Remote Asymmetric Induction

by

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Dedicated to my parents Morag and Terrence Smith, my wife Candace Glendenning-Smith, my beautiful baby daughter Rebecca Laura Glendenning-Smith and the memory of Jock.

Preface

The work described in this thesis was carried out at the University of Kent at Canterbury between October 1987 and September 1990. All work is original except where otherwise indicated and includes nothing which is the outcome of work done in collaboration or which has or is being submitted for any other qualification at this or any other establishment.

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Abstract: The synthesis and characterization of substrates suitable for the study of [1,3]-, [1,4]- and [1,5]-asymmetric induction was undertaken. Their reduction in the presence of Lewis acids was investigated. The extent and direction of asymmetric induction was investigated by variation of Lewis acid, solvent and reducing agent. Competing mechanisms in [1,5]-asymmetric reductions was demonstrated. Molecular mechanics calculations were used to predict the extent and direction of asymmetric induction on the basis of the lower energy conformers of suitable model structures. Crystal structures were used to develop a set of MM2 force field parameters for an octahedral titanium complex. An *ab initio* study was prepared in order to improve the parameterization of the MM2 force field.

CONTENTS Page

CHAPTER 3

CHAPTER 4

CHAPTER 5

CHAPTER 6

Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
Bn	benzyl
BP1	S.G.E. bonded phase capillary column, 25 m.
BP5	S.G.E. bonded phase capillary column, 25 m.
COSY	correlation spectroscopy
CSD	Cambridge Structural Database
DIBAL-H	diisobutylaluminium hydride
DMAP	4,4-dimethylaminopyridine
DMF	N,N-dimethylformamide
Et	ethyl
G.l.c.	gas-liquid chromatography
HMPA	hexamethylphosphoramide
Lp	lone pair
Me	methyl
MEM	methoxyethoxymethyl
MOM	methoxymethyl
MPA	*dodeca*-molybdo phosphoric acid (10 %, w./v.) in absolute ethanol
MP2	2nd order Møller-Plesset correction
MPLC	medium pressure liquid chromatography
MTM	methylthiomethyl
nBu	*n*-butyl
N.m.r.	nuclear magnetic resonance
iPr	isopropyl
tBu	*tert*-butyl
PCC	pyridinium chlorochromate
Pd-C	10 % palladium on charcoal
Ph	phenyl
RMS	root mean square 1st derivative
RT	room temperature
SCF	self-consistant field
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
T.l.c.	thin layer chromatography
TM	target molecule
THF	tetrahydrofuran
THP	tetrahydropyran
Ts	tosyl (*p*-toluenesulphonyl)
U.v.	ultraviolet
VDW	Van der Waals steric energy contribution
Pyr.	pyridine

1.1: INTRODUCTION

1.1.1: Chirality

An object is chiral (Gr., meaning handedness) if it has a non-superimposible mirror image. A tetravalent carbon atom may be substituted with four different groups. This situation leads to two stereoisomers, each of which is chiral and are known as enantiomers.

Such a carbon atom, or compound is commonly known as asymmetric. Although widely used and understood this is slightly misleading, since in implies that the objects are devoid of symmetry. While this is often true it is not a prerequisite for chirality. For instance, *trans*-1,2-dimethyl cyclopropane is chiral, but contains a C_2 rotational axis of symmetry (Figure 1.1).

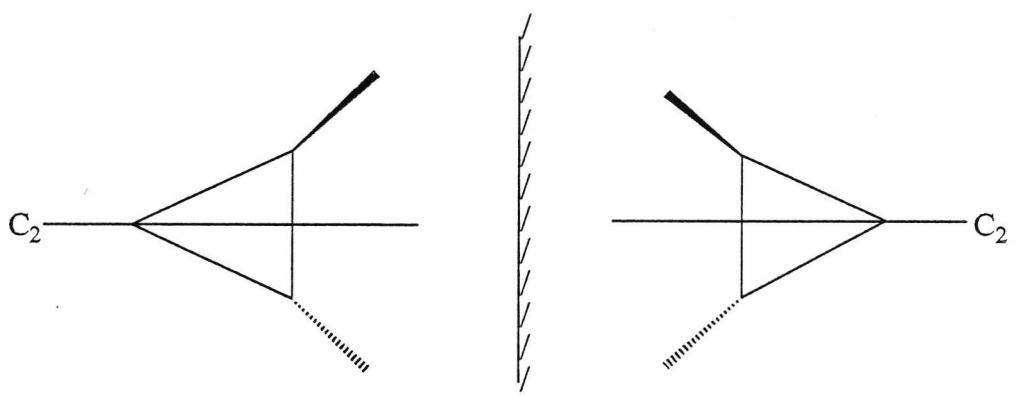


Figure 1.1

Similarly (+)- or (-)-diethyl tartrate are chiral and contain a C_2 axis (Figure 1.2).

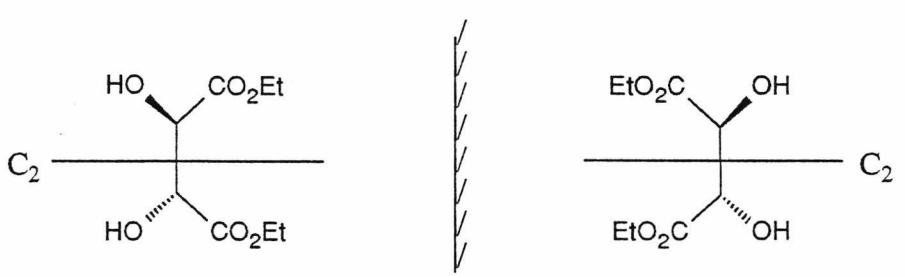


Figure 1.2.

In addition, compounds which do not possess an asymmetric carbon atom (or in general,

an asymmetric atomic centre) may also be chiral such as helicenes, hindered biphenyls and for instance tri-*o*-carvacrotide (which incidentally posesses a C_3 axis) (Figure 1.3).

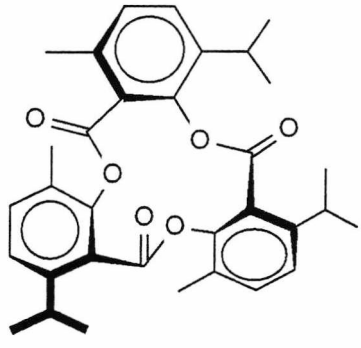


Figure 1.3.

In terms of symmetry, chiral objects may not possess a point of inversion ($i \equiv S_2$), a mirror plane ($\sigma \equiv S_1$) or a reflection-rotation axis (S_4).

In general, chiral compounds rotate plane polarized light. Each enantiomer will rotate the plane by equal and opposite amounts (at the same temperature, pressure and concentration). When a pair of enantiomers are present in equal concentrations no optical rotation is observed and the mixture is referred to as a racemate. For an enantiomeric pair with one asymmetric carbon atom, the absolute configuration of the enantiomers may be specified as (R) (L., rectus, right) or (S) (L., sinister, left), according to the Cahn-Ingold-Prelog system.[1]

If a molecule has two asymmetric centres then there are four possible stereoisomers. The relationship between them is shown below (Figure 1.4).

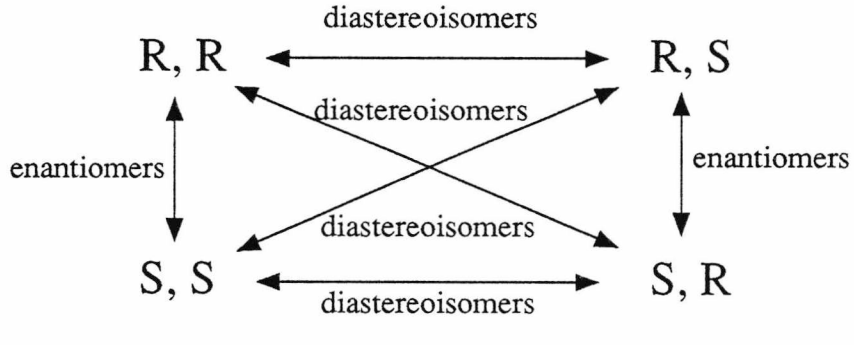


Figure 1.4.

Each of these components is chiral and in general will be expected to display optical activity. A special case occurs when a mirror plane exists between the two asymmetric

centres in the R,S:S,R stereoisomers. Here they are identical, no optical activity will be found, and the stereoisomer is know as the *meso* form.

The above situation may be generalized to a system with n chiral centres. In this case there will be 2^n stereoisomers, and 2^{n-1} diastereoisomers.

1.1.2: The Importance of Chirality

When a chiral substance is made in the laboratory from achiral starting materials (and without the presence of a chiral physical force[2]) then a racemate will result.

Living organisms are largely composed of chiral organic macromolecules. They require chiral material to live and grow, and synthesize chiral compounds usually with total stereoselectivity. Chemical reactions *in vivo* are catalysed by enzymes. Enzymes are composed predominantly of proteins (from essential chiral amino acids), and carbohydrate (from chiral sugars). Given the intrinsic handedness of life it would not be surprising to find that the therapeutic activity and pharmacological effect of a chiral drug may predominate or reside solely in one stereoisomer.

A commonly cited tragedy occurred with the sedative Thalidomide. This drug was marketed as a racemate in the 1960's, and was used widely by pregnant women. Later many of these gave birth to children with terrible abnormalities. It was discovered that the S-isomer, but not the R-isomer, had teratogenic effects when given to rats.[3] The abnormalities which occurred in the rats offspring were similar to those observed in man. One explanation for the toxicity observed considers hydrolysis of the RCONHR' amide linkages in Thalidomide by simple peptidases. As these enzymes are chiral one might expect that the enantiomers of Thalidomide may be hydrolysed at different rates or even selectively. Hydrolysis of the S-isomer may lead to a compound with similar properties to EDTA (EDTA-H_4 has been marketed to remove metal ions *in vivo*). It is thought that this hydrolysis product may then leach out calcium ions from the body, which would otherwise have been used in the budding limbs of the foetus.[4]

1.1.3: The Rôle of the Chemist in Asymmetric Synthesis

If one wishes to synthesize a novel stereochemically complex system, then there will undoubtedly be synthetic challenges to overcome. It would be rather wasteful, for instance, to attempt a natural product synthesis, which contained a step which required an unknown reaction, or which was based on undemonstrated stereocontrol. In attempting the synthesis, the majority of steps will have been developed by other workers and thus represent the chemists' "tool box". In the context of controlling the absolute stereochemical course of a synthetic transformation the chemist may:

(1) Tie together homochiral fragments obtained from the chiral pool;[5]

(2) Use relative asymmetric induction;

This may be sub-divided into three areas:

(i) Make use of chiral reagents to control the formation of one or more chiral centres on a substrate molecule;[6]

(ii) Use of chiral catalysts which may be used in small amounts to control the formation of many new chiral centres in substrate molecules;[7]

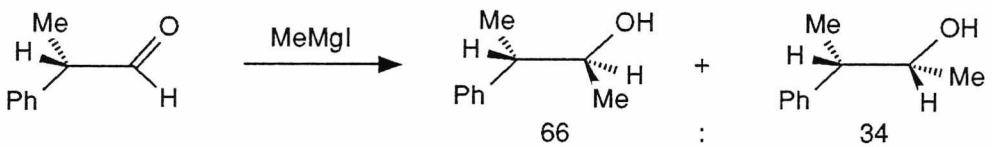
(iii) Use of existing chirality in a substrate molecule to influence the formation of a new chiral centre in the molecule.[8]

It is the last entry (2, iii) in the above strategies that is of interest in this work to extend the methodology available to the synthetic chemist.

1.2: Models for [1,2]-Asymmetric Induction

The phenomenon of relative asymmetric induction has long been known.[9]

The factors which controlled the resulting relative stereochemistry of products in such examples were less clear than the effect until Cram[10] and Prelog[11] set forth models for predicting the major diastereoisomer expected in nucleophilic additions to α-chiral carbonyl compounds (Scheme 1.1).



Scheme 1.1.

To paraphrase Cram's Rule *the major diastereoisomer will be formed when the entering nucleophile approaches the less hindered face of the double bond when the rotational conformation of the π-bond is flanked by the two less bulky groups attached to the adjacent chiral centre.* Figure 1.5 shows a schematic representation of the above statement. The most bulky group L was thought to lie antiperiplanar to the oxygen. A nucleophile R_1 may then find a low energy pathway by attacking at 90° to the plane of the carbonyl group. If the nucleophile were to attack the opposite face of the carbonyl group then a less favourable R_1:M interaction would be present.

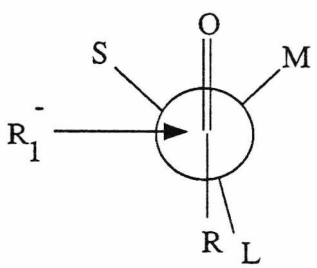
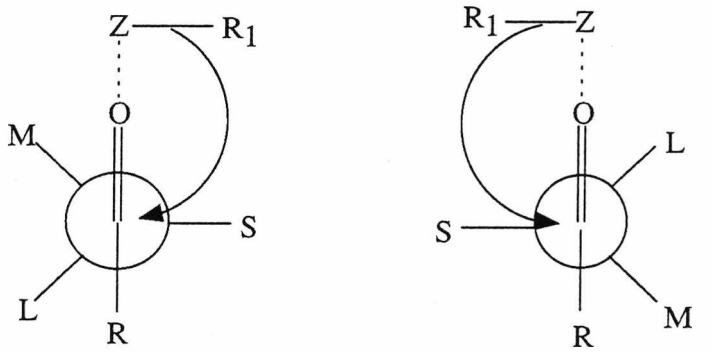


Figure 1.5.

In a later paper Cram and Kopecky[12] described an alternative model to that proposed above. This model takes into account the co-ordination of an organometallic reagent to the carbonyl group of the substrate and predicts the major stereoisomer (Figure 1.6).



Major Conformer Minor Conformer

Figure 1.6.

In these conformers the coordinated reagent R_1Z-O is thought to form the most bulky group in the intermediate and thus will tend to orient itself furthest away from the next most bulky group L.

Cornforth[13] pointed out that if one of the ligands was an electronegative group then carbonyl:ligand dipoles would interact most favourably when the group were oriented in an antiperiplanar fashion. In this dipolar model the incoming group would then be expected to attack from the side bearing the smaller of the remaining substituents.

Karabatsos[14] proposed an alternative rotameric transition state on the basis of the known minimum energy conformations of aldehydes and ketones, that is that one substituent on the α-carbon eclipses the carbonyl C=O bond. Three Newman projections may be drawn of such transition states. The two rotamers of interest have M-C=O eclipsed and L-C=O eclipsed. It is assumed that the first of these predominates and that attack of R_1 occurs at 90° to the carbonyl C=O on the side bearing S favouring R_1:S over R_1:L interactions.

Felkin[15] noted certain failures in the former models, in particular that they were unable to account for the increases in selectivity observed experimentally as R increases in steric bulk. The preceding models would predict a lowering of selectivity with increasing bulk of R. They proposed an alternative rotameric transition state (Figure 1.7).

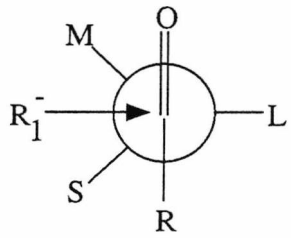


Figure 1.7.

In the Felkin model the interaction of O with M and S is ignored (i.e. that R:M ≫ O:M). Stereodifferentiation is seen to result from differential *gauche* R:M, R:S interactions. This assumption is rather dubious when considering aldehydes (i.e. R:M ≈ O:M).

Anh *et al.*[16] looked at the Cram, Cornforth, Karabatsos, and Felkin rotameric transition states using *ab initio* methods. They found that the Felkin rotamer was significantly lower in energy than the other rotamers. They suggested that when L is an electronegative group, such as chlorine, then there is a significant interaction between the π^*-orbital of the carbonyl group and the σ^*-orbital of the C-Cl bond, thus providing a lower lying LUMO for the attack of the nucleophile (Figure 1.8).

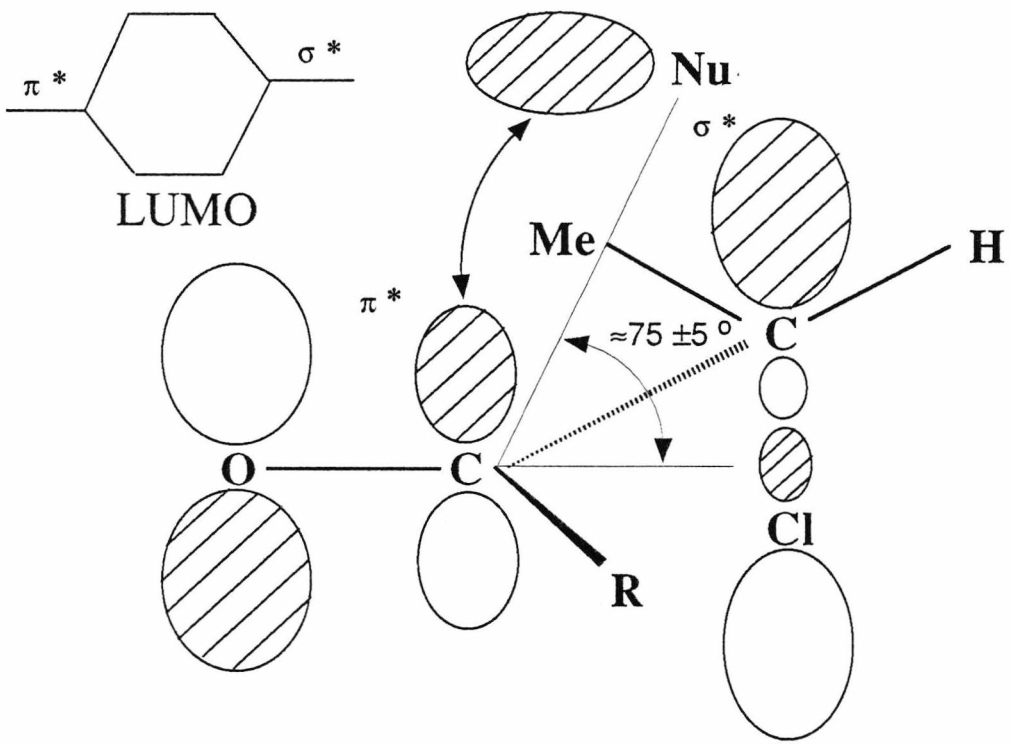
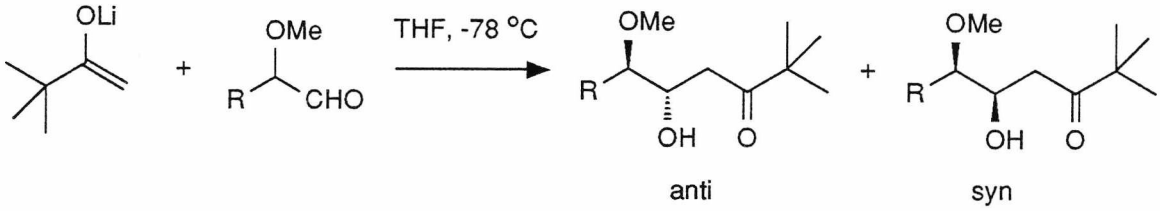


Figure 1.8.

Attack of the nucleophile is thought to occur along the Bürgi-Dunitz trajectory,[17] which

removes the necessity of making assumptions about the relative magnitudes of the O:M, and R:M interactions. This model has become know as the Felkin-Ahn model. Furthermore Fraser[18] has found good agreement between the calculated stabilization energies and experimental values for the Felkin-Ahn effect.

Heathcock[19] has demonstrated that steric effects may compete with the Ahn-Eisenstein effect. Part of the study involved addition of a simple lithium enolate to a series of α-methoxy aldehydes. The major diastereoisomer in each case is that predicted by the Felkin-Ahn model due to the fact that carbon-heteroatom bonds have significantly lower energy σ^*-orbitals than the corresponding carbon-carbon bonds. As expected diastereoselectivity was seen to increase with steric bulk across Me, Et, iPr, tBu (Scheme 1.2).



Aldehyde R=	anti : syn
Me	58 : 42
Et	76 : 24
iPr	92 : 8
tBu	93 : 7
Ph	83 : 17

Scheme 1.2.

The increase in selectivity when moving from iPr to tBu was not as great as expected. That is, the R group taking on the rôle M should increase selectivity as M increases in steric bulk, but given the difference in bulk between iPr and tBu only a modest increase in selectivity was observed. Furthermore, from the data in Scheme 1.2 the phenyl group is apparently a smaller M group than iPr in this reaction Scheme.

Heathcock's results lead him to the conclusion that one must take into account not only

the electronic nature of a substituent, but also steric bulk when assigning L, M, S.

To rationalize the results Heathcock considered the following rotamers (Figure 1.9).

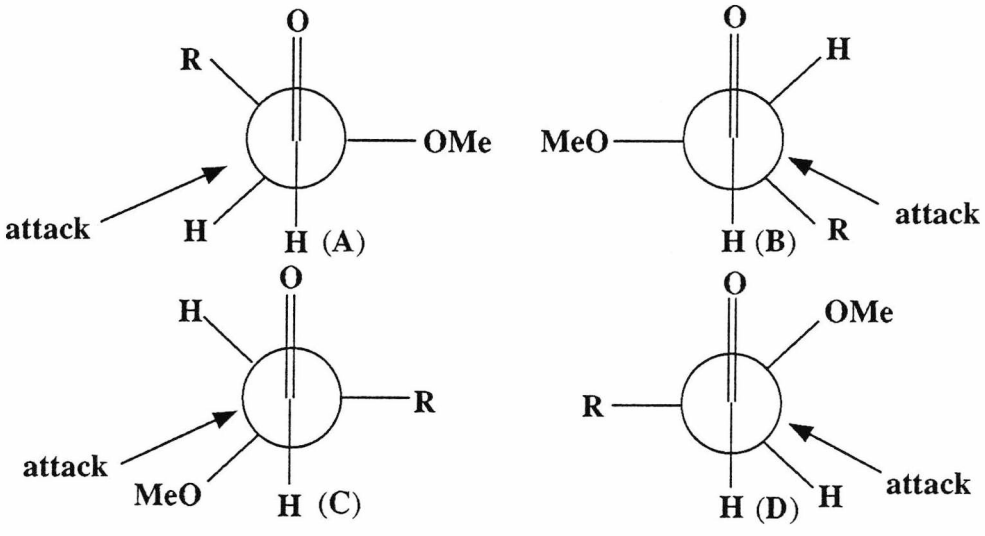


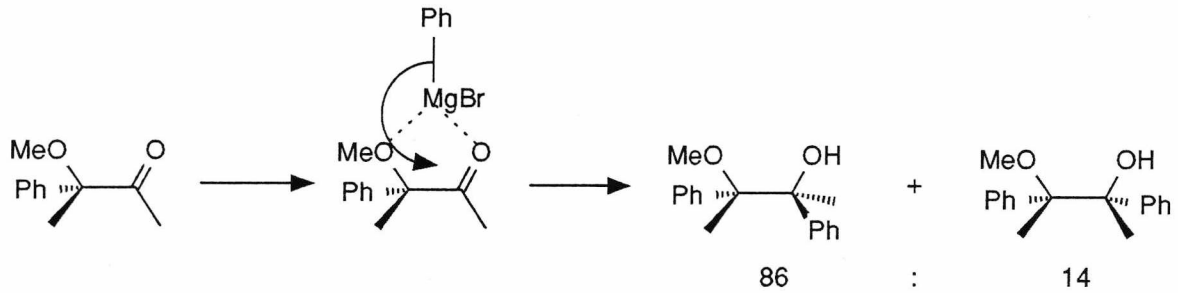
Figure 1.9.

In the case of Me, Et, iPr the electronic effect is very dominant and OMe is unambiguously L. In these cases the reaction should proceed through the Felkin-Ahn rotamer (**A**), with the minor diastereoisomer probably occurring through (**B**). However, when R=tBu the steric bulk becomes great enough to compete with the Ahn-Eisenstein effect from OMe. Heathcock proposed that rotamers (**C**) and (**D**) become important pathways where R behaves as L. When R=phenyl it is believed that the C_{sp^3}-C_{sp^2} σ^*-orbital interacts with the C=O π^*-orbital generating a second Ahn-Eisenstein effect to compete with that of provided by the OMe group. It was deduced that about one quarter of the reacting species to proceed through (**C**) and (**D**) whilst three quarter proceeds via the lower energy (**A**) type transition state.

1.3: Chelation Controlled [1,2]-Asymmetric Induction

For α-alkoxy or hydroxyl groups the electronegative oxygen substituent may potentially exert an analogous effect to the electronegative chlorine in the Felkin-Ahn model (Figure 1.8), due to the presence of a lower lying C_{sp^3}-O_{sp^3} σ^*-orbital. However, the phenomenon

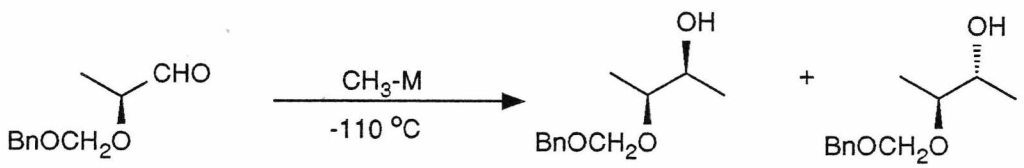
of chelation also is possible with these substituents. This has the result of making the opposite π-face more accessible, and Cram's cyclic model is applicable[12] (Scheme 1.3).



Scheme 1.3.

1.3.1: Additions to Aldehydes

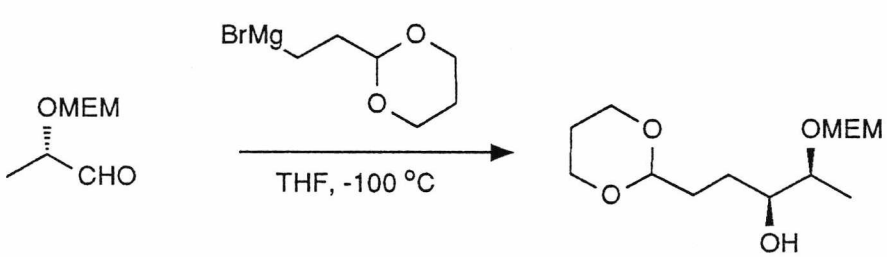
Still[20] has obtained reasonable diastereocontrol with β-alkoxy-α-chiral aldehydes by the use of organocuprate reagents. In the case of α-alkoxy aldehydes poor results were obtained with organocuprates. Grignard additions were found to be more selective (Scheme 1.4).



	syn	:	anti
CH_3-M= CH_3MgBr	10	:	1
$=(CH_3)_2CuLi$	2	:	1

Scheme 1.4.

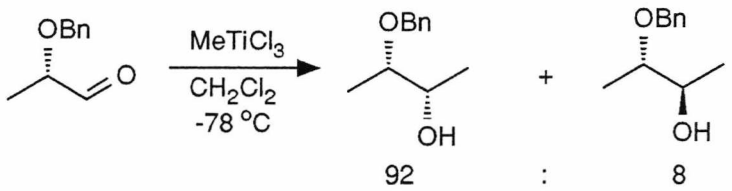
Kelly[21] has demonstrated chelation controlled [1,2]-asymmetric induction using a Grignard reagent in the synthesis of Rhodinose from (S)-ethyl lactate and obtained the required intermediate in the ratio 95:5, *syn:anti* (Scheme 1.5).



Scheme 1.5.

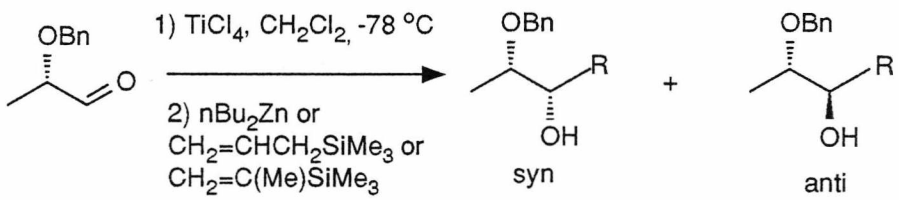
Although high levels of asymmetric induction have been seen in the above Schemes,

α-alkoxy aldehydes generally fail to give high levels of diastereocontrol with RMgX, RLi, or with other reagents such as allyl boron compounds.[22] However, Reetz[23] has shown organotitanium reagents to be effective in chelation controlled additions (Scheme 1.6).



Scheme 1.6.

It is well known that higher homologues of $RTiCl_3$ reagents tend to be rather unstable.[24] Consequently the above Scheme does not represent a general method of additions to aldehydes. This problem may be circumvented by application of titanium tetrachloride to form a chelate intermediate followed by addition of mild nucleophiles such as dialkylzinc, allylsilanes or allylstannanes in dichloromethane (Scheme 1.7).[23]

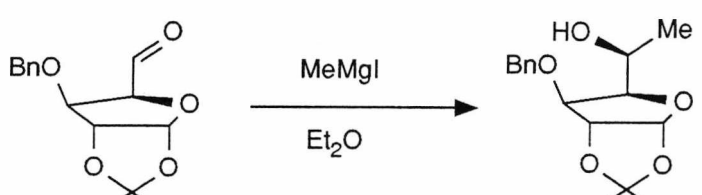


R=nBu	90	:	10
$R=CH_2CH=CH_2$	>93	:	<7
$R=CH_2C(Me)=CH_2$	>95	:	<5

Scheme 1.7.

Co-ordinating solvents such as tetrahydrofuran or diethyl ether should be avoided as they are capable of competing for the vacant sites on the titanium centre.[24b]

Wolfrom[25] obtained only one diastereoisomer when adding methyl magnesium iodide to 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose in ethereal solution at reflux. The product 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidine-β-L-*ido*(L-*glycero*-α-D-*xylo*-hexo)furanose was rationalized on the basis of Cram's cyclic model (Scheme 1.8).

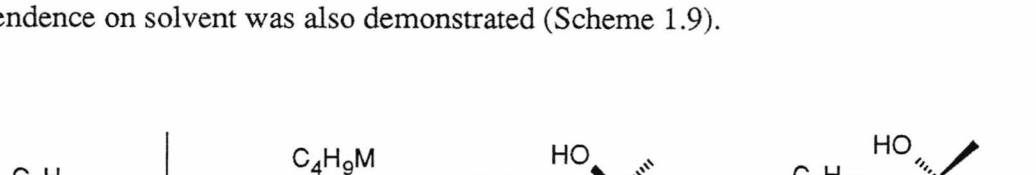


Scheme 1.8.

1.3.2: Additions to Ketones

Cram's pioneering work in this area led to the development of the cyclic model (Scheme 1.3). Although the model allowed rationalization of the product stereochemistry the levels of control were not high (typically ranging from 2:1 to 9:1).[12]

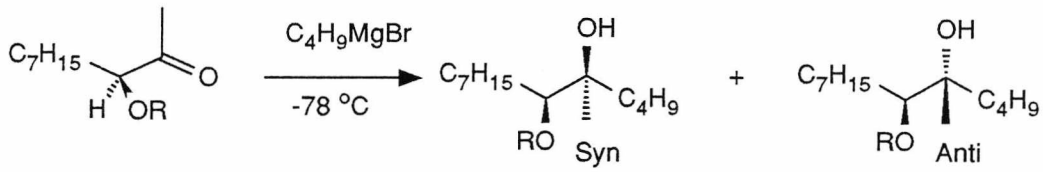
Still[26] has carried out systematic studies where the alkoxy group, solvent, temperature and nucleophile were varied. The results showed that alkyllithium reagents failed to react stereoselectively, but Grignard reagents showed high diastereofacial selectivity. A strong dependence on solvent was also demonstrated (Scheme 1.9).



Solvent	syn : anti	syn : anti
	M=Li	M=MgBr
C_5H_{12}	2:1	9:1
CH_2Cl_2	3:1	14:1
Et_2O	1:1	9:1
THF	0.7:1	>100:1

Scheme 1.9.

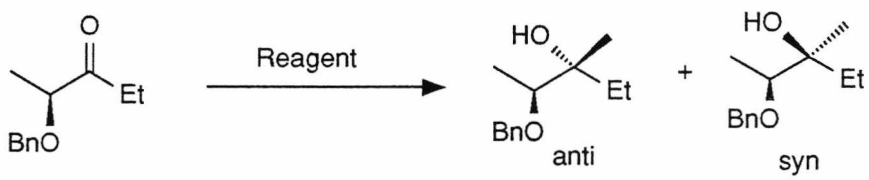
Still also investigated the effect of changing the nature of the α-alkoxy group, showing that such variations can be tolerated without sacrificing stereocontrol (Scheme 1.10).



Protecting group	Syn : Anti
R = -MEM, -MOM, -MTM, -CH_2-(furyl)	>100 : 1
= -Bn	200 : 1
= -CH_2OBn	100 : 1
= -THP	3 : 1

Scheme 1.10.

Reetz[27] has shown that organotitanium reagents may also be used in additions to ketones of this type. However, since Grignard reagents are well suited to additions to ketones their contribution is not as significant as was demonstrated with α-alkoxy aldehydes (Scheme 1.11).



Reagent	anti		syn
$MeTiCl_3$	>99	:	<1
$MeTi(OiPr)_3$	>99	:	<1
$MeLi/TiCl_4/Et_2O$	>99	:	<1
MeMgBr	>99	:	<1

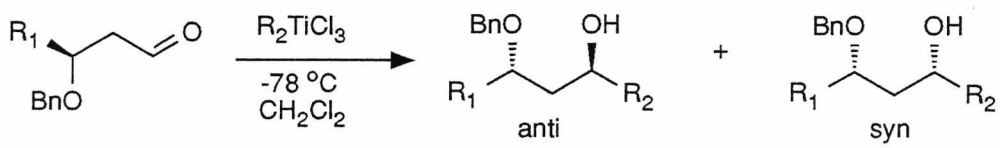
Scheme 1.11.

1.4: Chelation Controlled [1,3]-Asymmetric Induction

1.4.1: Additions to Aldehydes

For additions using Grignard, organolithium, organocuprates, lithium enolates or allylboron compounds with β-alkoxy aldehydes, asymmetric induction is not possible.[20, 28]

Reetz[28a] has shown that Lewis acidic organotitanium reagents, as seen previously, afford high levels of stereocontrol (Scheme 1.12).



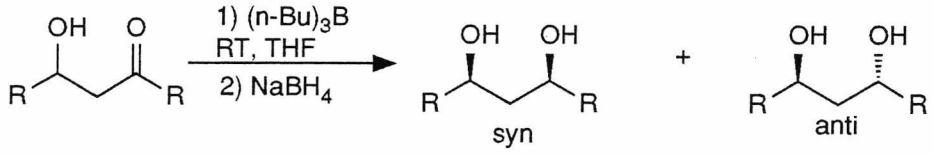
Reagent	R_1	R_2	anti:syn
$MeTiCl_3$	Me	Me	90 : 10
$TiCl_4/CH_2=CHCH_2SiMe_3$	Me	$CH_2=CHCH_2$	95 : 5
$TiCl_4/CH_2=C(Me)CH_2SiMe_3$	Me	$CH_2=C(Me)CH_2$	95 : 5
$TiCl_4/Zn(n\text{-}Bu)_2$	Me	n-Bu	90 : 10
$MeTiCl_3$	n-Bu	Me	91 : 9
$TiCl_4/CH_2=CHCH_2SiMe_3$	n-Bu	$CH_2=CHCH_2$	95 : 5
$TiCl_4/CH_2=C(Me)CH_2SiMe_3$	n-Bu	$CH_2=C(Me)CH_2$	99 : 1

Scheme 1.12.

The highly selective allylsilane additions provide a method for iteratively building repeated 1,3 oxygenated compounds via ozonolysis of the double bond followed by further addition to the resulting carbonyl group.[29]

1.4.2: Reduction of Ketones

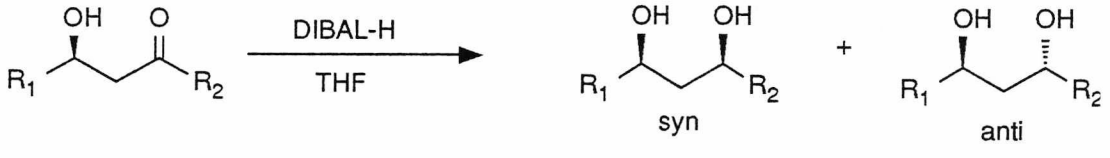
Narasaka[30] has explored the use of boron chelates in the asymmetric reduction of β-hydroxy ketones (Scheme 1.13). Chen has shown that selectivity may be slightly improved by replacement of one alkyl group on boron with an alkoxy group in similar reactions.[31]



Run	R	temp./°C	syn:anti
1	Ph	-78	98 : 2
2	n-Bu	-100	96 : 4
3	n-Bu	-78	88 : 12
4	cyclohexyl	-100	84 : 16
5	cyclohexyl	-78	88 : 12

Scheme 1.13.

Kiyooka[32] has obtained good results using DIBAL-H as both the chelating and reducing agent (Scheme 1.14).



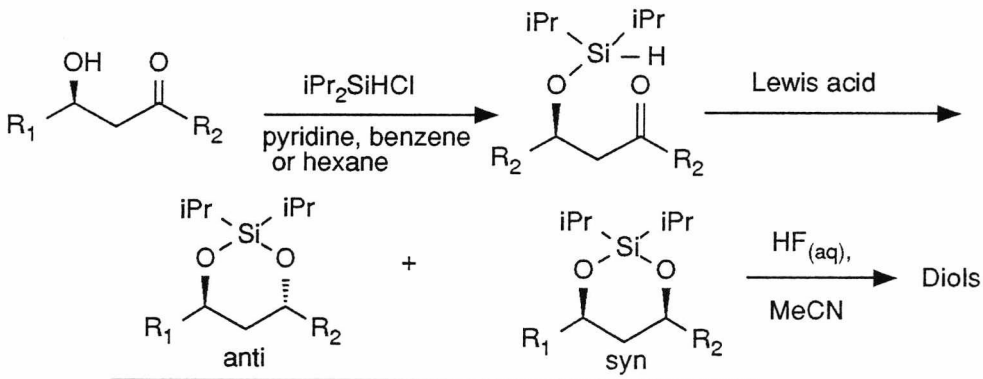
R_1	R_2	Temp./°C	syn:anti
i-Pr	Ph	0	70 : 30
i-Pr	Ph	-78	93 : 7
Ph	t-Bu	0	67 : 33
Ph	t-Bu	-78	92 : 8
Ph	Me	0	77 : 23
Ph	Me	-78	95 : 5
MePhCH-	t-Bu	0	72 : 28
MePhCH-	t-Bu	-78	93 : 7

Scheme 1.14.

In addition to this the use of n-Bu_3SnH, with AIBN, $ZnCl_2$, or $SnCl_4$ (in methanol, diethyl ether and dichloromethane) instead of DIBAL-H was studied. It was known that this hydride was a particularly mild reducing agent, but reacted more rapidly with carbonyls in the presence of a Lewis acid. Presumably the increased reactivity resulted from metal co-ordination and thus activation of the carbonyl carbon atom. The rationale is that only the chelated substrate will be reduced, thus allowing maximum diastereocontrol. However, these combinations tended to give lower selectivity (with the *syn* isomer predominating). The lower selectivities (ca. 85:15) may reflect the fact that these reactions needed to be

carried out at room temperature. Other examples of *syn* selective reductions of β-hydroxy ketones have been documented.[33]

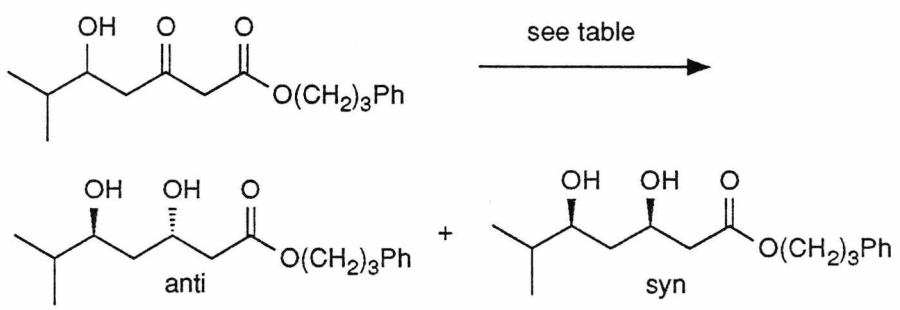
Davis[34] has developed a method of reducing β-hydroxy ketones to give high diastereoselectivity in the opposite sense to that seen above (Scheme 1.15).



R_1	R_2	Lewis Acid	anti:syn
iPr	iPr	$SnCl_4$	120 : 1
Bu	Bu	$SnCl_4$	40 : 1
iPr	Me	$SnCl_4$	50 : 1
Me	iPr	$SnCl_4$	40 : 1
iPr	iPr	$MgBr_2.OEt_2$	60 : 1
iPr	iPr	$TiCl_4$	30 : 1
iPr	iPr	$BF_3.OEt_2$	320 : 1

Scheme 1.15.

Evans[35] has made use of tetramethylammonium triacetoxyborohydride in the asymmetric reduction of β-hydroxy ketones. This methodology has also displayed high *anti* selectivity (Scheme 1.16).



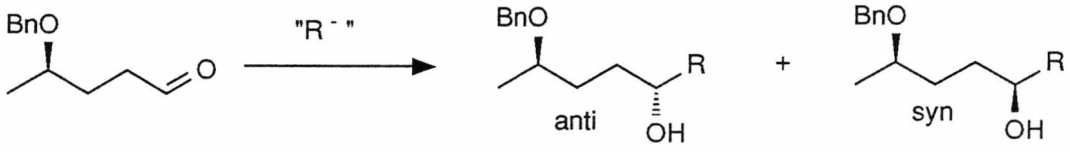
Hydride	Solvent	time	temp./°C	anti:syn
$Me_4NHB(OAc)_3$	THF	15 hrs.	25	69 : 31
$Me_4NHB(OAc)_3$	$THF/MeCO_2H$	30 mins.	25	79 : 21
$Me_4NHB(OAc)_3$	$MeCN/MeCO_2H$	30 mins.	25	98 : 2
$Me_4NHB(OAc)_3$	$MeCN/MeCO_2H$	5 hrs.	-40	95 : 5

Scheme 1.16.

1.5: Chelation Controlled [1,4]-Asymmetric Induction

1.5.1: Additions to Aldehydes

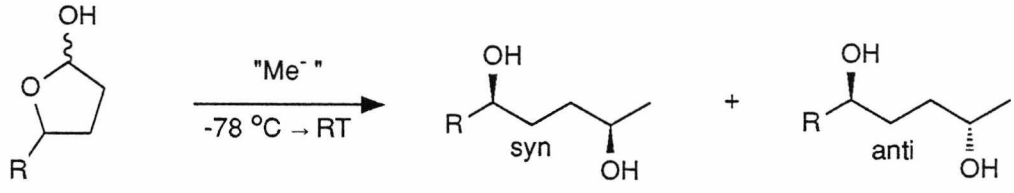
Reetz[23, 27a] has achieved high levels of diastereocontrol by the use of organotitanium reagents in [1,4]-asymmetric induction (Scheme 1.17).



Reagent	R	Temp./°C	anti:syn
$TiCl_4/Me_2Zn$	Me	-78	85 : 15
$TiCl_4/CH_2{=}CHCH_2SiMe_3$	$CH_2{=}CHCH_2$	-78	75 : 25
$TiCl_4/CH_2{=}C(Me_3)OSiMe_3$	$CH_2COC(Me_3)$	-78	76 : 24

Scheme 1.17.

An interesting approach to this longer range asymmetric induction has been developed by Tsuchihashi.[36] Use was made of organotitanium reagents reacting with the lactol tautomer of the hydroxy aldehyde analogue of the benzyloxy aldehyde above (Scheme 1.18).

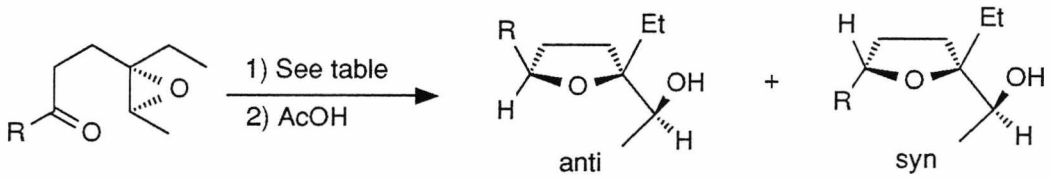


Reagent	R	Solvent	syn:anti
MeLi	CH_2OSiPh_2t-Bu	Et_2O	1.7 : 1
MeMgBr	"	THF	1.3 : 1
Me_3Al	"	CH_2Cl_2	1.1 : 1
$MeTiCl_3$	"	CH_2Cl_2	8.4 : 1
$MeTi(Oi\text{-}Pr)_3$	"	CH_2Cl_2	12 : 1
"	$BnOCH_2$	CH_2Cl_2	7.3 : 1
"	Me	CH_2Cl_2	12 : 1

Scheme 1.18.

1.5.2: Reduction of Ketones

Kishi[37] observed [1,4]-asymmetric reduction whilst generating an intermediate in the synthesis of Monensin (Scheme 1.19).

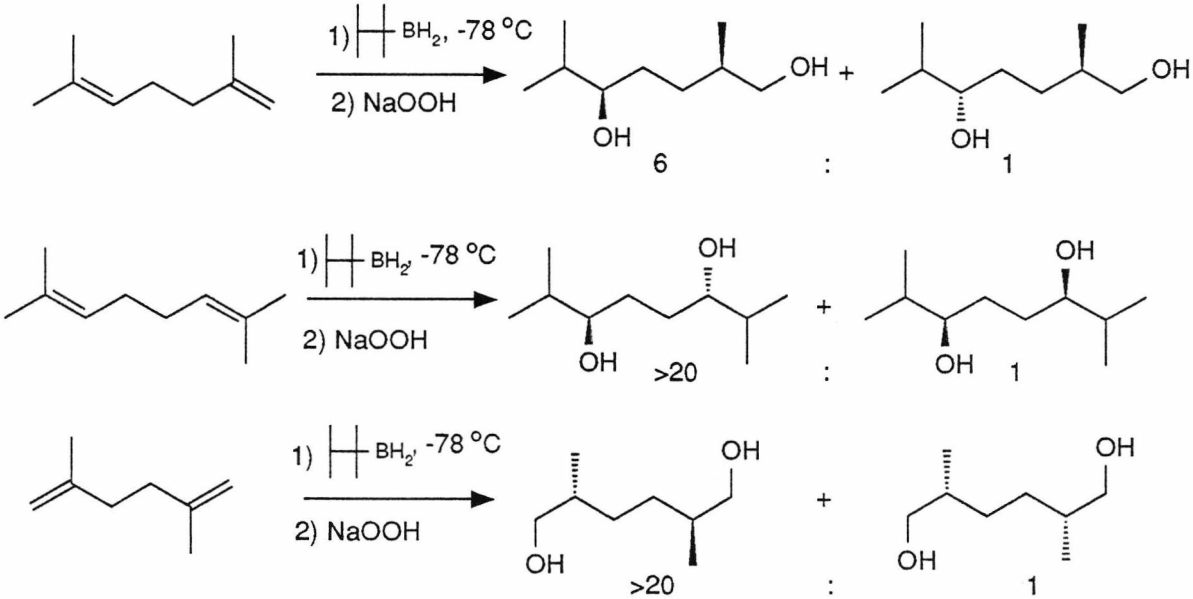


Reagent	R	Solvent	Temp./°C	anti:syn
$NaBH_4$	p-$MeOC_6H_4$	MeOH	RT	1 : 1
L-Selectride	"	Et_2O	RT	1 : 1
$LiAlH_4$	"	Et_2O	0	1 : 3
$LiAlH(Ot\text{-}Bu)_3$	"	Et_2O	0	1 : 4
$LiAlH_4$.diamine	"	Et_2O	-78	1 : 11
$LiAlH_4$.diamine	"	Et_2O	-78	1 : 10

diamine = dl-2-(o-2-toluidino-methyl)pyrrolidine

Scheme 1.19.

A rather different approach to those seen above has yielded good results. Still[38] has used hydroboration to generate high levels of [1,4]-asymmetric induction with alkenes (Scheme 1.20).

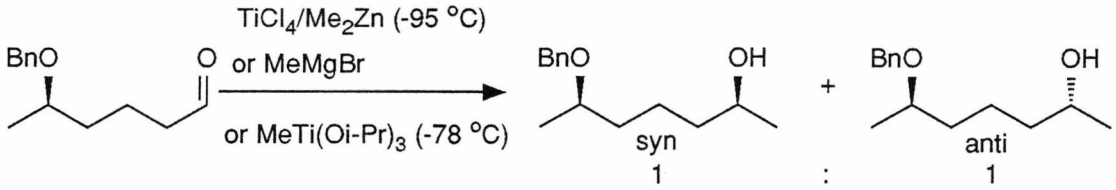


Scheme 1.20.

1.6: [1,5]-Asymmetric Induction

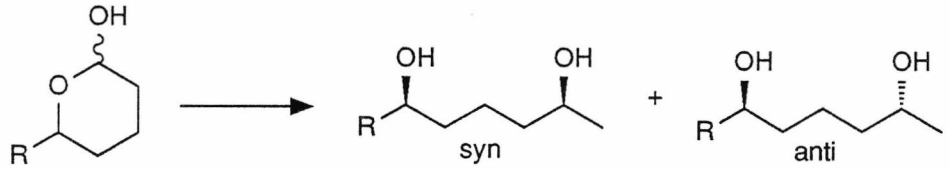
1.6.1: Additions to Aldehydes

Tsuchihashi[36] has failed to achieve diastereocontrol in the additions to 5-benzyloxy hexanal by the use of methyltitanium reagents (Scheme 1.21).



Scheme 1.21.

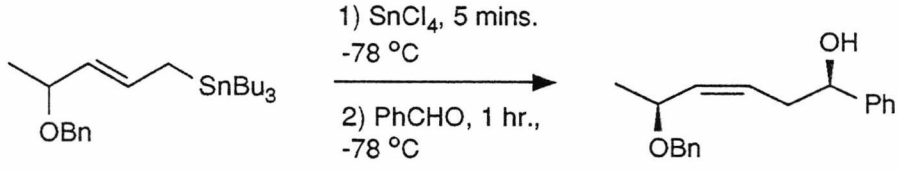
The lactol tautomer of the analogous 5-hydroxy hexanal derivatives afforded respectable levels of relative asymmetric induction (Scheme 1.22).



