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Synthesis and catalytic properties of novel C_2 symmetric guanidine bases.

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SYNTHESIS AND CATALYTIC PROPERTIES OF NOVEL C_2 SYMMETRIC GUANIDINE BASES.

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A thesis submitted to the
University of Wales
in the candidature for the degree of
Philosophiae Doctor

By

Dafydd Arthur Thomas

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Er cof am Taid.
I Mam a Nain

In Memory of my Grandfather
To my Mother and Grandmother

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I would like to take this opportunity to thank my supervisor Dr Paddy Murphy for his patience and guidance throughout the course of my project. Also I would like to thank my industrial supervisor Pete Caulkett of AstraZeneca for his advice and for making me welcome during my three month placement at Alderly Park. My thanks also go to all the chemistry department staff past and present for their hard work, especially Mr Eric Lewis and Mr Glyn Connolly for the NMR spectra over the years and Mr Gwynfor Davies for being there to borrow chemicals and equipment from.

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ABSTRACT

This thesis describes work carried out towards the synthesis of novel C_2 symmetric guanidine bases and their application to the catalysis of the nitroaldol and nitro-Michael reactions.

The following achievements were made.

1) The synthesis of a family of novel C_2 symmetric guanidine bases prepared from the addition of guanidine to (6S)-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-hex-1-en-3-one. The α,β-unsaturated ketone is prepared from (S)-(-)-malic acid.

2) Investigations were performed into the catalysis of the nitroaldol reaction of nitromethane to isopentanal and the nitro-Michael reaction of 2-nitropropane to *trans*-chalcone during which moderate enantioselectivity was observed.

3) Work was carried out on the development of a new family of guanidine bases intended to be more efficient asymmetric catalysts.

ABBREVIATIONS

Å	angstrom(s)
AcCl	acetyl chloride
AcOH	acetic acid
AIDS	acquired immune deficiency syndrome
Arg	arginine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
BuLi	butyl lithium
c	concentration
cat.	catalytic
CI	chemical ionisation
d	doublet
δ	chemical shift
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
Dec.	decompose
DEPT	distortionless enhancement by polarisation transfer
DIBAL	diisobutylaluminium hydride
DMAP	4-(*N*,*N*-dimethylamino) pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
e.e	enantiomeric excess
Equiv.	molar equivalents
Et	ethyl

EtOH	ethanol
EtOAc	ethyl acetate
FT-IR	Fourier transform infra-red
g	gram(s)
h	hour(s)
HCl	hydrochloric acid
HIV	human immunodeficiency virus
HRMS	high resolution mass spectroscopy
Hz	hertz
IC_{50}	concentration at which 50 % of the target cells are inhibited
J	coupling constant (in hertz)
l	litre
$LiAlH_4$	lithium aluminium hydride
LiBr	lithium bromide
M	molar
m	multiplet or of medium intensity
MeMgBr	methyl magnesium bromide
MeOH	methanol
$MgSO_4$	magnesium sulfate
MHz	megahertz
min	minute(s)
µg	microgram
ml	millilitre(s)
mm Hg	millimetres of mercury
mmol	millimole(s)
mpt	melting point
N	normal
$NaBH_4$	sodium borhydride
$NaHCO_3$	sodium hydrogen carbonate
NaOH	sodium hydroxide

ng	nanogram
υ	wavenumber(s)
NMR	nuclear magnetic resonance
p	*para* or pentet
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet
R_f	retention factor
rt	room temperature
s	singlet or strong intensity
sat.	saturated
t	triplet
TIPS	triisopropylsilyl
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
tlc	thin layer chromatography
w	weak intensity

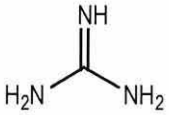
Chapter 1

Introduction

Introduction

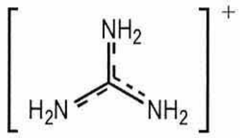
1.1 Guanidine

Guanidine, **1**, is a colourless, highly hygroscopic, crystalline solid which is exceedingly soluble in water. The guanidine moiety is one of the more versatile groups in nature, it appears in a host of molecules from toxins to enzymes almost always playing a key role in the activity of the molecule.



1

Guanidine is one of the strongest organic bases known, quaternary ammonium hydroxides being stronger bases, with a pK_a of 13.6 putting it on a par with the hydroxide ion with regard to its proton affinity. Guanidine as a free base is not overly stable and readily absorbs water and CO_2 from the atmosphere, behaviour typical of a strong base. However, protonation of guanidine gives rise to the highly stable guanidinium ion, **2**.[1]



2

This stability is due to resonance stabilisation leading to delocalisation of the positive charge throughout the π-system, Figure 1.[1] The most convincing evidence for this structure is the comparison of the C-N bond lengths in the guanidinium ion (1.18 Å, all three bonds being of equivalent length) with the C-N bond length for a single bond (1.48 Å) and for a double bond (1.28 Å). The small value for the bond length in guanidine implies a large resonance stabilisation in the molecule.[2]

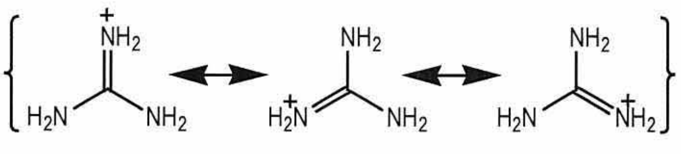


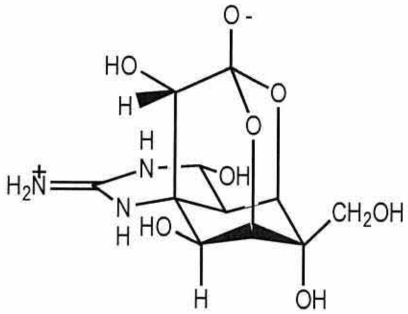
Figure 1. The resonance stabilisation of the guanidinium ion.

Further studies using the methylguanidinium ion support this finding giving an average C-N bond length in the methylguanidinium ion as being 1.29 Å as well as showing that the ion is planar in configuration, expected for the delocalised structure shown above.[3]

Other physical evidence for the delocalised structure of the guanidinium ion was obtained from the measurement of pK_a values of various N-methylated guanidines. The alkylation of guanidine should give rise to an increase in the value of the pK_a since the electron donating effect of the alkyl group stabilises the positive charge on the ion resulting from protonation of the guanidine. Experimental results showed that N-methylguanidine was a weaker base than unsubstituted guanidine but that N,N',N''-trimethylguanidine is a stronger base. The explanation for this is that while methyl groups are base strengthening, a substitution which destroys the equivalence of the nitrogens in guanidine will be base weakening because it reduces the resonance energy of the ion. The combined effect of several methyl groups outweighs this effect but the more symmetrical the substitutions the stronger the base.[4]

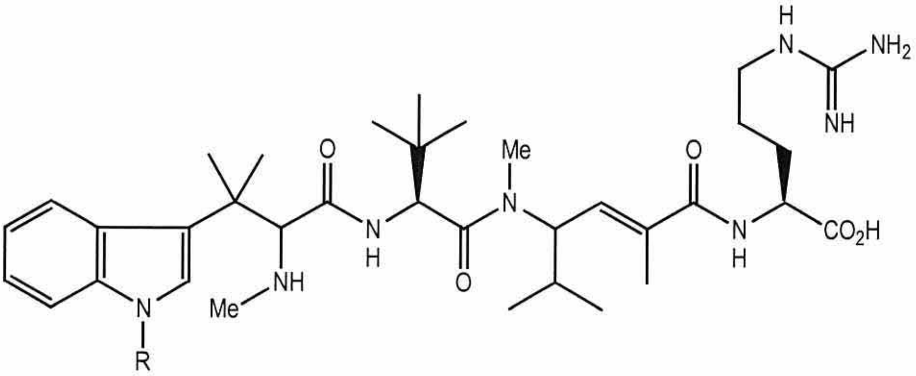
1.2 Guanidine in natural products.

The guanidine moiety appears in many natural products, produced by a whole range of organisms including microorganisms, algae, marine and terrestrial invertebrates as well as higher plants. Perhaps the most well known of these natural products is tetrodotoxin, **3**, most often associated with puffer fish but actually produced by microbes co-existing with the puffer fish. Although tetrodotoxin is primarily associated with the puffer fish it is also found in other organisms, for example in extracts obtained from the skin of *Atelopus subornatus, A. peruensis* and *A. oxyrhynchus* Bufonidae toads.[5] Tetrodotoxin is one of the most potent molecules known to selectively block the voltage-sensitive sodium channels of excitable tissues. As a result, tetrodotoxin inhibits or reduces the chances of an action potential being produced. The guanidinium ion is able to enter cells via the voltage sensitive Na^+ channels. It is likely that the guanidine containing ring is the part of the molecule that lodges in the channel leaving the rest of the molecule blocking its outer mouth. Interest in this molecule was promoted by the need to develop analytical methods for detecting cases of poisoning.



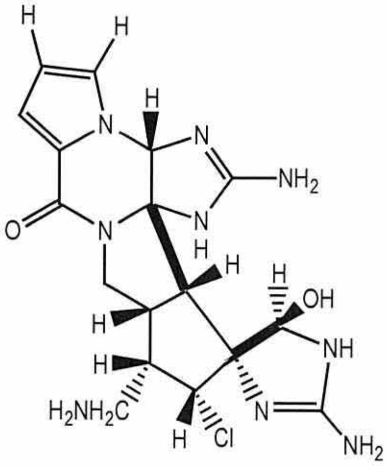
3

There are many more examples of guanidine containing natural products, a great many of which are of interest because of potentially useful biological activity. For example, among a series of polypeptides isolated from the *Cymbastela* sp. sponge were the criamides A, **4**, and B, **5**. Criamide B is a potent cytotoxic compound against a series of different tumour lines including murine leukaemia P388, human breast cancer MCF7, human glioblastoma/astrocytoma U373, human ovarian carcinoma, human colon LOVO and human lung A549 at levels as low as 0.2 μg ml^{-1} for some cell lines.[5] This compound would obviously be a powerful tool against cancer with such a broad range of affected cell lines.



4 R = H
5 R = Me

Palau'amine, **6**, which was isolated from the sponge *Stylotella aurantium*, is a complex bisguanidine alkaloid containing six fused rings that contain eight chiral centres. The antifungal, antitumour and immunosuppressive properties of the compound are currently undergoing preclinical studies. In mixed lymphocyte reactions palau'amine showed an activity at less than 18 ng ml^{-1} , and the cytotoxicity assay against murine lymphocytes showed an activity of 1.5 μg ml^{-1}.[6]



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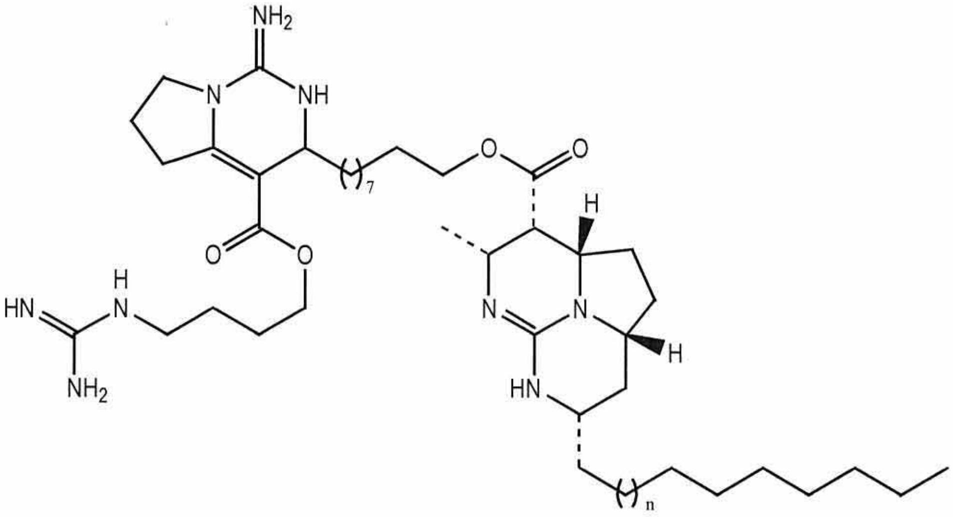
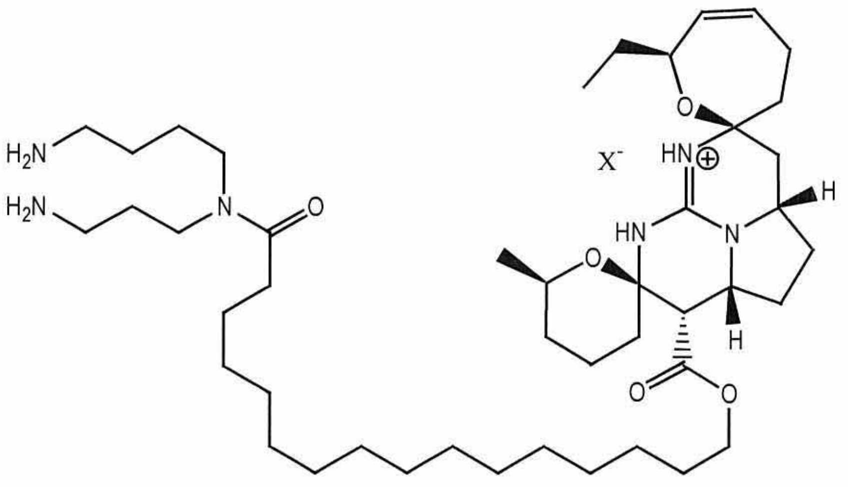
Another series of interesting guanidine containing compounds was isolated from the sponge *Batzella* sp., these compounds, known as batzelladines A-I, show possibly useful biological activity.[7] Batzelladine A, **7**, and the structurally similar batzelladine B inhibit the binding of the gp120 domain of HIV-envelope gp160 glycoprotein to the CD4 receptor on the surface of the human T cell. This binding interaction is the first stage of HIV-host cell binding, after which HIV penetrates the cell in order to replicate.[5] Disruption of this interaction in the body would possibly offer some protection from infection with HIV.



7 n = 1 (maj), 2, 3

Batzelladines F-I show a high level of activity in a p56^{lck}-CD4 dissociation assay. It has been established that immunological responses by T cells are mediated by CD4 expressed on cell surfaces. An important step in the understanding of the working of CD4 was taken when it was found that it interacted with a protein p56^{lck}. It has been reported that interaction of p56^{lck} with CD4 is required for antigenic activation. Thus a compound which prevents the binding of p56^{lck} to CD4 has potential as an immunosuppressive drug which could be optimised for the treatment of autoimmune diseases and transplant rejection.[7]

Ptilomycalin A, **8**, was isolated from the Caribbean sponge *Ptilocaulis spiculifer* and from a red *Hemimycale* sp. of the Red Sea.[8] The ptilomycalin A molecule contains a pentacyclic guanidine core similar to the structure found in closely related alkaloids the crambescins.



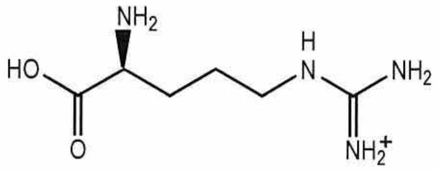
8

Ptilomycalin A shows cytotoxicity against P388 (IC_{50} 0.1 $\mu g\ ml^{-1}$), L1210 (IC_{50} 0.4 $\mu g\ ml^{-1}$) and KB (IC_{50} 1.3 $\mu g\ ml^{-1}$) cell lines, it also shows antifungal activity against *Candida albicans* (0.8 $\mu g\ ml^{-1}$) as well as good antiviral activity (HSV) at a level of 0.2 $\mu g\ ml^{-1}$.[9] These impressive activities have resulted in much interest in ptilomycalin A and a lot of research has gone into the synthesis of ptilomycalin A and potentially even more active analogues.

The above compounds are only a few of the guanidine containing natural products known, many of which have interesting biological activities, but it can be seen that guanidine containing natural products do have great potential for use as pharmaceuticals because of their biological activity.

1.3 Guanidine in receptors.

Guanidine plays an important role in enzyme chemistry as it is present in the amino acid arginine, **9**, which is present in the active site of many enzymes which bind to anionic groups in a substrate. It is also involved in the stabilization of enzyme tertiary structure due to formation of internal salt bridges with carboxylate residues on opposing amino acids.[10]



9

The presence of guanidine in arginine results in it being positively charged over a wide pH range due to the strong basicity of guanidine. This, along with the unique hydrogen bonding mode of guanidine with oxoanionic molecules, see Figure 2, which involves two parallel hydrogen bonds as well as the electrostatic attraction, probably resulted in the evolutionary selection of arginine as one of the core group of 20 amino acids used in nature.[10,11]

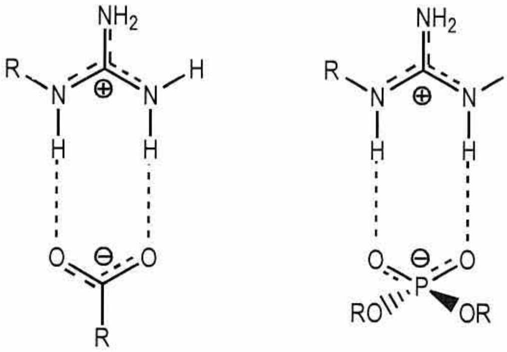


Figure 2 : The binding modes of the guanidinium group with carboxylate and phosphate oxoanions.

The bonding mode of guanidine is probably responsible for the consistent occurrence of two arginine residues in cytochrome c, an electron transport protein, over a range of species. Arginine is also present in other enzyme active sites, for example the binding of phosphates in staphylococcal nuclease, an enzyme which hydrolyzes phosphate bonds in DNA at a rate 10^{16} times faster than the background reaction.[3] Two arginine residues are present in the binding of phosphates, Arg-35 and Arg-87, and the binding is thought to be as shown in Figure 3.

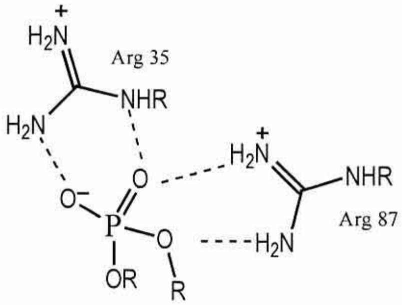


Figure 3: Proposed binding of phosphates in staphylococcal nuclease.

Carboxypeptidase enzymes hydrolize peptide bonds in polypeptides from either the C or N-terminus end. Carboxypeptidase A was the initial enzyme used for determining the C-terminal peptide in enzymes, used because it readily hydrolyzes the peptide bond between the penultimate and C-terminal residues and releases the C-terminal residue as a free amino acid. The mode of action of this enzyme is highly dependent on arginine in that the active site contains several arginine residues. In the active site when the C-terminus of a substrate is inserted Arg-145 forms a salt bridge with the carboxylate group of the terminal amino acid. Following this binding Arg-71, Arg-127, Tyr-198 and Phe-279 are thought to be involved in the initial recognition site in the early stages of substrate binding.[12,13] Arginine is also involved in the stabilization of protein structure; an example of this is the possible involvement of arginine-carboxylate salt bridges in the tertiary structure of the secretin hormone, which consists of 27 amino acid residues. See Figure 4 for an example of the type of binding expected.[14]

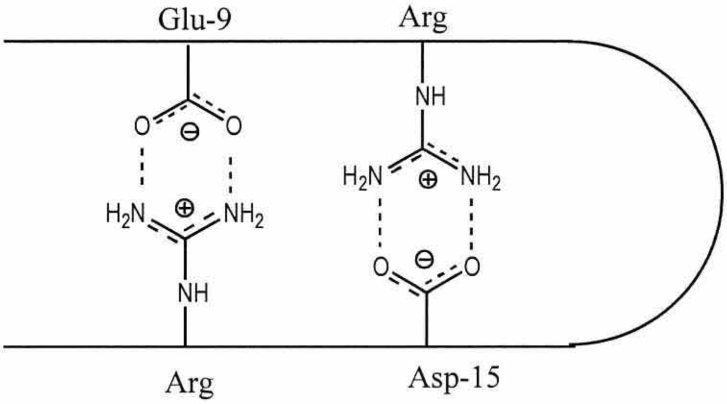
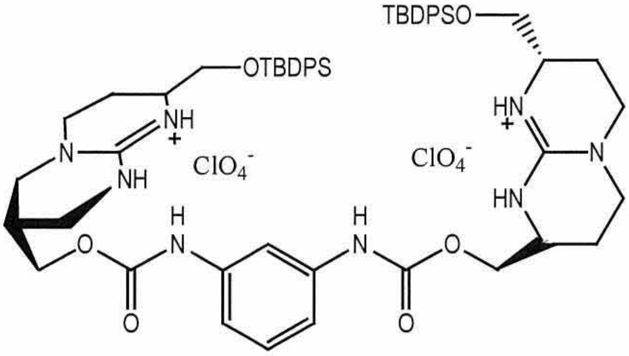


Figure 4: The suspected salt bridges present in secretin.

Since the guanidinium moiety is so widely used in nature for recognition and binding of anionic guest molecules, a considerable amount of research has been done on the use of guanidine in artificial receptor molecules. One interesting use is shown in the work of Kilburn and co-workers where a guanidine unit was placed in the centre of a 'tweezer' like receptor constructed from amino acids.[15] Similar receptors were shown to work by forming a complex with complimentary peptide chains in aqueous solutions; this form of receptor could selectively pick out peptide strands from solution with the added bonus of having the guanidine act as a binding site for the terminal carboxylate on the peptide guest.

Many other examples of guanidines in receptors exist, for example the bis-guanidinium compound, **10**, has been shown to extract dicarboxylates, succinate, fumarate, folate and N-acetyl-aspartate, but not monocarboxylates from an aqueous solution into chloroform. This selectivity is thought to be due to the bonding of both guanidinium groups to the carboxylates in the guest molecules.

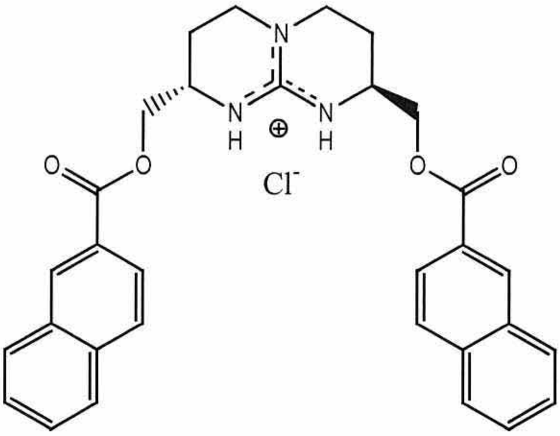


10

The receptor **10** has also shown some activity in the complexation of simple phosphates, such as cytidin-5'-phosphate, in methanol. The deprotected version of **10** with fluoride counter ions shows some binding to thymidine-5'-phosphate even in water, believed to be the first example of specific complexation of a mononucleotide to an artificial receptor in water.[16]

Chiral guanidinium containing receptor molecules have been shown to display some chiral recognition properties. The bicyclic guanidine **11**, displayed remarkable recognition and binding properties when extraction experiments were carried out on sodium *p*-nitrobenzoate in a water / chloroform two phase system. A chloroform solution of **11** quantitively extracted the sodium *p*-nitrobenzoate from the aqueous layer, whilst no traces of **11** were found in the aqueous layer despite the charged nature of the molecule.[17]

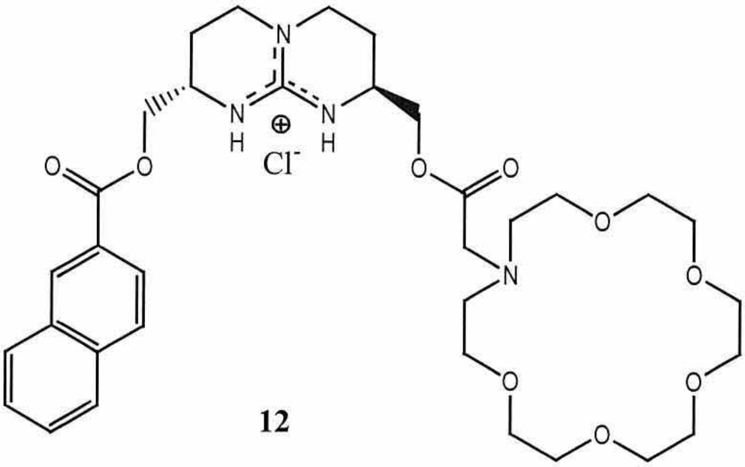
The exceptional binding of the host molecule **11** to the guest molecule is thought to be due not only to the guanidinium moiety interacting with the carboxylate group in the usual manner but also additional stability was obtained from π interactions between the benzene ring of the guest molecule and the naphthoyl rings of the host molecule, known as π stacking.



11

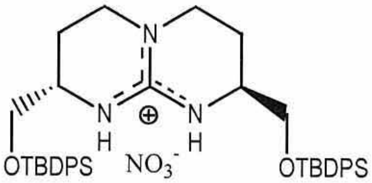
This host molecule also showed some chiral selectivity in its binding-extraction experiments with racemic aqueous solutions of N-acetyl and N-Boc derivatives of tryptophan. A chloroform solution of **11** resulted in moderate selectivity with diastereomeric excesses (de) of ca. 17 % in each case, for the L-tryptophan derivative. Free amino acids in zwitterionic form were not extracted from aqueous media.

Further work by the same research group has produced a similar receptor, **12**, which does extract amino acids from aqueous solution in their zwitterionic state. This receptor is able to bind to amino acids in their zwitterionic state because it has three binding sites for the different groups in the amino acids; the guanidinium group (for binding to carboxylates), the crown ether (for binding to the ammonium group) and the naphthalene ring system (interacts with any aromatic side chain in the amino acid). The best results for binding, not surprisingly, are for amino acids with aromatic side groups phenylalanine and tryphtophan. For the extraction of a mixture of 13 amino acids the relative ratios tend to show that π interaction between the host molecule and the guest are important. The highest relative ratios for the extraction are Phe 100 and Trp 46 with the next highest ratio being leucine 28; the ratios fall off sharply after these three examples and the majority lie around the 2-3 mark. Chiral recognition experiments carried out for Phe and Try show a high degree of selectivity with D isomers making up only 2 % and 0.5 % of the extracts from racemic solutions with the L isomer making up the remaining 98 % and 99.5 % respectively.[18]



12

Chiral bicyclic guanidines also have possible uses as chiral shift reagents as has been shown for **13** which displayed the separation of the N-acetyl protons in N-acetyl-D,L-alanine as well as several other chiral, α disubstituted acids, for example D,L-2-methylbutyric acid, D,L-lactic acid, D,L-2-bromobutyric acid and D,L-phenylalanine. These results were obtained without line broadening effects commonly seen with other chiral shift reagents, eg. chiral lanthanide reagents.[19]

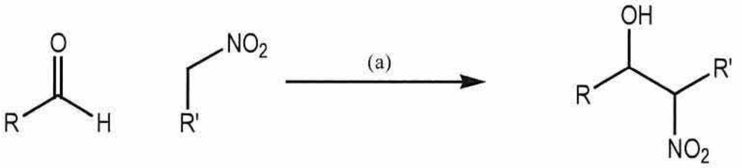


13

It can be seen that the guanidinium group has a huge potential in the field of molecular recognition and much research is going to be carried out on the versatile molecules which are possible to synthesise using this group. The next step from the binding of substrates using the guanidinium group is to further imitate nature and use the guanidinium group in catalysts.

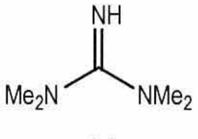
1.4 Guanidines in catalysis.

Since guanidines are strongly basic it should come as no surprise that they are widely used in base catalysed reactions. One reaction in which the use of guanidines as catalysts is prevalent is the nitroaldol (Henry) reaction. The nitroaldol reaction, Scheme 1, discovered by Henry in 1895 is one of the classic C-C bond forming reactions and much work has gone into designing new catalysts to carry out the reaction more efficiently and with some degree of enantioselectivity.[20]



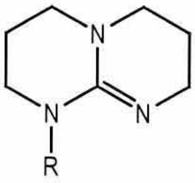
Scheme 1. The general nitroaldol reaction. a) base.

Initially, the catalysts of choice in promoting the nitroaldol reaction were alkoxides or hydroxides in alcoholic or aqueous solvent systems, however for some time 1,1,3,3-tetramethylguanidine (TMG), **14**, has been used to promote the nitroaldol reaction in solvents such as ether and THF.

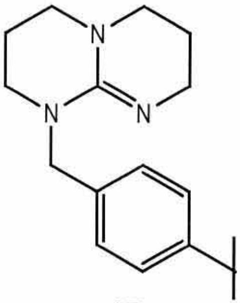


14

More recently the cyclic analogues of TMG, the bicyclic guanidines **15** and **16** as well as the polymer bound **17** have been prepared and shown to be useful additions to the growing number of achiral nonionic bases which are known to catalyse or promote the nitroaldol reaction. Work carried out on the activity of TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene **15,** in the nitroaldol reaction showed that the addition of nitroalkanes to various carbonyl compounds was promoted to a large extent, with the addition of nitromethane to benzaldehyde taking place at 0 °C over 5 minutes in 95 % yield.[21]

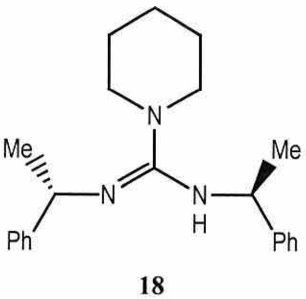


15, R=H
16, R=Me



17

A great deal of work has been carried out on the development of asymmetric catalysts for the nitroaldol reaction. Chiral guanidine containing compounds, **18** – **21**, have been prepared and their activity in the catalysis of the Henry reaction evaluated with moderate success, e.e of up to 54 % being observed (using **20**) for the catalysis of the reaction between nitromethane and isovaleraldehyde.[22]



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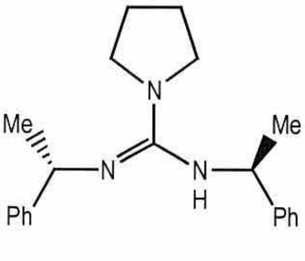

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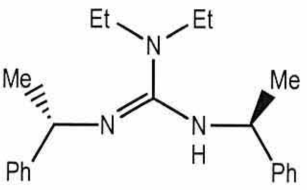

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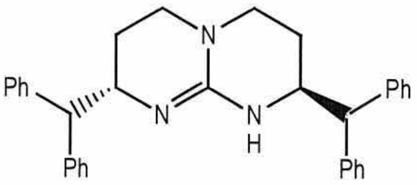


21

Undoubtedly the most successful type of catalyst for the asymmetric Henry reaction is the chiral binaphthol-lanthanide family of catalysts developed by Shibasaki and co-workers, a general example of which is shown in Figure 5. High chemical yields and ee values, + 97 % in some cases, have led to these ambifunctional cooperative catalysts becoming the most widely known catalysts for the asymmetric nitroaldol reaction.[19,23]

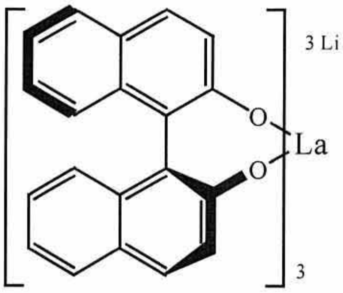
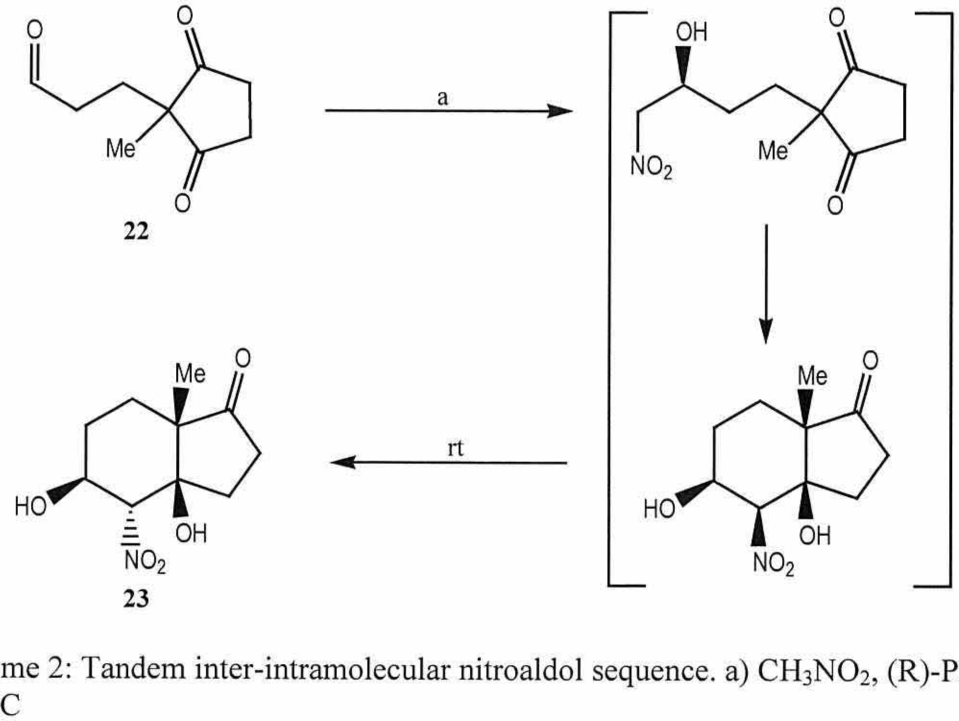


Figure 5: The S-BINOL complex with lanthanum.

