STUDIES IN ASYMMETRIC SYNTHESIS

THESIS

Submitted in Fulfilment of the
Requirements for
the degree of
DOCTOR OF PHILOSPHY
of Rhodes University

by

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December 1990

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To my dearest Penny, Ian and Clair,
who sacrificed so much for so long.

ABSTRACT

The concept of combining two well established areas of organic chemistry, *viz.*, organosilicon chemistry and the use of chiral auxiliaries, into a viable, alternative method of asymmetric synthesis has only very recently begun to receive attention. At the outset of this investigation, no asymmetric reactions of silyl enol ethers, chiral by virtue of optically active substituents on the silicon, had been reported.

A range of novel chiral silyl enol ethers have thus been prepared from a variety of ketones, including pinacolone, cyclohexanone, and α–tetralone, and employing menthol, borneol, and cholesterol as chiral auxiliaries. These preparations have been achieved *via* several distinct routes, including a novel convergent approach involving the isolation of either the chloro(menthyloxy)-dimethylsilane or the (bornyloxy)chlorodimethylsilane. The MS and NMR spectra of these silyl enol ethers were examined in detail and, in the case of the crystalline cholesteryloxy silyl enol ether, the X–ray structure has been determined.

The potential of chloroalkoxysilanes to act as general, chiral derivatizing agents has been established by the preparation of diastereomeric silyl acetal mixtures of *racemic* secondary alcohols (*e.g.* 1–phenylethanol and 2–octanol). The experimental diastereomeric ratios, obtained by GLC and ^{1}H NMR spectroscopy, approached the expected value of unity, confirming the potential of the alkoxychlorosilanes as chiral probes.

The chiral silyl enol ethers have been successfully oxidized to the corresponding α–siloxy ketones employing MCPBA, MMPP, and 2–(phenylsulphonyl)–3–

phenyloxaziridine as oxidizing agents and the diastereomeric excesses obtained, which varied from 0 to 16%, indicated some potential for stereochemical control. Alkylation and hydroxyalkylation reactions of the silyl enol ethers have yielded the expected α–*tert*–butyl and β–hydroxy ketones in good to excellent material yields, with the enantiomeric excesses, as determined by chiral shift reagent studies, reaching 14%.

To improve the stereocontrol in these reactions, attempts have been made to prepare chiral silyl enol ethers with auxiliaries possessing the potential for transition state complex co–ordination in the reactions under consideration. The preparation of such silyl enol ethers, incorporating the proline–derived auxiliaries, *N*–methyl–2–hydroxymethylpyrrolidine and 2–methoxymethylpyrrolidine met with only limited success. In an alternative approach, three derivatives of 2,3–dihydroxybornane have been prepared. However, two of these auxiliaries, *viz.*, 3–*exo*–benzyloxy–2–*exo*–hydroxybornane and 3–*exo*–(1–methoxyethoxy)–2–*exo*–hydroxybornane failed to form silyl enol ethers, even under considerably more vigorous conditions than normally employed. The third derivative, 3,3–ethylenedioxy–2–hydroxybornane has been successfully utilized in the preparation of a pinacolone–derived chiral silyl enol ether. Hydroxyalkylation of this compound with benzaldehyde has yielded the β–hydroxyketone with significantly improved enantiomeric excess (26%) and a transition state complex has been proposed to rationalize this improvement.

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ACKNOWLEDGEMENTS

Firstly, I would like to thank, Prof. Perry Kaye for the constant support, guidance, and confidence he showed throughout this investigation. It was both a privilege and an invaluable learning experience to work under his supervision. The discussions with Dr. Richard Lidell and all the other members of the research group during the past three years were very helpful. A special thank you to Mrs Stephanie Burton, for so diligently proof–reading the manuscript and for providing moral support when it was needed.

The willing and skilful technical assistance of Mr. Aubrey Sonneman and the computer programming expertise of Mr. David Sewry, played an important role in this project, which was appreciated.

I would also like to express my thanks to Rhodes University for their generous financial support and to Prof.T.M. Letcher and the entire academic staff of the Chemistry Department for their understanding of the restraints on my time.

ABBREVIATIONS

COSY – ^{1}H – ^{1}H shift correlated experiment

DMF – dimethylformamide

GC–MS – gas liquid chromatography / mass spectrometry

Eu(tfc)$_3$ – europium (III) *tris*[3–(trifluoromethylhydroxymethylene)camphorato]

GLC – gas-liquid chromatography

HETCOR – ^{1}H – ^{13}C shift correlated experiment

HPLC – high pressure liquid chromatography

IR – infrared spectrometry

KHMDS – potassium hexamethyldisilazine

LAH – lithium aluminium hydride

LDA – lithium diisopropylamide

MCPBA – *m*–chloroperbenzoic acid

MMPP – magnesium monoperoxyphthalate

MS – mass spectrometry

MTPA – α–methoxy–α–trifluoromethylphenylacetic acid

NMR – nuclear magnetic resonance spectroscopy

TBAF – tetrabutylammonium fluoride

THF – tetrahydrofuran

TLC – thin layer chromatography

TMSCl – chlorotrimethylsilane

TMSOTf – trimethylsilyl trifluoromethanesulfonate

Pr (tfc)$_3$ – praseodymium (III) *tris* [3–(trifluoromethylhydroxymethylene)camphorato]

INTRODUCTION

In biosynthetic processes, enzyme systems exert complete control over the optical purity of the product molecules. As a consequence of this absolute control, enantiomers of natural products often have very different biological effects. Thus, limonene and carvone enantiomers have different aromas, both enantiomers of sucrose are equally sweet but only the naturally occurring form is metabolized, and the teratogenic effects of thalidomide have been ascribed to only one enantiomeric form.[1] These differences in the biological properties of enantiomers place stringent demands on *in vitro* syntheses of chiral products for biological applications. Besides biological applications, the demand for enantiomerically pure compounds is increasing in the areas of molecular electronics, optical data storage, and speciality polymers.[1,2]

Recent advances in asymmetric synthetic techniques have facilitated the preferential preparation of one enantiomer over its mirror image in excesses often greater than 95 %. However, the ability to routinely emulate enzymes is still far from becoming a reality and remains one of the most demanding challenges facing modern organic chemists.

The aim of this introduction is, firstly, to place asymmetric synthesis in perspective with other methods of obtaining organic molecules of high optical purity. Secondly, while asymmetric synthesis has been extensively reviewed,[3] this introduction highlights the diversity of strategies employed, with particular reference to asymmetric reactions involving carbonyl compounds, which are of particular interest in the present investigation.

1.1 RESOLUTION OF RACEMIC MIXTURES TO OBTAIN OPTICALLY ACTIVE MOLECULES.

With few exceptions any method of obtaining chiral molecules must rely on the intervention of another chiral molecule, which is ultimately derived from a natural source. The exceptions include the rare instances in which enantiomeric crystals can be physically sorted from a racemic mixture; such a separation of racemic sodium ammonium tartrate was first achieved by Pasteur [4] and Pasteur's ideas have recently been extended by Addadi.[5] It is also possible for exclusive spontaneous crystallizations of one chiral form of a crystal to occur, as proved by Soret's work [6] on the crystallization of achiral sodium chlorate molecules to chiral crystals, under conditions which rigorously exclude accidental seeding; the enantioselectivity is, however, completely random. Under certain circumstances seeding of solutions of a racemate with crystals of one pure enantiomer can lead to separation of one enantiomer and the retention of the other in solution.[7]

Various separation techniques that utilize interactions between constituent enantiomers of a racemate and a second chiral agent can be identified, *viz.*,

classic resolutions *via* diastereomeric intermediates (Section 1.1.1),
asymmetric transformations (Section 1.1.2, p. 3), and
kinetic resolutions (Section 1.1.3, p. 4).

1.1.1 Classic Resolutions *via* Diastereomeric Intermediates.

These approaches are usually based on preparing stable diastereomeric derivatives of the racemic pair and then exploiting one of the differing physical properties to effect the separation. The work of Jacques *et al.*[8] in organizing and rationalizing much of the information in this regard has increased the effectiveness of these techniques.

The most general method is crystallization resolution in which one of the resulting diastereomeric derivatives is induced to crystallize preferentially. Recently, Fogassy *et al.*[9] have made attempts to develop quantitative analytical methods for predicting crystallization resolution behaviour.

Resolution of enantiomers can also be achieved by chromatography. In principle, diastereomeric mixtures can be separated on achiral stationary phases. An alternative chromatographic approach is to utilize diastereomeric interactions between a racemic mixture and a chiral stationary phase. Commercial chiral GLC and HPLC columns, although expensive, are becoming available.

The major disadvantages of classical resolutions are that, despite the work of Fogassy *et al.*[9], suitable conditions must be found, largely by trial and error, for each resolution. Furthermore, in such resolutions the racemic mixture affords a maximum of only 50% of the required isomer.

1.1.2 Asymmetric Transformations

An alternative approach is to make use of a process known as a thermodynamically controlled asymmetric transformation. This involves establishing an equilibrium between stereoisomers *via* experimental conditions in which a chiral centre becomes stereochemically labile. If the reactant and product are diastereomeric and only one chiral centre is stereochemically labile, then the free energies of the reactant and product may be expected to be different and, at equilibrium, there will be unequal amounts of each diastereomer. This interconversion of diastereomers is called a first order asymmetric transformation. If this equilibration is accompanied by precipitation of one of the diastereomers then the process is a second order asymmetric transformation.

Second order processes are very attractive options for obtaining chiral compounds. Since, if a dynamic equilibrium is established for a 50:50 mixture of diastereomers *via* a configurational change at a chiral centre, then precipitation of one diastereomer will drive the equilibrium to produce more of it. In principle, it is possible to convert the entire mixture to the less soluble isomer. Although this rarely occurs in practice, it is feasible to obtain more than the 50% yield theoretically possible by classical resolution techniques.

A variety of processes exist which permit eqiulibration of optically active molecules. For molecules which are chiral by virtue of a chiral carbon atom, mechanistic processes such as keto–enol tautomerism or carbanion formation (*i.e.* involving an achiral intermediate) may be used to establish equilibrium. For other types of chirality arising, for example, from trisubstituted tetrahedral atoms such as nitrogen or sulphur, or from restricted rotation around conformationally mobile bonds (*e.g.* in *ortho* substituted biphenyls), unimolecular inversion or rotation can be achieved simply by heating. Since the early reviews [10,11] on asymmetric transformations, numerous successful applications of second order approaches have, in fact, been reported.[12,13]

1.1.3 Kinetic Resolutions

Kinetic resolution, on the other hand, is based on the preferential reaction of one enantiomer with a chiral reagent to form a product which is easily separable from the starting enantiomers. In the ideal case, the rate of reaction for one enantiomer is so much greater than for the second that essentially complete conversion of one enantiomer occurs without significant competition from the other. In practice, the rates are never so different, but, if insufficient chiral reagent is used for complete conversion, then the recovered starting material will be enriched in the less reactive enantiomer.

1.2 THE USE OF ENZYME SYSTEMS TO OBTAIN OPTICALLY ACTIVE MOLECULES

Some of the most successful kinetic resolutions have been achieved using enzymes as chiral reagents. Early work by Greenstein *et al.*[14] is worth mentioning. *N*–Acetyl or *N*–chloroacetyl derivatives of racemic amino acids were digested with an enzyme from hog liver homogenates (Acylase I). The (*S*)–acylated enantiomer hydrolyses $1 \text{ X } 10^4 - 4 \text{ X } 10^4$ times faster than the (*R*)–enantiomer and separation of free amino acid from acylated derivative enables both enantiomers to be obtained in optical purities of 99.9%.

Enzymes, either purified or in yeasts or micro–organisms, can also be used to synthesize optically active molecules from achiral precursors.[15,16] They act as chiral catalysts and have several properties which make them useful for the catalysis of a broad spectrum of reactions. Enzyme reactions are usually achieved with greater efficiency and under milder conditions than standard synthetic methodology allows. They are very specific reagents and, thus, protecting groups are seldom necessary elsewhere in the molecule. They also have the ability to exert unique control over several stereochemical aspects of a single step reaction.

1.3 "THE CHIRAL POOL" AS A SOURCE OF OPTICALLY ACTIVE MOLECULES

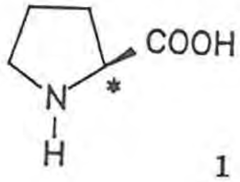
Naturally occurring chiral molecules can be used as starting points in syntheses of optically active molecules. Provided these syntheses are designed to prevent racemization of the introduced chiral centre, products of high optical purity can be expected. There are, however, several disadvantages to this approach, *viz.*,

i) the original chiral molecule is consumed in the synthesis,

ii) the range of available chiral molecules is limited, and consequently, extensive synthetic modifications are often necessary to obtain a suitable starting material, and

iii) commercially available optically pure molecules can be very expensive.

A wide variety of chiral starting materials have been used in the synthesis of important natural products. Amino acids have found extensive applications as illustrated by the use of (*S*)–proline (**1**) in the synthesis of pyrrolidine alkaloids,[17] such as compound (**2**) and by Woodward's classic synthesis of cephlalosporin C (**4**) from (*S*)–cysteine (**3**).[18] Optically pure carbohydrates are often used for the preparation of other sugar molecules,[19] while the use of chiral hydroxy acids in the preparation of prostaglandins is exemplified by the use of (*S*)–malic acid (**5**) in the synthesis of prostaglandin E_3 (**6**).[20] Chiral terpenes have also been successfully utilized *e.g.* (–) α–pinene (**7**) for the synthesis of the cannabinoid (**8**) [21] and (*S*)–citronellol (**9**) for the synthesis of the pheromone (**10**). [22]



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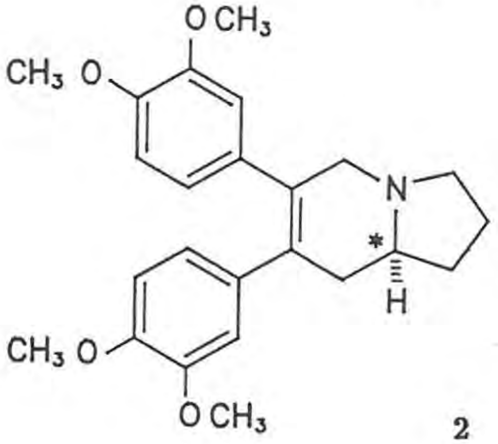

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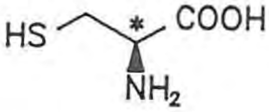

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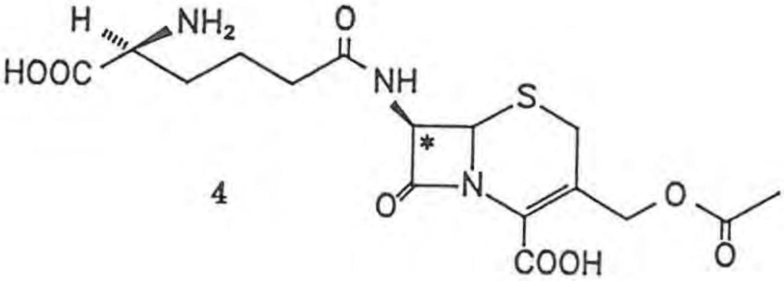

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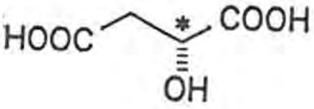

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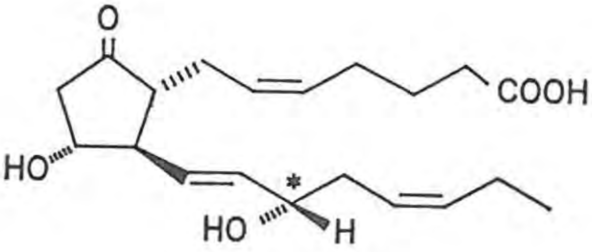

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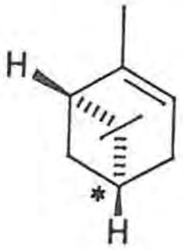

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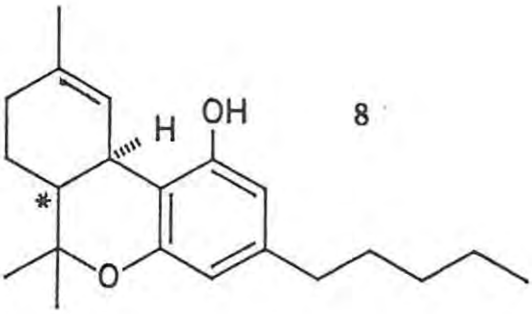

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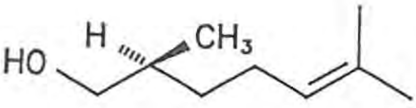

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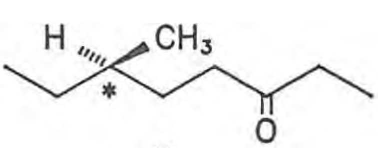

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The design of most modern syntheses of complex molecules is based on retrosynthetic analysis of the target molecule. When the target molecule is chiral the need to introduce the chirality must influence the choice of synthons. The more important considerations are:– the cost and availability of the chiral synthon (chiron); whether both enantiomers are accessible; and whether the synthetic pathway could lead to racemization of the introduced chiral centre.

1.4 ASYMMETRIC SYNTHESIS:– A Means of Obtaining Both Diastereo– and Enantiomerically Enriched Molecules

Asymmetric synthesis, in its most general form, may be described as a process whereby a prochiral unit (molecule or portion of a molecule) is converted into a chiral unit in such a way that unequal amounts of stereoisomeric products result.[23]

The foundations for asymmetric synthesis, as we know it today, were laid by Emil Fischer in 1894,[24] when he outlined his conversion of one sugar to its next highest homologue *via* cyanohydrin reactions. He assumed that in biosynthetic pathways carbon dioxide and water condensed to give formaldehyde under the influence of sunlight and chlorophyll. Further condensations were then assumed to afford more complex sugars in which each successive asymmetric carbon atom was incorporated stereoselectively. Fischer ascribed this asymmetric synthesis to the influence of optically active substances in the chlorophyll containing granules of the cells. While the modern description of the photosynthetic pathways occuring in cells is far more complex, Fischer's concept of asymmetric synthesis remains valid today.

In 1904, Marckwald [25] defined asymmetric synthesis as "....those reactions which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials[a] but with the exclusion of analytical processes." This definition has been extended and modified to accommodate recent developments.[23] Thus in 1974 Eliel [27]

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[a] In this review only optically active <u>molecules</u> will be considered, although sporadic attempts have been made to employ circularly polarized light as the optically active agent.[26]

proposed three guidelines for a good asymmetric synthesis, *viz.*,

i) it must lead to the desired enantiomer in high optical and chemical yields,

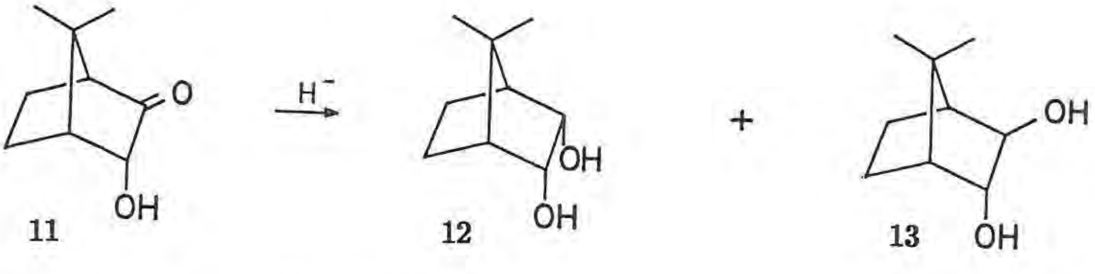
ii) the chiral product must be readily separable from the chiral auxiliary, and

iii) unless the chiral reagent is very much less expensive than the desired product, it must be possible to recover the auxiliary reagent in good yield with undiminished optical purity.

Morrison *et al.*[23] qualify the last point by adding that if the chiral reagent plays a catalytic role efficiently at low catalyst/substrate ratios then recovery of the reagent might not be essential.

It should be noted, that, in principle, it is possible to achieve a successful asymmetric synthesis that yields an achiral product, as illustrated by the reduction of the chiral hydroxy ketone (**11**) to the chiral glycol (**13**) and the achiral glycol (**12**) (Scheme 1).[28] Even if the reaction yielded 100% of the achiral compound (**12**) it would still be considered a highly successful diastereomeric transformation.

SCHEME 1

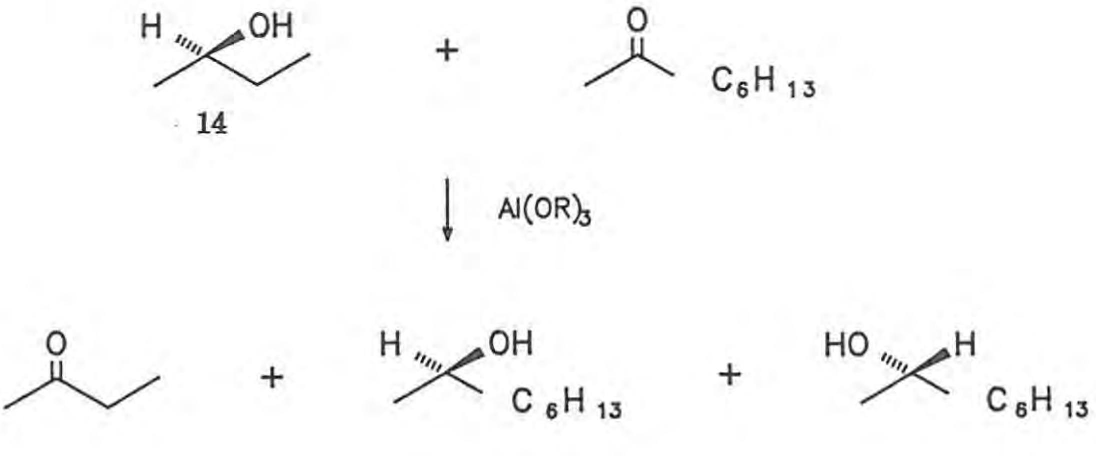


In the first half of the twentieth century very little progress was made in the field of asymmetric synthesis, although the period was not without controversy. In 1898, Japp had published a lecture on the topic "Stereochemistry and Vitalism" in which he claimed: " Only the living organism with its asymmetric tissue, or the asymmetric products of living organisms, or the living organism with its concept of asymmetry can produce this result. Only asymmetry can beget asymmetry." [29] The ensuing debate continued for many years and intensified in 1931, when McKenzie and Ritchie [30] introduced the concept of asymmetric induction to rationalize the optical activity achieved when methyl Grignard reagents reacted at the prochiral carbonyl of chiral esters of benzoyl formate. (see Section 1.4.3.3.a, p. 57.) Even at this time there were those who subscribed to the vitalistic heritage of all optically active molecules.

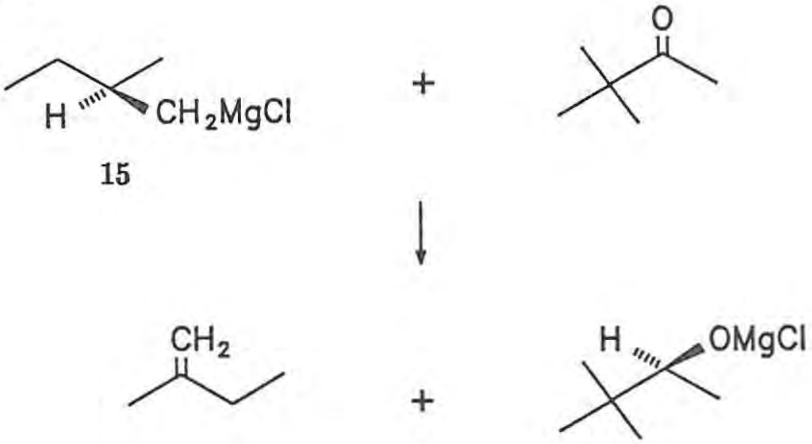
Between 1949 and 1952 several research groups began investigating reactions of ketones which yielded optically active alcohols. Doering *et al.*[31] carried out a Meerwein–Ponndorf–Verley reduction of a ketone with optically active alcohols (**14**) (Scheme 2). Mosher and La Combe.[32] (Scheme 3) and Vavon *et al.*[33] (Scheme 4) (see Section 1.4.3.1.c, p. 40) investigated reactions of chiral Grignard reagents [(**15**) and (**16**)] with ketones, in which similar reductions occurred instead of the expected Grignard addition. Prelog [34] re–examined reactions, originally carried out by McKenzie, of Grignard reactions of α–keto esters (prepared from optically active alcohols) which afforded α–hydroxy acids. Although Prelog's work has been developed into a method for establishing the configuration of secondary alcohols (see Section 1.4.3.3.a, p. 57) it can nevertheless be regarded as one of the pioneering efforts in the use of chiral auxiliaries for asymmetric synthesis.

Initial attempts to rationalize asymmetric synthesis were based on diastereoselective reactions in which a diastereomeric excess is obtained when a racemic compound undergoes reaction at a prochiral centre. This approach still receives considerable attention today and will be discussed in

SCHEME 2



SCHEME 3



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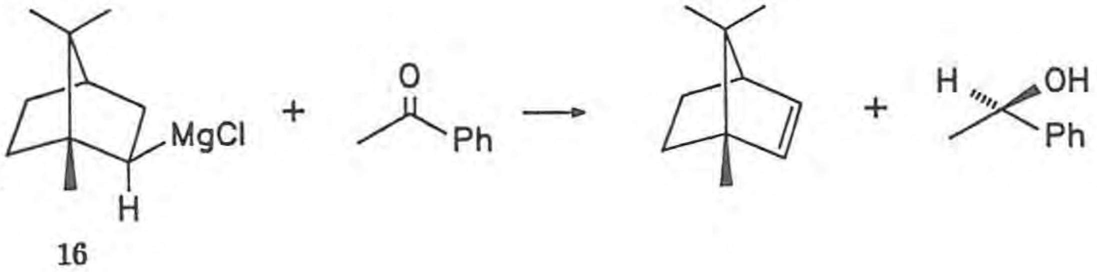
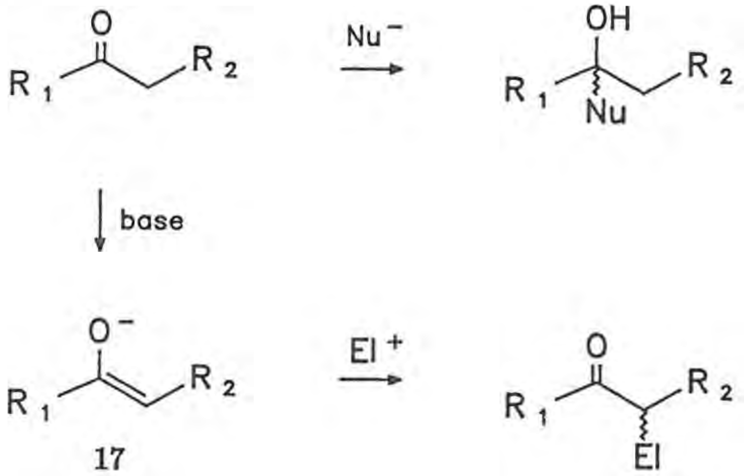


Section 1.4.1. (p. 14). The development of diastereoselective reactions contributed to the emergence of another, possibly more important, approach to asymmetric synthesis, *viz.*, enantioselective reactions, in which reactions at a prochiral centre yield the two possible stereoisomers in unequal amounts (Section 1.4.3, p. 29).

Reactions of the carbonyl group have been central to the development of asymmetric synthesis from the earliest investigations. This emphasis may be attributed to the ability of the carbonyl functionality to behave either as an electrophile or as a nucleophilic enolate (17), in a number of carbon–carbon bond forming reactions (Scheme 5). In the present review, attention will focus, largely, on these versatile and synthetically ubiquitous systems.

SCHEME 5



1.4.1 DIASTEREOSELECTIVE REACTIONS

Diastereoselective syntheses involving carbonyl compounds will be illustrated by means of three different types of reactions, *viz.*,

nucleophilic additions to the carbonyl group (section 1.4.1.1),
enolate alkylations (section 1.4.1.2, p. 18), and
aldol addition reactions (section 1.4.1.3, p. 23).

1.4.1.1 Diastereoselection in Nucleophilic Additions to the Carbonyl Group.

In 1952 Cram and Abd Elhafez [35] described Grignard reactions of aldehydes and ketones having a chiral centre adjacent to the carbonyl group. This research led to the well known Cram's rule for steric control of asymmetric induction, which is generally applicable to reactions of carbonyl compounds with organometallic and metal hydride reagents. In terms of the rule, the molecule is orientated so that the carbonyl group is flanked by the two smaller α–substituents (M and S) and the largest (L)[b] is eclipsed with the alkyl substituent (R). The nucleophile then approaches from the side of the smallest substituent (Figure 1a). The stereoselectivity of this type of reaction is seldom high. One successful example is the LAH reduction of α–phenyl ketones (**18**) where R_2 is *t*–butyl [36] (Scheme 6).

Several attempts have been made to refine the Cram model. *Ab initio* calculations were conducted by Anh and Eisenstein,[37] and the Felkin model [38] agrees best with these calculations (Figure 1b).

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[b] The L, M, S notation will always be used in this thesis although some authors prefer the R_L, R_M and R_S notation for the three α – substituents.

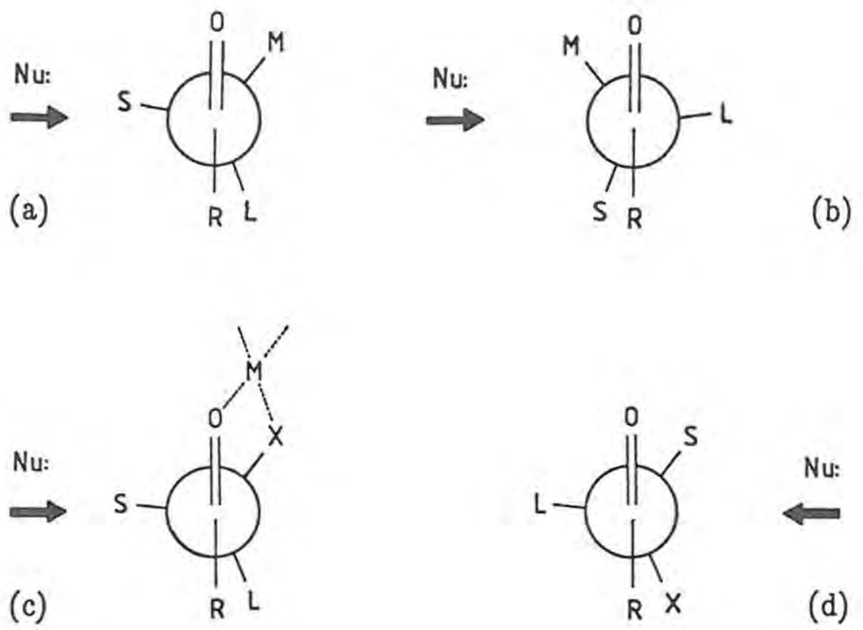
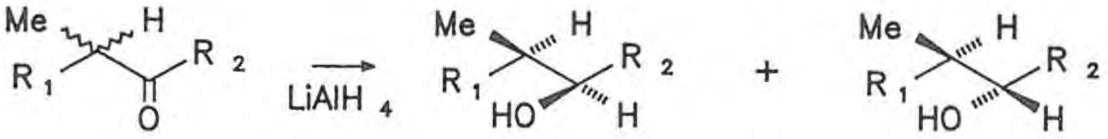


FIGURE 1 Representations of: (a) Cram's rule, open chain model; (b) Felkin's model; (c) Cram's rule, chelate, cyclic or rigid model; (d) Dipolar model.

SCHEME 6



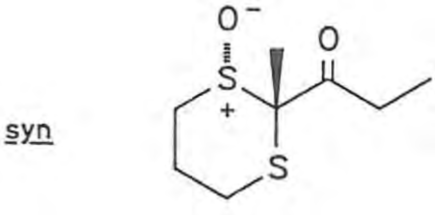
18 Major Minor

TABLE 1 Increase in stereoselectivity of the reaction in Scheme 6 as the steric bulk of the achiral group (R_2) increases

R_2	% d.e. (R_1= Ph)
Me	48
Bu^t	96

A second model was developed by Cram [38] to explain a steric outcome different to that predicted by his original rule, when one of the α–substiuents (*e.g.* OH, OR or NRR′) can chelate with the organometallic reagent . This invokes a cyclic model in which chelation holds the carbonyl and α–heteroatom *ca.* co–planar. The nucleophile subsequently approaches from the side of the smaller of the remaining substituents. This model is often referred to as the rigid or chelate model (Figure 1c). There are numerous examples in which high diastereomeric excesses may be rationalized in terms of the chelate model. A recently cited example is the the diastereoselective addition of Grignard reagents to 2–acyl–1,3–dithiane–1–oxides (**19** and **20**).[39] These compounds are easily prepared in a three step process from 2–alkyl–1,3–dithianes and the desired aldehydes. The resulting *syn* and *anti* diastereomers are separated by chromatography and subjected to attack by methylmagnesium iodide. The approach of the nucleophile to the chelated transition state of the *syn* substrate is directed by the large dithiane ring towards the face occupied by the considerably smaller methyl group. In the *anti* substrate, on the other hand, the chelation holds the dithiane ring approximately co–planar with the carbonyl group and, thus, only the methyl group (orthogonal to this plane) exerts an influence, resulting in less effective control than in the *syn* chelate. In both cases, however, the product distribution is as predicted by the chelate model (Figure 2a and b), yielding, under optimal conditions, exclusively one diastereomeric alcohol for the *syn* substrate and a diastereomeric ratio of 3:1 for the *anti* substrate.

A fourth model was proposed by Cornforth *et al.*[40] in which one of the α–substituents, X, is a dipolar, electronegative group. The carbonyl and C–X dipoles orientate themselves in an anti–periplanar manner and the approach of the nucleophile is from the side of the smaller of the remaining α–substituents.



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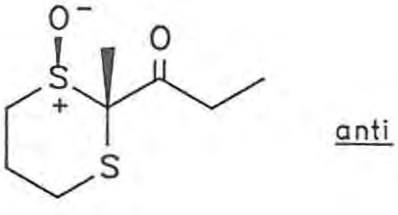

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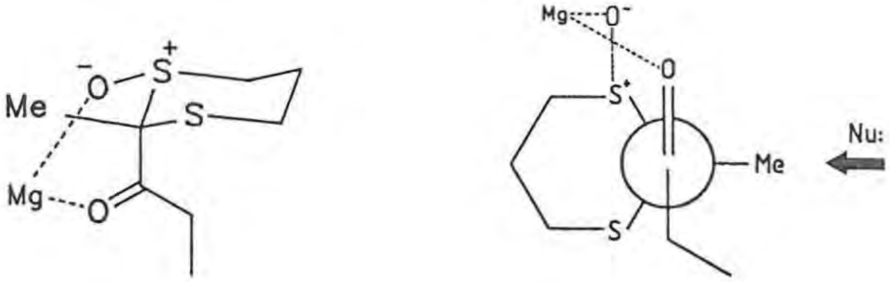
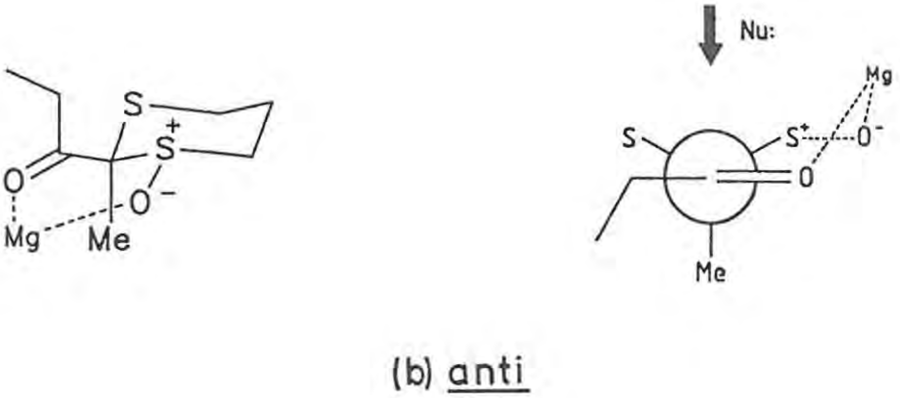
FIGURE 2 Chelated Cram type transition states for; (a) the *syn* substrate (**19**), (b) the *anti* substrate (**20**). The arrows indicate the preferred approach of the nucleophile in each case.



(a) syn



(b) anti

The dipolar model invariably predicts the opposite diastereomer to the chelate model because X is now on the opposite side of the molecule to the carbonyl oxygen and appears only to apply when X is a halogen or, in some cases, in preference to the chelate model, when $X = O^- Li^+$ or $O^- Mg^+$(Figure 1d).

All of the above models have similar limitations. The assignment of L, M or S is often difficult since it is not always the overall volume of the group that determines its behaviour *e.g.* a phenyl group must always be considered larger than a long aliphatic chain because, although it occupies a smaller volume, the effective bulk of the phenyl ring is concentrated in the close vicinity of the reaction site. In some cases it is difficult to discern whether a chelate or dipolar model is appropriate. The stereochemical course of the reaction can often be reversed by altering the solvent, reaction temperature, or reagent.

1.4.1.2 Diastereoselection in Enolate Alkylations

The enolization of non–symmetrical, cyclic, or acyclic ketones is generally accompanied by the possibility of two regioisomeric enolates, *viz.*, the kinetic and thermodynamic products. In certain acyclic ketones further complications are introduced by enolate geometric isomerism. Selective approaches to either the kinetic or thermodynamic product are now routine and comprehensive reviews are available. [41,42] As will be seen, in most cases where enolate alkylations occur with significant diastereoselectivity, the enolate geometry is predetermined and thus plays only a secondary role in determining the stereochemical outcome of the reaction. In aldol reactions the enolate geometry plays a more substantial role in the stereochemical control and the factors influencing enolate geometry will thus be considered when diastereoselective aldol addition reactions are discussed (Section 1.4.1.3, p. 23).

The diastereoselective reactions of alkyl halides with chiral enolates have probably been as well documented as nucleophilic additions to carbonyl groups. From the extensive activity in this field has emerged a comprehensive understanding of transition state structures and the factors that dictate enolate π–facial selectivity. Proximal chiral centres render the two faces of the enolate diastereotopic and the π–facial selectivity is influenced by both steric and stereoelectronic effects in the diastereomeric transition states.

Various stereoelectronic effects concerned with geometric constraints in the transition state may influence enolate alkylations.[43] When one of the possible transition states is significantly stabilised there will be an energetic advantage for the formation of the corresponding diastereomer. Diastereoselectivity is observed in the alkylation of enolates (**21**) obtained from substituted cyclohexanones (Scheme 7). Axial addition is postulated to proceed *via* a chair–like transition state and equatorial addition *via* a twist–boat conformation (**22**) to afford products (**23**) and (**24**) respectively. The greater stability of the chair form is proposed as the stereoelectronic reason for the selectivity obtained.[44] However, numerous examples indicate that several factors may influence the extent of stereoelectronic control. In compliance with the Hammond postulate,[45] that strongly exothermic processes proceed *via* transition states in which only a small perturbation from the reactant geometry has been incurred, the axial/equatorial selectivity will be small in highly exothermic enolate alkylations (Entry 1, Table 2).[46] As the reaction's exothermicity decreases, larger perturbations in the transition state geometry occur, with a concomitant increase in preference for axial alkylation (Entry 2, Table 2).[46] Furthermore, reduction in enolate nucleophilicity, as illustrated by the stabilized β–keto ester enolate (Entry 3, Table 2),[47] enhances axial alkylation.

SCHEME 7

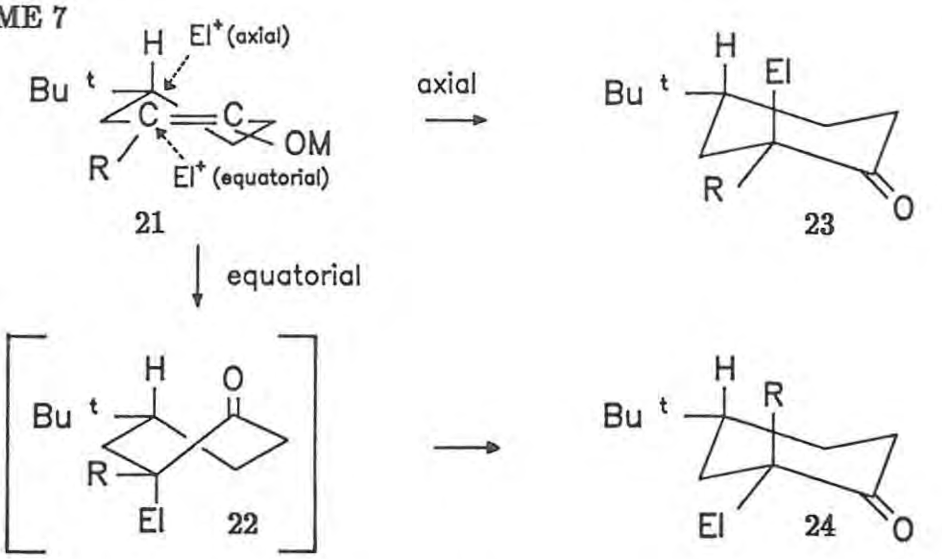


TABLE 2 Diastereoselectivitities of electrophilic reactions of enolate (21) under stereoelectronic control.

M	R	El	23:24
Li	H	MeI	55:45
Li	Et	HOAc/H_2O	80:20
Li	CO_2Et	MeI	83:17

SCHEME 8

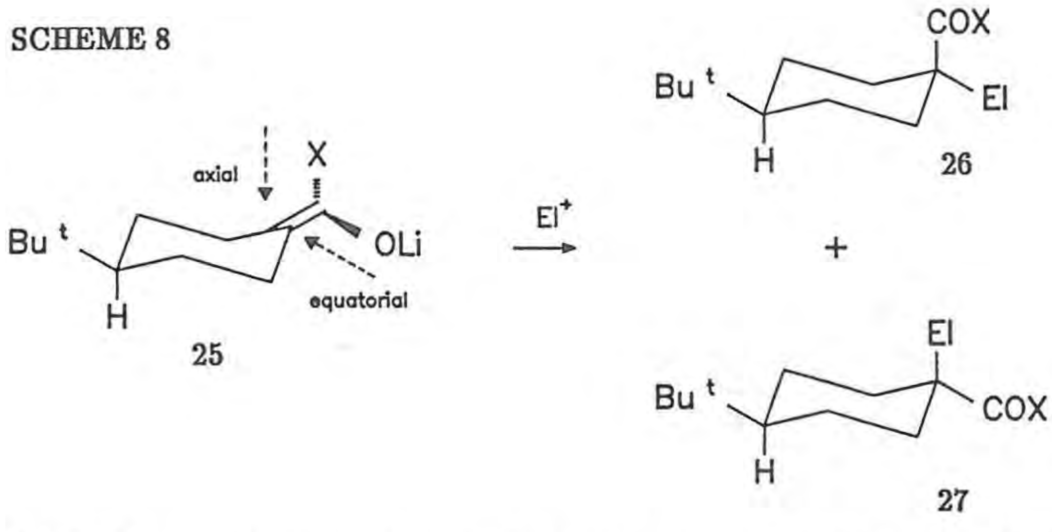


TABLE 3 Diastereoselective reactions of enolate (25) with alkyl halides under steric control.

X	El	26:27
Me	MeI	85:15
OMe	n-C_4H_9Br	87:13

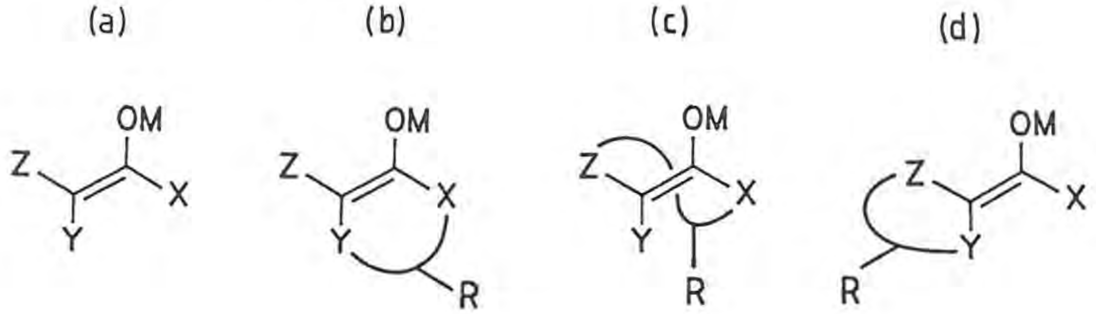
In most instances, however, π–facial selectivity is largely determined by steric factors. In these cases, reagent approach to one of the faces is sufficiently hindered by substituents to provide significant diastereoselection. A good example is the alkylation of the conformationally fixed enolate (**25**) (Scheme 8), investigated by both House and Bare,[48] and Krapcho and Dundulis.[49] In this case the geometric constraints imposed on both diastereomeric transition states are equivalent since the substrate is conformationally rigid. In all cases an equatorial approach is the preferred one, although the structure and nucleophilicity of the enolate and the nature of the electrophile influence the extent of the control.

Chirality transfer during enolate alkylations can be divided into three structural classes, *viz.*,

a) intraannular chirality transfer,
b) extraannular chirality transfer, and
c) chelate–enforced intraannular chirality transfer.

a) In intraannular chirality transfer the chiral centre is contained in a covalently bonded ring joined to the enolate framework at two points, as illustrated in Figure 3 where X, Y and Z represent the three possible connective points for cyclization and the chiral centre may be any carbon atom in the cycle.[50] The enolate geometry is generally fixed, except in the instances where the ring is large enough to accommodate the two geometric isomers. The facial selectivity appears to be predominantly steric, with the extent of stereoelectronic control depending on the nature of the substrate.

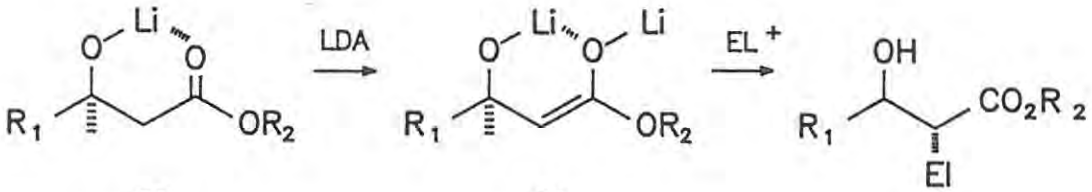
FIGURE 3 (b), (c) and (d) represent the three possible cyclic enolates obtained by co–valent bonding of the ring containing the chiral centre to any two of the connective points, X, Y or Z of (a).



b) In extraannular chirality transfer the chiral centre is only covalently bonded to the enolate *via* a single covalent bond. Consequently there is no conformational rigidity and thus diastereoselectivity is seldom significant.

c) Chelate–enforced intraanular chirality transfer is conceptually similar to the cyclic Cram model for diastereoselective addition to carbonyl compounds. Metal ion chelation fixes the stereochemical relationship between the chiral centre and the enolate moiety. A classic illustration is the alkylation of β–hydroxy ester enolates (Scheme 9). Initial abstraction of the hydroxyl proton yields the chelate (**28**) and further deprotonation of this conformationally rigid system can only yield the *Z* enolate (**29**). The ensuing alkylation often proceeds with high diastereoselection.[51,52]

SCHEME 9



28 **29**

1.4.1.3. Diastereoselection in Aldol Addition Reactions.

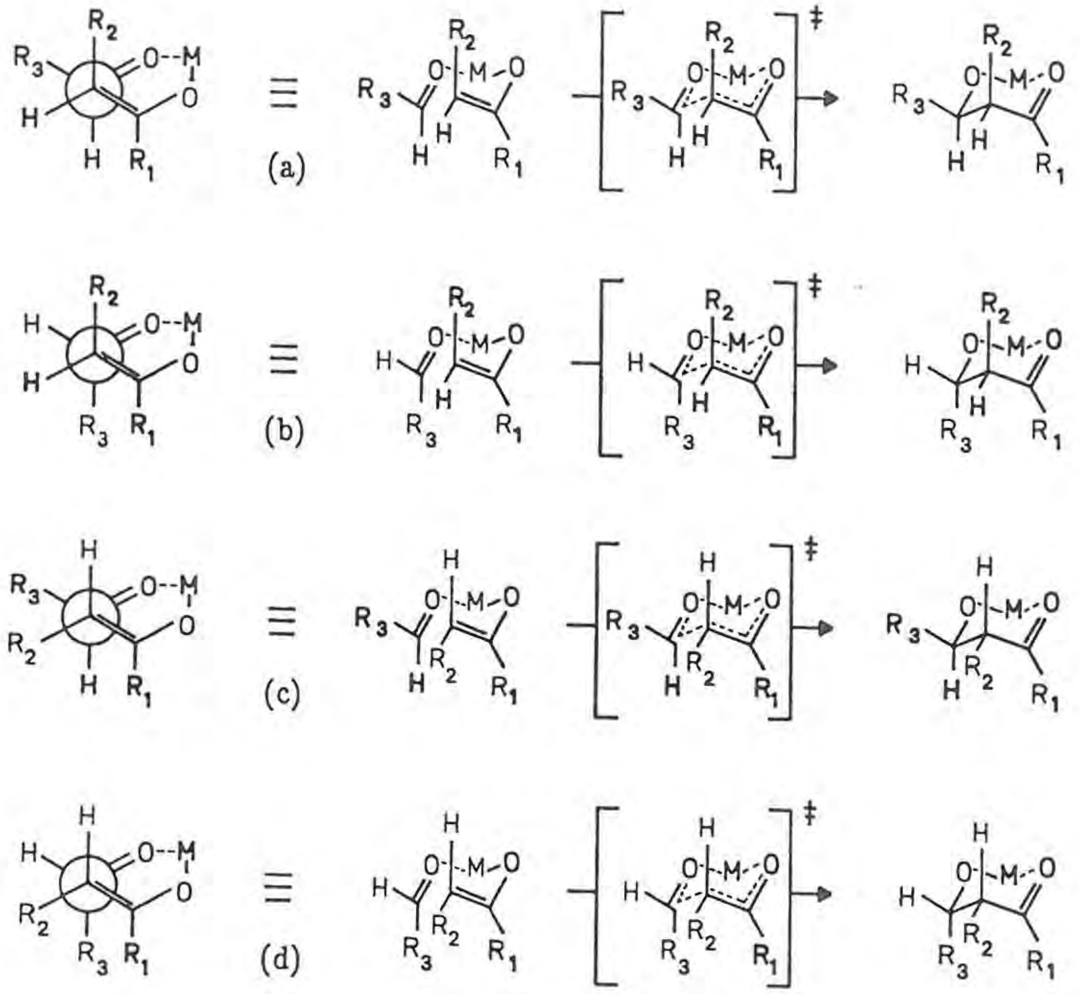
The reactions of carbonyl enolates with aldehydes or ketones, aldol reactions, have been known since 1838.[53] Diastereoselective aldol reactions are a combination of the two types of diastereoselections that have already been considered in Sections 1.4.1.1, p. 14 and 1.4.1.2, p. 18.

Since the early 1970's there have been extensive investigations into the stereochemical implications of these reactions. The reaction of a prochiral aldehyde or ketone with an enolate with homotopic π–faces yields a pair of enantiomeric aldols. If the enolate is also prochiral then a pair of racemic diastereomers will result. When one of these racemic diastereomers is formed preferentially then simple diastereoselection is said to have occurred.

The geometry of the enolate is central to control of the relative configuration at the two new chiral centres formed in the aldol reaction, under conditions of kinetic control. The stereochemistry of enolate formation is clearly understood and methods are available in many instances to selectively obtain either the *Z*– or *E*–isomer. There are a variety of approaches to the aldol reaction utilizing, for example enolates of Group I and Group II metals, certain transition metals, or Lewis acid catalysed reactions of silyl enol ethers. Each approach requires a separate analysis of the resulting stereochemistry. Diastereoselection of this type will be illustrated by means of the reactions of lithium and magnesium enolates. [The reactions of silyl enol ethers with aldehydes and ketones, developed by Mukaiyama,[54] will be considered in greater detail in the Discussion (Section 2.3.3, p. 180), when dealing with our own asymmetric adaptations of this reaction.]

When metals from Group I or II are the enolate counter ions, then the

FIGURE 4 Zimmerman–Traxler transition states: (a) *Z* enolate → *syn* aldol; (b) *Z* enolate → *anti* aldol; (c) *E* enolate → *anti* aldol; (d) *E* enolate → *syn* aldol.



Z–enolates favour formation of the *syn*–aldol and the *E*–enolates favour the *anti*–aldols.[c] Heathcock [55] has rationalized this correlation *via* Zimmerman – Traxler transition states, first proposed to explain the Ivanov condensation of phenylacetic acid with benzaldehyde.[56] This closed transition state model analyses the four possible transition states from the *E*– and *Z*–isomers as

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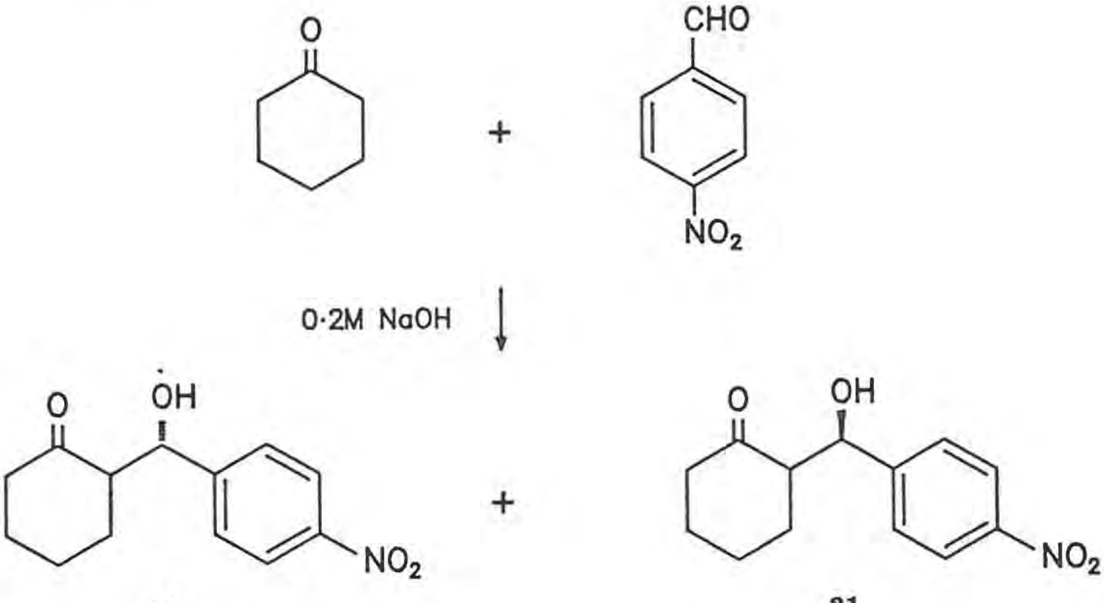
[c] In this review the *syn*, *anti* convention will be used to describe the relative stereochemistry of two chiral centres, assuming the carbon chain containing these asymmetric centres is drawn in an extended or zig–zag manner.

shown in Figure 4. In the case of the *Z*–enolates the dominant $R_1 - R_3$ interaction resulting in a preference for transition state (a) over (b) and thus predominant formation of the *syn*–product. The $R_1 - R_3$ interaction in the case of the *E*–enolates yields the *anti*–aldol *via* the preferred transition state (c).

The validity of this analysis is illustrated by the work of Stiles *et al.* on cyclohexanones.[57] Cyclohexanones can only form the *E*–enolate for geometric reasons and by reacting these enolates with *p*–nitrobenzaldehydes, Stiles obtained aldol products (**30**) and (**31**) in ratios of 1.8:1 to 4.4:1 depending on reaction conditions (Scheme 10).

SCHEME 10



30 **31**

The extent to which the above relationship between enolate geometry and relative stereochemistry holds is dependant on the size of group R_1 as illustrated by the reactions of a number of lithium enolates (**32**) obtained from ethyl ketones, with benzaldehyde (Scheme 11).[58] When R_1 is small, *e.g.* H, there may be no simple diastereoselection or the *syn:anti* ratio may be

SCHEME 11

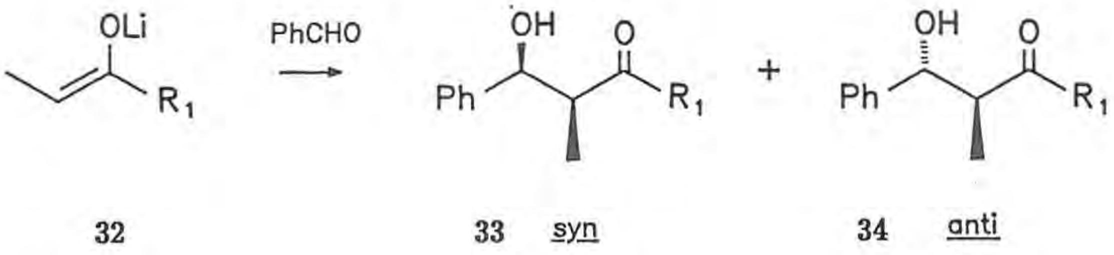


TABLE 4 Increasing simple diastereoselection of electrophilic reactions of enolate (**32**) as the size of R increases.

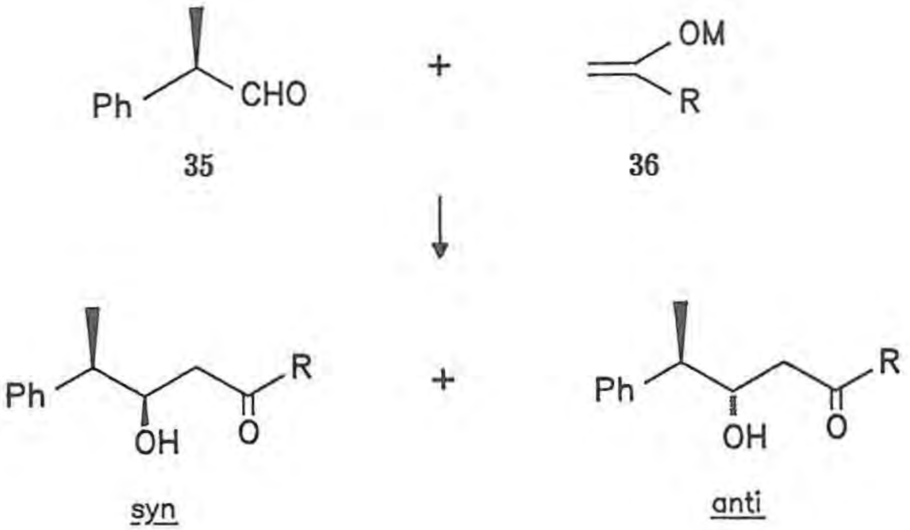
R_1	**33:34**
H	50:50
Pr^i	90:10
Bu^t	98:2

inverted. When the size of R_1 is significantly increased by introducing a *t*–butyl group the *syn:anti* ratios are as predicted by the transition state analysis. Improvements to the Zimmerman – Traxler transition state model have been made to rationalize further perturbations *e.g.* the skewed transition state.[58]

The preceding examples of the aldol reaction have involved achiral enolates and carbonyl compounds. When the aldehyde is chiral a different analysis is required. Chiral aldehydes have diastereotopic carbonyl faces. In this type of reaction diastereofacial selectivity becomes an additional factor in determining the distribution of the resulting diastereomers. The preferred diastereomer can often be predicted using Cram's rule or one of the updated versions thereof (see Section 1.4.1.1, p. 14). A reaction that illustrates this idea is that of

2–phenylpropanal (**35**) with a variety of enolates (**36**). The lithium enolates of acetone, pinacolone, methyl acetate and *N*,*N*–dimethylacetamide all give *syn*:*anti* ratios of approximately 3:1 [59] (Scheme 12). This selectivity is attributed to kinetic control as there is no apparent reason, in this case, why the *syn*–isomer should be more stable than the *anti*–isomer.

SCHEME 12

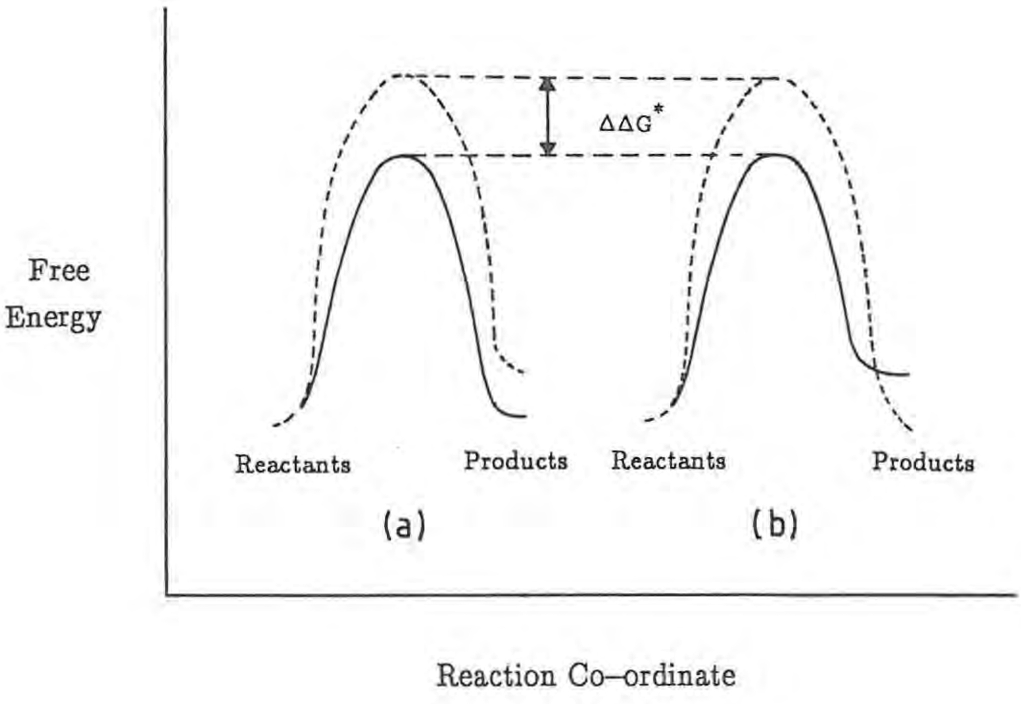


Other approaches to stereocontrolled aldol reactions include reactions of achiral carbonyl compounds with chiral enolates. Much of the reported work in these areas involves reactants which are not merely chiral, but also optically active, thus involving chirality transfer. These reactions are therefore no longer merely diastereoselective and appropriate examples will be considered when dealing with chiral auxiliaries (Section 1.4.3.3, p. 55). Another possibility is the reaction of homochiral carbonyl compounds with homochiral enolates, a strategy in asymmetric synthesis that is now known as double stereodifferentiation or double asymmetric synthesis. Double asymmetric synthesis has also been extensively investigated in three other major organic reactions, besides the aldol reaction, (*viz.*, the Diels–Alder reaction, catalytic hydrogenation and epoxidation).[60]

1.4.2 TRANSITION STATE THEORY AND ASYMMETRIC INDUCTION.

It can be clearly seen, from the diasteroselective reactions discussed above, that differences in the energies of diastereomeric transition states are crucial to effective asymmetric induction in kinetically controlled reactions. In principle, generation of a new chiral centre in an already chiral environment may be expected to involve two diastereomeric transition states or intermediate complexes. In an enantioselective reaction (involving the synthesis of optically active product) the reactant would be a single isomer (*e.g.* a prochiral substrate linked to a chiral auxiliary) whereas in a diastereoselective reaction, the reactant would be a racemic mixture. In either case the difference in free energies of activation ($\Delta\Delta G^*$) for the two competing pathways determines the extent of the asymmetric control. The ground state free energies of the products are not involved (Figure 5) since the question of whether, or not, the pathway of lower activation energy yields the product of lower free energy (Figure 5a versus 5b) is irrelevant in a kinetically controlled reaction.

FIGURE 5 Energy – reaction co–ordinate diagram for kinetically controlled asymmetric reactions.



1.4.3 ENANTIOSELECTIVE REACTIONS

Having discussed the historical background to asymmetric synthesis and the development of diastereoselective reactions, strategies for the synthesis of optically active molecules (involving enantioselective reactions) will now be considered. These strategies depend on the availability of enantiomerically pure molecules and, for the purposes of this introduction, they have been classified into three broad categories. These divisions may, in certain instances, be somewhat artificial or tenuous but, in general, they provide a useful system of classification.

The three categories are:

- i) the use of optically active reagents (Section 1.4.3.1, p. 30);
- ii) the use of chiral catalysts (Section 1.4.3.2, p. 44); and
- iii) the use of chiral auxiliaries – this approach being the particular focus of the present study (Section 1.4.3.3, p. 55).

Also included in this description of enantioselective syntheses is a review of the enantioselective reactions of optically active organosilanes
(Section 1.4.3.4, p. 75).

1.4.3.1 Optically Active Reagents

This category includes chiral reagents which generate new chiral centres in prochiral substrates. This type of approach is illustrated by two reaction types that generate a chiral centre without the formation of a new carbon–carbon bond, *viz.*,

a) asymmetric hydroborations, and

b) asymmetric reductions of carbonyl groups (p. 33),

as well as the reactions of several organometallic reagents, classified together as

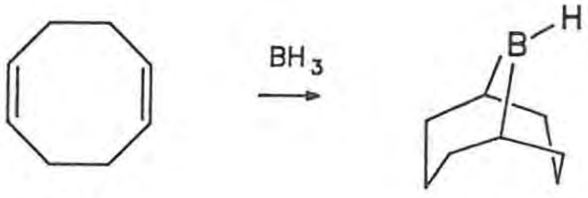
c) asymmetric carbon–carbon bond formation *via* optically active reagents (p. 40).

a) Asymmetric Hydroboration

Hydroboration[61-64] takes place with good regioselectivity if the alkene is unsymmetrical. Although both steric and electronic factors contribute to this selectivity, the steric influence is believed to be dominant. When both olefinic carbons are either monosubstituted or disubstituted, the typically poor regioselectivity achieved using BH_3 can be significantly improved by using sterically demanding organoboranes [*e.g.* 9–borabicyclo[3.3.1.]nonane (9–BBN) (**38**), prepared by the hydroboration of 1,5–cyclooctadiene (**37**) (Scheme 13 [65])].

The development of organoboranes in which the alkyl groups are **optically active** has led to some of the best known optically active reagents. These optically active organoboranes have been successfully applied to asymmetric hydroborations and reductions and a review of both of these aspects of chiral

SCHEME 13



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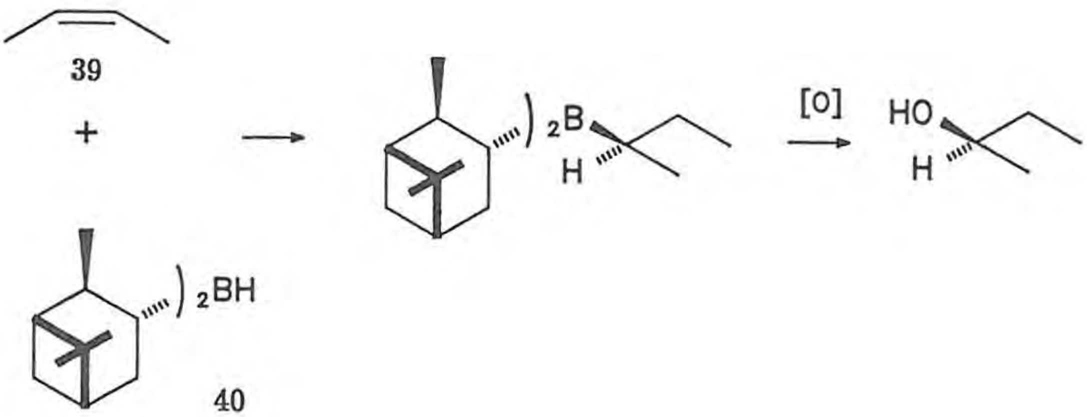
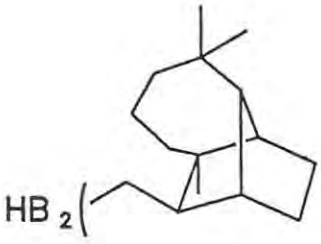
SCHEME 14





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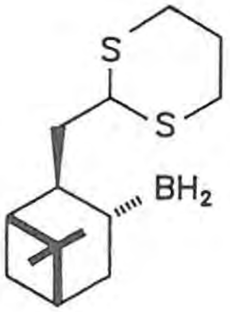

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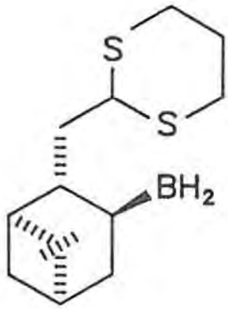

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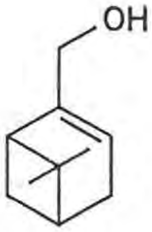

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organoborane chemistry has been published by Brown *et al.*[66] Diisopinocampheylborane (40), first prepared (by the hydroboration of α–pinene) and utilized in asymmetric hydroboration by Brown *et al.*,[67] produces alcohols from *cis*–alkenes in high optical yields. Improved syntheses afforded the reagent (40) in 99.8% optical purity and this material effects hydroboration of *cis*–butene (39) in 98.4% enantiomeric excess [68] (Scheme 14). Brown's early successes with this reagent, in 1961, are regarded as marking the beginning of practical, nonenzymatic asymmetric synthesis.

Diisopinocampheylborane induced hydroboration of <u>hindered</u> alkenes does not proceed with material or optical yields as high as those obtained with *cis*–alkenes. This shortcoming led to the development of dilongifolylborane (41) [69] and monoisopinocampheylborane (42) [70] increasing even further the versatility of asymmetric hydroborations. Stereocontrol is once again achieved *via* selective transition state formation, the chiral hydroborating agent preferentially approaching the enantiotopic face of the prochiral alkene to create the transition state with the minimal steric interaction.

It is usually very difficult to prevent the hydroboration of alkenes going beyond the monoalkylated stage, rendering the synthesis of monoisocampheylborane (42) by direct hydroboration, impossible. Brown [71] has developed several indirect syntheses to the monoalkylborane but more readily available mono-alkylhydroborating agents are continually being sought. One of the most recent alternatives to monoisocampheylborane is (+)– and (–)–[2–(1,3–dithianyl)]-myrtanylborane (43) and (44), which are solid, stable monoalkyl boranes, prepared in several steps from the corresponding enantiomers of myrtenol (45). The reaction is restricted to monohydroboration, due to intramolecular stabilization, facilitated by the dithiane ring. The enantiomeric excesses of the alcohols obtained from the hydroboration – oxidation of prochiral alkenes using these reagents [(**43**) and (**44**)] compare favourably with those obtained using monoisocampheylborane.[72]

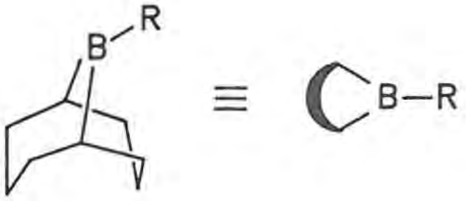
b) Asymmetric Reduction of Carbonyl Groups

Mono (**42**) – and diisopinocampheylborane (**40**) have been applied to the asymmetric reduction of ketones but the enantiomeric excesses achieved are considerably lower than those obtained in hydroboration reactions with these reagents. (Table 5).[66,73]

TABLE 5 Percentage enantiomeric excesses achieved in the reduction of carbonyl groups using mono (**42**) – and diisiocampheylborane (**40**).

Ketone	**40**	**42**
$C_2H_5COCH_3$	13	22
$(CH_3)_2CHCOCH_3$	37	46
$C_6H_5COCH_3$	9	15

The development of the trialkyl organoborane *B*–alkyl–9–borabicyclo[3.3.1]-nonanes (abbreviated *B*–alkyl–9–BBN) (**46**) by Midland *et al.*,[74] established the use of trialkyl organoboranes in reductions of carbonyl compounds (aldehydes rapidly at room temperature; ketones only under forcing conditions). The reaction is believed to proceed *via* a cyclic mechanism in which the *β*–hydride of the organoborane is transferred to the carbonyl carbon in a Meerwein–Ponndorf–Verley type process (Scheme 15).[74,75]



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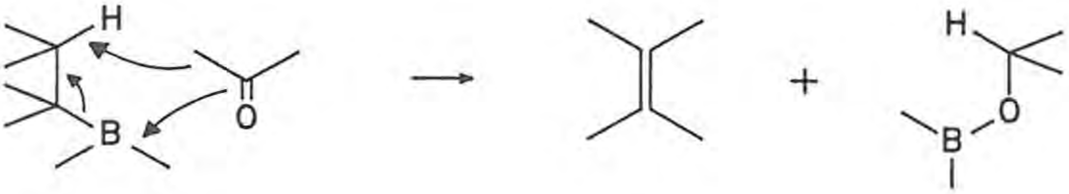
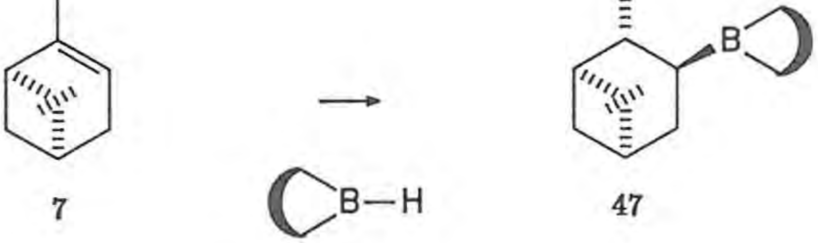
SCHEME 15



The high regio– and stereospecificity of hydroborations in general and of 9–BBN (**38**) mediated reactions in particular, enables **optically active reducing agents** to be prepared by the hydroboration of enantiomerically pure terpenes *e.g.*[α–pinene (**7**) or camphene] with 9–BBN (**38**) (Scheme 16).[76] The hydroboration product from α–pinene, commercially available from Aldrich Chemical Company, under the trade name Alpine–borane (**47**), effects the reduction of aldehydes in very high enantiomeric excesses.[76]

SCHEME 16



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In general the reduction of ketones with Alpine–Borane requires rigorous conditions and lengthy reaction times, and this reduction usually occurs with significantly reduced enantiomeric excess.[77] (Propargyl ketones,[78] α–haloketones, and α–keto esters [79] are atypical ketones in this regard, being reduced with good enantioselectivity.) The reduction in asymmetric control occurs because, during the extended reaction times, a second reduction mechanism, with a slower rate determining step, becomes significant. In addition to the cyclic β–hydride transfer, dehydroboration of Alpine–Borane (**47**) to 9–BBN (**38**) occurs and the reduction then proceeds *via* this achiral dialkyl borohydride.[75] To accomplish enantioselective reductions of ketones the dehydroboration pathway must be suppressed.[80] One of the most recent approaches to achieve this suppression is to conduct the reaction at elevated pressure, (typically 2000 atm). This is believed to accelerate the desired cyclic mechanism and reductions with moderate enantiomeric excesses have been achieved.[81]

An alternative approach to asymmetric reduction of carbonyl groups is to modify the classic reducing agents, lithium aluminium hydride (LAH) and sodium borohydride ($NaBH_4$), with chiral ligands. Reductions with a variety of optically active LAH derivatives have yielded only poor to modest enantiomeric excesses. The chiral ligands employed include terpene alcohols,[82] proline derived pyrrolidines,[83] and alkaloids [84]. A more successful modification has been the successive treatment of LAH with one equivalent of ethanol and then one equivalent of the (*R*)–binaphthol (**48**). Use of this modification to prepare the (*R*)–alcohol from acetophenone in almost 100% enantiomeric excess has been rationalized in terms of a diastereomeric, six–membered, cyclic transition state (Figure 6a) in which unfavourable interaction between the phenyl and binaphthyl group (Figure 6b) is eliminated.[85] However, this reagent gives only moderate enantioselective control when reducing acyclic ketones (*e.g.* 2–octanone is reduced to 2–octanol in only 24% enantiomeric excess). This failure can be rationalized in terms of the same mechanism since the effective steric bulk of different alkyl groups is small and thus the distinction between the two faces of the carbonyl group is also small.

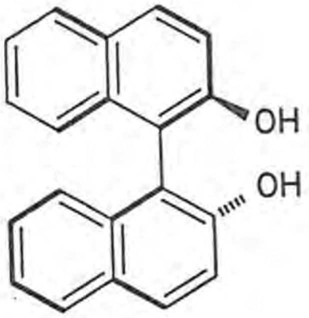

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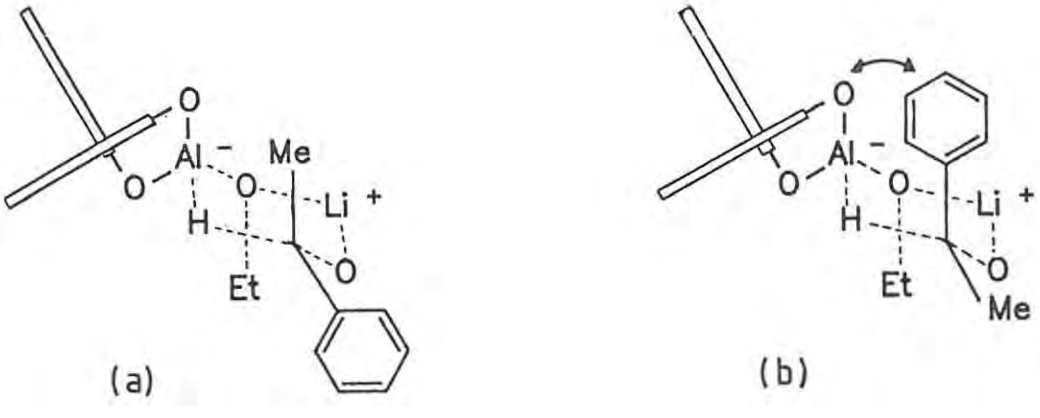
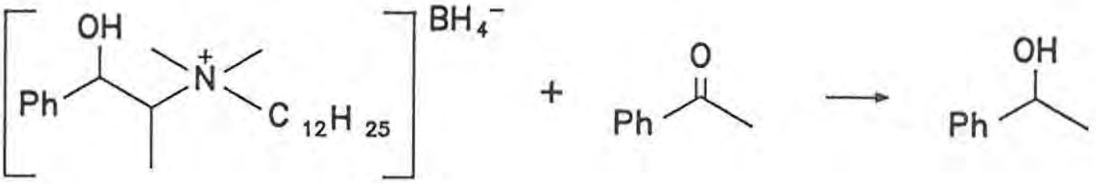
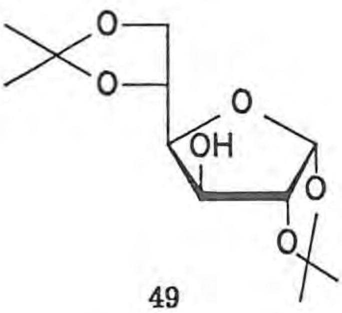
FIGURE 6 The two possible cyclic transition states for the reduction of acetophenone using the reducing agent derived from the treatment of LAH with ethanol and (*R*)–binaphthol.



$NaBH_4$ reductions are usually carried out in water or ethanol because the reagent is insoluble in many organic solvents. Alternatively such reductions

SCHEME 17





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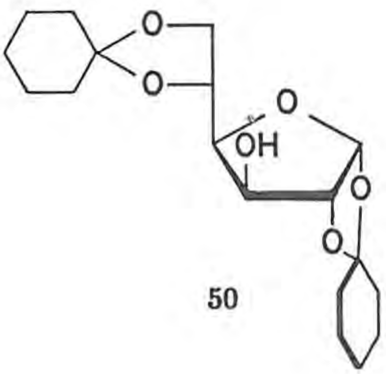

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TABLE 6 Percentage enantiomeric excesses achieved in the reduction of ketones using hydroxy monosaccharides (49) and (50) in the presence of either a Lewis – or carboxylic acid.

Ketone	49	49 – $ZnCl_2$	49 – RCO_2H	50 – R′ CO_2H
$C_6H_5COCH_3$	59	41	64	44
$C_6H_5COC_2H_5$	29	55	63	39

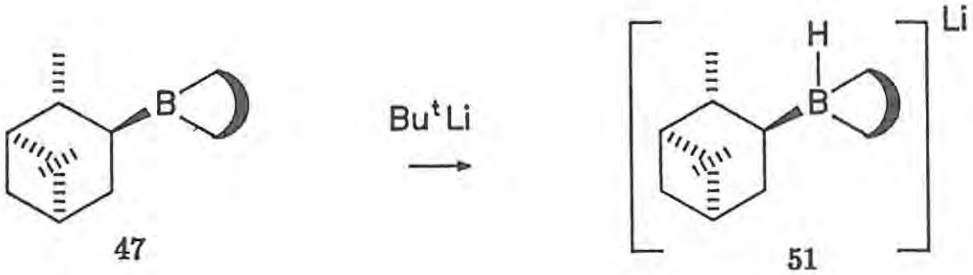
R = $(CH_3)_2$ CH

R′ = (±)-$C_6H_5CH(C_2H_5)CO_2H$

may be effected in organic solvents under phase transfer conditions. Asymmetric reductions have been attempted by replacing the sodium cation with an optically active ammonium ion, to afford an ionic species which serves both as a chiral template and a phase transfer catalyst. The enantioselectivity achieved by this approach is usually poor, the best result being the reduction of acetophenone in 39% enantiomeric excess (Scheme 17).[86] Both Morrison *et al.*[87] and Hirao *et al.*[88] have reduced ketones, in modest enantiomeric excesses, using $NaBH_4$ in the presence of monosaccharide derivatives (**49**) or (**50**). These reactions also require the addition of either a Lewis acid or a carboxylic acid to achieve the quoted yields and enantiomeric excesses (Table 6).

One of the more successful developments in asymmetric synthesis has been the "superhydride" class of trialkylborohydride reducing agents, which can be prepared by the reaction of trialkyl boranes with lithium hydride [89] or *tert*–butyllithium.[90] Treatment of "Alpine–borane" (**47**) with *tert*–butyllithium yielded lithium *B*–3–pinananyl–9–BBN–hydride (**51**) (marketed by Aldrich Chemical Company as "Alpine–Hydride") (Scheme 18).

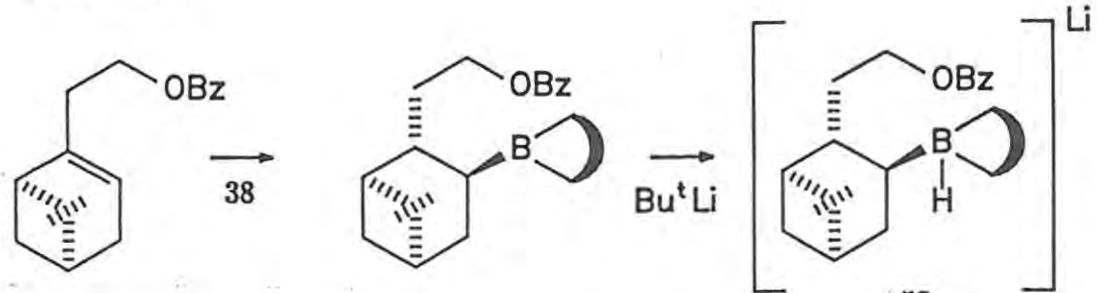
SCHEME 18



This reagent, however, has not been as successful as other boron reagents with similar chiral ligands [91] and following current trends in asymmetric synthesis, attempts have been made to incorporate into the molecule sites for coordination of the cation, and so increase the rigidity of the reagent.

Consequently, the hydride of the 9–BBN derivative of nopol benzyl ether (**52**) (now marketed by Aldrich as NB–Enantride) was prepared (Scheme 19).[92] This reagent was successfully used to reduce acetophenone to 1–phenylethanol in 70% enantiomeric excess [93] compared with the 17% enantiomeric excess obtained using "Alpine–hydride" (**51**). Some aliphatic ketones were similarly reduced to the corresponding secondary alcohols in optical yields greater than 75% enantiomeric excess.

SCHEME 19



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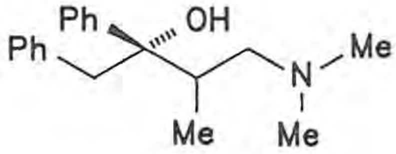
It should be noted, at this point, that there are also non–chiral borohydride reagents which will reduce carbonyl groups stereoselectively in chiral molecules (*e.g.* potassium and lithium tri–*sec*–butylborohydride which are marketed by Aldrich Chemical Company as K– and L–Selectride. This type of reagent has been employed in the present study to reduce the carbonyl group of camphor type compounds (see section 2.7, p.218).

A recently reported, alternative approach to the asymmetric reduction of carbonyl groups is the use of metal Complex Reducing Agent's (MCRA) of the form NaH–RONa–MX_n (where M is a metal *e.g.* Zn and the sodium alkoxide is derived from an optically active alcohol).[94] Modest enantiomeric excesses have been achieved in the reduction of ketones using ZnCRA and (2*S*,3*R*)–(+)–4–dimethylamino–1,2–diphenyl–3–methyl–butan–2–ol (**53**) as the chiral alcohol, available from the Aldrich Chemical Company under the trade name "Chirald."



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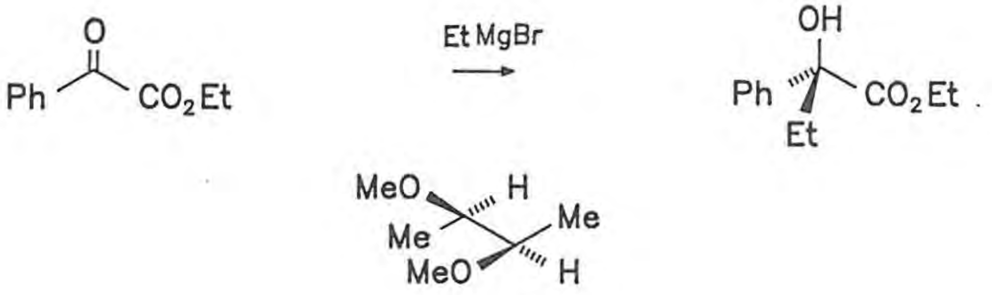
c) Asymmetric Carbon–Carbon bond Formation *via* Optically Active Reagents

Several organometallic reactions will be used to illustrate asymmetric reactions in this category.

The ability of Grignard reagents to effect reduction of carbonyl compounds to alcohols, (rather than addition) was first observed by Grignard himself,[95] and was initially applied to asymmetric reductions by Mosher and La Combe [32] and Vavon *et al.*[33] (see Section 1.4. p. 11). Certain optically active Grignard reagents have developed into useful asymmetric reducing agents, although the extent of the enantiomeric control is still substrate dependent.[96,97] In view of this competing reaction, alternative methods have been developed to achieve enantioselective additions of Grignard reagents to carbonyl compounds.

Chiral solvents can co–ordinate with achiral Grignard reagents to form chiral reagents. If the co–ordination is of sufficient strength to ensure that the solvent is associated with the transition state, then the resulting asymmetric control may be significant. The first attempts to form chiral complexes of Grignard reagents (Scheme 20) utilized chiral ethers [*e.g.* (2*R*,3*R*)–(+)–dimethoxybutane (**54**).[98]] However, the enantiomeric excesses achieved were very small.

SCHEME 20



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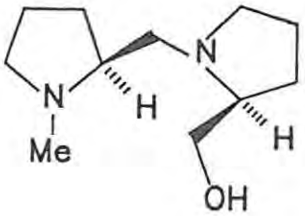

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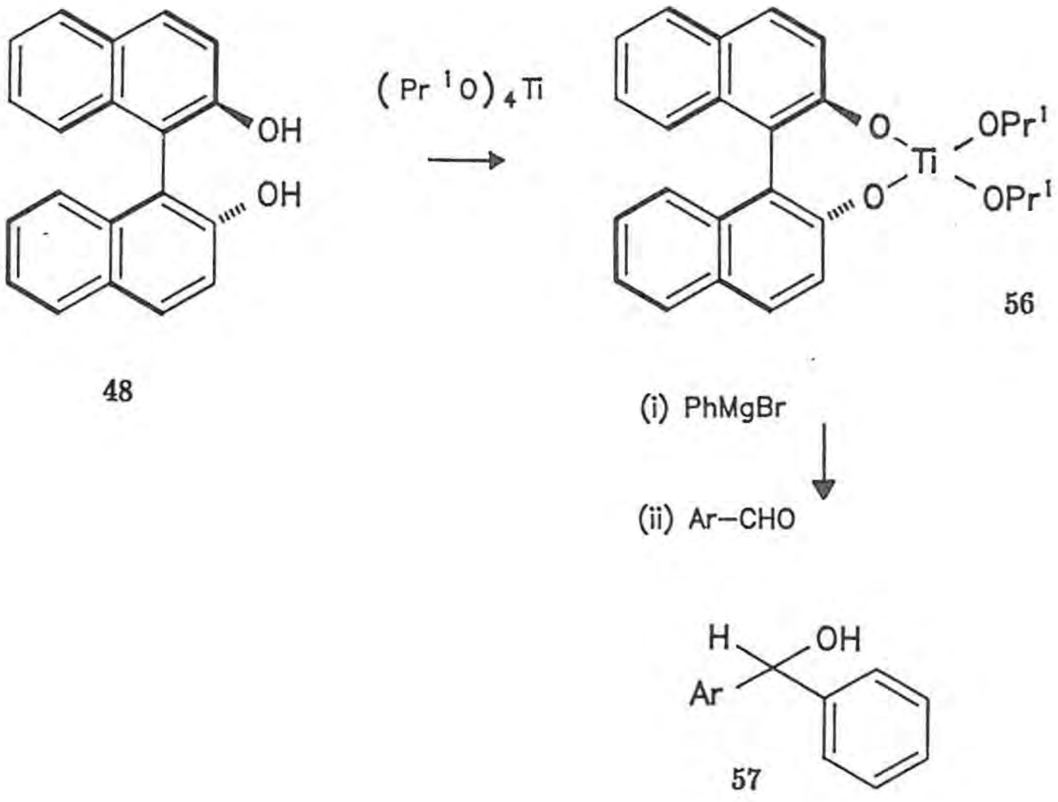
SCHEME 21



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57

A variety of other chiral ligands have been used in this approach with varing degrees of success. Mukaiyama first reported the promising ligand, (2*S*,2′S)–2–hydroxymethyl–1–(1–methylpyrrolidin–2–yl) methylpyrrolidine (**55**), for the asymmetric addition of alkyllithiums and dialkylmagnesiums to aldehydes.[99] Structural modification of the chiral ligand and the use of other organometallic reagents has facilitated even more effective stereocontrol *via* this approach.[100]

Chiral organotitanium reagents are more recent examples of organometallic reagents which add to carbonyl compounds with substantial asymmetric control. Seebach [101] first reported the reaction of aromatic aldehydes with chiral titanates, derived from optically active binaphthols (**48**), $(Pr^iO)_3TiCl$, and arylmagnesium halides. The enantiomeric excess of the benzhydrol products (**57**) are greater than 95% but these excesses decrease as the bulk of the *O*–alkyl groups increase. A more recent study utilizes the chiral titanium compound (**56**) (Scheme 21), prepared from chiral binapthol (**48**), $(Pr^iO)_4Ti$ and arylmagnesium halides.[102] This alternative approach affords the benzhydrols (**57**) in marginally better optical yields.

Duhamel has developed and utilized the concept of nucleofugal groups (leaving groups with a negative charge) to achieve asymmetric synthesis with chiral reagents.[103] The uniqueness of the nucleofugal group is that it is only associated with the prochiral substrate during the lifetime of the transition state. It is, thus, never formally bonded to the prochiral substrate. Duhamel has employed chiral mixed sulphates [*e.g.* (**58**)], derived from (+)–glucose, to methylate the Schiff bases (**59**) obtained from glycine (Scheme 22). Rigidity is imposed on the transition state by a co–ordination of the enolate metal, with an oxygen of the carbohydrate residue and the nucleofugal group is lost as the methylation proceeds. (Figure 7). While this novel approach is still in its infancy, significant enantiomeric excesses have already been achieved.