R	Reagent	Temp./°C	Solvent	syn:anti
$PhCH_2CH_2$	$MeTi(Oi\text{-}Pr)_3$	0	CH_2Cl_2	5.1 : 1
$PhCH_2CH_2$	MeMgBr	RT	THF	4.5 : 1
Me	$MeTi(Oi\text{-}Pr)_3$	-78 →RT	CH_2Cl_2	4.2 : 1

Scheme 1.22.

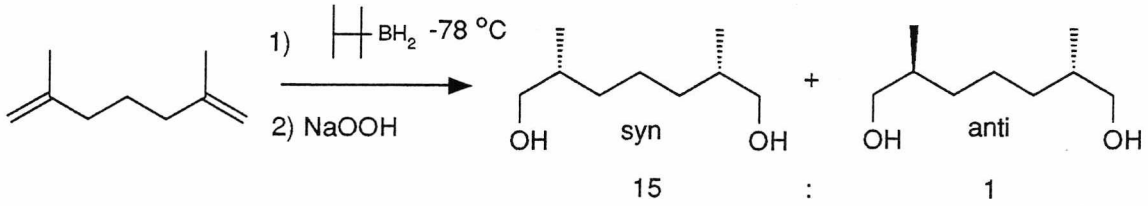
Recently Thomas[39] has shown excellent diastereofacial selectivity in the addition of an δ-alkoxyallylstannane to benzaldehyde. Less than 2 % of the *anti* isomer was formed in the reaction (Scheme 1.23).



Scheme 1.23.

1.6.2: Reduction of Alkenes

As a continuation of the work outlined in section 1.5.2, Still[38] has demonstrated high levels of [1,5]-asymmetric induction via hydroboration (Scheme 1.24).



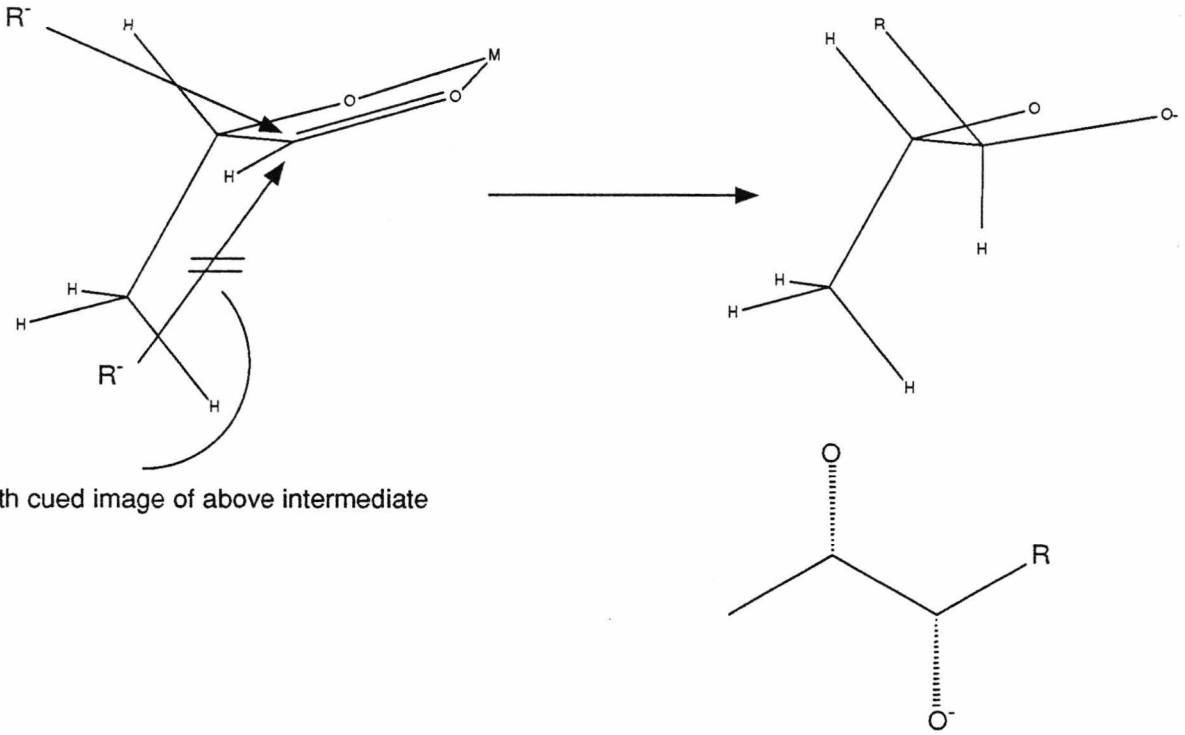
Scheme 1.24.

2.1: Cyclic Intermediates in Remote Asymmetric Induction

In Chapter 1, sections 1.3-1.6.2, a number of reaction schemes were presented which displayed asymmetric induction. In most cases it is thought that the diastereoselectivity observed results from cyclic intermediates or transition states. This chapter deals with the idea of diastereoselectivity resulting from such cyclic species. They are considered in a stepwise fashion for reasons of clarity.

2.2: [1,2]-Asymmetric Induction

In Schemes 1.4 to 1.8 asymmetric induction was seen in the addition of alkyl groups to a number of α-chiral-α-alkoxy aldehydes. In all of these cases *syn* selectivity was observed. Cram's cyclic model explains the selectivity. A 5-membered cyclic intermediate formed by metal chelation exposes its diastereotopic π-faces in different steric environments (Figure 2.1).



Depth cued image of above intermediate

Figure 2.1.

The stereochemistry observed by Still (Scheme 1.4) and Kelly (Scheme 1.5) may be rationalized by assuming an intermediate similar to that above.

Reetz has obtained high levels of asymmetric induction giving the *syn* isomer selectively by the application of organotitanium reagents (Scheme 1.6, 1.7). Furthermore Reetz has obtained n.m.r. evidence for the formation of the chelate intermediate below[40] (Figure 2.2).

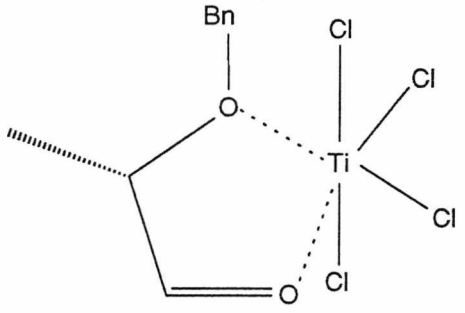


Figure 2.2.

The addition of a methyl group to the carbohydrate (Scheme 1.8) also corresponds to Cram's cyclic model (Figure 2.3).

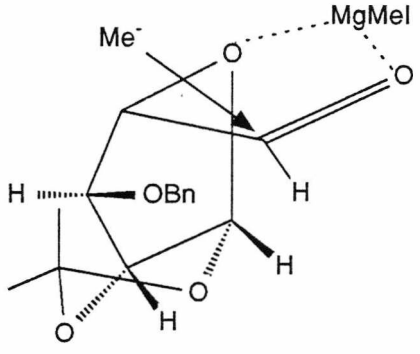


Figure 2.3.

In the examples of additions to ketones in Schemes 1.9-1.11 all of the examples conform to the expected products from the above cyclic model (Figure 2.1). In both Scheme 1.9 and 1.10 the *syn* product is favoured, but the *anti* product is the major isomer in Scheme 1.11. The difference observed here simply results from the fact that the group being added is of lower priority than the other substituent on the newly formed chiral centre. Thus the added group does not form part of the extended chain representation. In all of the preceding examples the newly added group does form part of the extended chain.

In Scheme 1.11 one of the organotitanium reagents used was methyl titanium tri-isopropoxide. In additions to aldehydes this reagent leads to the Felkin-Ahn product. This has been attributed to the lower Lewis acidity of $MeTi(OR)_3$ over $MeTiCl_3$.[41] However, the ketone π^*-orbital is higher in energy that the aldehydic orbital, thus should favour mixing with the appropriate σ^*-orbital to give the Felkin-Anh product. However, in the addition to the ketone presented (Scheme 1.11) excellent selectivity was obtained in the direction of the chelation controlled product. Reetz thought that chelate formation may be promoted in ketones due to increased Lewis basicity of the ketone carbonyl over the aldehydic carbonyl, or that some other reaction pathway to that described above was involved.[29]

2.3: [1,3]-Asymmetric Induction

In relation to β-alkoxy aldehydes, organotitanium reagents provide high levels of control (Scheme 1.12). Again chelate intermediates are thought to be involved. In this case a 6-membered intermediate will be involved. A schematic 6-membered intermediate is shown below. Attack of the incoming nucleophile is thought to occur from the upper side of the ring as shown (Figure 2.4).

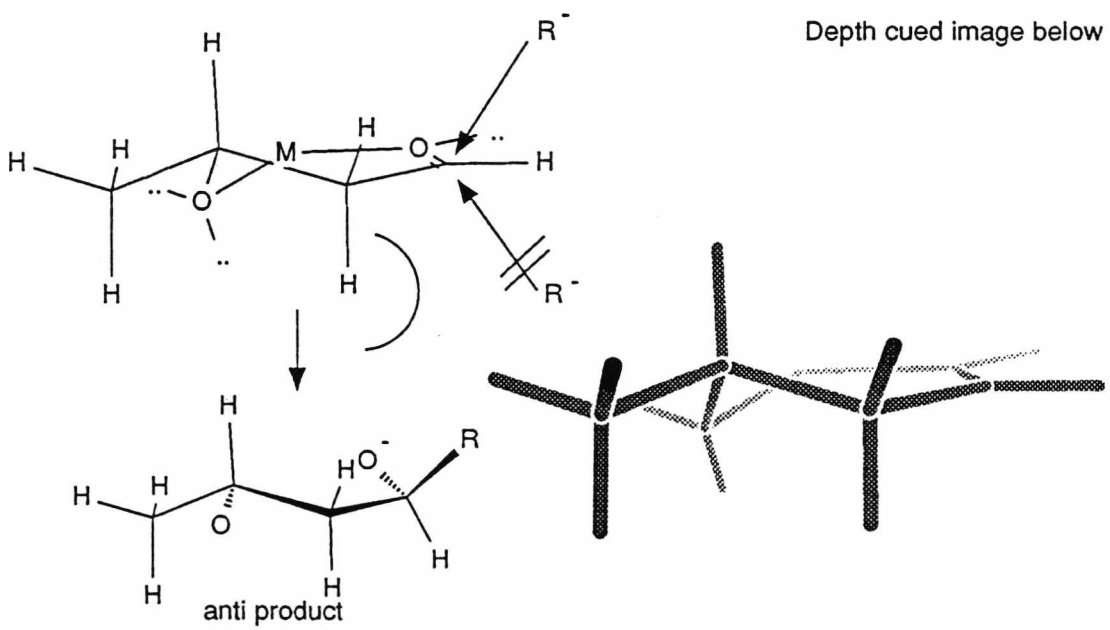


Figure 2.4.

Addition of an alkyl group to an intermediate with a similar geometry to the model above would be expected to attack at the less hindered face and give rise to the *anti* product in excess, as has been observed.

When hydride attacks a ketone with a geometry similar to the model chelate the *syn* product is expected. This has been demonstrated by Narasaka (Scheme 1.13) and Kiyooka (Scheme 1.14). This may be visualized easily by replacing the aldehydic H with an R group and replacing the carbon nucleophile with hydride and allowing attack on the model ring (Figure 2.5).

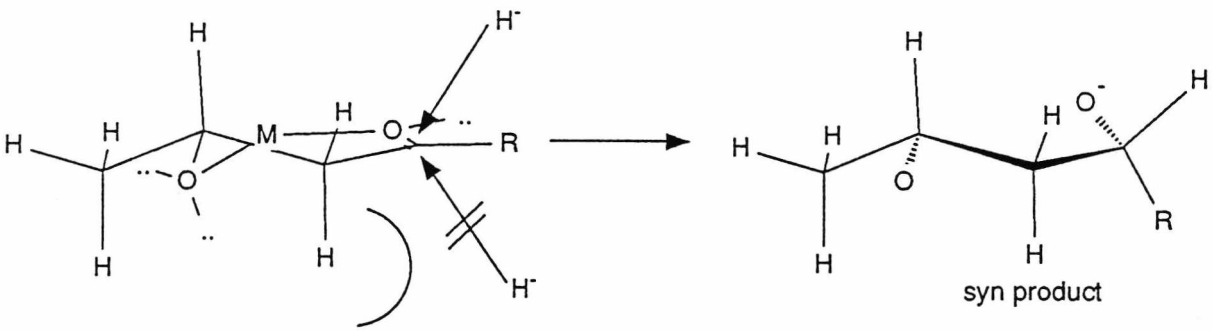


Figure 2.5.

Narasaka observed the formation of a dibutylboronic ester by n.m.r. This was assumed to exist in a chelated form through lone pair donation of the carbonyl group into the vacant site on the boron atom. Kiyooka assumed a similar intermediate with aluminium acting as M. Presumably one equivalent of DIBAL-H is consumed in the production of hydrogen. The resulting alkoxide may then covalently bind the newly formed diisobutylaluminium species, followed by co-ordination with the lone pair of the carbonyl on the aluminium centre. The chelate may then be attacked intermolecularly by another equivalent of DIBAL-H. Thus the *syn* isomer is formed in both cases as indicated by the model above (Figure 2.5).

Interestingly the work of Davis (Scheme 1.15) demonstrated the opposite diastereofacial selectivity, giving the *anti* isomer as the major product. The most striking feature of this work was the exceedingly high diastereoselection observed when using boron trifluoride etherate as the Lewis acid. This reagent is generally thought to be incapable of chelation,

as it has only one vacant site in its valence shell. Davis proposed the following chair like transition state (Figure 2.6).[34]

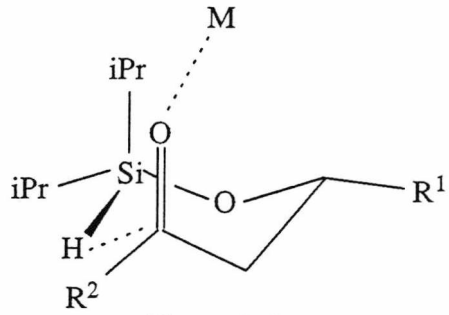


Figure 2.6.

Clearly this transition state would give rise to the observed relative stereochemistry. In the case of M being a Lewis acid capable of chelation then it is possible that a small proportion of the reaction proceeds via a chelate type intermediate (Figure 2.5). This would generate the *syn* isomer selectively and lower the overall *anti* selectivity of the process. With boron trifluoride this chelation pathway by co-ordination is not available and thus higher *anti* selectivity is observed.

Evans has also obtained *anti* diastereoselectivity in the reduction of β-hydroxy ketones with tetramethylammonium triacetoxyborohydride (Scheme 1.16). A similar method of hydride delivery was thought to be responsible for the observed selectivity. It was assumed that the hydroxyl group on the substrate displaced one of the acetoxy ligands on the reducing agent, (thus eliminating acetic acid) followed by intramolecular attack of hydride similar to that above (Figure 2.6).[35]

2.4: [1,4]-Asymmetric Induction

A chelate intermediate has been proposed by Reetz to explain the diastereoselectivity observed in additions of organotitanium reagents to the γ-benzyloxy aldehydes in Scheme 1.17. It was thought that the addition of titanium tetrachloride lead to the following 7-membered chelate ring (Figure 2.7).

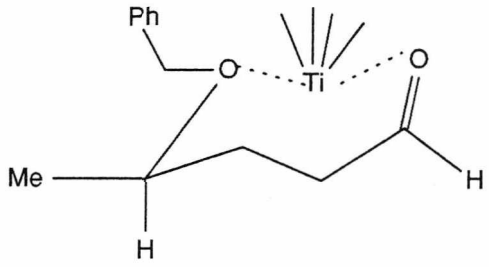


Figure 2.7.

Presumably, the proposed chelate was then attacked at the less hindered face of the co-ordinated carbonyl function. Clearly, it is less straightforward to predict the expected conformation of such an intermediate due to the increased ring size. However, the above structure was used to predict the *anti* selectivity of the addition of dimethyl zinc to the aldehyde.

As pointed out in the previous chapter, the lactol methodology used by Tsuchihashi gave *syn* selectivity (Scheme 1.18). The reaction was thought to proceed by the lactol first consuming one mole of organometallic reagent resulting in deprotonation of the hydroxyl group and complexation with the metal. The resulting complex was then thought to rearrange, followed by further co-ordination, to form a 7-membered chelate. Attack at the carbonyl carbon by another mole of the organometallic reagent, presumably at the least hindered face, was thought to account for the selectivity (Figure 2.8).

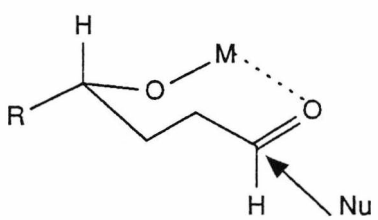


Figure 2.8.

It seems odd that two essentially similar chelates should expose different sides of the carbonyl group. One would have expected the same sort of geometry about the ring, thus giving rise to the same selectivity.

Kishi also used chelation to rationalize the observation that stereocontrol was obtained with lithium aluminium hydride in reductions of the keto-epoxide (Scheme 1.18).

In order to gain some insight into the diastereoselectivity expected in these cases molecular mechanics calculations using the MM2[42] force field and multiconformational analysis as implemented by Still's MacroModel[43] program were used to predict the global minimum energy conformer of a simple 7-membered unsaturated cyclic ether. Its geometry was then inspected in order to predict the relative stereochemistry expected by peripheral attack on the would-be carbonyl π-face (see Chapter 3 for a more detailed description of the general procedure). The global minimum energy conformer of a 7-membered system is shown below with oxygen at the $C_{sp}2$ centre and a metal symbol introduced for clarity (Figure 2.9).

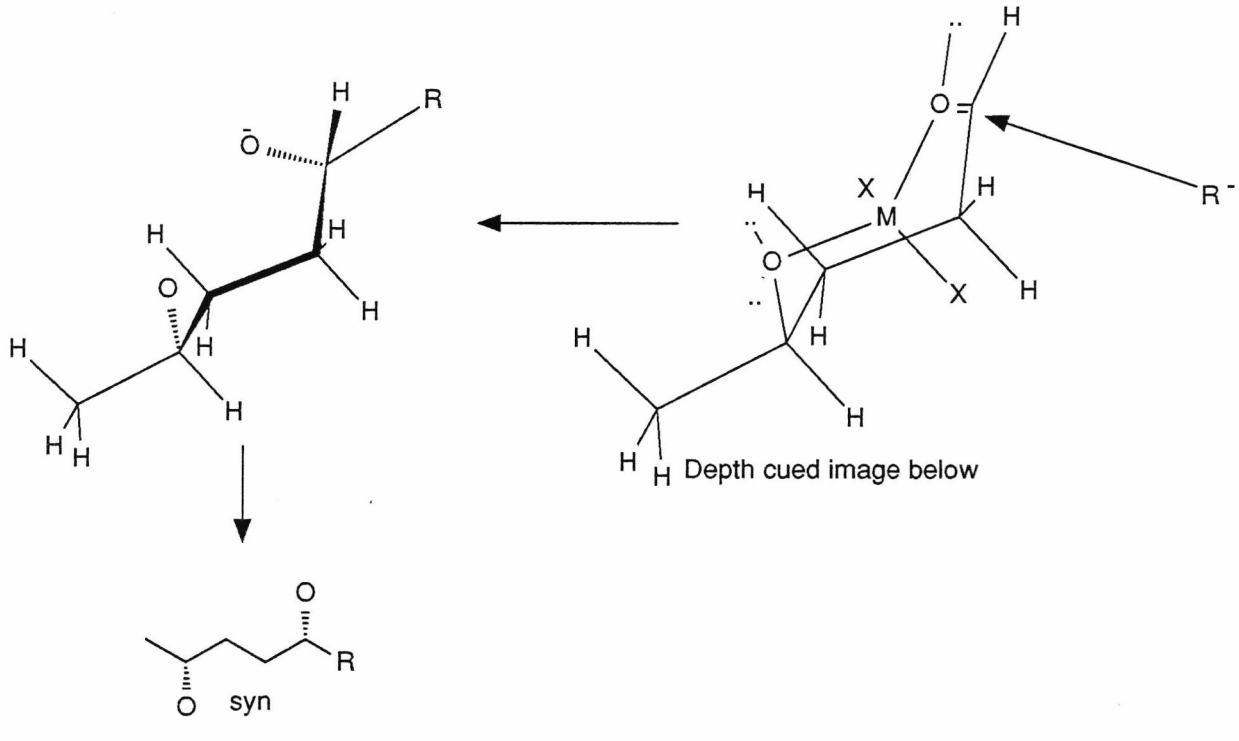


Figure 2.9.

It is interesting to note that this predicted *syn* selectivity is displayed by Tsuchihashi's methodology, but the *anti* selectivity displayed by Reetz's process is in contrast to that expected from the calculated model geometry.

If it is assumed that the diastereoselective reduction observed by Kishi (Scheme 1.19)

occurs via an intermediate with a geometry similar to that displayed in Scheme 2.9 one finds that the opposite stereoisomer to that observed is expected (Figure 2.10).

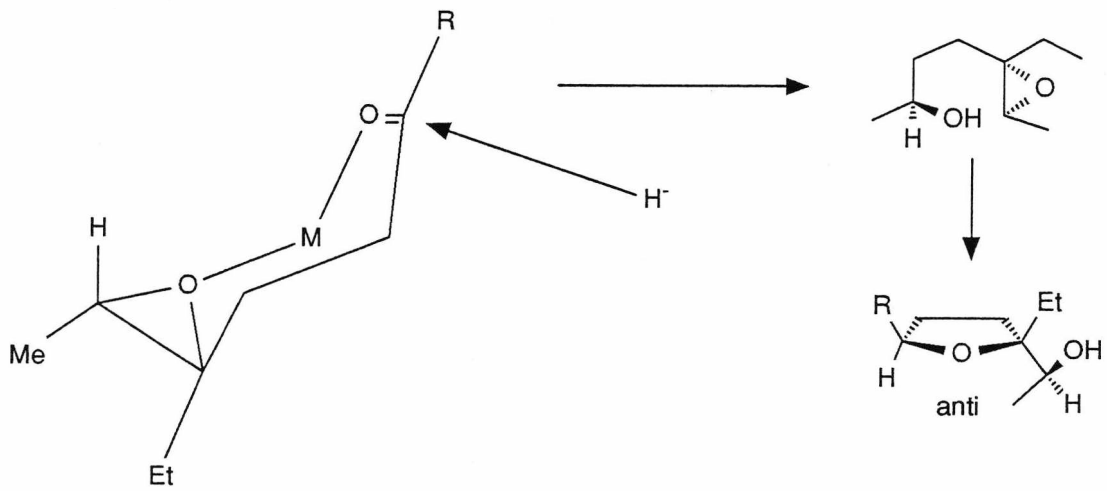


Figure 2.10.

In the additions reported by Still (Scheme 1.20), borane was thought to firstly add to one double bond, followed by formation of a cyclic intermediate or transition state during the second addition. A pair of cyclic transition states were proposed to explain the selectivity in a simple case (Figure 2.11).

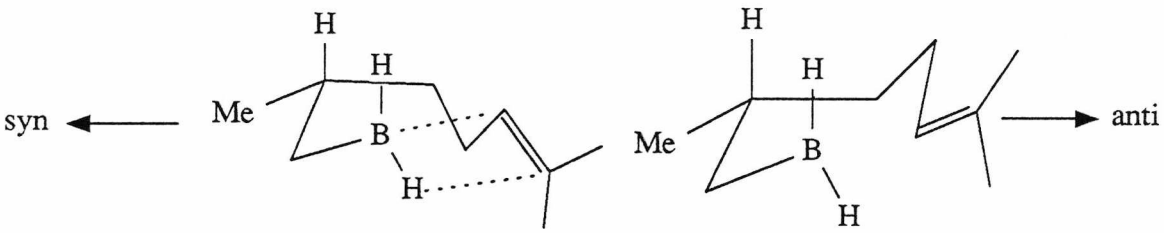


Figure 2.11.

2.5: [1,5]-Asymmetric Induction

Tsuchihashi has used an 8-membered chelate ring (Figure 2.12) to explain the diastereoselectivity observed (Scheme 1.22), but as in the preceding examples of [1,4]-asymmetric additions presented by Reetz, Tsuchihashi and Kishi no indication was given as to the method of choosing the most likely conformation of the ring.

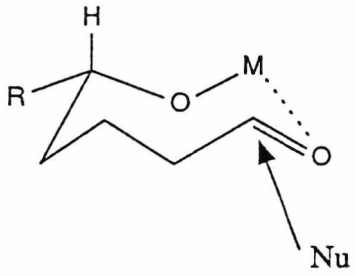


Figure 2.12

A simple 8-membered hydrocarbon ring was modelled using MM2 and multiconformational analysis in order to explore the geometry of the global energy minimum conformer. It was found that the calculated geometry predicted the *syn* selectivity observed experimentally (Figure 2.13).

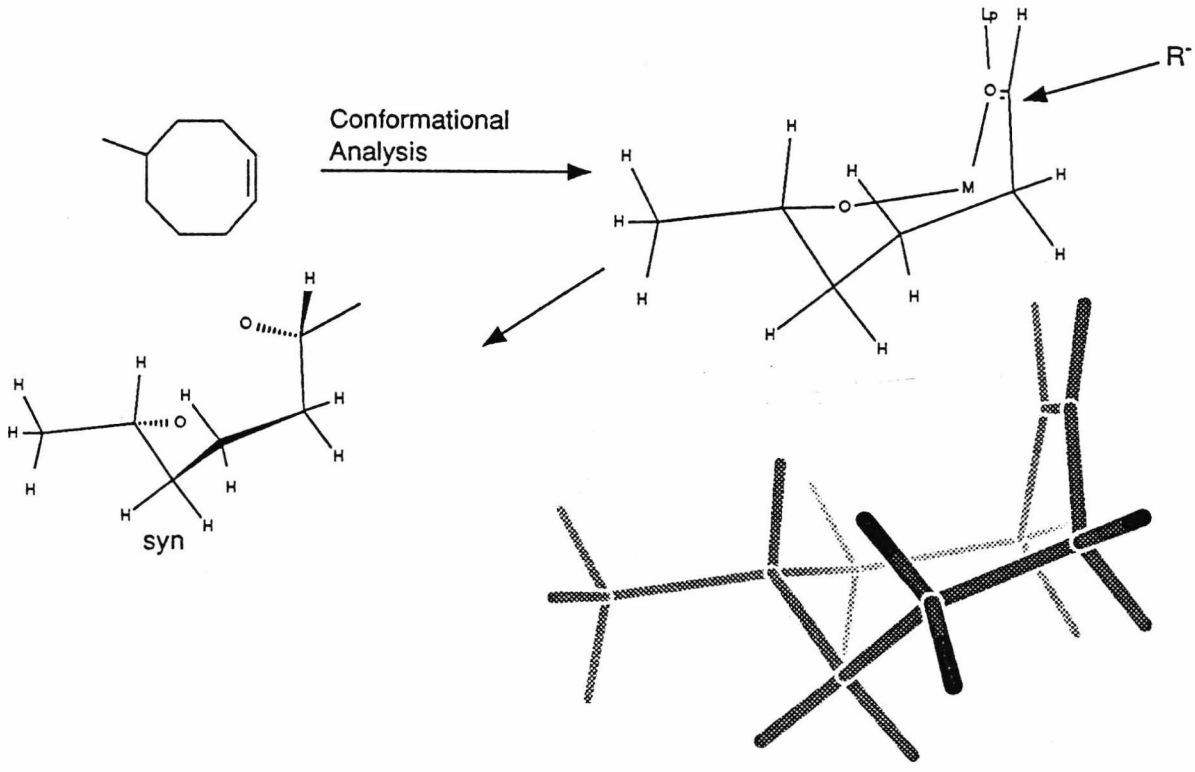


Figure 2.13

In the diastereoselective synthesis of the *cis*-alkene (Scheme 1.23) Thomas tentatively suggested a reaction pathway that accounted for the observed stereochemistry (Figure 2.14).[39]

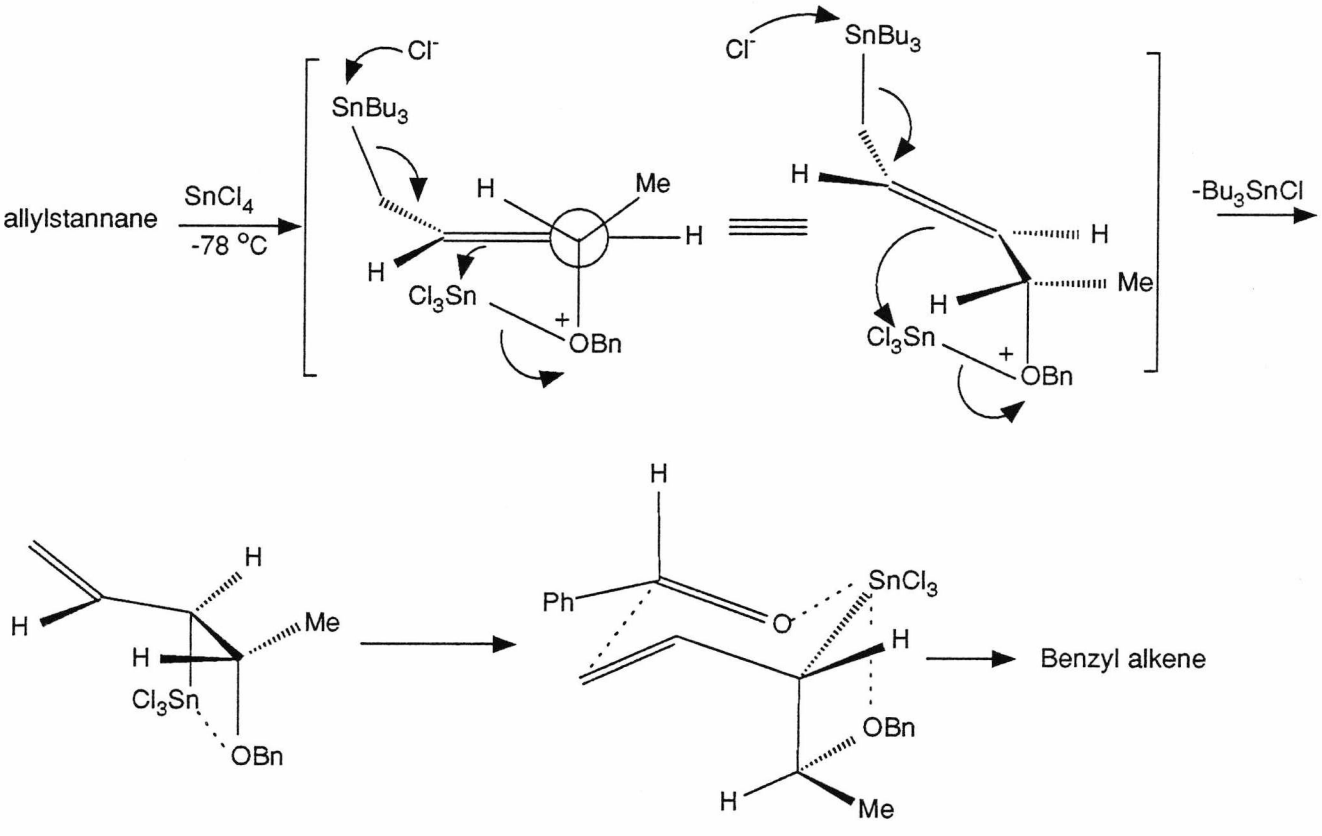


Figure 2.14.

It was thought that stereoselective formation of the allyl(trichloro)stannane intermediate was the primary factor in controlling the overall diastereoselectivity of the process.

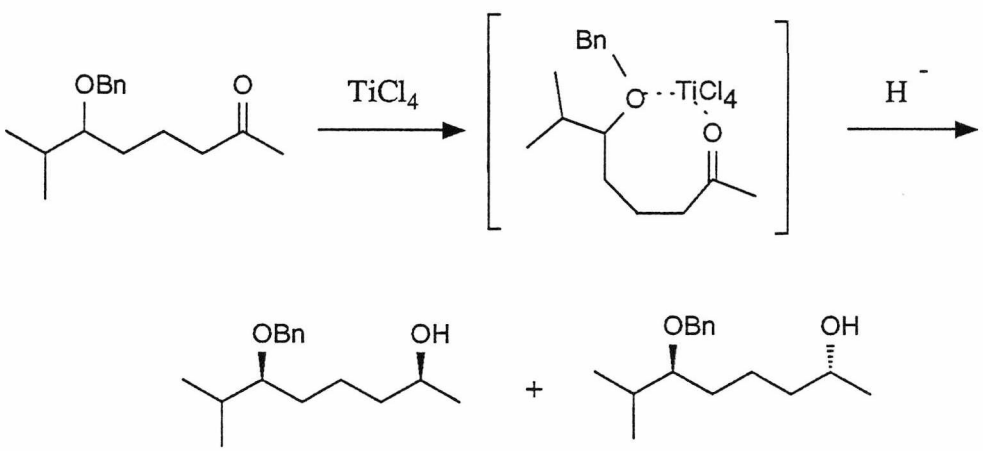
In Still's borane addition (Scheme 1.22) no intermediate is presented. However it was implicit that the reaction was thought to proceed via a process similar to that indicated in Figure 2.11.

3.1: Molecular Mechanics Calculations in Asymmetric Induction

Still[44] has had a great deal of success in predicting the extent and direction of remote asymmetric induction in the alkylation of cyclic ketones and lactones on the basis of the lower energy conformers of 8- to 12-membered enolates using MM2 calculations. Vedejs[45] has used a slightly different approach to rationalize the stereochemistry of osmylations and epoxidations by analysing the local environment of the reacting functional group and thus eliminating the need for a full conformational search. Weiler[46] has used conformational analysis with MM2 to predict the remote asymmetric induction observed in the reduction of a 14-membered macrolide.

3.2: Conformational Analysis of 8-Membered Rings

It was thought that methods might be developed to control the formation of a new chiral centre in δ-alkoxy ketones, for instance 6-benzyloxy-7-methyl octan-2-one with metals such as titanium tetrachloride, followed by attack of hydride (Scheme 3.1).



Scheme 3.1.

In chapter 2 cyclic intermediates were presented which on the whole accounted for the stereochemical outcome observed in the reactions seen in chapter 1. The success of the asymmetric reactions relies on reducing the degrees of freedom of a flexible acyclic chain of atoms by either chelation or some cyclic transition state allowing (to a first approximation) transannular non-bonded interactions to provide some conformational

bias, which has the effect of increasing the differentiation of the diastereotopic π-face in the substrate molecule.

It was hoped that molecular mechanics calculations using MM2 would allow analysis of the conformations of 8-membered rings pertinent to the synthetic studies in this work. As the force field is not parameterized for O-Ti coordinate bonds an appropriate simplified model was required. The proposed chelate (**A**) was initially analysed using the simple model (**B**). Other model rings were looked at, in order to generate a closer approximation to the chelate (**A**), for instance (**C**) (Figure 3.1).

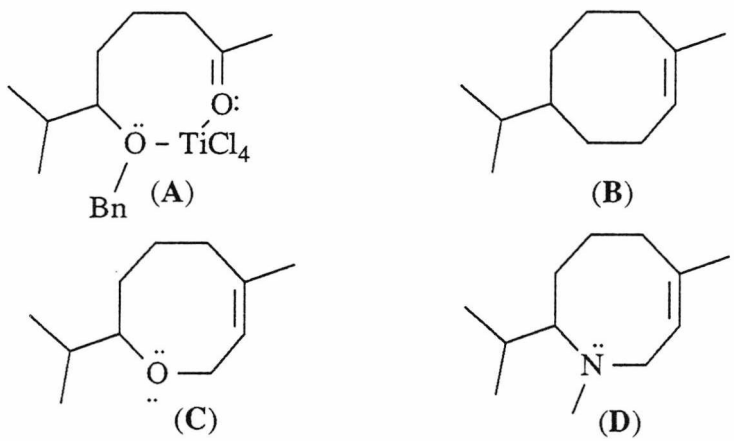


Figure 3.1.

Multiconformational analysis was used to generate a series of trial structures using 60 ° torsional angle increments with a closure window of 2 Å. These were then batch minimized using 250 iterations of the block diagonal Newton Raphson method, followed by 50 iterations using full Newton Raphson method. A test was then performed for minimum energy conformation. All structures more than 20 $kJ.mol^{-1}$ higher in energy than the global minimum energy conformer were discarded.

The model compound (**D**) was considered to be the best structure for which parameters existed in our modelling package. ***Note***: *two trial structures are required to analyse the system because of inversion of the methyl and lone pair substituents at the nitrogen.*

An array of low energy structures (constituting 99 % of the population) was generated.

They were then analysed by studying the ring puckering in each conformer. This was done by a least squares rigid superimposition of the H_3C-C=C-H π-face of the global minimum energy structure with that of the higher energy structures in the conformational array (Figure 3.2). Then numerical entries under the displayed structures refer to the conformer numbers.

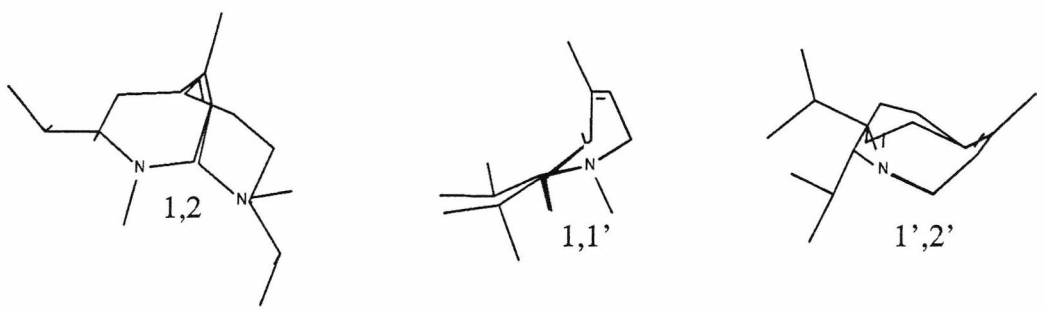


Figure 3.2.

It can be seen from the above models that the π-bond in the global minimum energy structures (1 and 1': two global minima due to the two sets of trial structures through inversion at N) is sitting approximately perpendicular to the plane of the ring, thus the two π-faces of each occupy very different steric environments. If one assumes that chelate (**A**) has a geometry similar to that of the models *and* that attack of an incoming nucleophile will occur preferentially (if not exclusively) on the less hindered (*exo*) π-face, then a mechanism for asymmetric induction exists.

However, it is apparent from Figure 3.2 that structure 2 offers the opposite π-face. This will result in the opposite diastereoselectivity through peripheral attack. If this structure is close in energy to that of the global minimum then the asymmetric induction may be poor.

Fortunately, the strain energies calculated using MM2 will allow a simple Boltzmann analysis of the relative populations of the conformers. The Boltzmann ratios for each conformer are contained in the entry for (n_i/q) (see Appendix A). The structures are minimized as can be seen from the RMS values, and correspond to minimum energy structures (Table 3.1).

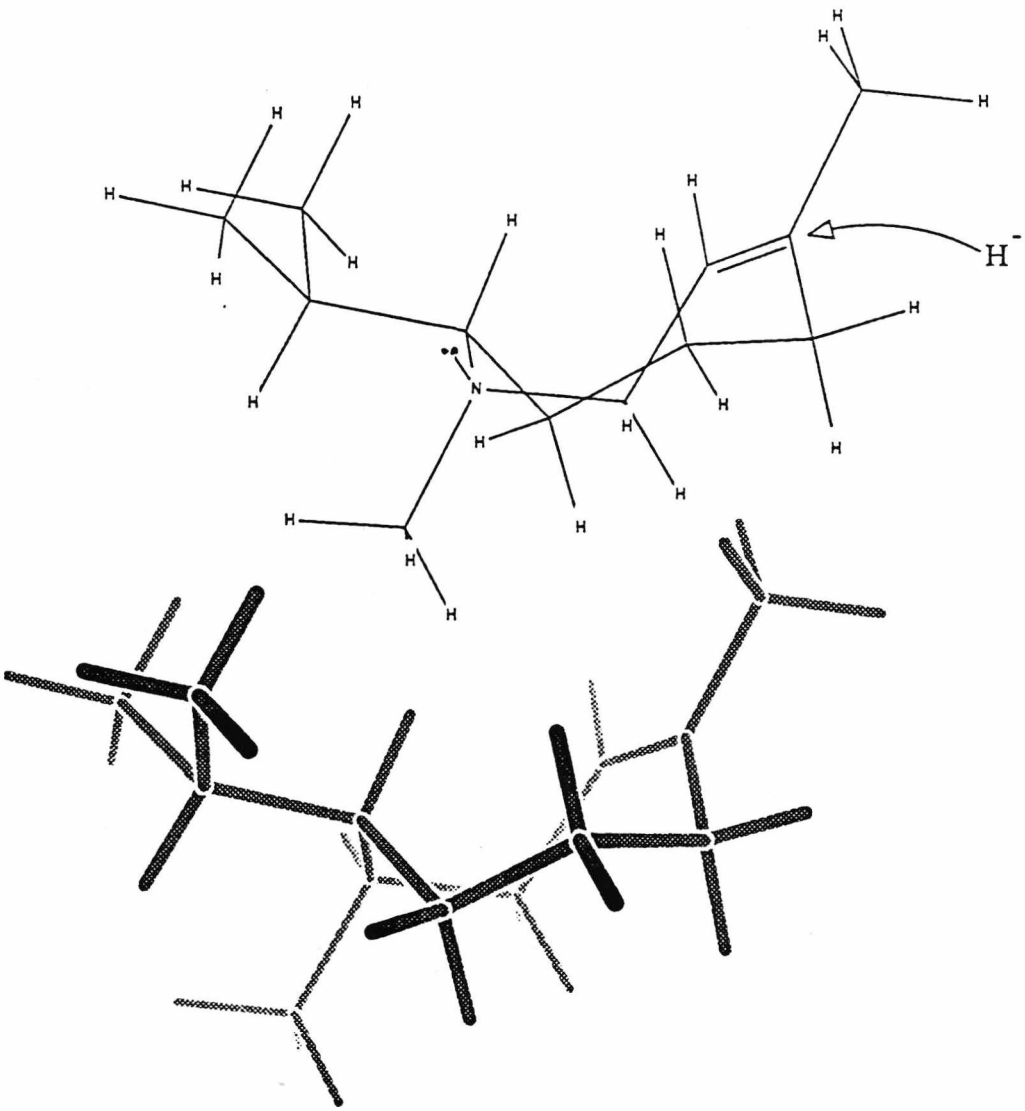
Conformation	Energy/kJ.mol^{-1}	RMS	MTEST	n_i/q (-78 °C)	Sense*
1	103.28	0.001	Minimum	0.6389	+
2	105.81	0.001	Minimum	0.1244	-
1'	105.19	0.000	Minimum	0.1969	+
2'	108.69	0.001	Minimum	0.0228	+

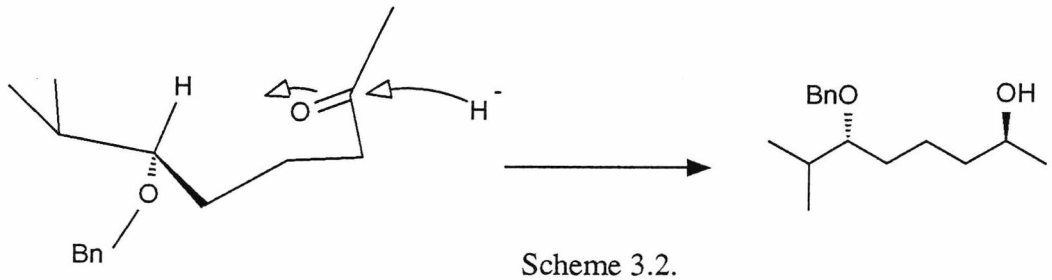
*The plus sign indicates the same selectivity as the global minimum energy conformation 1.

Table 3.1

From the data and simple Boltzmann analysis one may expect a selectivity of ca. **7:1** at -78 °C.

Below is shown the global minimum energy conformation of the model structure (**D**).





Scheme 3.2.

It is clear from Scheme 3.2 that peripheral attack of hydride on a chelate with a geometry similar to such a global energy minimum structure would lead to the formation of the ***anti*** benzyloxy-alcohol. This would then provide complementary selectivity to Tsuchihashi's method (Scheme 1.21) and has an added advantage due to differential functionalisation at the chiral centres for further synthetic manipulation.

If one were to replace the benzyl group in the above structure with an acetate group then the possibility exists for co-ordination of the sp^2 oxygen of the acetate group, allowing the possibility of 10-membered chelate formation. A suitable model structure was chosen for conformational analysis as before (Figure 3.3).

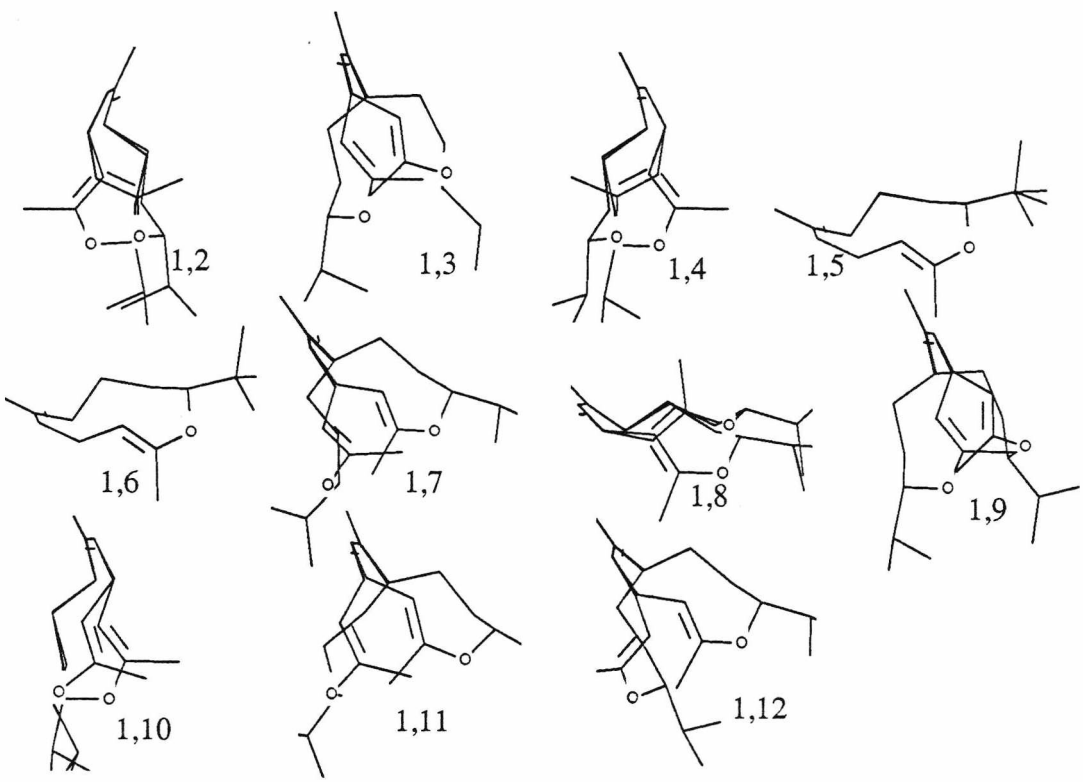


Figure 3.3.

The strain energies and the geometries of the conformers were used to predict the diastereoselectivity of chelation controlled reduction of the corresponding acetoxy ketone (Table 3.2).

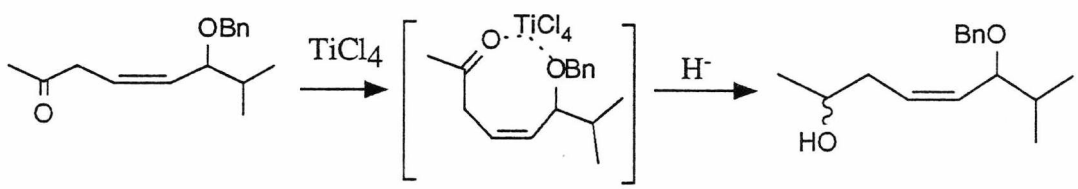
Conformer	Energy /kJ.mol^{-1}	RMS 1st Devivative	MTest	n_i/q (-78 °C)	Sense*
1	116.44	0.002	Minimum	0.3087	+
2	116.67	0.001	Minimum	0.2662	+
3	117.76	0.001	Minimum	0.1369	-
4	119.76	0.001	Minimum	0.0526	+
5	119.84	0.001	Minimum	0.0380	+
6	120.00	0.001	Minimum	0.0344	+
7	120.04	0.001	Minimum	0.0336	-
8	120.06	0.001	Minimum	0.0332	+
9	120.42	0.001	Minimum	0.0266	-
10	120.84	0.001	Minimum	0.0210	+
11	121.15	0.001	Minimum	0.0169	-
12	121.87	0.001	Minimum	0.0107	-

*The plus sign indicates the same selectivity as the conformation 1.

Table 3.2.

By inspecting the geometry of the lowest energy model conformer (assuming that its geometry is similar to the proposed real chelate) one finds that the ***anti*** product is expected with a selectivity of **3.4:1** at -78 °C.

Consider the following proposed reaction (Scheme 3.2).



Scheme 3.2.

It was thought that placement of a *cis* double bond in the chain might facilitate chelate formation, by reduction of ring strain (through removal of some transannular non-bonded interactions). In addition, since the two portions of the carbon chain bearing the co-ordinating oxygens are constrained to the same side of the double bond, the chances of an encounter leading to chelate formation may be increased. A simple all hydrocarbon model was looked at in order to obtain some idea of the expected conformational array of

the proposed chelate.

Preliminary calculations made use of an appropriately substituted cyclooctadiene. Inversion of co-ordinating ether of the chelate was taken into account by inversion at the analogous centre, resulting in two trial structures. These were minimized and analysed as before. The superimpositions of the conformational array on the appropriate π-face of the global energy minimum structure of a the simple (all hydrocarbon) model system are displayed (Figure 3.4).

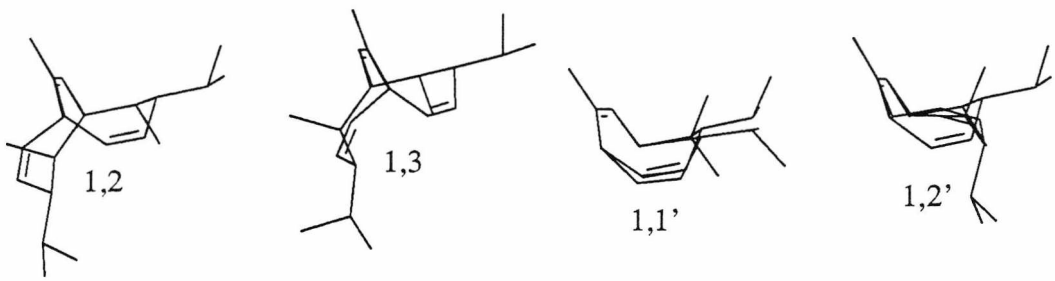


Figure 3.4.

