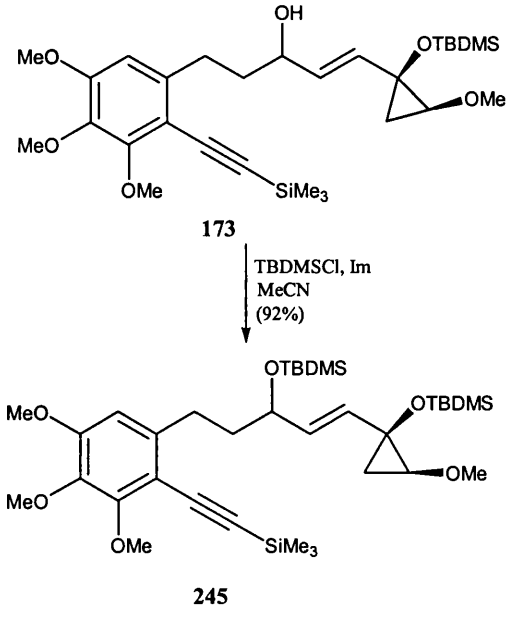
Reaction of the $[CpRu(CH_3CN)_3]PF_6$ catalyst **160** with *trans*-disubstituted cyclopropanes has been shown, in general, to lead to a mixture of regioisomers resulting from cleavage of both of the two possible cyclopropyl bonds. However, to our knowledge, such a reaction has not been previously performed on a substrate bearing an alkoxy group at the 2-cyclopropyl position. Hence, we remained hopeful that this approach would lead to the desired regioisomer.

With the $[CpRu(CH_3CN)_3]PF_6$ catalyst **160** now available, we then embarked upon the key reaction with the alkynyl-vinylcyclopropane **173**. The reaction was carried out in acetone at room temperature in the presence of 10 mol% ruthenium catalyst **160**, and complete consumption of starting material was noted after only 1 hour. To our dismay however, no cyclisation whatsoever had occurred. Instead, the Lewis acidic properties of the catalyst presumably facilitated the ring opening of the cyclopropyl ring followed by elimination of the hydroxyl group to give an aldehyde product **244** (Scheme 2.43). Interestingly, when this reaction was repeated using base washed glassware no reaction occurred and only unreacted alkynyl-vinylcyclopropane **173** was recovered, thereby confirming, as implied in the mechanism shown, that a proton was also required.



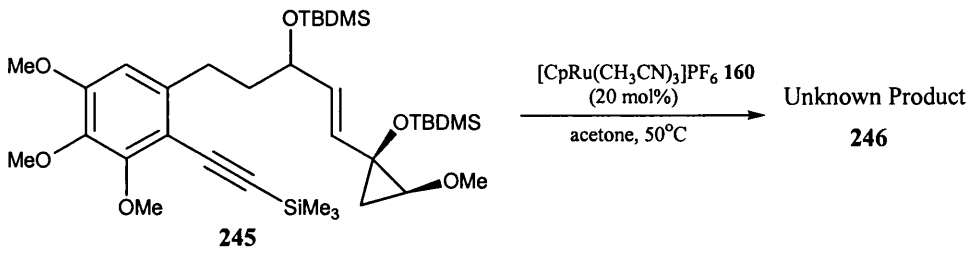
Scheme 2.43

We then reasoned that protection of the free alcohol would prevent the reaction of the catalyst in this manner and thereby circumvent the formation of this undesired aldehyde **244**. Thus, elaboration of alcohol **173** to the silyl ether **245** was readily achieved by reaction with *tert*-butyldimethylsilyl chloride and imidazole in acetonitrile, furnishing the protected alcohol **245** in an excellent 92% yield (Scheme 2.44).



Scheme 2.44

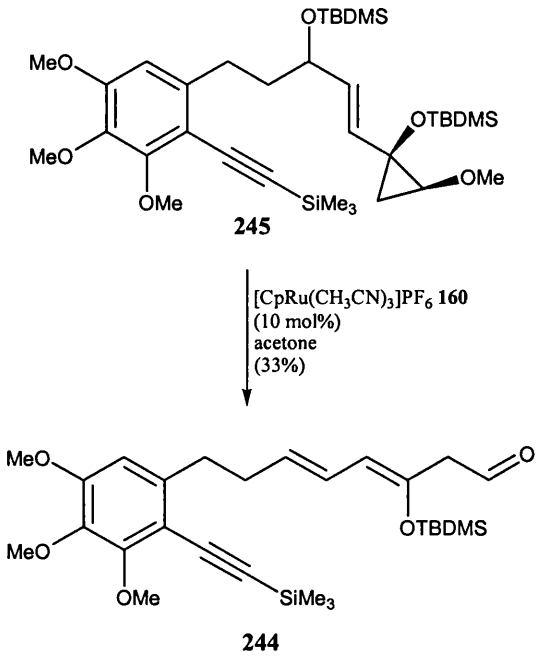
The protected alcohol **245** was then subjected to 10 mol% $[CpRu(CH_3CN)_3]PF_6$ **160** in acetone at room temperature. However, no reaction occurred even after 24 hours. An increase in reaction temperature to 50°C still provided no consumption of starting material, but addition of another portion of Ru-catalyst **160** resulted in complete consumption of the starting alkynyl-vinylcyclopropane **245** after only 3 hours to afford a single new product **246** (Scheme 2.45). Only a very small quantity of product (3 mg) was isolated after column chromatography, and on initial inspection of the ^1H NMR spectrum, we were optimistic that some form of cyclisation reaction had occurred, although unfortunately with loss of the crucial methoxy group of ring C. It was unlikely however that the alkyne moiety had taken part in the reaction, as there was no observed change in the chemical shift of the trimethylsilyl group. The presence of the three methoxy groups and the C-H of the aromatic ring were still apparent, as well as the two methylene groups adjacent to the aromatic ring, but the cyclopropyl protons and protecting silylether functionalities were now absent. Interestingly however, there were four new signals at 7.14, 5.31, 5.32 and 5.65 ppm suggesting the presence of four new olefinic protons, and there was also a new doublet at 2.84 ppm representing a single proton (see Appendix, Figure 3 and Figure 4). Most curious of all however was the fact that two methyl group signals were also detected in the ^1H NMR spectrum. However, as only a small amount of apparently labile material was available, it was decided to investigate this reaction on a larger scale and hence achieve full characterisation.



Scheme 2.45

At this point in time, it was however necessary to bring through more alkynyl-vinylcyclopropane cyclisation precursor **245**. Furthermore, the $[CpRu(CH_3CN)_3]PF_6$ catalyst **160** had also decomposed and consequently a fresh

batch was prepared. Unfortunately, to our horror, on using the new batch of alkynyl-vinylcyclopropane **245** and freshly prepared ruthenium catalyst **160**, it was not possible to repeat the reaction described above. In this instance, consumption of the starting material was occurring readily at room temperature with formation of the ring opened aldehyde product **244** previously observed in the reaction of the free alcohol precursor **173** (Scheme 2.46). However, in contrast to the earlier reaction of precursor **173**, performing the reaction in base washed glassware still provided the aldehyde **244**.

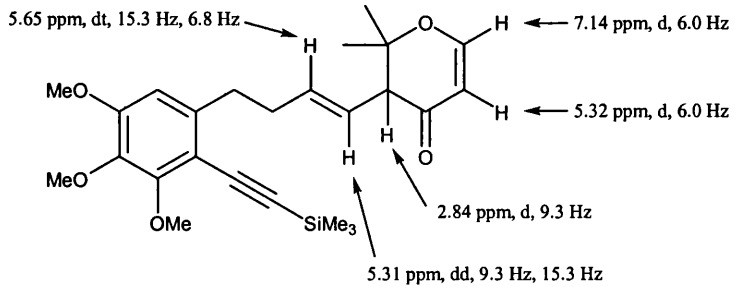


Scheme 2.46

It was then considered that the higher reaction temperature of 50°C previously employed might be required to facilitate the required cyclisation. However, such an increase in temperature once again led to formation of the undesired aldehyde **244**.

As it had proven impossible to reproduce the result obtained in the initial reaction, and since the original product had in fact undergone extensive decomposition, we were unfortunately unable to complete the full characterisation and hence confidently assign a structure to the product. However, closer inspection of the

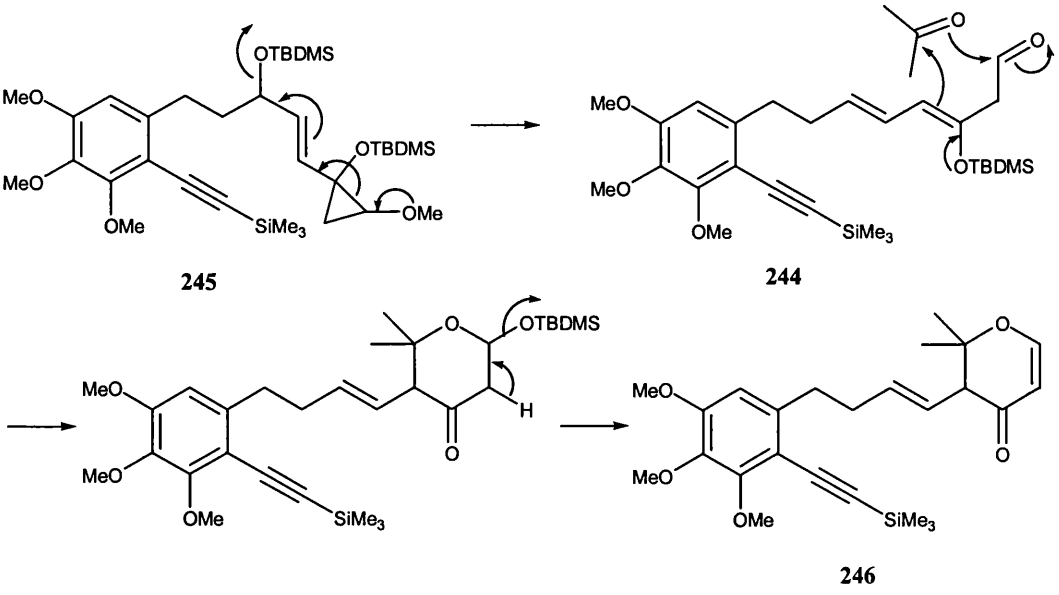
coupling constants of the ^{1}H NMR data and in particular of the significance of the two additional methyl groups, led to the proposition of a possible structure for **246** (Figure 2.2). Such postulation of the existence of a 2,2-dialkyl-2,3-dihydro-4*H*-pyran-4-one fragment is supported by comparison of the ^{1}H NMR data with literature data from Obrecht[125] on substituted and unsubstituted dihydropyranones of this type.



246

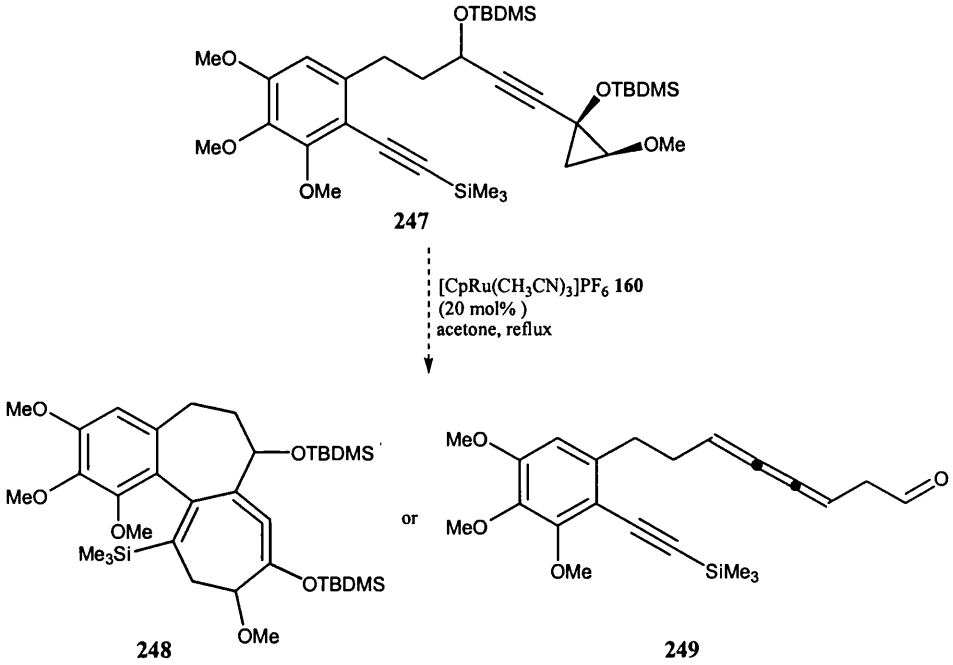
Figure 2.2

In retrospect, the simplest explanation for the presence of the two methyl groups in structure **246** is that they must have evolved from the incorporation of acetone into the reaction *via* an aldol-type reaction, as suggested in the following mechanism for the formation of **246** (Scheme 2.47).



Scheme 2.47

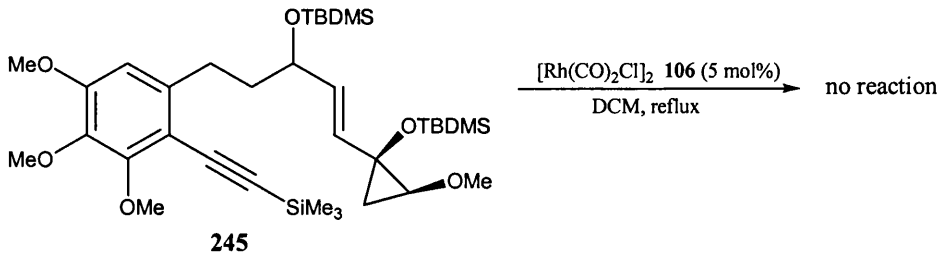
In a further attempt to understand the reactivity of this catalyst, it was also employed in the reaction of the alkynylcyclopropane **247** (Scheme 2.48). However, no reaction occurred in the presence of 20 mol% $[CpRu(CH_3CN)_3]PF_6$ catalyst **160**, even on heating the reaction at reflux in acetone for 24 hours. The observed lack of reactivity was not at all surprising, as a successful [5+2] cycloaddition reaction would have resulted in the formation of a high energy seven-membered allene intermediate **248**, which would not be particularly favoured. Alternatively, if the catalyst was once again to react as a Lewis acid on this substrate, the cumulene **249**, or isomers thereof, would have been produced.



Scheme 2.48

2.7.4 $[Rh(CO)_2Cl]_2$ Catalyst in the [5+2] Cycloaddition Reaction

The problematic [5+2] cycloaddition reaction was next attempted by employing $[Rh(CO)_2Cl]_2$ **106** as the catalyst. It was hoped that the desired reaction could be performed with this catalyst under suitably mild conditions to prevent decomposition of the starting material. Accordingly, alkynyl-vinylcyclopropane **245** was heated at reflux in DCM in the presence of 5 mol% $[Rh(CO)_2Cl]_2$ **106**, however, after 48 hours no reaction had taken place and the starting material was recovered (Scheme 2.49). Even upon the addition of further portions of catalyst **106**, no reaction occurred.



245

Scheme 2.49

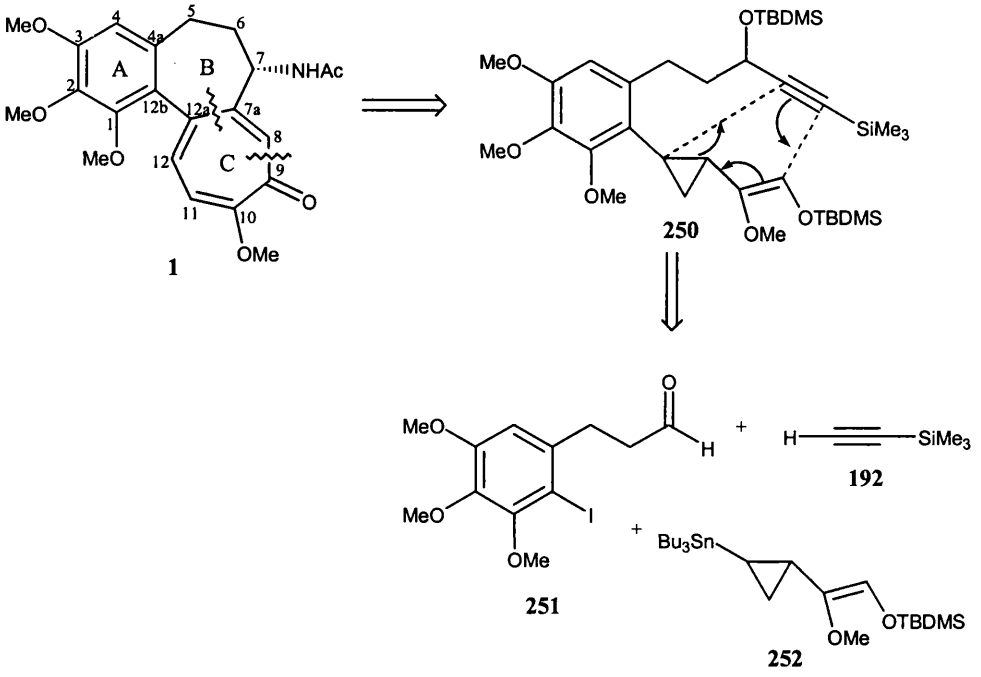
The use of the alkynyl-vinylcyclopropane **245** had thus proven to be an unsuccessful candidate for the transition metal catalysed [5+2] cycloaddition reaction. The escape route presented by the rich oxygenation pattern which is present in the alkynyl-vinylcyclopropane **245** was the root of the problem in failing to achieve the desired [5+2] cycloaddition reaction with the $[CpRu(CH_3CN)_3]PF_6$ **160** catalyst. Even although Trost[81] had successfully demonstrated the tolerance of both free and protected alcohols in his investigations, none of his examples exhibited such possibilities for elimination to a conjugated system such as ours.

2.8 The Design of a New Cycloaddition Precursor

Whilst the above studies were underway, a new alkynyl-vinylcyclopropane **250** was also under investigation for the cycloaddition reactions. The troublesome connectivity pattern previously present was absent in this molecule.

The suitability of this precursor **250** as a candidate for the [5+2] cycloaddition reaction to afford the desired colchicine framework was postulated on the basis of the retrosynthetic analysis of colchicine **1** shown in Scheme 2.50 and involving cleavage of bonds (7a-12a) and (8-9). Furthermore, it was also proposed that the synthesis of this molecule could be achieved in a highly convergent manner *via* coupling of three principal fragments, *viz.*, the aldehyde **251**, the cyclopropane **252** and commercially available trimethylsilylacetylene **192**. Introduction of the acetylenic component could be realised from coupling of trimethylsilylacetylene **192** with the aldehyde moiety **251**, and it was anticipated that formation of the

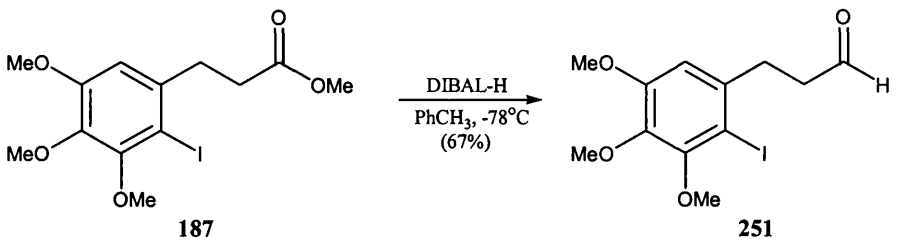
aryl-cyclopropyl bond could be accomplished *via* a transition metal catalysed crossed coupling such as a Stille reaction, or one of its many variants.[126,127]



Scheme 2.50

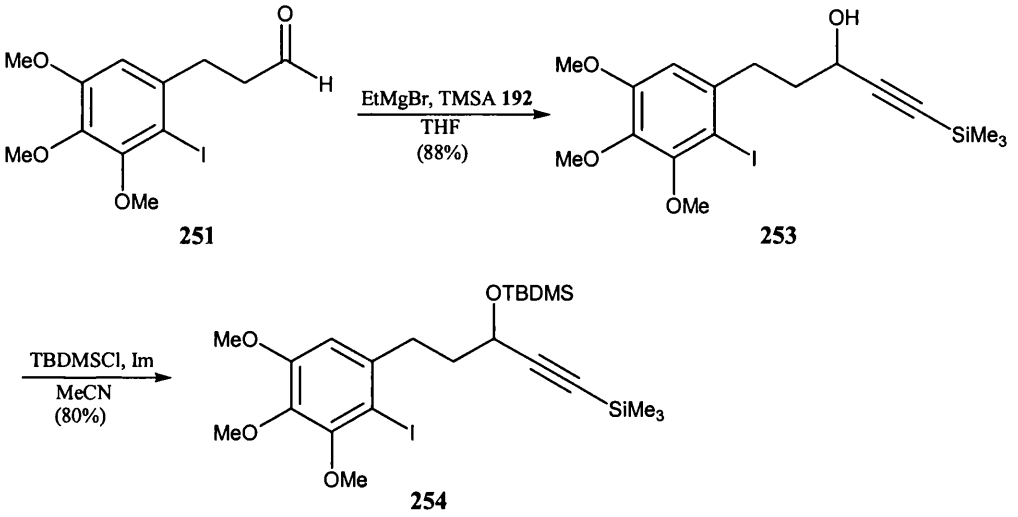
2.9 The Synthesis of Key Fragments

The iodo aldehyde **251** was readily available from reduction of the iodo ester **187**, which was prepared by the highly efficient route previously described in Scheme 2.7. On this occasion, reduction of the ester **187** with diisobutylaluminium hydride in toluene at -78°C provided a direct route to the aldehyde **251** in 67% yield (Scheme 2.51), thereby avoiding the reduction-oxidation method employed earlier (Scheme 2.8).



Scheme 2.51

Subsequent coupling of trimethylsilylacetylene **192** to the aldehyde **251** was easily achieved through a Grignard reaction. Thus, addition of the alkynylmagnesium bromide, formed *in situ* by reaction of trimethylsilylacetylene **192** with ethylmagnesium bromide, to the aldehyde **251** furnished the racemic propargylic alcohol **253** in an excellent 88% yield. Protection of the alcohol **253** as the TBDMS ether afforded the silyl ether **254** thus completing the northern fragment of the target alkynyl-vinylcyclopropane **250** (Scheme 2.52).

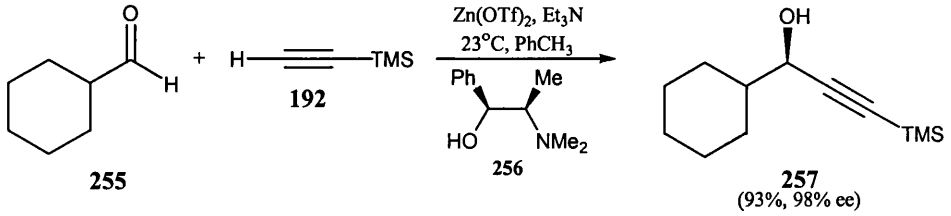


251 **253** **254**

Scheme 2.52

Although this route provided a convenient method to obtaining the racemic alcohol **253** in excellent yield, the acetylenic Grignard reaction provided the perfect opportunity to achieve the coupling reaction in an enantioselective manner and thereby furnish the desired optically active propargylic alcohol. We were particularly attracted by the recently reported method of Carreira[91,92] whereby the enantioselective addition of terminal acetylenes to aldehydes in the presence of zinc triflate, triethylamine and (+)- or (-)-*N*-methylephedrine as a chiral additive is used to prepare propargylic alcohols in high yields and with enantiomeric excesses of up to 99%. A key feature of these novel reactions is the *in situ* generation of the zinc acetylide, which can undergo subsequent addition to the aldehyde.

In one particular example, Carreira[91] has shown that the reaction of cyclohexane carboxaldehyde **255** and trimethylsilylacetylene **192**, proceeds in the presence of stoichiometric amounts of zinc triflate, triethylamine and (+)-*N*-methylephedrine **256** to furnish the (*R*)-propargylic alcohol **257** in an excellent 93% yield and 98% enantiomeric excess (Scheme 2.53).

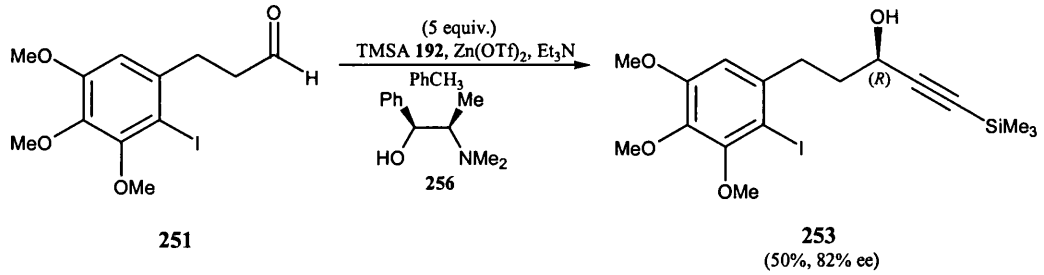


Scheme 2.53

Further studies have now led to the development of a catalytic method for these enantioselective addition reactions. In particular, Carreira has demonstrated that an increase in reaction temperature to 60°C facilitates the addition reaction in the presence of catalytic zinc triflate, triethylamine and *N*-methylephedrine with no depreciation in yield or enantiomeric excess.[93]

Initial attempts to apply this methodology to our reaction between aldehyde **251** and trimethylsilylacetylene **192** proved unsuccessful, as none of the desired coupling occurred. Consequently, it was decided to repeat the literature reaction described above to further understand at which point the reaction was failing (Scheme 2.53). However, once again none of the desired coupling occurred and the cyclohexane carboxaldehyde **255** was recovered unreacted at the end of the reaction. To our dismay, it proved impossible to repeat a simple literature reaction as described by Carreira,[91] especially as he had emphasised the ease of such reactions and the tolerance of moisture and oxygen. After undertaking a thorough investigation of each reagent, we were able to isolate some of the desired alcohol **257** along with unreacted starting aldehyde **255** in a 1:5 ratio. However, this required utilising zinc triflate purchased only from Fluka, purification of triethylamine to remove the primary and secondary amines and working under extremely dry conditions.

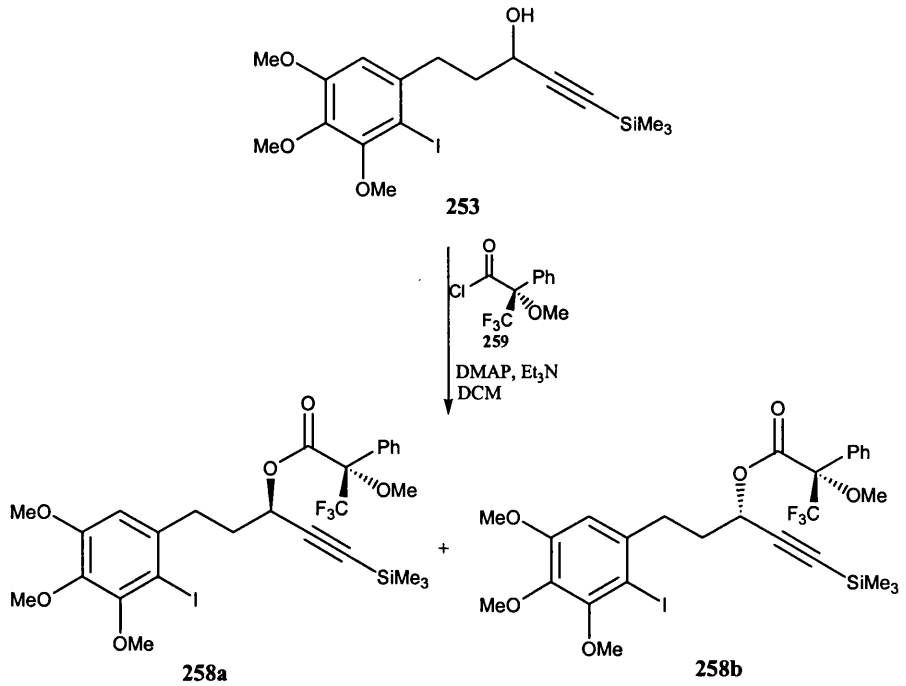
Having spent so much time investigating the conditions of this reaction, it was decided to apply it to our system regardless of the poor results obtained in the model reaction. However, reaction of aldehyde **251** with trimethylsilylacetylene **192** in the presence of stoichiometric amounts of zinc triflate, triethylamine and (+)-*N*-methylephedrine **256** led only to the polyaldol condensation of aldehyde **251** with none of the desired coupling reaction. Finally, in a total departure from the experimental method detailed by Carreira, a solution of aldehyde **251** in toluene was added over a 5 hour period to a toluene solution of 5 equivalents of all reagents and the desired propargylic alcohol **253** was isolated in a reasonable 50% yield and 82% ee. (Scheme 2.54).



251 **253** (50%, 82% ee)

Scheme 2.54

The determination of the enantiomeric excess was achieved by conversion of the alcohol **253** into the Mosher esters **258a** and **258b** by reaction with (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride **259**, triethylamine and dimethylaminopyridine in DCM (Scheme 2.55), followed by ^{19}F NMR integration of the two corresponding -CF_3 signals and confirmed by ^{1}H NMR integration of the Si(CH_3)$_3$ signals for each diastereoisomer **258a** and **258b**[128,129] (Table 2.4).



Scheme 2.55

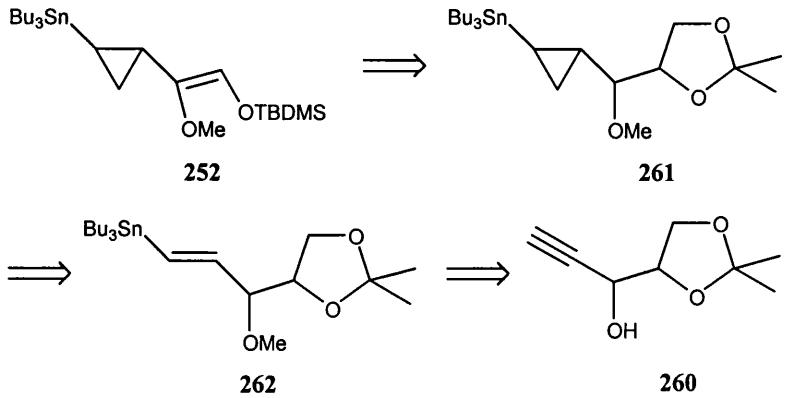
Nucleus	Chemical shift (ppm)	Ratio 258a:258b	% ee
^{19}F	-72.30 and –71.91	9.83:1	82
^{1}H	0.14 and 0.04	10.5:1	83

Table 2.4

After much effort, we were satisfied with this methodology for obtaining the desired chiral alcohol, and although the enantiomeric excess was not as high as we would have hoped for, it was anticipated that further investigation into the quantity and nature of the chiral auxiliary would provide an opportunity to further improve the present value. However, at this stage it was decided to continue the synthesis utilising the racemic alcohol **253**.

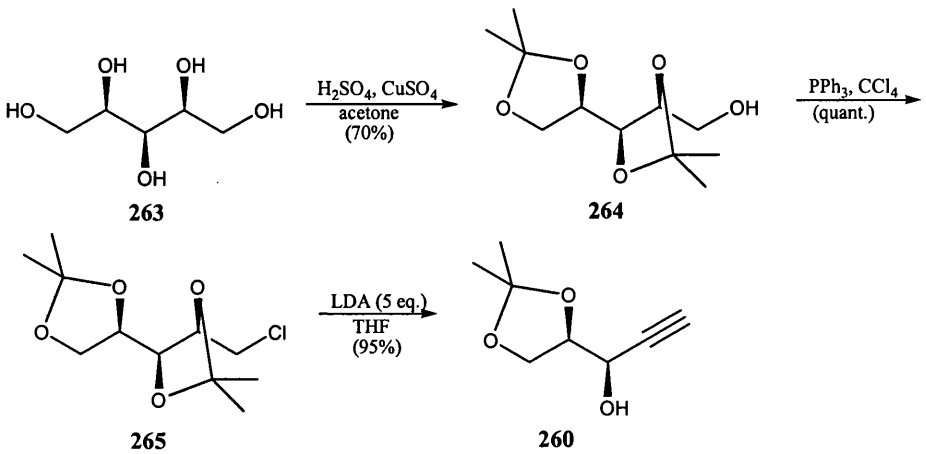
Our attention was now drawn to obtaining the cyclopropyl component **252**, which was required to complete the synthesis of the alkynyl-vinylcyclopropane **250**. The following synthetic operations were envisaged (Scheme 2.56). It was anticipated that the silylenol ether **252** could be obtained from the propargylic alcohol **260**,

via a sequence involving *O*-methylation, hydrostannylation, cyclopropanation and deprotection procedures.



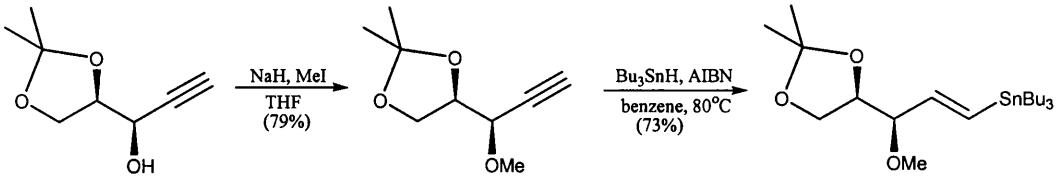
Scheme 2.56

The propargylic alcohol **260** was synthesised according to literature procedures[130,131,132] in three high yielding steps from the cheap, commercially available sugar, (D,L)-xylitol **263** (Scheme 2.57). The first step involved the selective protection of xylitol **263** at the 1,2- and 3,4-positions. This was achieved by reaction with copper sulphate and catalytic sulphuric acid in acetone furnishing on distillation, the diacetal **264** as a single diastereoisomer in 70% yield.[130,131] Conversion of the remaining primary alcohol to the chloro compound **265** was carried out in refluxing carbon tetrachloride in the presence of recrystallised triphenylphosphine. Finally, elaboration to the desired propargylic alcohol **260** was achieved by reaction with 5 equivalents of lithium diisopropylamide, in an excellent 95% yield.[132]



Scheme 2.57

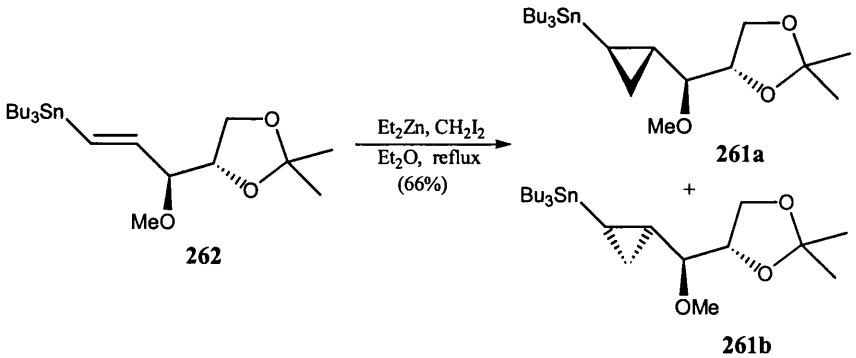
Conversion of the propargylic alcohol **260** to vinyl stannane **262** then required initial *O*-methylation of the alcohol **260** followed by hydrostannylation of the acetylene **266** (Scheme 2.58). Hence, reaction of alcohol **260** with sodium hydride and methyl iodide furnished the methyl ether **266** in 79% yield, which underwent subsequent reaction with tributyltin hydride in the presence of AIBN as initiator affording the vinyl stannane **262** in 73% yield exclusively as the (*E*)-isomer.



260 **266** **262**

Scheme 2.58

The cyclopropanation of **262** was then attempted, initially without any apparent success. The standard Furukawa[102] conditions were once again employed, but reaction of vinyl stannane **262** with diethyl zinc and diiodomethane in ether at room temperature led to recovery of unreacted starting material. Fortunately however, an increase in temperature to refluxing ether resulted in the formation of the desired cyclopropyl stannane as a 1:1 mixture of diastereoisomers **261a** and **261b** in 66% yield (Scheme 2.59).

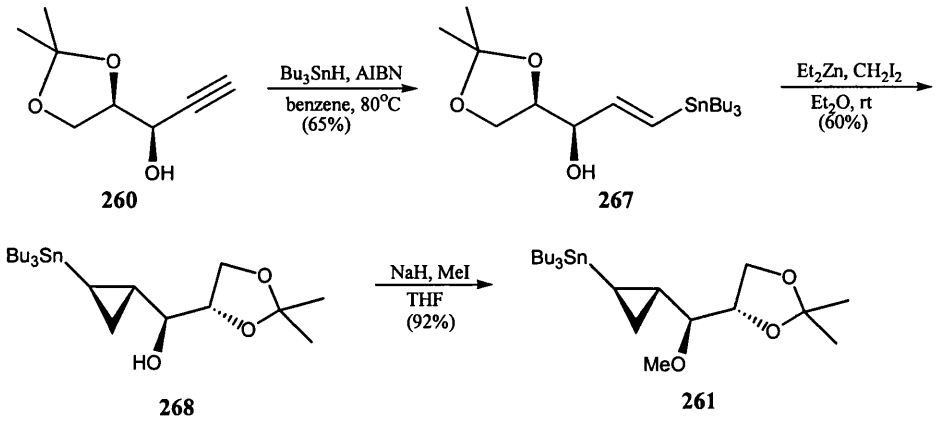


262 **261a** + **261b**

Scheme 2.59

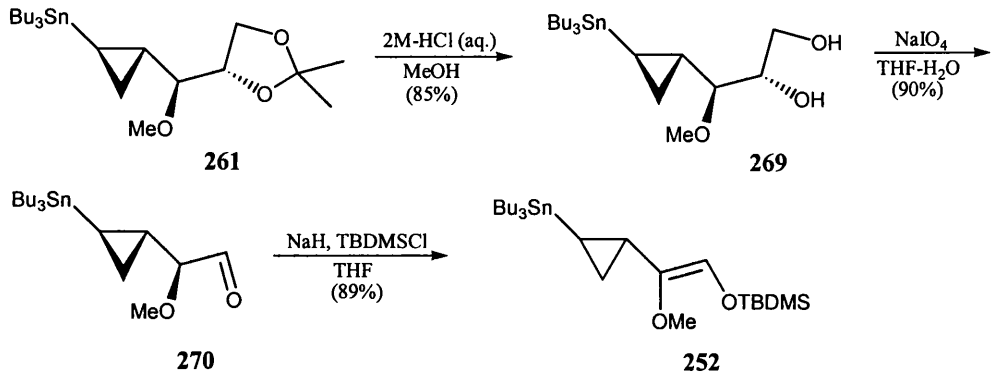
At a later stage, by altering the order of events and performing the hydrostannylation and cyclopropanation procedures prior to the *O*-methylation reaction, the cyclopropanation of the vinyl stannane **267** could be achieved with

much greater ease, thereby enabling the reaction to be performed at room temperature. In addition, the presence of the free hydroxyl group directed stereoselective cyclopropanation, thus providing a stereocontrolled route to **268**. Finally, *O*-methylation of the free hydroxyl **268** was achieved as before, by reaction with sodium hydride and methyl iodide to afford the cyclopropyl stannane **261** as a single diastereoisomer (Scheme 2.60).