SCHEME 22

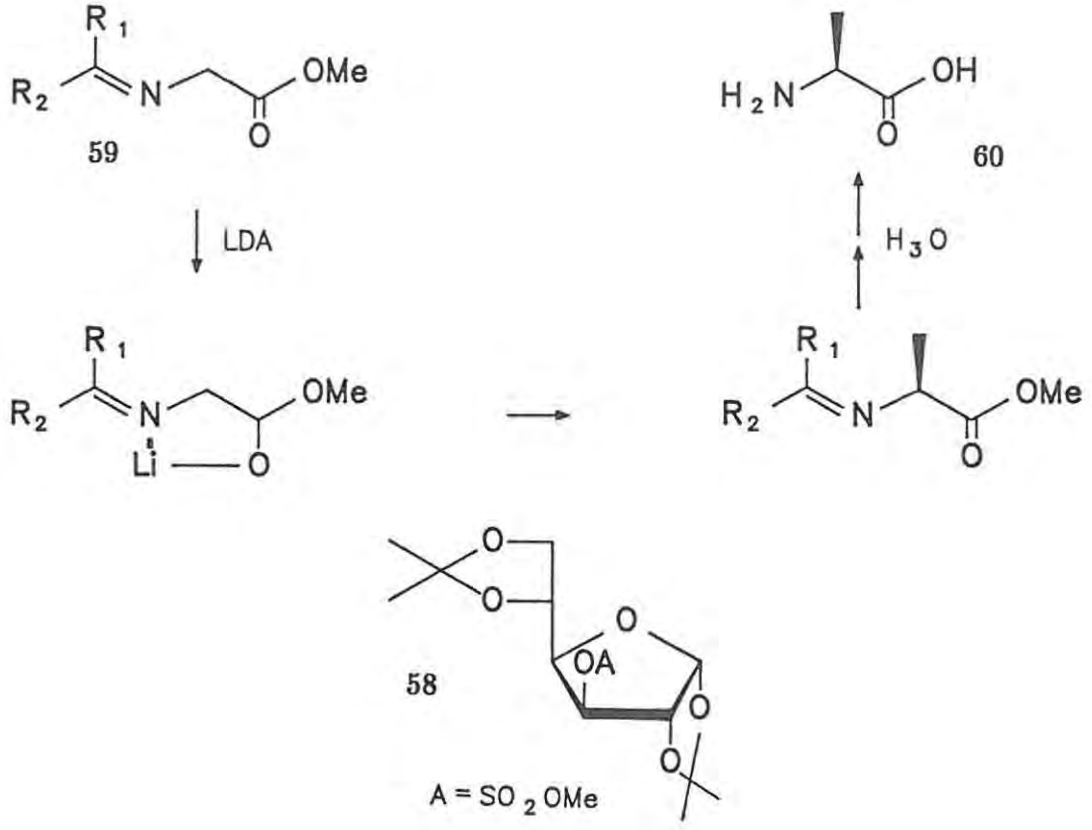
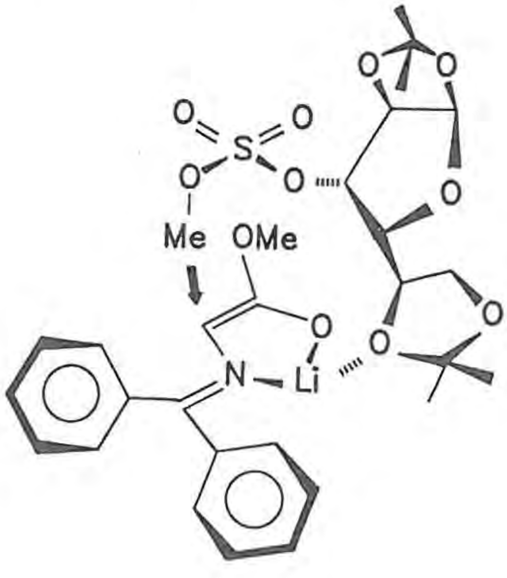


FIGURE 7 The transition state responsible for the *si* face methylation of the Schiff base (59) (where R_1 and R_2 = phenyl) by the chiral sulphate (58).



1.4.3.2 Chiral Catalysts and Chiral Promoters

The second broad class of asymmetric synthesis to be considered involves the use of optically active molecules in catalytic roles. Organic reactions may be catalysed in a variety of different ways but only homogenous chiral catalysis will be considered in the ensuing section. Homogenous catalysts may include transition metal complexes, nitrogenous bases, Lewis acids, and phase transfer catalysts, and attempts have been made to develop chiral equivalents of such catalysts. Transition metal complexes, for example, may be rendered chiral by complexing the metal with chiral ligands such as chiral amines available from the synthetic modification of naturally occurring amino acids and alkaloids. Chiral phase transfer catalysts, on the other hand may be obtained by preparing chiral quaternary ammonium salts.

The volume of literature dealing with asymmetric catalysis makes an exhaustive treatment beyond the scope of this introduction. Consequently, selected examples will be used to highlight different types of reaction. In keeping with the overall theme of asymmetric control in carbonyl chemistry, a variety of asymmetric reactions on substrates containing a carbonyl group, catalysed by optically active molecules, will be considered (Section a). However, two classic asymmetric catalyses, which do not involve carbonyl chemistry, will also be described to illustrate the diversity of chiral catalysts *viz.*,

b) the Sharpless asymmetric epoxidation (p. 49) and
c) homogenous asymmetric catalytic hydrogenation (p. 52).

Finally, a future approach to asymmetric catalysis, *viz.*,

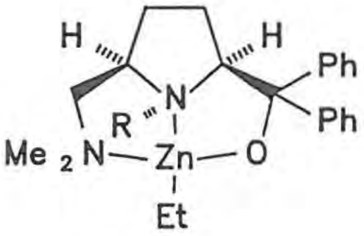
d) autocatalysis – the next generation of asymmetric synthesis, will be briefly introduced.

The strategy of using chiral promoters to achieve asymmetric induction is one that is difficult to classify in terms of the three broad approaches to asymmetric synthesis used in this introduction. Chiral promoters are used in quantities ranging from catalytic to stoichiometric, but, are, by definition, associated with neither the reagent nor the prochiral substrate at the outset of the reaction, being added independently, with or without a co–catalyst, to the reaction mixture. Although, in many instances, stoichiometric amounts of chiral promoters are employed, the manner in which they exert their chiral influence justifies their inclusion in this category.

a) Chiral Catalysis of Nucleophilic Additions to the Carbonyl Group.

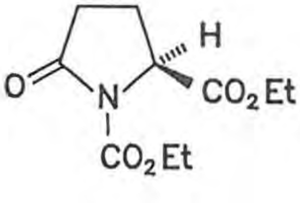
The discovery that chiral amino alcohols greatly enhance the rate of reaction of dialkylzinc reagents with aromatic aldehydes, to produce secondary alcohols of moderate enantiomeric purity,[104] stimulated considerable interest in the possibility of other asymmetric applications. Corey *et al.*,[105] for example, developed the zinc complexes, (**61**) and (**62**), of ethyl (*S*)–*N*– (ethoxycarbonyl)pyroglutamate (**63**) as very efficient enantioselective catalysts for this reaction and (*S*)–1–phenylpropanol (**65**) is obtained in 95% yield and 94% enantiomeric excess *via* the catalytic cycle outlined in Scheme 23. Corey rationalized the stereocontrol in terms of a three dimensional arrangement (**64**) which exposes the *si* face of the carbonyl carbon to the attacking ethyl group. The analogous three dimensional arrangement leading to formation of the (*R*)–isomer is destabilized by steric repulsion between the aldehyde and the (dimethylamino)-methyl substituents.

Corey submitted that these catalysts were sufficiently efficient to qualify as members of the "chemical enzyme" or "chemzyme" class of synthetic reagents.[106] Corey's criteria for qualification as such a reagent are as follows:–



61 R = H

62 R = Et



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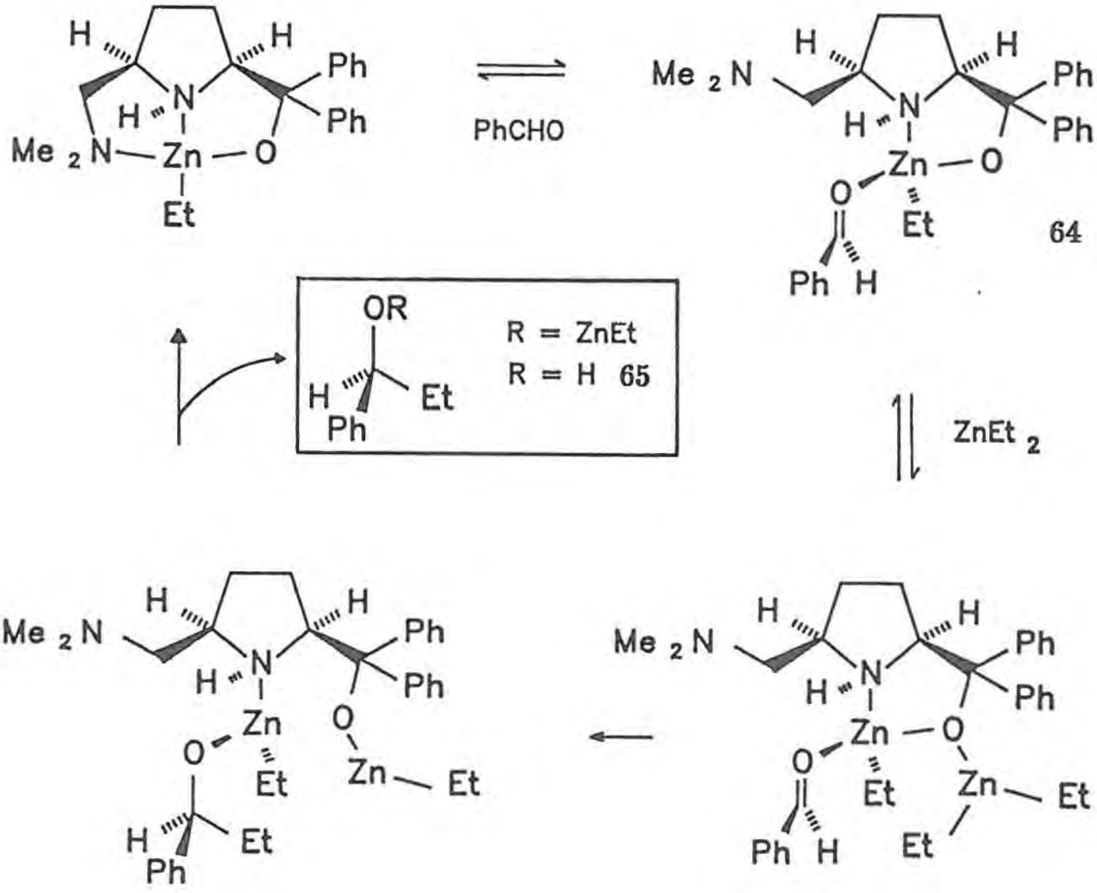
SCHEME 23

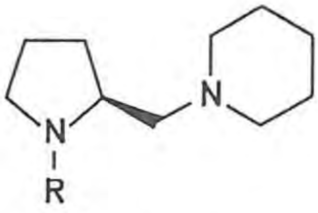


"...such chemzymes function in a clear–cut mechanistic way to bring two reactants into proximity with mutual activation and a strong control of three dimensional geometry which together lead to rapid reaction and high absolute stereoselectivity."

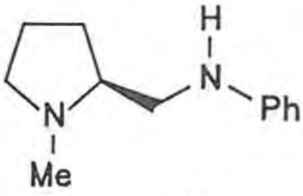
Chiral promoters have been used extensively in asymmetric aldol reactions and adaptations thereof. This type of approach to enantioselective control in the aldol reaction will be illustrated with several examples.

The use of tin(II) enolates is one of the numerous alternatives to lithium and magnesium enolates not mentioned in the preceeding review of diastereoselective aldol reactions (Section 1.4.1.3, p. 23). Mukaiyama *et al.*[107] have studied ways of forming such enolates, including treating ketones with tin(II) triflate in the presence of *N*–ethylpiperidine. Reaction of these enolates with aldehydes in the presence of optically active diamines (**66**) or (**67**) gives predominantly the *syn* aldol product (**69**) (*syn:anti* > 95:5) in 95% enantiomeric excess (Scheme 24).[108]

The reaction of silyl enol ethers and ketene silyl acetals with aldehydes and ketones, known as the "Mukaiyama reaction," has been very useful in synthesis.[54,109] Unlike other metal enolates, silicon enolates are insufficiently nucleophilic to undergo addition to aldehydes unless the reaction is catalysed by a Lewis acid. Reetz *et al.*[110] have investigated the use of optically active diamines as chiral promoters in the reaction of prochiral silyl enol ethers with prochiral aldehydes but the resulting enantiomeric excesses were disappointing. Mukaiyama [111], subsequently, developed chiral Lewis acid catalysts, the use of which led to good material and enantiomeric yields. These Lewis acids are obtained by co-ordinating an optically active diamine to tin(II) triflate and



66 R = Me
68 R = Et



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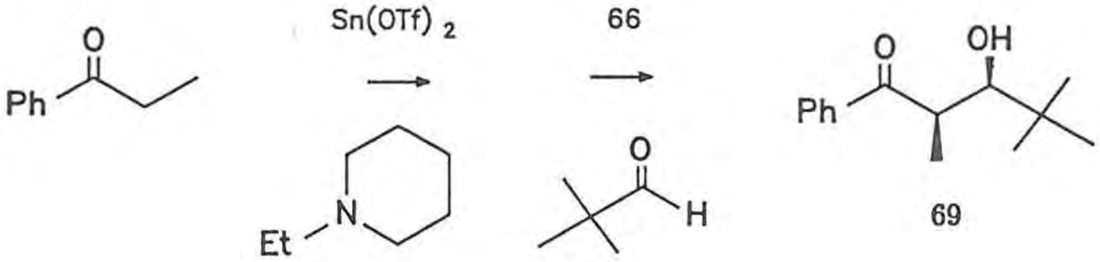
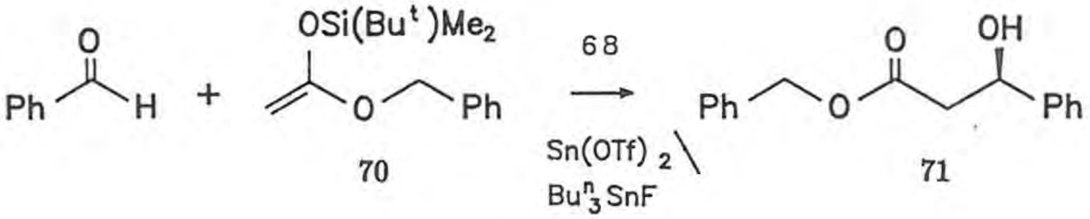
SCHEME 24



SCHEME 25



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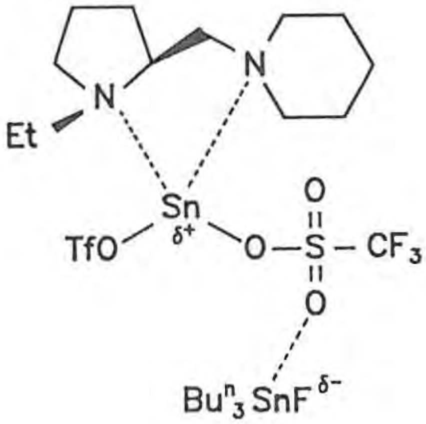


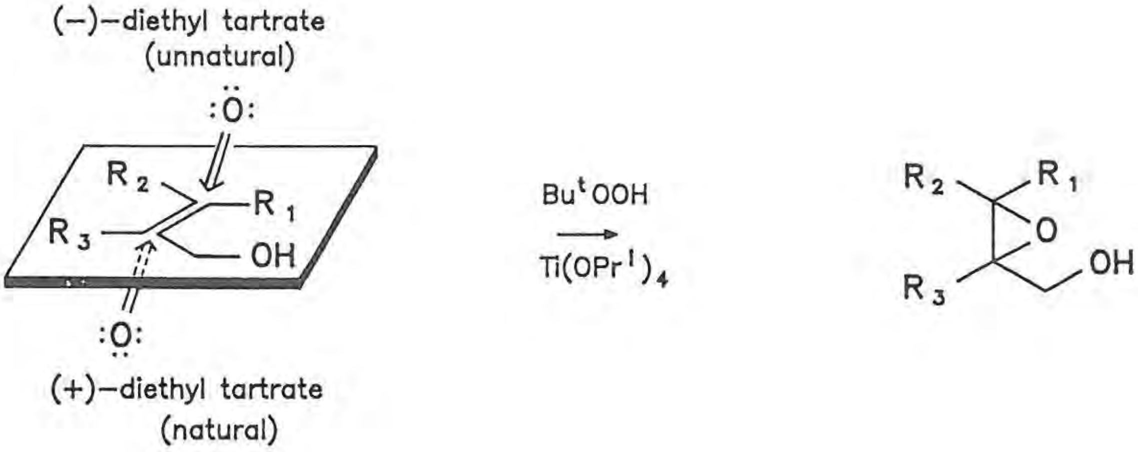
tributyltin fluoride. Such use of (S)–1–ethyl–2–[(piperidine–1–yl)methyl]—pyrrolidine (**68**) (Scheme 25) to catalyse the reaction of 1–*t*–butyldimethylsiloxy–1–benzyloxyethylene (**70**) with benzaldehyde, afforded the hydroxy esters (**71**) in 90% enantiomeric excess.

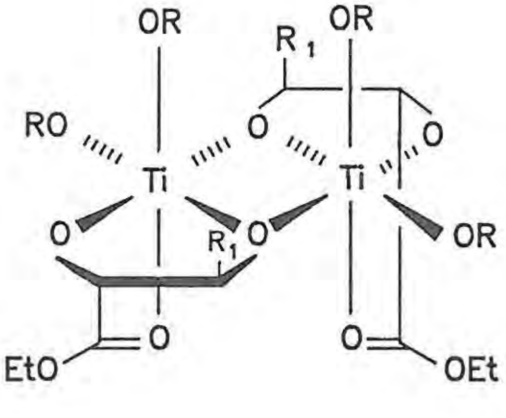
Tributyltin fluoride is crucial to the enantioselectivity of the reaction and Mukaiyama has proposed the active species (**72**) to explain its role. The reaction apparently proceeds *via* formation of a transition state in which the cationic centre of the tin(II) triflate moiety activates the aldehyde and electronegative fluoride interacts with the silicon of the silyl ketene acetal.[112]

b) The Sharpless Asymmetric Epoxidation

Epoxides and the readily derived 1,2–diols are important compounds in organic synthesis. The ability to control which enantiomer is produced in an epoxidation reaction was a much sought after synthetic process. This goal was attained in 1980 when Sharpless *et al.*[113] first reported the asymmetric epoxidation of allylic alcohols in good material yields and > 90% enantiomeric excesses using *tert*–butyl hydroperoxide in the presence of (+)– or (–)–diethyl tartrate and titanium tetraisopropoxide. This reaction has developed into one of the most significant asymmetric reactions for a variety of reasons; these include substrate generality, excellent enantioselectivity, practicality, and moderately priced reagents. Furthermore, the configuration of the intended product may be easily inverted by employing the enantiomeric tartrate. To date, no exceptions have been found to the enantiofacial selection rule (Scheme 26).

SCHEME 26

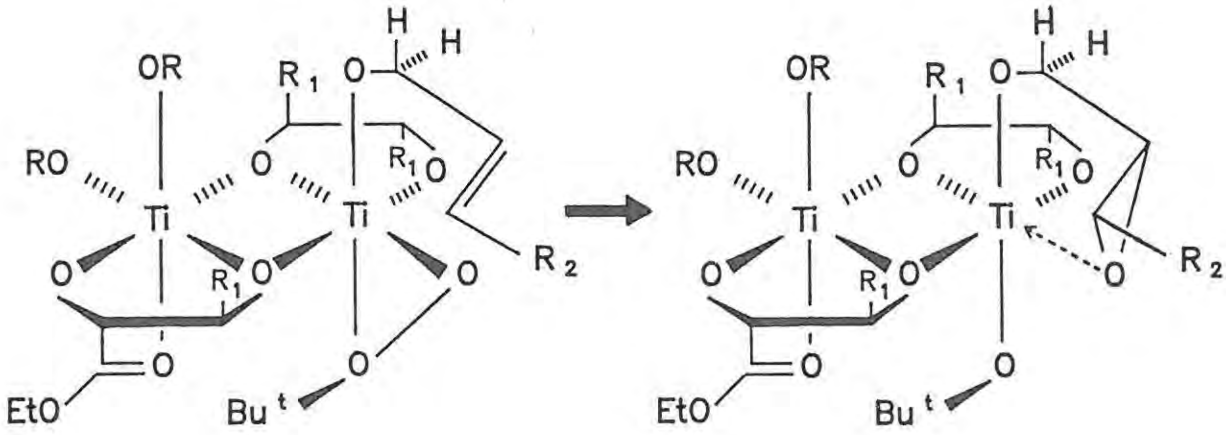




$R = Pr^i$
$R_1 = CO_2Et$

73

SCHEME 27



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Since the initial discovery there has been intense activity in studying two aspects of this process, *viz.*, the structure of the active catalyst and the reaction mechanism, in order to understand the source of the exceptional enantioselectivity. The present consensus of opinion is that the titanium alkoxide–tartrate complex is a dimeric, bridged, six co–ordinate structure, with geometry approaching that of octahedral, and C_2–symmetry[d] and two tartrate ester carbonyls associated with the titanium atoms (**73**). The allylic alkoxide binds *trans* to the co–ordinated ester carbonyl and subsequent dissociation of the carbonyl co–ordination to the titanium atom facilitates bidentate co–ordination of the alkyl peroxide, structure (**74**), permitting stereoselective oxygen transfer to the co–ordinated allyl alkoxide (**75**) (Scheme 27).[115]

The Sharpless epoxidation as originally reported required a stoichiometric amount of the titanium tartrate "catalyst". Conducting the reaction in the presence of molecular sieves allows the catalyst to be reduced to 5–10% of the stoichiometric amount, altering the system to a genuine asymmetric catalysis.[116] The role of the zeolite is believed to be one of removing both extraneous water and the water generated from minor side reactions. This water participates in harmful interactions with the catalyst and at low catalyst concentrations can seriously affect the yield and enantioselectivity of the reaction.

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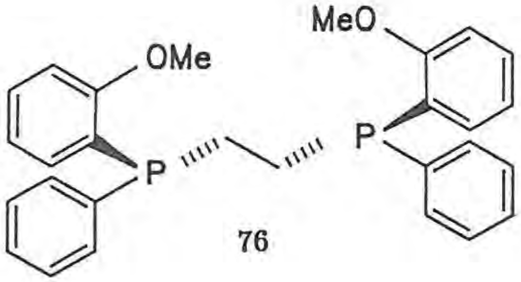
[d] The use of chiral catalysts and auxiliaries containing a C_2 symmetry axis is becoming more prevalent in asymmetric synthesis. A recent review of this approach indicates that in a large number of successful chiral inducing agents this symmetry element is, in fact, present.[114]

c) Homogenous Asymmetric Catalytic Hydrogenation[117,118]

From the mid 1950's many unsuccessful attempts were made to transfer chirality from a chiral ligand–metal complex to a prochiral olefin under hydrogenating conditions. In the late 1960's however, two different discoveries made asymmetric hydrogenation a reality. Wilkinson *et al.*[119] reported the homogenous catalysis of olefin hydrogenation using a rhodium–triphenylphosphine catalyst and Mislow [120] developed a general method for the preparation of chiral phosphines. The rhodium catalysts used in asymmetric hydrogenation are square planar systems in which two of the coordination sites are occupied by a bidentate chiral phosphine ligand such as the phosphines (**76**) and (**77**). [Another issue hitherto not considered in this introduction is illustrated in compound (**76**), *viz.*, that the chiral centre of the asymmetry inducing agent need not be a carbon atom. Any other atom that can exhibit chirality (*e.g.* phosphorous, sulphur, nitrogen or silicon) will also be capable of tranferring it.] Hydrogenation with the Wilkinson catalyst proceeds *via* bidentate chelation of the olefinic system to the rhodium catalyst, followed by oxidative addition of hydrogen to the metal and a subsequent migratory insertion step to transfer the hydrogen to the olefinic bond. The relative rates of formation of the initial diastereomeric catalyst–substrate adducts dictate the ultimate enantioselectivity of hydrogenation. In addition to the reactive olefinic site, a second, neighbouring polar group is necessary to anchor the substrate to the catalyst by chelation. It is this structural requirement that explains why hydrogenation of protected dehydro–α–amino acids (**78**) proceeds with high enantiomeric excess, whereas enantioselectivity for simple olefins is much poorer.



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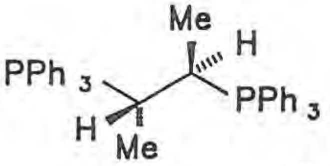

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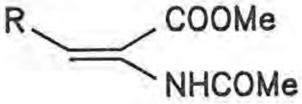

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d) Autocatalysis – the Next Generation of Asymmetric Synthesis [121]

One of the fundamental issues that will have to be addressed before the evolution of life, as we know it, is completely understood, is the origin of molecular chirality. Life could not exist in a racemic environment and numerous reviews [122,123,124] reflect the considerable interest in this unanswered question.

Both Mills,[125] in 1932, and Frank,[126] in 1953, developed mathematical statistical models to support the claims that "optical activity of living matter is an inevitable consequence of its property of growth" and that "spontaneous asymmetric synthesis is a natural property of life." Asymmetric autocatalysis is a concept that emerges from the above statements and Frank's mathematical conclusions can be described as follows:

If two achiral substances, **A** and **B** react to form a chiral product **C**, within the following boundary conditions, then asymmetric autocatalysis is, in principle, possible;

1) **C** must catalyse its own formation, and

2) one enantiomer of C *e.g.*(*R*)–C must catalyse the formation of (*R*)–C and inhibit the formation of (*S*)–C and *vice versa*.

If these conditions prevail and at a given time a slight excess of one enantiomer forms (statistically defined as a fluctuation), then the process can rapidly lead to the formation of one enantiomer. As yet no asymmetric autocatalysis has been achieved in the laboratory, due largely to the severity of the boundary conditions. However, asymmetric reactions in which the optically active product acts as a chiral catalyst are emerging,[127] and this approach represents one of the major challenges in future asymmetric synthesis.

1.4.3.3 Chiral Auxiliaries

In an achiral environment the faces of a planar molecule or functional group are indistinguishable and thus equally accessible. In simple addition reactions to prochiral molecules both enantiomers will form and the product will be racemic. Discrimination of the faces is best achieved by destroying the symmetry prior to addition, by attachment of a homochiral or enantiomerically pure group to another position in the reactant molecule. The faces would then be diastereotopic and would, in principle, react at different rates for reasons discussed previously (see Section 1.4.2, p. 28)

This destruction of the symmetry of a prochiral molecule *via* the incorporation of a homochiral group is the essence of the <u>chiral auxiliary approach</u> to asymmetric synthesis. The chiral auxiliaries (also referred to as chiral inducing agents or chiral adjuvants) are obtained from any of the sources of optically active molecules described in Sections 1.1 – 1.3. This approach to asymmetric synthesis involves three steps, *viz.*, attachment of the auxiliary to the prochiral substrate; execution of the reaction generating the chiral centre; and removal of the auxiliary.

Several criteria for a successful chiral auxiliary have been established.[2,128]

i) It must be readily available in homochiral form, preferably in both enantiomeric forms.

ii) Facile attachment, in high yields, to the substrate molecule is essential.

iii) It must induce highly stereoselective reactions.

iv) It must be easily removed from the resultant product molecule, preferably in a form that can be recycled. This removal of the auxiliary must occur without racemizing the product at all.

It should be noted, at this stage, that diastereoselective reactions [discussed previously (Section 1.4.1, p. 14)], yield diastereomers which are in fact, racemic pairs. However, if the chiral substrate molecule is a single enantiomer, *e.g.* by virtue of the attachment of an optically pure chiral auxiliary, then any new chiral centre formed will have a particular configuration, to the extent that the reaction is stereoselective. Thus the models proposed for diastereoselective reactions *e.g.* the Cram model (Section 1.4.1.1, p. 14) can be used to predict the preferred enantiomer for reactions involving a chiral auxiliary approach.

The use of chiral auxiliaries has become a major strategy in asymmetric organic synthesis and continues to expand very rapidly. The remainder of this section will highlight the work of some of the main contributors in this area. The illustrative examples, which include some of the original ideas and certain recent applications in the field of carbonyl chemistry, cover:–

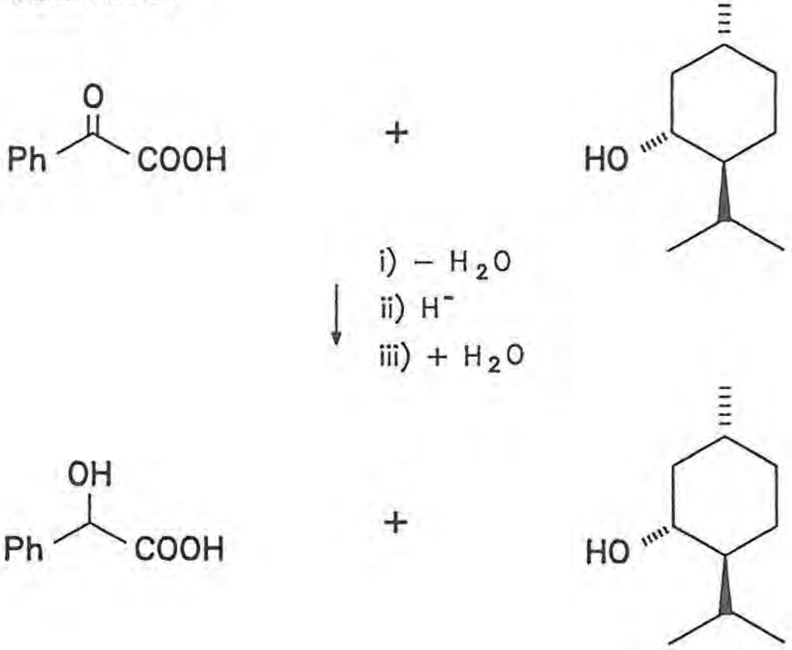
a) Enantioselective nucleophilic addition to carbonyls.
b) Enantioselective electrophilic addition to enolates.
c) Enantioselective aldol reactions.
d) Miscellaneous examples, *viz.*,
    1) chiral oxazolines,
    2) chiral enamines, metalloenamines, and hydrazones.
e) Chiral leaving groups.

a) Enantioselective Nucleophilic Addition to Carbonyl Compounds

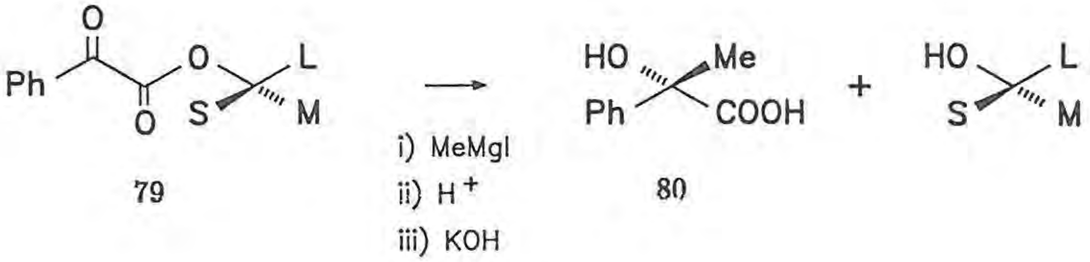
Kipping [129] and Cohen and Whitely [130] attempted to use chiral auxiliaries as early as 1900. They independently prepared esters of α–keto acids using the optically active alcohols, menthol and borneol (*e.g.* Scheme 28). Their attempts to create a new chiral centre *via* reductions of the ketone group failed to yield any optical activity. It is now believed, however, that asymmetric induction may well have occurred but that the products racemized during basic hydrolysis of the esters (due to enolisation involving the acidic α–proton). M^c^Kenzie [131] successfully applied the, then new, Grignard reaction to these same esters and isolated hydroxy acids with discernable optical activities. (The products from the Grignard reaction have no α–hydrogen and thus are not susceptible to racemization during hydrolysis.)

Prelog [34,132] developed this approach further and rationalized the relationship between the configuration of the optically active alcohol and the stereochemistry of the product. This was achieved using models, analogous to the Cram models, of non–bonded interactions in the transition state, in which the two carbonyl groups of the the α–keto ester (**79**) are arranged in an anticoplanar conformation while the three groups of the chiral alcohol portion are arranged so that the medium (M) and small (S) groups are staggered on either side of the ester carbonyl group. The reagent then approaches the keto carbonyl function preferentially from the side of the (S) group. It was this early work on the use of chiral auxiliaries by Prelog that led to his well known method for determining the configuration of secondary alcohols.[133] In this method, the benzoylformate esters (**79**) and methyl magnesium iodide are universally used. Provided the (L), (M) and (S) groups are hydrocarbons that follow the sequence rule order and, furthermore, have significantly different steric requirements, then an alcohol of *R*–configuration will yield (*R*)–(–)–atrolactic acid and conversely the (*S*)–isomer for an alcohol of S–configuration (**80**) (Scheme 29).

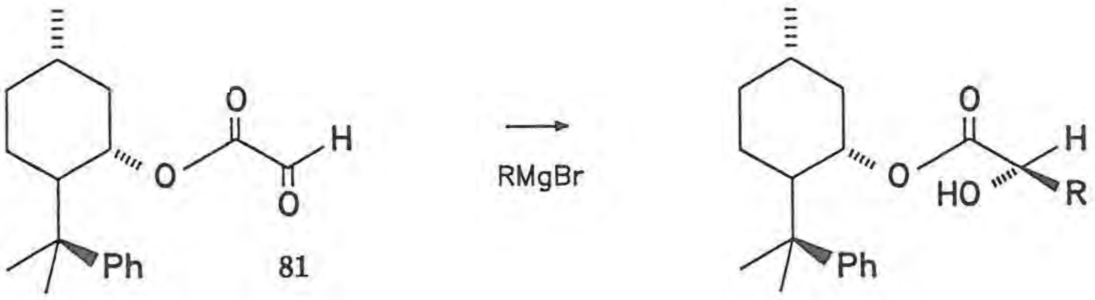
SCHEME 28



SCHEME 29



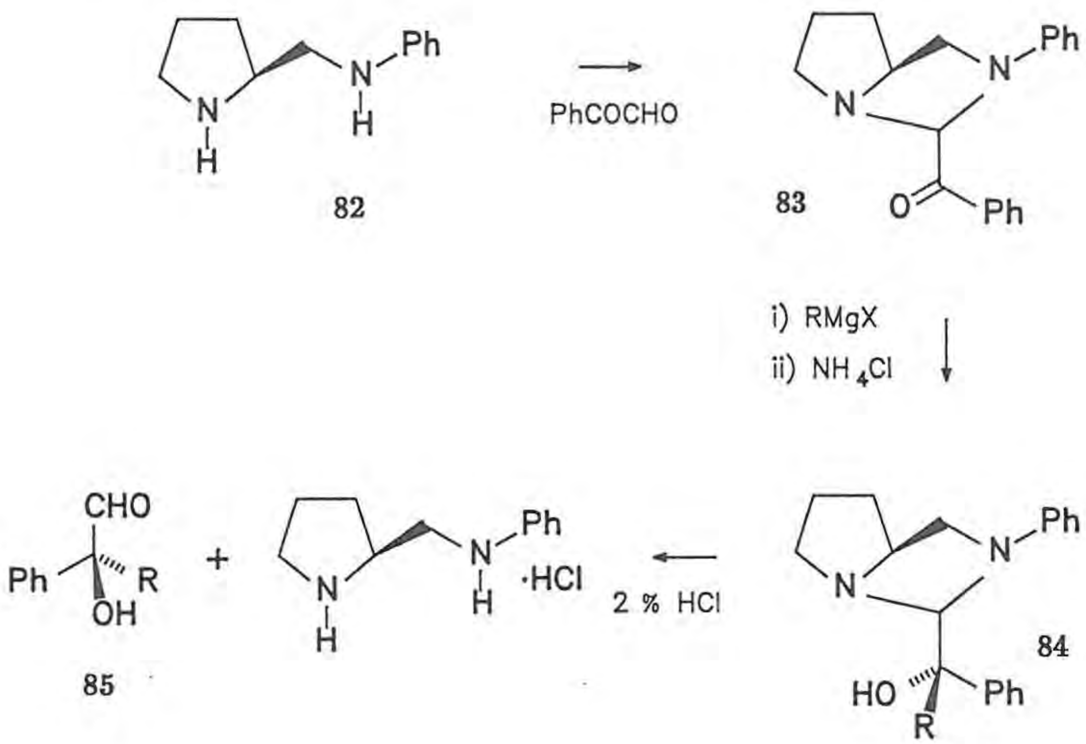
SCHEME 30



While this process is useful for the determination of the configuration of both chiral alcohols and tertiary α–hydroxy esters, the stereoselectivity is, in general, too low for efficient asymmetric synthesis. However, there have been isolated examples of successful applications of this type of approach. For example, Whitesell *et al.*[134] achieved enantiomeric excesses of 98% by adding various Grignard reagents to the glyoxylate ester of (–)–8–phenylmenthol (**81**) (Scheme 30).

The direct application of the Cram type rules to enantioselective syntheses are very difficult because, by definition, the original chiral centre and the generated centre must be bonded to each other and removal of the "chiral auxiliary" without loss of the induced chirality is likely to be impossible. Mukaiyama [135] and Eliel [136] have both devised asymmetric syntheses based on Cram's rigid model rule. The fundamental concepts of both approaches are similar and will be illustrated by means of Mukaiyama's example (Scheme 31). The chirality of the auxiliary (**82**) is transmitted to a centre adjacent to the carbonyl group, as in compound (**83**) and then the newly created chirality is further transferred, *via* a Cram chelate process, to the product (**84**). The intermediate chiral centre is then destroyed, the chiral auxiliary is cleanly recovered, and the last–generated chiral centre is liberated intact in compound (**85**).

SCHEME 31

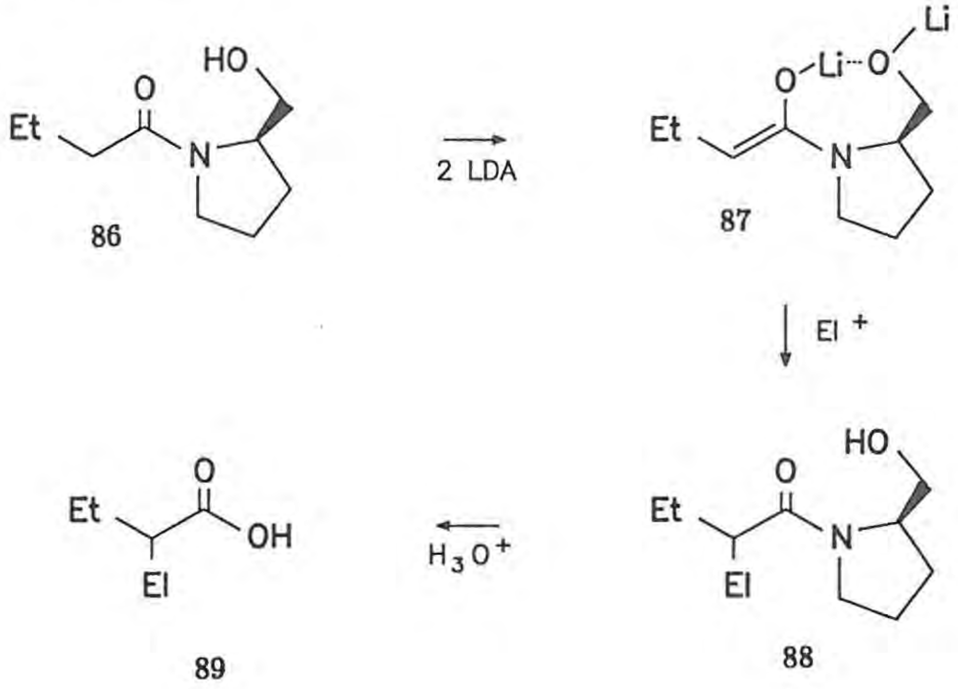


b) **Enantioselective Electrophilic Addition to Enolates.**

This type of reaction is well illustrated by Evans [137] synthesis of α–substituted carboxylic acids *via* (*S*)–prolinol derived chiral amides (**86**) (Scheme 32). Deprotonation and enolization is achieved with two equivalents of LDA, to yield the *Z* enolate (**87**) and alkylation then proceeds preferentially from the *si* face. This diastereofacial selectivity is often greater than 95% and because the prolinol is optically pure the reactions are enantioselective. The observed stereoselectivity is believed to be due to the relative orientation of the enolate group and the chiral centre which, in turn is determined by chelation with the lithium cation in the intermediate (**87**). *i.e.* the process involves chelate–enforced intraannular chirality transfer (See Section 1.4.1.2, p. 22). The amides (**88**) are hydrolysed under mildly acidic conditions, with minimal racemization, to yield the α–substituted carboxylic acids (**89**) in greater than

90% enantiomeric excess.

SCHEME 32



c) Enantioselective Aldol Reactions

The study of enantioselective aldol reactions has become a vast and diverse field and the factors influencing the stereochemical course of aldol reactions are continually being re–evaluated. Although most recent strategies rely on catalytic chiral controllers (see Section 1.4.3.2, p. 44) numerous successful asymmetric reactions have been conducted using chiral auxiliaries.

Since the discovery by Mukaiyama *et al.* that certain Lewis acids will catalyze aldolisations of silyl enol ethers [54] and *O*–silyl ketene acetals,[109] the stereochemical implications of these reactions have been extensively studied. Oppolzer and Marco–Contelles [138] have demonstrated the versatility of simple camphorsulphonic acid derivatives as chiral auxiliaries in numerous ways, including, using the dicyclohexylsulphonamide (90) in the synthesis of enantiomerically pure aldol products (Scheme 33). TiCl$_4$ promoted reactions of

SCHEME 33

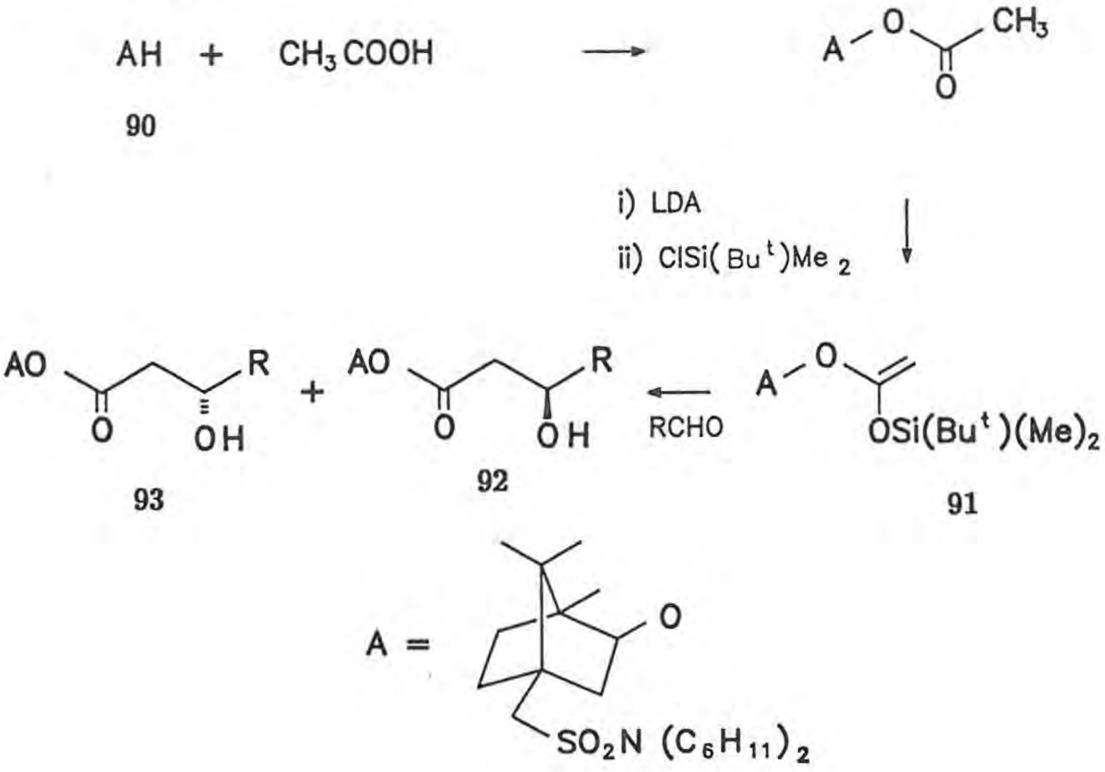
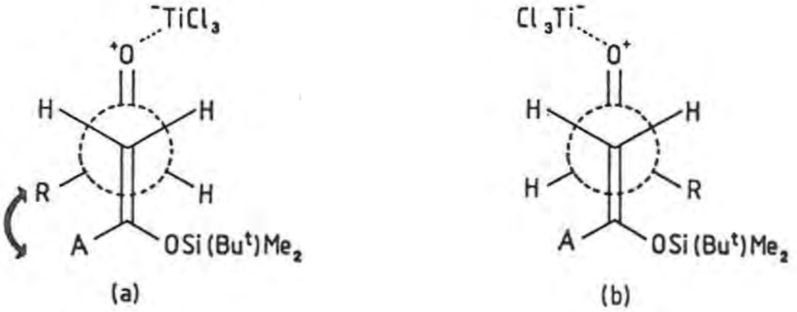


FIGURE 8 "Open" transition state topologies for the reaction of *O*-silyl ketene acetal (91) with aldehydes, showing the unfavourable *gauche* interaction in (a).



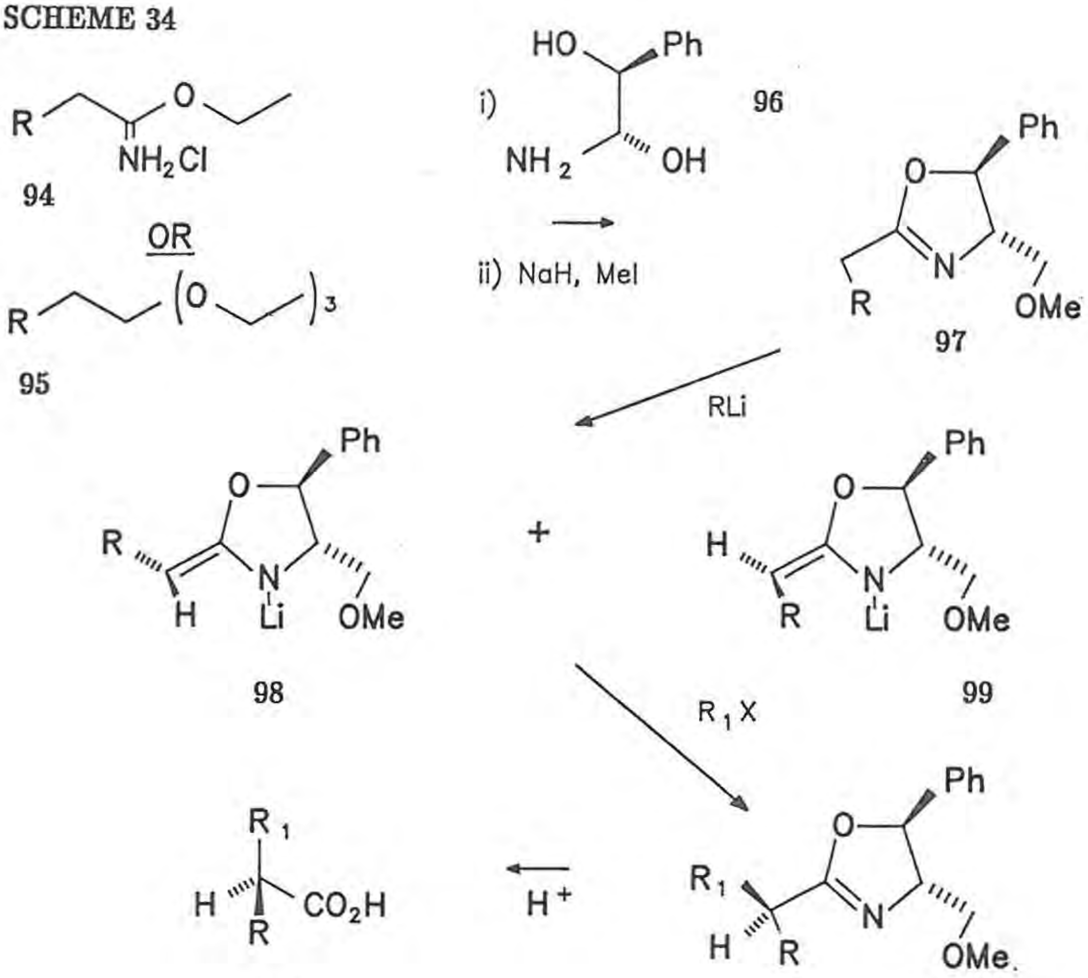
the *O*–silyl ketene acetal (**91**) with aldehydes yield the aldols (**92**) in overwhelming preference to the stereoisomers (**93**). Mild hydrolytic removal of the auxiliary and isolation of the *β*–hydroxy acids revealed the enantiomeric excess to be between 92 and 99%.

Rationalisation of this effective control is based on an analysis of the possible open transition–state topologies (Figure 8) since the Zimmerman–Traxler transition states (see Section 1.4.1.3, p.24) can only be applied when bridging, metal counter–ions (*e.g.* Li, B, or Zn) are present to facilitate chelation.

d1) Chiral Oxazolines

Through Meyers' pioneering efforts, the commercially available (1*S*,2*S*)–1–phenyl–2–amino–1,3–propanediol (**96**) has been developed into a versatile chiral auxiliary. This versatility stems from its ability to react with the ethyl imidate hydrochloride of acetonitrile (**94**) or the ethyl ortho ester (**95**) to produce the masked carboxylic acid, oxazoline (**97**) [139] (Scheme 34), from which a number of optically active acids, esters, lactones, and alcohols have been prepared. Asymmetric reactions involving these oxazolines are best illustrated by one of the early attempts to prepare *α*,*α*–dialkylated carboxylic acids. Metallation (Scheme 34) of the oxazoline (**97**) yielded a mixture of *E*–and *Z*–azaenolates (**98**) and (**99**), treatment of which with a variety of alkylating agents, followed by acid hydrolysis yields, the disubstituted carboxylic acids (**100**) in 72 to 82% enantiomeric excess.[140]

SCHEME 34



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95

96

97

98

99

100

d2) Chiral Enamines, Metalloenamines, and Hydrazones

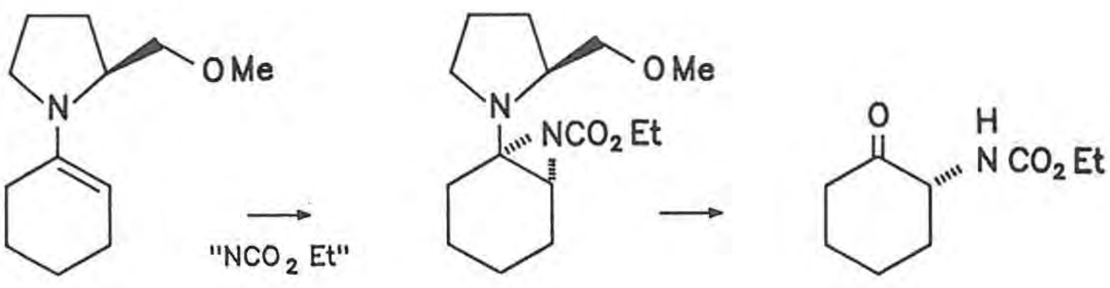
Electrophilic additions α to a carbonyl group, especially those involving carbon–carbon bond formation are of vital importance to synthetic chemistry. Classical coupling reactions involving enolate systems suffer from various problems, *e.g.* self–condensation, dialkylation, and the uncertain control of regiochemistry. Certain "temporary" C–N alternatives to carbonyl compounds, such as enamines, metalloenamines and hydrazones provide some improvement and considerable attention has been given to preparing such substrates from optically active primary and secondary amines.

Chiral enamines are readily prepared by condensation of optically active secondary amines and carbonyl compounds. The concept of employing chiral amines was pioneered by Yamada *et al.*[141] and the majority of reported examples involve α–addition (including alkylation [142] and bromination [143]), to cyclohexanone enamines prepared from chiral amine derivatives of proline. The advantage of cyclic enamines is that only one geometry of the double bond is possible unless the ring size is unusually large.

Pellacani *et al.*[144] have recently applied this technique to achieve a rare, asymmetric carbon–nitrogen bond formation by reacting (ethoxycarbonyl)nitrene (102) [generated *in situ* from ethyl *N*–(4–nitrophenylsulphonyloxy carbamate] with the chiral enamine (101), to form the α–amino ketone (104) *via* an unstable aziridine intermediate (103) (Scheme 35).

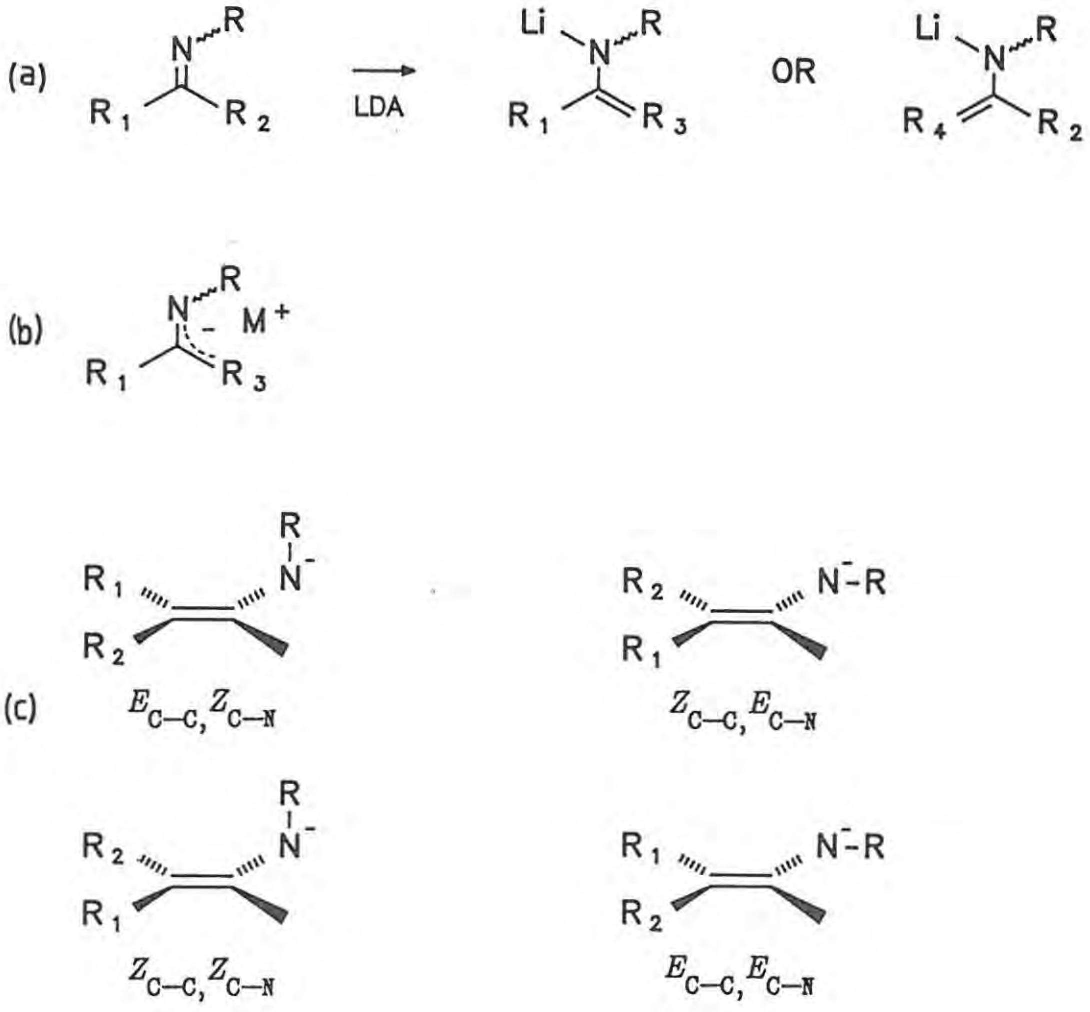
Chiral metalloenamines (or azaallyl metal reagents) are more reactive alternatives to the enamines, as reflected by their ability to react with primary alkyl halides. They are usually prepared by the deprotonation of imines, using Grignard reagents or organolithium bases. (Very few examples are cited using metals other than lithium or magnesium.) In the general case of an unsymmetrical imine, deprotonation can give rise to two regioisomers and various stereoisomers as a result of geometric isomerism about both the C–C and C–N bonds (Figure 9 a and c). LDA in THF is the base most often used for the deprotonation of aldimines and symmetric, cyclic ketimines although alternative methods are available for the deprotonation of unsymmetrical ketimines, which provide better regiocontrol.[145] The structure of the intermediate azaallyl metal reagent is crucial to the course of the subsequent asymmetric reaction.

SCHEME 35



101 102 103 104

FIGURE 9 (a) Deprotonation of a general imine to yield the two possible regioisomeric metalloenamines. (b) Delocalized structure of a metalloenamine. (c) The four possible stereoisomeric azaallyl anions.



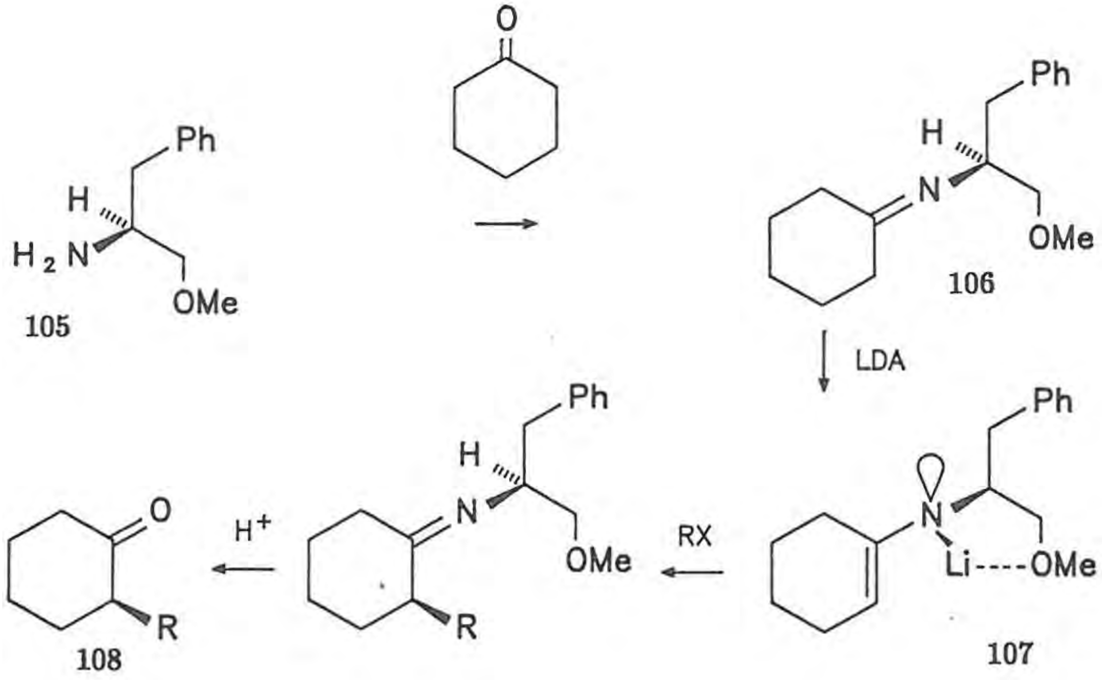
(Assuming that R_2 has a greater priority than R_1)

This approach to asymmetric synthesis is best illustrated by the α–alkylation of cyclohexanones, in which the regio– and stereochemical implications are clearly understood. Only the $(E)_{C-C}$ configuration is possible for cyclohexanone derivatives and there is extensive theoretical and experimental evidence that, in these cases, the carbon–nitrogen stereochemistry is always (*Z*).[146]

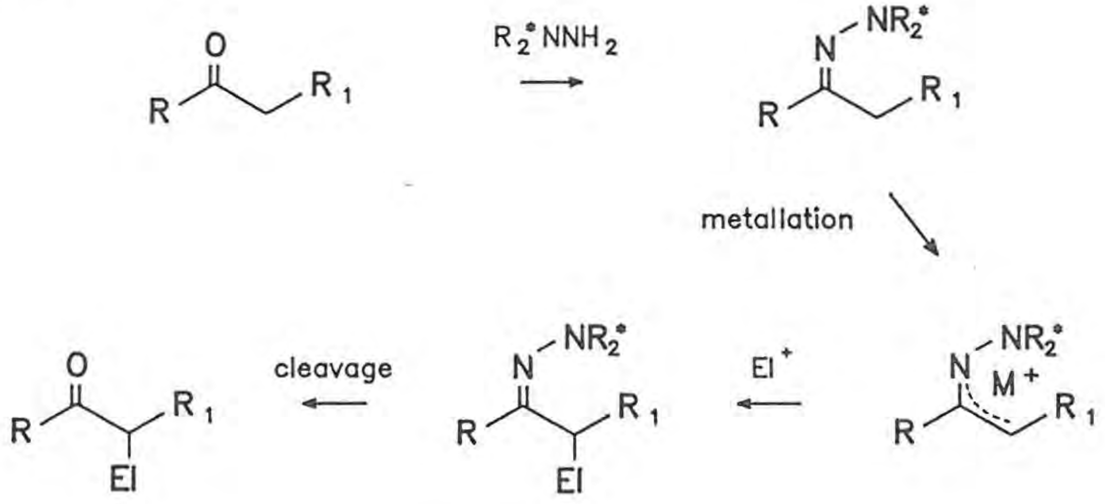
Horeau [147] initiated this work, utilizing imines of cyclohexanones derived from isobornylamine. Horeau's only electrophile was methyl iodide, with which he obtained 2–methylcyclohexanone in 72% enantiomeric excecess. This was the first reported asymmetric α–alkylation of cyclic ketones. When Meyers *et al.*[148] extended this work to a other alkyl halides the enantiomeric excesses were considerably lower, lying in the range 26–37%. Much better enantioselectivity has subsequently been achieved by application of the "rigid lithioenamine concept". This is achieved with chiral auxiliaries that contain functional groups (often ethers) that can co–ordinate, intramolecularly, to the metal to form a five membered chelate, whose topology influences the approach of the alkyl halide. This approach is illustrated by the reaction of Meyer's chiral amine (**105**) and cyclohexanone to afford the imine (**106**);[148,149] subsequent deprotonation yields the chelated structure (**107**), [if the chiral auxiliary configuration is (*S*)] and hence the carbonyl compound (**108**) as the favoured product (Scheme 36).

Chiral hydrazines provide a third alternative for introducing chiral auxiliaries into carbonyl substrates *via* carbon–nitrogen bonds. In 1976 Corey and Enders demonstrated the asymmetric potential of metallated dimethyl hydrazones [150] (Scheme 37). While many reactions of lithiated hydrazones parallel reactions of enamines, enolates, and azaallyl metal reagents, they do provide several advantages. These include higher yields, greater reactivity, and milder

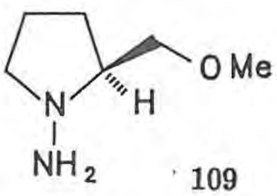
SCHEME 36



SCHEME 37



Where R* is optically active.



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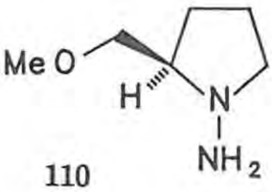


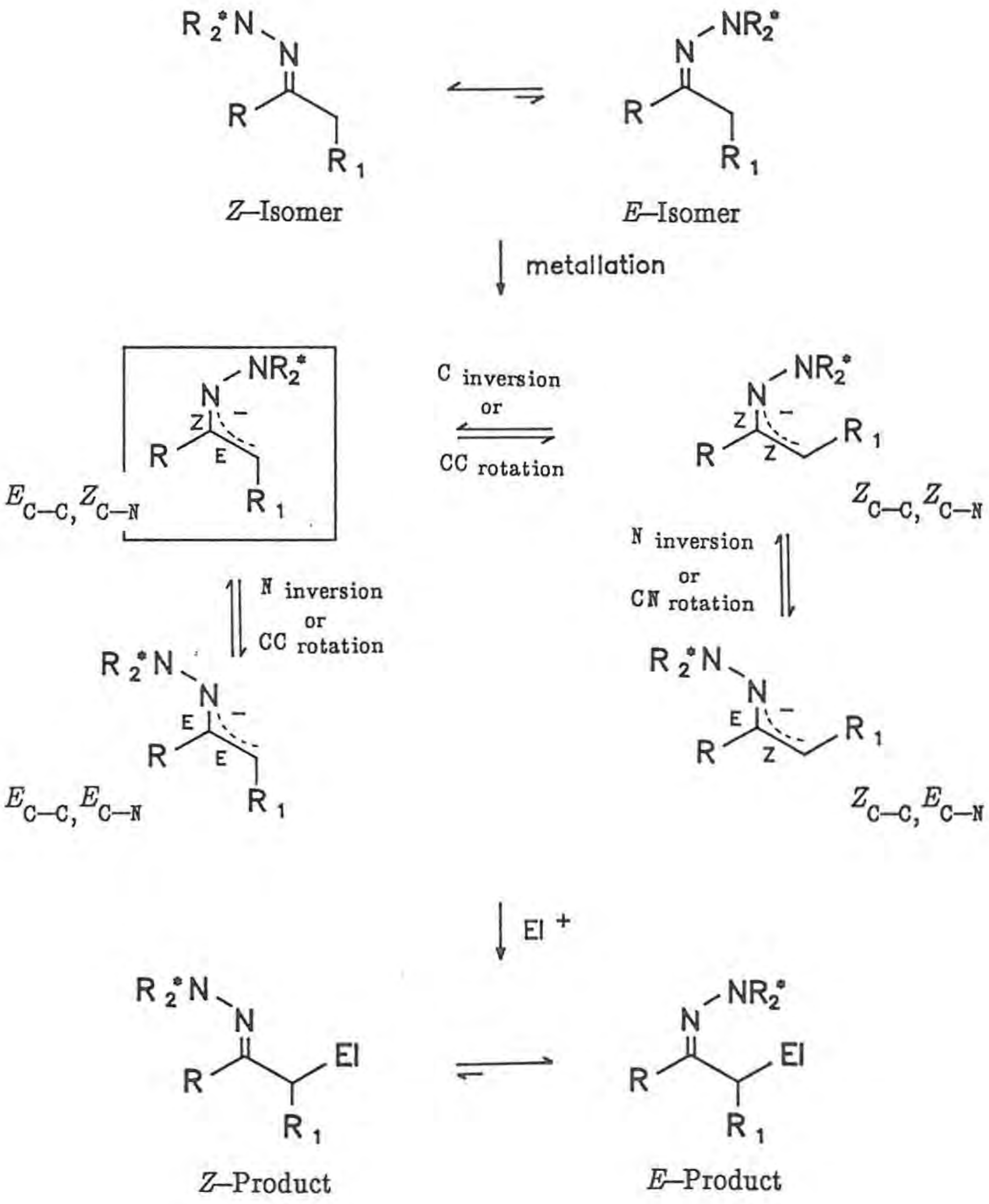
110

cleavage. Except in isolated instances, the regioselectivity of alkylations in unsymmetrical ketones is very high. The chiral auxiliaries that have been fundamental to this approach are the hydrazines (*S*)– and (*R*)–1–amino–2–methoxymethylpyrrolidine [*S*AMP (**109**) and *R*AMP (**110**)], developed by Enders. Both enantiomers are easily prepared from cheap, naturally occuring amino acids.[151,152]

The chiral hydrazones, prepared from these hydrazines, may be obtained in almost quantitative yields and deprotonation is achieved with *n*–butyllithium or LDA. Metallation of hydrazones, derived from unsymmetrical ketones, typically occurs at the least substituted α–carbon, resulting in highly regiospecific alkylations.[153,154] Numerous trapping experiments and NMR investigations have established that, of the four possible configurations of a 1–amino–1–azaallyl anion, formed under standard deprotonation conditions, the $(E)_{C-C}$, $(Z)_{C-N}$ configuration is generated with high stereoselectivity from SAMP and RAMP hydrazones, regardless of the (*E*)/(*Z*) ratio of the starting hydrazones.[155,156] Of the two possible alkylation products, the (*Z*) hydrazone is usually thermodynamically less stable and, depending on the R and R_1 substituents, may isomerize to varying extents to the more stable (*E*) isomer (Figure 10). The conformation about the N—N bond is still the subject of investigation but there is considerable evidence to support the hypothesis that the pyrrolidine nitrogen lone pair orbital is perpendicular to the azaallylic π–system. Furthermore, intramolecular chelation of the lithium cation by the methoxy group occurs has been established, thus supporting the intermediacy of the general structure (**111**), as depicted in Figure 11. Thus, chelation once again plays a crucial role in the success of the asymmetric control.

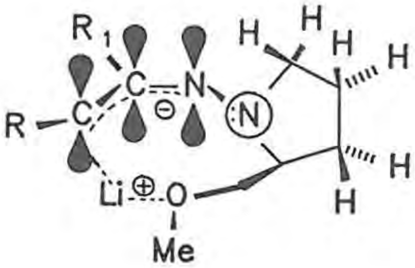
Application of these auxiliaries to asymmetric synthesis can once again be

FIGURE 10 Metallation of both *E*–and *Z*–isomers of either SAMP or RAMP hydrazones favours the $E_{C-C,}Z_{C-N}$ azaallyl anion and alkylation yields an equilibrium of alkylated hydrazones which tends to favour the *E*–product to varying extents.



(Priority: $R_1 > CH_2R_2$)

FIGURE 11 Structure of the lithiated SAMP hydrazones; a π–1–azaallyl$^-$ Li$^+$ intramolecular co–ordinated species, showing the pyrrolidine nitrogen lone pair orbital perpendicular to the azaallylic π system.



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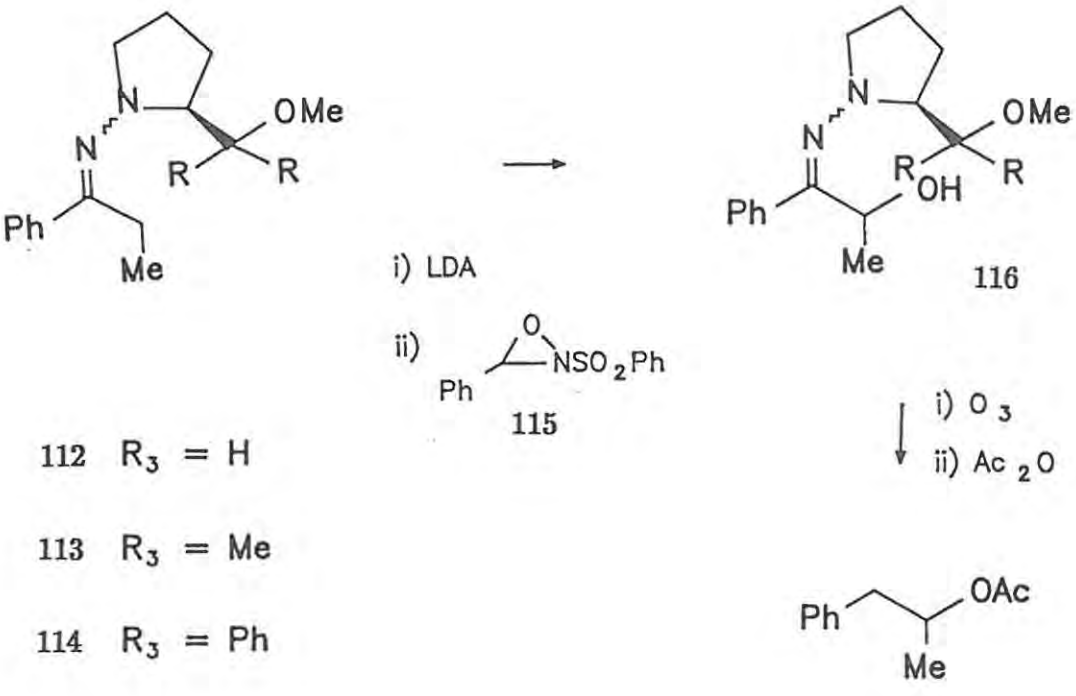
SCHEME 38



112 R_3 = H

113 R_3 = Me

114 R_3 = Ph

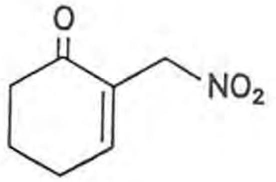
117

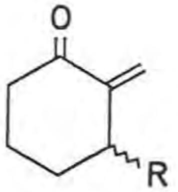
illustrated by the α–alkylation of cyclohexanones. Enders and Eichenauer.[151] developed this approach concurrently with the work of Meyers on azaallyl metal reagents. Both approaches permit equally good enantiomeric control. The SAMP hydrazone approach continues to find use in the solution of contemporary asymmetric problems. Enders and Bhusan [157] have recently demonstrated that the *S*AMP hydrazone (**112**) and the novel, more sterically demanding hydrazones (**113**) and (**114**) can be asymmetrically oxidized to the α–hydroxy ketone. The oxidizing agent employed is 2–(phenylsulphonyl)–3–phenyloxaziridine (**115**) and the reaction is analogous to the oxidation of other enolates and enol derivatives. The hydrazones (**116**) are cleaved by ozonolysis and the α–hydroxy ketones isolated as the α–acetoxy analogues (**117**) in optical yields greater than 90% (Scheme 38).

e) Chiral Leaving Groups

The chiral auxiliary mediated, enantioselective reactions described thus far all yield a diastereomeric primary product, from which the desired enantiomeric compound must be obtained by removal of the chiral auxiliary. If, however, the chiral auxiliary could behave as a chiral leaving group, then the enantiomeric product could be obtained directly. Tamura *et al.*[158] have recently reported one of the first successful enantioselective syntheses based on this concept. They had previously developed a synthetic method for the preparation of 3–substituted 2–*exo*–methylenecycloalkanones (**119**) from 2–(nitromethyl)cycloalkenones (**118**) by conjugate addition of organocuprates, followed by elimination of the nitro group.[159] The enantioselective synthesis was achieved by replacing the nitro group with a chiral amine, as in substrate (**120**), which in the presence of $ZnBr_2$ undergoes conjugate addition of lithium diorganocuprates, followed by elimination of the pyrrolidine upon aqueous workup, to yield optically active 3–substituted 2–*exo*–methylenecyclohexanones (**121**) in very

118





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SCHEME 39

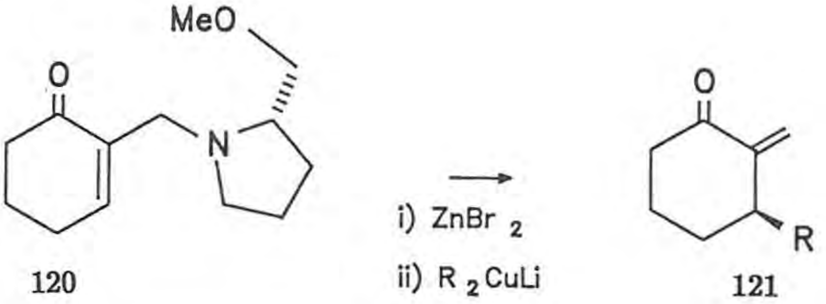
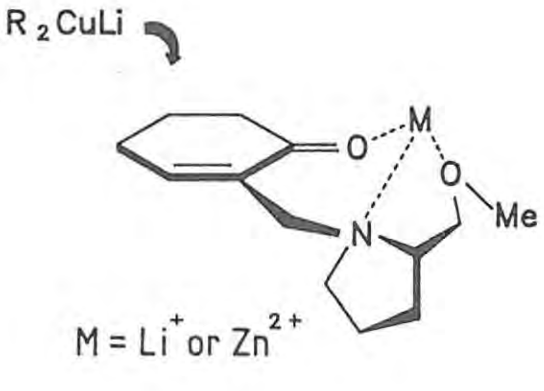


TABLE 7 Percentage enantiomeric excesses achieved in the lithium organocuprate addition to substrate (**120**) and subsequent elimination of the pyrrolidine to yield product (**121**) (Scheme 39).

R	% e.e.
Me	90
n-Bu	90
Et	90
vinyl	86

FIGURE 12 Transition state model in which the *re* face of the enone (120) is partially shielded, directing the organocuprate approach to the *si* face.



high enantiomeric excess (Scheme 39). A transition state model has been postulated in which either the Li^+ or the Zn^{2+} cation co–ordinates to the three hetero atoms, partially shielding the *re*–face (Figure 12). As a consequence of this partial shielding and the steric bulk of the cuprate complex, the addition occurs from the less hindered *si*–face.

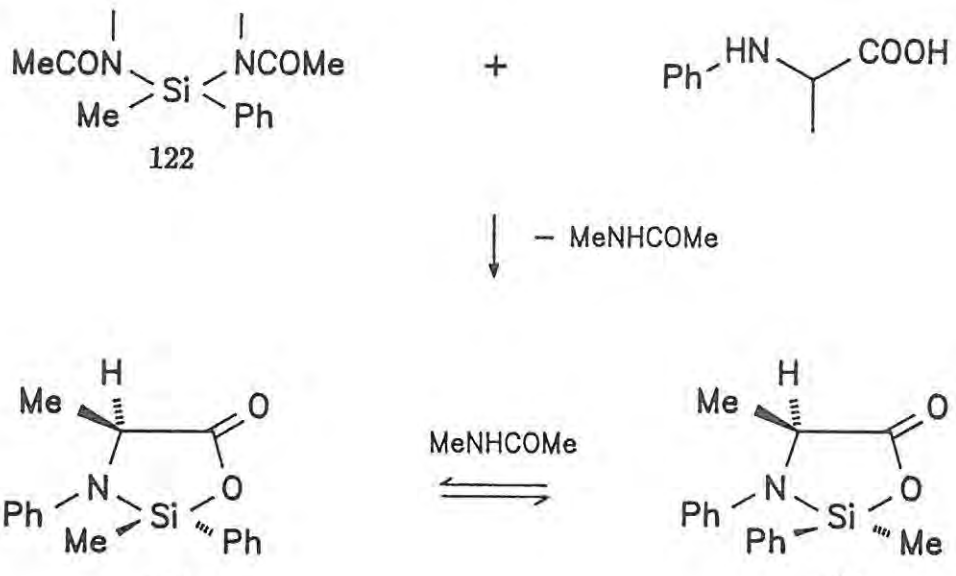
1.4.3.4 Enantioselective Synthesis Employing Optically Active Organosilanes.

It is well established that trimethylsilyl– or phenyldimethylsilyl groups, for example, when attached to a chiral centre, can induce high levels of diastereomeric control in a variety of reactions *e.g.* (electrophilic attack of allyl silanes, aldol reactions and Diels–Alder cycloadditions) *via* a combination of steric and electronic effects.[160] However, the reactions reviewed in this section represent attempts to achieve enantioselective synthesis *via* chirality transfer from an asymmetric silicon centre.

The mechanisms and stereochemistry of substitution reactions at silicon are well understood, due largely to the initial work of Sommer [161] and the subsequent, extensive research by Corriu.[162]

Optically active organosilanes can be obtained *via* similar methods to those described for carbon compounds in Sections 1.1, p. 2, 1.2 p. 5, and 1.3 p. 6. For example, the first useful resolution of a racemic organosilane was effected by reacting 1–naphthylphenylmethylmethoxysilane withh the potassium salt of (–)–menthol, followed by fractional crystallization of the resulting diastereomeric mixture.[163] The first optically active, bifunctionally substituted silanes were prepared *via* a reaction of the prochiral *bis*(*N*–methylacetamido)methylphenylsilane (**122**) (Scheme 40) with optically active amino acids. This reaction afforded diastereomeric mixtures of 2–siloxazolidin–5–ones, such as (**123**) and (**124**), and *N*–methylacetamide. In solution the acetamide catalyses an equilibration of the two diastereomers, one of which precipitates selectively, to effect a separation by means of a second order asymmetric transformation.[164]

SCHEME 40



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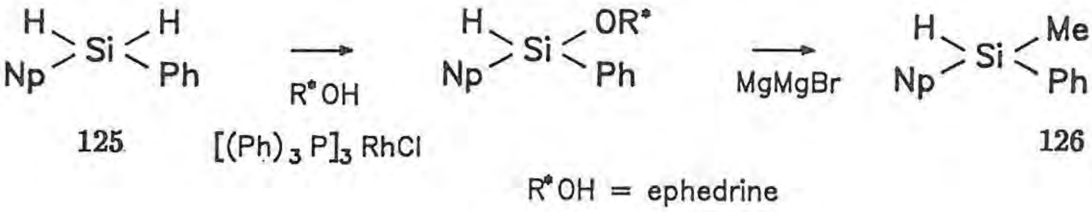
SCHEME 41



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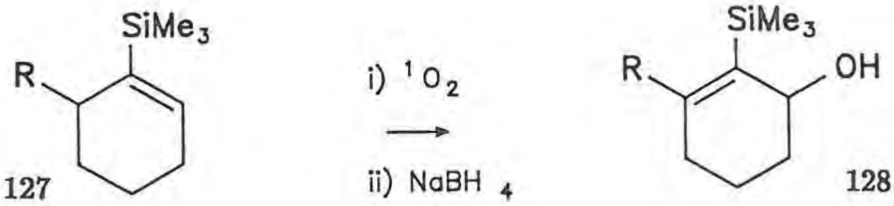
SCHEME 42



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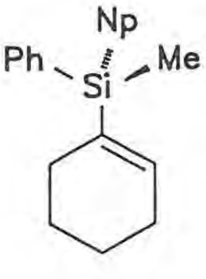

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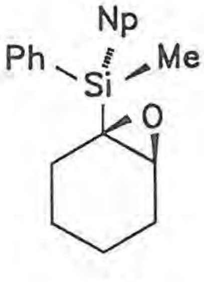

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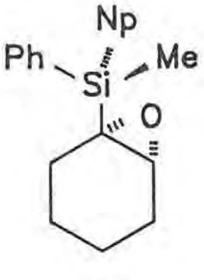

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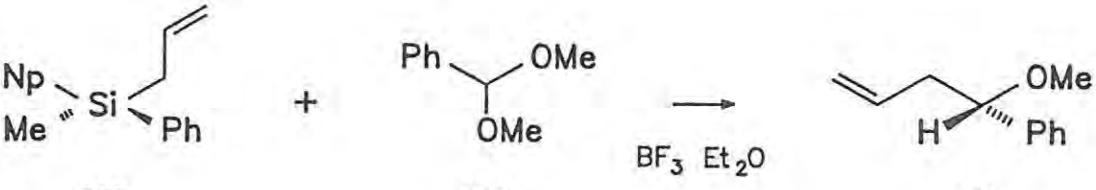
Asymmetric substitutions at a prochiral silicon centre, even when one or more of the substituents are optically active, normally yield only poor enantiomeric excesses. However, one such synthesis has yielded one of the few chiral auxiliaries with an asymmetric silicon centre, that has been successfully applied to chirality transfer from silicon to carbon. The preparation of this chiral auxiliary was achieved by alcoholysis of 1–naphthylphenylsilane (**125**) (Scheme 41) with ephedrine, in the presence of Wilkinson's catalyst $\{[(Ph_3)P]_3RhCl\}$. Further reaction of the resulting 78:22 diastereomeric mixture with methyl magnesium bromide followed by recrystallization, yielded the 1–naphthylphenylmethyl hydrosilane (MeNpPhSiH) (**126**) in 96% enantiomeric excess.[165] The absolute configuration of the hydrosilane is dependent on the choice of ephedrine enantiomer.

While the major application of optically active organosilanes has been in the examination of the mechanism and stereochemistry of nucleophilic displacement at silicon, there have been sporadic reports of the use of MeNpPhSiH (**126**) as a chiral auxiliary. It has been shown that vinyltrimethylsilanes (**127**) (Scheme 42) undergo regiospecific singlet oxygenation and subsequent $NaBH_4$ reduction of the hydroperoxide product to yield the β–silylated alcohol (**128**).[166] Daniels and Paquette .[167] first explored the potential of (+)–MeNpPhSiH [(+)–(**126**)] as a chiral inducing agent, by investigating the analogous, chiral reaction of the cyclic vinyl silane (**129**) with singlet oxygen, but all the attempted photo–oxygenations failed and the chiral vinylsilanes were recovered intact. An alternative oxidation of the vinyl silane (**129**), employing MCPBA, yielded a 43:57 mixture of the diastereomeric α,β–epoxysilanes (**130**) and (**131**). These epoxides, however, were resistant to all attempts to effect ring opening to the allylic alcohols.[167]

Hathaway and Paquette *et al.*[168] then examined the reaction of (–)–1–naphthylmethylphenylallylsilane (132) (Scheme 43) with aldehydes and dimethyl acetals, in the presence of Lewis acid catalysts. All the reactions with aldehydes failed, and $BF_3 \cdot Et_2O$ was the only Lewis acid to yield the desired homoallylic ether (134) from the dimethyl acetal (133). The chemical yields were less than 30%, in all reported cases, and the enantiomeric excesses were very low (approximately 5%), prompting Paquette's remark that "The following summary of our results may deter others from pursuing similar lines of investigation based upon this particular substrate."

SCHEME 43



132 133 134

There have, however, been further attempts to improve the enantioselectivity of this silicon chiral auxiliary, as illustrated by the following examples.

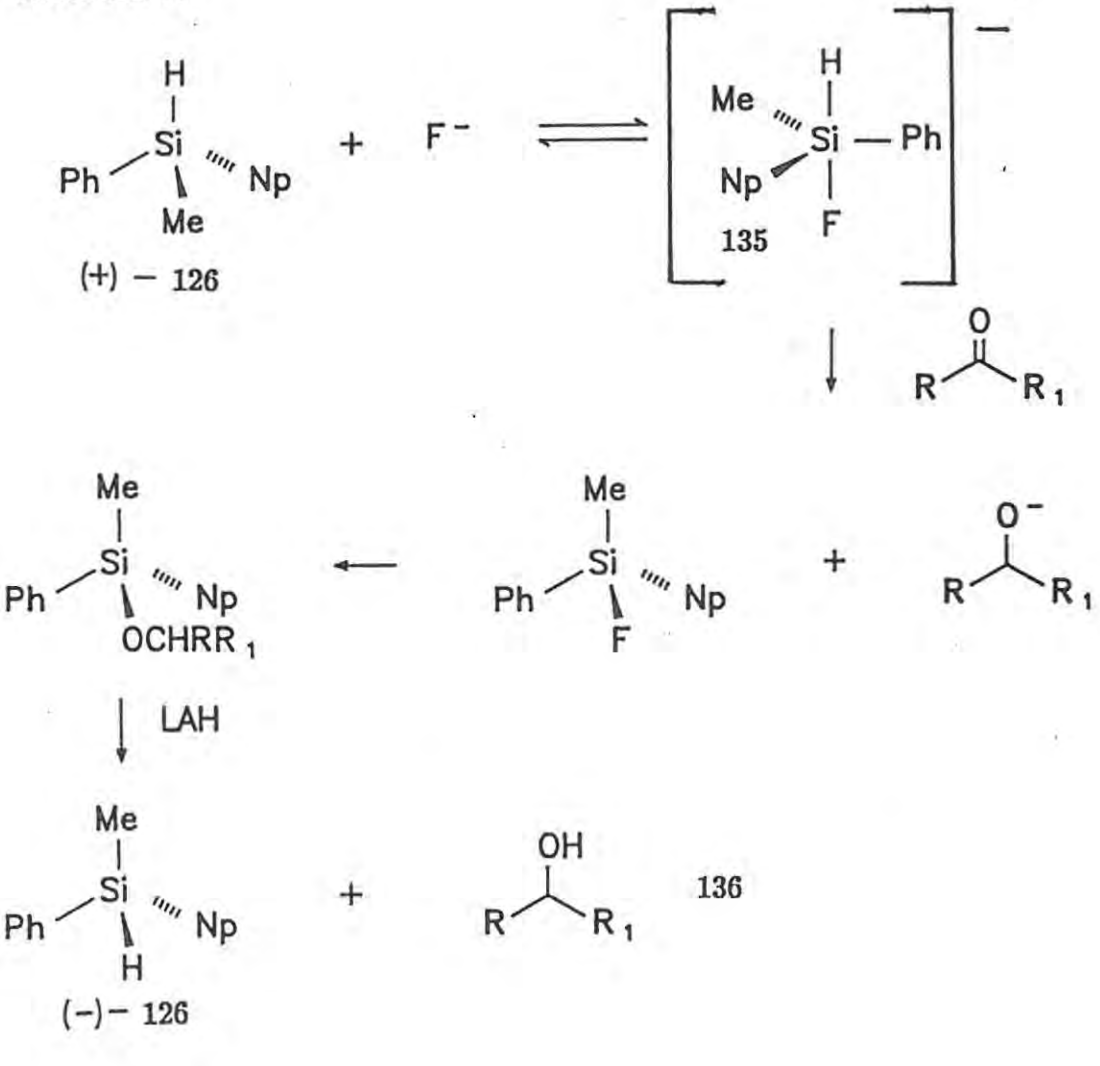
Vol'pin *et al.*[169] had established that fluoride ions catalyse the formation of alkoxysilanes from the reaction of organosilicon hydrides and certain aldehydes and ketones *via* the following sequence:

1) $R'_3SiH + F^- \rightleftharpoons R'_3SiFH^-$
2) $R'_3SiFH^- + R_2C{=}O \rightarrow R'_3SiF + R_2CHO^-$
3) $R'_3SiF + R_2CHO^- \rightarrow R'_3SiOCHR_2 + F^-$

(The intermediacy of valence expanded, penta–co–ordinate silicon species, as in R'_3SiFH^-, is well established in nucleophilic substitution reactions at silicon [170]).

Fry and McAdam.[171] have repeated this fluoride ion–catalysed reduction, using the enantiomerically pure (*R*)–(+)– organosilicon hydride [(*R*)–(+)–(**126**)], and examined the stereochemical outcome at <u>both</u> the carbon and silicon asymmetric centres in compounds (**126**) and (**136**) (Scheme 44). The predominantly inverted stereochemistry in the organosilicon hydride product (**126**) is to be expected for substitution at silicon of a good leaving group (H^-) by a strong nucleophile (F^-).[172] Although the enantioselectivity for the formation of the new chiral carbon centre in compound (**136**) is low, it is indicative of a chiral reducing species. These results can be accommodated (in terms of reactions 1 – 3 above) as outlined in Scheme 44 , where the trigonal bipyramidal penta–co–ordinate species (**135**), is the chiral reducing agent. The LAH cleavage of the alkoxysilane to the hydride (**126**) and the alcohol (**136**) proceeds with retention of configuration at silicon.

SCHEME 44



Larson *et al.*[173] reacted (*R*)–(–)–(1–naphthyl)phenylmethylsilylmethyl lithium prepared from (1–naphthyl)phenylmethylsilane (**126**), with a variety of aldehydes and ketones, to produce *β*–hydroxysilanes in good material yields, but poor diastereomeric excesses (3–4%).