It can be seen from the calculated structures that the π-faces of interest of the global energy minimum structure offer quite different steric environments to an attacking nucleophile, as required. Furthermore, analysis of the relative energies of the conformational array (Table 3.3) leads to a predicted ***anti*** diastereoselection of **10.7:1** at -78 °C

Conformation	Energy/kJ.mol^{-1}	RMS	MTEST	n_i/q (-78 °C)	Sense*
1	73.608	0.001	Minimum	0.803	+
2	77.477	0.001	Minimum	0.074	-
3	80.562	0.001	Minimum	0.011	-
1'	77.971	0.001	Minimum	0.055	+
2'	78.087	0.001	Minimum	0.051	+

*The plus sign indicates the same selectivity as the global minimum energy conformation 1.

Table 3.3.

However, when the MeCH portion of the model compound was replaced with MeN-Lp to more closely resemble BnO-Lp in the actual system (by analogy with model **D**), the

results were poor (Figure 3.5).

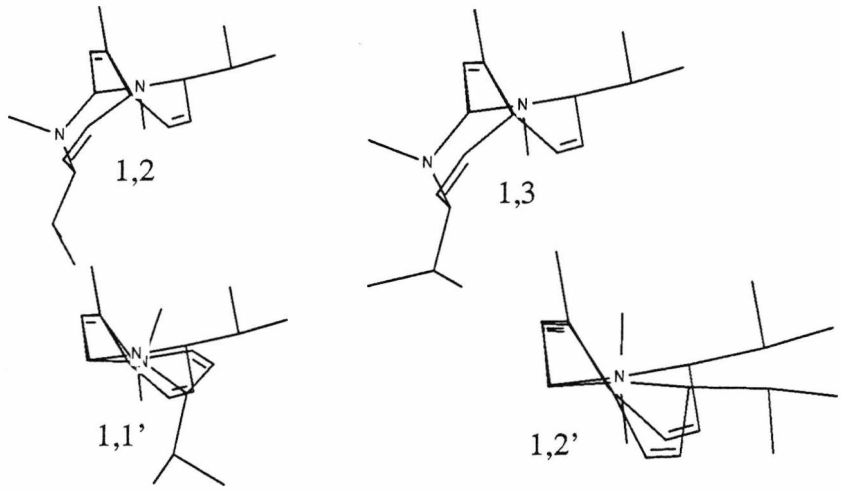


Figure 3.5.

Conformation	Energy/kJ.mol^{-1}	RMS	MTEST	n_i/q	Sense*
1	85.707	0.000	Minimum	0.64434	+
2	86.891	0.000	Minimum	0.31060	-
1'	91.001	0.001	Minimum	0.02467	+
2'	91.439	0.001	Minimum	0.01883	+

*The plus sign indicates the same selectivity as the global minimum energy conformation 1.

Table 3.4.

The four conformers displayed represent 99 % of the calculated conformational array. Using Boltzmann analysis and considering the ring geometries (Table 3.4) one expects **2.8:1** ***anti*** selectivity at -78 °C.

3.3: Parameterization of MM2 from Crystal Structures

It is an understatement to suggest that using a methylene group to model a distorted octahedral metal centre is unlikely to give a clear picture. This problem is compounded by using C=CH- groups to represent C=O- groups. Therefore, development of a set of parameters for MM2 which will allow calculation of an octahedrally co-ordinated titanium species has been looked into.

Helmchen[47] has isolated a 7-membered titanium tetrachloride chelate of a chiral dienophile whilst studying Lewis-acid-catalysed asymmetric Diels-Alder reactions (Figure 3.6).

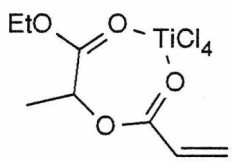


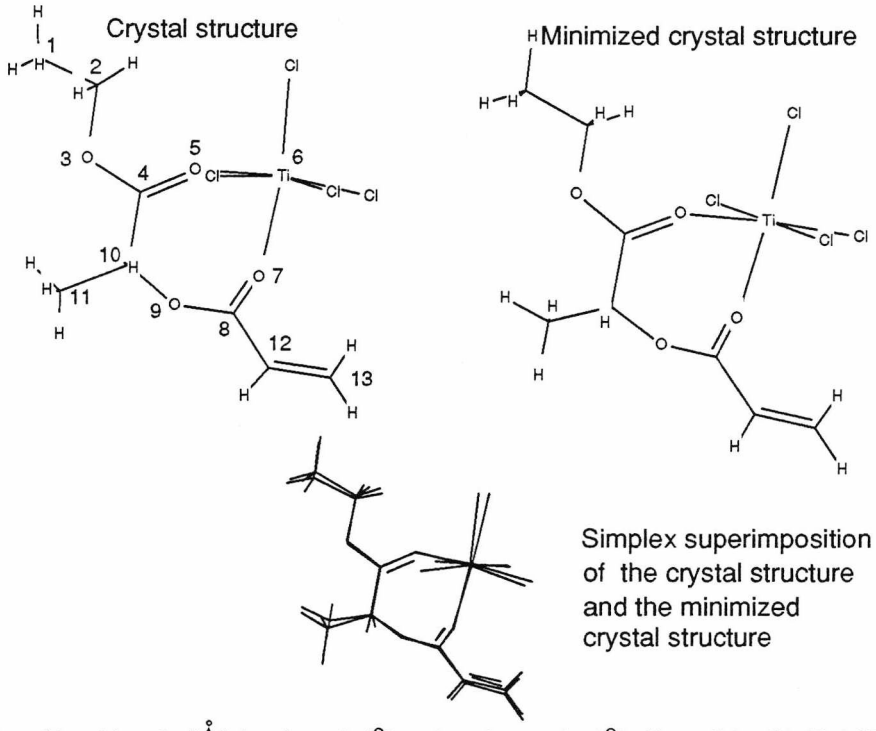
Figure 3.6.

The crystal structure of their chelate was obtained from the Cambridge Structural Database and imported into MacroModel. Bond lengths, bond angles, and dihedral angles in the structure were then inspected.

From this information a set of MM2 force field parameters was drawn up. It was thought that the first step in parameterization would be to generate a set of parameters which would cause minimum distortion to the crystal structure on minimization.

As can be seen from images and data (Figure 3.7) the minimized structure is not too different from that of the crystal structure. Differences are commonly observed between crystal structures and MM2 minimized structures; this is due to crystal lattice forces leading to distortions. Allinger expects bond lengths to vary by ca. 0.003 Å, 1° for bond angles, and torsional angles may vary by much more.[48] Clearly, our bond lengths and angles are in outside the expected error. This is not too surprising though, since Allinger's parameters have been optimized to a much higher level. It is interesting that the larger deviations in the minimized structure are in the regions where the standard MM2

parameters apply.



Selected bond lengths [Å], bond angels [°], and torsion angles [°]:- Expt, Calc: C1-C2 1.376, 1.533; C2-O3 1.524, 1.414; O3-C4 1.294, 1.367; C4-O5 1.215, 1.217; O5-Ti6 2.136, 2.135; Ti6-O7 2.189, 2.186; O7-C8 1.243, 1.244; C8-O9 1.346, 1.366; O9-C10 1.456, 1.417; C10-C11 1.506, 1.537; C8-C12 1.456, 1.477; C12-C13 1.311, 1.341: C4-O5-Ti6 132.0, 130.7; O5-Ti6-O7 81.4, 81.4; Ti6-O7-C8 134.1, 132.6; O7-C8-O9 122.7, 121.8; C8-O9-C10 119.8, 118.4; O9-C10-C4 109.2, 113.6: O3-C4-O5-Ti6 132.2, 106.1; C4-O5-Ti6-O7 49.2, 46.9; O5-Ti6-O7-C8 36.3, 45.3; Ti6-O7-C8-O9 -63.6, -58.6.

Figure 3.7.

The initial parameters used above were applied to two other titanium chelate crystal structures. Unfortunately the minimized structures were markedly different to the crystal structures. The parameters were re-examined and modified in order to be more applicable across the available data.

One major disadvantage in the parameterization of an octahedral system in MM2 is that the torsional term in the force field equations does not have the correct periodicity for the octahedral environment. For instance, if one wishes to describe the energy change on rotation about a double bond for a molecule such as ethylene, then a large V_2 would be used in E_v (Figure 3.8). The V_2 term has maxima when the torsional angle about the double bond is 90 ° and 270 °. This makes chemical sense since, at these angles overlap of the π-orbital should be zero due to orthogonality.

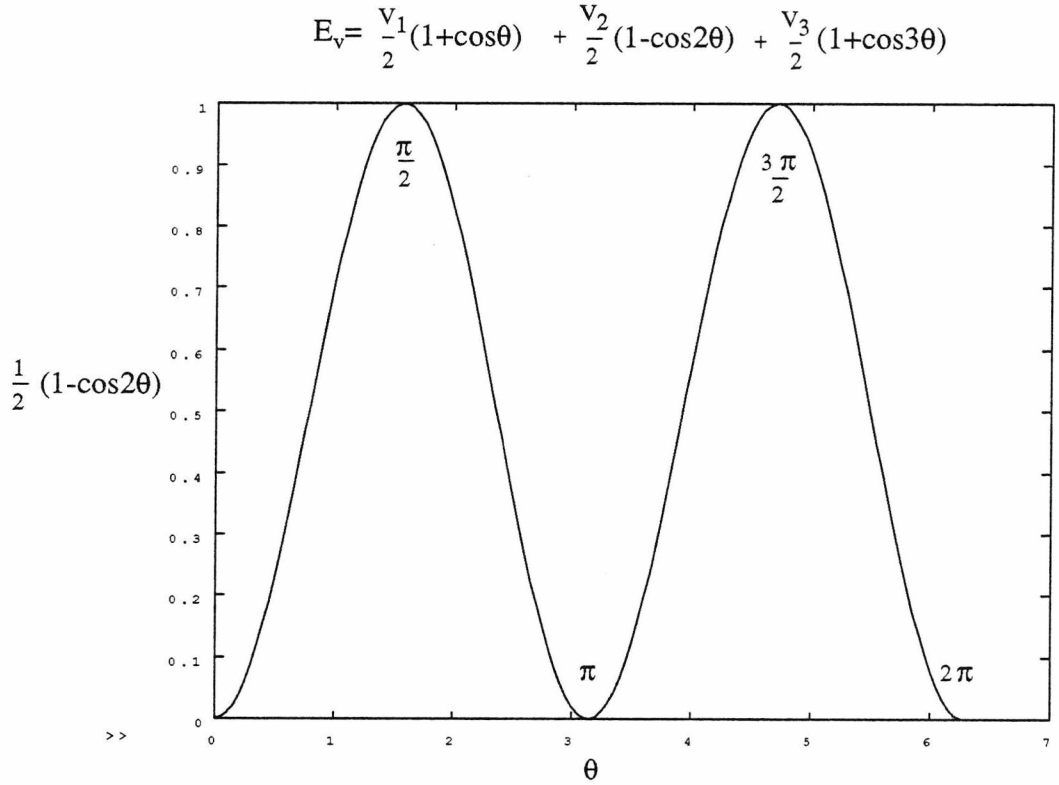


Figure 3.8.

In but-2-ene the *cis* isomer would have a higher internal energy than the *trans* isomer. This results from the increased steric interaction of the subsituents of the double bond when the torsional angle is 0°. Thus E_v would be higher at $\theta = 0$ and 2π than at $\theta = \pi$ in the above diagram. This would be described by addition of a V_1 term of appropriate magnitude as well as non-bonded terms. The V_1 term has maxima at 0 and 2π radians.

For rotation around a single bond in a hydrocarbon such as butane the V_3 term would allow a description of the variation of internal energy. Here the summation of the three terms in the torsional equation is required. When each term in the equation has the same value a plot is obtained which is close to the expected form. It would be tempting to adjust the parameters so that the plot closely resembles the actual variation of internal energy as a function of torsional angle so that the energy difference between the *eclipsed*, *gauche* and *anti* forms was more accurately represented (Figure 3.9).

$$E_v = \frac{1}{2}(1+\cos\theta) + \frac{1}{2}(1-\cos 2\theta) + \frac{1}{2}(1+\cos 3\theta)$$

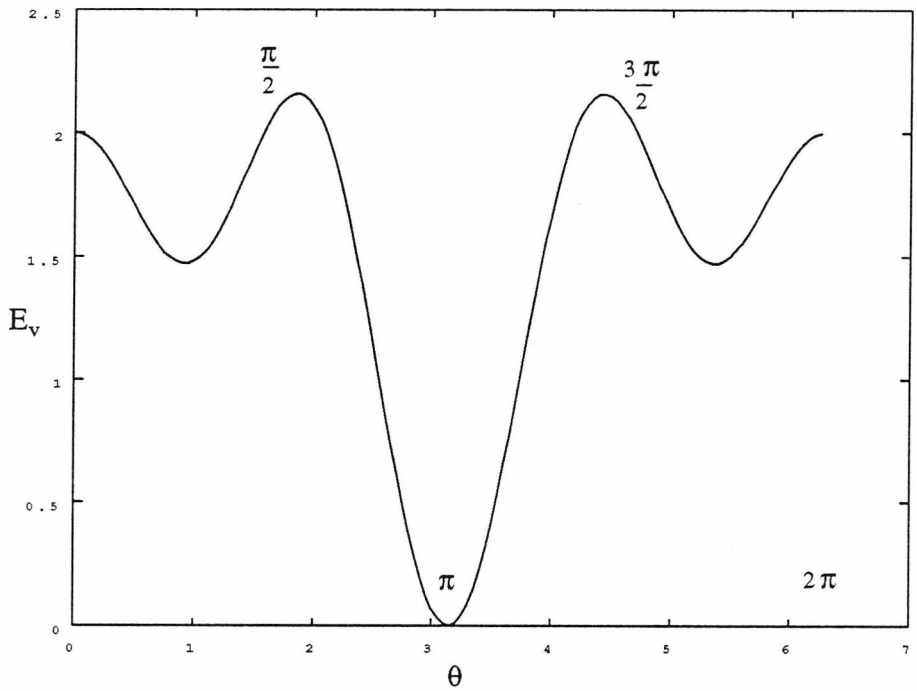


Figure 3.9.

If one looks at the torsional parameters used to to describe a four carbon fragment in MM2 one finds that they give rise to a potential energy function with a rather different shape to that expected (Figure 3.10).

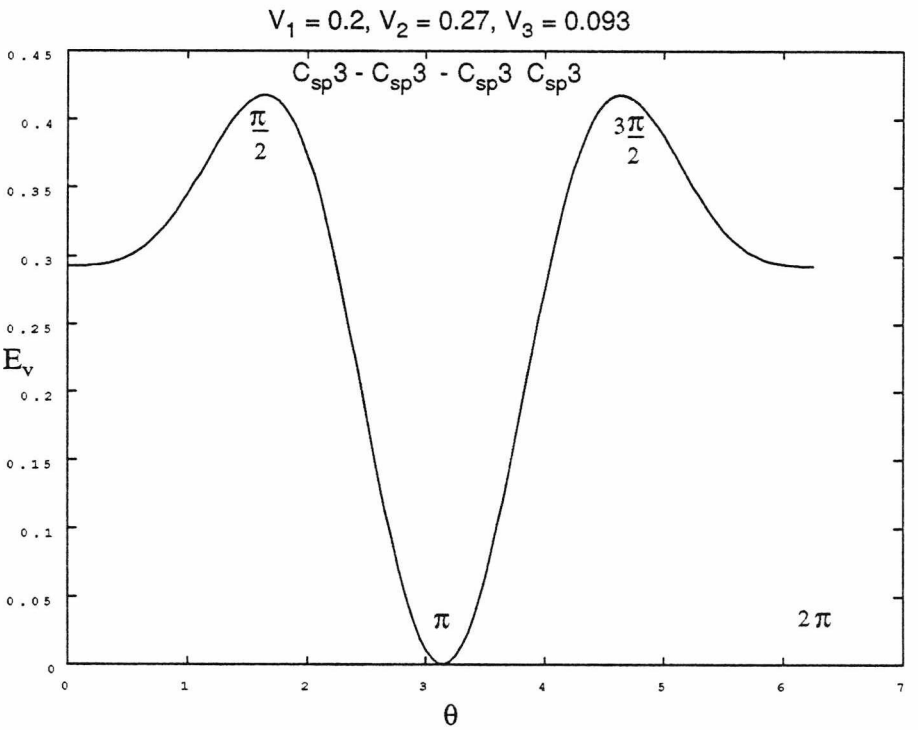


Figure 3.10.

The onefold torsional term has been likened to dipole interactions, the twofold term has

been thought to represent hyperconjugative interactions in alkanes and conjugation in alkenes and the threefold term represents steric interactions.[42]

For an octahedral species four fold periodicity is probably required in order to approximate the environment (Figure 3.11).

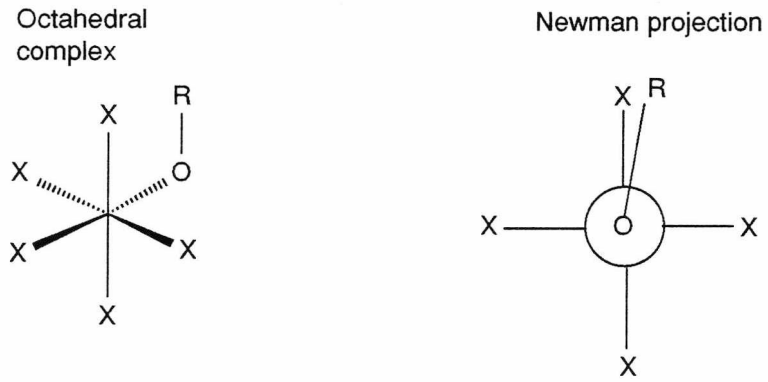


Figure 3.11.

The addition of a V_4 term in the force field equation would allow the above situation to be approximately described (Figure 3.12).

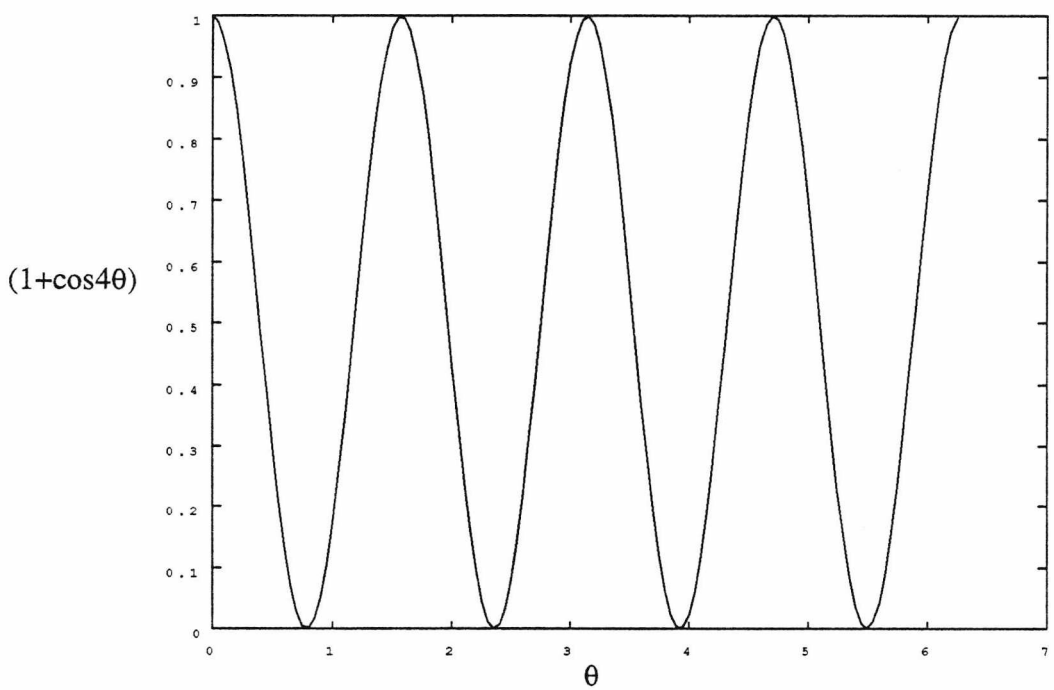


Figure 3.12.

As a result of the limitation of the torsional terms around the octahedral centre, the problematic torsional terms were set to zero.[49] It was hoped that Van der Waal's

interaction would give a rough estimate of the symmetry. This approach, while rather crude, was unavoidable. However, modification of Van der Waals terms to predict molecular geometries was persued prior to the introduction of the onefold an twofold torsional term into Allinger force field.[50]

The parameters were modified so that a more reasonable agreement across the crystal structures was obtained. The crystal structure obtained by Viard[51] was minimized. The result was a minimum energy structure. The calculated and experimental C=O and O-Ti bond lengths along with the O-Ti-O bond angle were compared (Figure 3.13).

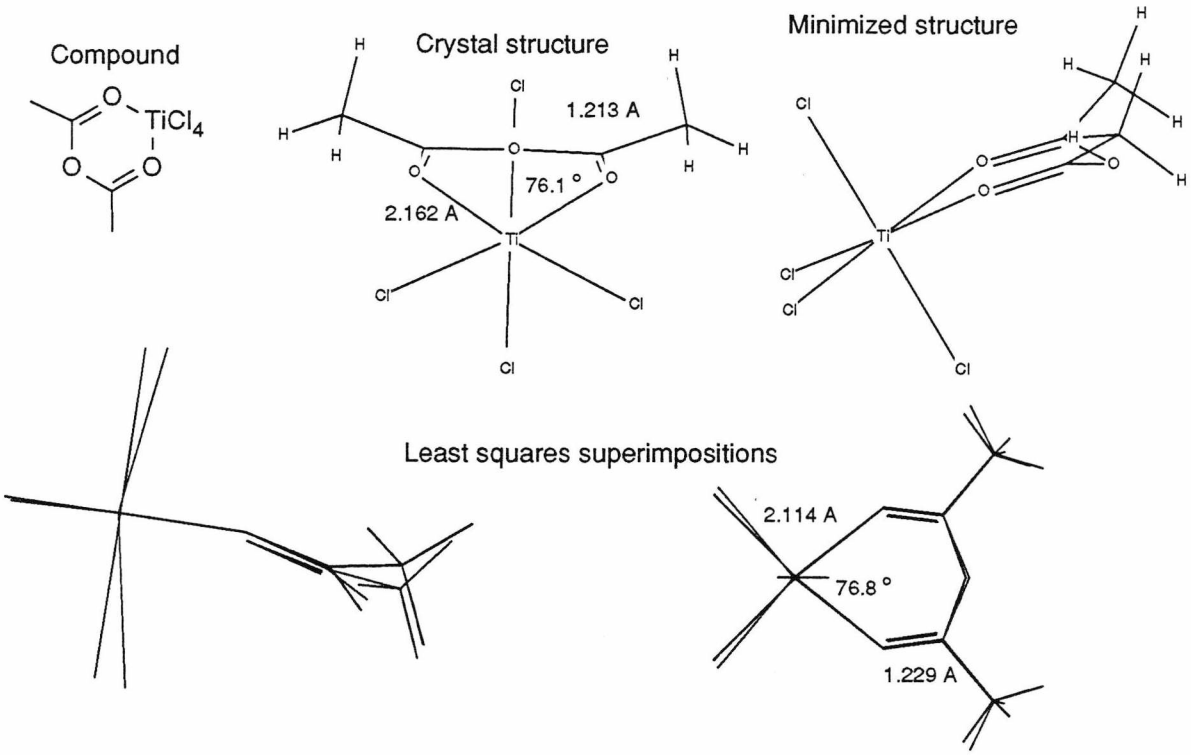
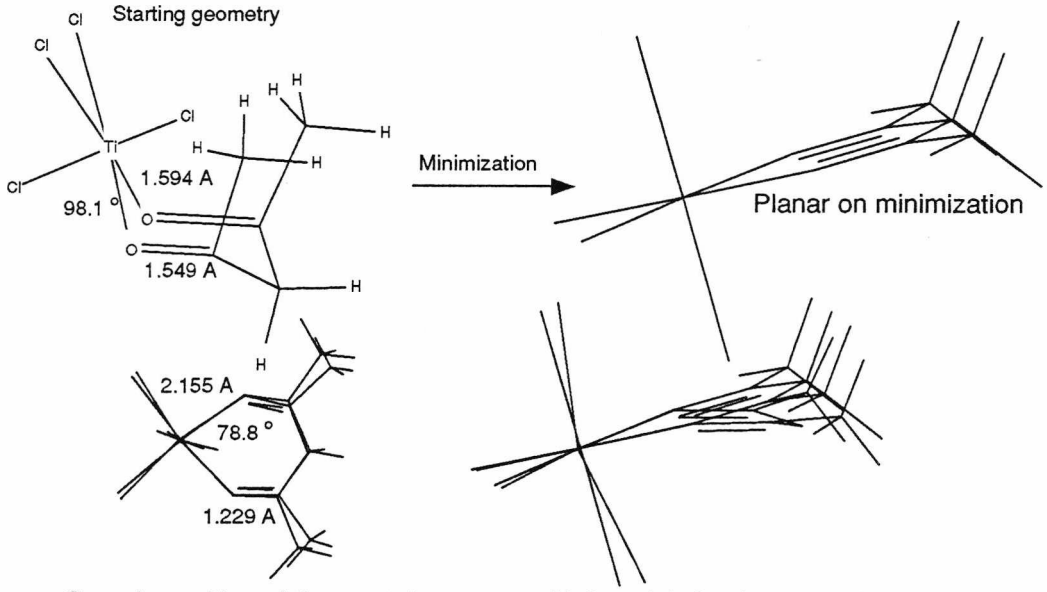


Figure 3.13.

The crystal structure puckered about C(Me)-$O_{sp}3$-C(Me) this was attributed to forces lattice causing distortions. This distortion was not intruduced into the force field parameters and thus it was expected that a planar geometry would be found on minimization. The failure to achieve planarity about the ring on minimization was attributed to the lack of parameterization for lone pair interaction. This was crudely tested by fusing an octahedral Cl_4TiC_2 portion with a O=CH-CH_2-CH=O fragment derived from a chair conformer of cyclohexane. Minimization of this structure did lead to the expected

planar geometry of the ring, thus it was concluded that the inclusion of parameters to take into account the missing lone pair interaction should lead to the expected result in the above example (Figure 3.14).



Superimposition of the crystal structure withthe minimized test starting geometry.

Figure 3.14.

Minimization of the crystal structure obtained by Sobota[52] gave the following geometry (Figure 3.15).

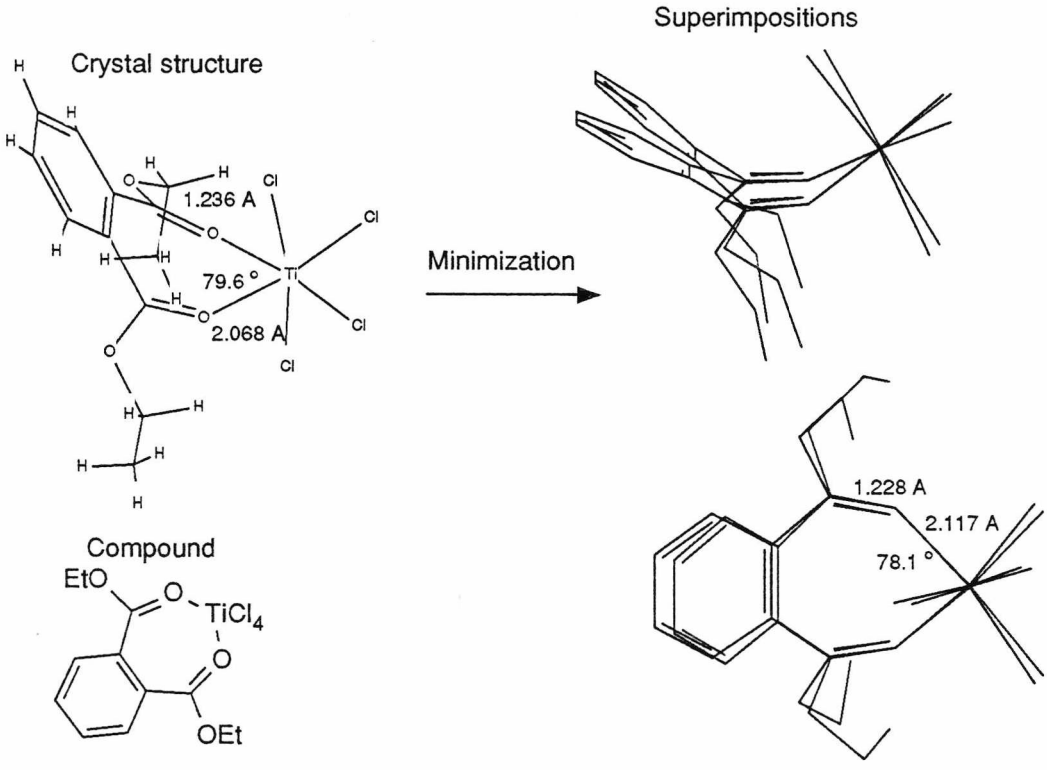


Figure 3.15.

The Helmchen crystal structure was re-minimized with the improved parameters (Figure 3.16).

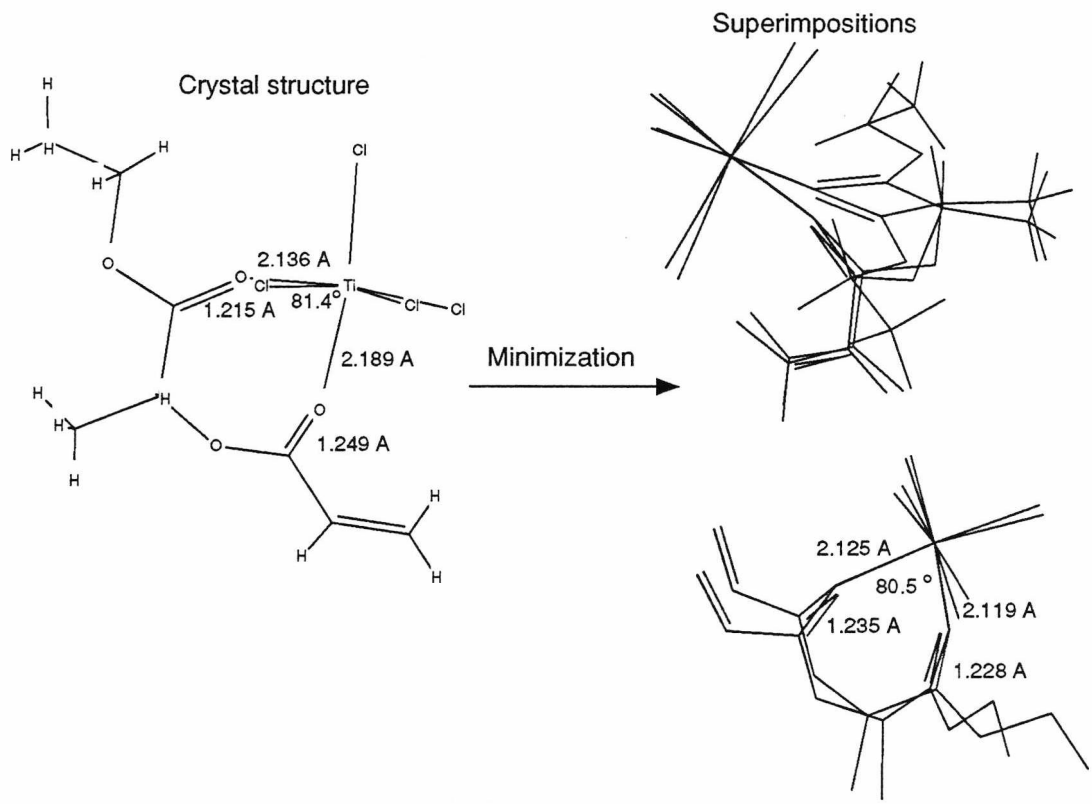


Figure 3.16.

Considerable distortions were observed on minimization of the crystal structure with the new parameters. Whilst the geometry around the titanium centres was in accord with that observed in the crystal structure, the puckering in the ring changed significantly.

In order to look into this it was thought that a reasonable test would be to compare a substituted cyclooctadiene with the corresponding eight membered chelate. Although the geometry around the HC=CH-CH_2-CH=CH portion would be expected to be quite different to the analogous HC=O-Ti-O=CH portion, it would not be unreasonable to assume that the ring puckering in the rest of the carbon framework would be similar in the two structures.

The result of the multiconformational analysis and minimization calculations was quite pleasing. Both rings were minimized. The global energy minimum structures were superimposed and (apart from the distortion around the titanium centre due to the

parameterization introduced here) the carbon chain conformation corresponded closely in each structure (Figure 3.17).

Stereoscopic View
Hydrocarbon E = 55.174 kJ.mol^{-1} RMS = 0.001 Minimum
Chelate E = 74.378 kJ.mol^{-1} RMS = 0.001 Minimum

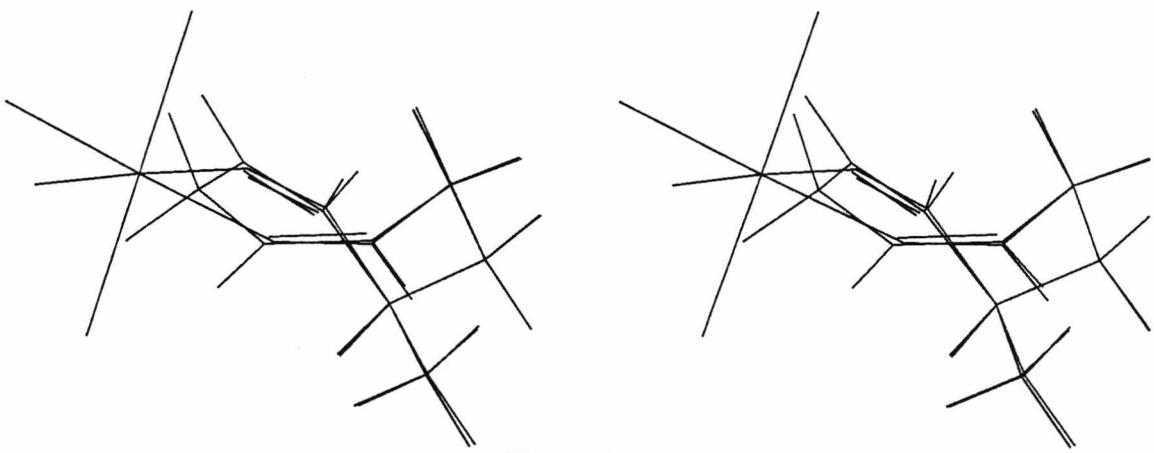


Figure 3.17.

The next higher energy conformers of each ring were superimposed. In this case their puckering was quite different. In addition, the all hydrocarbon system had a strain energy of only 0.4 kJ.mol^{-1} higher than the global minimum energy conformer, whereas the chelate model was some 18.5 kJ.mol^{-1} higher in energy. A number of the higher energy conformer in the hydrocarbon array were compared to the second chelate conformer, however there was little correspondence between their geometries.

An octahedral centre from the chelate was isolated, then inserted into the appropriate position of the second hydrocarbon conformer replacing the methylene. In the model chelates, minimization tended to give structures with strong elements of planarity about the C=O-Ti-O=C centre (cf. crystal structures and minimized crystal structures), whereas the hydrocarbon allowed deformation of this region with the C=C-CH_2-C=C methylene sitting more into the bulk of the ring. An energy calculation on the hydrocarbon and the new starting geometry (derived as explained above) was performed. The most striking feature of this was the difference in Van der Waals contribution to the strain energy of the two. For the hydrocarbon VDW = 19.7 kJ.mol^{-1}, whereas the new model chelate had

VDW = 2702 kJ.mol^{-1} (Figure 3.17). Stretching, bending, and torsional contributions were not radically different (Figure 3.18).

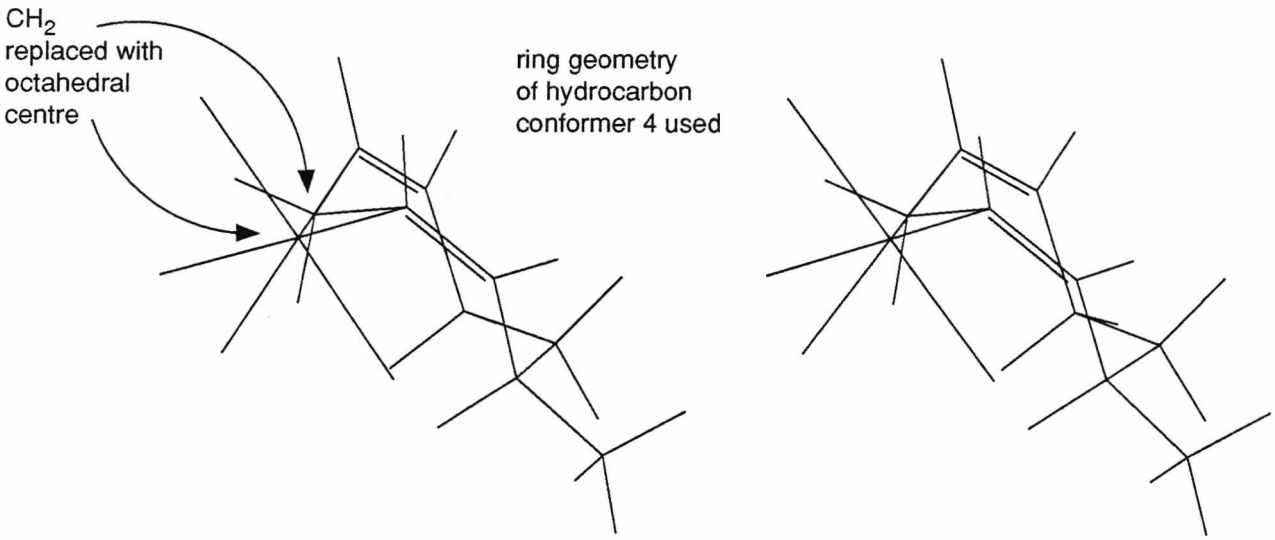


Figure 3.18.

It is clear from the above that one of the chlorine substituents in the chelate is sitting much further into the body of the ring than the axial hydrogen of the hydrocarbon. This is obviously due to the larger Ti-Cl bond length and the octahedral nature of the titanium centre. The above chelate was minimized and gave rise to an identical geometry to that of the fourth conformer discovered by multiconformational analysis with a strain energy of 93.951 kJ.mol^{-1} (Figure 3.19).

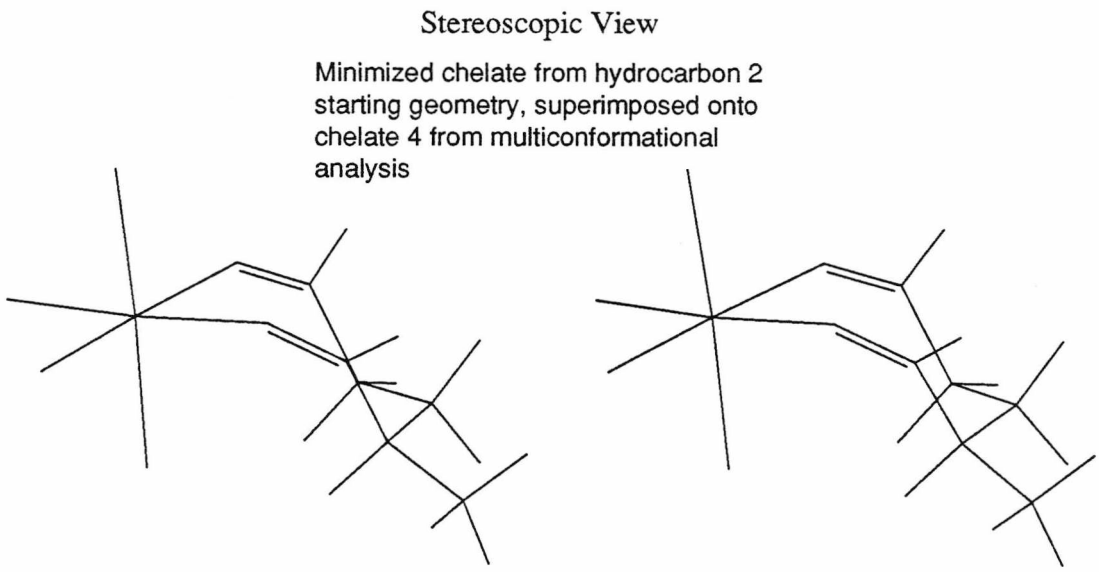


Figure 3.19.

The third hydrocarbon conformer was edited in the same way as described above. It gave rise to a high energy structure which was discarded. The process was not repeated further since 97 trial structures were generated for multiconformational analysis of the chelate system.

The parameters used in the above work were entered into the MM2 force field as a **Special Substructure.**[53] A sulphur atom was used in place of titanium as this is one of the atom types available in MacroModel. No attempt was made to modify the Van der Waals parameter for titanium, that is, the value for sulphur was used. The modifications to the MM2 force field were as follows (Figure 3.20):

```
-3
 C Wild card atoms and bonds to make parameters general
 9  00-C2(-00)=O0-S1(-Cl)(-Cl)(-Cl)(-Cl)-O0=C2-00
-2
 1    2    4                  1.2243     5.0000     0.0000
 1    4    5                  2.1173     5.0000     1.2000
 1    5    6                  2.2000     3.0000     0.0000
 1    5    7                  2.2000     3.0000     0.0000
 1    5    8                  2.2000     3.0000     0.0000
 1    5    9                  2.2000     3.0000     0.0000
 1    5   10                  2.1173     5.0000     1.2000
 1   10   11                  1.2243     5.0000     0.0000
 2    1    2    4            125.0000     0.6000
 2    3    2    4            125.0000     0.6000
 2   10   11   12            125.0000     0.6000
 2    2    4    5            132.0000     0.5000
 2    5   10   11            134.1400     0.5000
 2    4    5   10             76.0000     2.0000
 4   12   11   10    5          1.0000    10.0000     0.0000
 4    1    2    4    5          1.0000    10.0000     0.0000
 4    4    5   10   11          0.0000     1.2000    -0.3500
 4    5    4    2    3          1.0000    10.0000     0.0000
 4   10    5    4    2          0.0000     1.2000    -0.3500
 4    6    5   10   11          0.0000     0.0000     0.0000
 4    6    5    4    2          0.0000     0.0000     0.0000
```

Figure 3.20.

3.4: An *Ab Initio* Study of a Titanium Tetrachloride Complex

In the development of the parameters used above nothing was known of the magnitude of the force constants for bending or stretching interactions. In order to improve the situation an *ab initio* study of a titanium tetrachloride dimethyl ether formaldehyde complex was

attempted.

Although there has been some success at reproducing the geometries of crystal structures titanium tetrachloride complexes at the STO-3G level,[54] a minimal basis set would not be expected to reproduce energies or spectroscopic parameters well.[55]

As a result a larger external basis set, developed by Huzinaga *et al.*,[56] was used. The basis set notation is as follows (Figure 3.21):

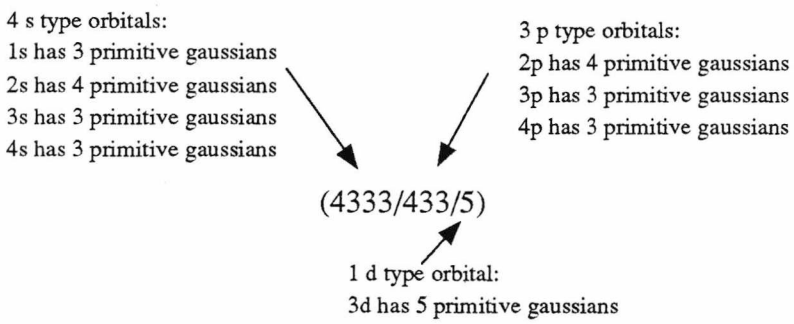


Figure 3.21.

The maximum number of basis functions possible was used for titanium (5333/53/5) and chlorine (533/53). As a result a slightly smaller basis set than available was used for carbon (53/5) and oxygen (53/5).

As stated, larger basis sets for carbon and oxygen were presented by Huzinaga, the largest being (73/7), but it is generally understood that one must choose basis sets with common expansion patterns (or more correctly, contraction pattern). For instance consider FCl: If one were to choose (333/33) for Cl then one would use (33/3) for F. If one were to use (433/43) for Cl then (433/4) for F would be used.[56]

The external basis set was tested against the STO-3G, 3-21G, 6-21G, 6-31G basis sets and compared to the published energies for single atom calculations on C, O, Cl and Ti using Gaussian 88[57] on a CRAY X-MP at the University of London Computing Centre (Table 3.5).

	Energy in Hartrees at SCF Level			
Basis set	C(^{3}P)	O(^{3}P)	Cl(^{2}P)	Ti(^{5}F)
sto-3g	-37.1983925	-73.8041503	*	*
3-21g	-37.4810698	-74.3936572	-457.2765518	not applicable
6-21g	-37.6589657	-74.7009403	-459.4331844	not applicable
6-31g	-37.6778370	-74.7803099	-459.4429392	not applicable
calc.	-37.6724408	-74.7773067	-459.3366853	-847.9262253
published	-37.67244070	-74.77730651	-459.3366842	

* Convergence criteria not met during SCF calculation

Table 3.5.

It can be seen from the Table that the external basis set used in the calculations was in good agreement with the values published by Huzinaga. In addition as the sophistication of the basis set was increased the calculated energy was lower. This is used as a measure of the goodness of the basis set. That is, the lower the energy the better the basis set and is a consequence of the variational theorem.[58]

A serier of geometry optimizations of water with the C_{2v} constraint were attempted (Table 3.6).

Basis Set	r(O-H)/Å	a(H-O-H)	Energy/Hartrees
STO-3G	0.9894	100.0207	-74.9659012
6-31G	0.9496	111.5447	-75.9853592
external basis set	1.0520	104.4969	-75.9006392
literature calc.[59]	0.953	104.93	-76.065980 [60]
expt.[59]	0.956	104.45	-76.481

Table 3.6.

Using the minimal basis set poor geometries and energies were obtained. The use of an extended basis set gave better bond lengths and a lower energy, but the bond angle increased significantly. The extenal basis set gave a bond length which was even longer

than that of the minimal basis set, but did give a reasonable bond angle. Popkie's[60] calculation gave the above energy which is considered to be 0.002 a.u. above the SCF level.

The minimal basis set is known to overestimate bond lenghts by about 0.003 Å and underestimate bond angles by about 4 °. Increasing the size of the basis set to the 4-31G level improves the bond lenghts, but overestimates the bond angles by about 5 °.[61] This pattern has been approximately reproduced in the calculations done in this work. The addition of polarization functions is recommended when accurate prediction of energies and geometries is required.[62]

In view of the above results it was hoped that the external basis sets would give reasonable results for geometry optimizations using titanium.

A simple model, $TiCl_4.OMe_2.O{=}CH_2$ was selected for calculation. This structure ought to give a good approximation to a general complex of interest. A Z-matrix was constructed (Appendix C) using a sensible starting geometry based on that seen in the crystal structures (Figure 3.22).

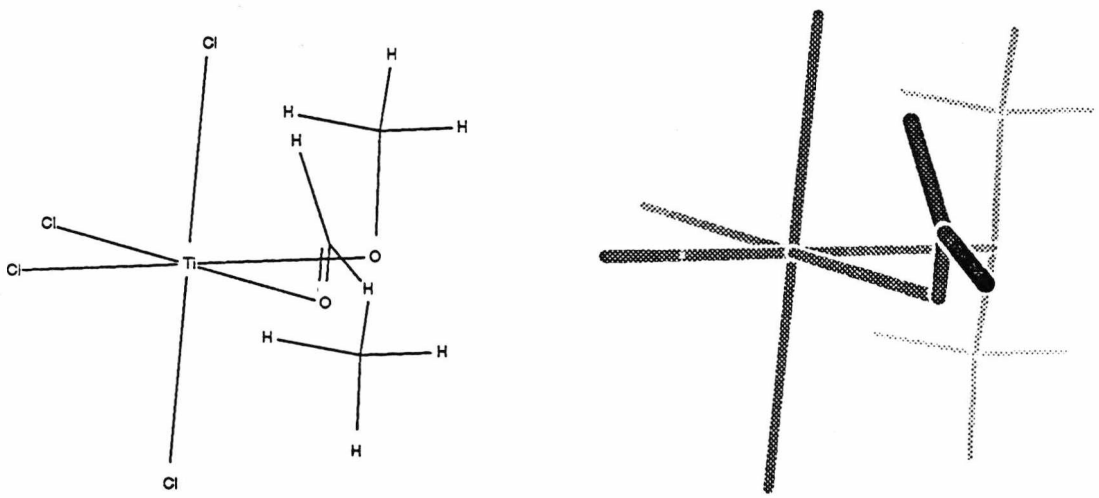


Figure 3.22.

A single point calculation of this geometry took 414 c.p.u. secs. using the STO-3G basis set. Geometry optimizations usually take about N/2 iterations to converge, where N is the

number of parameters to be optimized and each optimization usually takes twice the time of a single point calculation.[63] Given these guidelines one may estimate that a geometry optimization using the STO-3G basis set would take about 5.4 hrs. of CRAY c.p.u. time. That excludes any corrections for electron correlation such as configuration interaction or Møller-Plesset corrections. Furthermore in order to extract the information required here a frequency calculation would be required at the same level of theory as the geomery optimization.

The computational time for a given problem will increase approximately as $n^{3.5}$, where n is the number of primitive gaussians. On the basis of this it was calculated that a geometry optimization using the external basis set would take 16.1 hrs.

At the time of writing it was not possible to undertake the calculation using the STO-3G basis set or with the external basis set in the near future.

