Lewis Acid Mediated Reactions of Olefins with Carbonyls

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For the Degree of PhD

Of the University of Bath

2002

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Abstract

This thesis is divided into 5 chapters. The first chapter reviews the literature of Carbonyl-ene and Prins reactions. Recent advances in these areas and their application to natural product synthesis and other targeted syntheses are discussed.

The second chapter discusses the concept of desymmetrisation using selected examples, including desymmetrising Carbonyl-ene reactions.

Chapter Three introduces and discusses the work undertaken in studying the desymmetrising intramolecular carbonyl-ene of a *meso*-dialdehyde.

Chapter Four details the concept of pyruvate-Prins cyclisation giving examples of its potential use. The chapter also gives examples of the use of rigid stereodefined scaffolds and their application. The chapter describes the reactivity of substituted pyruvate esters with cyclic enol ethers, and the elaboration of the cyclised products.

The fifth chapter provides experimental details of the procedures reported.

Acknowledgements

Many thanks to Dr Mike Willis for all his help and guidance and boundless enthusiasm over the years; and for a detailed investigation of the local pubs. Special thanks go to all the past and present members of the group: Christelle (Fromage), Michael (for simultaneous writing-up blues), Selma, Stav, Phil, Mark, Vincent, Luke and Aaron.

Cheers to everyone who's worked in lab 0.28; Louise H, Cath (the original Fun Lovin' Criminal) Hague, Phil Perkins, Mike "soooo" good Edwards, Suvi the Flaxen Finn, Steve Hillier, and….Aaron.

To everyone else I've had the joy to work with in the department, a big, big thanks, to mention a few; the encyclopaedic Christian, Kerry (a golfing grandmaster), Paul M., Phil Black, the inventive Chappers, Stevie D, Jo H., Claudia, Kelly, Tim (oh the stress!), and J.P.

Thank you to Dr Mary Mahon for crystal structure analysis, and for being able to do so much with so little. Cheers to all the support staff: Sylvia, Sheila, Carol, Pam and Jane for all the help, encouragement and comments over many years. Thanks to the technical support staff, Sarah, Kirsty, John, Robert, Alan, Ahmed, and Russell, and for putting up with my many and varied requests.

An enormous thanks to those people who I cajoled, bribed and threatened into proofreading for me: Michael, Suvi, Mike E. (also MGE and SJMK for emailed article requests), Stav, Phil B., Chappers and in fact the entire organic section of the Chemistry Department.

To Diane, my wife: Thank you for everything, for being so understanding and supportive of the perpetual student.

Special thanks to my family, mum and dad for the huge amount you've done for me, for the constant support. Cheers to Bill, my bro - good luck to you too.

Cheers to the Ozric Tentacles – music to write a thesis to.

Well that just about does it, sorry to anyone a may have forgotten to mention – it certainly wasn't intentional.

And now…onto the important part…

Table of Contents

Abbreviations

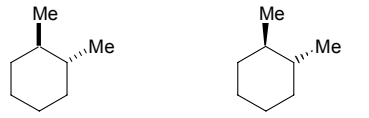
Ac	acetyl
Ap	apparent
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	2,2'-bis(hydroxyl)-1,1'-binaphthyl
Bn	benzyl
bp	boiling point
br. s	broad singlet
Bu	butyl
CAN	ceric ammonium nitrate
CI	Chemical Ionisation
conc.	concentrated
Cy	cyclohexyl
d	doublet
D	deuterium
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
de	diastereomeric excess
DET	diethyl tartrate
DHF	2,3-dihydrofuran
DHP	3,4-dihydropyran
DIBAL	di-*iso*-butyl aluminium hydride
DIC	di-*iso*-propylcarbodiimide
DIPT	di-*iso*-propyl tartrate
DMAP	4-dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DMSO	dimethylsulphoxide

dppe	1,2-*bis*(diphenylphosphino)ethane
EDCI	(3-dimethylamino-propyl)-ethyl-carbodiimide
ee	enantiomeric excess
EI	Electron Impact
eq.	equivalent
Et	ethyl
Et_2O	diethyl ether
FAB	Fast Atom Bombardment
g	gram
GC	Gas Chromatography
h	hour
HPLC	High Performance Liquid Chromatography
i	*iso*
IR	infra red
L	ligand
L^*	chiral ligand
LDA	lithium di-*iso*-propylamine
liq.	liquid
M	metal
m	multiplet
m	meta
Me	methyl
mg	milligram
mL	millilitre
Ms	methanesulphonyl

MS	molecular sieves
n	normal
NMR	nuclear magnetic resonance
o	ortho
P	protecting group
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PPTS	Pyridinium *p*-toluene sulphonate
Pr	propyl
q	quartet
rt	room temperature
s	singlet
t	triplet
t or *tert*	tertiary
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	triflate
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSE	Trimethylsilyl ethyl
tol	tolyl
Ts	*p*-toluenesulphonyl
UV	ultraviolet

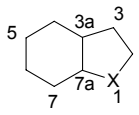
Stereochemical Notation and Compound Numbering

Throughout this thesis the representation of stereochemistry used is in accord with the convention proposed by Maehr.[1] Thus, solid and broken wedges are used to signify absolute configuration, while the use of solid and broken lines refers to racemic materials. For the former, greater narrowing of both solid and broken wedges indicates increasing distance from the viewer.



Racemic - *trans* Single Enantiomer

Compound names conform as closely as possible to IUPAC nomenclature and the assignment of protons and carbons in the NMR data follows the same numbering, as indicated. Fused ring systems follow IUPAC nomenclature as laid out in: "Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H, Pergamon Press, Oxford, 1979"; and "Guide to IUPAC Nomenclature of Organic Compounds (Recommendations 1993), 1993, Blackwell Scientific publications".



[2,3-*b*] fused ring system

(1) Maehr, H. *J. Chem. Ed.* **1985**, *62*, 114.

Chapter 1: The Carbonyl-Ene and Prins Reactions

Introduction – The Carbonyl-ene reaction and The Prins reaction

This chapter examines two related reactions of olefins with aldehydes, namely the carbonyl-ene reaction and the Prins reaction.

The Ene reaction

The ene reaction is a close cousin to the Diels-Alder reaction and Alder suggested the name "indirect substituting addition" for the process in his Nobel lecture.[1] It can be described as, "a pericyclic reaction between an olefin bearing an allylic proton (the ene) and an electron deficient multiple bond (the enophile), involving the formation of two σ-bonds, with the migration of a π-bond" (Figure 1).[2]

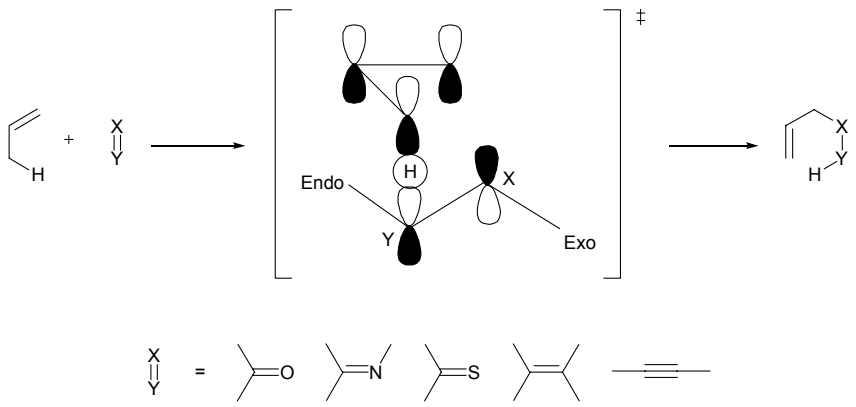
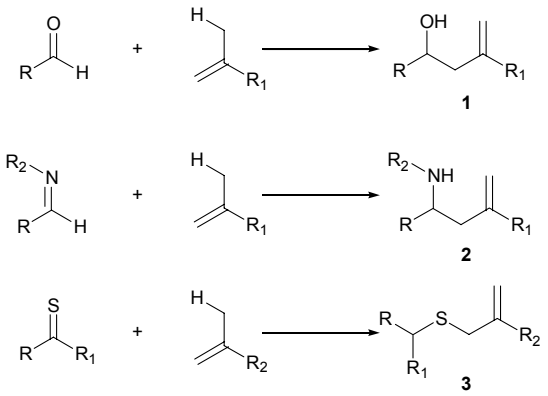


Figure 1

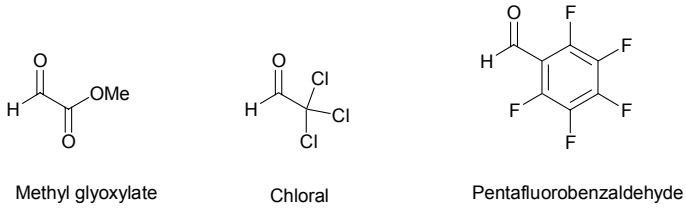
Ene reactions are of interest because of the diverse range of starting materials that can be used, and the wide variety of products this consequently produces. When the enophile of an ene reaction is a carbonyl group, such as an aldehyde, the reaction is commonly referred to as a carbonyl-ene reaction. Aldehyde carbonyl-ene reactions (Scheme 1) are particularly useful in that the products are

β-hydroxy olefins, **1**. Ene reactions with imines give homoallylic amines, **2**, and thiocarbonyls (formed *in situ*) give allylic sulphides, **3**. In the ene reactions of thiocarbonyls, whilst some homoallylic thiol product is formed, the major product is the allylic sulphide, **3**.



Scheme 1

Ene reactions have certain limitations. The two electrons in the allylic C-H σ-bond replace the two π-electrons of the diene in the Diels-Alder reaction. The activation energy is therefore higher than that in the corresponding Diels-Alder reaction. For thermal ene reactions, higher temperatures or highly activated starting materials are therefore required. During early developments, ene reactions often involved pyrolysis of the starting materials.[3] However, reagents such as glyoxylates, chloral and pentafluorobenzaldehyde (Figure 2) allow thermal carbonyl-ene reactions to occur at lower temperatures (80-220 °C).

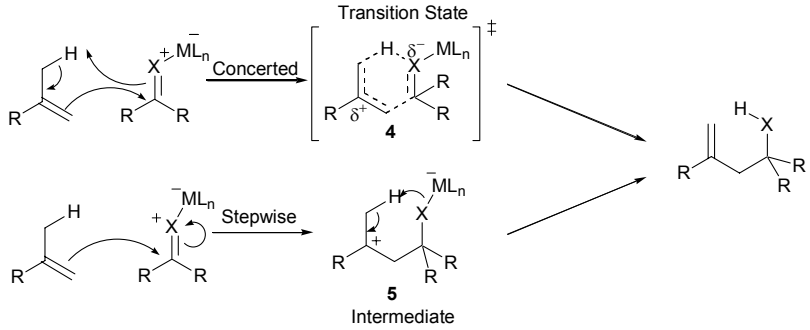


Methyl glyoxylate Chloral Pentafluorobenzaldehyde

Figure 2

Lewis acid catalysed Carbonyl-Ene Reactions

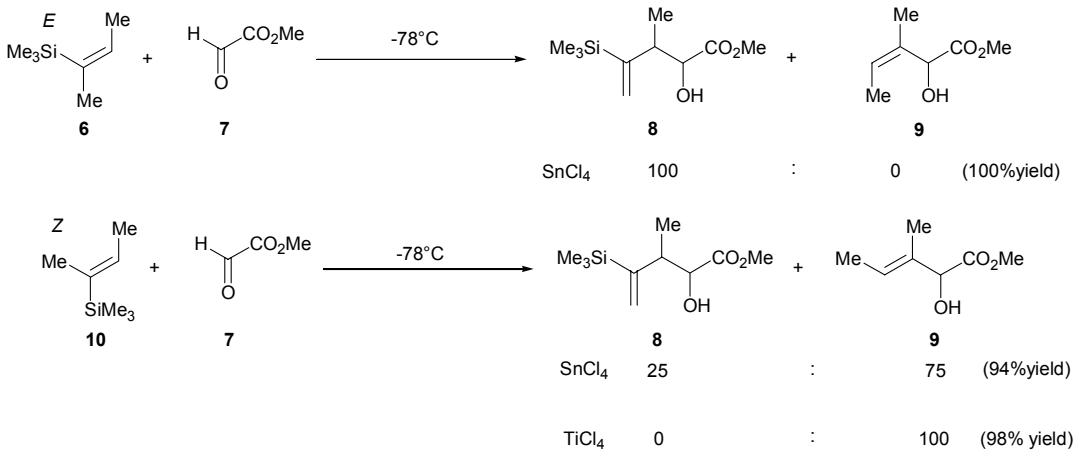
The development of Lewis acid catalysed reactions has allowed many reactions to be carried out at lower temperatures, often at room temperature and even –78 °C. The more active enophiles shown above, however, are still often required. Lewis acid catalysed reactions can proceed *via* a concerted mechanism with a polar transition state, **4**, or a stepwise mechanism, forming a zwitterionic intermediate, **5** (Scheme 2). The mechanism for Lewis acid catalysed reactions appears to depend on both the catalyst and reagents used. In general, it is possible to imagine a continuum, from the concerted to the stepwise mechanism. A reaction may fall at one end of the extremes of this continuum or somewhere in between, slightly favouring one mechanism over the other.



Scheme 2

Kinetic isotope effects have been used as tools to show whether the reaction under examination is stepwise or concerted. Stephenson and Orfanopoulos concluded that for a Lewis acid catalysed reaction, a concerted mechanism prevailed but that C-H bond breaking was only slightly progressed in the transition state.[4] Mikami *et al.*[5] utilised a change of Lewis acid from $SnCl_4$ to $TiCl_4$ to show a change from concerted to stepwise mechanisms in the ene reaction of methyl glyoxylate, **7**, and *Z*- and *E*-trimethyl-(1-methyl-propenyl)-

silane (**6** and **10**, Scheme 3). The *E*-vinylsilane **6** exclusively gave the ene product **8**, whereas changing to the *Z*-vinylsilane **10** gave a greater yield of the substitution product **9**. The substitution product is believed to arrive from the formation of a cationic intermediate akin to **5**. Using $TiCl_4$ gave exclusively the substitution product, **9**, the explanation being that if the optimum geometry for the ene reaction is unobtainable, the reaction proceeds *via* the alternative, non-ene route. $TiCl_4$, being the stronger Lewis acid was believed to stabilise the cationic intermediate. However, no examination was made between the *E*-vinylsilane **6** and $TiCl_4$.

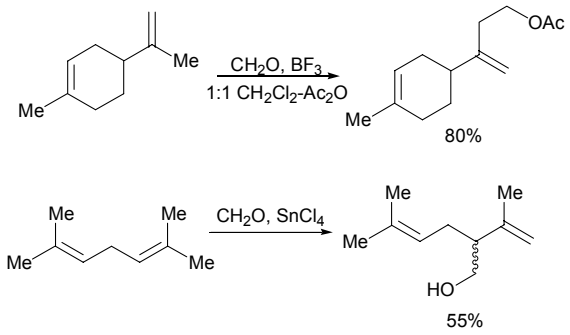


Scheme 3

A line must be drawn between the carbonyl-ene reaction and the closely related Prins reaction, which will be discussed in its own right, *vide infra*.[6,7] This difference between the two provides an insight into the carbonyl-ene mechanism. It is postulated that in the Prins reaction there is the formation of a carbocation intermediate. This leads to the possibility of attack by an external nucleophile, another aldehyde or the loss of a proton to give an allylic or homoallylic

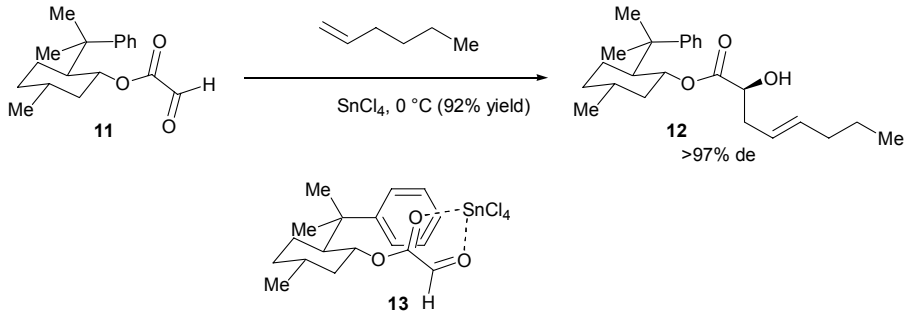
alcohol.[8] The carbonyl-ene reaction only gives homoallylic alcohols, suggesting that the mechanism is either concerted or, if stepwise, the intermediate is sufficiently short-lived not to allow nucleophilic attack.[9]

Amongst the earliest Lewis acid catalysed carbonyl-ene reactions were those using formaldehyde as the enophile (Scheme 4).[7,10]



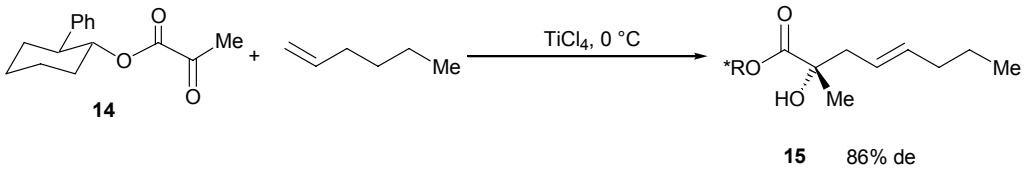
Scheme 4

The introduction of a chiral auxiliary allows some diastereocontrol of the carbonyl-ene reaction. The glyoxylate-ene reaction has been very thoroughly studied and is particularly amenable to use with chiral auxiliaries. Although the most common glyoxylate substituent is an alkyl group, a chiral auxiliary can be attached. For example, Whitesell used (-)-8-phenylmenthylglyoxal **11,** which gave hydroxyl ester **12** with good diastereoselectivity when used with an achiral Lewis acid.[11] It is believed that the phenyl group forms a π-complex **13** with the glyoxylate, successfully shielding one face from attack (Scheme 5).



Scheme 5

In addition, Whitesell reported a diastereoselective pyruvate-ene reaction with enantiopure 2-oxo-propionic acid 2-phenyl-cyclohexyl ester, **14** and 1-hexene (Scheme 6) to give **15** with good diastereomeric control.[12] When the 8-phenylmenthyl auxiliary **11** is used in the pyruvate-ene reaction, Whitesell reported that only self-condensation of the pyruvate is observed.

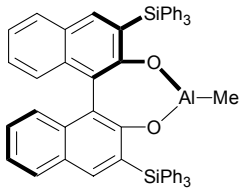


Scheme 6

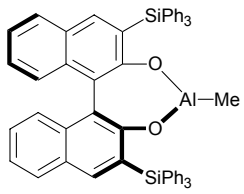
Enantioselective Carbonyl-ene Reactions

A number of enantioselective Lewis acid catalysts for the intermolecular carbonyl-ene reaction have been developed, although limitations exist for all these reactions.

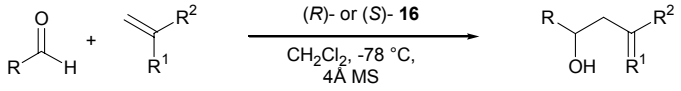
Yamamoto's reaction of activated aldehydes catalysed by binaphthol-derived organo-aluminium complex, **16**, was amongst the first reported enantioselective carbonyl-ene reactions (Scheme 7 and Table 1).[13]



(*R*)- **16**



(*S*)- **16**



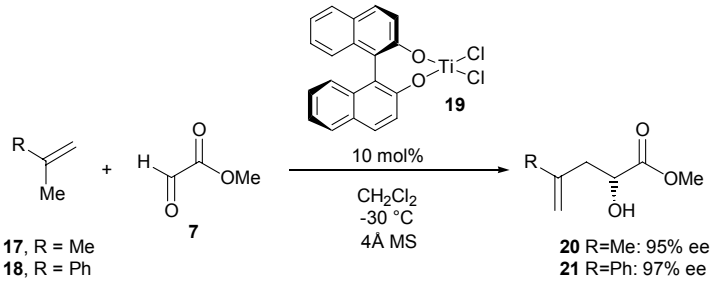
Scheme 7

Table 1 The ene reaction of activated aldehydes using chiral aluminium-binaphthol, **16**.

Entry	Aldehyde (RCHO)	Olefin	% Yield	% ee
1	C_6F_5CHO	$H_2C=C(Me)_2$	56	84
2		$H_2C=C(CH_2)_5$	42	86
3		$H_2C=C(CH_2)_6$	48	80
4		$H_2C=C(Me)^tBu$	42	92
5		$H_2C=C(Me)Ph$	85	71
6		$H_2C=C(Me)SPh$	90	88
7	Cl_3CHO	$H_2C=C(Me)_2$	60	30
8		$H_2C=C(CH_2)_6$	99	64
9		$H_2C=C(Me)Ph$	87	54
10		$H_2C=C(Me)SPh$	69	57
11	2,6-$Cl_2C_6H_3CHO$	$H_2C=C(Me)SPh$	96	65

As can be seen in Table 1, the yields and enantioselectivities reported reach very respectable values. However, the need to use such activated aldehydes has precluded general applications of this catalyst system.

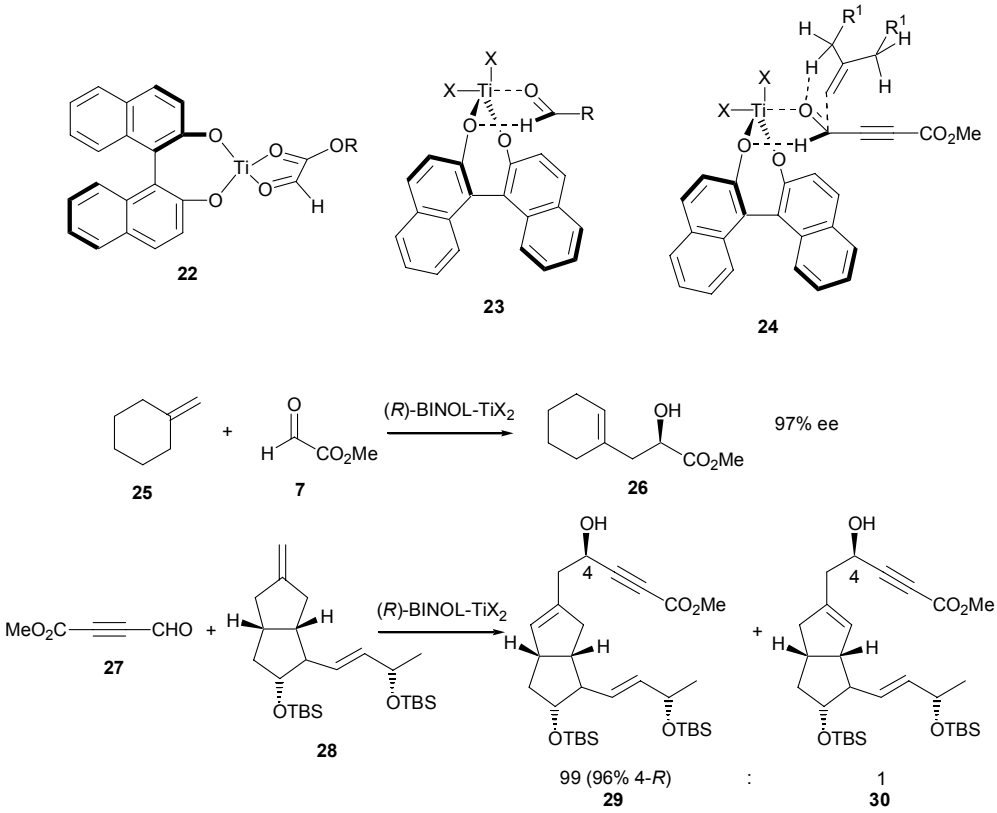
Mikami and Nakai developed a chiral titanium BINOL catalyst, (*R*)-**19**, for enantioselective use in the ene reaction with glyoxylate esters.[14] It has been found that whilst the ene components are limited to nucleophilic 1,1-disubstituted olefins such as isobutene, **17**, and α-methyl styrene, **18**, enantioselectivities are very high (Scheme 8).



Scheme 8

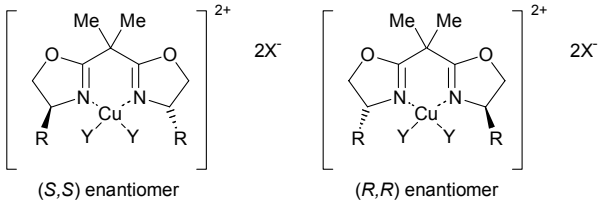
It was initially reported that activated molecular sieves were required for the titanium-BINOL catalysed enantioselective carbonyl-ene reaction and a comparison was drawn with the Sharpless asymmetric epoxidation.[15] Sharpless found that omitting 4Å molecular sieves caused the reaction to proceed slowly and stop at 50% conversion, requiring stoichiometric quantities of catalyst. Mikami noted that molecular sieves had a similarly important role in the carbonyl-ene reaction. Without molecular sieves, the reaction, still catalysed by (*R*)-BINOL and $Ti(O^iPr)_2Cl_2$, would give a lower enantiomeric excess. Preforming the catalyst by addition of $Ti(O^iPr)_2Cl_2$ and (*R*)-BINOL in the presence of 4Å molecular sieves showed a change in the ^{13}C spectrum of the complex compared to when the catalyst and ligand were mixed without

molecular sieves. The hydroxy-carbon signal in BINOL shifted from δ = 153 to δ = 160-163. However, later publications showed that reactions require that the molecular sieves be unactivated.[16] Unactivated molecular sieves contain approximately 5% H_2O. Rigorous drying of molecular sieves leads to a significant lowering of the yield and a lowering of the enantioselectivity of the reaction. Many theories regarding the possible structure of the active titanium-BINOL catalyst have been put forward and evidence has been found for the presence of μ_3-oxo bridging, yet to date the catalyst structure remains elusive. Whilst initial proposals by Mikami put forward the idea of chelation of the glyoxylate to the metal centre[2] (**23**, Scheme 9), Corey has proposed the following alternative perspective.[17] He argues that the high level of enantioselectivity found in reactions of alkynyl aldehydes and vinylogous glyoxylate esters, show that along with binding of the carbonyl lone pair to the titanium centre there is an interaction between the formyl hydrogen and one oxygen of the BINOL ligand (**23**, Scheme 9**)** (the so called "formyl-hydrogen bond"). For example, the reaction of **27** with **28** gives **29** and **30** in a 99:1 ratio with a 96% ee, without **27** being able to chelate to the titanium centre in a manner postulated for a glyoxylate. His proposed transition state, **24**, then gives the ene product with identical stereochemistry to that observed in the reaction. Corey has applied this argument to several other reaction transition states.[18-21]



Scheme 9

A range of chiral copper Lewis acid catalysts (Figure 3), which are active in a number of reactions including the glyoxylate- and pyruvate-ene reactions, have been developed. Particular use has been made of copper (II) catalysts with C_2-symmetric ligands such as the bis(oxazolines), or "box" ligands, **31** – **33**.

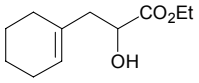
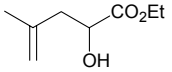
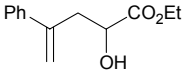
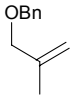
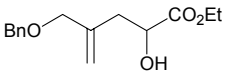
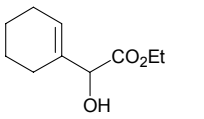
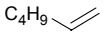
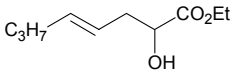


	R	X	Y
31	Ph	OTf	
32	t-Bu	SbF_6	
33	t-Bu	SbF_6	H_2O

Figure 3

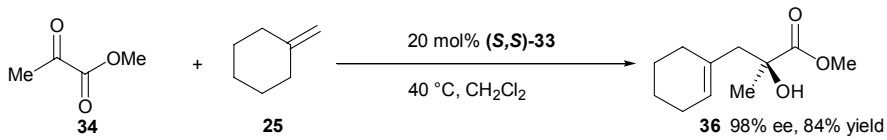
Evans applied these catalysts to ene reactions employing a range of alkenes, including 1,2-disubstituted and monosubstituted alkenes (Table 2).[22] Methyl and ethyl glyoxylate dimerise upon standing and in most reactions, they require cracking before use. However, it was shown that utilising these copper catalysts, product yields and enantioselectivities were unchanged when using the ethyl glyoxylate dimer in toluene, the glyoxylate being presumed to be cracked by the catalyst *in situ* prior to reacting.

Table 2 Examples of enantioselective Cu(II)box catalysed ene reactions.

Entry	Olefin	Product	Cat (mol%)	T /°C	Yield %	% ee (config.)
1			(*S,S*)-**33** (1)	0	90	97 (*S*)
2			(*S,S*)-**31**(10)		99	87 (*R*)
3			(*S,S*)-**33** (1)	0	83	96 (*S*)
4			(*S,S*)-**31** (10)		92	92 (*R*)
5			(*S,S*)-**33** (1)	0	97	93 (*S*)
6			(*S,S*)-**31** (10)		99	89 (*R*)
7			(*S,S*)-**33** (1)	25	62	98 (*S*)
8			(*S,S*)-**31** (10)		88	92 (*R*)
9			(*S,S*)-**32** (10)	0	95	98 (*S*)
10			(*S,S*)-**31** (10)		70	94 (*R*)
11			(*S,S*)-**32** (10)	25	96	98 (*S*)

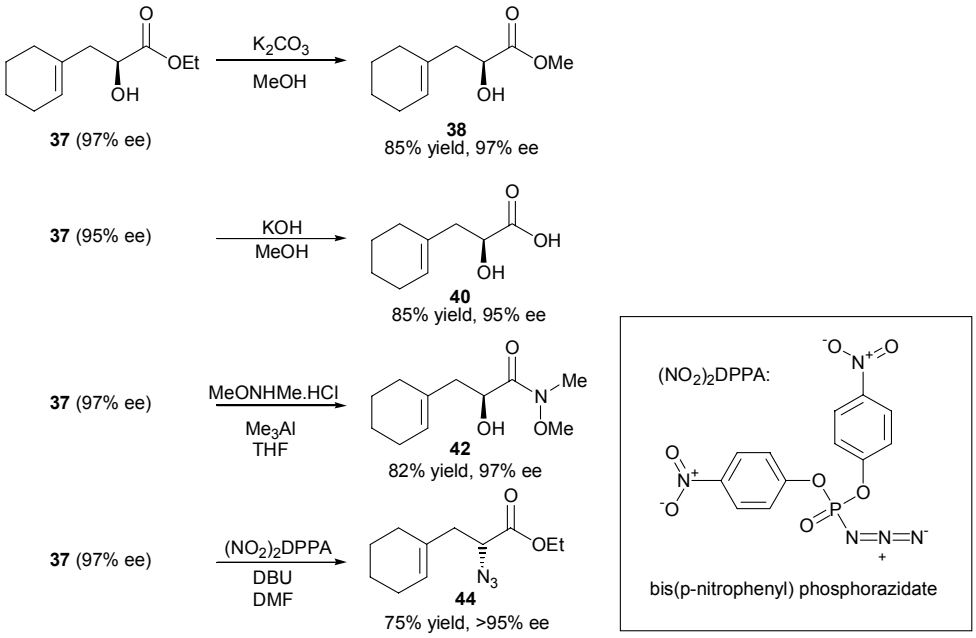
Evans' work in extending the range of alkenes, particularly with mono-substituted alkenes, which can be successfully used in the enantioselective carbonyl-ene reaction, represents a significant advance. Further advances were

made using (*S*,S)-**33** in the first example of an enantioselective pyruvate-ene reaction, (Scheme 10).



Scheme 10

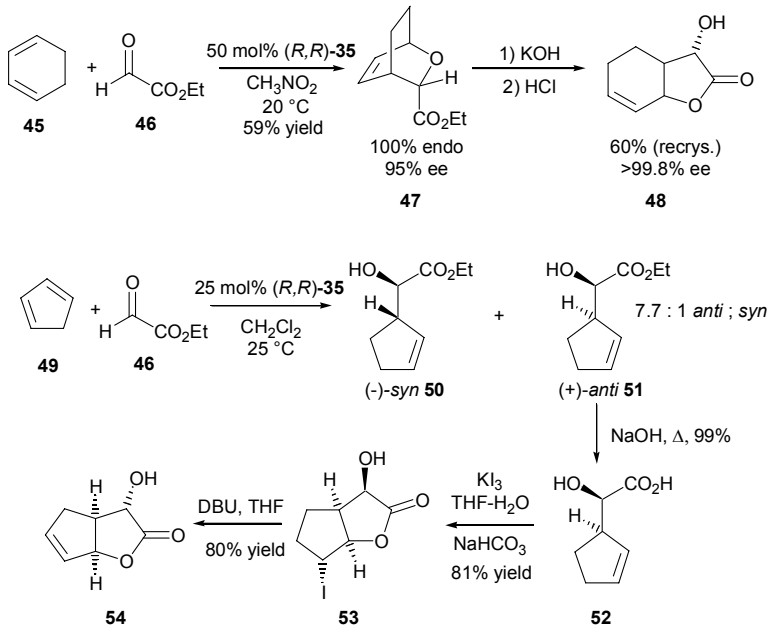
Enantiopure glyoxylate-ene and pyruvate-ene products are versatile building blocks. Under the correct conditions, racemisation can be avoided. Trans-esterification, ester hydrolysis, Weinreb amide synthesis and azide displacement have all been shown to proceed without racemisation (Scheme 11). Azide displacement gives access to unusual α-amino acids.



Scheme 11

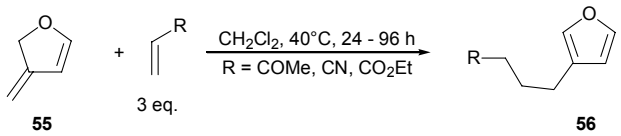
In an example of the flexibility of these Cu(II) Lewis acids, Jørgensen *et al.*[23] have used **31** to form the chiral bicyclic lactones **48** and **54** (Scheme 12). The initial route to these lactones was *via* the hetero-Diels-Alder reaction illustrated, followed by saponification-induced rearrangement. Whilst this was successful

using cyclohexadiene, **45,** and ethyl glyoxylate, **46**, the analogous reaction using cyclopentadiene, **49**, failed. Jørgensen *et al.* then looked to the enantioselective carbonyl-ene reaction as an alternative route and found that, whilst moderate in yield, **51** was produced with very good enantioselectivity. **51** could then easily be converted to the 5,5-bicyclic lactone **54**. One problem with these reactions is the large number of equivalents of catalyst required, 50 and 25 mol percent in the hetero-Diels-Alder and carbonyl-ene reactions respectively, this creates a problem with the cost of the box ligand (£90 – £250 / g).



Scheme 12

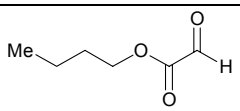
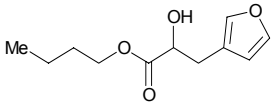
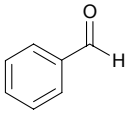
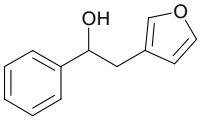
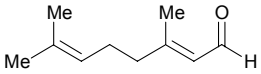
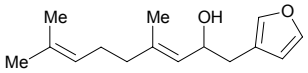
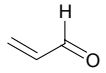
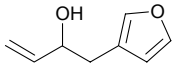
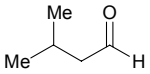
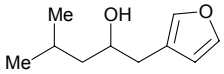
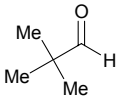
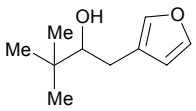
Miles and co workers developed the use of 3-methylene-2,3-dihydrofuran, **55**, as a novel method of introducing a furan moiety *via* the ene reaction. Methylene furan-**55** was found to take part in ene reactions with simple electron-deficient alkenes[24] (Scheme 13) and interestingly, C_{60}[25] as well as in carbonyl-ene reactions,[26] Table 3.



Scheme 13

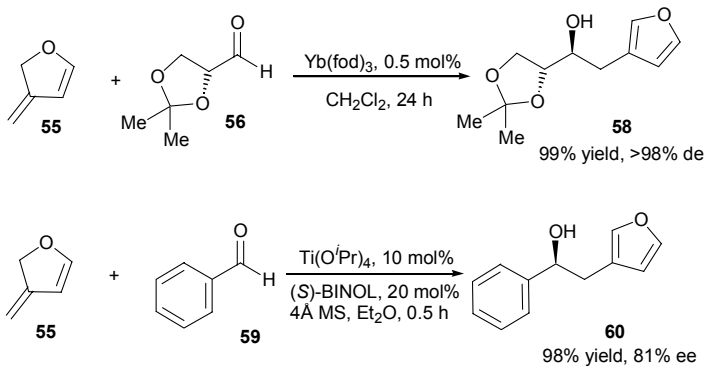
The reactive nature of methylene furan-**55** was demonstrated by the thermal carbonyl-ene reaction with butyl glyoxylate (entry 1). Other carbonyl enophiles did not undergo thermal ene reactions with methylene furan-**55**, but nevertheless underwent Lewis acid catalysed reactions in good yield (entries 3-10). One drawback is that methylene furan-**55** is not stable and must be distilled from ethylene glycol, hydrazine and potassium hydroxide prior to use as an ~4:1 mixture of **55**:3-methyl furan. Furthermore, trace amounts of acid present will cause decomposition to 3-methyl furan, including stirring with silica gel.

Table 3 Thermal and Lewis acid catalysed carbonyl-ene reactions of 3-methylene-2,3-dihydrofuran, **55**.

Entry	aldehyde	Lewis acid; time	Product	% yield
1		none; 1 h		85
2		none; 68 h		5
3	"	$Yb(fod)_3$, 0.5 mol%; 20 h	"	97
4	"	$Eu(fod)_3$, 0.5 mol%; 48 h	"	92
5	"	Me_3Al, 1.0 equiv.; 1 h	"	91
6	"	$Ti(O^iPr)_4$, 10 mol%; 20 h	"	94
7		$Yb(fod)_3$, 2 mol%; 68 h		88
8		Me_3Al, 1.2 equiv.; 1h		79
9		$Yb(fod)_3$, 1 mol%; 48 h		86
10		Me_3Al, 1.0 equiv.; 1h		79

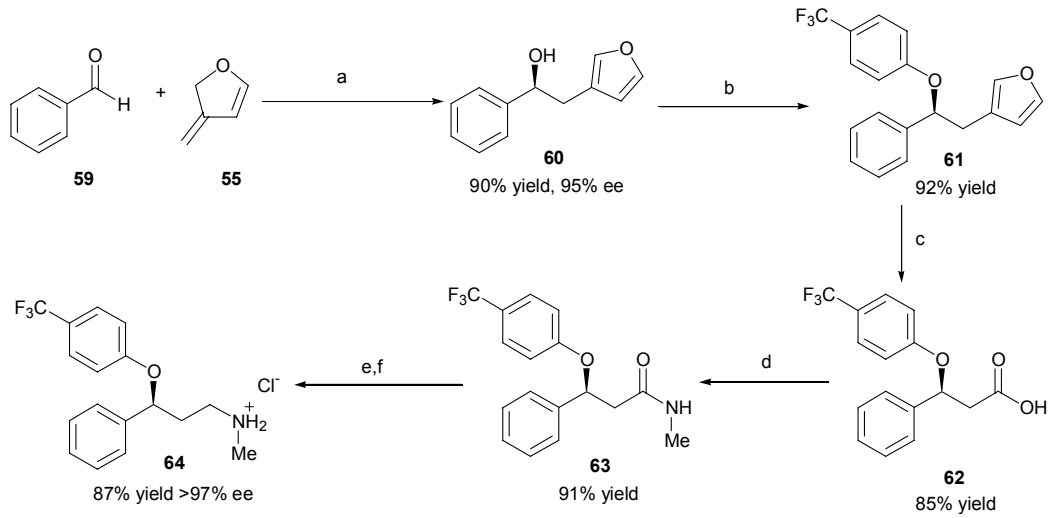
The application of **55** was examined by Miles in diastereoselective and enantioselective carbonyl-ene reactions (Scheme 14). **55** was found to react with both chiral reagents and chiral catalysts to give products with high

enantioselectivity. Using an achiral catalyst, $Yb(fod)_3$, and chiral aldehyde **57**, gave **58** in very good yield and diastereoselectivity. Chiral (*S*)-BINOL derived catalyst was used in the reaction of **55** and benzaldehyde, **59**, and gave **60** in good yield with high enantioselectivity.



Scheme 14

Miles *et al.* used this asymmetric carbonyl-ene reaction to synthesise fluoxetine hydrochloride,[27] **64** (better known as Prozac®), in both (*S*)- and (*R*)- forms in six steps (Scheme 15). The (*S*)-enantiomer was obtained in 56% yield and in >97% ee from benzaldehyde using a Ti-(*S*)-BINOL catalyst, establishing the desired stereochemistry in the very first step of the synthesis. By changing to (*R*)-BINOL, the opposite (*R*)-enantiomer was obtained in comparable yields and enantiopurities.

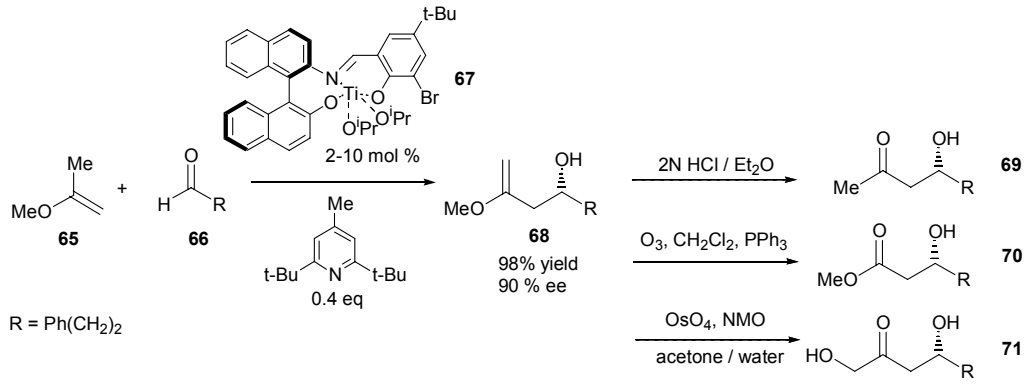


Scheme 15.

Reaction conditions: (a) $Ti(O^iPr)_4$, (*S*)-BINOL, 4Å MS, Et_2O; (b) NaH, DME, 4-fluorobenzotrifluoride; (c) $RuCl_3.xH_2O$, $NaIO_4$, EtOAc, H_2O; (d) hydroxybenzotriazole hydrate, *N*-methyl-morpholine, CH_3NH_2, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; (e) BH_3, THF, MeOH, 6M HCl; (f) HCl in Et_2O.