Scheme 2.60

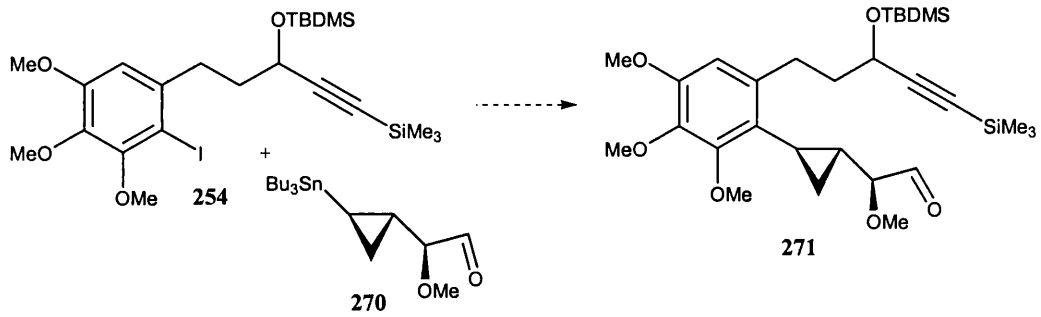
Concentrating now on the acetal fragment, deprotection of acetal **261** with aqueous hydrochloric acid in methanol provided the vicinal diol **269** in 85% yield which on subsequent cleavage with sodium *meta*-periodate led to the aldehyde **270**. Deprotonation with sodium hydride followed by quenching of the aldehyde enolate with *tert*-butyldimethylsilyl chloride afforded the desired silylenol ether **252** in an excellent 89% yield (Scheme 2.61). The highly electron rich silylenol ether **252** was of course extremely acid sensitive and could not be purified by column chromatography. Consequently, since it would have to be used without further purification, we decided that it would be less suited to subsequent steps, and the aldehyde **270** was therefore selected for the coupling reactions and conversion to the silylenol ether deferred to a later stage.



Scheme 2.61

2.10 Coupling of Aryl Iodide and Stannane Component

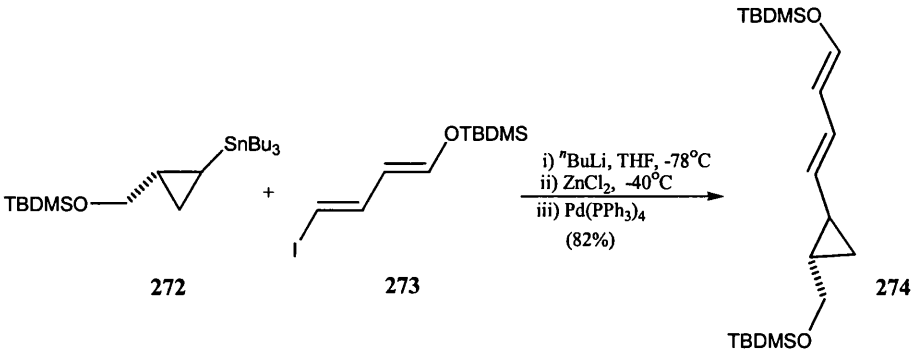
The stage was now set to investigate the crucial coupling of the cyclopropyl stannane **270** and aryl iodide **254** fragments to provide **271** (Scheme 2.62).



Scheme 2.62

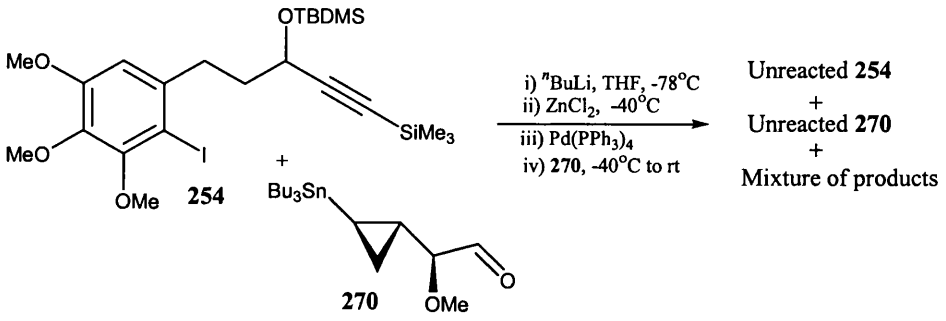
Whilst, in principle, the initial reaction of choice would of course be the Stille reaction,[126] there were no reported examples in the literature for which cyclopropyl stannanes, *per se*, had been employed as the tin-component, although, of course, a vinyl or aryl stannane can be routinely employed in such a reaction. We were in fact aware however, of methodology described by Piers,[133] who reported in 1987, that cyclopropyl stannanes could be used as precursors for coupling to vinyl iodides *via* a palladium-catalysed reaction. These reactions required initial conversion of the cyclopropyl stannane to the corresponding cyclopropylzinc halide, followed by palladium (0)-catalysed coupling of the two fragments to afford the required coupling products in high yields. In one particular example, reaction of cyclopropyl stannane **272** with *n*-butyllithium followed by zinc chloride enabled the cyclopropylzinc chloride to be generated *in situ*, which

underwent subsequent reaction with vinyl iodide **273** in the presence of 2 mol% palladium tetrakis(triphenylphosphine) to afford the cyclopropane product **274** in 82% yield (Scheme 2.63).



Scheme 2.63

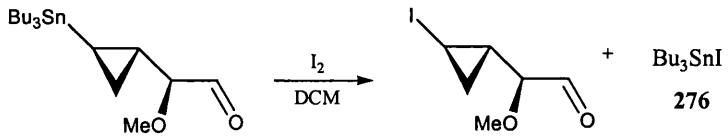
It was therefore our hope to apply this elegant methodology to the reaction between cyclopropyl stannane **270** and aryl iodide **254**, in order to achieve the desired carbon-carbon coupling reaction (Scheme 2.64). However, in this case, the expected coupling reaction did not take place and NMR analysis of the crude reaction mixture suggested that unreacted aryl iodide **254** remained. In addition, although some of the cyclopropyl stannane **270** was observed, several other products were also detected but not assigned, in the cyclopropyl region of the ^{1}H NMR spectrum. It is therefore likely that the initial transmetallation reaction with *n*-butyllithium had to some extent occurred, but that evolution of this intermediate was problematic.



Scheme 2.64

In a more recent publication, Piers suggested that the use of cyclopropylstannanes in these Negishi-type coupling reactions is in fact inefficient, and that the same reaction with the corresponding iodocyclopropanes proceeds much more satisfactorily.[134] These reactions invoke the same principle as for the cyclopropylstannanes, and hence involve initial lithium-halogen exchange of the iodocyclopropane, followed by transmetallation with zinc chloride to generate the cyclopropylzinc species which then undergoes subsequent palladium-catalysed coupling with the aryl or vinyl iodide.

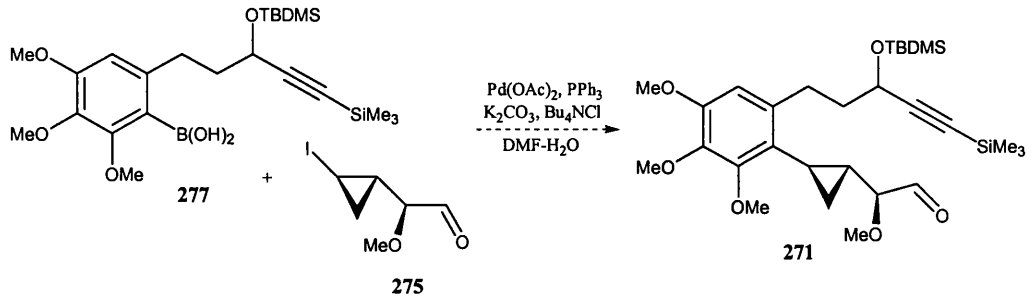
Unfortunately, attempts to convert the cyclopropylstannane **270** to the corresponding cyclopropyl iodide **275** proved unsuccessful. Although it appeared that the reaction of the stannane **270** with iodine in DCM was proceeding satisfactorily, it was not possible to separate the resultant iodocyclopropane **275** from the tributyltin iodide **276** by-product and hence **275** could only be isolated as an impure sample in extremely poor yield (Scheme 2.65).



270 **275**

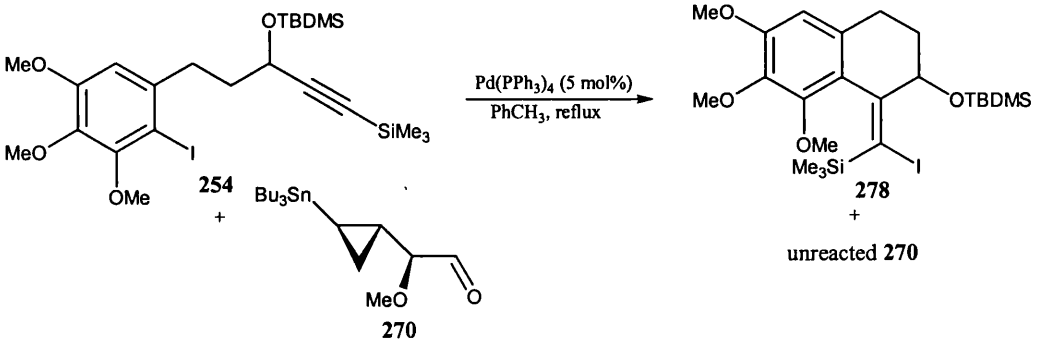
Scheme 2.65

A further possibility came from the group of Charette who have described Suzuki-type couplings of iodocyclopropanes with aryl- and alkenylboronic acids and esters.[135,136] This method would also provide a possible opportunity for obtention of the desired carbon-carbon bond, but relied heavily on obtaining the arylboronic acid **277** and iodocyclopropane **275** starting materials (Scheme 2.66). Unfortunately, as we have seen, it was already known that it was difficult to obtain the required iodocyclopropane **275** and likewise, attempts to convert the aryl iodide **254** to the corresponding boronic acid **277** proved unsuccessful.



Scheme 2.66

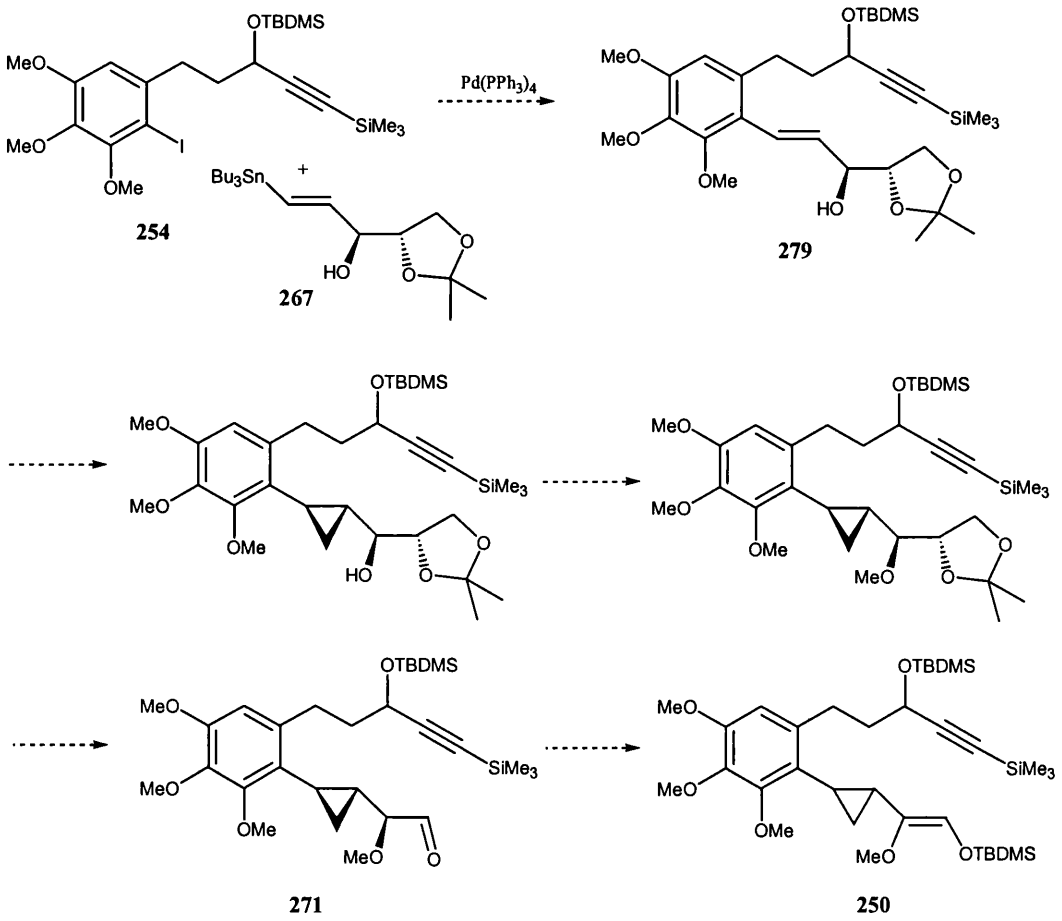
Consequently, it was decided to attempt a Stille reaction, regardless of the lack of literature precedent. Our initial attempts involved reaction of cyclopropyl stannane **270** and aryl iodide **254** in the presence of 5 mol% palladium tetrakis(triphenylphosphine) in refluxing toluene (Scheme 2.67). To our surprise however, and in contrast to the earlier attempts based on the work of Piers, where we had operated in THF at -78°C to room temperature, it appeared that the cyclopropylstannane **270** remained unreacted at the end of the reaction whilst the aryl iodide **254** had in fact reacted in an intramolecular manner to afford the bicyclic product **278**. The stereochemical assignment was based on nOe measurements at the OMe and TMS signals.



Scheme 2.67

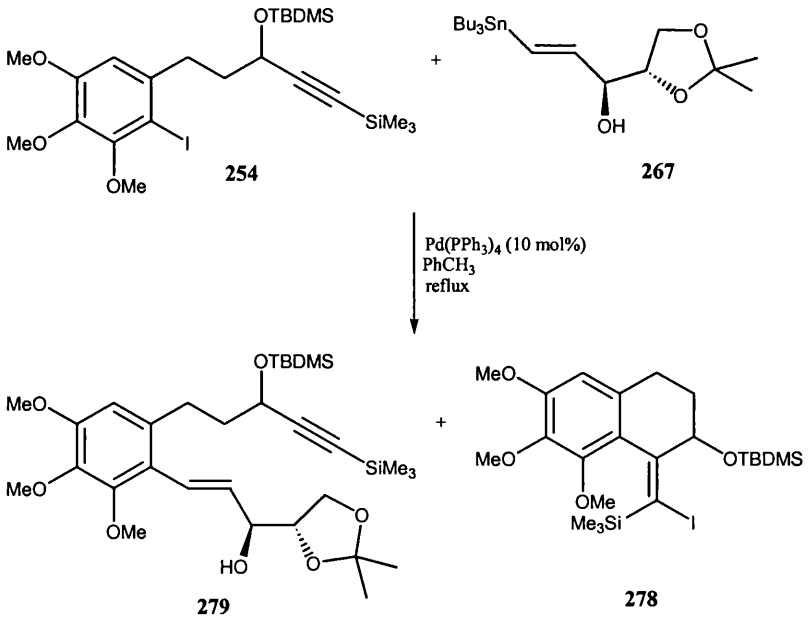
At this stage, we realised that any further attempts to accomplish the desired carbon-carbon bond formation would be best achieved by employing a standard Stille reaction involving reaction of the aryl iodide **254** with a vinyl stannane such as **267** to give **279**. This however, would then involve performing a relatively lengthy linear sequence of reactions including cyclopropanation, *O*-methylation,

and cleavage of the acetal to the silylenol ether. Nevertheless, this appeared to be most expedient option (Scheme 2.68).



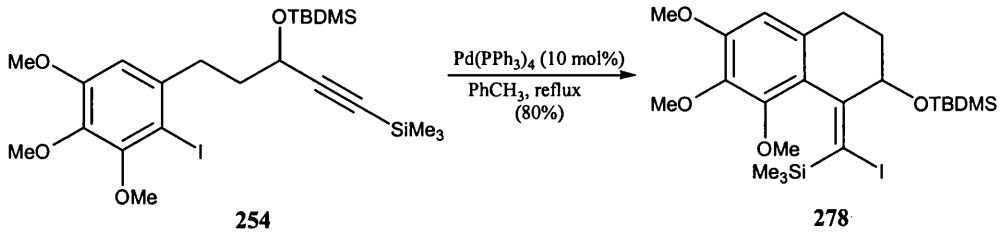
Scheme 2.68

Thus, treatment of a refluxing solution of aryl iodide **254** and vinyl stannane **267** with 10 mol% palladium tetrakis(triphenylphosphine) furnished the expected product **279**, but in a disappointing 30% yield (Scheme 2.69). An additional product was also produced in this reaction and identified as the bicyclic compound **278** obtained in the earlier reaction (Scheme 2.67). Unfortunately, on scaling this reaction up to a few hundred milligrams, even poorer yields were obtained, and as a result, we were not satisfied with this reaction as a route towards the desired product **279**.



Scheme 2.69

In fact, when a control experiment was performed in the absence of the stannane component **267**, the bicyclic compound **278** was obtained as the sole product in a high 80% yield (Scheme 2.70). Thus, in an effort to increase the ratio of desired product **279**, the coupling reactions were attempted at a lower temperature. These studies revealed that while at 50°C no reaction occurred, at 80°C the reaction favoured formation of the undesired **278** with only a trace of the desired product **279**.

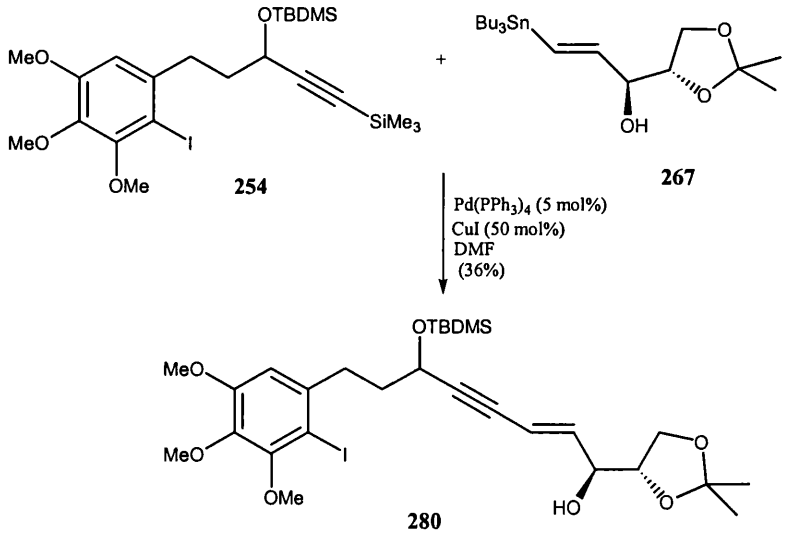


Scheme 2.70

With the hope of developing a more successful route to **279**, different reaction conditions were applied. Initial attempts involved performing the reaction in THF at reflux, however, in this case no reaction occurred and both starting materials were recovered. Alternatively, when the reaction was carried out in DMF at room temperature, the aryl iodide **254** remained unreacted but the vinyl stannane **267**

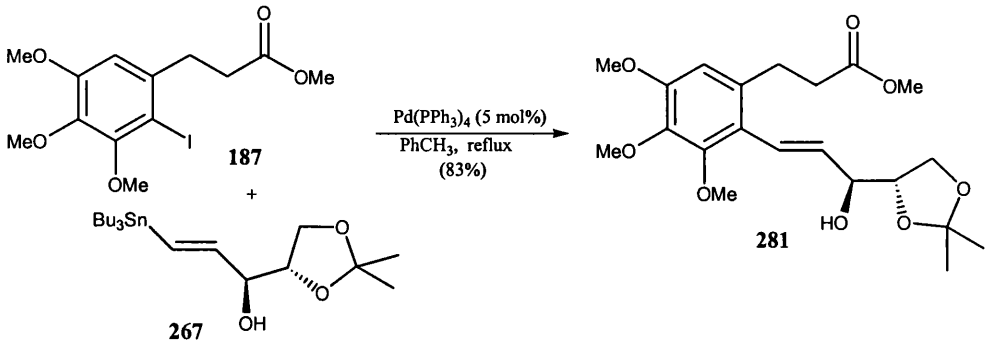
was completely consumed with formation of a complex mixture of unidentified products.

Conversely, when the same reaction was performed in the presence of 0.5 equivalents of copper iodide, the reaction proceeded with complete consumption of both starting materials. Close inspection of the NMR data revealed however that although coupling of the two fragments had occurred, the aryl iodide moiety had not taken part in the reaction and the new carbon-carbon bond was formed between the alkyne and alkene termini to furnish the product **280** in 36% yield (Scheme 2.71). It was however, unusual for such a coupling to occur at the substituted alkyne position, as a Sonogashira reaction would normally require the presence of a terminal alkyne and much stronger reaction conditions.



Scheme 2.71

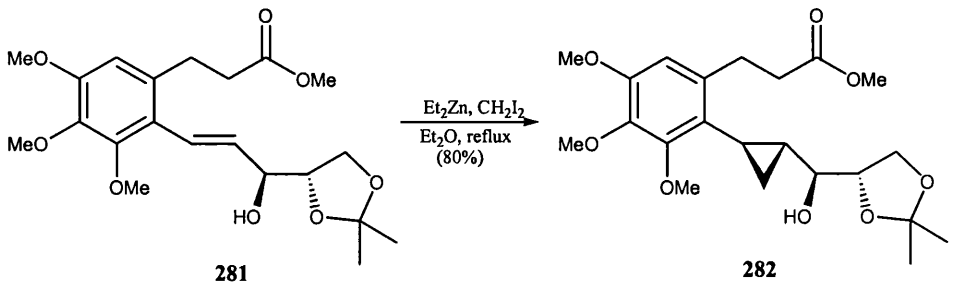
It appeared that the most efficient reaction was realised in initial attempts when the reaction was performed in refluxing toluene, if only the intramolecular side-reaction could be avoided. The obvious way to circumvent this undesired side reaction from occurring was to remove the alkyne moiety. In the event, the palladium catalysed reaction of aryl iodide **187** with vinyl stannane **267** led to the desired carbon-carbon bond formation yielding ester **281** in an excellent 83% yield (Scheme 2.72).



Scheme 2.72

Although this approach appeared to be very efficient in terms of achieving the desired carbon-carbon bond formation, many subsequent operations would be required to afford the target precursor for the cycloaddition reactions, and consequently the synthesis would become much more linear than was initially planned. Nevertheless, it was hoped that the subsequent steps would all be relatively simple and high yielding and therefore not affect the overall efficiency of the synthesis.

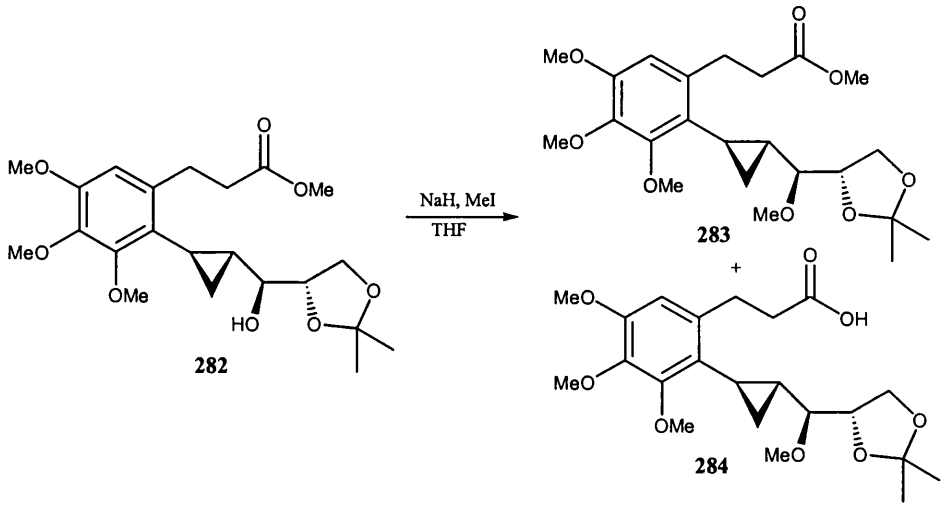
Cyclopropanation of the olefin **281** was readily achieved in the usual manner by reaction with diethyzinc and diiodomethane in ether at reflux furnishing the cyclopropane **282** in 80% yield as a single diastereoisomer (Scheme 2.73).



Scheme 2.73

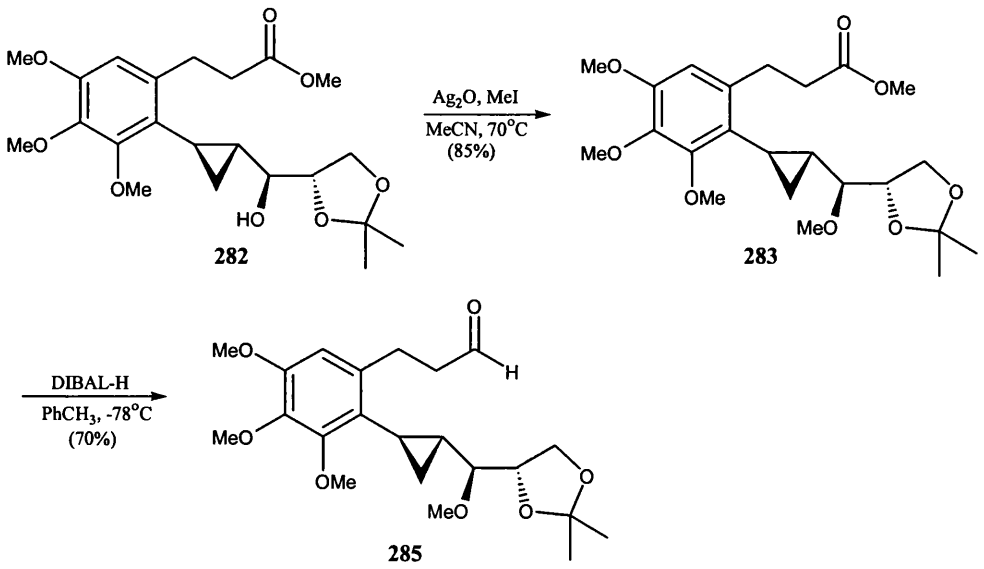
Initial attempts to convert the free alcohol **282** to the methyl ether **283** using sodium hydride and methyl iodide proved problematic, as the desired product **283** was obtained along with the carboxylic acid **284** in a 0.8:1 ratio (Scheme 2.74). Formation of this carboxylic acid **284** may have been due to the presence of

sodium hydroxide in the batch of sodium hydride, resulting in the observed hydrolysis of the ester **283**. Alternatively, it is possible that the sodium hydride may have facilitated the deprotonation of the acidic α-protons of the ester, resulting in formation of a ketene. If this were the case however, on quenching the reaction with methanol the methyl ester **283** should have been re-obtained and this was not observed.



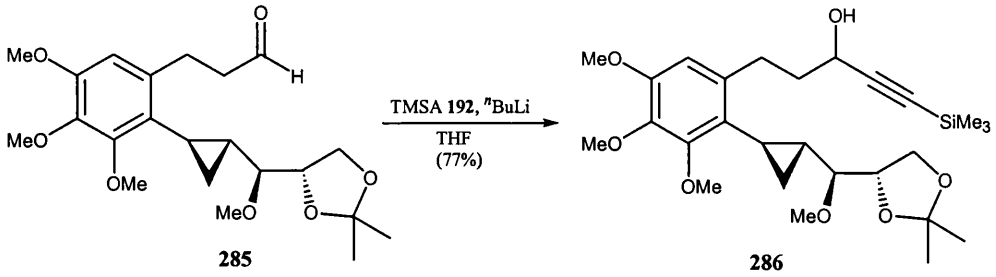
Scheme 2.74

It was however possible to avoid formation of the carboxylic acid **284** by selection of Purdie methylation as an alternative method.[137] Thus, reaction of **282** with silver (I) oxide and methyl iodide in acetonitrile at 70°C provided the methyl ether **283** as the sole product in 85% yield. Subsequent treatment with a solution of diisobutylaluminium hydride in toluene at -78°C then furnished the aldehyde **285** in a single step and 70% yield (Scheme 2.75).



Scheme 2.75

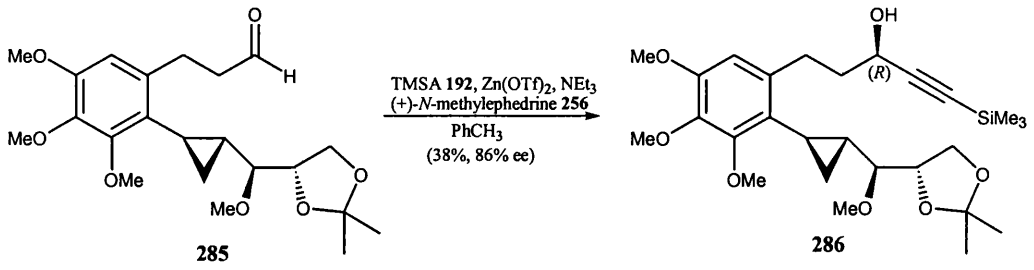
The next step was to introduce the alkynyl moiety. This was achieved by slow addition of the aldehyde **285** to a preformed solution of lithiated acetylene generated *in situ* by reaction of trimethylsilylacetylene **192** with *n*-butyllithium (Scheme 2.76). Thus, the alcohol **286** was isolated in 77% yield as a mixture of diastereoisomers.



Scheme 2.76

As we had invested some time earlier in investigating the formation of chiral propargylic alcohols by employment of Carreira's methodology,[91,92] it now appeared to be an excellent opportunity to utilise the same procedure. Therefore, reaction of aldehyde **285** with 5 equivalents of each of, trimethylsilylacetylene **192**, zinc triflate, triethylamine and (+)-*N*-methylephedrine **256** provided the (*R*)-

propargylic alcohol **286** in 38% yield and 86% ee (Scheme 2.77). The (*R*)-stereochemical assignment was based on the literature precedent.



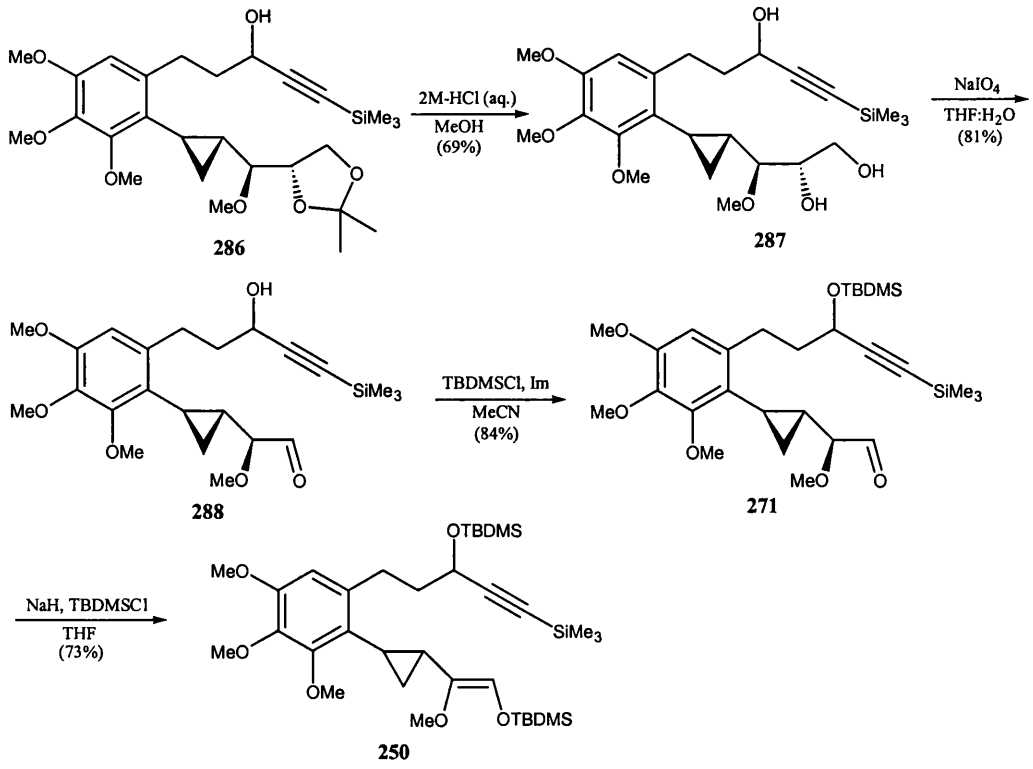
Scheme 2.77

As described previously, the enantiomeric excess was determined by conversion of the chiral alcohol to Mosher's ester,[128,129] followed by ^{19}F and ^{1}H NMR integration of the two diastereoisomers (Table 2.5). Once again, this methodology had provided a route to obtaining the (*R*)-propargylic alcohol **286** in good enantiomeric excess and only a slight improvement would be required to improve on that obtained in the total synthesis by Cha (90 %ee).[52] However, it was decided to once again proceed with the synthesis employing the racemic alcohol **286** at this stage.

Nucleus	Chemical shift ppm	Ratio (*R*,*S*):(*S*,*S*)	% ee
^{19}F	-72.29 and –71.84	13.22:1	86
^{1}H	0.14 and 0.03	14.74:1	87

Table 2.5

Deprotection of the acetal **286** was achieved in the presence of aqueous hydrochloric acid furnishing the triol **287** in 69%, which on subsequent treatment with sodium *meta*-periodate afforded the aldehyde **288** in 81% yield. The alcohol **288** was then protected in the usual manner with *tert*-butyldimethylsilyl chloride and imidazole thereby providing the silyl ether **271** in 84% yield (Scheme 2.78).



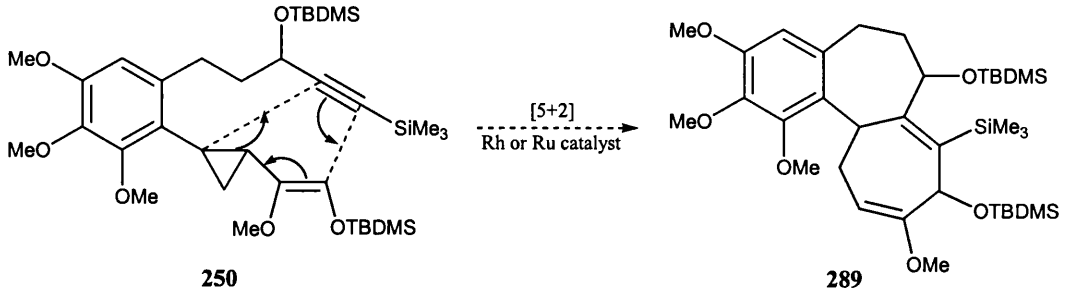
286 287 288 271 250

Scheme 2.78

Finally, conversion of the aldehyde **271** to the silylenol ether **250** was readily achieved in a satisfying 73% yield by initial treatment with sodium hydride followed by quenching with *tert*-butyldimethylsilyl chloride. It may have been possible to achieve both of the protection steps described in the final two steps of the synthesis in a single synthetic operation by reaction of the aldehyde **288** with two equivalents of sodium hydride and *tert*-butyldimethylsilyl chloride. However, at such a crucial stage in the synthesis it was not desirable to take any chances.

2.11 Cycloaddition Studies on Precursor (250)

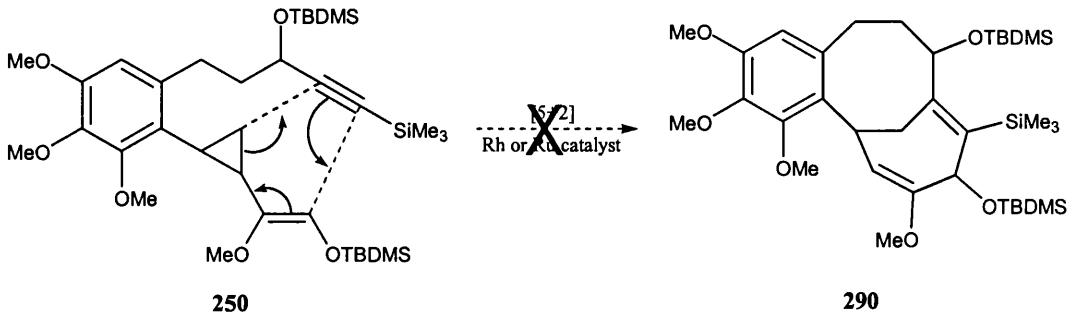
Now that we had the target alkynyl-vinylcyclopropane **250** in hand, the stage was set to investigate its application in the key transition metal catalysed [5+2] cycloaddition reaction. As before, it was hoped that the alkyne and vinylcyclopropane moieties would undergo the desired [5+2] cycloaddition reaction, in the presence of either a ruthenium or rhodium-catalyst, with construction of the two seven-membered rings leading to formation of the colchicine framework **289** (Scheme 2.79).



250 **289**

Scheme 2.79

In this case, it was anticipated that cleavage of the cyclopropyl ring would occur preferentially at the more substituted bond. The alternative regioisomer **290** resulting from cleavage of the less substituted cyclopropane bond, would lead to the formation of a bridgehead alkene and was therefore considered to be less favourable on energetic grounds according to Bredt's rule[138] (Scheme 2.80).