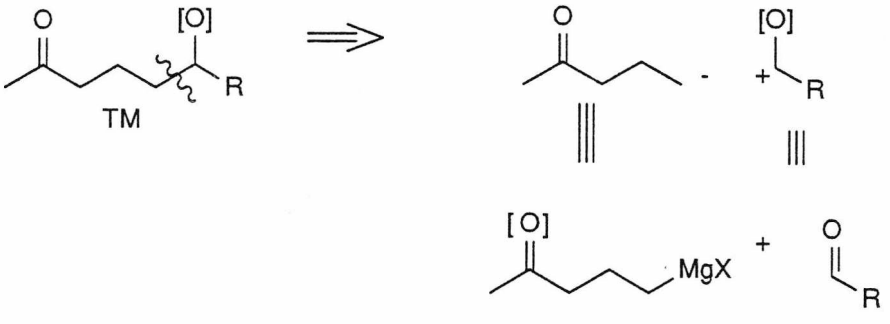
4.1: A Synthetic Approach to the Study of Remote Asymmetric Induction

One may break up the strategy used in this work into two areas. Firstly, the disconnection of carbon frameworks suitable for the study of remote asymmetric induction and the resulting synthesis of the appropriate molecules. Secondly, the steps required to analyse the diastereoisomeric ratios resulting from asymmetric reductions of these molecules.

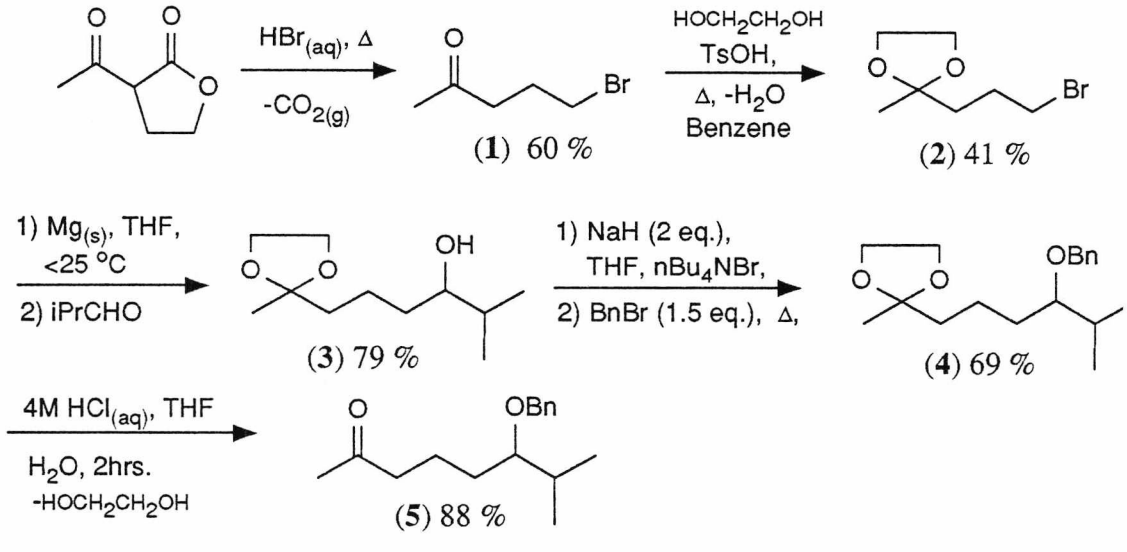
4.2: Synthesis for Studies in [1,5]-Asymmetric Induction

The following disconnection was chosen to guide our synthetic work into a general target molecule.

Disconnection:



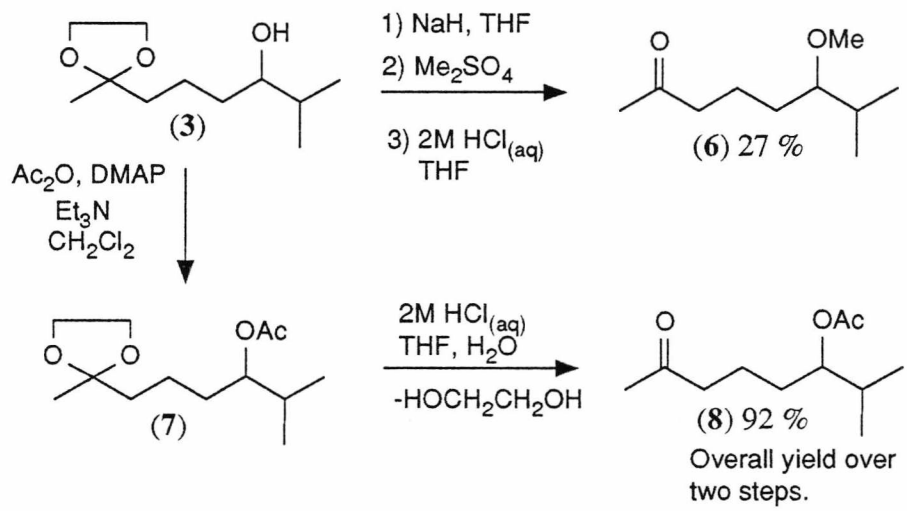
The synthesis of the target (**5**) was achieved as follows (Scheme 4.1)



Scheme 4.1.

2-Acetylbutyrolactone was opened with hydrobromic acid at reflux. The resulting intermediate readily underwent decarboxylation under the reaction conditions to give (**1**). The bromoketal (**2**) was obtained by acid catalysed reaction with ethylene glycol under a Dean and Stark trap. The Grignard reagent used in Scheme 4.1 is known to be unstable and on formation of the Grignard the temperature must be kept below 25 °C.[64] The yield of the keto-alcohol (**3**) presented, represents the best case. Generally, lower yields and contamination with side products resulted. This step was time consuming to implement and often gave disappointing results. The benzyloxy ketal (**4**) did not form with the above reagents at room temperature,[65] however the reaction proceeded smoothly on reflux.

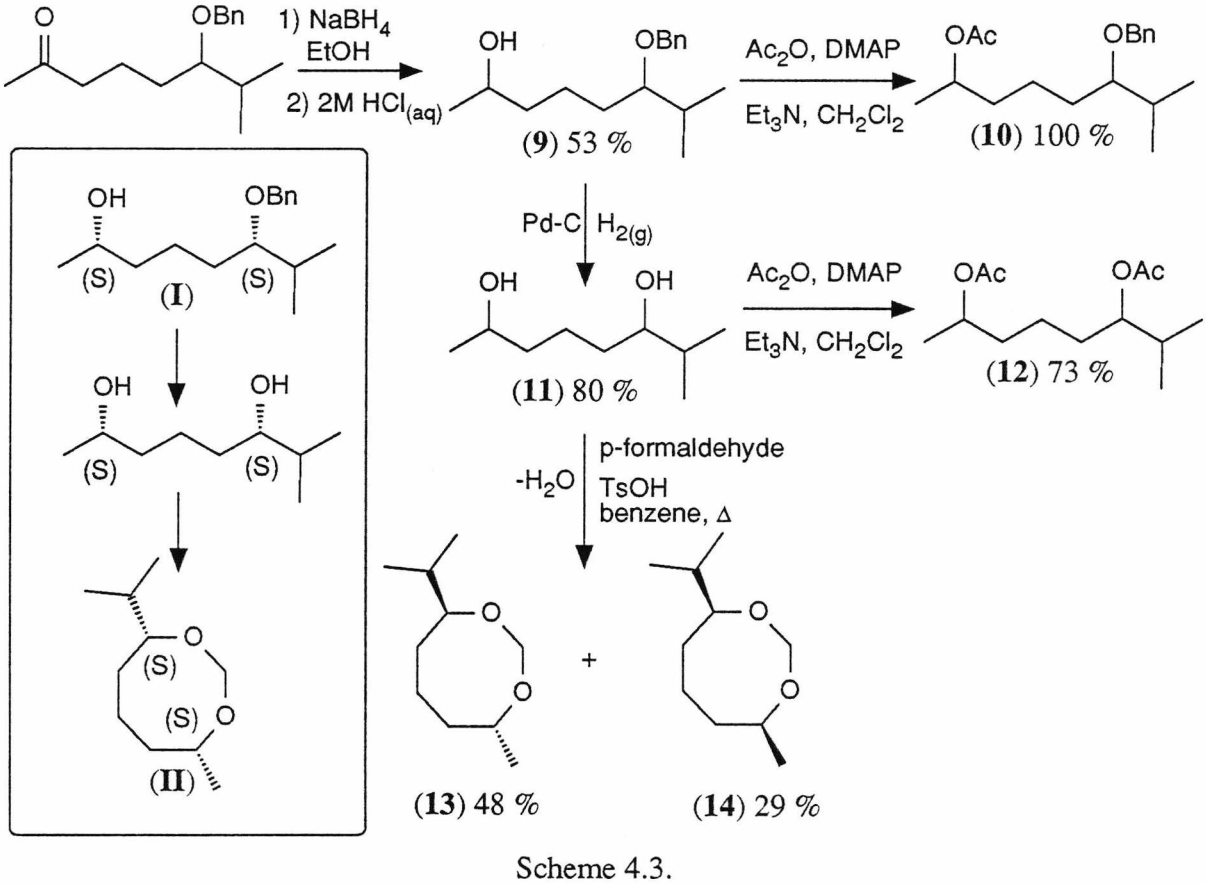
Use was made of the keto-alcohol (**3**) to extend the range of substrates for the study of asymmetric induction. Formation of the alkoxide ion of (**3**) followed by addition of dimethylsulphate[66] gave the crude ketal which was directly hydrolysed using aqueous hydrochloric acid to give (**6**). The yield from this reaction is poor, however it was only attempted once and the quality of the dimethylsulphate was not certain. The alcohol (**3**) was converted to the acetate catalysed by using acetic anhydride in dichloromethane in the presence of the catalyst DMAP with triethylamine as a proton mop.[67] (Scheme 4.2).



Scheme 4.2.

Sodium borohydride reduction of the ketone (**5**) gave the alcohol (**9**). The resulting diastereoisomers were distinguishable by high field carbon n.m.r. The stereochemical identity of the peaks in the carbon n.m.r. of (**9**) was known by comparison with the n.m.r.

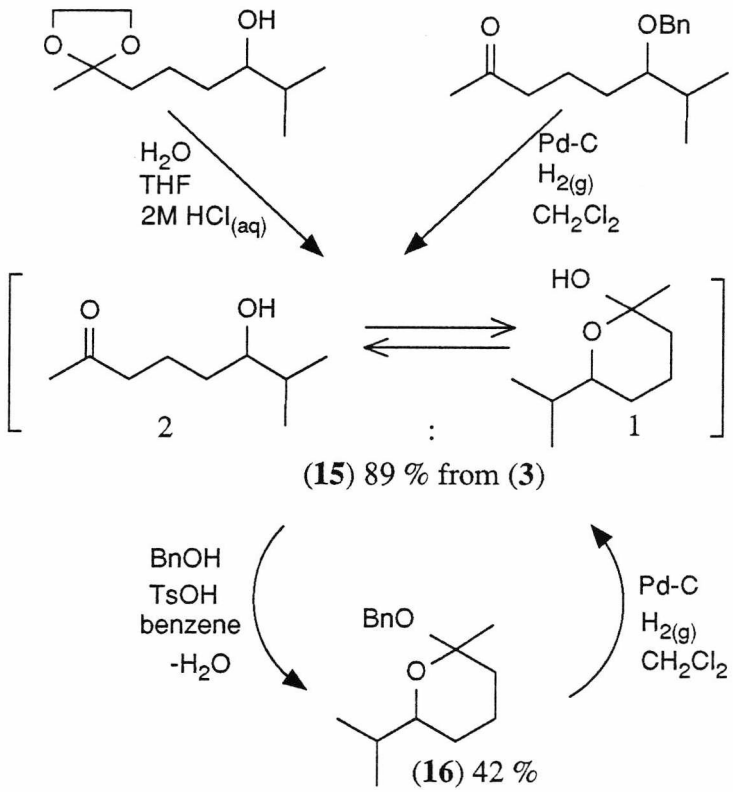
of (S,S)-6-benzyloxy-7-methyloctan-2-ol (**I**).[68] It was hoped that a complementary method could be found to determine the ratios of these diastereoisomers. The diastereomeric mixture of alcohols (**9**) were not separable by capillary g.c. The acetate derivative (**10**) was prepared, however the diastereoisomers were again not separable by capillary g.c. The alcohol (**9**) was converted to the diol (**11**) by catalytic hydrogenolysis of the benzyl group.[69a] This was transformed to the diacetate (**12**). Unfortunately the diastereomeric mixture was also not separable by capillary g.c. The diol was then used to form the corresponding dioxocane.[69b] The diastereoisomers (**13**) and (**14**) were separable by capillary g.c. and flash chromatography.[70] The relative stereochemistry of the dioxocanes (**13**) and (**14**) was assigned by conversion of the optically pure alcohol (**I**) to the optically pure dioxocane (**II**) followed by capillary g.c. analysis (Scheme 4.3).



Scheme 4.3.

The lower yield of (**14**) relative to (**13**) did not result from an unequal mixture of diol diastereoisomers, but was simply due to incomplete separation of the dioxocanes by flash chromatography resulting. The mixed fraction was not re-chromatographed and thus some of the slower moving (**14**) was effectively descarded.

Although it was intended to find methods to generate consistently high levels of asymmetric induction giving rise to products bearing different functional groups at the chiral centres (for ease of further synthetic manipulation), attempts were made to emulate the 'lactol method' of Tsuchihashi (Scheme 4.4).



Scheme 4.4.

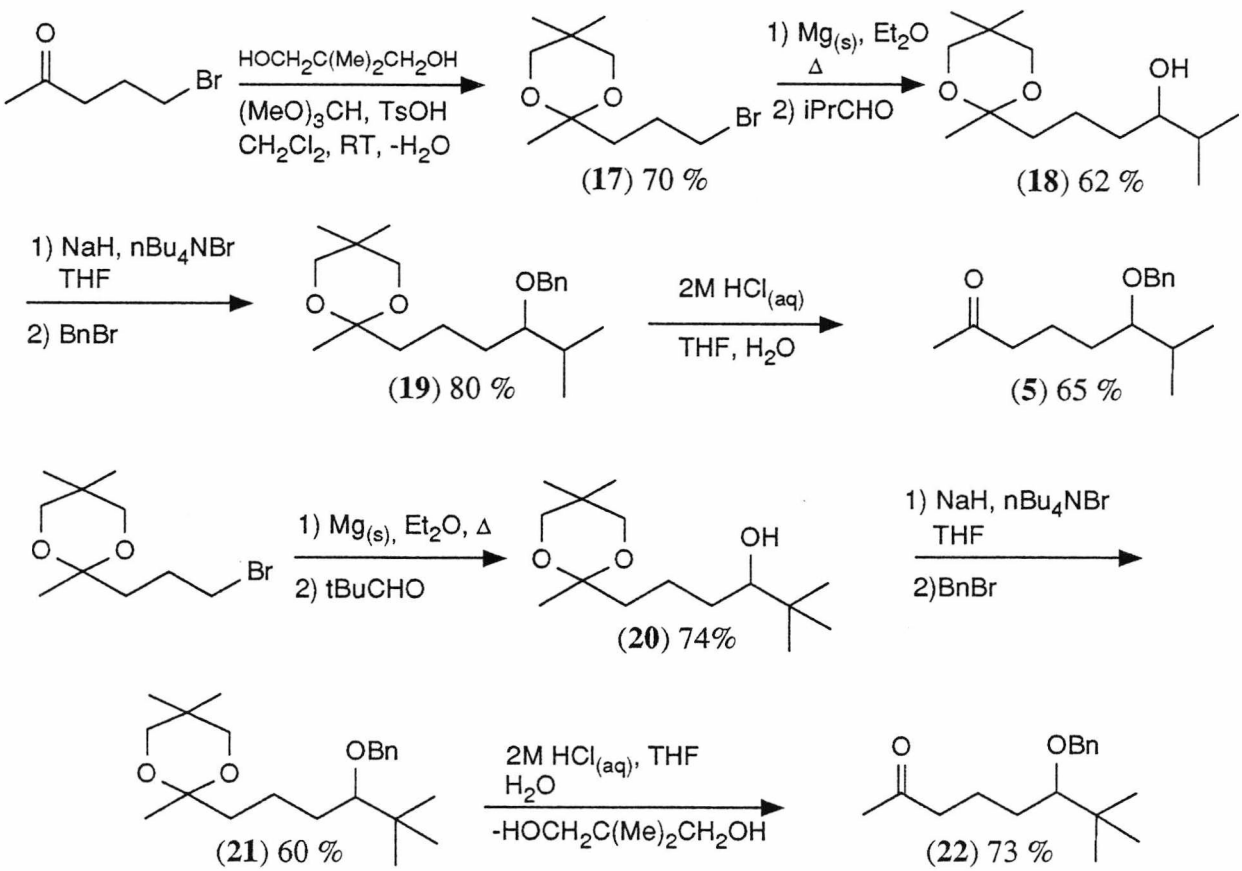
Synthesis of a lactol was initially approached by hydrolysing the ketal protecting group of (**3**). Unfortunately a mixture of hydroxy-ketone:lactol (**15**) was obtained in the ratio of 2:1. It was not surprising as the keto-lactol equilibrium should lie further to the left than the corresponding aldehyde-lactol equilibrium, due to the increased steric interactions when moving from a hydrogen to a methyl group. Hydrogenolysis of the benzyl group of the ketone (**5**) lead to a mixture of the ketone and lactol forms. The mixed ketal (**16**) was obtained by acid catalysed reaction of the mixture (**15**) with benzyl alcohol. It was then hoped that hydrogenolysis of the benzyl group in an aprotic solvent might allow the lactol tautomer to be trapped. However, a mixture of tautomers was regenerated by this approach.

As indicated earlier the Grignard reagent derived from (**2**) had limitations due to its poor

thermal stability. This may be due to intramolecular attack of the Grignard on its ketal group similar to that reported by Ponaras[71] with the lower homologue 2-(2-bromopropyl)-2-methyl-1,3-dioxolane. Or by intermolecular attack of one Grignard onto the ketal group of another etc.

It was noted from the literature that by protecting 3-bromopropanal with propan-1,3-diol and subsequent reaction with magnesium gave rise to a more thermally stable Grignard reagent[72] than the corresponding ethylene acetal used by Ponaras.[73] Whilst acetal formation using propan-1,3-diol proceeds easily with the 3-bromopropanal, ketal formation with 3-bromobutan-2-one fails. Stowell found that by using the 2,2-dimethylpropan-1,3-diol, ketal formation with the bromoketone is successful.[74a]

The use of this protecting group was investigated in the hope that it would allow synthesis of larger amounts of desired substrates with greater efficiency (Scheme 4.5).



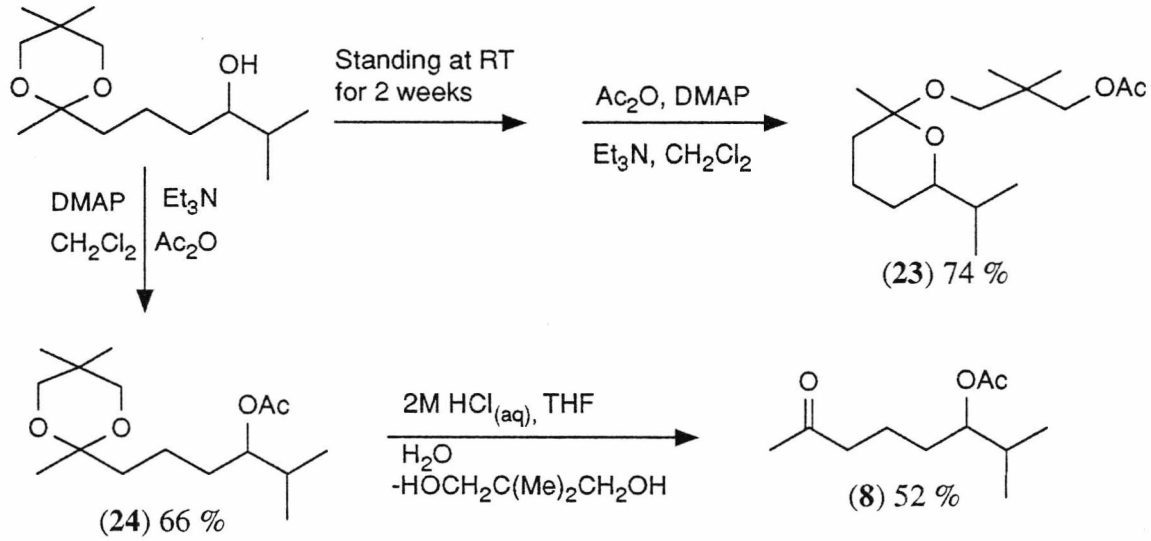
Scheme 4.5.

The yield of (**18**) via Grignard addition was somewhat lower than that obtained with the

ethylene glycol-protected analogue (**3**) (Scheme 4.2). However, the former Grignard reagent had a variable induction period and was liable to fail to form unless very careful drying of apparatus was ensured. Furthermore, careful and time-consuming control of temperature was required. However, very often low yields and mixtures of products were obtained. The Grignard reagent derived from (**17**) at least gave reproducible yields in a shorter time in refluxing diethyl ether.

Despite of ensuring high purity of the bromoketal (**17**) and isobutyraldehyde improvements in the yield of these Grignard additions was not achieved. The product (**18**) did not give a satisfactory capillary g.c. as it appeared to be composed of a number of compounds. The crude product from Grignard addition appeared to be one component by t.l.c. using MPA as the stain. However, anisaldehyde stain highlighted a number of other components from the Grignard addition. These were separated completely by MPLC and high field n.m.r. spectra were obtained. Unfortunately, their n.m.r. spectra did not allow formulation of these compounds structures. The masses of these other components more or less accounted for the low yield of (**18**).

The hydroxy ketal (**18**) appeared to be less stable than the ethylene glycol analogue (**3**). Fragmentation was observed on passage down a capillary g.c. column. It appeared to rearrange and polymerize on distillation. The hydroxy ketal (**18**) was also observed to rearrange on standing at room temperature (Scheme 4.6).



Scheme 4.6.

N.m.r. analysis of the product (**23**) showed that the $CH_2CMe_2CH_2$ methylenes had quite different chemical shifts. This was not expected for the desired product (**24**) on the basis of comparison with similar compounds, for instance the benzyloxyketal (**19**). Freshly prepared alcohol (**23**) was protected as the acetate to give (**24**). Removal of the ketal protecting group gave the ketone (**8**), which was known from previous work (see Scheme 4.2).

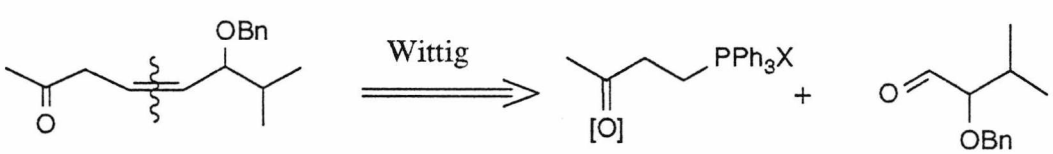
The Grignard reagent derived from (**17**) was also reacted with cyclohexanone and acetophenone in order to test its suitability in additions to ketones. The expected adducts (**25**) and (**26**) were obtained in 47 % and 63 % respectively. However, a similar pattern of side products was observed in the crude product from both reactions by t.l.c. using anisaldehyde stain.

It should be noted that use has been made of this Grignard by Upjohn Co. They conducted their reactions in THF and patented the fact that it yielded crystalline products in the synthesis of some key intermediates leading to 19-norandrostenedione.[74b]

4.2.1: An Alternative Substrate for [1,5]-Asymmetric Induction

In line with the reasoning outlined in Chapter 3, it was thought that placement of a *cis* double bond in the carbon chain of δ-benzyloxy ketone might lead to useful levels of remote asymmetric induction. The following target was disconnected to aid its construction.

Disconnection:

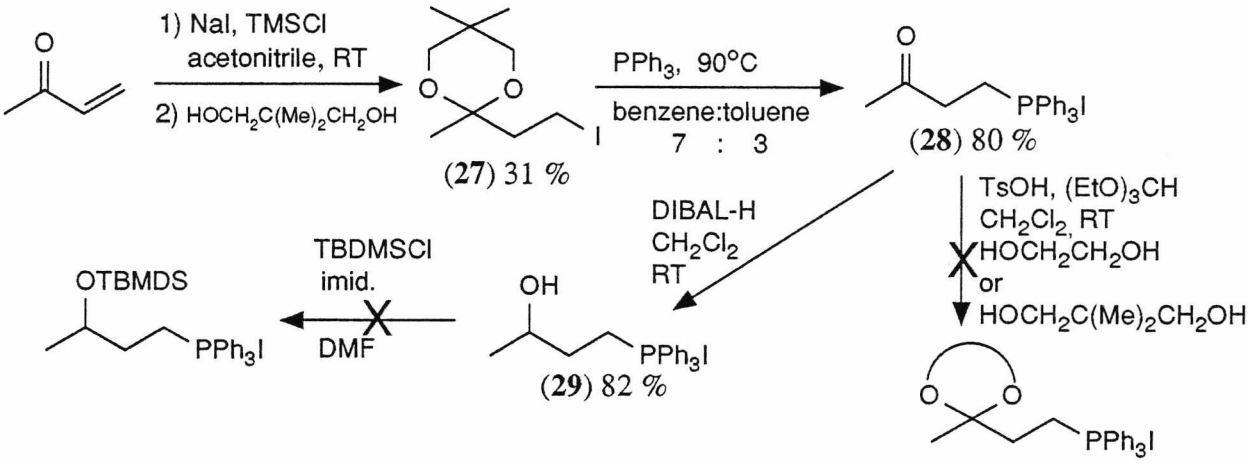


2-(2-Bromoethyl)-2-methyl-1,3-dioxolane has been shown to deketalize on treatment with triphenylphosphine at 80 °C and at lower temperatures the Wittig salt fails to form. The Wittig salt has been successfully prepared by the use of high pressure reaction conditions.[75] It was thought that use of 2-(2-iodoethyl)-2,5,5-trimethyl-1,3-dioxane (**27**)

instead of 2-(2-bromoethyl)-2-methyl-1,3-dioxolane would allow formation of an appropriate Wittig salt.

The rationale behind this choice was firstly that an acetal analogue of (**27**), 2-(2-bromoethyl)-1,3-dioxane, has been shown to react with triphenylphosphine in refluxing cyclohexane. The resulting Wittig salt has displayed *cis* selectivity when using potassium *tert*-butoxide to form the phosphorane.[76] Secondly, iodide was expected to be a better leaving group than bromide. Thirdly, the increased thermal stability of the Grignard reagent derived from (**17**) over the Grignard reagent derived from (**2**) *may* be transfered to the reaction conditions applicable here and allow formation of the desired Wittig salt at normal pressures and elevated temperatures.

The iodo ketal was prepared by a modification of the method of Larson and Kleese[77] (Scheme 4.7).



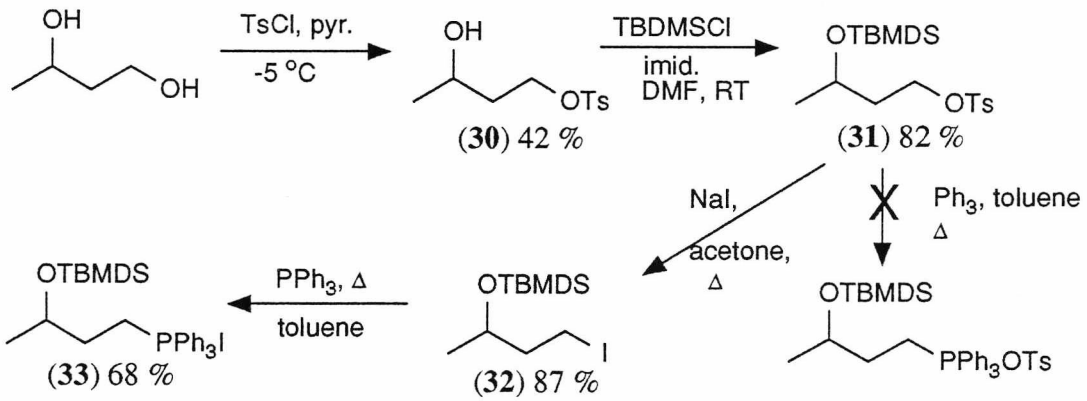
Scheme 4.7.

Unfortunately, at lower temperatures the reaction failed to proceed and at higher temperatures either complete or partial deprotection of (**27**) was observed and a suitable solvent system for purification of the partially deketalized material was not found. In addition, it was not possible to reketalize the resulting salt (**28**). The ylid prepared from the hydroxy triphenylphosphonium salt (**29**) has been shown to give high *trans* selectivity.[78] It was hoped that by protecting the hydroxy function a *cis* selective reagent

would be generated.

DIBAL-H reduction[79] of (**28**) gave (**29**). The TBDMS protecting group was considered to be a good choice since it may be easily removed in the presence of the double bond and benzyl group, and in addition it is less labile than the TMS protecting group. However, it was not possible to protect the hydroxyl function as indicated above.

Nevertheless, since the ketal protecting group appeared to be of little use, synthesis of the TBDMS protected triphenylphosphonium salt was attempted via a different route (Scheme 4.8).

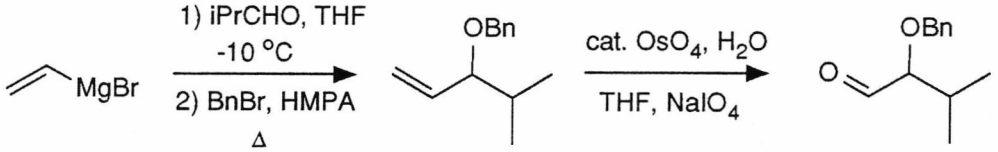


Scheme 4.8.

The hydroxyl group of the tosylate (**30**) was protected as the TBDMS ether (**31**).[80] Displacement of the tosyl group by triphenylphosphine (which may have given rise to a potentially useful Wittig salt) was attempted, but the reaction failed to proceed. Replacement of the tosyloxy group by iodide[78a] in refluxing acetone gave (**32**), which did react with triphenylphosphine to give the Wittig salt (**33**).

The aldehyde component of the disconnection was synthesized as follows (Scheme 4.9). Addition of commercially available vinyl magnesium bromide to isobutyraldehyde gave 3-hydroxy-4-methyl pentene. This alcohol was a little volatile. Rather than isolating the alcohol, *in situ* benzylation using benzyl bromide and a catalytic amount of tetra-*n*-butylammonium bromide was sought by making use of the alkoxide ion generated after the Grignard addition step (i.e. -OMgBr cf. -ONa). Unfortunately, this did not work. The reaction did proceed by the injection of an amount of HMPA into the reaction mixture

after Grignard addition was complete. Then addition of benzyl bromide, followed by reflux afforded the required allyl benzyl ether (**34**). The aldehyde (**35**) was then prepared by a one pot catalytic osmylation and periodate cleavage.[81]

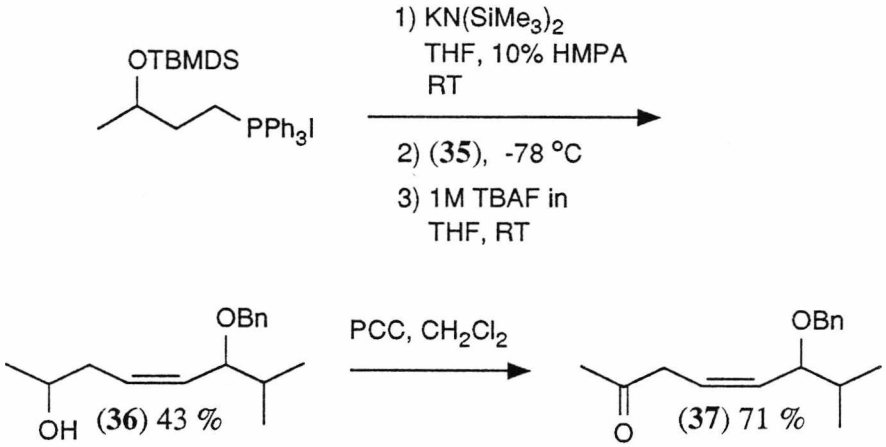


(**34**) 62 % (**35**) 58 %

Scheme 4.9.

It should be noted that the aldehyde was found to be rather unstable and had to be stored in the freezer or used directly.

The Wittig salt (**33**) and the aldehyde (**35**) were coupled under *cis*-selective salt-free conditions.[82] The TBDMS protected alkene was difficult to observe using t.l.c. using MPA, anisaldehyde, iodine, permanganate stains and u.v. Thus the Wittig reaction was followed with *in situ* removal of the silyl protecting group by application of TBAF[83] (Scheme 4.10).



Scheme 4.10.

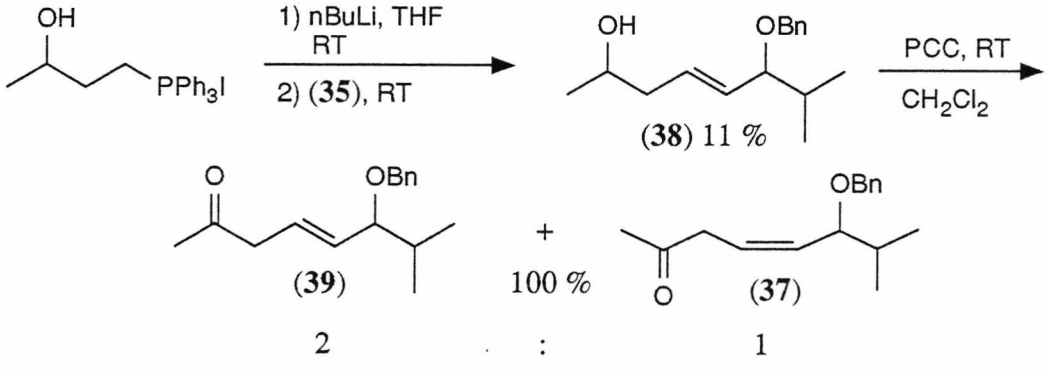
Two compounds were observed in the proton n.m.r. of (**36**) in the ratio of 2:1. By decoupling the methylene group adjacent to the double bond the HC=CH coupling constants were found to be 11.26 Hz and 11.53 Hz for the two components.

A one pot hydrogenolysis of the benzyl group and hydrogenation of the double bond of

(**36**), followed by dioxocane formation (to give a mixture of (**13**) and (**14**) from the resulting diol) allowed determination that the two compounds observed in the n.m.r. were the *syn* and *anti* diastereoisomers of (**36**). The *anti* isomer was the major component.

The ketone (**37**) was obtained cleanly by PCC[84] oxidation and was one component by n.m.r. with an HC=CH coupling constant of 11.26 Hz.

At this point it was not possible to assign the geometry of the double bond, since the observed coupling HC=CH coupling constants of (**36**) and (**37**) fall in the region where *cis* and *trans* coupling constants may overlap.[85] As mentioned earlier the Wittig salt (**29**) is known to be *trans* selective. Synthesis of the corresponding *trans* isomer (**38**) was achieved in the presence of lithium salts[78] (Scheme 4.11).



Scheme 4.11.

The proton n.m.r. specrum of (**38**) was quite complicated and it seemed that the sample contained a mixture of *cis* and *trans* isomers (each potentially composed of two diastereoisomers). The mixture was then oxidized as before to furnish a mixture of two compounds (**37**) and (**39**).

Reassuringly, the H-H coupling constant across the double bond of (**39**) was found to be 15.66 Hz, which is safely in the *trans* coupling constant region and thus confirmed unambiguous assignment of the *cis* geometry of (**37**).

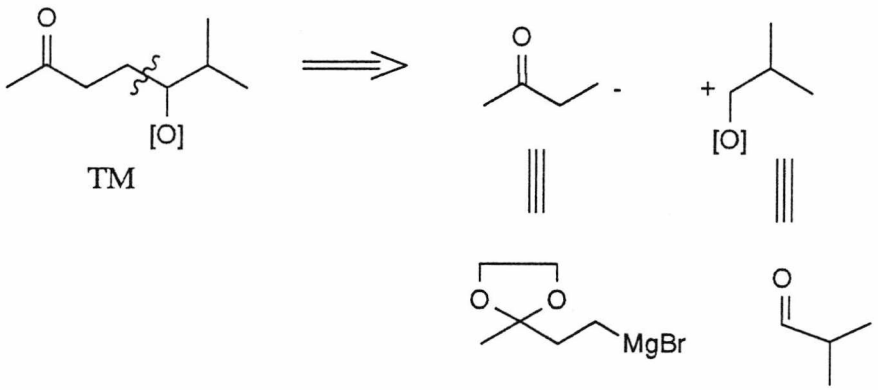
The *cis* and *trans* alcohols (**37**) and (**39**) had identical R_f values by t.l.c. While the reaction in Scheme 4.11 gave a mixture of *cis* and *trans* isomers, the Wittig reaction in Scheme

4.10 gave no trace of the *trans* isomer by high field n.m.r. or capillary g.c. on the BP1 column, which, in view of the R_f values of the two geometrical isomers and consequent difficulty in separating them, was pleasing.

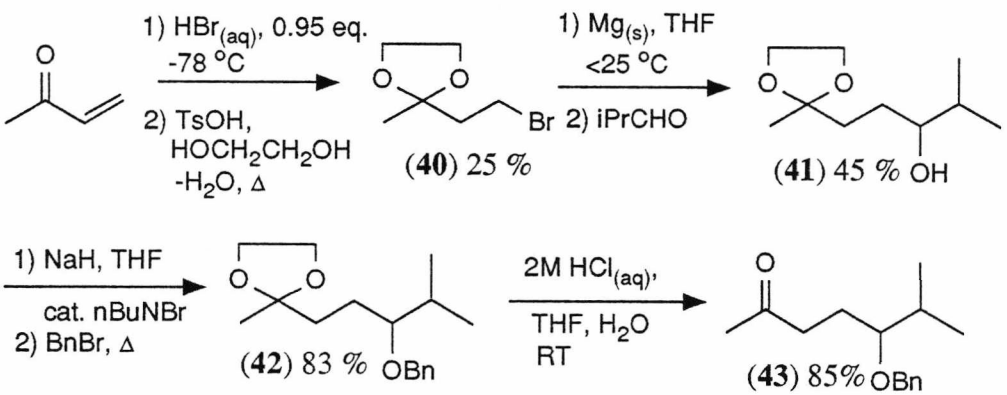
4.3: Synthesis for Studies in [1,4]-Asymmetric Induction

A similar strategy to that used in section 4.1. lead us into a suitable target for the study of [1,4]-asymmetric induction via the following disconnection.

Disconnection:



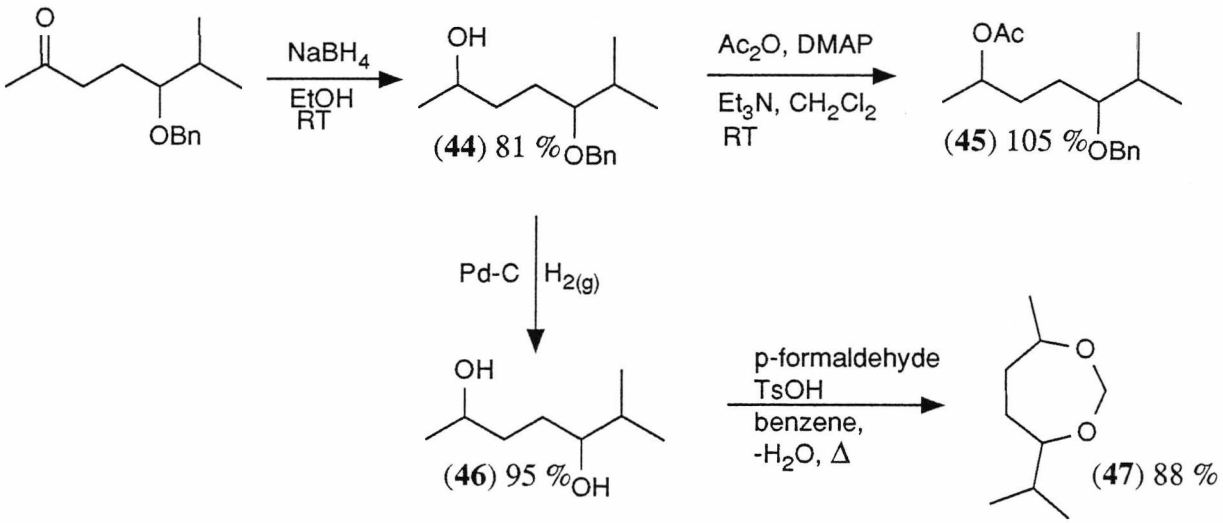
The synthesis of the target proceeded as follows (Scheme 4.12).



Scheme 4.12.

Addition of hydrogen bromide to methylvinylketone gave (**40**). The Grignard addition to isobutyraldehyde was guided by the work of Ponaras.[71] The alcohol (**41**) was protected as before leading to (**42**), followed by acid catalyzed hydrolysis of the ketal protecting group to give (**43**).

The ketone (**43**) was reduced to the alcohol (**44**) using sodium borohydride, which was then transformed to the acetate (**45**) (Scheme 4.13). The acetate diastereoisomers were separable by use of a programmed capillary g.c. run. The alcohol (**44**) was also hydrogenolyzed to give the diol (**46**), followed by conversion to the dioxepane (**47**). The *cis* and *trans* dioxepanes were readily separable by a programmed temperature ramped capillary g.c. run and were just separable by flash chromatography.



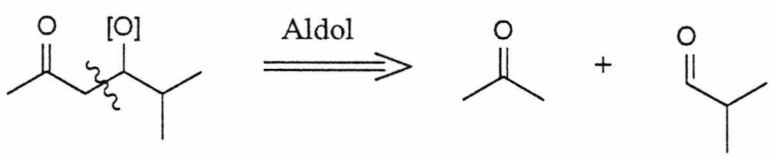
Scheme 4.13.

The formation of the dioxepanes was critical in assignment of the relative stereochemistry of the diastereomeric mixture of alcohols (**44**) by n.m.r. arguments (section 4.7).

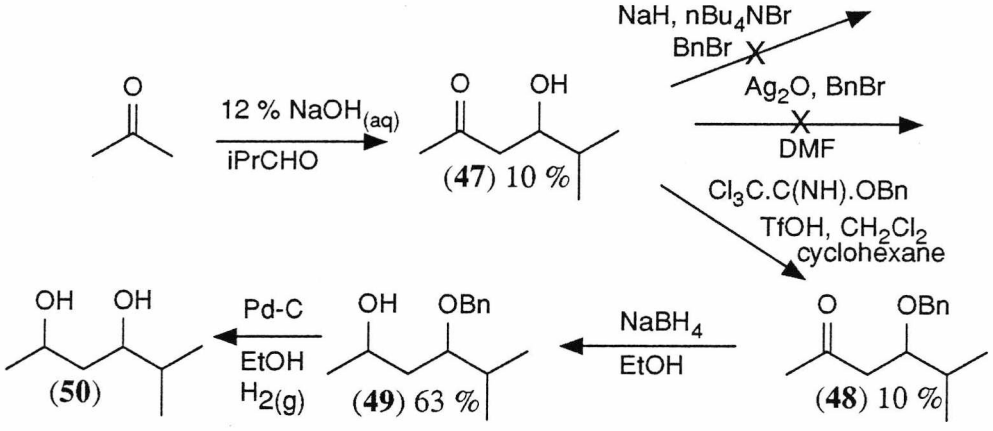
4.4: Synthesis for the Study of [1,3]-Asymmetric Induction

The following disconnection was made to guide the synthesis of a suitable substrate:

Disconnection:



The synthesis of an appropriate carbon framework was achieved by a classical aldol reaction. Not surprisingly, benzylation of the resulting alcohol (**47**) failed with the conditions used previously. In addition, the reaction failed using benzyl bromide and silver oxide in DMF.[86] (Scheme 4.14)



Scheme 4.14.

The benzyloxy ketone was successfully prepared by the use of benzyl 1,1,1-trichloroacetimidate.[87] Interestingly, sodium borohydride reduction in ethanol resulted in a *syn* diastereoselection of 1.4:1 in the alcohol (**49**), which as seen from section 2.2 was the product expected on the basis of a chelation controlled reaction. Removal of the benzyl group of (**49**) in the usual way lead to the diol (**50**), which allowed determination of the relative stereochemistry of the diastereomeric mixture of (**49**) (section 4.7).

4.5: Stereochemical Assignments in [1,5]-Asymmetric Induction

It was noted earlier in this section that the relative stereochemistry of the dioxocanes (**13**) and (**14**) was known by synthesis of the optically pure *cis*-dioxocane in two steps from (S,S)-6-benzyloxy-7-methyl octan-2-one (**I**). The proton n.m.r. of the *cis* and *trans* dioxocanes are noticeably different at the C-2 methylene. In the case of the *cis* isomer one observes a more-first order AB quartet. Whereas the *trans* isomer has a more second-order AB quartet originating from the proton resonances attached to C-2. The lower energy conformers of these compounds as predicted by MM2 using multiconformational analysis were looked at. The distances of each hydrogen atom at C-2 relative to the carbon attached to C-4 and C-8 were inspected. It was observed that the protons of the *trans* isomer's C-2 methylene occupied a more symmetrical environment than the *cis* isomer's (in terms of C-2-H:C-4-Me,C-8-iPr distances). To make the preceding statement more clear, the first four lowest energy conformers (as predicted by MM2 using multiconformational analysis)

for the *cis* and *trans* isomer are presented along with the distance of the indicated hydrogen from the carbons attached to C-4 and C-8 (Figure 4.1).

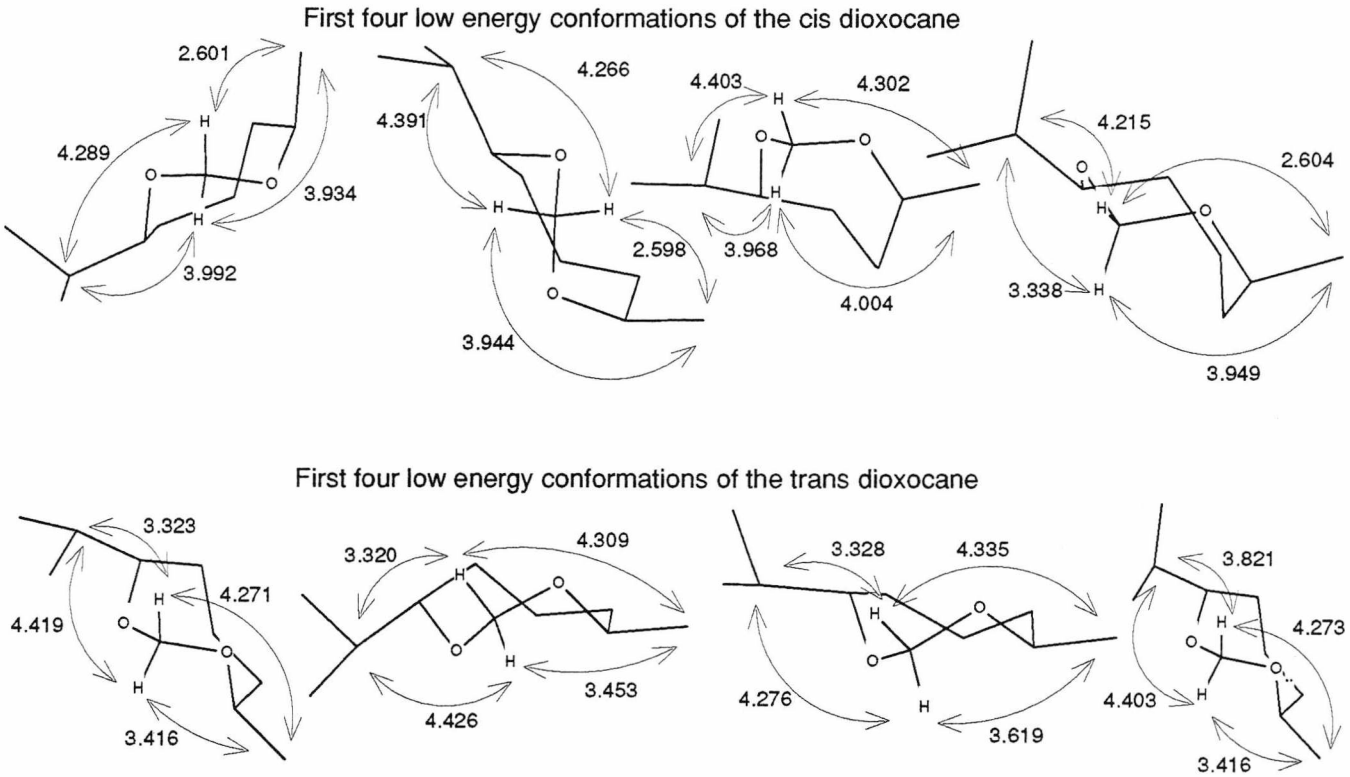


Figure 4.1.

Notice that in the *cis* isomer three of the conformers have one of the C-2 hydrogens in relatively close proximity to the methyl substituent. This is the same hydrogen in each case. To a first level of approximation it was assumed that it is the differential steric environment that accounts for the inequivalence each proton 'feels' at the C-2 position. As the protons in the *cis* isomer are in quite different environments their shielding will be more different and their resonance will tend to occur at different frequencies, thus giving the more first order AB quartet.

It was noted previously that the *cis* and *trans* dioxocanes were separable by capillary g.c. A 1:1 ratio of *cis* and *trans* dioxocanes (when starting from a 1:1 mixture of *syn* and *anti* diols as determined by carbon n.m.r.) was not observed. Formation of the dioxocanes was monitored as a function of time. A ratio of 0.928 by capillary g.c. was obtained 1 minute after the first drops of benzene:water azeotrope had been collected. Samples of the reaction mixture were taken every 5 minutes for 1 hour. The ratio remained essentially

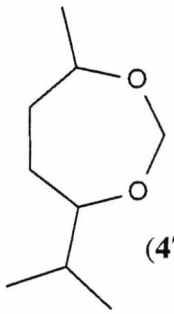
constant. It was determined, by comparison with the optically pure dioxocane, that the component with the longer retention time on the BP1 and BP5 capillary g.c. columns was the *cis* dioxocane. The *cis* isomer was always the smaller component when forming the dioxocanes from a 1:1 mixture of *syn* and *anti* diols.

Analysis of diastereomeric excesses in chelation controlled experiments was sometimes analysed by conversion of the product (**6**) to the corresponding diols followed by dioxocane formation. The ratio of *cis*:*trans* isomers was then determined by capillary g.c. In this analysis the additional error due to the failure to obtain a 1:1 ratio with the dioxocane method (as described in the previous paragraph) was not corrected for. Alternatively, the ratio of diastereoisomers was analysed by high field carbon n.m.r., ensuring that peak ratios were accurately represented by use of adequate digitization (128 K data points). It was then possible to choose which peaks corresponded to analogous positions on the two diastereoisomers' chains by inspection of the proton and carbon n.m.r. spectra via CH COSY experiments. Thus, from the n.m.r. alone, it was possible to deduce which diastereoisomer predominated in a sample where asymmetric induction had occured.

