UNIVERSITY OF SOUTHAMPTON

Part A: [2+2] Cycloadditions of Keteniminium Salts with Resin Bound Alkenes
Part B: Permanganate Oxidations of 1,5-Dienes

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A thesis submitted for the degree of Doctor of Philosophy

Department of Chemistry

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Declaration

I declare that this thesis is my own composition and that the work of which it is a record was carried out by myself unless otherwise acknowledged. No part of this thesis has been submitted in any previous application for a higher degree.

John Keily , June 2002

UNVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

Part A: [2+2] Cycloadditions of Keteniminium Salts with Resin Bound Alkenes

Part B: Permanganate Oxidations of 1,5-Dienes

By John Keily

The solid-phase synthesis of cyclobutanones and cyclobutyliminium salts was carried out employing the [2+2] cycloaddition between resin bound olefins and keteniminium salts, generated from tertiary amides. The substrate molecules were tethered to carboxylic acid functionalised polystyrene resin *via* an ester linkage, from which cyclobutanones, cyclobutanols and cyclobutylamines were isolated by transesterification, and by reductive cleavages.

Grignard addition to a cyclobutanone successfully resulted in the methylated product, whilst Beckmann rearrangement and Baeyer-Villiger oxidation allowed for the preparation of γ-lactams and γ-lactones respectively. Finally an unusual photochemically induced ring expansion/addition was carried out successfully with a resin bound cyclobutanone and imidazole to furnish the 2-imidazoyltetrahydrofuran.

The permanganate promoted oxidative cyclisation of geranyl benzoate was carried out under phase-transfer conditions. The reaction was optimised to give product THF diol in good yield (70%), then the optimised conditions were applied to *cis*- and electron deficient olefins. Our focus turned to the asymmetric oxidative cyclisation of phenone dienes using a chiral phase-transfer catalyst (CPTC). Asymmetric oxidation was optimised to give reasonable yields (47-50%) and good asymmetric induction (75%).

Approaches towards the synthesis of Annonaceous acetogenins were investigated. Key bifuranyl-5-ones were prepared employing the permanganate oxidative cyclisation of 1,5,9-trienes.

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Acknowledgements

The author would like to thank Joan Street and Neil Wells for the NMR spectroscopy along with John Langley and Julie Herniman for the Mass Spectrometry.

In addition we acknowledge the EPSRC for a QUOTA studentship and use of the Chemical Database at Daresbury.

Abbreviations

Ac	Acetyl
Acac	Acetylacetonate
aq.	Aqueous
Ar	Aryl
BHT	2,6-Di-*tert*-butyl-4-methylphenol (Butylated hydroxytoluene)
binap	2,2'-Bis(diphenylphosphino)-1,1'binaphthyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
b.p.	Boiling point
br	Broad (NMR and IR)
Bu	Butyl
CAS	Chemical Abstracts
cat.	Catalytic
Cy	Cyclohexyl
d	Doublet (NMR)
DEAD	Diethylazodicarboxylate
DIBAL	Diisobutylaluminium hydride
DIC	1,3-Diisopropylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Ethylene glycol dimethyl ether (1,2-Dimethoxyethane)
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
e.e.	Enantiomeric excess
equiv.	Equivalents
Et	Ethyl

Fmoc	9-Fluorenylmethoxycarbonyl
G	Glycine
GC	Gas Chromatography
Hep	Heptyl
HMDS	Hexamethyl disilazane
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
hr	Hour
HRMS	High resolution mass spectrometry
i	*iso*
IR	Infrared
J	Coupling constant (NMR)
L	Ligand (general) or Lysine
LDA	Lithium diisopropylamide
Lys	Lysine
m	Multiplet (NMR) or medium (IR)
M	Molar
MAS	Magic angle spinning
*m*CPBA	3-Chloroperbenzoic acid
Me	Methyl
min	Minute
m.p.	Melting point
MS	Mass spectrometry
m.wt.	Molecular weight
m/z	Mass / charge ratio
N	Normal
NMP	1-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
Nu	Nucleophile
Oct	Octyl
PDE	Phosphodiesterase
PEG	Poly(ethyleneglycol)
Ph	Phenyl

Pr	Propyl
PS	Polystyrene
rt	Room temperature
s	Singlet (NMR) or strong (IR)
t	Triplet (NMR)
t	*tert*
TBAF	Tetrabutylammonium fluoride
THP	Tetrahyropyran
THF	Tetrahydrofuran
Tf	Trifluoroacetate (Triflate)
TFA	Trifluoroacetic acid
T.L.C	Thin layer chromatography
TMS	Trimethylsilyl
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
Tol	Tolyl
Ts	Toluenesulfonyl (Tosyl)
UV	Ultraviolet
V	Valine
v/v	Volume/volume ratio
w	Weak (IR)
W	Watt

I would like to thank all the members of Dr Richard Browns group, but would particularly like to thank Jay-Dino, Rob, Nigel, Martyn and Jim for a great lab in my second year which will live long in my memory; and also Geoff and Alex who came along a bit later. You were all great friends. To Richard I must thank for two interesting projects, for encouraging me and for an excellent all round training. And last but not least, cheers Beryl.

Abigail, you did more for me over those three years than I can ever repay you for. Without your love and support during the darker moments it would have been unbearable.

Mum, hopefully your investment in my education has finally paid dividends and that one day we can find some stability as a result of it.

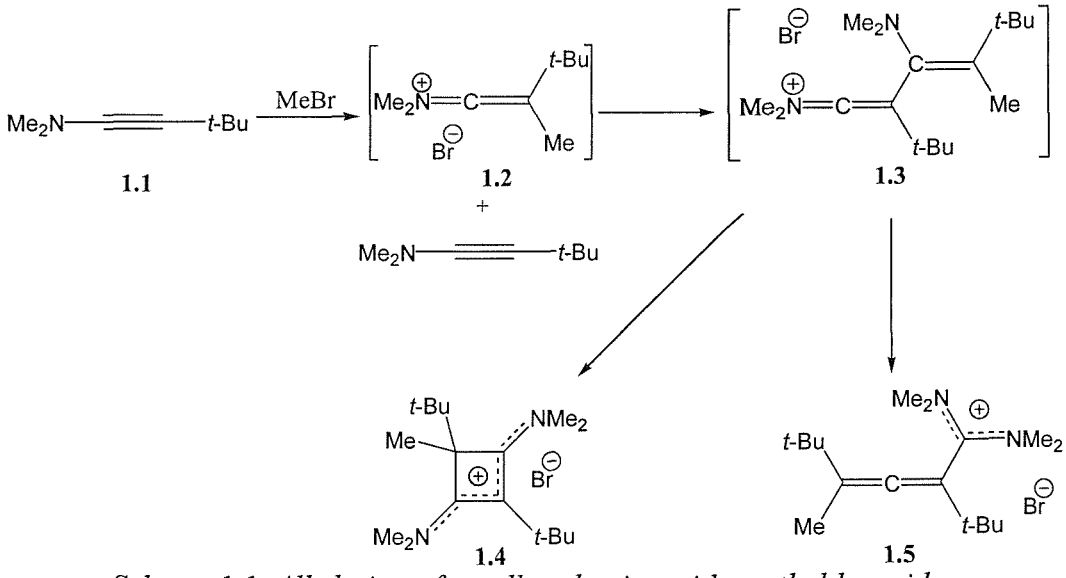
Dad, you have kind of cocked up a bit but I still remember you fondly as a kind and loving man.

Chapter 1: [2+2] Cycloadditions of Keteniminium Salts with Resin Bound Alkenes

INTRODUCTION

1.1 [2+2] Cycloaddition Between Keteniminium Salts and Olefins

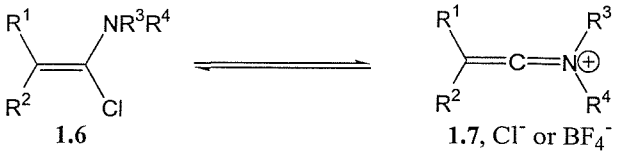
Initially keteniminium salts were regarded as unstable intermediates which were occasionally invoked as intermediates to explain the course of reactions, for example, in the work of Viehe *et al.* on alkynylamines in 1967.[1] Unexpectedly, they found that on alkylation of (3,3-dimethyl-1-butynyl)dimethylamine (**1.1**) with methyl bromide two products were formed, cyclobutylcyanine **1.4** (30%) and an allenyl amidinium salt **1.5** (65%) (Scheme 1.1). Viehe rationalised that these two products could be formed from a common intermediate **1.3** which itself was formed from keteniminium salt **1.2**. The keteniminium salt was formed from methylation of the alkynylamine, the suggestion is that keteniminium salt **1.2** is then alkylated with another molecule of alkynylamine to give the common intermediate **1.3**, which could cyclise to cyclobutylcyanine **1.4** or undergo rearrangement to allenyl amidinium salt **1.5**.



Scheme 1.1. Alkylation of an alkynylamine with methyl bromide.

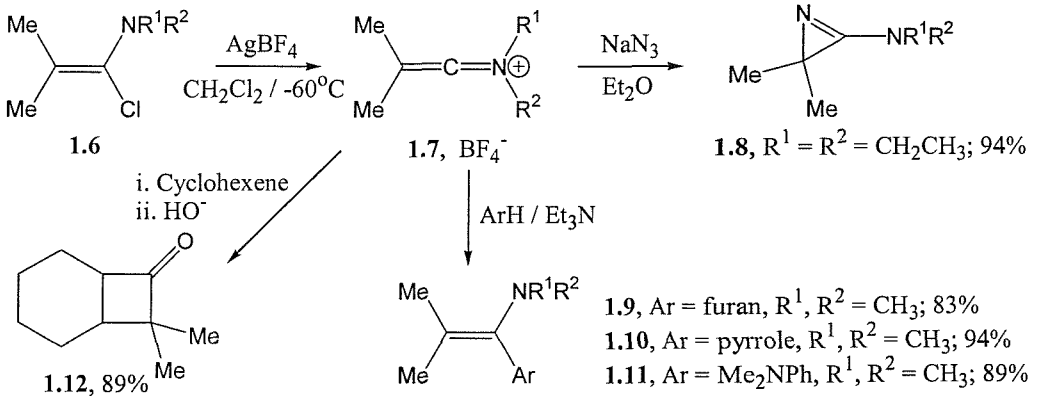
Two years later Ghosez and Viehe were working on α-chloroenamines and found marked differences in their reactivity compared to either enamines or vinylic

chlorides.[2] Studies showed that unlike enamines they were poorly nucleophilic at the β-position, whilst in contrast to vinylic chlorides they were very electrophilic at the α-position and reacted readily with organolithiums, Grignard reagents, thiolates, alkoxides and amines. To explain this observation they suggested that in solution an equilibrium exists between α-chloro enamine **1.6** and keteniminium chloride **1.7** (Scheme 1.2) and that the reactivity is due to the keteniminium species.



Scheme 1.2. Equilibrium between α-chloro enamines and keteniminium salts.

Ghosez established that silver tetrafluoroborate accelerated the rate of nucleophilic additions by trapping the chloride ion as insoluble silver chloride and replacing it with the non-nucleophilic tetrafluoroborate ion, hence forcing the equilibrium (Scheme 1.2) over to the right hand side.[3] Ghosez went on to investigate the extent to which keteniminium salts react with nucleophiles (Scheme 1.3). Amongst his early work he established keteniminium salts reacted with sodium azide to give novel cyclic amidines **1.8**,[Rens, 1970 #4] with electron rich aromatics (no acid catalyst needed) to provide aryl enamines **1.9-1.11** and with alkenes to afford cyclobutanones **1.12**.[3,4]



Scheme 1.3. Reactions of keteniminium salts with various nucleophiles.

Ghosez was interested in the [2+2] cycloaddition between keteniminium salts and olefins drawing comparison with analogous reactions between ketenes and olefins. By reacting keteniminium salts with ethylene at atmospheric pressure and room temperature in good yield (ketenes do not react), he showed keteniminium salts to be more reactive than ketenes.[5] Like ketenes, keteniminium salts react with 1,3-dienes to give purely the [2+2] cycloadduct (no Diels-Alder products were observed) and on reaction with *cis*- and *trans*-cyclooctenes the stereochemistry is retained in the

cyclobutanone products. This would suggest that like the ketene cycloaddition with olefins (Figure 1.1), the mechanism is a ($\pi 2_s + \pi 2_a$) concerted cycloaddition.[3]

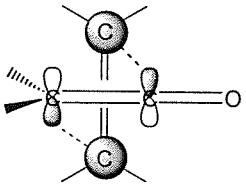
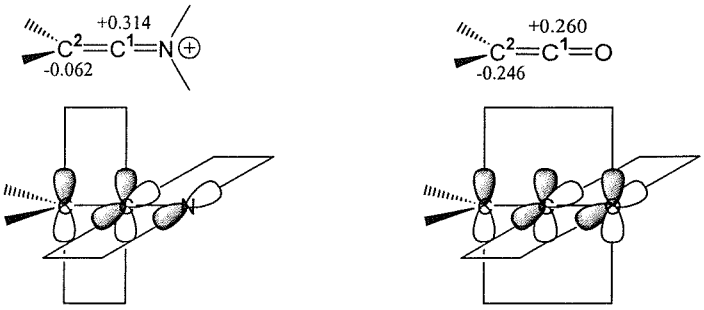


Figure 1.1. ($\pi 2_s + \pi 2_a$) concerted cycloaddition between a ketene and olefin.

However, further experimental and computational work has been carried out which suggests that the reaction is not concerted but involves a stepwise addition followed by cyclisation. Through computational studies it has been possible to estimate the net atomic charges on a simple keteniminium salt and ketene (Figure 1.2).[6] It can be seen that C^1 of both species is significantly electron deficient, however, whilst C^2 of the ketene is electron rich C^2 of the keteniminium salt has a very weak negative charge. Therefore, the ketene system has a nucleophilic centre (C^2) and an electrophilic centre (C^1) that allows ketenes to react in a concerted fashion. The keteniminium salt has a strongly electrophilic centre but C^2 is a poor nucleophilic centre, and suggests the cycloaddition proceeds *via* a step-wise mechanism.

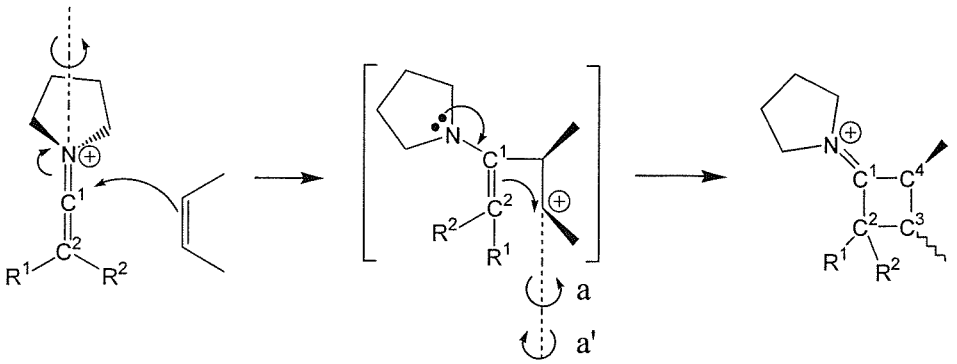


(a) Keteniminium Salt. (b) Ketene

Figure 1.2. Electron densities and π-bond orientations of keteniminium salt and ketene.

One of the loan pairs of electrons on the oxygen of the ketene is in the plane of the C^1-C^2 π-bond enabling it to donate into the double bond and giving the C^2 carbon enol like nucleophilicity. The nitrogen of the keteniminium salt does not have a loan pair of electrons to donate into the C^1-C^2 π-bond and hence C^2 does not have the same nucleophilicity. Recent computational studies agree with these earlier observations that the reaction has a step-wise mechanism (Scheme 1.4).[7,8] Initially there is nucleophilic attack by the olefin at C^1, the resulting positive charge will reside on the

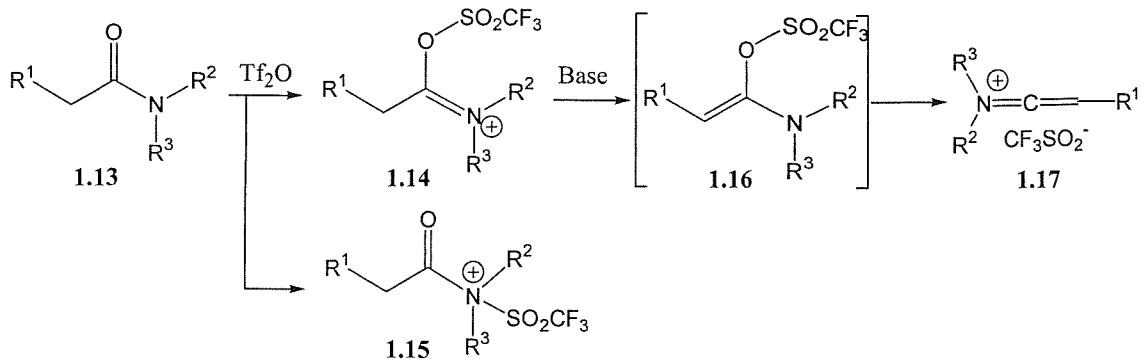
more stabilised carbon of the double bond, allowing the regiochemistry to be easily predicted. The carbocation is then attacked by the nucleophilic enamine.



Scheme 1.4. Mechanism for the keteniminium salt/olefin cycloaddition.

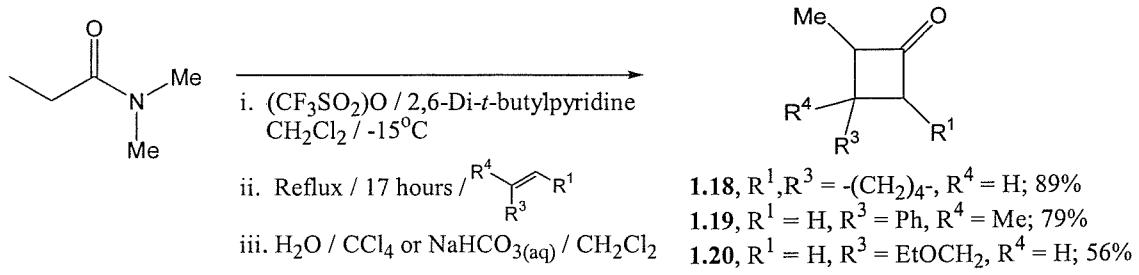
To create the nucleophilic enamine system a 90° rotation around the C-N bond is necessary for the nitrogen loan pair to be in conjugation with the C^1-C^2 π-bond, since the orbitals of the keteniminium ion (Figure 1.2) show the nitrogen loan pair lies orthogonal to C^1-C^2 π-bond. Rotation is also possible around axis *a* in the transition state. Where there are *cis* or *trans* olefins the shorter rotation *a* will retain the geometry seen in the double bond. Meanwhile rotation *a'* will give the opposite geometry, resulting in epimerisation at C^3 and is more common with a *cis*-olefin since it gives the more stable *trans*-cyclobutanone. Hydrolysis of the iminium salt to the corresponding cyclobutanone can be done in water, mild acid or mild base, although epimerisation can occur with base at the positions adjacent to the ketone (C^2,C^4).[9]

The cycloaddition reaction between keteniminium salts and olefins has a few advantages over the ketene cycloaddition: (a) keteniminium ions are more reactive than ketenes so can react with a wider range of alkenes, (b) keteniminium ions do not dimerise or polymerise unlike ketenes, and (c) keteniminium ions are prepared from cheap readily available starting materials, i.e. tertiary amides. However disadvantages include: (a) silver tetrafluoroborate is very expensive, (b) the starting α-chloroenamines were prepared using highly toxic phosgene, (c) some keteniminium ions once generated can react with unreacted α-chloro enamine and (d) 1,1-disubstituted alkenes do not undergo a [2+2] cycloaddition and preferentially give the Friedel-Crafts product.



Scheme 1.5. Preparation of keteiminium ions with triflic anhydride.

Ghosez looked to find improvements in the preparation of keteniminium salts, and found that silver tetrafluoroborate could be replaced with zinc (II) chloride.[5] However, currently the method that is most commonly used to prepare keteniminium salts is a one-pot preparation directly from the tertiary amide **1.13** (Scheme 1.5).[10] The treatment of a tertiary amide with triflic anhydride and a non-nucleophilic base (2,4,6-collidine or 2,4-di-*t*-butylpyridine) in a non-polar solvent will generate the keteniminium salt *in situ*, via *O*-sulphonylation of the amide. Ghosez was able to detect the generation of the *O*-sulphonylated species **1.14** by observing the chemical shift for the $N(CH_3)_2$ protons (δ = 3.63 and 3.80 ppm). He also deduced that another pair of singlets in the ^1H NMR spectrum at δ = 3.28 and 3.37 ppm could be assigned to the *N*-sulphonylated intermediate **1.15**. The ratio between the proposed *O*- and *N*-sulphonylated signals was 4:1. On addition of base the α-proton is removed converting the iminium salt to a dialkylaminoalkenyl sulphonate **1.16**. This intermediate was not detected, but triflate is immediately eliminated to give the keteniminium salt **1.17**.



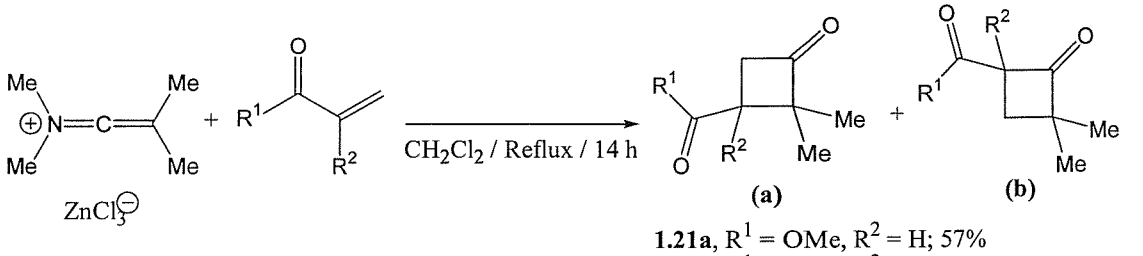
Scheme 1.6. Optimised conditions for [2+2] cycloaddition.[11]

Ghosez has published optimised conditions for the cycloaddition using triflic anhydride and base to generate the keteniminium salt.[11] The procedure can now be considered a synthetically useful reaction for the preparation of a wide range of cyclobutanones (Scheme 1.6). This procedure has also been shown to work very well

for amides with heteroatom substitution at the α-position, e.g. alkoxy, phthalimido and TsMeN-.

1.2 Scope of [2+2] Cycloaddition Reaction

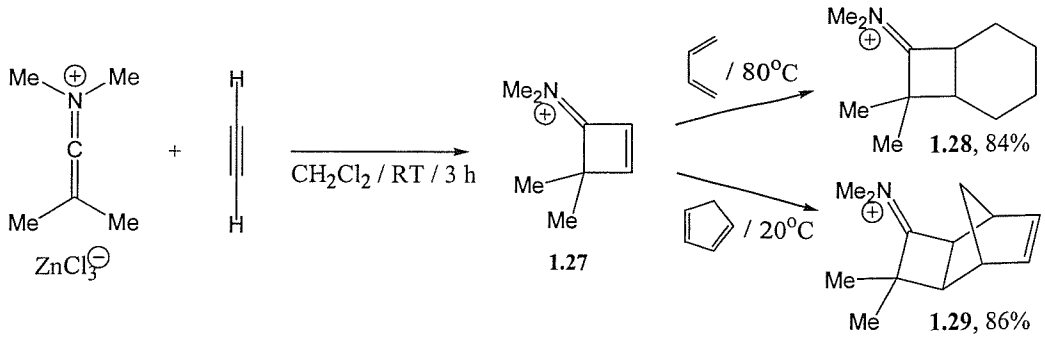
The development of [2+2] cycloadditions with keteniminium salts and alkenes into a synthetically useful reaction has been discussed, but further work was needed to discover the scope of the reaction. The reactivity of keteniminium salts with α,β-unsubstituted carbonyl compounds and alkynes was studied and comparisons were made with the reactivity of ketenes.



1.21a, R^1 = OMe, R^2 = H; 57%
1.22a, R^1 = OMe, R^2 = Me; 71%
1.23a, R^1 = NMe_2, R^2 = H; 65%
1.24a, R^1 = NMe_2, R^2 = Me; 20%: **1.24b** 10%
1.25, R^1 = Me, R^2 = H, 48%
1.26, R^1 = Me, R^2 = Me, 48%: **1.26b** 12%

Scheme 1.7. [2+2] Cycloaddition with α,β-unsubstituted carbonyl compounds.

Ketenes do not react with electron deficient double bonds, so the reactions in scheme 1.7 highlight the greater reactivity of keteniminium salts.[12] Reactions with methyl acrylate, methyl methacrylate, methylvinylketone and *N,N*-dimethyl acrylamide (**1.21a**, **1.22a**, **1.23a**, **1.24a** Scheme 1.7) proceeded in fair to good yields. However reactions with isopropenylmethylketone and *N,N*-dimethyl methacrylamide yielded significant amounts of the regio-isomers (**1.24b**, **1.26b**), and furthermore no reaction took place with any β-substituted acrylates. Regioselectivity was an even bigger problem when the cycloaddition with acetylenes was studied. A 3:1 ratio of regioisomers was observed for the reaction with propyne and 1:1 for the reaction with 3,3-dimethyl-1-butyne.[13] Yields, however, were good for symmetrical alkynes (56-100%) and even acetylene reacted at atmospheric pressure in excellent yield (80%) (scheme 1.8).



Scheme 1.8. Cycloaddition with acetylene followed by Diels-Alder reactions

Ghosez went on to demonstrate that cyclobutenyl iminium species were excellent dienophiles (Scheme 1.8) and underwent Diels-Alder reactions with butadiene and cyclopentadiene to give the iminium adducts **1.28** and **1.29** respectively, which were hydrolysed to give the cyclobutanones in 84% and 86% overall yield respectively.

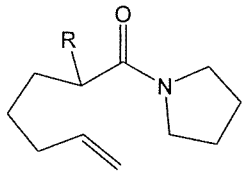
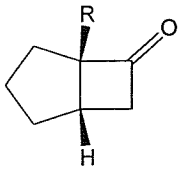
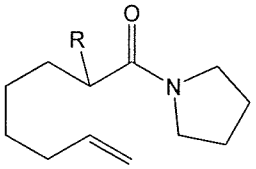
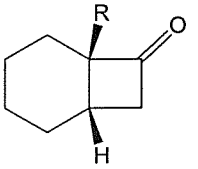
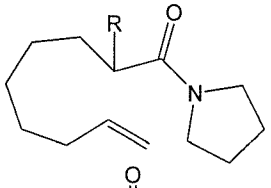
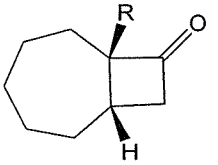
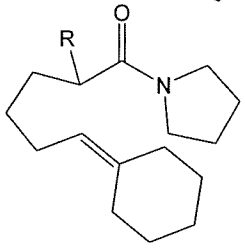
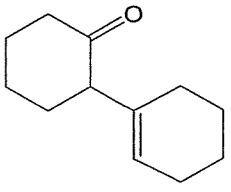
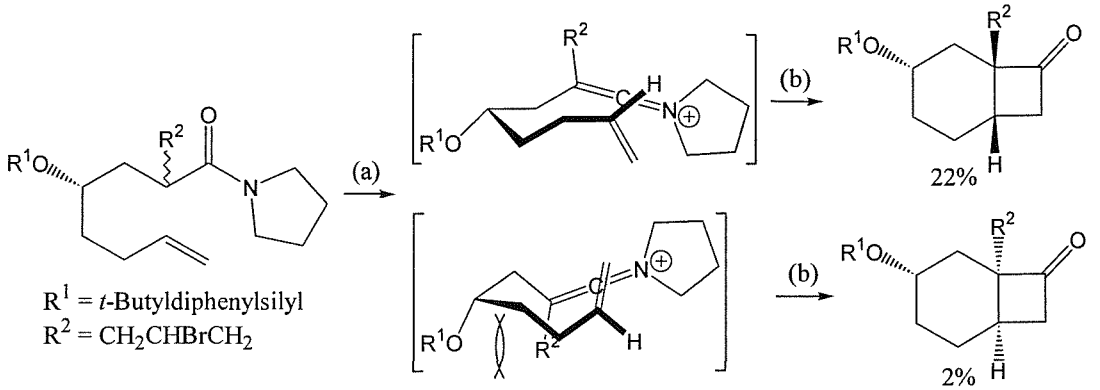
Entry	Unsaturated amide	Cyclobutanone	% Yield
1			R = H, 75% R = Me, 87%
2			R = H, 65% R = Me, 85%
3			R = H, 71% R = Me, 78%
4			55%

Table 1.1. Intramolecular [2+2] cycloadditions of some unsaturated amides.

Of particular importance in this field of chemistry is the intramolecular [2+2] cycloaddition since it has led to a number of natural product synthesis to be discussed later.[14,15,16,17,18] Table 1.1 summarises some results of intramolecular [2+2] cycloadditions undertaken by Ghosez.[19] The yields for entries 1-3 are excellent as

opposed to the corresponding ketene reactions which proceed poorly. However, a limitation to this reaction is when an allylic hydrogen *trans* to the tether is present (e.g. entry 4), an intramolecular ene reaction takes place which after hydrolysis yields the Friedel-Crafts product.

When considering an asymmetric cycloaddition with keteniminium salts and alkenes there have been two approaches: (a), use a chiral centre already installed on the carbon skeleton of the amide[14,15,17,20] or (b) use a chiral amine on the keteniminium salt.

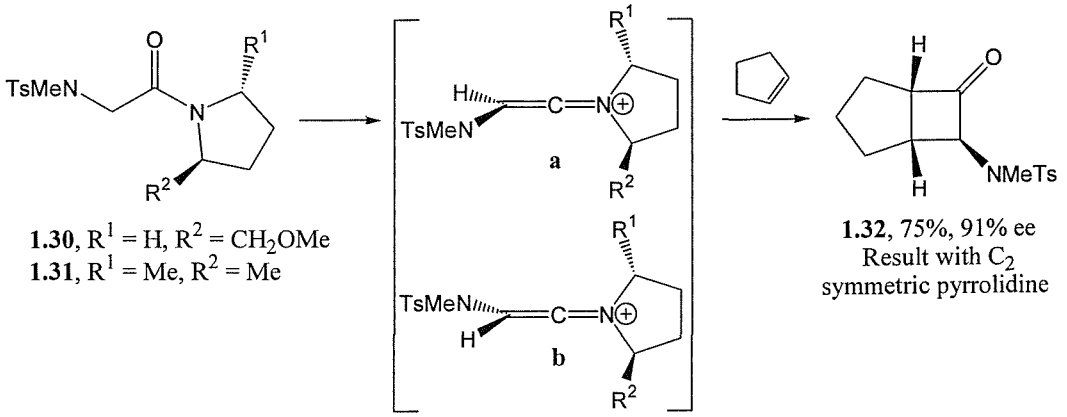


R^1 = *t*-Butyldiphenylsilyl
R^2 = $CH_2CHBrCH_2$

Reagents and conditions: (a) Tf_2O / 2,6-di-*t*-butyl-4-methylpyridine / CH_2Cl_2 / -20°C; (b) H_2O / CCl_4 / reflux

Scheme 1.9. 1,3-Asymmetric induction in [2+2] intramolecular cycloaddition.

Kim and Shim demonstrated 1,3-asymmetric induction for an intramolecular [2+2] cycloaddition using a chiral centre substituted with a bulky silyl ether installed in the starting material from L-glutamic acid (Scheme 1.9).[14] Although the d.e. (80%) was respectable unfortunately the yield of the cyclobutanones was poor.



1.30, R^1 = H, R^2 = CH_2OMe
1.31, R^1 = Me, R^2 = Me

1.32, 75%, 91% ee
Result with C_2 symmetric pyrrolidine

Scheme 1.10. Chiral induction with C_2 symmetric pyrrolidine.

For systems with no chiral centre in the reactants an alternative approach has been investigated, installing a chiral amine in the keteniminium salt (Scheme 1.10).[21,9] Intially (2*S*)-(methylmethoxy)pyrrolidine, derived from (*S*)-proline, was used as the auxiliary **1.30** and in cases where β-substituents of the keteniminium salt were the

same reasonable e.e.'s were obtained. However where the β-substituents of the keteniminium salt are different, two diastereomeric salts (a and b) are produced each with their own facial selectivities which will inevitably effect the observed enantiomeric excess. To overcome this a C_2 symmetrical amine, (2*R*,5*R*)-2,5-*trans*-dimethylpyrrolidine, was studied as an auxiliary **1.31** (Scheme 1.10).[22] In this case there is only one diastereoisomer of the keteniminium salt and the reaction between amide **1.31** and cyclopentene gave a good yield of cyclobutanone **1.32** (75%) and impressive enantiomeric excess (91%). This auxiliary approach has been used in the asymmetric intramolecular cycloaddition,[23]and to add a carboxylic acid and aldehyde across a double bond with the synthetically challenging 1,4-relationship.[24,22]

1.3 Biologically active Natural Products and Synthetic Molecules

In the ensuing section natural products and synthetic molecules with interesting biological activity will be discussed (a) containing the cyclobutane moiety, and (b) prepared via the Baeyer-Villiger oxidation, Beckmann rearrangement or methylene insertion reaction of cyclobutanones. Further transformations to give heterocycles and carbocycles will also be described.

Cyclobutanes

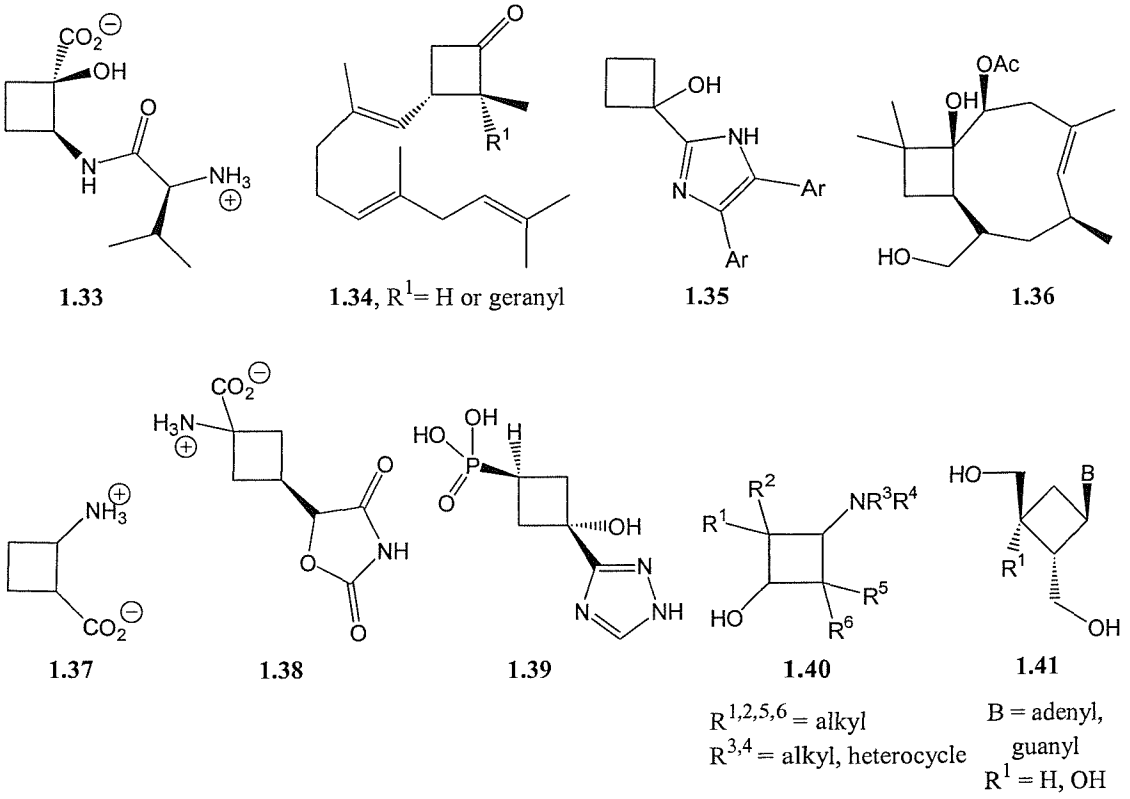
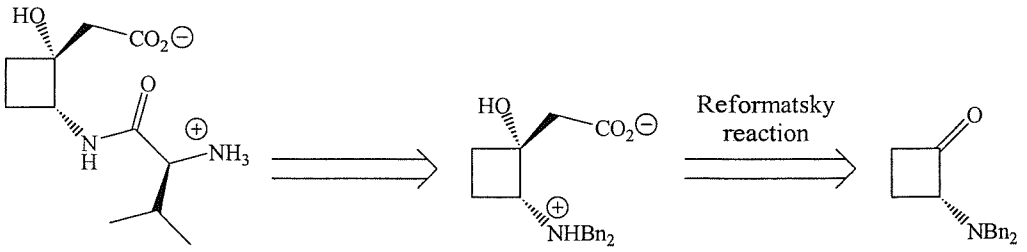


Figure 1.3. Biologically active cyclobutanes

There are a number of cyclobutane structures with interesting biological activity (Figure 1.3). Commonly the cyclobutyl ring has been used to constrain structures in biologically active conformations in order to improve receptor/enzyme binding, e.g. compound **1.38**, which was prepared as a potential treatment for neurological degeneration,[25] and compound **1.39** which has herbicidal activity.[26] A conformationally restricted analogue **1.37** of natural amino acid γ-aminobutyric acid (GABA) was shown to activate the GABA-dependent system, which has implications in Parkinson's disease, Huntington's chorea, epilepsy and schizophrenia.[27] Compounds **1.33** and **1.36** are natural products which show promising anti-microbial and immuno-suppressive properties respectively.[28,29] A number of aminocyclobutanol

analogues, e.g. **1.40**, display interesting activities such as reducing fever, edema, nervous excitement and blood pressure.[30] Biologically active cyclobutylamines have also been reported which have possible therapeutic applications in inflammation, asthma and in the cardiovascular system.[31] One route to analogues of the cyclobutylamines is from the reduction of the cyclobutyliminium salt which proceeds in poor to reasonable overall yield (12-80%) to give a mixture of isomers.[32] Cyclobutanone derivative **1.34** displays squalene synthase inhibition,[33] and compounds **1.37** and **1.41** have anti-inflammatory and antiviral activity respectively.[34,35,36]

Baldwin *et al.* prepared natural product **1.33** in which the key step was a Reformatsky reaction carried out on *N*-protected 2-aminocyclobutanone **1.43** (Scheme 1.11).[29] Clearly the cycloaddition of keteniminium salts and alkenes would provide an excellent route into analogues of this antiviral agent.



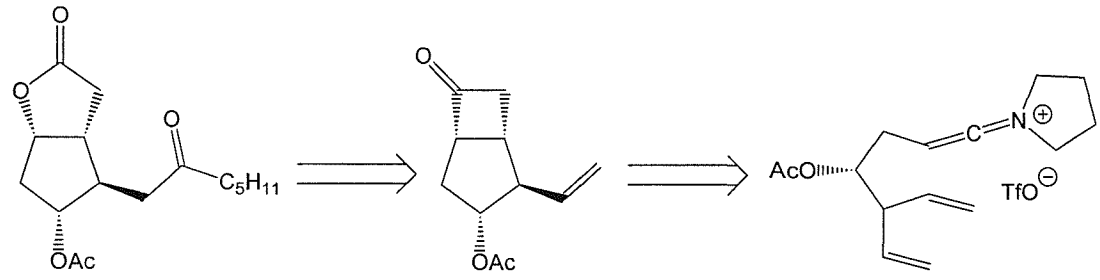
1.33 **1.42** **1.43**

*Scheme 1.11. Retrosynthetic analysis of Baldwin's synthesis of cyclobutanol **1.33**.*

Baeyer-Villiger, Beckmann Rearrangement and Methylene Insertions

The cyclobutanone ring is very strained, not just from angular strain but also due to the sp^2 carbon of the carbonyl which increases torsional strain. The release of this strain by ring expansion chemistry is favoured and will generally proceed in good yield. Unsurprisingly ring expansion chemistry on cyclobutanones, prepared from keteniminium salt cycloadditions with alkenes, have been used to prepare key intermediates for natural product synthesis. Lactone **1.44** (Scheme 1.12) is a key intermediate in the synthesis of prostaglandins, the retrosynthetic analysis demonstrates the route to lactone **1.44** from cyclobutanone **1.45** *via* Baeyer-Villiger oxidation.[37] An intramolecular [2+2] cycloaddition gives the bicyclic cyclobutanone **1.45**, which under Baeyer-Villiger oxidation conditions inserts the oxygen selectively between the carbonyl and the most electron rich centre. Further work has been carried

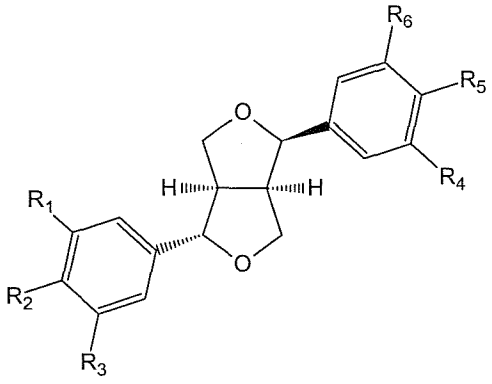
out to prepare the cyclobutanone asymmetrically and to take the synthesis to a key late stage intermediate.[18,17]



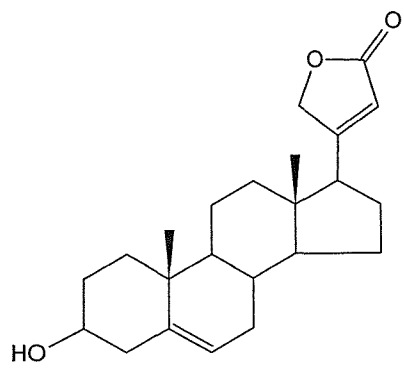
1.44 **1.45**

Scheme 1.12. Retrosynthetic analysis of an intermediate in the synthesis of prostaglandins.

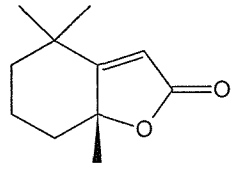
A number of other interesting intermediates and natural products have been prepared using the cycloaddition/Baeyer-Villiger methodology (Figure 1.4). The furofurans are a subclass of the lignans, the cycloaddition/Baeyer-Villiger methodology was used to install the first ring with the correct regiochemistry for the racemic total synthesis of three of the furofuran subclass (**1.46**, **1.47** and **1.48**).[38]



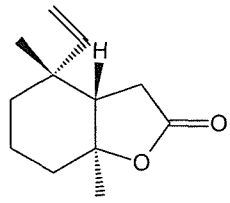
1.46, asarinin; R^1, R^2 = -OCH_2O-; R^3, R^6 = H; R^4, R^5 = -OCH_2O-
1.47, fargesin; R^1, R^2 = -OCH_2O-; R^3, R^4 = H; R^5, R^6 = OMe
1.48, epimagnolin A; R^1, R^2 , R^3, R^4 , R^5 = OMe; R^6 = H



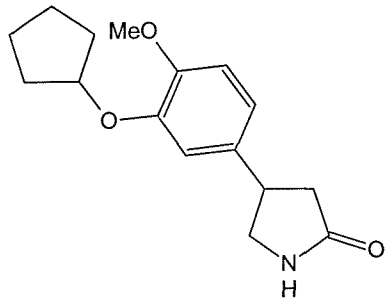
1.49 cardenolide intermediate



1.50, (-)-dihydroactinidiolide



1.51, (-)-anastrephin



1.52, rolepram

Figure 1.4. Compounds prepared following a [2+2] cycloaddition/Baeyer-Villiger strategy.

Other interesting compounds prepared using the cycloaddition/Baeyer-Villiger reaction sequence include: (-)-dihydroactinidiolide (**1.50**) and (-)-anastrephin (**1.51**) which are naturally occurring insect pheromones;[15] steroid **1.49**, an intermediate in the

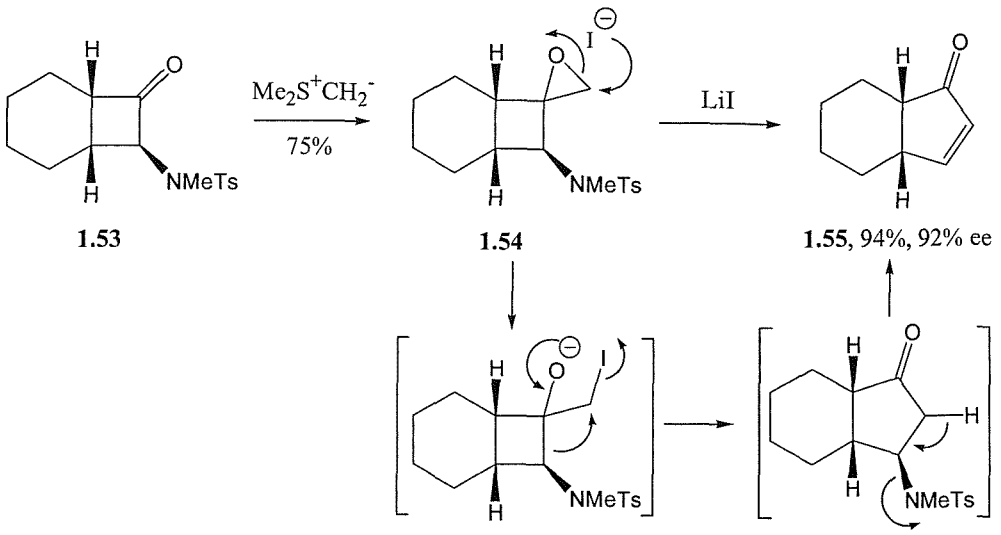
synthesis of cardenolides; and rolepram was prepared from the corresponding γ-lactone.[39]

There has been considerable interest in rolepram (**1.52**) from the pharmaceutical industry due its powerful inhibition of phosphodiesterase IV (PDE IV), an enzyme that is heavily implicated in inflammation and particularly asthma. Although rolepram suffers from the fact it is strongly emetic it remains an important lead compound in the search for commercial PDE IV inhibitors. It is perhaps surprising that rolepram was not prepared directly from the corresponding cyclobutanone via a Beckmann rearrangement. There are only a few examples where a keteniminium salt cycloaddition to an alkene followed by Beckmann rearrangement has been used and unfortunately either the wrong regioisomer or a mixture of regioisomers were obtained.[40,41] Similarly methylene insertions have not been widely exploited, however, the cyclobutanones in Scheme 1.9 were treated with diazomethane and a methylene group inserted between the carbonyl and the tertiary carbon in high yield (94%) and selectivity.[14]

Other Heterocycles and Carbocycles Derived from Cyclobutanones

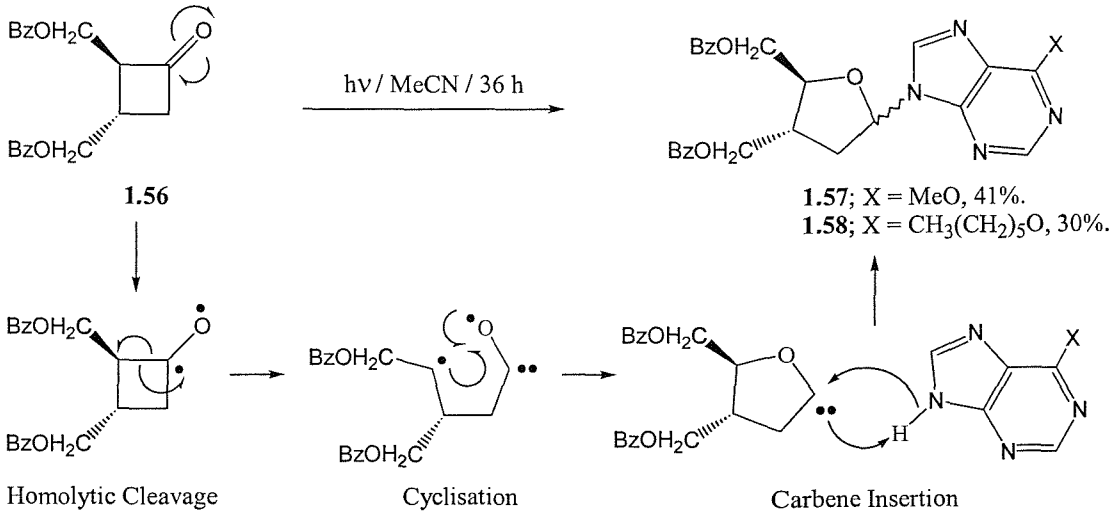
A number of other transformations that can be carried out on cyclobutanones warrant further discussion. Some further work by Ghosez on ring expansions and some reactions of cyclobutanone derivatives will be reviewed.

One of Ghosez's most recent publications on the [2+2] cycloaddition of keteniminium salts discusses their attempts to convert cyclobutanones into a cyclopentanones (Scheme 1.13).[42] They chose to do this using Corey's sulphur ylid, which was expected to initially produce epoxide **1.54** from ketone **1.53**, before rearrangement to the cyclopentanone under lithium iodide catalysis. The regioselectivity of the migration was controlled by the sulphonamide group. Epoxide **1.54** formed, as expected, in fair yield (48-75%) but unexpectedly the major product of the rearrangement was cyclopentenone **1.55**, in excellent yield (75-95%). Installing the cyclopentenone allows for α- and β-substitution with respect to the ketone and they are carrying on with this work to investigate applications towards natural product synthesis.



Scheme 1.13. Ring expansion of cyclobutanone to cyclopentenone via a spiro-epoxide.

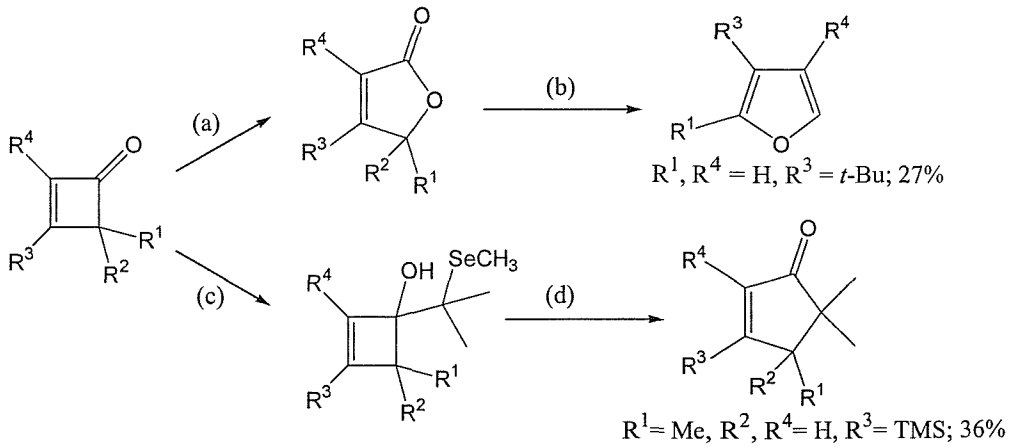
So far the ring expansions considered have inserted carbon, nitrogen and oxygen, but none of the expansions have added any substitutuent groups. The reaction in Scheme 1.14 is both a ring expansion and addition reaction, which is of particular interest in the field of nucleoside chemistry.[43,44]



Scheme 1.14. Photochemically initiated ring expansion/addition resction.

The reaction in Scheme 1.14 is initiated by UV light, which, it was proposed, homolytically cleaves the carbonyl group of cyclobutanone **1.56**. The reaction is then believed to involve a radical ring cleavage allowing the resulting carbon and oxygen radicals to cyclise. The carbene, which is generated, will insert into X-H bonds (X = C, N, O, S), where the hydrogen is weakly acidic, to give the two anomers of the tetrahydrofuran. Lee-Ruff *et al.* went on to use this reaction to prepare nucleotide analogues **1.57** and **1.58** (Scheme 1.14), which on deprotection displayed excellent HIV-1 protease inhibition.[45]

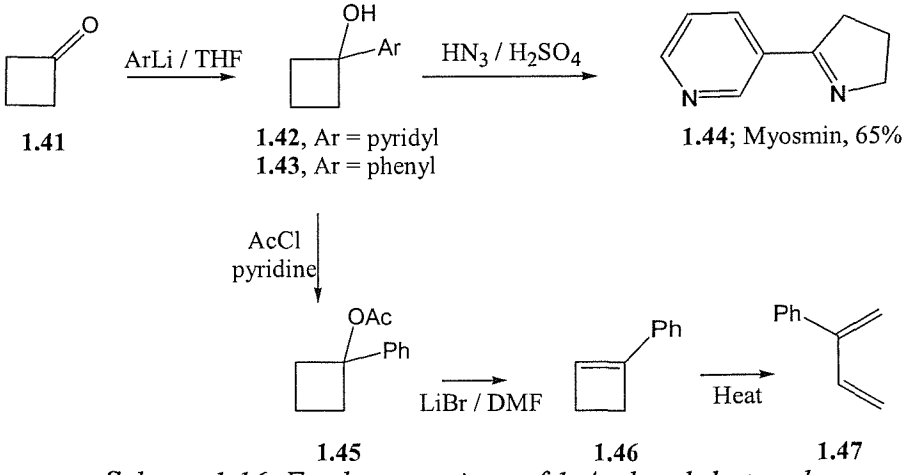
Following on from his work on [2+2] cycloadditions between keteniminium salts and alkynes (see above), Ghosez has shown how cyclobutenones can be converted to furans (*via* butenolides) and cyclopentenones (Scheme 1.15).[46]



Reagents and Conditions: (a) *m*CPBA (1.6 equiv.), $NaHCO_3$ (6.6 equiv.), CH_2Cl_2; (b) DIBAL (1.5 equiv.), THF, -20°C; (c) (i) $Me_2C(SeMe)Li$ (1 equiv.), ether, -78°C, (ii) NH_4Cl; (d) $BnEt_3NCl$, 50% KOH, $CHCl_3$.

Scheme 1.15. Ring expansions of cyclobutenones.

Cyclobutanones will be attacked readily by oganometallic compounds at the carbonyl since going from an sp^2 carbon to an sp^3 carbon will relieve torsional strain. The product of pyridyl addition to cyclobutanone (**1.59**), cyclobutanol **1.60**, has been shown to undergo ring expansion with hydrazoic acid to give a precursor to nicotine, myosmin (**1.62**) (Scheme 1.16).[47] Acetylated cyclobutanol **1.63** underwent elimination to give cyclobutenes in excellent yield (90%).[48] Cyclobutenes are interesting due to the electrocyclic rearrangement they undergo on heating to give 1,3-dienes (Scheme 1.16), that can be used in subsequent Diels-Alder [4+2] cycloadditions.



Scheme 1.16. Further reactions of 1-Arylcyclobutanols

1.4 Flexible Template in Solid-Phase Library Design

With the onset of automated screening techniques biochemists are able to screen much larger numbers of compounds. In order to keep up with the increased capacity of biochemical screening, chemists have looked at automating synthetic chemistry. Solid-phase chemistry has been shown to be an ideal tool for carrying out automated chemistry, particularly for multi-step synthesis. Work up and purification for solid-phase chemistry involves dispensing the solution onto the resin, agitation and filtration. These operations can be readily accomplished using automated techniques.

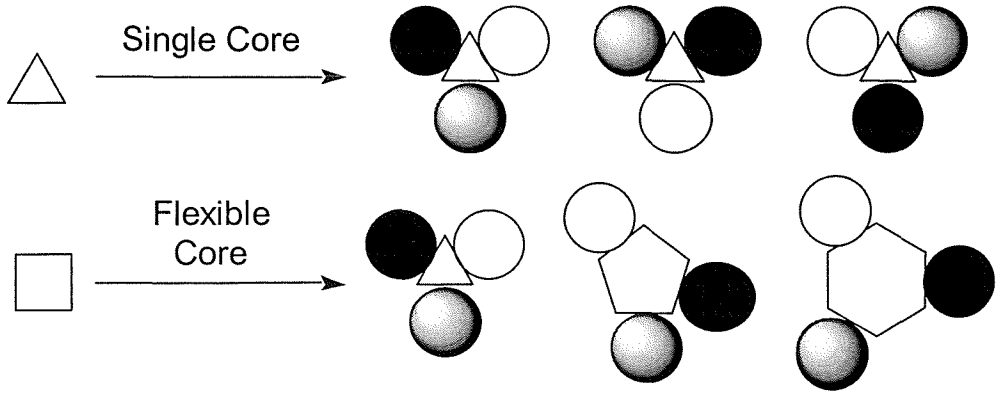
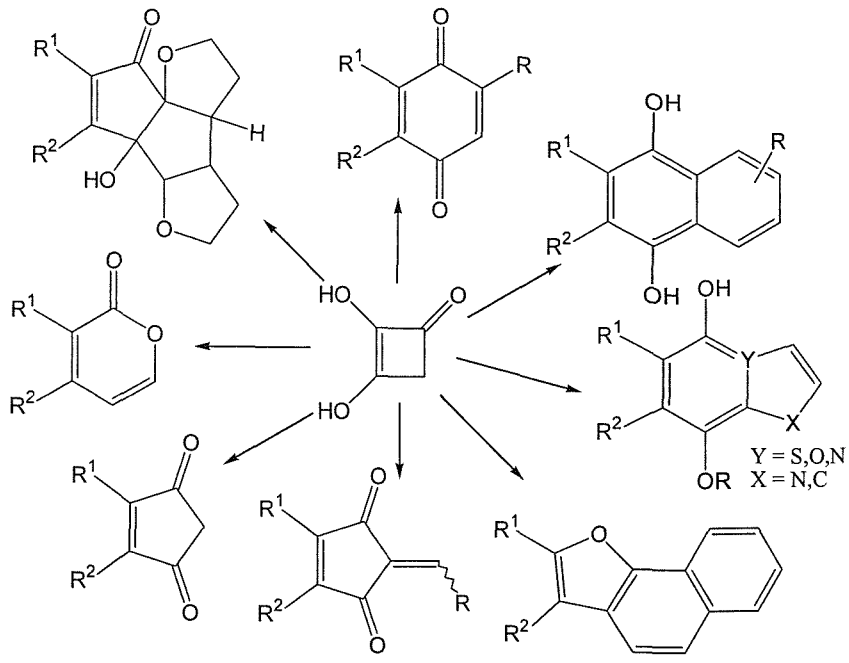


Figure 1.5. A flexible core allows a change in orientation of pendant groups.

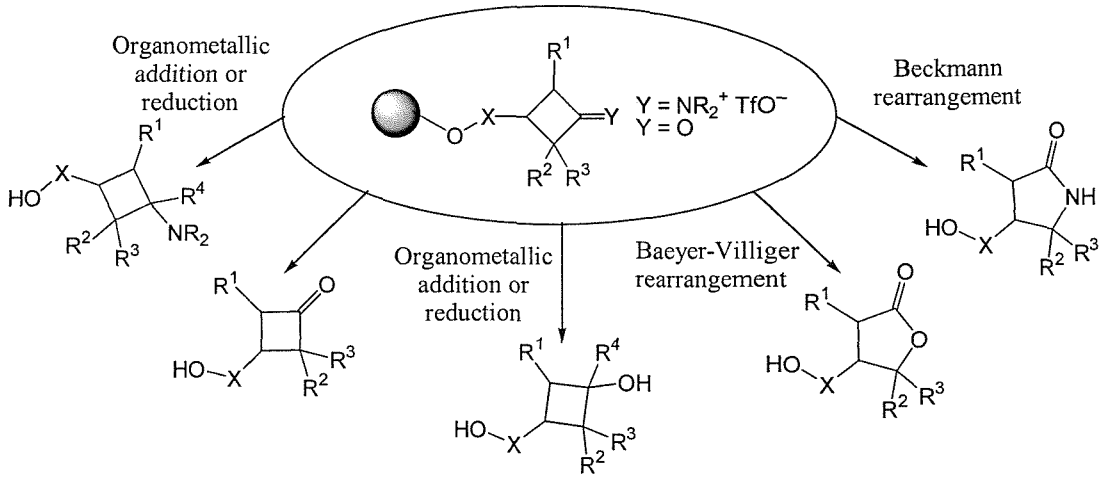
The most common approach to generating arrays of compounds (libraries) is to choose a resin bound template to which pendant groups can be added. Using this approach a large number of compounds can be generated. This approach has a number of drawbacks: (a) the core template may not be tolerated by the enzyme or receptor, reducing the likelihood of generating active compounds from the library, (b) interactions around the core itself are not investigated, and (c) particularly in the case of cyclic templates (the most common type) the orientation of pendant groups is fixed thus limiting the space investigated (Figure 1.5).

An alternative approach was introduced by Armstrong and Tempest in 1997.[49] They introduced the term 'multiple core template libraries' which describes a strategy that addresses the drawbacks of fixed orientated pendant groups and looks to vary the properties of the core. They proposed squaric acid as a flexible core since it can be readily converted to a range of aromatics and heteroaromatics. The manipulation of hydroxyls allows for the installation of two pendant groups, the core can then be converted to the desired structure.



Scheme 1.17. Proposed structures available from squaric acid.

In section 1.1 the [2+2] cycloaddition of keteniminium salts with alkenes to afford cyclobutanones was discussed, however, to our knowledge the reaction has not been carried out on solid-phase. Furthermore the resulting cyclobutanones and cyclobutyliminium salts are capable of a number of transformations (Scheme 1.18). With this in mind we concluded that the [2+2] cycloaddition, followed by further manipulations would be an ideal system to carry out a flexible core strategy by introducing groups at the cycloaddition stage.



Scheme 1.18. Cyclobutyliminum ion/cyclobutanone as a flexible template.

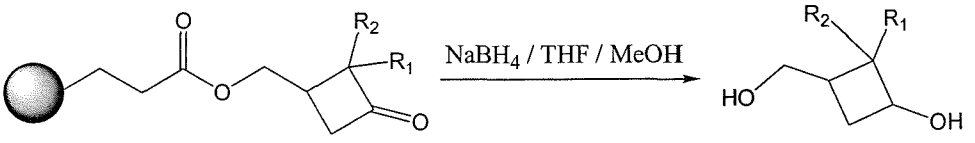
Ring expansion changes the orientation of the pendant groups, whilst changing the functionality between amine, alcohol, ketone, lactam and lactone alters the hydrogen bond accepting and donating properties of the template.

1.5 Solid-Phase Synthesis

Before embarking on solid-phase synthesis one must consider which polymer is to be used, and the linker which tethers the substrate molecule to the resin.

There are a number of polymers used for solid-phase synthesis but the oldest and most commonly used is polystyrene resin cross-linked with divinylbenzene. This polymer swells well in CH_2Cl_2 and THF, which are the solvents that were to be used in the cycloaddition chemistry, and it is relatively inexpensive.

The linker must be compatible with the chemistry in the synthetic sequence, otherwise the target molecule will be cleaved prematurely, and similarly the target molecule must be stable to cleavage conditions. The type of linker will also determine the functionality left in the cleaved product. Our approach was to use a robust ester linkage that would be cleaved by borohydride reduction to unmask an alcohol in the target molecule (Scheme 1.19). After initial optimisation we would hope to find a milder cleavage strategy that would enable the isolation of γ-lactones and cyclobutanones.



Scheme 1.19. Cleavage of cyclobutanols from resin bound cyclobutanones.

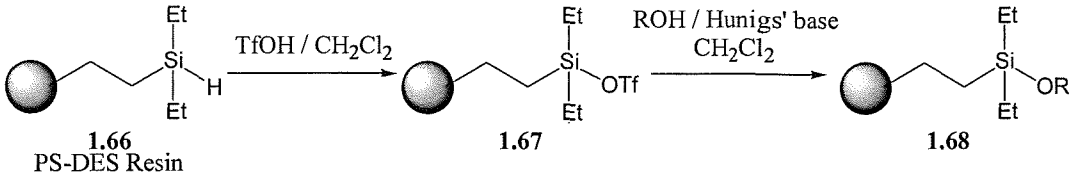
Cyclobutanones are relatively unstable to base and acid hydrolysis, so if milder conditions can not be found to cleave the ester linkage another type of linker must be considered. We decided that a silicon linker might provide the solution since they are cleaved under relatively mild conditions.

Silicon Linkers

The mild cleavage conditions required for silyl ethers makes them an attractive alternative for tethering alcohols to resin compared to many of the acid labile linkers that are commercially available. Chan *et al.* first prepared a silyl ether linker in 1985.[50] The procedure, *via* lithiated polystyrene, is difficult to reproduce, although Danishefsky has used this linker for the synthesis of oligosaccharides.[51]

Recently silyl ether linkers have received significant attention. Previous work has involved preforming silyl ethers in solution, the molecule was attached to resin *via* an amide linkage, a glycopeptide was synthesised and the resulting glycopeptide was

isolated from the resin by fluorolysis.[52] Recently polystyrene diethylsilane (PS-DES) resin (**1.66**) has become commercially available and a number of workers have used it to prepare a silyl ether functionality on resin (Scheme 1.20). [53,54,55,56] The simplest approach uses triflic acid to generate silyl triflate **1.67**. This silyl linker has been used to prepare thioglycosides[54] and the vitamin D_3 system.[56] Interestingly the silyl linker has also been used to attach enolisable α,β-unsaturated ketones as siloxydienes which can undergo solid-phase Diels-Alder reactions.[53] Significantly, resin bound silylester enolates have been shown to undergo the ester enolate Claisen rearrangment.[55]



1.66
PS-DES Resin

1.67

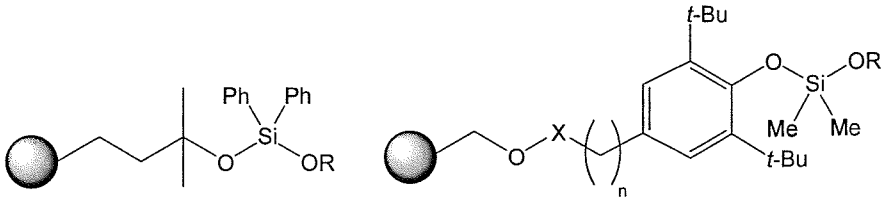
1.68

Scheme 1.20. Preparation of Silyl Ether Linker from PS-DES Resin.

Siloxanes have been introduced as alternative protecting groups to silyl ethers,[57,58] the inductive effect of the second electron withdrawing oxygen increases the silicon's reactivity towards nucleophiles, possibly *via* an inductively stabilised pentavalent siliconate complex.[59] By increasing the steric bulk around the silicon, the reactivity towards most nucleophiles can be eliminated whilst retaining an increased reactivity over silyl ethers towards the small fluoride ion. Rathke and Manis prepared (2,4,6-tri-*t*-butylphenoxy)dimethylsilyl chloride (TPS-Cl) and looked at the properties of the corresponding siloxyenol ethers.[58] A variety of aryloxysilyl enol ethers of acyclic and cyclic ketones were prepared in high yield. Their studies showed that whilst the TPS enol ether showed greater acid (0.05 M HCl) stability than its *t*-butyldimethylsilyl enol ether analogue it was extremely labile on treatment with potassium fluoride.

Further work was carried out to improve the hydrolytic stability of the siloxanes.[57] The half-lives of various siloxanes and silyl ethers of dodecanol, under acidic (0.01 N $HClO_4$, THF/H_2O (9:1)), fluoride (0.01 M TBAF, CH_2Cl_2/THF (9:1)) and basic conditions (0.05 M NaOD, THF-D_8/D_2O) were determined (Table 1.2). Notably the siloxanes are rapidly cleaved with fluoride, in contrast to the silyl ethers. The *t*-butyl diphenylsilyl ether (entry 8) is acid stable and *t*-butylmethoxyphenyl silyl ether (entry 6) has an outstanding stability but is accompanied by long reaction times with fluoride resulting in more forcing conditions and longer reaction times necessary for deprotection. The di-*t*-butyl phenol group (entry 5) was shown to have poor acid and

base stability, contrary to the results from Rathke and Manis that suggest particularly good base stability. However *t*-butoxy diphenylsilyl ether (entry 4) has much better stability, and should be relatively easy to prepare on solid phase. A *t*-alkoxydiphenylsiloxy linker **1.69** may prove to be at the very least complimentary to the di-*t*-butyl phenol derived linker **1.70**.



1.69

1.70a, X = CH_2
1.70b, X = C=O

Figure 1.6. t-Butoxy diphenylsilyl and TPS linkers.

The intention was to take these interesting results for the siloxane protecting groups and prepare a silicon linker with good acid and base stability yet readily cleavable under mild conditions. Both examples of the TPS linker and *t*-butoxy diphenylsilyl were to be prepared and assessed for loading and acid and base stability. The TPS group can be linked to the resin via an ester or ether bond, whilst the *t*-butoxy diphenylsilyl group will be prepared from a resin bound tertiary alcohol (Figure 1.6).

Table 1.2. Stability of various (dodecyloxy)silyl ethers.[57]

$$Me(CH_2)_{10}CH_2OR \xrightarrow[H^+,\ F^-\ \text{or}\ OH^-]{} Me(CH_2)_{10}CH_2OH$$

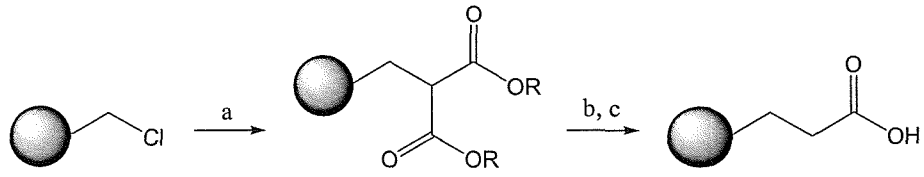
Entry	R	Conditions	$t_{1/2}$, h
1	$SiPh_2OMe$	H^+	0.12
		F^-	<0.03
		OH^-	<0.03
2	$SiPh_2O$-*i*-Pr	H^+	0.70
		F^-	<0.03
		OH^-	0.05
3	$SiPh_2O(2,6\text{-}Me_2Ph)$	H^+	4.0
		F^-	0.25
		OH^-	<0.03
4	$SiPh_2O$-*t*-Bu	H^+	17.5
		F^-	5.8
		OH^-	5.5
5	$SiMe_2O(2,6\text{-}t\text{-}Bu_2\text{-}4\text{-}MePh)$	H^+	4.0
		F^-	0.08
		OH^-	0.05
6	SiPh(OMe)-*t*-Bu	H^+	200
		F^-	22
		OH^-	45
7	$SiMe_2$-*t*-Bu	H^+	1.4
		F^-	140
8	$SiPh_2$-*t*-Bu	H^+	>200
		F^-	375

RESULTS AND DISCUSSION

1.6 Preparation of Linkers

The aim of the project was to carry out the [2+2] cycloaddition with keteniminium salts and resin bound olefins, followed by further elaborations of the resulting cyclobutyliminium salts and cyclobutanones to prepare cyclobutanols, cyclobutylamines, γ-lactones and γ-lactams. To carry out this chemistry suitable linkers had to be prepared. A carboxylic acid linker and a hindered siloxane linker were chosen to bind alkenols to the resin.