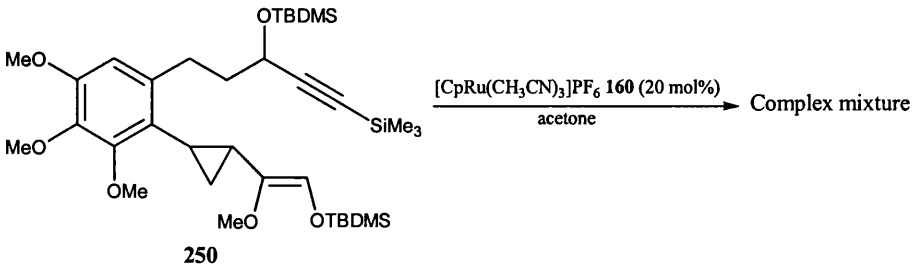
250 **290**

Scheme 2.80

2.11.1 $[CpRu(CH_3CN)_3]PF_6$ in the [5+2] Cycloaddition Reaction

Our studies commenced with the reactive $[CpRu(CH_3CN)_3]PF_6$ catalyst **160** as it was hoped that this catalyst would provide the opportunity for the mildest reaction conditions. We were extremely optimistic that $[CpRu(CH_3CN)_3]PF_6$ **160** would be successful in facilitating the desired cycloaddition reaction when exposed to **250**, as this precursor did not possess the conjugation pattern which had proven to be so problematic for the previous precursors **173** and **245**. Hence, a solution of alkynyl-vinylcyclopropane **250** in acetone was subjected to 20 mol% $[CpRu(CH_3CN)_3]PF_6$ **160** at room temperature (Scheme 2.81). However, complete decomposition of the starting material **250** was observed after only a few hours. ^1H NMR analysis of the crude material suggested the presence of many

compounds containing the aromatic C-H, -OMe, $-CH_2$, -OTBDMS and $-SiMe_3$ components, however the olefinic C-H and cyclopropyl protons were no longer observable. Moreover, IR analysis suggested that the alkyne moiety was still present.



250

Scheme 2.81

The $[CpRu(CH_3CN)_3]PF_6$ catalyst **160** is also known to exhibit the same reactivity in DMF solvent, and consequently the reaction was performed in DMF at room temperature (Table 2.6, entry 2). Contrastingly however, in DMF the ruthenium catalyst **160** did not facilitate any reaction when exposed to **250**, and only the starting material was recovered at the end of the reaction. Even when the reaction was performed in the presence of 20 mol% $[CpRu(CH_3CN)_3]PF_6$ **160** in DMF at 60°C for 24 hours, no reaction occurred (Table 2.6, entry 3).

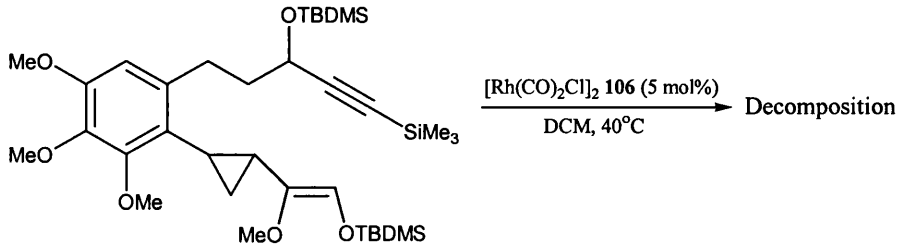
Entry	Solvent	Temperature	Outcome
1	acetone	rt	Decomposition
2	DMF	rt	No reaction
3	DMF	60°C	No reaction

Table 2.6

2.11.2 $[Rh(CO)_2Cl]_2$ in the [5+2] Cycloaddition Reaction

In a final attempt to achieve the key [5+2] cycloaddition reaction, it was decided to employ the $[Rh(CO)_2Cl]_2$ catalyst **106** in the reaction. Hence, alkynyl-vinylcyclopropane **250** was subjected to 5 mol% of the rhodium-catalyst **106** in DCM at room temperature. However, after 24 hours no reaction had taken place and only unreacted starting material remained. On the other hand, when the

reaction temperature was increased to 40°C complete decomposition of the alkynyl-vinylcylopropane **250** occurred, and no evidence could be adduced for the desired cycloaddition reaction (Scheme 2.82).



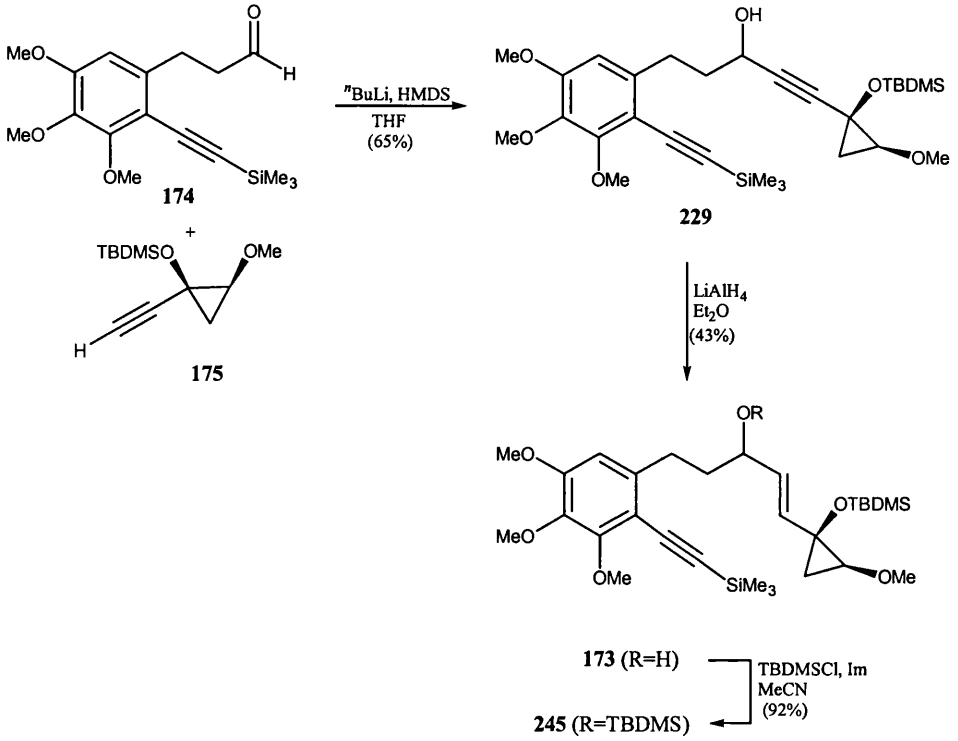
250

Scheme 2.82

2.12 Summary and Conclusions

The foregoing discussion describes the studies which were undertaken on our synthetic approach to colchicine **1**. Since the key feature of our synthetic plan was to apply a transition metal catalysed [5+2] cycloaddition reaction for construction of the two seven-membered rings, the majority of the discussion has inevitably dealt with the synthesis of the two alkynyl-vinylcyclopropane precursors **173** and **250**.

The first cyclisation precursor **173** was prepared in a highly convergent manner involving coupling of the aldehyde **174** and alkynylcyclopropane **175** fragments, followed by a selective reductive step as shown in Scheme 2.83. There was an issue of regiocontrol associated with this precursor **173**, as it presented the possibility of cleavage of either of the two cyclopropyl bonds. However, we were optimistic that electron release from the silyloxy group would be dominant in favouring cleavage of the less substituted bond leading to the desired regioisomer.

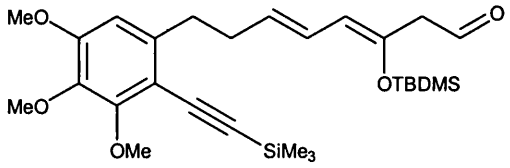


Scheme 2.83

Construction of the key alkynyl-vinylcyclopropane **173** directly from the two fragments **174** and **175** *via* preliminary hydrozirconation of the alkyne **175** followed by either a zirconocene-zinc transmetallation step or addition of "catalytic" silver (I) salt to enable subsequent coupling to the aldehyde **174** was initially attempted. However, this elegant methodology reported by Wipf[109] and Suzuki[108] proved unsuccessful. Although model studies of this reaction indicated that the aldehyde **174** was suited to such reaction conditions, the alkynylcyclopropane **175**, on the other hand, was not.

Unfortunately, our attempts to facilitate the transition metal catalysed [5+2] cycloaddition reaction on alkynyl-vinylcyclopropane **173** were without any apparent success. The relatively harsh conditions required when using Wilkinson's catalyst **98** resulted in complete decomposition of the starting material. It was therefore hoped that the much more reactive $[CpRu(CH_3CN)_3]PF_6$ catalyst **160** would provide the possibility of achieving the desired reaction by enabling the opportunity for much milder reaction conditions. However, the Lewis acidic nature of this catalyst dominated and thus led to the formation of the

aldehyde **244**, presumably *via* ring opening of the cyclopropane ring followed by elimination of the hydroxyl group. To our dismay, even the protected alcohol **245** also produced the same undesired aldehyde **244**. In a final effort, the reaction was investigated with $[Rh(CO)_2Cl]_2$ catalyst **106**, but in this case, no reaction occurred and the starting material was recovered.

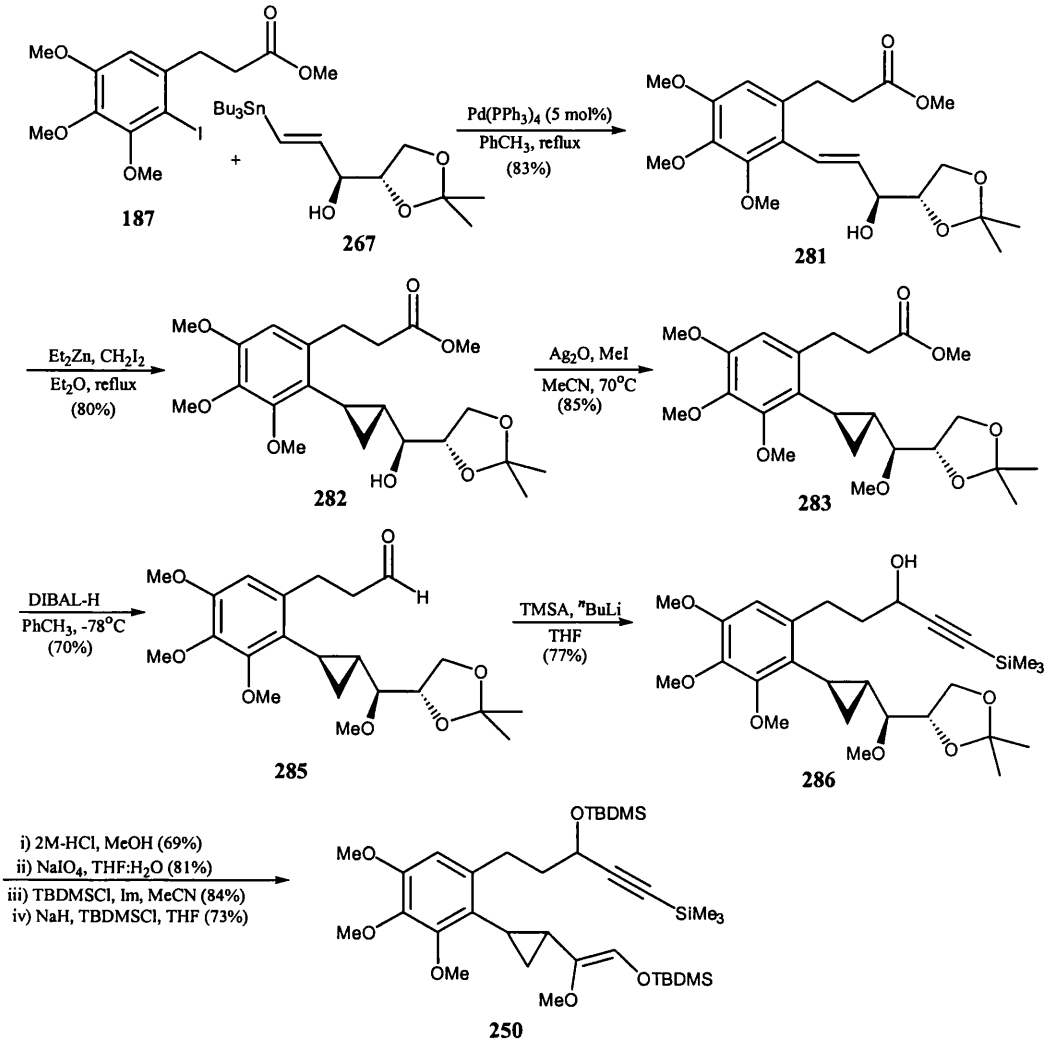


244

Figure 2.3

A second cyclisation precursor **250** was then designed which did not incorporate the connectivity pattern which had proven problematic in the previous molecules **173** and **245**. In addition, it was envisaged that cleavage of the cyclopropane ring would occur, in this case, exclusively at the most substituted bond. This prediction was based on energetic grounds, as cleavage of the less hindered bond would lead to the formation of an anti-Bredt bridgehead alkene.

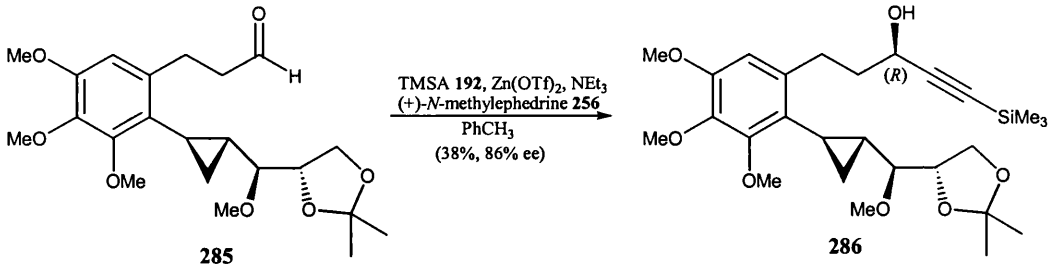
Although a highly convergent route was initially proposed for the synthesis of this alkynyl-vinylcyclopropane **250**, problems were encountered in efforts to achieve the cross-coupling reaction involving a cyclopropyl stannane. This was overcome by employing a more linear strategy which involved a palladium-mediated coupling reaction between aryl iodide **187** and the vinyl stannane **267** (Scheme 2.84).



187 267 281 282 283 285 286 250

Scheme 2.84

An investigation into Carreira's methodology for the synthesis of chiral propargylic alcohols enabled the (*R*)-propargylic alcohol **286** to be isolated in a moderate yield but with a relatively high enantiomeric excess of 86%. It was hoped that this (*R*)-alcohol could later serve as a platform for the introduction of the required (*S*)-acetamido functionality of colchicine **1** (Scheme 2.85).



Scheme 2.85

Once again, the employment of cyclisation precursor **250** in the transition metal catalysed [5+2] cycloaddition reaction was without success. When the reaction was carried out in acetone using $[CpRu(CH_3CN)_3]PF_6$ catalyst **160**, complete consumption of starting material occurred with formation of a complex mixture of products. Conversely, when DMF was used as solvent in place of acetone, no reaction occurred, and even an increase in temperature provided no new products. The use of $[Rh(CO)_2Cl]_2$ catalyst **106** also did not lead to the formation of any cycloaddition products.

To our disappointment, the transition metal catalysed [5+2] cycloaddition reaction had thus far proven to be an unsuccessful method as a route to achieving simultaneous formation of the two seven-membered rings of colchicine **1** for each of the designed precursors **173** and **250**.

CHAPTER THREE

EXPERIMENTAL

3.1 General Procedures

^{1}H NMR spectra were recorded at 500 MHz on a Bruker Avance 500, 400 MHz on a Bruker AMX-400 or at 300 MHz on a Bruker AMX-300. ^{13}C NMR spectra were recorded at 125 MHz, 100 MHz or 75 MHz on the above instruments. Assignments were supported by DEPT editing, COSY spectra and ^{1}H-^{13}C COSY spectra. Chemical shifts (δ) are referenced to the residual solvent peak and are quoted in parts per million (ppm). ^{19}F-NMR were recorded at 242 MHz on a Bruker AMX-300 and chemical shifts (δ) are referenced to $CFCl_3$ and quoted in parts per million (ppm). ^{31}P-NMR were recorded at 121 MHz on a Bruker AMX-300 and chemical shifts (δ) are quoted in parts per million (ppm). The abbreviations used to indicate multiplicity are s=singlet, d=doublet, t=triplet, q=quartet, dd=double doublet, ddd=double double doublet, dt=double triplet, m=multiplet, br=broad. The coupling constants (J) are given in Hertz (Hz). Infrared spectra were recorded as thin films on NaCl plates or as KBr discs on a Perkin-Elmer FT-IR 1605 instrument. Mass spectra were recorded either under fast atom bombardment (FAB) at the School of Pharmacy, University of London ULIRS service or chemical ionisation (CI) at the University College London Chemistry Department. Microanalyses were performed in the University College London Chemistry Department. Melting points were taken on a Reichert hot stage and are uncorrected. Boiling points refer to uncorrected air temperatures and pressure was recorded on a standard Gallenkamp manometer.

Analytical thin layer chromatography (tlc) was performed on pre-coated plastic sheets coated with silica gel $60F_{254}$ (Merck) and visualised with ultraviolet light (254 nm), iodine, basic potassium permanganate or acidic anisaldehyde solution. Flash chromatography was performed at low positive pressure using BDH silica gel (40-60 μm).

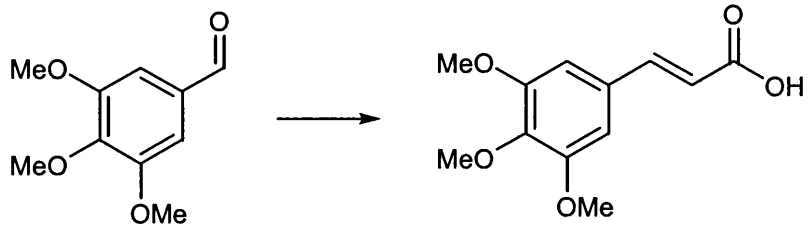
PE refers to either petroleum ether (b.p. 30-40 °C) or to petroleum ether (b.p. 40-60 °C). Diethyl ether (referred to as ether) and tetrahydrofuran were distilled from sodium-benzophenone. Dichloromethane was distilled from calcium hydride, benzene and toluene were distilled over sodium and methanol was distilled from magnesium turnings and iodine. Carbon tetrachloride was distilled over P_2O_5 and

stored over molecular sieves. Acetonitrile was pre-dried with silica, then refluxed with calcium hydride and fractionally distilled. Acetone was pre-dried with anhydrous calcium sulfate or anhydrous potassium carbonate and then distilled. DMF was dried with magnesium sulfate and distilled over Linde type 4A molecular sieves under reduced pressure. Diethylamine, triethylamine, *N,N*-diisopropylethylamine and pyridine were distilled from potassium hydroxide.

All glassware was oven dried and cooled under a flow of nitrogen prior to use. All reactions requiring dry solvents were carried out under an inert atmosphere of nitrogen.

3.2 Preparation of Individual Compounds

Synthesis of 3-(3,4,5-Trimethoxyphenyl)propenoic acid[94] 189

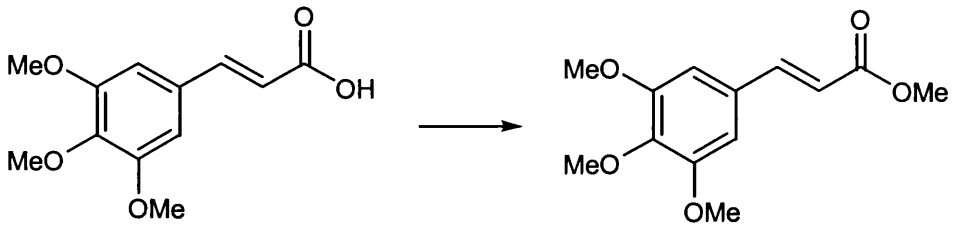


35 **189**

3,4,5-Trimethoxybenzaldehyde **35** (29.5 g, 0.15 mol) and malonic acid **188** (30.2 g, 0.29 mol) were dissolved in pyridine (60 ml) and heated to 50 °C. Piperidine (2.2 ml, 0.023 mol) was added and the mixture was stirred at 80 °C for 1 hour then heated at reflux for a further 4 hours. On cooling the reaction mixture was poured onto water (600 ml) and precipitated by the dropwise addition of conc. HCl (73.5 ml). The solid was isolated by filtration then dried in benzene (300 ml) under Dean-Stark conditions. Concentration *in vacuo* gave off-white crystals **189** (31.5 g, 88 %).

R_f(ether) 0.3; m.p. (methanol) 126-127 °C (lit.[139] 126-127 °C (benzene)); ν_{max} (KBr) / cm^{-1} 3089 (OH), 3005, 2583 (C-H), 1691 (C=O), 1627 (C=C), 1585, 1505, 1454, 1401, 1342, 1286, 1246, 1202, 1157, 1122, 998, 866, 829, 731, 620, 518; δ_H (400 MHz, $CDCl_3$) δ 3.86 (3H, s, *p*-OMe), 3.87 (6H, s, 2 x *m*-OMe), 6.33 (1H, d, $^3J_{trans}$ 15.9 Hz, ArCHC*H*), 6.75 (2H, s, aromatic), 7.68 (1H, d, $^3J_{trans}$ 15.9 Hz, ArC*H*CH); δ_C (100 MHz, $CDCl_3$) δ 56.08 (2 x *m*-OMe), 60.91 (*p*-OMe), 105.44 (2 x *o*-aromatic), 116.42 (ArCH*C*H), 129.41 (*i*-aromatic), 140.11 (*p*-aromatic), 146.99 (Ar*C*HCH), 153.37 (2 x *m*-aromatic), 172.48 (*C*O_2H); m/z (FAB) 238 (100 %, [M^+]), 221 (25 %, [M-OH]), 154 (25 %, [M-C_4H_3O]), 136 (25 %); HRMS: calculated 238.0841; found 238.0844.

Synthesis of Methyl 3-(3,4,5-trimethoxyphenyl)propenoate 190

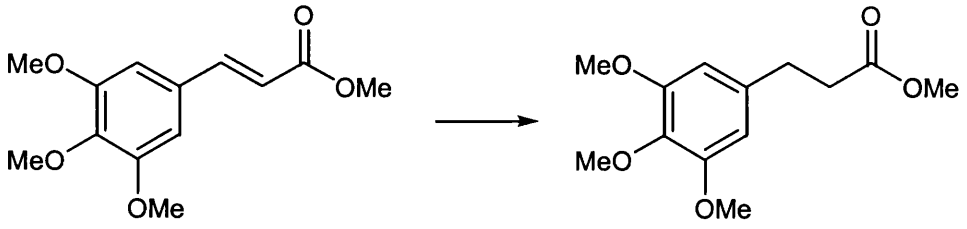


189 **190**

Acetyl chloride (23 ml, 0.32 mol) was added dropwise to methanol (140 ml) with stirring. After the exotherm had subsided, the solution was added to 3-(3,4,5-trimethoxyphenyl)propenoic acid **189** (30.1 g, 0.13 mol) and heated at reflux for 2 hours. On cooling, a precipitate formed which was collected by filtration to give white crystals **190** (27.6 g, 87 %).

R_f(ether) 0.5; m.p. (ethyl acetate/PE) 98-99 °C (lit.[140] 98-99 °C); ν_{max} (KBr) / cm^{-1} 2944, 2837 (C-H), 1697 (C=O), 1634 (C=C), 1582, 1505, 1461, 1421, 1339, 1288, 1250, 1188, 1128, 1039, 1004, 980, 852, 817, 732, 630, 605, 524; δ_H (400 MHz, $CDCl_3$) δ 3.75 (3H, s, CO_2Me), 3.82 (3H, s, *p*-OMe), 3.83 (6H, s, 2 x *m*-OMe), 6.29 (1H, d, $^3J_{trans}$ 16.0 Hz, ArCHC*H*), 6.70 (2H, s, aromatic), 7.56 (1H, d, $^3J_{trans}$ 16.0 Hz, ArC*H*CH); δ_C (100 MHz, $CDCl_3$) δ 51.57 (CO_2Me), 55.99 (2 x *m*-OMe), 60.82 (*p*-OMe), 105.05 (2 x *o*-aromatic), 116.89 (ArCH*C*H), 129.74 (*i*-aromatic), 139.95 (*p*-aromatic), 144.71 (Ar*C*HCH), 153.29 (2 x *m*-aromatic), 172.48 (*C*O_2Me); m/z (FAB) 252 (100 %, [M^+]), 237 (15 %, [M-CH_3]), 221 (45 %, [M-O]); HRMS: calculated 252.0998; found 252.1003.

Synthesis of Methyl 3-(3,4,5-trimethoxyphenyl)propanoate 191

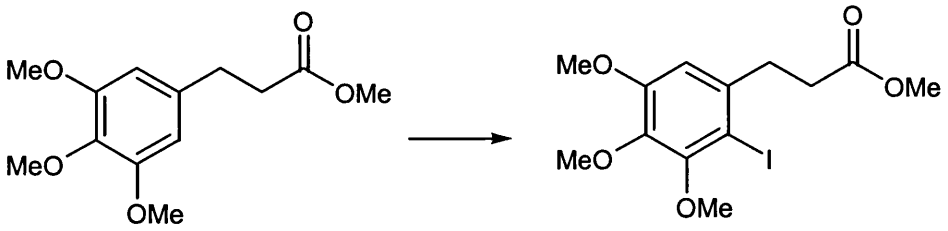


190 **191**

To a solution of methyl 3-(3,4,5-trimethoxyphenyl)propenoate **190** (10.4 g, 40.9 mmol) in methanol (300 ml) was added 10 % palladium on carbon (0.7 g, cat.). The flask was connected to the hydrogenation apparatus and the system was evacuated and H_2 gas introduced, this was repeated twice. The reaction mixture was stirred until hydrogen uptake had ceased and the system was evacuated and air introduced. Filtration and concentration *in vacuo* gave a yellow oil **191** which crystallised on standing (9.9 g, 98 %).

R_f(ether) 0.5; m.p. (ether/PE) 45-46 °C (lit.[141] 45-46 °C (hexane)); ν_{max} ($CHCl_3$) / cm^{-1} 3016, 2941, 2841 (C-H), 1732 (C=O), 1593, 1511, 1464, 1352, 1206, 1039, 1005, 976, 926, 904, 828, 734, 670, 626, 595; δ_H (400 MHz, $CDCl_3$) δ 2.59 (2H, t, ^3J 7.8 Hz, $ArCH_2CH_2$), 2.86 (2H, t, ^3J 7.8 Hz, $ArCH_2CH_2$), 3.63 (3H, s, CO_2Me), 3.78 (3H, s, *p*-OMe), 3.81 (6H, s, 2 x *m*-OMe), 6.38 (2H, s, aromatic); δ_C (100 MHz, $CDCl_3$) δ 31.27 ($ArCH_2CH_2$), 35.78 ($ArCH_2CH_2$), 51.60 (CO_2Me), 55.96 (2 x *m*-OMe), 60.76 (*p*-OMe), 105.05 (2 x *o*-aromatic), 129.74 (*i*-aromatic), 136.23 (*p*-aromatic), 153.11 (2 x *m*-aromatic), 173.22 (CO_2Me); m/z (FAB) 254 (100 %, [M^+]), 239 (5 %, [M-CH_3]), 223 (10 %, [M-O]), 181 (50 %, [M-CH_2CO]); HRMS: calculated 254.1154; found 254.1161.

Synthesis of Methyl 3-(2-iodo-3,4,5-trimethoxyphenyl)propanoate 187



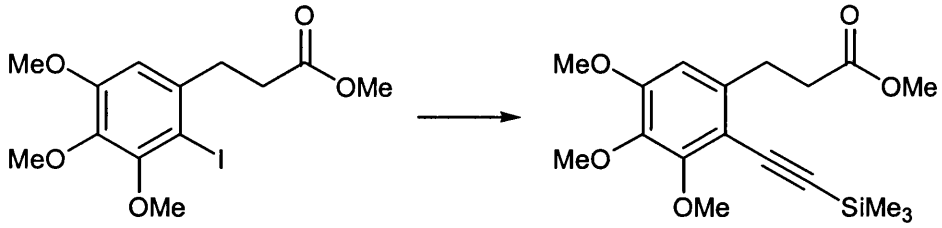
191 **187**

Methyl 3-(3,4,5-trimethoxyphenyl)propanoate **191** (19.0 g, 74.8 mmol) and silver trifluoroacetate (18.2 g, 82.4 mmol) were stirred in DCM (100 ml). A solution of iodine (21.2 g, 82.4 mmol) in DCM (350 ml) was added dropwise over a 3 hour period. The resulting red mixture was filtered and the filtrate washed successively with sat. aq. sodium thiosulfate solution (100 ml), water (100 ml) and sat. aq. sodium hydrogen carbonate solution (100 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (SiO_2, PE:ether / 50:50) gave a white solid **187** (25.3 g, 89 %).

R_f(PE:ether / 50:50) 0.3; m.p. (ether/PE) 40-42 °C (lit.[142] 36-37 °C); ν_{max} ($CHCl_3$) / cm^{-1} 3038, 2972, 2940 (C-H), 1732 (C=O), 1550, 1480, 1429, 1335, 1208, 1165, 1105, 1049, 1005, 971, 926, 838, 766, 671; δ_H (400 MHz, $CDCl_3$) δ2.59 (2H, t, ^3J 7.6 Hz, $ArCH_2CH_2$), 3.07 (2H, t, ^3J 7.6 Hz, $ArCH_2CH_2$), 3.66 (3H, s, CO_2Me), 3.80 (3H, s, OMe), 3.81 (3H, s, OMe), 3.83 (3H, s, OMe), 6.65 (1H, s, aromatic); δ_C (100 MHz, $CDCl_3$) δ34.29 ($ArCH_2CH_2$), 36.11 ($ArCH_2CH_2$), 51.64 (CO_2Me), 56.05 (OMe), 60.65 (OMe), 60.87 (OMe), 87.69 (C-2), 108.87 (C-6), 138.66 (C-4), 140.50 (C-1), 153.07 (C-5), 153.52 (C-3), 172.92 (CO_2Me); m/z (FAB) 380 (70 %, [M^+]), 307 (15 %, [M-$CH_2CO_2CH_3$]), 254 (100 %); HRMS: calculated 380.0121; found 380.0110.

Synthesis of

Methyl 3-(2-Trimethylsilylethynyl-3,4,5-trimethoxyphenyl)propanoate 186

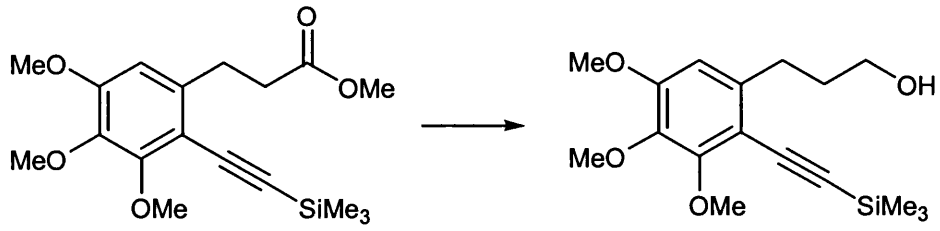


187 **186**

Trimethylsilylacetylene **192** (4 ml, 28.3 mol) was added to a stirred solution of methyl 3-(2-iodo-3,4,5-trimethoxyphenyl)propanoate **187** (3.0 g, 7.9 mmol), palladium acetate (0.096 g, 0.39 mmol), triphenylphosphine (0.40 g, 1.55 mmol) and cuprous iodide (0.1 g, 0.53 mmol) in diethylamine (40 ml). The reaction mixture was heated at gentle reflux for 2 hours. After cooling to room temperature the solution was concentrated *in vacuo* and partitioned between water and PE:ether / 80:20 (100 ml). The aqueous layer was extracted with PE:ether / 80:20 (3 x 50 ml) and the combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and pre-absorbed onto silica. Column chromatography (SiO_2, PE:ether / 50:50) gave an orange oil **186** (2.4 g, 88 %).

R_f(PE:ether / 50:50) 0.3; b.p 155-157 °C at ~ 0.5 mmHg; ν_{max} (neat) / cm^{-1} 2956, 2839 (C-H), 2149 (C≡C), 1740 (C=O), 1595, 1564, 1493, 1458, 1435, 1405, 1337, 1286, 1250, 1196, 1172, 1129, 1082, 1038, 992, 936, 875, 845, 789, 760, 669, 666, 631; δ_H (400 MHz, $CDCl_3$) δ 0.19 (9H, s, $Si(CH_3)_3$), 2.60 (2H, t, ^3J 7.9 Hz, $ArCH_2CH_2$), 2.96 (2H, t, ^3J 7.9 Hz, $ArCH_2CH_2$), 3.61 (3H, s, CO_2Me), 3.76 (3H, s, OMe), 3.78 (3H, s, OMe), 3.89 (3H, s, OMe), 6.48 (1H, s, aromatic); δ_C (100 MHz, $CDCl_3$) δ -0.20 ($Si(CH_3)_3$), 30.17 ($ArCH_2CH_2$), 34.31 ($ArCH_2CH_2$), 51.38 (CO_2Me), 55.81 (OMe), 60.92 (2 x OMe), 99.04 ($C{\equiv}CSiMe_3$), 101.46 ($C{\equiv}CSiMe_3$), 108.04 (C-6), 109.72 (C-2), 139.68 (C-4), 140.21 (C-1), 153.64 (C-5), 155.09 (C-3), 173.17 (CO_2Me); m/z (FAB) 350 (100 %, [M^+]), 335 (10 %, [M-CH_3]), 277 (15 %, [M-CH_2CO_2]), 205 (30 %); HRMS: calculated 350.1550; found 350.1535.

Synthesis of 3-(2-Trimethylsilylethynyl-3,4,5-trimethoxyphenyl)propanol 193

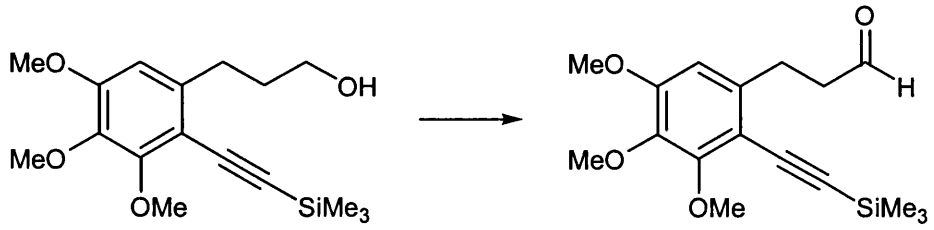


186 **193**

To a stirred suspension of lithium aluminium hydride (0.22 g, 5.68 mmol) in THF (20 ml) was added a solution of methyl 3-(2-trimethylsilylethynyl-3,4,5-trimethoxyphenyl)propanoate **186** (2.0 g, 5.68 mmol) in THF (30 ml) at 0 °C. The mixture was allowed to come to room temperature and stirred for 15 minutes. The reaction was quenched by the dropwise addition of sat. aq. NH_4Cl solution, filtered through celite and dried ($MgSO_4$). Concentration *in vacuo* gave an orange oil **193** (1.5 g, 80 %).

R_f(ether) 0.3; b.p. 192 °C at ~ 0.2 mmHg; ν_{max} (neat) / cm^{-1} 3427 (OH), 2985, 2869 (C-H), 2150 (C≡C), 1594, 1563, 1492, 1458, 1433, 1405, 1336, 1250, 1196, 1129, 1087, 1038, 989, 893, 844, 760, 734, 699, 631; δ_H (400 MHz, $CDCl_3$) δ 0.19 (9H, s, $Si(CH_3)_3$), 1.82 (2H, m, $ArCH_2CH_2$), 2.11 (1H, br s, O*H*), 2.76 (2H, t, ^3J 7.7 Hz, $ArCH_2CH_2$), 3.57 (2H, t, ^3J 6.2 Hz, CH_2OH), 3.77 (3H, s, OMe), 3.78 (3H, s, OMe), 3.89 (3H, s, OMe), 6.45 (1H, s, aromatic); δ_C (100 MHz, $CDCl_3$) δ -0.12 ($Si(CH_3)_3$), 30.60 ($ArCH_2CH_2$), 33.30 ($ArCH_2CH_2$), 55.80 (CH_2OH), 60.95 (2 x OMe), 61.58 (OMe), 99.84 (C≡$CSiMe_3$), 100.76 (C≡$CSiMe_3$), 107.85 (C-6), 109.80 (C-2), 139.88 (C-4), 141.12 (C-1), 153.74 (C-5), 155.01 (C-3); m/z (FAB) 322 (70 %, $[M^+]$), 277 (20 %, $[M-CH_2CH_2OH]$), 233 (20 %), 207 (25 %); HRMS: calculated 322.1600; found 322.1622.

Synthesis of 3-(2-Trimethylsilylethynyl-3,4,5-trimethoxyphenyl)propanal 174



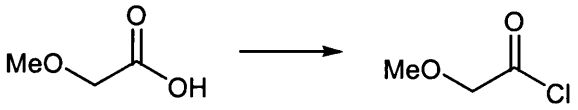
193 **174**

Dimethylsulfoxide (0.76 ml, 10.75 mmol) was added dropwise to a solution of oxalyl chloride (0.45 ml, 5.16 mmol) in DCM (40 ml) at -78 °C. The mixture was stirred for a further 15 minutes at -78 °C, then a solution of 3-(2-trimethylsilylethynyl-3,4,5-trimethoxyphenyl)propanol **193** (1.4 g, 4.3 mmol) in DCM (10 ml) was added dropwise. After 15 minutes of additional stirring at -78 °C, *N,N*-diisopropylethylamine (6 ml, 34.4 mmol) was added and the reaction was allowed to come to room temperature. After 1 hour, the reaction was poured into sat. aq. sodium hydrogen carbonate solution (20 ml) and the layers separated. The aqueous layer was extracted with DCM (2 x 20 ml) and the combined organic extracts were washed with brine (2 x 20 ml) and concentrated *in vacuo*. The residue was diluted with hexane (50 ml), washed with water (2 x 50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, PE:ether / 80:20) gave an orange oil **174** which crystallised on standing (1.0 g, 72 %).

R_f(PE:ether / 80:20) 0.13; m.p. 54-56 °C (PE:ether); ν_{max} ($CHCl_3$) / cm^{-1} 3019, 2965, 2939 (C-H), 2149 (C≡C), 1723 (C=O), 1595, 1492, 1464, 1406, 1346, 1208, 1130, 1084, 1035, 989, 929, 891, 845; δ_H (300 MHz, $CDCl_3$) δ 0.22 (9H, s, $Si(CH_3)_3$), 2.79 (2H, t, ^3J 7.4 Hz, $ArCH_2CH_2$), 3.01 (2H, t, ^3J 7.4 Hz, $ArCH_2CH_2$), 3.80 (3H, s, OMe), 3.83 (3H, s, OMe), 3.88 (3H, s, OMe), 6.50 (1H, s, aromatic), 9.80 (1H, s, CHO); δ_C (75 MHz, $CDCl_3$) δ 0.0 ($Si(CH_3)_3$), 27.47 ($ArCH_2CH_2$), 44.31 ($ArCH_2CH_2$), 56.03 (2 x OMe), 61.11 (OMe), 99.24 ($C{\equiv}CSiMe_3$), 101.80 ($C{\equiv}CSiMe_3$), 107.21 (C-6), 109.80 (C-2), 139.74 (C-4), 140.33 (C-1), 153.84 (C-5), 155.31 (C-3), 206.62 (CHO); m/z (FAB) 321 (95 %, [M+H]), 305 (40 %, [M-

CH_3]), 277 (80 %, [M-CO]), 205 (100 %), 136 (50 %); HRMS: calculated 321.1522; found 321.1530.