4.6: Stereochemical Assignments in [1,4]-Asymmetric Induction

Enantiomerically pure material for comparison with the benzyloxy alcohol (**44**) was not available. Consequently an alternative method of analysis was required to identify the diastereoisomer resulting from asymmetric induction. It was seen in the previous section that there was reasonable correlation between the calculated environment of the dioxocanes' C-2 protons with the proton n.m.r. obtained.

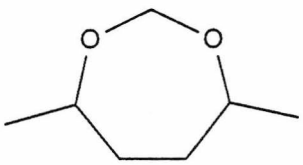
It was hoped that by looking at molecular mechanics models generated by multiconformational analysis of the corresponding seven membered dioxepane ring (**47**) tentative predictions as to the stereochemical identity of the diastereoisomers might be made on their basis of the proton n.m.r. spectra (Figure 4.2).



(47)

Figure 4.2.

Gianni[88] has used carbon and proton n.m.r. to identify the the *cis* and *trans* isomers of 4,7-dimethyl-1,3-dioxapane (**IV**) (Figure 4.3).



(**IV**)

Figure 4.3.

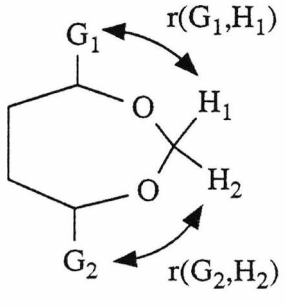
This was done by considering a series of Dreiding models. For the *trans* system seven conformers were initially looked at. Four of these were discarded as they were considered to be high energy structures on steric grounds. The first two of the remaining three conformers differed by one pseudorotation. A C_2 axis would be present along the interconversion pathway. The third conformer was not mentioned further. They deduced that an A_2 singlet at δ 4.7 resulted from these protons. In the case of the *cis* isomer eight conformers were initially looked at. After inspecting the geometries of the initial series of conformers, the list was reduced to four conformers, (by removal of the structures which they considered to contribute to less than 99 % of the population at normal temperatures). They concluded that in each of these conformers the C-2 protons retained their conformational integrity and thus should give rise to an AB spin system. They assigned the compound with an AB quartet centred around δ 4.85 and 4.53 as the *cis* isomer.

4,7-Dimethyl-1,3-dioxepane (**IV**) was analysed using molecular mechanics calculations and multiconformational analysis. For the *trans* isomer seven conformers were found which contributed to 99 % of the conformer array. The first pair were of equal energy and related by a C_2 operation, and thus the interconversion pathway will possess a C_2

symmetry element which will pass through C-2. The third conformer contained a C_2 axis. The fourth and fifth were of equal energy and related by a C_2 operation through C-2. Likewise the sixth and seventh conformers were of equal energy and related by a C_2 operation through C-2. These conformers will be expected to interconvert rapidly at normal temperatures and thus the C-2 protons will be equivalent on the n.m.r. time scale. In the case of the *cis* isomer four conformers were found which constituted 99 % of the conformer population. The first two were a *dl* pair, as were the second pair of conformers. As they interconvert a σ-axis of symmetry will be present at the *meso* transition state, however the C-2 protons will retain their conformational integrity and thus the C-2 protons in this system are non-equivalent.

In the ring (**47**) it was clear that due to the different nature of the substituents at C-4 and C-7 that no C_2 axis with respect to pseudorotamers interconversion will exist in the *trans* isomer. To get a feel for the problem, MM2 structures of the *cis*- and *trans*-(**47**), using multiconformational analysis, were looked at. The environments of the C-2 protons were considered. One way of doing this was to draw up some function which would give a measure of the differential distance of the ring substituents from each proton on C-2.

In fact two functions were used and the following should explain how they operate (Figure 4.4).



$\Theta_1 = |\, r(G_1,H_1) - r(G_2,H_1)|$

$\Theta_2 = |\, r(G_1,H_2) - r(G_2,H_2)|$

Figure 4.4.

An idea of the steric environment of the C2 protons may be obtained by plotting the Θ functions for the *cis* and *trans* isomers.

It was clear that the distance functions Θ for the *cis* isomer had similar values across the

conformer array, whereas the *trans* isomer had relatively large variations. It was concluded that in each conformer the C-2 protons of the *cis* isomer are in a more symmetrical environment (in terms of G,H distances) (Figure 4.5).

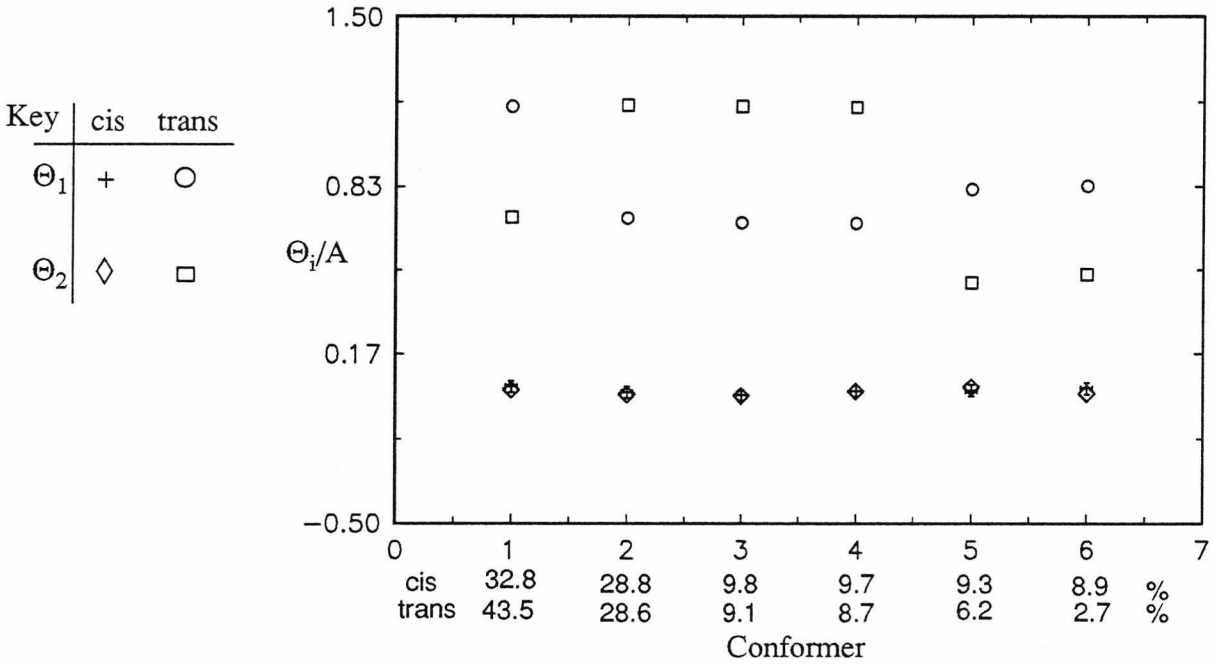


Figure 4.5.

It was assumed that these distances related to steric parameters in a simple way. Thus one may then expect that the *cis* isomer would give rise to a ***more*** second order proton n.m.r. relative to the *trans* isomer from the C2 protons.

In fact if one looks at the dimethyl (**IV**) analogue mentioned above, one also sees a similar pattern distances to that Figure 4.1. However, the C_2 symmetry considerations described remove the effect of the individual conformer asymmetry thus the *trans* isomer gives rise to a limiting second order A_2 spectrum and the *cis* isomer is more first order relative to it.

Using the above assumptions the relative stereochemistry on the basis of the proton n.m.r. of the *cis* and *trans* dioxepane (**47**) was assigned. **The *trans* isomer *should* have a more first order AB quartet arising from the C2 protons relative to the C2 spin system of the *cis* isomer.**

4.7: Stereochemical Assignments in [1,3]-Asymmetric Induction

It is well known that 1,3-diols exist in a intramolecularly hydrogen-bonded form[89] and that the carbinol carbons in the *anti* isomer always resonate up field relative to the *syn* isomer in the ^{13}C n.m.r. and is explained by the γ-gauche effect.[90]

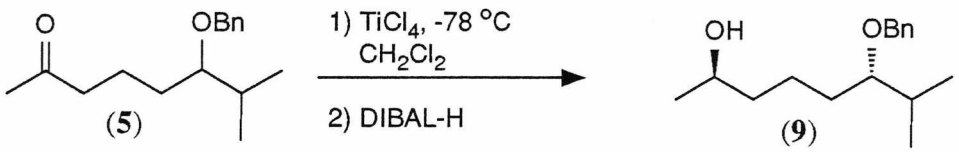
Unambiguous assignment of the carbon and proton n.m.r. spectra for a given ratio of benzyloxy alcohols (**49**, *syn*:*anti* = 1.4:1 or 1:1.4 as seen in Scheme 4.14) by CH COSY and COSY 90 was obtained. Hydrogenolysis of the benzyl group to gave the diol (**50**). Through subsequent carbon n.m.r. assignment of the carbinol resonances the resonances due to the *syn* and *anti* isomers (**49**) in the proton and carbon n.m.r. were identified.

By way of an explanation, if the ^{13}C n.m.r. peaks arising from the ***C***HOH of (**49**) are at 85 and 82 ppm and have the intensity ratio 1.4:1 respectively, and the corresponding ***C***HOH of the diol (**50**) has resonances at 84 and 81 ppm in the ratio 1.4:1 then clearly the *syn* isomer is the major product. The chemical shifts of the diastereoisomers of (**49**) would then be known. If the order of intensities of the carbonyl carbons of the diol (**50**) were reversed (i.e. 1:1.4) then one would still know how to assign the chemical shifts of the diastereoisomers of (**49**).

For instance, by this method it was possible to deduce that the more second order ^1H AB quartet centred at δ 4.5 originated from the methylene protons of the benzyl group in the *anti* isomer. The more first order ^1H AB quartet at δ 4.6, 4.4 resulted from the analogous protons of the *syn* isomer, thus these resonances in the proton n.m.r. were used to deduce product ratios of chelation controlled reductions.

5.1 Results of Asymmetric Reductions

Encouraging preliminary results had been obtained prior to the commencement of this work. An *anti* diastereoselectivity of 2.5:1 had been obtained via DIBAL-H reduction of (**5**) in the presence of $TiCl_4$ in dichloromethane at -78 °C (Scheme 5.1).[91]



Scheme 5.1.

Given this precedent, attempts were made to optimize the reaction conditions in order to maximize diastereocontrol. It became clear from the outset that this was not a trivial task. The first reduction under similar conditions resulted in 1.5:1 *syn* diastereoselectivity. Indeed it turned out that most reactions under a variety of conditions gave rise to the *syn* isomer selectively.

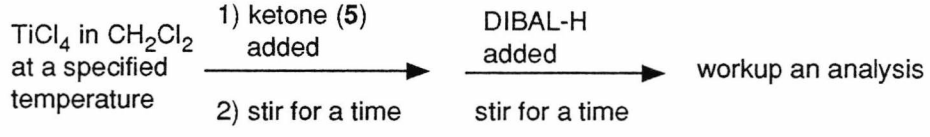
This reversal of diastereoselectivity indicated that there were two competing reaction pathways available. Sodium borohydride reduction (a non co-ordination pathway) gave a 1:1 mixture of *syn* and *anti* isomers. Hence when diastereofacial selectivity was observed, one must conclude the existence of some intermediate or transition state providing some conformational bias thus differentiating the carbonyl π-faces. Since the both π-faces had been attacked selectively it was concluded that two mechanisms exist.

The above conclusion leads to an interesting proposition form a synthetic view point, since it might be possible to find reaction conditions which favour one reaction path over another, and visa versa.

With the above in mind the variation of reaction conditions, such as order of addition of reagents, variation of solvent, Lewis acid, and reducing agent was undertaken. The use of syringe pumps and high dilution conditions was looked into. Addition of $TiCl_4$ (1 eq.) in

dichloromethane (5 ml) and the ketone (**5**) (0.1 g) in dichloromethane (5 ml) overnight by use of a syringe pump into stirred dichloromethane (50 ml) at -81 °C, followed by the addition of DIBAL-H (5 eq.) over 24 hrs. and then by work up gave 1.3:1 *syn* selectivity.

A reaction (Scheme 5.2) of the general form: $TiCl_4$ in dichloromethane at a specified temperature; ketone (**5**) (0.10 g) added; stir; DIBAL-H added; stir; workup; analysis, is presented in tabular form (Table 5.1).



Scheme 5.2.

In these experiments all apparatus was carefully dried, as were the solvents. The reactions were carried out under a nitrogen atmosphere. The temperature quoted was maintained through out the period of the reaction. Workup consisted of pouring the cold reaction mixture onto excess 2M $HCl_{(aq)}$ followed by extraction with dichloromethane. The organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a crude oil. The oil was analysed by t.l.c. When contamination from unreacted (**5**) was observed, flash chromatography was used to purify the oil followed by high field n.m.r., otherwise the crude oil was analysed by n.m.r. directly. Alternatively conversion to the dioxocanes (**13**) and (**14**) followed by capillary g.c. was used to analyse the ratio of diastereoisomers as described in Chapter 4, Section 4.5.

It was known that tetra-*n*-butylammonium borohydride has given the chelation controlled product in the presence of titanium tetrachloride with α-triazolyl ketones and is freely soluble in dichloromethane.[92] It was thought that the use of this reagent might lead to useful results. An overview of the reactions effected with this reducing agent, in the presence of titanium tetrachloride, is presented in Table 5.2. The general form of the reaction using the ketone (**5**) (0.1 g) was: Starting mixture at a specified low temperature; next addition of reagent; stir at low temperature for some time; workup; analysis. The highest diastereoselectivity observed (4.4:1) occurred with *in situ* removal of the benzyl group. This took place whilst the reaction mixture was stirring at room temperature for 24 hrs.

	$TiCl_4$ CH_2Cl_2	(5), CH_2Cl_2	Stir	DIBAL-H	Stir	syn : anti	Analysis	Temp. /°C
1)	1.2 eq. 20 ml	5 ml	3 hrs.	2 eq.	45 mins	1.5 : 1	n.m.r.	-78
2)	1.0 eq., 25 ml	neat	1 min.	1 eq.	20 mins.	1.08 : 1	n.m.r.	-76
3)	4.12 eq., 25 ml	neat	3 mins.	1.1 eq.	1 hr.	1.17 : 1	n.m.r.	-78
4)	4.12 eq., 20 ml	neat	12 mins.	1.1 eq.	1 hr.	1 : 1.4	n.m.r.	-74
5)	4.12 eq., 20 ml	neat	1.5 hrs.	1.1 eq.	0.75 hrs.	2.1 : 1	n.m.r.	-70
						2.4 : 1	diox.	
6)	8.25 eq., 15 ml	5 ml	1.5 hrs.	1.1 eq.	1 hr.	1 : 1	n.m.r.	-72
7)	8.25 eq., 15 ml	5 ml	1.5 hrs.	1.1 eq.	1 hr.	1 : 1	n.m.r.	-75
8)	4.12 eq., 20 ml	neat	1.5 hrs.	1.1 eq.	1.5 hrs.	1 : 1.5	n.m.r.	-75
9)	4.12 eq., 20 ml	neat	10 mins.	1.1 eq.	10 mins.	1 : 1	n.m.r.	-50

diox. refers to dioxocane formation followed by g.l.c. analysis

Table 5.1.

	Starting Mixture	Next Addition	Next Addition	Stir	syn : anti	Analysis	Temp/°C
1)	(5) CH_2Cl_2 20 ml	$TiCl_4$ 5 eq.	nBu_4NBH_4 3 eq. CH_2Cl_2 5 ml	4 hrs.	2.4 : 1	n.m.r	-84
2)	$TiCl_4$ CH_2Cl_2 30 ml	(5) CH_2Cl_2 10 ml	nBu_4NBH_4 1.5 eq. CH_2Cl_2 5 ml	4 hrs. at -70 →RT overnight	1.5 : 1 1.6 : 1	diox. n.m.r.	-70
3)	nBu_4NBH_4 1.5 eq. CH_2Cl_2 40 ml	$TiCl_4$ 2 eq. CH_2Cl_2 10 ml	(5) CH_2Cl_2 10 ml	overnight	2.4 : 1	diox.	-79
4)	nBu_4NBH_4 1.5 eq. CH_2Cl_2 40 ml	$TiCl_4$ 2 eq. CH_2Cl_2 10 ml	(5) CH_2Cl_2 10 ml	10 hrs.	4.4 : 1	diox.	-75
5)	nBu_4NBH_4 1.0 eq. CH_2Cl_2 40 ml	$TiCl_4$ 1.5 eq. CH_2Cl_2 10 ml	(5) CH_2Cl_2 10 ml	24 hrs.	1.8 : 1	diox.	-80
6)	nBu_4NBH_4 1.0 eq. CH_2Cl_2 40 ml	$TiCl_4$ 1.5 eq. CH_2Cl_2 10 ml	(5) CH_2Cl_2 10 ml	16.5 hrs.	1 : 1	n.m.r.	-78
7)	nBu_4NBH_4 1.0 eq. CH_2Cl_2 50 ml	$TiCl_4$ 1.5 eq. CH_2Cl_2 10 ml	(5) CH_2Cl_2 10 ml	overnight	2.4 : 1	diox.	-76
8)	nBu_4NBH_4 1.0 eq. CH_2Cl_2 50 ml	$TiCl_4$ 1.5 eq. CH_2Cl_2 10 ml	(5) CH_2Cl_2 10 ml	overnight	1.88 : 1	n.m.r.	-75

Table 5.2.

A general procedure was then used to study the effect of solvent on asymmetric induction. A Lewis acid was placed in a solvent at room temperature. To this was added the ketone (**5**) (0.1 g). The mixture was cooled to a specified low temperature and DIBAL-H was added. The mixture was allowed to stir at the low temperature overnight and then the reaction mixture was quenched as before. The results of this investigation are presented in Table 5.3.

Variation of solvent and Lewis acid in the reduction of (**5**)

Lewis Acid	Solvent	Temp./°C	syn : anti	Analysis
Al (DIBAL-H)	THF	-50	1 : 1	diox.
Al (DIBAL-H)	Et_2O	-65	1 : 1	diox.
Al (DIBAL-H)	CH_2Cl_2	-73	1.3 : 1	diox.
$ZnCl_2$	THF	-76	1 : 1	diox.
$ZnCl_2$	Et_2O	-74	1 : 1	diox.
$ZnCl_2$	CH_2Cl_2	-72	1.5 : 1	diox.
$SnCl_4$	THF	-67	1 : 1	diox.
$SnCl_4$	Et_2O	-65	1.3 : 1	n.m.r.
$SnCl_4$	CH_2Cl_2	-83	1.7 : 1	n.m.r.
$TiCl_4$	n-pentane	-75	1 : 1	n.m.r.
$TiCl_4$	n-pentane /CH_2Cl_2	-76	1 : 1	n.m.r.
$ZrCl_4$	THF	-76	1 : 1	n.m.r.
$ZrCl_4$	Et_2O	-76	1 : 1	n.m.r.
$ZrCl_4$	CH_2Cl_2	-74	1.8 : 1	n.m.r.
$MgBr_2$	THF	-76	1 : 1	n.m.r.
$MgBr_2$	Et_2O	-73	1 : 1	n.m.r.
$MgBr_2$	CH_2Cl_2	-78	1 : 1	n.m.r.

diox. refers to dioxocane formation followed by g.c. analysis

Reducing agent was DIBAL-H

Table 5.3.

The use of L-Selectride was also investigated with the ketone (**5**) (0.1 g) in solvent (5 ml). A solution of the ketone was cooled to a specified low temperature, followed by addition of titanium tetrachloride, shortly thereafter L-Selectride was added. The mixture was then stirred overnight at the same temperature, followed by workup as usual and analysis (Table 5.4).

Reduction of (**5**) with L-Selectride

Solvent	Lewis Acid	Temp./°C	syn : anti	Analysis
THF	$TiCl_4$ (2 eq.)	-78	1 : 1	n.m.r.
Et_2O	$TiCl_4$ (2 eq.)	-78	1 : 1.3	n.m.r.
CH_2Cl_2	$TiCl_4$ (2 eq.)	-78	1 : 1	n.m.r.

Table 5.4.

The hydroxy ketone-lactol mixture (**15**) was reduced with DIBAL-H (2.2 eq.) in the presence of $TiCl_4$ in diethyl ether (30 ml) and dichloromethane (30 ml). A solution of the ketone was cooled to a specified low temperature, followed by the addition of titanium tetrachloride. DIBAL-H was added to the mixture and stirring was continued overnight at a constant low temperature. In addition, the mixture (**15**) was also reduced using L-Selectride (2.2 eq.) (Table 5.5).

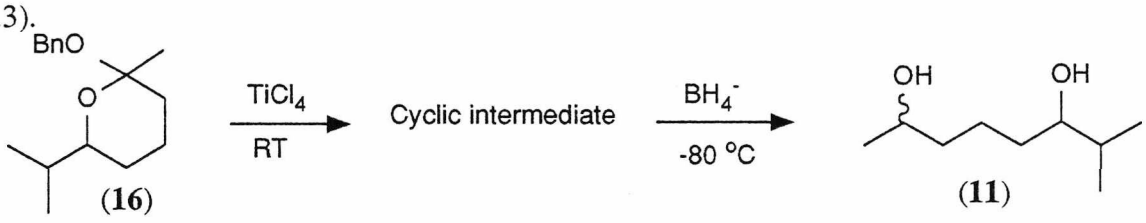
Reduction of the hydroxy ketal-lactol mixture (**15**)

Solvent	Lewis Acid	Temp../°C	syn : anti	Analysis
CH_2Cl_2	$TiCl_4$ (2 eq.)	-78	1 : 1	n.m.r.*
Et_2O	$TiCl_4$ (1.4 eq.)	-75	1 : 1	n.m.r.
CH_2Cl_2	$TiCl_4$ (2.5 eq.)	-70	1 : 1	n.m.r.

* Reducing agent was L-Selectride.

Table 5.5.

It was noted earlier that titanium tetrachloride was observed to remove the benzyl protecting group (see Table 5.2, entry 4). Partial deprotection of the benzyloxy alcohol (**9**) had been observed on occasions where the alcohol (**9**) had been allowed to warm to room temperature in the presence of titanium tetrachloride. It was hoped that the application of titanium tetrachloride to the tetrahydropyran (**16**) might allow removal of the benzyl group, followed by rearrangement to give *some* cyclic organometallic complex (Scheme 5.3).

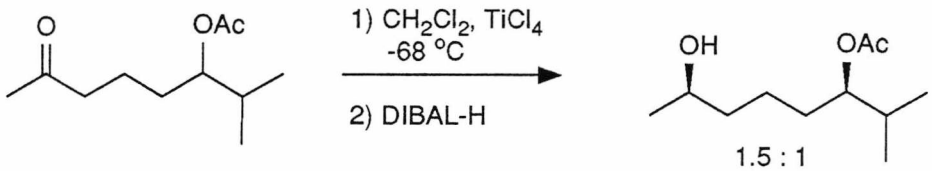


Scheme 5.3.

Thus the tetrahydropyran (0.05 g) was added to $TiCl_4$ (4 eq.) at room temperature and allowed to stir overnight. The mixture was cooled to -80 °C and nBu$_4$NBH$_4$ (1.5 eq.) was added the result was stirred for 24 hrs. followed by workup. Unfortunately, no starting material or expected diol (**11**) was found. The reaction was modified by preparing a solution of the above hydride and titanium tetrachloride in dichloromethane. The tetrahydropyran was added and the mixture cooled to -78 °C. After stirring overnight the

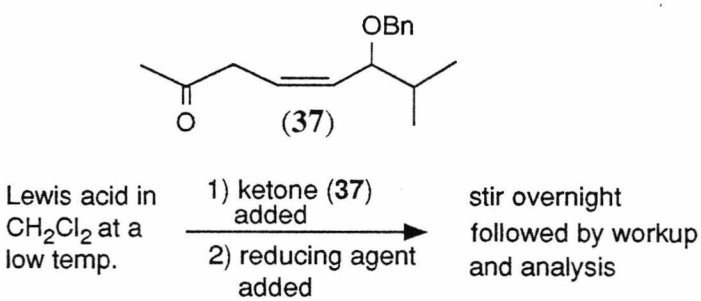
mixture was quenched and analysed by t.l.c. Again no starting material or the expected diol (**11**) was observed.

The keto acetate (**8**) (0.1 g) in dichloromethane (30 ml) with titanium tetrachloride was reduced with DIBAL-H at -68 °C to give the *syn* isomer with a selectivity of 1.5:1. The presence of the hydroxy acetate was confirmed by proton and carbon n.m.r. (1.5:1) followed by reductive cleavage of the acetate by further application of DIBAL-H to form the diol (**11**). Dioxocane formation (1.4:1) lead to the assignment of the major component (Scheme 5.4).



Scheme 5.4.

Reduction of the unsaturated benzyloxy ketone (**37**) was briefly looked at (Scheme 5.5). The reaction schemes followed the general pattern: Cooled solution of Lewis acid in dichloromethane; addition of the ketone (0.05 g); addition of the reducing agent followed by stirring overnight at the low temperature. (Table 5.6).



Scheme 5.5.

CH_2Cl_2	Lewis Acid	Temp./°C	Reducing Agent	syn : anti
20 ml	$TiCl_4$	-83	DIBAL-H	1 : 2
40 ml	$TiCl_4$	-90	L-Selectride	*
20 ml	$TiCl_4$	-78	nBu_4NBH_4	*
20 ml	$MgBr_2$	-78	nBu_4NBH_4	1 : 1

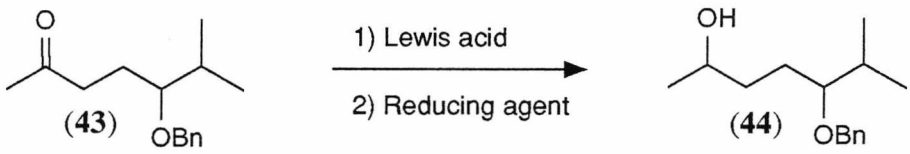
* Mixture of products obtained. No expected alcohol found.

Table 5.6.

The failure for the reduction to proceed with L-Selectride and tetra-*n*-butylammonium bromide may be related to the fact that anti-Markovnikov hydration of alkenes is possible

by the application of sodium borohydride and titanium tetrachloride.[93]

Reduction of the ketone (**43**) was initially attempted using tributyltin hydride in the presence of Lewis acids. These reactions destroyed the ketone (**43**) and lead to an unrecognisable mixture of products. The reactions followed the general pattern (Scheme 5.6): Solution of ketone (0.1 g) at low temperature; Lewis acid added; hydride added; stir at the low temperature overnight followed by workup (Table 5.7).



Scheme 5.6.

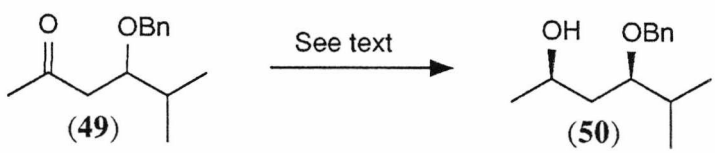
Solvent	Temp./°C	Lewis Acid	Reducing Agent	Ratio	Analysis
1) Et_2O, 40 ml	-77	$AlCl_3$ (1 eq.)	nBu_3SnH (2 eq.)	Failed	t.l.c.
2) Et_2O, 40 ml	-79	$FeCl_3$(1 eq.)	nBu_3SnH (2 eq.)	Failed	t.l.c.
3) Et_2O, 40 ml	-77	$ZnCl_2$(1 eq.)	nBu_3SnH (2 eq.)	Failed	t.l.c.
4) THF, 40 ml	-70	Al	DIBAL-H (4 eq.)	1 : 1	n.m.r.
5) Et_2O, 40 ml	-73	Al	DIBAL-H (4 eq.)	1 : 1	n.m.r.
6) CH_2Cl_2, 40 ml	-73	Al	DIBAL-H (4 eq.)	1 : 1*	n.m.r.
7) CH_2Cl_2, 15 ml	-78	$TiCl_4$ (1 eq.)	nBu_4NBH_4 (2 eq.)	2.5 : 1	n.m.r.

* Using 40 mg. of ketone, syn/anti stereoisomers not identified see text.

Table 5.7.

Unfortunately, analysis of the major diastereoisomer in entry 7 was not possible according to Chapter 3, section 4.6. Removal of the benzyl group of (**44**) was successful, however dioxepane formation failed.

As mentioned earlier, sodium borohydride reduction of (**49**) gave 1.4:1 diastereoselectivity with the *syn* isomer predominating. Reduction of (**49**) on the same scale and under the same conditions as entry 7 in Table 5.7 gave 2.6:1 *syn* selectivity at -78 °C (Scheme 5.7).



Scheme 5.7.

5.2: Discussion

In Table 5.1 the results of the reduction of the ketone (**5**) is presented. It is clear that under a variety of conditions low diastereoselectivity was obtained. Furthermore, the direction of asymmetric induction was seen to change. It was not possible to find conditions which gave predictable diastereoselectivity or control the direction of the process.

The data displayed in Table 5.2 shows that higher levels of asymmetric induction were possible with tetra-*n*-butylammonium borohydride. Attempts have been made to reproduce the conditions leading to the higher diastereoselectivities presented. However, generally little or no diastereoselectivity was observed.

The investigation of the effect of solvent on the extent of asymmetric induction indicates that the non co-ordinating solvent is more likely to give diastereocontrol. This is in line with the idea that co-ordinating solvents may interfere with chelation as pointed out by Reetz. However, it should be noted that the asymmetric induction observed in Table 5.3 is not in the direction predicted on the basis of peripheral attack of hydride on a chelate intermediate (see Chapter 3, section 3.2). It is interesting to note that L-Selectride reduction of (**5**) did give the expected *anti* isomer in the presence of diethyl ether, which of course is capable of co-ordination (Table 3.4).

The reduction of the acetate (**8**) gave poor selectivity in the direction of the *syn* isomer. Although the diastereoselectivity was not expected to be high (on the basis of the models considered in Chapter 3, section 3.2), was predicted to occur in the opposite direction to that observed.

It was rather disappointing to find that the maximum asymmetric induction observed in the reduction of the *cis*-alkene (**37**) was no better than the diastereoselectivity seen in the Wittig reaction which lead to it (Table 5.6). It should be noted that the direction of asymmetric induction in this case was in accord with the prediction outlined earlier and that induction is not expected to be high on the basis of the simple model used for

conformational analysis.

Table 5.7 shows preliminary studies in [1,4]-asymmetric induction. Again the control was not high. At the time of writing it was not possible to identify which isomer was the major component. For completeness a [1,3]-asymmetric reduction was attempted but gave very poor selectivity (Scheme 5.7).

It may be that some intramolecular hydride delivery occurs in the reactions leading to the *syn* isomer (similar to that proposed by Davis and Evans in their examples of [1,3]-asymmetric reductions, Scheme 1.15 and 1.16, also see Figure 2.6) thus giving the alternating diastereoselection seen in Table 5.1. Perhaps DIBAL-H may co-ordinate to the benzyl ether oxygen. Activation of the carbonyl group by co-ordination with titanium may then facilitate some form of intramolecular hydride delivery. Titanium and zirconium (VI) chlorides may react with borohydride to form the metal borohydride.[94] It may be some Lewis acidic borohydride may participate in intramolecular hydride delivery (see Table 5.2). However, this is highly speculative.

Some interesting colour changes have been observed on addition of the ketone (**5**) to titanium tetrachloride. These ranged from yellow through to orange and red. In the precedented 2.5:1 *anti* selective reduction of (**5**) a red colour was obtained.[91] Indeed it was initially hoped that this coloration signified the formation of some chelate. Unfortunately experience does not bear this out.

Colour changes were observed on the addition of tetra-*n*-butylammonium borohydride to titanium tetrachloride. Table 5.2, entries 3 and 4 show essentially the same quantities and conditions. In the first case a blue solution was obtained on mixing the Lewis acid and the borohydride. However, in the second example a yellow solution was obtained. This was quite interesting as it might give an indication of an intermediate which resulted in high diastereofacial selectivity in the reduction of the ketone. The variation of colour was investigate. It turned out that the mixture of hydride and titanium tetrachloride remained yellow until 2 eq. of hydride had been added. The reason of the reasonably abrupt change

was not clear. Reductions were carried out with just under 2 eq. of borohydride (yellow) and just over 2 eq. (blue), however the results were not significant. That is low selectivities were obtained.

5.3: Further Work

Little work has been done in the reduction of (**43**) and there is considerable scope for improvements in this area. This is also true of the ketone (**37**) and (**49**), although in the latter case Reetz has developed excellent methods of producing differentially substituted 1,3-dioxgenated compounds. Much more work is required in the reduction of (**38**), however time does not permit at the moment. In addition, asymmetric reduction of the ketones (**6**) and (**22**) have not received any attention to date (Figure 5.1).

Figure 5.1.

In view of the results obtained using the crude force field developed here, *ab initio* work is required to derive force constants, bond moments and atomic charges.[95] Investigation into the nature of the potential energy surface with respect to torsional increments is also required. It may then possible to fit the *ab inito* potential energy surface to the torsional equation or some modified torsional equation. This may then allow V_n (where n= 1, 2, 3 and possibly 4) parameters to be derived for the MM2 force field. A logical approach to this is provided by the SCRIPTION procedure.[95f]

It may be that chelation controlled processes via medium rings will always be problematic due to ring strain. As the ring size increases chelate formation may become more likely. If so then predicting the conformational bias in such systems may become important. In these cases parameterization for Lewis acid chelates displaying octahedral symmetry in their hypervalent states may be important in the prediction of conformational preferences. This is likely to be important where the co-ordinated centre is sitting in an unsymmetrical environment with respect to the ring plane (see Figure 3.17).

EXPERIMENTAL

Melting points were performed on Reichert melting point apparatus and are uncorrected. I.r. spectra were recorded on a Perkin Elmer 297 or 683 spectrometer. Low field proton n.m.r. spectra were recorded on Jeol PMX 60 (60 MHz) and Jeol PS 100 (100 MHz) spectrometers and high field proton and carbon n.m.r. spectra on a Jeol GX270 (270 MHz) instrument. High field proton n.m.r. spectra were recorded with a spectral width of 4.5 KHz. The FID consisted of 32K data points. The digital resolution was consequently subject to an error of 0.28 Hz. Standard carbon n.m.r. spectra were recorded with a spectral width of 18 KHz and a digital resolution of 32 K and thus the digital resolution was 1.099 Hz (0.016 ppm). Highly digitized carbon n.m.r. spectra were recorded with a spectral width of 18 KHz. The FID consisted of 128 K data points and the digital resolution was 0.275 Hz (0.004 ppm). Mass spectra, EI, CI and accurate mass determinations were performed by the Science an Engineering Research Council Mass Spectrometry unit at the University of Swansea. Elemental analyses were performed in the microanalytical laboratory at the University of Kent. MPLC was performed using Buchi preparative columns packed with Lichoprep (Merck 9390, 25-40 μm) and Gilson equipment. Flash chromatography employed silica gel (40-63 μm, Merck). All solvents for use in chromatography were purchased from Fisons; petroleum ether (40-60 °C) was flash distilled prior to use. T.l.c. was performed on foil-backed silica plates (thickness 0.2 mm) (Merck 5554). Capillary g.c. was performed on a Pye-Unicam PU 4500 instrument. Kugelrohr distillations were performed on a Buchi GKR-50 apparatus and operating conditions are quoted in the form: (Oven temperature, pressure). DMF was dried in the following manner: after refluxing over barium oxide and standing overnight, the DMF was decanted into another dry vessel and distilled under nitrogen; the pure, dry DMF was stored over 4Å molecular sieves and under nitrogen in a bottle fitted with a suba-seal. Titanium tetrachloride was distilled and stored under nitrogen. All chemical reactions were carried out using Pyrex Quickfit apparatus were dried in an oven at 170 °C where approprate.

The following three solvents were routinely dried in the following manner:

THF	Distilled from sodium and benzophenone
Diethyl ether	Distilled from sodium
Dichloromethane	Distilled from phosphorous pentoxide

5-Bromopentan-2-one (**1**).[96] To a refluxing solution of hydrobromic acid (48 %; 600 ml) was added 2-acetyl butyrolactone (240 g; 1.88 mol). The crude product was steam distilled from the reaction mixture into a Dean and Stark trap, dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a black oil (186.7 g). The oil was distilled under reduced pressure through a 12 cm Vigreux column (60-64 °C, 4.5-5.0 mmHg) to give (**1**) as a colourless oil (151.3 g; 60 %), δ_H (60 MHz; $CDCl_3$; TMS) 3.5 (2H, t, C***H***$_2$Br), 2.7 (2H, t, COC***H***$_2$), 2.2 (3H, s, ***Me***), and 2.15-1.95 (2H, m, C***H***$_2$CH$_2$Br).

2-(3-Bromopropyl)-2-methyl-1,3-dioxolane (**2**).[97] 5-Bromopentan-2-one (151.3 g; 1.12 mol), ethylene glycol (104.2 g; 1.68 mol) and *p*-toluene sulphonic acid (1 g) were placed in benzene (500 ml). The result was refluxed until no more water was collected. The mixture was allowed to cool and washed with 1% sodium bicarbonate solution. The organic phase was separated and dried over magnesium sulphate. After filteration and concentration a crude red-brown liquid was obtained (137.7 g; 57 % yield). The crude ketal was distilled through a 30 cm Vigreux column under reduced pressure (64-67 °C; 1.5 mmHg) to give (**2**) as a colourless liquid (96.1 g; 41 %), $\nu_{max.}$($CHCl_3$) 2970, 2870, and 1655; δ_H (60 MHz; $CDCl_3$; TMS) 3.9 (4H, s, OC***H***$_2$C***H***$_2$O), 3.4 (2H, t, C***H***$_2$Br), 1.8 (2H, m, C***H***$_2$CH$_2$Br), and 1.3 (3H, s, ***Me***); m/z, EI: 181 and 179 (17 %), 153 and 151 (3), 137 and 135 (8), 109 and 107 (19), 87, (100), 71 (22), 55 (23), and 43 (100); CI: 214 and 212 ($M+NH_4^+$, 11 %), 197 and 195 ($M+H^+$, 75), 181 and 178 (2), 150 (26), 133 (8), 115 (100), 99 (1), 87 (40), and 70 (3); (Found 195.0021 from $M+H^+$ in CI. Calc. for $C_6H_{12}BrO_2$: 195.0021).

2-(4-Hydroxy-5-methylhexyl)-2-methyl-1,3-dioxolane (**3**). Into a dried three necked round bottomed flask fitted with nitrogen inlet, dropping funnel and condenser was placed magnesium turnings (5.5 g, 0.23 mol). A solution of (**2**) (12.10 g; 58 mmol) in dry THF (13 ml) was placed in the dropping funnel. A small portion of this was added to the magnesium turnings and 1,2-dibromoethane (0.2 ml) was added to initiate. Addition was continued at such a rate to maintain a temperature of less than 30 °C. After addition was complete the mixture was stirred for 1½ hrs. At which time the mixture was diluted with

THF (30 ml). Isobutyraldehyde (2.8 g, 39 mmol) in THF (10 ml) was then added dropwise at -78 °C. The mixture was allowed to stir and come to room temperature overnight. The result was quenched on an ice slurry containing ammonium chloride (5 g) and a few drops of s.g. 0.88 ammonium hydroxide solution. The mixture was stirred for 10 mins. and then filtered. The upper organic phase was separated and washed with brine. The aqueous phase was extracted with diethyl ether. The organic phases were combined and dried over magnesium sulphate. After filtration and concentration under reduced pressure a pale yellow oil resulted (11.2 g; 96 %). The oil was kugelrohr distilled (150 °C, 0.1 mmHg) to give the *dioxolane* (**3**) as a pale yellow oil (6.2 g; 79 % yield), $\nu_{max.}$ (film) 3460 (br, OH), 2980 (C-H), and 2870 (C-H) cm^{-1}; δ_H (60 MHz; $CDCl_3$; TMS) 3.92 (4H, s, OCH_2CH_2O), 3.25 (1H, m, CH_2CHOH), 2.24 (1H, b, OH), 1.45 (7H, m, $CH_2CH_2CH_2$, $CHMe_2$), 1.32 (3H, s, $MeCCH_2CH_2$), and 0.92 (6H, d, $CHMe_2$).

2-(4-Benzyloxy-5-methylhexyl)-2-methyl-1,3-dioxolane (**4**). To a cooled, stirred solution of the alcohol (**3**) (1 g, 5 mmol) in THF (15 ml) under nitrogen was added sodium hydride (0.40 g, 60 % dispersion in mineral oil, 10 mmol). After stirring for 10 mins. tetra-*n*-butyl ammonium bromide was added. After stirring for a further 15 mins. benzyl bromide (1.3 g; 7.5 mmol) was added. The mixture was stirred under nitrogen for $1\frac{1}{2}$ days at 55 °C. The result was poured onto saturated brine and the organic phase separated. The aqueous phase was extracted with dichloromethane. The organic phases were combined and concentrated to give a crude yellow oil. The oil was taken up in dichloromethane and washed with water. The organic phase was separated, dried over magnesium sulphate and concentrated under reduced pressure to give a yellow oil (2.65 g). The oil purified by flash chromatography on silica gel (40-63 μm) eluting first with *n*-hexane to remove unreacted benzyl bromide and then with *n*-hexane-ethyl acetate (4:1). The appropriate fractions were combined and concentrated to give the *benzyloxy ketal* (**4**) as a yellow oil (1.0 g, 69 % yield), $\nu_{max.}$ (film) 2950 (C-H), and 2860 (C-H) cm^{-1}; δ_H (270 MHz; $CDCl_3$; TMS) 7.37-7.25 (5H, br m, CH_2Ph), 4.56 (1H, d, ^2J 12.91 Hz, CH_2Ph), 4.51 (1H, d, ^2J 12.91 Hz, CH_2Ph), 3.97-3.16 (4H, br m, OCH_2CH_2O), 3.16 (1H, m, $PhCH_2OCH$), 1.92 (1H, m, $CHMe_2$), 1.61-1.23 (6H, br m, $CH_2CH_2CH_2$), 1.31 (3H, s, MeC), 0.93 (3H, d, ^3J 6.87 Hz,

CH***Me***$_2$), and 0.91 (3H, d, ^3J 6.87 Hz CH***Me***$_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 139.23 (***Ph***), 128.25 (***Ph***), 127.75 (***Ph***), 127.33 (***Ph***), 110.12 (O***C***O), 84.18 (***C***HOBn), 71.79 (***C***H$_2$Ph), 64.62 (O***C***H$_2$***C***H$_2$O), 39.39 (CH$_2$C***H***$_2$CH$_2$), 30.52 (***C***HMe$_2$), 30.42 (***C***H$_2$CH$_2$CH$_2$), 23.77 (CH$_2$CH$_2$***C***H$_2$), 20.33 (***Me***CCH$_2$), 18.37 (CH***Me***$_2$), and 18.05 (CH***Me***$_2$); m/z, EI: 249 (2 %), 231 (1), 185 (15), 157 (2), 29 (141), 133 (6), 123 (66), 115 (9), 97 (24), 91 (76), 83 (37), 71 (6), 65 (3), 49 (100), 43 (15), and 37 (5); CI: 293 (M+H$^+$, 10 %), 273 (1), 249 (1), 201 (1), 185 (40), 170 (1), 159 (3), 141 (100), 123 (69), 108 (16), 97 (5), 87 (3), and 49 (2); (Found 293.2117 from M+H$^+$ in CI. $C_{18}H_{29}O_3$ requires 294.2117).

6-Benzyloxy-7-methyloctan-2-one (**5**). A mixture of the ketal (**4**) (1 g, 3.4 mmol), 4M $HCl_{(aq)}$ (12 ml) and THF (12 ml) was stirred for 24 hrs. at room temperature. The result was extracted with diethyl ether and brine. The organic phase was separated and dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a pale yellow oil (0.85 g). The crude product was kugelrohr distilled (150-165 °C, 0.2 mbar) to give the pure *ketone* (**5**) (0.75 g, 88 %), (Found: C, 77.53; H, 9.72; N, 0.00. $C_{16}H_{24}O_2$ requires C, 77.38; H, 9.74; N, 0.00 %); $\nu_{max.}$ (film) 2940 (C-H), 2860 (C-H), and 1710 (C=O) cm $^{-1}$; δ_H (270 MHz; $CDCl_3$; TMS) 7.40-7.20 (5H, m, ***Ph***), 4.54 (1H, d, ^2J 10.8 Hz, PhC***H***$_2$), 4.48 (1H, d, ^2J 10.8 Hz, PhC***H***$_2$), 3.15 (1H, q, ^3J 5.4 Hz, BnOC***H***), 2.40 (1H, t, ^3J 7.42 Hz, MeCOC***H***$_2$), 2.1 (3H, s, ***Me***CO), 2.0-1.85 (1H, m, C***H***Me$_2$), 1.8-1.52 (2H, m, MeCOCH$_2$CH$_2$C***H***$_2$), 1.52-1.40 (2H, m, MeCOCH$_2$C***H***$_2$CH$_2$), 0.93 (3H, d, ^3J 6.49 Hz, CH***Me***$_2$), and 0.91 (3H, d, ^3J 6.60 Hz, CH***Me***$_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 208.64 (Me***C***OCH), 139.15 (***Ph*** quarterary), 128.281 (***o-Ph***), 127.75 (***m-Ph***), 127.406 (***p-Ph***), 83.96 (BnO***C***), 71.71 (Ph***C***H$_2$O), 43.76 (MeCO***C***H$_2$), 30.44 (***C***HMe$_2$), 29.73 (MeCOCH$_2$***C***H$_2$CH$_2$), 29.58 (MeCOCH$_2$CH$_2$***C***H$_2$), 20.11 (***Me***CO), 18.44 (C***Me***$_2$), and 17.87 (C***Me***$_2$); m/z, EI: 243 (30 %), 201 (17), 173 (3), 155 (24), 129 (100), 115 (41), 97 (60), 91 (25), 69 (88), 57 (31), and 43 (71); CI: 266 (34 %, M+NH$_4^+$) 249 (100, M+H$^+$), 205 (4), 155 (35), 141 (100), 123 (3), 108 (15), and 91 (8); (Found 249.1858 from M+H$^+$ in CI. $C_{16}H_{25}O_2$ requires 249.1854).

6-Methoxy-7-methyloctan-2-one (**6**). Sodium hydride (0.64 g, 60 % dispersion in mineral

oil, 16 mmol) was suspended in THF (20 ml) with stirring under a nitrogen atmosphere and cooled in an ice salt bath. To this was added the ketal (**3**) (1.64 g, 8 mmol) in THF (5 ml). After the effervescence had ceased dimethyl sulphate (2.02 g, 16 mmol) was added. The mixture was allowed to stir and come to room temperature overnight. The reaction was quenched on ammonium chloride solution made just alkaline with a drop of conc. ammonium hydroxide. The resulting aqueous solution was extracted with dichloromethane (3 x 30 ml). The combined organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a crude yellow oil. The crude oil was taken up into THF (10 ml) and stirred vigorously with 2M $HCl_{(aq)}$ (10 ml) for 2 hrs. The result was poured onto saturated brine and extracted with diethyl ether (3 x 30 ml). The combined organic phases were dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a pale yellow oil. The oil was purified by flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (4:1) to give a pale yellow oil. Kugelrohr distillation (100 °C, 0.1 mmHg) afforded the *ketone* (**6**) as a colourless oil (0.370g, 27 %), $\nu_{max.}$ ($CHCl_3$) 2940 (C-H), and 1650 (C=O) cm^{-1}; δ_H (270 MHz; $CDCl_3$; TMS) 3.34 (3H, s, O***Me***), 2.89-2.85 (1H, m, C***H***OMe), 2.45 (2H, t, ^3J 7.14 Hz, MeCOC***H***$_2$), 2.14 (3H, s, ***Me***$COCH_2$), 1.87-1.38 (5H, br m, C***H***$_2$C***H***$_2$CH(OMe)C***H***), 0.89 (3H, d, ^3J 6.59 Hz, CH***Me***$_2$), and 0.86 (3H, d, ^3J 6.59 Hz, CH***Me***$_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 208.99 (***C***O), 86.10 (MeO***C***H), 57.72 (***Me***O), 57.65 (***Me***O), 57.57 (***Me***O), 43.90 (MeCO***C***H_2), 30.18 (***C***HMe_2), 29.82 (CH_2***C***H_2CH_2), 29.55 (CH_2CH_2***C***H_2), 20.24 (***Me***CO), and 18.23 (CH***Me***$_2$); m/z, EI: 129 (17 %), 87 (10), 71 (100), and 55 (5); CI: 173(84 %, $M+H^+$), and 141 (100); (Found 173.1542 from $M+H^+$in CI. $C_{10}H_{21}O_2$ requires 173.1540).

2-(4-Acetoxy-5-methylhexyl)-2-methyl-1,3-dioxolane (**7**). To a stirred solution of acetic anhydride (1.130 g, 11 mmol), triethylamine (1.130 g, 11 mmol) and a crystal of DMAP in dry dichloromethane (10 ml) was added the alcohol (**3**). A slight exotherm was noted. The resulting solution was allowed to stir under nitrogen for 24 hrs. The reaction mixture was quenched on ammonium hydroxide solution with a drop of conc. ammonium hydroxide solution. The organic phase was separated and the aqueous phase extracted with

dichloromethane (10 ml). The combined organic phase was dried over magnesium sulphate. A crude oil was obtained by filtration and removal of the solvent. The oil was purified by flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (4:1) followed by kugelrohr distillation (100 °C, 0.1 mmHg) to give the *ketal acetate* (**7**), $\nu_{max.}$ ($CHCl_3$) 3950 (C-H), 3860 (C-H), and 1710 (C=O) cm^{-1}; δ_H (270 MHz; $CDCl_3$; TMS) 4.72 (1H, q, ^3J 6.59 Hz, C***H***OAc), 3.90 (4H, m, OC***H***$_2$C***H***$_2$O), 2.03 (3H, s, ***Me***CO_2), 1.81-1.31 (7H, br m, ***Me***CC***H***$_2$C***H***$_2$), 1.28 (3H, s, ***Me***CCH_2), and 0.87 (6H, d, ^3J 6.6 Hz, CH***Me***$_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 170.90 (Me***C***O_2CH), 109.91 (O***C***O), 78.22 (AcO***C***H), 64.56 (O***C***H_2***C***H_2O), 38.91 (CH_2***C***H_2CH_2), 31.25 (CH_2CH_2***C***H_2), 31.14 (***C***HMe_2), 23.69 (MeC***C***H_2), 21.07 (***Me***CCH_2CH_2), 20.03 (***Me***CO_2CH), 18.45 (CH***Me***$_2$), and 17.55 (CH***Me***$_2$); m/z, EI: 229 (10 %), 169 (4), 141 (3), 123 (5), 115 (3), 99 (21), 87 (100), 82 (5), 71 (6), 55 (16), and 45 (3); CI: 262 (15 %, $M+NH_4^+$), 245 (77, $M+H^+$), 218 (2), 185 (85), 141 (12), 123 (65), 103 (3), 87 (100), and 58 (2); (Found 245.1753 from $M+H^+$ in CI. $C_{13}H_{25}O_4$ requires 245.1753).

