Synthesis and Palladium-catalyzed Carbonylation of Substituted Vinyl Triflates: Routes to Unsaturated Heterocycles

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(Faculty of Science)

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'It is only the half-truths that are dangerous'

George Bernard Shaw

'The future is never the same as it was and it never will be'

Arthur C. Clarke

'Who would have thought reading and writing would pay off'

Homer J. Simpson

Contents

Chapter 4-Total synthesis of the monoterpene (+)-mintlactone

Acknowledgements

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Statement

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Publications

Some of the work described in this thesis has been reported in the following publications:

'Palladium-Catalysed, Carbonylative, Intramolecular Coupling of Hydroxy Vinyltriflates. Synthesis of Substituted α,β-Butenolides.' Crisp, G.T., Meyer, A.G., *J. Org. Chem.*, 1992, **57**, 6972.

'Synthesis of Functionalised Vinyl Triflates from Terminal Alkynes.' Crisp, G.T., Meyer, A.G., *Synthesis*, 1994, 667.

Abbreviations

Ac - Acetyl
atm - atmosphere
BMS - Borane-methyl sulfide complex
Bn - Benzyl
Bu - Butyl
CO - Carbon monoxide
m-CPBA - *meta*-Chloroperbenzoic acid
DBU - 1,8-Diazabicyclo[4.3.0]undec-7-ene
DBN - 1,5-Diazabicyclo[4.3.0]non-5-ene
DCC - 1,3-Dicyclohexylcarbodiimide
DEAD - Diethyl azodicarboxylate
DIBALH - Diisobutylaluminium hydride
DMAP - 4-Dimethylaminopyridine
DMF - N,N-Dimethylformamide
DMI - 1,3-Dimethyl-2-imidazolidinone
dppf - Diphenylphosphinoferrocene
Et - Ethyl
GLC - Gas liquid chromatography
HMPA - Hexamethylphosphoramide
HRMS - High resolution mass spectrometry
IR - Infrared
KHMDS - Potassium hexamethyldisilazide
LDA - Lithium diisopropylamide
Me - Methyl
Ms - Mesyl (CH_3SO_2)
MTPA - α-methoxy-α-trifluoromethylphenylacetic acid
NADP - Nicotinamide adenine dinucleotide phosphate
NMR - Nuclear magnetic resonance
TDA-1 - Tris[2-(2-methoxyethoxy)ethyl]amine
TFA - Trifluoroacetic acid
Tf_2NPh - N-Phenyltriflimide
TLC - Thin layer chromatography
PCC - Pyridinium chlorochromate
Ph - Phenyl
Pht - Phthalyl
Pr - Propyl
py - pyridine
rt - room temperature
TBABr - Tetrabutylammonium bromide
TDMS - Thexyldimethylsilyl
Tf - Triflate
THF - Tetrahydrofuran
THP -
Ts - Tosyl ($CH_3C_6H_4SO_2$)
BDMS - tertbutyldimethylsilyl

Abstract

The synthesis of substituted hydroxy and amino vinyl triflates and their applicability to undergo an intramolecular palladium(0)-catalyzed carbonylation reaction was investigated. This has resulted in the general preparation of unsaturated heterocycles such as α-methylene γ-butyrolactones, α,β-butenolides and α,β-unsaturated β,γ and δ-lactams.

This methodology has been extended to include the synthesis of optically active monocyclic and bicyclic α,β-unsaturated γ-lactones from chiral starting materials generated from the fermenting baker's yeast reduction of 1,3-dicarbonyl compounds. The synthesis of the monoterpene (+)-mintlactone **234** was accomplished from this methodology.

Chapter 1

1.0 α-Methylene γ-butyrolactones

1.1 Occurrence and biological activity

The α-methylene γ-butyrolactone ring can be seen as an integral partial unit in approximately 10% of all structurally elucidated natural products. These compounds, mainly occuring in plants of the families *Frullanaceae*, *Magnoliaceae* and especially the species rich *Compositae*,[1] are generally either mono-,[2] sesqui-[3] or diterpenoids.[4] Most commonly fused to six-, seven-, ten- or fourteen-membered rings*, the lactone moiety, which is indicated by the suffix "olide", can have both *cis* and *trans* stereochemistry at the ring junction.

Of all natural products containing the α-methylene γ-butyrolactone ring, undoubtedly the most interest has centred on sesquiterpene lactones found as characteristic components mainly of the *Compositae*. These colourless, lipophilic, and often bitter-tasting compounds mainly occur in the leaf tissue, where they can constitute up to 5% of the dry weight.

Such sesquiterpene lactones exhibit interesting biological properties with the most noteworthy being the discovery of compounds that show pronounced cytotoxic or antitumour activity. Examples include vernolepin **1**[5], elephantopin **2**[6], and europarotin **3**[7] which are found to possess significant *in vivo* antitumour activities.[8] The high cytotoxicity of these sesquiterpene lactones is thought to be attributable to the inhibition of protein synthesis[9], DNA synthesis and/or transcription.[10]

Although little is known about the the relationship between structure and activity of these compounds,[8b] it appears to be associated with their ability to act as alkylating agents, by virtue of the conjugate addition of biological nucleophiles to the terminal end of the α-methylene γ-

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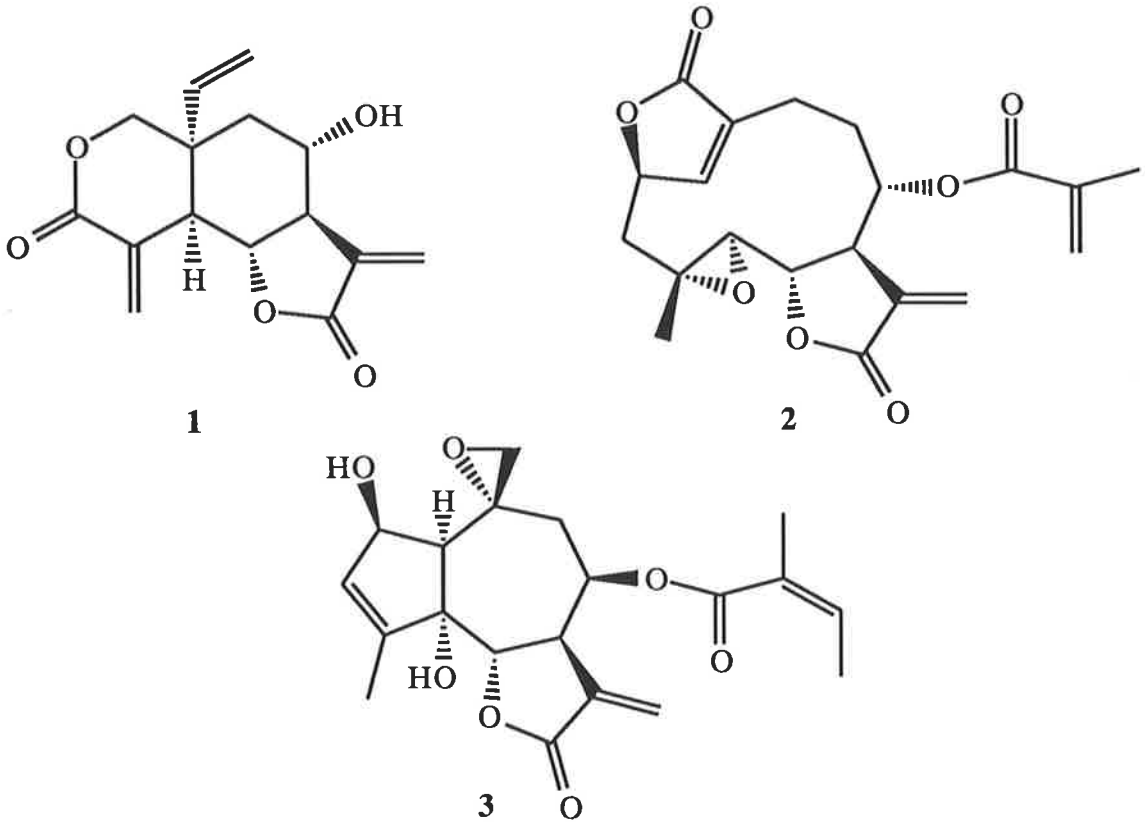
* A widely distributed class of marine natural products consisting of a 14-membered diterpene lactone are the Cembranolides.

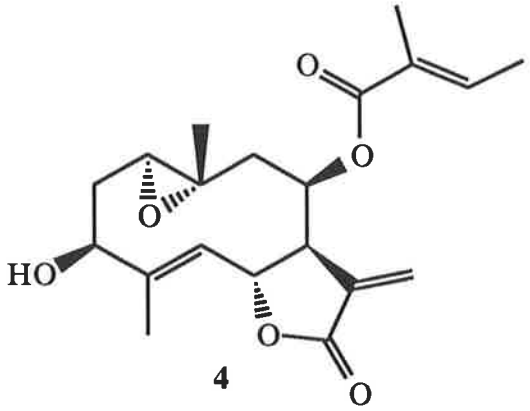


butyrolactone moiety.[11] These compounds alkylate substrates like *L*-cysteine[12] or the thiol portion of enzymes such as phosphofructokinase and glycogen synthetase, thus inhibiting the incorporation of selected amino acids into proteins.

Unfortunately, the unit responsible for biological activity is also responsible for its high reactivity. This has meant their use as pharmacological agents has been severely curtailed because of their high toxicity arising from indiscriminant reactions with nucleophillic cellular components. Unsuccessful attempts have been made to achieve selectivity of action by improving the transport properties of these compounds *via* attachment to an appropriate carrier such as a carbohydrate[13] or a steroid unit.[14] Derivatives of these compounds, such as simple vinyl and α-methylene γ-butyrolactone sulfonate esters, silyl enol ethers[15] and others, have also been made.

Sesquiterpene lactones have also been shown to function as both plant growth inhibitors and chemical defence weapons. Examples of the former include vernolepin **1**, from *Vernonia*

hymenolepsis, heliangin **4**[16], from the tuberous sunflower *Helianthus tuberosus L.*, and xanthatin **5**.[17]



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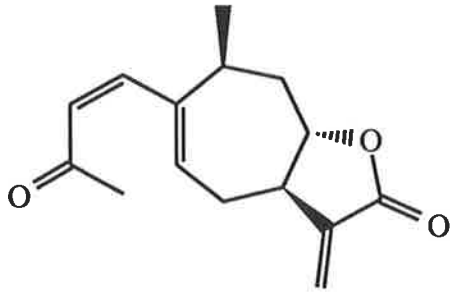

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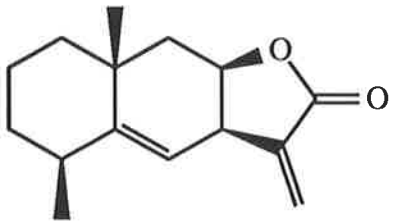
An abundant number of sesquiterpene lactones isolated from the common sunflower (*Helianthus annuus L.*) have been shown to play a role in its defence. α-Methylene γ-butyrolactones such as alantolactone **6** function as a chemical defence against insects[18a] and herbivorous mammals[18b] whereas other lactones, produced when the plant is under environmental stress, act against microorganisms. Similarly, euponin **7** in *Eupatorium japonicum* protects the plant from insect attack by inhibiting the development of fruit fly eggs.[19]



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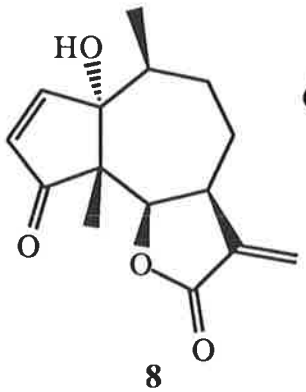

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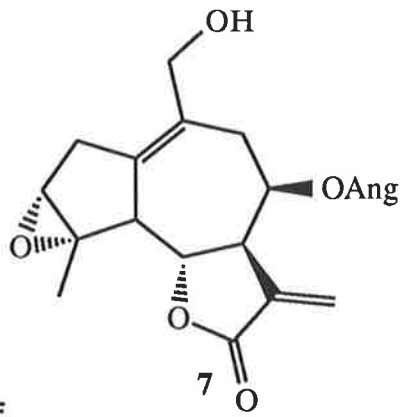

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In addition to the cyto- and phytotoxic activities described, allergenic activities caused by contact with plants, or their chemical constituents, are shown by a range of lactones.[20] An example is parthenin **8**, present in *Parthenium hysterophoros*, which causes severe allergic contact dermatitis. The mode of action is believed to occur through the bonding of the α-

methylene γ-butyrolactone to the skin *via* a Michael reaction which forms an antigen that causes sensitization of the lymphocytes.[21]

A number of other biological properties are exhibited by sesquiterpene lactones including bacterial, fungicidal and anthelminthic activities.

1.2 Biosynthesis

Sesquiterpenoid α-methylene γ-butyrolactones are derived from the precursor *trans*, *trans*-farnesyl pyrophosphate **9** which subsequently cyclizes to a strained cyclodecadiene skeleton of germacradiene (or germacratriene) **10**. A further intramolecular reaction forms a perhydroazulene system **11** (eg. guaine or pseudoguaiane) or a decalin system **12** (eg. eudesmine[22]) (**Scheme 1.1**).* Further rearrangements and oxidative modifications result in the wide structural diversity found in this class of compounds.

1.3 Synthesis

As a consequence of the wide range of physiological activity displayed by compounds possessing the α-methylene γ-butyrolactone ring this class of compound has been the subject of considerable synthetic activity, with several excellent reviews having appeared.[23] The methods of preparation can generally be divided into two main approaches:

1) non-transition metal-mediated approaches which include: a) the α-methylenation of preformed γ-butyrolactone rings or b) cyclizations of functionalized acyclic precursors incorporating an intact olefin unit.

2) transition metal-mediated syntheses.

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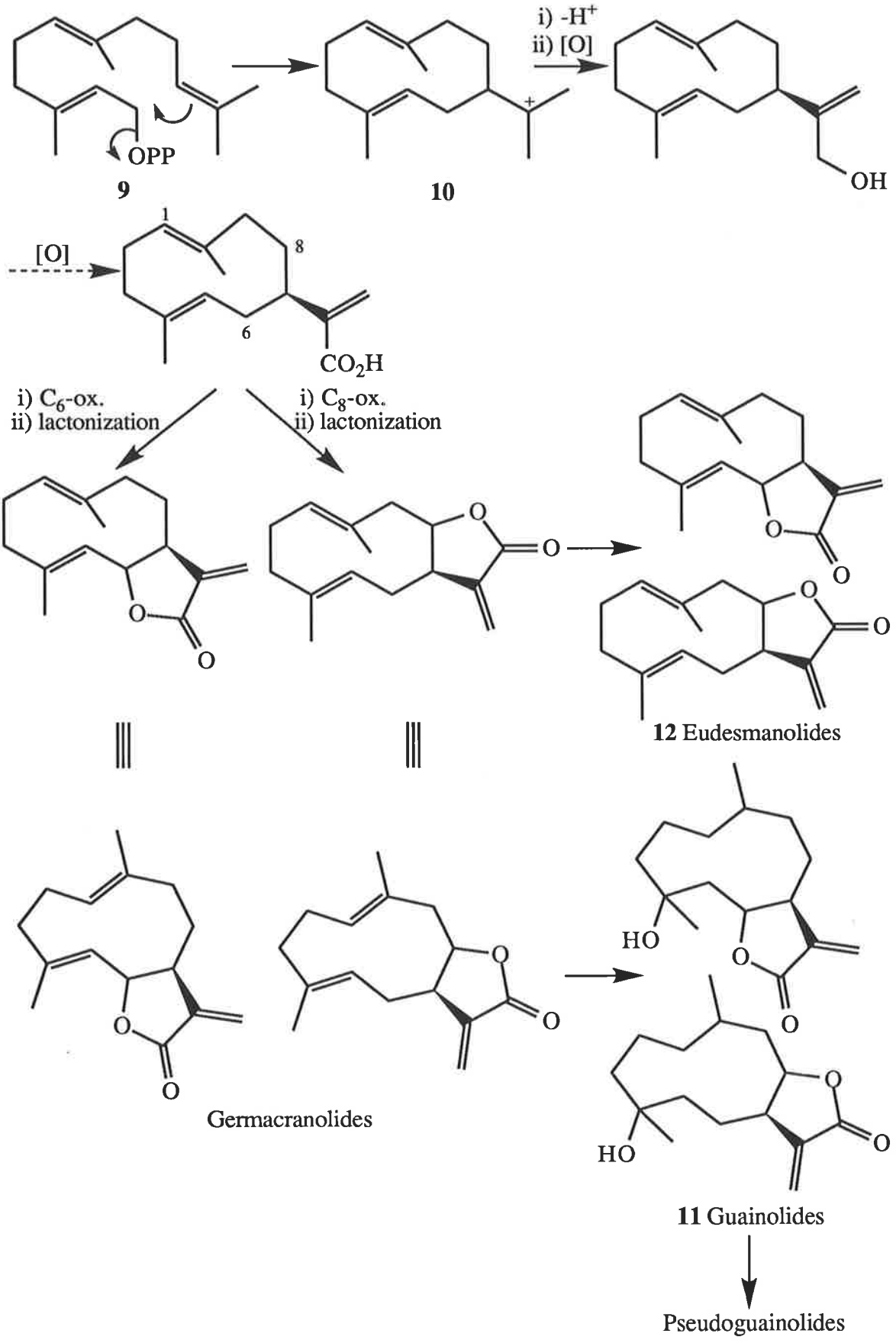
* The oxidation steps depicted in **Scheme 1.1** are not fully understood.

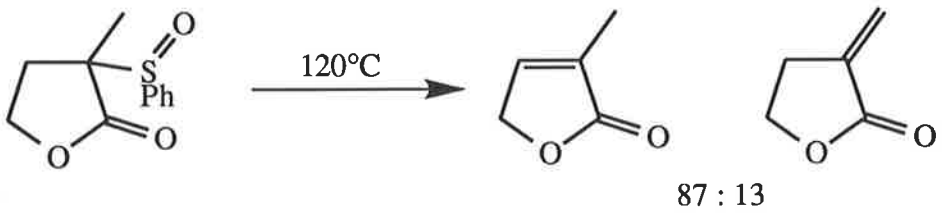

i) -H+
ii) [O]
OPP
OH
9
10
[O]
1
8
6
CO2H
i) C6-ox.
ii) lactonization
i) C8-ox.
ii) lactonization
O
12 Eudesmanolides
Germacranolides
HO
11 Guainolides
Pseudoguainolides

Scheme 1.1

1.3.1 α-Methylenation of preformed γ-butyrolactone rings

The late incorporation of an α-methylene group into a preformed γ-butyrolactone is a procedure that has found common use.[23a,b] This may occur through the introduction of a leaving group α to the carbonyl group with the double bond being formed by subsequent elimination.

An excellent example of this procedure is the thermal elimination of α-sulfinyl or α-seleno lactones which have been prepared with ease by trapping of enolates with, for example, diphenyl disulphide or selenide. However, a complication with this method is the possible formation of an endocyclic double bond which also competes (**Scheme 1.2**).[24]



87 : 13

Scheme 1.2

To avoid formation of an unwanted endocyclic bond, a one-carbon building block is introduced that contains a leaving group that will be β to the carbonyl group. Generation of the lactone enolate is followed by trapping with formaldehyde (or formic esters) and subsequent reduction to give a hydroxymethyl derivative. The hydroxy group is then converted to either a tosylate or mesylate with elimination occurring readily in the presence of base.

These α-methylenation methodologies have served as an entry point to the synthesis of a wide variety of sesquiterpene lactones.* Examples of these methodologies include the synthesis of the guaianolides (±)-bigelovin **13** (**Scheme 1.3**)[25] and (±)-damsin **14** (**Scheme 1.4**).[26]

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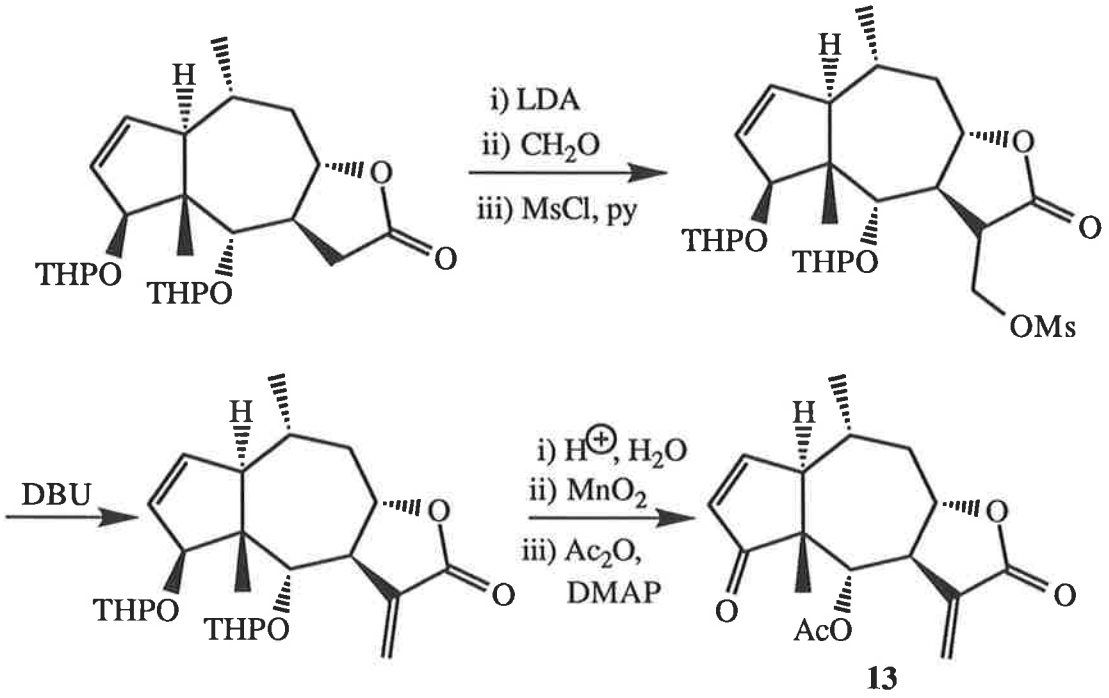
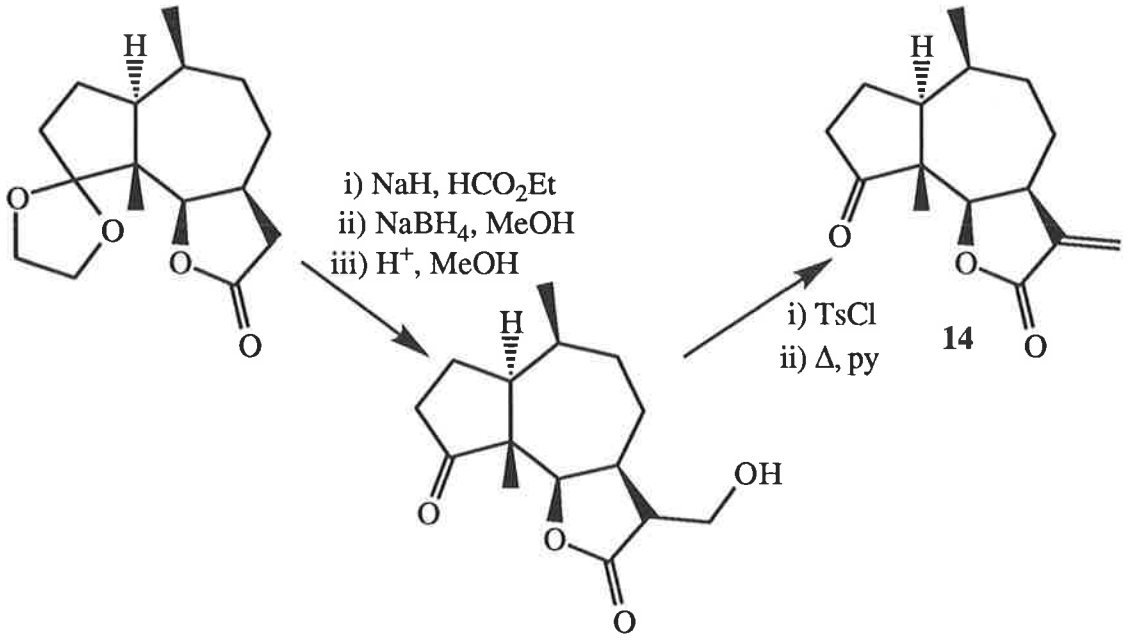
* These have included (±)-ambrosin, (±)-psilostachyin C, (±)-eriolangin and (±)-compressanolide.



Scheme 1.3

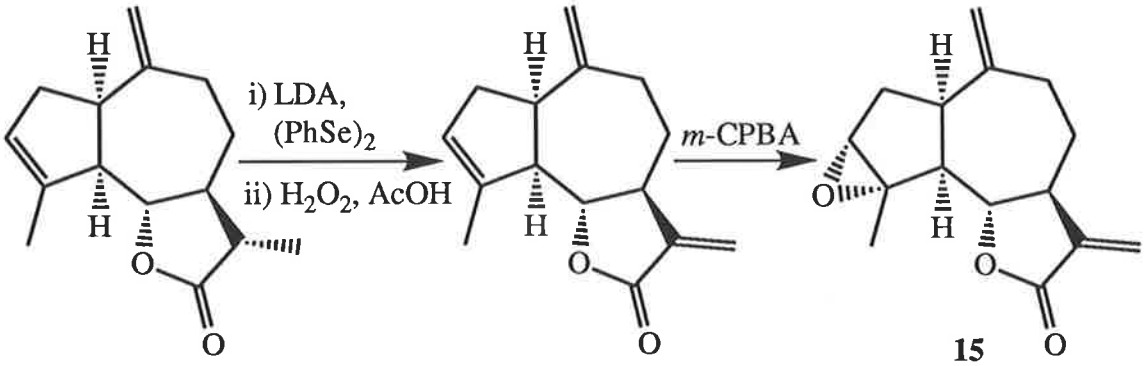


Scheme 1.4

Furthermore, the α-methylene unit may be introduced through the use of a $^+NR_3$ leaving group in a Hoffman-type elimination sequence. This group may be introduced *via* initial generation of an enolate and trapping with dimethyl(methylene) ammonium salts followed by quaternization of the nitrogen. Elimination then furnishes the double bond. This

general method has been employed in the synthesis of (±)-protolichesterinic acid[27a], (±)-eriolanin[27b] and vernolepin.[27c]

Sulfur (as sulfonates, sulfides and sulfoxides) and especially selenium (as selenoxides) have also shown to act as good β-leaving groups. A phenylseleno group may be incorporated by the alkylation of the intermediate enolate and subsequently eliminated to give the alkene.[29] Such a procedure was used to synthesize estafiatin **15** (**Scheme 1.5**).[28]

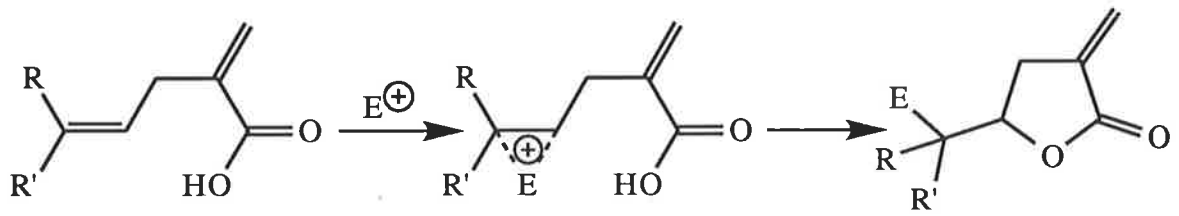


Scheme 1.5

1.3.2 Cyclizations of precursors incorporating an intact olefin unit

1.3.2.1 Cyclizations of α-methylene-γ,δ-unsaturated acids

A general approach to α-methylene γ-butyrolactones has involved the treatment of α-methylene-δ,γ-unsaturated acids or their derivatives **16** with suitable electrophiles. The lactones are derived from carboxyl group participation with the formed onium centre (**Scheme 1.6**).



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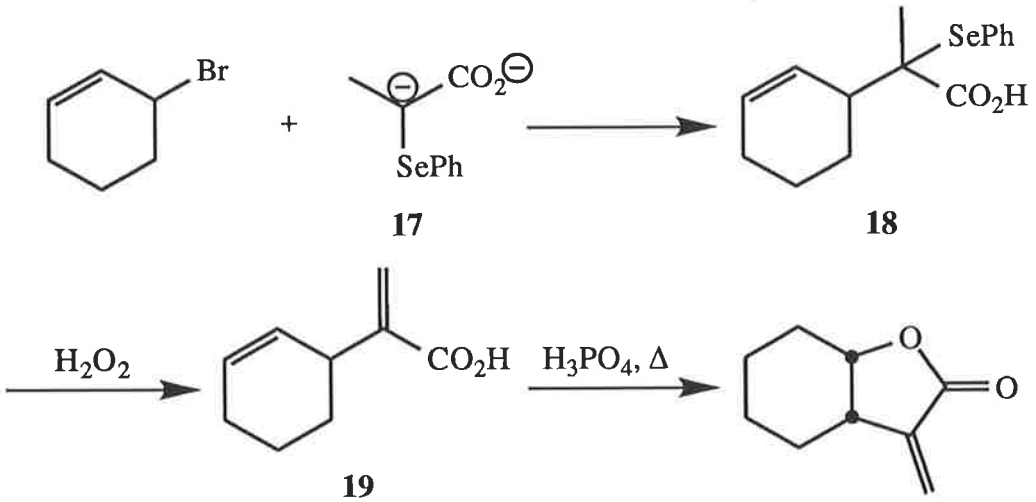
Scheme 1.6

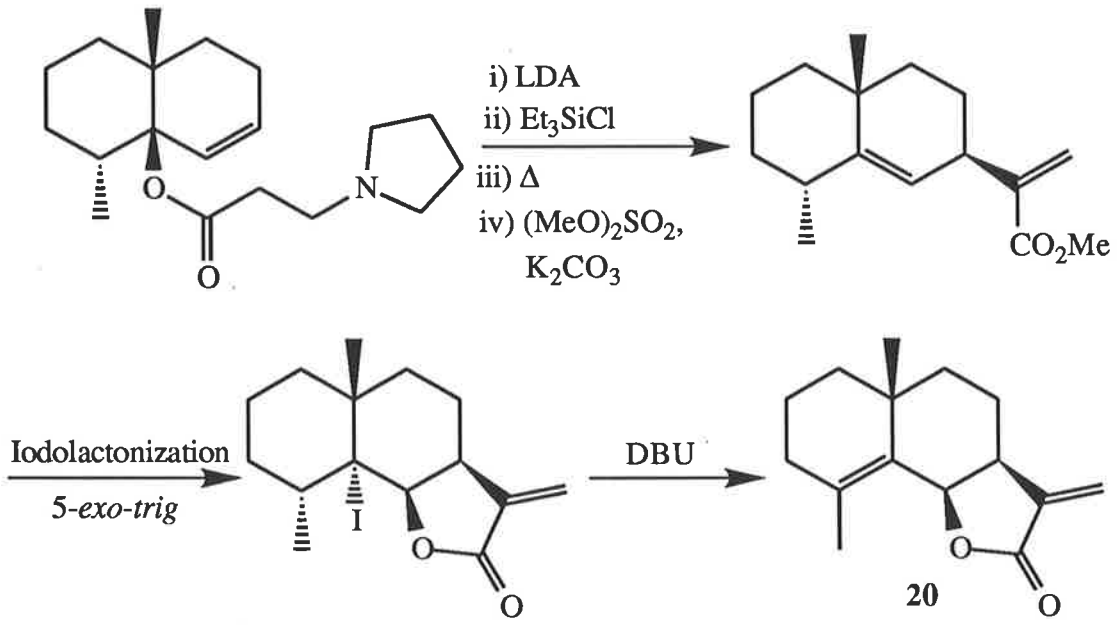
Intermediate **16** has often been produced through the transfer of an acrylate synthon, *via* its enolate, to an allylic substrate. However, because of the inherent instability of acrylic esters to basic conditions, the double bond is predominantly "masked" by adding groups at the α- or β-positions that are susceptible to facile elimination.

A representative procedure by Petragnani *et al.*[29] involved the reaction of a phenylselenoalkanoic acid dianion **17**, as a masked acrylate, with an allylic bromide. α-Methylene-γ,δ-unsaturated acid **19** was then obtained, by oxidative *syn*-elimination of the intermediate selenide **18**, which underwent subsequent lactonization (**Scheme 1.7**).



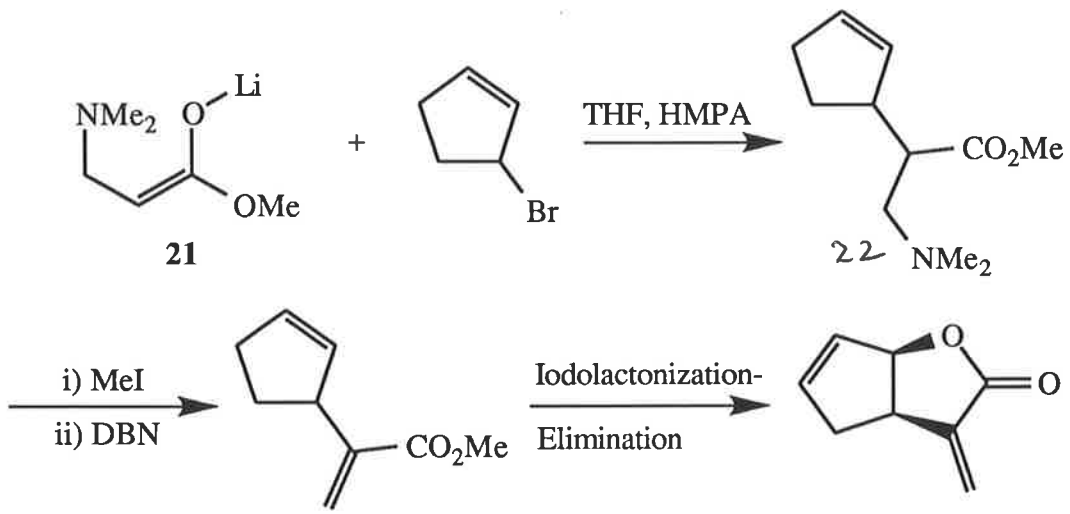
Scheme 1.7

An approach of interest involves the Claisen rearrangement of masked allylic acrylates. Still *et al.*[30] began with an allylic alcohol and used a triethylsilyl ketene acetal rearrangement (the Ireland variant) to synthesize a functionalized acrylic ester in one step. This procedure, followed by lactonization-elimination, furnished (±)-frullanolide **20** (**Scheme 1.8**).



Scheme 1.8

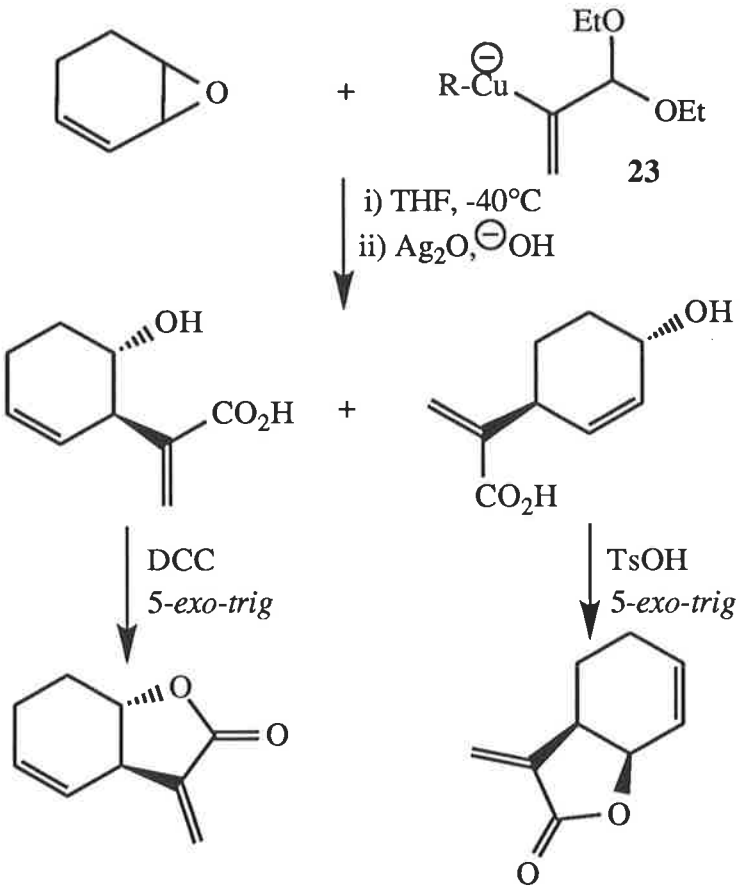
Helquist *et al.*, have used the acrylic building block lithio methyl-3-(dimethylamino) propanoate **21**, available from the Michael addition of dimethylamine to methyl acrylate, and reacted this with an allylic bromide to yield a masked α-methylene γ-δ-unsaturated ester **22**. The amino group was subsequently eliminated and the ester finally subjected to iodolactonization-elimination (**Scheme 1.9**).



Scheme 1.9

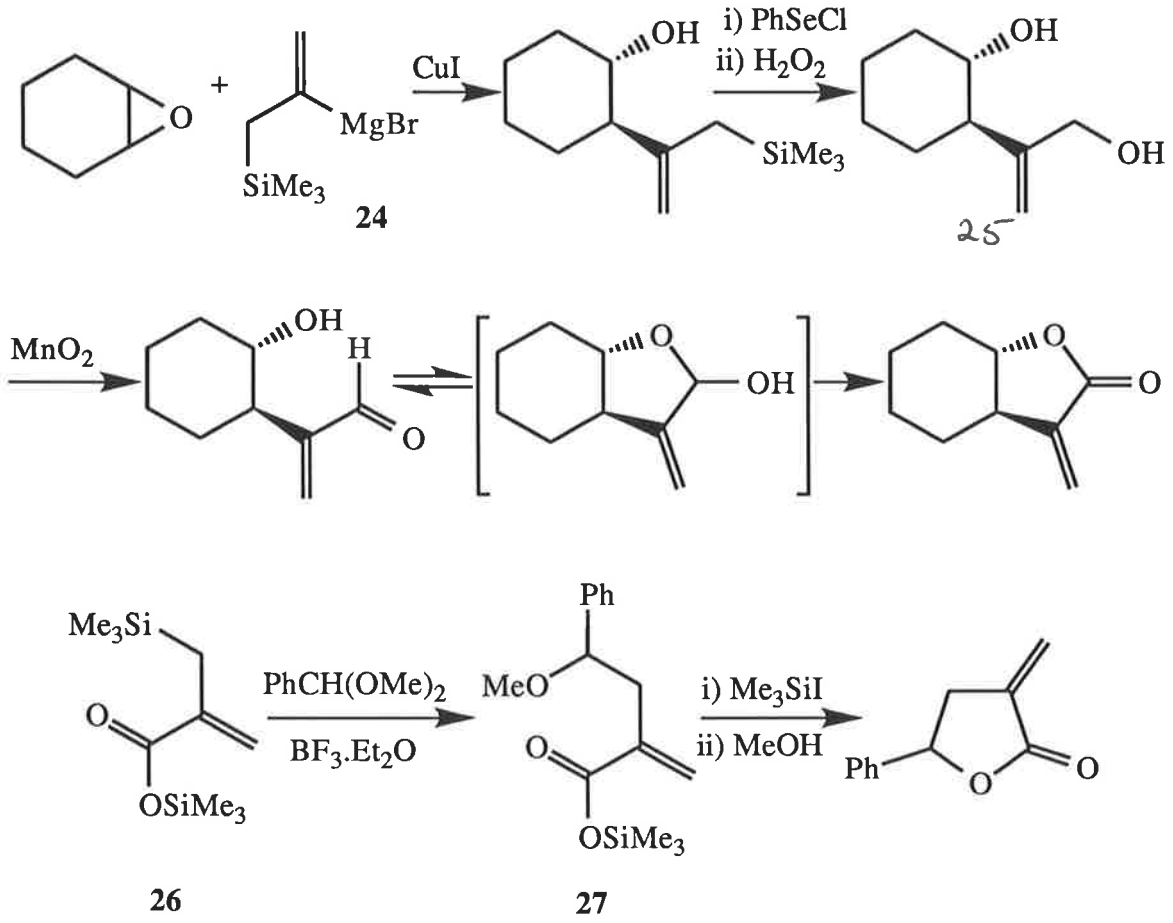
1.3.2.2 Cyclizations of 4-hydroxy-2-methylene butyric acids

Another common method to synthesize α-methylene γ-butyrolactones involves the cyclization of homoallylic alcohols or their derivatives in which the methylene group is part of an acrylic or masked acrylic acid. Such homoallylic alcohols have been often prepared in the past from the *trans*-diaxial opening of epoxides with malonic ester enolates[32] and more recently through the use of masked acrylate synthons such as α-phenylthio- and α-phenylselenopropanoic acid dianions or their ester enolates.[29] An expansion of this was by Marino *et al.*[33] who used vinyl cuprate **23** as an acrylic acid anion equivalent to open epoxy cyclohex-3-ene to generate two isomeric alcohols. Following oxidation to their respective acids, cyclization yielded the *cis*- and *trans*-fused α-methylene lactones (**Scheme 1.10**). Related to these procedures is the addition of acrylate synthons to α-acetoxyaldehydes.[34]



Scheme 1.10

Allyl silanes, possessing a highly nucleophillic double bond, have also been shown to act as precursors to functionalized homoallylic alcohols or their derivatives. For example, Itoh *et al.*[35] reacted allylsilane **24** with an epoxide to give, after desilylation-oxidation and oxidative rearrangement, homoallylic alcohol **25**.* Oxidation with MnO_2 gave selectively an α,β-unsaturated aldehyde which ultimately cyclized to yield the lactone. In a similar manner, Sakurai *et al.*[36] has used allylsilane **26** and reacted it with an acetal to furnish the desired intermediate **27** (**Scheme 1.11**).**



Scheme 1.11

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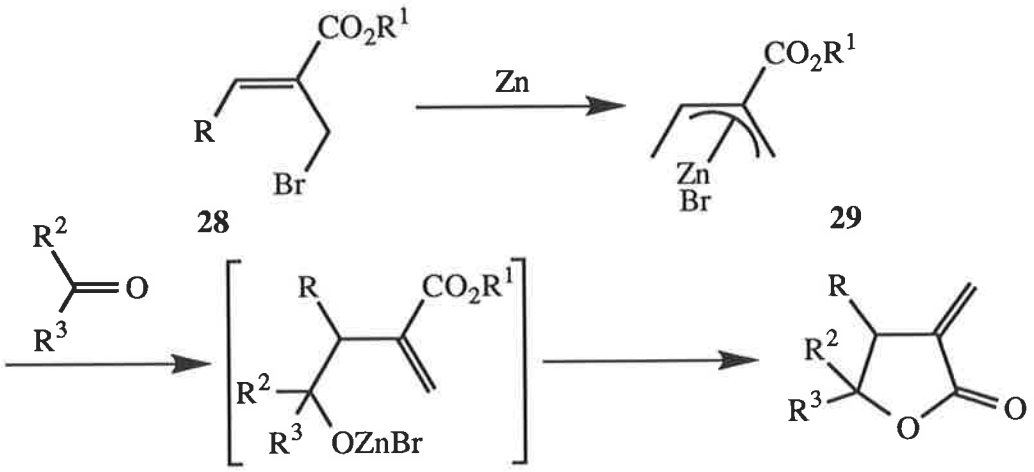
* Homoallylic alcohols such as **25** have acted as direct synthetic intermediates in a number of other routes to α-methylene γ-butyrolactones involving oxidative cyclization with MnO_2.

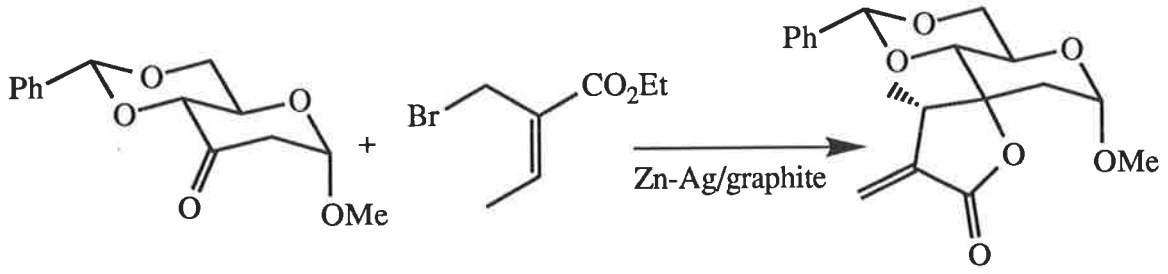
** A versatile approach of interest involves the synthesis of homallylic alcohols *via* an intramolecular Lewis acid catalyzed reaction of allylsilanes with carbonyl compounds. Such reactions are known as Hosomi reactions [see *Chapter 3* (*3.2.2*)].

A related procedure is the addition of methacrylate anion equivalents, in particular α-(bromomethyl)acrylic esters such as **28**, to carbonyl compounds which has proven to be a method of considerable importance (especially in the synthesis of structurally simple α-methylene γ-butyrolactones). An allylic bromide is treated with zinc to give an allylic metal species **29** which then couples with a carbonyl compound. This is followed by spontaneous cyclization of the intermediate alkoxide to yield the lactone (**Scheme 1.12**).*



Scheme 1.12

Recently Csuk *et al.*[37] has synthesized valuable spiroannellated carbohydrate-derived α-methylene lactones from such a reaction. Moreover, the β-position of the lactone was formed in a stereoselective manner *via* a low energy six-membered chair-like transition state (**Scheme 1.13**).



Scheme 1.13

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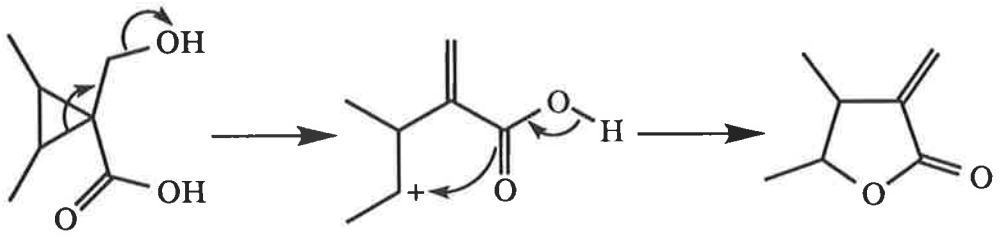
* Such reactions are known as Dreiding-Schmidt reactions

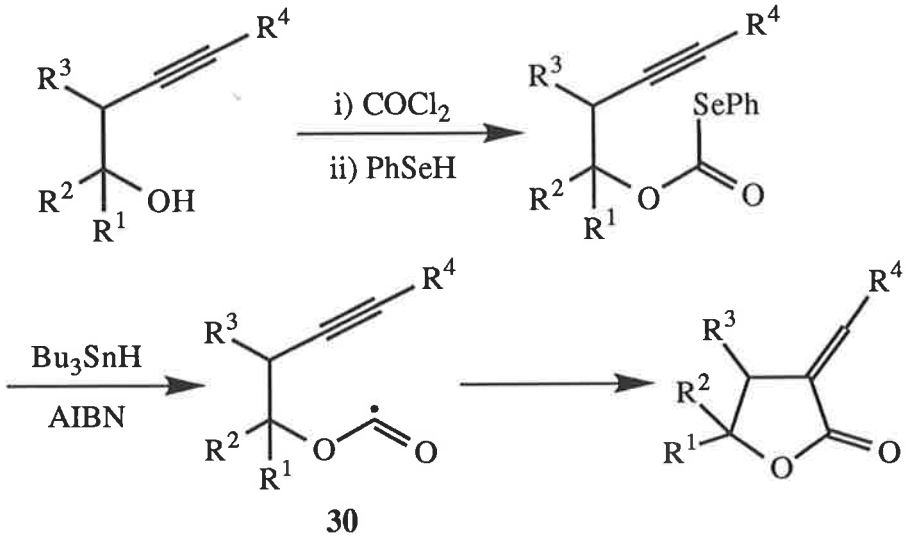
1.3.3 Miscellaneous Methods

The nature of these procedures is diverse, however, many of these are not applicable to general synthesis. Those that are include the oxidation of β-methylene furans, pericyclic reactions such as the Diels-Alder reaction and various rearrangements. An example of such a rearrangement is that which occurs with functionally substituted cyclopropanes (**Scheme 1.14**).[38]



Scheme 1.14

Carbon-carbon bonds may be generated by the reaction of carbon-centred radicals with electron-rich or electron-deficient π-systems. A recent example of this is the cyclization of phenylselenocarbonates *via* an alkoxy carbonyl radical **30** (**Scheme 1.15**).[39] Furthermore, free radical cyclization of β-bromoprop-2-ynyl ethers has readily formed β-methylene furans.[40]



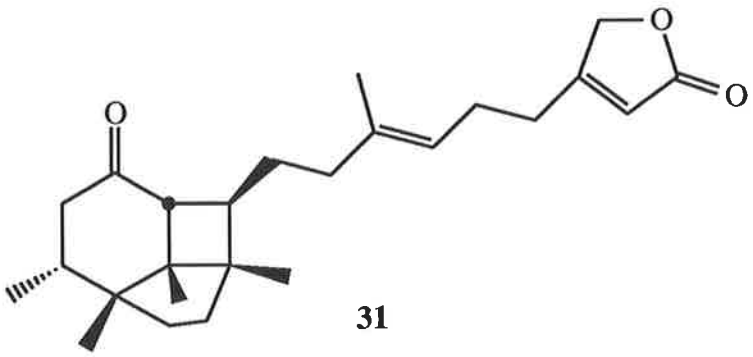
Scheme 1.15

2.0 α,β-Butenolides

2.1 Occurrence and biological activity

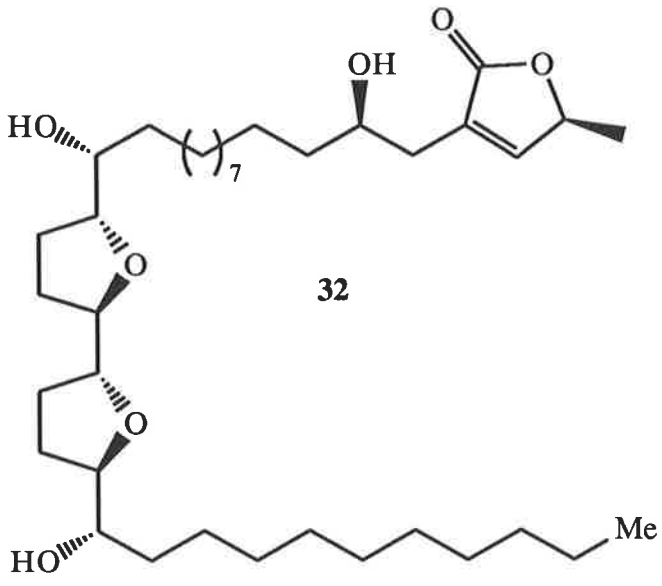
α,β-Butenolides (unsaturated five-membered lactones) frequently occur as structural features in many natural products.[41a] This ring system is widely present in the secondary metabolites of lichens, mold, fungi[41b] (e.g., patulin,[42] penicillic acid[43] or the pulvinones) and marine organisms. Examples of the latter include the carotenoid pigments of phytoplankton (e.g., peridinin), the polyhalogenated algal metabolites known as fimbrolides and the antibiotic strobilin.

The α,β-butenolide moiety is frequently encountered in the many complex sesquiterpenes of the family *Compositae* and in the steroidal glycosides of the families *Ranunculaceae*, *Liliaceae*, *Scrophulariaceae* and *Apocyanaceae*.[41] This unit is also found in diverse species such as sponges (e.g., the secondary metabolite lintenolide **31** from *Cacospongia* cf. *linteiformis*)[44] corals,[45] butterflies[46] and insects.[47] In the latter species they appear to act as sex pheromones and significant chemical defence weapons.



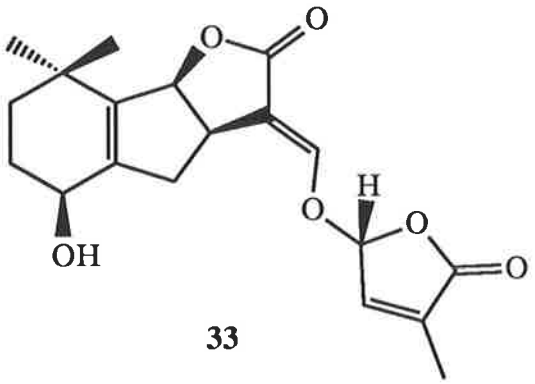
31

A number of α,β-butenolides exhibit cytotoxic and/or tumour inhibiting properties toward a variety of cancers. The presence of this functionality has shown to confer an enhancement in cytotoxic activity.[8b] A potent antitumour natural product isolated from *Annonaceaous acetogenins*, (±)-bullatacin **32**,[48] has shown both remarkable levels of cytotoxicity against human tumour cell lines and *in vivo* antitumour activity. The mode of action occurs through interference with mitochondrial electron transport processes by interaction with NADH-ubiquinone reductase.[49]



32

A variety of compounds exhibiting other interesting biological properties include the cardiac glycosides (e.g., digitoxigenin) which have shown a remarkable propensity to reduce the frequency, but increase the amplitude of the heart beat.[46] Others have found applications as insecticides,[50] fungicides,[51] herbicides[52] and plant and seed growth regulators.[53] For instance, strigol **33** is a highly potent seed germination stimulant for the harmful semi-parasitic weeds of the genera *Striga* and *Orobanche* which reduce the yields of graminaceous and legume crops respectively.[54]



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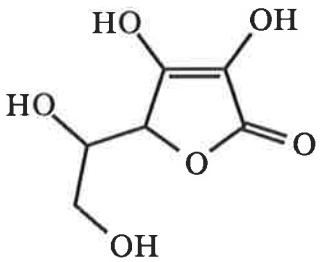


34

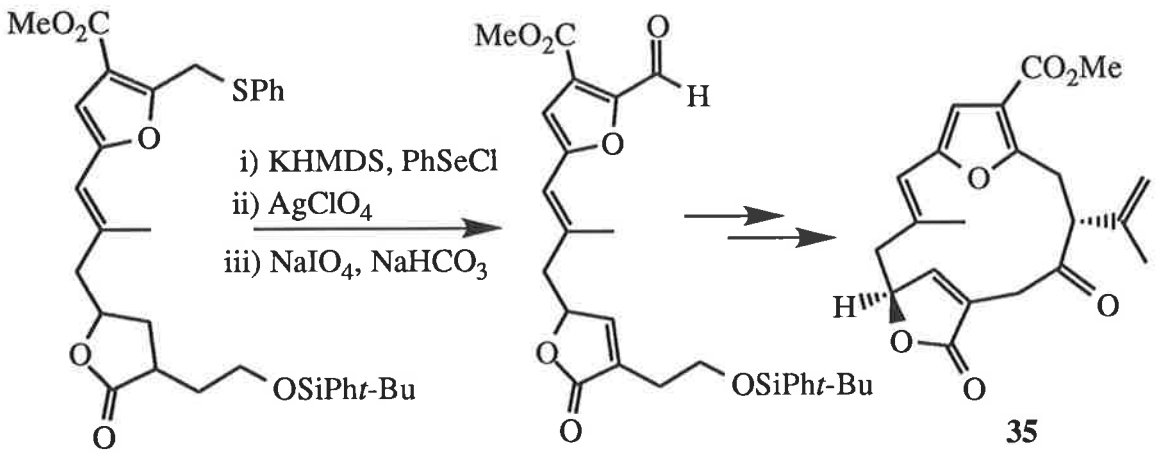
Probably the most physiologically important α,β-butenolide is vitamin C **34** which is a member of an important subclass of butenolides characterized by a hydroxyl group at the β-position (commonly known as tetronic acids). Such compounds have also been shown to act efficiently as food intake control substances.[55]

2.2 Synthesis

Of recent importance is the fact that α,β-butenolides have been shown to be remarkably versatile chiral building blocks in asymmetric synthesis. As a consequence of this, and their prominence in nature, considerable effort has been made in the development of generally applicable routes for the construction of this class of compound.[56]

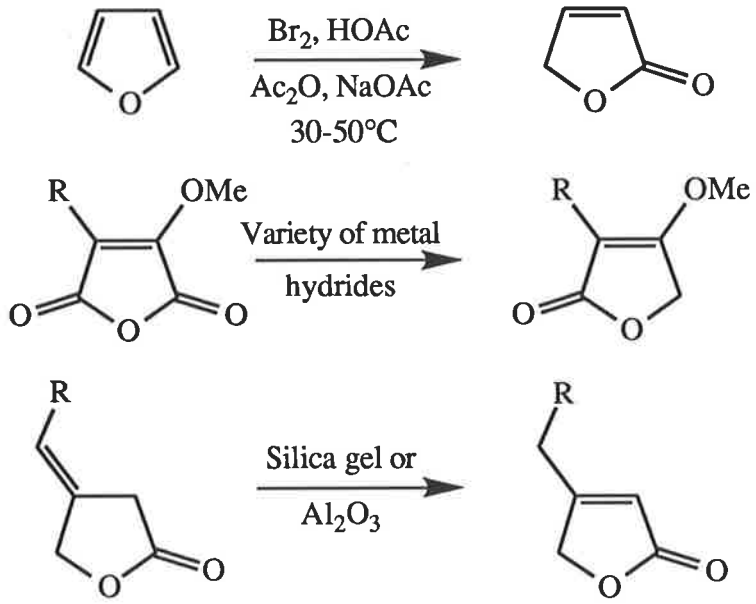
2.2.1 Elaboration of preformed γ-butyrolactone rings

Traditionally the method of choice for the synthesis of α,β-butenolides has been the elimination of a heteroatom at either the α- or β-position of a preformed lactone ring. As for their exocyclic counterparts, methods based upon the elimination of an organosulphur substituent are well documented.[57] Again the elimination of a β-alkylsulfinyl carbonyl compound is preferred by virtue of the regioselective generation of the double bond. Likewise selenoxides have been employed as leaving groups to generate unsaturation,[58] this having recently been utilised by Paquette *et al.*[45] in the synthesis of acerosolide **35** (**Scheme 1.16**).



Scheme 1.16

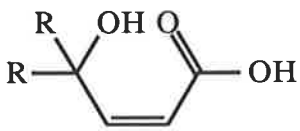
A number of other elaborative methods exist which include the oxidation of furan derivatives,[59] the partial reduction of maleic anhydrides[60] and the isomerization of ylidene γ-butyrolactones[61a] (an example being the synthesis of freelingnite[61b]) (**Scheme 1.17**).



Scheme 1.17

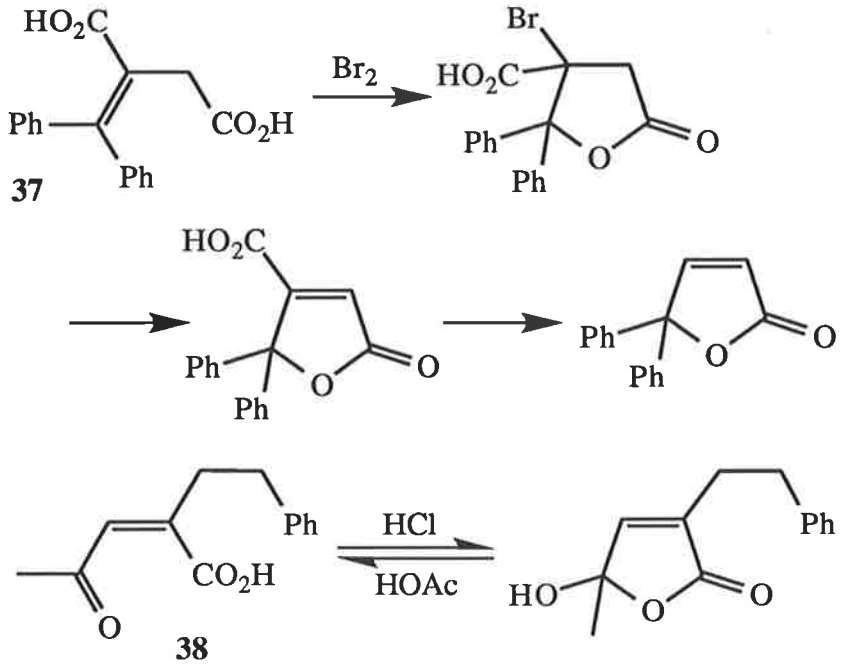
2.2.2 Cyclizations of precursors incorporating an intact olefin unit

Most known approaches to α,β-butenolides, involving acyclic precursors, can be considered to incorporate the cyclization of allylic alcohols or their derivatives **36** in which the double bond is part of an acrylic or masked acrylic acid.



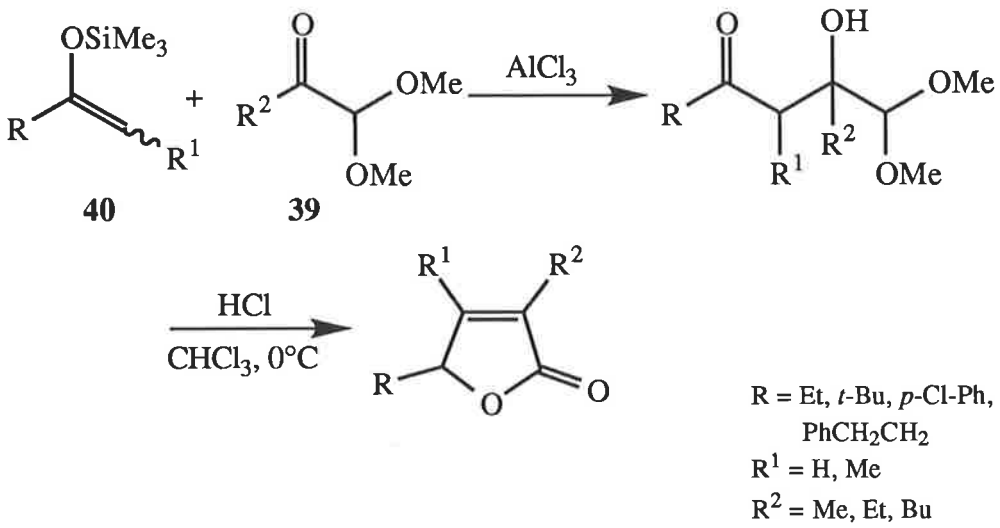
36

The synthesis of compounds of the type **36** can generally be accomplished by the condensation of suitable carbonyl compounds with the appropriate carbanion.[56a] Representative examples are the Stobbe condensation of diethyl succinate and benzophenone to give **37**[62] and the condensation of pyruvic acid derivatives with carbonyl compounds to give, for example, **38**.[63] The corresponding α,β-butenolides were obtained through the cyclizations outlined in **Scheme 1.18**.



Scheme 1.18

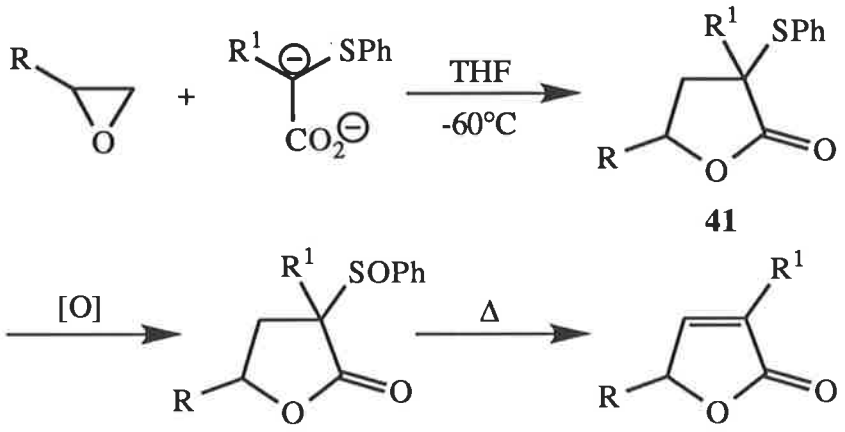
A recent example by Tanabe *et al.*[64] was the use of a crossed-Aldol condensation in the construction of 3,5-di- or 3,4,5-trisubstituted α,β-butenolides. α-Keto dimethyl acetal **39** underwent condensation with enol ether **40** to lead to an adduct which then cyclized to the required lactone (**Scheme 1.19**).