Synthesis of 1-Methoxyacetyl chloride 199



200 **199**

Method A:

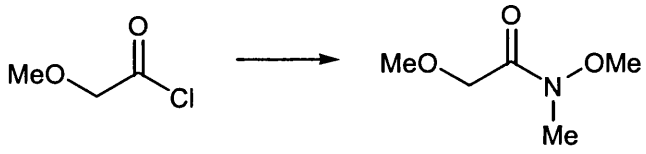
Methoxyacetic acid **200** (15.3 ml, 0.2 mol) was added dropwise to thionyl chloride (51 ml, 0.7 mol) and the mixture was heated at reflux for 1 hour. Distillation gave the product as a colourless liquid **199** (15.0 g, 70 %).

Method B:

Oxalyl chloride (4.3 ml, 49.3 mmol) and DMF (0.07 ml, 0.9 μmol) were added dropwise to a solution of methoxyacetic acid **200** (3.4 ml, 44.4 mmol) in DCM (70 ml) at 0 °C. The mixture was allowed to come to room temperature and stirred until gas evolution ceased. Distillation gave a colourless liquid **199** (4.6 g, 95%).

b.p. 112 °C (lit.[143] 112-113 °C); ν_{max} (neat) / cm^{-1} 3004, 2939, 2897 (C-H), 2834 (OCH_3), 1798 (COCl), 1456, 1408, 1352, 1336, 1283, 1234, 1202, 1134, 1007, 949, 913, 753; δ_H (400 MHz, $CDCl_3$) δ 3.45 (3H, s, OMe), 4.32 (2H, s, CH_2); δ_C (100 MHz, $CDCl_3$) δ 59.57 (OMe), 77.42 (CH_2), 171.76 (COCl).

Synthesis of *N*-Methoxy-*N*-methyl-2-methoxyamide 204

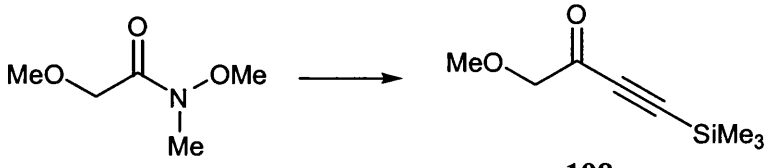


199 **204**

To a stirred solution of methoxyacetyl chloride **199** (14.5 g, 0.14 mol) and *N,O*-dimethylhydroxylamine hydrochloride (14.6 g, 0.15 mol) in DCM (180 ml) at 0 °C was added dropwise pyridine (23.5 ml, 0.29 mol). The resulting white suspension was stirred at 0 °C for 30 minutes and then at room temperature for 1 hour. The reaction mixture was diluted with DCM (75 ml), washed successively with water (75 ml) and brine (2 x 75 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Distillation afforded a colourless liquid **204** (12.5 g, 70 %).

R_f(ether) 0.3; b.p. 85-87 °C at ~ 15 mmHg; ν_{max} (neat) / cm^{-1} 3583, 3505, 2941 (C-H), 2823 (OCH_3), 1680 (C=O), 1448, 1423, 1391, 1332, 1288, 1201, 1138, 1092, 993, 969, 938, 913, 791, 665, 619; δ_H (400 MHz, $CDCl_3$) δ 2.99 (3H, s, NCH_3), 3.26 (3H, s, OCH_3), 3.50 (3H, s, $NOCH_3$), 4.02 (2H, s, CH_2); δ_C (100 MHz, $CDCl_3$) δ 31.57 (NCH_3), 58.84 ($NOCH_3$), 60.96 (OCH_3), 69.27 (CH_2), 170.42 (*C*=O); m/z (FAB) 134 (100 %, $[M^+]$); HRMS: calculated 134.0817: found 134.0816.

Synthesis of 1-Methoxy-4-trimethylsilylbut-3-yn-2-one 198

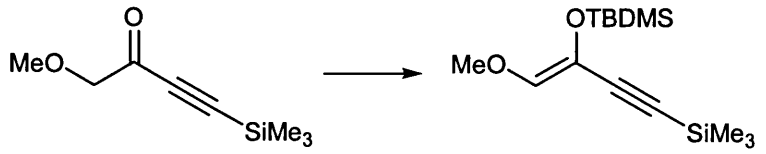


204 **198**

n-Butyllithium (30 ml, 66.17 mmol, 2.2 M in hexanes) was added dropwise to a solution of trimethylsilylacetylene **192** (9.4 ml, 66.17 mmol) in THF (50 ml) at -78 °C. The reaction was transferred to an ice bath and stirred at 0 °C for 30 minutes, then added dropwise to a solution of *N*-methoxy-*N*-methyl-2-methoxyacetamide **204** (8.0 g, 60.15 mmol) in THF (120 ml) over a 2 hour period. When addition was complete the mixture was stirred at 0 °C for a further 1 hour then poured onto cold 5 % HCl/ethanol solution (500 ml) and stirred at 0 °C for 30 minutes. The mixture was taken up in ether:DCM (500 ml, 1:1) then washed with brine (3 x 250 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Distillation (90 °C at ~12 mmHg) gave a yellow liquid **198** (7.2 g, 69 %).

R_f(PE:ether / 80:20) 0.4; b.p. 90 °C at ~12 mmHg; ν_{max} (neat) / cm^{-1} 2962, 2903 (C-H), 2828 (OCH_3), 2152 (C≡C), 1697 (C=O), 1451, 1412, 1253, 1201, 1148, 1109, 1086, 994, 979, 931, 847, 763, 703, 666, 623; δ_H (400 MHz, $CDCl_3$) δ 0.19 (9H, s, $Si(CH_3)_3$), 3.39 (3H, s, OMe), 4.12 (2H, s, CH_2); δ_C (100 MHz, $CDCl_3$) δ -0.99 ($Si(CH_3)_3$), 59.35 (OMe), 78.29 (CH_2), 99.43 ($C{\equiv}CSiMe_3$), 101.10 ($C{\equiv}CSiMe_3$), 184.42 (C=O); m/z (FAB) 171 (95 %, [M+H]), 155 (35 %, [M-CH_3]), 125 (90 %, [M-CH_2O]); HRMS: calculated 171.0841; found 171.0830.

Synthesis of (*Z*)-2-(*tert*-Butyldimethylsilyloxy)-1-methoxy-4-trimethylsilyl-but-1-en-3-yne 197

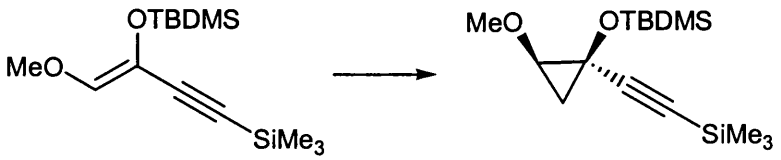


198 **197**

To a stirred solution of 1-methoxy-4-trimethylsilylbut-3-yn-2-one **198** (1.0 g, 5.9 mmol) and triethylamine (3 ml, 8.9 mmol) in benzene (100 ml) was added *tert*-butyldimethylsilyltrifluoromethylsulfonate (1.5 ml, 6.5 mmol) dropwise. The reaction mixture was stirred at room temperature for 20 hours, then poured onto water (75 ml) and extracted with ether (2 x 30 ml). The combined extracts were dried (Na_2SO_4), filtered and chromatographed (SiO_2, PE:ether / 90:10) to give a colourless liquid **197** (1.5 g, 87 %, single isomer).

R_f(PE:ether / 80:20) 0.64; ν_{max} (neat) / cm^{-1} 2957, 2897, 2859 (C-H), 2139 (C≡C), 1654 (C=C), 1467, 1408, 1338, 1226, 1134, 1072, 1011, 939, 842, 784, 695; δ_H (400 MHz, $CDCl_3$) δ 0.04 (9H, s, $Si(CH_3)_3$), 0.05 and 0.06 (6H, 2 x s, $SiC(CH_3)_3(CH_3)_2$), 0.83 (9H, s, $SiC(CH_3)_3(CH_3)_2$), 3.52 (3H, s, OMe), 5.84 (1H, s, *CH*); δ_C (100 MHz, $CDCl_3$) δ -4.57 ($SiC(CH_3)_3(CH_3)_2$), -0.52 ($Si(CH_3)_3$), 18.32 ($SiC(CH_3)_3(CH_3)_2$), 25.68 ($SiC(CH_3)_3(CH_3)_2$), 60.24 (OMe), 94.55 ($C{\equiv}CSiMe_3$), 101.78 ($C{\equiv}CSiMe_3$), 118.35 (*C*H), 140.87 (*C*-O); m/z (FAB) 285 (70 %, [M+H]), 269 (30 %, [M-CH_3]), 243 (25 %, [M-C_2H_2]), 147 (100 %, [M-$C_5H_4O_2$]), 115 (30 %); HRMS: calculated 285.1706; found 285.1712.

Synthesis of (*Z*)-1-(*tert*-Butyldimethylsilyloxy)-2-methoxy-1-(2-trimethylsilylethynyl) cyclopropane 196



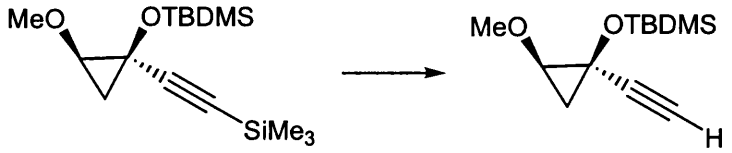
197 **196**

To a stirred solution of 2-(*tert*-butyldimethylsilyloxy)-1-methoxy-4-trimethylsilyl-but-1-en-3-yne **197** (1.2 g, 4.2 mmol) in ether (40 ml) was added a solution of diethylzinc (34 ml, 31.0 mmol, 15 %wt. in hexanes) at 0 °C. After a few minutes, diiodomethane (3.4 ml, 42.0 mmol) was added dropwise over a 10 minute period and the reaction mixture was allowed to come to room temperature. After 20 hours the mixture was poured onto sat. aq. NH_4Cl solution (100 ml) and stirred until a clear solution was obtained. The layers were separated and the aqueous layer was extracted with ether (2 x 50 ml), the combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (SiO_2, PE:ether / 99:1) gave a colourless liquid **196** (0.9 g, 68 %, single diastereoisomer).

R_f(PE:ether / 90:10) 0.4; ν_{max} (neat) / cm^{-1} 2959, 2930, 2898, 2858 (C-H), 2164 (C≡C), 1479, 1464, 1418, 1390, 1361, 1252, 1217, 1143, 1098, 1068, 1004, 938, 897, 841, 779, 760, 699, 667; δ_H (400 MHz, $CDCl_3$) δ 0.12 (9H, s, $Si(CH_3)_3$), 0.18 and 0.19 (6H, 2 x s, $SiC(CH_3)_3(CH_3)_2$), 0.87 (9H, s, $SiC(CH_3)_3(CH_3)_2$), 0.95 (1H, dd, $^3J_{trans}$ 4.7 Hz, ^2J 6.8 Hz, CH_2), 1.13 (1H, dd, $^3J_{cis}$ 7.4 Hz, ^2J 6.8 Hz, CH_2), 3.16 (1H, dd, $^3J_{trans}$ 4.7 Hz, $^3J_{cis}$ 7.4 Hz, CH), 3.44 (3H, s, OMe); δ_C (100 MHz, $CDCl_3$) δ -4.29 and -3.86 ($SiC(CH_3)_3(CH_3)_2$), -0.18 ($Si(CH_3)_3$), 17.91 ($SiC(CH_3)_3(CH_3)_2$), 23.60 (CH_2), 25.63 ($SiC(CH_3)_3(CH_3)_2$), 49.56 (*C*), 58.54 (OMe), 63.22 (CH), 87.19 (*C*≡CSiMe$_3$), 107.55 (C≡*C*SiMe$_3$); m/z (FAB) 299 (10 %, [M+H]), 175 (55 %, [M-$C_7H_{11}Si$]), 147 (100 %, [M-C_2H_4]), 136 (90 %), 125 (85 %), 115 (55 %), 107 (40 %); HRMS: calculated 299.1845; found 299.1863.

Synthesis of

***(Z)*-1-(*tert*-Butyldimethylsilyloxy)-2-methoxy-1-ethynylcyclopropane 175**

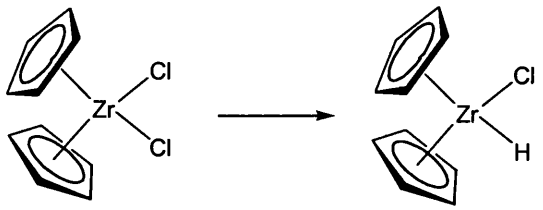


196 **175**

To a stirred solution of 1-(*tert*-butyldimethylsilyloxy)-2-methoxy-1-(2-trimethylsilylethynyl)cyclopropane **196** (0.8 g, 2.7 mmol) in methanol (40 ml) was added anhydrous potassium carbonate (0.4 g, 3.0 mmol). The reaction was stirred for 3 hours then partitioned between water and ether (40 ml, 1:1). The aqueous phase was extracted with ether (2 x 20 ml), washed with brine (40 ml) and dried (Na_2SO_4). Concentration *in vacuo* gave a colourless liquid **175** (0.4 g, 70 %, single diastereoisomer).

R_f(PE:ether / 99:1) 0.5; ν_{max} (neat) / cm^{-1} 3311 (C≡CH), 2957, 2935, 2897, 2858 (C-H), 2114 (C≡C), 1464, 1419, 1361, 1266, 1142, 1096, 998, 932, 871, 840; δ_H (400 MHz, $CDCl_3$) δ 0.16 and 0.20 (6H, 2 x s, $SiC(CH_3)_3(CH_3)_2$), 0.87 (9H, s, $SiC(CH_3)_3(CH_3)_2$), 0.98 (1H, dd, $^3J_{trans}$ 4.6 Hz, ^2J 6.9 Hz, CH_2), 1.14 (1H, dd, $^3J_{cis}$ 7.4 Hz, ^2J 6.9 Hz, CH_2), 2.36 (1H, s, C≡C*H*), 3.16 (1H, dd, $^3J_{trans}$ 4.6 Hz, $^3J_{cis}$ 7.4 Hz, C*H*), 3.44 (3H, s, OMe); δ_C (100 MHz, $CDCl_3$) δ -3.92 and -3.50 ($SiC(CH_3)_3(CH_3)_2$), 18.28 ($SiC(CH_3)_3(CH_3)_2$), 23.60 (CH_2), 25.99 ($SiC(CH_3)_3(CH_3)_2$), 49.28 (*C*), 58.97 (OMe), 63.26 (*C*H), 71.03 (*C*≡CH), 86.10 (C≡*C*H); m/z (FAB) 227 (15 %, [M+H]), 175 (75 %, [M-C_4H_3]), 136 (100 %), 115 (80 %), 107 (55 %).

Synthesis of Schwartz's Reagent[112] 205



211 **205**

Bis(cyclopentadienyl)zirconium dichloride **211** (3.0 g, 10.3 mmol) was dissolved in THF (20 ml) with gentle heating. A solution of lithium aluminium hydride (0.1 g, 2.83 mmol) in ether (5 ml) (prepared by stirring the suspension at room temperature for 10 minutes then filtering the clear solution *via* cannula) was added dropwise over 20 minutes. The resulting suspension was stirred at room temperature for 1.5 hours then Schlenk filtered under a nitrogen atmosphere. The white solid was washed with THF (4 x 5 ml), DCM (2 x 10 ml) and ether (4 x 4 ml) then dried *in vacuo* to give a white powder **205** (1.88 g, 71 %, 94 % pure*).

*Analysis :-

A sample (30 mg, 0.12 mmol) was suspended in benzene-d_6 and treated with a known excess of acetone (1.6 eq.). The relative areas for the mono- and diisopropoxides were determined by integration of the methyl doublets.

δ_H (400 MHz, C_6D_6) δ **0.97 (6H, d, 2 x C*H*$_3$), 1.08 (12H, d, 4 x C*H*$_3$)**, 1.55 (6H, s, residual acetone), 4.03 (1H, m, C*H*), 4.07 (2H, m, 2 x C*H*), 5.90 (10H, s, 2 x Cp), 5.96 (10H, s, 2 x Cp); ν_{max} (nujol) / cm^{-1} 3097 (C-H), 1840, 1744, 1398, 1086, 1051, 1037, 1013, 939, 840, 800, 729, 677, 609; Elemental analysis (calc., found) *C* 46.58, 47.71, *H* 4.30, 4.55, *Cl* 13.75, 13.37.

HYDROZIRCONATION REACTIONS

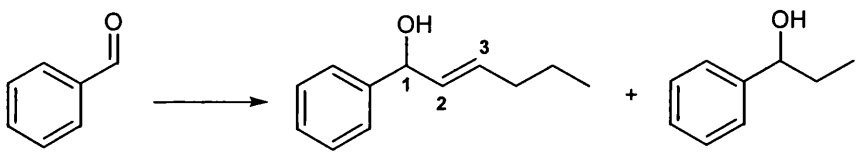
Method A - General Procedure for Transmetallation Reaction of Organozirconocenes

Schwartz's reagent **205** was added to a solution of alkyne in DCM (5 ml). The mixture was stirred at room temperature until a homogenous solution formed then cooled to -65 °C. Diethylzinc was added dropwise over 5 minutes and stirred for a further 10 minutes. The reaction mixture was cooled to 0 °C and a solution of aldehyde in DCM (5 ml) was added over a 10 minute period. After stirring at 0 °C for a further 1 hour, the solution was poured onto ice-cold sat. aq. sodium hydrogen carbonate solution (20 ml) and stirred vigorously at room temperature until gas evolution stopped. The mixture was extracted with ether (3 x 20 ml) and the combined organic layers were washed with brine (30 ml), dried (Na_2SO_4) and filtered through florisil.

Method B - General Procedure for Silver-Catalysed Reaction of Organozirconocenes

Schwartz's reagent **205** was added to a solution of alkyne in DCM (3 ml). After 10 minutes, a solution of aldehyde in DCM (3 ml) was added followed by $AgClO_4$ (5 mol%). The resultant mixture immediately turned dark brown and was allowed to stir at room temperature for a further 1 hour, then poured onto sat. aq. $NaHCO_3$ solution (10 ml). The mixture was extracted with ether (2 x 10 ml), dried ($MgSO_4$) and filtered through a pad of florisil.

Synthesis of 1-Phenylhex-2-en-1-ol[144] 215



214 **215** **216**

Method A was followed using Schwartz's reagent **205** (0.35 g, 1.34 mmol), 1-pentyne **213** (0.1 g, 1.47 mmol), diethylzinc (0.98 ml, 0.89 mmol, 15 %wt. in

hexanes) and benzaldehyde **214** (0.09 g, 0.89 mmol). A yellow liquid was obtained, which was a mixture of allylic alcohol **215** and secondary alcohol **216** (0.15 g, 65 %, 2:1).

Method B was followed using Schwartz's reagent **205** (0.15 g, 0.58 mmol), 1-pentyne **213** (0.04 g, 0.61 mmol), benzaldehyde **214** (0.05 g, 0.46 mmol) and $AgClO_4$ (0.005 g, 0.023 mmol). This reaction was abandoned as it would not go to completion.

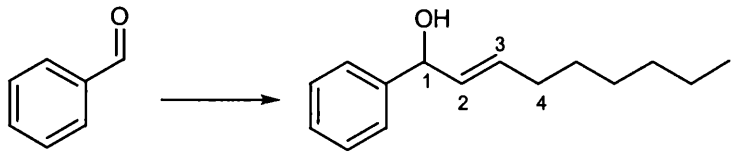
215 :

R_f(PE:ether / 80:20) 0.2; ν_{max} (neat) / cm^{-1} 3374 (OH), 3085, 3062 (C-H aromatic), 2960, 2930, 2833 (C-H), 1660, 1602 (C=C), 1493, 1453, 1379, 1262, 1200, 1094, 1071, 1014, 969, 911, 810, 735, 700, 666; δ_H (400 MHz, $CDCl_3$) δ 0.8 (3H, t, ^3J 7.3 Hz, CH_3), 1.33 (2H, m, CH_2), 1.94 (2H, m, CH_2), 2.26 (1H, br, O*H*), 5.04 (1H, d, ^3J 6.6 Hz, CH^1), 5.57 (1H, dt, $^3J_{trans}$ 15.4 Hz, ^3J 6.6 Hz, CH^3), 5.65 (1H, dd, ^3J 6.6 Hz, $^3J_{trans}$ 15.4 Hz, CH^2), 7.17-7.27 (5H, m, aromatic); δ_C (100 MHz, $CDCl_3$) δ 13.62 (*C*H_3), 22.14 (*C*H_2), 34.16 (*C*H_2), 75.03 (*C*HOH), 126.13 (2 x *C*H-aromatic), 127.45 (*C*H-aromatic), 128.38 (2 x *C*H-aromatic), 132.39 (*C*H), 132.59 (*C*H), 143.85 (*C*-aromatic).

216 :

δ_H (400 MHz, $CDCl_3$) δ 0.81 (3H, t, ^3J 7.3 Hz, CH_3), 1.66 (2H, m, CH_2), 4.46 (1H, t, ^3J 6.6 Hz, C*H*OH), 7.17-7.27 (5H, m, aromatic); δ_C (100 MHz, $CDCl_3$) δ 10.13 (*C*H_3), 31.86 (*C*H_2), 76.01 (*C*HOH), 125.95 (2 x *C*H-aromatic), 127.45 (*C*H-aromatic), 128.38 (2 x *C*H-aromatic), 158.13 (*C*-aromatic).

Synthesis of 1-Phenylnon-2-en-1-ol[145] 218



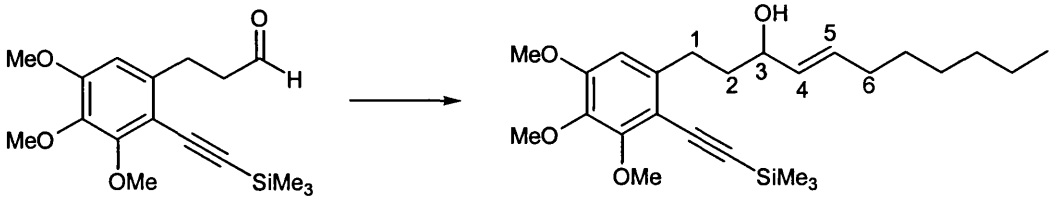
214 **218**

Method A was followed using Schwartz's reagent **205** (0.35 g, 1.34 mmol), 1-octyne **217** (0.16 g, 1.44 mmol), diethylzinc (0.98 ml, 0.89 mmol, 15 %wt. in hexanes) and benzaldehyde **214** (0.09 g, 0.89 mmol). A colourless oil was obtained **218** (0.15 g, 65 %).

Method B was followed using Schwartz's reagent **205** (0.15 g, 0.58 mmol), 1-octyne **217** (0.07 g, 0.61 mmol), benzaldehyde **214** (0.05 g, 0.46 mmol) and $AgClO_4$ (0.005 g, 0.023 mmol). A colourless oil was obtained **218** (0.05 g, 50 %).

R_f(PE:ether / 80:20) 0.3; ν_{max} (neat) / cm^{-1} 3369 (OH), 3081, 3059 (C-H aromatic), 2958, 2930, 2840 (C-H), 1660, 1608 (C=C), 1493, 1454, 1380, 1262, 1200, 1093, 1070, 1013, 969, 911, 810, 735, 700, 666; δ_H (400 MHz, $CDCl_3$) δ 0.79 (3H, t, ^3J 6.9 Hz, CH_3), 1.18 (8H, m, 4 x CH_2), 1.94 (2H, q, ^3J 6.8 Hz, CH_2^4), 2.26 (1H, br, O*H*), 5.03 (1H, d, ^3J 6.6 Hz, CH^1), 5.55 (1H, dt, ^3J 6.8 Hz, $^3J_{trans}$ 15.3 Hz, CH^3), 5.66 (1H, dd, ^3J 6.6 Hz, $^3J_{trans}$ 15.3 Hz, CH^2), 7.24 (5H, m, aromatic); δ_C (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.53 (CH_2), 28.80 (CH_2), 28.96 (CH_2), 31.61 (CH_2), 32.12 (CH_2), 75.04 (*C*HOH), 126.08 (2 x *C*H-aromatic), 127.30 (*C*H-aromatic), 128.31 (2 x *C*H-aromatic), 132.17 (*C*H), 132.61 (*C*H), 143.39 (*C*-aromatic); m/z (FAB) 218 (38 %, [M^+]), 133 (100 %, [M-C_6H_{13}]), 120 (38 %), 105 (28 %).

Synthesis of 1-(2-Trimethylsilylethynyl-3,4,5-trimethoxyphenyl)undec-4-en-3-ol 219



174 **219**

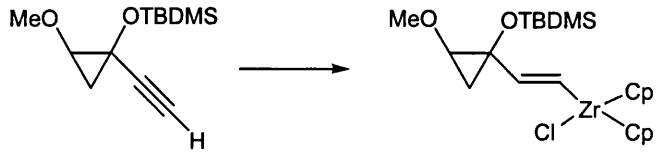
Method A was followed using Schwartz's reagent **205** (0.35 g, 1.34 mmol), 1-octyne **217** (0.07 g, 0.6 mmol), diethylzinc (0.9 ml, 0.77 mmol, 15 %wt. in hexanes) and 3-(2-trimethylsilylethynyl-3,4,5-trimethoxyphenyl)propanal **174** (0.18 g, 0.55 mmol). A yellow liquid was obtained as a mixture of allylic alcohol **219** and secondary alcohol **220** (0.18 g, 74 %, 3:1). Column chromatography (SiO_2, PE:DCM:EtOAc / 50:40:10) gave the desired allylic alcohol **219** (0.11 g, 46 %).

Method B was followed using Schwartz's reagent **205** (0.15 g, 0.58 mmol), 1-octyne **217** (0.07 g, 0.61 mmol), 3-(2-trimethylsilylethynyl-3,4,5-trimethoxyphenyl)propanal **174** (0.15 g, 0.46 mmol) and $AgClO_4$ (0.005 g, 0.023 mmol). A colourless oil was obtained **219** (0.15 g, 76 %).

R_f(PE:DCM:EtOAc / 50:40:10) 0.4; ν_{max} (neat) / cm^{-1} 3942 (O-H), 2957, 2930, 2855 (C-H), 2150 (C≡C), 1594, 1564, 1492, 1456, 1433, 1404, 1335, 1249, 1196, 1129, 1082, 1038, 990, 934, 892, 843, 760, 698, 666; δ_H (300 MHz, $CDCl_3$) δ 0.21 (9H, s, $Si(CH_3)_3$), 0.84 (3H, t, ^3J 6.9 Hz, CH_3), 1.15-1.33 (10H, m, 5 x CH_2), 1.78 (2H, m, CH_2), 2.76 (2H, q, ^3J 6.8 Hz, CH_2^2), 3.80 (3H, s, OMe), 3.81 (3H, s, OMe), 3.92 (3H, s, OMe), 4.03 (1H, q, ^3J 6.8 Hz, CH^3), 5.44 (1H, dd, ^3J 6.8 Hz, $^3J_{trans}$ 15.4 Hz, CH^4), 5.59 (1H, dt, ^3J 6.8 Hz, $^3J_{trans}$ 15.4 Hz, CH^5), 6.47 (1H, s, aromatic); δ_C (75 MHz, $CDCl_3$) δ 0.0 ($Si(CH_3)_3$), 14.01 (CH_3), 22.53 (CH_2), 28.79 (CH_2), 29.11 (CH_2), 30.86 (CH_2), 31.62 (CH_2), 32.18 (CH_2), 37.88 (CH_2), 55.84 (OMe), 60.99 (2 x OMe), 72.33, (CH^3), 99.74 (C≡CSiMe$_3$), 100.85 (C≡CSiMe$_3$), 107.86 (C-6), 109.79 (C-2), 132.18 (CH), 132.53 (CH), 139.63 (C-4), 141.41 (C-

1), 153.71 (C-5), 155.15 (C-3); m/z (FAB) 432 (29 %, [M^+]), 347 (100 %, [M-C_6H_{13}]), 205 (45 %), 136 (20 %); HRMS: calculated 432.2696; found 432.2702.

Hydrozirconation NMR Reaction

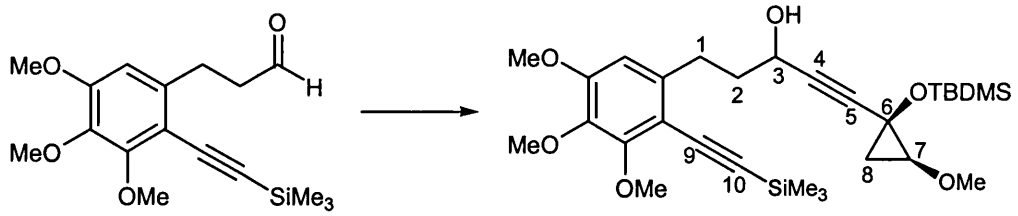


175 **222**

Schwartz's reagent **205** (0.04 g, 0.17 mmol) was added to a solution of alkyne **175** in deuterated DCM (1 ml) and the resulting mixture was stirred until a homogenous solution was obtained. NMR analysis indicated that the hydrozirconation reaction had proceeded efficiently with formation of the alkenylzirconocene **222**.

δ_H (400 MHz, $CDCl_3$) δ 0.10 and 0.15 (6H, 2 x s, $SiC(CH_3)_3(CH_2)_3$), 0.94 (9H, s, $SiC(CH_3)_3(CH_2)_3$), 0.91 (1H, dd, J_{trans} 4.1 Hz, ^2J 6.7 Hz, CH_2), 1.02 (1H, dd, J_{cis} 7.2 Hz, ^2J 6.7 Hz, CH_2), 2.81 (1H, dd, J_{trans} 4.1 Hz, J_{cis} 7.2 Hz, CH), 3.35 (3H, s, OMe), 5.78 (1H, d, ^3J 18.5 Hz, CH), 6.26 (10H, s, 2 x Cp), 6.68 (1H, d, ^3J 18.5 Hz, ZrCH); δ_C (100 MHz, CD_2Cl_2) δ -3.85 and –3.00 ($SiC(CH_3)_3(CH_2)_3$), 18.40 ($SiC(CH_3)_3(CH_2)_3$), 20.37 (CH_2), 25.99 ($SiC(CH_3)_3(CH_2)_3$), 58.46 (OMe), 61.74 (C), 63.92 (CH), 113.31 (Cp), 114.44 (Cp), 116.45 (Cp), 145.30 (CH), 169.92 ZrCH).

Synthesis of 1-[1-(*tert*-Butyldimethylsilanyloxy)-2-methoxycyclopropyl]-5-(3,4,5-trimethoxy-2-trimethylsilanylethynylphenyl)pent-1-yn-3-ol 229



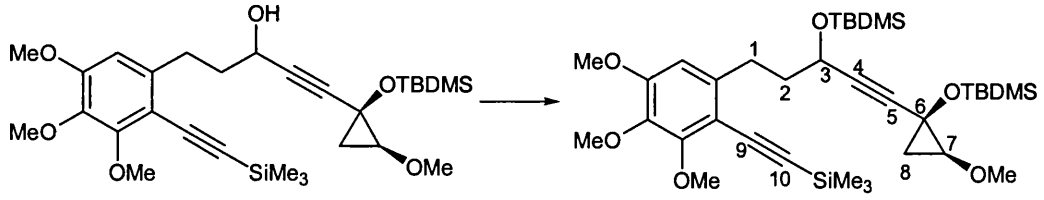
174 **229**

To a solution of hexamethyldisilazane (0.7 ml, 3.32 mmol) in THF (7 ml) was added *n*-butyllithium (1.4 ml, 3.38 mmol, 2.4 M in hexanes) at 0 °C. After 30 minutes, a solution of (*Z*)-1-(*tert*-butyldimethylsilyloxy)-2-methoxy-1-ethynylcyclopropane **175** (0.7 g, 3.07 mmol) in THF (7 ml) was added *via* cannula and the mixture stirred for a further 30 minutes. A solution of 3-(2-trimethylsilylethynyl-3,4,5-trimethoxyphenyl)propanal **174** (0.9 g, 2.93 mmol) in THF (7 ml) was added dropwise and the mixture was allowed to come to room temperature overnight. The reaction was quenched with sat. aq. NH_4Cl solution (40 ml) and extracted with ether (3 x 30 ml). Drying (Na_2SO_4) and concentration *in vacuo* gave an oil which was chromatographed (SiO_2, PE:ether / 50:50) to give a colourless oil **229** (1.1 g, 69 %, 1:1 mixture diastereoisomers).

R_f(PE:ether / 30:70) 0.5; ν_{max} (neat) / cm^{-1} 3450 (O-H), 2957, 2934, 2858 (C-H), 2151 (C≡C), 1595, 1493, 1462, 1434, 1405, 1337, 1252, 1196, 1130, 1085, 1066, 993, 928, 891, 842, 780, 760, 684; δ_H (500 MHz, $CDCl_3$) δ 0.15 and 0.19 (6H, 2 x s, $SiC(CH_3)_3(CH_3)_2$), 0.22 (9H, s, $Si(CH_3)_3$), 0.82 (9H, s, $SiC(CH_3)_3(CH_3)_2$), 0.97 (1H, dd, $^3J_{trans}$ 4.6 Hz, ^2J 6.9 Hz, CH_2^8), 1.10 (1H, dd, $^3J_{cis}$ 6.5 Hz, ^2J 6.9 Hz, CH_2^8), 1.99 (2H, m, CH_2^2), 2.83 (2H, t, ^3J 8.4 Hz, CH_2^1), 3.13 (1H, dd $^3J_{trans}$ 4.6 Hz, $^3J_{cis}$ 6.5 Hz, CH^7), 3.42 (3H, s, CHOMe), 3.80 (3H, s, OMe), 3.81 (3H, s, OMe), 3.92 (3H, s, OMe), 4.31 (1H, m, CH^3), 6.49 (1H, s, aromatic); δ_C (125 MHz, $CDCl_3$) δ -4.24 and –3.83 ($SiC(CH_3)_3(CH_3)_2$), 0.0 ($Si(CH_3)_3$), 17.82 ($SiC(CH_3)_3(CH_3)_2$), 22.92 (CH_2^8), 25.56 ($SiC(CH_3)_3(CH_3)_2$), 28.99 (CH_2^1), 38.15 (CH_2^2), 48.89 (C^6), 55.91 (OMe), 55.48 (CHOMe), 61.04 (2 x OMe), 61.65

(CH^3), 63.03 (CH^7), 83.24 (C^4), 86.84 (C^5), 99.63 (C^9), 101.21 (C^{10}), 108.09 (C-6), 109.93 (C-2), 140.17 (C-4), 140.42 (C-1), 153.78 (C-5), 155.28 (C-3); m/z (FAB) 569 (5 %, [M+Na]), 531 (10 %, [M-CH_3]), 514 (15 %, [M-O]), 497 (35 %), 277 (100 %, [$C_{15}H_{21}O_3Si$]), 205 (90 %); HRMS: calculated 569.2731; found 569.2720.

Synthesis of 1-{3-(*tert*-Butyldimethylsilanyloxy)-5-[1-(*tert*-butyldimethylsilanyloxy)-2-methoxycyclopropyl]pent-4-ynyl}-3,4,5-trimethoxy-2-trimethylsilanylethynyl benzene 247



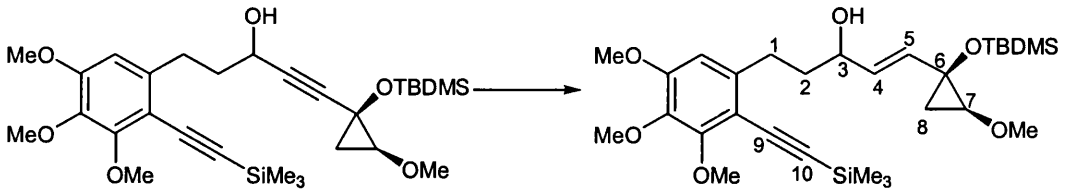
229 **247**

tert-Butyldimethylsilyl chloride (0.08 g, 0.55 mmol) and imidazole (0.07 g, 1.08 mmol) were added to a solution of alkynylcyclopropane **229** (0.1 g, 0.18 mmol) in acetonitrile (2 ml). The mixture was stirred overnight, and then concentrated *in vacuo*. The residue was dissolved in ether (10 ml) then washed with water (10 ml) and sat. aq. $NaHCO_3$ solution (10 ml) and dried (Na_2SO_4). Concentration *in vacuo* and column chromatography (SiO_2, PE:ether / 70:30) gave a colourless oil **247** (0.08 g, 67 %, 1:1 mixture diastereoisomers).

R_f(PE:ether / 50:50) 0.6; ν_{max} (neat) / cm^{-1} 2955, 2936, 2857 (C-H), 2151 (C≡C), 1593, 1564, 1491, 1461, 1404, 1338, 1253, 1196, 1130, 1086, 1040, 992, 960, 928, 840, 779, 683, 631; δ_H (500 MHz, $CDCl_3$) δ 0.08 and 0.10 (6H, 2 x s, $SiC(CH_3)_3(CH_3)_2$), 0.16 and 0.20 (6H, 2 x s, $SiC(CH_3)_3(CH_3)_2$), 0.23 (9H, s, $Si(CH_3)_3$), 0.89 (18H, s, 2 x $SiC(CH_3)_3(CH_3)_2$), 0.97 (1H, dd, $^3J_{trans}$ 4.6 Hz, ^2J 6.9 Hz, CH_2^8), 1.10 (1H, dd, $^3J_{cis}$ 7.3 Hz, ^2J 6.9 Hz, CH_2^8), 1.96 (2H, m, CH_2^2), 2.77 (2H, m, CH_2^1), 3.12 (1H, dd $^3J_{trans}$ 4.6 Hz, $^3J_{cis}$ 7.3 Hz, CH^7), 3.43 (3H, s, CHOMe), 3.81 (3H, s, OMe), 3.82 (3H, s, OMe), 3.93 (3H, s, OMe), 4.34 (1H, m, CH^3), 6.46 (1H, s, aromatic); δ_C (125 MHz, $CDCl_3$) δ -4.88 and -4.84

($SiC(CH_3)_3(CH_3)_2$), -4.33 and -4.21 ($SiC(CH_3)_3(CH_3)_2$), 0.09 ($Si(CH_3)_3$), 17.86 ($SiC(CH_3)_3(CH_3)_2$), 17.97 ($SiC(CH_3)_3(CH_3)_2$), 23.18 (CH_2^8), 25.63 ($SiC(CH_3)_3(CH_3)_2$), 31.17 (CH_2^1), 38.78 (CH_2^2), 48.98 (C^6), 55.93 (OMe), 58.51 (CHOMe), 61.06 (2 x OMe), 62.80 (CH^3), 63.04 (CH^7), 83.88 (C^4), 86.12 (C^5), 99.51 (C^9), 101.17 (C^{10}), 107.92 (C-6), 109.97 (C-2), 140.08 (C-4), 141.02 (C-1), 153.68 (C-5), 155.33 (C-3); m/z (FAB) 661 (5 %, [M+H]), 645 (15 %, [M-CH_3]), 497 (20 %), 277 (100 %, [$C_{15}H_{21}O_3Si$]), 247 (40 %); HRMS: calculated 661.3773; found 661.3800.