Carboxylic Acid Resin



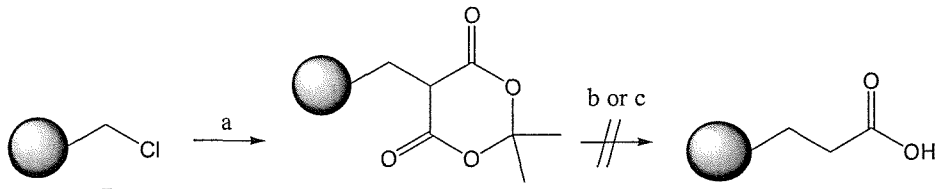
1.71 **1.72**, R = Et **1.73**, R = Me **1.74**

Reagents and Conditions: (a) NaH, Dialkylmalonate, DMF, 60°C; (b) KOH, water/THF (1:9); (c) 2M HCl, THF.

*Scheme 1.21. Synthesis of carboxylic acid resin **1.74**.*

The alkylation of Merrifield's resin (**1.71**) (1% divinylbenzene cross-linking, loading 1.0 or 2.0 mmol/g) was initially carried out with dimethylmalonate with NaH in DMF. The infrared spectrum of the resulting resin **1.73** had the characteristic $C{=}O_{str}$ band at 1736 cm^{-1}. After hydrolysis and decarboxylation, it was apparent that characterisation of the resin by infrared spectroscopy was going to be problematic owing to the close proximity of the broad carboxylic acid and ester bands. A strong carboxylic acid $C{=}O_{str}$ band at 1715 cm^{-1} was present in the infrared spectrum, however a shoulder on the band at 1735 cm^{-1} indicated that a significant amount of ester remained. The procedure was repeated, alkylating Merrifield's resin (**1.71**) (1% divinylbenzene cross-linking, loading 2.0 mmol/g) with diethylmalonate (Scheme 1.21), which again was identified by the characteristic $C{=}O_{str}$ band at 1736 cm^{-1} in the infrared spectrum. Hydrolysis and decarboxylation of the malonate gave resin **1.74**, which showed no shoulder at 1736cm^{-1} on the $C{=}O_{str}$ (1715 cm^{-1}) in the infrared spectrum. A basic

solution of bromocresol green in ethanol was used to confirm the presence of acidic groups, i.e. carboxylic acid, in resin **1.74**.



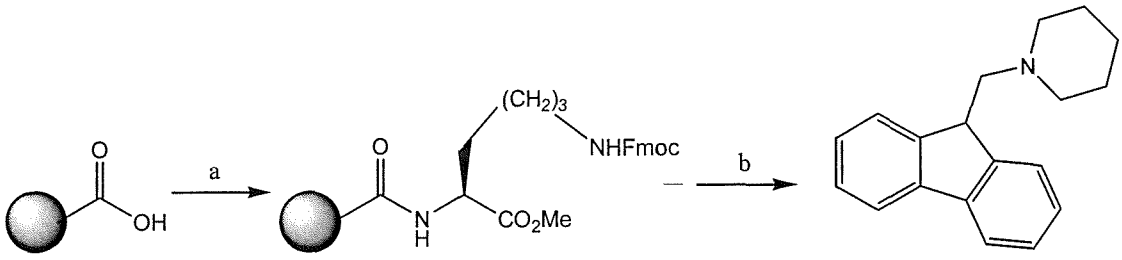
1.71 **1.75** **1.74**

Reagents and Conditions: (a) K_2CO_3, Meldrum's acid, DMF, 70°C; (b) 2M HCl, THF; (c) *p*TsOH, water/THF (1:9).

*Scheme 1.22. Attempted synthesis of resin **1.74** with Meldrum's acid.*

As an alternative method for the synthesis of resin **1.74**, alkylation of Meldrum's acid was considered (Scheme 1.22). After the alkylation of Merrifield's resin a strong $C{=}O_{str}$ appeared at 1741 cm^{-1} in the IR spectrum. Unfortunately a one pot acid hydrolysis/decarboxylation did not work with either 2 M HCl or *p*-toluenesulphonic acid, indicated by an unchanged IR spectrum and a negative bromocresol green test.

Resin Loading Determination



1.74 **1.76**

Reagents and Conditions: (a) N-ε-Fmoc-Lysine methyl ester.HCl, DIC, DMAP, Et_3N, CH_2Cl_2, NMP; (b) 20% Piperidine, DMF.

Scheme 1.23. The Fmoc Test for Determining Resin Loading.

In order to determine the loading of the carboxylated resin **1.74**, an Fmoc test was carried out. (*S*)-N-ε-Fmoc-lysine methyl ester was coupled to resin **1.74** using standard carbodiimide chemistry (Scheme 1.23). The coupling reaction was repeated on half of the resin. The two batches of resin (**1.76a** and **1.76b**) were scrupulously washed and dried. Two portions from each batch were treated with 20% piperidine in DMF in volumetric flasks and the resulting UV absorption at 302 nm was measured. Three of the four results were within experimental error, and the loading was determined to be 0.40 mmol/g (Table 1.3).

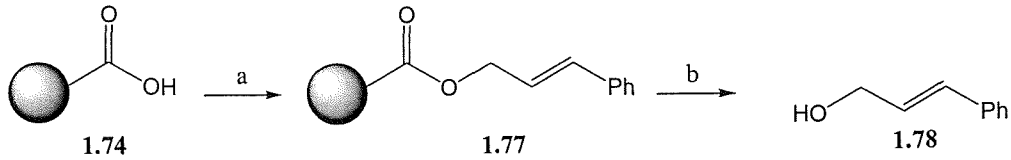
$$\text{Fmoc loading} = \frac{\text{Abs (302 nm) x Vol (mL) x 1000}}{\text{Weight of resin (mg) x 7800}} \quad \text{(mmol/g)}$$

Sample	Sample mass (mg)	Sample volume (mL)	Absorption @ 300nm	Loading Fmoc (mmol/g)	Loading (mmol/g)
1.76a	7.5	20	1.058	0.362	0.42
1.76a	5.0	20	0.682	0.349	0.40
1.76b	5.1	25	0.786	0.491	0.60
1.76b	7.7	25	0.792	0.330	0.38

NB: Resin **1.1.74** was prepared from Merrifield's resin (1.0 mmol/g)

Table 1.3. Results of Loading Measurements.

The quantitative analysis by gas chromatography (GC) of cinnamyl alcohol (**1.78**) cleaved off the resin was used as an alternative method to determine resin loading. One of the results in Table 1.3 at 0.60 mmol/g was at odds with the other three results. This inconsistency was mirrored by the studies of co-workers.[60] With this in mind an alternative method for determining resin loading was devised within the group. The features of this method were: loading of cinnamyl alcohol (**1.78**) onto resin **1.74** using carbodiimide chemistry to give resin **1.77** (Scheme 1.24), cleavage of the cinnamyl alcohol (**1.78**) by transesterification using organic soluble potassium trimethylsilanoxide (KOTMS) in CH_2Cl_2/MeOH, and quantification of the cleaved cinnamyl alcohol (**1.78**) by gas chromatographic analysis with an internal standard (naphthalene) (Table 1.4). The cleavage was key to developing this procedure, having been found to be quantitative and complete within three hours.



1.74 **1.77** **1.78**

Reagents and Conditions: (a) Cinnamyl alcohol, DMAP, DIC, CH_2Cl_2; (b) $TMSO^-K^+$, MeOH, CH_2Cl_2.

Scheme 1.24 Determination of resin loading by GC.

The loading analysis was carried out on resin **1.74** prepared from 2.0 mmol/g Merrifield's resin. The loading was established as 0.95 mmol/g, which was confirmed when the analysis was repeated and was consistent with co-workers results.[60]

$$M_{Ci} = \frac{(D_{Na} / D_{Ci}) \times M_{Na}}{(A_{Na} / A_{Ci})}$$

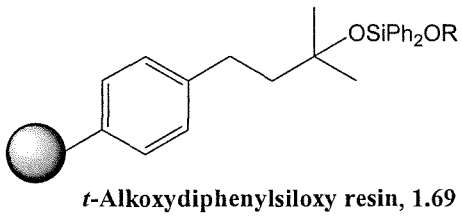
M_{Ci} mass of cinnamyl alcohol (mg), M_{Na} mass of naphthalene (mg); A_{Ci} area of cinnamyl alcohol peak, A_{Na} area of naphthalene peak; D_{Ci} detector response for cinnamyl alcohol, D_{Na} detector response for naphthalene.

Sample	Mass of Resin (mg)	D_{Na}/D_{Ci} Detector response ratio	Mass of cinnamyl alcohol, M_{Ci} (mg)	Loading (mmol/g)
Batch 1	115.9	1.252	14.9	0.959
Batch 2	100.1	1.214	12.7	0.947

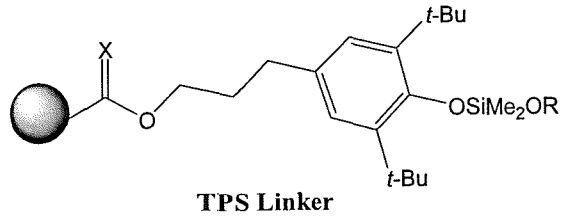
NB: Resin **1.74** was prepared from Merrifield's resin (2.0 mmol/g)

Table 1.4. Results from loading experiments using GC analysis.

Siloxane Resins



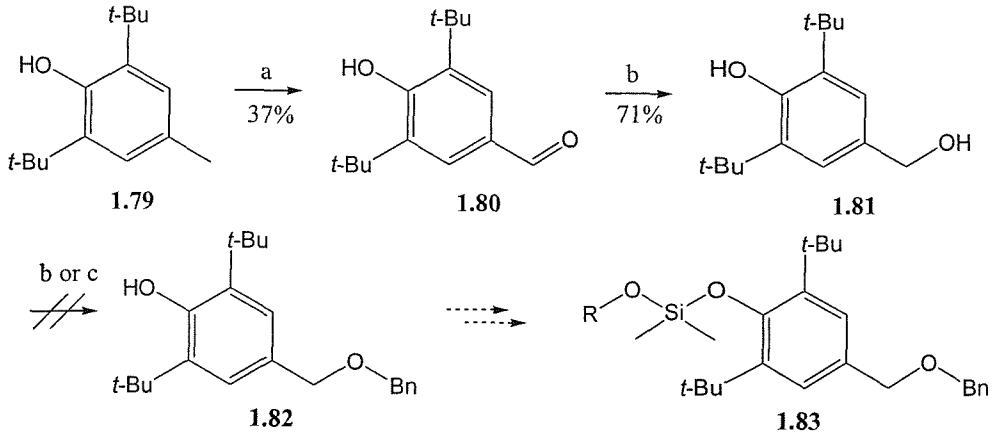
***t*-Alkoxydiphenylsiloxy resin, 1.69**



TPS Linker
1.70a, X = H_2
1.70b, X = O.

Figure 1.7. Proposed siloxane linkers.

The preparation of siloxane linkers in Figure 1.7 was considered to provide resins with good acid/base stability that could be readily cleaved with fluoride. For a linker to be useful it must be cheap, easy to prepare with reasonable loadings. Preparation of large libraries requires large quantities of resin. Resins themselves are expensive so the cost of a linker must be kept to a minimum in terms of materials and in terms of the time taken to prepare it, whilst the yield of compound from the resin must be maximised.

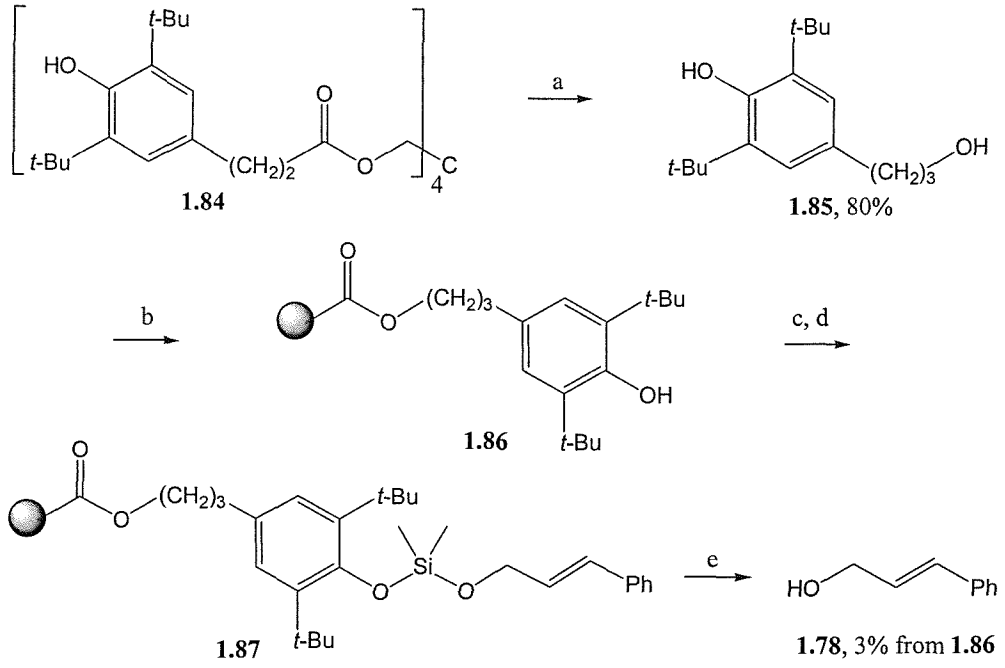


Reagents and Conditions: (a) Br_2, *t*-BuOH; (b) $LiAlH_4$, THF; (c) NaH (2eq), BnCl, DMF; (d) $BnOC(NH)CCl_3$, $BF_3.EtO_2$, THF.

Scheme 1.25. Proposed route to solution model for synthesis of TPS linker.

2,6-Di-*t*-butyl-4-(hydroxymethyl)phenol (**1.81**) was chosen as the linker since it can be prepared from inexpensive 2,6-di-*t*-butyl-4-methylphenol (**1.79**). 2,6-Di-*t*-butyl-4-(hydroxymethyl)phenol (**1.81**) was prepared by the oxidation of 2,6-di-*t*-butyl-4-methylphenol (**1.79**) to the aldehyde (**1.80**) with bromine followed by the reduction to the alcohol with lithium aluminium hydride (Scheme 1.25).[61] The yield for the oxidation was low, however conversion appeared to be high, which would suggest work up and purification required optimisation. Attempts to directly oxidise the benzylic position to the alcohol gave very poor yields (<5%). With 2,6-di-*t*-butyl-4-(hydroxymethyl)phenol (**1.81**) in hand, the preparation of a solution phase model of the polymer supported system was undertaken (Scheme 1.25). Treatment of **1.81** with two equivalents of sodium hydride to form the dianion followed by attempted preferential benzylation of the more reactive alkoxide were unsuccessful, as was the Lewis acid catalysed benzylation *via* benzyl trichloroacetimidate.[62,63] None of the desired benzyl ether **1.82** was isolated from either reaction. The benzylic position para- to the hydroxyl could be potentially sensitive to oxidation or acidic conditions, which may have been responsible for the difficulties.

It was envisaged that moving away from a single carbon spacer could circumvent the problems. The most convenient alternative was the three carbon spacer alcohol **1.85**, which could be prepared from the reduction of the cheap pentathreotol tetrakis(3,5-di-*t*-butyl-4-hydroxydihydrocinnamate) (**1.84**).[64] The single step to prepare alcohol **1.85** as a white crystalline material in reasonable yield suited the requirements for a linker.



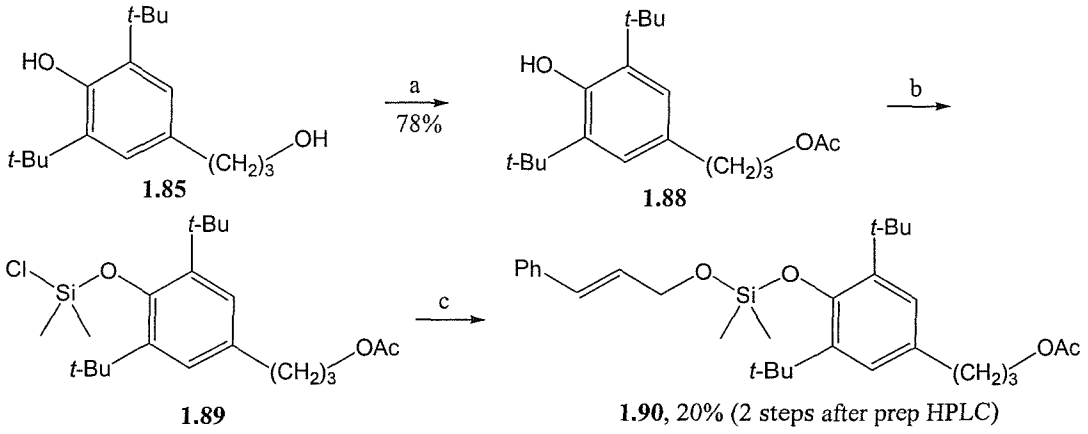
Reagents and Conditions: (a) $LiAlH_4$, THF; (b) Resin **1.74**, DIC, DMAP, CH_2Cl_2; (c) Me_2SiCl_2, Et_3N, CH_2Cl_2; (d) Cinnamyl alcohol, Et_3N, CH_2Cl_2; (e) TBAF, H_2O, CH_2Cl_2.

Scheme 1.26. Preparation of di-t-butylphenoxysilyl (TPS) linker.

Initially the linker was to be anchored to the resin *via* an ether linkage. Attempts to prepare the benzyl ether by double deprotonation of the alcohol followed by alkylation with benzyl chloride gave a mixture of products, including a trace of the desired product. Attempted alkylation of the alcohol with benzyltrichloroacetimidate with $BF_3.Et_2O$ or TFA catalysis gave a complex mixture of products under a variety of conditions.

Although a chemically inert ether attachment would be preferred, in order to assess the utility of the linker, alcohol **1.85** was anchored to the resin *via* an ester linkage. The coupling was carried out using standard carbodiimide chemistry to give resin **1.86**, and the infrared spectrum gave the expected ester $C{=}O_{str}$ at 1730 cm^{-1}. The synthetic route used by Gillard *et al.* to prepare their TPS protecting group was followed for preparation of the di-*t*-butylphenoxydimethylsilyl linker on solid-phase (Scheme 1.26).[57] The three steps were carried out consecutively in a peptide synthesis vessel using five fold excesses of reagents for each step except for TBAF (3 equivalents). The washings of the penultimate reaction were monitored for premature release of cinnamyl alcohol by HPLC. The mass of cinnamyl alcohol in the fourth washing was down to ~75 μg, and a further four washings removed any detectable signs of the

alcohol. The cleavage step was monitored by normal phase HPLC and, the yield was determined to be only 3 %, established from a calibration curve by HPLC.



Reagents and Conditions: (a) AcCl, Et_3N, CH_2Cl_2; (b) Me_2SiCl_2, Et_3N, DMAP, CH_2Cl_2; (c) cinnamyl alcohol, Et_3N, CH_2Cl_2.

Scheme 1.27. Solution model for TPS linker.

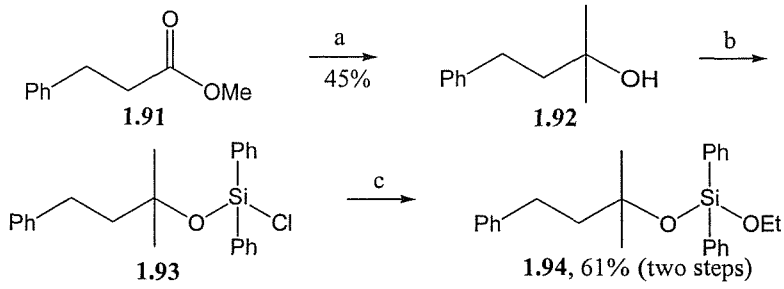
In view of the low yields of cinnamyl alcohol released from resin **1.87**, further investigation of the solution phase chemistry was deemed necessary to optimise the siloxane synthesis. Acylation of 2,6-*tert*-butyl-4-(3-hydroxy propyl)phenol (**1.85**) gave acetate **1.88** regioselectively in good yield. Gillard's *et al.* silylation conditions were then attempted without success. Distillation of triethylamine over calcium hydride and redistillation of dichlorodimethylsilane did not help. The amount of dichlorodimethylsilane was increased to 2 equivalents from 1 equivalent and proton NMR showed a ~40 % conversion to the target siloxy chloride **1.89**. Addition of dimethylaminopyridine (10 mol%) to the reaction mixture resulted in ~60 % conversion to siloxy chloride **1.89** after 18 hours of reflux, which dropped to ~50 % after 42 hours due to decomposition. The literature also suggested that using DMF as solvent would improve the yield, but this was not the case for this reaction.

After work up siloxy chloride **1.89** was treated with cinnamyl alcohol and triethylamine (Scheme 1.27). Initially the reaction looked unpromising by TLC, however following column chromatography proton NMR clearly showed that product **1.90** co-ran with unreacted 2,6-*tert*-butyl-4-(3-acetoxypropyl)phenol **1.88**. Product **1.90** was isolated by preparative HPLC in low yield (20% from **1.88**).

The results from the silylation chemistry in solution have demonstrated that the reaction required forcing conditions to get complete conversion. Preforming the phenolate ion before silylation may help, along with the use of excess reagents and

increasing the amount of DMAP. Our work however switched focus onto the *tert*-alkoxydiphenylsiloxy linker.

The potential benefits of a tertiary alkoxydiphenylsilyl chloride over the di-*t*-butylphenoxydimethylsilyl chloride have been mentioned (Section 1.5). This linker will not require a method of anchoring to the resin, though the preparation of the tertiary alcohol on resin needed to be investigated.



Reagents and Conditions: (a) i. MeLi, THF, -78° to RT; (b) Ph_2SiCl_2 (2 eq), Et_3N (2 eq), DMAP (10 mol%), CH_2Cl_2, reflux; (c) Et_3N, EtOH, CH_2Cl_2.

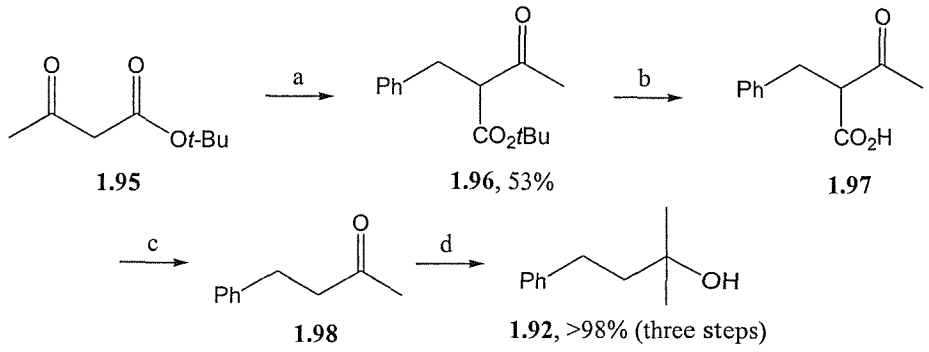
Scheme 1.28. Solution model for preparation of tert-alkoxydiphenylsiloxy linker.

Treatment of methyl dihydrocinnamate (**1.91**) at –78°C with methyl lithium gave tertiary alcohol **1.92** in 45 % yield (Scheme 1.28). The analytical results were consistent with literature data.[65] Side reactions possibly due to enolate formation or lithiation of the phenyl ring, could be avoided using the Grignard reagent or by transmetallating methyl lithium with cerium (III).

Silylation of tertiary alcohol **1.92** with dichlorodiphenylsilane was apparently unsuccessful by ^1H NMR spectroscopy however ^{13}C NMR spectroscopy showed the quaternary carbon adjacent to the hydroxyl had shifted from 71.1 ppm to 78.3 ppm. NMR data indicated complete conversion to the required product **1.93**, though the presence of the high boiling dichlorodiphenylsilane confuses the issue. Rapid chromatography was performed to remove this starting material, but gave a mixture of two products. The products appeared to be the silyl chloride **1.93** and its corresponding silanol. The mixture was treated with ethanol and triethylamine to give ethyl siloxane **1.94** in 61 % yield over 2 steps (Scheme 1.28).

With a view to preparing a tertiary alcohol on solid phase, a straightforward route was devised in solution (Scheme 1.29). The benzylation of *t*-butyl acetoacetate (**1.95**) resulted in a significant amount of dibenzylation, but this problem should be minimised on solid-phase. Surprisingly treatment of *t*-butyl ester **1.96** with 1:1 TFA/CH_2Cl_2 did not result in decarboxylation of the deprotected acid **1.97**, but that

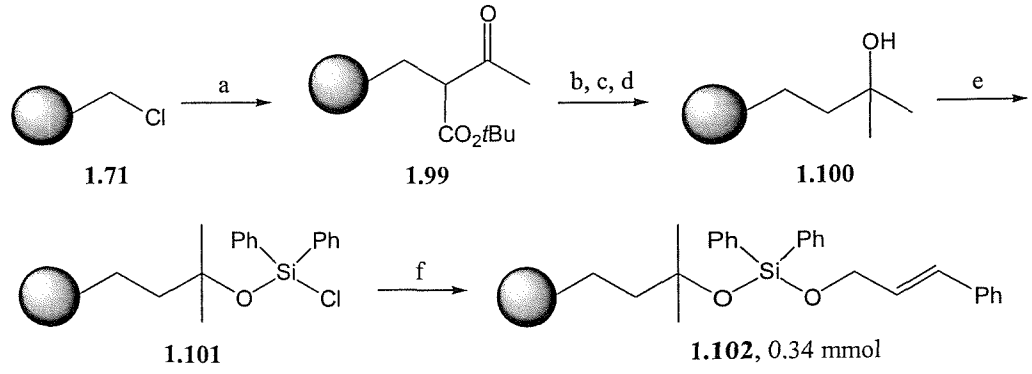
was facilitated with hot water to give 4-phenylbut-2-one (**1.98**) quantitatively over 2 steps. Quantitative Grignard addition gave tertiary alcohol **1.92** in 92% over 3 steps.



Reagents and Conditions: (a) i. NaH, THF; ii. benzyl chloride, reflux; (b) TFA/CH_2Cl_2 (1:1); (c) water/THF (1:4), 60°C; (d) 3M MeMgBr, THF, -10°C.

Scheme 1.29. Solution model for preparation of a tertiary alcohol.

Alkylation of Merrifields' resin (**1.71**) (2.0 mmol/g) under the same conditions as the solution phase model with five fold excess of the anion of ethyl acetoacetate gave resin **1.99** with an almost identical infrared spectrum to its solution counterpart (Scheme 1.30). The deprotection, decarboxylation and methylation steps were easily followed by infrared spectroscopy and were shown to work well to give tertiary alcohol resin **1.100**. The alcohol was silylated with dichlorodiphenylsilane, with triethylamine and DMAP, then treatment with cinnamyl alcohol and base gave siloxane resin **1.102**. The resin was characterised by MAS ^1H and ^{13}C NMR which confirmed the presence of the vinylic and allylic groups from the cinnamyl moiety. The loading was determined to be 0.34 mmol/g by cleaving cinnamyl alcohol (**1.78**) with fluoride, then analysis of cinnamyl alcohol by gas chromatography using naphthalene as an internal standard.



Reagents and Conditions: (a) Ethyl acetoacetate, NaH, THF, reflux; (b) TFA/CH_2Cl_2 (1:1); (c) water/THF (1:4), 60°C; (d) MeMgCl, THF, -10°C; (e) Ph_2SiCl_2 (10 eq), Et_3N (10 eq), DMAP (1 eq), CH_2Cl_2, reflux; (f) Cinnamyl alcohol (10 eq), Et_3N (10 eq), CH_2Cl_2, reflux.

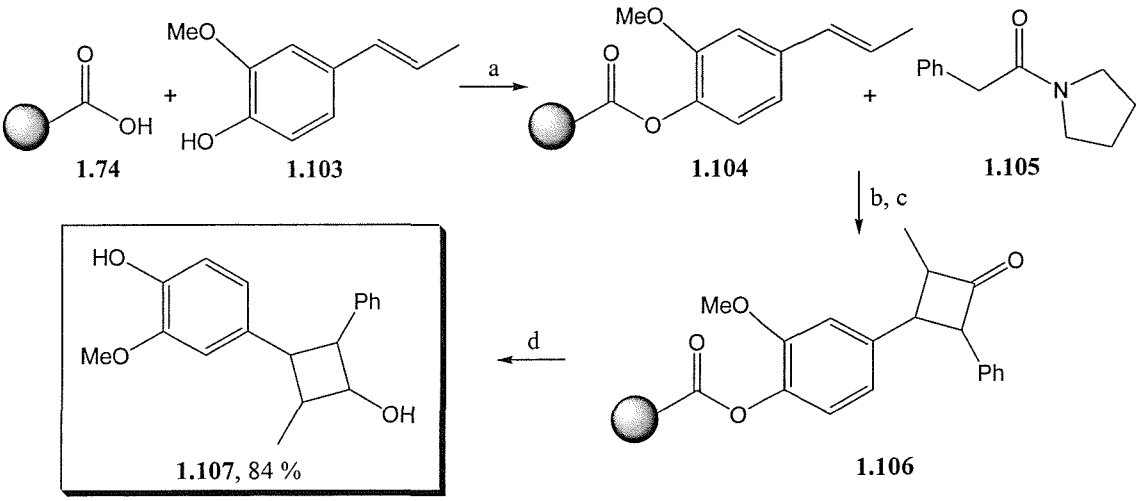
Scheme 1.30. Solid-phase synthesis of t-alkoxydiphenylsiloxy linker.

Conclusion

- Carboxylic acid resin **1.74** has been prepared. The loading was determined reliably using GC quantification and found to be 0.95 mmol/g, which is high enough to be synthetically useful.
- Siloxane linker **1.102** was prepared and the loading quantified by GC. The loading (0.34 mmol/g) was low and needs to be improved upon before the resin can be considered synthetically useful.
- Preparation of a second siloxane linker to give resin **1.87** was unsuccessful due to poor loading and will not be pursued any further.

1.7 [2+2] Cycloadditions

Our initial work on [2+2] cycloaddition chemistry was carried out on isoeugenol (**1.103**), which was attached to carboxylic acid resin **1.74** using standard carbodiimide chemistry. DMAP is usually used in catalytic quantities for carbodiimide couplings, however coupling on to the resin required five equivalents of DMAP due to the poor nucleophilicity of the phenolic OH. When only one equivalent of DMAP was used a rearrangement of the activated ester (derived from DIC) seemed to occur, which resulted in the appearance of a band in the infrared spectrum at 1685 cm^{-1}. To ensure that there were no free acid sites after the coupling, a slurry of the resin in CH_2Cl_2 was treated with a basic ethanolic solution of bromocresol green. The indicator remained dark blue pointing to the absence of any acidic groups on the resin.

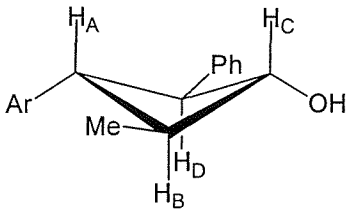


Reagents and Conditions: (a) DIC (5 eq), DMAP (5 eq), CH_2Cl_2; (b) Tf_2O (5 eq), 2,6-di-*t*-butylpyridine (5 eq), CH_2Cl_2; (c) $NaHCO_3$(aq), THF; (d) $LiBH_4$, THF, MeOH, -78°C to RT.

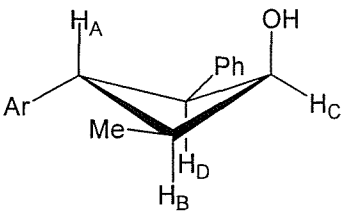
Scheme 1.31. [2+2] Cycloaddition between isoeugenol and a keteniminium salt.

The [2+2] cycloaddition was carried out following methodology developed by Ghosez (Scheme 1.31), using five equivalents of the reagents relative to the olefin.[66] Unfortunately the generation of the iminium ion could not be monitored by IR spectroscopy because the ester $C{=}O_{str}$ at 1735 cm^{-1} masked the $C{=}N_{str}$ band. After hydrolysis of the iminium salt the resin was analysed by infrared spectroscopy which showed the cyclobutanone $C{=}O_{str}$ at 1764 cm^{-1}. The product was reductively cleaved with lithium borohydride to give a crude mixture containing predominantly cyclobutanol **1.107** as a 3:2 mixture of two diastereoisomers. The reaction appeared to have gone to completion because the crude cleavage mixture contained no starting

material. When the mixture was purified by chromatography the two isomers were isolated (**1.107a** 51%, **1.107b** 33%) in good overall yield (84%).



1.107a



1.107b

	Data for **1.107a**				Data for **1.107b**	
Irradiated Peaks ➡	H_A	H_B	H_C	H_D	H_B	H_C
H_A		0.34		0.55		
H_B	-0.68		0.60	1.05		1.51
H_C	1.34	0.46			1.66	
H_D	-0.03	1.07	0			
Me	1.23	1.38	0.69	0	0.57	0.38

*Table 1.5. NOE data of **1.82a** and **1.82b** to ascertain geometry around cyclobutyl ring.*

The stereochemistry of the diastereoisomers has been established by NOE studies (Table 1.5). From this data it is apparent that the major isomer **1.107a** has a structure with all adjacent protons *trans* to one another, which according to the literature is the expected product. The NOE study on **1.107b** shows that H_C and H_B have a strong NOE interaction which would suggest that they are *cis* to one another. Unfortunately H_A and H_D are coincident in the ^1H NMR and so the NOE results for these protons were ambiguous. The geometry of H_A and H_D can be worked out from data in the literature. For example, in the literature, the relationship between pendant groups on the carbons involved in the cyclisation step of the mechanism are always *trans*, i.e. H_A will be trans to H_D. The geometry of the methyl and aryl groups in isoeugenol is likely to be retained especially since it is already in the sterically more favoured *trans* geometry. With this in mind the structure proposed for **1.107b** has the geometry depicted in above in Table 1.5. It appears that the [2+2] cycloaddition is stereoselective and that the two diastereoisomers are formed as a result of the reduction of the ketone. Any

selectivity is determined by the group opposite the ketone which directs hydride attack to the opposite face hence **1.107a** is the major product.[67]

The proposed mechanism (Scheme 1.4) for the [2+2] cycloaddition entails the olefin attacking the electrophilic keteniminium salt, resulting in a carbocation that in the case of isoeugenol resides on the benzylic carbon, which helps stabilise the intermediate (Figure 1.8). The stabilisation of the intermediate should ensure the reaction works well.

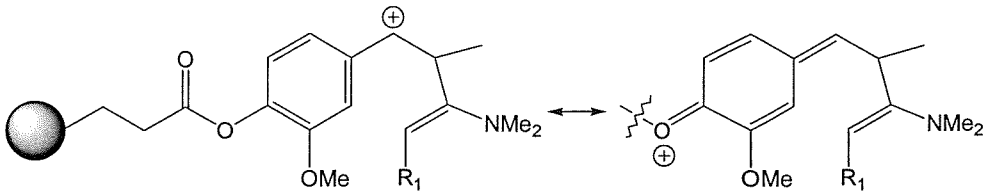


Figure 1.8. Resonance stabilisation of carbocation intermediate.

Whilst isoeugenol is an ideal substrate, allyl esters may not react as well. Ghosez established that the reactivity of an allyl ester is markedly reduced for these [2+2] cycloadditions.[68] It is thought that this is due to the carbocation intermediate of the [2+2] cycloaddition being destabilised by the electron withdrawing oxygen (Figure 1.9).

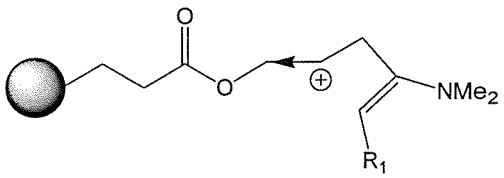
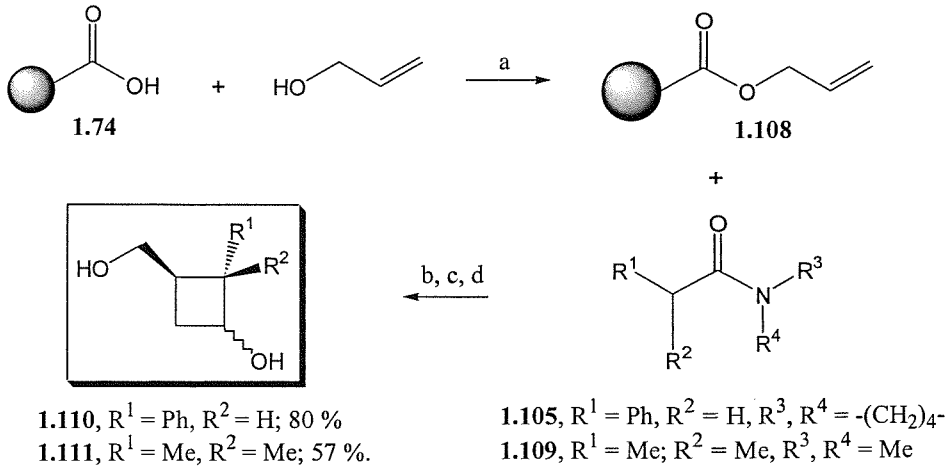


Figure 1.9. Destabilising effect of electron withdrawing oxygen.

Reaction of allyl acetate was carried out with 1-(phenylacetyl) pyrrolidine (**1.105**) to assess the reaction first in solution. Normally the cycloaddition reaction can be followed by observing the $C=N_{str}$ of the iminium salt, but the $C=O_{str}$ of the acetate again masked it. However the hydrolysis of the ketone could be followed by infrared spectroscopy ($C=O_{str}$ 1782 cm^{-1}), which looked encouraging. However work up and purification resulted in significant decomposition of the cyclobutanone and the product was isolated in poor yield (4 %). Decomposition of the highly strained cyclobutanones is not uncommon, however conversion during the reaction was promising and it was anticipated that the problems with isolating the product might be avoided on solid-phase.

The resin bound allyl ester **1.108** was prepared in the same way as before and the bromocresol green test showed that there were no free carboxylic acid sites left on the resin (Scheme 1.32). The resin bound olefin **1.108** was first treated with the keteniminium salt prepared from phenyl acetamide **1.105**, then hydrolysed to the cyclobutanone and reductively cleaved to give cyclobutanol **1.110**. The crude cleavage mixture showed no signs of allyl alcohol which would probably have been removed during work up, and ^{1}H NMR showed that there was one major product, ~80-90% pure. One of the impurity peaks is likely to be an isomer of cyclobutanol **1.110**, however the impurities were not isolated.



1.110, R^1 = Ph, R^2 = H; 80 %
1.111, R^1 = Me, R^2 = Me; 57 %.

1.105, R^1 = Ph, R^2 = H, R^3, R^4 = -$(CH_2)_4$-
1.109, R^1 = Me; R^2 = Me, R^3, R^4 = Me

Reagents and Conditions: (a) DIC (10 eq), DMAP (10 eq), CH_2Cl_2; (b) Tf_2O (9 eq), 2,6-di-*t*-butylpyridine, CH_2Cl_2; (c) $NaHCO_3$(aq), THF; (d) $LiBH_4$, THF, MeOH, -78°C.

Scheme 1.32. [2+2] Cycloaddition with resin bound allyl ester.

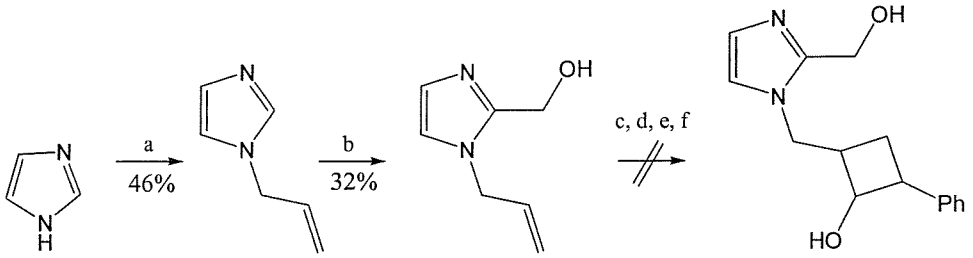
Comparisons were made between ^{1}H NMR spectra of cyclobutanol **1.110** and isomers **1.107a** and **1.107b**. The ^{1}H NMR spectra of the major diastereoisomer of cyclobutanol **1.110** corresponded closely with that of isomer **1.107a**, whilst the chemical shifts of the major impurity matched that of **1.107b**. It would be reasonable to assume based upon the results with isoeugenol, literature precedent[67] and the similarities in the chemical shifts between **1.110** and **1.107a** that the stereochemistry of the substituents is all *trans* relative to adjacent substituents.

The cycloaddition/hydrolysis/reduction sequence was undertaken successfully with allyl ester resin **1.108** and *N,N*-dimethyl-2-methylpropanamide (**1.109**). The crude reaction mixture was made up of entirely two diastereoisomers of cyclobutanol **1.111** in a ratio of 7:1 in a lower yield (57%) than cyclobutanol **1.110**. Unfortunately the diastereoisomers were not separable but the structure of **1.111** is simple and the

diastereoisomers must have resulted from the reduction of the ketone preferentially introducing the hydride on the opposite face of the cyclobutyl ring to the hydroxymethyl group.

Various attempts were made to react *N,N*-dimethyl-2-phenoxyacetamide with resin **1.108**, including using twenty equivalents of the reagents, refluxing in CH_2Cl_2, refluxing in DCE and sonication for 17 hours. None of the desired product was ever isolated. The reaction probably did not work because the keteniminium salt was not very soluble. Similarly there was no reaction between *N,N*-dimethylacetamide and resin **1.108** using ten equivalents of reagents in refluxing CH_2Cl_2 for 20 hours because the keteniminium salt precipitated out and therefore could not reach the resin bound olefin.

We were also interested to investigate whether heterocycles (e.g. imidazole, pyridine) would be compatible with the keteniminiun/olefin cycloaddition. 1-Allyl-2-hydroxymethylimidazole (**1.113**) was prepared by phase transfer allylation[69] followed by hydroxymethylation[70] in low overall yield (15 %) (Scheme 1.33). Coupling to acid resin **1.74** was carried out using standard carbodiimide chemistry and the cycloaddition was carried out using ten equivalents of the reagents (1-phenylacetyl pyrrolidine [**1.105**]). After hydrolysis and reductive cleavage none of the desired product **1.114** was isolated. This work was not taken any further.



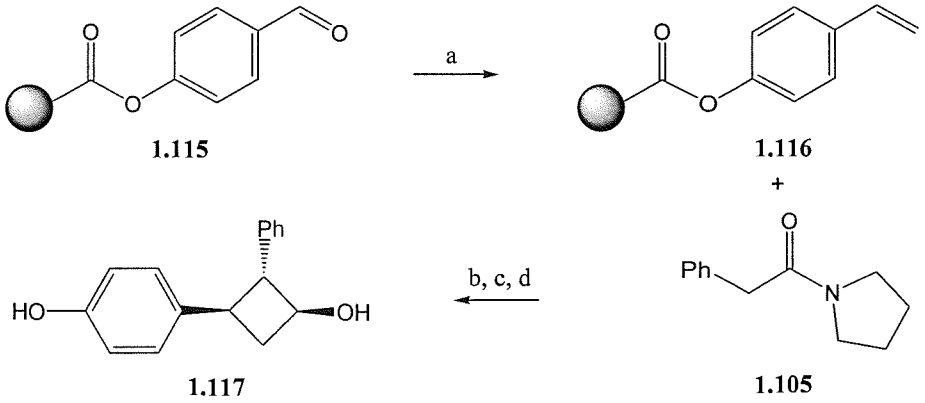
1.112 **1.113** **1.114**

Reagent and Conditions: (a) Allyl bromide, 6M NaOH, TBAB, CH_2Cl_2; (b) H_2CO(aq), 120°C; (c) Resin **1.74**, DIC, DMAP, CH_2Cl_2; (d) Amide **1.105**, Tf_2O, 2,6-di-*t*-butylpyridine, CH_2Cl_2; (e) $NaHCO_3$(aq), THF; (f) $LiBH_4$, THF, MeOH.

Scheme 1.33. Attempted [2+2] cycloaddition with resin bound N-allylimidazole.

Another objective of this project was to prepare olefins on the solid phase that could subsequently undergo [2+2] cycloadditions. The Wittig reaction was chosen to prepare olefins and 4-hydroxybenzaldehyde chosen because the resulting styrene would react in the same way as isoeugenol. Coupling 4-hydroxybenzaldehyde to resin **1.74** went to completion (positive bromocresol green test) to give resin **1.115** (Scheme 1.34).

Methyltriphenylphosphonium bromide was treated with *n*-butyl lithium to give the methylene ylid, which was chosen to avoid complicating the study with stereochemical issues, and was then added to resin **1.115**. The reaction proceeded until the aldehyde $C{=}O_{str}$ at 1701cm^{-1} had disappeared to give resin **1.116**. The ester was transesterified with potassium trimethylsilanoxide in $MeOH/CH_2Cl_2$ to give a 6:1 mixture of styrene:benzaldehyde (identified by 1H NMR and comparison to literature values[71]). Resin **1.116** was subjected to [2+2] cycloaddition conditions with 1-(phenylacetyl) pyrrolidine (**1.105**). Following hydrolysis and reductive cleavage cyclobutanol **1.117** was isolated in poor yield (15 %) as a colourless crystalline solid. From ^{1}H NMR spectrum of the crude cleaved material the majority of the material could not be identified, however the product and maybe a trace of other diastereoisomers were apparent.



Reagents and Conditions: (a) $Ph_3P^+MeBr^-$, *n*-BuLi, THF; (b) Tf_2O (9 eq), 2,6-di-*t*-butylpyridine, CH_2Cl_2; (c) $NaHCO_3$(aq), THF; (d) $LiBH_4$, THF, MeOH, -78°C.

Scheme 1.34. Preparation of olefin on solid-phase followed by cycloaddition.

From a slowly evaporating CH_2Cl_2 solution a crystal of the cyclobutanol **1.117** was produced from which a crystal structure was obtained (Figure 1.10, see appendix for data). The structure of **1.117** has the same geometry as cyclobutanols **1.107a** and **1.110**, which were determined by ^{1}H NMR studies.

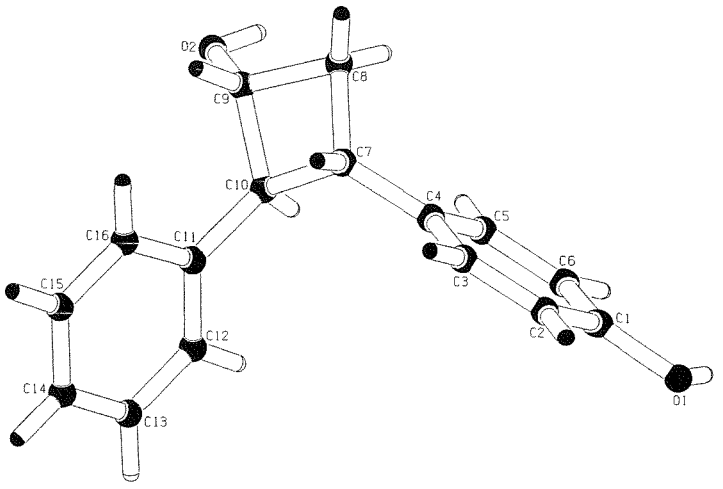
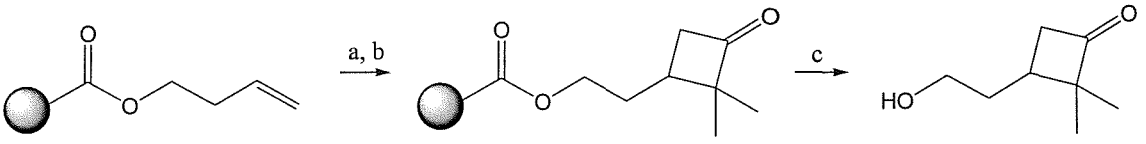


Figure 1.10. Structure determined by X-ray crystallography.

To try to identify the reasons for the poor yield an analogous solution reaction was carried out using 4-formylphenylpropionate, that was prepared from propanoyl chloride and 4-hydroxybenzaldhyde. The Wittig reaction with 4-formylphenyl propionate yielded 4-vinylphenylpropionate, albeit in low yield (10%), along with 4-hydroxystyrene and 4-hydroxybenzaldehyde. The labile phenol ester bond in the product and starting material were presumably cleaved by lithium hydroxide present in the reaction mixture. Despite having established the cause of the poor yield no further attempts were made to optimise this reaction because the focus of the work was moving towards carrying out transformations on cyclobutanones.



1.118 **1.119** **1.120**, 99% from **1.118**

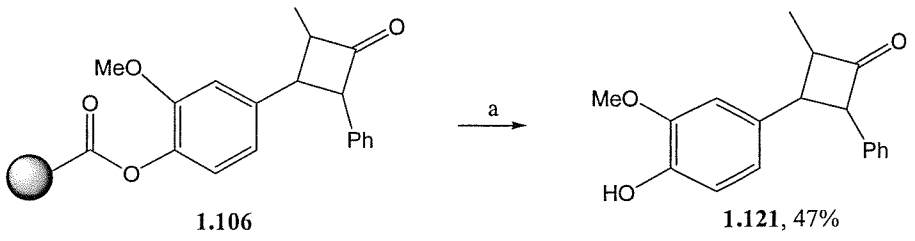
Reagents and Conditions: (a) **1.109**, Tf_2O (5 eq), 2,6-di-*t*-butylpyridine (5 eq), CH_2Cl_2; (b) $NaHCO_3$(aq), THF; (c) KOTMS, MeOH/CH_2Cl_2 (1:5).

*Scheme 1.35. [2+2] Cycloaddition and cleavage of cyclobutanone **1.120**.*

The [2+2] cycloaddition with the resin bound homologue of allyl alcohol (**1.118**), 3-buten-1-ol, was investigated to see whether the yields would improve as the electron withdrawing oxygen is shifted further away from the intermediate carbocation. The acid resin was treated with 3-buten-1-ol under our standard coupling conditions to give the resin bound ester (Scheme 1.35). The [2+2] cycloaddition was carried out using the standard procedure to give the cyclobutyliminium salt on resin, of which some was held back to establish the stability of the resin bound iminium salt and to carry out some further reactions. The remaining iminium salt was hydrolysed to the ketone

1.119 with sodium bicarbonate (FTIR $C{=}O_{str}$ band at 1774 cm^{-1}). To our delight the cyclobutanone was cleaved cleanly by transesterification with potassium trimethylsilanoxide, to give pure cyclobutanone **1.120** in a 99% yield.

The mild transesterification cleavage procedure had already been used to cleave cinnamyl alcohol from the resin for loading calculations and to cleave 4-hydroxystyrene, but this was the first example of a cyclobutanone being successfully cleaved from the resin. Unfortunately, α-phenylcyclobutanones were not stable to the transesterification conditions, however an α-phenylcyclobutanone **1.121** (from resin **1.106**), which was linked to the resin *via* a phenyl ester, was isolated by treating the resin with pyrrolidine all be it in modest yield (47%) (Scheme 1.36).

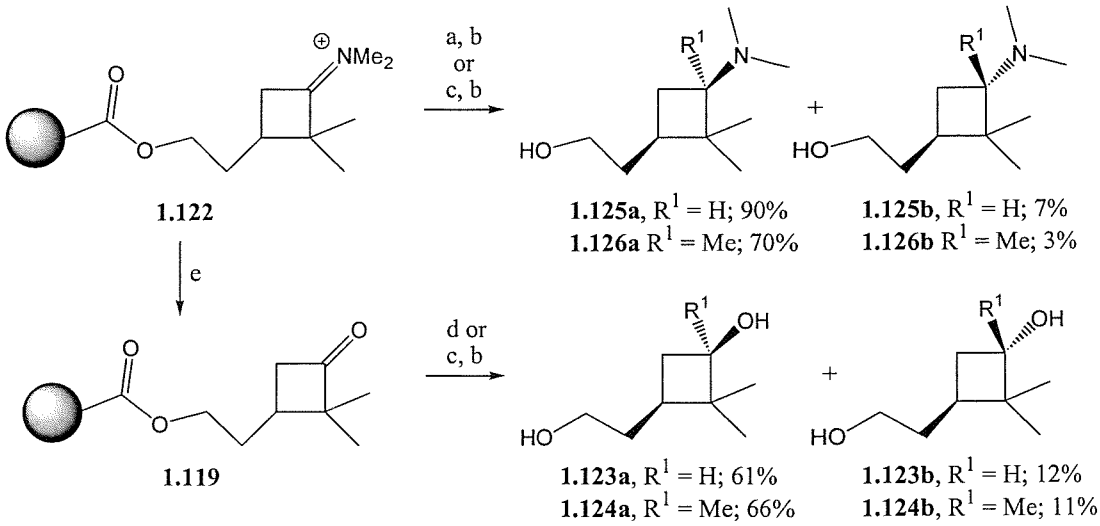


1.106 **1.121**, 47%

Reagents and Conditions: (a) Pyrrolidine, CH_2Cl_2.

*Scheme 1.36. Cleavage of cyclobutanone **1.121** from resin **1.106**.*

Pleasingly the quantitative conversion to cyclobutanone **1.119** allowed us to assess subsequent reactions knowing that only the cyclobutanone was bound to the resin. The cyclobutanone resin **1.119** was treated with lithium borohydride, which gave cyclobutanol **1.123** in good yield (73%) as a 5:1 mixture of diastereoisomers.



1.122

1.125a, R^1 = H; 90% **1.125b**, R^1 = H; 7%
1.126a R^1 = Me; 70% **1.126b** R^1 = Me; 3%

1.119

1.123a, R^1 = H; 61% **1.123b**, R^1 = H; 12%
1.124a, R^1 = Me; 66% **1.124b**, R^1 = Me; 11%

Reagents and Conditions: (a) $Me_4NBH(OAc)_3$, CH_2Cl_2; (b) KOTMS, MeOH/CH_2Cl_2 (1:5); (c) MeMgCl, THF, -20°C; (d) $LiBH_4$, THF, MeOH, -78°C to RT; (e) $NaHCO_3$(aq), THF.

Scheme 1.37. Preparation of cyclobutylamines and cyclobutanols.

Hydride attack was directed to the opposite face to the hydroxyethyl group to give diastereoisomer **1.123a** as the major product (Scheme 1.37). Similarly a 6:1 mixture of diastereoisomers resulted when resin **1.119** was treated with methyl Grignard and cleaved by transesterification to give cyclobutanol **1.124** in good yield (77%).

Previous attempts to reduce cyclobutyliminium salts prepared from [2+2] cycloadditions with keteniminium salts had been successful, however the yields have been modest, and addition of organometallics to the iminium species have given poor yields.[32] The iminium species could not be purified because of the its hydrolytic instability, which probably effected the yields of subsequent steps in solution. On solid-phase however, the iminium salt **1.122** can be cleaned up readily under anhydrous conditions and as a result, the reduction and the Grignard addition to iminium salt **1.122** both proceeded in excellent yields (97% for **1.125** and 73% for **1.126** respectively) (Scheme 1.37). The manipulation of this unstable intermediate proved to be an advantage of this solid phase strategy. Encouragingly FTIR analysis of the resin demonstrated very little hydrolysis had occurred when iminium resin **1.122** was stored at room temperature in a screw top vial for a month, demonstrating the stabilising effect on the species of being cocooned within the hydrophobic resin. The additions on resin **1.122** gave predominately one diastereoisomer (13-20:1) in contrast to the alcohols from resin **1.119**.

Conclusions

- [2+2] Cycloadditions between keteniminium salts and olefins has been carried out successfully for the first time on solid-phase.
- The structure of cyclobutanols **1.107a**, **1.110** and **1.117** resulting from the cycloaddition/hydrolysis/reduction sequence have been determined by either NOE studies, X-ray crystallography or by correlating NMR data. The stereochemistry around the cyclobutyl ring of cyclobutanols **1.107a**, **1.110** and **1.117** was consistent and displayed a *trans* relationship between adjacent groups around the ring.
- It appears that nucleophilic functionality, i.e. imidazole, on the olefin is incompatible with the [2+2] cycloaddition conditions and that the reaction failed.
- Cyclobutanone **1.120** was isolated using mild transesterification conditions in quantitative conversion from the resin bound olefin, demonstrating higher yields

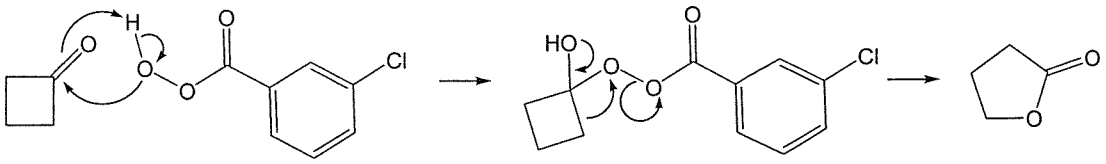
on solid-phase for the cycloaddition than in solution. However α-phenyl cyclobutanones were incompatible with the cleavage conditions.

- A variety of transformations, i.e. reduction and Grignard addition, may be carried out on iminium or cyclobutanone resins. This is particularly useful in the case of the iminium species as such transformations are low yielding in solution.

1.8 Further Transformations of Resin Bound Intermediates

Baeyer-Villiger Oxidation

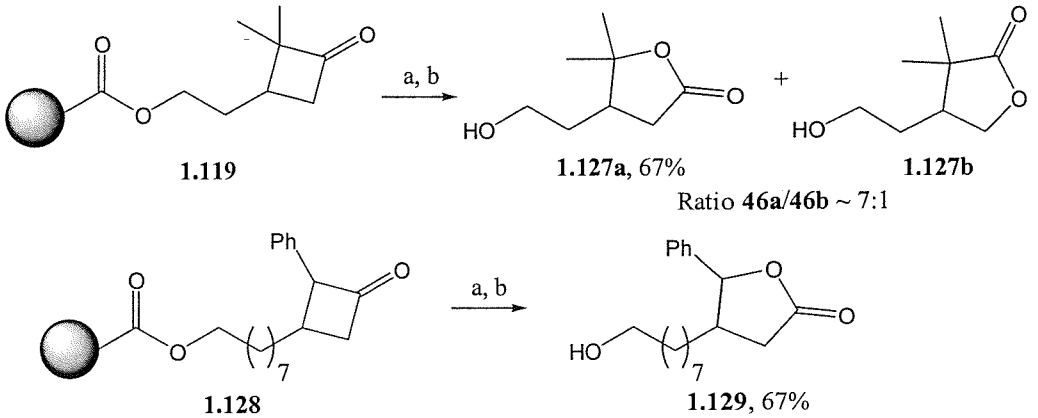
The Baeyer-Villiger reaction allows for the preparation of γ-lactones from cyclobutanones, a transformation that is favourable due to the release of angular and torsional strain. The reaction is facilitated by peracids which attack the carbonyl, this is followed by the migration of one of the carbons adjacent to the carbonyl onto the peracid oxygen, eliminating the carboxylate, and the carbonyl is reformed to give the lactone (Scheme 1.38). The most electron rich carbon will migrate allowing the regiochemical outcome of the reaction to be predicted.



Approximate order of migration: tertiary alkyl > secondary alkyl, aryl > primary alkyl > methyl

Scheme 1.38. Mechanism of the Baeyer-Villiger oxidation.

Resin bound cyclobutanone **1.119** was subjected to the Baeyer-Villiger conditions with the expectation that the tertiary carbon should migrate preferentially.



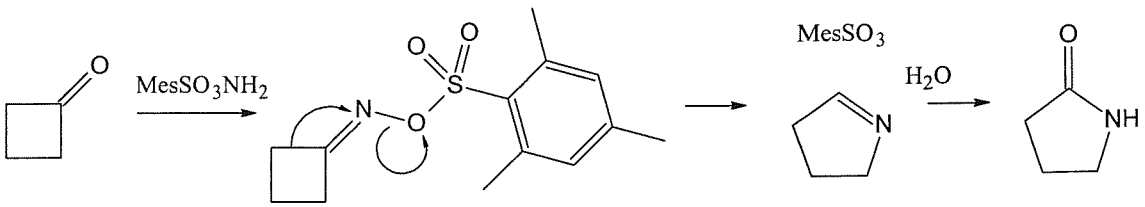
Reagent and Conditions: (a) *m*CPBA, CH_2Cl_2, 3 days; (b) i. KOTMS, MeOH/CH_2Cl_2 (1:5); ii. HCl.

Scheme 1.39. Bayer-Villiger oxidation on resin bound cyclobutanones.

Resin **1.119** was treated with *m*-chloroperbenzoic acid at room temperature and monitored by IR (Scheme 1.39), although this was not easy since the cyclobutanone $C{=}O_{str}$ (1774 cm^{-1}) came close to the lactone $C{=}O_{str}$ (1757 cm^{-1}). The reaction proved to be very slow, requiring 3 days to go to completion. The lactone was cleaved off the resin using the transesterification procedure. However the cleavage formed what was assumed to be the ring opened methyl ester so the cleavage mixture was stirred with 1M HCl(aq) for five minutes to close up the lactone. The crude reaction mixture contained two components, the predicted product of tertiary carbon migration, lactone **1.127a**, and what appeared to be the product from the migration of the primary carbon migration, lactone **1.127b**, in a ratio of 7:1. Although the minor product was not isolated or characterised, a doublet at 3.94 ppm in the ^1H NMR spectrum of the crude mixture was tentatively assigned to the product of migration of the primary carbon, lactone **1.127b**. The major product, compound **1.127a**, was isolated by chromatography in good yield (67%). Resin **1.128** was prepared by a co-worker and was subjected to the same oxidation procedure as before. A mixture of products was expected since the α-carbons should have similar migrating power however surprisingly the crude cleavage mixture showed that the carbon with the phenyl group almost exclusively migrated with only trace impurities present. After purification γ-lactone **1.129** was isolated in good yield (67%).

Beckmann Rearrangement

Ketones react with hydroxylamine derivatives to give oxime derivatives, which can under go the Beckmann rearrangement. This is initiated by the elimination of the oxygen of the oxime followed by migration of the α-carbon *anti* to the oxygen (Scheme 1.40). The resulting carbocation is quenched with water to give the lactam.

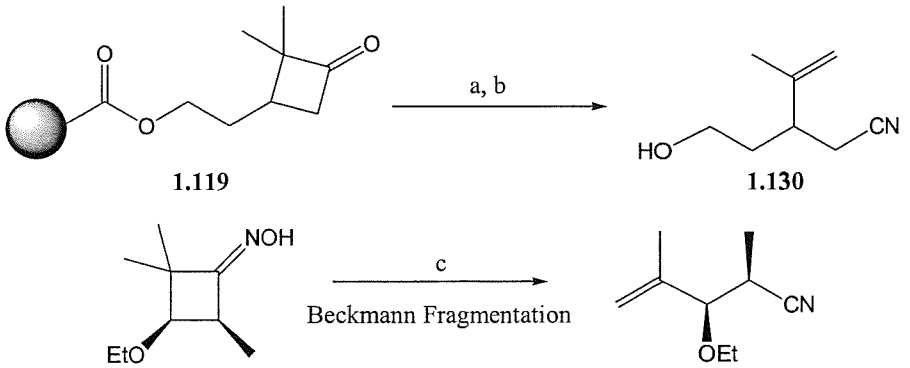


Scheme 1.40. Mechanism for Beckmann rearrangement.

The α-carbon that migrates is determined by the geometry of the oxime, which is determined mainly by steric factors. The carbon with the bulkiest substituents will be the carbon that migrates preferentially, because steric factors will put the bulky group *trans* to the oxygen, however mixtures are common. In order to aid elimination of the

oxygen conversion to a good leaving group, e.g. protonation by acid, is required. We chose to use a hydroxylamine derivative with a leaving group already installed, *O*-(mesitylensulphonyl) hydroxylamine.[72] This hydroxylamine is prepared in two steps from mesitylene sulphonyl chloride and acetimidate protected hydroxylamine.

Cyclobutanone **1.119** was treated with the Beckmann reagent and the reaction was monitored by FTIR for the disappearance of the ketone $C{=}O_{str}$. However analysis of the cleavage mixture was not consistent with the expected product. From the literature it is apparent that cyclobutanones with α-tertiary carbon undergo a Beckmann fragmentation (Scheme 2.41).[73] The crude cleavage mixture was predominantly one product **1.130**, which was consistent with the expected product of the Beckmann fragmentation, and FTIR confirmed the presence of a nitrile (CN_{str} @ 2247cm^{-1}).

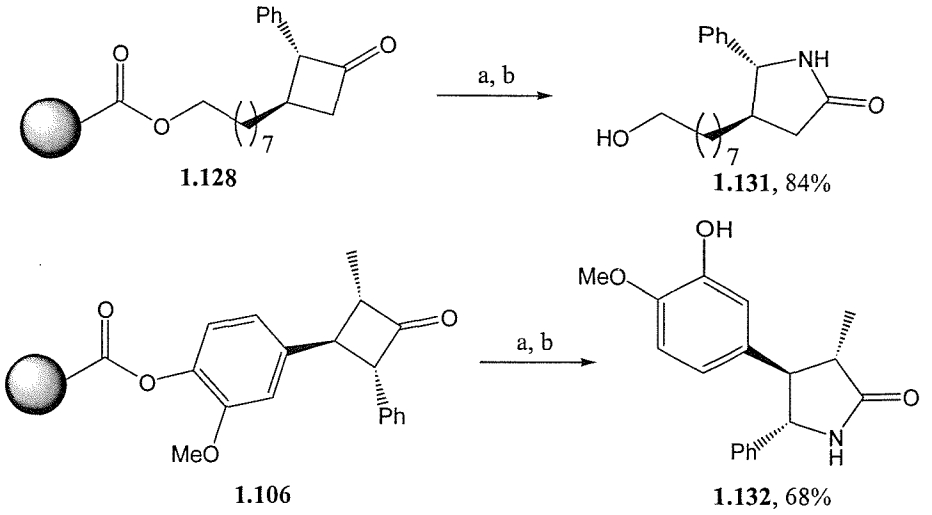


Reagents and Conditions: (a) $MesSO_3NH_2$, CH_2Cl_2; (b) KOTMS, MeOH/CH_2Cl_2 (1:5); (c) *m*-nitrobenzoyl chloride, CH_2Cl_2.

Scheme 1.41. Beckmann fragmentation of cyclobutanones.

The sterically crowded cyclobutanone **1.106** was treated with *O*-(mesitylensulphonyl) hydroxylamine, then monitored by IR. The carbonyl band had gone after 20 hours whilst the less hindered cyclobutanone **1.128** reacted in an hour (Scheme 1.42).

Having carried out Beckmann rearrangement on resin **1.128**, the cleaved products were analysed by ^{1}H NMR, which showed the presence product **1.131** and of impurities related to the mesitylene group. This would indicate that the rearrangement of the mesitylenesulphonyloxime had not gone to completion whilst there were no such products in the cleavage mixture from resin **1.106** which was left to react for longer. Whilst γ-lactam **1.131** was isolated as a single regioisomer, the cleavage mixture from resin **1.106** contained a 3:1 mixture of regioisomers in favour of γ-lactam **1.132**.



1.128 **1.131**, 84%

1.106 **1.132**, 68%

Reagents and Conditions: (a) $MesSO_3NH_2$, CH_2Cl_2; (b) KOTMS, MeOH/CH_2Cl_2 (1:5).

Scheme 1.42. Beckmann rearrangement on solid-phase.

One of the more interesting aspects of this work is the structure of compound **1.132**, an analogue of Rolepram (**1.52**) (see section 1.3, figure 1.4), which demonstrates the potential of this work to prepare drug-like molecules.

Photochemically Induced Ring Expansions of Cyclobutanones

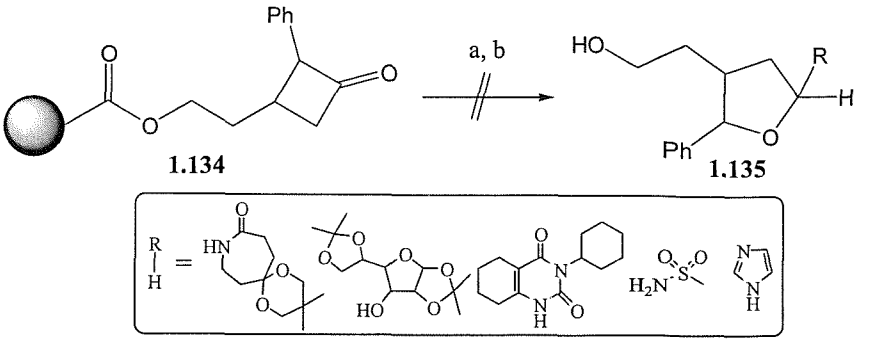
The photochemical ring expansion was first attempted on resin **1.119** with the addition of imidazole across the resulting carbene (Scheme 1.43). Imidazole was chosen due to the insolubility of the preferred purines in suitable solvents.

1.119 **1.133**, 68%

Reagents and Conditions: (a) Imidazole, hυ, THF; (b) KOTMS, MeOH, CH_2Cl_2.

*Scheme 1.43. Tandem ring expansion/addition of imidazole to cyclobutanone **1.119**.*

The reaction proceeded surprisingly well and compound **1.133** was isolated in 68% yield. With this in mind further work was carried out on α-phenylcyclobutanone resin **1.134** (Scheme 1.44), which was prepared using the established conditions.