Scheme 1.19

Furthermore, allylic alcohols have been produced from the opening of epoxides by masked acrylate synthons such as α-phenylthio- or α-phenylselenopropanoic acid dianions or

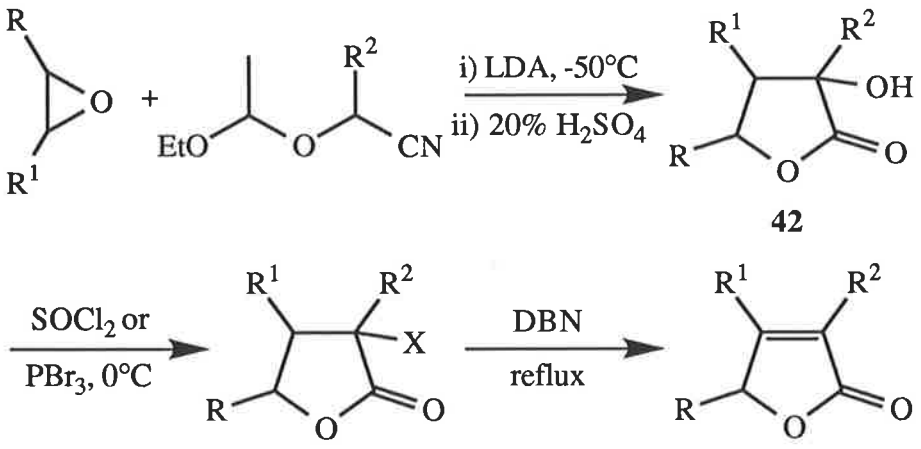
ester enolates. For example, Uda *et al.*[65] reported that reaction of an epoxide with the dianion of phenylthiopropanoic acid derivatives gave thiobutyrolactone **41** that was subsequently subjected to oxidation-elimination (**Scheme 1.20**). This methodology was exemplified in the synthesis of the antibiotic lepiochlorin.[66]



R = Me, *n*-Bu, Ph; R^1 = H, Me, Et

Scheme 1.20

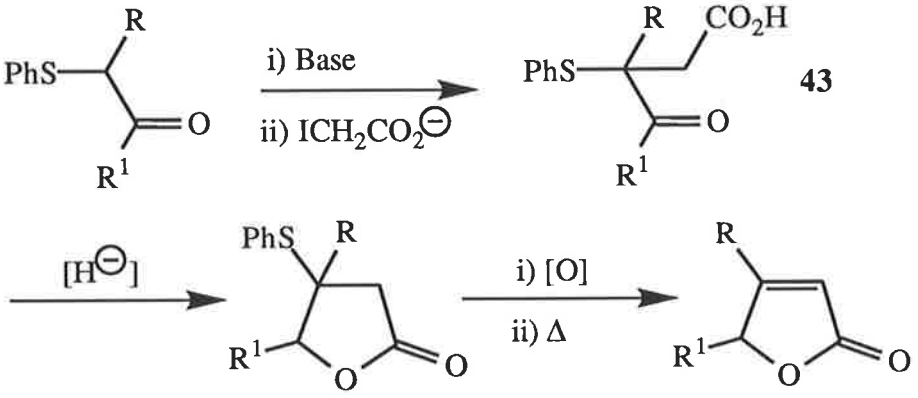
Epoxides have also been opened by cyanopropanoic ester and protected cyanohydrin anions. Tamariz *et al.*[67] has reported a recent example of the latter case where the *in situ* generated anion reacts to furnish, following acid hydrolysis, the α,β-butenolide precursor **42** (**Scheme 1.21**).



R = H, Me, Ph; R^1 = H, Ph
R^2 = Me, *n*-Pr, Ph, CH_2=CH, Me, CH=CH, 2-furyl
X=Cl, Br

Scheme 1.21

Acrylate synthons have also been widely used in reactions with α-halo carbonyl compounds where such a reaction can formally be regarded as a Knoevenagel condensation. A representative procedure by Warren *et al.*[68] involves the reaction of α-phenylthioketone enolates with iodoacetate anion to give **43**. Reduction yielded the corresponding thiobutyrolactone which subsequently underwent oxidation-elimination (**Scheme 1.22**). Similarly, acrylate synthons masked as the ketene bis(trimethylsilyl)acetal group have undergone reactions with both α-chlorosulfides[69] and α-haloacetals.[70]



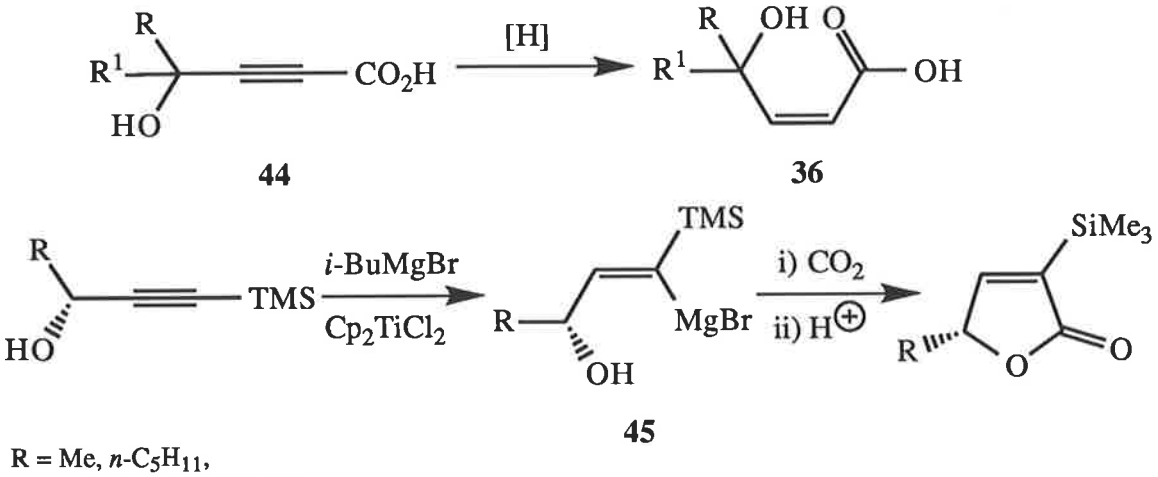
R = H, Me, Et
R^1 = Me, *t*-Bu, Ph

Scheme 1.22

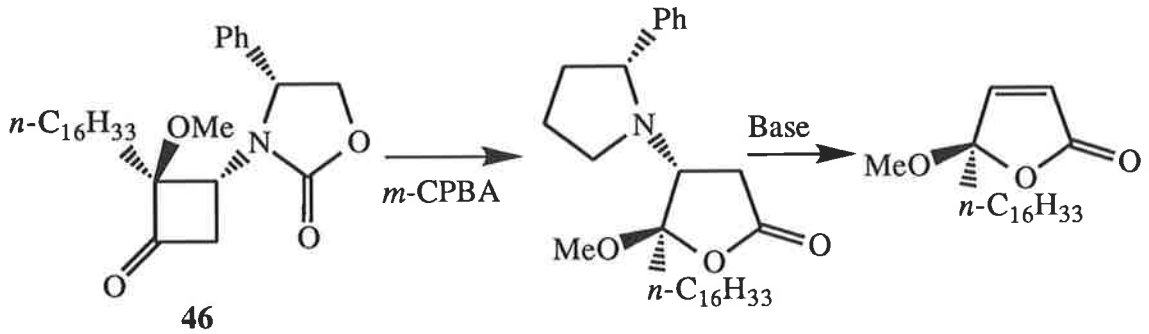
Another common method used to generate the allylic alcohol **36** is to partially reduce γ-hydroxy α-alkynoic acid **44**. Homologues of such systems have recently been produced by a hydromagnesiation reaction of γ-trimethylsilyl propargylic alcohols.[71] Subsequent reaction of intermediate **45** with carbon dioxide yielded α,β-butenolides in high optical purity (**Scheme 1.23**).

2.2.3 Miscellaneous methods

An extensive range of additional procedures exists, however many of those developed do not qualify as general methods. A very good example of a general procedure is the Baeyer-Villiger oxidation of cyclobutanones to yield the corresponding lactone. Hegedus *et al.*[72] oxidized cyclobutanone **46** to the corresponding lactone which subsequently underwent base-induced elimination to form an optically active butenolide isolated from the marine sponge *Plakortis lita* (**Scheme 1.24**).



Scheme 1.23



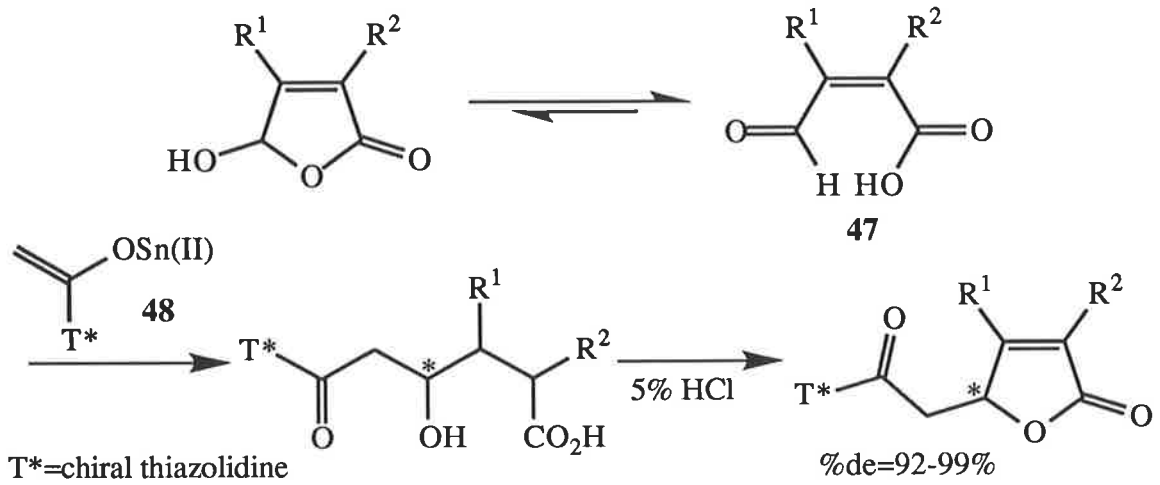
Scheme 1.24

2.3 α,β-Butenolides as chiral synthetic intermediates

Optically active butenolides have proven to be valuable chiral synthons (chirons) in the asymmetric synthesis of a wide range of biologically interesting substances related to antibiotics and carbohydrates. As a result numerous reports exist for the preparation of optically active α,β-unsaturated γ-lactones,[73] often having been obtained from natural sources such as carbohydrates, ascorbic, tartaric and glutamic acids and from synthetic compounds such as chiral α-acetylenic acids, hydroxy sulfoxides and epoxides.

A simple and general method for the asymmetric synthesis of γ-alkylated butenolides has been reported by Nagao *et al.*[73] where *Z*-olefinic aldehydic acids **47** underwent a highly diastereoselective alkylation with chiral tin(II) enolate **48**. The resultant hydroxy carboxylic

acids underwent lactonization to provide the optically pure α,β-butenolides (**Scheme 1.25**).*



Scheme 1.25

γ-Alkoxybutenolides have been widely used by Hanessian[74a], and to a lesser extent by Feringa,[74b] as enantiomerically pure functional intermediates in the stereocontrolled synthesis of cyclic and acyclic molecules bearing multiple stereocentres. In particular, Hanessian has used (*R*)- and (*S*)-4-(hydroxymethyl)-2-buten-4-olides as chiral templates to effect stereoselective functionalization at the β-position of these compounds through a 1,4-addition of a nucleophile. An illustration of this is the synthesis of the C_{17}-C_{22} subunit of the ionophore ionomycin.[75a] Utilizing a butenolide replication protocol the butenolide **49** underwent conjugate addition and further modification to eventually yield **50**. Further conjugate addition and elaboration gave the desired tetrol **51** (**Scheme 1.26**).

The butenolide template may also undergo vicinal disubstitution in a tandem alkylation approach. An enolate obtained after 1,4-addition is quenched with, for example, an alkyl halide to yield an *anti* substitution product. This approach has lead directly to a variety of

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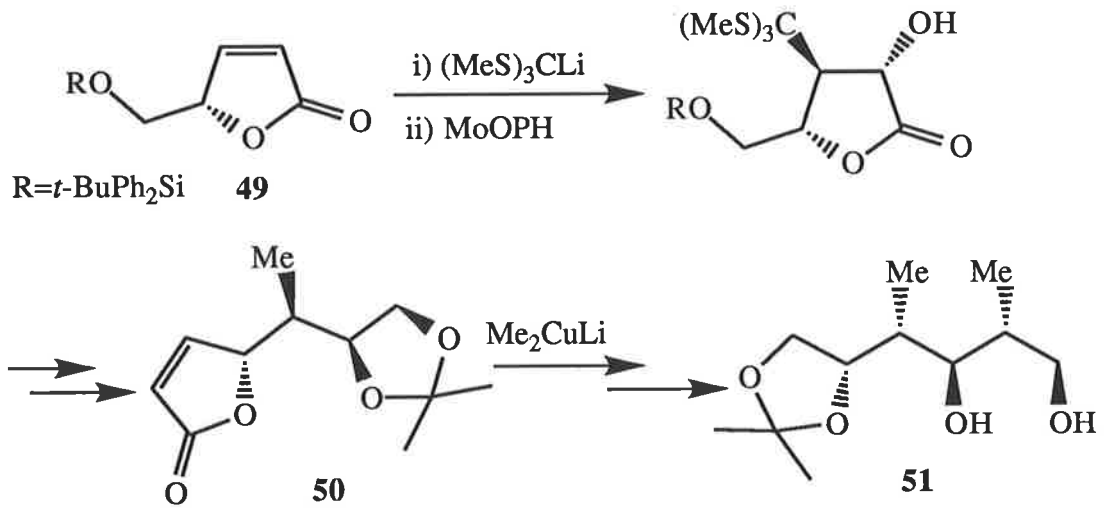
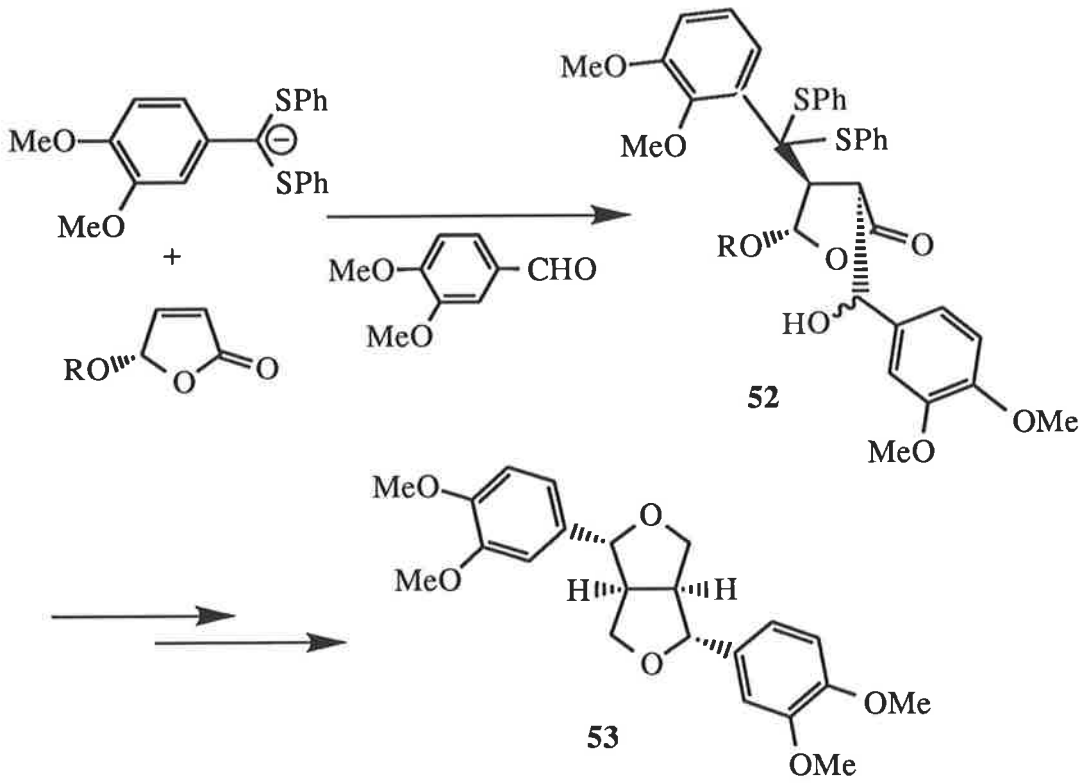
* An efficient utility of these chiral butenolides was exemplified by the synthesis of optically pure Geissman-Waiss lactone derivatives.



Scheme 1.26

useful five-carbon chirons with predisposed vicinal substitution.[75b] The introduction of two benzyl substituents into the γ-butyrolactone ring has formed the basis of a number of synthetic strategies to lignans, a class of compounds displaying a wide variety of biological activity.[76] The total synthesis of (-)-eudesmin **53** (**Scheme 30**) exemplifies this with the formation of dibenzyllactone **52** as the key step.

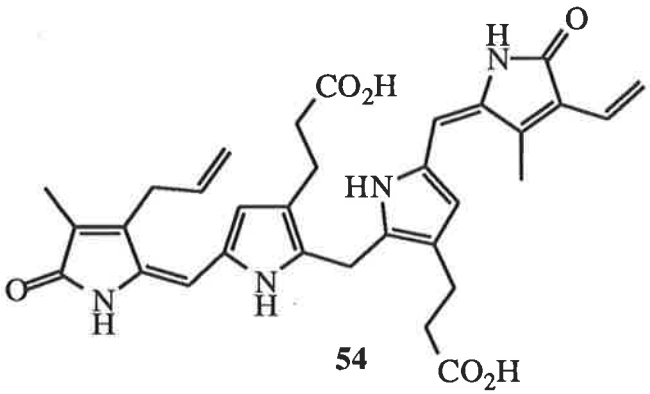


Scheme 30

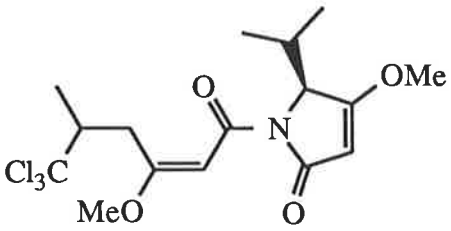
3.0 α,β-Unsaturated lactams

3.1 Occurrence and biological activity

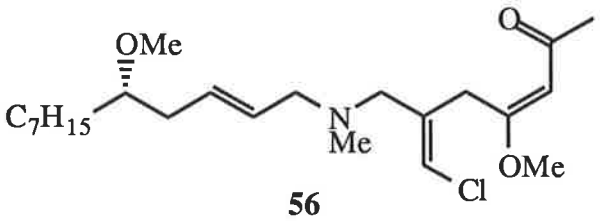
Unsaturated lactams are known to be essential constituents in a wide range of natural and non-natural products. In particular, γ-lactams have been encountered in products as diverse as the bile pigment bilirubin **54**, the sponge metabolite dysidin **55** and the marine blue-green algae irritant malyngamide A **56**. A number of 5-ylidine pyrrol-2(5*H*)ones, known as pukeleimides, have been isolated from the blue-green algae *Lyngbya majusula*. This class of compound is potentially useful as antitumour agents[77a] as are the precursors.[77b]



54



55



56

The well known β-lactam family has aquired a status of unparalleled importance in modern times. These compounds constitute a large class of broad spectrum antibiotics that effectively combat bacterial infections. β-Lactam antibiotics include penicillins, cephalosporins, carbapenems, norcardins and monobactams.[78] Such antibiotics inhibit the cross-linking of peptidoglycan strands in the final stage of bacterial cell-wall synthesis.[79] Since the peptidoglycan layer determines the shape of the bacterial cell and prevents osmotic lysis, a structurally weakened cell-wall results in rupture and death of the cell.

Penicillin resistance is often caused by the production of one of a series of enzymes known as β-lactamases.[80] These secondary defence enzymes cleave the reactive β-lactam moiety of the antibiotic and render it ineffective. Recently a number of potent β-lactamase inhibitors with the α-methylene β-lactam unit as a common structural feature have been developed (**Figure 1.1**).[81]

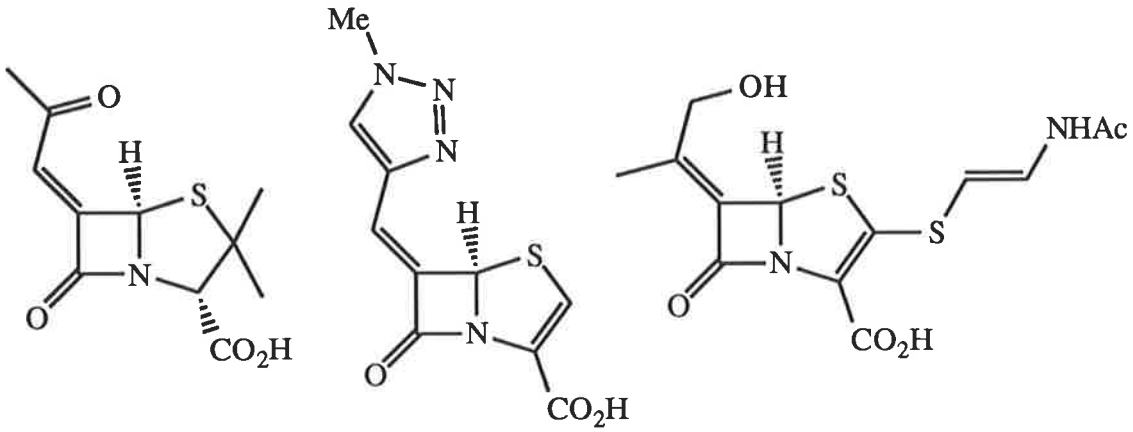
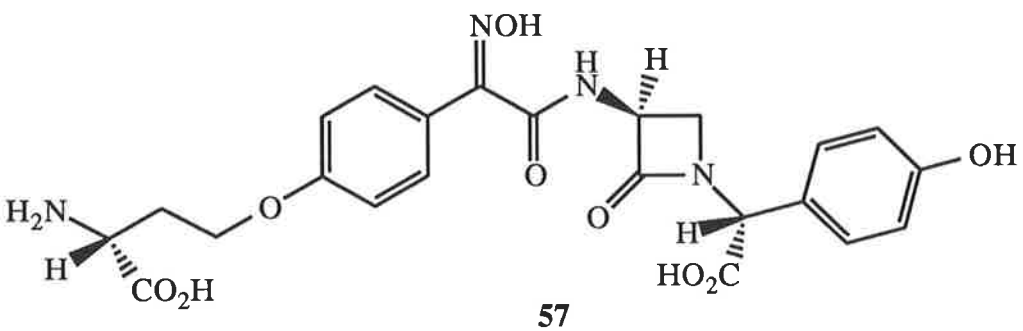


Figure 1.1

However, such inhibitors are usually only active against certain types of β-lactamase with few known inhibitors of class B zinc-containing β-lactamases.[82] These inhibitors serve to inactivate the defences of the bacteria long enough for a second antibiotic to locate its key enzymatic target. The known mechanisms of inhibition usually involve a non-reversible acylation of a serine hydroxyl at an active site.[83]

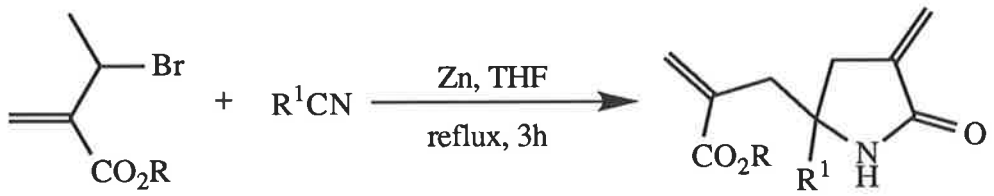
α-Methylene β-lactams have also been shown to be useful synthetic precursors for the introduction of the side chains common to the carbapenems[84] and for the synthesis of other useful targets such as α-keto-β-lactams. Monocyclic β-lactam antibiotics such as nocardicin **57** have utilized α-keto-β-lactams as intermediates in their synthesis.[85]



57

3.2 Synthesis

Methods for the synthesis of γ- and δ-lactams are scarce with few investigations existing in the literature. Although diverse, the most often utilized method has been a Reformatsky reaction of the organozinc reagent derived from 2-(bromomethyl)acrylates **58** with imines[86a] or nitriles.[86b] In the latter case, new compounds **59** resulted from two successive additions of the organozinc intermediate reagent to the nitrile function, followed by cyclization (**Scheme 1.28**). This class of α-methylene γ-lactam is reported to exhibit action against P388 leukaemia and lung tumour cells due to the presence of the two electrophillic methylene units.

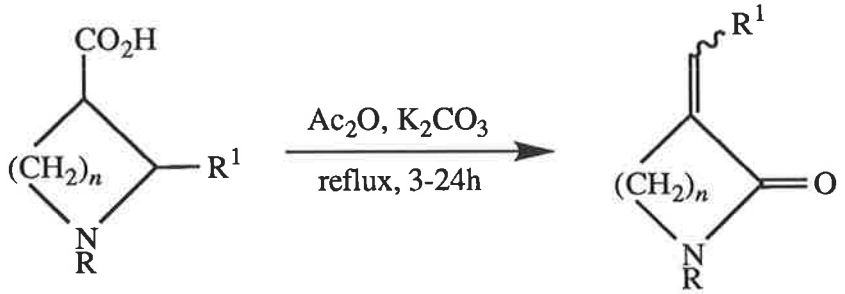


58 **59**

R = Et, *t*-Bu
R^1 = Me, *i*-Pr, Ph, $MeOCH_2$, $Me_2C{=}C(CO_2Et)$, 3,4,5-$(MeO)C_6H_2$

Scheme 1.28

A general rearrangement reaction has been reported by Rapoport *et al.*[87] where cyclic β-amino acids **60** were converted to α-methylene lactams upon heating with acetic anhydride (**Scheme 1.29**).



60

n = 1,2,3
R = Me, *i*-Pr, Bn, CH_2Bn
R^1 = H, Me, CO_2H, CO_2Me

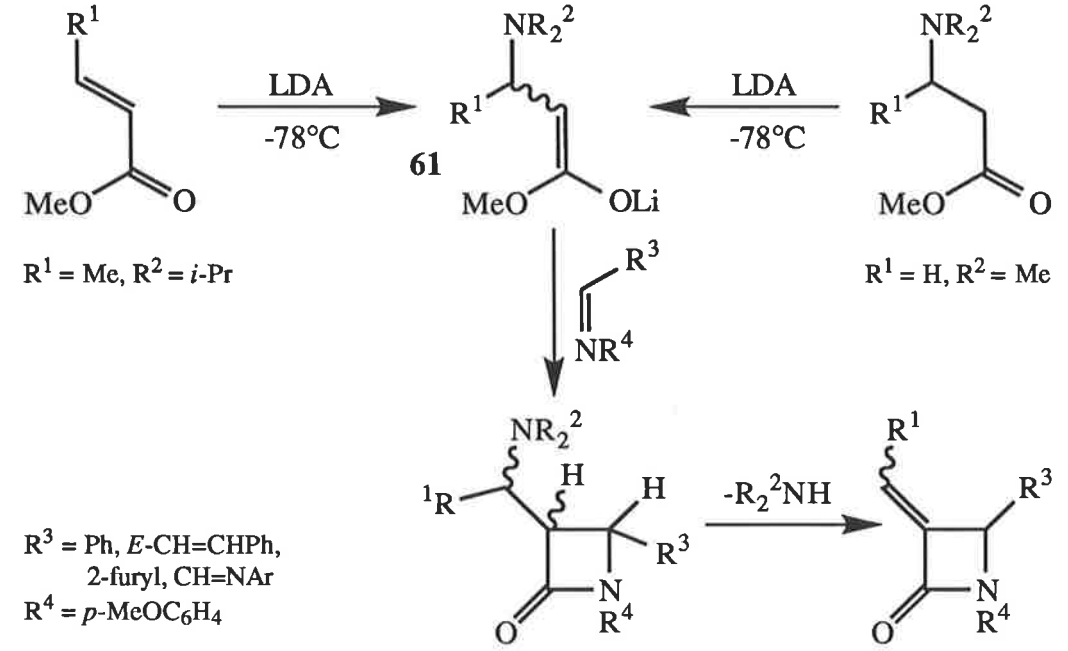
Scheme 1.29

Additional methods have included the α-elimination from a preformed lactone of an organoselenide or sulfur substituent to furnish a variety of α,β-unsaturated bicyclic lactams.[88a] Such compounds have shown to be valuable substrates for asymmetric conjugate additions,[88b] cycloadditions[88c] as well as palladium-catalyzed Stille and Suzuki couplings.[88d] Furthermore, the reaction of isocyanates with *ortho*-manganated acetophenones has yielded 3-alkylidine phthalimides,[89] core units of a number of isoindole derived alkaloids.

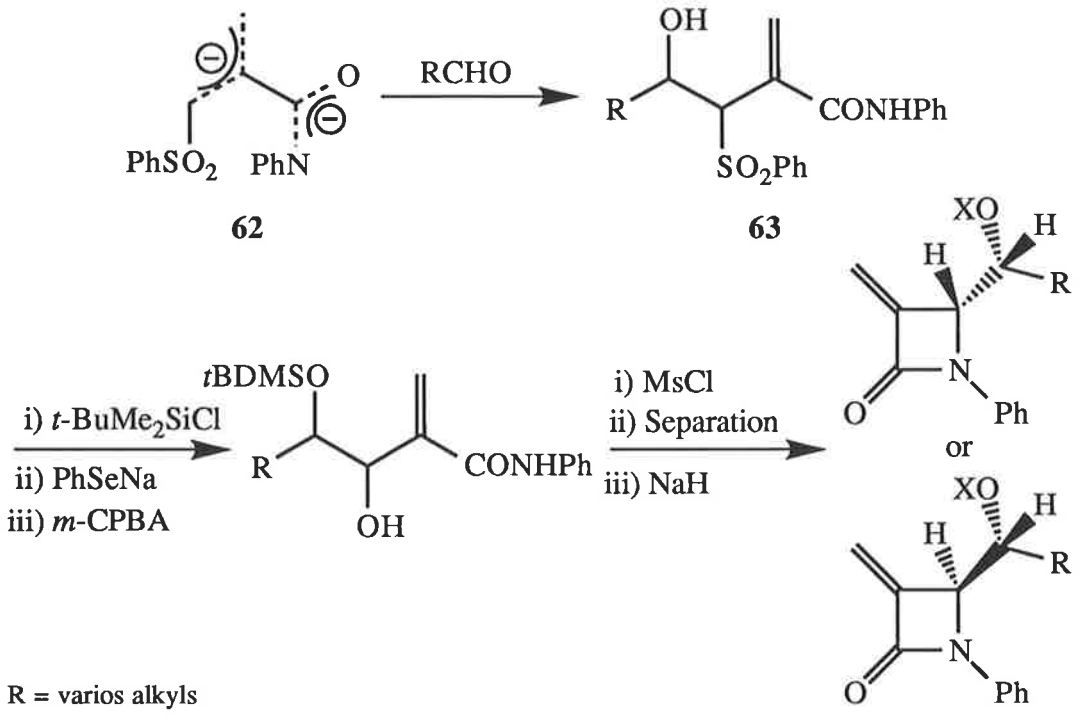
Due to the pharmacological importance of β-lactam antibiotics routes to their synthetic preparation are numerous. These methodologies can generally be divided into either [2+2] cycloadditions, intramolecular cyclizations, carbene insertion reactions or ring expansion/contractions. However, methods for the synthesis of α-methylene β-lactams are distinctly less varied and abundant.

Typical procedures have utilized α-methylenation of preformed β-lactam rings,[90] the addition of chlorosulfonyl isocyanate to functionalized allenes[84] or reactions *via* acrylamide or masked acrylamide units. Two representative procedures involving the use of α-acrylate synthons have been reported by Barrett *et al.*[91] *via* a Shapiro reaction and Alcaide *et al.*[92] In the latter case, lithium β-(N,N-dialkylamino)ester enolates **61** were obtained by either the conjugate addition of LDA to methyl crotonate or by treating the related β-aminoester with LDA. This intermediate enolate reacted with imines and, following deamination, gave the corresponding α-methylene β-lactams (**Scheme 1.30**).

A preparation of interest has been reported by Tanaka *et al.*[93] involving the regio- and stereoselective substitution of carbanions of the form **62** derived from α,β-unsaturated amides. Alkylation thus gives hydroxyl carboxamide **63** which is then protected with a concomitant [2,3]-sigmatropic rearrangement occurring to convert the sulfonyl group to a hydroxy function. Protection to the mesylate is then followed by separation of the resultant diastereomers and cyclization (**Scheme 1.31**).



Scheme 1.30



Scheme 1.31

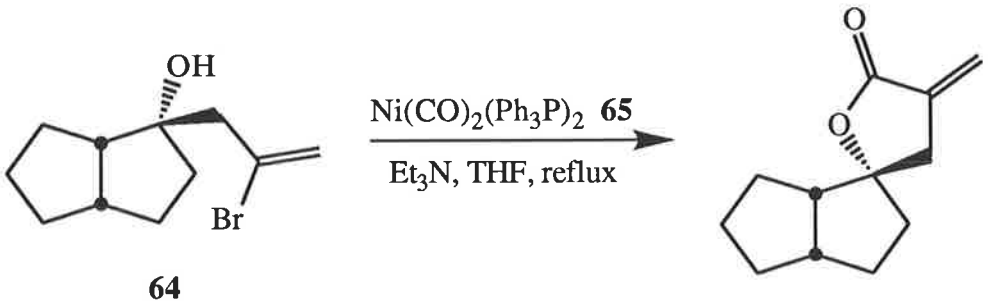
4.0 Transition metal-catalyzed syntheses of α,β-unsaturated heterocycles

An attractive and intensively studied approach to the synthesis of unsaturated five-membered lactones is through the use of transition-metal catalyzed intramolecular

carbonylation reactions. Using zero-valent nickel and in particular palladium catalysis, a number of clean, general and facile syntheses to this broad group of compounds have been developed.[94]

4.1 Intramolecular carbonylative coupling of hydroxy or amino vinyl halides

Since Corey and Hegedus first developed the base-promoted carbonylation of vinyl and aryl halides using nickel carbonyl in 1969,[95] hydroxy substituted vinyl halides have been widely used as precursors in an intramolecular version of this reaction to yield α-methylene γ-butyrolactones. Semmelhack *et al.*[96] and Matsuda *et al.*[97] utilized 3-bromohomoallylic alcohols in a nickel-induced reaction with stoichiometric nickel tetracarbonyl or bis(triphenylphosphine)dicarbonyl nickel **65**. Trost *et al.*[98] similarly produced the requisite alcohol **64** by joining a functionalized allyl silane to a carbonyl compound. Subsequent carbonylation yielded a tricyclic spiro-α-methylene γ-lactone stereoselectively (**Scheme 1.32**).

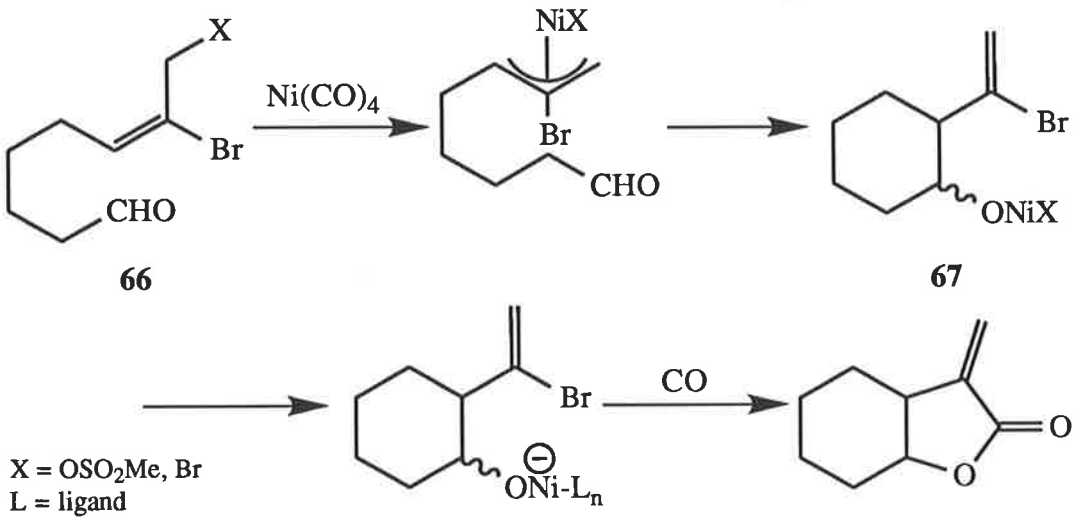


64

Scheme 1.32

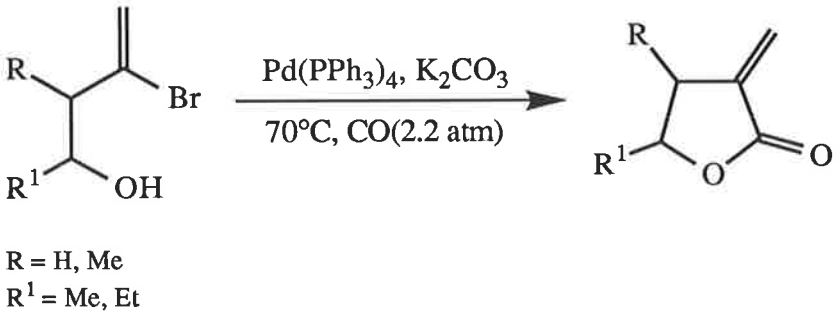
A variation of the above procedure employs the allylic system **66** which is first activated as a π-allyl nickel complex and cyclized with the aldehydic function to **67**. Nickel tetracarbonyl then functions as a carbonylating agent to form the α-methylene γ-butyrolactone (**Scheme 1.33**).[99] A more elaborate application of this procedure was used in the synthesis of the sesquiterpene lactone (±)-frullanolide.[100]

However, due to the inherant volatility and toxicity of nickel carbonyl catalysts, palladium catalysts have generally replaced these reagents. Stille *et al.*[101] provided the



Scheme 1.33

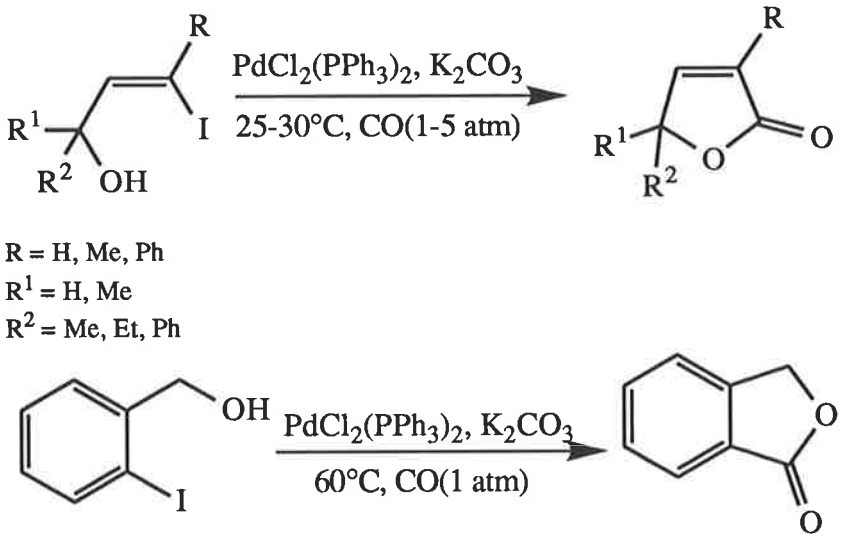
archetypal example through the use of 3-bromohomoallylic alcohols in a palladium-catalyzed carbonylation reaction to α-methylene lactones (**Scheme 1.34**). Whereas Ban *et al.*[102a] has used the more reactive 3-iodo analogues to produce not only five-, but also six- and seven-membered α-methylene lactones.



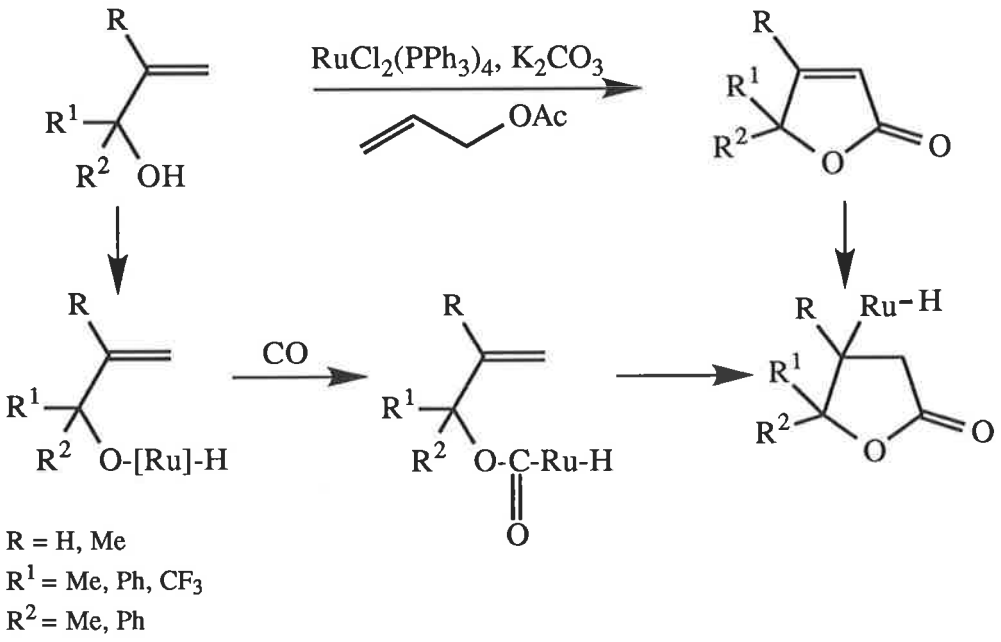
Scheme 1.34

In a similar manner α,β-butenolides and phthalides have been synthesized from functionalised allylic alcohols and *ortho*-halobenzyl alcohols respectively (**Scheme 1.35**).[103]

Recently, in a related procedure, Watanabe *et al.*[104] have utilized allylic alcohols in a novel oxidative carbonylation sequence using ruthenium catalysis. **Scheme 1.36** shows a tentative mechanism in which 1,1-disubstituted allylic alcohols oxidatively added to the active ruthenium with insertion of carbon monoxide followed by β-elimination to generate the α,β-butenolide.

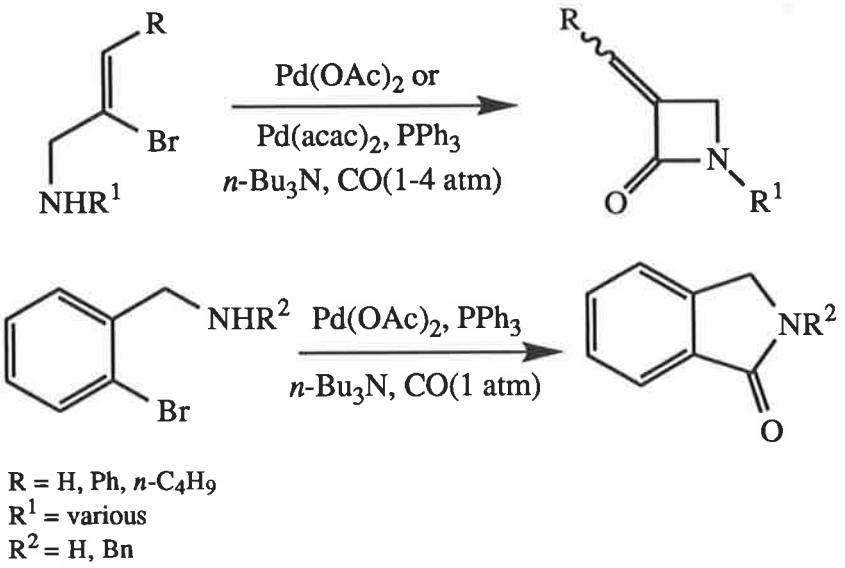


Scheme 1.35



Scheme 1.36

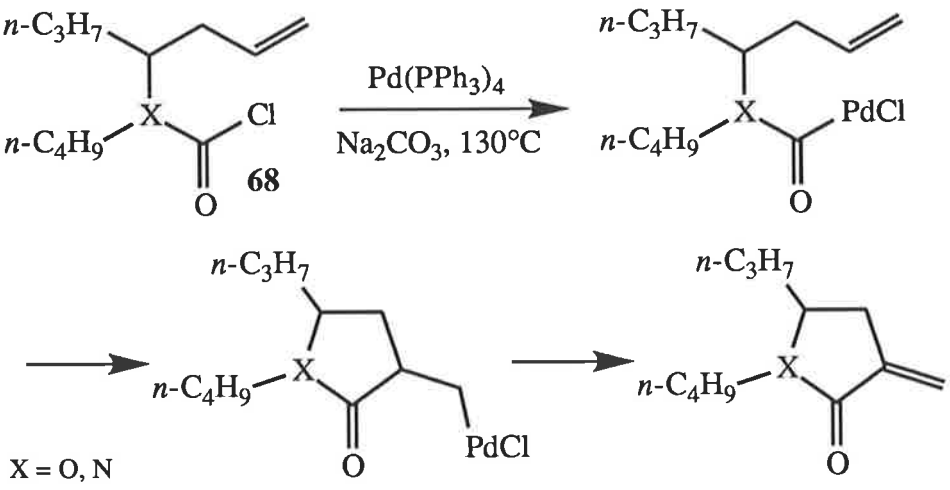
Palladium-catalyzed carbonylation of functionalized allylic amines, in this case 2-bromo-3-propene derivatives, was used by Ban *et al.*[102b] to afford α-methylene β-lactams. By analogy, *ortho*-bromobenzyl amines or amides served as substrates in palladium-catalyzed carbonylations to benzolactams[102c] or cyclic imides[102d] respectively (**Scheme 1.37**).



Scheme 1.37

Appropriate extension of a vinyl or aryl halide aminoalkyl chain has been used to produce α-methylene γ, δ and ε-lactams (including bicyclic pyrrolizidine and indolizidine derivatives)[102a] and five-, six- and seven-membered benzolactams[102c] respectively. The latter procedure was used to produce the 1,4-benzodiazepine skeleton and was applied to the synthesis of prothracarcin and tomaymycin.[102e]

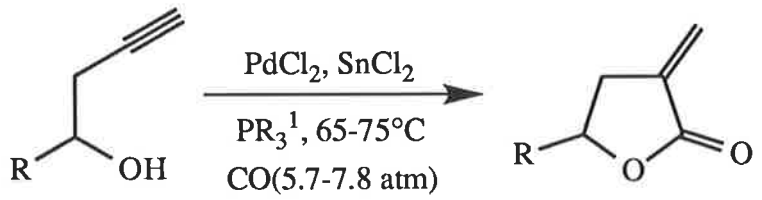
An approach by Henin *et al.*[105] has not involved a palladium-catalyzed carbon monoxide insertion reaction. In this case a homoallylic alcohol or amine was esterified with the one-carbon building block phosgene to give the chloroformate or chloroformamide **68** which was cyclized to give an α-methylene γ-butyrolactone or lactam respectively (**Scheme 1.38**).



Scheme 1.38

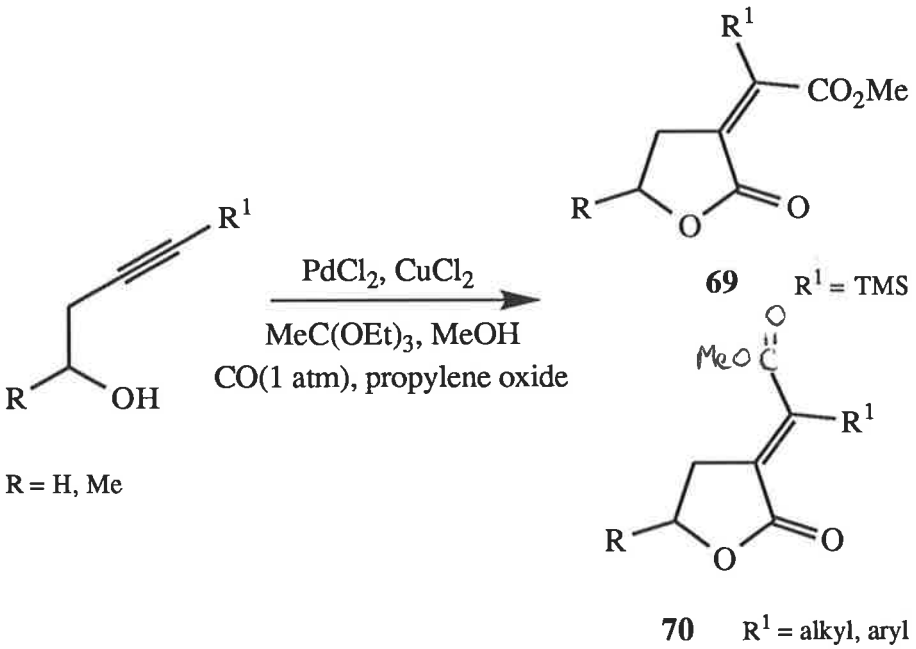
4.2 Carbonylation of ethynyl alcohols and their derivatives

The legacy of work done by Reppe *et al.*[106] is the synthesis of acrylic esters by the nickel-catalyzed carbonylation of acetylene. An intramolecular version of this was reported by Norton *et al.*[107] where homopropargyl alcohols were converted to their corresponding α-methylene γ-butyrolactones, **Scheme 1.39**, which superceded an earlier version using stoichiometric quantities of nickel tetracarbonyl.[108] The former approach has been extended to form both *cis*- and *trans*-fused α-methylene lactones from ethynyl cycloalkanols.



R = H, $CH_2CH_2CH{=}CH_2$, CH_2CH_2Br
R_1 = PPh_3, PBu_3

Scheme 1.39



R = H, Me

69 R^1 = TMS

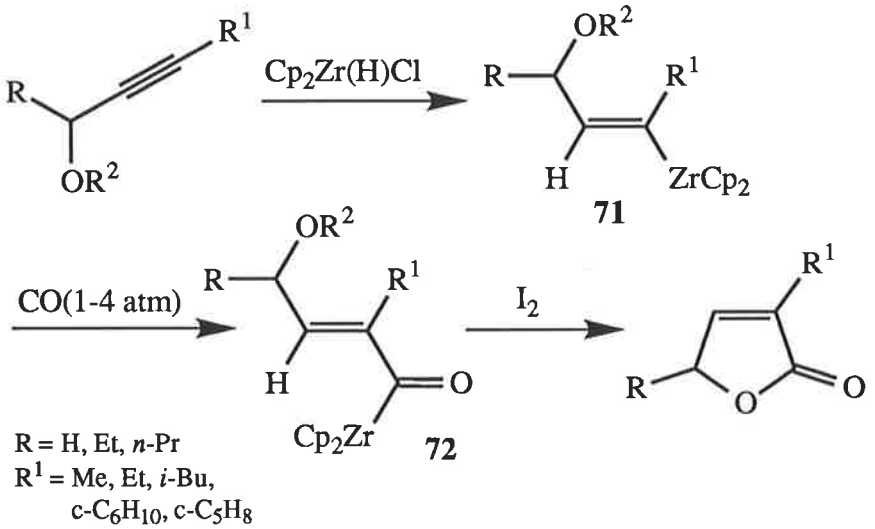
70 R^1 = alkyl, aryl

Scheme 1.40

A recent variation reported by Tamaru *et al.*[109] involved a variety of homoallylic alcohols undergoing a palladium(II)-catalyzed carbonylation to α-methylene γ-butyrolactones.

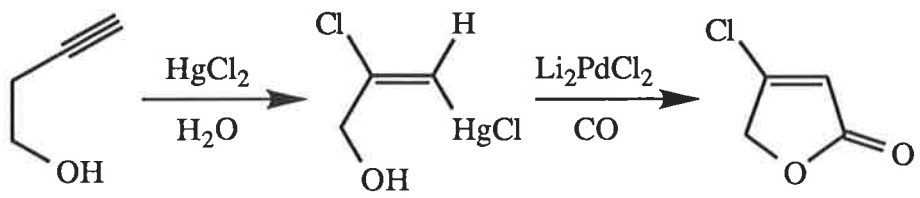
Depending on the type of sustituent at the acetylenic termini (R^1), two distinct products were obtained under identical conditions. When R^1 was a trimethylsilyl group, *cis*-dicarbonylation proceeded selectively to form **69**, but when R^1 was an alkyl or aryl group **70** was formed by selective *trans* alkoxycarbonylation (**Scheme 1.40**).

A related approach involves the conversion of protected propargylic alcohols into vinyl zirconocenes **71** *via* a hydrozirconation reaction.[110] Carbonylation of this intermediate affords an acyl zirconocene complex **72** which subsequently is treated *in situ* with iodine to provide the required butenolides (**Scheme 1.41**).



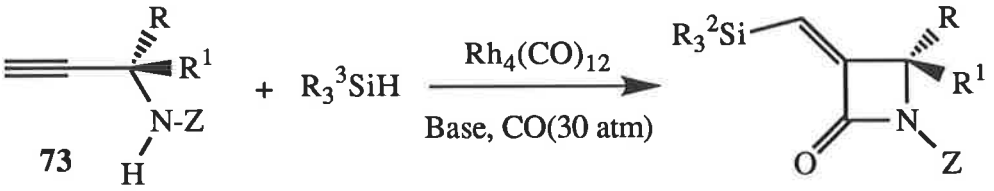
Scheme 1.41

Hydroxy substituted vinyl mercurials[111] and tellurides,[112] available from the hydromercuration or telluration of the corresponding ethynyl alcohols, have been used as precursors to α,β-butenolides. In the first instance a stoichiometric quantity of palladium (II) catalyst was required to effect the desired transmetallation/carbonylation sequence (**Scheme 1.42**).



Scheme 1.42

A novel approach to α-silylmethylene β-lactams by Matsuda *et al.*[113] has involved a one-pot rhodium-catalyzed silylcarbonylation of a substituted propargyl amine derivative **73** (**Scheme 1.43**).

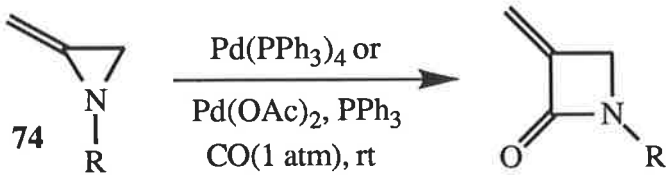


R = H, Me
R^1 = H, Me, *i*-Bu, *n*-C_5H_{11}
R^2 = *t*-$BuMe_2$, $PhMe_2$
Z = NH_2, Ts, CO_2Me, CO_2Bn

Scheme 1.43

4.3 Miscellaneous carbonylations

A variety of methods have used transition metal carbonylation reactions to synthesize unsaturated heterocycles. For instance, methyleneaziridines **74** were converted to α-methylene β-lactams in the presence of palladium compounds.[114a] The site of carbon monoxide incorporation is fixed through palladium coordination to the nitrogen lone pair and the π-electrons of the double bond (**Scheme 1.44**).

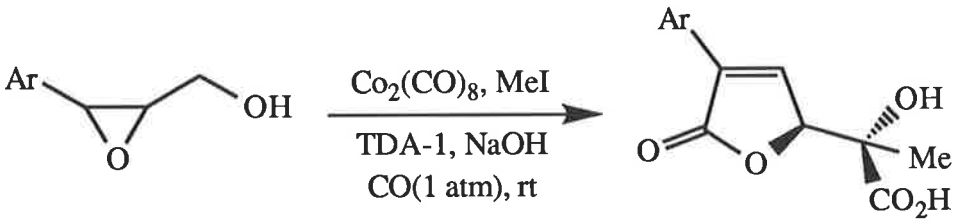


R = *n*-C_4H_9, *n*-C_6H_{13}, 1-adamantyl
$CH_2CH_2CH_2OCH_3$

Scheme 1.44

This work by Alper *et al.* was similarly followed by a cobalt- and phase-transfer-catalyzed carbonylation of β-epoxy alcohols to 2-C-lactic acids in a diastereospecific process.

This constituted the first example of a net triple carbonylation reaction (**Scheme 1.45**).[114b] A butenolide system has also been synthesized by a double carbonylation of (2-bromoethyl)benzene catalyzed by $Sn[Co(CO)_4]_4$.[115*]



Scheme 1.45

4.4 Non-carbonylative routes to unsaturated lactones

4.4.1 Palladium-catalyzed C-C bond forming reactions of acrylic esters

Two procedures of note have been carried out using α,β-acetylenic esters as starting reagents. Cacchi *et al.*[116] has utilized a palladium-catalyzed stereo- and regioselective one-pot hydroarylation/cyclization reaction of 4-hydroxy-2-alkynoates **75** to effect a transformation to substituted butenolides. Whereas Lu *et al.*[117a] has constructed β-γ-disubstituted α-(*Z*)-(chloromethylene)butyrolactones in a highly diastereoselective manner *via* a palladium(II)-catalyzed cyclization of 1-alkyl 4-chloro-2-alkenyl-2-alkynoates **76** (**Scheme 1.46**).[**]

An associated procedure reported by Larock *et al.*[118] involved a transmetallation/cyclization reaction of the allylic esters of chloromercurioacetic acid **77** using stoichiometric palladium. Concomitant double bond isomerization yielded the desired α,β-butenolides (**Scheme 1.47**).

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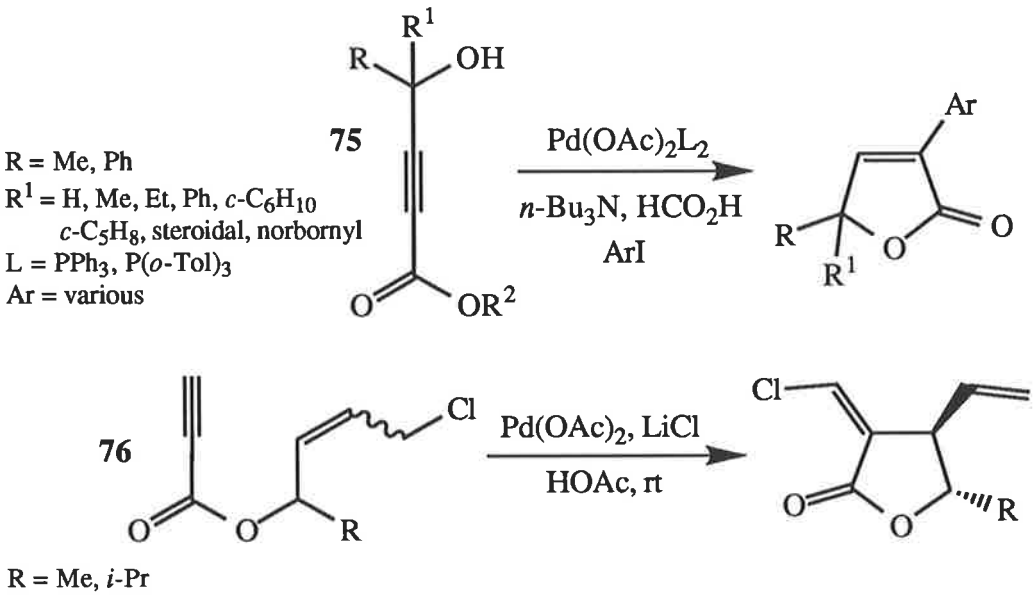
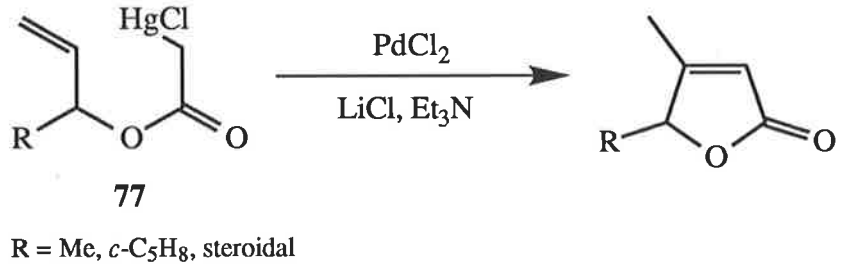
* A further variant is the insertion of CO *via* the Shapiro reaction where CO_2 functions as the CO building block.

** Similar reactions conducted under an atmosphere of CO produced α-chloromethylene γ-butyrolactone β-acetic acid derivatives with high stereoselectivity.[117b]



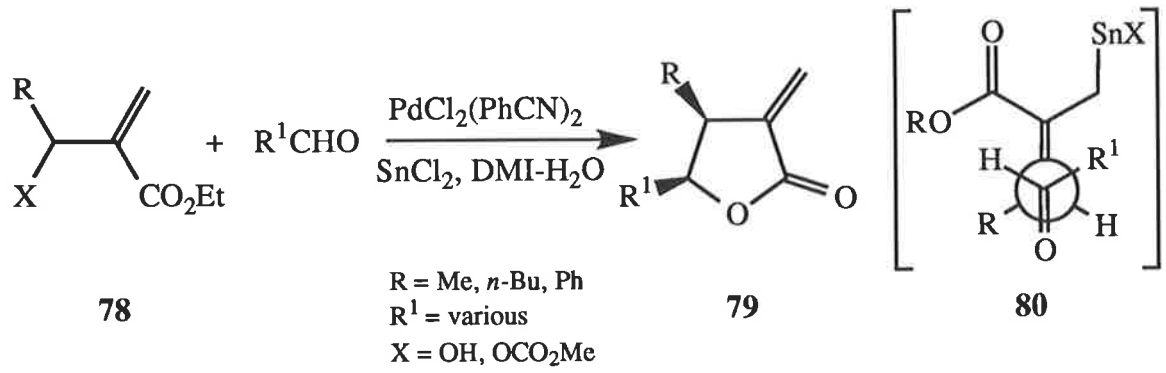
Scheme 1.46



Scheme 1.47

4.4.2 Transition-metal catalysed carbonyl allylation

Metal-mediated 2-alkoxycarbonylallylation of aldehydes by 2-(bromomethyl)acrylates is a widely used and attractive method of forming α-methylene γ-butyrolactones.[119] A recent approach overcomes the difficulties in the preparation and stability of 2-(bromomethyl)acrylates by using stable 2-(hydroxymethyl)acrylates.[120] A carbonyl allylation reaction in the presence of $PdCl_2/SnCl_2$ consequently gave α-methylene γ-butyrolactones. When the acrylate **78** bore a substituent at the allylic position, i.e. R ≠H, high levels of diastereoselection were achieved, providing the *syn* isomer **79** probably *via* an acyclic, antiperiplanar transition state **80** (**Scheme 1.48**).



78 R = Me, *n*-Bu, Ph; R^1 = various; X = OH, OCO_2Me **79** **80**

Scheme 1.48

5.0 Vinyl halides as synthetic intermediates

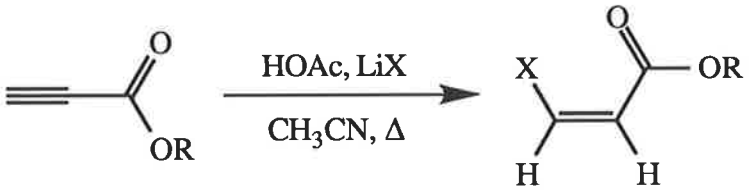
As outlined in this chapter (*3.3.1*), intramolecular versions of the palladium-catalyzed carbonylation of hydroxy or amino substituted vinyl halides gave rise to α-methylene γ-butyrolactones, α,β-butenolides and α-methylene β, γ and δ-lactams. However, the synthetic utility of such methodology is restricted because of the necessity to form vinyl halides as the direct precursors to these reactions. Although vinyl halides are widely used in a variety of metal-catalyzed coupling reactions, their mode of preparation presents several synthetic drawbacks.

5.1 Vinyl halide synthesis

A number of diverse methods for the synthesis of vinyl halides exist, however many of these suffer from a lack of generality with respect to regio- and stereochemical control and compatibility with functional groups that may be present.