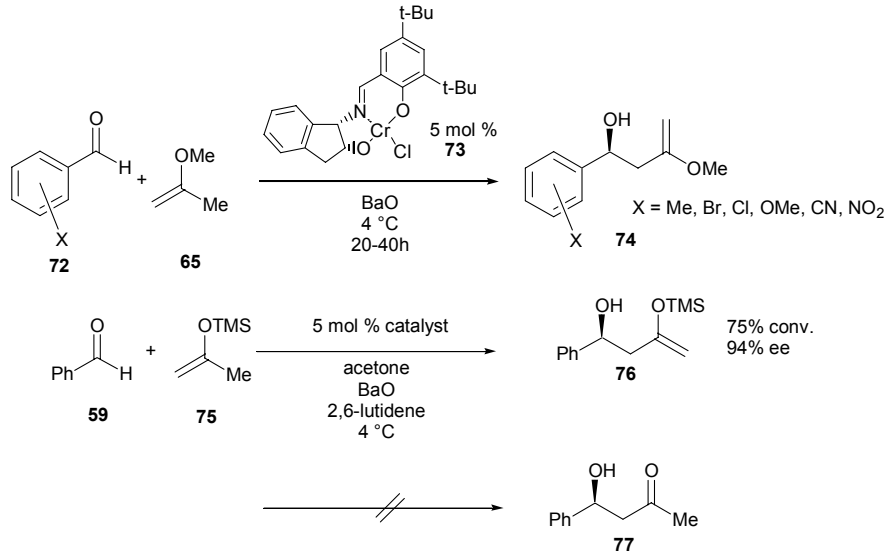
Hetero-carbonyl-ene reactions

The use of a heteroatom substituted alkene, such as an enol ether, as the ene component leads to a hetero-ene reaction, giving synthetically useful β-hydroxyenol ethers as products. The enantioselective reaction of 2-methoxypropene, **65**, with aliphatic aldehydes was first reported by Carreira as an aldol reaction,[28] as "aldol-like" products, **69**, were easily obtainable by stirring the hetero-ene product with ether/2N HCl (Scheme 16). In addition, the enol ether products, **68**, can also be easily converted to esters, **70**, and α-hydroxy ketones, **72**. This catalyst has successfully used in enantioselective acetate aldol reactions using an *O*-trimethylsilyl *O*-methyl ketene acetal producing adducts in 94 – 97% ee. However, the structure of the active catalyst is unknown.



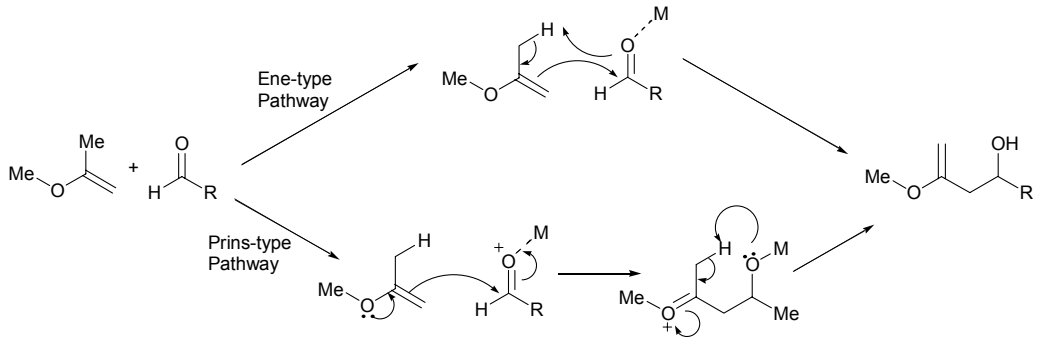
Scheme 16

Jacobsen reported that chiral chromium(III) complexes[29] such as **73** effectively catalyse the hetero-ene reaction of 2-methoxypropene **65** with *ortho, meta* and *para*-substituted benzaldehydes **72**, with 70-96% ee (Scheme 17). One example of an aliphatic aldehyde, n-hexanal, gave 84% ee but with a much lower yield (54%), than the aromatic aldehydes. Interestingly, use of 2-trimethylsilyloxy-propene **75**, gives the ene adduct **76** and not the aldol adduct **77**. This makes the reaction useful for preparing TMS-enol ethers for subsequent aldol reactions.



Scheme 17

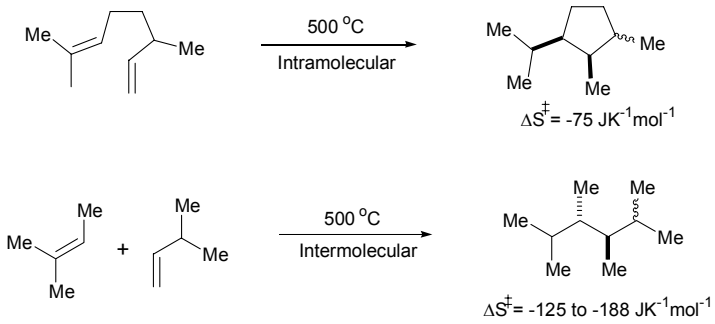
Whilst these reactions are regarded as hetero-ene reactions for the purposes of this thesis, it must be pointed out that the mechanism of the reaction has not been fully elucidated. It is possible that the reaction is in fact a Prins-type reaction, with involvement of the oxygen of the enol ether in the form of an oxonium ion (Prins-type pathway, Scheme 18). However, Jacobsen argues that the formation of **76** over **77** points to a concerted, ene-type pathway.



Scheme 18

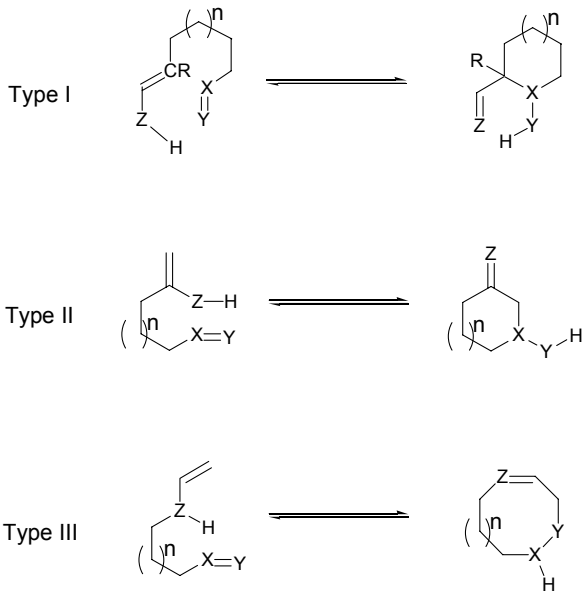
Ene cyclisations

Ene cyclisations (an intramolecular ene reaction) are generally more facile than the intermolecular ene reaction (Scheme 19).[30] This is due in part to entropic factors; for example, the entropy of activation of the intramolecular reaction ($\Delta S^{\ddagger}$ = -75 J K^{-1} mol^{-1}) is less negative than that of the intermolecular case ($\Delta S^{\ddagger}$ = -125 to -188 J K^{-1} mol^{-1}).



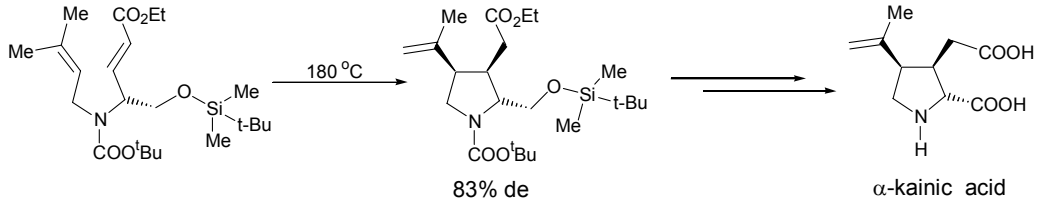
Scheme 19

The most common types of intramolecular carbonyl-ene reactions have been classified by Oppolzer as Type I, Type II and Type III cyclisations. The terminology refers to cyclisations where the enophile is linked by an appropriate bridge, either to the olefinic terminal (Type I), the central atom (Type II), or the allylic terminal (Type III) of the ene unit (Scheme 20).



Scheme 20

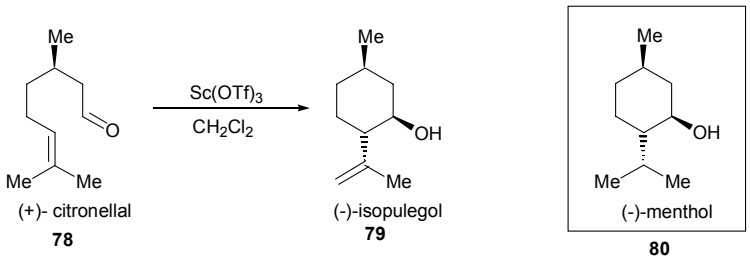
Using enantiopure starting materials, diastereoselective control of Type I cyclisations have been reported. Oppolzer's synthesis of α-kainic acid is an elegant example of relative asymmetric induction; the high selectivity of this example can be attributed to the steric bulk of the TBDMS group, Scheme 21.



Scheme 21

Aggarwal *et al.*[31] used scandium triflate to catalyse the intramolecular cyclisation of (+)-citronellal, **78** (Scheme 22). This reaction, to form isopulegol, **79**, is an important step in the industrial synthesis of (-)-menthol, **80**. Present methods use 1 equivalent of zinc bromide in benzene to catalyse the reaction, giving a single isomer in 70% yield and high selectivity for (-)-isopulegol (a ratio of 94:6 of

isopulegol to other isomers). The enantiomeric purity can be raised to 100% ee by recrystallisation. Most other Lewis acids have been reported to give the product in moderate yields and selectivity. Aggarwal found that using scandium triflate allowed the catalyst loading to be significantly lowered to as little as 5 mol%, Table 4. It was also possible to recover and reuse the catalyst by aqueous extraction without loss in yield and diastereoselectivity. Aggarwal's use of scandium triflate for intermolecular olefin-aldehyde reactions will be discussed in detail later.



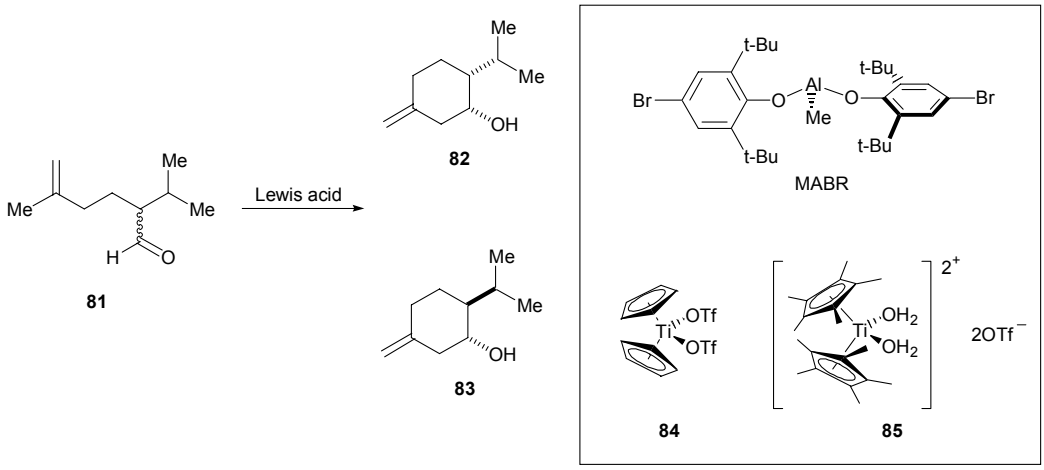
Scheme 22

Table 4 Scandium triflate catalysed intramolecular reaction of citronellal.

Entry	mol% $Sc(OTf)_3$	Temp/ °C	Time/ h	Isolated yield / %	Ratio of isopulegol : other isomers
1	0	25	8	0	–
2	5	25	2	58	80:20
3	10	-40	0.5	86	88:12
4	10	-78	1	>95	94:6
5	5	-78	1.5	>95	94:6

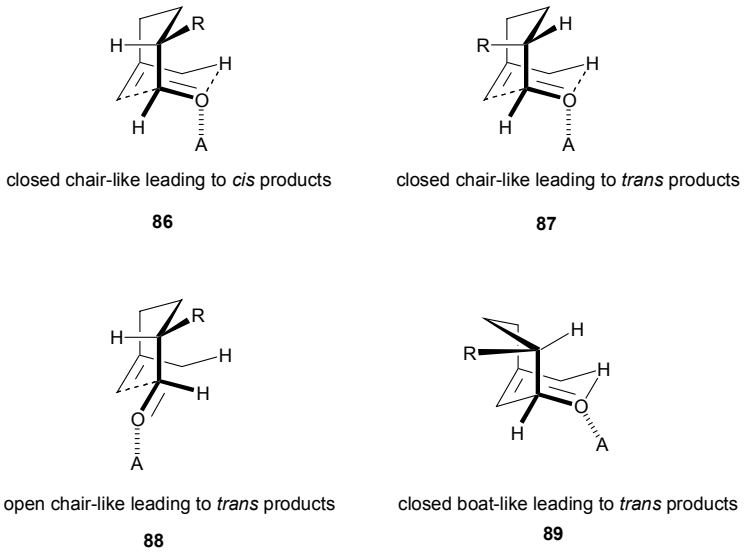
Brown *et al.*[32] used BCl_3, $SnCl_4$, methyl-aluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide (MABR), $Sc(OTf)_3$ and titanocenes **84** and **85** as catalysts in the intramolecular carbonyl ene-reactions of aldehyde **81** (Scheme 23). Using BCl_3

and $SnCl_4$ as catalysts, the intramolecular carbonyl-ene reaction of **81** proceeded to yield a 9:1 ratio of **82** to **83** as also reported by Snider and co workers (Scheme 23). The selectivity was rationalised by Snider as going through "closed" chair-like transition states **86** and **87**, Figure 4. When the bulky MABR catalyst was used, a highly selective reaction occurred with opposite stereochemical preference, as reported by Yamamoto. The results were explained using an open transition state **88**.



81 **82** **83** **84** **85**

Scheme 23



closed chair-like leading to *cis* products **86**

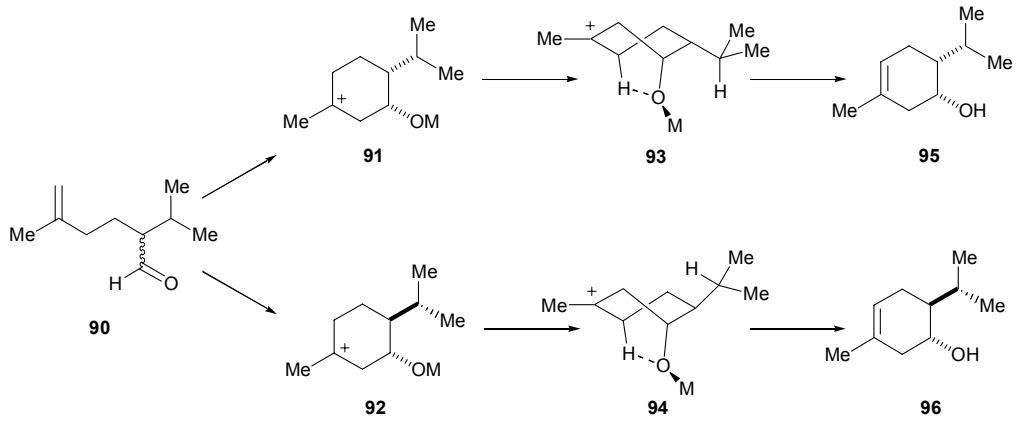
closed chair-like leading to *trans* products **87**

open chair-like leading to *trans* products **88**

closed boat-like leading to *trans* products **89**

Figure 4

However, Brown showed experimentally by deuterium labelling that the open transition state **88** was not a viable explanation and a closed boat-like transition state **89** was applicable instead. Evidence for the open transition state was provided in the reaction of **90** using $Sc(OTf)_3$ and titanocenes **84** and **85** (Scheme 24). Here instead of the "normal" ene products **82** and **83**, ene products with an internal alkene, **95** and **96**, were formed.

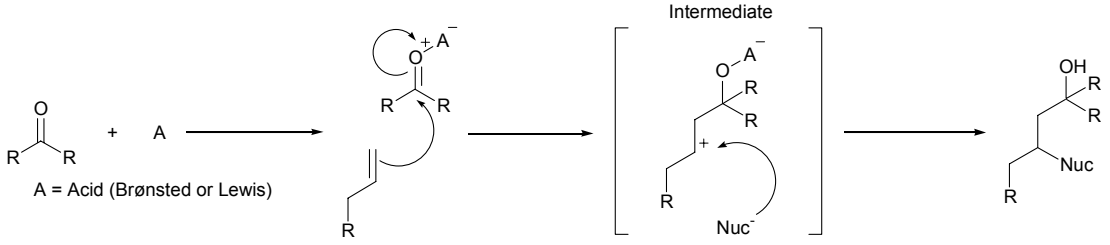


Scheme 24

Brown rationalised this as the formation of the methylcyclohexyl cations (**91** and **92**) that exist in twist-boat conformations (**93** and **94**). These are achieved *via* an initial open transition state (**88**). Carrying out standard Prins acid-promoted reactions using Amberlyst 15 or *p*-TsOH gave a complex mixture, including **82**, **83**, **95**, and **96**. They concluded that unlike the wholly stepwise Prins reactions, the Lewis acid catalysed reactions occurred *via* controlled proton transfer.

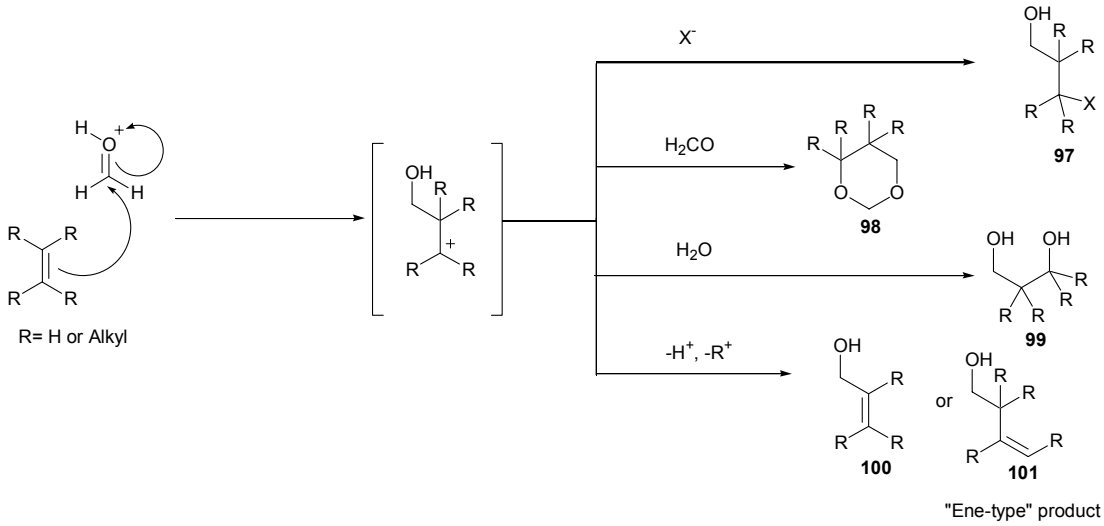
The Prins reaction

The Prins reaction is closely related to the carbonyl-ene reaction. The Prins reaction is the acid promoted / catalysed addition of an olefin to a carbonyl compound with the formation of a carbocation intermediate (Scheme 25).[6-8] This intermediate can be attacked by a nucleophile giving a substituted alcohol.



Scheme 25

Early Prins-type reactions involved the reaction of a simple olefin with formaldehyde in the presence of a mineral acid to give a mixture of four products, whose relative yields depend on the exact reaction conditions (Scheme 26).



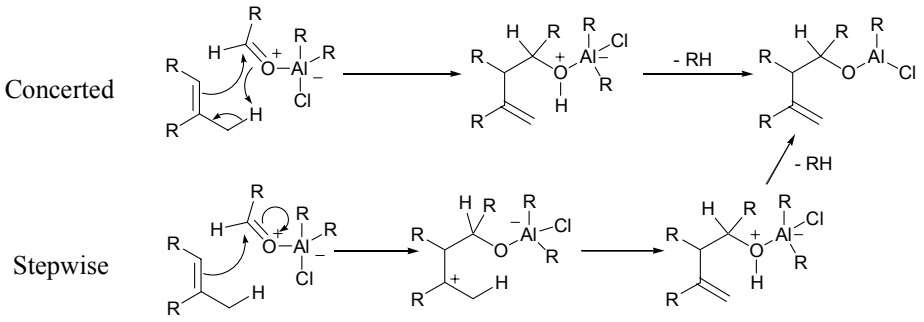
Scheme 26

Early reviews of Prins chemistry have predominantly focused on the synthesis of 1,3-dioxanes (**98**) due to considerable industrial interest into their physical properties at the time, and they will not be discussed here.[8]

The dividing line between the ene and the Prins reaction is narrow, mention of this has been made elsewhere. "Ene-type" products are seen in Prins reactions, especially cyclisations. This occurs where loss of a proton can occur to give a homoallylic alcohol (101). In the literature, there is significant overlap between Prins and ene chemistry and for the purposes of this thesis some clarification must be given. A number of reports describe ene reactions, when Prins-products are formed and *vice versa*. Much of this can be seen in Snider's use of trimethyl aluminium and alkyl aluminium halides as catalysts in both ene and Prins reactions. Here, small changes in Lewis acid, ene or enophile can completely change the products.

Snider reports the decreasing trend of Lewis acidity in the series of reagents, to be: $AlCl_3$>$EtAlCl_2$>Me_2AlCl>Me_3Al.[33] $EtAlCl_2$ and Me_2AlCl have also been reported to act as proton scavengers, losing ethane and methane respectively.[34]

As in many other examples, whether the reaction is stepwise or concerted is generally elucidated from the products obtained from the reaction, and evidence for both mechanisms can be found (Scheme 27).

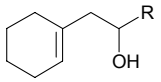
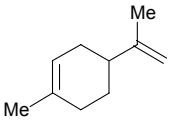
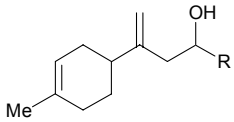
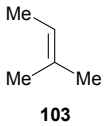
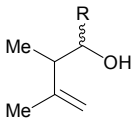
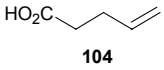
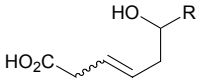


Scheme 27

Snider put forward the hypothesis that acting as proton scavengers, these reagents reduce the side reactions and hence the number of by-products that are seen when $AlCl_3$ is used.[35] However, they cannot strictly be classed as catalysts, as Snider repeatedly does, due to the fact that they are not unchanged during the course of the reaction.

Both Me_2AlCl and $EtAlCl_2$ have been shown to be capable of producing "ene-type" products in good yield in the reaction of mono-, 1,1-di-, and trisubstituted alkenes with alkyl and aryl aldehydes, Table 5. In common with the Mikami titanium-BINOL system, these results show that the alkyl aluminium halides give optimum yields with more reactive 1,1-disubstituted nucleophilic alkenes, such as methylene cyclohexane, **25**. However, unlike both the Mikami and Evans' systems, less activated enophiles, such as *t*-butanal (R = $C(CH_3)_3$) and long chain aliphatic aldehydes, such as nonanal (R = *n*-C_8H_{13}) and heptanal (R = *n*-C_6H_{13}) can be employed. Whilst trisubstituted and mono-substituted alkenes (**102-104**) do indeed react, yields are lower as these alkenes are less nucleophilic.[36,37]

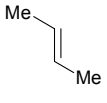
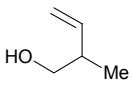
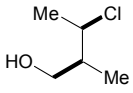
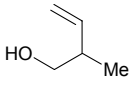
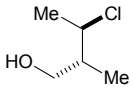
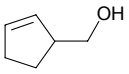
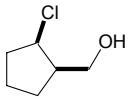
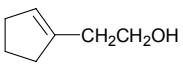
Table 5 Alkyl aluminium halide catalysed carbonyl-ene reactions

Entry	Alkene	Promoter	Products	Aldehyde RCHO (% Yield)
1	 **25**	Me_2AlCl		R = H (80) R = CH_3 (91) R = $CH_2CH(CH_3)_2$ (74) R = Ph (69) R = $C(CH_3)_3$ (93)
2	 **102**	Me_2AlCl		R = CH_3 (65) R = $CH_2CH(CH_3)_2$ (79)
3	 **103**	Me_2AlCl		R = CH_3 (56) R = $CH_2CH(CH_3)_3$ (38) R = *n*-C_8H_{17} (42)
4	 **104**	$EtAlCl_2$		R = CH_3 (60), (*E*):(*Z*) = 4:1 R = *n*-C_6H_{13} (41), (*E*):(*Z*) = 4:1

It was found that chlorohydrins were formed in significant quantities in the dimethyl aluminium chloride promoted reactions of formaldehyde and alkenes,[38] capable of forming secondary carbocations (e.g. **105**, **108** and **110**, Table 6). Similarities with the incorporation of chloride into the products of Lewis acid mediated Prins reactions led Snider to conclude that these dimethyl aluminium chloride promoted reactions were stepwise (Entries 1, 3 and 5). No evidence of tertiary chloride formation was found using olefins capable of forming tertiary carbocations. Increasing the amount of Lewis acid used, from 1 to 1.5

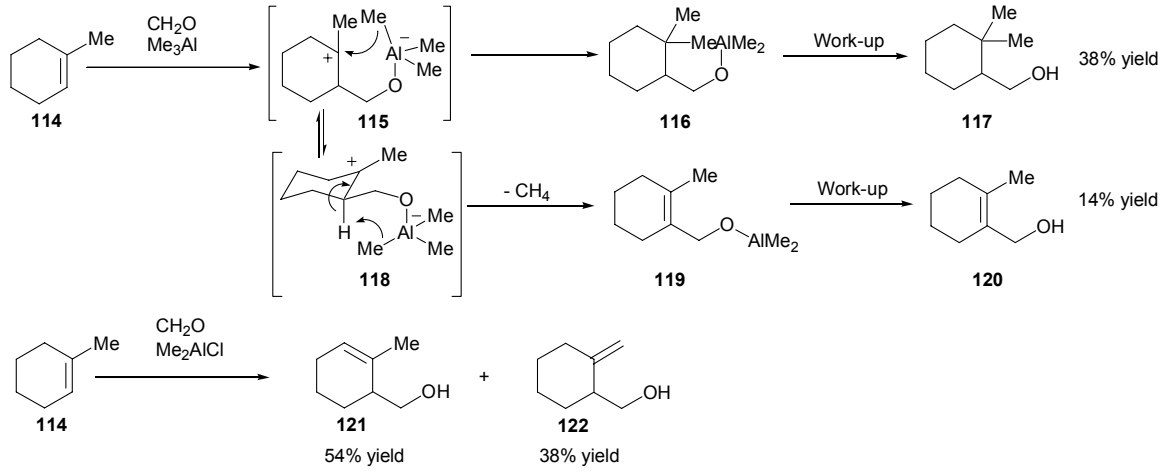
equivalents, caused a significant increase in the yield of the ene-adduct and a corresponding drop in the yield of chlorohydrin (Entries 2, 4 and 6).

Table 6 Formation and suppression of chlorohydrin products using Me_2AlCl.

Entry	Alkene	Equivalents Me_2AlCl	Products (% yield)		
	 **105**		 **106**	 **107**	
1		1	20	50	
2		1.5	58	1	
	 **108**		 **106**	 **109**	
3		1	20	39	
4		1.5	73	2	
	 **110**		 **111**	 **112**	 **113**
5		1	7	39	1
6		1.5	44	4	10

Me_3Al was examined for its suitability as a promoter in the carbonyl-ene reaction, and to see if generation of chloride containing by-products could be avoided.[33] However, it was found that Me_3Al promoted a Prins reaction, with one of the methyl groups acting as a nucleophile to give the gem-dimethyl

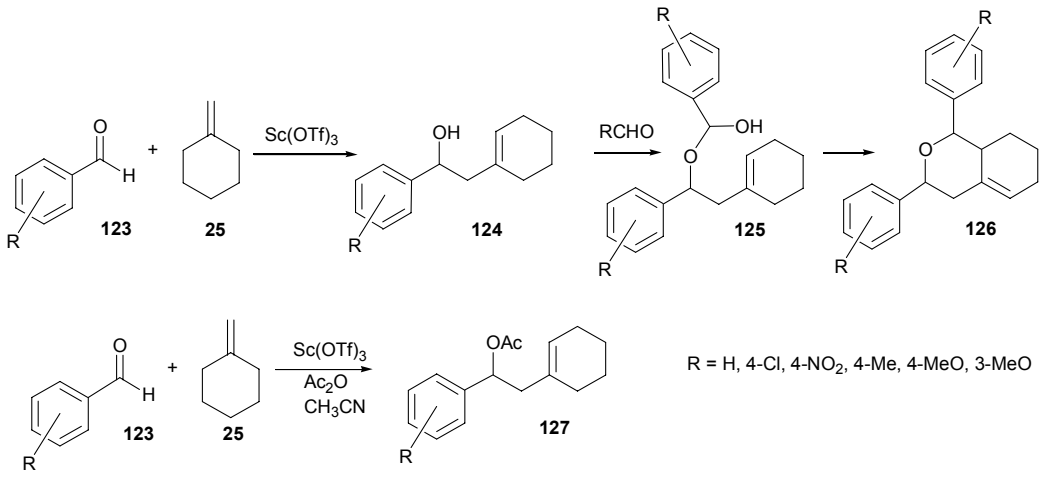
product **117** (more commonly seen with metal halides, *vide infra*) or the allylic alcohol **120.** The allylic alcohol was obtained *via* proton abstraction, **118**, and loss of methane (Scheme 28). Ene-reactions are stated as involving migration of a π-bond. However, **120** has the π-bond in the same position and **117** does not have a π-bond. Therefore, the reaction of formaldehyde and 1-methyl-cyclohexene, **114** in the presence of Me_3Al cannot be an ene-reaction. Using Me_2AlCl yields the ene products **121** and **122**, with a greater predominance for the endocyclic homoallylic alcohol.



Scheme 28

Aggarwal *et al.*[31] published results using scandium triflate as a catalyst in the intermolecular-ene reaction between methylene cyclohexane, **25**, and a range of un-activated aromatic aldehydes, **123** (Scheme 29). During their study, it was found that under the reaction conditions, the ene-product, **124**, would react with further aldehyde to give the complex pyran **126**. Aggarwal used the catalytic acylation of alcohols by scandium triflate with acetic anhydride in acetonitrile to trap the ene-type products, **127**. Highly electron-rich or poor aromatic (R = 3-MeO, 4-MeO, 4-NO_2) aldehydes give poor yields (29%, 0% and 40%

respectively). Benzaldehyde or mildly electron-rich or poor aromatics (R = H, 4-Me, 4-Cl) give much better yields (73%, 61% and 75% respectively).

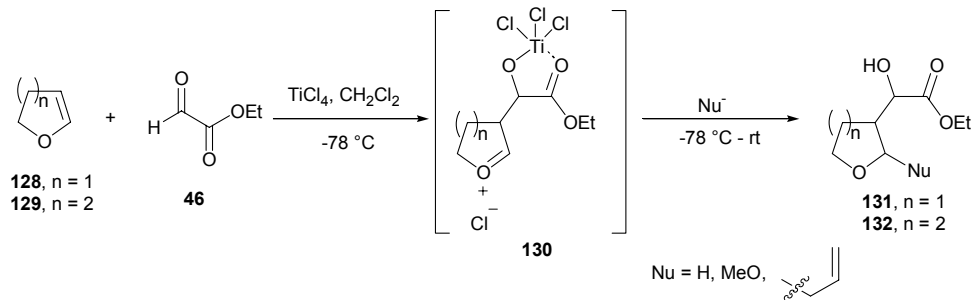


123 25 124 125 126

123 25 127

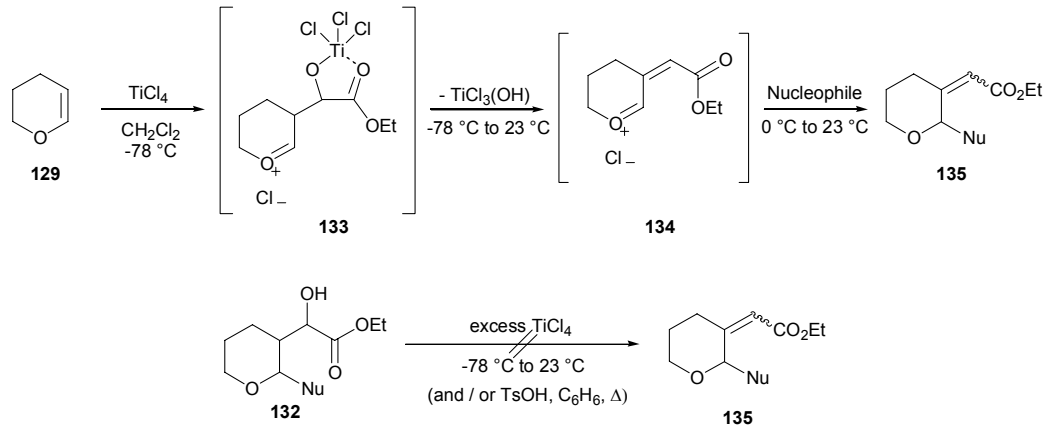
Scheme 29

The reaction of an enol ether with an aldehyde results in a hetero-Prins reaction, in relation to the hetero-ene reaction, *vide supra*. In a similar vein to the reporting of hetero-ene reactions, Ghosh and Kawahama[39] reported their efforts as, "$TiCl_4$ promoted three component coupling reactions", not as Prins-related reactions. The stepwise intermolecular Prins reactions of dihydropyran, **128**, and dihydrofuran, **129**, with ethyl glyoxylate, **46**, and subsequent addition of a nucleophile are a major departure from previously reported intermolecular Prins reactions (Scheme 30). The presence of the oxygen allows the formation of an oxonium ion, **130**, which stabilises the reaction intermediate. Most intermolecular Prins reactions reported in the literature involve nucleophilic attack by a component of the acid used to promote the reaction, e.g. Cl^- from a Lewis acid of type MCl_n or from HCl. Addition of triethylsilane, methanol and allyl trimethylsilane introduce H, MeO and allyl functionality respectively at the 2-position.



Scheme 30

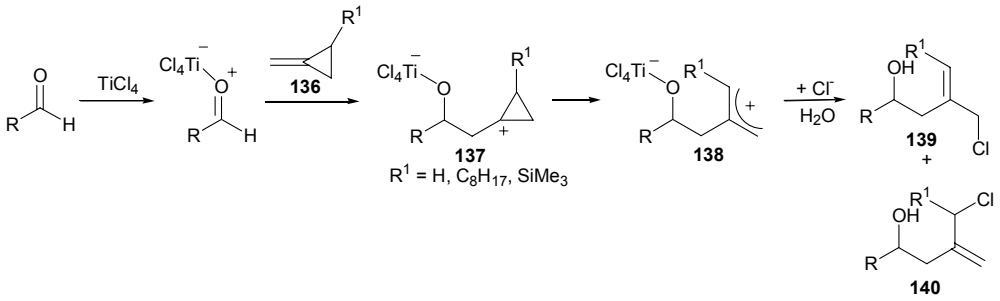
Ghosh found that warming the reaction to room temperature and subsequent cooling before adding the nucleophile, caused dehydration to give substituted tetrahydropyrans[40] **135** (Scheme 31). Interestingly, when the original α-hydroxymethyl-tetrahydropyrans, **132**, were subjected to excess $TiCl_4$ at -78°C to 23°C, *p*-toluene sulphonic acid and / or camphorsulphonic acid refluxing in benzene, the starting material was recovered and dehydration did not occur.



Scheme 31

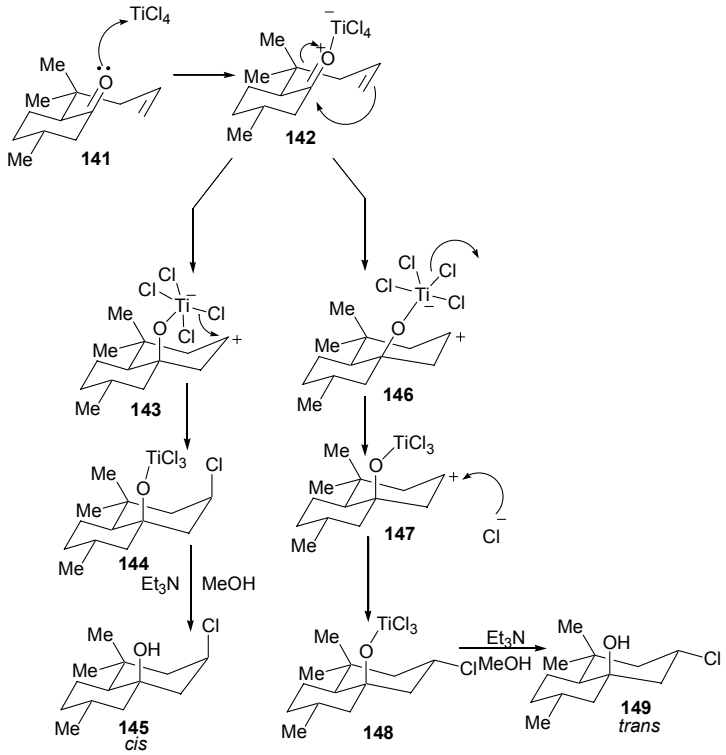
Methylenecyclopropanes, **136**, have been used by Hosomi[41] in intermolecular Prins reactions with aldehydes and by Kilburn intramolecularly, *vide infra*. The cationic cyclopropane intermediate, **137**, opens to give a π-allyl cation, **138**, which is attacked by chloride (Scheme 32). Yields were good to moderate with aliphatic aldehydes, but poor with aromatic aldehydes and ketones other than

methylene cyclohexanone. When R = H, **139** is found to be the sole product, however, methylenecyclopropanes with alkyl or TMS R-groups gave a mix of products **139** and **140**, presumably from stabilisation of the positive charge at the substitution point rather than at the terminus of the allyl system.



Scheme 32

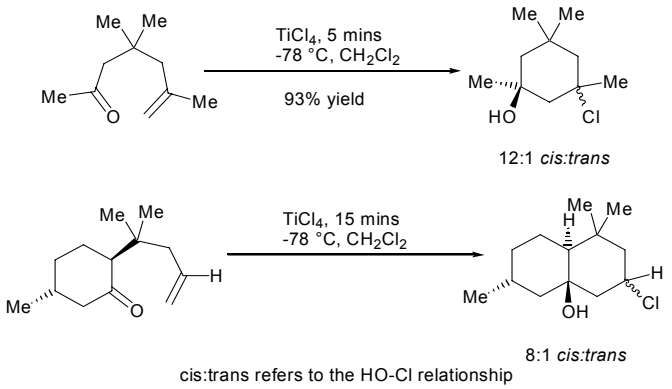
The most common Prins cyclisations are those in which the intermediate undergoes attack by a chloride ion, resulting in the formation of a chlorohydrin. This chloride ion attack occurs with both HCl and chlorinated Lewis acids, e.g. $TiCl_4$, $SnCl_4$, etc. (Scheme 33). The Lewis acid activates the carbonyl (**141**), which then undergoes attack by the olefin (**142**). Chloride incorporation can occur *via* intramolecular attack by chloride (**143**) or loss of Cl^- followed by attack (**146**-**147**), which after work-up gives *cis*- and *trans*-chlorohydrins **145** and **149**.



Scheme 33

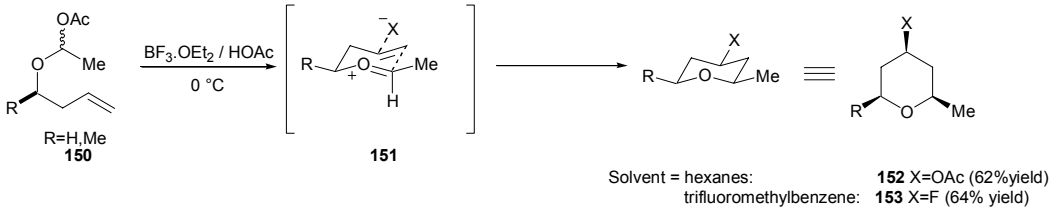
Coates and Davis[42] have investigated this process and argued that intramolecular transfer of the chloride, **143** (to give the "cis" product) from the titanium was

faster than loss of chloride and subsequent attack, as shown in **146-147** (giving the "*trans*" product, Scheme 34).



Scheme 34

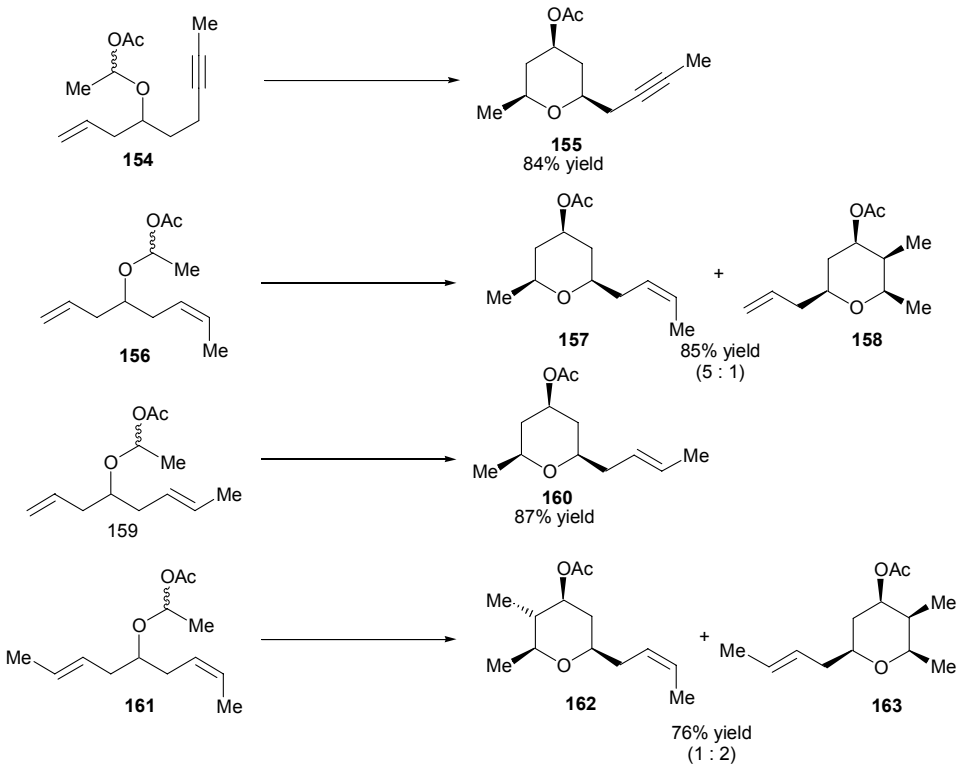
This incorporation of a halide from the Lewis acid is common in transition metal catalysed Prins reactions using MX_n. Using boron trifluoride etherate, Rychnovsky[43] found that fluoride incorporation in the Prins reaction of **150** could be suppressed by using non-polar solvents (yielding **152**) and, conversely, promoted by polar solvents (to give **153**). Using hexanes and premixing $BF_3.OEt_2$ and acetic acid gave incorporation of OAc. (Scheme 35). The highly stereoselective nature of the reaction arises from cyclisation *via* a chair-like transition state, **151**, with the substituents of the incipient THP ring preferring pseudo-equatorial positions.