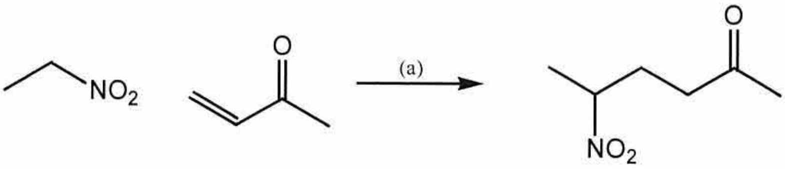
These complexes have been used in the synthesis of interesting compounds, including (s)-propanolol, a β-blocker.[24] A remarkable example of this methodology is the tandem inter-intramolecular catalytic asymmetric cyclisation sequence that sets up four new stereocentres in a ‘one-pot’ method, Scheme 2.[25]



Scheme 2: Tandem inter-intramolecular nitroaldol sequence. a) CH_3NO_2, (R)-PrLB, -40 °C

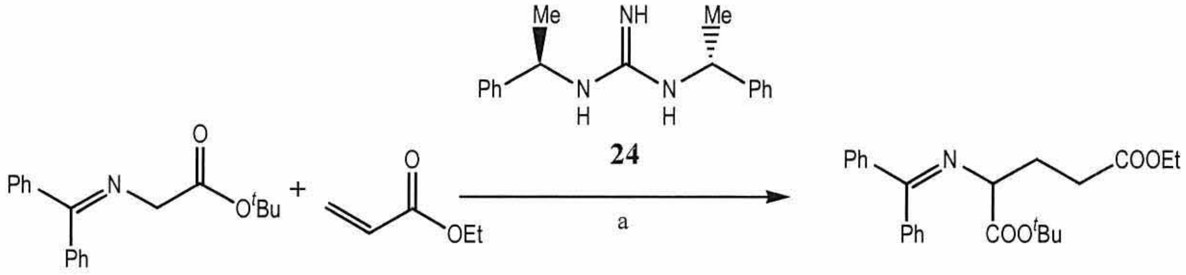
Treatment of **22** with nitromethane and 5 mol% of a praseodymium complex (PrLi$_3$tris((R)-binaphthoxide)) gave **23** in 65 % ee crude (79 % ee and 41 % yield after recrystallisation). It is proposed that the Pr centre acts as a Lewis acid and activates the aldehyde. The Li-naphthoxide portion then functions as a Brønsted base and deprotonates the nitromethane. Coordination of the aldehyde in the presence of a chiral template and delivery of the nucleophile by the bridging lithium complex results in intramolecularisation of the reaction and hence good enantioselectivity. Transfer of a proton from the ligand to the new alkoxide regenerates the catalyst. Selective attack on the diketone moiety is thought to be controlled solely by the configuration at the new hydroxyl functionality.

The previously mentioned guanidine TBD, **15**, also catalyses the Michael reaction efficiently, for the reaction between nitroethane and methyl vinyl ketone proceeds in 75 % yield in only 5 minutes, see Scheme 3.[26]



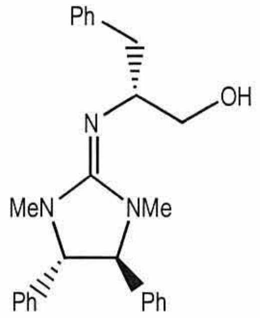
Scheme 3. Michael addition of nitroethane to methyl vinyl ketone using TBD as catalyst. a) 10 Mol % TBD in toluene.

Again, as for the Henry reaction, chiral guanidines have been prepared with a view to asymmetric catalysis of the Michael reaction. The chiral bicyclic guanidine **21** synthesised by Davis, showed catalytic activity in the Michael addition of some nitroalkanes but showed only low enantioselectivity (approx. 10 % ee). Higher ee values, up to 30.4 % ee, were observed in the case of the Michael addition of glycine derivatives to acrylic esters using **24**, as reported by Ma and co-workers, Scheme 4.[27]


Me
NH
Me
Ph
N
H
N
H
Ph
24
Ph
N
O
O^{t}Bu
+
O
OEt
Ph
a
Ph
N
COOEt
Ph
COO^{t}Bu

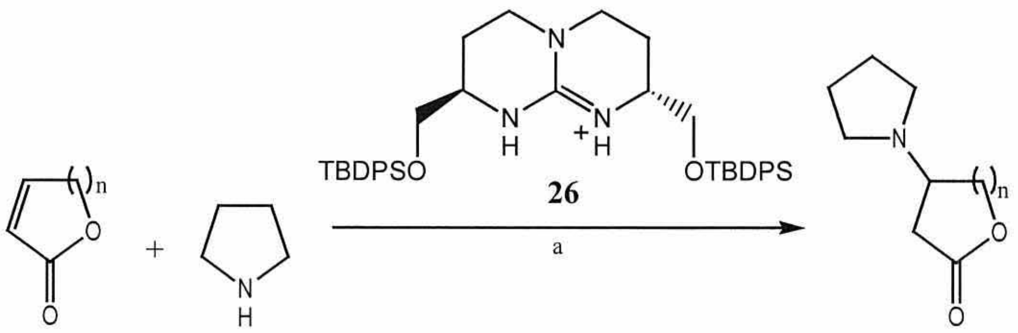
Scheme 4. a) **24** 20 mol%, THF, -78 °C to -10 °C over 48 h. 30.4 % ee.

For the same reaction Ishikawa and co-workers achieved more impressive ee values using a range of chiral guanidine bases. For example using chiral base **25** ee's of up to 97 % were observed.[28]


Ph
OH
N
MeN
NMe
Ph
Ph

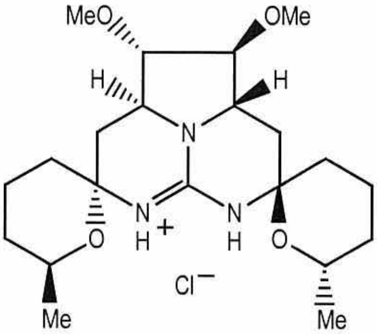
25

In addition Mendoza has used the bicyclic guanidine **26,** and others, to stabilise the transition state in the addition of nucleophiles to α,β-unsaturated lactones; a rate increase equivalent to a factor of 10 was found for the best case, but no enantioselectivity was observed, Scheme 5.[29,30]


N
N
H
+
N
H
TBDPSO
OTBDPS
26
n
O
O
+
N
H
a
N
n
O
O

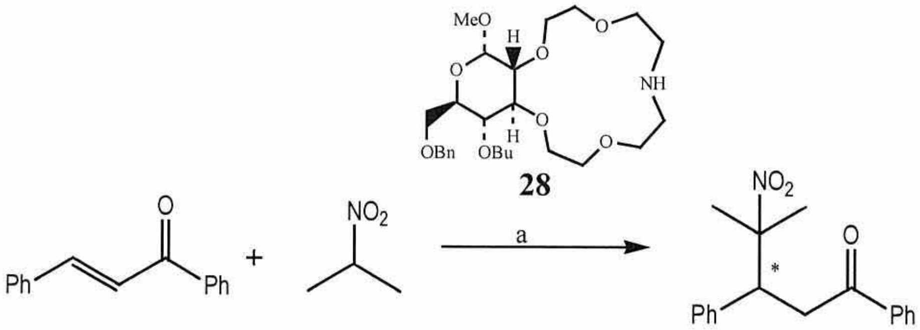
Scheme 5. a) **26** 10 mol%, $CDCl_3$, 27 °C.

This reaction was also catalysed by a series of bases developed by Nagasawa and co-workers designed on a rationale from our own work (see chapter 1.5) the most efficient base being **27** resulting in an increase in relative rate of 8.3, again with no enantioselectivity.[31]


MeO
OMe
H
H
N
N
H
N
H
O
O
Cl⁻
Me
Me

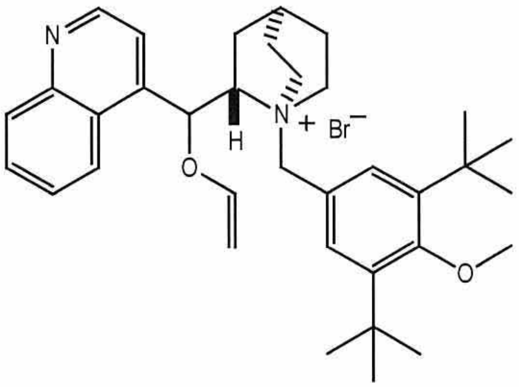
27

Other methods of achieving asymmetric nitro-Michael additions include a series of chiral crown ethers developed by Tőke and co-workers.[32] Best results were obtained when using crown ether **28** to carry out the Michael addition of 2-nitropropane to chalcone, Scheme 6, with 82 % yield and a 90 % ee being observed.


MeO
H
O
O
NH
O
O
O
O
H
OBn
OBu
28
O
NO2
Ph
Ph
+
a
NO2
O
*
Ph
Ph

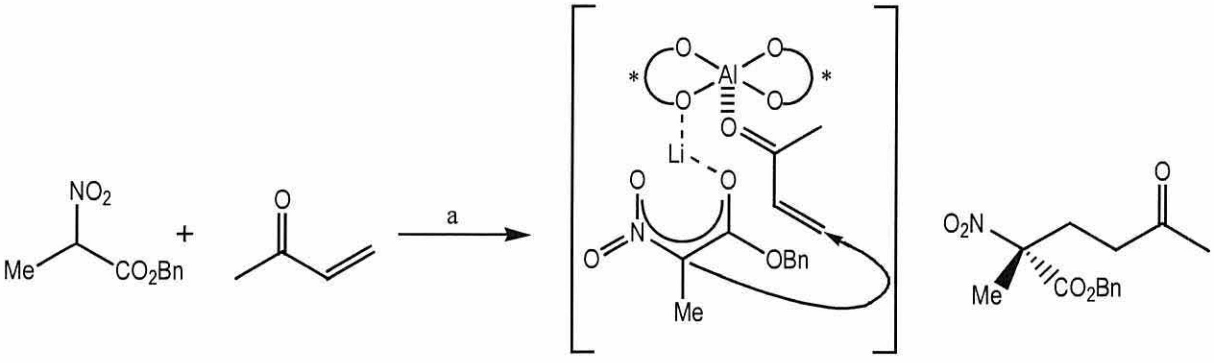
Scheme 6. a) NaOBu^t 30 mol %, **28** 7 mol %, toluene, rt, 24 h.

The enantioselective Michael reaction of nitroalkanes with chalcones has also been catalysed by a series of chiral quaternary ammonium salts developed by Kim and co-workers.[33] Most efficient was salt **29** which resulted in high yields, in the range of 94%, and ee values, in the range of 70%.



29

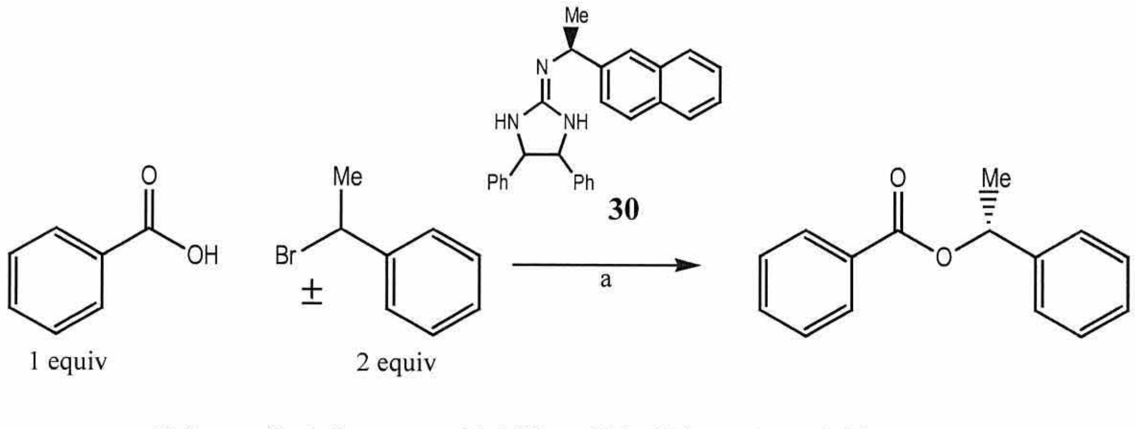
The lanthanide-binaphthol family of catalysts have been shown to be excellent catalysts for the asymmetric Michael reaction. For example it has been shown that α-nitroesters undergo asymmetric nitro-Michael addition to α,β-unsaturated ketones when treated with aluminium-lithium bis(binaphthol) (ALB), resulting in a yield of 81% and an ee of 80%.[34] The 1,4-addition reaction is proposed to proceed *via* double coordination of the Michael donor as well as coordination of the Michael acceptor to the heterobimetallic catalyst in accordance with the mechanism proposed by Shibasaki and co-workers, Scheme 7. The lithium naphthoxide moiety can function as a Brønsted base and the aluminium alkoxide functions as a Lewis acid.



Scheme 7. a) (R)-Aluminium-lithium bis(binaphthoxide) 5 mol%, THF, -30 °C, 96 h.

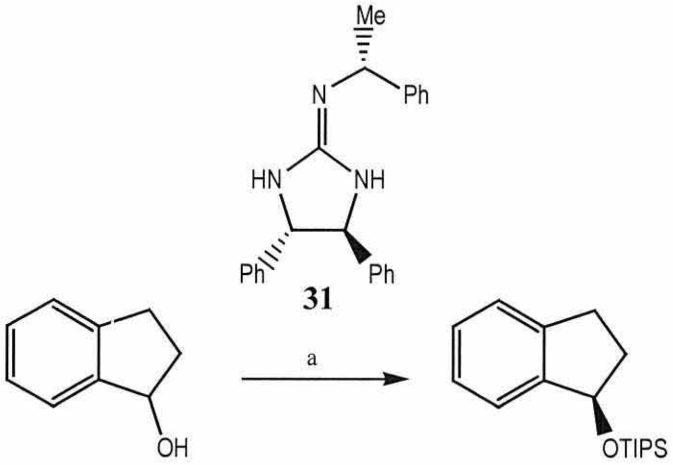
The reaction of the α-nitroester with the ‘AlLiBINOL’ complex gives the corresponding lithium enolate . This enolate then reacts with the enone, which is pre-coordinated to the aluminium Lewis acid centre. The resulting alkoxide reacts with an acidic hydrogen of a Michael donor to generate the desired Michael adduct and the ‘AlLiBINOL’ complex is regenerated to react in the following catalytic cycle.

Continuing work on the use of guanidines in organic synthesis has led to the development of several methods that utilise chiral guanidine bases in catalysis. Work carried out by Ishikawa and co-workers has resulted in asymmetric alkylative esterification catalysed by guanidine **30** with good yields, 74 %, although only modest ee’s, in the region of 15 %, were observed, Scheme 8.[35]



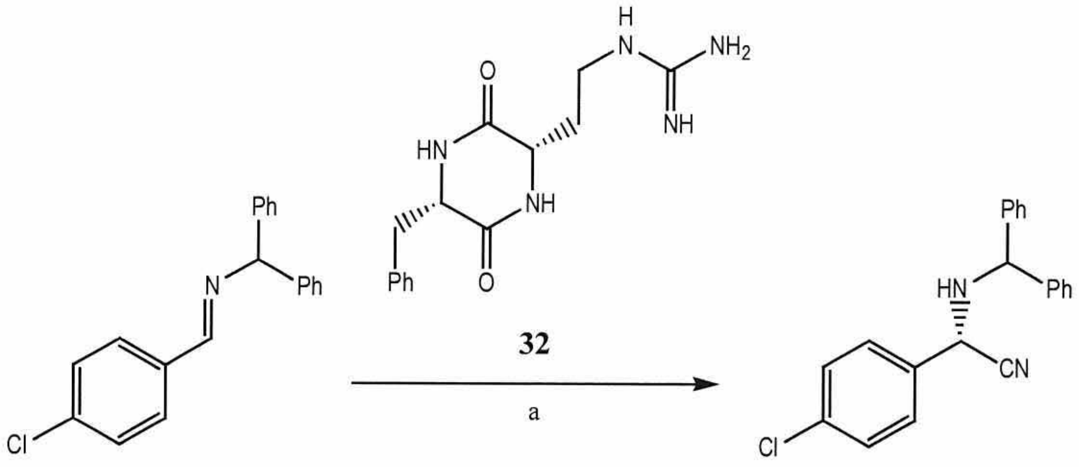
Scheme 8. a) Benzene, **30** 100 mol%, 48 hr, 74 % yield, 15 % e.e.

Ishikawa and co-workers also developed an asymmetric silylation of secondary alcohols catalysed by a series of chiral guanidines with ee's of up to 70 % being reported.[36] The higher ee values were reported for the reaction of TIPSCl with an excess of indan-1-ol using guanidine **31**, Scheme 9, while lower values were reported for reactions involving the less bulky TBSCl reagent.



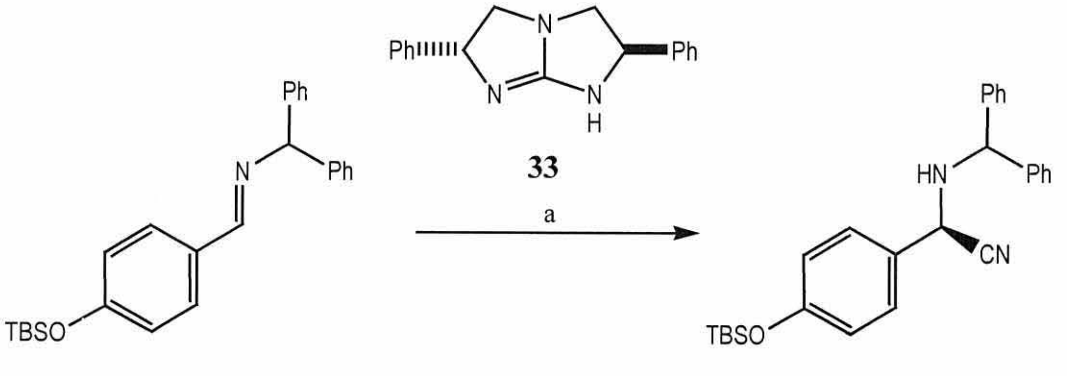
Scheme 9. Asymmetric silylation of indan-1-ol. a) TIPSCl, DCM, **31**, rt, 6 days.

A further example of an asymmetric reaction catalysed by a chiral guanidine is the enantioselective Strecker synthesis developed by Lipton and co-workers.[37] Guanidine **32** catalysed the addition of HCN to a variety of N-benzylhydrylimines, to yield the corresponding amino nitriles in excellent yield and ee, >99% ee, Scheme 10.


Ph
N
Ph
Cl
H
N
NH2
NH
O
HN
NH
Ph
O
32
a
Ph
HN
Ph
CN
Cl

Scheme 10. **29** 10 mol %, HCN, toluene, - 40 °C, 20 h.

Work has also been carried out by Corey and co-workers, with guanidine **33** catalysing the addition of HCN to a selection of N-benzhydrylimines with excellent yield , up to 96 %, and high ee, in the region of 88 %, Scheme 11.[38]


Ph
N
Ph
TBSO
Ph
N
Ph
N
N
H
33
a
Ph
HN
Ph
CN
TBSO

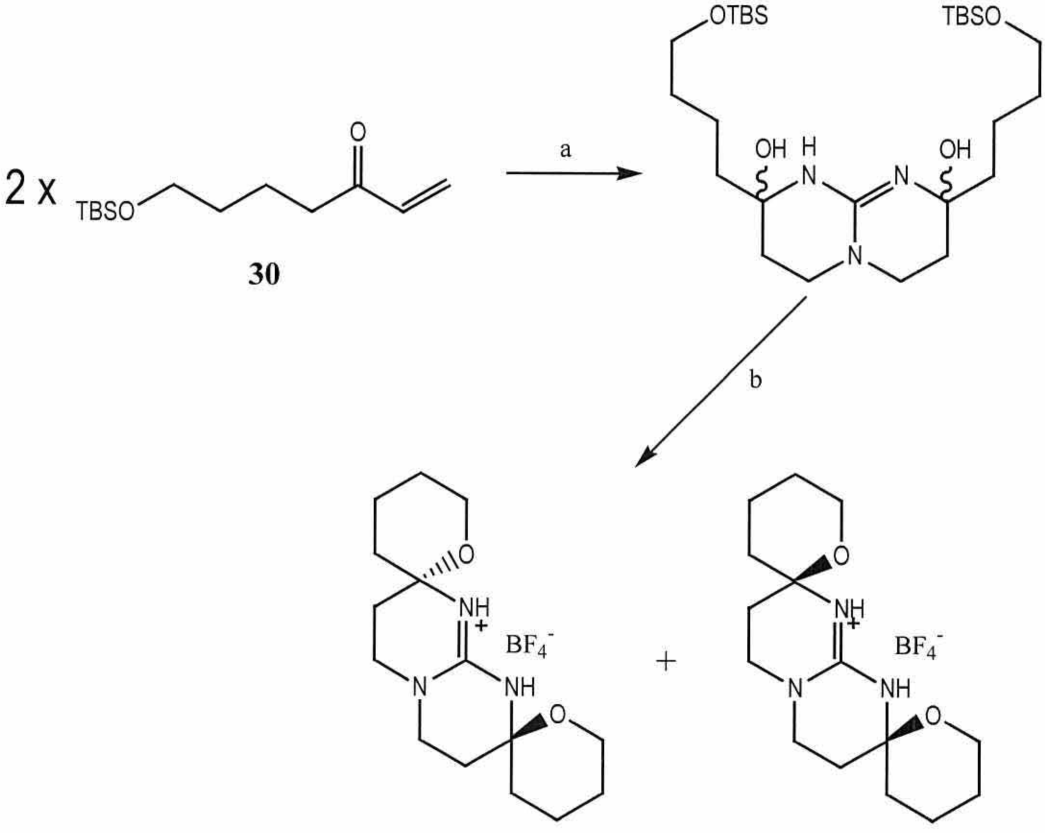
Scheme 11. a) **33** 10 mol%, HCN (2 equiv), toluene, -40 °C, 20 hr.

1.5 Conclusion.

It can be seen that guanidines show promise as asymmetric catalysts but further work needs to be carried out in order to optimise their use, in order to achieve higher ee values, and to develop new catalytic systems.

1.6 Aims.

During the course of work carried out in our research group directed towards the synthesis of the marine natural products ptilomycalin A the conjugate addition of guanidine to the α,β-unsaturated ketone **30** was studied, Scheme 12. After acid catalysed deprotection and subsequent cyclisation the isomeric guanidinium salts **31** and **32** were formed as a 1:1 mixture.[39]



30

31 **32**

Scheme 12. a) guanidine, DMF, 0°C to rt over 12 h. b) MeOH, HCl, 0 °C; rt 3 h. c) saturated $NaBF_4$, 17 h.

This distribution was found to be an equilibrium mixture, since isolation of either isomer by recrystallisation and treatment with a catalytic amount of acid resulted in the regeneration of a 1:1 mixture. On inspection of **31** it was decided that if it were available as a single enantiomer and the propensity for equilibrium was blocked, the system may represent a new type of C_2 symmetric guanidine base.

It was envisioned that modification of the base by the inclusion of groups onto the pyran rings would lead to a stable conformation, with the groups acting as conformational locks for the entire system. Thus the preferred configuration will be as depicted in A/A' in which both R groups are equatorial. The alternate isomers in which one (i.e. B/B') or two R groups are situated in an axial fashion will be disfavoured, Figure 6.

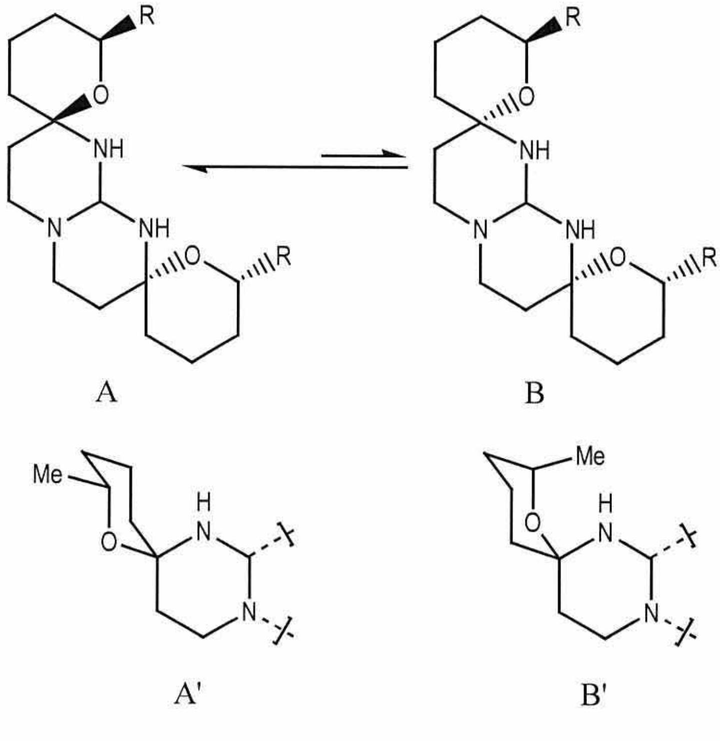
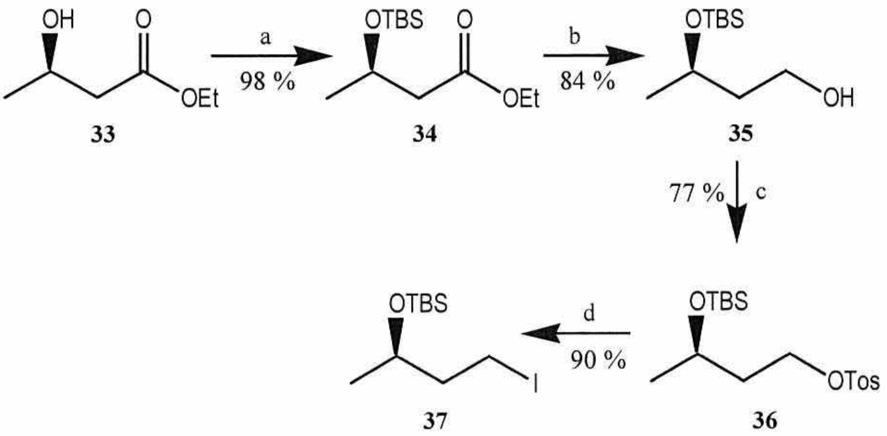


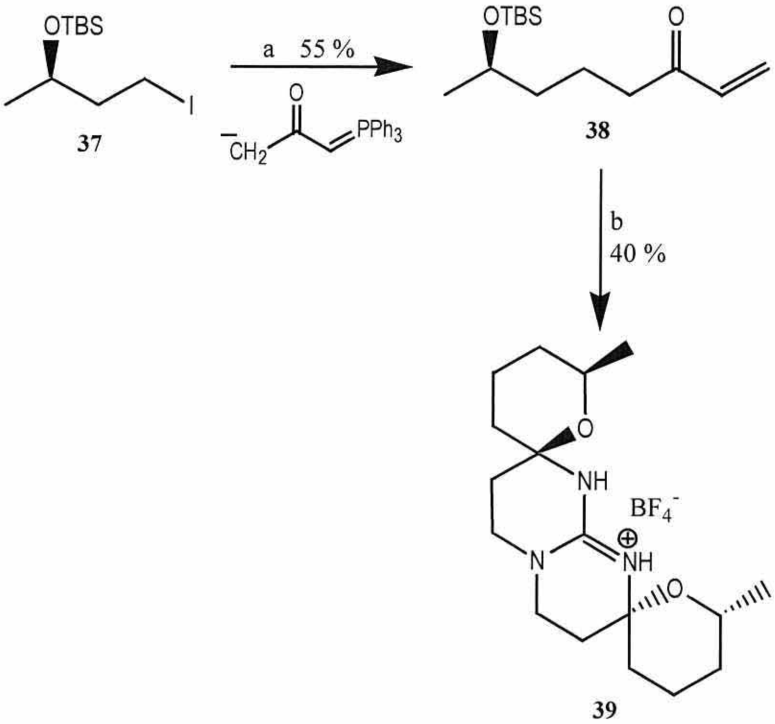
Figure 6. Proposed structure for the conformationally locked C_2 symmetric guanidine base. R = alkyl.

The work on developing a conformationally locked guanidine base resulted in the synthesis of **39**.[40] The base was synthesised from a commercially available starting material ethyl (R)-(-)-3-hydroxybutyrate **33**, which was protected with the TBDMS protecting group to give **34** and was reduced with DIBAL to give the monoprotected diol **35**. This diol was then converted to the tosylate **36** using tosyl chloride in pyridine. Treatment with NaI in refluxing acetone gave the iodide **37** in high yield, see Scheme 13.



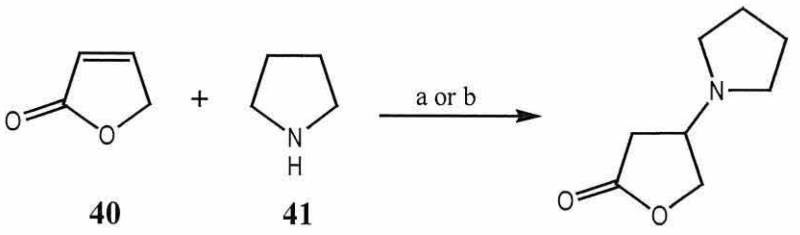
Scheme 13. a) imidazole, TBSCl, dry DMF; b) DIBAL, dry hexane, -78 °C; c) tosyl chloride, dry pyridine, 24h; d) NaI, acetone, reflux, 4 h.

All of the above steps gave reasonably high yields up to and including the formation of the iodide **37**. The next step involved the alkylation of the iodide with deprotonated acetylmethylene triphenylphosphorane followed by Wittig reaction with formaldehyde to give the unsaturated ketone **38**. The final step in the scheme was reaction of the unsaturated ketone with guanidine which undergoes double Michael reaction to give the base followed by treatment with methanolic HCl, and a saturated $NaBF_4$ solution to give the base **39**, Scheme 14, these last two steps proceeded in modest yields in the initial synthesis.



Scheme 14. a) (i) acetylmethylene triphenylphosphorane, dry THF, BuLi, -78 °C to ambient temp over 17 h; (ii) formaldehyde, DCM; b) (i) guanidine, dry DMF, 24 h, (ii) HCl/MeOH, 0 °C, 3 h (iii) saturated $NaBF_4$, 17h.