Bonini *et al.*[174] have prepared (*R*)–(–)–(1–naphthyl)phenylmethylsilylmethyl thioketone (**138**) (Scheme 45) from the corresponding ketone (**137**) and have achieved moderate to good stereoselectivity in two different reactions with this thioketone. A cycloaddition reaction with buta–1,3–diene yielded the two diastereomeric thiopyrans (**139**), which on protodesilylation with TBAF yielded 2–phenyl–3,6–dihydro–2*H*–thiopyran (**140**) in 51 ± 8% enantiomeric excess.[174] Thiophilic addition of a variety of organometallic reagents to the thioketone (**138**) and subsequent quenching with methanol, yielded the *α*–silylsulphides (**141**) in modest diastereomeric excesses (Scheme 45).[175]

Learned [176] had established that insertion of symmetrically substituted alkenylidenecarbenes into the Si —H bond of (*S*)–(–)–MeNpPhSiH [(*S*)–(–)–**126**] proceeds, with at least 98% stereospecificity. Stang and Learned [177] have applied this reaction to dissymmetrically substituted alkenylidenecarbenes (**142**) and (**143**) (Scheme 46), in an attempt to introduce axial chirality into the resulting silaallenes (**144**) and (**145**). [(Partial rearrangement to the sila-alkyne (**146**) occurs spontaneously.)]

Multiple integration of the appropriate diastereomeric ^{1}H n.m.r. signals indicated the diastereomeric excesses to be 3.5 ± 0.5% for the methyl derivative and 10.5 ± 0.5% for the *tert*–butyl derivative. Two plausible transition states, (**147**) and (**148**), have been proposed and Stang and Learned [177] have suggested the *tert*–butyl–phenyl interaction (Figure 13a) are

SCHEME 45

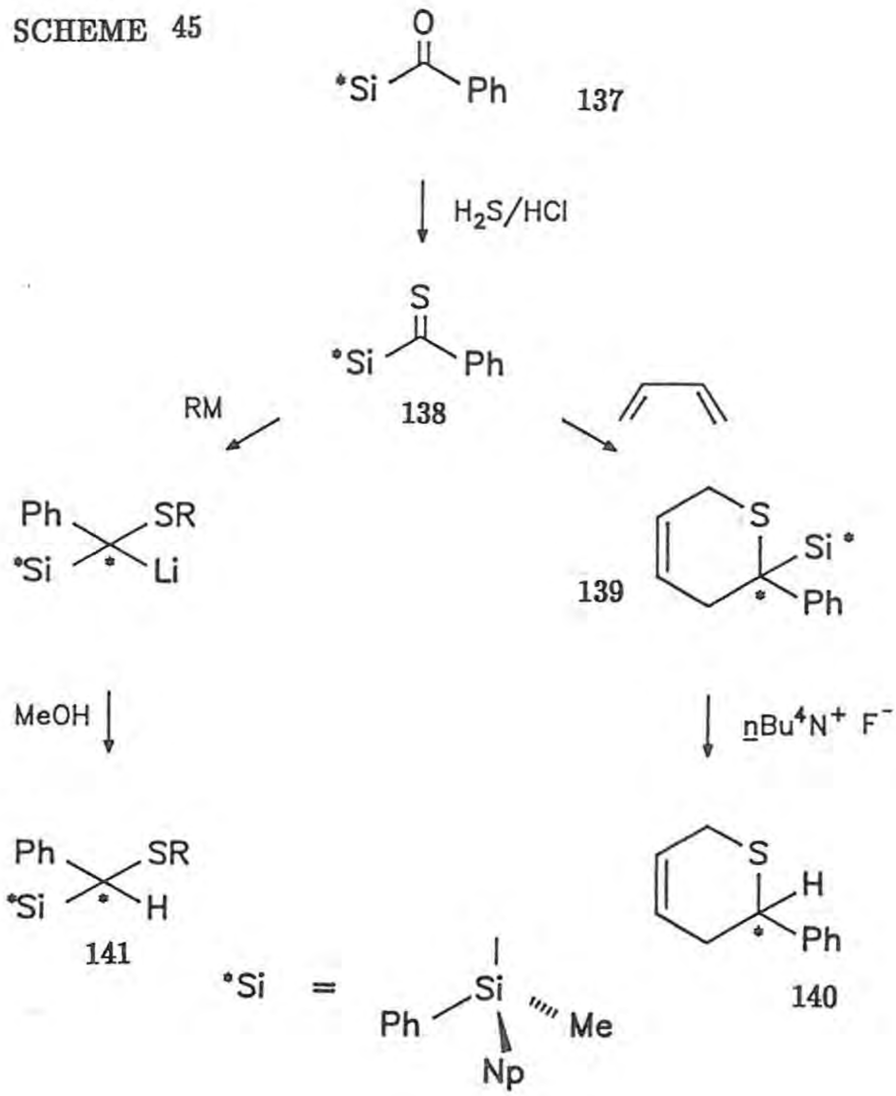


TABLE 8 Percentage diastereomeric excess achieved in the reactions of organometallic reagents with the α–silylthioketone (138).

RM	% d.e.
MeLi	53
PhLi	40
MeMgBr	40
PhMgBr	76

SCHEME 46

142 $R = Me$

143 $R = Bu^t$

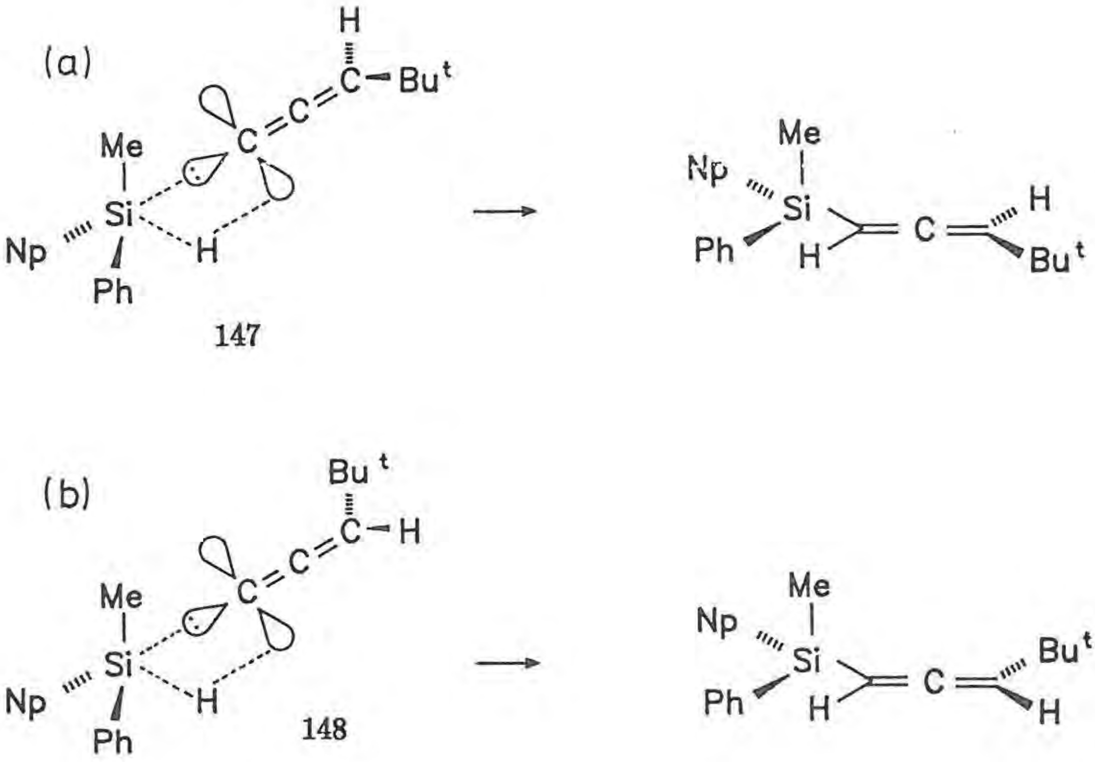
$$[RCH{=}C{=}C:] \xrightarrow{(-)\text{-MeNpPhSiH}} RCH{=}C{=}CHSiMeNpPh + RCH_2C{\equiv}CSiMeNpPh$$

144 $R = Me$

145 $R = Bu^t$

146

FIGURE 13 (a) Transition state (147) – *tert*–butyl/phenyl interaction. (b) Transition state (148) – *tert*–butyl/naphthyl interaction.



less serious than the *tert*–butyl–naphthyl interaction (Figure 13b), thus favouring transition state (147), which leads to the preferential formation of the (*R*,*S*)–diastereomer. The increase in asymmetric induction from methyl to *tert*–butyl substrates is merely a function of the steric bulk of the allene.

Kusnezowa *et al.*[178] have prepared *cis–trans* silyl enol ether mixtures from a range of acyclic dicarbonyl compounds and chloro(1–naphthyl)phenylmethylsilane. However, these silyl enol ethers bearing a stereogenic silicon atom are susceptible to intramolecular silyl group migration between the oxygen atoms and do not appear to have been applied to asymmetric synthesis attempts.

From the above examples, it can be clearly seen that the application of silicon–centred optically active organosilanes to effect chirality transfer, has, in general, been disappointing, both in terms of the poor enantioselectivity attained and the limited selection of chemically successful reactions that are available. The reasons for the relative failure of silicon–centred chiral auxiliaries, when compared to carbon–centred chiral auxiliaries, are believed to include the following:–

i) The difficulties encountered in obtaining enantiomerically pure organosilanes; this must be achieved *via* synthetic or resolution techniques as no chiral silicon "pool," analogous to the natural carbon chiral "pool," exists.

ii) The chiral auxiliary almost exclusively employed is MePhNpSiH (126) and, thus, any induced stereoselectivity depends on the difference between a 1–naphthyl and a phenyl group, a difference which could, in terms of chiral recognition, be insufficient.

iii) The overall steric bulk of the MePhNpSiH group may be large enough to inhibit numerous reactions which might, otherwise, be quite feasible.

However, the concept of combining the highly developed fields of achiral organosilicon chemistry and chiral auxiliary mediated asymmetric synthesis, into a viable, alternative strategy for asymmetric synthesis remains a very attractive one. The aim of our present investigation and those of a few other research groups worldwide, has been to explore methods for successfully achieving this combination.

1.5 METHODS OF DETERMINING ENANTIOMERIC EXCESSES

The ability to measure product enantiomeric ratios is essential to the evaluation of the asymmetric syntheses. Numerous methods for determining enantiomeric excesses have been developed and these include:

Polarimetry (Section 1.5.1)
Isotope–dilution techniques (Section 1.5.2)
Chromatographic techniques (Section 1.5.3, p. 86)
Nuclear magnetic resonance techniques (Section 1.5.4, p. 87)

1.5.1 Polarimetry

The correlation of optical rotation with a percentage enantiomeric excess is possible if one of the pure enantiomers of the desired product has been isolated previously.

However, there are several disadvantages associated with this technique, *viz.*, the optical activity of the pure enantiomer is often unavailable, the demands of purifying the reaction mixture may be severe, the chiral product must be isolated without accidental enantiomer enrichment or racemisation, the accuracy of the determination depends on the magnitude of the rotation (this can be very small, especially in cases where the asymmetric induction is low) and the measured rotations may be solvent and temperature dependent.

1.5.2 Isotope–Dilution Techniques [179]

Isotope–dilution analyses can be applied to the determination of enantiomeric excess provided certain requirements are fulfilled, *viz.*, it must be possible to isolate a pure sample of the compound to be analysed, and an isotopically labelled sample of the product must be accessible in known enantiomeric purity.

The analytical procedure involves three steps.

a) The isotopically labelled sample is mixed with the test sample of unknown enantiomeric purity.

b) A sample is isolated from this mixture.

c) The isotope content of this isolated sample is determined and from this result the enantiomeric composition of the original test sample can be determined.

The isotopic concentration of both the isotopically labelled sample and the sample isolated after mixing must be accurately measured. For radioactive isotopes *e.g.* (^{14}C), scintillation counting is the most convenient technique, while for non–radioactive isotopes, mass spectrometry *e.g.* (^{15}N), and ^{1}H NMR for deuterium labels, have been successfully applied.

1.5.3 Chromatographic Techniques

It has been noted earlier (Section 1.1.1, p. 2) that chromatographic techniques are available for the isolation of optically active molecules. The application of such techniques to the measurement of enantiomeric excesses [180,181] may involve use of either indirect or direct methods. The indirect method relies on the conversion of enantiomeric mixtures into diastereomeric mixtures *via* derivatization with an enantiomerically pure resolving agent. Subsequent chromatographic analysis of the resulting diastereomers and integration of the resolved signals yields the original enantiomeric composition. Inherent in this method are several potential sources of error, *viz.*,

a) the derivatization may proceed with significant racemization or kinetic resolution and

b) accidental fractionation may occur during the purification of the derivatizing reaction mixture.

The direct method, on the other hand, involves chromatography of the enantiomeric mixture on an optically active stationary phase and is proving to be more reliable. The rapid, reversible interactions of the racemic analytical sample and the stationary phase almost entirely eliminate the errors associated with indirect methods. The major disadvantages are associated with finding a suitable stationary phase and the price of commercial columns.

1.5.4 Nuclear Magnetic Resonance Techniques

All the NMR methods of determining enantiomeric excesses rely on rendering isochronous enantiotopic nuclei anisochronous by converting the enantiomeric mixture into a diastereomeric one. The parameters of the analysis are then the relative intensities of selected anisochronous signals from diastereotopic groups. The enantiomers can be rendered diastereomeric by:– reacting the enantiomers with optically pure derivatizing agents, using chiral solvating agents, or using chiral shift reagents.

A chiral derivatizing agent must carry an appropiate NMR probe that affords clearly separated NMR signals, preferably singlets, for at least one NMR active nucleus, *e.g.* methyl, methoxyl or *tert*–butyl groups. Furthermore, the derivatizing agent must have a well–defined conformational preference to ensure that the diastereotopic groups will be situated in markedly different magnetic environments. A reagent that fulfils these requirements remarkably well is the Mosher reagent, *α*–methoxy–*α*–trifluoromethylphenylacetic acid, MTPA (149).[182] It is stable to racemization even under extreme pH conditions,

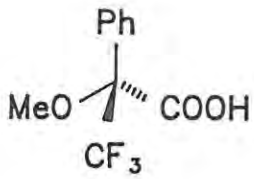


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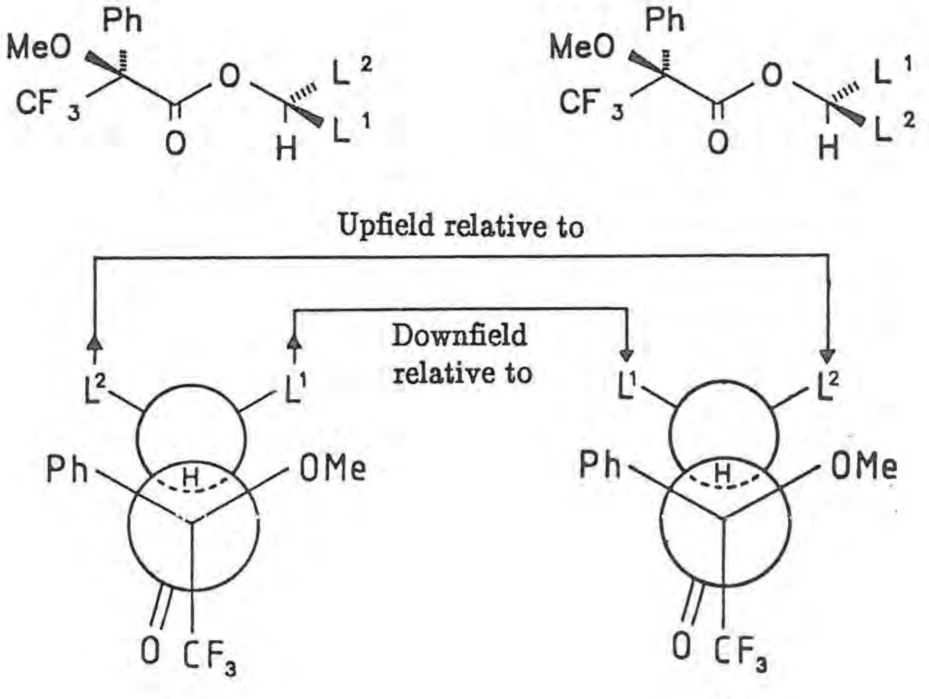
FIGURE 14 The two diastereomeric esters formed by the reaction of the Mosher reagent with a general enantiomeric alcohol (CHOHL¹L²), showing the shielding effect of the α–phenyl group.



(a) (b)

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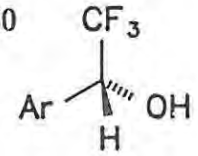
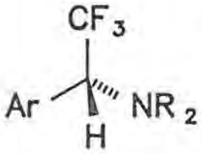


Ar = 1 – naphthyl

151



Ar = Ph , R = Me

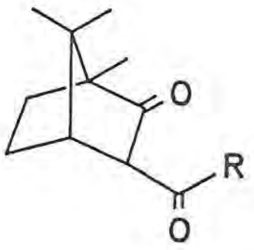
largely due to the absence of any α–hydrogens. The methoxy group is an effective probe and the preferred conformation of MTPA esters is known to be that in which the CF_3 and carbonyl groups are eclipsed [183] (Figure 14). Chemical non–equivalence in the diastereomeric MTPA derivatives is often enhanced due to selective shielding by the α–phenyl group.

A further advantage of the the MTPA derivatives is that ^{19}F chemical shift non–equivalence is also observed. The chemical shift differences of the diastereotopic α–CF_3 groups are generally larger (0.11 – 0.71 ppm) than those of the proton signals (0.03 – 0.13 ppm).

Pirkle [184] and Mislow [185] first realized the potential of chiral solvating agents when they independently demonstrated that enantiomers exhibit different NMR spectra when dissolved in optically active solvents. The majority of such experiments are conducted by dissolving the enantiomeric mixture in an achiral, aprotic, and relatively nonpolar solvent and adding a 3 – to 5 – fold excess (relative to the enantiomeric mixture) of the solvating agent.

The observed anisochrony is assumed to originate from a binary association of the individual enantiomers with the optically pure solvating agent. Aryl groups, bonded directly to the chiral centre of the solvating agents, enhance the difference in local magnetic environments of the sensor nuclei in the diastereomeric association complexes. In general, the solvating agents rely on hydrogen bonding as the primary binding force. Due to their general applicability and commercial availability, the aryltrifluoromethylcarbinols (**150**) and 1–arylethylamines (**151**) are among the most extensively employed solvating agents. The choice of whether to use [(**150**) or (**151**)] is dictated by whether the compound to be analysed is a hydrogen bond donor or acceptor.

Hinckley [186] was the first to describe the effect of shift reagents on the ^1H NMR spectrum and considerable effort has subsequently been devoted to developing these reagents. Shift reagents are hexa–co–ordinate lanthanide organometallics, which as Lewis acids, are capable of forming weak addition complexes with numerous organic bases. The ability of chiral shift reagents to induce significantly different shifts for protons in different stereochemical environments was first described by Whitesides and Lewis.[187] Their initial shift reagent was europium 3–pivaloyl–*d*–camphor $Eu(pvc)_3$. Among the most effective chiral shift reagents currently known are the acyl camphors (**152**) and (**153**).[188,189,190]



152 $R = CF_3$ Metal = Eu $[Eu(tfc)_3]$

153 $R = CF_3$ Metal = Pr $[Pr(tfc)_3]$

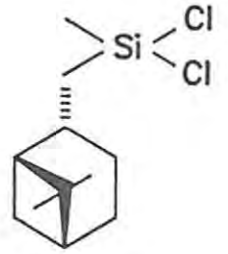
Two mechanisms have been proposed to explain how the resolution of enantiomeric signals is accomplished *via* chiral shift reagents.[188] In one it is assumed that the two diastereomeric complexes have different stabilities, and as a result, all the signals in the more strongly bound isomer will be affected to a greater extent than those of the other diastereomeric complex. In the second each enantiomer is considered to form complexes of different geometries, thus accounting for different induced shifts.

During the latter half of the twentieth century sophisticated methods for obtaining optically pure molecules have been developed. Now that the advantages of increasing the rigidity of the transition state are clearly understood, asymmetric syntheses are regularly effected with enantiomeric selectivities exceeding 95%. More importantly, in many cases, the favoured enantiomer can be predicted. While the horizons of synthetic organic chemistry have been considerably broadened by these enhanced asymmetric capabilities, new approaches must be continually developed and evaluated to bring ever closer the synthetic goal of routinely emulating enzymatic enantioselectivity.

2.DISCUSSION

When this investigation began, in January 1988, the concept of combining the well established fields of organosilicon mediated synthesis and chiral auxiliary induced asymmetric control into a viable, alternative method of asymmetric synthesis (*via* organosilicon chiral auxiliaries) had been restricted, largely, to approaches in which the asymmetric atom of the auxiliary was the silicon itself (Section 1.4.3.4, p. 75). With few exceptions,[174,175] this strategy has failed to accomplish chirality transfer in acceptable material or optical yields, prompting the investigation of chiral organosilicon auxiliaries in which the chirality is located at a site remote from the silicon atom. This strategy, which is the focus of the present investigation, is gaining momentum worldwide and asymmetric syntheses employing certain chiral organosilicon substrates have recently yielded moderate to good enantiomeric control, as will be seen in the ensuing discussion.

Asymmetric syntheses employing optically active organosilanes, which derive their chirality from asymmetric carbon atoms rather than silicon atoms, were pioneered in 1983, by Chan and Wang.[191] They prepared the chiral chlorosilanes (**154**) and (**156**), from β–pinene, *via* the well known, platinum catalysed, hydrosilation reaction; [192] subsequent LAH reduction of these chlorosilanes yielded the hydrosilanes (**155**) and (**157**). Achiral hydrosilanes have been used to reduce prochiral ketones to optically active alcohols in the presence of chiral catalysts.[193,194] In an analogous asymmetric reaction Chan and Wang [191] used the hydrosilane (**155**) to reduce alkyl and aryl prochiral ketones in the presence of the Wilkinson catalyst [$(Ph_3P)_3RhCl$], to yield secondary alcohols in enantiomeric excesses ranging from 8.8 to 25.7%.



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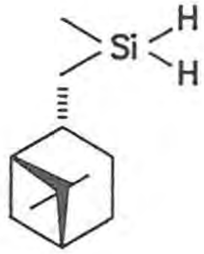

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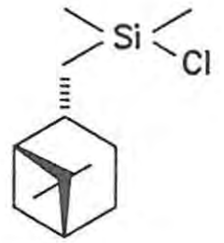

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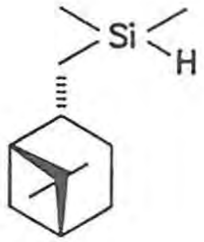

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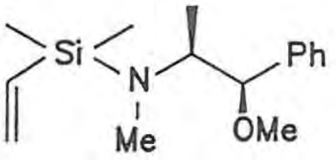

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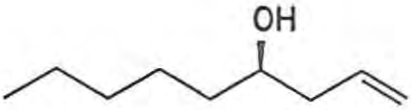

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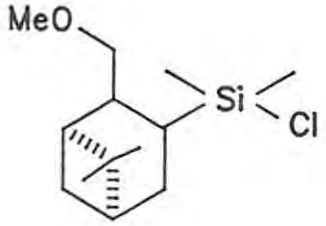

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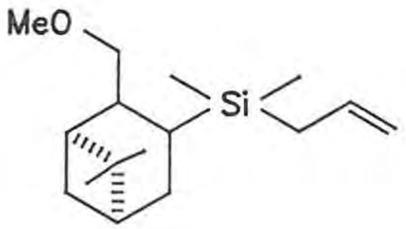

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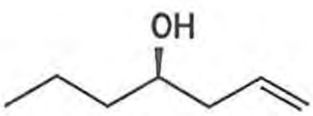

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Tamao *et al.*[195] were the first to attempt the asymmetric applications of known reactions of vinyl silanes.[196] Using (–)–ephedrine–derived chiral vinylsilanes such as (**158**), they applied their previous results [197,198] to the preparation of optically active alcohols [*e.g.* (**159**) in enantiomeric excess of 60%, as determined by ^{1}H NMR chiral shift reagent studies].

Taddei *et al.*[199] used the chiral chlorosilane (**160**) [derived from (1*R*)–(–)–myrtenal, by applying a method described by Fleming *et al.*[200] that makes use of silyl–cuprate addition to α,β–unsaturated aldehyde] to synthesize the first C–centred optically active allylsilane (**161**). Treatment of this optically active allylsilane with butanal, in the presence of $TiCl_4$, yielded, under optimized conditions, the homoallylic alcohol (**162**)[a] and regenerated the chlorosilane (**160**).The enantiomeric excess of the isolated homoallylic alcohol was 46%, established by both Mosher's method [182] and by comparison of optical rotation data with known values for the product (**162**). The material yields of the reaction were, however, disappointing, never exceeding 58%. Chan and Wang [202] have reported similar reactions of chiral allylsilanes, using their pinene derived chlorosilane (**156**) as a chiral auxiliary, which significantly improved the material yields, but reduced optical yields. At best, they achieved a 15% enantiomeric excess with propanal, using $SnCl_4$ as the Lewis acid. The absolute configuration of the homoallylic alcohol was found to be highly dependent on the Lewis acid employed; $SnCl_4$ and $BF_3\cdot OEt_2$ always yielded an excess of the (*S*)–enantiomer, while $TiCl_4$ consistently yielded an excess of the (*R*)–enantiomer.

At the time this investigation was initiated, the above examples represented

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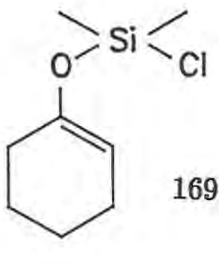
[a] The achiral reactions of allyl silanes and carbonyl compounds are well known, having been first described by Hosomi and Sakurai.[201]

the "state of the art" of asymmetric synthesis employing chiral auxiliaries, bonded to a prochiral substrate *via* silicon. A comprehensive literature search revealed that applications of this novel approach to the versatile and well understood silyl enol ether systems [203-205] remained unexplored. If chiral silyl enol ethers could, in fact be used as successful substrates for asymmetric synthesis, then asymmetric variation of the many synthetically important reactions of these compounds could be easily envisaged.

Consequently, the objectives of this investigation were clearly defined as the following:–

- **i) To develop general methods for the preparation of enantiomerically pure silyl enol ethers, chiral by virtue of optically active auxiliaries attached to silicon.**
- **ii) To examine and evaluate the potential of such silyl enol ethers to undergo asymmetric electrophilic reactions**

While our initial literature search did not reveal any reactions of such chiral silyl enol ethers, one report, published by Walkup,[206] in 1987, on their preparation was discovered. Walkup had prepared by a "one pot" procedure, a variety of pinacolone (**163**)–derived silyl enol ethers, including several optically active examples (**164–167**) (Scheme 47). Walkup also described the isolation of the intermediate chloro silyl enol ether (**168**), itself an unusual compound, since only one other chloro silyl enol ether (**169**) had been reported at that time.[207] Walkup was concerned with the steric and electronic effect of alkoxy ligands on the reactivity of silyl enol ethers, relative to the better known trialkyl silyl enol ethers.



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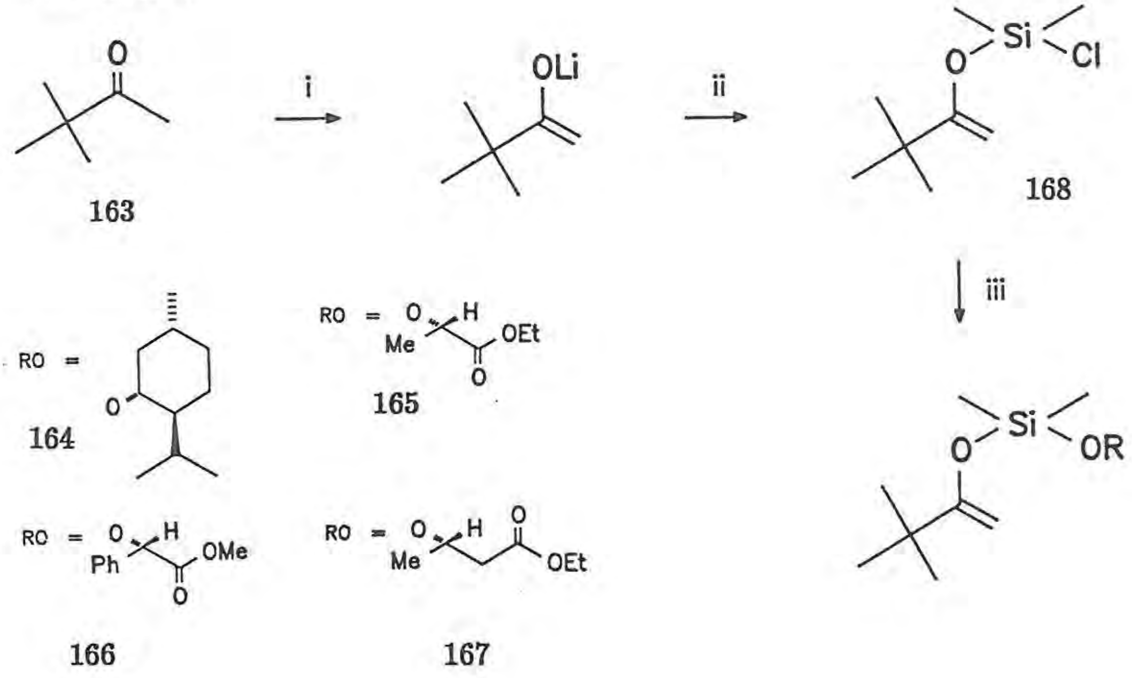
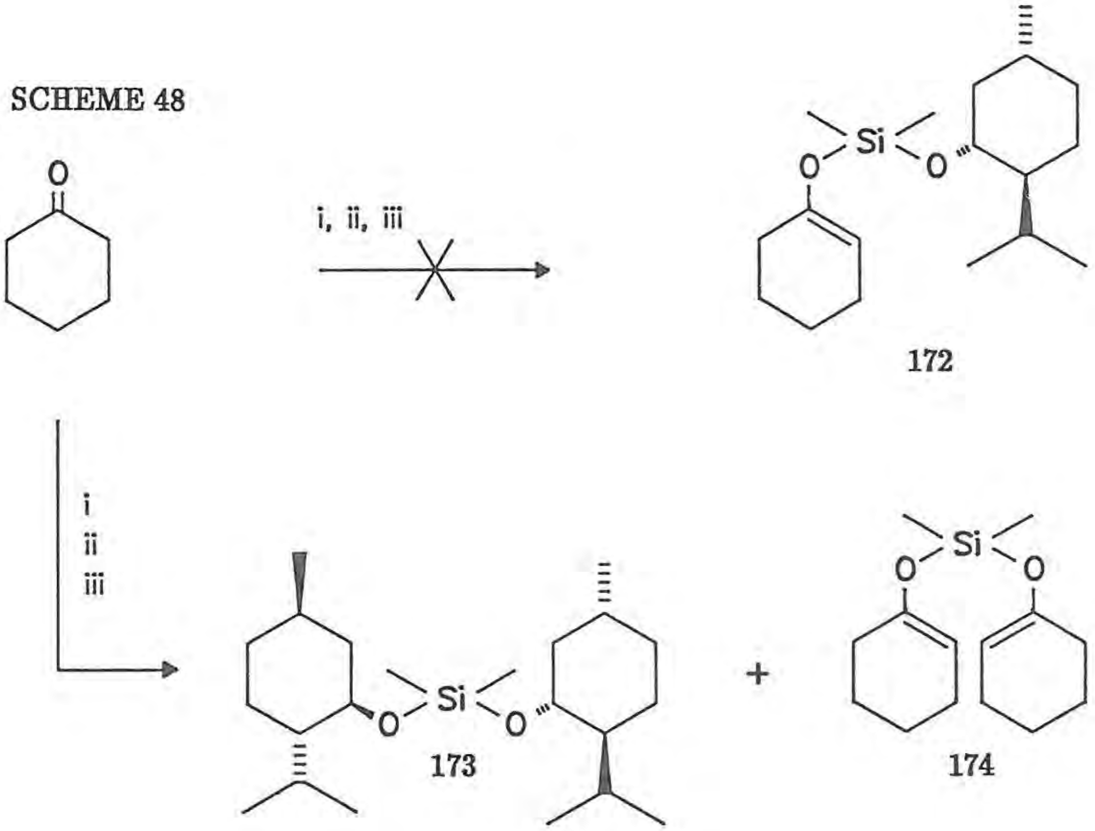
SCHEME 47



Reagents

i) LDA, ii) Cl_2SiMe_2, iii) ROH/Et_3N

SCHEME 48



Reagents

i) LDA, ii) Cl_2SiMe_2, iii) $Menthol/Et_3N$

2.1 PREPARATION OF OPTICALLY ACTIVE SILYL ENOL ETHERS[208]

The synthetic potential of silyl enol ethers *e.g.* trimethyl– or *tert*–butyldimethylsilyl derivatives as isolable, carbonyl enolate equivalents, was first realized, independently, by House *et al.*[209] and Stork and Hudrlik.[210] The former workers described, in detail, how these silyl enol ethers could be prepared and the conditions necessary to selectively obtain either the kinetic or thermodynamic product in the case of unsymmetrical ketones. The thermodynamically favoured products are obtained by refluxing the ketone in DMF in the presence of Et_3N and TMSCl – conditions permitting equilibration. The kinetic products, on the other hand, were obtained by proton abstraction of the most acidic proton using non–nucleophilic lithium bases (*e.g.* LDA) and subsequent addition of TMSCl at low temperature. While a variety of alternative preparations have since been reported,[211-213] the original methods remain the classic routes to silyl enol ethers.

In the present study it was considered desirable to examine, in the first instance, chiral silyl enol ethers prepared from symmetrical ketones (to obviate competition between kinetic and thermodynamic control) and readily available, inert chiral auxiliaries. The terpenoid alcohol, menthol, used by Walkup, met these criteria. (Chan *et al.*[214] have subsequently employed menthol and other similar terpenoid alcohols, in an extension of their work on optically active allyl silanes, to prepare chiral 2,4,6–trisubstituted tetrahydropyrans in modest enantiomeric excess.) Our initial efforts were, thus, directed towards repeating and extending Walkup's work. The menthol silyl enol ether (**164**) was, consequently, prepared following the published route (Scheme 47).[206] The isolated yield of the silyl enol ether (**164**) was considerably lower than that quoted in the literature.

These reactions are typically conducted at low temperature in order to enhance the established reactivity order of halosilanes towards nucleophilic attack, *viz.*,

$SiCl_4 > RSiCl_3 > R_2SiCl_2 > R_3SiCl$.[215]

The reaction of alcohols with halosilanes, in the presence of Et_3N, as utilized in the *in situ* conversion of the chloro silyl enol ether (**168**) to the chiral alkoxy silyl enol ether (**164**) (Scheme 47) has become important in synthetic organic chemistry. Its significance was first realized by Pierce [216] in 1968 and it provided one of several vital stimuli that has led to the dramatic development of organosilicon chemistry.[b]

Having established, with some reservations, the reproducibility of Walkup's procedure, it was necessary for our purposes to extend this "one pot" preparation to a variety of ketones. The initial choice of ketones was dictated by two important criteria, *viz.*,

i) As stated previously, a symmetrical ketone molecule was essential to avoid having to establish kinetic or thermodynamic control over the course of the enolization. (Although pinacolone is unsymmetrical, there is only one form of α–proton and hence the enolization can only proceed in one direction.)

ii) Except in one case where this criterion was deliberately ignored [See compound (**186**)], the possibility of geometric isomerism in the enolate had to be avoided. This was achieved

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[b] Other major contributions were the work of Peterson [217] on a silicon equivalent to the Wittig reaction, and the work of House [209] and Stork [210] on silyl enol ethers, already mentioned above.

> by either chosing ketones in which the enol double bond formed in the terminal position and hence no (*E*)/(*Z*) isomerism was possible (as in the case of pinacolone) or by making use of cyclic ketones, which, unless the ring size is unusually large, automatically imposes an (*E*) geometry to the enolate.[c] In their original publication House *et al.*[209] observed varing degrees of geometric control when employing the LDA approach.

The obvious choice for such a ketone was cyclohexanone. Our attempts to apply the "one pot" preparation to the synthesis of the chiral cyclohexanone silyl enol ether (**172**) proved, however, unsuccessful, affording instead the *bis*–substituted silanes (**173**) and (**174**) (Scheme 48, p. 96).The reason for the increased reactivity of the cyclohexanone lithium enolate (relative to the analogous pinacolone enolate under identical conditions) leading to complete substitution of dichlorodimethyl silane by the available enolate is unclear. The formation of the *bis*–(menthyloxy)silane (**173**) is then simply ascribed to disubstitution of the remaining dichlorosilane by the excess alcohol, present at that stage of the reaction. Walkup only detected the analogous

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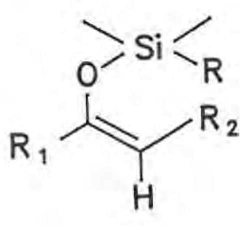
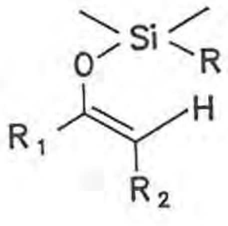
[c] When considering geometric isomers of silyl enol ethers in this thesis the (*E*)/(*Z*) notational format for olefins is adopted, with the proviso that for the C_1 enolate substituents, R_1 and $OSiMe_2R$, the highest priority is always assigned to O–silyl group. Thus, general silyl enol ethers (**170**) and (**171**) are defined as having (*Z*) and (*E*) geometries respectively.

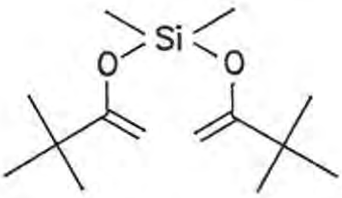


(*Z*) 170



(*E*) 171

bis–alkenyloxysilane (**175**) from the pinacolone enolate if the reaction was conducted with only 0.5 molar equivalents of dichlorodimethylsilane. The reasons for this discrepancy were not investigated any further but rather an alternative synthesis was sought in order to obtain the desired silyl enol ethers as quickly as possible.



175

An attractive alternative appeared to be a convergent synthesis in which the chloro(menthyloxy)silane (**176**) would be prepared, isolated, and subsequently reacted with the cyclohexanone lithium enolate to yield the desired cyclohexanone silyl enol ether (**172**) (Scheme 49). The chloro silane (**176**) was easily prepared from (–)–menthol and one equivalent of dichlorodimethylsilane in moderate yields.[d] This material gave satisfactory IR, MS, and ^{1}H NMR spectra but elemental analysis was impossible due to the reactive nature of the compound. If stored in an anhydrous, cold environment, this clear liquid was stable for several weeks at least. The composition of the small amounts of precipitate that formed during storage was not established but this material did not appear to affect the integrity of the supernatant liquid in any way.

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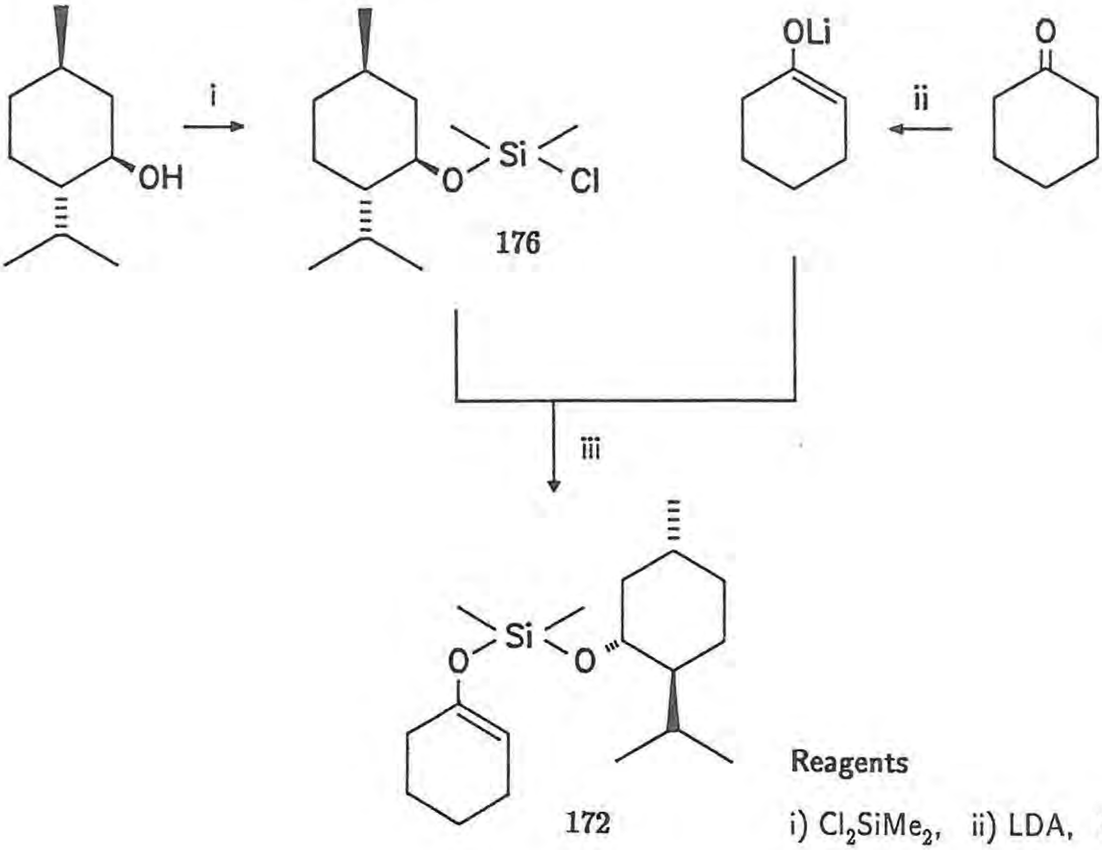
[d] Chan *et al.*[218] in work to be discussed later (see Section 2.3), have alluded to the preparation of this compound.

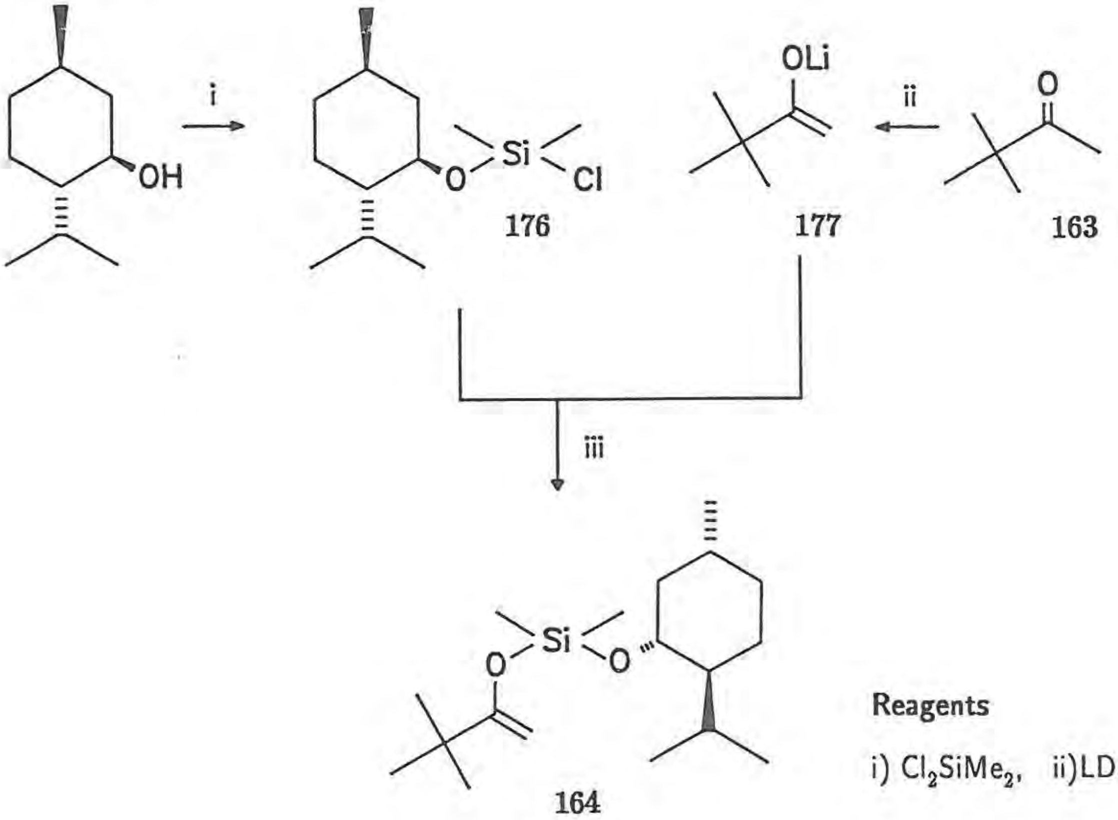
SCHEME 49



Reagents

i) Cl_2SiMe_2, ii) LDA, iii) Et_2O

SCHEME 50



Reagents

i) Cl_2SiMe_2, ii)LDA, iii)Et_2O

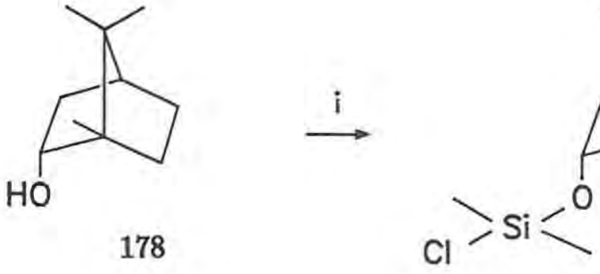
Examination of the residual material, after distillation of the reaction mixture, by GLC and ^{1}H NMR analyses, revealed it to be predominantly the *bis*–menthyloxysilane (**173**), which has a boiling point considerably higher than that of the chlorosilane (**176**).

This chlorosilane (**176**) was then reacted with the lithium enolate of cyclohexanone, affording the desired silyl enol ether(**172**) in 77% yield and minimising, although not completely eliminating, the formation of competion products (**173**) and (**174**); [GLC analysis of the reaction mixture after work up but prior to any purification procedures indicated the approximate ratio of compounds (**172**):(**173**):(**174**) to be 15.0 : 1.0 : 1.5].

In order to further compare the efficacy of our convergent synthesis and Walkup's "one pot" procedure the preparation of the pinacolone silyl enol ether (**164**) was repeated using the approach outlined in Scheme 50. The isolated yield of compound (**164**) was a significant improvement on that which we had obtained for this compound *via* the "one pot" method.

A second terpenoid alcohol, *viz.*, (–)–borneol (**178**) had been identified, along with (–)–menthol, as a suitable chiral auxiliary for our initial studies. By an approach entirely analogous to the preparation of the chloro(menthyloxy)silane (**176**), the novel (bornyloxy)chlorosilane (**179**) (Scheme 51) was obtained, characterized in similar fashion to the chloro(menthyloxy)silane (**176**).

SCHEME 51



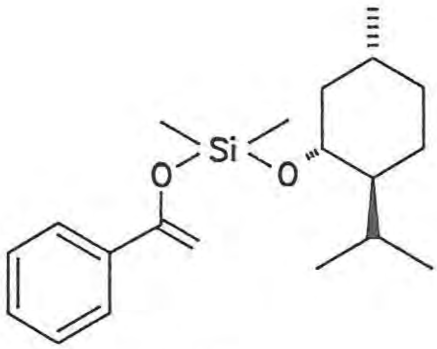
178 179

Reagents

i) Et_3N and Cl_2SiMe_2

Thus, with these two chiral chloroalkoxysilanes [(**176**) and (**179**)], and a reliable method for silyl enol ether formation in hand, the preparation of the additional novel silyl enol ethers [(**180**) – (**186**)] was set about, the choice of ketones being dictated by the criteria described earlier. While each preparation yielded different amounts of contaminants, in particular the *bis*–(menthyloxy)silane (**173**) [reaching a GLC estimated maximum of 20% in the preparation of the aromatic silyl enol ether (**180**)], and provided a unique set of purification problems, ultimately all the pre–selected silyl enol ethers were isolated in moderate to good yields.[208] The range of compounds prepared clearly indicates the generality of the method for the preparation of menthyloxy and/or bornyloxy silyl enol ethers from a variety of aliphatic, alicyclic, and aromatic ketones. The extension of the method to other chiral alkoxy compounds, although not investigated, would appear to be quite feasible provided facile distillation of the alkoxy silyl chlorides were possible.

In order to examine whether silyl enol ethers of ketones, capable of geometric isomerism of the enolate, could be obtained in isomeric ratios high enough to



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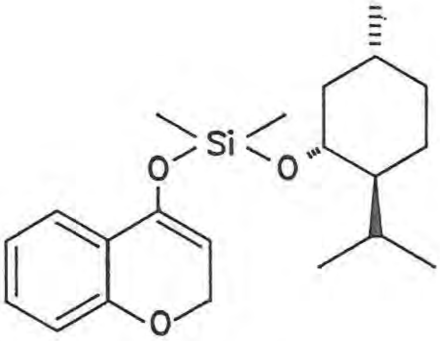

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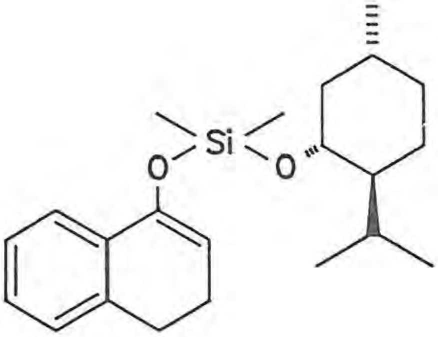

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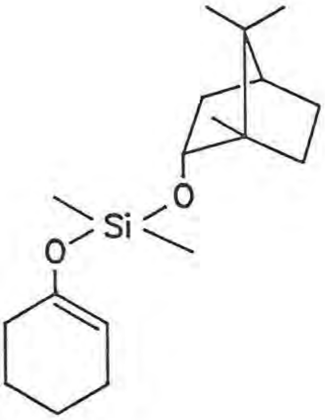

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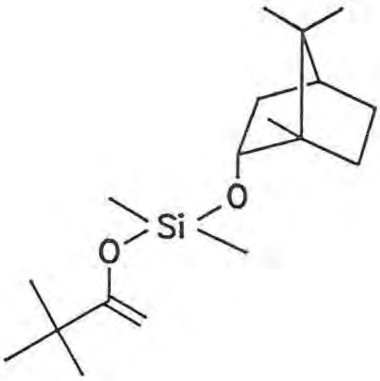

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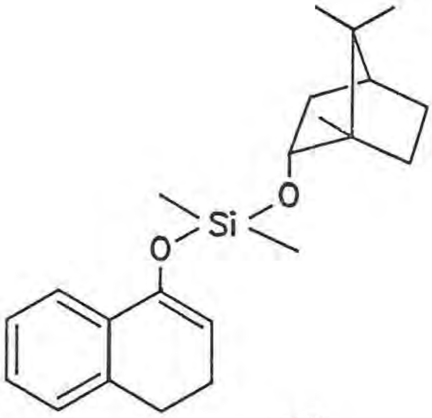

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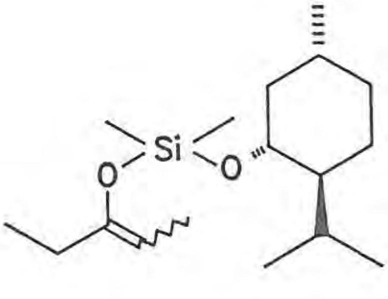


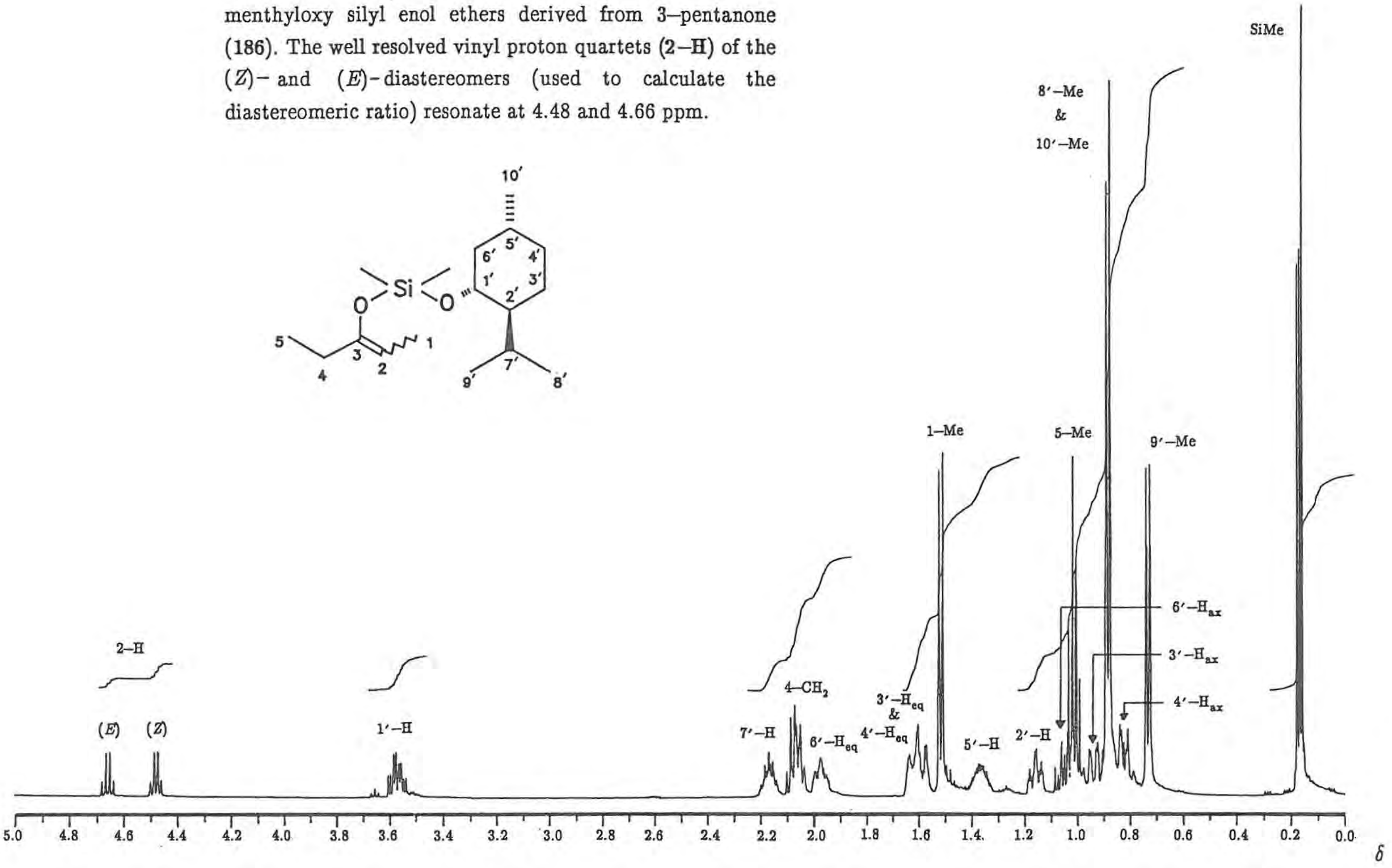
186

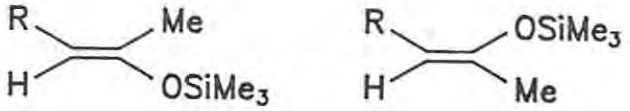
be synthetically useful, the menthyloxy silyl enol ether of pentan–3–one (**186**) was prepared. (In this case geometric isomerism, but not regioisomerism of the enolate is possible.) House and Kramar [220] had previously noted that the ^{1}H NMR chemical shift of the β–vinyl proton, of enol ethers and enol acetates capable of geometric isomerism, was helpful in assigning the stereochemistry about the double bond. They deduced that, in benzene–d_6 solutions, the β–vinyl proton in the (*E*)–enolate resonates at a field 0.2 – 0.3 ppm lower than in the case of the (*Z*)–enolate. In their publication on trimethyl silyl enol ethers, House *et al.*,[209] by studying the ^{1}H NMR spectra of mixtures of known composition of (*E*)– and (*Z*)–isomers of certain silyl enol ethers *e.g.* (**187**) and (**188**), (**189**) and (**190**), and (**191**) and (**192**), postulated that the same relationship holds for silyl enol ethers in general. The chemical shift differences they observed are listed in Table 9.

TABLE 9 Table of the chemical shift differences of β–vinyl protons for the (*E*)– and (*Z*)-enolates of isomeric trimethylsilyl enol ethers in benzene–d_6 and CCl_4 solutions.[209]

Silyl enol ether *E*/*Z* Mixture	$\Delta\delta$	
	C_6D_6	CCl_4
(**187**)/(**188**)	0.29	0.18
(**189**)/(**190**)	0.55	0.43
(**191**)/(**192**)	0.23	0.15

FIGURE 15 500 MHz ^{1}H NMR specrtum of the diastereomeric menthyloxy silyl enol ethers derived from 3–pentanone (**186**). The well resolved vinyl proton quartets (**2–H**) of the (*Z*)– and (*E*)–diastereomers (used to calculate the diastereomeric ratio) resonate at 4.48 and 4.66 ppm.



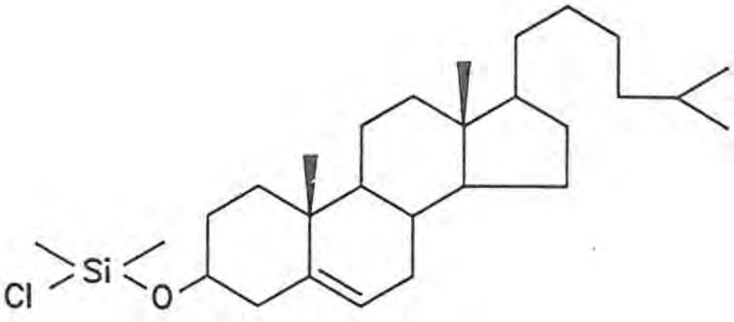


R = nBu	187	188
R = Ph	189	190
R = Me	191	192

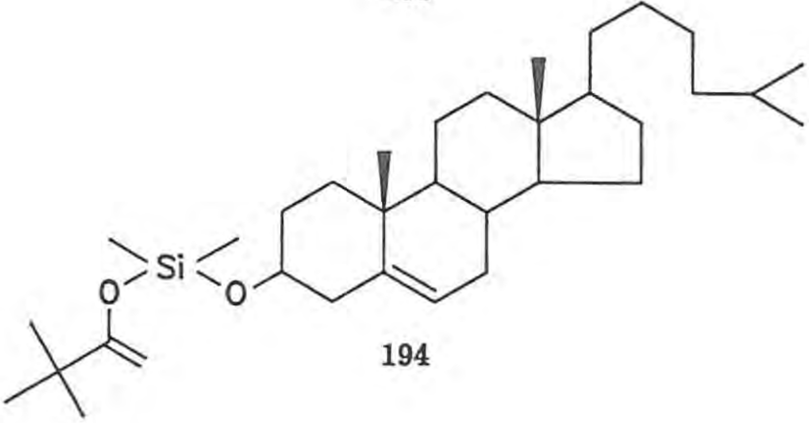
The 500 MHz ^{1}H NMR spectrum of the menthyloxy silyl enol ether of 3–pentan–one (**186**) in CDCl$_3$ (Figure 15) shows two clearly resolved quartets in the β–vinyl proton region; one at 4.48 δ and one at 4.66 δ, a $\Delta\delta$ value of 0.18, in close agreement with the values obtained by House *et al.*[209] for trimethylsilyl enol ethers. Thus, it would appear that the relationship established by House *et al.* for their original silyl enol ethers can be extended to these chiral alkoxy silyl enol ether systems. If that is the case the (*E*)/(*Z*) ratio in the pentan–3–one silyl enol ether (**186**) can be estimated as 1.0 : 1.55 by comparing the intensities of the respective signals in the high field ^{1}H NMR spectrum. (The integral values for the vinyl signals were established by summing the intensities of the individual lines comprising each quartet.) The established (*E*)/(*Z*) ratio could be used to assign the three ^{1}H NMR SiMe singlets observed, *viz.*, in the (*E*)–isomer the non–equivalent silyl methyls appear as a singlet, while in the (*Z*)–isomer two singlets are evident, separated by 4.73 Hz.

Similar ratios were also obtained by GLC analysis of both crude and distilled material. Physical separation of the two isomers could not be achieved and hence the NMR assignment of the (*E*)– and (*Z*)–isomers could not be substantiated by GLC. Further confirmation that two products obtained were in fact isomeric was provided by a GC–MS analysis, the two GLC peaks yielding almost identical mass spectra. In view of the observed lack of geometric control further exploration of aliphatic chiral silyl enol ethers of this type was not pursued.

The chiral silyl enol ether (**194**) was also prepared by reacting the lithium enolate of pinacolone with dichlorodimethylsilane and cholesterol *via* the "one pot" procedure of Walkup. The use of cholesterol as a chiral auxiliary was attractive because of its availability, steric bulk, and lack of additional functionality, besides the olefinic bond in the B ring. The chosen synthetic route was dictated by a concern that purification of (cholesteryloxy)dimethylsilyl chloride (**193**) by distillation would be difficult, if not impossible, and any other means of purification would not be feasible. The preparation of pinacolone silyl enol ethers by the "one pot procedure" of Walkup, employing lithium enolates of pinacolone was once again shown to be adequate by the the isolation of compound (**194**) in 63% yield.



193



194

2.1.1 X–Ray Diffraction Study of the Cholesteryloxy Silyl Enol Ether (194) [221]

As part of the attempt to understand the three dimensional structure of the chiral silyl enol ethers, the solid state structure of the cholesteryloxy silyl enol ether (**194**) was investigated by X–ray diffraction analysis.[221] The experimental details relating to this analysis, the resulting atomic co–ordinates, bond lengths and angles, derived parameters, and anisotropic temperature factors are listed in Appendix 1. The poor definition of the electron density map for the steroid side chain and siloxy enolate portion of the molecule suggests that the compound packs rather uneasily into a crystalline form [four molecules per unit cell (Figure 17)]. As a result of the poor resolution,the carbon – carbon bond lengths in the *tert*–butyl and isopropyl groups had to be restrained to 1.54 Å and, thus, the final temperature factors on these terminal carbons are correspondingly high. A full matrix least squares refinement, with calculated H–atom positions, converged at $R = 0.083$. (Other crystallographic studies of cholesterol derivatives [222,223] have also been affected by poor resolution at the end of the acyclic chain.[e]) Besides one unusual feature, described below, the structure is unremarkable and the bond lengths and angles all lie within expected ranges.

The poor definition at the extremities of the molecule was unfortunate as the enolate moiety constituted one extremity. The crystal packing forces the *tert*–butyl group, comprising C32–C35 (Figure 16) into close proximity with the cholesteryl A–ring system (C1–C5 and C10), to the extent that the sphere

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[e] It is interesting to note the structure determined in reference 223 was the methyl ether of cholesterol and constituted the first reported structure of a cholesterol ether. To the best of our knowledge, our own work is the first structure of a silyl ether of cholesterol. In the analysis of both the methyl ether [223] and our silyl enol ether, SHELX–76 [224] failed to provide a solution and the structure was finally solved using the SHELXS–86 program.[225]

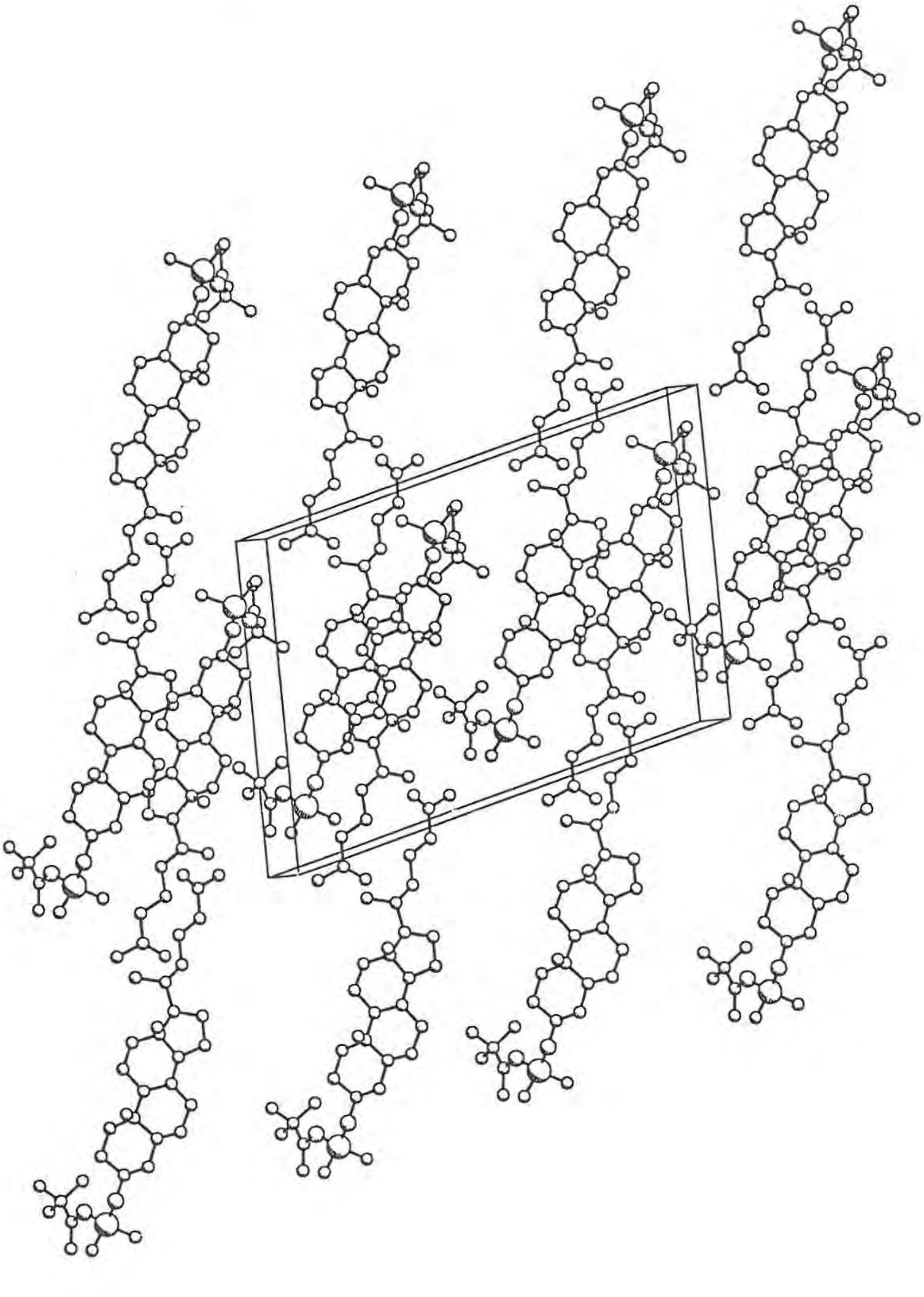

FIGURE 17 Packing diagram of (cholesteryloxy)dimethyl(3,3–dimethylbut–1–en–2–yloxy) silane (**194**), viewed along the orthogonal Y axis.

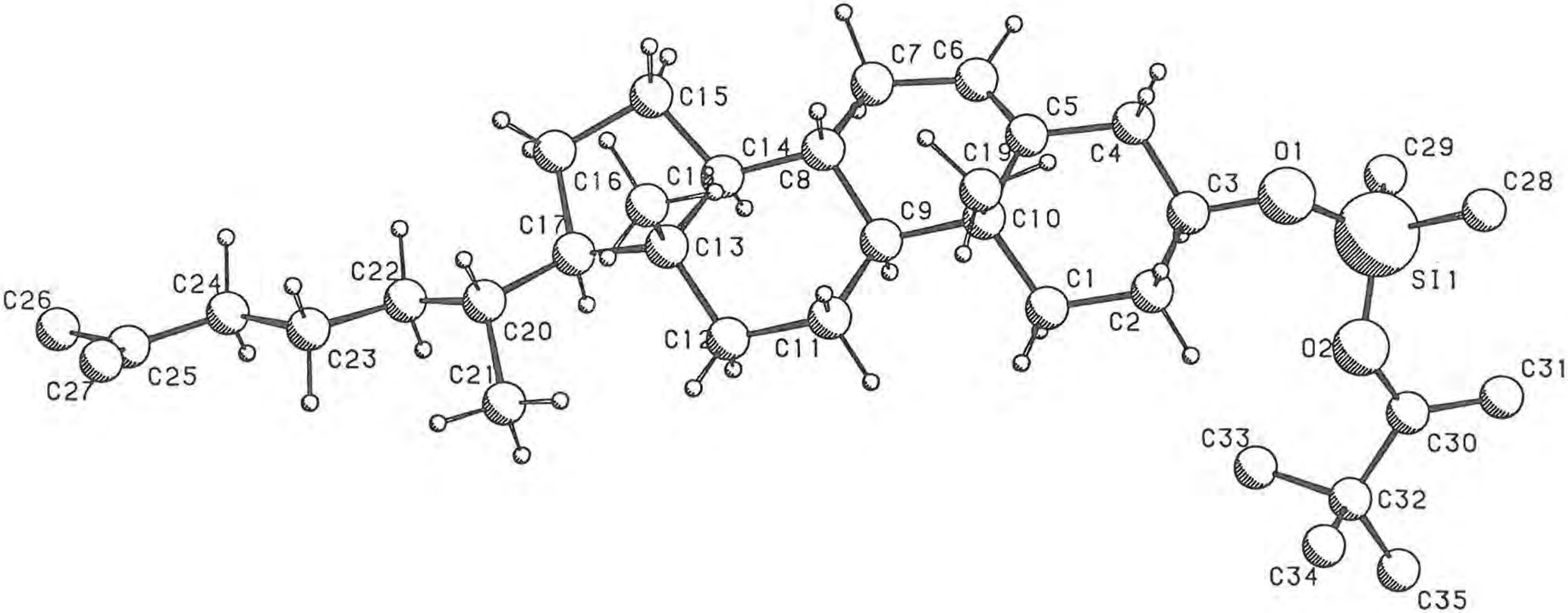

FIGURE 16 Molecular structure of (cholesteryloxy)dimethyl(3,3—dimethylbut–1–en–2–yloxy) silane (194), viewed from the position of minimum overlap. The atoms are numbered crystallographically.

of influence of C33[f] is only 0.08 Å distant from the van der Waals sphere of one of the hydrogen atoms bonded to C2. This crystal packing significantly shields one of the prochiral enolate faces in the solid state. However, in solution these restraints are removed and without any other means of maintaining the favourable solid state conformation, both faces of the enolate become accessible as reflected by the small enantiomeric excesses subsequently achieved in reactions of this chiral silyl enol ether (see Section 2.3.3, p180). In view of these results, the intended conformational analysis (of which the X–ray study was to form an integral part) of this chiral silyl enol ether was not pursued.

2.1.2 Spectroscopic Studies of the Chiral Silyl Enol Ethers.

Both the high field ^{1}H and ^{13}C NMR spectra (500 and 125 MHz respectively) of all the prepared silyl enol ethers were examined in detail and complete signal assignments made. (The complete assignment of these NMR spectra was of vital importance to subsequent stages of this investigation, in which the spectra of products from attempted asymmetric reactions and other analogous compounds had to be evaluated for diastereomeric excess.) In many cases, these assignments were only possible with the aid of two dimensional COSY and HETCOR NMR experiments as well as published NMR data for menthol, borneol, cholesterol, and their derivatives.[226-231] These complete assignments are included in the collection of physical data in the Experimental section. However, reproductions of the high field ^{1}H and ^{13}C NMR spectra of compound (**164**) (Figures 18 and 19)and the ^{1}H NMR and two dimensional COSY spectra of compound (**185**) (Figures 20 and 21) are included here to illustrate the general nature of the spectra of these compounds and to highlight several

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[f] The sphere with centre at C33 and radius 2.28Å [the sum of the C—H bond length (1.08Å) and the van der Waals radius of a hydrogen atom (1.2Å)].

FIGURE 18 500 MHz ^{1}H NMR spectrum of the menthyloxy silyl enol ether (164)

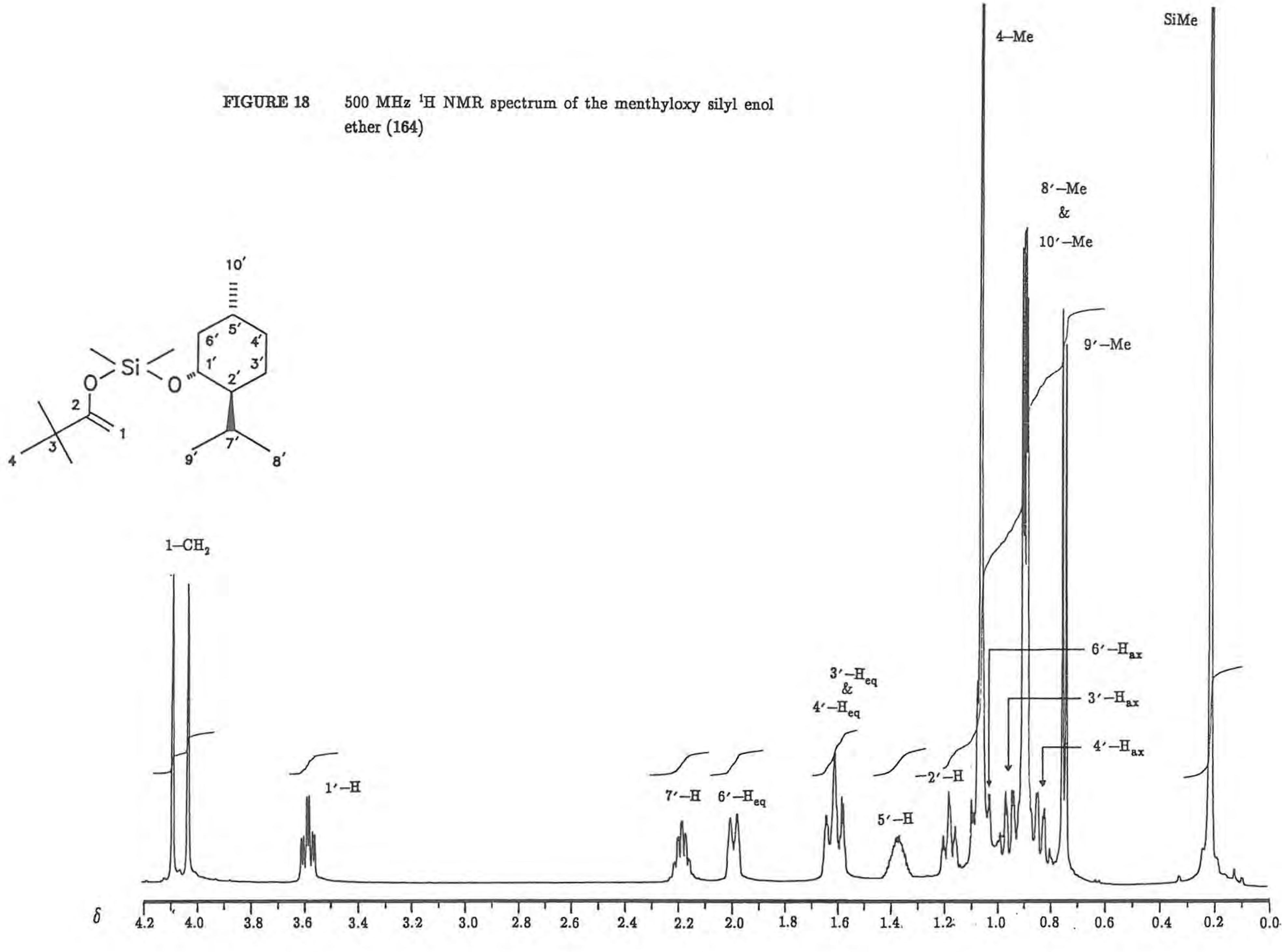


FIGURE 19 125 MHz ^{13}C NMR spectrum of the menthyloxy silyl enol ether (164)

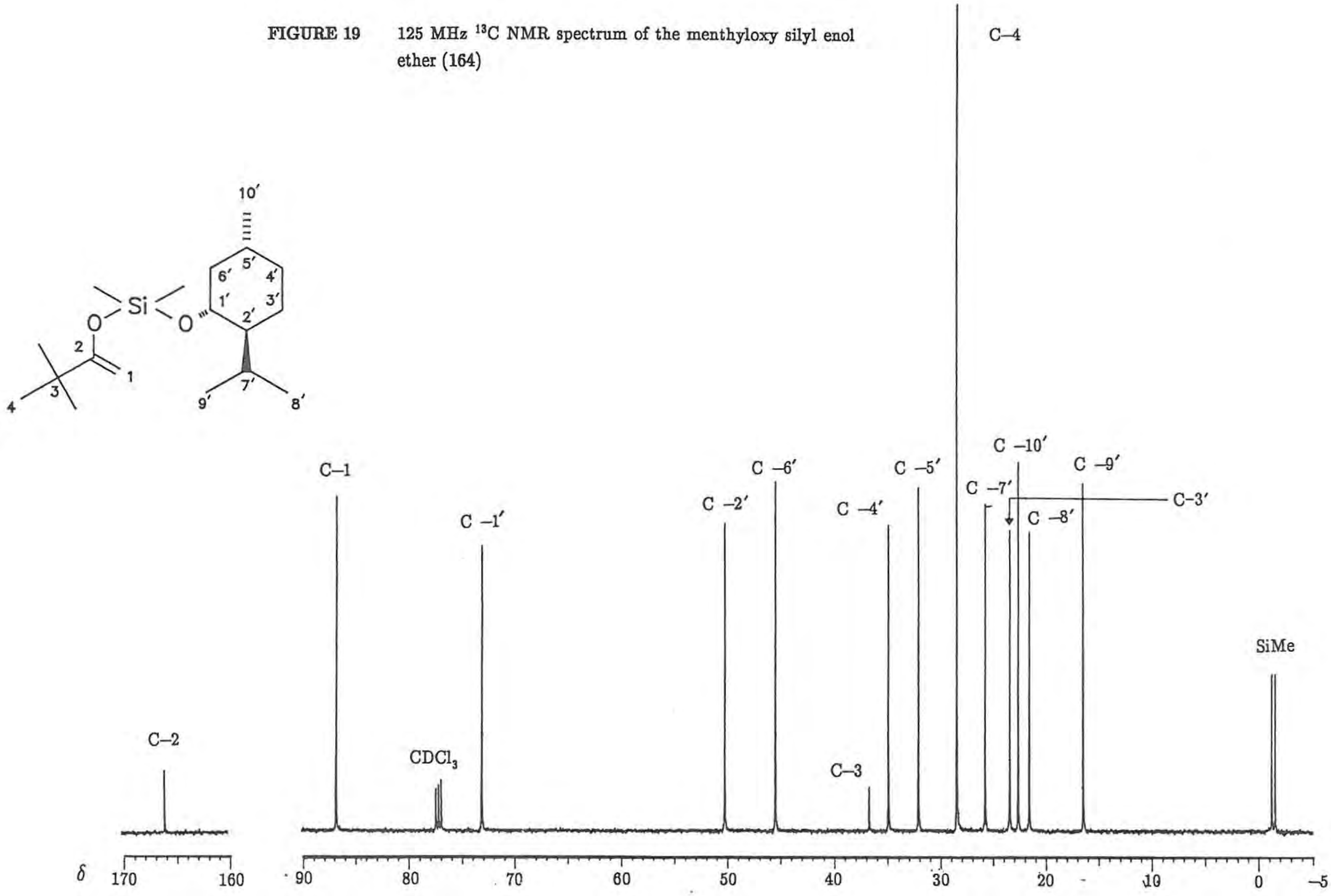
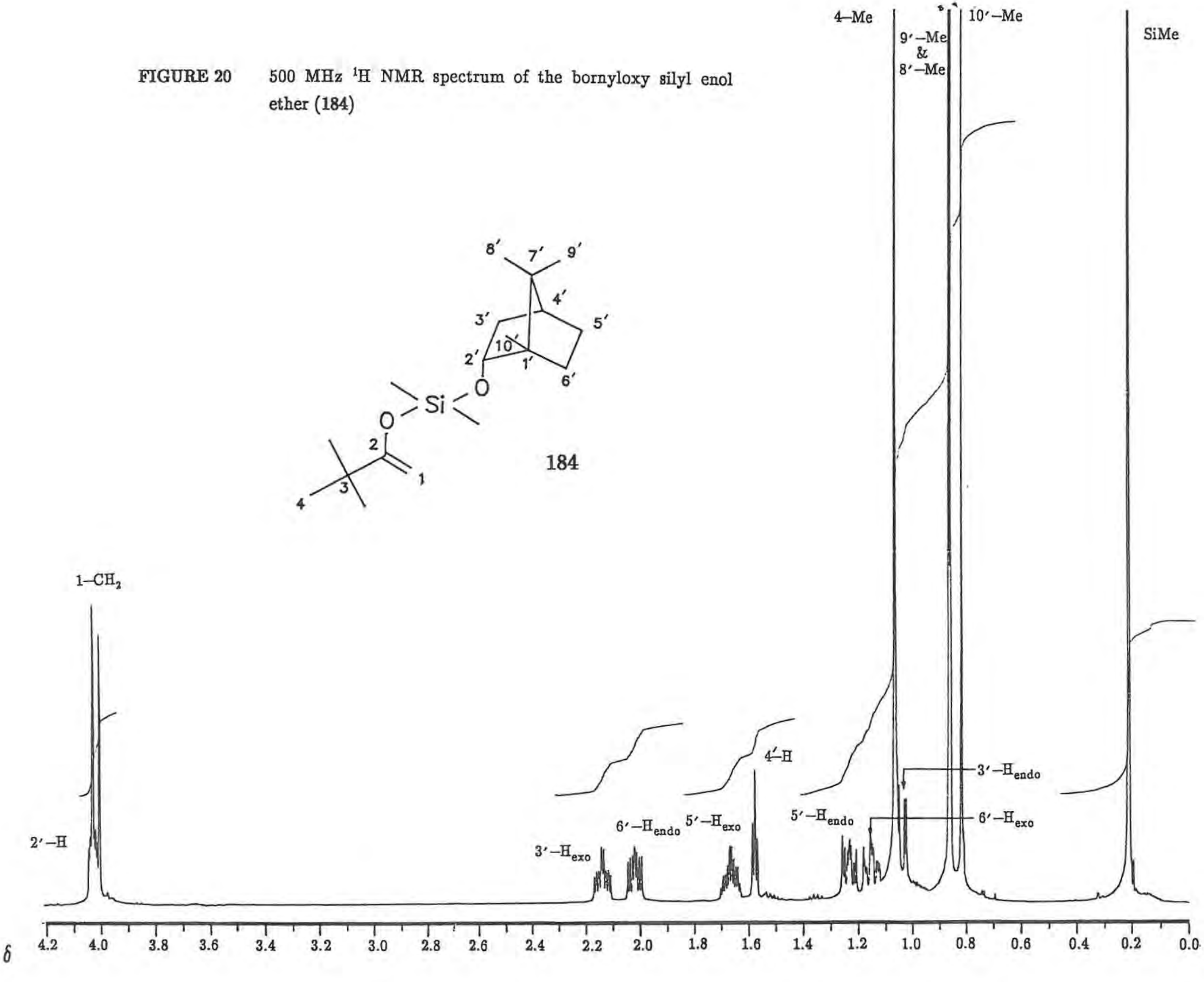


FIGURE 20 500 MHz ^1H NMR spectrum of the bornyloxy silyl enol ether (184)



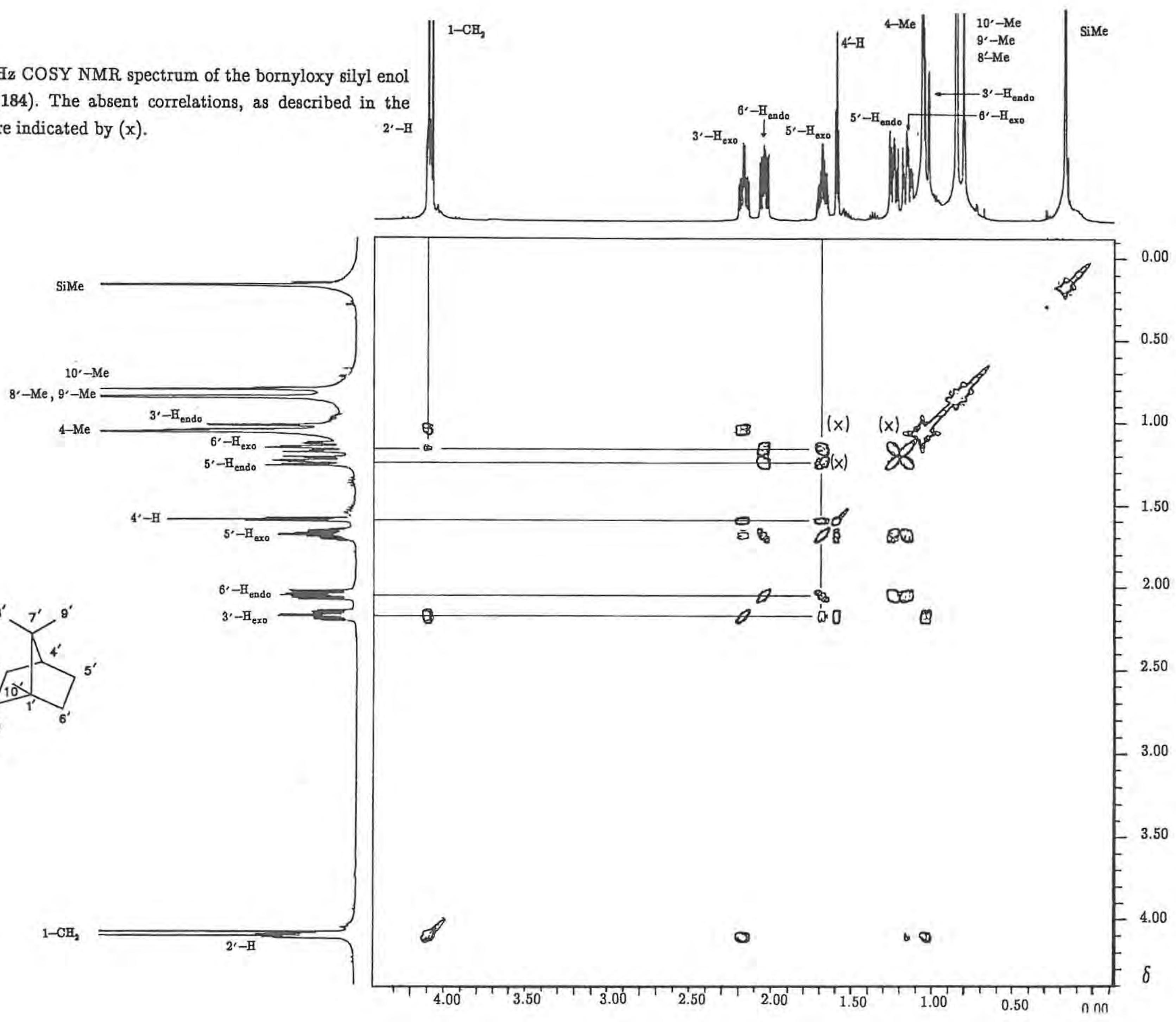
salient features, *viz.*,

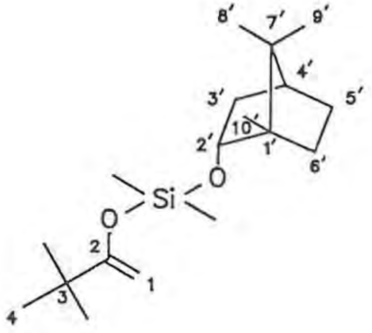
i) For both the chosen examples, the ^{1}H NMR spectra do not reflect the non–equivalence of the SiMe groups but in the ^{13}C NMR spectra the SiMe singlets are clearly resolved. This is typical of these compounds; the ^{13}C SiMe singlets are split in all cases, except the cholesteryl silyl enol ether (**194**), while in the proton spectra the splitting of the SiMe singlets is less common and never exceeds 0.01 ppm when it does occur. [The ^{1}H NMR spectrum of the (*Z*)–isomer of compound (**186**) provides one example in which resolution of the SiMe peaks is observed (see Figure 15)]

ii) In these silyl enol ethers the geminal vinyl protons typically show no coupling, as illustrated in Figures 18 and 20. The cholesteryl compound (**194**) is an exception, exhibiting a coupling of 1.2 Hz.

iii) The coupling patterns in both the menthol and borneol cyclic systems are complex (Figures 18 and 20.), preventing evaluation of coupling constants. Briggs *et al.*[228] established the chemical shifts and coupling constants for all the protons in borneol itself by using induced paramagnetic shifts. A detailed analysis of the COSY spectrum we obtained for the bornyloxy silyl enol ether (**184**) (Figure 21) indicated that the chemical shifts and couplings of the bicyclic protons are comparable to those determined by Briggs *et al.* for the parent alcohol. The $5'\text{–H}_{exo}$ proton illustrates the complexity of the system, exhibiting five separate couplings, four with the geminal $5'\text{–H}_{endo}$ and the vicinal $4'$– and two $6'$–H protons. The fifth coupling is a long range coupling with the $3'\text{–H}_{exo}$ proton, indicating that the geometry of that portion of the molecule approaches, the ideal spatial arrangement for **W** coupling. The comparable $6'\text{–H}_{exo}$ – $2'\text{–H}_{exo}$ long range coupling (not specified by Briggs *et al.*) is weakly evident in the COSY spectrum, but the analogous $3'\text{–H}_{endo}$ –

FIGURE 21 500 MHz COSY NMR spectrum of the bornyloxy silyl enol ether (184). The absent correlations, as described in the text, are indicated by (x).





5′–H$_{endo}$ coupling is not observed. Further, Briggs' study indicated that two sets of adjacent protons exhibited no coupling and the COSY spectrum confirms these absences. The lack of coupling between the **4′– H** and both the **5′–H$_{endo}$** and **3′–H$_{endo}$** protons (to which the absent correlations are ascribed) is expected as, in both cases, the dihedral angle approaches 90°. All other couplings are established by the COSY spectrum.

A similar analysis of the COSY spectrum of menthyl silyl enol ether (**164**) (in which the coupling of the ring protons are also complex) was undertaken. A comparison of these results, with a literature analysis of the menthol ^{1}H NMR spectrum, [226] indicates little deviation of the menthyl protons in the silyl enol ether from those of the parent system.

The mass spectra (Figures 22,23) of the menthyloxy silyl enol ethers exhibit many expected fragmentations *e.g.* loss of a methyl ($M^+ - 15$) or isopropyl group ($M^+ - 43$). There are, however, several unexpected fragmentations associated with the silicon atom. The first of these is characterized by an $M^+ - 137$ fragment [Ion(a), Table 10, p.124). This represents loss of a species two mass units less than that expected for the loss of the menthyl residue. The $M^+ - 137$ fragment is always significant and in several examples is, in fact, the base peak. A possible fragmentation pathway which involves loss of the menthyl group and concomitant transfer of two hydrogen atoms is outlined in Scheme 52 (Pathway A). Such fragmentation would afford the allylic radical (**195**) and the silanol cation [**Ion (a)**]. In the instance of the tetralone–derived silyl enol ether (**182**), a high resolution mass spectral analysis, obtained for the $M^+ - 137$ peak, was consistent with the proposed cation (**196**) (Found: 221.0995. $C_{12}H_{17}O_2Si$ requires 221.0958).