The direct electrophillic addition of the elements H-X to alkynes to afford the corresponding vinyl halides is one of the oldest and most important synthetic methods known. Such additions have been studied extensively with regards to both a synthetic and mechanistic viewpoint, with Markovnikov addition frequently observed. However, this process is plagued by the aforementioned lack of control of both regio- and stereo-isomers at the double bond, and also the possible racemization of chiral centres in precursors due to the inherent presence of acid in these preparations.

Conversely, anti-Markovnikov additions of H-X to alkynes has occurred for example *via* the hydroboration of terminal alkynes to alkenylboronic acids and the reaction of propynoic acids with a lithium halide.[121] Of interest is this latter case since the hydrohalogenation was stereospecific to afford the thermodynamically unfavourable (*Z*)-3-halopropenoic acids **81** (**Scheme 1.49**).



X = Cl, Br, I **81**

Scheme 1.49

Vinyl halides have also been generated from the electrophillic trapping of vinyl lithium compounds generated under the conditions of the Shapiro reaction.

6.0 Triflates as halide substitutes

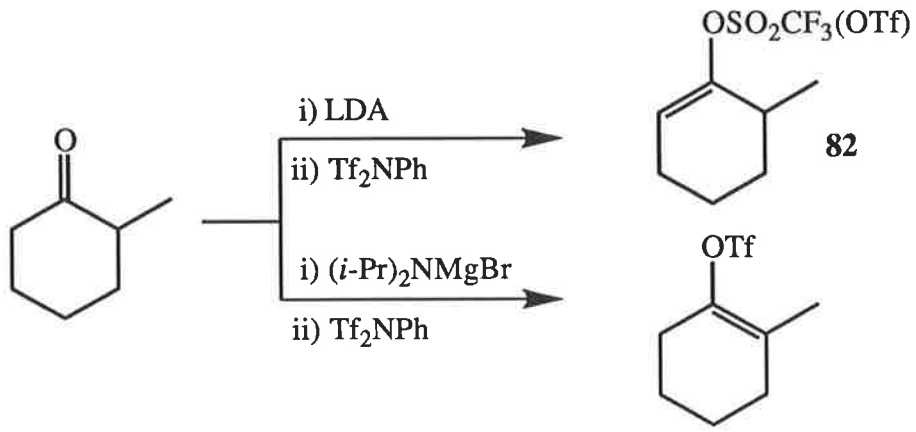
In recent times vinyl and aryl trifluoromethanesulfonates (triflates) have found widespread use as synthetic analogues of the corresponding organic halides particularly in metal-catalyzed carbon-carbon bond forming reactions.[122] This is due in part to their facile preparation from carbonyl compounds and phenols and their compatibility with common functional groups.

6.1 Triflate synthesis

The advantageous nature of vinyl triflates lies in the fact that they may be formed regioselectively from ketones and enones using known enolate chemistry.[123] It is thus possible to control the regiochemistry of the double bond by placing the reaction under kinetic or thermodynamic control, since the configuration of the enolate is conserved in the triflating step.

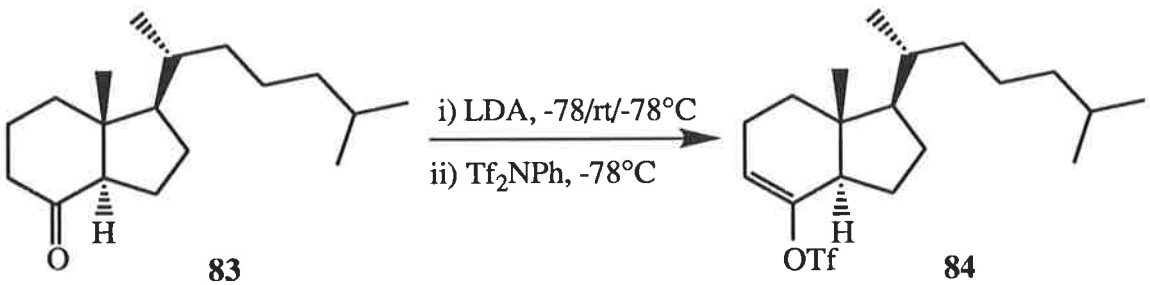
This was exemplified by the selective enolization of 2-methylcyclohexanone by deprotonation at the the sterically less encumbered site by the hindered amine base LDA to

give the kinetic enolate. Trapping with N-phenyltrifluoromethanesulfonimide (N-phenyltriflimide, Tf_2NPh) gave vinyl triflate **82** with a regioselectivity of 95:5.[124] The thermodynamic enolate was obtained under equilibrating conditions through the use of bromomagnesium diisopropylamide to give the two products in a ratio of 3:97 (**Scheme 1.50**).[125]



Scheme 1.50

A variety of highly regioselective transformations utilizing kinetic control in the formation of vinyl triflates has been reported. The particular base has varied from LDA (two bases commonly used are lithium or sodium hexamethyldisilazide) but the trapping reagent of choice has proven to be Tf_2NPh. For example, Mouriño *et al.*[126] used regioselective vinyl triflate formation, from the unsymmetrical cycloalkanone **83**, to furnish the coupling partner **84** in the synthesis with enynes of the vitamin D_3 metabolite 1α,25-dihydroxy vitamin D_3 (**Scheme 1.51**).



Scheme 1.51

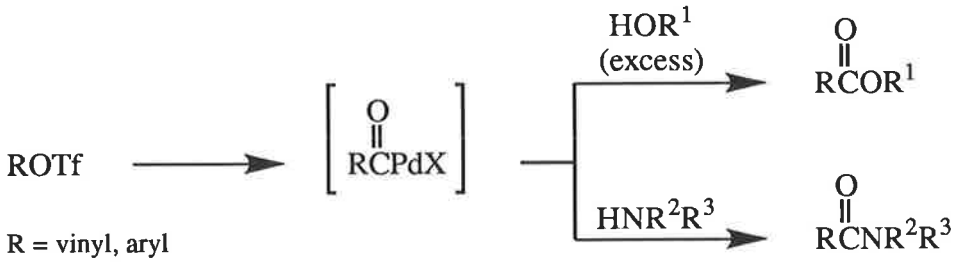
Furthermore, acyclic ketones have been converted to vinyl triflates derived from regio- and stereoselectively generated *Z*-enolates.[127] α-Substituted vinyl triflates from methyl ketones have also been synthesized with defined regiochemistry through kinetic control. Examples may be found in *Chapters 3* (*3.3*) and *4* (*4.3*).

6.2 Vinyl and aryl triflates as synthetic intermediates

The application of vinyl and aryl triflates to synthetic transformations has expanded enormously in the last decade.[128] Much of this has occurred through their application in carbon-carbon bond forming reactions since such reactions have shown to proceed under mild conditions and in good yield. The scope of these reactions can generally be divided into three catagories; 1. Palladium-catalyzed carbonylations, 2. Cross-coupling reactions with organometallics and 3. Addition reactions to alkenes and alkynes.

6.2.1 Carbonylation reactions*

Carbonylations of vinyl and aryl triflates can be considered to be parallel reactions to those involving the corresponding organic halides (**Scheme 1.52**). In the case of vinyl triflates the net result can be considered as the transformation of ketones, *via* a two-step regioselective procedure, into homologues containing an additional carbon unit. These have included α,β-unsaturated esters,[129a] acids[129b] and amides.[129c] Such methodology has found widespread use in multistep natural product synthesis.



Scheme 1.52

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* Carbonylations involving sp and sp^2 hybridised triflates will only be briefly discussed at this point. For a more detailed discussion see *Chapter 2* (*2.3*).

In addition, vinyl and aryl triflates have been reported to undergo efficient palladium-catalyzed carbonylative cross-coupling reactions. Using a variety of organostannanes, alkynes and trimethylsilyloxy cyclopropanes both symmetrical and unsymmetrical ketones have been formed.

6.2.2 Cross-coupling reactions with organometallics

The cross-coupling of vinyl and aryl triflates with organometallic compounds is a widely used tool for carbon-carbon bond formation.[128] In addition to exploiting the inherent advantages of triflate chemistry, the reactions most often proceed with retention of configuration in the coupling partners. Direct coupling only occurs with organocuprates which is in contrast to cross-couplings involving organotin (Stille reaction), -boron (Suzuki reaction), -zinc, -aluminium or -silicon compounds. Catalysis by a transition metal, such as nickel or palladium, is generally required for these less reactive organometallics. Since the order of reactivity with respect to vinyl and aryl halides is Ar-I>Ar-Br~Ar-OTf>>Ar-Cl; Vinyl-OTf>Ar-Br, selective triflate transformations may be carried out.

6.2.3 Addition reactions to alkenes and alkynes

The palladium-catalyzed vinyl- and arylation of alkenes is universally known as the Heck reaction.[130] This reaction takes place with a variety of vinyl and aryl triflates and mono, α-disubstituted or cyclic alkenes in the presence of base and catalytic palladium(II) The double bond stereochemistry of the final product is normally the result of a palladium-catalyzed equilibration. Generally triflates have proved to be superior to halides with respect to regio- and diastereoselectivity. Conjugated alkynes are also readily available *via* the palladium-catalyzed coupling of vinyl and aryl triflates with monosubstituted alkynes.[128]

A variety of other carbon-carbon, carbon-heteroatom and carbon-metal bond forming reactions also exist. Furthermore, vinyl triflates may be reduced to the corresponding alkenes or methylene compounds.

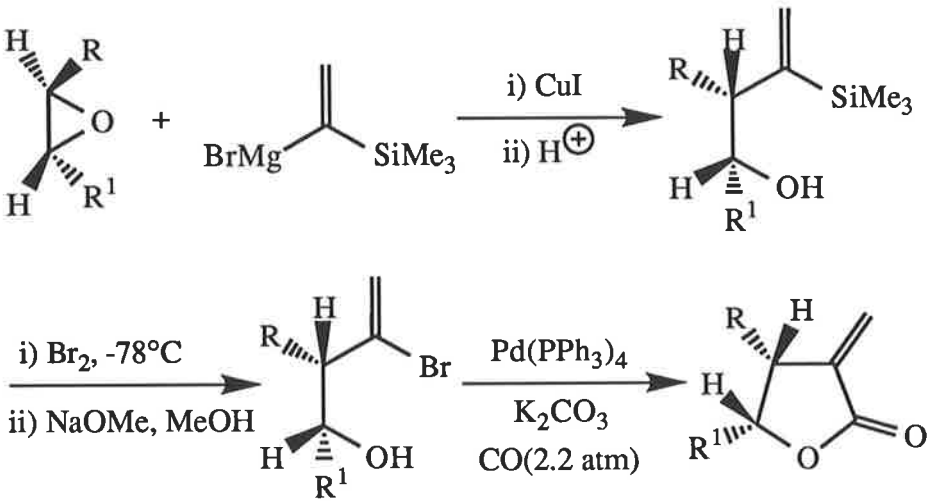
7.0 Aims

As outlined, the palladium-catalyzed carbonylation reaction has proven to be an efficient tool for the facile preparation of a wide variety of unsaturated heterocycles. Hydroxy or amino vinyl halides have consequently been shown to be ideal precursors to such compounds, however, they suffer from intrinsic preparative limitations.

Due to the impressive ability of vinyl and aryl triflates to undergo carbon-carbon bond forming reactions, hydroxy and amino vinyl triflates seemed perfect analogues to undergo intramolecular carbonylation reactions. Hence, it was intended to use such compounds in novel carbonylation procedures since this methodology possesses a number of inherent advantages. Moreover, catalytic reactions are amenable to large scale preparation of compounds due to the economical use of catalytic reagents.[131] Furthermore, the utility of such a synthetic sequence would also be manifestly enhanced if common reaction intermediates could be employed in most cases.

Vinyl and aryl triflates have most recently been generally seen as precursors to palladium-catalyzed coupling reactions. However, it would be interesting if the stability and/or reactivity of the triflate moiety was also investigated. Thus, functional group manipulation in the presence of this unit would be of considerable significance.

It has been shown by Stille *et al.*[101] that optically active precursors employed in a palladium-catalyzed carbonylation reaction do not undergo racemization. Thus, hydroxy substituted vinyl bromide **85** was prepared by a regio- and stereospecific epoxide ring opening and subsequent electrophillic substitution of the trimethylsilyl group by bromine. Due to the the non-involvement of asymmetric carbons in the intramolecular carbonylation reaction, optically active α-methylene γ-butyrolactones were obtained (**Scheme 1.53**). This precedent implies that the palladium-catalyzed carbonylation of optically active hyroxy vinyl triflates would seem a desirable route to optically active lactones.



85

Scheme 1.53

The particular compounds prepared for the anticipated transformations, including the important enantiomerically pure examples, and the carbonylation reactions to which they were subjected are outlined in the ensuing chapters.

Chapter 2

Palladium(0)-catalyzed intramolecular carbonylative couplings of hydroxy and amino vinyl triflates

2.1 Introduction

As outlined in the introduction, it was our aim to synthesize a variety of hydroxy and amino vinyl triflates from readily obtainable starting materials and to utilize the inherent advantages of regio- and stereocontrol bestowed upon such triflates. Considering the precedent set by the corresponding vinyl and aryl halides, these compounds were envisaged to readily undergo an intramolecular palladium-catalyzed carbonylation reaction to form a range of unsaturated lactones and lactams.

2.2 Background to the carbonylation reaction

Almost sixty years ago the first well-defined carbonylation reaction, the hydroformylation reaction (or oxo process), was discovered by Roelen *et al.*[132] at the Ruhrchemie laboratories at Oberhausen-Holten, Germany. During studies into the high pressure, cobalt catalyzed Fisher-Tropsch synthesis of hydrocarbons from carbon monoxide and hydrogen (Eqn. **1**), it was observed that the addition of ethylene to the CO/H_2 feed gas (synthesis gas) led to the formation of propionaldehyde in high yield. The reaction comes about by the addition of hydrogen to one end of the alkene double bond and a formyl group, from carbon monoxide, at the other (Eqn. **2**). This process has been extensively studied and was the first catalytic transition metal carbonyl reaction to be explained in detail.[133]

$$\underset{\text{synthesis gas}}{m\text{-CO} + n\text{-H}_2} \xrightarrow{\text{cat.}} \text{"CHO products"} \quad (\mathbf{1})$$

$$\text{RCH=CH}_2 + \text{CO} + \text{H}_2 \xrightarrow[\substack{90\text{-}150^\circ\text{C} \\ 100\text{-}400\text{ bar}}]{\text{Co(CO)}_8} \underset{\text{oxo aldehyde}}{\text{RCH}_2\text{CH}_2\text{CHO}} \quad (\mathbf{2})$$

A class of reactions analogous to the hydroformylation reaction (Reppe reactions) involve the introduction of carbon monoxide, *via* addition to unsaturated compounds (such as aliphatic alkenes and alkynes) or insertion into existing bonds (e.g., alcohols), in the presence of a nucleophile with an active H-atom and a metal carbonyl. For instance, the carbonylation of unsaturated compounds with CO and water or an alcohol yields carboxylic acids (hydrocarboxylation) or esters (hydroesterification) respectively (Eqns. **3** and **4**). A representative carbonylation is the production of acrylic ester from acetylene, CO and ROH (e.g., BASF, Röhm & Haas 140,000 t/a each). However, a major synthetic drawback of hydrocarboxylation and esterification is that often at least two isomeric products are formed and non-selective rearrangements may occur.* The carbonylation of methanol is also an important process since it forms the basis of the manufacture of acetic acid, *via* the Monsanto process (Eqn. **5**)[136], and acetic anhydride.

$$H_2C{=}CH_2 + CO + H_2O \xrightarrow{\text{cat.}} CH_3CH_2CO_2H \quad (3)$$

$$HC{\equiv}CH + CO + H_2O \xrightarrow{\text{cat.}} H_2C{=}CHCO_2H \quad (4)$$

$$CH_3OH + CO \xrightarrow[180°C,\ 30\ bar]{\text{Rh cat., } I^{\ominus}} \underset{99\%}{CH_3CO_2H} \quad (5)$$

It is worth noting, however, that the above processes have often been characterized by the use of high pressures of CO, high temperatures and toxic or unstable catalysts such as $Ni(CO)_4$, $Fe(CO)_5$ or $HCo(CO)_4$. As a consequence, it took the discovery of stable but extremely active palladium and rhodium organophosphine catalysts to catapult carbonylation chemistry into being a generally useful techniques for the synthesis of fine organic chemicals. Most organic transformations can thus be accomplished by judicious choice from a relatively small number of accessible metal complexes.

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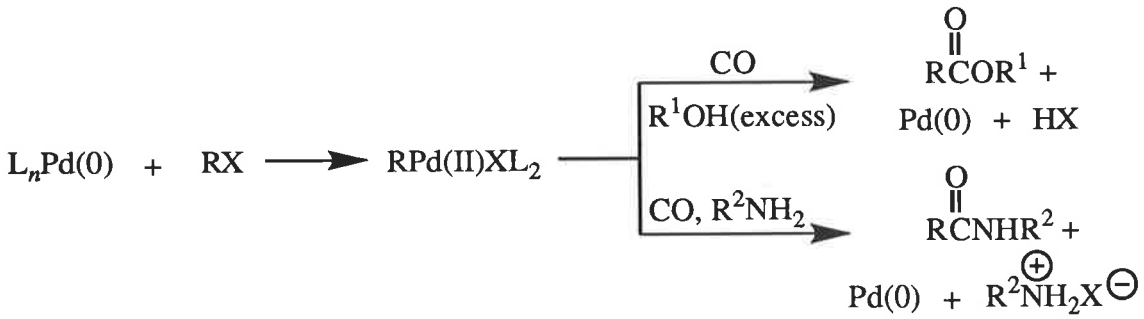
* Alper *et al.*[134] have recently shown that palladium complexes, in the presence of formic or oxalic acid and bidentate phosphine ligands, act to selectively hydrocarboxylate alkenes and alkynes. In addition, useful α-and β-silyl esters have been synthesized by Takeuchi *et al.*[135] by a regioselective hydroesterification of vinyl silanes.

A synthetic application of importance, having been covered in several reviews,[130,137] is the insertion of CO into organic halides, particularly those that are unsaturated or aromatic. This methodology is based upon the oxidative addition-insertion chemistry of palladium(0), and to a lesser extent nickel(0), complexes. Organic halides form σ-alkyl palladium(II) complexes which undergo carbonylation to yield acyl palladium(II) complexes that are readily attacked by nucleophiles. Reductive elimination then gives the organic product and regenerates a Pd(0) species (theoretically this system can thus be made catalytic). In this context, the synthesis of carboxylic esters and their derivatives following **Scheme 2.1** is a well known process having been developed primarily by Richard F. Heck and John K. Stille. Aryl, benzyl,[138] vinyl and heteroaromatic[139] halides have been readily carbonylated to esters in the presence of an alcohol or to amides in the presence of a primary amine.* The reaction may be catalyzed by either $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ in the presence of a tertiary amine employed to remove the HX generated. Several other transition metals also act as carbonylation catalysts (including those of neutral or anionic metal carbonyls and metal acyl "ate" complexes) to affect similar chemistry.



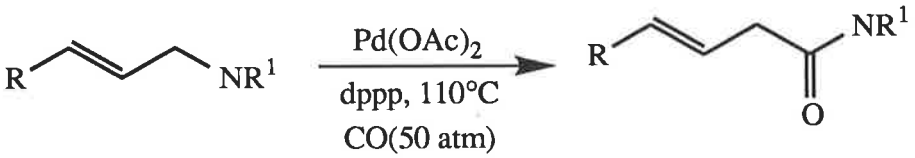
Scheme 2.1

A number of intramolecular versions of this catalytic carbonylation of vinyl and aryl halides has lead to a number of useful heterocyclic systems including, amongst others, the α-

* Furthermore, arene diazonium salts have been shown to undergo a catalytic carbonylation to aromatic acids in the presence of palladium acetate. The reaction proceeds *via* a mixed anhydride as the initial product.[140]

methylene γ-butyrolactone and α,β-butenolide units [these methods being outlined in *Chapter 1 (3.3.1)*].

The carbonylation of allylic compounds enables the straightforward synthesis of β,γ-unsaturated carbonyl compounds. A range of allylic compounds including halides, acetates, phosphates and carbonates have been found to effect this transformation. A further example by Murahashi *et al.* involved the carbonylation of allylamines to β,γ-unsaturated amides in the presence of a palladium catalyst (**Scheme 2.2**).*



R = alkyl, phenyl
R^1 = H, Me, Ph, Bn,
c-C_6H_6, (*E*)-crotyl

Scheme 2.2

The double carbonylation reaction, where two CO molecules are introduced into an organic compound in a single step, has gained prominance in the last decade. Specific syntheses of a variety of α-keto acids, esters and amides is now possible. Independent work by both Yamamoto[143a] and Tanaka[143b] has shown that both aryl and vinyl halides undergo a palladium-catalyzed double carbonylation to the corresponding α-keto amides (**Scheme 2.3**). Such reactions become selective toward the doubly carbonylated product when the catalyst possesses bulky phosphine ligands, the pressure of CO is increased and solvents of low polarity are used.

The palladium(0)-catalyzed carbonylative cross-coupling reaction of organic halides (alkyl, allyl, vinyl and aryl) with various organometallic compounds has been shown to be a

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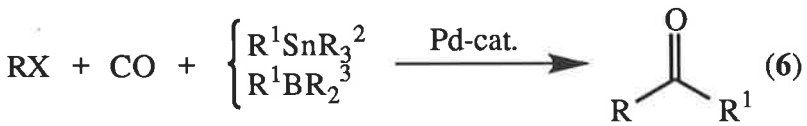
* Tsuji and Mandai *et al.*[142] have shown that the palladium-catalyzed carbonylation reaction of 2-alkynyl carbonates affords a variety of allenyl esters.

R = vinyl, aryl
R^1 = alkyl
X = Br, I

Scheme 2.3

useful synthetic tool for unsymmetrical ketone synthesis.[130] Recent reports by Stille[144] and Suzuki[145] have proven alkenyl-, alkynyl- and phenylstannanes and trivalent boron compounds to be promising substrates due to their ready availability and broad applicability (Eqn. **6**). In both cases the reaction is conducted under mild conditions and both coupling partners may contain a variety of functional groups.



(6)

The above transition-metal carbonylation reactions involve an intramolecular "migratory insertion" of CO, where a covalently metal bound alkyl, vinyl or aryl group migrates to an adjacent coordinated CO. Kinetic data for various metal-alkyl groups, associated with a variety of ligands, is consistent with a mechanism involving a reversible CO/R reaction to form a coordinatively unsaturated acyl intermediate. Another ligand, L, then occupies the vacant coordination site created by the insertion (Eqn. **7**). The incoming ligand, L, may be any Lewis base, including the solvent. A σ-acyl metal complex is then produced which is subsequently cleaved to produce the organic carbonyl compound.* The most adept cleavages are those that involve the departure of stable transition-metal fragments. In effect, the metal coordination increases the susceptibility of CO toward a nucleophillic attack by the incoming

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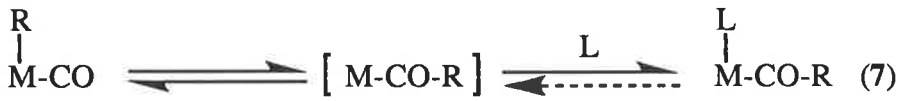
* Double carbonylation reactions of aryl iodides initially occur through the insertion of CO into the Ar-Pd bond. The final step has been shown to proceed *via* an intermediate σ-acyl σ-alkoxycarbonyl Pd(II) complex formed from the attack of an alcohol on a coordinated CO ligand.[146]

ligand (or a non-coordinating nucleophile). For complexes of palladium, both carbon monoxide insertion and σ-acyl metal bond cleavage are often facile processes.



(7)

R=H, alkyl, vinyl, aryl, -COR
L=Lewis base

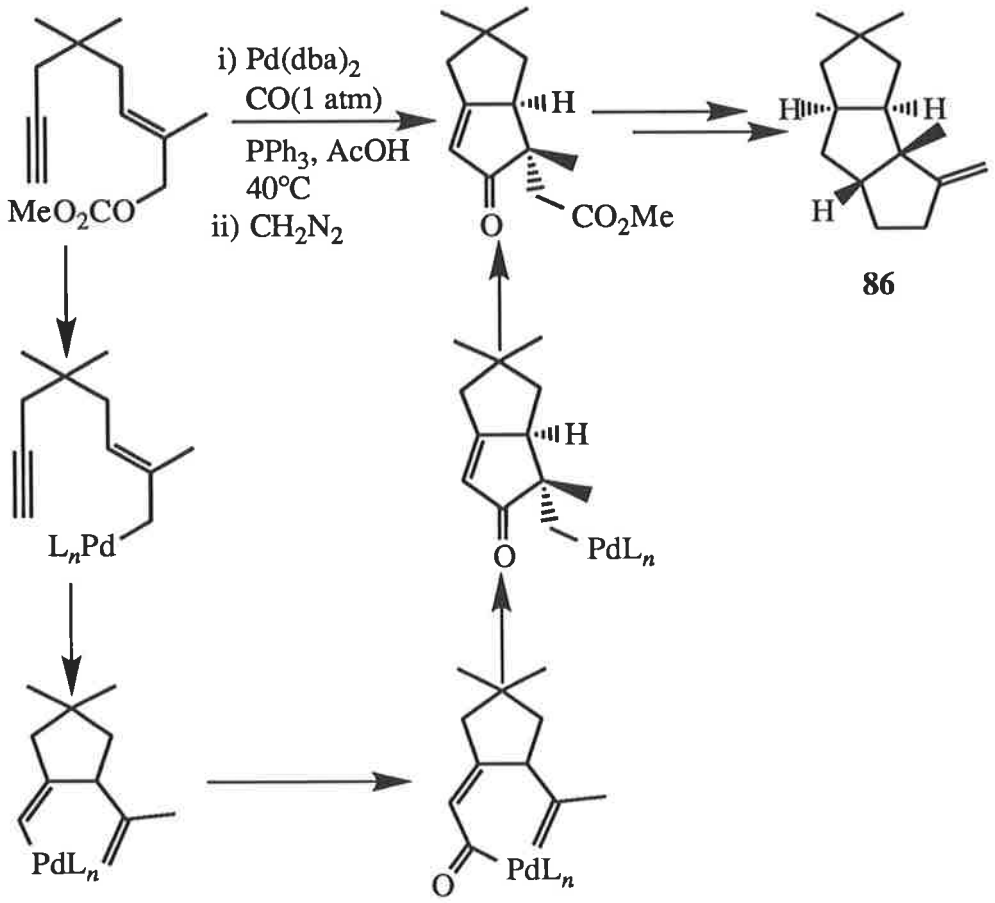
Carbonylation reactions may also occur *via* an intermolecular nucleophillic attack on a metal-bound carbon monoxide, followed by either insertion or reductive elimination. An intramolecular version of this followed by insertion of an alkene was used by Semmelhack *et al.*[99] in the synthesis of α-methylene lactones. Furthermore, an intramolecular alkyne carbonylation by Norton *et al.*[107] has furnished α-methylene γ-butyrolactones [both examples are described in *Chapter 1* (*4.1* and *4.2*)].

Interestingly, carbonylation reactions may occur *via* the copolymerization of alkenes and carbon monoxide to form polyketones.[147] An intramolecular version of this, recently reported by Oppolzer *et al.*,[148] involved the synthesis of (±)-hirsutene **86** *via* a catalytic allylpalladium-alkyne cyclization/carbonylation reaction cascade. This sequence employed an acyl palladium-alkene insertion as one of the key steps in a procedure that allowed the stereoselective formation of four carbon-carbon bonds in a single process (**Scheme 2.4**).

Since most of the elementary steps in carbonylation reactions are reversible, it is thus possible to decarbonylate organic compounds with transition-metal complexes. The most efficient complex is $RhCl(PPh_3)_3$, better known as Wilkinson's catalyst, which readily decarbonylates aldehydes, acyl halides and diketones.[149]

2.3 The palladium(0)-catalyzed carbonylation of vinyl and aryl triflates

The scope and understanding of the palladium-catalyzed carbonylation of vinyl and aryl triflates has expanded enormously in recent times.[128] As with the corresponding halides, carbon monoxide is readily inserted into carbon-palladium σ-bonds to form acyl palladium(II) complexes. In particular, the carbonylation of vinyl triflates may be represented as one step in



Scheme 2.4

an overall two-step regioselective conversion of ketones to α,β-unsaturated carboxylic acid derivatives. Pioneering work by Cacchi and Ortar *et al.*[150a] involved the synthesis of α,β-unsaturated esters and amides from the palladium-catalyzed carbonylation of vinyl triflates.* The example of steroidal triflate **87** is representative (**Scheme 2.5**). In this context, the reaction has gained widespread acceptance as a generally facile and efficient means to prepare a variety of acids, esters and amides.

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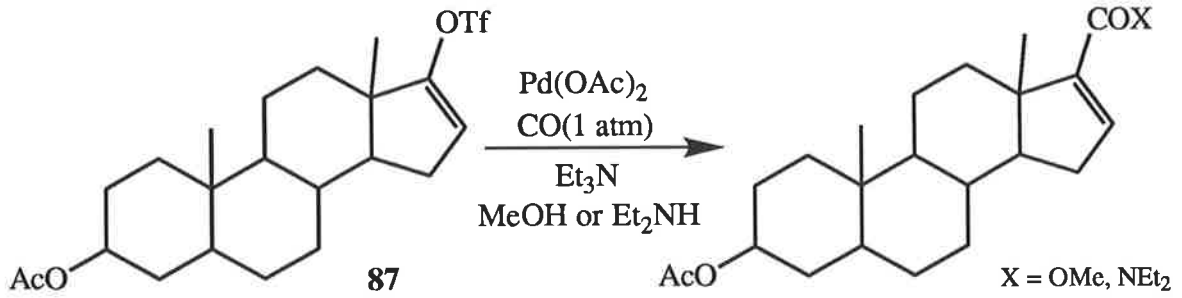
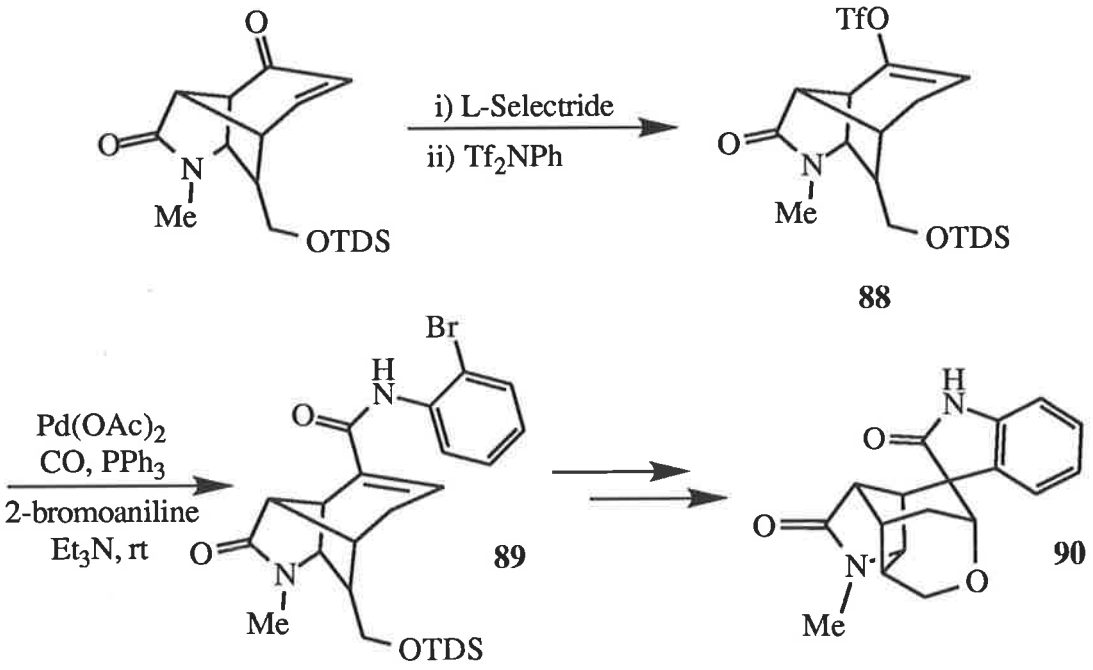
* Cacchi *et al.*[150b] also synthesized carboxylic acids directly by the carbonylation of vinyl and aryl halides in the presence of potassium acetate and subsequent hydrolysis of the resultant mixed anhydride.



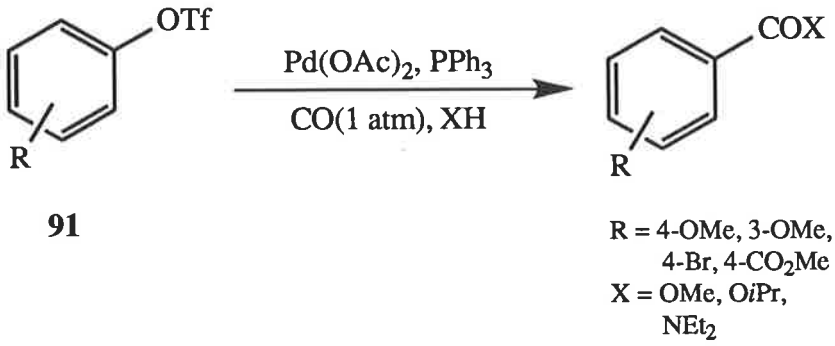
Scheme 2.5

This methodology has found widespread application in natural product synthesis due to the mild reaction conditions and absolute control over the position of both the double bond and the carbonyl group. Such an example is the approach to the alkaloid (±)-gelsemine **90**, where carbonylation of vinyl triflate **88** in the presence of 2-bromoaniline gave the desired intermediate **89** (**Scheme 2.6**).[150] This also demonstrates the relative reactivity, with respect to oxidative addition to palladium(0), of vinyl triflates compared to aryl bromides.



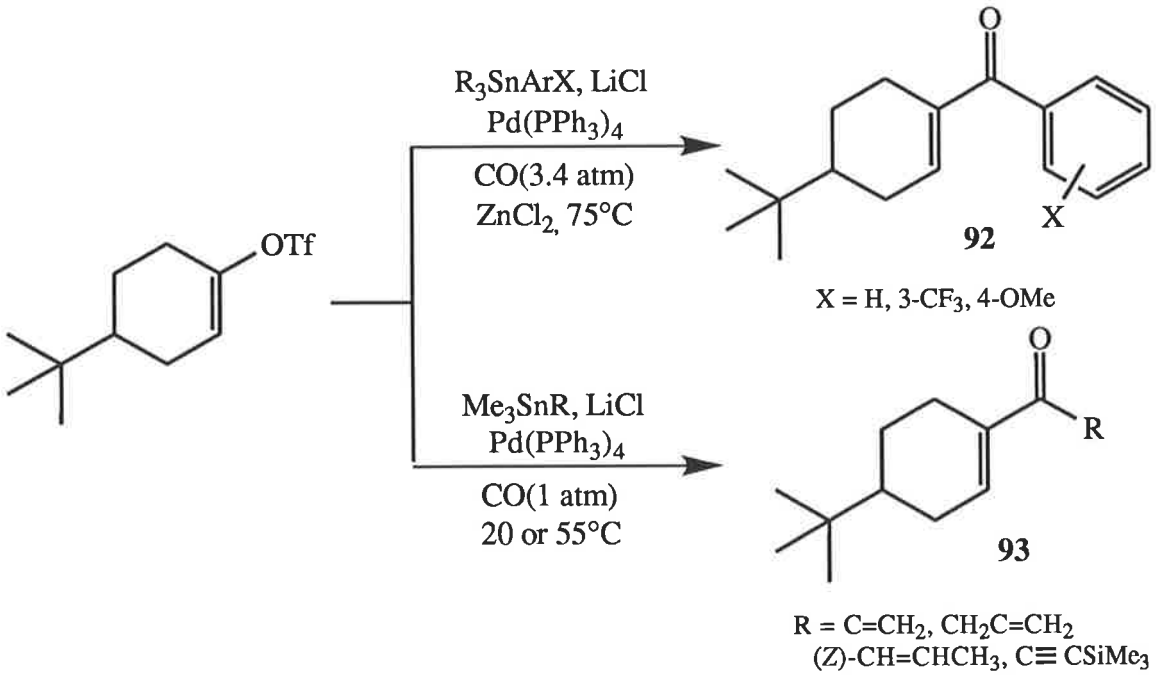
Scheme 2.6

In a similar manner, arene carboxylic acid derivatives have been synthesized from phenols. Thus aryl (and heteraromatic and napthyl) triflates **91** undergo a palladium-catalyzed amino- or alkoxycarbonylation to the corresponding esters and amides (**Scheme 2.7**).[151]



Scheme 2.7

As for the corresponding halides, vinyl triflates have been shown to furnish ketones from a palladium(0)-catalyzed carbonylative cross coupling reaction in the presence of organostannanes.[152] It has been found that the addition of lithium chloride is necessary for the reaction to proceed.

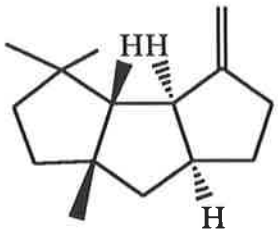


Scheme 2.8

Consequently, α,β-unsaturated ketones such as **92** and **93** have been directly obtained from the cross coupling of vinyl triflates with a variety of organostannanes (alkyl-, alkenyl-, alkynyl- or arylstannanes) in the presence of carbon monoxide. (**Scheme 2.8**).[152a] The stereochemistry of (Z)-alkenylstannanes was maintained in the product which was in contrast

to vinyl iodides where no such retention was observed.[152a] In order to optimize the reactions of some stannanes, minor modifications were necessary in the carbonylative coupling procedures. For instance, at temperatures above 40°C alkynylstannanes underwent direct cross coupling between the vinyl triflate and the stannane. Furthermore, an equivalent of zinc chloride was found to be necessary for the couplings of alkyl- and arylstannanes.[152a]

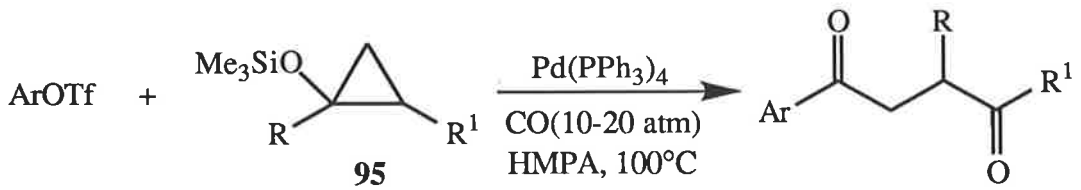
Such methodology has once again been exploited in natural product synthesis. Probably the most often cited example is the synthesis of $\Delta^{9(12)}$-capnellene **94** *via* a route incorporating carbonylative couplings at two points.[152a]



94

Likewise, aryl triflates also carbonylatively cross couple with alkyl-,alkenyl-, alkynyl and arylstannanes to give aryl ketones in the presence of $Pd(dppf)Cl_2$ as the catalyst.[152b] However, it was found that for allylstannanes only direct coupling occurred.

Alkynes have also undergone palladium-catalyzed carbonylative cross coupling reactions with aryl triflates in a synthesis of acetylenic ketones.[153] Furthermore, when aryl triflates underwent an addition to trimethylsiloxycyclopropanes **95** in the presence of CO 1,4-diketones or 1,4-oxo esters were formed (**Scheme 2.9**).[154]

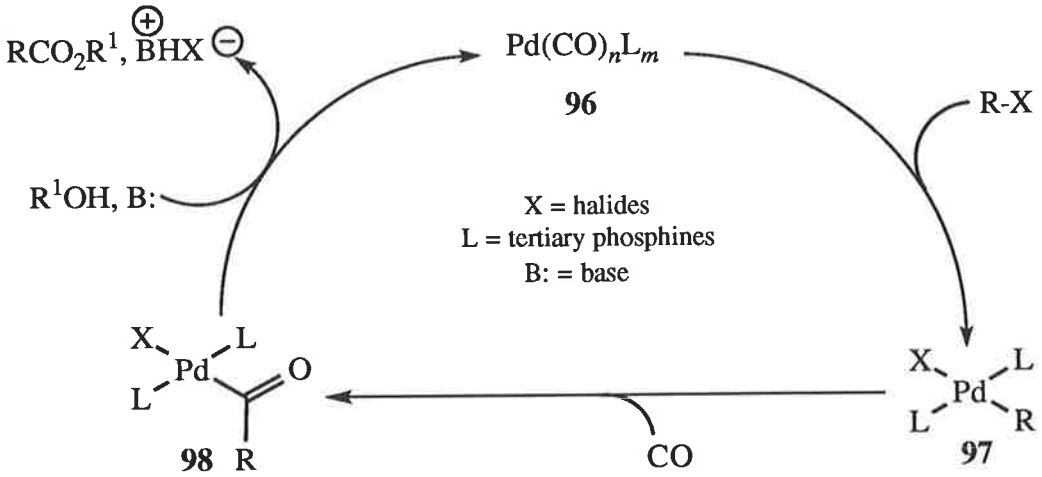


Ar = Ph, napthyl, pyridyl
R = alkyl, aryl
R^1 = alkoxy

Scheme 2.9

2.4 Mechanistic details of the palladium(0)-catalyzed carbonylation reaction

Mechanistic insights into the palladium(0)-catalyzed carbonylation reaction of organic electrophiles has mainly come about through investigations carried out on aryl halides containing monodentate phosphines using predominantly stoichiometric platinum.[146,155] The reaction is known to proceed through a series of transformations common to palladium including oxidative addition, carbonyl insertion and reductive elimination.[156] The general mechanism has been proposed to follow the pathway depicted in **Scheme 2.10**. Intimate coverage of the carbonylation of aryl halides will not be attempted here, especially with respect to the oxidative addition and reductive elimination steps (these mechanisms have been adequetely determined/postulated). In this context, only the carbonyl insertion will be dealt with in detail. Vinyl halides and triflates will be considered separately, building upon mechanistic details gleaned from the aryl analogues. For simplicity, the alkoxycarbonylation reaction will only be shown in this and ensuing cases. The lack of mechanistic detail with respect to intramolecular carbonylation reactions excludes any detailed discussion.

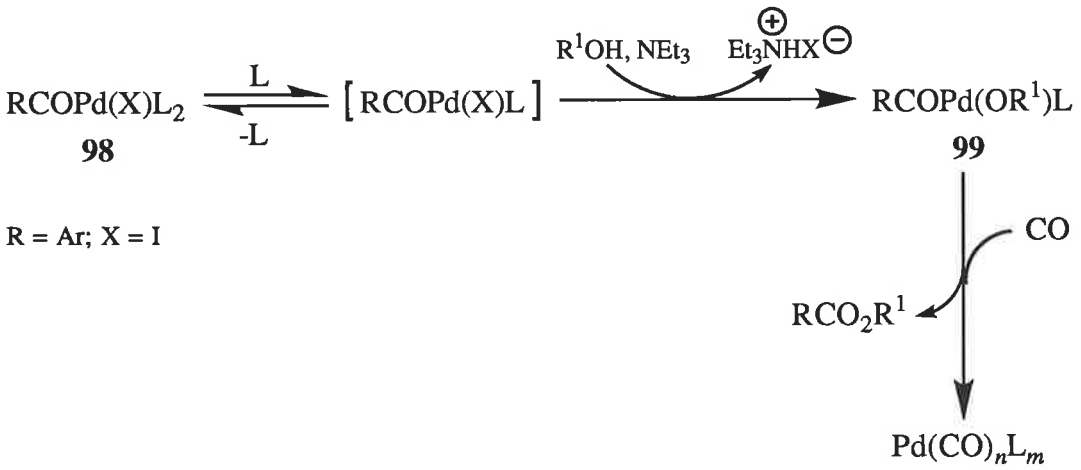


Scheme 2.10

The cycle begins with either a palladium(0) catalyst directly, commonly tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$), or by reduction of a palladium(II) precursor such as palladium(II) acetate or bis(triphenylphosphine)palladium(II) chloride ($PdCl_2(PPh_3)_2$). Such a Pd(II) precursor is reduced in the presence of CO, alcohol and base to a zero-valent species. The initial low ligated Pd(0) species may be represented as

$Pd(CO)_nL_m$ **96**, which oxidatively adds the aryl halide to give a *trans*-Pd(II)Ar(X)L_2 complex **97**. Subsequent insertion of carbon monoxide into the Ar-Pd σ-bond yields *trans*-Pd(II)(COAr)XL_2 **98**. This acyl metal species then undergoes base-assisted alcoholysis to afford the carboxylic ester with concomitant regeneration of the active catalyst.

Although numerous studies have shown that the presence of the base is to deprotonate the alcohol, thus generating the stronger alkoxide nucleophile,[146,156a] it has been implicitly inferred that attack occurs at the carbonyl carbon of the acyl palladium complex. However, evidence for this remains scarce. In contrast, direct attack at metal centres by nucleophiles is ubiquitous (a process central to ligand exchange)[157,158] and would result in the formation of a σ-acyl σ-alkoxy Pd(II) species. Yamamoto *et al.*[146] has thus determined that rather than this direct attack on the acyl ligand, the complex **98** undergoes alcoholysis to form an RCOPd(OR^1)(PPh_3) intermediate **99** (nucleophillic attack by an alcohol on the CO ligand coordinated to an arylpalladium complex is considered too slow a process). Complex **99** then undergoes a reductive elimination to form the ester (**Scheme 2.11**).



Scheme 2.11

The same workers have reported that σ-acetyl σ-aryloxy Pd(II) complexes readily undergo reductive elimination of aryl acetate.[159] However, it is unfortunate that little data has been collated on the analogous acyl alkoxy compexes. Overall, an ambiguity exists with respect to the exact mechanistic details of the decomposition of intermediate **99**. As a

consequence, no pertinent information is available regarding the intermediacy of these acyl alkoxy complexes.

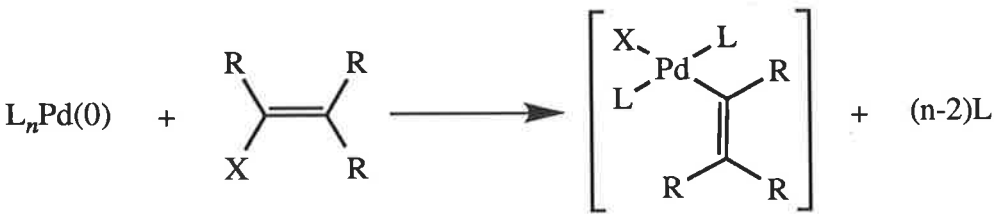
In special cases, where CO insertion into the Pd-C bond is difficult or not favoured (*vide infra*), carbomethoxy complexes may be involved. In the case of amide formation from aryl halides, Yamamoto *et al.*[143a] has determined that due to the increased nucleophillicity (compared to alcohols) of the secondary amine present, attack on the CO ligand coordinated to the arylpalladium complex was occurring. This process was deemed faster than the CO insertion into the aryl palladium bond.

2.4.1 Carbonylation of vinyl electrophiles

As stated, the carbonylation reaction of sp^2 substituted electrophiles is initiated by their oxidative addition to a low ligated zero-valent palladium which is followed by a subsequent carbonyl insertion. Reductive elimination yields the product with the reaction considered to proceed *via* a chain cycle. These three steps with respect to primarily vinyl electrophiles (halides and triflates) will be considered below.

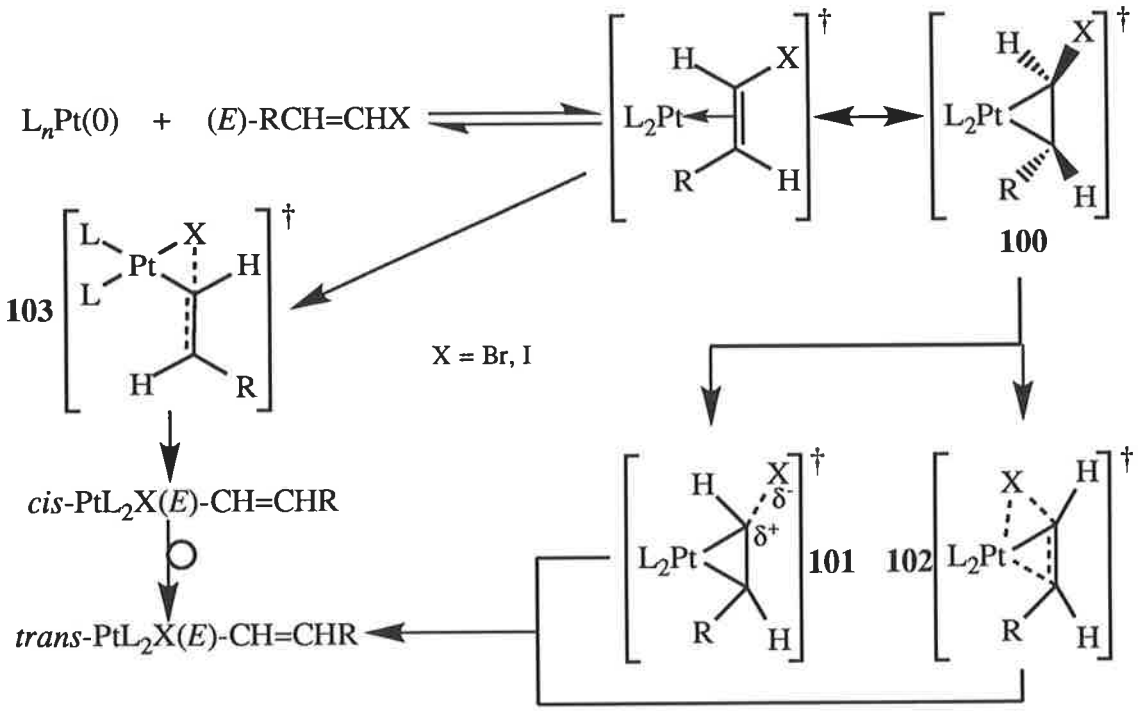
2.4.1.1 Oxidative addition

The oxidative addition of vinyl halides to palladium(0) complexes takes place rapidly with the ease of reaction depending upon the halide and the ligands on palladium (**Scheme 2.12**). The reaction, as is the case for nickel(0) and platinum(0), is stereospecific with retention of geometry being observed in all cases. Although no intermediates have been isolated, it is believed that a reaction mechanism involving a rearrangement of a three-membered π-alkene palladium complex occurs.[160]



Scheme 2.12

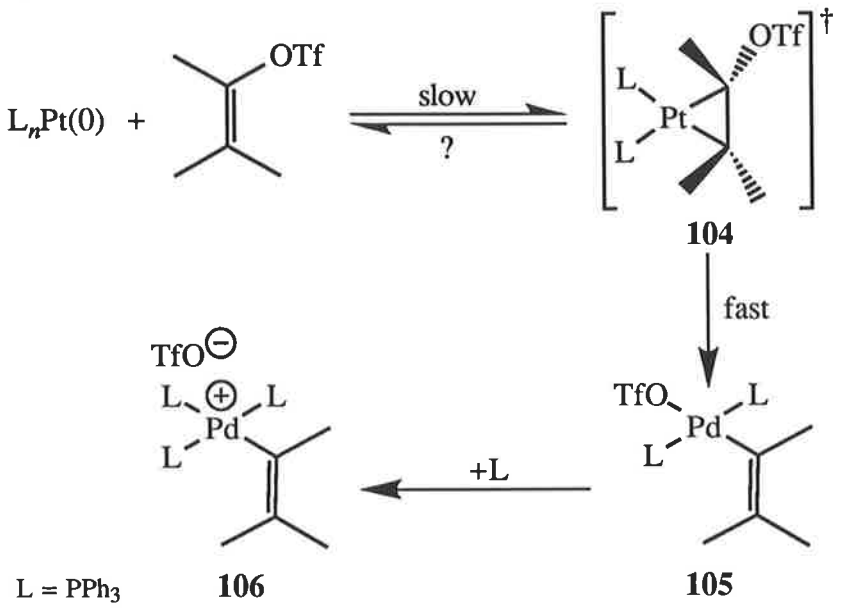
The mechanistic details are again by analogy from the corresponding platinum complexes.[160] The reaction proceeds by coordination of the carbon-carbon double bond to the metal which may form an intermediate platinacyclopropane complex **100**. The rearrangement then occurs, depending on the solvent polarity, *via* the two possible extreme intermediates **101** and **102**. This rearrangement is consistent with the observed retention of configuration in the final vinyl complex. However for less electronegatively substituted complexes, possessing less platinacyclopropane character, the existence of a concerted reaction mechanism is possible *via* **103** (**Scheme 2.13**). The rate of oxidative addition to vinyl halides for these platinum complexes falls into the order I>Br>Cl (no reaction with F). The mechanism for vinyl chlorides is considered to be of a similar nature to that of vinyl triflates (*vide infra*).[160]



Scheme 2.13

The mechanism of oxidative addition of vinyl triflates has again been determined by the employment of stoichiometric platinum as the basis for the analogy to palladium.[161] The reaction occurs by a rate-determining, possibly reversible, reaction of $Pt(PPh_3)_4$ with the vinyl triflate to result in the stereospecific formation of a π-alkene platinum complex **104**. This intermediate then undergoes rapid rearrangement to a σ-vinyl coordinated complex **105**.

Addition of triphenylphosphine yields the σ-vinyl cationic platinum(II) complex **106** (**Scheme 2.14**).

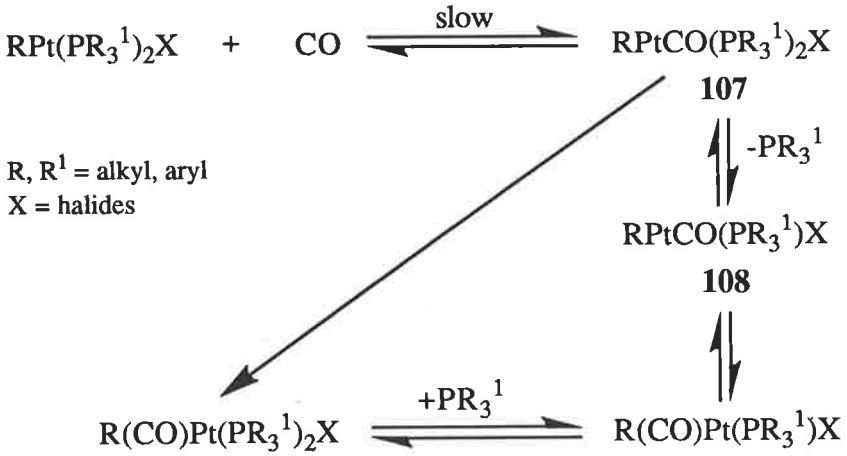


Scheme 2.14

Utilizing NMR studies involving stoichiometric palladium, Farina and Roth[162] have suggested that, depending upon the solvent, aryl triflates undergo oxidative addition to form analogues of intermediates such as **103**.

2.4.1.2 Carbonyl insertion

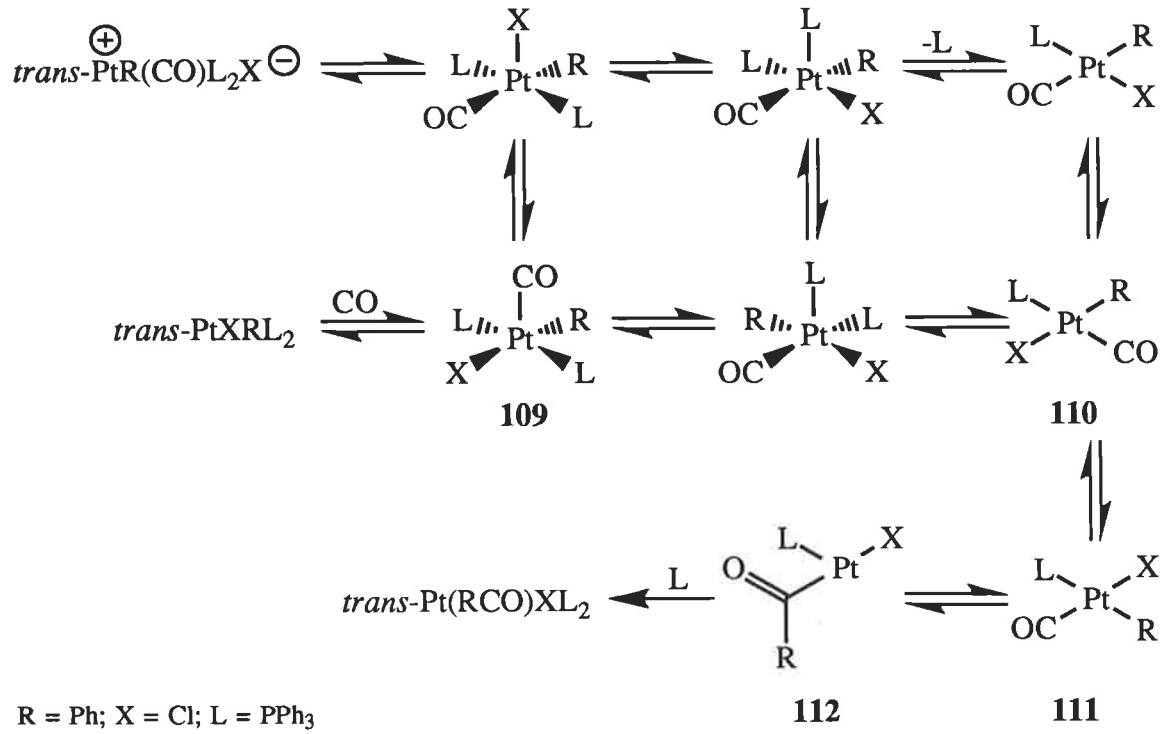
The mechanism of the insertion of carbon monoxide into the C-Pd(II) σ-bond has been the subject of several experimental[163] and theoretical[164] reviews. Most studies have centred on the carbonylation of square planar 16-electron complexes of palladium(II) or platinum(II) aryl complexes containing monodentate phosphine ligands. For instance Heck *et al.*[163b], using mainly aryl Pt(II) halide complexes, has established that migration of an aryl group occurs by initial slow reaction of carbon monoxide to form a fluxional pentacoordinate species (of an unclear geometry) **107** which then reacts *via* two possible routes. The most dominant case involves the conversion to a four-coordinate complex **108** after dissociation of one phosphine ligand. It is from this four-coordinate complex that carbonyl insertion then occurs



Scheme 2.15

(**Scheme 2.15**). Generally this route is favoured by less basic triarylphosphines, which are more readily displaced from Pt by CO. The other possible route proceeds *via* a direct migratory insertion from **107**.

In more detailed studies Anderson *et al.*[163c] have determined that the sequence for the carbonylation of the Pt-R bond, in a complex of the form *trans*-L_2PtRX, may be represented as in **Scheme 2.16**. A molecule of carbon monoxide associates to the Pt centre to form a pentacoordinate species **109** (this exists as a cationic square planar metal carbonyl in polar media)[163d] which is followed by ligand displacements and isomerization of the four- and five-coordinate Pt-CO intermediates shown. Migration of the R group (which is favoured by a partial negative charge on R and a partial positive charge on CO) to a *cis*-coordinated CO molecule is followed by stabilization of the unsaturated 14-electron T-shaped product **112** by ligand association. This migration will rapidly reverse unless ligand stabilization occurs. Despite **110** possessing an aryl group *cis* to carbon monoxide it does not undergo insertion, but rearranges to **111**, whose reactivity is heightened because the trans effect of the phosphine ligand weakens the R-Pt σ-bond. This is consistent with R migration being the reaction mechanism. By analogy this has been used to explain the mechanism for the insertion of carbon monoxide into square planar palladium(II) complexes. Furthermore, elegant work by Stille *et al.*[165] has shown that CO insertion into Pd-C bonds occurs with retention of configuration at carbon.



Scheme 2.16

The ligand displacements and isomerizations shown in **Scheme 2.16** are presumed to occur through formation of trigonal bipyramidal intermediates and psuedorotation. In addition, the necessity for ligand displacement is highlighted by the fact that related complexes possessing bidentate phosphine ligands do not undergo carbonylation.*

This has also been borne out in the case of intramolecular carbonylations where bidentate phosphine ligands severely retarded the reaction of halo alcohols **113**.[103] The presence of a hydroxyl group, although not a good ligand for palladium, was assumed to block a coordination site on the metal. This necessitates that a phoshine ligand must dissociate in order for CO to coordinate to the metal prior to insertion. Such a rationale has been put forward in the case of iridium complexes with aryl groups featuring coordinating *ortho*-methoxy groups.[166]

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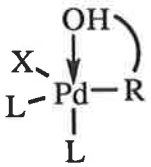
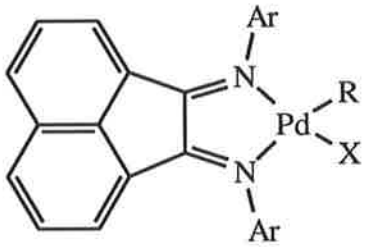
* The reactions are faster for palladium than platinum and occur most readily for triarylphosphine complexes. This is expected to be the case in light of a mechanism involving displacement of a tertiary phosphine.



113 L, L = diphos; X = halides

It is of interest to note, however, that the carbonylation of complexes with more rigid chelating ligands, such as bidentate N-N or N-N-N ligands,[167] has revealed evidence for other low-energy pathways for carbon monoxide insertion. Elsevier *et al.*[168] has observed the facile insertion of carbon monoxide into alkyl palladium bonds of complexes **114** containing the rigid bidentate nitrogen donor ligand bis(arylamino)acenaphthene (Ar-BIAN) from which ligand displacement is unlikely. However, no such intimate studies have been made on insertions into the aryl analogues.



114 R = alkyl; X = Cl

A pathway has been proposed for these complexes and is illustrated in **Scheme 2.17**. Carbon monoxide insertion occurs *via* an initial displacement of a halide, rather than the ligand *trans* to the organic group, to form a four-coordinate cationic species **115**.* This is believed to account for the high reactivity toward insertion reactions of complexes containing Ar-BIAN ligands where their rigidity disables displacement of one ligating N atom. This is in contrast to the case where flexible bidentate ligands are present, since preferential diplacement of the coordinating atom trans to the organic ligand would occur to form **116**. Such a complex can not undergo subsequent insertion of carbon monoxide.

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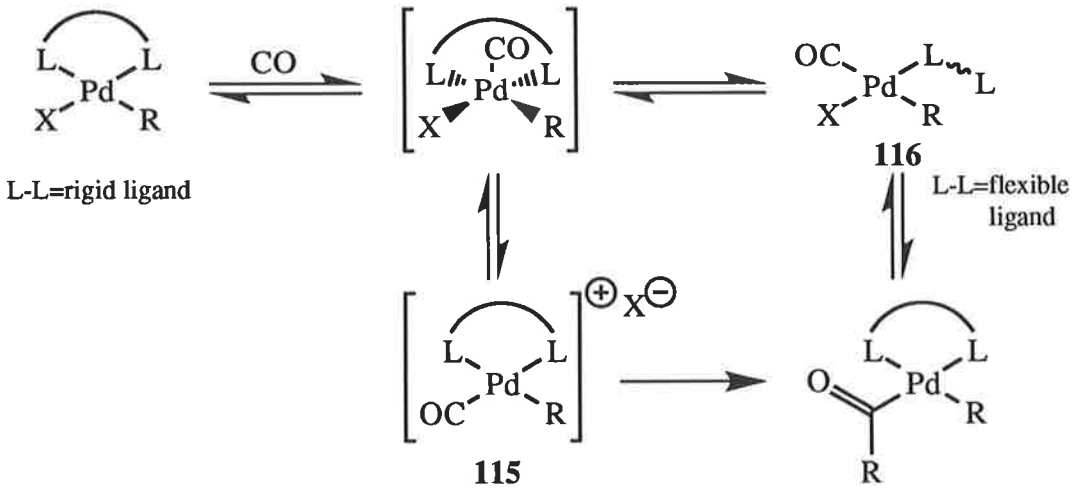
* The chloride may, however, remain in the vicinity of the Pd in the cationic complex thus making very little difference betwen a five- or a four-coordinate complex.