Scheme 35

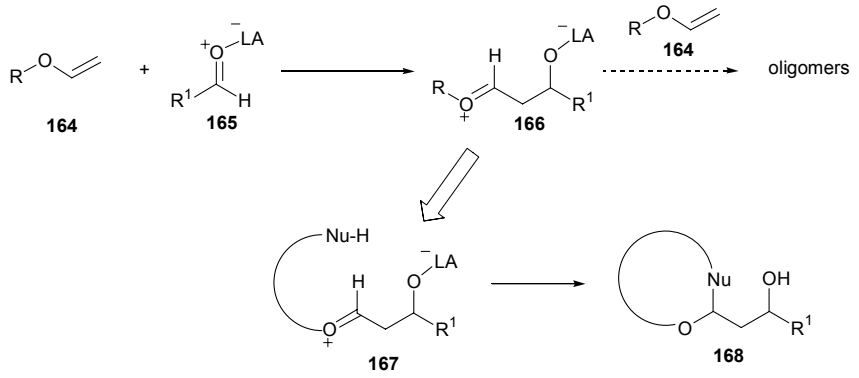
Rychnovsky also examined the regioselectivity of the Prins cyclisation in more complex adducts with multiple alkene functionality (Scheme 36), with the possibility of reaction at more than one site and therefore producing a mix of products.

It was found that with vinyl alkenes *vs.* alkynes (**154**) and *E*-alkenes (**159**) reaction occurred predominantly at the terminal alkene to give products **155** and **160**. However, *Z*-alkenes (**156**) gave a 5:1 mix (**157**:**158**) of products in favour of reaction at the terminal alkene, and cyclisation of a *Z*- *vs.* an *E*-alkene (**161**) favoured reaction at the *Z*-alkene to give **163** and **162** in a 2:1 ratio. The relative order of cyclisation is observed to be vinyl > *Z*-alkene > *E*-alkene > alkyne.



Scheme 36

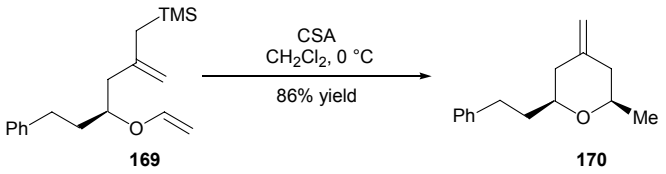
Rychnovsky and Kopecky applied the study of a hetero-Prins cyclisation cascade to a formal total synthesis of Leucascadrolide A.[44] Here, initial reaction of the enol ether **164** with aldehyde **165** gives intermediate oxonium **166**. This intermediate is a very reactive enophile and is therefore highly susceptible to reaction with more of the starting enol ether **164** to give oligomers (Scheme 37). In order to avoid this, Rychnovsky examined introducing a nucleophile (**167**) tethered to the oxygen of the enol ether that would trap the intermediate, giving a cyclic product (**168**). In this case, an alkene is used as the nucleophile, and thus this trapping reaction is itself a Prins reaction (loss of R^+, Scheme 27).



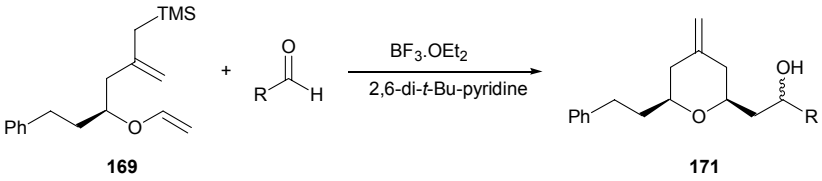
Scheme 37

Preliminary studies of terminal alkenes as trapping agents, lead to only partial suppression of the competing polymerisation. 1,1-Disubstituted alkenes bearing a TMS group, **169**, were then examined (Scheme 38) and it was found that in the presence of a protic acid, such as CSA, protonation followed by intramolecular cyclisation occurred preferentially give THP-**170** rather than the desired intermolecular reaction with another aldehyde, followed by cyclisation. However, in intermolecular Lewis acid catalysed reactions with aldehyde enophiles, this protonation was competitive with the desired cyclisation. Addition of 2,6-di-*tert*-butylpyridine was found to suppress this reaction giving the desired products (**171**) (Scheme 39). The reaction is very tolerant in respect

to the aldehyde used; aliphatic and aromatic-bearing aldehydes were all found to react in good yield (Table 7).

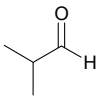
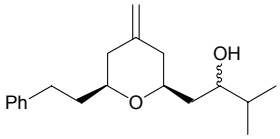
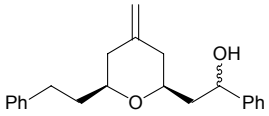
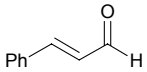
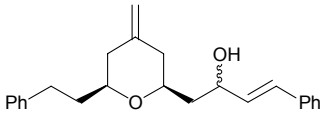
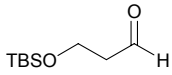
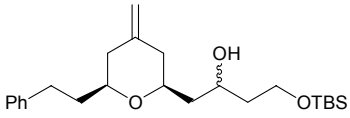
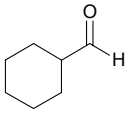
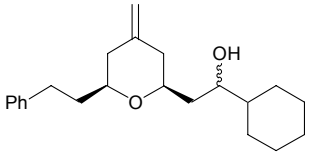


Scheme 38



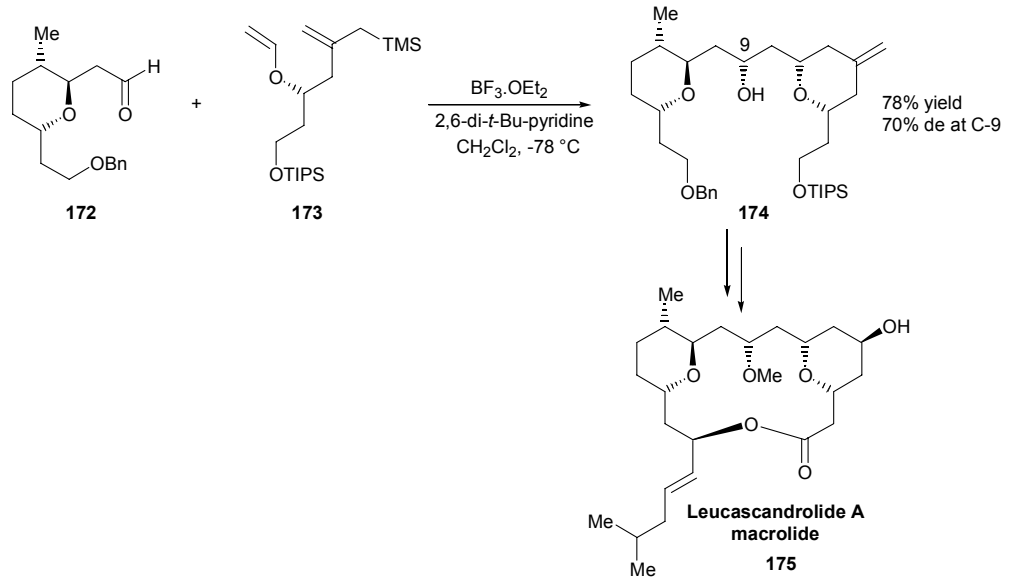
Scheme 39

Table 7 Intermolecular Prins reaction with intramolecular trapping.

Entry	Aldehyde	Yield	Product
1		98%	
2		84%	
3		87%	
4		87%	
5		72%	

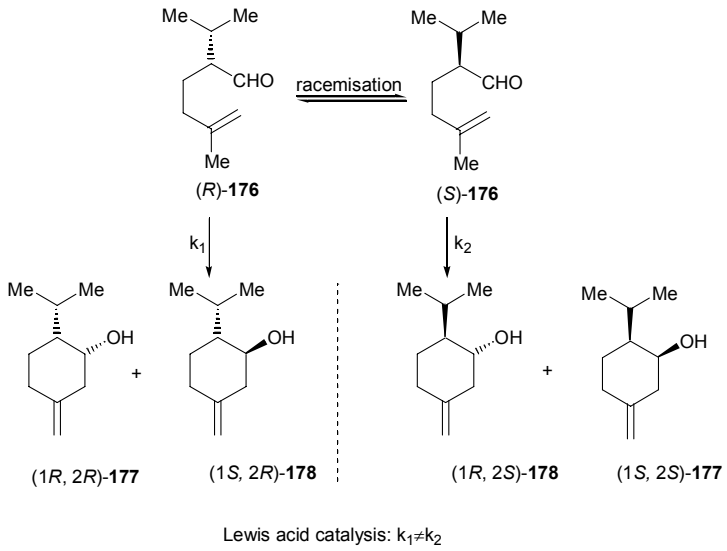
In work towards the total synthesis of leucascandrolide A, Rychnovsky used chiral aldehyde **172** to induce diastereoselectivity, giving **174** with a 70% de.

The framework was then elaborated to give leucascandrolide A macrolide, **175**; the side chain for leucascandrolide A can then be attached in two steps, representing a formal total synthesis (Scheme 40).



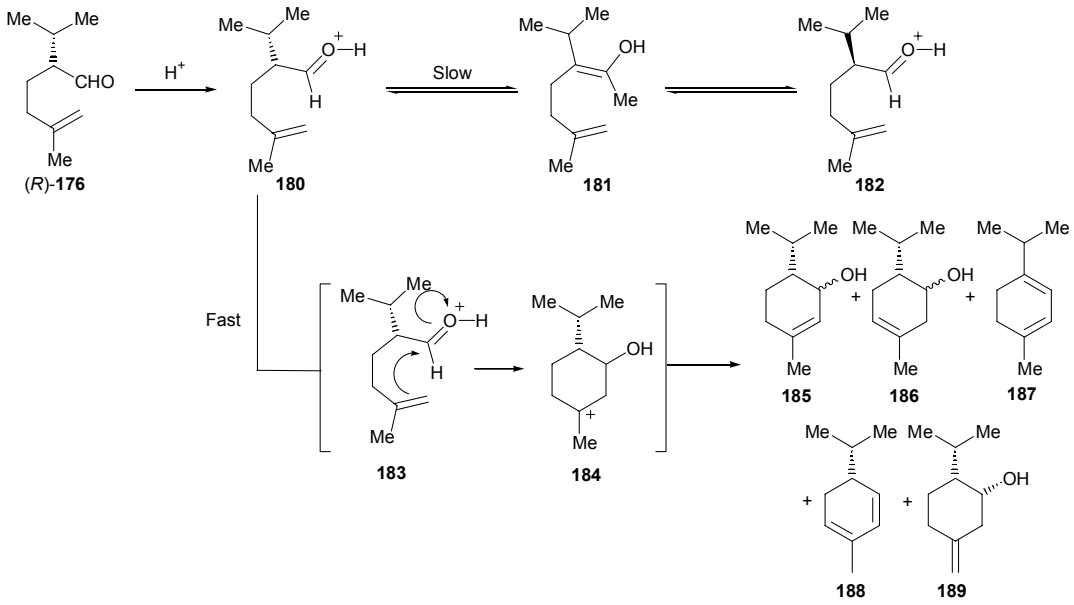
Scheme 40

The close relationship between Prins and Ene chemistry was noted by Brown, whilst examining the possibilities of a dynamic kinetic resolution (DKR) being incorporated into the Type II ene cyclisation of 2-isopropyl-5-methylhex-5-enal, **176** (Scheme 41).



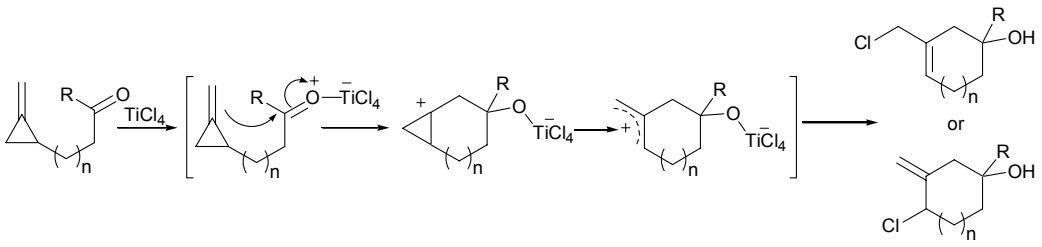
Scheme 41

Various acidic reagents were examined to affect the racemisation without inhibiting the alkyl-aluminium catalyst. Unfortunately, those reagents that were shown to have any activity at all (Amberlyst 15 and *p*-Tosic acid), in fact lead to the Prins cyclisation of the protonated aldehyde. This is an example of protonation of the aldehyde allowing the Prins cyclisation (**180** → **184**) to occur faster than racemisation of the aldehyde (**180** → **182**) (Scheme 42). A complex mixture was isolated, containing products of the Prins cyclisation resulting both from proton loss, to give allylic (**185**) and homoallylic alcohols (**186** and **189**), and dehydration to give conjugated dienes (**187** and **188**).



Scheme 42

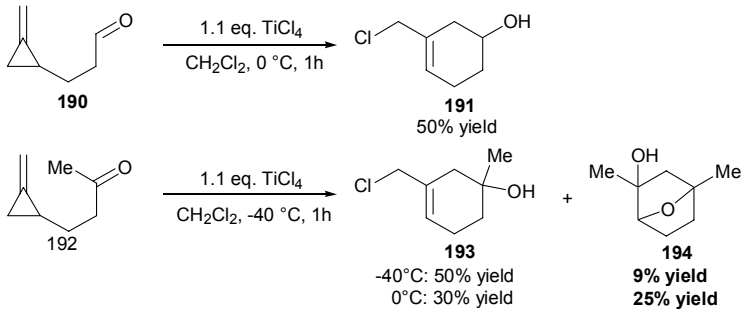
Kilburn *et al*.[45] investigated the intramolecular Prins-cyclisation of methylene cyclopropyl ketones, aldehydes and ketals with $TiCl_4$ and $SnCl_4$. Kilburn proposed an analogous mechanism to that put forward by Hosomi, *vide supra*, when considering the intermolecular Prins reaction of methylene cyclopropanes (Scheme 43).



Scheme 43

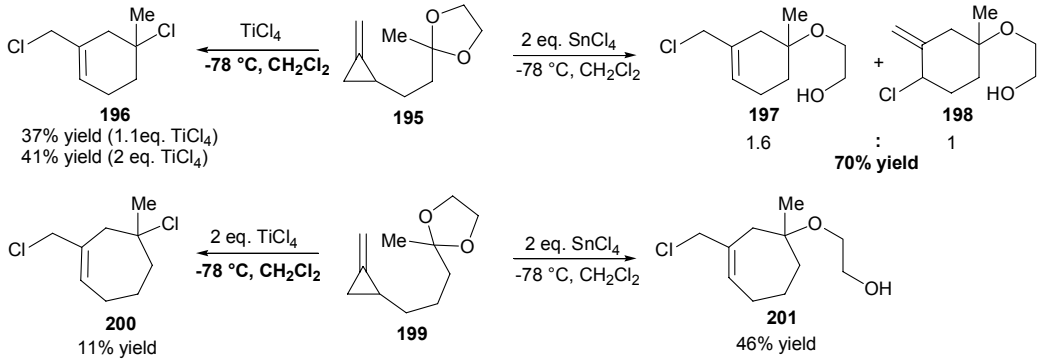
Kilburn found that with $TiCl_4$, aldehyde **190** gave exclusively cyclohexene **191**, although in moderate yield. Altering the temperature had an adverse effect on the yield. Using $SnCl_4$, $BF_3.OEt_2$ or $ZnCl_2$ gave very low yields, a complex mix

of products, or no reaction, respectively. Ketone **192** showed similar reactivity towards a similar range of Lewis acids and showed no reaction with Et_2AlCl, $EtAlCl_2$ and HCl. At 0 °C significant quantities of bicyclic alcohol **194** were found, presumably from intramolecular trapping of the intermediate allyl cation by the alkoxide (Scheme 44).



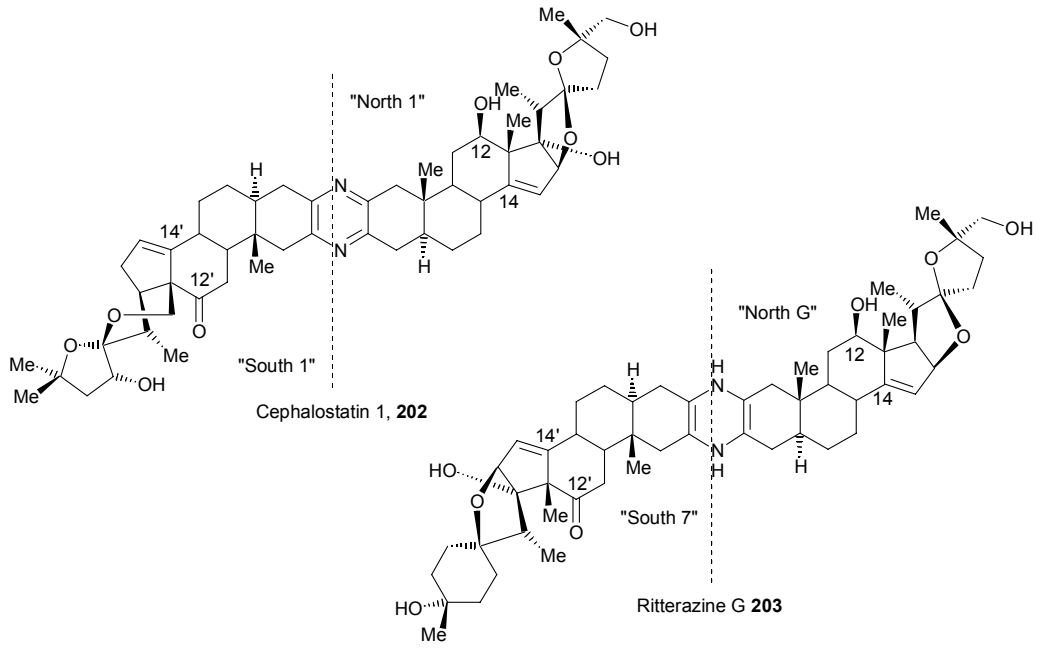
Scheme 44

Treatment of ketals **195** and **199** by Kilburn with $TiCl_4$ gave dichlorides **196** and **200**, requiring greater equivalents of $TiCl_4$ to increase the yield (Scheme 45). When the same reaction was carried out with $SnCl_4$, higher yields of **197** and **198** were obtained and in the cycloheptane forming reaction, a single regioisomer **201** was formed. The intramolecular Prins reaction using methylene cyclopropanes offers a novel route to functionalised cyclohexanes and cycloheptanes.



Scheme 45

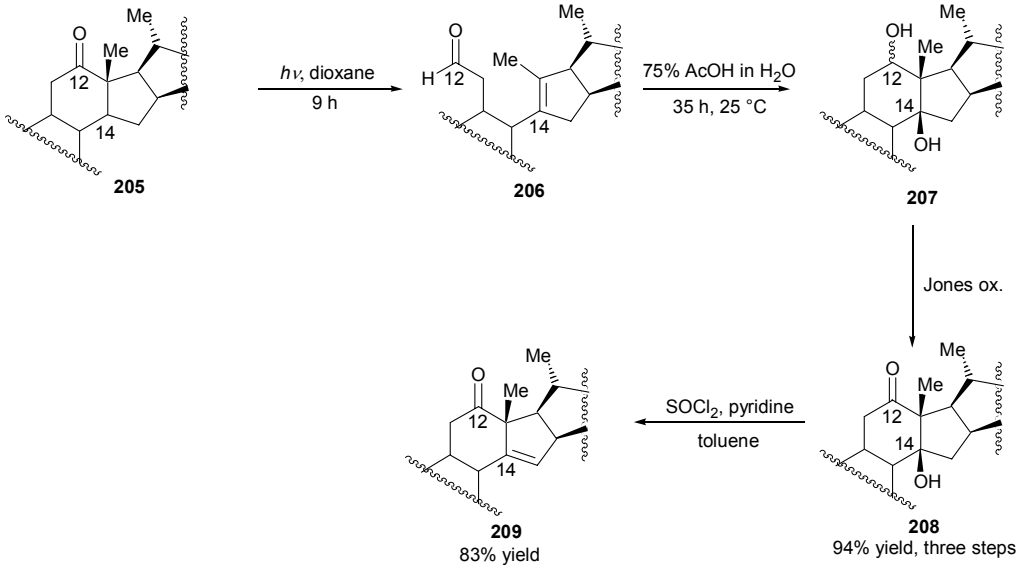
Prins cyclisations have been incorporated into the total synthesis of very complex targets. Fuchs[46] used an intramolecular Prins in the first total synthesis of cephalostatin 1, **202**, the north hemisphere of ritterazine G, **203** and analogue, ritterostatin G_N1_N, **204** (Scheme 46). Cephalostatin 1, **202**, is amongst the most powerful anticancer agents ever tested by the National Cancer Institute. Ritterostatin G_N1_N, **204**, a novel analogue developed by Fuchs, showed activity approaching that of taxol and superior to that of many standard chemotherapeutics.



Ritterostatin G_N1_N = "North 1" + "North G", **204**

Scheme 46

The Prins reaction was used in the assembly of the C12-C14 section in the northern hemisphere and C12'-C14' in the southern hemisphere (Scheme 47). Starting from **205**, photolysis yields the δ,ε-unsaturated aldehyde **206**. Subsequent intramolecular Prins cyclisation of the crude mixture followed by immediate Jones oxidation of dihydroxy **207** gave keto alcohol **208** in 94% yield over three steps. Dehydration to the keto olefin **209** proceeded in 83% yield.



Scheme 47

Conclusions

The carbonyl-ene and Prins reaction have been shown to be efficient methods for carbon-carbon bond formation, and recent developments of asymmetric variants have extended the scope and applicability of these reactions to pertinent synthetic problems. Whilst the carbonyl-ene reaction is much studied and reported on, the Prins reaction, due to the range of possible products from varying conditions, has remained relatively underdeveloped and often misreported. However, properly developed, this reaction has been shown to be key in accessing important synthetic targets.

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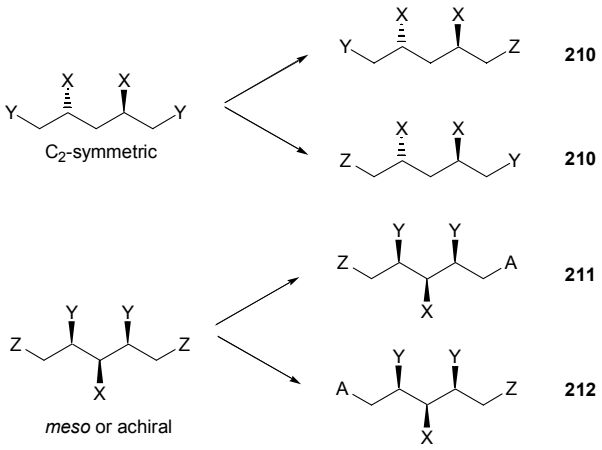
Chapter 2: Desymmetrisation

Desymmetrisation

Desymmetrisation is becoming a powerful tool in organic synthesis, especially with the continuing advances in enantioselective catalysis. There are two main types of desymmetrisation: With C_2 symmetric compounds, the functional groups of interest are homotopic, altering either group, Y, produces the same product (**210**, Scheme 48); hence, desymmetrisation relies on mono-functionalisation and can be achieved with simple achiral reagents. The functional groups in achiral or *meso*-molecules are enantiotopic, and the choice of one terminus, Z, over another will produce different enantiomers (**211** and **212** Scheme 48). Hence controlling the desymmetrisation of an achiral or *meso*-molecule requires the use of a chiral reagent, catalyst or enzyme. Whilst the numbers of enzymatic desymmetrisations are legion and will not be covered here, the number of non-enzyme based examples is steadily increasing. The following section will give a number of brief examples, focusing on enantioselective catalysis. For a recent review of desymmetrisation, see Willis and references therein.[1]

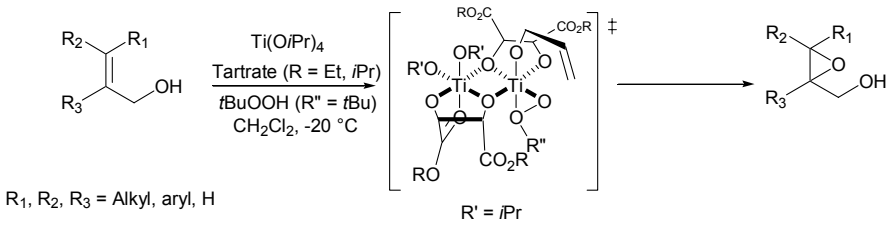


Scheme 48

Examples of Desymmetrisation

The Sharpless Asymmetric Epoxidation

The Sharpless asymmetric epoxidation[2] (SAE) has become one of the most widely studied enantioselective operations. It has been adapted to desymmetrisation and consequently applied to natural product syntheses. The standard SAE involves the epoxidation of an allylic alcohol using a chiral titanium catalyst formed from titanium tetraisopropoxide and either (+) or (–)-diethyl tartrate (Scheme 49). With the exclusion of water, using 3Å or 4Å molecular sieves and the use of 10-20 mol% excess of the tartrate ligand, the reaction is catalytic. Enantioselectivities for the SAE are generally in the region of 90-98% ee for simple allylic alcohols. Amongst prochiral allylic alcohols, enantiofacial selection can be seen to follow a general rule, which can be visualised using the Sharpless mnemonic (Figure 5): Placing the hydroxymethyl group to the lower right and the alkene vertically, (+) diethyl tartrate directs epoxidation to the bottom face, whilst (–) diethyl tartrate directs epoxidation to the top face. The reaction also benefits from the wide range of allylic alcohols that can be used, due in part to the fact that many functional groups tolerate the reaction conditions, Table 8.



Scheme 49

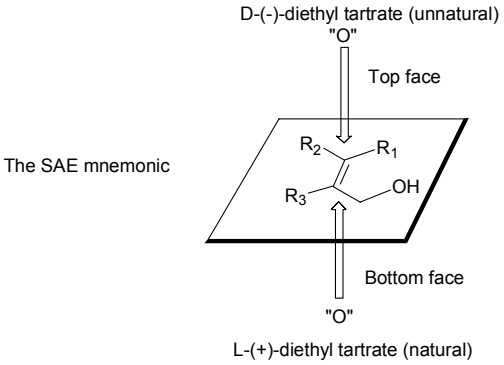


Figure 5

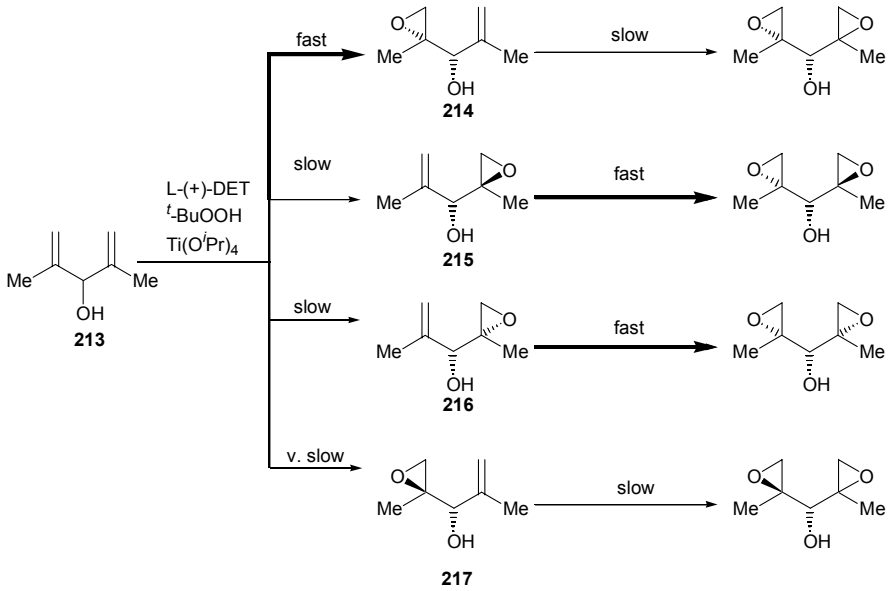
Table 8 Functional group tolerance of the Sharpless Asymmetric Epoxidation.[3]

Entry	Functional Group
1	–OH*, **
2	–OR (R = alkyl, benzyl, aryl)
3	–OCH_2OR, –OCR_2OR (including MOM*, MEM and THP acetals)
4	–OSiRR'R"
5	–OC=OR, –OCO_2R, –OCONRR'*, **
6	–OSO_2R
7	–NRC=OR', –NSO_2R, –NO_2, –N_3
8	–$P=OR_2$*
9	–$CH(OR)_2$, –$CR(OR')_2$
10	–C=OR, ** –CO_2R, –CONRR', –C(=NR)OR'
11	–CN
12	–CR=CR'R", –$CH=CHCH_2SiR_3$, –$CH=CRSiR_3$
13	–C≡CR, –$C\equiv CSiR_3$

* Enantioselectivity may be lower if this group is near the allylic alcohol.

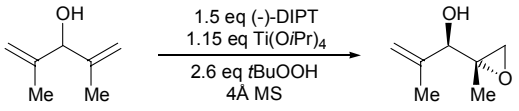
** Product may undergo *in situ* intramolecular cyclisation if this group is near the generated epoxide.

The SAE desymmetrisation relies on the relative rates of formation of the different products. An example of the SAE applied to desymmetrisation is epoxidation of divinyl alcohol **213** (Scheme 50). Only epoxy alcohol **214** is obtained in significant amounts, as the other products are "destroyed" as they are converted to their respective bis epoxide. The yield and enantiomeric excess are both high. The desymmetrisation involves both reagent control (by facial discrimination) and substrate control (as the *syn* epoxide is favoured). As **215** and **216** are destroyed, so the de of **214** will rise. Likewise, as **217** is destroyed, so the ee of **214** will rise.[4]



Scheme 50

Schreiber also showed that as the reaction progressed, percentage enantiomeric and diastereomeric enrichment increased with conversion and time and formulated a mathematical model to account for the selectivity. This was illustrated experimentally (Scheme 51).[4]

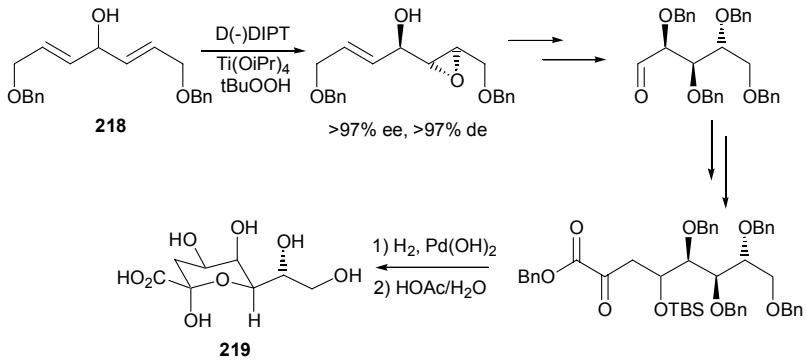


213 **215** 85% yield

Time (/h)	ee (/%)	de (/%)
0.5	88	99
1.0	94	99
1.5	99.3	99

Scheme 51

The SAE desymmetrisation has been applied to many natural product syntheses. Schreiber *et al.* applied it to the synthesis of 3-deoxy-D-manno-2-octulosonic acid ((+)-KDO) **219**, starting from alcohol **218** (Scheme 52). (+)-KDO is found in the cell walls of gram-negative bacteria and is essential for cell wall structure. As such, (+)-KDO has been the target of several total syntheses.



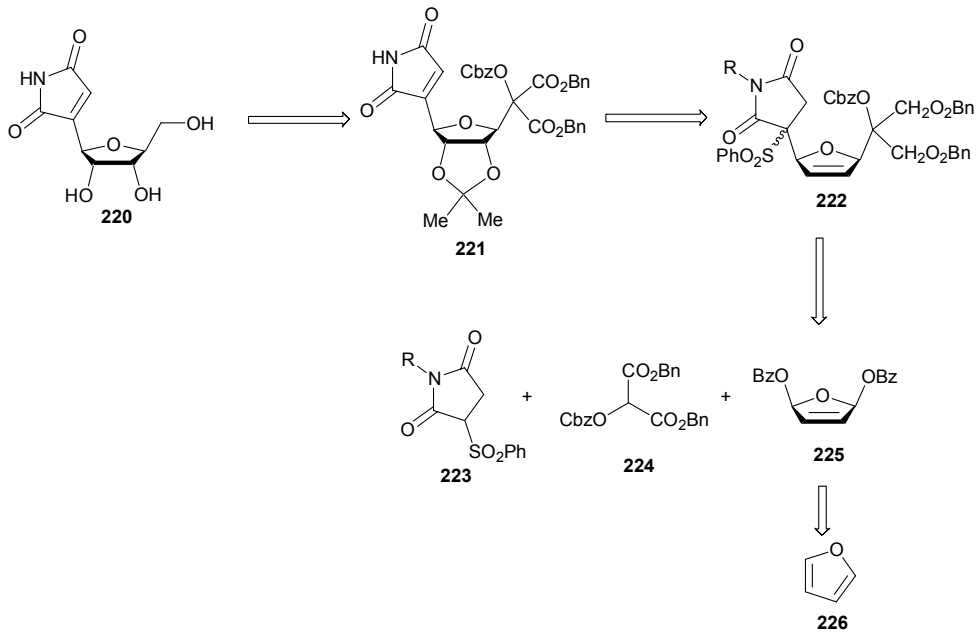
218 >97% ee, >97% de

219

Scheme 52

Schreiber was able to use the desymmetrisation early in the synthetic pathway, which set up the requisite stereochemistry so that further manipulations used this inherent stereochemistry without recourse to additional enantioselective reactions.

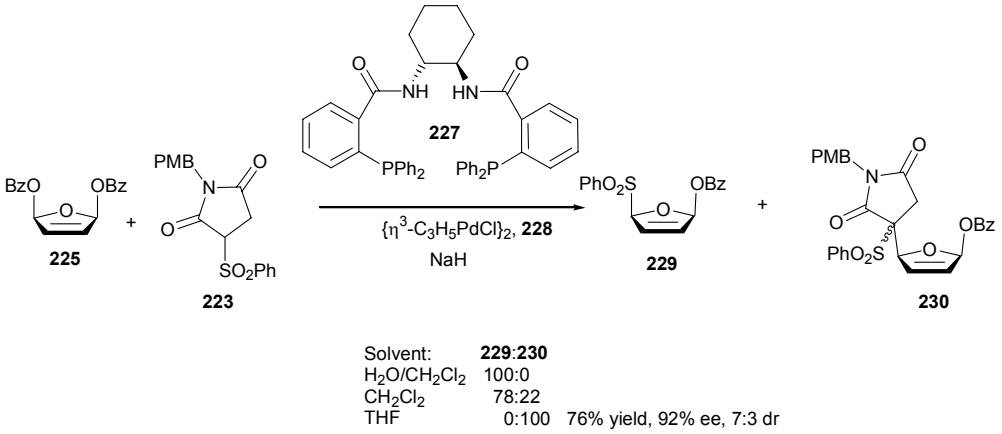
Trost has produced many examples of desymmetrising reactions. One example of this work has been his strategy towards syntheses of *C*-nucleoside analogues, beginning with the synthesis of the unnatural L-showdomycin,[5] **220** (Scheme 53). At the heart of this flexible strategy is the first reported carbon nucleophile desymmetrisation of a heterocyclic substrate. Whilst in this case sulphone **223** and malonate **224** were used as the nucleophilic components, the route allowed for the palladium-catalysed incorporation of different nucleophiles by the desymmetrisation of common intermediate **225** (Scheme 53). The double bond in the 3,4-position of dihydrofuran **222** also allows greater structural diversity to be attained if desired.



Scheme 53

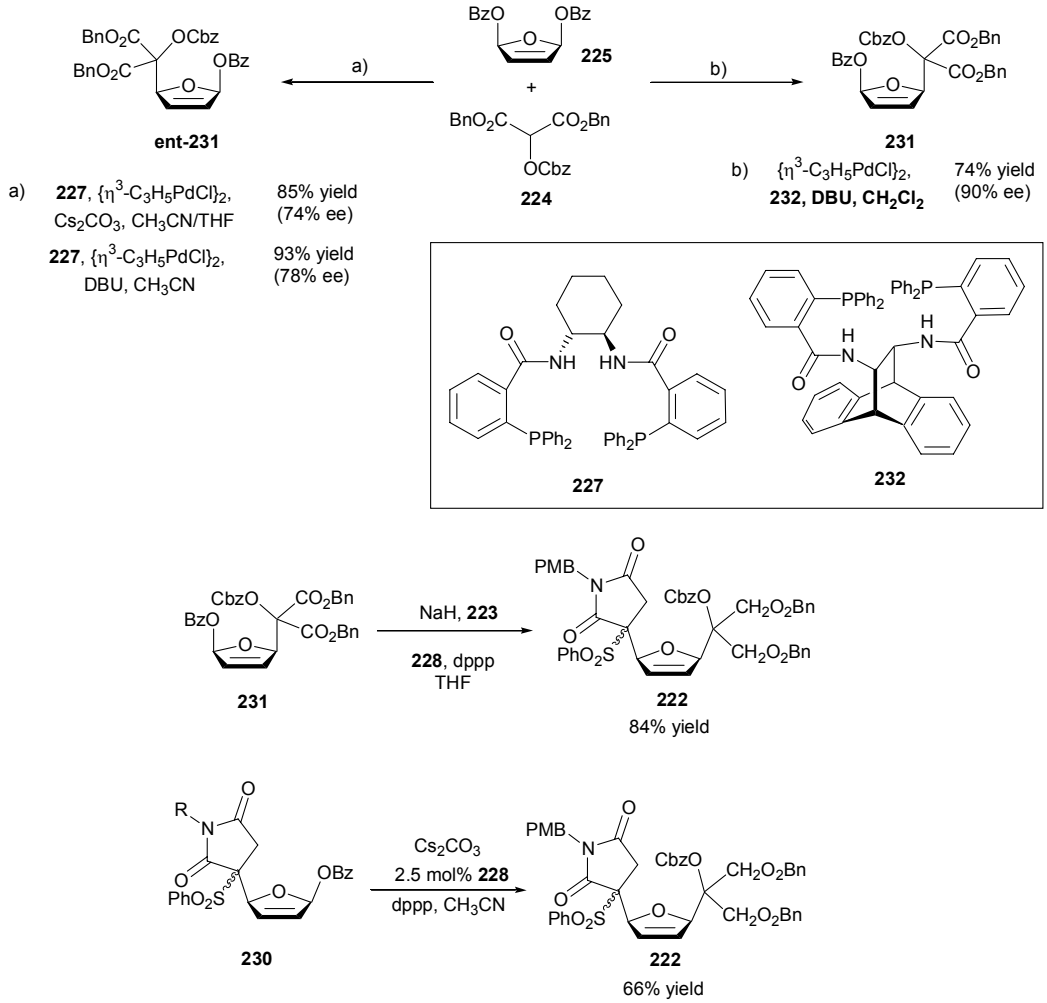
From *meso*-dibenzoate **225**, Trost examined the order of introduction of nucleophiles **223** and **224**. Solvent effects played an important role in the palladium-catalysed alkylation of **225** by *p*-methoxybenzyl-*N*-protected **223**

(Scheme 54). Polar protic solvents, such as water, led to the elimination of the sulphinate, which acted as a nucleophile. However, changing the solvent to THF led to exclusive formation of the desired product **230**. This product was obtained with high enantioselectivity, although the reaction was not optimised.



Scheme 54

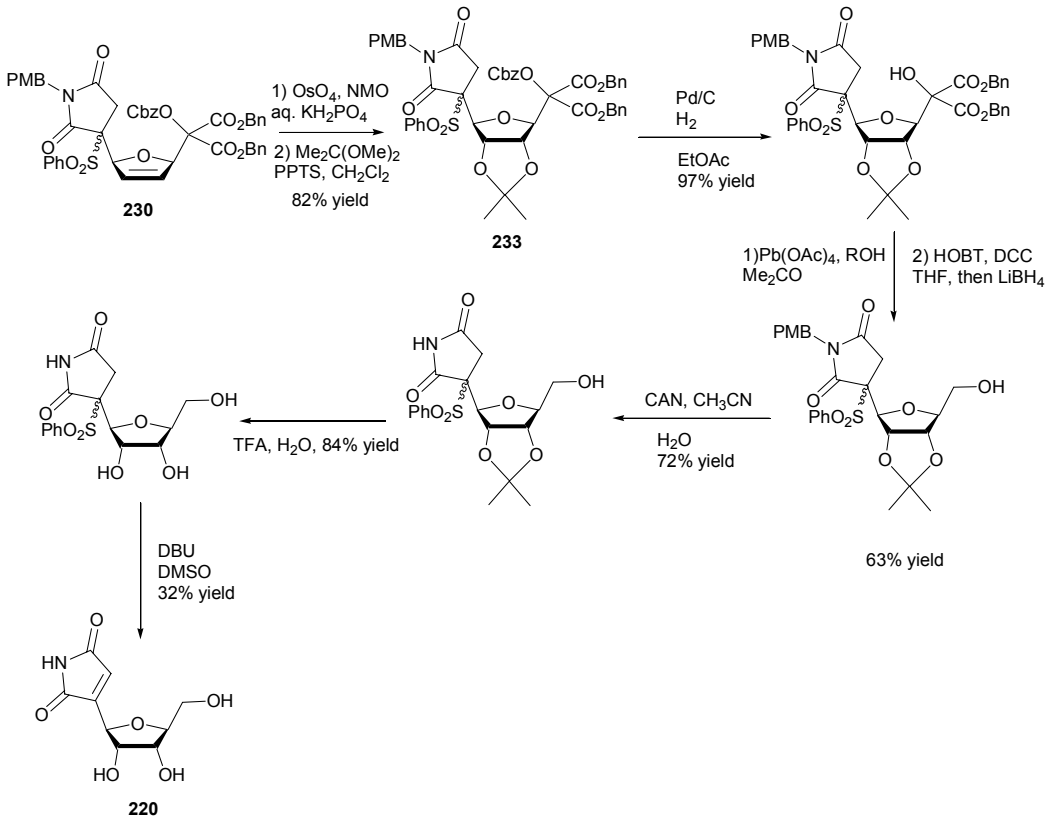
Next, the incorporation of the second nucleophilic fragment, dibenzoate **224**, was examined (Scheme 56). With C_2 symmetric cyclohexylamino-diphosphine ligand **227** and palladium allyl chloride dimer **228**, the addition of **224** occurred with the same sense as the addition of sulphone **223**, and yielded ***ent*-231**, which could be taken through to the natural D-showdomycin. However, changing to the more rigid bridged ligand **232** gave the desired product **231** in good yield and with much greater enantioselectivity. Addition of the remaining nucleophile fragment proceeded in better yield from dibenzoate **231** than from sulphone **230**.