Synthesis of 1-[1-(*tert*-Butyldimethylsilanyloxy)-2-methoxycyclopropyl]-5-(3,4,5-trimethoxy-2-trimethylsilanylethynylphenyl)pent-1-en-3-ol 173



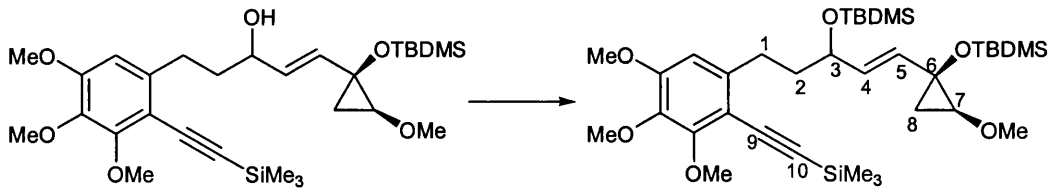
A solution of propargylic alcohol **229** (1 g, 1.83 mmol) in ether (20 ml) was added to a suspension of lithium aluminium hydride (0.08 g, 2.0 mmol) in ether (40 ml) at 0 °C. The resulting mixture was stirred at room temperature for 3 hours, then quenched by the dropwise addition of water and filtered through celite. Drying (Na_2SO_4) and concentration *in vacuo* gave an oil which was chromatographed (SiO_2, PE:ether / 30:70). A colourless oil **173** (0.43 g, 43 %, *E*-isomer, 1:1 mixture diastereoisomers) was obtained.

R_f(PE:ether / 30:70) 0.4; ν_{max} (neat) / cm^{-1} 3475 (OH), 2957, 2933, 2857 (C-H), 2151 (C≡C), 1594, 1565, 1493, 1462, 1433, 1404, 1360, 1337, 1251, 1130, 1065, 1038, 992, 966, 936, 841, 779, 760, 698; δ_H (500 MHz, $CDCl_3$) δ 0.08 and 0.10 (6H, 2 x s, $SiC(CH_3)_3(CH_3)_2$), 0.24 (9H, s, $Si(CH_3)_3$), 0.89 (9H, s, $SiC(CH_3)_3(CH_3)_2$), 1.00 (1H, dd, $^3J_{trans}$ 4.1 Hz, ^2J 7.3 Hz, CH_2^8), 1.05 (1H, dd, $^3J_{cis}$ 7.1 Hz, ^2J 7.3 Hz, CH_2^8), 1.67 (1H, br, OH), 1.82 (2H, m, CH_2^2), 2.81 (2H, m,

CH_2^1), 2.86 (1H, dd $^3J_{trans}$ 4.1, $^3J_{cis}$ 7.1 Hz, CH^7), 3.39 (3H, s, CHOMe), 3.81 (3H, s, OMe), 3.83 (3H, s, OMe), 3.93 (3H, s, OMe), 4.07 (1H, q, ^3J 5.1 Hz, CH^3), 5.52 (2H, m, CH^4 and CH^5), 6.48 (1H, s, aromatic); δ_C (125 MHz, $CDCl_3$) δ -3.61 and –3.15 ($SiC(CH_3)_3(CH_3)_2$), 0.08 ($Si(CH_3)_3$), 18.11 ($SiC(CH_3)_3(CH_3)_2$), 20.57 and 20.62 (CH_2^8), 25.86 ($SiC(CH_3)_3(CH_3)_2$), 31.00 and 31.08 (CH_2^1), 38.06 and 38.12 (CH_2^2), 55.97 (OMe), 58.47 and 58.50 (CHOMe), 58.97 and 59.01 (C^6), 61.09 (2 x OMe), 63.03 and 63.05 (CH^7), 71.42 and 71.66 (CH^3), 99.84 and 99.86 (C^9), 101.04 and 101.08 (C^{10}), 108.00 (C-6), 109.88 and 109.89 (C-2), 129.11 and 129.24 (CH^4), 134.19 and 134.56 (CH^5), 140.09 and 140.10 (C-4), 141.20 and 141.22 (C-1), 153.84 and 153.87 (C-5), 155.28 (C-3); m/z (FAB) 571 (10 %, [M+Na]), 548 (5 %, [M^+]), 517 (10 %, [M-OCH_3]), 491 (40 %), 427 (20 %), 277 (20 %, [$C_{15}H_{21}O_3Si$]), 227 (100 %); HRMS: calculated 571.2887; found 571.2900.

Synthesis of

1-{3-(*tert*-Butyldimethylsilanyloxy)-5-[1-(*tert*-butyldimethylsilanyloxy)-2-methoxycyclopropyl]pent-4-enyl}-3,4,5-trimethoxy-2-trimethylsilanylethynyl benzene 245



173 **245**

tert-Butyldimethylsilyl chloride (0.1 g, 0.72 mmol) and imidazole (0.06 g, 0.90 mmol) were added to a solution of vinylcyclopropane **173** (0.2 g, 0.36 mmol) in acetonitrile (2 ml). The mixture was stirred for 4 hours, then concentrated *in vacuo*. The residue was dissolved in ether (20 ml) then washed with water (20 ml) and sat. aq. $NaHCO_3$ solution (20 ml) and dried (Na_2SO_4). Column chromatography (SiO_2, PE:ether / 50:50) gave a colourless oil **245** (0.18 g, 75 %, *E*-isomer, 1:1 mixture diastereoisomers).

R_f(PE:ether / 80:20) 0.6; ν_{max} (neat) / cm^{-1} 2956, 2897, 2857 (C-H), 2151 (C≡C), 1594, 1564, 1492, 1462, 1404, 1338, 1253, 1196, 1131, 1087, 993, 966, 935, 840, 778, 698; δ_H (500 MHz, $CDCl_3$) δ 0.02 and 0.05 (6H, 2 x s, $SiC(CH_3)_3(CH_3)_2$), 0.07 and 0.10 (6H, 2 x s, $SiC(CH_3)_3(CH_3)_2$), 0.23 (9H, s, $Si(CH_3)_3$), 0.89 (18H, s, 2 x $SiC(CH_3)_3(CH_3)_2$), 1.01 (2H, m, CH_2^8), 1.72 (1H, m, CH_2^2), 1.80 (1H, m, CH_2^2), 2.66 (1H, m, CH_2^1), 2.76 (1H, m, CH_2^1), 2.83 (1H, dd $^3J_{trans}$ 4.3 Hz, $^3J_{cis}$ 6.9 Hz, CH^7), 3.39 (3H, s, CHOMe), 3.81 (3H, s, OMe), 3.82 (3H, s, OMe), 3.93 (3H, s, OMe), 4.13 (1H, m, CH^3), 5.53 (1H, dd, ^3J 6.2, 15.5 Hz CH^4), 5.50 (1H, d, ^3J 15.5 Hz, CH^5), 6.45 (1H, s, aromatic); δ_C (125 MHz, $CDCl_3$) δ -4.62, -4.59, -4.14 and -4.06, ($SiC(CH_3)_3(CH_3)_2$), -3.21 and –3.16 ($SiC(CH_3)_3(CH_3)_2$), 0.14 ($Si(CH_3)_3$), 18.08 ($SiC(CH_3)_3(CH_3)_2$), 18.27 ($SiC(CH_3)_3(CH_3)_2$), 20.35 and 20.45 (CH_2^8), 25.85 ($SiC(CH_3)_3(CH_3)_2$), 31.36 and 31.48 (CH_2^1), 38.97 and 38.99 (CH_2^2), 55.94 (OMe), 58.44 (CHOMe), 59.87 and 58.99 (C^6), 61.05 and 61.11 (2 x OMe), 63.06 and 63.19 (CH^7), 73.12 and 73.29 (CH^3), 99.64 and 99.65 (C^9), 100.90 and 100.93 (C^{10}), 107.70 and 107.77 (C-6), 109.90 and 109.88 (C-2), 129.82 (CH^4), 133.24 and 133.56 (CH^5), 139.95 and 139.97 (C-4), 141.83 (C-1), 153.71 and 153.72 (C-5), 155.32 (C-3); m/z (FAB) 685 (2 %, [M+Na]), 435 (15 %), 277 (100 %, [$C_{15}H_{21}O_3Si$]), 227 (55 %); HRMS: calculated 685.3752; found 685.3733.

Synthesis of *Bis*(η^6-benzene)di-μ-chlorodichlorodiruthenium[123] 235

$$RuCl_3.xH_2O \longrightarrow [(C_6H_6)RuCl_2]_2$$

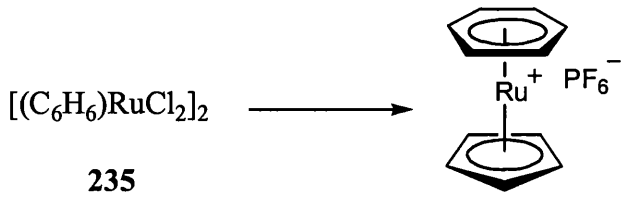
239 **235**

To a solution of ruthenium chloride hydrate **239** (0.8 g, 3.0 mmol) in 90 % aq. ethanol (50 ml) was added 1,3-cyclohexadiene (2.8 ml, 29.0 mmol) and the resultant mixture was heated at 45 °C for 3 hours. On cooling to room temperature, the volume was concentrated to 15 ml and the resulting red precipitate collected by filtration, washed with ethanol and dried *in vacuo*. A red solid was obtained **235** (0.63 g).

m.p. 242 °C (dec) (lit.[123] 249 °C (dec)); ν_{max} (nujol) / cm^{-1} 3043 (C-H), 1436, 1146, 1014, 976, 847, 668, 615; δ_H (500 MHz, CD_3CN) δ 5.69 (12 H, s, aromatic); δ_C (75 MHz, CD_3CN) δ 85.46 (aromatic); m/z (FAB) 455 (20 %), 441 (45 %), 433 (40 %), 419 (65 %), 363 (100 %), 307 (60 %); Elemental analysis (calc., found) *C* 28.80, 28.43, *H* 2.42, 2.27, *Cl* 28.40, 27.10.

Synthesis of

(η^6-Benzene)(η^5-2,4-cyclopentadien-1-yl)ruthenium hexafluorophosphate 236

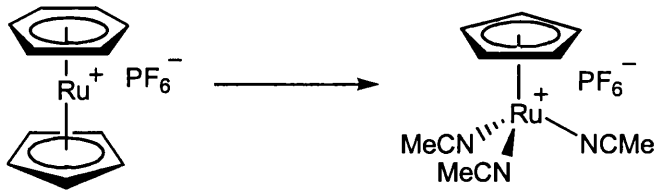


235 **236**

Lithium cyclopentadienide (0.1 g, 1.44 mmol) was added to a solution of *bis*(η^6-benzene)di-μ-chlorodichlorodiruthenium **235** (0.24 g, 0.48 mmol) in acetonitrile (70 ml). After stirring for 1 hour, the reaction mixture was filtered and the filtrate concentrated *in vacuo*. The solid obtained was recrystallised from acetonitrile/ether, then dissolved in water (5 ml) and filtered. The filtrate was treated with aq. NH_4Cl solution (0.16 g, 0.96 mmol), precipitating a tan coloured solid which was isolated by filtration. The solid was dissolved in acetone and filtered through a short pad of alumina to give white crystals **236** (0.11g, 61 %).

m.p. 284-287 °C (dec.) (lit.[118] 288-290 °C (dec.)); ν_{max} (KBr) / cm^{-1} 3101 (C-H), 1445, 1419, 825; δ_H (500 MHz, CD_3CN) δ 5.33 (5H, s, cp), 6.08 (6H, s, aromatic); δ_C (125 MHz, CD_3CN) δ 79.96 (cp), 85.69 (aromatic); δ_F (282 MHz, acetone-d_6) δ 103.1, 105.9; δ_P (100 MHz, acetone-d_6) δ 173.81 (septet, *J* 5.8 Hz); m/z (FAB) 320 (20 %), 247 (60 %, [M(^{104}Ru)+1-PF_6]), 245 (100 %, [M(^{102}Ru)+1-PF_6]), 244 (65 %, [M(^{101}Ru)+1-PF_6]), 243 (45 %, [M(^{100}Ru)+1-PF_6]), 242 (43 %, [M(^{99}Ru)+1-PF_6]), 241 (11 %, [M(^{98}Ru)+1-PF_6]), 239 (17 %, [M(^{96}Ru)+1-PF_6]), 176 (25 %), 167 (20 %).

Synthesis of *Tris*(acetonitrile)(η^5-2,4-cyclopentadien-1-yl)ruthenium hexafluorophosphate[118] 160

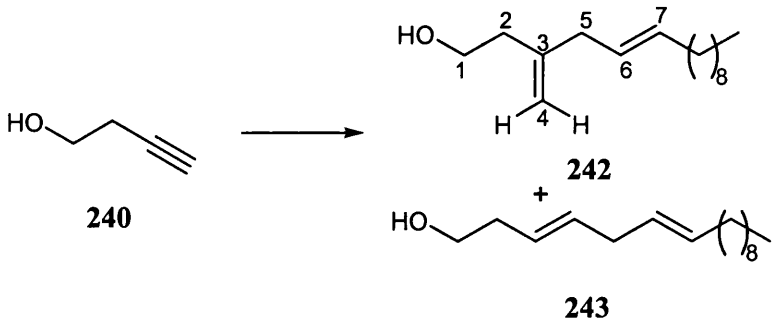


236 **160**

(η^6-Benzene)(η^5-2,4-cyclopentadien-1-yl)ruthenium hexafluorophosphate **236** (0.11 g, 0.28 mmol) was dissolved in acetonitrile (70 ml) and irradiated with a 450 W Hanovia medium pressure medium pressure mercury lamp for 6 hours. The solvent was removed *in vacuo* to give the desired compound as a brown solid **160** (0.12 g, quant.).

m.p. 122-124 °C (dec.) (lit.[118] 117-118 °C (dec.)); ν_{max} (KBr) / cm^{-1} 3119, 3012, 2946 (C-H), 2283, 2146, 1653, 1414, 1375, 1100, 1037, 998, 834; δ_H (500 MHz, acetone-d_6) δ 2.50 (9H, s, 3 x MeCN), 4.30 (5H, s, cp); δ_C (125 MHz, acetone-d_6) δ 3.30 (MeCN), 69.47 (cp); δ_F (282 MHz, acetone-d_6) δ 103.4, 105.9; δ_P (100 MHz, acetone-d_6) δ 143.03 (septet, J 5.8 Hz); m/z (FAB) 289 (10 %, [M-PF_6]), 247 (65 %, [M(^{104}Ru)-(3 x NH)], 245 (100 %, [M(^{102}Ru)-(3 x NH)], 244 (70 %, [M(^{101}Ru)-(3 x NH)], 243 (53 %, [M(^{100}Ru)-(3 x NH)], 242 (50 %, [M(^{99}Ru)-(3 x NH)], 241 (10 %, [M(^{98}Ru)-(3 x NH)], 239 (22 %, [M(^{96}Ru)-(3 x NH)], 154 (50 %), 136 (50 %), 107 (35 %); HRMS: calculated 244.9904; found 244.9920.

Synthesis of 3-Methylene-pentadec-5-en-1-ol[124] 242



$[CpRu(CH_3CN)_3]PF_6$ **160** (0.01g, 0.025 mmol, 10 mol%) was added to a solution of but-3-yn-1-ol **240** (0.02 ml, 0.25 mmol) and 1-dodecene **241** (0.07 ml, 0.30 mmol) in DMF (0.5 ml). The mixture was stirred at room temperature for 4 hours, then the solvent was removed *in vacuo*. Column chromatography (SiO_2, PE:ether / 70:30) gave a colourless oil which was an inseparable mixture of the branched **242** and linear **243** products (0.04 g, 67 %, **242:243**/7.3:1).

242:

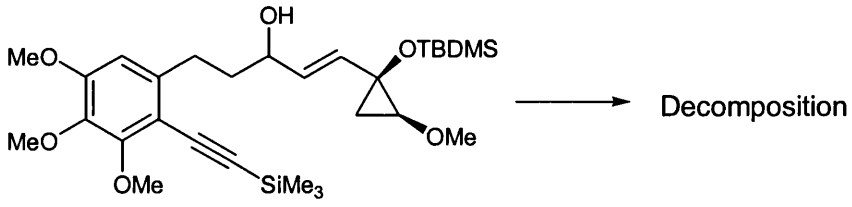
R_f(PE:ether / 70:30) 0.2; ν_{max} (neat) / cm^{-1} 3340 (OH), 2925, 2854 (C-H), 1646 (C=C), 1462, 1435, 1376, 1170, 1048, 970, 893, 865, 721; δ_H (500 MHz, $CDCl_3$) δ 0.86 (3H, t, ^3J 7.0 Hz, CH_3), 1.24 (12H, m, 6 x CH_2), 1.34 (2H, m, CH_2), 1.39 (1H, br, O*H*), 1.99 (2H, q, ^3J 7.0 Hz, CH_2), 2.28 (2H, t, ^3J 6.5 Hz, CH_2^2), 2.78 (2H, d, ^3J 6.5 Hz, CH_2^5), 3.69 (2H, t, ^3J 6.2 Hz, CH_2^1), 4.82 (1H, d, ^2J 1.5 Hz, CH_2^4), 4.87 (1H, d, ^2J 1.5 Hz, CH_2^4), 5.37 (1H, dt, ^3J 6.7, 15.1 Hz, CH^6), 5.45 (1H, dt, 15.1 Hz, ^3J 6.6, CH^7); δ_C (125 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.67 (CH_2), 29.17 (CH_2), 29.32 (CH_2), 29.46 (CH_2), 29.49 (CH_2), 29.58 (CH_2), 31.89 (CH_2), 32.51 (CH_2), 39.00 (CH_2^2), 39.33 (CH_2^5), 60.28 (CH_2^1), 112.35 (CH_2^4), 127.06 (CH^6), 133.01 (CH^7), 145.34 (*C*); m/z (CI) 238 (100 %, [M^+]), 221 (40 %, [M-OH]), 193 (15 %, [M-C_2H_4]), 151 (20 %), 95 (80 %), 81 (70 %); HRMS: calculated 239.2375; found 239.2376.

243:

δ_H (500 MHz, $CDCl_3$) δ 3.62 (2H, t, ^3J 6.2 Hz, CH_2OH), all other signals are masked by **242**.

ATTEMPTED [5+2] CYCLOADDITION OF PRECURSOR 173

Using Wilkinson's Catalyst (98)

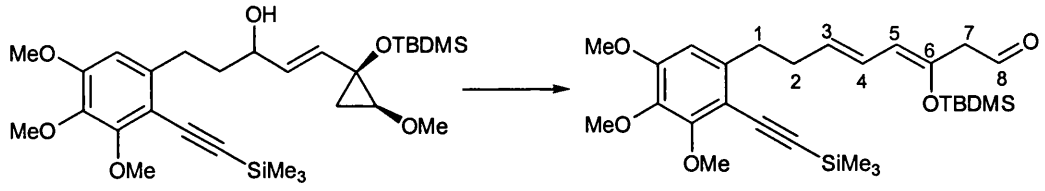


173

Wilkinson's catalyst **98** (0.004 g, 0.004 mmol, 5 mol%) and AgOTf (0.001 g, 0.004 mmol, 5 mol%) were added to toluene (1 ml) and stirred at room temperature. After 5 minutes, a solution of alkynyl-vinylcyclopropane **173** (0.045 g, 0.08 mmol) in toluene (1 ml) was added *via* cannula and the reaction mixture was heated at reflux for 1 hour. Complete decomposition of the starting **173** was observed.

Using $[CpRu(CH_3CN)_3]PF_6$ (160)

3-(*tert*-Butyldimethylsilanyloxy)-8-(3,4,5-trimethoxy-2-trimethylsilanylethynylphenyl)octa-3,5-dienal 244



173 **244**

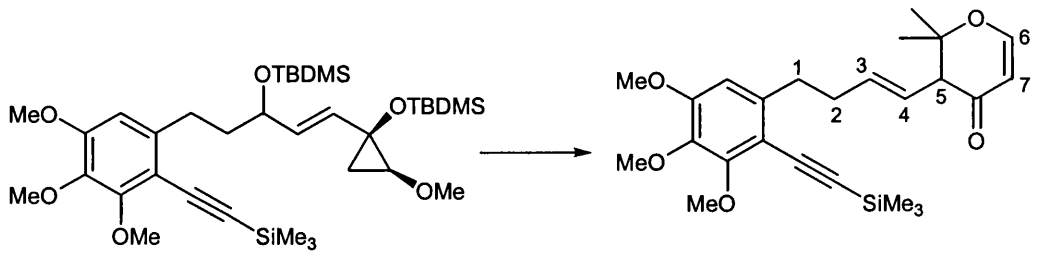
$[CpRu(CH_3CN)_3]PF_6$ **160** (0.002 g, 0.005 mmol, 10 mol%) was added to a solution of vinylcyclopropane **173** (0.03 g, 0.05 mmol) in acetone (1 ml). The resultant solution was stirred at room temperature overnight. Column chromatography (SiO_2, PE:ether / 50:50) gave a colourless oil **244** (0.012 g, 43 %).

R_f(ether) 0.5; ν_{max} (neat) / cm^{-1} 2957, 2859 (C-H), 2151 (C≡C), 1729 (C=O), 1658, 1620 (C=C), 1594, 1565, 1492, 1463, 1434, 1363, 1328, 1253, 1195, 1078, 1038, 971, 892, 841, 782, 760, 669; δ_H (500 MHz, $CDCl_3$) δ 0.12 (6H, s, $SiC(CH_3)_3(CH_3)_2$), 0.23 (9H, s, $Si(CH_3)_3$), 0.93 (9H, s, $SiC(CH_3)_3(CH_3)_2$), 2.40 (2H, q, ^3J 6.8 Hz, CH_2^2), 2.78 (2H, m, CH_2^1), 3.06 (2H, d, ^3J 2.6 Hz, CH_2^7), 3.81 (3H, s, OMe), 3.83 (3H, s, OMe), 3.93 (3H, s, OMe), 5.32 (1H, d, $^3J_{trans}$ 10.6 Hz, CH^5), 5.59 (1H, dt, $^3J_{trans}$ 15.5 Hz, ^3J 6.8 Hz, CH^3), 6.27 (1H, dd, $^3J_{trans}$ 10.6 Hz, $^3J_{trans}$ 15.5 Hz, CH^4), 6.45 (1H, s, aromatic), 9.64 (1H, t, ^3J 2.6 Hz, CH^8); δ_C (125 MHz, $CDCl_3$) δ -3.95 ($SiC(CH_3)_3(CH_3)_2$), 0.09 ($Si(CH_3)_3$), 18.18 ($SiC(CH_3)_3(CH_3)_2$), 25.64 ($SiC(CH_3)_3(CH_3)_3$), 33.79 (CH_2^2), 34.64 (CH_2^1), 51.47 (CH_2^7), 55.95 (OMe), 61.07 (OMe), 61.08 (OMe), 91.56 ($C{\equiv}CSiMe_3$), 101.02 ($C{\equiv}CSiMe_3$), 107.98 (C-6), 109.90 (C-2), 114.06 (CH^5), 124.29 (CH^4), 130.75 (CH^3), 140.00 (C-4), 141.22 (C-1), 142.20 (C^6), 153.61 (C-5), 155.15 (C-3), 198.81 (CH^8); m/z (FAB) 303 (20 %, [M-$C_{11}H_{21}O_2Si$]), 277 (100 %, [M-C_2H_2]), 261 (40 %), 245 (35 %), 231 (20 %), 217 (30 %).

ATTEMPTED [5+2] CYCLOADDITION OF PRECURSOR 245

Using [CpRu(CH$_3$CN)$_3$]PF$_6$ (160)

Initial Attempt (Proposed Structure 246):



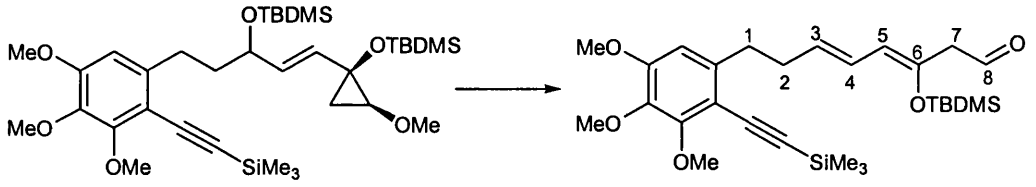
245 **246**

[CpRu(CH$_3$CN)$_3$]PF$_6$ **160** (0.005 g, 0.011 mmol, 10 mol%) was added to a solution of vinylcyclopropane **245** (0.037 g, 0.056 mmol) in acetone (1 ml). The resultant solution was stirred at room temperature overnight. The reaction temperature was the increased to 50 °C, and after 3 hours at this temperature a further portion of [CpRu(CH$_3$CN)$_3$]PF$_6$ **160** (0.005 g, 0.011 mmol, 10 mol%) was added. The resultant mixture was allowed to stir at 50 °C for a further 3 hours, then concentrated *in vacuo*. The residue was dissolved in DCM and filtered

through a pad of alumina. Column chromatography (SiO_2, PE:ether / 50:50) gave a colourless oil **246** (0.003 g, 14 %).

R_f(ether) 0.5; δ_H (500 MHz, $CDCl_3$) δ 0.24 (9H, s, $Si(CH_3)_3$), 1.21 (3H, s, CH_3), 1.29 (3H, s, CH_3), 2.40 (2H, dt, ^3J 6.8, 7.5 Hz, CH_2^2), 2.78 (2H, t, ^3J 7.5 Hz, CH_2^1), 2.84 (1H, d, ^3J 9.3 Hz, CH^5), 3.82 (3H, s, OMe), 3.84 (3H, s, OMe), 3.93 (3H, s, OMe), 5.31 (1H, dd, ^3J 9.3, 15.3 Hz, CH^4), 5.32 (1H, d, ^3J 6.0 Hz, CH^7), 5.65 (1H, dt, ^3J 15.3, 6.8 Hz, CH^3), 6.43 (1H, s, aromatic), 7.14 (1H, d, ^3J 6.0 Hz, CH^6).

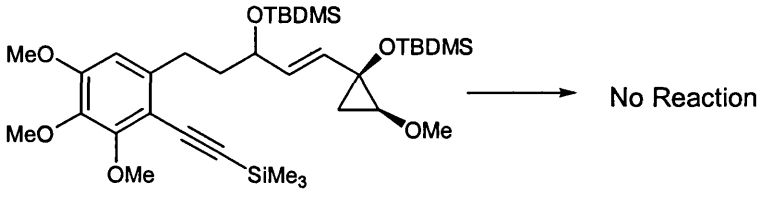
Subsequent Attempts:



245 **244**

$[CpRu(CH_3CN)_3]PF_6$ **160** (0.001 g, 0.003 mmol, 20 mol%) was added to a solution of vinylcyclopropane **254** (0.01 g, 0.015 mmol) in acetone (0.25 ml). The resultant solution was stirred at room temperature for 6 hours, then filtered through a pad of alumina to give a yellow oil **244** (0.005 g, 65 %).

Using $[Rh(CO)_2Cl]_2$ (106)

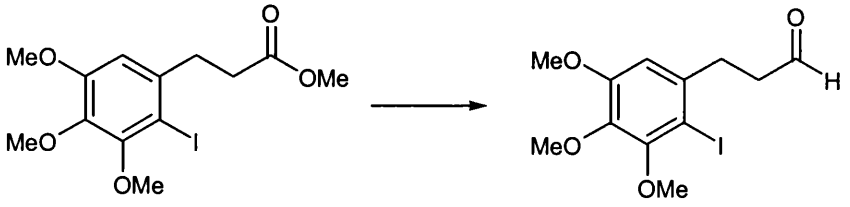


245

$[Rh(CO)_2Cl]_2$ **106** (0.001 g, 0.002 mmol, 5 mol%) was added to a solution of alkynyl-vinylcyclopropane **245** (0.02 g, 0.03 mmol) in DCM (0.5 ml). The

resultant mixture was heated at reflux for 48 hours, then filtered through a pad of alumina. ^{1}H NMR analysis indicated that only starting material was present.

Synthesis of 3-(2-Iodo-3,4,5-trimethoxyphenyl)propanal 251

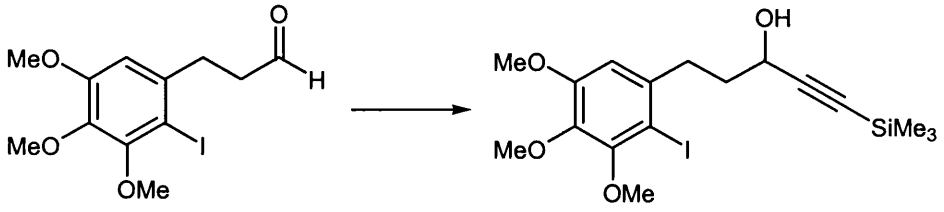


187 **251**

Diisobutylaluminium hydride (5.4 ml, 6.4 mmol, 20 % sol. in toluene) was added dropwise to a solution of methyl 3-(3,4,5-trimethoxyphenyl)propanoate **187** (2 g, 5.2 mmol) in toluene (25 ml) at –78°C. After 1 hour, methanol (1.2 ml) was added and the mixture was allowed to come to room temperature. 1M HCl (150 ml) was added and the product extracted with ether (3 x 70 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, PE:ether / 50:50) gave a colourless oil **251** (1.2 g, 67 %).

R_f(PE:ether / 50:50) 0.4; ν_{max} (neat) / cm^{-1} 2937, 2835, 2724 (C-H), 1722 (C=O), 1563, 1477, 1388, 1334, 1243, 1198, 1163, 1040, 1006, 925, 838, 804; δ_H (500 MHz, $CDCl_3$) δ 2.77 (2H, dt, ^3J 1.2, 7.8 Hz, $ArCH_2CH_2$), 3.03 (2H, t, ^3J 7.8 Hz, $ArCH_2CH_2$), 3.82 (6H, s, 2 x OMe), 3.86 (3H, s, OMe), 6.66 (1H, s, aromatic), 9.81 (1H, t, ^3J 1.2 Hz, CHO); δ_C (125 MHz, $CDCl_3$) δ 33.37 ($ArCH_2CH_2$), 44.11 ($ArCH_2CH_2$), 56.11 (OMe), 60.70 (OMe), 60.92 (OMe), 87.66 (C-2), 109.06 (C-6), 138.65 (C-4), 140.56 (C-1), 153.19 (C-5), 153.63 (C-3), 200.96 (CHO); m/z (FAB) 350 (60 %, M^+), 307 (75 %, [M-C_2H_3O]), 224 (95 %, [C_5H_7O]), 181 (100 %, [M-COMe]); HRMS: calculated 350.0015; found 350.0001.

Synthesis of 5-(2-Iodo-3,4,5-trimethoxyphenyl)-1-trimethylsilanyl-pent-1-yn-3-ol 253

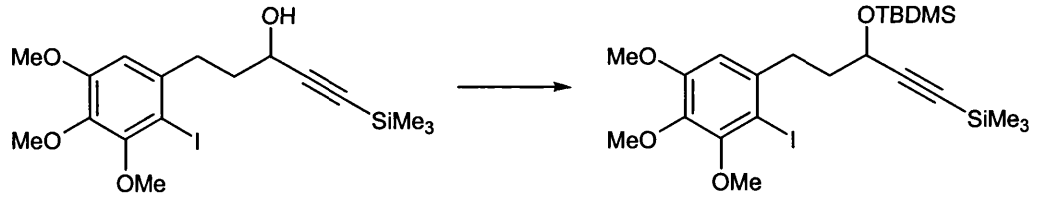


251 **253**

Ethylmagnesium bromide (6.2 ml, 6.2 mmol, 1M sol. in THF) was added dropwise to a solution of trimethylsilylacetylene **192** (1 ml, 6.8 mmol) in THF (25 ml) at -78°C. The mixture was allowed to come to room temperature, then heated at reflux for 30 minutes. On cooling to room temperature, the solution was added dropwise to a solution of 3-(2-iodo-3,4,5-trimethoxyphenyl)propanal **251** (1.2 g, 3.4 mmol) in THF (25 ml) at -78°C. On completion of reaction, the mixture was allowed to come to room temperature then poured onto sat. aq. NH_4Cl solution (60 ml) and extracted with ether (3 x 50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, PE:ether / 50:50) gave a colourless oil **253** (0.9 g, 60 %, 1:1 mixture isomers).

R_f(PE:ether / 50:50) 0.3; ν_{max} (neat) / cm^{-1} 3442 (OH), 2957, 2859 (C-H), 2171 (C≡C), 1562, 1478, 1388, 1332, 1249, 1199, 1164, 1105, 1065, 1007, 964, 904, 845, 761; δ_H (500 MHz, $CDCl_3$) δ 0.16 (9H, s, Si(CH_3)$_3$), 1.86 (1H, d, ^3J 5.5 Hz, O*H*), 1.96 (2H, m , $ArCH_2CH_2$), 2.89 (2H, m, $ArCH_2CH_2$), 3.84 (6H, s, 2 x OMe), 3.85 (3H, s, OMe), 4.39 (1H, q, ^3J 6.3 Hz, C*H*OH), 6.65 (1H, s, aromatic); δ_C (125 MHz, $CDCl_3$) δ -0.11 (Si(CH_3)$_3$), 36.67 ($ArCH_2CH_2$), 37.81 ($ArCH_2CH_2$), 56.11 (OMe), 60.71 (OMe), 60.95 (OMe), 62.10 (C*H*OH), 87.96 (C-2), 90.08 (*C*≡CSiMe$_3$), 106.20 (C≡*C*SiMe$_3$), 108.88 (C-6), 139.60 (C-4), 140.40 (C-1), 153.12 (C-5), 153.54 (C-3); m/z (FAB) 449 (45 %, [M^+]), 434 (40 %, [M-CH_3]), 321 (15 %), 307 (100 %), 181 (75 %); HRMS: calculated 449.0645; found 449.0660.

Synthesis of 1-[3-(*tert*-Butyldimethylsilanyloxy)-5-trimethylsilanyl-pent-4-ynyl]-2-iodo-3,4,5-trimethoxyphenyl 254

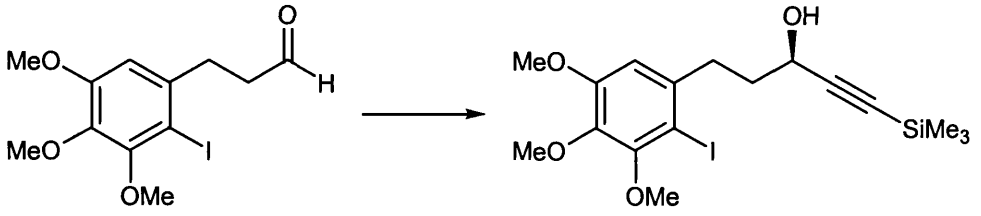


253 **254**

tert-Butyldimethylsilyl chloride (0.6 g, 4.0 mmol) and imidazole (0.34 g, 5.0 mmol) were added to a solution of 5-(2-iodo-3,4,5-trimethoxyphenyl)-1-trimethylsilanyl-pent-1-yn-3-ol **253** (0.9 g, 2.0 mmol) in acetonitrile (10 ml). The mixture was stirred at room temperature overnight, then the solvent was removed *in vacuo*. The residue was dissolved in ether (20 ml), then washed with water (20 ml) and sat. aq. $NaHCO_3$ solution (20 ml) and dried (Na_2SO_4). Column chromatography (SiO_2, PE:ether / 90:10) gave a colourless oil **254** (0.9 g, 80 %, 1:1 mixture isomers).

R_f(PE:ether / 80:20) 0.5; ν_{max} (neat) / cm^{-1} 2955, 2857 (C-H), 2172 (C≡C), 1563, 1476, 1388, 1335, 1251, 1198, 1166, 1102, 1009, 924, 842, 778; δ_H (500 MHz, $CDCl_3$) δ 0.13 and 0.14 (6H, 2 x s, $SiC(CH_3)_3(CH_3)_2$), 0.16 (9H, s, $Si(CH_3)_3$), 0.91 (9H, s, $SiC(CH_3)_3(CH_3)_2$), 1.92 (2H, m, $ArCH_2CH_2$), 2.84 (2H, m, $ArCH_2CH_2$), 3.82 (6H, s, 2 x OMe), 3.84 (3H, s, OMe), 4.40 (1H, t, ^3J 6.3, CHOTBDMS), 6.66 (1H, s, aromatic); δ_C (125 MHz, $CDCl_3$) δ -4.85 and –4.37 ($SiC(CH_3)_3(CH_3)_2$), -0.16 ($Si(CH_3)_3$), 18.30 ($SiC(CH_3)_3(CH_3)_2$), 25.85 ($SiC(CH_3)_3(CH_3)_2$), 37.03 ($ArCH_2CH_2$), 38.76 ($ArCH_2CH_2$), 56.10 (OMe), 60.68 (OMe), 60.95 (OMe), 62.81 (CHOTBDMS), 88.02 (C-2), 89.12 ($C{\equiv}CSiMe_3$), 107.19 ($C{\equiv}CSiMe_3$), 108.74 (C-6), 140.16 (C-4), 140.28 (C-1), 153.07 (C-5), 153.49 (C-3); m/z (FAB) 561 (20 %, [M-H]), 547 (45 %, [M-CH_3]), 435 (70 %, [M-C_5H_8OSi]), 307 (100 %, [M-$C_7H_{16}Si$]), 181 (35 %); HRMS: calculated 561.1353; found 561.1330.