FIGURE 22 Mass spectrum of the menthyloxy silyl enol ether (**164**)

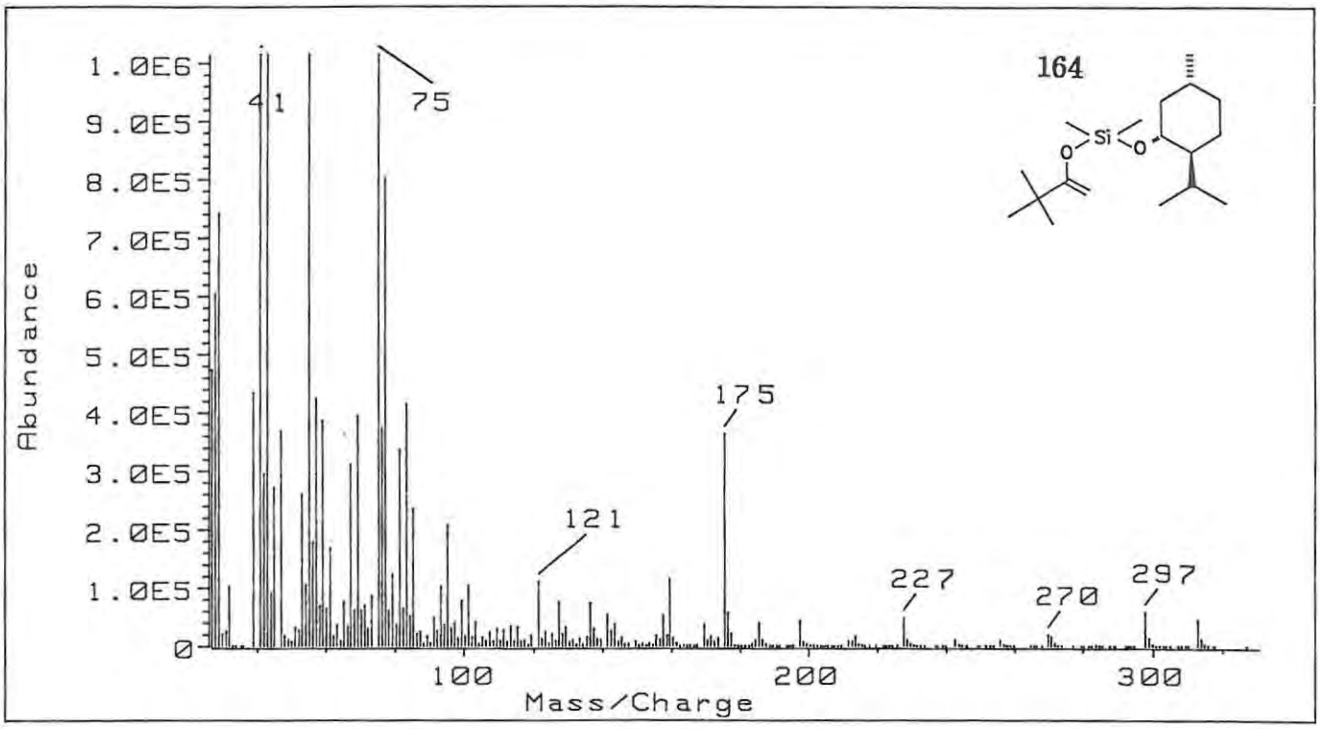
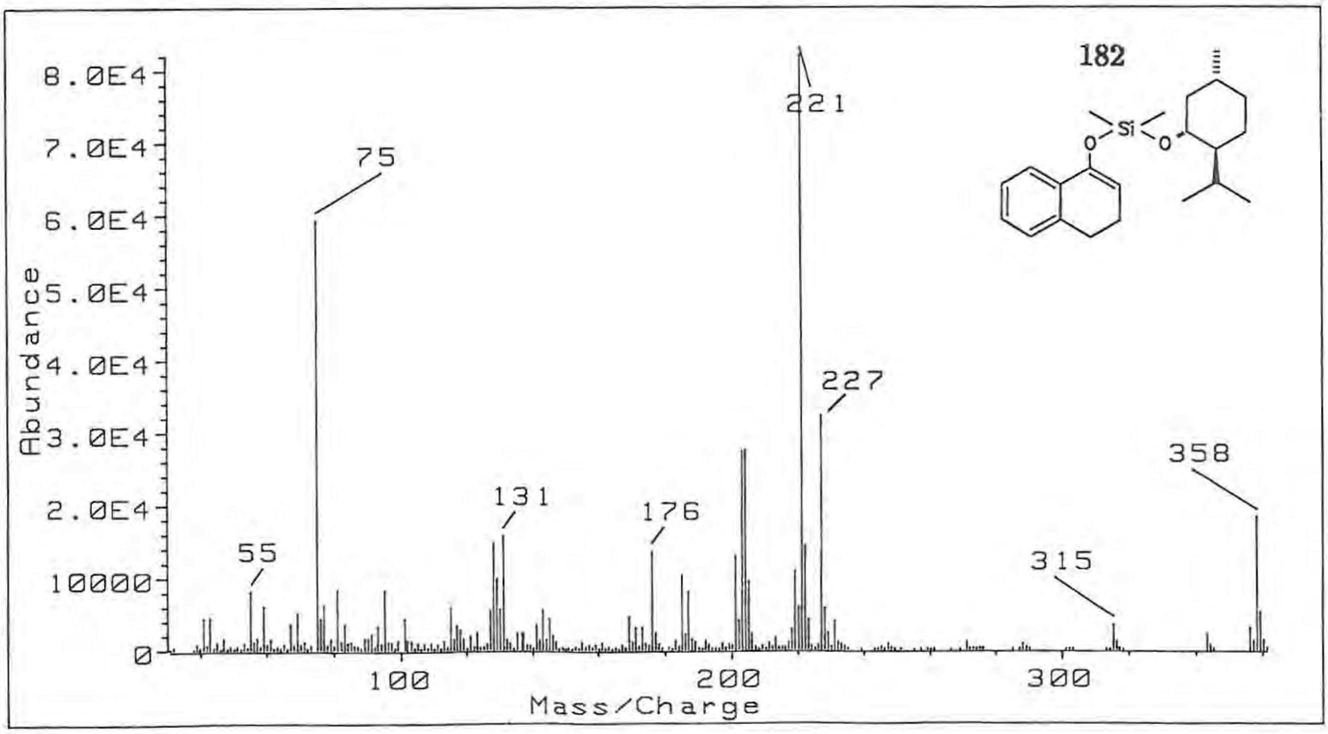
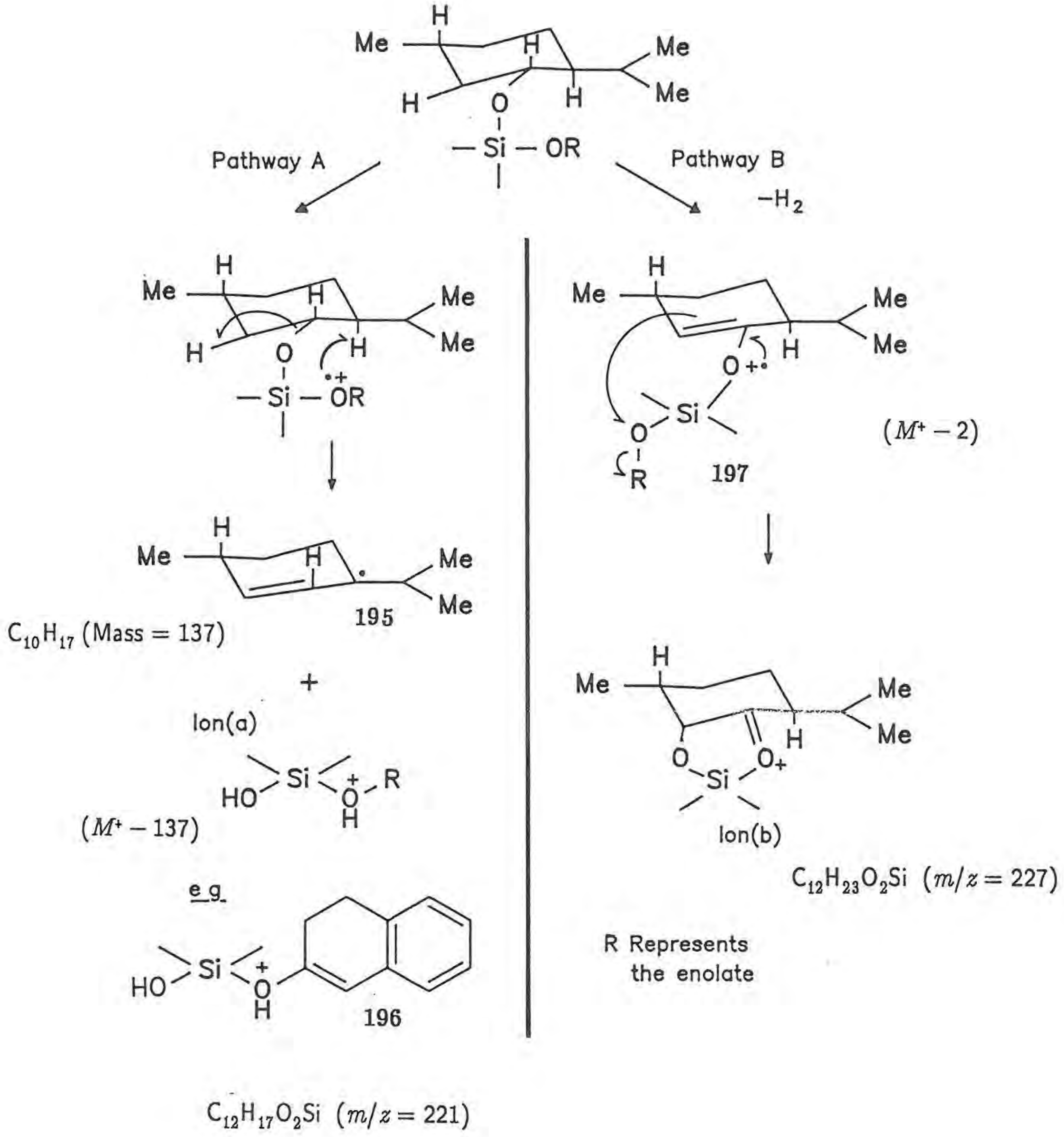


FIGURE 23 Mass spectrum of the menthyloxy silyl enol ether (**182**)



SCHEME 52


Pathway A
Pathway B
−H2
Me
H
O
Si
OR
C10H17 (Mass = 137)
195
Ion(a)
(M+ − 137)
e.g.
196
C12H17O2Si (m/z = 221)
(M+ − 2)
197
Ion(b)
C12H23O2Si (m/z = 227)
R Represents the enolate

A second fragmentation (Pathway B) results in an even–electron ion of $m/z =$ 227 for all of the menthyloxy silyl enol ethers examined. The resultant peak is not as intense as that for the previous fragmentation (Pathway A), giving relative intensity values ranging from 5 – 39% [Ion(b), Table 10, p]. A possible explanation of this fragmentation (outlined in Scheme 52, Pathway B) involves initial two hydrogen atom loss to form the enol cation (**197**) and subsequent loss of the enolate portion of the molecule to form the cyclic ion [**Ion(b)** ($m/z = 227$)].

For the bornyloxy silyl enol ethers (Figures 24 and 25) an analogous "Pathway B" fragmentation (giving rise to $m/z = 225$) appears to be relatively insignificant (2 – 6% relative intensity; Table 10). The analogous "Pathway A" fragmentation giving rise to a fragment at ($M^{+} - 135$) is only really significant (41% relative intensity) for the bornyloxy silyl enol ether (**185**). These distinct differences may arise from a number of contributing factors rendering competing pathways more facile; including the different stereochemical arrangement of the hydrogen atoms to be transferred and possible skeletal rearrangements of the bicyclic system.

It must be emphasized that, while the investigation of mass spectra of trimethyl silyl enol ethers by House *et. al.*[209] provides some precedent for the types of hydrogen transfer proposed, the fragmentations in Pathways A and B remain tentative attempts to explain the available experimental data; the elucidation of definitive fragmentation patterns is to be the subject of future research.

House *et al.* have also ascribed the peaks at $m/z = 73$ and 75 typically shown by <u>trimethyl</u> silyl enol ethers to the $^{+}Si(CH_3)_3$ and $H{-}O^{+}{=}Si(CH_3)_2$ ions

FIGURE 24 Mass spectrum of the bornyloxy silyl enol ether (184)

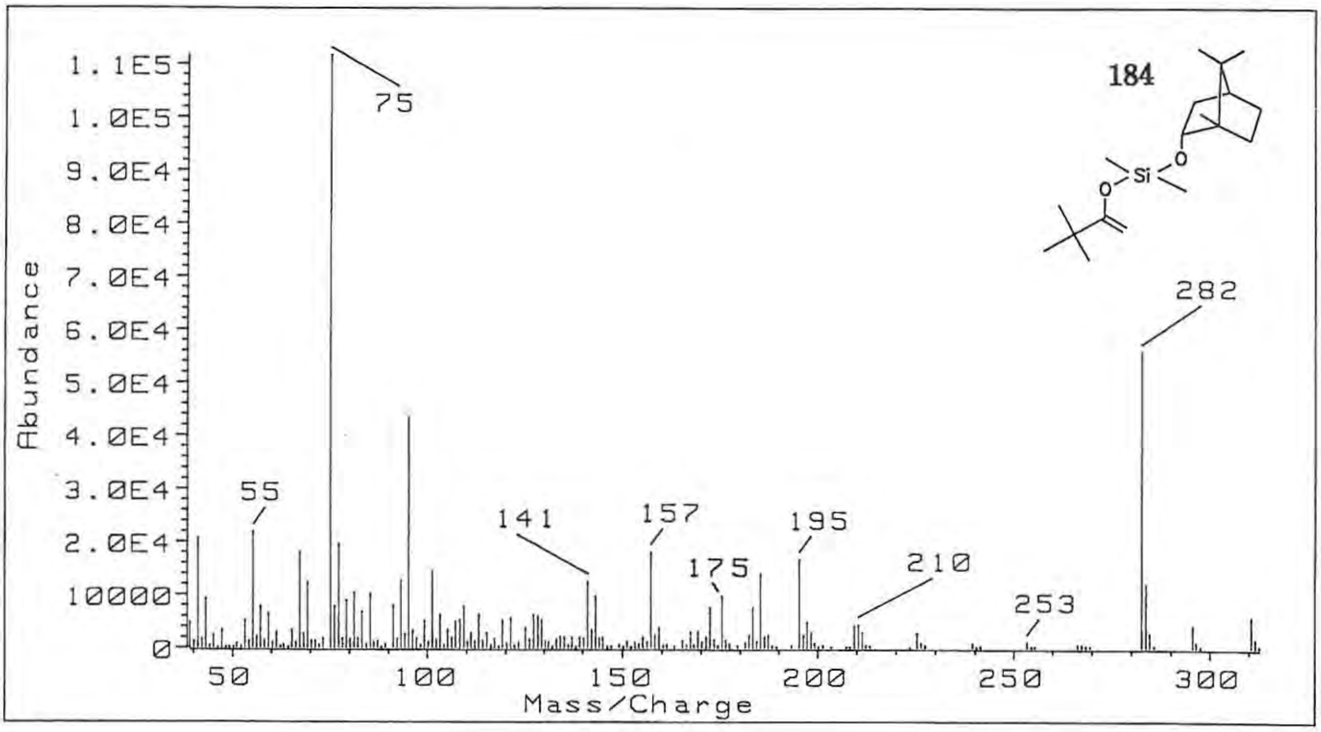
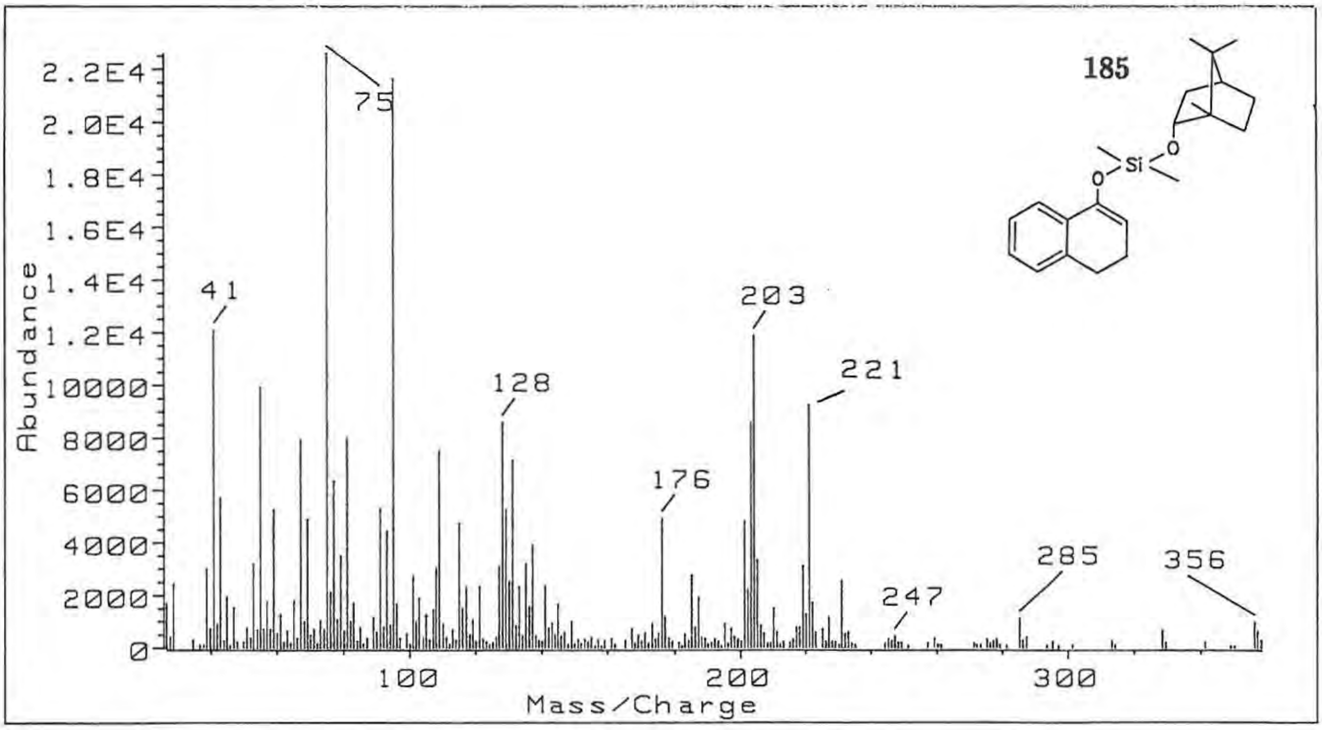
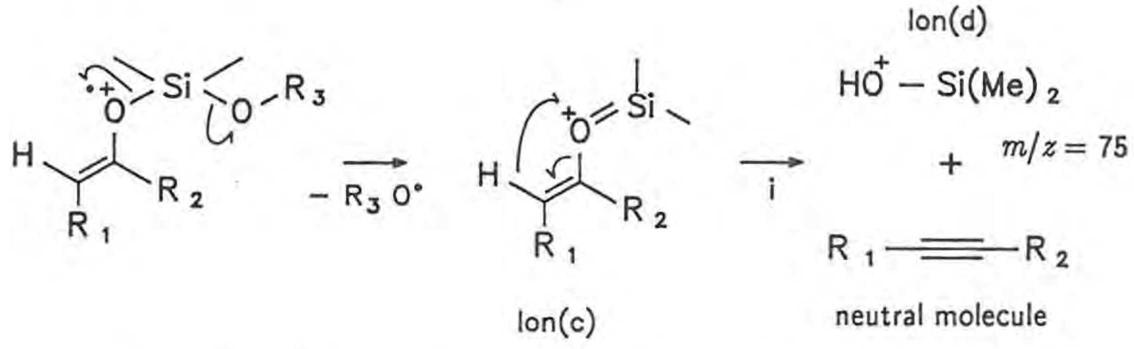


FIGURE 25 Mass spectrum of the bornyloxy silyl enol ether (185)



respectively. In our dimethyl silyl compounds formation of the ion at $m/z = 73$ is not possible. However, the peak at $m/z = 75$ [**Ion(d)**, Table 10, P.124] is observed in the mass spectrum of all of the chiral silyl enol ethers studied. A possible fragmentation pathway for the formation of this ion **(d)** *via* **Ion(c)**, analogous to that proposed by House *et al.*, is outlined in Scheme 53. The alternative fragmentation, *viz.*, initial homolysis of the enolate Si— O bond (Scheme 54), while also occurring, appears to be considerably less favoured [based on the relative intensities of **Ion(c)** and the analogous **Ion(e)**].

SCHEME 53



i) H Transfer and C–O bond cleavage

SCHEME 54

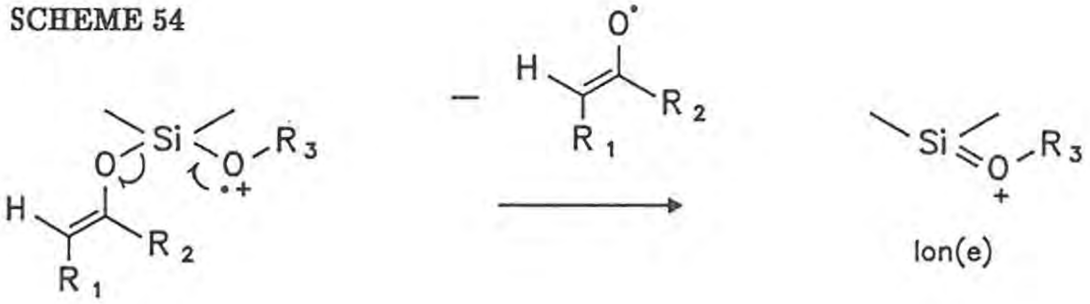


TABLE 10: Selected mass spectral fragments of the chiral silyl enol ethers [(**165**), (**172**), (**180**) – (**186**), and (**194**)]. Relative intensities are included in parentheses.

Compound	M^+	Ion(a)	Ion(b)	Ion(c)	Ion(d)
164[g]	312(7)	175(36)	227(8)	157(8)	75(100)
172[g]	310(15)	173(100)	227(16)	155(27)	75(65)
180[g]	332(8)	195(73)	227(26)	177(40)	75(100)
181[g]	360(4)	223(88)	227(35)	205(100)	75(61)
182[g]	358(25)	221(100)	227(39)	203(35)	75(80)
186[g]	298(8)	161(38)	227(5)	143(15)	75(100)
183[h]	308(9)	173(9)	225(2)	155(17)	75(100)
184[h]	310(5)	175(9)	225(6)	157(16)	75(100)
185[h]	356(4)	221(41)	225(3)	203(53)	75(100)
194[i]	542(32)	175(100)	457(1)	157(6)	75(60)

---

[g] For menthyloxy silyl enol ether: [**Ion(a)**] will always be $M^+ - 137$, [**Ion(b)**] will always have $m/z = 227$, and [**Ion(c)**] will always be $M^+ - 155$.

[h] For bornyloxy silyl enol ethers: [**Ion(a)**] will always be $M^+ - 135$, [**Ion(b)**] will always have $m/z = 225$, and [**Ion(c)**] will always be $M^+ - 153$.

[i] Cholesteryloxy silyl enol ether.

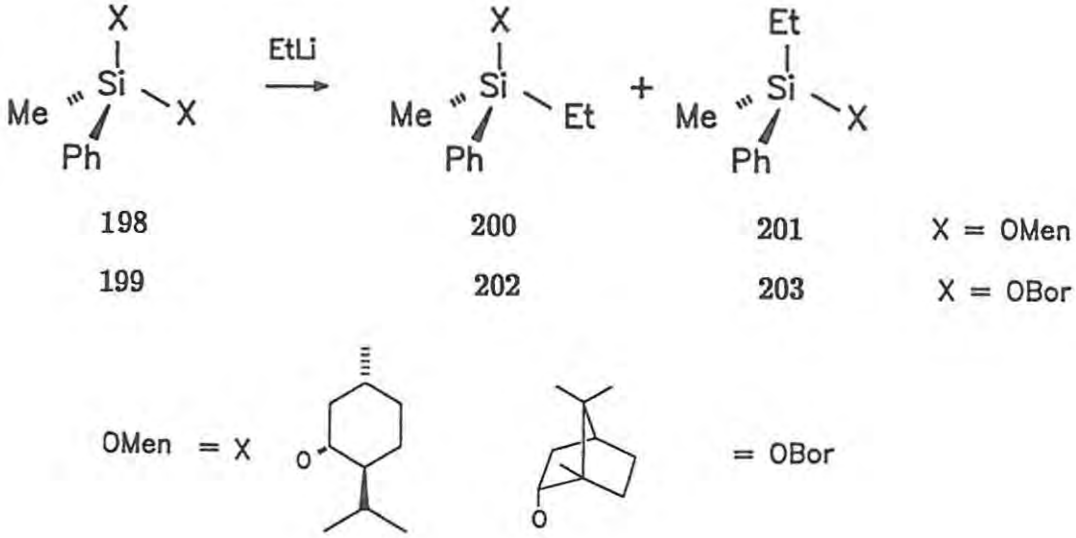
2.2 THE EVALUATION OF (MENTHYLOXY)– AND (BORNYLOXY)DIMETHYLCHLOROSILANES [(176) AND (179)] AS DERIVATIZING AGENTS FOR MEASURING ENANTIOMERIC EXCESSES.[232]

The determination of enantiomeric excess is fundamental to the evaluation of asymmetric induction methodologies. (see Section 1.5,p.85) and the current literature reflects a continuing interest in further development of these techniques for enantiomer differentiation. Having prepared a series of optically active silyl enol ethers one of the factors influencing the choice of reaction to which they should be subjected was the manner in which the resultant enantiomeric excess could be measured. It was hoped that, in certain instances, reactions could be chosen in which the chiral alkoxydimethyl silyl group would remain bonded to the product; the newly created chiral centre then providing a diastereomeric mixture in which the enantiomeric control at this new chiral centre could be conveniently determined by NMR or chromatographic methods. Having realized that our chiral alkoxydimethyl silanes could possibly serve the dual purpose of chiral auxiliary and chiral probe, a question arose, concerning the capability of our chiral alkoxydimethylchloro silanes [(176) and (179)] to act as general chiral derivatizing agents, for the analysis of enantiomeric mixtures.

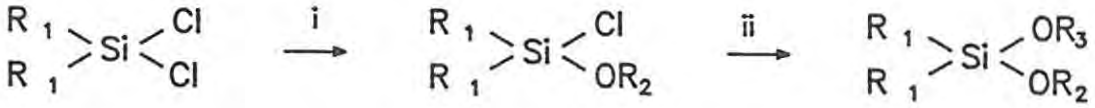
Consequently, before proceeding with asymmetric reactions of the chiral silyl enol ethers in hand, it was decided to evaluate the ability of chiral alkoxydimethyl silyl groups to act as chiral probes. Whereas the derivatizing capabilities of achiral organosilicon compounds *e.g.* trimethylsilyl and *tert*–butyldimethylsilyl chloride are well known, the literature reflected that the application of chiral organosilicon systems to the analysis of enantiomeric or diastereomeric mixtures, had received little attention. However, some of the work which had been reported indicated that the very chiral systems that were of interest to us, could act as effective chiral probes. Richter [219] used ^{13}C NMR to examine the stereoselectivity of organometallic reactions of prochiral siloxanes *e.g.* the menthyloxysilane **(198)** or bornyloxysilane **(199)** were reacted with ethyl lithium to yield the diastereomeric siloxane mixtures [**(200)** and **(201)**, and **(202)**and **(203)** respectively, (Scheme 55)]. The diastereoselectivity was evaluated from the intensities of the SiMe signals in the ^{13}C NMR spectra.

Chan *et al.*[218] prepared a number of diastereomeric silyl acetals *e.g.* [**(206)** – **(210)**] from a variety of enantiomeric secondary alcohols (including 2–butanol, 2–octanol, and 1–phenylethanol) using optically pure methyl mandelate, quinine, or menthol as chiral probes (Scheme 56). These preparations proceeded, often *in situ*, *via* the chiral alkoxychlorosilanes **(204)**, **(205)**, or the menthyloxychlorosilane **(176)**, the detailed preparation and isolation of which has been described in Sections 2.1 and 3.2,(p. 237). Integral ratios of well resolved diastereomeric signals in the ^{1}H NMR spectra of the diastereomeric alcohols *e.g.* SiMe and $CHCH_3$ accurately reflected the original enantiomeric ratio of the secondary alcohols in all cases. Chan *et al.* obtained the best resolution of diastereomeric signals using (+)–methyl mandelate and dichlorodiphenyl silane. These workers did not provide an evaluation of the compounds of particular interest to us [*i.e.* the menthyloxydimethyl silyl acetals such as compound **(210)**]. It was decided to proceed with a more detailed evaluation of the menthyloxy and bornyloxy silyl systems *via* an NMR approach, analogous to that developed by Chan *et al.*[218] These systems were obviously of particular importance to us, since all the previously prepared optically active silyl enol ethers incorporated these particular siloxy entities.

SCHEME 55



SCHEME 56



R_1 = Me or Ph

204 R_1 = Me
R_2OH = methyl mandelate

205 R_1 = Ph
R_2OH = methyl mandelate

176 R_1 = Me
R_2OH = menthol

206 R_1 = Me
R_2OH = methyl mandelate
R_3OH = (±)–2–butanol

207 R_1 = Ph
R_2OH = methyl mandelate
R_3OH = (±)–2–octanol

208 R_1 = Ph
R_2OH = methyl mandelate
R_3OH = (±)–1–phenylethanol

209 R_1 = Me
R_2OH = quinine
R_3OH = (±)–1–phenylethanol

210 R_1 = Ph
R_2OH = menthol
R_3OH = (±)–1–phenylethanol

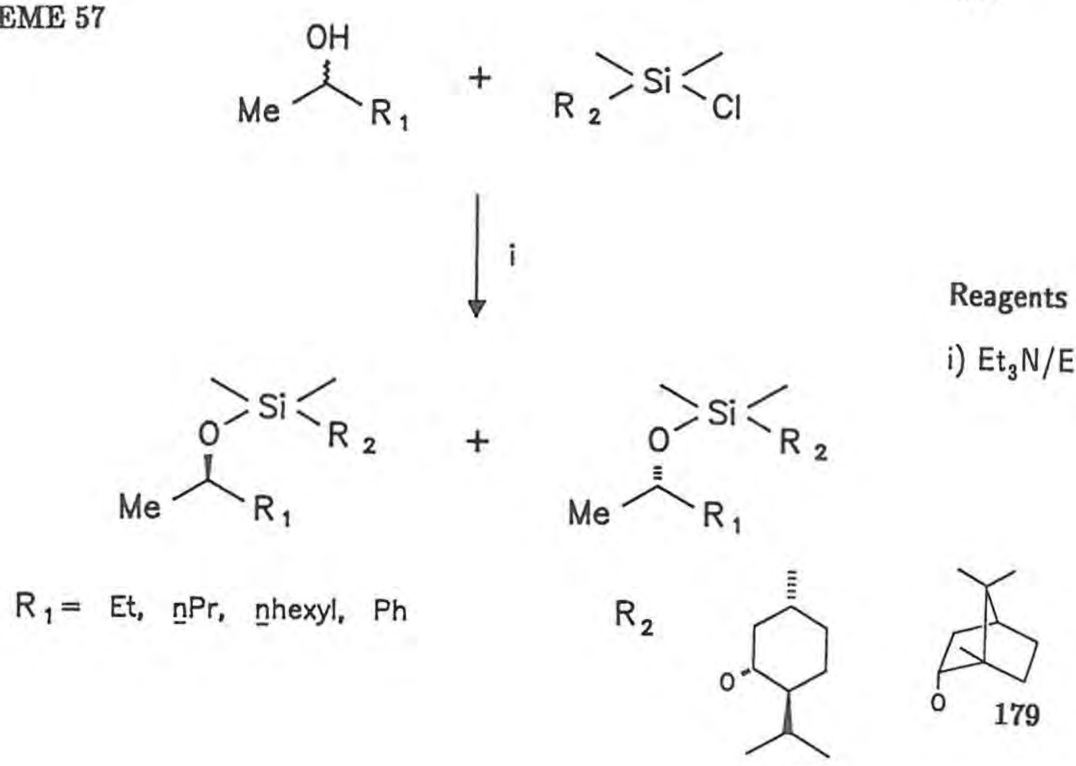
Reagents

i) R_2OH/pyridine, ii) R_3OH/pyridine

To our knowledge, no applications of silyl chiral probes in GLC analyses of enantiomeric mixtures had been reported. Thus, a novel technique was envisaged in which menthyloxy and bornyloxy diastereomeric silyl acetals would be subjected to GLC analysis and the diastereomeric ratio established by integration of the resolved peaks. If successful, this alternative technique would permit comparison of GLC and NMR analyses of diastereomeric silyl acetals, as general methods for the determination of enantiomeric composition.

Thus, a series of diastereomeric silyl acetals [**(210)** – **(214)**] were prepared by reacting either the chloro(menthyloxy)dimethylsilane **(176)** or the bornyloxychlorodimethylsilane **(179)** with a variety of racemic secondary alcohols in the presence of Et_3N, as outlined in Scheme 57. (The racemic character of all the secondary alcohols was confirmed by polarimetry.) The reactions were conducted under conditions which were expected to minimize any kinetic resolution effects *i.e.* using a significant excess of the chlorosilanes and extended reaction times in order to ensure complete conversion. Particular care was exercised during the chromatography or distillation of the reaction mixtures, to ensure that as much as possible of the product was recovered, thus minimizing distortions of the diastereomeric composition. No attempt was made to separate the individual diastereomers, nor were the reactions repeated on optically pure alcohols since it was believed that the quality of the technique could be established by determining the deviation of the experimental diastereomeric ratios from the expected ratio of unity.

SCHEME 57

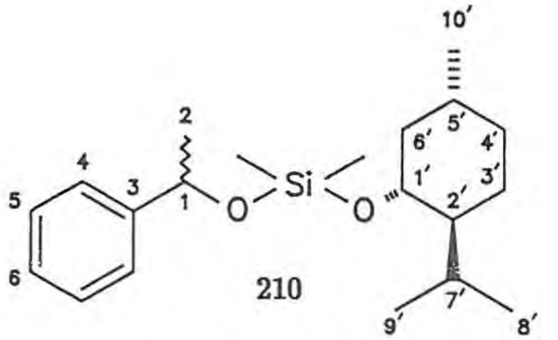


176

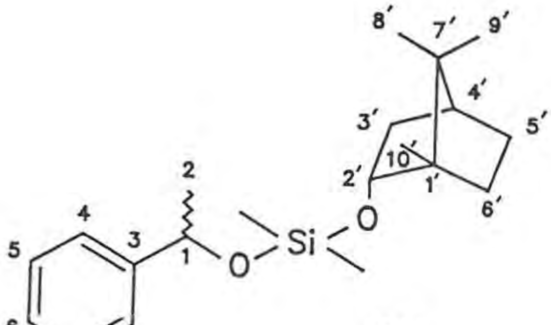
179

Reagents

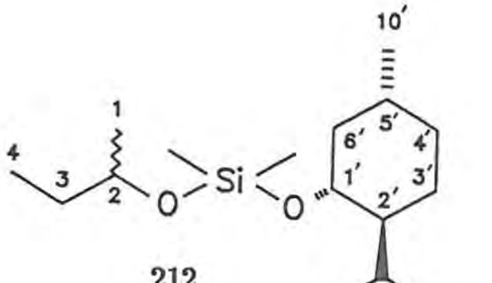
i) Et_3N/Et_2O



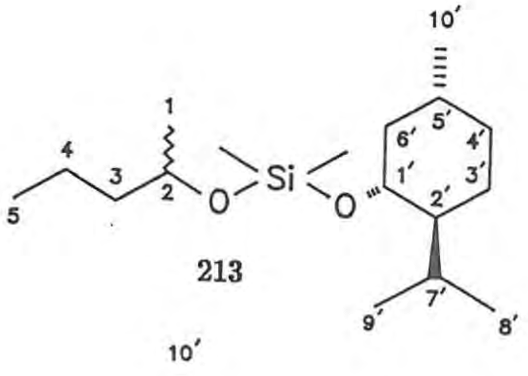
210



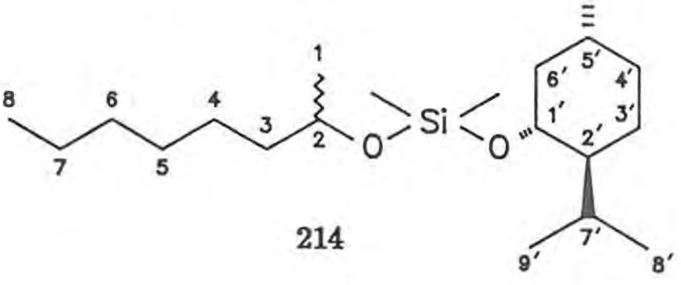
211



212



213



214

2.2.1 NMR Analyses of the Diastereomeric Silyl Acetals, (210) – (214)).[232]

A detailed analysis of the complex, high field ^1H and ^{13}C NMR spectra of the diastereomeric silyl acetals [(210) –(214)] was necessary in order to ascertain to what extent diasteromeric duplication of signals was occuring in each spectrum. This analysis was achieved by applying the comprehensive chemical shift information gained from prior spectral assignment of the chiral silyl enol ethers (164), (172), and (180) – (186) (See Section 2.1, p. 97 for these analyses) to ascertain all the menthyl or bornyl signals. Assignment of the remaining signals to particular nuclei of the secondary alcohols was achieved by analysing the chemical shifts and coupling constants in the normal way. The results of these analyses are included, in detail, in the Experimental section pertaining to these diastereomeric mixtures. Reproductions of the ^1H NMR spectra of compounds (210) and (211) (Figures 26 and 27) and pertinent expansions of these spectra (Figures 28 – 33) are included here, while the remainder of the ^1H and ^{13}C spectra are reproduced in the appendices (see p. appendix II, p. i–viii). The high field ^1H and ^{13}C NMR spectra of all the diastereomeric silyl acetals [(210) – (214)] exhibited doubling of various signals. Table 11 summarizes all the signals in ^1H and ^{13}C NMR spectra of these silyl acetals, that are clearly split by diastereotopic differences. Included in the Table are the corresponding ^1H integral – the experimental parameter facilitating the evaluation of the technique.

From the spectra obtained and the data summarized in Table 11 (p. 135), a number of conclusions concerning the validity of the technique can be drawn. While some of the splittings are small, others are significant and permit effective differentiation of the enantiomeric alcohol derivatives. In all the menthyloxy derivatives, *viz.*, (210), (212), (213), and (214) the doublet due to

FIGURE 26 500 MHz ^1H NMR spectrum of the diastereomeric silyl acetals (210).

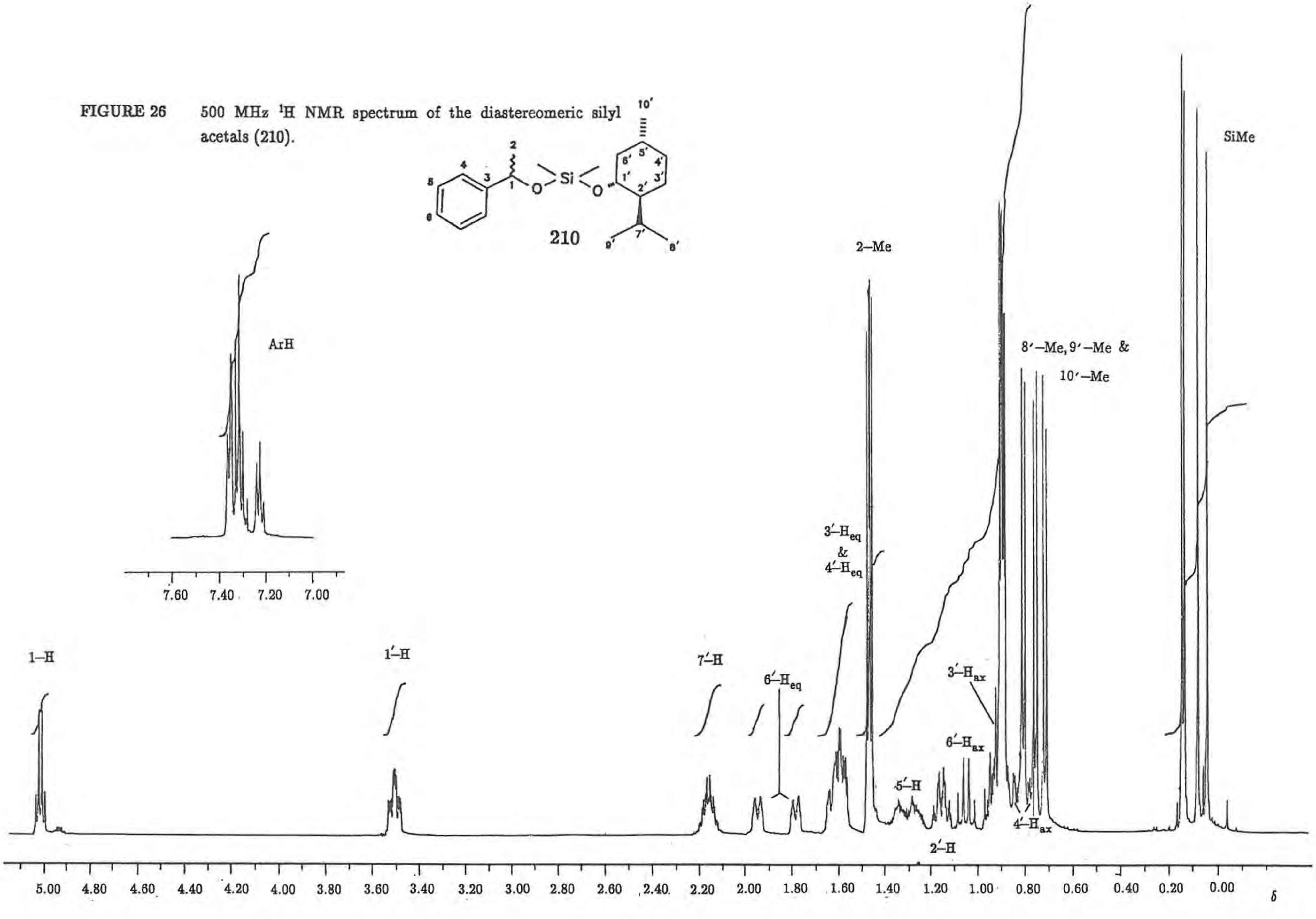
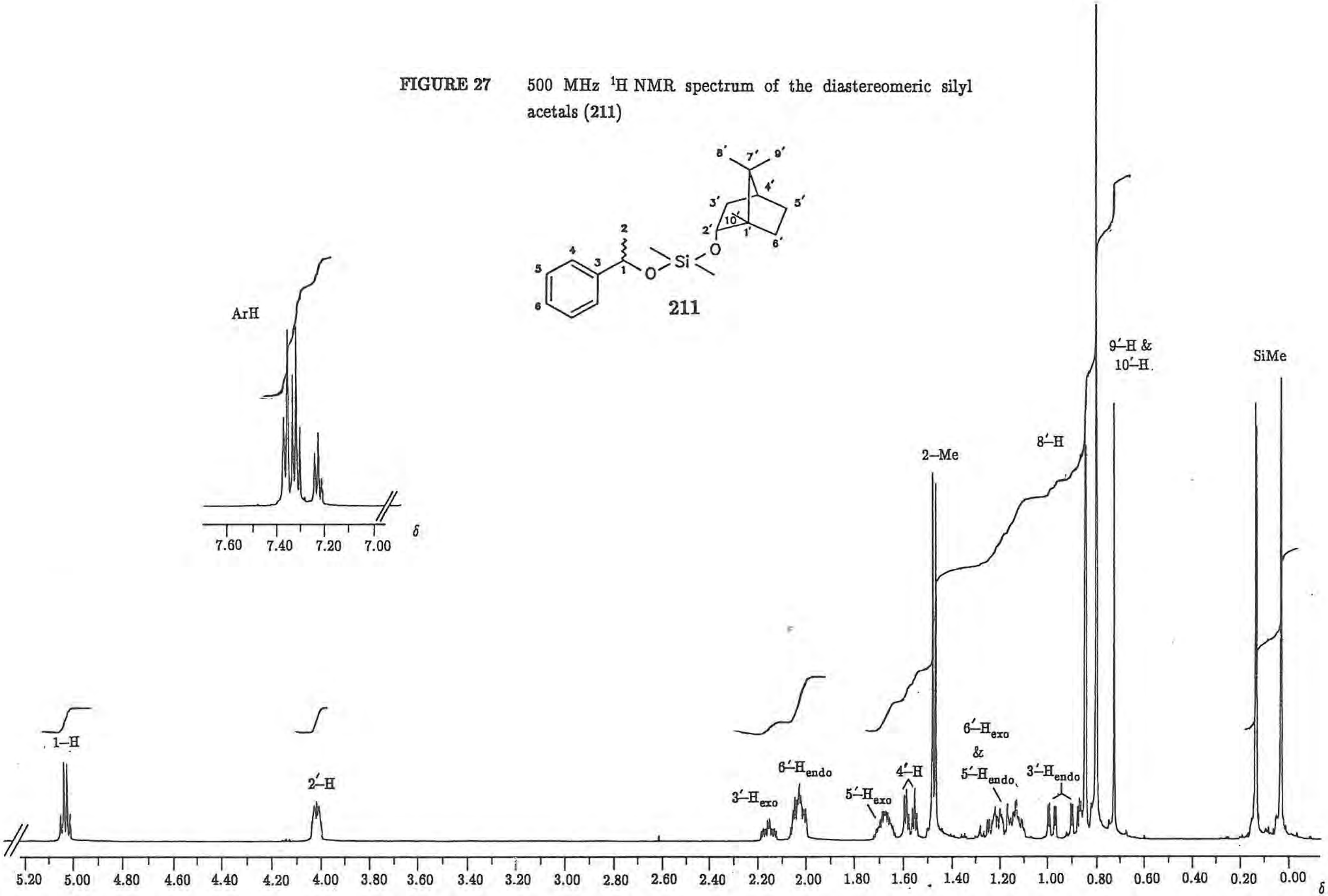


FIGURE 27 500 MHz ^{1}H NMR spectrum of the diastereomeric silyl acetals (211)



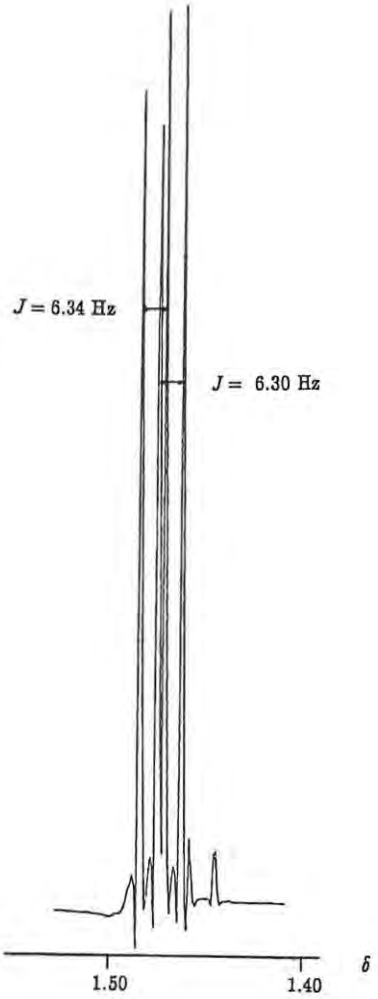


FIGURE 28

Expansion of the 13–Me doublets in the ^{1}H NMR spectrum of (**210**).

FIGURE 29 Expansion of the 8′–Me, 9′–Me, and 10′–Me signal in the ^{1}H NMR spectrum of (**210**). Three chemically non – equivalent methyl groups in each diastereoisomer give rise to six doublets.

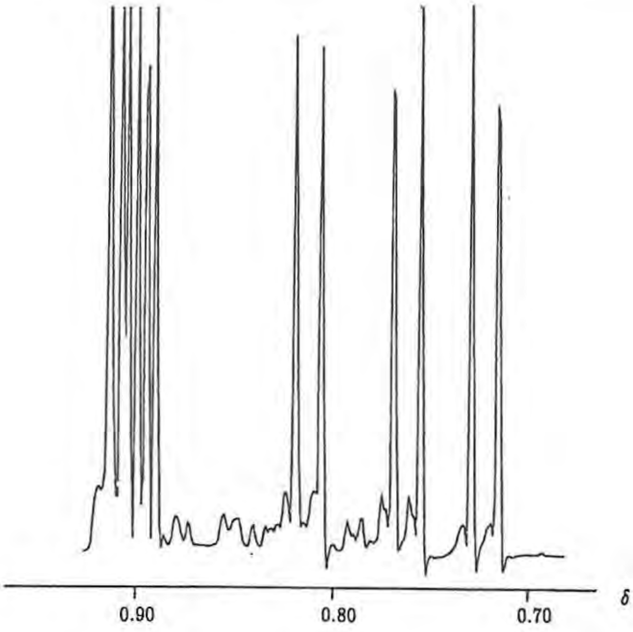
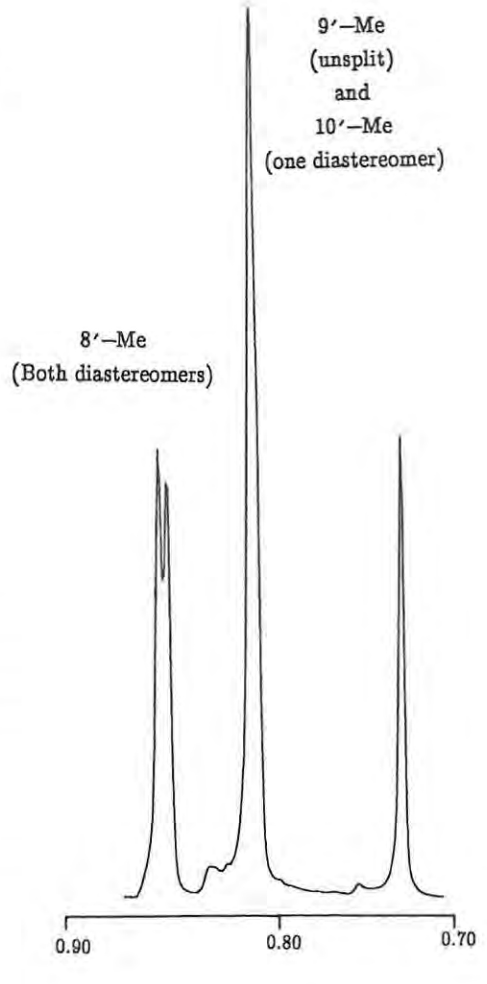
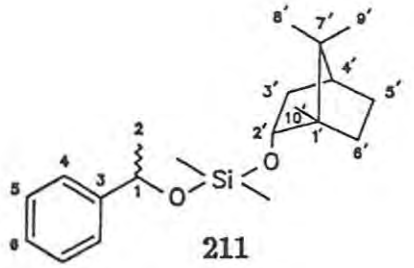


FIGURE 30 Expansion of the 8′–Me, 9′–Me, and 10′–Me signal in the ^{1}H NMR spectrum of (**211**). One of the diastereotopic singlets of 10′–Me is superimposed on the unsplit signal of 9′–Me. Note, however that the assignment of these two methyl singlets may be interchanged.





211

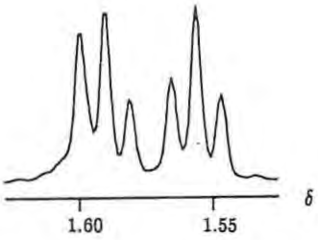
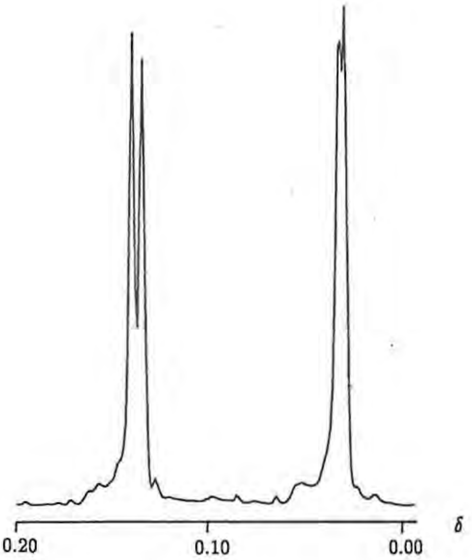


FIGURE 32

Expansion of the 4′–H signal in the ^{1}H NMR spectrum of (211).

FIGURE 33

Expansion of the four chemically non–equivalent, diastereotopic SiMe singlets in the ^{1}H NMR spectrum of (211).



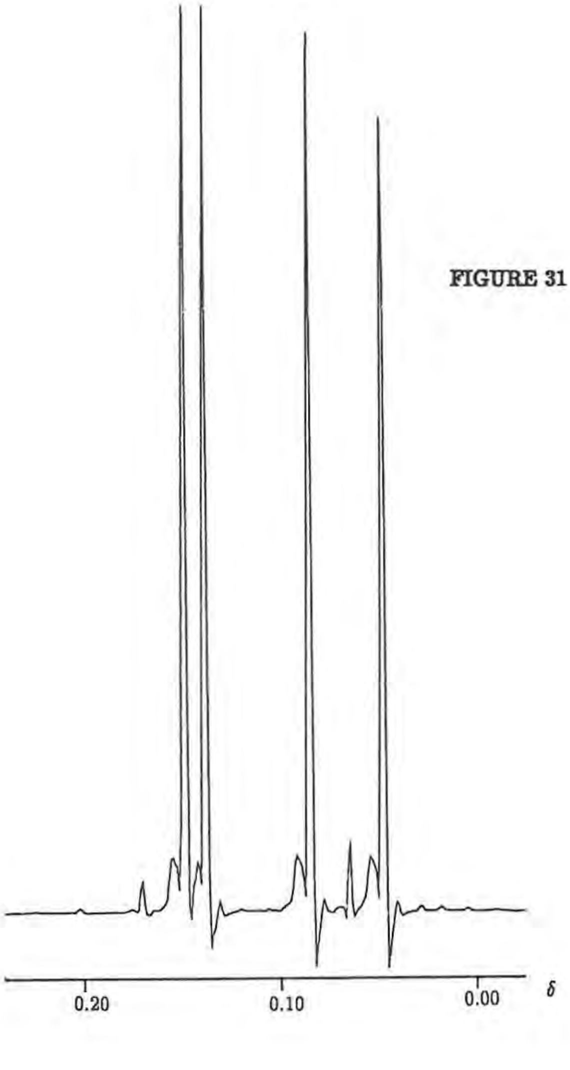
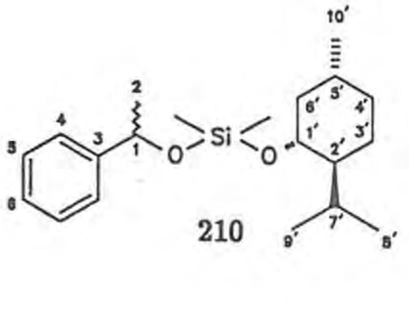


FIGURE 31

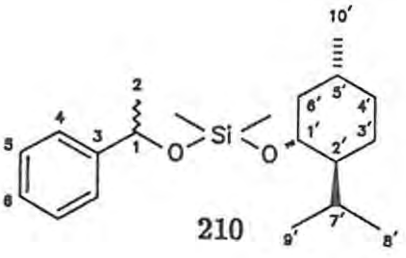
Expansion of the four chemically non–equivalent, diastereotopic SiMe singlets in the ^{1}H NMR spectrum of (210).

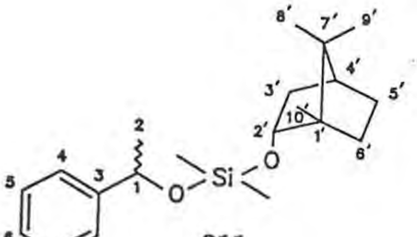


210

TABLE 11: Doubled NMR Signals for the diastereomeric silyl acetals (210) – (214).

	^{1}H	^{13}C
(210)	0.05, 0.09, 0.14 and 0.15, (0.89:0.93: 0.94:1.00), 4 x s, SiMe; 1.28 and 1.34, br m, 5–H′; 1.47 and 1.48, (1.00 :0.98), 2 x d, 2–Me; 1.79 and 1.96, (0.98: 1.00), 2 x m, 6′–H$_{eq}$.	–1.85, –1.75, –1.71 and –1.40, SiMe; 15.92 and 15.94, C–9′; 22.12 and 22.23, C–10′; 31.59 and 31.65, C–5′; 45.23 and 45.37, C–6′; 125.30 and 125.36, C–4.
(211)	0.030, 0.032, 0.133 and 0.135, (1.00:0.94:0.89: 0.94), 4 x s, SiMe; 0.73 and 0.81, 2 x s, 10′–Me); 0.847 and 0.841, (0.93:1.00) 2 x s, 8′–Me; 0.90 and 0.99, 2 x dd, 3′–H$_{endo}$; 1.56 and 1.59, (0.90:1.00), 2 x t, 4′–H; 2.03 and 2.16, 2 x m, 3′–H$_{exo}$.	–2.11, –1.98 & –1.75, SiMe; 13.34 and 13.47, C–10′; 28.25 and 28.29, C–5′; 39.13 and 39.18, C–3′; 45.18 and 45.22, C–4′.
(212)	0.859 and 0.863, 2 x t, 4–Me; 1.13 and 1.14, (0.99:1.00), 2 x d, 1–Me; 1.42 and 1.47, 2 x m, 3–CH$_2$.	–1.66, –1.56, –1.49 and –1.36, 4 x q SiMe; 45.39 and 45.44, 2 x t, C–6′.
(213)	1.13 and 1.14,(0.91: 1.00), 2 x d, 1–Me.	–1.60, –1.46 and –1.32, SiMe; 23.58 and 23.66 C–1; 45.39 and 45.44, C–6′.
(214)	1.13 and 1.14,(0.81: 1.00), 2 x d, 1–Me.	–1.63, –1.40 and –1.34, SiMe; 23.58 and 23.66 C–1.


210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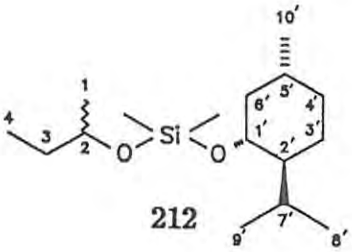
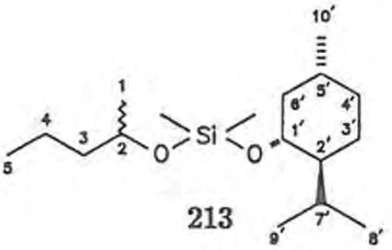

212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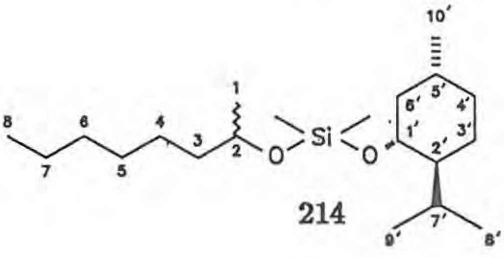

214

the protons of the methyl group [**2–Me** for compound (**210**) and **1–Me** for the aliphatic alcohols (**212**) – (**214**)] bonded to the chiral centre of the secondary alcohol exhibits significant splitting (0.01 ppm). In each diastereomer, the four lines of this composite signal were paired into diastereomeric doublets by assuming that coupling with the adjacent methine proton, is comparable to that observed in the starting alcohol. Either of the other two possible pairings would imply coupling constants significantly different from the parent alcohol (Figure 28, p. 133). The **2–Me** diastereomeric doublets of the aromatic acetal (**210**) have an integral ratio of 1.00 : 0.98 as determined by summing the individual line intensities. The ratios of comparable signals in the aliphatic acetals (**212**), (**213**), and (**214**) (**1–Me**) are 0.99 : 1.00, 0.91 : 1.00, and 0.81 : 1.00 respectively. In each case the **1–Me** signal is superimposed on the 2′–H multiplet. This superposition is believed to be the reason for the distortion of the integral ratios in acetals (**213**) and (**214**). The signal for the methyl group of the R_1 alkyl susbtituent (Scheme 57) is only split in the 2–butanol derived acetal (**212**) but the integral ratio of these (**4–Me**) multiplets was impossible to determine due to the complexity of the spectrum in that region. The absence of any splitting of this methyl signal in acetals (**213**) or (**214**) is most likely due to the increased distance from the chiral centres responsible for the effect. No attempt was made to evaluate the diastereomeric nature of the (**1–H**) or (**2–H**) methine proton signal or any of the methylene signals in the acetals (**213**) and (**214**).

The aromatic acetals (**210**) and (**211**) show more significant diastereomeric splittings than those of the aliphatic acetals. In the menthyloxy acetal (**210**) the three non–equivalent methyl groups of the chiral derivatizing agent, in each diastereomer, give rise to a complex signal comprising twelve lines (Figure 29, p. 133). In the case of the bornyloxy acetal (**211**) the signal for the three, uncoupled methyl groups of the chiral derivatizing agent, in each diastereomer, is somewhat different (Figure 30, p. 133). Based on a literature precedent,[229] the highest field signal is assigned to the **10′–Me** methyl group and the assignments of **8′–Me** and **9′–Me** are regarded as being interchangeable [(See assignment of chiral silyl enol ethers **(183)** – **(185)** (Section 3.3. p. 238)]. Our explanation of the signals obtained for the diastereomeric mixture **(211)** is that the diastereomeric **10′–Me** singlets are well separated and one of these singlets superimposes the unsplit **9′–Me** signal. The remaining two lines, further downfield, are ascribed to diastereomeric splitting of the **8′–Me** signal; this splitting is considerably smaller than that of the **10′–Me** signal. The explanation of the observed pattern holds equally well if the assignments of **8′–Me** are **9′–Me** interchanged. The diastereomeric ratio may thus be determined from the integral ratio of the low field signals (**8′**– or **9′–Me**); this ratio was found to be 0.93:1.00.

Only in the case of the acetals derived from 1–phenylethanol [**(210)** and **(211)**], are the expected, four silyl methyl singlets (two non–equivalent methyls in each diastereomer), observed in the ^{1}H NMR spectra (Figures 31 and 33, p. 134). In the remainder of the acetal mixtures the four, theoretically non–equivalent silyl methyl groups, resonate as one singlet. The four SiMe singlets in the spectra of compounds **(210)** and **(211)**, could in all probability be arranged into diastereomeric pairs, based on comparisons of the magnitude of the separations of the singlets with similar signals in the ^{1}H NMR spectra of other diastereomerically pure dimethylsilyl compounds. This has, in fact, been done in subsequent work in this study, but, in this case was deemed unnecessary as the diastereomeric ratios could be obtained by simply comparing the intensities of all four of the singlets as shown in Table 11. Chan *et al.*[218] in similar work that has already been discussed, also prepared compound (**210**) from *racemic* 1–phenylethanol and obtained its ^{1}H NMR spectrum at an unspecified field strength. Their only comment concerning this spectrum is that the SiMe signal separation ($\Delta\delta$) is 0.039 ppm. This statement appears to be somewhat ambiguous, bearing in mind the fact that we have established that the signal comprises four singlets.

In both of the aromatic diastereomeric acetal mixtures (**210**) and (**211**) there are, however, signals ideally suited to analysing enantiomeric mixtures due to their apparent sensitivity to diastereomeric influences in these silyl acetals. In the menthyloxy silyl acetal of 1–phenylethanol (**210**) the **6′–H$_{eq}$** multiplets are separated by 0.17 ppm or **85 Hz** in an area of the spectrum that is devoid of any other signals! (figure 26, p. 131) In the analogous bornyloxy acetal (**211**), the **4′–H** signals are separated by 0.13 ppm and neither signal is impinged upon by adjacent signals (Figures 27 p. 132 and 32, p. 134). In both of these cases, the experimental diastereomeric ratios approach unity. The **3′–H$_{exo}$** and **3′–H$_{endo}$** diastereomeric signals are also well separated by 0.13 and 0.09 ppm respectively. However, in the **3′–H$_{exo}$** the upfield diastereomeric signal is totally obscured by the **6′–H$_{endo}$** multiplet and in the **3′–H$_{endo}$** case, the upfield diastereomeric signal is partially obscured by the **8′–H** singlet, making calculation of the diastereomeric ratios impossible.

From the summary of ^{13}C data in Table 11 it can also be seen that in each of the examples, except acetal (212), in which the diastereomeric effect relies on the differences between the similar methyl and ethyl groups, most of the carbons bearing protons that exhibit diastereomeric splitting, are split themselves. In addition there are carbons that exhibit splitting while the protons bonded to them are unsplit. The most prominent examples are the silyl methyl carbon signals that are diastereomerically split in every example, while the analogous proton signals are only split in the aromatic acetals **(210)** and **(211)**. This would seem to indicate that ^{13}C nuclei are more sensitive to diastereomeric influences than the ^{1}H nuclei.

An appraisal of the detailed NMR data obtained in this study leads to the following conclusions:–

i) Even in cases where the substituent R_1 is similar to the methyl substituent (*e.g.* ethyl) both ^{1}H and ^{13}C signal doubling occurs.

ii) If a particular signal for both diastereomers does not overlap any neighbouring signals, then the integral ratio of these signals will accurately establish the diastereomeric distribution of the sample acetal, and hence accurately reflect the original enantiomeric composition of the secondary alcohol.

iii) If the two alkyl substituents of the secondary alcohol are markedly different then these chiral alkoxysilyl groups appear to have real potential as convenient enantio–differentiating NMR probes.

iv) With suitable pulse delay techniques, the observed doubling of ^{13}C NMR signals may permit a more sensitive and flexible quantification of enantiomer distribution.

2.2.2 GLC Analyses of the Diastereomeric Silyl Acetals (210) – (214).[232]

The novel GLC resolution of the diastereomeric silyl acetals [**(210)** – **(214)**] was investigated using 30 and 60 m medium polarity fused silica columns (see Section 3.5, p 251 for a detailed description of the chromatographic conditions).

Under optimum temperature–programme conditions, resolution of the components was obtained for each of the diastereomeric systems **(210)**, **(211)**, and **(214)**, using both available column lengths (Figure 34). However, no

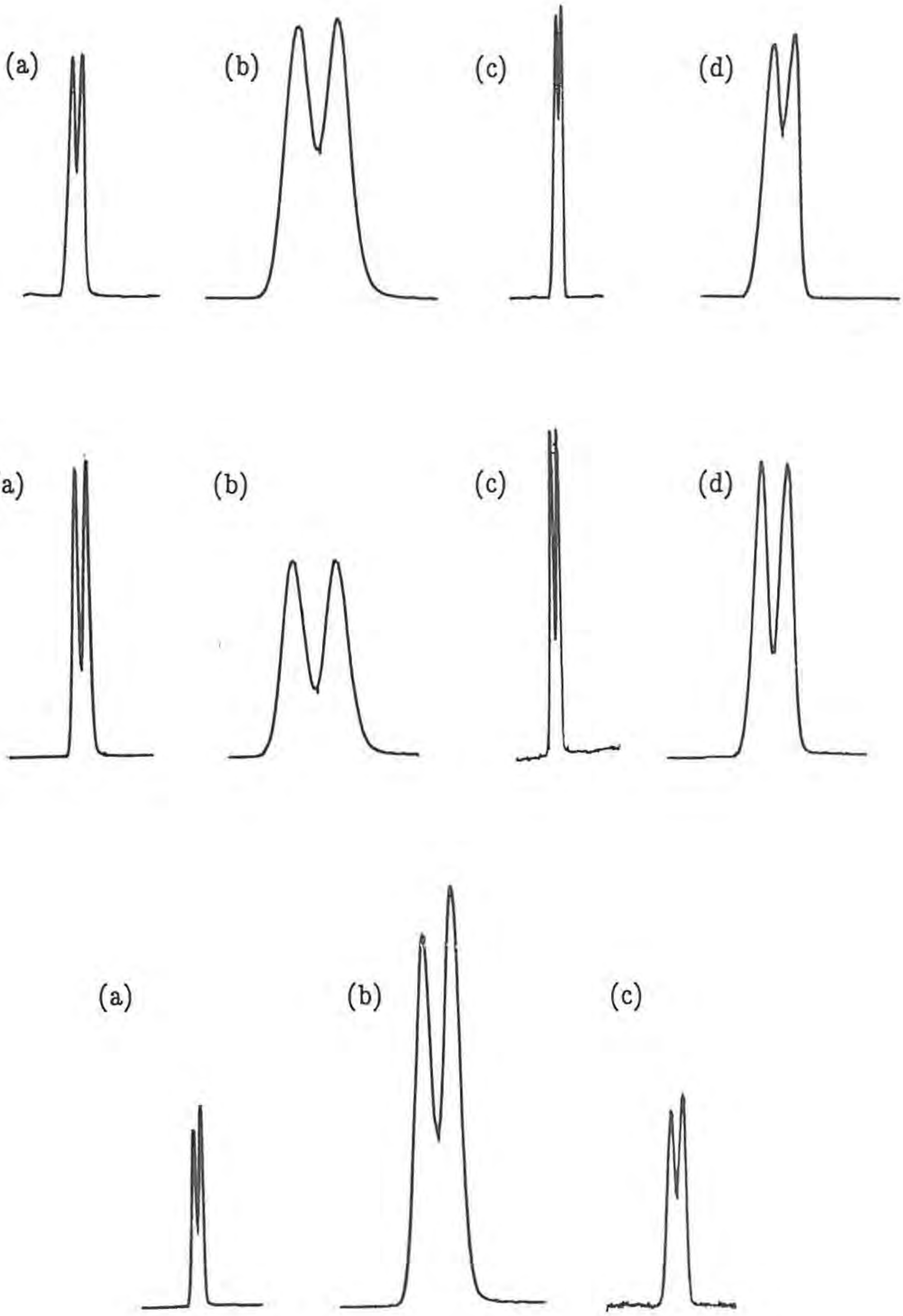


Figure 34 : Partial gas chromatograms illustrating the resolution of the diastereomeric silyl acetals (**210**), (**211**), and (**214**) : (a) 60 m column; (b) 60 m column, chart speed doubled; (c) 30 m column; (d) 30 m column, chart speed doubled.

conditions were obtained to permit separation of the diastereomeric acetals in systems (**214**) and (**215**), using either 30 or 60 m columns.

In order to report the three successful separations in chromatographic terms, the peak resolution (R_s) and the separation factor (α) were calculated in each case.

Peak resolution $(R_s) = \frac{2\Delta W}{W_a + W_b}$, where ΔW is the distance by which the peaks are separated and W_a and W_b are the baseline widths of peaks A and B, obtained by approximating the tangents to both sides of each peak (Figure 35).[233] The separation factor (α), is the ratio of the two peaks' observed retention times.[234]

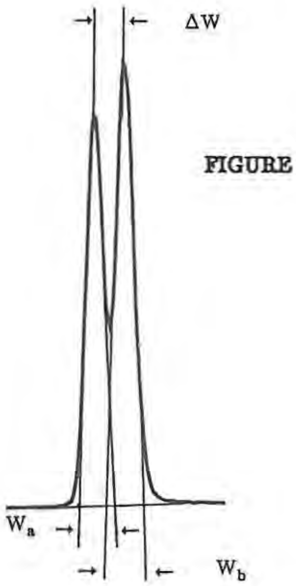


FIGURE 35 The peak resolution (R_s) was determined by the expression

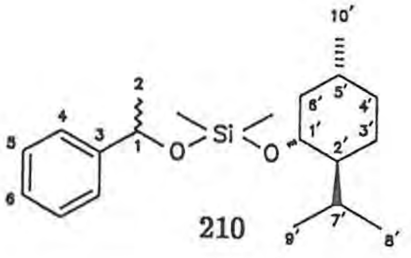
$$(R_s) = \frac{2\Delta W}{W_a + W_b}.$$

ΔW is the distance by which the peaks are separated and W_a and W_b are the baseline widths of peaks A and B, obtained by approximating the tangents to both sides of each peak.[233]

The optimised temperature programmes, retention times, peak resolution (R_s), separation factors (α) and relative areas for the diastereomeric silyl acetals (**210**), (**211**), and (**214**) are summarised in Table 12.

TABLE 12: Temperature programmes used to separate the diastereomeric silyl acetals **(210)**, **(211)**, and **(214)**, and the resulting retention times, peak resolution values (R_s), separation factors (α), and relative peak areas.

	Temperature Programmes to Separate the Diastereomers.	Retention Times / min; (Relative Peak Areas); R_s and α.
(210)	30 m 60–140° C at 4° C / min then 140–170° C at 1° C / min.	43.00 and 43.16 (1.00:0.98) $\alpha = 1.004$ $R_s = 0.38$
	60 m 60–140° C at 2° C / min then 140–170° C at 1° C / min.	88.37 and 88.68 (0.93:1.00) $\alpha = 1.004$ $R_s = 0.63$
(211)	30 m 60–140° C at 4° C / min then 140–170° C at 1° C / min.	41.14 and 41.35 (1.00:1.00) $\alpha = 1.005$ $R_s = 0.80$
	60 m 60–140° C at 2° C / min then 140–170° C at 1° C / min.	84.37 and 84.70 (0.95:1.00) $\alpha = 1.004$ $R_s = 0.88$
(214)	30 m 60–120° C at 4° C / min then 120–160° C at 1° C / min.	35.60 and 35.78 (0.88:1.00) $\alpha = 1.005$ $R_s = 0.69$
	60 m 60–120° C at 2° C / min then 120–160° C at 1° C / min.	71.63 and 71.84 (0.85:1.00) $\alpha = 1.003$ $R_s = 0.75$



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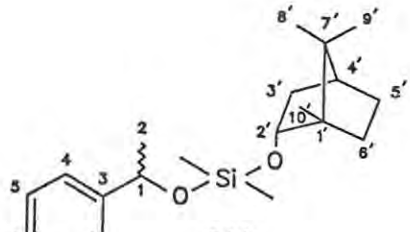

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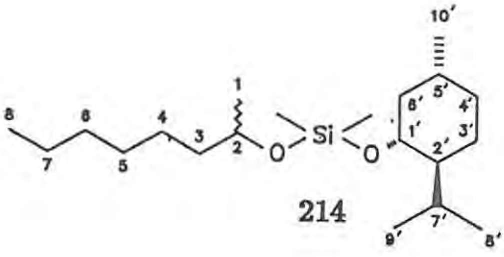


214

It can be seen from the above expression for peak resolution that any value of $R_s \geq 1$ represents baseline to baseline separation of the peaks under scrutiny. Doubling the length of the column had no significant effect on the separation factors (α) but did increase the peak resolution (R_s) in all three examples.

It would appear that, as in the case of the NMR analyses, significant differences between the substituents of the secondary alcohols are necessary to differentiate the diastereomers. It does seem however, that these demands are more stringent in the GLC analysis, as no resolution at all was achieved for the acetals **(213)** (R_1 = Et) and **(213)** (R_1 = Pr). To our mind the above data and analysis comprehensively illustrates the potential of these particular chiral silyl derivatizing agents in the GLC analysis of enantiomers.

A comparison of the results from both NMR and GLC techniques reflects close correlation between the diastereomeric integral ratios obtained. It is also apparent that both methodologies have the potential to accurately determine enantiomeric ratios of secondary alcohols, and while not investigated in this study, extension of the method to a variety of other functional groups may be easily envisaged. Furthermore, in reactions of silyl enol ethers in which the chiral alkoxy silyl group remains bonded to the product, then either of these two methods of analysis, could possibly be used to measure enantiomeric induced excess.

2.3 REACTIONS OF CHIRAL SILYL ENOL ETHERS (164), (172), (180), (181), (182), (185) AND (194) WITH CARBON AND OXYGEN ELECTROPHILES.[235,236]

From the vast array of known electrophilic reactions of silyl enol ethers,[203-205] transformations had to be chosen that would best serve the purpose of evaluating the potential of the prepared chiral silyl enol ethers as substrates for asymmetric synthesis. The primary considerations influencing the final selection of such transformations were:

i) Only a single new chiral centre was to be generated, either in a position α or β to the carbonyl group of the original ketone.

ii) The ensuing enantiomeric or diastereomeric product mixtures had to be amenable to the determination of the enantiomeric excess, – the intention being, where possible, to use the methods described in Sections 2.2.1 and 2.2.2, p. 130 and 139.

iii) The reaction should proceed in adequate yields even when being conducted on a small scale and, if at all possible, without any complicating side reactions.

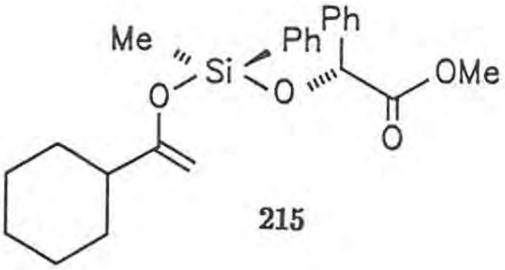
[These considerations were inherent in the initial choice of ketones (Section 2.1.)]

At this stage of our investigation, an important publication appeared in the literature. In this publication Walkup and Obeyesekere [237] reported the first reactions of silyl enol ethers with chiral alkoxy groups attached to the silicon. Using the method described in Walkup's initial paper in this field [206] (See section 2.1, p. 97 and 3.3, p.238), they prepared a number of novel chiral silyl enol ethers, including the (*S*)–methyl mandelate derived systems [**(215)** – **(219)**]. Silyl enol ether **(215)** was then separated from its diastereomer **(216)**, by preparative HPLC, as were the diastereomers **(217)** and **(218)** separated from each other. The absolute configurations of the silicon centres of the silyl enol ethers [**(215)** – **(218)**] had, however, not been assigned.

Walkup and Obeyesekere [237] reacted the diastereomeric silyl enol ethers **(217)** and **(218)** separately, and the dimethyl silyl enol ether **(219)** with MCPBA in the presence of powdered $NaHCO_3$, to yield the very unusual diastereomeric (*Z*)–silyloxy epoxides **(220)** and **(221)** respectively. (See section 2.3.1, p. 149 for a discussion on the unusual nature of these compounds.) The diastereomeric ratios of these epoxides ranged between 55:45 and 58:42. These authors also established that the absolute configuration at the silicon centre had little effect on the induced diastereofacial selectivity, *e.g.* the same major diastereomer was obtained in the diastereomeric epoxide mixture **(220)** whether the silyl enol ether **(217)** or the silyl enol ether with the opposite configuration at the silicon centre **(218)** was the epoxidation substrate. They concluded, therefore, that the epoxidation occurred from the same face of the enolate, regardless of the absolute configuration of the silicon atom and hence, any diastereoselectivity is induced by the chiral alkoxy group and not by the chiral silicon centre.

The appearance of the Walkup paper, at this particular stage of our investigation unavoidably influenced our own approach.

The reaction of Walkup and Obeyesekere [237] represented an application of the original peracid oxidation of trimethylsilyl enol ethers [(pioneered by three independent research groups [238-241] (see Section 2.3.1)] to yield α–siloxy or α–hydroxy ketones depending on the reaction conditions. Applied to our silyl



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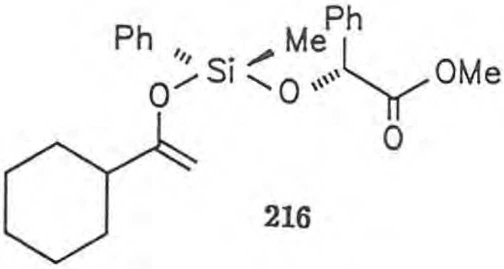

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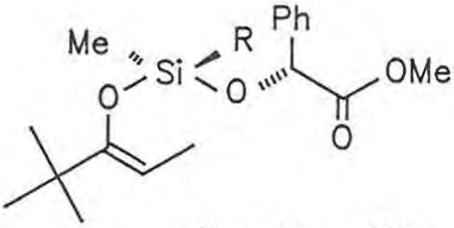
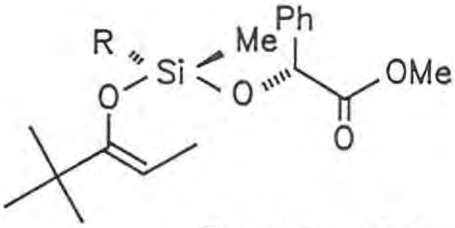
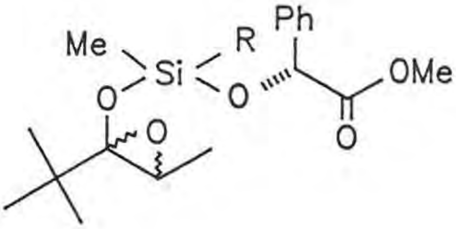


R = Ph **217**

R = Me **219**



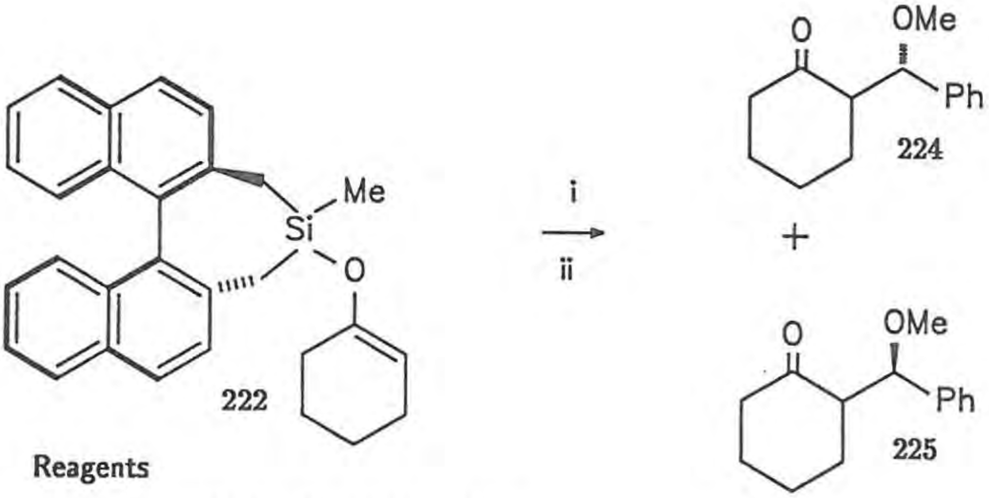
R = Ph **218**



R = Ph **220**

R = Me **221**

SCHEME 58



Reagents

i) PhCH(OMe)$_2$ (**223**), ii) TMSOTf

enol ether systems, this reaction would suitably satisfy the criteria we laid down, its special attraction being the apparent retention of the silyl group in the product molecule which could thus act as a chiral probe. This application would also furnish the opportunity to extend the work of Walkup to additional silyl enol ether systems. The peracid oxidation thus became one of the reactions chosen to act as a model system for the ensuing asymmetric reactions.

Other silyl enol ether reactions, which adequately satisfied our criteria for these test reactions, also appeared to be available. From this selection, two specific types of reaction were chosen, that, to our minds represented a cross–section of the more useful achiral synthetic applications of these systems. These were the $TiCl_4$ catalysed reaction of carbonyl compounds with silyl enol ethers, developed by Mukaiyama *et al.*[54] (Section 2.3.3, p. 180) and the alkylation of silyl enol ethers employing alkyl halides capable of forming carbocations [203] (Section 2.3.2, p. 172).

Thus by way of a summary, the three types of model reactions we selected to investigate asymmetric electrophilic reactions of silyl enol ethers were;

i) peracid oxidations (Section 2.3.1, p. 149),

ii) alkylation of silyl enol ethers using tertiary alkyl halides and Lewis acid catalysts (Section 2.3.2),

iii) the "Mukaiyama reaction" – in which carbonyl compounds react with silyl enol ethers in the presence of Lewis acid catalysts (Section 2.3.3).

Apart from the paper by Walkup and Obeyesekere [237] and our own publications,[235,235] to the best of our knowledge, only one other report, by Jung and Hogan,[242] describing reactions of silyl enol ethers with chiral ligands on the silicon, has appeared in the literature. Jung and Hogan prepared a number of binaphthylic silyl enol ethers and ketals, *e.g.* the cyclohexanone derived silyl enol ether (**222**) and reacted these compounds with benzaldehyde dimethyl ketal (**223**) in the presence of a Lewis acid catalyst. Their most successful asymmetric reaction, illustrated in Scheme 58 (p. 146), yielded the separable *erythro* (**224**) and *threo* diastereomers (**225**) in 17 and 35% enantiomeric excesses respectively. In our opinion, this reaction had one major disadvantage, *viz.*, two new chiral centres were created and thus the resulting diastereomers had to be separated before the enantiomeric excess of the reaction could be determined and, hence, we did not consider applying it to any of our own systems.

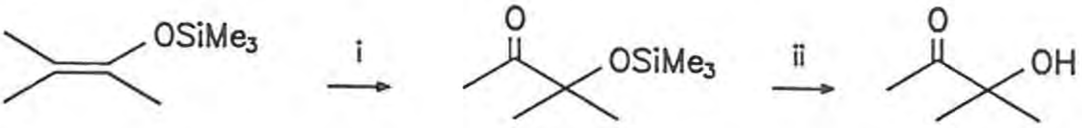
2.3.1 Peracid Oxidation of Selected Chiral Silyl Enol Ethers.

2.3.1.1 The Background and Development of MCPBA Oxidations of Achiral Silyl Enol Ethers

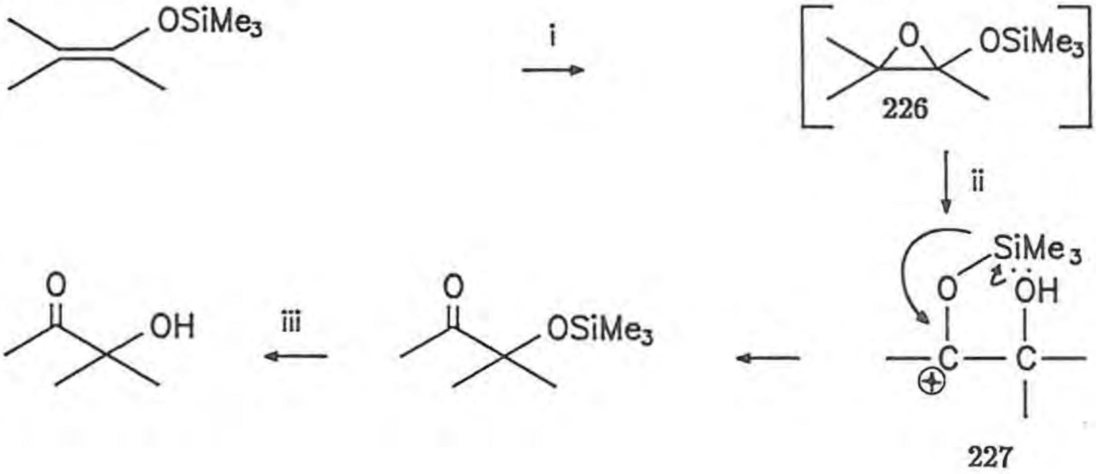
As has been mentioned above, trimethylsilyl enol ethers were first oxidized with MCPBA by Rubottom *et al.*,[238] to yield the α–siloxy ketones, which, in turn could be easily hydrolized to the α–hydroxy ketones as illustrated in Scheme 59. At that stage, the intermediacy of the epoxide (**226**) was assumed, by analogy with peracid oxidation of olefins and more specifically enol acetates in which the intermediacy of the analogous epoxy ketones is well established.[243] However, during his initial investigation and in a subsequent examination of the mechanism of these epoxidations [241] Rubottom *et al.* found no evidence for the existence of the intermediate epoxide.

At the same time, however, but independently of Rubottom *et al.*, Brook and Macrae [239] also explored MCPBA oxidations of trimethyl– and triphenysilyl enol ethers, regarding them as 1,4 oxygen–to–oxygen silyl shifts. The mechanism they considered most likely is illustrated in Scheme 60. This involves the oxacarbonium ion (**227**) which is stabilized by delocalization of the oxygen lone pair, which would not be possible in the alternative carbonium ion. They could not detect the intermediate siloxyepoxide (**226**) and commented that it was unclear as to whether the oxacarbonium ion formed directly from the reaction of MCPBA on the siloxyalkene or *via* protonation of the possible siloxyepoxide intermediate. In a third, independent study Hassner *et al.*[240] reported similar results on analogous ketone derived silyl enol ethers but obtained the ketal derivative (**229**) when oxidizing silyl enol ethers of aldehydes. They postulated that the *in situ* opening of the intermediate epoxide (**228**) by *m*–chlorobenzoic acid (Scheme 61) was involved in the

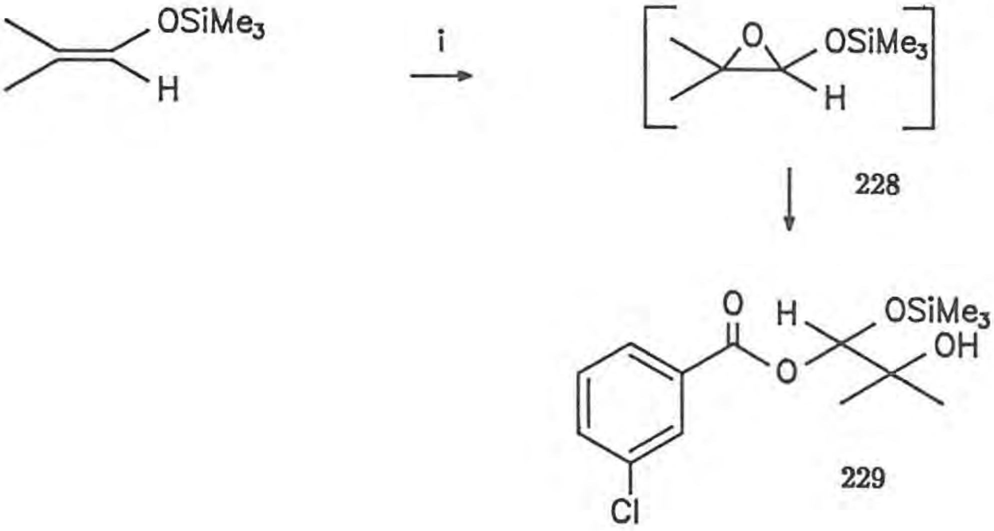
SCHEME 59



SCHEME 60



SCHEME 61



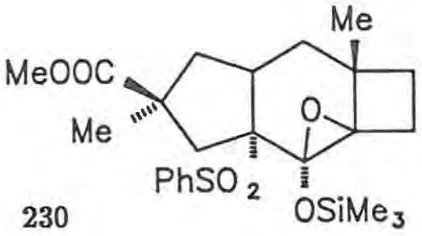
Reagents

i) MCPBA, ii) H^+, iii) H_2O

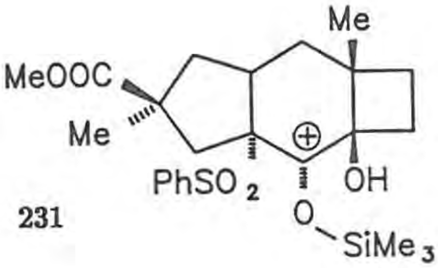
formation of the product (**229**) but once again no evidence of the intermediate epoxide was found.