Scheme 55

Subsequent catalytic dihydroxylation proceeded diastereoselectively due to steric constraints, and was followed by immediate protection of the diol as the acetonide to form **233**, (Scheme 56). Whilst using these conditions the Cbz group was removed cleanly by hydrogenolysis, the *p*-methoxybenzyl group resisted removal under the same conditions. Over two steps, the hydroxymethyl group was unmasked. Attempted removal of the sulphinate using DBU in the presence of the PMB group led over time to a mixture of endo- and exocyclic alkenes. Attempts to remove the PMB using ceric ammonium nitrate (CAN) after DBU removal of the sulphinate led to a complex mix of products. The order of deprotection was very important. Initial removal of the PMB by CAN followed by subsequent removal of the acetonide with TFA and then the

sulphinate by DBU led to the synthesis of **220**. The low yield of the final step is a problem in this synthetic route to natural and unnatural C-nucleosides, which has the potential for great diversity from the initial desymmetrisation.

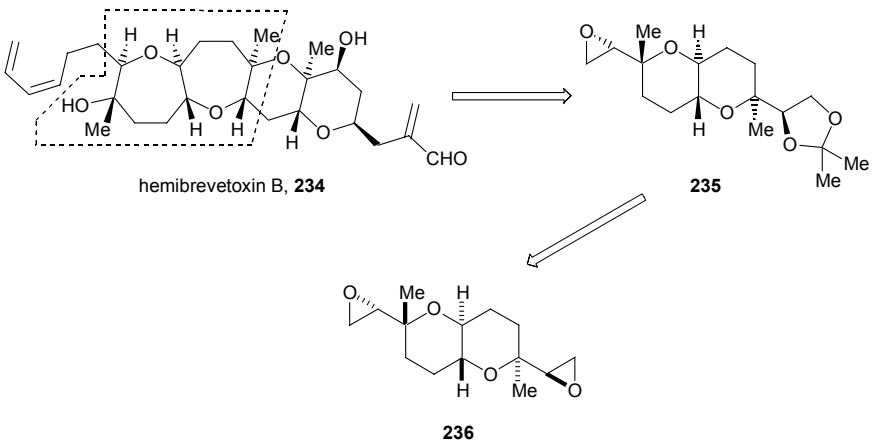


Scheme 56

The desymmetrising palladium asymmetric allylic substitution has been used in the synthesis of a number of other compounds.[6-12]

Desymmetrisation is often most effective when used with two-directional synthesis. Large complex molecules can be built up with relative ease by manipulations of both "ends" of a compound, often a chain, followed by a timely desymmetrisation which then imparts the vital stereochemical point of difference.

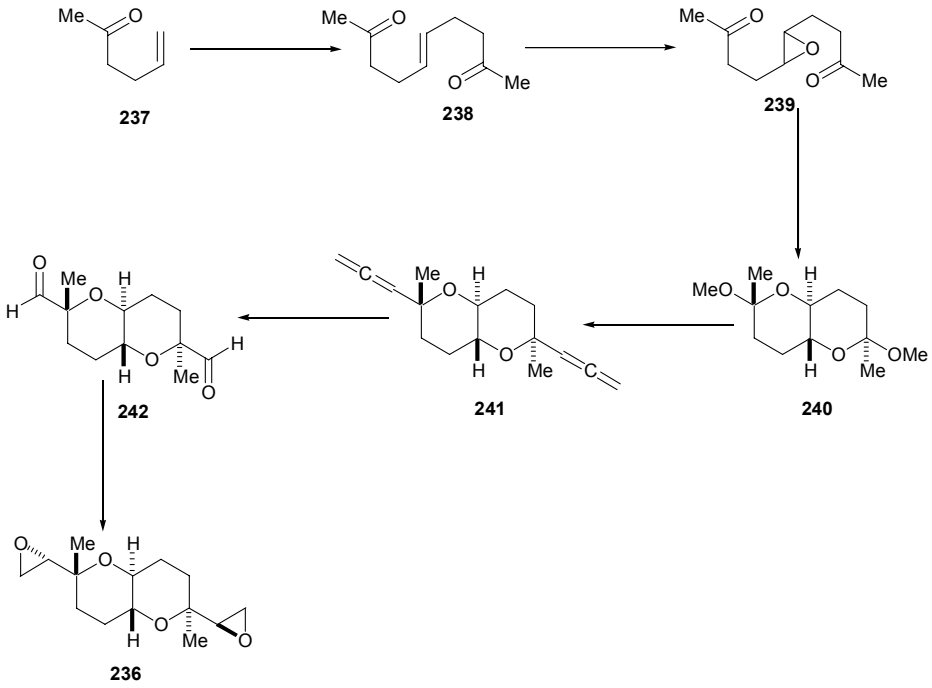
An example of this is Nelson[13] and co-workers' desymmetrisation of centrosymmetric diepoxide **236** using hydrolysis mediated by Jacobsen's chiral salen complex, as the key to the synthesis of epoxide **235**, used to form the AB ring system in the total synthesis of hemibrevetoxin B, **234**. Several syntheses of hemibrevetoxin B have been reported, yet none have taken advantage of the centrosymmetric motif within the target (Scheme 57). Epoxide **235** has previously been synthesised from geranyl acetate in 22 steps and 14% overall yield, and has been converted in 32 steps into hemibrevetoxin B.



Scheme 57

Starting from **237**, Nelson used cross-metathesis to gain access to diketone alkene **238** in 92% yield (Scheme 58). Epoxidation to give **239** was the starting

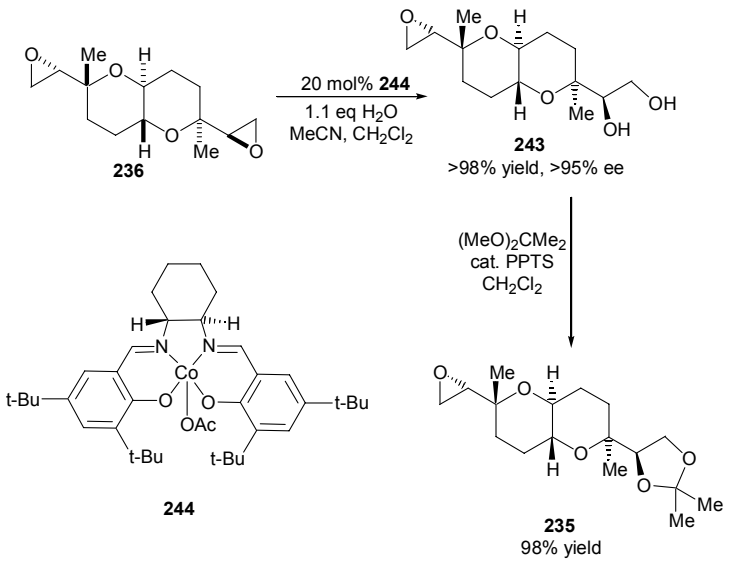
point for the two-directional synthesis. Cyclisation of **239** using pyridinium *p*-toluenesulphonate (PPTS) occurred in 85% yield and, in forming centrosymmetric **240**, was the key step in the enantioselective synthesis of **235**. From diacetal **240**, both ends of the bicyclic system were elaborated. Firstly nucleophilic substitution gave di-allenyl **241**, the allene groups being preferentially introduced axially, in 92% yield with a >99:1 diastereoselectivity. Reductive ozonolysis gave dialdehyde **242** in 98% yield; the sulphur ylide-mediated epoxidation then gave di-epoxide **236**, in 75% yield as a 20:1 mixture of centrosymmetric and unsymmetrical isomers.



Scheme 58

The desymmetrisation of **236** using the Jacobsen catalyst **244** and 1.1 equivalents of water gave diol **243** in very high yield and enantiopurity (Scheme 59). Diol **243** was then finally converted into the known hemibrevetoxin B acetonide fragment **235**. This synthesis shows a desymmetrisation utilised late in a

synthetic pathway, drastically lowering the number of steps to a key intermediate.

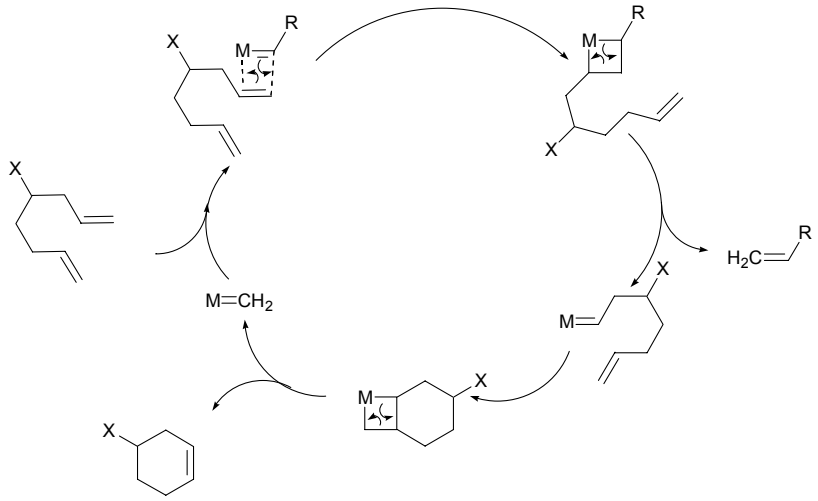


Scheme 59

Desymmetrising Metathesis

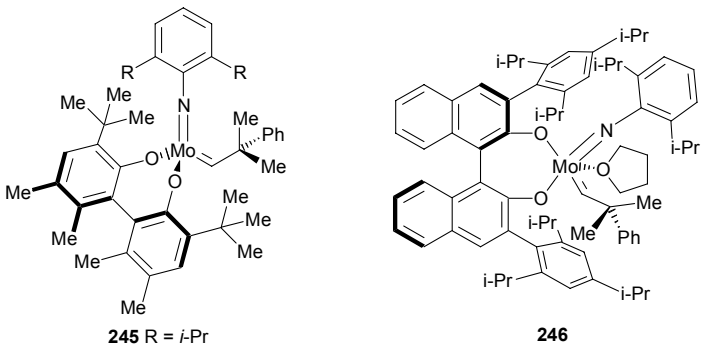
The asymmetric ring-opening and ring-closing metathesis reaction (ROM and RCM respectively) are also desymmetrisation processes. RCM and ROM have largely been used in an achiral fashion. That is, whilst the substrate upon which the metathesis is being carried out upon may be nonracemic and the product asymmetric, the metathesis reaction plays no part in the act of defining stereochemistry (Scheme 60).

Ring closing Metathesis catalytic cycle



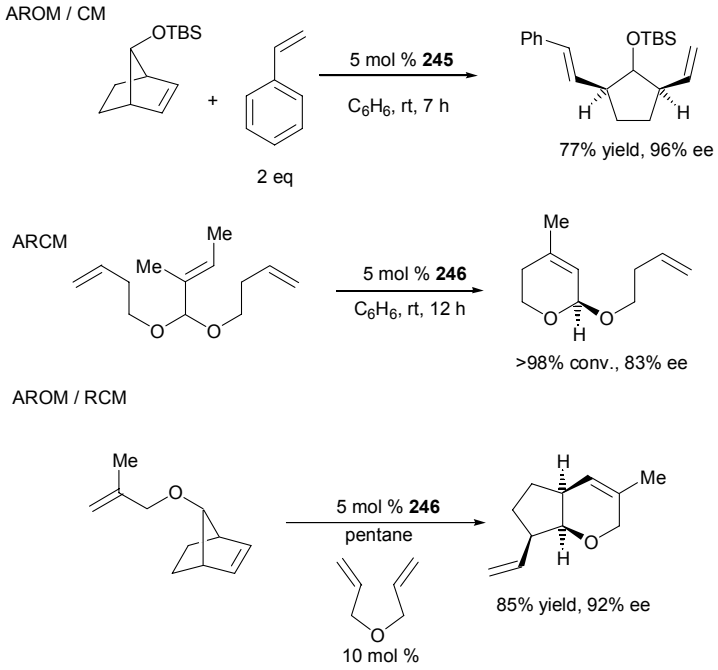
Scheme 60

Recently Schrock and Hoveyda[14-16] have demonstrated the use of chiral molybdenum catalysts (Figure 6) in enantioselective desymmetrising ROMs and RCMs (given the prefix A (*A*symmetric), and therefore called AROM and ARCM) (Scheme 61). From the AROM reaction, intermolecular trapping of the alkylidene-Mo complex (cross-metathesis or AROM/CM) can occur or intramolecular trapping in a ring-closing metathesis (AROM/RCM) to give highly complex enantio-enriched products (Scheme 61).



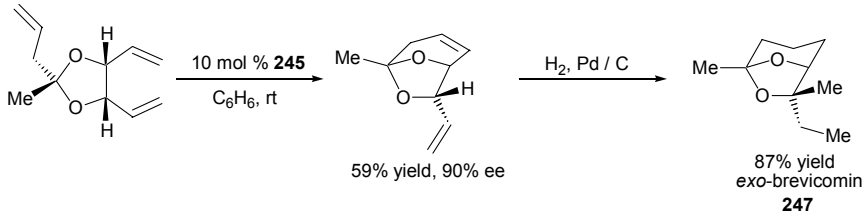
245 R = *i*-Pr **246**

Figure 6



Scheme 61

Burke has used this methodology in a brief enantioselective total synthesis of *exo*-brevicomin (Scheme 62) with a desymmetrising ARCM being the key step.



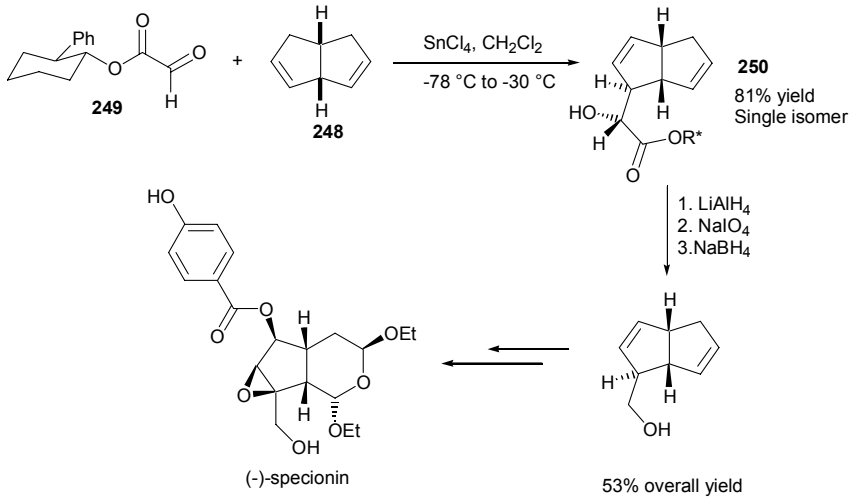
Scheme 62

In the last decade, ring-closing metathesis has become a trusted method for the formation of small to medium sized rings. The ability to carry out asymmetric metathesis increases the utility of this already widely used transformation. Ring-opening metathesis, in comparison, has been less well used.

Examples of carbonyl-ene desymmetrisations

Chiral Auxiliary Controlled Desymmetrising Carbonyl-ene Reaction

The first example of a carbonyl-ene desymmetrisation is in Whitesell's use of chiral auxiliaries.[17,18] Reaction of cyclic diene **248** with **249**, a chiral glyoxylate gave the ene adduct **250** in 81% yield as a single isomer. This reaction was incorporated into an eight-step synthesis of optically pure (–)-specionin (Scheme 63).[19]

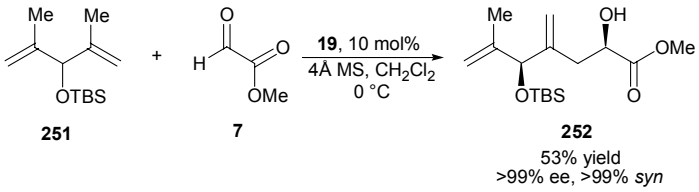


Scheme 63

Catalytic Enantioselective Desymmetrising Carbonyl-ene

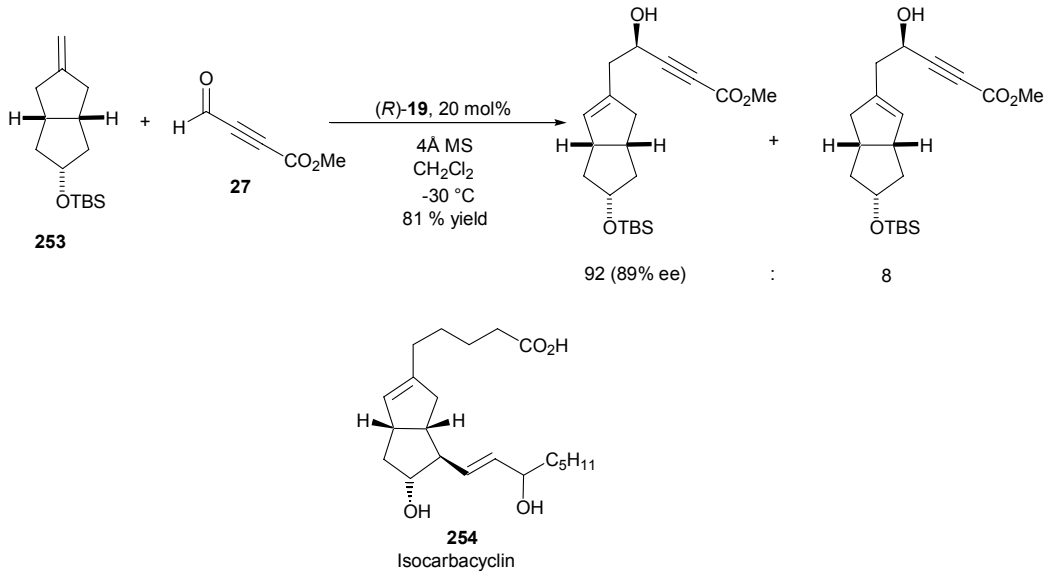
Mikami's chiral Ti(IV)BINOL complex, **19**, has been used extensively in the carbonyl-ene reaction (See Chapter 1) and Mikami has used this Lewis acid in many examples of desymmetrising intermolecular ene reactions.[20] The first reported example is the desymmetrisation of bis-allylic silyl ether, **251**, with methyl glyoxylate, **7** (Scheme 64) to give the highly functionalised **252**, yet only in moderate yield.[21] The ability to use an enantioselective catalyst provides a

useful move away from chiral auxiliaries that require additional and wasteful protection/deprotection steps. More importantly, this procedure allows the enantioselective synthesis of a product with two chiral centres from achiral- and *meso*-reagents.



Scheme 64

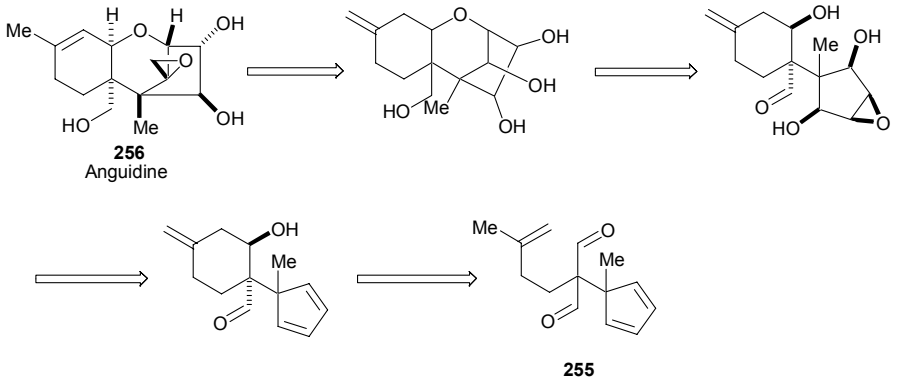
Mikami extended this approach to exocyclic alkene-containing **253**, which was subsequently applied to the synthesis of isocarbacyclin, **254**, and isocarbacyclin derivatives (Scheme 65).[22] Again, the desymmetrisation of a *meso*-intermediate, that is relatively simple to synthesise, with high enantioselectivity shows the utility of these reactions.



Scheme 65

Whilst Mikami concentrated on the desymmetrisation of alkene components using achiral aldehydes, Ziegler[23] took the converse approach, using a *meso*-dialdehyde **255** in an intramolecular carbonyl-ene reaction, as part of his route to the total synthesis of the trichothecene Anguidine, **256** (Scheme 66).

Retrosynthetic analysis

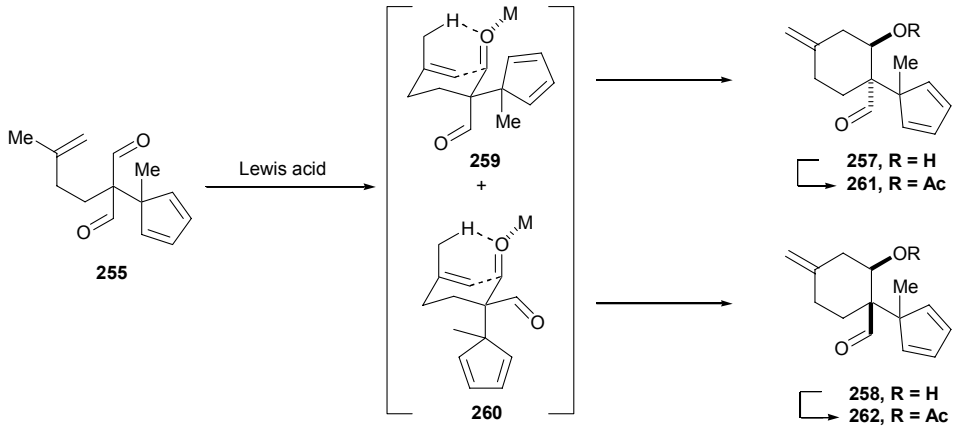


Scheme 66

The desymmetrisation of dialdehyde **255** gave promising results, however it was one step in a long synthetic pathway and therefore the carbonyl-ene desymmetrisation was not optimised. Ziegler noted, "While these results indicate that asymmetric induction is feasible in the case of the malondialdehyde (**255**), a more extensive study, in the context of the synthesis, would be warranted only if subsequent operations proved successful."

Ziegler found that dialdehyde **255** cyclised to a racemic mixture upon exposure to silica gel. Whilst the homoallylic alcohols **257**, **258** were inseparable by normal chromatographic techniques, *in situ* conversion to the acetates **261**, **262** led to a separable mixture. The major *trans* isomer **261** arises from transition state **258**, (Scheme 67), where the methylcyclopentadienyl group occupies the

equatorial position, as its steric bulk is relatively greater than that of the non-reacting formyl group.



Scheme 67

Various Lewis acids were examined for diastereoselectivity, and $Eu(fod)_3$ with *in situ* drying by addition of crushed 4Å molecular sieves was found to give the best selection for the desired *trans*-diastereomer. Chiral Lewis acid catalysts (Figure 7) were also examined to discover if enantioselective induction was possible. Modest ee's were obtained but diastereoselectivity was not as high as desired (Table 9).

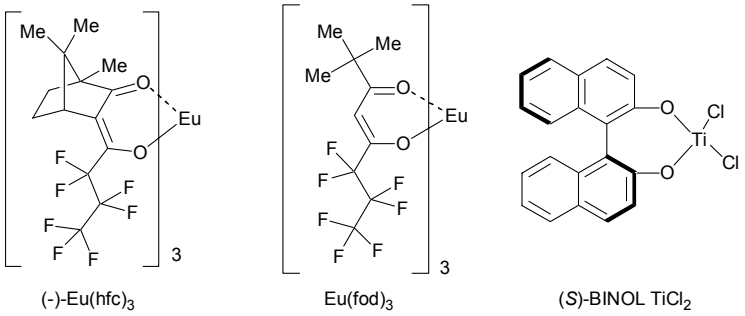


Figure 7

Table 9 Lewis acid enantioselective and diastereoselective intramolecular carbonyl-ene desymmetrisation

Entry	Lewis acid	Ratio **257**:**258**	% ee **258** (absolute configuration not determined)
1	Me_2AlCl	2:1	0
2	$Eu(fod)_3$	5:1	0
3	$Eu(fod)_3$ + 4Å MS	8:1	0
4	(+)-$Eu(hfc)_3$	5:1	20
5	(+)-$Eu(dppm)_3$	4.5:1	31
6	(*S*)-(–)-BINOL $TiCl_2$	4.5:1	38

The catalysts in entries 4-6 provided the same enantiomer in excess, however (–)-$Eu(hfc)_3$ provided the opposite enantiomer in excess.

Conclusions

Enantioselective desymmetrisation has become an increasingly powerful and widely used tool. The encouraging results of Ziegler, coupled with the advances in enantioselective catalysis and desymmetrisation, examples of which are detailed above, encouraged the author to pursue the development of a desymmetrising carbonyl-ene cyclisation, the results of which are detailed in the next chapter.

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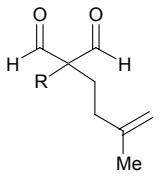
Chapter 3: An Investigation of the Desymmetrising Carbonyl-ene Cyclisation

Introduction

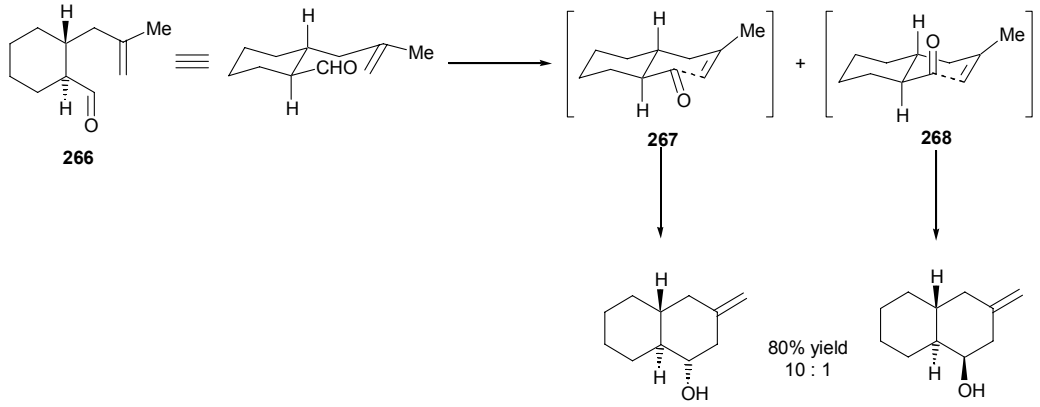
The carbonyl-ene cyclisation has been extensively studied and enantioselective systems have been developed (Chapter 1), however, very little work has been carried out on the desymmetrising carbonyl-ene reaction (for examples see Chapter 2). The work carried out by Ziegler gave encouragement that this area might provide interesting and useful results. The products of a desymmetrising carbonyl-ene cyclisation provide useful building blocks in the synthesis of complex carbocyclic systems which feature in many natural products. Ziegler's work towards the total synthesis of anguidine (Chapter 2) presented an interesting area of chemistry.[1] In Ziegler's study some selectivity was shown, although the full potential of the reaction was not studied in the course of the total synthesis. Dialdehydes, such as **265** provided a simple system that could be thoroughly examined (Figure 8).



265

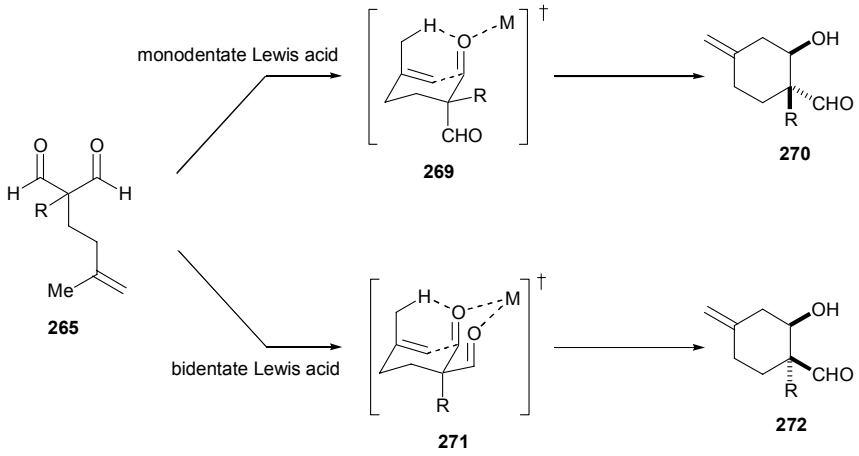
Figure 8

The stereochemistry of carbonyl-ene cyclisations has been studied at length and the cyclisation of dialdehydes of type-**265** is expected to proceed *via* a chair-like transition state, with the reacting carbonyl positioned axially, following studies by Snider and Ziegler (Chapters 1 and 2). Studies by Yamamoto,[2,3] using the bulky MABR (methylaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide)) reagent with aldehyde **266** raised the possibility of the carbonyl group occupying the equatorial position (**267**) and not axially (**268**) as expected, specifically in the case of aldehyde **266**, Scheme 68. However these findings were challenged by Brown,[4] arguing a boat-like transition state (Chapter 1).



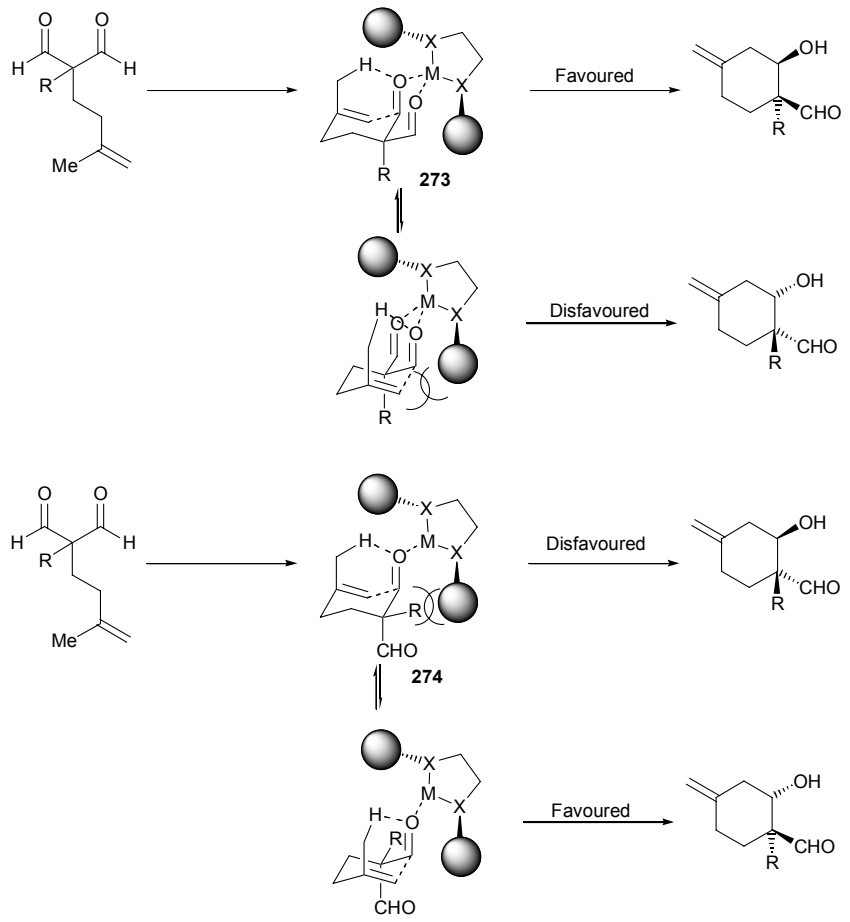
Scheme 67

From dialdehyde **265**, the relative relationship between the resulting hydroxyl group and the aldehyde groups at the two newly formed asymmetric centres will be determined by the orientation of the two aldehyde groups in the transition state. As with Ziegler's work, if the R-group adopts a pseudo-axial position, then the hydroxyl and aldehyde will be *cis* to each other. Conversely, if the second aldehyde is axial, then the two groups will be *trans* to each other (Scheme 69). A monodentate Lewis acid and / or a R-group with relatively large steric bulk should react *via* transition state **269**, and therefore give the *trans*- product, **270**. A bidentate Lewis acid and / or a sterically less demanding R-group should favour transition state **271**, giving the *cis* product, **272**. This approach would allow the reaction to proceed with diastereofacial selection from achiral materials.



Scheme 68

An enantioselective desymmetrisation reaction would rely on discrimination of the two enantiotopic aldehyde groups. This can be achieved by the formation of an asymmetric catalyst-substrate complex by the complexation of a Lewis acid with a chiral ligand, such as a C_2-symmetric ligand (Scheme 70). The co-ordination of the ligand to the metal creates an asymmetric 3-dimensional environment around the metal, affecting both how the carbonyl(s) coordinate to the metal and orientation of the reacting olefin. The steric bulk of the pendant groups in the ligand attached to groups X can serve to block one aldehyde from reacting (transition state **273**) or allow a bulky R-group to occupy the equatorial position (transition state **274**), thereby controlling which enantiotopic aldehyde undergoes reaction. Scheme 70 shows the anticipated cases for both mono- and bidentate Lewis acids.



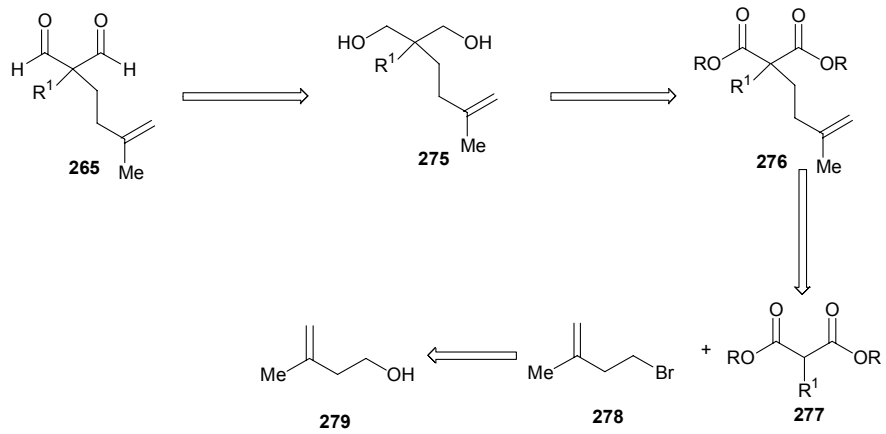
Scheme 70

Preparation of the dialdehyde

Oxidation/Reduction Strategy

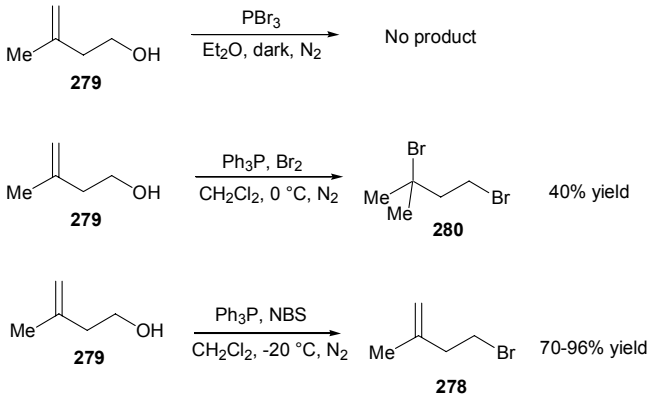
Retrosynthetic analysis of dialdehyde **265** revealed the possibilities of a reductive / oxidative route *via* diol **275**, from malonate **276** (Scheme 71). This malonate is in turn accessible from the alkylation of malonate **277** by bromide **278**, finally leading to commercially available homoallylic alcohol **279**. Varying malonate **277** would allow the introduction of different R-groups, with different steric requirements, e.g. H, Me, Et, ^{i}Pr, Bn etc, and the determination of their effect on the selectivity of the carbonyl-ene reaction. In order to avoid possible

complications introduced by enolisation of the dialdehyde it was decided to use methyl dimethylmalonate as the alkylating agent, and begin with R = Me.



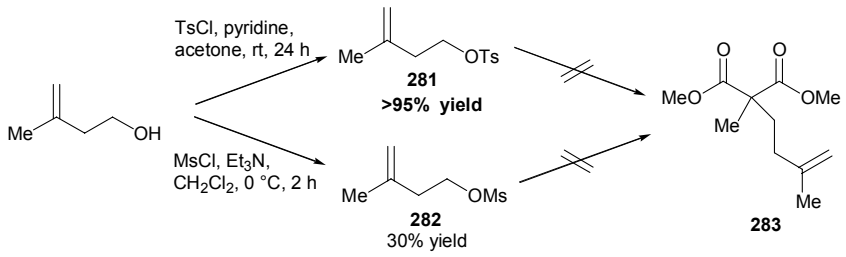
Scheme 71

Initial attempts to form bromide **278** from homoallylic alcohol **279** using phosphorous tribromide led to decomposition with no recovery of starting material or product (Scheme 72). The use of bromine with triphenyl phosphine as the brominating agent was also unsuccessful, causing over-bromination to the dibrominated product **280**. However, bromide **278** was synthesised according to procedures by Bose,[5,6] with careful use of triphenylphosphine and *N*-bromosuccinimide (Scheme 72) and the reaction proceeded in good yield. Care had to be taken when purifying bromide **278** by distillation in order to obtain optimum yields. Bromide **278** is volatile (lit. bp 40 °C at 40 mmHg) and when purifying the product by distillation care had to be taken. Overheating caused a lowering of product yield by decomposition to a black tar, possibly by *in situ* formation of the phosphonium salt in the presence of remaining triphenylphosphine.



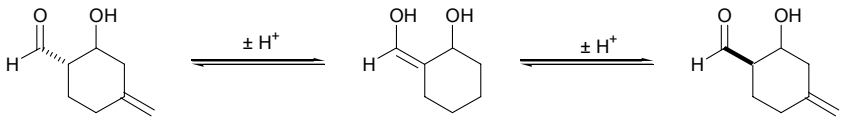
Scheme 72

As an alternative to the use of bromide **278**, mesylation and tosylation of homoallylic alcohol **279**, were also carried out (Scheme 73), the tosylate being particularly high yielding. However, the alkylation reaction gave very poor results with both the tosylate **281** and the mesylate **282,** and these were abandoned.



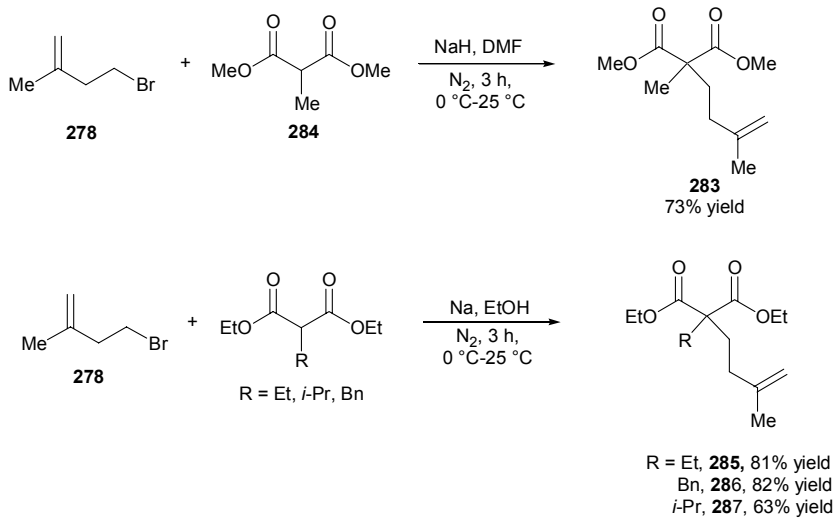
Scheme 73

Where R = H there is a possibility that enolisation could occur (Scheme 74), leading to racemisation, and so this malonate was discounted, and dimethyl methylmalonate (**283**, where R = Me) was chosen as the simplest starting malonate.



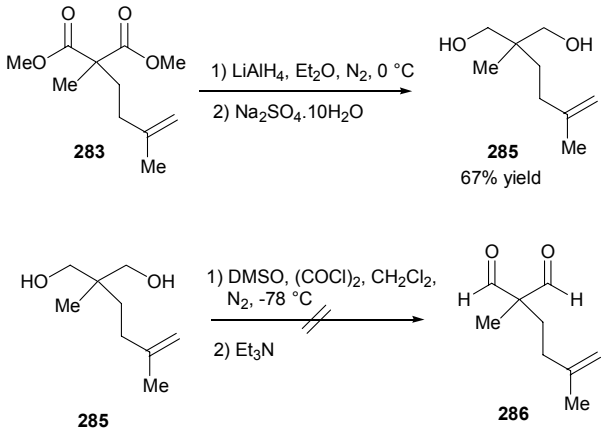
Scheme 74

Alkylation to form the methyl malonate **283** was carried out from dimethyl methylmalonate **284**, bromide **278** and sodium hydride in DMF.[7] For R = Et **285**, Bn **286**, *i*-Pr **287**, sodium in ethanol was used as the base for alkylation (Scheme 75).



Scheme 75

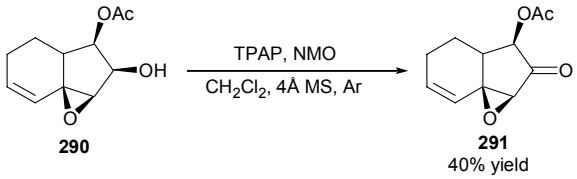
Reduction of methylmalonate **283** to the diol **288** proceeded smoothly and in good yield using a modified $LiAlH_4$ reduction[8] (Scheme 76); work-up was carried out using $Na_2SO_4 \cdot 10H_2O$, after the suspension had turned completely white it was filtered through a pad of Mg_2SO_4 and washed with hot THF. However, oxidation to the dialdehyde **289** proved to be problematic. Initial attempts to repeat Ziegler's double Swern oxidation resulted in decomposition and no product was obtained (Scheme 76). Ziegler's dialdehyde was reported to cyclise on exposure to silica gel and the much smaller size of the methyl group, compared with the bulk of the methyl cyclopentadienyl group used by Ziegler, makes dialdehyde **289** more reactive and hence prone to cyclisation.



Scheme 76

Alternative oxidations were examined to obtain dialdehyde **289**. PDC is a mild oxidising agent and sparingly soluble in DCM, but reaction times can be reduced by sonication and this can help with particularly sensitive compounds. However, when applied to diol **288**, the reaction mixture turned bright orange and as any dialdehyde formed it became irretrievably chelated to the chromium metal. The chromium was retained by the dialdehyde even with extended stirring with Rochelle's salt, as witnessed by the intense colouration of the organic layer and colourless aqueous phase. Pyridine·SO_3 complex in DMSO used as an alternative to the Swern oxidation also yielded no dialdehyde.