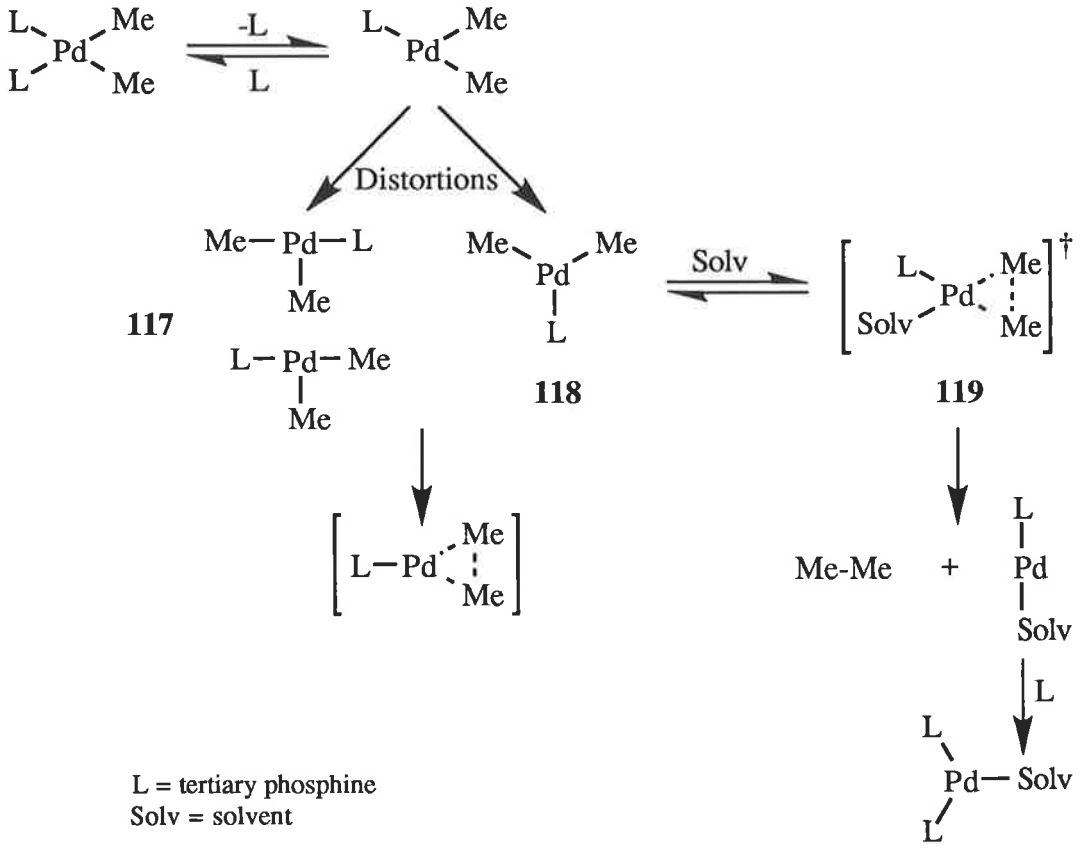
Scheme 2.17

2.4.1.3 Reductive elimination

Theoretical calculations indicate the reductive elimination of organic groups bound to palladium (in a 16-electron d^8 complex of the form *trans*-Pd(II)RR^{1}L$_2$) is an allowed process only when the two groups are *cis*, or the complex is in a trigonal planar-like configuration.[169] The elimination may proceed by mechanistic pathways which are dependent on the ligands (their size and electronic characteristics), the organic groups present and the reaction conditions (e.g., the ratio of palladium:ligand, the presence of RX and the nature of the solvent).[160] In essence, the reductive elimination reaction represents an overall reduction of two in the formal oxidation state and coordination number of the metal.

There exist a number of conceivable pathways by which the two organic groups in a *trans* complex can attain positions adjacent to one another prior to coupling: i) prior dissociation of a phosphine ligand to give a three coordinate intermediate; ii) prior association of a phosphine ligand to give a five-coordinate intermediate; iii) conversion of the complexes in i) and ii) to a *cis* square planar complex by recoordination or dissociation (after rearrangement) respectively; iv) distortion of a *trans* complex into a transient tetrahedral geometry; and v) oxidative addition of an organic halide to the palladium(II) complex followed by subsequent elimination.[160]

Experimental data suggests that reductive coupling from a *cis* palladium dialkylbis(phosphine) complex (e.g., $PdMe_2L_2$) proceeds *via* a tricoordinate 14-electron T- or Y-shaped intermediate (**117** or **118**) formed *via* the dissociation of a phosphine ligand (a geometrically attractive trigonal planar structure represents an energy hill).[160] The presence of a coordinating solvent promotes reductive elimination by either enhancing the dissociation of a phosphine by solvation or by occupying a vacant coordination site in the T- or Y-shaped complex. The reductive elimination may occur from either a *cis* square-planar complex containing coordinated solvent **119** or from intermediates **117** or **118**.* Overall it is an intramolecular and concerted process (**Scheme 2.18**).[170] The reaction is also enhanced by

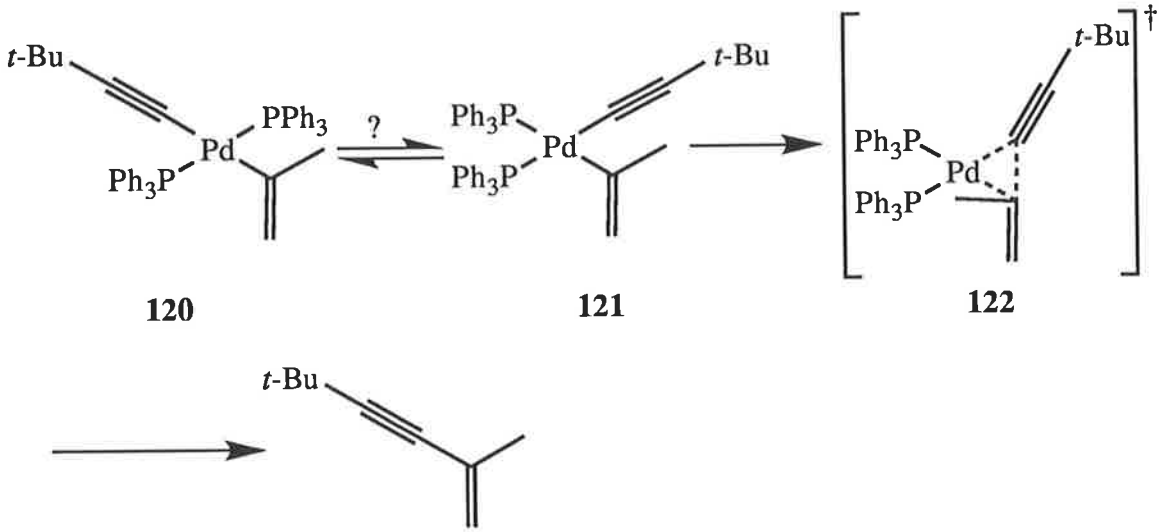


Scheme 2.18

* Reductive elimination may be occurring from either the T or Y complex, however, it is unclear from which intermediate this may take place since the activation energies of both are nearly identical and the activation energy for isomeric interconversion is low.

organic groups bearing electron donating groups and retarded by those bearing electron withdrawing groups. In addition, the elimination reaction produces an unsaturated palladium(0) complex, $Pd(0)L_2$, which forms a complex of the form $Pd(S)_nL_2$ in the presence of a coordinating solvent. This also has been calculated to lower the energy for the reductive elimination.

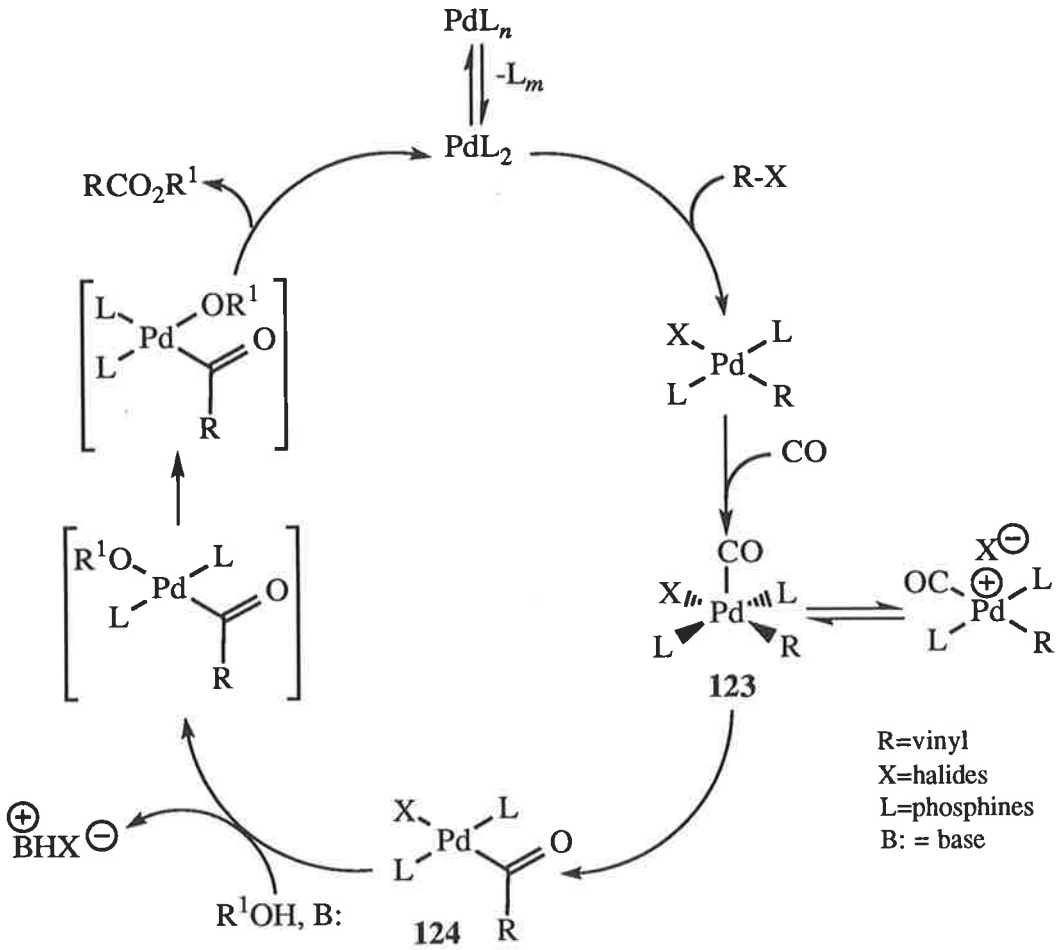
When one of the organic groups being eliminated possesses a sp or sp^2 hybridized group the energy of activation for the reductive elimination is considerably lowered. Stang *et al.*[171] have shown that the reductive coupling of a platinum(II) *cis* complex **121** does not seem to require the dissociation of phosphine, elimination occurring directly from this four-coordinate complex (since the $\Delta G^{\ddagger}$ for elimination from a four-coordinate complex is lower than the ΔG_f of the three-coordinate intermediate). This process was thus found to readily occur at low temperatures *via* a concerted process incorporating a strained three-membered transition state **122** (**Scheme 2.19**). This was in contrast to the corresponding *trans* complex **120** where a prior phosphine dissociation, presumably to attain the *cis* isomer, was necessary to effect the reductive elimination.



Scheme 2.19

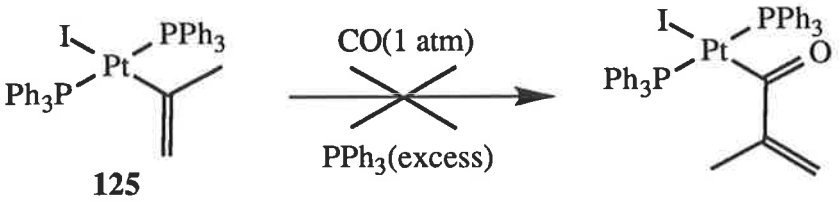
2.4.1.4 Carbonylation of vinyl halides

The mechanism of the palladium-catalyzed carboalkoxylation of vinyl halides (**Scheme 2.20**) has only recently been elucidated in detail by Stang *et al.*[172] using the corresponding platinum complexes in stoichiometric quantities.

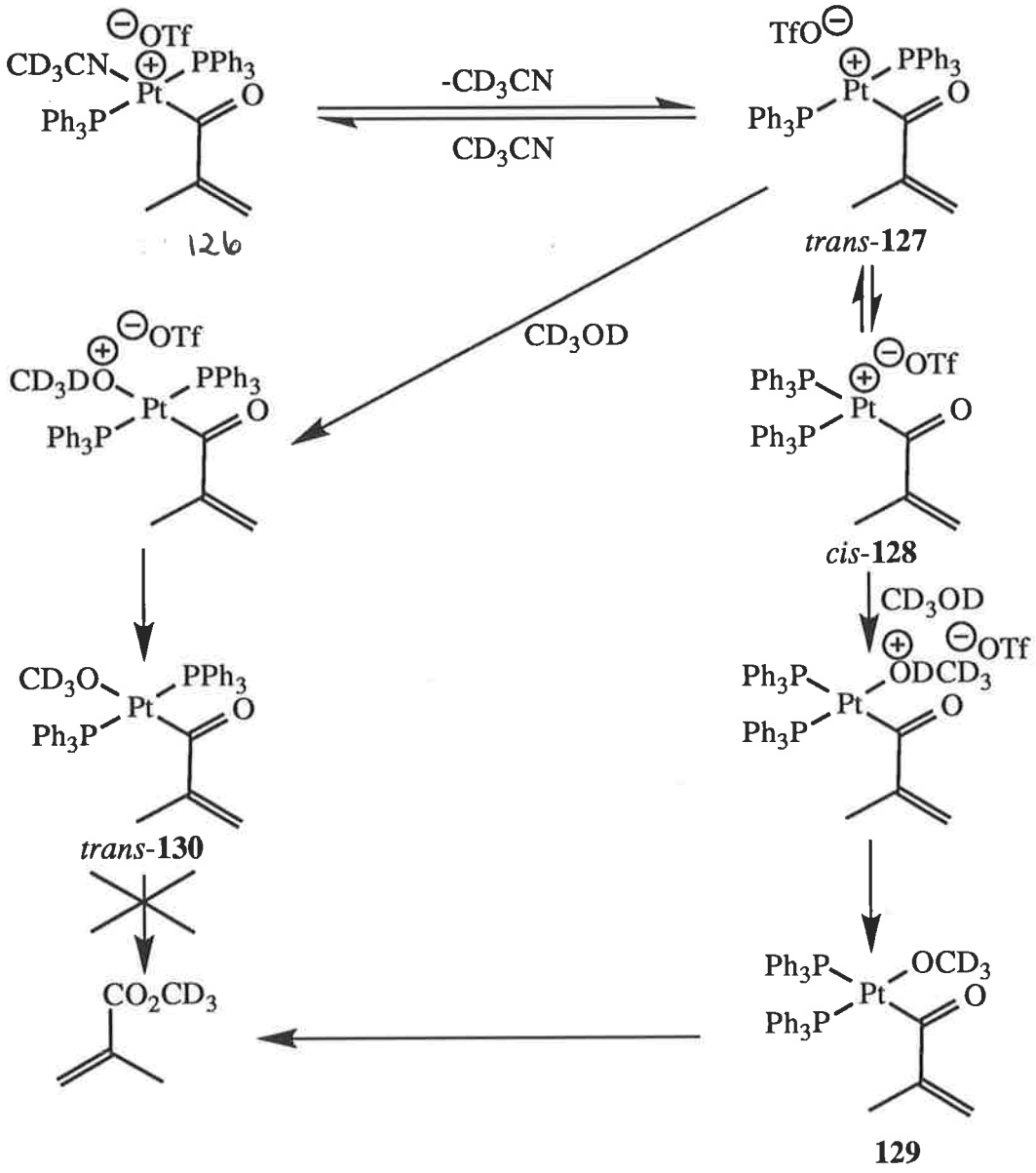


Scheme 2.20

The proposed sequence is initiated by the well established oxidative addition of vinyl electrophiles to zero-valent palladium. Carbonyl insertion into the vinyl palladium(II)-carbon σ-bond forms the square planar intermediate 124. Solution chemistry indicates that this process procedes *via* a pentacoordinate carbonyl species 123 where phosphine dissociation occurs prior to migratory insertion of carbon monoxide (*vide supra*). This was demonstrated by the fact that migratory insertion did not occur in complex 125 in the presence of excess phosphine ligands (**Scheme 2.21**). However, the possibility of direct migratory insertion could not be ruled out entirely.



Scheme 2.21



Scheme 2.22

(Scheme 2.20)

Subsequent alcoholysis of the vinylic Pd(II) complexes **124** occurs with the intimate mechanism determined using highly labile cationic vinylic acyl Pt(II) complex **126** (**Scheme**

2.22).* Kinetic and NMR spectral studies indicated that the reaction proceeds *via* a preequilibration to form a reactive, trigonal-planar intermediate *trans*-**127**. A rate determining *trans-cis* isomerization is followed by nucleophillic attack of an alcohol on *cis*-**128** to result in the formation of *cis* σ-acyl σ-alkoxy Pt(II) complex **129**. Facile reductive elimination then gives the α,β-unsaturated carboxylic esters. Since theoretical calculations suggest that reductive elimination from d^8 complexes must proceed *via* a *cis* or trigonal-planar orientation, the other possible mechanism, *via trans*-**130**, is symmetry forbidden. Again by analogy the same processes are envisaged to be occurring with palladium.

2.4.1.5 Carbonylation of vinyl triflates

The catalytic cycle for the palladium-mediated carboalkoxylation of vinyl triflates can be generalized as in **Scheme 2.23**, where again Stang *et al.*[173] have utilized platinum complexes to elucidate the precise mechanism. Initial oxidative addition of the vinyl triflate to platinum(0) produces a σ-organo Pt(II) triflate complex **131**. As a consequence of the superior leaving group ability of the triflate ligand, carbon monoxide replaces it to generate a cationic σ-organo Pt(II) carbonyl **132** *via* nucleophillic substitution. Alkoxide then adds to the CO ligand to form a σ-bonded alkoxy carbonyl complex **133**. The addition of alcohols to many transition metal carbonyls is well known with the general addition of nucleophiles to the carbonyl ligand occurring in the catalytic carbonylation to amides,[143,174] α-keto amides[175] and α-keto esters.[146,176] Such complexes then readily reductively eliminate the desired α,β-unsaturated carboxylic esters.

Phosphine inhibition and activation parameters strongly suggest that the reductive elimination of *trans* σ-alkoxycarbonyl σ-vinyl Pt(II) complexes involves a rate determining *trans-cis* isomerization to *cis*-128 which occurs *via* an initial preequilibration involving phosphine dissociation (**Scheme 2.24**). Again a concerted transition state for the reductive elimination from the *cis* isomer may be invoked and a direct analogy to palladium drawn.

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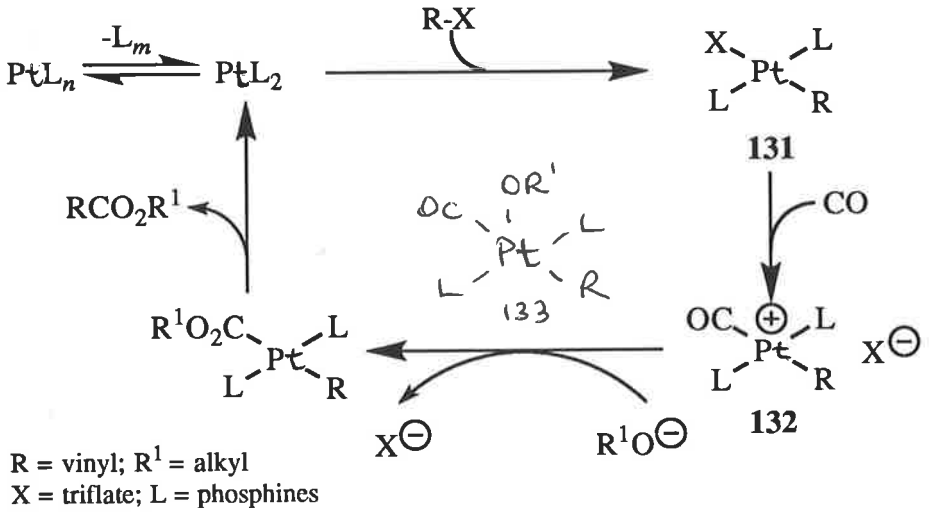
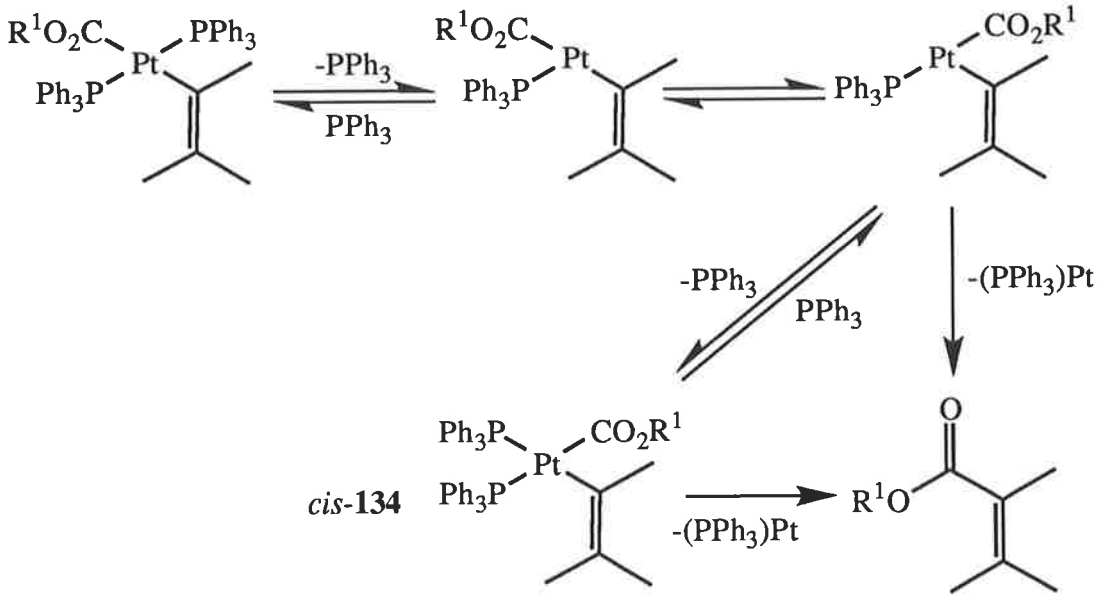
* The high reactivity is attributed to the ready dissociation of the CD_3CN ligand.



Scheme 2.23



Scheme 2.24

Although the exact mechanism for the carbonylation of aryl triflates has not been corroborated, it could generally be assumed to be similar in nature to that determined for the vinyl analogue.

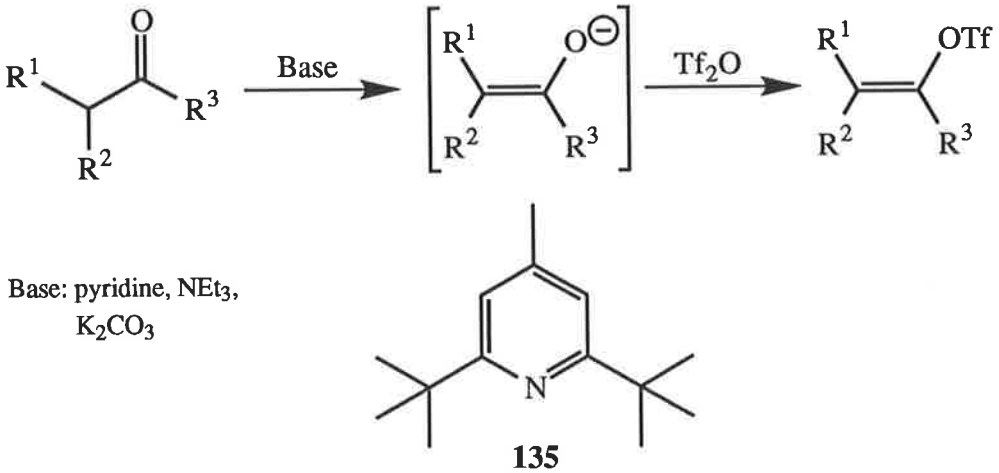
2.5 Results and discussion

A variety of hydroxy or amino vinyl triflates have been prepared in order to undergo the palladium-catalyzed intramolecular carbonylation reaction. The applicability and scope of introducing the triflate moiety several steps prior to the coupling was also investigated.

Synthesis of substituted α,β-butenolides

2.5.1 Preparation of hydroxy vinyl triflates

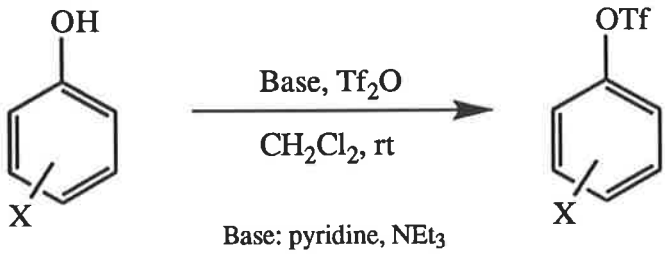
Vinyl triflates are most often prepared from the corresponding carbonyl compounds by treatment directly with trifluoromethanesulfonic anhydride(Tf_2O) and a non-nucleophillic base (**Scheme 2.25**).[177] Sterically hindered bases such as 2,6-di-*tert*-butyl-4-methylpyridine **135** have been reported to increase the yield of triflate since the formation of salts with Tf_2O is minimized.[178] A polymer-bound form of this base has also been noted.[179] A lack of stereochemical control , to give mixtures of *E*- and *Z*-vinyl triflates, is an inherant problem in the case of acyclic carbonyl compounds. As expected the thermodynamically more stable *E*-isomer predominates.



135

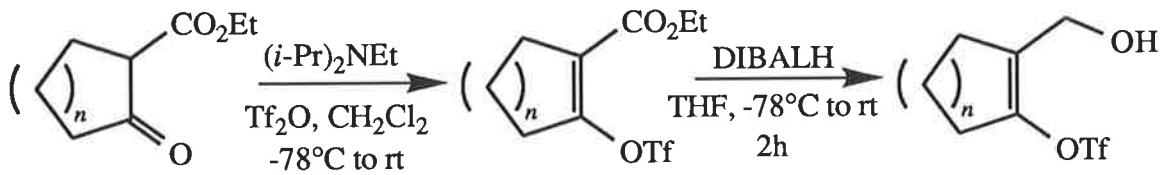
Scheme 2.25

In a similar manner aryl triflates are usually prepared from the corresponding hydroxy arenes again using Tf_2O in the presence of a base such as pyridine or triethylamine (**Scheme 2.26**).[176] Sodium or potassium phenolates have also been used.



Scheme 2.26

For the palladium-catalyzed carbonylation reactions under study, a variety of cyclic hydroxy vinyl triflates were readily prepared from the corresponding highly enolizable β-keto esters *via* a two-step procedure (**Scheme 2.27**). Firstly, vinyl triflate formation was carried out by adding up to five molar equivalents of N,N-diisopropylethylamine (Hünigs base) to a dichloromethane solution of the cyclic β-keto ester at -78°C. Whilst at low temperature Tf_2O was subsequently added.[180] Distillation of the resultant dark red crude material gave the corresponding ethoxycarbonyl substituted vinyl triflates **136** in good yields for ring sizes five through eight. These reactions were either monitored by TLC or GLC analysis for the dissappearance of ketone and formation of ester since extended reaction times are reported to lower the yields of vinyl triflates.[177] To these vinyl triflates, in THF at -78°C, was added two equivalents of diisobutylaluminium hydride (DIBALH) which resulted in the clean reduction of the ester to the corresponding hydroxy methylene compounds **137**. Reduction of the triflate group was not observed. The same conditions were also used on ethyl salicylate to furnish 2-[(trifluoromethanesulfonyl)oxy]benzoate[181] and 2-[(trifluoromethanesulfonyl)oxy]benzyl alcohol **138**.[153b]

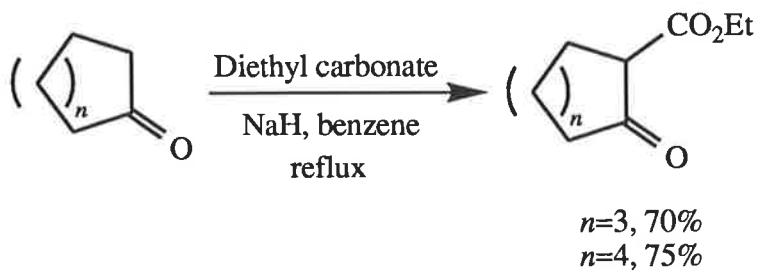


136a *n*=1, 77%
b *n*=2, 61%
c *n*=3, 77%
d *n*=4, 95%

137a *n*=1, 77%
b *n*=2, 77%
c *n*=3, 89%
d *n*=4, 68%

Scheme 2.27

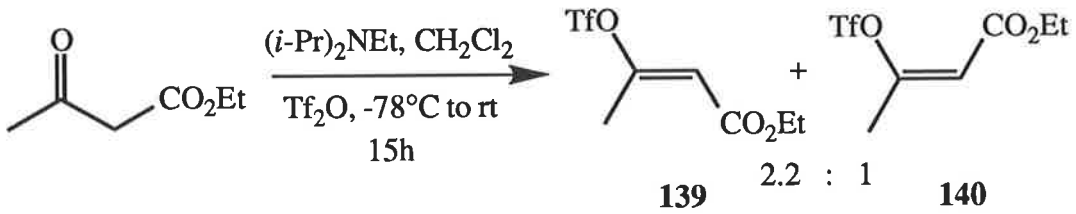
The starting β-keto esters for ring sizes five and six were commercially available, however it was necessary to synthesize those of ring sizes seven and eight. This was achieved by treatment of the appropriate cyclic ketone with diethyl carbonate and base.[182] This gave the necessary precursors in good yield (**Scheme 2.28**).



Scheme 2.28

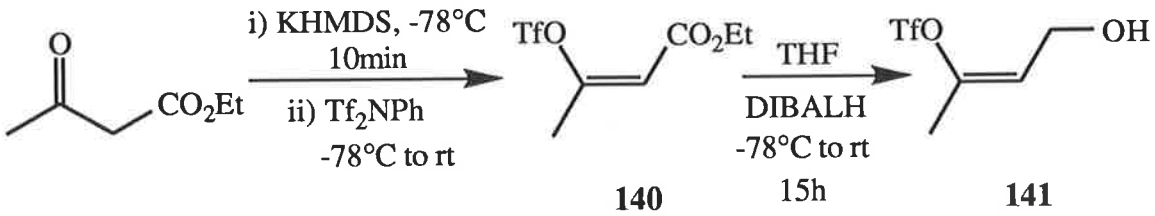
The corresponding twelve-membered β-keto ester could not be converted into a vinyl triflate by the method outlined in **Scheme 2.27**. A complex mixture of products was obtained which could not be purified. Furthermore, reaction in the presence of KHMDS and Tf_2NPh also resulted in the formation of an array of unidentifiable reaction products. It is not clear why these methods failed, although the increase in the number of possible ring conformations the twelve-membered ring may adopt perhaps inhibits the approach of the base and/or the triflating agent.

Attention was subsequently directed toward the synthesis of acyclic hydroxy vinyl triflates utilizing a route similar to that described above. However, control of regio- and stereochemistry becomes a critical factor in the triflating step. When ethyl acetoacetate was reacted with N,N-diisopropylamine and Tf_2O (as described in **Scheme 2.27**) a 2.2:1 mixture of *E*- **139** and *Z*-3-[(trifluoromethanesulphonyl)oxy]-2-butenoate **140** was obtained (**Scheme 2.29**). The relative proportions of each product was determined from the crude ^1H NMR (vinylic resonances at δ5.95(*s*) and δ5.77(*s*) were diagnostic for the *E*- and *Z*-isomers respectively). This was in agreement with data obtained by Saulnier *et al.*[180] where a similar ratio of 2.5:1 was found.



Scheme 2.29

Not suprisingly, it was noted by Stille *et al.*[103] that the palladium-catalyzed intramolecular carbonylative coupling reaction to butenolides may only proceed when the hydroxy vinyl iodides possessed a *Z*-configuration about the double bond. Thus a method was sought that would deliver the required vinyl triflate with a high degree of *Z*-stereospecificity. The addition of ethyl acetoacetate to a THF solution of KHMDS at -78°C, with subsequent stirring for 10 minutes, was followed by the addition of Tf_2NPh to give the required ethyl *Z*-3-[(trifluoromethanesulfonyl)oxy]-2-butenoate **140** in 76% yield as the only isolated product. Subsequent reduction yielded the *Z*-hydroxy vinyl triflate **141** in 72% yield (**Scheme 2.30**). It can be assumed that the observed stereoselectivity is a consequence of an effective potassium cation mediated chelation between the formed enolate and the ester moiety (**Figure 2.1**).



Scheme 2.30

However, when ethyl 2-benzylacetoacetate was treated under identical conditions a 3:1 mixture of *E*- and *Z*- isomers (as identified by crude ^1H NMR; characteristic methyl resonances at δ2.45(*s*) and δ2.20(*s*) respectively) was obtained from which 12% of Z-vinyl

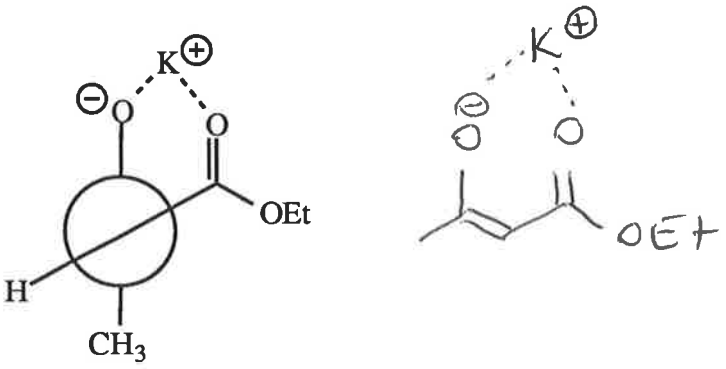
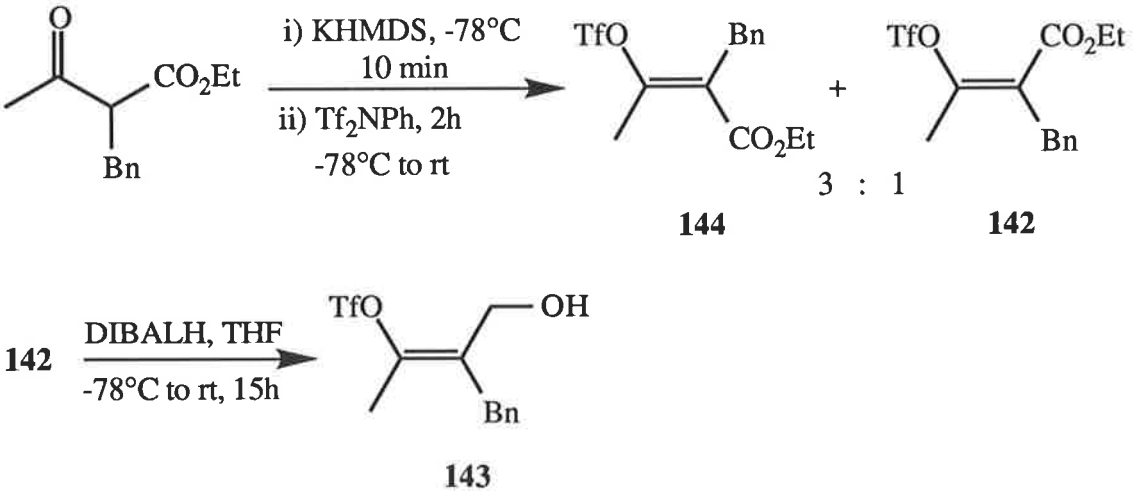


Figure 2.1

triflate **142** was isolated by chromatography. Again the reduction to the *Z*-hydroxy compound **143** proceeded smoothly (**Scheme 2.31**). Presumably the increase in steric interactions between the benzyl and methyl groups reduces the effectiveness of the assumed chelation (**Figure 2.2**). Less steric demands are placed upon the stereoselective triflation of ethyl acetoacetate (**Figure 2.1**).



Scheme 2.31

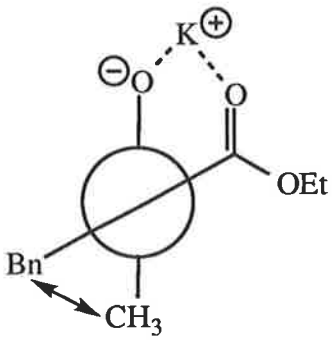
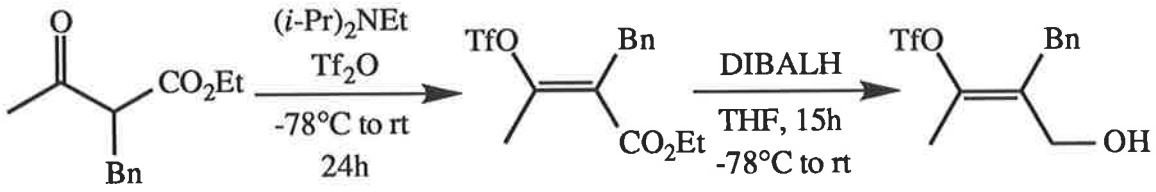


Figure 2.2

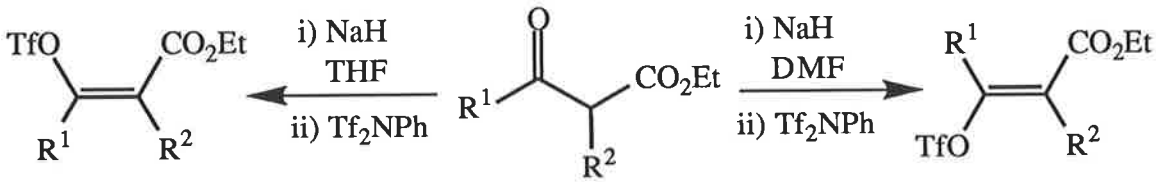
Interestingly, when ethyl 2-benzylacetoacetate was treated under the equilibrating conditions described in **Scheme 2.29** only the thermodynamically favoured *E*-vinyl triflate **144** was obtained in 75%.* This compound was also smoothly reduced with DIBALH to afford *E*-hydroxy vinyl triflate **145** (**Scheme 2.32**).



144 **145**

Scheme 2.32

Stereoselective formation of vinyl triflates from β-keto esters has also been reported by using sodium hydride as base.[183] Moreover, the choice of solvent can determine the stereochemistry obtained (**Scheme 2.33**).[184]



R^1=Me, Bu, Bn
R^2=H, Bn

Scheme 2.33

2.5.2 Palladium(0)-catalyzed intramolecular carbonylations of hydroxy vinyl triflates[185]

The initial conditions employed were of a similar nature to that described by Stille for the reaction of hydroxy vinyl iodides.[103] Hence, to an acetonitrile solution of cyclic vinyl triflate, presaturated with carbon monoxide, was added $Pd(PPh_3)_4$ (10 mole%), potassium carbonate and lithium chloride. This was then placed under one atmosphere of carbon monoxide

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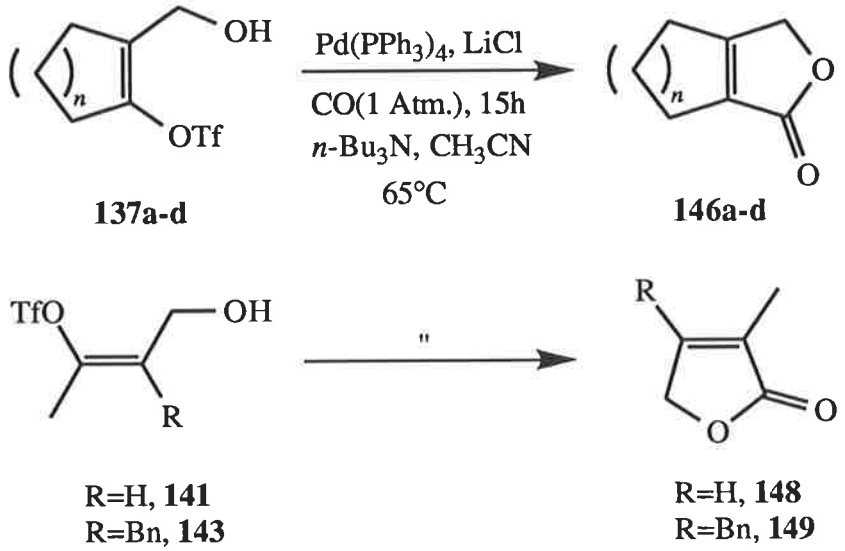
* An attempt to form the vinyl triflate of ethyl 2-benzylacetoacetate in the presence of Na_2CO_3 and Tf_2O in a dichloromethane solution only resulted in the recovery of the starting β-keto ester.

(supplied by balloon) and heated to 65°C for 15 hours. The resultant 3,4-disubstituted α,β-butenolides were obtained after purification in 40-50% yield.[186]

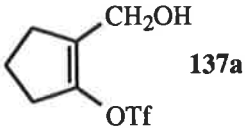
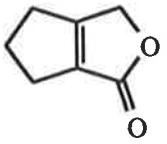
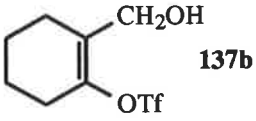
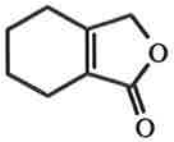
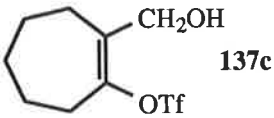
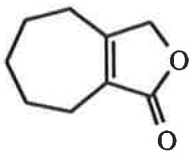
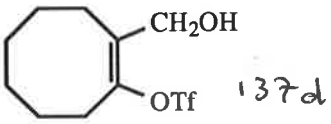
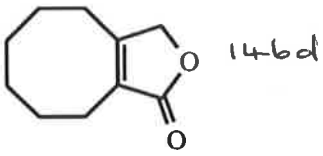
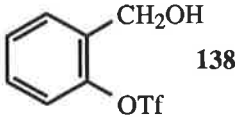
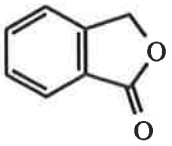
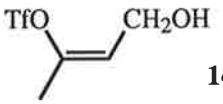
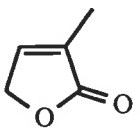
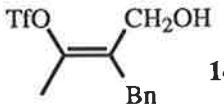
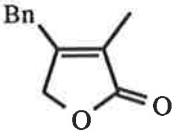
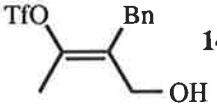
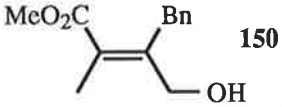
Improved yields of products (75-95%) were obtained by conducting the intramolecular carbonylations in the presence of an organic non-nucleophillic base, tri-*n*-butylamine, to yield a variety of 3,4-disubstituted α,β-butenolides (**Scheme 2.34**).



Scheme 2.34

The results of these carbonylations are summarized in **Table 2.1**. Overall the ring size appeared to have a negligible influence on the yield of the α,β-butenolide (entries 1-4, **Table 2.1**). Furthermore, the hydroxy aryl triflate 2-[(trifluoromethanesulfonyl)oxy]benzyl alcohol **138** readily underwent the intramolecular coupling reaction to give **147** (entry 5, **Table 2.1**). Acyclic hydroxy vinyl triflates **141** and **143** also underwent the carbonylation reaction with ease (entries 6-7, **Table 2.1**). The *E*-hydroxy vinyl triflate **145**, in the presence of an excess of methanol (5 molar equivalents), gave the expected methyl ester **146** in low yield with the absence of any lactone product (such a product could only form through an *E* to *Z* isomerization of the double bond). The low yield may be attributable to a possible intermolecular interception of the palladium(II) acyl complex by the alcohol functionality of a further molecule of hydroxy vinyl triflate. However, when the reaction was repeated in the absence of methanol no such aggregated material, or any other identifiable products, could be

Table 2.1 Palladium-catalyzed carbonylations of hydroxy vinyl triflates.

Entry	Hydroxy vinyl triflate	Product	Yield[a]
1	 **137a**	 **146a**	83
2	 **137b**	 **146b**	75
3	 **137c**	 **146c**	95
4	 137d	 146d	81
5	 **138**	 **147**	60
6	 **141**	 **148**	75
7	 **143**	 **149**	71
8	 **145**	 **150**	23

Reactions carried out by heating a mixture of the particular hydroxy vinyl triflate, $Pd(PPh_3)_4$ (10 mol%), LiCl (1.0 eq), *n*-Bu_3N (2.0 eq) in CH_3CN at 65°C under one atmosphere of carbon monoxide for a period of 15 hours.

[a] Isolated yield of pure material.

isolated from the reaction mixture.

In general the reaction mixtures changed from an initial yellow colour through orange and sometimes black. The black colour was presumably caused by the precipitation of palladium and always indicated that the reaction was complete. The course of the reaction was conveniently monitored by TLC analysis of the mixture and isolation of the product was by simple extraction and usually chromatography. In the case of 3-methyl-2(5*H*)-furanone **148** (entry 6, **Table 2.1**), since decomposition occurred on chromatographic silica, isolation was effected by kugelrohr distillation of the crude residue.

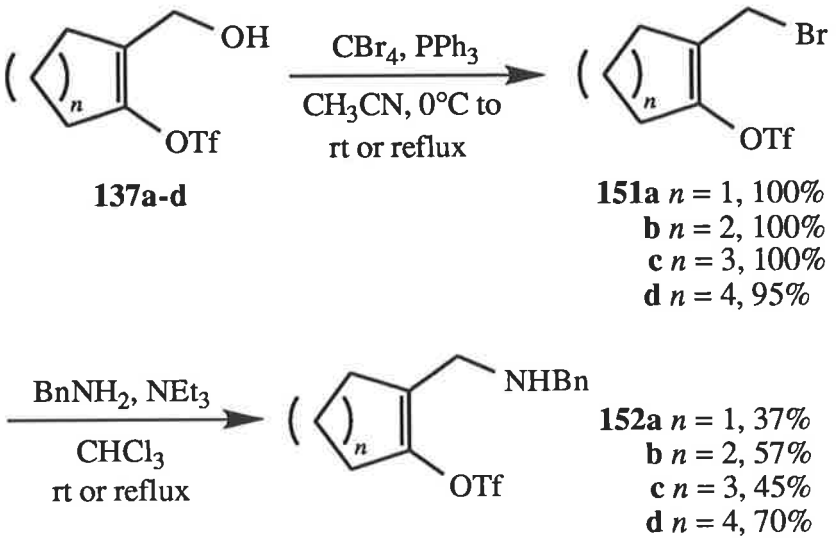
Synthesis of substituted α,β-unsaturated lactams

2.5.3 Preparation of amino vinyl triflates

The applicability of synthetic methodology is always strengthened if the necessary precursors of a reaction sequence can be obtained using an extension of previously developed techniques. Such was the case that presented itself to us in the development of amino vinyl triflates required for intramolecular carbonylations to 3,4-disubstituted α,β-unsaturated γ-lactams.

Utilizing the cyclic hydroxy vinyl triflates synthesized above it was able to be shown that amino vinyl triflates could be produced in an additional two-steps (**Scheme 2.35**). Thus cyclic hydroxy vinyl triflates, with ring sizes five through eight, were converted to the corresponding bromides, often quantitatively, by the slow addition of triphenylphosphine to a solution of the alcohol and carbon tetrabromide in acetonitrile at 0°C.[187] For compounds possessing five, six and eight membered rings refluxing of the reaction solution for between 1.5 and 15 hours was necessary. Analysis by TLC ensured that the reactions were stopped once all the starting alcohol had been consumed. The resultant allyl bromides **151** were subsequently converted to amino vinyl triflates **152** by modification of a procedure reported by Ban *et al.*[102b] Hence, benzylamine was added to a chloroform solution of the bromide and triethylamine at 0°C and, depending upon the substrate, followed by either stirring at ambient temperature or refluxing for between 2 and 3 hours. The reaction was again easily monitored

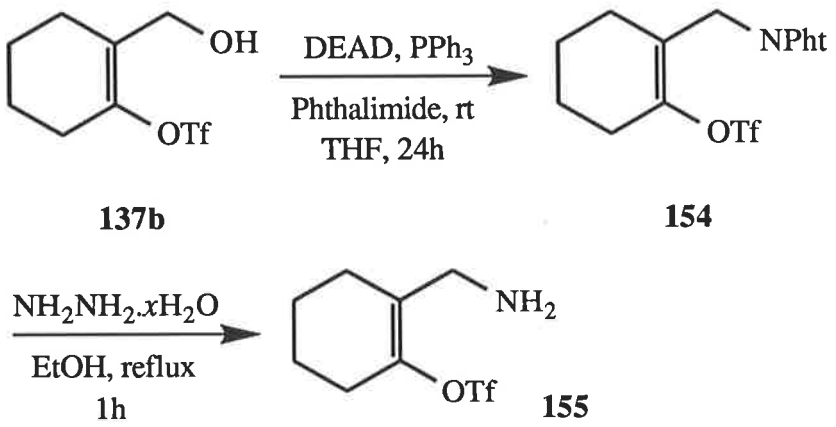
by TLC analysis of the crude reaction mix. The same conditions were used on 2-[(trifluoromethanesulfonyl)oxy]benzyl alcohol **138** to furnish 2-[(trifluoromethanesulfonyl)oxy]benzyl bromide and N-benzyl-2-[(trifluoromethanesulfonyl)oxy]benzylamine **153**.



Scheme 2.35

As a further element of our program to probe the reactivity of the triflate group it was envisaged that the six-membered hydroxy vinyl triflate, 2-[(trifluoromethanesulfonyl)oxy]-1-cyclohexenylmethanol **137b**, could be converted to the corresponding primary amino analogue (**Scheme 2.36**). Initially to a THF solution of the hydroxy compound, triphenylphosphine and phthalimide, was added dropwise diethylazodicarboxylate (DEAD) with stirring for 24 hours.[188] Following work up and purification the phthalimido derivative **154** was obtained in high yield (96%). It is believed that this is the first example of a Mitsunobu reaction[189] being carried out in the presence of a vinyl triflate moiety. Subsequent hydrolysis of the phthalimido unit, by heating an ethanol solution of it in the presence of an excess of hydrazine hydrate, gave the primary amine **155** (71%).[187] This convenient method of hydrolysis is known as the Ing-Manske procedure.[190]

Once again a variety of acyclic amino vinyl triflates were required for the intramolecular carbonylation reaction. A common method to generate vinyl triflates involves the

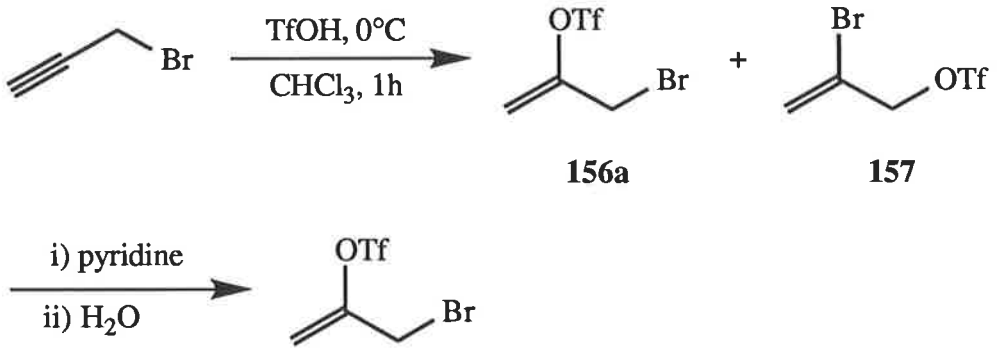


Scheme 2.36

Markovnikov addition of trifluoromethanesulphonic (triflic) acid (TfOH) to an alkyne, however this method is generally incompatible with highly functionalized organic substrates. In addition, a lack of regio- and stereochemical control in unsymmetrical alkynes is an inherant problem and also the product must possess a vinylic hydrogen atom.[177] Despite these shortfalls, this method represented a convenient entry point to a range of α-methylene lactams of varying ring sizes. Furthermore, the necessary presence of additional functionality contained within the alkyne molecule presented a challenge not only to generate the vinyl triflate, but to probe its subsequent displacement.

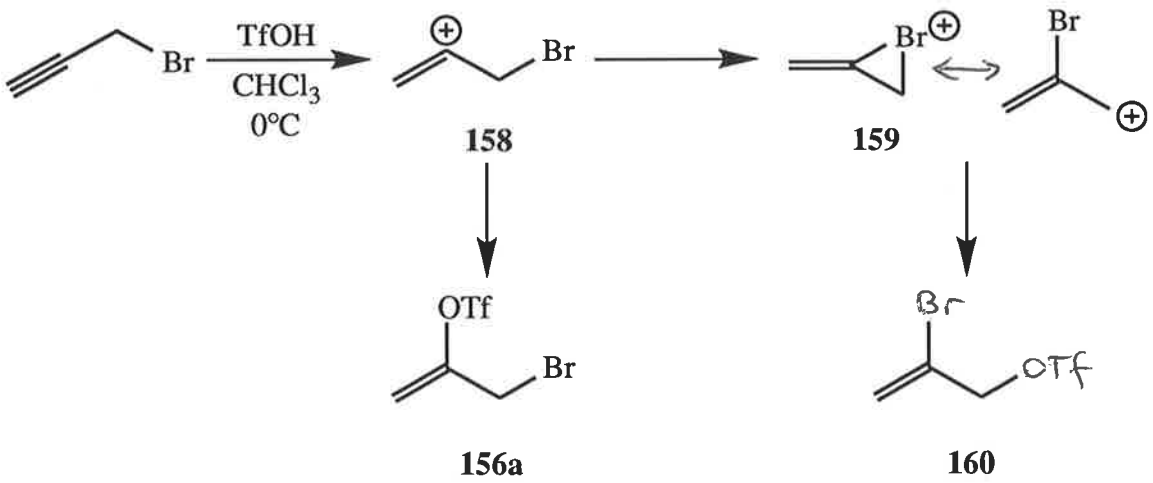
It was found that the addition of one equivalent of triflic acid to a chloroform solution of propargyl bromide at 0°C gave a mixture of regioisomers containing the desired vinyl triflate **156a** (17%) and unwanted vinyl bromide **157** (**Scheme 2.37**). The vinyl triflate was clearly identifiable by ^{1}H NMR since both the allylic singlet and the pair of vinylic doublets were shifted upfield relative to the vinyl bromide. These regioisomers could not be seperated by distillation or chromatography but a simple method for their separation involved the addition of pyridine to the crude reaction mixture. This method is based upon the extreme electrophillic nature of allyl triflates compared to allyl bromides.[191a] Consequently, the allylic triflate reacts readily with pyridine to form an N-allylpyridinium salt which may be removed by an aqueous wash. The addition of triflic acid to alkynyl halides was invariably

characterized by highly coloured solutions perhaps indicating the formation of polymeric material.



Scheme 2.37

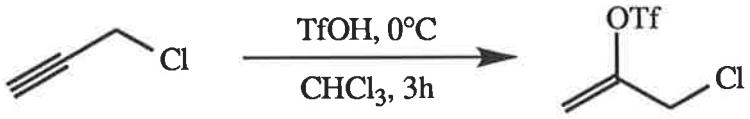
The vinyl triflate is presumably formed from the triflate anion reacting with the vinyl cation **158**, whereas the vinyl bromide may arise *via* an intermediate bromonium ion **159** (or an allyl cation). The allylic carbon then similarly reacts with the triflate anion to give **160** (**Scheme 2.38**).



Scheme 2.38

Since the unwanted vinyl bromide was probably formed *via* stabilization of the vinylic cation by bromine, it was of interest to determine the effect of employing a more electronegative atom in its place. Thus propargyl chloride was reacted with two equivalents of triflic acid, whilst in chloroform at room temperature, and left to stir for 3 hours. As expected only the desired regioisomer, vinyl triflate **161**, was obtained in 66% yield (**Scheme 2.39**).

Optimum reaction conditions were predetermined by ^{1}H NMR experiments in deuterochloroform where the disappearance of the starting alkyne and the appearance of the vinyl triflate (characterized by vinylic protons at δ5.39 and an allylic singlet at δ4.16) could be easily monitored.



161

Scheme 2.39

An obvious extension to this work was to add triflic acid to extended alkyl chain homologues of the previous propargyl derivatives. This would then serve as a means to ultimately synthesize a variety of α-methylene lactams of varying ring sizes. However, the synthesis of the one carbon homologue, 4-bromobut-1-yne **163**, was unable to be accomplished effectively. Beginning with the corresponding commercially available alkynyl alcohol, 3-butyn-1-ol **162**, several standard bromination techniques were applied without success (**Table 2.2**). Most reactions were characterized by a complicated set of products by ^{1}H NMR analysis of the crude reaction mixture. In the case of entry 4 the reaction was successful (^{1}H NMR resonances at δ2.12(*t*), 2.77(*dt*), 3.45(*t*) for the crude mix), however, the product bromide was unable to be isolated owing to its extreme volatility and the complicating presence of triphenylphosphine oxide.

An attempt to circumvent this involved the synthesis of the alkynyl triflate, 3-butynyltrifluoromethanesulphonate[193] **164a**, derived from the corresponding alkynyl alcohol. It was envisaged that the triflate group would be readily displaced by bromide through the use of tetrabutylammonium bromide.* ^{1}H NMR tube experiments indicated that displacement

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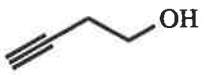
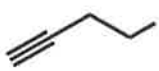
* It had been shown earlier that tetraethylammonium bromide readily displaced the triflate group of propargyl triflate.[194]

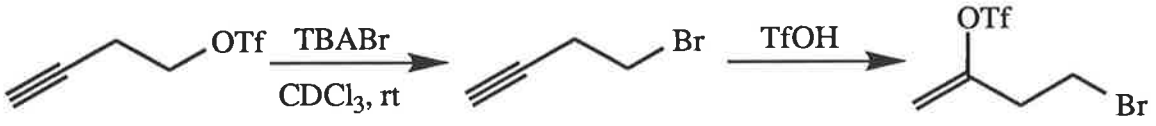
Table 2.2

Entry	Alkynyl alcohol	Reaction Conditions	Result/Product
1	 **162**	A*	Unidentifiable mix of products
2	162	B[192]	Unidentifiable mix of products
3	162	C	Unidentifiable mix of products
4	162	D	 **163**†
5	162	E[192]	Unidentifiable mix of products

A = PBr_3, -10°C to rt.
B = PBr_3, pyridine, ether, -10°C to rt to reflux, 15h.
C = as for B with freshly distilled PBr_3.
D = CBr_4, PPh_3, CH_3CN, 0°C to rt, 15h.
E = Me_3SiCl, LiBr, CH_3CN, rt to reflux, 15h.
* Reaction carried out with neat reagents.
† Isolation was unable to be accomplished.

occurred almost instantaneously (indicated by the methylene triplet of alkynyl bromide **163** being shifting upfield from δ4.59 to δ3.46 relative to **164**). Subsequent addition of one equivalent of triflic acid to the tube resulted in slow formation of only vinyl triflate **166**, however, significant amounts of starting bromide were present even after 16 hours (**Scheme 2.40**). Perhaps the presence of tetrabutylammoniumtriflate in the reaction mixture may be adversely affecting the attack by the triflate anion at the vinyl cation.

As a consequence of this, and since it is known that the addition of excess triflic acid to terminal alkynes results in isomerization of the double bond into the alkyl chain,[177] it was thus

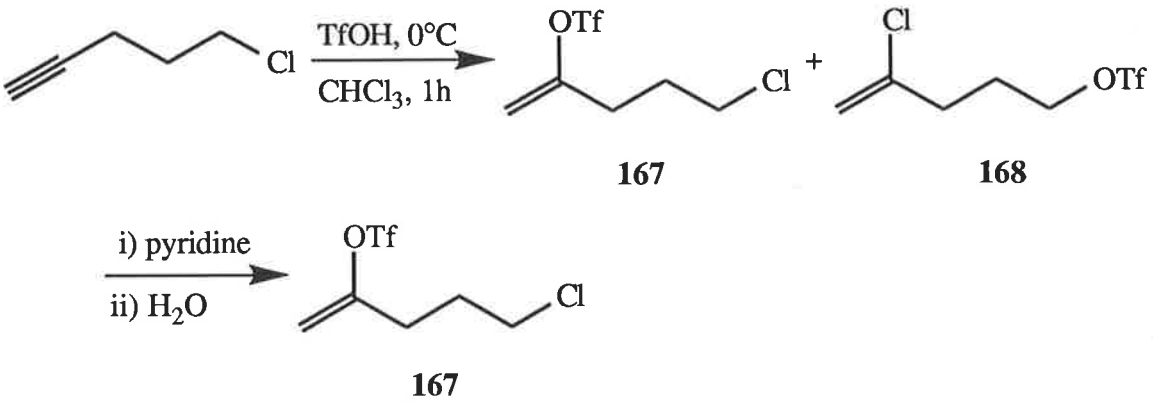


164a **163** **166**

Scheme 2.40

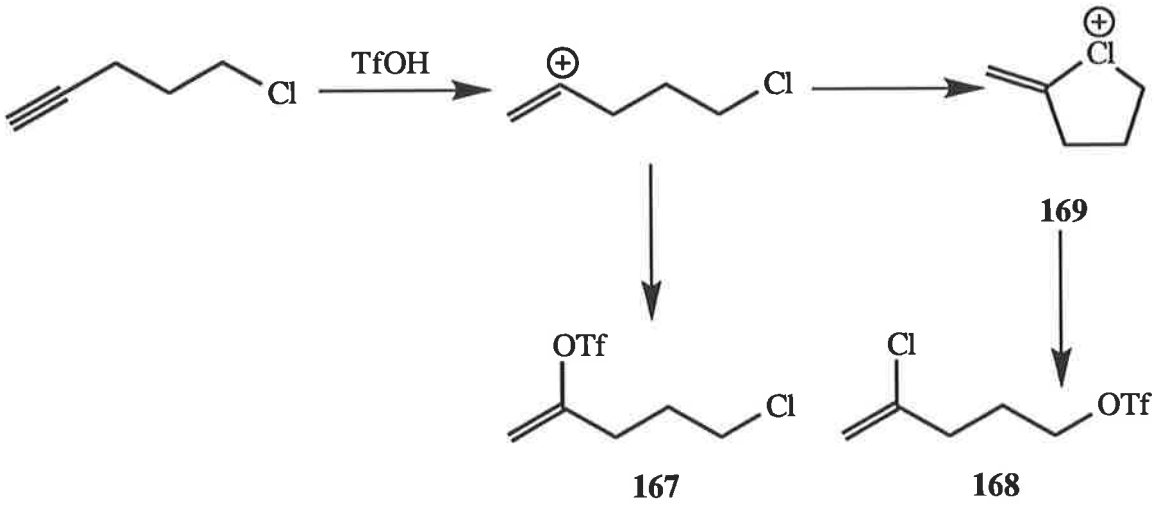
deemed necessary to isolate the alkynyl bromide prior to triflic acid addition. Hence a trial reaction sequence was attempted and repeated as above save that the alkynyl bromide was co-distilled with chloroform due to its volatile nature (*vide supra*). To this solution at 0°C was added one equivalent of triflic acid followed by stirring at ambient temperature for one hour. ^{1}H NMR analysis showed that the desired vinyl triflate was produced as characterized by the presence of a pair of vinylic doublets (δ5.11 and δ5.29). However, subsequent attempts at scaling up the reaction resulted in only very poor yields of product. Due to these difficulties encountered, further investigation was not undertaken.

A conceptually simpler approach involved the addition of 0.9 equivalents of triflic acid to the commercially available 5-chloropent-1-yne. This gave a not unexpected mixture of regioisomers. The presence of both the desired vinyl triflate **167** and the vinyl chloride **168** (in a ratio *ca* 2:3 respectively) could again be clearly visualised by ^{1}H NMR analysis of the crude reaction mixture (a pair of doublets at δ5.04, 5.17 and δ5.25, 5.27 for **167** and **168** respectively). The subsequent addition of pyridine, aqueous work up and kugelrohr distillation of the residue, resulted in the isolation of pure **167** (39%) (**Scheme 2.41**).