Reagents and Conditions: (a) hv, R-H, THF; (b) KOTMS, $MeOH/CH_2Cl_2$ (1:5).

Scheme 1.44. Failed attempts at photochemical ring expansions.

It was reacted with a range of reagents with acidic protons which should add across a carbene. Unfortunately none of the expected products were isolated. Presumably the aromatic substitution is not suitable for this reaction unlike the tertiary centre. The reaction is presumably specific for cyclobutanones with an α-tertiary centre, therefore greatly reducing the utility of this reaction and so no further work was carried out on this reaction.

Conclusion

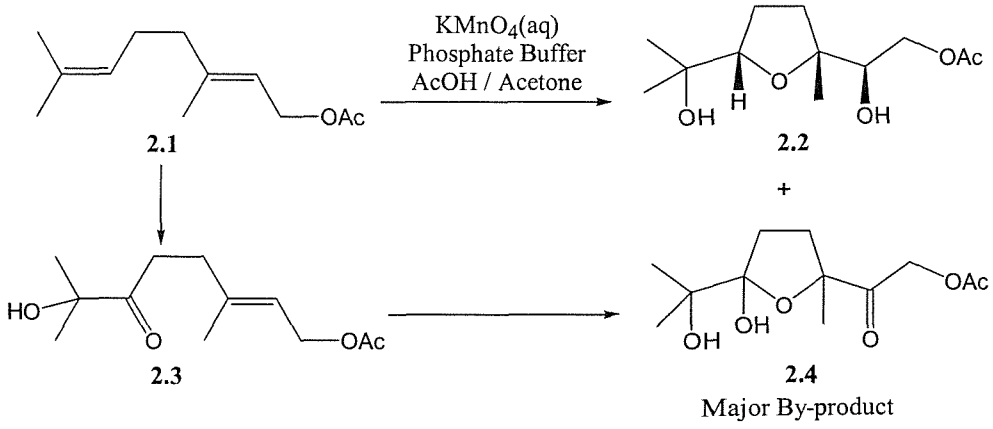
- The conversion of cyclobutanones to γ-lactones and γ-lactams has been demonstrated, including an analogue of phosphodiesterase IV inhibitor, Rolepram.
- The photochemically induced ring expansion of cyclobutanone **1.119** was carried out for the first time on solid-phase, unfortunately the scope of this reaction appears to be limited. To our knowledge, at the time of this work, there had been no reported cases of photochemically generated carbene/radical species on solid-phase, other than photolabile linkers, which is probably due to difficulties asscociated with UV radiation getting to the resin bound species

Chapter 2: Permanganate Oxidations of 1,5-Dienes

INTRODUCTION

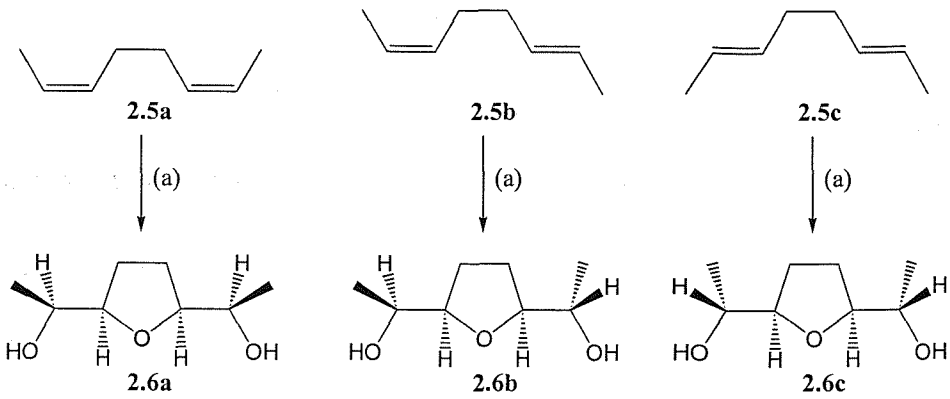
2.1 Permanganate Promoted Oxidative Cyclisation of 1,5-Dienes

The oxidation of 1,5-dienes under neutral conditions was first reported by Kotz and Steche in 1924,[74] they isolated a product that they could not identify and it was not until 1965 that Klein and Rojahn identified the product as a 2,5-bis(hydroxymethyl)tetrahydrofuran (THF diol).[75] The crystal structure of the product from the oxidative cyclisation of geranyl acetate (**2.1**) was established, and they found that all three oxygens were introduced to the same face of the diene resulting in only one diastereoisomer of THF diol **2.4** being formed. It would be expected under the neutral conditions of the reaction that lactol **2.4**, from two hydroxyketones, was the major impurity however it was not reported by Klein and Rojahn. Later a hydroxyketone impurity was reported by Wolfe and Ingold.[76]



Scheme 2.1. Oxidative cyclisation of geranyl acetate.

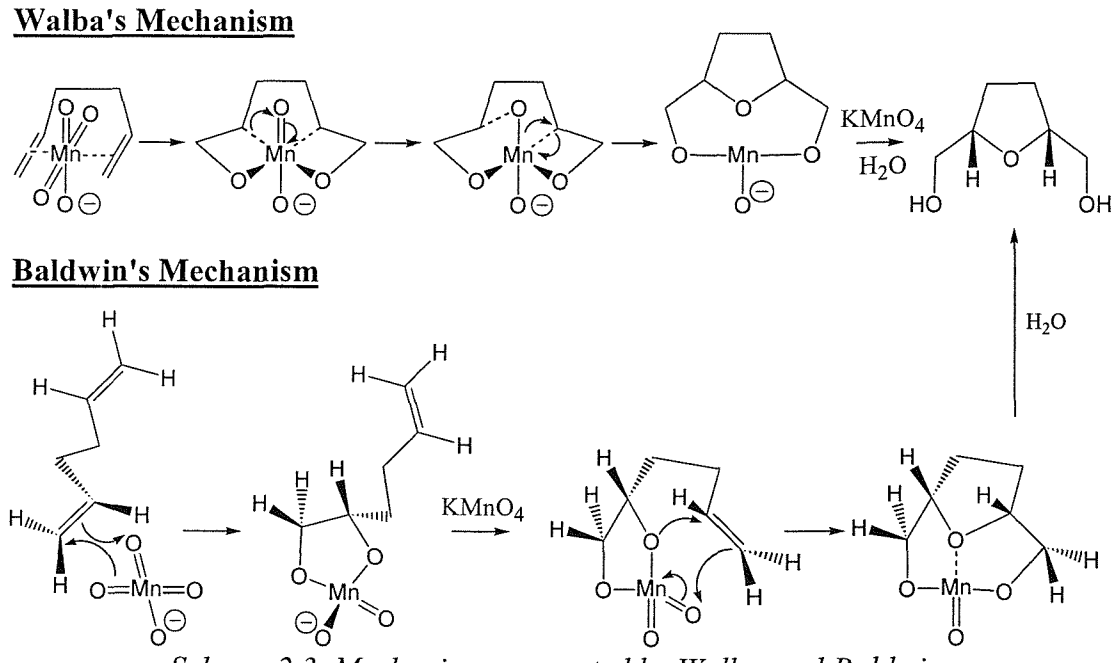
It was not until 1979 that further work was carried out on this powerful reaction where up to four stereocentres can be introduced. Walba *et al.* examined the oxidation of dienes **2.5a-c** and showed that the stereochemistry of the hydroxymethyl groups in the THF diols **2.6a-c** was determined by the geometry of the double bonds (Scheme 2.2).[77] They found that there was a 97% stereoselectivity in favour of the major isomer formed.



Reagents and Conditions: (a) $KMnO_4$(aq) / CO_2(ebullition) / acetone / -20°C / 30 mins

Scheme 2.2. Stereochemistry determined by geometry of the double bond.

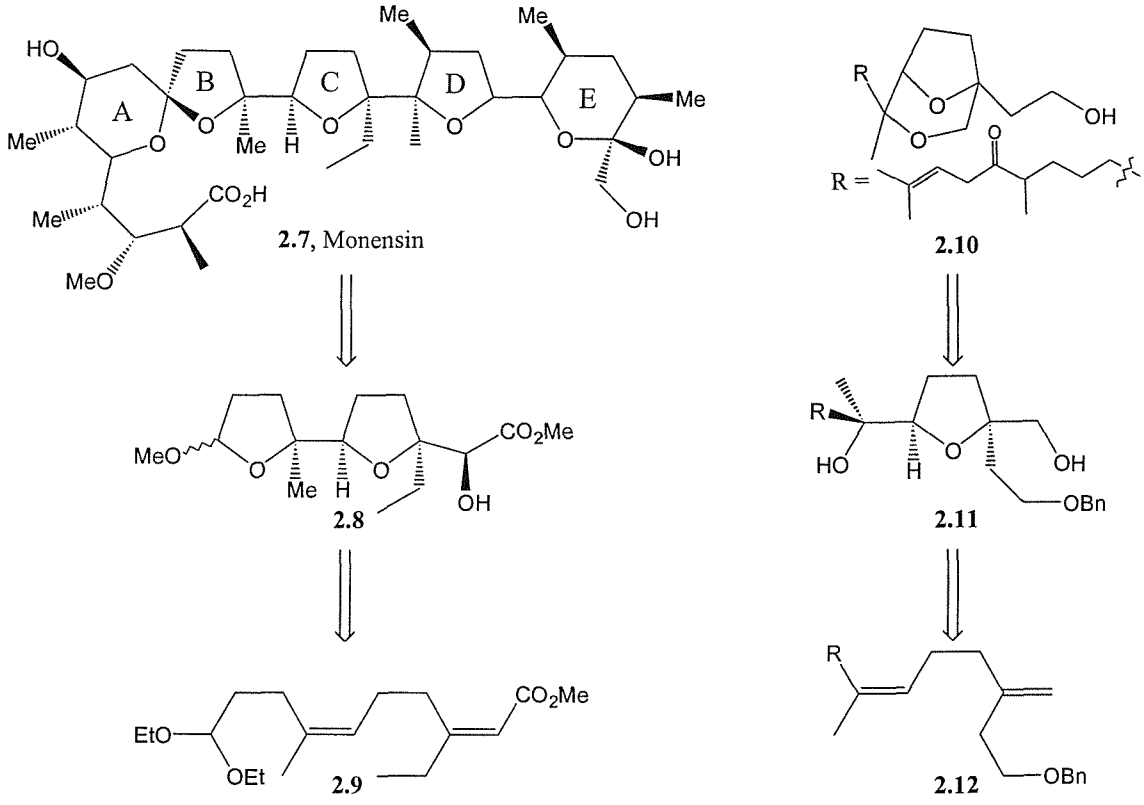
A mechanism was proposed by Walba inspired by an earlier publication by Sharpless (Scheme 2.3).[78] Sharpless suggested that metal oxo species oxidise alkenes via a [2+2] cycloaddition. Walba suggested that initially the double bonds would form a π-complex with a permanganate ion. The double bonds then insert between two of the metal-oxo bonds, followed by sequential reductive eliminations with migration of carbons from the manganese to oxygen with retention of configuration. Several variations of this mechanism, i.e. step-wise [2+2] cycloadditions, were also considered reasonable.



Scheme 2.3. Mechanisms suggested by Walba and Baldwin.

In the same year Baldwin *et al.* suggested their own mechanism which involved the formation of a cyclic manganate(V) intermediate by a [3+2] cycloaddition. They proposed the manganese(V) species is oxidised to manganese(VI) which then

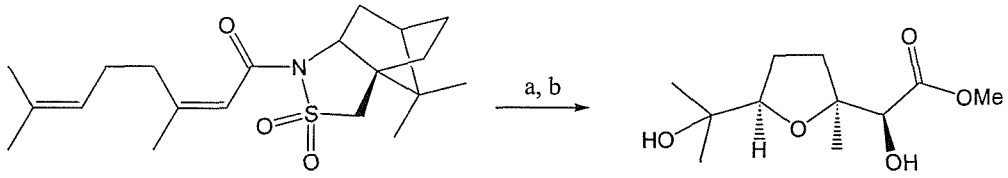
undergoes an intramolecular cycloaddition to form the tetrahydrofuran. Both mechanisms seem reasonable however work by Wolfe and Ingold which involved using ^{18}O labelled water as the reaction solvent showed incorporation of an ^{18}O into the 2,5-bis(hydroxymethyl)tetrahydrofuran.[76] This would suggest that a manganese complex with a coordination number greater than four incorporating water from the solvent is involved in the mechanism for the reaction. Neither of the proposed mechanisms account for this observation thus the exact mechanism remains unresolved.



Scheme 2.4. Synthetic approaches to monensin and montanol.

Walba continued his early work on the oxidative cyclisation to prepare some key intermediates in natural product synthesis (Scheme 2.4).[79,80] He identified the BC rings of monensin (**2.7**) as a system that could be efficiently introduced *via* the oxidative cyclisation of diene **2.9** to give THF lactol **2.8**. The oxidation of diene **2.9** successfully gave the correct diastereoisomer of **2.8**, however the yield was disappointing (20%). A derivative of naturally occurring montanol, bicycle **2.10**, was identified as possessing interesting biological activity. Walba prepared bicyclic system by cyclisation of an alkoxide eliminating a tosylate prepared from the THF diol **2.11**, which was given as a single diastereoisomer from diene **2.12**, using the same oxidative cyclisation procedure as before.

The permanganate promoted oxidative cyclisation has been shown to introduce four stereocentres with controlled relative stereochemistry, and Walba *et al.* has gone on to develop an asymmetric reaction using a chiral auxiliary to control absolute stereochemistry (Scheme 2.5).[81] Oppolzer's sultam was utilised as a chiral auxiliary on α,β-unsaturated carbonyl diene **2.13** and good diastereoselectivity was observed (80% d.e.). The induction was possible because permanganate firstly attacks the more reactive alkene adjacent to the carbonyl. The stabilising effect of an adjacent carbonyl on the intermediate of the oxidation is discussed in section 2.2.



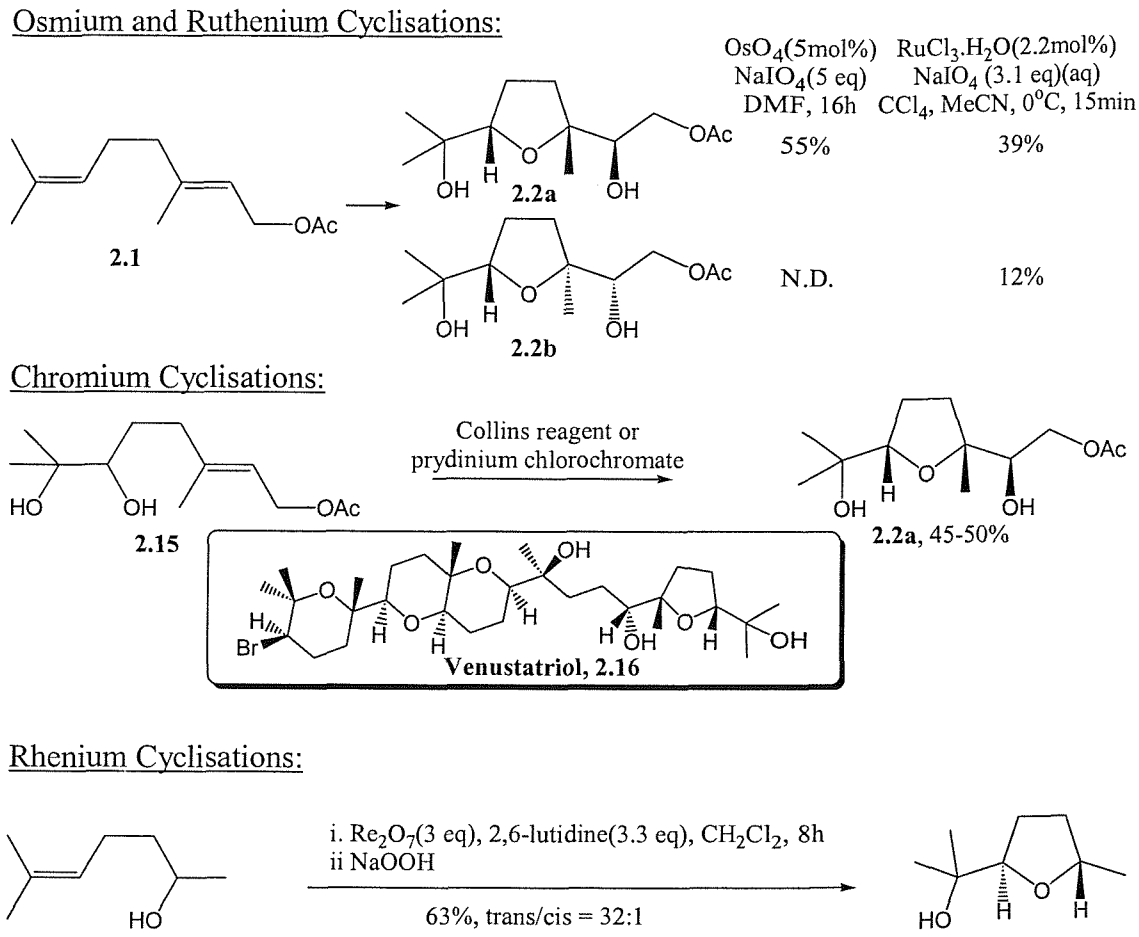
2.13 **2.14**, 38%, 80% ee

Reagents and conditions: (a) $KMnO_4$(aq), CO_2 ebullition, acetone, -30°C; (b) MeOMgBr

Scheme 2.5. Asymetric oxidative cyclisation of 1,5-dienes.

This approach has been used by Kocienski and Brown in the total synthesis of Salinomycin.[82] Interestingly they used modified conditions for the oxidative cyclisation, replacing carbon dioxide ebullition with AcOH/NaOAc buffer and observed an improved yield (54%).[83]

Other metallo-oxo species can carry out oxidative cyclisations to prepare 2,5-substituted tetrahydrofurans with differing selectivities for *cis*- and *trans*- substituted THF's complimenting the selectivity shown by $KMnO_4$ (Scheme 2.6). Catalytic osmium tetroxide with sodium periodate was reported to show similar reactivity to permanganate.[84] Following the oxidation of geranyl acetate with osmium tetroxide and chromatography only the *cis*-THF diol was isolated in reasonable yield (55%). Donohoe *et al.* have gone on to show that the initial attack on 1,5-dienes can be directed by installing a hydrogen bond donator adjacent to one of the olefins in the substrate, leading to an improved yield of THF diol.[85] Whilst looking to improve catalytic ruthenium tetroxide oxidations, Sharpless *et al.* found that this system also oxidatively cyclised geranyl and neryl acetate to their respective THF diols, however the selectivity of the geometry around the ring was poor (3:1, cis:trans). Recently Piccialli *et al.* went on to look at the oxidations of more 1,5-dienes and also described the oxidative cyclisation of 1,6-dienes to 2,6-bis(hydroxymethyl)tetrahydropyrans which gives *trans*-substituted THP's selectively.[84,86]



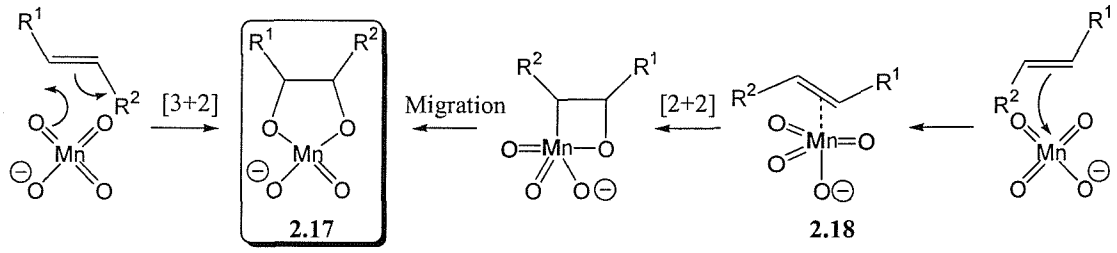
Scheme 2.6. Oxidative cyclisations with alternative metal-oxo reagents.

Rhenium and chromium oxo reagents have also been found to induce the oxidative cyclisation of 5-hydroxyalkenes to give 2,5-bis substituted THF's. In 1976 an attempted oxidation of such an alcohol to a ketone with Collins reagent was found to only give a *cis*-THF, which spurred Walba and Stoudt to investigate this oxidative cyclisation on the diol derivatives of geranyl acetate **2.15** (Scheme 2.6).[87,88] He found that the reaction using Collins reagent or pyridinium chlorochromate gave exclusively the cis product **2.2a** in reasonable yield (45-50%), which was exploited later by Corey and Ha to prepare the THF diol portion of Venustatriol **2.16**, a naturally occurring compound which displays interesting antiviral activity.[89] The hydroxyl formed adjacent to the THF could be reasonably expected to react further were there an appropriately positioned double bond. This was carried out by McDonald and Towne and they found that although the yields were low, due to oxidative cleavage of the hydroxy-THF bond, that the polycyclisation did indeed take place.[90] The geometry of the second THF ring was to a greater or lesser extent trans, depending upon the

geometry of the first double bond. More recently Kennedy has pioneered oxidative cyclisations with rhenium(VII) oxide.[91,92,93] Like chromium, rhenium oxidatively cyclises 5-hydroxyalkenes. Unlike chromium, it has not been shown to work with 1,2-diols, it gives the *trans*-substituted THF and yields tend to be higher (from 50% up to 98%). Much like chromium, polycyclisations have also been carried out, however the third THF ring is formed as a mixture of *cis* and *trans* isomers.[94] Further work on rhenium oxidative cyclisations will be discussed in section 2.4.

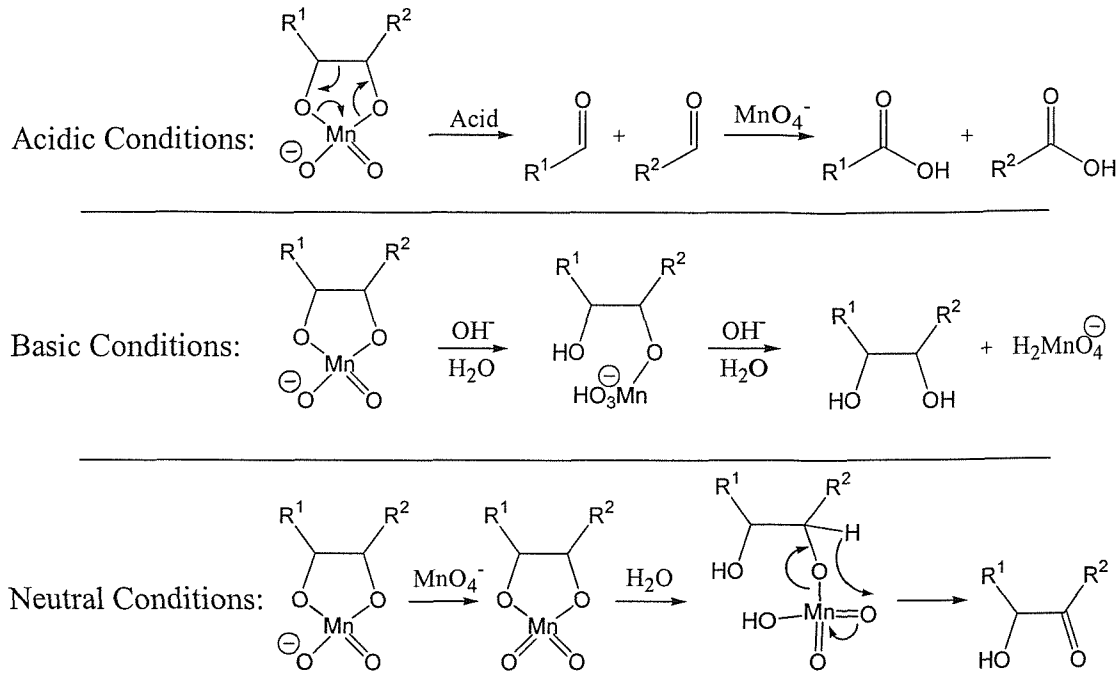
2.2 Permanganate Phase-Transfer Oxidation of Olefins

The oxidation of alkenes by permanganate has been known for a long time and the generally accepted intermediate was proposed more than a hundred years ago (Scheme 2.7).[95] It is believed that the cyclic manganate(V) diester **2.17** is formed from either a [3+2] cycloaddition or via a π-manganese complex **2.18** which then undergoes a [2+2] cycloaddition followed by migration of the carbon from the manganese to an oxygen.



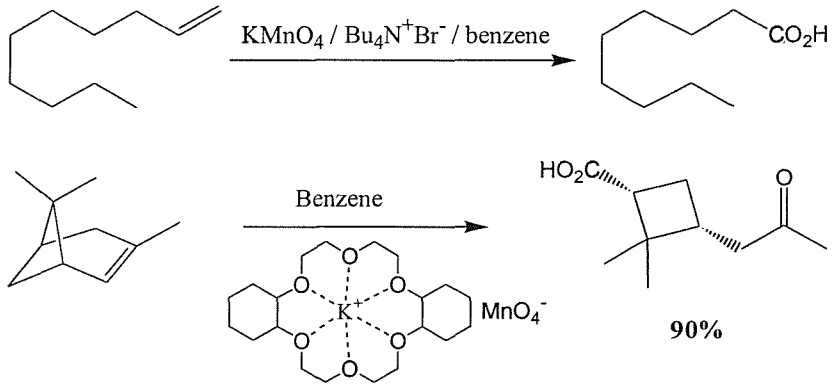
Scheme 2.7. Proposed routes to cyclic manganate(V) diester.

Having established the cyclic manganate(V) diester as the intermediate, the pH of the system will determine the products observed (Scheme 2.8). Under alkaline conditions the intermediate is hydrolysed to a diol, whilst acidic conditions result in cleavage of the double bond to aldehydes which are oxidised to carboxylic acids. When pH is kept neutral the predominant product is a hydroxyketone, which results from oxidation of the cyclic manganate(V) diester **2.17** then hydrolysis and reductive elimination of the manganese(IV) species. Although an hydroxyketone is the major product, there is usually contamination with both diol and cleavage products.



Scheme 2.8. Products of permanganate oxidation of alkenes.

Permanganate oxidations before 1971 were carried out in water, with the addition of a miscible organic solvent to help the solubility of the alkene substrate. However for highly non-polar substrates the oxidation did not proceed well. In 1971 Starks used a biphasic mixture of water and benzene with tetrabutylammonium bromide to oxiditively cleave double bonds of lipophilic substrates (Scheme 2.9).[96] The following year Sam and Simmons used a crown ether as a phase-transfer catalyst to effect oxidative cleavages of alkenes.[97]



Scheme 2.9. Early phase-transfer catalysed alkene cleavages.

The phase-transfer oxidations with permanganate can be done using an aqueous solution of permanganate (liquid-liquid phase-transfer catalysis) or using solid permanganate (solid-liquid phase-transfer catalysis). The factors effecting these two processes are very similar: the ability of the phase-transfer catalyst to carry

permanganate into the organic phase from the solid state/aqueous phase, and the extent to which the permanganate will exist as an ion pair in the organic phase.[98]

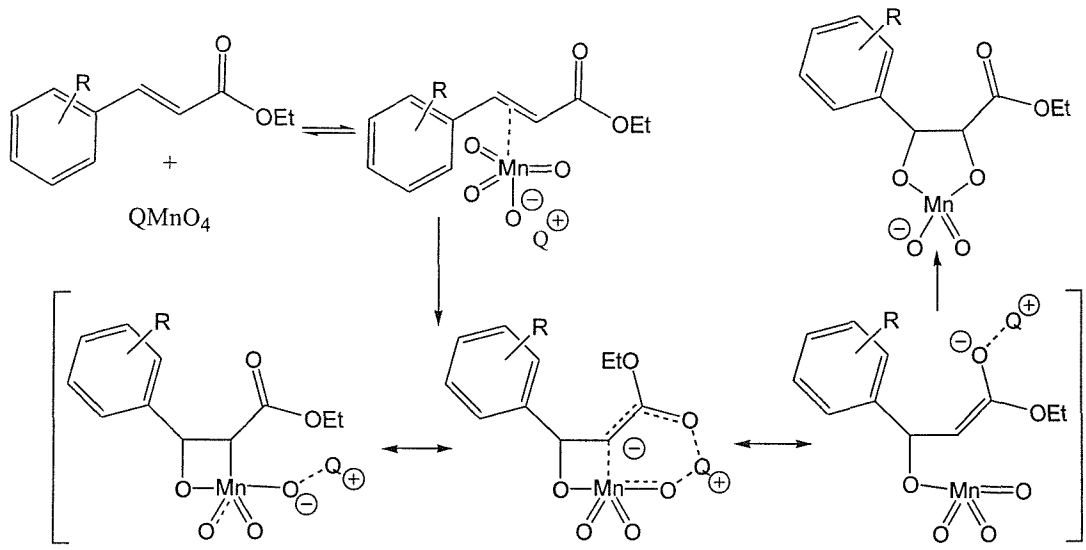
The degree to which the permanganate is carried into the organic phase will depend upon the polarity of the phase-transfer catalyst and the solvent. For example tetraethylammonium bromide is an efficient phase-transfer reagent with permanganate in CH_2Cl_2 however it is insoluble in $CHCl_3$, benzene, CCl_4 and pentane. Benzylethylammonium bromide is a good phase-transfer reagent with CH_2Cl_2 and $CHCl_3$ but is insoluble in benzene, CCl_4 and pentane. Adogen 464, which is a lipophilic quaternary ammonium salt bearing a methyl group and three long alkyl chains (C8-C10), is an effective catalyst in all of the solvent previously mentioned. Thus a lipophilic phase-transfer catalyst will allow a range of solvents to be used and the more polar phase-transfer catalysts will require a more polar solvent.

In water the permanganate ion exists as a solvated ion, however in an organic phase it will exist predominantly as an ion pair with the phase-transfer catalyst. The extent to which this happens is dependent upon the dielectric constant of the organic solvent and the structure of the phase transfer catalyst. The more non-polar the solvent the tighter the permanganate will be paired with the phase-transfer catalyst, and conversely more polar solvents will solvate permanganate ions to a greater degree and thus ion pairing will be weaker.

Lee *et al.* investigated the phase-transfer oxidations of alkenes and decided to use methyl cinnamates as a model.[99] The phenyl ring was substituted to look at the effect of electron withdrawing and electron donating groups on the rate of the reaction, and they then went on to use this system to study a range of phase transfer catalysts. He found that electron withdrawing groups increased the rate of reaction and concluded that the reaction progressed via an electron rich intermediate (scheme 2.10). He also found that for symmetrical tetraalkylammonium ions the longer the four alkyl chains the slower the rate of reaction. Whilst the rate increased markedly if one of the long chain alkyl groups was replaced with a methyl group.

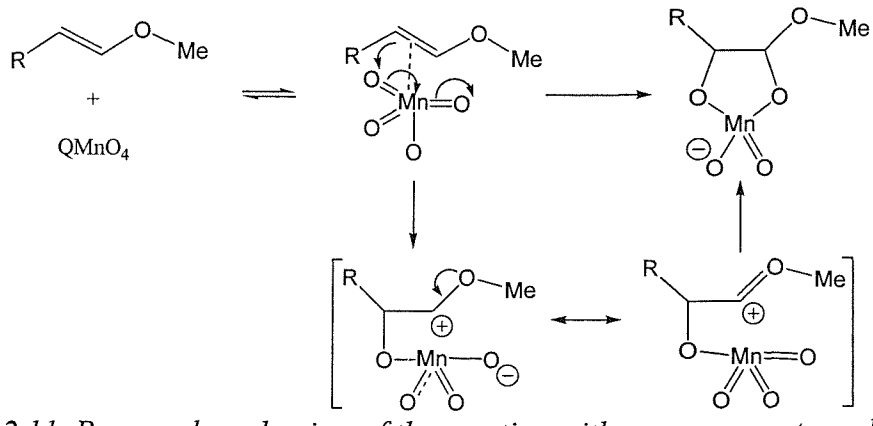
Lee concluded that the presence of a methyl group on the ammonium salt allows the permanganate ion to get closer to the phase-transfer catalyst and thus form a tighter ion pair which results in a faster reaction rate. He proposed a mechanism that involves an initial [2+2] cycloaddition between permanganate and the olefin of ethyl cinnamate (Scheme 2.10). The complex is stabilised by an enolate-like contribution to the transition state, which also aids in the Mn-C bond breaking that is necessary for the

rearrangement to the cyclic manganate(V) diester. The stability of the electron rich enolate complex is increased with electron withdrawing groups and from association between the carbonyl oxygen and the nitrogen cation. The latter being maximised by a tight ion pair.



Scheme 2.10. Proposed mechanism for phase-transfer permanganate oxidations.

The results from Lee's study was in stark contrast to Toyoshima, Okuyama and Fueno.[100] They looked at substituent effects on the oxidation of enol ethers and found that the rate increased with increasing electron donating power of the substituent, implying that the transition state is electron deficient (Scheme 2.11). Lee proposed that this reaction proceeded via a different intermediate that had a positive charge on the carbon bearing the oxygen, which can be stabilised through an oxonium ion. They went onto describe the permanganate as ambiliphilic (i.e. both nucleophilic and electrophilic).



Scheme 2.11. Proposed mechanism of the reaction with permanganate and enol ethers to cyclic manganate(V) diester.

The phase-transfer catalysed reaction of permanganate with olefins has been exploited to prepare carboxylic acids[101], diols[102] and hydroxyketones[103], as well as diones which are the major product formed in acetic anhydride.[104] However the oxidation of 1,5-dienes to yield 2,5-(bishydroxymethyl)tetrahydrofurans has not been carried out under phase transfer conditions.

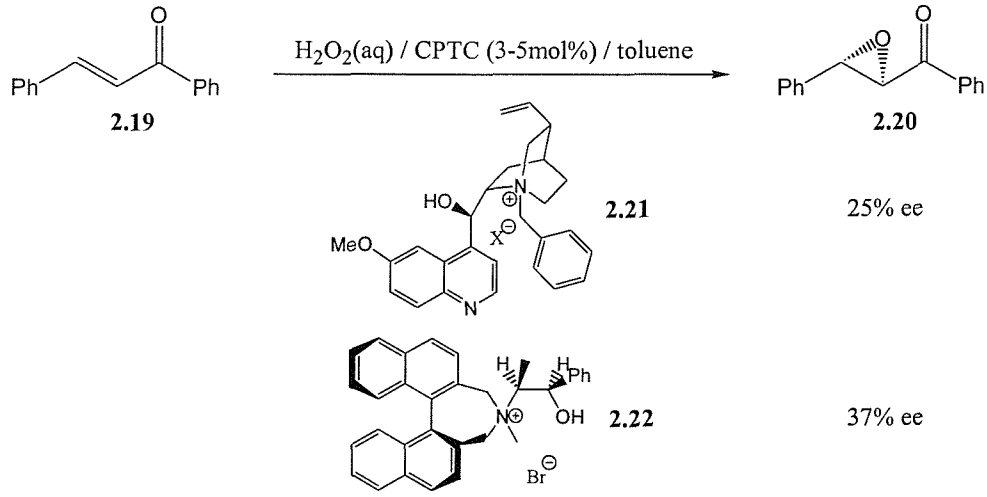
Carrying out the oxidative cyclisation under phase transfer conditions offers a number of advantages over the traditional single-phase conditions.

- Currently acetone/water is used but phase transfer conditions allow for more hydrophobic solvents to be used which should solubilise non-polar dienes and trienes.
- Under phase-transfer conditions non-polar solvents can be investigated in an attempt to improve the selectivity of the reaction (i.e. cyclisation versus hydroxyketone formation).
- By varying the amounts of phase transfer reagent the concentration of permanganate in the organic phase can be controlled. This could allow us to minimise side reactions and optimise the yield of the final product.
- Recently phase-transfer reactions were carried out on achiral substrates using chiral phase-transfer catalysts to give products of high optical purity. This is an extremely attractive prospect and would dramatically increase the utility of the oxidative cyclisation reaction.

Our hope was to isolate the THF product and impurities from the oxidative cyclisation of geranyl benzoate. The intention was then to study the reaction by carrying out a series of parallel reactions which can be quantified by HPLC or GC analysis, in order to optimise the oxidation under phase-transfer conditions and maybe find out more about the reaction.

2.3 Chiral Phase-Transfer Oxidations

Chiral phase-transfer catalysts (CPTC) were first used in the mid-seventies to look at asymmetric alkylations and Michael additions. One of the earliest workers in this field, Wynberg, started looking at the oxidation of α,β-unsaturated carbonyl compounds to epoxides (Scheme 2.12).[105] Wynberg used quaternary ammonium salt **2.21** derived from the benzylation of quinine, to carry out the phase-transfer oxidation of chalcone **2.19** with peroxide between water and toluene, to give epoxide **2.20** in an enantiomeric excess of 25%. He found that using *t*-BuOOH or sodium hypochlorite[106] reversed the stereochemical outcome, as did changing the phase-transfer catalyst from the quinine derivative to *N*-benzylated quinidine. Later it was suggested that the peroxide gave a different isomer due to hydrogen bonding with the hydroxyl on the phase-transfer catalyst.[107] Wynberg found that using sodium hypochlorite increased the utility of the reaction, since it worked with more enones whilst retaining the enantiomeric excesses achieved with peroxide.

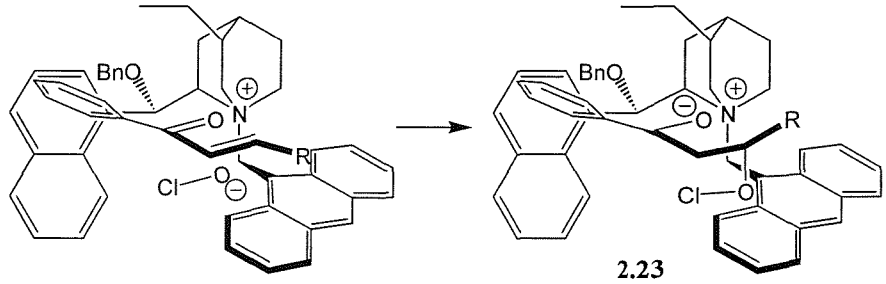


*Scheme 2.12. Early chiral phase transfer catalysis applied to the oxidation of chalcone **2.19**.*

Following Wynberg's work a number of groups started look at alternative phase-transfer catalysts for the oxidation of chalcones. Cyclodextrins[108], chiral crown ethers[109] and chiral pyrrolidine based quaternary ammonium salts[110] were all less successful than the alkaloid based catalysts, however some improvement was found with a phase-transfer catalyst derived from (-)-ephedrine **2.22** (37% ee).[111]

Although these results were very encouraging no further advances were made until 1998 when Lygo *et al.* looked at the *cinchona* alkaloids again.[112,113] They had found

that *N*-anthracenyl methylcinchonidinium salts were very effective as chiral phase transfer catalysts for alkylations and chose to use the catalyst for the epoxidation of chalcones with sodium hypochlorite.[114,115,107,116] Initially the e.e.'s were modest however they greatly improved when the hydroxyl of the catalyst was benzylated, the resulting yields and optical purities for a range of chalcones were found to be excellent (75-98%, 84->98% e.e.). The other enantiomers were also prepared, using the catalyst derived from cinchonine, with equally impressive yields and optical purities. Lygo has proposed an intermediate **2.23**, which involves a Michael type intermediate with an enolate character that is stabilised by interaction with the quaternary ammonium salt (Scheme 2.13). The quinoline and anthracene sterically restrict the catalyst to allow for chiral induction.

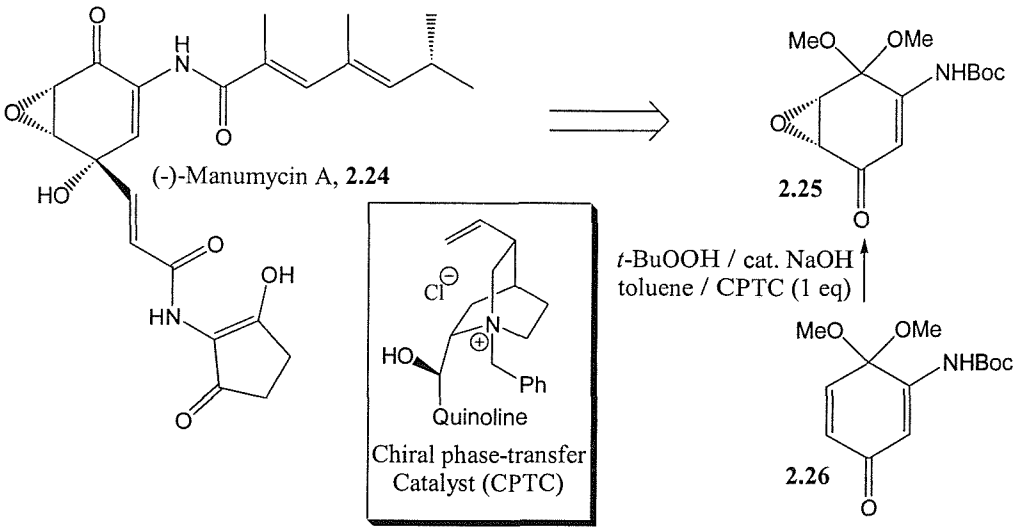


2.23

Scheme 2.13. Proposed intermediate in the phase-transfer catalysed nucleophilic epoxidation of olefins.

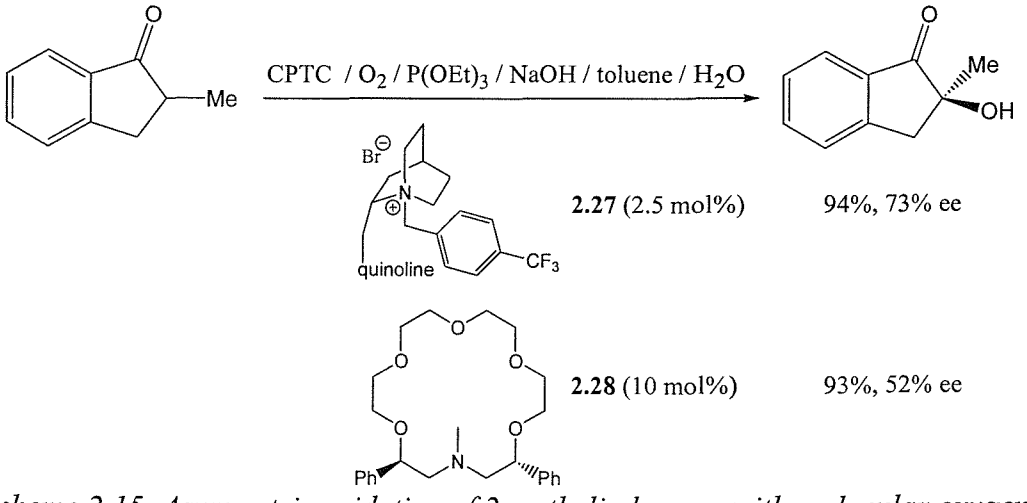
Wynberg made good early progress with oxidations of chalcones, however he was unable to get anything other than trace asymmetric induction for the epoxidation of cyclohexenones.[105] He later achieved improved e.e.'s (25%) by using solid NaOH instead of aqueous hydroxide[117], and went on to epoxidise quinones with better asymmetric induction (45% ee).[118] The epoxidation of naphthoquinones was carried out using the improved *N*-anthracenyl methylcinchonidinium phase-transfer catalyst and the e.e.'s improved accordingly (41-76% ee), increasing as the substituent on the epoxidised alkene increases.[119] Around the same time Taylor *et al.* were interested in the synthesis of some of the manumycin group of natural products which include manumycin A **2.24** (Scheme 2.14).[120,121] Their approach to the synthesis of the core epoxide **2.25** was key to the whole synthesis and they chose a chiral phase-transfer epoxidation of the readily available enone **2.26**.

The yield of epoxide **2.25** was good (71%) and the enantioselectivity was impressive (89% e.e.), however it must be noted that stoichiometric amounts of the phase-transfer reagent were necessary to achieve this result.



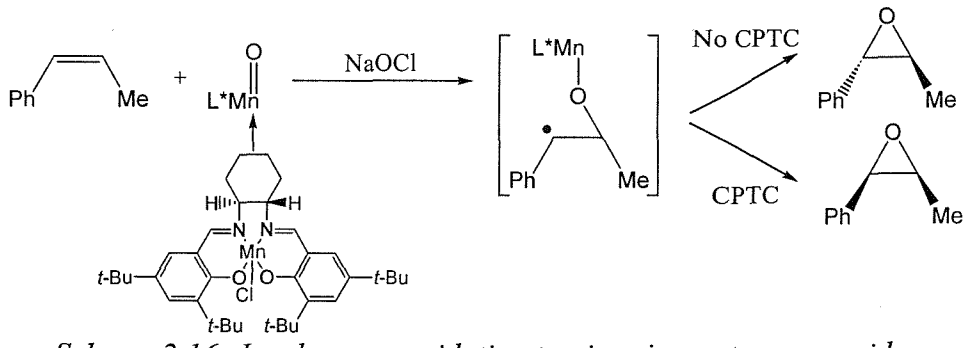
Scheme 2.14. Synthesis of key intermediate ***2.25*** *in the synthesis of manumycin A.*

Optically active α-hydroxyketones are often used as starting materials and intermediates in natural product synthesis. In 1988 the first catalytic enantioselective oxidation of achiral ketones was carried out to give optically active α-hydroxyketones (Scheme 2.15).[122] The procedure used molecular oxygen, triethylphosphite, NaOH(aq), toluene with an *N*-arylmethylcinchonidonium **2.27** catalyst to oxidise 2-alkyl tetralones and indanones in good yield and enantiomeric excess (>90%, 48-79% ee). This reaction has also been tried using a chiral crown ether **2.28** with similar results.[123]



Scheme 2.15. Asymmetric oxidation of 2-methylindanone with molecular oxygen.

An unusual however successful use of *N*-benzylated *cinchona* alkaloids or an ephedrine derivative in the (salen)Mn-catalysed epoxidation was reported by Jacobsen *et al.* in 1994.[124] The manganese complex had already been shown to catalyse the asymmetric epoxidation of *cis*-disubstituted and trisubstituted olefins, however *trans*-olefin epoxidation proceeded poorly and with no chiral induction. The reaction normally gives both *cis*- and *trans*-epoxides (from >99:1 to 3:1) due to a mechanism that is believed to proceed *via* a step-wise path (Scheme 2.16). If the intermediate is able to be stabilised sufficiently to allow rotation of the C-C bond then the *trans*-epoxide may be formed selectivity. Interestingly they found that addition of 20 mol% of the chiral phase-transfer catalyst gave predominantly the *trans*-epoxide (~10:1 trans:cis). The quaternary ammonium salts appear to be more than just phase-transfer catalysts in the reaction and confusingly appear to have no bearing on the enantioselectivity of the reaction.



Scheme 2.16. Jacobsens epoxidation to give cis- or trans-epoxides.

The extent to which oxidations have been carried out under chiral phase-transfer conditions has been covered, however the most interesting observation is the similarity between the mechanism proposed by Lygo (Scheme 2.13) for nucleophilic epoxidations and the mechanism suggested by Lee (Section 2.2, Scheme 2.10) for permanganate oxidations under phase-transfer catalysis. It would seem reasonable that if both mechanisms are correct, asymmetric induction may also be achieved for permanganate oxidations with chiral phase-transfer catalysis.

2.4 Oxidative Cyclisations For The Synthesis of Annonaceous Acetogenins

The Annonaceous acetogenins are a group of natural products isolated from the *Annonaceae* (custard-apple) family of plants.[125] They are derived from C-32/C-34 fatty acids, a number of which contain either one or two adjacent THF rings flanked with hydroxyls (**2.29** and **2.30**) and a butenolide fragment at the end of one of two long chain arms (Figure 2.1).

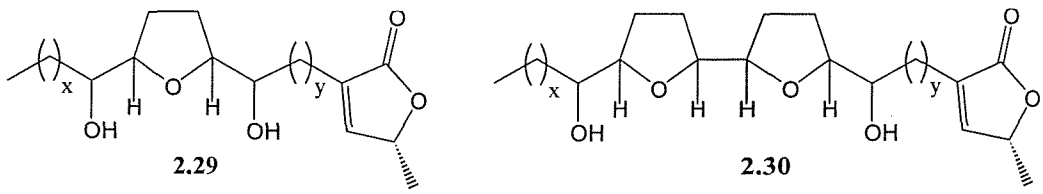
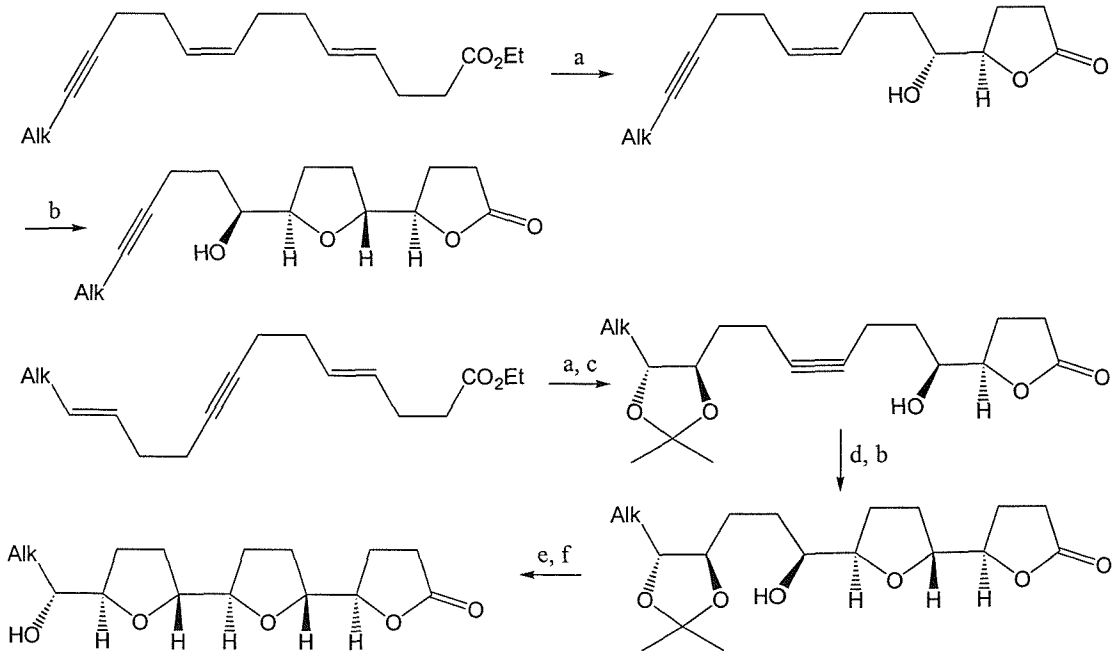


Figure 2.1. General structures of the most common Annonaceous acetogenins.

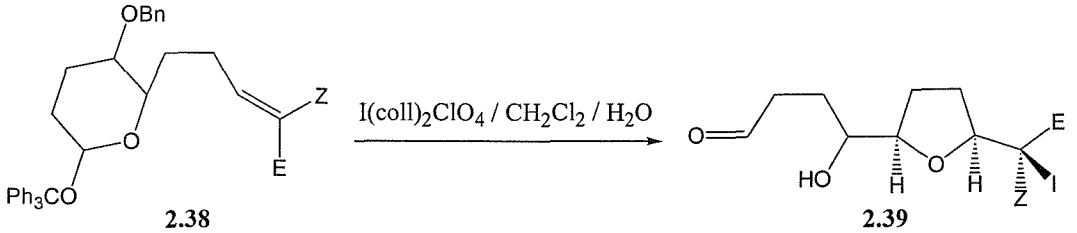
Although there are a lot of other structural variations in this family the structures in Figure 2.1 are the most interesting due to their exciting biological activity, and in particular their potent cytotoxic activity which has implications in cancer. A number of acetogenins have been found to be active against drug resistant cancer cell lines.



Reagents and Conditions: (a) i. AD-mix-β, $BuOH/H_2O$; ii. KOH(aq) then HCl; iii. TsOH, CH_2Cl_2 (b) Re_2O_7, lutidine, CH_2Cl_2 (c) dimethoxypropane, acetone, TsOH (d) $Pd/CaCO_3/Pb$ (10% w/w), hexane/cyclohexane, Et_3N (e) MsCl, Et_3N, CH_2Cl_2 (f) i. TsOH, $MeOH/H_2O$; ii. pyridine, 100°C.

*Scheme 2.17. Routes to key intermediates **2.33** and **2.37** for acetogenin synthesis.*

It has already been shown that metal oxo reagents oxidatively cyclise 1,5-dienes and 5-hydroxyalkenes to give 2,5-substituted THF's. However only rhenium(VII) oxide has been used in the preparation of Annonaceous acetogenins.[126,127,128,129,130,131,132,133,134,135,136] The general strategy involves creating polyolefin carbon skeletons **2.31** and **2.34** which can be manipulated to give either the mono or bis THF intermediates **2.33** and **2.37** respectively. The mono-THF is formed from the selective asymmetric dihydroxylation of the *trans*-olefin to give a lactone and a free hydroxyl (**2.32**) which undrgoes the oxidative cyclisation to give intermediate **2.33**. The bis-THF ring system is formed by bis-dihydroxylation of the olefins, the hydroxylactone is formed and the 1,2 diol is protected (acetonide) to give **2.35**, the alkyne can then be reduced to an olefin to allow the rhenium(VII) oxide promoted oxidative cyclisation to be carried out forming **2.36**. Mesylation of the free hydroxyl followed by diol deprotection and cyclisation gives intermediate **2.37**. There are variations on these routes, but they tend to differ in the order in which the reactions are carried out. Polycyclisations have been attempted using rhenium oxide however the selectivity for the second cyclisation was not as good as for the first ring[136], which was reported previously by Towne and Macdonald.[90]

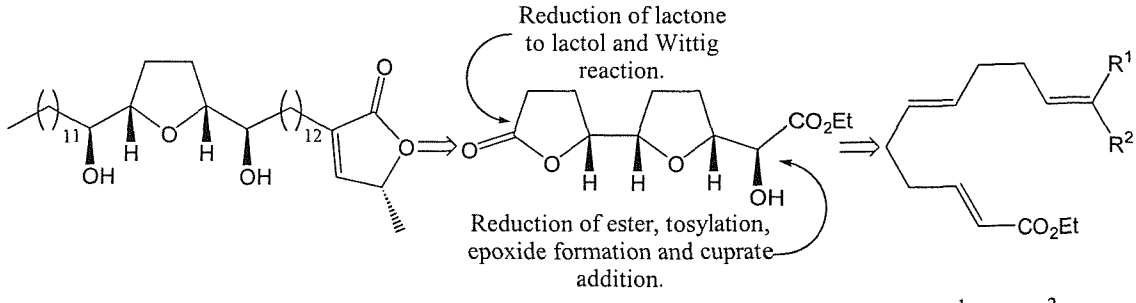


2.38 **2.39**

Scheme 2.18. Cyclisation to give trans-THF rings (8:1 to >20:1 cis:trans).

The permanganate promoted oxidative cyclisation of 1,5-dienes looks like an ideal way to access key intermediates for the synthesis Annonaceous acetogenins with *cis* geometry around the THF ring. Whilst there have been many routes to *trans*-THF Annonaceous acetogenins there are very few routes to prepare *cis*-THF Annonaceous acetogenins. One route used by Mootoo *et al.* exploits an iodoetherification cyclisation to prepare *cis*-THF **2.39** from a pyranoside-alkene **2.38** (Scheme 2.18).[137]

A further aim of this work was to prepare lactone **2.41** from the oxidative cyclisation of a triene **2.36**, e.g. trienes **2.42** or **2.43**, followed by diol cleavage, then elaborate further towards the total synthesis of *cis*-solamin (**2.40**).



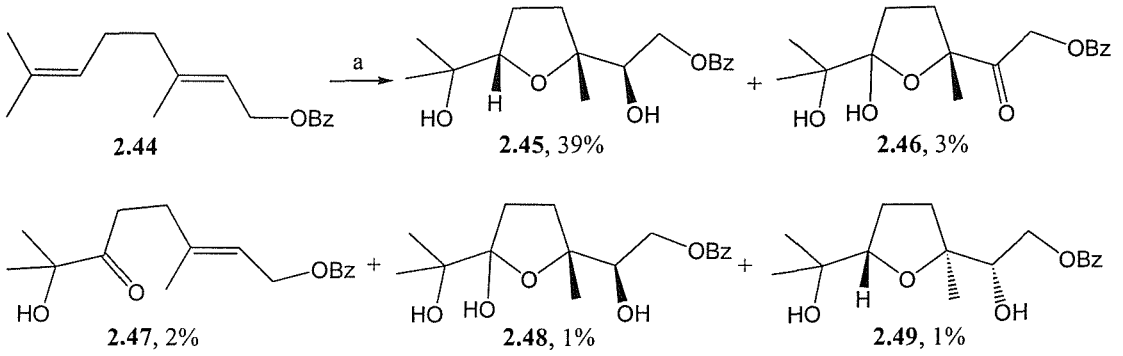
***cis*-solamin, 2.40** **2.41** **2.42**, R^1= Me, R^2= Me;
2.43, R^1= H, R^2= CO_2Et.

Scheme 2.19. Retrosynthetic analysis to prepare cis-solamin via lactone ***2.41****.*

Results and Discussion

2.5 Phase-Transfer Oxidative Cyclisations

The aim of this work was to develop an optimised procedure for the oxidation of geranyl benzoate. The products of the oxidative cyclisation were isolated to allow the product profile of subsequent permanganate oxidations of geranyl benzoate to be established. The oxidation was optimised by carrying out a series of parallel reactions, which were quantified by HPLC analysis. Finally the optimised oxidation reaction conditions were applied to the oxidation of other 1,5-dienes.



Reagent and Conditions: (a) 0.4 M $KMnO_4$(aq) (1.5 eq), AcOH (2.2 eq), phosphate buffer (pH 6.2), -20°C

Scheme 2.20. Oxidative cyclisation of geranyl benzoate and the products isolated.

The oxidative cyclisation of geranyl benzoate (**2.44**) was carried out in acetone/water with 1.5 equivalents of $KMnO_4$ (Scheme 2.20). Five products were isolated from the reaction with THF diol **2.45** as the major product. The yields of products **2.45-2.49** do not reflect the actual yields of the reaction, but are lower due to repeated chromatography required to isolate pure material. Lactol **2.46**, the major impurity, was the product of consecutive oxidations of the double bonds to α-hydroxyketones. The product of mono-oxidation, hydroxyketone **2.47**, was also isolated, proving that the gem dimethyl substituted olefin is more reactive to permanganate than the allyl benzoate olefin. Under neutral or mildly acidic conditions dihydroxylation also occurred, demonstrated by the isolation of lactol **2.48**, which is the product of dihydroxylation of hydroxyketone **2.47**. Oxidative cleavages will also take place however products from cleavage were likely to be removed on work up. Interestingly the *trans*-THF diol **2.49** was also isolated albeit in low yield (1%). An absolute lower

limit of 97% stereospecificity (in favour of the *cis*-THF diol) was set by Walba following his study into permanganate oxidative cyclisations.[77] The stereospecificity for the oxidative cyclisation was 98%, within Walba's limit.

Having established the identity of the principle impurities of the oxidative cyclisation of geranyl benzoate, the oxidation was carried out under phase transfer conditions. An excess of TBAB (phase-transfer reagent, 1.5 equivalents) was used along with 1.5 equivalents of permanganate, 2.2 equivalents of acetic acid and phosphate buffer (pH 6.2). The conditions chosen were largely taken from the homogenous phase oxidation (Scheme 2.20), however TBAB was chosen as the phase-transfer reagent due to its availability in house. The reaction proceeded rapidly at room temperature and THF diol **2.45** was isolated in 28% yield. When the reaction was carried out at 0°C the yield dropped to 19%, which prompted us to carry out optimisation experiments at 20°C.

A series of parallel reactions were run, systematically looking at each parameter (stoichiometries are all relative to geranyl benzoate). The reactions were quenched with ($Na_2S_2O_5$(aq) then made up to 100 mL in volumetric flasks, and then analysed by HPLC. THF diol **2.45** was quantified by analysing standards across a range of concentrations. A calibration curve was plotted from which the yields could be established. Linear regression analysis on the calibration curves gave r-values > 0.99.

Effects of Varying Acetic Acid and Buffer

To establish the need for either buffer or acetic acid the reaction was carried out without either (Table 2.1, entry 1), with just phosphate buffer (entry 2), with just acetic acid (entry 3) and with both (entry 4).

Entry	Acetic Acid (3 eq)	Phosphate buffer	Yield of **2.45**
1	NO	NO	8%
2	NO	YES	8%
3	YES	NO	45%
4	YES	YES	47% and 48%

Reagents and Conditions: $KMnO_4$ (2 eq), TBAB (100 mol%), CH_2Cl_2.

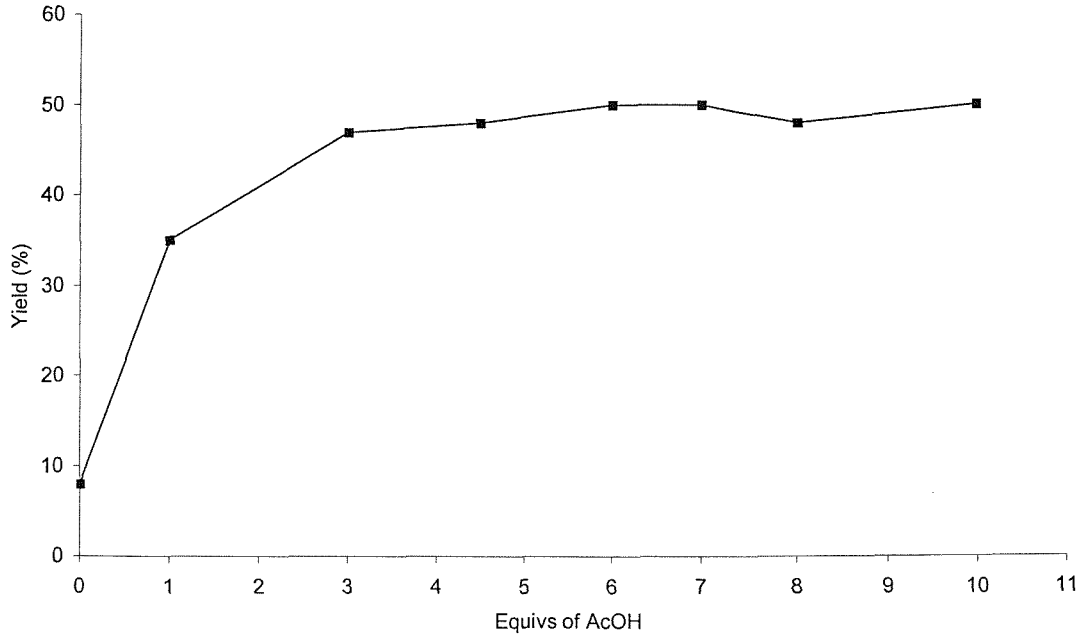
Table 2.1. Reactions with and without acetic acid and buffer.

The conclusion from these reactions was that the buffer had little effect on the yield whilst acetic acid was essential. Interestingly the reaction with both acid and buffer was carried out in duplicate and HPLC quantification gave very similar yields (Table 2.1, entry 4) which encouragingly demostrated the reproducibility of the reaction conditions and the quantification. On the basis of these results buffer was not used in subsequent reactions.

It should be noted that a problem was encountered with standard solutions of THF diol **2.45**. When left at room temperature for a few days the formation of another product was observed, thought to be as a result of benzoate migration to the secondary alcohol. However, this decomposition was inhibited by the presence of acetic acid in the standard solutions, and therefore was avoided in crude reaction mixtures.

Stoichiometry of Acetic Acid

Having established that acetic acid was necessary for the reaction, the amount of acetic acid necessary to sustain the yield was determined by running a series of reactions with varying equivalents of carboxylic acid.



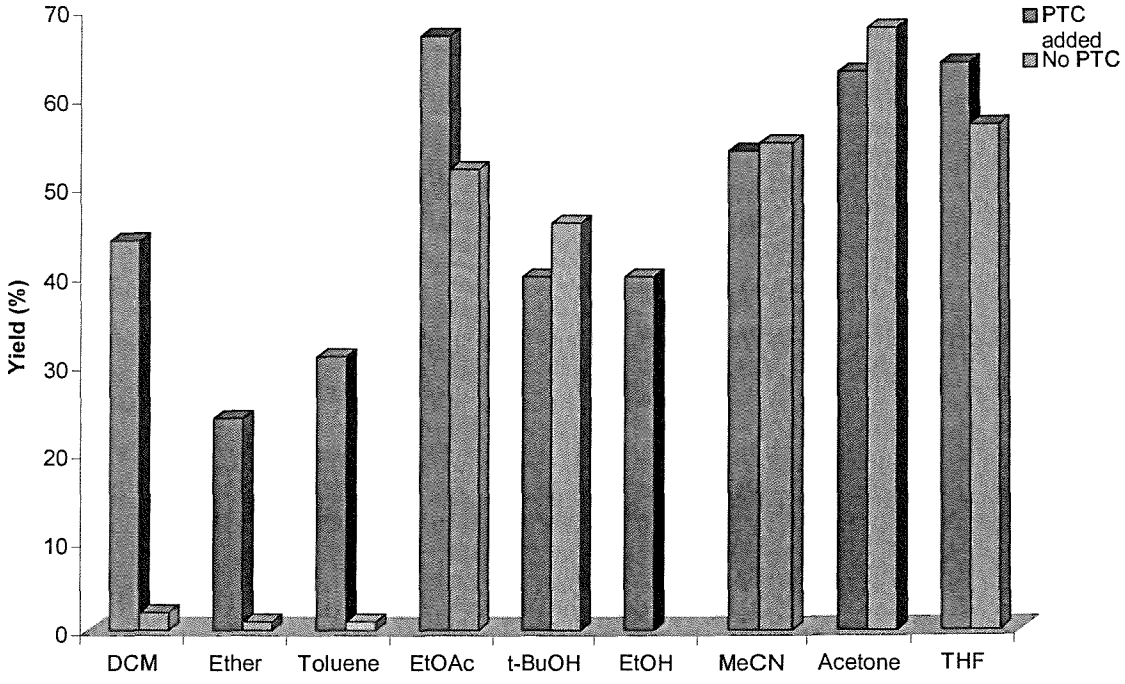
Reagents and Conditions: 0.4 M $KMnO_4$(aq) (2 eq), TBAB (100 mol%), CH_2Cl_2, AcOH, RT.

Graph 2.1. Yield of THF diol ***2.45*** *with various equivalents of acetic acid.*

The yields were sustained down to three equivalents of acetic acid however the yield dropped when only one equivalent of acetic acid was used. Even up to ten equivalents of acetic acid there was no detrimental effect on the yield. Subsequent reactions were carried out with four equivalents of acetic acid.

Effect of Solvents and Phase-Transfer Reagent

Solvent was expected to have a big effect on the reaction. The polarity of the solvent determines whether the p ermanganate exists as an ion pair or as a solvated ion. To investigate the extent to which the solvents solubilise the permanganate ion test reactions were carried out with and without phase-transfer reagent.



Reagents and Conditions: 0.4 M $KMnO_4$(aq) (2 eq), TBAB (100 mol%), AcOH (4 eq), RT.

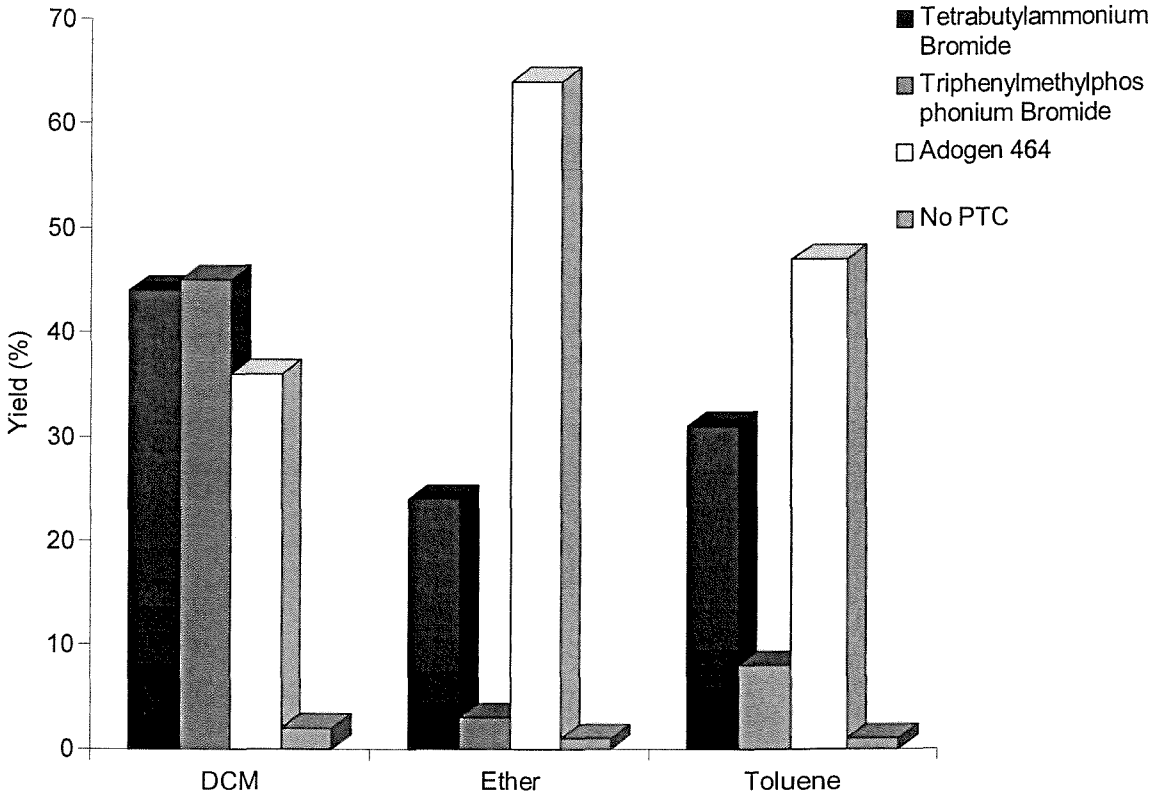
Graph 2.2. Yield of THF diol ***2.45*** *with various solvents with and without phase-transfer reagent.*

The best yields of THF diol **2.45** were achieved using the more polar solvents acetone and THF, however the yields were unaffected by the presence of phase-transfer reagent. This proved that the reaction progressed efficiently through an alternative route to the phase-transfer promoted pathway in polar solvents. With ethyl acetate the

yield was improved by 15% with the presence of phase-transfer reagent. The three most hydrophobic solvents, toluene, CH_2Cl_2 and ether, gave only a trace of THF diol **2.45** in the absence of phase-transfer reagent, whilst the yields improved dramatically in the presence of phase-transfer reagent. These systems are genuinely mediated *via* a phase-transfer mechanism and were investigated further.