Tetrapropylammonium perruthenate (TPAP) has been extensively developed as a very mild catalytic oxidant by Ley.[9] TPAP has been shown to be tolerant of an exhaustive list of functional and protecting groups, which are not stable under other oxidative conditions, for example, the oxidation of epoxy alcohol **290** to epoxy ketone **291** was achieved in 40% yield (Scheme 77). In the same reaction PCC, Collins, Swern, SO_3·pyridine/DMSO, TFAA/DMSO and P_2O_5/DMSO oxidations all failed.

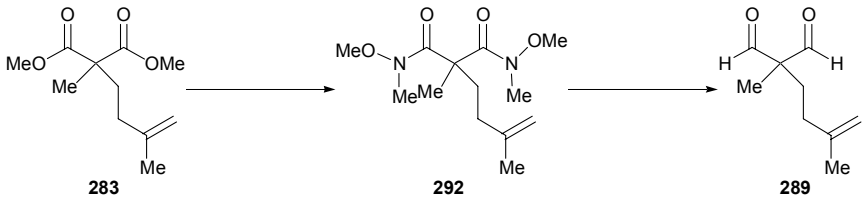


Scheme 77

In light of this versatility and ability to give products where other reagents have failed, an attempt was made to utilise the TPAP oxidation. TPAP did not however, succeed and Ley explains the failure of certain TPAP oxidations on the possibility that chelation to the ruthenium may stop catalyst turnover; once again chelation is a highly probable occurrence in the production of the dialdehyde. Therefore, a system where chelation would not occur was deemed necessary.

Bis-Weinreb Amide Direct Reduction to Dialdehyde **289**

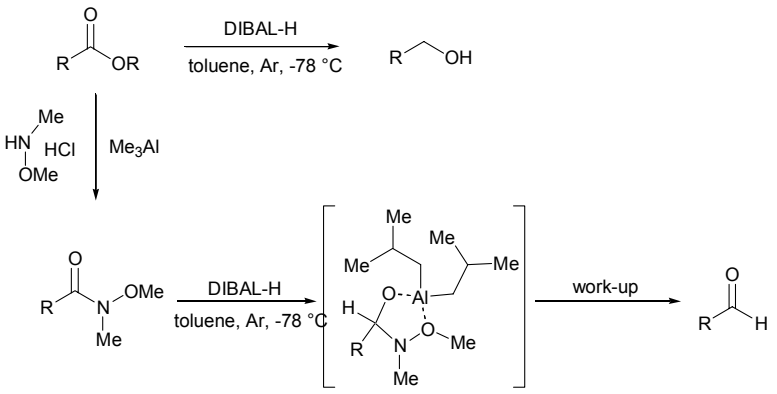
As an alternative to a reductive / oxidative route, the possibilities of a direct reduction approach were examined. Direct reduction of the malonate to the dialdehyde was not attempted as it was felt that it would be difficult to control, especially avoiding over-reduction. Instead, malonate **283** was chosen to be converted to the bis-Weinreb amide **292**, and then reduced from the *bis*-Weinreb amide directly to the dialdehyde (Scheme 78).



Scheme 78

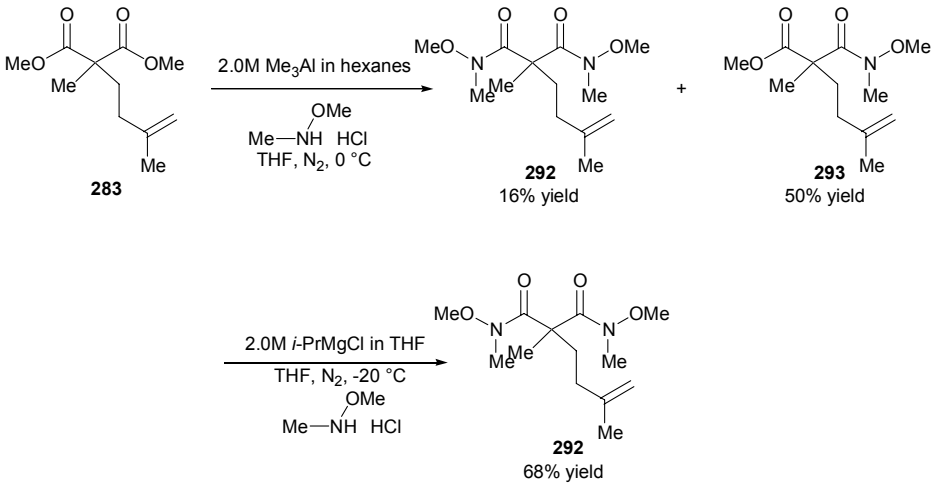
Weinreb amides can be reduced to aldehydes with DIBAL-H, without reduction to the alcohol that often occurs when esters are treated with DIBAL-H (Scheme 79). This is the result of formation of a DIBAL-amide complex, which only

decomposes on work-up, giving the aldehyde without possibility of further reaction.[10]



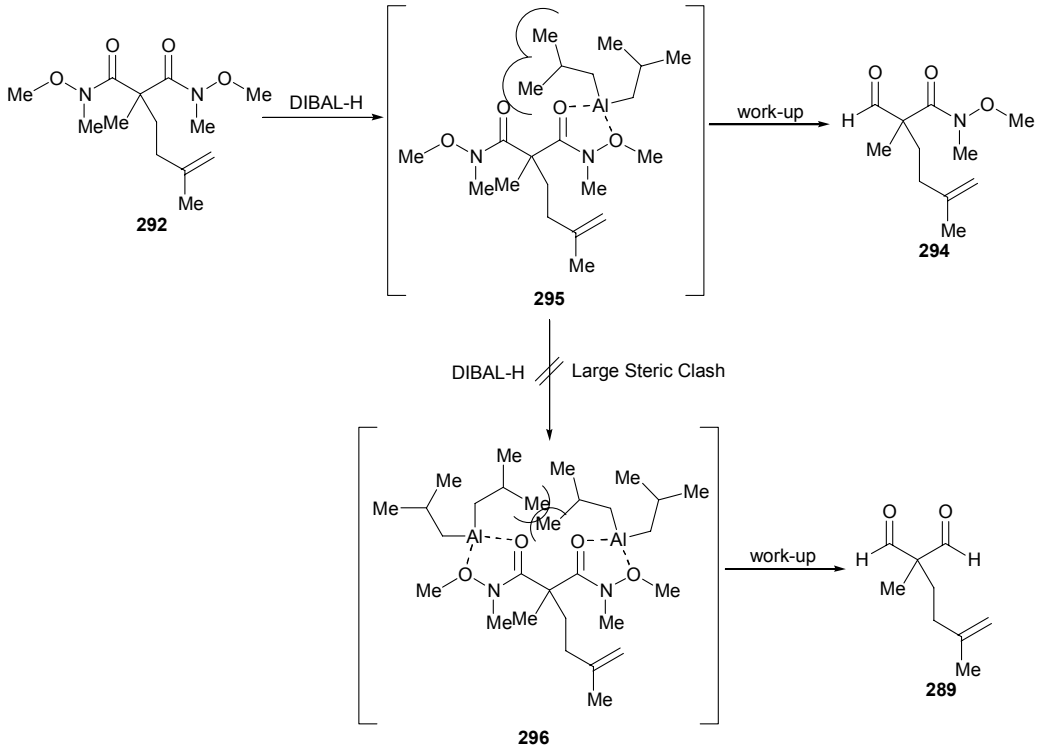
Scheme 79

Preliminary attempts using trimethyl aluminium and *N,O*-dimethoxy-hydroxylamine hydrochloride to obtain *bis*-Weinreb amide **292**, gave poor yields and large quantities of mono-Weinreb amide **293**, and it was discovered that *iso*-propyl magnesium chloride could be used as an alternative to trimethyl aluminium. This gave much higher yields of the desired *bis*-Weinreb amide and no mono-amide formation (Scheme 80).



Scheme 80

Reduction studies of the *bis*-Weinreb amide **292** were disappointing. DIBAL-H reduction gave low yields of mono-amido-aldehyde **294**; and reduction with a large excess of DIBAL-H failed to improve matters (Scheme 81). The close proximity of the Weinreb amide groups may inhibit the incorporation of the second DIBAL unit (**295** vs. **296**) due to the steric bulk of the di-isobutyl groups attached to the aluminium centre. No amount of DIBAL-H was able to drive the reaction to completion. Weinreb noted that in some cases $LiAlH_4$ could be used in the reduction of Weinreb amides,[10] however, attempts to use this strategy failed and the diol **288** was recovered.

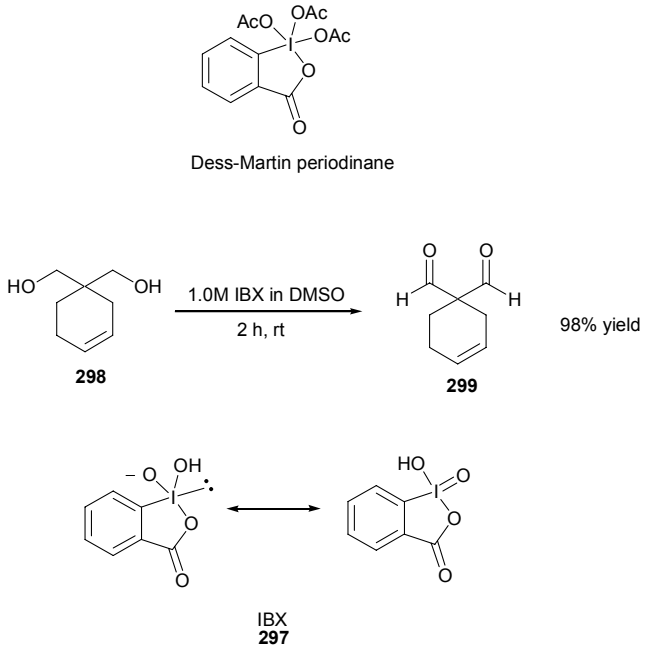


Scheme 81

Oxidation using hypervalent iodine reagents

It was decided to return to the oxidation of diol **288**, this time using the Dess-Martin periodinane (Scheme 82). The Dess-Martin periodinane was first reported in 1983 as a mild and selective reagent for the oxidation of primary and

secondary alcohols. Its main advantages are: The selectivity for rapid exchange of acetate ligands with hydroxyl functionality compared to that of other functional groups; and that the work-up does not require the removal of toxic or carcinogenic metals, which are often used as the basis of other oxidants. Whilst no dialdehyde was isolated from these reactions, this led to a discovery in the literature of work by Santagostino *et al*.[11,12] Santagostino reported that *o*-iodoxybenzoic acid (IBX, **297**), the precursor to the Dess-Martin periodinane (DMP) could be used as a mild and selective oxidant, and gave examples of diol to dialdehyde oxidation (e.g. **298** →**299**, Scheme 82). For clarity the iodine lone pair electrons, present in the left-hand tautomer of IBX will be omitted unless explicitly involved in a reaction mechanism.

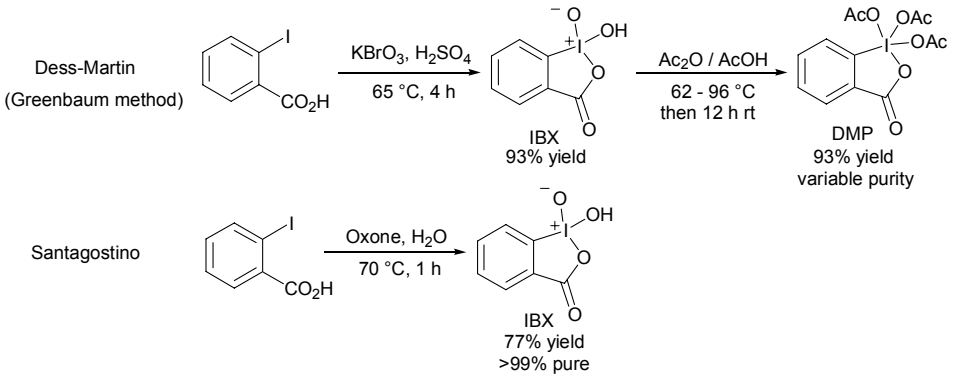


Scheme 82

IBX had previously been discarded by Dess and Martin as being too insoluble in organic solvents to study its chemical properties,[13] however Santagostino showed that stirring for 20 minutes in DMSO led to complete dissolution. Compounds

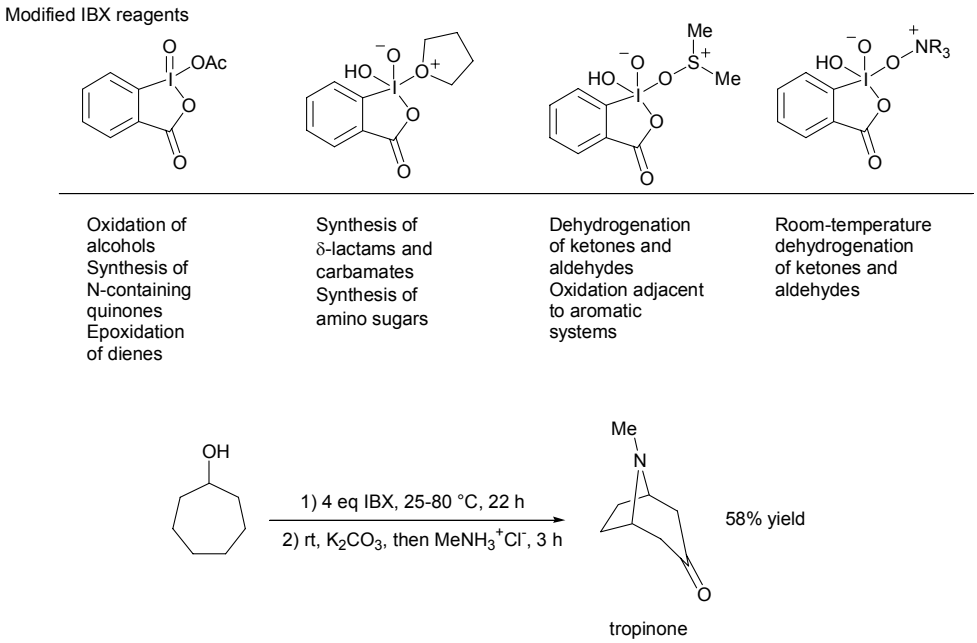
not soluble in DMSO could be added in the minimum amount of THF, or a THF / DMSO mix, without lowering the yield of the product.

In order to form IBX Dess and Martin used a modification of the procedure of Greenbaum (Scheme 83).[13,14] This procedure used 2-iodobenzoic acid with potassium bromate in hot sulphuric acid (0.73M), giving off copious amounts of bromine (62 g/mol of IBX) in the process, both factors combine to cause severe corrosion of metal reaction parts (stirring rods, vent needles, etc.). Recommendation is made to avoid any exposed metal parts if following this procedure. IBX is then converted to the Dess-Martin periodinane by warming in an acetic anhydride-acetic acid mixture. In addition, and separately, Ireland[15] and Schreiber[16] noted that the yield and purity in the final Dess-Martin periodinane were not always reproducible and put forward modifications. Santagostino detailed a more accessible and reproducible route to IBX in later correspondence (Scheme 83) using oxone in water at 70 °C.[17] Nicolaou has commented that the reports of the explosive nature of IBX are probably due to contamination of IBX obtained using Greenbaum's procedure with bromine by-products, and that no incidents have been reported using the Santagostino procedure.[18]



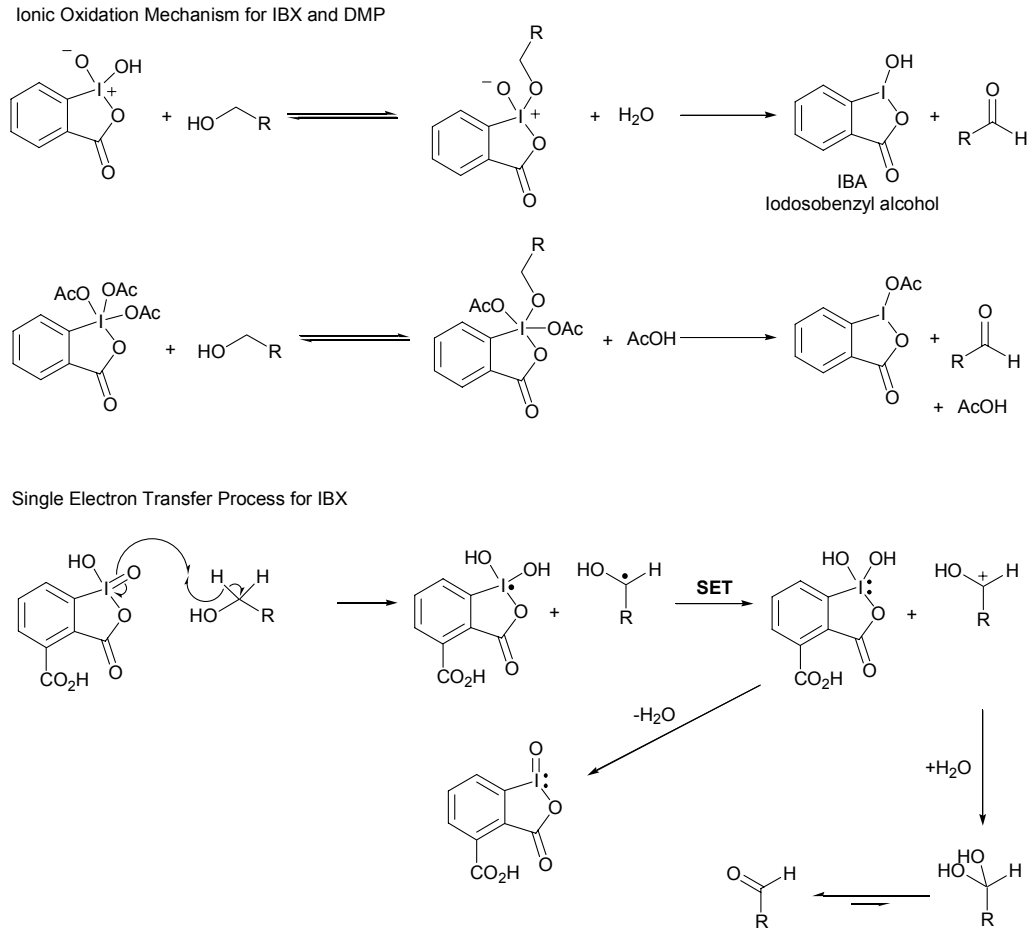
Scheme 83

It has been reported recently by Nicolaou that IBX is not limited to the oxidation of alcohols to aldehydes and ketones. Complexation with a suitable ligand (Scheme 84) and reaction at elevated temperatures (55 °C → 80 °C) has led to the development of IBX in the epoxidation of dienes, synthesis of δ-lactams,[19] and amino sugars,[20] the dehydrogenation of ketones and aldehydes[21,22] and oxidation adjacent to aromatic systems.[23] An example of the use of IBX as a dehydrogenation agent is the one-pot synthesis of tropinone from cycloheptanol (Scheme 84).



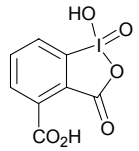
Scheme 84

IBX and the Dess-Martin periodinane are reported to oxidise alcohols using similar ionic mechanisms (Scheme 85). Due to the formation of two equivalents of acetic acid, pyridine is often used to buffer the solution when using the Dess-Martin periodinane with acid sensitive compounds. However, recently Nicolaou[22] has put forward a single electron transfer mechanism to explain the results when IBX is applied to dehydration reactions forming α,β-unsaturated carbonyl compounds, and in the production of heterocyclic compounds.



Scheme 85

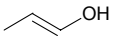
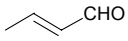
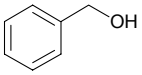
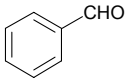
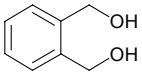
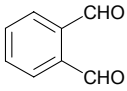
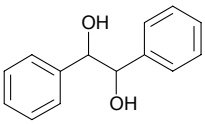
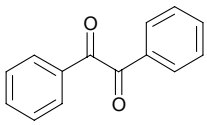
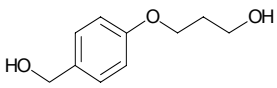
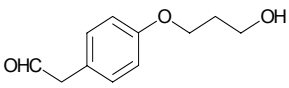
Vinod and Thottumkara[24] have applied this mechanism to a modified water soluble IBX, with an additional carboxylic acid group, able to oxidise alcohols to aldehydes and ketones in water (Figure 9, Table 9). However, an excess of mIBX was required in most cases in order to achieve oxidation. Vinod and Thottumkara's main claim is that oxidations using mIBX are carried out in water and therefore it is a "green-oxidant", not requiring organic solvents. Whilst the synthesis of mIBX was high yielding, the final step to uses the Greenbaum synthesis of IBX with $KBrO_3$ in H_2SO_4, and the potential of the Santagostino Oxone® in water method was not examined.



"modified IBX": mIBX
water soluble

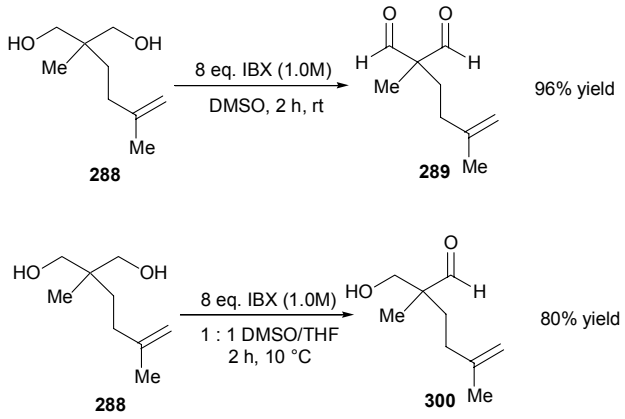
Figure 9

Table 9

Entry	Substrate	Product	Conditions*	% Yield
1			1:2, rt, 18 h	86
2			1:1.5, 60 °C, 3 h	95
3			1:2.5, 60 °C, 3 h	80
4			1:2.5, 60 °C, 3 h**	81
5			1:2, 60 °C, 3 h	94

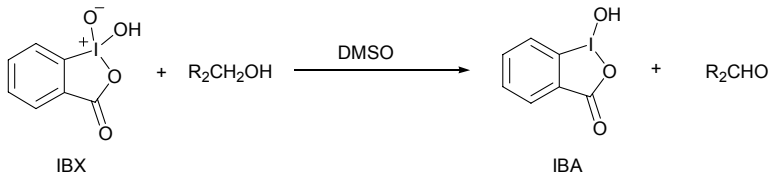
* Conditions relate to: substrate:mIBX ratio, temperature, time. ** 1:1 (v/v) H_2O:THF.

In the oxidation of diol **288** to the desired dialdehyde **289**, IBX initially appeared to be highly successful (Scheme 86), albeit requiring 8 equivalents of the reagent to be employed. Attempts to affect a milder oxidation, by lowering the temperature to 10 °C and using a DMSO / THF solvent mixture led to mono-oxidation products.



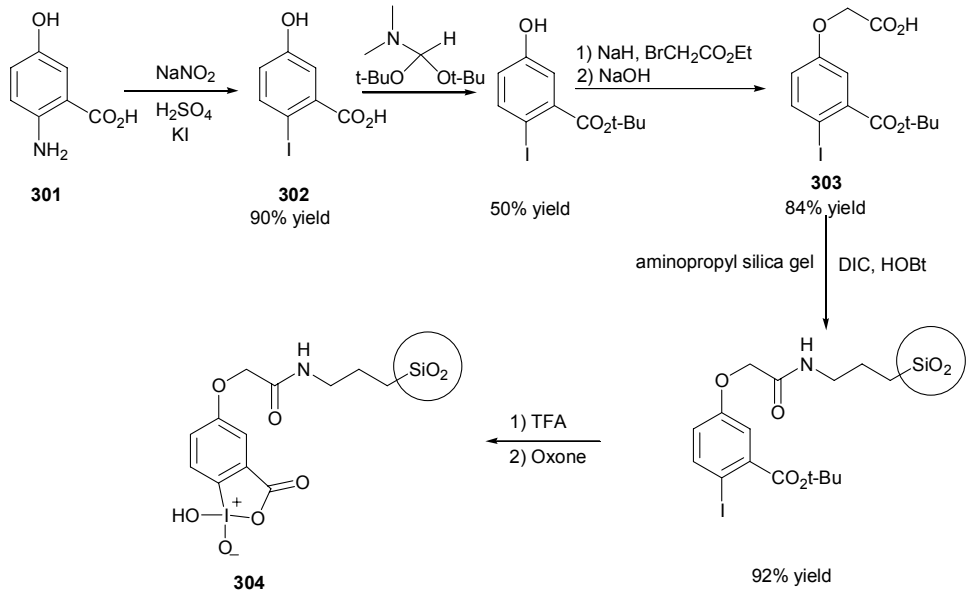
Scheme 86

However, during the course of examining the suitability of IBX as an oxidant for **288**, a number of problems were highlighted. Firstly, the work-up procedure is to dilute the reaction mixture with water, causing precipitation of the excess IBX and IBA, the iodosobenzyl alcohol by-product (Scheme 87). This is then removed by filtration and an organic solvent, for example ether, is used to extract the product. It came to light that the pH of the solution after addition of water falls to extremely low levels (0-1) and this can cause racemisation/decomposition of acid sensitive compounds, and was a concern in the case of dialdehyde **289**, with decomposition of the dialdehyde. Furthermore, the micro-precipitate formed proved difficult to handle, especially in this case where filter agents were to be avoided (Ziegler: Chapter 2, re. the cyclisation of methylcyclopentadienyl dialdehyde **259** in the presence of silica gel). Finally, minute traces of IBX / IBA thwarted attempts to prepare HPLC assay conditions in relation to identifying dialdehyde **289**. The IBX/IBA contaminants were found to have such a large response to the UV detector that no other material present was registered. All of these problems were multiplied in this system; as such large excesses of IBX were needed. Efforts to reduce the quantity of IBX used resulted in very low yields.



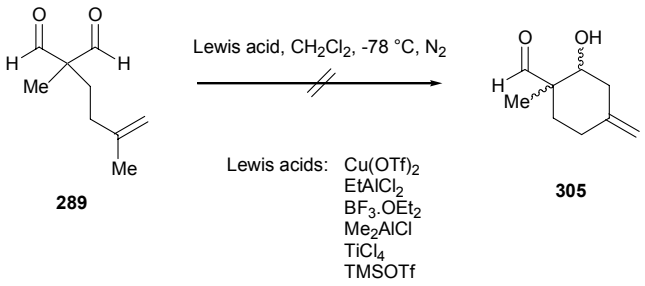
Scheme 87

A simple way to avoid these handling problems would be to support IBX on a solid support. In 2002, some time after this solution had been recognised, Giannis and Mülbaier[25] reported the use of IBX attached to a functionalised silica gel support as an oxidant for primary alcohols. In 1990, IBA had been immobilised onto silica, Nylon-6 and titanium dioxide by Moss and Chung[26] for the cleavage of phosphates. Giannis used the commercially available 2-amino-5-hydroxybenzoic acid **301** (Scheme 88), obtaining the iodide **302** by diazotisation in the same manner as Moss. The acid was then protected and the phenolic hydroxyl alkylated using α-bromoacetate, to give **303**. **303** was attached to the silica support using DIC (di-*iso*-propylcarbodiimide) and HOBt (1-hydroxy-1*H*-benzotriazole). Deprotection of the phenyl ester was followed by oxidation to the solid supported IBX, **304**. Furthermore, Giannis reports that the reduced form of **304** can be regenerated after filtration using oxone. Reagent **304** provides a significant step forward, in that the reactions can be carried out in THF rather than DMSO.



Scheme 88

Given that small amounts of dialdehyde **289** were available, we attempted to study the cyclisation reactions. The intramolecular carbonyl-ene reaction of dialdehyde **289** was studied using a variety of Lewis acids. Copper(II)triflate, boron trifluoride etherate, diethyl aluminium chloride, trimethylsilyl triflate, titanium di-*iso*-propoxide dichloride and pyridinium *p*-toluene sulphonate were all examined for effectiveness in the reaction of dialdehyde **289**, however, no cyclised products, **305**, were identified. The limited amounts of **289** available meant the investigations are inconclusive as to the effectiveness of the proposed cyclisations.



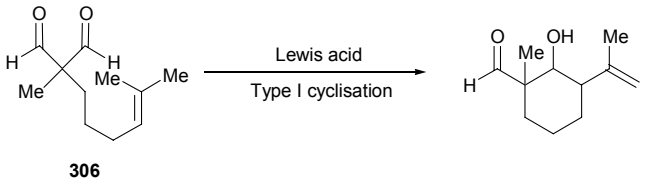
Scheme 89

Conclusions and Further Work

The development of dialdehyde **289** has drawn attention to the many different oxidation reactions available to the organic chemist. Awareness has also been brought of the relative oxidation states of the carbonyl group and the different methods that can be employed to obtain that particular functionality have been demonstrated.

The preparation of the more substituted dialdehydes (R = Et, *i*Pr, Bn) is required in order to ascertain whether the lack of results from the cyclisation of dialdehyde **289** may be in part due to its reactivity. An increase of steric bulk at this centre may prove beneficial by leading to an increased control in the cyclisation reaction. An integral part of this work would be the development of (non-silica bound) solid supported IBX. This is based on firm literature foundations and would be relatively straightforward to achieve. In light of reported recycling of solid supported IBX, this could prove an extremely efficient and expedient process for the oxidation of the sensitive substrates in this project. IBX has shown itself to be versatile as a reagent for the oxidation of alcohols and new facets of its behaviour and reactivity are currently being discovered and reported in the literature.

To advance this study a more reliable method for the formation of dialdehyde **289** must be established. The system could then be extended to related aldehydes, such as **306** which could be used in a type I carbonyl-ene cyclisation (Scheme 90).

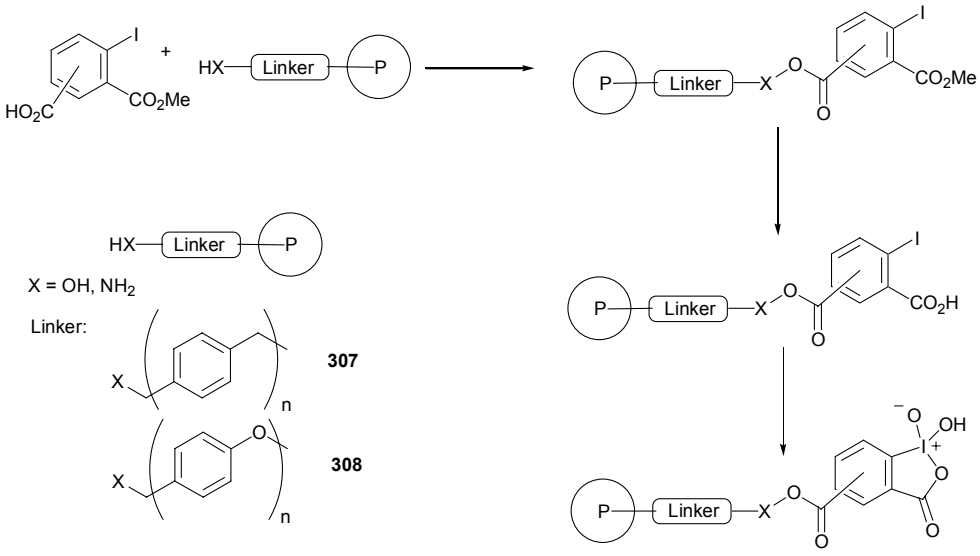


306

Scheme 90

Suggested synthesis of non-silica bound solid supported IBX

Non-silica bound IBX is required, as silica gel has been reported by Ziegler to cause cyclisation of related dialdehydes (Chapter 2). A polystyrene resin, linker **307**, with an amine or an alcohol terminal group would provide an amide or ester bound IBX; alternatively Wang resin and Wang amide resin could be used, having hydroxyl and amino functionality respectively attached to a benzyloxy, **308**, linker.



Scheme 91

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19) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233-2244.

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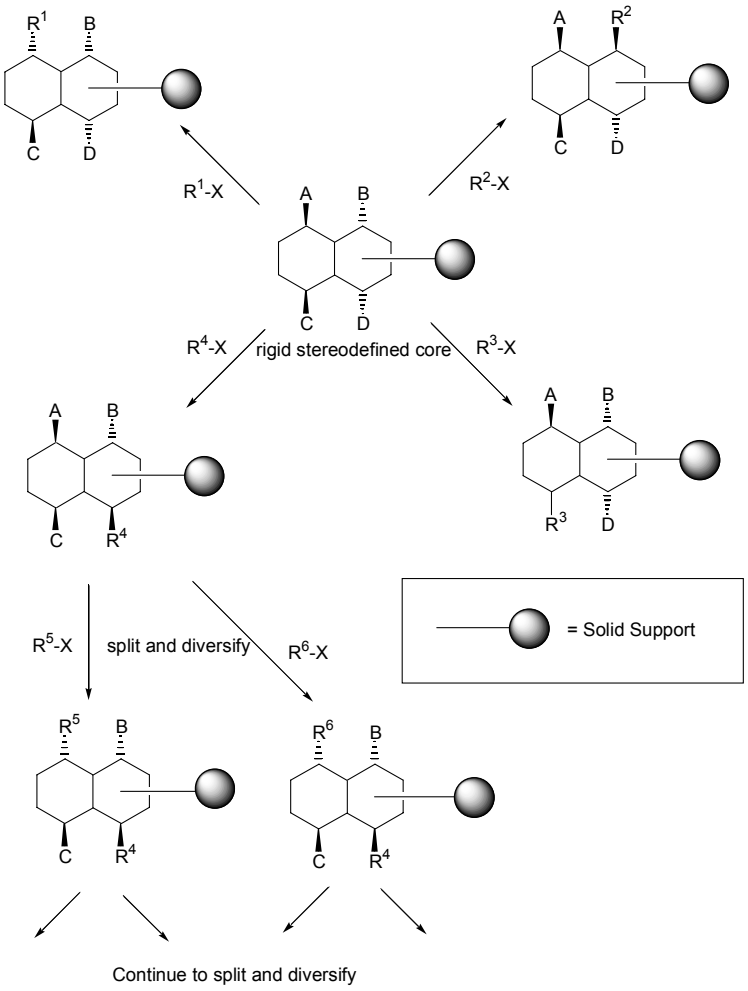
Chapter 4: An Investigation of the Intramolecular Prins-Cyclisation

Prins chemistry

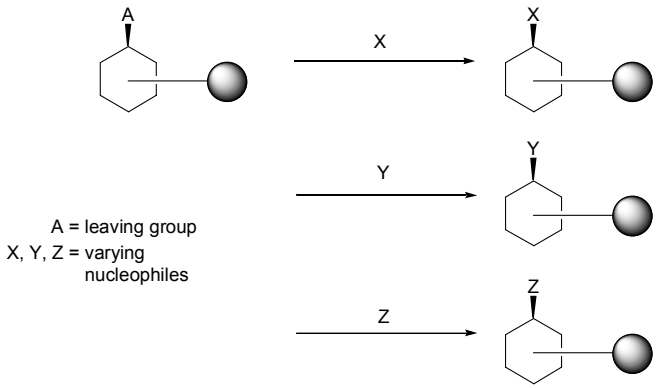
Functionalised cyclic scaffolds for synthetic elaboration

Scaffold systems in which a central motif containing several different functional groups, which allow for a diverse range of products, have become the subject of much recent research. The heart of such systems is often a rigid stereodefined core that is used to impart stereochemical information; in much the same way compounds from the chiral pool are used. Chiral pool compounds are often used as an alternative to enantioselective catalysis, where the inherent stereochemistry of the natural product directs the reaction, giving enantio- or diastereomerically-enriched products. The incorporation of several different functional groups provides a number of "points of diversification", and therefore large libraries of products can be constructed (Scheme 92). Here whilst the reaction of each functional group represented (A, B, C, D) is different, the reaction which that functional group undergoes with different R-groups is the same. For example; if $A \rightarrow R^1$ is an esterification, then $A \rightarrow R^5$ and $A \rightarrow R^6$ will also be esterifications. This type of scaffold has been extensively studied by Schreiber, *vide infra*.



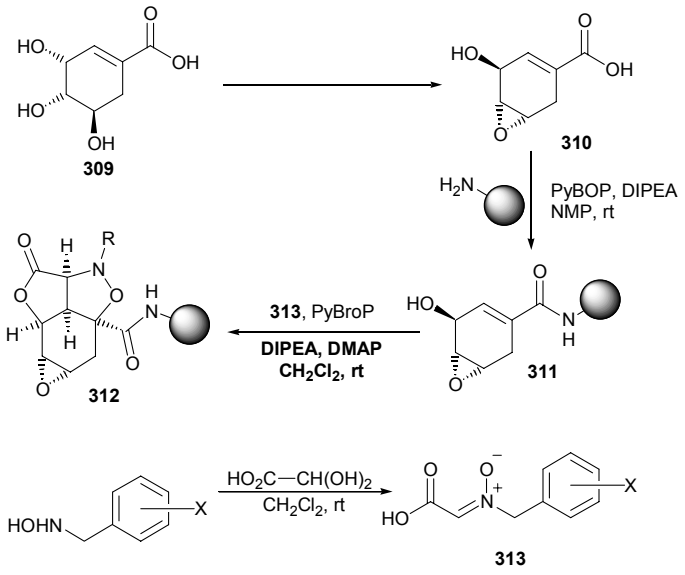
Scheme 92

Another development of scaffolds is the use of functional groups that have wide-ranging reactivity, producing many different products depending upon the reagents used (Scheme 93). Unlike the previous example where each functional group underwent the same reaction, here the functional group is selected to undergo different reactions; hence, A $\rightarrow$ X is a different reaction from A $\rightarrow$Y, which is different again from A $\rightarrow$ Z. For ease of manipulation, these scaffolds are often attached to solid supports that simplify purification and can allow the process to be mechanised. An example of the utility of this type of scaffold has been demonstrated by Nicolaou, *vide infra*.



Scheme 93

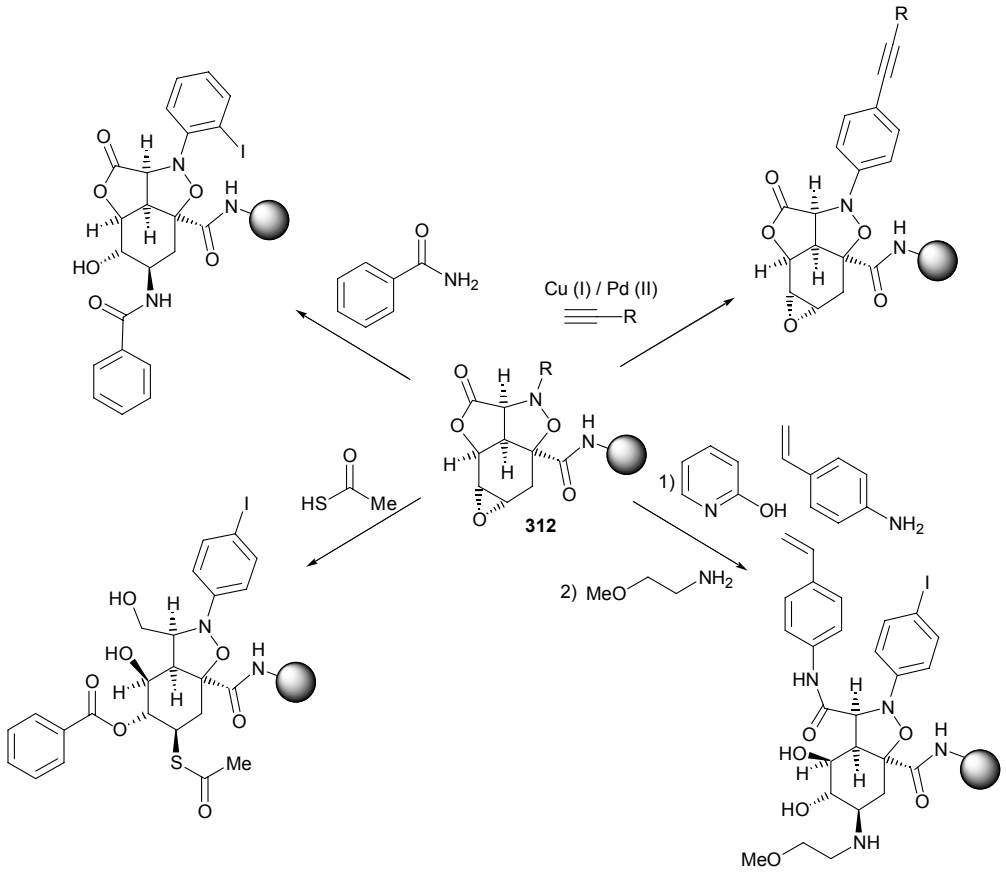
Schreiber[1] has used solid supported tetracyclic systems as scaffolds for use in "split-and-pool" techniques to gain access to a library of over two million compounds. Shikimic acid **309** is converted into (+) or (-)-epoxylcyclhexanol **310** (the (-) enantiomer can be made *via* a Mitsunobu reaction to invert the hydroxy group). With **310** attached to a solid support as amide **311**, substituted nitrone carboxylic acids, **313**, were used in a 1,3-dipolar cycloaddition under esterification conditions to give the highly functionalised tetracycle **312** with complete regio- and stereoselectivity (Scheme 94).