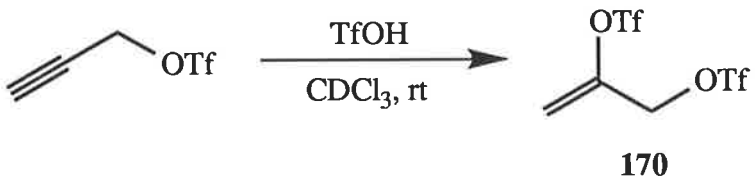
Scheme 2.41

The products can again be rationalized by protonation of the alkyne and attack by the triflate anion, or an intramolecular attack by chlorine to afford a favourable intermediate 5-membered chloronium ion **169**. Attack by a triflate anion on the γ-carbon of this intermediate gives the observed vinyl chloride (**Scheme 2.42**).



Scheme 2.42

In order to avoid the production of the unwanted regioisomer formed in the previous cases, it was envisaged that triflic acid could be reacted with the corresponding alkynyl triflates. In all cases both possible reaction pathways discussed above would ultimately lead to the same product. Propargyl triflate, prepared from propargyl alcohol,[191a] was thus treated with varying increasing molar equivalents of triflic acid, to give vinyl triflate **170**, in several ^{1}H NMR tube studies (**Scheme 2.43**).* Upon the addition of ten equivalents of acid, and after 24 hours, the ratio of starting alkyne to vinyl triflate was *ca.* 3.4:1. At 72 hours the proportion of vinyl triflate had increased, however, other reaction by-products had also formed. The extreme nature of the reaction conditions made this method altogether unattractive and consequently it was not pursued.



Scheme 2.43

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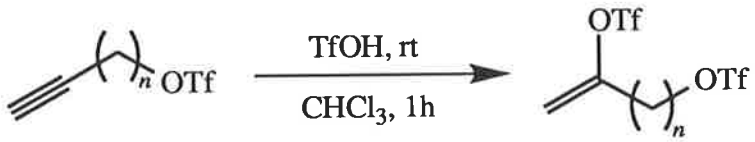
* It had previously been shown that the addition of 3.5 equivalents of triflic acid to propargyl triflate did not result any addition products being observed.[194]

However, it was found that when 3-butynyl trifluoromethanesulphonate[191a,b] **164a** was treated with 3.5 equivalents of triflic acid, with stirring for one hour at room temperature, the unstable vinyl triflate **165a** was obtained. In a similar manner the next higher homologue, derived from 4-pentynyl trifluoromethanesulphonate[191a,c] **164b**, was formed using 2.5 equivalents of triflic acid to give the somewhat more stable vinyl triflate **165b** (**Scheme 2.42**). Not suprisingly, **165b** was observed to undergo a slow internal double bond isomerization (clearly evidenced by the appearance of a broad vinylic triplet at δ5.34) when the reaction was allowed to proceed beyond one hour. In both cases the molar proportions of triflic acid and the reaction times were predetermined by preliminary ^{1}H NMR tube experiments in deuterochloroform. For reactions carried out on larger scales it was occassionally necessary to add further triflic acid to the reaction mix if the addition had not gone to completion as indicated by ^{1}H NMR analysis.

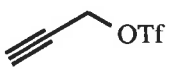
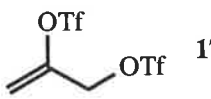
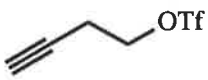
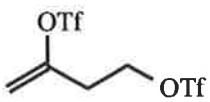
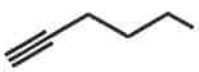
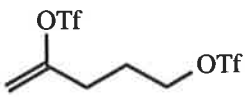


164a $n = 2$
164b $n = 3$

165a $n = 2$
165b $n = 3$

Scheme 2.42

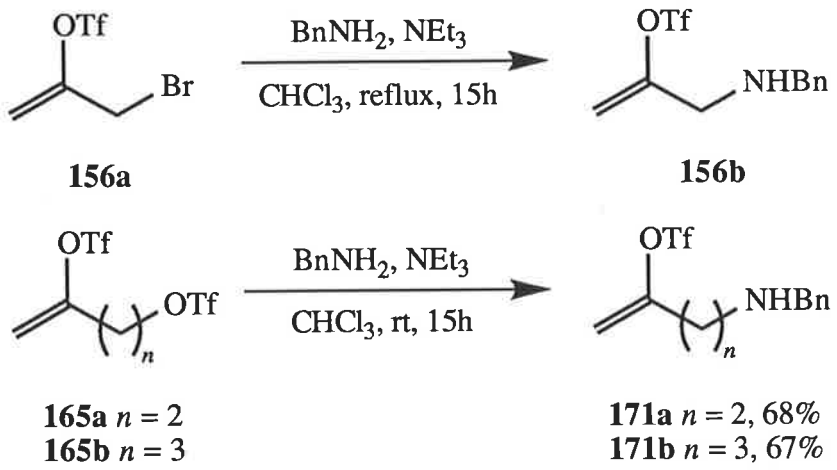
Table 2.3

Alkynyl triflate	molar equivalents of TfOH	Functionalized vinyl triflate	Yield[a]
	10	 **170**	not determined
 **164a**	3.5	 **165a**	65
 **164b**	2.5	 **165b**	71

[a] Isolated yield of pure material

A clearly evidenced trend, with regards to the molar quantities of triflic acid necessary to effect the addition reaction, had become apparent. It can thus be said that the closer the proximity of the triflate moiety to the alkyne, the greater is the retardation to triflic acid addition. Presumably the strong electron withdrawing inductive effect of the triflate group reduces the ability of the alkyne to undergo protonation. This is summarized in **Table 2.3**.

For this series of vinyl triflates the subsequent ease at which nucleophillic displacement occurred for the alkyl triflate or halide group was investigated. Reaction, again with benzylamine, would lead to the corresponding carbonylation precursors. It was found that the allylic bromide of **156a** was readily displaced by benzylamine to yield **156b** through the use of the conditions described in **Scheme 2.35**. Both the triflate groups of **165a** and **165b** showed a somewhat greater propensity to be displaced, such that the reactions were conducted at room temperature, to yield the required N-benzyl vinyl triflate derivatives **171a** and **171b** respectively (**Scheme 2.45**).

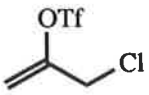
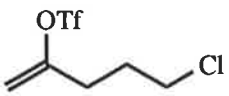


Scheme 2.45

However, both the allylic and the γ-substituted chloride group of vinyl triflates **161** and **167** were unable to be displaced by benzylamine. Changes in the solvent, base or the temperature at which the reaction was conducted failed to yield the desired N-benzyl vinyl triflate giving either starting material or decomposition. Attempts to exchange the γ-substituted chloride group of **167** for a more labile iodine atom *via* a Finkelstein reaction only resulted in a complicated mixture of products (entries 7 and 8, **Table 2.4**). The vinyl triflate group can

consequently be considered to be unstable under the conditions of the halogen exchange reaction. The above reactions are summarized in **Table 2.4.**

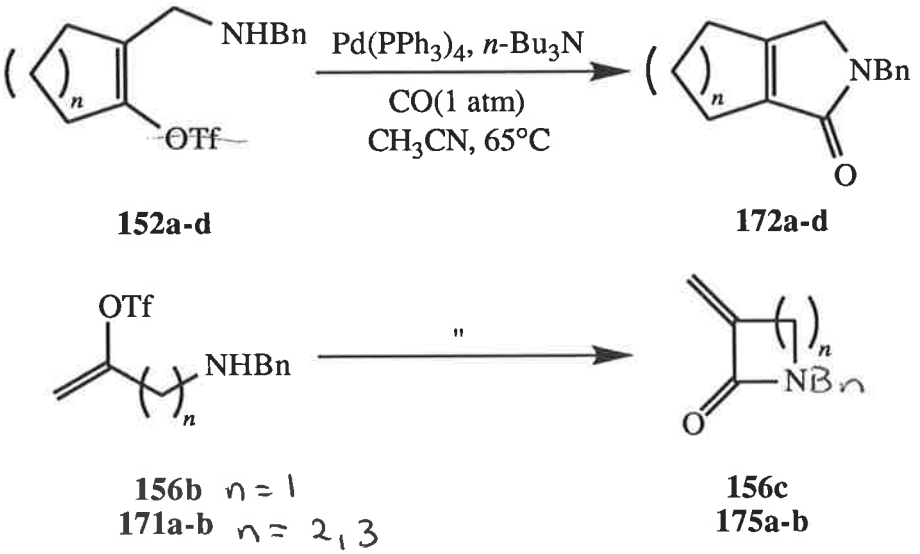
Table 2.4

Entry	Functionalized vinyl triflate	Reaction conditions	Result
1	 **161**	A	Starting triflate **161**
2	**161**	B	**161** and unidentifiable products*
3	**161**	C	**161**
4	 **167**	D	**167**
5	**167**	E	Unidentifiable mix of products
6	**167**	F	Unidentifiable mix of products
7	**167**	G	**167**
8	**167**	H	**167** and unidentifiable products
9	**167**	I	Unidentifiable mix of products
10	**167**	J	Unidentifiable mix of products

A = $BnNH_2$, Et_3N, $CHCl_3$, rt, 15h then reflux 18h.
B = $BnNH_2$, NaH, DMF or THF, rt, 15h.
C = $BnNH_2$, Et_3N, LiBr, $CHCl_3$, rt 15h then reflux 15h.
D = $BnNH_2$, Et_3N, $CHCl_3$, rt, 15h.
E = $BnNH_2$, Et_3N, $CHCl_3$, rt to reflux, 15h.
F = $BnNH_2$, Et_3N, CH_3CN rt, 3d then reflux 5h.
G = $BnNH_2$, NaH, THF, rt, 2h then reflux 1h.
H = NaI, acetone, rt, 15h.
I = NaI, acetone, reflux, 2h.
J = $BnNH_2$, $AgNO_3$, dark, rt, 48h.
* trace of **156b** was observed by ^1H NMR.

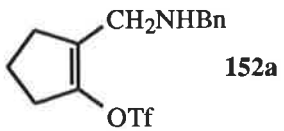
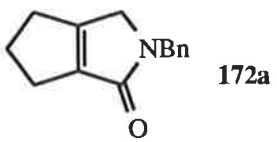
2.5.4 Palladium(0)-catalyzed intramolecular carbonylations of amino vinyl triflates

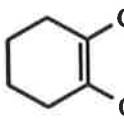
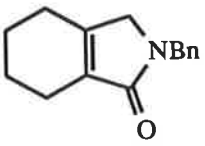
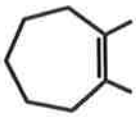
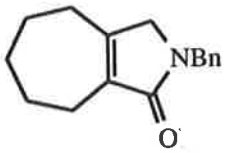
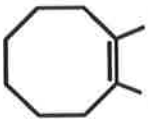
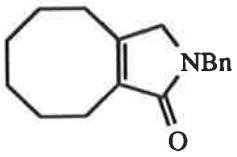
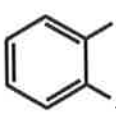
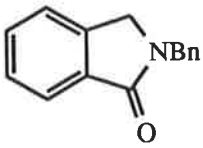
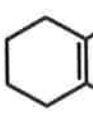
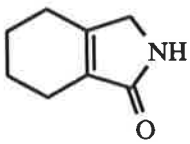
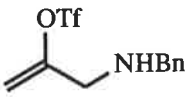
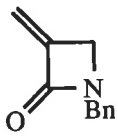
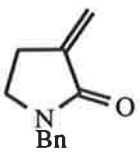
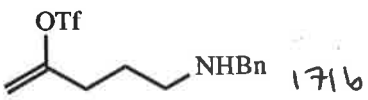
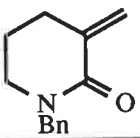
The carbonylation reactions of amino vinyl triflates were conducted as for the hydroxy derivatives save that lithium chloride was not added to the reaction mixtures (**Scheme 2.46**). These results are summarized in **Table 2.5**. Again the ring size of the cyclic amino vinyl triflates did not alter the reaction or affect the isolated yield of 3,4-disubstituted α,β-unsaturated γ-lactam **172** (entries 1-4, **Table 2.5**). In a similar manner N-benzyl-2-(trifluoromethanesulphonyl)oxy-benzylamine **153** also underwent an intramolecular carbonylation to afford **173** (entry 5, **Table 2.5**). Cyclohexenyl triflate **155**, containing a primary amino group, was similarly converted to the corresponding γ-lactam **174** (entry 6, **Table 2.5**). The acyclic amino vinyl triflates also underwent the carbonylation reaction with ease and in good to excellent yields (enteries 7-9, **Table 2.5**).



Scheme 2.46

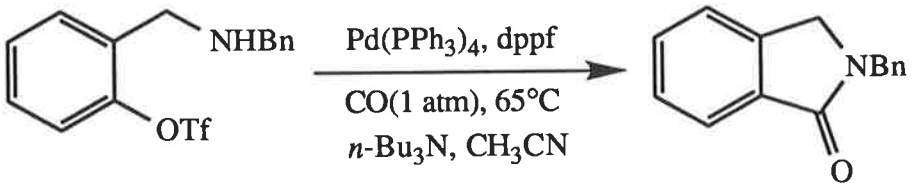
Table 2.5

Entry	Amino vinyl triflate	Conditions /time	Product	Yield[a]
1	 **152a**	A/2h	 **172a**	100

2	 **152b**	A/2h	 **172b**	89
3	 **152c**	A/2h	 **172c**	100
4	 **172d**	A/2h	 **172d**	98
5	 **153**	B/2h	 **173**	63
6	 **155**	A/2h	 **174**	93
7	 **156b**	A/15h	 **156c**	73
8	 171a	A/15h	 **175a**	100
9	 171b	A/15h	 **175b**	72

Reactions carried out by heating a mixture of the particular amino vinyl triflate under either catalyst system A or B, *n*-Bu_3N (2.0 eq) in CH_3CN at 65°C under one atmosphere of carbon monoxide for the period of time indicated.
A = $Pd(PPh_3)_4$ (10 mol%).
B = $Pd(PPh_3)_4$ (10 mol%), dppf (20 mol%).
[a] Isolated yield of pure material.

However, it was found that to effect the transformation of aryl triflate **153** the addition of the chelating ligand 1,1'-bis(diphenylphosphino)ferrocene(dppf) was necessary (**Scheme 2.47**). In fact, in its absence palladium precipitation occurred within ten hours such that ^{1}H NMR analysis revealed that the reaction was only approximately one-third completed. The use of freshly prepared $Pd(PPh_3)_4$ catalyst gave an identical result.

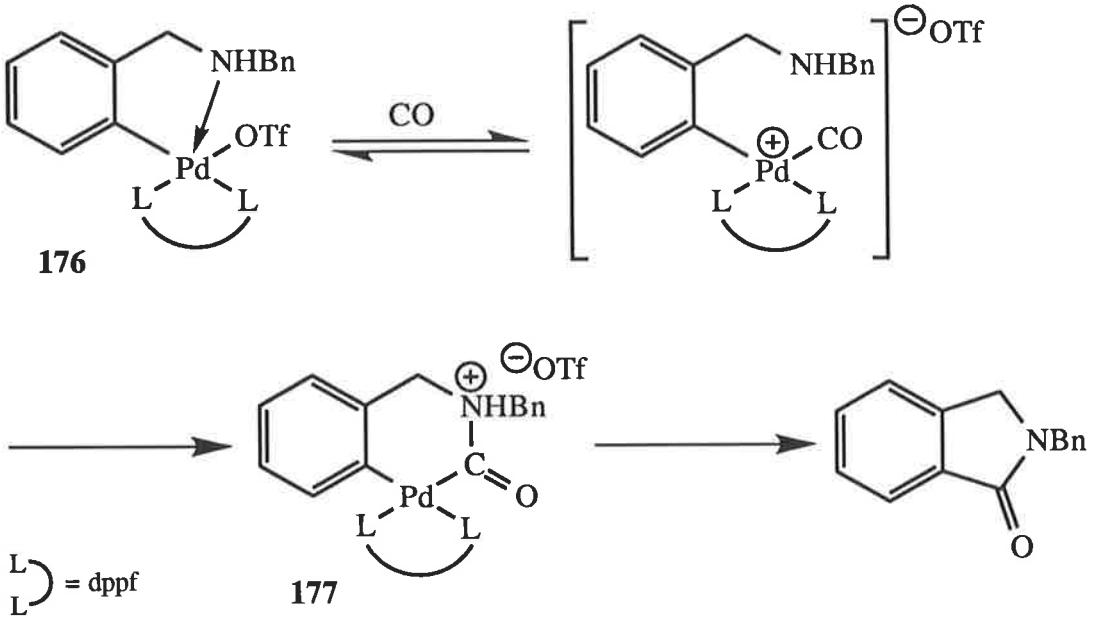


153 **173**

Scheme 2.47

This follows the experimental observations by Cacchi and Ortar[152] in their synthesis of arenecarboxylic acid derivatives from aryl triflates. In this case, the 1,3-bis(diphenylphosphino)propane(dppp) ligand was shown to produce rate enhancements in carbonylation reactions of aryl triflates.[195] With reference to the carbonyl insertion mechanism discussed in this chapter (*2.4.1.2*), it can be envisaged that the effect of the dppf ligand is due to its obligatory *cis* arrangement in the palladium(II) carbonyl complex **176**. This is in contrast to the general *trans* arrangement of the PPh_3 ligands in vinyl triflate complexes having undergone oxidative addition.[176] Presumably the reaction follows the outline of **Scheme 2.48**, where the leaving group ability of the triflate ligand enables the subsequent formation of the amino carbonyl species **177**. Facile reductive elimination of these *cis* components would produce the arene lactam.

Despite the effect of a possible chelation by the nitrogen linker arm present, the lability of the triflate ligand would enable a molecule of CO to readily replace it on palladium. An analogous reaction was found to not occur in the case of halo alcohols (*vide supra*).[103] This then also serves to strengthen the results of Stang *et al.*[173] who proposed that such a simple diplacement of the triflate ligand was occurring rather than the reaction proceeding through a pentacoordinate species (involving prior coordination of a CO molecule).



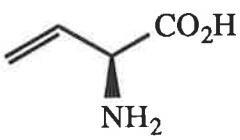
Scheme 2.48

It is of interest to report that an attempted one-pot carbonylation/cyclization of 1-chloro-2-[(trifluoromethanesulfonyl)oxy]prop-2-ene **161**, under the conditions described in **Scheme 2.46** in the presence of benzylamine, yielded quantitatively N,N'-dibenzylurea **161a** as the only isolated product.

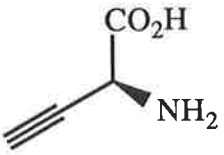
2.5.5 Synthesis of an α,β-unsaturated amide derivative of proline

α-Amino acids exist in nature as the monomeric building blocks of peptides, proteins and enzymes and thus possess a vital biochemical and physiological significance. Although there exist only twenty amino acids that commonly occur in proteins, the number of naturally occurring amino acids is well over five hundred. In addition, unnatural amino acids have become of increasing importance particularly in areas such as the pharmaceutical and agricultural industries,[196] as flavours,[197] taste enhancers and sweeteners.[198] These unnatural amino acids act by vitue of their ability to mimic the biological roles or enzymatic functions of their natural counterparts. Furthermore, novel peptides and proteins may be synthesized from these unnatural amino acids to obtain information on the mode of action of particular enzymes.[199] Their use also as synthetic intermediates and chiral auxiliaries can not be understated.

Non-proteinogenic α-amino acids bearing a vinylic or acetylenic group in the α-side chain constitute an important class of molecules. Their significance lies in their ability to act as irreversible mechanism based inhibitors (also known as k_{cat} inhibitors or suicide substrates) of pyridoxal phosphate and flavin dependent enzymes.[200] Their mode of action lies in their ability to deactivate specific target enzymes *via* the target enzyme catalytically unmasking a latent functional group at a point in the catalytic cycle of the enzyme. Two common examples include vinylglycine **178** and propargylglycine **179**.

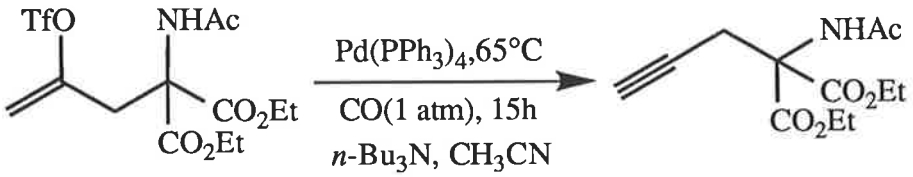


178



179

A convenient entry point toward the construction of an α,β-unsaturated amide derivative of proline, utilizing a palladium-catalyzed intramolecular carbonylation reaction, involved the use of vinyl triflate **156a** (synthesized from propargyl bromide as described in *2.5.3*). This was used to alkylate the sodium salt of diethylacetamidomalonate to produce the corresponding vinyl triflate **180**.[194] Carbonylative coupling under the standard conditions for fifteen hours gave a black solution that upon TLC analysis showed a spot of an identical R_f to that of the starting triflate. Subsequent flash chromatography of the residue furnished quantitatively a clear viscous oil that was confirmed by ^1H NMR to be propargylmalonate derivative **181**. This was presumably formed by the elimination of triflic acid under the reaction conditions (**Scheme 2.49**).

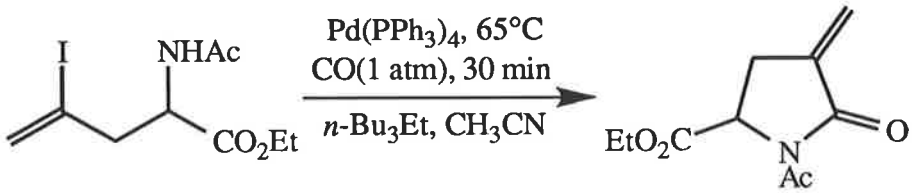


180 **181**

Scheme 2.49

To circumvent this problem a vinyl iodide derivative, γ-iodoallylglycinate **182**, seemed an attractive alternative (this derivative being synthesized *via* an iododestannylation of the

corresponding tributylstannylallylglycinate).[194] Under the conditions of the carbonylative coupling reaction the solution rapidly turned from the characteristic initial yellow colour to a dark brown in 30 minutes. Inspection by TLC indicated the reaction had gone to completion and following two sets of flash chromatographic purification (the presence of coloured impurities made this necessary) the desired proline derivative **183** was obtained in moderate yield (63%) (**Scheme 2.50**).*



182 **183**

Scheme 2.50

* Carbonylation of vinyl iodide **182**, in the presence of ethanol and $PdCl_2(PPh_3)_2$ as catalyst, was recently shown to yield a derivative of 4-methylene glutamic acid.[201]

Chapter 3

Synthesis of optically active α,β-unsaturated γ-lactones *via* a key step palladium(0)-catalyzed carbonylation reaction

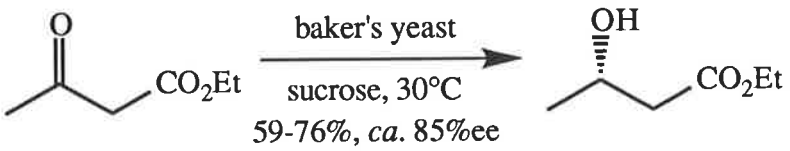
3.1 Introduction

Our interest toward the synthesis of optically active α,β-unsaturated γ-lactones stemmed from the general ability of the palladium(0)-catalyzed carbonylation reaction to effect transformations without racemization (or epimerization) of any chiral centre(s) present in a starting molecule. In order to utilize this inherant advantage, a need was created for an efficacious means of producing enantio- and diastereomerically pure starting materials. Ideal precursors would be those that could be easily generated essentially chirally pure, in appreciable quantities, with environmental friendliness and at a low cost. Consequently, chiral molecules derived from an asymmetric baker's yeast reduction of 1,3-dicarbonyl compounds were investigated.

3.2 Background to the baker's yeast reduction of 1,3-dicarbonyl compounds

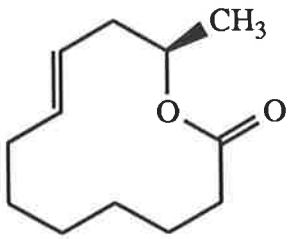
Microbial transformations, and in particular yeast-mediated transformations, have had widespread application over thousands of years for the production of bread, alcoholic beverages and dairy products. In more recent times baker's yeast (*saccharomyces cerevisiae*) has found widespread acceptance amongst organic chemists as a stereoselective microbial reducing agent to generate small chiral synthetic intermediates, that may be highly functionalized, in high enantiomeric excess for the synthesis of enantiomerically pure compounds. In this context, several comprehensive review articles have appeared.[202] Although often considered somewhat difficult to manage experimentally, this fact is outweighed by the possibility of producing valuable chiral synthons. The use of baker's yeast as a synthetic reagent is thus an alternative, complementary approach to the use of asymmetric synthetic reagents, chiral pool templates and the resolution of racemates.

The baker's yeast reduction of carbonyl compounds, and in partcular β-keto esters, has been one of the most extensively studied areas involving the production of chiral molecules for asymmetric synthesis. One of the compounds most widely subjected to reduction is ethyl acetoacetatate which gives ethyl (*S*)-(+)-3-hydroxybutanoate **184** with good reproducibility on a multi-kilo scale (**Scheme 3.1**). Moreover, a number of natural products have been synthesized from this enantiopure intermediate including (*R*)-(+)-recifeiolide **185** and (*S*)-(+)-sulcatol **186**.

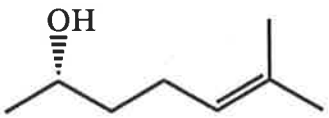


184

Scheme 3.1



185



186

Since most of the enzymes in baker's yeast display their properties under similar conditions, the nature of the substrate determines the direction in which the reaction is driven. The observed selectivity of these reductions thus depends upon the nature and size of the substituents adjacent to both the carbonyl and the ester groups. Furthermore, in some instances, changes in substrate or sucrose concentration, the pH and the cultivation conditions of the yeast also affect the absolute stereochemistry and the chemo- and enantioselectivity observed in the products.

Sih *et al.*[203] has attributed the stereochemical outcome of baker's yeast reductions of β-keto esters by a modification of the Prelog model.[204] The yeast produces several (and perhaps many) enzymes (oxido-reductases) that are able to differentiate stereoheterotropic faces of a trigonal carbonyl function due to the adjacent steric bulk. This results in a differing

rate of hydrogen delivery to one face over the other. This difference in bulk of a small group versus a large one controls the kinetics of the reaction to eventually yield a selective reduction (**Figure 3.1**).[205] The nature and specificity of three of these enzymes has been somewhat elucidated and agree with this representation. However, an overall uncertainty exists in predicting the absolute configurations of products from yeast-mediated reductions in all but the best precedented cases.

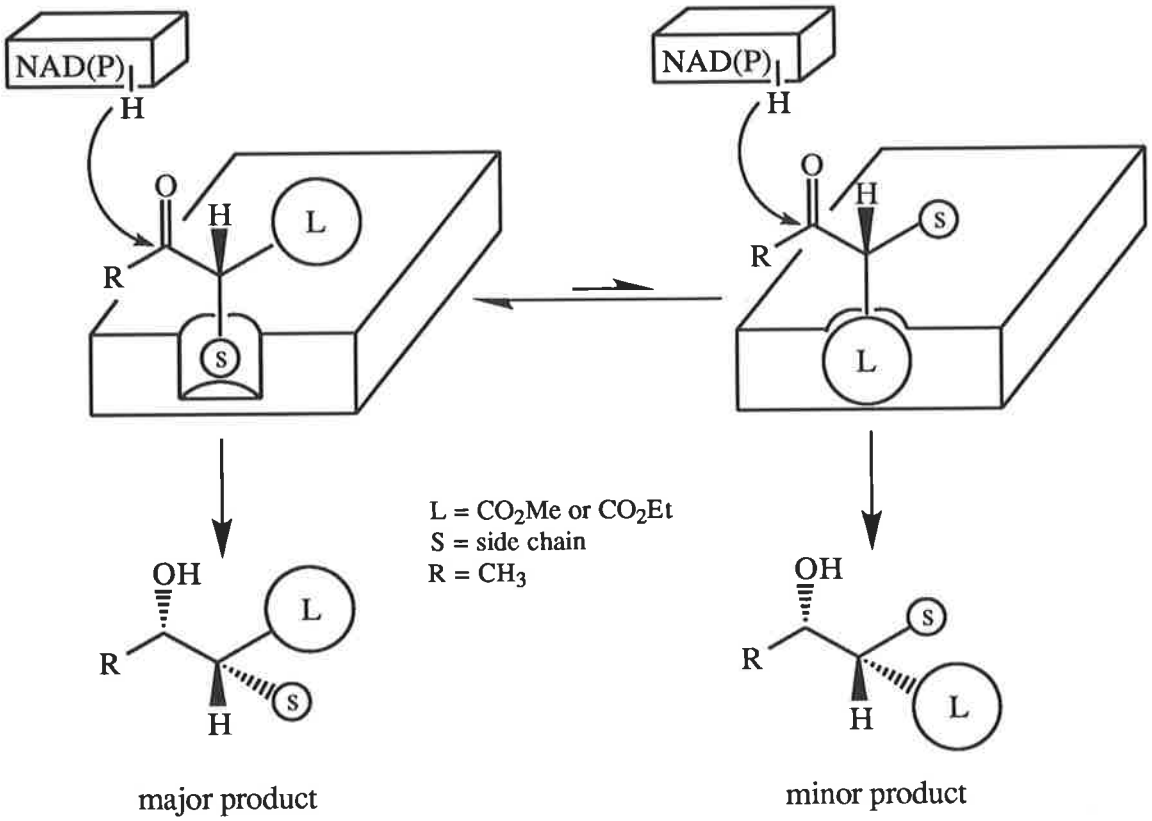
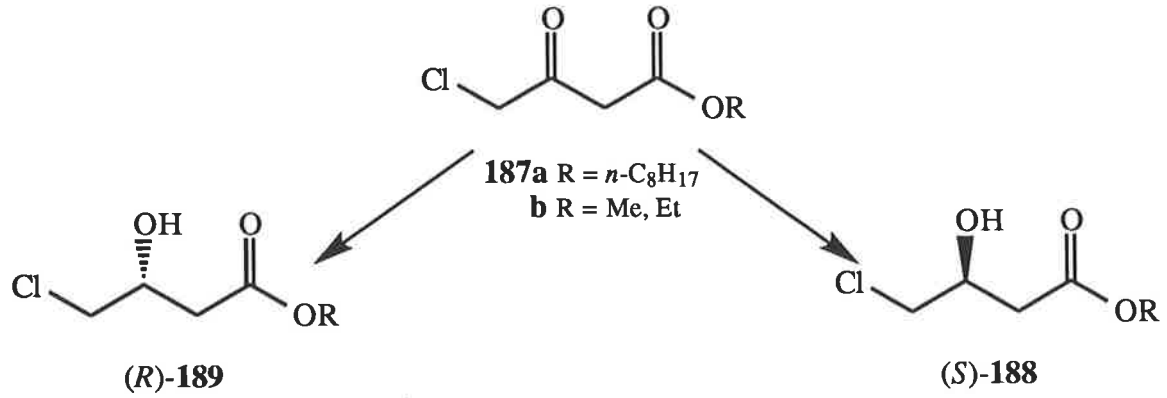


Figure 3.1

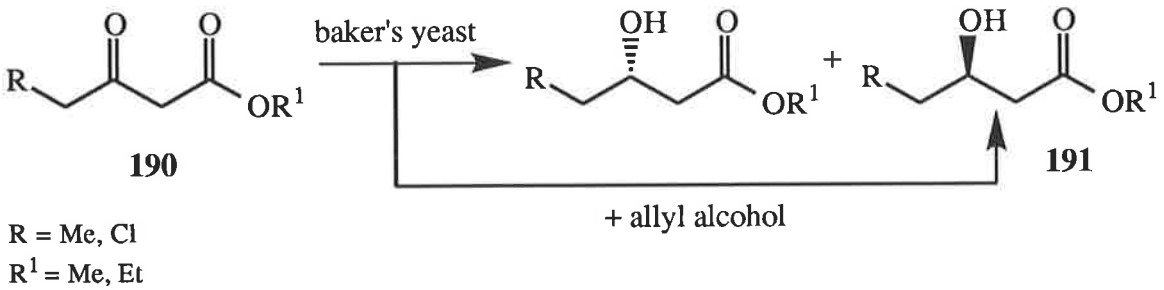
Such a rationale is exemplified by the reduction of γ-chloroacetoacetate **187a** which gave (*S*)-**188** with up to 65% ee whereas **187b** furnished (*R*)-**189** in 97% ee (**Scheme 3.2**).

Unsatisfactory stereoselectivity of β-hydroxy esters in reductive enzyme-mediated processes has been attributed to the two or more oppositely stereochemically preferenced oxido-reductases operating in conflict (each with a high degree of stereoselectivity).



Scheme 3.2

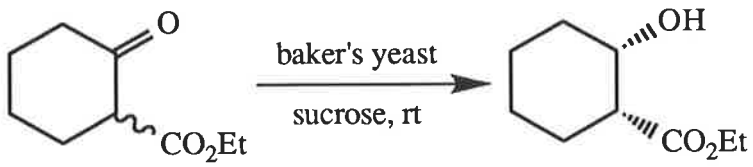
However, the enantiomeric excess of the products may be increased by several methods including the structural modification of the substrate to increase the rate of reduction by a specific enzyme (as in **Scheme 3.2**). Further to this, for γ-substituted β-keto alkyl esters the prefered substrates for the enzymes to give *R*-type products were those possessing a large hydrophobic group at C-4 whereas enzymes yielding *S*-type products preferred substrates bearing large hydrophobic ester substituents.[206] Moreover, in some cases it has also been illustrated that the enzyme operating in the wrong preference may be selectively inactivated by the addition of either unsaturated alcohols or ketones. For example, the addition of allyl alcohol to the baker's yeast fermentation of β-keto esters **190** proved to be effective in inhibiting one of the oxido-reductases, thus shifting the stereochemical outcome towards hydroxy ester **191** (**Scheme 3.3**).[207]



Scheme 3.3

The reduction of (±)-α-substituted β-keto esters has proven to be a valuable method to yield diastereoselective and enantiospecific α-substitued β-hydroxy esters possessing two asymmetric centres. A diverse range of substrates have been effectively reduced including α-

methyl-, α-alkyl-, α-hydroxy-, α-sulphenyl-, α-chloro- and α-amino-β-keto-alkanoates.[202] Moreover, various cyclic β-keto esters have also been investigated and generally proceed with a higher enantioselectivity than those of the open chain form. Thus, a number of examples exist that involve the reduction of 2-oxocycloalkanecarboxylates, with high diastereoselection and enantiomeric excess, to the resultant 2-hydroxy esters that are predominantly of a 1*R*,2*S* configuration.[208] The absolute configuration is again as predicted by the model developed by Sih *et al.* (**Figure 3.1**). For example, various reductions of the six-membered cycloalkanone **192** have yielded (+)-(1*R*,2*S*)-2-hydroxycyclohexanecarboxylate **193** in 65-85% chemical yield with an ee of 86-99% and a diastereoselection giving rise to a de of 76-99% (**Scheme 3.4**).[209]

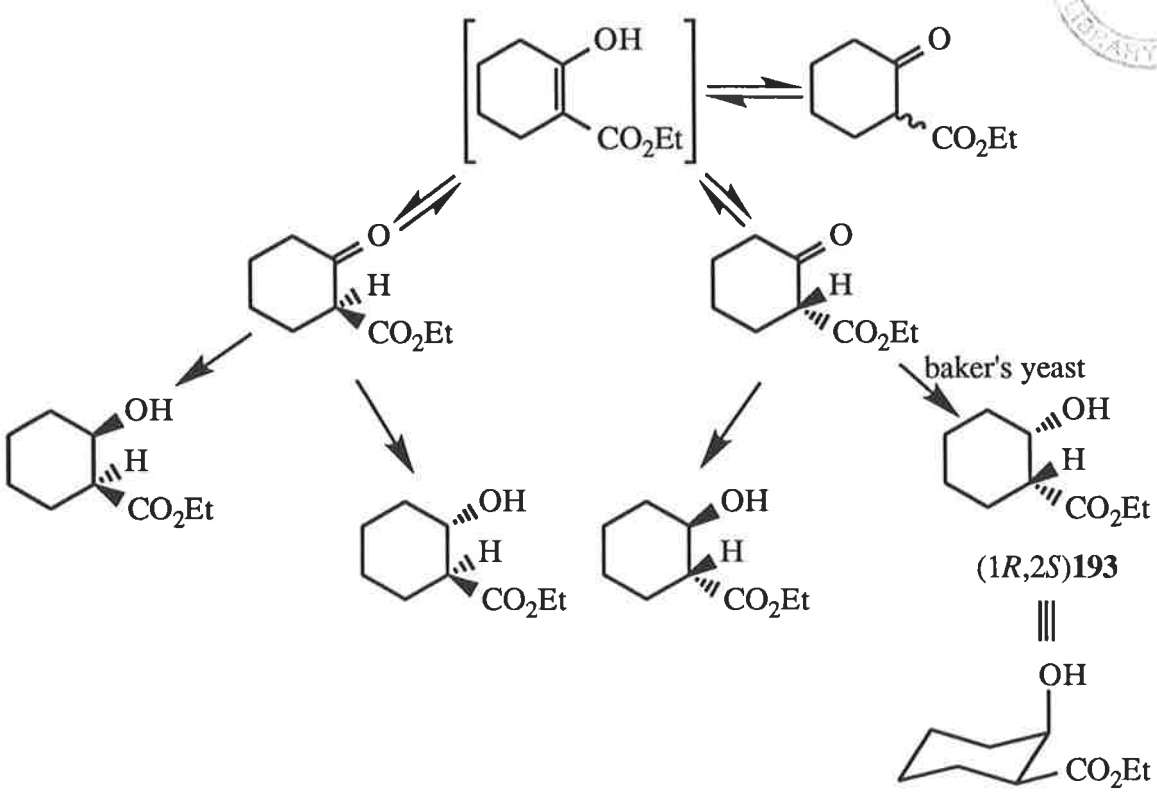


192 **193**

Scheme 3.4

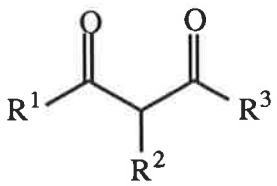
The diastereomer of *cis* configuration forms in excess since the two enantiomeric forms of the β-keto ester undergo a fast spontaneous equilibrium in the incubation media to the enolic form. This is then most likely followed by a fast reduction of one of the two enantiomeric substrates to give only one of four possible stereoisomers (providing the difference in rates between racemization of the undesired and desired enantiomer is great enough) (**Scheme 3.5**).[209c] The effect of the enzyme is consequently to not only selectively reduce one face of the carbonyl, but also to distinguish between the two enantiotopic homomorphic groups attached to the tetrahedral prochiral centre. A recent complementary abiological method involves the use of catalytic hydrogenation in the presence of an asymmetric BINAP-Ru(II) complex.[210]

The reduction of a β-diketone to a β-hydroxy ketone is of importance since this unit appears in biologically active compounds and has been used as a chiral synthon in the



Scheme 3.5

stereospecific synthesis of antibiotics[211a] and pheromones.[211b] In general, the reduction of symmetrical acyclic β-diketones **194** (R^2=H, alkyl) involves enantiotopic or diastereotopic facial selectivity whereas for unsymmetrical **194** (R^2=H, alkyl, $R^1 \neq R^3$) regio-selectivity also becomes an issue. Various acyclic β-diketones[212] and non-enolizable 1,3-cycloalkanediones[213] have been reduced enantio- and diastereoselectively and regiospecifically to give β-hydroxy ketones of an *S* configuration in 20-60% chemical yield and 92-99% ee. The diol from double reduction does not occur which is in contrast to the yeast reduction of 1,4-diketones where the corresponding (*S*,*S*)-diol is obtained exclusively.[214]



194

A wide variety of carbonyl-containing substrates, including examples featuring an array of additional functionality, have also been asymmetrically reduced by baker's yeast.[202] This method continues to be useful for obtaining optically active secondary alcohols with new examples appearing regularly. However, in the context of this current work these examples will not be introduced.

3.3 Results and Discussion

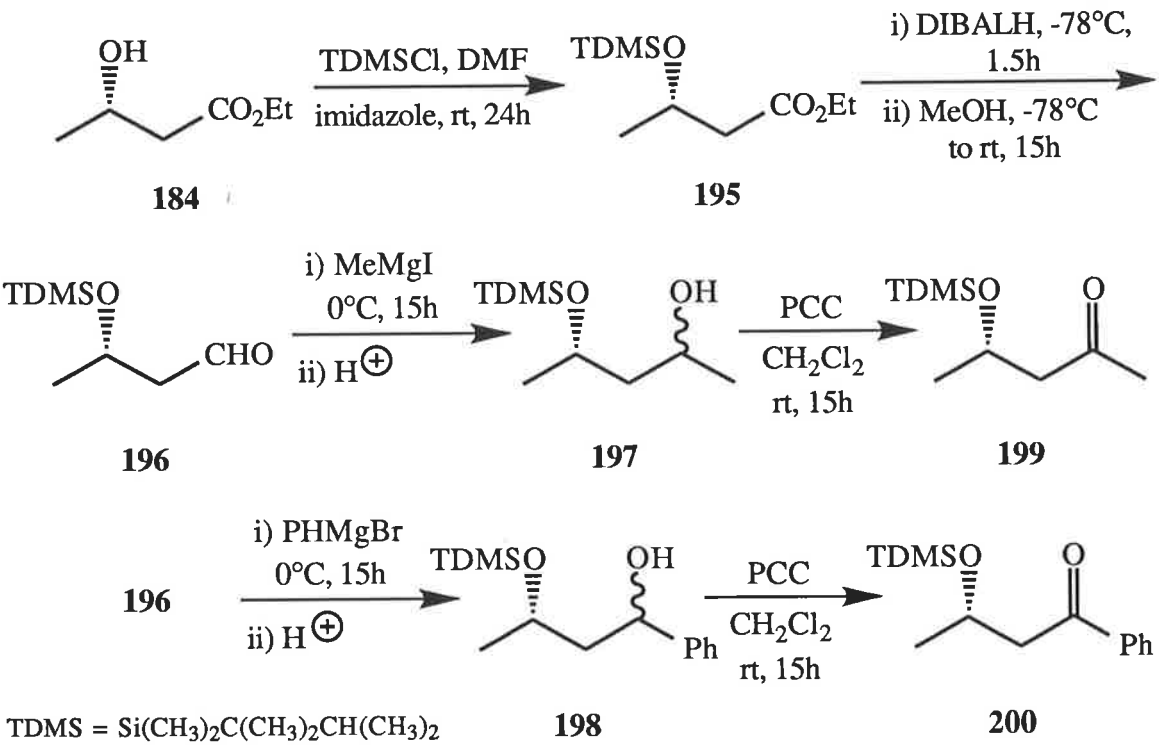
3.3.1 Synthesis of the optically active α-methylene γ-butyrolactone (-)-(*S*)-dihydro-5-methyl-3-methylene-2(3*H*)-furanone

The baker's yeast asymmetric reduction of ethyl acetoacetate to (*S*)-(+)-ethyl 3-hydroxybutanoate is probably the best known of the whole-cell biotransformations. It thus seemed a particularly acceptable starting point for this chiral synthesis.

Hence, ethyl acetoacetate was reduced with commercially available baker's yeast in the presence of table sugar and tap water over 60 hours whilst being kept at between 25 and 30°C. Accurate confirmation of the optical purity of (3*S*)-(+)-3-hydroxybutenoate **184** was *via* a ^{1}H NMR study in the presence of the chiral shift reagent (+)-Eu(hfc)$_3$ and shown to be ≥95% ee.[186] It is of interest to note that the enantioselectivity of this reduction has been shown to fluctuate between 70 and >98% ee which is usually accounted for by differences in the yeast strain and the fermentation conditions. Furthermore, it has also been reported that low concentrations of substrate (1g/l) results in the isolation of the alcohol in very high ee.[215] Enhancement of the optical purity to 100% may, however, be achieved by several crystallizations of the 3,5-dinitrobenzoate derivative.

It was envisaged that for a general synthetic sequence to be constructed the ability to convert the ester moiety of (3*S*)-(+)-3-hydroxybutanoate to a series of correspondingly substituted ketones was essential. Such intermediates may then be elaborated regio- and stereoselectively to the corresponding vinyl triflates (*vide supra*). A palladium(0)-catalyzed carbonylation reaction of such a vinyl triflate was then seen as an appropriate key step toward the synthesis of a number of optically active α,β-unsaturated γ-lactones.

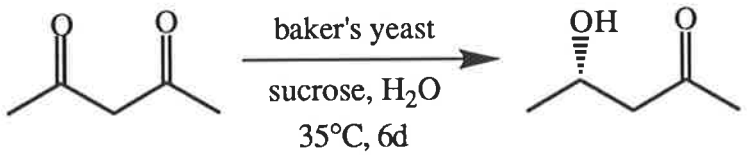
Firstly, necessary protection of the alcohol function was achieved by reaction with thexyldimethylsilylchloride in the presence of imidazole over 15 hours. This furnished (3*S*)-ethyl 3-[(thexyldimethylsilyl)oxy]butanoate **195** in good yield (85%). Reduction of the ester moiety directly to the aldehyde, (3*S*)-3-[(thexyldimethylsilyl)oxy]butanal **196**, was accomplished with DIBALH also in good yield (83%). The most appropriate means of introducing alkyl or aryl functionality to the aldehyde moiety was found to be with organomagnesium reagents. Thus, aldehyde **196** was reacted with methylmagnesium iodide to give the corresponding alcohol, (4*S*)-4-[(thexyldimethylsilyl)oxy]pentan-2-ol **197**, in excellent yield (95%) as an approximate 1:1 mixture of diastereomers as characterized by ^{1}H NMR. Furthermore, reaction with phenylmagnesium bromide resulted in the formation of (3*S*)-1-phenyl-3-[(thexyldimethylsilyl)oxy]butan-1-ol **198** (89%), again approaching a 1:1 diastereomeric mix. Mild oxidation of both **197** and **198** with pyridinium chlorochromate (PCC) gave the corresponding methyl ketone **199** and phenyl ketone **200** in 80 and 74% yields respectively. The preceeding synthetic methodology is summarized in **Scheme 3.6**.[186]



Scheme 3.6

However, a conceptually simpler synthetically route to methyl ketone **199** would involve the direct synthesis of (4*S*)-(+)-4-hydroxypentan-2-one **201** from a baker's yeast reduction of the β-diketone acetylacetone.

Hence, acetylacetone was reduced with baker's yeast according to the procedure of Veschambre *et al.*[212b] (**Scheme 3.7**). The reaction mix was monitored by both capillary GC and TLC to ensure the absence of starting β-diketone. Purification, however, became lengthy by virtue of the formation of unidentified side products. As a consequence of distillation and multiple chromatographic separations, (4*S*)-(+)-4-hydroxypentan-2-one **201** was obtained in poor yield (20%).*



201

Scheme 3.7

It is of interest to report that discrepencies in the measured values for the specific rotations of **201** arose when a comparison was made between that described by Vescambre and other workers (**Table 3.1**). The β-hydroxy ketone **201** may be assigned an absolute stereochemistry of *S* by comparison with the literature data (this is also consistent with the general rule on yeast reductions). The hydroxyl moiety of (+)-(4*S*)-hydroxypentan-2-one was then subsequently protected as the thexyldimethylsilyl ether (as described previously) to yield the desired methyl ketone **199** in good yield (70%).

The ability to regioselectively synthesize α-substituted vinyl triflates derived from methyl ketones through a kinetically generated enolate has been reported, being utilized

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* Although the yield is low compared to that of Veschambre (90%), it is comparable to that obtained by Ohta et al.[212c] (18%). Furthermore, the yield is also reportedly influenced by the concentration of substrates and the pH of the medium.[212c]

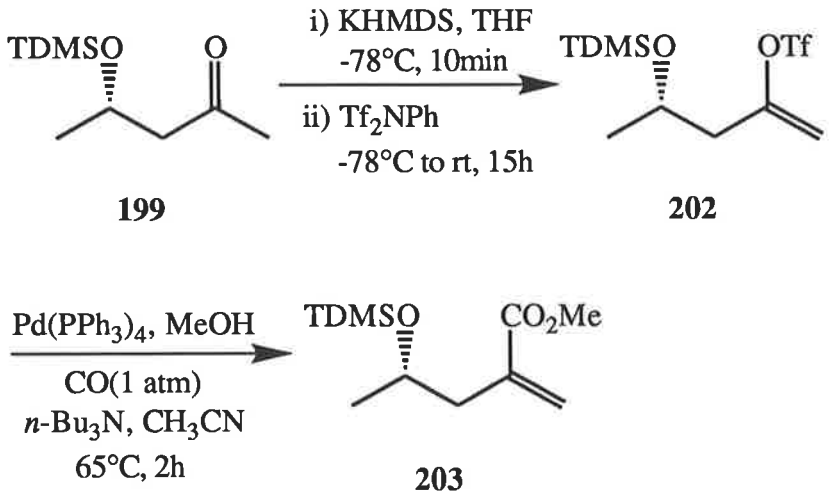
Table 3.1

	$[\alpha]_D$	$[\alpha]_J$	ee%	Absolute config.
Experimental values	+78.5° (*c*=2.0)	+90° (*c*=0.04)		
Veschambre *et al.*	-	+40° (*c*=0.04)	99*	S-(+)
Ohta *et al.*	+64° (*c*=2.0)	-	>99†	S-(+)

* as determined by chiral capillary GC analysis.
† as determined by HPLC analysis of the MPTA ester.
D - Sodium D line, 589nm.
J - Mercury J line, 578nm.
All samples recorded as a chloroform solution at the concentrations shown.

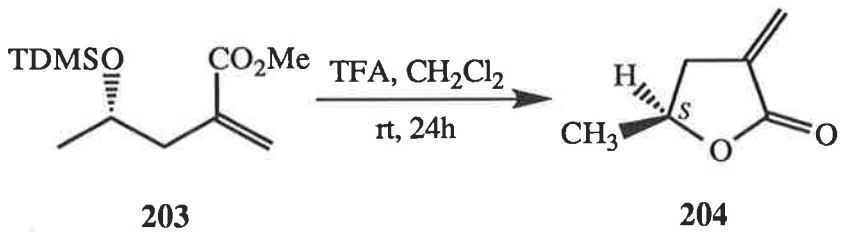
primarily in Stille coupling reactions.[215] Under standard non-equilibrating conditions, the most commonly used base has been LDA whilst the triflating agent has varied from N-phenyltriflimide to 4-*t*-BuPhN$(Tf)_2$. However, for methyl ketone **199** it was found convenient to use KHMDS as the base. This also readily generated the kinetic enolate which was subsequently trapped by N-phenyltriflimide at low temperature. As a consequence the corresponding (*S*)-vinyl triflate **202** was obtained as one regioisomer in excellent yield (97%). This vinyl triflate was then subjected to a one-carbon homologation *via* a palladium(0)-catalyzed carbomethoxylation reaction in the presence of excess methanol. Utilizing the standard conditions outlined in *Chapter 2* (*2.5.2*) the corresponding acrylate, (+)-methyl-(4*S*)-2-methylene-4-[(thexyldimethylsilyl)oxy]pentanoate **203**, was obtained in good yield (73%).(**Scheme 3.8**).

Treatment of acrylate **203** with three equivalents of trifluoroacetic acid (TFA) for 24 hours gave the somewhat volatile (thus probably accounting for the diminished yield) α-methylene γ-butyrolactone, (5*S*)-(-)-dihydro-5-methyl-3-methylene-2(3*H*)-furanone, **204** in 46% yield (**Scheme 3.9**). The optimal lactonization conditions were predetermined from ^1H NMR experiments in deuterochloroform since the vinylic protons of the product clearly resonated at δ6.24(*dt*) and δ5.67(*dt*). Prior attempts at removing the silyl protecting group



Scheme 3.8

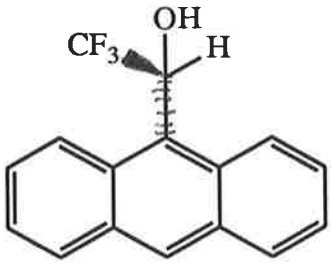
with subseqent cyclization through the use of tetrabutylammonium fluoride were not successful. In all cases starting material was returned despite often long reaction times (>3days) and the application of both heat and sonication to the reaction mixtures. It is of interest to note that attempts at a one-pot carbonylation and deprotection-cyclization reaction directly from vinyl triflate **202** also failed to yield any detectible quantities of lactone **204**.[186]



Scheme 3.9

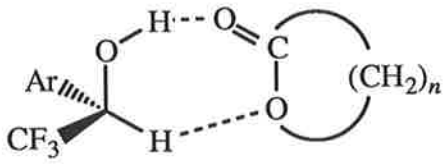
Determination of enantiomeric composition and absolute configuration of chiral γ-lactones by ^1H NMR studies in the presence of chiral solvating agents such as (-)-(*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol **205** has been reported.

The basis of these predictions arise from a solvation model proposed by Pirkle *et al.*[217] Solvation of the lactone occurs primarily through hydrogen bonding between the hydroxyl of **205** and the carbonyl of the lactone with subsequent weaker interactions between the ring oxygen and the hydrogen of **205**. This weaker interaction effectively controls conformer



205

population to result in **206** being the major solution conformer (**Figure 3.2**). Substituents on either face of the lactone are then influenced differently by the shielding effect of the anthracene ring. The effect of this shift reagent is to render the ^{1}H NMR spectrum of lactone enantiomers nonequivalent by virtue of the formation of these diastereomeric solvates.



Ar = 9-anthryl **206**

Figure 3.2

Consequently, the enantiomeric purity and absolute stereochemistry of lactone **204** was determined by employing chiral reagent **205**.[217a] The observed effect in the case of racemic **204*** was to split the methyl doublet into a pair of partially resolved, somewhat overlapping doublets at a 5:1 ratio of **205** to **204** (**Figure 3.3**)** [Enhancing the resolution of this resonance gave a somewhat clearer impression (**Figure 3.4**)]. However, the ^{1}H NMR spectrum of (*S*)-**204** in the presence of **205** resulted only in the appearance of one doublet thus indicating the presence of predominantly one enantiomer (**Figure 3.5**). This doublet

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* Racemic dihydro-5methyl-3-methylene-2(3H)-furanone **204** was synthesized according to the procedure of Norton *et al.*[107] (3-butyn-1-ol, $PdCl_2$, $SnCl_2$, PPh_3, CH_3CN, 15h under 7 atm of CO, 53%).

** It is reported that effective solvation is enhanced by the use of severalfold excesses of **205**.

corresponds to the upfield portion of the pair of doublets in the spectrum of the racemate and was confirmed by 'spiking' the solution of **205** and (*S*)-**204** with racemic **204**.

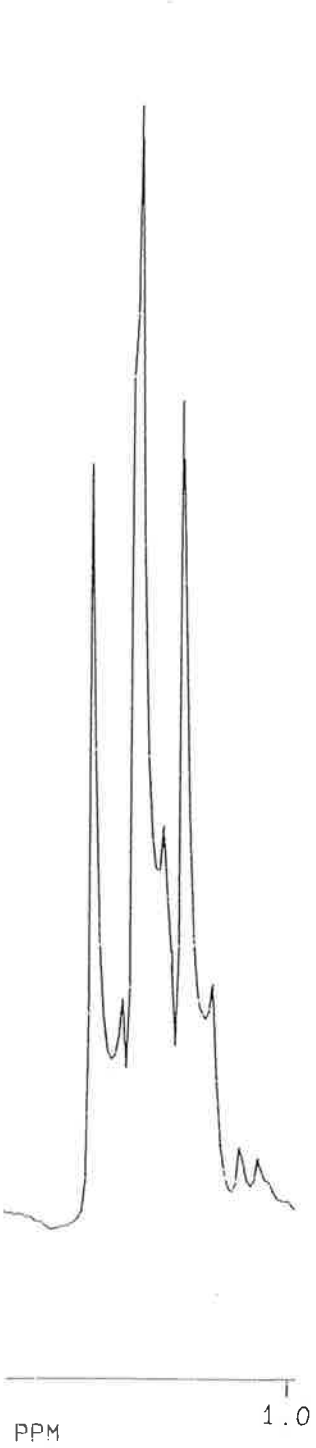


Figure 3.3
CH_3 resonance of racemic **204** in the presence **205**.

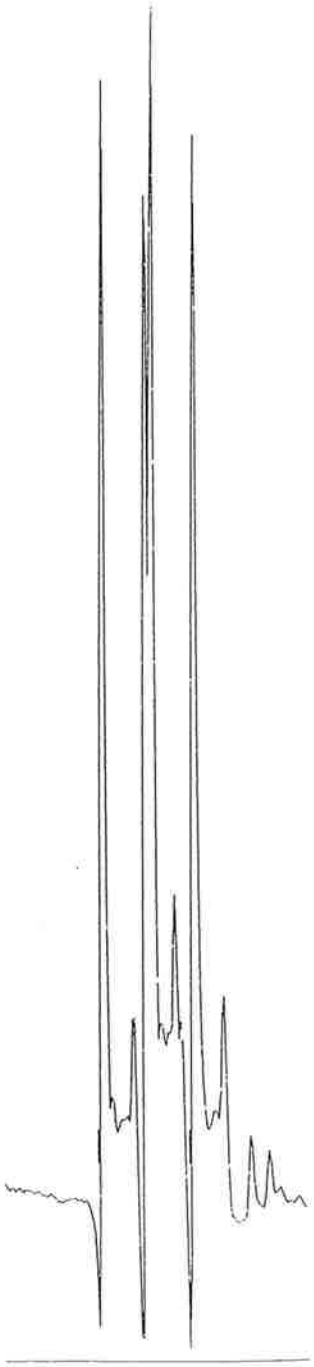


Figure 3.4
Resolution enhanced ^1H NMR spectrum for racemic **204** in the presence of **205**.

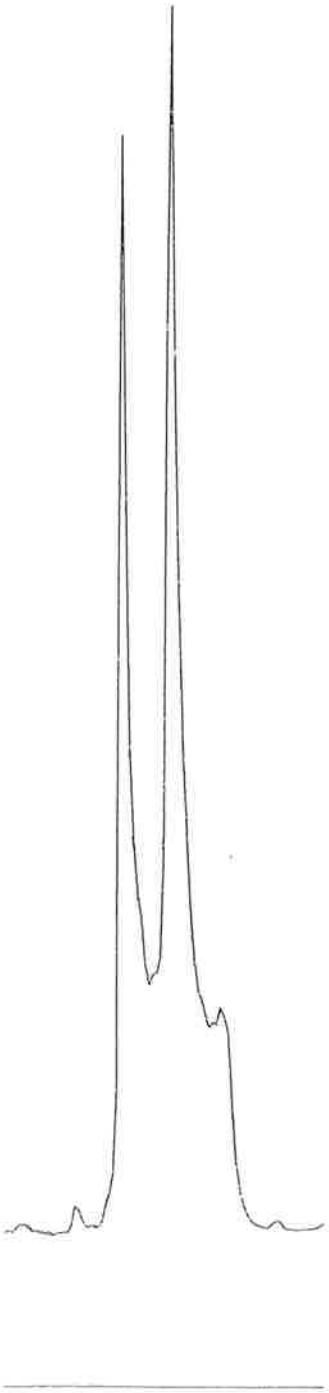
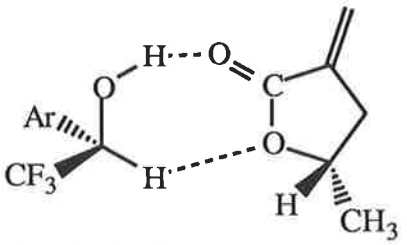


Figure 3.5
CH_3 resonance of (*S*)-**204** in the presence of **205**.

Applying the model of Pirkle to lactone **204** revealed that the methyl group of (*S*)-**204** is *cis* to Ar and should resonate upfield relative to the opposite enantiomer (**Figure 3.6**). Since this was observed in the ^{1}H NMR experiment the *S*-configuration may be assigned to lactone **204**. Furthermore, the fact that the *R*-enantiomer of **204** was synthesized by Stille *et al.*[101] (where the methyl doublet corresponded to the downfield portion of the pair of doublets in the racemate) confirms the stereochemical assignment. Moreover, the specific rotation of (*S*)-**204**, $[\alpha]_D$ -32.4° (*c*=5.8, CH_2Cl_2), is virtually identical to that for (*R*)-**204**, $[\alpha]_D$ +33.8° (*c*=5.82, CH_2Cl_2).*



Ar = 9-anthryl

Figure 3.6

The solvation model was further explored through the application of the molecular modelling program PCMODEL. Individual docking experiments between both the *S* and *R*-enantiomers of lactone **204** and the chiral solvent, (*R*)-2,2,2-trifluoroanthryl ethanol, were undertaken to determine an energy minimimum for the two sets of diastereomeric complexes. Hydrogen bonding, as indicated in the proposed solvation model, was assumed. It can be seen that for the (*S*)-lactone the methyl group is positioned such that it is within the shielding region of the anthracene substituent (**Figure 3.7**). This result acts to clarify the observed upfield shift of the methyl doublet in the ^{1}H NMR spectrum. Conversely, the methyl group of the *R*-enantiomer, being aligned on the other face of the lactone, is deshielded by the anthracene substituent and can be considered to be the downfield portion of the pair of

* A ^{1}H NMR experiment performed on *S*-**204** in the presence of (+)-Eu(hfc)$_3$ failed to realize splitting of any spectral resonances.

doublets in the racemate (**Figure 3.8**). This latter model also confirms the interpretations of Stille.

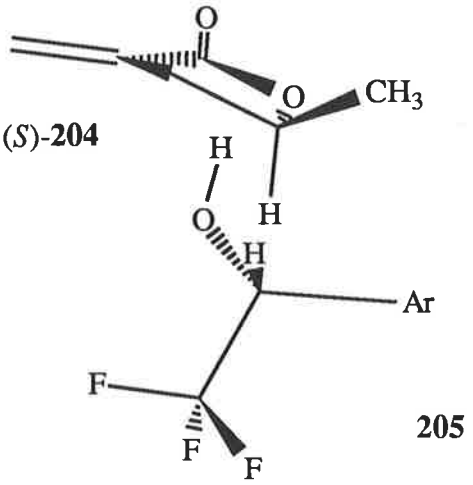


Figure 3.7

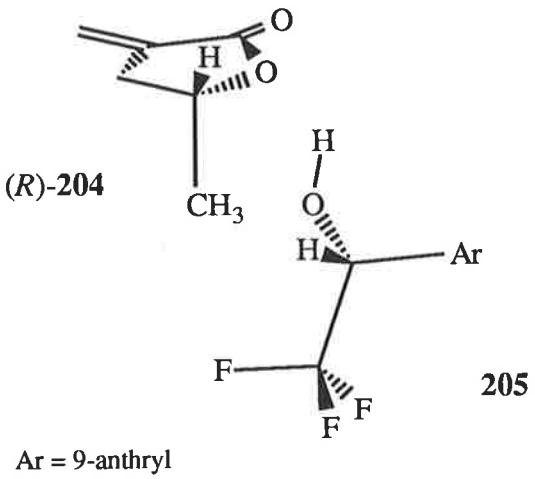


Figure 3.8

A similar approach was envisaged for the elaboration of (3*S*)-1-phenyl-3-[(thexyldimethylsilyl)oxy]butan-1-one **200** to the corresponding optically active α-methylene γ-butyrolactone. However, all attempts at stereospecifically generating the desired *E*-vinyl triflate were unsuccessful. Standard methods to synthesize vinyl triflates typically yielded either starting material, complex mixtures or *trans*-benzoyl-3-methylbuten-2-ene **207** (entries 1-5, **Table 3.2**). Compound **207** was most likely the result of a *trans*-antiperiplanar elimination of the silyl protecting group [vinylic ^{1}H NMR resonances at δ6.91 (*d*, J_{trans}14.05Hz) and δ7.08 (*dq*, J_{trans}15.19Hz) confirm the assigned *E*-stereochemistry].