The Effect of Various Phase-Transfer Reagents

Tetrabutylammonium bromide may not be the best phase-transfer reagent since four butyl chains would inhibit a close ion pair to be formed. Two other phase-transfer reagents were investigated each of which have a methyl substituent, which allowed a tighter ion pair to be formed. The reactions were carried out in toluene, CH_2Cl_2 and ether.



Reagents and Conditions: $KMnO_4$ (2 eq), PTC (100 mol%), AcOH (4 eq).

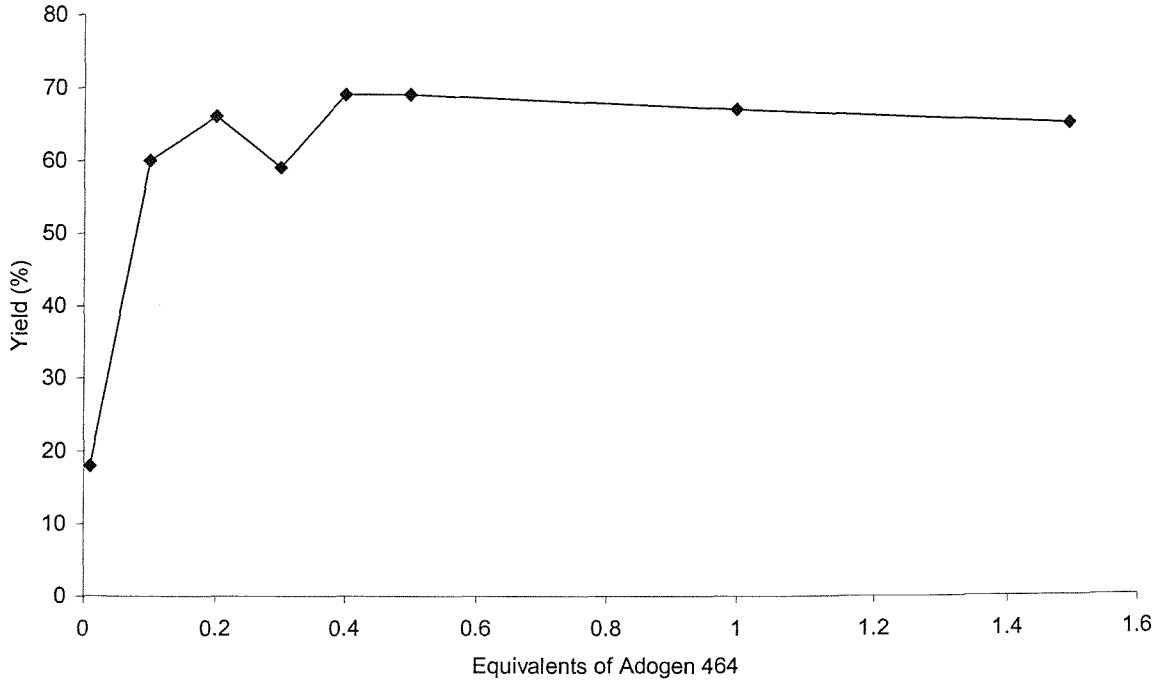
Graph 2.3. Yield of THF diol ***2.45*** *with various solvents and phase-transfer reagent.*

Clearly the phase-transfer reagents gave similar yields of THF diol **2.45** in CH_2Cl_2, whilst yields varied considerably in toluene and ether. Triphenylmethylphosphonium

bromide was insoluble in toluene and ether, which explained the poor yields. TBAB was sparingly soluble in toluene and ether and so the yields were slightly better but Adogen 464 was soluble in both solvents and the yields increased markedly. The yield of THF diol (64%) in ether using Adogen 464 was particularly exciting. The profile of this reaction was compared to the reactions carried out in CH_2Cl_2. In CH_2Cl_2 the ratio between the major impurity, lactol **2.46**, and THF diol **2.45** was ~1:2.5, however in ether the ratio was 1:8. Carrying out the reaction in ether was more selective for the preparation THF diol **2.46**, although the reasons for this were not immediately apparent.

Effect of the Stoichiometry of Phase-Transfer Reagent

Up to this point an equivalent of phase-transfer reagent had been used, although it would obviously be preferable to carry out the reaction in the presence of a catalytic quantity of phase-transfer catalyst. The effect of phase-transfer reagent on the reaction was investigated from 150 mol% down to 1 mol%.



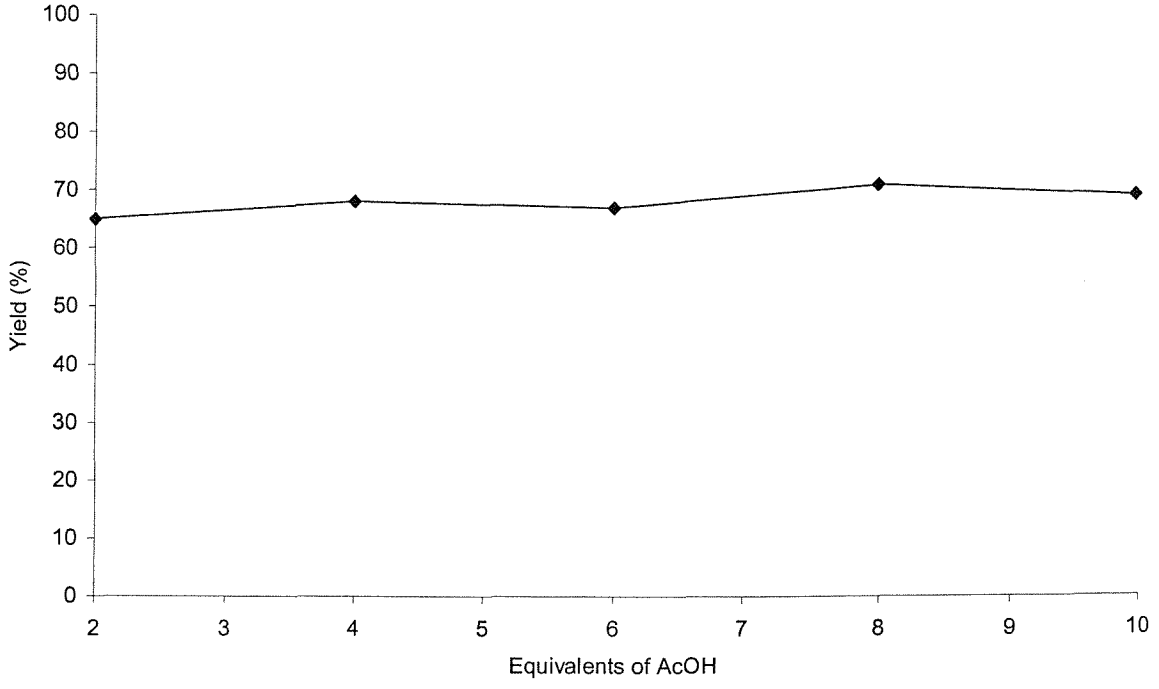
Reagents and Conditions: $KMnO_4$ (2 eq), AcOH (3 eq), ether.

Graph 2.4. Effect of phase-transfer reagent on the yield of THF diol ***2.45****.*

The result for 30 mol% of Adogen 464 appears to be worse than expected having considered the yields of THF diol **2.45** for 20 mol% and 40 mol% of Adogen 464. However the general trend appears to be that the yields hold up down to 10 mol%, below which the yield of THF diol drops off. Thus it was demonstrated that Adogen 464 could indeed be used catalytically, and future reactions were carried out using 40 mol% of Adogen 464.

Further Optimisation Experiments

Having changed solvent from CH_2Cl_2 to ether, the effect of acetic acid on the reactions may have changed, therefore a series of reactions were run varying the equivalents of acetic acid. In the range from two to ten equivalents of acetic acid there was little variation in the yield of THF diol **2.45** (65-71%).



Reagents and Conditions: $KMnO_4$ (2 eq), Adogen 464 (40 mol%), ether, RT.

Graph 2.5. Effect of AcOH stoichiometry on the yield of THF diol ***2.45*** *in ether.*

The concentration of the organic phase of the reaction mixture was also considered and four reactions were run across a range of concentrations (1.9 M, 0.39 M, 97 mM, 38 mM). At 97 mM and 0.39 M the yields of THF diol **2.45** (71 and 69% respectively) were close enough to be within experimental error. At 1.9 M and 38 mM the yields

drop off markedly (43 and 55% respectively). Unsurprisingly, as the organic phase became more concentrated the reaction proceeded more rapidly.

Having optimised the conditions on a small scale (100 mg) the oxidation of geranyl benzoate (**2.44**) was carried out on a slightly larger scale (500 mg) to determine an isolated yield for the reaction under the optimised conditions. Pleasingly the yield of **2.45** was 70%, which was the same as the yield established using HPLC quantification on a small scale during the optimisation procedure. Lactol **2.46** was isolated in a 9% yield to give a THF diol **2.45** to lactol **2.46** ratio of 7:1.

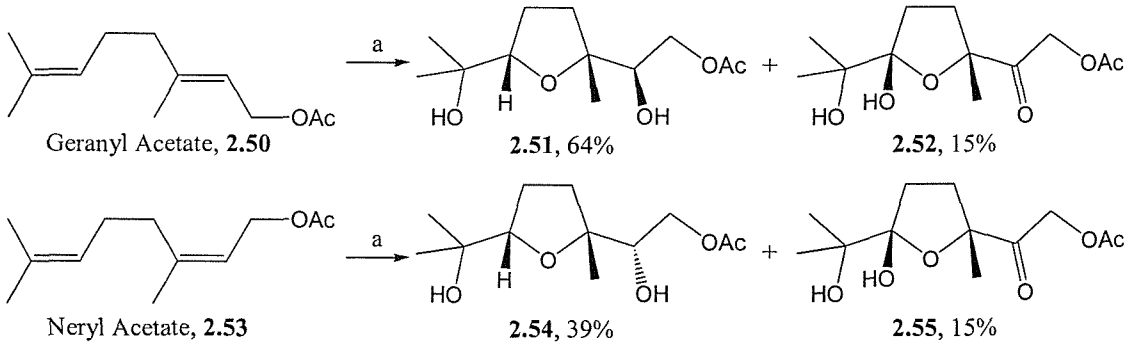
Conclusion

The phase-transfer mediated oxidative cyclisation has been demonstrated on geranyl benzoate (**2.44**) to give THF diol **2.45**. This transformation was then optimised and the following conclusions have been made.

- Three equivalents or more of acetic acid are required for the oxidative cyclisation reaction, and a large excess is not detrimental to the yield of THF diol **2.45**.
- The oxidative cyclisation in polar solvents works as well without phase-transfer reagent as with one. The reaction does not progress *via* a phase-transfer mechanism.
- In non-polar solvents the yields were very poor in the absence of phase-transfer reagent, and reacted poorly if the phase-transfer reagent had poor solubility in the solvent.
- The ratio of THF diol **2.45** to lactol **2.46** was better in ether than in CH_2Cl_2, which resulted in higher yields of THF diol **2.45** in ether.
- The yields of THF diol **2.45** are good using between 10-150 mol% of phase-transfer reagent (Adogen 464) in ether, hence the reaction is a catalytic phase-transfer reaction.
- The yield of THF diol **2.45** at concentrations of geranyl benzoate (**2.44**) in the organic phase between 1 mM and 0.4 M remained high, i.e. ~70%, whilst yields were shown to drop off above 2 M and below 40 nM.

2.6 Further Phase-Transfer Oxidations of 1,5-Dienes

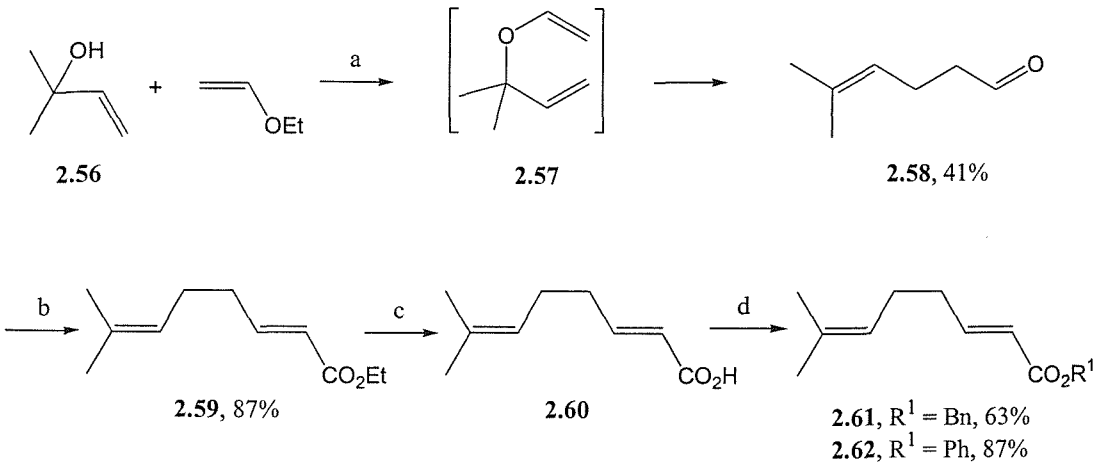
Having established optimised conditions for the oxidative cyclisation of geranyl benzoate, the generality of these conditions were tested initially on similar 1,5-diene systems then on 1,5-dienes with a more electron deficient olefin. As expected the oxidation of geranyl acetate (**2.50**) proceeded well to give THF diol **2.51** in good yield (64%), however when neryl acetate (**2.53**) was oxidised the yield of THF diol **2.54** was disappointing (34%) (Scheme 2.21). Surprisingly the ratio of THF diol **2.51** to lactol **2.52** for the oxidation of geranyl acetate (**2.50**) was 4:1 (c.f. oxidation of geranyl benzoate, 9:1), and the ratio was worse for the oxidation of neryl acetate (2:1). The reasons for this are unclear, but going from a *trans* to a *cis*-olefin under these conditions was detrimental for the formation of THF diol **2.54**. Since no other products were isolated from the oxidation of neryl acetate it was concluded that oxidative cleavage was the predominant reaction.



Reagent and Conditions: (a) 0.4 M $KMnO_4$(aq) (1.5 eq), Adogen 464 (40 mol%), AcOH (2.2 eq), ether.

Scheme 2.21. Permanganate oxidation of geranyl and neryl derivatives.

The oxidative cyclisation of 1,5-dienes with an electron deficient olefin was investigated using ester diene **2.59**, which was prepared by a Wittig olefination on aldehyde **2.58** (Scheme 2.22). A trace of a minor impurity in diene **2.59**, assigned to be the *cis*-olefin, was detected by GC, however the peak was too small to be integrated. Aldehyde **2.58** was the starting point in a number of syntheses in this work, and was prepared by treating 3-methyl-1-buten-3-ol (**2.56**) with catalytic phosphoric acid in ethyl vinyl ether at 120°C in a pressure vessel.[138] 3-Methyl-1-buten-3-ol (**2.56**) reacted to give allyl vinyl ether **2.57** which underwent a Claisen rearrangement to give aldehyde **2.58** in reasonable yield (41%).



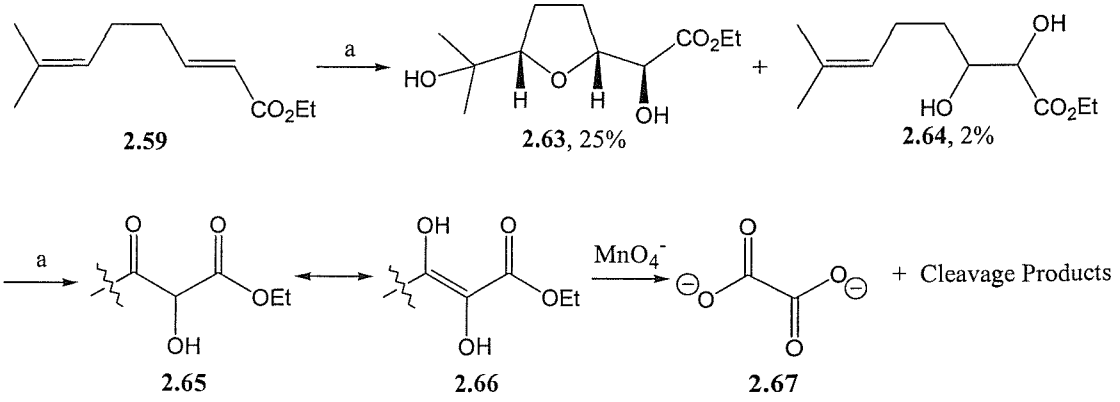
2.56 **2.57** **2.58**, 41%

2.59, 87% **2.60** **2.61**, R^1 = Bn, 63%
2.62, R^1 = Ph, 87%

Reagents and Conditions: (a) H_3PO_4, 120°C; (b) Ph_3PCHCO_2Et, CH_2Cl_2, RT; (c) LiOH, MeOH, water; (d) R^1OH, DCC, DMAP (10 mol%), CH_2Cl_2.

Scheme 2.22. Preparation of ester 1,5-dienes.

Lee *et al.* concluded from their work that phase-transfer conditions increase the rate of permanganate oxidation of α,β-unsaturated carbonyl compounds through the stabilisation of an enolate-like transition state by the cationic phase-transfer catalyst (Section 2.2).[99] The isolation of the by-product **2.64,** albeit in 2% yield, from the phase-transfer oxidative cyclisation of diene **2.59** (Scheme 2.23) demonstrated the increased reactivity of the alkene adjacent to the ester over the trisubstituted olefin. THF diol **2.63** was isolated in a disappointing yield (25%), along with recovered starting material. The major side reaction was expected to be oxidation of the olefins to α-hydroxyketones, though surprisingly no products related to this transformation were isolated. However a crystal isolated from the aqueous phase after work up was found to be an oxalate salt **2.67** by X-ray crystallography.



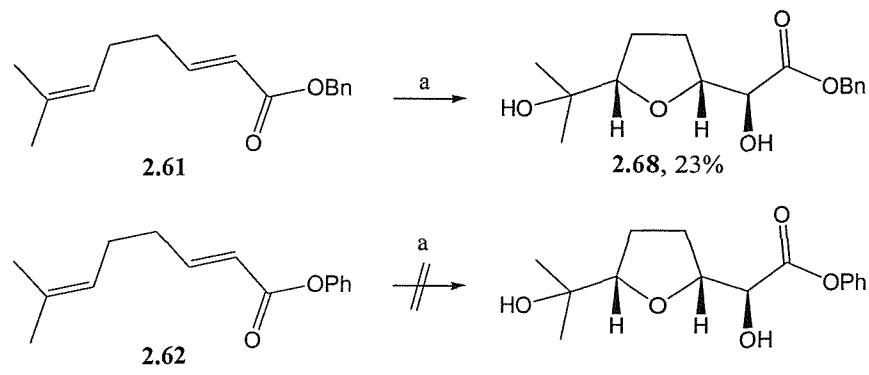
2.59 **2.63**, 25% **2.64**, 2%

2.65 **2.66** **2.67**

Reagents and Conditions: (a) 0.4 M $KMnO_4$ (2 eq), Adogen 464 (40 mol%), AcOH (4 eq), Ether.

Scheme 2.23. Oxidation of 1,5-diene with an electron deficient olefin.

To explain the absence of any α-hydroxyketone derivatives the product of the oxidation of the α,β-unsaturated ester was examined (Scheme 2.23). The α-hydroxy-β-ketoester **2.65** was the proposed product, which was in resonance with an electron rich 1,2-dihydroxyolefin **2.66**. In the literature,[100] it has been shown that oxidation of electron rich olefins under phase-transfer catalysis is rapid, which we suggest may produce cleavage products that due to high polarity or volatility were removed on work up. The isolation of an oxalate salt was good evidence to support the theory, along with the recovery of starting material that was not oxidised due to the consumption of permanganate by the proposed oxidative cleavage reactions.



Reagents and Conditions: (a) 0.4 M $KMnO_4$ (2 eq), Adogen 464 (40 mol%), AcOH (4 eq), Ether.

Scheme 2.24. Oxidation of other 1,5-dienones with an electron deficient olefins.

The oxidations of the benzyl and phenyl ester dienes, **2.61** and **2.62** respectively, were carried out following the same procedure as above. The oxidation of phenyl ester **2.62** gave no THF diol product, possibly due to a competing reaction similar to the oxidative dimerisation of phenols with permanganate. Benzyl ester diene **2.61** was oxidised successfully to THF diol **2.68**, however again the yield was poor (23%).

Conclusions

- The oxidation procedure gave disappointing yields of THF diol for neryl acetate (**2.53**) (39%) and dienes **2.59** and **2.61** (25 and 23% respectively). 1,5-Dienes with either *cis*-olefins or electron deficient olefins will require alternative conditions, optimised specifically for each substrate.

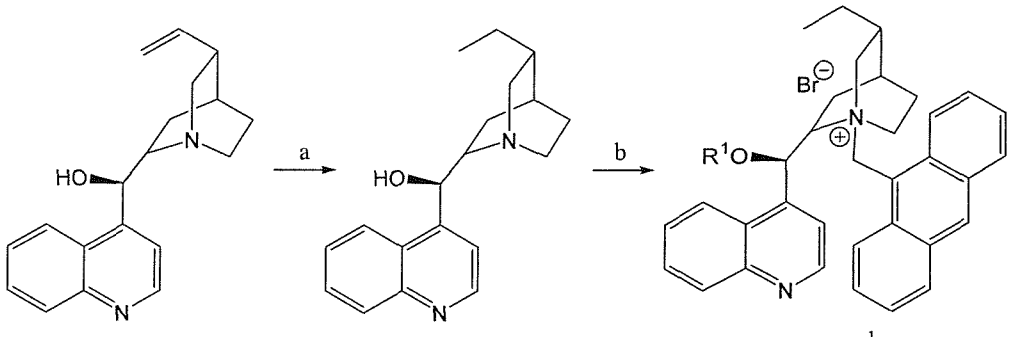
- The isolation of diol **2.64** demonstated that the electron deficient olefin was more reactive than the more electron rich olefin under the reaction conditions, which was consistent with the findings of Lee.[99]
- A proposal has been made concerning the oxidation of dienones that the α-hydroxy ketone product from the oxidation of the olefin adjacent to the carbonyl was susceptible to oxidative cleavage, the resulting products of which were lost on work up.

2.7 Chiral Phase-Transfer Catalysed Oxidative Cyclisation

Earlier the mechanism for the phase-transfer permanganate oxidations of α,β-unsaturated carbonyl compounds (Section 2.2) and the proposed mechanism of the chiral phase-transfer catalysed nucleophilic epoxidation of α,β-unsaturated phenones (Section 2.3) were discussed. The intermediates suggested for the two reactions were very similar and led us to consider the possibility of an asymmetric permangante oxidation of 1,5-dienes using a chiral phase-transfer catalyst. The anticipated outcome of an asymmetric oxidation would be an optically enriched THF diol, which would, to our knowledge, be the first asymmetric permanganate oxidation from an achiral starting material. The oxidation studies were carried out using a chiral phase-transfer catalyst (CPTC) derived from cinchonidine (**2.69**) and a diene containing the phenone moiety. Having carried out the initial reaction under chiral and achiral phase-transfer catalysis and the results assessed, the reaction was optimised in order obtain the best yield and asymmetric induction.

Preparation of Chiral Phase-Transfer Catalyst (CPTC) and Phenone Diene

Chiral phase-transfer catalyst **2.72** was chosen, despite concerns about oxidation of the quinoline to the *N*-oxide or oxidation of the methylene group adjoining the quaternary ammonium centre, because of the ease of its synthesis, and the excellent results achieved in the asymmetric epoxidation of α,β-unsaturated phenones[114,107,115,116]



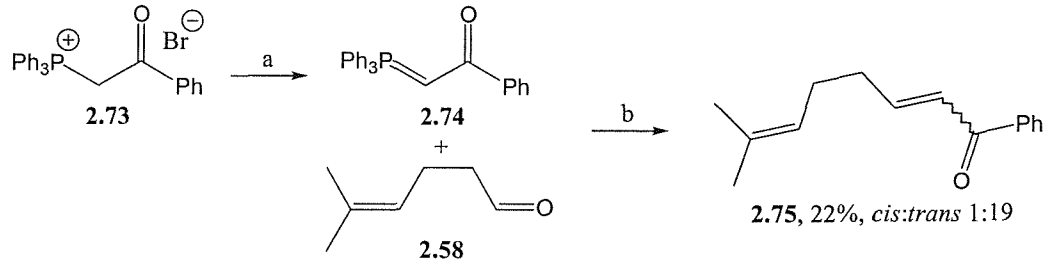
Cinchonidine, **2.69** — **2.70**, 100% — **2.71**, R^1 = H, 79%; **2.72**, R^1 = Bn, 86%

Reagents and Conditions: (a) Tosylhydrazide (6 eq), NaOAc (6 eq), THF, water; (b) 9-chloromethyl anthracene, toluene, reflux; (c) BnBr, 50% KOH(aq), CH_2Cl_2.

*Scheme 2.25. Preparation of CPTC **2.72** from cinchonidine.*

Chiral phase-transfer catalyst **2.72** was prepared following a procedure developed by Corey et al. (Scheme 2.25).[139] Before the quaternary ammonium salt could be prepared it was required to remove the double bond in order to prevent oxidation by permanganate, which would in turn increase the polarity of the catalyst and reduce it's ability to pass into the organic phase. The double bond of cinchonidine was reduced in the presence of tosyl hydrazide and sodium acetate to afford dihydrocinchonidine (**2.70**) in quantitative yield. Quaternary ammonium salt **2.71** was then prepared by refluxing dihydrocinchonidine (**2.70**) and 9-(chloromethyl) anthracene in toluene. Isolation was trivial since the product precipitates out from a CH_2Cl_2 solution on addition of ether. The preparation of the desired benzyl ether **2.71** was carried out with aqueous sodium hydroxide in the presence of benzyl bromide in CH_2Cl_2. Product **2.72** was subsequently readily isolated by precipitation and filtration in good overall yield (68%, over three steps).

The target diene, phenone **2.75**, was prepared from aldehyde **2.58** following a similar approach to the preparation of ester diene **2.59**. Phosphorane **2.74**, which was prepared from commercially available phenacyltriphenylphosphonium bromide (**2.73**), was treated with aldehyde **2.58** and stirred for 19 hours. Unfortunately, the reaction did not go to completion therefore the yield was poor (22%). The reaction required more forcing conditions than was required for the preparation of diene **2.59** because the phenone adjacent to the phosphorane decreased the reactivity of the phosphorane. Analysis by GC and GC/MS established the *cis*:*trans* ratio to be 1:19, which was acceptable for our oxidation studies.

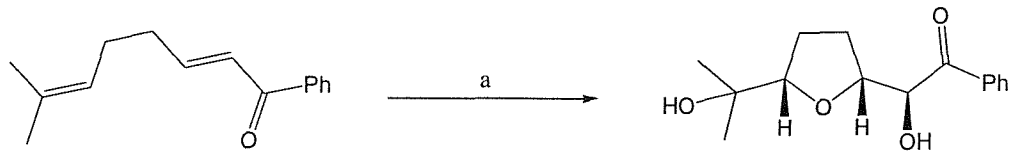


Reagents and Conditions: (a) 1M NaOH(aq), CH_2Cl_2; (b) CH_2Cl_2, 19 h.

Scheme 2.26. Preparation of phenone diene 2.75.

Oxidation of 1,5-Diene 2.75 under Homogeneous and Phase-Transfer Conditions

Initially the permanganate promoted oxidative cyclisation was carried out in acetone and water on diene **2.75** to facilitate the isolation of racemic THF diol **2.76** (Scheme 2.27).



2.75 **2.76, 49%**

Reagents and Conditions: (a) 0.4 M $KMnO_4$(aq), AcOH (2.9 eq), phosphate buffer (pH 6.2), acetone, -20°C.

Scheme 2.27. Oxidative cyclisation of ***2.75*** *in acetone/water.*

The product was isolated in reasonable yield (49%) as a colourless crystalline solid. Recrystallisation from ethanol/hexane gave a crystal from which the structure could be determined by X-ray crystallography (Figure 2.2).[140] The structure clearly shows that the oxygens have been installed stereospecifically on one side of the molecule.

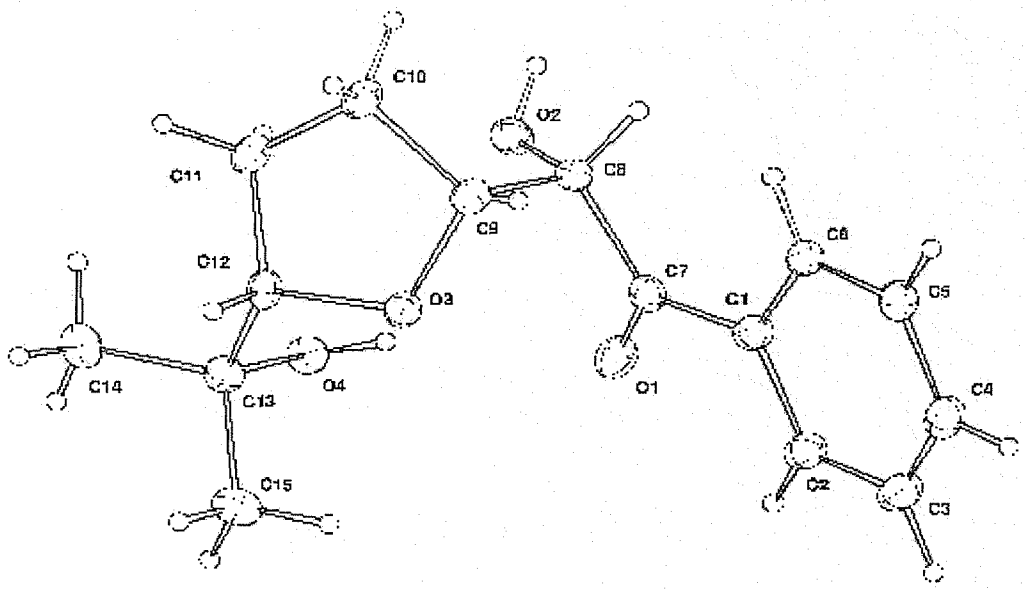
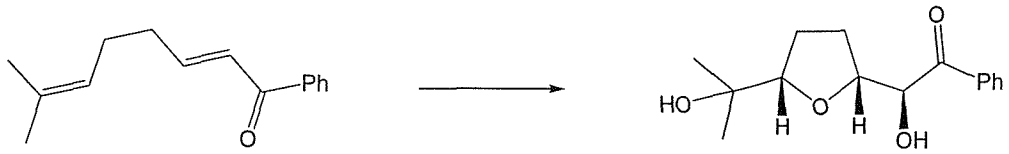


Figure 2.2. Crystal structure of THF diol ***2.76****.*

The conditions for the chiral phase-transfer permanganate oxidation were similar to those used for the achiral oxidation however ether was replaced with CH_2Cl_2 due the poor solubility of CPTC **2.72** in ether (Scheme 2.28). The yield of THF diol **2.76** was very disappointing (13%), however having established a chiral HPLC method for the separation of the enantiomers, the enantiomeric excess was determined to be 39%.

Whilst the yield was poor the asymmetric induction was encouraging, but further work was required to optimise the conditions.



2.75 **2.76**, 13%, 39% ee

Reagents and Conditions: (a) 0.4M $KMnO_4$(aq), CPTC **2.72** (30 mol%), AcOH (3 eq), CH_2Cl_2, 0°C.

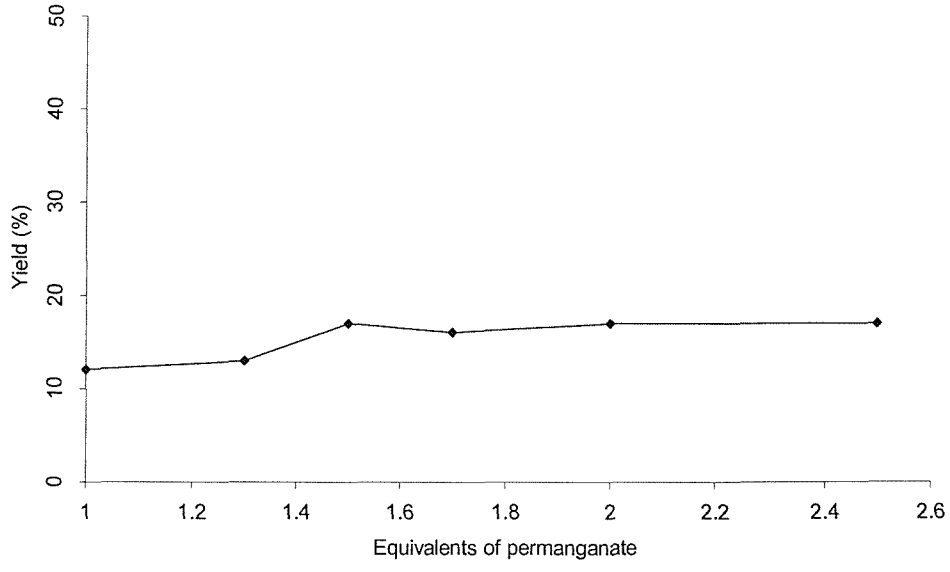
*Scheme 2.28. Chiral phase-transfer oxidation of diene **2.75**.*

Optimisation of Chiral Phase-Transfer Oxidation of Diene 2.75

The approach to the optimisation of the chiral phase-transfer oxidation of diene **2.75** was similar to that used to optimise the phase-transfer oxidation of geranyl benzoate. Each parameter was investigated systematically starting with establishing the optimum amount of permanganate, and the yields were quantified by HPLC.

Effect of Stoichiometry of Permanganate

A range of equivalents of permanganate were investigated (1.5-2.5 equivalents), whilst retaining the molar ratio between permanganate and acetic acid to 2:3.



Reagents and Conditions: 0.4M $KMnO_4$(aq), CPTC **2.72** (30 mol%), AcOH, CH_2Cl_2, 0°C.

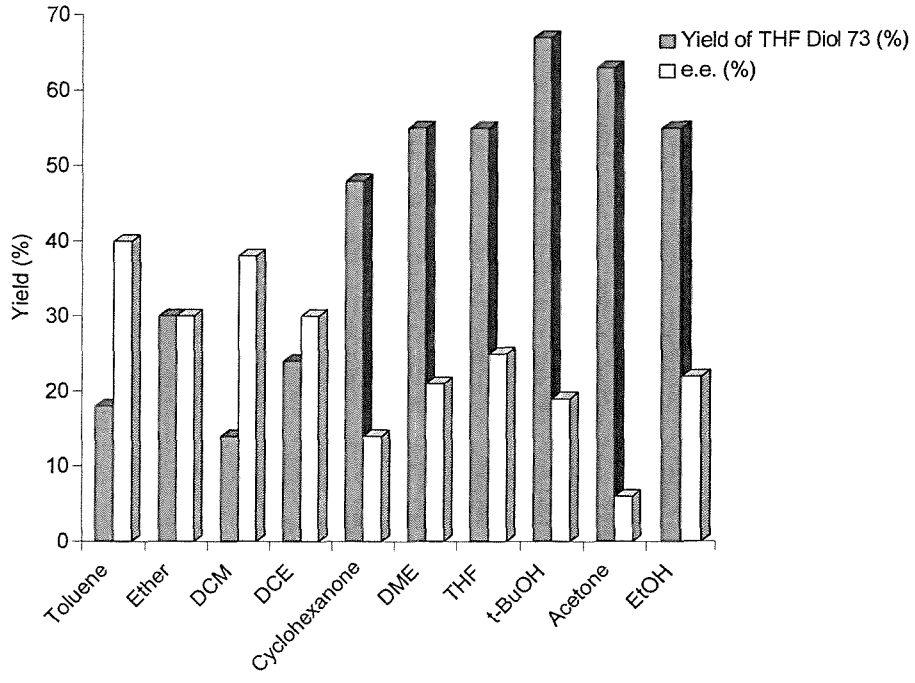
*Graph 2.6. Yield of THF diol **2.76** with changing quantities of permanganate.*

Acetic acid was added to the reaction mixture for two reasons: firstly the presence of acetic acid accelerates the rate of reaction,[141] and secondly the acetic acid is there to neutralise any hydroxide produced during the oxidation. Since the amount of hydroxide generated is determined by the amount of permanganate reduced, it was felt necessary to keep the permanganate/acetic acid ratio constant.

There was no great improvement in the yield of THF diol **2.76** by changing the equivalents of permanganate. The yield drops off at below 1.5 equivalents of permanganate, however addition of an excess of permanganate appeared to have no detrimental effect upon the yield. Further reactions were carried out with 1.5 equivalents of permanganate.

Effect of Various Solvents

Optimisation of the phase-transfer catalysed oxidation of geranyl benzoate showed that solvent had a major effect upon the reaction. Ten solvents were tested for the oxidation across a range of polarities and the yields and e.e.'s were established.

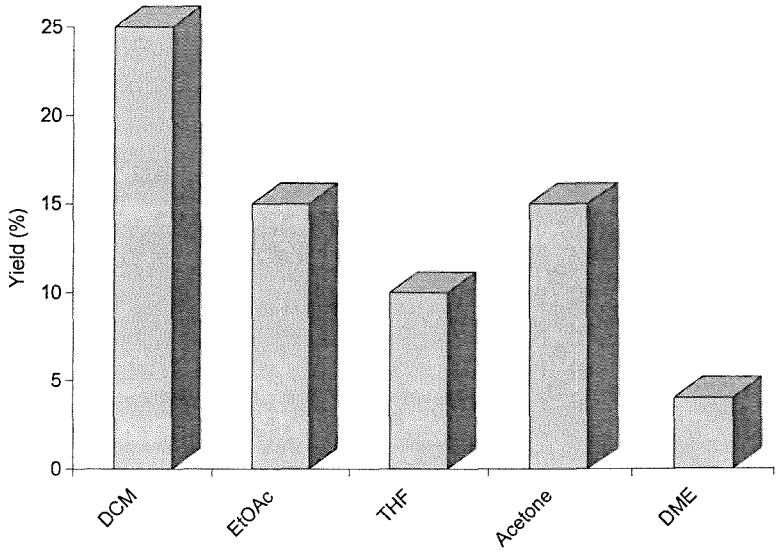


Reagents and Conditions: 0.4 M $KMnO_4$(aq), CPTC **2.72** (30 mol%), AcOH (2.25 eq), 0°C.

*Graph 2.7. Yields and e.e.'s of THF diol **2.76** with various solvents.*

The general trend was found to be that the more polar solvents gave higher yields, however as the polarity of the solvent increased so the enantiomeric excess decreased. The fall in e.e. with increasing solvent polarity was to be expected. As the solvent polarity increases so the permanganate ion would be increasingly solvated, resulting in the permanganate being held further away from the phase-transfer catalyst and as a consequence too far removed from the chiral environment to effectively induce asymmetric attack upon the 1,5-diene substrate. Toluene gave the highest asymmetric induction albeit in low yield (18%). CPTC **2.72** did not disolve completely in toluene, however complete solubility in the organic solvent did not appear to be essential, which was demonstrated by a reasonable yield and e.e. from the oxidation in ether (30%, 30% e.e.). The asymmetric induction from this set of reactions, although promising, was lower than hoped, but it was believed that some improvement would be possible reducing the reaction temperature to well below 0 °C. Unfortunately the aqueous phase would freeze at such low temperatures. It was with this in mind that a solid-liquid phase-transfer system was investigated.

Effect of Various Solvents (solid-liquid phase-transfer)



Reagents and Conditions: $KMnO_4$(s) (1.5 eq), CPTC **2.72** (30 mol%), AcOH (2.25 eq), 0°C.

*Graph 2.8. Yields of THF diol **2.76** with various solvents under solid-liquid phase-transfer catalysis.*

Again a range of solvents were used in the solid-liquid phase-transfer oxidative cyclisation of 1,5-diene **2.75**, including THF, acetone and 1,2-dimethoxyethane. The polar solvents were included because in the absence of water, with which they are miscible, they may not solvate the permanagante ion so well increasing the asymmetric induction whilst retaining the high yields observed in the liquid-liquid phase-transfer system. Disappointingly the more polar solvents gave low yields. Surprisingly CH_2Cl_2 gave a higher yield (25%, 40% e.e.) for a solid-liquid phase system than for the analogous liquid-liquid phase system (14%). Encouragingly with CH_2Cl_2 a lot of starting material remained at the end of reaction and if the reaction could be forced to completion the yield of THF diol **2.76** may be improved. An array of reactions were carried out looking at key parameters that would allow the oxidation of diene **2.75** to go to completion under solid-liquid phase-transfer conditions (Table 2.2).

Altered Reaction Condition	**Yield of THF diol 2.76 (%)**
None	25
AcOH - 4 equivalents	32
AcOH - 6 equivalents	**38**
CPTC **2.72** – 100 mol%	13
$KMnO_4$(s) – 3 equivalents	20
[Diene **2.75**] – 0.04 mmol/mL	16

Reagents and conditions: [Diene **2.75**] 0.12 mmol/mL, $KMnO_4$ (1.5 eq), CPTC **2.72** (30mol%), AcOH (2.25 eq), CH_2Cl_2, 0°C.

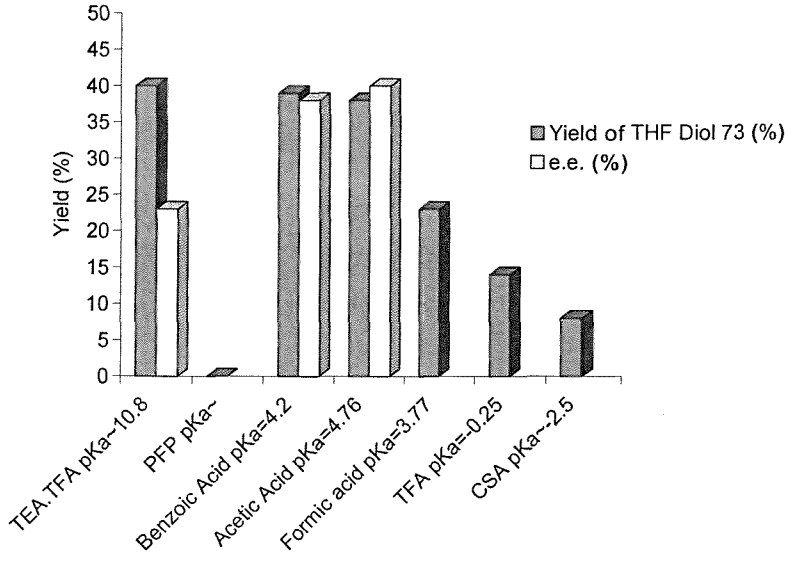
*Table 2.2. Effect of changing parameters for the solid-liquid chiral phase-transfer catalysed oxidation of diene **2.75**.*

Far from increasing the yield of desired THF diol **2.76**, increasing the amount of permanganate or CPTC **2.72** was detrimental to the yield. Carrying out the reaction at a higher dilution also gave a lower yield. However increasing the number of equivalents of acetic acid from 2.25 to 6 resulted in the starting material being consumed and an increase of yield from 13% to 38%. The reason for the increased

yield of THF diol **2.76** was not clear, but it could be due to a complex containing phase-transfer catalyst being formed in the relatively anhydrous conditions of the reaction mixture that was broken up in the presence of excess acetic acid. To test the theory, acetic acid was added slowly to a mixture of the remaining reagents (including permanganate). It was envisaged that as acetic acid was added disassociation of the complex would occur. If CPTC **2.72** was not held in a complex and continued to transfer permanganate into the organic phase, oxidation of diene **2.75** would continue in the absence of acetic acid which would be expected to be detrimental to the yield of THF diol **2.76**. The yield of **2.76** was poor (22%), therefore it remained unclear the reasons for such improvements in yield with increasing acid concentration. The Subsequent reactions were carried out using 6 equivalents of acid.

Effect of Various Proton Sources

The only acid that so far had been considered was acetic acid. A number of alternative proton sources were chosen as alternatives to acetic acid with varying pKa's (Graph 2.9).



Reagents and Conditions: $KMnO_4$(s) (1.5 eq), CPTC **2.72** (30 mol%), CH_2Cl_2, 0°C.

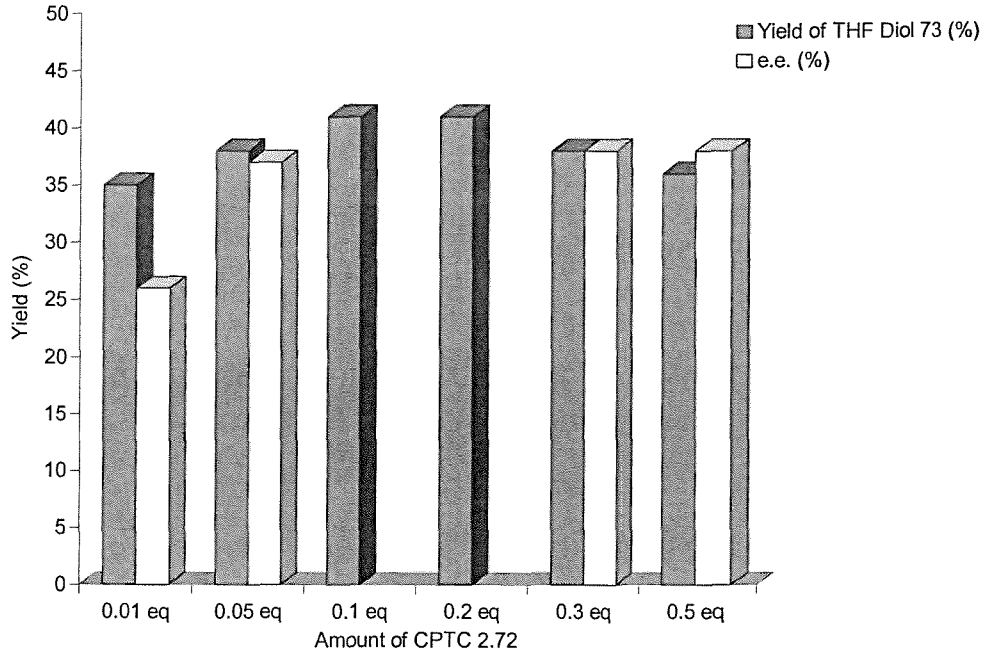
Graph 2.9. Effect of various proton sources on oxidation of diene ***2.76****.*

No product was observed with pentafluorophenol (PFP), but with triethylammonium triflouroacetate (TEA.TFA) and benzoic acid the yields were comparable with acetic acid (~40%). As pKa of the proton source decreased so the yield of THF diol **2.76**

dropped. THF diol **2.76** was isolated from the reactions with triethylammonium triflouroacetate (TEA.TFA) and benzoic acid. It was found that the enantiomeric excess was similar to acetic acid for benzoic acid, however with triethylammonium triflouroacetate (TEA.TFA) the asymmetric induction dropped to 23%, possibly because the triethylammonium salt was a competing achiral phase-transfer reagent.

*Effect of Stoichiometry of Chiral Phase-Transfer Catalyst (CPTC) **2.72***

The permanganate promoted oxidative cyclisation of 1,5-diene **2.75** had been shown to give enantiomerically enriched THF diol **2.76** in moderate yield under catalytic chiral-phase-transfer conditions. Until this point 30 mol% of CPTC **2.72** was used for the oxidations, however the catalyst is relatively costly to prepare and the amount used in the reaction should be kept to a minimum. An array of reactions were performed to establish the lower limit of CPTC **2.72** necessary to maintain the yield and enantiomeric excess of THF diol **2.76** (Graph 2.10).



Reagents and Conditions: $KMnO_4$(s) (1.5 eq), AcOH (6 eq), CH_2Cl_2, 0°C.

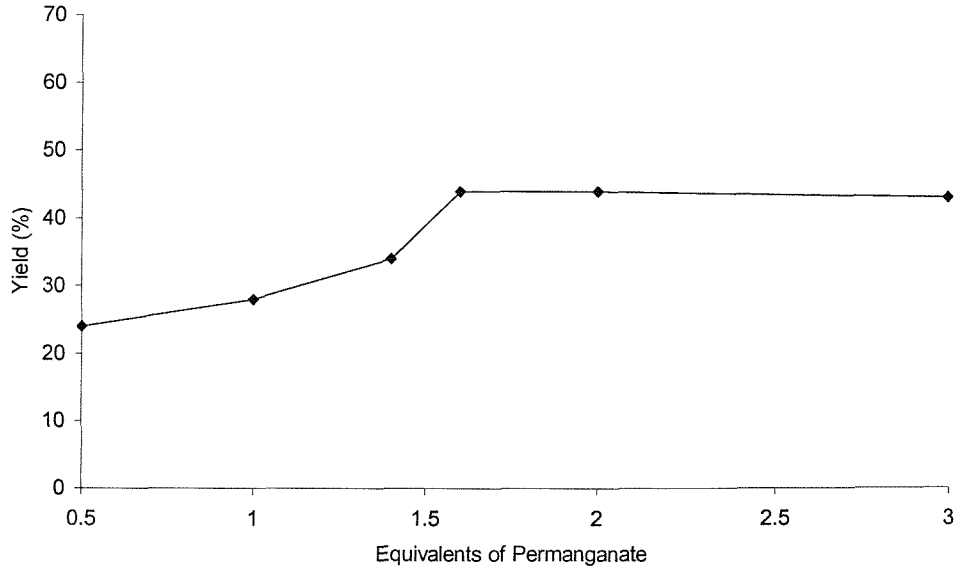
*Graph 2.10. Yield and e.e. of THF diol **2.76** with decreasing amounts of CPTC **2.72**.*

The yields of THF diol **2.76** were consistent even down to 1 mol% of catalyst, however there was a marked drop in e.e. between 5 and 1 mol% of CPTC **2.72**. The

yield and asymmetric induction was reasonable down to 5 mol% however to keep within a comfort zone 10 mol% of CPTC **2.72** was used in subsequent reactions.

Effect of Permanganate Stoichiometry

The stoichiometry of permanganate had previously been partially optimised in a liquid-liquid phase-transfer system, but it was deemed necessary to validate the stoichiometry of permanganate in a solid-liquid phase-transfer system. Previously the stoichiometry of permanganate was optimised whilst maintaining a 2:3 ratio between permanganate and acetic acid. Later this was found to be far from optimum and a ratio of 1:4 gave much improved yields. However, in the series of experiments illustrated in Graph 2.11 the amount of permanganate was varied whilst acetic acid concentration was kept at 6 equivalents with respect to diene **2.75**.



Reagents and Conditions: $KMnO_4$(s), CPTC **2.72** (10 mol%), AcOH (6 eq), CH_2Cl_2, 0°C.

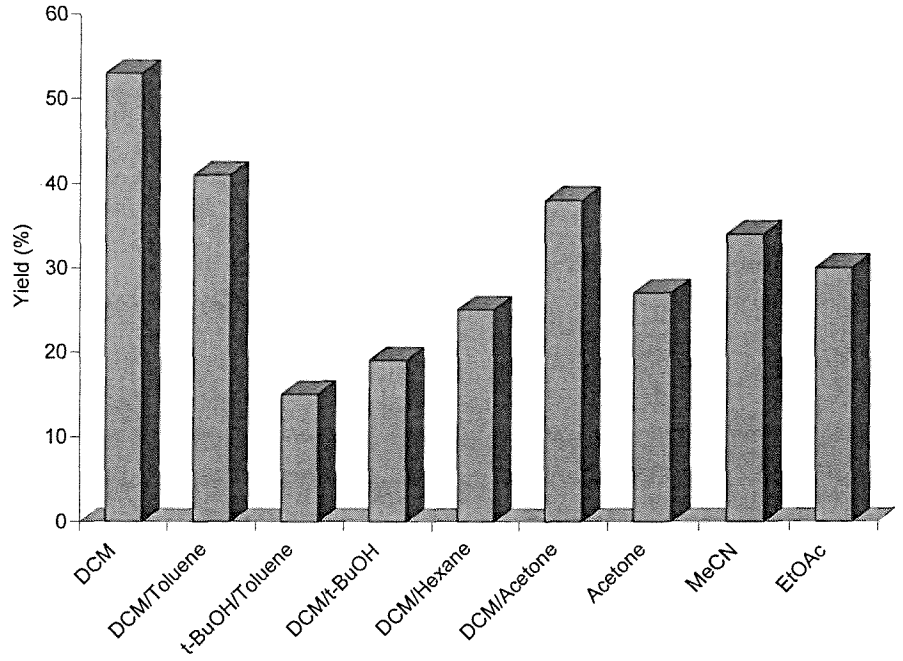
Graph 2.11. Effect of permanganate stoichiometry on the yield of THF diol ***2.76****.*

At half an equivalent of permanganate the yield of THF diol **2.76** went down to 24% and as the equivalents of permanganate increased so the yield of **2.76** increased, up to 1.6 equivalents (44%). Excess permanganate was not detrimental, as the yields of **2.76** using 1.6 and 3 equivalents of permanganate were identical. Contrary to this finding, when THF diol **2.76** was resubjected to the oxidation conditions, over the same reaction time (1 hour), 76% of **2.76** was recovered, suggesting that the product does

degrade under the reaction conditions. A single experiment was carried out with 1.6 equivalents of permanganate and 6.5 equivalents of acetic acid, thus re-establishing ~1:4 relationship between permanganate and acetic acid, and the yield of THF diol **2.76** improved to 53%.

Further Work with Solvents Using Optimised Conditions

Modified conditions had already led to improved yields of THF diol **2.76** from 13% to 53% whilst retaining the level of asymmetric induction. The yields in other solvent systems using the modified conditions were considered, and a range of single and dual solvent systems were utilised in an array of oxidations of diene **2.75** (Graph 2.12).



Reagents and Conditions: $KMnO_4$(s) (1.6 eq), CPTC **2.72** (10 mol%), AcOH (6.5 eq), 0°C.

*Graph 2.12. Effect of different solvent systems on the chiral phase-transfer oxidation of diene **2.75**.*

In summary, the yields of **2.76** were disappointing and no improvements were observed for the other solvent systems compared to CH_2Cl_2. However, the CH_2Cl_2 /toluene mixed solvent system gave a reasonable yield (41%) with a lot of starting material left unreacted. Further work is advised on the mixed CH_2Cl_2/toluene solvent system which may offer improved yields should the reaction be pushed to completion,

then varying CH_2Cl_2 and toluene ratios may also lead to improvements in yield and or enantiomeric excess.

Optimised conditions for the solid-liquid chiral phase-transfer permanganate oxidative cyclisation of diene **2.75** have been established, where the yield of THF diol **2.76** has been improved from 13% to 53%. The asymmetric induction however was not improved during the optimisation work.

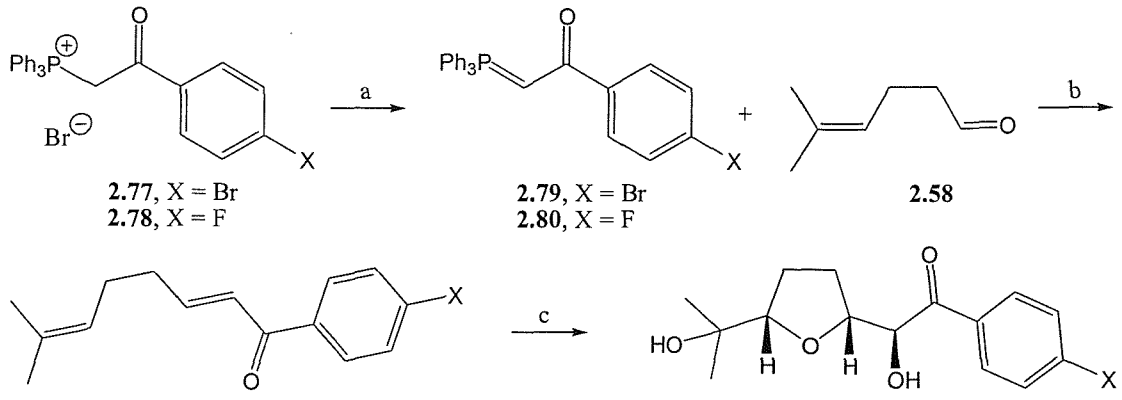
Assymetric Oxidative Cyclisations at Low Temperatures

Ion pair formation between permanganate and CPTC **2.72**, and binding of the substrate diene to CPTC **2.72** are vital to ensure good asymmetric induction. As these are both entropically disfavoured processes, a reduction in the temperature of the reaction should facilitate tighter binding of permanganate and 1,5-diene with CPTC **2.72**. The oxidation of diene **2.75** was performed at –30°C under the previously optimised conditions. THF diol **2.76** was isolated by chromatography in moderate yield (47%), and chiral HPLC determined that the enantiomeric excess increased to 58%.

Effects of Phenyl Ring Substitution on the Oxidative Cyclisation

Corey *et al.* reported small improvements in asymmetric induction were observed in the nucleophilic epoxidation of α,β-substituted phenones when the phenyl ring was substituted with an electronegative substituent, i.e. -F, -Oalkyl.[116] Dienes **2.81** and **2.82** (Scheme 2.29) were prepared in order to look at the effect of substitution of the phenyl ring on the enantiomeric enrichment of the resulting THF diols **2.83** and **2.84** respectively.

Phosphonium salts **2.77** and **2.78** were precipitated from a solution of triphenylphosphine and commercially available phenacylbromides in CH_2Cl_2/hexane (2:5) in high yield (99 and 89% respectively). Phosphoranes **2.79** and **2.80**, which were prepared by deprotonation with hydroxide, were stirred with aldehyde **2.58** for 4 days leading to the isolation of dienes **2.81** and **2.82** in reasonable yields (Scheme 2.29). GC and GC/MS showed that dienes **2.81** and **2.82** were a mixture of *cis* and *trans* isomers (1:15 and 1:19 respectively) though they were sufficeiently pure enough to be used in the oxidative cyclisation.



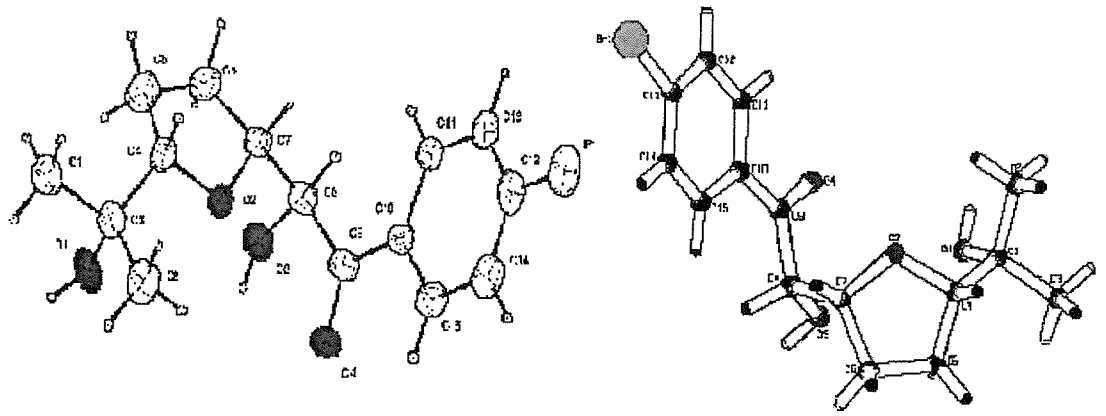
Reagents and Conditions: (a) 1M NaOH(aq), CH_2Cl_2; (b) CH_2Cl_2, 4 days; (c) $KMnO_4$(s) (1.6 eq), CPTC **2.72** (10 mol%), AcOH (6.5 eq), CH_2Cl_2, -40°C, 4 h.

Scheme 2.29. Preparation and asymmetric oxidative cyclisation of dienes 74 and 75.

Oxidative cyclisation of fluoro-substituted diene **2.82** gave THF diol **2.84** in comparable yield to unsubstituted phenone diene **2.76**, but encouragingly the e.e. increased to 72%. That could have been partly due to the reaction being carried out at –40°C compared to –30°C for the oxidation of diene **2.76**. The e.e. increased from 38 to 58% with a drop in reaction temperature of 30°C, it seems unlikely that a further drop of 10°C would account for an increase from 58 to 72% e.e.. Therefore it was concluded that fluoride substitution was responsible for an improvement in the asymmetric induction.

Oxidative cyclisation of bromo-substituted diene **2.81** gave THF diol **2.83** in a much lower yield but a slightly improved e.e. (75%). Once again the change in substituent on the phenyl ring resulted in a change in enantioselectivity. The poor yield must have been due to the presence of the bromide substituent, but how it came about is not immediately explicable.

Both THF diols **2.83** and **2.84** were isolated as crystalline solids, which were recrystallised from ethanol/hexane to give crystals from which structures could be determined by X-ray crystallography (Figure 2.3).[142,143]



2.83 **2.84**

*Figure 2.3. Crystal structures of THF diols **2.83** and **2.84**.*

It should be noted that both structures were isolated from enantiomerically enriched samples, however whilst the crystal of THF diol **2.83** was of a single enantiomer, the crystal of THF diol **2.84** was racemic. The presence of a heavey atom on THF diol **2.83**, and the fact the crystal was of a single enantiomer allowed the absolute stereochemistry to be established. However the crystal was recrystallised from an enantiomerically enriched sample and it was not confirmed that it corresponded with the major enantiomer of the mixture. To confirm this result it would be worthwhile determining the structure of a crystal recovered from a enantiomerically pure sample of THF diol **2.83**. However the crystal structure of **2.83** is consistent with the expected facial attack observed in asymmetric epoxidations using CPTC **2.72** (Section 2.3, Scheme 2.13).[115,107,114,116]

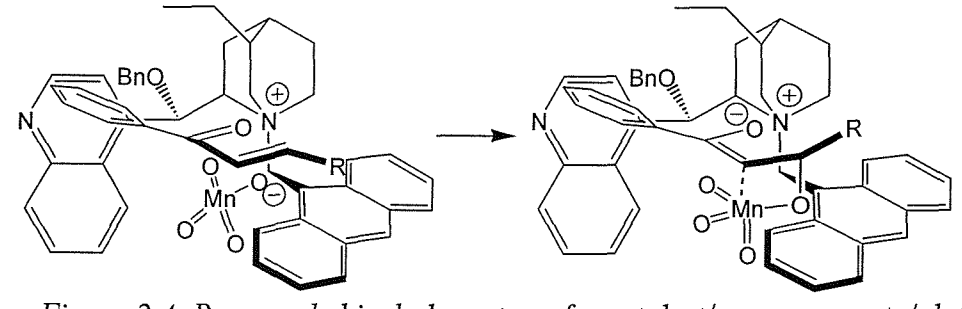


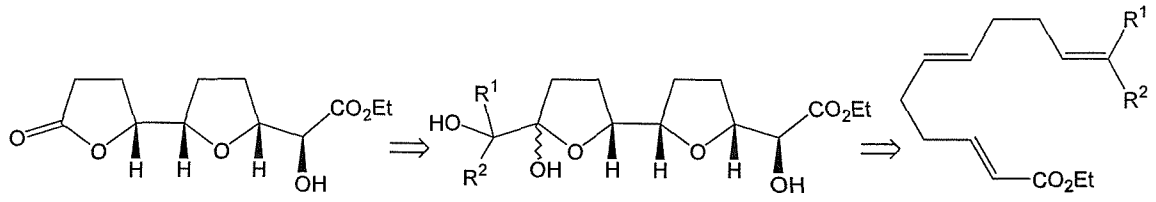
Figure 2.4. Proposed chiral phase-transfer catalyst/permanganate/olefin complex

In the proposed intermediate is shown (Figure 2.4), where the permanganate ion is held in an asymmetric environment. The phenyl group of the phenone is proposed to interact *via* an orthogonal π–π interaction, meanwhile the anthracene blocks the bottom face of the permanganate complex, this ensures that permanganate attack on the α,β-unsaturated olefin is directed to the lower face of the phenone-1,5-diene. Lee alludes to an electron rich transition state in the oxidation of α,β-unsaturated esters with permanganate that is stabilised by electrostatic interaction with the phase-transfer

catalyst,[99] which is depicted by the enolate intermediate in Figure 2.4 adjacent to the quaternary ammonium centre. This is a highly polarised view of the transition state, it is likely there will be a partial interaction between the manganese and α-carbon.

2.7 Permanganate Oxidations of 1,5,9-Trienes: Towards the Synthesis of Annonaceous Acetogenins

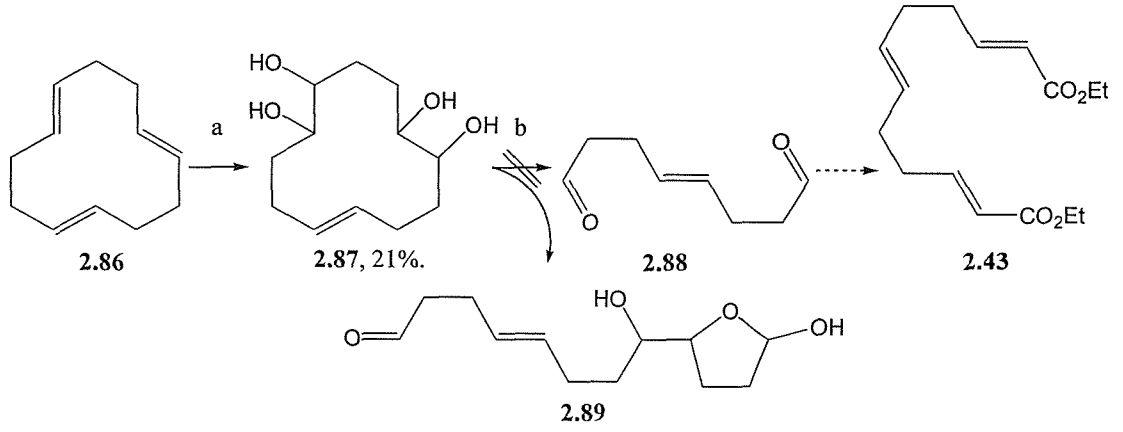
Lactone **2.41** had been identified as a key intermediate for the synthesis of *cis*-THF containing Annonaceous acetogenins. The permanganate oxidative cyclisation of 1,5,9-trienes (**2.42** and **2.43**) followed by the diol cleavage, in lactol **2.85**, was seen as a short diastereoselective route to lactone **2.41**.



Scheme 2.31. Preparation of intermediate ***2.41*** *in Annonaceous acetogenin synthesis.*

Synthesis and Oxidation of 1,5,9-Triene 2.43

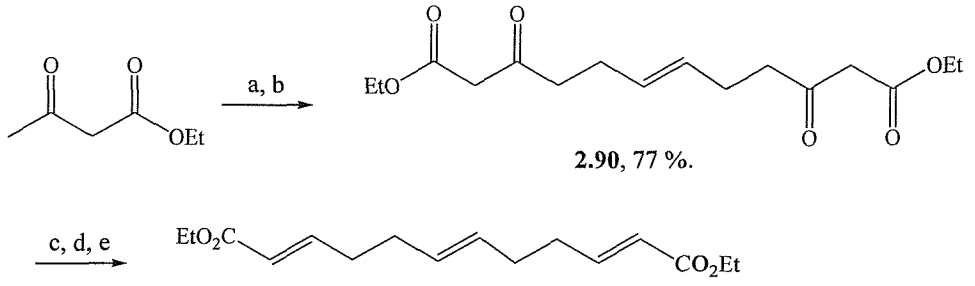
Diester triene **2.43** offered a possible advantage over triene **2.42**. The major side reaction typically observed in the permanganate oxidative cyclisation is α-ketol formation. In the case of substrate **2.43**, side reaction to produce an α-ketol in one of the enoate double bonds would provide an intermediate which could still undergo oxidative cyclisation to the desired product. In the case of **2.42** this would not be possible. Triene **2.43** is also desymmetrised during the reaction.



Reagents and Conditions: (a) cat. OsO_4, $K_3Fe(CN)_6$, t-BuOH, water; (**b**) $NaIO_4$(aq) (2 eq), acetone.

Scheme 2.32. Attempted preparation of triene ***2.43****.*

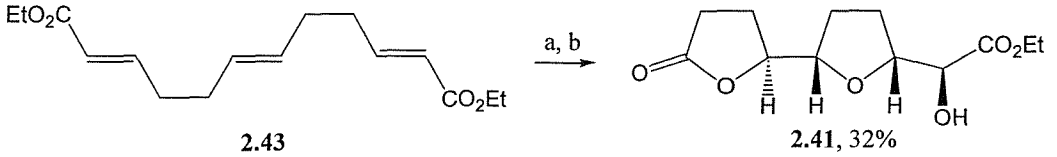
Dialdehyde **2.88** was identified as an intermediate from which triene **2.43** could be prepared, *via* a double Wittig olefination. A synthesis of dialdehyde **2.88**, *via* a route previously reported by Hoye and Ye, was started from 1,5,9-*cis*,*cis*,*cis*-cyclododecatriene, unfortunately no experimental detail was given (Scheme 2.32).[144] The double dihydroxylation gave a poor yield (22%), due to isolation problems of the tetraol (high aqueous solubility). Unfortunately no product was isolated from periodate promoted diol cleavage. The failure of the reaction was possibly due to the formation of lactol **2.89**, which would be formed after the first diol cleavage, inhibiting the second cleavage.



Reagents and Conditions: (a) LDA (2 eq), THF; (b) 1,4-dibromobut-2-ene (0.5 eq); (c) $NaBH_4$ (2 eq), MeOH; (d) $MeSO_2Cl$ (2 eq), Et_3N (2 eq), CH_2Cl_2, 0°C; (e) DBU (2 eq), CH_2Cl_2.