The first isolation of siloxy epoxides was only achieved twelve years after the discovery of the reaction, when Paquette *et al.*[244] *en route* to the synthesis of a natural product, obtained the siloxy epoxide (**230**) from the corresponding silyl enol ether using MCPBA in the presence of excess $NaHCO_3$. The acid sensitivity of this compound was demonstrated in the subsequent step of Paquette's synthesis, when the epoxide was converted to the α–siloxy ketone in the presence of an acid as weak as benzoic acid. The isolability of the epoxide (**230**) may be attributed to a combination of the neutralizing effect of the $NaHCO_3$, and the significant inductive effect of the proximal benzenesulphonyl group, deterring transient formation of the carbonium (**231**). It was this work that first provided conclusive experimental evidence that oxidation to α–siloxy ketones proceeds *via* epoxides and carbonium ions as first envisaged.[238,239]

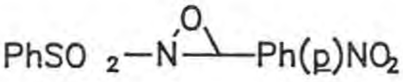
In, what must have been a concurrent study, Davis and Sheppard [245] isolated siloxy epoxides by oxidizing a variety of trimethyl silyl enol ethers with the aprotic, neutral oxidizing agent 2–(phenylsulphonyl)–3–(*p*–nitrophenyl)oxaziridine (**232**). They also attempted asymmetric oxidations of the silyl enol ethers (**234**) and (**235**) using the optically active oxaziridine (+)–(*R*,*R*)–(**233**), isolating the α–hydroxy ketones (**236**) and (**237**) in 7.5 and 11.0% enantiomeric excess. The poor enantiomeric excesses were ascribed to the small steric differences in the approach of the oxidizing agent to the *si* and *re* faces of the silyl enol ethers. Chenault and Danishefsky [246] and Adam *et al.*[247] have also isolated silyl epoxides from the oxidation of silyl enol ethers when using dimethyldioxirane (**238**) as an oxidizing agent. This reagent is mild, yet reacts



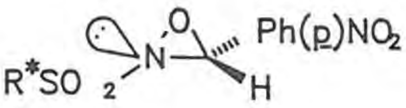
230



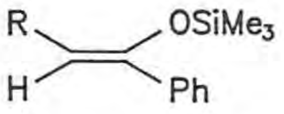
231



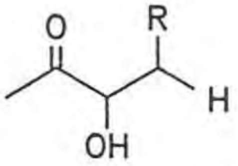
232



(+)-(*R*,*R*)-(**233**) R* = (S)-PhCH(Me)NCH$_2$ Ph
|



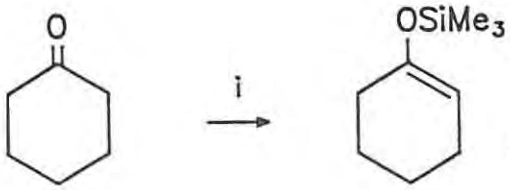
R = Me **234**
R = Ph **235**



R = Me **236**
R = Ph **237**

238

SCHEME 62

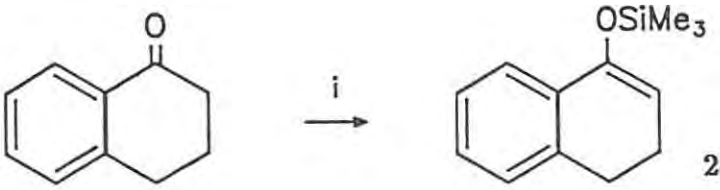


239

Reagents

i) TMSCl and Et$_3$N

SCHEME 63



240

Reagents

i) TMSCl, NaI, and Et$_3$N

at low temperature (–78° C to –40° C) and does not promote acid catalysed rearrangement of the silyl epoxides.

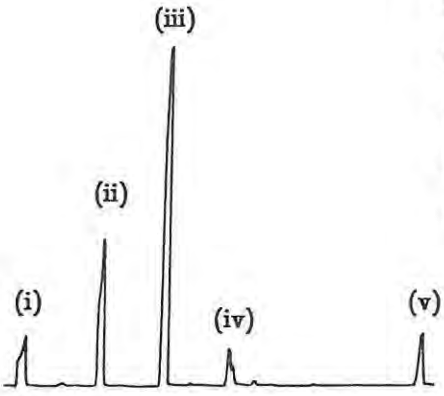
The significance of Walkup and Obeyesekere [237] isolating the relatively rare silyl epoxides from their MCPBA oxidations is easily appreciated in the light of what is now known concerning oxidations of silyl enol ethers in general and our own experience in particular.

2.3.1.2 Preparation and Peracid Oxidation of Model, Achiral Silyl Enol Ethers

The chiral silyl enol ethers, due to the nature of their preparation, were not accesible in large quantities. It was decided, therefore, before proceeding to the peracid oxidation studies of these chiral silyl enol ethers, to develop, in our own laboratories, reliable experimental protocols for these reactions by using simple achiral silyl enol ethers as model substrates. The trimethyl silyl enol ethers of cyclohexanone (**239**) [prepared by the original method of House *et al.*,[209] (Scheme 62)] and α–tetralone (**240**) [prepared using TMSCl, NaI, and Et_3N [211] (Scheme 63)] were chosen as models for the analogous chiral silyl enol ethers [(**172**), (**182**), and (**185**) already identified as promising substrates for the asymmetric epoxidation studies. Furthermore, it appeared that the MCPBA oxidation of such simple silyl enol ethers in the presence of $NaHCO_3$ had received surprisingly little attention. It was hoped that our test reactions would provide, to our minds at least, some clarity on the advantage of using $NaHCO_3$.

The MCPBA oxidations of the model systems proved to be difficult to monitor and the workup and isolation of the products were fraught with complications. Oxidation of the cyclohexanone silyl enol ether, in the absence of $NaHCO_3$, (Scheme 64) yielded a crude reaction mixture containing **five** components [as indicated by GLC (Figure 36)].

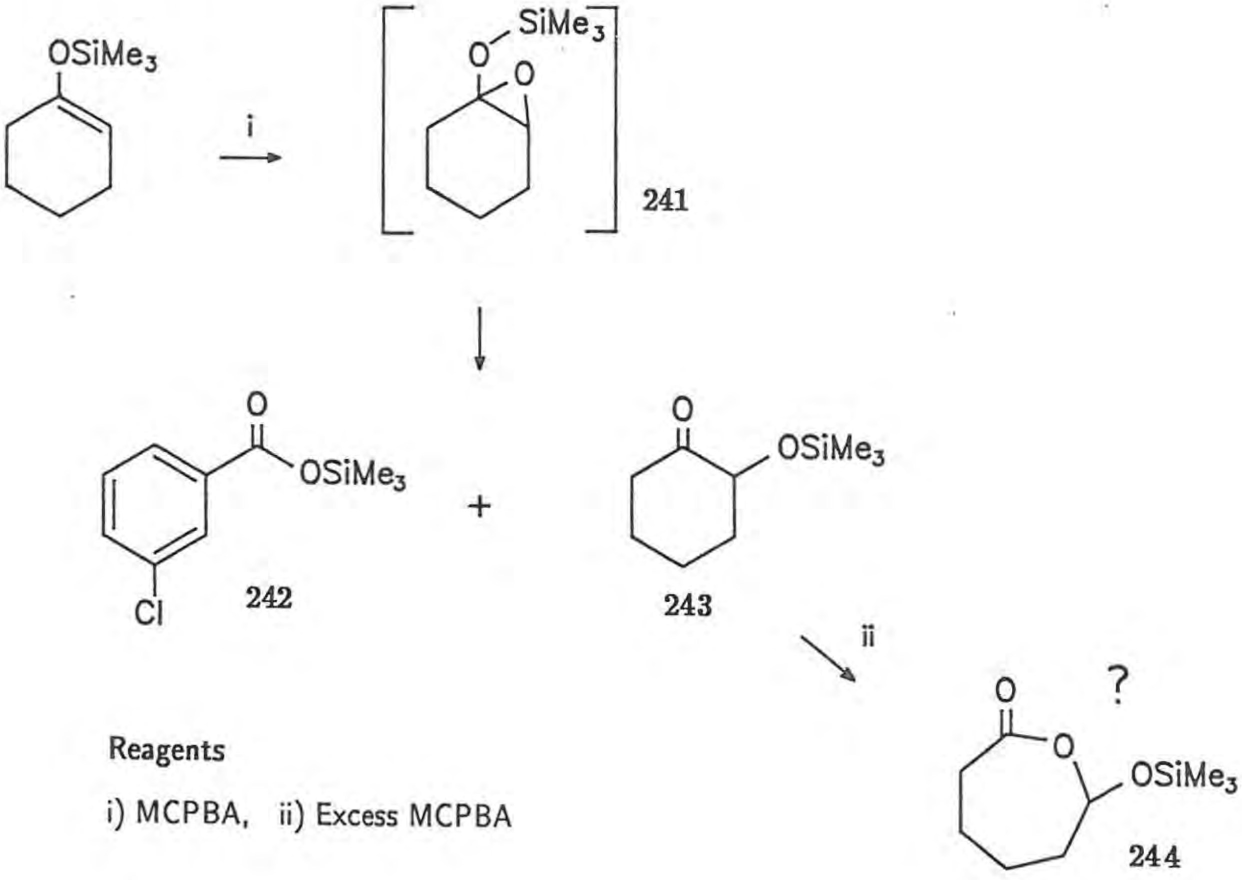
FIGURE 36 GLC of the crude reaction mixture from the MCPBA oxidation of the cyclohexanone trimethylsilyl enol ether (**239**). The retention time, in minutes, and the percentage intensities are provided.



(i)	4.49 (11.3%)
(ii)	6.66 (24.4)
(iii)	8.45 (51.6)
(iv)	10.19 (4.8)
(v)	15.4 (8.3)

Fractional distillation of this mixture produced several fractions, one of which proved to be the α–siloxy ketone (243) (peak iii, Figure 36), as confirmed by ^1H NMR, IR, and mass spectroscopy. Spectral information of particular importance in confirming the structure was the single ^1H NMR SiMe singlet, the strong carbonyl absorbtion at 1725 cm^{-1} and the absence of any OH band in the IR and, while no molecular ion peak was evident, a significant signal for an M^+–15 fragmentation (the loss of a methyl fragment from trimethyl siloxy moieties is well established [209]). A higher boiling fraction comprised a mixture (peaks iii – v, Figure 36) whose ^1H NMR spectrum indicated a significant amount of aromatic material, which was unexpected, as all the chloroperbenzoic acid and chlorobenzoic acid should have been removed during

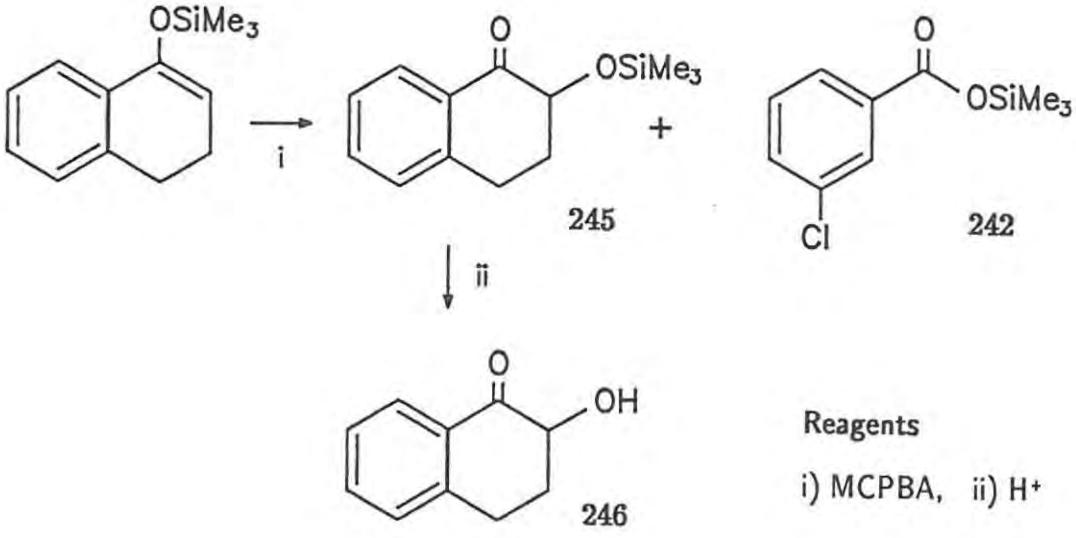
SCHEME 64



Reagents

i) MCPBA, ii) Excess MCPBA

SCHEME 65



Reagents

i) MCPBA, ii) H⁺

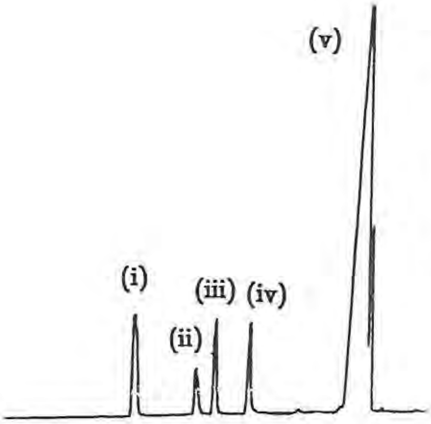
work–up. GC–MS analysis of this fraction provided a mass spectrum of the aromatic compound that was consistent with the trimethylsilyl ester of chlorobenzoic acid (**242**). Attempted preparative GLC purification of this fraction failed, due, we believe, to the hydrolysis of the silyl ester under the chromatographic conditions employed. The silyl ester (**242**) was then prepared from chlorobenzoic acid and TMSCl and subjected to GLC co–chromatography with the MCPBA reaction mixture, co–eluting under a variety of conditions with peak (v) in the reaction mixture. It should be noted that the specially prepared silyl ester (**242**) exhibited severe instability, decomposing to the solid chlorobenzoic acid within days, even when stored at 10° C.

GC–MS analyses of the crude reaction mixture, prior to distillation, confirmed the nature of peaks (iii) and (v) and permitted identification of peaks (i) and (ii) as cyclohexanone and the starting silyl enol ether (**239**) respectively. The minor (*ca.* 5%) component responsible for peak (iv) was never isolated although GC–MS analysis indicated a trimethylsiloxy derivative (due to the diagnostic peaks at $m/z = 75$ and 73)[209] and the highest m/z value peak at 186. Possible products, consistent with the mass spectrum are the silyl epoxide (**241**) or the ring expanded lactone (**244**), produced by the known Baeyer–Villiger type reaction of silyl enol ethers.[239] The reaction was repeated several times with reproducible results, confirming that in the absence of $NaHCO_3$ little or no epoxide could be isolated.

Repetition of the oxidation of the cyclohexanone silyl enol ether (**239**) in the presence of $NaHCO_3$, however, did not appear to alter the nature of the products formed. In fact, GLC analysis of the crude material after work–up revealed a far higher percentage of both cyclohexanone and the starting silyl enol ether (**239**).

MCPBA oxidation of the α–tetralone silyl enol ether (**240**) was somewhat easier to evaluate (Scheme 65, p. 155). This was due, primarily, to the properties of the α–siloxy ketone product (**245**); it was more stable and less volatile than the analogous cyclohexanone product and it was formed in significantly higher yields. Conducting the oxidation in the absence of $NaHCO_3$ yielded, on work–up, a crude reaction mixture which was shown to contain at least five components by GLC (Figure 37).

FIGURE 37 GLC of the crude reaction mixture from the MCPBA oxidation of the α–tetralone trimethyl silyl enol ether(**240**). The retention time, in minutes, and the percentage intensities are provided.



(i)	9.09 (6.9%)
(ii)	10.77 (2.8%)
(iii)	11.30 (4.1%)
(iv)	12.26 (4.5%)
(v)	15.52 (71.0%)

GC–MS analysis permitted identification of the major product, [peak (v), Figure 37] as the α–siloxy ketone (**245**) and facilitated a confident identification of most of the minor products. Peaks (ii) and (iii) gave mass spectra consistent with α–tetralone and the silyl ester (**242**) respectively. The mass spectrum of peak (iv) is indicative of the α–hydroxy ketone (**246**), showing a significant M^+ peak at m/z = 162 and a characteristic alcohol fragmentation of M^+–18. Flash chromatography of the reaction mixture enabled the α–siloxy ketone (**245**) to be isolated in moderate yields. Repetition of the oxidation of the α–tetralone trimethyl silyl enol ether (**240**) in the presence of $NaHCO_3$, yielded a similar product distribution, with the siloxy ketone (**245**) once again being the only major product,in contrast to the work of Watanabe and Ishimura,[248] who have reported the isolation of the corresponding silyl epoxide under similar reaction conditions.

It was, thus, obvious that the addition of $NaHCO_3$ to the MCPBA oxidation of the simple cyclic silyl enol ethers *e.g.* (**239**) and (**240**) made very little difference to the outcome of these peracid oxidations and that the major product formed was always the α–siloxy ketone.

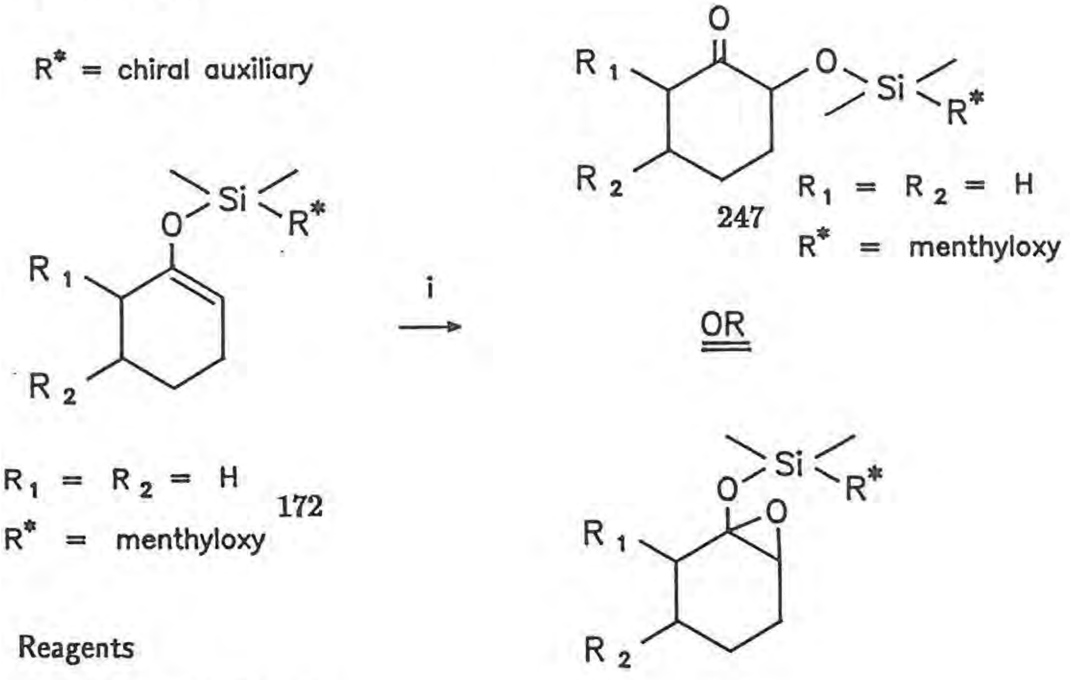
In spite of the uncertainty in predicting the major product of these reactions, even in the presence of $NaHCO_3$, we conducted the examination of the peracid oxidations of silyl enol ethers with chiral substituents. In the event the reactions afforded almost exclusively the α–siloxy products as will be seen in the ensuing section.

2.3.1.3 Evaluation of Asymmetric Peracid Oxidations of the Chiral Silyl Enol Ethers (172), (181), (182), and (185)[235].

The experimental protocol decided upon was an MCPBA oxidation, in the presence of excess $NaHCO_3$, similar to that employed by Walkup *et al.*[237,249] Although the reaction product was uncertain (Sections 2.3.1.1, p. 149 and 2.3.1.2, p. 153) either possible course would adequately fulfil our stipulated criteria (Section 2.3) if the cyclic silyl enol ethers were employed as substrates (Scheme 66). The formation of α–siloxy ketones would generate the ideal situation in which one new asymmetric centre is generated, with our own chiral probe in place. On the other hand, the formation of stable siloxy epoxides from cyclic enol ether substrates, while generating two new chiral centres, would

SCHEME 66

R* = chiral auxiliary



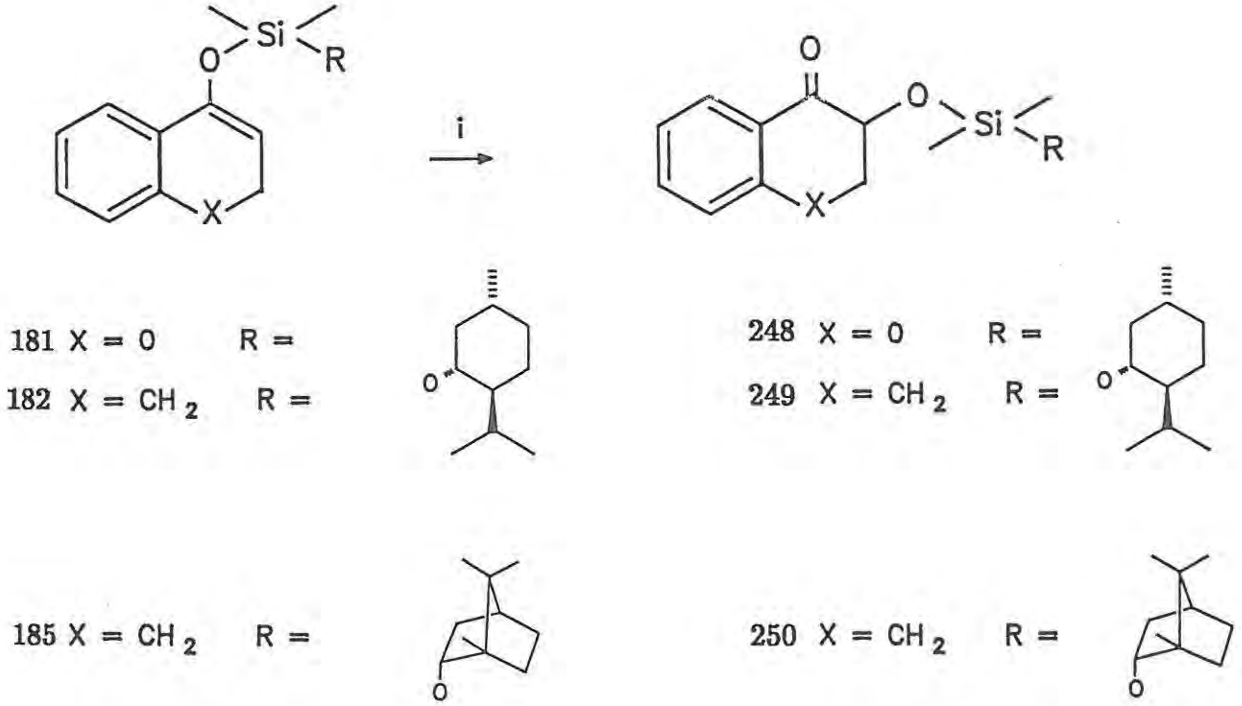
$R_1 = R_2 = H$ 172
$R^* =$ menthyloxy

247 $R_1 = R_2 = H$
$R^* =$ menthyloxy

Reagents

i) MCPBA and $NaHCO_3$

SCHEME 67



181 X = O R =
182 X = CH_2 R =

185 X = CH_2 R =

248 X = O R =
249 X = CH_2 R =

250 X = CH_2 R =

Reagents

i) MCPBA and $NaHCO_3$

still only lead to two diastereomers due to the geometric constraints of the oxirane ring.

Having found the oxidation of the α–tetralone trimethylsilyl enol ether **(240)** to be more succesful than the cyclohexanone analogue **(239)** the asymmetric oxidations of the chiral, α–tetralone and chromanone silyl enol ethers **(181)**, **(182)**, and **(185)** (Scheme 67) were explored first. Treatment of these menthyloxy– and bornyloxy silyl enol ethers with MCPBA at 0°C according to the experimental protocol decided upon, **yielded the α–siloxy ketones (248), (249), and (250)**, as diastereomeric mixtures in excellent material yields. Use of the non–hydrolytic work–up procedure[j] presumably facilitated isolation of these silylated α–ketols, in which the erstwhile chiral auxiliary could now serve as a chiral NMR or chromatographic probe for the direct determination of asymmetric induction. In light of this success, the method was extended to include the oxidation of the cyclohexanone silyl enol ether **(172)**; once again, the α–siloxy ketone **(247)** was isolated, albeit in considerably reduced material yields in this instance (Scheme 66). The IR spectra of these products were, in all cases, characterized by the presence of a strong carbonyl band at approximately 1700 cm^{-1} indicative of the α–siloxyketones rather than the intermediate epoxides, for which no evidence was detected. The sole isolation of α–silyloxyketones lends support to the assertion by Walkup[248] that it is the bulky substituents on the mandelate silyl enol ethers [**(217)** – **(219)**,p.146] that enables the stable silyl epoxides **(220)** and **(221)** to be isolated. When we attempted the MCPBA oxidation of the pinacolone derived silyl enol ether **(164)** in the presence of $NaHCO_3$ the α–siloxyketone **(251)** was isolated (Scheme 68, p. 162) without any trace of the intermediate epoxide.

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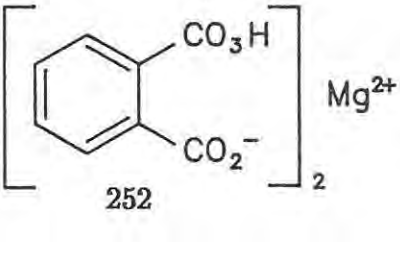
[j] The 5% aq. Na_2CO_3 used in the work–up appears to have no hydrolytic effect on the α–siloxyketones.

The steric bulk of the relevant substituents in the menthyl silyl enol ether (**164**) and in Walkup's mandelate silyl enol ethers [(**217**) – (**219**)] are similar; both having a bulky alkoxy group on the silicon and a *tert*–butyl group adjacent to the carbon where the oxacarbonium ion must develop during rearrangement to the *α*–siloxyketone (Scheme 60, p.150). If the steric bulk of the substituents is, in fact, a significant factor in determining the course of the reaction, then the absence of the methyl group in our silyl enol ether (**164**) (the only difference between compounds (**164**) and (**219**) in the immediate vicinity of the enolate) is sufficient to render the analogous silylepoxide too unstable for isolation.

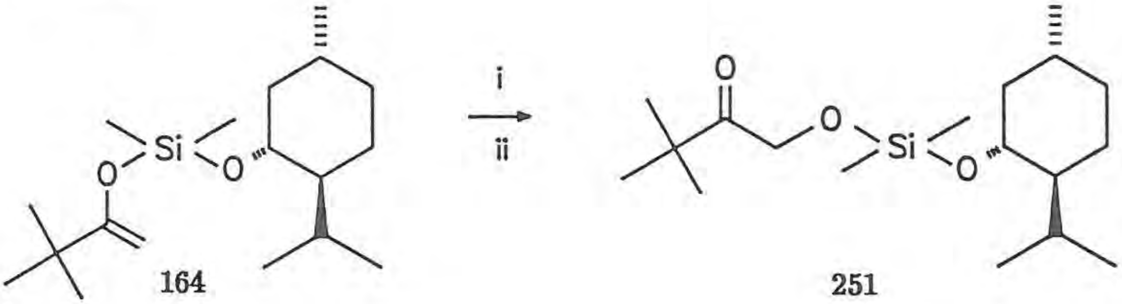
It had thus been established that the MCPBA oxidations of the chiral silyl enol ethers [(**164**), (**172**), (**181**), (**182**), and (**185**)] could be successfully achieved. Certain of the reactions were then repeated at various temperatures to study the effect, if any, on the asymmetric induction achieved. In the case of the tetralone silyl enol ether (**182**) two alternative oxidizing agents were also investigated, *viz.*, magnesium monoperphthalate (MMPP) (**252**) and 2–(phenylsulphonyl)–3–phenyloxaziridine (**256**) and the results of all these reactions are summarized in Table 13.

(MMPP) (**252**), a reagent frequently being proffered as a modern alternative to MCPBA, achieved, in poor yields, the oxidation of the silyl enol ether (**182**) to the *α*–siloxyketone (**249**).



252

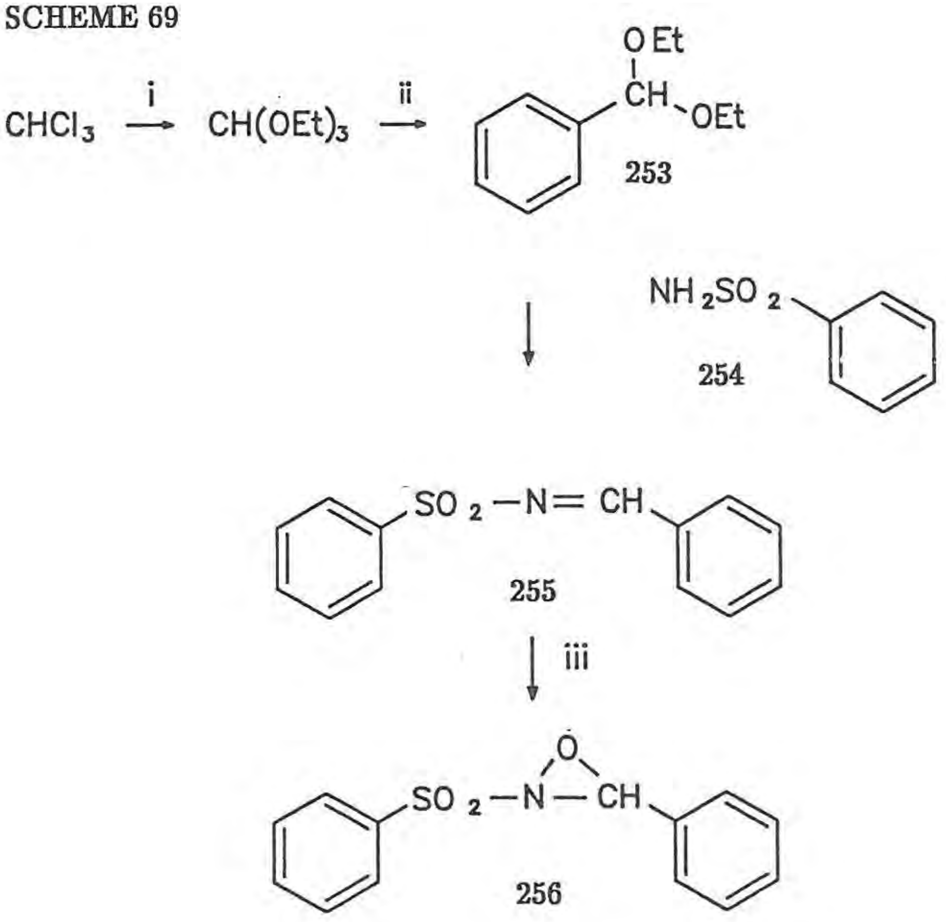
SCHEME 68



Reagents

i) MCPBA and $NaHCO_3$

SCHEME 69



Reagents

i) Na/EtOH, ii) PhCHO, iii) MCPBA

An attempted oxidation employing *tert*–butyl hydroperoxide [249] in the presence of CuCl failed to yield any of the desired product; TLC examination of the reaction mixture after 24 h at room temperature indicated the presence of considerable starting material as well as several other components, none of which corresponded to the desired product. The isolation of silylepoxides from the oxidation of trimethylsilyl enol ethers employing 2–sulphonyloxaziridine has already been described [245] (section 2.3.1.1, p.) An analogous, less substituted oxaziridine, 2–(phenylsulphonyl)–3–phenyloxaziridine (**256**) (required for the attempted preparation of a subsequent chiral auxiliary in this study) was applied to the oxidation of the chiral silyl enol ether (**182**), yielding the α–siloxy ketone (**249**) in excellent material yields. [The oxidizing reagent was prepared by standard methods *via* benzaldehyde diethyl acetal (**253**) and benzene sulphonamide (**254**) (Scheme 69).[250-253]] By using acid free $CDCl_3$ instead of acid free $CHCl_3$ the course of the sulphonyl oxaziridine oxidation could be monitored by ^1H NMR spectroscopy. The disappearance of characteristic silyl enol ether peaks, as well as the emergence of the α–siloxyketone peaks, were easily followed. No additional peaks, that could be ascribed to the silyl epoxide, were detected in the spectrum at any stage of the reaction. This result meant that in none of the variety of oxidations conducted on these chiral silyl enol ether systems was any trace of the intermediate silylepoxide detected.

TABLE 13 Summary of peracid oxidations of chiral silyl enol ethers, including reaction temperatures, material yields, the oxidizing agent employed and the diastereomeric excesses where applicable.

Sub–strate	Siloxy ketone	Temp (°C)	Yield (%)	Oxidizing Agent	% d.e.[k]
182	**249**	0	100	MCPBA	6 (60)
182	**249**	RT	71	MCPBA	10 (500)
182	**249**	–60	84	MCPBA	6 (60)
182	**249**	RT	25	MMPP	0 (60)
182	**249**	60	92	(**256**)[l]	2 (60)
182	**249**	RT	91	(**256**)	4 (60)
172	**247**	RT	35	MCPBA	14 (60)
185	**250**	0	96	MCPBA	2 (500)[m]
181	**248**	0	95	MCPBA	16 (60)
181	**248**	–50	100	MCPBA	10 (60)
164	**251**	25	50	MCPBA	——

[k] The diastereomeric excesses as measured by integration of the SiMe peaks in the ^{1}H NMR spectra. The number in parentheses after the percentage represents the field strength of the spectrometer used. In the case of the 60 MHz instrument the integration is always by means of digitisation. In the case of the 500 MHz spectrometer the integration was achieved by the conventional method. The experimental details of how the diastereomeric excesses were arrived at are included in the Experimental section pertaining to these reactions (Section 3.6, p.256). An evaluation of the digitizing technique will be provided below.

[l] The oxidizing agent was 2–(phenylsulphonyl)–3–phenyloxaziridine (**256**).

[m] In this isolated instance the diastereomeric excess was confirmed by integration of the 10′–Me singlet for each diastereomer.

2.3.1.3.1 Measuring the Diastereomeric Excesses of the α–Siloxy Ketones [(247) – (250)]

Attempts to utilize the previously described (Section 2.2.2, p.139) potential of the menthyloxy– or bornyloxysily groups as chromatographic chiral probes proved unsuccessful for the analysis of the diastereomeric ratios of the α–siloxyketones. The relative instability of these compounds resulted in decomposition under GLC conditions and HPLC failed to resolve the diastereomers.

However, the menthyloxy– and bornyloxysilyl groups imposed substantial diastereomeric differences on the ^{1}H NMR spectra of the pair of α–siloxyketones constituting each product mixture. Even at 60 MHz, significant splitting of the SiMe signals in the ^{1}H NMR spectra of the diastereomeric mixtures was observed in most cases (*e.g.* Figure 38). The magnitude of these separations were:– siloxy ketones (**247**), 5.3 Hz; siloxy ketones (**248**), 2.0 Hz; and siloxy ketones (**249**), 3.3 Hz. [The bornyl siloxy ketone (**250**), however showed no splitting of the SiMe singlets.] While the two SiMe groups in any particular α–siloxy ketone diastereomer are diasterotopic it's been assumed that splitting of the SiMe signals of a particular diastereomer is not observed at 60 MHz. This assumption is based on a comparison with the 60 MHz spectra of other diastereomerically pure, dimethyl silyl compounds prepared in this study. For example, none of the chiral silyl enol ethers exhibited any splitting whatsoever of the SiMe singlets at 60 MHz. Further examples of methyl groups of a particular diastereomer that show no splitting at 60 MHz are provided by the homochiral alkoxy silyl chlorides (**176**) and (**179**) and the diastereomeric silyl acetals [(**212**) – (**214**)].

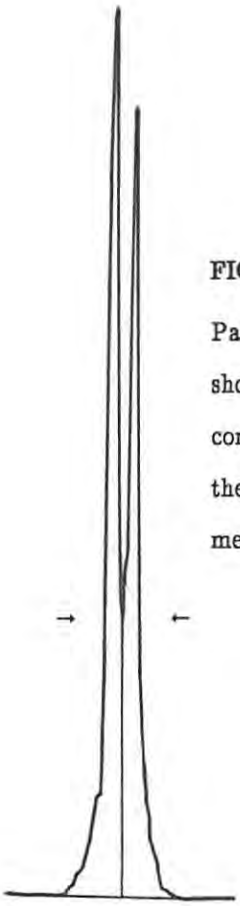


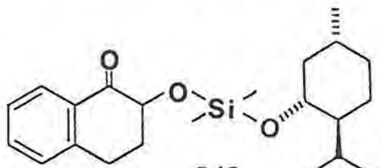
FIGURE 38

Partial 60 MHz ^{1}H NMR spectrum of the α-siloxyketones (**249**) showing the SiMe signals at δ *ca.* 0.1 ppm. Also shown is the constructed perpendicular that divides the unresolved portion of the signal. The arrows indicate the height at which the peaks merge.

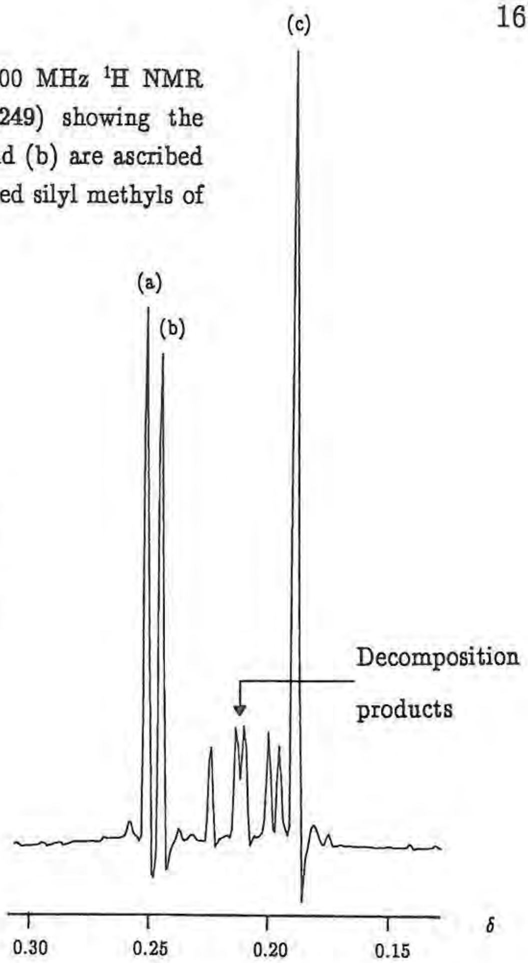
At 500 MHz the inherent non equivalence of the silyl methyl groups in each diastereomer appears to be reflected in further splittings of the SiMe signals [three singlets for (**248**) and (**249**) and four singlets for (**250**) (Figures 39 and 40)]. This interpretation is supported by the high field spectra of the enantiomerically pure chiral silyl enol ethers which, in most cases, do exhibit a separation of the SiMe signal into two singlets. The size of this separation for the silyl enol ethers is, however, never greater than 0.01 ppm. In the α-siloxyketones (**248**), (**249**), and (**250**), two different size separations are apparent. The smaller of these separations is in the range 1.0 – 3.0 Hz (0.002 –

FIGURE 39 Expansion of the SiMe signal in the 500 MHz ^{1}H NMR spectrum of the α siloxy tetralone (249) showing the resolution of three SiMe singlets; (a) and (b) are ascribed to one diastereomer and (c) the unresolved silyl methyls of the second diastereomer.

(a) 124.889 Hz, 0.250 δ
(b) 121.887 Hz, 0.244 δ
(c) 93.851 Hz, 0.188 δ



249



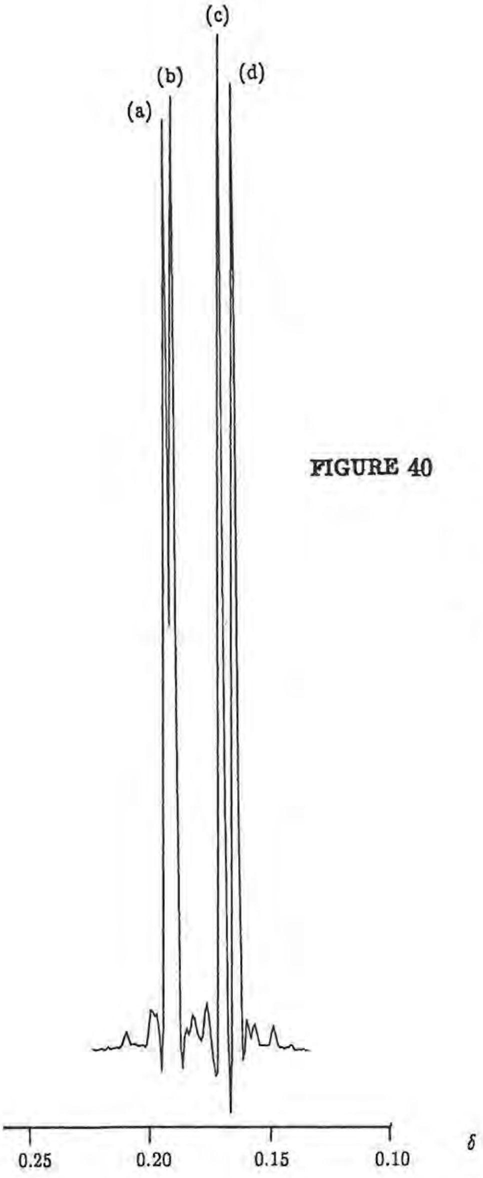
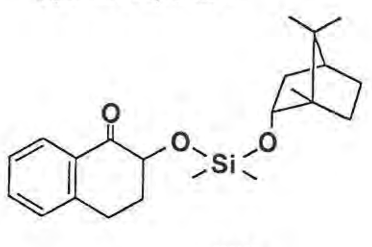


FIGURE 40 Expansion of the SiMe signal in the 500 MHz ^{1}H NMR spectrum of α siloxy tetralone (250) showing the separation of the four singlets; (a) and (b) are ascribed to one diastereomer and (c) and (d) to the second diastereomer.

(a) 95.386 Hz, 0.191 δ
(b) 94.396 Hz, 0.189 δ
(c) 84.475 Hz, 0.169 δ
(d) 81.701 Hz, 0.163 δ



250

0.006 ppm) and in each compound the second separation is an order of magnitude larger. By comparing these separations to those in the chiral silyl enol ether spectra the peaks of each diastereomer were assigned and this assignment formed the basis of the diastereomeric ratio determinations of the α–siloxy ketones using 500 MHz ^{1}H NMR spectra.

The determination of the diastereomeric excess in the α–siloxy ketones [**(247)** – **(250)**] by ^{1}H NMR techniques was impaired by two factors, *viz.*, the relative instability of the siloxy ketones and inadequate separation of the SiMe signals for reliable spectrometer integration at 60 MHz. These difficulties and methods to overcome them will be discussed below.

It was hoped that the diastereomeric excesses achieved in these oxidations could be determined by comparitive integration of the SiMe singlet of each diastereomer but spectrometer integration at 60 MHz appeared to be unreliable due to the close proximity of the two singlets (never separated by more than 5.3 Hz). The spectrometer had the capability of scanning the spectrum and integral both from low field to high field and in the reverse direction. The unreliability of comparative integration using a 60 MHz spectrometer, when the peaks of interest are $\leq$ 5 Hz apart was confirmed when significant discrepancies in the integral ratios of the diastereomeric silyl methyl peaks were obtained when scanning in the forward and reverse directions.

Thus, an alternative method for integrating the SiMe peaks of the 60 MHz spectrum was required to evaluate the diastereomeric excess of the products. This was achieved by electronically digitising the photoenlarged SiMe signals in ^{1}H NMR spectra. The overlapping portion of the two singlet signal was resolved by constructing a perpendicular from the point where the two peaks merge to the base line (Figure 38, p. 166). The details of how this digitisation was achieved and the computations necessary to calculate the relative areas of the peaks are included in the Experimental (Section 3.6, p. 256). The diastereomeric excesses obtained by the electronic digitisation technique are included in Table 13, p. 164.

The α-siloxy ketones [**(247)** – **(250)**], while isolable, nevertheless tended to decompose [within hours in the case of the cyclohexanone derivative **(247)**]. This decomposition was clearly evident in the far upfield region of the ^1H NMR spectra of these compounds, where several other singlets, ascribed to the silyl methyl singlets of the decomposition products, appeared. (The 60 MHz spectra were obtained immediately after purification of the siloxy ketones to eliminate any distortion of the diastereomeric excess this decomposition may have caused.). An obvious solution to the unreliable integration at 60 MHz (due to the close proximity of the peaks of interest) was to make use of a higher field spectrometer. However, dispatching of samples to the high field instruments at our disposal involved, at best, a delay of several days before the spectrum could be recorded. The decomposition which occurred in certain samples, during this period, rendered the desired measurement impossible. This dilemma was one of the reasons leading to the development of the electronic digitizing technique. However, in the instance of the bornyloxysilylketone **(250)** no splitting of the silyl methyl peaks occurred at 60 MHz and the high field ^1H NMR spectroscopy was the only method available to measure the diastereomeric ratios. Fortunately, this compound appeared to exhibit the least instability and the decomposition product signals detected at high field were insignificant. A high field ^1H NMR determination of the diastereomeric ratio was also possible for the siloxy ketone **(249)**, although the decomposition was more significant. [See Figures 39 and 40 (p. 167) for the silyl methyl region of these high field ^{1}H NMR spectra.] The diastereomeric excesses obtained in this manner are included in Table 13, p. 164.

None of the ^{1}H NMR signals of the menthyl and bornyl protons (the $6'$–H_{eq} signal in the menthyl system and the $3'$–H_{exo}, $3'$–H_{endo}, and $4'$–H signals of the bornyl system) which showed so much promise as indicators of diastereomeric ratios in the chiral silyl acetal derivatives of 1–phenylethanol (210) and (211) (section 2.2.1, p. 130 and Table 11, p. 135), were sufficiently resolved in the ^{1}H NMR spectra of the α–siloxy ketones to be of any assistance. The 10′–Me signals in the ^{1}H NMR spectrum of the bornyl α–siloxyketone (250) provided the only other signal which could be used to measure a diastereomeric ratio and this confirmed the value obtained from the SiMe integration. The 9′–Me doublets in the case of the menthyl α–siloxyketone (251) were sufficiently resolved, but, were complicated by superposition on what appeared to be a decomposition product signal. In all other cases the terpenoid methyl signals were either unresolved or too complex to evaluate the individual integrals.

2.3.1.3.2 Evaluation of the Various Oxidations of the Chiral Silyl Enol Ethers (172), (181), (182), and (185).

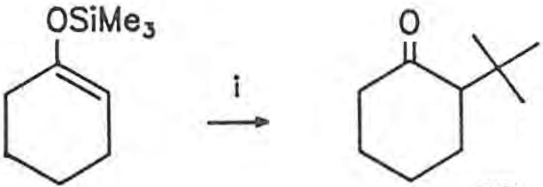
The stereoselectivities observed in the preparation of the α–siloxy ketones [(247) – (250)] (as listed in Table 13, p. 164), while comparable to those obtained by Walkup and Obeyesekere.[237] in similar peracid oxidations, are marginal at best (*ca.* 0 – 16 % d.e.). Decreasing the reaction temperature of the MCPBA oxidations did not improve the stereochemical control and the alternative oxidizing agents [MMPP (252) and the sulphonyl oxaziridine (256)] on the basis of the results obtained appeared worse than MCPBA as diastereselective oxidizing agents.

In some cases, the measured diastereomeric excess approaches the experimental limit of the digitization technique and thus, the absolute values in these cases must be viewed with some circumspection. However, the consistency of the relative peak shape and area, the downfield signal always being the largest – reflected even in the high field spectra, is to our minds a further indication that at least some asymmetric induction occurred. Due to the small diastereomeric excesses achieved, no attempt was made to propose transition states that would lead to the formation of a favoured stereoisomer or what the configuration of the favoured isomer would be. These initial results on asymmetric reactions of silyl enol ethers mirrored the early stereochemical control obtained by other workers, attempting analogous asymmetric reactions of allyl silanes (See p 92) and, we believe, provided sufficient encouragement to pursue the idea further.

2.3.2 Alkylations of the Chiral Silyl Enol Ethers (181), (182), and (185)[236].

The advent of the Friedel–Crafts type alkylation of silyl enol ethers [254] (the preparation of 2–*tert*–butylcyclohexanone (**257**) is illustrated in Scheme 70) has facilitated the successful introduction of a tertiary alkyl group α to a carbonyl group. Routine α–alkylation had previously been restricted, largely, to primary and secondary alkyl halides due to the susceptibility of tertiary alkyl halides to elimination under the basic conditions used for enolate formation. Reetz *et al.*[255] have subsequently expanded the original idea to include other allyl and benzyl halides that can ionize to carbonium ions in the presence of a Lewis acid [(**258**) – (**260**)].

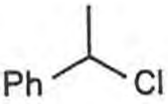
SCHEME 70



257

Reagents

i) Bu^t Cl and TiCl$_4$



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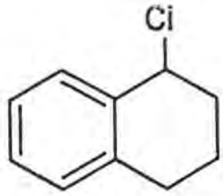

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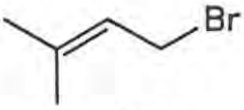
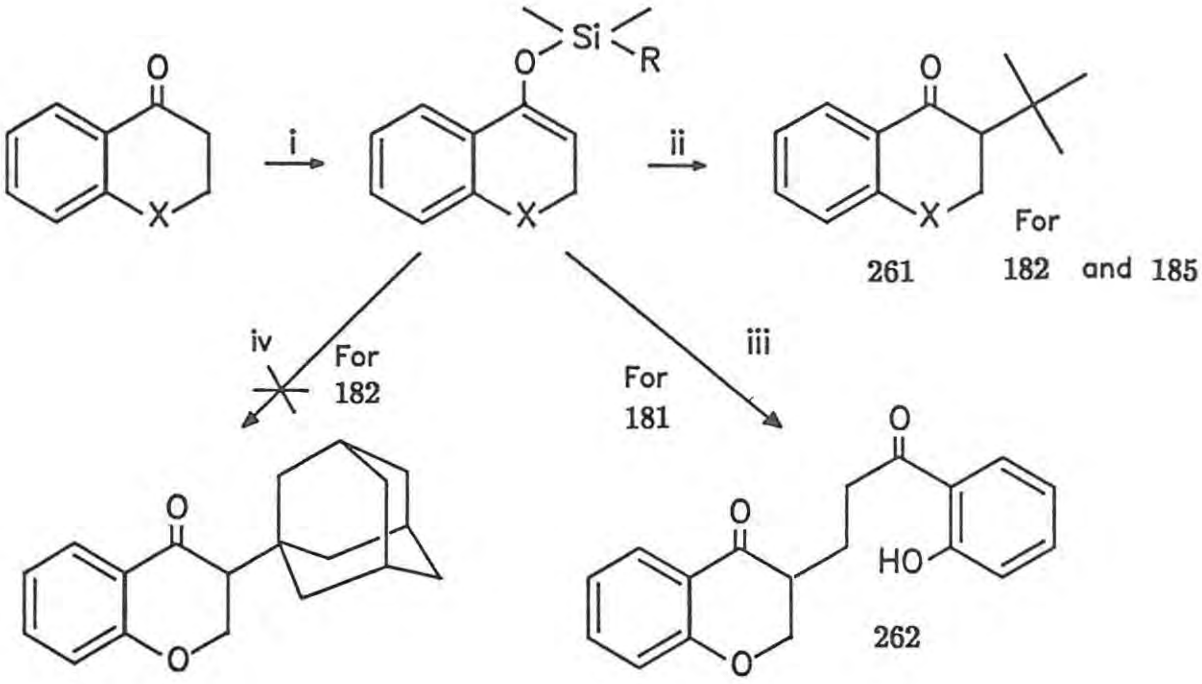
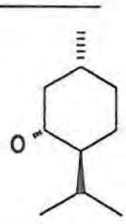
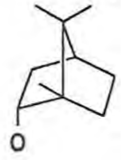


260

Alkylation was chosen as the second model reaction for evaluating the asymmetric potential of the chiral silyl enol ethers. The substrates chosen were the tetralone silyl enol ethers (**182**) and (**185**) and the chromanone silyl enol ether (**181**) (Scheme 71). The yields typically reported for achiral substrates

SCHEME 71



	X	R
182	CH_2	
181	O	
185	CH_2	

Reagents

i) LDA and the chlorosilane (**176**), ii) Bu^t Cl and $TiCl_4$

iii) Distilled Bu^t Cl and $TiCl_4$,

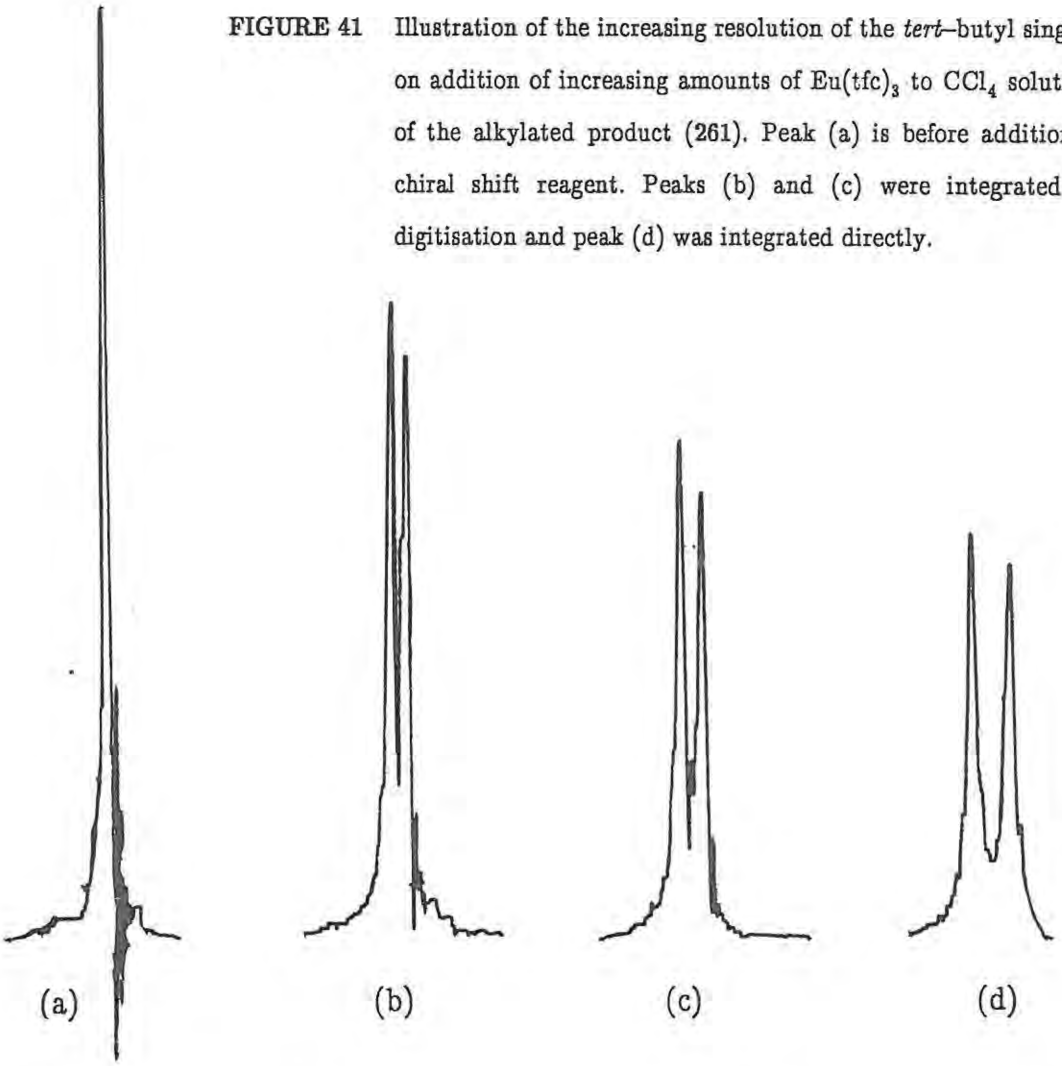
iv) Adamantyl bromide and $TiCl_4$

are only moderate but this disadvantage is outweighed by the generation of a single asymmetric centre and the apparent lack of competing side reactions. It was recognized at the outset, that this reaction (Scheme 71) would involve displacement of the chiral siloxy group and hence the removal of the *in situ* chiral probe. However, alkylation with tertiary butyl halides would provide a ^{1}H NMR signal amenable to the determination of enantiomeric excess *via* the application of chiral shift reagents. (See Introduction Section 1.5.4 , p. 87 for the background to chiral shift reagents.)

The $TiCl_4$ catalysed, tertiary butyl chloride alkylations (at *ca.* –23° C) of the menthyloxy and bornyloxy silyl enol ethers of α–tetralone **(182)** and **(185)** respectively (Scheme 71) were achieved in moderate material yields (Table 14); the product in each case being the tertiary butyl α–tetralone **(261)**. Attempting the same alkylation of the silyl enol ether **(182)** at –78° C yielded only trace quantities of the desired product **(261)**; the major components being α–tetralone and menthol.

The samples of the tertiary alkyl halide **(261)** exhibited marginal optical activity (specific rotations of – 0.5° and – 0.8° respectively). No optical activity data was available for the enantiomerically pure compound **(261)** and thus these rotations could not be correlated to an enantiomeric excess. The determination of the enantiomeric excess achieved thus hinged upon adequate resolution of the enantiomeric tertiary butyl singlets by a chiral shift reagent. The addition of increasing amounts of the praseodymium chiral shift reagent [Pr(tfc_3)] induced incremental upfield shifts of the signal but failed to effect any resolution of the singlets. Addition of the europium analogue Eu(tfc)$_3$, however, induced significant separation of the singlets with a concomitant downfield shift of the entire spectrum (Figure 41).

FIGURE 41 Illustration of the increasing resolution of the *tert*–butyl singlets on addition of increasing amounts of Eu(tfc)$_3$ to CCl$_4$ solutions of the alkylated product (**261**). Peak (a) is before addition of chiral shift reagent. Peaks (b) and (c) were integrated by digitisation and peak (d) was integrated directly.



The enantiomeric excess of alkylated product from the menthyloxy silyl enol ether (**182**) reaction was investigated at 60 MHz. Addition of the optimum amount of shift reagent provided approximately 7Hz separations of the singlets. These separations were deemed large enough to facilitate reliable spectrometer integration, and consistent ratios from repeated integrations in both the forward and reverse scan directions were obtained (Section 2.3.1.3, p. 158). Increasing the amount of the shift reagent resulted in superposition of the tertiary butyl peaks on other peaks present in the spectrum, while addition of smaller amounts of shift reagent yielded separations too small for spectrometer integration at 60 MHz. On pairs of signals separated by approximately 3 Hz, integration was achieved by digitisation, as discussed earlier. [This experiment provided an opportunity to compare the two methods of integration. The correlation was disappointing (see Table 14). Several factors probably contributed to this discrepancy, including the general difficulty of accurately determining small enantiomeric excess and possible difficulties with spectrometer integration although the separation of the signals is somewhat larger than that assumed to be insufficient.] In the instance of the product (**261**) obtained from the bornyloxy silyl enol ether (**185**), the enantiomeric excess was evaluated from a 300 MHz spectrum. Two separate experiments were conducted and the differing amounts of added shift reagent induced shifts of 5 and 12 Hz. In both instances the integral ratio of these separated peaks was measured using direct spectrometer integration as well as digitisation. The alkylation reactions conducted on the silyl enol ethers (**182**) and (**185**) and the enantiomeric excesses, established by both integration techniques, are summarized in Table 14.

TABLE 14 Summary of tertiary butyl alkylations of the tetralone silyl enol ethers **(182)** and **(185)** including reaction temperatures, material yields, and the enantiomeric excesses.

Substrate	Temp (°C)	Yield	% e.e.[n]
182	–23	42	12[o] (60d) 6 (60i)
182	–78	0	———
185	–23	48	4 (300d) 4 (300i)

Reaction of the chromanone silyl enol ether **(181)** under similar conditions to the previous alkylations, failed to yield any of the expected alkylated product **(261)** affording instead the novel 1,5 diketone **(262)** (Scheme 71, p. 173). Formation of the 1,5–diketone can be rationalized in terms of nucleophilic attack [pathway (a)(Scheme 72)] by the silyl enol ether **(181)** on the α,β–unsaturated carbonyl system **(263)** generated, in turn, by an alternative, intra–molecular π–electron mobilisation pathway (b). All the spectral data obtained for this compound **(262)** is consistent with the proposed structure except for the apparent absence of the IR hydroxyl absorbtion band, although the hydroxyl proton is clearly evident and exchangeable with D_2O in the ^1H NMR spectrum. This absence is attributed to severe broadening and shifting of the OH band due to strong hydrogen bonding (Figure 42) between the *ortho*

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[n] The number in parentheses after the percentage represents the field of the spectrometer used. Furthermore, an "i" denotes conventional integration and "d" implies application of the digitisation technique. All the quoted enantiomeric ratios are the average values of two determinations.

[o] Digitisation results from a duplicate reaction provided an identical enantiomeric excess.

SCHEME 72

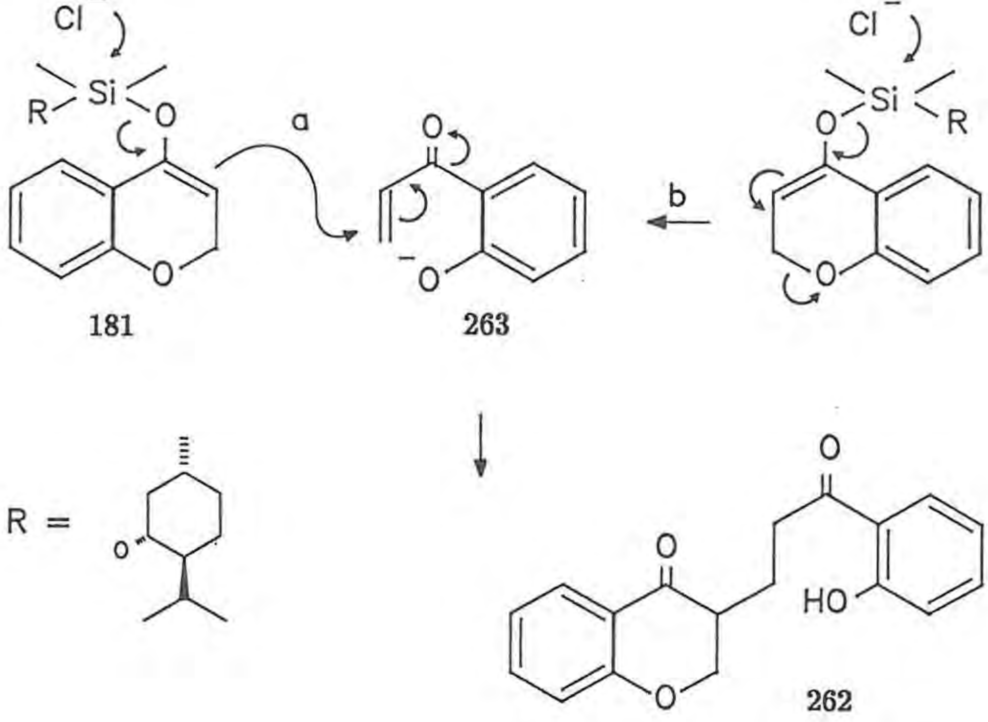
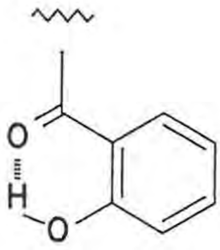


FIGURE 42 Illustration of the hydrogen bonding believed to be responsible for the absence of a hydroxyl absorbtion band in the IR spectrum of the 1,5–diketone (262).



carbonyl and hydroxyl substituents, forming a stable six membered ring.[256] In a repetition of this reaction using $TiCl_4$ freshly distilled from CaH_2 the 1,5–diketone (**262**) was again isolated, in comparable yields.

Attempts to effect adamantyl alkylations of the silyl enol ether (**182**) proved unsuccessful, only menthol and α–tetralone being isolated from the reaction mixture.

The foregoing alkylations, along with the concurrent work of Jung and Hogan.[242] represented the first reactions of chiral silyl enol ethers with electrophiles. As reflected by Table 14, the enantiomeric excesses obtained in these alkylations were disappointing. The first two model reactions (peroxidation and alkylation) indicated the potential of simple chiral alkoxy ligands to exert asymmetric control in electrophilic reactions of silyl enol ethers to be low. However, it was decided to proceed with an asymmetric variation of the "Mukaiyama" reaction because of possible advantages not present in the previous two reaction types (see following section). Furthermore, once these aldol–type reactions had been completed a more comprehensive evaluation of these chiral auxiliaries in asymmetric silyl enol ether reactions would be possible.

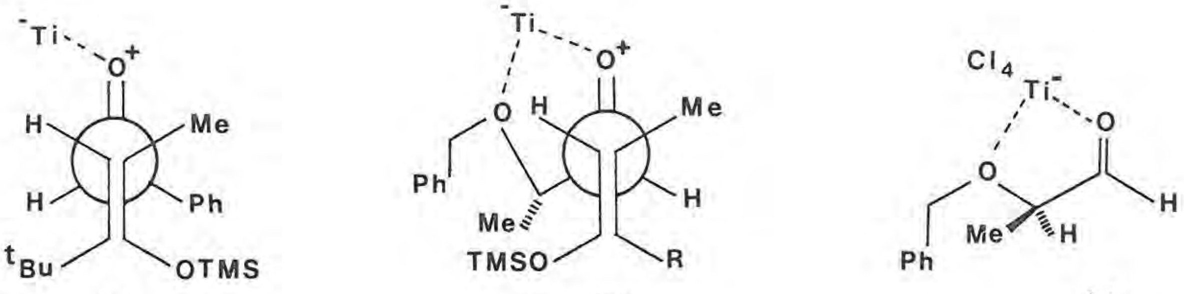
2.3.3 Reactions of the Chiral Silyl Enol Ethers (164), (180), and (194) with Benzaldehyde[236].

The facile nucleophilic attack by silyl enol ethers or silyl enol acetals on carbonyl compounds, activated by Lewis acids, to yield β–hydroxy carbonyl compounds, was pioneered by Mukaiyama *et al.*[54] and has subsequently become a widely applied reaction. Mukaiyama *et al.* proposed that the reaction proceeded *via* a transition state in which the Lewis acid co–ordinates to both the silyl enol ether and the carbonyl compound (Section 2.4, p. 191). Asymmetric applications of this adaptation of aldol condensations have been extensively investigated. Heathcock *et al.*[257] have studied simple diastereoselection in the reaction of prochiral silyl enol ethers and prochiral aldehydes, and diastereofacial selectivity in the reactions of prochiral silyl enol ethers and chiral aldehydes. Instances of good, simple diastereoselection have been explained in terms of minimizing dipole–dipole and steric interactions in **"open" transition state topologies** (Figure 43a). It is important to note this rationalization of the observed control in the cited examples specifically excludes the chelated transition states outlined in Mukaiyama's initial proposal. The argument used by Heathcock *et al.* to support this theory is twofold:–

i) the corresponding lithium enolates, in which six-centred lithium chelated transition states are known to occur, yield solely *syn*–products, whereas, enol silanes yield, predominantly, the *anti*–aldol; and

ii) when using Lewis acids which are unlikely to facilitate chelation [*e.g.* (BF_3)], the diastereoselectivity is undiminished.

FIGURE 43 "Open" transition state topologies for (a) simple diastereoselectivity and (b) diastereofacial selectivity in the reactions of prochiral silyl enol ethers and aldehydes. (c) Represents the intramolecular chelation of the aldehyde by the Lewis acid.



(a) (b) (c)

Heathcock *et al.*[257] also examined the diastereofacial reactions using racemic benzyloxyacetaldehyde as the chiral (but optically inactive) aldehyde. The excellent diastereoselectivity obtained is once again explained *via* "open" transition states (Figure 43b). In this case intramolecular chelation of the aldehyde by the Lewis acid (Figure 43c), directs the approach of the nucleophile to the less sterically encumbered face of the aldehyde.

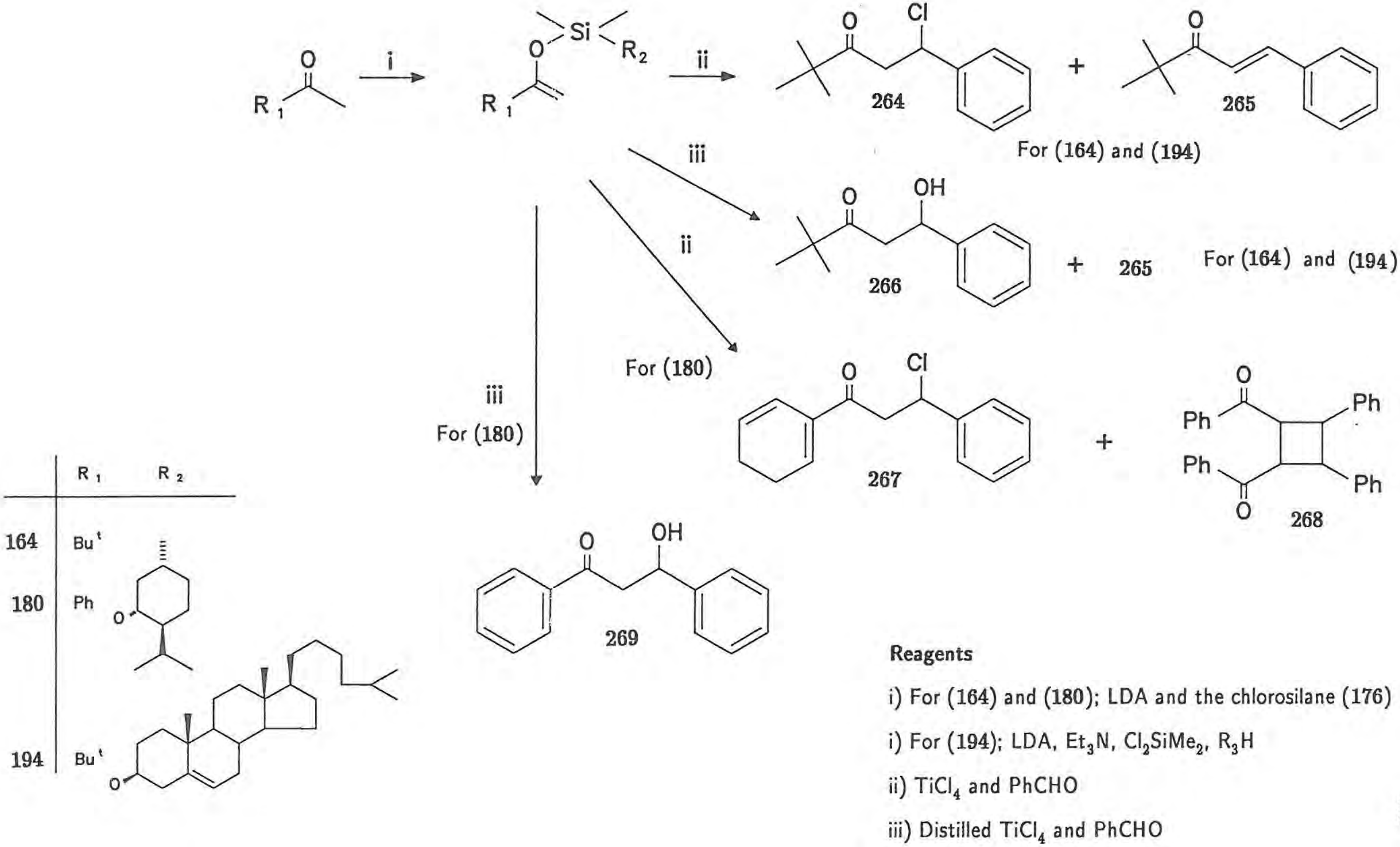
The chiral auxiliary approach to enantioselective adaptations of Mukaiyama type reactions is a topic of current interest, as reflected by the work of Oppolzer and Marco–Contelles [138] (See Introduction, Section 1.4.3.3, p.61) who have used camphor sulphonamide derivatives as auxiliaries, and the work of Gennari *et al.*[258] employing ephedrine adjuvants.

To the best of our knowledge, the single report by Jung and Hogan [242] represents the only attempt to extend this reaction to silyl enol ethers with optically active ligands on the silicon. To what extent Lewis acid catalysed reactions of such silyl enol ethers with aldehydes would proceed, *via* open transition states (as proposed by Heathcock *et al.* ^{257}) or by some form of chelated transition state as proposed by Mukaiyama has yet to be evaluated.

The cyclic silyl enol ethers used extensively in our peroxidation and alkylation studies would on hydroxy alkylation yield two new chiral centres and, hence, would require the diastereomers to be distinguished before any enantiomeric excess could be measured. The use of the pinacolone and acetophenone silyl enol ethers **(164)**, **(180)**, and **(194)** obviates that dilemma and has the added variation that the single new chiral centre is generated β–to the carbonyl group, instead of α as in the previous reaction types. The choice of both silyl enol ether and aldehyde were influenced by the need to obtain products for which the enantiomeric excesses could be readily determined. A summary of all the reactions conducted on these silyl enol ethers, including, where applicable, the enantiomeric excess achieved is provided in Table 15, p.189.

The $TiCl_4$ catalysed reactions of the pinacolone silyl enol ethers **(164)** and **(194)** with benzaldehyde were expected to afford the β–hydroxyketone [**(266)**, Scheme 73]. In the event, reactions using commercial $TiCl_4$, yielded two products (entries 1 and 6, Table 15), one of which was identified as the α,β–unsaturated ketone **(265)**. The infrared spectrum of the second compound failed to exhibit a hydroxyl band and its spectral data, in particular the mass spectrum, confirmed the formation of the β–chloroketone **(264)**. In Entry 1, Table 15, the $TiCl_4$ had been added to a solution of the silyl enol ether and benzaldehyde. Adding a solution of the silyl enol ether to a mixture of the Lewis acid and benzaldehyde yielded the same products although the overall conversion was significantly improved (entry 2, Table 15). Similar treatment of

SCHEME 73



Reagents

i) For (164) and (180); LDA and the chlorosilane (176)

i) For (194); LDA, Et_3N, Cl_2SiMe_2, R_3H

ii) $TiCl_4$ and PhCHO

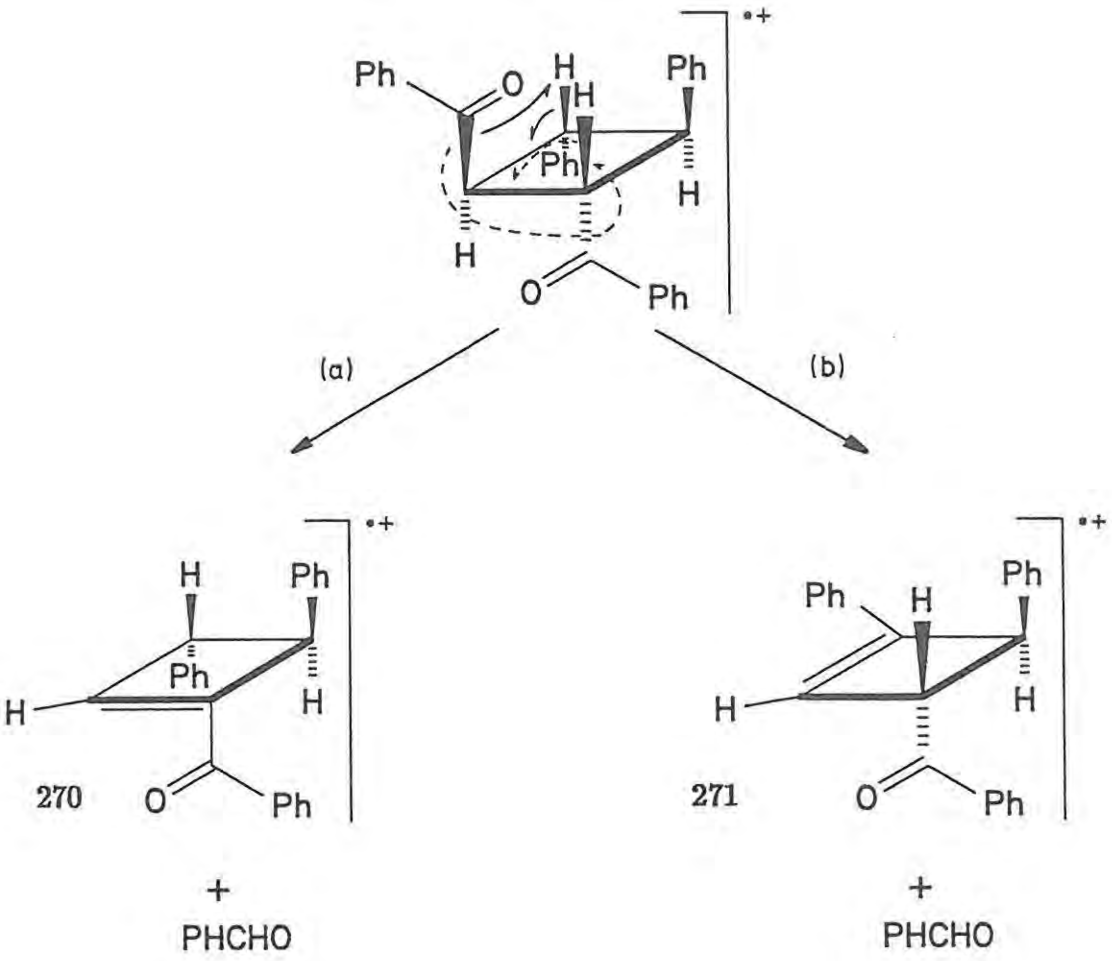
iii) Distilled $TiCl_4$ and PhCHO

the acetophenone silyl enol ether (**180**) afforded a small amount of the analogous β–chloroketone (**267**) and trace quantities of the known,[259] yet unusual chalcone dimeride, 1,2–dibenzoyl–3,4–diphenylcyclobutane (**268**) (entry 8, Table 15). Comparisons of the melting point of compound (**268**) with literature melting points of both chalcone itself and analogous dimerides indicated the stereochemistry of the molecule to be *trans*, *trans*, *trans* with respect to the substituents on the cyclobutane ring. Although insufficient material was isolated to obtain a 60 MHz ^1H NMR spectrum and the high field spectra, obtained some time later, indicated complete isomerisation to the more conventional chalcone, mass spectrometry provided convincing evidence for the isolation of the proposed dimeride (**268**).

[The molecule (**268**) is almost certainly strained due to the four sterically demanding substituents and puckering of the cyclobutane ring is unlikely to alleviate this strain.] No molecular ion peak was detected but the base peak corresponded to the loss of 106 mass units. An accurate mass analysis of this peak confirmed the fragment formula $C_{23}H_{18}O$ corresponding to the loss of benzaldehyde. Two possible fragmentations leading to the loss of this neutral molecule and the formation of the cyclobutene radical cations (**270**) and (**271**) are outlined in Scheme 74. The driving force for either fragmentation is, in all probability, the significantly reduced strain in the resulting planar cyclobutene ring in which one of the substituents and the ring are co–planar and the remaining two substituents, are *trans* to one another. An added benefit would appear to be the increased conjugation in the proposed radical cations.

To establish the reason for chlorination during the hydroxyalkylation of the silyl enol ethers (**164**), (**180**), and (**194**) the experimental parameters initially employed were systematically varied. The reactions described above had been

SCHEME 74



Solid arrows indicate fragmentation pathway (b)

Hatched arrows indicate fragmentation pathway (a) quenched with pyridine after warming to room temperature, instead of the more conventional aqueous $NaHCO_3$ work–up. This was done in an attempt to circumvent the formation of severe emulsions sporadically obtained using aqueous work–up methods. Repeating the reaction of compound (**164**) and quenching with aqueous $NaHCO_3$ [a procedure followed for all subsequent reactions (entry 3, Table 15)] had no significant effect on the yield or product distribution. However, when the reaction was repeated a second time, using $TiCl_4$ that had been freshly distilled from CaH_2 in an inert atmosphere, the **β–hydroxy** ketone (**266**) and the α,β–unsaturated product (**265**) were obtained in approximately equimolar amounts and the formation of the β–chloroketone (**264**) was completely eliminated (entry 4, Table 15). A final variation of the experimental protocol in which the reaction was quenched at – 78° C rather than allowing it to warm to room temperature before quenching, entirely suppressed the concomitant formation of the dehydrated product (**265**) (entry 5, Table 15). Under the same conditions, repetition of the reaction of the cholesteryloxy silyl enol ether (**194**) with benzaldehyde yielded a comparable result (entry 7, Table 15) and the hydroxyalkylation of the acetophenone silyl enol ether (**180**) afforded the analogous diphenyl β–hydroxyketone (**269**) (entry 9, Table 15).

In light of the above results, the formation of the β–chloroketones is attributed to the action of hydrogen chloride (shown to be present in undistilled $TiCl_4$) on the β–hydroxy ketones and/or their dehydration products. Using gas phase IR specrophotometry and working under strictly anhydrous conditions, it was confirmed that significantly more HCl is present in commercial $TiCl_4$ than in freshly distilled material. (The extreme reactivity of $TiCl_4$ with atmospheric moisture accounts for the ready formation of HCl.)

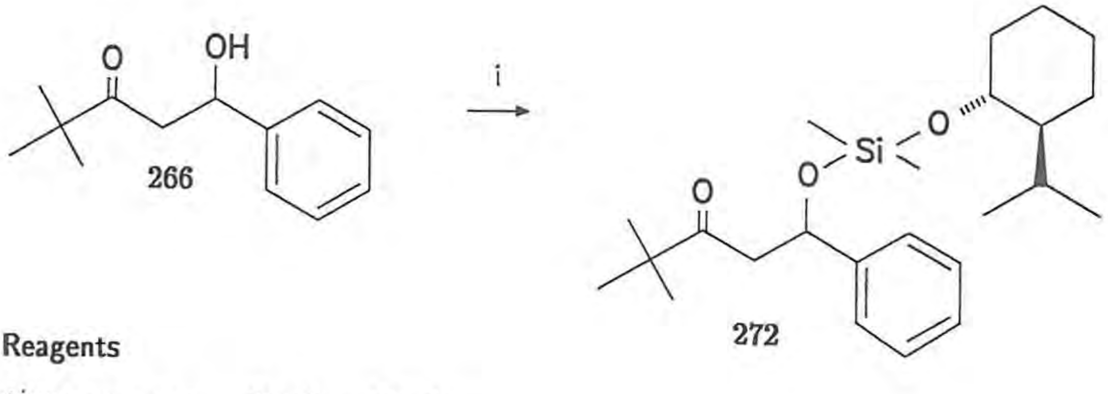
The enantiomeric excesses achieved in the formation of compounds with new chiral centres [(**264**), (**266**), and (**269**) were evaluated by one or more of several possible methods, dictated by characteristics of the particular compound. In the instance of the β–hydroxyketone (**266**) the intense tertiary butyl singlet made the use of ^{1}H NMR chiral shift reagents the method of choice. While $Eu(tfc)_3$ failed to separate the tertiary butyl singlets of each enantiomer, the analogous praseodymium reagent, $Pr(tfc)_3$, achieved the desired resolution at 60 MHz (Figure 44). The integral ratios of the enantiomeric signals were then determined by digitisation, which indicated an enantiomeric excess of **14%** (entry 5, Table 15). Identical treatment of the data from the reaction of the cholesteryloxy silyl enol ether (**194**) with benzaldehyde also yielded an enantiomeric excess of **14%** (entry 7, Table 15).

In a second approach the sample of β–hydroxyketone (**266**) obtained from the hydroxyalkylation of the silyl enol ether (**164**) was successfully derivatized with the chloro(menthyloxy)silane (**176**) to yield the β–siloxyketone (**272**) (Scheme 75). Unsuccessful attempts were made to utilize the chiral siloxy group as an *in situ* chiral probe in similar fashion to the methods previously described (Sections 2.2.1, p. 130 and 2.2.2, p. 139). At 60 MHz the silyl methyl signals were insufficiently resolved for spectrometer integration or digitisation. The inherent delays in dispatching samples to the high field instruments at our disposal resulted in almost complete degradation of the material to a mixture of the α,β–unsaturated ketone (**265**) and an unidentified menthyloxy species. Furthermore, no GLC conditions could be found to resolve the diastereomeric mixture.

Due to the absence of a suitable singlet, the ^{1}H NMR spectrum of the diphenyl β–hydroxyketone (**269**) was not amenable to chiral shift reagent studies.

FIGURE 44 Optimum resolution of the enantiomeric *tert*-butyl singlets obtained on the addition of $Pr(tfc)_3$ to a CCl_4 solution of the β-hydroxy ketone (266)

SCHEME 75

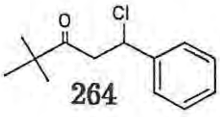


Reagents

i) The chlorosilane (176) and Et_3N

TABLE 15 Summary of the $TiCl_4$ catalysed reactions of the chiral silyl enol ethers (164), (180), and (194), with benzaldehyde. The reaction conditions, material yields and enantiomeric excesses are included.

Entry	Substrate	Reaction Conditions	Product	Yield (%)	e.e. (%)[p]
1	164	Method A1[q]	264	43	4
			265	8	—
2	164	Method A2[r]	264	68	6
			265	26	—
3	164	Method B[s]	264	52	—
			265	17	—
4	164	Method C[t]	265	50	—
			265	50	—
5	164	Method D[u]	266	97	14
6	194	Method A2	264	47	6
			265	42	—
7	194	Method D	266	79	14
8	180	Method A2	267	8	—
			268	2	—
9	180	Method D	269	66	10


264

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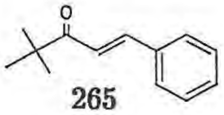
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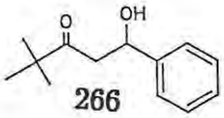
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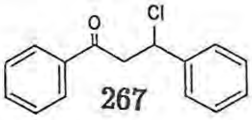
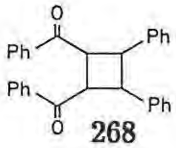
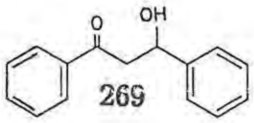

267


268


269

[p] The enantiomeric excesses were determined by 60 MHz ^1H NMR spectroscopy using either spectrometer integration or digitisation of the enantiomeric tertiary butyl singlets, resolved by the addition of chiral shift reagents. In isolated cases comparison of optical rotation data with that of pure enantiomers was made use of. The experimental details of these determinations are included in the experimental section pertaining to the preparation of these compounds (Section 3.9).

[q] Method A1:	Lewis acid added to a mixture of benzaldehyde and the silyl enol ether. Reaction quenched with pyridine at room temperature.
[r] Method A2:	The silyl enol ether added to a mixture of benzaldehyde and the Lewis acid. Reaction quenched with pyridine at room temperature.
[s] Method B	As for Method A2 except quenched with 5% aq. $NaHCO_3$ at room temperature.
[t] Method C:	As for Method B but employing $TiCl_4$ freshly distilled from CaH_2.
[u] Method D:	As for Method C but quenching at –78° C.

However, both enantiomers of this compound had been previously isolated in greater than 98% optical purity [260] and, thus, the enantiomeric excess of **10%** was determined by comparing the specific rotation of the isolated product with that of the corresponding pure enantiomer (entry 9, Table 15).

The enantiomeric excesses of the *β*–chloroketone (**264**), obtained from the reactions of both the menthyloxy– and cholesteryloxy silyl enol ethers (**164**) and (**194**) were also determined with the aid of the chiral shift reagent, $Eu(tfc)_3$ (entries 2 and 6, Table 15). The 6% e.e. determined for both these samples provides some insight into the manner in which the chlorination occurred. The presence of some enantiomeric excess eliminates the possibility that the *β*–chloro ketone (**264**) formed solely from the hydrohalogenation of the *α,β*–unsaturated ketone (**265**) or from an SN1 displacement (involving symmetrically solvated ions) of the hydroxy group of compound (**266**). However, an SN1 (involving unsymmetrically solvated ions) or an SN2 mechanism could contribute to the observed optical activity.

In spite of the possibilities for transition state co–ordination, the stereoselectivities observed in these hydroxyalkylations were similar to those obtained for the peracid oxidations and alkylations. From the reactions conducted on these chiral silyl enol systems it became apparent that they were poor substrates for asymmetric reactions. The probable reasons for this failure and our efforts towards enhancing the asymmetric induction of electrophilic reactions of silyl enol ethers are described in the following sections.

2.4 EVALUATION OF THE INITIAL OXIDATIONS, ALKYLATIONS, AND HYDROXYALKYLATIONS OF THE SILYL ENOL ETHERS [(164), (172), (180), (181), (182), (185), AND (194)]

In the Introduction, the need to impose rigidity on transition states of asymmetric reactions was emphasized, and a variety of examples showing chiral auxiliaries capable of imposing such rigidity, by means of co–ordination, were provided.

When considering the transition states for the oxidation, alkylation, and hydroxyalkylation reactions of the chiral silyl enol ethers under investigation, two fundamental questions arise, *viz.*,

i) are rigid, co–ordinated transition states feasible and

ii) is the timing of bond breaking and forming in the transition state such that the chiral siloxy group is still exerting an asymmetric influence when the new chiral centre forms?

Previously proposed mechanisms for the three model reactions would suggest that, in all three instances, asymmetric bond formation is likely to occur with the siloxy chiral auxiliary in place. In the case of peracid oxidation, the postulated mechanism (*via* the intermediate epoxide and subsequent ring cleavage, followed by 1,4 oxygen to oxygen silyl shift,[239,241] would ensure that the chiral auxiliary remains bonded in the transition state (Figure 45). Friedel–Crafts type transition state complexes have been proposed for both the alkylation and hydroxyalkylation reactions [54](Figures 46 and 47); Heathcock *et al.*[257] have, however, cast doubt on the involvement of such transition states in some applications of the Mukaiyama reaction. Whether the processes outlined in Figures 46 and 47 are concerted or not, the fact that some asymmetric induction did occur in the all the reactions examined, implies that the chiral auxiliary was associated with the transition state, in some way.

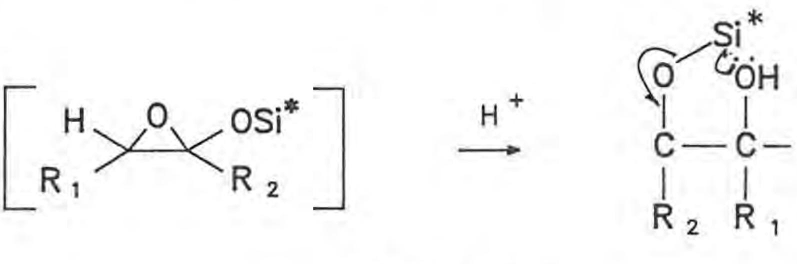


FIGURE 45

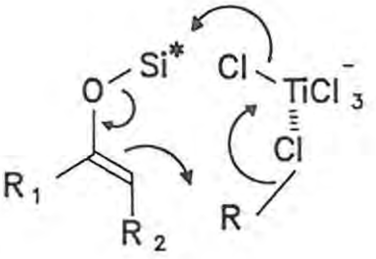


FIGURE 46

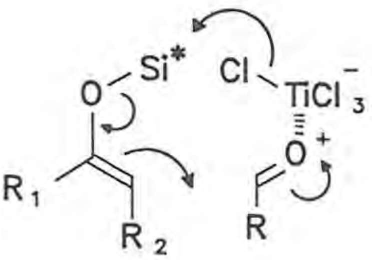


FIGURE 47

Transition state complexes involved in the peracid oxidation, alkylation, and hydroxyalkylation of chiral silyl enol ethers.

However, although the Lewis acid may be expected to facilitate co–ordination of nucleophiie and electrophile in the alkylation and hydroxyalkylation transition states, the menthyloxy, bornyloxy, and cholesteryloxy chiral auxiliaries are in no way constrained, by chelation, to adopt a particular transition state conformation, as in many successful asymmetric reactions.

Thus, the disappointing enantiomeric excesses (never greater than 16%), obtained in all of the reactions carried out on the bornyloxy, cholesteryloxy, or menthyloxy silyl enol ethers, appeared to be due to shortcomings of the chiral auxiliaries themselves rather than to a flaw in the concept of chiral auxiliary mediated asymmetric reactions of silyl enol ethers.

There appeared to be two major disadvantages of the silyl enol ether systems initially employed:–

i) The chiral auxiliary moiety was too far removed from the enolate site at which the reaction had to take place.

ii) The simple terpenoid auxiliaries lacked substituents with the potential to co–ordinate the incoming electrophile and/or the Lewis acid catalyst and hence, failed to impose effective conformational constraints on the transition state, which were required to ensure a preferential approach of the electrophile to a particular face of the enolate species.

Concurrent investigations of asymmetric reactions of **allylsilanes**, employing similar chiral silyl auxiliaries had revealed similar difficulties. Some of the reported approaches to improve asymmetric induction in reactions of allylsilanes did not appear to be suitable for application to our silyl enol ether reactions. Removing the oxygen between the silicon atom and the chiral auxiliary was the obvious means of bringing the enolate and the auxiliary into closer proximity. The hydrosilation of β–pinene, developed by Chan and Wang[191] (p. 92) yields optically active silyl chlorides in which this oxygen has been replaced by a carbon atom. This approach, however, offers no advantage in reducing separation between the chiral auxiliary and the silicon atom and alternative methods were explored [Section 2.5 (p. 195)] .