6-Acetoxy-7-methyloctan-2-one (**8**). The oil (**7**) obtained in the previous preparation was stirred vigorously in THF (10 ml) and 2M $HCl_{(aq)}$. After 2 hrs. the mixture was poured onto saturated brine and extracted with diethyl ether (3 x 30 ml). The combined organic phases were dried over magnesium sulphate, filtered and concentrated under reduced pressure to give pale yellow oil. The oil was purified using flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (9:1) followed by kugelrohr distillation (100 °C, 0.1 mmHg) to give the *ketone* (**8**) (1.09 g, 92 % over two steps), (Found: C, 66.32; H, 10.38; N, 0.00. $C_{11}H_{20}O_3$ requires C, 65.97; H, 10.07; N, 0.00 %); $\nu_{max.}$($CHCl_3$) 2950 (C-H), 2860 (C-H), and 1710 (C=O) cm^{-1}; δ_H (270 MHz, $CDCl_3$; TMS) 4.70 (1H, q, ^3J 5.77 Hz, C***H***OAc), 2.45-2.38 (2H, m, MeOC***H***$_2$), 2.10 (3H, s, ***Me***CO), 2.03 (3H, s, ***Me***CO_2), 1.83-1.76 (1H, m, C***H***Me_2), 1.58-1.47 (4H, m, C***H***$_2$C***H***$_2$CHOAc), and 0.86 (6H, d, ^3J 6.86 Hz, CH***Me***$_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 208.44 (Me***C***O), 170.93 (Me***C***O_2), 77.81 (AcO***C***H), 43.17 (MeCO***C***H_2), 31.23 (CH_2***C***H_2CH_2), 30.39 (CH_2CH_2***C***H_2), 29.79 (***C***HMe_2), 21.02 (***Me***CO), 19.57 (***Me***CO_2), 18.41 (CH***Me***$_2$), and 17.55 (CH***Me***$_2$); m/z, EI: 201 (1 %), 157 (157), 141 (32), 115 (85), 97

(75), 82 (100), 71 (42), 55 (36), and 49 (12); CI: 218 (70 %, $M+NH_4^+$), 201 (8, $M+H^+$), 158 (3), 141 (100), 123 (2), and 82 (2); (Found 218.1756 form $M+NH_4^+$ in CI. $C_{11}H_{24}NO_3$ requires 218.1756).

6-Benzyloxy-7-methyloctan-2-ol (**9**). To a stirred solution of the benzyloxy ketone (**5**) (1.0 g, 3.4 mmol) in absolute ethanol (50 ml) was added sodium borohydride (0.25, 6.6 mmol). The mixture was left to stir for 1 hr. Distilled water (30 ml) was then added and the mixture acidified with 4M $HCl_{(aq)}$. After a few minutes the mixture was extracted with dichloromethane and dried over magnesium sulphate, filtered and concentration under reduced pressure to give a pale yellow oil (1.0 g). The crude product was purified by flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (4:1). The appropriate fractions were combined and concentrated under reduced pressure to give the *alcohol* (**9**) as a colourless oil (0.53 g, 53%), (Found: C, 76.75; H, 10.47; N, 0.00. $C_{16}H_{26}O_2$ requires C, 76.96; H, 11.28; N, 0.00 %); $\nu_{max.}$ (film) 3360 (br, OH), 2950 (C-H), 2910 (C-H), 2860 (C-H), and 1460 cm^{-1}; δ_H (270 MHz; $CDCl_3$; TMS) 7.37-7.24 (5H, m, ***Ph***), 4.54 (1H, d, ^2J 11.53 Hz, PhC***H***$_2$O), 4.47 (1H, d, ^2J 11.53 Hz, PhC***H***$_2$O), 3.97-3.72 (1H, m, MeC***H***OH), 3.17-3.12 (1H, m, BnOC***H***), 1.97-1.89 (1H, m, C***H***Me_2), 1.68 (1H, br s, O***H***), 1.53-1.25 (6H, br m, C***H***$_2$C***H***$_2$C***H***$_2$), 1.16 (3H, d d, ^3J 6.32 Hz, ^4J 0.55 Hz, ***Me***CHOH), 0.93 (3H, d, ^{3}J 6.87 Hz, CH***Me***$_2$), and 0.91 (3H, d, ^3J 6.87 Hz, CH***Me***$_2$); COSY 90; δ_C (67.8 MHz; $CDCl_3$; TMS) 139.19 (***Ph***, *syn*), 139.16(***Ph***, *anti*), 128.28 (***Ph***, *syn*, *anti*), 127.81 (***Ph***, *anti*), 127.79 (***Ph***, *syn*), 127.41 (***Ph***, *syn*), 127.40 (***Ph***, *anti*), 84.23 (BnO***C***H, *anti*), 84.14 (BnO***C***H, *syn*), 71.82 (Ph***C***H_2O, *anti*), 71.76 (Ph***C***H_2O, *syn*), 68.04 (Me***C***HOH, *syn*), 67.94 (Me***C***HOH, *anti*), 39.51 (MeCH(OH)***C***H_2, *syn*, *anti*), 30.52 (***C***HMe_2, *syn*, *anti*), 30.16 (***C***H_2CHOBn, *syn*), 30.10 (***C***H_2CHOBn, *anti*), 23.48 (***Me***COH, *anti*), 23.42 (***Me***CHOH, *syn*), 22.01 (MeCOCH_2***C***H_2CH_2, *anti*), 21.84 (MeCOCH_2***C***H_2CH_2, *syn*), 18.43 (CH***Me***$_2$, *syn*, *anti*), 17.99 (CH***Me***$_2$, *syn*), and 17.92 (CH***Me***$_2$, *anti*); DEPT 45, 90, 135; CH COSY. Stereochemical assignments were made by comparison with the optically pure alcohol (**I**).

7-Acetoxy-3-benzyloxy-2-methyloctane (**10**). The alcohol (**9**) (0.05 g, 0.17 mmol), acetic

anhydride (0.02 g, 0.24 mmol), triethylamine (0.017 g, 0.26 mmol) and DMAP (0.003 g) were placed in a 5 ml round bottomed flask, with dichloromethane (1ml) and allowed to stir for 30 hrs. at room temperature. The resulting mixture was washed with 2M $HCl_{(aq)}$, then extracted with dichloromethane. The organic phase was separated and dried over magnesium sulphate. After filtration and concentration under reduced pressure a crude colourless oil was obtained. The oil was purified by flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (4:1). Concentration of the appropriate fractions the *acetate* (**10**) as a pale yellow oil (0.06 g, 100% yield), (Found: C, 73.76; H, 9.99; N, trace. $C_{18}H_{28}O_3$ requires C, 73.93; H, 9.65; N, 0.00 %); δ_H (60MHz; $CDCl_3$; TMS) 7.39 (5H, s, ***Ph***), 4.9 (1H, m, AcOC***H***), 4.56 (2H, s, PhC$\boldsymbol{H}_2$O), 3.2 (1H, m, BnOC***H***), 2.04 (3H, s, ***Me***CO_2), 1.7-1.2 (6H, br m, MeCH(OAc)C$\boldsymbol{H}_2$C$\boldsymbol{H}_2$C$\boldsymbol{H}_2$), and 0.96 (6H, d, CH***Me***$_2$); m/z, EI: no M^+, 249 (10 %), 189 (10), 149 (10), 126 (17), 125 (10), 105 (20), 100 (79), 82 (18), 91 (100), 82 (18), 69 (21), 57 (16), 56 (19), 43 (43), 41 (19), and 29 (10).

2-Methyloctan-3,7-diol (**11**). The alcohol (**9**) (0.246 g, 0.98 mmol) was placed in a round bottomed flask with absolute ethanol (10 ml) and 5% palladium on charcoal (0.1 g) was added. The mixture was stirred under an atmosphere of hydrogen for 45 mins., then filtered through Celite. The ethanol removed under reduced pressure to give a colourless viscous oil (0.145 g, 92 %). The oil was kugelrohr distilled (190 °C, 4 mmHg) to give the pure *diol* (**11**), (Found: C, 67.79; H, 13.09; N, 0.00. $C_9H_{20}O_2$ requires C: 67.45; H: 12.58; N: 0.00 %); δ_H (270 MHz; $CDCl_3$; TMS) 3.88-3.75 (1H, m, MeC***H***OHCH$_2$), 3.40-3.30 (1H, m, iPrC***H***OH), 2.05 (2H, br s, O***H***), 1.75-1.55 (1H, m, C***H***Me$_2$), 1.55-1.30 (6H, m, C$\boldsymbol{H}_2$C$\boldsymbol{H}_2$C$\boldsymbol{H}_2$), 1.19 (3H, d, ^3J 6.04 Hz, ***Me***CHOH), and 0.915 (6H, d, ^3J 6.86 Hz, CH***Me***$_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 76.7 (***Me***CHOH), 68.03 (iPr***C***HOH), 67.76 (iPr***C***HOH), 39.25 (MeCHOH***C***H$_2$), 39.07 (MeCHOH***C***H$_2$), 33.99 (***C***H$_2$CHOH***C***HMe$_2$), 33.68 (***C***H$_2$CHOH***C***HMe$_2$), 33.58 (***C***H$_2$CHOH***C***HMe$_2$), 23.61 (***Me***CHOH), 23.49 (***Me***CHOH), 22.22 (CH$_2$***C***H$_2$CH$_2$), 22.14 (CH$_2$***C***H$_2$CH$_2$), 18.85 (CH***Me***$_2$), 18.81 (CH***Me***$_2$), and 17.29 (CH***Me***$_2$); m/z, EI: no M^+, 117 (27 %), 109 (15), 99 (95), 81 (100), 91 (13), 73 (41), 70 (28), 55 (78), 43 (70), 41 (22), and 29 (11); CI: 178 (100 %,

$M+NH_4^+$), 161 (25, $M+H^+$), 143 (8), 99 (6), and 81 (2).

2,6-Diacetoxy-7-methyloctane (**12**). To a stirred solution of acetic anhydride (0.100 g, 1.3 mmol), triethylamine (0.100 g, 1.3 mmol) and DMAP (0.006 g, 0.05 mmol) in dry dichloromethane (5 ml) under a nitrogen atmosphere was added the diol (**11**) (0.5 g, 2 mmol). The resulting solution was stirred at room temperature for 5 days. The reaction mixture was quenched on 2M $HCl_{(aq)}$ and extracted with dichloromethane. The combined organic phases were washed with saturated sodium hydrogen carbonate solution (10 ml). The organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a crude pale yellow oil. The oil was kugelrohr distilled (120 ° C, 0.7 mmHg) to give the *diacetate* (**12**) as a colourless oil (0.040 g, 73 %). δ_H (60 MHz; $CDCl_3$; TMS) 2.8 (2H, m, AcOC***H***), 2.02 (3H, s, ***Me***CO_2), 2.0 (3H, s, ***Me***CO_2), 2.0-1.4 (7H, m, C***H***$_2$C***H***$_2$C***H***$_2$C***H***(OAc)$CHMe_2$), 1.20 (3H, d, ***Me***CHOAc), and 0.90 (6H, d, CH***Me***$_2$).

cis- and trans-4-(2-Methylethyl)-7-methyl-1,3-dioxocane (**13**, **14**). 2-Methyloctan-3,7-diol (**11**) (0.425 g, 2.83 mmol) was placed in a round bottomed flask with benzene (50 ml), *p*-formaldehyde (0.5 g, 16.7 mmol) and a crystal of *p*-methyl toluene sulphonic acid. This was refluxed under a Dean and Stark trap until the first few drops of benzene-water azeotrope were collected (2ml). The cooled mixture was washed with excess 1 % sodium bicarbonate solution. The organic layer was separated, dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a crude yellow oil (0.457 g, 100 %). The diastereoisomers were separated using flash chromatography on silica gel (40-63 μm) eluting with dichloromethane. After concentration of the appropriate fractions the two diastereomeric oils with a distinctive musty odour were obtained: *trans isomer* (**13**) (0.235 g, 48%), (Found: C, 70.06; H, 12.18; N, 0.00. $C_{10}H_{20}O_2$ requires C, 69.72; H, 11.70; N 0.00 %); δ_H (270M Hz; $CDCl_3$; TMS) 4.75 (1H, d, ^2J 6.04 Hz, OC***H***$_2$O), 4.69 (1H, d, ^2J 6.04 Hz, OC***H***$_2$O), 3.74-3.67 (1H, m, OC***H***Me), 3.39-3.32 (1H, m, OC***H***iPr), 1.94-1.85 (1H, m, CHC***H***Me_2), 1.70-1.52 (4H, m, C***H***$_2$CH_2C***H***$_2$), 1.51-1.36 (2H, m, CH_2C***H***$_2$$CH_2$), 1.16 (3H, d, ^3J 6.60 Hz, CH***Me***), 0.91 (3H, d, ^3J 6.05 Hz, CH***Me***$_2$), and 0.88 (3H, d, ^3J

5.77 Hz, CH***Me***$_2$); COSY 90; δ_C (67.8 MHz; $CDCl_3$; TMS) 95.13 (O***C***H$_2$O), 81.62 (iPr***C***H), 74.15 (Me***C***H), 36.08 (***C***HMe$_2$), 34.12 (***C***H$_2$CH$_2$CH$_2$), 32.35 (CH$_2$***C***H$_2$CH$_2$), 22.61 (***Me***CH), 20.95 (CH$_2$CH$_2$***C***H$_2$), 19.22 (CH***Me***$_2$), and 18.07 (CH***Me***$_2$); CH COSY; m/z, CI: 190(8 %, M+NH_4^+), 178(100), 161 (11), 143 (5), 74 (8), 63 (5), 58 (5), 52 (93), and 49 (2); *cis isomer* (**14**) (0.131 g, 27 %), (Found: C, 69.85; H, 12.06; N, 0.00. $C_{10}H_{20}O_2$ requires C, 69.72; H, 11.70; N, 0.00 %); δ_H (270 MHz; $CDCl_3$; TMS) 5.10 (1H, d, ^2J 7.14 Hz, OC***H***$_2$O), 4.53 (1H, d, ^2J 7.14 Hz, OC***H***$_2$O), 3.84-3.73 (1H, m, OC***H***Me), 3.36-2.28 (1H, m, OC***H***iPr), 1.89-1.85 (1H, m, CHC***H***Me$_2$), 1.85-1.42 (6H, m, C***H***$_2$C***H***$_2$C***H***$_2$), 1.122 (3H, d,^3J Hz, CH***Me***), 0.91 (3H, d, ^3J 6.82 Hz, CHCH***Me***$_2$), and 0.88 (3H, d, ^3J 6.87 Hz, CHCH***Me***$_2$); COSY 90; δ_C (67.8 MHz; $CDCl_3$; TMS) 92.28 (O***C***H$_2$O), 84.36 (iPr***C***H), 74.90 (Me***C***H), 37.38 (***C***HMe$_2$), 33.68 (***C***H$_2$CH$_2$CH$_2$), 33.08 (CH$_2$***C***H$_2$CH$_2$), 23.09 (***Me***CH), 20.68 (CH$_2$CH$_2$***C***H$_2$), 19.19 (CH***Me***$_2$), and 18.34 (CH***Me***$_2$); m/z, CI: 190 (46 %, M+NH_4^+), 178 (100), 161 (13), 143 (3), 99 (3), 85 (2), 74 (7), 63 (3), 58 (2), and 52 (71). The identification of the *cis* and *trans* isomers was obtained by conversion of (S,S)-6-benzyloxy-7-methyl octan-2-one (**I**) to the optically pure *cis* dioxocane (**II**) followed by glc analysis. The *trans* isomer was found to be the less polar component on silica gel (40-63 μm) eluting with dichloromethane and the more volatile component (i.e. shorter retention time) in capillary g.c. using BP1 and BP5 columns.

Hydrolysis 2-(4-Hydroxy-5-methylhexyl)-2-methyl-1,3-dioxolane (**15**). The hydroxy ketal (**3**) (0.5 g, 13 mmol), distilled water (10 ml), THF (30 ml) and *p*-toluene sulphonic acid (0.2 g) were refluxed for 1½ hrs. The result was washed with sodium bicarbonate solution and brine followed by extracted with diethyl ether. The organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a crude yellow oil (0.35 g, 89 %). The oil failed to give satisfactory t.l.c. spot. A small amount of the *oil* (**15**) was distilled (80-150 °C, 0.05 mmHg). δ_H (270 MHz; $CDCl_3$; TMS) 3.5 (⅓H, m, C***H***OH, lactol), 3.3 (⅔H, m, C***H***OH, ketone), 3.0 (⅓H, br s, O***H***, lactol), 2.6 (⅔H, br s, O***H***, ketone), 2.4 (1⅓H, t, ^3J 7.28 Hz, MeCOC***H***$_2$CH$_2$, ketone), 2.1 (2H, s, ***Me***COCH$_2$, ketone), 1.9-1.0 (5⅔H, br m, CH$_2$C***H***$_2$C***H***$_2$CHOHC***H***Me$_2$, C***H***$_2$C***H***$_2$C***H***$_2$CH(O-)C***H***Me$_2$, ketone, lactol), 1.4 (1H, s, ***Me*** , lactol), 0.90 (4H, d, ^3J 6.87 Hz, CH***Me***$_2$, ketone), and 0.86

(2H, d, ^3J 6.86 Hz, CH***Me***$_2$, lactol); δ_C (67.8 MHz; $CDCl_3$; TMS) 209.39(***C***=O) 76.09, 43.63, 33.68, 33.47, 20.33, 18.84, 17.40; lactol, 95.39, 74.76, 34.79, 32.89, 30.67, 29.79, 27.13, 19.34, and 18.24 peak ratios are approximately 2:1. Further smaller resonances possibly resulting from lactol-OH_{eq}; m/z, CI: 176 (4 %, M+NH_4^+), 176 (4), 157 (6), 141 (100, M^+-OH·), 123 (5), and 85 (6).

Hydrogenolysis of (**4**). A mixture of the benzyloxy ketal (**4**) (0.5 g, 2 mmol) and 5 % palladium on charcoal (0.1 g) in ethanol (15 ml) was stirred rapidly for 48 hrs. The mixture was filtered through Celite and concentrated to give a colourless oil. The oil was passed down a silica gel column eluting with dichloromethane. After concentration of the appropriate fractions an oil was obtained which appeared to be a mixture of ketone and lactol tautomers by 60 MHz nmr. A strong ***Me***C=O singlet was observed at 2.1 ppm .

2-Benzyloxy-2-methyl-6-(2-methylethyl)tetrahydropyran (**16**). The ketone-lactol mixture (**15**) (0.9 g, 5.7 mmol), benzyl alcohol (0.9 g, 8.3 mmol), *p*-toluene sulphonic acid (0.1 g) and benzene (40 ml) was refluxed under a Dean and Stark trap for 20 mins. The cooled reaction mixture was washed with excess sodium hydrogen carbonate solution. The organic phase was separated, dried over magnesium sulphate, filtered and concentrated under reduced pressure to give pale yellow oil. The oil was purified by flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (95:5). The appropriate fractions were combined and concentrated to give the *ketal* (**16**) give pale yellow oil (0.6g, 42%), δ_H (270 MHz, $CDCl_3$; TMS) 7.39-7.23 (5H, m, ***Ph***CH_2), 4.54 (1H, d, ^2J 11.95 Hz, PhC***H***$_2$O), 4.47 (1H, d, ^2J 11.95 Hz, PhC***H***$_2$O), 3.33 (1H, d d d, ^3J 8.97 Hz,^3J 6.86 Hz, ^3J 2.19 Hz, iPrC***H***O), 2.11-1.00 (7H, m, C***H***$_2$C***H***$_2$C***H***$_2$, C***H***Me_2), 1.38 (3H, s, ***Me***), and 0.96 (3H, d, ^3J 6.87 Hz, CH***Me***$_2$), 0.88 (3H, d, ^3J 6.87 Hz, CH***Me***$_2$); δ_C (67.8 MHz; $CHCl_3$; TMS) 139.60 (***Ph***), 128.26 (***Ph***), 127.17 (***Ph***), 127.00 (***Ph***), 98.34 (O***C***O), 75.31 (iPr***C***HOC), 61.91 (Ph***C***H_2), 35.73 (***C***H_2), 33.09 (***C***HMe_2), 27.23 (***C***H_2), 25.13 (***C***H_2), 19.27 (***Me***), 18.62 (***Me***), and 18.61 (***Me***); m/z, EI: 205 (4 %), 157 (19), 141(100, M^+-BnO·), 123 (12), 108 (13), 91 (69), 83 (14), 79 (8), 71 (14), 59 (9), and 55 (9); CI: 266 (3 %, M+NH_4^+), 249 (4, M+H^+), 211 (23), 141 (100), 123

(4), and 91 (5).

Hydrogenolysis of the Tetrahydropyran (**16**). A small amount of the tetrahydropyran (**16**) was hydrogenated in dichloromethane with 5% palladium on charcoal for 1 hr. The mixture was filtered through Celite and concentrated under reduced pressure. A 60 MHz nmr of the crude product was consistent with the removal of the benzyl group. It appeared that the hydroxy ketone tautomer was present due to the presence of a singlet at 2.1 ppm; m/z; CI: 176 (3%, $M+NH_4^+$), and 141 (100, M^+-OH·).

2-(3-Bromopropyl)-2,5,5-trimethyl-1,3-dioxane (**17**).[74b] A solution of 5-bromo-pentan-2-one (53.120 g, 0.332 mol), trimethyl orthoformate (47.656 g, 0.450 mol), 2,2-dimethylpropan-1,3-diol (33.488g, 0.322 mol) and *p*-toluene sulphonic acid (0.10 g) in dichloromethane (250 ml) was stirred at room temperature for 3 hrs. The solution was washed with saturated sodium hydrogen carbonate solution (2 x 100 ml) and dried over magnesium sulphate and concentrated to give a crude oil. The crude oil was purified by distillation through a 12" Vigreux column under reduced pressure (72-76 °C, 0.5 mbar) to give the ketal (**17**) (56.378 g, 70 %), $\nu_{max.}$ ($CHCl_3$) 2940 (C-H), 2860 (C-H), 1450, 1390, and 1370 cm^{-1}; δ_H (270 MHz, $CDCl_3$; TMS) 3.57 (2H, d, ^2J 11.27 Hz, $OCH_2CMe_2CH_2O$), 3.42 (2H, d, ^2J 11.27 Hz, $OCH_2CMe_2CH_2O$), 3.45 (2H, t, ^3J 6.6 Hz, CH_2CH_2Br), 2.09-2.00 (2H, m, $CH_2CH_2CH_2Br$), 1.99-1.79 (2H, m, CH_2CH_2Br), 1.37 (3H, s, $MeCCH_2$), 1.03 (3H, s, $CH_2CMe_2CH_2$), and 0.87 (3H, s, $CH_2CMe_2CH_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 98.39 (*O*CO), 70.38 ($OCH_2CMe_2CH_2O$, 70.32 ($OCH_2CMe_2CH_2O$), 70.26 ($OCH_2CMe_2CH_2O$), 37.22($MeCCH_2$), 34.27(CH_2Br), 29.82 ($CH_2CMe_2CH_2$), 26.87(CH_2CH_2Br), 22.80 ($CH_2CMe_2CH_2$), 22.41 ($CH_2CMe_2CH_2$), and 20.26 ($MeCCH_2$) ; m/z, EI: 235 (3 %), 129 (25), 69 (25), 56 (35), and 43 (100); CI: 253 and 251(100, $M+H^+$), 85 (3), and 44 (6); (Found 251.0647 from $M+H^+$ in CI. Calc. for $C_{10}H_{20}BrO_2$: 251.0647).

2-(4-hydroxy-5-methylhexyl)-2,5,5-trimethyl-1,3-dioxane (**18**). Into a three necked oven dried round bottomed flask fitted with a leibig condenser, thermometer and dropping funnel was placed magnesium turnings (3.0 g, 0.125 mol) and dry diethyl ether (10 ml).

To this was added 1,2-dibromoethane (0.5 ml). The bromo ketal (**17**) (5.0 g, 0.02 mol) in diethyl ether (10 ml) was added dropwise to the resulting refluxing solution so that reflux was maintained (35-36 °C). The resulting mixture was allowed to stir and come to room temperature over $\frac{1}{2}$ hr. and then cooled to 0 °C. Isobutyraldehyde (1.58 g, 0.22 mol) in diethyl ether (5 ml) was added dropwise so that the reaction temperature remained at 0 °C. After addition was complete the mixture was allowed to stir and come to room temperature over $1\frac{1}{2}$ hrs. The mixture was quenched on ammonium chloride solution with a drop of conc. ammonium hydroxide added. The organic phase was separated and dried over magnesium sulphate. The solvent was removed under reduced pressure to afford a colourless oil (4.62 g, 95 %). The oil was purified using flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (4:1) giving the *keto alcohol* (**18**) as a colourless oil (3.004 g, 62 %). It was found that this oil was unstable at elevated temperature and it was not possible to purify this compound further by distillation, (Found: C, 64.69; H, 11.10; N, 0.00. $C_{14}H_{28}O_3$ requires C, 68.81; H, 11.55; N, 0.00 %); $\nu_{max.}$ ($CHCl_3$) 3600 (OH), 3450, 2940 (C-H), 2860 (C-H), 1500, 1460, and 1370 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 3.52 (2H, d, ^2J 11.27 Hz, OC***H***$_2$CMe$_2$C***H***$_2$O), 3.43 (2H, d, ^2J 11.27 Hz, OC***H***$_2$CMe$_2$C***H***$_2$O), 3.45 (2H, t, ^3J 10.7 Hz, MeCC***H***$_2$), 3.38 (1H, m, C***H***OH), 1.8-1.1 (7H, br m, C***H***$_2$C***H***$_2$C***H***$_2$, C***H***Me$_2$), 1.37 (3H, s, ***Me***), 1.03 (3H, s, OCH$_2$C***Me***$_2$CH$_2$O), 0.92 (3H, d, ^3J 6.86 Hz, CH***Me***$_2$), 0.91 (3H, d, ^3J 6.86 Hz, CH***Me***$_2$), and 0.88 (3H, s, OCH$_2$C***Me***$_2$CH$_2$O); δ_C (67.8 MHz; $CDCl_3$; TMS) 99.04 (O***C***O), 77.50 (***C***HOH), 70.38 (***C***H$_2$CMe$_2$***C***H$_2$), 38.27 (***C***H$_2$CHOH), 34.26 (MeC***C***H$_2$), 33.54 (***C***HMe$_2$), 29.99 (CH$_2$***C***Me$_2$CH$_2$), 22.85 (CH$_2$C***Me***$_2$CH$_2$), 22.51 (CH$_2$C***Me***$_2$CH$_2$), 20.09 (CH$_2$***C***H$_2$CH$_2$), 19.89 (CH***Me***$_2$), 18.86 (CH***Me***$_2$), and 17.19 (***Me***CCH$_2$); m/z, EI: 229 (14 %), 129 (100), 115 (16), 97 (20), 83 (5), 69 (25), 55 (10), and 43 (55); CI: no M^+, 229 (35 %), 201 (5), 159 (2), 141 (100), 129 (100), 115 (9), 97 (15), 83 (10), 69 (20), 55 (15), and 41 (31).

2-(4-Benzyloxy-5-methylhexyl)-2,5,5-trimethyl-1,3-dioxane (**19**). To a suspension of sodium hydride (0.330 g, 60 % dispersion in mineral oil, 0.82 mmol) in dry THF (25 ml) under nitrogen and cooled over an ice bath, was added the keto alcohol (**18**) (1.000 g, 4.1

mmol). After stirring for 10 mins. a crystal of tetra-*n*-butyl ammonium bromide was added. To this was added benzyl bromide (1.000 g, 5.8 mmol). The mixture was refluxed overnight. The cooled reaction mixture was poured onto saturated brine and extracted with diethyl ether (3 x 30 ml). The organic phases were combined and dried over magnesium sulphate, filtered and concentrated under reduced pressure a crude yellow oil was obtained (1.624 g). Flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (9:5) gave a pale yellow oil (1.326 g, 98 %). The oil was kugelrohr distilled (220 °C, 0.4 mbar) to give the *benzyl ketal* (**19**) as a colourless oil (1.326 g, 80 %), (Found: C, 75.90; H, 10.60; N, 0.00. $C_{21}H_{34}O_3$ requires C, 75.41; H, 10.25; N, 0.00 %); δ_H (270 MHz; $CDCl_3$; TMS) 7.38-7.24 (5H, m, ***Ph***), 4.5 (2H, s, C***H***$_2$Bn), 3.53 (2H, d, ^2J 11.27 Hz, OC***H***$_2$CMe$_2$C***H***$_2$O), 3.43 (2H, d, ^2J 11.27 Hz, OC***H***$_2$CMe$_2$C***H***$_2$O), 3.18-3.15 (1H, m, C***H***OBn), 1.94-1.89 (1H, m, CHC***H***Me$_2$), 1.69-1.43 (6H, br m, C***H***$_2$C***H***$_2$C***H***$_2$), 0.99 (3H, s, CH$_2$C***Me***$_2$CH$_2$), 0.93 (3H, d, ^3J 6.87 Hz, CH***Me***$_2$), 0.92 (3H, d, ^3J 6.87 Hz, CH***Me***$_2$), and 0.89 (3H, s, CH$_2$C***Me***$_2$CH$_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 139.24 (***Ph***), 128.23 (***Ph***), 127.74 (***Ph***), 127.31 (***Ph***), 99.01 (O***C***O), 84.26 (***C***HOBn), 71.84 (Ph***C***H$_2$O), 70.35 (O***C***H$_2$CMe$_2$***C***H$_2$O), 38.10 (***C***H$_2$CHOBn), 30.57 (MeC***C***H$_2$, ***C***HMe$_2$), 29.97 (CH$_2$***C***Me$_2$CH$_2$), 22.79 (CH$_2$C***Me***$_2$CH$_2$), 22.55 (CH$_2$C***Me***$_2$CH$_2$), 20.45 (CH$_2$***C***H$_2$CH$_2$), 19.79 (***Me***CCH$_2$CH$_2$), 18.32 (CH***Me***$_2$), and 18.03 (CH***Me***$_2$); m/z, EI: 142 (3 %), 129 (11), 113 (2), 91 (100), 82 (2), 65 (5), 55 (3), and 43 (20); CI: 335 (16 %, M+H$^+$), 319 (2), 291 (6), 249 (58), 229 (9), 205 (11), 181 (2), 157 (2), 141 (100), 129 (35), 108 (15), 99 (3), 91 (100), 82 (8), 65 (5), 55 (2), and 43 (9); (Found 335.2586 from M+H$^+$ in CI. $C_{21}H_{35}O_3$ requires 335.2586).

Hydrolysis of 2-(4-Benzyloxy-5-methylhexyl)-2,5,5-trimethyl-1,3-dioxane. A mixture of the ketal (**19**) (1.456 g, 4.5 mmol) in THF (20 ml) and 2M $HCl_{(aq)}$ was stirred overnight. The mixture was poured onto saturated brine and extracted with diethyl ether (2 x 50 ml). The combined organic phases were washed with water (2 x 50 ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a crude oil. The oil was purified using flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (4:1), followed by kugelrohr distillation (180 °C, 0.4 mbar) to

give the pure *ketone* (**5**) (0.798 g, 71 %).

2-(4-Hydroxy-5,5-dimethylhexyl)-2,5,5-trimethyl-1,3-dioxane (**20**). Into a three necked oven dried round bottomed flask fitted with a leibig condenser, thermometer and dropping funnel was placed magnesium turnings (0.576 g, 24 mmol) and dry diethyl ether (10 ml). To this was added 1,2-dibromoethane (0.5 ml). The bromoketal (**17**) (3.00 g, 12m mol) in diethyl ether (10 ml) was added dropwise to the resulting refluxing solution so that reflux was maintained (35-36 °C). The resulting mixture was allowed to stir and come to room temperature over ½ hr. and then cooled to 0 °C. Pivalaldehyde (1.13 g, 13 mol) in diethyl ether (5 ml) was added dropwise so that the reaction temperature remained at 0 °C. After addition was complete the mixture was allowed to stir and come to room temperature over 1½ hrs. The reaction mixture was quenched on ammonium chloride solution with a drop of conc. ammonium hydroxide added. The organic phase was separated and dried over magnesium sulphate. The solvent was removed under reduced pressure to afford a colourless oil (2.568 g, 83 %). The oil was purified using flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (4:1) giving the *keto alcohol* (**20**) as a colourless oil (2.568 g, 83 %). A small portion of the oil (0.250 g) was further purified by flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (4:1) to give a colourless oil (0.222 g, 89 %, 74 % overall), δ_H (270 MHz; $CDCl_3$; TMS) 3.56 (2H, d, ^2J 11.28 Hz, C***H***$_2$CMe$_2$C***H***$_2$), 3.43 (2H, d, ^2J 11.28 Hz, C***H***$_2$CMe$_2$C***H***$_2$), 3.19 (1H, d, ^3J 10.32 Hz, C***H***COH), 2.75 (1H, br s, O***H***), 1.8-1.1 (4H, br m, C***H***$_2$C***H***$_2$), 1.19 (3H, s, ***Me***CCH$_2$), 1.02 (3H, s, CH$_2$C***Me***$_2$CH$_2$), and 0.95 (12H, s, CH$_2$C***Me***$_2$CH$_2$, C***Me***$_3$); δ_C (67.8 MHz; $CDCl_3$; TMS) 99.06 (O***C***O), 79.56 (***C***HOH), 70.32 (***C***H$_2$CMe$_2$***C***H$_2$), 38.14 (***C***H$_2$CHOH) 34.90(***C***Me$_3$), 31.59 (MeC***C***H$_2$CH$_2$), 29.94 (CH$_2$***C***Me$_2$CH$_2$), 25.76 (C***Me***$_3$), 22.82 (CH$_2$C***Me***$_2$CH$_2$), 22.49 (CH$_2$C***Me***$_2$CH$_2$), 20.82 (CH$_2$***C***CH$_2$CH$_2$), and 20.14 (***Me***CCH$_2$CH$_2$); CH-COSY.

2-(4-Benzyloxy-5,5-dimethylhexyl)-2,5,5-trimethyl-1,3-dioxane (**21**). To a suspension of sodium hydride (0.700 g, 60 % dispersion in mineral oil, 16.8 mmol) in dry THF (40 ml) under nitrogen and cooled over an ice bath, was added the keto alcohol (**20**) (2.188 g, 8.4

mmol). Effervescence was noted. After stirring for 10 mins. tetra-*n*-butyl ammonium bromide (0.050 g) was added. To this was added benzyl bromide (2.170 g, 12.7 mmol) and the mixture was refluxed overnight. The cooled reaction mixture was poured onto saturated brine and extracted with diethyl ether (3 x 50 ml). The organic phases were combined and dried over magnesium sulphate. After removal of the drying agent and concentration under reduced pressure a crude yellow oil was obtained. Flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (9:1) afforded a pale yellow oil (1.972 g, 67 %). The oil was kugelrohr distilled (155 °C, 0.4 mbar) to give the *benzyloxy ketone* (**21**) as a colourless oil (1.764 g, 60 %), (Found: C, 76.17; H, 10.83; N, 0.00. $C_{22}H_{36}O_3$ requires C, 75.82; H, 10.41; N, 0.00 %); $\nu_{max.}$ ($CHCl_3$) 3280, 2940, 2860, 1700, and 1470 cm^{-1}; δ_H (270 MHz; $CDCl_3$; TMS) 7.38-7.23 (5H, m, ***Ph***), 4.64 (1H, d, ^2J 11.35 Hz, C***H***$_2$Ph), 4.57 (1H, d, ^2J 11.35 Hz, C***H***$_2$Ph), 3.53 (2H, d, ^2J 11.27 Hz, C***H***$_2$CMeC***H***$_2$), 3.42 (2H, d, ^2J 11.27 Hz, C***H***$_2$CMeC***H***$_2$), 3.00 (1H, d d, $^3J_{HHa}$ ca. 6.0 Hz, $^3J_{HHb}$ 3.84 Hz, C***H***OBnCH$_a$H$_b$), 1.72-1.47(6H, br m, C***H***$_2$C***H***$_2$C***H***$_2$), 1.34 (3H, s, ***Me***CCH$_2$), 0.94 (12H, s, CH$_2$C***Me***$_2$CH$_2$, C***Me***$_3$), and 0.89 (3H, s, CH$_2$C***Me***$_2$CH$_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 139.34 (***Ph***), 128.20 (***Ph***), 127.50 (***Ph***), 127.23 (***Ph***), 98.96 (O*C*O), 88.50 (***C***HOBn), 75.09 (***C***H$_2$Ph), 70.35 (***C***H$_2$CMe$_2$***C***H$_2$), 38.36 (***C***H$_2$CHOBn), 36.10 (***C***Me$_3$), 31.56 (MeC***C***H$_2$CH$_2$), 29.95 (CH$_2$***C***Me$_2$CH$_2$), 26.50 (C***Me***$_3$), 22.75 (CH$_2$C***Me***$_2$CH$_2$), 22.53 (CH$_2$C***Me***$_2$CH$_2$), 21.34 (CH$_2$***C***H$_2$CH$_2$), and 20.39 (***Me***CCH$_2$); m/z, EI: 333 (3 %), 291 (23), 205 (6), 195 (4), 177 (8), 155 (2), 142 (7), 129 (87), 113 (12), 99 (20), 91 (100), 82 (5), 69 (26), 57 (28), and 43 (37); CI: 266 (4 %, M+NH_4^+), 249 (75, M+H^+), 333 (4), 291 (291), 266 (6), 250 (40), 243 (51), 205 (3), 195 (1), 177 (3), 155 (100), 141 (48), 129 (50), 108 (26), 99 (10), 91 (49), and 58 (1); (Found 349.2674 from M+H^+ in CI. $C_{22}H_{37}O_3$ requires 349.2743).

6-Benzyloxy-7,7-dimethyloctan-2-one (**22**). A solution of the ketal (**21**) (1.456 g, 4.2 mmol) in THF (20 ml) was stirred overnight with 2M $HCl_{(aq)}$ (15 ml). The mixture was then poured onto saturated brine and extracted with diethyl ether (2 x 50 ml). The combined organic phase was washed with water, dried over magnesium sulphate, filtered and concentrated to give a crude oil. The oil was purified using flash chromatography on

silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (4:1) to give a pale yellow oil. The oil was kugelrohr distilled (180 °C, 0.4 mbar) to give the pure *ketone* (**22**) (0.798 g, 73 %), (Found: C, 78.55; H, 10.38; N, 0.00. $C_{17}H_{26}O_2$ requires C, 77.82; H, 9.99; N, 0.00 %); $\nu_{max.}$ ($CHCl_3$) 2940 (C-H), 2860 (C-H), 1700 (C=O), and 1595 cm^{-1}; δ_H (270 MHz; $CDCl_3$; TMS) 7.38-7.22 (***Ph***), 4.60 (CH_2Ph), 2.99 (1H, d d, $^3J_{HHa}$ 8.51, $^3J_{HHb}$ 2.74 Hz, $CHOBnCH_aH_b$), 2.41 (2H, d t, ^3J 8.24 ^4J 2.2 Hz, $MeCOCH_2CH_2$), 2.10 (3H, s, MeCO), 1.82-1.39 (4H, br m, CH_2CH_2CHOBn), and 0.94 (9H, s, CMe_3); δ_C (67.8 MHz; $CDCl_3$; TMS) 208.85 (***C***O), 139.18 (***Ph***), 128.26 (***Ph***), 127.47 (***Ph***), 127.34 (***Ph***), 88.29 (***C***HOBn), 75.01 (***C***H_2Ph), 44.05 ($MeCOCH_2$), 36.15 (CH_2CH_2), 30.86 (CH_2CH_2), 29.81 (CMe_3), 26.47 (CMe_3), and 21.85 (***Me***CO); m/z, EI: 205 (22 %), 156 (9), 137 (4), 113 (20), 91 (100), 85 (3), 77 (4), 65 (20), 57 (35), 51 (3), and 43 (34); CI: 280 (10 %, $M+NH_4^+$), 263 (100, $M+H^+$), 249 (10), 227 (2), 205 (61), 181 (17), 172 (2), 155 (100), 137 (64), 123 (2), 113 (47), 91 (100), 85 (5), 65 (12), 57 (10), and 43 (15); (Found 263.2011 from $M+H^+$ in CI, $C_{17}H_{27}O_2$ requires 263.2011).

2-(3-acetoxy-2,2-dimethylpropyloxy)-2-methyl-6-(2-methylethy l)tetrahydropyran (**23**). A sample of the alcohol (**18**) (1.732 g, 1.1 mmol) which had been sitting at room temperature for 2 weeks, acetic anhydride (1.130 g, 1.1 mmol), triethylamine (1.130 g, 1.1 mmol) and a crystal of DMAP in dichloromethane (20 ml) was stirred at room temperature for 24 hrs. The result was poured a solution of ammonium chloride with a drop of conc. ammonium hydroxide and then extracted with dichloromethane (3 x 40 ml). The combined organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a crude oil. The crude product was purified using flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (19:1) to give an oil (0.680 g). Kugelrohr distillation (180 °C, 0.2 mbar) gave the pure *tetrahydropyran* (**23**) (0.675 g, 33 %), (Found: C, 67.28; H, 11.11; N, 0.00. $C_{16}H_{30}O_4$ requires C, 67.10; H, 10.54; N, 0.00 %); δ_H (270 MHz; $CDCl_3$; TMS) 3.91 (2H, s, $COCH_2CMe_2CH_2OAc$), 3.21 (1H, d d d, ^3J 11.26 Hz, ^3J 6.59 Hz, ^3J 1.92 Hz, $OCHCHMe_2$), 3.14 (2H, s, $COCH_2CMe_2CH_2OAc$), 2.06 (3H, s, $MeCO_2$), 1.8-1.02 (7H, br m, $CH_2CH_2CH_2CHCHMe_2$), 1.25 (3H, s, $MeCCH_2CH_2$), 0.95 (3H, s, $CH_2CMe_2CH_2$),

0.93 (3H, s, $CH_2CMe_2CH_2$), 0.94 (3H, d, ^3J 6.59 Hz, $CHMe_2$), 0.91 (3H, d, ^3J 6.87 Hz, $CHMe_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 171.16 ($MeCO_2$), 97.46 (OCO), 75.01 ($CHCHMe_2$), 70.10 ($OCH_2CMe_2CH_2$), CH_2OAc), 35.89, 34.96, 33.06, 27.44, 24.68, 22.33, 22.30, 20.95, 19.30, 18.70, and 18.60; m/z, EI: 141(100 %), 129 (66), 123 (25), 97 (3), 83 (11), 69 (29), 55 (11), 43 (55); CI: 164 (26 %), 141 (100), 129 (27), 83 (4), 58 (4), and 43 (3).

2-(4-Acetoxy-5-methylhexyl)-2,5,5-trimethyl-1,3-dioxane (**24**). A solution of freshly prepared alcohol (**18**) (4.634 g, 19 mmol), acetic anhydride (2.90 g, 28 mmol), triethylamine (2.90 g, 28 mmol) and a crystal of DMAP was stirred for 30 hrs. at room temperature. The mixture was washed with 2M $HCl_{(aq)}$ and then with saturated sodium hydrogen carbonate solution. The organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a pale yellow oil (4.02 g, 83 %). Kugelrohr distillation (170 °C, 0.3 mbar) gave a desired *acetate* (**24**) as colourless oil (3.19 g, 59 %), (Found: C, 67.50; H, 10.94; N, 0.00. $C_{16}H_{30}O_4$ requires C, 67.10; H, 10.56; N, 0.00 %); $\nu_{max.}$ ($CHCl_3$) 3010 (C-H), 2930 (C-H), 1750 (C=O), 1495, and 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$; TMS) 4.76 (1H, q, ^3J 5.5 Hz, CHOAc), 3.54 (1H, d, ^2J 11.68 Hz, $CH_2CMe_2CH_2$), 3.42 (1H, d, ^2J 11.68 Hz, $CH_2CMe_2CH_2$), 3.54 (1H, d, ^2J 11.68 Hz, $CH_2CMe_2CH_2$), 3.41 (1H, d, ^2J 11.68 Hz, $CH_2CMe_2CH_2$) 2.05 (3H, s, $MeCO_2$), 1.83-1.36 (7H, br m, $CH_2CH_2CH_2$, $CHMe_2$), 1.35 (3H, s, $CH_2CMe_2CH_2$), 1.01 (3H, s, $CH_2CMe_2CH_2$), 0.89 (3H, d, ^3J 4.12 Hz, $CHMe_2$), and 0.88 (3H, d, ^3J 2.75 Hz, $CHMe_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 170.92 (CO), 98.85 (OCO), 78.27 (CHOAc), 70.32 ($CH_2CMe_2CH_2$), 38.01 (CH_2CHOAc), 31.30 ($MeCCH_2$), 31.23 ($MeCO_2$), 29.94 ($CHMe_2$), 22.77 ($CH_2CMe_2CH_2$), 22.51 ($CH_2CMe_2CH_2$), 21.13 (CH_2CMeCH_2), 20.20 ($CHMe_2$), 19.43 ($CHMe_2$), 18.52 ($CH_2CH_2CH_2$), and 17.59 ($MeCCH_2$); m/z, EI: 271 (19 %), 141 (11), 129 (100), 115 (3), 97 (5), 83 (3), 69 (20), 55 (6), and 43 (65); CI: 287($M+H^+$,100 %), 271 (2), 227 (4), 141 (21), and 129 (20); (Found 287.2222 from $M+H^+$ in CI. $C_{16}H_{31}O_4$ requires 287.2222).

Hydrolysis of the Ketal Acetate (**24**). A solution of the ketal (**24**) (2.78 g, 9.7 mmol) in

THF (10 ml) was stirred with 2M $HCl_{(aq)}$ for 2 hrs. After which time the reaction mixture was poured onto saturated brine and extracted with diethyl ether (3 x 30 ml). The combined organic phases were washed with saturated sodium hydrogen carbonate solution, dried over magnesium sulphate, filtered and concentrated to give a crude oil. The oil was purified using flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (9:1) to give a pale yellow oil. Kugelrohr distillation (170 °C, 0.3 mbar) afforded the pure colourless *ketone* (**9**) (1.30 g, 67 %).

2-(3-[1-hydroxycyclohexyl]-propyl)-2,5,5-trimethyl-1,3-dioxane (**25**). Into a dry round bottomed flask fitted with a condenser, septum and needle thermocouple was placed magnesium turnings (0.10 g, 4 mmol) in diethyl ether (3 ml). To this was added a few drops of 1,2-dibromoethane. The bromo ketal (**17**) (0.50 g, 2 mmol) in diethyl ether (3 ml) was added to maintain reflux. After reflux had ceased the mixture was allowed to come to room temperature over ½ hr. with stirring. The mixture was cooled to 0 °C over an ice bath. Cyclohexanone (0.22 g, 2.2 mmol) was added to the reaction vessel dropwise. The mixture was allowed to stir for a further ½ hr. and come to room temperature. The reaction mixture was quenched on a solution of ammonium chloride with a drop of conc. ammonium hydroxide, followed by extraction with diethyl ether. The organic phase was dried over magnesium sulphate, filtered and concentrated to give a colourless oil (0.432 g, 80 %). Flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (4:1) afforded the alcohol (**25**) as a colourless oil (0.256 g, 47 %), (Found: C, 71.42; H,11.70; N, 0.00. $C_{16}H_{30}O_3$ requires C, 71.07; H, 11.18; N, 0.00 %); δ_H (270 MHz; $CDCl_3$; TMS) 3.54 (2H, d, ^2J 11.4 Hz, $CH_2CMe_2CH_2$), 3.42 (2H, d, ^2J 11.4 Hz, $CH_2CMe_2CH_2$), 1.65-1.10 (16H, br m, $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2$), 1.36 (3H, s,, $MeCCH_2$), 1.01 (3H, s, $CH_2CMe_2CH_2$), and 0.87 (3H, s, $CH_2CMe_2CH_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 99.04 (OCO), 71.22 (COH), 70.28 ($CH_2CMe_2CH_2$), 42.69, 38.71, 37.41, 29.94, 25.92, 22.85, 22.53, 22.25, 20.22, and 16.87; m/z, EI: no M^+, 255 (10 %), 237 (1), 167 (4), 149 (16), 141 (11), 129 (100), 99 (10), 86 (11), 81 (13), 69 (39), 55 (25), and 45 (2); CI: no M^+, 255 (3 %), 167 (100), 149 (35), and 129 (20).