Scheme 2.33. Synthesis of triene ***2.43****.*

An alternative procedure by Hoye *et al.* was used to prepare triene **2.43** in 25% overall yield (Scheme 13).[145] The dianion of ethyl acetoacetate was used to dialkylate (*E*)-1,4-dibromobut-2-ene to give diketone **2.90** in 77% yield. The diketone was reduced with sodium borohydride then the diol was mesylated and the elimination was facilitated by DBU to give exclusively the two α,β-unsaturated esters with *trans* geometry. The yield for the borohydride reduction was poor due to transesterification with methanol, the yield would have been better had ethanol been used for the reduction.

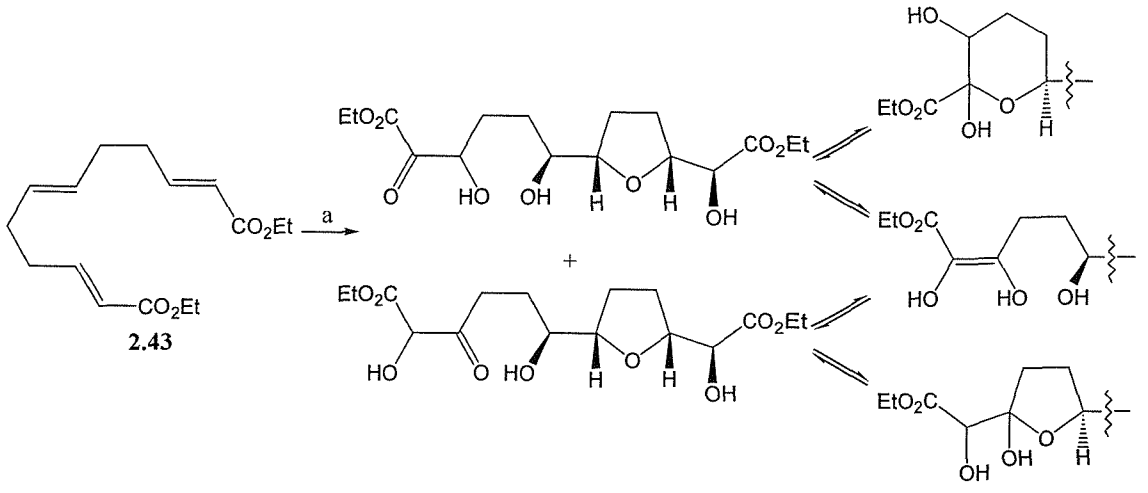


Reagents and Conditions: (a) 0.4M $KMnO_4$(aq) (3 eq), AcOH (4 eq), phosphate buffer pH 6.2, acetone, water, -20°C; (b) $NaIO_4$(aq), acetone.

Scheme 2.34. Two step synthesis of lactone ***2.41*** *from triene* ***2.43****.*

The oxidative cyclisation of triene **2.43** gave predominantly one product by TLC, however the ^1H NMR spectrum was very complex. On further purification the

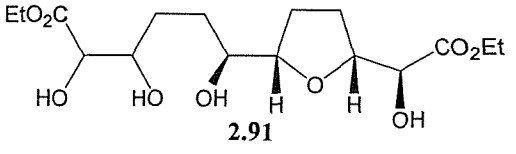
spectrum of the mixture did not get any simpler, therefore the periodate cleavage was carried out on the mixture to give the expected lactone **2.41**, in 32% yield.



Reagents and Conditions: (a) 0.4M $KMnO_4$(aq) (3 eq), AcOH (4 eq), buffer pH 6.2, acetone/water, -20°C.

Scheme 2.35. Equilibration of the product of oxidative cyclisation of triene ***2.43****.*

The complex mixture that resulted from oxidative cyclisation of triene **2.43** was likely to be due to the conversion of the two possible α-hydroxy ketones into a number of products (Scheme 2.35). The α-keto-β-hydroxy ester will cyclise to the δ-lactol, whilst α-hydroxy-β-keto ester will cyclise to the γ-lactol. The mixture is further complicated by the inter-conversion of α-keto-β-hydroxy ester and α-hydroxy-β-keto ester *via* a 1,2-dihydroxyolefin. The ^{13}C NMR spectrum was consistent with a mixture of diastereoisomers of lactol peaks at 107 and 108 ppm and the presence of an α-hydroxyketone ketone at 202 ppm. Encouragingly ESI/MS gave the appropriate peaks for M+Na, M+K, and 2M+Na that corresponded to the molecular weight of all the possible products in Scheme 2.35.



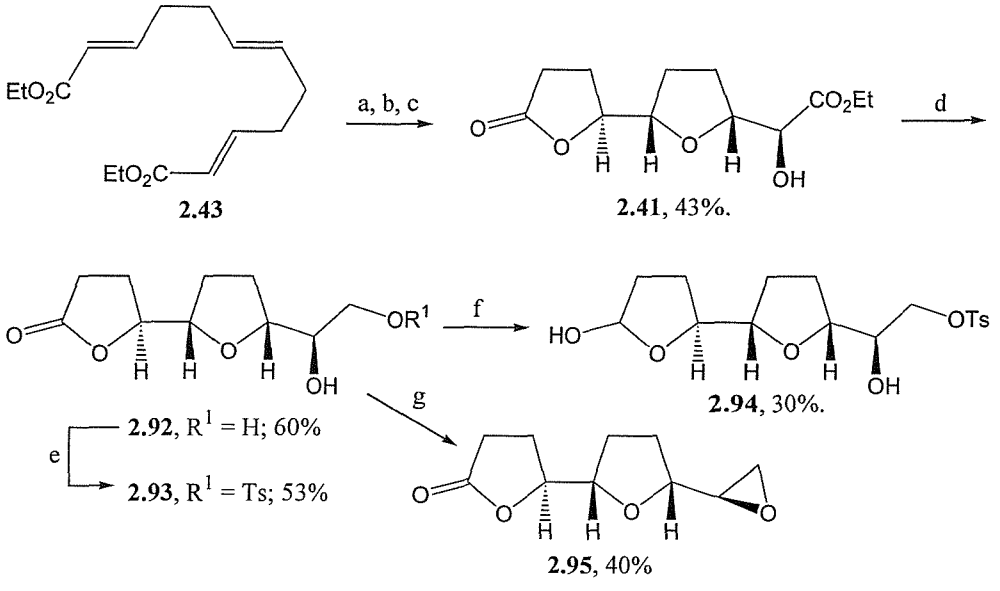
2.91

Figure 2.4. Tetraol ***2.91*** *product from oxidative cyclisation of triene* ***2.43****.*

Two other products were isolated from the permanganate oxidation mixture, tetraol **2.91** (7%) and lactone **2.41** (10 %). The tetraol **2.91** was associated with an oxidative cyclisation followed by dihydroxylation of the remaining double bond. The most surprising result from this experiment was the isolation of lactone **2.41** from the oxidative cyclisation of triene **2.43**. Lactone **2.41** was thought to have arisen due to further permanganate oxidation of the 1,2-dihydroxyolefin intermediate (Scheme 2.35). The oxidation of a 1,2-dihydroxyolefin intermediate was also proposed to

explain the absence of α-hydroxyketone products from the oxidation of ethyl ester diene **2.59**.

An attempt was made to improve the yield for the preparation of lactone **2.41** in one step by phase-transfer oxidative cyclisation using a large excess of permanganate (10 equivalents), ensuring the oxidative cyclisation/cleavage went to completion. The yield of lactone was 32%, compared to 43% for the two step procedure. Although the yield was modest the synthetic sequence has proved a rapid route to intermediate lactone **2.41**.



Reagents and conditions: (a) $KMnO_4$, AcOH, phosphate buffer, acetone; (b) $NaIO_4$, acetone/water; (c) *p*-TsOH, CH_2Cl_2; (d) $BH_3.Me_2S$, $NaBH_4$, THF; (e) TsCl, Et_3N, CH_2Cl_2; (f) DIBALH, THF, -78°C; (g) $CuBr.Me_2S$, *n*-BuLi in hexanes, ether.

Scheme 2.36. Steps on route to synthesis of cis-THF Annonaceous acetogenins.

The yield of lactone **2.41** was improved further for the two step synthesis (oxidative cyclisation/diol cleavage) by treating the crude mixture, after the diol cleavage, with *p*-toluenesulphonic acid in CH_2Cl_2. Any γ-hydroxycarboxylic acid remaining in the reaction mixture, which would otherwise be removed on work up, was lactonised on addition of acid, therefore increasing the yield by 11% to 43%.

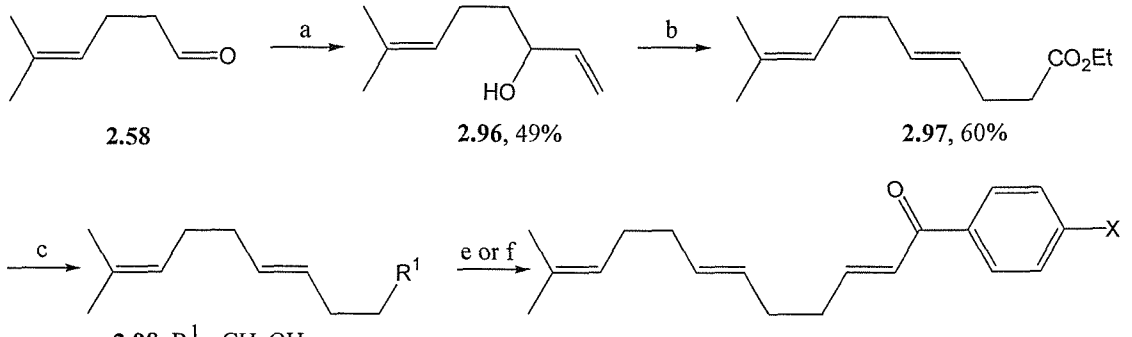
In order to take the synthesis further the lactone and α-hydroxy ester had to be selectively manipulated. It has been reported that $BH_3.Me_2S$ with $NaBH_4$ selectively reduces α-hydroxy esters to 1,2-diols.[146] Diol **2.92** was prepared using this reaction but the yield was low (60%) and the product was difficult to isolate from a close running impurity. The tosylation of the primary alcohol to give tosylate **2.93** did not go to completion and therefore went in disappointing yield (53%), however excess tosyl chloride and DMAP should push the reaction to completion and increase the

yield. Attempted cuprate ($LiCuBu_2$) addition to tosylate **2.93** gave none of the desired alkylation product, but epoxide **2.95**, which was the expected intermediate of the reaction, was isolated and characterised.

An alternative approach was to reduce the γ-lactone to a γ-lactol with DIBAL. Unfortunately the reduction of the lactone **2.92** to lactol **2.94** proceeded in low yield (30%). The synthesis of late stage intermediate **2.95** is significant since it has functionality that allows the side chains to be sequentially installed, however the yields of the previous four steps have to be improved. Due to time constraints and focusing efforts on the chiral phase-transfer chemistry we did not pursue this further.

Synthesis and Oxidation of 1,5,9-Trienes 2.99 and 2.100

With a view to producing enantiomerically enriched lactone **2.41**, the asymmetric oxidation of 1,5,9-trienes **2.99** and **2.100** were considered. Initially we looked at the synthesis of trienes **2.99** and **2.100** then assessed the asymmetric induction for the chiral phase-transfer oxidative cyclisation of these trienes.

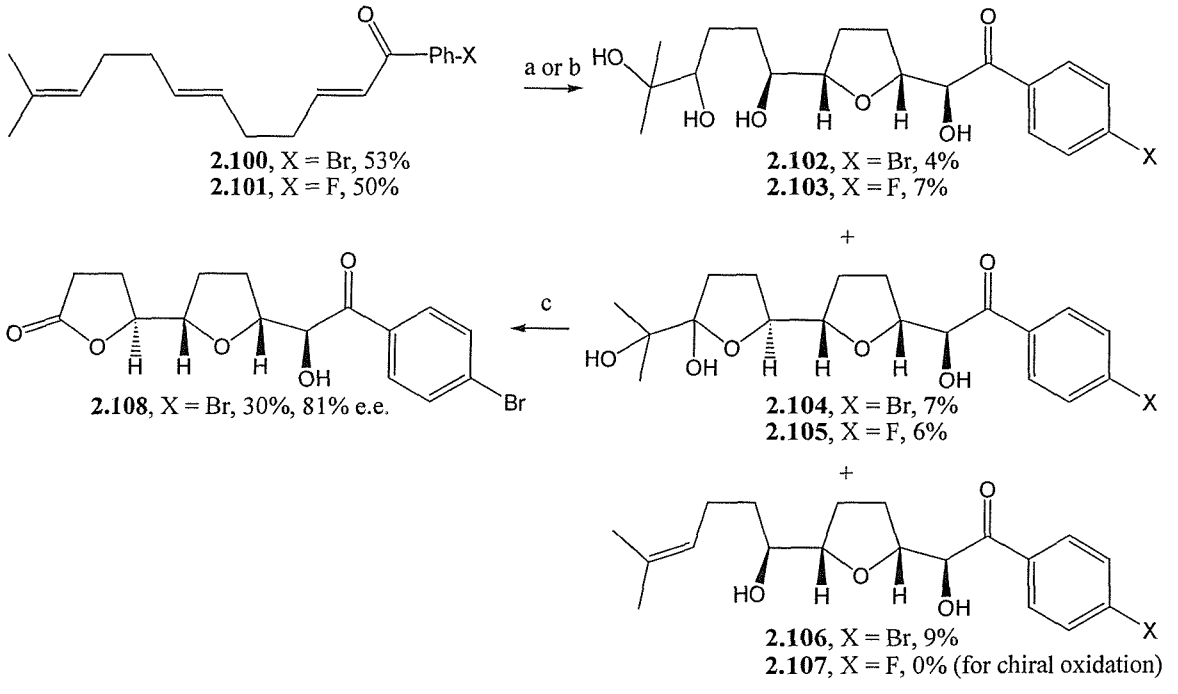


Reagents and Conditions: (a) Vinylmagnesium bromide, THF, -15°C; (b) $CH_3C(OEt)_3$, propanoic acid, xylene, reflux; (c) $LiAlH_4$, THF; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -70°C to RT; (e) 4-BrPhCOCHPPh$_3$, toluene, 19 h; (f) 4-FPhCOCH$_2$P(O)(OEt)$_2$, K_2CO_3, THF, reflux, 4 h.

Scheme 2.37. Synthesis of trienes 2.99 and 2.100.

A literature procedure was used to prepare diene **2.97** from aldehyde **2.58**.[134] The conversion to allylic alcohol **2.96** from aldehyde **2.58** was reasonably clean by TLC analysis however decomposition of the product on distillation led to a poor yield (49%). The Claisen-Johnson rearrangement gave clean conversion to 1,5-diene **2.97**, however due to the volatility of the product some material was lost on evaporation of xylene, resulting in the modest yield (60%). Having prepared diene **2.97** the reduction ($LiAlH_4$) and oxidation sequence (Swern oxidation) went in high yield to give

aldehyde **2.99**. The brominated triene **2.100** was prepared *via* a Wittig olefination in moderate yield (50%, *cis*:*trans* 14:1), unfortunately the purification was very arduous (prep HPLC). Due to the problems associated with purification, the Wittig olefination was rejected for the synthesis of triene **2.101**, with 4-fluorophenone, in favour of the Horner-Emmons olefination. The diethylphosphonate was prepared from the commercially available 2-bromo-4'-fluoroacetophenone and triethylphosphite, i.e. the Arbuzov reaction,[147] in low yield (24%). From GC analysis of triene **2.101**, obtained from the Horner-Emmons reaction, it was unclear whether any of the *cis*-olefin was generated, however ^{1}H NMR spectrum showed no trace of the *cis*-isomer.



Reagents and Conditions: (a) $KMnO_4$(s) (4 eq), Adogen 464 (10 mol%), AcOH (12 eq), CH_2Cl_2; (b) $Pb(OAc)_4$, NaOAc, CH_2Cl_2; (b) $KMnO_4$(s) (4 eq), CPTC **2.72** (10 mol%), AcOH (12 eq), CH_2Cl_2; (c) $Pb(OAc)_4$, NaOAc, CH_2Cl_2.

*Scheme 2.38. Oxidations of trienes **2.99** and **2.100**.*

The oxidation of triene **2.100** was carried out under achiral and chiral phase-transfer conditions. From the achiral phase-transfer oxidation, using Adogen 464 (10 mol%), three products were isolated, albeit in low yields. The desired product, lactol **2.104**, was isolated in a very disappointing yield (7%), however having been characterised lactol **2.104** was subjected to oxidative cleavage of the diol ($Pb(OAc)_4$) to give lactone **2.108**, in poor yield (30%). The other products of oxidation were THF diol **2.106** (9%) with the olefin intact and tetraol **2.102** that was the product of oxidative cyclisation followed by dihydroxylation. Compound **2.102** was fully characterised, and the structures of **2.104**, **2.108** and **2.106** were elucidated by ^{1}H and ^{13}C NMR spectroscopy

and mass spectrometry. The yield of lactol **2.104** was not established for the chiral phase-transfer oxidation, but was of the same order as the achiral phase-transfer oxidation. Having oxidatively cleaved the diol of lactol **2.104**, the lactone was isolated. With both the racemic and enantiomerically enriched samples of lactone **2.108**, it was possible, using chiral HPLC to establish the asymmetric induction for the chiral phase-transfer catalysed oxidative cyclisation (81% e.e.).

The oxidative cyclisation of triene **2.100** mirrored the poor yield observed for the oxidative cyclisation of the analogous diene **2.81** (26%). The bromophenone moiety appears quite unstable to permanganate oxidations, so the fluorophenone analogue, triene **2.101**, was investigated (Scheme 2.38). Under achiral phase-transfer oxidation conditions TLC analysis of the reaction mixture after 3 hours, showed that triene **2.101** had been consumed. The products of the fluorophenone series appear to have very similar Rf values to those of the bromophenone series. With this in mind the major product in the reaction mixture was not lactol **2.105**, but THF diol **2.107** with an olefin intact. The major product was also the only product on the TLC plate to stain in $KMnO_4$, which was consistent with the presence of an olefin. Another batch of $KMnO_4$ (3 eq) and acetic acid (12 eq) was added to the reaction mixture to oxidise the final double bond to give lactol **2.105**, which was characterised by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. Unfortunately it appeared that the relative reactivities of the olefin and the fluorophenone moiety to permanganate oxidation were similar. So although oxidation of the final olefin in **2.107** was pushed to completion the yield of the resulting lactol **2.105** was low (6%).

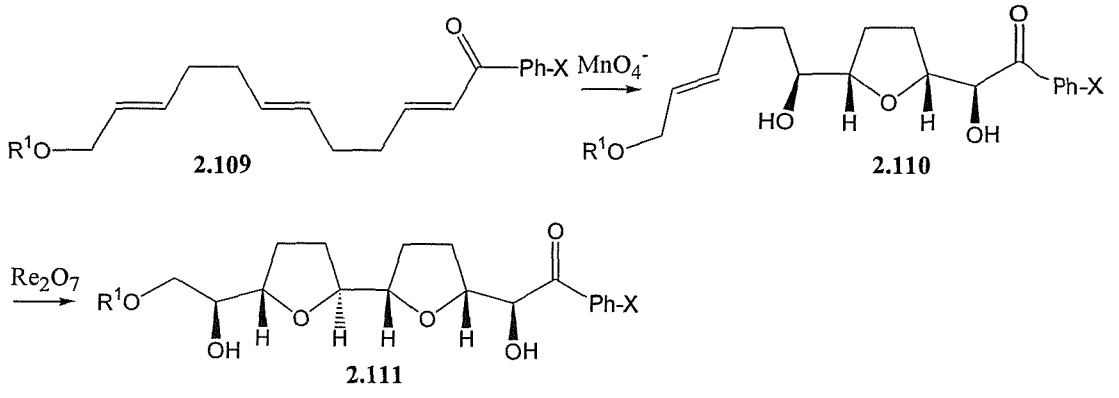
Conclusion

In conclusion, the oxidative cyclisation of symmetrical diester triene **2.43**, was carried out and preparation of lactone **2.41**, which is a key intermediate in the proposed synthesis of Annonaceous acetogenins, was successfully achieved in one (directly from oxidative cyclisation) and in two steps (oxidative cyclisation/diol cleavage) in 32 and 43% respectively. Further elaboration on lactone **2.41** was carried out towards the synthesis of Annonaceous acetogenins, albeit in yields that require further optimisation.

Bromo and fluorophenone trienes **2.100** and **2.101** were also prepared *via* a five step synthesis that with care should prove to be high yielding. The oxidations of trienes **2.100** and **2.101** gave disappointing yields of lactols **2.104** and **2.105** due to the instability of the phenone moiety to permanganate. However in the relatively low reactivity of the third olefin could well be exploited in further work.

Further Work

Following on from the observations made during the oxidative cyclisation an interesting route to Annonaceous acetogenins has emerged. The oxidative cyclisation of triene **2.101**, by TLC analysis, appeared to go to completion whilst the final olefin was more or less left in tact. By reducing the reactivity of the final olefin further, i.e. introduction of an allylic oxygen (triene **2.109**), oxidation of the olefin during the oxidative cyclisation can be minimised (Scheme 2.39). The resulting THF diol **2.110** could then be subjected to rhenium oxidative cyclisation to yield a cis, trans-octahydrobifuran diol **2.111**. The two ends can then be manipulated separately to allow the attachment of the side arms of acetogenins. The synthetic route would thus be an elegant route into the important *cis,trans*-bis-THF Annonaceous acetogenins.

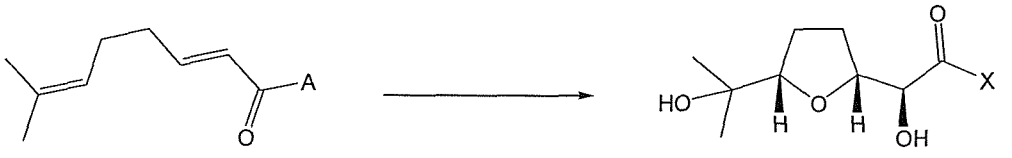


Scheme 2.39. Proposed route to key intermediate in synthesis of cis,trans-bis-THF Annonaceous acetogenins

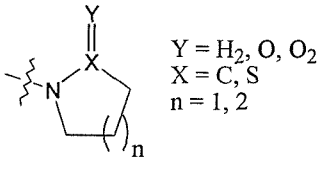
Further development of the oxidative cyclisation of 1,5-dienes can be looked at in three areas. More work could be carried out investigating the system that has been developed with CPTC **2.72** and phenone diene **2.75**. A replacement for the phenone moiety, which some cases is unstable to permanganate, could be found. Alternative phase-transfer catalysts may give better results than cinchonidine based catalysts.

From the optimisation work carried out on the chiral phase-transfer oxidation of 1,5-diene **2.75**, the most interesting observation that was not exploited came in the solid-liquid phase-transfer catalysed oxidation performed in a toluene/CH_2Cl_2 system. A brief optimisation of this system may well provide improved yields and e.e.'s.

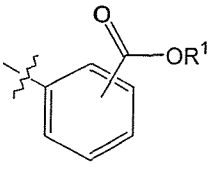
Changing phenyl substitution of the α,β-unsaturated carbonyl group to an unsaturated cyclic system may offer advantages in further manipulation of the resulting THF diol as well potentially improved e.e.'s. A urethane or acylsulphonamide system would allow for easier selective manipulation in Annonaceous acetogenins synthesis and also potentially offer a further interaction with CPTC **2.72** that may improve asymmetric induction (Scheme 2.40). Substitution of the phenone moiety with a ester/carboxylic acid may also allow for further interactions between CPTC and 1,5-diene substrate that should improve yields.



Alternative substituents off carbonyl group (A):



$Y = H_2, O, O_2$
$X = C, S$
$n = 1, 2$



Scheme 2.40. Further substituents for the oxidative cyclisation of 1,5-dienes.

Lastly the chiral phase-transfer catalyst itself may be improved by looking to improve the catalysts solubility in solvents that have shown in other chiral phase-transfer reactions to give high asymmetric induction, e.g. toluene. Inspite of the good results from this work using CPTC **2.72**, derived from cinchonidine, other phase-transfer catalysts may be more appropriate. For example (-)-ephedrine derivatives were used successfully to give modest e.e.'s (37%) for the nucleophilic epoxidation of phenones.[111]

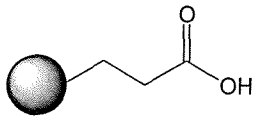
Chapter 3: Experimental

General Methods

^{1}H NMR and ^{13} C NMR were recorded on 300 MHz (Bruker AC300 or Bruker AM300) and 400 MHz (Bruker DPX400) spectrometers (300 and 400 MHz, ^{1}H NMR respectively and 75 and 100 MHz, ^{13} C NMR respectively) in deuteriochloroform ($CDCl_3$) with chloroform (δ 7.27 ppm ^{1}H, δ 77.2 ppm ^{13}C) as the internal standard. Fourier transform infrared (FTIR) spectra were recorded on a Perkin-Elmer 1600 FT-IR instrument, a Bio-Rad FTS 135 instrument using a Golden Gate adaptor or a Nicolet Impact 400 instrument using a Thunderdome adaptor. Absorptions were recorded in wave numbers (cm^{-1}) and are described as strong (s), medium (m), weak (w) or broad (br). UV studies were carried out on a Perkin-Elmer Lambda 2 UV/VIS spectrophotometer or a Hewlett-Packard 8452A diode array spectrophotometer. Melting points were measured on a Gallenkamp electrothermal melting point apparatus and obtained in open capillary tubes and are uncorrected. All air or moisture sensitive reactions were carried out under an inert atmosphere, in oven-dried glassware. The following solvents were distilled before use: THF (from Na/benzophenone), CH_2Cl_2 (from CaH_2) and DMF (from CaH_2) , and where appropriate, other reagents and solvents were purified by standard techniques.[148] TLC was performed on aluminium plates coated with silica gel 60 with F_{254} indicator; the chromatograms were visualised under UV light (254 nm) and or by staining with 20% phosphomolybdic acid in ethanol, cerium sulphate/ammonium molybdate in 2 M sulphuric acid, Brady's reagent in ethanol or 0.4 M $KMnO_4$(aq). Bromocresol green (solution in ethanol basified with 2 M NaOH) indicator solution was used to test for the presents of carboxylic acid groups on polystyrene resin. Flash chromatography was performed with 40-63μm silica gel (Merck) for which the masses used are quoted. Reverse phase HPLC was carried out on a Hewlett Packard HP1090, analytical and chiral normal phase HPLC were carried out on a Hewlett Packard HP1050 and preparative HPLC was carried out on a Perkin-Elmer Series 3B Liquid Chromatograph. GC analysis was done out using a Varian 3800 fitted with an autosampler and a DB120 fused silica column (30 m x 0.52 mm) with helium as the

carrier gas and a flame ionisation detector from which data was collected *via* a Hewlett Packard 3396 Series II integrator.

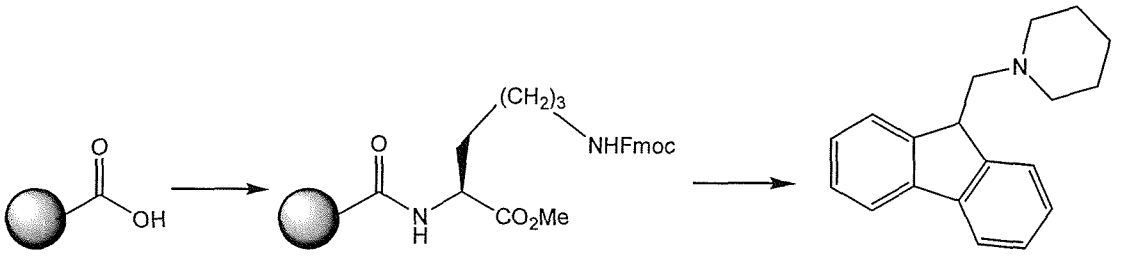
3.1 Carboxylic Acid Resin 1.74.



1.74

To a suspension of sodium hydride (60% dispersion in mineral oil, 1.32 g, 33.0 mmol) in anhydrous DMF (30 mL) under nitrogen was added diethylmalonate (5.28 g, 33.0 mmol) dropwise over 10 minutes. After 5 minutes Merrifield's resin [1% cross linked] (5.0 g, 5.0 mmol, 1.0 mmol/g) was added and the mixture was heated for 18 hours at 60°C. The resin was collected by filtration, then sequentially washed with DMF (20 mL), water (2 x 20 mL), THF (2 x 20 mL), MeOH (20 mL), CH_2Cl_2 (20 mL), Ether (20 mL) and dried under vacuum (10 mmHg, 50°C) to give the intermediate diethylmalonate resin **1.72** as a white solid (5.13 g): FTIR ν_{max} (on bead): 1735m, 1452m, 756m, 696s cm^{-1}. To a slurry of the resin in THF (100 mL) was added 2 M potassium hydroxide (10 mL, 20 mmol) and the mixture was refluxed for 24 hours. The resin was collected by filtration and sequentially washed with water (2 x 20 mL), THF (2 x 20 mL) and ether (2 x 20 mL). To the resin were added THF (100 mL) and 2M HCl (10 mL) and the mixture was refluxed for 2 hours. The resin was collected by filtration, then sequentially washed with water (2 x 20 mL), THF (2 x 20 mL), MeOH (20 mL), ether (2 x 20 mL) and dried under vacuum (10 mmHg, 50°C) to furnish the required product resin **1.74** as a white solid (4.98 g); spectroscopic details are consistent with those observed in the literature:[60] FTIR ν_{max} (on bead): 3025w, 2920m, 1716s, 1493s, 1452s, 753s, 697vs cm^{-1}.

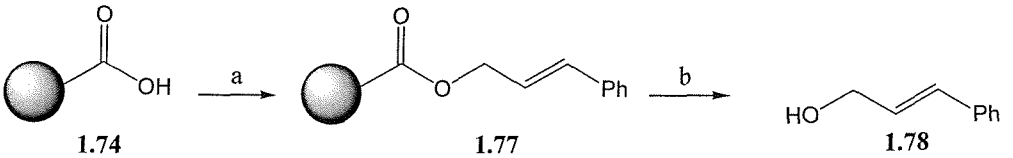
3.2 Resin 1.76 and Loading Determinations



1.74 **1.76** UV @ 302 nm

To a slurry of resin **1.74** (100 mg) in CH_2Cl_2 (1 mL) was added diisopropylcarbodiimide (38 mg, 0.30 mmol) and 1-hydroxybenzotriazole (41 mg, 0.30 mmol) and the slurry was stirred for 30 minutes. Fmoc-Lysine methyl ester hydrochloride (131 mg, 0.30 mmol) in N-methylpyrrolidinone (1 mL) was treated with diisopropylethylamine (39 mg, 0.30 mmol), the solution was added to the slurry and the reaction was stirred for 18 hours. The resin was collected by filtration, sequentially washed with DMF (2 x 3 mL), CH_2Cl_2 (6 x 3 mL), methanol (3 mL), ether (2 x 3 mL), and dried under vacuum (10 mmHg, 50°C) to give the desired product resin **1.76** as a white solid. Treating resin **1.76** with Bromocresol green indicated no free carboxylic acid sites. Half of the resin was retained for loading analysis, resin **1.76a**, and the coupling procedure was repeated on the other half of the resin to give a white solid, resin **1.76b**. FTIR ν_{max} (on bead): 3027w, 2920m, 1729s, 1682m, 1602w,1512w, 1492m, 1451s, 741m, 698vs cm^{-1}. Resins **1.76 a** and **b** (5-8 mg) were treated separately with 20% piperidine in DMF (10 mL) in volumetric flasks and periodically agitated for 20 minutes. The mixtures were made up to the volume of the volumetric flasks by the addition of 20% Piperidine in DMF, then samples were taken for UV analysis at 302 nm.

3.3 Loading determination of resin 1.74

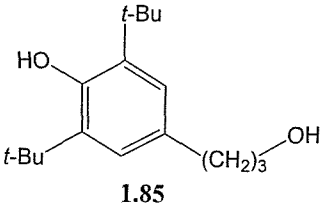


1.74 **1.77** **1.78**

Cinnamyl alcohol (3.08 g, 23.0 mmol), DMAP (2.81 g, 23.0 mmol) and resin **1.74** (2.00 g) in CH_2Cl_2 (20 mL) were stirred together for 10 minutes. Diisopropylcarbodiimide (3.60 mL, 23.0 mmol) was added and the mixture was stirred for 19 hours. The resin was collected by filtration, then washed with CH_2Cl_2 (8 x 20 mL) and dried in a vacuum oven (50°C @ 10 mmHg) to give resin **1.77** as a pale

yellow solid: FTIR ν_{max} (on bead): 3024w, 2921m, 1731s, 1601m, 1492s, 1449s, 1148s, 963s, 747m, 696s cm^{-1}. To a slurry of resin **1.77** (100 mg) and naphthalene (5-10 mg, internal standard) in CH_2Cl_2 (3 mL) was added MeOH (0.5 mL), followed by potassium trimethylsilanoxide (50 mg, 0.39 mmol). The mixture was stirred for 4 hours, the resin was collected by filtration then washed with CH_2Cl_2 (4 x 4 mL). The filtrate and washings were combined and made up in a volumetric flask (25 or 20 mL). The solution was analysed by gas chromatography [150°C, DB624 30 m x 0.53 cm ID, 30μm film, FID, Rt (cinnamyl alcohol) = 4.2 min, Rt (naphthalene) = 2.2 min]. A standard solution of cinnamyl alcohol and naphthalene was used to determine the relative response factors, allowing the mass of cinnamyl alcohol in the sample to be determined by comparison with naphthalene. Cleavage and analysis was carried out in duplicate.

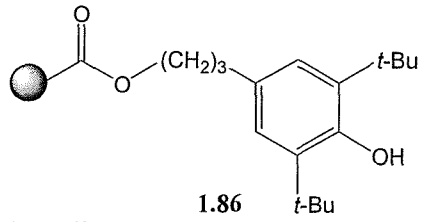
3.4 2,6-Di-tert-butyl-4-(3-hydroxypropyl)phenol 1.85



1.85

To a solution of pentathreotol tetrakis(3,5-di-*t*-butyl-4-hydroxydihydrocinnamate) (5 g, 4.24 mmol) in anhydrous THF (60 mL) at 0°C under nitrogen was added lithium aluminium hydride (0.65 g, 16.98 mmol) batchwise over 20 minutes. The reaction was warmed to room temperature and stirred for 18 hours. The reaction was quenched by careful sequential addition of water (6.5 mL), 2 M NaOH(aq) (1.0 mL) and water (6.5 mL). The mixture was acidified to pH 1 with 2M HCl then partitioned between diethyl ether (150 mL) and water (100 mL). The organic phase was collected, dried ($MgSO_4$) and the solvent was removed to give colourless oil. The oil was purified by flash chromatography on silica gel (150 g) eluting with ethyl acetate/hexane (1:5) to furnish the title compound **1.85** as a white crystalline solid (3.48 g, 14.5 mmol, 80 %); spectroscopic details are consistent with those observed in the literature:[149] m.p. 65-66°C (lit[149] m.p. 66-67°C); FTIR ν_{max} (neat) 3646m, 3354br, 2952s, 1435s, 1233s, 1153m, 1057m cm^{-1}; ^1H NMR (300 MHz): δ 7.01 (2H, s, Ar**H**), 5.06 (1H, s, ArO**H**), 3.72 (2H, t, J = 6.5 Hz, C$\mathbf{H_2}$OH), 2.62 (2H, t, J = 7.9 Hz, ArC$\mathbf{H_2}$), 1.88 (2H, tt, J = 8.0, 6.5 Hz, $ArCH_2C\mathbf{H_2}CH_2OH$), 1.44 (18H, s, $ArC(C\mathbf{H_3})_3$).

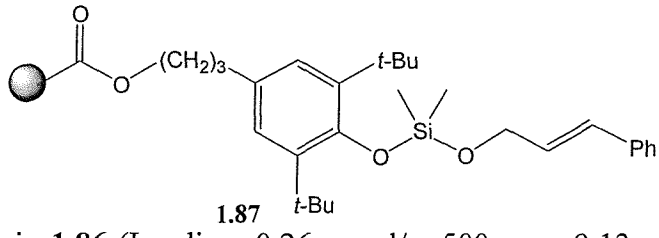
3.5 2,6-tert-Butyl-4-(3-hydroxypropyl)phenol Resin 1.86



1.86

Carboxylic acid resin **1.74** (Loading: 0.26 mmol/g, 2.0 g, 0.52 mmol) was stirred with 2,6-*tert*-butyl-4-(3-hydroxypropyl)phenol (0.66 g, 2.60 mmol) and DMAP (0.32 g, 2.60 mmol) in CH_2Cl_2 (13 mL) for 10 minutes, then diisopropylcarbodiimide (0.33 g, 2.60 mmol) was added and the reaction was stirred for 19 hours. The resin was collected by filtration, then sequentially washed with CH_2Cl_2 (6 x 10 mL), methanol (2 x 10 mL), ether (2 x 10 mL) and dried in a vacuum oven (10 mmHg, 50°C) to give the title resin **1.86** as a white solid (2.04 g): FTIR ν_{max} (on bead): 3025w, 2918m, 1730s, 1602w, 1492m, 1450s, 1155s, 1029w, 754 s cm^{-1}.

3.6 Cinnamyl siloxy Resin 1.87

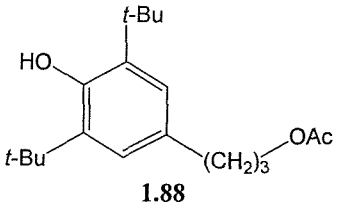


1.87

To a slurry of resin **1.86** (Loading: 0.26 mmol/g, 500 mg , 0.13 mmol) in anhydrous CH_2Cl_2 (5 mL) was added sequentially dichlorodimethylsilane (0.16 g, 1.30 mmol) and triethylamine (0.13 g, 1.30 mmol), then the reaction was refluxed for 40 hours. The resin was collected by filtration and washed with anhydrous CH_2Cl_2 (6 x 5 mL) to give a white solid. The resin in anhydrous CH_2Cl_2 (5 mL) was treated with cinnamyl alcohol (87 mg, 0.65 mmol) and triethylamine (90 μg, 0.65 mmol) and agitated with nitrogen bubbling for 24 hours. The resin was collected by filtration and washed with CH_2Cl_2 (8 x 5 mL) to give resin **1.87** as a white solid. The solid was taken up in CH_2Cl_2 (10 mL) and treated with tetrabutylammonium fluoride in water (75% by weight, 90 mg, 0.26 mmol) and stirred for 2 hours. At 45 minutes a sample (20 μL) was taken for HPLC analysis [(Supelcosil SiO_2, 4.6 x 150 mm , 2 mL/min, 1:1 ether/hexane) Rt = 3.02 min] and its absorbance compared to a cinnamyl alcohol standard (0.98 mg/mL). The analysis revealed the yield to be just 3% of the maximum

theoretical yield from based upon the loading of carboxylic acid resin **1.74**. A sample of the reaction mixture taken after 2 hours gave identical results.

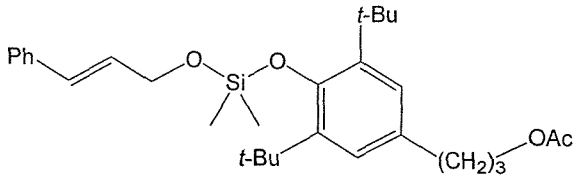
3.7 3-(3,5-Di-t-butyl-4-hydroxyphenyl)propyl acetate 1.88



1.88

To a solution of 2,6-*tert*-butyl-4-(3-hydroxypropyl)phenol (**1.86**) (2.0 g, 7.80 mmol) and acetyl chloride (0.59 mL, 8.24 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (1.15 mL, 8.24 mmol) in CH_2Cl_2 (5 mL) at 0°C. The reaction was warmed to room temperature and stirred for 14 hours. The reaction mixture was washed sequentially with water (2 x 10 mL), dried ($MgSO_4$) and the solvent was removed under vacuum to give the title compound **1.88** as a pale pink solid (1.87 g, 6.11 mmol, 78%): m.p. 60-63°C; TLC (SiO_2, EtOAc:hexane (1:5), Rf 0.60); FTIR ν_{max} (neat): 2952m, 1718s, 1434s, 1390m, 1364m, 1257s, 1232s, 1115s, 1040s, 892m cm^{-1}; ^1H NMR (400 MHz) δ 6.98 (2H, s, Ar**H**), 5.06 (1H, s, ArO**H**), 4.12 (2H, t, J = 6.5 Hz, CH_2OAc), 2.61 (2H, t, J = 9.5 Hz, $ArCH_2$), 2.07 (3H, s, $CH_3C=O$), 1.93 (2H, tt, J = 9.5, 6.5 Hz, CH_2CH_2OAc), 1.45 (18H, s, $C(CH)_3$); ^{13}C NMR (100 MHz) δ 171.4 (s, **C**=O), 152.1 (s, Ar), 136.0 (2C, s, Ar), 131.9 (s, Ar), 125.0 (2C, d, Ar), 64.3 (t, $AcOCH_2$), 34.5 (2C, s, CMe_3), 32.3 (t, CH_2), 30.7 (t, CH_2), 30.5 (6C, q, $C(CH_3)_3$), 21.2 (q, $CH_3C=O$); LRMS (EI) *m/z* (relative intensity) 306 (65) $[M]^{\bullet+}$, 57 (100) $[t\text{-}Bu]^+$; UV_{max} (nm): 234, 278; HRMS (EI) calculated for $C_{19}H_{30}O_3$ 306.21950, found 306.21980.

3.8 3-{3,5-Di-t-butyl-4-[(1,1-dimethyl-1-{[(E)-3-phenyl-2-propenyl]oxy}silyl)oxy] phenyl}propyl acetate 1.90



1.90

To a solution of compound **1.88** (200 mg, 0.654 mmol) and dichlorodimethylsilane (155 μL, 1.31 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0°C under nitrogen was added Et_3N (228 μL, 1.31 mmol). DMAP (8 mg, 65 μmol) was added and the mixture was refluxed for 42 hours. The solvent was removed under vacuum and the resulting residue was taken up in 1:1 ether/hexane then filtered. The filtrate was collected and the solvent was removed under vacuum to give a colourless oil which was shown to contain ~50 % of the intermediate silyl chloride **1.89** by NMR; ^{1}H NMR (300MHz) δ 7.27 (2H, s, Ar**H**) 4.08 (2H, t, J = 6.9 Hz, C**H**$_2$OAc), 2.58 (2H, t, J = 7.9 Hz, ArC**H**$_2$), 2.09 (3H, s, C**H**$_3$C=O), 1.91 (2H, quintet, J = 6.9 Hz, C**H**$_2$CH$_2$OAc), 1.43 (18H, s, C(C**H**$_3$)$_3$), 0.34 (6H, s, Si(C**H**$_3$)$_2$). To the mixture containing compound **1.89** in anhydrous CH_2Cl_2 (5 mL) at 0°C under nitrogen was added sequentially cinnamyl alcohol (87 mg, 0.648 mmol), Et_3N (113 μL, 0.810 mmol) and DMAP (4 mg, 32.4 μmol). The reaction was warmed to room temperature and stirred for 20 hours. The mixture was washed with water (5 mL), dried ($MgSO_4$) and the solvent was removed under vacuum to give a colourless oil. The oil was purified by flash chromatography on silica gel (10 g) eluting with ether/hexane (3:17 then 1:5) to give a mixture of the title compound **1.90** and phenol **1.88**. The title compound **1.90** was isolated by preparative HPLC (Luna SiO_2, 250 x 21.2 mm, MTBE:hexane (1:9), Rt = 6.40 min) as a colourless oil (66 mg, 0.133 mmol, 20%). TLC (SiO_2, EtOAc:hexane (1:5), Rf 0.60); FTIR ν_{max} (neat): 2953w, 1734s, 1261s, 1233s, 1117s, 922s, 797s cm^{-1}; ^{1}H NMR (400 MHz) δ 7.40 (2H, d, J = 7.5 Hz, Ar**H**), 7.33 (2H, t, J = 7.5 Hz, Ar**H**), 7.25 (1H, d, J = 7.5 Hz, Ar**H**), 7.08 (2H, s, Ar**H**), 6.66 (1H, d, J = 16.0 Hz, PhC**H**), 6.33 (1H, dt, J = 16.1, 5.0 Hz, PhCHC**H**), 4.54 (2H, dd, J = 5.0, 1.8 Hz, PhCHCHC**H**$_2$), 4.11 (2H, t, J = 6.8 Hz, C**H**$_2$OAc), 2.61 (2H, t, J = 8.0 Hz, ArC**H**$_2$), 2.07 (3H, s, C**H**$_3$C=O), 1.96 (2H, tt, J = 9.0, 6.5 Hz, C**H**$_2$CH$_2$OAc), 1.44 (18H, s, C(C**H**$_3$)$_3$), 0.37 (6H, s, Si(C**H**$_3$)$_2$); ^{13}C NMR (100 MHz) δ 171.5 (s, **C**=O), 151.1 (s, Ar), 140.8 (s, Ar), 137.2 (s, Ar), 133.0 (s, Ar), 130.1 (d, C**H**Ph), 128.7 (d, Ph), 128.4 (s, Ph), 127.6 (d, Ph), 126.5 (d, PhCHC**H**), 125.9 (d, Ar), 64.3 (**C**H$_2$OAc), 63.6 (**C**H$_2$O), 35.4 (2C, s, **C**Me$_3$), 32.0 (t, **C**H$_2$), 31.4

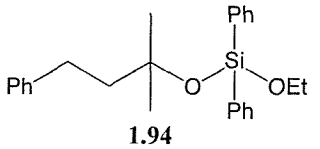
(6C, q, C($\mathbf{C}H_3)_3$), 30.5 (t, $\mathbf{C}H_2$), 21.2 (q, $\mathbf{C}H_3$C=O), -0.11 (2C, q, Si($\mathbf{C}H_3)_2$); LRMS (EI) *m/z* (relative intensity) 307 (23) $[AcO(CH_2)_3Ph(t\mathrm{Bu})_2OH]^{\bullet+}$, 117 (100) $[PhCHCHCH_2]^+$; Analysis calculated $C_{30}H_{44}O_4Si$: C, 72.54; H, 8.93. Found: C, 72.17; H, 9.01.

3.9 2-Methyl-4-phenylbutan-2-ol 1.92

1.91 **1.92**

To a stirring solution of methyl 3-phenylpropanoate (**1.91**) (1.0 g, 6.10 mmol) in anhydrous THF (20 mL) at –78°C under nitrogen was added 1.0 M methyl lithium in THF/cumene (30 mL, 30.49 mmol) over 30 minutes. The reaction was warmed to room temperature and stirred for 1 hour. The mixture was poured into cold saturated $NH_4Cl_{(aq)}$ (30 mL) and extracted with ether (50 mL). The ethereal extracts were dried ($MgSO_4$) and the solvent was removed under vacuum to give a colourless residue. The residue was purified by column chromatography on silica gel (40 g) eluting with ether/hexane (2:3) to furnish the title compound **1.92** as a colourless oil (0.45 g, 2.74 mmol, 45%); spectroscopic details are consistent with those observed in the literature:[65] TLC (SiO_2, ether/hexane (1:1), Rf 0.20); FTIR ν_{max} (neat): 3369br, 3027m, 2970s, 2936m, 1495m, 1455m, 1378s, 1213s, 1154s, 912s, 739s, 698s cm^{-1}; ^{1}H NMR (300MHz) δ 7.35-7.18 (5H, m, Ph**H**), 2.73 (1H, dd, *J* = 12.4, 5.0 Hz, PhCH(**H**)), 2.73 (1H, t, *J* = 8.7 Hz, PhCH(**H**)), 1.82 (1H, dd, *J* = 12.4, 5.0 Hz, CH(**H**)CMe_2OH), 1.82 (1H, t, *J* = 8.5 Hz, CH(**H**)CMe_2OH), 1.79 (1H, brs, O**H**), 1.32 (6H, s, C(OH)($C\mathbf{H}_3)_2$); ^{13}C NMR (75MHz) δ 128.6 (2C, d, Ph), 128.5 (2C, d, Ph), 125.9 (d, Ph), 71.1 (s, $\mathbf{C}Me_2OH$), 45.9 (t, Ph$\mathbf{C}H_2$), 30.9 (t, $PhCH_2\mathbf{C}H_2$), 29.5 (q, $\mathbf{C}H_3$).

3.10 (1,1-Dimethyl-3-phenylpropoxy)(ethoxy)diphenylsilane 1.94

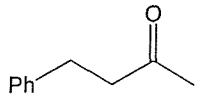


1.94

To a solution of dichlorodiphenylsilane (0.31 g, 1.22 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0°C under nitrogen was added Et_3N (0.14 g, 1.34 mmol) followed by alcohol **1.92** (0.20 g, 1.22 mmol) and DMAP (15 mg, 0.122 mmol). The reaction was refluxed for 20 hours, then the solvent was removed under vacuum to give a white residue. The

residue was triturated with 1:1 ether/hexane, the supernatant was collected by filtration and the solvent was removed under vacuum to give a colourless oil, containing predominantly siloxy chloride **1.93**. ^{1}H NMR (300 MHz) δ 7.78-7.72 (4H, m, SiPh**H**), 7.52-7.39 (6H, m, Ph**H**), 7.33-7.26 (2H, m, Ph**H**), 7.24-7.16 (3H, m, Ph**H**), 2.80 (1H, t, J = 8.5 Hz, PhC(**H**)HCH$_2$), 2.80 (1H, dd, J = 12.5, 4.4 Hz, PhC(**H**)HCH$_2$)), 1.93 (1H, t, J = 8.5 Hz, PhCH$_2$C(**H**)H), 1.93 (1H, dd, J = 12.5, 4.4 Hz, PhCH$_2$C(**H**)H), 1.41 (6H, s, C(C**H$_3$**)$_2$). ^{13}C NMR (75 MHz) δ 142.7 (s, Ph), 134.9 (2C, s, SiPh), 134.5 (4C, d, SiPh), 130.8 (2C, d, Ph), 128.5 (2C, d, Ph), 128.1 (6C, d, SiPh), 125.9 (d, Ph), 78.3 (s, **C**Me$_2$), 46.5 (t, Ph**C**H$_2$), 30.9 (t, PhCH$_2$**C**H$_2$), 29.8 (q, CH$_3$). To a solution of compound **1.93** and ethanol (1 mL) in CH$_2$Cl$_2$ (5 mL) at 5°C was added Et$_3$N (0.25 g, 2.44 mmol) dropwise. The reaction was warmed to room temperature, stirred for 17 hours and the solvent was removed under vacuum to give a white residue. The residue was purified by column chromatography on silica gel (25 g) eluting with CH$_2$Cl$_2$/hexane (1:4) to give the title compound **1.94** as a colourless oil (0.29 g, 0.744 mmol, 61%): FTIR ν_{max} (neat): 2964w, 1420m, 1123s, 1114s, 1077s, 1049s cm^{-1}; ^{1}H NMR (300 MHz) δ 7.74-7.68 (4H, m, SiPh**H**), 7.46-7.15 (11H, m, Ph**H**), 3.85 (2H, q, J = 6.6 Hz, CH$_3$C**H$_2$**OSi), 2.81 (1H, t, J = 8.8 Hz, PhC(**H**)HCH$_2$), 2.81 (1H, dd, J = 13.2, 5.2 Hz, PhC(**H**)HCH$_2$), 1.85 (1H, t, J = 8.8 Hz, PhCH$_2$C(**H**)H), 1.85 (1H, dd, J = 13.2, 5.2 Hz, PhCH$_2$C(**H**)H), 1.35 (6H, s, C(OSi)(C**H$_3$**)$_3$), 1.25 (3H, t, J = 6.6 Hz, C**H$_3$**CH$_2$OSi); ^{13}C NMR (75 MHz) δ 143.1 (s, Ph), 135.4 (2C, s, SiPh), 135.1 (4C, d, SiPh), 130.0 (2C, d, Ph), 128.5 (2C, d, Ph), 127.8 (6C, d, SiPh), 125.7 (d, Ph), 75.6 (s, **C**Me$_2$), 58.9 (t, CH$_3$**C**H$_2$O), 46.9 (t, Ph**C**H$_2$), 31.0 (t, PhCH$_2$**C**H$_2$), 30.0 (2C, q, C(**C**H$_3$)$_2$OSi), 18.4 (q, **C**H$_3$CH$_2$O); LRMS (EI) *m/z* (relative intensity) 313 (20) [M-C$_6$H$_5$]$^+$, 227 (46) [SiPh$_2$OEt]$^+$, 146 (100) [Ph(CH$_2$)$_2$CMeCH$_2$]$^+$; HRMS (EI) calculated for C$_{25}$H$_{30}$O$_2$Si 390.20151, found 390.20146.

3.11 4-Phenylbutan-2-one 1.98

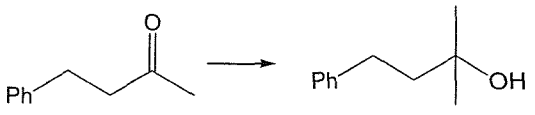


1.98

To a stirring solution of *t*-butylacetoacetate (**1.95**) (2.0 g, 12.7 mmol) in anhydrous THF (15 mL) at 0°C under nitrogen was added 60% sodium hydride in mineral oil (0.51 g, 12.7 mmol). The mixture was stirred for 15 minutes then treated with benzyl chloride (1.55 mL, 12.7 mmol) and refluxed for 18 hours. The reaction mixture was partitioned between CH_2Cl_2 (50 mL) and 10% citric acid in water (50 mL). The aqueous phase was washed with CH_2Cl_2 (30 mL) and the organic extracts were combined, washed with brine (30 mL), dried ($MgSO_4$), then the solvent was removed under vacuum to give a colourless oil. The oil was purified by flash chromatography on silica gel (100 g) eluting with CH_2Cl_2/hexane (3:7 then 1:1 and finally 4:1) to give the benzylated product **1.96** as a colourless oil (1.60 g, 6.45 mmol, 53%); spectroscopic details are consistent with those observed in the literature:[150] TLC (SiO_2, 30% ether/hexane, Rf 0.5); FTIR ν_{max} (neat): 2979w, 1733s, 1714s, 1368m, 1255m, 1141s, 743m, 700m cm^{-1}; ^1H NMR (300 MHz): δ 7.30-7.17 (5H, m, Ph**H**), 3.70 (1H, t, J = 7.4 Hz, C**H**CO_2tBu), 3.13 (1H, J = 7.3 Hz, C(H)HPh), 3.12 (1H, J = 6.9 Hz, C(H)HPh), 2.19 (3H, s, C**H**$_3$C=O), 1.39 (9H, s, C(C**H**$_3$)$_3$). To a solution of **1.96** (1.00 g, 4.03 mmol) in CH_2Cl_2 (2 mL) at 0°C was added a mixture of TFA / CH_2Cl_2 (5 ml / 3 mL). The reaction mixture was warmed to room temperature stirred for 1 hour. The solvent was removed under vacuum and the residue was azeotroped with toluene (3 x 5 mL) to give a yellow oil, which spectral analysis showed to be the deprotected carboxylic acid **1.97**; TLC (SiO_2, ether/hexane (3:7), Rf 0.2); FTIR ν_{max} (neat): 1732s, 1715s, 1267m, 1146m, 913m, 736s cm^{-1}; ^1H NMR (300 MHz) δ 7.34-7.15 (5H, m, Ph**H**), 3.86 (1H, t, J = 7.7 Hz, C**H**CO_2H), 3.19 (2H, dd, J = 7.4, 1.5 Hz, C**H**$_2$Ph), 2.23 (3H, s, C**H**$_3$C=O). The yellow oil **1.97** in THF / water (4 mL / 1 mL) was warmed to 60°C for 1 hour and gas was evolved. The mixture partitioned between CH_2Cl_2 (5 mL) and water (5 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed under vacuum to give the title compound **1.98** (0.68 g, 4.59 mmol, 53%, over 3 steps) as a colourless oil; spectroscopic details are consistent with those observed in the literature:[151] TLC (SiO_2, ether/hexane (3:7), Rf 0.45); FTIR ν_{max} (neat): 3027w, 1712s,

1495w, 1453w, 1356m, 1160m, 747s, 697s cm^{-1}; ^1H NMR (300 MHz) δ 7.33-7.14 (5H, m, PhH), 2.90 (2H, t, J = 7.4 Hz, CH_2Ph), 2.76 (3H, t, J = 7.4 Hz, $CH_2C{=}O$), 2.15 (3H, s, $CH_3C{=}O$); LRMS (EI) *m/z* (relative intensity) 148 (100) $[M]^{\bullet+}$, 105 (90) $[PhCH_2CH_2]^+$, 91 (86) $[PhCH_2]^+$, 77 (74) $[C_6H_5]^+$.

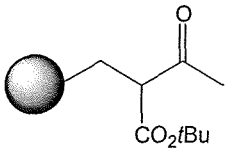
3.12 2-Hydroxy-4-phenylbutan-2-ol 1.92



1.98 **1.92**

To a solution of compound **1.98** (0.10 g, 0.68 mmol) in anhydrous THF (2 mL) under nitrogen at –10°C was added 3 M MeMgCl (0.25 mL, 0.74 mmol). After 10 minutes the reaction was partitioned between ether (5 mL) and water (5 mL). The ethereal extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give the title compound **1.92** (0.12 g, 0.68 mmol, 100%) as a colourless oil; the spectroscopic data was consistent with compound **1.92**.

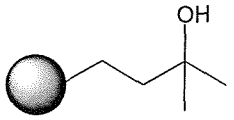
3.13 tert-Butyl acetoacetate Resin 1.99



1.99

To a solution of *t*-butylacetoacetate (**1.95**) (9.09 g, 57.5 mmol) in anhydrous THF (50 mL) at 0°C under nitrogen was added 60% sodium hydride in mineral oil (2.30 g, 57.5 mmol). Merrifields' resin (5.0 g, loading 2.3 mmol/g, 11.5 mmol) was added to the brown solution and the mixture was refluxed for 19 hours. The resin was collected by filtration, then sequentially washed with THF (20 mL), water (20 mL), THF (20 mL), water (20 mL), THF (20 mL), CH_2Cl_2 (2 x 20 mL), MeOH (2 x 20 mL), ether (2 x 20 mL) and dried in a vacuum oven (50°C @ 10 mmHg) to give the title resin **1.99** (6.87 g) as a pale yellow solid; FTIR ν_{max} (on bead) 2981m, 1733s, 1712s, 1602m, 1492m, 1450s, 1139s, 698s cm^{-1}.

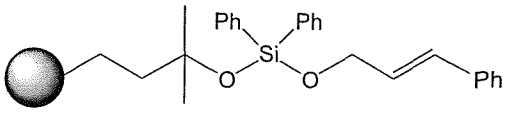
3.14 tert-Alcohol Resin 1.100



1.100

To a slurry of resin **1.99** (1.0 g, 2.30 mmol) in CH_2Cl_2 (6 mL) at 0°C was added a mixture of TFA / CH_2Cl_2 (8 mL / 2 ml) dropwise over 10 minutes. The slurry was warmed to room temperature and stirred for 2 hours. The resin was collected by filtration, washed with CH_2Cl_2 (8 x 7 mL) and dried for 3 hours to give an off-white solid: FTIR ν_{max} (on bead) 2916m, 1712s, 1492m, 1450m, 1154m, 697s cm^{-1}. The resin was taken up in THF (6 mL) then water (2 mL) was added and the mixture was heated for 2 hours at 60°C. The resin was collected by filtration, then washed sequentially with THF (2 x 5 mL), CH_2Cl_2 (2 x 5 mL), MeOH (2 x 5 mL), ether (2 x 5 mL) and dried in a vacuum oven (50°C @ 10 mmHg) to give an off-white solid: FTIR ν_{max} (on bead) 2917s, 2854m, 1712s, 1601m, 1492s, 1448s, 1012m, 967s, 696s cm^{-1}. To a stirring slurry of the resin (0.50 g, 1.15 mmol) in anhydrous THF (3 mL) was added 3.0 M MeMgCl in anhydrous THF (3 mL, 9.0 mmol). The resin was stirred for 1 hour then 5 drops of glacial acetic acid were added. The resin was collected by filtration, washed with THF (5 mL), water (5 mL), THF (2 x 5 mL), CH_2Cl_2 (2 x 5 mL), and then dried in a vacuum oven (50°C @ 10 mmHg) for 5 hours to give the title resin **1.100** as a white solid (4.92 g). FTIR ν_{max} (on bead) 3377br, 2920m, 1601m, 1492m, 1450s, 697 cm^{-1}.

3.15 Resin 1.102

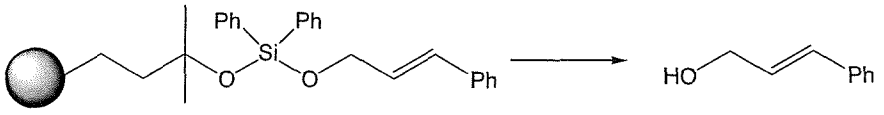


1.102

Resin **1.100** (0.20 g, 0.46 mmol), dichlorodiphenylsilane (0.96 mL, 4.60 mmol), triethylamine (0.63 mL, 4.60 mmol) and DMAP (56 mg, 0.46 mmol) in anhydrous CH_2Cl_2 (5 mL) were refluxed under nitrogen for 16 hours. The resin was collected by filtration, washed with CH_2Cl_2 (6 x 5 mL) and dried under a stream of nitrogen to give resin **1.101**. Resin **1.101** was slurried in anhydrous CH_2Cl_2 (5 mL), then treated with cinnamyl alcohol (0.62 g, 4.60 mmol), and triethylamine (0.64 mL, 4.60 mmol), and refluxed for 4 hours. The resin was collected by filtration, washed with CH_2Cl_2 (8 x 5

mL) and dried in a vacuum oven (50°C @ 10 mmHg) to give resin **1.102** as a colourless solid: FTIR ν_{max} (on bead) 2920s, 1602m, 1492s, 1450s, 1257m, 1154m, 1029s, 756s cm^{-1}; MAS ^1H NMR (400 MHz) δ 6.52 (1H, s, C**H**Ph), 6.24 (1H, s, C**H**CH_2OSi), 4.35 (2H, s, CH_2OSi), 1.23 (2H, s, CH_2CMe_2), 1.20 (6H, s, $C(CH_3)_2$); MAS ^{13}C NMR (100 MHz): δ 70.8 (s, CMe_2), 63.3 (t, CH_2OSi).

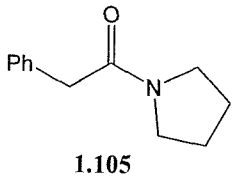
3.16 Loading determination of Resin 1.102



1.102

Resin **1.102** (0.10 g, 0.23 mmol) in CH_2Cl_2 (2 mL) was treated with TBAF (75% by weight in water) (0.24 mL, 0.69 mmol) and stirred for 3 hours. The resin was collected by filtration and washed with CH_2Cl_2 (4 x 3 mL). The filtrate and washings were combined and made up in a volumetric flask (20 mL) with naphthalene (internal standard) then analysed by gas chromatography (see experiment **3.3**) to establish the resin loading.

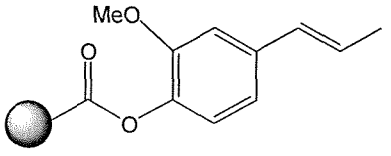
3.17 1-(phenylacetyl)pyrrolidine 1.105



1.105

To a solution of phenylacetyl chloride (5.00 g, 32.4 mmol) in CH_2Cl_2 (15 mL) at 0^0C was added a solution of pyrrolidine (2.42 g, 34.0 mmol) and triethylamine (6.76 mL, 48.6 mmol) in CH_2Cl_2 (10 mL). The mixture was warmed to room temperature and left to stir for 20 hours. The reaction mixture was washed with 10% citric acid in water (15 mL), then saturated $NaHCO_3$(aq) (15 mL). The organic solution was dried ($MgSO_4$), the solvent was removed under vacuum and the resulting oil was purified by vacuum distillation (54-56°C @ 0.5 mmHg) to furnish the target compound **1.105** (67%) as a colourless oil. Spectroscopic details are consistent with those observed in the literature:[152] ^1H NMR (300 MHz) δ 7.38-7.20 (5H, m, Ph**H**), 3.66 (2H, s, CH_2Ph), 3.50 (2H, t, J = 6.7 Hz, pyrrolidine CH_2), 3.43 (2H, t, J = 6.7 Hz, pyrrolidine CH_2), 1.94-1.80 (4H, m, pyrrolidine CH_2).

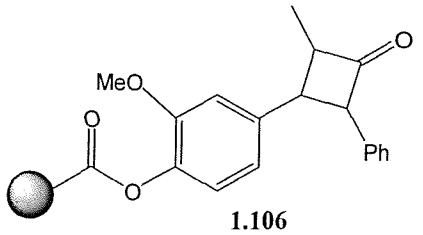
3.18 Isoeuginol resin 1.104



1.104

Diisocarbodiimide (0.71 g, 5.60 mmol) was added to a mixture of resin **1.74** (2.0 g, loading 0.56 mmol/g, 1.12 mmol), isoeuginol (**1.103**) (0.92 g, 5.60 mmol) and DMAP (0.68 g, 5.60 mmol) in CH_2Cl_2 (13 mL) and stirred for 19 h. The resin was collected by filtration, washed sequentially with CH_2Cl_2 (5 x 20 mL), MeOH (2 x 20 mL), ether (2 x 20 mL) and dried under vacuum (10 mmHg, 50°C) to give resin **1.104** as a white solid (2.09 g). Bromocresol green test indicated the reaction had gone to completion: FTIR ν_{max} (on bead) 2924m, 1730 s, 1601 m, 1509m, 1493s, 1414m, 1263m, 1198s, 1119s, 1031m, 962m, 758s, 698 s cm^{-1}.

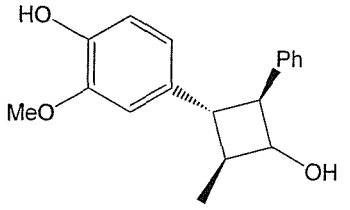
3.19 Cyclobutanone resin 1.106



1.106

To a solution of 1-(phenylacetyl)pyrrolidine (**1.105**) (1.06 g, 5.60 mmol) in anhydrous CH_2Cl_2 (10 mL) at -5°C was added consecutively triflic anhydride [distilled over P_2O_5] (0.94 mL, 5.60 mmol), 2,6-di-*t*-butylpyridine (1.07 mL, 5.60 mmol) and resin **1.104** (2.00 g, loading 0.56 mmol/g, 1.12 mmol). The mixture was stirred at room temperature for 18 hours. The resin was collected by filtration, washed with CH_2Cl_2 (5 x 10 mL), to give an orange solid, which was mixed with THF (15 mL) and saturated $NaHCO_3$(aq) (3 mL) and stirred for 3 hours. The resin was collected by filtration, washed sequentially with water (2 x 10 mL), THF (2 x 10 mL), MeOH (10 mL), CH_2Cl_2 (10 mL), MeOH (10 mL), ether (2 x 10 mL) and dried under vacuum (10 mmHg, 50°C) to give resin **1.106** (1.97 g) as an orange solid: FTIR ν_{max} (on bead) 3027w, 2923m, 1764s, 1731s, 1601s, 1493s, 1450s, 1122s, 1030m, 697vs cm^{-1}.

3.20 4-(3-Hydroxy-2-methyl-4-phenylcyclobutyl)-2-methoxyphenol 1.107

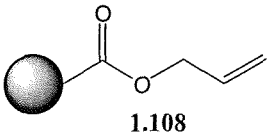


1.107

To a slurry of resin **1.106** (1.15 g) in anhydrous THF (15 mL) at –78°C was added 2 M $LiBH_4$ solution in THF (1.93 mL, 3.86 mmol) followed by methanol (100 μL). The mixture was warmed to room temperature and stirred for 12 h. The resin was collected by filtration and washed with CH_2Cl_2 (2 x 5 mL), THF (5 mL) and saturated NH_4Cl(aq) (5 mL). The filtrate and washings were combined, then partitioned. The organic extracts were dried ($MgSO_4$) and the solvent was removed under vacuum to give a colourless residue (224 mg). The residue was purified by flash chromatography on silica gel (10 g) eluting with MeOH/CH_2Cl_2 (1:99) to give 2 diastereoisomers of the title compound **1.107**. Both diastereomers required further purification by radial chromatography on silica gel eluting with MeOH/CH_2Cl_2 (1:99) to give them each as colourless glasses (major diastereomer **1.107a**, 82 mg, 0.27 mmol 51 %; minor diastereomer **1.107b**, 53 mg, 0.17 mmol, 33 %). Data for **1.107a**: TLC (SiO_2, ether:hexane (1:1) Rf 0.25); FTIR ν_{max} (neat) 3311br, 2950m, 1601m, 1514s, 1450s, 1372m, 1264s, 1236s, 1160m, 1123s, 1067s, 1033s, 909s, 813m, 734s, 699s cm^{-1}; ^1H NMR (400 MHz) δ 7.35-7.20 (5H, m, Ph**H**), 6.87 (1H, d, J = 8.1 Hz, Ar**H**), 6.77 (1H, d, J = 8.4 Hz, **ArH**), 6.76 (1H, s, **ArH**), 5.56 (2H, sbr, ArO**H** + O**H**), 3.87 (3H, s, C**H**$_3$OAr), 3.82 (1H, t, J = 7.4 Hz, C**H**OH), 3.23 (1H, dd, J = 10.0, 8.0 Hz, PhC**H**), 2.53 (1H, t, J = 9.5 Hz, C**H**Ar), 2.19 (1H, dquintet, J = 9.6, 6.8 Hz, C**H**CH$_3$), 1.28 (3H, d, J = 6.6 Hz, C**H**$_3$); ^{13}C NMR (100 MHz) δ 146.7 (s, Ar), 144.3 (s, Ar), 141.7 (s, Ar), 134.5 (s, Ph), 128.6 (2C, d, Ph), 126.9 (2C, d, Ph), 126.7 (d, Ph), 119.9 (d, Ar), 114.5 (d, Ar), 109.6 (d, Ar), 77.3 (d, **C**HOH), 56.3 (q, **C**H$_3$OAr), 56.3 (d, **C**HPh), 46.5 (d, **C**HAr), 45.8 (d, **C**HMe), 17.5 (q, **C**H$_3$CH); LRMS (EI) *m/z* (relative intensity) 226 (11) [4-HO-3-MeOPh(CH)$_2$Ph]$^{\bullet+}$, 164 (100) [4-HO-3-MeOPh(CH)$_2$Me]$^{\bullet+}$, 91 (81 [PhCH$_2$]$^+$. Data for **1.107b**: TLC (SiO_2, ether:hexane (1:1) Rf 0.10); FTIR ν_{max} (neat) 3425br, 2923m, 1602m, 1513s, 1450s, 1430m, 1368m, 1265s, 1156s, 1121s, 1032s, 985s, 910m, 736m, 701s cm^{-1}; ^1H NMR (400 MHz) δ 7.40-7.22 (5H, m, Ph**H**), 6.87 (1H, d, J = 8.0 Hz, Ar**H**), 6.79 (1H, dd, J = 8.0, 2.0 Hz, Ar**H**), 6.75 (1H, d, J = 1.5 Hz, Ar**H**), 5.54 (1H, br, ArO**H**), 4.62-4.59 (1H, m, C**H**OH), 3.87 (3H, s, C**H**$_3$OAr), 3.65-

3.62 (2H, m, C**H**Ph & C**H**Ar), 2.55-2.46 (1H, m, C**H**Me), 1.51 (1H, br, CHO**H**), 1.24 (3H, d, J = 6.6 Hz, C**H**$_3$CH); ^{13}C NMR (100 MHz) δ 146.6 (s, Ar), 144.2 (s, Ar), 137.8 (s, Ar), 135.3 (s, Ar), 128.7 (2C, d, Ph), 128.5 (2C, d, Ph), 126.9 (s, Ph), 119.4 (d, Ar), 114.4 (d, Ar), 109.3 (d, Ar), 70.9 (d, MeCH**C**HOH), 56.0 (q, **C**H$_3$OPh), 50.1 (d, **C**HPh), 49.3 (d, **C**HAr), 40.7 (d, **C**HMeCHOH), 12.5 (q, **C**H$_3$CHCHOH); LRMS (EI) *m/z* (relative intensity) 226 (11) [4-HO-3-MeOPh(CH)$_2$Ph]$^{\bullet+}$, 164 (100) [4-HO-3-MeOPh(CH)$_2$Me]$^{\bullet+}$, 91 (81 [PhCH$_2$]$^+$; HRMS (EI) calculated for $C_{18}H_{20}O_3$ 284.14124, found 284.14107.