Scheme 94

312 is a rigid scaffold, densely packed with a variety of functional groups, which allows further elaboration without the need for protecting group manipulation (Scheme 95). Reliance on protecting group "juggling" can cause a drastic reduction in efficiency and yield when reaching for synthetic targets. The iodoaryl group was introduced using palladium cross-coupling reactions in the building of the library. This gives a further point of elaboration for use with additional cross-coupling reactions. In fact, 23 different alkynes were used, with over 90% conversion and purity. The lactone and the epoxide can react with nucleophiles, simultaneously unmasking an alcohol. Schreiber used an exhaustive number of carboxylic acids, amines and thiols to open the lactone and epoxide, giving rise to the greatest diversity in the library. In addition, the *N-O* bond can be cleaved, although Schreiber did not report any *N-O* cleaved products. Most important is the rigid sterically defined structure of the tetracycle **312** and its antipode. Because of the characteristics imparted by its structure, manipulation of **312** can be carried out to

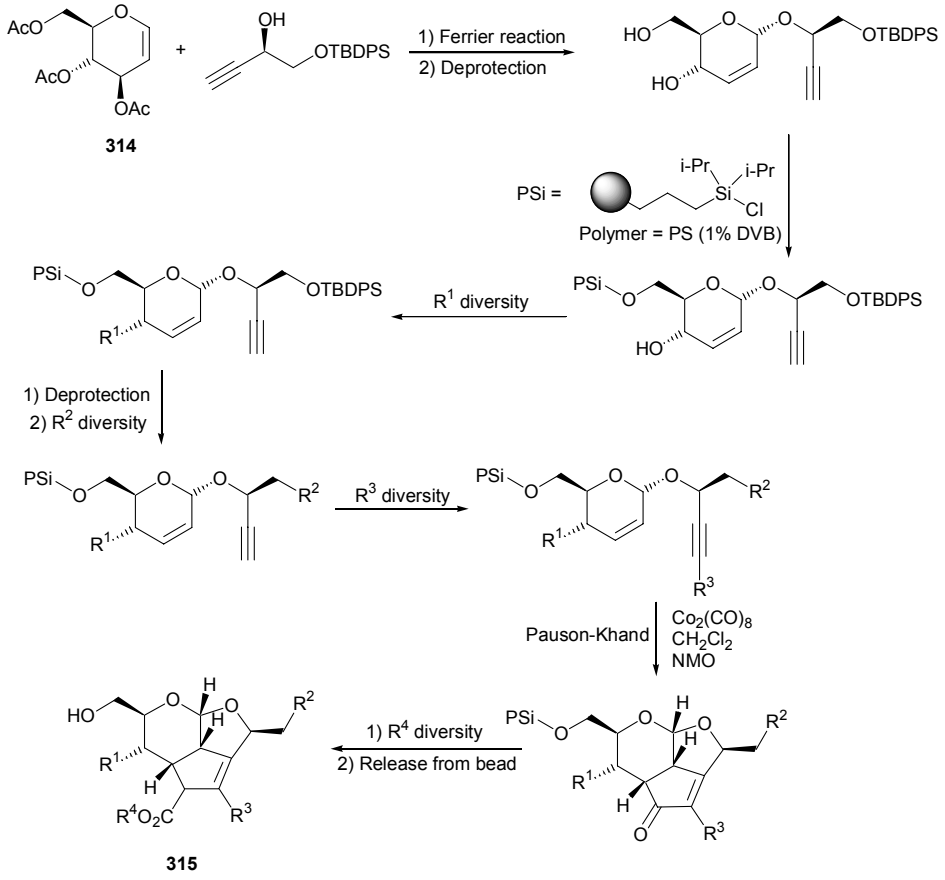
afford complex products with complete stereo- and regiocontrol using the stereochemistry and functionality present.



Scheme 95

This methodology has been developed for what Schreiber terms as "diversity-orientated complexity generating synthesis", in which central core building blocks are assembled in modular form allowing wide-ranging diversity at the core. These scaffolds are then used to control both stereochemistry and have sufficient functionality to allow further "branching out" from the core building block, giving a huge number of possible products. Using the shikimic acid-based template, Schreiber was able to prepare over two million individual molecules. Another

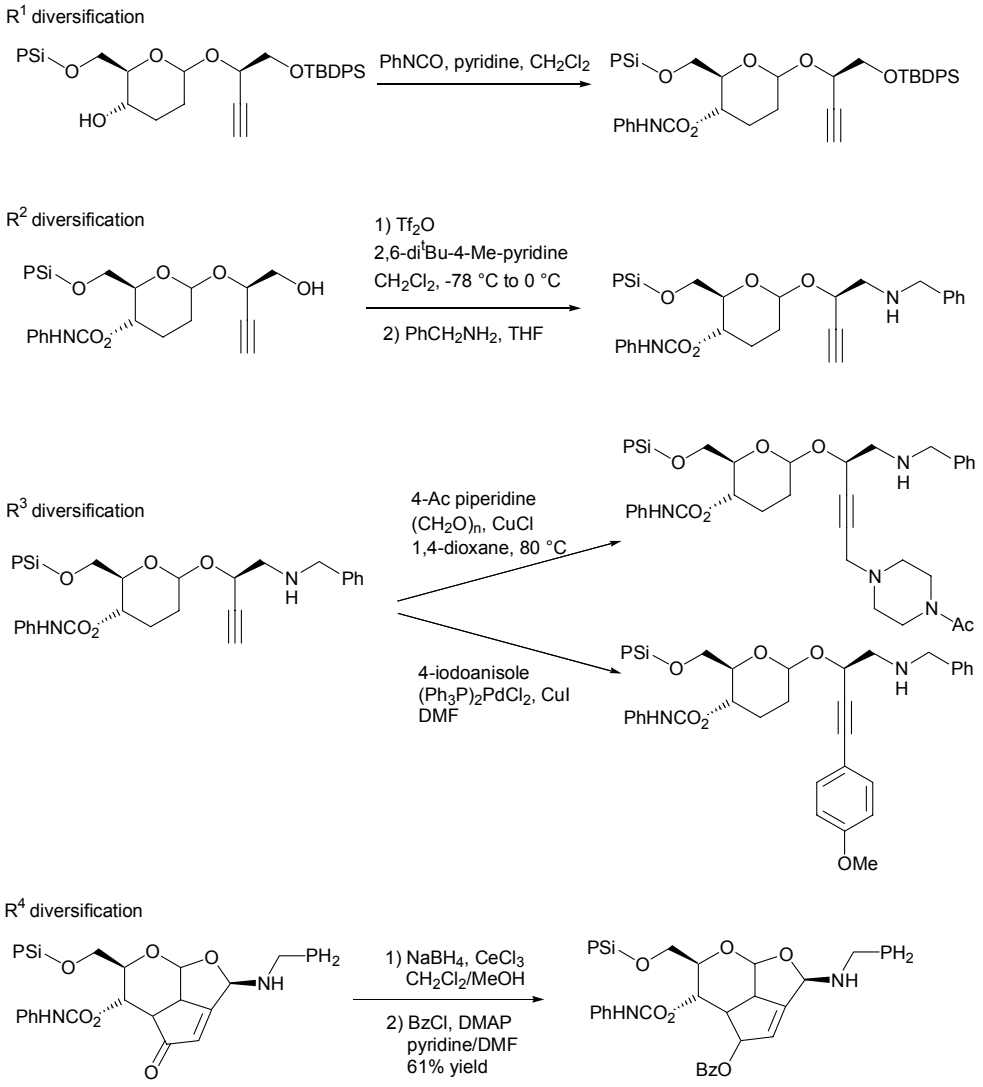
example of this strategy was the use of a glycal template, [2] **314**, to build up highly stereodefined tricyclic heterocycles, **315**, containing four clear points of diversification (Scheme 96).



Scheme 96

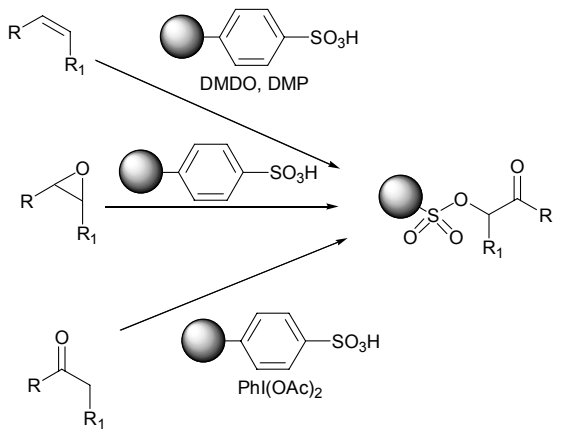
As the template is built up, Schreiber allows diversification to be introduced at distinct points in the synthesis. Examples of R^1 diversification are the formation of acetates, benzoates or carbamates using isocyanates (Scheme 97). With R^2 Schreiber formed secondary amines *via* the triflate, which can be further functionalised. R^3 diversification can use the alkyne Mannich reaction and Sonogashira reaction to introduce *N,N*-diakylaminomethyl and aromatic groups

respectively to the terminus of the alkyne. After reduction of the ketone, R^4 diversification occurs in a similar manner to R^1.



Scheme 97

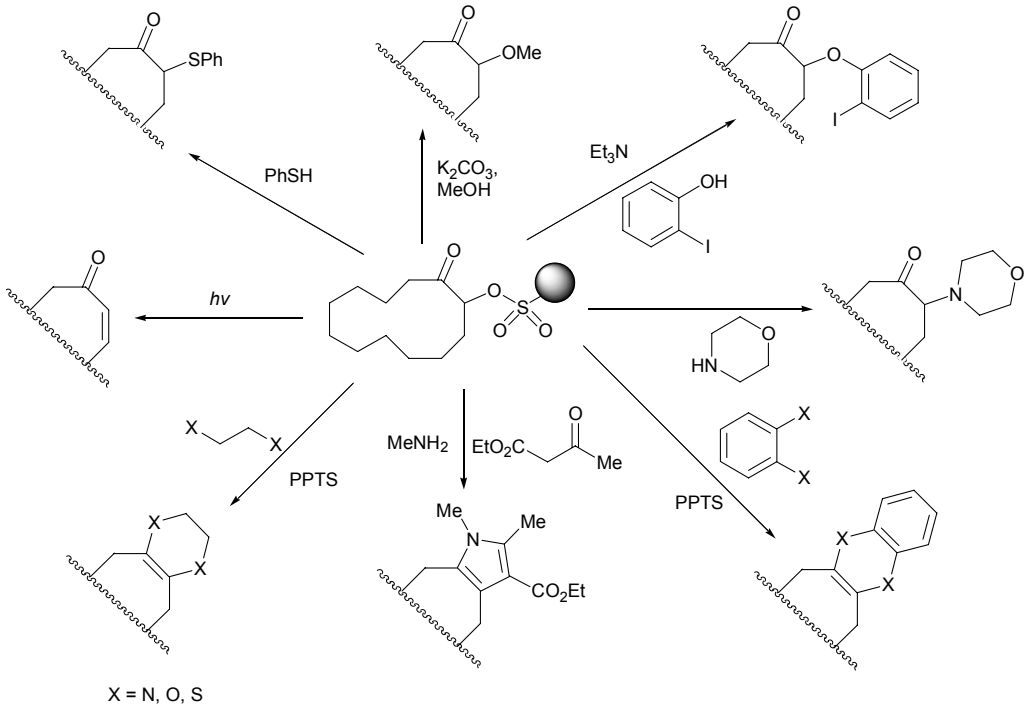
Nicolaou[3] has recently shown that olefins, epoxides, and ketones can be attached to solid supports (Scheme 98) for use as versatile building blocks.



Scheme 98

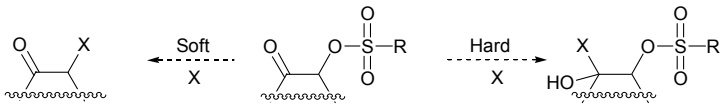
From these immobilised supports synthesis of "privileged heterocyclics" and natural product-like compounds are readily accessible (Scheme 99). Additionally, the tosyl-support linkage allows cleavage to act as a form of a traceless linker (for example using *hv* to obtain the α,β unsaturated ketone), but also the reactivity of the tosyl-linker acts to mediate the reactivity of the attached substrate, rather than as most solid support linkages that simply act as a tether.

The large variety of different compounds accessible from the α-tosyloxy ketone starting material is particularly wide ranging, making this a very useful intermediate. Oxygen, sulphur and nitrogen based nucleophiles all carry out substitution of the tosyl group, whilst *bis*-functional nucleophiles form heterocyclic systems. Nicolaou has also shown that the procedure can be carried out with a non-solid supported toluene sulphonic acid.



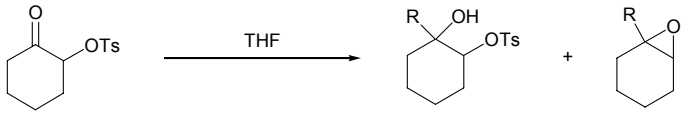
Scheme 99

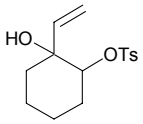
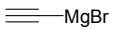
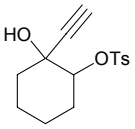
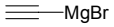
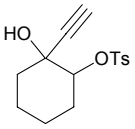
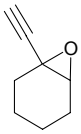
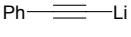
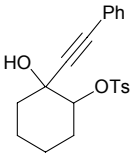
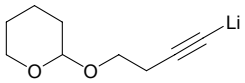
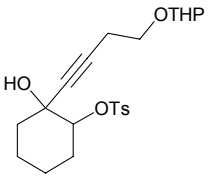
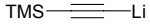
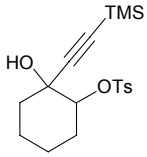
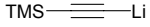
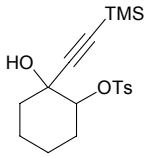
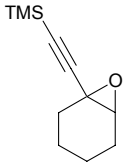
Nicolaou proposed that "hard" nucleophiles (carbon-centred nucleophiles e.g. Grignard and alkyl lithium reagents) would attack at the ketone position, whilst "soft" nucleophiles (non-carbon-centred e.g. *S, N,* and *O*) would proceed *via* initial displacement of the tosyl group (Scheme 100). Evidence for this was offered by the study of carbon-carbon bond formation using α-tosyloxy ketones with carbon nucleophiles such as Grignard and organolithium reagents (Table 10). The main products were formed from single addition of the nucleophile, although in some cases epoxide formation was observed.



Scheme 100

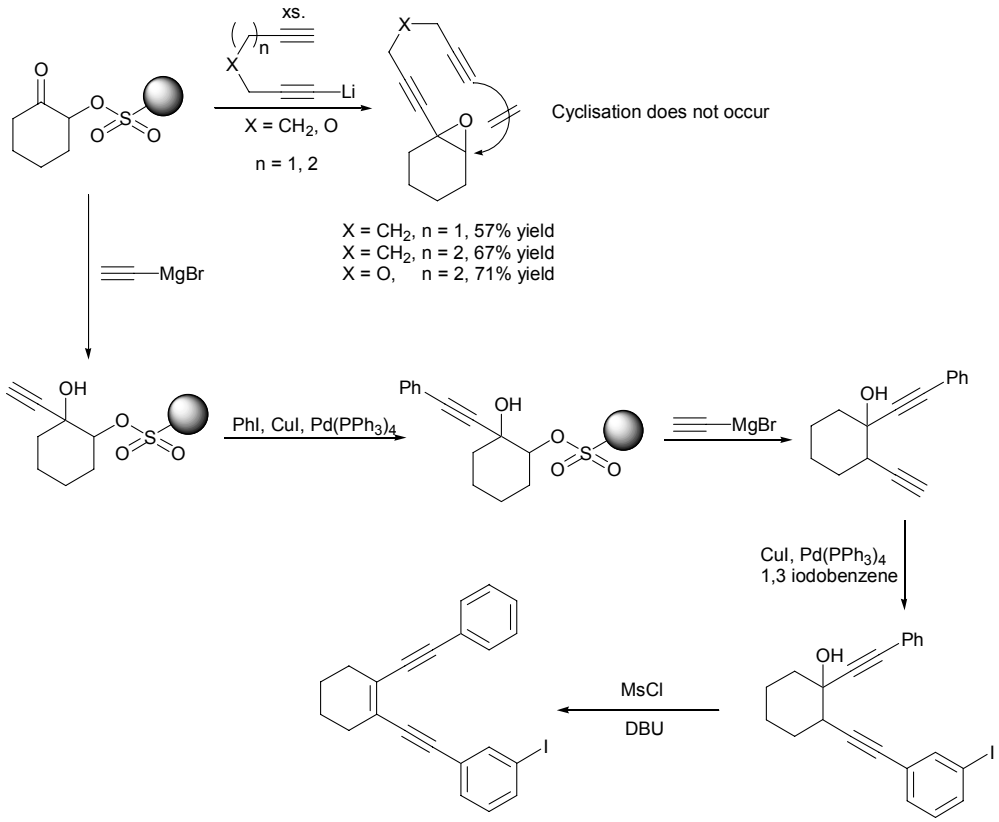
Table 10 Examples of α-tosyloxy ketone reactions with carbon nucleophiles.



Entry	Carbon-nucleophile	Eq.	Conditions	Products, %Yield	
1		1.25	–40 °C to 0 °C, 0.5 h	 89	–
2		1.25	–78 °C to 25 °C, 1 h	 86	–
3		2.0	–78 °C to 25 °C, 1 h	 77	 20
4		1.2	–40 °C to –10 °C, 0.5 h	 84	–
5		1.2	–40 °C to –10 °C, 0.5 h	 92	–
6		1.2	–40 °C to –10 °C, 0.5 h	 71	–
7		2.0	–78 °C to 25 °C, 0.5 h	 10	 85

From these results Nicolaou attempted to synthesise enediynes by applying the techniques developed (Scheme 101). Initial attempts to access bicyclic products *via* nucleophilic addition to the epoxide failed although addition to the carbonyl of the

α-tosyl ketone did occur. However, a stepwise approach was successful and led to a range of enediynes.

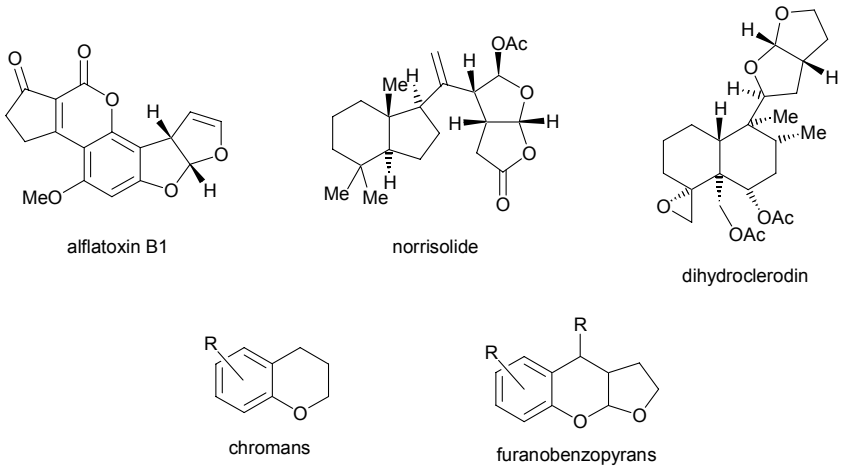


Scheme 101

The ability to access α-tosyloxy ketones starting from a variety of different functional groups gives great versatility to this reaction. Solid support of the α-tosyloxy ketone allows further manipulation with later release as a complex heterocycle.[3]

Furo[2,3-b]pyrans and furo[2,3-b]furans as building blocks for synthesis of natural products

Many natural products share common structural motifs and examples of 6,5- and 5,5 hetero-bicyclic moieties can be found in the aflatoxins, norrisolide and dihydroclerodin, the chromans and furanobenzopyrans (Scheme 102). These compounds are attractive synthetic targets due to the challenge of constructing the rigid stereodefined bicyclic core, and a number of approaches have been reported.

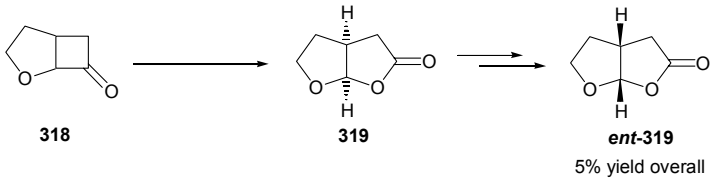


Scheme 102

For the purpose of this thesis the furo[2,3-*b*]pyran, **316**, and furo[2,3-*b*]furan, **317**, systems will be referred to as furopyrans and furofurans respectively (Figure 10).

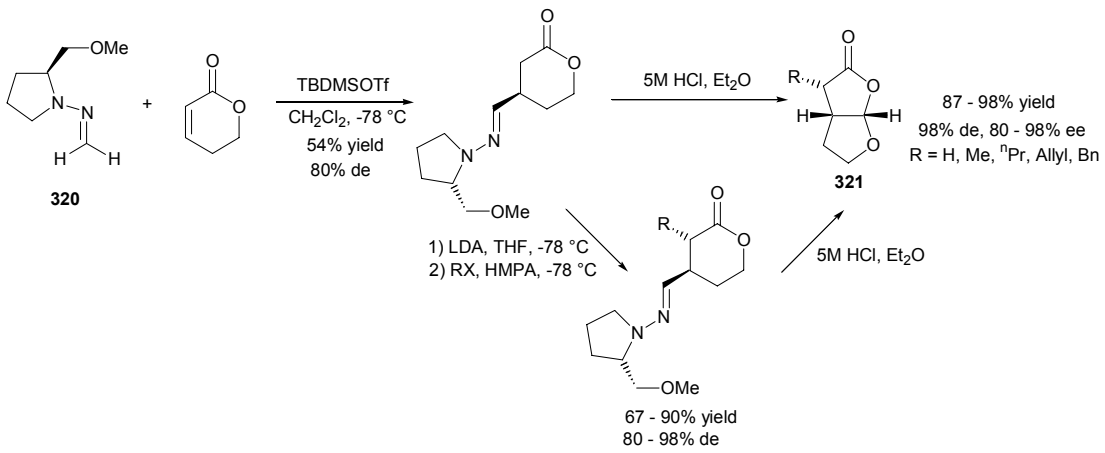
Figure 10

Furtoss[4] described an enzymatic Baeyer-Villiger oxidation of bicyclic cyclobutanone **318** (Scheme 103), and furo[2,3-*b*]furan-2-one **319**, although obtained in quantitative yield, was of the opposite stereochemistry to that desired. Five steps were required to convert **319** to its enantiomer ***ent*-319**, resulting in an overall yield of 5%.



Scheme 103

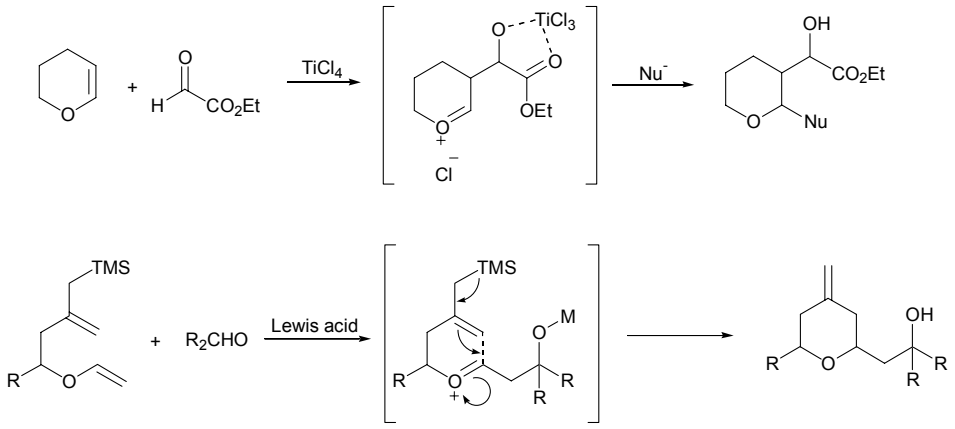
In 1999 Enders *et al.* reported a diastereo- and enantioselective synthesis of substituted furan[2,3-*b*]furan-2-ones using formaldehyde SAMP hydrozone, **320** (Scheme 104). The procedure is particularly useful with the incorporation of a diastereoselective alkylation that allows introduction of R-groups not feasible in other synthetic routes, such as Furtoss'. The Michael addition of hydrozone **320** proceeded in 54% yield, 80% de. Subsequent alkylation occurred in 80% to >98% de. The final step to form the furofuran **321** was realised using 5N HCl to facilitate cleavage of the hydrozone moiety, opening of the lactone ring and formation of the furofuran **321** *via* the hemiacetal intermediate.



Scheme 104

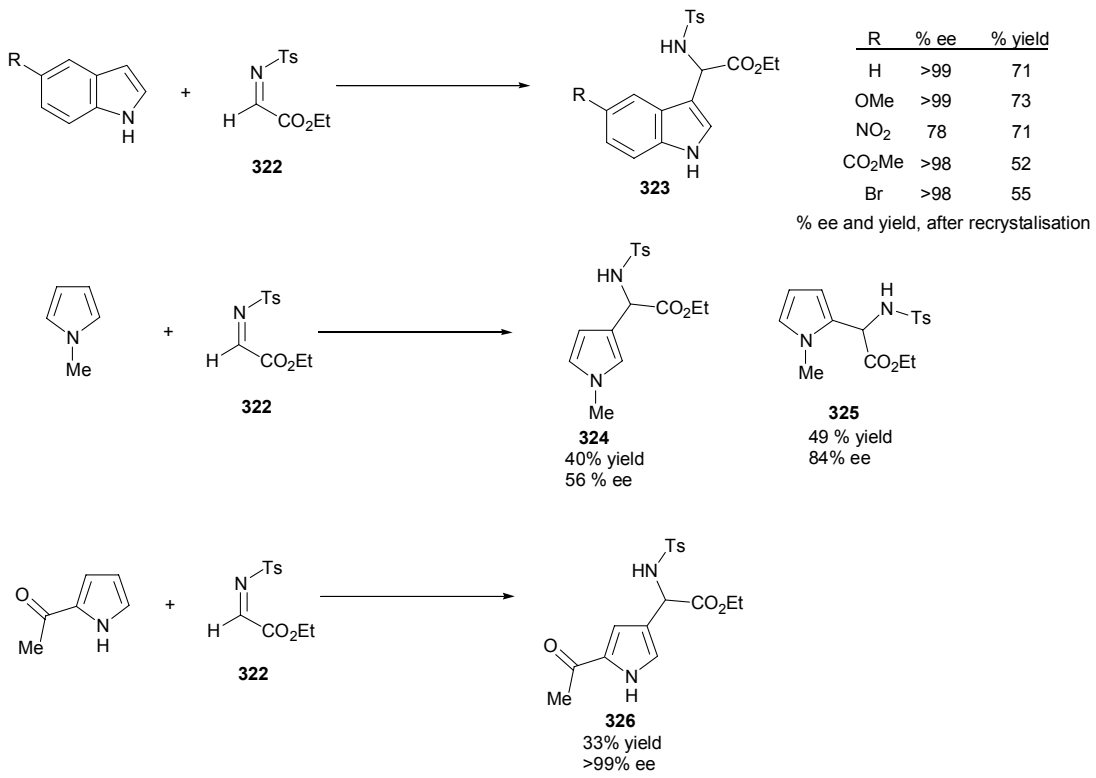
Development of the Pyruvate-Prins Cyclisation

Two interesting and separate developments in Prins-chemistry have been the hetero-Prins reactions proposed by Ghosh[5,6] and Rychnovsky[7] (Scheme 105, and Chapter 1). Ghosh's work has led to the development of an intermolecular three-component coupling using cyclic enol ethers as a core element to yield 2,3- disubstituted tetrahydropyrans and furans (Scheme 105). Rychnovsky has developed an intermolecular hetero-Prins reaction, using an intramolecular Prins trap to provide 2,4,6-trisubstituted tetrahydropyrans.



Scheme 105

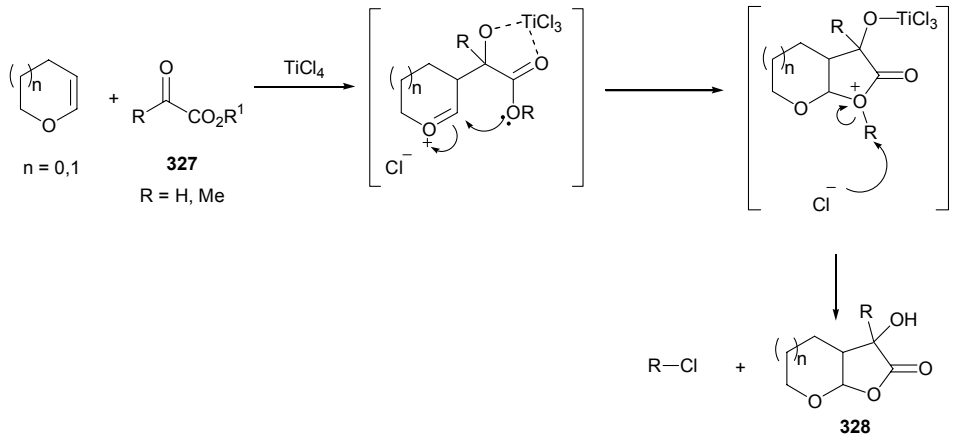
In 1999 Johannsen[8] reported the enantioselective electrophilic addition of *N*-tosylimino esters **322** to indole and pyrrole using copper (I) Tol-BINAP catalysts (Scheme 106). Indole reacts with very good enantioselectivity and yield to give 3-substituted products **323**, whereas *N*-methylpyrrole gives a mixture of products resulting from both 2- and 3-substitution **324** and **325**. Deactivated 2-acetylpyrrole gives 4-substituted products, **326**, in good yield and very high enantioselectivity.



Scheme 106

A fusion of these chemistries, initial intermolecular reaction of a cyclic enol ether, followed by intramolecular trapping could potentially lead to 6,5- and 5,5 bicyclic systems (Scheme 107), most notably furo[2,3-*b*]pyrans and furo[2,3-*b*]furans, **328**.

Using Ghosh's[6] cyclic enol ether hetero-Prins reactions as a basis for the study, an enophile, **327**, must be developed with a suitable leaving group, R, in the fashion of Rychnovsky. Glyoxylates, due to their reactivity and tendency to dimerise, led to the choice of pyruvates for investigation.



Scheme 107

The expected product of the pyruvate-Prins cyclisation is also a rigid, highly stereodefined and functionalised system, **328**. This structure provides several points for structural development in a similar fashion to that reported by Schreiber (Figure 11).

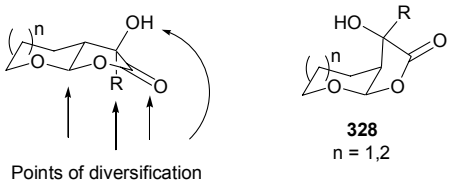
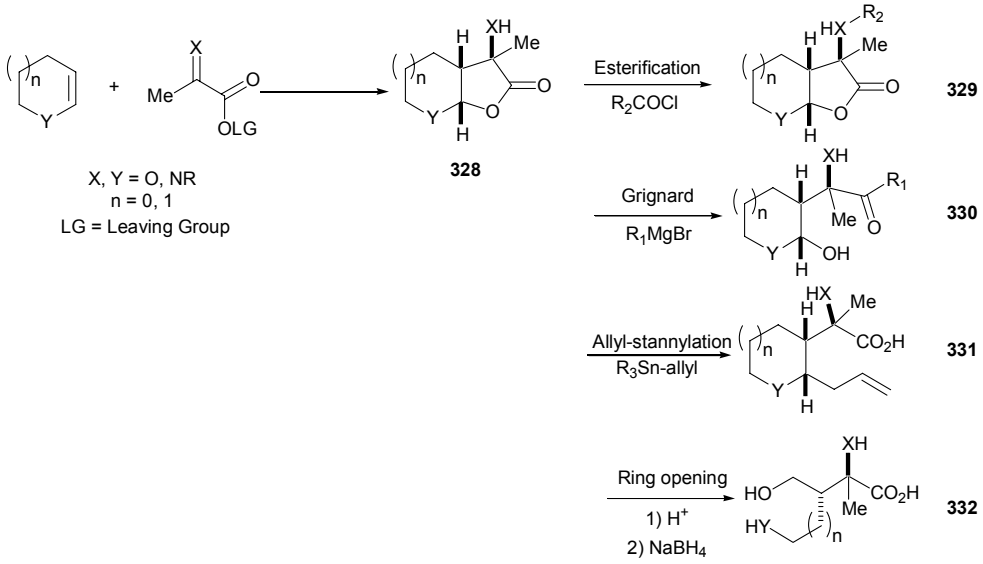


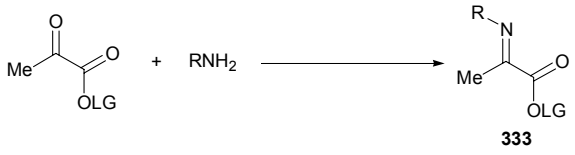
Figure 11 Examples of rigid bicyclic furopyrans.

Examples of simple elaborations would be esterification or amide formation, **329** (Scheme 108). Grignard reagents react at the lactone carbonyl to give hydroxy-ketones **330**, and allyl stannylation affords the ε-unsaturated acid **331**. Opening the acetal ring would reveal an aldol motif **332**.



Scheme 108

Furthermore, imines and heterocyclic nitrogen compounds could be incorporated to extend the range of possible products. Whilst the reaction has been discussed mainly in terms of the pyruvate-system, *in situ* imine formation would lead to the imine derivatives such as **333**, (Scheme 109)

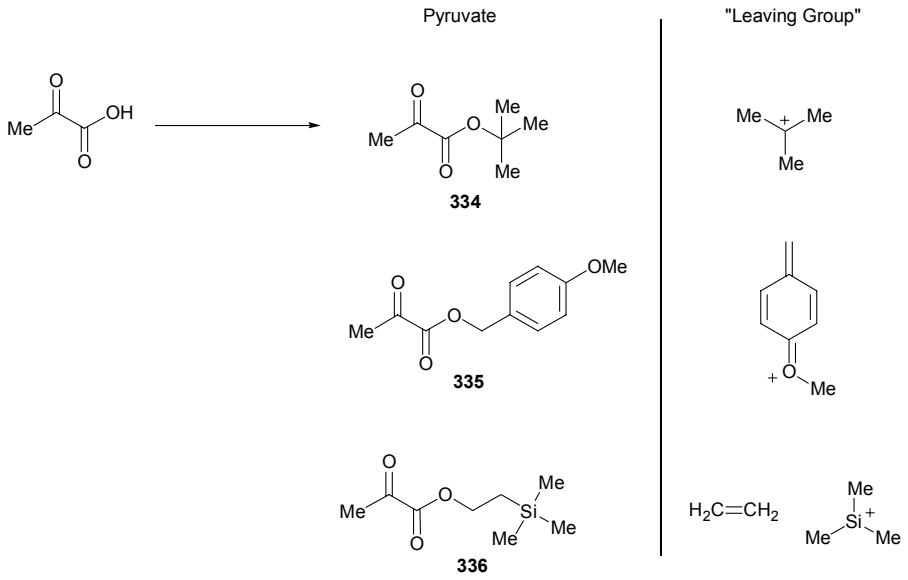


Scheme 109

Identification of a suitable leaving group

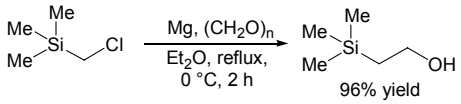
One of the crucial variables to be explored was that of the leaving group. Rychnovsky used TMS as a leaving group in his hetero-Prins reactions, however *O*-trimethyl silyl esters are very labile groups and were thought unlikely to survive the

reaction conditions. Therefore a preliminary investigation into suitable candidates was made. *Tert*-butyl **334**, *p*-methoxy benzyl **335**, or a trimethylsilylethyl (TMSE) esters **336** were all considered as attractive alternatives, as all were accessible from pyruvic acid (Scheme 110), and contained potentially good leaving groups.



Scheme 110

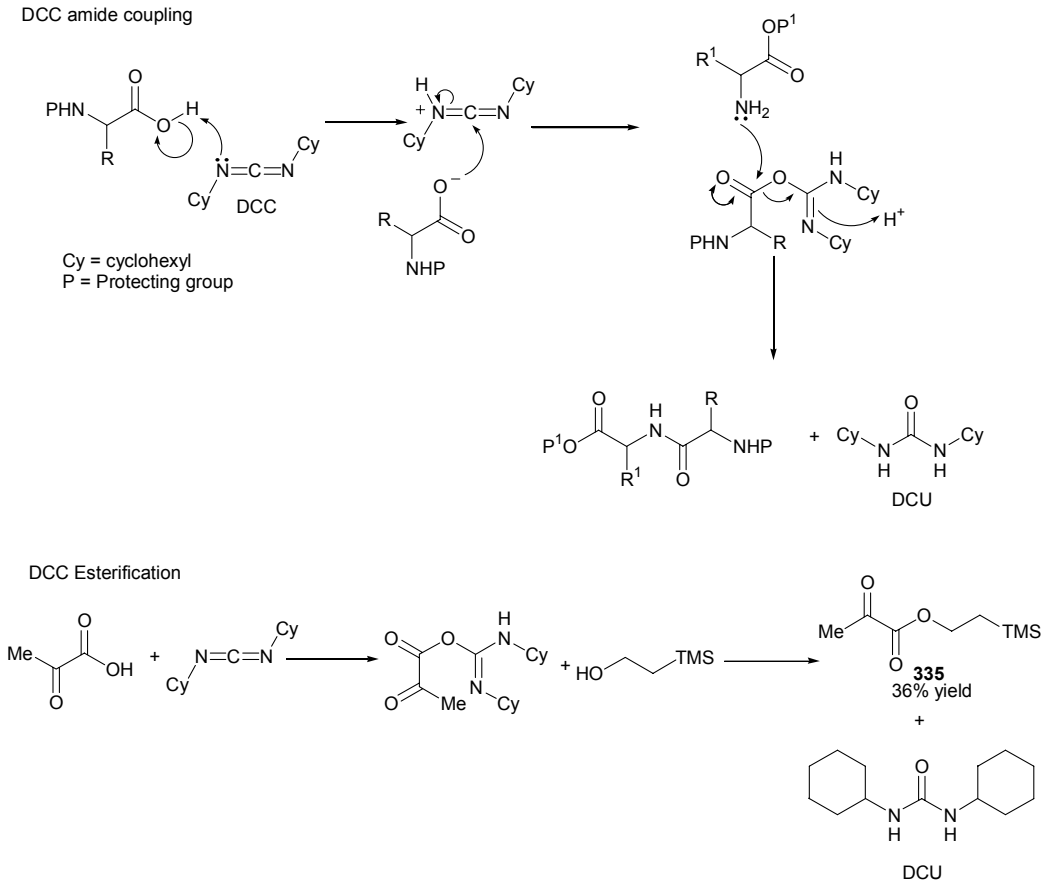
2-Trimethylsilyl ethanol is commercially available, if somewhat expensive, and is easily obtainable from the Grignard reaction of α-(chloromethyl)-trimethylsilane, magnesium and paraformaldehyde (Scheme 111).[9]



Scheme 111

Dicyclohexylcarbodiimide (DCC) is frequently used as a coupling reagent for amide formation between carboxylic acids and amines (Scheme 112). DCC has also been

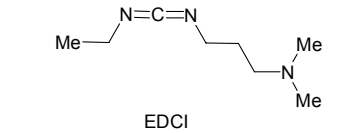
described in the coupling of carboxylic acids and alcohols to form esters. When applied to the TMSE- pyruvate system, DCC caused complications in chromatographic purification, giving the TMSE-pyruvate **336** in low yield. Whilst the central urea group is very polar, the combination with the large hydrophobic cyclohexyl groups causes dicyclohexyl urea (DCU) to interact in a variable manner with the silica gel, causing DCU to be found in most fractions taken from the column.



Scheme 112

EDCI is an alternative to DCC, having much smaller alkyl substituents, reducing its hydrophobic nature, and an amino group, thereby increasing the polarity, to the

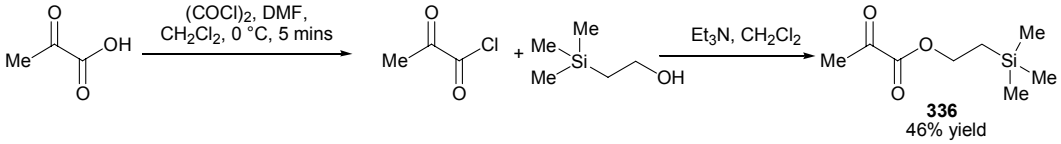
extent that it can be easily removed by aqueous extraction. Surprisingly, using EDCI however made no appreciable improvement to the yield. This is thought to be due to the highly reactive nature of carbodiimides.



EDCI
(3-Dimethylamino-propyl)-ethyl-carbodiimide

Figure 12

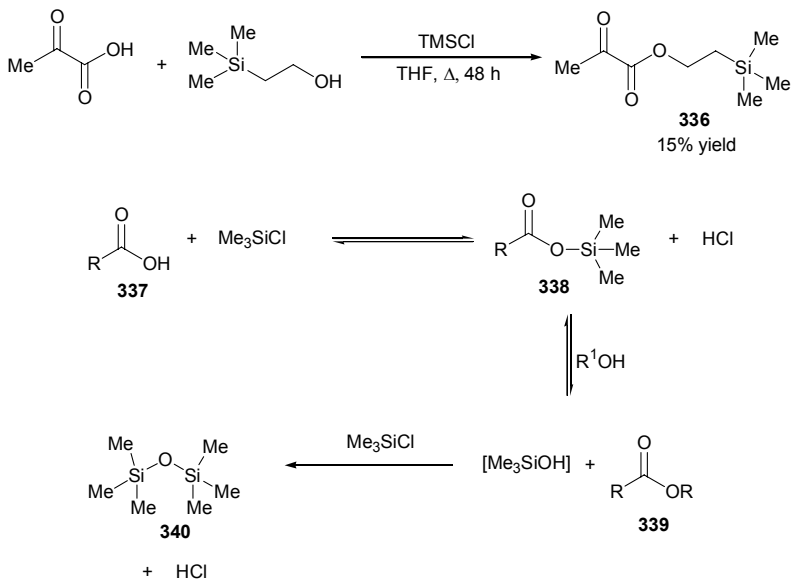
Conversion of pyruvic acid to its acid chloride using oxalyl chloride[10] was examined (Scheme 113), but found to give only slightly better results than the DCC coupling. This is probably due to the sensitivity of the acid chloride intermediate.



336
46% yield

Scheme 113

Trimethylsilyl chloride has been shown by Chan[11] to be useful for the formation of esters, including 2-trimethylsilyl ethyl esters of a range of aromatic and aliphatic acids (Scheme 114). Activation of acid **337** by conversion to the silyl ester **338** is followed by attack by the alcohol, forming the ester **339** and trimethylsilanol, which finally reacts with additional trimethylsilyl chloride to form the hexamethyldisiloxane, **340**. However, when applied to the pyruvate system, yields of the desired ester were very low.



Scheme 114

Finally, sodium hydrogen sulphate on silica gel was found to be an excellent reagent for the esterification procedure. In 1999 Das[12] reported that aliphatic carboxylic acids could be esterified in the presence of aromatic carboxylic acids using sodium hydrogen sulphate on silica gel (Table 11). Furthermore, Das demonstrated that the selectivity occurred in molecules possessing both aliphatic and aromatic carboxylic acids as well as in competition experiments (Table 11, entries 12-14).

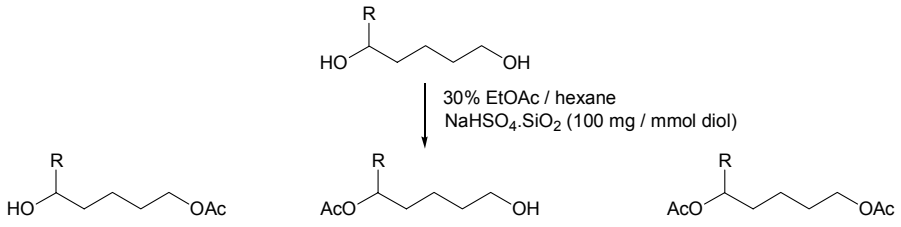
Table 11 $NaHSO_4.SiO_2$ mediated esterification of aromatic and aliphatic acids.