In this preliminary work the catalytic properties of the base were investigated by using base **39** to catalyse the addition of nucleophiles to unsaturated lactones under the conditions described by Mendoza *et al.*[29] Thus, equimolar amounts of pyrrolidine **40** and 2(5H)-furanone **41** in $CDCl_3$ were combined in the presence of 0.1 mol. equiv. of **39** (as either the BF_4 of BPh_4 salt), Scheme 15, and the reaction monitored by NMR.



Scheme 15. a) (i) **39**.BF_4 10 mol %, b) (i) **39**.BPh_4 10 mol %; rt, $CDCl_3$

The results show that **39** is an efficient catalyst for the addition of nucleophiles to unsaturated lactones, with the BPh_4 salt achieving a 16.5 fold rate increase and the BF_4 salt giving a 4.3 fold increase, comparing favourably with Mendoza's catalyst which achieved a 10 fold rate increase. Although the increased rate of reaction was a welcome result, no enantioselectivity was induced by the catalyst, with no ee being observed in the product.[40, 41]

Work carried out by Nagasawa and co-workers led to the synthesis of a series of pentacyclic guanidine bases, Figure 7, based on a rationale from our own work.[31, 41] These bases were similarly tested for their ability to catalyse the hetero-Michael reaction of pyrrolidine with 5H-furan-2-one, see Table 1.

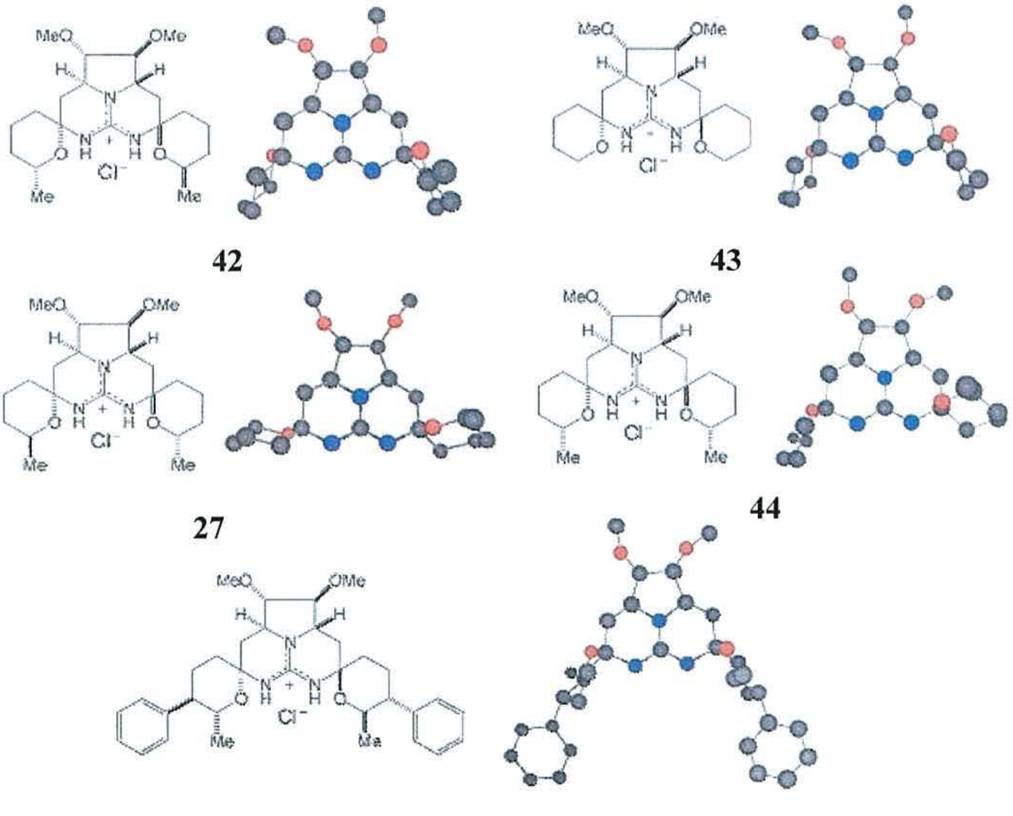

42 **43** **27** **44** **45**

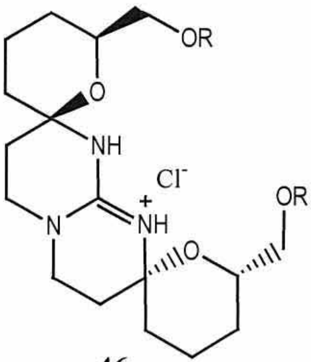
Figure 7. Guanidine bases synthesised by Nagasawa and co-workers.

base	$t_{1/2}$	rel. rate increase
None	190	---
42	82	2.3
43	78	2.4
27	23	8.3
44	57	3.4
45	30	6.3

Table 1. Results for the catalysis of the hetero-Michael reaction of pyrrolidine with 5H-furan-2-one with a series of guanidine bases.

Using guanidines **42**, **43** and **44** as catalysts resulted in relative rate increases of 2.3, 2.4 and 3.4 respectively over the uncatalysed reaction whereas guanidine **27** gave a relative rate increase of 8.3. This difference can be explained by the fact that in bases **42**, **43** and **44** the cavity around the guanidine moiety is more restricted than in **27** causing the bases to be less active in the coordination, and subsequent activation, of the lactone. Base **45** results in a relative rate increase of 6.3, showing that although it is similar to base **42** and **43** in terms of cavity shape and size it is more active as a catalyst. This is thought to be due to the presence of the phenyl substituents at C3 on the spiro rings, resulting in π-π interactions between the phenyl groups of **45** and the unsaturated lactone leading to more efficient coordination of the lactone to the guanidine. Thus it can be seen that the reaction rate may be controlled by a combination of varying the cavity size around the guanidine core and substituents on the spiro rings of the base.

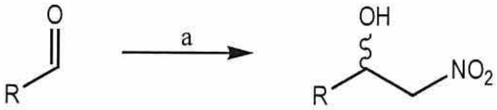
The initial aim of my work was to confirm and, wherever possible, improve on the synthetic strategy leading to the formation of **39,** especially the final two steps leading to the formation of the base. As well as this work to improve on the synthesis of **39,** a further aim of my work was to develop new synthetic methodologies leading to the synthesis of a range novel chiral guanidine bases. Of particular interest was the synthesis of bases **46** which as well as having probable catalytic properties may have uses as receptor molecules.



46

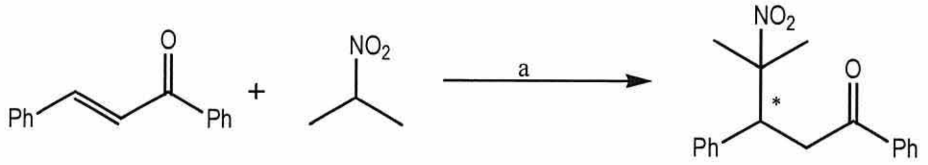
R = Alkyl, Silyl, H

A further aim of my work was to investigate the application of the guanidine bases in catalysis. It was known that guanidines are widely used in catalysis, in particular the catalysis of the nitroaldol reaction and the catalysis of the nitro-Michael reaction. It was decided that the conditions used by Nájera *et al* for the nitroaldol reaction using their bicyclic guanidine base, Scheme 16, should be used to study the catalytic properties of the bases developed so that some comparison could be made of the relative efficiencies of the bases.



Scheme 11. a) nitromethane, catalyst 10 mole %. R = alkyl, aryl.

It was decided that the use of the guanidine bases developed would also be tested for their ability to catalyse the nitro-Michael reaction, specifically the addition of 2-nitropropane to chalcone as investigated by Tőke *et al*, Scheme 17.[32]



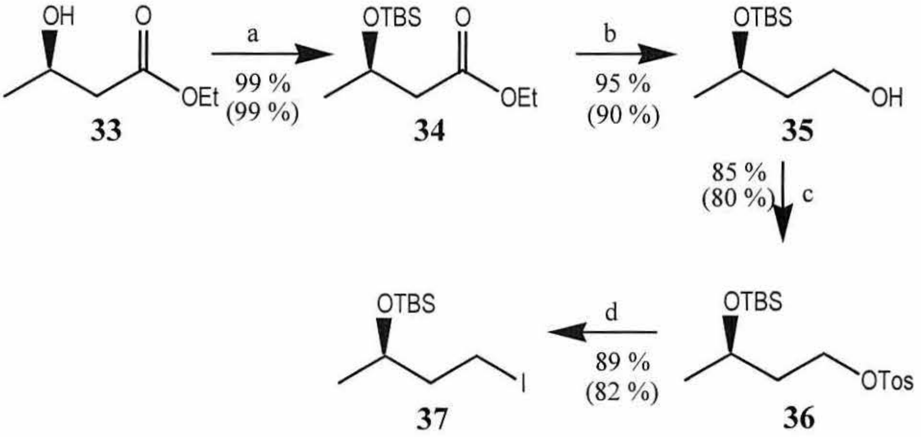
Scheme 17. a) guanidine base 10 mol %, rt, 24 hr.

Chapter 2

Discussion

2.1 Synthesis of Guanidine Base 39.

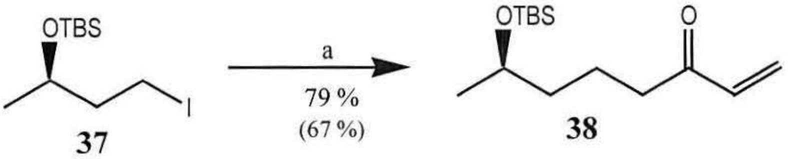
The initial objective of my work was to optimise the preparation of guanidine base **39**, initially synthesised by a previous group member.[40] The initial steps of the scheme proceeded well with some improvement in yields being obtained for all steps leading to the preparation of **37**, Scheme 18. The initial preparation of **34** proceeded in 84 % yield, optimisation lead to an improved yield of 99 % (99 % average over 4 repetitions), yields for the reduction of ester **34** to the alcohol **35** initially proceeded in 70 % yield, optimisation lead to an improved yield of 95 % (90 % average over 5 repetitions) being obtained. Optimisation of the tosylation step to give **36** lead to an improved yield of 85 % (80 % average over 5 repetitions) which compares favourably with the initial yield of 67 % obtained. For the conversion of the tosylate **36** to the iodide **37** the initial yield was 80 %, during optimisation of the reaction the yield was increased to 89 % (82 % average over 5 repetitions).



Scheme 18. a) imidazole, dry DMF, 0 °C, TBSCl, 3 h; b) dry hexane, -78 °C, DIBAL; c) dry pyridine, 0 °C, TosylCl, 16 h; d) acetone, NaI, reflux, 4 h. Average yields over the 5 highest yielding repetitions are shown in brackets.

The preparation of the α,β-unsaturated ketone **38** gave some problems. During the initial synthesis yields of 55 % were obtained, initial attempts at optimisation of the reaction gave yields in the region of 4-10 %, which obviously was unacceptable.

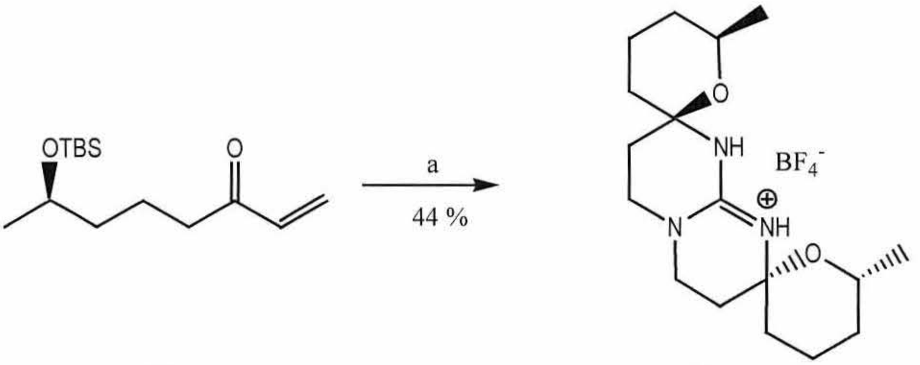
For subsequent reactions only THF which gave a high value for the molarity of the BuLi, >2M, when a titration was carried out against diphenylacetic acid would be used. Another possibility was that since the anion formed was strongly coloured, a high percentage of the phosphorane might not be in the anion form. Since the initial preparation was to leave the anion to form for 30 min at -78 °C, it was decided that leaving the anion to form at -60 °C for 1h might have increased the proportion of the phosphorane deprotonated. The next reaction, carried out using the modified conditions, gave a yield of 42 %, a much more acceptable yield. Taking the modifications forward and allowing the reaction to warm to approx -55 °C for 1h, as well as warming the reaction slowly after the addition of the iodide **37** gave a yield of 79 %, Scheme 19, with the average yield over the five best repetitions being 67 %.



Scheme 19. a) (i) BuLi, acetylmethylene triphenylphosphorane, THF, -70 °C to -55 °C 1h, **37**, to ambient temp, 17 h; (ii) formaldehyde, DCM, 17 h.

The slower warming of the reaction was the most noticeable change in procedure in the last reaction and this may decrease the amount of the anion which decomposes before reacting with the iodide.

The final step in the scheme to form the base itself also presented us with some problems initially with poor yields being achieved 8-20 % initially. The poor initial yields might have been due to a degradation in the quality of the guanidine used as well as the possibility that the α,β-unsaturated ketone was beginning to decompose. The synthesis of fresh guanidine raised the yield obtained to 37 % when using freshly prepared α,β-unsaturated ketone. The highest yielding reaction so far, using freshly prepared, α,β-unsaturated ketone, and taking great care to keep the guanidine used under an argon atmosphere, gave a yield of 44 %, after purification by column chromatography, Scheme 20, a slight improvement over the 40 % yield recorded in the initial synthesis.

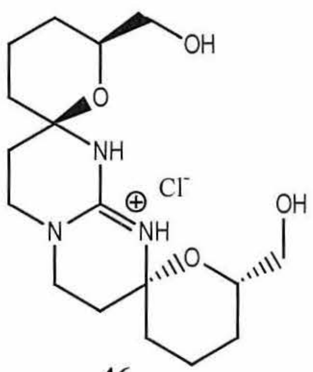


38 **39**

Scheme 20. a) (i) guanidine, dry DMF, 0 °C 15 min, stir 16 h; (ii) 0 °C, methanolic HCl, 3 h; (iii) sat. $NaBF_4$ solution, 16 h.

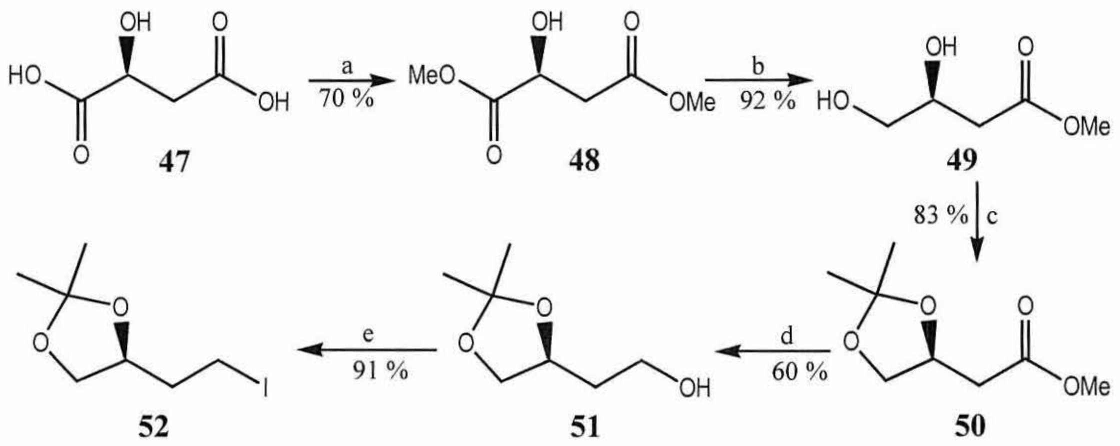
2.2 Synthesis of Guanidine Base 46.

As well as optimising the synthesis of base **39**, we were also investigating the synthesis of other guanidine bases. One major goal was the synthesis of a base with pendent hydroxyl groups, **46**, which could be used to attach a variety of other substituents.


OH
O
NH
Cl⁻
⊕
OH
N
NH
O

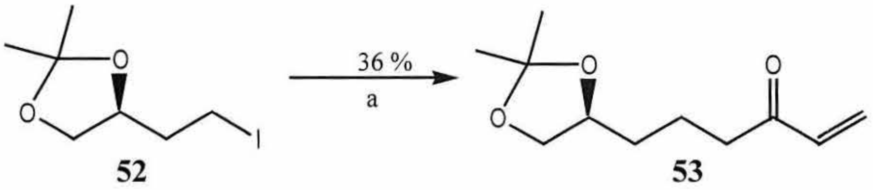
46

It was decided that the synthesis of base **46** could be achieved from iodide **52** which had been prepared by a previous group member for use in another synthetic project, Scheme 21.[42]


OH
O
HO
OH
O
47
a
70 %
OH
O
MeO
OMe
O
48
b
92 %
OH
O
HO
OMe
49
83 %
c
O
O
O
OMe
50
d
60 %
O
O
OH
51
e
91 %
O
O
I
52

Scheme 21. a) (S)-malic acid, MeOH, AcCl, 24 h; b) Borane dimethylsulphide complex, dry THF, $NaBH_4$; c) 2-methoxypropene, dry DCM, Tosyl-OH; d) $LiAlH_4$, dry ether; e) Triphenylphosphine, imidazole, ether/acetonitrile 3/1, I_2, 1 h, 0 °C.

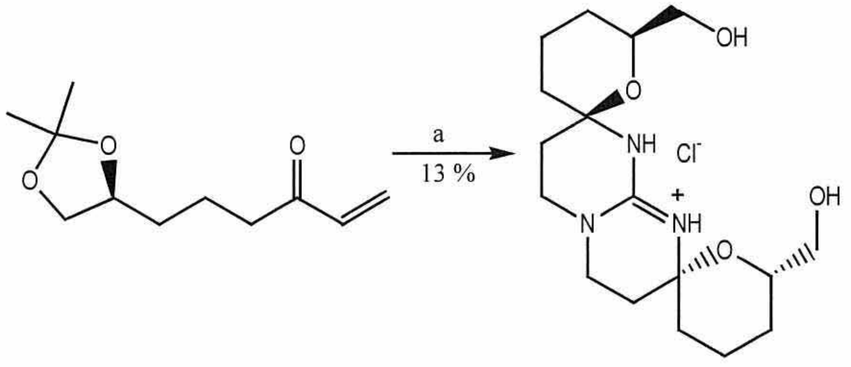
Initial work with an existing sample of the iodide **52** showed that the α,β-unsaturated ketone **53** could be prepared using the modified conditions for the alkylation reaction developed during the work carried out on base **39** giving an initial yield of 36 %, Scheme 22.



Scheme 22. a) i) acetylmethylene triphenylphosphorane, BuLi, dry THF - 78 °C to ambient 17 hr ii) formaldehyde, DCM.

Following this encouraging result, further iodide, **52**, was prepared from the starting material, S-malic acid, **47**. During the preparation of **52**, the key steps were optimised, the yield for the selective reduction of **48** to **49** was increased from 60 % in the original work to 92 % (83 % average over 4 repetitions), and the yield for the transformation of alcohol **51** to the iodide **52** was optimised to give a yield of 91 % (82 % average over 4 repetitions) from the previously recorded 73 % yield. Synthesis of the α,β-unsaturated ketone, **53**, was improved from the initial 36 % yield to 72 % (65 % average over 4 repetitions).

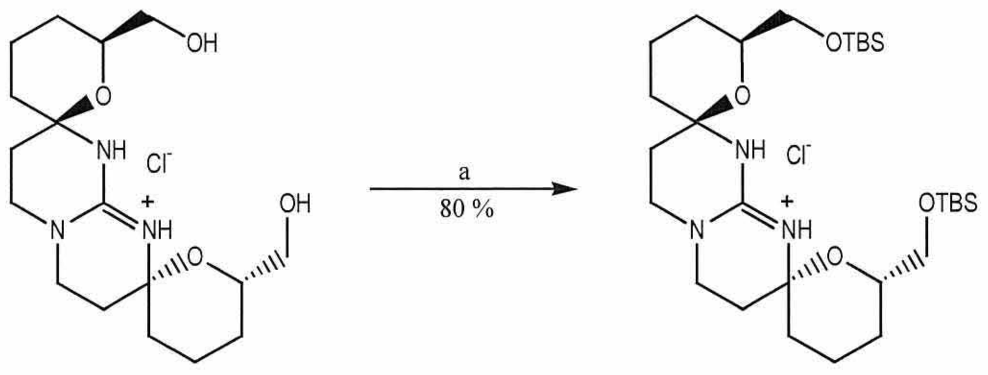
Reaction of the ketone with free guanidine using the same basic procedure as for base **39** gave disappointing results since none of the expected product was isolated. This was thought to be due to the probable high water solubility of the molecule, since the workup involved washing of the reaction mixture with water and saturated LiBr solution. Back extraction of the aqueous phases combined with 'salting-out' resulted in the isolation of base **46** as the hydrochloride salt in low yield. Due to the water solubility of the product, the workup was modified so that no aqueous washings were carried out. The modified workup involved *in vacuo* removal of the solvent (DMF) and purification of the reaction by column chromatography, Scheme 23. This resulted in the isolation of the hydrochloride salt **46** in low yield, 13%, as a very hydroscopic solid.



53 **46**

Scheme 23. a) i) guanidine, dry DMF, 0 °C, 24 h ii) MeOH, AcCl, 3h.

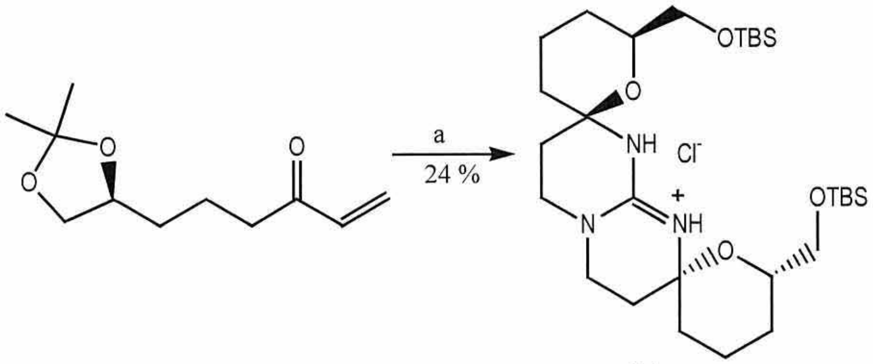
The hygroscopic character of **46** was thought to be due to the presence of the two hydroxy groups together with the guanidinium chloride. To decrease the tendency for the compound to take up water it was decided to protect the hydroxy functionality *in situ* as the silyl ether using *tert*-butyldimethylchlorosilane, Scheme 24, to form the protected base, **54**, in 80 % yield.



46 **54**

Scheme 24. a) imidazole, TBSCl, DMF, 24 hr.

Silyl ether **54** displayed no tendency to absorb water from the atmosphere and it was therefore decided to incorporate this protection step into the reaction of α,β-unsaturated ketone **53** with guanidine and thus attempt to form the protected base **54** in a one-pot reaction, Scheme 25.

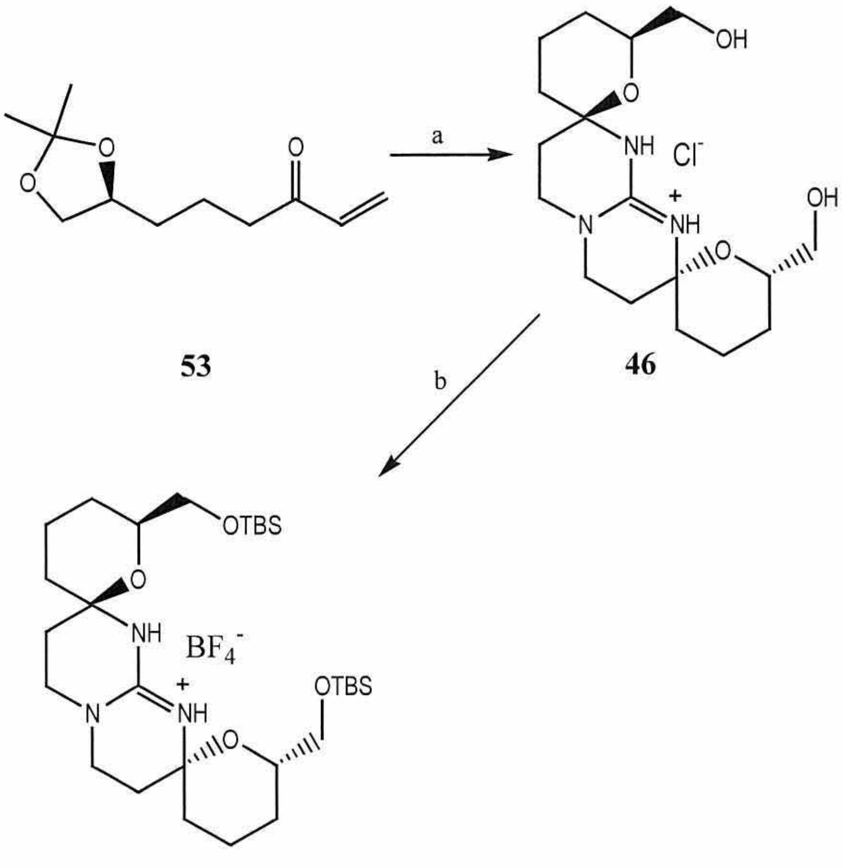


53 **54**

Scheme 25. a) i) guanidine, dry DMF, 24 h, ii) MeOH, AcCl, 3 h, iii) imidazole, TBSCl, DMF, 24 h.

Using this modified procedure the reaction of **53** with guanidine was carried out as normal followed by the removal of the solvent (DMF / MeOH) to yield a solid which was then re-dissolved in dry DMF for the protection. Base **54** was thus isolated, in 24% overall yield. This was converted to the corresponding BF_4^- salt by stirring with a saturated solution of $NaBF_4$. The resultant base, **55**, could be recrystalised from ether however, disappointingly the crystals obtained were not suitable for x-ray structure determination.

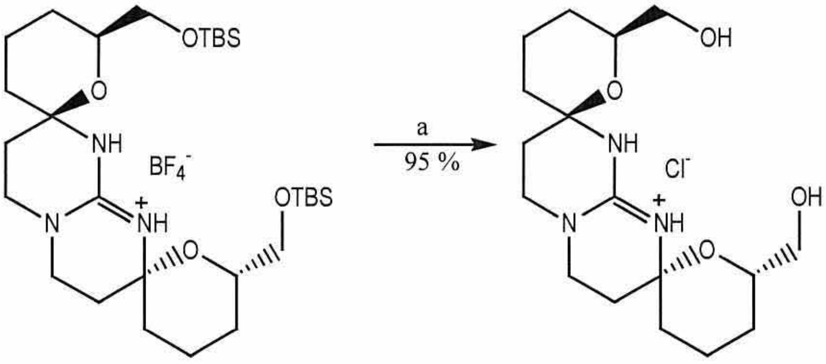
Due to the disappointingly low yield of the base obtained, and the fact that the yield was highly variable, it was decided that we would repeat the original procedure where the base **46** was formed, purified by column chromatography, protected with TBSCl and then counterion exchanged to give **55**, Scheme 26.



Scheme 26. a) i) guanidine, dry DMF, 24 h, ii) MeOH, AcCl, 3 h; purify by column chromatography. b) i) imidazole, TBSCl, dry DMF, ii) saturated $NaBF_4$ sol, 29 % overall.

The yields using this method were consistent but still disappointingly low with the best yield being 29% overall from the α,β-unsaturated ketone. The low yield may be due to the use of the dioxolane protecting group for the 1,2-diol, whereas in the synthesis of base **39** the substrate contained only one hydroxy group, protected by a silyl ether.

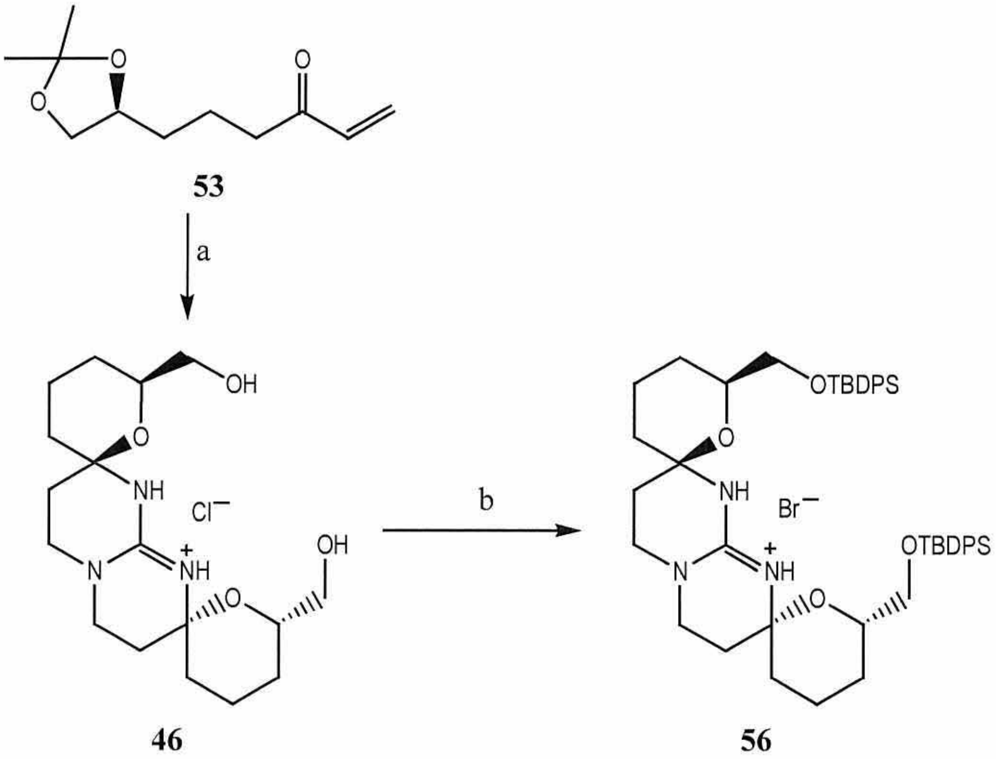
It was envisaged that the base **55** would be used for the synthesis of macrocyclic bases containing two of the guanidine bases linked by a bis-acid chloride, for example adipoyl chloride. In order to carry out this reaction it was necessary that the base be converted back to the dihydroxy version, **46,** by removal of the silyl protecting groups. In anticipation of this, the deprotection of the base **55** was carried out using methanolic HCl, prepared from dry MeOH and AcCl, and it was found that base **46** was easily obtained in a pure form in 95 % yield, Scheme 27.



55 **46**

Scheme 27. a) MeOH, AcCl, 24 h, rt, 95 %.

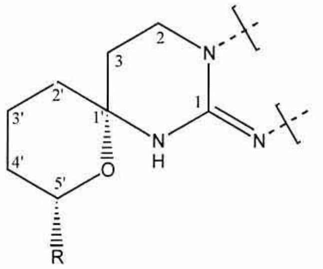
Modification of the protecting group results in moderately improved yields. Reaction of the α,β-unsaturated ketone **53** with guanidine to yield base **46**, which was then purified by column chromatography and protected with TBDPSCl, gave base **56**, Scheme 28, in a 36 % overall yield.


53
a
46
b
56
OH
Cl⁻
Br⁻
OTBDPS

Scheme 28. a) i) guanidine, dry DMF, 24 h, ii) MeOH, AcBr, 3 h; b) imidazole, TBSCl, dry DMF, 36% overall.

2.3 Correlation of NMR data for the synthetic bases.

Comparison of the NMR data for the synthetic bases **39**, **46**, **55** and **56** shows that a high degree of correlation exists between the ^{13}C NMR spectra of the four bases, leading to the conclusion that the bases are all structurally similar. A comparison of ^{13}C data for the bases is shown in Table 2.