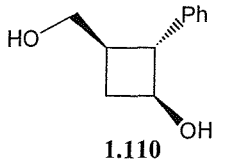
3.21 Allyl ester resin 1.108



1.108

To a stirring slurry of resin **1.74** (3 g, loading 0.40 mmol, 1.20 mmol) in CH_2Cl_2 (24 mL) was added diisopropylcarbodiimide (1.88 mL, 1.51 g, 12.0 mmol), N,N'-dimethylaminopyridine (0.73 g, 6.0 mmol) and allyl alcohol (0.81 mL, 0.70 g, 12.0 mmol). The mixture was stirred for 16 hours. The resin was collected by filtration, washed sequentially with CH_2Cl_2 (5 x 20 mL), MeOH (20 mL), ether (20 mL) and dried under vacuum (10 mmHg, 50°C) to give resin **1.108** (3.02 g) as a white solid. Bromocresol green test indicated the reaction had gone to completion: FTIR ν_{max} (neat) 3025w, 2920m, 2848w, 1731s, 1602w, 1492m, 1452s, 1417w, 1274w, 1152w, 823w, 757s, 696vs cm^{-1}.

3.22 (1S*,2R*,3R*)-3-Hydroxymethyl-2-phenylcyclobutanol 1.110

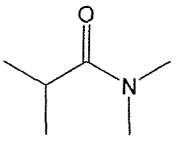


1.110

To a solution of 1-(phenylacetyl)pyrrolidine (**1.105**) (0.33 g, 1.75 mmol) in anhydrous CH_2Cl_2 (10 mL) at -5°C was added consecutively triflic anhydride (0.29 mL, 0.49 g, 1.75 mmol), 2,6-di-*t*-butylpyridine (0.39 mL, 0.33 g, 1.75 mmol) and resin **1.108** (0.50 g, 0.40 mmol/g, 0.20 mmol). The mixture was refluxed for 20 h. The resin was collected by filtration, and washed sequentially with CH_2Cl_2 (2 x 10 mL), THF (10 mL), water (2 x 10 mL), THF (10 mL), MeOH (10 mL), ether (2 x 10 mL) to give an

orange solid. The resin was slurried with THF (5 mL) and saturated $NaHCO_3$(aq) (1 mL), then refluxed for 2 hours. The resin was collected by filtration, then washed sequentially with water (3 x 10 mL), THF (3 x 10 mL), MeOH (2 x 10 mL), ether (2 x 10 mL) and dried under vacuum (10 mmHg, 50°C) to give cyclobutanone resin (0.51 g) as a pale orange solid: FTIR ν_{max} (neat) 3026w, 2921m, 2850w, 1783m, 1733s, 1601w, 1493s, 1451s, 1152w,1029w, 908w, 747m, 696vs cm^{-1}. To a slurry of the cyclobutanone resin (0.51 g, 0.20 mmol) in anhydrous THF (5 mL) at –78°C was added 2 M $LiBH_4$ in THF (0.53 mL, 1.05 mmol) followed by methanol (40 μL). The mixture was warmed to room temperature and stirred for 18 hours. The resin was collected by filtration and washed with CH_2Cl_2 (2 x 5 mL), THF (5 mL) and saturated NH_4Cl(aq) (5 mL). The filtrate and washings were combined, partitioned and the aqueous phase was then extracted with CH_2Cl_2 (3 x 5 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give an orange residue (30 mg). The residue was purified by flash chromatography on silica gel (5 g) eluting with ether/hexane (7:3 then 9:1 and finally 100:0) to give the title compound **1.110** (25 mg, 0.14 mmol, 80 %) as a colourless oil: TLC (SiO_2, Ether, Rf 0.20); FTIR ν_{max} (neat) 3309br, 2933s, 1602w, 1496w, 1449w, 1134m, 1054m, 1006m, 911m, 739s, 700s cm^{-1}; ^{1}H NMR (400 MHz) δ 7.36-7.21 (5H, m, Ar**H**), 4.18 (1H, q, J = 7.7 Hz, C**H**OH), 3.79 (1H, dd, J = 11.1, 5.5 Hz, C**H**$_2$OH), 3.74 (1H, dd, J = 11.1, 5.5 Hz, C**H**$_2$OH), 3.08 (1H, t, J = 8.5 Hz, C**H**Ph), 2.47 (1H, dt, J = 10.0, 7.5 Hz, C**H**(H)CHOH), 2.16 (1H, dtt, J = 10.0, 8.1, 5.5 Hz, C**H**CH$_2$OH), 1.73 (1H, td, J = 10.5, 8.5 Hz, C**H**(H)CHOH); ^{13}C NMR (100 MHz) δ 141.7 (s, Ph), 128.7 (2C, d, Ph), 127.0 (2C, d, Ph), 126.7 (d, Ph), 70.8 (d, **C**HOH), 65.8 (t, **C**H$_2$OH), 54.2 (d, **C**HPh), 34.7 (d, **C**HCH$_2$OH), 32.6 (t, **C**H$_2$CHOH); LRMS (CI, ammonia) *m/z* (relative intensity) 178 (7) $[M]^{\bullet+}$, 196 (48) $[M+NH_4]^+$, 161 (100) $[M-H_2O]H^+$; HRMS (EI) calculated for $C_{11}H_{12}O$ 160.08843, found 160.08882.

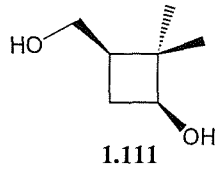
3.23 N,N-Dimethyl-2-methylpropanamide 1.109



1.109

Isobutyryl chloride (5.00 g, 46.9 mmol) was added dropwise to a stirring mixture of dimethylamine hydrochloride (5.74 g, 70.4 mmol), CH_2Cl_2 (20 mL) and 2 M $NaOH_{(aq)}$ (100 mL) at 0°C. The reaction mixture was warmed to room temperature and stirred for 4 hours. The two phases were partitioned, the aqueous phase was saturated with $NaCl_{(s)}$ and extracted with CH_2Cl_2 (4 x 50 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a colourless oil. The oil was purified by vacuum distillation (78°C @ 18 mmHg) to give the title compound **1.109** as a colourless oil (3.32 g, 62%); spectroscopic details are consistent with those observed in the literature:[153] ^{1}H NMH (300 MHz) δ 3.03 (3H, s, C**H**$_3$N), 2.93 (3H, s, C**H**$_3$N), 2.80 (1H, septet, J = 6.9 Hz, C**H**Me$_2$), 1.10 (6H, d, J = 7.0 Hz, CH(C**H**$_3$)$_2$).

3.24 (1S*,3R*)-3-Hydroxymethyl-2,2-dimethylcyclobutanol 1.111

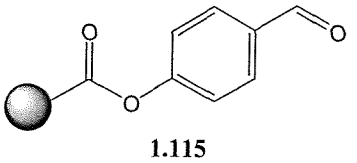


1.111

To a solution of N,N-dimethyl-2-methylpropanamide (**1.109**) (0.20 g, 1.75 mmol) in anhydrous CH_2Cl_2 (5 mL) under nitrogen at 0°C was added consecutively triflic anhydride [distilled over P_2O_5] (0.29 mL, 1.75 mmol), 2,6-di-*tert*-butylpyridine (0.39 mL, 1.75 mmol) and allyl ester resin **1.108** (0.50 g, 0.29 mmol/g, 0.145 mmol). The reaction was warmed to room temperature and stirred for 18 h. The resin was collected by filtration, and washed sequentially with CH_2Cl_2 (4 x 5 mL), methanol (2 x 5 mL), diethyl ether (2 x 5 mL) to give orange resin. The resin was refluxed with THF (5 mL) and saturated $NaHCO_3$(aq) (1 mL) for 2 hours. The resin was collected by filtration, washed with THF and water alternately (2 x 5 mL), then with methanol (2 x 5 mL), ether (2 x 5 mL), and dried under vacuum (10 mmHg, 50°C) to give the cyclobutanone resin as an orange solid: FTIR ν_{max} (on bead) 2917m, 1779s, 1731s, 1601s, 1492s, 1451s, 1150m, 1113m, 1065m, 1029m, 756m, 697vs cm^{-1}. To a slurry of the cyclobutanone resin in anhydrous THF (5 mL) at –78°C under nitrogen was added a 2

M solution of $LiBH_4$ in THF (0.53 mL, 1.05 mmol), followed by MeOH (40 μL). The reaction was warmed to room temperature and stirred for 17 h. The resin was collected by filtration and washed sequentially with CH_2Cl_2 (2 x 5 mL), THF (5 mL) and saturated NH_4Cl(aq) (5 mL). The filtrate and washings were combined, partitioned and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give an orange residue (30 mg). The residue was purified by flash chromatography on silica gel (5 g) eluting with MeOH/CH_2Cl_2 (1:19) to furnish a colourless film the title compound **1.111** as a 7:1 mixture of diastereomers (11 mg, 84.6 μmol, 57%). The following data is for the major diastereomer: TLC (SiO_2, MeOH:CH_2Cl_2 (1:19), Rf .25); FTIR ν_{max} (neat) 3310br, 2956s, 2867s, 1461s, 1211m, 1132s, 1063m, 1005s, 739m cm^{-1}; ^1H NMR (300 MHz) δ 3.78 (1H, t, J = 7.7 Hz, C**H**OH), 3.63 (2H, m, C**H**$_2$OH), 2.34 (1H, dt, J = 11.0, 7.4 Hz, CH(**H**)CHOH), 1.76 (1H, dq, J = 9.6, 7.7 Hz, C**H**CH$_2$OH), 1.51 (2H, brs, **OH**), 1.48 (1H, dt, J = 11.0, 8.1 Hz, CH(**H**)CHOH), 1.15 (3H, s, C**H**$_3$), 1.02 (3H, s, C**H**$_3$); ^{13}C NMR (100 MHz) δ 72.5 (d, **C**HOH), 63.8 (t, **C**H$_2$OH), 43.7 (s, **C**Me$_2$), 39.6 (d, **C**HCH$_2$OH), 31.7 (t, **C**H$_2$CHOH), 29.2 (q, **C**H$_3$), 15.4 (q, **C**H$_3$); LRMS (CI, ammonia) *m/z* (relative intensity) 131 (44) $[M+H]^+$, 41 (100) $[C_3H_5]^+$, 69 (79) $[CH_2CHCMe_2]^+$; HRMS (EI) calculated for $C_7H_{13}O_2$ 129.09134, found 129.09155. Data for minor epimer of compound **1.111**: ^{13}C NMR (100 MHz) δ 73.3 (d, **C**HOH), 64.4 (t, **C**H$_2$OH), 42.1 (s, **C**Me$_2$), 40.5 (d, **C**HCH$_2$OH), 31.1 (t, **C**H$_2$CHOH), 22.9 (q, **C**H$_3$), 22.5 (q, **C**H$_3$).

3.25 4-Formylphenylester Resin 1.115

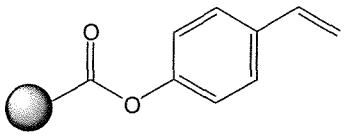


1.115

Carboxylic acid resin **1.74** (2 g, 0.26 mmol/g, 0.52 mmol), 4-hydroxybenzaldehyde (0.32 g, 2.60 mmol) and DMAP (0.32 g, 2.60 mmol) in CH_2Cl_2 (13 mL) were stirred for 15 minutes, then diisopropylcarbodiimide (0.33 g, 2.60 mmol) was added and the mixture was stirred for 14 hours. The resin was collected by filtration, washed sequentially with CH_2Cl_2 (5 x 10 mL), MeOH (5 x 10 mL), ether (5 x 10 mL) and dried in a vacuum oven (10 mm Hg, 50°C) to give the title resin **1.115** as a white solid.

Bromocresol green test indicated the reaction had gone to completion; FTIR ν_{max} (on bead) 3025m, 2923s, 1731s, 1702s, 1600m, 1493s, 1450s, 1206s, 1155s, 755s.

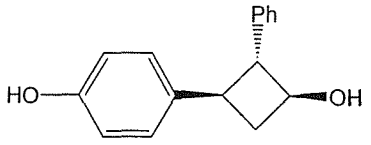
3.26 4-Vinylphenylester Resin 1.116



1.116

To a suspension of methyltriphenylphosphorane bromide (1.00 g, 2.80 mmol) in anhydrous THF (10 mL) was added 1.6 M n-butyl lithium in THF/cumene (1.75 mL, 2.80 mmol) at 0°C under nitrogen and the mixture was stirred for 90 minutes. The precipitate was allowed to settle and a sample (3 mL) of the clear yellow solution was added to Resin **1.115** (0.50 g, 0.26 mmol/g, 0.13 mmol) and the mixture was left to stir for 4 hours. The resin was collected, washed sequentially with DMF (2 x 5mL), water (2 x 5 mL), THF (2 x 5mL), CH_2Cl_2 (5 mL), methanol (2 x 5 mL), ether (2 x 5 mL), and dried in a drying pistol (1mmHg, 60°C) to give the title resin **1.116** as a pale yellow solid; FTIR ν_{max} (on bead) 3025s, 2924s, 1735s, 1601s, 1576s, 1493s, 1453s, 759s cm^{-1}. Resin **1.116** (100 mg, 0.026mmol) in CH_2Cl_2 (2.5 mL) and MeOH (0.5 mL) was treated with potassium trimethylsiloxide (50 mg, 0.39 mmol), then stirred for 1 hour. The resin was collected by filtration and washed with CH_2Cl_2 (3 mL). The filtrate and washings were combined, washed with 10% citric acid, dried ($MgSO_4$) and the solvent was removed under vacuum to give a colourless residue (2.2 mg, 18.3 μmol, 70%). ^{1}H NMR was consistent with an 11:2 mixture of 4-hydroxystyrene and 4-hydroxybenzaldehyde:[71] ^{1}H NMR (300 MHz) δ 9.88 (1H, s, ArC**H**O), 7.30 (2H, d, J = 8.8 Hz, Ar**H**), 6.81 (2H, d, J = 8.8 Hz, Ar**H**), 6.67 (1H, dd, J = 17.7, 11.0 Hz, ArC**H**CH_2), 5.61 (1H, d, J = 17.7 Hz, C(**H**)H=CHAr), 5.13 (1H, d, J = 11.0 Hz, C(**H**)H=CHAr).

3.27 4-[(1R*, 2R*,3S*)-3-Hydroxy-2-phenylcyclobutyl]phenol 1.117

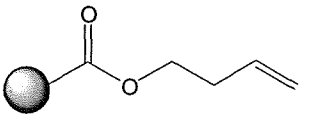


1.117

To a solution of 1-(phenylacetyl)pyrrolidine (**1.105**) (380 mg, 2.00 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0°C under nitrogen was added consecutively triflic anhydride (Distilled over P_2O_5) (340 μL, 2.00 mmol), 2,6-di-*tert*-butylpyridine (450 μL, 2.00 mmol) and resin **1.116** (1.00 g, 0.18 mmol). The reaction was refluxed for a 23 hours, then the resin was collected by filtration and washed with CH_2Cl_2 (6 x 10 mL) to give an orange solid. The resin was slurried with THF (10 mL) and saturated $NaHCO_3$(aq) (2 mL) and the mixture was stirred for 5 hours. The resin was collected by filtration, washed sequentially with water (2 x 10 mL), THF (10 mL), water (2 x 10 mL), THF (10 mL), MeOH (10 x 5 mL), ether (10 x 5 mL) and dried in a vacuum oven (10mm Hg, 50°C) to furnish cyclobutanone resin as an orange solid; FTIR ν_{max} (on bead) 3026m, 2926s, 2849w, 1783w, 1734s, 1686s, 1602m, 1495s, 1453s, 760s cm^{-1}. To a slurry of the cyclobutanone resin in anhydrous THF (5 mL) at –78°C under nitrogen was added 2.0 M $LiBH_4$ in THF (1.50 mL, 2.40 mmol), followed by MeOH (60 μL). The mixture was warmed to room temperature and stirred for 16 hours. The resin was collected by filtration then washed sequentially with CH_2Cl_2 (2 x 10 mL), THF (10 mL) and saturated NH_4Cl(aq). The filtrate and washings were combined, partitioned and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a pale yellow residue. The residue was purified by flash chromatography on silica gel (5 g) eluting with MeOH / CH_2Cl_2 (1:24) to give a colourless oil which required further purification by rotary chromatography on silica gel eluting with MeOH/CH_2Cl_2 (1:24) to furnish the title compound **1.117** as a colourless crystalline solid (15 mg, 62.5 μmol, 16 %): TLC (SiO_2, MeOH:CH_2Cl_2 (1:24), RF 0.25); FTIR ν_{max} (neat) 3406br, 3157br, 3029m, 2971w, 2936w, 1613m, 1601m, 1515s, 1451s, 1371m, 1237s, 1167s, 1104s, 1076s, 1028s, 826s, 733s, 693s cm^{-1}; ^1H NMR (400 MHz) δ 7.38-7.20 (5H, m, Ph**H**), 7.11 (2H, d, J = 8.5 Hz, Ar**H**), 6.78 (2H, d, J = 8.5 Hz, Ar**H**), 4.82 (1H, s, PhO**H**), 4.26 (1H, q, J = 7.5 Hz, C**H**OH), 3.30 (1H, dd, J = 9.6, 8.0 Hz, PhC**H**), 3.03 (1H, td, J = 10.0, 8.0 Hz, C**H**Ar), 2.77 (1H, dt, J = 10.5, 7.3 Hz, CH(**H**)CHOH), 2.08 (1H, s, O**H**), 2.03 (1H, td, J = 10.5, 8.6 Hz, CH(**H**)CHOH); ^{13}C NMR (100 MHz) δ

154.1 (s, Ar), 141.4 (s, Ar), 135.4 (s, Ph), 128.5 (2C, d, Ph), 128.0 (2C, d, Ar), 126.8 (d, Ph), 126.6 (d, Ar), 115.3 (d, Ar), 70.3 (d, **C**HOH), 59.2 (d, **C**HPh), 37.4 (t, **C**H_2CHOH), 36.5 (d, **C**HAr); LRMS (CI, ammonia) *m/z* (relative intensity) 258 (2) $[M+NH_4]^+$, 223 (2) $[M-H_2O]H^+$, 196 (18) $[4\text{-}HOPh(CH)_2Ph]^{\bullet+}$, 120 (100) $[4\text{-}HOPhCHCH_2]^{\bullet+}$, 91 (56) $\{PhCH_2]^+$; HRMS (EI) calculated for $C_{16}H_{16}O_2$ 240.11503, found 240.11480.

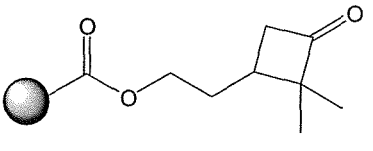
3.28 3-Buten-1-oxycarboxy Resin 1.118



1.118

Resin **1.74** (5.0 g, 0.95 mmol/g, 4.75 mmol) was stirred with 3-buten-1-ol (2.04 mL, 23.75 mmol) and 4-dimethylaminopyridine (2.90 g, 23.75 mmol) in CH_2Cl_2 (40 mL) for 10 minutes. Diisopropylcarbodiimide (3.71 mL, 23.75 mmol) was added to the slurry and the reaction mixture was stirred for 19 hours. The resin was collected by filtration, washed sequentially with CH_2Cl_2 (6 x 30 mL), MeOH (2 x 30 mL), ether (2 x 30 mL), and dried in a vacuum oven (50°C @ 10 mmHg) to give the title resin **1.118** as a pale yellow solid (5.21 g). Bromocresol green test indicated the reaction had gone to completion: FTIR ν_{max} (on bead) 2920m, 1731s, 1579w, 1492m, 1450m, 1149m, 757m, 697s cm^{-1}.

3.29 Cyclobutanone resin 1.119

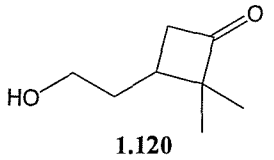


1.119

To a solution of N,N-dimethyl-2-methylpropanamide (**1.109**) (1.36 g, 11.90 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0°C under nitrogen was added consecutively triflic anhydride (2.00 mL, 11.90 mmol), 2,6-Di-*t*-butylpyridine (2.67 mL, 11.90 mmol) and resin **1.118** (2.50 g, 0.95 mmol/g, 2.38 mmol). The reaction mixture was warmed to room temperature and stirred for 16 hours. The resin was collected by filtration, washed with CH_2Cl_2 (4 x 20 mL) under nitrogen then dried in a vacuum oven (50°C @ 10 mmHg) to give cyclobutyliminium resin **1.122** as an orange solid (2.95 g). FTIR (on bead) showed significant quantities of reagents that had not been removed in the

washing procedure. Resin **1.122** (2.4 g) was stirred with THF (20 mL) for 10 minutes then saturated $NaHCO_3$(aq) (5 mL) was added and the reaction was stirred for 3 hours. The resin was collected by filtration, washed sequentially with THF / H_2O (1/1, 15 mL), H_2O (15 mL), THF / H_2O (1/1, 15 mL), H_2O (15 mL), THF (2 x 15 mL), CH_2Cl_2 (2 x 15 mL), ether (2 x 15 mL), and dried in a vacuum oven (50°C @ 10 mmHg) for 5 hours to give the title resin **1.119** as an orange solid (2.13 g): FTIR ν_{max} (on bead) 2923s, 1774s, 1731s, 1601m, 1492m, 1450s, 1152s, 1064s, 1029m, 698s cm^{-1}.

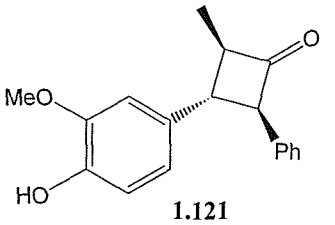
3.30 2,2-Dimethyl-3-(2-hydroxyethyl)butanone 37



1.120

To a slurry of resin **1.119** (0.20 g, 0.95 mmol/g, 0.19 mmol) in CH_2Cl_2 (5 mL) was added MeOH (1 mL) followed by potassium trimethylsilanoxide (0.10 g, 0.78 mmol) and the mixture was stirred for 4 hours. The resin was collected by filtration and washed with CH_2Cl_2 (4 x 5 mL). The filtrate and washings were combined and washed with 10% citric acid in water (10 mL). The aqueous phase was saturated with NaCl(s) and extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to furnish the title compound **1.120** as a colourless oil (28 mg, 0.19 mmol, 100 %): FTIR ν_{max} (neat) 3372br, 2962m, 1771s, 1263m, 1068m, 1030m, 798m cm^{-1}; TLC (SiO_2, ether, Rf 0.60); ^{1}H NMR (300 MHz) δ 3.66 (2H, q, J = 6.5 Hz, C**H**$_2$OH), 3.13 (1H, dd, J = 17.9, 9.4 Hz, CH(**H**)C=O), 2.72 (1H, dd, J = 17.4, 7.4 Hz, CH(**H**)C=O), 2.15 (1H, tdd, J = 9.4, 7.4, 5.5 Hz, C**H**CH$_2$CH$_2$OH), 1.94 (1H, broad, O**H**), 1.90 (1H, dtd, J = 13.9, 6.5, 5.5 Hz, CH(**H**)CH$_2$OH), 1.62 (1H, ddt, J = 13.9, 9.9, 6.5 Hz, CH(**H**)CH$_2$OH), 1.17 (3H, s, C**H**$_3$), 1.08 (3H, s, C**H**$_3$); ^{13}C NMR (75 MHz) δ 215.2 (s, **C**=O), 61.8 (t, C**H**$_2$OH), 61.1 (s, **C**Me$_2$), 48.6 (t, **C**H$_2$C=O), 33.8 (t, **C**H$_2$CH$_2$OH), 33.2 (d, **C**HCMe$_2$), 23.6 (q, **C**H$_3$), 17.4 (q, **C**H$_3$); LRMS (CI, ammonia) *m/z* (relative intensity) 160 (100%) $[M+NH_4]^+$, 143 (50%) $[M+H]^+$; HRMS (EI) calculated for $C_8H_{15}O_2$ 143.10720, found 143.10763.

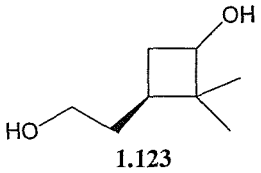
3.31 4-[(2R*,3R*,4S*)-2-methyl-3-oxo-4-phenylcyclobutyl]-2-methoxyphenol 1.121



1.121

Resin **1.106** (150 mg, 0.36 mmol/g, 54.0 μmol) was stirred with pyrrolidine (30 mg, 420 μmol) in CH_2Cl_2 (2 mL) for 7 hours. The resin was collected by filtration and washed with CH_2Cl_2/MeOH (4:1) (4 x 3 mL). The filtrate and washings were combined, washed with 10% citric acid in water (10 mL), dried ($MgSO_4$) and the solvent was removed under vacuum to give an orange residue. The residue was purified by flash chromatography on silica gel (5 g) eluting with ether:hexane (1:1) to furnish the title compound **1.121** (7 mg, 24.8 μmol, 47%) as a pale yellow oil: FTIR ν_{max} (neat) 3427br, 1773s, 1602w, 1516s, 1264m, 1238m, 1034w, 912w, 740m cm^{-1}; TLC (SiO_2, ether:hexane (1:1), Rf 0.40); ^1H NMR (400 MHz) δ 7.36-7.25 (5H, m, Ph**H**), 6.94 (1H, d, J = 8.0 Hz, Ar**H**), 6.89 (1H, dd, J = 8.0, 2.0 Hz, Ar**H**), 6.83 (1H, d, J = 2.0 Hz, Ar**H**), 5.53 (1H, s, ArO**H**), 4.53 (1H, dd, J = 9.6, 2.5 Hz, PhC**H**), 3.90 (3H, s, ArOC**H**$_3$), 3.45 (1H, dqd, J = 9.0, 7.0, 2.0 Hz, C**H**Me), 3.21 (1H, t, J = 9.0 Hz, C**H**Ar), 1.35 (3H, d, J = 7.0 Hz, C**H**$_3$CH); ^{13}C NMR (100 MHz) δ 208.0 (s, **C**=O), 146.9 (s, Ar), 144.9 (2C, s, Ar), 134.0 (s, Ph), 128.9 (2C, d, Ph), 127.4 (3C, d, Ph), 119.3 (d, Ar), 114.8 (d, Ar), 109.3 (d, Ar), 68.8 (d, **C**HPh), 59.5 (d, **C**HMe), 56.2 (q, **C**H$_3$O), 46.0 (d, **C**HAr), 12.9 (q, **C**H$_3$CH); LRMS (CI, ammonia) *m/z* (relative intensity) 283 (100) [M+H], 300 (6) $[M+NH_4]^+$, 264 (46) [4-Me-3HOPhCHCHMe]$^{\bullet+}$.

3.32 2,2-Dimethyl-3-(2-hydroxyethyl)cyclobutan-1-ol 1.123

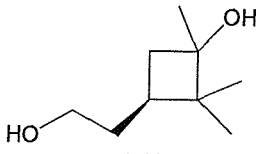


1.123

To a slurry of resin **1.119** (0.20 g, 0.95 mmol/g, 0.19 mmol) in anhydrous THF (3 mL) at –78°C under nitrogen was added 2 M $LiBH_4$ in THF (0.57 mL, 1.14 mmol) followed by MeOH (50 μL). The reaction mixture was warmed to room temperature and stirred for 16 hours, then quenched with saturated NH_4Cl(aq) (2 mL). The resin was collected by filtration and washed sequentially with water (3 mL), THF (3 mL)

and CH_2Cl_2 (3 x 3 mL). The filtrate and washings were combined, partitioned and the aqueous phase was saturated with NaCl(s) then extracted with CH_2Cl_2 (3 x 5 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a pale yellow oil. The oil was purified by flash chromatography on silica gel (5 g) eluting with MeOH/CH_2Cl_2 (1:19) to give the title compound **1.123** as a 5:1 mixture of diastereoisomers (20 mg, 0.139 mmol, 73%). An attempt was made to separate the diastereoisomers by rotary chromatography (SiO_2, 5% MeOH/CH_2Cl_2), which gave the major diastereoisomer **1.123a** (9 mg, 62.5 μmol, 33%) as a colourless oil. Spectroscopic details are consistent with those observed in the literature:{Karpf, 1981 #12} FTIR ν_{max} (neat) 3304br, 2935s, 1461m, 1132m, 1055s cm^{-1}; TLC (SiO_2, ether, Rf 0.25); ^1H NMR (400 MHz) δ 3.67 (1H, dd, J = 8.5, 7.5 Hz, C**H**OH), 3.51 (1H, dd, J = 8.5, 6.5 Hz, C(**H**)HOH), 3.51 (1H, ddd, J = 8.5, 6.5 Hz, C(**H**)HOH), 2.29 (1H, dt, J = 10.5, 7.0 Hz, CH(**H**)CHOH), 1.63-1.56 (1H, m, CH(**H**)CH_2OH), 1.52-1.40 (4H, m, C**H**CMe_2 + (2 x O**H**) + CH(**H**)CH_2OH), 1.37 (1H, dt, J = 10.5, 8.6 Hz, CH(**H**)CHOH); ^{13}C NMR (100 MHz) δ 73.3 (d, **C**HOH), 62.7 (t, **C**H_2OH), 44.9 (s, **C**Me_2), 35.7 (t, **C**H_2CHOH), 34.5 (d, **C**HCMe_2), 34.1 (t, **C**H_2CH_2OH), 29.0 (q, **C**H_3), 16.0 (q, **C**H_3); LRMS (CI, ammonia) *m/z* (relative intensity) 143 (100) $[M-H]^+$.

3.33 3-(2-Hydroxyethyl)-1,2,2-trimethylcyclobutanol 1.124

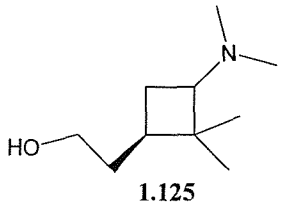


1.124

To a slurry of resin **1.119** (0.20 g, 0.95 mmol/g, 0.19 mmol) in anhydrous THF (2 mL) at –78°C under nitrogen was added 3.0 M MeMgCl in THF (127 μL, 0.38 mmol). The mixture was stirred for 30 minutes, then warmed to –20°C (over 90 minutes). An additional portion of 3 M MeMgCl in THF (100μL, 0.30 mmol) was added and the mixture was stirred for a further 45 minutes at between –30 and –20°C. The reaction was monitored by FTIR (on bead) for the disappearance of the ketone $C{=}O_{str}$ at 1774 cm^{-1}. The reaction mixture was quenched with glacial acetic acid (0.50 mL) and warmed to room temperature. The resin was collected by filtration, washed sequentially with THF (5 mL), water (5 mL), THF (5 mL), water (5 mL), THF (5 mL), CH_2Cl_2 (2 x 5 mL), ether (2 x 5 mL) and dried in a vacuum oven (50°C @ 10 mmHg) to give the cyclobutanol resin as a pale orange solid (150 mg); FTIR ν_{max} (on bead)

3306br, 2924m, 1730s, 1492m, 1449s, 1151m, 698s cm^{-1}. To a slurry of the cyclobutanol resin (150 mg, 0.95 mmol/g, 0.14 mmol) in CH_2Cl_2 (3 mL) was added MeOH (0.5 mL) followed by potassium trimethylsilanoxide (75 mg, 0.58 mmol) and the mixture was stirred for 16 hours. The resin was collected by filtration and washed with CH_2Cl_2 (4 x 5 mL). The filtrate and washings were combined and washed with 10% citric acid in water (10 mL). The aqueous phase was saturated with NaCl(s), then washed with CH_2Cl_2 (4 x 5 mL). The organic extracts were combined, dried (Na_2SO_4) and the solvent was removed under vacuum to give a pale brown oil (30 mg). The oil was purified by flash chromatography on silica gel (5 g) eluting with MeOH/CH_2Cl_2 (1:20 then 1:16 and finally 2:23) to give the title compound **1.124** as (17 mg, 77%) a colourless oil and as a 6:1 mixture of diastereoisomers: FTIR ν_{max} (neat) 3321br, 2961s, 2932s, 2865m, 1464m, 1372s, 1240s, 1052s cm^{-1}; TLC (SiO_2, ether, Rf 0.3); ^1H NMR (400 MHz) δ 3.50 (1H, t, J = 4.7 Hz, C(**H**)HOH), 3.50 (1H, t, J = 4.7 Hz, C(**H**)HOH), 1.99 (1H, dd, J = 8.2, 5.5 Hz, CH(**H**)CMeOH), 1.67-1.52 (5H, m, (2 x O**H**) + CH(**H**)CMeOH + C(**H**)HCH2OH + C**H**CMe$_2$), 1.46 (1H, ddt, J = 12.6, 7.7, 4.7 Hz, C(**H**)HCH$_2$OH), 1.10 (3H, s, COHC**H$_3$**), 0.94 (3H, s, CMeC**H$_3$**), 0.89 (3H, s, CMeC**H$_3$**); ^{13}C NMR (100 MHz) δ 73.3 (s, **C**MeOH), 62.2 (t, **C**H$_2$OH), 45.3 (s, **C**Me$_2$), 41.2 (t, **C**H$_2$CMeOH), 34.5 (d, **C**HCMe$_2$), 33.4 (t, **C**H$_2$CH$_2$OH), 24.0 (q, **C**H$_3$COH), 23.9 (q, **C**H$_3$), 18.0 (q, **C**H$_3$); LRMS (CI, NH_3) *m/z* (relative intensity) 157 (100) $[M-H]^+$; HRMS (EI) calculated for $C_9H_{18}O_2$ 159.13850, found 159.13924.

3.34 2-(3-Dimethylamino-2,2-dimethylcyclobutyl)ethanol 1.125

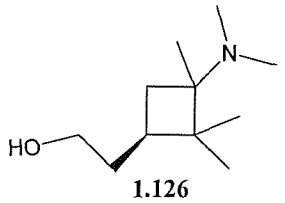


1.125

Resin **1.122** (0.28 g, 0.95 mmol/g, 0.27 mmol) was washed with anhydrous THF (2 x 3 mL) then CH_2Cl_2 (2 x 3 mL). The resin was slurried in anhydrous CH_2Cl_2 (2 mL), then treated with $NMe_4B(OAc)_3H$ (0.18 g, 0.68 mmol) and stirred for 17 hours. The resin was collected by filtration, washed sequentially with CH_2Cl_2 (2 x 3 mL), MeOH (3 mL), THF (3 mL), water (3 mL), THF (3 mL), CH_2Cl_2 (2 x 3 mL), MeOH (2 x 3 mL), Et_2O (2 x 3 mL) and dried in a vacuum oven (50°C @ 10 mmHg) to give cyclobutylamine resin as an orange solid (0.19 g): FTIR ν_{max} (on bead) 2923m, 1730s,

1492m, 1450s, 1223m, 1151s, 1028s, 698s cm^{-1}. The resin (0.19 g,0.95 mmol/g, 0.18 mmol) was stirred in CH_2Cl_2 (5 mL) for 5 minutes. To the slurry was added MeOH (1 mL) followed by potassium trimethylsilanoxide (0.10 g, 0.78 mmol) and the reaction was stirred for 4 hours. The resin was collected by filtration and washed sequentially with CH_2Cl_2 (3 x 3 mL) and MeOH (3 mL). The filtrate and washings were combined and the solvent was removed under vacuum to give a pale yellow solid. The solid was purified by flash chromatography on silica gel (5 g) eluting with 0.880 NH_3/MeOH/CH_2Cl_2 (1:6:93) to give the title compound **1.125** (30 mg, 0.171 mmol, 97 %,) as a colourless oil and as a 13:1 mixture of diastereoisomers: FTIR ν_{max} (neat) 2949s, 2861m, 2812m, 2767m, 1458s, 1053s cm^{-1}; TLC (SiO_2, 0.880 NH_3/MeOH/CH_2Cl_2 (1:5:94), Rf 0.10); ^{1}H NMR (400 MHz) δ 3.60 (1H, t, J = 6.9 Hz, C(**H**)HOH), 3.60 (1H, t, J = 6.9 Hz, C(**H**)HOH), 2.12-2.01 (3H, m, O**H** + C**H**NMe_2 + CH(**H**)CHNMe_2), 2.09 (6H, s, N(C**H**$_3$)$_2$), 1.72-1.62 (2H, m, C**H**CMe_2, CH(**H**)CH_2OH), 1.49 (1H, ddt, J = 11.0, 6.5, 4.0 Hz, CH(**H**)CH_2OH), 1.36 (1H, quartet, J = 9.8 Hz, CH(**H**)CHNMe_2), 1.11 (3H, s, CMe(C**H**$_3$)), 1.01 (3H, s, CMe(C**H**$_3$)); ^{13}C NMR (100 MHz) δ 69.3 (d, **C**HNMe_2), 61.8 (t, **C**H_2OH), 43.7 (q, N(**C**H_3)$_2$), 41.2 (s, **C**Me_2), 35.6 (d, **C**HCMe_2), 33.2 (t, **C**H_2CH_2OH), 30.2 (q, CMe(**C**H_3)), 30.1 (t, **C**H_2C$HNMe_2$), 16.2 (q, CMe(**C**H_3)); LRMS (ES +ve) *m/z* (relative intensity) 172 (100) $[M+H]^+$.

3.35 2-(3-Dimethylamino-2,2,3-trimethylcyclobutyl)ethanol 1.126

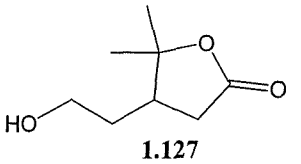


1.126

To a slurry of resin **1.122** (0.25 g, 0.95 mmol/g, 0.24 mmol) in anhydrous THF (3 mL) at –30°C under nitrogen was added 3.0 M MeMgCl in THF (0.32 mL, 0.95 mmol) and the reaction mixture was stirred for 2 hours. The reaction was quenched with saturated NH_4Cl(aq) (1 mL) and warmed to room temperature. The resin was collected by filtration, washed sequentially with THF (3 mL), water (3 mL), THF (3 mL), water (3 mL), THF (3 mL), CH_2Cl_2 (2 x 3 mL), Et_2O (2 x 3 mL) and dried in a vacuum oven (50°C @ 10 mmHg) to give cyclobutylamine resin (125 mg) as a pale yellow solid: FTIR ν_{max} (on bead) 2924m, 1731s, 1601w, 1492m, 1450s, 1151s, 1028m, 756m, 698s

cm^{-1}. The resin (0.13 g, 0.95 mmol/g, 0.12 mmol) was stirred in CH_2Cl_2 (3 mL) for 5 minutes. To the slurry was added MeOH (1 mL) followed by potassium trimethylsilanoxide (50 mg, 0.39 mmol) and the reaction mixture was stirred for 4 hours. The resin was filtered and washed sequentially with CH_2Cl_2 (2 x 3 mL), MeOH (3 mL), CH_2Cl_2 (2 x 3 mL). The filtrate and washings were combined and the solvent was removed under vacuum to give a pale yellow residue. The residue was purified by flash chromatography on silica gel (5 g) eluting with 0.880 NH_3/MeOH/CH_2Cl_2 (1:5:94) to give the title compound **1.126** as a colourless oil (16 mg, 87.6 μmol, 73 %), and as a 20:1 mixture of diastereoisomers: FTIR ν_{max} (neat) 3332br, 2932s, 2861m, 2816m, 2774m, 1461m, 1369m, 1052s cm^{-1}; TLC (SiO_2, 0.880 NH_3/MeOH/CH_2Cl_2 (1:10:89), Rf 0.10); ^{1}H NMR (400 MHz) δ 3.59 (2H, t, J = 6.8 Hz, C**H**$_2$OH), 2.00 (1H, s, O**H**), 1.99 (6H, s, N(C**H**$_3$)$_2$), 1.79-1.62 (3H, m, CH(**H**)CH_2OH + C**H**CMe_2 + CH(**H**)$CMeNMe_2$), 1.56-1.44 (2H, m, CH(**H**)CH_2OH + CH(**H**)$CMeNMe_2$), 1.06 (3H, s, C(C**H**$_3$)NMe_2), 1.03 (3H, s, C**H**$_3$CMe), 1.00 (3H, s, C**H**$_3$CMe); ^{13}C NMR (100 MHz) δ 62.0 (t, **C**H_2OH), 61.8 (s, **C**NMe_2), 42.6 (s, **C**Me_2), 38.7 (2C, q, N(**C**H_3)$_2$), 37.5 (t, **C**$H_2CMeNMe_2$), 35.0 (d, **C**$HCMe_2$), 33.2 (t, **C**H_2CH_2OH), 25.3 (q, C**C**H_3Me), 18.8 (q, C**C**H_3NMe_2), 10.6 (q, **C**H_3CMe); LRMS (ES +ve) *m/z* (relative intensity) 186 (100) $[M+H]^+$.

3.36 4-(2-Hydroxyethyl)-5,5-dimethyldihydrofuran-2-one 1.127

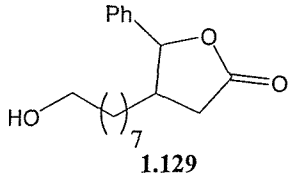


1.127

Resin **1.119** (0.30 g, 0.95 mmol/g, 0.285 mmol) and 50% *m*-chloroperbenzoic acid (0.30 g, 0.855 mmol) in CH_2Cl_2 (5 mL) were stirred for 5 days. The resin was collected by filtration, washed sequentially with CH_2Cl_2 (7 x 5 mL), MeOH (2 x 5 mL), ether (2 x 5 mL) and dried under a stream of air to give lactone resin as a pale yellow solid (276 mg): FTIR ν_{max} (on bead) 2922m, 1765s, 1729s, 1602w, 1492w, 1450m, 1249s, 699s cm^{-1}. Lactone resin (0.15 g, 0.95 mmol/g, 0.14 mmol) was stirred in CH_2Cl_2 (3 mL) for 5 minutes. To the slurry was added MeOH (0.5 mL) followed by potassium trimethylsilanoxide (75 mg, 0.59 mmol) and the reaction mixture was stirred for 4 hours. The resin was collected by filtration and washed with CH_2Cl_2 (4 x 4 mL). The filtrate and washings were combined, stirred with 2 M HCl (5 mL) for 5

minutes and partitioned. The aqueous phase was saturated with NaCl(s) and washed with CH_2Cl_2 (2 x 5 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to furnish the title compound **1.127** (15 mg, 94.9 μmol, 67%) as a colourless oil. Spectroscopic details are consistent with those observed in the literature:[154] FTIR ν_{max} (neat) 3447br, 2938m, 1757s, 1275m, 1129m, 1059m, 958w cm^{-1}; ^1H NMR (400 MHz) δ 3.74 (1H, dt, J = 10.5, 6.0 Hz, CH(**H**)OH), 3.66 (1H, ddd, J = 10.0, 7.0, 6.0 Hz, CH(**H**)OH), 2.69 (1H, dd, J = 16.1, 7.3 Hz, CH(**H**)C=O), 2.45-2.38 (1H, m, C**H**CMe_2), 2.34 (1H, dd, J = 15.6, 11.5 Hz, CH(**H**)C=O), 1.77 (1H, dtd, J = 14.0, 7.0, 3.5 Hz, CH(**H**)CH_2OH), 1.64 (1H, s, O**H**), 1.55 (1H, dq, J = 14.1, 6.0 Hz, CH(**H**)CH_2OH), 1.47 (3H, s, C(C**H**$_3$)Me), 1.28 (3H, s, C(C**H**$_3$)Me); ^{13}C NMR (100 MHz) δ 175.9 (s, **C**=O), 86.9 (s, **C**OC=O), 61.3 (t, **C**H_2OH), 42.8 (d, **C**HCMe_2), 35.1 (t, **C**H_2C=O), 32.5 (t, **C**H_2CH_2OH), 27.5 (q, **C**H_3), 22.1 (q, **C**H_3); LRMS (CI, NH_3) *m/z* (relative intensity) 159 (100) $[M+H]^+$, 141 (45) $[M-H_2O]^+$; HRMS (EI) calculated for $C_7H_{11}O_3$ 143.07114, found 143.07082.

3.37 4-(8-Hydroxyoctyl)-5-phenylyldihydrofuran-2-one 1.129

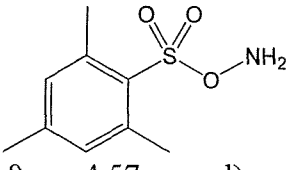


1.129

The procedure followed in experiment **3.36** was repeated to give the lactone resin (92 mg), from resin **1.128** (0.10 g, 0.36 mmol/g, 36.0 μmol) and *m*-chloroperbenzoic acid (0.13 g, 0.36 mmol) in CH_2Cl_2 (2 mL). The lactone resin (92 mg, 33.1 μmol) was stirred in CH_2Cl_2 (2 mL) for 5 minutes. To the slurry was added MeOH (0.5 mL) followed by potassium trimethylsilanoxide (40 mg, 0.31 mmol) and the reaction mixture was stirred for 20 hours. The resin was collected by filtration and washed with CH_2Cl_2 (4 x 3 ml). The filtrate and washings were combined, stirred with 2 M HCl (5 mL) for 5 minutes and partitioned. The aqueous phase was saturated with NaCl(s) and extracted with CH_2Cl_2 (5 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a colourless oil. The oil was purified by flash chromatography on silica gel (5 g) eluting with ether to give compound **1.129** (6.4 mg, 22.1 μmol, 67%) as a colourless oil: FTIR ν_{max} (neat) 3382br, 2925s, 2854s, 1777s, 1459w, 1224w, 1150w, 994w cm^{-1}; TLC (SiO_2, ether, Rf 0.15); ^1H NMR (300 MHz) δ 7.5-7.2 (5H, m, Ph**H**), 5.01 (1H, d, J = 7.4 Hz, PhC**H**),

3.63 (2H, t, J = 6.5 Hz, C**H**$_2$OH), 2.80 (1H, dd, J = 15.4, 6.5, CH(**H**)C=O), 2.39 (1H, m, **CH**CHPh), 2.33 (1H, dd, J = 15.8, 9.9 Hz, CH(**H**)C=O), 1.7-1.1 (14H, m, (C**H**$_2$)$_7$CH$_2$OH, O**H**); ^{13}C NMR (75 MHz) δ 176.5 (s, **C**=O), 138.5 (s, Ph**H**), 128.9 (d, Ph**H** x 3), 126.2 (d, Ph**H** x 2), 87.1 (d, **C**HPh), 63.1 (t, **C**H$_2$OH), 45.1 (d, **C**HCHPh), 35.5 (t, **C**H$_2$C=O), 32.8 (t, **C**H$_2$CH$_2$OH), 32.3 (t, **C**H$_2$(CH$_2$)$_2$OH), 29.6 (t, **C**H$_2$CHCHPh), 29.5 (t, **C**H$_2$(CH$_2$)$_3$OH), 29.4 (t, **C**H$_2$(CH$_2$)$_4$OH), 27.8 (t, **C**H$_2$(CH$_2$)$_5$OH), 25.8 (t, **C**H$_2$(CH$_2$)$_6$OH); LRMS (CI, ammonia) *m/z* (relative intensity) 291 (100) [M+H], 308 (22) [M+NH$_4$]$^+$, 273 (31) [M-H$_2$O]H$^+$; HRMS (EI) calculated for $C_{18}H_{26}O_3$ 290.18819, found 290.18828.

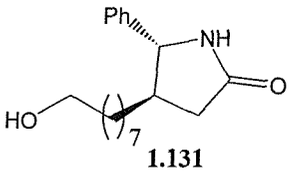
3.38 O-Mesitylenesulphonylhydroxylamine



Mesitylenesulphonyl chloride (1.0 g, 4.57 mmol) was added batchwise over 20 minutes to a solution of Et_3N (0.64 mL, 4.57 mmol) and ethyl-*N*-hydroxyacetimidate (0.47 g, 4.57 mmol) in DMF (1 mL) at 0°C under nitrogen. Triethylamine (60 μL, 0.43 mmol) was added to ensure the solution did not become acidic. The reaction mixture was kept below 10°C for 20 minutes, then was poured into iced water (15 mL). After stirring for 5 minutes the white solid was collected by filtration then washed with copious amounts of water. The solid was taken up in ether (10 mL), dried with ($MgSO_4$) and the solvent was removed under vacuum to give a white solid. The solid was triturated with hexane and dried in a vacuum desiccator to give the *N*-protected hydroxylamine (0.69 g, 3.51 mmol, 53%) as a white solid; spectroscopic details are consistent with those observed in the literature:[72] m.p. 55-57°C (Lit.[72] 54-56°C); ^{1}H NMR (300 MHz) δ 6.98 (2H, s, Ar**H**), 3.91 (2H, q, J = 7.4 Hz, C**H**$_2$OH), 2.66 (6H, s, ArC**H**$_3$), 2.32 (3H, s, ArC**H**$_3$), 2.05 (3H, s, C**H**$_3$C=N(OEt)), 1.20 (3H, t, J = 7.4 Hz, C**H**$_3$CH$_2$O). To the imidate (0.69 g, 2.42 mmol) in dioxan (1 mL) at 0°C was added 70% $HClO_4$(aq) (0.27 mL). The mixture became pasty and was stirred for a further 10 minutes. The mixture was poured into iced water, the resulting solid was collected by filtration, washed sequentially with cold water (30 mL), cold hexane (30 mL) and dried under vacuum to give the title compound as a white solid (0.32 g, 1.49 mmol, 33%). Spectroscopic details are consistent with those observed in the literature:[72] m.p.

93-94°C (Lit.[72] 93-94°C); FTIR ν_{max} (neat) 1597s, 1345s, 1171s cm^{-1}; ^1H NMR (300 MHz) δ 7.02 (2H, s, Ar**H**), 3.29 (2H, s, N**H**$_2$), 2.66 (6H, s, (C**H**$_3$)$_2$), 2.34 (3H, s, $ArCH_3$).

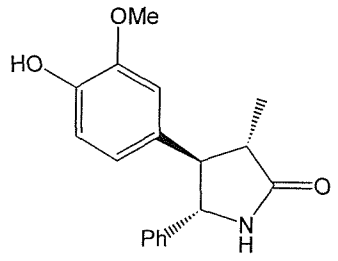
3.39 (4R*,5R*)-4-(8-Hydroxyoctyl)-5-phenylpyrrolidin-2-one 1.131



1.131

Resin **1.128** (0.19 g, 0.36 mmol/g, 68.4 μmol) and *O*-(mesitylenesulphonyl) hydroxylamine (63 mg, 0.34 mmol) in CH_2Cl_2 (2 mL) were stirred for 1 hour. The resin was collected by filtration, washed sequentially with CH_2Cl_2 (4 x 5 mL), 1:1 THF/water (2 x 5 mL), THF (5 mL), MeOH (2 x 5 mL), ether (5 mL), and dried in a vacuum oven (50°C @ 10 mmHg) to give the lactam resin (160 mg) as a pale orange solid: FTIR ν_{max} (on bead) 2925s, 2853m, 1729s, 1701s, 1492m, 1452s, 755s cm^{-1}. The lactam resin (76 mg, 27.3 μmol) was treated as in experiment **3.30** with trimethylsilanoxide (40 mg, 0.31 mmol) with MeOH (0.5 mL) and CH_2Cl_2 (3 mL) to give a pale yellow solid. The solid was purified by flash chromatography on silica gel (5 g) eluting with MeOH/CH_2Cl_2 (3:97) to give the title compound **1.131** (7 mg, 24.2 μmol, 84%) as a colourless glass: FTIR ν_{max} 3233br, 2926m, 2853w, 1690s, 1064w, 1057w cm^{-1}; TLC (SiO_2, MeOH:CH_2Cl_2 (3:97), Rf 0.25); ^1H NMR (300 MHz) δ 7.5-7.2 (5H, m, Ph**H**), 5.95 (1H, s, N**H**), 4.28 (1H, d, J = 6.9 Hz, C**H**Ph), 3.62 (2H, t, J = 6.5 Hz, C**H**$_2$OH), 2.61 (1H, dd, J = 15.4, 7.0 Hz, CH(**H**)C=O), 2.20 (1H, m, C**H**CHPh), 2.12 (1H, dd, J = 15.4, 8.4 Hz, CH(**H**)C=O), 1.70-1.10 (14H, m, (C**H**$_2$)$_7$CH$_2$OH, O**H**); ^{13}C NMR (75 MHz) δ 177.6 (s, **C**=O), 141.9 (s, Ph), 129.0 (2C, d, Ph), 128.3 (2C, d, Ph), 126.5 (d, Ph), 64.6 (d, **C**HPh), 63.1 (t, **C**H$_2$OH), 45.8 (d, **C**HCHPh), 37.0 (t, **C**H$_2$C=O), 33.3 (t, **C**H$_2$CH$_2$OH), 32.9 (t, **C**H$_2$(CH$_2$)$_2$OH), 29.6 (t, **C**H$_2$CHCHPh), 29.5 (t, **C**H$_2$(CH$_2$)$_3$OH), 29.4 (t, **C**H$_2$(CH$_2$)$_4$OH), 27.7 (t, **C**H$_2$(CH$_2$)$_5$OH), 25.8 (t, **C**H$_2$(CH$_2$)$_6$OH); LRMS (ESI +ve) *m/z* (relative intensity) 290 (73) $[M+H]^+$, 391 (100) $[M+Et_3NH]^+$, 579 (32) $[2M+H]^+$; HRMS (ESI) calculated for $C_{18}H_{27}NNaO_2$ 312.1934002, found 312.1935240.

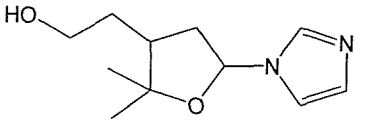
3.40 (3S*,4R*,5S*)-4-(4-Hydroxy-3-methoxyphenyl)-3-methyl-5-phenylpyrrolidin -2-one 1.132



1.132

Resin **1.106** (0.10 g, 0.36 mmol/g, 36.0 μmol) and *O*-(mesitylenesulphonyl) hydroxylamine (33 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) were stirred for 20 hours. The resin was collected by filtration, washed sequentially with CH_2Cl_2 (4 x 3 mL), 1:1 THF/water (2 x 3 mL), THF (3 mL), MeOH (2 x 3 mL), ether (3 mL), and dried in a vacuum oven (50°C @ 10 mmHg) to give a pale orange solid (70 mg): FTIR ν_{max} (on bead) 2923s, 1730m, 1642s, 1492m, 1450s, 1114m cm^{-1}. The resin was treated as in experiment **3.30** with trimethylsilanoxide (40 mg, 0.31 mmol), MeOH (0.5 mL) and CH_2Cl_2 (3 mL) to give a pale yellow solid. The solid was purified by flash chromatography on silica gel (5 g) eluting with MeOH/CH_2Cl_2 (3:97) to give the title compound **1.132** (11 mg) as a 10:1 mixture of isomers. The major isomer was isolated by HPLC (SiO_2 (Supelcosil), 15 cm x 4.6 mm, 15 μm, 2% MeOH/CH_2Cl_2, 3 mL/min, 254 nm, Rt = 3.66 min) to give a colourless glass (7 mg, 24.5 μmol, 68 %): FTIR ν_{max} (neat) 3250br, 1695s, 1519s, 1456m, 1271s cm^{-1}; TLC (SiO_2, MeOH:CH_2Cl_2 (3:97), Rf 0.30); ^{1}H NMR (400 MHz) δ 7.34-7.28 (3H, m, Ph**H**), 7.16-7.12 (2H, m, Ph**H**), 6.87 (1H, d, J = 8.0 Hz, Ar**H**), 6.65 (1H, dd, J = 8.0, 2.0 Hz, Ar**H**), 6.50 (1H, d, J = 2.0 Hz, Ar**H**), 5.78 (1H, broad, PhO**H**), 5.57 (1H, s, N**H**), 4.58 (1H, d, J = 8.0 Hz, C**H**Ph), 3.80 (3H, s, PhOC**H**$_3$), 2.79 (1H, t, J = 7.5 Hz, C**H**Ar), 2.74 (1H, dq, J = 8.0, 6.5 Hz, C**H**Me), 1.22 (3H, d, J = 6.5 Hz, C**H**$_3$CH); ^{13}C NMR (100 MHz) δ 178.8 (s, **C**=O), 146.7 (s, Ar), 145.1 (s, Ar), 140.2 (s, Ar), 130.2 (s, Ph), 128.9 (2C, d, Ph), 128.4 (d, Ph), 126.4 (2C, d, Ph), 120.7 (d, Ar), 114.8 (d, Ar), 110.7 (d, Ar), 64.2 (d, **C**HPh), 60.8 (d, **C**HMe), 56.1 (q, ArO**C**H$_3$), 44.3 (d, **C**HAr), 14.1 (q, CH**C**H$_3$); LRMS (ES +ve) *m/z* (relative intensity) 298 (5) $[M+H]^+$, 153 (100) $[4\text{-MeO-5-HOPhCHCHMe}]^{\bullet+}$, 595 (12) $[2M+H]^+$; HRMS (ESI +ve) calculated for $C_{18}H_{20}NO_3$ 298.1437699, found 298.1440990.

3.41 2-(5-Imidazol-1-yl-2,2-dimethyltetrahydrofuran-3-yl)ethanol 1.133

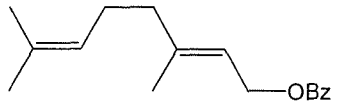


1.133

Resin **1.119** (0.20 g, 0.95 mmol/g, 0.19 mmol) and imidazole (0.13 g, 1.90 mmol) in THF (3 mL) in a quartz tube were irradiated with a 450 W medium pressure mercury arc lamp with water cooled immersion well. The reaction was stirred for 42 hours, meanwhile the reaction was monitored by FTIR (on bead) for the disappearance of the ketone $C{=}O_{str}$ at 1774 cm^{-1}. The resin was collected by filtration, then washed sequentially with THF (4 x 5 mL), ether (2 x 5 mL) and dried in a stream of air to give an orange solid (180 mg). To the resin were added CH_2Cl_2 (3 mL), MeOH (1 mL) and potassium trimethylsilanoxide (70 mg) and the reaction was stirred for 4 hours. The resin was collected by filtration, then washed CH_2Cl_2/MeOH (3:1) (3 x 5 mL). The filtrate and washings were combined and the solvent was removed under vacuum to give a pale orange residue. The residue was purified by flash chromatography on silica gel (5 g) eluting with 0.880 NH_3 /MeOH/CH_2Cl_2 (1:8:91) to furnish the title compound **1.133** (28 mg, 0.133 mmol, 78%) as a colourless glass and as a 4:3 mixture of anomers: FTIR ν_{max} 3216br, 2972w, 1061m, 913m, 733s cm^{-1}; TLC (SiO_2, 0.880 NH_3:MeOH:CH_2Cl_2 (1:3:96), Rf 0.21); Major anomer: ^{1}H NMR (400 MHz) δ 7.66 (1H, s, Ar**H**), 7.08 (1H, s, Ar**H**), 7.05 (1H, s, Ar**H**), 5.82 (1H, dd, *J* = 8.5, 6.0 Hz, C**H**Ar), 3.80-3.65 (2H, m, C**H$_2$**OH), 2.67 (1H, dt, *J* = 12.5, 6.0 Hz, CH(**H**)CHAr), 2.32-2.18 (1H, m, C**H**), 2.04 (1H, td, *J* = 12.5, 8.5 Hz, CH(**H**)CHAr), 1.72-1.65 (2H, m, CH(**H**)CH_2OH, O**H**), 1.60-1.45 (1H, m, CH(**H**)CH_2OH), 1.36 (3H, s, C**H$_3$**), 1.20 (3H, s, C**H$_3$**); ^{13}C NMR (100 MHz) δ 129.9 (d, Ar), 85.8 (d, Ar), 85.4 (d, Ar), 85.0 (d, **C**HAr), 84.6(s, **C**Me$_2$), 61.8 (t, **C**H_2OH), 45.5 (d, **C**H), 39.5 (t, **C**H_2), 32.6 (t, **C**H_2CH_2OH), 27.9 (q, **C**H_3), 24.0 (q, **C**H_3); Minor anomer: ^{1}H NMR (400 MHz) δ 7.66 (1H, s, Ar**H**), 7.08 (1H, s, Ar**H**), 7.02 (1H, s, Ar**H**), 5.85 (1H, d, *J* = 5.5 Hz, C**H**Ar), 3.80-3.65 (2H, m, C**H$_2$**OH), 2.45-2.37 (1H, m, CH(**H**)CHAr), 2.32-2.18 (1H, m, CH(**H**)CHAr), 1.72-1.65 (3H, m, C**H**, CH(**H**)CH_2OH, O**H**), 1.60-1.45 (1H, m, CH(**H**)CH_2OH), 1.40 (3H, s, C**H$_3$**), 1.14 (3H, s, C**H$_3$**); ^{13}C NMR (100 MHz) δ 129.9 (d, Ar), 85.8 (d, Ar), 85.4 (d, Ar), 85.0 (d, **C**HAr), 84.6 (s, **C**Me$_2$), 61.8 (t, **C**H_2OH), 43.6 (d, **C**H), 39.8 (t, **C**H_2), 32.8 (t, **C**H_2CH_2OH), 28.2 (q, **C**H_3), 22.9 (q, **C**H_3); LRMS

(ES +ve) *m/z* (relative intensity) 211 (38) $[M+H]^+$, 127 (100) $[C_8H_{15}O]^+$, 421 (6) $[2M+H]^+$.

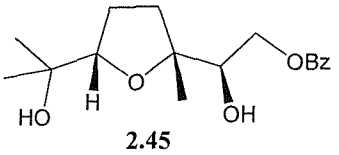
3.42 Geranyl Benzoate 2.44



2.44

To a solution of geraniol (10.0 g, 64.9 mmol) and benzoyl chloride (9.12 g, 64.9 mmol) in CH_2Cl_2 (100 mL) at 0°C was added triethylamine (9.93 mL, 71.4 mmol) in CH_2Cl_2 (30 mL). The reaction was warmed to room temperature and stirred for 4 h. The reaction mixture was washed with 10% citric acid in water, then dried ($MgSO_4$) and the solvent was removed under vacuum to give a yellow oil. The oil was purified by distillation (96-105°C at 18 mmHg) to give the title compound **2.44** (14.1 g, 54.5 mmol, 84%) as a colourless oil, spectroscopic details are consistent with those observed in the literature:[155] ^{1}H NMR (400 MHz): δ 8.08 (2H, m, Ph**H**), 7.55 (1H, tt, J = 7.0, 1.3 Hz, Ph**H**), 7.44 (2H, td, J = 7.3, 1.5 Hz, Ph**H**), 5.48 (1H, tq, J = 7.0, 1.3 Hz, C**H**CMe$_2$), 5.11 (1H, tt, J = 7.0, 1.3 Hz, C**H**CH$_2$OBz), 4.86 (2H, d, J = 7.0 Hz, C**H**$_2$OBz), 2.18-2.05 (4H, m, C**H**$_2$C**H**$_2$), 1.78 (3H, s, C**H**$_3$), 1.69 (3H, s, C**H**$_3$), 1.61 (3H, s, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9 (s, **C**=O), 142.8 (s, **C**Me$_2$CH), 133.2 (d, Ph), 132.2 (s, **C**Me$_2$), 131.0 (s, Ph), 130.0 (2C, d, Ph), 128.7 (2C, d, Ph), 124.2 (d, **C**HCMe$_2$), 118.8 (d, **C**HCMe), 62.3 (t, **C**H$_2$OBz), 40.0 (t, **C**H$_2$), 26.7 (t, **C**H$_2$), 26.0 (q, C**C**H$_3$), 18.1 (q, CMe**C**H$_3$), 18.1 (q, CMe**C**H$_3$).

3.43 (2R*)-2-Hydroxy-2-[(2R*,5S*)-5-(1-hydroxy-1-methylethyl)-2-methyltetrahydrofuran-2-yl]ethyl benzoate 2.45

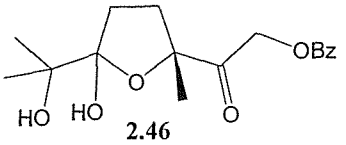


2.45

To a solution of geranyl benzoate (0.25 g, 0.969 mmol) in acetone (20 mL) with phosphate buffer [0.067 M KH_2PO_4 (1.4 mL), 0.067 M Na_2HPO_4 (0.6 mL)] was added a mixture of acetic acid (0.12 g, 2.03 mmol) and 0.4 M $KMnO_4$ (3.6 mL, 1.45 mmol) at -20 °C over 20 minutes. The reaction was stirred at –20°C for a further 1 h, poured onto ice and treated with saturated $Na_2S_2O_5$(aq) to give a colourless solution. The solution was saturated with NaCl(s) and extracted with CH_2Cl_2 (5 x 30 mL). The

organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under reduced pressure to give a colourless oil. The oil was purified by flash chromatography on silica gel (13 g) eluting with CH_2Cl_2/hexane (50:50) to give fractions 1-12 containing starting material then eluting with ether/hexane (50:50) to give fractions13-24 and finally eluting with ether to give fraction 25. Fractions 13-21 were combined and re-purified by HPLC [Supelcosil (SiO_2), 4.6 x 150 mm, 2 mL/min, 240 nm, 0.5% EtOH/30% CH_2Cl_2/ 50% Hexane] to give compounds **2.47** (5 mg, 17.2 μmol, 2%) and **2.48** (3 mg, 9.26 μmol, 1%) as colourless oils. Fractions 22-25 were combined and purified by HPLC [Supelcosil (SiO_2), 4.6 x 150 mm, 2 mL/min, 240 nm, 1% EtOH/50% CH_2Cl_2/ 50% Hexane] to give the title compound **2.45** as a white solid (115 mg, 0.373 mmol, 39%), lactol **2.46** (9 mg, 28.0 μmol, 3%) as an epimeric mixture at C-2 in the lactol ring and *trans*-THF diol **2.49** (5 mg, 15.3 μmol, 2%) as a white solid. Analytical data for compound **2.45**: m.p. 70-71°C; TLC (SiO_2, MeOH:EtOAc:CH_2Cl_2 (0.5:30:69.5), Rf 0.30); FTIR ν_{max} (neat) 3376br, 2967w, 1717s, 1451m, 1379m, 1316m, 1276s, 1119s, 1095s, 1070s, 1026m, 950w cm^{-1}; ^1H NMR (300 MHz): δ 8.07 (2H, d, J = 7.0 Hz, Ph**H**), 7.57 (1H, t, J = 7.4 Hz, Ph**H**), 7.45 (2H, t , J = 7.7 Hz, Ph**H**), 4.56 (1H, dd, J = 11.9, 3.5 Hz, CH(**H**)OBz), 4.40 (1H, dd, J = 11.4, 7.9 Hz, CH(**H**)OBz), 3.89 (1H, t, J = 7.4 Hz, THF), 3.85 (1H, dd, J = 7.6, 3.0 Hz, C**H**OH), 2.42 (2H, brs, O**H**), 2.24 (1H, ddd, J = 12.4, 8.9, 5.0 Hz, THF), 1.87-2.10 (2H, m, THF), 1.72 (1H, dt, J = 11.9, 8.4 Hz, THF), 1.29 (3H, s, C**H**$_3$), 1.28 (3H, s, C**H**$_3$), 1.14 (3H, s, C**H**$_3$); ^{13}C NMR (75 MHz): δ 166.9 (s, **C**=O), 133.3 (d, Ph), 131.0 (s, Ph), 129.9 (2C, d, Ph), 128.5 (2C, d, Ph), 85.8 (d, THF), 84.4 (s, THF), 75.6 (s, **C**Me$_2$OH), 72.0 (d, **C**HOH), 66.7 (t, **C**H$_2$OBz), 35.8 (t, THF), 27.8 (q, CMeOH**C**H$_3$), 26.7 (t, THF), 25.4 (q, CMeOH**C**H$_3$), 23.2 (q, **C**H$_3$); LRMS (CI, NH_3) *m/z* (relative intensity): 309 (5) $[M+H]^+$, 105 (100) $[PhCO]^+$, 291 (86) $[M-H_2O]H^+$; Elemental analysis calculated for $C_{17}H_{23}O_5$: C 66.43, H 7.54%. Found: C 66.14, H 7.90%.