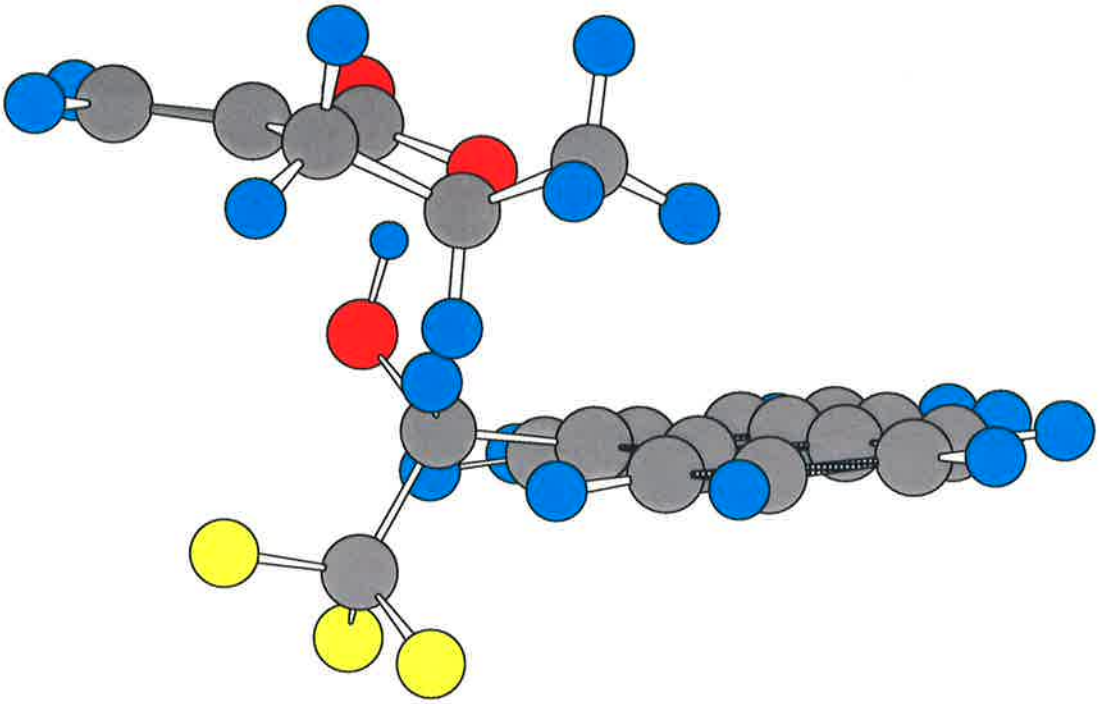


Figure 3.7

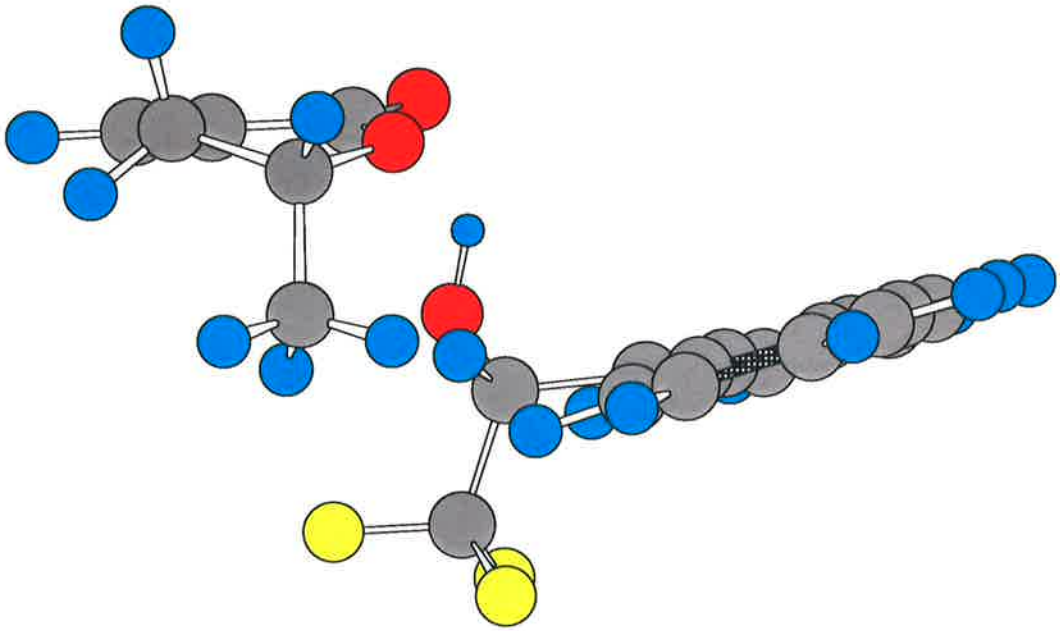


Figure 3.8

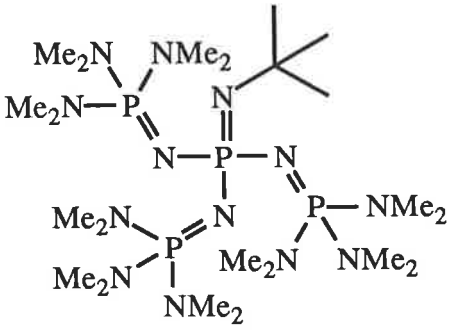
Atom colour code:

Grey - Carbon

Blue - Hydrogen

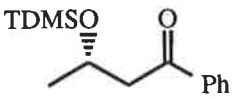
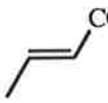
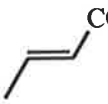
Red - Oxygen

Yellow - Fluorine



t-Bu P4 base **208**

Table 3.2

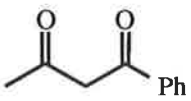
Entry	Ketone	Reaction conditions	Result/product
1	 **200**	A	Unidentifiable mix of products
2	**200**	B	Unidentifiable mix of products
3	**200**	C	Starting Ketone **200**
4	**200**	D	 **207***
5	**200**	E	 **207**
6	**200**	F	**200** + unidentifiable products
7	**200**	G	Unidentifiable mix of products

A = i) KHMDS, THF, -20°C, ii) Tf_2NPh, -78°C to rt.
B = as for A except wholly conducted at -78°C.
C = i) NaH, THF, -78°C, ii) Tf_2NPh, -78°C to rt.
D = i) $[(CH_3CH]_2NEt$, CH_2Cl_2, -78°C; ii) Tf_2O, -78°C to rt, 15h.
E = 2,6-di-*t*-Bu-4-methylpyridine, Tf_2O, CH_2Cl_2, rt, 3h.
F = *t*-Bu P4 base, Tf_2NPh, THF, -78°C to rt, 15h.
G = i) *t*-Bu P4 base, THF, -78°C, 10min, ii) Tf_2NPh, -78°C to rt, 15h.
* isolated by flash chromatography (hexanes:ethyl acetate; 9:1), 84%.

Recently it has been reported that the use of P4-phosphazene base[218] **208** is applicable to the C-alkylation of labile, elimination-prone enolates. It is suggested that since the base contains 4P and 13N atoms, each capable of bearing a positive charge to form a highly conjugated $P4H^+$ cation, inherently labile enolates are thus stabilized.[219] Extension of this methodology by using this base under standard triflating conditions gave either the starting ketone or complex reaction mixtures (entries 6-7, **Table 3.2**). The above attempts are summarized in **Table 3.2**.

An alternative approach would be to prepare an *E*-vinyl triflate derivative of phenyl ketone **200** *via* the direct stereoselective triflation of benzoyl acetone **209**. A stereoselective reduction of this derivative would then yield an allylhydroxy vinyl triflate. It was envisaged that this intermediate would undergo an intramoleculer palladium(0)-catalyzed carbonylation (*vide supra*) to form the corresponding optically active α,β-butenolide. Unfortunately all attempts at forming this *E*-vinyl triflate, including attempts to generate stereoisomeric triflate mixtures, unexpectedly resulted in predominant recovery of the starting ketone. These methods are condensed in **Table 3.3**.

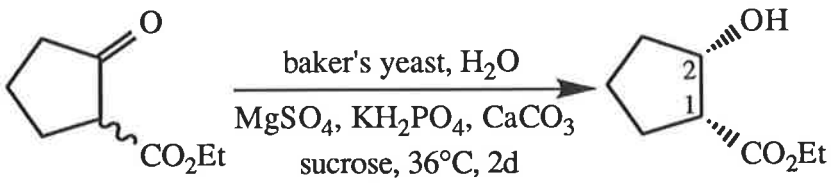
Table 3.3

Entry	Ketone	Reaction conditions	Result
1	 **209**	A	Starting ketone **209** + unidentifiable mix of products
2	**209**	B	**209**
3	**209**	C	**209**
4	**209**	D	**209**

A = i) $[(CH_3)_2CH]_2NEt$, CH_2Cl_2, -78°C, ii) Tf_2O, -78°C to rt, 15h.
B = as for A except Tf_2NPh used as triflating agent.
C = i) K_2CO_3, Tf_2NPh, 1,4-dioxane:H_2O (4:1), rt, 15h.
D = i) KHMDS, THF, -78°C, 10min, ii) Tf_2NPh, 15h.

3.3.2 Synthesis of an optically active α-methylene γ-butyrolactone fused to a five-membered carbocyclic ring

Having demonstrated that the most feasible synthetic pathway to optically active α-methylene γ-butyrolactones was *via* the general methodolgy described in *3.3.1*, its expansion to bicyclic systems was investigated. Again the starting point for the following synthesis took advantage of the ready availability of chirally pure starting materials utilising the baker's yeast reduction of a cyclic β-keto ester. The ester chosen was ethyl 2-oxocyclopentanecarboxylate which, following the procedure of Rauk *et al.*[220], was reduced to (+)-ethyl (1*R*,2*S*)-2-hydroxycyclopentanecarboxylate **210** in moderate yield (65%) (**Scheme 3.10**).



210

Scheme 3.10

It is known that the *cis* and *trans* configuration of cyclohexane substituents may be determined by measurement of the relevant ^{1}H NMR signal widths at half height ($W_{0.5h}$).[221] Generally an axial proton has a $W_{0.5h}$ larger than 15Hz whereas for an equatorial proton it is below 12Hz. Extending this to the analysis of the ^{1}H NMR spectrum of **210**, the data was consistent with the assumption that the β-hydroxy ester was indeed a pure *cis* diastereomer [resonances at δ2.68 (*m*), $W_{0.5h}$22.97Hz axial-like proton, H-C(1) and δ4.44 (*m*), $W_{0.5h}$10.87Hz equatorial-like proton, H-C(2)]. The absolute configuration may be assigned as written since the specific rotation of **210**, $[\alpha]_D$ +15.2° (*c*=1.57, $CHCl_3$), was virtually identical to that obtained by Rauk, $[\alpha]_D$ +15.1° (*c*=1.57, $CHCl_3$) (where confirmation of enantiomeric purity was by ^{1}H and ^{13}C NMR studies on the MTPA ester of **210**).*

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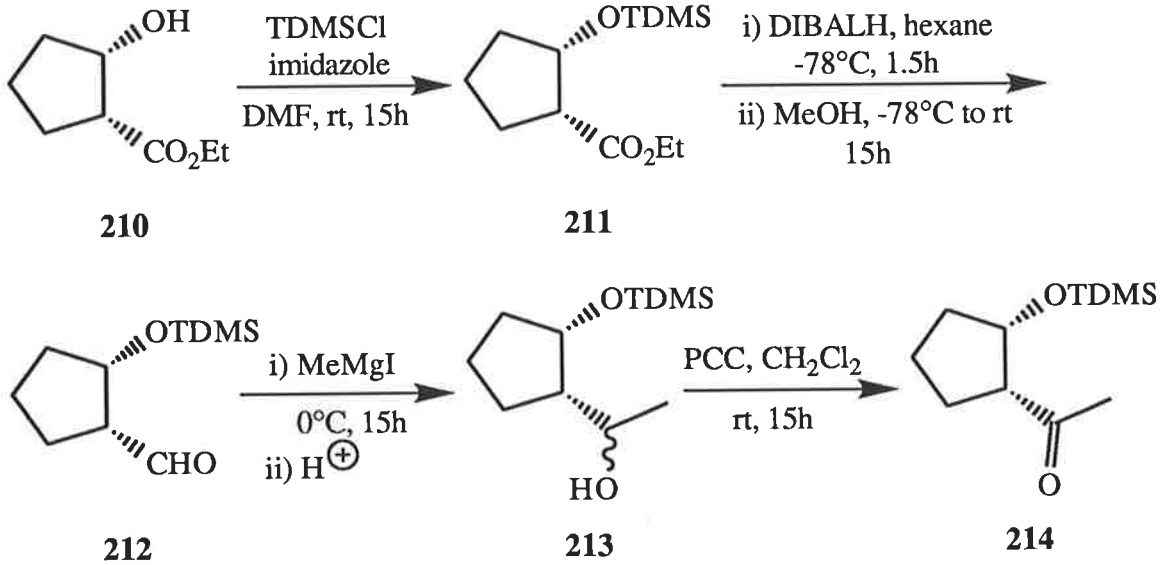
* The specific rotation is also slightly higher than that reported earlier by Ridley *et al.*,[209a] $[\alpha]_D$ +14.1° (*c*=1.7, $CHCl_3$).

Furthermore, the model of Sih (**Figure 3.1**) and the application of Brewster's rules[222] to this dextrorotatory enantiomer predicts such a stereochemical outcome.

Again protection of the hydroxyl moiety as the thexyldimethylsilyl ether **211** (73%) was followed by reduction of the ester group to the corresponding, somewhat unstable, aldehyde **212** in good yield (68%). Methylation with methylmagnesium iodide afforded alcohol **213** as an approximate 1:1.5 diastereomeric mix (75%). Subsequent oxidation with PCC afforded the methyl ketone, (+)-(1*R*,2*S*)-2-[(thexyldimethylsilyl)oxy]-1-cyclopentane methyl ketone **214** also in good yield (77%). This reaction sequence is outlined in **Scheme 3.11**.

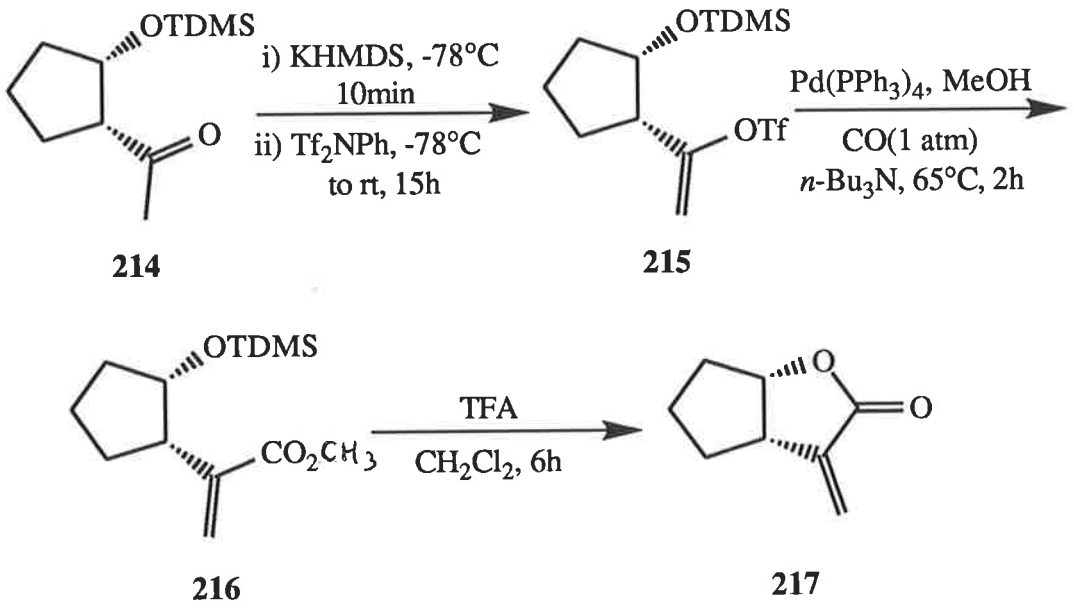


210 **211** **212** **213** **214**

TDMS = $Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$

Scheme 3.11

Subsequent generation of the kinetic enolate, with KHMDS at low temperature, and trapping by N-phenyltriflimide afforded vinyl triflate **215** regiospecifically and in good yield (71%). Carbomethoxylation in the presence of $Pd(PPh_3)_4$ (10 mol%) and methanol gave the desired acylate **216** good yield (89%). This provided the necessary precursor to form the corresponding optically active carbocyclic ring fused α-methylene γ-butyrolactone. The protected cyclopentanol derivative thus underwent lactonization readily when treated with trifluoroacetic acid to form (-)-(3a*R*,6a*S*)-hexahydro-3-methylene-2*H*-cyclopenta[b]furan-2-one **217** in good yield (86%) (**Scheme 3.12**).

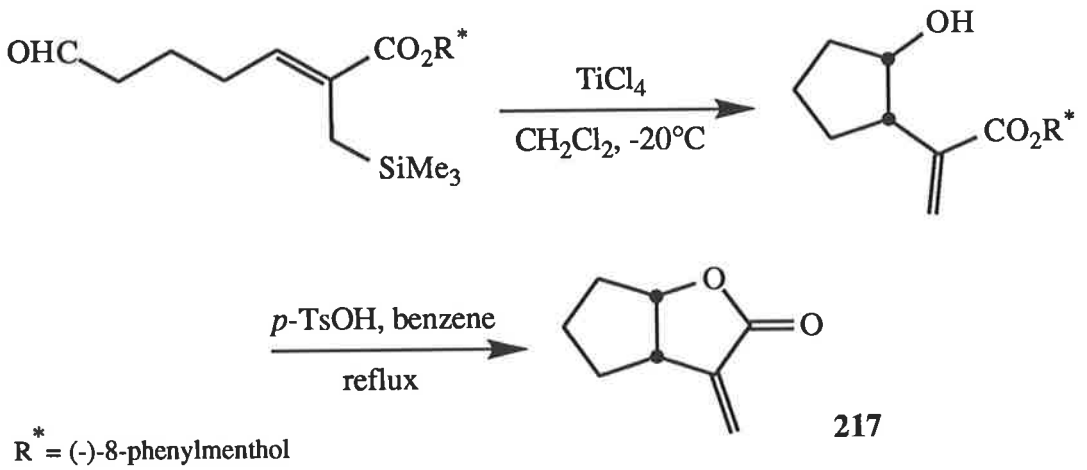


214 **215** **216** **217**

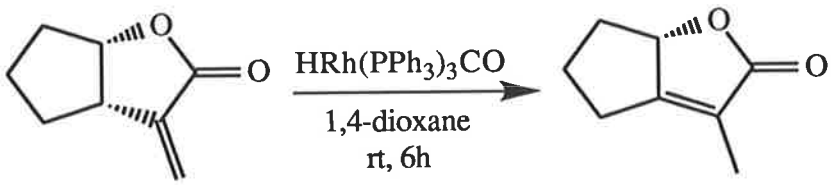
Scheme 3.12

The *cis*-α-methylene lactone **217** has been synthesized by Yamakawa *et al.*[223] *via* an intramolecular Hosomi reaction in varying enantiomeric excesses (75-84%) (**Scheme 3.13**). The enantiomeric excess was estimated from the intensity of the vinylic proton signals in the presence of the chiral shift reagent (+)-Eu(hfc)$_3$. A similar ^{1}H NMR experiment performed on lactone **217** revealed no such splitting, or indeed broadening, of the vinylic resonances [δ5.65 (*d*) and δ6.25 (*d*)]. It can thus be assumed that (-)-(3a*R*,6a*S*)-hexahydro-3-methylene-2*H*-cyclopenta[b]furan-2-one has been produced as predominantly one enantiomer (where the absolute stereochemistry may be inferred from that possessed by the starting β-hydroxy ester). Furthermore, the quoted value of the specific rotation by Yamakawa, $[\alpha]_D$ +125.6° ($CHCl_3$), is somewhat less than that obtained for **217**, $[\alpha]_D$ -161.3° (*c*=0.53, $CHCl_3$).

The applicability of the above reaction sequence would be enhanced if the corresponding carbocyclic ring fused α,β-butenolide could be produced. Such a transformation was envisaged to occur through a double bond isomerization of the *exo* to the *endo* alkene. Consequently, treatment of α-methylene lactone **217** with a metal hydride known to be an excellent double bond isomerization catalyst, $HRh(PPh_3)_3CO$,[107] produced (-)-(6a*S*)-4,5,6,6a-tetrahydro-3-methyl-2*H*-cyclopenta[b]furan-2-one **218** in excellent yield (95%) (**Scheme 3.14**).



Scheme 3.13



217 **218**

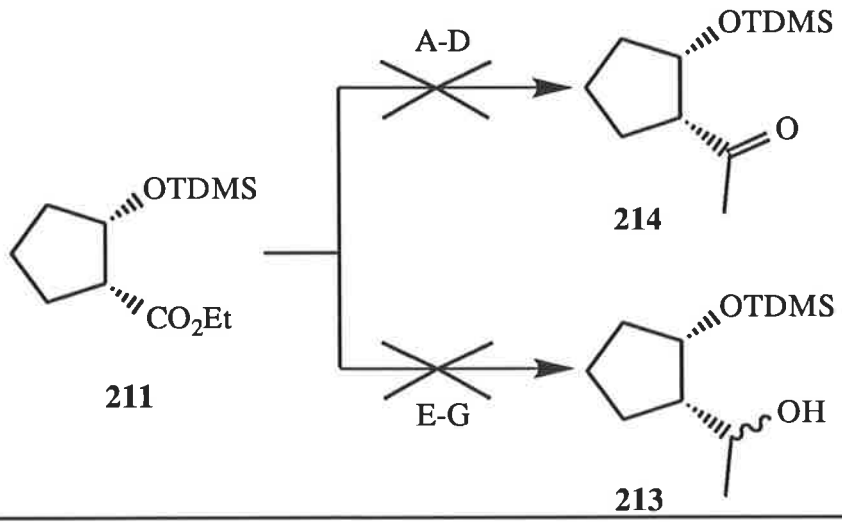
Scheme 3.14

A point of interest was that the above synthetic sequence was characterized by the lack of stability of (+)-(*1R,2S*)-2-[(thexyldimethylsilyl)oxy]-1-cyclopentane carbaldehyde **212**. This prompted the exploration of possible methods to bypass this aldehyde and proceed directly to one of the intermediates further along the synthetic pathway. Ideally, the ester group would be converted directly by a Grignard reagent to methyl ketone **214**. However, a convenient and general method of converting an ester to a ketone is scarce owing to the formation of tertiary alcohols. This is due to the preferential attack on the more reactive ketone intermediate by the organometallic reagent.

Despite this the Grignard reaction of aliphatic esters in hexamethylphosphoramide (HMPA) has been reported to be useful in preparing aliphatic ketones.[224a] It is proposed that the reaction proceeds *via* unreactive ketonic enolates that form by subsequent enolization of the intermediate ketones. Similar methodology employing an excess of an amine base to further facilitate the formation of these intermediate enolates has also been noted.[224b] However,

attempts at both methods including trying to trap the intermediate enolate with N-phenyltriflimide, usually only resulted in the recovery of the starting ester (conditions A-D, **Scheme 3.15**). This lack of reactivity can presumably be explained by partial enolization of the starting ester due to the presence of an α-hydrogen.

Furthermore, it has also been reported that an *in situ* reduction of the initially formed ketone with a hydride source such as lithium borohydride occurs faster than the further addition of Grignard reagent. This particular hydride has been used since it rapidly reduces ketones and not esters. Such a procedure has been consequently shown to yield secondary alcohols.[225] However all attempts, including varying the Grignard reagent or the temperature at which the reaction was conducted, resulted in the recovery of the starting ester (conditions E-G, **Scheme 3.15**). The aforementioned procedures at generating either the methyl ketone or secondary alcohol from ester **211** are summarized in **Scheme 3.15**.



A = i) MeMgI, HMPA, 80°C, 3h, ii) H_2O.
B = i) MeMgI, HMPA, 80°C, 3h, ii) Tf_2NPh.
C = i) MeMgI, Et_2O, NEt_3, -30°C, 15min, ii) HCl.
D = MeMgI, Et_2O, -78°C, to rt, 15h, ii) HCl.
E = MeMgI, $LiBH_4$, THF, -20°C, 24h.
F = as for E except Et_2O used as solvent.
G = MeMgBr, $LiBH_4$, Et_2O, -20°C, 15h.

Chapter 4

Total synthesis of the monoterpene (+)-mintlactone

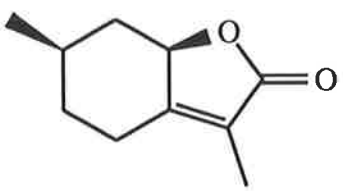
4.1 Introduction

Since the fused butenolide unit is present in a number of natural products of biological interest, numerous methods for the construction of this ring system have been developed.[56] Applying the general synthetic methodology outlined in *Chapter 2*, and particularly *Chapter 3*, a total synthesis of the naturally occurring butenolide mintlactone was undertaken.

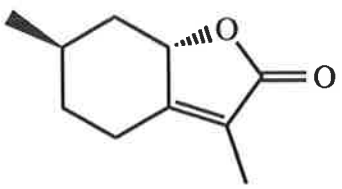
4.2 Background

The essential oil of *mentha piperita* L. (peppermint oil) is of commercial importance worldwide as a flavouring agent and is produced in many countries. The chemical composition of this oil has been explored and has revealed the presence of more than 300 components. (-)-Menthol (40%), (-)-menthyl acetate (3.5), (+)-*iso*menthone (3.5), (-)-pulegone (1.0), (-)-piperitone (0.5) and (+)-3-octanol (0.3) were found to be the major constituents of this oil.

Amongst the minor trace components the menthane derivatives, (-)-mintlactone **219** and its C-3 epimer (+)-*iso*mintlactone **220**, were isolated from a sample of American peppermint oil.[226] These two compounds have also occurred as synthetic intermediates in several procedures with, for instance, racemic **219** appearing in the pathway to menthofurane.[227]



(-)-**219**

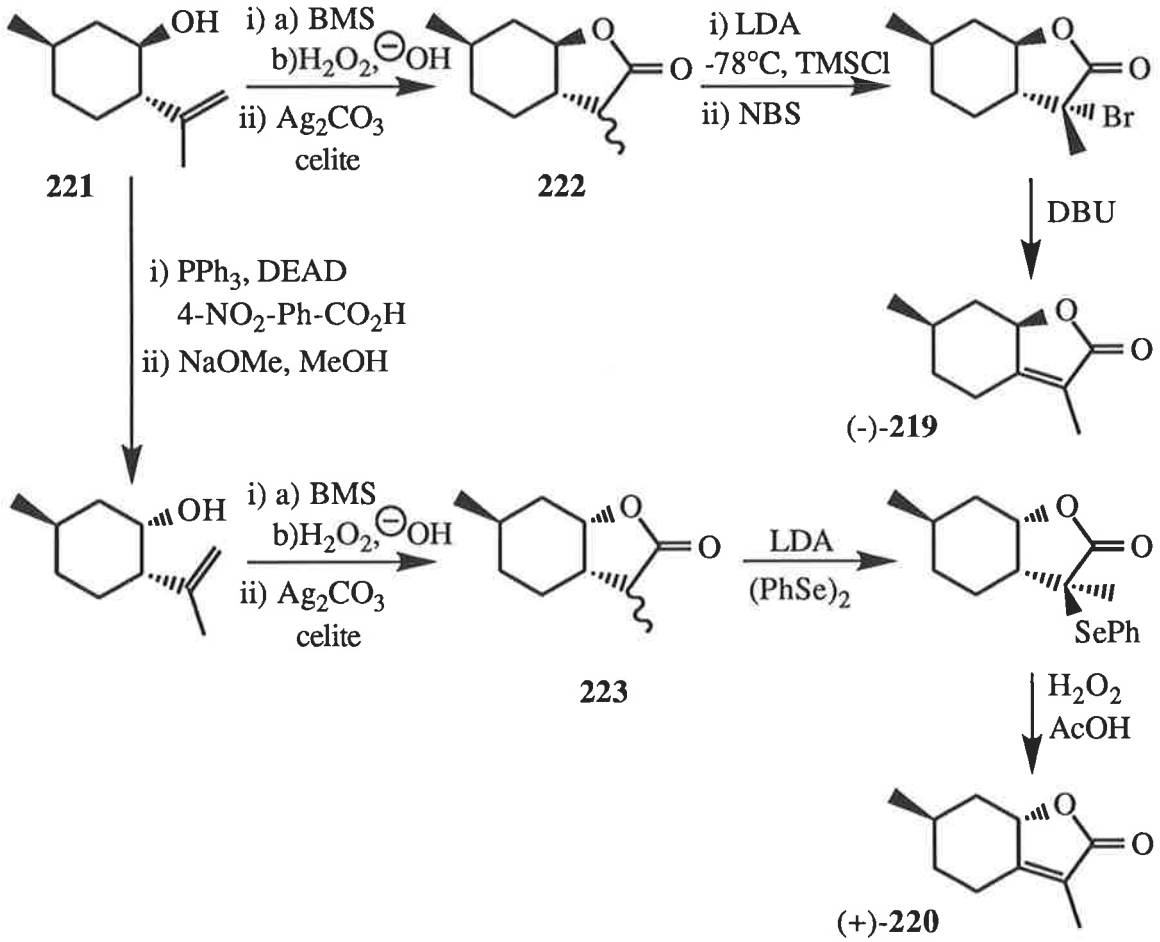


(+)-**220**

Initial synthetic methods toward the butenolide monoterpenes **219** and **220** yielded these compounds in racemic form.[227,228] Recently, however, both have been synthesized in their natural, optically pure form by varied approaches. Shishido *et al.*[229] reported the first

stereoselective synthesis based upon an intramolecular [3+2] cycloaddition of a nitrile oxide to generate the butenolide unit as the key step. This was shortly followed by a method, featuring a stereoselective intramolecular, radical-mediated ring closure, that involved twelve or more steps. This procedure by Carda *et al.*[230] utilized the same chiral starting material for the synthesis of both (-)-**219** and (+)-**220**.

The most efficient synthesis of these compounds has been only relatively recently reported by Chavan *et al.*[231] Using (-)-pulegol **221** as the common source of chirality, the fundamental intermediates dihydro mintlactone **222** and *iso*mintlactone **223** were produced in good yields (the necessary trans stereochemistry for (+)-*iso*mintlactone was obtained by an inversion at the C-OH centre of **221**). The double bond for each compound was then formed *via* the introduction of a bromide or seleno group with subsequent elimination to generate (-)-**219** and (+)-**220** respectively (**Scheme 4.1**).

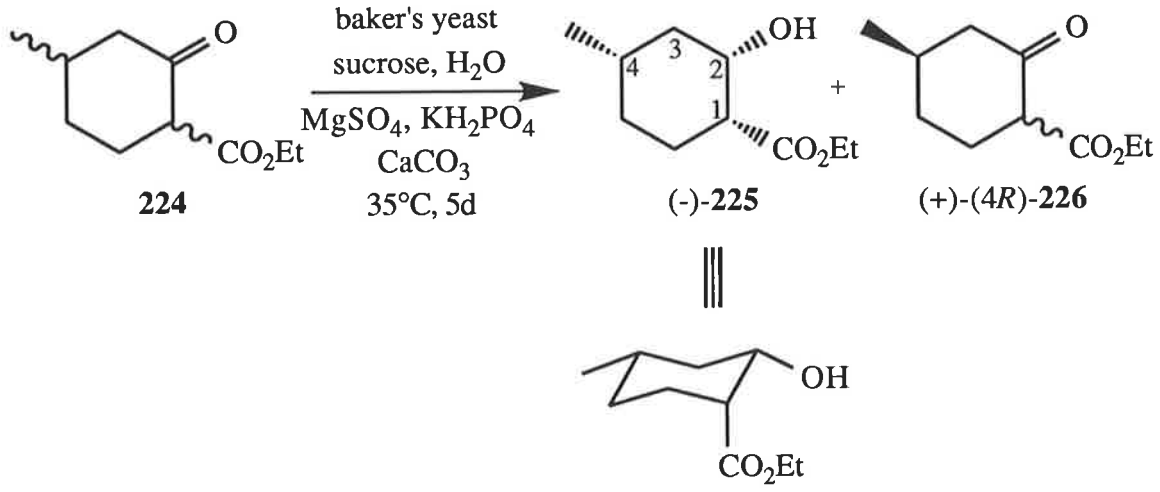


Scheme 4.1

It is of interest to note that (+)-mintlactone has neither, despite a number of approaches to the natural enantiomer, been synthetically generated or isolated from a natural source. This absence prompted investigation toward its total synthesis by utilizing the chemistry developed in the previous chapters.

4.3 Results and Discussion

A suitable starting chiral synthon for the total synthesis of (+)-mintlactone was the fermenting baker's yeast reduction product of the β-keto ester (±)-4-methyl-2-cyclohexanone-1-carboxylate **224**. Following the procedure of Rauk *et al.*[220] β-hydroxy ester, (-)-ethyl (1*R*,2*S*,4*S*)-2-hydroxy-4-methyl-1-cyclohexanecarboxylate, (-)-**225** was obtained in 44% yield. Also recovered was unreacted ester (50%) that had been partially resolved to include an excess of (+)-(4*R*)-**226** (**Scheme 4.2**).* The stereochemical outcome of this reduction can be assumed to yield **225** with an absolute stereochemistry at C-1 and C-2 of *R* and *S* respectively (*vide supra*). The absolute configuration of C-4, at the time the reduction was conducted, was presumed to be *S* since this would be similar to that observed in related systems. Indeed, reductions of these related systems are reported to give product ee's of up to 98%.[232]



Scheme 4.2

* The specific rotation of (+)-ethyl (4*R*)-4-methyl-2-cyclohexanone-1-carboxylate **226**, $[\alpha]_D$ +19.1° (*c*=1.3), was considerably less than that reported, $[\alpha]_D$ +86° (*c*=1.3).[233]

However, this precise reduction has recently been reported by Gilbert *et al.*[234] to give **225** with the predicted absolute stereochemistry. However, these workers report that the product β-hydroxy ester was obtained in only 45±2% ee, where enantiomeric purity was determined by ^{1}H NMR analysis of (-)-**225** in the presence of (+)-Eu(hfc)$_3$. In this case resolution of the ester methyl triplet was sufficient for the determination of ee. A similar ^{1}H NMR experiment conducted on the product obtained from the reduction carried out as per **Scheme 4.2** realized no such defined splitting of the methyl triplet with only the diastereotopic ester methylene group being resolved. Unfortunately the spectrum was insufficiently clean to enable an accurate confirmation of the ee of (-)-**225** based upon analysis of the aforementioned ester methyl resonance. Furthermore the specific rotation, $[\alpha]_D$ -24.5° (*c*=0.52, $CHCl_3$), is somewhat higher than that reported by Gilbert, $[\alpha]_D$ -18.3° (*c*=1.0, $CHCl_3$). Overall this suggests that the reduction to (-)-**225** has proceeded in significantly higher ee than that previously reported.*

Moreover, the configuration at C-1 and C-2 of (-)-**225** may be deduced from the ^{1}H NMR spectrum since $J(1,2)\approx4$Hz and $J(2,3_{ax})\approx11$Hz which is conclusive for the axial position of the ester and the equatorial position of the hydroxyl group. Also the signal widths at half height ($W_{0.5h}$) are consistent with these assignments [δ2.89 (*ddd*), $W_{0.5h}$11.83Hz, H_{eq}-C(1) and δ3.66 (*dt*, after D_2O exchange), $W_{0.5h}$20.29Hz, H_{ax}-C(2)].

Utilizing the analogous methodology presented in *Chapter 3* (*3.3*), β-hydroxy ester (-)-**225** was initially protected as the thexyldimethylsilyl ether to afford **227** (61%). Reduction to the corresponding aldehyde **228** [aldehydic proton at δ10.07 (*s*)] was characterized by a lack of reactivity of **227** since in most cases the reductions resulted in the presence of significant quantities of starting ester. Consequently, the aldehyde/ester mixtures were methylated to form alcohol **229** (83%) with the recovery of unreacted ester during

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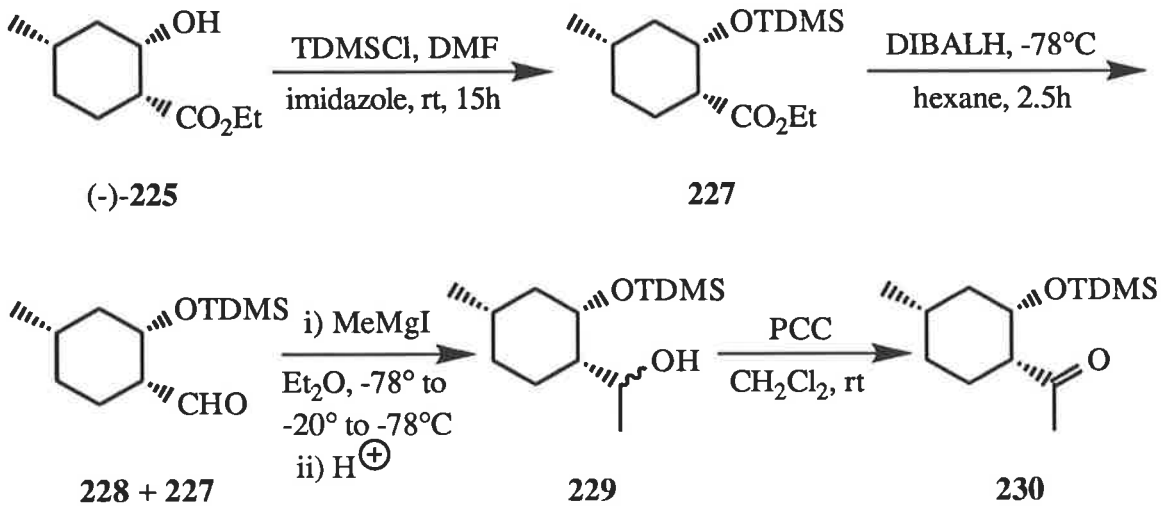
* Identical reduction of **224**, using a different brand of baker's yeast, yielded (-)-**225** with a slightly lower specific rotation, $[\alpha]_D$ -21.2° (*c*=0.5, $CHCl_3$). This suggests that the product ee is dependent upon the particular yeast strain used.

purification. Subsequent oxidation of the alcohol unit yielded methyl ketone **230** (74%) (**Scheme 4.3**).



TDMS = $Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$

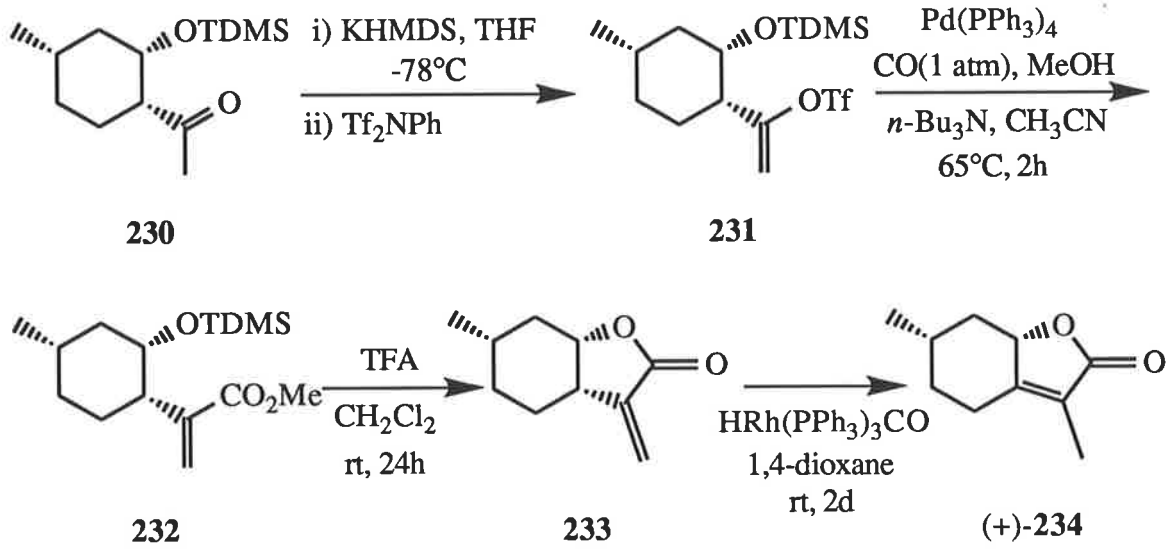
Scheme 4.3

Regioselective triflation produced vinyl triflate **231** in near quantitative yield (98%) and an ensuing palladium-mediated carbomethoxylation afforded acrylate **232** (57%). Quantitative lactonization to **233*** was followed by a rhodium-catalyzed double bond isomerization to yield (+)-mintlactone **234**, possessing a pleasant sweet aroma (28% overall yield from **225**) (**Scheme 4.4**).

The spectral data for (+)-mintlactone was found to be identical in all repects to the data reported in the literature for (-)-mintlactone **219**.[230,231] The specific rotation, $[\alpha]_D$ +59.9° (*c*=0.75, EtOH), is in good agreement to that reported for the natural enantiomer, $[\alpha]_D$ -51.8° (*c*=10, EtOH)[226] and -56.6° (*c*=2.2, EtOH),[231] indicating that no loss of stereochemical integrity has occurred during the synthesis. The successful completion of this synthesis also

* A ^1H NMR chiral shift experiment in the presence of (+)-Eu(hfc)$_3$ revealed no splitting or broadening of any resonances.

constitutes a definite confirmation of the enantiomeric purity and absolute configuration of the chiral β-hydroxy ester (-)-**225**.



230 **231** **232** **233** **(+)-234**

Scheme 4.4

Experimental General

Solvents were purified by standard procedures with all reactions conducted under nitrogen unless otherwise stated. Ether refers to diethyl ether. All organic extracts were dried over sodium sulfate unless otherwise indicated. TLC analysis of reaction mixtures were performed on aluminum backed plates of Kieselgel 60_{F254} silica and were visualized with a 245nm lamp or either an ethanol solution of 5% phosphomolybdic acid or an acidic solution of 10% ammonium molybdate. Column chromatography was carried out on Merck silica gel 60_{PF254}.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACP 300 spectrometer in $CDCl_3$ unless otherwise stated with tetramethylsilane as an internal standard. ^{1}H NMR resonance spectra were recorded at 300 MHz and ^{13}C NMR resonance spectra at 75.5 MHz. ^{1}H and ^{13}C NMR for compounds **229-231** were recorded on a Varian Gemini 200 spectrometer. Chemical shifts are quoted as δ in parts per million downfield from the internal standard. Infrared spectra were recorded on a Hitachi 270-30 spectrophotometer. Multiplicities used to define peak shape for the various spectra are abbreviated to: ^{1}H and ^{13}C NMR; *s*, singlet; *d*, doublet; *t*, triplet; *q*, quartet; *m*, multiplet; *br*, broad; IR; *s*, strong; *m*, medium; *w*, weak; *br*, broad.

Electron impact mass spectra were recorded with an AEI-GEC 3074 mass spectrometer at 70eV. Low resolution spectra for compounds **199**, **227**, **229-232** and **234** were run on a Jeol AX505H mass spectrometer and their high resolution spectra on a VG 70/70 mass spectrometer.

Specific rotations were recorded on a Perkin Elmer 141 spectropolarimeter as solutions of either chloroform, dichloromethane or ethanol at room temperature. Elemental analysis were carried out by Chemical and Micro Analytical Services Pty. Ltd., Victoria, Australia. Melting points were recorded on a Kofler hot-stage under a Reichert microscope and are uncorrected. Gas-liquid chromatography was performed on a DANI 8510 chromatograph using a 10% OV-101 column.

The concentrations of all Grignard reagents were estimated using the colour charge transfer complex of 1,10-phenanthroline as an indicator that decomposed upon titration with butan-2-ol.

The following compounds were prepared by literature procedures: ethyl 2-[(trifluoromethane sulfonyl)oxy]-1-cyclopentene-1-carboxylate **136a**;[235] ethyl 2-[(trifluoromethanesulfonyl)oxy]-1-cyclohexene-1-carboxylate **136b**;[236] 1-hydroxymethyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclopentene **137b**;[180] ethyl 2-[(trifluoromethanesulfonyl)oxy]benzoate;[181] 2-[(trifluoromethanesulfonyl)oxy]benzyl alcohol;[153b] tetrakis(triphenylphosphine) palladium(0), $Pd(PPh_3)_4$;[237] N-phenyl triflimide, Tf_2NPh.[238]

Experimental: Chapter 2

2.5.1

Ethyl 2-[(trifluoromethanesulfonyl)oxy]-1-cycloheptene-1-carboxylate (136c)

Ethyl 2-cycloheptanone carboxylate (8.0g, 43.7mmol) was dissolved in dry dichloromethane (100ml) and cooled to -78°C. *N,N*-Diisopropylethylamine (38ml, 218.3mmol) was added and the mixture allowed to stir for 10min. Tf_2O (8.8ml, 52.4mmol) was added dropwise followed by slow warming to room temperature for 15h. The mixture was washed with water (150ml), 10% citric acid solution (2x150ml), dried and the solvent removed under reduced pressure. The resultant red-brown oil was distilled (69-70°C/0.06mm) to yield a pale yellow oil (10.6g, 77%). ^{1}H NMR: δ1.32 (*t*, *J*7.21Hz, 3H, CH_3), 1.72 (*m*, 6H, cycloheptenyl CH_2), 2.55 (*m*, 4H, CH_2C=), 4.26 (*q*, *J*7.08Hz, 2H, OCH_2); ^{13}C NMR: δ13.9, 23.8, 25.3, 28.1, 30.6, 33.7, 61.6, 118.4 (*q*, J_{CF}324.5Hz), 128.3, 154.5, 165.8; IR (neat): ν_{max}2930 *s*, 1725 *s* (C=O), 1655 *m* (C=C), 1425 *s* (asymS=O), 1350 *s*, 1295 *s*, 1250 *s* (asymC-OSO_2), 1210 *s* (C-F), 1140 *s* (symS=O), 1100 *m* (S-O), 1030 *m*, 1005 *s*, 935 *m*, 870 *s*, 790 *m*, 595 *s* cm^{-1}; MS, m/z: 316 (M^+, 8%), 271 ($[M-OC_2H_5]^+$, 45), 204 (9), 183 ($[M-Tf]^+$, 18), 176 (9), 167 ($[M-OTf]^+$, 44), 138 ($C_8H_{10}O_2^+$, 100); HRMS calc. for $C_{11}H_{15}F_3O_5S$: 316.05923; Found: 316.06010; Anal. calc. for $C_{11}H_{15}F_3O_5S$: C, 41.77%; H, 4.78%; Found: C, 41.43%; H, 4.95%.

Ethyl 2-[(trifluoromethanesulfonyl)oxy]-1-cyclooctene-1-carboxylate (136d)

To ethyl 2-cyclooctanone carboxylate (5.0g, 25.2mmol) in dichloromethane (70mL) at -78° was added *N,N*-diisopropylethylamine (22.0ml, 126.1mmol). The reaction was stirred for 10min, followed by the addition of Tf_2O (5.1ml, 30.3mmol) and warming to room temperature overnight. GLC analysis of the mixture indicated that starting material was still present, so an additional 2 equivalents of Tf_2O (8.0ml) and *N,N*-diisopropylethylamine (10ml) were added and the mixture stirred for an additional 48h. At this point all the starting material was consumed, the mixture was washed with water (100ml), a 10% citric acid solution (2x100ml), dried and the solvent removed under reduced pressure. The resultant red/black oil was distilled (70-71°/0.03mm) to give a pale yellow oil (7.89g, 95%). ^{1}H

NMR: δ1.33 (t, *J*7.05Hz, 3H, CH_3), 1.57 (*m*, 4H, cyclooctenyl CH_2), 1.76 (*m*, 4H, cyclooctenyl CH_2), 2.50 (*m*, 4H, CH_2C=), 4.28 (*q*, *J*6.86Hz, 2H, OCH_2); ^{13}C NMR: δ13.8, 25.4, 26.0, 27.8, 28.3, 29.4, 30.9, 61.5, 118.3 (*q*, J_{CF}317.9Hz), 125.5, 151.5, 152.1; IR (neat): ν_{max}2930, 1730, 1580, 1425, 1215, 1135, 950 cm^{-1}; MS, m/z: 330 (M^+, 4%), 331($[M+1]^+$, 26), 285 ($[M-OC_2H_5]^+$. 54), 202 (25), 197 ($[M-Tf]^+$, 15), 190 (36), 181 ($[M-OTf]^+$, 31), 180 ($[M-TfOH]^+$, 35), 169 (22), 151(100); HRMS calc. for $C_{12}H_{18}F_3O_5S$ (M+1): 331.08270; Found: 331.08315; Anal. calc. for $C_{12}H_{17}F_3O_5S$: C, 43.63%; H, 5.19%; Found: C, 43.69%; H, 5.28%.

-2-[(trifluoromethanesulfonyl)oxy]-1-cyclohexene ylmethanol (137b)

To a THF (100ml) solution of ethyl 2-[(trifluoromethanesulfonyl)oxy]-1-cyclohexene-1-carboxylate **136b** (3.0g, 9.92mmol) at -78° was added dropwise DIBALH (3.89ml, 21.83mmol). The solution was warmed slowly to room temperature over 2hr and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane (100ml), washed with water (2x100ml), dried and the solvent removed under reduced pressure. The residue was purified by flash chromatography (hexanes:ethyl acetate; 7:3) to give the title compound as a pale yellow oil (1.99g, 77%). A small sample was distilled by kugelrohr (60-70°C/0.02mm). ^1H NMR: δ1.66 (*m*, 2H, cyclohexenyl CH_2), 1.76 (*m*, 2H, cyclohexenyl CH_2), 2.34 (*m*, 4H, CH_2C=), 4.20 (*m*, 2H, $C\underline{H}_2OH$). ^{13}C NMR: δ21.3, 22.8, 26.1, 27.5, 59.4, 118.2 (*q*, J_{CF} 317.6Hz), 129.8, 143.9; IR (neat): ν_{max}3370 *s* (O-H), 2940 *s*, 1715 *m*, 1660 *w*, 1415 *s* (asymS=O), 1250 *m* (asymC-OSO_2), 1215 *s* (C-F), 1140 *s* (symS=O), 1025 *m* (S-O), 940 *w*, 890 *m*, 815 *m*, 765 *m* cm^{-1}. MS, m/z: 260 (M^+, 2%), 259 ($[M-1]^+$, 2), 243 ($[M-OH]^+$, 20), 185 (1), 171 (1), 133 (4), 127 ($[M-Tf]^+$, 15), 111 (10), 81 (38) 69 (100, CF_3^+); HRMS calc. for $C_8H_{11}F_3O_4S$: 260.0330; Found: 260.0332; Anal. calc. for $C_8H_{11}F_3O_4S$: C, 36.92%; H, 4.26%; Found: C, 36.85%; H, 4.33%.

2-[(trifluoromethanesulfonyl)oxy]-1-cycloheptene ylmethanol (137c)

This compound was prepared from ethyl 2-[(trifluoromethanesulfonyl)oxy]-1-cycloheptene-1-carboxylate **136c** (3.5g, 11.1mmol) in an analogous manner to that described for **137b**. Flash chromatography (hexanes:ethyl acetate; 7:3) gave the title compound as a yellow oil (2.70g, 89%). A small sample was distilled by kugelrohr (85-90°C/ 0.03mm). ^1H

NMR: δ1.63-1.76 (*m*, 6H, cycloheptenyl CH_2), 2.36 (*m*, 2H, CH_2C=), 2.53 (*m*, 2H, CH_2C=), 4.17 (*s*, 2H, $C\underline{H}_2OH$); ^{13}C NMR: δ24.4, 25.6, 28.4, 30.5, 32.8, 61.2, 118.3 (*q*, J_{CF} 319.4Hz), 134.9, 147.5; IR (neat): ν_{max}3370 *m* (O-H), 2930 *s*, 1690 *m* (C=C), 1415 *s* (asymS=O), 1250 *s* (asymC-OSO_2), 1215 *s* (C-F), 1145 *s* (symS=O), 1035 *m* (S-O), 990 *s*, 925 *m*, 875 *s*, 780 *m*, 760 *m*, 595 *s* cm^{-1}; MS, m/z: 274 (M^+, 2%), 256 ([M-H_2O]$^+$, 73), 203 (31), 176 (16), 141 ([M-Tf]$^+$, 28), 123 (37), 107 (35), 95 (100); HRMS calc. for $C_9H_{13}F_3O_4S$: 274.04867; Found: 274.04959; Anal. calc. for $C_9H_{13}F_3O_4S$: C, 39.42%; H, 4.78%; Found: C, 39.40%; H, 5.03%.

2-[(trifluoromethanesulfonyl)oxy]-1-cyclooctenyl methanol (137d)

This compound was prepared from ethyl 2-[(trifluoromethanesulfonyl)oxy]-1-cyclooctene-1-carboxylate **136d** (3.5g, 10.6mmol) in an analogous manner to that described for **137b**. Flash chromatography (hexanes:ethyl acetate; 3:1) gave the title compound as a yellow oil (2.09g, 68%). A small sample was distilled by kugelrohr (105-110°C/0.02mm). ^1H NMR: δ1.53-1.70 (*m*, 8H, cyclooctenyl CH_2), 2.37 (*m*, 2H, CH_2C=), 2.50 (*m*, 2H, CH_2C=), 4.21 (*m*, 2H, $C\underline{H}_2OH$); ^{13}C NMR: δ25.8, 26.0, 27.8, 28.0, 29.1, 29.8, 59.5, 118.4 (*q*, J_{CF}324.5Hz), 132.1, 145.3; IR (neat): ν_{max}3365 *s* (O-H), 2930 *s*, 1690 *m* (C=C), 1410 *s* (asymS=O), 1250 *s* (asymC-OSO_2), 1210 *s* (C-F), 1140 *s* (symS=O), 1070 *m* (S-O), 1030 *m*, 910 *s*, 870 *m*, 810 *m*, 730 *m* cm^{-1}; MS, m/z: 288 (M^+, 3%), 155 ([M-Tf]$^+$, 14), 138 ([M-TfOH]$^+$, 11), 67 (100); HRMS calc. for $C_{10}H_{15}F_3O_4S$: 288.06431; Found: 288.06337; Anal. calc. for $C_{10}H_{15}F_3O_4S$: C, 41.66%; H, 5.24%; Found: C, 41.76%; H, 5.44%.

Ethyl *Z* 3-[(trifluoromethanesulfonyl)oxy]-2-butenoate (140)[180]

A solution of ethyl acetoacetate (0.60g, 4.61mmol) in THF (10ml) was added to KHMDS (0.5M in toluene) (11.10ml, 5.53mmol) at -78°C. Whilst at -78°C Tf_2NPh (1.98g, 5.53mmol) was added and the mixture was allowed to warm to room temperature overnight. The mixture was washed with water (50ml), 10% citric acid solution (2x50ml), dried and the solvent removed under reduced pressure. The residue was purified by flash chromatography (hexanes:ethyl acetate; 19:1) and gave the titled compound as a clear, pale yellow oil (0.92g, 76%). A small amount was distilled by kugelrohr (50-55°C/0.03mm). ^1H NMR: δ1.30 (*t*,

*J*6.96Hz, 3H, $CH_2C\underline{H}_3$), 2.18 (*s*, 3H, CH_3), 4.25 (*q*, *J*7.12Hz, 2H, OCH_2), 5.77 (*m*, 1H, vinyl); ^{13}C NMR: δ13.8, 20.7, 61.1, 112.7, 118.2 (*q*, J_{CF}317.6Hz), 155.1, 162.2; IR (neat): ν_{max}2990 *w*, 1735 *s* (C=C), 1690 *m* (C=C), 1430 *s* (asymS=O), 1320 *m*, 1295 *m*, 1255 *m* (asymC-OSO_2), 1210 *s* (C-F), 1140 *s* (symS=O), 1050 *m*, 930 *s*, 860 *m*, 780 *m*, 720 *m* cm^{-1}; MS, m/z: 262 (M^+, 6%), 233 ([M-C_2H_5]$^+$, 8), 217 (32), 153 (10), 113 ([M-OTf]$^+$, 3), 87 (36), 84 (31), 69 (100, CF_3^+), 43 (61); HRMS calc. for $C_7H_9F_3O_5S$: 262.01228; Found: 262.01123.

Ethyl *E*-3-[(trifluoromethanesulfonyl)oxy]-2-butenoate (139)

This compound was prepared from ethyl acetoacetate (0.5g, 3.84mmol) in an analogous manner to that described for **136c**. Flash chromatography (hexanes:ethyl acetate; 24:1) gave the title compound as a pale orange oil (0.42g, 42%). ^1H NMR: δ1.31 (*t*, *J*7.01Hz, 3H, $CH_2C\underline{H}_3$), 2.52 (*s*, 3H, CH_3), 4.23 (*q*, *J*7.02Hz, 2H, $C\underline{H}_2CH_3$), 5.95 (*s*, 1H, vinylic); ^{13}C NMR: δ14.1, 18.4, 61.2, 113.3, 118.3 (*q*, J_{CF}319.9Hz), 162.0, 164.2; All other spectral data was identical to **140**. The *Z*-isomer was also obtained during purification (0.19g, 19%) (see **140** for characterization).

***Z* 3-[(trifluoromethanesulfonyl)oxy]-2-buten-1-ol (141)**

This compound was prepared from ethyl *Z* 3-[(trifluoromethanesulfonyl)oxy]-2-butenoate **140** (0.3g, 1.14mmol) in an analogous manner to that described for **137b**. Flash chromatography (hexanes:ethyl acetate, 20:3) gave the titled product as a colourless oil (0.18g, 72%). A small sample was distilled by kugelrohr (50-55°C/ 0.03mm). ^1H NMR: δ2.10 (*s*, 3H, CH_3), 4.27 (*br s*, 2H, $C\underline{H}_2OH$), 5.55 (*dd*, *J*6.90, 5.92Hz, 1H, vinyl); ^{13}C NMR: δ19.5, 56.5, 118.3 (q, J_{CF} 319.2Hz), 120.9, 146.1; IR (neat): ν_{max}3360 *m* (O-H), 2930 *w*, 1705 *m* (C=C), 1420 *s* (asymS=O), 1250 *s* (asymC-OSO_2), 1215 *s* (C-F), 1150 *s* (symS=O), 1020 *m* (S-O), 955 *m*, 910 *s*, 745 *m*, 730 *m*, 635 *m* cm^{-1}; MS, m/z: 220 (M^+, 1%), 202 ([M-H_2O]$^+$, 3), 121 (5), 95 (4), 87 ([M-Tf]$^+$, 42), 71 ([M-OTf]$^+$, 45), 69 (100, CF_3^+); HRMS calc. for $C_5H_7F_3O_4S$: 220.00171; Found: 220.00226; Anal. calc. for $C_5H_7F_3O_4S$: C,27.28%; H, 3.15%; Found: C, 26.95%; H, 3.34%.

Ethyl *Z* 2-benzyl-3-[(trifluoromethanesulfonyl)oxy]-2-butenoate (142)[180]

This compound was prepared from ethyl benzylacetoacetate in an analogous manner to that described for **140**. Flash chromatography (hexanes:ethyl acetate; 19:1) gave the titled product as a pale yellow oil (0.34g, 12%). ^{1}H NMR: δ1.21 (*t*, *J*7.24Hz, 3H, $CH_2C\underline{H}_3$), 2.20 (*s*, 3H, CH_3), 3.74 (*s*, 2H, $C\underline{H}_2Ph$), 4.20 (*q*, *J*7.25Hz, 2H, OCH_2), 7.12-7.33 (*m*, 5H, aromatic); ^{13}C NMR: δ13.7, 17.8, 34.9, 61.7, 118.3 (*q*, J_{CF}319.9Hz), 126.8, 128.0, 128.4, 128.6, 136.7, 149.1, 164.8; IR (neat): ν_{max}2985 *w*, 1730 *s* (C=O), 1665 *w* (C=C), 1605 *w*, 1500 *w*, 1420 *s* (asymS=O), 1250 *s* (asymC-OSO_2), 1215 *s* (C-F), 1140 *s* (symS=O) , 1095 *m*, 1060 *m* (S-O), 955 *m*, 845 *m*, 750 *m*, 700 *m* cm^{-1}; MS, m/z: 307 ([M-OEt]$^+$, 3%), 219 ([M-Tf]$^+$, 5), 178 (12), 173 (25), 147 (5), 131 (24), 104 (100); HRMS calc. for $C_{12}H_{10}F_3O_4S$ (M-OEt)$^+$: 307.02519; Found: 307.02406. The *E*-isomer was also obtained during purification in 36% yield (see **144** for characterization).

***Z* 2-Benzyl-3-[(trifluoromethanesulfonyl)oxy]-2-buten-1-ol (143)**

This compound was prepared from ethyl *Z* 2-benzyl-3-[(trifluoromethanesulfonyl)oxy]-2-butenoate **142** (0.25g, 0.71mmol) in an analogous manner to that described for **137b**. Flash chromatography (hexanes:ethyl acetate; 19:1) gave the title product as a colourless oil (0.14g, 81% corrected for recovered starting material). A small sample was distilled by kugelrohr (105-110°C/0.04mm). ^{1}H NMR: δ2.21 (*s*, 3H, CH_3), 3.62 (*s*, 2H, $C\underline{H}_2Ph$), 4.18 (*m*, 2H, $C\underline{H}_2OH$), 7.18-7.35 (*m*, 5H, aromatic); ^{13}C NMR: δ16.8, 34.1, 58.4, 118.3 (*q*, J_{CF}318.9Hz), 126.7, 128.3, 128.7, 131.1, 137.3, 142.9; IR (neat): ν_{max}3385 *s* (O-H), 2930 *m*, 1690 *m* (C=C), 1605 *w*, 1500 *m*, 1410 (asymS=O), 1250 *s* (asymC-OSO_2), 1210 *s* (C-F), 1140 *s* (symS=O), 1085 *m* (S-O),1015 *m*, 910 *s*, 830 *s*, 740 *m*, 700 *m* 630 *s* cm^{-1}; MS, m/z: 310 (M$^+$, 3%), 219 ([M-C_7H_7]$^+$, 4), 205 (2), 177 ([M-Tf]$^+$,), 159 (46), 142 (45), 117 (35), 91 ($C_7H_7^+$, 100); HRMS calc. for $C_{12}H_{13}F_3O_4S$: 310.04866; Found: 310.05022; Anal. calc. for $C_{12}H_{13}F_3O_4S$: C, 46.45%; H, 4.22%; Found: C, 46.31%; H, 4.57%.

Ethyl *E* 2-benzyl-3-[(trifluoromethanesulfonyl)oxy]-2-butenoate (144)[239]

This compound was prepared from ethyl benzylacetoacetate (3.5g, 15.9mmol) in an analogous manner to that described for **136c**. Flash chromatography (hexanes:ethyl acetate,

19:1) gave the title product as a pale yellow oil (3.33g, 64%). ^{1}H NMR: δ1.15 (*t*, *J*7.02Hz, 3H, $CH_2C\underline{H}_3$), 2.47 (*s*, 3H, CH_3), 3.81 (*s*, 2H, $C\underline{H}_2Ph$), 4.13 (*q*, *J*7.10Hz, OCH_2), 7.07-7.32 (*m*, 5H, aromatic); ^{13}C NMR: δ13.8, 18.9, 33.7, 61.5, 118.2 (*q*, J_{CF}317Hz), 126.3, 126.7, 128.0, 128.5, 137.2, 153.7, 165.8. All other spectral and analytical data were identical to **142**.

E 2-benzyl-3-[(trifluoromethanesulfonyl)oxy]-2-buten-1-ol (145)

This compound was prepared from ethyl *E* 2-benzyl-3-[(trifluoromethanesulfonyl)oxy]-2-butenoate **144** (1.0g, 2.84mmol) in an analogous manner to that described for **137b**. Flash chromatography (hexanes:ethyl acetate; 19:1) gave the title product as a colorless oil (0.44g, 50%). ^{1}H NMR: δ2.21 (*s*, 3H, CH_3), 3.68 (*s*, 2H, $C\underline{H}_2Ph$), 4.08 (*m*, 2H, $C\underline{H}_2OH$), 7.22-7.35 (*m*, 5H, aromatic); ^{13}C NMR: δ16.6, 34.0, 60.0, 118.3 (*q*, J_{CF}319.8Hz), 126.8, 128.7, 128.9, 130.5, 137.3, 144.2. All other spectral and analytical data were identical to **143**.