39 R = Me
46 R = CH_2OH
55 R = $CH_2OTBDPS$
56 R = CH_2OTBS

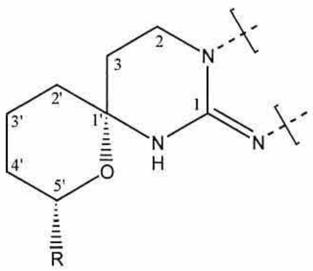
R =	-Me	$-CH_2OTBS$	$-CH_2OTBDPS$	$-CH_2OH$[a]
	39	**55**	**56**	**46**
1	148.46	148.58	148.45	149.98
2	42.86	42.50	42.84	43.51
3	33.64[b]	33.65[b]	33.65[b]	34.75[b]
1'	78.94	78.56	78.84	80.02
2'	33.12[b]	32.61[b]	32.93[b]	33.62[b]
3'	17.55	17.90	17.21	18.74
4'	32.15[b]	26.42[b]	26.17[b]	27.42[b]
5'	67.08	71.54	71.74	72.89

Table 2. Showing the comparison of ^{13}C NMR shifts for the prepared bases.

a) values corrected for CD_3OD using -0.96 ppm. Wiley.[43]
b) interchangeable assignments.

Comparison of the ^1H NMR spectra for the bases provided further evidence for the consistency of the framework of the molecule, with the ^1H NMR for bases **39**, **46**, **55** and

56 containing the distinctive axial-equatorial, axial-axial coupling pattern for the proton at the 5' position that would be expected for this system, Table 3.

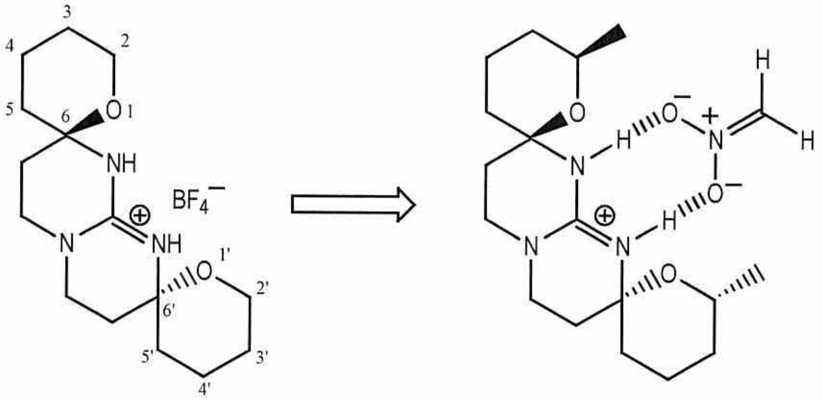


Base	Coupling constants for 5' proton
39	J = 5.0, 12.4 Hz
55	J = 6.0, 11.0 Hz
56	J = 6.0, 12.0 Hz
46	Obscured

We can therefore be confident of that the bases produced share a common structural motif due to the high degree of correlation present in the NMR data.

2.4 Development of new synthetic strategies for the synthesis of novel C_2 symmetric guanidine bases.

Following the successful synthetic preparation of the bases **39**, **55** and **56** and in anticipation of the application of these bases in synthesis (see chapter 3), we were keen to discover how our bases might behave as catalysts in enantioselective aldol reactions. Whilst at AstraZeneca we performed some molecular modelling docking studies on the base **39** using the X-ray structure determined for the bicyclic guanidine **31** obtained from the Cambridge Data Centre in the form of Cambridge refcodes, YAYXOL, YAYXUR, and ZOPCAI. These co-ordinates were input into the Accelrys software, Quanta, to build the models.[44] The structure was modified to give the salt **57** by the incorporation of two methyl groups at the 2 and 2' positions of the pyran rings and the replacement of the fluoroborate anion with a nitroenolate, Figure 8..



31 **57**

Figure 8. modification of crystal structure of base **31** to provide starting point for docking studies of aldehydes with base **39**.

The results of docking an acetaldehyde with **57**, assuming tetrahedral approach geometry, are shown in Figure 9. The first important factor to note is that the chiral centres at C-2 and C-2' on the pyran rings are very remote from the reactive centre of the molecule.

This would help explain the lack of enantioselectivity in the work of Mendoza,[29,30] Nagasawa[31] and our own studies,[41] where the acceleration of a hetero-Michael reaction was investigated.

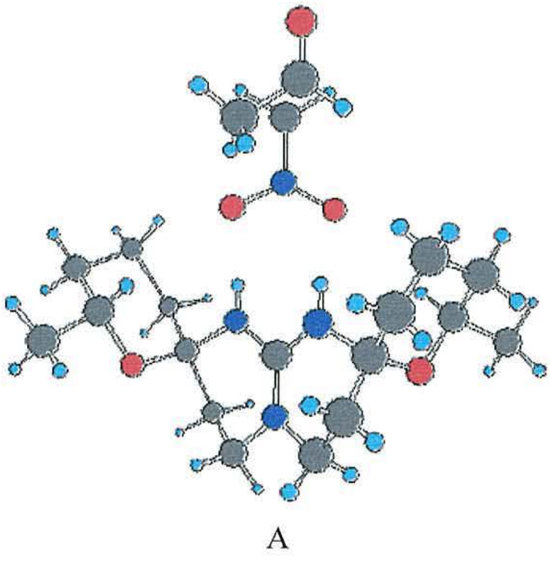
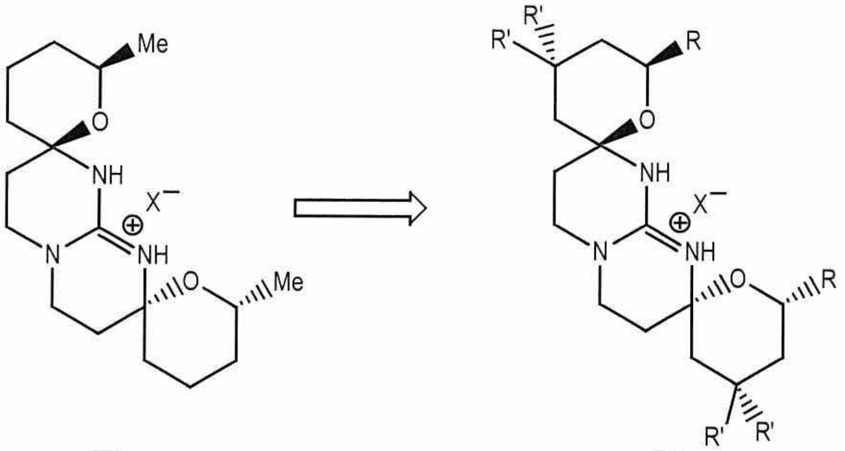


Figure 9. Showing the proposed modes of approach of ethanal toward nitromethane co-ordinated to guanidine base **39**.

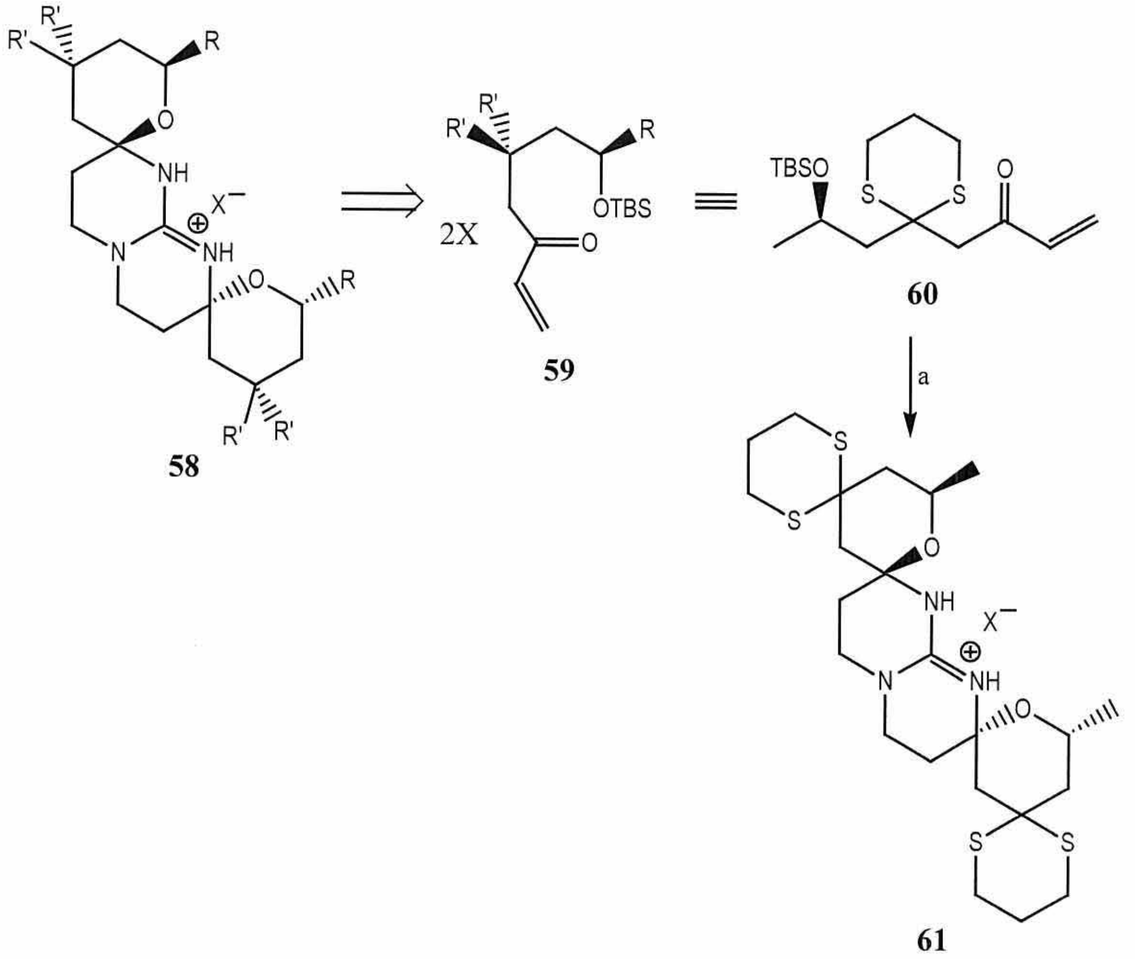
What is apparent is that the approach of the acetaldehyde to the enolate is less hindered in the minimised structure A when compared to structure B. In this structure the methyl group of the acetaldehyde has an interaction with the axial proton at the 4-position of the tetrahydropyran ring of the base. It is thus reasonable to assume that modification of the base at this position (Figure 10), will lead to larger steric interaction with any approaching electrophile, leading to greater enantioselectivity in reactions on the part of the base.



39 **58**

Figure 10. Proposed framework for novel C_2 symmetric guanidine bases with modification at the 4,4' position of the tetrahydropyran rings to give **58**. R = alkyl, aryl, R' = alkyl, aryl, generalised fragment.

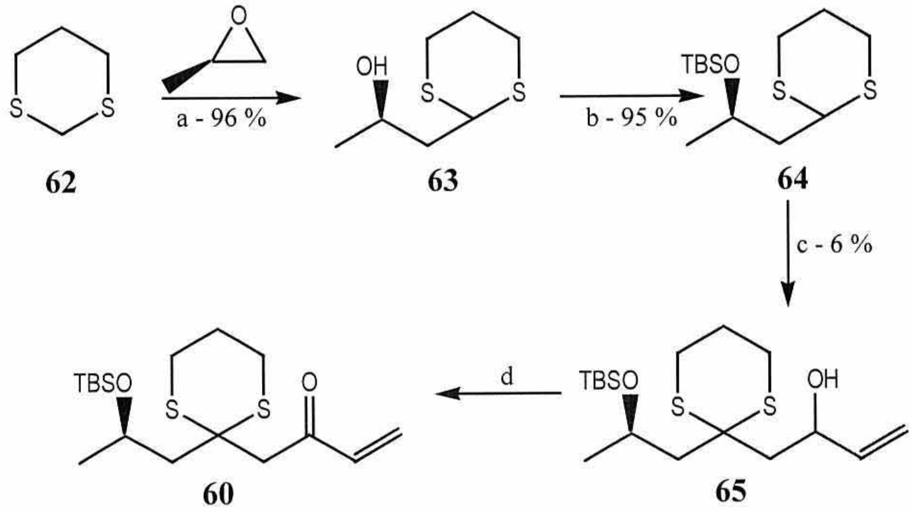
Retrosynthetic analysis of **58** led us to seek a general synthesis of enones **59**. Our first approach to these molecules was to replace the R' groups with a dithiane moiety and to again use the methyl group as our conformational lock, therefore we required a synthesis of **60**. Reaction with guanidine under our standard conditions would lead to the base **61**, in which the dithiane rings are acting as the steric blocking groups which will hopefully lead to an enhancement in selectivity, Scheme 29.


R'
R'
R
O
NH
X−
⊕
N
NH
O
R
R'
R'
58
2X
R'
R'
R
OTBS
O
59
TBSO
S
S
O
60
a
S
S
O
NH
X−
⊕
N
NH
O
S
S
61

Scheme 29. Retrosynthetic analysis of **58** to give general target enone **59**, and subsequent proposed synthesis of base **61** from enone **60**. a) i)guanidine, DMF. ii) MeOH, HCl.

2.5 Attempted synthesis of dithiane based C_2 symmetric guanidine base.

The proposed scheme for the synthesis of the α,β-unsaturated ketone **60** involves the sequential addition of the dithiane anion to two epoxides (*R*-propylene oxide and butadiene epoxide) which should give alcohol **65.** On oxidation **65** will lead to the target enone **60**, Scheme 30.[45]

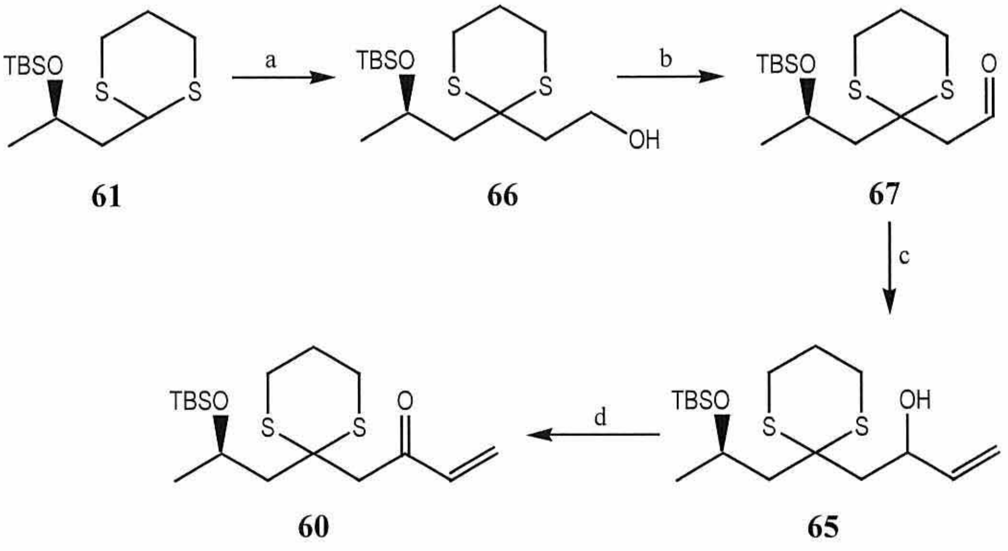


Scheme 30. a) THF, -40°C, BuLi, 2 h, 2 h at 0 °C, -40 °C, R-propylene oxide, 2 h. b) DMF, imidazole, TBSCl, 24 h. c) THF, -20 °C, BuLi, warm to rt over 3 h, -15 °C, butadiene epoxide, 24 h, followed by 48 h at 0 °C, d) Swern oxidation.

Initial steps proceeded well with the ring opening of the chiral epoxide, R-propylene oxide, proceeding in 96 % yield. Subsequent protection of the alcohol **63** as the silyl ether using TBSCl gave the protected alcohol **64** in 95 % yield. Addition of the anion of **64** by ring opening to a second epoxide, butadiene epoxide, was more problematic, with the initial attempt yielding the desired alcohol, **65**, in a disappointingly low yield of 6 %. The addition of **64** to butadiene monoxide was further investigated in an attempt to optimise the yield of this step.

It was thought that the low yield of **65** might be due to the incomplete formation of the dithiane anion. Changing the base used in the reaction to *tert*-BuLi and LDA in an attempt to ensure complete deprotonation of the dithiane **64** also resulted in no reaction being observed. In the literature it was noted that the addition of $BF_3.Et_2O$ has been observed to be beneficial in the addition of carbon nucleophiles to epoxides, therefore the reaction was attempted using a stoicheometric amount of $BF_3.Et_2O$.[46] Using this method, the reaction again yielded none of the desired product.

It was thought that the use of a more reactive epoxide might lead to a more efficient approach to the synthesis of **60,** with this in mind the proposed synthesis was modified. It was proposed that the reaction of **64** with ethylene oxide would yield alcohol **66**, which could be modified to the previously prepared alcohol **65** via an oxidation - Grignard protocol, Scheme 31.



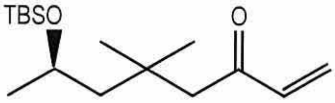
Scheme 31. a) THF, -20 °C, BuLi, 0 °C for 3 h, -20 °C, ethylene oxide, 3 h
b) Swern oxidation, c) $CH_2CHMgBr$, THF, d) Swern oxidation.

Initial attempts did not proceed well with the desired product not being obtained. Modification of the reaction conditions, reaction stirred for 3 h at 0 °C rather than at -20 °C, yielded the desired product (**66**) in 13 % yield. Further modifications of the reaction procedure did not result in improved yields for the reaction.

It was decided that this approach was not a realistic methodology for the production of the desired base **58**, due to the restrictions placed on the addition of the second epoxide ring. It is not known if the lack of reactivity of the dithiane towards the epoxide is due to the incomplete deprotonation of the dithiane or the formation of a stabilised anion that reacts poorly. It was therefore decided that a new approach should be considered.

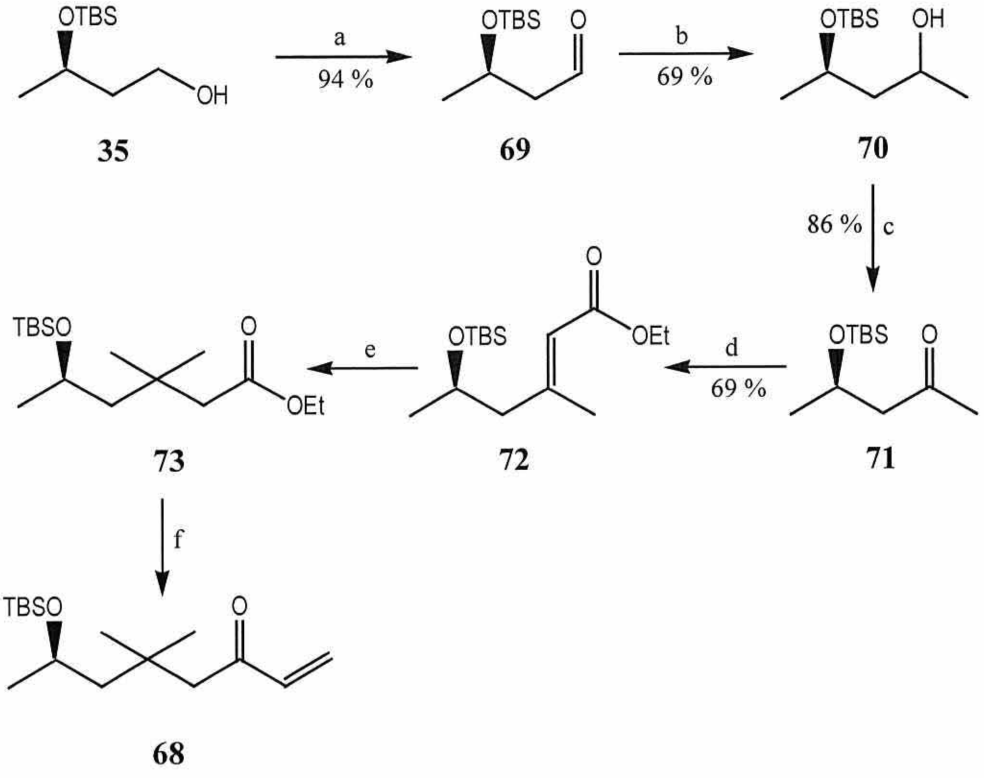
2.6 Attempted synthesis of the dimethyl based C_2 symmetric guanidine base.

We decided that we would target a different enone which would give simpler groups on the 4 position of the final product, thus the dimethylated intermediate **68** was proposed.



68

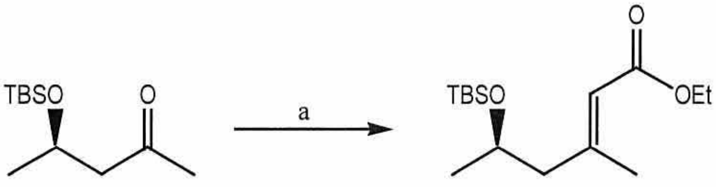
Our synthetic approach is detailed in Scheme 32 and begins with the previously prepared alcohol **35**. It was intended that alcohol **35** be converted to the ketone **71** *via* a oxidation – Grignard – oxidation sequence. We then intended to prepare the α,β-unsaturated ester **71** by Wadsworth-Emmons chemistry and to incorporate the second methyl group *via* an organocuprate. Methodology was already in place within the group to convert esters such as **73** into the enone **68**.[47]



Scheme 32. a) Swern oxidation, b) Et_2O, 0°C, MeMgBr, 24 h, c) Swern oxidation, d) triethyl phosphonate, THF, BuLi, -78°C to 0°C over 4 h, e) Et_2O, 0°C, CuI, MeLi, -78°C, **68**, to -5°C over 3 h, f) 2 x CH_2=PPh_3, CH_2O

Initial steps progressed well, with the Swern oxidation of alcohol **35** giving the aldehyde **69** in 94 % yield, which was used in subsequent steps without further purification. Reaction of the aldehyde **69** with MeMgBr gave the alcohol **70** in acceptable yield (69 %) which was converted to the ketone **71** by Swern oxidation in 86 % yield.

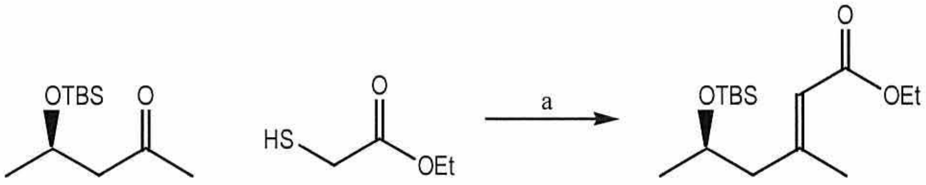
Initially we attempted to prepare the α,β-unsaturated ester **72** using Wadsworth-Emmons chemistry. Thus reaction of **71** with lithiated triethyl phosphonate was attempted, however it was found to be unsuccessful.[48] Attempts to modify the reaction, by varying the time for carbanion formation from 3 h to 12 h and varying the base used to NaH were also unsuccessful and it was decided that an alternative method should be sought, Scheme 33.



71 **72**

Scheme 33. a) triethyl phosphonate, THF, NaH, 3 to 12 h, -78°C add **71** warm to 0°C over 4 h.

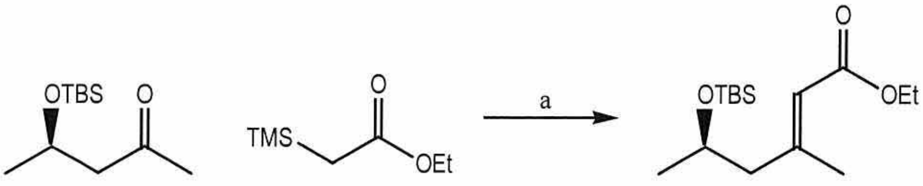
From the literature it was found that lithium enolates of *O*-alkyl S-alkoxycarbonylmethyl monothiocarbonates have been found to be efficient reagents for the synthesis of α,β-unsaturated esters.[49] Using this methodology ketone **71** was reacted with the dianion of ethyl mercaptoacetate, **74**, in an attempt to form **72**, Scheme 34. Again this approach was unsuccessful and the desired product was not obtained.



71 **74** **72**

Scheme 34. a) -78°C, THF, LDA, TMEDA, **74**, 1 h, **71**, 2 h, ethyl chloroformate, rt, 1h.

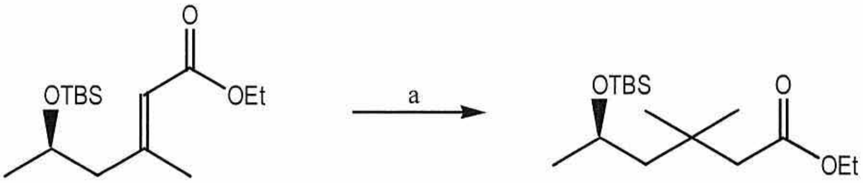
Going back to the literature it was found that the Peterson olefination is an efficient method for the conversion of carbonyl functionality to the corresponding substituted alkenes.[50] Thus the reaction of **71** with ethyl (trimethylsilyl)acetate, **75**, was attempted, Scheme 35.



71 **75** **72**

Scheme 35. a) THF, LDA, -78 °C, **75**, 15 min, add **71** and warm to -10 °C over 3 h.

Using this methodology the reaction proceeded well giving the desired product, **72**, in 69 % yield (63 % average over 3 attempts) in a mixture of *E* and *Z* isomers. With ester **72** in hand we required a method for incorporating the second methyl group at C-4 to give **73**, initial thoughts were to make use of organocuprate chemistry to carry out the 1,4-addition of the methyl group to **72**, Scheme 36.[51]

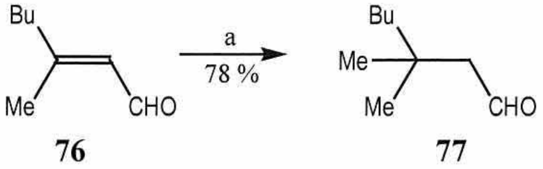


72 **73**

Scheme 36. a) dry ether, 0 °C, CuI, MeLi, cool -78 °C, **72**, warm to -5 °C over 3 h.

Unfortunately reaction of **72** with lithium dimethyl cuprate yielded none of the desired product giving only recovered starting material. Modification of the conditions by varying the temperature and reaction time failed to yield the desired product, again giving mostly recovered starting material.

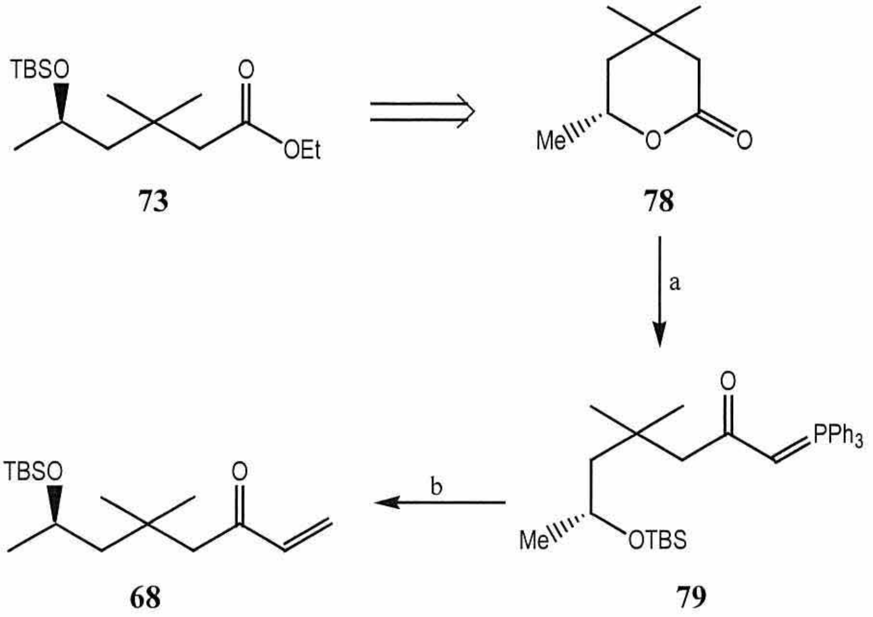
Turning to the literature it was found that the copper catalysed 1,4-addition of organomanganese compounds might be another potential method for carrying out the desired reaction to give **73**. Of particular note is the 1,4-addition of methylmanganese chloride to the stericaly hindered α,β-unsaturated aldehyde **76** which is similar in nature to our ester **72,** Scheme 37.[52]



Scheme 37. a) THF, -30 °C, MeMgCl, $MnCl_2$,
5% CuCl, 30 min.

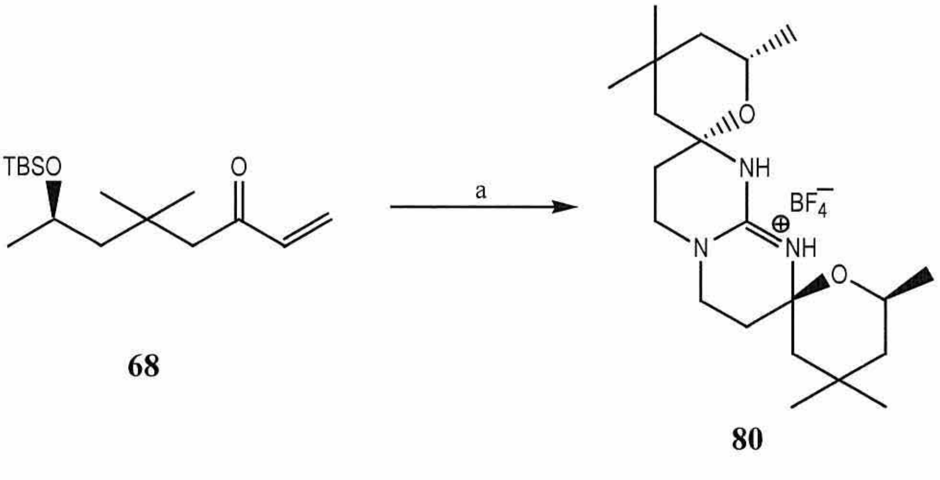
With this in mind the reaction of MeMnCl (prepared by the addition of MeMgCl to a cooled (0 °C) solution of $MnCl_2$ in THF) with ester **72**, catalysed by 5 mol % of CuCl, was investigated. Unfortunately several attempts with varying reaction temperatures, and over varying time scales, did not lead to the production of the desired product.

At this point it was decided that this line of investigation was again proving fruitless, and it was decided that a new approach should be developed. On consideration of the required ester **73** it is apparent that it could be accessed from the lactone **78**. In turn, this lactone could be converted to the required enone **68** using chemistry previously developed in our laboratories, Scheme 38.[53]


TBSO
O
OEt
73
Me
O
O
78
a
O
PPh3
Me
OTBS
79
b
TBSO
O
68

Scheme 38. a) i) 2 x CH_2PPh_3; ii) TBSCl, imidazole, DMF; b) THF, CH_2O.

Reaction of enone **68** under the usual conditions should then yield the base **80**, containing the methyl blocking groups at C-4 on the pyran rings, Scheme 39.

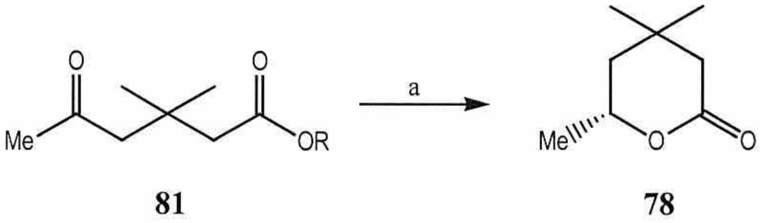

TBSO
O
68
a
O
NH
BF_4^-
N
⊕
NH
O
80

Scheme 39. a) i) guanidine, DMF, 3h; ii) MeOH, HCl, 0 °C to rt, 24 h;
iii) Saturated aq. $NaBF_4$.

We thus required a synthesis of the lactone **78** or a close analogue of it.