Synthesis of (*R*)-5-(2-Iodo-3,4,5-trimethoxyphenyl)-1-trimethylsilanyl-pent-1-yn-3-ol 253

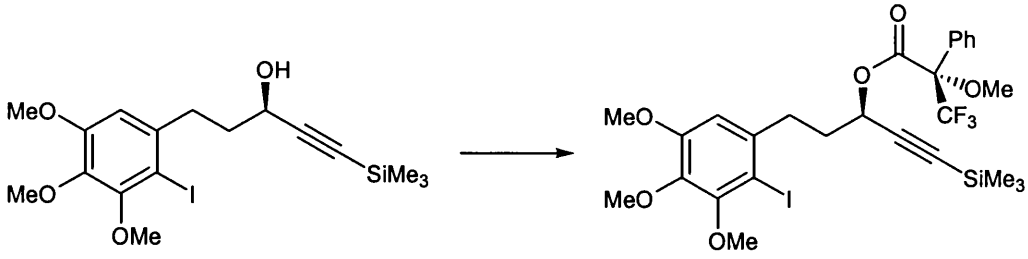


251 **253**

Zinc triflate (0.53 g, 1.45 mmol) and (+)-*N*-methylephedrine **256** (0.27 g, 1.5 mmol) were purged with nitrogen for 15 minutes. To the flask was added toluene (2 ml) and triethylamine (0.2 ml, 1.5 mmol) and the resulting mixture was stirred vigorously at room temperature for 2 hours. Trimethylsilylacetylene **192** (0.2 ml, 1.5 mmol) was added in a single portion and stirring continued for a further 30 minutes. A solution of 3-(2-iodo-3,4,5-trimethoxyphenyl)propanal **251** (0.1 g, 0.29 mmol) in toluene (3 ml) was added over a 12 hour period *via* syringe pump. The reaction was quenched by the dropwise addition of sat. aq. NH_4Cl solution (15 ml), then extracted with ether (3 x 20 ml). The combined organic extracts were washed with brine (50 ml) and dried ($MgSO_4$). Column chromatography (SiO_2, PE:ether / 40:60) gave a colourless oil **253** (0.06 g, 50 %, 82 % ee).

R_f(PE:ether / 50:50) 0.3; ν_{max} (neat) / cm^{-1} 3442 (OH), 2957, 2859 (C-H), 2171 (C≡C), 1562, 1478, 1388, 1332, 1249, 1199, 1164, 1105, 1065, 1007, 964, 904, 845, 761; δ_H (500 MHz, $CDCl_3$) δ 0.17 (9H, s, $Si(CH_3)_3$), 1.81 (1H, d, ^3J 4.4 Hz, O*H*), 1.96 (2H, m, $ArCH_2CH_2$), 2.89 (2H, m, $ArCH_2CH_2$), 3.82 (3H, s, OMe), 3.83 (3H, s, OMe), 3.85 (3H, s, OMe), 4.39 (1H, dt, ^3J 4.4, 6.6 Hz, C*H*OH), 6.65 (1H, s, aromatic); δ_C (125 MHz, $CDCl_3$) δ -0.11 ($Si(CH_3)_3$), 36.68 ($ArCH_2CH_2$), 37.82 ($ArCH_2CH_2$), 56.12 (OMe), 60.72 (OMe), 60.96 (OMe), 62.12 (C*H*OH), 87.97 (C-2), 90.11 (*C*≡CSiMe3), 106.19 (C≡*C*SiMe3), 108.89 (C-6), 139.60 (C-4), 140.41 (C-1), 153.14 (C-5), 153.56 (C-3); m/z (FAB) 449 (45 %, $[M^+]$), 434 (40 %, $[M-CH_3]$), 321 (15 %), 307 (100 %), 181 (75 %); HRMS: calculated 449.0645; found 449.0660.

Synthesis of Mosher's Ester 258



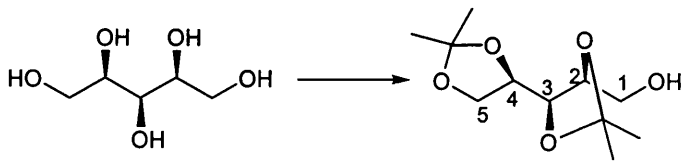
253 **258**

(*R*)-(-)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride **259** (0.005 g, 0.02 mmol) was added to a solution of (*R*)-5-(2-iodo-3,4,5-trimethoxyphenyl)-1-trimethylsilanyl-pent-1-yn-3-ol **253** (0.007 g, 0.016 mmol), triethylamine (0.003 g, 0.033 mmol) and DMAP (ca. 1 mg) in DCM (1 ml). The resultant mixture was stirred until complete conversion to the diastereomeric Mosher's esters was observed. Concentration *in vacuo* gave an oil **258** which was analysed by ^{1}H and ^{19}F NMR.

δ_F (282 MHz, $CDCl_3$) δ (*R,S*-isomer) –72.30 (CF_3), (*S,S*-isomer) –71.91 (CF_3), ratio 9.83:1, 82 % ee.

δ_H (300 MHz, $CDCl_3$) δ (*R,S*-isomer) 0.14 (9H, s, $Si(CH_3)_3$), (*S,S*-isomer) 0.04 (9H, s, $Si(CH_3)_3$), ratio 10.5:1, 83 % ee.

Synthesis of Diisopropylidine-DL-xylitol[131] 264

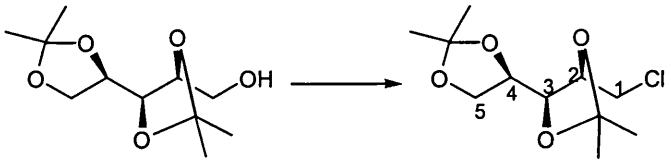


263 **264**

To a solution of xylitol **263** (10.0 g, 65.7 mmol) in acetone (150 ml) was added $CuSO_4$ (21.0 g, 131.4 mmol) and conc. H_2SO_4 (0.3 ml, 6.6 mmol). The mixture was allowed to stir at room temperature for 24 hours, then filtered. The filtrate was made basic by addition of triethylamine, then concentrated *in vacuo* and taken up in ethyl acetate (150 ml). The solution was washed with water (100 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Distillation gave a colourless oil **264** (10.5 g, 70 %, single diastereoisomer).

R_f(ether) 0.5; b.p. 65 °C at ~ 0.4 mmHg (lit.[131] 90-100 °C at ~0.3 Torr); ν_{max} (neat) / cm^{-1} 3472 (OH), 2988, 2936, 2880 (C-H), 1457, 1376, 1217, 1160, 1057, 858; δ_H (500 MHz, $CDCl_3$) δ 1.34 (3H, s, CH_3), 1.39 (9H, s, 3 x CH_3), 2.27 (1H, dd, ^3J 5.1, 7.5 Hz, O*H*), 3.59 (1H, ddd, ^3J 4.3, 7.5 Hz, ^2J 12.0 Hz, CH_2^1), 3.77 (1H, ddd, ^3J 3.6, 5.1 Hz, ^2J 12.0 Hz CH_2^1), 3.82 (1H, dd, ^3J 7.3, 8.3 Hz, CH_2^5), 3.93 (1H, dd, ^3J 4.4, 8.2 Hz, CH^3), 4.00 (2H, m, CH^2 and CH_2^5), 4.15 (1H, dt, ^3J 4.4, 6.9 Hz, CH^4); δ_C (125 MHz, $CDCl_3$) δ 25.37 (CH_3), 26.08 (CH_3), 26.91 (CH_3), 27.05 (CH_3), 62.06 (CH_2^1), 65.53 (CH_2^5), 74.99 (CH^4), 76.75 (CH^3), 77.61 (CH^2), 109.57 (*C*), 109.70 (*C*); m/z (FAB) 233 (25 %, [M+H]), 217 (100 %, [M-CH_3]), 175 (35 %, [M-$(CH_3)_2C$]); HRMS: calculated 233.1389; found 233.1384.

Synthesis of 1-Chloro-1-deoxy-2,3,4,5-*O*-isopropylidine-DL-xylitol 265

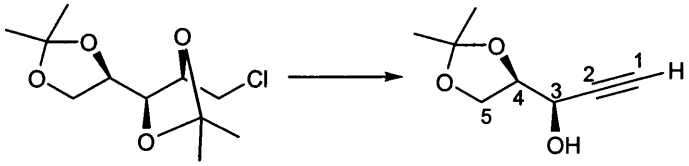


264 **265**

Triphenylphosphine (7.0 g, 28.1 mmol) was added to a solution of alcohol **264** (9.5 g, 40.9 mmol) in carbon tetrachloride (100 ml). The reaction mixture was heated at reflux overnight. On cooling to room temperature, dried PE 30-40 (100 ml) was added and stirring continued for 10 minutes. The precipitate of triphenylphosphine oxide was removed by filtration and washed with dried PE 30-40 (3 x 50 ml). Concentration *in vacuo* gave an oil which was chromatographed (SiO_2, PE:ether / 80:20) to give a colourless oil **265** (10.5 g, quant., single diastereoisomer).

R_f(PE:ether / 80:20) 0.3; ν_{max} (neat) / cm^{-1} 2988, 2937, 2894 (C-H), 1454, 1376, 1218, 1159, 1070, 996, 898, 853, 748; δ_H (500 MHz, $CDCl_3$) δ 1.34 (3H, s, CH_3), 1.40 (9H, s, 3 x CH_3), 3.58 (1H, dd, ^3J 5.0 Hz, ^2J 11.6 Hz, CH_2^1), 3.64 (1H, dd, ^3J 5.0 Hz, ^2J 11.6 Hz, CH_2^1), 3.87 (1H, dd, ^3J 6.8 Hz, ^2J 8.3 Hz, CH_2^5), 3.95 (1H, dd, ^3J 4.0, 7.4 Hz, CH^3), 4.03 (1H, dd, ^3J 6.8 Hz, ^2J 8.3 Hz, CH_2^5), 4.17 (1H, dt, ^3J 5.0, 7.4 Hz, CH^2), 4.21 (1H, dt, ^3J 4.0, 6.8 Hz, CH^4); δ_C (125 MHz, $CDCl_3$) δ 25.29 (CH_3), 26.07 (CH_3), 27.10 (CH_3), 27.18 (CH_3), 44.49 (CH_2^1), 65.56 (CH_2^5), 74.78 (CH^4), 76.74 (CH^3), 78.45 (CH^2), 109.78 (C), 110.26 (C); m/z (FAB) 253 (3 %, [M(^{37}Cl)+H]), 251 (25 %, [M(^{35}Cl)+H]), 235 (100 %, [M-CH_3]), 193 (10 %, [M-$C(CH_3)_2$]; HRMS: calculated 251.1050; found 251.1045.

Synthesis of 1-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-prop-2-yn-1-ol[132] 260

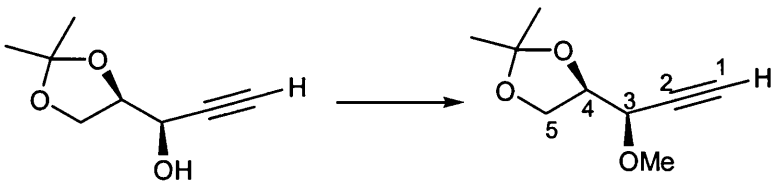


265 **260**

n-Butyllithium (43 ml, 100 mmol, 2.3 M in hexanes) was added to a solution of diisopropylamine (514 ml, 100 mmol) in THF (200 ml) at –10 °C. The mixture was stirred for 1 hour at this temperature, then cooled to –78 °C. A solution of 1-chloro-1-deoxy-2,3,4,5-*O*-isopropylidine-DL-xylitol **265** (5.0 g, 20 mmol) in THF (100 ml) was added *via* cannula and the mixture was allowed to come to room temperature, then quenched with sat. aq. NH_4Cl solution (200 ml). The organic phase was extracted with ether (3 x 150 ml) then washed with brine (200 ml), and dried ($MgSO_4$). Concentration *in vacuo* and column chromatography (SiO_2, PE 30-40:ether / 40:60) gave a colourless oil **260** (3.0 g, 97 %, single diastereoisomer).

R_f(PE:ether / 50:50) 0.2; ν_{max} (neat) / cm^{-1} 3423 (OH), 3284 (C≡C-H), 2989, 2937, 2894 (C-H), 2118 (C≡C), 1635, 1457, 1378, 1257, 1215, 1156, 1067, 970, 946, 848, 795; δ_H (500 MHz, $CDCl_3$) δ 1.35 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.46 (1H, d, ^4J 2.2 Hz, CH^1), 2.57 (1H, br, O*H*), 3.89 (1H, dd, ^3J 5.5 Hz, ^2J 8.8 Hz, CH_2^5), 4.08 (1H, dd, ^3J 6.5 Hz, ^2J 8.8 Hz, CH_2^5), 4.18 (1H, dt, ^3J 5.5, 6.5 Hz, CH^4), 4.29 (1H, br d, CH^3); δ_C (125 MHz, $CDCl_3$) δ 25.15 (CH_3), 26.70 (CH_3), 63.85 (CH^3), 65.92 (CH_2^5), 74.35 (CH^1), 78.57 (CH^4), 81.10 (C^2), 110.49 (C); m/z (FAB) 157 (85 %, [M+H]), 141 (90 %, [M-CH_3]); HRMS: calculated 157.0865; found 157.0862.

Synthesis of 4-(1-Methoxy-prop-2-ynyl)-2,2-dimethyl-[1,3]dioxolane 266

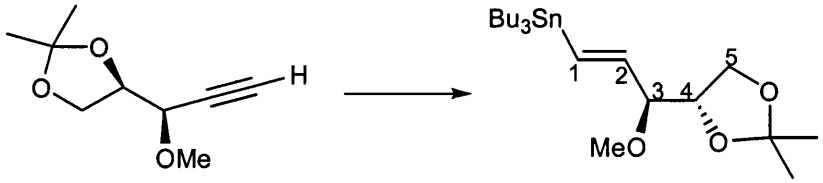


260 **266**

A solution of 1-(2,2-dimethyl-[1,3]dioxolan-4-yl)-prop-2-yn-1-ol **260** (1 g, 6.4 mmol) in THF (20 ml) was added to a suspension of sodium hydride (0.1 g, 7.7 mmol, 60 % dispersion in mineral oil) in THF (30 ml) at 0 °C. The mixture was allowed to come to room temperature then stirred for a further 30 minutes. Methyl iodide (1.2 ml, 19.2 mmol) was added and stirring was continued overnight. The reaction was quenched with sat. aq. NH_4Cl solution (100 ml) and extracted with ether (3 x 80 ml). The combined extracts were washed with water (100 ml) and brine (100 ml), then dried ($MgSO_4$). Column chromatography (SiO_2, PE:ether / 80:20) gave a colourless oil **266** (0.85 g, 79 %, single diastereoisomer).

R_f(PE:ether / 50:50) 0.6; ν_{max} (neat) / cm^{-1} 3258 (C≡C-H), 2987, 2937, 2838 (C-H), 2114 (C≡C), 1704, 1458, 1375, 1328, 1213, 1101, 974, 936, 854, 794, 667; δ_H (500 MHz, $CDCl_3$) δ 1.35 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.45 (1H, d, ^4J 2.1 Hz, CH^1), 3.45 (3H, s, OMe), 3.89 (1H, dd, ^3J 6.6 Hz, ^2J 8.8 Hz, CH_2^5), 3.99 (1H, dd, ^3J 7.3 Hz, ^4J 2.1 Hz, CH^3), 4.09 (1H, dd, ^3J 6.6 Hz, ^2J 8.8 Hz, CH_2^5), 4.22 (1H, q, ^3J 6.6 Hz, CH^4); δ_C (125 MHz, $CDCl_3$) δ 25.33 (CH_3), 26.59 (CH_3), 56.98 (OMe), 66.30 (CH_2^5), 73.24 (CH^3), 75.65 (CH^1), 77.04 (CH^4), 79.01 (C^2), 110.46 (C); m/z (FAB) 171 (8 %, [M+H]), 155 (70 %, [M-CH_3]); HRMS: calculated 171.1021; found 171.1024.

Synthesis of Tributyl-[3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3-methoxy-propenyl]-stannane 262

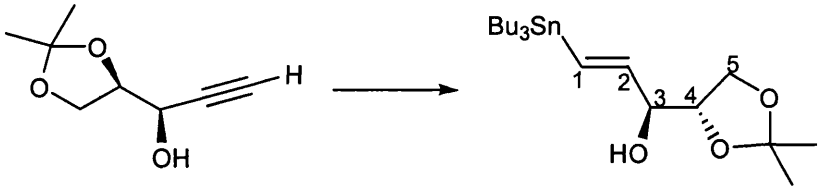


266 **262**

Tributyltin hydride (1.9 ml, 1.7 mmol) was added to a solution of alkyne **266** (0.8 g, 4.7 mmol) in benzene (25 ml) and AIBN (0.07 g, 0.4 mmol) at 0 °C. The mixture was placed into a pre-heated oil bath (80 °C) and stirred for 3 hours. On cooling to room temperature, the solvent was removed *in vacuo*. Column chromatography (PE:ether / 90:10) gave a colourless oil **262** (1.58 g, 73 %, single diastereoisomer).

R_f(PE:ether / 90:10) 0.3; ν_{max} (neat) / cm^{-1} 2956, 2925 (C-H), 1600 (C=C), 1460, 1375, 1256, 1213, 1156, 1102, 1068, 995, 960, 855; δ_H (500 MHz, $CDCl_3$) δ 0.86 (15 H, m, 3 x CH_3 and 3 x CH_2), 1.28 (6H, m, 3 x CH_2), 1.35 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.47 (6H, m, 3 x CH_2), 3.31 (3H, s, OMe), 3.54 (1H, td, ^3J 7.6 Hz, ^4J 0.8 Hz, CH^3), 3.61 (1H, dd, ^3J 7.6 Hz, ^2J 8.4 Hz, CH_2^5), 3.87 (1H, dd, ^3J 6.6 Hz, ^2J 8.4 Hz, CH_2^5), 4.10 (1H, dt, ^3J 6.6, 7.6 Hz, CH^4), 5.70 (1H, dd, ^3J 7.6 Hz, $^3J_{trans}$ 19.1 Hz, CH^2), 6.30 (1H, dd, $^3J_{trans}$ 19.1 Hz, ^4J 0.8 Hz, CH^1); δ_C (125 MHz, $CDCl_3$) δ 9.53 (CH_2), 13.68 (CH_3), 25.51 (CH_3), 26.68 (CH_3), 27.18 (CH_2), 29.07 (CH_2), 56.38 (OMe), 66.14 (CH_2^5), 77.44 (CH^4), 77.60 (CH^3), 109.88 (C), 136.33 (CH^1), 143.58 (CH^2); m/z (FAB) 410 (16 %, [M(^{124}Sn)-C_4H_7]), 408 (14 %, [M(^{122}Sn)-C_4H_7]), 406 (80 %, [M(^{120}Sn)-C_4H_7]), 405 (28 %, [M(^{119}Sn)-C_4H_7]), 404 (60 %, [M(^{118}Sn)-C_4H_7]), 403 (24 %, [M(^{117}Sn)-C_4H_7]), 402 (32 %, [M(^{116}Sn)-C_4H_7]), 317 (40 %, [M-$C_4H_9O_2$]), 291 (100 %, [M-[C_2H_2]), 235 (100%, [M-C_3H_4O]); HRMS: calculated 406.1530; found 406.1540.

Synthesis of 1-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3-tributylstannyl-prop-2-en-1-ol 267

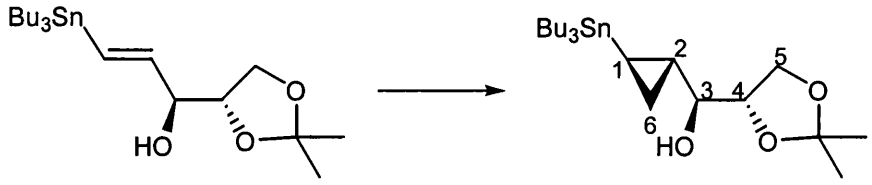


260 **267**

Tributyltin hydride (7 ml, 26.3 mmol) was added to a solution of alkyne **260** (2.7 g, 17.5 mmol) and AIBN (0.2 g, 1.36 mmol) in benzene (60 ml) at 0 °C. The mixture was placed into a pre-heated oil bath (80 °C) and stirred for 2 hours. On cooling to room temperature, the solvent was removed *in vacuo*. Column chromatography (SiO_2, PE:ether / 90:10) gave a colourless oil **267** (5 g, 65 %, single diastereoisomer).

R_f(PE:ether / 80:20) 0.25; ν_{max} (neat) / cm^{-1} 3469 (OH), 2957, 2927, 2872 (C-H), 1603 (C=C), 1460, 1419, 1376, 1340, 1256, 1212, 1155, 1068, 994, 961, 917, 856, 797, 770, 689, 665, 594; δ_H (500 MHz, $CDCl_3$) δ 0.86 (15 H, m, 3 x CH_3 and 3 x CH_2), 1.28 (6H, m, 3 x CH_2), 1.34 (3H, s, CH_3), 1.42 (1H, s, CH_3), 1.43 (6H, m, 3 x CH_2), 2.40 (1H, d, ^3J 3.2 Hz, O*H*), 3.72 (1H, dd, ^3J 5.8 Hz, ^2J 8.4 Hz, CH_2^5), 3.93 (1H, dd, ^3J 6.4 Hz, ^2J 8.4 Hz, CH_2^5), 3.98 (1H, ddd, ^3J 3.2, 5.8, 6.4 Hz, CH^3), 4.02 (1H, dt, ^3J 5.8, 6.4 Hz, CH^4), 5.88 (1H, dd, ^3J 5.8 Hz, $^3J_{trans}$ 19.0 Hz, CH^2), 6.30 (1H, dd, $^3J_{trans}$ 19.0 Hz, $^2J_{Sn}$ 0.9 Hz, CH^1); δ_C (125 MHz, $CDCl_3$) δ 9.43 (CH_2), 13.65 (CH_3), 25.35 (CH_3), 26.78 (CH_3), 27.19 (CH_2), 29.00 (CH_2), 65.88 (CH_2^5), 76.94 (CH^3), 78.72 (CH^4), 109.76 (C), 132.82 (CH^1), 145.44 (CH^2); m/z (FAB) 395 (9 %, [M(^{124}Sn)-C_4H_8]), 393 (9 %, [M(^{122}Sn)-C_4H_8]), 391 (35 %, [M(^{120}Sn)-C_4H_8]), 390 (15 %, [M(^{119}Sn)-C_4H_8]), 389 (30 %, [M(^{118}Sn)-C_4H_8]), 388 (14 %, [M(^{117}Sn)-C_4H_8]), 387 (20 %, [M(^{116}Sn)-C_4H_8]), 291 (50 %, [M-$C_5H_8O_2$]), 235 (40 %, [M-C_3H_4O]), 177 (100%, [SnC_4H_9]), 137 (45 %); HRMS: calculated 391.1295; found 391.1301.

Synthesis of (2,2-Dimethyl-[1,3]dioxolan-4-yl)-(2-tributylstannane-cyclopropyl)-methanol 268

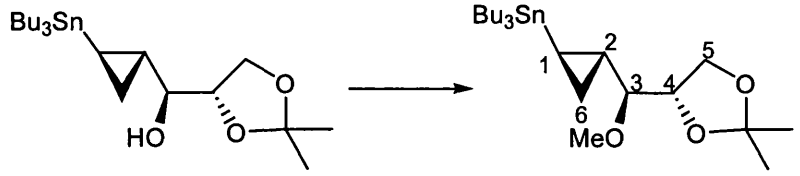


267 **268**

Diethylzinc (70 ml, 69.6 mmol, 1 M in hexanes) was added to a solution of vinylstannane **267** (4.0 g, 8.7 mmol) in ether (150 ml) at 0 °C. After a few minutes, diiodomethane (11 ml, 139.2 mmol) was added dropwise and the mixture was allowed to come to room temperature. After 20 hours, the mixture was poured onto sat. aq. NH_4Cl solution and stirred until both layers were clear. The organic layer was extracted with ether (2 x 100 ml) and dried ($MgSO_4$). Column chromatography (SiO_2, PE:ether/ 80:20) gave a colourless oil **268** (3.0 g, 60 %, single diastereoisomer).

R_f(PE:ether / 50:50) 0.4; ν_{max} (neat) / cm^{-1} 3444 (OH), 2957, 2925, 2872, 2854 (C-H), 1650, 1457, 1418, 1377, 1340, 1251, 1214, 1149, 1067, 976, 960, 950, 864, 834; δ_H (500 MHz, $CDCl_3$) δ -0.29 (1H, dt, $^3J_{cis}$ 10.3 Hz, $^3J_{trans}$ 7.0 Hz, CH^1), 0.53 (1H, ddd, ^2J 4.2 Hz, $^3J_{trans}$ 7.0 Hz, $^3J_{cis}$ 10.3 Hz, CH_2^6), 0.67 (1H, ddd, $^3J_{cis}$ 10.3 Hz, $^3J_{trans}$ 7.0 Hz, ^2J 4.2 Hz, CH_2^6), 0.77 (6H, m, 3 x CH_2), 0.82 (1H, m, CH^2), 0.85 (9H, t, 3 x CH_3), 1.27 (6H, m, 3 x CH_2), 1.35 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.44 (6H, m 3 x CH_2), 2.37 (1H, br, O*H*), 2.75 (1H, t, ^3J 7.4 Hz, CH^3), 3.73 (1H, dd, ^3J 6.9 Hz, ^2J 8.1 Hz, CH_2^5), 3.99 (1H, dd, ^3J 6.5 Hz, ^2J 8.1 Hz, CH_2^5), 4.09 (1H, q, ^3J 6.6 Hz, CH^4); δ_C (125 MHz, $CDCl_3$) δ -2.78 (*C*H^1), 6.93 (*C*H$_2^6$), 8.57 (*C*H$_2$), 13.65 (*C*H$_3$), 18.39 (*C*H^2), 25.40 (*C*H$_3$), 26.72 (*C*H$_3$), 27.33 (*C*H$_2$), 29.04 (*C*H$_2$), 66.17 (*C*H$_2^5$), 78.68 (*C*H^3), 79.69 (*C*H^4), 109.19 (C); m/z (FAB) 461 (5 %, [M^+]), 409 (2 %, [M(^{124}Sn)-C_4H_8]]), 407 (3 %, [M(^{122}Sn)-C_4H_8]), 405 (10 %, [M(^{120}Sn)-C_4H_8]), 404 (3 %, [M(^{119}Sn)-C_4H_8]), 403 (4 %, [M(^{118}Sn)-C_4H_8]), 402 (3 %, [M(^{117}Sn)-C_4H_8]), 401 (3 %, [M(^{116}Sn)-C_4H_8]), 291 (70 %, [M-$C_6H_{10}O_2$]), 235 (45 %, [M-C_4H_8]), 177 (100 %, [SnC_4H_{10}]), 137 (40 %); HRMS: calculated 405.1452; found 405.1447.

Synthesis of Tributyl-{2-[(2,2-dimethyl-[1,3]dioxolan-4-yl)-methoxymethyl]-cyclopropyl}-stannane 261



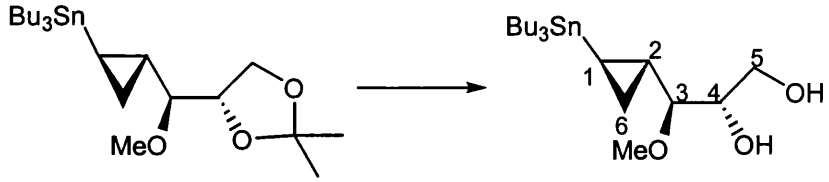
268 **261**

A solution of cyclopropane **268** (2.5 g, 5.4 mmol) in THF (50 ml) was added dropwise to a suspension of sodium hydride (0.33 g, 8.1 mmol, 60 % dispersion in mineral oil) in THF (50 ml) at 0 °C. The mixture was allowed to come to room temperature and stirring continued for a further 30 minutes. Methyl iodide (1 ml, 16.2 mmol) was added and the reaction mixture was stirred overnight. The reaction was quenched with sat. aq. NH_4Cl solution (100 ml) and extracted with ether (3 x 100 ml). The combined organic extracts were washed with water (200 ml), then brine (200 ml) and dried ($MgSO_4$). Concentration *in vacuo* and column chromatography (SiO_2, PE:ether / 95:5) gave a colourless oil **261** (2.3 g, 92 %, single diastereoisomer).

R_f(PE:ether / 90:10) 0.5; ν_{max} (neat) / cm^{-1} 2957, 2926 (C-H), 1461, 1374, 1253, 1215, 1156, 1135, 1102, 1076, 976, 864, 664; δ_H (500 MHz, $CDCl_3$) δ -0.39 (1H, dt, $^3J_{cis}$ 9.9 Hz, $^3J_{trans}$ 7.0 Hz, CH^1), 0.62 (1H, m, CH_2^6), 0.75 (2H, m, CH^2 and CH_2^6), 0.79 (6H, m, 3 x CH_2), 0.87 (9H, m, 3 x CH_3), 1.28 (6H, m, 3 x CH_2), 1.36 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.43 (6H, m 3 x CH_2), 2.49 (1H, t, ^3J 7.6, CH^3), 3.50 (3H, s, OMe), 3.68 (1H, t, ^3J 8.0 Hz, CH_2^5), 3.96 (1H, dd, ^3J 6.3 Hz, ^2J 8.0 Hz, CH_2^5), 4.14 (1H, q, ^3J 7.0 Hz, CH^4); δ_C (125 MHz, $CDCl_3$) δ -4.60 (CH^1), 8.60 (CH_2), 8.61 (CH_2^6), 13.68 (CH_3), 15.77 (CH^2), 25.70 (CH_3), 26.68 (CH_3), 27.37 (CH_2), 29.07 (CH_2), 57.81 (OMe), 66.34 (CH^5), 79.47 (CH^4), 87.10 (CH^3), 109.06 (C); m/z (FAB) 423 (2 %, [M(^{124}Sn)-C_4H_8]), 421 (2 %, [M(^{122}Sn)-C_4H_8]), 419 (15 %, [M(^{120}Sn)-C_4H_8]), 418 (7 %, [M(^{119}Sn)-C_4H_8]), 417 (12 %, [M(^{118}Sn)-C_4H_8]), 416 (6 %, [M(^{117}Sn)-C_4H_8]), 415 (8 %, [M(^{116}Sn)-C_4H_8]), 291 (45 %), 235 (40 %, [M-$C_{10}H_{16}O_3$]), 177 (100 %, [SnC_4H_{10}]), 151 (15 %); HRMS: calculated 419.1608; found 419.1672.

Synthesis of

3-Methoxy-3-(2-tributylstannanyl-cyclopropyl)-propane-1,2-diol 269

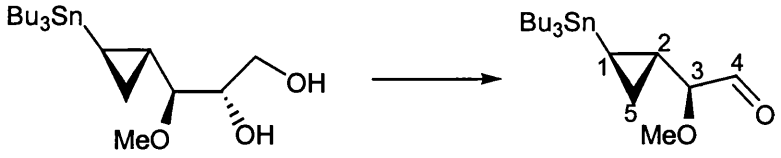


261 **269**

To a solution of cyclopropane **261** (2.35 g, 5 mmol) in methanol (250 ml) was added 2M HCl (50 ml) dropwise and stirring was continued for 3 hours. The resultant mixture was neutralised by the addition of sat. aq. $NaHCO_3$ solution. The methanol was removed *in vacuo* and the product was taken up in ethyl acetate (200 ml) and washed with brine (150 ml). Drying ($MgSO_4$) and concentration *in vacuo* gave an oil which was chromatographed (SiO_2, PE:ether / 40:60) to give a colourless oil **269** (1.7 g, 81 %, single diastereoisomer).

R_f(ether) 0.4; ν_{max} (neat) / cm^{-1} 3430 (OH), 2959, 2927 (C-H), 1461, 1417, 1378, 1358, 1341, 1289, 1251, 1189, 1118, 1085, 1046, 961, 867, 666; δ_H (500 MHz, $CDCl_3$) δ -0.38 (1H, dt, $^3J_{trans}$ 6.9, $^3J_{cis}$ 10.1 Hz, C*H*^{1}), 0.66 (1H, ddd, $^3J_{cis}$ 10.1 Hz, $^3J_{trans}$ 6.9 Hz, ^2J 4.0 Hz, CH_2^6), 0.75 (1H, ddd, $^3J_{cis}$ 10.1 Hz, $^3J_{trans}$ 6.9 Hz, ^2J 4.0 Hz, CH_2^6), 0.80 (1H, m, C*H*^{2}), 0.81 (6H, m, 3 x CH_2), 0.87 (9H, t, 3 x CH_3), 1.28 (6H, m, 3 x CH_2), 1.44 (6H, m, 3 x CH_2), 2.25 (1H, dd, ^3J 5.4, 7.0 Hz, CH_2OH), 2.50 (1H, dd, ^3J 5.7, 8.7 Hz, C*H*^{3}), 2.80 (1H, d, ^3J 4.6 Hz, O*H*), 3.48 (3H, s, OMe), 3.65 (2H, m, C*H*^{4} and CH_2^5), 3.72 (1H, dd, ^3J 7.3 Hz, ^2J 12.7 Hz, CH_2^5); δ_C (125 MHz, $CDCl_3$) δ -5.04 (*C*H^1), 8.61 (*C*H_2), 9.22 (*C*H_2^6), 13.68 (*C*H_3), 15.21 (*C*H^2), 27.37 (*C*H_2), 29.06 (*C*H_2), 57.24 (OMe), 64.08 (*C*H_2^5), 74.41 (*C*H^4), 87.34 (*C*H^3); m/z (FAB) 383 (13 %, [M(^{124}Sn)-C_4H_8]), 381 (12 %, [M(^{122}Sn)-C_4H_8]), 379 (65 %, [M(^{120}Sn)-C_4H_8]), 378 (26 %, [M(^{119}Sn)-C_4H_8]), 377 (49 %, [M(^{118}Sn)-C_4H_8]), 376 (20 %, [M(^{117}Sn)-C_4H_8]), 375 (30 %, [M(^{116}Sn)-C_4H_8]), 291 (55 %, [M-$C_4H_8O_2$]), 251 (40 %), 177 (100 %, [SnC_4H_{10}]); HRMS: calculated 379.1295; found 379.1287.

Synthesis of Methyl-(2-tributylstannanyl-cyclopropyl)-acetaldehyde 270

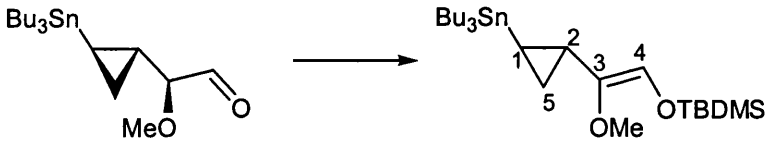


269 **270**

Sodium *meta*-periodate (2.2 g, 10.2 mmol) was added to a solution of diol **269** (1.5 g, 3.4 mmol) in THF:water (120 ml, 1:1). After 2 hours, the reaction was diluted with ether (150 ml) and washed with water (100 ml) and brine (100 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (SiO_2, PE:ether / 90:10) gave a colourless oil **270** (1.2 g, 89 %, single diastereoisomer).

R_f(PE:ether / 90:10) 0.3; ν_{max} (neat) / cm^{-1} 2959, 2926, 2851 (C-H), 1737 (C=O), 1461, 1418, 1377, 1340, 1292, 1252, 1193, 1163, 1099, 1076, 1048, 1002, 959, 937, 878, 772, 746, 689, 664, 595; δ_H (500 MHz, $CDCl_3$) δ -0.13 (1H, ddd, $^3J_{trans}$ 7.1, $^3J_{cis}$ 10.1 Hz, $^2J_{Sn}$ 0.9 Hz, CH^1), 0.64 (1H, ddd, $^3J_{cis}$ 10.1 Hz, $^3J_{trans}$ 7.1 Hz, ^2J 4.3 Hz, CH_2^5), 0.73 (1H, ddd, $^3J_{cis}$ 10.1 Hz, $^3J_{trans}$ 7.1 Hz, ^2J 4.3 Hz, CH_2^5), 0.78 (6H, m, 3 x CH_2), 0.80 (10H, m, 3 x CH_3 and CH^2), 1.26 (6H, m, 3 x CH_2), 1.43 (6H, m 3 x CH_2), 2.92 (1H, dd, ^3J 2.4, 8.2 Hz, CH^3), 3.43 (3H, s, OMe), 9.60 (1H, d, ^3J 2.4 Hz, CH^4); δ_C (125 MHz, $CDCl_3$) δ -4.81 (*C*H^1), 8.09 (*C*H_2^5), 8.66 (*C*H_2), 13.66 (*C*H_3), 14.61 (*C*H^2), 27.33 (*C*H_2), 29.03 (*C*H_2), 57.69 (OMe), 90.43 (*C*H^3), 201.18 (*C*H^4); m/z (FAB) 351 (4 %, [M(^{124}Sn)-C_4H_8]), 349 (4 %, [M(^{122}Sn)-C_4H_8]), 347 (20 %, [M(^{120}Sn)-C_4H_8]), 346 (7 %, [M(^{119}Sn)-C_4H_8]), 345 (16 %, [M(^{118}Sn)-C_4H_8]), 344 (6 %, [M(^{117}Sn)-C_4H_8]), 343 (10 %, [M(^{116}Sn)-C_4H_8]), 291 (25 %, [M-C_4H_8]), 235 (40 %, [M-C_3H_4O]), 177 (100 %, [SnC_4H_{10}]); HRMS: calculated 347.1033; found 347.1038.

Synthesis of *tert*-Butyl-[2-methoxy-2-(2-tributylstannanyl-cyclopropyl)-vinyloxy]-dimethyl-silane 252

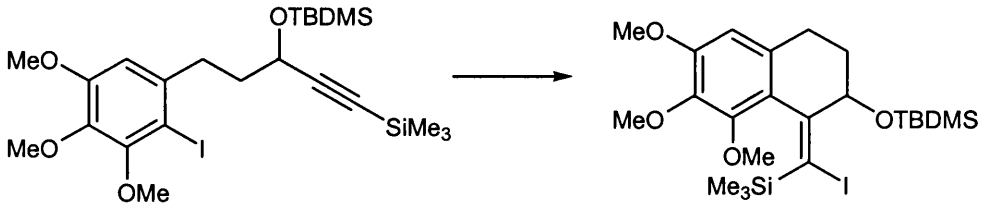


270 **252**

Sodium hydride (0.07 g, 1.72 mmol, 60% dispersion in mineral oil) and *tert*-butyldimethylsilyl chloride (0.05 g, 0.32 mmol) were added to a solution of aldehyde **270** (0.065 g, 0.16 mmol) in THF (2 ml) at 0 °C. The mixture was allowed to come to room temperature and stirred overnight, then filtered through a pad of silica. Concentration *in vacuo* gave a colourless oil **252** (0.075 g, 89 %).