2.5.2

3,4,5,6-Tetrahydro-1*H*-cyclopenta[c]furan-1-one (146a)[240]

Carbon monoxide was bubbled through a solution of **137a** (0.30g, 1.22mmol), $Pd(PPh_3)_4$ (0.14g, 0.122mmol), tri-*n*-butylamine (0.58ml, 2.44mmol) and lithium chloride (0.052g, 1.22mmol) in acetonitrile (40ml) for 20min. The mixture was heated at 65°C under one atmosphere of carbon monoxide (balloon placed over the reflux condenser) for 12h. Ether (20ml) was added to the cooled solution, the mixture filtered through a pad of kenite and the pad further rinsed with ether (2x10ml). The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane and purified by flash chromatography (hexanes:ethyl acetate, 7:3) to give the title product as reddish crystals. Recrystallization from hexane/benzene gave oblong, translucent crystals (0.13g, 83%). M.pt. 48-49°C, lit.[238] 48-49°C. ^{1}H NMR: δ2.43-2.54 (*m*, 4H, CH_2), 2.62-2.69 (*m*, 2H, CH_2C=), 4.79 (*m*, 2H, CH_2O); ^{13}C NMR: δ24.8, 28.7, 29.1, 69.2, 137.2, 170.0, 174.2; IR (nujol mull): ν_{max}2925 *s*, 1750 *m* (C=O), 1660 *w* (C=C), 1465 *s*, 1380 *s*, 1250 *s*, 1160 *m*, 1040, 725 *m*, 635 *m* cm^{-1}; Ms, m/z: 125 ([M+1]$^+$, 48%), 124 (M$^+$, 32), 95 ([M-CHO]$^+$, 100), 79 (6).

4,5,6,7-Tetrahydro-1(3*H*)-isobenzofuranone (146b)[241]

This compound was prepared from 2-[(trifluoromethanesulfonyl)oxy]-1-cyclohexenylmethanol **137b** (0.3g,1.15mmol) in an analogous manner to that described for **146a** using hydroxy vinyltriflate. Flash chromatography (hexanes:ethyl acetate, 9:1) gave the title product as a red/brown solid. Recrystallization from chloroform/hexanes gave oblong, translucent crystals (0.12g, 75%). M.pt. 53-54°C, lit.[240] 53-54°C. ^{1}H NMR: δ1.67 (*m*, 4H, cyclohexenyl CH_2), 2.10-2.14 (*m*, 2H, CH_2C=), 2.24 (*m*, 2H, CH_2C=), 4.60 (*s*, 2H, CH_2O); ^{13}C NMR: δ19.8, 21.3, 21.5, 23.5, 72.0, 126.2, 161.0, 174.3; IR (CH_2Cl_2): ν_{max}2930 *s*, 1750 *s* (C=O), 1690 *m* (C=C), 1450 *s*, 1345 *m*, 1250 *s*, 1140 *m*, 1095 *m*, 1040 *m*, 980 *m*, 740 *m* cm^{-1}; Ms, m/z: 139 ([M+1]$^+$, 73%), 138 (M$^+$, 31), 109 ([M-CHO]$^+$, 100), 81 (38), 79 (27).

3,4,5,6,7,8-Hexahydro-1*H*-cyclohepta[c]furan-1-one (146c)[242]

This compound was prepared from 2-[(trifluoromethanesulfonyl)oxy]-1-cycloheptenylmethanol **137c** (0.3g, 1.09mmol) in an analogous manner to that described for **146a**. Flash chromatography (hexanes:ethyl acetate, 9:1) gave the title product as a colourless oil (0.16g, 95%). ^{1}H NMR: δ1.59-1.86 (*m*, 6H, cycloheptenyl CH_2), 2.41 (*m*, 4H, CH_2C=), 4.60 (*s*, 2H, CH_2O); ^{13}C NMR: δ25.0, 26.8, 26.9, 28.5, 30.6, 71.6, 128.8, 146.0, 162.5; IR (neat): ν_{max}2925 *s*, 1755 *s* (C=O), 1675 *m* (C=C), 1450 *m*, 1345 *m*, 1265 *m*, 1140 *m*, 1100 *m*, 1085 *m*, 1030 *m*, 995 *m*, 890 *w*, 765 *m* cm^{-1}; MS, m/z: 153 ([M+1]$^+$, 2%), 152 (M$^+$, 2), 123 ([M-CHO]$^+$, 6), 105 (8), 86 (35), 84 (52), 49 (100); HRMS calc. for $C_9H_{12}O_2$: 152.08373; Found: 152.08316.

1,3,4,5,6,7,8,9-Octahydro-3*H*-cyclooct[c]furan-1-one (146)[243]

This compound was prepared from 2-[(trifluoromethanesulfonyl)oxy]-1-cyclooctenylmethanol **137d** (0.3g, 1.04mmol) in an analogous manner to that described for **146a**. Flash chromatography (hexanes:ethyl acetate; 9:1) gave the titled product as a colourless oil (0.14g, 81%). ^{1}H NMR: δ1.49-1.60 (*m*, 4H, cyclooctenyl CH_2), 1.69 (*m*, 2H, cyclooctenyl CH_2), 1.80 (*m*, 2H, cyclooctenyl CH_2), 2.45 (*m*, 4H, CH_2C=), 4.63 (*s*, 2H, $C\underline{H}_2OH$); ^{13}C NMR: δ22.9, 26.1, 26.7, 26.8, 27.3, 27.8, 72.3, 127.6, 162.3, 176.2; IR (neat); ν_{max}2930 *s*, 1745 *s* (C=O), 1670 *m* (C=C), 1455 *m*,

1350 *m*, 1095 *m*, 1020 *s*, 780 *w* cm^{-1}; MS, m/z: 166 (M^+, 78%), 137 ($[M-CHO]^+$, 100), 67 (56); HRMS Calc. for $C_{10}H_{14}O_2$: 166.09938; Found: 166.09983.

1(3*H*)-Isobenzofuranone (147)[244]

This compound was prepared from 2-[(trifluoromethanesulfonyl)oxy]benzyl alcohol **138** (0.2g, 0.78mmol) in an analogous manner to that described for **146a**. Flash chromatography (hexanes:ethyl acetate; 19:1) gave the titled product (45mg, 60% corrected for recovered starting material). ^1H NMR: δ5.34 (*s*, 2H, CH_2O), 7.30-7.95 (*m*, 4H, aromatic); ^{13}C NMR: δ69.7, 125.8, 128.7, 129.1, 129.4, 130.0, 134.0, 160.1; IR (CH_2Cl_2): ν_{max}2930 *m*, 1740 *s* (C=O), 1600 *m*, 1580 *w*, 1500 *m*, 1450 *m*, 1340 *m*, 1040 *s*, 995 *m*, 740 *s* cm^{-1}; Ms, m/z: 134 (M^+), 105 ($[M-CHO]^+$, 100); HRMS calc. for $C_8H_6O_2$: 134.03678; Found: 134.03771.

3-Methyl-2(5*H*)-furanone (148)[245]

This compound was prepared from *Z* 3-[(trifluoromethanesulfonyl)oxy]-2-buten-1-ol **141** (0.3g, 1.36mmol) in an analogous manner to that described for **146a**. Upon workup this compound was not subjected to flash chromatography but distilled (55-60°C/2mm) (Lit.[244] 82°C/7mm) to give the title product as a colorless oil (0.10g, 75%). ^1H NMR: δ1.89 (*ddd*, *J*2.15, 1.98, 1.60Hz, 3H, CH_3), 4.74 (*m*, 2H, OCH_2), 7.09 (*dd*, *J*1.52, 1.38Hz, 1H, vinylic); ^{13}C NMR: δ10.7, 70.0, 129.9, 144.9, 174.8; IR (neat): ν_{max}2960 *m*, 1750 *m* (C=O), 1655 *w* (C=C), 1455 *w*, 1260 *s*, 1090 *s*, 1050 *s*, 800 *s* cm^{-1}; MS, m/z: 99 ($[M+1]^+$, 21%), 98 (M^+, 12), 69 ($[M-CHO]^+$, 64), 57 (100); HRMS calc. for $C_5H_6O_2$: 98.03678; Found: 98.03705.

3-Methyl-4-benzyl-2(5*H*)furanone (149)

This compound was prepared from *Z* 2-benzyl-3-[(trifluoromethanesulfonyl)oxy]-2-buten-1-ol **143** (0.14g, 0.45mmol) in an analogous manner to that described for **146a**. Upon workup this compound was distilled by kugelrohr (150-160°C/0.04mm) to give the title product as a pale yellow oil (60mg, 71%). ^1H NMR: δ1.93 (*s*, 3H, CH_3), 3.74 (*s*, 2H, $C\underline{H}_2Ph$), 4.56 (*br s*, 2H, $OC\underline{H}_2$), 7.13-7.37 (*m*, 5H, aromatic); ^{13}C NMR: δ8.5, 33.3, 71.2, 123.4, 127.1, 128.3, 128.9, 136.1, 158.4, 175.2; IR (neat): ν_{max}2925 *m*, 1745 *s*

(C=O), 1680 *m* (C=C), 1600 *w*, 1500 *m*, 1455 *m*, 1335 *m*, 1080 *m*, 1030 *m*, 755 *m*, 705 *m* cm^{-1}; MS, m/z: 188 (M^+, 14%), 159 ($[M-CHO]^+$, 9), 142 (45), 129 (18), 110 ($[M-C_6H_6]^+$, 95), 91 ($C_7H_7^+$, 100); HRMS calc. for $C_{12}H_{12}O_2$: 188.08373; Found: 188.08466; Anal. calc. for $C_{12}H_{12}O_2$: C, 76.57%; H, 6.43%; Found: C, 76.92%; H, 6.45%.

Methyl *E* 2-methyl-3-benzyl-2-buten~~-1-ol~~oate (150)

Carbon monoxide was bubbled through a solution of *E*-2-benzyl-3-[(trifluoromethanesulphonyl)oxy]-2-buten-1-ol **145** (0.15g, 0.48mmol), $Pd(PPh_3)_4$ (0.056g, 0.048mmol), tri-*n*-butylamine (0.23ml, 0.96mmol), lithium chloride (0.021g, 0.48mmol) and methanol (0.1ml, 2.42mmol) in acetonitrile (20ml) for 20min. The mixture was heated to 65°C under 1 atmosphere of carbon monoxide. Work up as described for **146a** gave the titled compound as a yellow oil (0.025g, 23%). ^1H NMR: δ1.99 (*s*, 3H, CH_3), 3.77 (*s*, 3H, OCH_3), 3.80 (*s*, 2H, $C\underline{H}_2Ph$), 4.14 (*s*, 2H, $C\underline{H}_2OH$), 7.17-7.32 (*m*, 5H, aromatic); ^{13}C NMR: δ15.4, 37.4, 51.8, 61.3, 126.4, 127.1, 128.6, 128.9, 139.0, 143.9, 170.2; IR (neat): δ3410 *m* (O-H), 2950 *m*, 1715 *s* (C=O), 1655 *m* (C=C), 1600 *w*, 1495 *m*, 1455 *m*, 1435 *m*, 1280 *m*, 1235 *m*, 1165 *m*, 1100 *m*, 1010 *m*, 740 *m*, 700 *m* cm^{-1}; MS, m/z: 202 ($[M-H_2O]^+$, 66%), 186 (35), 159 (38), 143 ($[M-C_6H_5]^+$, 100), 115 (45), 91 ($C_7H_7^+$, 80); HRMS calc. for $C_{13}H_{14}O_2$ ($[M-H_2O]^+$): 202.0994; Found: 202.0977; Anal. calc. for $C_{13}H_{16}O_3$: C, 70.89%; H, 7.32%; Found: C, 70.62%; H, 7.52%.

2.5.3

~~1-Bromomethyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclopentene~~2-Bromomethylcyclopent-1-enyltrifluoromethanesulfonate (151a)

To a solution of ~~1-hydroxymethyl-~~2-[(trifluoromethanesulfonyl)oxy]-1-cyclopentenylmethanol **137a** (0.44g, 17.9mmol) and carbon tetrabromide (1.19g, 3.57mmol) in acetonitrile (35ml) was added triphenylphosphine (0.94g, 3.57mmol) portionwise at 0°C. The solution was then subsequently refluxed for 15h. Evaporation of the solvent under reduced pressure was followed by flash chromatography (hexanes:ethyl acetate, 49:1) of the residue to yield the title compound as a pale yellow liquid (0.55g, 100%). A small sample was distilled by kugelrohr (50-60°C/0.01mm). ^1H NMR: δ2.04 (*m*, 2H, *J*7.76Hz, cyclopentenyl CH_2), 2.55 (*m*, 2H, CH_2C=), 2.68 (*m*, 2H, CH_2C=), 4.00 (*s*, 2H, CH_2Br); ^{13}C NMR: δ19.1, 21.0, 23.4,

31.2, 118.3 (*q*, J_{CF}320.0Hz), 127.8, 145.3; IR (neat): ν_{max}2950 *m*, 1680 *m* (C=C), 1420 *s* (asym S=O), 1330 *m*, 1295 *m* (asym C-OSO_2), 1210 *s* (C-F), 1130 *s* (sym S=O), 990 *s*, 905 *w*, 840 *s*, 760 *m* cm^{-1}; MS m/z: 310/308 (M^+, 1%), 229 ($[M-Br]^+$, 149/147 (1), 135/133 (3), 125 (5), 105 (5), 99 (12), 79 (25), 69 (CF_3^+, 24); HRMS Calc. for $C_7H_8{}^{79}BrF_3O_3S$: 307.93296; Found: 307.93196; Anal. calc. for $C_7H_8BrF_3O_3S$: C, 27.20%; H, 2.61%; Found: C, 27.50%; H, 2.82%.

1-(Benzylamine)methyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclopentene (152a)

To a chloroform (25ml) solution of ~~1-bromomethyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclopentene~~ **151a** (0.45g, 1.46mmol) at 0°C was added triethylamine (0.41ml, 2.91mmol) and benzylamine (0.32ml, 2.91mmol) dropwise. Stirring at room temperature for 15h was then followed by a 2h reflux upon which the reaction solution changed from yellow to orange in colour. The solvent was removed under reduced pressure and the residue purified by flash chromatography (hexanes:ethyl acetate; 9:1) to yield the title compound as a yellow oil (0.18g, 37%). A small sample was distilled by kugelrohr (150-160°C/0.06mm). ^{1}H NMR: 1.98 (*m*, 2H, cyclopentenyl CH_2), 2.47 (*m*, 2H, CH_2C=), 2.63 (*m*, 2H, CH_2C=), 3.37 (*s*, 2H, $C\underline{H}_2NH$), 3.74 (*s*, 2H, $C\underline{H}_2Ph$), 7.24-7.34 (*m*, 5H, aromatic); ^{13}C NMR: δ19.4, 29.9, 30.9, 44.4, 53.5, 118.3 (J_{CF}319.9Hz), 127.1, 128.1, 128.4, 131.0, 139.7, 143.9; IR(neat): ν_{max}3350 *w* (N-H), 2930 *m*, 1700 *m* (C=C), 1605 *w*, 1590 *w*, 1500 *m*, 1460 *m*, 1425 *s* (asym S=O), 1335 *m*, 1300 *m*, 1250 *s* (asym C-OSO_2), 1210 *s* (C-F), 1140 *s* (sym S=O), 1025 *m*, 1005 *m*, 905 *m*, 860 *s*, 740 *m*, 700 *m*, 610 *s* cm^{-1}; MS, m/z: 336 ($[M+1]^+$, 9%), 335 (M^+, 3), 334 ($[M-1]^+$, 2), 244 ($[M-C_7H_7]^+$, 9), 202 ($[M-Tf]^+$, 100), 106 (10), 91 ($C_7H_7^+$, 80); HRMS calc. for $C_{14}H_{16}F_3NO_3S$: 335.08030; Found: 335.07982; Anal. calc. for $C_{14}H_{16}F_3NO_3S$: C, 50.14%; H, 4.81%; N, 4.18%; Found: C, 50.39%; H, 4.56%; N, 4.18%.

2-Bromomethylcyclohex-1-enyltrifluoromethanesufonate

~~1-Bromomethyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclohexene~~ (151b)

This compound was prepared from ~~1-hydroxymethyl-~~2-ylmethanol [(trifluoromethanesulfonyl)oxy]-1-cyclohexene **137b** (0.32g, 1.23mmol) in an analogous manner to that described for compound **151a** save that three molar equivalents of both CBr_4

and PPh_3 was used. Flash chromatography (hexanes:ethyl acetate; 49:1) yielded the title compound as a clear oil (0.40g, 100%). A small sample was distilled by kugelrohr (90-100°C/0.07mm). ^1H NMR: δ1.70 (*m*, 2H, homoallylic CH_2), 1.79 (*m*, 2H, homoallylic CH_2), 2.36 (*m*, 4H, CH_2C=), 4.02 (*s*, 2H, CH_2Br); ^{13}C NMR: δ21.3, 22.8, 27.4, 27.8, 28.1, 118.2 (*q*, J_{CF}319.8Hz), 126.8, 145.4; IR (neat): ν_{max}2950 *m*, 1680 *m* (C=C), 1410 *s* (asymS=O), 1250 *m* (asymC-OSO_2), 1210 *s* (C-F), 1120 *s* (symS=O), 1080 *m*, 1015 *s* (S-O), 905 *s* (symC-OSO_2), 845 *m*, 795 *s*, 750 *m*, 650 *m* cm^{-1}; MS, m/z: 324/322 (M^+, 11%), 243 ($[M-Br]^+$, 100), 179 (28), 175/173 ($[M-OTf]^+$, 2), 135/133 (2), 120/118 (2), 113 (8), 93 (85); HRMS Calc. for $C_8H_8{}^{79}BrF_3O_3S$: 321.94861; Found: 321.94763; Anal. calc. for $C_8H_8BrF_3O_3S$: C, 29.74%; H, 3.12%; Found: C, 29.35%; H, 3.35%.

1-(Benzylamine)methyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclohexene (152b)

This compound was prepared from ~~1-bromomethyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclohexene~~ **151b** (0.42g, 1.30mmol) in an analogous manner to that described for compound **152a**. Flash chromatography (hexanes:ethyl acetate; 9:1) yielded the title compound as a yellow oil (0.24g, 58%). A small sample was distilled by kugelrohr (120-130°C/0.07mm). ^1H NMR: δ1.63 (*m*, 2H, homoallylic CH_2), 1.73 (*m*, 2H, homoallylic CH_2), 2.30 (*m*, 4H, CH_2C=), 3.35 (*s*, 2H, $C\underline{H}_2NH$), 3.75 (*m*, 2H, $C\underline{H}_2Ph$), 7.22-7.33 (*m*, 5H, aromatic); ^{13}C NMR: δ21.6, 23.0, 27.4, 27.6, 47.9, 53.6, 118.3 (*q*, J_{CF}319.9Hz), 127.0, 128.1, 128.4, 129.2, 139.9, 144.6; IR (neat); ν_{max}3350 *w* (N-H), 3025 *m*, 2950 *s*, 1700 *m* (C=C), 1600 *w*, 1500 *m*, 1460 *s*, 1420 *s* (asymS=O), 1360 *m*, 1250 *s* (asymC-OSO_2), 1210 *s* (C-F), 1140 *s* (symS=O), 1030 *s* (S-O), 935 *m* (symC-OSO_2), 900 *s*, 820 *s*, 770 *m*, 740 *s*, 700 *s*, 620 *s* cm^{-1}; MS m/z: 349 (M^+, 4%), 348 ($[M-1]^+$, 4), 272 ($[M-C_6H_5)^+$, 2), 258 ($[M-C_7H_7]^+$, 13), 243 (2), 217 (14), 216 ($[M-Tf]^+$, 100); HRMS Calc. for $C_{15}H_{18}F_3NO_3S$: 349.09595; Found: 349.09675; Anal. calc. for $C_{15}H_{18}F_3NO_3S$: C, 51.57%; H, 5.19%; N, 4.01%; Found: C, 51.58%; H, 5.25%; N, 4.09%.

2-Bromomethylcyclohept-1-enyl trifluoromethanesulfonate

~~1-Bromomethyl-2-[(trifluoromethanesulfonyl)oxy]-1-cycloheptene~~ (151c)

This compound was prepared from ~~1-hydroxymethyl-~~2-yl methanol [(trifluoromethanesulfonyl)oxy]-1-cycloheptene **137c** (0.25g, 0.91mmol) in an analogous

manner to that described for compound **151a** save that within five minutes the reaction was complete as evidenced by the precipitation of Ph_3PO. Flash chromatography (hexanes:ethyl acetate; 49:1) yielded the title compound as a clear liquid (0.31g, 100%). A small sample was distilled by kugelrohr (60-70°C/0.05mm). ^1H NMR: δ1.60 (*m*, 6H, cycloheptenyl CH_2), 2.33 (*m*, 2H, CH_2C=), 2.56 (*m*, 2H, CH_2C=), 4.03 (*s*, 2H, CH_2Br); ^{13}C NMR: 24.2, 25.7, 30.5, 30.6, 30.9, 33.0, 118.3 (*q*, J_{CF}319.7Hz), 131.5, 148.8; IR (neat): ν_{max}2930 *s*, 1680 *m* (C=C), 1415 *s* (asymS=O), 1250 *s* (asymC-OSO_2), 1220 *s* (C-F), 1140 *s* (symS=O), 1105 *m*, 990 *m*, 935 *s* (symC-OSO_2), 870 *s*, 810 *m*, 760 *m*, 670 *s* cm^{-1}; MS m/z: 338/336 (M^+, 2%), 257 ([M-Br]$^+$, 100), 203/205 ([M-Tf]$^+$, 1), 187/189 ([M-OTf]$^+$, 1), 153 (33); HRMS Calc. for $C_9H_{12}{}^{79}BrF_3O_3S$: 335.96426; Found: 335.96519; Anal. calc. for $C_9H_{12}BrF_3O_3S$: C, 32.06%; H, 3.59%; Found: C, 32.08%; H, 3.67%.

1-(Benzylamine)methyl-2-[(trifluoromethanesulfonyl)oxy]-1-cycloheptene (152c)

This compound was prepared from ~~1-bromomethyl-2-[(trifluoromethanesulfonyl)oxy]-1-cycloheptene~~ **151c** (0.2g, 0.59mmol) in an analogous manner to that described for compound **152a** save that the reaction solution was refluxed for 3.5h. Flash chromatography (hexanes:ethyl acetate; 19:1) yielded the title compound as a viscous yellow oil (97mg, 45%). A small sample was distilled by kugelrohr (110-120°C/0.06mm). ^1H NMR: δ1.52-1.77 (*m*, 6H, cycloheptenyl CH_2), 2.31 (*m*, 2H, CH_2C=), 2.51 (*m*, 2H, CH_2C=), 3.30 (*s*, 2H, $C\underline{H}_2NH$), 3.74 (*s*, 2H, $C\underline{H}_2Ph$), 7.21-7.34 (*m*, 5H, aromatic); ^{13}C NMR: 24.5, 24.6, 29.4, 30.7, 32.8, 49.8, 53.6, 118.3 (*q*, J_{CF}319.7Hz), 127.0, 128.1, 128.3, 134.2, 140.1, 147.9; IR (neat): ν_{max}3025 *m* (N-H), 1690 *m* (C=C), 1605 *w*, 1500 *m*, 1455 *s*, 1410 *s* (asymS=O), 1360 *s*, 1245 *s* (C-OSO_2), 1210 *s* (C-F), 1140 *s* (symS=O), 985 *s*, 910 *s*, 880 *s*, 780 *m*, 740 *s*, 700 *s*, 620 *s* cm^{-1}; MS m/z: 364 ([M+1]$^+$,1%), 363 (M^+, 1), 362 ([M-1]$^+$, 1), 272 ([M-C_7H_7]$^+$, 2), 230 ([M-Tf]$^+$, 59), 214 ([M-OTf]$^+$, 8); HRMS calc. for $C_{16}H_{20}F_3NO_3S$: 363.1116; Found: 363.11257; Anal. calc. for $C_{16}H_{20}F_3NO_3S$: C, 52.88%; H, 5.55%; N3.85%; Found: C, 52.74%; H, 5.62%; N, 3.88%.

2-Bromomethylcyclooct-1-enyl trifluoromethanesulfonate

~~1-Bromomethyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclooctene~~ (151d)

This compound was prepared from ~~1-hydroxymethyl-~~2-[(trifluoromethanesulfonyl)oxy]-1-cyclooctenyl methanol **137d** (0.41g, 1.42mmol) in an analogous manner to that described for compound **151a** save that the reaction mix was refluxed for only 1.5h and gave a solution black in colour. Flash chromatography (hexanes:ethyl acetate; 97:3) yielded the title compound as an unstable yellow liquid (0.47g, 95%). ^{1}H NMR: δ1.57 (*m*, 4H, cyclooctenyl CH_2), 1.74 (*m*, 4H, cyclooctenyl CH_2), 2.36 (*m*, 2H, CH_2C=), 2.53 (*m*, 2H, CH_2C=), 4.04 (*s*, 2H, CH_2Br); ^{13}C NMR: 25.8, 27.8, 28.3, 29.3, 29.7, 29.9, 31.6, 118.4 (*q*, J_{CF}319.8Hz), 128.8, 147.2; IR (neat): ν_{max}2930 *s*, 1680 *m* (C=C), 1470 *m*, 1450 *m*, 1415 *s* (asymS=O), 1240 *s* (asymC-OSO_2), 1215 *s* (C-F), 1140 *s* (symS=O), 1105 *m*, 1070 *m* (S-O), 1030 *m*, 935 *s*, 865 *s*, 820 *s*, 655 *s* cm^{-1}; MS m/z: 352/350 (M^+, 1%), 271 ([M-Br]$^+$, 5), 171 (100); HRMS calc. for $C_{10}H_{14}{}^{79}BrF_3O_3S$: 349.97991; Found: 349.97853; Compound unsuitable for microanalysis.

1-(Benzylamine)methyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclooctene (152d)

This compound was prepared from ~~1-bromomethyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclooctene~~ **151d** (0.22g, 0.63mmol) in an analogous manner to that described for **152a** save that the reaction mix was refluxed for 3h. Flash chromatography (hexanes:ethyl acetate; 19:1) yielded the title compound as a colourless oil (0.165g, 70%). A small sample was distilled by kugelrohr (120-130°C/0.01mm). ^{1}H NMR: δ1.53 (*m*, 4H, cyclooctenyl CH_2), 1.67 (*m*, 4H, cyclooctenyl CH_2), 2.34 (*m*, 2H, CH_2C=), 2.49 (*m*, 2H, CH_2C=), 3.33 (*s*, 2H, $C\underline{H}_2NH$), 3.76 (*s*, 2H, $C\underline{H}_2Ph$), 7.22-7.33 (*m*, 5H, aromatic); ^{13}C NMR: δ25.8, 26.1, 27.9, 28.7, 29.2, 29.9, 47.6, 53.8, 118.4 (*q*, J_{CF}319.7Hz), 127.0, 128.1, 128.4, 131.6, 140.0, 145.6; IR (neat): ν_{max}3025 *w* (N-H), 2925 *s*, 1685 *w* (C=C),1605 *w*, 1500 *w*, 1455 *m*, 1410 *s* (asymS=O), 1250 *m* (asymC-OSO_2), 1215 *s* (C-F), 1140 *s* (symS=O), 1110 *m*, 1065 *m*, 1025 *m* (S-O), 920 *s*, 870 *s*, 735 *s*, 700 *m*, 625 *m* cm^{-1}; MS m/z: 378 ([M+1]$^+$, 22%), 376 ([M-1]$^+$, 3), 244 ([M-Tf]$^+$, 70), 142 (70), 91 ([C_7H_7]$^+$, 100); HRMS calc. for $C_{17}H_{22}F_3NO_3S$: 378.13508 ([M+1]$^+$); Found: 378.13418; Anal. calc. for

$C_{17}H_{22}F_3NO_3S$: C, 54.10%; H, 5.88%; N, 3.71%; Found: C, 54.15%; H, 5.80%; N, 3.79%.

2-[(Trifluoromethanesulfonyl)oxy]benzyl bromide

This compound was prepared from 2-[(trifluoromethanesulphonyl)oxy]benzyl alcohol **138** (0.72g, 2.81mmol) in an analogous manner to that described for **151a**. Flash chromatography (hexanes:ethyl acetate; 49:1) yielded the title compound as a clear oil (0.90g, 100%). A small sample was distilled by kugelrohr (60-70°C/0.05mm). ^{1}H NMR: δ4.53 (*m*, 2H, CH_2Br), 7.25-7.55 (*m*, 4H, aromatic); ^{13}C NMR: δ25.6, 118.5 (*q*, J_{CF}320.2Hz), 121.7, 128.8, 130.5, 132.2, 147.1, 171.1; IR (neat): ν_{max}2910 *w*, 1605 *m*, 1580 *w*, 1500 *w*, 1420 *s* (asymS=O), 1250 *s* (asymC-OSO_2), 1210 *s* (C-F), 1140 *s* (symS=O), 1075 *m* (S-O),1040 *m*, 900 *s*, 860 *m*, 805 *m*, 760 *s*, 710 *m* cm^{-1}; MS m/z: 320/318 (M^+, 2%), 239 ($[M-Br]^+$, 100), 186/184 (4), 170/168 (3), 159/157 (4), 110 (80), 106 (61), 78 ($C_5H_6^+$, 50), 77 ($C_6H_5^+$, 38); HRMS calc. for $C_8H_6{}^{81}BrF_3O_3S$: 319.91527; Found: 319.91663; Anal. calc. for $C_8H_6BrF_3O_3S$: C, 30.11%; H, 1.90%; Found: C, 30.34%; H, 1.81%.

N-Benzyl-2-[(trifluoromethanesulfonyl)oxy]benzylamine (153)

This compound was prepared from 2-[(trifluoromethanesulfonyl)oxy]benzyl bromide (1.40g, 4.39mmol) in an analogous manner to that described for **152a** save that the reaction was let to stir only at ambient temperature and for 36 hours. Flash chromatography (hexanes:ethyl acetate; 9:1) yielded the title compound as a yellow oil (0.30g, 20%). A small sample was distilled by kugelrohr (100-110°C/0.04mm). ^{1}H NMR: δ3.82 and 3.91 (2x*s*, 4H, C<u>H</u>$_2$NH and C<u>H</u>$_2$Ph), 7.25-7.35 (*m*, 9H, aromatic); ^{13}C NMR: δ47.3, 53.4, 118.5 (*q*, J_{CF}319.9Hz), 121.3, 127.1, 128.2, 128.3, 128.4, 128.8, 131.0, 133.2, 139.8, 147.0; IR (neat): ν_{max}3025 (N-H) *m*, 2925 *m*, 1600 *w*, 1580 *w*, 1500 *m*, 1460 *m*, 1420 *s* (asymS=O), 1250 *m* (asymC-OSO_2), 1210 *s* (C-F), 1140 *s* (symS=O), 1080 *m* (S-O), 890 *s*, 770 *m*, 750 *m*, 740 *m*, 700 *m* cm^{-1}; MS m/z: 346 ($[M+1]^+$, 5%), 345 (M^+, 14), 344 ($[M-1]^+$, 20), 268 ($[M-C_6H_5]^+$, 12), 254 ($[M-C_7H_7]^+$, 29), 239 (12), 211 (16), 121 (18), 107 (20), 106 (22), 91 ($C_7H_7^+$, 100); HRMS calc. for $C_{15}H_{14}F_3NO_3S$: 345.06465; Found: 345.06514; Anal. calc. for $C_{15}H_{14}F_3NO_3S$: C, 52.17%; H, 4.09%; N, 4.06%; Found: C, 52.14%; H, 4.23%; N, 4.02%.

1-(Phthalimido)methyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclohexene (154)

A solution of 1-hydroxymethyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclohexene **137b** (0.1g, 0.38mmol), PPh_3 (0.15g, 0.58mmol) and phthalimide (0.07g, 0.46mmol) in THF (2ml) was placed under vigorous stirring. To this was added dropwise a solution of diethylazodicarboxylate (91µl, 0.58mmol) in THF (0.5ml) (to give a yellow solution) and the reaction mixture allowed to stir at ambient temperature for 15h. The solvent was then removed under reduced pressure and the residue purified by flash chromatography (hexanes:ethyl acetate; 9:1) to yield the title compound as a white crystalline solid (96%). Mpt. 127-130°C. ^{1}H NMR: δ1.60 (*m*, 2H, cyclohexenyl CH_2), 1.73 (*m*, 2H, cyclohexenyl CH_2), 2.05 (*m*, 2H, CH_2C=), 2.40 (*m*, 2H, CH_2C=), 4.50 (*br s*, 2H, $C\underline{H}_2NH$), 7.75 (*m*, 2H, aromatic), 7.86 (*m*, 2H, aromatic); ^{13}C NMR: 21.1, 22.6, 25.9, 27.5, 36.7, 118.3 (*q*, J_{CF}319.6Hz), 123.4, 124.9, 131.8, 134.1, 145.0, 167.8; IR (nujol mull): ν_{max}2920 *s*, 1770 *s* (C=O), 1615 *w*, 1465 *s*, 1400 *m*, 1380 *m*, 1250 *m*, 1200 *m*, 1140 *m*, 1030 *m*, 970 *m*, 935 *m*, 730 *m*, 710 *m* cm^{-1}; MS, m/z: 391 ([M+1]$^+$, 1%), 390 (M$^+$, 4), 320 ([M-C_4H_2]$^+$, 1), 257 ([M-Tf]$^+$, 20), 256 (100), 240 ([M-TfOH]$^+$, 52), 160 (55), 148 (50), 130 (38), 109 (65), 81 (63); HRMS Calc. for $C_{16}H_{14}F_3NO_5S$ ([M+1]$^+$): 390.06231; Found: 390.06117; Anal. calc. for $C_{16}H_{14}F_3NO_5S$: C, 49.36%; H, 3.62%; N, 3.60%; Found: C, 48.96%; H, 3.62%; N, 3.60%.

1-Aminomethyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclohexene (155)

Hydrazine hydrate (0.46ml, 9.25mmol) was added to a suspension of 1-(phthalimido)methyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclohexene **154** (0.36g, 0.93mmol) in ethanol (30ml). The solution was heated at 60°C for two hours and then allowed to cool to ambient temperature with subsequent removal of the solvent under reduced pressure. The residue was dissolved in dichloromethane and the resultant white solid removed by filtration. Kugelrohr distillation (100-110°C/0.04mm) of the residue yielded the title compound as a colourless liquid (71%). ^{1}H NMR: δ1.68 (*m*, 2H, cyclohexenyl CH_2), 1.78 (*m*, 2H, cyclohexenyl CH_2), 2.30 (*m*, 4H, CH_2C=), 3.39 (*s*, 2H, $C\underline{H}_2NH_2$); ^{13}C NMR: δ21.6, 23.0, 26.8, 27.6, 41.0, 118.3 (*q*, J_{CF}319.2Hz), 131.1, 143.3; IR (neat):

ν_{max}3395 *m* (N-H), 3305 *m* (N-H), 2935 *s*, 1695 *m* (C=O), 1595 *m*, 1410 *s* (asymS=O), 1245 *s* (asymC-OSO_2), 1215 *s* (C-F), 1145 *s* (symS=O), 1070 *m* (S-O), 1020 *s*, 900 *s*, 815 *s*, 765 *m* cm^{-1}; MS, m/z: 260 ($[M+1]^+$, 12%), 243 (9), 233 (6), 126 ($[M-Tf]^+$, 100), 109 ($[M-TfOH]^+$, 55); HRMS Calc. for $C_8H_{12}F_3NO_3S$: 260.05711 ($[M+1]^+$); Found: 260.05634; Anal. calc. for $C_8H_{12}F_3NO_3S$: C, 37.06%; H, 4.67%; N, 5.40%; Found: C, 36.84%; H, 4.94%; N, 5.58%.

1-Bromo-2-[(trifluoromethanesulfonyl)oxy]prop-2-ene (156a)

Triflic acid (2.32ml, 26.23mmol) was added dropwise under a nitrogen atmosphere over a 10 minute period to a stirred solution of propargyl bromide (2.0ml, 26.23mmol) in chloroform (30ml) at 0°C. The ice bath was removed and the dark solution was stirred at ambient temperature for 60 minutes with pyridine (5ml) then added cautiously. The solution was washed with water (50ml) and dilute hydrochloric acid (2x50ml). The organic phase was dried and the solvent evaporated. The residue was purified by kugelrohr distillation to yield the title compound as a colourless liquid (1.20g, 17%). B.p.: *ca* 100°/15mm; ^{1}H NMR: δ4.00 (*s*, 2H, CH_2Br), 5.32 (*d*, J_{gem}3.90Hz, 1H, vinylic), 5.36 (*d*, J_{gem}3.80Hz, 1H, vinylic); ^{13}C NMR: δ27.9, 108.6, 118.5 (J_{CF}320.0Hz), 150.8; IR (neat): ν_{max}1660 *m* (C=C), 1425 *s* (asymS=O), 1250 *s* (asymC-OSO_2), 1210 *s* (C-F), 1140 *s* (symS=O), 1120 *w*, 1060 *w* (S-O), 965 *s* , 890 *s*, 780 *w*, 715 *w*, 670 *m*, 610 *m* cm^{-1}; MS m/z; 270/268 (M^+, 1%), 189 ($[M-Br]^+$, 60), 137/135 ($[M-Tf]^+$, 5), 121/119 ($[M-OTf]^+$, 15), 93 (29), 69 (CF_3^+, 25), 59 (47), 42 (77), 39 (100); HRMS calc. for $C_4H_4{}^{79}BrF_3O_3S$: 267.9017; Found: 267.9004. Without the addition of pyridine, certain amounts of 2-bromo-3-[(trifluoromethanesulphonyl)oxy]prop-1-ene **157** was obtained; ^{1}H NMR: δ4.07 (*s*, 2H, CH_2OTf), 5.38 (*d*, J_{gem}4.00Hz, 1H, vinylic), 5.44 (*d*, J_{gem}3.90Hz, 1H, vinylic).

1-Chloro-2-[(trifluoromethanesulfonyl)oxy]prop-2-ene (161)

Triflic acid (5.94ml, 67.1mmol) was added dropwise over a 20 minute period to a stirred solution of propargyl chloride (2.5g, 33.6mmol) in chloroform (40ml) at ambient temperature. The solution rapidly discolored to black and was allowed to stir for 3 hours. The solution was then slowly added to water (40ml) and the organic phase partitioned, dried and the solvent evaporated. The residue was purified by kugelrohr distillation to yield the title

compound as a colorless liquid (5.1g, 68%). B.p.: ambient temperature/0.05mm; ^{1}H NMR: 4.16 (*s*, 2H, CH_2Cl), 5.39 (*br m*, 2H, CH_2=C); ^{13}C NMR: δ42.1, 108.6, 118.4 (*q*, J_{CF}319.9Hz), 150.6; IR (neat): ν_{max}3020 *w*, 1665 *m* (C=C), 1425 *s* (asymS=O), 1260 *s* (asymC-OSO_2), 1225 *s* (C-F), 1145 *s* (symS=O), 970 *s*, 920 *s* (symC-OSO_2), 890 *s*, 785 *w*, 740 *m*, 695 *m*, 615 *s* cm^{-1}; MS m/z: 226/224 (M^+, 5%), 191/189 ([M-Cl]$^+$, 5), 125 (52), 69 (CF_3^+, 100); Anal. calc. $C_4H_4ClF_3O_3S$: C, 21.39%; H, 1.80%; Found: C, 21.40%; H, 1.86%.

5-Chloro-2-[(trifluoromethanesulfonyl)oxy]pent-1-ene (167)

Triflic acid (1.55ml, 17.50mmol) was added dropwise over a 10 minute period to a stirred solution of 5-chloro-1-pentyne (2.0g, 19.50mmol) in chloroform (30ml) at 0°C. The ice bath was then removed and the black mixture allowed to stir for 60 minutes. The ice bath was replaced and pyridine (5ml) was added cautiously. The mixture was then washed with water (30ml), dilute hydrochloric acid (2x30ml), dried and the solvent evaporated. The residue was purified by kugelrohr distillation to yield the title compound as a clear liquid [1.05g, 39% (based upon recovered 5-chloro-1-pentyne)]. B.p.: ambient temperature/0.15mm. ^{1}H NMR: δ2.03 (*m*, 2H), 2.56 (*t*, *J*7.21Hz, 2H), 3.60 (*t*, *J*6.11Hz, 2H, CH_2Cl), 5.03 (*d*, J_{gem}3.50Hz, 1H, vinylic), 5.18 (*d*, J_{gem}3.59Hz, 1H, vinylic); ^{13}C NMR: δ28.5, 31.0, 43.1, 105.4, 118.4 (*q*, J_{CF}319.9Hz), 155.0; IR (neat): ν_{max}2965 *w*, 1670 *m* (C=C), 1415 *s* (asymS=O), 1250 *s* (asymC-OSO_2), 1215 *s* (C-F), 1145 *s* (symS=O), 1040 *w* (S-O), 980 *w*, 910 *s* (symC-OSO_2), 855 *m*, 795 *w*, 735 *m*, 705 *m*, 610 *s* cm^{-1}; MS m/z: 254/252 (M^+, 1%), 219/217 ([M-Cl]$^+$, 1), 121/119 ([M-Tf]$^+$, 5), 103 (2), 69 (CF_3^+, 100); Anal calc. for $C_6H_8ClF_3O_3S$: C, 28.53%; H, 3.19%; Found: C, 28.53%; H, 3.26%.

3-[(Trifluoromethanesulfonyl)oxy]-3-butenyltrifluoromethanesulfonate (165a)

Triflic acid (0.66ml, 7.44mmol) was added dropwise over a 10 minute period to a stirred solution 3-butynyltrifluoromethanesulfonate **164a** (0.43g, 2.13mmol) in chloroform (30ml) at ambient temperature. The yellow solution was let to stir for 60 minutes upon which it was slowly added to water (30ml). The organic phase was partitioned, dried and the solvent removed to give a dark red oil that was purified by kugelrohr distillation to yield the title

compound as room temperature unstable colorless oil (0.34g, 46%). B.p.: *ca* 90-100°/0.04mm). ^{1}H NMR: δ2.89 (*t*, *J*5.98Hz, 2H, CH_2C=), 4.69 (*t*, *J*6.04Hz, 2H, CH_2OTf), 5.20 (*d*, J_{gem}3.96Hz, 1H, vinylic), 5.37 (*d*, J_{gem}4.14Hz, 1H, vinylic); ^{13}C NMR: δ34.4, 71.3, 108.7, 118.4 (*q*, J_{CF}318.4Hz), 118.5 (*q*, J_{CF}319.8Hz), 149.6; IR(neat): ν_{max}2985 *w*, 1670 *m* (C=C), 1420 *s* (asymS=O), 1250 *s* (asymC-OSO_2), 1220 *s* (C-F), 1145 *s* (symS=O), 1060 *w* (S-O), 935 *s* (symC-OSO_2), 845 *m*, 790 *m*, 740 *m*, 705 *m*, 705 *m*, 615 *s* cm^{-1}; MS m/z; 289 (22%), 202 ([M-TfOH]$^+$, 51), 201 (58), 138 (64), 133 (Tf^+, 55), 112 (53), 69 (CF_3^+, 100); HRMS Calc. for $C_6H_6F_6O_6S_2$ ([M-TfOH]$^+$): 201.99115; Found: 201.99236.

4-[(Trifluoromethanesulfonyl)oxy]-4-pentenyltrifluoromethanesulfonate (165b)

Triflic acid (0.51ml, 5.78mmol) was added dropwise over a 10 minute period to a stirred solution of 4-pentenyltrifluoromethanesulfonate **164b** (0.50g, 2.31mmol) in chloroform (35ml) at 0°C. The resultant yellow solution was then allowed to stir at ambient temperature for 15 hours. The solution was then slowly added to water (85ml) and the organic phase partitioned, dried and the solvent evaporated. The resultant dark brown oil was purified by kugelrohr distillation to yield the title compound as a clear oil (0.60g, 71%). B.p.: *ca* 90-100°/0.03mm; ^{1}H NMR: δ2.11 (*m*, 2H, CH_2), 2.54 (*t*, *J*7.45Hz, 2H, CH_2C=), 4.60 (*t*, *J*5.99Hz, 2H, CH_2OTf), 5.07 (*d*, J_{gem}3.70Hz, 1H, vinylic), 5.24 (*d*, J_{gem}3.80Hz, 1H, vinylic); ^{13}C NMR: δ25.7, 29.8, 75.1, 106.2, 118.4 (*q*, J_{CF}320.2Hz), 118.6 (*q*, J_{CF}319.3Hz); IR (neat); ν_{max}3005 *w*, 2980 *w*, 1670 *m* (C=C), 1420 *s* (asymS=O), 1250 *s* (asymC-OSO_2), 1210 *s* (C-F), 1140 *s* (symS=O), 1080 *w* (S-O), 995 *m*, 935 *s* (symC-OSO_2), 830 *m*, 740 *m*, 705 *m* cm^{-1}; MS m/z: 280 (7%), 216 ([M-TfOH]$^+$, 35), 189 (28), 151 (19), 126 (30), 86 (100); HRMS: Calc. for $C_7H_8F_6O_6S_2$ ([M-TfOH]$^+$): 216.00680; Found: 216.00627; Anal. calc. for $C_7H_8F_6O_6S_2$: C, 22.96%; H, 2.20%; Found: C, 23.02%; H, 2.29%.

N-Benzyl 2-[(trifluoromethanesulfonyl)oxy]-2-propenylamine (156b)

A solution of benzylamine (81μl, 0.74mmol) in chloroform (4ml) was added dropwise to a mixture of 1-bromo-2-[(trifluoromethanesulfonyl)oxy]-prop-2-ene **156a** and

triethylamine (0.1ml, 0.74mmol) in chloroform (4ml) at 0°C. The solution was then heated at reflux for 15 hours. The mixture was then washed with water (10ml), the organic extracts dried and the solvent evaporated. The residue was purified by flash chromatography (hexanes: ethyl acetate; 9:1) to yield the title compound as a light yellow solid (60mg, 55%). M.p.: 100-102°C; ^{1}H NMR: δ3.45 (*s*, 2H, CH_2C=), 3.81 (*s*, 2H, $C\underline{H}_2Ph$), 5.21 (*d*, J_{gem}3.34Hz, 1H, vinylic), 5.25 (*d*, J_{gem}3.40Hz, 1H, vinylic), 7.32 (*m*, 5H, aromatic); ^{13}C NMR: δ52.5, 54.5, 105.6, 119.9 (*q*, J_{CF}322.1Hz), 127.3, 128.8, 128.9, 129.1, 133.3; IR (nujol mull): ν_{max}3400 *w*, 1670 *m* (C=C), 1500 *w*, 1425 *m* (asymS=O), 1325 *w*, 1250 *w* (C-OSO_2), 1210 *s* (C-F), 1180 *s*, 1135 *s* (S=O), 1090 *m* (S-O), 1010 *m*, 935 *w* (C-OSO_2), 800 *m*, 745 *m*, 700 *m*, 605 *s* cm^{-1}; MS m/z: 296 ([M+1]$^+$, 1%), 295 (M$^+$, 1), 294 ([M-1]$^+$, 2), 238 (3), 218 ([M-C_6H_5]$^+$, 1), 204 ([M-C_7H_7]$^+$, 4), 162 ([M-Tf]$^+$, 20), 91 ($C_7H_7^+$, 100); HRMS Calc. for $C_{11}H_{12}F_3NO_3S$: 295.04090; Found: 295.04830; Anal. calc. for $C_{11}H_{12}F_3NO_3S$: C, 44.74%; H, 4.10%; N,4.74%; Found: C, 44.70%; H, 4.02%; N, 4.79%.

N-Benzyl 3-[(trifluoromethanesulfonyl)oxy]-3-butenylamine (171a)

A solution of benzylamine (31μl, 0.28mmol) in chloroform (2ml) was added dropwise to a mixture of 3-[(trifluoromethanesulfonyl)oxy]-3-butenyltrifluoromethanesulfonate **165a** (50mg, 0.14mmol) and triethylamine (40μl, 0.28mmol) at 0°C. This was then stirred at ambient temperature for 15 hours, the organic phase washed with water (10ml), dried and the solvent evaporated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 4:1) to yield the title compound as a clear yellow oil (30mg, 68%). A small sample was distilled by kugelrohr (*ca* 100-110°/0.02mm). ^{1}H NMR: δ2.55 (*t*, *J*6.75Hz, 2H), 2.85 (*t*, *J*6.76Hz, 2H), 3.81 (*s*, 2H, $C\underline{H}_2Ph$), 5.02 (*d*, J_{gem}3.45Hz, 1H, vinylic), 5.16 (*d*, J_{gem}3.62Hz, 1H, vinylic), 7.26-7.36 (*m*, 5H, aromatic); ^{13}C NMR: δ34.4, 44.9, 53.5, 105.4, 118.4 (*q*, J_{CF}320.0Hz), 127.0, 128.0, 128.3, 139.7, 154.6; IR(neat): ν_{max}3305 *w* (N-H), 3030 *w*, 1670 *s* (C=C), 1500 *w*, 1455 *m*, 1420 *s* (asymS=O), 1250 *m* (asymC-OSO_2), 1210 *s* (C-F), 1140 *s* (symS=O), 1030 *m* (S-O), 935 *s* (symC-OSO_2), 845 *w*, 740 *s*, 700 *s* cm^{-1}; MS m/z: 310 ([M+1]$^+$, 12%), 235 (4), 121 (65), 91 ($C_7H_7^+$, 100); HRMS Calc. for $C_{12}H_{14}F_3NO_3S$ ([M+1]$^+$): 310.07248. Found: 310.07380; Anal. calc. for

$C_{12}H_{14}F_3NO_3S$: C, 46.60%; H, 4.56%; N, 4.53%; Found: C, 46.85%; H, 4.51%; N, 4.53%.

N-Benzyl 4-[(trifluorometanesulfonyl)oxy]-4-pentenylamine (171b)

This compound was prepared from 4-[(trifluoromethanesulfonyl)oxy]-4-pentenyltrifluoromethanesulfonate **165b** (0.24g, 0.65mmol) in an analagous manner to that described for **171a**. Flash chromatography (hexanes/ethyl acetate, 7:3) gave the title compound as a clear oil that discoloured quickly upon standing (0.14g, 67%). A small sample was distilled by kugelrohr (110-120°/0.02mm). ^{1}H NMR: δ1.75 (*m*, 2H, CH_2), 2.43 (*t*, *J*7.51Hz, 2H), 2.69 (*t*, *J*6.97Hz, 2H), 3.79 (s, 2H, $C\underline{H}_2Ph$), 4.94 (*d*, J_{gem}3.49Hz, 1H, vinylic), 5.09 (*d*, J_{gem}3.55Hz, 1H, vinylic), 7.26-7.36 (*m*, 5H, aromatic); ^{13}C NMR: δ26.4, 31.6, 47.8, 104.3, 118.4 (q, J_{CF}319.9Hz), 127.0, 127.6, 128.2, 140.1, 156.5; IR (neat): ν_{max}3330 *w* (N-H), 3025 *w*, 2930 *m*, 1670 *m* (C=C), 1605 *w*, 1495 *w*, 1455 *m*, 1420 *s* (asymS=O), 1250 *s* (asymC-OSO_2), 1220 *s* (C-F), 1140 *s* (symS-O), 1030 *w* (S-O), 945 *s* (symC-OSO_2), 790 *w*, 735 *m*, 700*m* cm^{-1}; MS m/z; 324 ($[M+1]^+$, 1%), 322 (1), 190 ($[M-Tf]^+$, 15), 120 (20), 91 ($C_7H_7^+$, 100); HRMS: Calc. for $C_{13}H_{16}F_3NO_3S$ ($[M+1]^+$): 324.08813; Found: 324.08901; Anal. calc. for $C_{13}H_{16}F_3NO_3S$: C, 48.29%; H, 4.99%; N, 4.33%; Found: C, 48.29%; H, 4.89%; N, 4.49%.

2.5.4

N-Benzyl-3,4,5,6-tetrahydro-1*H*-cyclopenta[c]pyrolid-1-one (172a)

Carbon monoxide was bubbled through a solution of 1-(benzylamine)methyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclopentene **152a** (0.12g, 0.36mmol), $Pd(PPh_3)_4$ (0.041g, 0.036mmol), tri-*n*-butylamine (0.17ml, 0.72mmol) in acetonitrile (15ml) for 25 min. The reaction mixture was then heated to 65°C under one atmosphere of carbon monoxide (supplied by the placement of a balloon over the reflux condenser) for 2h. The solution was then allowed to cool to room temperature upon which ether (15ml) was added and the solution filtered through a pad of kenite. The pad was subsequently thoroughly rinsed with ether (3x10ml). The solvent was then removed under reduced pressure and the residue dissolved in dichloromethane and purified by flash chromatography (hexanes:ethyl acetate; 5:1) to yield the

title compound as a pale yellow oil (100%). A small sample was distilled by kugelrohr (150-160°C/0.06mm). ^{1}H NMR: δ2.36 (*m*, 2H, cyclopentenyl CH_2), 2.53 (*m*, 4H, CH_2C=), 3.74 (*s*, 2H, $C\underline{H}_2Ph$), 4.62 (*s*, 2H, CH_2N), 7.24-7.36 (*m*, 5H, aromatic); ^{13}C NMR: δ25.8, 27.7, 29.4, 46.4, 49.1, 127.3, 127.9, 128.6, 137.8, 142.3, 161.4, 168.8; IR (neat): ν_{max}3025 *w*, 2950 *s*, 1670 *s* (C=O), 1600 *w*, 1580 *w*, 1490 *m*, 1440 *s*, 1400 *s*, 1350 *m*, 1230 *m*, 1260 *m*, 1220 *m*, 1170 *m*, 1120 *m*, 740 *m*, 700 *m* cm^{-1}; MS m/z: 214 ([M+1]$^+$, 11%), 213 (M$^+$, 100), 212 ([M-1]$^+$, 14), 195 ([M-H_2O]$^+$, 4), 185 ([M-CO]$^+$, 4), 136 ([M-C_6H_5]$^+$, 8), 110 (60), 109 (84), 108 (24), 91 ($C_7H_7^+$, 45); HRMS calc. for $C_{14}H_{15}NO$: 213.11536; Found: 213.11511; Anal. calc. for $C_{14}H_{15}NO$: C, 78.84%; H, 7.09%; N, 6.57%; Found: C, 78.64%; H, 7.11%; N, 6.49%.

N-Benzyl-1,3,4,5,6,7-Hexahydroisoindolin-1-one (172b)[246]

This compound was prepared from 1-(benzylamine)methyl-2-[(trifluoromethanesulfonyl)oxy]-1-cyclohexene **152b** (50mg, 0.14mmol) in an analogous manner to that described for compound **172a**. Flash chromatography (hexanes:ethyl acetate; 9:1) yielded the title compound as a yellow oil (33mg, 89%). ^{1}H NMR: δ1.71 (*m*, 4H, cyclohexenyl CH_2), 2.22 (*m*, 4H, CH_2C=), 3.65 (*s*, 2H, CH_2N), 4.61 (*s*, 2H, $C\underline{H}_2Ph$), 7.23-7.35 (*m*, 5H, aromatic); ^{13}C NMR: δ20.3, 21.8, 22.0, 24.1, 45.9, 52.5, 127.3, 127.9, 128.5, 131.8, 137.9, 150.0, 171.8; IR (neat): 3025 *w*, 2950 *s*, 1670 *s* (C=O), 1600 *w*, 1580 *w*, 1500 *m*, 1460 *s*, 1420 *s*, 1360 *m*, 1280 *m*, 1260 *m*, 1220 *m*, 1140 *m*, 1110 *m*, 1090 *m*, 750 *s*, 700 *s* cm^{-1}; MS m/z: 228 ([M+1]$^+$, 11%), 227 (M$^+$, 63), 226 ([M-1]$^+$, 21), 142 (100), 91 ($C_7H_7^+$, 56); HRMS Calc. for $C_{15}H_{17}NO$: 227.13101; Found: 227.13168.

1,2,3,4,5,6,7,8-Octahydro-1*H*-cyclohepta[c]pyrolid-1-one (172c)

This compound was prepared from 1-(benzylamine)methyl-2-[(trifluoromethanesulfonyl)oxy]-1-cycloheptene **152c** (0.1mg, 0.28mmol) in an analogous manner to that described for compound **172a**. Flash chromatography (hexanes:ethyl acetate; 9:1) yielded the title compound as a yellow oil (66mg, 100%). A small sample was distilled by kugelrohr (150-160°C/0.02mm). ^{1}H NMR: δ1.57-1.82 (2x*m*, 6H, cycloheptenyl CH_2), 2.32 (*m*, 2H, CH_2C=), 2.45 (*m*, 2H, CH_2C=), 3.62 (*s*, 2H, CH_2N), 4.60 (*s*, 2H, $C\underline{H}_2Ph$), 7.23-7.34 (*m*, 5H, aromatic); ^{13}C NMR: 24.9, 26.9, 27.0, 29.4, 30.7, 45.9, 53.0, 127.1,

127.8, 128.4, 131.8, 137.4, 152.3, 172.3; IR (neat): ν_{max}3025 *w*, 2920 *s*, 1680 *s* (C=O), 1605 *w*, 1580 *w*, 1500 *m*, 1455 *s*, 1410 *s*, 1290 *s*, 1230 *m*, 1145 *m*, 1080 *m*, 960 *m*, 920 *m*, 730 *s*, 700 *s* cm^{-1}; MS m/z: 242 ($[M+1]^+$, 23%), 241 (M^+, 100), 240 ($[M-1]^+$, 16), 198 (15), 91 ($C_7H_7^+$, 73); HRMS calc. for $C_{16}H_{19}ON$: 241.14666; Found: 241.14748; Anal. calc. for $C_{16}H_{19}ON$: C, 79.63%; H, 7.94%; N, 5.80%; Found: C, 79.83%; H, 8.11%; N, 5.61%.

1,3,4,5,6,7,8,9-Octahydro-3*H*-cycloocta[c]pyrolid-1-one (172d)

This compound was prepared from 1-(benzylamine)methyl-2-[(trifluoromethanesufonyl)oxy]-1-cyclooctene **152d** (74mg, 0.20mmol) in an analogous manner to that described for compound **172a**. Flash chromatography (hexanes:ethyl acetate; 9:1) yielded the title compound as a pale yellow oil (49mg, 98%). A small sample was distilled by kugelrohr (130-140°C/0.03mm). ^{1}H NMR: δ1.50 (*m*, 4H, cyclooctenyl CH_2), 1.70 (*m*, 4H, cyclooctenyl CH_2), 2.41 (*m*, 2H, CH_2C=), 2.49 (*m*, 2H, CH_2C=), 3.63 (*s*, 2H, CH_2N), 4.63 (*s*, 2H, $C\underline{H}_2Ph$), 7.21-7.35 (*m*, 5H, aromatic); ^{13}C NMR: δ22.2, 25.6, 25.8, 26.6, 27.4, 27.5, 46.1, 52.5, 127.3, 127.9, 128.6, 132.5, 137.7, 151.0, 172.3; IR (neat): ν_{max}3030 *m*, 2925 *s*, 1670 *s* (C=O), 1605 *m*, 1590 *w*, 1500 *m*, 1450 *s*, 1410 *s*, 1360 *m*, 1320 *m*, 1295 *m*, 1280 *m*, 1250 *m*, 1150 *m*, 1110 *m*, 1075 *m*, 1030 *m*, 735 *s*, 700 *s* cm^{-1}; MS m/z: 256 ($[M+1]^+$, 15%), 255 (M^+, 78), 254 ($[M-1]^+$, 9), 198 (17), 91 ($C_7H_7^+$, 100); HRMS calc. for $C_{17}H_{21}NO$: 255.16231; Found: 255.16345; Anal. calc. for $C_{17}H_{21}NO$: C, 79.96%; H, 8.29%; N, 5.49%; Found: C, 80.01%; H, 8.50%; N, 5.43%.

N-Benzylisoindolin-1-one (173)[102c]

To a solution that had been saturated with carbon monoxide for 20 minutes was added N-benzyl-2-[(trifluoromethanesulphonyl)oxy]-benzylamine **153** (25mg, 0.007mmol), $Pd(PPh_3)_4$ (8.4mg, 0.7μmol), *n*-Bu_3N (0.05ml, 0.014mmol) and diphenylphosphinoferrocene (8mg, 0.014mmol). The mixture was heated at 65°C under one atmoshere of carbon monoxide for 3h. The residue was purified by flash chromatography (hexanes:ethyl acetate; 4:1) to yield the title compound as white 'dendritic-like' crystals (93%). M.pt. 90-91°C, lit.[102c] 90-91°C. ^{1}H NMR: δ4.26 and 4.81 (2x*s*, 4H, CH_2N and $C\underline{H}_2Ph$),

7.26-7.52 (*m*, 5H, aromatic); ^{13}C NMR: δ46.3, 49.4, 122.7, 123.9, 127.6, 128.0, 128.1, 128.8, 131.3, 132.6, 137.0, 141.2, 168.5; IR ($CHCl_3$ solution): ν_{max}2920 *w*, 1680 *s* (C=O), 1620 *m*, 1495 *w*, 1470 *m*, 1455 *m*, 1415 *m*, 1360 *m*, 1305 *m*, 1145 *m*, 980 *m*, 900 *m*, 770 *w* cm^{-1}; MS, m/z: 224 ([M+1]$^+$, 17%), 223 (M$^+$, 100), 222 ([M-1]$^+$, 34), 181 (10), 169 (10), 145 ([M-C_6H_6]$^+$, 17), 132 ([M-C_7H_7]$^+$, 34), 119 (79), 91 ($C_7H_7^+$, 76), 69 (57), 65 (17); HRMS Calc. for $C_{15}H_{13}NO$: 223.09971; Found: 223.09959.

4,5,6,7-Tetrahydrophthalimidine (174)[247]

This compound was prepared from 1-aminomethyl-2-[(trifluoromethanesufonyl)oxy]-1-cyclohexene **155** (50mg, 0.19mmol) in an analogous manner to that described for compound **172a**. The resultant black/brown residue was dissolved in dichloromethane (20ml), washed with 10% hydrochloric acid (20ml) and distilled by kugelrohr (100-110°C/0.05mm) to give a yellow solid. Recrystallization (dichloromethane/hexanes) yielded the title compound as colourless prisms (15mg, 63%). M pt. 115-116°C, lit.[246] 113-114°C. ^{1}H NMR: δ1.73 (*m*, 4H, cyclohexenyl CH_2), 2.22 (*m*, 2H, CH_2C=), 2.28 (*m*, 2H, CH_2C=), 3.89 (*s*, 2H, $C\underline{H}_2$NH), 6.68 (*br s*, 1H, NH); ^{13}C NMR: δ20.0, 21.8, 21.9, 24.5, 48.9, 131.9, 153.3, 175.4; IR ($CHCl_3$ solution): ν_{max}3250 *m* (N-H), 2930 *m*, 1680 *s* (C=O), 1490 *w*, 1450 *m*, 1405 *w*, 1350 *m*, 1120 *m*, 975 *m*, 895 *m*, 865 *m* cm^{-1}; MS, m/z: 138 ([M+1]$^+$, 12%), 137 (M$^+$, 100), 136 ([M-1]$^+$, 7), 109 ([M-CO]$^+$, 25), 108 (26), 96 (19), 95 (30), 94 (25); HRMS Calc. for $C_8H_{11}O$: 137.08406; Found: 137.08461.