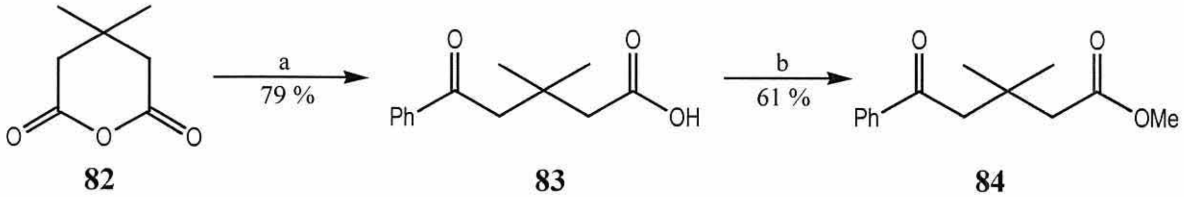
2.7 Synthesis of (*S*)-4,4-Dimethyl-6-methyl-tetrahydro-pyran-2-one, 78.

In order to embark on this synthetic effort we required a enantioselective synthesis of the lactone **78** or an analogue. One possible method is from the enantioselective reduction of the corresponding keto-ester **81**, Scheme 40.



Scheme 40. a) chiral reducing agent.

On inspection of the literature it was found that the related lactone **86** could be prepared in high yield by the Friedel-Crafts reaction of 3,3-dimethylglutaric anhydride, **82**, with benzene.[54] We attempted this chemistry and found that the reaction proceeded in 79 % yield, and that the acid **83** was then converted to the corresponding methyl ester **84,** by stirring with a methanolic solution of HCl, in 61 % yield, Scheme 41.

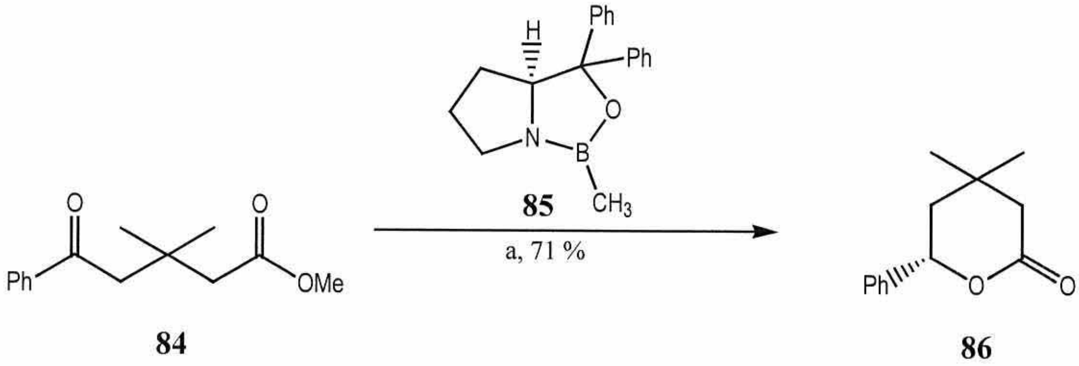


Scheme 41. a) benzene, $AlCl_3$, reflux 3h; b) MeOH, HCl, rt, 3h.

The stereoselective reduction of the methyl ester **84** proved problematic in the early stages. The literature indicated that the structure of **84** made it a possible candidate for chiral reduction using fermenting yeast.[55] Initial attempts to carry out the reactions however indicated that the ester **84** was not suitable for use as a substrate in the reduction as no conversion of **84** to the relevant alcohol was observed. A chemical method to achieve the conversion was therefore sought.

The reaction was initially attempted using the 9-BBN-H dimer and (*S*)-(-)-α-pinene as the chiral reducing agent *in situ*.[56] However, this reaction proved to be ineffective and the desired product was not formed.

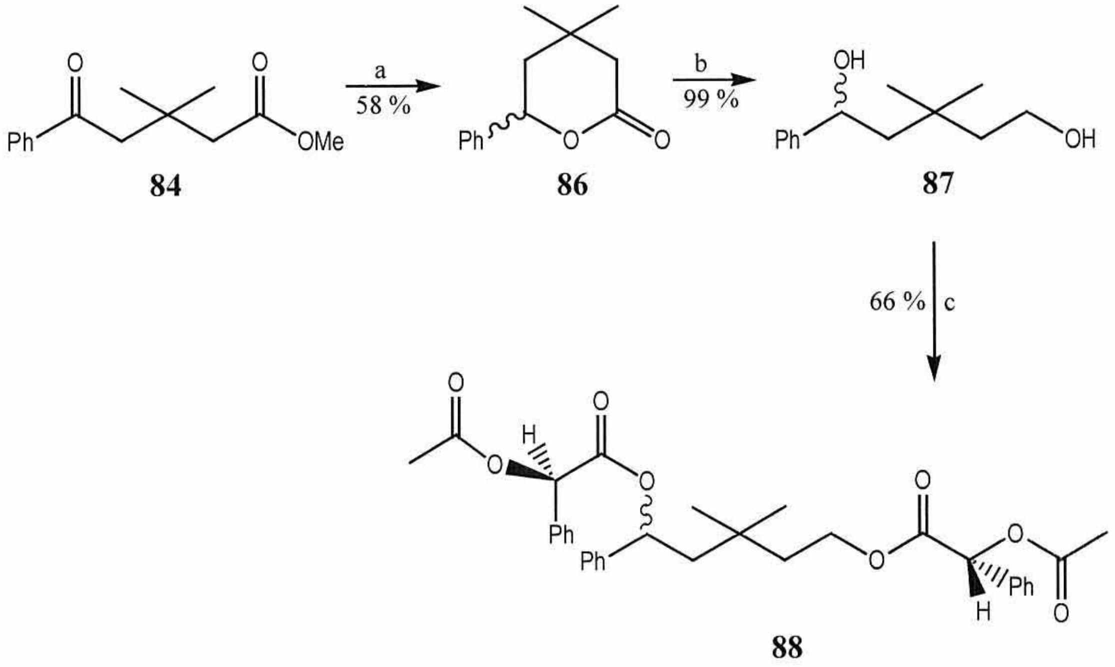
Looking to the literature, it was decided to attempt the desired reaction using the chiral oxazaborolidine catalysts that have been shown to be effective in the this type of reaction.[57] Specifically we found that the reaction of **84** with (*R*)-2-methyl-CBS-oxazaborolidine (**85**) and BH_3.THF complex in THF at 0°C, gave the desired product in 71 % yield after cyclisation with camphor sulphonic acid, Scheme 42.



Scheme 42. a) i) THF, BH_3.THF, 0°C, 45 min, ii) DCM, camphor sulphonic acid (cat).

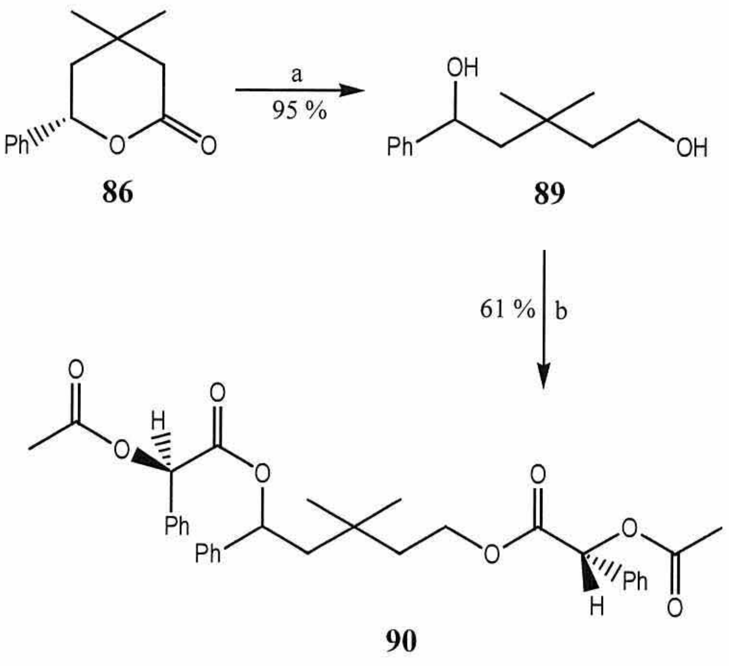
Following the successful synthesis of **86** it was necessary to determine the enantiomeric excess of the product. Initial attempts were made to determine the e.e. using chiral GC and chiral HPLC however these techniques were unsuitable for e.e. determination using the chiral columns available to us.

We thus decided to approach the problem from a synthetic angle. It was decided to form the bis (*R*)-*O*-acetylmandelic acid derivative of the racemic diol **87**, obtained from the reduction of a sample of the racemic lactone ±-**86**, prepared by $NaBH_4$ reduction of **84**. Reduction of the lactone **86** using DIBAL proceeded well with the diol **87** being formed in 99 % yield, the diol was then converted to the mandelic acid derivative **88** using R-*O*-acetylmandelic acid and DCC together with a catalytic amount of DMAP, Scheme 43.



Scheme 43. a)MeOH, $NaBH_4$, 0 °C, 2h; b) DCM, DIBAL, -78 °C to rt over 12 h; c) DCM, R-*O*-acetylmandelic acid, DMAP, DCC, 12 h.

Following this, the mandelate of chiral lactone **86** was prepared in the same manner giving **90**, Scheme 44.



Scheme 44. a) DCM, DIBAL, -78°C to rt over 12 h; b) DCM, R-*O*-acetylmandelic acid, DMAP, DCC, 12 h.

Analysis of the mandelate derivatives by H^1 NMR gives a clear indication as to the e.e. of the chiral lactone. Signals between 0.5 and 1.1 ppm on the spectra correspond to the methyl groups at C-3 of the chain. The presence of the mandelate groups provides an interaction which causes the methyl groups to be clearly defined on the spectrum with a difference of at least 0.5 ppm in the chemical shifts.

Careful measurement of the relative intensities of the signals allows us to determine the e.e. of the lactone as the ratio of the integration of the signals to one another. As can be seen from the spectra in Figure 11, the selective reduction using CBS complex resulted in a highly selective reduction giving e.e. greater than 92 % (96:4).

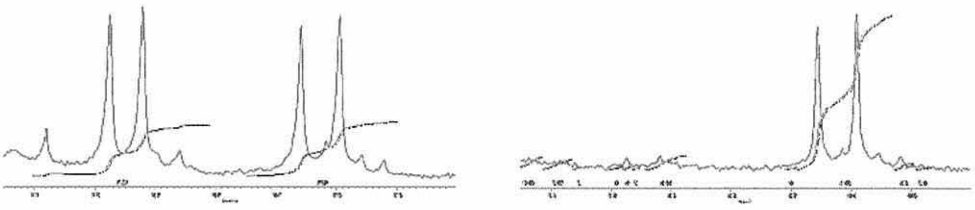


Figure 11. Showing the regions between 0.5 and 1.1 ppm for the H^1-NMR spectra of **88** and **90**.

The absolute stereochemistry of **86** was also determined by absolute X-ray structure determination. The resulting structure, Figure 12, indicates that the lactone is the S enantiomer.

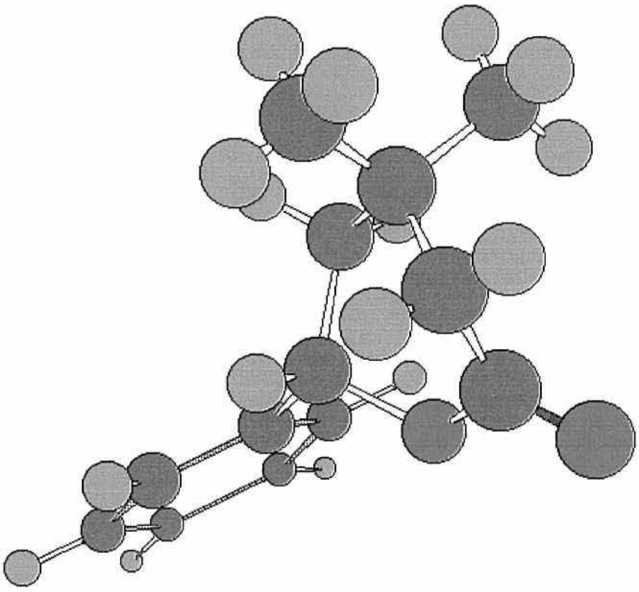
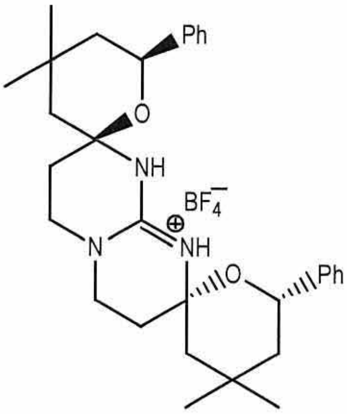


Figure 12. X-ray crystal structure of lactone **78** showing the stereochemistry about the chiral centre being S.

Unfortunately we were unable to convert *S*-**86** to the desired base due to lack of time, however we believe that this work offers a great deal of potential for the synthesis of the C_2 symmetric base **91** and further work is being carried out in the research group.



91

Chapter 3

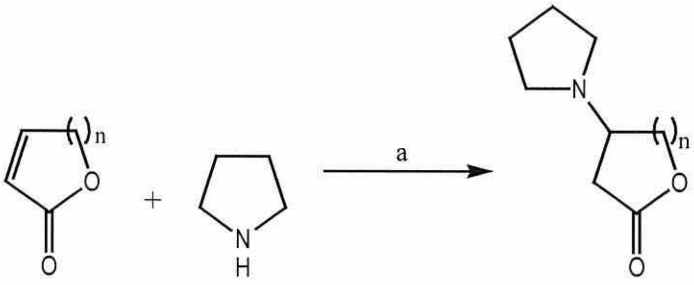
Catalytic Studies

3.1 Introduction.

At the start of the project the intention was to prepare novel C_2 symmetric guanidine bases and to study their use as catalysts for the Henry (nitroaldol) reaction and the nitro-Michael reaction.[22, 32] Before the catalytic work on these reactions was initiated it was decided that we would revisit the work of a past group member and look at the catalysis of the Michael reaction of pyrrolidine with 2(5*H*)-furanone, as carried out by Mendoza *et al*, section 1.6.[17]

3.2 Catalysis of the addition of pyrrolidine to 2(5H)-furanone.

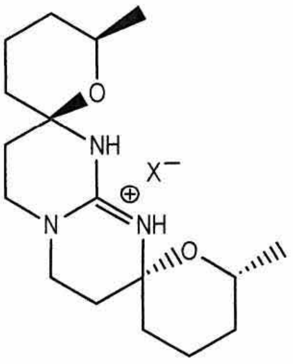
It was decided that we should asses the use of our guanidinium salts as a catalysts for the reaction of pyrrolidine, **41**, and 2(5H)-furanone, **40**, using the experimental details set out by Mendoza *et al*, Scheme 45.[29]



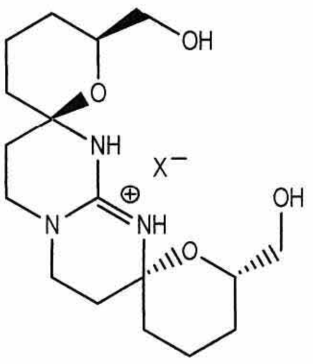
40 **41** **92**

Scheme 45. a) guanidinium salt 10 mol%, $CDCl_3$, 27 °C.

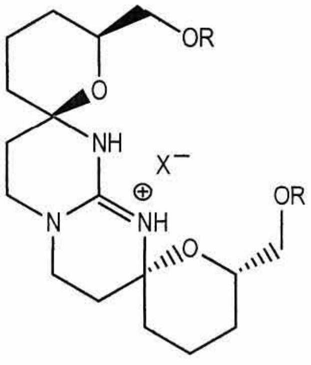
It was decided that we would look at the catalytic activity of a range of guanidinium bases formed during the course of the work, Figure 13.



39 X = BF_4



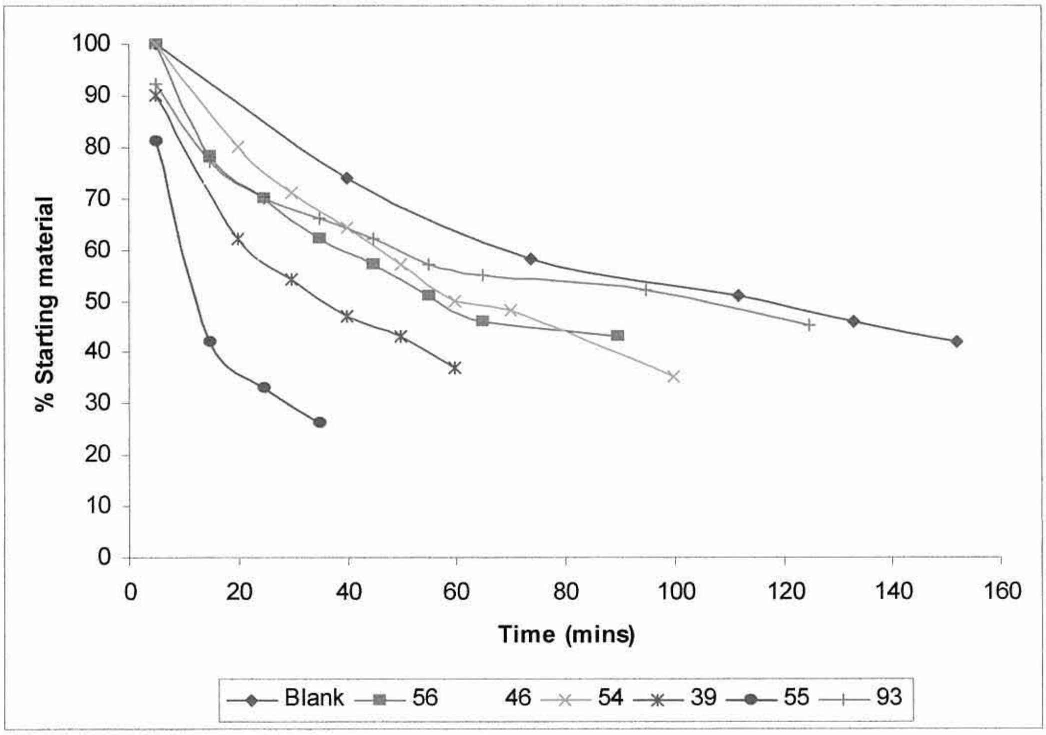
46 X = Cl



54 X = Cl, R = TBS
55 X = BF_4, R = TBS
56 X = Br, R = TBDPS
93 X = BF_4, R = TBDPS

Figure 13. Guanidinium salts to be studied.

Thus, equimolar amounts of **40** and **41** in $CDCl_3$ (0.3 M) were combined in the presence of the requisite guanidine base. The progress of the reaction was monitored (H^1 NMR) by integration of the methylene proton α to the oxygen atom in the lactone starting material relative to one of the protons α to the carbonyl in the product **92**. The results of the NMR experiments are shown in Graph 1.



From the above graph it was possible to calculate the half life time ($t_{1/2}$) of the reaction, and compare the results to those obtained by previous workers, Table 4.[29, 39, 40]

Guanidinium Salt	$t_{1/2}$ (min)
---	115
39	35
46	43
54	61
55	12
56	57
93	108

Table 4. Reaction conditions: [**40**] = [**41**] = 0.3 M
[Guanidinium salt] = 0.03 M, $CDCl_3$, RT.

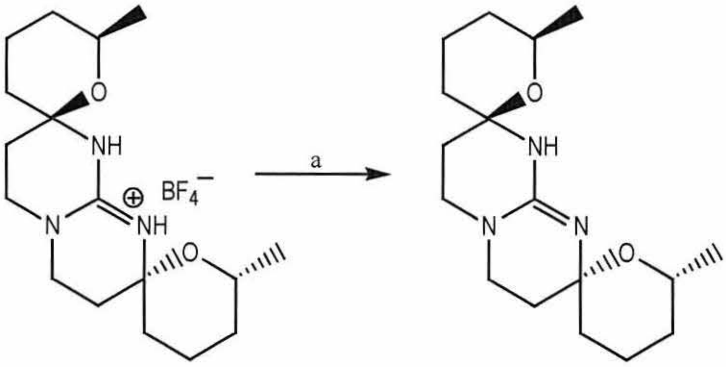
It can be seen from the table that the guanidine salts do indeed catalyse the reaction. Relative rate increases varied between a 1.06 fold rate increase for base **93** to a 9.6 fold increase for base **55**, thus putting it on a par with base **26** (Page 18), the best catalyst reported by Mendoza, which gave a 10 fold relative rate increase.[29] It should be noted that previous work within our group has shown that the BPh_4 salts of bases gave higher relative rate increases than the corresponding halide and BF_4 salts that are the object of this series of tests (Chapter 1, Section 1.6) and therefore there is scope for improved relative rate increases.

The variation of the rate increase for base **56** (Br^- salt) and **93** (BF_4^- salt) might be due to the steric bulk of the TBDPS protecting groups, which may lead to the BF_4^- counterion being more strongly bound to the guanidinium function. Additionally, in the presumed intermediate where the lactone is hydrogen bonded to the guanidine salt, there may be increased steric hindrance, and also the non polar nature of the *t*-$BuPh_2Si$ function might be a factor.

3.3 Catalysis of nitroaldol reaction.

After the preparation of the bases **39**, **55** and **56** their use as catalysts for the Henry (nitroaldol) reaction was investigated. Previous work by Nájera and coworkers showed that chiral guanidines could be used as catalysts in the asymmetric Henry reaction.[22] This work indicated at the time that increased chiral discrimination was achieved using guanidines containing C_2 symmetry. We reasoned that our base would also be able to catalyse the nitroaldol reaction in an asymmetric manner because of the fixed C_2 symmetry of the base.

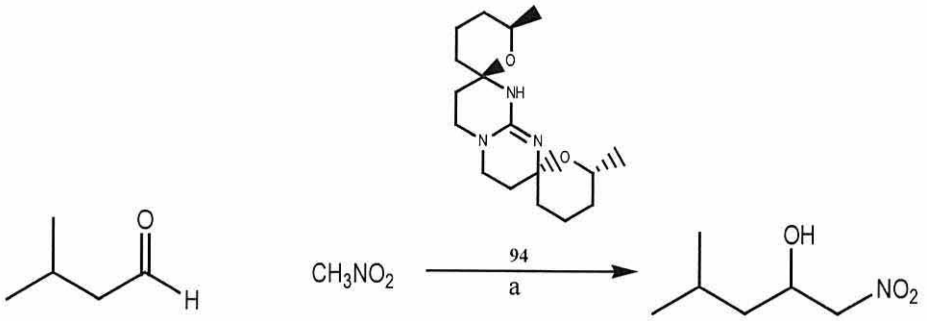
Initially the free bases were prepared from their tetrafluoroborate salts by stirring with sodium methoxide (0.9 eq) in dry methanol for 30 min. This was followed by the removal of the methanol under vacuum and redissolution of the base in the required solvent, which was then filtered, Scheme 46.



39 **94**

Scheme 46. a) dry methanol, NaOMe, 30 min.

It was decided to follow the same methodology and use the same reaction as used in the previous work by Nájera, i.e. using nitromethane as the nitroalkane (1.5 eq) and isovaleraldehyde as the aldehyde component (1.0 eq) which were added sequentially to a solution of the base in the required solvent at the required temperature, Scheme 47



95 **96** **97**

Scheme 47. a) free base **94** 10 mol %, dry solvent.

The initial reaction, using the free base of **39** (**94**) in THF at room temperature, proceeded well giving one spot by TLC compared to no new spots for a blank reaction without the catalyst. Crude NMR showed that no aldehyde was present and the reaction was purified by column chromatography to yield the product, 4-Methyl-1-nitropentan-2-ol in 50 % yield, and also recover the catalyst for reuse. The optical rotation of the product measured in ethanol was $[\alpha]^{24}_{D} = +2.7$ (c = 1), and as Nájera has quoted an $[\alpha]_D$ of −11.9 for an R product of ee 54 % we can thus assume our product is S and has an ee of 12 %.[22]

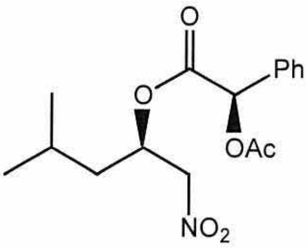
It was then decided to test the catalyst at a lower reaction temperature since the work carried out by Nájera showed that the enantiomeric excess of the product increases with decreasing temperature. The same amounts of materials were used and the reaction was carried out at -70 °C; observation of the reaction by GC indicated no reaction over the course of 24 h and a further experiment carried out at -20 °C again indicated no reaction by GC. Investigation of the effect of solvent on the reaction was then carried out by performing four parallel reactions at 0 °C in THF, ether, dichloromethane and carbon tetrachloride using the same amounts of reagents and catalyst as for the initial reaction. The results of GC traces from the reactions are tabulated below, percentages are for relative peak areas of the isovaleraldehyde peak compared to the product peak, Table 5.

	24 h at 0°C		3 h at r.t		27 h at r.t		50 h at r.t	
	S.M (%)	Prod (%)	S.M (%)	Prod (%)	S.M (%)	Prod (%)	S.M (%)	Prod (%)
DCM	12.0	88.0	----	----	----	----	----	----
ether	84.0	16.0	43.0	57.0	17.0	83.0	14.9	85.1
THF	77.8	22.2	47.0	53.0	18.0	82.0	14.8	85.2
CCl_4	100	0	30	70	----	----	----	----

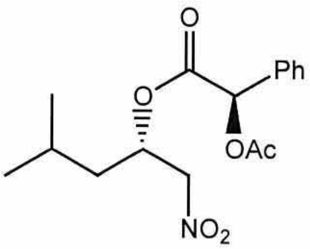
Table 5. Data for the nitroaldol reaction in a series of solvents, relative amounts measured by GC.

It can be seen from the table that dichloromethane is a far better solvent at lower temperatures for this reaction than ether, THF or CCl_4. These solvents work well when the reaction is warmed to room temperature.

To assess the degree of enantioselectivity incured in the final product by the catalyst it was decided to prepare *R*-*O*-acetylmandelic acid derivatives of the products to enable more accurate determination of ee's achieved. The preparation of mandelic acid derivatives results in the formation of a diastereomeric mixture of compounds, *R*- and *S*-**98,** the relative amounts of which can be determined by ^{1}H NMR experiments.



RR-**98**



SR-**98**

Due to the differing environments of the protons α to the nitro group measurement of the appropriate peaks on ^{1}H spectra of the mixture, between 4.2 and 4.6 ppm, gives the ratio of the diastereomeric mixture. Once the ratio is known the ee of the mixture can be determined, Table 6.

Solvent/Temp (°C)	Purified Yield.	e.e (%)	$[\alpha]_D^{24}$	R/S
THF/rt	40 %	12[a]	+2.6	R
THF/0°C	30 %	16[b]	---	---
DCM/0°C	38 %	4[b]	---	---
Ether/0°C	45 %	4[b]	---	---
CCl_4/rt	52 %	20[b]	---	---

Table 6. Results of the nitroaldol reaction between **95** and **96** using base **39**.

a) by optical rotation Lit. $[\alpha]_D^{24}$ -11.9 (c=1, EtOH) (54 % e.e) for S enantiomer.

b) by ^{1}H NMR of the *R-O*-Acetylmandelic derivatives

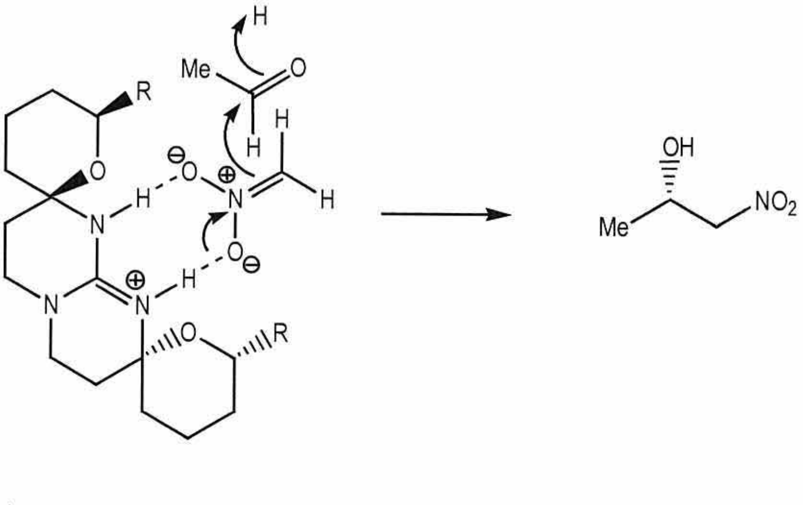
This table shows that unexpectedly the reaction proceeds best in terms of ee obtained when using THF (at 0 °C) and carbon tetrachloride (at rt). We thus concluded from these results that the base **39** does in fact catalyse the nitroaldol reaction in an asymmetric fashion to a small extent.

Using the optimum conditions from the above experiments the reaction was carried out using guanidine bases obtained from salts **55** and **56** in place of **39**, with the free base being prepared using the same methodology as for **39**, see Table 7.

Base	Solvent / Temp	Yield (%)	e.e (%)	$[\alpha]_D^{24}$	R/S
39	CCl_4 / rt	52	20[a]	---	---
39	THF / 0°C	30	16[a]	---	---
55	CCl_4 / rt	48	8[b]	+1.7	R
55	THF / 0°C	40	3[b]	+0.6	R
56	CCl_4 / rt	46	7[b]	+1.5	R
56	THF / 0°C	42	4[b]	+0.9	R

Table 7. Results for the nitroaldol reaction of **95** with **96**
a) by ^1H NMR of the *R*-O-Acetomandelic derivatives
b) by optical rotation Lit. $[\alpha]_D^{24}$ -11.9 (c=1, EtOH) (54 % e.e) for S enantiomer

Looking at the proposed mechanism for this reaction based on the molecular modelling studies it is possible to postulate the expected stereochemistry in the end product. As can be seen in Scheme 48 the approach of the aldehyde as predicted by the modelling should lead to the S enantiomer.

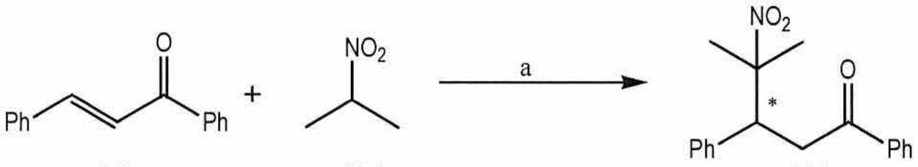


Scheme 48. Showing the proposed nitroaldol reaction involving the guanidine bases tested, selecting the S enantiomer over the R enantiomer.

Our experimental results seem to give this selectivity, which reinforces the modelling studies. However it will be necessary to rigorously prove this selectivity by synthesis of a known compound.[22]

3.4 Catalysis of the nitro-Michael reaction.

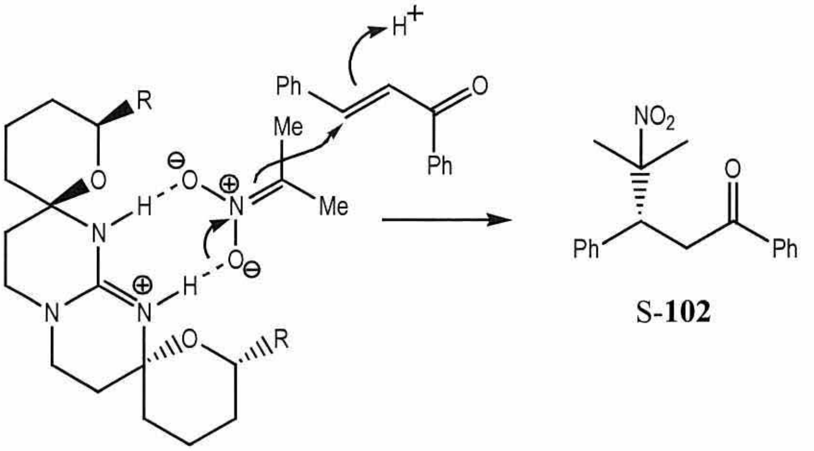
Within our program of catalytic studies we also briefly looked at the use of our guanidine base **39** in the nitro Michael reaction. It was decided to attempt the catalysis of the nitro-Michael reaction of 2-nitropropane, **100**, with chalcone, **99**, as described by Tőke and co-workers, Scheme 49.[32] The reaction was carried out using the same relative amounts as by Tőke and co-workers with **99** (1 equiv.) and **100** (2.3 equiv.) being added to a solution of the guanidine base **39** (0.1 equiv.) and NaO^{t}Bu (0.09 equiv.) in the required solvent at the desired temperature.