2-(4-Hydroxy-4-phenylheptyl)-2,5,5-trimethyl-1,3-dioxane (**26**). Into a dry round bottomed flask fitted with a condenser, septum and needle thermocouple was placed magnesium turnings (0.10 g, 4 mmol) in diethyl ether (3 ml). To this was added a few drops of 1,2-dibromoethane. The bromo ketal (**17**) (0.50 g, 2 mmol) in diethyl ether (3 ml) was added to maintain reflux. After reflux had ceased the mixture was allowed to come to room temperature over $\frac{1}{2}$ hr. with stirring. The mixture was cooled to 0 °C over an ice bath. Acetophenone (0.26 g, 2.2 mmol) was added to the reaction vessel dropwise. The mixture was allowed to stir for a further $\frac{1}{2}$ hr. and come to room temperature. The reaction mixture was quenched on a solution of ammonium chloride with a drop of conc. ammonium hydroxide, followed by extraction with diethyl ether. The organic phase was dried over magnesium sulphate, filtered and concentrated to give a colourless oil (0.540 g, 93 %). Flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (4:1) gave the *alcohol* (**26**) as a white waxy solid (0.365 g, 63 %), m.p. 50-52 °C (Found: C, 73.89; H, 9.90; N, 0.00. $C_{18}H_{28}O_3$ requires C, 73.93; H, 9.65; N, 0.00 %); δ_H (270 MHz; $CDCl_3$; TMS) 7.46-7.41 (2H, m, ***o-Ph***), 7.36-7.30 (2H, m, ***m-Ph***), 7.23-7.19 (1H, m, ***p-Ph***), 3.50 (2H, d, ^2J 11.53 Hz, $CH_2CMe_2CH_2$), 3.37 (2H, d, ^2J 11.53 Hz, $CH_2CMe_2CH_2$), 1.90 (1H, s, O***H***), 1.85-1.79(2H, br m, CH_2CHOH), 1.67-1.61 (2H, br m, $MeCCH_2CH_2$), 1.56 (3H, s, COH***Me***), 1.43-1.35 (2H, br m, $CH_2CH_2CH_2$), 1.29 (3H, s, ***Me***CCH_2), 0.97 (3H, s, $CH_2CMe_2CH_2$), and 0.86 (3H, s, $CH_2CMe_2CH_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 148.15 (***Ph***), 128.11 (***Ph***), 126.47 (***Ph***), 124.76 (***Ph***), 99.01 (O*C*O), 74.67 (COH), 70.30 ($CH_2CMe_2CH_2$), 44.27, 38.27, 30.07, 29.92, 22.77, 22.51, 20.13, and 17.99; m/z, EI: no M^+, 277 (18 %), 259 (5), 189 (100), 171 (100), 157 (1), 144 (12), 129 (100), 121 (21), 105 (10), 86 (15), 77 (4), 69 (19), 55 (5), and 49 (4); CI: no M^+, 275 (2 %), 206 (5), 189 (100), 171 (70), 129 (21), and 119 (3).

2-(2-Iodoethyl)-2,5,5-trimethyl-1,3-dioxane (**27**).[98] To a rapidly stirred solution of sodium iodide (30 g, 0.2 mol) and methylvinylketone (12.727 g, 0.182 mol) in dry acetonitrile (500 ml) was added trimethylchlorosilane (21.72 g, 0.2 mol) under nitrogen. A yellow suspension resulted. After 5 mins. stirring 2,2-dimethylpropan-1,3-diol (20.8 g, 0.2 mol) was added. A dark yellow-orange suspension resulted. This was allowed to stir for 10

mins. and then poured onto 5 % sodium hydrogen carbonate solution (200 ml) which was then overlaid with cyclohexane (650 ml). After shaking the lower aqueous layer was removed. The two remaining organic layers were shaken with saturated sodium thiosulphate solution (25 ml). The orange coloration in the lower acetonitrile layer disappeared. The lower aqueous layer was removed and the organic layers were shaken with saturated brine (100 ml). This extraction was continued until the acetonitrile was removed. The remaining homogeneous organic phase was dried over magnesium sulphate, filtered and concentrated to give a crude pale yellow oil (34.148 g, 66 %). Purification using flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (19:1) gave pure *iodo ketal* (**27**) as a pale yellow oil (16.013 g, 31 %), δ_H (60 MHz; $CDCl_3$; TMS) 3.8-3.1 (6H, AB q, m, $CH_2CMe_2CH_2$, CH_2I), 2.5-2.2 (2H, m, CH_2CH_2I), 1.4 (3H, s, $MeCCH_2$), 1.04 (3H, s, $CH_2CMe_2CH_2$), and 0.84 (3H, s, $CH_2CMe_2CH_2$).

3-Oxobutyltriphenylphosphonium Iodide (**28**). Triphenylphosphine (29.3 g, 0.11 mol) and the iodo ketal (**28**) (16.0 g, 0.056 mol) in benzene-toluene (7:3) were heated slowly to 90 °C at which point reflux began. Shortly after the onset of reflux a viscous orange oil was observed as the lower layer. Reflux was continued for 3 hrs. The upper layer was decanted off. Acetone (50 ml) was added to the remaining oil. A white crystalline solid formed. The solid was isolated by filtration. The mother liquor was concentrated under reduced pressure and a further crop of crystals was obtained. The combined solid was washed with diethyl ether and dried *in vacuo* to give the pure *Wittig salt* (**28**) (20.662 g, 80 %), (Found: C, 57.33; H, 4.73; N, 0.00. $C_{22}H_{23}IOP$ requires C, 57.28; H, 5.03 N, 0.00 %); $\nu_{max.}$ (KBr) 3050 (C_{Ar}-H), 2960 (C-H), 2880 (C-H), 2820 (C-H), and 1710 (s, C=O) cm^{-1}; δ_H (270 MHz; $CDCl_3$; TMS) 7.62 (15H, m, ***Ph***), 3.82 (2H, d t, $^2J_{PH}$ 13.36 Hz, $^3J_{HH}$ 6.68 Hz, CH_2P^+), 3.18 (2H, d t, $^3J_{PH}$ 14.28 Hz, $^3J_{HH}$ 7.14 Hz, $CH_2CH_2P^+$), and 2.15 (3H, s, ***Me***CO); δ_P (109.25 MHz; $CDCl_3$; H_3PO_4) 26.14 (P^+Ph); δ_C (67.8 MHz; $CDCl_3$; TMS) 203.78 (d,$^5J_{CP}$ 9.3 Hz, ***C***O), 135.38 (d, J_{CP} 2.76 Hz, ***Ph***), 133.64 (d, J_{CP} 9.92 Hz, ***Ph***), 130.73 (d, J_{CP} 12.67 Hz, ***Ph***), 117.79 (d, J_{CP} 86.48 Hz, ***Ph***), 36.21 (d, $^3J_{CP}$ 3.31 Hz, $CH_2CH_2P^+$), 30.28 (s, ***Me***CO) and 17.25 (d, $^1J_{CP}$ 55.63 Hz, CH_2P^+); m/z, EI: 445 (1 %),

417 (1), 262 (100), 183 (39), 170 (1), 152 (5), 128 (7), 108 (21), 77 (7), 55 (16), and 43 (14); CI: 263 (100 %).

3-Hydroxybutyltriphenylphosphonium Iodide (**29**).[78] To a solution of the phosphonium salt (**28**) (10 g, 0.024 mol) in dry dichloromethane (150 ml) under nitrogen was added DIBAL-H (36 ml, 1.0 M in hexanes, 0.036 mol). After stirring for 2 hrs. at room temperature the reaction mixture was quenched on water. A gelatinous suspension resulted. A little 2M $HCl_{(aq)}$ was added. The organic and aqueous phases were repeatedly extracted with dichloromethane portions. The combined organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a white solid. The solid was dissolved in hot methanol and insoluble material (presumed aluminium salts) was removed by filtration. Diethyl ether was added to turbidity. A white solid formed on cooling. The mother liquor was concentrated and further crystalline matter was obtained by solution in hot methanol followed by addition of diethyl ether to turbidity followed and cooling. This process was repeated until no more solid was obtained. The crystalline solids were combined and dried *in vacuo* to give the Wittig salt (**29**) (8.191 g, 82 %), Mpt. 234-240 °C (Found: C, 54.33; H, 5.26; N, 0.00. $C_{22}H_{25}IOP$ requires C, 57.03; H, 5.44; N, 0.00 %); $\nu_{max.}$ (KBr) 3360 (br, OH), 3055 (C_{Ar}-H), 2980 (C-H), 2895 (C-H), and 2860 (C-H) cm^{-1}; δ_H (270 MHz; D_3COD; TMS) 7.95-7.77 (15H, m, ***Ph***), 3.90 (1H, m, MeC***H***OH), 3.52 (2H, m, $CH_2C\boldsymbol{H}_2P^+$), 1.73 (2H, m, $C\boldsymbol{H}_2CH_2P^+$), and 1.20 (3H, d, ***Me***CHOH); δ_P (109.25 MHz; D_3COD, H_3PO_4) 25.73 (***P***$^+$Ph); m/z, EI: 262 (100 %), 183 (100), 152 (10), 128 (5), 108 (48), 91 (1), 77 (30), 51 (77), and 39 (40); CI: 263 (100 %).

3-Hydroxybutyl 4-methylbenzenesulphonate (**30**).[99] To a solution of freshly recrystallized[100] *p*-toluene sulphonyl chloride (15 g, 0.077 mol) in pyridine (30 ml) at -15 °C was added butan-1,3-diol (7.081 g, 0.077 mol) in pyridine (20 ml) over $\frac{1}{2}$ hr. and stirred overnight at -5 °C. The reaction mixture was diluted with diethyl ether (150 ml) and washed with 2M $HCl_{(aq)}$ (4 x 150 ml). The organic phase was then washed with saturated sodium hydrogen carbonate solution (2 x 100 ml). The organic phase was dried over

magnesium sulphate, filtered and concentrated under reduced pressure to give a crude pale yellow oil (13.642 g, 70 %). The crude product was purified using flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (3:2). Concentration of the appropriate fractions gave the tosylate as a pale yellow oil (7.9 g, 42 %), δ_H (100 MHz; $CDCl_3$; TMS) 7.33 (2H, d, ^3J 8 Hz, ***Ph***), 6.92 (2H, d, ***Ph***), 4.92 (2H, m, C***H***$_2$OTs), 4.87 (1H, m, C***H***OH), 2.32 (3H, s, Ph***Me***), 1.68 (2H, m, CHOHC***H***$_2$), and 1.10 (3H, d, ^3J 6 Hz, ***Me***CH); m/z, EI: 229 (1 %), 172 (33), 155 (11), 107 (20), 91(100), 77 (8), 72 (27), 65 (41), 57 (29), 51 (7), 43 (40), and 38 (1); CI: 262 (100 %), 245 (19), 227 (27), 190 (2), 108 (10), 91 (5), 82 (2), 72 (4), and 65 (2); (Found 262.1113 from M+NH_4^+ in CI, $C_{11}H_{20}NO_4S$ requires 262.1113).

3-*t-Butyldimethylsilyloxybutyl 4-methylbenzenesulphonate* (**31**). To a stirred solution of imidazole (1.36 g, 20 mmol) in dry DMF (15 ml) at 0 °C was added *t*-butyldimethylchlorosilane (2.265 g, 15 mmol). After stirring for 15 mins. the alcohol (**30**) (2.5 g, 10 mmol) was added. The mixture was allowed to stir and come to room temperature over 1½ hrs. and then poured onto water (200 ml). The aqueous mixture was shaken with diethyl ether (250 ml). The organic layer separated and washed with water (5 x 100 ml). The organic solution was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a pale yellow oil (3.606 g, 100 %). The oil was purified using flash chromatography on silica gel (40-63 μm) to give a pale yellow oil (2.952 g, 82 %). A small portion of this oil was kugelrohr distilled (250 °C, 2 mbar) to give a colourless oil, (Found: C, 56.20; H, 8.77; N, 0.00. $C_{17}H_{30}O_4SSi$ requires C, 56.94; H, 8.43; N, 0.00 %); δ_H (100 MHz; $CDCl_3$ TMS) 7.44 (2H, d, ^3J 8 Hz, m-***Ph***), 7.04 (2H, d, ^3J 8 Hz, o-***Ph***), 3.96 (2H, t, ^{3}J 6 Hz, CH_2OTs), 3.7 (1H, m, MeC***H***CH_2), 2.35 (3H, s, **Me**Ph), 1.7 (2H, CHC***H***$_2CH_2OTs$), 1.08 (3H, d, ^3J 5 Hz, ***Me***CH), 0.84 (9H, s, t***Bu***), 0.04 (3H, s, Si***Me***$_2$), -0.04 (3H, s, Si***Me***$_2$); m/z, EI: 301 (1 %), 245 (3), 229 (51), 187 (1), 172 (28), 155 (14), 145 (2), 131 (2), 107 (20), 91 (100), 72 (26), 65 (32), 55 (23), and 43 (30); CI: 359 (10 %, M+H^+), 262 (100), 245 (24), 227 (77), 187 (5), 155 (1), 132 (3), 108 (20), 91 (26), 82 (3), 72 (11), 65 (3), and 39 (3); (Found 359.1712 from M+H^+ in CI. $C_{17}H_{31}SSiO_4$ requires 359.1712).

3-t-Butyldimethylsilyloxy-1-iodobutane (**32**). The tosylate (**31**) (13.0 g, 36.3 mmol), sodium iodide (21.787 g, 145 mmol) were refluxed in acetone (250 ml) for 2 hrs. The solvent was removed under reduced pressure and the resulting oily solid was shaken with diethyl ether (200 ml) and water (200 ml). The organic phase was washed with saturated sodium hydrogen carbonate solution followed by shaking with saturated sodium thiosulphate solution (25 ml) to decolorize. The solution was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a pale yellow oil (11.275 g, 99 %). A small portion of the oil (0.465 g) was purified using flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (4:1) gave the pure *tosylate* (**31**) (0.410 g, 87 % overall), (Found: C, 38.00; H, 7.58; N, 0.00. $C_{10}H_{23}IOSi$ requires C, 38.22; H, 7.38; N, 0.00 %); δ_H (270 MHz; $CDCl_3$; TMS) 3.94-3.83 (1H, m, C***H***OTBDMS), 3.31-3.16 (2H, m, C$\boldsymbol{H}_2$I), 1.99-1.84 (2H, m, C$\boldsymbol{H}_2$CH$_2$I), 1.15 (3H, d, ^3J 6.04 Hz, ***Me***CHOTBDMS), 0.89 (9H, s, ***tBu***), 0.10 (3H, s, Si***Me***), and 0.08 (3H, s, Si***Me***); δ_C (67.8 MHz; $CDCl_3$; TMS) 68.32 (***C***HOTMBMS), 43.33 (MeCH***C***H$_2$), 25.88 (C***Me***$_3$), 23.45 (***Me***CHCH$_2$), 18.03 (***C***H$_2$I), 3.47 (***C***Me$_3$), -4.22 (***Me***Si), and -4.59 (***Me***Si); m/z, EI: 271 (2 %), 257 (75), 229 (100), 215 (7), 185 (85), 159 (5), 129 (29), 115 (7), 101 (12), 87 (6), 75 (71), 59 (20), and 41 (20); CI: 315(14 %, M+H$^+$), 257 (83), 229 (76), 202 (20), 185 (44), 159 (3), 129 (30), 115 (5), 101 (4), 92 (2), 85 (1), 75 (100), 59 (20), and 41 (20); (Found 315.0641 from M+H$^+$ in CI. $C_{10}H_{24}IOSi$ requires 315.0641).

(3-t-Butyldimethylsilyloxybutyl)triphenylphosphonium iodide (**33**). The iodo ether (**32**) (0.490 g, 1.6 mmol) and triphenylphosphine (0.9 g, 3.4 mmol) were placed in toluene and refluxed for 4 hrs. On cooling a viscous oily lower phase separated out. The upper phase was decanted off and the oily residue was dissolved on acetone (10 ml). Diethyl ether was added to turbidity. The resulting mixture was chilled overnight. The *iodide* (**32**) was obtained as a white crystalline solid by filtration by washing with diethyl ether and drying *in vacuo* (0.615 g, 68 %), m.p. 190-195 °C (Found: C, 57.91; H, 6.41; N, 0.00. $C_{28}H_{38}IOPSi$ requires C, 58.33; H,6.64; N, 0.00 %); δ_H (270 MHz; $CDCl_3$; TMS)

7.86-7.68 (15H, m, ***Ph***), 4.22-4.16 (1H, m, C***H***OH), 3.91-3.84 (1H, m, C$\boldsymbol{H_2}$P$^+$), 3.47-3.40 (1H, m, C$\boldsymbol{H_2}$P$^+$), 1.89-1.61 (2H, m, C$\boldsymbol{H_2}$CH$_2$P$^+$), 1.24, 1.22 (3H, d, ***Me***CHOH), 0.86 (9H, s, ***Bu***$_3$CSi), and 0.09 (6H, s, ***Me***$_2$Si); δ_C (67.8 MHz; $CDCl_3$; TMS) 135.28 (d, J_{CP} 2.75 Hz, ***Ph***), 133.56 (d, J_{CP} 9.91 Hz, ***Ph***), 130.69 (d, J_{CP} 12.67 Hz, ***Ph***), 118.01 (d, J_{CP} 86.49 Hz, ***Ph***), 67.60 (d, $^3J_{CP}$ 15.97 Hz, ***C***HOSi), 31.85 (s, ***C***H$_2$CH$_2$P$^+$), 25.88 (s, ***tBu***), 23.63 (s, ***Me***CHOSi), 17.97 (s, ***C***HP$^+$), -4.27 (s, ***Me***Si), and -4.35 (***Me***Si); m/z, EI: 449 (10 %), 289 (1), 262 (33), 229 (2), 199 (9), 183 (56), 170 (1), 147 (25), 131 (7), 108 (40), 75 (100), and 51 (20); CI: 449 (39 %), 373 (10), 335 (6), 315 (1), 263 (100), 200 (3), 187 (4), 132 (4), 91 (10), and 74 (2); (Found 449.2430 from M-I$^+$, $C_{28}H_{38}OPSi$ requires 449.2430). ***Note*:** Some deprotection was observed with this reaction at a larger scale. The procedure should be modified in the following way. Place 1:1 mixture of triphenylphosphine and the iodide (no solvent) in a round bottomed flask. Heat the mixture to about 100 °C over an oil bath. On heating the triphenylphosphine will dissolve. After a short time crystalline material will form. **Remove from the heat source** and dissolve the mixture in acetone. Any deprotected material (**29**) present will not dissolve in the acetone and may be removed by filtration. Addition of diethyl ether to the filtrate may be used to precipitate the desired Wittig salt. Isolate the product by filtration. Concentrate the mother liquor which will contain unreacted (**32**) and triphenylphosphine in the ratio 1:1. Repeat the procedure until no more product is formed. (The procedure will probably need to be repeated 2 or 3 times.)

3-benzyloxy-4-methylheptene (**34**). To a cooled solution of vinylmagnesium bromide (33 ml, 0.78 M in THF, 26 mmol) under nitrogen, was added isobutyraldehyde (1.853 g, 26 mmol) dropwise with vigorous stirring, so that the temperature remained below -10 °C. After addition was complete the mixture was allowed to come to room temperature. HMPA (10 ml) was added followed by the addition of benzyl bromide (4.402 g, 26 mmol). The resulting mixture was refluxed overnight under nitrogen. The reaction mixture was poured onto saturated brine and diethyl ether (250 ml) was added. After shaking and standing gelatinous material was observed at the aqueous-organic interface. The aqueous layer was removed and the organic and gelatinous layers were washed with water. The

washing was continued until a single organic phase remained. The organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a crude yellow oil (4.277 g, 87 %). Flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate followed by kugelrohr distillation (70 °C, 0.2 mbar) furnished the pure *benzyl alkene* (**34**) (3.04 g, 62 %), (Found: C, 82.02; H, 9.80; N, 0.00. $C_{13}H_{18}O$ requires C, 82.06; H, 9.54; N, 0.00 %); $\nu_{max.}$ ($CHCl_3$) 3040 (C_{Ar}-H), 2940 (C-H), 2860 (C-H), and 1695 (w, C=C) cm^{-1}; δ_H (270 MHz; $CDCl_3$; TMS) 7.33 (5H, m, ***Ph***), 5.66 (1H, d d d, $^3J_{trans}$ 18.46 $^3J_{cis}$ 10.40 $^3J_{vic}$ 8.05 Hz, CH_2=C***H***CHOBn), 5.21 (2H, d d d, $^3J_{trans}{}^3J_{cis}{}^2J_{gem}$, C***H***$_2$=CHCHOBn), 4.60 (1H, d, ^2J 12.09 Hz, C***H***$_2$Bn), 4.32 (1H, d, ^2J 12.09 Hz, C***H***$_2$Bn), 4.75 (1H, t, ^3J 7.39, CHC***H***OBnCHMe$_2$), 1.86-1.74 (1H, o,CHC***H***Me$_2$),0.960 (3H, d, ^3J 6.71 Hz, CH***Me***$_2$), and 0.88 (3H, d, ^3J 7.05 Hz, CH***Me***$_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 139.02 (***Ph***), 128.21 (***Ph***), 127.62 (***Ph***), 127.25 (***Ph***), 137.38 (***C***H$_2$=), 86.00 (=***C***H,) 70.12 (***C***H$_2$Ph), 32.58 (***C***HMe$_2$), 18.70 (CH***Me***$_2$), and 18.39 (CH***Me***$_2$); m/z, EI: 147 (10 %), 91 (100), 77 (5), 65 (10), 55 (5), 50 (2), and 41 (9); CI: 208(35 %, M+NH_4^+), 191(2, M+H^+), 173 (2), 142 (5), 108 (21), 100 (21), 91 (12), and 83 (10); (Found 208.1701 from M+NH_4^+ in CI. $C_{13}H_{22}NO$ requires 208.1701).

2-Benzyloxy-3-methylbutanal (**35**). To a rapidly stirred mixture of the alkene (0.564 g, 3.0 mmol) in THF (20 ml) and water (20 ml) was added osmium tetroxide (0.011 g). The mixture became dark grey-black after a few moments. After 5 mins. stirring sodium *meta*-periodate (3.176 g, 14.8 mmol) was added. The mixture was stirred for 2 hrs. and then poured onto saturated brine. The aqueous solution was extracted with diethyl ether (100 ml). The organic phase was dried over sodium sulphate, filtered and concentrated to give a black oil. Flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (9:1) gave the *aldehyde* (**35**) as a colourless oil (0.328 g, 58 %). The aldehyde was observed to darken on standing at room temperature. Only a slight darkening was observed when the aldehyde was stored in the freezer for long periods of time. $\nu_{max.}$ ($CHCl_3$) 3040 (C_{Ar}-H), 2950 (C-H), 2866 (C-H), 1715 (C=O), 1690 (C=O) cm^{-1}; δ_H (270 MHz; $CDCl_3$; TMS) 9.63 (1H, d, ^3J 2.47 Hz, C***H***O), 7.33-7.25 (5H,

s, ***Ph***), 4.65 (1H, d, ^2J 11.81 Hz, C***H***$_2$Ph), 4.45 (1H, d, ^2J 11.81 Hz, C***H***$_2$Ph), 3.44 (1H, d d, ^3J 5.77 Hz, ^3J 2.47 Hz, C***H***OBn), 2.13-2.01 (1H, m, C***H***Me$_2$), 0.98 (3H, d, ^3J 6.86 Hz, CH***Me***$_2$), and 0.95 (3H, d, ^3J 6.87 Hz, CH***Me***$_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 204.20 (***C***=O), 137.57 (***Ph***), 128.41 (***Ph***), 128.29 (***Ph***), 127.89 (***Ph***), 88.06 (***C***HOBn), 72.77 (Ph***C***H$_2$), 29.94 (***C***HMe$_2$), 18.43 (CH***Me***$_2$), and 17.55 (CH***Me***$_2$); m/z, EI: 182 (1 %), 163 (6), 105 (5), 91 (100), 83 (1), 77 (7), 71 (5), 65 (18), 55 (5), 51 (11), and 39 (19); CI: 210 (55 %, M+NH_4^+), 193 (5, M+H^+), 182 (1), 171 (5), 163 (2), 143 (1), 125 (2), 108 (100), 91 (60), 82 (2), 71 (2), 65 (2), 58 (3), 44 (3), and 39 (2); (Found 210.1494 from M+NH_4^+ in CI. $C_{12}H_{20}NO$ requires 210.1494).

Potassium Hexamethyldisilazide.[101] Potassium hydride (17.19 g, 35 % dispersion in mineral oil, 0.15 mol) under nitrogen was washed with dry THF (3 x 50 ml). Excess THF was removed under reduced pressure. To the hydride was added dry THF (100 ml). Hexamethyldisilazane (16.14 g, 0.1 mol) was added dropwise with stirring. Effervescence was noted. After addition of the amine was complete the reaction was allowed to stir at room temperate for 1 hr. The reaction mixture was left to sit at room temperature for several hrs. to settle. The organic solution was transfered to a Sure Seal^{TM} bottle through a cannula. The solution was cloudy but cleared in a few days on standing in the freezer. The solution was titrated against diphenylacetic acid in THF and found to be 1.0 M.

cis-6-Benzyloxy-7-methyloct-4-en-2-ol (**36**). To a stirred suspension of the Wittig salt (**33**) (0.300 g, 0.52 mmol) in dry THF (9 ml) and HMPA (1 ml) under nitrogen at room temperature was added potassium hexamethyldisilazide (0.52 ml, 1.0 M in THF, 0.52 mmol). An orange suspension resulted. The suspension was stirred for 5 mins. and then cooled to -87 °C. The aldehyde (**35**) (0.10 g, 0.52 mmol) was added and the mixture was stirred at -87 °C for 4 hrs. TBAF (1.56 ml, 1.0 M in THF, 1.56 mmol) was added. The mixture was allowed to come to room temperature over 2 hrs. with stirring, then poured onto saturated brine (100 ml) and shaken with diethyl ether (100 ml). The aqueous layer was removed and the organic layer was washed with water (3 x 100 ml). The organic phase was dried over magnesium sulphate, filtered and concentrated under reduced

pressure to give a crude oil. Flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (7:3) gave the pure *alkene* (**36**) (0.056 g, 43 %), δ_H (270 MHz; $CDCl_3$; TMS) 7.37-7.22 (5H, m, ***Ph***, *syn*, *anti*), 5.77-5.67 (1H, m, CH_2CH=CH, *syn*, *anti*), 5.53-5.44 (1H, m, CH_2CH=C***H***, *syn*, *anti*), 4.57 ($\frac{2}{3}$H, d, ^2J 12.08 Hz, C***H***$_2$Ph, *anti*), 4.34 ($\frac{2}{3}$H, d, ^2J 12.08 Hz, C***H***$_2$Ph, *anti*), 4.57 ($\frac{1}{3}$H, d, ^2J 12.08 Hz, C***H***$_2$Ph, *syn*), 4.32 ($\frac{1}{3}$H, d, ^2J 12.08 Hz, C***H***$_2$Ph, *syn*), 3.88-3.78 (2H, m, C***H***OBn, C***H***OH, *syn*, *anti*), 2.30-2.09 (2H, m, C***H***$_2$CH=CH, *syn*, *anti*) 1.85-1.77 (1H, m, C***H***Me$_2$, *syn*, *anti*), 1.64 (1H, br s, O***H***, *syn*, *anti*), 1.20 (2H, d, ^3J 6.60 Hz, ***Me***CHOH, *anti*), 1.19 (1H, d, ^3J 6.59 Hz, ***Me***CHOH, *syn*), 0.99 (1H, d, ^3J 6.6 Hz, CH***Me***$_2$, *syn*), 0.88 (1H, d, ^3J 6.59 Hz, CH***Me***$_2$, *syn*), 0.98 (2H, d, ^3J 6.59 Hz, CH***Me***$_2$, *anti*), and 0.87 (2H, d, ^3J 6.86 Hz, CH***Me***$_2$, *anti*); Decoupling irradiation at 2.19 ppm caused multiplet at 5.77-5.69 to collapsed into a pair of doublet in the ratio 2:1; $^3J_{syn}$ 11.26 Hz, $^3J_{anti}$ 11.53 Hz; multiplet at 5.53-5.54 collapsed into a pair of doublet of doublets in the ratio of 2:1; $^3J_{syn}$ 11.26 Hz, $^3J_{anti}$ 11.26 Hz; δ_C (67.8 MHz, $CDCl_3$; TMS) 139.08 (***Ph***, *syn*, *anti*), 132.17 (***C***=C, *anti*), 132.01 (***C***=C, *syn*), 129.78 (C=***C***, *anti*), 129.7 (C=***C***, *syn*), 128.26 (***Ph***, *anti*), 128.21 (***Ph***, *syn*), 127.67 (***Ph***, *anti*), 127.61 (***Ph***, *syn*), 127.34 (***Ph***, *syn*, *anti*), 79.27 (***C***HOBn, *anti*), 79.17 (***C***HOBn, *syn*), 69.98 (***C***H$_2$Ph, *anti*), 69.92 (***C***H$_2$Ph, *syn*), 67.74 (***C***HOH, *syn*, *anti*), 37.74 (***C***H$_2$C=C, *anti*), 37.71 (***C***H$_2$C=C, *syn*), 33.00 (***C***HMe$_2$, *syn*), 32.93 (***C***HMe$_2$, *anti*), 23.13 (***Me***CHOH, *anti*), 23.03 (***Me***CHOH, *syn*), 18.77 (CH***Me***$_2$, *syn*, *anti*) 18.39 (CH***Me***$_2$, *syn*), and 18.28 (CH***Me***$_2$, *anti*); Ratio of diastereoisomers found 2:1 *anti*:*syn*; m/z, EI: no M+NH_4^+, no M+H^+, 205 (2 %), 124 (2 %), 107 (3), 97 (10), 91 (100), 81 (6), 65 (6), 51 (5), 45 (15), and 39 (9); CI: no M^+, 205 (2 %), 141 (11), 123 (20), 108 (5), 97 (30), 91 (100), 81 (5), 71 (1), 65 (6), 55 (1), and 41 (6). Ratio *anti*:*syn* 2:1 by nmr. A small portion of the *alkene* was hydrogenated in ethanol using 5 % palladium on charcoal to give the diol (**11**) followed by formation of the dioxocanes (**13**) and (**14**). Capillary g.c. analysis of the dioxocanes lead to the assignment of the major component as the *anti* diastereoisomer of *alkene* since the ratio (**14**) to (**13**) was found to be 1.75:1.

Pyridinium Chlorochromate.[84] To 6M $HCl_{(aq)}$ (184 ml, 1.1 mol) was added chromium trioxide (100 g, 1 mol) with rapid stirring. After 5 mins. the solution was cooled to 0 °C

and pyridine (79.1 g, 1 mol) was added slowly. An exotherm was noted. The mixture was cooled to 0 °C and filtered to give a yellow-orange solid. The product was dried over night in vacuo (187.35 g, 87 %).

cis-6-Benzyloxy-7-methyloct-4-en-2-one (**37**). To a stirred solution of the alcohol (**36**) (0.170 g, 0.71 mmol) in dichloromethane (20 ml) was added PCC (0.738 g, 3.4 mmol). The mixture was stirred for 4 hrs. at room temperature after which time pentane (40 ml) was added to the reaction mixture. The mixture was filtered through Celite. The filtrate was concentrated under reduced pressure to give a crude yellow oil (0.176 g). Flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (9:1) followed by kugelrohr distillation (150 °C, 0.1 mbar) afforded a pure *ketone* (**37**) as a yellow oil (0.124 g, 71 %), $\nu_{max.}$ ($CHCl_3$) 2940 (C-H), 2860 (C-H), and 1705 (C=O) cm^{-1}; δ_H (270 MHz; $CDCl_3$; TMS) 7.37-7.22 (5H, m, ***Ph***), 5.90 (1H, d t d, $^3J_{HaHb}$ 11.26 Hz,$^3J_{HbHd}$ 7.14 Hz, $^4J_{HbHd}$ 0.83 Hz, $CH_{d_2}CH_a$=C***H***$_b$$CH_c$OBn), 5.54 (1H, d d t, $^3J_{HaHb}$ 11.26 Hz, $^3J_{HaHd}$ 9.07 Hz, $^4J_{HaHc}$ 1.64 Hz, CH_{d_2}C***H***$_a$=$CH_b$$CH_c$OBn), 4.57 (1H, d, ^2J 12.09 Hz, C***H***$_2$Bn), 4.31 (1H, d, ^2J 12.09 Hz, C***H***$_2$Bn), 3.70 (1H, d d d, $^3J_{HcHb}$ 9.33 Hz, $^3J_{HcHe}$ 6.87 Hz, $^4J_{HcHa}$ 0.55 Hz, CH_a=CH_bC***H***$_c$(OBn)$CH_e$$Me_2$), 3.14 (2H, d d d, $^3J_{HdHa}$ 7.14 Hz, $^4J_{HdHb}$ 2.74 Hz, $^5J_{HdHe}$ 1.65 Hz, C***H***$_{d_2}$$CH_a$=$CH_b$$CH_c$OBn), 2.12 (3H, s, ***Me***CO), 1.85-1.74 (1H, m, C***H***Me_2), 0.98 (3H, d, ^3J 6.59 Hz, CH***Me***$_2$), and 0.87 (3H, d, ^3J 6.87 Hz, CH***Me***$_2$); Decoupling irradiation at 3.14 ppm caused the doublet of triplet doublets at 5.90 ppm to collapse into a doublet ^{3}J 11.26 Hz and the doublet of doublet triplets at 5.54 ppm to collapse into a doublet of doublets $^3J_{HC=CH}$ 11.26 Hz, $^3J_{HC-CH}$ 9.07 Hz; m/z, EI: 203 (6 %), 196 (1), 159 (2), 139 (5), 121 (4), 105 (10), 95 (17), 91 (100), 82 (12), 77 (13), 71 (3), 65 (9), 55 (5), 51 (16), 43 (49), and 39 (11); CI: 264 (16 %, M+NH_4^+), 247(11, M+H^+), 203 (5), 190 (5), 173 (5), 156 (6), 139 (100), 121 (5), 108 (15), 95 (5), 91 (9), and 82 (3); (Found 264.1964 from M+NH_4^+ in CI. $C_{16}H_{26}NO_2$ requires 264.1964).

trans-6-Benzyloxy-7-methyloct-4-en-2-ol (**38**). To a stirred suspension of the Wittig salt (**29**) (0.241 g, 0.52 mmol) in THF (4 ml) under nitrogen was added *n*-butyl lithium (0.326 ml, 1.6 M in THF, 0.52 mmol) at room temperature. An orange suspension resulted. The

mixture was cooled to -86 °C. The aldehyde (**35**) was added dropwise. The reaction mixture was stirred at -89 °C for 3 hrs. The reaction mixture was quenched on water and shaken with diethyl ether (50 ml). The organic phase was separated and dried over sodium sulphate, filtered and concentrated under reduced pressure to give a colourless oil (0.157 g). Flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (7:3) afforded a mixture of *cis* (**36**) and *trans* (**38**) *alcohols* as a pale yellow oil (0.014 g, 11 %), δ_H (270 MHz; $CDCl_3$; TMS) 7.32 (5H, m, ***Ph***), 5.7-5.4 (2H, br m, C***H***=C***H***, *cis*, *trans*), 4.58 (1H, d,^2J 12.09 Hz, C$\boldsymbol{H}_2$Bn, *cis*, *trans*), 4.34 ($\frac{2}{3}$H, d,^{2}J 11.81 C$\boldsymbol{H}_2$Bn, *trans*) 4.32 ($\frac{1}{3}$H, d, ^2J 12.09 Hz, C$\boldsymbol{H}_2$Bn, *cis*), 3.84-3.78(1$\frac{1}{3}$H, m, C***H***OH, *cis*, C***H***OBn, *cis*, C***H***OH, *trans*), 3.44-3.38 ($\frac{2}{3}$H, m, C***H***OBn, *trans*), 2.30-2.04 (2H, m, C$\boldsymbol{H}_2$CHOH, *cis*, *trans*), 1.90 (1H, m, C***H***Me$_2$, *cis*, *trans*), 1.8 ($\frac{1}{3}$H, br s, O***H***, *cis*), 1.75 ($\frac{2}{3}$H, br s, O***H***, *trans*), 1.2 (3H, d, ***Me***CHOH, *cis*, *trans*), and 0.98-0.60 (6H, dd, CH***Me***$_2$, *cis*, *trans*); m/z, EI: 205 (5 %), 162 (2), 117 (30), 91 (100), 77 (8), 65 (7), 51 (9), 45 (36), and 39 (10); CI: 266 (100 %, M+NH_4^+), 249 (10, M+H^+), 237 (1), 212 (8), 195 (3), 180 (25), 158 (70), 141 (38), 123 (40), 108 (37), 97 (10), 91 (14), and 81 (1); (Found 266.2120 from M+NH_4^+) in CI. $C_{16}H_{28}NO_2$ requires 266.2120).

trans-6-Benzyloxy-7-methyloct-4-en-2-one (**39**). The mixture of *cis* and *trans* alcohols obtained above (**36**) and (**38**) (0.157 g, 0.6 mmol) were stirred in dichloromethane (10 ml). PCC (0.680 g, 3.1 mmol) for 2 hrs. Pentane (20 ml) was added to the mixture followed by filtration through Celite. The filtrate was concentrated under reduced pressure to give a crude oil. Flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (9:1) gave an *oil* (0.015 g, 100 %) composed of *cis* and *trans* isomers, δ_H (270 MHz; $CDCl_3$; TMS) 5.9 ($\frac{1}{3}$H, d t d, CH=C***H***CHOBn, *cis*), 5.72 ($\frac{2}{3}$H, d t d, $^3J_{HbHa}$ 15.66 Hz, $^3J_{HbHc}$ 6.87 Hz, $^4J_{HbHd}$ 0.55 Hz, CH$_d$CH$_a$=C***H***$_b$CH$_c$OBn, *trans*), 5.54 ($\frac{1}{3}$H, d t d, $^3J_{HaHd}$ 9.34 Hz, $^4J_{HaHc}$ 1.65 Hz, CH$_{d_2}$C***H***$_a$=CH$_b$CH$_c$OBn, *cis*), 5.46 ($\frac{2}{3}$H, d d t, $^3J_{HaHb}$ 15.66 Hz, $^3J_{HaHd}$ 8.24 Hz, $^4J_{HaHc}$ 1.10 Hz, CH$_d$C***H***$_a$=CH$_b$CH$_c$OBn, *trans*), 4.58 ($\frac{2}{3}$H, d, ^2J 12.09 Hz, C$\boldsymbol{H}_2$Ph, *trans*), 4.57 ($\frac{1}{3}$H, d, ^2J 12.09, C$\boldsymbol{H}_2$Ph, *cis*), 4.34 ($\frac{2}{3}$H, d, ^2J 12.09 Hz, C$\boldsymbol{H}_2$Ph, *trans*), 4.30 ($\frac{1}{3}$H, d, ^2J 12.09 Hz, C$\boldsymbol{H}_2$Ph, *cis*), 3.70 ($\frac{1}{3}$H, d d, $^3J_{HcHb}$ 9.34 Hz, $^3J_{HcHe}$ 6.87 Hz, CH$_a$=CH$_b$C***H***$_c$CH$_e$Me$_2$, *cis*), 3.43 ($\frac{2}{3}$H, t, ^3J 7.42 Hz, C***H***OBn,

trans), 3.22 (1$\frac{1}{3}$H, d, ^3J 7.14 Hz, MeCOC$\boldsymbol{H}_2$, *trans*), 3.14 ($\frac{2}{3}$H, d d d, MeCOC$\boldsymbol{H}_2$, *cis*), 2.18 (2H, s, ***Me***CO, *trans*), 2.13 (1H, s, ***Me***CO), 1.86-1.76 (1H, m, CH$\boldsymbol{Me}_2$, *cis*, *trans*), 0.98 (1H, d, ^3J 6.32 Hz, CH$\boldsymbol{Me}_2$, *cis*), 0.95 (2H, d, ^3J 6.86 Hz, CH$\boldsymbol{Me}_2$, *trans*), 0.87 (2H, d, ^3J 6.87 Hz, CH$\boldsymbol{Me}_2$, *trans*), and 0.86 (1H, d, ^3J 6.87 Hz, CH$\boldsymbol{Me}_2$, *cis*).

2-(2-Bromoethyl)-2-methyl-1,3-dioxolane (**40**).[102] Hydrogen bromide was bubbled through methyl vinyl ketone (50 g, 0.714 mol) at -78 °C. The extent of the reaction was measured by periodic weighing. When 0.95 equivalents of hydrogen bromide had been added the reaction mixture was allowed to come to room temperature overnight. Benzene (400 ml), ethylene glycol (44 g, 0.714 mol) and *p*-toluene sulphonic acid (0.1 g) was added and the resulting mixture was refluxed under a Dean and Stark trap until no more water was collected. The reaction mixture was allowed to cool and come to room temperature, then washed with saturated sodium hydrogen carbonate solution (100 ml). The separated organic solution was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a crude black oil. The oil was distilled through a 7" Vigreux column (61-64 °C, 1 mmHg) to give the ketal (**40**) (35 g, 25 %). $\nu_{max.}$ ($CHCl_3$) 2970 (C-H), 2870 (C-H), 1655 cm^{-1}; δ_H (60 MHz; $CDCl_3$; TMS) 3.92 (4H, br s, OC$\boldsymbol{H}_2$C$\boldsymbol{H}_2$O), 3.44 (2H, t, $CH_2C\boldsymbol{H}_2Br$), 2.24 (2H, t, C$\boldsymbol{H}_2CH_2Br$), and 1.32 (3H, s, ***Me***CCH); m/z, EI: 181 and 179 (17 %), 153 and 151 (3), 137 and 135 (8), 109 and 107 (19), 87 (100), 71 (22), 55 (23), and 43 (100); CI: 214 and 212 (11 %, M+NH_4^+), 197 and 195 (75, M+H^+), 181 and 179 (2), 150 (26), 133 (8), 115 (100), 99 (1), 87 (40), 70 (3), and 44 (2).

2-(3-Hydroxy-4-methyl)-2-methyl-1,3-dioxolane (**41**). Into an oven dried three necked round bottomed flask fitted with a nitrogen inlet, dropping funnel, leibig condenser and thermometer was placed magnesium turnings (1.87 g, 77 mmol). A solution of 4-bromobutan-2-one (5.0 g, 26 mmol) in dry THF (10 ml) was placed in the dropping funnel. A little of this solution was introduced to the reaction vessel. 1,2-Dibromo ethane (0.2 ml) was added and reflux began. Addition of the bromo ketal was continued over 4$\frac{1}{2}$ hrs. so that the temperature remained at, or below 25 °C. After addition was complete the mixture was allowed to stir for 1 hr. The mixture was cooled over an ice-water bath and

isobutyraldehyde (2.25 g, 31.2 mmol) in dry THF (10 ml) was added dropwise so that the temperature remained below 18 °C. After addition of the aldehyde was complete the reaction mixture was allowed to stir at room temperature for a further ½ hr. and then quenched on 10 % ammonium chloride solution containing a drop of ammonia. The resulting slurry was extracted with diethyl ether. The organic phase was separated, dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a pale yellow oil (4.446 g, 91 %). Flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (4:1) followed by kugelrohr distillation (110 °C, 0.5 mmHg) gave the *keto alcohol* (**41**) (3.260 g, 67 %), (Found: C, 63.80; H, 11.22; N, 0.00. $C_{10}H_{20}O_3$ requires C, 63.80; H, 10.71; N, 0.00 %); δ_H (270 MHz; $CDCl_3$; TMS) 3.98-3.92 (4H, m, $OC\boldsymbol{H}_2C\boldsymbol{H}_2O$), 3.32 (1H, d d d, ^3J 8.79 Hz, ^3J 5.22 Hz,^{3} *J* 3.30 Hz,$CH_2C\boldsymbol{H}OHCH$), 2.49 (1H, br s, O***H***), 1.89 (5H, br m, $C\boldsymbol{H}_2C\boldsymbol{H}_2CHOHC\boldsymbol{H}Me$), 1.33 (3H, s, $\boldsymbol{Me}CCH_2$), 0.92 (3H, d, ^3J 6.60 Hz, $CH\boldsymbol{Me}_2$), and 0.91 (3H, d, ^3J 6.87 Hz, $CH\boldsymbol{Me}_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 110.20 (O***C***O), 76.58 (***C***HOH), 64.60 (OCH_2CH_2O), 35.66 ($MeCCH_2$), 33.72 ($CHMe_2$), 28.40 (CH_2CHOH), 23.76 ($\boldsymbol{Me}CCH_2$), 18.86 ($CH\boldsymbol{Me}_2$), and 17.48 ($CH\boldsymbol{Me}_2$); m/z, EI: 173 (9), 155 (3), 145 (15), 127 (10), 109 (15), 101 (22), 87 (100), 73 (31), 67 (1), 55 (4), and 43 (100); CI: 127(100 %), 109 (2), and 87 (7).

2-(3-Benzyloxy-4-methylpentyl)-2-methyl-1,3-dioxolane (**42**). To a solution of the alcohol (**41**) (1.712 g, 9.1 mmol) in dry THF (10 ml) under nitrogen was added sodium hydride (0.73 g, 60 % dispersion in mineral oil, 18.2 mmol). After stirring for 10 mins. tetra-*n*-butylammonium bromide (0.1 g) was added and allowed to stir for a further 10 mins. Benzyl bromide (2.34 g, 14 mmol) was added and the mixture was refluxed for 24 hrs. The reaction mixture was quenched on brine and the organic layer was separated. The aqueous portion was extracted with diethyl ether (3 x 30 ml). The combined organic layers were dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a pale yellow oil (3.296 g). Flash chromatography on silica gel (40-63 μm) eluting with petroleum ether (b.p. 40-60 °C):ethyl acetate (85:15) followed by kugelrohr distillation (200 °C, 0.1 mmHg) gave the *benzyloxy ketal* (**42**) as a colourless oil (2.116 g, 83 %), (Found: C, 74.14; H, 9.73; N, 0.00. $C_{17}H_{26}O$ requires C, 73.35; H, 9.41; N, 0.00

%); δ_H (270 MHz; $CDCl_3$; TMS) 7.35-7.23 (5H, m, ***Ph***), 4.49 (2H, s, C***H***$_2$Ph), 3.92-3.86 (4H, m, OC***H***$_2$C***H***$_2$O), 3.15-3.13 (1H, m, C***H***OBn), 1.90-1.59 (5H, br m, C***H***$_2$C***H***$_2$CHOBnC***H***Me$_2$), 1.31 (3H, s, ***Me***CCH$_2$), 0.95 (3H, d, ^3J 6.59 Hz, CH***Me***$_2$), and 0.91 (3H, d, ^3J 6.59 Hz, CH***Me***$_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 139.18 (***Ph***), 128.22 (***Ph***), 127.65 (***Ph***), 127.31 (***Ph***), 110.15 (O***C***O), 84.15 (***C***HOBn), 71.57 (Ph***C***H$_2$), 64.56 (O***C***H$_2$***C***H$_2$O), 34.75 (MeC***C***H$_2$), 30.59 (***C***HMe$_2$), 24.49 (***C***H$_2$CHOBn), 23.78 (***Me***CCH$_2$), 18.55 (CH***Me***$_2$), and 18.12 (CH***Me***$_2$); m/z, 235 (24 %), 172 (11), 143 (11), 127 (40), 109 (70), 91 (100), 65 (20), 55 (10), and 43 (54); CI: 279 (35 %, M+H$^+$), 235 (2), 171 (21), 127 (100), 109 (16), and 87 (31).

5-Benzyloxy-6-methylheptan-2-one (**43**). To a solution of the ketal (**42**) (1.00 g, 36 mmol) in THF (20 ml) was added 2M $HCl_{(aq)}$ (20 ml). The mixture was stirred at room temperature for 24 hrs. After neutralization with sodium hydrogen sulphate the mixture was extracted with diethyl ether (4 x 30 ml). The combined organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a pale yellow oil (0.828 g, 98 %). Kugelrohr distillation (160 °C, 0.7 mmHg) gave a pure *ketone* (**43**) (0.712 g, 85 %), (Found: C, 76.76; H, 9.78; N, 0.00. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46; N, 0.00 %); δ_H (270 MHz; $CDCl_3$; TMS) 7.35-7.25 (5H, m, ***Ph***), 4.54 (1H, d, ^2J 11.50 Hz, C***H***$_2$Ph), 4.42 (1H, d, ^2J 11.50 Hz, C***H***$_2$Ph), 3.16 (1H, d d d, ^3J 8.24 Hz, ^3J 5.49 Hz, ^3J 3.57 Hz, C***H***OBn), 2.54-1.57 (2H, m, MeCOC***H***$_2$), 2.09 (3H, s, ***Me***CO), 1.97-1.57 (3H, m, C***H***$_2$CHOBnC***H***Me$_2$), 0.96 (3H, d, ^3J 6.87 Hz, CH***Me***$_2$), and 0.92 (3H, d, ^3J 6.86 Hz, CH***Me***$_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 209.08 (***C***=O), 138.92 (***Ph***), 128.35 (***Ph***), 127.83 (***Ph***), 127.50 (***Ph***), 83.21 (***C***HOBn), 71.62 (CHPh), 39.72 (***C***H$_2$CHOBn), 30.38 (MeCO***C***H$_2$), 29.94 (***C***HMe$_2$), 23.89 (***Me***COCH$_2$), 18.70 (CH***Me***$_2$), and 17.52 (CH***Me***$_2$); m/z, EI: 191 (11 %), 164 (21), 143 (5), 127 (3), 107 (5), 91 (100), 77 (18), 65 (36), 51 (10), and 43 (86); CI: 235 (30 %, M+H$^+$), 191 (2), 143 (4), 127 (100), 108 (10), 91 (43), and 43 (2); (Found 235.1709 from M+H$^+$ in CI. $C_{15}H_{23}O_2$ requires 235.1698).

5-Benzyloxy-6-methylheptan-2-ol (**44**). Sodium borohydride (0.25 g, 6 mmol) was added to a solution of the ketone (**43**) (0.712 g, 3 mmol) in absolute ethanol (30 ml) and allowed

to stir for 1 hr. at room temperature. 2M $HCl_{(aq)}$ was added until effervescence ceased followed by addition of sodium hydrogen carbonate until the solution was neutral. The mixture was poured onto saturated brine (50 ml) and extracted with diethyl ether (3 x 50 ml). The combined organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a crude oil. Kugelrohr distillation (150 °C, 0.1 mbar) gave the *alcohol* (**44**) as a colourless oil (0.581 g, 81 %), δ_H (270 MHz; $CDCl_3$; TMS) 7.33-7.23 (5H, m, ***Ph***), 4.54(1H, d, C***H***$_2$Ph), 4.42 (1H, d, C***H***$_2$Ph), 3.67 (1H, m, C***H***OH), 3.15 (1H, m, C***H***OBn), 2.22 (1H, br s, O***H***), 1.94 (1H, m, C***H***Me_2), 1.64-1.29 (4H, m, C***H***$_2$C***H***$_2$), 1.15 (3H, d d, ^3J 6.04 Hz, ^4J 1.65 Hz, ***Me***CHOH), 0.93 (3H, d d, ^3J 7.69 Hz, ^4J 1.1 Hz, CH***Me***$_2$), and 0.89 (3H, d d, ^3J 6.59 Hz, ^4J 2.19 Hz, CH***Me***$_2$); COSY 90; δ_C (67.8 MHz; $CDCl_3$; TMS) 138.89 (***Ph***), 138.87 (***Ph***), 128.30 (***Ph***), 127.80 (***Ph***), 127.47 (***Ph***), 127.45 (***Ph***), 84.50 (***C***HOBn), 84.26 (***C***HOBn), 71.72 (Ph***C***H_2), 71.60 (Ph***C***H_2), 68.06 (***C***HOH), 67.99 (***C***HOH), 36.39 (***C***H_2CH_2), 35.30 (***C***H_2CH_2), 30.39 (***C***HMe_2), 30.29 (***C***HMe_2), 26.25 (CH_2***C***H_2), 26.06 (CH_2***C***H_2), 23.52 (***Me***CHOH), 23.50 (***Me***CHOH), 18.68 (CH***Me***$_2$), 18.57 (CH***Me***$_2$), and 17.76 (CH***Me***$_2$); CH COSY; m/z, EI: 237 (4 %), 193 (14), 175 (3), 163 (5), 151 (12), 129 (19), 107 (50), 91 (100), 77 (23), 65 (69), 55 (21), and 41 (69); CI: 237 (100 %, M+H$^+$), 129 (50), 108 (17), 85 (6), 58 (4), and 44 (8); (Found 237.1873 from M+H$^+$ in CI. $C_{15}H_{25}O_2$ requires 237.1854).