The chiral auxiliaries developed by both Taddei *et al.*[199,261] (p. 94) and Jung and Hogan [242] (See Scheme 58, p.146) appeared to be improvements on the simple terpenoid alcohols. However, to our minds, the expense of the chiral auxiliary employed by Jung and Hogan was prohibitive and compounds developed by Taddei *et al.* required elaborate syntheses.

The remainder of the present investigation was concerned with developing alternative approaches to chiral auxiliaries suitable for use with silyl enol ethers.

2.5 ATTEMPTS TO PREPARE MENTHYL– AND BORNYLSILANE CHIRAL AUXILIARIES.

The successful preparation of menthyl– and bornylsilane chiral auxiliaries (as opposed to the previously employed menthyloxy– and bornyloxysilanes) would allow the preparation of chiral silyl enol ethers in which the chiral auxiliary was that much closer to the enolate site, having dispensed with the oxygen between the silicon and the auxiliary. The most direct route to these systems appeared to be the reaction of organometallic reagents, derived from menthyl or bornyl chloride, with dialkyldichlorsilanes (*e.g.* Scheme 76), once again making use of the potential of dichlorosilanes for selective nucleophilic substitutions. The application of this approach to the preparation of optically active chlorosilanes appeared to be viable for two reasons;

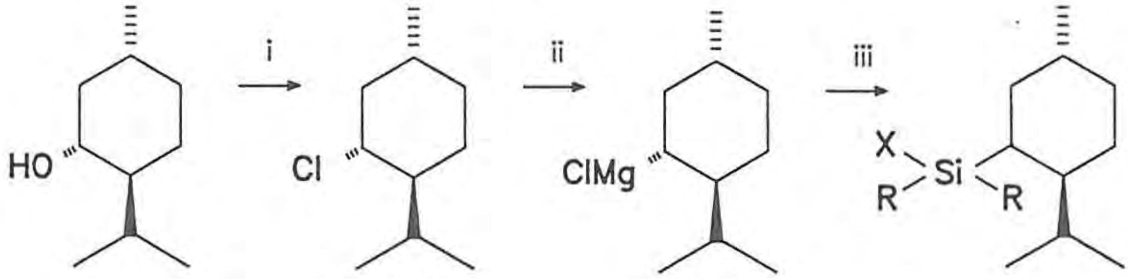
i) menthyl chloride (**273**) can be prepared from menthol with complete retention of configuration, using $ZnCl_2$ and aqueous HCl [262] and

ii) menthyl magnesium chloride has been shown to behave as a configurationally stable Grignard reagent.[263]

(Both of these important properties are utilized routinely in the preparation of optically active phosphines.[263,264])

In our hands, the chlorination of menthol and the subsequent preparation of THF solutions of the menthyl Grignard reagent proceeded smoothly. However, the reactivity of these Grignard reagents towards chlorosilanes seemed very low. In a test reaction the reaction of the Grignard reagent (**274**) with trimethychlorosilane afforded the expected menthyltrimethylsilane (**275**) in poor yields, after excessively long reaction times. (The progress of the reaction was monitored by titrating aliquots of the reaction mixture against 2–butanol

SCHEME 76



273 **274**

R = X = Me **275**

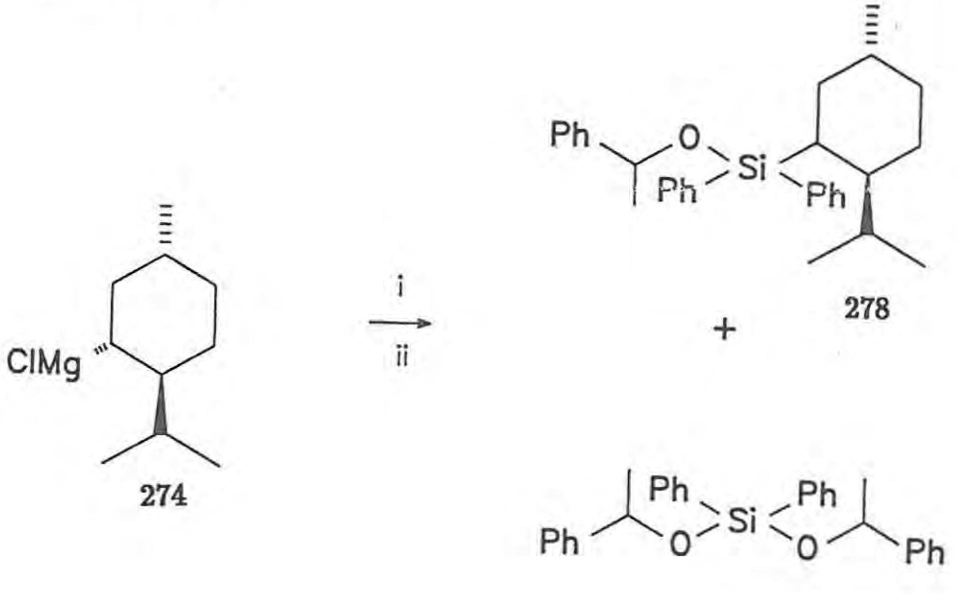
R = Me, X = Cl **276**

R = Ph, X = Cl **277**

Reagents

i) $ZnCl_2$ and aq. HCl, ii) Mg turnings, iii) R_2SiXCl

SCHEME 77



274 **278** **279**

Reagents

i) Cl_2SiPh_2, ii) 1–Phenylethanol and Et_3N

using 1,10–phenanthroline [265] as an indicator.) However, attempts to prepare the menthyldimethylchlorosilane (**276**) *via* this approach were unsuccessful, fractional distillation of the crude reaction mixture yielding several multi–component fractions. In order to investigate the reactions of bulky Grignard reagents with dichlorosilanes, an attempt was made to generate the chloromenthyldiphenylsilane (**277**) *in situ* and trap it as the silyl ether of 2–phenylethanol. The major component isolated from this reaction was the diastereomeric diphenyl[*bis*(1–phenylethoxy)]silane (**279**) (Scheme 77), indicating that very little of the menthyl Grignard reagent had reacted with the silyl chloride. The disappearance of the Grignard reagent (followed by titration of aliquots of the reaction mixture) can only be attributed to slow decomposition of the organometallic reagent over the extended reaction time (*ca.* 72 h). A second component (*ca.* 5%) was isolated from the crude reaction mixture and was tentatively assigned the structure (**278**) based solely on the 60 MHz ^{1}H NMR spectrum. From these results, it became obvious that the reactivity of the menthyl Grignard reagent (**274**) with chlorosilanes is too low to be of any synthetic value. The preparation of analogous Grignard reagents from bornyl chloride [266] has been shown by Erickson and Fry to be unsuccessful.[267]

The preparation of both menthyl and bornyl lithium by metal–halogen exchange between the terpenoid chlorides and lithium sand have both been reported.[267,268] In our hands, however, neither of these preparations could be repeated, the failure being largely attributed to the insufficiently small particle size of the lithium sand. No experimental method to reduce the particle size of the lithium sand could be found and, as a result, attempts to prepare these lithium reagents were abandoned. Thus, as neither Grignard or organolithium reagents, provided entry into chiral silyl enol ether systems in which the oxygen atom between the chiral auxiliary and the silicon is absent this approach was not pursued. The alternative approach to improving the asymmetric control of reactions of chiral silyl enol ethers, *viz.*, enhancing the co–ordination potential of the auxiliary thus became the focus of the investigation.

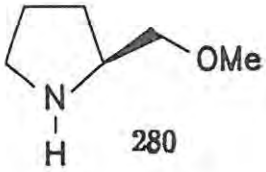
2.6 NITROGENOUS CHIRAL AUXILIARIES.

2.6.1 Proline Derived Auxiliaries (280) and (281).

Some of the most versatile of chiral auxiliaries presently available are the pyrrolidine compounds (**280**) and (**281**) derived from either enantiomer of the amino acid, proline (**1**) (see section 1.4.3.3, p 65, and p 69). The proven ability of these auxiliaries to effect asymmetric control (due, to a large degree, to the combined co–ordinating capabilities of the nitrogen atom and the oxygenated side chain) made them excellent candidates with which to initiate the revised approach to asymmetric reactions of silyl enol ethers.

Other investigations [199,261,269] of the chiral auxiliary controlled asymmetric reactions of allyl silanes were proceeding concurrently with our own research. Chan and Wang [269] arrived at similar conclusions to our own concerning the co–ordination requirements of the chiral auxiliary; in the case of allylsilanes, co–ordination of the Lewis acid with the ligands on the silyl moiety favour the synclinal transition state (**283**), over the alternative antiperiplanar transition state (**282**). Chan and Wang [269] also chose proline derived auxiliaries to achieve this co–ordination and significantly improved the enantiomeric control in the formation of homoallylic alcohols (**286**) from the allylic silanes (**284**) and (**285**) (Scheme 78). Chan and Pellon [270] have recently used these same auxiliaries to achieve excellent enantiomeric control in the formation of arylcarbinols from benzylsilane via the lithiated intermediate (**287**)

The pyrrolidine chiral auxiliaries of choice [(**280**) and (**281**)] were prepared from (L)–proline by standard methods[271,272], as outlined in Schemes 79 and 80. Attempts to prepare auxiliary (**280**) from the more readily available



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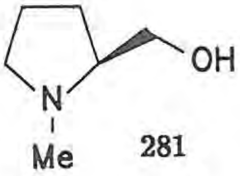

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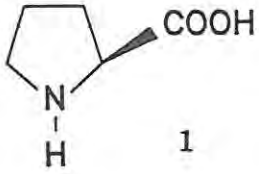
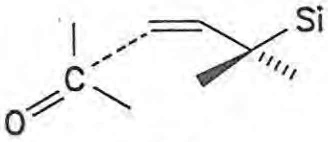


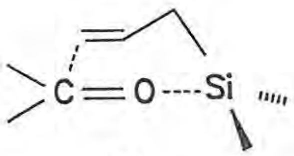
1

antiperiplanar



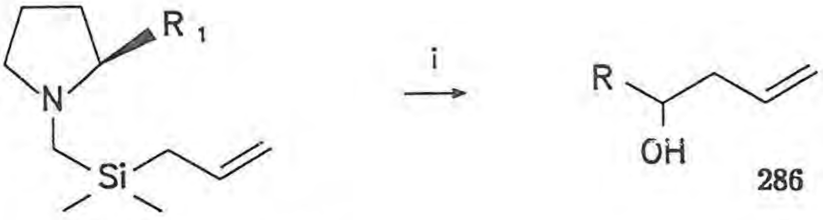
282

synclinal



283

SCHEME 78



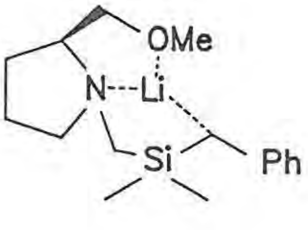
286

R_1 = CO_2Me 284

R_1 = CH_2OMe 285

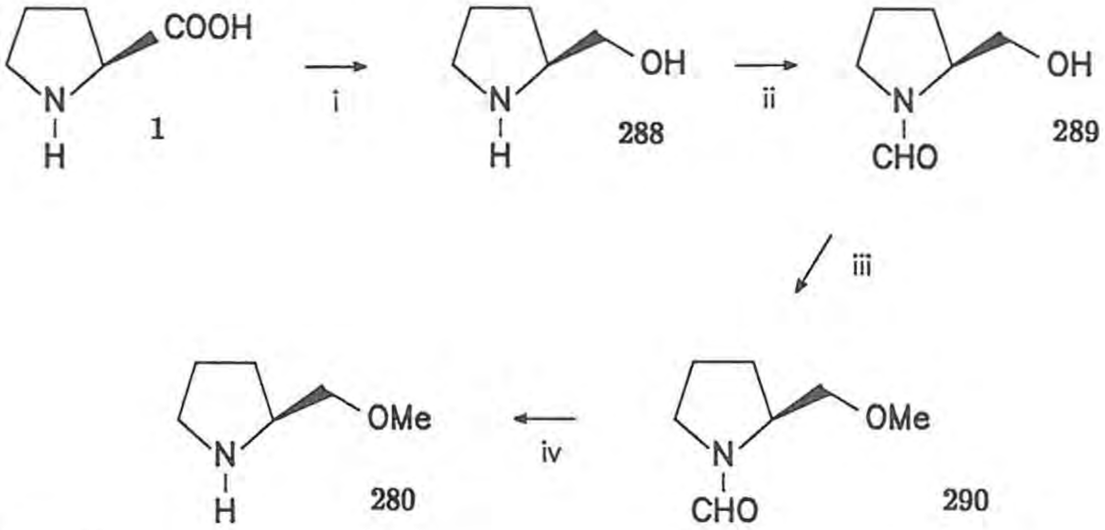
Reagents

i) RCHO and $TiCl_4$



287

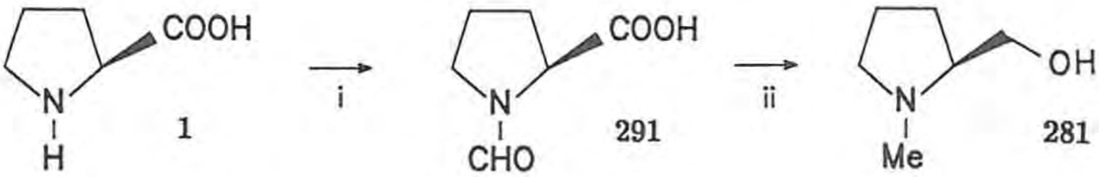
SCHEME 79



Reagents

i) LAH, ii) HCOOEt, iii) NaH/MeI, iv) 10% KOH

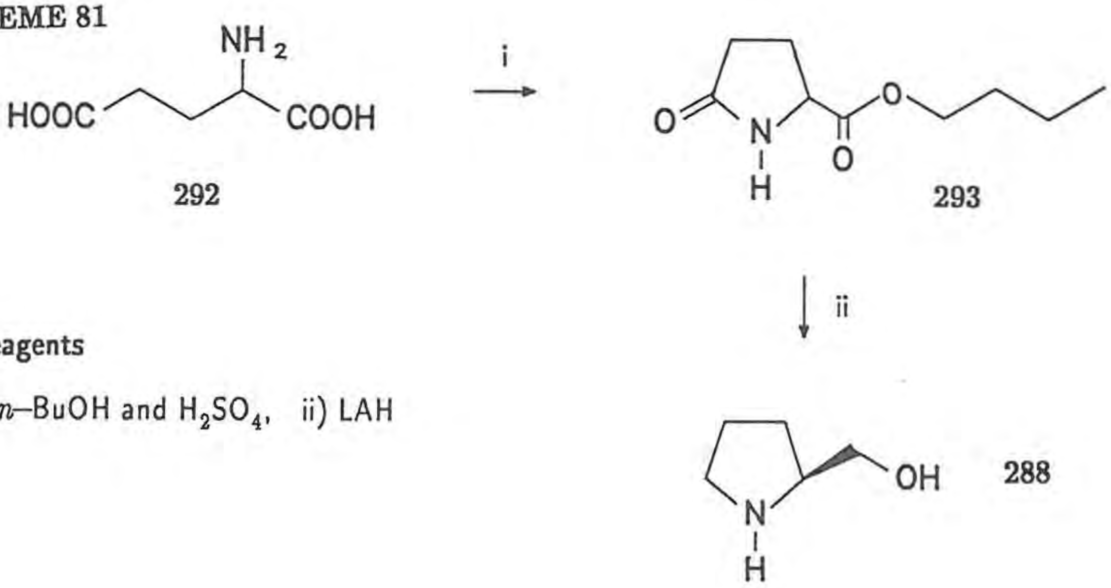
SCHEME 80



Reagents

i) Formic acid and acetic anhydride, ii) LAH

SCHEME 81

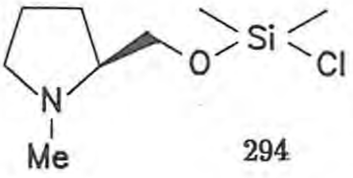


Reagents

i) *n*–BuOH and H_2SO_4, ii) LAH

(L)–glutamic acid (**292**) were disappointing due to poor yields of the reduction of the cyclooxocarbamate intermediate (**293**) (Scheme 81)[273].

The preparation of silyl enol ethers incorporating the pyrrolidine auxiliaries (**280**) and (**281**) however, was fraught with problems, some of which proved to be insuperable. The preparation of the chlorosilane (**294**) [analogous to the menthyloxy– and bornyloxychlorosilanes, (**176**) and (**179**)], was unsuccessful; GC–MS analysis, following addition of 1–phenylethanol to the crude product showed it to contain *ca.* 50% of unreacted 1–phenylethanol and at least six other unidentified components, all of similar concentration.



294

The conclusion was drawn that the chlorosilane (**294**) was not isolable and, consequently, *in situ* preparations of silyl enol ethers of several ketones *via* Walkup's method[206] were attempted. Examination of the crude mixtures from such reactions of cyclohexanone and tetralone indicated little, if any of the desired product and these reactions were not pursued further.

The reaction of the lithium enolate of pinacolone with the lithium alkoxide[u] of *N*–methyl prolinol (**295**) and dichlorodimethylsilane (Scheme 82) yielded (as shown by GC–MS) three major components. The mass spectra of two of these compounds were consistent with the desired silyl enol ether (**296**) and the

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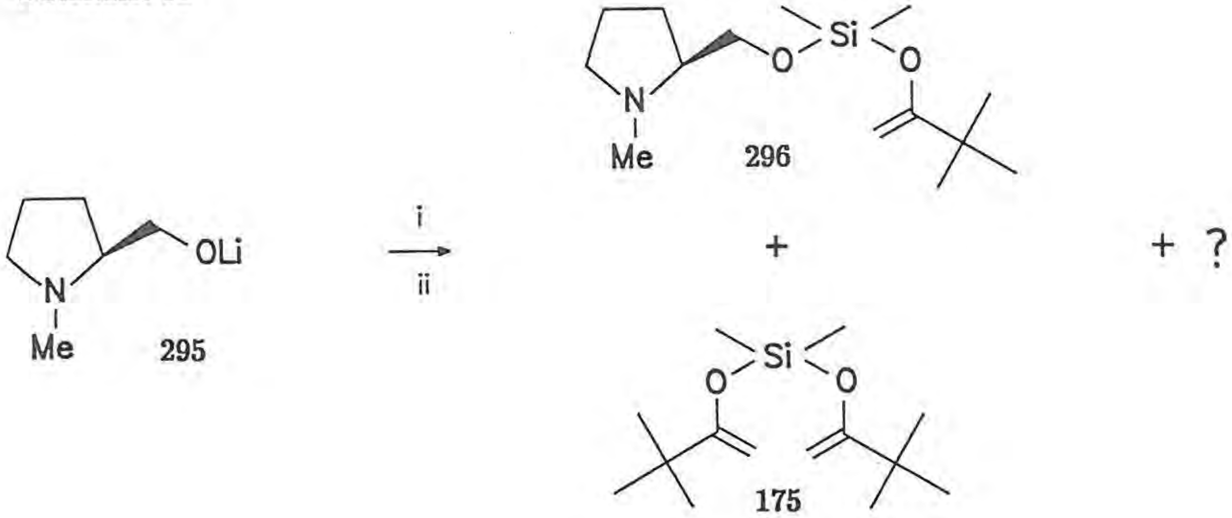
[u] The use of the preformed lithium salt of the amine (**281**) was to avoid generation of HCl and the possibility of precipitating the amine as the hydrochloride salt.

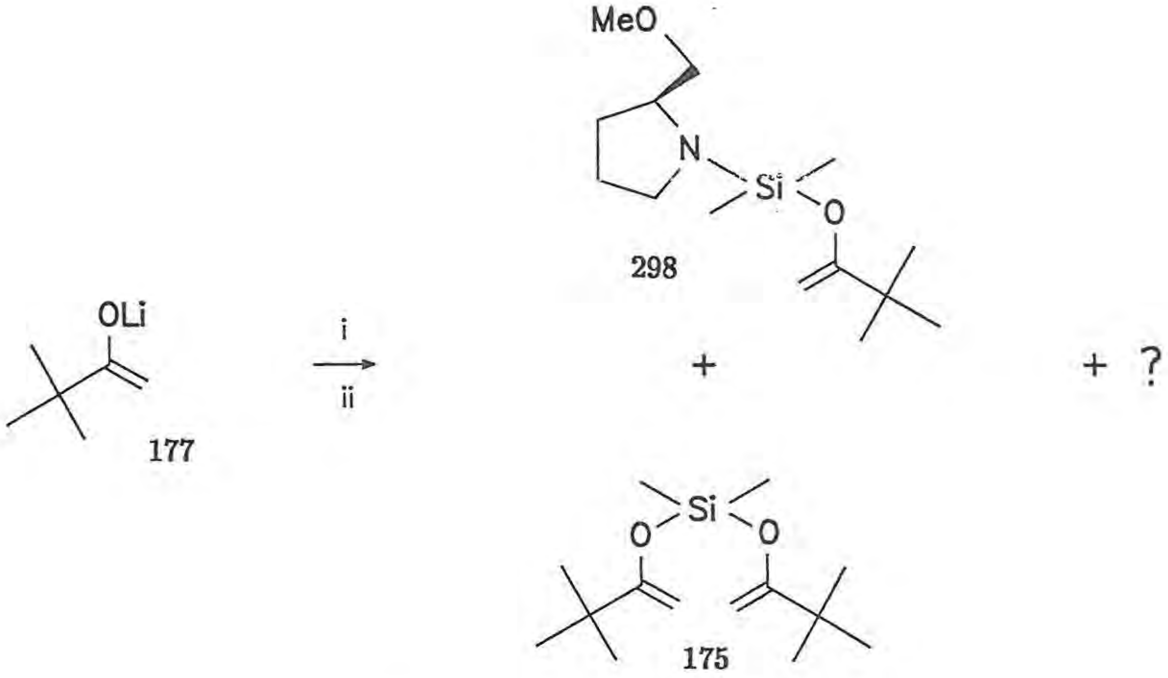
SCHEME 82



Reagents

i) Cl_2SiMe_2 ii) Lithium enolate of pinacolone

SCHEME 83

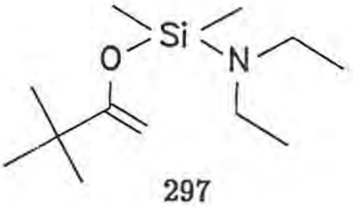


Reagents

i) Cl_2SiMe_2 ii) Amine (**280**) and Et_3N

bis–substituted silane (**175**). The third silyl containing component was not identified. The *bis*–substituted silane (**175**) could be separated from the mixture by distillation or chromatography and was subsequently fully characterized. However, the remaining two components, present in approximately equal amounts, were inseparable, preventing use of the silyl enol ether (**296**) in asymmetric reactions. Thus, the feasible routes to silyl enol ethers with the auxiliary (**281**) appeared impractical and asymmetric syntheses involving these chiral auxiliaries were not pursued any further.

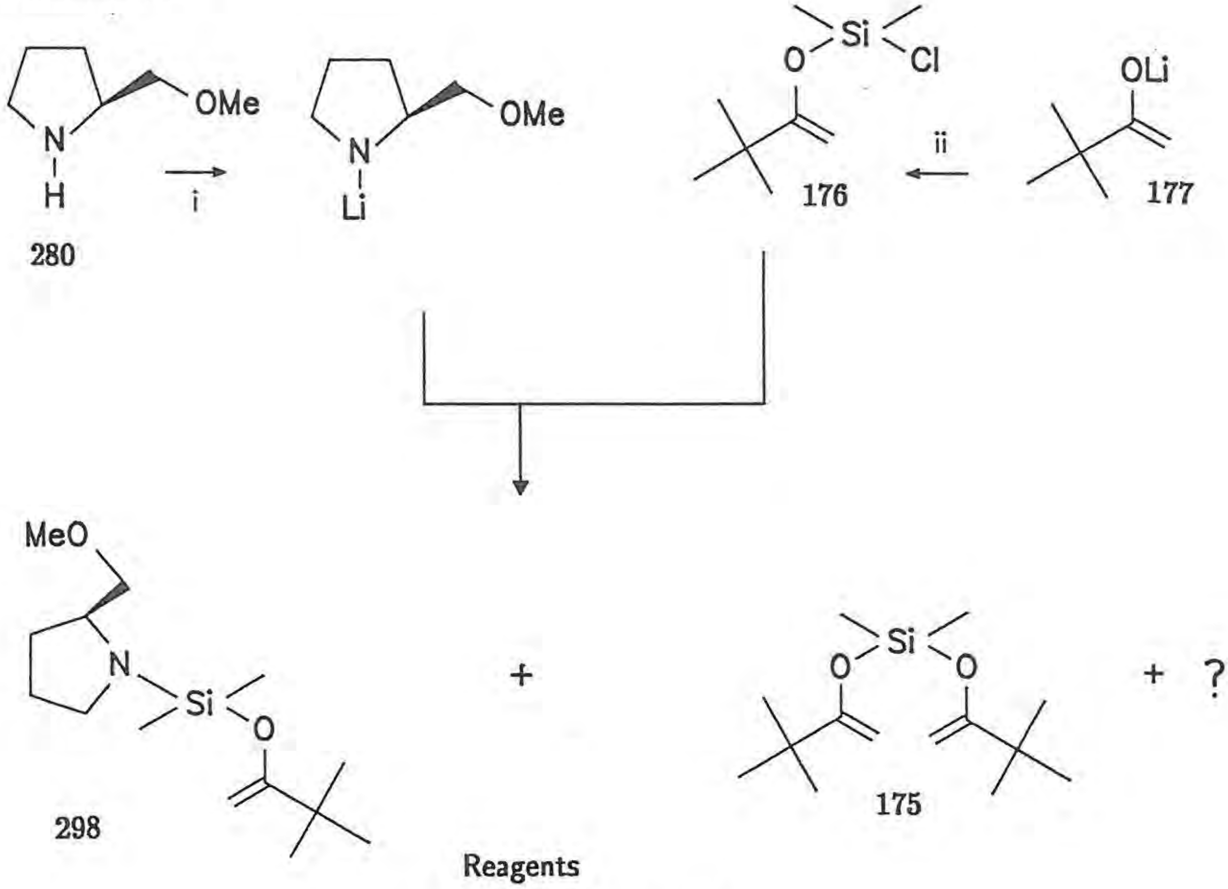
The preparation of silyl enol ethers from the second of these pyrrolidine auxiliaries (**280**) required the formation and isolation of silyl enol ethers containing a silicon – nitrogen bond. Walkup [206] had prepared the pinacolone – derived (**297**), thus establishing the feasibility of such compounds (although this nitrogen containing silyl enol ether appears to be less stable than the other silyl enol ethers reported).



297

Our attempts to prepare enol silanes from the amine (**280**) (Scheme 83) were marginally more successful than our efforts using *N*–methylprolinol (**281**). The reaction of the lithium enolate of pinacolone with dichlorodimethylsilane and the amine (**280**) yielded the desired silyl enol ether (**298**) together with the *bis*–substituted silane (**175**) and the unidentified product obtained previously. The use of various techniques to effect purification of the silyl enol ether (**298**) never yielded samples of greater than 75% purity. Reaction of the lithium salt

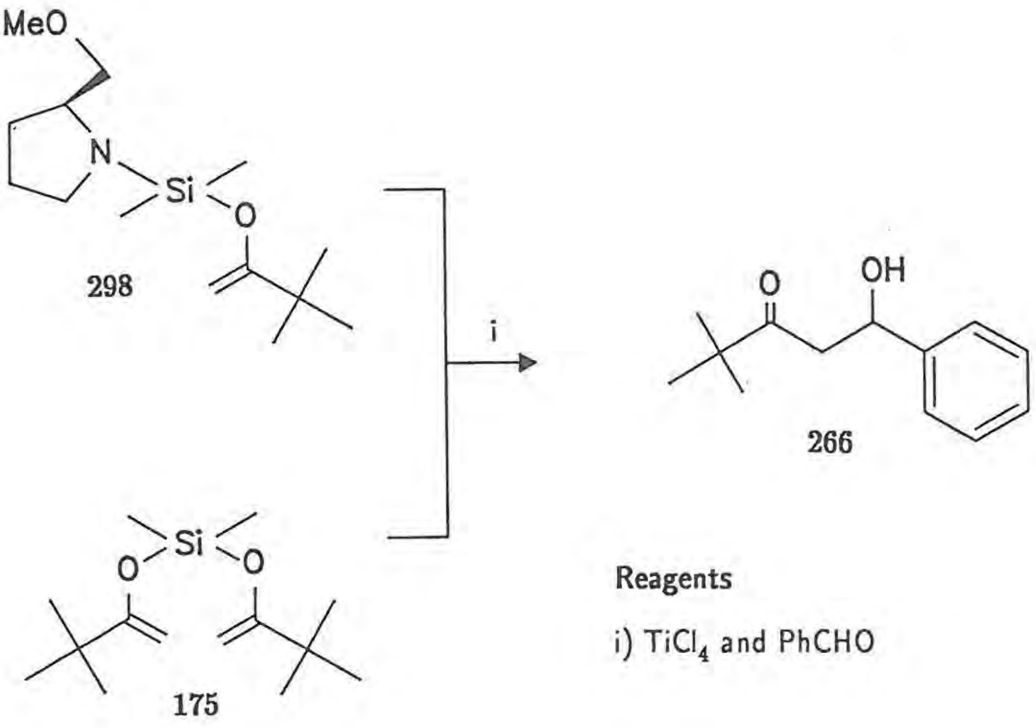
SCHEME 84



Reagents

i) Bu^t Li ii) Cl_2SiMe_2

SCHEME 85



Reagents

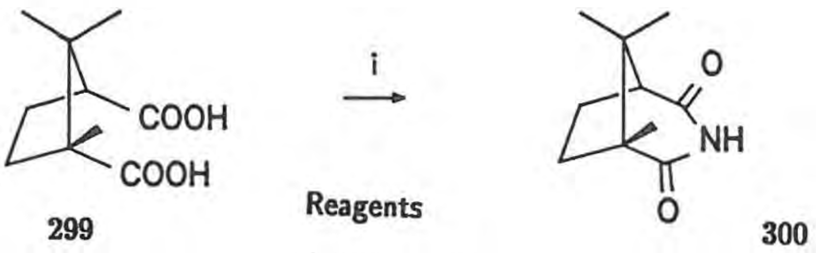
i) $TiCl_4$ and PhCHO

of amine (**280**) (Scheme 84) with the isolated and purified chloro silyl enol ether (**176**) failed to improve the product distribution. The mixture containing 75% of the silyl enol ether (**298**) was subjected to a hydroxyalkylation with benzaldehyde and $TiCl_4$ (Scheme 85). The enantiomeric excess of the β–hydroxyketone (**266**) was determined by chiral shift reagent studies, as before, and found to be 8%. Even allowing for the possibility of the formation of some *racemic* β–hydroxyketone from the hydroxyalkylation of the disubstituted silane contaminant (**175**), there appears to be no significant improvement in the enantiomeric excess achieved by replacing the simple alkoxy silanes with these pyrrolidine systems. In light of this result and the severe difficulties experienced in purifying the necessary pyrrolidine silyl enol ethers it became apparant that the pyrrolidine based chiral auxiliaries were not amenable to silyl enol ether formation.

2.6.2 Derivatives of Camphorimide (300) as Chiral Auxiliaries.

During the planning stages of the present investigation, the readily available and inexpensive camphoric acid (**299**) appeared to be a good precursor for the preparation of several compounds that had received little or no attention as chiral auxiliaries. One such compound was camphorimide (**300**), easily prepared from camphoric acid in aqueous ammonia at elevated temperature and pressure (Scheme 86). In other work undertaken in these laboratories the reduction product of camphorimide, camphidine (**307**), was used to examine asymmetric reactions of chiral enamines. This amine lacks any functionality capable of co–ordination and was thus deemed to be unsuitable for application to silyl enol ether systems. However, other reactions of camphorimide were

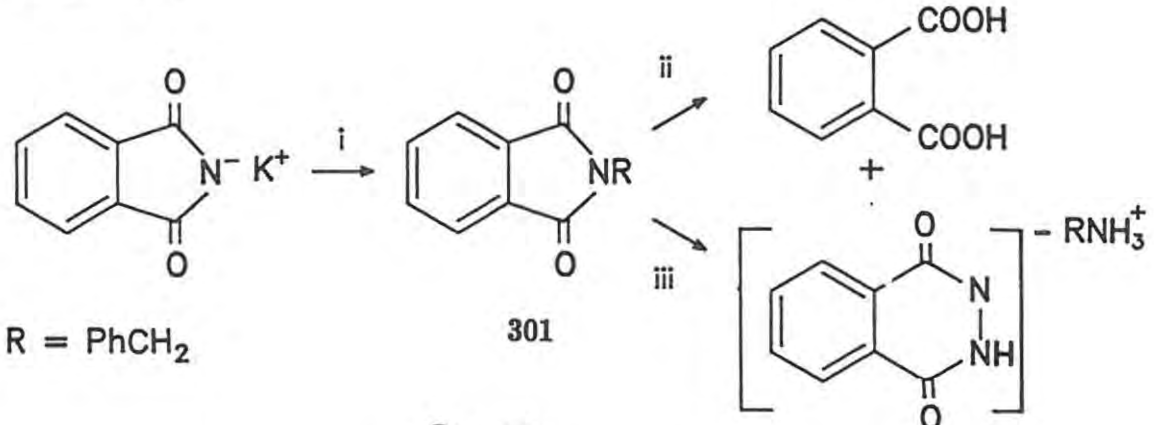
SCHEME 86



Reagents

i) 25% aq. NH_3

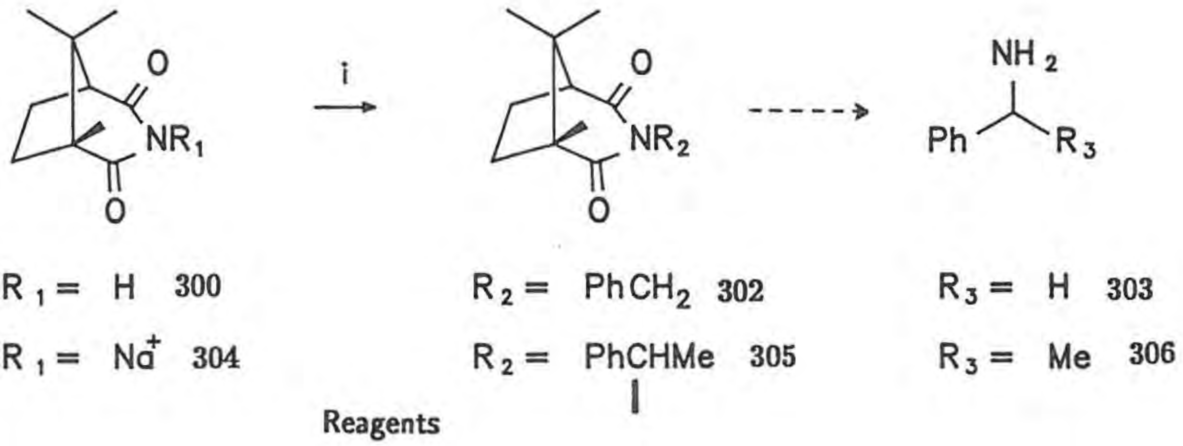
SCHEME 87



Reagents

i) R Halogen, ii) H^+, iii) $NH_2—NH_2$

SCHEME 88



Reagents

i) For (**300**); KOH and benzyl chloride

i) For (**304**); PhCH(Br)Me

examined and several novel concepts in asymmetric synthesis, unrelated to the investigation of chiral silyl enol ethers, were explored.

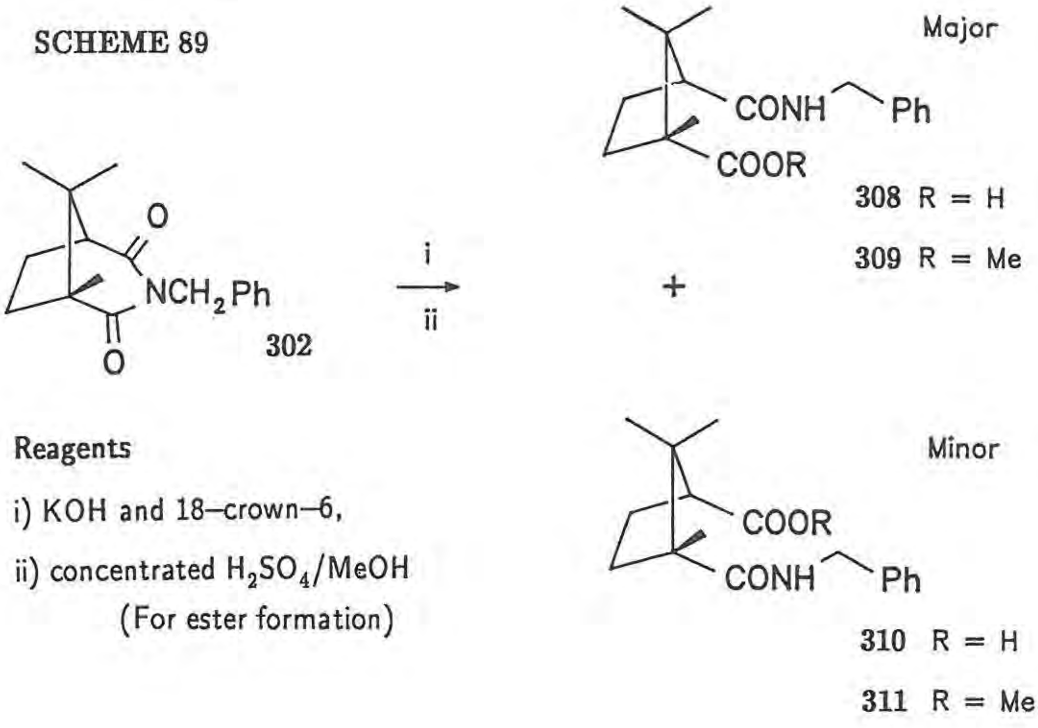
307

In the Gabriel synthesis amines are prepared by hydrolysis or hydrazinolysis of *N*–alkyl phthalimides (Scheme 87).[274] We were interested in the prospects of developing chiral syntheses of secondary amines or amino acids by applying the strategy of the Gabriel synthesis to *N*–alkyl camphorimides. These syntheses were envisaged to involve abstraction of a proton α to the imide nitrogen and then reprotonation or reaction with (suitably protected) α–haloacids under the asymmetric influence of the chiral imide, as illustrated in Scheme 88. As test reactions the *N*–alkyl camphorimides (**302**) (no new chiral centre to be generated) and (**305**) were duly prepared as outlined in Scheme 88. After ensuring that the available hydrazine hydrate yielded benzylamine from *N*–benzyl phthalimide (**301**) in adequate yields, the analogous hydrazinolysis of the model imide derivative (**302**), was attempted. In the event, this hydrazinolysis failed to afford benzylamine and, in fact, freeing of the amine from the imide (**302**) proved to be remarkably difficult. Hot, concentrated acid or base was ineffective, as no benzylamine was detected in the reaction mixtures. Phase transfer catalysed reactions in two phase systems were also also ineffective, as were attempts at methanolysis, using sodium methoxide, and aminolysis, employing aqueous ammonia at elevated temperatures and pressures. Only by resorting to the extreme conditions of heating the imide (**302**) with soda lime could benzylamine be obtained, albeit in poor yields. Due to the harsh reaction conditions required to free the amine from the *N*–alkyl camphorimides the concept of employing these imides in an asymmetric Gabriel type synthesis seemed impractical and was not investigated further.

However, amongst the varied attempts to cleave the imide (**302**), one reaction had emerged that exhibited potential as an entry point into convenient syntheses of camphoric acid derived chiral auxiliaries. The reaction of the imide (**302**) with KOH in refluxing toluene (Scheme 89), in the presence of a catalytic amount of 18–crown–6, yielded, as major and minor products (*ca* 13:1) the two ring opened amide–acids (**308**) and (**310**). (The amide bond in these molecules proved to be resistant to hydrolysis, being unaffected by prolonged heating in concentrated aqueous acid or alkali). While the major product (**308**) could be obtained by repeated recrystallizations, esterification of the crude hydrolysis mixture facilitated the separation of the products as their methyl esters (**309**) and (**311**). The assignment of structures to the isomeric products required high field, one and two dimensional ^{1}H and ^{13}C NMR studies on derivatives of these compounds (see p 213).

Nitrogenous camphor derivatives *e.g.* (**312**) and (**313**) have been used in various asymmetric applications, including chiral modifiers of LAH [275] and as chiral auxiliaries in Diels Alder reactions.[276] The LAH reduction of compound (**309**) was expected to yield the amino alcohol auxiliary (**314**). In the event, the LAH reduction, afforded instead, the cyclic amine (**315**) (Scheme 90) and the partially reduced compound (**316**) (*ca* 1.0:1.5) (even when using large excesses of LAH and prolonged reaction times). Two possible routes to the cyclic amine (**315**) are illustrated in Schemes 91 and 92. The first route (Scheme 91) involves initial reduction to the amine (**317**), followed by cyclization to the lactam intermediate (**318**). In the second, the anion (**319**) displaces the methoxy group of the ester to re–form the imide intermediate (**302**). [In

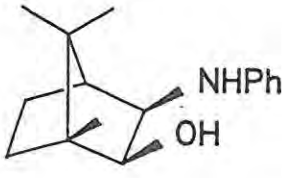
SCHEME 89



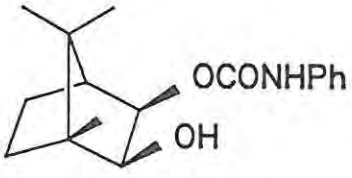
Reagents

i) KOH and 18–crown–6,

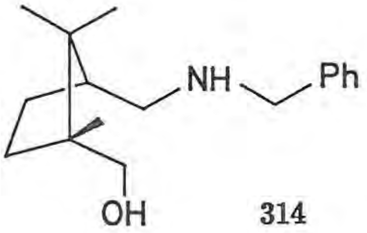
ii) concentrated H_2SO_4/MeOH
(For ester formation)



312

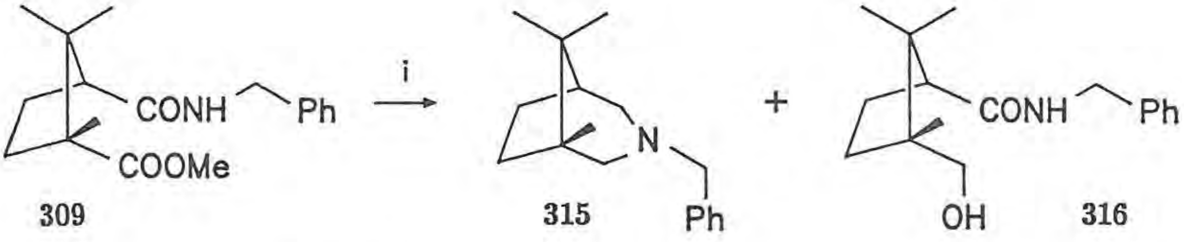


313



314

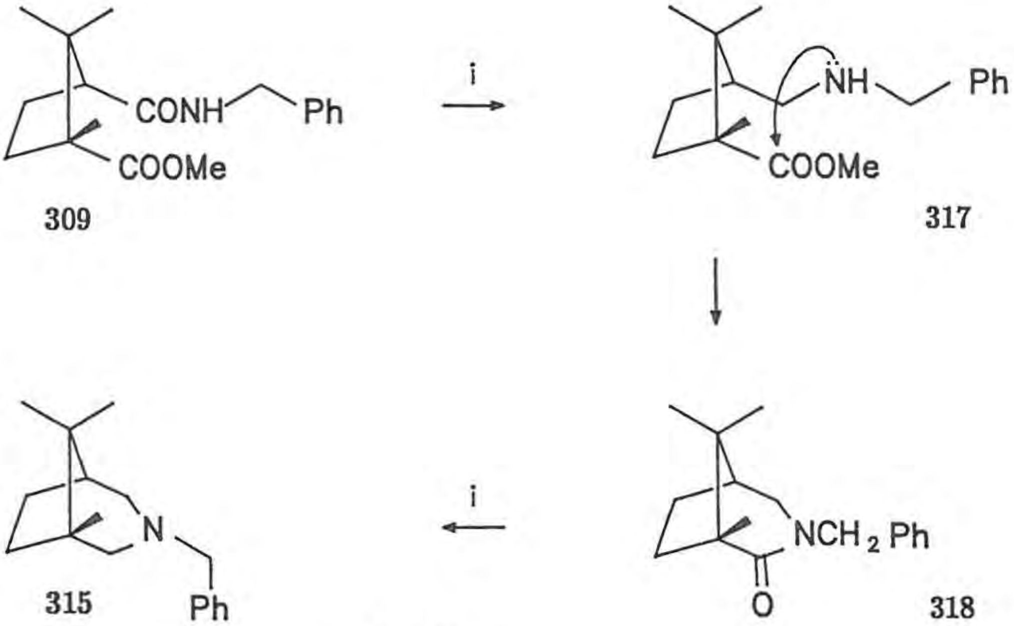
SCHEME 90



Reagents

i) LAH

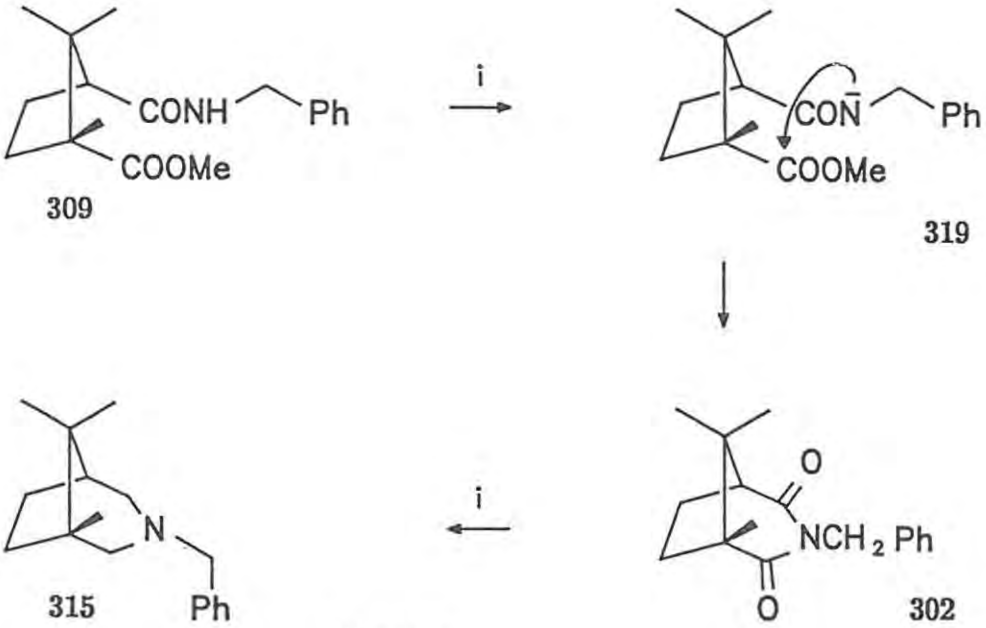
SCHEME 91



Reagents

i) LAH

SCHEME 92

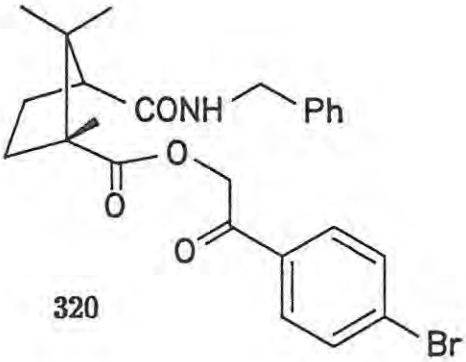


Reagents

i) LAH

subsequent work in these laboratories, the reduction of this imide (**302**) has been shown to proceed smoothly.]

The crystalline bromophenacyl (**320**) and the 3,5–dinitrobenzoyl ester (**321**) derivatives were prepared with the view to establishing the structure of the acid amide (**308**) by X–ray crystallography. However, isolation of the half reduced hydroxy amide (**316**) made it possible, to establish, by NMR spectroscopy, the regiochemistry of the ring–opened products (**308**) and (**309**).



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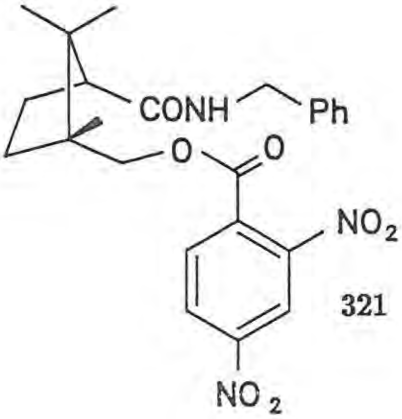
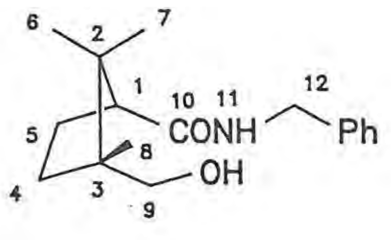


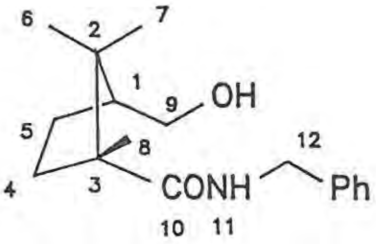
321

Initially, calculation of the theoretical chemical shifts of carbons C–9 and C–12 in both regio–isomers [(**316a**) and (**316b**),provided some evidence for structure (**316a**) (Table 16)

TABLE 16 Calculated[277] and observed chemical shifts for the C–9 and C–12 carbons in the regio–isomers:(**316a**) and (**316b**).



316 a



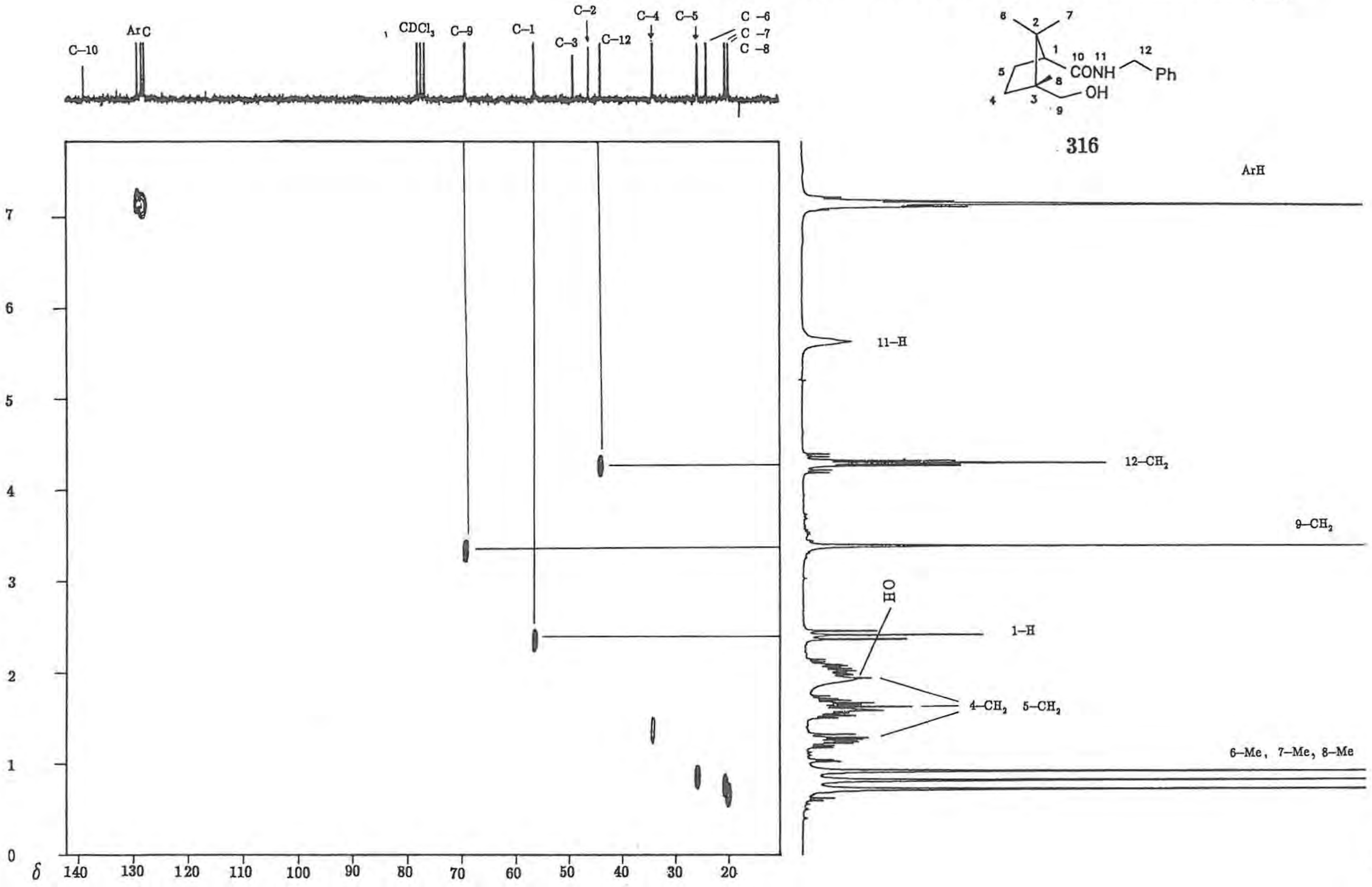
316 b

NOTE: The numbering in compound (**316b**) is not systematic but does facilitate direct comparison with compound (**316a**).

Compound	Chemical Shift (δ)	
	C–9	C–12
316a	69.3	48.6
316b	61.4	48.6
Observed	69.1	44.0

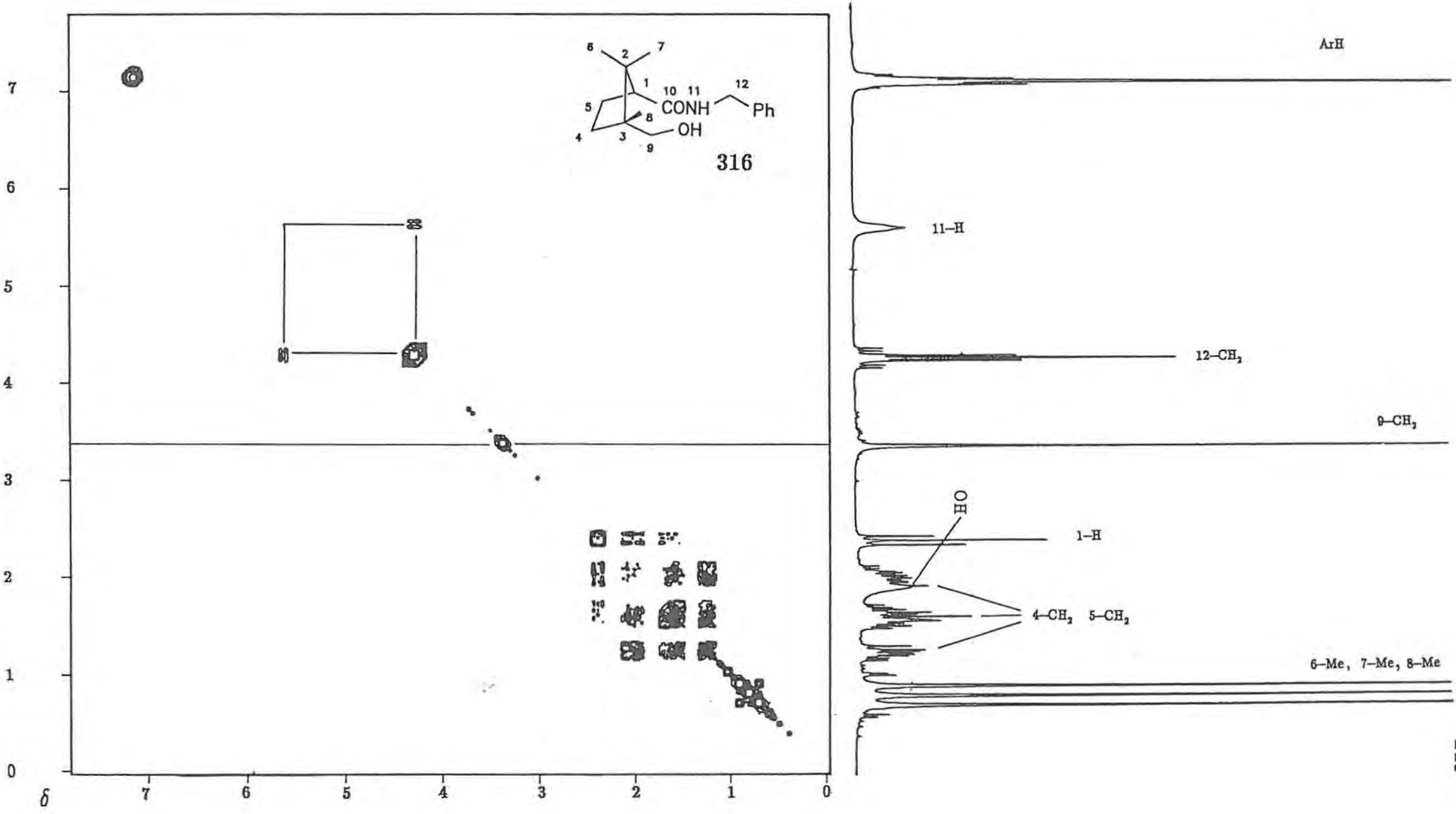
Secondly, more sophisticated 200 and 300 MHz NMR techniques were used to locate the 9–CH_2 group adjacent to the quaternary carbon (C–3) in compound (**316a**). Intuitive assignment of the 12–CH_2 signal downfield from the 9–CH_2 (in either molecule) was confirmed by the COSY (Figure 49) spectrum in which the coupling between the amide proton (11–H) and the 12–CH_2 proton is clearly evident. (The broad, rounded amide and hydroxyl protons had been

FIGURE 48 200 MHz HETCOR NMR spectrum of the amide alcohol (**316**).



316

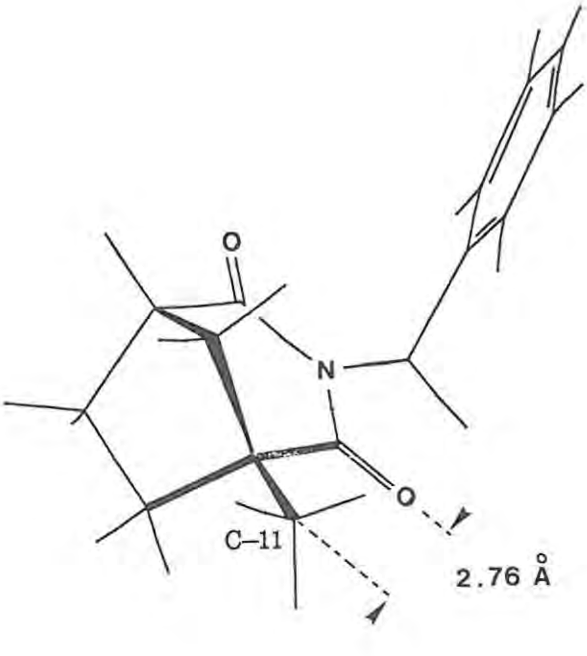
FIGURE 49 200 MHz COSY NMR spectrum of the amide alcohol (**316**).



distinguished by rapid D_2O exchange of the latter and, furthermore, the signal assigned to the amide proton exhibited no correlations in the HETCOR spectrum (Figure 48) and no additional correlations in the COSY spectrum). Having identified the 9–CH_2 signal unequivocally, the structure assignment then depended on evaluation of the couplings to these protons, in particular the coupling to the 1–H methine proton (readily identified in the HETCOR spectrum). The 9–CH_2 signal is, in fact, a sharp singlet (even at 300 MHz) and exhibits no correlations whatsoever in the COSY spectrum. The available NMR data is thus consistent with structure (**316a**) in which no coupling to the 9–CH_2 nuclei is expected, and strongly indicates the major product of the initial hydrolysis (Scheme 89) to be the acid amide (**308**). This structural assignment is at variance with the work of Bell,[277] in which a similar base hydrolysis of the imide (**302**) yielded a compound with the same physical data as our product (**308**), but, the product was assigned structure (**310**). Bell's assignment appears to be based on the assumption that nucleophilic attack of this imide system (**302**) always occurs at the less sterically hindered carbonyl group.

Possible explanations for the surprising regioselective hydroxide ion attack at the more sterically hindered carbonyl (to afford the amide–acids (**308**) and (**310**) in a *ca.* 13:1 ratio), involve alleviating unfavourable steric interactions in the substrate molecule. Computer modelling of the imide (**302**) reveals a separation of 2.76 Å between the C–11 methyl group and the proximate carbonyl oxygen (Figure 50). This internuclear separation is significantly less than the sum (3.40 Å) of the van der Waals radii of the methyl group and the carbonyl oxygen. The unfavourable eclipsing interaction could be somewhat alleviated by bending the carbonyl group in question out of the imide plane. The consequent reduction in conjugation could render this carbonyl group more electrophilic. An alternative explanation may lie in the nature of the two competing transition states. As hydrolysis proceeds and the carbonyl carbon becomes tetrahedral, the relief of steric strain in the transition state for the favoured pathway should significantly lower the activation energy (relative to the competing pathway) and hence account for the observed regioselectivity.

FIGURE 50 Computer model of *N*–benzylcamphorimide (**302**), indicating the distance between the C–11 methyl group and the proximate carbonyl oxygen; a possible cause of unfavourable steric interactions in this molecule.

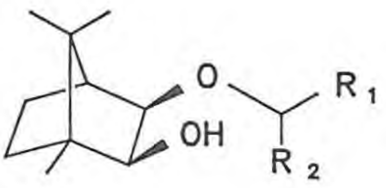


In view of the unexpected cyclisation to form the amine (**315**) and the reluctance of the hydroxy amide (**316**) to undergo further reduction, attention was focussed on attempts to modify camphor–based systems to meet the requirements of our silyl enol ether reactions.

2.7 THE APPLICATION OF CAMPHOR DERIVED CHIRAL AUXILIARIES TO SILYL ENOL ETHER SYSTEMS.

Camphor derived chiral auxiliaries have been widely used in asymmetric synthesis. Reasons for this popularity include the availability of camphor itself, the conformational rigidity of the bicyclic system, and the ease with which additional functionality can be introduced. The use of such auxiliaries has recently been reviewed [278] and 2,3–dioxybornane systems, like those prepared by Oppolzer *et al.*[279] [*e.g.* compounds **(322)** and **(323)**] appeared to best suit our needs. Oppolzer *et al.*[279] employed three general synthetic routes for the preparation of such compounds, making use of the intermediate compounds [**(324)** – **(327)**].

In light of the synthetic strategies available, we chose to prepare three chiral auxiliaries, **(328)**, **(329)**, and **(330)**, all of which would permit linking of the silyl enolate to the more sterically demanding side of the auxiliary. Auxiliaries **(328)** and **(330)** were known [279] [although compound **(330)** had not been employed as a chiral auxiliary, but, merely as an intermediate in the synthesis of other more established auxiliaries] and compound **(329)** was, to the best of our knowledge, novel. These particular compounds were selected because, to our minds, they each possessed unique features, that could well enhance the stereoselectivity of the silyl enol ether reactions under consideration (See Section 2.4, p.191). Relative to the bicyclic system, compound **(330)** contains a close co–ordination site, compound **(329)** incorporates both close and more distant co–ordination sites, while the third compound **(328)** possesses a close co–ordination site and a distant bulky group. It was felt that these three independent features would permit an adequate initial evaluation of the ability of this type of chiral auxiliary.



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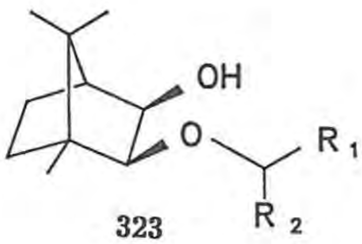

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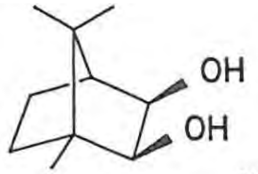
R_1 = Ph, naphthyl, Bu^t

R_2 = Ph, H



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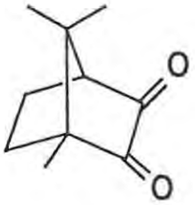

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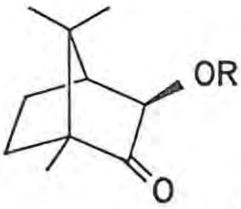

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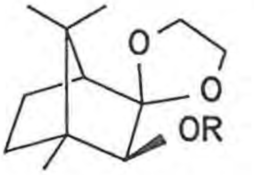

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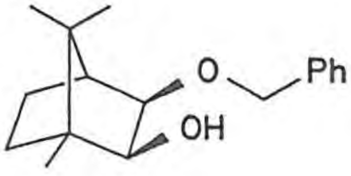

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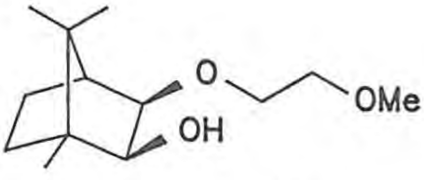

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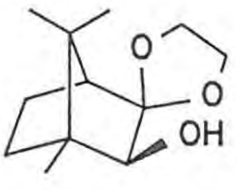

330

Our initial endeavours to prepare the chosen auxiliaries involved different approaches to those employed by Oppolzer. In an attempt to facilitate access into these systems, stereoselective oxidation of the trimethylsilyl enol ether (**331**) (Scheme 94) and the potassium enolate of camphor (Scheme 95) were explored, with the view to subsequent alkylation and reduction of the α–hydroxy ketone product (**332**).

In our hands, the reported[280] preparation of the trimethysilyl enol ether of camphor (**331**) from bromocamphor in the presence of TMSCl and Zn metal failed. However, by employing an LDA approach (Scheme 93) (surprisingly reputed to be an inconvenient preparation of this particular silyl enol ether [211]) we obtained compound (**331**) in adequate yields. MCPBA oxidation of this compound (Scheme 94), however, yielded the diastereomeric *endo* –(**333**) and *exo* –(**332**) α–hydroxy ketones in approximately equal amounts [together with a small amount of camphorquinone (**325**)].(The diastereoselectivity was easily established by ^{1}H NMR spectroscopy – the *endo* C*H*–OH doublet and the corresponding broad *exo* methine singlet were separated by approximately 0.5 ppm.) When oxidising the potassium enolate of camphor, using 2–(phenylsulphonyl)–3–phenyloxaziridine (**256**) (Scheme 95), as reported by Davis *et al.*,[291] we obtained, almost exclusively, the *exo* product (**332**).[v] The inconvenience, however, of using the pyrophoric, solid base, KHMDS, on a scale large enough to prepare sufficient quantities of the auxiliaries made this highly diastereoselective approach impractical and the more lengthy synthetic procedures of Oppolzer *et al.*[279] were deemed to be the only feasible

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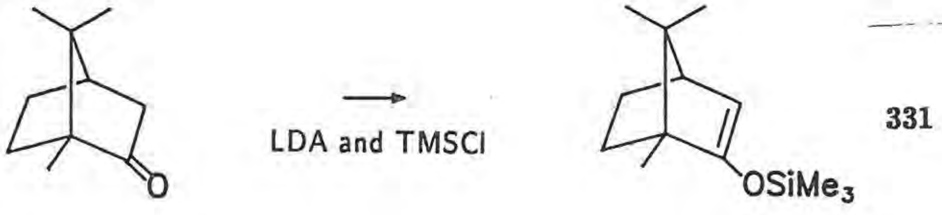
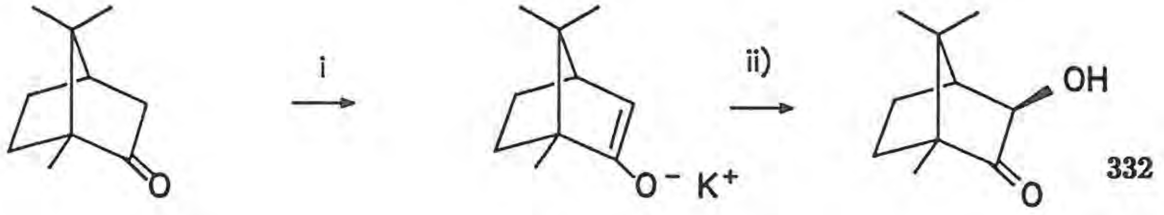
[v] It is perhaps, worthy of a note in passing, that Davis *et al.*[91] imply, in the table summarizing their results, that the product formed is the *endo* diastereomer (**187**). This implication is believed to be in error.

SCHEME 93



SCHEME 94

SCHEME 95

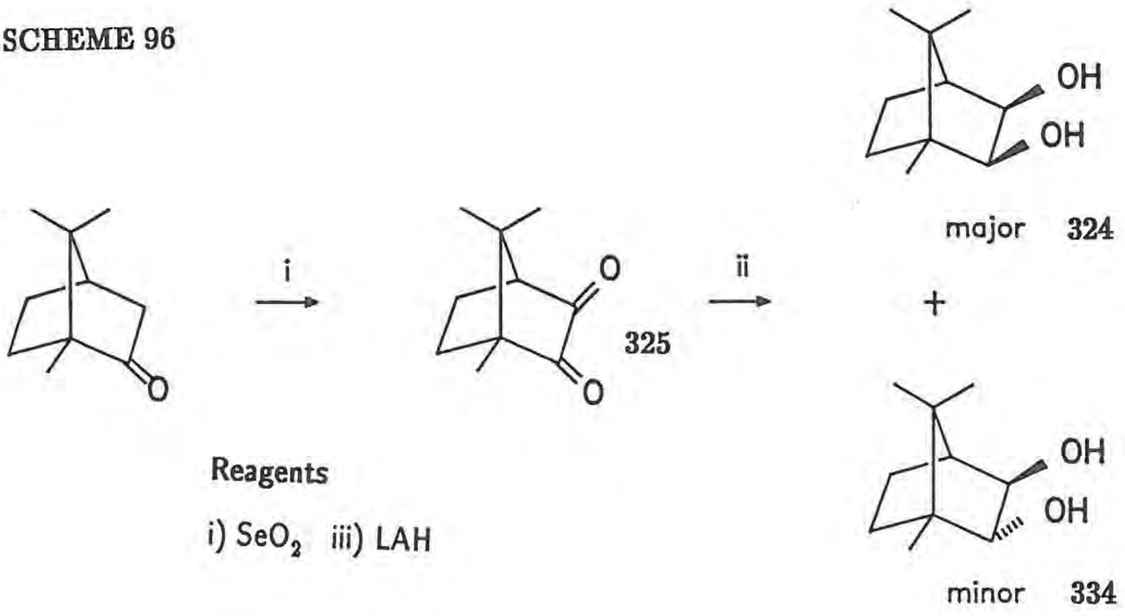


Reagents

i) KHMDS (Potassium hexamethyldisilazine)

ii) 2–(phenylsulphonyl)–3–oxaziridine (256)

SCHEME 96



Reagents

i) SeO_2 iii) LAH

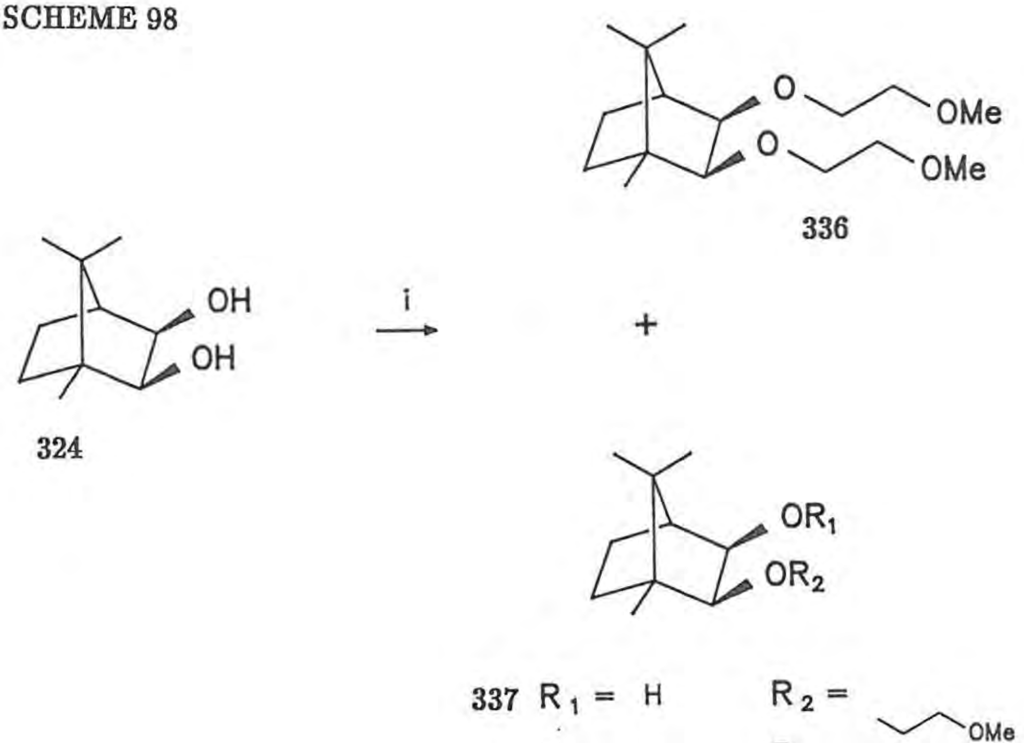
alternatives. Applications of the simplest of these approaches is outlined in Schemes 96, 98, and 99.

The dihydroxy compound (**324**) was prepared (Scheme 96) by the stereoselective reduction of camphorquinone (**325**) (which, in turn, was easily prepared by means of the SeO_2 oxidation of camphor). A minor contaminant (essentially removed by steam distillation) was present in the crude product (**324**) and, based on the original report of this reaction [282] was presumed to be the 2–*endo*–3–*exo* diol (**188**).

The alkylating agent (**335**) [283] (Scheme 97) was used in attempt to prepare chiral auxiliary (**329**) (Scheme 98). Three products were, in fact, obtained, *viz.*, both monoalkylated products (**337**) and (**338**) (in approximately equal concentration), and the dialkylated product (**336**). Unlike the compounds prepared by Oppolzer *et al.*,[279] the monoalkylated products (**337**) and (**338**) proved to inseparable.

Concurrent with the work on compound (**324**), the possibility of preparing similar chiral auxiliaries from the reduction product of camphoric acid (**299**), diol (**339**) was investigated. Although this cyclopentane diol system is less conformationally rigid than that of the [2.2.1] bicyclic ring system, it has the advantage of being accessible in a single step from camphoric acid (**299**).[284] The necessary reduction (Scheme 99) proceeds in excellent yield and no

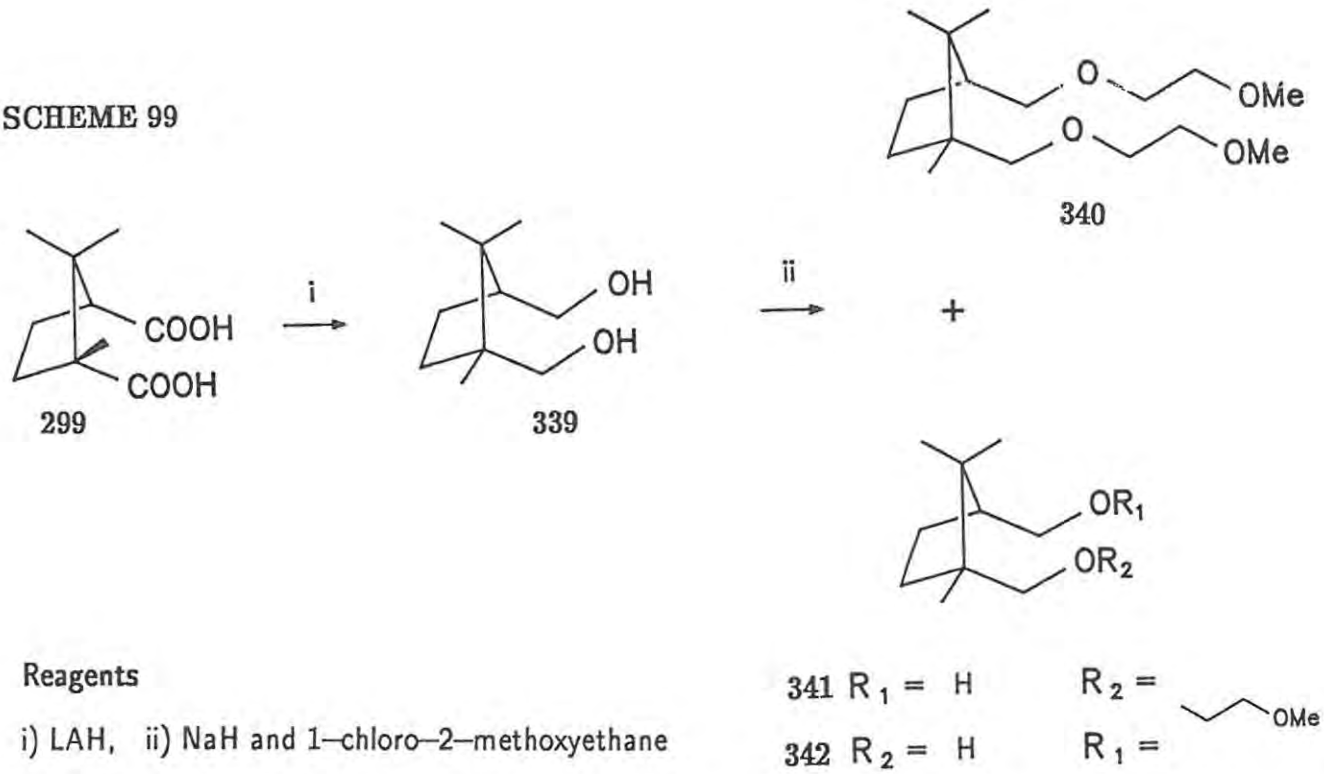
SCHEME 98



Reagents

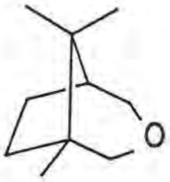
i) NaH and 1–chloro–2–methoxyethane

SCHEME 99



Reagents

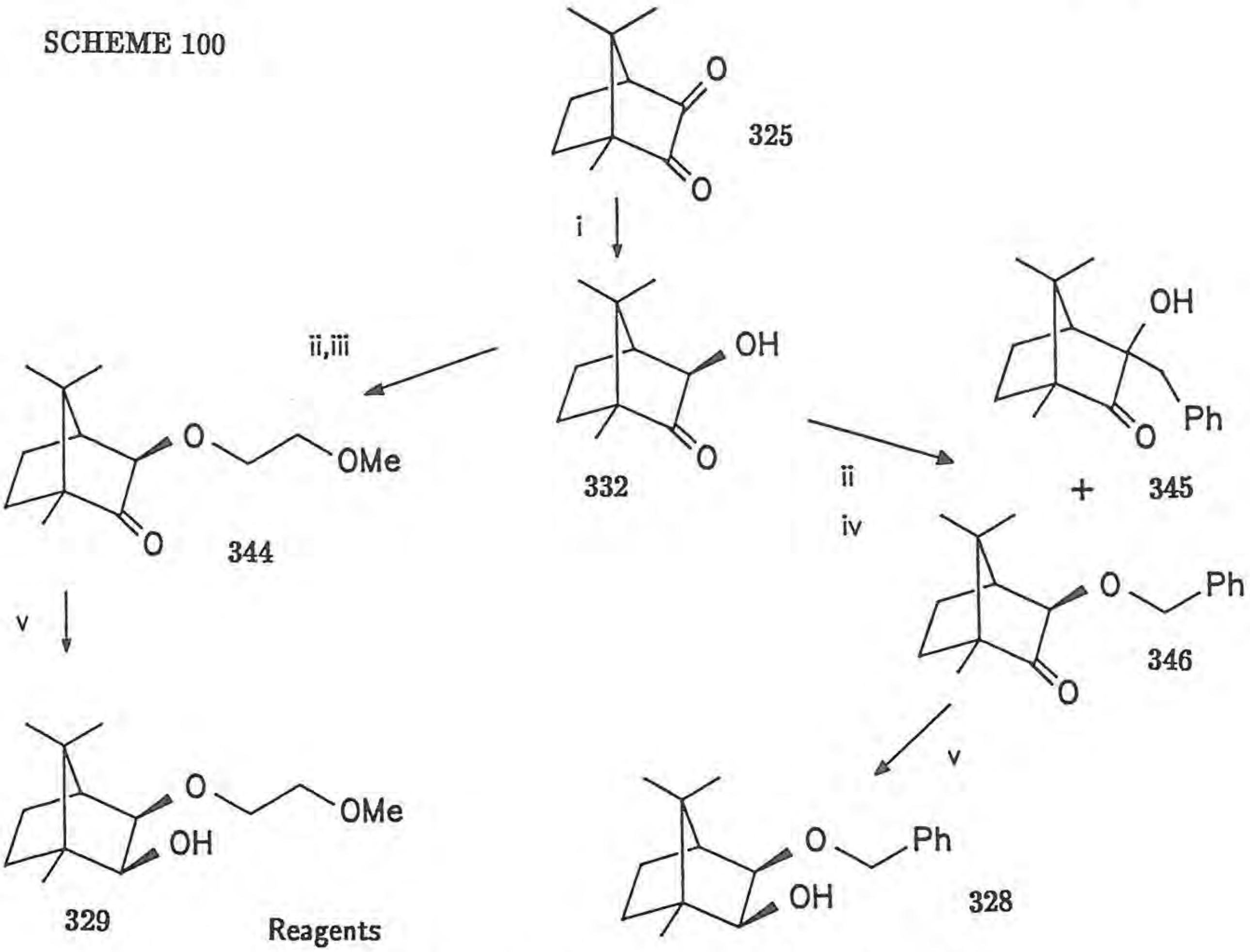
i) LAH, ii) NaH and 1–chloro–2–methoxyethane stereochemical ambiguity is possible. However, the analogous alkylation fails as a viable synthetic route to chiral auxiliaries for identical reasons, *viz.*, the formation of a significant amount of the dialkylated product (**340**) and an inability to separate the monoalkylated products (**341**) and (**342**) (formed in approximately equal amounts) (Scheme 99). Also detected in the reaction mixture (GC–MS) was the cyclic ether (**343**), a compound known to form from the diol (**339**).



343

The crucial reaction in a second approach [279] was the regioselective reduction of camphorquinone. This was successfully achieved *via* Raney nickel catalysed reduction [285] to yield almost exclusively the 3–*exo*–hydroxy camphor (**332**) in good yields (Scheme 100). Alkylation of this compound with both 2–chloro–1–methoxyethane (**335**) and benzyl bromide afforded complex reaction mixtures from which the desired alkylated compounds (**344**) and (**346**) were isolated in moderate yields. In the case of the benzyl bromide alkylation, a second major compound (**345**) in the reaction was also isolated and identified as the product of C–alkylation of the enol form (**347**) of the α–hydroxy ketone (**332**) (Scheme 101). In the case of the 1–chloro–2–methoxyethane alkylation of compound (**332**), a second major component was also formed but was not isolated; this was assumed to be analogous to compound (**345**). In the original description of the preparation of such compounds, Oppolzer *et al.*[279] make no mention of C–alkylation although the reported yield of the desired compound,

SCHEME 100

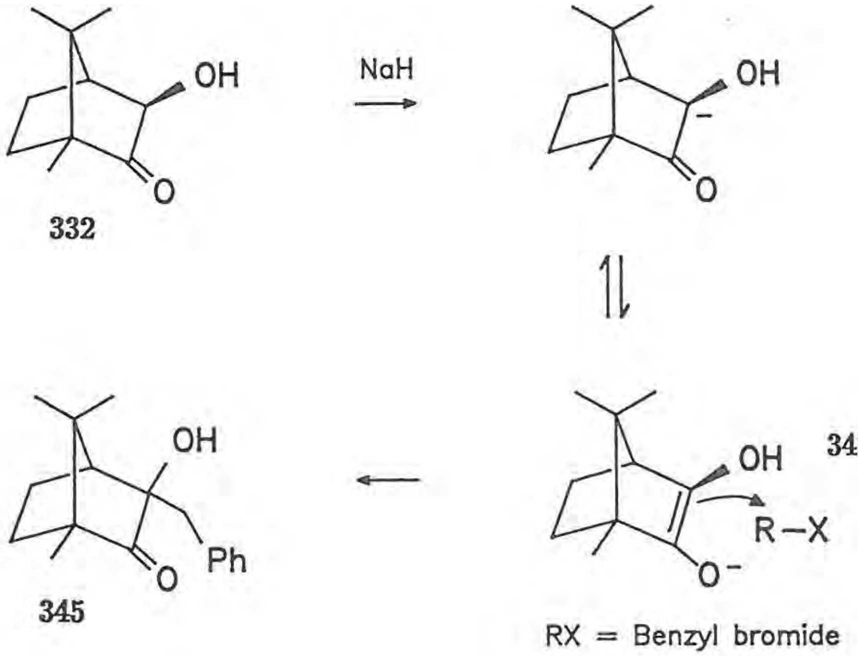


Reagents

i) Raney Ni/H_2, ii) NaH, iii) 1–chloro–2–methoxyethane

iv) Benzyl bromide, v) L–Selectride

SCHEME 101



in the example provided, is below 50%. The stereoselective reductions of the α–alkoxy ketones (**344**) and (**346**) (Scheme 100) to the desired chiral auxiliaries (**329**) and (**328**) were achieved in good yields employing the commercially available reducing agent, L–Selectride.

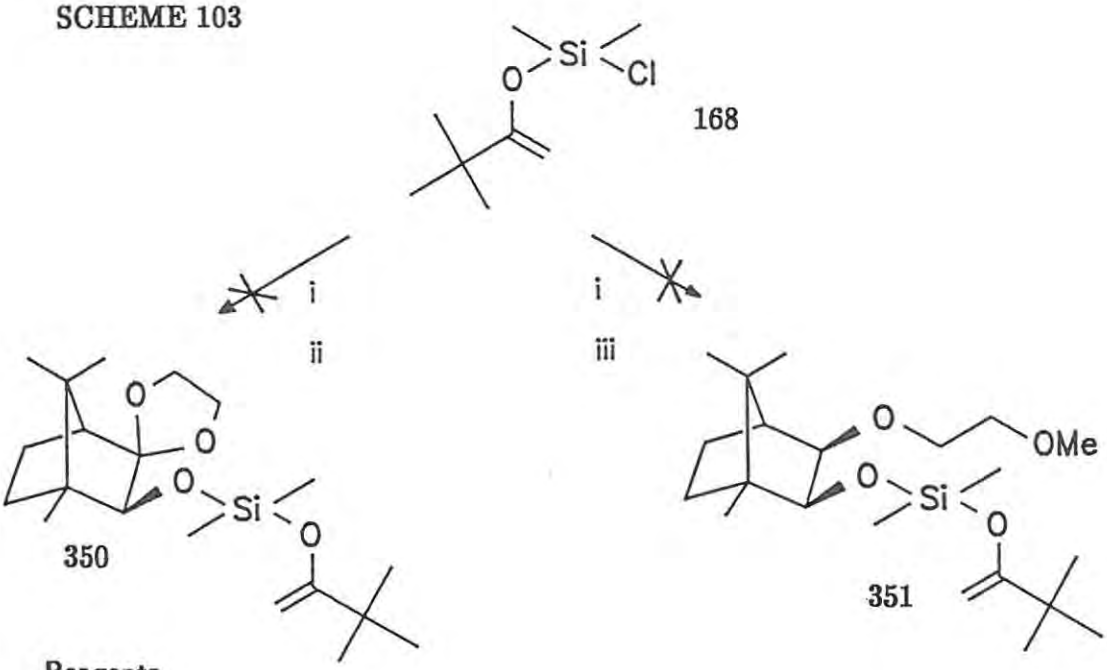
A viable synthesis of two of the selected chiral auxiliaries was thus in hand. The third auxiliary (**330**) was prepared in two steps *via* a third approach previously employed by Oppolzer *et al* [279] (Scheme 102). Selective ketalization of camphorquinone (**325**) [286] and subequent L–Selectride reduction of the monoketal (**348**) afforded the auxiliary (**330**) in adequate overall yield.

2.8 PREPARATION AND REACTION OF SILYL ENOL ETHERS FROM THE CAMPHOR DERIVED AUXILIARIES (328), (329), and (330).

In view of the difficulties in preparing chloro silyl enol ethers such as compound (**349**), it was decided to prepare the readily accessible pinacolone silyl enol ethers (**328**), (**329**), and (**330**).

In the event, the auxiliaries (**329**) and (**330**) failed to react with the chloro silyl enol ether (**168**) (Scheme 103). The obviously reduced reactivity of these alcohols towards chlorosilanes was believed to be primarily due to steric effects which are illustrated in the computer models of the auxiliaries [(**328**)–(**330**)] (Figure 51). The bulky groups proximate to the hydroxyl functionality may impair its ability to react with chlorosilanes. Initial abstraction of the hydroxyl proton from compound (**330**) (Scheme 104) and subsequent reaction of the alkoxide with the chloro silyl enol ether (**186**), employing THF as a solvent, afforded the silyl enol ether (**350**) in moderate yield . However, attempts to prepare the analogous silyl enol ethers from the benzyl (**328**) and methoxyethane (**329**) chiral auxiliaries using the identical method, failed, the starting alcohols being recovered. This result provides further evidence for the involvement of steric effects in impairing the reactions of these auxiliaries with chlorosilanes; only the auxiliary (**330**), with the least bulky co–ordinating, group reacts under the harsher conditions of the NaH reactions. In an

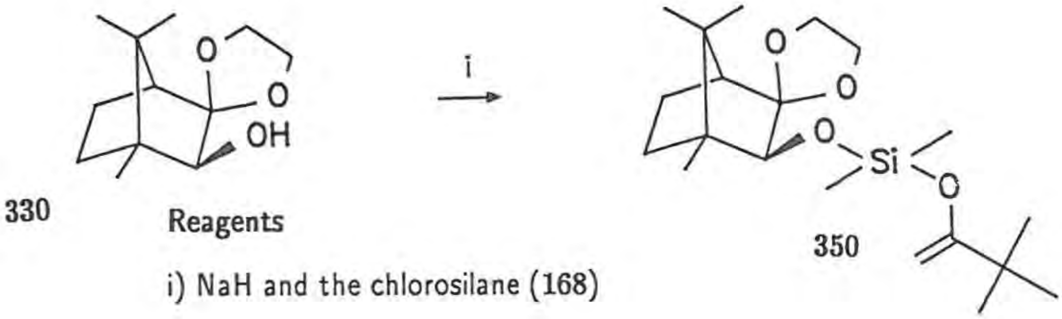
SCHEME 103



Reagents

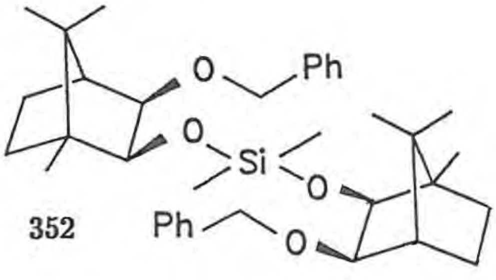
i) Et_3N, ii) Alcohol (**330**), iii) Alcohol (**329**)

SCHEME 104



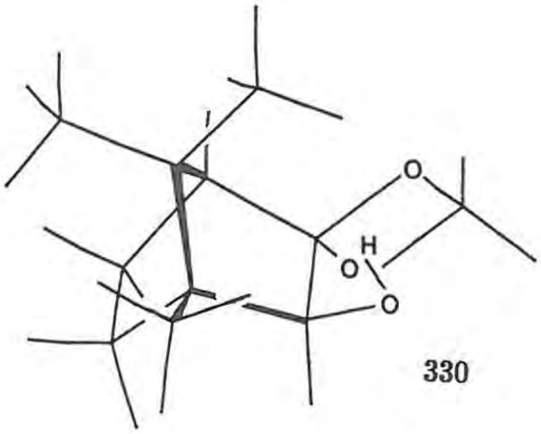
Reagents

i) NaH and the chlorosilane (**168**)



352

FIGURE 51 Computer models of the chiral auxiliaries [(**328**) – (**330**)], indicating the close proximity of the bulky co–ordinating groups to the hydroxyl functionality.