2-[5-Hydroxy-5-(1-hydroxy-1-methylethyl)-2-methyltetrahydrofuran-2-yl]-2-oxoethyl benzoate **2.46**

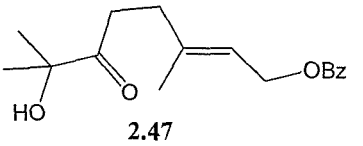


2.46

Analytical data for compound **2.46**: FTIR ν_{max} (neat) 3472br, 1721s, 1452m, 1370m, 1280s, 1129s, 1026s cm^{-1}; TLC (SiO_2, EtOAc/hexane (1:1), Rf 0.35); HPLC [Supelcosil (SiO_2), 4.6 x 150 mm, 2 mL/min, 240 nm, 1% EtOH/40% CH_2Cl_2/ 60%

Hexane, Rt 5.39 min]; GC [3% Cyanopropylphenyl / Dimethylsiloxane; 250°C; FID; Rt 3.70 min]; ^{1}H NMR (400 MHz): δ 8.10 (2H, td, *J* = 7.0, 1.5 Hz, Ph**H**), 7.59 (1H, td, *J* = 7.5, 1.3 Hz, Ph**H**), 7.47 (2H, t, *J* = 7.5 Hz, Ph**H**), 5.48 (1H, d, *J* = 17.6 Hz, C**H**$_2$OBz), 5.29 (1H, d, *J* = 17.6 Hz, C**H**$_2$OBz), 5.23 (1H, s, O**H**), 3.87 (1H, br, O**H**), 2.67-2.57 (1H, m, γ-lactol), 2.12-2.03 (1H, m, γ-lactol), 2.01-1.86 (2H, m, γ-lactol), 1.43 (3H, s, γ-lactol-C**H**$_3$), 1.36 (3H, s, C(C**H**$_3$)MeOH), 1.31 (3H, s, C(C**H**$_3$)MeOH); ^{13}C NMR (100 MHz): δ 207.3 (s, **C**=O), 166.4 (s, Ph**C**=O), 133.4 (d, Ph), 130.1 (2C, d, Ph), 128.7 (s, Ph), 128.6 (2C, d, Ph), 111.0 (s, γ-lactol), 89.0 (s, γ-lactol), 74.6 (s, **C**Me$_2$OH), 66.3 (t, **C**H$_2$OBz), 34.4 (t, γ-lactol), 31.9 (t, γ-lactol), 26.5 (q, CMe(**C**H$_3$)OH), 24.5 (q, CMe(**C**H$_3$)OH), 23.9 (q, γ-lactol-**C**H$_3$); LRMS (CI, NH$_3$) *m/z* (relative intensity): 322 (7) $[M+H]^+$, 305 (100) $[M-H_2O]H^+$, 105 (98) $[PhCO]^+$; HRMS (ESI) calculated for $C_{17}H_{22}O_6Na$ 345.1308, found 345.1311.

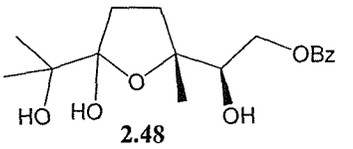
(*E*)-7-Hydroxy-3,7-dimethyl-6-oxooct-2-enyl benzoate **2.47**



2.47

Analytical data for compound **2.47**: FTIR ν_{max} (neat) 3492br, 1715s, 1272s, 1113m, 1070w, 715m cm^{-1}; TLC (SiO_2, MeOH:EtOAc:CH_2Cl_2 (0.5:30:59.5), Rf 0.80); HPLC [Supelcosil (SiO_2), 4.6 x 150 mm, 2 mL/min, 240 nm, 1% EtOH/40% CH_2Cl_2/ 60% Hexane, Rt 2.13 min]; GC [3% Cyanopropylphenyl / Dimethylsiloxane; 250°C; FID; Rt 4.17 min]; ^{1}H NMR (300 MHz): δ 8.05 (2H, d, *J* = 7.0 Hz, Ph**H**), 7.57 (1H, t, *J* = 7.4 Hz, Ph**H**), 7.44 (2H, t, *J* = 7.4 Hz, Ph**H**), 5.49 (1H, t, *J* = 6.9 Hz, C**H**CH$_2$OBz), 4.84 (2H, d, *J* = 7.0 Hz, CHC**H**$_2$OBz), 3.72 (1H, s, O**H**), 2.72 (2H, t, *J* = 8.1 Hz, C**H**$_2$C=O), 2.39 (2H, t, *J* = 7.9 Hz, C**H**$_2$), 1.80 (3H, s, C**H**$_3$), 1.39 (6H, s, C(C**H**$_3$)$_2$OH); ^{13}C NMR (75 MHz): δ 140.6 (s, **C**MeCH), 133.1 (d, Ph), 131.0 (s, Ph), 129.7 (2C, d, Ph), 128.5 (2C, d, Ph), 119.3 (d, **C**=CCH$_3$), 61.8 (t, **C**H$_2$OBz), 33.9 (t, C=C(CH$_3$)**C**H$_2$), 33.2 (t, **C**H$_2$C=OCMe$_2$OH), 26.7 (q, C(**C**H$_3$)$_2$OH), 16.9 (q, C=C**C**H$_3$); LRMS (CI, NH$_3$) *m/z* (relative intensity): 308 (5) $[M+NH_4]^+$, 169 (100) $[M-PhCO_2]^+$; HRMS (ESI) calculated for $C_{17}H_{22}O_4Na$ 313.1410303, found 313.1412040.

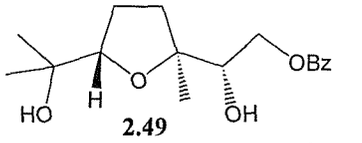
2-Hydroxy-2-[5-hydroxy-5-(1-hydroxy-1-methylethyl)-2-methyltetrahydrofuran-2-yl]ethyl benzoate **2.48**



2.48

Analytical data for compound **2.48**: FTIR ν_{max} (neat) 3483br, 1720s, 1275s, 1109s, 1094s, 1071m, 1024m, 921m, 712s cm^{-1}; TLC (SiO_2, EtOAc/hexane (1:1), Rf 0.60); HPLC [Supelcosil (SiO_2), 4.6 x 150 mm, 2 mL/min, 240 nm, 1% EtOH/40% CH_2Cl_2/ 60% Hexane, Rt 2.62 min]; GC [3% Cyanopropylphenyl / Dimethylsiloxane; 250°C; FID; Rt 3.55 min]; ^{1}H NMR (400 MHz) δ 8.06 (2H, dd, *J* = 7.0, 1.5 Hz, Ph**H**), 7.58 (1H, tt, *J* = 7.0, 1.5 Hz, Ph**H**), 7.45 (2H, dd, *J* = 7.5, 1.5 Hz, Ph**H**), 4.29 (1H, dd, *J* = 11.4, 6.0 Hz, CH(**H**)OBz), 4.19 (1H, dd, *J* = 11.4, 6.0 Hz, CH(**H**)OBz), 4.04 (1H, t, *J* = 6.0 Hz, C**H**OH), 2.28 (2H, brs, O**H**), 2.02 (1H, td, *J* = 12.1, 4.0 Hz, γ-lactol), 1.99-1.86 (2H, m, γ-lactol), 1.71 (1H, td, *J* = 12.0, 4.0 Hz, γ-lactol), 1.57 (3H, s, C**H**$_3$), 1.35 (3H, s, C(C**H**$_3$)MeOH), 1.34 (3H, s, C(C**H**$_3$)MeOH); ^{13}C NMR (100 MHz): δ 133.3 (d, Ph), 130.2 (s, Ph), 129.9 (2C, d, Ph), 128.6 (2C, d, Ph), 113.5 (s, γ-lactol), 85.3 (s, γ-lactol), 80.5 (d, **C**HOH), 70.5 (s, **C**Me$_2$OH), 64.3 (t, **C**H$_2$OBz), 35.8 (t, γ-lactol), 32.5 (t, γ-lactol), 25.7 (q, C(**C**H$_3$)CH$_3$OH), 24.6 (q, **C**H$_3$), 16.1 (q, C(**C**H$_3$)CH$_3$OH); LRMS (ESI +ve) *m/z* (relative intensity) 671 (22) $[2M+Na]^+$, 653 (90) $[M+[M-H_2O]]Na^+$, 635 (97) $[2[M-H_2O]+Na]^+$, 347 (63) $[M+Na]^+$, 307 (100) $[M-H_2O]H^+$; HRMS (ESI) calculated for $C_{17}H_{22}O_5Na$ 329.1359449, found 329.1359130.

(2*S**)-2-Hydroxy-2-[-(2*S**, 5*S**)-5-(1-hydroxy-1-methylethyl)-2-methyltetra hydrofuran-2-yl]ethyl benzoate **2.49**

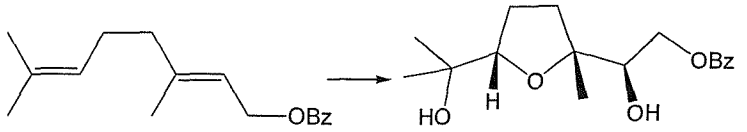


2.49

Analytical data for compound **2.49**: m.p. 108-109°C; FTIR ν_{max} (neat) 3432br, 2970w, 1705s, 1315m, 1276s, 1120m, 1059m, 1026m cm^{-1}; TLC (SiO_2, MeOH/CH_2Cl_2 (1:9), Rf 0.40); ^{1}H NMR (400 MHz) δ 8.12 (2H, dd, *J* = 7.0, 1.5 Hz, Ph**H**), 7.58 (1H, tt, *J* = 7.0, 1.2 Hz, Ph**H**), 7.46 (2H, dd, *J* = 7.6 Hz, Ph**H**), 5.22 (1H, dd, *J* = 5.5, 3.5 Hz, C**H**OH), 3.98 (1H, dd, *J* = 12.5, 6.0 Hz, C(**H**)HOBz), 3.93 (1H, dd, *J* = 12.0, 3.5 Hz, C(**H**)HOBz), 3.84 (1H, dd, *J* = 8.6, 6.5 Hz, THF), 2.50 (2H, brs, O**H**), 2.15 (1H, ddd, *J* = 12.6, 9.0, 4.0 Hz, THF), 2.05 (1H, dq, *J* = 11.5, 8.0 Hz, THF),

1.89-1.81 (1H, m, THF), 1.76 (1H, dt, J = 12.0, 8.5 Hz, THF), 1.35 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.34 (3H, s, CH_3); ^{13}C NMR (100 MHz): δ 167.2 (s, Ph**C**=O), 133.4 (d, Ph), 130.2 (2C, d, Ph), 130.0 (s, Ph), 128.7 (2C, d, Ph), 86.0 (d, THF), 84.3 (s, THF), 79.6 (d, **C**HOH), 70.9 (s, **C**Me_2OH), 62.7 (t, **C**H_2OBz), 35.6 (t, THF), 28.0 (q, C(**C**H_3)CH_3OH), 26.4 (t, THF), 25.2 (q, C(**C**H_3)CH_3OH), 24.1 (q, **C**H_3); LRMS (ESI +ve) *m/z* (relative intensity) 639 (100) $[2M+Na]^+$, 309 (13) $[M+H]^+$, 331 (17) $[M+Na]^+$, 617 (25) $[2M+H]^+$; Elemental analysis calculated for $C_{17}H_{23}O_5$: C 66.43, H 7.54%. Found: C 66.10, H 8.00%.

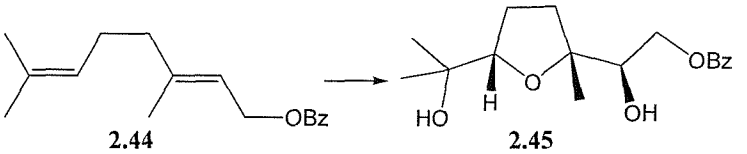
3.44 Optimisation of the Oxidation of Geranyl benzoate



2.44 **2.45**

In a typical procedure: To a solution of geranyl benzoate (**2.44**) (50 mg, 0.194 mmol) and phase transfer catalyst in solvent (2 mL) was added a mixture of AcOH and 0.4 M $KMnO_4$ over 2 minutes. The reaction was stirred vigorously for 1 h, then an aqueous solution of (10% w/v) oxalic acid (2 mL) was added. The solvents were removed under reduced pressure, to give a red residue. The residue was dissolved in 1:1 MeOH/water (100 mL). The solution was analysed by HPLC [Xorbax ODS-3, 150 x 4.6 mm; Gradient (MeCN / water) 50-100% MeOH (15 mins); UV @ 254 nm; Rt (THF diol **2.45**) = 5.1 min] and a calibration curve allowed yields to be established. THF diol **2.45** and lactol **2.46** were isolated by removing the solvent under reduced pressure, then purifying the resulting residue by flash chromatography (silica, 0.1% MeOH, 20-30% EtOAc, 80-70% CH_2Cl_2) to give target compounds as white solids.

3.45 Optimised Procedure for Oxidation of Geranyl benzoate 2.44

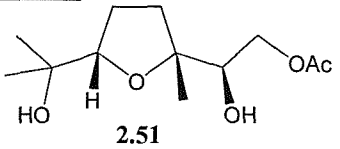


2.44 **2.45**

To a rapidly stirring mixture of geranyl benzoate (**2.44**) (0.50 g, 1.94 mmol) with Adogen 464 (0.36 g, 0.776 mmol) in ether (10 mL) was added a mixture of AcOH (0.47 mL, 7.76 mmol) and 0.4 M $KMnO_4$(aq) (9.7 mL, 3.88 mmol) over 2 minutes. After 1 h the reaction was treated with 10% oxalic acid in water (10 mL) and was

stirred for 5 minutes. The mixture was partitioned and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a colourless oil. The oil was purified by flash chromatography on silica gel (30 g) eluting with MeOH:EtOAc:CH_2Cl_2 (0.5:30:69.5) to give the target compound **2.45** (221 mg, 78%) as a colourless oil.

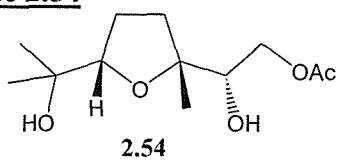
3.46 (2R*)-2-Hydroxy-2-[(2R*,5S*)-5-(1-hydroxy-1-methylethyl)-2-methyltetrahydrofuran-2-yl]ethyl acetate 2.51



2.51

The optimised procedure in experiment **3.45** was followed using geranyl acetate (**2.50**) (0.50 g, 2.55 mmol) with Adogen 464 (1.78 g, 3.83 mmol), AcOH (1.75 mL, 30.61 mmol) and 0.4 M $KMnO_4$(aq) (19.0 mL, 7.65 mmol) in ether (40 mL) to give a red residue which was purified by flash chromatography on silica gel (30 g) eluting with MeOH:EtOAc:CH_2Cl_2 (0.5:30:69.5 then 0.5:40:59.5) to furnish the title compound **2.51** (0.40 g, 1.63 mmol, 64 %) as a colourless crystalline solid: m.p. 102-104°C (lit.[75] 107-108°C); FTIR ν_{max} (neat) 3334br, 1732s, 1250s, 1236s, 1056m, 1037s, 843s cm^{-1}; TLC (SiO_2, MeOH:EtOAc:CH_2Cl_2 (0.5:50:49.5), Rf 0.20); ^1H NMR (400 MHz, $CDCl_3$): δ 4.31 (1H, dd, J = 11.5, 3.0 Hz, CH(**H**)OAc), 4.11 (1H, dd, J = 11.5, 8.5 Hz, CH(**H**)OAc), 3.87 (1H, t, J = 7.5 Hz, THF), 3.70 (1H, dd, J = 8.5, 3.0 Hz, C**H**OH), 2.41 (2H, sbr, O**H**), 2.18 (1H, ddd, J = 12.0, 9.0, 5.0 Hz, THF), 2.11 (3H, s, C**H**$_3$CO$_2$), 2.05-1.88 (2H, m, THF), 1.69 (1H, dt, J = 12.1, 8.5 Hz, THF), 1.28 (3H, s, C**H**$_3$), 1.22 (3H, s, C**H**$_3$), 1.13 (3H, s, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6 (s, **C**=O), 85.8 (d, THF), 84.3 (s, THF), 75.5 (s, **C**HOH), 72.0 (d, **C**Me$_2$OH), 66.2 (t, **C**H$_2$OAc), 35.7 (t, THF), 27.8 (q, C(**C**H$_3$)CH$_3$OH), 26.7 (t, THF), 25.4 (q, C(**C**H$_3$)CH$_3$OH), 23.1 (q, **C**H$_3$), 21.2 (q, **C**H$_3$C=O); LRMS (CI, ammonia) *m/z* (relative intensity): 247 (5) $[M+H]^+$, 229 (100) $[M-H_2O]H^+$. Elemental analysis calculated for $C_{12}H_{22}O_5$ C 58.52, H 9.00%; found C 58.50, H 9.16%.

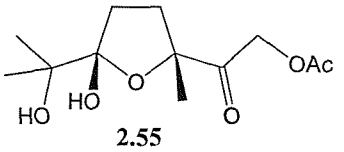
3.47 (2S*)-2-Hydroxy-2-[(2R*,5S*)-5-(1-hydroxy-1-methylethyl)-2-methyltetrahydrofuran-2-yl]ethyl acetate 2.54



2.54

The optimised procedure in experiment **3.45** was followed using neryl acetate (0.44 g, 2.25 mmol) with Adogen 464 (0.47 g, 1.02 mmol), AcOH (0.61 g, 10.20 mmol) and 0.4 M $KMnO_4$(aq) (12.8 mL, 0.510 mmol) in ether (10 mL) to give a red residue which was purified by flash chromatography on silica gel (30 g) eluting with MeOH:EtOAc:CH_2Cl_2 (0.5:20:79.5 then 0.5:30:69.5) to furnish the title compound **2.54** (188 mg, 0.764 mmol, 34%) and lactol **2.55** (97 mg, 0.370 mmol, 16%) as colourless viscous oils: analysis for compound **2.54**; FTIR ν_{max} (neat) 3334br, 1732s, 1250s, 1236s, 1056m, 1037s, 947m cm^{-1}; TLC (SiO_2, MeOH:EtOAc:CH_2Cl_2 (0.5:30:69.5), Rf 0.10); ^1H NMR (400 MHz, $CDCl_3$): δ 4.39 (1H, dd, *J* = 11.5, 2.5 Hz, CH(**H**)OAc), 3.96 (1H, dd, *J* = 11.6, 8.0 Hz, CH(**H**)OAc), 3.83 (1H, t, *J* = 7.5 Hz, THF), 3.82 (1H, dd, *J* = 8.0, 2.5 Hz, C**H**OH), 2.56 (2H, sbr, O**H**), 2.20 (1H, ddd, *J* = 12.5, 9.0, 5.5 Hz, THF), 2.10 (3H, s, C**H**$_3$CO$_2$), 2.04-1.87 (2H, m, THF), 1.57 (1H, dt, *J* = 12.6, 8.5 Hz, THF), 1.29 (3H, s, C**H**$_3$), 1.21 (3H, s, C**H**$_3$), 1.12 (3H, s, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (s, **C**=O), 85.2 (d, THF), 84.5 (s, THF), 75.4 (s, **C**Me$_2$OH), 71.8 (d, **C**HOH), 66.4 (t, **C**H$_2$OAc), 33.2 (t, THF), 27.9 (q, C(**C**H$_3$)CH$_3$OH), 26.7 (t, THF), 25.5 (q, C(**C**H$_3$)CH$_3$OH), 23.3 (q, **C**H$_3$), 21.1 (q, **C**H$_3$C=O); LRMS (CI, ammonia) *m/z* (relative intensity) 247 (4) $[M+H]^+$, 229 (100) $[M-H_2O]H^+$; Elemental analysis calculated for $C_{12}H_{22}O_6$ C 58.52, H 9.00%; found C 58.64, H 9.21%.

2-[5-Hydroxy-5-(1-hydroxy-1-methylethyl)-2-methyltetrahydrofuran-2-yl]-2-oxoethyl acetate **2.55**

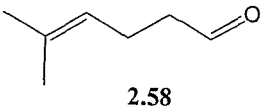


2.55

Analysis for the major diastereoisomer compound **2.55** which was isolated as a 2:1 mixture of diastereoisomers: FTIR ν_{max} (neat) 3452br, 2981w, 1729s, 1374m, 1233s, 1033m, 1024s cm^{-1}; TLC (SiO_2, MeOH:EtOAc:CH_2Cl_2 (0.5:30:69.5), Rf 0.13); ^1H NMR (400 MHz, $CDCl_3$): δ 5.23 (1H, d, *J* = 18.1 Hz, CH(**H**)OAc), 5.04 (1H, d, *J* =

17.6 Hz, CH(**H**)OAc), 3.83 (1H, brs, O**H**), 3.26 (1H, brs, O**H**), 2.57-2.44 (1H, m, γ-lactol), 2.18 (3H, s, C**H**$_3$CO), 2.07-1.82 (3H, m, γ-lactol), 1.56 (1H, s, O**H**), 1.37 (3H, s, C**H**$_3$), 1.34 (3H, s, C**H**$_3$), 1.28 (3H, s, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.6 (s, **C**=O), 170.8 (s, CH_3**C**=O), 111.0 (s, γ-lactol **C**OH), 88.9 (s, γ-lactol), 74.6 (s, **C**Me$_2$OH), 65.9 (t, **C**H$_2$OAc), 34.3 (t, γ-lactol), 31.9 (t, γ-lactol), 24.8 (q, **C**H$_3$), 24.6 (q, **C**H$_3$), 24.1 (q, **C**H$_3$), 20.7 (q, **C**H$_3$C=O); LRMS (CI, ammonia) *m/z* (relative intensity) 260 (7) $[M]^{\bullet+}$, 243 (100) $[M\text{-}H_2O]H^+$; HRMS (ESI) calculated for $C_{12}H_{20}O_6Na$ 283.1152095, found 283.1154860.

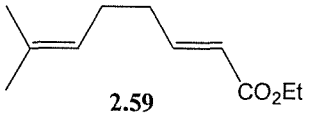
3.48 5-Methyl-4-hexenal 2.58



2.58

3-Methyl-1-buten-3-ol (50 mL, 0.48 mmol) and phosphoric acid (0.5 mL) in ethyl vinyl ether (100 mL, 1.05 mmol) were heated to 105°C in a sealed vessel for 19 h. The reaction was cooled to room temperature, treated with acetone (125 mL) and 2 M HCl (125 mL) then stirred for 90 minutes. The mixture was extracted with ether (2 x 250 mL), the ethereal extracts were combined, dried ($MgSO_4$) and the solvent was removed by distillation at ambient pressure to give a yellow oil. The oil was purified by vacuum distillation (72-75°C @ 20 mmHg) to give 5-methyl-4-hexenal (**2.58**) as a colourless oil (22.9 g, 0.204 mmol, 43%). The spectra are consistent with those reported in the literature:[156] FTIR ν_{max} (neat) 2972m, 1725s, 1377m, 1102m, 1059s cm^{-1}; TLC (SiO_2, CH_2Cl_2:hexane (1:1), Rf 0.25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, t, J = 1.5 Hz, C**H**O), 5.13-5.06 (1H, m, Me$_2$CC**H**), 2.47 (2H, t, J = 6.6 Hz, C**H**$_2$CHO), 2.34 (2H, t, J = 6.6 Hz, C**H**$_2$CH$_2$CHO), 1.69 (3H, s, C**H**$_3$), 1.64 (3H, s, C**H**$_3$).

3.49 Ethyl (*E*)-7-methylocta-2,6-dienoate 2.59

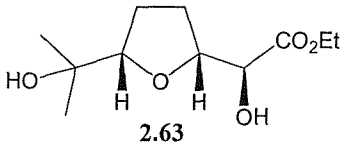


2.59

To a solution of aldehyde **2.58** (0.25 g, 2.23 mmol) in CH_2Cl_2 (5 mL) was added (carbethoxymethylene)triphenylphosphorane (0.78 g, 2.23 mmol) and stirred at room temperature for 24 h. The solvent was removed under vacuum to give an orange oil, which was purified by flash chromatography on silica gel (15 g) eluting with

CH_2Cl_2/hexane (30:70) to furnish the title compound **2.59** (117 mg, 0.643 mmol, 29%) as a colourless oil. The spectra are consistent with those reported in the literature:[157] FTIR ν_{max} (neat) 2971w, 2924w, 1721s, 1655w, 1367w, 1312w, 1264m, 1184m, 1147m, 1042m, 976w cm^{-1}; TLC (SiO_2, 50% CH_2Cl_2 / 50% hexane, Rf 0.45); ^1H NMR (300 MHz, $CDCl_3$): δ 6.97 (1H, dt, J = 15.5, 6.6 Hz, C**H**CHCO$_2$Et), 5.83 (1H, d, J = 16.2 Hz, CHC**H**CO$_2$Et), 5.11 (1H, t, J = 5.9 Hz, Me$_2$CC**H**), 4.19 (2H, q, J = 7.4 Hz, CO$_2$C**H$_2$**CH$_3$), 2.28-2.13 (4H, m, C**H$_2$**C**H$_2$**), 1.70 (3H, s, C**H$_3$**), 1.61 (3H, s, C**H$_3$**), 1.29 (3H, t, J = 7.4 Hz, CO$_2$CH$_2$C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1 (s, **C**O$_2$Et$_3$), 149.3 (d, **C**HCHCO$_2$Et), 133.1 (s, **C** Me$_2$), 123.2 (d, **C**HCMe$_2$), 121.7 (d, CH**C**HCO$_2$Et), 60.4 (t, CO$_2$**C**H$_2$CH$_3$), 32.8 (t, **C**H$_2$CHCHCO$_2$Et), 26.9 (t, **C**H$_2$CHCMe$_2$), 26.0 (2C, q, C(**C**H$_3$)$_2$), 14.6 (q, CO$_2$CH$_2$**C**H$_3$); LRMS (CI, NH_3) *m/z* (relative intensity): 183 (100) $[M+H]^+$, 200 (93) $[M+NH_4]^+$.

3.50 Ethyl (2S*)-2-hydroxy-[(2R*,5S*)-5-(1-hydroxy-1-methylethyl)tetrahydrofuran-2-yl]acetate 2.63

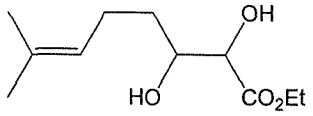


2.63

To a mixture of diene **2.59** (0.50 g, 2.75 mmol) in ether (15 mL) was added a mixture of 0.4 M $KMnO_4$(aq) (13.7 mL, 5.50 mmol) and acetic acid (0.66 mg, 10.99 mmol) over 2 minutes at room temperature. After 10 minutes the reaction mixture was treated with saturated 10% oxalic acid in water (15 mL), stirred for 10 minutes and then partitioned. The aqueous phase was saturated with NaCl(s) and re-extracted with CH_2Cl_2 (4 x 20 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a pale yellow oil. The oil was purified by flash chromatography on silica gel (25 g) eluting with MeOH/EtOAc/CH_2Cl_2 (0.5:30:69.5) to give the title compound **2.63** (162 mg, 0.698 mmol, 25%) and alkene diol **2.64** (80 mg, 0.370 mmol, 13%) as colourless viscous oils. Analytical data for compound **2.63**: FTIR ν_{max} (neat) 3434br, 2974w, 1734s, 1197s, 1161s, 1122s, 1078s, 1025m, 952m cm^{-1}; TLC (SiO_2, MeOH:EtOAc:CH_2Cl_2 (0.5:40:59.5), Rf 0.30); ^1H NMR (400 MHz, $CDCl_3$) δ 4.34 (1H, ddd, J = 8.0, 5.0, 2.5 Hz, THF), 4.22 (1H, q, J = 7.0 Hz, COC**H$_2$**), 4.20 (1H, q, J = 7.0 Hz, COC**H$_2$**), 4.04 (1H, d, J = 2.5 Hz, C**H**OH), 3.68 (1H, t, J = 7.3 Hz, THF), 2.71 (2H, brs, O**H**), 2.11-1.91 (3H, m, THF), 1.81-1.75 (1H, m, THF), 1.24 (3H, t, J = 7.0 Hz, CO$_2$CH$_2$C**H$_3$**), 1.18 (3H, s, C**H$_3$**), 1.04 (3H, s,

CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9 (s, CO_2Et), 85.1 (d, THF), 78.4 (d, THF), 72.3 (d, $CHOHCO_2Et$), 70.4 (s, CMe_2OH), 60.2 (t, CO_2CH_2), 26.6 (t, THF), 26.6 (q, $C(CH_3)_2OH$), 24.7 (t, THF), 23.6 (q, $C(CH_3)_2OH$), 12.7 (q, $CO_2CH_2CH_3$); LRMS (CI, ammonia) *m/z* (relative intensity): 232 (5) $[M]^{\bullet+}$, 215 (100) $[M-H_2O]H^+$, 250 (19) $[M+NH_4]^+$; HRMS (ESI) calculated for $C_{11}H_{20}O_5Na$ 255.1202948, found 255.1202830.

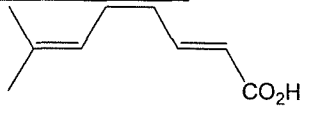
Ethyl 7-methylocta-2,3-dihydroxy-6-enoate **2.64**



2.64

Analytical data for compound **2.64**: FTIR ν_{max} (neat) 3454br, 2917w, 1736s, 1440m, 1375m, 1276s, 1208s, 1120s, 1061s, 1024s cm^{-1}; TLC (SiO_2, MeOH:ether:hexane (0.5:40:59.5), Rf 0.55); ^1H NMR (400 MHz) δ 5.31 (1H, s, **OH**), 5.17-5.12 (1H, m, $CHCMe_2$), 4.30 (2H, q, J = 7.5 Hz, $CO_2CH_2CH_3$), 4.08 (1H, brs, $CHOHCO_2Et$), 3.90 (1H, ddd, J = 8.0, 5.5, 2.0 Hz, **CH**OH), 2.18 (1H, dd, J = 14.6, 7.5 Hz, CH(**H**)$CHCMe_2$), 2.11 (1H, dd, J = 14.6, 7.0 Hz, CH(**H**)$CHCMe_2$), 1.98 (1H, brs, **OH**), 1.70 (3H, s, CH_3), 1.68-1.64 (2H, m, CH_2CHOH), 1.63 (3H, s, CH_3), 1.32 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 173.8 (s, **C**=O), 132.7 (s, CMe_2), 123.6 (d, $CHCMe_2$), 73.3 (d, $CHOHCO_2Et$), 72.3 (d, **C**HOH), 34.0 (t, CH_2CHCMe_2), 25.9 (q, $C(CH_3)_2OH$), 24.4 (t, CH_2), 17.9 (q, $C(CH_3)_2OH$), 14.3 (q, $CO_2CH_2CH_3$); LRMS (CI, ammomia) *m/z* (relative intensity): 217 (100) $[M+H]^+$, 234 (54) $[M+NH_4]^+$; HRMS (ESI) calculated for $C_{11}H_{20}O_4Na$ 239.1253802, found 239.1257850.

3.51 (E)-7-Methylocta-2,6-dienoic acid 2.60

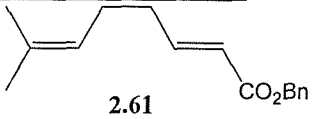


2.60

Ethyl ester **2.59** (2.95 g, 16.21 mmol), NaOH (3.90 g, 97.30 mmol) and $NaHCO_3$ (0.68 g, 8.11 mmol) were stirred together in MeOH (20 mL) and water (90 mL) at 50°C for 3 h. The reaction mixture was washed with CH_2Cl_2 (50 mL), then acidified with citric acid and extracted with ether (3 x 50 mL). The ethereal extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give the title compound **2.60** (2.50 g, 16.21 mmol, 100%) as a colourless oil; The spectra are consistent with those reported in the literature:[158] FTIR ν_{max} (neat) 2971w, 2919w, 1696s, 1650m, 1420m,

1287m, 1218m, 975m, 935m cm^{-1}; TLC (SiO_2, EtOAc:hexane (30:70), Rf 0.31); ^1H NMR (300 MHz, $CDCl_3$) δ 11.4 (1H, brs, $CO_2\mathbf{H}$), 7.10 (1H, dt, J = 15.4, 6.6 Hz, $\mathbf{CH}CHCO_2H$), 5.84 (1H, dt, J = 15.4, 1.5 Hz, $\mathbf{CH}CO_2H$), 5.11 (1H, tq, J = 6.6, 1.5 Hz, $\mathbf{CH}CMe_2$), 2.28 (2H, q, J = 6.6 Hz, $\mathbf{CH_2}CHCHCO_2H$), 2.17 (2H, q, J = 7.0 Hz, $\mathbf{CH_2}CHCMe_2$), 1.71 (3H, s, $\mathbf{CH_3}$), 1.61 (3H, s, $\mathbf{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (s, **C**=O), 152.2 (d, **C**HCHCO$_2$H), 133.1 (s, CH**C**Me$_2$), 122.8 (d, **C**HCMe$_2$), 120.9 (d, **C**HCO$_2$H), 32.7 (t, **C**H$_2$CHCHCO$_2$H), 26.6 (t, **C**H$_2$CHCMe$_2$), 25.8 (q, **C**H$_3$), 17.9 (q, **C**H$_3$); LRMS (CI, ammomia) *m/z* (relative intensity): 155 (42) $[M+H]^+$, 172 (32) $[M+NH_4]^+$, 139 (100) $[M-CH_3]^+$, 109 (24) $[M+CO_2H]^+$, 69 (26) $[CH_2CHCMe_2]^+$.

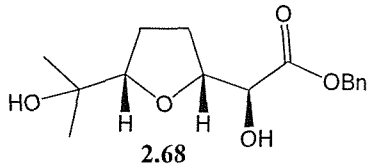
3.52 Benzyl (E)-7-methylocta-2,6-dienoate 2.61



2.61

To a solution of acid **2.60** (0.40 g, 2.60 mmol), benzyl alcohol (0.56 g, 5.12 mmol) and DMAP (32 mg, 0.260 mmol) in CH_2Cl_2 (10 mL) at 0°C was added a solution of DCC (0.75 g, 3.64 mmol) in CH_2Cl_2 (5 mL). The reaction was slowly warmed to room temperature and stirred for 18 h. The mixture was filtered, half the solvent was removed then filtered again. The solvent was removed under vacuum to give a residue which was purified by flash chromatography on silica gel (25 g) eluting with CH_2Cl_2:hexane (30:70) to give contaminated product which was purified again by flash chromatography on silica gel (25 g) eluting with CH_2Cl_2:hexane (20:80) to give the title compound **2.61** (0.40 g, 1.64 mmol, 63%) as a colourless oil: TLC (SiO_2, ether:hexane (1:1), Rf 0.80); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.31 (5H, m, Ph**H**), 7.03 (1H, dt, J = 15.6, 6.5 Hz, $\mathbf{CH}CHCO_2Bn$), 5.89 (1H, dt, J = 15.6, 1.5 Hz, $CH\mathbf{CH}CO_2Bn$), 5.19 (2H, s, $\mathbf{CH_2}Ph$), 5.14-5.03 (1H, m, $\mathbf{CH}CMe_2$), 2.25 (2H, q, J = 6.5 Hz, $\mathbf{CH_2}CHCHCO_2Bn$), 2.15 (2H, q, J = 7.5 Hz, $\mathbf{CH_2}CHCMe_2$), 1.70 (3H, s, $\mathbf{CH_3}$), 1.61 (3H, s, $\mathbf{CH_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7 (s, **C**=O), 149.9 (d, **C**HCHCO$_2$Bn), 133.0 (s, **C**Me$_2$), 129.9 (s, Ph), 128.7 (2C, d, Ph), 128.4 (2C, d, Ph), 128.3 (d, Ph), 123.0 (d, **C**HCMe$_2$), 121.2 (d, **C**HCO$_2$Bn), 66.2 (t, **C**H$_2$Ph), 32.7 (t, **C**H$_2$CHCHCO$_2$Bn), 26.7 (t, **C**H$_2$), 25.6 (q, **C**H$_3$), 17.9 (q, **C**H$_3$).

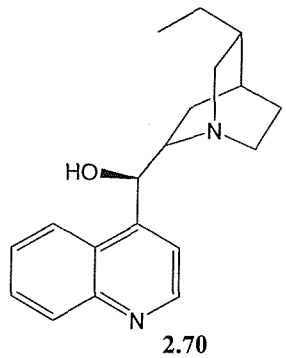
3.53 Benzyl (2S*)-hydroxy-[(2R*,5S*)-5-(1-hydroxy-1-methylethyl)tetrahydrofuran-2-yl]acetate 2.68



2.68

To a solution of diene **2.61** (0.20 g, 0.820 mmol) and Adogen 464 (0.11 g, 0.246 mmol) in ether (15 mL) at 0°C was added a mixture of AcOH (0.47 mL, 8.20 mmol) and 0.4 M $KMnO_4$(aq) (5.1 mL, 2.05 mmol) over 5 minutes. After 20 minutes the reaction was treated with saturated $Na_2S_2O_5$(aq) (10 mL), the aqueous phase was then saturated with NaCl(s) then acidified with 10% citric acid in water (5 mL). The mixture was partitioned and the aqueous phase was re-extracted with CH_2Cl_2 (3 x 15 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum resulting in a colourless oil (0.11 g). The oil was purified by flash chromatography on silica gel (10 g) eluting with MeOH:EtOAc:CH_2Cl_2 (0.5:30:69.5) to give a mixture of products which were separated by preparative HPLC (Luna SiO_2, 250 x 21.2 mm, IPA:hexane (10:90), 20 mL/min, 254 nm, Rt = 8.60 min) to provide the title compound **2.68** (33 mg, 0.112 mmol, 14%) as a colourless oil: FTIR ν_{max} (neat) 3392br, 1746s, 1264m, 1190s, 1157s, 1122s, 1079s, 955s cm^{-1}; TLC (SiO_2, MeOH:EtOAc:CH_2Cl_2 (0.5:50:49.5), Rf 0.40); ^1H NMR (400 MHz) δ 7.31-7.19 (5H, m, Ph**H**), 5.20 (1H, d, *J* = 12.1 Hz, CH(**H**)Ph), 5.15 (1H, d, *J* = 12.1 Hz, CH(**H**)Ph), 4.36 (1H, ddd, *J* = 7.5, 4.5, 2.0 Hz, THF), 4.09 (1H, d, *J* = 2.0 Hz, C**H**OH), 3.66 (1H, t, *J* = 7.3 Hz, THF), 3.17 (2H, br, O**H**), 2.11 (1H, m, THF), 1.95 (2H, ddt, *J* =16.0, 11.0, 8.0, THF), 1.76 (1H, ddt, *J* = 14.0, 11.0, 7.0, THF), 1.15 (3H, s, CC**H**$_3$MeOH), 1.03 (3H, s, CC**H**$_3$MeOH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4 (s, **C**=O), 135.5 (s, Ph), 128.8 (d, Ph), 128.6 (d, Ph), 128.4 (d, Ph), 86.7 (d, THF), 80.0 (t, THF), 74.1 (d, **C**HOH), 72.1 (s, **C**Me$_2$OH), 67.4 (t, **C**H$_2$Ph), 28.3 (t, THF), 28.0 (q, **C**H$_3$), 26.4 (t, THF), 25.3 (q, **C**H$_3$); LRMS (CI, ammomia) *m/z* (relative intensity): 312 (26) [M+NH_4], 295 (5) $[M+H]^+$, 294 (294) $[M]^{\bullet+}$, 277 (100) $[M-H_2O]H^+$.

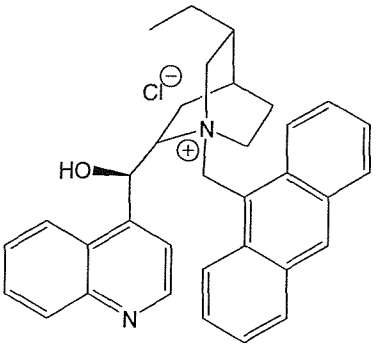
3.54 (-)-Dihydrocinchonidine 2.70



2.70

Tosylhydrazide (3.76 g, 20.23 mmol), (-)-Cinchonidine (**2.69**) (1.0 g, 3.40 mmol) and sodium acetate (1.66 g, 20.23 mmol) in THF (20 mL) and water (20 mL) were refluxed for 6 h. About half the solvent was removed under vacuum, the mixture was treated with saturated $NaHCO_3$(aq) (pH 11) and the resulting white solid was collected by filtration. The solid was dried in a vacuum oven (20 mmHg at 50°C) to give the title compound **2.70** (1.01 g, 20.23 mmol, 100%) as a white crystalline solid. The spectra are consistent with those reported in the literature:[159] m.p. 233-235°C (Lit.[159] 236-237; FTIR ν_{max} (neat) 2956w, 2938w, 2928w, 1592w, 1507w, 1455w, 1238w, 1163w, 1120m, 1040m, 1007m, 813m, 759s, 688s cm^{-1}; TLC (SiO_2, 0.880 NH_3:MeOH:CH_2Cl_2 (1:10:89), Rf 0.20); ^1H NMR (300 MHz): δ 8.93 (1H, d, J = 4.5 Hz, Ar**H**), 8.40 (1H, d, J = 8.4 Hz, Ar**H**), 8.12, (1H, d, J = 8.4 Hz, Ar**H**), 7.83 (1H, t, J = 8.4 Hz, Ar**H**), 7.70 (1H, t, J = 8.4 Hz, Ar**H**), 7.65 (1H, d, J = 4.5 Hz, Ar**H**), 5.38 (1H, s br, ArC**H**OH), 3.43 (1H, s br, CHOHC**H**N), 3.41-3.13 (2H, m, C**H**$_2$N), 2.99-2.82 (1H, m, C**H**$_2$N), 2.59-2.39 (1H, m, C**H**$_2$N), 2.36-2.14 (1H, m, C**H**-ring), 1.92-1.61 (4H, m, C**H**-ring),1.55-1.32 (4H, m, C**H**-ring + C**H**$_2$CH$_3$), 0.89 (3H, t, J = 6.6 Hz, CH$_2$**CH$_3$**); LRMS (ESI +ve) *m/z* (relative intensity): 297 (100) $[M+H]^+$, 593 (6) $[2M+H]^+$.

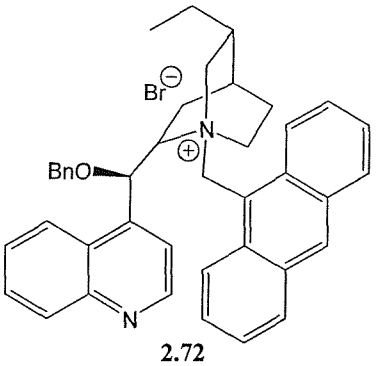
3.55 (2S,5R,1'R)-1-(1-Anthracenyl)methyl-5-ethyl-2-[(1S)-1-hydroxy-1-(quinol-4-yl)]methyl-1-azoniabycyclo[2.2.2]octane chloride 2.71



2.71

Dihydro-(-)-cinchonidine **2.70** (0.64 g, 2.16 mmol) and 9-chloromethylanthracene (0.49 g, 2.16 mmol) were refluxed in toluene (10 mL) for 4 h. The reaction mixture was cooled to room temperature, treated with ether (30 mL), the precipitate was collected by filtration and the solid was dried in a vacuum oven (20 mmHg at 50°C) to give the title compound **2.71** (0.89 g, 1.70 mmol, 79%) as a yellow solid. The spectra are consistent with those reported in the literature:[115] m.p. 149-153°C (Lit.[115] 155-156°C); FTIR ν_{max} (neat) 2964w, 1512w, 1451w, 1053w, 855w, 836w, 784m, 760m, 736s cm^{-1}; TLC(SiO_2, 0.880 NH_3:MeOH:CH_2Cl_2, (1:15:84), Rf 0.10); ^1H NMR (400 MHz) δ 8.88 (1H, d, *J* = 4.5 Hz, Ar**H**), 8.90-8.86 (1H, m, Ar**H**), 8.83 (1H, d, *J* = 8.5 Hz, Ar**H**), 8.77 (1H, d, *J* = 9.0 Hz, Ar**H**), 8.17 (1H, d, *J* = 5.5 Hz, Ar**H**), 8.12-8.10 (1H, m, Ar**H**), 8.10 (1H, s, Ar**H**), 7.86 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.73 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.66 (1H, d, *J* = 8.04 Hz, Ar**H**), 7.44-7.15 (4H, m, Ar**H**), 7.08 (1H, t, *J* = 4.3 Hz, ArC**H**OH), 6.69 (1H, d, *J* = 13.6 Hz, Anthracene-C**H**), 6.58 (1H, d, *J* = 13.5 Hz, Anthracene-C**H**), 4.80 (1H, s br, CHOHC**H**N^+), 4.61 (1H, m, C**H**N^+), 3.50 (1H, d, *J* = 12.5 Hz, CH(**H**)N^+), 2.63 (1H, dd, *J* = 12.6,10.5 Hz, CH(**H**)N^+), 2.42 (1H, td, *J* = 12.2, 3.5 Hz, CH(**H**)N^+), 1.97-1.86 (2H, m, C**H**-ring), 1.81 (1H, brs, O**H**), 1.70 (1H, brs, C**H**-ring), 1.29 (1H, sbr, C**H**-ring), 1.22-1.02 (4H, m, CH_3CH_2 + C**H**-ring), 0.43 (3H, t, *J* = 7.3 Hz, CH_3CH_2), 0.57 (3H, t, *J* = 7.3 Hz, CH_3); LRMS (ESI +ve) *m/z* (relative intensity): 487 (100%) $[M]^+$, 1009 (40) $[2M+^{35}Cl]^+$.

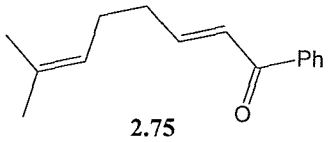
3.56 (2S,5R,1'R)-1-(1-Anthracenyl)methyl-5-ethyl-2-[(1S)-1-benzyloxy-1-(quinol-4-yl)]methyl-1-azoniabycyclo[2.2.2]octane chloride 2.72



2.72

To a solution of alcohol **2.71** (0.39 mg, 0.746 mmol) and benzyl bromide (0.38 mg, 2.24 mmol) in CH_2Cl_2 (5 mL) was added 50% KOH(aq) (0.21 g, 3.73 mmol). The reaction was stirred for 4 h at room temperature. The mixture was diluted with water (15 mL), then extracted with CH_2Cl_2 (3x10 mL). The organic extracts were combined, dried ($MgSO_4$), concentrated to ~10 mL, treated with ether (50 mL) and the resulting solid was filtered. The solid was washed with ether and dried in a vacuum oven (20 mmHg at 50°C) to give the title compound **2.72** (0.42 g, 86%) as a yellow solid. The spectra are consistent with those reported in the literature:[115] m.p. 148-153°C(d.) (Lit.[115] 138-139°C); FTIR ν_{max} (neat) 1739w, 1451w, 1063w, 840w, 764m, 752m, 746s, 739s cm^{-1};TLC (SiO_2, 0.880 NH_3:MeOH:CH_2Cl_2 (1:15:84), Rf 0.10); ^1H NMR (400 MHz, CD_3OD) δ 9.07 (1H, d, J = 4.5 Hz, Ar**H**), 8.84 (1H, s, Ar**H**), 8.70 (1H, d, J = 8.9 Hz, Ar**H**), 8.59 (1H, sbr, Ar**H**), 8.25-8.17 (3H, m, Ar**H**), 8.12-8.07 (2H, m, Ar**H**), 7.99-7.92 (2H, m, Ar**H**), 7.79 (1H, t, J = 7.9 Hz, Ar**H**), 7.71 (2H, d, J = 7.4 Hz, Ar**H**), 7.77-7.48 (5H, m, Ar**H**), 7.34 (1H, t, J = 7.9 Hz, Ar**H**), 7.05 (1H, s, ArC**H**OBn), 6.26 (1H, d, J = 13.4 Hz, N^+**CH_2**Anthracene), 5.80 (1H, d, J = 13.9 Hz, N^+**CH_2**Anthracene), 5.00 (1H, d, J = 11.9 Hz, PhC(**H**)HOCH), 4.95 (1H, d, J = 11.4 Hz, PhC(**H**)HOCH), 4.50-4.32 (2H, m, C**H**N^+ + CHOHC**H**N^+), 3.53-3.44 (1H, m, C**H**N^+), 3.10 (1H, t, J = 11.4 Hz, C**H**N^+), 2.76 (1H, td, J = 10.9, 5.5 Hz, C**H**N^+), 2.52 (1H, dd, J = 12.4, 8.4 Hz, C**H**-ring), 2.11 (1H, br, CH-ring), 1.92 (1H, s, CH-ring), 1.66-1.42 (3H, m, CH_3C**H_2** + CH-ring), 1.22 (2H, quint, J = 7.4 Hz, CH-ring) 0.79 (3H, t, J = 7.4 Hz, **CH_3**CH_2); LRMS (ESI +ve) *m/z* (relative intensity): 577 (100) [M^+].

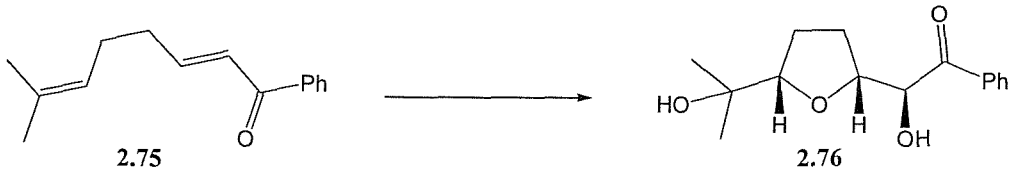
3.57 7-Methyl-(*E*)-1-phenylocta-2,6-dien-1-one 2.75



2.75

To a solution of phenacyl triphenylphosphonium bromide (1.0 g, 2.17 mmol) in CH_2Cl_2 (5 mL) was added 1 M NaOH (2.5 mL) and the mixture was stirred for 2 hours. The organic phase was collected, dried ($MgSO_4$) and treated with 5-methyl-4-hexenal (**2.58**) (0.24 g, 2.17 mmol). The reaction was stirred for 19 h, then the reaction mixture was treated with hexane (10 mL) and purified by flash chromatography on silica gel (50 g) eluting with CH_2Cl_2:hexane (40:60) to give the title compound **2.75** (0.10 g, 0.467 mmol, 22%) as a colourless oil; A trans:cis ratio of 19:1, by GC analysis (DB-Wax, 30 m x 0.53 mm, 190°C; Rt(cis) = 4.07 min, Rt(trans) = 4.86 min); FTIR ν_{max} (neat) 2912w, 1671s, 1621s, 1448m, 1286m, 978m, 770m, 695s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (2H, d, *J* = 7.0 Hz, Ph**H**), 7.56 (1H, td, *J* = 7.5, 1.5 Hz, Ph**H**), 7.47 (2H, t, *J* = 7.0 Hz, Ph**H**), 7.06 (1H, dt, *J* = 15.6, 7.0 Hz, 1H; C**H**CHCOPh), 6.88 (1H, dt, *J* = 15.6, 1.5 Hz, C**H**COPh), 5.18-5.13 (1H, m, C**H**CMe_2), 2.36 (2H, q, *J* = 8.0 Hz, CH_2CHCMe_2), 2.23 (2H, q, *J* = 7.2 Hz, CH_2CHCHCOPh), 1.71 (3H, s, CH_3), 1.63 (3H, s, CH_3); ^{13}C NMR (100 MHz): δ 190.8 (s, **C**=O), 149.4 (d, **C**HCHCOPh), 137.8 (s, Ph), 132.6 (s, **C**Me_2), 132.3 (d, Ph), 128.3 (2C, d, Ph), 128.3 (2C, d, Ph), 125.9 (d, **C**HCOPh), 122.7 (d, **C**HCMe_2), 32.9 (t, CH_2CHCHCOPh), 26.6 (t, CH_2CHCMe_2), 25.5 (q, CH_3), 17.6 (q, CH_3); LRMS (CI, NH_3) *m/z* (relative intensity): 232 (8) $[M+NH_4]^+$, 215 (100) $[M+H]^+$, 105 (58) $[PhCO]^+$.

3.58 Optimisation of the Oxidation of Enone 2.75

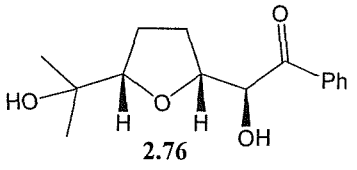


2.75 **2.76**

In a typical procedure: To a solution of enone **2.75** (50 mg, 0.234 mmol), AcOH and chiral phase transfer catalyst **2.72** in solvent (2 mL) at 0°C was added powdered $KMnO_4$, or for liquid-liquid phase-transfer oxidations AcOH and 0.4 M $KMnO_4$(aq) were added together. The reaction was stirred vigorously for 1 h, then an aqueous solution of (10% w/v) oxalic acid (2 mL) was added. The solvents were removed under reduced pressure, to give a red residue. The residue was dissolved in 1:1

MeOH/water (100 mL). The solution was analysed by HPLC (Xorbax ODS-3, 150 x 4.6 mm; Gradient 50% to 100% MeOH (10 mins), 230 nm; Rt (THF diol) = 4.2 min) and a calibration curve allowed the yields to be established for THF diol **2.76**. THF diol **2.76** was isolated by removing the solvent under reduced pressure, then purifying the resulting residue by flash chromatography on silica gel (5 g) eluting with MeOH:EtOAc:CH_2Cl_2 (0.5:20:79.5) to give target compound as a white solid, which was analysed by chiral chromatography (OD column, 1 ml/min, propan-2-ol:hexane (10:90), 254 nm, major enantiomer Rt = 9.1 min, minor isomer Rt = 11.1 min) to establish the enantiomeric excesses.

3.59 (2S)-2-Hydroxy-2-[-(2R,5S)-5-(1-hydroxy-1-methylethyl)tetrahydrofuran-2-yl]-1-phenyl ethanone 2.76

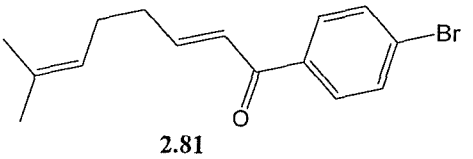


2.76

To a stirring solution of diene **2.75** (150 mg, 0.701 mmol), CPTC **2.72** (10 mol%, 46 mg, 70.1 μmol) and AcOH (270 mg, 4.56 mmol) in CH_2Cl_2 (6 mL) at –30°C under nitrogen was added finely powdered potassium permanganate (180 mg, 1.12 mmol). After 3 h the reaction was treated with 10% oxalic acid in water (5 mL) and the mixture was partitioned. The aqueous phase was saturated with NaCl(s) then extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a yellow residue. The residue was purified by flash chromatography on silica gel (8 g) eluting with MeOH:EtOAc:CH_2Cl_2 (0.5:20:79.5) to give the title compound **2.76** (87 mg, 0.330 mmol, 47%) as a white solid. The enantiomers were separated using chiral chromatography (AD column, 1 ml/min, propan-2-ol:hexane (15:85), 254 nm, major enantiomer Rt = 23.2 min, minor isomer Rt = 38.7 min) to show an enantiomeric excess of 58%; $[\alpha]_D$ –37.2 (*c* 0.274, $CHCl_3$, 28% e.e.); m.p. 106-108°C; FTIR ν_{max} (neat) 3428br, 2971w, 1684s, 1444w, 1241m, 1121s, 1076s, 961s cm^{-1}; TLC (SiO_2, *i*-PrOH:hexane (1:9), Rf 0.20); ^1H NMR (400 MHz) δ 7.92 (2H, d, *J* = 7.0 Hz, Ph**H**), 7.62 (1H, t, *J* = 7.5 Hz, Ph**H**), 7.51 (2H, t, *J* = 7.8 Hz, Ph**H**), 5.11 (2H, d, *J* = 2.5 Hz, C**H**OH), 4.41 (1H, ddd, *J* = 7.5, 5.5, 2.5 Hz, C**H**), 3.62 (1H, t, *J* = 7.0 Hz, C**H**), 3.03 (2H, s broad, O**H**), 2.19-2.29 (1H, m, C(H)**H**), 2.04 (2H, dtd, *J* = 15.0, 7.5, 5.0 Hz, CH_2), 1.74-1.84 (1H, m, C(H)**H**), 1.23 (3H, s, CH_3),1.11 (3H, s, CH_3); ^{13}C NMR (100 MHz) δ 200.1 (s, **C**=O), 134.6 (s, Ph),

134.1 (d, Ph), 129.1 (2C, d, Ph), 128.7 (2C, d, Ph), 87.0 (d, THF), 80.1 (d, THF), 76.0 (**C**HOH), 71.8 (s, **C**Me$_2$OH), 28.5 (t, THF), 28.0 (q, **C**H$_3$), 26.3 (t, THF), 25.0 (q, **C**H$_3$); MS (CI, ammonia): *m/z* (%): 265 (5) $[M+H]^+$, 247 (100) $[M^+-H_2O]H^+$, 105 (74) $[PhCO]^+$; Elemental analysis calculated for $C_{15}H_{20}O_4$ C 68.16, H 7.63%, Found C 68.36, H 7.61%.

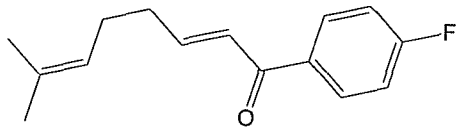
3.60 (*E*)-1-(4'-Bromophenyl)-7-methyl -2,6-octadienone 2.81



2.81

To a solution of 2-bromo-4'-bromoacetophenone (2.0 g, 7.19 mmol) in 50:50 CH_2Cl_2:hexane (10 mL) was added triphenylphosphine (1.88 g, 7.19 mmol) and immediately a precipitate was formed. After 5 h the solid was collected by filtration and dried at 50°C under vacuum to give the white phosphonium salt **2.77** (3.84 g, 7.11 mmol, 99%). The phosphonium salt **2.77** (1.38 g, 2.56 mmol) was suspended in CH_2Cl_2 (4 mL), then treated with 1 M NaOH (2.6 mL) and stirred for 1 h. The organic phase was dried (Na_2SO_4), then treated with 5-methyl-4-hexenal (**2.58**) (0.13 g, 1.161 mmol) and stirred for 4 days. The solvent was removed under vacuum to give an orange residue which was purified by flash chromatography on silica gel (60 g) eluting with CH_2Cl_2:hexane (5:95 then 10:90 and finally 15:85) to give the target enone **2.81** as a colourless liquid (0.21 g, 0.717 mmol, 60%), with a trans:cis ratio of 15:1, by GC analysis (DB-Wax, 30 m x 0.53 mm, Gradient: 200°C (2 mins) to 250°C (10°C/min), 250°C (10 mins); Rt(cis) = 5.64 min, Rt(trans) = 6.12 min); FTIR ν_{max} (neat) 1671s, 1620s, 1585s, 1070s, 1009s cm^{-1} ; TLC (SiO_2, ether:hexane (20:80), Rf 0.65); ^{1}H NMR (400 MHz) δ 7.80 (2H, dt, *J* = 8.5, 2.0 Hz, Ar**H**), 7.61 (2H, dt, *J* = 8.5, 2.0 Hz, Ar**H**), 7.08 (1H, dt, *J* = 15.1, 6.5 Hz, C**H**CHCOPh), 6.83 (1H, dt, *J* = 15.6, 1.5 Hz, C**H**COPh), 5.17-5.12 (1H, m, C**H**Me$_2$), 2.36 (2H, q, *J* = 7.0 Hz, C**H$_2$**CHCHCOPh), 2.22 (2H, q, *J* = 7.2 Hz, C**H$_2$**CHCMe$_2$), 1.72 (3H, s, C**H$_3$**), 1.63 (3H, s, C**H$_3$**); ^{13}C NMR (100 MHz) δ 190.0 (s, **C**=O), 150.4 (d, **C**HCHCOPh), 136.9 (s, Ar), 133.1 (s, **C**Me$_2$), 132.0 (2C, d, Ar), 130.3 (2C, d, Ar), 127.8 (s, Ar), 125.8 (d, CH**C**HCOPh), 123.0 (d, **C**HCMe$_2$), 33.3 (t, **C**H$_2$CHCHCOPh), 26.9 (t, **C**H$_2$CHCMe$_2$), 25.9 (q, **C**H$_3$), 18.0 (q, **C**H$_3$); LRMS (CI, NH$_3$) *m/z* (relative intensity) 293 (16) [M+H], 295 (16) [M+H], 224 (30) $[M-C_5H_9]^{\bullet+}$, 226 (30) $[M-C_5H_9]^{\bullet+}$, 183 (22) $[4\text{-Br-PhCO}]^+$, 185 (22) $[4\text{-Br-PhCO}]^+$; HRMS (CI) calculated for $C_{15}H_{17}{}^{79}BrO_5$ 291.03766, found 291.03845.

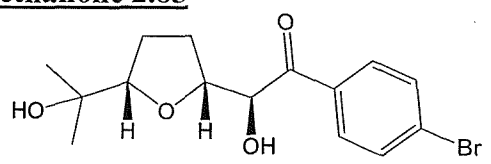
3.61 (*E*)-1-(4'-Fluorophenyl)-7-methyl-2,6-octadien-1-one 2.82



2.82

To a solution of 2-bromo-4'-fluoroacetophenone (2.0 g, 9.22 mmol) in 50:50 CH_2Cl_2:hexane (10 mL) was added triphenylphosphine (2.42 g, 9.22 mmol) and immediately a precipitate was formed. After 5 h the solid was collected by filtration and dried at 50°C under vacuum to give the white phosphonium salt **2.78** (3.94 g, 8.21 mmol, 89%). The phosphonium salt **2.78** (1.21 g, 2.54 mmol) was suspended in CH_2Cl_2 (4 mL), then treated with 1 M NaOH (2.6 mL) and stirred for an hour. The organic phase was dried (Na_2SO_4), then treated with 5-methyl-4-hexenal (**2.58**) (0.13 g, 1.161 mmol) and stirred for 4 days. The solvent was removed under vacuum to give an orange residue which was purified by flash chromatography on silica gel (60 g) eluting with CH_2Cl_2:hexane (5:95, then 10:90 and finally 15:85) to give the target enone **2.82** as a colourless liquid (152 mg, 0.655 mmol, 56%), with a trans:cis ratio of 19:1, by GC analysis (DB-Wax, 30 m x 0.53 mm, Gradient: 200°C (2 mins) to 250°C (10°C/min), 250°C (10 mins); Rt(cis) = 2.73 min, Rt(trans) = 3.09 min); FTIR ν_{max} (neat) 1674s, 1622s, 1599s, 1232s, 1157s cm^{-1}; TLC (SiO_2, ether:hexane (20:80), Rf 0.60); ^1H NMR (400 MHz) δ 7.97 (2H, dd, J = 8.7, 5.2 Hz, Ar**H**), 7.14 (2H, t, J = 8.5 Hz, Ar**H**), 7.06 (1H, dt, J = 15.6, 6.8 Hz, C**H**CHCOAr), 6.86 (1H, dt, J = 15.6, 1.5 Hz, C**H**COAr), 5.18-5.12 (1H, m, C**H**Me_2), 2.36 (2H, q, J = 7.2 Hz, C**H**$_2$CHCHCOPh), 2.23 (2H, q, J = 7.2 Hz, C**H**$_2$CHCMe_2), 1.72 (3H, s, C**H**$_3$), 1.56 (3H, s, C**H**$_3$); ^{13}C NMR (100 MHz) δ 189.5 (s, **C**=O), 169.6 (s, Ar), 150.0 (d, **C**HCHCOPh), 131.3 (2C, dd, J = 6.9 Hz, Ar), 125.9 (d, **C**HCOPh), 123.1 (d, **C**HCMe_2), 115.8 (2C, dd, J = 21.3 Hz, Ar), 33.3 (t, **C**H_2CHCHCOPh), 26.9 (t, **C**H_2CHCMe_2), 25.9 (q, **C**H_3), 18.0 (q, **C**H_3); LRMS (CI, ammonia) *m/z* (relative intensity): 233 (100) [M+H], 164 (30) [M-C_5H_9]$^{\bullet+}$, 123 (32) [4-F-PhCO]$^+$; HRMS (CI) calculated for $C_{15}H_{17}OF$ 232.12634, found 232.12575.

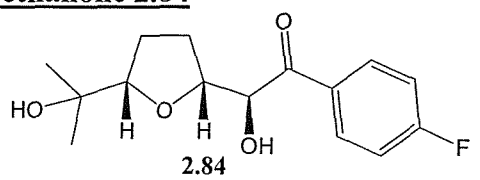
3.62 (2S)-1-(4-Bromophenyl)-2-Hydroxy-2-[-(2R,5S)-5-(1-hydroxy-1-methylethyl) tetrahydrofuran-2-yl] ethanone 2.83



2.83

To a stirring solution of diene **2.81** (200 mg, 0.683 mmol), CPTC **2.72** (10 mol%, 39 mg, 58.8 μmol) and AcOH (229 mg, 3.84 mmol) in CH_2Cl_2 (6 mL) at –40°C under nitrogen was added finely powdered potassium permanganate (150 mg, 0.941 mmol). After 4 hours the reaction was warmed to –30°C, stirred for a further 2 hours then treated with saturated $Na_2S_2O_5$ in water (5 mL) and the mixture was partitioned. The aqueous phase was saturated with NaCl(s) then extracted with CH_2Cl_2 (4 x 10 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a yellow residue. The residue was purified by flash chromatography on silica gel eluting (8 g) with CH_2Cl_2:hexane (50:50) then with MeOH:EtOAc:CH_2Cl_2 (0.5:20:79.5 and finally 0.5:30:69.5) to give the title compound **2.83** (60 mg, 0.175 mmol, 26%) as a colourless crystalline solid as well as recovered starting material (43 mg, 0.147 mmol, 22%). The enantiomers were separated using chiral chromatography (AD column, 1 ml/min, propan-2-ol:hexane (15:85), 254 nm, major enantiomer Rt = 34.2 min, minor isomer Rt = 23.4 min) to show an enantiomeric excess of 76%; m.p. 114-116°C; FTIR ν_{max} (neat) 1684s, 1165m, 1073s, 1064m, 969m, 951m cm^{-1}; TLC (SiO_2, MeOH:EtOAc:CH_2Cl_2 (0.5:30:69.5), Rf 0.35); ^1H NMR (400 MHz) δ 7.79 (2H, d, J = 8.0 Hz, Ar), 7.76 (2H, d, J = 8.5 Hz, Ar), 5.04 (1H, d, J = 2.0 Hz, C**H**OH), 4.39 (1H, ddd, J = 7.6, 5.5, 2.5 Hz, THF), 3.63 (1H, t, J = 7.3 Hz, THF), 2.29-2.21 (1H, m, THF), 2.10-1.99 (2H, m, THF), 1.85-1.76 (1H, m, THF), 1.17 (3H, s, C**H**$_3$), 1.09 (3H, s, C**H**$_3$); ^{13}C NMR (100 MHz) δ 199.3 (s, **C**=O), 133.3 (s, Ar**H**), 132.4 (2C, d Ar**H**), 130.1 (2C, d Ar**H**), 129.3 (s, Ar**H**), 87.0 (d, THF), 80.0 (d, THF), 76.2 (d, **C**HOH), 71.9 (s, **C**Me$_2$OH), 28.6 (t, THF), 28.0 (q, **C**H$_3$), 26.3 (t, THF), 25.0 (q, **C**H$_3$); Elemental analysis calculated for $C_{15}H_{19}O_4Br$: C 52.49, H 5.58%. Found: C 52.50, H 5.61%.

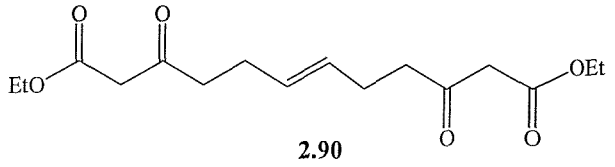
3.63 (2S)-1-(4-Fluorophenyl)-2-Hydroxy-2-[-(2R,5S)-5-(1-hydroxy-1-methylethyl) tetrahydrofuran-2-yl] ethanone 2.84



2.84

To a stirring solution of diene **2.82** (90 mg, 0.388 mmol), CPTC **2.72** (10 mol%, 25 mg, 38.8 μmol) and AcOH (151 mg, 2.52 mmol) in CH_2Cl_2 (4 mL) at –40°C under nitrogen was added fine powdered potassium permanganate (98 mg, 0.621 mmol). After 4 hours the reaction was treated with saturated $Na_2S_2O_5$ in water (5 mL) and the mixture was partitioned. The aqueous phase was saturated with NaCl(s) then extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined, dried (Na_2SO_4) and the solvent was removed under vacuum to give a yellow residue. The residue was purified by flash chromatography on silica gel (7 g) eluting with MeOH:EtOAc:CH_2Cl_2 (0.5:20:79.5 then 0.5:30:69.5) to give the title compound **2.84** (54 mg, 0.191 mmol, 50%) as a colourless crystalline solid. The enantiomers were separated using a chiral chromatography (AD column, 1 ml/min, propan-2-ol:hexane (15:85), 254 nm, major enantiomer Rt = 24.0 min, minor isomer Rt = 27.5) to show an enantiomeric excess of 72%; m.p. 108-109°C; FTIR ν_{max} (neat) 3431br, 2966w, 1685s, 1597s, 1228s, 1131s, 1082s, 1052s, 958s cm^{-1}; TLC (SiO_2, MeOH:EtOAc:CH_2Cl_2 (0.5:30:69.5), Rf 0.30); ^1H NMR (400 MHz) δ 7.97 (2H, dd, J = 9.0, 5.5 Hz, Ar**H**), 7.19 (2H, t, J = 8.5 Hz, Ar**H**), 5.06 (1H, d, J = 2.5 Hz, C**H**OH), 4.41 (1H, ddd, J = 7.5, 5.5, 2.5 Hz, THF), 3.64 (1H, t, J = 7.5 Hz, THF), 2.29-2.20 (1H, m, THF), 2.10-2.00 (2H, m, THF), 1.85-1.77 (1H, m, THF), 1.18 (3H, s, CH_3), 1.08 (3H, s, CH_3); ^{13}C NMR (100 MHz) δ 198.5 (s, **C**=O), 166.4 (d, J = 255.0 Hz, Ar), 131.4 (2C, dd, J = 9.7 Hz, Ar), 130.9 (s, Ar), 116.3 (2C, dd, J = 22.2 Hz, Ar), 87.0 (d, THF), 80.1 (d, THF), 76.0 (d, **C**HOH), 71.8 (s, **C**Me_2OH), 28.6 (t, THF), 28.0 (q, **C**H_3), 26.3 (t, THF), 25.0 (q, **C**H_3); MS (CI, ammonia) *m/z* (relative intensity) 282 (6) $[M]^{\bullet+}$, 265 (100) $[M-H_2O]H^+$, 123 (78) $[4\text{-F-PhCO}]^+$; Elemental analysis calculated for $C_{15}H_{19}O_4F$: C 63.82, H 6.78%, found: C 63.89, H 6.88%.