R_f(PE:ether / 99:1) 0.2; ν_{max} (neat) / cm^{-1} 2956, 2926, 2854 (C-H), 1730, 1677, 1461, 1461, 1415, 1378, 1342, 1254, 1222, 1195, 1177, 1144, 1043, 1003, 960, 836, 780, 669; δ_H (500 MHz, $CDCl_3$) δ -0.02 (1H, td, $^3J_{trans}$ 7.0, $^3J_{cis}$ 10.2 Hz, CH^1), 0.12 (6H, s, SiC(CH_3)$_2$(CH_3)$_3$), 0.51 (1H, dt, $^3J_{trans}$ 7.0 Hz, ^2J 3.6 Hz, CH_2^5), 0.74 (1H, m, CH_2^5), 0.78 (6H, m, 3 x CH_2), 0.86 (9H, m, 3 x CH_3), 0.91 (9H, s, SiC(CH_3)$_2$(CH_3)$_3$), 1.15 (1H, m, CH^2), 1.26 (6H, m, 3 x CH_2), 1.46 (6H, m, 3 x CH_2), 3.68 (3H, s, OMe), 5.67 (1H, s, CH_4); δ_C (125 MHz, $CDCl_3$) δ -5.37 (CH^1), -1.28 (SiC(CH_3)$_2$(CH_3)$_3$), 8.01 (CH_2^5), 8.77 (CH_2), 13.72 (CH_3), 14.43 (CH^2), 18.33 (SiC(CH_3)$_2$(CH_3)$_3$), 25.73 (SiC(CH_3)$_2$(CH_3)$_3$), 27.34 (CH_2), 29.10 (CH_2), 58.38 (OMe), 122.29 (CH^4), 143.79 (C^3); m/z (FAB) 523 (2 %, [M(^{124}Sn)+H]), 521 (2 %, [M(^{122}Sn)+H]), 519 (10 %, [M(^{120}Sn)+H]), 518 (4 %, [M(^{119}Sn)+H]), 517 (8 %, [M(^{118}Sn)+H]), 516 (3 %, [M(^{117}Sn)+H]), 515 (5 %, [M(^{116}Sn)+H]), 461 (10 %, [M-C_4H_9]), 291 (45 %), 227 (40 %), 177 (40 %, [SnC_4H_{10}]), 73 (100%); HRMS: calculated 519.2680; found 519.2687.

Synthesis of 2-(*tert*-Butyldimethylsilanyloxy)-1-(iodo-trimethylsilanyl-methylene)-6,7,8-trimethoxy-1,2,3-tetrahydronaphthalene 278

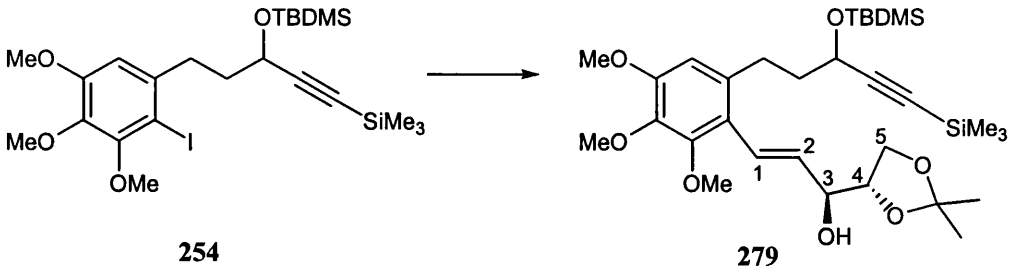


254 **278**

Palladium tetrakis(triphenylphosphine) (0.02 g, 0.018 mmol, 10 mol%) was added to a solution of 1-[3-(*tert*-butyldimethylsilanyloxy)-5-trimethylsilanyl-pent-4-ynyl]-2-iodo-3,4,5-trimethoxyphenyl **254** (0.1 g, 0.18 mmol) in toluene (2 ml). The resulting solution was heated at reflux for 2 days. On cooling to room temperature, the solvent was removed *in vacuo*. Column chromatography (SiO_2, PE:ether / 80:20) gave a colourless oil **278** (0.08 g, 80 %).

R_f(PE:ether / 80:20) 0.5; ν_{max} (neat) / cm^{-1} 2952, 2855 (C-H), 1600, 1485, 1462, 1409, 1346, 1251, 1196, 1140, 1041, 1005, 939, 909, 836, 776, 772, 695, 665; δ_H (500 MHz, $CDCl_3$) δ 0.04 (9H, s, $Si(CH_3)_3$), 0.08 and 0.09 (6H, 2 x s, $SiC(CH_3)_3(CH_3)_2$), 0.70 (9H, s, $SiC(CH_3)_3(CH_3)_2$), 1.59 (1H, tdd, ^3J 4.0, 7.1 Hz, ^2J 13.5 Hz, $ArCH_2CH_2$), 2.10 (1H, tdd, ^3J 5.0, 7.7 Hz, ^2J 13.5 Hz $ArCH_2CH_2$), 2.45 (1H, dt, ^3J 7.4 Hz, ^2J 15.8 Hz, $ArCH_2CH_2$), 2.64 (1H, dt, ^3J 6.5 Hz, ^2J 15.8 Hz, $ArCH_2CH_2$), 3.65 (3H, s, OMe), 3.83 (3H, s, OMe), 3.84 (3H, s, OMe), 5.32 (1H, dd, ^3J 4.0, 5.0 Hz, CHOTBDMS), 6.41 (1H, s, aromatic); δ_C (125 MHz, $CDCl_3$) δ -4.03 and –3.83 ($SiC(CH_3)_3(CH_3)_2$), 0.40 ($Si(CH_3)_3$), 17.85 ($SiC(CH_3)_3(CH_3)_2$), 25.72 ($SiC(CH_3)_3(CH_3)_2$), 26.64 ($ArCH_2CH_2$), 32.62 ($ArCH_2CH_2$), 55.85 (OMe), 60.47 (OMe), 60.79 (OMe), 80.51 (CHOTBDMS), 105.85 (C-6), 113.04 (C=CI), 122.40 (C-2), 135.22 (C=CI), 139.64 (C-4), 149.03 (C-1), 151.80 (C-5), 152.71 (C-3); m/z (FAB) 563 (5 %, [M+H]), 547 (20 %, [M-CH_3]), 437 (85 %, [M-$C_6H_{10}Si$]), 277 (100 %), 147 (50 %); HRMS: calculated 563.1510; found 563.1516.

Synthesis of 3-{6-[3-(*tert*-Butyldimethylsilanyloxy)-5-trimethylsilanyl-pent-4-ynyl]-2,3,4-trimethoxyphenyl}-1-(2,2-dimethyl-[1,3]dioxolan-4-yl)-prop-2-en-1-ol 279

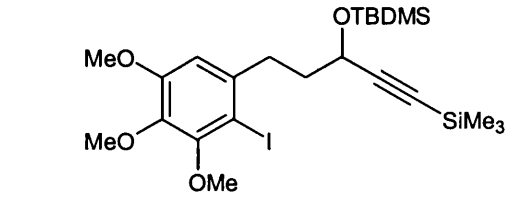


Palladium tetrakis(triphenylphosphine) (0.1 g, 0.18 mmol, 10 mol %) was added to a solution of aryl iodide **254** (0.1 g, 0. 18 mmol) and vinyl stannane **267** (0.1 g, 0.22 mmol) in toluene (2 ml). The mixture was heated at reflux for 4 hours, then cooled to room temperature. Concentration *in vacuo* and column chromatography (SiO_2, PE:ether / 50:50) gave a yellow oil **279** (0.03 g, 30 %, mixture of diastereoisomers).

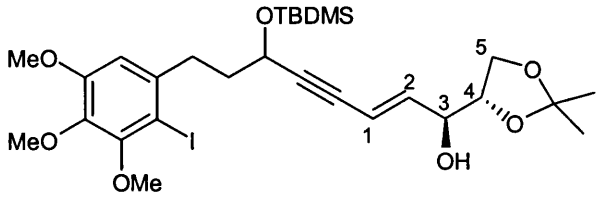
R_f(PE:ether / 50:50) 0.2; ν_{max} (neat) / cm^{-1} 3472 (O-H), 2933, 2857 (C-H), 2214 (C≡C), 1597, 1485, 1463, 1408, 1372, 1347, 1252, 1150, 1092, 1006, 951, 837, 774, 689; δ_H (500 MHz, $CDCl_3$) δ 0.01 and 0.02 (6H, 2 x s, $SiC(CH_3)_3(CH_3)_2$), 0.23 (9H, s, $SiMe_3$), 0.65 (9H, s, $SiC(CH_3)_3(CH_3)_2$), 1.28 and 1.29 (3H, 2 x s, CH_3), 1.31 (3H, s, CH_3), 1.92 (1H, d, ^3J 2.4 Hz, O*H*(*dA*)), 1.97 (2H, m, $ArCH_2CH_2$), 2.33 (1H, d, ^3J 2.4 Hz, O*H*(*dB*)), 2.61 (1H, m, $ArCH_2CH_2$), 2.74 (1H, m, $ArCH_2CH_2$), 3.52 (1H, dd, ^3J 5.8 Hz, ^2J 8.5 Hz, CH_2^5(*dA*)), 3.55 (1H, dd, ^3J 5.8 Hz, ^2J 8.5 Hz, CH_2^5(*dB*)), 3.60 (3H, s, OMe), 3.71 (1H, m, CH_2^5), 3.76 (1H, m, CH^4), 3.79 (3H, s, OMe), 3.81 (3H, s, OMe), 3.85 (1H, m, CH^3), 4.86 (1H, dd, ^3J 7.0 Hz, $^3J_{trans}$ 15.9 Hz, CH^2(*dA*)), 4.93 (1H, dd, ^3J 7.0 Hz, $^3J_{trans}$ 15.9 Hz, CH^2(*dB*)), 4.95 (1H, m, CHOTBDMS), 6.26 (1H, d, $^3J_{trans}$ 15.9 Hz, CH^1(*dA*)), 6.33 (1H, d, $^3J_{trans}$ 15.9 Hz, CH^1(*dB*)), 6.37 (1H, s, aromatic); δ_C (125 MHz, $CDCl_3$) δ -4.30 and –3.85 ($SiC(CH_3)_3(CH_3)_2$), 1.33 ($Si(CH_3)_3$), 17.83 ($SiC(CH_3)_3(CH_3)_2$), 25.39 (CH_3), 25.52 ($SiC(CH_3)_3(CH_3)_2$), 26.78 and 26.87 (CH_3), 29.12 ($ArCH_2CH_2$), 39.56 and 39.67 ($ArCH_2CH_2$), 55.88 and 55.91 (OMe), 60.75 and 60.79 (OMe), 61.31 and 61.33 (OMe), 65.88 and 65.98 (CH_2^5),

70.21 and 70.25 (*C*HOTBDMS), 74.74 and 74.77 (*C*H^3), 78.85 and 79.06 (*C*H^4), 106.29 and 106.32 (C-6), 109.29 and 109.58 (C), 123.02 and 123.15 (C-1), 125.29 and 126.06 (*C*H^2), 133.29 and 133.57 (*C*≡CSiMe$_3$), 134.24 and 134.36 (C≡*C*SiMe$_3$), 137.69 (*C*H^1), 140.08 and 140.14 (C-4), 147.36 and 147.65 (C-2), 150.90 and 150.93 (C-5), 152.23 and 152.28 (C-3); m/z (FAB) 615 (75 %, [M+Na]), 577 (65 %, [M-CH$_3$]), 207 (100 %), 181 (40 %); HRMS: calculated 615.3149; found 615.3159.

Synthesis of 6-(*tert*-Butyldimethylsilanyloxy)-1-(2,2-dimethyl-[1,3]dioxolan-4-yl)-8-(2-iodo-3,4,5-trimethoxyphenyl)-oct-2-en-4-yn-1-ol 280



254

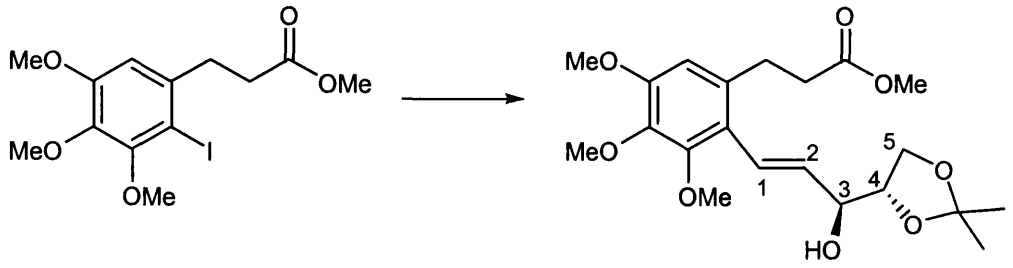


280

Palladium tetrakis(triphenylphosphine) (0.02 g, 0.018 mmol, 10 mol%) and cuprous iodide (0.017 g, 0.09 mmol) were added to a solution of aryl iodide **254** (0.1 g, 0.18 mmol) and vinylstannane **267** (0.08 g, 0.18 mmol) in DMF. The resultant mixture was stirred for 6 hours, then diluted with ethyl acetate (10 ml) and washed with water (10 ml) and brine (10 ml). Concentration *in vacuo* gave an oil which was taken up in acetonitrile (20 ml) and washed with hexane (5 x 20 ml). Column chromatography (PE:ether / 50:50) gave a brown oil **280** (0.04 g, 40 %, mixture of diastereoisomers).

R_f(PE:ether / 50:50) 0.2; ν_{max} (neat) / cm^{-1} 3466 (OH), 2934, 2856 (C-H), 2214 (C≡C), 1564, 1480, 1427, 1387, 1335, 1252, 1200, 1161, 1104, 1008, 961, 838, 778; δ_H (500 MHz, $CDCl_3$) δ 0.12 and 0.13 (6H, 2 x s, $SiC(CH_3)_3(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3(CH_3)_2$), 1.29 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.93 (2H, m, $ArCH_2CH_2$), 2.41 (1H, d, ^3J 4.2 Hz, O*H*), 2.80 (1H, ddd, ^3J 7.4, 8.8 Hz, ^2J 13.6 Hz, $ArCH_2CH_2$), 2.87 (1H, ddd, ^3J 7.4, 8.8 Hz, ^2J 13.7 Hz, $ArCH_2CH_2$), 3.76 (1H, m, CH_2^5), 3.82 (6H, s, 2 x OMe), 3.84 (3H, s, OMe), 3.99 (2H, m, CH^4 and CH_2^5), 4.07 (1H, m, CH^3), 4.52 (1H, dd, ^3J 4.9, 6.2 Hz, CHOTBDMS), 5.85 (1H, d, $^3J_{trans}$ 15.8 Hz, CH^1), 6.01 (1H, dd, ^3J 6.1 Hz, $^3J_{trans}$ 15.8 Hz, CH^2), 6.62 (1H, s, aromatic); δ_C (125 MHz, $CDCl_3$) δ -4.93 and –4.14 ($SiC(CH_3)_3(CH_3)_2$), 18.26 ($SiC(CH_3)_3(CH_3)_2$), 25.19 (CH_3), 25.83 ($SiC(CH_3)_3(CH_3)_2$), 26.70 (CH_3), 36.90 ($ArCH_2CH_2$), 38.84 ($ArCH_2CH_2$), 56.12 (OMe), 60.68 (OMe), 60.94 (OMe), 62.75 (CHOTBDMS), 65.74 (CH_2^5), 73.04 (CH^3), 78.34 (CH^4), 82.18 (CHC≡C), 88.01 (C-2), 92.15 (CHC≡C), 108.76 (C-6), 109.94 (*C*), 112.42 (CH^1),140.04 (C-4), 140.10, (C-1), 140.13 (CH^2), 153.06 (C-5), 153.49 (C-3); m/z (FAB) 669 (15 %, [M+Na]), 616 (50 %, [M-C_2H_6]), 307 (100 %, [M-$C_{16}H_{25}O_4Si$]), 281 (20 %, [M-C_2H_2]), 207 (35 %), 181 (35 %), 147 (10 %); HRMS: calculated 669.1721; found 669.1744.

Synthesis of 3-{2-[3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3-hydroxypropenyl]-3,4,5-trimethoxyphenyl}propionic acid methyl ester 281

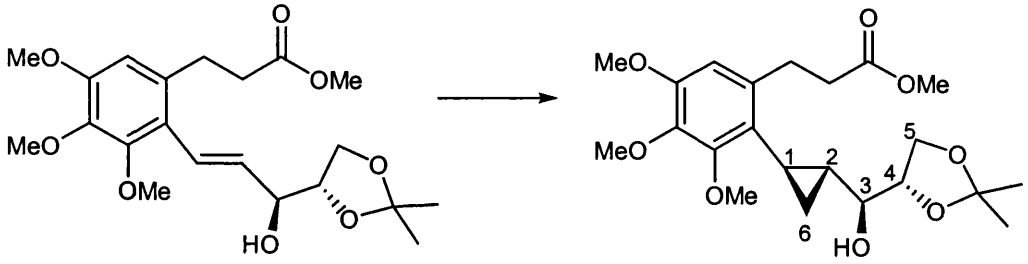


187 **281**

Palladium tetrakis(triphenylphosphine) (0.12 g, 0.10 mmol, 5 mol%) was added to a solution of aryl iodide **187** (0.7 g, 0.18 mmol) and vinyl stannane **267** (0.8 g, 0.18 mmol) in toluene (16 ml). The resultant mixture was heated at reflux overnight. On cooling to room temperature, the solvent was removed *in vacuo*. Column chromatography (SiO_2, PE:ether / 40:60) gave a yellow oil **281** (0.59 g, 84 %, single diastereoisomer).

R_f(ether) 0.3; ν_{max} (neat) / cm^{-1} 3480 (OH), 2986, 2938 (C-H), 1732 (C=O), 1596, 1568, 1489, 1455, 1405, 1371, 1330, 1243, 1209, 1157, 1126, 1068, 988, 915, 856, 792; δ_H (500 MHz, $CDCl_3$) δ 1.33 (3H, s, CH_3), 1.46 (3H, s, CH_3), 2.49 (1H, d, ^3J 3.8 Hz, O*H*), 2.53 (2H, t, ^3J 8.0 Hz, $ArCH_2CH_2$), 2.93 (2H, t, ^3J 8.0 Hz, $ArCH_2CH_2$), 3.66 (3H, s, CO_2Me), 3.75 (3H, s, OMe), 3.82 (3H, s, OMe), 3.83 (3H, s, OMe), 3.84 (1H, ^3J 6.5 Hz, ^2J 8.4 Hz, CH_2^5), 4.03 (1H, dd, ^3J 6.5 Hz, ^2J 8.4 Hz, CH_2^5), 4.11 (1H, q, ^3J 6.5 Hz, CH^4), 4.19 (1H, ddd, ^3J 3.8, 6.8 Hz, ^4J 1.1 Hz, CH^3), 6.06 (1H, dd, $^3J_{trans}$ 16.1 Hz, ^3J 6.8 Hz, CH^2), 6.50 (1H, s, aromatic), 6.60 (1H, dd, $^3J_{trans}$ 16.1 Hz ^4J 1.1 Hz, CH^1); δ_C (125 MHz, $CDCl_3$) δ 25.32 (CH_3), 26.80 (CH_3), 29.03 ($ArCH_2CH_2$), 35.19 ($ArCH_2CH_2$), 51.69 (CO_2Me), 55.91 (OMe), 60.40 (OMe), 60.87 (OMe), 65.97 (CH_2^5), 74.83 (CH^3), 79.02 (CH^4), 108.56 (C-6), 109.86 (*C*), 122.33 (C-2), 125.84 (CH^1), 131.97 (CH^2), 134.50 (C-1), 140.96 (C-4), 152.22 (C-5), 152.48 (C-3), 173.23 (CO_2Me); m/z (FAB) 411 (10 %, [M+H]), 393 (45 %, [M-OH]), 335 (95 %, [$M-C_3H_6O$]), 310 (100 %), 303 (45 %), 291 (45 %); HRMS: calculated 411.2019; found 411.2004.

Synthesis of 3-(2-{2-[(2,2-Dimethyl-1[1,3]dioxolan-4-yl)-hydroxymethyl]-cyclopropyl}-3,4,5-trimethoxyphenyl)propionic acid methyl ester 282



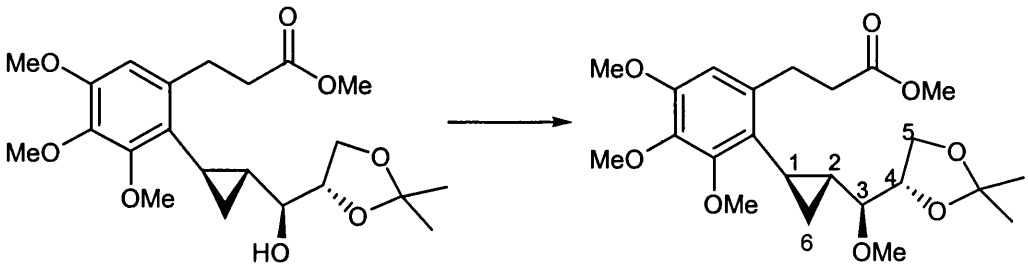
281 **282**

Diethyl zinc (8.6 ml, 7.8 mmol, 15 % sol. in hexanes) was added to a solution of alkene **281** (0.53 g, 1.3 mmol) in ether (35 ml) at 0 °C. After a few minutes, diiodomethane (1 ml, 13.0 mmol) was added dropwise and the mixture allowed to come to room temperature, then heated at reflux for 4 hours. On cooling to room temperature, the reaction was quenched with sat. aq. NH_4Cl solution (40 ml), and extracted with ether (3 x 40 ml). Drying ($MgSO_4$) and column chromatography (SiO_2, PE:ether / 10:90) gave a colourless oil **282** (0.45 g, 85 %, single diastereoisomer).

R_f(ether) 0.4; ν_{max} (neat) / cm^{-1} 3502 (O-H), 2985, 2930 (C-H), 1736 (C=O), 1649, 1597, 1572, 1492, 1456, 1403, 1371, 1329, 1200, 1127, 1071, 995, 924, 847; δ_H (500 MHz, $CDCl_3$) δ 0.72 (1H, ddd, $^3J_{trans}$ 5.6 Hz, $^3J_{cis}$ 8.5 Hz, ^2J 4.4 Hz, CH_2^6), 1.12 (1H, ddd, $^3J_{tran}$ 5.6 Hz, $^3J_{cis}$ 8.5 Hz, ^2J 4.4 Hz, CH_2^6), 1.26 (1H, td, $^3J_{trans}$ 5.6 Hz, ^3J 5.6 Hz, $^3J_{cis}$ 8.5 Hz, CH^2), 1.38 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.65 (1H, td, $^3J_{trans}$ 5.6 Hz, $^3J_{cis}$ 8.5 Hz, CH^1), 2.38 (1H, d, ^3J 4.8 Hz, O*H*), 2.56 (1H, ddd, ^3J 6.8, 9.3 Hz, ^2J 15.8 Hz, $ArCH_2CH_2$), 2.60 (1H, ddd, ^3J 6.8, 9.3 Hz, ^2J 15.8 Hz, $ArCH_2CH_2$), 3.00 (1H, ddd, ^3J 6.8, 9.3 Hz, ^2J 14.3 Hz, $ArCH_2CH_2$), 3.10 (1H, ddd, ^3J 6.8, 9.3 Hz, ^2J 14.3 Hz, $ArCH_2CH_2$), 3.52 (1H, q, ^3J 5.5 Hz, CH^3), 3.67 (3H, s, CO_2Me), 3.79 (6H, s, 2 x OMe), 3.85 (3H, s, OMe), 3.86 (1H, dd, ^3J 6.4 Hz, ^2J 8.4 Hz, CH_2^5), 4.10 (1H, dd, ^3J 6.4 Hz, ^2J 8.4 Hz, CH_2^5), 4.19 (1H, q, ^3J 6.3 Hz, CH^4), 6.45 (1H, s, aromatic); δ_C (125 MHz, $CDCl_3$) δ 10.57 (CH_2^6), 12.66 (CH^1), 22.77 (CH^2), 25.40 (CH_3), 26.73 (CH_3), 28.51 ($ArCH_2CH_2$), 34.96 ($ArCH_2CH_2$), 51.64 (CO_2Me), 55.88 (OMe), 60.70 (OMe), 60.85 (OMe), 66.37

(CH_2^5), 73.12 (CH^3), 79.06 (CH^4), 107.88 (C-6), 109.36 ($C(CH_3)_2$), 124.75 (C-2), 136.75 (C-1), 140.56 (C-4), 151.83 (C-5), 153.49 (C-3), 173.45 (CO_2Me); m/z (FAB) 424 (100 %, [M^+]), 349 (40 %, [M-$C_3H_7O_2$]), 335 (25 %, [M-CH_2]), 331 (50 %), 317 (30 %); HRMS: calculated 424.2097; found 424.2111.

Synthesis of 3-(2-{2-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)-methoxymethyl]-cyclopropyl}-3,4,5-trimethoxyphenyl)propionic acid methyl ester 283



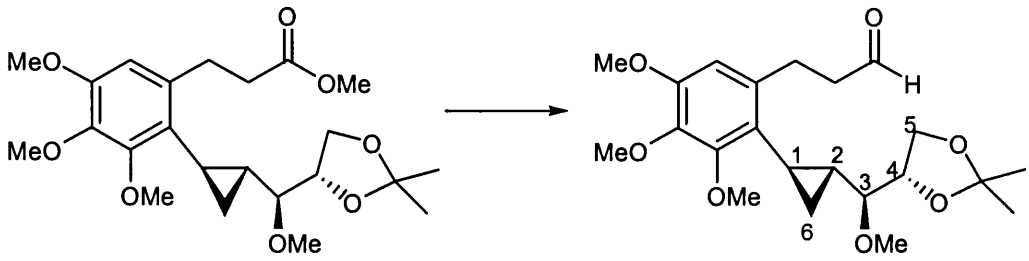
282 **283**

Methyl iodide (2 ml, 33.0 mmol) and silver (I) oxide (1.0 g, 4.6 mmol) were added to a solution of alcohol **282** (1.3 g, 3.1 mmol) in acetonitrile (30 ml). The resultant mixture was heated at 70 °C overnight. On cooling to room temperature, the solid was removed by filtration and the filtrate concentrated *in vacuo*. Column chromatography (SiO_2, PE:ether / 50:50) gave a colourless oil **283** (1.0 g, 75 %, single diastereoisomer).

R_f(PE:ether) 0.3; ν_{max} (neat) / cm^{-1} 2984, 2938, 2834 (C-H), 1737 (C=O), 1597, 1573, 1492, 1456, 1402, 1371, 1127, 999, 923, 850; δ_H (500 MHz, $CDCl_3$) δ 0.75 (1H, ddd, $^3J_{trans}$ 5.8 Hz, $^3J_{cis}$ 8.6 Hz, ^2J 4.2 Hz, CH_2^6), 1.11 (1H, ddd, $^3J_{trans}$ 5.8 Hz, $^3J_{cis}$ 8.6 Hz, ^2J 4.2 Hz, CH_2^6), 1.21 (1H, ddd, ^3J 4.8 Hz, $^3J_{trans}$ 5.8 Hz, $^3J_{cis}$ 8.6 Hz, CH^2), 1.37 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.55 (1H, td, $^3J_{trans}$ 5.8 Hz, $^3J_{cis}$ 8.6 Hz, CH^1), 2.58 (1H, ddd, ^3J 6.9, 9.0 Hz, ^2J 15.7 Hz, $ArCH_2CH_2$), 2.60 (1H, ddd, ^3J 6.9, 9.0 Hz, ^2J 15.7 Hz, $ArCH_2CH_2$), 3.02 (1H, ddd, ^3J 7.2, 8.9 Hz, ^2J 14.3 Hz, $ArCH_2CH_2$), 3.08 (1H, ddd, ^3J 7.2, 8.9 Hz, ^2J 14.3 Hz, $ArCH_2CH_2$), 3.31 (1H, dd, ^3J 4.8, 7.0 Hz, CH^3), 3.45 (3H, s, CHOMe), 3.51 (3H, s, CO_2Me), 3.78 (1H, t, ^3J 8.0 Hz, ^2J 8.0 Hz, CH_2^5), 3.76 (6H, s, 2 x OMe), 3.85 (3H, s, OMe), 4.07 (1H, dd,

^3J 6.4 Hz, ^2J 8.4 Hz, CH_2^5), 4.23 (1H, q, ^3J 6.6 Hz, CH^4), 6.52 (1H, s, aromatic); δ_C (125 MHz, $CDCl_3$) δ 10.98 (CH_2^6), 11.79 (CH^1), 15.22 (CH^2), 25.56 (CH_3), 26.61 (CH_3), 28.56 ($ArCH_2CH_2$), 34.99 ($ArCH_2CH_2$), 51.64 (CO_2Me), 55.89 (OMe), 59.35 (CHOMe), 60.69 (OMe), 60.87 (OMe), 66.23 (CH_2^5), 78.87 (CH^4), 82.05 (CH^3), 107.87 (C-6), 109.18 ($C(CH_3)_2$), 124.82 (C-2), 136.65 (C-4), 140.62 (C-1), 151.76 (C-5), 153.46 (C-3), 173.40 (CO_2Me); m/z (FAB) 439 (60 %, [M+H]), 349 (30 %, [M-$C_4H_9O_2$]), 337 (100 %, [M-C]), 331 (45 %); HRMS: calculated 439.2332; found 439.2324.

Synthesis of 3-(2-{2-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)-methoxymethyl]-cyclopropyl}-3,4,5-trimethoxyphenyl)propionaldehyde 285



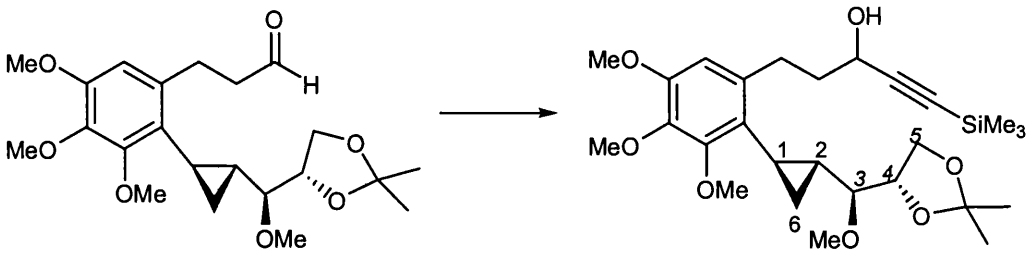
283 **285**

To a solution of ester **283** (1.0 g, 2.3 mmol) in toluene (15 ml) was added diisobutylaluminium hydride (2.4 ml, 2.9 mmol, 20 % sol. in toluene) at –78°C. After 1 hour, methanol (0.5 ml) was added the mixture was allowed to come to room temperature. 1M HCl (60 ml) was added and the product extracted with ether (3 x 60 ml). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and filtered. Column chromatography (SiO_2, PE:ether / 20:80) gave a colourless oil **285** (0.65 g, 70 %, single diastereoisomer).

R_f(PE:ether / 50:50) 0.3; ν_{max} (neat) / cm^{-1} 2985, 2937, 2831 (C-H), 1725 (C=O), 1675, 1597, 1493, 1456, 1404 1328, 1197, 1126, 1090, 999, 853; δ_H (500 MHz, $CDCl_3$) δ 0.71 (1H, ddd, $^3J_{trans}$ 5.8 Hz, $^3J_{cis}$ 8.9 Hz, ^2J 4.2 Hz, CH_2^6), 1.07 (1H, ddd, $^3J_{trans}$ 5.8 Hz, $^3J_{cis}$ 8.9 Hz, ^2J 4.2 Hz, CH_2^6), 1.20 (1H, ddd, $^3J_{trans}$ 5.8 Hz, $^3J_{cis}$ 8.9 Hz, ^3J 4.8 Hz, CH^2), 1.34 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.51 (1H, td, $^3J_{trans}$

5.8 Hz, $^3J_{cis}$ 8.9 Hz, C*H*^{1}), 2.71 (1H, ddd, ^3J 1.4, 6.8 Hz, ^2J 10.4 Hz, ArCH$_2$C*H*$_2$), 2.74 (1H, ddd, ^3J 1.4, 6.8 Hz, ^2J 10.4 Hz, ArCH$_2$C*H*$_2$), 2.99 (1H, ddd, ^3J 6.6, 8.9 Hz, ^2J 14.7 Hz, ArC*H*$_2$CH$_2$), 3.27 (1H, ddd, ^3J 6.6, 8.9 Hz, ^2J 14.7 Hz, ArC*H*$_2$CH$_2$), 3.49 (3H, s, CHOMe), 3.27 (1H, dd, ^3J 4.8, 6.9 Hz, C*H*^{3}), 3.74 (1H, dd, ^3J 6.5 Hz, ^2J 8.4 Hz, C*H*$_2^5$), 3.76 (3H, s, OMe), 3.77 (3H, s, OMe), 3.83 (3H, s, OMe), 4.04 (1H, dd, ^3J 6.5 Hz, ^2J 8.4 Hz, C*H*$_2^5$), 4.20 (1H, q, ^3J 6.9 Hz, C*H*^{4}), 6.45 (1H, s, aromatic), 9.80 (1H, t, ^3J 1.4 Hz, C*H*O); δ_C (125 MHz, CDCl$_3$) δ 10.96 (*C*H$_2^6$), 11.80 (*C*H^1), 20.22 (*C*H^2), 25.45 (*C*H$_3$), 25.53 (*C*H$_3$), 26.52 (ArCH$_2$CH$_2$), 44.59 (ArCH$_2$*C*H$_2$), 55.83 (OMe), 59.25 (CHOMe), 60.59 (OMe), 60.78 (OMe), 66.10 (*C*H$_2^5$), 78.66 (*C*H^4), 81.89 (*C*H^3), 107.88 (C-6), 109.09 (*C*(CH$_3$)$_2$), 124.72 (C-2), 136.44 (C-4), 140.56 (C-1), 151.75 (C-5), 153.46 (C-3), 201.45 (*C*HO); m/z (FAB) 431 (10 %, [M+Na]), 408 (10 %, [M$^+$]), 261 (70 %, [M-C$_7$H$_{15}$O$_3$]); HRMS: calculated 431.2046; found 431.2053.

Synthesis of 5-(2-{2-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)-methoxymethyl]-cyclopropyl}-3,4,5-trimethoxyphenyl)-1-trimethylsilanylpent-1-yn-3-ol 286

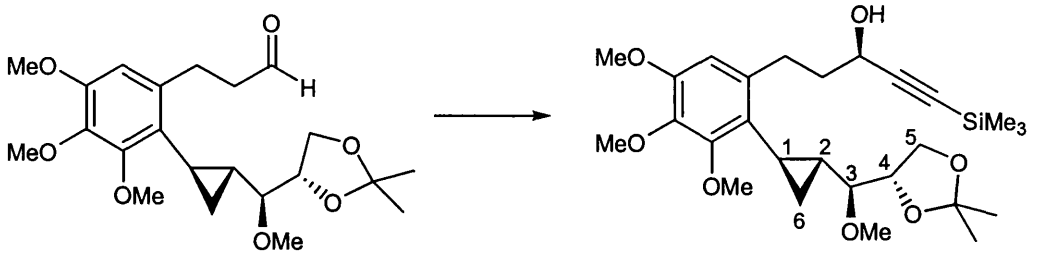


285 **286**

n-Butyllithium (1.38 ml, 3.3 mmol, 2.4 M in hexanes) was added to a solution of trimethylsilylacetylene **192** (0.47 ml, 3.3 mmol) in THF (9 ml) at 0°C. After stirring for 1 hour at this temperature, a solution of aldehyde **285** (0.53 g, 1.3 mmol) in THF (9 ml) was added *via* syringe pump over a 4 hour period. The reaction was quenched with sat. aq. NH$_4$Cl solution (50 ml) and extracted with ether (3 x 50 ml), then dried (MgSO$_4$) and concentrated *in vacuo*. Column chromatography (SiO$_2$, PE:ether / 50:50) gave a colourless oil **286** (0.50 g, 77 %, mixture of diastereoisomers).

R_f(PE:ether / 50:50) 0.3; ν_{max} (neat) / cm^{-1} 3444 (O-H), 2937, 2887, 2834 (C-H), 2248, 2170 (C≡C), 1596, 1574, 1491, 1455, 1404, 1375, 1333, 1250, 1202, 1127, 1058, 996, 910, 843, 761, 734, 648; δ_H (500 MHz, $CDCl_3$) δ 0.15 (9H, s, $Si(CH_3)_3$), 0.75 (1H, m, CH_2^6), 1.10 (1H, m, CH_2^6), 1.24 (1H, m, CH^2), 1.36 and 1.37 (3H, 2 x s, CH_3), 1.40 and 1.41 (3H, 2 x s, CH_3), 1.55 (1H, m, CH^1), 1.95 (2H, m, $ArCH_2CH_2$), 2.29 (1H, d, ^3J 5.2 Hz, O*H*(*dA*)), 2.41 (1H, d, ^3J 6.2 Hz, O*H*(*dB*)), 2.80 (1H, m, $ArCH_2CH_2$), 2.95 (1H, m, $ArCH_2CH_2$), 3.26 (1H, dd, ^3J 5.2, 6.7 Hz, CH^3(*dA*)), 3.37 (1H, dd, ^3J 4.6, 6.4 Hz, CH^3(*dB*)), 3.49 and 3.50 (3H, 2 x s, CHOMe), 3.77 (3H, s, OMe), 3.78 (3H, s, OMe), 3.80 (3H, s, OMe), 3.83 (1H, m, CH_2^5), 4.05 (1H, m, CH_2^5), 4.25 (1H, m, CH^4), 4.38 (1H, m, C*H*OH), 6.46 (1H, s, aromatic); δ_C (125 MHz, $CDCl_3$) δ -0.15 ($Si(CH_3)_3$), 11.15 and 11.38 (CH_2^6), 11.97 and 12.08 (CH^1), 19.78 and 20.11 (CH^2), 25.52 and 25.54 (CH_3), 26.59 and 26.60 (CH_3), 28.90 and 29.06 ($ArCH_2CH_2$), 38.55 and 39.02 ($ArCH_2CH_2$), 55.86 (OMe), 59.19 and 59.21 (CHOMe), 60.65 and 60.67 (OMe), 60.82 and 60.83 (OMe), 62.33 and 62.41 (C*H*OH), 66.09 and 66.20 (CH_2^5), 78.23 and 78.67 (CH^4), 81.62 and 82.30 (CH^3), 89.43 and 89.65 ($C{\equiv}CSiMe_3$), 106.58 and 106.78 ($C{\equiv}CSiMe_3$), 108.21 (C-6), 109.19 and 109.22 ($C(CH_3)_2$), 124.76 and 124.93 (C-2), 137.53 and 137.60 (C-4), 140.35 and 140.36 (C-1), 151.65 and 151.70 (C-5), 153.37 and 153.45 (C-3); m/z (FAB) 529 (20 %, [M+Na]), 506 (35 %, [M^+]), 333 (55 %, [M-$C_9H_{17}O_3$]), 233 (55 %); HRMS: calculated 529.2598; found 529.2585.