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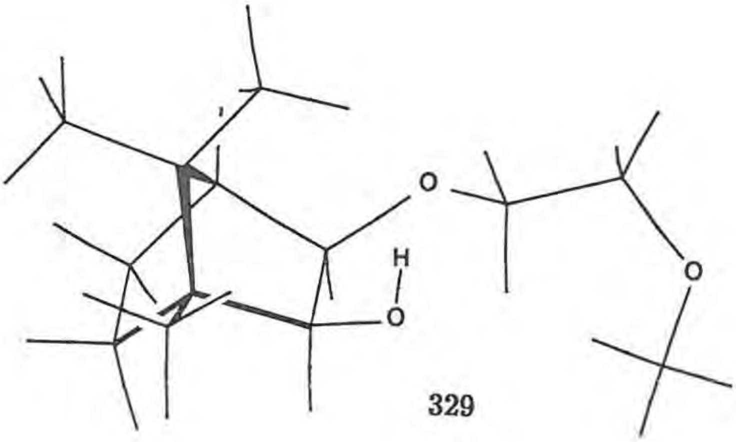

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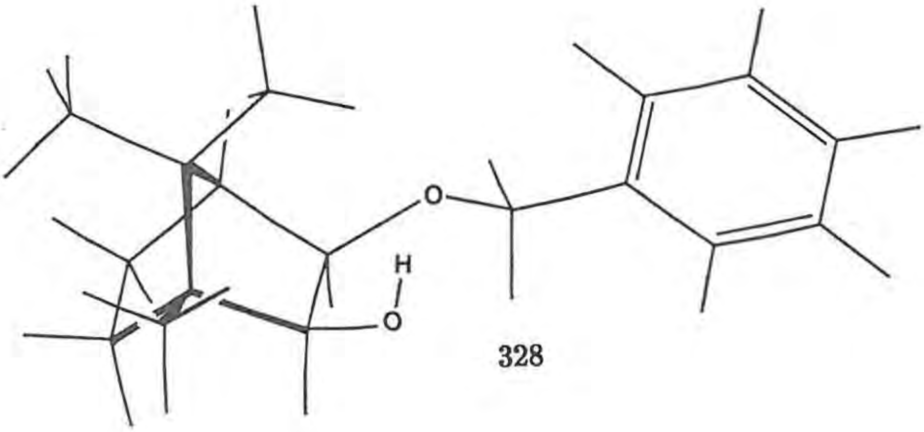
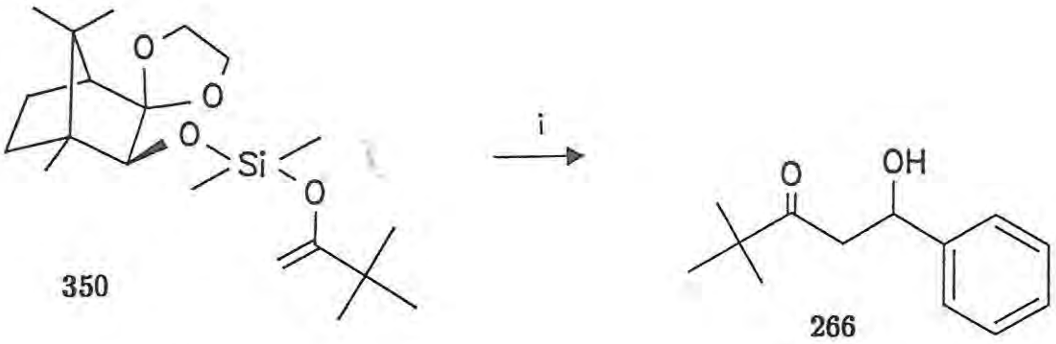


328

alternative approach, proton abstraction from the benzyl auxiliary (**328**) was attempted in DMF; subsequent addition of the chloro silyl enol ether (**168**) afforded a complex reaction mixture. The major isolated product appeared to be the *bis*–substituted siloxy compound (**352**) and no conclusive evidence for the formation of the desired silyl enol ether was found.

The chiral silyl enol ether (**350**) was reacted with benzaldehyde and $TiCl_4$ to yield the β–hydroxy ketone (**266**) (Scheme 105) in good yields.

SCHEME 105



350

266

Reagents

i) $TiCl_4$ and PhCHO

Two independent chiral shift reagent experiments and subsequent digitisation of the resolved *tert*–butyl singlets (Figure 52) indicated an enantiomeric excess of **26%**. This represents a significant improvement on the enantiomeric excess obtained in earlier hydroxy alkylations; the previous best being 14% (see Table 15, p. 189). This improvement may be attributed to the enhanced co–ordination capabilities of the auxiliary, where close co–ordination sites are provided by the ketal oxygens (see p. 218). In a proposed transition state complex co–ordination of one or both ketal oxygens with titanium locates the Lewis acid–aldehyde complex in a "channel" between parallel ketal and silyl enol ether moieties (Figure 53). In the case of benzaldehyde, the steric bulk of

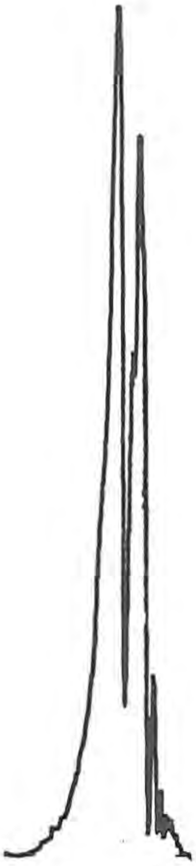


FIGURE 52

Optimum resolution of the enantiomeric *tert*–butyl singlets obtained on the addition of $Pr(tfc)_3$ to a CCl_4 solution of the *β*–hydroxy ketone (**266**), isolated from the hydroxyalkylation of the silyl enol ether (**350**).

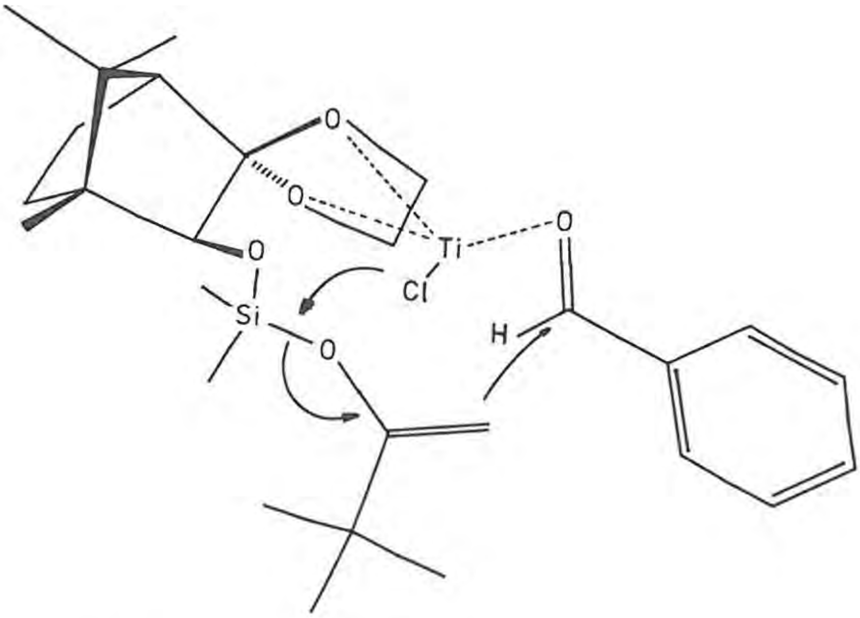


FIGURE 53 A representation of the proposed transition state complex responsible for improved stereocontrol in the hydroxyalkylations of pinacolone–derived silyl enol ethers.

the bicyclic auxiliary then dictates preferential entry with the aldehyde proton leading and the phenyl group trailing, thus accounting for the observed stereocontrol. A detailed investigation of the stereochemical implications of this transition state model will be the subject of future research.

This result indicated that 2,3–disubstituted bornane auxiliaries had the potential to improve the asymmetric induction in hydroxyalkylation reactions of chiral silyl enol ethers. It was on this encouraging note that the present investigation was concluded.

2.9 CONCLUSIONS.

This investigation is one of the first attempts to achieve asymmetric induction using alkoxy silanes as chiral auxiliaries and represents the most detailed work, to date, on employing such chiral auxiliaries in the asymmetric reactions of silyl enol ethers. This research, which has already led to several publications, involved:–

i) development of a more general route to the synthesis of chiral silyl enol ethers;[208]

ii) detailed spectroscopic and crystallographic [221] analyses of the novel chiral silyl enol ethers;

iii) demonstrating the potential of menthyloxy and bornyloxy chlorosilanes as chiral probes for the GLC and NMR analysis of enantiomers;[232]

iv) exploring peracid oxidation[240], alkylation, and hydroxyalkylation[241] reactions of chiral silyl enol ethers;

v) the synthesis and use of chiral auxiliaries with enhanced co–ordination capabilities to improve stereocontrol.

It would thus appear that chiral silyl enol ethers are potentially useful substrates for asymmetric induction. To fully realize this potential, future research must involve further development, introduction, and evaluation of efficient chiral auxiliaries.

3. EXPERIMENTAL

3.1 General.

Melting points were measured on a Kofler hot–stage apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 180 spectrophotometer, as liquid films or KBr discs. NMR spectra were recorded on the following instruments; Perkin–Elmer R12 A, Bruker AM 300, Bruker WM500, or a Varian Gemini 200 MHz. When no signal multiplicities are quoted for ^{13}C spectra, then DEPT 135 spectra were obtained in place of the off resonance decoupled spectra. Calculated ^{13}C chemical shifts were obtained using standard correlation tables.[287] The ^{1}H NMR spectra of all the dimethyl silyl compounds prepared were recorded in CCl_4 without TMS as an internal standard. All other spectra were recorded in $CDCl_3$ with TMS as internal standard, unless otherwise stated. Low resolution mass spectra were recorded on a Hewlett Packard 5988A mass spectrometer. High resolution mass spectra were obtained on a Varian Mat 212 spectrometer. Optical rotations were conducted on a Perkin–Elmer 141 polarimeter.

The atom numbering used in quoting the NMR data follows the systematic nomenclature. For all compounds incorporating the menthyloxy or bornyloxy group the "dashed" notation (e.g $4'$–H_{exo} or $10'$–Me) is used for the labelling of protons and carbons in the chiral auxiliary moieties to facilitate comparison of signals for the variety of compounds prepared.

GLC analyses were conducted on a Hewlett Packard 5980A gas chromatograph using N_2 as carrier gas and flame ionisation detection, with hydrogen and synthetic air as feeder gases. Fused silica columns were always used. The stationary phase for each application, as well as the specific chromatographic conditions, are described in the text. GC–MS analyses were conducted by linking the same model GLC, as described above, to the Hewlett Packard 5988A spectrometer. Preparative GC separations were achieved using a Perkin–Elmer 900 gas chromatograph with accompanying additional instrumentation to enable sample collection. A variety of glass–walled columns, packed as required, with the desired stationary phase on Chromosorb W solid supports were used for these separations. HPLC analyses, when attempted, were carried out using a Hewlett Packard 1050 pump and a Perkin–Elmer LC 155 UV detector. Flash chromatography [288] was achieved using Silica gel 60 [particle size 0.040–0.063 mm (230–400 mesh)]. (Merck) TLC analyses were carried out on Silica gel 60 F_{254} precoated plates (Merck).

Reactions at elevated pressures were conducted in a Berghof Laboratory High Pressure Autoclave.

All chiral auxiliaries and other optically pure compounds were ultimately derived from one of the following, commercially available, homochiral molecules; (the common name of each molecule is used throughout to facilitate quick recognition):

i) (1*S*)–(–)–borneol
ii) (1*R*)–(+)–camphor
iii) (1*R*,3*S*)–(+)–camphoric acid
iv) (–)–cholesterol
v) (1*R*,2*S*,5*R*)–(–)–menthol
vi) (*S*)–(–)–proline

Anhydrous solvents were obtained as follows:

(i) Et_2O, THF, benzene, toluene, and hexane were dried by refluxing over sodium wire, in the presence of benzophenone.

(ii) CH_2Cl_2 was refluxed over polymer–supported P_2O_5, fractionally distilled, and stored over 3A molecular sieves.

(iii) DMF was refluxed over 4A molecular sieves, distilled under reduced pressure, and stored over 4A molecular sieves.

(iv) EtOH and MeOH were refluxed over $Et(OMg)_2$ and $Me(OMg)_2$ respectively.

(v) Et_3N was dried in the same manner as DMF.

All transfers of the chiral shift reagents $Eu(tfc)_3$ and $Pr(tfc)_3$ were done under an inert atmosphere and all weighings of these reagents were carried out in sealed containers. Inert atmospheres were achieved with spectroscopic grade argon or nitrogen.

The computer modelling was conducted on an CW16 AT microcomputer, using "Alchemy II, Molecular Modelling Software" supplied by Tripos Assosciates and the resulting hard copies were recorded on a Hewlett Packard Color Pro plotter.

Digitisation was achieved using a Summagraphics Digitising Table and the data was processed on the same micrcomputer as described above.

3.2 Reaction of cyclohexanone with LDA, Cl_2SiMe_2, and menthol via Walkup's "one pot" synthesis.

A solution of cyclohexanone (4.05 g, 41 mmol) in Et_2O (15 ml) was added in an inert atmosphere at –78° C to a solution of lithium diisopropylamide (LDA) (44 mmol) [prepared from diisopropylamine (4.40 g, 44 mmol) and 1.5 M BuLi (29.3 ml, 44 mmol) at –78° C] in Et_2O (100 ml). After 30 min, Cl_2SiMe_2 (5.42 g, 42 mmol) was added and the reaction mixture then allowed to warm to room temperature over 5 h. Et_3N (4.4 g, 40 mmol) and then a solution of (–)–menthol (6.24 g, 40 mmol) in Et_2O (15 ml) were added to the cooled (0° C) mixture which was then stirred overnight at room temperature before being poured into cold, saturated, aq. $NaHCO_3$. The resulting mixture was extracted with Et_2O, and the organic layer dried ($MgSO_4$) and concentrated in *vacuo*. Fractional distillation of the residual oil afforded 2 fractions, *viz.* *bis*(cyclohex–1–en–2–yloxy)dimethylsilane **(174)** [289] (3.5 g, 33%), b.p. 94–96° C / 0.4 mmHg[a]; ν_{max} (liquid film) 1650 (C ═C —O), and 1250 cm^{-1} (Si —Me); δ_H (500 MHz; $CDCl_3$) 0.20 (6H, s, SiMe), 1.49 and 1.64 (8H, 2 x m, 2 x 4–$CH_2$and 2 x 5–CH_2), 2.00 (8H, m, 2 x 3–CH_2 and 2 x 6–CH_2), and 4.97 (2H, m, 2 x 2–H); δ_C (125 MHz; $CDCl_3$) –2.13 (q, SiMe), 22.27 (t), 23.12 (t), 23.78 (t), 29.57 (t) (cyclohexene carbons), 104.86 (d, C–2), and 149.50 (s,C–1–); m/z 252(M^+, 30%), 155(33%), and 75(100) (Found: M^+ 252.1550. Calc. for $C_{14}H_{24}O_2Si$, M^+, 252.1546);

and

bis(menthyloxy)dimethylsilane **(173)** (3.40 g, 22%), b.p. 130–134° C / 0.4 mmHg (lit.[290] 157–158° C / 2.5 mmHg); ν_{max} (liquid film) 1250 (Si — Me) and

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[a] The preparation of compound **(174)** is mentioned by Fataftah [289] but no physical data are provided.

1065 cm^{-1} [Si —O (O)]; δ_H (500 MHz; $CDCl_3$)[b] 0.10 (6H, d, SiMe), 0.72 (6H, d, 9′–Me), 0.82 (2H, qd, 4′–H_{ax}), 0.88 (12H, d, 8′–Me and 10′–Me), 0.93 (2H, qd, 3′–H_{ax}), 1.02 (2H, q, 6′–H_{ax}), 1.14 (2H, m, 2′–H), 1.35 (2H, m, 5′–H), 1.54–1.67 (4H, m, 3′–H_{eq} and 4′–H_{eq}), 1.94 (2H, m, 6′–H_{eq}) 2.17 (2H, m, 7′–H) and 3.50 (2H, dt, 1′–H); δ_C(125 MHz, $CDCl_3$) –1.29 (q, SiMe), 15.91 (q, C–9′), 21.25 (q, C–8′), 22.24, (q, C–10′), 22.93 (t, C–3′), 25.25 (d, C–7′), 31.73 (d, C–5′), 34.56 (t, C–4′), 45.47 (t, C–6′), 49.97 (d, C–2′), and 72.39 (d, C–1′); m/z 368(M^+, 6%), 283(36) and 75 (100) (Found : M^+ 368.3111. Calc. for $C_{22}H_{44}O_2Si$, M^+, 368.3114).

3.3 Preparation of chloro(menthyloxy)dimethylsilane (176) and (bornyloxy)chlorodimethylsilane (179).

These reactions were conducted under anhydrous conditions, in an inert atmosphere, using pre–dried reagents and solvents. The filtration of the reaction mixtures and any transfers of the products were also effected in an inert atmosphere. These reactive chlorosilanes could be isolated and stored for at least several weeks under an argon atmosphere. They were characterized spectroscopically, but, due to their reactive nature no elemental analyses were attempted.

3.3.1 *Chloro(menthyloxy)dimethyl silane* (176)

A solution of (–)–menthol (18.70 g, 0.12 mol) in Et_2O (35 ml) was added slowly to a stirred solution of Cl_2SiMe_2 (15.00 g, 0.12 mol) and Et_3N (18.0 ml,

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[b] Throughout this thesis the menthyloxy (and bornyloxy) carbons and protons will be numbered 1′–10′ to distinguish them from the carbons and protons of the second substituent on the silicon (see Sections 3.3.1 and 3.3.6 for examples of this numbering). The silyl methyl group will always be designated SiMe.

0.18 mol) in Et_20 (150 mml). The thick slurry which resulted from the exothermic reaction was stirred overnight and then filtered. Removal of the solvent from the filtrate by distillation at atmospheric pressure, followed by vacumn distillation of the residue afforded chloro(menthyloxy)dimethylsilane **(176)**, (19.00 g, 65%), b.p. 86°C / 2 mmHg (lit.[290] 95.5–96°C / 4mmHg); ν_{max} (liquid film) 1240 (Si— Me) and 1045 cm^{-1} [Si —O (C)]); δ_H (60 MHz; CCl_4) 0.31 (6H, s, SiMe), 0.61 – 0.85 (9H, m, 8′,–9′,and 10′–Me), 0.85 – 2.1 (9H, m, menthyl CH_2 and CH), and 3.65 (1H, br m, 1′–H); *m/z* 248 (M^+, ^{35}Cl, 0,2%), 165(38), 163(100), 139(31) and 95(55).

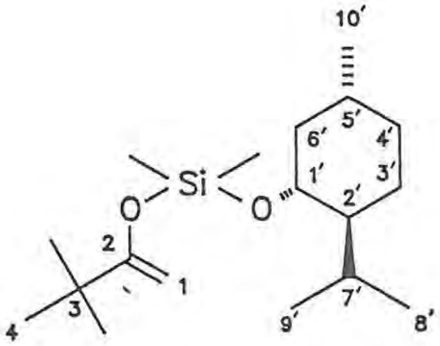
3.3.2 *(Bornyloxy)chlorodimethylsilane* (179)

A solution of (–)–borneol **(178)** (6.6 g, 43 mmol) in Et_2O (20 ml) was added slowly to a stirred solution of Cl_2SiMe_2 (5.50 g, 43 mmol) and Et_3N (8.9 ml, 65 mmol) in Et_20 (100 mml). The thick slurry which resulted from the exothermic reaction was stirred overnight and then filtered. Removal of the solvent from the filtrate by distillation at atmospheric pressure, followed by vacumn distillation of the residue afforded *(bornyloxy)chlorodimethylsilane* **(179)** (6.60 g, 63%), b.p. 63°C / 0.7 mmHg; ν_{max} (liquid film) 1255 (Si — Me) and 1070 cm^{-1} [Si—O (C)]; δ_H (60 MHz; CCl_4) 0.44 (6H, s, SiMe), 0.82 and 0.90 (9H, 2 x s, 8′,–9′,and 10′–Me), 1.00 to 2.5 (8H, m, bornyl CH_2 and CH) and 4.05 (1H, br d, 1′–11); *m/z* 246 (M^+), 137(6), and 95(100).

3.4 Preparation of chiral silyl enol ethers (164), (172), (180), (181), (182), (183), (184), (185), (186), and (194).

All these preparations were conducted under anhydrous conditions in an inert atmosphere, using pre–dried reagents and solvents. GLC analyses on these compounds were conducted using the general conditions described earlier and, using a DB225 fused silica capillary column with a temperature programme of 100 – 200° C at 10° C/min. Except for the two crystalline silyl enol ethers (**164**) and (**194**), isolation of analytically pure products proved impossible. Thus, after verifying the purity of the products by GLC, elemental analyses were obtained by high resolution MS on either the molecular ion peak or, in instances where the intensity of that peak was too low, on the closest unambiguous fragmentation peak, (usually $M^+ - 15$). [Even for the crystalline products (**164**) and (**194**) the percentage carbon analysis could not be obtained closer than 0.55% of the calculated value.] ^{1}H and ^{13}C NMR signals were assigned with the aid of two dimensional spectra (HETCOR and COSY) and using published chemical shift values for menthol, borneol, and cholestrol.[226–231] The coupling patterns in the ^{1}H NMR spectra of menthol and borneol are complex and specialised techniques are required to establish the magnitude of the coupling constants.[226,228] (see section 2.1.2, p. 112). The coupling pattern for the protons bonded to the ring carbons of the menthyl and bornyl groups, in the silyl enol ethers, are equally complex and the coupling constants have not been established. Couplings which can be unambiguously assigned are included.

3.4.1 *(Menthyloxy)dimethyl(3,3–dimethylbut–1–en–2–yloxy)silane* (164)



Method A (Convergent synthesis) [208]

A solution of pinacolone (1.00 g, 10 mmol) in Et_2O (10 ml) was added to a stirred solution of LDA (11 mmol) in Et_2O (40 ml) at –78° C. After 1 h, during which time the temperature of the solution rose to *ca* –50° C, a solution of chloro(menthyloxy)dimethylsilane (**176**) (3.00 g, 12 mmol) in Et_2O (15 ml) was added dropwise. The resulting mixture was allowed to warm to room temperature overnight, then poured into saturated aq. $NaHCO_3$, and the resulting mixture extracted with Et_2O. The dried ($MgSO_4$) extract was concentrated and the residual oil solidified upon standing overnight at 10° C. The solid material was recrystallized from hot anhydrous acetone to yield menthyloxydimethyl(3,3–dimethylbut–1–en–2–yloxy)silane (**164**) (2.20 g, 70%), m.p. 36° C[c] (Found: C, 68.7; H, 11.7. Calc. for $C_{18}H_{36}O_2Si$: C, 69.2; H, 11.5%); $[\alpha]_D^{25}$ –41.5° (*c* 2.4 in Et_2O); ν_{max} (KBr) 1623 (C ═C), 1250 (Si — Me), and 1065 cm^{-1} [Si —O (C)]; δ_H(500 MHz; $CDCl_3$) 0.18 and 0.19 (6 H, 2 x s, SiMe), 0.73 (3H, s, 9′–Me), 0.82 (1H, qd, 4′–H_{ax}), 0.87 (3H, d, 10′–Me), 0.88 (3H, d, 8′–Me), 0.94 (1H, qd, 3′–H_{ax}), 1.05 (10H, 1 x s, 4–Me, and 1 x m, and 6′–H_{ax}), 1.17 (1H, tt, 2′–H), 1.37 (1H, m, 5′–H), 1.59 (1H, m, 3′–H_{eq}), 1.62, (1H, m, 4′–H_{eq}), 1.99 (1H, m, 6′–H_{eq}), 2.18 (1H, m, 7′–H), 3.59 (1H, m, 1′–H), and 4.04 and 4.10 (2H, 2 x s, 1–CH_2); δ_C(125 MHz; $CDCl_3$) –2.06 and –1.75 (2 x q, C–11 and C–12), 16.01 (q, C–9), 21.23 (q, C–8), 22.27 (q, C–10), 23.07 (t, C–3), 25.38 (d, C–7), 28.08 (q, C–16), 31.75 (d, C–5), 34.59 (t, C–4), 36.41 (s, C–15), 45.17 (t, C–6), 49.95 (d, C–2), 72.94 (d, C–1), 86.61 (t, C–14), and 166.20 (s, C–13); *m/z* 312(M^+,7%), 227(8), 175(36), 157(8), and 75(100).

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[c] Walkup *et al.*[206] prepared this compound but did not quote any physical data.

Method B (Walkup's "one pot" synthesis)[206]

A solution of pinacolone (4.12 g, 41 mmol) in Et_2O (15 ml) was added to a stirred solution of LDA (44 mmol) in Et_2O (100 ml) at –78° C. The resulting solution was stirred at this temperature for 30 min after which Cl_2SiMe_2 (5.41 g, 42 mmol) was added and the reaction mixture was then allowed to warm to room temperature over 5 h. After cooling the reaction mixture to 0° C, Et_3N (4.40 g, 43 mmol) and a solution of (–)–menthol (6.24 g, 40 mmol) in Et_2O (15 ml) were added. The reaction mixture was stirred overnight at room temperature and then worked up as described in Method A. The residual oil was distilled to yield dimenthyloxydimethyl(3,3–dimethylbut–1–en–2–yloxy)-silane (**164**) as a colourless oil which crystallized on standing (4.97 g, 38%), b.p. 86–88° C /0.4 mmHg, (m.p. 36° C.)

3.4.2 *(Cyclohex–1–en–1–yloxy)(menthyloxy)dimethylsilane* (172) *via Method A.*

Cyclohexanone (0.99 g, 10 mmol), LDA (11 mmol) and chloro(menthyloxy)dimethylsilane (**176**) (3.00 g, 12 mmol) were reacted according to Method A as described previously for compound (**164**). Distillation of the residual oil yielded *(cyclohex–1–en–1–yloxy)(menthyloxy)-dimethylsilane* (**172**) as a colourless oil (2.40 g, 77%), b.p. 106–108° C /0.3 mmHg; $[\alpha]_D^{25}$ –38.9° (*c* 1,5 in $CHCl_3$); ν_{max} (liquid film) 1670 (C ═C), 1255 (Si — Me), and 1080 cm^{-1} [Si — O (C)]; δ_H(500 MHz; $CDCl_3$) 0.16 (6H, s, SiMe), 0.73 (3H, d, 9′–Me), 0.81 (1H, qd, 4′–H_{ax}), 0.87 (6H, d, 10′–Me and 8′–Me), 0.93 (1H, qd, 3′–H_{ax}), 1.03 (1H, dd, 6′–H_{ax}), 1.15 (1H, m, 2′–H), 1.36 (1H, m, 5′–H), 1.49 (2H, m, 5–CH_2), 1.57 (1H, m, 3′–H_{eq}), 1.61 (1H, m, 4′–H_{eq}), 1.64 (2H, m, 4–CH_2), 1.95 (1H, m, 6′–H_{eq}), 1.99 (4H, m, 3 and 6–CH_2), 2.16 (1H, m, 7′–H), 3.55 (1H, m, 1′–H), and 4.91 (1H, m, 2–H); δ_C(125 MHz; $CDCl_3$) –1.62 and –1.37 (2 x q, SiMe), 15.93 (q, C–9′), 21.20 (q, C–8′), 22.25 (q, C–10′), 22.32 (t, C–5,), 22.98 (t, C–4), 23.16 (t, C–3′), 23.81 (t, C–2), 25.33 (d, C–7′), 29.76 (t, C–6), 31.72 (d, C–5′), 34.55 (t, C–4′), 45.21 (t, C–6′), 49.90 (d, C–2′), 72.80 (d, C–1′), 104.45 (d, C–2), and 149.67 (s, C–1)[d]; *m/z* 310(M^+,15%), 227(16), 173(100), 155(27), and 75(65) (Found: M^+, 310.2361. $C_{18}H_{34}O_2Si$ requires M^+, 310.2328).

3.4.3 *(Menthyloxy)dimethyl(1–phenylethen–1–yloxy)silane* (180) *via* *Method A.*

Acetophenone (1.20 g, 10 mmol), LDA (11 mmol) and chloro(menthyloxy)dimethyl silane (**176**) (3.0 g, 12 mmol) were reacted according to Method A, as described for compound (**164**). After work–up, flash chromatography [hexane – EtOAc (99:1)] of the reaction mixture (shown by GLC and ^{1}H NMR analysis to comprise a 5:1 mixture) yielded the desired chiral silyl enol ether (**180**) and the *bis*(menthyloxy)silane (**173**), as a pale yellow oil (2.7 g). Fractional distillation of this oil yielded a fraction containing *ca.* 90% of the desired compound (**180**) (2.1 g, *ca.* 55%), b.p. 134–136°C /0.25 mmHg. Preparative gas chromatography (5% OV–17 on Chromosorb W) or further flash chromatography (using the same eluant as above) of this fraction afforded *(menthyloxy)dimethyl(1–phenylethen–1–yloxy)silane* (**180**). $[\alpha]_D^{25}$ –41.0° (0.6 in $CHCl_3$); ν_{max} (liquid film) 1620 (C ═C), 1255 (Si — Me), and 1065 cm^{-1} [Si —O (C)]; δ_H(500 MHz; $CDCl_3$) 0.32 and 0.33 (6H, 2 x s, SiMe), 0.73 (3H, d, 9′–Me), 0.90 (1H, m, 4′–H_{ax}), 0.93 (3H, d, 10′–Me), 0.96, (3H, d, 8′–Me), 0.99 (1H, qd, 3′–H_{ax}), 1.14 (1H, dd, 6′–H_{ax}), 1.26 (1H, m, 2′–H), 1.40 (1H, m, 5′–H), 1.65 (1H, m, 3′–H_{eq}), 1.68

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[d] The assignments of 4–CH_2 and 5–CH_2 as well as the C–3, C–4, C–5, and C–6 assignments may be interchanged.

(1H, m, 4′–H_{eq}), 2.06 (1H, m, 6′–H_{eq}), 2.27 (1H, m, 7′–H), 3.70 (1H, m, 1′–H), 4.62 and 4.98 (2H, 2 x d, $J_{2a\text{-}2b}$ 1.7 Hz, 2–CH_2), 7.35 (3H, m, ArH), and 7.65 (2H, m, ArH); δ_C(125 MHz; $CDCl_3$) –2.00 and –1.76 (2 x q, SiMe), 15.98 (q, C–9′), 21.19 (q, C–8′), 22.20 (q, C–10′), 23.01 (t, C–3′), 25.41 (d, C–7′), 31.68 (d, C–5′), 34.51 (t, C–4′), 45.15 (t, C–6′), 49.92 (d, C–2′), 73.15 (d, C–1′), 91.60 (t, C–2), 125.18, 127.98 and 128.12 (3 x d, 3 x ArC), 137.40, (s, ArC), and 154.99 (s, C–1); *m/z* 332(M^+, 8%), 227(26), 195(73), 177(40), and 75 (100); (Found: M^+, 332.2172. $C_{20}H_{32}O_2Si$ requires M^+ 332.2181).

3.4.4 *(2$\underline{H}$–1–benzopyran–4–yloxy)(menthyloxy)dimethylsilane* (181) *via Method A.*

Chroman–4–one (3.36 g, 23 mmol), LDA (25 mmol) and chloro(menthyloxy)dimethylsilane (**176**) (6.45 g, 26 mmol) were reacted according to Method A, as described for compound (**164**). (All solvent volumes were doubled to accomodate the larger scale reaction). Flash chromatography [hexane – EtOAc (97:3)] of the reaction mixture, followed by fractional distillation yielded *(2H–1–benzopyran–4–yloxy)(menthyloxy)dimethylsilane* (**181**) (4.05 g, 51%[e]), b.p. 145–150°C (0.09 mmHg); $[\alpha]_D^{25}$ –33.8° (c 1.5 in $CHCl_3$); ν_{max} (liquid film) 1650 (C$=$C), 1260 (Si — Me), and 1065 cm^{-1} [Si —O (C)]; δ_H (500 MHz; $CDCl_3$) 0.26 & 0.27 (6H, 2 x s, SiMe), 0.73 (3H, d, 9′–Me), 0.81 (1H, m, 4′–H_{ax}), 0.86 (3H, d, 10′–Me), 0.89 (3H, d, 8′–Me), 0.93 (1H, m, 3′–H_{ax}), 1.06 (1H, dd, 6–H'_{ax}), 1.18 (1H, m, 2′–H), 1.36 (1H, m, 5′–H), 1.59 (1H, m, 3′–H_{eq}), 1.62 (1H, m, 4′–H_{eq}), 1.97 (1H, m, 6′–H_{eq}), 2.16 (1H, m, 7′–H), 3.62 (1H, td, 1′–H), 4.83 (2H, d, $J_{2\text{-}3}$ 4 Hz, 2–CH_2), 5.00 (1H, t, $J_{3\text{-}2}$ 4 Hz, 3–H), 6.75 – 7.88 (4H, m, ArH); δ_C (125 MHz; $CDCl_3$) –2.00

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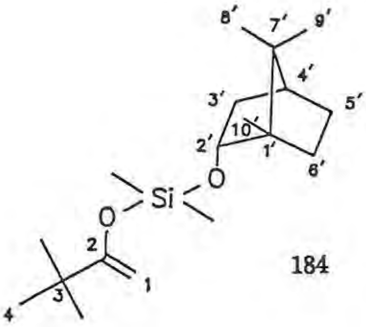
[e] Careful fractionation was necessary to obtain an analytically pure sample. The overall yield was estimated to be 66% by GLC analysis (DB225) of the crude reaction mixture.

and –1.76 (2 x q, SiMe), 15.93 (q, C–9′), 21.16 (q, C–8′), 22.18 (q, C–10′), 22.96 (t, C–3′), 25.42 (d, C–7′), 31.67 (d, C–5′), 34.45 (t, C–4′), 45.16 (t, C–6′), 49.88 (d, C–2), 65.74 (t, C–2), 73.27 (d, C–1′), 98.65 (d, C–3), 115.36 (d, ArC), 120.75 (d, ArC), 121.63 (s, ArC), 122.41 (d, Ar), 129.47 (d, Arom–C), 145.15 (s, C–4), and 165.62 (s, Ar–C6); *m/z* 360(*M*+, 4%), 359(13), 227(35), 223(88), 205(100), and 75(61) (Found: *M*+–H 359.2046 . $C_{21}H_{32}O_3Si$ requires *M*+–H, 359.2042).

3.4.5 *(3,4–Dihydronaphthyl–1–oxy)(menthyloxy)dimethylsilane* (182) *via Method A.*

α–Tetralone (3.07 g, 21 mmol), LDA (22 mmol) and chloro(menthyloxy)dimethyl silane (176) (6.00 g, 24 mmol) were reacted according to Method A, described for compound (164). (All solvent volumes were doubled to accommodate the larger scale reaction.) Flash chromatography of the reaction mixture [hexane – EtOAc (95:5)], followed by fractional distillation yielded *(3,4–dihydronaphthyl–1–oxy)(menthyloxy)dimethylsilane* (182) (6.05 g, 80%), b.p. 132–138°C / 0.04 mmHg); $[\alpha]_D^{25}$ –35.9° (*c* 4.2 in $CHCl_3$); ν_{max} (liquid film) 1640 (C ═C), 1250 (Si — Me), and 1065 cm^{-1} [Si —O (C)]; δ_H (500 MHz; $CDCl_3$) 0.29 & 0.30 (6H, 2 x s, SiMe), 0.78 (3H, d, 9′–Me), 0.87 (1H, m, 4′–H_{ax}), 0.91 (3H, d, 10′–Me), 0.94 (3H, d, 8′–Me), 0.98 (1H, dq, 3′–H_{ax}), 1.11 (1H, dd, 6′–H_{ax}), 1.24 (1H, m, 2′–H), 1.39 (1H, m, 5′–H), 1.64 (1H, m, 3′–H_{eq}), 1.67 (1H, m, 4′–H_{eq}), 2.04 (1H, m, 6′–H_{eq}), 2.25 (1H, m, 7′–H), 2.35 (2H, dt, $J_{3\text{-}2}$ 5 Hz, $J_{3\text{-}4}$ 8 Hz, 3–CH_2), 2.79 (2H, t, $J_{4\text{-}3}$ 8 Hz, 4–CH_2), 3.67 (1H, dt, 1′–H) 5.33 (1H, t, $J_{2\text{-}3}$ 4.6 Hz, 2–H), 7.13 (3H, m, ArH), and 7.49 (1H, d, ArH); δ_C (125 MHz; $CDCl_3$) –1.86 & –1.62 (2 x q, SiMe), 15.97 (q, C–9′), 21.21 (q, C–8′), 22.20 (q, C–10′ and t, C–3), 23.00 (t, C–3′), 25.41 (d, C–7′), 28.13 (t, C–4), 31.69 (d, C–5′), 34.52 (t, C–4′), 45.22 (t, C–6′), 49.93 (d, C–2′), 73.07 (d, C–1′), 105.49 (d, C–2), 121.79 (d, ArC), 126.09 (d, ArC), 126.89 (d, ArC), 127.22 (d, ArC), 133.35 (s, ArC), 136,99 (s, ArC), and 147.49 (s, C–1); *m/z* 358 (M^+,25%), 227(39), 221(100), 203(35), 131(21) and 75(80) (Found : M^+, 358.2337. $C_{22}H_{34}O_2Si$ requires M^+, 358.2328 and M^+–137, 221.0095. $C_{22}H_{34}O_2Si$ requires *M*+–137, 221.0958).

3.4.6 *(Bornyloxy)dimethyl(3,3–dimethylbut–1–en–2–yloxy)silane* (184) *via Method A*



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Pinacolone (1.23g, 12 mmol), LDA (13 mmol) and (bornyloxy)chlorodimethylsilane (**179**) (3.40 g, 14.8 mmol) were reacted according to Method A, as described described for compound (**164**). Distillation of the crude oil yielded, *(bornyloxy)dimethyl(3,3–dimethylbut–1–en–2–yloxy)silane* (**184**) (2.51 g, 65%), b.p. 92° C /0.25 mmHg; $[\alpha]_D^{25}$ –21.3° (*c* 1.9 in $CHCl_3$); ν_{max} (liquid film) 1615 (C ═C), 1260 (Si — Me), and 1070 cm^{-1} [Si —O (C)]; δ_h (500 MHz; $CDCl_3$) 0.164 and 0.167 (6H, 2 x s, SiMe), 0.78 (3H, s, 10′–Me), 0.84 (3H, s, 9′–Me), 0.85 (3H, s, 8′–Me)[f], 1.03 (1H, m, 3′–H_{endo}), 1.05 (9H, s, 3 x 4–Me), 1.15 (1H, m, 6′–H_{exo}), 1.23 (1H, m, 5′–H_{endo}), 1.59 (1H, t, 4′–H), 1.68 (1H, m, 5′–H_{exo}), 2.04 1H, m, 6′–H_{endo}), 2.17 (1H, m, 3′–H_{exo}), 4.07 and 4.10 (2H, 2 x s, 1–CH_2) and 4.10 (1H, m, 2′–H); δ_C (125 MHz; $CDCl_3$) –2.40 & –2.16 (2 x q, SiMe), 13.52 (q, C–10′), 18.81 (q, C–9′), 20.26, (q, C–8′), 26.25 (t, C–6′),

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[f] The 8–Me and 9–Me signals may be interchanged in both the ^1H and ^{13}C NMR spectra.

28.09 (q, C–4), 28.23 (t, C–5′), 36.43 (s, C–3), 39.08 (t, C–3′), 45.31 (d, C–4′), 47.34 (s, C–7′), 49.71 (s, C–1′), 77.52 (d, C–2′), 86.63 (t, C–1), and 166.25 (s, C–2); *m/z* 310(M+, 5%), 282(50), 225(6), 175(9), 185(13), 157(16), and 75(100) (Found: *M*+, 310.2300. $C_{18}H_{34}O_2Si$ requires *M*+ 310.2328).

3.4.7 *(Bornyloxy)(cyclohex–1–en–1–yloxy)dimethylsilane* **(183)** *via Method A.*

Cyclohexanone (1.92 g, 19 mmol), LDA (21 mmol) and (bornyloxy)chlorodimethylsilane **(179)** (5.40 g, 23 mmol) were reacted according to Method A, as described for compound **(164)**. Distillation of the crude oil yielded *(bornyloxy)(cyclohex–1–en–1–yloxy)dimethylsilane* **(183)**, (3.6 g, 60%), b.p. 110–115°C /0.3 mmHg; $[\alpha]_D^{25}$ –22.5° (*c* 1.1 in $CHCl_3$); ν_{max} (liquid film) 1670 (C=C),1255 (Si — Me), and 1065 cm^{-1} [Si —O (C)]; δ_H (500 MHz; $CDCl_3$) 0.18 (6H, s, SiMe), 0.76 (3H, s, 10′–Me), 0.82 (6H, s, 8′–Me and 9′–Me), 0.95 (1H, m, 3′–H_{endo}), 1.11 (1H, m, 6′–H_{exo}), 1.23 (1H, m, 5′–H_{endo}), 1.48 (2H, m, 5–CH_2), 1.55 (1H, t, 4′–H), 1.62 (2H, m, 4–CH_2), 1.67 (1H, m, 5′–H_{exo}), 1.98 (4H, m, 3– and 6–CH_2), 2.13 (1H, m, 6′–H_{endo}), 2.22 (1H, m, 3′–H_{exo}), 3.99 (1H, m, 2′–H), and 4.92 (1H, m, 2–H); δ_C (125 MHz; $CDCl_3$) –2.01 & –1.80 (2 x s, C–SiMe), 13.45 (q, C–10′), 18.76 (q, C–9′), 20.20 (q, C–8)[g], 22.31 (t, C–5), 23.14 (t, C–4), 23.77 (t, C–2), 26.17 (t, C–6′), 28.27 (t, C–5′), 29.72 (t, C–6), 39.06 (t, C–3′), 45.23 (d, C–4′), 47.28 (s, C–7′), 49.66 (s, C–1′), 77.40 (d, C–2′), 104.46 (d, C–2), and 149.67 (s, C–11)[h]; *m/z* 308(*M*+, 9%), 280(50), 225(2), 183(36), 173(9), 123(7), 155(17) and 75(100); (Found: *M*+, 308.2168. $C_{18}H_{32}O_2Si$ requires *M*+, 308.2172).

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[g] The 8–Me and 9–Me signals may be interchanged.

[h] The assignments of 4–CH_2 and 5–CH_2 as well as the C–3, C–4, C–5, and C–6 assignments may be interchanged.

3.4.8 *(Bornyloxy)(3,4–dihydronaphthyl–1–oxy)dimethylsilane* (185) *via Method A.*

α–Tetralone (3.60 g, 26 mmol), LDA (30 mmol) and (bornyloxy)chlorodimethylsilane (179) (6.6 g, 27 mmol) were reacted according to Method A, as described for compound (164). (All solvent volumes were doubled to accommodate the larger scale reaction.) Flash chromatography [hexane – EtOAc (95:5)], of the reaction mixture followed by fractional distillation yielded *(bornyloxy)(3,4–dihydronaphthyl–1–oxy)dimethylsilane* **(185)** (6.40 g, 69%), b.p. 130–134°C /0.06 mmHg; $[\alpha]_D^{20}$ –17.4° (*c* 5.2 in $CHCl_3$); ν_{max} (liquid film) 1640 (C ═C), 1255 (Si — Me), and 1085 cm^{-1} [Si —O (C)]; δ_H (500 MHz; $CDCl_3$) 0.24 (6H, s, SiMe), 0.79 (3H, s, 10′–Me), 0.82 (3H, s, 9′–Me), 0.84 (3H, s, 8′–Me), 1.01 (1H, dd, 3′–H_{endo}), 1.16 (1H, m, 6′–H_{exo}), 1.20 (1H, m, 5′–H_{endo}), 1.58 (1H, t, 4′–H), 1.68 (1H, m, 5′–H_{exo}), 2.05 (1H, m, 6′–H_{endo}), 2.14 (1H, m, 3′–H_{exo}), 2.33 (2H, m, 3–CH_2), 2.76 (2H, t, $J_{3\text{-}4}$ 7.9 Hz, 4–CH_2), 4.13 (1H, m, 2′–H), 5.30 (1H, t, $J_{2\text{-}3}$ 4.7 Hz, 2–H), 7.05 – 7.30 (3H, m, ArH), and 7.43 – 7.46 (1H, m, ArH); δ_C (125 MHz; $CDCl_3$) –1.84 and –1.65 (2 x q, SiMe), 13.49 (q, C–10′), 16.77 (q, C–9′), 20.22 (q, C–8′), 22.18 (t, C–3), 26.22 (t, C–6′), 28.13 (t, C–4), 28.33 (t, C–5′), 39.06 (t, C–3′), 45.26 (d, C–4′), 47.33 (s, C–7′) 49.73 (s, C–1′), 77.65 (d, C–2′), 105.50 (d, C–2), 121.76 (d, ArC), 126.12 (d, ArC), 126.89 (d, ArC), 127.21 (d, ArC), 133.34 (s, ArC), 136.99 (s, ArC), and 147.47 (s, C–1); *m/z* 356 (M^+, 4%), 225(3), 221(41) 203(53), 137(17) 128(38), 95(96), and 75(100)[i].

3.4.9 *(Menthyloxy)dimethyl(pent–2–en–3–yloxy)silane* (186) *via Method* A.

Pentan–3–one (0.86 g, 10 mmol), LDA (11 mmol), and

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[i] A high resolution MS analysis of the *M*⁺ peak could not be obtained for this compound.

chloro(menthyloxy)dimethylsilane (**176**) (3.00 g, 12 mmol) were reacted according to Method A, as described for compound (**164**). Distillation of the material obtained after work–up yielded, a 1:1.55 mixture (as determined by GLC and ^{1}H NMR spectroscopy) of the (*E*)– and (*Z*)– (menthyloxy)dimethyl-(pent–2–en–3–yloxy)silanes, (**186**) (3.5 g, 42%), b.p. 100–103° C /0.25 mmHg; ν_{max} (liquid film) 1680 (C ═C), 1255 (Si — Me), and 1065 cm^{-1} [Si —0 (C)] ; δ_H (500 MHz, CDCl$_3$)[j] 0.15, 0.16, and 0.17 (6H, 3 x s, SiMe), 0.725 and 0.728 (3H, 2 x d, 9′–Me), 0.83 (1H, m, 4′–H$_{ax}$), 0.88 (6H, d, 10′–Me and 8′–Me), 0.92 (1H, m, 3′–H$_{ax}$), 0.98 and 1.01 (3H, 2 x t, 5–Me), 1.03 (1H, m, 6′–H$_{ax}$), 1.15 (1H, m, 2′–H), 1.36 (1H, m, 5′–H), 1.51 (3H, d, 11–Me), 1.58 (1H, m, 3′–H$_{eq}$), 1.62 (1H, m, 4′–H$_{eq}$), 1.97 (1H, m, 6′–H$_{eq}$), 2.05 and 2.07 (2H, 2 x q, 4–CH$_2$), 2.16 (1H, m, 7′–H), 3.57 (1H, m, 1′–H), and 4.48 and 4.66 (1H, 2 x q, 2–H); δ_C (125 MHz, CDCl$_3$) [k] –1.76, –1.50, –1.42, and –1.15 (3 x s, SiMe), 10.62 and 11.59 (2 x q, 5–Me), 11.72 (q, 1–Me), 15.92 and 15.97 (2 x q, C–9′), 21.20 (q, C–8′), 22.24 (q, C–10′), 23.01 (t, C–3′), 24.03 and 29.44 (2 x t, C–4), 25.35 and 25.37 (2 x d, C–7′), 31.73 (d, C–5′), 34.57 (t, C–4′), 45.21 and 45.31 (2 x t, C–6′), 49.96 (d, C–2′), 72.81 (d, C–1′), 100.60 (d, C–2), and 152.31 and 152.61 (s, C–3); *m/z* [l] 298(M$^+$, 8%), 284(11), 227(5), 161(38), 159(35), 143(15), and 75 (100) (Found: *M*$^+$, 298.2321. $C_{17}H_{34}0_2Si$ requires *M*$^+$ 298.2328).

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[j] When the signals for a particular proton or group of protons in the two isomers are clearly separated, then both signals are described.

[k] Whenever the ^{13}C signals are split into isomeric pairs the chemical shifts of both signals are described.

[l] GLC/MS on the isomeric mixture gave almost identical mass spectra for both isomers.

3.4.10 *(Cholesteryloxy)dimethyl(3,3–dimethylbut–1–en–2–yloxy)silane* (194) *via Method B.*

Pinacolone (4.12 g, 41 mmol), dichlorodimethylsilane (5.42 g, 42 mmol), Et$_3$N (4.4 g, 40 mmol) and cholesterol (15.40 g, 40 mmol) were added sequentially to a solution of LDA (44 mmol) as described previously for the synthesis pf compound (**164**). Work–up afforded a pale yellow solid which was flash chromatographed (hexane) to yield *(cholesteryloxy)dimethyl(3,3–dimethylbut–1–en–2–yloxy)silane* (**194**) (13.70 g; 62%), m.p. 77–79°C (Found: C, 77.9; H, 11.8. C$_{35}$H$_{62}$O$_2$Si requires C, 77.35, H, 11.7%); $[\alpha]_D^{25}$ –22.68° (c 1.1 in hexane); ν_{max} (KBr) 1660 (C ═C), 1612 [C ═C (O)], 1250 (Si — Me), and 1100 cm^{-1} [Si —O (C)]; δ_H (500 MHz; CDCl$_3$) 0.18 and 0.19 (6H, 2 x s, SiMe), 0.66 (3H, s, 18–Me), 0.854 and 0.849 (6H, 2 x d, 26–, 27–Me), 0.90 (3H, d, 21–Me), 0.99 (3H, s, 19–Me), 1.05 (9H, s, 3 x 4–Me), 0.80 – 1.65 (20H, m, CH's and CH$_2$'s of C and D rings and aliphatic side chain *i.e.* 8′–H, 9′–H, 11′–H, 12′–H, 14′–H, 15′–H, 16′–H, 17′–H, 20′–H, 22′–H, 23′–H, 24′–H, and 25′–H), 1.80 (3H, m, 1′–H$_{ax}$, 1′–H$_{eq}$ and 2′–H$_{ax}$), 1.98 (3H, m, 2′–H$_{eq}$, 7′–H$_{ax}$, and 7′–H$_{eq}$), 2.28 (2H, m, 4d–H$_{ax}$ and 4′–H$_{eq}$), 3.67 (1H, m, 3′–H), 4.07 and 4.10 (2H, 2 x d, J_{gem} 1.2 Hz, 1–CH$_2$), and 5.29 (1H, m, 6′–H); δ_C (125 MHz; CDCl$_3$) 2.23 (q, SiMe), 12.39 (q, C–18′), 18.76 (q, C–21′), 19.41 (q, C–19′), 21.11 (t, C–11′), 22.59 (q, C–27′), 22.84 (q, C–26′), 23.88 (t, C–23′), 24.33 (t, C–15′), 28.07 (d, C–25 and q,C–4), 28.27 (t, C–16′), 31.73 (t, C–2′), 31.97 (C–7 and d, C–8), 35.82 (d, C–20′), 36.25 (t, C–22′), 36.41 (s, C–3), 36.59 (s, C–10′), 37.40 (t, C–1′), 39.56 (t, C–24′), 39.86 (t, C–12′), 42.38 (t, C–4′, and d, C–13′), 50.23 (d, C–9′), 56.22 (d, C–14′), 56.84 (d, C–17′), 72.60 (d, C–3′), 86.66 (t, C–1), 121.44 (d, C–6′), 141.23 (s, C–5′), and 166.21 (s, C–2); *m/z* 542(M^+,32%), 175(100), 157(6), and 75(60).

3.5 Preparation of the diastereomeric silyl acetals (210), (211), (212), (213), and (214).[232]

All the reactions were carried out under anhydrous conditions in an inert atmosphere, using pre–dried reagents and solvents. Chloro(menthyloxy)-dimethylsilane (**176**) and chloro(bornyloxy)dimethylsilane (**179**) were prepared as described earlier (See section 3.2, p. 237). None of the neat secondary alcohols employed for the preparation of the silyl acetals showed any optical activity.

All of the product acetals were isolated as diastereomeric mixtures. No attempt was made to separate these diastereoisomers, nor were the reactions repeated on optically pure alcohols. Thus, the physical data quoted refers to the diastereomeric mixtures.

When the diastereomers exhibit discrete NMR signals, then the chemical shifts of both signals comprising the pair are quoted in a single signal descriptor and footnotes are used, where necessary, to describe the signals more clearly (see Discussion, p. 130). The signals were assigned with the aid of two dimensional NMR spectra (HETCOR and COSY) of other menthyl and bornyl silyl compounds prepared in this study, (See Section 3.4, p. 239) and of the published chemical shift data of menthol and borneol.[226-231] The high field ^1H and ^{13}C NMR spectra, described in detail in this section, are reproduced in the discussion (p. 131 and 132) or in the Appendix II (p. i – viii).

3.5.1 *(Menthyloxy)dimethyl(1–phenylethoxy)silane* (210)

A solution of chloro(menthyloxy)dimethylsilane (**176**) (2.98 g, 12 mmol) in Et_2O (10 ml) was added dropwise to a stirred solution of *racemic* 1–phenylethanol (0.98 g, 8 mmol) and Et_3N (1.20 g, 12 mmol) in Et_2O (20 ml) at room temperature. The reaction mixture was stirred overnight before being poured into cold, saturated, aq. $NaHCO_3$. The resulting mixture was extracted with Et_2O and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography [elution with hexane–EtOAc (95:5)] gave, as an oil, the diastereomeric mixture, menthyloxydimethyl(1–phenylethoxy)silane (**210**)[m] (1.89 g, 71%); ν_{max} (liquid film) 1260 (Si — Me) and 1065 cm^{-1} [Si — O (C)]; δ_H (500 MHz; $CDCl_3$) 0.05, 0.09, 0.14 and 0.15 (6H, 4 x s, 4 x SiMe)[n], 0.72, 0.76, 0.81, 0.89, 0.90 and 0.905 (9H, 6 x d, 8′–,9′–, and 10′–Me), 0.82 (1H, m, 4′–H_{ax}), 0.92 (1H, m, 3′–H_{ax}), 1.06 (1H, q, 6′–H_{ax}), 1.17 (1H, m, 2′–H), 1.28 and 1.34 (1H, 2 x br m, 5–H), 1.47 and 1.48 (3H, 2 x d, *J* 6.34 and 6.30 Hz respectively, 2–Me), 1.61 (2H, m, 3′–H_{eq} and 4′–H_{eq}), 1.79 and 1.96 (1H, 2 x m, 6′–H_{eq}), 2.17 (1H, m, 7′–H), 3.51 (1H, tq, 1′–H), 5.02 (1H, q, *J* 6.30 Hz, 1–H) and 7.29 (5H, m, ArH); δ_C (125 MHz; $CDCl_3$) –1.85, –1.75, –1.71 and –1.40 (4 x s, SiMe), 15.92 and 15.94 (2 x q, C–9′), 21.16 (q, C–8′), 22.12 and 22.23 (2 x q, C–10′), 23.00 (t, C–3′), 25.34 (d, C–7′), 26.95 (q, C–2), 31.59 and 31.65 (2 x d, C–5′), 34.50 (t, C–4′), 45.23 and 45.37 (2 x t, C–6′), 49.88 (d, C–2′), 70.44 (d, C–1), 72.54 (d, C–1′), 125.30 and 125.36 (2 x d, C–4), 126.80 (d, C–6), 128.08 (d, C–5),[o] and 146.39 (d, C–3); *m/z* 334 (M^+,1%), 319(11), 249(32), 195(90), 77(43) and 75(100) (Found: M^+-CH_3, 319.2099. Calc. for $C_{20}H_{34}O_2Si$, M^+-CH_3, 319.2093.)

3.5.2 *(Bornyloxy)dimethyl(1–phenylethoxy)silane* (211)

A solution of chloro(bornyloxy)dimethylsilane (**179**) (3.80 g, 16 mmol) in Et_2O (10 ml) was added dropwise to a stirred solution of *racemic* 1–phenylethanol

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[m] Analytical data for the diastereomeric silyl acetals (**210**) (reported by Chan *et al.*[218]) have not been described previously.

[n] The four methyl singlets were not assigned to diastereomeric pairs.

[o] The assignments for C–5, and C–4 could be interchanged.

(1.22 g, 10 mmol) and Et_3N (1.00 g, 10 mmol) in Et_2O (20 ml). After stirring overnight, the resulting slurry was poured into cold, saturated, aq. $NaHCO_3$. The resulting mixture was extracted with Et_2O and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography [elution with hexane–EtOAc (98:2)] gave as a diastereomeric mixture, (bornyloxy)dimethyl-(1–phenylethoxy)silane (**211**) (1.90 g, 57%); ν_{max} (liquid film) 1257 (Si —Me) and 1067 cm^{-1} [Si —O (C)]; δ_H(500 MHz; $CDCl_3$) 0.030, 0.032, 0.133 and 0.135 (6H, 4 x s, 4 x SiMe), 0.77 (3H, 2 x s, 10′Me) 0.81 (3H, s, 9′–Me), 0.847 and 0.851 (3H, 2 x s, 8′–Me), 0.90 and 0.99 (1H, 2 x dd, 3–H_{endo}), 1.14 (1H, m, 6–H_{exo}), 1.21 (1H, m, 5–H_{endo}), 1.47 (3H, d, *J* 7 Hz, 2–Me), 1.56 and 1.59 (1H, 2 x t, 4′–H), 1.68 (1H, m, 5′–H_{exo}), 2.03 (1H, m, 6′–H_{endo}), 2.03 and 2.16 (1H, 2 x m, 3′–H_{exo})[p], 4.02 (1H, m, 2′–H), 5.03 (1H, q, *J* 7 Hz, 1–H), and 7.30 (5H, m, ArH); δ_C (125 MHz; $CDCl_3$) –2.11, –1.98, and –1.75 (3 x s, SiMe), 13.34 and 13.47 (2 x q, C–10′), 18.68 (q, C–9′), 20.18 (q, C–8′) 26.13 (t, C–6′), 26.84 (q, C–2), 28.25 and 28.29 (2 x t, C–5′), 39.13 and 39.18 (2 x t, C–3′), 45.18 and 45.22 (2 x d, C–4′), 47.24 (s, C–7′), 49.60 (s, C–1′), 70.19 (d, C–1), 76.95 (d, C–2′), 125.24 (d, C–4), 126.70 (d, C–6), 128.03 (d, C–5)[q], and 146.33 (s, C–15); *m/z* 332 (M^+, 0.3%), 317(0.8%), 227(4), 179(3), 178(7), 135(21), 109(79) and 75(100) [Found: M^+– (PhCH —O), 227.1468. Calc. for $C_{20}H_{32}O_2Si$, M^+ – (PhCH —O), 227.1467).

3.5.3 *2–butoxy(menthyloxy)dimethylsilane* (212)

A solution of chloro(menthyloxy)dimethylsilane (**176**) (1.94 g, 8 mmol) in Et_2O (10 ml) was added dropwise to a stirred solution of *racemic* 2–butanol (0.50 g,

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[p] The integral ratios indicate that the upfield diastereomeric signal for 3–H_{exo} is obscured by the 6–H_{endo} signal.

[q] The assignments for C–5 and C–4 could be interchanged.

7 mmol) and Et_3N (0.80 g, 8 mmol) in Et_2O (20 ml). After stirring overnight, the resulting slurry was poured into cold, saturated, aq. $NaHCO_3$. The resulting mixture was extracted with Et_2O and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography [elution with hexane–EtOAc (95:5)] gave, as a diastereomeric mixture, 2–butoxy(menthyloxy)dimethylsilane, **(212)**, (1.40 g, 72%); ν_{max} (liquid film) 1250 (Si —Me) and 1055 cm^{-1} [Si —O (C)]; δ_H (500 MHz; $CDCl_3$) 0.10 (6H, s, 4 x SiMe), 0.72 (3H, d, 9′–Me), 0.81 (1H, qd, 4′–H_{ax}), 0.859 and 0.863 (3H, 2 x t, 4–Me), 0.87 (6H, d, 8′–Me and 10′–Me), 0.93 (1H, qd, 3′–H_{ax}), 1.02 (1H, q, 6′–H_{ax}), 1.13 and 1.14 (3H, 2 x d, J 6.18 and 6.03 Hz respectively, 1–Me), 1.135 (1H, m, 2–H)[r], 1.36 (1H, m, 5′–H), 1.42 and 1.47 (2H, 2 x m, 3–CH_2), 1.57 (1H, m, 3′–H_{eq}), 1.61 (1H, m, 4′–H_{eq}), 1.92 (1H, m, 6′–H_{eq}), 2.16 (1H, m, 7′–H), 3.52 (1H, td, 1′–H) and 3.83 (1H, m, 2–H); δ_C (125 MHz; $CDCl_3$) –1.66, –1.56, –1.49 and –1.36 (4 x q, SiMe), 9.99 (q, C–4), 15.91 (q, C–9′), 21.18 (q, C–8′), 22.24 (q, C–10′ and t, C–1), 22.96 (t, C–3′), 25.30 (d, C–7′), 31.70 (d, C–5′), 32.23 (t, C–3), 34.57 (t, C–4′), 45.39 and 45.44 (2 x t, C–6′), 49.96 (d, C–2′) 69.75 (d, C–2), and 72.44 (d, C–1′); m/z 286 (M^+, 4%), 271(11), 257(25), 201(54), and 75(100) (Found M^+–CH_3, 271.2069. Calc. for $C_{16}H_{34}O_2Si$, M^+–CH_3 271.2093).

3.5.4 *(Menthyloxy)dimethyl(2–pentyloxy)silane* (213)

A solution of chloro(menthyloxy)dimethyl silane **(176)** (3.13 g, 13 mmol) in Et_2O (10 ml) was added dropwise to a stirred solution of *racemic* 2–pentanol (0.74 g, 8 mmol) and Et_3N (1.27 g, 12 mmol) in Et_2O (20 ml). After stirring overnight, the resulting slurry was poured into cold, saturated, aq. $NaHCO_3$, and the resulting mixture was extracted with Et_2O. The organic layer was

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[r] The 2–H multiplet is almost completely obscured by the superposition of the 13–H signal upon it.

dried ($MgSO_4$) and concentrated *in vacuo*, and distillation yielded, as a diastereomeric mixture, (menthyloxy)dimethyl(2–pentyloxy)silane **(213)** (1.93 g, 76%), b.p. 90°C /0.25 mmHg; ν_{max} (liquid film) 1255 (Si —Me) and 1065 cm^{-1} [Si — O (C)]; δ_H(500 MHz; $CDCl_3$) 0.08 (6H, s, SiMe), 0.72 (3H, d, 9′–Me), 0.80 (1H, m, 4′–H_{ax}), 0.87 (6H, d, 8′–Me and 10′–Me), 0.89 (3H, q, 5–Me), 0.92 (1H, m, 3′–H_{ax}), 1.02 (1H, q, 6′–H_{ax}), 1.13 and 1.14 (3H, 2 x d, *J* 5.94 and 6.15 Hz respectively, 1–Me), 1.135 (1H, m, 2′–H),[s] 1.32 (4H, m, 3–CH_2 and 11–CH_2), 1.46 (1H, m, 5′–H), 1.57 (1H, m, 3′–H_{eq}), 1.62 (1H, m, 4′–H_{eq}), 1.92 (1H, m, 6′–H_{eq}), 2.16 (1H, m, 7′–H), 3.50 (1H, td, 1′–H) and 3.91 (1H, m, 2–H); δ_C (125 MHz; $CDCl_3$) –1.60, –1.46 and –1.32 (3 x q, SiMe), 14.13 (q, C–5), 15.93 (q, C–9′), 18.95 (t, C–4), 21.21 (q, C–8′), 22.26 (q, C–10′), 22.97 (t, C–3′), 23.58 and 23.66 (2 x q, C–11), 25.31 (d, C–7′), 31.72 (d, C–5′), 34.56 (t, C–4′), 41.84 (t, C–3), 45.39 and 45.44 (2 x t, C–6′), 49.95 (d, C–2′), 68.28 (d, C–2) and 72.45 (d, C–1′); *m/z* 300 (M^+, 3%), 285(9), 257(25), 215(26), 145(12), 75(63) and 43(100) (Found M^+–C_3H_7, 257.1969. Calc. for $C_{17}H_{36}O_2Si$, M^+–C_3H_7, 257.1939).

3.5.5 *(Menthyloxy)dimethyl(2–octyloxy)silane* (214)

A solution of chloro(menthyloxy)dimethylsilane (176) (3.96 g, 16 mmol) in Et_2O (10 ml) was added dropwise to a stirred solution of *racemic* 2–octanol (1.30 g, 8 mmol) and Et_3N (1.00 g, 10 mmol) in Et_2O (20 ml). After stirring overnight, the resulting slurry was poured into cold saturated, aq. $NaHCO_3$. The resulting mixture was extracted with Et_2O and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography [elution with hexane–EtOAc (95:5)], followed by distillation of the material obtained from the chromatography yielded, as a diastereomeric mixture,

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[s] The 2–H multiplet is almost completely obscured by the superposition of the 13–H signal upon it.

(menthyloxy)dimethyl(2–octyloxy)silane **(214)** (1.70g, 50%), b.p. 94°C (0.25 mmHg); ν_{max} (liquid film) 1255 (Si — Me) and 1065 cm^{-1} [Si —O (C)]; δ_H(500 MHz; $CDCl_3$) 0.10 (6H, s, 4 x SiMe), 0.72 (3H, d, 9′–Me), 0.80 (1H, qd, 4′–H_{ax}), 0.87 (3H, t, 8–Me), 0.88 (6H, d, 8′–Me and 10′–Me), 0.95 (1H, qd, 3′–H_{ax}), 1.02 (1H, q, 6′–H_{ax}), 1.13 and 1.14 (3H, 2 x d, *J* 5.85 and 6.03 Hz respectively, 1–Me), 1.14 (1H, m, 2′–H)[t], 1.25 and 1.35 (10H, 2 x m, octanyl CH_2)[u], 1.46 (1H, m, 5′–H), 1.57 (1H, m, 3′–H_{eq}), 1.61 (1H, m, 4′–H_{eq}), 1.93 (1H, m, 6′–H_{eq}), 2.16 (1H, m, 7′–H), 3.50 (1H, tq, 1′–H), and 3.89 (1H, m, 2–H); δ_C (125 MHz; $CDCl_3$) –1.63, –1.40 and –1.34 (3 x q, SiMe), 14.08 (q, C–8), 15.92 (q, C–9′), 21.20 (q, C–8′), 22.25 (q, C–10′), 22.65 (t, C–7), 22.96 (t, C–3′), 23.58 and 23.66 (2 x q, C–1), 25.31 (d, C–7′), 25.77 (t, C–6), 29.39 (t, C–5), 31.72 (d, C–5′), 31.92 (t, C–4), 34.57 (t, C–4′), 39.62 (t, C–3)[v], 45.44 (t, C–6′), 49.96 (d, C–2′), 68.54 (d, C–2), and 72.43 (d, C–1′); *m/z* 342 (M^+, 2%), 327(5), 257(23), 75(58), 43(100) (Found: M^+–CH_3, 327.2705. Calc. for $C_{20}H_{42}O_2Si$, M^+–CH_3, 327.2719).

3.6 Gas–liquid chromatographic analyses of the diastereomeric silyl acetals (210), (211), (212), (213) and (214).[232]

The silyl acetals were chromatographed as 0.1 to 0.2% solutions in Et_2O on a 30 m J&W DB225 fused silica capillary column having a 0.25 μ film thickness and 0.25 mm internal diameter. When a 60 m column was used, two 30 m columns were joined in the manner recommended by the column suppliers.

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[t] The 2–H multiplet is almost completely obscured by the superposition of the 13–H signal upon it.

[u] The two chemical shift values, in this case, are not implying a diastereomeric splitting but are merely a combination of the octanyl methylene groups.

[v] The assignment of the octyl methylene carbons is based on their relative proximity to the deshielding oxygen atom.

Helium was used as the carrier gas with a flow of *ca.* 40 ml/min. A purge time of 0.5 min was used and detection was by flame ionization using hydrogen and synthetic air as feed gases for the detector. Inlet and detector temperatures were set to 210° C.

The optimised temperature programmes employed in these analyses were as follows:

Diastereomeric acetals (210)

30 m	60 – 140° C at 4° C/min then 140 – 170° C at 1° C/min
60 m	60 – 140° C at 2° C/min then 140 – 170° C at 1° C/min

Diastereomeric acetals (211)

30 m	60 – 140° C at 4° C/min then 140 – 170° C at 1° C/min
60 m	60 – 140° C at 2° C/min then 140 – 170° C at 1° C/min

Diastereomeric acetals (214)

30 m	60 – 120° C at 4° C/min then 120 – 160° C at 1° C/min
60 m	60 – 120° C at 2° C/min then 120 – 160° C at 1° C/min

No separation could be effected for the diastereomeric acetals **(212)** and **(213)** under the variety of chromatographic conditions attempted. Replacing the column with a J & W DB1 fused silica column resulted in a complete loss of resolution for the previously separated acetals **(210)**, **(211)**, and **(214)**. The peak intensities were obtained by electronic integration. The detailed results and evaluation of this data are presented in the Discussion (See section 2.2.2, p. 139)

3.7 Preparation and oxidation of achiral silyl enol ethers (239) and (240)

The MCPBA used in these reactions was supplied by the TCI Chemical Company and was found to be 85% peracid, as analysed by iodometric titration prior to use. The cyclohexanone and α–tetralone were pre–distilled and stored over 3A molecular sieves. The NaI was pre–dried by heating in an evacuated oven at 140° C for 48 h. The TMSCl was used as supplied. All the reactions were carried out under an inert atmosphere. The general GLC conditions were as indicated earlier and a DB1 column was used for the analyses in this section.

3.7.1 *Preparation of (cyclohex–1–en–1–yloxy)trimethylsilane (239)*

Cyclohexanone (8.14 g, 83 mmol) was added, dropwise, to a stirred solution of TMSCl (10.00 g, 93 mmol) and Et_3N (20.20 g, 0.2 mol) in DMF (35 ml) at room temperature. Once the addition was complete the reaction mixture was refluxed for 4 h. After cooling, the resultant slurry was diluted with pentane (100 ml) and washed with cold, saturated aq. $NaHCO_3$ (3 x 100 ml). The organic layer was then washed, in rapid succession, with 1.5 M HCl and cold aq. $NaHCO_3$, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was distilled to yield (cyclohex–1–en–1–yloxy)trimethylsilane (239) as a clear liquid (11.40 g, 81%), b.p. 82–86° C/27 mmHg (lit.[209] 74–75° C/20 mmHg); ν_{max} 1670 (C ═ C), 1250 (Si —Me), and 1190 cm^{-1} (Si —O); δ_H(60 MHz; CCl_4) 0.1 (9H, s, SiMe), 1.3 – 1.8 (8H, 2 x m, 4 x CH_2), and 4.2 (1H, m, CH ═C).

3.7.2 *Preparation of (3,4–dihydronaphthyl–1–oxy)trimethylsilane* (240).

A solution of NaI (14.90 g, 100 mmol) in acetonitrile (80 ml) was added to a mixture of α–tetralone (11.60 g, 80 mmol), TMSCl (11.10 g 102 mmol), and Et_3N (10.00 g, 100 mmol) at room temperature. Once the addition was complete the reaction mixture was refluxed for 1 h, then, after cooling, it was diluted with cold pentane (50 ml) and ice water (50 ml). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. GLC (100 – 200°C at 10°C/min) of the dark residual oil revealed it consisted of a 50 : 50 mixture of the starting ketone (retention time 10.8 min) and a second component (retention time 12.9 min). Flash chromatography [hexane – EtOAc (98 : 2)] of this oil separated the two components, the one with the longer retention time being identified as the desired (3,4–dihydronaphthyl–1–oxy)trimethylsilane (**240**) (4.41 g, 25%),[w] [211]; ν_{max} 1640 (C ═C), 1250 (Si —Me), and 1190 cm^{-1} (Si —O); δ_H(60 MHz; CCl_4) 0.05 (9H, s, SiMe), 2.08 and 2.50 (4H, 2 x m, 2 x CH_2), 4.92 (1H, t,CH ═C), and 6.80 – 7.40 (4H, m, ArH).

3.7.3 *MCPBA oxidation of the (cyclohex–1–en–1–yloxy)trimethylsilane (239)*

A solution of the silyl enol ether (**239**) (3.40 g, 20 mmol) in CH_2Cl_2 (30 ml) was added to an ice cooled solution of 85% MCPBA (4.04 g, 20 mmol) in CH_2Cl_2 (70 ml). This addition was exothermic and continual cooling was necessary to maintain the reaction temperature below 10°C. Once the addition was complete the resulting suspension was stirred for an additional 3.5 h at 5°C. Pentane (100 ml) was added to complete the precipitation of the chlorobenzoic acid and the mixture was then filtered. The precipitation procedure was repeated and the filtrate was then dried, ($MgSO_4$), and concentrated *in vacuo* to yield a crude oil.

GLC analysis of this mixture (temperature programme: 100 – 150°C at 8°C / min) indicated a five component mixture:

i) 4.49 (11.3%) – same retention time as a cyclohexanone standard

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[w] This material was not purified by distillation, thus a comparison of the b.p. with the literature was not made. The spectroscopic data, however compared favourably to quoted data.

		under identical chromatographic conditions.
ii)	6.66 (24.4%) –	same retention time as standard (**239**) under identical chromatographic conditions.
iii)	8.45 (51.6%) –	α–siloxyketone (**243**)
iv)	10.19 (4.8%) –	unidentified
v)	15.4 (8.3%) –	silyl ester (**242**)

GC–MS analyses of peaks (iii) – (v) yielded the following mass spectral data:

Peak (iii)	*m/z* 171(100%), 143(34), 129(42), 75(70), and 73(35);
Peak (iv)	*m/z* 186 (5%), 168(6), 159(6), 143(6), 129(11), 117(16), 103(45), 75(100), and 73(42); and
Peak (v)	*m/z* 230(3%), 228(11), 215(34), 213(100), 171(14), 169(39), 141(18), 139(56), 113(12), 111(44), 75(19), and 73(6).

Fractional distillation of the crude oil obtained after work–up yielded the following fractions:

a) Cyclohexanone (35 mg), b.p. 34–38° C/0.55 mmHg, [Peak(i)]

b) (2–trimethylsiloxy)cyclohexanone (**243**) [Peak (iii)] (750 mg, 20%),b.p. 54–56° C / 0.55 mmHg[x]; ν_{max} 1725 (C ═O) and 1250 cm^{-1} (Si —Me); δ_H(60 MHz; CCl$_4$) 0.00 (9H, s, SiMe), 1.10 – 2.60 (8H, m, 4 x CH$_2$), and 4.00 [1H, m, CH(OSi)]; *m/z* 171(M^+–15, 22%), 143(11), 129(20), 75(100), and 73(50).

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[x] Brook and Macrae [239] have isolated this α–siloxy ketone and claim its characteristics to be consistent with the proposed structure. However, none of these physical properties are quoted.

c) 874 mg of what was shown by GLC to be a mixture of peaks (iii) – (v).

Preparative GLC on fraction (c) was attempted using a 1.85 m glass column, with a 3.11 mm internal diameter, packed with 5% S.E. 30 on chromosorb W. The oven temperature was varied between 100 and 200° C while the manifold temperature was maintained at 250° C. Only very small amounts of material relative to the total sample size applied were eluted and these fractions were shown by capilliary GLC to be multicomponent mixtures.

3.7.4 *MCPBA oxidation of the (cyclohex–1–en–1–yloxy)trimethylsilane (239) in the presence of NaHCO$_3$.*

A solution of the silyl enol ether (**239**) (5.00 g, 29 mmol) in CH_2Cl_2 (30 ml) was added to an ice cooled mixture of 85% MCPBA (7.24 g, 36 mmol) and $NaHCO_3$ (5.04 g, 60 mmol) in CH_2Cl_2 (100 ml). This addition was exothermic and continual cooling was necessary to maintain the reaction temperature below 10° C. Once the addition was complete the resulting suspension was stirred for an additional 3.5 h at 5° C. The reaction was worked–up as for reaction 3.7.3. GLC analysis of the resulting crude oil revealed the same five components (allowing for minor fluctuations of retention times) as present in the crude oil from the previous reaction. The relative amounts of these five components as determined by integration are as follows:

Peak (i) – cyclohexanone	(52%)
Peak (ii) – silyl enol ether (**239**)	(17%)
Peak (iii) – α–siloxy ketone (**243**)	(17%)
Peak (iv) – Unidentified	(10%)
Peak (v) – silyl ester (**242**)	(2%)

No further purification was carried out on this crude mixture.

3.7.5 *Preparation of trimethylsilyl m–chlorobenzoate* (242)

TMSCl (2.48 g, 23 mmol) was added, under an inert atmosphere, to a stirred solution of *m*–chlorobenzoic acid (3.00 g, 19 mmol) and pyridine (1.82 g, 23 mmol) at room temperature. The reaction was stirred at room temperature for 2.5 h and then refluxed for 0.5 h. The bulk of the pyridine was distilled off and the pyridinium hydrochloride was removed from the resulting suspension by filtration. The filtrate was purified by vacumn distillation to yield trimethylsilyl *m*–chlorobenzoate **(242)** (3.8 g, 88%), b.p. 77–78°C / 0.3 mmHg [291]; ν_{max} 1705 (C ═O), 1255 (Si —Me) and 1130 cm^{-1} (Si — O); δ_H(60 MHz; CCl_4) 0.15 (9H, s, SiMe), 6.95 – 8.00 (4H, m, ArH); *m/z* 230(M^+ ^{37}Cl, 3%), 228(M^+ ^{35}Cl, 8), 215(35), 213(96), 171(20), 169(55), 141(34), 139(100), 113(27), 111(96), 75(41), and 73(34).

3.7.6 *MCPBA oxidation of (3,4–dihydronaphthyl–1–oxy)trimethylsilane* (240).

A solution of the silyl enol ether **(240)** (2.00 g, 9 mmol) in CH_2Cl_2 (20 ml) was added dropwise to an ice/salt bath cooled solution of MCPBA (2.50 g, 12 mmol) in CH_2Cl_2 (40 ml). The rate of addition was adjusted to maintain a reaction temperature of 0°C and the reaction was stirred at that temperature for a further 1 h after the addition was completed. A cold solution of Na_2SO_3 (2.00 g) in H_2O (10 ml) and saturated aq. $NaHCO_3$ (50 ml) were added to the reaction mixture. The organic layer was separated, dried ($MgSO_4$), and concentrated *in vacuo* to yield a crude oil. GC–MS analysis of the crude mixture (temperature programme: 100 – 200°C at 10°/min) indicated a five component mixture. The retention times and relative percentages of the individual peaks as well as the major peaks of their mass spectra are listed below:

i)[y]	9.09 (6.9%)	*m/z* 172(8%), 170(25), 141(30), 139(100), 113(18), 111(64), and 75(48).
ii)	10.77 (2.8%)	*m/z* 146(53), 118(100), and 90(82).(α–tetralone)
iii)	11.30 (4.1%)	*m/z* 230(1%), 228(6), 215(26), 213(76), 171(17), 169(48), 141(29), 139(100), 113(31), 111(76), 75(68), and 73(20).[silyl ester (**242**)].
iv)	12.26 (4.5%)	*m/z* 162(23%), 144(14), 118(100), and 90(87).[α–hydroxytetralone (**246**)].
v)	15.52 (71.0%)	*m/z* 218(100%), 118(38), 75(90), and 73(40).[α–siloxyketone (**245**)].

Flash chromatography of the crude oil [hexane – EtOAc 95:5)] yielded (*2–trimethylsiloxy*)(*3,4–dihydronaphthy–1–one*) (**245**) (0.95 g, 44%), b.p. 102–105° C / 0.5 mmHg; ν_{max} 1705 (C ═O) and 1255 cm^{-1} (Si —Me); δ_H(60 MHz; CCl$_4$) 0.07 (9H, s, SiMe), 1.80 – 2.40 [2H, m, CH$_2$*CH*$_2$CH(O)], 2.94 (2H, t, Ar*CH*$_2$CH$_2$), 4.20 (1H, dd, CHOSi), and 6.80 – 8.10 (4H, m, ArH); *m/z* 218(*M*$^+$–15, 100%), 118(38), 75(90), and 73(40).

3.7.7 *MCPBA oxidation of (3,4–dihydronaphthyl–1–oxy)trimethylsilane* (240) *in the presence of NaHCO$_3$.*

A solution of the silyl enol ether (**240**) (1.80 g, 8 mmol) in CH$_2$Cl$_2$ (15 ml) was added dropwise to an ice/salt bath cooled mixture of MCPBA (2.50 g, 12 mmol) and NaHCO$_3$ (2.90 g, 35 mmol) in CH$_2$Cl$_2$ (40 ml). The rate of addition was adjusted to maintain a reaction temperature of 0° C and the reaction was stirred at that temperature for an additional 1 h after the addition was completed. The reaction was worked– up as for reaction 3.6.6. GLC analysis of this mixture (temperature programme: 100 – 200° C at 10°/min) indicated a

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[y] This component was not identified.

five component mixture, very similar to that obtained in the previous reaction. The relative percentages of the individual peaks are listed below:

Peak (i)	8.2%
Peak (ii) – α–tetralone	5.77%
Peak (iii) – silyl ester (**95**)	6.1%
Peak (iv) – α–hydroxy ketone (**99**)	4.3%
Peak (v) α–siloxy ketone (**98**)	70.9%

This reaction mixture was not purified any further.

3.8 Peracid oxidation of chiral silyl enol ethers (164), (172), (181), (182), and (185).

The MCPBA used in these reactions was supplied by the TCI Chemical Company and was found to be 85% peracid, as analysed by iodometric titration prior to use. Acid–free $CHCl_3$ and $CDCl_3$ were ensured by standing spectroscopic grade solvent over Na_2CO_3 for 48 h. The CH_2Cl_2 solutions of the silyl enol ethers were dried over 3A molecular sieves immediately before use. All the reactions were conducted under an inert atmosphere and the experimental procedure followed was similar to that of Walkup.[249]

All the α–siloxy ketones tended to decompose, within hours, in the case of compound (**247**) and as a result of this instability neither elemental analysis nor high resolution mass spectroscopy were attempted on these products. High field ^1H and ^{13}C NMR spectra were obtained for all the diastereomeric α–siloxyketones, except compound (**247**), although in some instances significant decomposition product peaks were present in the spectra. The signals were assigned in the same manner as for previous menthyloxy– and bornyloxy silyl compounds. When the diastereomers exhibit discrete NMR signals, then the chemical shifts of both signals comprising the pair are quoted in a single signal descriptor.

Digitisation was effected on a Summagraphics ID Data Tablet/Digitiser. The digitised data were captured and written to an input/output file by a GWBASIC programme. The digitiser had a resolution of 0.1 mm and errors in digitisation were further reduced by placing the enlarged reproductions on the data tablet with the peak axis at approximately 45° to the digitiser axes. This angle maximized the difference in both the x and y directions between consecutive digitised points. The GWBASIC file containing the digitised points provided the input for a Modula–2 [287] program which computed the area of the irregular polygon enclosed by the peak and the base line, using an algorithm based on the trapezoid rule for approximate integration.[288] This was achieved by summing the area of each trapezoid subtended by the line $x_n y_n \rightarrow x_{n+1} y_{n+1}$ and the arbitary x axis (Figure 54). The fraction of the trapezoid area not enclosed by the peak (shaded in figure 54) is then subtracted from the total trapezoid area as the summation is completed.

Total area of the peak

$$= \sum_{n=1}^{n} y_n \left(x_{n+1} - x_n \right) + \left(\frac{x_{n+1} - x_n}{2} \right) \left(y_{n+1} - y_n \right)$$

where n = number of digitised points.

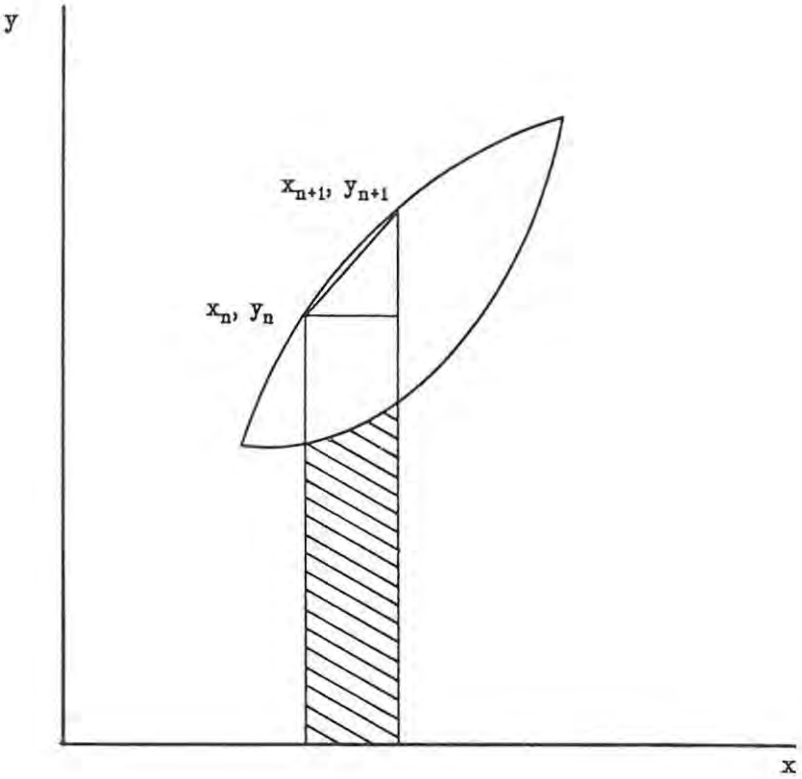

FIGURE 54 Diagramatic representation of the nth trapezoid used in the calculation of the area of the irregular polygon, enclosed by the peak and its baseline.

An equimolar binary mixture of compounds was prepared that exhibited a ^1H NMR spectrum in which singlets from each component were separated by approximately 5 Hz and 25% of the total peak heights were unresolved. Trial integration of these signals, by the digitising method, yielded ratios that varied from 48:52 to 52:48. These fluctuations were considered sufficiently small to allow significant enantiomeric excesses to be quantified.

3.8.1 *Preparation of the α–siloxyketone* (249)

$NaHCO_3$ (0.35 g, 4 mmol) and solid MCPBA (0.28 g, 1.4 mmol) were added sequentially to a stirred solution of the silyl enol ether (**182**) (0.50 g, 1.4 mmol) in CH_2Cl_2 (35 ml) at 0° C and the resulting slurry was stirred for 2 h at 0° C. Saturated aq. Na_2CO_3 (90 ml) was added and the resulting mixture was extracted with Et_2O (1 x 90 ml, 1 x 50 ml). The combined extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was flash chromatographed (elution with hexane–EtOAc (98:2)] to yield, as a colourless oil, the diastereomeric mixture 2–[(menthyloxy)dimethylsiloxy]–3,4–dihydro–1(2*H*)—naphthylone (**249**) (0.52 g, 100%); ν_{max} (liquid film) 1702 (C$=$O) cm^{-1}; δ_H(500 MHz; $CDCl_3$) 0.19, 0.24 and 0.25 (6H, 3 x s, 4 x SiMe), 0.718 and 0.721 (3H, 2 x d, 9′–Me)[z], 0.81 (1H, m, 4′–H_{ax}), 0.89 (6H, m, 8′ and 10′–Me), 0.95 (1H, m, 3′–H_{ax}), 1.02 (1H, m, 6′–H_{ax}), 1.14 (1H, m, 2′–H), 1.38 (1H, m, 5′–H), 1.57 (1H, m, 3′–H_{eq}), 1.60 (1H, m, 4′–H_{eq}), 1.94 (1H, m, 6′–H_{eq}), 2.18 (1H, m, 7′–H), 2.32 (2H, m, 3–CH_2), 3.04 (2H, m, 4–CH_2), 3.58 (1H, dt, 1′–H), 4.51 (1H, dd, 2–H), 7.15 – 7.34 (3H, m, ArH), and 7.99 (1H, dd, ArH); δ_C (125 MHz; $CDCl_3$) –2.15, –2.06, –1.75 and –1.38 (4 x q, SiMe), 15.93 (q, C–9′), 21.14 (q, C–8′), 22.21 (q, C–10′), 22.93 (t, C–3′), 25.32 (d, C–7′), 27.83 (t, C–4), 31.60 (d, C–5′), 32.72 and 32.77 (2 x t, C–3), 34.49 (t, C–4′), 45.22 and 45.34 (2 x t, C–6′), 50.09 (d, C–2′), 72.46 (d, C–1′), 74.70 and 74.75 (2 x d, C–2), 126.58 (d, ArC), 127.57 (d, ArC), 128.43 (d, ArC), 131.73 and 131.76 (2 x s, ArC), 133.24 (d, ArC), 143.36 (s, ArC), and 196.83 (s, C–1); m/z 359(M^+–CH_3, 8%), 219(92) and 75(100).

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[z] Peaks arising from the decomposition products occur with significant intensity in this region of the spectrum.

The diastereomeric excess was measured, by digitising the SiMe peaks in the 60 MHz ^{1}H NMR spectrum and computing the areas as described above, to be **53:47**. (This is a mean value from two separate reactions).

The reaction was repeated in exactly the same manner as described above, except for the reaction temperature which was varied as follows:

1) Room temperature which yielded compound (**249**) (0.37 g, 71%). In this case the diastereomeric excess was established, by spectrometer integration at 500 MHz, to be **55:45**. The high field spectrum also revealed some decomposition especially in the SiMe and 9′–Me regions of the spectrum.

3) –60°C which yielded compound (**249**) (0.44 g, 84%). The diastereomeric excess was measured by digitisation of 60 MHz spectrum and found to be **53:47**. (This value is a mean of three different data sets from the same reaction.)

3.8.2 *Preparation of the α–Siloxyketone* (**247**)

The silyl enol ether (**172**) (0.50 g, 1.6 mmol) was reacted with $NaHCO_3$ (0.40 g, 4.8 mmol) and MCPBA (0.32 g, 1.6 mmol) at room temperature in identical fashion to that described for the preparation of compound (**249**). Flash chromatograpy of the residual oil [elution with hexane–EtOAc (96:4)] yielded, as a diastereomeric mixture, 2–[(menthyloxy)dimethylsiloxy]cyclohexanone (**247**) (0.18 g, 35%); ν_{max} (liquid film) 1725 cm^{-1} (C=O); δ_H(60 MHz; CCl_4) 0.00 and 0.07 (6H, 2 x s, 4 x SiMe), 0.8 and 1.8 (26H, 2 x m, 8′–, 9′–, and

10′–Me, 3′–, 4′–,5′–, 3–, 4–, 5–, and 6–CH_2, and 2′–, 5′–, and 7′–H), 3.5 (1H, m, 1′–H), and 4.2 (1H, m, 2–H).[ba]

The diastereomeric excess was measured, by digitising the SiMe peaks in the 60 MHz ^1H NMR (the NMR spectrum was obtained immediately after the chromatography was completed to minimize the distortion of the enantiomeric ratio by the decomposition products) and computing the areas, as described above, to be **57:43**.