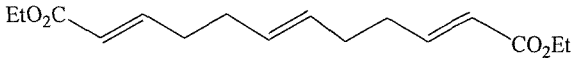
3.64 (*E*)-3,10-Dioxo-dodec-6-enedioate 2.90



2.90

To a solution of diisopropylamine (65.4 mL, 0.467 mol) in anhydrous THF (500 mL) at –78°C under nitrogen was added 1.6 M butyl lithium in hexanes (311 mL, 0.467 mol) whilst maintaining the temperature below -50°C to give a yellow solution. The mixture was warmed to room temperature for 10 minutes then cooled to –70°C and ethyl acetoacetate (29.6 mL, 0.234 mol) was added. The solution was warmed to room temperature and stirred for 90 minutes after which time the solution had turned dark orange. The solution was cooled to –60°C, then 1,4-dibromobut-2-ene (25.0 g, 0.117 mol) in THF (150 mL) was added and the mixture was stirred for 30 minutes. The reaction mixture was warmed to room temperature, then treated with water (300 mL), 10% citric acid (500 mL) and ether (700 mL). The mixture was partitioned and the aqueous phase was re-extracted with ether (800 mL). The ethereal extracts were combined, dried ($MgSO_4$) and the solvent removed under vacuum to give an orange oil. The oil was purified by flash chromatography on silica gel (300 g) eluting with ether/hexane (20:80 then 30:70) to give the title compound **2.90** (28.0 g, 77%) as a white solid; m.p. 30-31°C; FTIR ν_{max} (neat) 1731s, 1709s, 1416m, 1338w, 1317m, 1244m, 1178s, 1116m, 1084m, 1041m, 964m, 924w cm^{-1}; TLC (SiO_2, Ether/hexane (50:50), Rf 0.25); ^1H NMR (300 MHz) δ 5.44 (2H, t, J = 3.7 Hz, C**H**C**H**), 4.20 (4H, quartet, J = 7.4 Hz, 2 x $CO_2C\mathbf{H}_2$), 3.43 (4H, s, C(O)C$\mathbf{H}_2CO_2$Et), 2.60 (4H, t, J = 7.4 Hz, C(O)C$\mathbf{H}_2$), 2.28 (4H, td, J = 7.4, 4.4 Hz, C$\mathbf{H}_2$CHCHC$\mathbf{H}_2$), 1.29 (3H, t, J = 7.4 Hz, 2 x $CO_2CH_2C\mathbf{H}_3$); ^{13}C NMR (75 MHz) δ 202.3 (2C, s, **C**=O), 167.3 (2C, s, **C**O_2Et), 129.5 (d, **C**H**C**H), 61.5 (2C, t, $CO_2\mathbf{C}H_2$), 49.5 (2C t, C(O)**C**H_2CO_2Et), 42.7 (t, 2 **C**H_2CH=CH), 26.4 (2C, t, C(O)**C**H_2CH_2), 14.3 (2C, q, **C**H_3); LRMS (CI, ammonia) m/z (relative intensity) 169 (72) $[C_{10}H_{16}O_2]^+$, 110 (46) $[C_7H_{10}O]^{\bullet+}$, 41 (100) $[C_3H_5]^+$; Elemental analysis calculated for $C_{16}H_{24}O_6$: C 61.52, H 7.74%, found: C 61.21, H 7.67%.

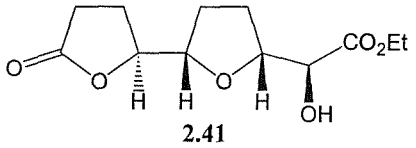
3.65 Diethyl (*E*, *E*, *E*)-dodeca-2,6,10-trienedioate 2.43



2.43

To a solution of diketone **2.90** (3.70 g, 11.86 mmol) in MeOH (40 mL) was added $NaBH_4$ (0.44 g, 11.86 mmol) at 0°C. The reaction was stirred at 0°C for 20 minutes and stirred at room temperature for 20 minutes. The reaction was quenched with 10% citric acid (50 mL) then extracted with CH_2Cl_2 (2 x 50 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a colourless oil. The oil was taken up in CH_2Cl_2 (50 mL) and treated with triethylamine (11.50 mL, 83.02 mmol) and methanesulphonyl chloride (1.84 mL, 23.72 mmol) at 0°C under nitrogen. After 20 minutes the reaction was warmed to room temperature and stirred for 17 hours. The reaction mixture was washed with 10% citric acid (50 mL), dried ($MgSO_4$) and the solvent was removed under vacuum to give a brown oil. The oil was taken up in ether, adsorbed onto silica and purified by flash chromatography on silica gel (150 g) eluting with ether/hexane (20:80) to give the title compound **2.43** (0.98 g, 30%) as a colourless oil. Spectroscopic details are consistent with those observed in the literature:[160] FTIR ν_{max} (neat) 1719s, 1653w, 1367w, 1312w, 1270m, 1204m, 1187m, 1041m, 970m cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.94 (2H, dt, *J* = 15.9 ,6.5 Hz, C**H**CHCO$_2$Et), 5.82 (2H, dt, *J* = 15.4, 1.5 Hz, CHC**H**CO$_2$Et), 5.44 (2H, tt, *J* = 3.5, 1.5 Hz, CH_2C**H**C**H**CH_2), 4.18 (4H, q, *J* = 6.9 Hz, CO$_2$C**H**$_2$), 2.31-2.21 (4H, m, C**H**$_2$CHCHCO$_2$Et), 2.20-2.11 (4H, m, C**H**$_2$CHCHC**H**$_2$), 1.29 (6H, t, *J* = 7.0 Hz, CO$_2$CH$_2$C**H**$_3$); ^{13}C NMR (75 MHz) δ 166.8 (2C, s, **C**O$_2$Et), 148.6 (2C, d, **C**HCHCO$_2$Et), 130.0 (2C, d, **C**HCH), 121.8 (2C, d, **C**HCO$_2$Et), 60.3 (2C, t, CO$_2$**C**H$_2$), 32.2 (2C, t, **C**H$_2$), 31.1 (2C, t, **C**H$_2$), 14.4 (2C, q, **C**H$_3$); LRMS (CI, NH_3) *m/z* (relative intensity): 281 (100) $[M+H]^+$.

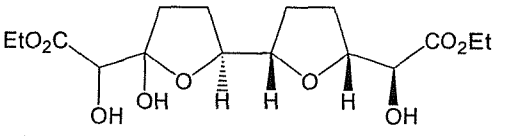
3.66 Ethyl (S*)-hydroxy-{(2S*,5R*,2'S*)-5'-oxo-octahydro-[2,2']bifuranyl-5-yl} acetate 2.41



2.41

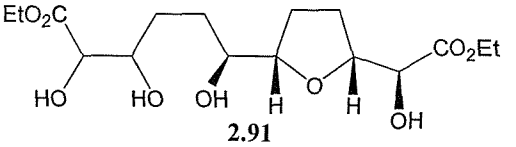
To a solution of triene **2.43** (0.25 g, 0.893 mmol) and acetic acid (0.22 mL, 3.66 mmol) in acetone (25 mL) at –20°C was added a mixture of 0.4 M $KMnO_4$ (6.7 mL, 2.68 mmol) and phosphate buffer [0.067 M KH_2PO_4 (1.6 mL), 0.067 M Na_2HPO_4 (0.4

mL)], ensuring the temperature was kept below –20°C. The mixture was stirred for 20 minutes, then treated with saturated $Na_2S_2O_5$(aq) (10 mL). The solution was saturated with NaCl(s), then 10% citric acid (5 mL) was added so that the mixture went clear. The mixture was extracted with CH_2Cl_2 (5 x 20 mL), the organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a colourless oil (0.26 g). A sample was purified by flash chromatography on silica gel (5 g) eluting with MeOH:EtOAc:CH_2Cl_2 (1:30:69) to give a sample of tetraol **2.91** as a colourless oil and a sample containing a complex mixture of lactols (by ^{1}H NMR) which should include the structure below:



Analytical data for lactol mixture: FTIR ν_{max} (neat) 1735s, 1273m, 1201m, 1127m, 1027m cm^{-1}; TLC (SiO_2, MeOH:CH_2Cl_2 (1:9), Rf 0.25); LRMS (ESI +ve) *m/z* (relative intensity) 385 (32) $[M+Na]^+$, 401 (7) $[M+K]^+$, 345 (4) $[M-H_2O]H^+$, 711 (10) $[2(M-H_2O)+Na]^+$, 747 (4) $[2M+Na]^+$.

Ethyl 6-[5-(ethoxycarbonyl-hydroxymethyl)tetrahydrofuran-2-yl]-2,3,6-trihydroxy hexanoate **2.91**



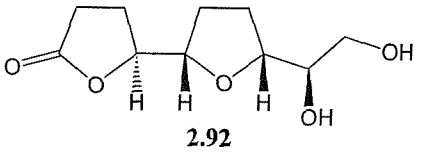
2.91

Analytical data for tetraol **2.91** which was isolated and characterised as a mixture of diastereoisomers: FTIR ν_{max} (neat) 3433br, 1733s, 1447w, 1370w, 1270m, 1202m, 1130s, 1073m, 1025m, 860w cm^{-1}; TLC (SiO_2, MeOH:CH_2Cl_2 (1:9), Rf 0.10); ^{1}H NMR (400 MHz) δ 4.34-4.27 (1H, m, THF), 4.26-4.15 (4H, m, $CO_2C\mathbf{H_2}$), 4.04 (1H, d, *J* = 2 Hz, THF-C**H**OHCO$_2$Et), 4.02 (1H, d, *J* = 2.5 Hz, CHOHC**H**OHCO$_2$Et), 4.00 (1H, d, *J* = 2.0 Hz, CHOHC**H**OHCO$_2$Et), 3.89-3.84 (1H, m, C**H**OHCHOHCO$_2$Et), 3.80 (1H, ddd, *J* = 14.0, 7.0, 5.0 Hz, THF), 3.49-3.40 (1H, m, THF-C**H**OH), 2.13-1.92 (2H, m, THF), 1.92-1.84 (2H, m, THF), 1.80-1.68 (2H, m, C$\mathbf{H_2}$CHOHCHOH), 1.65-1.55 (2H, m, C$\mathbf{H_2}$CH$_2$CHOHCHOH), 1.24 (3H, t, *J* = 7.2 Hz, CO$_2$CH$_2$C$\mathbf{H_3}$), 1.20 (3H, t, *J* = 7.2 Hz, CO$_2$CH$_2$C$\mathbf{H_3}$); ^{13}C NMR (100 MHz) δ 173.8 + 173.7 (2C, s, **C**O$_2$Et), 83.5 + 83.4 (d, THF), 80.4 (d, THF), 74.5 + 73.9 (d, CHOH**C**HOHCO$_2$Et), 74.2 (d, THF-**C**HOH), 73.3 (d, THF-CHOH**C**O$_2$Et), 73.0 + 72.9 (d, **C**HOHCHOHCO$_2$Et), 62.3 (2C, t, CO$_2$**C**H$_2$), 31.2 (t, THF-CHOH**C**H$_2$), 31.0 + 30.4 (t, **C**H$_2$CHOHCHOH),

28.8 + 28.7 (t, THF), 28.0 (t, THF), 14.6 (2C, q, $CO_2CH_2\mathbf{C}H_3$); LRMS (ESI +ve) *m/z* (relative intensity) 365 (23) $[M+H]^+$, 387 (100) $[M+Na]^+$, 751 (67) $[2M+Na]^+$, 711 (11) $[2M-H_2O]H^+$, 403 (4) $[M+K]^+$.

The remainder of the oil was taken up in acetone (10 mL) cooled to 0°C then was treated with a solution of $NaIO_4$ (0.38 g, 1.79 mmol) in water (10 mL) over 15 minutes. The mixture was stirred for 20 minutes at 0°C, then for an hour at room temperature. Ether (20 mL) and water (20 mL) were added to the reaction mixture and the phases were partitioned. The aqueous phase was extracted with CH_2Cl_2 (4 x 20 mL), the organic extracts were then combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a colourless film (0.19 g). The film was taken up in CH_2Cl_2 (5 mL) and *p*-toluenesulphonic acid (5 mg) was added. The mixture was stirred for 30 minutes, the solution was reduced in volume (~1 mL) under vacuum then purified by flash chromatography on silica gel (15 g) eluting with MeOH:EtOAc:hexane (0.5:20:79.5 then 0.5:30:69.5) to give the title compound **2.41** (100 mg, 0.388 mmol, 43%) as a colourless viscous oil: FTIR ν_{max} (neat) 3500br, 2980m, 2956m, 1772s, 1741s, 1268m, 1187s, 1125s, 1028m, 914m cm^{-1}; TLC (SiO_2, MeOH:CH_2Cl_2 (1:9), Rf 0.65); ^1H NMR (400 MHz) δ 4.52 (1H, ddd, *J* = 8.4, 5.5, 3.0 Hz, γ-lactone), 4.30 (1H, td, *J* = 5.9, 2.5 Hz, THF), 4.26 (1H, q, *J* = 7.4 Hz, $CO_2C(\mathbf{H})H$), 4.26 (1H, q, *J* = 7.4 Hz, $CO_2C(\mathbf{H})H$), 4.07 (1H, d, *J* = 2.5 Hz, $\mathbf{C}HOHCO_2Et$), 3.99 (1H, td, *J* = 7.2, 3.0 Hz, THF), 2.90 (1H, br, O**H**), 2.61 (1H, ddd, *J* = 17.4, 9.9, 7.4 Hz, γ-lactone), 2.43 (1H, ddd, *J* = 17.4, 9.9, 6.0 Hz, γ-lactone), 2.34-2.23 (1H, m, γ-lactone), 2.21-1.91 (5H, m, γ-lactone, 2 x THF), 1.30 (3H, t, *J* = 6.9 Hz, $CO_2CH_2C\mathbf{H_3}$); ^{13}C NMR (100 MHz) δ 178.2 (s, γ-lactone), 172.9 (s, $\mathbf{C}O_2CH_2CH_3$), 82.1 (s, THF), 80.9 (s, γ-lactone), 80.6 (s, THF), 73.3 (d, $\mathbf{C}HOHCO_2Et$), 62.2 (t, $CO_2\mathbf{C}H_2CH_3$), 28.5 (t, THF), 27.9 (t, THF), 27.8 (t, γ-lactone), 25.0 (t, γ-lactone), 14.6 (q, $CO_2CH_2\mathbf{C}H_3$); LRMS (CI, ammonia) *m/z* (relative intensity): 276 (77) $[M+NH^4]^+$, 259 (100) $[M+H]^+$, 241 (49) $[M-H_2O]H^+$; HRMS (CI) calculated for $C_{12}H_{22}NO_6$ 276.14471, found 276.14595.

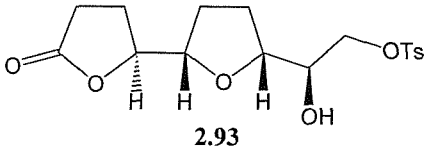
3.67 (2*S,5*R**,2'*S*)-5'-[(1*R**)-1,2-Dihydroxyethyl]tetrahydro-[2,2']bifuranyl-5-one 2.92**



2.92

To a solution of compound **2.41** (80 mg, 0.310 mmol) in anhydrous THF (5 mL) was added 2M $BH_3.Me_2S$ in THF (163 μL, 0.326 mmol). The reaction was stirred for 15 h, then $NaBH_4$ (0.6 mg, 16.3 μmol) was added and stirred for 4 h. The reaction mixture was quenched with MeOH (0.5 mL) and the solvent was removed under vacuum to give a yellow oil. The oil was purified by flash chromatography on silica gel (7 g) eluting with MeOH:CH_2Cl_2 (11:89) to give the title compound **2.92** (40 mg, 0.185 mmol, 60%) as a colourless film: FTIR ν_{max} (neat) 3407br, 2951w, 2871w, 1765s, 1185s, 1066s, 1048s, 1022s cm^{-1}; TLC (SiO_2, MeOH:CH_2Cl_2 (1:9), Rf 0.30); GC [3% Cyanopropylphenyl; Gradient: 200°C (2 mins)-(10°C / min)-250°C; FID] Rt = 6.89 mins; ^1H NMR (400 MHz) δ 4.51 (1H, ddd, *J* = 7.5, 5.5, 3.5 Hz, γ-lactone), 4.05-3.97 (2H, m, THF), 3.69 (1H, dd, *J* = 11.0, 3.5 Hz, CH(**H**)OH), 3.61 (1H, dd, *J* = 11.0, 5.5 Hz, CH(**H**)OH), 3.57 (1H, td, *J* = 5.5, 3.5 Hz, C**H**OHCH$_2$OH), 2.64 (1H, ddd, *J* = 17.6, 9.5, 6.0 Hz, γ-lactone), 2.50 (1H, ddd, *J* = 17.0, 10.0, 7.0, γ-lactone), 2.35-2.27 (1H, m, γ-lactone), 2.17 (1H, dddd, *J* = 17.1, 10.0, 7.0, 6.0 Hz, γ-lactone), 2.07-1.95 (4H, m, THF); ^{13}C NMR (100 MHz) δ 178.0 (s, **C**=O), 81.5 (d, γ-lactone), 81.4 (d, THF), 81.4 (d, THF), 74.3 (d, **C**HOH), 64.8 (t, **C**H$_2$OH), 28.7 (t, THF), 28.2 (t, THF), 27.9 (t, γ-lactone), 24.9 (t, γ-lactone); LRMS (ESI +ve) *m/z* (relative intensity) 455 (28) $[2M+Na]^+$, 396 (30) $[2(M-H_2O)]^{\bullet+}$; HRMS (ESI) calculated for $C_{10}H_{16}O_5$ 239.0889947, found 239.0892640.

3.68 (2*R)-2-Hydroxy-2-[(2*S**,5*R**,2'S*)-5'-oxo-octahydro-[2,2']bifuranyl-5-yl] ethyl toluene-4-sulphonate 2.93**

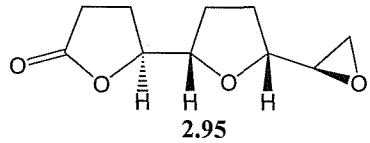


2.93

Et_3N (36 μL, 0.257 mmol) was added to a solution of diol **2.92** (40 mg, 0.183 mmol) and *p*-TsCl (49 mg, 0.257) in CH_2Cl_2 (5 mL) at 0°C under nitrogen. The reaction mixture was warmed to room temperature, stirred for 4 days, then washed with 10% citric acid(aq) (5 mL), saturated $NaHCO_3$(aq) (5 mL), dried ($MgSO_4$), and the solvent

was removed under vacuum to give a yellow oil. The oil was purified by flash chromatography on silica gel (5 g) eluting with EtOAc:hexane (25:75) to give the title compound **2.93** (36 mg, 97.3 μmol, 53%) as a colourless oil which gave a white solid on trituration with ether; m.p. 60-62°C; FTIR ν_{max} (neat) 1773s, 1361s, 1190s, 1177s, 979s cm^{-1}; TLC (SiO_2, MeOH:CH_2Cl_2 (1:9), Rf 0.70); ^1H NMR (400 MHz) δ 7.80 (2H, d, J = 6.5, Ar**H**), 7.37 (2H, d, J = 8.0 Hz, Ar**H**), 4.49 (1H, ddd, J = 8.5, 5.5, 3.0 Hz, γ-lactone), 4.06-3.96 (4H, m, THF, C**H**$_2$OTs), 3.71 (1H, td, J = 5.5, 4.0 Hz, C**H**OHCH$_2$OTs), 2.57 (1H, ddd, J = 17.6, 10.0, 6.5 Hz, γ-lactone), 2.45 (1H, ddd, J = 17.6, 10.0, 7.0 Hz, γ-lactone), 2.45 (3H, s, C**H**$_3$Ar), 2.27 (1H, dddd, J = 12.5, 10.0, 8.0, 6.5 Hz, γ-lactone), 2.14 (1H, dddd, J = 12.6, 9.5, 6.5, 5.5 Hz, γ-lactone), 2.05-1.85 (4H, m, THF); ^{13}C NMR (100 MHz) δ 177.7 (s, **C**=O), 145.2 (s, Ar), 132.8 (s, Ar), 130.1 (2C, d, Ar), 128.2 (2C, d, Ar), 81.3 (d, THF), 80.7 (d, γ-lactone), 79.5 (d, THF), 71.4 (t, **C**H$_2$OTs), 71.0 (d, **C**HOH), 28.4 (t, THF), 27.9 (t, THF), 27.5 (t, γ-lactone), 24.7 (t, γ-lactone), 21.8 (q, **C**H$_3$Ar); LRMS (CI, NH_3) *m/z* (relative intensity): 216 (24) $[(M\text{-}p\text{TsOH})+NH_4]^+$, 200 (100) $[(M\text{-}MePhSO_2)+H]^+$.

3.69 5'-(2*R)-Oxiranyl-(2'*S**,5'*R**,2*S**)-tetrahydro-[2,2']bifuranyl-5-one 2.95**

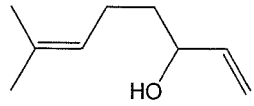


2.95

To a suspension of CuBr.Me_2S [recrystallised from *t*-BuOH/Me_2S] (74 mg, 0.228 mmol) in anhydrous ether (3 mL) at –40°C under argon was treated with 1.75 M *n*-BuLi in hexanes (0.26 mL, 0.456 mmol) to give a brown suspension. The suspension was cooled to –78°C and tosylate **2.93** (42 mg, 0.114 mmol) in ether/THF (1:4, 5 mL) was added. The reaction was warmed to –10°C and stirred for 3 hours. The reaction mixture was quenched with saturated NH_4Cl(aq) (5 mL), the phases were partitioned and aqueous phase was extracted with CH_2Cl_2 (4 x 5 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a colourless oil. The oil was purified by flash chromatography on silica gel (10 g) eluting with MeOH:EtOAc:CH_2Cl_2 (0.5:10:89.5 to 0.5:20:79.5 then 0.5:30:30:69.5) which unfortunately did not furnish the required butylated product but epoxide **2.95** (9 mg, 45.4 μmol, 40%) was isolated as a white solid: m.p. 46-47°C; FTIR ν_{max} (neat) 2921w, 1770s, 1180m cm^{-1}; TLC (SiO_2, MeOH:EtOAc:CH_2Cl_2 (0.5:30:69.5), Rf 0.40); ^1H NMR (400 MHz) δ 4.50 (1H, ddd, J = 8.0, 5.5, 2.5 Hz, γ-lactone), 4.08 (1H,

td, J = 6.0, 2.5 Hz, THF), 3.74 (1H, q, J = 6.0 Hz, THF), 2.95 (1H, ddd, J = 7.0, 5.3, 3.3 Hz, epoxide C**H**), 2.76 (1H, t, J = 6.6 Hz, epoxide C**H$_2$**), 2.69 (1H, ddd, J = 17.6, 10.0, 7.5 Hz, γ-lactone), 2.61 (1H, dd, J = 6.6, 3.9 Hz, epoxide C**H$_2$**), 2.47 (1H, ddd, J = 18.0, 9.5, 6.5 Hz, γ-lactone), 2.33-2.21 (2H, m, γ-lactone), 2.05-1.93 (4H, m, THF); ^{13}C NMR (100 MHz) δ 178.0 (s, **C**=O), 81.5 (d, γ-lactone), 81.3 (d, THF), 81.1 (d, THF), 77.4 (d, γ-lactone), 53.8 (d, epoxide **C**H), 44.0 (t, epoxide **C**H$_2$), 28.6 (t, THF), 28.5 (t, THF), 27.8 (t, γ-lactone), 24.5 (t, γ-lactone); LRMS (CI, ammonia) *m/z* (relative intensity) 216 (36) $[M+NH_4]^+$, 200 (100) $[M+H]H^+$; HRMS (ESI) calculated for $C_{10}H_{14}O_4Na$ 221.0784, found 221.0786.

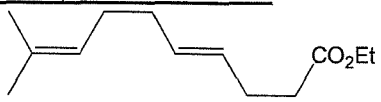
3.70 7-Methylocta-1,6-dien-3-ol 2.96



2.96

To a solution of aldehyde **2.58** (11.2 , 0.10 mol) in anhydrous THF (100 mL) at 15°C under nitrogen was added 1M vinylmagnesium bromide in THF (100 mL, 0.10 mol) over 40 minutes. After 5 minutes the mixture was quenched with 10% citric acid in water (50 mL) and extracted with ether (2 x 200 mL). The ethereal extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give an orange oil, which was purified by distillation (150°C @ 15 mmHg) to give allylic alcohol **2.96** (6.80 g, 48.6 mmol, 49%) as a pale yellow liquid. Spectroscopic details are consistent with those observed in the literature:[161] FTIR ν_{max} (neat) 3408br, 2969w, 2936w, 1377m, 1158s, 1060s, 990s cm^{-1}; TLC (SiO_2, ether:hexane (1:1), Rf 0.50); ^{1}H NMR (300 MHz) δ 5.88 (1H, ddd, J = 16.9, 10.3, 5.9 Hz, CH_2C**H**CHOH), 5.24 (1H, d, J = 16.9 Hz, C(**H**)H=CHCHOH), 5.18-5.09 (1H, m, Me_2CC**H**), 5.12 (1H, d, J = 10.3 Hz, C(**H**)H=CHCHOH), 4.12 (1H, q, J = 6.2 Hz, CH_2CHC**H**OH), 2.09 (2H, q, J = 7.4 Hz, C**H$_2$**CHCMe_2), 1.70 (3H, s, **CH$_3$**), 1.61 (3H, s, **CH$_3$**), 1.59 (2H, dt, J = 8.1, 5.9 Hz, C**H$_2$**CHOH).

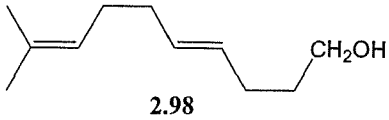
3.71 Ethyl (*E*)-9-methyldeca-4,8-dienoate 2.97



2.97, 60%

Allylic alcohol **2.96** (6.80 g, 48.6 mmol), triethyl orthoacetate (16.1 g, 97.1 mmol) and propionic acid (0.36 g, 4.86 mmol) in xylene (55 mL) were refluxed for 2 h. The solvent was removed under vacuum to give a yellow oil, which was distilled (90°C @ 15 mmHg) to give the title compound **2.97** (6.10 g, 29.2 mmol, 60%) as a colourless oil: FTIR ν_{max} (neat) 2914w, 1738s, 1374w, 1169m, 1046w, 967m cm^{-1}; TLC (SiO_2, CH_2Cl_2:hexane (1:1), Rf 0.27); GC [3% Cyanopropylphenyl; Gradient: 200°C (2 mins)-(10°C / min)-250°C; FID; Rt = 6.89 min]; ^1H NMR (400 MHz) δ 5.52-5.38 (2H, m, **CHCH**), 5.13-5.08 (1H, m, **CHCMe$_2$**), 4.13 (2H, q, *J* = 7.0 Hz, CO_2CH_2), 2.39-2.28 (4H, m, $CH_2CH_2CO_2Et$), 2.04-1.99 (4H, m, CH_2CH_2), 1.69 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.26 (3H, t, *J* = 7.0 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 173.4 (s, **C**=O), 131.8 (s, **C**Me$_2$), 131.6 (d, **C**HCH), 128.4 (d, **C**HCH), 124.2 (d, **C**HCMe$_2$), 60.4 (t, CO_2CH_2), 34.6 (t, CH_2), 32.9 (t, CH_2), 28.2 (t, CH_2), 28.1 (t, CH_2), 25.9 (q, CH_3), 17.9 (q, CH_3CH_2O), 14.5 (q, CH_3); LRMS (CI, NH_3) *m/z* (relative intensity) 211 (100) $[M+H]^+$, 165 (64) $[M-OEt]^+$, 69 (96) $[C_5H_9]^+$.

3.72 9-(*E*)-Methyldeca-4,8-dien-1-ol 2.98

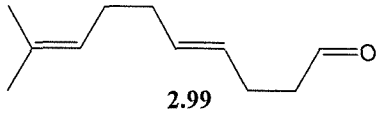


2.98

To a solution of ester **2.97** (2.00 g, 9.52 mmol) in anhydrous THF (20 mL) at 0°C under nitrogen was added batchwise $LiAlH_4$ (0.36 g, 9.52 mmol). The reaction was warmed to room temperature and stirred for 10 minutes. The reaction mixture was cooled to 0°C then quenched by careful dropwise addition of water (3.6 mL), 1M NaOH(aq) (0.36 mL) and water (3.6 mL), which gave a white precipitate which was removed by filtration and washed with ether (2 x 10 mL) and CH_2Cl_2 (2 x 10 mL). The filtrate and washings were combined and the solvent was removed under reduced pressure to give the title alcohol **2.98** (1.22 g, 7.24 mmol, 76%) as a colourless oil; FTIR ν_{max} (neat) 3380br, 2929m, 2852w, 1448w, 1437w, 1378w, 1057s, 967s, 833s cm^{-1}; TLC (SiO_2, ether:hexane (1:1), Rf 0.15); ^1H NMR (400 MHz) δ 5.48 (1H, dt, *J* = 15.1, 5.0 Hz, **CH**CH), 5.42 (1H, dt, *J* = 15.1, 5.5 Hz, **CH**CH), 5.14-5.08 (1H, m, **CH**CMe$_2$), 3.65 (2H, t, *J* = 6.3 Hz, CH_2OH), 2.09 (2H, q, *J* = 7.0 Hz, CH_2CH), 2.05-

1.99 (4H, m, 2 x CH_2CH), 1.69 (3H, s, CH_3), 1.64 (2H, quintet, J = 7.0 Hz, CH_2CH_2OH), 1.60 (3H, s, CH_3), 1.47 (1H, s, OH); ^{13}C NMR (100 MHz) δ 131.8 (s, CMe_2), 131.6 (d, CHCH), 129.8 (d, CHCH), 124.3 (d, $CHCMe_2$), 62.7 (t, CH_2OH), 33.2 (t, CH_2), 32.8 (t, CH_2), 29.3 (t, $CH_2CH_2CH_2OH$), 28.5 (t, $CH_2CH_2CH_2OH$), 26.1 (q, CH_3), 17.9 (q, CH_3); LRMS (Cl, NH_3) *m/z* (relative intensity) 168 (4) $[M]^{\bullet+}$, 69 (100) $[C_5H_9]^+$; HRMS (EI) calculated for $C_{11}H_{20}O$ 168.15142, found 168.15169.

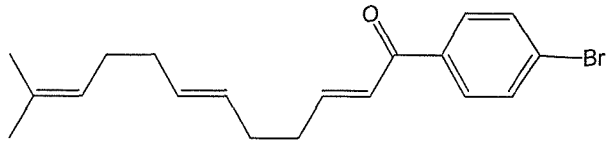
3.73 9-(*E*)-Methyldeca-4,8-dienal 2.99



2.99

To a solution of oxalyl chloride (1.01 g, 7.92 mmol) in anhydrous CH_2Cl_2 (20 mL) at –70°C under nitrogen was added DMSO (0.96 g, 12.2 mmol) in anhydrous CH_2Cl_2 (5 mL) over 2 minutes. The mixture was stirred for 2 minutes then alcohol **2.98** (1.21 g, 7.20 mmol) was added over 5 minutes. After 15 minutes Et_3N (3.64 g, 36.0 mmol) was added dropwise over 2 minutes. The orange solution was stirred at –60°C for 5 minutes then warmed to room temperature. The reaction mixture was quenched with water (10 mL) and the organic phase was separated. The aqueous phase was re-extracted with CH_2Cl_2 (20 mL), then the organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under a vacuum to give an orange oil. The oil was purified by flash chromatography on silica gel (100 g) eluting with ether:hexane (30:70) to give the title aldehyde **2.99** (1.10 g, 6.62 mmol, 84 %) as colourless oil: FTIR ν_{max} (neat) 2927m, 2854w, 2846w, 1727s, 1438m, 970s cm^{-1}; TLC (SiO_2, ether:hexane (1:1), Rf 0.65); ^1H NMR (400 MHz) δ 9.77 (1H, t, J = 1.5 Hz, CHO), 5.49 (1H, dt, J = 15.0, 6.0 Hz, CHCH), 5.42 (1H, dt, J = 15.6, 5.8 Hz, CHCH), 5.13-5.07 (1H, m, $CHCMe_2$), 2.49 (2H, td, J = 7.0, 1.5 Hz, CH_2CHO), 2.34 (2H, td, J = 7.0 Hz, 6.0 Hz, CH_2CH_2CHO), 2.05-1.99 (4H, m, CH_2CH_2), 1.69 (3H, s, CH_3), 1.60 (3H, s, CH_3); ^{13}C NMR (100 MHz) δ 202.6 (s, CHO), 131.9 (s, CMe_2), 131.8 (d, 128.1 (d, CHCH), CHCH), 124.1 (d, $CHCMe_2$), 43.7 (t, CH_2CHO), 32.9 (t, CH_2CH_2), 28.2 (t, CH_2CH_2), 25.9 (q, CH_3), 25.4 (t, CH_2CH_2CHO), 17.9 (q, CH_3); LRMS (CI, ammonia) *m/z* (relative intensity) 184 (27) $[M+NH_4]^+$, 166 (7) $[M]^{\bullet+}$, 149 (26) $[M-H_2O]H^+$, 69 (100) $[C_5H_9]^+$, 97 (35) $[M-C_5H_9]^+$; HRMS (EI) calculated for $C_{11}H_{18}O$ 166.13577, found 166.13567.

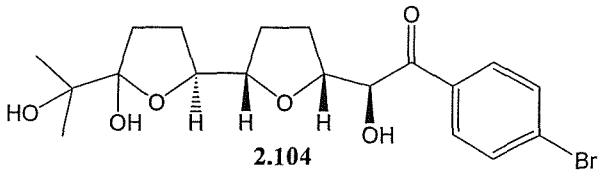
3.74 (*E*,*E*)-1-(4-Bromophenyl)-11-methyldodeca-2,6,10-trien-1-one 3.100



2.100

To a suspension of phosphonium bromide **2.77** (3.19 g, 5.91 mmol) in CH_2Cl_2 (20 mL) was added 1 M NaOH(aq) (6.0 mL, 6.00 mmol) and the mixture was stirred for 20 minutes. The organic phase was collected and aqueous phase was extracted with CH_2Cl_2 (20 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a white foam (2.02 g, 4.40 mmol). The foam was taken up in CH_2Cl_2 (20 mL) and treated with aldehyde **2.99** (0.61 g, 3.67 mmol). The reaction was refluxed for 4 hours, CH_2Cl_2 was removed under vacuum, toluene (30 mL) was added and the reaction mixture was refluxed for 19 hours. The solvent was removed under vacuum to give an orange residue, which was purified by flash chromatography on silica gel (50 g) eluting with CH_2Cl_2:hexane (20:80 then 30:70) to furnish the title triene **2.100** (0.46 g, 1.33 mmol, 36 %) as a colourless oil. Triene **2.100** was prepared as a trans:cis ratio of 14:1, by GC analysis (DB-Wax, 30 m x 0.53 mm, Gradient: 50°C to 250°C (10°C/min), 250°C (10 mins); Rt(cis) = 9.93 min, Rt(trans) = 10.10 min): FTIR ν_{max} (neat) 2920w, 1669s, 1618s, 1585s, 1391m, 1349m, 1282m, 1220m, 1071s, 1010s cm^{-1}; TLC (SiO_2, ether:hexane (3:7), Rf 0.30); HPLC (Luna SiO_2, 250 x 21.2 mm, 254 nm, 20 mL/min, MTBE:hexane (1:99), Rt = 16.9 min); ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (2H, d, J = 8.5 Hz, Ar**H**), 7.61 (2H, d, J = 8.5 Hz, Ar**H**), 7.06 (1H, dt, J = 15.1, 6.8 Hz, C**H**CHCOAr), 6.83 (1H, dt, J = 15.6, 1.5 Hz, C**H**COAr), 5.55-5.47 (1H, m, C**H**CH), 5.44 (1H, dt, J = 15.6, 6.0 Hz, C**H**CH), 5.14-5.08 (1H, m, C**H**CMe_2), 2.39 (2H, q, J = 7.5 Hz, C**H**$_2$CHCHCOAr), 2.23 (2H, q, J = 6.7 Hz, C**H**$_2$$CH_2$CHCHCOAr), 2.03 (4H, t, J = 3.0 Hz, C**H**$_2$C**H**$_2$), 1.69 (3H, s, C**H**$_3$), 1.60 (3H, s, C**H**$_3$); ^{13}C NMR (100 MHz) δ 190.0 (s, **C**=O), 150.2 (d, **C**HCHCOAr), 136.9 (s, Ar), 132.0 (2C, d, Ar), 131.9 (s, **C**Me_2), 131.8 (d, **C**HCH), 130.3 (2C, d, Ar), 128.7 (d, **C**HCH), 125.9 (d, CH**C**HCOAr), 124.1 (d, **C**HCMe_2), 33.3 (t, **C**H_2), 32.9 (t, **C**H_2), 31.3 (t, **C**H_2), 28.3 (t, **C**H_2), 25.9 (q, **C**H_3), 17.9 (q, **C**H_3); LRMS (CI, NH_3) *m/z* (relative intensity) 347 (35) $[M+H]^+$, 349 (37) $[M+H]^+$, 183 (56) $[4\text{-BrPhCO}]^+$, 185 (54) $[4\text{-BrPhCO}]^+$, 149 (100) $[C_{11}H_{17}]^+$; HRMS (EI) calculated for $C_{19}H_{24}O^{79}Br$ 347.10105, found 347.09903.

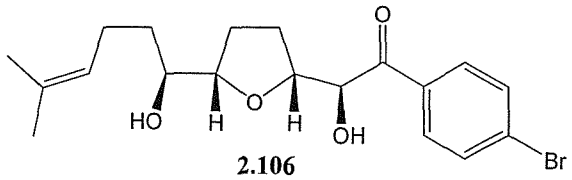
3.75 (2*S)-1-(4-Bromophenyl)-2-hydroxy-2-[(2*S**,5*R**,2'*S**)-5'-hydroxy-5'-(1-hydroxy-1-methylethyl)octahydro-[2,2']bifuranyl-5-yl]ethanone 2.104**



2.104

To a solution of triene **2.100** (0.24 g, 0.692 mmol), Adogen 464 (32 mg, 69.2 μmol) and AcOH (0.46 g, 7.75 mmol) in CH_2Cl_2 (7 mL) under nitrogen was added finely powdered $KMnO_4$ (0.31 g, 1.94 mmoL) at between –10 to –20°C. The reaction was stirred for 90 minutes, then treated with saturated $Na_2S_2O_5$(aq) (5 mL) and the phases were partitioned. The aqueous phase was saturated with NaCl(s) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a yellow solid (0.30 g). The solid was purified by flash chromatography on silica gel (15 g) eluting with MeOH:EtOAc:CH_2Cl_2 (0.5:10:89.5 to 0.5:20:79.5 to 0.5:30:69.5 to 0.5:40:59.5 finally 0.5:50:49.5) to give the title compound **2.104** (21 mg, 49.0 μmol, 7%) as a colourless oil, with compound **2.106** (23 mg, 62.3 μmol, 9%) and an impure sample of compound **2.102**. **2.102** was purified by prep HPLC (Luna SiO_2, 250 x 21.2 mm, 254 nm, 20 ml/min, IPA:hexane (20:80), Rt = 9.2 min) to give **2.102** (10 mg, 19.2 μmol, 4%) as a colourless oil. Analytical data for the major diastereoisomer of the title compound **2.104**: TLC (SiO_2, MeOH:EtOAc:CH_2Cl_2 (0.5:40:59.5), Rf 0.15); ^{1}H NMR (400 MHz) δ 7.81 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.63 (2H, d, *J* = 8.5 Hz, Ar**H**), 5.01 (1H, d, *J* = 2.0 Hz, C**H**OH), 4.41-4.36 (1H, m, THF), 3.98 (1H, ddd, *J* = 9.0, 6.0 , 2.0 Hz, THF), 3.89 (1H, td, *J* = 7.8, 2.5 Hz, γ-lactol), 2.68 (1H, dt, *J* = 17.6, 7.0 Hz, γ-lactol), 2.31-2.21 (1H, m, γ-lactol), 2.19-2.02 (3H, m, THF + γ-lactol), 1.96-1.82 (3H, m, THF + γ-lactol), 1.40 (3H, s, C**H**$_3$), 1.31 (3H, s, C**H**$_3$); ^{13}C NMR (100 MHz) δ 199.7 (s, **C**=O), 133.5 (s, Ar), 132.4 (2C, d, Ar), 130.2 (2C, d, Ar), 130.2 (s, Ar), 109.7 (s, γ-lactol), 82.3 (d, γ-lactol), 81.2 (d, THF), 80.1 (d, THF), 76.5 (d, **C**HOH), 73.5 (s, **C**Me$_2$OH), 32.9 (t, γ-lactol), 28.7 (t, THF), 28.5 (t, γ-lactol), 27.4 (q, **C**H$_3$), 24.5 (t, THF), 24.3 (q, **C**H$_3$); LRMS (CI, NH_3) *m/z* (relative intensity): 883 (16) $[2M+Na]^+$, 881 (27) $[2M+Na]^+$, 879 (14) $[2M+Na]^+$, 453 (100) $[M+Na]^+$, 451 (93) $[M+Na]^+$.

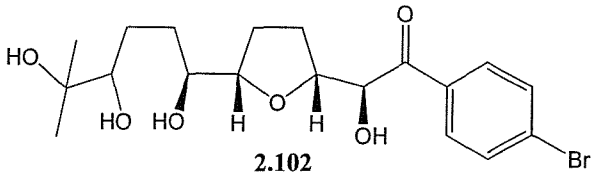
(2*S**)-1-(4-Bromophenyl)-2-hydroxy-2-[(2*R**,5*S**)-5-(-(1*S**)-1-hydroxy-5-methylhex-4-enyl)tetrahydrofuran-2-yl]ethanone **2.106**



2.106

Analytical data for 2.106: TLC (SiO_2, MeOH:EtOAc:CH_2Cl_2 (0.5:40:59.5), Rf 0.70); ^{1}H NMR (400 MHz) δ 7.79 (2H, d, *J* = 8.5 Hz, ArH), 7.65 (2H, d, *J* = 8.0 Hz, ArH), 5.09 (1H, t, *J* = 6.8 Hz, $CHCMe_2$), 5.02 (1H, d, *J* = 1.5 Hz, CHOHCOAr), 4.36 (1H, t, *J* = 6.5 Hz, THF), 3.72 (1H, dd, *J* = 11.5, 6.5 Hz, THF), 3.36 (1H, quintet, *J* = 4.5 Hz, CHOH), 2.28 (1H, t, *J* = 7.5 Hz, $C(H)HCHCMe_2$), 2.25 (1H, m, $C(H)HCHCMe_2$), 2.14-2.01 (3H, m, 2 x THF + $C(H)HCHCMe_2$), 1.88 (2H, quartet, *J* = 7.0 Hz, 2 x THF), 1.69 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.50-1.34 (2H, m, CH_2OH); ^{13}C NMR (100 MHz) δ 199.1 (s, COAr), 133.2 (s, Ar), 132.4 (d, Ar), 132.3 (s, CMe_2), 130.2 (d, Ar), 129.3 (s, Ar), 124.2 (d, $CHCMe_2$), 83.5 (d, THF), 80.1 (d, THF), 75.6 (d, CHOHCOAr), 73.7 (d, CHOH), 34.4 (t, CH_2), 28.4 (t, CH_2), 28.2 (t, CH_2), 25.9 (q, CH_3), 24.4 (t, CH_2), 17.9 (q, CH_3).

(2*S**)-1-(4-Bromophenyl)-2-hydroxy-2-[(2*R**,5*S**)-5-(-(1*S**)-1,4,5-trihydroxy-5-methylhexanyl)tetrahydrofuran-2-yl]ethanone **2.102**

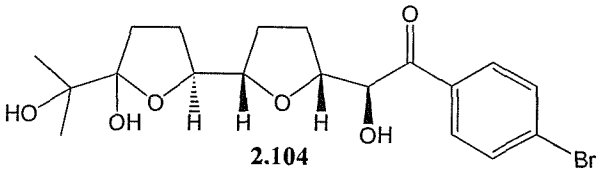


2.102

Analytical data for **2.102** as a ~1:1 mixture of isomers: FTIR ν_{max} (neat) 3478br, 1690s, 1586s, 1395w, 1069s cm^{-1}; TLC (SiO_2, MeOH:EtOAc:CH_2Cl_2 (0.5:40:59.5) Rf 0.35); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (2H, dd, *J* = 8.5, 6.5 Hz, Ar**H**), 7.62 (2H, dd, *J* = 11.0, 8.0 Hz, Ar**H**), 4.97 (1H, d, *J* = 2.0 Hz, C**H**OHCOPh), 4.84 (1H, d, *J* = 2.0 Hz, C**H**OHCOPh), 4.74 (1H, ddd, *J* = 7.5, 4.0, 2.0 Hz, THF), 4.37 (1H, ddd, *J* = 7.0, 5.0, 2.0 Hz, THF), 3.87-3.82 (1H, m, THF), 3.81-3.72 (1H, m, C**H**OH), 3.52 (1H, dd, *J* = 10.5, 4.5 Hz, THF), 3.42 (1H, dt, *J* = 11.0, 2.5 Hz, THF), 2.27-2.17 (1H, m, THF), 2.13-1.68 (7H, m, 3 x THF + $C\mathbf{H}_2OHC(\mathbf{H})HOH$), 1.67-1.51 (1H, m, $CH_2OHC(\mathbf{H})HOH$), 1.38 (3H, s, $C\mathbf{H}_3$), 1.37 (3H, s, $C\mathbf{H}_3$), 1.17 (3H, s, $C\mathbf{H}_3$), 1.15 (3H, s, $C\mathbf{H}_3$); ^{13}C NMR (100 MHz): δ 199.6 (s, **C**=O), 198.9 (s, **C**=O), 134.6 (s, Ar), 132.3 (d, Ar), 132.0 (d, Ar), 130.3 (d, Ar), 130.2 (d, Ar), 128.3 (s, Ar), 86.6 (d, THF), 80.7 (d, THF), 80.3 (d, THF), 80.0 (d, THF), 77.9 (d, **C**HOHCOAr), 77.4 (d,

CHOHCOAr), 76.5 (d, THF CHOH), 74.2 (d, CHOHCMe$_2$OH), 71.7 (s, CMe$_2$OH), 28.6 (t, THF), 28.5 (t, THF), 28.4 (q, CH$_3$), 28.2 (q, CH$_3$), 28.0 (t, CH$_2$CH$_2$), 27.9 (t, CH$_2$CH$_2$), 27.6 (t, THF), 25.5 (t, CH$_2$CH$_2$), 25.4 (t, CH$_2$CH$_2$), 16.5 (q, CH$_3$); LRMS (ESI +ve) *m/z* (relative intensity) 413 (94) [M-H$_2$O]H$^+$, 415 (88) [M-H$_2$O]H$^+$, 435 (91) [M-H$_2$O]Na$^+$, 437 (100) [M-H$_2$O]Na$^+$, 847 (13) [2(M-H$_2$O)]Na$^+$, 849 (23) [2(M-H$_2$O)]Na$^+$, 851 (15) [2(M-H$_2$O)]Na$^+$.

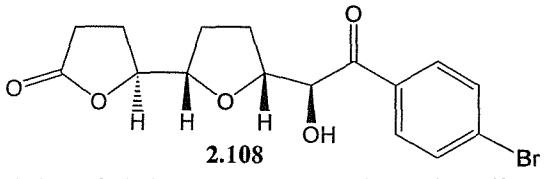
3.76 Asymmetric Oxidative Cyclisation



2.104

To a solution of triene **2.100** (0.14 g, 0.403 mmol), CPTC **2.72** (27 mg, 40.3 μmol) and AcOH (0.29 g, 4.84 mmol) in CH$_2$Cl$_2$ (10 mL) under nitrogen was added finely powdered KMnO$_4$ (0.19 g, 1.21 mmoL) at between –30 to –40°C. The reaction was stirred for 90 minutes, then treated with saturated Na$_2$S$_2$O$_5$ in water (5 mL) and the phases were partitioned. The aqueous phase was saturated with NaCl(s) and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The organic extracts were combined, dried (MgSO$_4$) and the solvent was removed under vacuum to give a yellow solid. The solid was purified by flash chromatography on silica gel (10 g) eluting with MeOH:EtOAc:CH$_2$Cl$_2$ (0.5:30:69.5 then 0.5:40:59.5) to give the title compound **2.104** (7 mg, 16.0 μmol, 4%) as a colourless oil. See above for characterisation.

3.77 5'-[(2*S*)-2-(4-Bromophenyl)-1-hydroxy-2-oxoethyl]-(2*S*,2'*S*,5'*R*)-octahydro-[2,2']bifuranyl-5-one 2.108

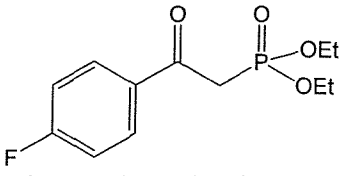


2.108

To a solution of lactol **2.104** (21 mg, 49.1 μmol) and sodium acetate (6.9 mg ,98.2 μmol) in CH$_2$Cl$_2$ (2 mL) at 0°C under argon was added Pb(OAc)$_4$ (23 mg, 49.1 μmol) batchwise. The reaction was warmed to room temperature and stirred for 2 hours. The reaction mixture was filtered (celite) then purified by flash chromatography on silica gel (5 g) eluting with MeOH:EtOAc:CH$_2$Cl$_2$ (0.5:40:59.5 to 0.5:50:49.5) to give the title compound **2.108** (5.4 mg, 14.7 μmol, 30%) as a colourless film; FTIR ν_{max} (neat)

1772s, 1682s, 1585s, 1179s, 1125s, 1071s, 983s cm^{-1}; TLC (SiO_2, ether:hexane (3:7), Rf 0.30); ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.66 (2H, d, *J* = 8.5 Hz, Ar**H**), 4.99 (1H, dd, *J* = 7.0, 2.5 Hz, C**H**OH), 4.44 (1H, ddd, *J* = 8.5, 5.0, 3.0 Hz, γ-lactone), 4.31 (1H, td, *J* = 6.7, 2.5 Hz, THF), 3.87 (1H, td, *J* = 7.0, 3.0 Hz, THF), 3.66 (1H, d, *J* = 7.0 Hz, O**H**), 2.59 (1H, ddd, *J* = 17.6, 10.0, 7.5 Hz, γ-lactone), 2.42 (1H, ddd, *J* = 17.6, 10.0, 6.0 Hz, γ-lactone), 2.27-2.17 (2H, m, THF + γ-lactone), 2.07-1.87 (4H, m, THF + γ-lactone); ^{13}C NMR (100 MHz) δ 198.2 (s, **C**=O), 132.4 (d, Ar), 130.2 (d, Ar), 127.7 (s, Ar), 81.9 (d, γ-lactone), 80.9 (d, THF), 80.4 (d, THF), 77.4 (d, γ-lactone), 75.2 (d, **C**HOH), 28.2 (t, THF), 27.8 (t, γ-lactone), 27.1 (t, THF), 14.3 (t, γ-lactone).

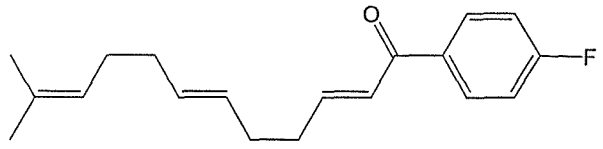
3.78 [2-(4-Flourophenyl)-2-oxoethyl]phosphonic acid diethyl ester



Triethylphosphite (3.68 g, 22.2 mmol) and 2-bromo-4'-fluoroacetophenone (5.00 g, 23.4 mmol) in Xylene were heated at 100°C for 16 hours. The solvent was removed under vacuum to give an orange oil which was taken up in ether (10 mL) and extracted into 2M NaOH(aq) (20 mL). The aqueous phase was washed with ether (2 x 10 mL) then acidified with citric acid (5 g) and extracted with ether (2 x 20 mL). The ethereal extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a yellow oil. The oil was purified by flash chromatography on silica gel (100 g) eluting with EtOAc:hexane (65:45 then 75:25) to give the title compound (1.27 g, 4.64 mmol, 24%) as a colourless oil. Spectroscopic details are consistent with those observed in the literature:[162] FTIR ν_{max} (neat) 1681m, 1598m, 1278m, 1249s, 1054s, 1023s, 963s, 820m cm^{-1};TLC (SiO_2, EtOAc, Rf 0.60); ^1H NMR (400 MHz): δ 8.06 (2H, dd, *J* = 9.0 ,5.5 Hz, Ar**H**), 7.15 (2H, t, *J* = 8.5 Hz, Ar**H**), 4.15 (1H, q, *J* = 7.0 Hz, C**H**$_2$O), 4.15 (1H, q, *J* = 7.0 Hz, C**H**$_2$O), 4.13 (1H, q, *J* = 7.0 Hz, C**H**$_2$O), 4.13 (1H, q, *J* = 7.0 Hz, C**H**$_2$O), 3.59 (2H, d, *J* = 23.1 Hz, C**H**$_2$C=O), 1.29 (6H, t, *J* = 7.0 Hz, C**H**$_3$CH$_2$O); ^{13}C NMR (100 MHz): δ 190.5 (d, *J* = 6.8 Hz, **C**=O), 166.3 (d, *J* = 254.1 Hz, Ar), 133.2 (d, *J* = 4.8 Hz, Ar), 132.0 (dd, *J* = 9.7 Hz, Ar), 115.9 (dd, *J* = 22.2 Hz, Ar), 62.9 (td, *J* = 6.8 Hz, **C**H$_2$O), 38.7 (td, *J* = 128.5 Hz, **C**H$_2$C=O), 16.4 (qd, *J* = 5.8

Hz, CH_3CH_2O); LRMS (CI, NH_3) *m/z* (relative intensity): 275 (43) $[M+H]^+$, 123 (100) $[FPhCO]^+$.

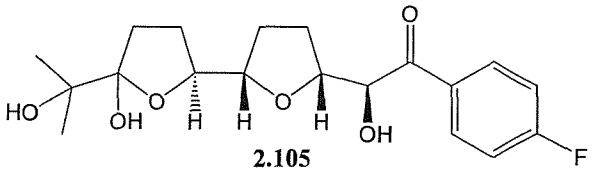
3.79 1-(4-Fluorophenyl)-11-(*E*,*E*)-methyldodeca-2,6,10-trien-1-one 2.101



2.101

Aldehyde **2.58** (0.52 g, 3.16 mmol) and [2-(4-Flourophenyl)-2-oxoethyl]phosphonic acid diethyl ester (0.75 g, 3.32 mmol) and $K_2C_2O_3$ (0.92 g, 6.64 mmol) in THF (30 mL) were refluxed for 20 hours. The mixture was partitioned between water (50 mL) and CH_2Cl_2 (50 mL), the organic phase was collected, dried ($MgSO_4$) and the solvent was removed under vacuum to give a pale orange oil. The oil was purified by vacuum distillation (200°C @ 0.1 mmHg) to give a single geometric isomer of the title triene **2.101** (0.52 g, 1.82 mmol, 58%) as a pale yellow oil: FTIR ν_{max} (neat) 2916m, 1672s, 1622s, 1598s, 1299m, 1230s, 1156s, 970s cm^{-1}; TLC (SiO_2, Et_2O:hexane (1:9), Rf 0.60); ^1H NMR (400 MHz): δ 7.96 (2H, dd, *J* = 8.9, 5.5 Hz, Ar**H**), 7.14 (2H, t, *J* = 8.9 Hz, Ar**H**), 7.06 (1H, dt, *J* = 15.4, 6.9 Hz, C**H**CHCOAr), 6.86 (1H, dt, *J* = 15.4, 1.2 Hz, CHC**H**COAr), 5.56-5.38 (2H, m, C**H**C**H**), 5.11 (1H, sbr, C**H**CMe_2), 2.39 (2H, q, *J* = 7.7 Hz, CH_2CH_2COAr), 2.23 (2H, q, *J* = 6.9 Hz, CH_2CH_2COAr), 2.03 (4H, t, *J* = 3.0 Hz, CH_2CH_2), 1.68 (3H, s, CH_3), 1.59 (3H, s, CH_3) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.6 (s, **C**=O), 165.9 (sd, *J* = 252.3 Hz, Ar), 149.9 (d, **C**HCHCOPh), 134.7 (s, **C**Me_2), 131.9 (sd, *J* = 66.4 Hz, Ar), 131.8 (2C, dd, *J* = 39.2 Hz, Ar), 129.0 (2C, d, **C**HCH), 126.2 (d, **C**HCOPh), 124.4 (d, **C**HCMe_2), 116.0 (2C, dd, *J* = 21.8 Hz, Ar), 33.3 (t, **C**H_2), 33.2 (t, **C**H_2), 31.6 (t, **C**H_2), 28.5 (t, **C**H_2), 26.1 (2C, q, **C**H_3); LRMS (CI, NH_3) *m/z* (relative intensity): 287 (4) $[M+H]^+$, 123 (100) $[FPhCO]^+$; HRMS (EI) calculated for $C_{19}H_{24}FO$ 286.17329, found 286.17337.

3.80 (2*S)-1-(4-Fluorophenyl)-2-hydroxy-2-[(2*S**,5*R**,2'*S**)-5'-hydroxy-5'-(1-hydroxy-1-methylethyl)octahydro-[2,2']bifuranyl-5-yl]ethanone 2.105**

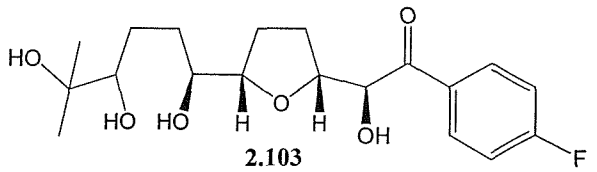


2.105

To a stirring solution of triene **2.101** (0.40 g, 1.398 mmol), CPTC **2.72** (92 mg, 0.140 mmol, 10 mol%) and acetic acid (1.0 mL, 16.78 mmol) in CH_2Cl_2 (5 mL) at –40°C

under nitrogen was added $KMnO_4$(s) (0.66 g, 16.78 mmol) and the mixture was stirred for 3 hours after which time triene **2.101** had disappeared to form was postulated to be THF diol **2.107** with the dimethyl-substituted olefin in tact. A further portion of $KMnO_4$(s) (0.66 g, 16.78 mmol) and acetic acid (1.0 mL, 16.78 mmol) was added to the reaction mixture, the mixture was then allowed to slowly warm to room temperature and was allowed to stir for 18 hours. The product proposed to be **2.107** had been consumed so the reaction was quenched with saturated $Na_2S_2O_5$ in water (5 mL). The mixture was evaporated down under vacuum to give a pale orange solid which was extracted with ether (2 x 5 mL) then CH_2Cl_2 (2 x 5 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed under vacuum to give a yellow glass. The mixture was purified by flash chromatography on silica (10 g) eluting with *iso*-propyl alcohol:hexane (20:80 to 30:70 then finally 40:60) to give the title compound **2.105** (29 mg, 78.8 μmol, 6%) and THF tetraol **2.103** (36 mg, 97.3 μmol, 7%) as colourless films, each as a mixture of diastereoisomers. Analytical data for **2.105**: FTIR ν_{max} (neat) 3423br, 1682s, 1600s, 1505s, 1241s, 1060s, 1080s, 959s cm^{-1}; TLC (SiO_2, IPA:hexane (1:1), Rf 0.70); ^1H NMR (400 MHz): δ 8.02-7.94 (2H, m, Ar**H**), 7.17 (2H, t, J = 8.5 Hz, Ar**H**), 5.04 (1H, sbr, C**H**OHCOAr), 4.43-4.37 (1H, m, THF), 4.00 (1H, ddd, J = 9.5, 6.5, 2.5 Hz, THF), 3.89 (1H, td, J = 7.5, 2.5 Hz, γ-lactol), 2.70 (1H, dt, J = 18.1, 7.5 Hz, γ-lactol), 2.31-2.23 (1H, m, γ-lactol), 2.21-2.03 (3H, m, THF + γ-lactol), 1.97-1.86 (3H, m, THF + γ-lactol), 1.61 (3H, sbr, O**H**), 1.40 (3H, s, C**H**$_3$), 1.30 (3H, s, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.5 (2C, dd, J = 9.7 Hz, Ar), 116.4 (2C, d, Ar), 82.2 (d, γ-lactol), 81.1 (d, THF), 80.2 (d, THF), 76.5 (d, **C**HOH), 74.3 (s, **C**Me$_2$OH), 33.0 (t, γ-lactol), 28.8 (t, THF), 28.6 (t, γ-lactol), 27.4 (q, **C**H$_3$), 24.5 (t, THF), 24.3 (q, **C**H$_3$); LRMS (CI, NH_3) *m/z* (relative intensity): 287 (4) $[M+H]^+$, 123 (100) $[FPhCO]^+$.

(2*S**)-1-(4-Bromophenyl)-2-hydroxy-2-[(2*R**,5*S**)-5-(-(1*S**)-1,4,5-trihydroxy-5-methylhexanyl)tetrahydrofuran-2-yl]ethanone **2.103**



2.103

Analytical data for **2.103**: LRMS (ESI +ve) *m/z* (relative intensity) 353 (38) $[M-H_2O]H^+$, 375 (100) $[M-H_2O]Na^+$, 727 (47) $[2(M-H_2O)]Na^+$.

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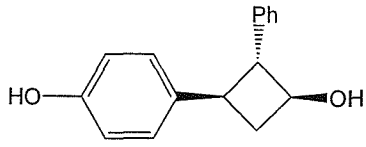
Appendix

Crystal structure of cyclobutanol **1.117**.



1.117

Table 1. Crystal data and structure refinement.

Identification code	**01sot155**	
Empirical formula	$C_{16}H_{16}O_2$	
Formula weight	240.29	
Temperature	291(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 5.4447(2) Å	α = 90°
	b = 16.0352(7) Å	β = 99.544(2)°
	c = 15.1862(8) Å	γ = 90°
Volume	1307.51(10) Å^3	
Z	4	
Density (calculated)	1.221 Mg / m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	512	
Crystal	Block; colourless	
Crystal size	0.15 x 0.06 x 0.03 mm^3	
θ range for data collection	3.00 – 27.50°	
Index ranges	$-6 \le h \le 7$, $-20 \le k \le 20$, $-19 \le l \le 19$	
Reflections collected	13998	
Independent reflections	2969 [R_{int} = 0.1010]	
Completeness to θ = 27.50°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9976 and 0.9882	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2969 / 0 / 166	
Goodness-of-fit on F^2	1.003	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0638, $wR2$ = 0.1628	
R indices (all data)	$R1$ = 0.1509, $wR2$ = 0.2101	
Extinction coefficient	0.039(8)	
Largest diff. peak and hole	0.200 and –0.187 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:
Chirality: C7 and C10 = S.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	3147(5)	1755(1)	9008(2)	67(1)	1
C2	1173(5)	2206(2)	9198(2)	74(1)	1
C3	385(4)	2905(1)	8698(2)	65(1)	1
C4	1543(4)	3163(1)	8002(1)	57(1)	1
C5	3505(4)	2688(1)	7816(2)	70(1)	1
C6	4312(5)	1990(1)	8314(2)	72(1)	1
C7	698(4)	3933(1)	7481(2)	63(1)	1
C8	120(5)	3914(2)	6452(2)	82(1)	1
C9	1176(6)	4794(2)	6454(2)	82(1)	1
C10	2608(4)	4640(1)	7394(2)	64(1)	1
C11	3052(4)	5317(1)	8083(1)	62(1)	1
C12	5173(6)	5341(2)	8691(2)	107(1)	1
C13	5574(7)	5952(3)	9339(3)	144(2)	1
C14	3873(8)	6552(2)	9381(3)	112(1)	1
C15	1772(8)	6545(2)	8781(2)	111(1)	1
C16	1350(6)	5931(2)	8143(2)	94(1)	1
O1	3945(4)	1076(1)	9530(1)	99(1)	1
O2	2533(6)	5023(2)	5771(1)	131(1)	1

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

C1–C2	1.365(3)
C1–C6	1.370(4)
C1–O1	1.375(3)
C2–C3	1.383(3)
C2–H2	0.9300
C3–C4	1.381(3)
C3–H3	0.9300
C4–C5	1.379(3)
C4–C7	1.497(3)
C5–C6	1.382(3)
C5–H5	0.9300
C6–H6	0.9300
C7–C8	1.542(3)
C7–C10	1.559(3)
C7–H7	0.9800
C8–C9	1.522(3)
C8–H8A	0.9700
C8–H8B	0.9700
C9–O2	1.417(3)
C9–C10	1.529(3)
C9–H9	0.9800
C10–C11	1.499(3)
C10–H10	0.9800
C11–C12	1.354(3)
C11–C16	1.365(3)
C12–C13	1.379(4)
C12–H12	0.9300
C13–C14	1.344(5)
C13–H13	0.9300
C14–C15	1.340(5)
C14–H14	0.9300
C15–C16	1.373(4)
C15–H15	0.9300
C16–H16	0.9300
O1–H1	0.8200
O2–H2A	0.8200
C2–C1–C6	119.9(2)
C2–C1–O1	118.8(2)
C6–C1–O1	121.3(2)
C1–C2–C3	119.8(2)
C1–C2–H2	120.1
C3–C2–H2	120.1
C4–C3–C2	121.6(2)
C4–C3–H3	119.2
C2–C3–H3	119.2
C5–C4–C3	117.4(2)
C5–C4–C7	121.8(2)
C3–C4–C7	120.8(2)
C4–C5–C6	121.5(2)
C4–C5–H5	119.3
C6–C5–H5	119.3
C1–C6–C5	119.9(2)
C1–C6–H6	120.1
C5–C6–H6	120.1
C4–C7–C8	120.89(19)
C4–C7–C10	119.58(19)
C8–C7–C10	87.44(17)
C4–C7–H7	109.0
C8–C7–H7	109.0
C10–C7–H7	109.0

C9–C8–C7	88.08(18)
C9–C8–H8A	114.0
C7–C8–H8A	114.0
C9–C8–H8B	114.0
C7–C8–H8B	114.0
H8A–C8–H8B	111.2
O2–C9–C8	118.7(2)
O2–C9–C10	118.5(3)
C8–C9–C10	89.27(18)
O2–C9–H9	109.6
C8–C9–H9	109.6
C10–C9–H9	109.6
C11–C10–C9	122.3(2)
C11–C10–C7	120.04(19)
C9–C10–C7	87.22(17)
C11–C10–H10	108.5
C9–C10–H10	108.5
C7–C10–H10	108.5
C12–C11–C16	116.5(2)
C12–C11–C10	121.2(2)
C16–C11–C10	122.4(2)
C11–C12–C13	121.5(3)
C11–C12–H12	119.3
C13–C12–H12	119.3
C14–C13–C12	120.9(3)
C14–C13–H13	119.5
C12–C13–H13	119.5
C15–C14–C13	118.6(3)
C15–C14–H14	120.7
C13–C14–H14	120.7
C14–C15–C16	120.7(3)
C14–C15–H15	119.7
C16–C15–H15	119.7
C11–C16–C15	121.9(3)
C11–C16–H16	119.1
C15–C16–H16	119.1
C1–O1–H1	109.5
C9–O2–H2A	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	79(2)	46(1)	71(2)	2(1)	0(1)	4(1)
C2	85(2)	68(2)	71(2)	10(1)	19(1)	8(1)
C3	66(1)	62(1)	69(2)	2(1)	13(1)	7(1)
C4	60(1)	52(1)	59(1)	−6(1)	8(1)	0(1)
C5	78(2)	60(2)	74(2)	2(1)	22(1)	3(1)
C6	76(2)	54(1)	86(2)	−8(1)	15(1)	9(1)
C7	67(1)	53(1)	66(2)	2(1)	8(1)	0(1)
C8	97(2)	71(2)	72(2)	2(1)	−6(1)	−16(1)
C9	114(2)	67(2)	63(2)	6(1)	5(1)	−15(1)
C10	72(1)	55(1)	64(2)	0(1)	11(1)	−2(1)
C11	73(2)	52(1)	60(1)	−2(1)	14(1)	−3(1)
C12	82(2)	129(3)	103(2)	−48(2)	−7(2)	20(2)
C13	101(3)	188(4)	132(3)	−88(3)	−10(2)	1(3)
C14	125(3)	103(3)	114(3)	−49(2)	43(2)	−33(2)
C15	143(3)	75(2)	119(3)	−24(2)	30(2)	20(2)
C16	104(2)	76(2)	96(2)	−11(2)	−2(2)	25(2)
O1	119(2)	67(1)	107(2)	21(1)	7(1)	21(1)
O2	211(3)	118(2)	71(1)	−5(1)	37(1)	−68(2)