99 **100** **101**

Scheme 49. a) Guanidine base 10 mol %, NaOBu^t 9 mol %, dry solvent, rt, 24 h.

Using the proposed mechanism that was used for the nitroaldol reaction it is possible to postulate the stereochemistry of the nitro-Michael reaction of **100** to **101**, which based on this model should give the S enantiomer, *S*-**102,** Scheme 50.



S-**102**

Scheme 50. The proposed mechanism of the nitro-Michael reaction of **100** with **99** using our guanidine bases giving selectively the S-enantiomer.

The reaction was therefore attempted using base **39** as the catalyst (10 mol %) together with **99** (1 equiv.) and **100** (2.3 equiv.) in a series of solvents, THF, CCl_4 and neat **100** at room temperature. No reaction was observed when using CCl_4 or neat **100** as solvents, however using THF as a solvent the nitro adduct **102** was obtained in 70% yield. Changing the reaction conditions so that the free base of **39** is prepared in the same manner as in the nitroaldol reaction, re-dissolved in THF, filtered and **99** and **100** added sequentially to the solution, also gave **102** but in a much lower yield. Measurement of the optical rotations and comparison to literature value gives the e.e of the product obtained, Table 8.

Solvent	Yield (%)	e.e (%)	$[\alpha]_D^{24}$
THF	70	23[a]	18.5
THF	36	19[a]	15.2

Table 8. Data for the reaction of **100** with **99** in the presence of base **39** (10 mol %) in THF at room temperature.
a) from $[\alpha]_D$ measurement S-**101**; $[\alpha]_D^{24} = +80.8$ (c = 1, CH_2Cl_2)[32]

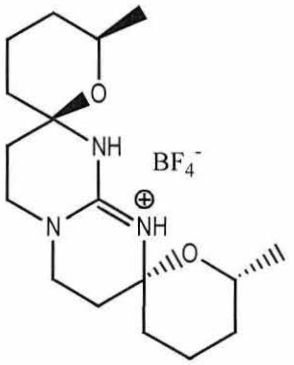
With this experimental support for the proposed mechanism it is thought that we can confidently predict the stereoselectivity that would result from the use of our guanidine bases in these reactions. At this time the work was brought to a close due to time constraints. However further catalytic studies need to be carried out if the development of base **91** or an analogue is successful, since the chemistry does show promise. If such a base can be prepared we would predict higher levels of stereoselectivity.

Chapter 4

Summary

4.1 Summary

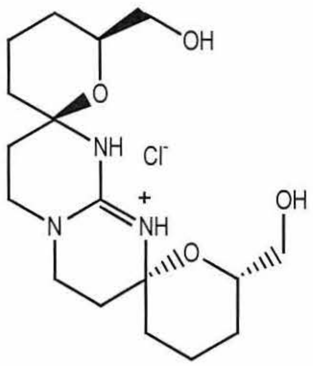
The aims of this project were the optimisation of the synthesis of base **39** and the synthesis of novel C_2 symmetric guanidine bases and the investigation of the catalytic properties of the bases in the Henry (nitroaldol) and nitro-Michael reactions.



39

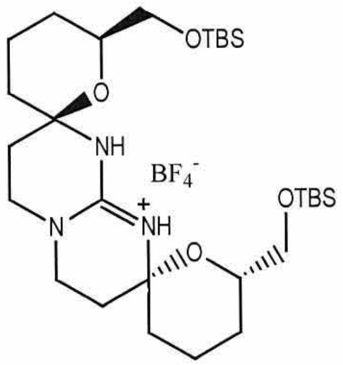
During the optimisation process for the synthesis of base **39** several key steps were improved, most notably the synthesis of the relevant α,β-unsaturated ketone **38** the yield of which has been increased from 55 % in the original synthesis to 79 % during the course of this work.

With the optimisation of **39** having been achieved the synthesis of novel C_2 symmetric guanidine base **46** was attempted. Although initially problematic due to the hydroscopic nature of the molecule, the objective was met and base **46** has been synthesised in a yield of 13 % from the corresponding α,β-unsaturated ketone **53**.

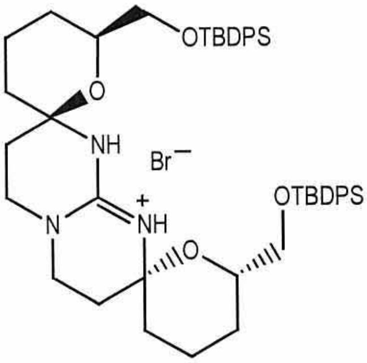


46

Modification of the reaction conditions lead to the synthesis of the protected variations **55** and **56** in 28 % and 36 % yield respectively from the α,β-unsaturated ketone **53**. Although the yields of the final products were unspectacular sufficient material was prepared for the catalytic phase of the project.

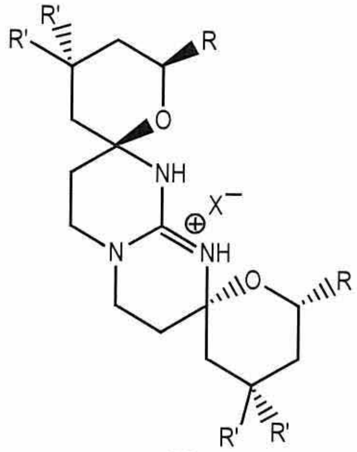


55



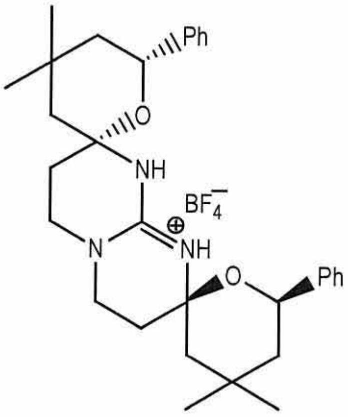
56

Molecular modelling studies of the base **39** gave some indication that the base would be selective since it was suggested that bulky groups approaching the base would approach in a way that gave the least interaction between the approaching group and the 4-position of the pyran rings. Although some selectivity was expected it was not thought to be to a great extent since there appeared to be only a small difference on the steric interaction between the base and the approaching groups. It was therefore proposed that the inclusion of bulky groups at the 4-position of the pyran rings to give a base of the general structure **58** would give rise to a more efficient catalyst.



58

Initial attempts towards the synthesis of a base of the general type **58** were unsuccessful, with the work on a dithiane containing base and a 4,4-dimethyl base proving fruitless. A great deal of progress has been made towards the preparation of an analogue of **58**, base **91**, with the successful synthesis of a key intermediate in the form of the chiral lactone **86** which it is proposed can be converted to the base using chemistry previously developed in our laboratories.



91

Investigation of the catalytic properties of the bases **39**, **55** and **56** indicate that the bases do catalyse the nitroaldol reaction of nitromethane to isovaleraldehyde in a stereoselective manner with e.e values of 20 % being obtained for **39**, the most effective base. Catalytic studies of the nitro-Michael reaction of 2-nitropropane to chalcone show that **39** also catalyses this reaction in an asymmetric manner with e.e values of up to 23 % being obtained.

Use of molecular modelling studies also led to the development of a model for the mode of action of the base in the nitroaldol and nitro-Michael reaction that allows us to predict the stereochemistry expected in the end product, and this model is supported by the experimental results obtained during the catalytic studies.

4.2 Future Work

The work already carried out on the development of a new family of guanidine bases shows great promise and this work should be taken forward in order to synthesise novel guanidine bases with the inclusion of functionality at the 4- position of the pyran ring. These novel bases should then be assessed in their ability to asymmetrically catalyse the nitroaldol and nitro-Michael reactions covered in this work to determine if the expected increase in the efficiency of the base as an asymmetric catalyst is observed.

Chapter 5

Experimental

REAGENTS

Reagents were obtained from commercial suppliers and were used without further purification. Reactions using *n*-Butyl lithium and diisobutylaluminium hydride refer to the use of these reagents in hexane.

SOLVENTS

All solvents used in reactions were purified using methods described in the literature.[58] Using these methods, diethyl ether and tetrahydrofuran were distilled from benzophenone and sodium wire whilst chloroform and carbon tetrachloride were distilled from P_2O_5. Dichloromethane and Dimethylformide were dried over CaH and freshly distilled. Methanol was dried by distillation from magnesium and iodine, whereas petrol was distilled and collected between boiling range of 40-60°C.

CHROMATOGRAPHY

Tlc was performed on glass plates coated with kieselgel 60 F254 (Art. 5554; Merck) with eluent specified in each case. The eluent percentage refers to a solution of the more polar solvent in the least polar solvent. Compounds were visualised using ultraviolet light and/or iodine. Staining reagents were also used, in particular solutions of phosphomolybdic acid (PMA) in EtOH or vanillin in $EtOH/H_2SO_4$, with heating.[54] Column chromatography was performed using Merck 7736 silica gel (particle size 40 – 63 μm) under medium pressure with the eluent specified in each case.

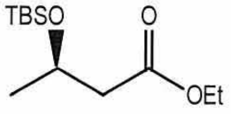
ANALYTICAL METHODS

Melting points were recorded with a Gallenkamp MF370 apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1600 FTIR spectrometer as thin film or solution as appropriate with the solvent quoted in each case. Absorption frequencies are reported in wavenumber ν, whose unit is the reciprocal centimetre (cm^{-1}). Absorption intensities are reported quantitatively as strong (s), medium (m), weak (w) and broad (br). Electron impact (EI) and chemical ionisation (CI) were recorded on a VG Masslab Model 12/253 spectrometer and high resolution mass spectra (HRMS) on a VG Analytical ZAB-E spectrometer at the EPSRC Mass Spectrometry Service Centre at Swansea. Mass measurements are reported in daltons. Optical rotation was determined using a polAAr 2001 machine, where all α_D values are relative to the solvent, concentration of the sample and temperature, which are specified in all cases. Proton NMR spectra were recorded in deuteriochloroform on a Bruker AC 250 spectrometer at 250 MHz . ^{13}C NMR spectra and DEPT experiments were also recorded in deuteriochloroform on a Bruker AC250 spectrometer at 62.5 MHz and were gate decoupled. Chemical shifts are reported as δ values (ppm) relative to tetramethylsilane as an internal standard. Spin couplings are denoted as J values (Hz), whilst splitting patterns are reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or any combination of these.

MISCELLANEOUS

All non-aqueous reactions were performed using oven dried glassware (250°C) and were conducted under a positive atmosphere of argon. All new compounds were homogeneous by tlc (unless otherwise stated). Solids were purified by either recrystallisation or chromatography, whilst liquids and oils were purified either by chromatography or distillation. The term 'dried' refers to the treatment of a solution of the compound with anhydrous magnesium sulphate. *n*-butyllithium in hexanes was titrated against diphenylacetic acid in THF immediately before use.[54] The term *in vacuo* refers to the reduced pressure of a Büchi rotary evaporator, at water pump pressure (14 mm Hg) at 30-50°C, or at 1 mm Hg at 25°C for higher boiling solvents. All yields quoted are for the purified compounds (unless otherwise stated).

Synthesis of ethyl (*R*)-3-((*tert*-butyldimethylsilyl)oxy)butyrate, 34.[40]



34

A solution of imidazole (9.76 g, 99.48 mmol) in dry DMF (20 ml) was cooled (0 °C) and ethyl (*R*)-(-)-3-hydroxybutyrate, **33**, (5.06 g, 38.26 mmol) was added followed by *tert*-butyldimethylsilyl chloride (7.6 g, 49.74 mmol). The reaction was allowed to warm to ambient temperature and stirred for 3 h, at the end of this time the solution was extracted with hexane (3 x 60 ml). The organic extracts were combined and washed with aqueous acetic acid solution (2 % v/v, 60 ml) and water (3 x 60 ml) before being dried ($MgSO_4$) and the solvent removed by rotary evaporation to give the title compound as a clear oil (9.28 g, 98.5 %). Data was in accordance with the literature.[40]

^{1}H NMR : δ = 4.23 (1H, m, CH), 4.07 (2H, q, J = 7.2 Hz), 2.43 (1H, dd, J = 7.5, 14.5 Hz), 2.31 (1H, dd, J = 5.4, 14.5 Hz), 1.22 (3H, t, Me, J = 7.2 Hz), 1.16 (3H, d, Me, J = 6.1 Hz), 0.83 (9H, s, 3 x Me), 0.01, 0.30 (2 x 3H, 2 x s, 2 x Me).

^{13}C NMR : δ = 171.66 (C=O), 65.85 (CH), 60.23 (CH_2), 44.95 (CH_2), 25.71 (3 x CH_3), 23.91 (CH_3), 17.93 (C), 14.18 (CH_3). –4.53 (CH_3), -4.76 (CH_3).

FT-IR : ν_{max} ($CHCl_3$) 1739 cm^{-1} (s, C=O str).

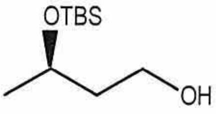
***m/z* (CI)** : 247 (100% $[M+H]^+$), 189 (10% $[M-{}^tBu]^+$), 132 (5%), 92 (5%) daltons.

HRMS : found 247.1729, $C_{12}H_{27}O_3Si$ ($[M+H]^+$) requires 247.1729 daltons.

tlc : R_f = 0.62 (10% ether/petrol)

$[\alpha]^{25}$: -26.4 (*c* 0.35 in $CHCl_3$).

Synthesis of (*R*)-3-((*tert*-butyldimethylsilyl)oxy)butan-1-ol, 35.



35

Ethyl (*R*)-3-((*tert*-butyldimethylsilyl)oxy)butyrate, **34**, (9.14 g, 37.14 mmol) was dissolved in dry hexane, cooled (-78 °C), and diisobutylaluminium hydride (100 ml, 100 mmol) was added dropwise over 30 min. The reaction was allowed to stir overnight, warming slowly to ambient temperature. The reaction was cooled (0 °C) and methanol (6 ml) followed by hexane (100 ml) and saturated ammonium chloride (50 ml). The white precipitate formed was filtered using a sinter and washed with ether (3 x 50 ml). The solid residue was added to water (100 ml) and extracted with EtOAc (3 x 50 ml) and filtered through a pad of Celite. The combined organic fractions were washed with water (2 x 100 ml), dried ($MgSO_4$) and the solvent removed by rotary evaporation to yield the product as an oil (7.2 g, 95 %). Data was in accordance with the literature.[40]

^{1}H NMR : δ = 4.05 (1H, m), 3.76 (1H, m), 3.58 (1H, m), 2.85 (1H, br s, OH), 1.65-1.78 (1H, m), 1.55-1.64 (1H, m), 1.16 (3H, d, Me, J = 6.1 Hz), 0.86 (9H, s, 3 x Me), 0.04, 0.06 (6H, 2 x s, 2 x Me).

^{13}C NMR : δ = 68.29 (CH), 60.40 (CH_2OH), 40.47 (CH_2), 25.78 (3 x CH_3), 23.42 (CH_3), 17.92 (C), -4.38 (CH_3), -4.54 (CH_3).

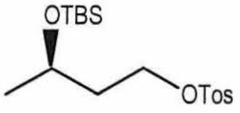
FT-IR : ν_{max} ($CHCl_3$) 3345 cm^{-1} (bs, OH str).

***m/z* (CI)** : 205 (100% $[M+H]^+$), 202 (2%), 132 (5%), 92 (12%), 91 (10%) daltons.

HRMS : found 205.1642, $C_{10}H_{24}O_2Si$ ($[M+H]^+$) requires 205.1624 daltons.

[α]^{25} : -31.9 (*c* 0.41 in $CHCl_3$).

Synthesis of (*R*)-3-((*tert*-butyldimethylsilyl)oxybutan-1-*para*-toluene sulphonate, 36.



36

A solution of (*R*)-3-((*tert*-butyldimethylsilyl)oxy)butan-1-ol, **35**, (15.08 g, 73.86 mmol) in dry pyridine (25 ml) was cooled (0 °C) and treated with a solution of p-toluenesulphonyl chloride (15.49 g, 81.25 mmol) in dry pyridine (25 ml) and the reaction stirred overnight. The solution was diluted with hexane (400 ml) and washed with H_2SO_4 (3 x 200 ml, 2M) and water (2 x 200 ml), dried over $MgSO_4$ and the solvent removed by rotary evaporator to yield the title compound as an oil (22.5 g, 85 %). Data was in accordance with the literature.[40]

^{1}H NMR : δ = 7.79 (2H, d, J = 8.2 Hz), 7.34 (2H, d, J = 8.2 Hz), 4.10 (2H, t, J = 6.1 Hz), 2.89 (1H, m), 2.45 (3H, s, Ph-Me), 1.10 (3H, d, Me, J = 6.1 Hz), 0.82 (9H, s, 3 x Me), 0.02 (6H, s, 2 x Me).

^{13}C NMR : δ = 144.68 (ArC), 133.04 (ArC), 129.81 (2 x ArCH), 127.90 (2 x ArCH), 67.88 (OCH_2), 64.62 (CH), 38.48 (CH_2), 25.73 (3 x CH_3), 23.86 (CH_3), 21.61 (CH_3), 17.86 (C), -4.37 (CH_3), -5.07 (CH_3)

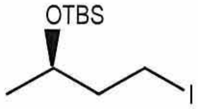
***m/z* (CI)** : 359 (100% $[M+H]^+$), 302 (15% $[MH-{}^tBu]^+$), 301 (10%), 246 (10%), 229 (60%), 227 (30%) $[M-TBSO]^+$), 91 (18%) daltons.

HRMS : found 359.1712, ($[M+H]^+$) $C_{17}H_{31}O_4SiS$ requires 359.1712 daltons.

$[\alpha]^{25}$: -19.3 (*c* 0.46 in $CHCl_3$).

tlc : R_f = 0.28 (5% ether/petrol).

Synthesis of (*R*)-3-((*tert*-butyldimethylsilyl)oxy)-1-iodobutane, 37.



37

To (*R*)-3-((*tert*-butyldimethylsilyl)oxy-butan-1-*para*-toluene sulphonate, **36**, (7.06 g, 19.73 mmol) in dry acetone (260 ml) was added sodium iodide (16.27 g, 108.52 mmol) and the reaction was refluxed for four hours. The reaction was then filtered *via* a sinter and the filter pad washed with ether (300 ml), the solvent was removed by rotary evaporator to give a solid residue. The solid was triturated with hexane (5 x 100 ml), and the hexane was filtered and evaporated to give an oil. Purification by column chromatography (5 % ether/petrol) yielded the product as a clear oil (5.5 g, 89 %). Data was in accordance with the literature.[40]

^{1}H NMR : δ = 3.87 (1H, apparent sextet), 3.23 (2H, dt, J= 7.4, 2.8 Hz), 1.93 (2H, t, J=7.5 Hz), 1.55 (3H, d, J=6.1 Hz), 0.90 (9H, s, 3 x Me), 0.12 (3H, s, Me), 0.11 (3H, s, Me).

^{13}C NMR : δ = 68.25 (CH), 43.23 (CH_2), 25.87 (3 x CH_3), 23.48 (CH_3), 3.69 (CH_2), -4.21 (CH_3), -4.60 (CH_3).

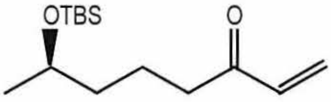
***m/z* (CI)** : 315 (100% $[M+H]^+$), 274 (10%), 189 (38%), 187 (40% $[M-I]^+$), 132 (90% $[M-TBSO]^+$), 92 (18%), 91 (30%) daltons.

HRMS : found 315.0641, ($[M+H]^+$) $C_{10}H_{24}OSiI$ requires 315.0641 daltons.

$[\alpha]^{25}$: -38.9 (*c* 0.37 in $CHCl_3$).

tlc : R_f = 0.81 (5% ether/petrol).

Synthesis of (*R*)-7-oxo-((*tert*-butyldimethylsilyl)oxy)oct-1-ene-3-one, 38.



38

Acetylmethylene triphenylphosphorane (8.26 g, 28.9 mmol) was dissolved in dry THF (140 ml), cooled (-78 °C) whereupon BuLi (2.2 M, 11.9 ml, 26.3 mmol) was added dropwise over 5 min. The deep red solution that formed was then stirred at -60 °C for 1 h. The reaction was then cooled (-78 °C) and (*R*)-3-((*tert*-butyldimethylsilyl)oxy)-1-iodobutane, **37**, (8.26 g, 26.3 mmol) in THF (42 ml) was added and the reaction warmed to ambient temperature by removal of the cooling bath followed by stirring overnight. Water (90 ml) was added and the solution was separated and the aqueous fraction extracted with DCM (3 x 50 ml), dried ($MgSO_4$) and the reaction concentrated by rotary evaporation to approximately 50 ml. Formaldehyde solution was then prepared by adding aqueous formaldehyde (94 ml) to DCM (50 ml) and removing the water with excess $MgSO_4$. The formaldehyde solution was added to the reaction through a funnel containing a cotton wool plug and stirred overnight. The reaction was diluted with ether (60 ml) and washed with water (2 x 60 ml), dried ($MgSO_4$) and the solvent was removed by rotary evaporation. Purification by column chromatography (4 % ether/petrol) gave the title compound as a clear oil (5.34 g, 79 %). Data was in accordance with the literature.[40]

^{1}H NMR : δ = 6.36 (1H, dd, J=10.1, 17.6 Hz), 6.21 (1H, dd, J=1.5, 17.6 Hz), 5.81 (1H, dd, J=1.5, 10.1 Hz), 3.79 (1H, apparent sextet, J=6.0 Hz), 2.57 (2H, t, J=7.3 Hz), 1.37 - 1.73 (4H, cm), 1.14 (3H, d, J=6.1 Hz), 0.88 (9H, s, 3 x Me), 0.05 (6H, s, 2 x Me).

^{13}C NMR : δ = 200.84 (C=O), 136.52 (CH), 127.86 (=CH), 68.34 (CH), 39.67 (CH_2), 39.06 (CH_2), 25.87 (3 x CH_3), 23.70 (CH_3), 20.24 (CH_2), 18.09 (C), -4.41 (CH_3), -4.75 (CH_3).

FT-IR : ν_{max} (neat) 2928-2856 (s, C-H str), 1684 (s, C=O str), 1615.8 (m, C=C str).

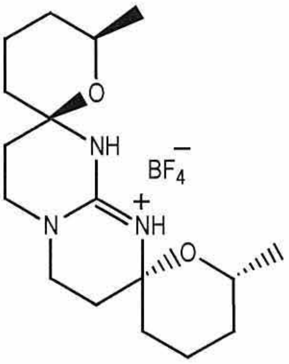
***m/z* (CI)** : 257 (5% $[M+H]^+$), 201 (45% $[MH-{}^tBu]^+$), 132 (50%), 74 (100%) daltons.

HRMS : found 257.1937, ($[M+H]^+$) $C_{14}H_{28}O_2Si$ requires 257.1937 daltons.

$[\alpha]^{25}$: -13.4 (*c* 1.1 in $CHCl_3$).

tlc : $R_f = 0.19$ (2% ethyl acetate/petrol).

Synthesis of (6*R*, 6''*R*, 2*R*, 2''*R*)-6,6''-dimethyldispiro[tetrahydropyran-2,2'-(2,3,4,6,7,8- hexahydro-1H-pyrimido[1,2-a]pyrimidine)-8',2''-tetrahydropyran]-9'-ium tetrafluroborate, 39.



39

All the manipulations using guanidine were carried out under an argon atmosphere and care was taken to keep the reaction vessel under an argon atmosphere. (*R*)-7-oxo-((*tert*-butyldimethylsilyl)oxy)oct-1-ene-3-one (1.99 g, 7.77 mmol) was dissolved in dry DMF (35 ml), cooled (0 °C) and a solution of guanidine in DMF (0.23 g, 3.89 mmol) was added dropwise over 5 min. The reaction was kept at 0 °C for 15 min before being allowed to warm to ambient temperature and stirred overnight. The reaction was then cooled (0 °C) and methanolic HCl (40 ml) added (prepared by slowly adding acetyl chloride (4 ml) to cooled (0 °C) methanol (36 ml)). The reaction was warmed to ambient temperature, and stirred vigorously for 3 h. The reaction was then diluted with DCM (200 ml) and washed with a saturated solution of LiBr (3 x 150 ml) and water (3 x 100 ml). The aqueous washings were backwashed with DCM (50 ml) and the combined organic washings were dried ($MgSO_4$) and the solvent removed by rotary evaporation until approximately 30 ml of solution remained. The organic phase was then added to a saturated solution of $NaBF_4$ (30 ml) and stirred overnight. The organic phase was separated and washed with water (3 x 30 ml) and dried ($MgSO_4$) and the solvent removed by rotary evaporation. Purification by column chromatography (graduated solvent system from neat chloroform to 1.5% methanol/chloroform in 0.25 % steps of 140 ml each) gave the title compound as a solid (670 mg, 44 %). Data was in accordance with the literature.[40]

^{1}H NMR : δ = 7.50 (2H, br s, 2 x NH), 3.84 (2H, ddq, J = 2.1, 11.8, 6.1 Hz, 2 x CH), 3.68 (2H, apparent dt, J = 5.0, 12.4 Hz) 3.22 (2H, ddd, J = 1.6, 5.8, 12.5 Hz), 1.50 - 2.20 (14H, cm), 1.18 (2H, m, 2 x CH), 1.11 (6H, d, J= 6.1 Hz, 2 x CH_3),

^{13}C NMR : δ = 148.40 (Guanidyl CN), 78.86 (2 x C-O), 66.90 (2 x CH), 42.68 (2 x CH_2), 33.57 (2 x CH_2), 33.57 (2 x CH_2), 32.10 (2 x CH_2), 21.72 (2 x CH_3), 17.66 (2 x CH_2).

FT-IR : ν_{max} (in $CHCl_3$) 3378 (bm, NH str), 3034-2944 (s, CH str), 1667 (m, C=N str), 1599 (m, C=N str).

***m/z* (CI)** : 308 (100% $[M-BF_4^-+H]^+$) daltons.

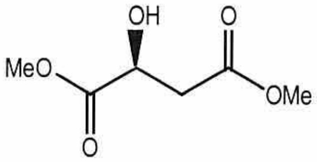
HRMS : found 308.2338, ($[M+H]^+$) $C_{17}H_{30}N_3O_2$ requires 308.2338 daltons.

Mpt : 181 – 182°C

$[\alpha]^{25}$: +45.2 (*c* 0.65 in $CHCl_3$).

tlc : R_f = 0.39 (5% MeOH/$CHCl_3$).

Synthesis of dimethyl (*S*)-malate, 48.

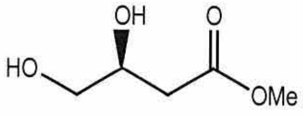


48

(*S*)-(-)-malic acid (54 g, 409 mmol) was added to a methanolic solution, prepared by adding acetyl chloride (17 ml) to MeOH (330 ml). The solution was allowed to stand overnight at room temperature after which the solvent was removed by rotary evaporation. Purification by distillation (132-134 °C, 8.6 mbar) yielded the title compound as a colourless liquid (45.7 g, 70 %). Data was in accordance with the literature.[42]

^{1}H NMR : δ = 4.35 (1H, m), 3.7 (1H, br s), 3.6 (3H, s), 3.5 (3H, s), 2.65 (2H, t, J=5.7 Hz).

Synthesis of methyl-(3*S*)-3,4-dihydroxybutanoate, 49.



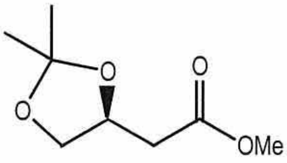
49

Borane-dimethylsulphide complex (2M, 85 ml, 170 mmol) was added to dimethyl (*S*)-malate (27.0 g, 167 mmol) in THF (340 ml) and the reaction stirred for 30 min at room temperature; $NaBH_4$ (0.33 g, 8.6 mmol) was then added and the resulting mixture stirred for a further 30 min. Once the reaction was complete by TLC, dry methanol (100 ml) was added and stirring continued for a further 30 min.

The solvent was removed by rotary evaporation to give a colourless oil that was purified by column chromatography (EtOAc) to give the pure product (20.7 g, 92 %). Data was in accordance with the literature.[42]

^{1}H NMR : δ = 4.2 (1H, br m), 4.0 (OH), 3.9 (OH), 3.6 (3H, s), 3.5 (1H, br m), 3.4 (1H, br m), 2.42 (2H, d, J = 6.6 Hz).

Synthesis of methyl (4*S*)-2,2-dimethyl-1,3-dioxolane-4-acetate, 50.

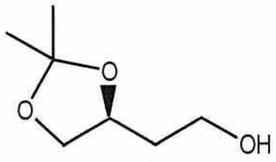


50

2-methoxypropene (11.76 g, 15.6 ml, 163 mmol) was added to a cooled 0 °C solution of methyl-(3*S*)-3,4-dihydroxybutanoate (16.77 g, 125.1 mmol) in DCM (175 ml) together with a catalytic amount of p-toluenesulphonic acid (0.38 g, 2.0 mmol) and the mixture stirred for 1 h. The solvent was then removed by rotary evaporation to give a dark brown oil which was used in subsequent steps without further purification (22.2 g, 102 %). Data was in accordance with the literature.[42]

^{1}H NMR : δ = 4.43 (1H, p, J = 6.2 Hz), 4.11 (1H, dd, J = 6.3 Hz, 6.0 Hz), 3.66 (3H, s), 3.64 (1H, dd, J = 6.3 Hz, 6.6 Hz), 2.66 (1H, dd, J = 6.6 Hz. 7.2 Hz), 2.51 (1H, dd, J = 7.2 Hz), 1.37 (3H, s), 1.32 (3H, s).

Synthesis of (4*S*)-2,2-dimethyl-1,3-dioxolane-4-ethanol, 51.

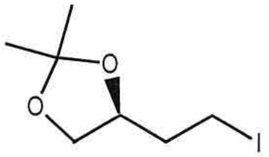


51

To a cooled (0 °C) suspension of $LiAlH_4$ (2.49 g, 92 mmol) in dry ether (200 ml) was added slowly methyl (4*S*)-2,2-dimethyl-1,3-dioxolane-4-acetate (22.2 g, 127 mmol) as a solution in dry ether (200 ml) over 30 min, and the reaction stirred for a further 3 h. When the reaction was complete by TLC it was cooled (0 °C), NH_4Cl sat. (80 ml) added slowly, and the reaction extracted with ether (2 x 30 ml). The organic layers were then combined, dried ($MgSO_4$) and the solvents removed by rotary evaporation. Purification by column chromatography (EtOAc) gave the product as a clear oil (12.2 g, 60 %). Data was in accordance with the literature.[42]

^{1}H NMR : δ = 4.23 (1H, p, J = 5.9 Hz), 4.05 (1H, dd, J = 8.0 Hz, 8.0 Hz), 3.75 (2H, t, J = 5.9 Hz), 3.6 (1H, dd, J = 8.0 Hz, 8.0 Hz), 2.57 (OH), 1.83 (2H, q, J = 6.1 Hz), 1.39 (3H, s), 1.33 (3H, s).

Synthesis of (4*S*)-2,2-dimethyl-1,3-dioxolane-4-iodoethane, 52.