2-Acetoxy-5-benzyloxy-6-methylheptane (**45**). A solution of the alcohol (**44**) (0.060 g, 0.25 mmol), acetic anhydride (0.037 g, 0.36 mmol), triethylamine (0.037 g, 0.36 mmol) and DMAP (0.003 g) in dichloromethane (1 ml) under nitrogen was stirred at room temperature for 30 hrs. The solution was diluted with dichloromethane (5 ml) and washed with 2M $HCl_{(aq)}$ (5 ml). The organic layer was separated, dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a colourless oil (0.078 g). The oil was kugelrohr distilled (165 °C, 0.2 mbar) to yield the colourless *acetate* (**45**) (0.74 g, 105 %). δ_H (270 MHz; $CDCl_3$; TMS) 7.36-7.24 (5H, m, ***Ph***), 4.89-4.84 (1H, m, C***H***OAc), 4.53 (1H, d, ^2J 11.26 Hz, C***H***$_2$Bn, *syn*, *anti*), 4.48 (½H, d, ^2J 11.26 Hz, PhC***H***$_2$), 4.67 (½H, d, ^2J 11.26 Hz, PhC***H***$_2$), 3.15-3.11 (1H, m, C***H***OBn), 2.02 (1½H, s, ***Me***CO_2), 2.01 (1½H, s, ***Me***CO_2), 2.00-1.73 (1H, m, C***H***Me_2), 1.72-1.46 (2H, br m, CHCH), 1.208 (1½H, d, ^3J 6.31

Hz; ***Me***CHOAc), 1.193 (1½H, d, ^3J 6.32 Hz, ***Me***CHOAc), 0.933 (1½H, d, ^3J 6.59 Hz, CH***Me***$_2$), 0.930 (1½H, d, ^{3}J 5.21 Hz, CH***Me***$_2$), and 0.904 (3H, d, ^3J 6.32 Hz, CH***Me***$_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 170.73 (***C***=O), 139.08 (***Ph***), 128.30 (***Ph***), 127.73 (***Ph***), 127.44 (***Ph***), 84.06 (***C***HOBn), 83.68 (***C***HOBn), 71.83 (***C***HOAc), 71.70 (***C***HOAc), 71.36 (***C***H_2Ph), 70.89 (***C***H_2Ph,) 32.01 (***C***H_2CHOBn), 31.75 (***C***H_2CHOBn), 30.57 (***C***HMe_2), 30.47 (***C***HMe_2), 26.08 (***C***H_2CHOAc), 25.69 (***C***H_2CHOAc), 21.34(***Me***CO_2), 20.08 (***Me***CHOAc), 20.00 (***Me***CHOAc), 18.52 (CH***Me***$_2$), 18.46 (CH***Me***$_2$), 17.97 (CH***Me***$_2$), and 17.92 (CH***Me***$_2$); m/z, EI: 175 (6 %), 127 (1), 112 (9), 101 (2), 91 (100), 85 (40), 77 (5), 65 (21), 55 (5), and 43 (55); CI: 296 (40 %, M+NH_4^+), 279 (54, M+H^+), 219 (100), 201 (2), 171 (9), 146 (4), 127 (65), 108 (48), 91 (30), 85 (31), and 58 (1); (Found 279.1960 from M+H^+ in CI. $C_{17}H_{27}O_3$ requires 279.1960).

6-Methylheptan-2,5-diol (**46**). The benzyl alcohol (**44**) (0.240 g, 1 mmol), 5 % palladium on charcoal (0.05 g) in absolute ethanol (10 ml) was stirred under hydrogen for 2 hrs. The mixture was then filtered through Celite and concentrated under reduced pressure to give a crude viscous oil. The oil was kugelrohr distilled (170 °C, 0.1 mbar) to give the pure *diol* (**46**) (0.14 g, 95 %), δ_H (270 MHz; D_3COD; TMS) 3.79-3.66 (1H, m, C***H***OH), 3.32-3.20 (1H, m, C***H***OBn), 1.66-1.36 (5H, br m, C***H***$_2$C***H***$_2$CHOBnC***H***), 1.16 (3H, d, ^3J 6.31 Hz, ***Me***CHOH), and 0.91 (6H, d, ^3J 6.87 Hz, CH***Me***$_2$); δ_C (67.8 MHz; D_3COD; TMS) 77.70 (***C***OHiPr), 77.44 (***C***OHiPr), 68.91 (Me***C***HOH), 68.60 (Me***C***HOH), 36.90 (***C***H_2CHOHiPr), 36.67 (***C***H_2CHOHiPr), 34.90 (MeCHOH***C***H_2), 34.87 (MeCHOH***C***H_2), 31.41 (***C***HMe_2), 31.19 (***C***HMe_2), 23.63 (***Me***CHOH), 23.58 (***Me***CHOH), 19.36 (CH***Me***$_2$), 17.95 (CH***Me***$_2$), and 17.92 (CH***Me***$_2$); m/z, EI: 129 (10 %), 111 (21), 103 (7), 95 (14), 85 (100), 73 (17), 67 (37), 57 (45), 53 (2), and 43 (85); CI: 164 (18 %, M+NH_4^+), 147 (100, M+H^+), 129 (90), 111 (10), 85 (11), 58 (2), and 44 (1); (Found 147.1390 from M+H^+ in CI. $C_8H_{19}O_2$ requires 147.1385).

4-(2-Methylethyl)-7-methyl-1,3-dioxepane (**47**). The diol (**46**) (0.11 g, 0.75 mmol), p-formaldehyde (0.22 g) and a crystal to p-toluenesulphonic acid in benzene (40 ml) was refulxed under a Dean and Stark trap for ½ hr. The cooled reaction mixture was poured

onto excess saturated sodium hydrogen carbonate solution. The organic layer was separated, dried over magnesium sulphate, filtered and concentrated to give a musty-sweet smelling yellow *oil* (**47**) (0.104 g, 88 %), δ_H (270 MHz; $CDCl_3$; TMS) 5.09 ($\frac{1}{2}$H, d, ^2J 7.41 Hz, OC***H***$_2$O, *trans*), 4.84 ($\frac{1}{2}$H, d, ^2J 4.94 Hz, OC***H***$_2$O, *cis*), 4.73 ($\frac{1}{2}$H, d, ^2J 4.94 Hz, OC***H***$_2$O, *cis*), 4.58 ($\frac{1}{2}$H, d, ^2J 7.41 Hz, OC***H***$_2$O, *trans*), 3.87 (1H, m, MeC***H***O, *cis*, *trans*), 3.33 (1H, m, iPrC***H***O, *cis*, *trans*), 1.78-1.12 (5H, br m, C***H***$_2$C***H***$_2$CHC***H***Me$_2$, *cis*, *trans*), 1.23 (1$\frac{1}{2}$H, d, ^3J 6.32 Hz, ***Me***CH), 1.21 (1$\frac{1}{2}$H, d, ^3J 6.04 Hz, ***Me***CH), 0.92 (6H, m, CH***Me***$_2$).

4-Hydroxy-5-methylhexan-2-one (**48**).[103] A solution of isobutyraldehyde (50 g, 0.69 mol) in diethyl ether (20 ml) was added to a rapidly stirred mixture of acetone (100 ml), 12 % $NaOH_{(aq)}$ (50 ml) over 2 hrs. at 10 °C. After a further 2$\frac{1}{2}$ hrs. the aqueous layer was separated and extracted with diethyl ether (2 x 100 ml). The organic layers were combined and neutralized with acetic acid and then shaken with saturated sodium hydrogen carbonate solution. The aqueous layer was separated and extracted with diethyl ether (100 ml). The combined organic layer was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a crude oil. The oil was purified by distillation (85 °C, 10 mmHg) to give the ketone (**48**) (10.35 g, 10 %), (Found: C, 64.37; H, 11.41; N, 0.00. $C_7H_{14}O_2$ requires C, 64.58; H, 10.84; N, 0.00 %); δ_H (270 MHz; $CDCl_3$; TMS) 3.85-3.13 (1H, m, C***H***OH), 3.12 (1H, bs, O***H***), 2.64-2.21 (2H, m, C***H***$_2$), 2.1 (3H, s, ***Me***CO), 1.72-1.64 (1H, oct, C***H***Me$_2$), 0.94 (3H, d, ^3J 6.32 Hz, CH***Me***$_2$), and 0.91 (3H, d, ^3J 6.32 Hz, CH***Me***$_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 210.24 (***C***=O), 72.25 (***C***HOH), 47.13 (***C***H$_2$), 33.15 (***Me***), 30.83 (***C***HMe$_2$), 18.38 (CH***Me***$_2$), and 18.76 (CH***Me***$_2$); m/z, EI: 97 (2 %), 87 (21), 72 (5), 69 (2), 58 (6), 55 (5), 43 (100), and 40 (1); CI: 148 (100 %, M+NH_4^+), 131 (68, M+H^+), and 113 (27).

4-Benzyloxy-5-methylhexan-2-one (**49**). To a stirred solution of the alcohol (**48**) (1.00 g, 7.7 mmol) and benzyl-1,1,1-trichloroacetimidate (2.9 g, 12 mmol) in cyclohexane (6 ml) and dichloromethane (2 ml) under nitrogen was added triflic acid (130 µl). An exotherm was noted. The mixture was allowed to stir at room temperature for 1 hr. and then poured onto saturated sodium hydrogen carbonate solution (10 ml). The organic phase was

separated, dried over magnesium sulphate, filtered and concentrated to give a crude oil. Flash chromatography on silica gel (40-63 μm) failed to purify the oil. MPLC allowed purification of benzyloxy ketone to give the pure *ketone* (**49**) brown waxy solid (0.273 g, 10 %), $\nu_{max.}$ ($CHCl_3$) 2940 (C-H), 2905 (C-H), 2860, 1700 (C=O), 1350, and 1065; δ_H (270 MHz; $CDCl_3$; TMS) 7.35-7.26 (5H, m, ***Ph***), 4.56 (1H, d, ^2J 11.26 Hz, C***H***$_2$Ph), 4.48 (1H, d, ^2J 11.26 Hz, C***H***$_2$Ph), 3.80 (1H, d d d, ^3J 8.51 Hz, ^3J 4.94 Hz, ^3J 3.84 Hz, C***H***OBn), 2.70 (1H, d d, ^2J 15.93 Hz, ^3J 8.51 Hz, C***H***$_2$CHOBn), 2.45 (1H, d d, ^2J 15.93 Hz, ^3J 3.85 Hz, C***H***$_2$CHOBn), 2.16 (3H, s, ***Me***CO), 1.94 (1H, m, C***H***Me$_2$), 0.93 (6H, d, ^3J 6.6 Hz, CH***Me***$_2$); δ_C (67.8 MHz; $CDCl_3$; TMS) 208.15 (***C***=O), 128.30 (***Ph***), 127.72 (***Ph***), 127.49 (***Ph***), 80.33 (***C***HOBn), 72.21 (***C***HPh), 45.10 (***C***H$_2$), 31.23 (***C***HMe$_2$), 31.09 (***Me***CO), 18.24 (CH***Me***$_2$), 17.53 (CH***Me***$_2$); m/z, EI: 181 (1 %), 162 (1), 114 (34), 91 (100), 79 (9), 71 (51), 57 (9), and 43 (38); CI: 221 (48 %, M+H$^+$), 203 (1), 181 (17), 163 (27), 143 (1), 129 (10), 113 (33), 91 (100), 71 (11), 55 (2), and 43 (15); (Found 221.1542 from M+H$^+$ in CI. $C_{14}H_{21}O_2$ requires 221.1542).

4-Benzyloxy-5-methylhexan-2-ol (**50**). To a stirred solution of the ketone (**49**) (0.100 g, 0.45 mmol) in absolute ethanol (5 ml) was added sodium borohydride (0.030 g, 0.8 mmol). The mixture was allowed to stir at room temperature for 1½ hrs. The resulting mixture was quenched on 2M $HCl_{(aq)}$ (20 ml) and then extracted with diethyl ether (3 x 40 ml). The combined organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a pale yellow oil. The crude oil was purified using flash chromatography on silica gel (40-63 μm) eluting with hexane-ethyl acetate (9:1) to give the *alcohol* (**50**) as a colourless oil (0.063 g, 53 %), $\nu_{max.}$ ($CHCl_3$) 3460 (OH), 2950 (C-H), 2905 (C-H), 2860, and 1650 cm^{-1}; δ_H (270 MHz; $CDCl_3$; TMS) 7.37-7.24 (5H, m, ***Ph***, *syn*, *anti*), 4.66 (⅔H, d, $^2J_{syn}$ 11.26 Hz, C***H***$_2$Bn, *syn*), 4.58 (⅓H, d, $^2J_{anti}$ 11.26 Hz, C***H***$_2$Bn, *anti*), 4.53 (⅓H, d, $^2J_{anti}$ 11.26 Hz, C***H***$_2$Bn, anti), 4.42 (⅔H, d, $^2J_{syn}$ 11.26 Hz, C***H***$_2$Bn, *syn*), 4.12-4.00 (⅓H, m, C***H***OH, *anti*), 3.98-3.92 (⅔H, m, C***H***OH, *syn*), 3.58-3.48 (⅔H, m, C***H***OBn, *syn*), 3.46-3.42 (⅓H, m, C***H***OBn, *anti*), 2.17-2.01 (1H, m, C***H***Me$_2$, *syn*, *anti*), 1.65-1.50 (2H, br m, C***H***$_2$, *syn*, *anti*), 1.18 (1H, d, $^3J_{anti}$ 6.32 Hz, ***Me***CHOH, *anti*), 1.15 (2H, d, $^3J_{syn}$ 6.05 Hz, ***Me***CHOH, *syn*), 0.95 (1H, d, ^3J 6.87 Hz, CH***Me***$_2$, *anti*), 0.90

(2H, d, ^3J 7.14, $CHMe_2$, *syn*), 0.95 (2H, d, ^3J 6.87 Hz, $CHMe_2$, *syn*), and 0.89 (1H, d, ^3J 6.87 Hz, $CHMe_2$, *anti*); COSY 90; δ_C (67.8 MHz; $CDCl_3$; TMS) 138.53 (***Ph***, *syn*, *anti*), 138.07 (***Ph***, *syn*, *anti*), 128.52 (***Ph***, *syn*, *anti*), 128.43 (***Ph***, *syn*, *anti*), 128.33 (***Ph***, *syn*, *anti*), 127.97 (***Ph***, *syn*, *anti*), 127.88 (***Ph***, *syn*, *anti*), 127.79 (***Ph***, *syn*, *anti*), 127.69 (***Ph***, *syn*, *anti*), 84.81 (***C***HOBn, *syn*), 81.85 (***C***HOBn, *anti*), 71.88 (***C***H_2Ph, *anti*), 71.00 (***C***H_2Ph, *syn*), 68.03 (***C***HOH, *syn*), 64.85 (***C***HOH, *anti*), 37.93 (***C***H_2, *anti*), 37.26 (***C***H_2, *syn*), 30.22 (***C***HMe_2, *anti*), 29.14 (***C***HMe_2, *syn*), 23.90 (***Me***CHOH, *anti*), 23.62 (***Me***CHOH, *syn*), 19.04 (CH***Me***$_2$, *anti*), 17.53 (CH***Me***$_2$, *anti*), 18.59 (CH***Me***$_2$, *syn*), and 15.95 (CH***Me***$_2$, *syn*); CH COSY; Ratio of *syn* to *anti* was found to be 2:1; m/z, EI: 179 (10 %), 161 (18), 146 (1), 135 (10), 107 (20), 98 (14), 91 (100), 87 (9), 79 (13), 70 (24), 65 (42), 56 (9), 51 (3), and 43 (17); CI: 240 (4 %, $M+NH_4^+$), 223 (100, $M+H^+$), 205 (3), 161 (1), 150 (1), 133 (1), 115 (10), 108 (20), 97 (7), 91 (13), and 44 (1); (Found 223.1698 from $M+H^+$ in CI $C_{14}H_{23}O_2$ requires 223.1690).Stereochemical assignments were deduced by converting a small amount of (**50**) to the diol (**51**) by hydrogenolysis of the benzyl group. Carbon nmr of the diol allowed identification of the *syn* and *anti* material through the observation that the *syn* isomer CHOH carbons resonate down field of the *anti* isomer, δ_H (270 MHz; $CDCl_3$; TMS) 4.10 (1H, m, C***H***OH), 3.70 (1H, m, C***H***OH), 1.6 (3H, br m, C***H***$_2$, C***H***Me_2), 1.26 (3H, d, ^3J 6.31 Hz, ***Me***CHOH, *anti)*, 1.22 (3H, d, ^3J 6.04 Hz, ***Me***CHOH, *syn*) 0.92 (6H, d, ^3J 6.87 Hz, CH***Me***$_2$, syn), 0.91 (6H, d, ^3J 6.6 Hz, CH***Me***$_2$, anti), 73.93 (***C***HOH, 8.29 %, *anti*), 77.99 (***C***HOH, 12.56 %, *syn*), 69.36 (***C***HOH, 11.27 %, *syn*), 65.71 (***C***HOH, 7.90 %, *anti*). The signal intensities of the diol allowed correlation with those of the benzyloxy alcohol (**50**).

Tetra-*n*-butylammonium Borohydride.[104] Tetra-*n*-butylammonium hydrogen sulphate (5 g, 15 mmol) was dissolved in water (5 ml). The solution was placed in a separating funnel. A solution of sodium borohydride (0.63 g, 16 mmol) in water (1.5 ml) was added. The resulting solution was immediately shaken with dichloromethane (50 ml). The organic phase was separated and dried over potassium carbonate, filtered and concentrated to give an oil. The oil was taken up in ethyl acetate filtered and *n*-hexane was added to obtain a white crystalline solid. The solid was isolated by filtration and dried under reduced

pressure to give the desired product (3.1 g, 80 %). The borohydride was not purified further, δ_H (270 MHz; $CDCl_3$; $CHCl_3$) 3.15 (8H, t, $^3J_{H\text{-}N}$ 8.4 Hz, $C\boldsymbol{H}_2N^+$), 1.44 (8H, m, $C\boldsymbol{H}_2CH_2N^+$), 1.25 (8H, m, $MeC\boldsymbol{H}_2$), 0.8 (12H, t, ^3J 6.04 Hz, $\boldsymbol{Me}CH_2$), 0.30 ($\frac{4}{5}$H, septet, $^2J_{B\text{-}H}$ 27.47 Hz, $^{10}B_{I=3}\boldsymbol{H}_4$), -0.17 ($3\frac{1}{5}$H, q, $^2J_{H\text{-}B}$ 81.58 Hz, $^{11}B_{I=\frac{2}{3}}\boldsymbol{H}_4$).

Appendix A

The Boltzmann Distribution

Given a set of energy levels E_1, E_2, E_3, E_4, E_5... then the Boltzmann distribution describes the population of these levels for a set of non-interacting molecules. The first energy level $E_1=0$ by definition. Thus, for a series of measured energies ϵ_i, the Boltzmann distribution has the form:

$$\frac{n_i}{q} = \frac{e^{-(\epsilon_i-\epsilon_1)/k_BT}}{\sum e^{-(\epsilon_j-\epsilon_1)/k_BT}}$$

$$\equiv \frac{e^{-\epsilon_i/k_BT} \cdot e^{\epsilon_1/k_BT}}{e^{\epsilon_1/k_BT} \cdot \sum e^{-\epsilon_j/k_BT}}$$

Where n_i is the number of molecules in state ϵ_i, k_B is the Boltzmann constant, T is absolute temperature, and q is the partition function. The ratio n_i/q gives the proportion of the total population in state ϵ_i.

Since in the evaluation of the ratio the ϵ_1 exponential term cancels and that $R=L.k_B$ we may evaluate our population ratios using the following:

$$\frac{n_i}{q} = \frac{e^{-E_i.1000/RT}}{\sum e^{-E_j.1000/RT}}$$

Where E_i is the MM2 strain energy if the conformer i in $kJ.mol^{-1}$. The partition function q is in general an infinite sum, however it may be truncated in our case after the contribution of the higher energy conformers becomes small, typically less than 1%.

Thus the strain energies may simply be plugged into the above formula, and a sum done of the n_i/q's offering one π-face. Similarly for the remaining conformers and the ratio of these sums will be the predicted selectivity. If a given conformer were to offer each side of the π-face in similar steric environments then one would divide it's n_i/q by 2 and add that

contribution to both sums.

In this analysis one makes the assumption that the less hindered *exo* π-face is attacked exclusively. Furthermore, it assumed that the energy differences between the transition states derived from each conformer is the same as the energy difference between the ground state conformers. This is a slightly more formal way of saying that the selectivity will depend only on the population of the isolated conformer array.

Appendix B

Program MMOL was used to import Formatted MacroModel Structure Files into Molecular Design Ltd.'s ChemText™ program. The program is written in FORTRAN 77 and compiled using VAX/VMS FORTRAN compiler. Note: It is important that the compiler used writes out real numbers such that 0>n>-1 with a leading zero. If not then ChemText™ will error on reading the resulting MolFile.

Since the MacroModel structure file format may be converted to MolFile format then MacroModel structures may be displayed using the SHADEMOL programm[105] to produce the depth cued images seen in this work.

```
      PROGRAM MMOL
C     Alan A. Smith 20:5:90
      IMPLICIT INTEGER (A-Z)
      REAL XYZ
      LOGICAL ERR,LONE,CARBON,RLONE,CHARGE

      COMMON /ATOM/ ATOM(1996,4),COUNT,LAST
      COMMON /XYZ/ XYZ(999,3),NA,NAT
      COMMON /INFO/ INFO(999,13)
      COMMON /BOOL/ LONE,CARBON,RLONE,CHARGE

      CHARACTER A*1, ANS*50, HELP(9)*60

      DATA HELP /
     +          'Input     -  Read in a MacroModel formatted structure file',
     +          'Output    -  Write out a MolFile (MDL format)',
     +          'Delete    -  Removes all atom text symbols',
     +          'Lone      -  Lone pair removal',
     +          'Charge    -  Charge symbol removal',
     +          'Restore   -  Restores all atom symbols after remove',
```

```
+                 'Spawn      -   Spawns a DCL subprocess',
+                 'Exit       -   Exit from the program',
+                 '?          -   Print this help message'/

      CARBON = .FALSE.
      RLONE  = .FALSE.
      CHARGE = .TRUE.

      PRINT *
      PRINT *,'FORMATTED MACROMODEL FILE CONVERTED TO MDL
      FORMAT UTILITY'
      PRINT
      *,'*********************************************************'
      PRINT *
      PRINT *,'? - For help'
      PRINT *


C     Do the main programme loop.

      10        CALL GTINPT (ANS,'MMol: ')
                A = ANS(1:1)

      IF (A .EQ. 'I' .OR. A .EQ. 'i') THEN
      CALL GTINPT (ANS,'Enter MacroModel file name: ')
                IF (ANS(1:1) .NE. ' ') THEN
                CALL OPNFIL(ANS, 'R', UNIT, ERR)
                          IF (.NOT. ERR) THEN
                          CALL RDMMFL (UNIT)
                ENDIF
      END IF

      ELSE IF (A.EQ.'O' .OR. A.EQ.'o') THEN
      CALL GTINPT (ANS,'Enter Mol file name: ')
                IF (ANS(1:1) .NE. ' ') THEN
                CALL OPNFIL(ANS, 'W', UNIT, ERR)
                  IF (.NOT.ERR) THEN
                  CALL ORDMFL
                  CALL WRTMDL(UNIT)
                  END IF
                END IF

      ELSE IF (A.EQ.'L' .OR. A.EQ.'l') THEN
                RLONE = .TRUE.

      ELSE IF (A.EQ.'D' .OR. A.EQ.'d') THEN
                CARBON = .TRUE.

      ELSE IF (A.EQ.'C' .OR. A.EQ.'c') THEN
      CHARGE = .FALSE.

      ELSE IF (A.EQ.'R' .OR. A.EQ.'r') THEN
                CARBON = .FALSE.
                RLONE  = .FALSE.
                CHARGE = .TRUE.

      ELSE IF (A.EQ.'S'.OR.A.EQ.'s') THEN
                CALL LIB$SPAWN

      ELSE IF (A.EQ.'?') THEN
                PRINT *,' '
```

```
                DO 13 I=1,9
                        PRINT *,HELP(I)
13              CONTINUE
                PRINT *,' '

        ELSE IF (A.EQ.'E'.OR.A.EQ.'e') THEN
           GOTO 2

        ELSE
                PRINT *,'Do not understand ',ANS

        END IF

        GOTO 10
2       CLOSE(UNIT)
        STOP
        END


        SUBROUTINE GTINPT (ANS,PROMPT)

        IMPLICIT INTEGER (A-Z)
        CHARACTER *(*) ANS, PROMPT

        WRITE (*,10)PROMPT

        10    FORMAT(1X,A,$)
        READ(*,20)ANS
        20    FORMAT(A)
        RETURN
        END



        SUBROUTINE OPNFIL (FILE, READ, UNIT, ERR)

C       Open a file.

        IMPLICIT INTEGER (A-Z)
        LOGICAL ERR
        CHARACTER*(*) FILE, READ

        IF (READ .EQ. 'R') THEN
        OPEN (UNIT=1, FILE = FILE, STATUS = 'OLD', ERR =900)
        UNIT = 1

        ELSE IF (READ .EQ. 'W') THEN
        OPEN (UNIT=2, FILE=FILE,STATUS ='NEW',FORM='FORMATTED'
+       ,ERR=901)
        UNIT = 2
        END IF

        ERR = .FALSE.
        RETURN

900     ERR = .TRUE.
        PRINT *,'FILE DOES NOT EXIST.'
        RETURN
901     ERR = .TRUE.
        PRINT *,'FILE ALREADY EXISTS. CHOOSE ANOTHER NAME.'
        RETURN
```

```
      END


      SUBROUTINE RDMMFL (UNIT)

      IMPLICIT INTEGER *4  (A-Z)
      REAL XYZ

      COMMON /INFO/ INFO(999,13)
      COMMON /XYZ/ XYZ(999,3),NA,NAT

C     Read the MacroModel connectivity table.

      READ (UNIT,300,ERR=996,END=997)NA,TITLE
300   FORMAT(1X,I5,2X,A)

C     INFO contains atom  type descriptors, connected atoms, and
C     Bond orders. XYZ contains the x, y, and z coordinates of
C     the structure.

      DO 500 I=1,NA
        READ (UNIT, 400, ERR=996, END=997) (INFO(I,J),J=1,13),
     +  (XYZ(I,K),K=1,3)
500   CONTINUE

400   FORMAT(1X,I3,6(1X,I5,1X,I1),1X,3(F11.6,1X))
      CLOSE (UNIT)
      RETURN

996   PRINT *,'ERROR IN READING FILE.'
      RETURN
999   PRINT *,'END OF FILE.'
      RETURN
      END


      SUBROUTINE ORDMFL


      IMPLICIT INTEGER *4 (A-Z)
      REAL XYZ
      LOGICAL LONE,CARBON,RLONE,CHARGE

      COMMON /INFO/ INFO(999,13)
      COMMON /XYZ/ XYZ(999,3),NA,NAT
      COMMON /ATOM/ ATOM(1996,4),COUNT,LAST
      COMMON /BOOL/ LONE,CARBON,RLONE,CHARGE


      COUNT = 0
      LAST = 0
      NAT=0

      DO 10 I = 1,NA

C     Test to see if lone pairs are required.

      TESTLP = .NOT.((INFO(I,1).EQ.63).AND.(RLONE))

      IF ((INFO(I,1).NE.0).AND.(TESTLP)) THEN
```

```
C       NAT keeps track of how may atoms there are in the structure.

        NAT=NAT+1
          DO 20 J = 1,6
          IF (INFO(I,2*J).NE.0) THEN
                    COUNT= COUNT + 1
C       Put all required connectivity information into ATOM.
                    ATOM(COUNT,2) = I
                    ATOM(COUNT,1) = INFO(I,2*J)
          END IF
20        CONTINUE
        END IF
10      CONTINUE

        CURRENT = 0

C       The next nested loop checks for duplicated connectivity
C       information. Duplicates are eliminated by a zero.

        DO 210 I = 1, COUNT
        IF (ATOM(I,1).NE.0) THEN
        CURRENT = I + 1
                  DO 220 J = CURRENT, COUNT
            IF ((ATOM(I,1).EQ.ATOM(J,2)).AND.
+                 (ATOM(J,1).EQ.ATOM(I,2))) THEN
                  ATOM(J,1) = 0
                  END IF
220         CONTINUE
        END IF
210     CONTINUE

C       The next loop now compresses ATOM placing needed information
C       in the space left by the removed duplicates.

        LAB2 = 0
        NATM = 0

        DO 50 LAB = 1,COUNT
5       IF (ATOM(COUNT,1).NE.0) THEN
        LAB2 = LAB2 + 1
                  IF (ATOM(LAB,1).EQ.0) THEN
                  NATM = NATM + 1
                  ATOM(LAB,1) = ATOM(COUNT,1)
                  ATOM(LAB,2) = ATOM(COUNT,2)
                  COUNT = COUNT - 1
                  END IF
        ELSE
                  COUNT = COUNT - 1
                  GOTO 5
        END IF
50      CONTINUE

        LAST = 0
        LAST = LAB2 - NATM

C       Bubble sort the array ATOM.

        CALL BUBBLE
```

```
C       Now look at the MacroModel atom type descriptor to see what
C       bond order to associate with atom Q.

        DO 800 Q=1,LAST
        T=INFO(ATOM(Q,1),1)

        IF((T.EQ.2).OR.(T.EQ.7).OR.(T.EQ.8).OR.(T.EQ.15).OR.
+       (T.EQ.25).OR.(T.EQ.29).OR.(T.EQ.30).OR.(T.EQ.36)
+       .OR.(T.EQ.37)) THEN
                BNDODR=2
        ELSE IF ((T.EQ.1).OR.(T.EQ.9)) THEN
                BNDODR=3
        ELSE
                BNDODR=1
        END IF
        ATOM(Q,3)=BNDODR

C       Find the bond order of atom Q's connection

        DO 805 J=1,6
        IF (ATOM(Q,2).EQ.INFO(ATOM(Q,1),2*J)) THEN
                BNDODR = INFO(ATOM(Q,1),2*J+1)
        END IF
        ATOM(Q,4)=BNDODR

805     CONTINUE
800     CONTINUE
        RETURN
        END

C       We now have ATOM(atom1,atom2,BOatom1,BOatom2)


        SUBROUTINE WRTMDL (UNIT)

        IMPLICIT INTEGER *4 (A-Z)
        REAL XYZ,X,Y,Z,SCALE
        CHARACTER*2 L,ATM
        LOGICAL LONE,CARBON,RLONE,CHARGE

        COMMON /ATOM/ ATOM(1996,4),COUNT,LAST
        COMMON /XYZ/  XYZ(999,3),NA,NAT
        COMMON /INFO/ INFO(999,13)
        COMMON /BOOL/ LONE,CARBON,RLONE,CHARGE

C       Check to see if there are any lone pairs on the structure.
C       Count them up.

        LP=0

        DO 22 Q=1,NA
        IF ((INFO(Q,1).EQ.63).AND.(.NOT.(RLONE))) THEN
                LP=LP+1
        END IF
22      CONTINUE

        IF (LP.NE.0) THEN
                LONE = .TRUE.
        END IF

C       Work out how many bonds are on the structure. Made simple by
```

```
C       the Bubble sort since the maximum value in ATOM(J,
C       must be equal to the number of bonds in the structure.

        BONDS = 0
        DO 32 J=1, LAST
        IF  (ATOM(J,1).LE.NAT) THEN
                BONDS = BONDS+1
        END IF
32      CONTINUE

C       Write out two blank lines. KERMIT will add 1 on transfer.

        WRITE(UNIT,*)
        WRITE(UNIT,*)
        WRITE(UNIT,10) NAT,BONDS,2*LP

C       Assign the atom symbol and charge on the basis of the
C       MacroModel atom type descriptor.

        DO 30 J=1,NA

        CHRG = 0

        IF (CARBON) THEN
                IF ((INFO(J,1).EQ.18).AND.(CHARGE)) THEN
                        CHRG = 5
                ELSE IF (((INFO(J,1).GE.31).AND.(INFO(J,1).LE.37)).AND.
+               (CHARGE)) THEN
                        CHRG = 3
                ELSE IF ((INFO(J,1).EQ.44).AND.(CHARGE))  THEN
                        CHRG = 3
                ELSE IF ((INFO(J,1).EQ.45).AND.(CHARGE)) THEN
                        CHRG = 5
                END IF
          ATM = 'C'

        ELSE IF ((INFO(J,1).GT.0).AND.(INFO(J,1).LE.14)) THEN
          ATM = 'C'

        ELSE IF ((INFO(J,1).GE.15).AND.(INFO(J,1).LE.23)) THEN
                IF ((INFO(J,1).EQ.18).AND.(CHARGE)) THEN
                CHRG = 5
                END IF
          ATM = 'O'

        ELSE IF ((INFO(J,1).GE.24).AND.(INFO(J,1).LE.40)) THEN
                IF (((INFO(J,1).GE.31).AND.(INFO(J,1).LE.37)).AND.
+               (CHARGE)) THEN
                        CHRG = 3
                END IF
          ATM = 'N'

        ELSE IF ((INFO(J,1).GE.41).AND.(INFO(J,1).LE.45)) THEN
                IF ((INFO(J,1).EQ.44).AND.(CHARGE))  THEN
                        CHRG = 3
                ELSE IF ((INFO(J,1).EQ.45).AND.(CHARGE)) THEN
                        CHRG = 5
                END IF
          ATM = 'H'

        ELSE IF ((INFO(J,1).GE.49).AND.(INFO(J,1).LE.52)) THEN
```

```
                ATM = 'S'

              ELSE IF (INFO(J,1).EQ.53) THEN
                ATM = 'P'

              ELSE IF (INFO(J,1).EQ.56) THEN
                ATM = 'F'

              ELSE IF (INFO(J,1).EQ.57) THEN
                ATM = 'Cl'

              ELSE IF (INFO(J,1).EQ.58) THEN
                ATM = 'Br'

              ELSE IF (INFO(J,1).EQ.59) THEN
                ATM = 'I'

              ELSE IF (INFO(J,1).EQ.60) THEN
                ATM = 'Si'

              ELSE IF (INFO(J,1).GT.60) THEN
                ATM = 'C'
END IF

              TESTLP = .NOT.((INFO(J,1).EQ.63).AND.(RLONE))

C             Write out coordinates, atom type, and charge.

              IF ((INFO(J,1).NE.0).AND.(TESTLP)) THEN
                WRITE(UNIT,40) (XYZ(J,I),I=1,3),ATM,CHRG
              END IF
30            CONTINUE

C             Look to see which bond order to use, then write out
C             connectivities, and bond order information.

              DO 35 J=1,BONDS

                  IF (ATOM(J,3).LE.ATOM(J,4)) THEN
                                BNDODR = ATOM(J,3)
                      ELSE IF (ATOM(J,3).GT.ATOM(J,4)) THEN
                                BNDODR = ATOM(J,4)
                      END IF

              WRITE(UNIT,50) ATOM(J,1),ATOM(J,2),BNDODR
35            CONTINUE

C             Write out text symbols for lone pairs if required.

              IF ((LONE).AND.(.NOT.(RLONE))) THEN
              DO 37 K= 1, NA
                      IF (INFO(K,1).EQ.63) THEN
                                WRITE (UNIT,60) 'A',K
                                WRITE (UNIT,65) '^..'
                      END IF
37            CONTINUE
              END IF
              WRITE(UNIT,*)

10            FORMAT(1X,2(I3),24X,I3)
40            FORMAT(1X,3(F10.4),1X,A2,4X,I1)
```

```
50          FORMAT(1X,3(I3))
60          FORMAT(1X,A1,2X,I3)
65          FORMAT(1X,A3)

            CLOSE(UNIT)
            RETURN
            END


            SUBROUTINE BUBBLE

            IMPLICIT INTEGER (A-Z)
            COMMON /ATOM/ ATOM(1996,4),COUNT,LAST

            IF (LAST.EQ.1) GOTO 101
            DO 201 A1 = 1,LAST-1
            DO 301 A2 = A1+1,LAST

            IF (ATOM(A1,1).LE.ATOM(A2,1)) GOTO 401
                        TEMP = ATOM(A1,1)
                        ATOM(A1,1)= ATOM(A2,1)
                        ATOM(A2,1)=TEMP

                        TEMP=ATOM(A1,2)
                        ATOM(A1,2)=ATOM(A2,2)
                        ATOM(A2,2)=TEMP
            ENDIF
401         CONTINUE
301         CONTINUE
201         CONTINUE
101         CONTINUE
            RETURN
            END
```

Appendix C

The following is a Gaussian 88 or Gaussian 90 input deck to optimize the geometry of the $Me_2O.TiCl_4.O{=}CH_2$ complex. The geometry is derived from that observed in the Helmchen crystal structure.[47] The starting geometry is distorted so that no symmetry is present. All parameters will be allowed to vary independently. The geometry optimization is followed by a frequency job.

Entries in curly brackets { } will not be present in the real input deck.

```
{Start of input cards}
# QSUB -r tiopt                          {These are the start of ULCC job control lines}
# QSUB -lM 2.0Mw -lm 2.0Mw
# QSUB -lT 50 -lt 50                     {These values are altered to cpu requirements}
# QSUB -eo                               {end of ULCC job control lines}
rungauss <<\EOF                          {run gaussian system script}
%chk=ti.chk                              {specify checkpoint file}
#n rhf gen opt test

                                         {one blank line}
titanium/carbonyl/ether

                                         {one blank line}
0 1                                      {charge and spin multiplicity}
ti1                                      {start of z-matrix specifying starting geometry}
cl2     ti1     rcl1
cl3     ti1     rcl2        cl2     acl1
cl4     ti1     rcl3        cl2     acl2        cl3     tcl1
cl5     ti1     rcl4        cl3     acl3        cl2     tcl2
o6      ti1     rtos        cl2     aclos       cl3     tclo
```

c7	o6	rcos1		ti1	acot1	cl2	tccl1
c8	o6	rcos2		ti1	acot2	c7	tcc7
h9	c8	rch1		o6	ahco1	c7	thh9
h10	c8	rch1		o6	ahco1	h9	thh10
h11	c8	rch11		o6	acho11	h9	thh11
h12	c7	rch12		o6	acho12	c8	thh12
h13	c7	rch13		o6	acho13	h12	thh13
h14	c7	rch14		o6	acho14	h12	thh14
o15	ti1	rtod		cl2	aocl	cl3	tocl3
x16	o15	1.0		ti1	90.0	cl2	-90.0
c17	o15	rcod		x16	acx	cl2	tocl2
h18	c17	rhcd		o15	ah180	x16	toh18
h19	c17	rchd		o15	ah190	x16	toh19

rcl1	2.26
rcl2	2.26
rcl3	2.26
rcl4	2.26
rtos	2.40
rcos1	1.414
rcos2	1.414
rch1	1.08
rch11	1.08
rch12	1.08
rch13	1.08
rch14	1.08
rtod	2.189
rcod	1.243
rhcd	1.101
rchd	1.101
acl1	90.1
acl2	90.0
acl3	90.1
aclos	90.0
acot1	109.2
acot2	109.2
ahco1	109.5
acho11	109.4
acho12	109.5
acho13	109.4
acho14	109.5
aocl	90.0
acx	120.0
ah190	122.7
ah180	122.75
tcl1	90.0
tcl2	180.05
tclo	180.0
tccl1	210.0
tcc7	120.04
thh9	60.0
thh10	120.01
thh11	-120.0
thh12	60.0
thh13	120.01
thh14	-120.0
tocl3	-90.0
tocl2	180.01
toh18	90.01
toh19	-90.0

{start of parameters to be optimized}

```
-h 0                                                    {start of external basis set}
S   5 1.00
0.1130560000D+02  0.2214060000D-01
0.2071730000D+01  0.1135410000D+00
0.5786480000D+00  0.3318160000D+00
0.1975720000D+00  0.4825700000D+00
0.7445270000D-01  0.1935720000D+00
****
-c 0                                                    {3P K2s(2)2p(2)  (53/5)}
S   5 1.00
1.1362770000D+03 -0.0062406000D+00
1.7122313000D+02 -0.0461454000D+00
3.9001479000D+01 -0.1988050000D+00
1.0835972000D+01 -0.4861328000D+00
3.2924871000D+00 -0.4106105000D+00
S   3 1.00
5.1948489000D+00 -0.0846341000D+00
0.4737651400D+00  0.5702789000D+00
0.1494798700D+00  0.5124198000D+00
P   5 1.00
1.8967303000D+01  0.0137754000D+00
4.1741709000D+00  0.0859797000D+00
1.2095407000D+00  0.2884617000D+00
0.3855578000D+00  0.5007918000D+00
0.1216104100D+00  0.3463376000D+00
****
-o 0                                                    {3P K2s(2)2p(4)  (53/5)}
S   5 1.00
2.0480478000D+03  0.0062086000D+00
3.0909891000D+02  0.0459923000D+00
7.0414098000D+01  0.1992855000D+00
1.9701169000D+01  0.4874045000D+00
6.0314474000D+00  0.4076605000D+00
S   3 1.00
1.0229716000D+01 -0.0837369000D+00
0.9340918500D+00  0.5714905000D+00
0.2862465600D+00  0.5136243000D+00
P   5 1.00
3.4971176000D+01  0.0155923000D+00
7.8450917000D+00  0.0983900000D+00
2.3033164000D+00  0.3085950000D+00
0.7219823900D+00  0.4912910000D+00
0.2155271300D+00  0.3394114000D+00
****
-cl 0                                                   {2P KL3s(2)3p(5)  (533/53)}
S   5 1.00
9.9575936000D+03  0.0057873000D+00
1.5082197000D+03  0.0429534000D+00
3.4488236000D+02  0.1887409000D+00
9.7580445000D+01  0.4780557000D+00
3.0178350000D+01  0.4267551000D+00
S   3 1.00
5.2308580000D+01 -0.0993588000D+00
5.6485972000D+00  0.5976602000D+00
2.1855069000D+00  0.4762618000D+00
P   5 1.00
2.7456022000D+02  0.0106404000D+00
6.3901367000D+01  0.0761998000D+00
1.9771323000D+01  0.2764051000D+00
6.8169995000D+00  0.5066224000D+00
2.4144184000D+00  0.3292910000D+00
```

```
S   3 1.00
3.3305688000D+00  0.1903271000D+00
0.4731705000D+00 -0.6944957000D+00
0.1708556800D+00 -0.4242388000D+00
P   3 1.00
0.1259841700D+00  0.3113366000D+00
1.0170836000D+00  0.2849377000D+00
0.3668857200D+00  0.5455777000D+00
****
-ti 0                                   {5F KL3s(2)3p(6)3d(2)4s(2)  (5333/53/5)}
S   5 1.00
1.7783650000D+04 -0.0054019000D+00
2.6648626000D+03 -0.0407268000D+00
6.0601734000D+02 -0.1816278000D+00
1.7076671000D+02 -0.4729256000D+00
5.2689149000D+01 -0.4399439000D+00
S   3 1.00
8.9921928000D+01 -0.1051857000D+00
1.0266912000D+01  0.6078721000D+00
4.1664156000D+00  0.4658745000D+00
P   5 1.00
5.1181029000D+02  0.0099512000D+00
1.2058957000D+02  0.0720632000D+00
3.8078415000D+01  0.2669128000D+00
1.3552786000D+01  0.5068977000D+00
4.9809761000D+00  0.3314110000D+00
S   3 1.00
6.8198023000D+00  0.2214156000D+00
1.0977523000D+00 -0.7108778000D+00
0.4402786200D+00 -0.4190506000D+00
P   3 1.00
2.4349883000D+00  0.3146517000D+00
0.9403856900D+00  0.5536153000D+00
0.3491456700D+00  0.2529165000D+00
D   5 1.00
2.0556045000D+01  0.0291745000D+00
5.4450459000D+00  0.1472480000D+00
1.7374644000D+00  0.3539062000D+00
0.5423670500D+00  0.4727976000D+00
0.1492841800D+00  0.3733074000D+00
S   3 1.00
0.5621160500D+00 -0.1407333000D+00
0.0617602900D+00  0.7505513000D+00
0.0230856200D+00  0.3365015000D+00
****
                                        {one blank line}
--Link1--                               {start frequency calculation}
%chk=ti.chk                             {point to the chechpoint file}
#n rhf gen freq geom=checkpoint guess=check test
                                        {one blank line}
Frequency calculation
                                        {one blank line}
0 1                                     {specify the charge and multiplicity}

-h 0                                    {start of external basis set}
S   5 1.00
0.1130560000D+02  0.2214060000D-01
0.2071730000D+01  0.1135410000D+00
0.5786480000D+00  0.3318160000D+00
0.1975720000D+00  0.4825700000D+00
0.7445270000D-01  0.1935720000D+00
```

```
****
-c 0
S   5 1.00
1.1362770000D+03 -0.0062406000D+00
1.7122313000D+02 -0.0461454000D+00
3.9001479000D+01 -0.1988050000D+00
1.0835972000D+01 -0.4861328000D+00
3.2924871000D+00 -0.4106105000D+00
S   3 1.00
5.1948489000D+00 -0.0846341000D+00
0.4737651400D+00  0.5702789000D+00
0.1494798700D+00  0.5124198000D+00
P   5 1.00
1.8967303000D+01  0.0137754000D+00
4.1741709000D+00  0.0859797000D+00
1.2095407000D+00  0.2884617000D+00
0.3855578000D+00  0.5007918000D+00
0.1216104100D+00  0.3463376000D+00
****
-o 0
S   5 1.00
2.0480478000D+03  0.0062086000D+00
3.0909891000D+02  0.0459923000D+00
7.0414098000D+01  0.1992855000D+00
1.9701169000D+01  0.4874045000D+00
6.0314474000D+00  0.4076605000D+00
S   3 1.00
1.0229716000D+01 -0.0837369000D+00
0.9340918500D+00  0.5714905000D+00
0.2862465600D+00  0.5136243000D+00
P   5 1.00
3.4971176000D+01  0.0155923000D+00
7.8450917000D+00  0.0983900000D+00
2.3033164000D+00  0.3085950000D+00
0.7219823900D+00  0.4912910000D+00
0.2155271300D+00  0.3394114000D+00
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-cl 0
S   5 1.00
9.9575936000D+03  0.0057873000D+00
1.5082197000D+03  0.0429534000D+00
3.4488236000D+02  0.1887409000D+00
9.7580445000D+01  0.4780557000D+00
3.0178350000D+01  0.4267551000D+00
S   3 1.00
5.2308580000D+01 -0.0993588000D+00
5.6485972000D+00  0.5976602000D+00
2.1855069000D+00  0.4762618000D+00
P   5 1.00
2.7456022000D+02  0.0106404000D+00
6.3901367000D+01  0.0761998000D+00
1.9771323000D+01  0.2764051000D+00
6.8169995000D+00  0.5066224000D+00
2.4144184000D+00  0.3292910000D+00
S   3 1.00
3.3305688000D+00  0.1903271000D+00
0.4731705000D+00 -0.6944957000D+00
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1.0170836000D+00  0.2849377000D+00
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0.3668857200D+00  0.5455777000D+00
****
-ti 0
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6.0601734000D+02 -0.1816278000D+00
1.7076671000D+02 -0.4729256000D+00
5.2689149000D+01 -0.4399439000D+00
S   3 1.00
8.9921928000D+01 -0.1051857000D+00
1.0266912000D+01  0.6078721000D+00
4.1664156000D+00  0.4658745000D+00
P   5 1.00
5.1181029000D+02  0.0099512000D+00
1.2058957000D+02  0.0720632000D+00
3.8078415000D+01  0.2669128000D+00
1.3552786000D+01  0.5068977000D+00
4.9809761000D+00  0.3314110000D+00
S   3 1.00
6.8198023000D+00  0.2214156000D+00
1.0977523000D+00 -0.7108778000D+00
0.4402786200D+00 -0.4190506000D+00
P   3 1.00
2.4349883000D+00  0.3146517000D+00
0.9403856900D+00  0.5536153000D+00
0.3491456700D+00  0.2529165000D+00
D   5 1.00
2.0556045000D+01  0.0291745000D+00
5.4450459000D+00  0.1472480000D+00
1.7374644000D+00  0.3539062000D+00
0.5423670500D+00  0.4727976000D+00
0.1492841800D+00  0.3733074000D+00
S   3 1.00
0.5621160500D+00 -0.1407333000D+00
0.0617602900D+00  0.7505513000D+00
0.0230856200D+00  0.3365015000D+00
****
```

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Polarization functions may be added to improve the basis set. These are additional p or d type gaussians and may be appended to the external basis set for each atom as required.

Polarization Functions

One-membered and two membered polarization sets:

```
For carbon
D   1 1.00
0.6000000000D+00  0.1000000000D+01
or
D   2 1.00
0.2880000000D+00  0.1000000000D+01
1.3350000000D+00  0.1000000000D+01

For oxygen
D   1 1.00
1.1540000000D+00  0.1000000000D+01
or
D   2 1.00
```

0.5350000000D+00 0.1000000000D+01
2.7040000000D+00 0.1000000000D+01

For chlorine
D 1 1.00
0.5140000000D+00 0.1000000000D+01
or
D 2 1.00
0.2200000000D+00 0.1000000000D+01
0.7970000000D+00 0.1000000000D+01

For titanium (^{5}F) 3d(3)
P 1 1.00
0.0650000000D+00 0.1000000000D+01
or
P 1 1.00
0.0280000000D+00 0.1000000000D+01
0.8300000000D+00 0.1000000000D+01

The addition of these funtions either one-membered or better still the two-membered terms should lead to a better geometry and more reliable molecular properties (at the expense of computational time).

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