1-Benzyl-3-methylene-azetidin-2-one (156c)[102b]

This compound was prepared from N-benzyl 2-[(trifluoromethanesufonyl)oxy]-2-propenylamine **156b** (35mg, 0.12mmol) in an analogous manner to that described for compound **172a** save that the reaction was heated at 65°C for 5 h. Flash chromatography twice (hexanes:ethyl acetate; 19:1) yielded the title compound as a white amorphous solid (15mg, 73%). M.pt. 29-30°C, lit.[102b] 32°C. ^{1}H NMR: δ3.65 (*dd*, *J*1.50, 1.31Hz, 2H, CH_2C=), 4.52 (*s*, 2H, $C\underline{H}_2$Ph), 5.17 (*dt*, *J*1.05, 1.34Hz, 1H, vinylic), 5.74 (*dt*, *J*1.73, 1.52Hz, 1H, vinylic), 7.25-7.39 (*m*, 5H, aromatic); ^{13}C NMR: δ46.1, 47.9, 109.7, 127.8, 128.2, 128.9, 135.3, 145.1, 163.6; IR (nujol mull): ν_{max}3025 *w*, 2920 *s*, 1745 *s* (C=O), 1675 *w* (C=C), 1500 *w*, 1455 *m*, 1400 *s*, 1355 *m*, 1260 *m*, 1220 *m*, 1105 *m*, 1075 *m*, 1030

m, 930 *m*, 800 *m*, 750 *w*, 700 *s* cm^{-1}; MS, m/z: 174 ($[M+1]^+$, 9%), 173 (M^+, 33), 172 ($[M-1]^+$, 22), 133 (40), 132 (18), 105 (22), 104 (22), 91 ($C_7H_7^+$, 100); HRMS calc. for $C_{11}H_{11}NO$: 173.08406; Found: 173.08475.

1-Benzyl-3-methylene-2-pyrolidone (175a)[102a]

This compound was prepared from N-benzyl 3-[(trifluoromethanesufonyl)oxy]-3-butenylamine **171a** (45mg, 0.15mmol) in an analogous manner to that described for compound **172a** save that the reaction mixture was heated for 15h. Flash chromatography (hexanes:ethyl acetate; 9:1) yielded the title compound as a pale yellow oil (27mg, 100%). ^1H NMR: δ2.74 (*ddt*, *J*6.67, 6.45, 2.73Hz, 2H, CH_2C=), 3.28 (*dd*, *J*7.04, 6.44Hz, 2H, CH_2N), 4.55 (*s*, 2H, $C\underline{H}_2Ph$), 5.36 (*dt*, *J*0.63, 2.39Hz, 1H, vinylic), 6.04 (*dt*, *J*0.66, 2.87Hz, 1H, vinylic), 7.25-7.37 (*m*, 5H, aromatic); ^{13}C NMR: 23.9, 43.4, 47.2, 115.7, 127.6, 128.2, 128.7, 136.2, 139.5, 167.9; IR (neat): ν_{max}3030 *w*, 2925 *m*, 1690 *s* (C=O), 1605 *w*, 1495 *m*, 1450 *s*, 1430 *m*, 1305 *s*, 1265 *m*, 1190 *w*, 1160 *w*, 910 *s*, 805 *w*, 735 *s*, 700 *s* cm^{-1}; MS, m/z: 188 ($[M+1]^+$, 19%), 187 (M^+, 100), 186 ($[M-1]^+$, 24), 158 (14), 143 (24), 91 ($C_7H_7^+$, 81); HRMS Calc. for $C_{12}H_{13}NO$: 187.09971; Found: 187.09915.

1-Benzyl-3-methylene-2-piperidone (175b)[248]

This compound was prepared from N-benzyl 4-[(trifluoromethanesufonyl)oxy]-4-pentenylamine **171b** (40mg, 0.12mmol) in an analogous manner to that described for compound **172a** save that the reaction was heated for 15h. Flash chromatography (hexanes:ethyl acetate; 9:1) yielded the title compound as a yellow oil (18mg, 72%). ^1H NMR: δ1.84 (*m*, 2H, piperidone CH_2), 2.58 (*m*, 2H, CH_2C=), 3.30 (*dd*, *J*5.95, 5.81Hz, 2H, CH_2N), 4.67 (*s*, 2H, $C\underline{H}_2Ph$), 5.33 (*ddd*, *J*1.57, 1.82, 2.02Hz, 1H, vinylic), 6.28 (*ddd*, *J*1.80, 1.66, 1.65Hz, 1H, vinylic), 7.24-7.35 (*m*, 5H, aromatic); ^{13}C NMR: δ23.1, 30.1, 47.7, 50.7, 122.0, 127.3, 128.0, 128.5, 137.1, 137.7, 164.3; IR (neat): ν_{max}3050 *w*, 2925 *m*, 1655 *s* (C=O), 1615 *s*, 1490 *m*, 1455 *m*, 1340 *m*, 1265 *m*, 1220 *m*, 1200 *m*, 975 *m*, 735 *s*, 700 *s* cm^{-1}; MS, m/z: 202 ($[M+1]^+$, 26%), 201 (M^+, 100), 200 ($[M-1]^+$, 7), 172 (21), 110 ($[M-C_7H_7]^+$, 25), 104 (25), 91 ($C_7H_7^+$, 57); HRMS calc. for $C_{13}H_{15}NO$: 201.11536; Found: 201.11591.

N,N'-Dibenzylurea (161a)

This compound was prepared from a reaction mixture containing 1-chloro-2-[(trifluoromethanesulfonyl)oxy]prop-2-ene **161** (0.2g, 0.90mmol), $Pd(PPh_3)_4$ (0.10g, 0.09mmol), *n*-Bu_3N (0.42ml, 1.80mmol) and benzylamine (0.1ml, 0.90mmol) in an analogous manner to that described for **172a** save that the reaction was heated for 15h. Flash chromatography (hexanes:ethyl acetate; 9:1) followed by recrystallization (ethyl acetate/hexanes) gave the title compound as white needles (0.22g, 100%). M.pt. 165-166°C, lit.[251] 170°C. ^{1}H NMR: δ4.36 and 4.38 (2x*s*, 4H, 2xC$\underline{H_2}$Ph), 4.72 (*m*, 2H, 2xNH), 7.25-7.34 (*m*, 10H, aromatic); ^{13}C NMR: δ44.5, 127.3, 127.4, 128.6, 139.0, 158.1; IR (nujol mull): ν_{max}3305 *m* (NH), 1625 *m* (C=O), 1575 *m*, 1495 *m*, 1295 *m*, 1245 *m*, 1060 *w*, 1030 *w*, 750 *m*, 722 *m* cm^{-1}; MS, m/z: 241 ([M+1]$^+$, 53%), 240 (M$^+$, 59), 207 (20), 206 (18), 148 ([M-C_7H_8]$^+$, 27), 105 (100), 91 ($C_7H_7^+$, 58), 79 (17), 65 (14).

Ethyl 1-acetyl-3-methylene-2-pyrolidone-5-carboxylate (183)

This compound was prepared from ethyl N-acetyl-4-iodoglycinate **182** (0.2g, 0.66mmol) in an analogous manner to that described for **172a** save that the reaction was heated for 30 min. The dark red residue was purified twice by gradient flash chromatography (hexanes:ethyl acetate; 49 to 9:1) to give the title compound as an orange oil (90mg, 63%). A small sample was distilled by kugelrohr (130-140°C/0.005mm) to give a colourless viscous oil. ^{1}H NMR: δ1.28 (*t*, *J*6.98Hz, 3H, $CH_2C\underline{H_3}$), 2.61 (*s*, 3H, $COCH_3$), 2.75 [*dq*, *J*17.56, 2.36Hz, 1H, H-C(4)], 3.1 [*ddt*, *J*17.58Hz, 10.21, 3.01Hz, 1H, H-C(4)], 4.21 (*q*, *J*7.04Hz, 2H, C$\underline{H_2}$CH$_3$), 4.74 (*dd*, *J*3.19, 3.24Hz, 1H, CHN), 5.60 (*t*, *J*2.54Hz, 1H, vinylic), 6.29 (*t*, *J*2.64Hz, 1H, vinylic); ^{13}C NMR: δ14.0, 24.7, 27.5, 54.5, 61.8, 121.9, 137.1, 166.6, 170.6, 171.5; IR (neat): ν_{max}2985 *m*, 1740 *s* (C=O), 1705 *s* (C=O), 1660 *m* (C=C), 1445 *m*, 1380 *s*, 1320 *s*, 1280 *s*, 1200 *s*, 1125 *m*, 1020 *s*, 955 *m*, 910 *w*, 860 *w*, 810 *m*, 610 *s* cm^{-1}; MS, m/z: 212 ([M+1]$^+$, 15%), 211 (M$^+$, 54), 183 ([M-CO]$^+$, 4), 169 (63), 166 ([M-EtO]$^+$, 31), 165 ([M-EtOH]$^+$, 25), 139 (53), 138 ([M-CO_2Et]$^+$, 63), 97 (65), 96 (100); HRMS calc. for $C_{10}H_{13}NO_4$: 211.08446; Found: 211.08375. Compound unsuitable for microanalysis.

Experimental: Chapter 3

3.3.1

(+)-(4*S*)-4-[(Thexyldimethylsilyl)oxy]pentan-2-one (199)

To a solution of PCC (0.40g, 2.05mmol) in dichloromethane (30ml) was added a dichloromethane (15ml) solution of (4*S*)-4-[(thexyldimethylsilyl)oxy]pentan-1-ol **197** (0.25g, 1.02mmol) dropwise *via* syringe. The solution was then stirred at room temperature for 15h upon which it was filtered through a bed of kenite with extensive washing of the residues with dichloromethane. The organic extracts were washed with 5% aqueous $NaHCO_3$ (40ml), dried and the solvent removed under reduced pressure. The brown-black residue was purified by flash chromatography (hexanes:ethyl acetate; 19:1) to yield the title compound as a colourless oil (0.2g, 80%). A small sample was distilled by kugelrohr (75-80°C/0.05mm). ^{1}H NMR: δ0.07 (*s*, 3H, $SiCH_3$), 0.10 (*s*, 3H, $SiCH_3$), 0.81 (s, 6H, $C(CH_3)_2$), 0.87 (*d*, *J*6.84Hz, 6H, $CH(C\underline{H}_3)_2$), 1.16 (*d*, *J*6.24Hz, 3H, $C\underline{H}_3CH$), 1.60 (*m*, 1H, $C\underline{H}(CH_3)_2$), 2.16 (*s*, 3H, CH_3CO), 2.42 [*dd*, *J*5.37, 5.37Hz, 1H, H-C(3)], 2.64 (*dd*, *J*6.99, 6.99Hz, 1H, H-C(3)], 4.27 (*sextet*, *J*5.58Hz, 1H, CHOSi); ^{13}C NMR: δ-3.1, -2.5, 18.4, 18.5, 20.1, 20.2, 23.9, 24.6, 31.5, 34.0, 53.1, 65.4, 208.0; IR (neat): ν_{max}2960 *s*, 1720 *s* (C=O), 1470 *m*, 1380 *s*, 1250 *s*, 1180 *m*, 1130 *s*, 1090 *s*, 1020 *s*, 900 *m*, 875 *m*, 830 *s*, 775 *s* cm^{-1}; MS, m/z: 245 ($[M+1]^+$, 10%), 229 ($[M-CH_3]^+$, 13), 201 ($[M-CH_3CO]^+$, 3), 187 (14), 160 (47), 159 (100), 145 (16), 115 (94), 103 (37); HRMS calc. for $C_7H_{15}O_2Si$ ($[M-C_6H_{13}]^+$); 159.08413; Found: 159.0840; $[\alpha]_D$ +22.35° (*c*=0.5, CH_2Cl_2).

(+)-(4*S*)-4-Hydroxypentan-2-one (201)[212b,c]

A suspension of baker's yeast (200g, Mauripan dried) and sugar (30g) in deionized H_2O (4l) was mechanically stirred at 35°C for 30min. Acetylacetone (5.0g, 49.9mmol) was then added and the mixture allowed to stir at 35°C for 24h. Analysis by GLC and TLC prompted the further addition of yeast (10g) and sugar (50g) after 3,4 and 5 days. After 6 days GLC analysis indicated that the reaction had gone to completion and the mixture was filtered by gravity through a sintered glass funnel. The solution was saturated with $(NH_4)_2SO_4$ and extracted with ether (4x500ml) with methanol being used to break up an

emulsion. The extracts were then washed with brine (1l) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by kugelrohr distillation (*ca.* 100°C/20mm, lit.[249] 75-76°C/21mm) and flash chromatography (hexanes:ethyl acetate; 7:3) to yield the title compound as a colourless liquid (1.01g, 20%). ^{1}H NMR: δ1.19 (*d*, *J*6.33Hz, 3H, C<u>H</u>$_3$CH), 2.18 (*s*, 1H, CH_3CO), 2.55 [*dd*, *J*8.49, 8.62Hz, 1H, H-C(3)], 2.65 [*dd*, *J*3.38, 3.37Hz, 1H, H-C(3)], 4.23 (*m*, 1H, C<u>H</u>OH); ^{13}C NMR: δ22.1, 30.3, 51.3, 63.6, 209.6; IR (neat): ν_{max}3450 *s* (O-H), 2960 *s*, 1710 *s* (C=O), 1455 *s*, 1380 *m*, 1250 *m*, 1110 *s*, 1030 *s*, 920 *m*, 735 *s* cm^{-1}; MS, m/z: 103 ([M+1]$^+$, 23%), 102 (M$^+$, 5), 87 ([M-CH_3]$^+$, 8), 59 ([M-CH_3CO]$^+$, 100), 58 (65), 45 (50); $[\alpha]_D$ +78.5° (*c*=2.0, $CHCl_3$), $[\alpha]_J$ +90° (*c*=0.04, $CHCl_3$), lit.[212b,c] $[\alpha]_D$ +64° (*c*=2.0, $CHCl_3$) and $[\alpha]_J$ +40° (*c*=0.04, $CHCl_3$).

(+)-(4*S*)-2-[(Trifluoromethanesulfonyl)oxy]-4-[(thexyldimethylsilyl)oxy] pent-1-ene (202)

A solution of (4*S*)-4-[(thexyldimethylsilyl)oxy]pentan-2-one **199** (0.3g, 1.23mmol) in THF (5ml) was added dropwise *via* syringe to a solution of KHMDS (0.5M in toluene) (2.95ml, 1.48mmol) that had been precooled to -78°C. The mixture was allowed to stir for 10 minutes upon which a solution of N-phenyltriflimide (0.53g, 1.48mmol) in THF (5ml) was added dropwise and the solution allowed to warm to room temperature over 15h. The solvent was evaporated under reduced pressure and the residue dissolved in dichloromethane (20ml), washed with water (20ml) and the solvent evaporated under reduced pressure. The yellow residue was purified by flash chromatography (hexanes) to yield the title compound as a colourless oil (0.45g, 97%). ^{1}H NMR: δ0.07 (*s*, 3H, $SiCH_3$), 0.10 (*s*, 3H, $SiCH_3$), 0.82 (*s*, 6H, $C(CH_3)_2$), 0.83 (*d*, *J*3.99Hz, 6H, $CH(C\underline{H}_3)_2$), 1.19 (*d*, *J*5.97Hz, 3H, C<u>H</u>$_3$CH), 1.59 (*m*, 1H, C<u>H</u>$(CH_3)_2$), 2.40 [*dd*, *J*5.61, 5.62Hz, 1H, H-C(3)], 2.47 [*dd*, *J*6.96, 6.96Hz, 1H, H-C(3)], 4.05 (*sextet*, *J*5.93Hz, 1H, CHOSi), 4.99 (*d*, J_{gem}3.36Hz, 1H, vinylic), 5.13 (*d*, J_{gem}3.33Hz, 1H, vinylic); ^{13}C NMR: δ-2.5, -3.0, 18.4, 18.5, 20.1, 20.2, 23.4, 24.8, 34.1, 44.5, 65.1, 106.6, 118.6 (*q*, J_{CF}319.8Hz), 154.3; IR (neat): ν_{max}2950 *s*, 1675 *m* (C=C), 1470 *m*, 1425 *s* (asymS=O), 1380 *m*, 1255 *s* (asymC-OSO_2), 1210 *s* (C-F), 1140 *s* (symS=O), 1100 *m* (S-O), 1000 *m*, 950 *m*, 910 *m*, 830 *m*, 780 *m*, 705 *m* cm^{-1}; MS, m/z: 377 ([M+1]$^+$, 36%), 361 ([M-CH_3]$^+$, 4), 291 ([M-C_6H_{13}]$^+$, 54), 251 (65), 227 ([M-OTf]$^+$,

42), 207 (17), 187 (100); HRMS calc. for $C_{14}H_{27}F_3O_4SSi$: 376.1353; Found: 376.1371; Anal. calc. for $C_{14}H_{27}F_3O_4SSi$: C, 44.66%; H, 7.23%; Found: C, 44.83%; H, 7.11%; $[\alpha]_D$ 0° (*c*=0.5, CH_2Cl_2).

(+)-Methyl (4*S*)-2-methylene-4-[(thexyldimethylsilyl)oxy]pentanoate (203)

To an acetonitrile (50ml) solution that had been saturated with carbon monoxide for 20 minutes was added (+)-(4*S*)-2-[(trifluoromethanesulfonyl)oxy]-4-[(thexyldimethylsilyl)oxy]pent-1-ene **202** (0.49g, 1.30mmol), $Pd(PPh_3)_4$ (0.15g, 0.13mmol), *n*-Bu_3N (0.62ml, 2.60mmol), methanol (5.27ml, 130mmol) and lithium chloride (0.06g, 1.30mmol). The reaction was then heated at 65°C for 2h. Upon cooling to ambient temperature, ether (50ml) was added and the solution filtered through a bed of kenite with extensive ether washing of the residues. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexanes:ethyl acetate; 49:1) to yield the title compound as a colourless oil (0.33g, 90%). ^{1}H NMR: δ0.01 (*s*, 3H, $SiCH_3$), 0.06 (*s*, 3H, $SiCH_3$), 0.81 (*s*, 6H, $C(CH_3)_2$), 0.86 (*d*, *J*6.85Hz, 6H, $CH(CH_3)_2$), 1.25 (*d*, *J*4.81Hz, 3H, $C\underline{H}_3CH$), 1.61 (*m*, 1H, $C\underline{H}(CH_3)_2$), 2.40 (*d*, *J*6.33Hz, 2H, $CHC\underline{H}_2$), 3.75 (*s*, 3H, OCH_3), 3.98 (*sext*, 1H, CHOSi), 5.59 (*d*, J_{gem}1.26Hz, 1H, vinylic), 6.20 (*d*, J_{gem}1.75Hz, 1H, vinylic); ^{13}C NMR: δ-2.5, -3.1, 18.5, 18.6, 20.2, 20.3, 23.6, 24.7, 34.0, 42.7, 51.7, 67.0, 127.9, 137.5, 167.6; IR (neat): ν_{max}2950 *s*, 1720 *s* (C=O), 1630 *m* (C=C), 1440 *m*, 1380 *m*, 1330 *m*, 1280 *s*, 1250 *m*, 1195 *s*, 1160 *s*, 1095 *s*, 1005 *s*, 950 *m*, 890 *m*, 830 *s*, 775 *s*, 680 *m* cm^{-1}; MS, m/z: 271 ($[M-CH_3]^+$, 2%), 255 ($[M-OCH_3]^+$, 5), 201 ($[M-C_6H_{13}]^+$, 100), 169 (75), 157 (29), 127 ($[M-OSiC_8H_{19}]^+$, 7), 103 (64); HRMS calc. for $C_{15}H_{30}O_3Si$ ($[M-OCH_3]^+$): 255.17803; Found: 255.17885; $[\alpha]_D$ +10.96° (*c*=0.52, $CHCl_3$).

(-)-(5*S*)-Dihydro-5-methyl-3-methylene-2(5*H*)-furanone (204)

To a solution of (+)-methyl (4*S*)-2-methylene-4-[(thexyldimethylsilyl)oxy]pentanoate **203** (0.33g, 1.15mmol) in dichloromethane (20ml) was added trifluoroacetic acid (0.27ml, 3.46mmol) dropwise *via* syringe. The solution was stirred at room temperature for 24h upon which it was washed with 5% aqueous $NaHCO_3$, dried and the solvent removed by a stream of nitrogen over the solution. The residue was purified by kugelrohr distillation (100-

105°C/15mm, lit.[250] 86-90°C/13mm) to yield the title compound as a colourless oil (0.06g, 46%). ^{1}H NMR: δ1.43 (*d*, *J*6.17Hz, 3H, CH_3), 4.69 (*sextet*, *J*6.20Hz, 1H, C<u>H</u>CH_3), 2.55 [*d of m*, J_d17.02Hz, 1H, H-C(4)], 3.10 [*d of m*, J_d17.0Hz, 1H, H-C(4)], 5.64 (*t*, *J*2.47Hz, 1H, vinylic), 6.24 (*t*, *J*2.82Hz, 1H, vinylic); ^{13}C NMR: δ22.0, 35.1, 74.0, 122.1, 134.8, 144.9; IR (neat): ν_{max}2980 *s*, 1760 *br s* (C=O), 1665 *s* (C=C), 1440 *m*, 1390 *s*, 1340 *s*, 1260 *s*, 1205 *m*, 1165 *s*, 1085 *s*, 1040 *s*, 955 *m*, 870 *m*, 815 *m*, 755 *m* cm^{-1}; MS, m/z: 112 (M^+, 7%), 73 (65), 67 ([M-HCO_2]$^+$, 77), 43 (CH_3CO^+, 100); $[\alpha]_D$ -32.8° (*c*=5.8, CH_2Cl_2), lit.[101] for (+)-**204** $[\alpha]_D$ +33.8 (*c*=5.82, $CHCl_3$).

3.3.2

(+)-Ethyl (1*R*,2*S*)-2-hydroxy-1-cyclopentanecarboxylate (210)[220]

A suspension of baker's yeast (Mauripan dried, 12.0g), sugar (152.0g), $MgSO_4$ (1.0g), KH_2PO_4 (4.0g) and $CaCO_3$ (5.0g) in deionized water (1l) was stirred gently at 36°C for 45 min. Ethyl 2-oxocyclopentane carboxylate (10.2g, 65.3mmol) was added dropwise and the mechanically stirred solution was kept at 36°C for 2 days. At this point GLC analysis indicated the absence of starting material. The mixture was filtered through a sintered glass funnel by gravity and the solution extracted with ether (5x250ml), washed with brine (500ml) and dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave a yellow oil that was purified by fractional distillation (46-47°C/0.04mm, lit.[220] 59-61°C/0.4mm) to yield the title product as a colourless liquid (6.72g, 65%). ^{1}H NMR: δ1.29 (*t*, *J*7.18Hz, 3H, CH_3), 1.64 (*m*, 1H, cyclopentane CH), 1.78 (*m*, 2H, cyclopentane CH), 1.96 (*m*, 3H, cyclopentane CH), 2.68 [*ddd*, *J*4.32, 4.26, 4.34Hz, 1H, H-C(1)], 3.16 (*br s*, 1H, OH), 4.19 (*q*, *J*7.21Hz, 2H, C<u>H</u>$_2$$CH_3$), 4.44 [*ddd*, *J*3.70, 3.55, 3.61Hz, 1H, H-C(2)]; ^{13}C NMR: δ14.0, 21.8, 26.0, 33.8, 49.4, 60.4, 73.6, 174.6; IR (neat): ν_{max}3480 *s* (O-H), 2970 *s*, 1735 *s* (C=O), 1450 *m*, 1375 *m*, 1350 *m*, 1305 *m*, 1195 *s*, 1100 *m*, 1035 *s*, 860 *w*, 735 *w* cm^{-1}; MS, m/z: 129 ([M-C_2H_5]$^+$, 27%), 112 ([M-C_2H_5OH]$^+$, 18), 100 (100), 72 (88); $[\alpha]_D$ +15.2° (*c*=1.57, $CHCl_3$), lit.[220] $[\alpha]_D$ +15.1° (*c*=1.57, $CHCl_3$).

(+)-Ethyl (1*R*,2*S*)-2-[(thexyldimethylsilyl)oxy]-1-cyclopentanecarboxylate (211)

To a DMF (45ml) solution of thexyldimethylsilyl chloride (10.38mmol, 2.04ml) and imidazole (20.76mmol, 1.41g) was added (+)-ethyl (1*R*,2*S*)-2-hydroxycyclopentanecarboxylate **210** (1.5g, 9.43mmol). The mixture was allowed to stir at ambient temperature for 15h upon which it was extracted with hexane (3x50ml). The organic extracts were washed with H_2O (2x150ml), dried and the solvent evaporated under reduced pressure to give a colourless liquid. Purification by flash chromatography (hexanes: ethyl acetate; 19:1) yielded the title compound as a colourless liquid (2.08g, 73%). A small sample was distilled by kugelrohr (90-100°C/0.03mm). ^{1}H NMR: δ0.05 (*s*, 3H, $SiCH_3$), 0.08 (*s*, 3H, $SiCH_3$), 0.79 (*s*, 6H, $C(CH_3)_2$), 0.84 (*d*, *J*6.85Hz, 6H, $CH(C\underline{H}_3)_2$), 1.26 (*t*, *J*7.21Hz, 3H, $CH_2C\underline{H}_3$), 1.57 (*m*, 1H, cyclopentane CH), 1.61 (m, 1H, $C\underline{H}(CH_3)_2$), 1.67-1.82 (*m*, 3H, cyclopentane CH), 1.89 (*m*, 1H, cyclopentane CH), 2.16 (*ddtt*, *J*14.65, 7.07, 5.78, 6.80Hz, 1H, cyclopentane CH), 2.71 [*ddd*, *J*4.95, 4.89, 5.00Hz, 1H, H-C(1)], 4.01 (*dq*, *J*7.23, 7.14Hz, 1H, diastereotopic $C\underline{H}_2CH_3$), 4.19 (*dq*, *J*7.24, 7.09Hz, 1H, diastereotopic $C\underline{H}_2CH_3$), 4.47 [*ddd*, *J*3.65, 4.55, 3.60Hz, 1H, H-C(2)]; ^{13}C NMR: δ-3.3, -2.6, 14.1, 18.4, 18.5, 19.9, 20.0, 20.1, 20.5, 21.8, 34.1, 35.2, 51.4, 60.1, 75.4, 172.6; IR (neat): ν_{max}2950 *s*, 1740 *s* (C=O), 1470 *m*, 1370 *m*, 1250 *s*, 1180 *s*, 1110 *m*, 1060 *s*, 930 *m*, 830 *s*, 775 *s* cm^{-1}; MS, m/z: 280 ($[M-H_2O]^+$, 2%), 215 ($[M-C_6H_{13}]^+$, 4), 187 (9), 133 (6), 103 (12), 75 (35), 31 (100); HRMS calc. for $C_{10}H_{19}O_3Si$ ($[M-C_6H_{13}]^+$): 215.11035; Found: 215.11096; $[\alpha]_D$ +21.6° (*c*=0.5, $CHCl_3$).

(+)-(1*R*,2*S*)-2-[(Thexyldimethylsilyl)oxy]-1-cyclopentanecarbaldehyde (212)

To a hexane (60ml) solution of (+)-ethyl (1*R*,2*S*)-2-[(thexyldimethylsilyl)oxy]-1-cyclopentanecarboxylate **211** (1.54g, 5.12mmol) at -78°C was added DIBALH (1.0ml, 5.64mmol) dropwise *via* syringe over 5 min. The mix was kept at -78°C for 2h upon which TLC analysis prompted further addition of DIBALH (0.18ml, 1.02mmol) with additional stirring for 1h. The reaction was quenched with a slow addition of methanol (8ml) and allowed to warm to ambient temperature over 15h. The organic extracts were washed with 10% aqueous citric acid (2x100ml), brine (100ml) and dried. The solvent was evaporated

under reduced pressure and the residue purified by flash chromatography (hexanes:ethyl acetate; 9:1) to yield the title product as an unstable colourless oil (0.89g, 68%). ^{1}H NMR: δ0.08 (*s*, 3H, $SiCH_3$), 0.10 (*s*, 3H, $SiCH_3$), 0.80 (*s*, 6H, $C(CH_3)_2$), 0.86 (*d*, *J*6.86Hz, 6H, $CH(CH_3)_2$), 1.61 (*m*, 1H, $C\underline{H}(CH_3)_2$), 1.53-1.80 (*m*, 4H, cyclopentane CH), 1.88 (*m*, 1H, cyclopentane CH), 2.16 (*ddtt*, *J*13.84, 4.59, 4.59, 6.95Hz, 1H, cyclopentane CH), 2.65 [*ddt*, *J*5.65, 2.88, 8.36Hz, 1H, H-C(1)], 4.62 [*ddd*, *J*4.82, 3.89, 3.51Hz, 1H, H-C(2)], 9.75 (*d*, *J*2.75Hz, 1H, CHO); ^{13}C NMR: δ-3.0, -2.5, 18.3, 18.4, 20.0, 20.2, 22.3, 23.1, 24.7, 34.1, 35.9, 56.9, 75.7, 204.0; IR (neat): ν_{max}2955 *s*, 2720 *w* (H-CO), 1725 *s* (C=O), 1470 *m*, 1380 *m*, 1250 *s*, 1160 *m*, 1115 *m*, 1050 *s*, 940 m, 830 *s*, 780 *s* cm^{-1}; MS, m/z: 257 ([M+1]$^+$, 2%), 205 (12), 187 (8), 171 ([M-C_6H_{13}]$^+$, 100), 75 (47); HRMS calc. for $C_{14}H_{29}O_2Si$ ([M+1]$^+$): 257.19369; Found: 257.19466; $[\alpha]_D$+15.8° (*c*=0.5, $CHCl_3$).

(+)-(1S,2*S*)-2-[(Thexyldimethylsilyl)oxy]-1-cyclopentanemethanol (213)

To an ether (35ml) solution of (+)-(1*R*,2*S*)-2[(thexyldimethylsilyl)oxy]-1-cyclopentanecarbaldehyde **212** (0.89g, 3.47mmol) at 0°C was added dropwise *via* syringe a solution of methylmagnesium iodide (2.2M in ether) (6.94mmol, 3.15ml) over 5min. The clear solution was then allowed to warm over 15h upon being quenched by aqueous 10% NH_4Cl (10ml) at 0°C. The two phases were partitioned and the aqueous layer was extracted with ether (3x30ml). The combined organic extracts were washed with brine (100ml), dried and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (hexanes:ethyl acetate; 19:1) to yield the title compound as a colourless oil (0.71g, 75%). A small sample was distilled by kugelrohr (100-110°C/0.02mm). ^{1}H NMR: δ0.14 (*s*, 6H, $Si(CH_3)_2$), 0.84 (*d*, *J*3.97Hz, 6H, $C(CH_3)_2$), 0.87 (*d*, *J*3.95Hz, 3H, $CHC\underline{H}_3$), 0.89 (*d*, *J*3.98Hz, 3H, $CHC\underline{H}_3$), 1.15 and 1.19 (*d*, *J*6.45 and 6.32Hz, 3H, $CHC\underline{H}_3$), 1.48-1.80 (*m*, 6H, $C\underline{H}(CH_3)_2$ and cyclopentane CH), 1.94 (*m*, 1H, cyclopentane CH), 3.38 (*br s*, 1H, OH), 3.87 and 4.14 (2x*dq*, *J*7.88, 6.41Hz and 12.58, 6.42Hz, 1H, $C\underline{H}OH$), 4.31 and 4.37 [2x*ddd*, *J*2.64, 2.61, 2.80 and 4.46, 4.58, 4.12Hz, 1H, H-C(2)]; ^{13}C NMR: δ-3.1, -2.3, 18.3, 18.7, 19.9, 20.5, 21.6, 21.8, 22.0, 22.4, 34.1, 36.3, 50.1, 67.1, 77.7; IR (neat): ν_{max}3455 *m* (O-H), 2960 *s*, 1470 *m*, 1370 *m*, 1255 *s*, 1140 *m*, 1045

s, 910 *m*, 830 *s*, 775 *s*, 740 *m* cm^{-1}; MS, m/z: 187 ($[M-C_6H_{13}]^+$, 27%), 95 (58), 74 (92), 31 (100); HRMS calc. for $C_{11}H_{19}O_2Si$ ($[M-C_6H_{13}]^+$): 187.11544; Found: 187.11472; Anal. calc. for $C_{15}H_{32}O_2Si$: C, 66.11%; H, 11.84%; Found: C, 65.98%; H, 11.54%.

(+)-(1*R*,2*S*)-2-[(Thexyldimethylsilyl)oxy]-1-cyclopentyl methyl ketone (214)

This compound was prepared from (+)-(1*S*,2*S*)-2-[(thexyldimethylsilyl)oxy]-1-(1-hydroxyethyl)cyclopentane **213** (0.68g, 2.50mmol) in an analogous manner to that described for **199**. Flash chromatography (hexanes:ethyl acetate; 19:1) gave the title compound as a colourless oil (0.52g, 77%). A small portion was distilled by kugelrohr (120-130°C/0.04mm). ^1H NMR: δ0.08 (*s*, 3H, $SiCH_3$), 0.10 (*s*, 3H, $SiCH_3$), 0.78 (*s*, 6H, $C(CH_3)_2$), 1.52-1.75 (*m*, 5H, $C\underline{H}(CH_3)_2$ and cyclopentane CH), 1.84 (*m*, 1H, cyclopentane CH), 2.17 (*m*, 1H, cyclopentane CH), 2.17 (*s*, 3H, CH_3CO), 2.78 [*ddd*, *J*5.14, 5.29, 5.36Hz, 1H, H-C(1)], 4.58 [*ddd*, *J*4.19, 3.35, 4.54Hz, 1H, H-C(2)]; ^{13}C NMR: δ-3.2, -2.3, 18.3, 18.5, 19.9, 20.2, 22.0, 23.8, 24.7, 30.1, 34.0, 35.5, 58.8, 75.9, 208.1; IR (neat): ν_{max}2950 *s*, 1715 *s* (C=O), 1470 *m*, 1380 *m*, 1250 *s*, 1155 *m*, 1110 *m*, 1060 *s*, 875 *m*, 835 *s*, 775 *s* cm^{-1}; MS, m/z: 185 ($[M-C_6H_{13}]^+$, 37%), 141 (12), 115 (4), 106 (4), 91 (9), 75 (22), 58 ($[CH_2=C(OH)CH_3]^+$, 15), 43 (CH_3CO^+, 100); HRMS calc. for $C_9H_{17}O_2Si$ ($[M-C_6H_{13}]^+$): 185.09979; Found: 185.10045; Anal. calc. for $C_{15}H_{30}O_2Si$: C, 66.61%; H, 11.18%; Found: C, 66.72%; H, 11.18%; $[\alpha]_D$ +14.3° (*c*=0.51, $CHCl_3$).

(+)-(1*R*,2*S*)-2-[(Thexyldimethylsilyl)oxy]-1-{1-methylene-1-[(trifluoro methanesulfonyl)oxy]}cyclopentane (215)

This compound was prepared from (+)-(1*R*,2*S*)-2-[(thexyldimethylsilyl)oxy]-1-cyclopentyl methyl ketone **214** (0.42g, 1.55mmol) in an analogous manner to that described for **202**. Flash chromatography (hexanes) gave the title compound as a colourless oil (0.36g, 71%). A small portion was distilled by kugelrohr (110-120°C/0.03mm). ^1H NMR: δ0.06 (*s*, 3H, $SiCH_3$), 0.08 (*s*, 3H, $SiCH_3$), 0.79 (*s*, 6H, $C(CH_3)_2$), 0.85 (*d*, *J*5.99Hz, 6H, $CH(C\underline{H}_3)_2$), 1.53-1.93 (*m*, 7H, $C\underline{H}(CH_3)_2$ and cyclopentane CH), 2.59 [*br dt*, *J*3.62, 7.62Hz, 1H, H-C(1)], 4.35 [*ddd*, *J*2.45, 1.16, 3.89Hz, 1H, H-C(2)], 4.99 (*dd*, *J*1.49, 1.48Hz, 1H, vinylic), 5.16 (*d*, J_{gem}3.55Hz, 1H, vinylic); ^{13}C NMR: δ-3.5, -2.6, 18.5,

18.6, 20.1, 20.3, 21.5, 24.8, 26.3, 34.2, 34.9, 50.9, 73.4, 105.3, 118.5 (*q*, J_{CF}320.0Hz), 156.8; IR (neat): ν_{max}2955 *s*, 1670 *m* (C=C), 1420 *s* (asymS=O), 1250 *s* (asymC-OSO_2), 1210 *s* (C-F), 1140 *s* (symS=O), 1100 *m*, 1060 *m* (S-O), 925 *s*, 830 *m*, 780 *m*, 735 *s* cm^{-1}; MS, m/z: 317 ([M-C_6H_{13}]$^+$, 14%), 227 (9), 167 (24), 103 (100); HRMS calc. for $C_{10}H_{16}F_3O_4SSi$ ([M-C_6H_{13}]$^+$): 317.04907; Found: 317.04992; Anal. calc. for $C_{16}H_{29}F_3O_4SSi$: C, 47.74%; H, 7.26%; Found: C, 47.76%; H, 7.29%; $[\alpha]_D$ +10.0° (*c*=0.5, $CHCl_3$).

methyl 2-[2-(thexyldimethylsilyl)oxycyclopent-1-yl]propenoate

(+)-(1*R*,2*S*)-~~2-[(Thexyldimethylsilyl)oxy]-1-[1-(methoxycarbonyl)ethen-1-yl]cyclopentane~~ (216)

This compound was prepared from (+)-(1*R*,2*S*)-2-[(thexyldimethylsilyl)oxy]-1-{1-methylene-1-[(trifluoromethanesulfonyl)oxy]}cyclopentane **215** (0.27g, 0.67mmol) in an analogous manner to that described for **203**. Flash chromatography (hexanes:ethyl acetate; 99:1) gave the title compound as a pale yellow viscous oil (0.22g, 89%). A small sample was distilled by kugelrohr (130-140°C/0.01mm) to give a colourless oil. ^{1}H NMR: δ0.06 (*s*, 3H, $SiCH_3$), 0.08 (*s*, 3H, $SiCH_3$), 0.79 (*s*, 6H, $C(CH_3)_2$), 0.85 (*d*, *J*6.77Hz, 6H, $CH(C\underline{H}_3)_2$), 1.46-1.67 (*m*, 4H, $C\underline{H}(CH_3)_2$ and cyclopentane CH), 1.74-1.93 (*m*, 3H, cyclopentane CH), 2.75 [*br m*, 1H, H-C(1)], 3.73 (*s*, 3H, OCH_3), 4.32 [*m*, 1H, H-C(2)], 5.58 (*t*, *J*1.31Hz, 1H, vinylic), 6.26 (*s*, 1H, vinylic); ^{13}C NMR: δ-3.3, -2.8, 18.5, 18.6, 20.2, 20.4, 21.5, 24.7, 26.5, 34.3, 35.4, 47.5, 51.6, 74.1, 125.5, 139.2, 168.0; IR (neat): ν_{max}2950 *s*, 1720 *s* (C=O), 1630 *m* (C=C), 1440 *m*, 1380 *m*, 1250 *s*, 1150 *s*, 1055 *s*, 985 *m*, 930 *s*, 815 *s*, 775 *s*, 735 *m* cm^{-1}; MS, m/z: 297 ([M-CH_3]$^+$, 1%), 281 (4), 227 ([M-C_6H_{13}]$^+$, 100), 195 (82), 185 (70); HRMS calc. for $C_{16}H_{29}O_3Si$ ([M-CH_3]$^+$): 297.18732; Found: 297.18937; Anal. calc. for $C_{17}H_{32}O_3Si$: C, 65.33%; H, 10.32%; Found: C, 64.98%; H, 10.19%; $[\alpha]_D$ +40.4° (*c*=0.52, $CHCl_3$).

(-)-(3a*S*,6a*S*)-Hexahydro-3-methylene-cyclopenta[b]furan-2-one (217)

This compound was prepared from (+)-(1*R*,2*S*)-2-[(thexyldimethylsilyl)oxy]-1-[1-(methoxycarbonyl)ethen-1-yl]cyclopentane **216** (50mg, 0.16mmol) in an analogous manner to that described for **204** save that the reaction was conducted over 6h. Flash chromatography (hexanes:ethyl acetate; 9:1) gave the title compound as a pale yellow liquid

(42mg, 86%). ^{1}H NMR: δ1.57 (*dt*, *J*5.89, 11.75Hz, 1H, cyclopentane CH), 1.65-1.78 (*m*, 3H, cyclopentane CH), 1.95 (*ddt*, *J*2.87, 8.81, 6.08Hz, 1H, cyclopentane CH), 2.07 (*m*, 1H, cyclopentane CH), 3.43 [*m*, 1H, H-C(3a)], 5.00 [*t*, *J*5.18Hz, 1H, H-C(6a)], 5.65 (*d*, J_{gem}2.26Hz, 1H, vinylic), 6.25 (*d*, J_{gem}2.61Hz, 1H, vinylic); ^{13}C NMR: δ23.0, 33.8, 35.6, 42.9, 83.2, 122.8, 140.4, 171.2; IR (neat): ν_{max}2960 *s*, 1750 *s* (C=O), 1660 *m* (C=C), 1455 *m*, 1405 *s*, 1320 *s*, 1265 *s*, 1200 *m*, 1150 *m*, 1110 *s*, 1040 *m*, 980 *s*, 950 *m*, 810 *m*, 735 *w* cm^{-1}; MS, m/z: 138 (M^+, 23%), 109 ([M-CHO]$^+$, 64), 85 (100), 83 (68), 81 (50); HRMS calc. for $C_8H_{10}O_2$: 138.06808: Found: 138.06749; $[\alpha]_D$ -161.32° (*c*=0.53, $CHCl_3$), lit.[223] for **217** of unknown absolute stereochemistry at C(3a and 6a) $[\alpha]_D$ +125.6 ($CHCl_3$).

(-)-(6a*S*)-4,5,6,6a-Tetrahydro-3-methyl-2*H*-cyclopenta[b]furan-2-one (218)

(-)-(3a*R*,6a*S*)-Hexahydro-3-methylene-cyclopenta[b]furan-2-one **217** (25mg, 0.18mmol) and 1,4-dioxane (2ml) were added *via* syringe to $HRh(PPh_3)_3CO$ (0.12g, 0.14mmol). The solution quickly darkened to a brown/orange and was allowed to stir at ambient temperature with hourly monitoring by TLC. After 6h the solvent was removed under reduced pressure to yield a red oil. Flash chromatography (hexanes:ethyl acetate; 9:1) gave the title compound as a yellow oil (24mg, 95%). ~~^{1}H NMR: δ0.86 (*m*, 1H, cyclopentane CH), 1.23 (*t*, ^5J7.04Hz, 3H, CH_3), 1.83-2.05 (*m*, 3H, cyclopentane CH), 2.83 (*m*, 2H, cyclopentane CH), 4.87 [*dt*, *J*1.59, 5.50Hz, 1H, H-C(6a)]~~; ^{13}C NMR: δ11.3, 25.9, 29.7, 32.8, 84.3, 139.9, 169.1, 188.8; IR (neat): ν_{max}2960 *m*, 1765 *s* (C=O), 1700 *m* (C=C); $[\alpha]_D$ -1.8° (*c*=0.55, $CHCl_3$). All other spectral data identical to **217**.

Experimental: Chapter 4

(-)-Ethyl (1*R*,2*S*,4*S*)-2-hydroxy-4-methyl-1-cyclohexanecarboxylate (225)[234]

A suspension of baker's yeast (6.0g, Mauripan dried), sugar (76g), $MgSO_4$ (0.5g), KH_2PO_4 (1.0g) and $CaCO_3$ (2.5g) in deionized H_2O (500ml) was allowed to gently stir at 35°C for 45 min. Ethyl 4-methyl-2-cyclohexanone-1-carboxylate (5.0g, 27.14mmol) was then added and the mix allowed to stir at 35°C for 5 days. During this period TLC analysis prompted the addition of further portions of yeast (4.0g) and sugar (20g) at 15, 24, 40, 48, 72 and 96 hours. The mixture was filtered by gravity through a sintered glass funnel and the residues washed with H_2O (100ml) and ethyl acetate (100ml). The combined aqueous solution was saturated with NaCl and extracted with ethyl acetate (4x250ml). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. Gradient flash chromatography (hexanes:ethyl acetate; 19 to 9:1) yielded the title compound as a colourless liquid (1.1g, 44% based on recovered starting material). A small sample was distilled by kugelrohr (80-90°C/0.02mm). ^{1}H NMR: δ0.85 (*m*, 1H, cyclohexane CH), 0.93 (*d*, *J*6.11Hz, 3H, CH_3), 1.29 (*t*, *J*7.12Hz, $CH_2C\underline{H}_3$), 1.33 (*m*, 1H, cyclohexane CH), 1.40-1.64 (*m*, 3H, cyclohexane CH), 1.88 (*d of m*, J_d12.84Hz, 1H, cyclohexane CH), 2.14 (*dq*, *J*13.94, 3.25Hz, 1H, cyclohexane CH), 2.82 [*ddd*, *J*4.21, 3.99, 3.63Hz, H_{eq}-C(1)], 3.50 (*d*, *J*10.43Hz, 1H, OH, exchangeable with D_2O), 3.58 [*m* (*dt* after D_2O exchange, *J*11.34, 4.42Hz), 1H, H_{ax}-C(2)], 4.20 (*ddq*, *J*21.02, 3.83, 6.72Hz, 2H, $C\underline{H}_2CH_3$); ^{13}C NMR: δ14.0, 21.8, 26.5, 30.3, 31.3, 40.2, 44.9, 60.2, 70.5, 174.4; IR (neat): ν_{max}3460 *s* (O-H), 2925 *s*, 1730 *s* (C=O), 1455 *m*, 1380 *m*, 1335 *m*, 1305 *m*, 1255 *m*, 1180 *s*, 1130 *m*, 1095 *m*, 1060 *m*, 1030 *s*, 970 *w*, 950 *w*, 920 *w*, 860 *w*, 835 *w*, 735 *m* cm^{-1}; MS, m/z: 187 ($[M+1]^+$, 3%), 186 (M^+, 6), 185 ($[M-1]^+$, 3), 168 ($[M-H_2O]^+$, 15), 158 ($[M-CO]^+$, 35), 141 ($[M-OC_2H_5]^+$, 120), 115 (47), 101 (82), 96 (94), 73 ($CO_2C_2H_5^+$, 71), 46 (100); HRMS calc. for $C_{10}H_{18}O_3$: 186.12559; Found: 186.12489; $[\alpha]_D$ -24.52° (*c*=0.52, $CHCl_3$), lit.[234] -18.3° (*c*=1.0, $CHCl_3$).

(-)-Ethyl (1*R*,2*S*,4*S*)-2-[(thexyldimethylsilyl)oxy]-4-methyl-1-cyclohexanecarboxylate (227)

This compound was prepared from (-)-ethyl (1*R*,2*S*,4*S*)-2-hydroxy-4-methyl-1-cyclohexanecarboxylate **225** (0.73g, 3.92mmol) in an analogous manner to that described for **211**. Flash chromatography (hexanes:ethyl acetate; 49:1) gave the title compound as a colourless oil (0.79g, 61%). A small sample was distilled by kugelrohr (120-130°C/0.005mm). ^{1}H NMR: δ0.08 (*s*, 6H, Si(CH_3)$_2$), 0.81 (*s*, 6H, C(CH_3)$_2$), 0.86 (*d*, *J*6.86Hz, 6H, CH($C\underline{H}_3$)$_2$), 0.97 (*d*, *J*5.71Hz, 3H, CH$C\underline{H}_3$), 1.25 (*t*, *J*7.11Hz, 3H, $CH_2C\underline{H}_3$), 1.36-1.48 (*m*, 4H, cyclohexane CH), 1.50-1.64 (*m*, 3H, cyclohexane CH), 1.76 (*m*, 1H, cyclohexane CH), 1.90 (*dq*, *J*13.62, 3.38Hz, 1H, cyclohexane CH), 2.76 [*ddd*, *J*5.06, 4.29, 4.20Hz, 1H, H_{ax}-C(2)], 3.79 [*dddd*, *J*5.06, 5.25, 5.32, 4.95Hz, 1H, H_{eq}-C(1)], 4.08 (*ddq*, *J*20.56, 3.41, 7.18Hz, 2H, $C\underline{H}_2CH_3$); ^{13}C NMR: δ-3.0, -2.6, 14.2, 18.5, 18.6, 20.1, 20.2, 22.1, 24.7, 25.8, 29.1, 30.7, 34.1, 39.1, 46.1, 59.7, 71.3, 173.7; IR (neat): ν_{max}2950 s, 1735 s (C=O), 1460 m, 1340 m, 1320 m, 1250 s, 1180 s, 1105 s, 1070 s, 1000 m, 955 m, 890 m, 825 s, 775 s, 665 m cm^{-1}; MS, m/z: 313 ([M-CH_3]$^+$, 1%), 283 ([M-C_2H_5O]$^+$, 1), 243 ([M-C_6H_{13}]$^+$, 32), 215 (6), 197 (5), 143 (2), 120 (3), 118 (3), 103 (8), 95 (10), 85 ($C_6H_{13}^+$, 66), 83 (100), 75 (25), 73 (10); HRMS calc. for $C_{17}H_{33}O_3Si$ ([M-CH_3]$^+$): 313.21989; Found: 313.2203; Anal. calc. for $C_{18}H_{36}O_3Si$: C, 65.80%; H, 11.04%; Found: C, 66.10%; H, 11.18%; $[\alpha]_D$ -19.68° (*c*=0.49, $CHCl_3$).

(-)-(1*R*,2*S*,4*S*)-2-[(Thexydimethylsilyl)oxy]-4-methyl-1-(1-hydroxyethyl)cyclohexane (229)

A 1:1 mixture (as determined by ^{1}H NMR) of (+)-(1*R*,2*S*,4*S*)-2-[(thexyldimethylsilyl)oxy]-4-methyl-1-cyclohexanecarbaldehyde **228** (0.25g, 0.88mmol) and **227** in ether (50ml) was cooled to -78°C. A solution of methylmagnesium iodide (2.35M in ether) was then added dropwise *via* syringe over 5 min. The solution was slowly warmed to -20°C and allowed to stir at this temperature for 1h. Lowering the temperature to -78°C was followed by quenching of the reaction with aqueous 10% NH_4Cl (10ml). The two phases were partioned and the aqueous layer extracted with ether (3x10ml). The combined organic extracts were washed with brine (100ml), dried and the solvent evaporated under reduced

pressure. Flash chromatography (hexanes:ethyl acetate; 19:1) gave recovered **227** and the title compound as a viscous colourless oil (0.22g, 83%). ^{1}H NMR: δ0.13 (*s*, 3H, $SiCH_3$),0.15 (*s*, 3H, $SiCH_3$), 0.89 (*d*, *J*7.00Hz, 6H, $CH(C\underline{H}_3)_2$), 1.04 (*d*, *J*6.87Hz, 3H, $CHC\underline{H}_3$), 1.23 (*d*, *J*6.36Hz, $CH(OH)C\underline{H}_3$), 1.13-1.26 (*m*, 1H, cyclohexane CH), 1.37-1.54 (*m*, 4H, cyclohexane CH), 1.57-1.95 (*m*, 3H, cyclohexane CH and $C\underline{H}(CH_3)_2$), 1.90 (*m*, 1H, cyclohexane CH), 2.43 (*s*, 1H, OH), 3.98 [*m*, 1H, H_{ax}-C(2)], 4.03 (*dq*, *J*4.30, 6.32Hz, 1H, $C\underline{H}OH$); ^{13}C NMR: δ-2.9, -1.8, 18.5, 18.6, 19.7, 20.2, 20.5, 21.7, 22.2, 24.9, 29.2, 30.8, 33.9, 39.6, 46.6, 68.7, 73.5; IR (neat): 3390 s (O-H), 2950 s, 1460 m, 1380 m, 1250 s, 1105 s, 1060 s, 1040 s, 995 m, 970 m, 925 m, 870 s, 830 s, 775 s, 665 m cm^{-1}; MS, m/z: 216 ([M+1]$^+$, 1%), 215 (M$^+$, 5), 141 (2), 133 (2), 123 (26), 95 (4), 85 (4), 81 (32), 75 (100), 73 (47), 67 (8), 58 (7), 53 (17); HRMS calc. for $C_{11}H_{22}O_2Si$ ([M-C_6H_{13}]$^+$): 215.14674; Found: 215.1464.

(-)-(1*R*,2*S*,4*S*)-2-[(Thexyldimethylsilyl)oxy]-4-methyl-1-cyclohexyl methyl ketone (230)

This compound was prepared from (-)-(1*R*,2*S*,4*S*)-2-[(thexyldimethylsilyl)oxy]-4-methyl-1-(1-hydroxyethyl)cyclohexane **229** (0.23g, 0.77mmol) in an analogous manner to that described for **214**. Flash chromatography (hexanes:ethyl acetate; 24:1) gave the title product as a pale yellow oil (0.17g, 74%). ^{1}H NMR: δ0.11 (*s*, 6H, $Si(CH_3)_2$), 0.83 (*s*, 6H, $C(CH_3)_2$), 0.87 (*d*, *J*7.64Hz, 6H, $CH(C\underline{H}_3)_2$), 0.95 (*d*, *J*5.20Hz, 3H, $CHC\underline{H}_3$), 1.30-1.49 (*m*, 3H, cyclohexane CH), 1.53-1.69 (*m*, 3H, cyclohexane CH and $C\underline{H}(CH_3)_2$), 1.91 (*dt*, *J*9.52, 3.22Hz, 1H, cyclohexane CH), 2.19 (*s*, 3H, CH_3CO), 2.25 (*m*, 1H, cyclohexane CH), 2.88 [*m*, 1H, H_{eq}-C(1)], 3.85 [*dt*, *J*9.32, 5.34Hz, 1H, H_{ax}-C(2)]; ^{13}C NMR: δ-2.7, -2.3, 18.6, 18.8, 20.3, 20.5, 22.2, 25.0, 25.7, 29.6, 31.2, 33.0, 34.2, 39.9, 52.2, 72.6, 211.5; IR (neat): ν_{max}2950 *s*, 1715 *s* (C=O), 1460 *m*, 1380 *m*, 1350 *m*, 1250 *s*, 1180 *m*, 1160 *m*, 100 *s*, 1065 *s*, 1050 *s*, 945 *w*, 915 *w*, 870 *s*, 825 *s*, 775 *s*, 665 *m* cm^{-1}; MS, m/z: 283 ([M-CH_3]$^+$, 0.4%), 214 (20), 213 ([M-C_6H_{13}]$^+$, 100), 169 (26), 120 (5), 105 (8), 93 (3), 75 (7); HRMS calc. for $C_{16}H_{31}O_2Si$ ([M-CH_3]$^+$): 283.20932; Found: 283.2095; $[\alpha]_D$ -28.0° (*c*=0.5, $CHCl_3$).

(-)-(1*R*,2*S*,4*S*)-2-[(Thexyldimethylsilyl)oxy]-4-methyl-1-{1-methylene-1-[(trifluoromethanesulfonyl)oxy]}cyclohexane (231)

This compound was prepared from (-)-(1*R*,2*S*,4*S*)-2-[(thexyldimethylsilyl)oxy]-4-methyl-1-cyclohexane methyl ketone **230** (0.12g, 0.39mmol) in an analogous manner to that described for **215**. Flash chromatography (hexanes) gave the title compound as a colourless oil (0.24g, 98%). ^{1}H NMR: δ0.08 (*s*, 3H, $SiCH_3$), 0.10 (*s*, 3H, $SiCH_3$), 0.82 (*s*, 6H, $C(CH_3)_2$), 0.86 (*d*, *J*6.84Hz, 6H, $CH(C\underline{H}_3)_2$), 0.99 (*d*, *J*6.24Hz, 3H, $CHC\underline{H}_3$), 1.13-1.26 (*m*, 2H, cyclohexane CH), 1.37-1.68 (*m*, 4H, cyclohexane CH and $C\underline{H}(CH_3)_2$), 2.00 (*m*, 1H, cyclohexane CH), 2.32 (*m*, 1H, cyclohexane CH), 2.68 [*ddd*, *J*4.86, 4.00, 3.95Hz, 1H, H_{eq}-C(1)], [*dddd*, *J*4.48, 4.60, 4.04, 4.46Hz, 1H, H_{ax}-C(2)], 5.26 (*d*, J_{gem}2.58Hz, 1H, vinylic), 5.33 (*d*, J_{gem}3.52Hz, 1H, vinylic); ^{13}C NMR: δ-3.2, -2.5, 18.6, 20.2, 20.3, 21.8, 24.0, 24.5, 24.9, 29.6, 30.3, 34.1, 38.7, 45.6, 70.3, 107.4, 118.5 (*q*, J_{CF}320.0Hz), 156.5; IR (neat): ν_{max}2950 *s*, 1670 *w* (C=O), 1460 *m*, 1420 *s* (asymS=O), 1250 *s* (asymC-OSO_2), 1210 *s* (C-F), 1150 *s* (symS=O), 1100 *m* (S-O), 1070 *m*, 1050 *m*, 925 *m*, 875 *m*, 830 *m*, 780 *m*, 615 *m* cm^{-1}; MS, m/z: 415 ($[M-CH_3]^+$, 0.25%), 345 ($[M-C_6H_{13}]^+$, 36), 277 (2), 207 (5), 195 (12), 121 (100), 105 (9), 93 (77), 79 (36), 75 (7), 67 (4); HRMS calc. for $C_{12}H_{20}F_3O_4SSi$ ($[M-C_6H_{13}]^+$): 345.08036; Found: 345.0800; $[\alpha]_D$ -7.84° (*c*=0.51, $CHCl_3$).

Methyl 2-[2-(Thexyldimethylsilyl)oxy-4-methyl

(-)-(1*R*,2*S*,4*S*)-2-[(Thexyldimethylsilyl)oxy]-4-methyl-1-[1-(methoxycarbonyl)ethen-1-yl]cyclohexane (232) cyclohex-1-yl] propenoate

This compound was prepared from (-)-(1R,2S,4S)-2-[(thexyldimethylsilyl)oxy]-4-methyl-1-{1-methylene-1-[(trifluoromethanesulfonyl)oxy]cyclohexane **231** (0.24g, 0.56mmol) in an analogous manner to that described for **216**. Flash chromatography (hexanes:ethyl acetate; 99:1) gave the title compound as a pale yellow oil (0.11g, 58%). ^{1}H NMR: δ0.05 (*s*, 3H, $SiCH_3$), 0.18 (*s*, 3H, $SiCH_3$), 0.92 (*s*, 3H, CCH_3), 0.94 (*s*, 3H, CCH_3), 1.01 (*d*, *J*7.30Hz, 6H, $CH(C\underline{H}_3)_2$), 1.21 (*d*, *J*6.95Hz, 3H, $CHC\underline{H}_3$), 1.17-1.54 (*m*, 2H, cyclohexane CH), 1.65-1.91 (*m*, 4H, cyclohexane CH and $C\underline{H}(CH_3)_2$), 2.05 (*m*, 1H, cyclohexane CH), 2.27 (*m*, 1H, cyclohexane CH), 2.92 [*m*, 1H, H_{eq}-C(1)], 3.86 (*s*, 3H, OCH_3), 4.16 [*dddd*, *J*3.38, 2.67, 3.02, 3.48Hz, 1H, H_{ax}-C(2)], 5.82 (*s*, 1H, vinylic), 6.41

(*s*, 1H, vinylic); ^{13}C NMR: δ-3.2, -2.3, 18.6, 18.7, 20.3, 20.4, 21.7, 22.6, 24.8, 28.4, 31.1, 34.0, 38.8, 42.4, 51.6, 70.1, 126.1, 141.4, 168.2; IR (neat): ν_{max}2950 *s*, 1720 *s* (C=O), 1630 *w* (C=C), 1465 *m*, 1440 *m*, 1380 *w*, 1250 *s*, 1210 *m*, 1145 *s*, 1050 *s*, 1000 *m*, 890 *m*, 830 *m*, 775 *m* cm^{-1}; MS, m/z: 325 ($[M-CH_3]^+$, 1%), 309 (1), 255 ($[M-C_6H_{13}]^+$, 100), 223 (23), 195 (9), 149 (4), 129 (4), 120 (23), 105 (50), 89 (20), 73 ($CO_2C_2H_5^+$, 31); HRMS calc. for $C_{18}H_{33}O_3Si$ ($[M-CH_3]^+$): 325.21989; Found: 325.2194; $[\alpha]_D$ -9.52° (*c*=0.42, $CHCl_3$).

(-)-(3a*R*,6*S*,7a*S*)-Hexahydro-6-methyl-3-methylene-2(3*H*)benzofuranone (233)

This compound was prepared from (-)-(3*R*,2*S*,4*S*)-2-[(thexyldimethylsilyl)oxy]-4-methyl-1-[1-(methoxycarbonyl)ethen-1-yl]cyclohexane **232** (86mg, 0.25mmol) in an analogous manner to that described for **217**. Flash chromatography (hexanes:ethyl acetate; 97:3) gave the title compound as a colourless oil (42mg, 100%). ^1H NMR: δ0.78-1.01 (*m*, 2H, cyclohexane CH), 0.91 (*d*, *J*6.48Hz, 3H, CH_3), 1.37 (*br m*, 1H, cyclohexane CH), 1.50 (*d of m*, J_d13.75Hz, 1H, cyclohexane CH), 1.76 (*m*, 1H, cyclohexane CH), 2.08 (*m*, 1H, cyclohexane CH), 2.12 (*m*, 1H, cyclohexane CH), 3.12 [*m*, 1H, H-C(3a)], 4.63 [*ddd*, *J*6.80, 3.09, 6.87Hz, 1H, H-C(7a)], 5.50 (*d*, J_{gem}3.31Hz, 1H, vinylic), 6.28 (*d*, J_{gem}3.32Hz, 1H, vinylic); ^{13}C NMR: δ21.9, 23.8, 28.5, 28.9, 38.9, 40.0, 77.5, 119.8, 137.4, 170.8; IR (neat): ν_{max}2925 *s*, 1765 *s* (C=O), 1665 *w* (C=C), 1455 *m*, 1405 *w*, 1315 *m*, 1255 *m*, 1230 *m*, 1220 *m*, 1100 *m*, 990 *m*, 815 *w*, 750 *w* cm^{-1}; $[\alpha]_D$ -19.2° (*c*=0.5, $CHCl_3$).

(+)-Mintlactone (234)

This compound was prepared from (-)-(3a*R*,6*S*,7a*S*)-hexahydro-6-methyl-3-methylene-2(3*H*)benzofuranone **233** (27mg, 0.16mmol) in an analogous manner to that described for **218** save that the reaction was stirred over 2 days. Gradient flash chromatography (hexanes:ethyl acetate; 19 to 9:1) gave the title compound as a colourless liquid (16mg, 59%). ^1H NMR: δ0.89-1.09 (*m*, 2H, cyclohexane CH), 1.01 (*d*, *J*6.69Hz, 3H, CH_3), 1.71 (*m*, 1H, cyclohexane CH), 1.81 (*t*, ^5J1.50Hz, 3H, CH_3C=), 1.95 (*d of m*, J_d13.15Hz, 1H, cyclohexane CH), 2.19 (*br ddd*, *J*5.51, 5.33, 5.79Hz, 1H, cyclohexane CH), 2.42 (*m*, 1H,

cyclohexane CH), 2.79 (*ddd*, *J*14.24, 2.61, 1.77Hz, 1H, cyclohexane CH), 4.63 [*br dd*, *J*5.53, 6.38Hz, 1H, H-C(7a)]; ^{13}C NMR: δ8.2, 21.2, 25.4, 29.7, 34.5, 41.9, 79.9, 119.5, 162.3, 174.9; IR (neat): ν_{max}2925 *s*, 1750 *s* (C=O), 1690 *m* (C=C), 1455 *m*, 1380 *w*, 1330 *m*, 1300 *m*, 1230 *w*, 1100 *m*, 1070 *m*, 1030 *s*, 1000 *m*, 860 *m*, 765 *m*, 750 *m*, 685 *m* cm^{-1}; MS, m/z: 167 ([M+1]$^+$, 12%), 166 (M$^+$, 100), 151 ([M-CH_3]$^+$, 3), 138 ([M-CO]$^+$, 45), 137 ([M-CHO]$^+$, 77), 123 (26), 120 (11), 109 (64), 105 (22), 95 (60), 91 (20), 81 (84), 67 (91); HRMS calc. for $C_{10}H_{14}O_2$: 166.09974; Found: 166.0991; $[\alpha]_D$ +59.9° (*c*=0.75, EtOH), lit.[226] $[\alpha]_D$ for (-)-mintlactone -51.8° (*c*=10, EtOH).

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