52

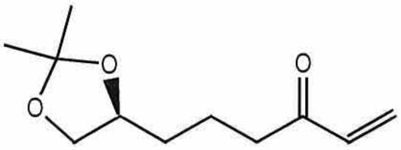
Triphenylphosphine (33.2 g, 126 mmol) and imidazole (8.6 g, 126 mmol) were dissolved in an ether : acetonitrile mixture (3:1, 490 ml) and the reaction cooled (0 °C). Solid iodine (33.1 g, 126 mmol) was then added in portions over 20 min with vigorous stirring. The reaction was then stirred for 10 min at 0 °C, warmed to room temperature (water bath), cooled (0 °C) and (4*S*)-2,2-dimethyl-1,3-dioxolane-4-ethanol (16.8 g, 115 mmol) added dropwise over 15 min. The reaction was then allowed to warm to room temperature and after 1 h the reaction was cooled (0 °C) again and diluted with pentane (400 ml) followed by the addition of $NaHCO_3$ solution (5%, 300 ml), the aqueous layer was washed with pentane (2 x 160 ml) and the organic layers were combined, dried ($MgSO_4$) and the solvent removed by rotary evaporator. The solid obtained was triturated with pentane (2 x 160 ml), filtered and the solvent removed by rotary evaporation to give an oil which was purified by column chromatography (5% ether/petrol) to give the product as an oil (26.8 g, 91 %). Data was in accordance with the literature.[59]

^{1}H NMR : δ = 4.24 - 405 (2H, m, CH_2), 3.60 (1H, apparent t, CH), 3.25 (2H, m, CH_2), 2.10 (2H, m, CH_2), 1.41 (3H, s, Me), 1.36 (3H, s, Me).

^{13}C NMR : δ = 109.17 (C), 75.68 (CH), 68.63 (CH_2), 3786 (CH_2), 26.96 (CH_3), 25.52 (CH_3), 21.21 (CH_2).

$[\alpha]_D$ = -20.1° (*c* 8, $CHCl_3$), lit = -20.8 (*c* 8, $CHCl_3$)

Synthesis of (6*S*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)-hex-1-en-3-one, 53.



53

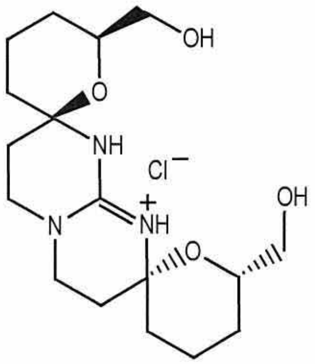
Acetylmethylene triphenylphosphorane (2.73 g, 8.6 mmol) was dissolved in dry THF (40 ml), cooled (-70 °C) and BuLi (2.22 M, 3.87 ml, 8.6 mmol) was then added slowly over 15 min. The reaction was then stirred for 1 h at –50 °C then re-cooled (-78 °C). (4*S*)-2,2-dimethyl-1,3-dioxolane-4-iodoethane (2.05 g, 7.81 mmol) was then added as a solution in THF (3 ml) and the reaction allowed to warm to room temperature over 12 h. Water (40 ml) was added and the mixture extracted with DCM (3 x 20 ml). The organic layers were combined, dried ($MgSO_4$) and the solvent removed by rotary evaporator. Formaldehyde in DCM (prepared by drying ($MgSO_4$) a mixture of aqueous formaldehyde (37 % w/v, 28 ml) and DCM (30 ml)) was added and the reaction stirred for a further 24 h. After washing with water (2 x 30 ml), the organic fraction was dried ($MgSO_4$) and the solvent removed by rotary evaporator. The solid obtained was triturated with ether (5 x 30 ml), and the resulting oil purified by column chromatography (5% ether/petrol) to yield the desired product as a clear oil (1.08 g, 72%).

^{1}H NMR : δ = 6.35 (1H, dd, J = 10.1, 17.7 Hz), 6.20 (1H, dd, J = 1.6, 17.7 Hz), 5.83 (1H, dd, J = 16, 10.1 Hz), 4.07 (2H, m), 3.54 (1H, apparent t, J = 6.7), 2.65 (2H, aparent t, J = 6.8, 7.1 Hz), 1.85 - 1.5 (4H, m), 1.40 (3H, s, Me), 1.35 (3H, s, Me).

^{13}C NMR : δ = 200.3 (C=O), 136.49 (CH), 12809 (CH_2), 108.76 (C), 75.77 (CH), 69.34 (CH_2), 32.94 (CH_2), 26.92 (CH_3), 25.68 (CH_3), 2009 (CH_2).

FT-IR : ν_{max} (thin film) 2985 (s, CH str), 1701 (s, C=O str), 1681 (C=C str), 1369 (s, CH bend).

Synthesis of (6*R*, 6"*R*, 2*R*, 2"*R*)-6,6"-dihydroxymethyldispiro[tetrahydropyran-2,2'-(2,3,4,6,7,8- hexahydro-1H-pyrimido[1,2-a]pyrimidine)-8',2"-tetrahydropyran]-9'-ium tetrafluroborate, 46.



46

(6*S*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)-hex-1-en-3-one (0.5 g, 2.5 mmol) was dissolved in dry DMF (2 ml) and cooled (0 °C); guanidine (0.068 g, 1.2 mmol) as a solution in DMF (5 ml) was then added and the reaction allowed to warm to room temperature over 24 h. Methanolic HCl (7 ml), prepared from acetyl chloride (1 ml) and dry methanol (6 ml), was then added and the reaction stirred for a further 3 h. Removal of the solvent by rotary evaporation followed by column chromatography (graduated solvent system $CHCl_3$, 1%, 3%, 5%, 10%, 15%, 20%, 40% MeOH/$CHCl_3$) collecting the fractions eluting at 15 – 20 % yielded the desired compound as a hygroscopic white solid (0.23 g, 45 %).

^{1}H NMR (D_2O) : δ = 3.88 (4H, m, 2 x CH_2), 3.6 (4H, d, 2 x CH_2), 3.4 (2H, m, 2 x CH), 2.2-1.7 (14H, cm), 1.45 (4H, m, 2 x CH_2).

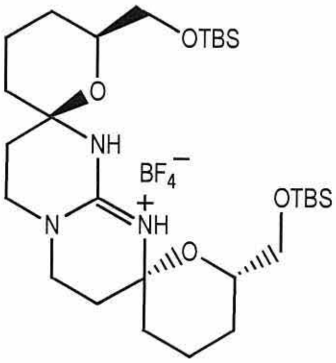
^{13}C NMR : δ = 151.15 (C), 81.17 (C-O), 73.97 (CH), 67.33 (CH_2), 44.57 (CH_2), 35.88 (CH_2), 34.71 (CH_2), 28.56 (CH_2), 20.08 (CH_2).

HRMS : found 340.2236, ($[M]^+$) $C_{17}H_{30}N_3O_4$ requires 340.2236 daltons.

FT-IR : ν_{max} (thin film).

$[\alpha]_D$ = 28.4° (c 0.5, MeOH),

Synthesis of (6*R*, 6''*R*, 2*R*, 2''*R*)-6,6''-di(*t*-butyldimethylsiloxymethyl)dispiro [tetrahydropyran-2,2'-(2,3,4,6,7,8-hexahydro-1H-pyrimido[1,2-a]pyrimidine)-8',2''-tetrahydropyran]-9'-ium tetrafluroborate, 55.



55

(6*S*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)-hex-1-en-3-one (2.84 g, 14.3 mmol) was dissolved in dry DMF (64 ml) and cooled (0 °C), guanidine (403 mg, 6.8 mmol) as a solution in DMF (5 ml) was then added and the reaction allowed to warm to room temperature over 24 h. Methanolic HCl (25 ml), prepared from acetyl chloride (5 ml) and dry methanol (20 ml), was then added and the reaction stirred for a further 4 h. The solvent was removed by rotary evaporator followed by high vacuum and the resulting oil purified by column chromatography (graduated solvent system $CHCl_3$, 3%, 5%, 10%, 15%, 20%, 50%, MeOH/$CHCl_3$) with the fraction eluted at 10% being collected. The purified compound was redissolved in dry DMF (20 ml), the solution cooled (0°C) and TBSCl (3.1 g, 20.6 mmol) followed by imidazole (1.87 g, 27.5 mmol) were added, and the reaction allowed to stir for 24 h with warming to ambient temperature. At the end of this time the reaction was diluted with DCM (30 ml) the organic fraction washed sequentially with water (5 x 30 ml), sat. LiBr solution (1 x 30 ml) and water (1 x 30 ml), the organic layer was dried ($MgSO_4$) and the solvent removed by rotary evaporation to approximately 30 ml of solution. The organic phase was then treated with saturated $NaBF_4$ solution (30 ml) and stirred overnight. The organic phase was separated, washed with water (3 x 30 ml), dried

($MgSO_4$) and the solvent removed by rotary evaporation. Purification by column chromatography (graduated solvent system $CHCl_3$, 0.5%, 1%, 2%, 5%, 10%, 20% MeOH/$CHCl_3$) collecting the fractions eluted at 1 – 5 % MeOH/$CHCl_3$, yielded the desired product as a white solid (1.31 g, 29 %).

^{1}H NMR : δ = 7.45 (2H, Br s, NH), 3.7 (4H, m, 2 x CH_2), 3.51 (4H, d, 2 x CH_2, J = 5.0 Hz), 3.18 (2H, dd, 2 x CH, J = 5.2, 12.3 Hz), 2.0 (4H, m, 2 x CH_2), 1.88 - 1.7 (6H, m, 3 x CH_2), 1.66 - 1.5 (6H, m, 3 x CH_2), 1.2 (2H, m, 2 x CH), 0.85 (18H, s, 6 x CH_3), -0.03 (12H, s, 4 x CH_3).

^{13}C NMR : δ = 148.46 (C, CN_3), 80.57 (C), 78.88 (C), 71.78 (CH), 66.34 (CH_2), 44.93 (CH_2), 33.76 (CH_2), 32.97 (CH_2), 26.24 (CH_2), 25.81 (6 x CH_3) 18.22 (C), 17.09 (CH_2), -5.25 (4 x Si-CH_3).

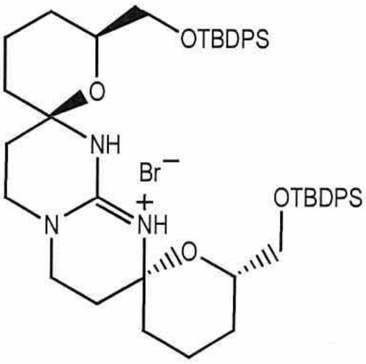
FT-IR : ν_{max} (in $CHCl_3$) = 3370 (NH str), 2953 (CH str), 1660 (NH bend) cm^{-1}

HRMS : found 567.3876, ($[M]^+$) $C_{29}H_{57}N_3O_4Si_2$ requires 567.3888 daltons.

Mpt : 207 – 209 °C (Dec)

[α]^{25} : +46.8 (*c* 0.5 in $CHCl_3$)

Synthesis of (6*R*, 6''*R*, 2*R*, 2''*R*)-6,6''-di(*t*-butyldidiphenylsiloxymethyl)dispiro [tetrahydropyran-2,2'-(2,3,4,6,7,8-hexahydro-1H-pyrimido[1,2-a]pyrimidine)-8',2''-tetrahydropyran]-9'-ium bromide, 56.



(6*S*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)-hex-1-en-3-one (2.97 g, 15 mmol) was dissolved in dry DMF (43 ml) and cooled (0 °C), guanidine (400 mg, 6.8 mmol) as a solution in DMF (5 ml) was then added and the reaction allowed to warm to room temperature over 24 h. Methanolic HCl (30 ml), prepared from acetyl chloride (4 ml) and dry methanol (26 ml), was then added and the reaction stirred for a further 3 h. The solvent was removed by rotary evaporator followed by high vacuum and the resulting oil purified by column chromatography (graduated solvent system $CHCl_3$, 3%, 5%, 10%, 15%, 20%, 50%, MeOH/$CHCl_3$) with the fraction eluted at 10% being collected. The purified compound was redissolved in dry DMF (30 ml), the solution cooled (0 °C) and TBDPSCl (5.61 g, 20.4 mmol) followed by imidazole (1.87 g, 27.2 mmol) added, and the reaction allowed to stir for 28 h with warming to ambient temperature. At the end of this time the reaction was diluted with DCM (30 ml) the organic fraction washed sequentially with water (5 x 30 ml), sat. LiBr solution (1 x 30 ml) and water (1 x 30 ml), the organic layer was dried ($MgSO_4$) and the solvent removed by rotary evaporation. Purification by column chromatography (graduated solvent system $CHCl_3$, 2%, 3%, 4%, 5%, 10%, 15%, 20%,

$MeOH/CHCl_3$) collecting the fractions eluted at 4 – 5 % $MeOH/CHCl_3$, yielded the desired product as a white solid (2.21 g, 36 %).

^{1}H NMR : δ = 9.5 (2H, Br s, NH), 7.68 (4H, m, Ar), 7.4 (6H, m, Ar), 4.1 (2H, m, 2 x CH), 3.65 (6H, m, 3 x CH_2), 3.06 (2H, m, 2 x CH), 2.53 (2H, m), 2.0 - 1.56 (12H, m, 6 x CH_2), 1.3 (2H, m), 1.04 (18H, s, 6 x CH_3).

^{13}C NMR : δ = 148.45 (C, CN_3), 135.60 (CH, Ph), 133.55 (C, Ph), 129.76 (CH, Ph), 127.73 (CH, Ph), 78.92 (C, CNO), 71.75 (CH), 66.89 (CH_2), 42.88 (CH_2), 33.71 (CH_2), 32.95 (CH_2), 26.81 (CH_3), 26.22 (CH_2), 19.32 (C, *t*-Bu), 17.24 (CH_2).

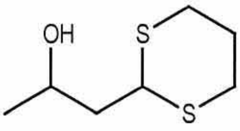
FT-IR : ν_{max} (in $CHCl_3$) = 3360 (NH str), 2947 (CH str), 1664 (NH bend) cm^{-1}

HRMS : found 816.4583, ($[M]^+$) $C_{49}H_{66}N_3O_4Si_2$ requires 816.4592 daltons.

Mpt : +200°C (Dec)

$[\alpha]^{25}$: +44.0 (*c* 0.5 in $CHCl_3$)

Synthesis of ±-1-[1,3]dithian-2-yl-propan-2-ol, 63.

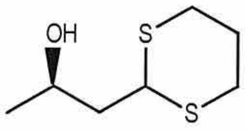


63

To a cooled (-40 °C) solution of dithiane (3.17 g, 26 mmol) in THF (40 ml) was added dropwise BuLi (15.6 ml, 2.5 M, 39 mmol) and the mixture stirred for 2 h at –40 °C, warmed (0 °C) and stirred for another 2 h. The reaction was then cooled (-40 °C) and propylene oxide (1.68 ml, 24 mmol) was added dropwise and the reaction allowed to stir for a further 2 h. A solution of NH_4Cl (sat, 40 ml) was then added and the reaction extracted with EtOAc (3 x 50 ml), the combined organic fractions dried ($MgSO_4$) and the solvent removed by rotary evaporation. Purification by column chromatography (20 %; 40 % EtOAc in Petrol) yielded the desired product as a colourless oil (2.44 g, 53 %).

^{1}H NMR : δ = 4.25 (1H, dd, J = 7.0, 7.4 Hz), 4.13 (1H, br. s, OH), 2.83 - 3.0 (4H, m, 2 x CH_2) 2.15 (1H, m), 1.82 – 2.0 (4H, m, 2 x CH_2), 1.25 (3H, d, J = 7.4 Hz).

Synthesis of (*R*)-1-[1,3]dithian-2-yl-propan-2-ol, 63.



63

To a cooled (-40 °C) solution of dithiane (5.15 g, 42.8 mmol) in THF (40 ml) was added dropwise BuLi (16.6 ml, 2.5 M, 41.4 mmol) and the mixture stirred for 2 h at –40 °C, warmed (0 °C) and stirred for another 2 h. The reaction was then cooled (-40 °C) and (*R*)-(+)-propylene oxide (2.0 ml, 28.5 mmol) was added dropwise and the reaction allowed to stir for a further 2 h followed by slow warming (0 °C). A solution of NH_4Cl (sat. 40 ml) was then added and the reaction extracted with DCM (3 x 50 ml), the combined organic fractions dried ($MgSO_4$) and the solvent removed by rotary evaporation. Purification by column chromatography (20 %; 40 % EtOAc in Petrol) yielded the desired product as a colourless oil (4.87 g, 96 %).

^{1}H NMR : δ = 4.25 (1H, dd, J = 7.0, 7.4 Hz), 4.13 (1H, br. s, OH), 2.83 - 3.0 (4H, m, 2 x CH_2) 2.15 (1H, m), 1.82 – 2.0 (4H, m, 2 x CH_2), 1.25 (3H, d, J = 7.4 Hz).

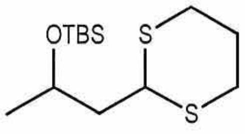
^{13}C NMR : δ = 65.07 (CH-OH), 44.37 (CH_2-CHOH), 44.28 (CHS_2), 30.31 (S-CH_2), 30.12 (S-CH_2), 25.89 (CH_2), 23.57 (CH_3).

FT-IR : ν_{max} (thin film) 3404 (bm, OH str), 2900 (s, CH str).

HRMS : found 178.0485, (M^+) $C_7H_{14}OS_2$ requires 178.0486 daltons.

tlc : R_f = 0.2 (40% EtOAc/petrol).

Synthesis of ±-*tert*-butyl-(2-[1,3]dithian-2-yl-1-methyl-ethoxy)-dimethyl-silane, 64.

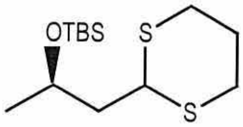


64

To a cooled (0 °C) solution of imidazole (3.3 g, 48.6 mmol) in DMF (17 ml) was added TBSCl (3.7 g, 24.55 mmol), to this mixture was added 1-[1,3]dithian-2-yl-propan-2-ol (3.33 g, 18.7 mmol) and the reaction allowed to warm to ambient temperature overnight. Water (25 ml) was added and the reaction extracted with ether (6 x 20 ml), the combined organic fractions were dried ($MgSO_4$) and the solvent removed by rotary evaporation. Purification by column chromatography (petrol; 10 % ether/petrol) gave the desired product as a colourless oil (4.44 g, 81 %).

^{1}H NMR : δ = 4.05 (2H, m), 2.8-2.69 (4H, m), 2.04 (1H, m), 1.83-1.59 (3H, m), 1.07 (3H, d, J = 6.1 Hz), 0.79 (9H, s), 0.0 (3H, s), -0.02 (3H, s).

Synthesis of *(R)*-*tert*-butyl-(2-[1,3]dithian-2-yl-1-methyl-ethoxy)-dimethyl-silane, 64.



64

To a cooled (0 °C) solution of imidazole (1.99 g, 29.2 mmol) in DMF (10 ml) was added TBSCl (2.2 g, 14.6 mmol), to this mixture was added (*R*)-1-[1,3]dithian-2-yl-propan-2-ol (2.0 g, 11.2 mmol) and the reaction allowed to warm to ambient temperature overnight. Water (20 ml) was added, the reaction extracted with ether (6 x 25 ml), the combined organic fractions dried ($MgSO_4$) and the solvent removed by rotary evaporation. Purification by column chromatography (petrol; 10 % ether/petrol) gave the desired product as a colourless oil (3.13 g, 95 %).

^{1}H NMR : δ = 4.05 (2H, m), 2.8-2.69 (4H, m), 2.04 (1H, m), 1.83-1.59 (3H, m), 1.07 (3H, d, J = 6.1 Hz), 0.79 (9H, s), 0.0 (3H, s), -0.02 (3H, s).

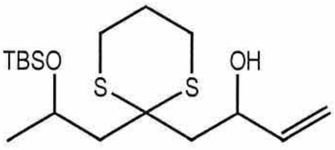
^{13}C NMR : δ = 64.82 (CH-OH), 45.08 (CH_2-CHOH), 44.23 (CHS_2), 30.60 (S-CH_2), 30.04 (S-CH_2), 26.09 (CH_2), 25.88 (3 x CH_3, ^{t}Bu), 23.99 (Me), 18.06 (C, ^{t}Bu), -4.79, -4.36 (2 x Si-CH_3).

HRMS : found 293.1431, ($[M+H]^+$) $C_{13}H_{28}OS_2Si$ requires 293.1429 daltons.

$[\alpha]^{25}$: -27.6 (*c* 1 in $CHCl_3$)

tlc : R_f = 0.55 (10% ether/petrol).

Attempted synthesis of 1-{2-[2-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-[1,3]dithian-2-yl}-but-3-en-2-ol, 65.



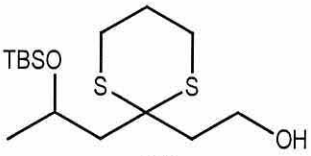
65

To a cooled (-20 °C) solution of the protected alcohol (1 g, 3.42 mmol) in dry THF (20 ml) was added BuLi (1.64 ml, 4.1 mmol), and the reaction allowed to warm to ambient temperature and stirred for 3 h. At the end of this time the reaction was cooled (-15 °C), butadiene monoxide (0.33 ml, 4.1 mmol) added and the reaction stirred for 24 h at -15 °C followed by 2 days at 0 °C. At the end of this time the reaction was diluted with ether (60 ml) and washed with water (3 x 20 ml), NaOH (2M, 15 ml) and brine (3 x 20 ml), the combined organic fractions were dried ($MgSO_4$) and the solvent removed by rotary evaporator. Purification by column chromatography (graduated solvent system petrol, 5 %, 10 %, 20 %, 100 % ether/petrol) gave the desired product eluting at 10 % ether/petrol as an oil (72 mg, 6 %).

^{1}H NMR : δ = 5.91-5.72 (1H, m), 5.3 (1H, dt, J = 1.6, 17.1 Hz), 5.09 (1H, tt, J = 1.6, 10.0 Hz), 4.62-4.42 (1H, m), 4.35-4.2 (1H, m), 2.9-2.68 (4H, m), 2.54-2.0 (5H, m), 1.97 (2H, m), 1.27 (3H, d, Me, J = 6.0 Hz), 0.9 (9H, s, ^{t}Bu), 0.15 (3H, s), 0.1 (3H, s).

HRMS : found 363.1849, (M+H) $C_{17}H_{34}O_2S_2Si$ requires 363.1848 daltons.

Attempted synthesis of 2-{2-[2-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-[1,3]dithian-2-yl}-ethanol, 66.



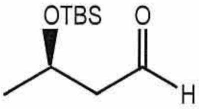
66

To a cooled (-20 °C) solution of the protected alcohol (0.5 g, 1.69 mmol) in dry THF (5 ml) was added BuLi (0.93 ml, 1.86 mmol), the reaction was warmed (0 °C) and stirred for 3 h. The reaction was then cooled (-20 °C) and ethylene oxide bubbled through the stirred reaction mixture for 2 min. After 3 h the reaction was diluted with ether (30 ml) quenched with water (10 ml), the organic fraction washed with brine (10 ml) and the combined aqueous phases were extracted with ether (2 x 10 ml). The combined organic phases were dried ($MgSO_4$) and the solvent removed by rotary evaporation. Purification by column chromatography (graduated solvent system petrol, 5 %, 10 %, 20 %, 100 % ether/petrol) gave the desired product eluting at 20 % ether/petrol as an oil (75 mg, 13 %).

^{1}H NMR : δ = 4.5 (1H, s), 4.18 (1H, m), 3.21 (2H, m), 2.8 (2H, dd, J = 10.1, 15.6 Hz)) 2.5 (2H, m), 2.28 (1H, d, J = 15.6 Hz), 2.09 (1H, m), 1.92 (1H, m), 1.2 (3H, d, J = 6.1 Hz), 1.02 (9H, s), 0.35 (3H, s), 0.25 (3H, s).

^{13}C NMR : δ = 59.9 (CH-OH), 37.86 (CH_2), 32.5 (CS_2), 21.17 (3 x CH_3, ^{t}Bu), 17.26 (CH_2), 16.79 (CH_2), 16.41 (CH_3), 16.15 (CH_2), 12.62 (C), -12.2 (Si-Me), -12.79 (Si-Me).

Synthesis of (*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-butyraldehyde, 69.

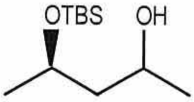


69

A cooled (-78 °C) solution of oxalyl chloride (0.68 ml, 7.8 mmol) in dry DCM (60 ml) was treated with dimethyl sulfoxide (0.97 ml, 13.7 mmol) to give an effervescent mixture which was stirred for 10 min. To this reaction mixture was added (*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-butan-1-ol (0.97 g, 4.9 mmol) and the reaction stirred at –60 °C for 10 min. The reaction was again cooled (-78 °C) triethylamine (4.1 ml, 29.4 mmol) added and the reaction stirred at room temperature for 2 h. The reaction was then diluted with hexane (70 ml), washed with water (2 x 40 ml), AcOH solution (7% v/v, 2 x 40 ml) and brine (2 x 40 ml). The combined aqueous fractions were extracted with DCM (2 x 20 ml), the combined organic fractions were dried ($MgSO_4$) and the solvents removed by rotary evaporation to yield the desired compound as an oil (1g) that was utilised in subsequent reactions without further purification.

^{1}H NMR : δ = 9.8 (1H, s, CHO), 4.37 (1H, m), 2.5 (2H, m), 1.22 (3H, d, J = 6.2 Hz), 0.86 (9H, s), 0.07 (3H, s), 0.05 (3H, s).

Synthesis of (*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-pentan-2-ol, 70.



70

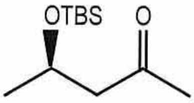
To a cooled (0 °C) solution of (*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-butyraldehyde (6.16 g, 30 mmol) in dry ether (250 ml) was added slowly MeMgBr (20.2 ml, 61.0 mmol) over 20 min. The reaction was allowed to stir for 24 h with slow warming to ambient temperature. At the end of this time the reaction was quenched with NH_4Cl solution (10%, 150 ml), extracted with ether (3 x 150 ml) and washed with brine (2 x 150 ml), the combined organic phases were dried ($MgSO_4$) and the solvent removed by rotary evaporation. Purification by column chromatography (20 % ether/petrol) yielded the desired product as a clear oil (4.57 g, 69 %). Data was in accordance with the literature.[60]

^{1}H NMR : δ = 4.28-3.9 (1H, m), 1.7-1.4 (2H, m), 1.24 (3H, d, J = 6.4 Hz), 1.18 (3H, m), 0.92 (9H, s), 0.85 (1H, OH), 0.1 (6H, s, 2 x Me).

^{13}C NMR : δ = 70.15 (CH-OH), 64.37 (CH-OTBS), 47.45 (CH_2), 25.76 (3 x CH_3, ^{t}Bu), 25.63 (CH_3), 23.69 (CH_3), 17.34 (C), -3.6(Si-Me) –4.89 (Si-Me).

HRMS : found 219.1780, ($[M+H]^+$) $C_{11}H_{26}O_2Si$ requires 219.1780 daltons.

Synthesis of *(R)*-4-(*tert*-Butyl-dimethyl-silanyloxy)-pentan-2-one, 71.



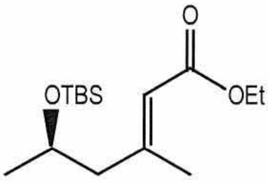
71

Dimethyl sulfoxide (0.51 ml, 7.2 mmol) was added to a cooled (-78 °C) solution of oxalyl chloride (0.36 ml, 4.1 mmol) in dry DCM (30 ml) and the solution stirred for 10 minutes. (*R*)-4-(tert-Butyl-dimethyl-silanyloxy)-pentan-2-ol (0.56 g, 2.6 mmol) was added as a solution in DCM (5 ml) and the reaction stirred for a further 10 min at –60 °C, whereupon the reaction was cooled (-78 °C) and triethylamine (2.14 ml, 15.4 mmol) was added and the reaction stirred at room temperature for 2.5 h. The reaction was quenched with water (20 ml) washed with AcOH solution (5 % v/v, 2 x 20 ml) and brine (2 x 20 ml), the organic fraction was dried ($MgSO_4$) and the solvent removed by rotary evaporator to give the desired product as a brown oil (0.52 g, 86 %) which was used in subsequent steps without further purification. Data was in accordance with the literature.[61]

^{1}H NMR : δ = 4.29 (1H, m), 2.65 (1H, dd, J = 7.3, 15.0 Hz), 2.43 (1H, dd, J = 5.2, 15.0 Hz), 2.15 (3H, s), 1.15 (3H, d, J = 6.1 Hz), 0.86 (9H, s), 0.06 (3H, s), 0.02 (3H, s).

^{13}C NMR : δ = 132.92, (C=O), 65.64 (CH-OTBS), 53.13 (CH_2), 31.63 (3H, CH_3), 25.76 (3 x CH_3, ^{t}Bu), 23.99 (CH_3), 17.96 (C), -3.61(Si-Me) –5.02 (Si-Me).

Attempted synthesis of *(R)*-5-(tert-butyl-dimethyl-silanyloxy)-3-methyl-hex-2-enoic acid ethyl ester, 72.



72

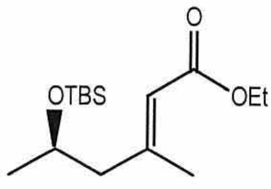
Method 1:

A cooled (0 °C) solution of Triethyl phosphonate (0.64 ml, 3.24 mmol) in THF (6 ml) was treated with BuLi (1.3 ml, 2.78 mmol) and allowed to stir for 1 h at room temperature. The reaction was then cooled (-78 °C) and (*R*)-4-(*tert*-butyl-dimethyl-silanyloxy)-pentan-2-one (0.5 g, 2.3 mmol) as a solution in THF (2 ml) added in a dropwise manner and the reaction allowed to stir for 3.5 h with slow warming to ambient temperature. The reaction was quenched with water (10 ml), extracted with ether (2 x 10 ml), the combined organic fractions dried ($MgSO_4$) and the solvent removed by rotary evaporator. ^1H NMR did not show the desired product.

Method 2:

To a cooled (-40 °C) solution of LDA [prepared by the addition of BuLi (2.0 ml, 5.06 mmol) to diisopropylamine (0.64 ml, 4.6 mol) in dry THF (4 ml) at –40 °C followed by stirring for 0.5 h] and TMEDA (0.69 ml, 0.46 mmol) was added ethyl 3-mercaptoacetate (0.23 ml, 2.1 mmol) as a solution in THF (0.74 ml) and the solution stirred for 1 h. To this solution was added (*R*)-4-(*tert*-butyl-dimethyl-silanyloxy)-pentan-2-one (0.5 g, 2.3 mmol) and the reaction stirred for 2 h, the reaction was cooled (-78 °C) whereupon ethyl chloroformate (0.2 ml, 2.1 mmol) was added as a solution in THF (0.5 ml) and the reaction stirred for 30 min followed by stirring at room temperature for 1 h. The reaction was quenched with NH_4Cl solution (sat, 1 ml), HCl (2M, 6 ml) added and the combined aqueous fractions extracted with ether (4 x 6 ml). The combined organic fractions were washed with brine (2 x 6 ml) dried ($MgSO_4$) and the solvent removed by rotary evaporator. ^1H NMR did not show the desired product.

Synthesis of (*R*)-5-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-hex-2-enoic acid ethyl ester, 72.



72

To a cooled 30 °C) solution of diisopropylamine (0.97 ml, 6.34 mmol) in THF (14 ml) was added BuLi (3.17 ml, 6.97 mmol), and the reaction stirred for 10 min, followed by 10 min at 0 °C. The reaction was cooled (-78 °C), ethyl (trimethylsilyl)acetate (1.44 ml, 7.9 mmol) added and the reaction stirred for 15 min, at which time (*R*)-4-(*tert*-butyl-dimethyl-silanyloxy)-pentan-2-one (1.42 g, 6.57 mmol) was added and the reaction was stirred for a further 3 h with slow warming (–10 °C). The reaction was diluted with ether (15 ml), quenched with water (20 ml), washed with brine (2 x 10 ml), the organic fraction was dried ($MgSO_4$) and the solvent removed by rotary evaporator. Purification by column chromatography (graduated solvent system 1%, 2%, 5% ether/petrol) yielded the desired product as a clear oil (1.29 g, 69 %).

^{1}H NMR : δ = 5.71 (1H, s, CH=C), 4.12 (2H, q, J = 7.0 Hz), 2.9 (1H, dd, J = 4.1, 12.2 Hz), 2.59 (1H, dd, J = 8.2, 12.2 Hz), 1.95 (3H, s), 1.58 (1H, s), 1.26 (3H, t, J = 7.0 Hz), 1.19 (3H, d, J = 6.1 Hz), 0.89 (9H, s), 0.02 (3H, s), 0.0 (3H, s).