Entry	Acid	Alcohol	Time (h)	Isolated yield A*	Isolated yield B**
1	4-Hydroxyphenylacetic acid	MeOH	5	95	
2	4-Hydroxyphenylacetic acid	EtOH	5	92	
3	4-Hydroxyphenylacetic acid	*i*-PrOH	5.5	89	
4	Phenylacetic acid	EtOH	5	96	
5	Phenylacetic acid	BnOH	6	88	
6	Stearic acid	MeOH	5	92	
7	Pyruvic acid	BnOH	6	87	
8	2-Carboxyphenylacetic acid	MeOH	4.5	96	0
9	Benzoic acid	MeOH	14		6
10	3,5-Dinitrobenzoic acid	MeOH	6		4
11	3-Chlorobenzoic acid	MeOH	15		5
12	Phenylacetic acid and benzoic acid	MeOH	6	95	3
13	4-hydroxyphenylacetic acid and benzoic acid	EtOH	7	94	3
14	Stearic acid and 3-chlorobenzene	MeOH	6	91	2

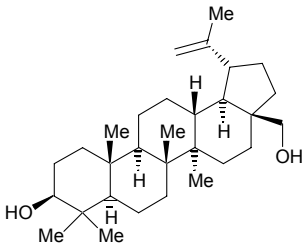
*A: Ester derived from aliphatic carboxylic acid group.

**B: Ester derived from aromatic carboxylic acid group.

In 1997, Breton[13] described the monoacetylation of unsymmetrical diols using sodium hydrogen sulphate on silica gel and ethyl acetate (Scheme 115). The reaction showed selectivity towards primary over secondary alcohols. The main by-product was the diester, in up to 12% yield, with the secondary ester only being produced in 4% yield.



R	% yield of 1° monoester	ratio of 1° to 2° ester
Me	70	95:5
Et	72	98:2
n-Bu	70	95:5
s-Bu	72	97:3

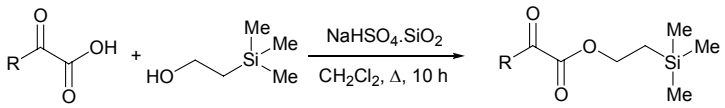


69

Scheme 115

Modification of Breton's method,[12,13] using DCM heated to reflux, rather than hexane gave the TMSE-pyruvate **336** in good yield (Scheme 116). This reaction also proved useful in producing homologues of the pyruvate, substituting methyl for

ethyl. An attempt was made to synthesise the phenyl and benzyl derivatives, but these reactions were lower yielding and were not able to be optimised.

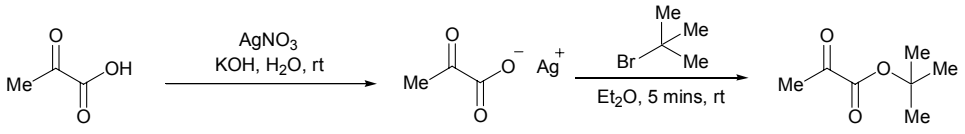


336, R = Me, 62% yield
341, R = Et, 36% yield

Scheme 116

The *p*-methoxybenzyl group proved to be too labile and all of the procedures detailed in obtaining the TMSE-substituted pyruvate were unsuccessful; this compound was therefore abandoned.

Reaction of pyruvic acid with basic $AgNO_3$ gave the pyruvate silver salt, **342** (Scheme 117). Shaking the silver salt of pyruvic acid with 2-bromo-2-methylpropane for 5 minutes in dry ether gave *t*-butyl pyruvate **334** in overall 50% yield.



342

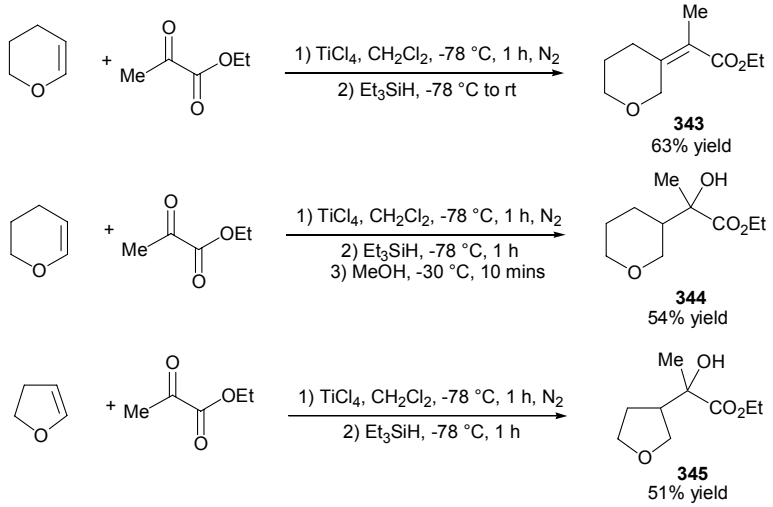
334
50% yield overall

Scheme 117

Pyruvate-Prins addition and cyclisation reactions

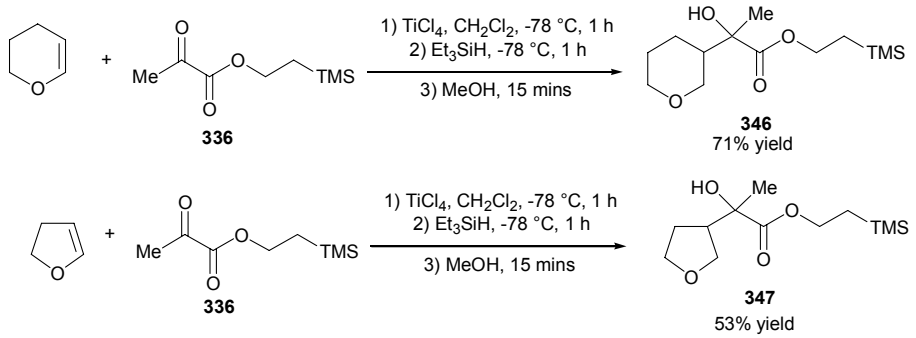
Before embarking on reactions with pyruvates, to ascertain whether pyruvates would be as successful as glyoxylates in the hetero-Prins reaction, 2,3-dihydrofuran and

3,4-dihydropyran were reacted with ethyl pyruvate at –78 °C using $TiCl_4$, followed by triethylsilane to furnish the mono-substituted heterocyclic product. The product of the reaction of 3,4-dihydropyran with ethyl pyruvate was found to be the *conjugated ester* **343** resulting from elimination of water (Scheme 118). An excess of methanol added at –30 °C was found to suppress this elimination, to give hydroxyl **344**. Elimination in the pyruvate series is believed to occur more readily than in the glyoxylate series due to the favourable formation of the tetrasubstituted alkene. Reaction of 2,3-dihydrofuran under the same reaction conditions led directly to *hydroxy product* **345** without the need to add any quenching agent. In both cases, no clear evidence could be observed in the ^1H NMR spectrum of the hydroxy products for the presence of diastereomers. A possible reason for no elimination being observed in the five-membered ring system is that an alkene in this position in a five-membered ring would constrain the bond angles (hence $\theta \neq 120°$), whereas a six-membered ring would be less constrained and therefore elimination is more energetically favourable.



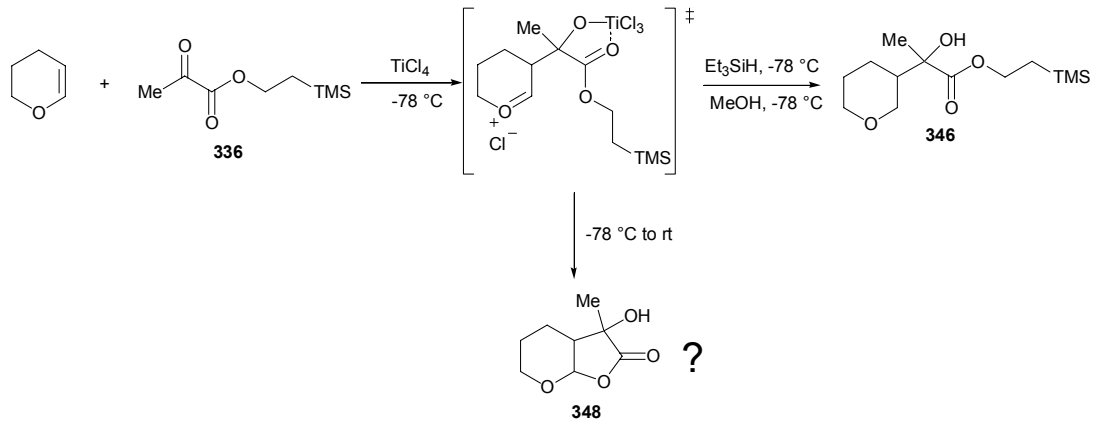
Scheme 118

Following these results, hetero-Prins reactions involving TMSE-pyruvate and *t*-butyl pyruvate were examined to determine if they would perform in the same manner. In the reaction of TMSE-pyruvate with dihydropyran and dihydrofuran, the use of methanol to quench the reaction at –78 °C allowed access to the hydroxy-TMSE esters **346** and **347** (Scheme 119).



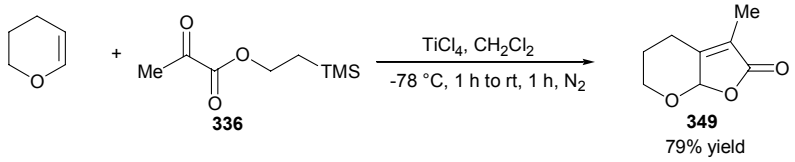
Scheme 119

At –78 °C it was found that even under extended reaction times (> 48 h) the cyclisation reaction using TMSE-pyruvate failed to occur and the addition product was obtained. Following Ghosh's original procedure, after the addition of the pyruvate the reaction was allowed to warm to room temperature with removal of the cool-bath. It was believed that after the initial intermolecular reaction, as the temperature rose, the cyclisation would occur (Scheme 120).



Scheme 120

Use of the *t*-butyl pyruvate only ever gave the addition product and this compound was abandoned. However, using TMSE-pyruvate with 3,4-dihydropyran, the cyclisation reaction occurred in good yield. Unfortunately, elimination occurred to give the bicyclic α,β-unsaturated γ-lactone **349** (Scheme 121).

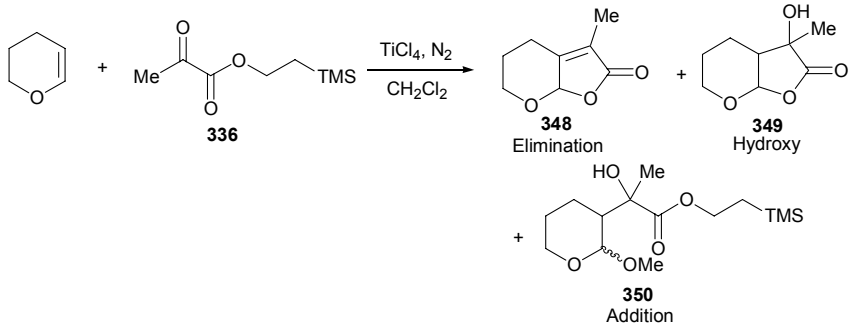


Scheme 121

The work-up reported by Ghosh was to pour the reaction mixture into saturated sodium bicarbonate and to extract the organic layer, however it was observed that this regularly led to an awkward white precipitation that occupied the phase boundary between the organic and aqueous layers. This precipitate was particularly difficult to remove by filtration and made separation techniques troublesome. It was considered possible that the elimination was occurring during the work-up of the reaction. Altering the aqueous medium, into which the reaction was poured, from sodium bicarbonate to ammonium chloride, gave two clear phases that were easily

separated. Whilst this made the reaction much easier to work-up, it had no effect on the elimination.

Referring back to reactions of 3,4-dihydropyran and 2,3-dihydrofuran with ethyl pyruvate, it was decided to use a methanol quench before work-up in an attempt to suppress the elimination. However, the question arose: At what temperature could the quench be used? Considering that at –78 °C the addition, but not cyclisation occurs, and when the reaction is warmed to room temperature elimination occurs, the temperature at which the cyclised hydroxy product is formed is crucial. It was found that after reaction for 12 hours between –30 °C and –40 °C the cyclisation had occurred, but not elimination (Scheme 122 and Table 13). The addition product **350** was never isolated in a pure form.



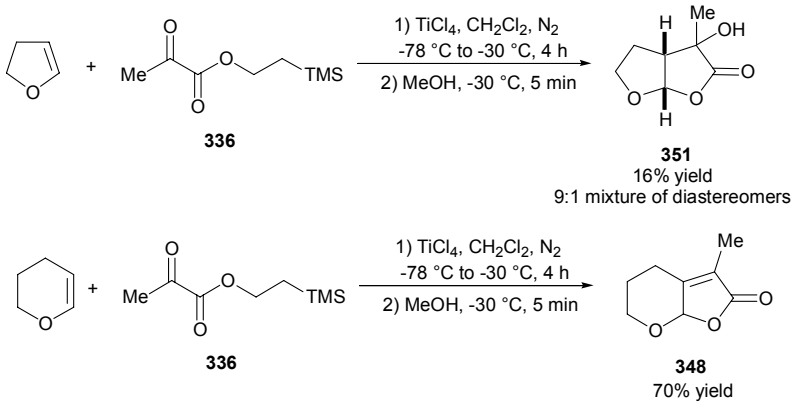
Scheme 122

Table 13 Examination of cyclisation temperature

Entry	Temperature (°C)*	Product
1	-78	Addition **350**
2	-60	Addition **350**
3	-50	Addition **350**
4	-40	Hydroxy **349**
5	-30	Hydroxy **349**
6	-20	Elimination **348**

* One hour at –78 °C followed by 12 hours at given temperature, then quench with MeOH and warming to room temperature.

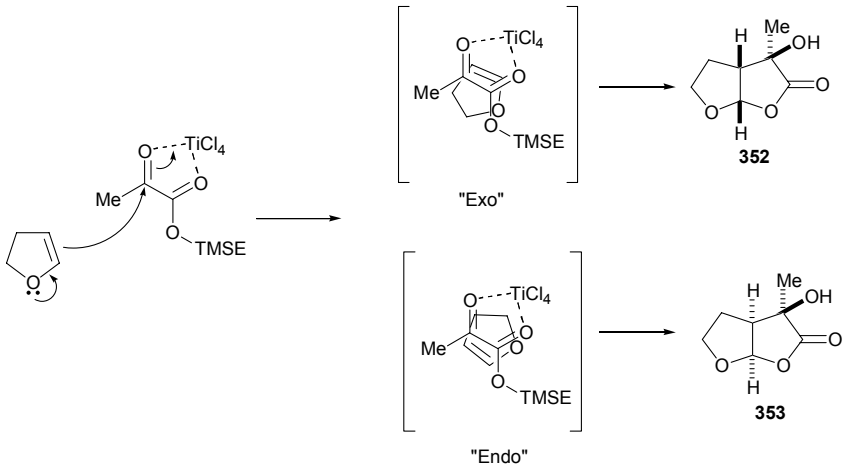
With 2,3-dihydrofuran, a methanol quench gave the desired 5,5-bicyclic hydroxy product **351**, albeit in low yield (Scheme 123). However, when 3,4-dihydropyran was exposed to identical reaction conditions, elimination still occurred.



Scheme 123

From ^{1}H NMR analysis, **351** was seen to be a diastereomeric mixture and a doublet at 6.11 (major) and 5.95 (minor) for the acetal protons was observed in a 9:1 ratio. Similarly, a diastereomeric signal was observed for the methyl group at 1.20 (minor) and 1.19 (major) in the same 9:1 ratio. The major diastereomer with regards to the acetal position is most likely to be a *cis*-fused ring system (Scheme 124). Attack of the dihydrofuran on the Ti-pyruvate complex can occur from either face, although top-face attack is illustrated in **352** and **353**. In the "endo"-type transition state, the ring of the dihydrofuran is away from the titanium centre, and in the "exo"-type transition state the dihydrofuran ring eclipses the titanium centre. Due to the lack of secondary orbital interactions, the less sterically demanding "exo" transition state is the most plausible. However, only after separation of the diastereomers could NOE

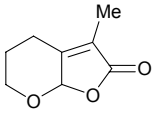
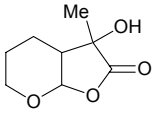
experiments and x-ray analysis of crystalline derivatives shed light on the orientation of the methyl group.



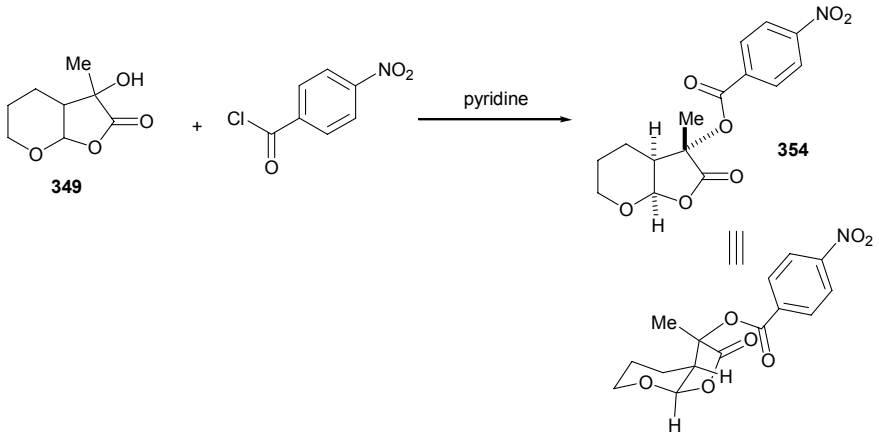
Scheme 124

After attempts at suppressing elimination in the 6,5-system using methanol failed, a number of different additives were examined for effectiveness, including triethylamine and ethylene glycol, however no hydroxyl product was observed. It was then decided to examine how changing the solvent affected the reaction, as all reactions to that point had been carried out in DCM. Toluene and THF were chosen as less-polar and more-polar solvents respectively (Table 14). Whilst the reaction failed in toluene, THF provided the hydroxy product **349** in 17% yield.

Table 14 Solvent effect on the reaction of 3,4-dihydropyran and TMSE-pyruvate

Entry	Solvent	Product	Yield (%)
1	DCM	 **348**	70
2	Toluene	No product recovered	–
3	THF	 **349**	17

Interestingly, no diastereomeric signals for the acetal proton or the methyl protons could be seen in the ^{1}H NMR spectrum of 6,5-hydroxy **349** indicating only a single diastereomer was present. Reaction of 6,5-hydroxy product **349** with 4-nitro benzoyl chloride gave the *p*-nitro benzoate ester **354** which crystallised from DCM / petrol. X-ray analysis of this compound showed *cis*-ring fusion and the hydroxyl group on the same face as the ring-junction protons (Scheme 125 and Figure 13).



Scheme 125

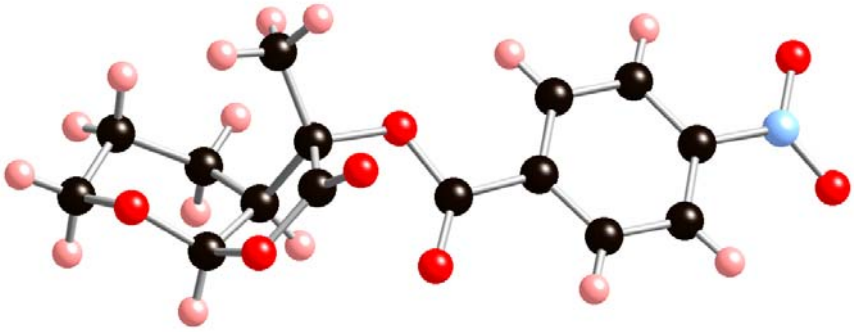
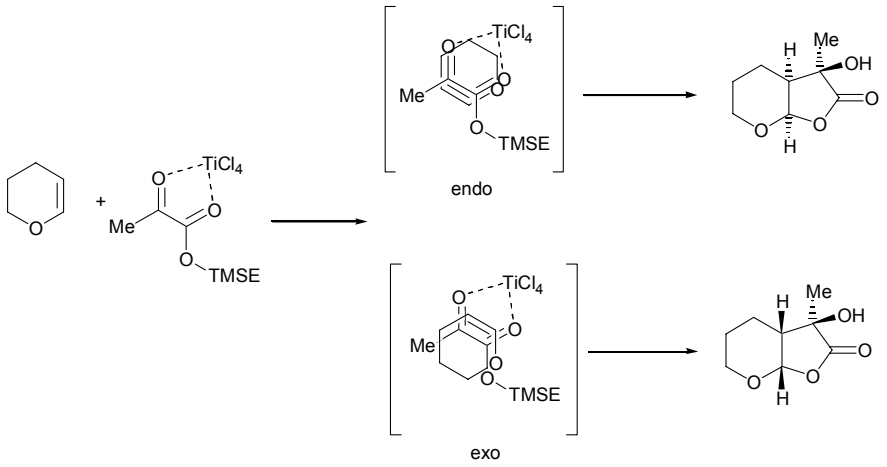


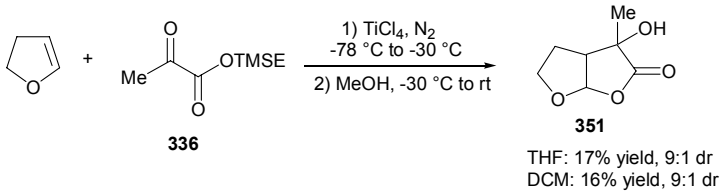
Figure 13 X-ray crystal structure of **354**

In a similar fashion to the reaction of dihydrofuran, dihydropyran can occupy an "endo" or "exo" position on attack (Scheme 126), however the cyclohexyl ring is more sterically demanding and so products of the "endo" transition state are less likely to be found. As the x-ray structure shows, the initial attack by dihydropyran occurs with the hydroxyl group *cis* to the ring-junction protons and the methyl group positioned over the pyran ring.



Scheme 126

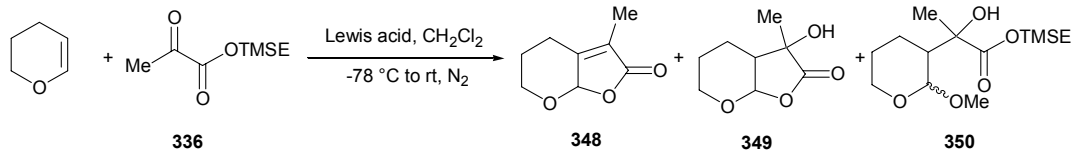
After finding that hydroxy **348** was accessible using THF, the reaction using 2,3-dihydrofuran and TMSE-pyruvate was carried out in THF, to discover if the yield of **351** could be improved. However, despite all attempts, the reaction in THF afforded no significant increase in yield and no change in the diastereoselectivity (Scheme 127).



Scheme 127

Titanium tetrachloride is generally considered a strong Lewis acid, and the low yield of the hydroxy-products could possibly be due to decomposition of the products promoted by $TiCl_4$. To probe this hypothesis the less-Lewis acidic titanium *iso*-propoxide trichloride and titanium di-*iso*-propoxide dichloride were studied for their effectiveness in the Prins reaction (Scheme 128). It was found that whilst both

reagents promoted the addition of the cyclic enol ether to the pyruvate, conditions were not found to promote the cyclisation.



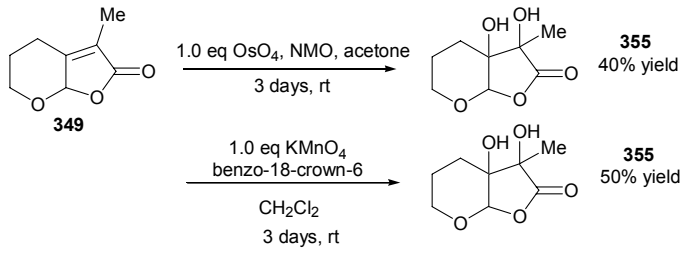
336 **348** **349** **350**

	%yield:		
	348	**349**	**350***
Ti(O*i*-Pr)Cl_3	0	0	67
Ti(O*i*-Pr)$_2Cl_2$	0	0	65

* based on crude yield

Scheme 128

With access to moderate amounts of **349**, functionalisation was investigated with the dihydroxylation of the double bond (Scheme 129) to give dihydroxy **355**. Both osmium tetroxide and potassium permanganate with benzo-18-crown-6 were found to perform the dihydroxylation, albeit in moderate yield over extended reaction times.



349

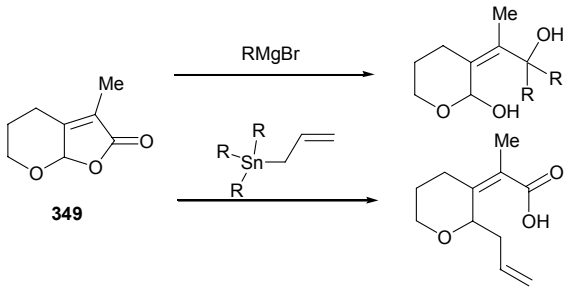
355 40% yield

355 50% yield

Scheme 129

Conclusions and Further Work

The first successful pyruvate-Prins reaction has been demonstrated using simple substrates for example ethyl pyruvate. The pyruvate-Prins reaction has been shown to be effective in producing bicyclic furo[2,3-*b*]pyrans and furo[2,3-*b*]furans. The trimethylsilylethyl group has been shown to be a very successful leaving group and particularly efficient in effecting the cyclisation. Cyclisations using TMSE-pyruvate were successfully accomplished. Unsaturated lactone bicycle **349** has been synthesised in good yield; has been dihydroxylated and shows promise for further elaboration, e.g. allyl stannylation addition or reaction with Grignard reagents (Scheme 130).



Scheme 130

Whilst yields of hydroxy products **348** and **351** are not high, due to time constraints these reactions have not been optimised. Further investigation of reaction solvents is required; ether has been shown to be a good solvent for titanium catalysed-ene reactions and in light of results using THF, may well prove advantageous. Further screening of Lewis acids should also be investigated, as even though titanium tetrachloride has so far been demonstrated to be most effective, being required in stoichiometric amounts, it is certainly not ideal. The rigid, stereodefined nature of

hydroxy furo[2,3-*b*]pyran **348** has been demonstrated by x-ray crystallography of the *p*-nitrobenzoate derivative **354**.

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Chapter 5: Experimental Section

General Experimental

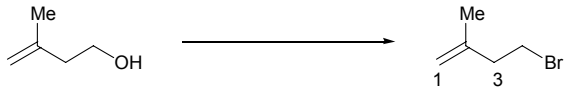
Prior to use, solvents were dried and purified in the following manner: Diethyl ether, tetrahydrofuran, hexane, and toluene were distilled under nitrogen from sodium, using the anion of benzophenone ketal as an indicator where necessary; dichloromethane and acetonitrile were distilled under nitrogen from calcium hydride. Petrol refers to the fraction of light petroleum, possessing bp 40-60 °C.

Unless otherwise stated, commercially available reagents were used as purchased. Purification, where appropriate, followed procedures detailed in Purifications of Laboratory Chemicals (D. D. Perin, W. L. F. Armarego, 3rd Ed., 1988, Pergammon Press, Oxford). All experiments were performed under an inert atmosphere of nitrogen (N_2) or argon (Ar) unless otherwise stated.

^{1}H NMR spectra were recorded from samples in either $CDCl_3$ or d_6-DMSO solution at 270 MHz; 300 MHz or 400 MHz using JEOL EX 270 MHz; BRUKER AM 300 MHz or JEOL EX 400 MHz instruments respectively. Chemical shifts are reported in parts per million (ppm) using tetramethyl silane (δ_H = 0.00 ppm) or residual $CHCl_3$ (δ_H = 7.26) as an internal reference. ^{13}C NMR spectra were recorded in $CDCl_3$ at 100 MHz; 75 MHz; and 68 MHz using a JEOL 400 MHz; a BRUKER AM-300 MHz and JEOL EX 270 MHz spectrometer respectively, using $CDCl_3$ (δ_C = 77.0 ppm) as an internal reference. All *J* couplings are quoted in Hz. IR spectra were recorded in the range of 4000-600 cm^{-1} as liquid films or as Nujol mulls, using a Perkin Elmer FT1000 spectrometer. Mass Spectra were recorded at the University of Bath using a Finnigan MAT 8340 instrument or at the EPSRC Mass Spectroscopy Centre, Swansea. Thin layer chromatography was carried out using glass-backed plates with Merck Kieselgel 60 GF_{254} coating or aluminium-backed plates with Merck G/UV_{254} coating. Plates were visualised using UV light (254 nm) and/or by

staining with potassium permanganate, vanillin, cerium ammonium molybdate, *p*-anisaldehyde, or phosphomolybdic acid followed by heating, or with iodine on silica as required. Flash chromatography was carried out using Merck 60 H silica gel. Samples were loaded onto the column as either a saturated solution or pre-absorbed onto silica gel before purification.

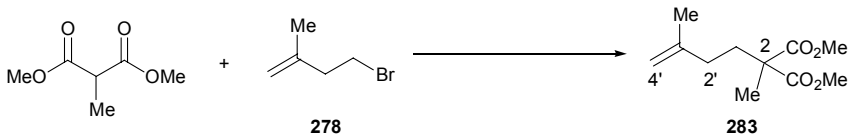
Preparation of 4-bromo-2-methyl-but-1-ene (278)[1]



279 **278**

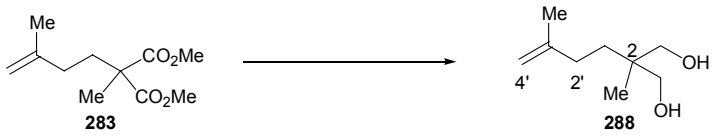
N-Bromosuccinimide (2.27 g, 12.8 mmol) was added carefully with vigorous stirring to a solution of triphenylphosphine (3.65 g, 13.9 mmol) and 3-methyl-3-buten-1-ol (1.17 mL, 11.6 mmol) in DCM (3 mL) and maintained at –20 °C, then stirred for an additional hour at –20 °C. The reaction was warmed to room temperature and diethyl ether (10 mL) was added and the reaction mixture washed with saturated $NaHCO_3$ (2 × 5 mL), brine (5 mL) and the organic layer was dried with $MgSO_4$. Then the organic layer was treated with petrol causing a precipitate to form. The precipitate was removed by filtration through a short pad of silica. The solvents were removed by distillation at atmospheric pressure to yield a yellow oil. The product was purified by distillation under reduced pressure to give bromide **278** (1.70 g, 97 %) as a clear colourless liquid. R_f 0.9 (petrol); bp. 45 °C at 42 mmHg (lit bp. 40 °C at 40 mmHg); ν_{max} (liquid film)/cm^{-1} 3097 (C=C-H), 2970, 2936 (CH_2, CH_3), 1652 (C=C), 1450 (CH_2), 895 ($R_2C=CH_2$), 644 (C-Br); δ_H (400 MHz; $CDCl_3$) 4.85 (1H, s, 1 × H-1), 4.75 (1H, s, 1 × H-1), 3.48 (2H, t, *J* 7.3, 2 × H-4), 2.58 (2H, t, *J* 7.3, 2 × H-3), 1.75 (3H, s, 2-Me); δ_C (75 MHz; $CDCl_3$) 142.7 (C-2), 113.2 (C-1), 41.3 (C-3), 31.0 (C-4), 22.5 (2-Me); *m/z* (EI+) 151.0, 149.9 (5 %, *M*-H)$^+$, 149.0, 147.9 (25, *M*-H)$^+$, 68.9 (100, *M*-HBr)$^+$, 55.0 (54, C_4H_7)$^+$, 41.0 (86, C_3H_5)$^+$; Found (*M*)$^+$ 146.9811, C_5H_8Br requires 146.9809.

Preparation of 2-methyl-2-(3-methyl-but-3-enyl)-malonic acid dimethyl ester (283)



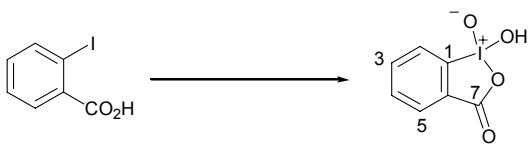
Freshly distilled dimethyl methylmalonate (13.40 mL, 100 mmol) was added dropwise to a stirred solution of sodium hydride (3.86 g, 100 mmol, 60 % dispersion in oil) (washed with anhydrous hexane to remove oil) in distilled DMF (150 mL) cooled by an ice/water bath to 0 °C. A white precipitate formed. The reaction mixture was stirred for 30 minutes at 0 °C, and then bromide **278** (10.0 g, 67.0 mmol) was added dropwise and the reaction was stirred for three hours at room temperature. The reaction mixture was poured into ice/water and extracted three times with diethyl ether (3 × 150 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc – petrol) to furnish *malonate* **283** (10.57 g, 73 %) as a yellow liquid; R_f 0.72 (20 % EtOAc – petrol); ν_{max} (liquid film)/cm^{-1} 3076 ($C=CH_2$), 2954, 2854 (CH_2, CH_3), 1736 (C=O), 1650 (C=C), 1435 (CH_2), 1378 (CH_3), 887 ($C=CH_2$); δ_H (400 MHz; $CDCl_3$) 4.61 (1H, s, *J* 5.7, 1 × H-4'), 4.59 (1H, s, *J* 5.7, 1 × H-4'), 3.62 (6H, s, 2 × OMe), 2.01-1.92 (2H, m, 2 × H-1'), 1.91-1.87 (2H, m, 2 × H-2'), 1.63 (3H, s, 3'-Me), 1.34 (3H, s, 2-Me); δ_C (75 MHz; $CDCl_3$) 173.0 (2 × C-1), 145.1 (C-3'), 109.5 (C-4'), 56.6 (C-2), 52.7 (2 × MeO), 34.1 (C-1'), 32.7 (C-2'), 22.8 (3'-Me), 20.2 (2-Me); *m/z* (CI+) 215.0 (100 %, M+H)$^+$, 145.9 (10, M-C_5H_9)$^+$, 69.1 (7, C_5H_9)$^+$; Found (M +H)$^+$ 215.1284, $C_{11}H_{19}O_4$ requires 215.1283.

Preparation of 2-methyl-2-(3-methyl-but-3-enyl)-propane-1,3-diol (288)



A solution of malonate **283** (0.50 g, 2.3 mmol) in dry diethyl ether (10 mL) was added dropwise to a stirred solution of lithium aluminium hydride (0.18 g, 4.7 mmol) in diethyl ether (5 mL), at 0 °C under N_2. The mixture was warmed to room temperature and allowed to stir for 3 hours. The reaction was then quenched by the careful addition of excess $Na_2SO_4 \cdot 10\ H_2O$. The mixture was then stirred overnight and the resulting white suspension was filtered through a $MgSO_4$ plug and washed thoroughly with hot THF (50 mL). The solvent was then removed *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc – petrol, then 50 % EtOAc – petrol) to give *diol* **288**, which was recrystallised from diethyl ether-petrol to provide colourless needles (0.22 g, 67 %). R_f 0.12 (20 % EtOAc – petrol); ν_{max} (nujol)/cm^{-1} 3362 (OH), 3073 (C=CH_2), 2928 (CH_2, CH_3), 1648 (C=C), 1470 (CH_2, CH_3), 1387 (CH_3), 1033 (C–O), 885 (C=CH_2); δ_H (270 MHz; $CDCl_3$) 4.71 (2H, s, 2 × H-4'), 3.56 (4H, s, 4 × H-1), 2.07-1.91 (2H, m, 2 × H-2'), 1.78 (3H, s, 3'-Me), 1.45-1.32 (2H, m, 2 × H-1'), 0.93 (3H, s, 2-Me). δ_C (75 MHz; $CDCl_3$) 145.3 (C-3'), 107.5 (C-4'), 68.5 (2 × C-1), 36.7 (C-2), 30.0 (C-2'), 29.3 (C-1'), 20.6 (3'-Me), 16.3 (2-Me); *m/z* (CI+) 159.0 (100 %, M+H)$^+$, 143.0 (10, M-OH)$^+$, 104.0 (38, M-C_4H_7)$^+$, 88.0 (35, M-$C_5H_{11}O$)$^+$; Found (M +H)$^+$ 159.1383, $C_9H_{19}O_2$ requires 159.1385.

Preparation of IBX



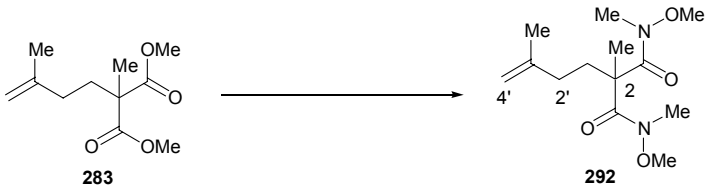
IBX was prepared according to the method of Santagostino.[2] CAUTION: IBX is reported to explode on impact and heating above 230 °C.

2-Iodobenzoic acid (5.0 g, 20 mmol) was added to a 0.45 M solution of oxone (potassium monopersulphate triple salt, 37.2 g, 61 mmol) in deionised water (200 mL) in a 0.5 L flask. The suspension was stirred at 70 °C (internal temperature) for 1 h, giving a clear solution. The solution was cooled to 0 °C for 30 minutes, then filtered using a sintered funnel. The crystals were washed with water (6 × 100 mL) and acetone (2 × 100 mL) and dried overnight at ambient temperature and pressure to give IBX (4.7 g, 80 % yield) as small colourless cubes. The washing liquors were treated with solid Na_2SO_3 (185.4 g, 122 mmol) and the pH adjusted to 7 using 1M NaOH before disposal (NB. exothermic). δ_H (300 MHz; $CDCl_3$) 8.15 (1H, d, *J* 11.5, H-5), 8.04 (1H, d, *J* 6.4, H-2), 7.95 (1H, t, *J* 6.4, H-3), 7.85 (1H, t, *J* 11.5, H-4), 3.75-3.12 (1H, br. s, OH); δ_C (100 MHz; $CDCl_3$) 167.3 (C-7), 146.4 (C-3), 133.2 (C-6), 132.8 (C-5), 131.2 (C-1), 130.0 (C-2), 124.8 (C-4).

Preparation of 2-methyl-2-(3-methyl-but-3-enyl)-malonaldehyde (289)

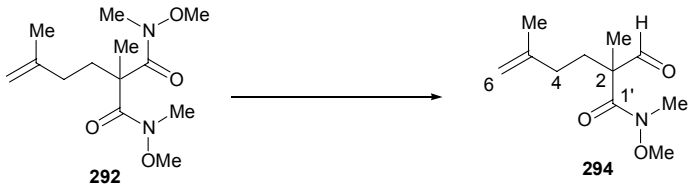
A 1.0 M solution of IBX was prepared by dissolution of IBX (1.40 g, 5.1 mmol) in DMSO (5 mL). Diol **288** (0.10 g, 0.63 mmol) in DMSO (5.0 mL) was added to the IBX solution and the reaction followed by TLC (40 % EtOAc – petrol). After 2 hours the reaction mixture was poured into water (20 mL) and the mixture extracted with diethyl ether (3 × 50 mL). The ethereal extracts were washed with water (100 mL) and dried with Na_2SO_4. The solvent was removed *in vacuo* to afford *dialdehyde* **289** (0.07 g, 72 % yield) as clear, straw-coloured oil. R_f 0.6 (40 % EtOAc – petrol); ν_{max} (liquid film)/cm^{-1} 3077 (C=CH_2), 2984, 2939 (CH_2, CH_3), 1746 (C=O), 1650 (C=C), 1439, 1373 (CH_2, CH_3), 847 (C=CH_2); δ_H (400 MHz; $CDCl_3$) 9.68 (2H, s, 2 × H-1), 4.76 (1H, s, 1 × H-4'), 4.63 (1H, s, 1 × H-4'), 2.08-1.92 (4H, m, 2 × H-2', 2 × H-1'), 1.72 (3H, s, 3'-Me), 1.33 (3H, s, 2-Me); δ_C (75 MHz; $CDCl_3$) 200.4 (2 × C-1), 144.0 (C-3'), 111.0, (C-4'), 62.1 (C-2), 31.8 (C-2'), 22.4 (C-1'), 22.4 (3'-Me), 14.7 (2-Me); (CI+) 172 $(M+NH_4)^+$, 155 $(M+H)^+$, 137 $(M-H_2O)^+$, 96; Found $(M+H)^+$ 155.1075, $C_9H_{15}O_2$ requires 155.1072.

Preparation of *N,N'*-dimethoxy-2,*N,N'*-trimethyl-2-(3-methyl-but-3-enyl)-malonamide (292)



Isopropyl magnesium chloride (2.0 M in THF, 36.2 mL, 72.4 mmol) was added dropwise using a syringe pump to a vigorously stirred solution of *malonate* **283** (5.0 g, 23.3 mmol) and *N,O*-dimethyl hydroxylamine hydrochloride (10.0 g, 102.7 mmol) in THF (20 mL) at –20 °C. The reaction was stirred at –20 °C overnight then poured directly into saturated ammonium chloride solution (250 mL), and extracted with diethyl ether (3 × 100 mL). The organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography (SiO_2, 20 % EtOAc – petrol) to give *bis-Weinreb amide* **292,** (2.0 g, 40 % yield) as a colourless oil. R_f 0.2 (20 % EtOAc – petrol); ν_{max} (liquid film)/cm^{-1} 2938 (CH_3, CH_2), 1658 (C=O), 1455 (NMe), 1371, 1173, 1113, 998, 889; δ_H (270 MHz; $CDCl_3$) 4.65 (1H, s, 1 × H-4'), 4.62 (1H, s, 1 × H-4'), 3.54 (6H, s, 2 × MeO-N), 3.02 (6H, s, 2 × Me-N), 1.87 (4H, ap. s, 2 × H-2', 2 × H-1'), 1.67 (3H, s, 3'-Me), 1.30 (3H, s, 2-Me); δ_C (75 MHz; $CDCl_3$) 176.2 (C-1), 145.4 (C-3'), 109.7 (C-4'), 60.9 (MeO), 50.9 (C-2), 33.7 (Me-N), 33.5 (C-2'), 31.5 (C-1'), 22.9 (3'-Me), 20.8 (2-Me).