Synthesis of (*R*)-5-(2-{2-[(2,2-Dimethyl-[1,3]dioxolan-4-yl)-methoxymethyl]-cyclopropyl}-3,4,5-trimethoxyphenyl)-1-trimethylsilanyl-pent-1-yn-3-ol 286



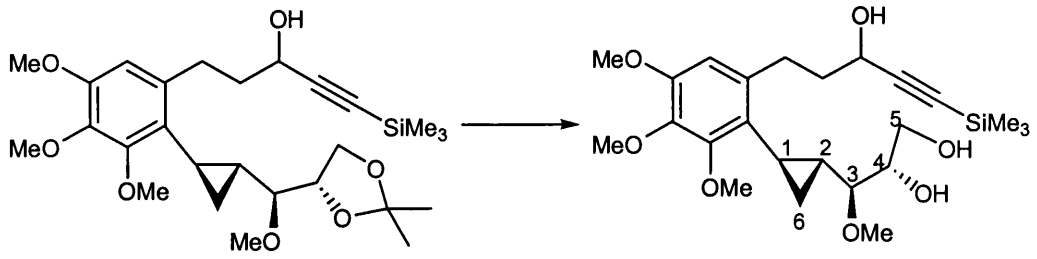
285 **286**

Zinc triflate (0.45 g, 1.25 mmol) and (+)-*N*-methylephedrine **256** (0.23 g, 1.28 mol) were placed in a flask and purged with nitrogen. After 15 minutes, toluene (2 ml) and triethylamine (0.18 ml, 1.28 mmol) were added and the mixture was stirred vigorously for 2 hours. Trimethylsilylacetylene **192** (0.18 ml, 1.28 mmol) was added in a single portion and stirring continued for 30 minutes. A solution of aldehyde **285** (0.1 g, 0.25 mmol) in toluene (3 ml) was added over a 5 hour period *via* syringe pump. The reaction was quenched by the dropwise addition of sat. aq. NH_4Cl solution (15 ml) and extracted with ether (3 x 20 ml). The combined organic extracts were washed with brine (40 ml) and dried ($MgSO_4$). Concentration *in vacuo* and column chromatography (SiO_2, PE:ether / 50:50) gave a colourless oil **286** (0.05g, 42 %, 86 % ee).

R_f(PE:ether / 50:50) 0.3; ν_{max} (neat) / cm^{-1} 3444 (O-H), 2937, 2887, 2834 (C-H), 2248, 2170 (C≡C), 1596, 1574, 1491, 1455, 1404, 1375, 1333, 1250, 1202, 1127, 1058, 996, 910, 843, 761, 734, 648; δ_H (500 MHz, $CDCl_3$) δ 0.15 (9H, s, $SiMe_3$), 0.76 (1H, m, CH_2^6), 1.11 (1H, m, CH_2^6), 1.24 (1H, m, CH^2), 1.36 and 1.38 (3H, 2 x s, CH_3), 1.40 and 1.42 (3H, 2 x s, CH_3), 1.55 (1H, m, CH^1), 1.95 (2H, m, $ArCH_2CH_2$), 2.29 (1H, br s, O*H* (*dA*)), 2.41 (1H, br s, O*H* (*dB*)), 2.80 (1H, m, $ArCH_2CH_2$), 2.95 (1H, m, $ArCH_2CH_2$), 3.27 (1H, dd, ^3J 5.2, 6.7 Hz, CH^3 (*dA*)), 3.38 (1H, dd, ^3J 4.5, 6.5 Hz, CH^3 (*dB*)), 3.49 and 3.51 (3H, 2 x s, CHO*Me*), 3.78 (3H, s, OMe), 3.80 (3H, s, OMe), 3.85 (3H, s, OMe), 3.86 (1H, m, CH_2^5), 4.07 (1H, m, CH_2^5), 4.25 (1H, m, CH^4), 4.39 (1H, m, C*H*OH), 6.46 (1H, s, aromatic); δ_C (125 MHz, $CDCl_3$) δ -0.12 ($SiMe_3$), 11.18 and 11.44 (CH_2^6), 11.99 and 12.12 (CH^1), 19.78 and 20.14 (CH^2), 25.55 and 25.57 (CH_3), 26.62 and 26.64 (CH_3),

28.91 and 29.11 ($ArCH_2CH_2$), 38.59 and 39.11 ($ArCH_2CH_2$), 55.91 (OMe), 59.23 and 59.26 (CHOMe), 60.70 and 60.73 (OMe), 60.86 (OMe), 62.43 and 62.52 (*C*HOH), 66.12 and 66.24 (CH_2^5), 78.21 and 78.69 (CH^4), 81.60 and 82.35 (CH^3), 89.56 and 89.81 ($C{\equiv}CSiMe_3$), 106.49 and 106.72 ($C{\equiv}CSiMe_3$), 108.22 (C-6), 109.24 and 109.26 ($C(CH_3)_2$), 124.80 and 124.98 (C-2), 137.53 and 137.62 (C-4), 140.39 and 140.40 (C-1), 151.70 and 151.75 (C-5), 153.42 and 153.51 (C-3); m/z (FAB) 529 (20%, [M+Na]), 506 (35%, [M^+]), 333 (55%, [$M-C_9H_{17}O_3$]), 233 (55%); HRMS: calculated 529.2598; found 529.2585.

Synthesis of 3-{2-[6-(3-Hydroxy-5-trimethylsilanylpent-4-ynyl)-2,3,4-trimethoxyphenyl]-cyclopropyl}-3-methoxypropane-1,2-diol 287



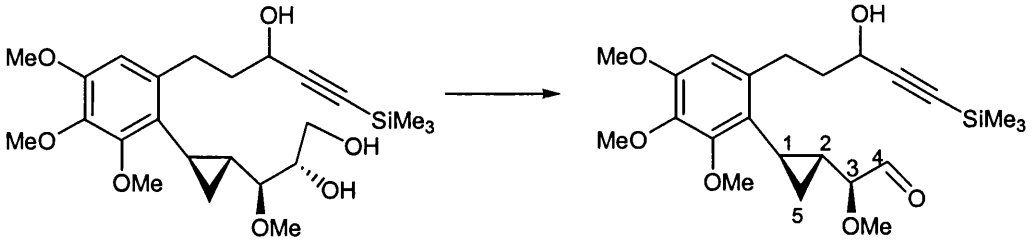
286 **287**

To a solution of acetal **286** (0.35 g, 0.69 mmol) in methanol (30 ml) was added 2M-HCl (3 ml). After 2 hours, the solution was neutralised with sat. aq. $NaHCO_3$ solution, then taken up in ethyl acetate (50 ml) and washed with brine (40 ml). Drying ($MgSO_4$) and concentration *in vacuo* gave an oil which was chromatographed (SiO_2, PE:ethyl acetate / 10:90) to give a colourless oil **287** (0.19 g, 60 %, mixture of diastereoisomers).

R_f(ethyl acetate) 0.4; ν_{max} (neat) / cm^{-1} 3420 (OH), 2940, 2845 (C-H), 2170 (C≡C), 1737, 1597, 1574, 1491, 1456, 1401, 1332, 1249, 1196, 1127, 1055, 963, 842, 762; δ_H (500 MHz, $CDCl_3$) δ 0.16 and 0.17 (9H, s, $Si(CH_3)_3$), 0.94 (1H, m, CH_2^6), 1.11 (1H, m, CH_2^6), 1.42 (1H, m, CH^2), 1.50 (1H, m, CH^1), 1.96 (2H, m, $ArCH_2CH_2$), 2.81 (1H, m, $ArCH_2CH_2$), 2.90 (1H, m, CH^3), 3.00 (1H, m, $ArCH_2CH_2$), 3.49 (3H, s, CHOMe), 3.78 (3H, s, OMe), 3.79 (2H, m, CH_2^5), 3.81

(3H, s, OMe), 3.88 (3H, s, OMe), 3.90 (1H, m, C*H*^{4}), 4.42 (1H, m, C*H*OH), 6.48 (1H, s, aromatic); δ_C (125 MHz, $CDCl_3$) δ -0.09 (Si(C*H*$_3$)$_3$), 12.07 (*C*H^1), 14.45 and 14.58 (*C*H$_2^6$), 19.98 and 20.01 (*C*H^2), 28.72 and 28.87 (Ar*C*H$_2$CH$_2$), 38.52 and 38.81 (ArCH$_2$*C*H$_2$), 55.93 (OMe), 57.92 and 59.80 (CHOMe), 60.70 (OMe), 61.07 (OMe), 62.40 and 62.45 (C*H*OH), 63.85 and 63.92 (*C*H$_2^5$), 73.50 and 73.59 (*C*H^4), 85.07 and 85.30 (*C*H^3), 89.69 and 89.74 (*C*≡CSiMe$_3$), 106.46 and 106.54 (C≡*C*SiMe$_3$), 108.26 and 108.40 (C-6), 124.15 and 124.18 (C-2), 137.71 and 137.73 (C-4), 140.30 and 140.31 (C-1), 151.93 (C-5), 153.15 and 153.17 (C-3); m/z (CI) 466 (20 %, [M$^+$]), 417 (25 %, [M-CH$_5$O$_2$]), 333 (40 %), 73 (25 %), 41 (100 %); HRMS: calculated 466.2387; found 466.2380.

Synthesis of {2-[6-(3-Hydroxy-5-trimethylsilanylpent-4-ynyl)-2,3,4-trimethoxyphenyl]-cyclopropyl}-methoxypropane acetaldehyde 288



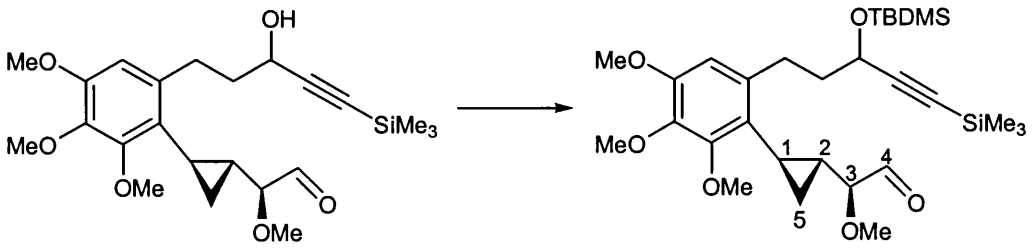
287 **288**

Sodium *meta*-periodate (0.22 g, 1.0 mmol) was added to a solution of diol **287** (0.16 g, 0.34 mmol) in THF:water (12 ml, 1:1). After 2 hours, the reaction was diluted with ether (20 ml) and washed with water (20 ml) and brine (20 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Column chromatography (SiO_2, PE:ether / 20:80) gave a colourless oil **288** (0.12 g, 81 %, mixture of diastereoisomers).

R_f(ether) 0.5; ν_{max} (neat) / cm^{-1} 3421 (OH), 2956, 2867, 2823 (C-H), 2169 (C≡C), 1736 (C=O), 1596, 1574, 1491, 1456, 1400, 1333, 1250, 1196, 1127, 1056, 910, 843, 761, 700; δ_H (500 MHz, $CDCl_3$) δ 0.17 (9H, s, Si(C*H*$_3$)$_3$), 0.89 (1H, m, C*H*$_2^5$), 1.13 (1H, m, C*H*$_2^5$), 1.41 (1H, m, C*H*^{2}), 1.73 (1H, m, C*H*^{1}), 1.96 (2H, m, ArCH$_2$C*H*$_2$), 2.82 (1H, m, ArC*H*$_2$CH$_2$), 2.97 (1H, m, Ar*C*H$_2$CH$_2$), 3.36 (1H, m,

C*H*[3]), 3.47 (3H, s, CHOMe), 3.79 (6H, s, 2 x OMe), 3.81 (3H, s, OMe), 4.40 (1H, m, C*H*OH), 6.46 (1H, s, aromatic), 9.75 (1H, m, C*H*O); δ_C (125 MHz, $CDCl_3$) δ-0.10 (Si(*C*H$_3$)$_3$), 12.05 and 12.07 (*C*H[1]), 12.44 (*C*H$_2$[5]), 20.29 and 20.31 (*C*H[2]), 28.79 and 29.01 (Ar*C*H$_2$CH$_2$), 38.51 and 38.54 (ArCH$_2$*C*H$_2$), 55.88 (OMe), 58.13 (CHOMe), 60.17 (2 x OMe), 62.39 and 62.52 (*C*HOH), 87.90 and 89.92 (*C*H[3]), 89.86 and 89.92 (*C*≡CSiMe$_3$), 106.44 and 106.47 (C≡*C*SiMe$_3$), 108.10 (C-6), 124.01 and 124.03 (C-2), 137.54 and 137.54 (C-4), 140.32 (C-1), 152.07 and 152.09 (C-5), 153.54 (C-3), 201.89 (*C*HO); m/z (CI) 434 (20 %, [M$^+$]), 417 (30 %, [M-OH]), 385 (10 %, [M-CH$_3$OH]), 333 (25 %, [M-C$_4$H$_4$]), 293 (25 %), 207 (10 %), 73 (10 %); HRMS: calculated 434.2125; found 434.2119.

Synthesis of (2-{6-[3-(*tert*-Butyldimethylsilanyloxy-5-trimethylsilanylpent-4-ynyl)-2,3,4-trimethoxyphenyl}-cyclopropyl)-methoxypropane acetaldehyde 271



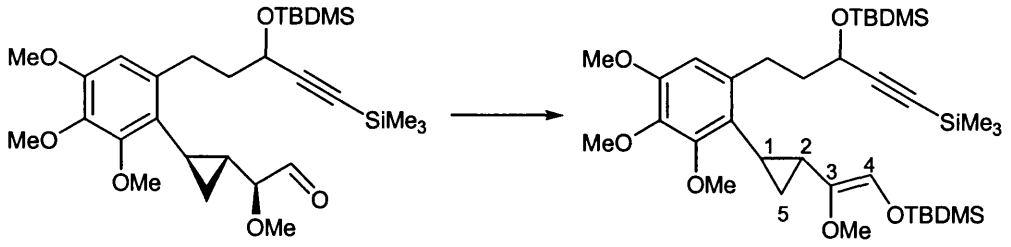
288 **271**

tert-Butyldimethylsilyl chloride (0.07 g, 0.46 mmol) and imidazole (0.04 g, 0.58 mmol) were added to a solution of alcohol **288** (0.1 g, 0.23 mmol) in acetonitrile (2 ml). The resulting mixture was stirred at room temperature for 4 hours, and then the solvent was removed *in vacuo*. The product was taken up in ether (10 ml) and washed with water (10 ml) then sat. aq. $NaHCO_3$ solution (10 ml). Drying (Na_2SO_4) and concentration *in vacuo* gave an oil that was chromatographed (SiO_2, PE:ether / 80:20) to give a colourless oil **271** (0.1 g, 83 %, mixture of diastereoisomers).

R_f(PE:ether/ 50:50) 0.5; ν_{max} (neat) / cm^{-1} 2956, 2932, 2857 (C-H), 2171 (C≡C), 1736 (C=O), 1597, 1492, 1464, 1407, 1334, 1251, 1196, 1128, 1092, 1009, 910,

841, 779, 666; δ_H (500 MHz, $CDCl_3$) δ 0.12 and 0.13 (6H, 2 x s, $SiC(CH_3)_3(CH_3)_2$), 0.14 and 0.15 (9H, 2 x s, $Si(CH_3)_3$), 0.85 (1H, m, CH_2^5), 0.90 (9H, s, $SiC(CH_3)_3(CH_3)_2$), 1.10 (1H, m, CH_2^5), 1.39 (1H, m, CH^2), 1.71 (1H, m, CH^1), 1.91 (2H, m, $ArCH_2CH_2$), 2.69 (1H, m, $ArCH_2CH_2(dA)$), 2.77 (1H, m, $ArCH_2CH_2(dB)$), 2.88 (1H, m, $ArCH_2CH_2(dA)$), 2.98 (1H, m, $ArCH_2CH_2(dB)$), 3.12 (1H, m, CH^3), 3.45 (3H, s, CHOMe), 3.77 (6H, s, 2 x OMe), 3.80 (3H, s, OMe), 4.39 (1H, m, CHOTBDMS), 6.44 (1H, s, aromatic), 9.75 (1H, m, CHO); δ_C (125 MHz, $CDCl_3$) δ -4.92, –4.89 and -4.46, -4.43 ($SiC(CH_3)_3(CH_3)_2$), -0.21 ($Si(CH_3)_3$), 11.90 and 11.97 (CH^1), 12.52 and 12.64 (CH_2^5), 18.26 ($SiC(CH_3)_3(CH_3)_2$), 20.20 and 20.24 (CH^2), 25.74 and 25.80 ($SiC(CH_3)_3(CH_3)_2$), 29.10 and 29.17 ($ArCH_2CH_2$), 39.31 and 39.44 ($ArCH_2CH_2$), 55.86 (OMe), 58.03 and 58.05 (CHOMe), 60.60 and 60.64 (2 x OMe), 63.05 and 63.21 (CHOTBDMS), 87.97 and 88.10 (CH^3), 88.94 and 88.03 ($C{\equiv}CSiMe_3$), 107.34 ($C{\equiv}CSiMe_3$), 107.98 and 108.01 (C-6), 123.93 (C-2), 138.02 (C-4), 140.13 (C-1), 151.99 (C-5), 153.38 and 153.41 (C-3), 201.51 and 201.54 (CHO); m/z (CI) 548 (35 %, $[M^+]$), 447 (20 %, $[M-C_5H_9O_2]$), 417 (60 %), 333 (100 %), 293 (45 %), 73 (50 %); HRMS: calculated 548.2989; found 548.2983.

Synthesis of 2-{2-[2-(*tert*-Butyldimethylsilanyloxy)-1-methoxyvinyl]-cyclopropyl}-1-[3-(*tert*-butyldimethylsilanyloxy)-5-trimethylsilanylpent-4-ynyl]-3,4,5-trimethoxy benzene 250



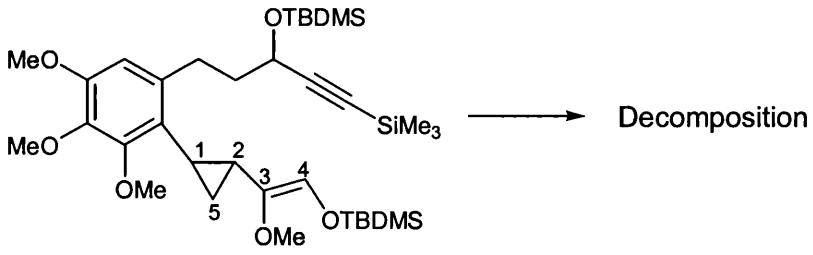
271 **250**

A solution of aldehyde **271** (0.05 g, 0.09 mmol) in THF (1 ml) was added to a suspension of sodium hydride (0.04 g, 0.90 mmol, 60 % dispersion in mineral oil) at 0 °C. *tert*-Butyldimethylsilyl chloride (0.03 g, 0.18 mmol) was added and the mixture was allowed to come to room temperature and stirred for 3 hours. The mixture was filtered through a pad of silica and concentrated *in vacuo* to give a yellow oil **250** (0.4 g, 80 %, mixture of isomers).

R_f(PE:ether/ 70:30) 0.6; ν_{max} (neat) / cm^{-1} 2956, 2932, 2857 (C-H), 2172 (C≡C), 1678, 1596, 1574, 1491, 1460, 1405, 1335, 1253, 1196, 1130, 1088, 1005, 939, 839, 780, 667; δ_H (500 MHz, $CDCl_3$) δ 0.11 and 0.12 (12H, 2 x s, 2 x $SiC(CH_3)_3(CH_3)_2$), 0.15 (9H, s, $Si(CH_3)_3$), 0.79 (1H, m, CH_2^5), 0.91 and 0.94 (18H, 2 x s, 2 x $SiC(CH_3)_3(CH_3)_2$), 1.07 (1H, m, CH_2^5), 1.55 (1H, m, CH^2), 1.89 (1H, m, CH^1), 1.92 (2H, m, $ArCH_2CH_2$), 2.84 (1H, m, $ArCH_2CH_2$), 3.75 (3H, s, CHOMe), 3.80 (3H, s, OMe), 3.81 (3H, s, OMe), 3.84 (3H, s, OMe), 4.37 (1H, m, CHOTBDMS), 5.85 and 5.86 (1H, 2 x s, CH^4), 6.46 and 6.47 (1H, 2 x s, aromatic); δ_C (125 MHz, $CDCl_3$) δ -5.32, -4.85, -4.38, -3.59 (2 x $SiC(CH_3)_3(CH_3)_2$), -0.17 ($Si(CH_3)_3$), 12.53 and 12.71 (CH_2^5), 14.51 (CH^1), 18.27 and 18.31 (2 x $SiC(CH_3)_3(CH_3)_2$), 20.50 and 20.45 (CH^2), 25.63 and 25.84 (2 x $SiC(CH_3)_3(CH_3)_2$), 29.21 ($ArCH_2CH_2$), 39.55 and 39.66 ($ArCH_2CH_2$), 55.92 (OMe), 59.07 and 59.12 (CHOMe), 60.98 (OMe), 61.12 (OMe), 63.23 (CHOTBDMS), 88.95 ($C{\equiv}CSiMe_3$), 107.49 ($C{\equiv}CSiMe_3$), 108.21 (C-6), 122.82 and 122.82 (CH^4), 125.35 (C-1), 138.31 and 138.35 (C-2), 140.30 (C-4), 141.63 and 141.77 (C^3), 151.58 (C-5), 153.72 (C-3); m/z (CI) 663 (40 %, [M+H]), 647

(50 %, [M-CH_3]), 605 (100 %, [M-C_2H_2O]), 531 (90 %), 399 (60 %), 317 (25 %), 73 (40 %); HRMS: calculated 663.3932; found 663.3920.

ATTEMPTED [5+2] CYLOADDITION OF PRECURSOR 250



250

Using [CpRu(CH_3CN)$_3$]PF_6 (160)

[CpRu(CH_3CH)$_3$]PF_6 **160** (0.002 g, 0.004 mmol, 20 mol%) was added to a solution of alkynyl-vinylcyclopropane **250** (0.015 g, 0.022 mmol) in acetone (0.25 ml). The resultant mixture was stirred at room temperature, and after 5 hours complete decomposition of the starting material **250** was observed.

Using [Rh(CO)$_2$Cl]$_2$ (106)

[Rh(CO)$_2$Cl]$_2$ **106** (0.001 g, 0.002 mmol, 5 mol %) was added to a solution of alkynyl-vinylcyclopropane **250** (0.02 g, 0.03 mmol) in DCM (0.5 ml) and the mixture was heated at 40 °C. After 24 hours, decomposition of **250** had occurred.

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APPENDIX

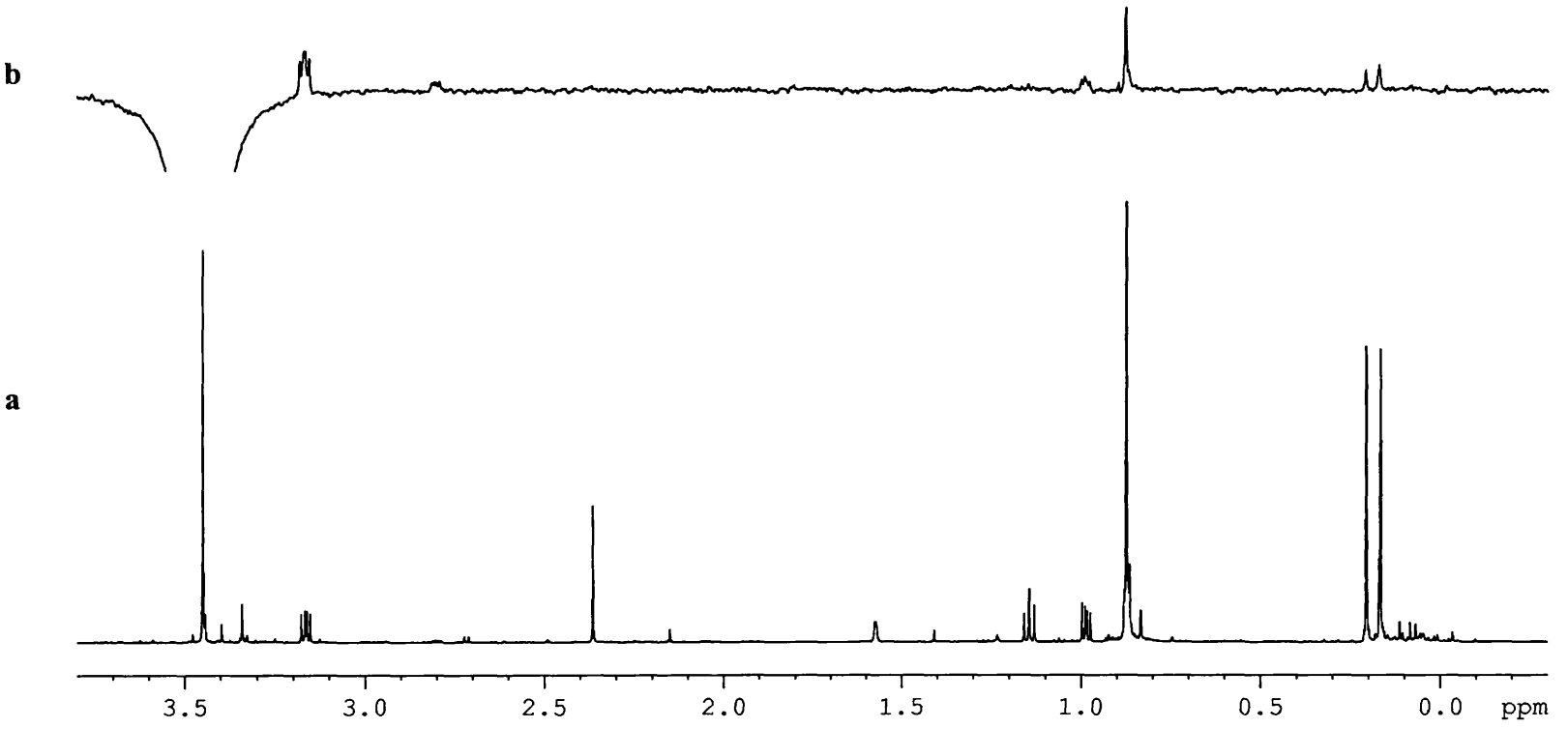

Figure 1 a) ^{1}H NMR spectrum of alkynylcyclopropane **175**, b) nOe spectrum (mixing time 600ms), the OMe protons were selectively refocused.

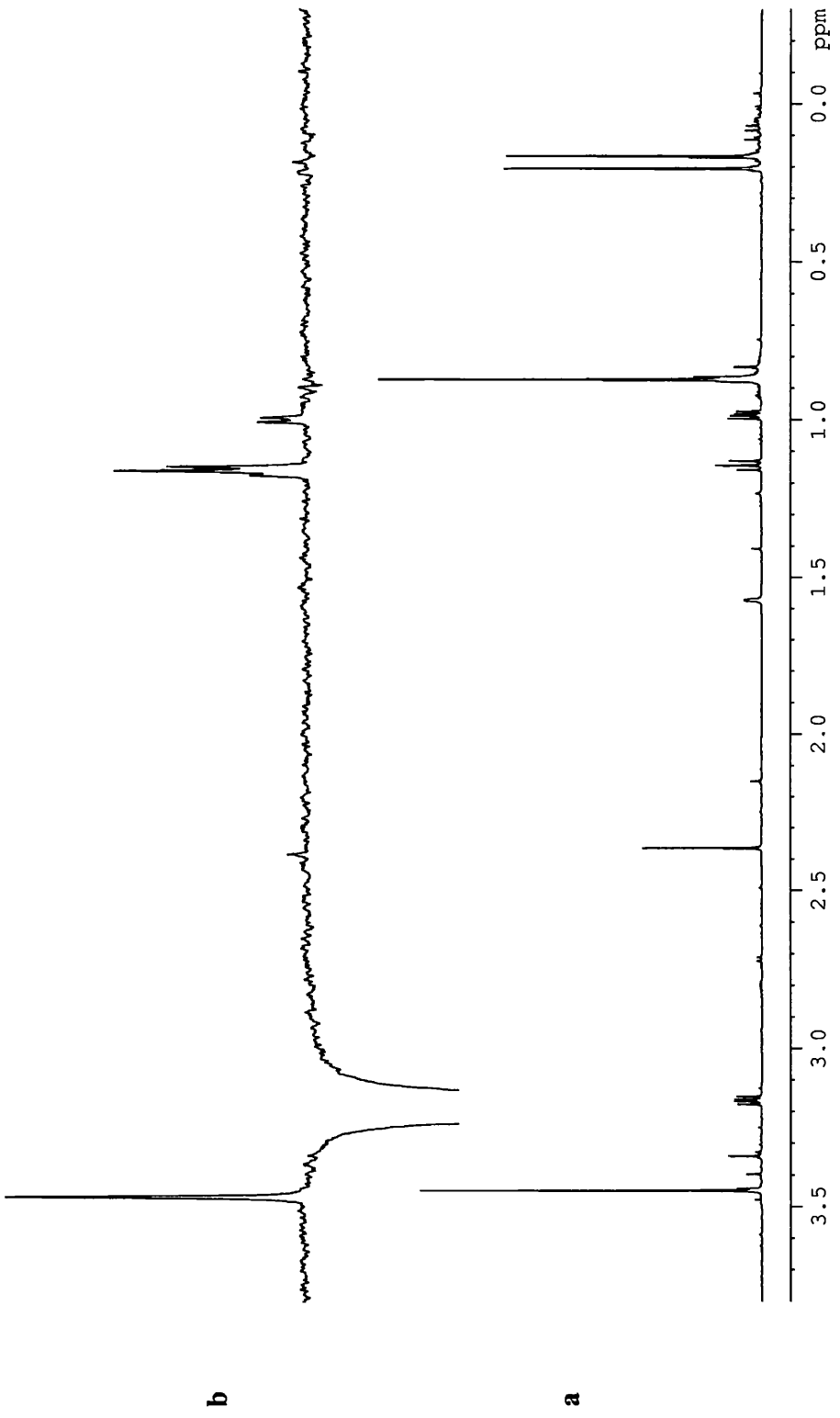

Figure 2 a) ^{1}H NMR spectrum of alkynylcyclopropane **175**, b) nOe spectrum (mixing time 600ms), the cyclopropyl CH proton was selectively refocused.

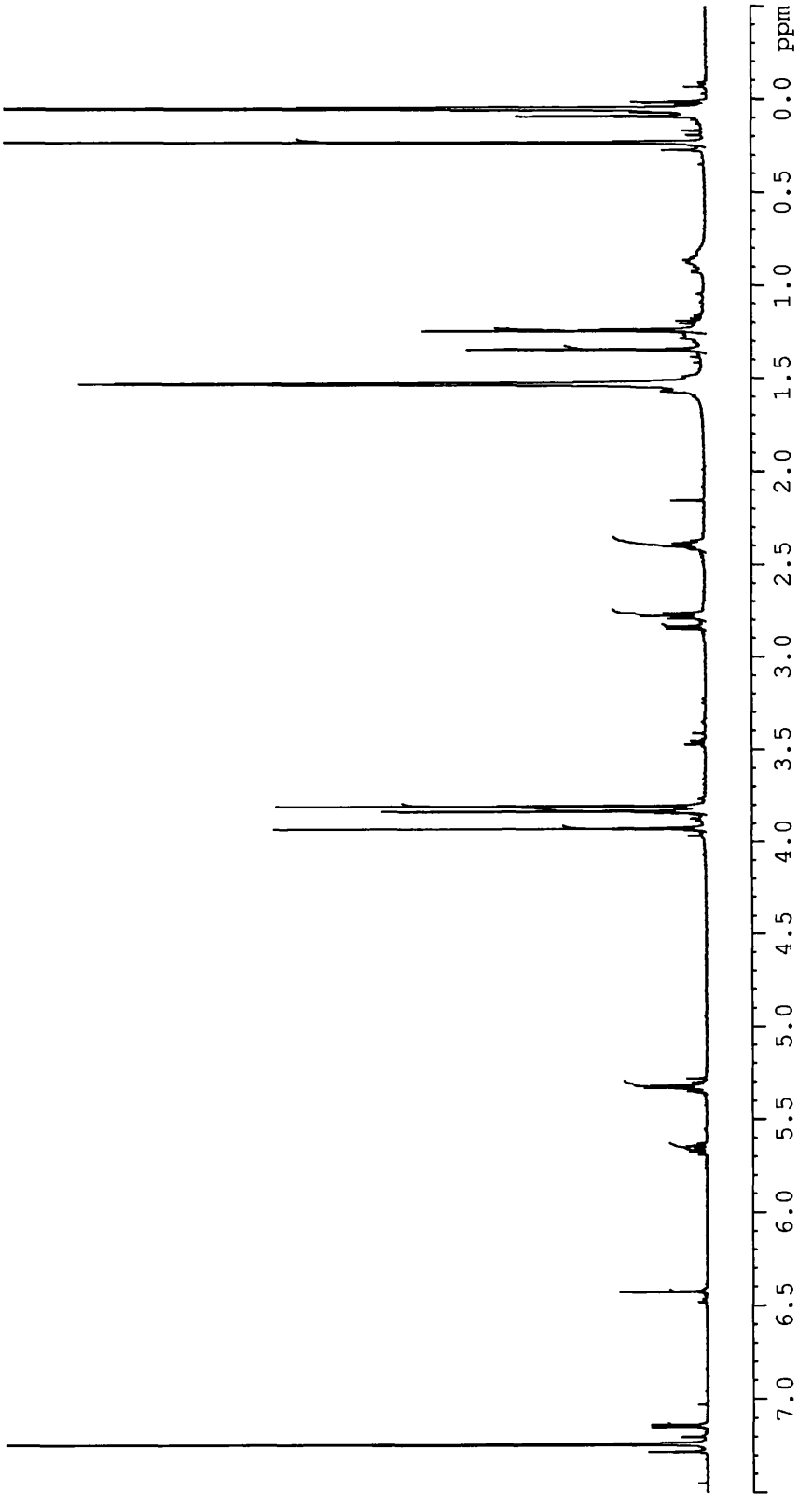

Figure 3 ^{1}H NMR spectrum for compound **246**

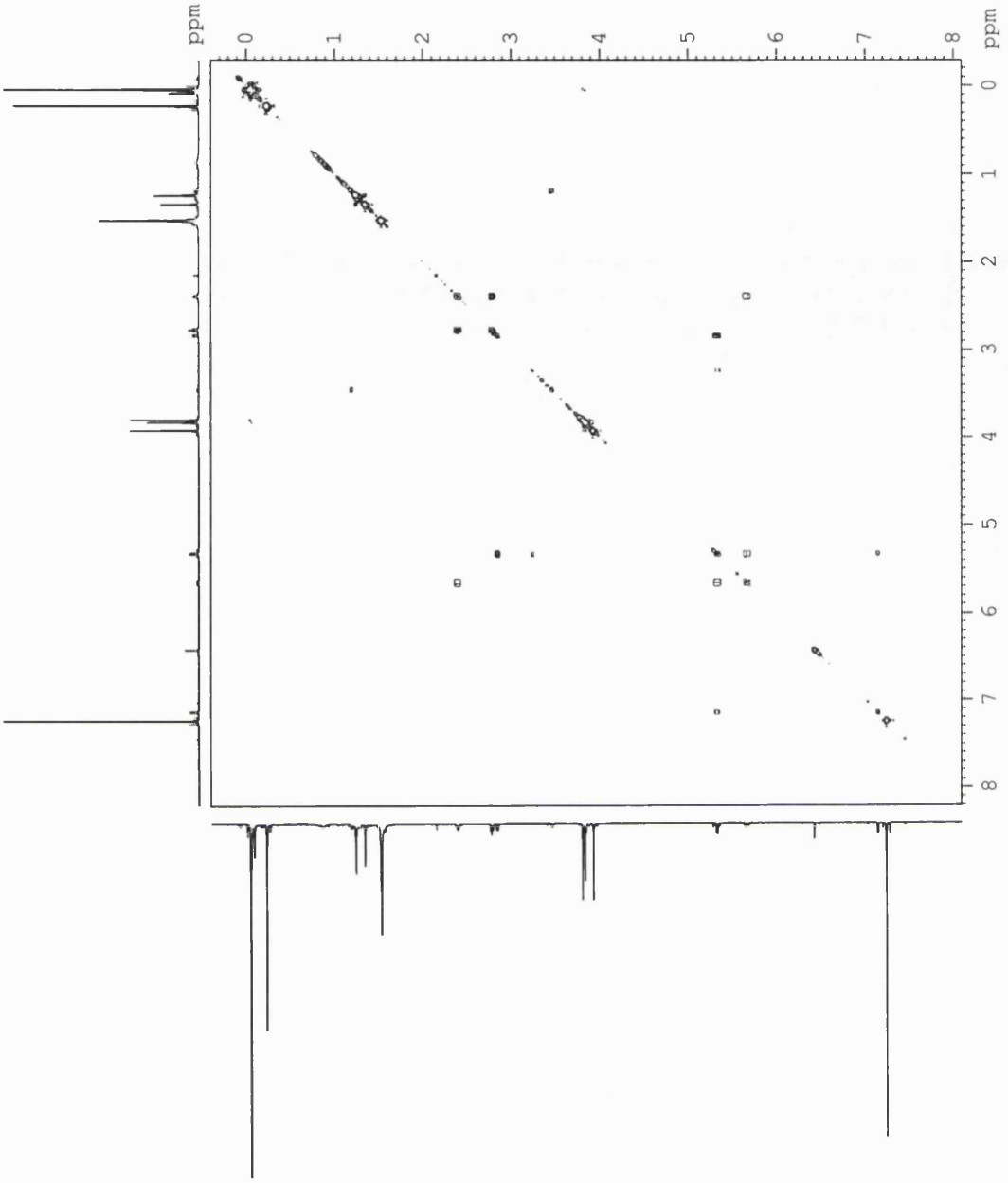

Figure 4 COSY spectrum for compound **246**