^{13}C NMR : δ = 166.34 (C=O), 158.86 (C=C), 117.06 (CH=C), 68.70 (CH-OTBS), 42.99 (CH_2), 27.35 (CH_3), 25.82 (3 x CH_3, ^{t}Bu), 24.17 (CH_3), 17.97 (C, ^{t}Bu), 14.30 (CH_3), -4.6, -4.8 (2 x Si-CH_3).

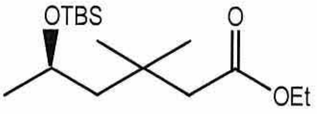
HRMS : found 287.2043, ($[M+H]^+$) $C_{15}H_{30}O_3Si$ requires 287.2042 daltons.

FT-IR : ν_{max} (thin film) 2956 (s, CH str), 1718 (s, C=O str), 1649 (s, C=C str).

$[\alpha]^{25}$: -45.1 (*c* 1 in $CHCl_3$)

tlc : R_f = 0.55 (10% ether/petrol).

Attempted synthesis of (*R*)-5-(*tert*-butyl-dimethyl-silanyloxy)-3,3-dimethyl-hexanoic acid ethyl ester, 73.



73

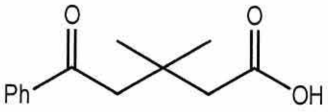
Method 1:

A cooled (0°C) solution of copper iodide (0.133 g, 0.7 mmol) in dry ether (2.6 ml) and MeLi (1.4 ml, 0.7 mmol) added dropwise resulting in a clear pale yellow solution. The reaction was cooled (-78°C) and R-5-(tert-Butyl-dimethyl-silanyloxy)-3-methyl-hex-2-enoic acid ethyl ester (0.2 g, 0.7 mmol) added as a solution in dry ether (1 ml) over a period of 3 minutes and the reaction stirred for 3 h with slow warming (–5°C). At the end of this time NH_4Cl solution (sat. 10 ml) was added followed by stirring in air during which time the colour of the aqueous layer becomes blue. The organic layer was separated, dried ($MgSO_4$) and the solvent removed by rotary evaporator to give an oil. ^1H NMR did not indicate the presence of the desired product.

Method 2:

To a cooled (0 °C) solution of $MnCl_2$ (0.33 g, 2.6 mmol) in THF (1.5 ml) was added MeMgCl (0.87 ml, 2.6 mmol) and the reaction stirred for 10 minutes, at this time CuCl (17.5 mg, 0.13 mmol) was added and the reaction cooled (-30 °C). To this reaction was added dropwise (*R*)-5-(*tert*-butyl-dimethyl-silanyloxy)-3-methyl-hex-2-enoic acid ethyl ester (0.371 g, 1.29 mmol) over 10 minutes. The reaction was warmed (0 °C) over a period of 10 minutes and stirred for 1 h. At the end of this time the reaction was diluted with ether (10 ml), NH_4Cl solution (sat. 5 ml) added and the reaction extracted with ether (2 x 10 ml). The combined organic fractions were dried ($MgSO_4$) and the solvent removed by rotary evaporator. ^1H NMR did not indicate the presence of the desired product.

Preparation of 3,3-dimethyl-5-oxo-5-phenyl-pentanoicacid, 83.



83

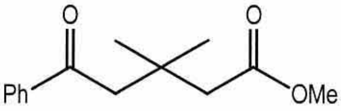
A solution of 3,3-dimethylglutaric anhydride (25 g, 176 mmol) in anhydrous benzene (75 ml) was added slowly to a stirred suspension of crushed anhydrous aluminium chloride (50 g, 375 mmol) in dry benzene (125 ml). The mixture was heated to reflux for 3 h and was carefully hydrolyzed at the end of this time with a solution of concentrated HCl (75 ml) in water (75 ml). The benzene layer was diluted with ether (150 ml) and washed with saturated sodium bicarbonate solution (4 × 100 ml). Acidification of the alkaline extract to pH 1 gave an oil which was taken up in ether (50 ml), washed with brine (100 ml) and dried ($MgSO_4$). The solvent was removed by rotary evaporator to give an oil (30.5 g, 79%). The data was in accordance with the literature.[62]

^{1}H NMR : δ = 11.3 (1H, br. s, OH), 8.0 (2H, d, aromatic), 7.5 (3H, m, aromatic), 3.2 (2H, s, CH_2), 2.6 (2H, s), 1.2 (6H, s, 2×Me).

^{13}C NMR : δ = 200.68 (C, PhC=O), 176.27 (C, COOH), 137.89 (C, Ph), 133.21 (CH, Ph), 128.58 (CH, Ph), 128.22 (CH, Ph), 46.75 (CH_2, $PhCOCH_2$), 33.23 (CH2, CH_2COOH), 28.52 (CH_3, 2× Me).

FT-IR : ν_{max} (thin film) 3060 (br, OH str), 2960 (CH str, alkane), 1704 (S, C=O str).

Preparation of 3,3-dimethyl-5-oxo-5-phenyl-pentanoicacid-methylester, 84.



84

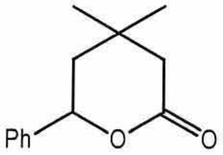
3,3-dimethyl-5-oxo-5-phenyl-pentanoic acid (10.1 g, 0.046 mole) was added to MeOH/HCl (100 ml), prepared by adding AcCl (10 ml) to dry MeOH (90 ml) at 0 °C, and stirred at room temperature for 3 h. The solvent was then removed by rotary evaporation and the product was redissolved in DCM (25 ml), washed with saturated $NaHCO_3$ (2 × 20 ml), dried ($MgSO_4$) and the solvent removed by rotary evaporator to give an oil (6.53 g, 61 %). Data was in accordance with the literature.[63]

^{1}H NMR : δ = 3.6 (3H, S, CH_3); 3.1 (2H, S, CH_2O; 2.6 (2H, S, CH_2); 1.2 (6H, S, 2×CH_3).

^{13}C NMR : δ = 199.6 (C); 172,6 (C); 138.2 (C); 132.8 (CH); 128.5 (CH); 127.9 (CH); 51.1 (CH_3); 47.1 (CH_2); 44.7 (CH_2); 32.9 (C); 28.3 (2×CH_3).

FT-IR : ν_{max} (thin film) 2953.6cm-1 (CH str), 1733.9cm-1 (C=O str., carbonyl), 1686.5cm-1 (C=O str., ester).

Preparation of ±-4,4-dimethyl-6-phenyl-tetrahydro-pyran-2-one, 86.

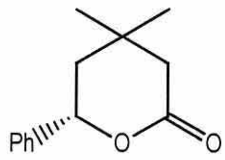


86

3,3-dimethyl-5-oxo-5-phenyl-pentanoic acid-methyl ester (6.0 g, 26 mmol) was dissolved in dry methanol (120 ml) and cooled (0 °C), $NaBH_4$ (2.5 g, 66 mmol) was then slowly added, and the reaction was stirred for 2 h. The reaction was then diluted with ether (80 ml), washed with brine (2 × 75 ml), dried ($MgSO_4$), and the solvent removed by rotary evaporator give an oil. Purification by column chromatography (15 % EtOAc / Petrol) gave a white solid (3.1 g, 58 %).

Mpt : 50-51°C (Lit : 50-51°C)[64]

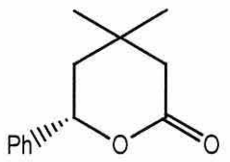
Attempted preparation of (*S*)-4,4-dimethyl-6-phenyl-tetrahydro-pyran-2-one, 86.



86

9-BBN-H-dimer (2.27 g) and (*S*)-(-)-α-pinene were heated at 65 °C for 6 h, the mixture was then cooled (0 °C), treated with 3,3-dimethyl-5-oxo-5-phenyl-pentanoicacid-methyl ester (1.95 g, 8.3 mmol) in a dropwise manner and the resulting solution was left to stir at room temperature for 4 h. The reaction was then diluted with ether (10 ml), followed by addition of ethanolamine (1.3 ml), and left to stir for 30 min at which time Camphor-sulphonic-acid (150 mg) and DCM (15 ml) were added. The mixture was stirred for 45 min and the reaction was then washed with dilute HCl (2 × 15 ml) and dried ($MgSO_4$) and the solvent was removed by rotary evaporation. The proton NMR did not show the expected compound.

Preparation of (*S*)-4,4-dimethyl-6-phenyl-tetrahydro-pyran-2-one, 86.



86

(*R*)-2-Methyl-CBS-oxazaborolidine (0.93 g) as a solution in THF (5 ml) was cooled (0 °C) and 3,3-dimethyl-5-oxo-5-phenyl-pentanoicacid methyl ester (1.03 g, 4.4 mmol) in THF (5 ml) and BH_3·THF complex were added simultaneously and the reaction left to stir for 45 min. The reaction was then quenched with water (15 ml) and extracted with ether (2×10 ml), washed with brine (2×15 ml) and dried ($MgSO_4$) and the solvent removed. The isolated oil was redissolved in DCM (15 ml) and a small amount of Camphor-sulphonic-acid was added and the reaction stirred for 48 h. The reaction was washed with water (2 × 15 ml), dried ($MgSO_4$) and the solvent removed. Purification by column chromatography (20 % EtOAc /Petrol) gave a white solid (0.64 g, 71 %).

^{1}H NMR : δ = 7.3 (5H, m, aromatic); 5.4 (H, dd, CH); 2.43 (2H, dd, 2×CH); 1.9 (2H, m, CH_2); 1.2 (3H, S, CH_3); 1.1 (3H, S, CH_3).

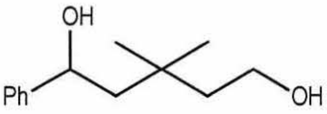
^{13}C NMR : δ = 128.6 (CH, Ph); 128.2 (CH, Ph); 125.7 (CH, Ph); 78.9 (CH, PhCH); 45.1 (CH_2, CH_2CO); 43.9 (CH_2); 31.0 (CH_3); 30.2 (C, CMe_2); 27.4 (CH_3).

HRMS (CI): found 205.1228, ($[M+H]^+$) $C_{13}H_{16}O_2$ requires 205.1228.

$[\alpha]_D^{19}$ = -16.00 (*c* 1, $CDCl_3$)

e.e = >92 % e.e. (by NMR)

Preparation of ± 3,3-dimethyl-1-phenyl-pentane-1,5-diol, 87.



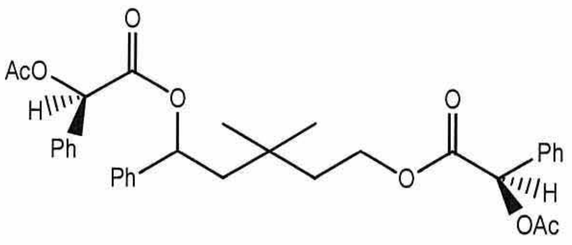
87

To a cooled (-78 °C) solution of 4,4-dimethyl-6-phenyl-tetrahydro-pyran-2-one (200 mg, 0.98 mmol) in dry DCM (4 ml) was added DIBAL (2.3 ml, 2.3 mmol) and the reaction was left to stir for 2 h, at which point a further portion of DIBAL (4.6 ml, 4.6 mmol) was added and the reaction stirred for 18 h with warming to ambient temperature. The reaction was once more cooled (-78 °C) and a further portion of DIBAL (1.5 ml, 1.5 mmol) added and the reaction left to stir for a further 72 h with warming to ambient temperature. At this time the reaction was diluted with EtOAc (10 ml) and sat. NH_4Cl (15 ml) added. The suspension was filtered through a plug of Celite, washed through with EtOAc (10 ml), dried ($MgSO_4$) and the solvent removed. Purification by column chromatography (using a graduated solvent system 20%, 30% EtOAc/Petrol) gave the product as an oil (0.20 g, 99 %).

^{1}H NMR : $\delta = 7.3$ (5H, m, Ph); 4.9 (H, dd, CH), 3.8 (2H, m, CH_2OH); 2.45 (2H, s, 2×OH); 2.0 (2H, m, CH_2); 1.5 (2H, dd, CH_2); 1.1 (3H, s, Me); 0.9 (3H, s, Me).

^{13}C NMR : $\delta = 146.55$ (C); 128.46 (CH); 127.26 (CH); 125.56 (CH); 72.01 (CH); 59.73 (CH_2); 50.55 (CH_2); 43.43 (CH_2); 32.5 (C); 28.77 (Me); 28.86 (Me).

Preparation of (*R*)-O-acetyl mandelic acid derivates of ±3,3-dimethyl-1-phenyl pentane-1,5-diol, 88.



88

To a cooled (0 °C) solution of (*R*)-O-acetyl mandelic acid (407 mg, 2.1 mmol), 3,3-dimethyl-1-phenyl-pentane-1,5-diol (140mg, 0.7mmol) and catalytic 4-(dimethylamino)-pyridine in DCM (2 ml), was added dropwise dicyclohexylcarbodiimide as a solution in DCM (2 ml) and the reaction stirred overnight at room temperature. The white precipitate of dicyclohexylurea was removed by filtration and the filtrate washed with water (10ml), dilute copper (II) sulphate solution (10 ml), dried ($MgSO_4$) and the solvent removed by rotary evaporation. The product was purified by column chromatography (20 % Ether/Petrol) to give a solid (250mg, 66%).

Selected data for (*R*)-3,3-dimethyl-1-phenyl pentane-1,5-bis(*R*)-O-acetyl mandelate.

^{1}H NMR : $\delta = 0.98$ (s, CH_3).

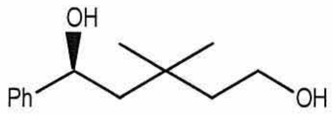
$\delta = 0.92$ (s, CH_3).

Selected data for (*S*)-3,3-dimethyl-1-phenyl pentane-1,5-bis(*R*)-O-acetyl mandelate.

^{1}H NMR : $\delta = 0.66$ (s, CH_3).

$\delta = 0.59$ (s, CH_3).

Preparation of (*S*)-3,3-dimethyl-1-phenyl-pentane-1,5-diol, 89.



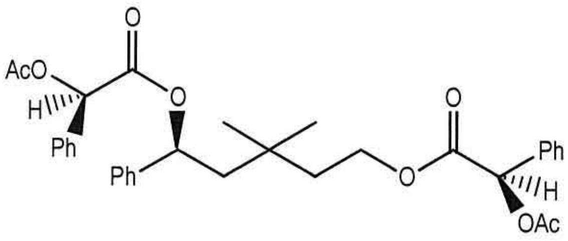
89

To a cooled (-78 °C) solution of (*S*)-4,4-dimethyl-6-phenyl-tetrahydro-pyran-2-one (200 mg, 0.98 mmol) in dry DCM (4 ml) was added DIBAL (6.0 ml, 6.0 mmol) and the reaction left to stir for 72 h with warming to ambient temperature. At this time the reaction was diluted with EtOAc (10 ml) and saturated NH_4Cl (15 ml) added. The suspension obtained was filtered through a plug of celite, washed with EtOAc (10 ml), the combined organic fractions dried ($MgSO_4$) and the solvent removed. Purification by column chromatography (using a graduated solvent system 20%, 30% EtOAc/Petrol) gave the product as an oil (0.19 g, 95 %).

^{1}H NMR : δ = 7.3 (5H, m, Ph); 4.9 (H, dd, CH), 3.8 (2H, m, CH_2OH); 2.45 (2H, s, 2×OH); 2.0 (2H, m, CH_2); 1.5 (2H, dd, CH_2); 1.1 (3H, s, Me); 0.9 (3H, s, Me).

^{13}C NMR : δ = 146.55 (C); 128.46 (CH); 127.26 (CH); 125.56 (CH); 72.01 (CH); 59.73 (CH_2); 50.55 (CH_2); 43.43 (CH_2); 32.5 (C); 28.77 (Me); 28.86 (Me).

Preparation of (*R*)-O-acetyl mandelic acid derivates of (*S*)-3,3-dimethyl-1-phenyl-pentane-1,5-diol, 90.



90

To a cooled (0 °C) solution of (*R*)-O-acetyl mandelic acid (428 mg), (*S*)-3,3-dimethyl-1-phenyl-pentane-diol (150 mg, 0.73 mmol) and catalytic 4-(dimethylamino)-pyridine in DCM (2 ml), was added dropwise dicyclohexylcarbodiimide (454 mg, 2.2 mmol) in DCM (2 ml) and the reaction stirred overnight at room temperature. The white precipitate of dicyclohexylurea was removed by filtration and the filtrate washed with water (10ml), dilute copper (II) sulphate solution (10 ml), dried ($MgSO_4$) and the solvent removed by rotary evaporation. The product was purified by column chromatography (20 % Ether/Petrol) to give a solid (256 mg, 61%).

Selected data for (*R*)-3,3-dimethyl-1-phenyl pentane-1,5-bis(*R*)-O-acetyl mandelate.

^{1}H NMR : $\delta = 0.98$ (s, CH_3).

$\delta = 0.92$ (s, CH_3).

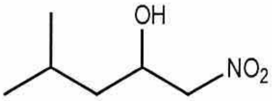
Selected data for (*S*)-3,3-dimethyl-1-phenyl pentane-1,5-bis(*R*)-O-acetyl mandelate.

^{1}H NMR : $\delta = 0.66$ (s, CH_3).

$\delta = 0.59$ (s, CH_3).

ee = 92 % (96:4) (*c* 1, $CDCl_3$)

General procedure for the catalysis of the nitroaldol reaction to give 1-nitro-4-methyl-2-pentanol, 97.



97

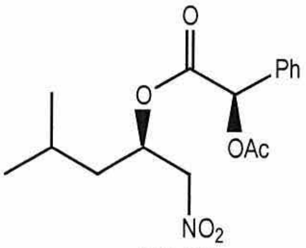
To the guanidine base (0.25 mmol, 0.1 eq) in dry methanol (3 ml) was added sodium methoxide (8.6 mg, 0.22 mmol) as a solution in dry methanol, and the solution stirred for 30 min. The solvent was then removed under vacuum and the solid dried under high vacuum. The solid free base was dissolved in the solvent of choice (3 ml), isovaleraldehyde (0.16 ml, 2.3 mmol, 1.0 eq) added and the solution brought to the required temperature. To the solution was added nitromethane (0.18 ml, 3.41 mmol, 1.5 eq) and the reaction monitored by a combination of tlc (Rf 0.31 in 20 % EtOAc/Petrol) and GC (Rf 3.31min over 50-170°C at 30°C/min). When the reaction was complete the solution was diluted with DCM (10 ml), washed with HCl (2 M, 5 ml), followed by H_2O (2 x 5 ml) the organic layer was then dried over $MgSO_4$ and the solvent removed by rotary evaporation. The product was purified by column chromatography 20 % EtOAc/Petrol. Data was in accordance with the literature.[65]

^{1}H NMR : δ = 4.40 (3H, m, CH+CH_2), 2.58 (1H, Br s, OH), 1.85 (1H, m, C*H*HCHOH), 1.52 (1H, m, CH*H*CHOH), 1.24 (1H, m, Me_2C*H*), 0.98 (3H, d, J=3.7 Hz, Me), 0.96 (3H, d, J=3.6 Hz, Me).

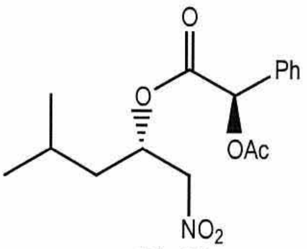
^{13}C NMR : δ = 80.98, 66.94, 42.40, 24.29, 23.15, 21.73.

m/z (CI) = 130 (M^+-OH).

Preparation of the (*R*)-*O*-acetylmandelic acid derivatives of 1-nitro-4-methyl-2-pentanol 30 and 31.



(*R*)-**98**



(*S*)-**98**

To a solution of 1-nitro-4-methyl-2-pentanol (70 mg, 0.49 mmol) in dry DCM (1 ml) was added (*R*)-*O*-acetylmandelic acid (140 mg, 0.72 mmol) and DMAP (10 mg) as a solution in dry DCM (1ml). The solution was cooled (0 °C), and a solution of DCC (148 mg, 0.72 mmol) in dry DCM (1 ml) added. The reaction was stirred for 17 h, resulting in a white precipitate. The reaction was filtered through a cotton wool plug, and the solvent removed *via* rotary evaporation. The resulting solid was triturated with ether (4 x 8 ml) and filtered through a plug of silica. The organic layer was washed with water (5ml), sat. $NaHCO_3$ (5 ml) and water (5 ml), dried ($MgSO_4$) and the solvent removed by rotary evaporator, yielding a yellow oil (58 mg, 47 %), consisting of a diastereomeric mixture.

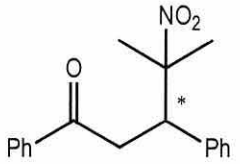
Selected data for (*R*)-**98**.

^{1}**H NMR** : $\delta = 4.52$ (AB of an ABX, CH_2, $J_{AB} = 13$ Hz, $J_{AX} = 6.5$ Hz, $J_{BX} = 5$ Hz).

Selected data for (*S*)-**98**.

^{1}**H NMR** : $\delta = 4.38$ (d, CH_2, J = 6 Hz).

General procedure for the catalysis of the nitro-Michael reaction to 4-methyl-4-nitro-1,3-diphenyl-pentan-1-one, 101.



To a solution of the appropriate guanidine base (0.126 mmol, 0.1 equiv.) in the desired dry solvent (2 ml) was added KO*ᵗ*Bu (0.09 equiv.) and the reaction stirred for 5 minutes. The reaction was then adjusted to the desired temperature and 2-nitropropane (0.26 ml, 2.9 mmol, 2.3 equiv.) followed by chalcone (0.26 g, 1.26 mmol, 1 equiv.) added. The reaction was stirred at the desired temperature and monitored by TLC (Rf = 0.3 in 30 % Et_2O/petrol) visualised by a combination of UV and PMA. When complete the reaction was diluted with DCM (5 ml) washed with water (5 ml), the organic fraction was dried ($MgSO_4$) and the solvent removed by rotary evaporation to give a solid. Purification by column chromatography (30 % 30 % Et_2O/petrol) gave the desired product as a white solid (262 mg, 70 %). Data was in accordance with the literature.[32]

^{1}H NMR : δ = 7.87 (2H, d, Ar-H); 7.6-7.4 (3H, m, Ar-H); 7.28 (5H, d, Ar-H); 4.19 (1H, dd, J = 3.4, 10.4 Hz); 3.7 (1H, dd, J =10.4, 17.1 Hz); 3.3 (1H, dd, J = 3.4, 17.1 Hz); 1.65 (3H, s, Me); 1.56 (3H, s, Me).

^{13}C NMR : δ = 196.71 (C, C=O); 137.86 (C, Ar); 136.60 (C, Ar); 133.23 (CH, Ar); 129.23 (CH, Ar); 128.61 (CH, Ar); 128.44 (CH, Ar); 128.22 (CH, Ar); 127.96 (CH, Ar); 127.76 (CH, Ar); 91.21(C, C-NO_2); 48.96 (CH); 39.09 (CH_2); 26.19 (CH_3); 22.59 (CH_2).

HRMS (CI): found 287.1400, ($[M+NH_4]^+$) $C_{16}H_{15}NO_2$ requires 287.1396.

Mpt : 145-147°C (lit. 146-148°C).

Chapter 6

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Chapter 7

Appendix

5.1 Data for crystal structure of lactone 78.

Table 1. Crystal data and structure refinement for scoles.

Contact	Simon Parsons, S.Parsons@ed.ac.uk
A. CRYSTAL DATA	
Empirical formula	C13 H16 O2 C13 H16 O2
Formula weight	204.27
Wavelength	1.54180 A
Temperature	293 K
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 6.1132(5) A alpha = 90 deg. b = 12.8140(11) A beta = 90 deg. c = 14.6438(11) A gamma = 90 deg.
Volume	1147.1 A^3
Number of reflections for cell	0 (0 < theta < 0 deg.)
Z	4
Density (calculated)	1.183 Mg/m^3
Absorption coefficient	0.623 mm^-1
F(000)	441.286
B. DATA COLLECTION	
Crystal description	Colourless block
Crystal size	0.66 x 0.57 x 0.46 mm
Instrument	
Theta range for data collection	4.59 to 69.74 deg.
Index ranges	-6<=h<=6, -15<=k<=15, -10<=l<=17

Reflections collected	4223
Independent reflections	2095 [R(int) = 0.10]
Scan type	\w/2\q
Absorption correction	Gaussian integration (Tmin= 0.695, Tmax=0.818)

C. SOLUTION AND REFINEMENT.

Solution	direct (SIR92)
Refinement type	Full-matrix least-squares on F
Program used for refinement	CRYSTALS
Hydrogen atom placement	geom
Hydrogen atom treatment	noref
Data	1896
Parameters	138
Goodness-of-fit on F^2	1.0552
R	0.0406
Rw	0.0441
Absolute structure parameter	-0.07(12)
Extinction coefficient	54.8(108)
Final maximum delta/sigma	0.000330
Weighting scheme	Chebychev Polynomial
Largest diff. peak and hole	0.25 and -0.23 e.A^-3

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

	x	y	z	U(eq)
O(1)	2360(2)	6655(1)	6648(1)	61
C(1)	1859(3)	5869(1)	7226(1)	63
O(2)	3079(3)	5132(1)	7267(1)	89
C(2)	-246(3)	5983(1)	7736(1)	68
C(3)	-539(2)	7059(1)	8191(1)	57
C(4)	661(4)	7060(1)	9107(1)	82
C(5)	-2951(3)	7241(2)	8350(2)	88
C(6)	437(3)	7909(1)	7566(1)	63
C(7)	841(2)	7531(1)	6606(1)	52
C(8)	1852(2)	8329(1)	5977(1)	51
C(9)	723(3)	8639(1)	5204(1)	61
C(10)	1613(3)	9387(1)	4624(1)	74
C(11)	3620(3)	9799(1)	4801(1)	74
C(12)	4770(3)	9491(1)	5577(1)	71
C(13)	3872(2)	8762(1)	6164(1)	61

Table 3. Bond lengths [A] and angles [deg] for scoles.

O(1)-C(1)	1.3502(16)
O(1)-C(7)	1.4586(15)
C(1)-O(2)	1.205(2)
C(1)-C(2)	1.495(2)
C(2)-C(3)	1.5416(19)
C(2)-H(21)	0.998
C(2)-H(22)	1.001
C(3)-C(4)	1.529(2)
C(3)-C(5)	1.511(2)
C(3)-C(6)	1.5433(18)
C(4)-H(41)	1.000
C(4)-H(42)	0.998
C(4)-H(43)	1.001
C(5)-H(51)	0.997
C(5)-H(52)	0.999
C(5)-H(53)	1.002
C(6)-C(7)	1.5074(19)
C(6)-H(61)	0.998
C(6)-H(62)	1.003
C(7)-C(8)	1.5089(16)
C(7)-H(71)	1.001
C(8)-C(9)	1.3832(18)
C(8)-C(13)	1.381(2)
C(9)-C(10)	1.392(2)
C(9)-H(91)	0.998
C(10)-C(11)	1.360(3)
C(10)-H(101)	0.998
C(11)-C(12)	1.393(2)
C(11)-H(111)	0.998
C(12)-C(13)	1.383(2)
C(12)-H(121)	0.999
C(13)-H(131)	0.999
C(1)-O(1)-C(7)	117.1(1)
O(1)-C(1)-O(2)	118.35(14)
O(1)-C(1)-C(2)	115.89(12)
O(2)-C(1)-C(2)	125.71(13)
C(1)-C(2)-C(3)	113.74(11)
C(1)-C(2)-H(21)	108.419
C(3)-C(2)-H(21)	108.501
C(1)-C(2)-H(22)	108.221
C(3)-C(2)-H(22)	108.363
H(21)-C(2)-H(22)	109.551
C(2)-C(3)-C(4)	108.91(12)
C(2)-C(3)-C(5)	108.55(13)
C(4)-C(3)-C(5)	109.47(14)
C(2)-C(3)-C(6)	109.30(11)
C(4)-C(3)-C(6)	109.50(12)
C(5)-C(3)-C(6)	111.07(13)
C(3)-C(4)-H(41)	109.381
C(3)-C(4)-H(42)	109.466
H(41)-C(4)-H(42)	109.634

C(3)-C(4)-H(43)	109.321
H(41)-C(4)-H(43)	109.431
H(42)-C(4)-H(43)	109.595
C(3)-C(5)-H(51)	109.473
C(3)-C(5)-H(52)	109.346
H(51)-C(5)-H(52)	109.794
C(3)-C(5)-H(53)	109.199
H(51)-C(5)-H(53)	109.567
H(52)-C(5)-H(53)	109.446
C(3)-C(6)-C(7)	112.9(1)
C(3)-C(6)-H(61)	108.814
C(7)-C(6)-H(61)	108.717
C(3)-C(6)-H(62)	108.535
C(7)-C(6)-H(62)	108.440
H(61)-C(6)-H(62)	109.370
O(1)-C(7)-C(6)	108.2(1)
O(1)-C(7)-C(8)	106.64(9)
C(6)-C(7)-C(8)	114.7(1)
O(1)-C(7)-H(71)	113.938
C(6)-C(7)-H(71)	105.885
C(8)-C(7)-H(71)	107.619
C(7)-C(8)-C(9)	119.32(11)
C(7)-C(8)-C(13)	121.17(11)
C(9)-C(8)-C(13)	119.51(12)
C(8)-C(9)-C(10)	120.13(14)
C(8)-C(9)-H(91)	120.030
C(10)-C(9)-H(91)	119.837
C(9)-C(10)-C(11)	120.24(14)
C(9)-C(10)-H(101)	119.887
C(11)-C(10)-H(101)	119.877
C(10)-C(11)-C(12)	120.04(13)
C(10)-C(11)-H(111)	119.989
C(12)-C(11)-H(111)	119.967
C(11)-C(12)-C(13)	119.86(14)
C(11)-C(12)-H(121)	119.959
C(13)-C(12)-H(121)	120.184
C(8)-C(13)-C(12)	120.20(13)
C(8)-C(13)-H(131)	119.968
C(12)-C(13)-H(131)	119.832

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for scoles.

The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	77(1)	44(1)	61(1)	4(1)	10(1)	6(1)
C(1)	87(1)	43(1)	61(1)	1(1)	1(1)	0(1)
O(2)	114(1)	55(1)	97(1)	15(1)	15(1)	21(1)
C(2)	87(1)	50(1)	67(1)	3(1)	6(1)	-12(1)
C(3)	65(1)	51(1)	55(1)	3(1)	6(1)	-2(1)
C(4)	107(1)	74(1)	65(1)	0(1)	-8(1)	-8(1)
C(5)	74(1)	85(1)	104(1)	23(1)	15(1)	5(1)
C(6)	78(1)	48(1)	63(1)	-2(1)	15(1)	-4(1)
C(7)	57(1)	46(1)	55(1)	3(1)	-2(1)	-1(1)
C(8)	62(1)	42(1)	50(1)	0(1)	1(1)	2(1)
C(9)	73(1)	56(1)	53(1)	-2(1)	-4(1)	3(1)
C(10)	104(1)	62(1)	55(1)	7(1)	-3(1)	7(1)
C(11)	113(1)	49(1)	60(1)	3(1)	21(1)	-2(1)
C(12)	74(1)	56(1)	82(1)	-1(1)	12(1)	-13(1)
C(13)	64(1)	56(1)	63(1)	6(1)	-3(1)	-4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for scoles.

	x	y	z	U(eq)
H(21)	-301	5436	8221	81
H(22)	-1479	5874	7297	81
H(41)	480	7756	9406	99
H(42)	41	6505	9508	99
H(43)	2253	6923	9001	99
H(51)	-3167	7936	8644	106
H(52)	-3539	6680	8755	106
H(53)	-3736	7224	7749	106
H(61)	1854	8150	7831	75
H(62)	-611	8511	7540	75
H(71)	-630	7346	6353	63
H(91)	-734	8327	5062	73
H(101)	775	9624	4077	88
H(111)	4271	10320	4373	88
H(121)	6241	9796	5707	85
H(131)	4689	8548	6724	73