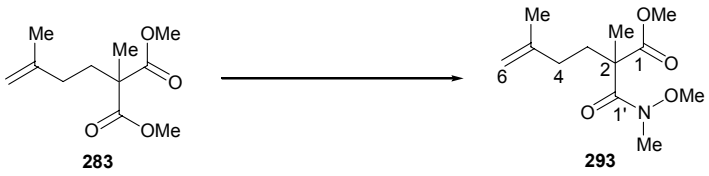
Preparation of 2-Formyl-2,5-dimethyl-hex-5-enoic acid methoxy-methyl-amide (294)



DIBAL-H (2.0M in toluene, 7.34 mL, 14.7 mmol) was added dropwise to a solution of bis-Weinreb amide **292** (1.0 g, 3.67 mmol) in toluene at –78 °C. The reaction was followed by TLC (20 % EtOAc – petrol). After 8 hours, the reaction mixture was poured into a saturated aqueous Na/K tartrate solution ("Rochelle's Salt", 50 mL) and the biphasic mixture stirred until both layers were clear. The layers were separated and the aqueous layer washed with EtOAc (4 × 50 mL), dried using Na_2SO_4 and the solvent removed *in vacuo*. Purification by flash chromatography (20 % EtOAc – petrol) gave *amido-aldehyde* **294** (0.48 g, 62 % yield) as a straw coloured oil. R_f 0.6 (20 % EtOAc – petrol); ν_{max} (liquid film) /cm^{-1} 3074 (H_2C=C), 2968, 2938 (CH_3, CH_2), 1724 (C=O), 1661 (O=C-N), 1458 (CH_2, CH_3), 1373 (CH_3), 1170 (N-OMe), 888 (C=C); δ_H (400 MHz; $CDCl_3$) 9.48 (1H, s, H-1), 4.63 (2H, s, 2 × H-6), 3.50 (3H, s, OMe), 3.14 (3H, s, N-Me), 2.84-1.86 (4H, m, 2 × H-3, 2 × H-4), 1.66 (3H, s, 5-Me), 1.25 (3H, s, 2-Me); δ_C (100 MHz; $CDCl_3$) 197.7 (C-1), 172.9 (C-1'), 144.9 (C-5), 110.0 (C-6), 60.6 (C-2), 56.0 (O-Me), 33.0 (N-Me), 32.0 (C-4), 31.7 (C-3), 22.6 (5-Me), 18.0 (2-Me).

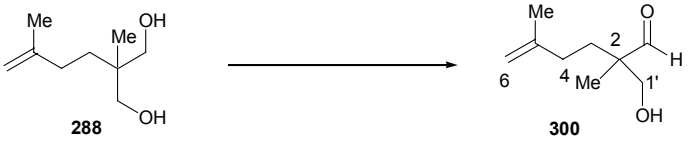
Miscellaneous Data

2-(Methoxy-methyl-carbamoyl)-2,5-dimethyl-hex-5-enoic acid methyl ester (293)



δ_H (270 MHz; $CDCl_3$) 4.64 (2H, s, 2 × H-6), 3.63 (3H, s, CO_2Me), 3.54 (3H, s, NOMe), 3.12 (3H, s, NMe), 1.98-1.85 (4H, m, 2 × H-3, 2 × H-4), 1.66 (3H, s, 5-Me), 1.32 (3H, s, 2-Me); δ_C (68 MHz; $CDCl_3$) 173.6 (C-1), 173.3 (C-1'), 145.2 (C-5), 109.9 (C-6), 60.5 (N-O-Me), 52.0 (O-Me), 51.9 (C-2), 33.5 (N-Me), 31.9 (C-4), 22.6 (C-3), 20.3 (5-Me), 14.1 (2-Me).

2-Hydroxymethyl-2,5-dimethyl-hex-5-enal (300)



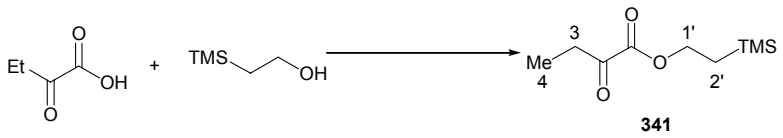
δ_H (270 MHz; $CDCl_3$) 9.49 (1H, s, 1 × H-1), 4.62 (2H, br s, 2 × H-6), 3.68 (1H, d, *J* 14 Hz, 1× H-7), 3.53 (1H, d, *J* 14 Hz, 1 × H-7), 1.91 (2H, m, 2 × H-4), 1.67 (3H, s, 5-Me), 1.57 (1H, m, 1 × H-3), 1.39 (1H, m, 1 × H-3), 1.05 (3H, s, 3-Me).

Preparation of 2-oxo-propionic acid trimethylsilanyl-ethyl ester (336)

336

Sodium hydrogen sulphate on silica (0.1 g/mmol of hydroxyl prepared according to the procedure of Breton)[3] was added to a stirred solution of pyruvic acid (4.3 mL, 62.0 mmol) and 2-(trimethylsilyl) ethanol (8.0 mL, 56.0 mmol) in DCM (100 mL). The reaction mixture was heated at reflux overnight. The mixture was cooled to room temperature, filtered and the solvent removed *in vacuo*. The residue was taken up in EtOAc (50 mL) and washed with saturated sodium bicarbonate (100 mL), then saturated brine (50 mL). The organic layer was dried with Na_2SO_4, filtered and the solvent removed *in vacuo*. Purification by flash chromatography (20 % EtOAc – petrol) followed by distillation under reduced pressure gave *TMSE-pyruvate* **336**, (6.54 g, 62 % yield) as a pungent colourless liquid. R_f 0.56 (20 % EtOAc – petrol); bp 100 °C at 2 mmHg; ν_{max} (liquid film) /cm^{-1} 2995, 2899 (CH_3, CH_2) 1732 (C=O), 1298, 1251, 1138, 861, 839; δ_H (300 MHz; $CDCl_3$) 4.28 (2H, m, 2 × H-1'), 2.40 (3H, s, 3 × H-3), 1.04 (2H, m, 2 × H-2'), 0.0 (9H, s, 3 × MeSi); δ_C (75 MHz; $CDCl_3$) 192.6 (C-2), 161.4 (C-1), 65.4 (C-1'), 27.1 (C-3), 17.7 (C-2'), -1.2 (3 × Me-Si); *m/z* (CI+) 206.1 (94 %, *M* $+NH_4)^+$, (EI+) 145.0 (*M*-MeC=O)$^+$, 101.1 $(Me_3SiCH_2CH_2)^+$, 73 $(Me_3Si)^+$; Found 206.1211 $(M+NH_4)^+$, $C_8H_{20}NO_3Si$ requires 206.1212.

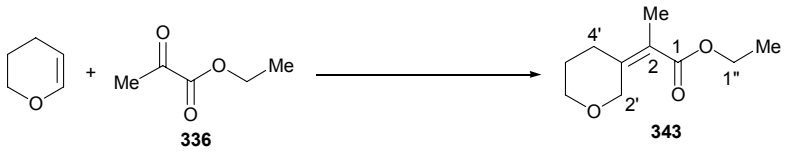
Preparation of 2-oxo-butyric acid trimethylsilanyl-ethyl ester (341)



341

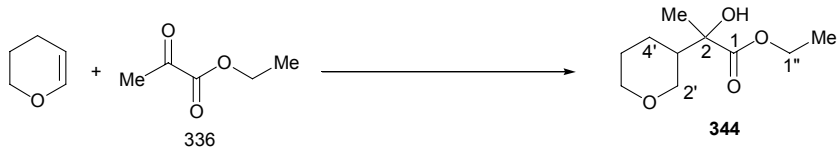
Sodium hydrogen sulphate on silica (0.1 g/mmol of hydroxyl) was added to a stirred solution of 2-oxo-butyric acid (1.1g, 10 mmol) and 2-(trimethylsilyl) ethanol (1.2 mL, 8.4 mmol) in DCM (100 mL). The reaction mixture was heated at reflux overnight. The mixture was cooled, filtered and the solvent removed *in vacuo*. The residue was taken up in EtOAc (50 mL) and washed with saturated sodium bicarbonate (100 mL), then saturated brine (50 mL). The organic layer was dried with Na_2SO_4, filtered and the solvent removed *in* vacuo. Purification by flash chromatography (20 % EtOAc – petrol), followed by bulb-to-bulb distillation under reduced pressure gave the *TMSE-ethyl pyruvate* **341,** (0.71 g, 36 % yield) as a pungent brown liquid. R_f 0.6 (20 % EtOAc – petrol); bp 150 °C at 2 mmHg; δ_H (300 MHz; $CDCl_3$) 4.34 (2H, m, 2 × H-1'), 2.85 (2H, q, *J* 7.2, 2 × H-3), 1.09-1.01 (5H, m, 2 × H-2', 3 × H-4), 0.0 (9H, s, 3 × MeSi) δ_C (75 MHz; $CDCl_3$) 196.9 (C-2), 163.0, (C-1), 66.4 (C-1'), 34.3 (C-3), 18.9 (C-2'), 8.5 (C-4), 0.0 (3 × Me-Si); *m/z* (CI+) 220.0 (100 %, M+NH_4)$^+$ 192.0 (33), 172.0 (25), 167.0 (17), 118.0 (18), 90.0 (86); Found 220.1367 (M+NH_4)$^+$, $C_9H_{22}NO_3Si$ requires 220.1369.

Preparation of 2-(dihydro-pyran-3-ylidene)-propionic acid ethyl ester (343)



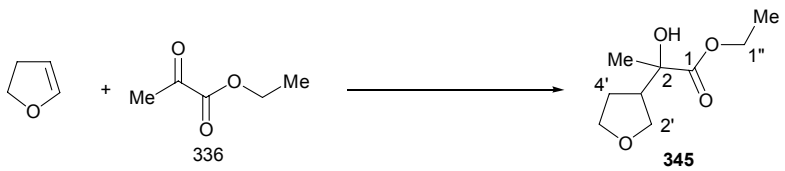
Titanium tetrachloride (0.22 mL, 2 mmol) was added to a stirred solution of 3,4-dihydro-2H-pyan (0.27 mL, 3mmol) and ethyl pyruvate (0.23 mL, 2 mmol) in DCM (20 mL) at –78 °C, and the resulting suspension stirred for 1 hour at –78 °C. Triethylsilane (0.30 mL, 2.0 mmol) was added and the reaction stirred for a further hour whilst allowing the reaction to warm to room temperature. The reaction was poured into saturated sodium bicarbonate (50 mL), and then extracted with EtOAc (50 mL). The organic fraction was washed with saturated brine (50 mL) and dried over Na_2SO_4; the solvent was then removed *in vacuo*. Purification by flash chromatography (40 % EtOAc – petrol) yielded *ester* **343** (0.23 g, 63 % yield) as a straw-coloured oil. R_f 0.57 (40 % EtOAc – petrol); ν_{max} (liquid film)/cm^{-1} 2955 (CH_3, CH_2), 2836 (CH_3, CH_2), 1704 (C=O), 1632 (C=C), 1445, 1366, 1092; δ_H (300 MHz; $CDCl_3$), 4.45 (2H, s, 2 × H-2'), 4.18 (2H, q, *J* 7.1, 2 × H-1"), 3.72 (2H, t, *J* = 5.6, H-6'), 2.42 (2H, t, *J* 6.4, H-4'), 1.80 (3H, s, 3 × H-3), 1.77 (2H, ap. quintet, *J* 6.4, H-5'), 1.28 (3H, t, *J* = 7.1, 3 × H-2"); δ_C (75 MHz; $CDCl_3$) 169.3 (C-1), 144.0 (C-3'), 122.6 (C-2), 69.6 (C-2'), 67.6 (C-6'), 60.9 (C-1"), 27.4 (C-5'), 26.6 (C-4'), 15.2 (C-3), 14.62 (C-2"); *m/z* (EI+) 184.1 (48 %, M^+), 155.1 (100, M-Et)$^+$, 139.1 (31, M-OEt)$^+$, 111.1 (15, M-CO_2Et)$^+$, 29.0 (12, C_2H_5); Found (M^+) 184.1098, $C_{10}H_{16}O_3$ requires 184.1099.

Preparation of 2-hydroxy-2-(tetrahydro-pyran-3-yl)-propionic acid ethyl ester (344)



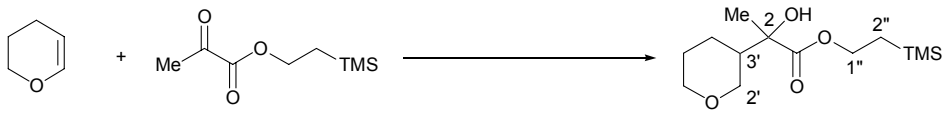
Titanium tetrachloride (0.22 mL, 2.0 mmol) was added to a stirred solution of 3,4-dihydro-2H-pyran (0.27 mL, 3.0 mmol) and ethyl pyruvate (0.23 mL, 2.0 mmol) in DCM (20 mL) at –78 °C, and the resulting suspension stirred for 1 hour at –78 °C. Triethyl silane (0.30 mL, 2.0 mmol) was added and the reaction stirred overnight at –78 °C. Methanol (1.0 mL) was added and the reaction stirred for 5 minutes at –78 °C until the solution had cleared. The reaction was then poured directly into saturated sodium bicarbonate (50 mL) and extracted with EtOAc (50 mL). The organic fraction was washed with saturated brine (50 mL) and dried over Na_2SO_4, followed by removal of the solvent *in vacuo*. Purification by flash chromatography (40 % EtOAc – petrol) gave the *hydroxyester* **344** (0.22 g, 54 % yield) as a colourless oil. R_f 0.2 (40 % EtOAc – petrol); ν_{max} (liquid film)/cm^{-1} 3500 (OH), 2938 (CH_3, CH_2), 2849 (CH_3, CH_2), 1728 (C=O), 1449, 1245, 1141, 1078, 1040; δ_H (300 MHz; $CDCl_3$) 4.25 (1H, s, OH), 4.19 (1H, dd, *J* = 7.5 and 2.7, 1 × H-2'), 4.13 (1H, dd, *J* = 4.5 and 2.7, 1 × H-2'), 4.22-4.10 (2H, m, 2 × H-1"), 3.94-3.86 (1H, m, 2 × H-6'), 3.38–3.26 (1H, m, H-6'), 1.77–1.64 (2H, m, 2 × H-5'), 1.59–1.46 (2H, m, 1H × 3' and 2 × H-4'), 1.35 (3H, s, 3 × H-3), 1.24 (3H, t, *J* = 7.1, 3 × H-2"); δ_C (75 MHz; $CDCl_3$) 175.8 (C-1), 105.2 (C-2), 76.3 (C-2'), 65.9 (C-6'), 61.7 (C-1"), 56.5 (C-3'), 49.4 (C-5'), 25.7 (C-4'), 24.2 (C-3), 14.7 (C-2"); *m/z* (EI+) 172.1 (15 %, *M*-Et)$^+$, 127.0 (100, *M*-CO_2Et)$^+$, 115.1 (69, *M*-THP)$^+$, 85.1 (24, THP)$^+$, 29.0 (16, Et)$^+$; Found (*M*-H)$^+$ 201.1123, $C_{10}H_{17}O_4$ requires 201.1127.

Preparation of 2-hydroxy-2-(tetrahydro-furan-3-yl)-propionic acid ethyl ester (345)



Titanium tetrachloride (0.22 mL, 2.0 mmol) was added to a stirred solution of 2,3-dihydrofuran (0.23 mL, 3.0 mmol) and ethyl pyruvate (0.23 mL, 2.0 mmol) in DCM (10 mL) at –78 °C, and the resulting suspension stirred for 1 hour at –78 °C. Triethyl silane (0.3 mL, 2.0 mmol) was added and the reaction stirred for 1 hour at –78 °C. The reaction was poured into saturated sodium bicarbonate solution (20 mL) and extracted with EtOAc (30 mL). The organic fraction was washed with saturated brine (30 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. Purification by flash chromatography (40 % EtOAc – petrol) afforded *hydroxy furan* **345** (0.28 g, 51 % yield) as an inseparable mix of diastereomers (14:1) as a colourless oil. R_f 0.3 (40 % EtOAc – petrol); ν_{max} (liquid film)/cm^{-1} 3512 (OH), 2979 (CH_3, CH_2), 2874 (CH_3, CH_2), 1732 (C=O), 1449, 1374, 1257, 1128, 919; δ_H (300 MHz; $CDCl_3$) 4.21 (1H, dq, *J* = 3.5 and 3.5, 1 × H-1”), 4.16 (1H, dq, *J* = 3.5 and 3.5, 1 × H-1”), 3.84 (1H, app t, *J* = 8.3, 1 × H-5’), 3.76 (1H, dd, *J* = 8.7 and 6.5, 1 × H-2’), 3.68 (1H, app t, *J* = 8.7 and 6.5, 1 × H-5’), 3.65 (1H, dd, *J* = 8.7 and 6.5, 1 × H-2’), 3.38 (1H, br. s, OH), 2.56 (1H, apparent quintet, 1 × H-3’), 1.70 (2H, q, *J* 7.8, 2 × H-4’), 1.35 (0.21H, s, H-3_{min}), 1.31 (2.79H, s, H-$2”_{maj}$), 1.24 (2.79H, t, *J* = 6.8, 2.79 × 1”-Me_{maj}), 1.23 (0.21H, t, *J* = 6.8, 0.21 × 1”-Me_{min}); δ_C (75 MHz; $CDCl_3$) 177.0 (C-1), 74.4 (C-2), 68.9 (C-5’), 68.4 (C-2’), 62.4 (C-1”), 47.2 (C-3’), 27.4 (C-4’), 25.1 (C-3), 14.5 (C-2”).

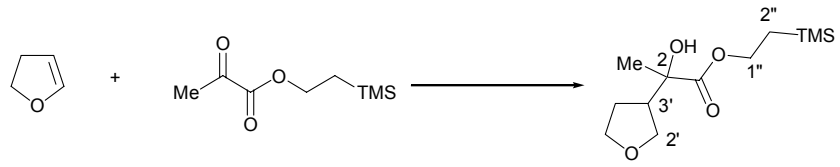
Preparation of 2-hydroxy-2-(tetrahydro-pyran-3-yl)-propionic acid trimethylsilanyl-ethyl ester (346)



336 **346**

Titanium (IV) chloride (0.22 mL, 2.0 mmol) was added to a solution of 3,4-dihydro-2H-pyran (0.27 mL, 3.0 mmol) and TMSE-pyruvate **336** (0.3 g, 1.5 mmol) in DCM (15 mL) at –78 °C. The reaction mixture was stirred for one hour at –78 °C, forming a yellow/brown suspension. Triethyl silane (0.6 mL, 4 mmol) was added dropwise and the reaction was allowed to stir for 1 hour at –78 °C. Methanol (1.0 mL) was then added at –78 °C, causing dissolution of the suspension. The mixture was poured into saturated sodium bicarbonate (25 mL) and the layers separated. The aqueous layer was washed with EtOAc (3 × 50 mL) and the combined organic layers washed with saturated brine (1 × 50 mL). The organic layer was dried with Na_2SO_4 and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography (40 % EtOAc – petrol) to give the *tetrahydropyran* **346** (0.29 g, 71 % yield) as a colourless oil. R_f 0.2 (40 % EtOAc – petrol); δ_H (300 MHz; $CDCl_3$) 4.21 (2H, m, 2 × H-1”), 4.02 (1H, dd, J = 11 and 3.8, 1 × H-2’), 3.85-3.80 (1H, m, 1 × H-2’), 3.26 (2H, app t, J = 11, 2 × H-6’), 1.89-1.83 (1H, m, H-3’), 1.60-1.37 (4H, m, 2 × H-4’, 2 × H-5’), 1.27 (3H, s, 3 × H-3), 0.99 (2H, m, 2 × H-2”), -0.1 (9H, s, 3 × Me-Si); δ_C (75 MHz; $CDCl_3$) 178.4 (C-1), 76.6 (C-2), 69.7 (C-6’), 69.6 (C-2’), 66.2 (C-1”), 44.6 (C-3’), 27.4 (C-5’), 25.7 (C-4’), 25.0 (C-3), 19.0 (C-2”), 0.0 (3 × Me-Si).

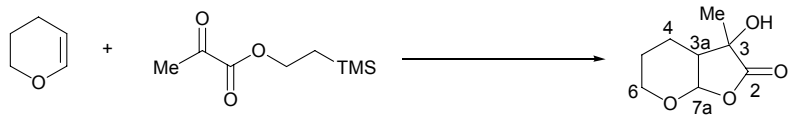
Preparation of 2-hydroxy-2-(tetrahydro-furan-3-yl)-propionic acid trimethylsilanyl-ethyl ester (347)



336 **347**

Titanium (IV) chloride (0.22 mL, 2.0 mmol) was added to a solution of 2,3-dihydro-2H-furan (0.23 mL, 3.0 mmol) and TMSE-pyruvate **336** (0.3 g, 1.5 mmol) in DCM (15 mL) at –78 °C. The reaction mixture was stirred for one hour at –78 °C, forming a yellow/brown suspension. Triethyl silane (0.6 mL, 4 mmol) was added dropwise and the reaction was allowed to stir for 1 hour at –78 °C. Methanol (1.0 mL) was added at –78 °C, and after the suspension had dissolved, the mixture was poured into saturated sodium bicarbonate solution (25 mL) and the layers separated. The aqueous layer was washed with EtOAc (3 × 50 mL) and the combined organic layers washed with saturated brine (1 × 50 mL). The organic layer was dried with Na_2SO_4 and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography (40 % EtOAc – petrol) to give *tetrahydrofuran* **347** (0.21 g, 53 %) as a colourless oil. R_f 0.26 (40 % EtOAc – petrol); δ_H (300 MHz; $CDCl_3$) 4.26-4.20 (2H, m, 2 × H-1”), 3.85 (1 H, app t, *J* = 8.7, 1 × H-5’), 3.80-3.63 (3H, m, 1 × H-2’) 3.34 (1H, br. s, OH), 2.55 (1H, ap. quintet, *J* = 7.9, H-3’), 1.70 (2H, dt, *J* = 7.7 and 7.5, 2 × H-4’), 1.30 (3H, s, 3 × H-3), 1.01 (2H, m, 2 × H-2”), 0.05 (9H, s, 3 × MeSi); δ_C (75 MHz; $CDCl_3$) 178.3 (C-1), 75.5 (C-2), 70.0 (C-5’), 69.7 (C-2’), 66.2 (C-1”), 48.3 (C-3’), 28.7 (C-4’), 26.4 (C-3), 19.0 (C-2”), 0.0 (3 × Me-Si)

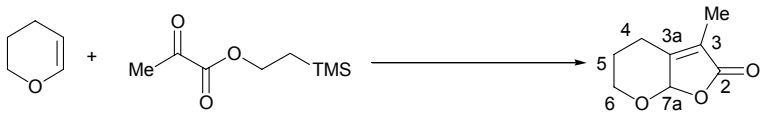
Preparation of 3-hydroxy-3-methyl-tetrahydro-furo[2,3-b]pyran-2-one (348)



336 **348**

Titanium (IV) chloride (0.11 mL, 1.0 mmol) was added to a stirred solution of 3,4-dihydro-2H-pyran (0.27 mL, 3.0 mmol) and TMSE-pyruvate **336** (0.19 g, 1.5 mmol) in THF (10 mL) at –78 °C. The reaction mixture was stirred for 1 hour at –78 °C followed by stirring at –30 °C for 12 h. The reaction mixture was poured into saturated ammonium chloride solution (30 mL). EtOAc was added (30 mL), the layers were separated and the aqueous phase washed with additional EtOAc (3 × 25 mL). The combined organic fractions were washed with saturated brine (50 mL) and dried with Na_2SO_4. The solution was filtered and the solvent removed *in vacuo*. Flash chromatography (40 % EtOAc – petrol) gave *alcohol* **348** (28 mg, 17 % yield) as a colourless oil. R_f 0.27 (40 % EtOAc – petrol) ν_{max} (liquid film)/cm^{-1} 3410 (OH), 2929 (CH_3, CH_2), 1770 (C=O), 1390 (CH_2), 1080, 930; δ_H (300 MHz; $CDCl_3$) 5.95 (1H, d, J = 3, H-7a), 3.77-3.61 (2H, m, 2 × H-6), 2.71 (1H, br s, OH), 2.25-2.18 (1H, m, H-3a), 1.84-1.12 (4H, m, 2 × H-5, 2 × H-4), 1.42 (3H, s, 3-Me); δ_C (75 MHz; $CDCl_3$) 177.2 (C-2), 101.9 (C-7a), 79.8 (C-3), 63.4 (C-6), 44.7 (C-3a), 23.8 (C-5), 21.9 (C-4), 20.3 (3-Me); *m/z* (CI+) 190.1 (34 %, M+NH_4)$^+$, 172.0 (15, M)$^+$, 155.0 (4, M-OH)$^+$, 127.0 (4, M-CO_2)$^+$, 85 (100, $C_7H_{12}O$); Found (M+NH_4)$^+$ 190.1079, $C_8H_{16}NO_4$ requires 190.1077.

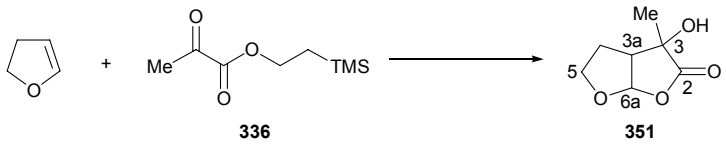
Preparation of 3-methyl-5,6-dihydro-4*H*,7a*H*-furo[2,3-b]pyran-2-one (349)



336 **349**

Titanium (IV) chloride (0.22 mL, 2.0 mmol) was added to a stirred solution of 3,4-dihydro-2H-pyran (0.27 mL, 3.0 mmol) and TMSE-pyruvate **336** (0.30 g, 1.5 mmol) in DCM (10 mL) at –78 °C. The reaction mixture was stirred for 1 h at –78 °C, then at room temperature for 1 hour. The reaction mixture was poured into saturated ammonium chloride solution (30 mL) and EtOAc was added (30 mL). The layers were separated and the aqueous phase washed with additional EtOAc (3 × 25 mL). The combined organic fractions were washed with saturated brine (1 × 100 mL) and dried with Na_2SO_4. The solution was filtered and the solvent removed *in vacuo*. Purification by flash chromatography (40 % EtOAc – petrol) gave *lactone* **349** (0.18 g, 79 % yield) as a pale yellow oil. R_f 0.3 (40 % EtOAc – petrol); ν_{max} (liquid film)/cm^{-1} 2995, 2928, 2858 (CH_3, CH_2), 1770 (lactone C=O), 1703 (α,β-unsat-γ-lactone C=C), 1446 (CH_3, CH_2), 1348 (CH), 1234 (CH_2), 1037, 1011 (O-C-O); δ_H (300 MHz; $CDCl_3$) 5.45 (1H, s, H-7a), 4.08-3.97 (1H, m, H_{eq}-6), 3.75-3.61 (1H, m, H_{ax}-6), 2.84-2.72 (1H, m, H_{eq}-4), 2.24 (1H, ddd, J = 11.1, 6.7 and 4.0, 1 × H-3a), 1.88-1.70 (2H, m, 2 × H-5), 1.76 (3H, s, 3-Me); δ_C (75 MHz; $CDCl_3$) 170.6 (C-2), 155.3 (C-3), 120.4 (C-3a), 97.3 (C-7a), 63.6 (C-6), 24.8 (C-5), 22.5 (C-4), 6.5 (3-Me); *m/z* (CI+) 171.9 (100 %, M+$NH_4)^+$, 154.9 (6, $M)^+$; Found (M+$NH_4)^+$ 172.0974, $C_8H_{14}NO_3$ requires 172.0974.

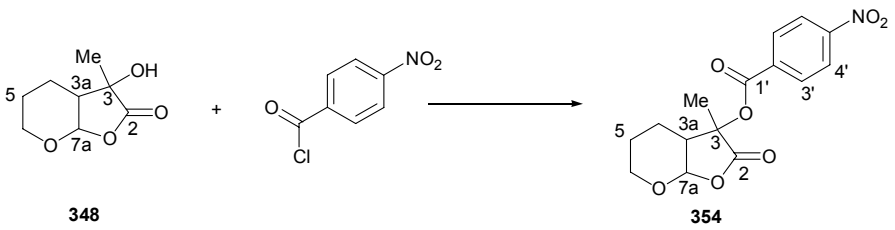
Preparation of 3-hydroxy-3-methyl-tetrahydro-furo[2,3-b]furan-2-one (351)



336 **351**

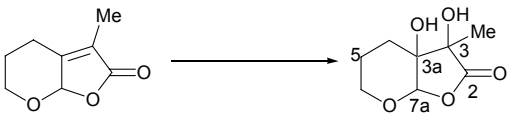
Titanium (IV) chloride (0.11 mL, 1.0 mmol) was added to a stirred solution of 2,3-dihydro-2H-furan (0.23 mL, 3.0 mmol) and TMSE-pyruvate **336** (0.19 g, 1.5 mmol) in DCM (10 mL) at –78 °C. The reaction mixture was stirred for 1 hour at –78 °C then at –30 °C for 4 h. Methanol (1 mL) was added, and after 5 minutes, the reaction mixture was poured into saturated ammonium chloride solution (30 mL). EtOAc (30 mL) was added, the layers were separated and the aqueous phase washed with EtOAc (3 × 25 mL). The combined organic fractions were washed with saturated brine solution (30 mL) and dried with Na_2SO_4. The solution was filtered and the solvent removed *in vacuo*. Flash chromatography (40 % EtOAc – petrol) gave *alcohol* **351** (38 mg, 16 % yield), an inseparable mixture of diastereomers (9:1), as a colourless oil. R_f 0.25 (40 % EtOAc – petrol); ν_{max} (liquid film)/cm^{-1} 3423 (OH), 2929 (CH_3, CH_2), 1776 (C=O), 1379 (CH_2), 1147, 1099 (O-C-O), 968, 930; δ_H (300 MHz; $CDCl_3$) 6.11 (0.9H, d, J = 4.7, H-6a$_{maj}$), 5.95 (0.1H, d, J = 4.7, H-6a$_{min}$), 4.07-3.86 (2H, m, 2 × H-5), 2.92(1H, ddd, J = 8.5, 6.7 and 4.7, 1 × H-3a) 2.63 (1H, br s, OH), 2.13-2.00 (1H, m, 1 × H-4) 1.76-1.63 (1H, m, 1 × H-4), 1.20 (0.3, H, s, 3-Me$_{min}$), 1.19 (2.7H, s, 3-Me$_{maj}$); δ_C (75 MHz; $CDCl_3$) 175.9 (C-2), 107.6 (C-6a), 76.6 (C-3), 69.2 (C-5), 51.3 (C-3a), 25.6 (C-4), 21.1 (3-Me); *m/z* (CI+) 159.0 (100 %, M+H)$^+$, 141.0 (82, M-H_2O)$^+$, 113.0 (47, M-CO_2)$^+$, 71.0 (52, C_4H_7O); Found (M+H)$^+$ 159.0657, $C_7H_{11}O_4$ requires 159.0657.

Preparation of 4-nitro-benzoic acid 3-methyl-2-oxo-hexahydro-furo[2,3-b]pyran-3-yl ester (354)



4-nitro-benzoyl chloride (15 mg, 0.070 mmol) in DCM (2 mL) was added dropwise to a stirred solution of alcohol **348** (11 mg, 0.064 mmol) and dry pyridine (6 μL, 0.077 mmol) in dry DCM (3 mL) at 0 °C under N_2. After 4 h the reaction was filtered through a short pad of silica and the pad washed with DCM. The reaction mixture was then poured into saturated ammonium chloride (15 mL) and the layers separated. The aqueous portion was extracted with DCM (3 × 10 mL) and the combined organic portions washed with saturated brine (20 mL). The organic portions were dried with Na_2SO_4, filtered, and the solvent removed *in vacuo* to give crude *4-nitro-benzoate* **354** which was recrystallised from DCM and hexane to give pure *4-nitro-benzoate* **354** (14 mg, 68 % yield). R_f 0.55 (40 % EtOAc – petrol); δ_H (300 MHz; $CDCl_3$) 8.22 (2H, d, *J* 10, 2 × H-3') 8.05 (2H, d, *J* = 10.0, 2 × H-4'), 5.74 (1H, d, *J* = 2.6, H-7a), 3.86-3.60 (2H, m, 2 × H-6), 3.09 (1H, ddd, *J* = 8.4, 7.0 and 4.2, 1 × H-3a), 1.99-1.85 (2H, m, 2 × H-5), 1.71 (3H, s, 3-Me), 1.74-1.41 (2H, m, 2 × H-4); δ_C (75 MHz; $CDCl_3$) 175.2 (C-2), 168.0 (C-1'), 156.4 (C-5'), 130.7 (C-2'), 123.3 (C-4'), 122.5 (C-3'), 98.4 (C-7a), 84.3 (C-3), 62.1 (C-6), 44.3 (C-3a), 21.3 (C-5), 20.1 (C-4), 15.7 (3-Me); for x-ray crystal data see appendix.

Preparation of 3,3a-Dihydroxy-3-methyl-tetrahydro-furo[2,3-b]pyran-2-one (355)



349 **355**

Potassium permanganate (0.12 g, 0.77 mmol) was added to a stirred solution of unsaturated lactone **349** (0.12 g, 0.77 mmol) and benzo-18-crown-6 (0.36 g, 1.16 mmol) in DCM (10 mL) and the reaction mixture was stirred at room temperature for 3 days. The mixture was poured into water (10 mL) and the layers separated. The aqueous layer was washed with DCM (3 × 10 mL) and the combined organic layers were dried with Na_2SO_4. The solution was filtered and the solvent was removed *in vacuo*. Purification by flash chromatography (50 % EtOAc – petrol) gave *diol* **355** (72 mg, 50 % yield) as a brown oil. R_f 0.15 (40 % EtOAc – petrol); ν_{max} (liquid film)/cm^{-1} 3425 (OH), 2956 (CH_3, CH_2), 1776 (C=O), 1174, 1125, 1026, 936, 915; δ_H (300 MHz; $CDCl_3$) 5.62 (1H, s, H-7a), 3.82-3.74 (1H, m, 1 × H-6_{eq}), 3.73-3.63 (1H, app dt, 1 × H-6_{ax}), 3.00 (1H, br. s, OH), 2.81 (1H, br. s, OH), 2.01-1.79 (2H, m, 2 × H-4), 1.61-1.45 (2H, m, 2 × H-5), 1.38 (3H, s, 3-Me); δ_C (75 MHz; $CDCl_3$) 173.8 (C-2), 103.6 (C-7a), 79.0 (C-3), 72.6 (C-3a), 62.6 (C-6), 27.6 (C-4), 20.5 (C-5), 16.8 (3-Me); *m/z* (CI+) 206.0 (100 %, M+NH_4)$^+$, 188.9 (5, M)$^+$, 172.0 (8, M-OH)$^+$, 126.0 (3, M -CO_3H)$^+$, 110.9 (4, $C_6H_7O_2$); Found (M+NH_4)$^+$ 206.1027, $C_8H_{16}NO_5$ requires 206.1028.

References:
(1) Bose, A. K.; Lal, B. *Tet. Lett.* **1973**, 3937.
(2) Santagostino, M.; Frigerio, M. *Tet. Lett.* **1994**, *35*, 8019-8022.
(3) Breton, G. W. *J. Org. Chem.* **1997**, *62*, 8952-8954.

Appendices

Appendix 1: X-ray crystal data

Table 1. Crystal data and structure refinement for 1.

Identification code	k02mcw2
Empirical formula	C15 H15 N O7
Formula weight	321.28
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 8.3590(2)Å $\alpha = 90^o$
	b = 17.0720(5)Å $\beta = 91.8160(10)^o$
	c = 10.1250(4)Å $\gamma = 90^o$
Volume	1444.16(8) $Å^3$
Z	4
Density (calculated)	1.478 Mg/m^3
Absorption coefficient	0.119 mm^{-1}
F(000)	672
Crystal size	0.35 x 0.33 x 0.33 mm
Theta range for data collection	3.33 to 27.51^o
Index ranges	-10<=h<=10; -22<=k<=22; -13<=l<=13
Reflections collected	18707
Independent reflections	3307 [R(int) = 0.0737]
Reflections observed (>2σ)	2412
Data Completeness	0.996
Max. and min. transmission	0.9618 and 0.9596
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3307 / 0 / 209
Goodness-of-fit on F^2	1.021
Final R indices [I>2σ(I)]	$R_1 = 0.0417$ $wR_2 = 0.1019$
R indices (all data)	$R_1 = 0.0646$ $wR_2 = 0.1121$
Largest diff. peak and hole	0.236 and -0.221 $eÅ^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1.U (eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(1)	1157(2)	-559(1)	4300(1)	44(1)
O(2)	1570(2)	555(1)	3378(1)	57(1)
O(3)	6662(1)	380(1)	9288(1)	33(1)
O(4)	7025(1)	1538(1)	8268(1)	28(1)
O(5)	6460(1)	1760(1)	11112(1)	40(1)
O(6)	8888(1)	1217(1)	11345(1)	35(1)
O(7)	11237(1)	1825(1)	11058(1)	35(1)
N	1792(2)	84(1)	4270(1)	34(1)
C(1)	2928(2)	301(1)	5358(2)	26(1)
C(2)	3076(2)	-191(1)	6441(2)	29(1)
C(3)	4198(2)	-3(1)	7425(2)	28(1)
C(4)	5122(2)	672(1)	7322(1)	25(1)
C(5)	4919(2)	1167(1)	6236(2)	27(1)
C(6)	3813(2)	977(1)	5235(2)	29(1)
C(7)	6341(2)	831(1)	8403(1)	26(1)
C(8)	8261(2)	1761(1)	9244(1)	25(1)
C(9)	8428(2)	2640(1)	9094(2)	34(1)
C(10)	7707(2)	1584(1)	10641(2)	30(1)
C(11)	10315(2)	1188(1)	10600(2)	31(1)
C(12)	9778(2)	1266(1)	9147(2)	28(1)
C(13)	11117(2)	1546(1)	8254(2)	37(1)
C(14)	12259(2)	2137(1)	8919(2)	41(1)
C(15)	12673(2)	1889(1)	10312(2)	42(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-N	1.2192(18)	O(2)-N	1.2191(19)
O(3)-C(7)	1.2057(18)	O(4)-C(7)	1.3440(18)
O(4)-C(8)	1.4568(17)	O(5)-C(10)	1.1976(19)
O(6)-C(10)	1.3528(19)	O(6)-C(11)	1.4327(19)
O(7)-C(11)	1.4037(19)	O(7)-C(15)	1.443(2)
N-C(1)	1.478(2)	C(1)-C(6)	1.379(2)
C(1)-C(2)	1.383(2)	C(2)-C(3)	1.385(2)
C(3)-C(4)	1.392(2)	C(4)-C(5)	1.393(2)
C(4)-C(7)	1.497(2)	C(5)-C(6)	1.388(2)
C(8)-C(9)	1.516(2)	C(8)-C(12)	1.529(2)
C(8)-C(10)	1.533(2)	C(11)-C(12)	1.530(2)
C(12)-C(13)	1.538(2)	C(13)-C(14)	1.530(2)
C(14)-C(15)	1.502(3)		
C(7)-O(4)-C(8)	117.42(11)	C(10)-O(6)-C(11)	110.14(12)
C(11)-O(7)-C(15)	110.07(12)	O(2)-N-O(1)	123.71(14)
O(2)-N-C(1)	117.80(14)	O(1)-N-C(1)	118.48(14)
C(6)-C(1)-C(2)	123.07(14)	C(6)-C(1)-N	118.42(14)
C(2)-C(1)-N	118.50(14)	C(1)-C(2)-C(3)	118.06(14)
C(2)-C(3)-C(4)	120.17(14)	C(3)-C(4)-C(5)	120.52(14)
C(3)-C(4)-C(7)	117.49(13)	C(5)-C(4)-C(7)	121.98(14)
C(6)-C(5)-C(4)	119.74(14)	C(1)-C(6)-C(5)	118.41(14)
O(3)-C(7)-O(4)	124.29(14)	O(3)-C(7)-C(4)	123.92(14)
O(4)-C(7)-C(4)	111.79(12)	O(4)-C(8)-C(9)	104.87(12)
O(4)-C(8)-C(12)	112.56(11)	C(9)-C(8)-C(12)	117.49(13)
O(4)-C(8)-C(10)	110.26(11)	C(9)-C(8)-C(10)	108.57(13)
C(12)-C(8)-C(10)	103.05(12)	O(5)-C(10)-O(6)	122.41(15)

O(5)-C(10)-C(8)	127.60(15)	O(6)-C(10)-C(8)	109.92(13)
O(7)-C(11)-O(6)	104.88(12)	O(7)-C(11)-C(12)	113.05(12)
O(6)-C(11)-C(12)	106.22(12)	C(8)-C(12)-C(11)	101.85(12)
C(8)-C(12)-C(13)	119.10(13)	C(11)-C(12)-C(13)	113.28(13)
C(14)-C(13)-C(12)	113.74(13)	C(15)-C(14)-C(13)	110.42(15)
O(7)-C(15)-C(14)	110.01(13)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for 1. The anisotropic displacement factor exponent takes the form: -2 gpi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U

Atom	U11	U22	U33	U23	U13	U12
O(1)	40(1)	41(1)	49(1)	-15(1)	-12(1)	-2(1)
O(2)	58(1)	74(1)	38(1)	16(1)	-22(1)	-11(1)
O(3)	37(1)	32(1)	28(1)	5(1)	-7(1)	-4(1)
O(4)	31(1)	28(1)	25(1)	1(1)	-7(1)	-3(1)
O(5)	33(1)	51(1)	37(1)	-10(1)	6(1)	-2(1)
O(6)	36(1)	41(1)	26(1)	5(1)	-4(1)	-2(1)
O(7)	36(1)	35(1)	35(1)	-4(1)	-8(1)	-5(1)
N	28(1)	45(1)	29(1)	-7(1)	-4(1)	3(1)
C(1)	23(1)	33(1)	23(1)	-6(1)	-3(1)	4(1)
C(2)	30(1)	28(1)	29(1)	-4(1)	-1(1)	-3(1)
C(3)	32(1)	29(1)	23(1)	1(1)	-2(1)	-1(1)
C(4)	24(1)	30(1)	22(1)	-3(1)	-1(1)	2(1)
C(5)	26(1)	28(1)	28(1)	-1(1)	0(1)	0(1)
C(6)	29(1)	32(1)	25(1)	3(1)	-1(1)	5(1)
C(7)	28(1)	27(1)	23(1)	-1(1)	1(1)	2(1)
C(8)	27(1)	27(1)	22(1)	-2(1)	-4(1)	-1(1)
C(9)	38(1)	26(1)	37(1)	0(1)	-8(1)	2(1)
C(10)	31(1)	31(1)	27(1)	-5(1)	-2(1)	-4(1)
C(11)	30(1)	27(1)	36(1)	1(1)	-6(1)	1(1)
C(12)	28(1)	25(1)	31(1)	-4(1)	-2(1)	1(1)
C(13)	32(1)	42(1)	36(1)	-8(1)	5(1)	-2(1)
C(14)	33(1)	44(1)	47(1)	-4(1)	5(1)	-7(1)
C(15)	27(1)	42(1)	57(1)	-4(1)	-7(1)	-5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

Atom	x	y	z	U(eq)
H(2)	2426	-645	6507	35
H(3)	4338	-334	8174	34
H(5)	5535	1633	6181	32
H(6)	3669	1306	4483	34
H(9A)	7378	2888	9175	51
H(9B)	8850	2760	8225	51
H(9C)	9165	2841	9786	51
H(11)	10898	683	10757	37
H(12)	9442	734	8832	33
H(13A)	11741	1086	7973	44
H(13B)	10626	1789	7451	44
H(14A)	13249	2175	8411	49
H(14B)	11750	2660	8925	49
H(15A)	13231	1377	10305	50
H(15B)	13403	2278	10734	50

Appendix 2: NMR Spectra