3.8.3 *Preparation of the α–Siloxyketone* (**250**).

The silyl enol ether (**185**) (0.50 g, 1.4 mmol) was reacted with $NaHCO_3$ (0.35 g, 4.2 mmol) and MCPBA (0.28 g, 1.4 mmol) at 0° C in identical fashion to that described for compond (**249**). Flash chromatograpy of the residual oil [eluting with hexane–EtOAc (98:2)] yielded, as a clear oil, the diastereomeric mixture, 2–[(bornyloxy)dimethylsiloxy]–3,4–dihydro–1(2*H*)–naphthylone (**250**) (0.50 g, 96%); ν_{max} (liquid film) 1702 cm^{-1} (C$=$O); δ_H(500 MHz; $CDCl_3$) 0.163, 0.169, 0.189 and 0.191 (6H, 4 x s, 4 x SiMe), 0.75 and 0.78 (3H, 2 x s, 10′–Me), 0.84 (3H, s, 9′–Me), 0.85 (3H, s, 8′–Me), 0.94 (1H, m, 3′–H_{endo}), 1.11 (1H, m, 6′–H_{exo}), 1.23 (1H, m, 5′–H_{endo}), 1.56 (1H, m, 4′–H), 1.66 (1H, m, 5′–H_{exo}), 1.99 (1H, m, 6′–H_{endo}), 2.18 (1H, m, 3′–H_{exo}) 2.30 (2H, m, 3–CH_2), 3.05 (2H, m, 4–CH_2), 4.15 (1H, m, 2′–H), 4.47 (1H, dd, 2–H), 7.16– 7.40 (3H, m, ArH) and 7,98 (1H, dd, ArH); δ_C (125 MHz; $CDCl_3$) –1.98, –1.83, –1.30 and –1.02 (4 x q, SiMe), 13.73 (q, C–10′), 19.05 (q, C–9′), 20.47 (q, C–8′), 26.37 (t, C–6′), 28.03 (t, C–4), 28.49 (t, C–5′), 32.99 (t, C–3), 39.46 (t, C–3′), 45.41 (d, C–4′), 47.48 (s, C–7′), 49.83 (s, C–1′), 74.61 and 74.65 (2 x d, C–2), 77.18 and 77.26 (2 x d, C–2′), 126.75 (d, ArC), 127.94

[ba] Due to the rapid decomposition of this compound no further characterisation was possible.

(d, ArC), 128.44 (d, ArC), 132.05 (s, ArC), 133.17 (d, ArC), 143.26 (s, ArC), and 196.10 and 196.15 (2 x s, C–1); *m*/*z* 357(M$^+$–15, 1%), 219(100) and 75(8).

At 60 MHz the SiMe signal showed no splitting and thus the diastereomeric excess could not be determined by digitisation. At 500 MHz however, the peaks were resolved and spectrometer integration indicated a ratio of **51:49**.

3.8.4 *Preparation of the α–Siloxyketone* (**248**).

The silyl enol ether (**181**) (0.50 g, 1.4 mmol) was reacted with $NaHCO_3$ (0.35 g, 4.2 mmol) and MCPBA (0.28 g, 1.4 mmol) at 0°C in identical fashion to that described for the preparation of compound (**249**). Flash chromatograpy of the residual oil [hexane–EtOAc (98:2)] yielded, as a clear oil, the diastereomeric mixture 3–[(menthyloxy)dimethylsiloxy]–2,3–dihydro–*4H*–1–benzopyran–4–one (**248**) (0.50 g, 95%); ν_{max} 1710 cm^{-1} (C=O); δ_H(500 MHz; $CDCl_3$) 0.187, 0.191 and 0.227 (3 x s, 4 x SiMe) 0.72 (3H, d, 9′–Me), 0.83 (1H, m, 4′–H$_{ax}$), 0.89 (6H, m, 8′– and 10′–Me), 0.94 (1H, m, 3′–H$_{ax}$), 1.01 (1H, q, 6′–H$_{ax}$), 1.14 (1H, q, 2′–H), 1.38, (1H, m, 5′–H), 1.59 (1H, m, 3′–H$_{eq}$), 1.64 (1H, m, 4′–H$_{eq}$), 1.90 (1H, m, 6′–H$_{eq}$), 2.13 (1H, m, 7′–H), 3.55 (1H, dt, 1′–H), 4.23 and 4.44 (2H, dt and m, 2–H$_{ax}$ and 2–H$_{eq}$), 4.61 (1H, m, 3–H), 6.84 – 7.03 (2H, m, ArH), 7.41 (1H, m, ArH) and 7.84 (1H, dd, ArH); δ_C (125 MHz; $CDCl_3$) –1.87, –1.71, –1.26 and –0.81 (4 x q, SiMe), 16.21 (q, C–9′), 21.41 (q, C–8′), 22.53 (q, C–10′), 23.18 (t, C–3′), 25.57 (d, C–7′), 31.85 (d, C–5′), 34.73 (t, C–4′), 45.41 and 45.57 (2 x t, C–6′), 50.03 and 50.06 (2 x d, C–2′), 70.37 and 70.40 (d, C–3), 71.24 (t, C–2), 72.70 (d, C–1′), 117.64 (d, ArC), 120.13 (s, C–4a), 121.62 (d, ArC), 127.77 (d, ArC), 135.54 (d, ArC), 161.48 (s, C–8a), and 191.33 (s, C–4); *m*/*z* 361(M$^+$–CH_3, 4%), 221(100) and 75(60).

The diastereomeric excess was measured, by digitising the SiMe peaks in the 60 MHz ^{1}H NMR and computing the areas, as described above, to be **58:42**.

A second reaction was carried out in which the silyl enol ether (**181**) (1.00 g, 2.8 mmol) was reacted with $NaHCO_3$ (0.70 g, 8.4 mmol) and MCPBA (0.56 g, 2.8 mmol) at –50° C in identical fashion to that described above, to yield, after chromatography, the α–siloxy ketone (**248**) (1.05 g, 100%).

The diastereomeric excess was measured, by digitising the SiMe peaks in the 60 MHz ^{1}H NMR and computing the areas as described above, to be **55:45**. (This value is a mean of six different data sets from the same reaction.)

3.8.5 *1–[(menthyloxy)dimethylsiloxy]–3,3–dimethyl–2–butanone* (**251**)

$NaHCO_3$ (0.15 g, 1.8 mmol) and solid MCPBA (0.12 g, 0.6 mmol) were added sequentially to a stirred solution of the silyl enol ether (**164**) (0.19 g, 0.6 mmol) in dry CH_2Cl_2 (15 ml) at 25° C and the resulting slurry was stirred for 2 h at 25° C. Saturated aq. Na_2CO_3 (30 ml) was added and the resulting mixture extracted with Et_2O (2 x 20 ml). The combined extracts were dried ($MgSO_4$), concentrated *in vacuo* and flash chromatography [eluting with hexane–EtOAc (95:5)] yielded, as a colourless oil, *1–[(menthyloxy)dimethylsiloxy]–3,3–dimethyl–2–butanone* (**251**) (0.08 g, 43%); ν_{max} (liquid film) 1720 cm^{-1} (C $=$ O); δ_H(60 MHz; CCl_4) 0.00 (6H, s, 2 x SiMe), 0.75 (9H, m, 8′–, 9′–, and 10′–Me), 1.1 (9H, s, 3 x 4–Me), 1.4–2.2 (9H, m, 2′–, 7′–, and 5′–H and 3′–, 4′–, and 6′–CH_2), 3.2 – 3.8 (1H, m, 1′–H), and 4.4 (2H, s, 1–CH_2); δ_C (125 MHz; $CDCl_3$) –3.09 and –2.75 (2 x q, SiMe), 14.12 (q, C–9′), 19.44 (q, C–8′), 20.44 (q, C–10′), 21.14 (t, C–3′), 23.45 (d, C–7′), 24.44 (q, C–4), 29.93 (d, C–5′), 32.76 (t, C–4′), 43.30 (s, C–3), 43.66 (t, C–6′), 48.17 (d, C–2′), 62.04

(t, C–1), 70.60 (d, C–1′), and 213.27 (s, C–2); *m/z* 314(M^+, 9%) 173(100) and 75 (45).

Menthol (40 mg)[bb] was also isolated during the chromatography of the crude reaction mixture. It was apparent from the TLC plates of the collected fractions that further hydrolysis of the α–siloxyketone (**251**) to the corresponding hydroxy compound occurred during the chromatography. Any of the volatile α–hydroxyketone formed by hydrolysis during the reaction or work–up would have been lost while concentrating the sample *in vacuo.*

3.8.6 *Preparation of* (249) *from* (182) *employing magnesium monoperphthalate* (*MMPP*)

The silyl enol ether (**182**) (1.00 g, 2.8 mmol) dissolved in anhydrous DMF (3 ml) was added to a solution of 80% MMPP (2.07 g, 3.4 mmol) dissolved in DMF (20 ml) at room temperature. The reaction mixture was stirred for 7 h at room temperature and then poured into cold water and the resulting mixture extracted with Et_2O (2 x 25 ml). The ether layer was then washed with water (2 x 25 ml), dried ($MgSO_4$), and concentrated *in vacuo.* The residual oil was purified by flash chromatography [elution with hexane – EtOAc (98:2)] to yield the desired α–siloxy ketone (**249**) (0.26 g, 25%).
Digitisation of four independent data sets from the SiMe singlets at 60 MHz shows the average enantiomeric ratio to be **50:50**.

3.8.7 *Oxidation of the chiral silyl enol ether* (182) *using 2–(phenylsulphonyl)–3–phenyloxaziridine* (256) [253]

i) A solution of the silyl enol ether (**182**) (1.00 g, 2.8 mmol) in acid free

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[bb] Identified by its m.p. (37–38° C , lit.[294] 44° C), ^1H NMR, and IR spectra.

$CHCl_3$ (1 ml) was added dropwise to a solution of the sulphonyloxaziridine (**256**) (0.73 g, 2.8 mmol) in $CHCl_3$ (5 ml) at room temperature. The reaction mixture was refluxed for 2 h and then cooled and diluted with pentane (80 ml). The precipitated solid was removed by filtration and the filtrate evaporated *in vacuo*. Flash chromatography of the residual oil [elution with hexane – EtOAc (95:5)] yielded the α–siloxyketone (**249**) (0.96 g, 92%).

The diastereomeric excess was measured, by digitising the SiMe peaks in the 60 MHz ^1H NMR and computing the areas as described above, to be **51:49**.

ii) The reaction of the silyl enol ether (**182**) (0.50 g, 1.4 mmol) and the sulphonyloxaziridine (**256**) (0.36 g, 1.4 mmol) was repeated at room temperature, overnight, in similar fashion to that described above, to yield the α–siloxyketone (**249**) (0.48 g, 91%).

The diastereomeric excess was once again measured, by digitising the SiMe peaks in the 60 MHz ^1H NMR and computing the areas as described above, to be **52:48**.

iii) To monitor the reaction by ^1H NMR it was repeated in identical fashion to that described in (i), using $CDCl_3$ instead of $CHCl_3$ as the solvent. NMR spectra of the reaction mixture were then obtained at regular intervals.

3.9 Preparation of 2–(phenylsulphonyl)–3–phenyloxaziridine (256)

3.9.1 *Preparation of ethyl orthoformate* [250]

To an ice–cooled solution of $CHCl_3$ (160.0 g, 1.1 mol) in absolute EtOH (1000 ml) Na metal (69.0, 3.0 mol) was added piecewise. Once the exothermic addition was complete, the reaction mixture was allowed to cool and then the NaCl precipitate was removed by filtration. Fractional distillation of the filtrate removed the excess solvent and subsequently yielded the ethyl orthoformate (24.5 g, 15%), b.p. 143 – 144°C (lit.[250] 140 – 146°C); δ_H (60 MHz, $CDCl_3$) 1.08 (9H, t, J 8 Hz, 3 x CH_3CH_2), 3.50 (6H, q J 8 Hz, 3 x CH_2CH_3), and 5.07 (1H, s, CH).

3.9.2 *Preparation of benzaldehyde diethyl ketal* (253).[251]

Benzaldehyde (16.00 g, 0.15 mol) was added dropwise to a mixture of ethyl orthoformate (24.68 g, 0.17 mol) and *p*–toluene sulphonic acid (0.2 g) during which time the temperature of the reaction mixture rose to 55°C. Once the addition was complete the reaction mixture was heated to 140°C, then allowed to cool and subsequent fractional distillation yielded the desired ketal (**253**) (24.51 g, 97%), b.p. 112 – 114°C / 15mmHg (lit.[295] b.p. 220°C); δ_H (60 MHz, $CDCl_3$) 1.23 (6H, t, J 7 Hz, 2 x CH_3CH_2), 3.60 (4H, q, J 7 Hz, 2 x CH_2CH_3), and 5.50 (1H, s, C*H*), and 7.20 – 7.80 (5H, m, ArH).

3.9.3 *Preparation of Benzenesulphonanamide* (254).

25% aq. NH_3 (200 ml) was added to freshly distilled benzene sulphonyl chloride (50.00 g, 0.28 mol) and the resulting suspension was well stirred for 30 min at *ca.* 70°C. The crude solid obtained after filtration was washed with ice cold H_2O and then recrystallized from boiling H_2O to yield benzenesulphonamide (**254**) (37.15 g, 84%), m.p.153 – 155°C (lit.[296] 153°C).

3.9.4 *Preparation of the sulphonimine* (255) [252,297]

Benzaldehyde diethyl ketal (**253**) (24.00 g, 0.15 mol) and benzene sulphonamide (**254**) (22.80 g, 0.15 mol) were mixed together and heated to *ca.* 170° C. The heating was maintained until the distillation of the ethanol formed in the reaction had ceased (45 min). The residual liquid was placed under high vacuum (0.1 mmHg) while cooling to room temperature. Dissolving the residue in CH_2Cl_2 and adding pentane precipitated the crystalline sulphonimine (**255**) (32.60 g, 92%), m.p. 77 – 79° C (lit.[297] 80° C); δ_H (60 MHz, $CDCl_3$) 7.20 – 8.20 (10H, m, ArH) and 8.95 (1H, s,N ═CH).

3.9.5 *Preparation of the 2–sulphonyloxaziridine* (256) [253]

A solution of 85% MCPBA (9.10 g, 45 mmol) in $CHCl_3$ (100 ml) was added dropwise to a well stirred, ice–cooled mixture of the sulphonimine (**255**) (10.00 g, 41 mmol), saturated aq. $NaHCO_3$ (100 ml), and the phase transfer catalyst, benzyl triethylammonium chloride (1.12 g, 5 mmol). The reaction mixture was stirred for 2 h at room temperature after which the $CHCl_3$ layer was separated and washed successively with H_2O (50 ml), 10% aq. Na_2SO_3 (50 ml), H_20 (2 x 50 ml), and finally brine (20 ml). The organic layer was dried and concentrated *in vacuo*. The residual oil was crystallized from EtOAc – *n*–pentane to yield 2–(phenylsulphonyl)–3–phenyloxaziridine (**256**) (6.12 g, 57%), m.p. 93 – 96° C (lit. [252] 103° C); δ_H (60 MHz, $CDCl_3$) 5.60 (1H, s, N—CH—O) and 7.30 – 8.30 (10H, m, ArH).

3.10 Alkylations of chiral silyl enol ethers (181), (182), and (185).

All reactions were carried out under an inert atmosphere and the $TiCl_4$ additions were via a stainless steel canula under a positive argon pressure. The alkyl halides and the silyl enol ethers were freshly distilled prior to use. The $TiCl_4$ was either used as supplied by the *Merck Chemical Company* or distilled from CaH_2 to remove any HCl present in the reagent. Digitisation of the photo–enlarged tertiary butyl singlets was achieved as described for the peroxidation studies [Sections (2.3.1.3.1, p. 165) and (3.7, p. 258)]. The NMR characterization of the products was carried out at 300 MHz and the enantiomeric excess determinations at 60 and/or 300 MHz.

3.10.1 *Reaction of (3,4–dihydronaphthyl–1–oxy)(menthyloxy)dimethylsilane* (182) *with tert–butyl chloride.*

A pre–cooled (*ca.* –23° C) solution of $TiCl_4$ (1.10 g, 6 mmol) in CH_2Cl_2 (5 ml), was added rapidly to a solution of *tert*–butyl chloride (0.56 g, 6.0 mmol) and the silyl enol ether (182) (2.00 g, 6 mmol) in anhydrous CH_2Cl_2 (20 ml) at *ca.* –23° C. (The resulting exothermic reaction raised the temperature to –15° C.) After stirring for 3 h at *ca.* –23° C ice cold water (100 ml) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (20 ml) and the combined organic layers were washed with saturated aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo.* The desired product was separated from the free chiral auxiliary by flash chromatography [elution with hexane–EtOAc (96 : 4)] to yield, as a colourless oil, 2–(1,1–dimethylethyl)–3,4–dihydro–1(*2H*)–naphthylone (261)[298] (470 mg, 42%); $[\alpha]_D^{25}$ –0.5° (c 4.4 in CCl_4); ν_{max} (liquid film) 1690 (C =O) cm^{-1}; δ_H(300 MHz; $CDCl_3$) 1.10 (9H, s, Bu^t), 1.94 (1H, m, 2–CH), 2.30 (2H, m, 3–CH_2), 2.99 (2H, m, 4–CH_2), 7.10–7.45 (3H, m, ArH), and 7.95 (1H, d, ArH); *m/z* 202(M^+, 2%), 187(3), 146(100), 131(12), and 57(5).

The enantiomeric excess achieved in the reaction was evaluated at 60 MHz by both spectrometer integration and digitisation of the enantiomeric tertiary butyl singlets, separated on the addition of Eu(tfc)$_3$:

i) Addition of Eu(tfc)$_3$ (30 and 50 mg) to a solution of (**261**) (55 mg) in CCl_4 separated the *tert*–butyl signals by 2.7 and 4.0 Hz (65 and 105 Hz downfield shift) respectively. Digitisation of these signals gave an average enantiomeric ratio of **56:44**.

ii) Addition of Eu(tfc)$_3$ 112 and 118 mg to a solution of (**261**) (55 mg) in CCl_4 separated the *tert*–butyl signals by 6.7 Hz. Spectrometer integration at 60 MHz of both these pairs gave an average enantiomeric ratio of **53:47**.

The alkylation reaction was repeated in identical fashion but at a reaction temperature of –78° C. A TLC analysis of the crude reaction mixture revealed only trace quantities of the desired compound, (**261**), the major components being tetralone and menthol.

3.10.2 *Reaction of (bornyloxy)(3,4–dihydronaphthyl–1–oxy)dimethylsilane* (**185**) *with tert–butyl chloride.*

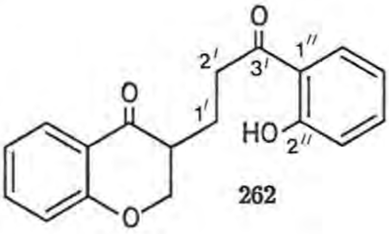
The silyl enol ether (**185**) (2.00 g, 6 mmol) was reacted with *tert*–butyl chloride (0.56 g, 6.0 mmol) and $TiCl_4$ (1.10 g, 6 mmol) in the same manner as for (**182**) to yield, after chromatography, compound (**261**) (0.44 g, 39%), $[\alpha]_D^{25}$ –0.8° (*c* 5.4 in CCl_4).

The enantiomeric excess achieved in the reaction was again evaluated by spectrometer integration and digitisation on the *tert*–butyl singlets separated on the addition of Eu(tfc)$_3$. In this case, the chiral shift reagent experiments were conducted at 300 MHz. This experiment was conducted on our behalf, by an independent organization. Neither the amount of shift reagent added or the concentration of the sample solution is available. However, the downfield shifts induced were 87 and 31 Hz respectively, with concomitant induced separations of 12 Hz and 5 Hz:

i) Digitisation of the two data sets gave an average enantiomeric ratio of **52:48**.

ii) Integration of the same two data sets gave an average enantiomeric ratio of **52:48**.

3.10.3 *Reaction of (2–H–1–benzopyran–4–yloxy)(menthyloxy)dimethyl silane* **(181)** *with tert–butyl chloride.*



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The silyl enol ether (**181**) (2.00 g, 6 mmol) was reacted with *tert*–butyl chloride (0.56 g, 6.0 mmol) and TiCl$_4$ (1.10 g, 6 mmol) in the same manner as for compound (**185**) to yield, after flash chromatography [elution with benzene–EtOAc, (95:5)], the novel *3–[3–(2–hydroxyphenyl)–3–oxopropyl]–2,3–dihydro–4H–1–benzopyran–4–one* (**262**), (400 mg, 48%[bc]), m.p. 105–106°C (from Et$_2$O); ν_{max} (KBr) 1692, 1645, and 1602 cm^{-1}; δ_H(300 MHz; CDCl$_3$) 1.98 and 2.19 (2H, 2 x m,

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[bc] Yield of the 1,5–diketone (**262**) is based on 0.5 equivalents of the silyl enol ether (**181**) because ultimately both reactants must be provided by this compound.

H–1_a′ and H–1_b′), 2.79 (1H, m, 3–H), 3.23 (2H, m, 2′–H), 4.30 (1H, dd, $J_{2a,2b}$ 12 Hz and $J_{2a,3}$ 9 Hz, 2_a–H), 4.56 (1H, dd, $J_{2b,2a}$ 12 Hz and $J_{2b,3}$ 5 Hz, 2_b–H), 6.94 (4H, m, ArH), 7.45 (2H, m, ArH), 7.78 (1H, dd, ArH), 7.86 (1H, dd, ArH) and 12.20 (1H, s, OH); δ_C (125 MHz; $CDCl_3$) 21.11 (C–1′), 35.65 (C–2′), 44.91 (C–3), 70.82 (C–2), 117.66 (ArC), 118.39 (ArC), 118.91, (ArC), 119.10 (C–1′′), 120.33 (C–4a), 121.26 (ArC), 127.20 (ArC), 129.80 (ArC), 135.86 (ArC), 136.31 (ArC), 161.26 (C–8a), 162.20 (C–2′′), 194.12 (C–3′) and 205.21 (C–4); *m/z* 296(M^+, 10%), 278(3), 147(77) and 121(100) (Found M^+, 296.1045. $C_{18}H_{16}O_4$ requires M^+, 296.1048).

The reaction was repeated in identical fashion using **(181)** (3.00 g, 10 mmol), *tert*–butyl chloride (0.79 g, 8.5 mmol) and $TiCl_4$ (1.57 g, 8.3 mmol) that had been freshly distilled from CaH_2. The 1,5–diketone **(262)** (0.50 g, 41%) was once again isolated and no evidence for the desired *α–tert*–butylated chromanone was found.

3.10.4 *Reaction of (3,4–dihydronaphthyl–1–oxy)(menthyloxy)dimethylsilane* **(182)** *with adamantyl bromide.*

The silyl enol ether **(182)** (0.55 g, 1.5 mmol) was reacted with adamantyl bromide (0.34 g, 1.6 mmol) and $TiCl_4$ (0.29 g, 1.5 mmol) in the same manner as for compound **(182)** and *tert*–butyl chloride. TLC analyses of the crude oil obtained from the work–up procedure described above indicated a complex mixture. Extensive flash chromatography [elution with hexane–EtOAc (80:20)] facilitated the isolation of menthol (0.22 g) and tetralone (0.05 g). These two components of the reaction mixture were identified by their ^1H NMR spectra. No evidence for the desired alkylated product could be found.

3.11 Hydroxy alkylations of chiral silyl enol ethers (164), (180), and (194) with benzaldehyde.

All the reactions were conducted under an inert atmosphere. The benzaldehyde was distilled under reduced pressure immediately prior to use. The $TiCl_4$ was obtained from the Merck Chemical Company and was either used as supplied or distilled from CaH_2, under strictly anhydrous conditions. CH_2Cl_2 solutions of the silyl enol ethers were dried over 3A molecular sieves prior to their addition to the reaction. Digitisation of the resolved peaks was achieved as before (see sections 3.7, p. 265 and 3.10, p. 277).

3.10.1 *Reaction of (menthyloxy)(3,3–dimethylbut–1–en–2–yloxy)dimethylsilane* **(164)** *with benzaldehyde.*

Method A1

A solution of $TiCl_4$ (0.65 g, 0.37 ml, 3.4 mmol) in CH_2Cl_2 (4 ml) was added to a solution of the silyl enol ether (**164**) (1.00 g, 3.2 mmol) and benzaldehyde (0.36 g, 3.4 mmol) in CH_2Cl_2 (20 ml) at –78° C. The resulting yellow slurry was stirred at –78° C for 4 h and then allowed to warm to room temperature overnight, during which time the colour of the reaction mixture became bright red. Pyridine (250 ↑l) was added, which discharged the red colour and produced a white precipitate. Filtration of the reaction mixture and addition of Et_2O to the filtrate completed the precipitation of the insoluble salts. The filtrate was dried and the solvent removed *in vacuo* to yield an orange oil. Flash chromatography [elution with hexane–EtOAc (9:1)] followed by preparative TLC of the mixed fractions [elution with benzene–Et_2O (95:5)] yielded, 1–chloro–4,4–dimethyl–1–phenyl–3–pentanone (**264**) (0.31 g, 43%), m.p. 31–32° C (from hexane) (lit.,[299] 33–34° C); $\downarrow_{max}$ (liquid film) 1710 (C $=$ O) cm^{-1}; $\mathscr{B}_H$(300 MHz; $CDCl_3$) 1.10 (9H, s, Bu^t), 3.05 and 3.45 (2H, 2 x dd $J_{2a\text{-}2b}$ 17 Hz, $J_{2a\text{-}1}$ 5 Hz, $J_{2b\text{-}1}$ 9 Hz, 2–CH_2), 5.44 (1H, dd, $J_{1\text{-}2a}$ 5 Hz, $J_{1\text{-}2b}$ 9

Hz, 1–CH), 7.33 (3H, m, ArH), and 7.56 (2H, m, ArH); δ_C (125 MHz; $CDCl_3$) 25.89 (C–5), 44.10 (C–4), 46.79 (C–2), 57.65 (C–1), 126.85 (ArC), 128.31 (ArC), 28.55 (ArC), 140.90 (ArC), and 210.80 (C–3); *m/e* 224(M^+, ^{35}Cl, 13%), 167(15), 131(25), 125(68), 104(64) and 57(100).

and

the α,β–unsaturated ketone, *trans* 4–dimethyl–1–phenyl–pent–1–en–3–one (**265**) (0.05 g, 8%), m.p. 39° C (from hexane) (lit.[300] 43° C); ν_{max} (liquid film)[bd] 1685 (C=O) and 1610 (C=C) cm^{-1}; δ_H(300 MHz; $CDCl_3$) 1.22 [9H, s, Bu^t], 7.11 (1H, d, J_{1-2} 15.5 Hz[be], 1–H), 7.36 (3H, m, ArH), 7.55 (2H, m, ArH), and 7.67 (1H, d, J_{2-1} 15.5 Hz, 2–H); δ_C (125 MHz; $CDCl_3$) 26.32 (C–5), 43.24 (C–4), 120.61 (C–1), 128.15 (ArC), 128.71 (ArC), 130.06 (ArC), 14.81 (ArC), 142.74 (C–2), and 203.99 (C–3); *m/e* 188(M^+, 32%), 131(100), 103(30), and 77(15).[bf]

The enantiomeric excess achieved in this reaction was evaluated by spectrometer integration and digitisation of the enantiomeric tertiary butyl singlets, resolved by the addition of $Eu(tfc)_3$.

i) Addition of $Eu(tfc)_3$ (58 mg) to a solution of compound (**264**) (62 mg) induced a 12 Hz separation of the tertiary butyl group singlets for the two enantiomers with a concommitant 45 Hz

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[bd] The infra–red spectra of compounds (**264**) and (**265**) were obtained before the purified oils crystallized.

[be] The coupling constant of 15.5 Hz for the vinyl protons establishes compound (**265**) as the *trans* isomer. GC–MS indicates trace quantities of a second compound with an identical mass spectrum *i.e* the *cis* isomer of (**265**).

[bf] GC–MS revealed three trace contaminants, *viz.*, benzaldehyde, the β–chloro ketone (**264**), and the *cis* isomer of (**265**).

downfield shift. The separation of the singlets at 60 MHz was large enough for reliable spectrometer integration, thus no high field chiral shift reagent studies were carried out on compound (**264**). Averaging the integrals from three independent data sets gave the enantiomeric ratio as **52:48**. (A data set is regarded as the resolved tertiary butyl ^{1}H NMR signals. Independent data sets are thus obtained by repeating the spectrum of a particular NMR sample.)

ii) Digitising two independent data sets as described previously [different from the data sets used in (i)] also gave an enantiomeric ratio of **52:48**.

iii) No optical activity could be detected for compound (**264**) against the background noise of the instrument when measuring a sample solution where *c* 5.3 in CCl_4.

Method A2

Benzaldehyde (0.37 g, 3.4 mmol) and $TiCl_4$ (0.65 g, 3.4 mmol) were mixed in CH_2Cl_2 (20 ml) and the resulting yellow suspension cooled to –78°C. A solution of the silyl enol ether (**164**) (1.00 g, 3.2 mmol) in CH_2Cl_2 (10 ml) was then added and the temperature of the resulting reaction mixture was maintained at *ca.* –78°C for 4 h and then allowed to warm to room temperature overnight. To the resulting red solution, pyridine (300 μl) dissolved in Et_2O (10 ml) was added and the ensuing precipitate removed by filtration. This procedure was repeated to yield a crude oil which was flash chromatographed [elution with benzene–hexane (8:2)] to yield the β–chloroketone (**264**) (0.45 g, 68%) and the α,β–unsaturated ketone (**265**) (0.16 g, 26%).

i) Addition of $Eu(tfc)_3$ (71 mg) to a solution of compound (**264**)

(54 mg) induced a 63 Hz downfield shift of tertiary butyl signal while resolving the enantiomeric singlets by 15 Hz. Integration of twenty seven independent data sets gave an average enantiomeric ratio of **53:47**.

ii) Digitising two independent data sets as described previously [different from the data sets used in (i)] gave an enantiomeric ratio of **52:48**.

Method B

The reaction of the silyl enol ether (**164**) (1.00 g, 3.2 mmol), benzaldehyde (0.37 g, 3.4 mmol), and $TiCl_4$ (0.65 g, 3.4 mmol) was repeated in similar fashion to Method A2. The addition of the pyridine to the reaction mixture is replaced by quenching of the reaction with 5% aq. $NaHCO_3$. The resultant mixture was extracted with Et_2O. The separated organic layer was dried and concentrated *in vacuo*. Flash chromatography of the resultant crude oil using the same conditions as for Method A2, yielded compounds (**264**) (375 mg, 52%) and (**265**) (100 mg, 17%).

No attempt was made to measure the enantiomeric excess achieved in this reaction as it was essentially a repetition of Method A2.

Method C

The reaction of the silyl enol ether (**164**) (1.00 g, 3.2 mmol), benzaldehyde (0.37 g, 3.4 mmol), and $TiCl_4$ (0.65 g, 3.4 mmol) was repeated in identical fashion to Method B, except that in this instance $TiCl_4$, freshly distilled from CaH_2, was utilized. TLC analysis of the reaction mixture (benzene–hexane, 8:2) indicated a complete absence of the β–chloroketone (**264**), a significant amount of the α,β–unsaturated ketone (**265**), some unreacted benzaldehyde and two spots of similar R_f, lower than that of compound (**265**). The lower of these two spots was identified as menthol by comparitive TLC with a standard menthol sample, using a variety of benzene/Et_2O/hexane solvent systems. Flash chromatography (elution with benzene–Et_2O, 8:2) yielded three distinct fractions:

i) a mixture of (**265**) and unreacted benzaldehyde (0.55 g).

ii) the compound corresponding to the low R_f spot on the TLC plate (0.20 g) identified as 1–hydroxy–4,4–dimethyl–1–phenyl–3–pentanone (**266**),[301] ν_{max} (liquid film) 3450 (OH) and 1702 cm^{-1} (C =O); δ_H(60 MHz; CCl_4) 0.97 (9H, s, Bu^t), 2.65 (2H, m, 2–CH_2), 3.50 (1H, br s, OH), 4.98 (1H, m, 1–CH), and 7.92 (5H, s, ArH); *m/e* 206 (M^+,14%), 149(50), 107(100), and 57(95).

iii) a mixture (**266**) and the liberated chiral auxiliary, menthol (0.63 g).

Additional chromatography to further purify the above mixtures was deemed unnecessary and the overall yield of the reaction was estimated, from the ^1H NMR spectra of the above fractions and the theoretical amount of menthol, to be β–hydroxyketone (**266**) (330 mg, 50%) and the dehydrated product (**265**) (300 mg, 50%).

Method D

The reaction of (**164**) (1.00 g, 3.2 mmol), benzaldehyde (0.37 g, 3.4 mmol) and $TiCl_4$ (0.65 g, 3.4 mmol) was repeated in identical fashion to Method C. In this instance, however, the reaction was not warmed to ambient temperature overnight but instead, after stirring for 4.5 h, it was quenched at –78° C, by adding 5% aq $NaHCO_3$. Identical workup procedures to those employed in Method C, yielded a pale orange oil. TLC analysis of the reaction mixture [elution with benzene–Et_2O (8:2)] indicated the presence of some benzaldehyde, the desired compound, 1–hydroxy–4,4–dimethyl–1–phenylpentan–3–one (**266**) and the liberated menthol. No dehydrated product, (**265**), could be detected in the reaction mixture. Flash chromatography [elution with benzene–Et_2O (8:2)] resulted in the isolation of menthol (0.49 g, 3.1 mmol) and the β–hydroxyketone (**266**) (0.63 g, 97%).

The enantiomeric excess achieved in this reaction was evaluated in the same way as before.

i) Addition of $Pr(tfc)_3$ (12 mg) to a solution of (**266**) (53 mg) in CCl_4 induced a 40 Hz upfield shift of the tertiary butyl peak while resolving the enantiomeric singlets by 2.7 Hz. Digitisation of two independent data sets gave an average enantiomeric ratio of **57:43**.

ii) An addition of $Pr(tfc)_3$ (30 mg) marginally increased the overall upfield shift and increased the separation of the enantiomeric singlets to 4.7 Hz. However, this increased shift superimposed one of the singlets on another peak present in the spectrum.

iii) The $[\alpha]_D^{25}$ of (**266**) = -1.74° ($c = 1.7$, CCl_4)

The diastereomeric ratio of the (menthyloxy)dimethylsilyl derivative (**272**) (see reaction 3.11.2, p. 287), prepared from the β–hydroxyketone (**266**) could not be determined by high field NMR due to decomposition of the sample during the unavoidable delays in dispatching the sample to the instrument at our disposal. Attempts to separate the diastereomers by gas chromatography using a variety of temperature programs and a 30 m DB 225 column were unsuccessful.

3.11.2 *Reaction of Chloro(menthyloxy)dimethylsilane* (176) *and 1–hydroxy–4,4–dimethyl–1–phenyl–3–pentanone* (266)

A solution of (**176**) (0.943 g, 3,9 mmol) in anhydrous Et_2O (5 ml) was added to a solution of the β–hydroxyketone (**266**) (0.54 g, 2.6 mmol) and Et_3N (0.94 g, 3.9 mmol) in anhydrous Et_2O (20 ml) at room temperature. The reaction mixture was stirred overnight at room temperature and then saturated aq. $NaHCO_3$ was added. The resultant mixture was extracted with Et_2O and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was flash–chromatographed [elution with hexane–Et_2O (95:5)] to yield, as a colourless oil 1–[(menthyloxy)dimethylsiloxy]–4,4–dimethyl–1–phenyl–3–pentanone (**272**) (1.07 g, 99%), ν_{max} (liquid film) 1710 (C ═O), 1255 (Si—Me), and 1075 cm^{-1} [Si —O —C); δ_H(60 MHz, CCl_4) –0.24 and –0.23 (6H, 2 x s, 2 x SiMe), 0.30 – 0.76 (9H, m, 8′–, 9′–, and 10′–Me), 0.80 (9H, s, Bu^t), 1.10 – 2.20 (9H, m, 3′–, 4′–, and 6′–CH_2 and 2′–, 5′–, and 7′–H), 2.20 – 1.90 (2H, m, 2–CH_2), 3.1 (1H, br s, 1′–H), 5.10 (1H, dd, 1–H), and 7.08 (5H, s, ArH); *m/z* 320(1%), 279(7), 263(29), 205(44), 75(100), and 57(52).

3.11.3 *Reaction of (Cholesteryloxy)dimethyl(3,3–dimethylbut–1–en–2–yloxy)-silane* (194) *with benzaldehyde*

Method A2

The silyl enol ether (**194**) (1.73 g, 3.2 mmol), benzaldehyde (0.37 g, 3.4 mmol) and $TiCl_4$ (0.65 g, 3.4 mmol) were reacted via Method A2 as described previously for compound (**164**). Flash chromatography [elution with benzene–hexane (8:2)] resulted in the isolation of β–chloroketone (**264**) (0.32 g, 47%) and the dehydrated product (**265**) (0.25 g, 42%).

The enantiomeric excess achieved in this reaction was evaluated by the techniques described previously.

i) Addition of $Eu(tfc)_3$ (62 mg) to a solution of (**264**) (50 mg) induced a 13 Hz separation of the enantiomeric tertiary butyl singlets. Repeated integration of five independent data sets (running both the spectrum and the integrals in the forward and reverse directions) gave an average enantiomeric ratio of **53:47**.

ii) Digitising two further data sets, as described previously, gave an enantiomeric ratio of **52:48**.

iii) No optical activity could be detected against the background noise of the instrument, using a sample solution where *c* 2.5 in CCl_4.

Method D

The silyl enol ether (**194**) (1.73 g, 3.2 mmol), benzaldehyde (0.37 g, 3.4 mmol), and HCl free $TiCl_4$ (0.65 g, 3.4 mmol) were reacted via Method D as described previously for compound (**164**). Flash chromatography [elution with benzene–Et_2O (8:2)] resulted in the isolation of the *β*–hydroxyketone (**266**) (520 mg, 79%).

The enantiomeric excesses achieved in this reaction were determined as described before.

i) Addition of $Pr(tfc)_3$ (21 mg) to a solution of compound (**266**) (55 mg) in CCl_4 induced a 33 Hz upfield shift of the tertiary butyl peak while resolving the enantiomeric singlets by 3.3 Hz. Digitisation of two independent data sets gave an average enantiomeric ratio of **57:43**.

ii) A 3.3 Hz separation of the singlets of interest was too small for reliable spectrometer integration at 60 MHz. Increasing the amount of chiral shift reagent in the solution to 38 mg increased the separation to 4.0 Hz. However, this size of shift superimposed one of the singlets on another peak in the spectrum.

iii) The $[\alpha]_D^{25}$ of compound (**266**) = –1.02° (c 1.9, CCl_4)

3.11.4 *Reaction of (menthyloxy)dimethyl(1–phenylethen–2–yloxy)* (**180**) *with benzaldehyde*

Method A2

The silyl enol ether (**180**) (1.06 g, 3.2 mmol), benzaldehyde (0.37 g, 3.4 mmol), and $TiCl_4$ (0.65 g, 3.4 mmol) were reacted *via* Method A2, as described previously for compound (**164**). Flash chromatography [elution with benzene–hexane (8:2)] followed by preparative TLC, on the mixed fractions using the same eluant yielded unreacted benzaldehyde (0.13 g), 1–chloro–1,3–diphenylpropan–3–one (**267**) (0.06 g, 8%), m.p.112–113°C (from hexane) (lit.[302] 114–115°C); ν_{max} (liquid film) 1687 cm^{-1} (C=O); δ_H(300 MHz; $CDCl_3$) 3.59 and 3.94 (2H, 2 x dd, $J_{2a\text{-}2b}$ 18 Hz, $J_{2a\text{-}1}$ 6 Hz, $J_{2b\text{-}1}$ 8 Hz, 2–H_a and 2–H_b), 5.60 (1H, dd, $J_{1\text{-}2a}$ 6 Hz, $J_{1\text{-}2b}$ 8 Hz, 1–CH), and 7.20 – 8.10 (10H, m, ArH); δ_C (75 MHz; $CDCl_3$) 48.32 (C–1), 57.57 (C–2), 126.95, (ArC). 128.08 (ArC), 128.45 (ArC), 128.65 (ArC), 128.69 (ArC), 133.46 (ArC), 136.38 (ArC), 140.90 (ArC), and 195.57 (C–3); m/z 244(M^+, ^{35}Cl, 11%), 208(10), 105(100) and 77(49)

and

the unusual chalcone dimeride, *trans, trans, trans*–1,2–dibenzoyl–3,4–diphenylcyclobutane (**268**) (0.02 g, 2%), m.p. 125–127°C (from hexane) (lit.[259]

125–126.5° C); ν_{max} (liquid film) 1643 cm^{-1} (C═O);[bg] *m/z* 310 (85%), 233(58), 105(51) and 77(100) (Found: M^+–PhCHO, 310.1336. Calc. for $C_{30}H_{24}0_2$: M^+–PhCHO, 310.1356).

The specific rotation of compound **(267)** $[\alpha]_D^{25}$=–1.3° (*c* = 7.7 in $CHCl_3$). The enantiomerically pure β–chloroketone **(267)** is unknown and thus this specific rotation could not be related to an enantiomeric excess.

Method D

The silyl enol ether **(180)** (0.50 g, 1.5 mmol), benzaldehyde (0.16 g, 1.6 mmol), and HCl free $TiCl_4$ (0.35 g, 3.4 mmol) were reacted via Method D as described previously for compound **(164)**. Flash chromatography [elution with benzene–Et_2O (8:2)] afforded the 1–hydroxy–1,3–diphenylpropan–3–one **(269)** (0.24 g, 66%), m.p. 50–51° C (from Et_2O / hexane) (lit.[301] 53–54° C), ν_{max} (liquid film) 3480 (OH) and 1677 cm^{-1} (C ═O); δ_H(60 MHz; CCl_4) 3.15 (2H, d, $J_{1\text{-}2}$ 6 Hz, 2–CH_2), 3.50 (1H, s, OH), 5.15 (1H, m, 1–CH) and 7.2 – 8.0 (10H, m, ArH); *m/z* 226 (M^+, 11%), 208(27), 120(50), 105(99), and 77(100).

The specific optical rotation, $[\alpha]_D^{26}$ = –3.12° (*c* 1.9 in methanol). The literature value for the enantiomer with (S)– configuration at greater than 98% optical purity is $[\alpha]_D^{25}$ = –32.50° (*c* 0.4 in methanol) [260]. These optical rotations enable the enantiomeric excess achieved to be calculated as **10%**.

[bg] The amount of the chalcone dimeride **(268)** isolated was insufficient to obtain a 60 MHz ^1H NMR spectrum. The high field ^1H NMR spectrum obtained some time later, indicated complete isomerisation to the conventional chalcone.

3.12. Reactions of chlorosilanes with organometallic reagents.

3.12.1 *Preparation of Menthyl Chloride* (273) [262]

Solid (–)–menthol (7.80 g, 50 mmol) was added to a solution of $ZnCl_2$ (22.60 g, 170 mmol) in 34% aq. HCl (20 ml) and the resulting heterogeneous mixture was vigorously stirred for 5 h at 35° C. The reaction mixture was extracted with hexane (2 x 30 ml) and the combined organic layers washed with portions of concentrated H_2SO_4 (10 ml) until the acid layer no longer discoloured. The organic layer was then washed with H_2O (50 ml), dried ($MgSO_4$), and concentrated *in vacuo*, without heating. Distillation of the residual liquid afforded [2–(*S*)–(2α,1β,5β)]–1–chloro–5–methyl–2–(methylethyl)cyclohexane [bh] (**273**) (6.20 g, 71%), b.p. 104° C / 28 mmHg (lit.,[262] 101–101.5° C/21 mmHg); $[\alpha]_D^{26}$ –44.5° (neat liquid) [lit.,[262] $[\alpha]_D^{20}$ –45.0° (neat liquid)]; ν_{max} (liquid film) 1470 and 730 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 0.75 (3H, d, 9′–Me), 0.86 (1H, m, 4′–H_{ax}), 0.90 (6H, d, 10′– and 8′–Me), 0.95 (1H, m, 3′–H_{ax}), 1.14 (1H, m, 6′–H_{ax}), 1.35 (1H, q, 2′–H), 1.44 (1H, m, 5′–H), 1.70 (2H, m, 3′–H_{eq} and 4′–H_{eq}), 2.22 (1H, m, 6′–H_{eq}), 2.33 (1H, m, 7′–H), and 3.74 (1H, m, 1–H); *m/z* 139(8%), 123(25), 96(62), and 81(100).

3.12.2 *Preparation of Bornyl Chloride* [266,267]

Anhydrous HCl gas was bubbled through a solution of (–)–α–pinene in anhydrous pentane (110 ml) until the flask attained constant mass (this procedure required *ca.* 4 h). The solvent was evaporated *in vacuo* and the residual solid recrystallized from hot methanol to yield 2–chloro–1,7,7–trimethylbicyclo [2.2.1] heptane (22.76 g, 40%), m.p. 123° C

[bh] While this numbering system does not give the lowest numbered locants and the name is thus not systematically correct, the numbering was used to maintain consistency in all the menthyl compounds prepared in this investigation. (The numbering system employed is based on a cyclohexanol parent system.)

(lit.,[267] 131–132° C); $[\alpha]_D^{26}$ –28.5° (*c* 2.6 in EtOH) [lit.[303,266] $[\alpha]_D^{27}$ = **+25.5°**[bi] (*c* 2.0 in EtOH)]; δ_H(60 MHz; $CDCl_3$) 0.90 and 0.95 (9H, 2 x s, 8′–, 9′– and 10′–Me), 1.00 – 2.20 (7H, m, 3–,5–, and 6–CH_2 and 4–H), and 4.15 (1H, m, 2–H).

3.12.3 *Preparation of THF solutions of menthyl magnesium chloride* (274)[263]

EtBr (0.12 ml) was added to a suspension of Mg (1.73 g, 71 mmol) in anhydrous THF (15 ml). The reaction mixture was heated to *ca.* 50° C and a solution of menthyl chloride (**273**) in THF (20 ml) was added dropwise over a period of 1.5 h. The resultant mixture was then refluxed for 1 h and on cooling the supernatant decanted, under an inert atmosphere, from the residual magnesium (0.67 g, 27 mmols). This magnesium was washed with THF (2 x 3 ml) and these washings were added to the decanted solution. The quantity of magnesium remaining is indicative of a 79% conversion to the Grignard reagent.

Gilman's back titration [304]: Quenching an aliquot of the Grignard solution (1.00 ml) in standard 0.1 M HCl (20.00 ml) and titrating with standard 0.1 M NaOH (average titre volume 11.25 ml) showed the concentration of the Grignard solution to be 0.87 M. (Taking into account the total volume of the decanted solution, this concentration reflects a conversion of *ca.* 80%.)

Titration with 2–butanol using 1,10–phenanthroline as indicator:[265] An aliquot of the Grignard solution (5.00 ml) was added to a solution of

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[bi] In a personal communication, G.W. Erickson [303] conceded, in light of the optical rotation values obtained by both ourselves and Zeiss and Zwanzig,[266] that the direction of their reported rotation was in error.

1,10–phenanthroline (*ca.* 2 mg) in anhydrous benzene (10.00 ml). Titration of this solution with 1.060 M 2–butanol in xylene (average titre volume 3.90 ml) revealed the concentration of the Grignard solution to be 0.81 M.

(In subsequent preparations of the Grignard reagent only the 1,10–phenanthroline titration was employed.)

3.12.4 *Reaction of Menthyl Magnesium Chloride* (274) *with Chlorotrimethylsilane.*

TMSCl (1.40 g, 13 mmol) was added to a 0.8 M solution of menthyl magnesium chloride in THF (16.4 ml). The reaction mixture was then refluxed for 2 h and stirred at room temperature thereafter, until titration of aliquots of the reaction mixture with 2–butanol, using 1,10–phenanthroline as an indicator, showed all the Grignard to be consumed (*ca.* 72 h). The reaction mixture was poured into cold saturated aq. $NaHCO_3$ and the resultant mixture extracted with Et_2O (2 x 25 ml). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to afford a multi–component mixture. Distillation of this residual material afforded a fraction containing 52% of a particular component plus a number of smaller components. Preparative GLC separation (5% SE30 on Chromosorb W) of a portion of this fraction afforded, as an oil, menthyltrimethylsilane (**275**) (31%[bj]), $[\alpha]_D^{26}$ –69.4° (*c* 1.7 in hexane); ν_{max} (liquid film) 1250 cm^{-1} (Si —Me); δ_H(500 MHz; $CDCl_3$) 0.09 (9H, s, 3 x SiMe) 0.71 (3H, d, 9′–Me), 0.86 (1H, m, 4′–H_{ax}), 0.90 (6H, d, 10′– and 8′–Me), 0.92 (1H, m, 3′–H_{ax}), 0.98 (1H, q, 6′–H_{ax}), 1.10 (1H, q, 2′–H), 1.35 (1H, m, 5′–H), 1.56 (2H, m, 3′–H_{eq} and 4′–H_{eq}), 1.82 (1H, m, 6′–H_{eq}), 2.12 (1H, m, 7′–H), and 3.36 (1H, dt, 1′–H); *m/z* 212(5%), 143(100), 75(54), and 73(34).

[bj] Approximate yield based on the capilliary GLC of the crude reaction reaction mixture.

3.12.5 *Reaction of Cl_2SiPh_2 with Menthyl Magnesium Chloride* (275) *and 1–Phenylethanol*

A solution of dichlorodiphenylsilane (6.33 g, 25 mmol) in anhydrous THF (40 ml) was added to 0.8 M menthyl magnesium chloride solution (32 ml). The reaction mixture was refluxed until titration of aliquots of the reaction mixture with 2–butanol, using 1,10–phenanthroline as an indicator, showed all the Grignard to be consumed (*ca.* 72 h). Et_3N (2.02 g, 20 mmol) and a solution of 1–phenylethanol (2.44 g, 20 mmol) in THF (7 ml) were sequentially added to the reaction mixture, resulting in an exothermic reaction and the immediate precipitation of a white solid. This suspension was stirred overnight at room temperature and then poured into saturated aq. $NaHCO_3$. The resultant mixture was extracted with Et_2O (2 x 50 ml) and the combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography of the residual oil [elution with hexane:EtOAc (98:2)] afforded, as the major component, the diastereomeric diphenyl[*bis*(1–phenylethoxy)]silane *(*279*)* (2.4 g, 40%), ν_{max} (liquid film) 1430 and 1110 (Si — Ph) and 1030 cm^{-1}[Si — O(C)] ; δ_H(60 MHz; $CDCl_3$) 1.35 (6H, t[bk], CH_3CH), 5.00 (2H, m, CH_3CH), and 7.10 – 7.90 (20H, m, ArH); δ_C(125 MHz; $CDCl_3$)[bl] 26.51 and 26.77 (2 x q, CH_3CH), 71.25 and 71.29 (2 x d, CH_3CH), 125.27 (d, ArC), 125.40 (d, ArC), 126.76 (d, ArC), 126.86 (d, ArC), 127.54 (d, ArC), 127.66 (d, ArC), 127.72 (d, ArC), 128.03 (d, ArC), 128.07 (d, ArC), 129.99 (d, ArC), 130.08 (d, ArC), 133.46 (s, ArC), 135.03 (d, ArC), 145.79 (s, ArC), and 145.92 (s, ArC); *m/z*

[bk] Although the signal appears in the spectrum as a well defined triplet, it must comprise the two partially superimposed doublets of the CH_3CH group in each diastereomer.

[bl] Duplication of the methyl and methine carbon signals are due to the two diastereomers present. A similar effect is seen for the majority of the aromatic carbons.

409 (M^+–CH_3, 8%), 346(16), 319(22), 199(100), 139(41), 105(31), and 77(30) (Found 409.1627. Calc. for $C_{28}H_{28}O_2Si$ M^+–CH_3, 409.1624.)

During the course of the flash chromatography to purify compound (**279**) a minor compound was also isolated. This compound was not fully characterized, but, based on the 60 MHz ^1H NMR obtained, the compound was tentatively identified as menthyldiphenyl(1–phenylethoxy)silane (**278**) (0.50 g, 5%), δ_H(60 MHz; $CDCl_3$) 0.40 – 2.70 (22H, 2 x m, menthyl CH_3, CH_2, and CH and CH_3CH—O), 4.90 – 5.40 (1H, m, CH_3C*H*—O), and 7.10 – 8.10 (15H, m, ArH).

3.13 Preparation of the proline derived chiral auxiliaries (280) and (281)

3.13.1 *Preparation of (S)–(+)–2–hydroxymethylpyrrolidine* (288).

Finely divided L–proline (20.00 g, 174 mmol) was added, under an inert atmosphere, to a suspension of LAH (9.60 g, 250 mmol) in anhydrous THF (400 ml) and the resulting mixture was refluxed overnight. The excess LAH was destroyed by the cautious addition of H_2O (9 ml), 15% KOH (9 ml), and H_2O (30 ml) to the cooled reaction mixture. After refluxing this mixture for 15 min the granular, white, inorganic precipitate was removed by filtration. This solid material was refluxed for 24 h in fresh THF (200 ml) and once again filtered. The filtrates were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Distillation of the resultant oil yielded (S)–(+)–2–hydroxymethyl-pyrrolidine (288) (4.10 g, 23%), b.p. 87° C / 5 mmHg (lit.[305] 79 – 82° C / 10 mmHg); $[\alpha]_D^{26}$ +31.5° (*c* 1.0 in benzene); δ_H(60 MHz; $CDCl_3$) 1.70 (4H, m, $CH_2—CH_2$), 2.90 (2H, m, N — CH_2), 3.45 (3H, m, N — CH and O — CH_2), and 3.85 (2H, s, OH and NH).

3.13.2 *Preparation of (S)–(–)–N–formyl–2–hydroxymethylpyrrolidine* (289)

Ethyl formate (4.23 g, 57 mmol) was added dropwise to prolinol (288) at 0° C and the mixture was stirred at that temperature for 30 min before being allowed to warm to room temperature. The resulting oil was vacumn distilled to afford, as a pale yellow oil, (*S*)–(–)–*N*–formyl–2–hydroxymethylpyrrolidine (289) (4.70 g, 70%), b.p. 126 – 130° C / 0.3 mmHg (lit.[306] 122° C / 0.5 mmHg); $[\alpha]_D^{26}$ –32.2° (*c* 2.0 in benzene) [lit.[306] –18.° C (*c* 2.0 in benzene)]; ν_{max} (liquid film) 3350 (OH) and 1625 cm^{-1} (C=O) ; δ_H(60 MHz; $CDCl_3$) 1.90 (4H, m, $CH_2—CH_2$), 3.45 (5H, m, N — CH_2, N — CH, and O — CH_2), 5.10 (1H, s, OH), and 8.40 (1H, m, CHO).

3.13.3 *Preparation of (S)–(–)–N–formyl–2–methoxymethylpyrrolidine* (290)

Compound (**289**) (4.40 g, 34 mmol) and methyl iodide (7.26 g, 51 mmol) were dissolved in anhydrous THF (50 ml). Under an inert atmosphere, 50% NaH dispersion in oil (2.74 g, 56 mmol) was added portion–wise to the reaction mixture. The white suspension resulting from the exothermic addition was refluxed for 1 h and then poured into brine. This mixture was extracted with CH_2Cl_2 and the organic layer was then dried ($MgSO_4$) and concentrated *in vacuo*. The residual oil was vacumn distilled to afford, as an oil, (*S*)–(–)–*N*–formyl–2–methoxymethylpyrrolidine (**290**) (1.90 g, 34%), b.p. 78–80°C / 0.3 mmHg (lit. ^{306} 67°C / 0.25 mmHg); $[\alpha]_D^{26}$ –34.3° (*c* 2.2 in toluene) [lit. ^{306} –43.5°C (*c* 2.0 in benzene)]; ν_{max} (liquid film) 1665 cm^{-1} (C$=$O) ; δ_H(60 MHz; $CDCl_3$) 1.95 (4H, m, CH_2—CH_2), 3.45 (3H, s, OMe), 3.30 – 3.60 (5H, m, N—CH_2, N—CH, and O—CH_2), and 8.40 (1H, m, CHO).

3.13.4 *Preparation of (S)–(+)–2–methoxymethylpyrrolidine* (280)

A mixture of compound (**290**) (1.46 g, 10 mmol) and 10% aq. KOH (20 ml) was vigorously stirred at 130°C for 4 h. The mixture was then cooled and extracted with Et_2O (4 x 20 ml) and the Et_2O layer was separated, dried ($MgSO_4$) and evaporated *in vacuo* without heating. The residual oil was distilled to afford (*S*)–(+)–2–methoxymethylpyrrolidine (**280**) (0.67 g, 58%), b.p. 73– 75°C / 40 mmHg (lit. ^{306} 62°C / 40 mmHg); ν_{max} (liquid film) 3300 cm^{-1} (NH); δ_H(60 MHz; $CDCl_3$) 1.55 – 2.22 (4H, m, CH_2—CH_2), 2.55 (1H, s, NH), 3.40 (3H, s, OMe), and 2.80 – 3.60 (5H, m, N—CH_2, N—CH, and O—CH_2).

The above reactions (3.13.1 – 3.13.4) have been reported to illustrate the isolation and partial characterization of the known intermediate compounds

[(**288**) – (**290**)] *en route* to the desired auxiliary (**280**). In subsequent, larger scale preparations the methoxymethylpyrrolidine (**280**) was obtained in 48% overall yield from proline by not purifying any of the intermediate compounds.[271]

3.13.5 *Preparation of n–butyl 5–oxopyrrolidine–2–carboxylate* (**293**)

L–glutamic acid (29.43 g, 0.2 mol), *n*–butanol (118.60 g, 1.6 mol), and H_2SO_4 (24.5 g, 0.25 mol) were mixed in a reaction vessel equipped with a Dean and Stark trap, charged with 4A molecular sieves. The reaction mixture was refluxed for 12 h and then the pH was increased to 4.5 by the addition of 1 M aq. Na_2CO_3. The excess butanol was evaporated *in vacuo* and benzene (100 ml) added to the residue. This residue was neutralised with 5 M NaOH and the organic layer was separated. The aq. layer was re–extracted with further benzene (100 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Distillation of the residual oil afforded the *n*–butyl 5–oxopyrrolidine–2–carboxylate (**293**) (20.8 g, 56%), b.p. 154 – 160°C / 0.6 mmHg (lit. [273] 180°C / 6.5 mmHg); ν_{max} (liquid film) 3225 (NH) and 1700 cm^{-1} (C=O); δ_H(60 MHz; $CDCl_3$) 0.95 (3H, t, CH_3CH_2), 1.50 (4H, m, 3–CH_2 and CH_3CH_2), 2.25 (4H, m, 4–CH_2 and $CH_2CH_2CH_2$), 4.15 (3H, m, O–CH_2 and 2–H), and 7.95 (1H, s, NH).

3.13.6 *LAH reduction of compound* (**293**)

A solution of compound (**293**) (18.00 g, 97 mmol) in anhydrous Et_2O (150 ml) was added dropwise to a suspension of LAH (6.46 g, 0.17 mol) in anhydrous Et_2O (500 ml). To the cooled reaction mixture H_2O (6 ml), 15% KOH (6 ml), and H_2O (18 ml) were added successively. The granular, white precipitate was removed by filtration and the filtrate was dried ($MgSO_4$) and concentrated *in vacuo*. Distillation of the resultant oil yielded (*S*)–(+)–2–hydroxymethylpyrrolidine (**288**) (1.60 g, 16%), b.p. 78° C / 2.5 mmHg (lit.[305] 79 – 82° C / 10 mmHg).

3.13.7 *Preparation of (S)–(–)–N–methylprolinol* (281)

Acetic anhydride (60 ml) was added to a solution of L–proline (10.00 g, 87 mmol) in 97% formic acid (185 ml) at 5 –10° C and the resulting mixture was stirred at room temperature for 2 h. Concentration of the reaction mixture afforded the crude *N*–formylproline (**291**) which was immediately dissolved in anhydrous THF (40 ml) and cautiously added to a suspension of LAH (16.50 g, 0.44 mol) in dry THF (250 ml). The resulting mixture was refluxed for 48 h and after cooling the excess LAH was destroyed by the successive addition of H_2O (16 ml), 15% KOH (16 ml), and H_20 (50 ml). The granular precipitate was removed by filtration and the filtrate was dried ($MgSO_4$) and concentrated *in vacuo*. Distillation of the residual oil afforded (*S*)–(–)–2–hyrdoxymethyl–*N*––methylpyrrolidine (**281**) (5.40 g, 56%), b.p. 57 – 58° C/ 2 mmHg (lit.[307] 57° C / 2 mmHg); $[\alpha]_D^{26}$ –51.4° (*c* 2.2 in toluene) [lit.,[272] –50° (MeOH)]; ν_{max} (liquid film) 3400 cm^{-1} (OH) ; δ_H(60 MHz; $CDCl_3$) 1.80 (4H, m, CH_2—CH_2), 3.45 (3H, s, NCH_3), 2.10 – 2.60 (2H, m, N —C H_2), 3.10 (1H, m, N —C H), 3.65 (2H, d, HO —CH_2), and 4.40 (1H, s, OH).

3.14 Preparation of silyl enol ethers incorporating the chiral auxiliaries (280) and (281).

The same precautions, to ensure rigorously anhydrous conditions, were observed as for the preparation of the previous silyl enol ethers. All the GLC studies described in this section employed fused silica DB225 columns.

3.14.1 *Reaction of the lithium enolate of pinacolone, the lithium alkoxide of auxiliary* (281), *and* $Cl_2Si\ Me_2$

1.5 M BuLi (6 ml) was added to a solution of compound (**281**) in Et_2O (15 ml) at –78°C. A precipitate formed immediately and the resulting slurry was allowed to warm to room temperature over 2 h. Dry THF (20 ml) was added to the slurry in an attempt to enhance the solubility of the precipitate. This slurry was transferred, *via* a heavy gauge canula, to a solution of Cl_2SiMe_2 (1.12 g, 9 mmol) in Et_2O (20 ml) at room temperature. This mixture was stirred for 4 h at room temperature and then a solution of the pinacolone lithium enolate [prepared from pinacolone (0.87 g, 9 mmol), 1.5 M BuLi (6 ml, 9 mmol), and diisopropylamine (0.91 g, 9 mmol) as described previously] was added to the reaction mixture at –78°C. The reaction mixture was allowed to warm to room temperature overnight and then poured into cold saturated aq. $NaHCO_3$. The resulting mixture was extracted with Et_2O and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. GC–MS (GLC temperature programme: 100 – 200°C at 10°C / min) of the residual oil indicated three major components:–

i) Retention time – 5.1 min. *m/z* 256 (M^+, 9%), 241(8), 199(45), 170(42), 141(57), and 75(100). This mass spectrum is consistent with the dimethyl*bis*(3,3–dimethylbut–1–en–2—

yloxy)silane (**175**).[bm]

ii) Retention time – 7.5 min. m/z 330 (M^+,4%), 244(23), 231(84), 215(83), 149(100), 133(93) and 83(48). The compound consistent with this mass spectrum could not be identified.

iii) Retention time – 9.7 min. m/z 271 (M^+, 4%), 256(1), 172(89), and 84(100). This mass spectrum is consistent with the silyl enol ether, dimethyl(3,3–dimethylbut–1–en–2–yloxy)-(*N*–mehtylprolinyloxy)silane (**296**).

Flash chromatography of a portion of the crude oil (1.00g) (eluting with hexane) yielded, as an oil, *dimethylbis(3,3–dimethylbut–1–en–2–yloxy)silane* (**175**) (420 mg)[bn]; ν_{max} (liquid film) 1625 (C ═C), and 1260 cm^{-1} (Si — Me); δ_{H} (500 MHz; CDCl$_3$) 0.25 (6H, s, 2 x SiMe), 1.05 (18H, s, 2 x Bu^t), and 4.12 (4H, s, 2 x vinyl CH$_2$); δ_{C} (125 MHz; CDCl$_3$) –2.86 (q, SiMe), 28.01 (q, C–4), 36.35 (s, C–3), 87.03 (t, C–1), and 165.91 (s, C–2).

(The remaining two components could not be eluted, even when using a CHCl$_3$:MeOH (9:1) eluant. Fractional distillation also failed to separate the silyl enol ether (**296**) and the unidentified contaminant.)

3.14.2 *Reaction of the lithium enolate of pinacolone, Cl$_2$SiMe$_2$, and methoxymethylpyrrolidine* (280)

1.5 M BuLi (22 ml, 33 mmol) was added to a solution of diisopropylamine (3.33 g, 33 mmol) in anhydrous ether (75 ml) at –78° C and the resulting solution was stirred at that temperature for 30 min. A solution of pinacolone (2.97 g, 30 mmol) in Et$_2$0 (15 ml) was added and the mixture stirred for a further 1 h at

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[bm] Walkup [206] detected this *bis*–substituted silane (**175**) but did not report its characterization.

[bn] The amount of compound (**296**) isolated from a portion of the crude oil (1.00 g) is indicative of a total yield of *ca.* 40%.

–78°C. Cl_2SiMe_2 (3.87 g, 30 mmol) was added to the reaction mixture which was then allowed to warm to room temperature over 5 h. The resulting suspension was cooled in ice and Et_3N (3.02 g, 30 mmol) and the amine (**280**) were added consecutively to the reaction mixture. After stirring overnight, saturated aq. $NaHCO_3$ was added to the mixture which was then extracted with Et_2O. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Distillation of the residual oil yielded two fractions:–

i) dimethyl*bis*(3,3–dimethylbut–1–en–2–yloxy)silane (**175**) (*ca.* 1.00 g), b.p. 40 – 45°C / 0.4 mmHg.

ii) 1–[dimethyl(3,3–dimethylbut–1–en–2–yloxy)silyl]–2–methoxymethylpyrrolidine) (**298**) [5.61 g, (75% purity by GLC)], b.p. 72 – 80°C / 0.35 mmHg; ν_{max} (liquid film) 1618 (C ═C), and 1255 cm^{-1} (Si — Me); δ_H (200 MHz; $CDCl_3$)[bo] 0.20 (6H, s, SiMe), 1.06 (9H, s, Bu^t), 1.81 (4H, m, CH_2—C H_2), 3.39 (3H, s, OCH_3), 2.94 – 3.66 (3H, m, N —C H_2 and N —C H), and 4.10 (4H, m, MeO —CH_2 and vinyl CH_2); GC–MS (100 – 200°C, 10°C / min, retention time = 10.6 min) *m/z* 271(M^+, 0.1%), 256(0.7), 226(100), 157(51), 75(96).

3.14.3 *Preparation of chlorodimethyl(3,3–dimethylbut–1–en–2–yloxy)-silane (*176*).*

1.5 M BuLi (43 ml, 65 mmol) was added to a solution of diisopropylamine (6.46 g, 64 mmol) in anhydrous ether (150 ml) at –78°C and the resulting solution

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[bo] The high field ^1H NMR spectrum reflects the contamination of the sample with the unidentified component and the *bis* substituted silane (**175**). Due to the extent of the contamination, optical rotation measurements, elemental analysis and ^{13}C NMR spectroscopy were not conducted.

was stirred at that temperature for 30 min. A solution of pinacolone (6.00 g, 60 mmol) in Et_20 (30 ml) was added and the mixture stirred for a further 1 h at –78° C. Cl_2SiMe_2 (7.74 g, 61 mmol) was added to the reaction mixture which was then allowed to warm to room temperature overnight. The inorganic salts were allowed to precipitate and the supernatant was then decanted under an inert atmosphere. The solvent was removed by distillation under an inert atmosphere and vacumn distillation of the residue afforded chlorodimethyl(3,3–dimethylbut–1–en–2–yloxy)silane (**176**) (4.27 g, 37%), b.p. 52 – 53° C / 10 mmHg (lit.[206] 27 – 30° C / 2.1 mmHg); ν_{max} (liquid film) 1625 (C ═C), and 1260 cm^{-1}(Si — Me); δ_H (60 MHz; $CDCl_3$) 0.50 (6H, s, SiMe), 1.05 (9H, s, Bu^t), and 4.30 (2H, s, vinyl CH_2).

3.14.3 *Reaction of 1′ –[dimethyl(3,3–dimethylbut–1–en–2–yloxy)silyl]–(2′ –methoxymethylpyrrolidine)* (**298**) *with benzaldehyde.*

The contaminated silyl enol ether (**298**) (0.87 g, 3.2 mmol), benzaldehyde (0.37 g, 3.4 mmol), and HCl free $TiCl_4$ (0.65 g, 3.4 mmol) were reacted via Method D as described for compound (**164**) (See Section 3.11.1, p. 285). Flash chromatography [elution with benzene–Et_2O (8:2)] resulted in the isolation of the β–hydroxy ketone (**266**) (0.49 g, 71%).

Addition of $Pr(tfc)_3$ (12 mg) to a solution of compound (**266**) (50 mg) in CCl_4 induced a 8 Hz upfield shift while resolving the the enantiomeric singlets by 2.6 Hz. Digitisation of two independent data sets gave an average enantiomeric ratio of 54:46.

3.15 Preparations of camphorimide (300) derivatives and attempts to achieve asymmetric modifications of the Gabriel synthesis.

High field ^1H and ^{13}C NMR spectra were obtained for the majority of the camphorimide derivatives prepared in this section. This was necessary in order to assign the signals in the spectra of the novel compounds and to facilitate the structure elucidation of the unknown products. The absolute and relative chemical shifts of the four methylene protons of the cyclopentane ring in all these derivatives proved to be remarkably sensitive to the nature of the ring substituents. No attempt was made to assign these protons, except in the isolated instances when two dimensional spectroscopy was conducted or when the spectrum of a closely analogous compound had been assigned. Even in these cases the assignment is somewhat tentative.

3.15.1 *Preparation of camphorimide* (300)

Camphoric acid (299) (30.00 g, 150 mmol) and 25% aq. NH_3 (20 ml) were mixed together and the mixture heated to 200° C and 22 bar in an autoclave for 5 h. After cooling overnight the resultant solid was washed with ice cold H_2O and recrystallized from 10% acetic acid to afford 1,8,8–trimethyl–2,4–dioxo–3–aza–bicyclo[3.2.1]octane (300) (24.70 g, 91%), m.p. (sealed tube) 240 – 242° C (lit. [307] 243° C); $[\alpha]_D^{26}$ +2.4° (c 2.4 in acetone) ; ν_{max} (KBr) 3200 (NH) and 1715 and 1685 cm^{-1} [C(O)—NH—C(O)]; δ_H(300 MHz; $CDCl_3$)[bp] 0.94, 1.00, and 1.14 (9H, 3 x s, 9–, 10–, and 11–Me), 1.80 (1H, m, 6–H_{exo}), 1.93 (2H, m, 7–H_{exo} and 7–H_{endo}), 2.18 (1H, m, 6–H_{endo}), 2.58 (1H, dd, $J_{5\text{-}6exo}$ 2

[bp] The 6–H_{exo} and 6–H_{endo} protons were distinguished from the 7–H_{exo} and 7–H_{endo} protons by the correlations of two of the four protons with the 5–H proton in the COSY spectrum. The assignments of the 6–H_{endo} and 6–H_{exo} protons for the 6–CH_2 group are tentative, based on the chemical shifts of each signal and the complexity of the signals relative to the expected coupling.

Hz, $J_{5\text{-}6endo}$ 7 Hz, 5–H), and 8.30 (1H, s, NH); δ_C (125 MHz; $CDCl_3$) 13.23, 19.43, and 21.92 (C–9, C–10, and C–11), 25.33 (C–6), 34.29 (C–7), 45.12 (C–8), 53.89 (C–1), 56.05 (C–5), and 176.43 and 178.40 (C–2 and C–4).

3.15.2 *Preparation of N–benzylcamphorimide* (302)

Benzyl chloride (4.00 g, 32 mmol) was added to a solution of camphorimide (5.70 g, 32 mmol) in 1.1 M ethanolic KOH (31 ml) and the resulting slurry was refluxed for 2 h. The ethanol was evaporated *in vacuo*. The sticky residue was diluted with 1% aq. KOH and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with hexane – EtOAc (85:15) afforded, as a colourless oil (which could not be crystallized), *N*–benzyl–1,8,8–trimethyl–2,4–dioxo–3–aza–bicyclo[3.2.1]octane (**302**) $[\alpha]_D^{26}$ = +11.7° (*c* 2.9 in EtOH) [lit.[308] +12.7° (*c* 1.8 in EtOH)] ; ν_{max} (liquid film) 1715 and 1670 cm^{-1} [C(O)—NH—C(O)]; δ_H(500 MHz; $CDCl_3$)[bq] 0.87, 0.92, and 1.17 (9H, 3 x s, 9–, 10–, and 11–Me), 1.73 (1H, m, 6–H_{exo}), 1.85 (2H, m, 7–H_{exo} and 7–H_{endo}), 2.19 (1H, m, 6–H_{endo}), 2.70 (1H, d, 5–H), 4.83 (2H, s, N–CH_2), and 7.18 – 7.32 (5H, m, ArH); δ_C (125 MHz; $CDCl_3$) 13.92, 18.94, and 21.86 (3 x q, C–9, C–10, and C–11), 25.10 (t, C–6), 34.03 (t, C–7), 42.33 (t, C–12), 44.10 (s, C–8), 54.29 (s, C–1), 56.43 (d, C–5), 127.13 (d, C–16), 128.16 and 128.53 (2 x d, C–14 and C–15), 137.13 (s, C–13), and 175.97 and 177.93 (2 x s, C–2 and C–4); *m/z* 271 (*M*$^+$, 60%), 160(48), and 106(100).

3.15.3 *Preparation of 1–bromo–1–phenylethane*

Cold 45% (w/v) aq. HBr (26.00 g, 330 mmol) was added to styrene (10.00 g, 96

[bq] The assignment of the 6–H_{exo}, 6–H_{endo}, 7–H_{exo}, and 7–H_{endo} signals is by analogy with the assignments made for camphorimide (**300**).

mol) at 5°C. The resulting mixture was allowed to stir at room temperature overnight and then poured into H_2O. The mixture was extracted with Et_2O and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Fractional distillation of the residual oil afforded 1–bromo–1–phenylethane (8.90 g, 51%), b.p. 92 – 95°C / 12 mmHg (lit. [308] 94°C / 16mmHg); δ_H(60 MHz; $CDCl_3$) 2.05 (3H, d, *J* 7 Hz,CHBr — C*H*$_3$), 5.20 (1H, q, *J* 7 Hz,C*H*Br — CH_3), and 7.15 – 7.60 (5H, m, ArH).

3.15.4 *Preparation of N–[1–(1–phenylethyl)]benzylcamphorimide* (305)

A solution of camphorimide (**300**) (2.50 g, 14 mmol) in benzene (10 ml) was added dropwise to a solution of EtOH (1 ml) and sodium metal (0.315 g, 14 mmol) in benzene (2.5 ml). Additional benzene (10 ml) was added to the resulting slurry before refluxing the mixture for 1 h. The crude sodium salt of camphorimide (**304**) was filtered and dried in a vacumn dessicator. It was subsequently added, as a solid, to a solution of 1–bromo–1–phenylethane (2.00 g, 11 mmol) in DMF (20 ml) and the mixture was then refluxed for 4 h. After cooling, the suspension was poured into H_2O and the resulting mixture was extracted with $CHCl_3$ (2 x 50 ml). The combined organic layers were washed with 0.2 M NaOH and H_2O (50 ml), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography [elution with hexane:EtOAc (80:20)] of the residual oil afforded 1,8,8–trimethyl–2,4–dioxo–3–(*N*–phenylethyl)–3–aza–bicyclo[3.2.1]-octane (**305**), δ_H(60 MHz; $CDCl_3$) 0.95, 1.10, and 1.18 (9H, 3 x s, 9–, 10–, and 11–Me), 1.75 (3H, d, *J* 7 Hz, CH — C*H*$_3$), 1.90 and 2.65 (5H, 2 x m, 6–CH_2, 7–CH_2, and 5–H), 5.95 (1H, d, *J* 7 Hz, C*H* — CH_3), and 7.35 (5H, s, ArH). *m*/*z* 285 (M^+, 100%), 173(99), 119(53) and 105(56).

3.15.5 *Preparation of N–benzylphthalimide* (301)

An intimate mixture of phthilamide (10.00 g, 68 mmol) and K_2CO_3 (5.00 g) was prepared and then treated with benzyl chloride (10.00 g, 80 mmol). The resulting slurry was heated in an oil bath until complete solidification occured, at which time DMF (10 ml) was added and the solution was then refluxed for 3 h. The excess benzyl chloride was removed by steam distillation and the residual solid washed with H_2O and recrystallized from acetic acid to afford *N*–benzylphthalimide (**301**) (12.30 g, 74%), m.p. 116 – 117° C (lit. [309] 116° C); *m*/*z* 237(*M*+, 100%), 220(36), and 104 (52).

3.15.6 *Hydrazinolysis of N–benzylphthalimide* (301)

Hydrazine hydrate (0.63 g, 13 mmol) was added to a suspension of *N*–benzylphthalimide (**301**) in MeOH. The resultant slurry was refluxed for 2 h. The reaction mixture was then acidified to pH 1 with 6 M HCl and filtered to remove the precipitated solid. The filtrate was concentrated *in vacuo*, to remove the excess MeOH, and the residue was basified to pH 12 with 10% NaOH and extracted with Et_2O (2 x 20 ml). The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo* to afford benzylamine (0.80 g, 58%); δ_H(60 MHz; $CDCl_3$) 1.80 (2H, s, NH_2), 3.85 (2H, s, CH_2), and 7.35 (5H, s, ArH).

3.15.7 *Heating of N–benzylcamphorimide* (302) *with soda lime*

N–benzylcamphorimide (**302**) (2.00 g, 7 mmol) and soda lime (5.00 g) were mixed in cold–cup distillation apparatus and the mixture was strongly heated. The liquid that collected in the cold–cup was diluted with CH_2Cl_2 (10 ml) and acidified with concentrated HCl. This acidic solution was extracted with H_2O (10 ml) and the aqueous layer was basified with NaOH and re–extracted into CH_2Cl. The CH_2Cl_2 was evaporated in a stream of nitrogen and the residue was vacumn distilled to yield benzylamine (0.080 mg, 10%), b.p. 135 – 140° C. Confirmation of the distillate identity was obtained from ^1H NMR spectroscopy and TLC, against a standard benzylamine sample, [elution with BuOH – AcOH – H_2O (4:1:5)].

3.15.8 *18–Crown–6 catalysed hydrolysis of N–benzylcamphorimide (***302***) and subsequent esterification to yield the amide esters (***309***) and* (**311**)

A mixture of *N*–benzylcamphorimide (22.00 g, 81 mmol), KOH (8.90 g, 160 mmol), and 18–crown–6 (4.60 g) in toluene (250 ml) was refluxed for 3 h with vigorous stirring. On cooling, H_2O (400 ml) was added to the two phase mixture and, after thorough mixing, the layers were separated. The aqueous layer was washed with further toluene (100 ml) and then acidified to pH 1 with 6 M HCl. The resultant precipitate was dissolved in EtOAc (100 ml) and the aq. layer extracted with further EtOAc (100 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo* to yield a colourless oil which was crystallized from EtOAc – hexane to yield a mixture of the amide–acids (**308**) and (**310**) (17.03 g). Repeated recrystallization from the same solvent system removed sufficient of the minor product, *cis* 3–(*N*–benzylcarbamoyl)–2,2,3–trimethylcyclopentanecarboxylic acid (**310**) to adequately characterize the major, *cis* 3–(*N*–benzylcarbamoyl)–1,2,2–trimethylcyclopentanecarboxylic acid (**308**), m.p. 115–120° C [br] (Found: C, 70.8; H, 8.3; N, 4.9. $C_{17}H_{23}NO_3$ requires C, 70.6; H, 8.0; N, 4.8.)[bs]; $[\alpha]_D^{26}$ +29° (*c* 3.3 in EtOH); ν_{max} (KBr) 3500 – 2400 [C(O) — *OH*], 3370 [C(O) — *NH*],

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[br] Bell [277] hydrolysed *N*–benzyl camphorimide (**302**) with ethanolic NaOH to yield a compound with the same physical data. However, Bell has assigned the structure of the amide–acid he obtained, to be the one resulting from hydroxyl ion attack at the less sterically hindered carbonyl group.

[bs] The isomeric contaminant (**310**), known to be present in small quantities, would not be reflected in the elemental analysis but it does appear to significantly depress the melting point.[277]

1700 [*C(O)* — OH] , and 1635 and 1565 cm^{-1} [*C(O)* — NH]; δ_H(500 MHz; $CDCl_3$) 0.88, 1.21, and 1.33 (9H, 3 x s, 6–, 7–, and 8–Me), 1.52, 1.85, 2.18, and 2.35 (4H, 4 x m, 4–CH_2 and 5–CH_2), 2.81 (1H, dd, 3–H), 4.41 (2H, m, NCH_2), 5.94 (1H, s, NH) and 7.22 – 7.33 (5H, m, ArH); δ_C (125 MHz; $CDCl_3$) 21.01, 21.76, and 22.37 (3 x q, C–6, C–7, and C–8), 23.23 (t, C–4), 32.72 (t, C–5), 43.60 (t, NCH_2), 47.12 (s, C–2), 52.79 (d, C–3), 55.86 (s, C–1), 127.68 (d, ArC), 127.68 and 128.67 (2 x d, ArC and ArC), 138.28 (s, ArC), and 175.41 and 179.34 [2 x s, *C*(O)N and *C*(O)O]. *m/z* 289 (M^+, 18%), 271(10), 243(13), 109(33), and 91(100).

A mixture of the crude amide–acids (**308**) and (**310**) (15.00 g, 52 mmol), H_2SO_4 (2 ml) in anhydrous MeOH (130 ml) was refluxed for 24 h in a reaction vessel equipped with a Dean and Stark trap charged with 3A molecular sieves. The MeOH was then evaporated *in vacuo* and the residue was neutralized with 5% aq. Na_2CO_3. The resultant mixture was extracted with EtOAc (3 x 100 ml) and the organic layers were then combined, dried ($MgSO_4$), and concentrated *in vacuo* to yield a white foam. Flash chromatography [elution with benzene – Et_2O (8:2)] of this material yielded, as the major component, the oil methyl *cis* 3–(*N*–benzylcarbamoyl)–1,2,2–trimethylcyclopentanecarboxylate (**309**) (11.33 g, 71%) [277]; $[\alpha]_D^{26}$ +41.4° (*c* 4.2 in MeOH); ν_{max} (liquid film) 3370 [C(O) — *NH*], 1735 [*C(O)* — OMe] , and 1645 and 1520 cm^{-1} [*C(O)* — NH]; δ_H(500 MHz; $CDCl_3$) 0.79, 1.19, and 1.29 (9H, 3 x s, 6–, 7–, and 8–Me), 1.50, 1.81, 2.05, and 2.35 (4H, 4 x m, 4–CH_2 and 5–CH_2), 2.77 (1H, dd, 3–H), 3.65 (3H, s, OMe), 4.40 (2H, m, NCH_2), 5.95 (1H, s, NH) and 7.22 – 7.30 (5H, m, ArH); δ_C (125 MHz; $CDCl_3$) 21.19, 21.77, and 22.39 (3 x q, C–6, C–7, and C–8), 23.28 (t, C–4), 32.59 (t, C–5), 43.42 (t, NCH_2), 47.01 (s, C–2), 51.35 (q, OMe), 52.61 (d, C–3), 55.75 (s, C–1), 127.30 (d, ArC), 127.59 and 128.57 (2 x d, ArC and ArC), 138.46 (s, ArC) and 174.49 and 175.14 [2 x s, C(O)N and C(O)O]; *m/z* 303 (*M*$^+$, 8%), 272(5), 271(4), 243(6), 106(53), 91(97) and 83(100) (Found: *M*$^+$, 303.1812. Calc. for $C_{18}H_{25}NO_3$ *M*$^+$, 303.1834).

and

methyl *cis* 3–(*N*–benzylcarbamoyl)–2,2,3–trimethylcyclopentanecarboxylate (**311**) (0.87 g, 6%); ν_{max} (liquid film) 3320 [C(O) — *NH*], 1725 [*C(O)* — OMe], and 1645 and 1525 cm^{-1} [*C(O)* —NH]; δ_H(500 MHz; $CDCl_3$) 0.74, 1.11, and 1.16 (9H, 3 x s, 6–, 7–, and 8–Me), 1.41, 1.70, 2.12, 2.42 (5H, 4 x m, 1–H, 4–CH_2, 5–CH_2), 3.58 (3H, s, OMe), 4.35 (2H, m, NCH_2), 6.25 (1H, s, NH) and 7.15 – 7.26 (5H, m, ArH); δ_C (125 MHz; $CDCl_3$) 21.00, 21.57, and 23.03 (3 x q, C–6, C–7, and C–8), 23.12 (t, C–5), 32.34 (t, C–4), 43.38 (t, NCH_2), 46.39 (s, C–2), 51.19 (q, OMe), 54.00 (d, C–1), 55.89 (s, C–3), 127.08 (d, ArC), 127.53 and 128.35 (2 x d, ArC and ArC), 138.46 (s, ArC), and 172.36 and 176.12 [2 x s, C(O)N and C(O)N]; *m/z* 303 (*M*$^+$,11%), 272(4), 271(6), 243(6), 106(38), and 91(100) (Found: *M*$^+$, 303.1812. Calc. for $C_{18}H_{25}NO_3$ *M*$^+$, 303.1834).

3.15.9 *LAH reduction of the ester amide* (309)

A solution of the ester (**309**) (11.00 g, 36 mmol) in THF (30 ml) was added to a large excess of LAH (12.00 g, 315 mmol) suspended in THF (300 ml) and the resulting mixture was refluxed for 36 h. H_2O (12 ml), 10% NaOH (12 ml) and H_2O (36 ml) were added sequentially to the cooled reaction mixture. The granular solid was removed by filtration and the filtrate was dried ($MgSO_4$) and concentrated *in vacuo*. Distillation of the residual oil afforded *N*–benzyl–1,8,8–trimethy–3–azabicyclo[3.2.1]octane (**315**) (3.51 g, 39%), b.p. 112 – 116°C / 0.5 mmHg; (lit. [310] b.p. 165 / 30 mmHg) $[\alpha]_D^{26}$ +40.7° (*c* 3.3 in benzene); ν_{max} (liquid film) 1450 and 590 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 0.77, 0.87, and 0.92 (9H, 3 x s, 9–, 10–, and 11–Me), 1.56 and 1.76 (5H, 2 x m, 5–H, 6–CH_2 and 7–CH_2), 2.26 (2H, dd, $J_{2exo\text{-}2endo}$ 11 Hz, 2–H_{exo} and 2–H_{endo}), 2.46 (1H, dd, $J_{4endo\text{-}5}$ 3.5 Hz, $J_{4endo\text{-}4exo}$ 11 Hz, 4–H_{endo}), 2.60 (1H, d, $J_{4endo\text{-}4exo}$ 11 Hz, 4–H_{exo}), 3.56 (2H, m, NCH_2), and 7.21 – 7.40 (5H, m, ArH); δ_C (125 MHz; $CDCl_3$) 17.87, 18.32, and 24.42 (3 x q, C–9, C–10, and C–11), 24.42 (t, C–6), 35.60 (t, C–7), 41.67 (s, C–8), 42.79 (s, C–1), 46.13 (d, C–5), 54.63 (t, NCH_2), 61.21 and 61.89 (2 x t, C–2 and C–4), 126.58 (d, ArC), 128.04 and 128.61 (2 x d, C–ArC and ArC), and 139.80 (s, ArC); *m/z* 243 (M^+,11%), 242(15), 166(6), 152(11), 134(19), and 91(100) (Found: M^+, 243.1970. Calc. for $C_{17}H_{25}N$ M^+, 243.1987)

and

the residual glassy material from the distillation, *cis N–benzyl–3–hydroxymethyl–2,2,3–trimethylcyclopentanecarboximide (***316***)* (5.50 g, 55%), m.p. 142 – 144° C (from EtOH/H_2O) (Found: C, 73.4; H, 9.5; N, 5.1. $C_{17}H_{25}NO_2$ requires C, 74.1, H, 9.15, N, 5.1%); ν_{max} (KBr) 3300 [C(O) —*NH* and OH], and 1655 and 1590 cm^{-1} [*C(O)* —NH]; δ_H(200 MHz; $CDCl_3$) 0.71, 0.81, and 0.91 (9H, 3 x s, 6–, 7–, and 8–Me), 1.25, 1.62, 2.02 (4H, 3 x m, 4–CH_2 and 5–CH_2), 2.01 (1H, br s, OH), 2.40 (1H, t, 1–H), 3.38 (2H, s, 9–CH_2), 4.28 (2H, m, NCH_2), 5.63 (1H, br s, NH), and 7.15 (5H, m, ArH); δ_C (50 MHz; $CDCl_3$) 20.00, 20.59, and 25.80 (C–6, C–7, and C–8), 24.06 (C–5), 34.14 (C–4), 43.92 (NCH_2), 46.11 (C–2), 49.05 (C–3), 56.34 (C–1), 69.17 (C–9), 127.89 (d, ArC), 128.34 and 129.10 (2 x ArC), 138.90 (ArC), and 174.07 C(O)N; *m/z* 275 (M^+,9%), 257(3), 244(8), and 91(100).

3.15.10 *Preparation of the* 3,5*–dinitrobenzoate derivative of the partially reduced product* (316)

A solution of compound (**316**) (0.60 g, 2.2 mmol) in THF (5 ml) was added to a solution of 3,5–dinitrobenzoyl chloride (0.53 g, 2.3 mmol) in THF (10 ml). The resulting solution was refluxed for 1 h and dilute aq. Na_2CO_3 was added. The resulting mixture was extracted with EtOAc (2 x 20 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to yield *cis N–benzyl–2,2,3–trimethyl–3–(3,5–dinitrobenzoyloxymethyl)cyclopentanecarboximide* (**321**) (0.45 g, 41%). m.p. 84– 85°C (from EtOH); ν_{max} (liquid film) 3380 and 3270 [C(O) —*NH*], 1735 [*C(O)* —OR] , and 1640 and 1545 cm^{-1} [*C(O)* —NH]; δ_H(300 MHz; $CDCl_3$) 0.95, 1.10, and 1.15 (9H, 3 x s, 6–, 7–, and 8–Me), 1.58, 1.89, and 2.28 (4H, 3 x m, 5–CH_2 and 6–CH_2), 2.61 (1H, t, 1–H), 4.39 (2H, s, OCH_2), 4.45 (2H, m, NCH_2), 5.64 (1H, m, NH), 7.24 – 7.35 (5H, m, ArH) and 9.10 – 9.21 (3H, m, ArH); δ_C (75 MHz; $CDCl_3$) 20.19, 20.92, and 25.13 (3 x q, C–6, C–7, and C–8), 23.75 (t, C–5), 34.10 (t, C–4), 43.42 (t, NCH_2), 46.25 (s, C–2), 47.72 (s, C–3), 55.70 (d, C–1), 72.30 (t, OCH_2), 122.33, 127.56, 127.97, 128.80, 129.26 (5 x d, ArC)[bt], 134.05, 138.00, 140.00, and 148.75 (4 x s, ArC), and 162.52 and 172.54 [2 x s, C(O)N and C(O)O].

3.15.11 *Preparation of the bromophenacyl ester of acid amide* (320)

The amide–acid (**308**) (0.50 g, 2 mmol) was dissolved in EtOH (10 ml) and 5% aq. NaOH was added to the solution until it was just pink to phenolphthalein. A solution of *p*–bromophenacylbromide (0.47 g, 2 mmol) in warm EtOH (10 ml) was added to the solution and the resulting mixture was refluxed for 1 h. The EtOH was then evaporated *in vacuo*, H_2O (10 ml) was added to the residue which was then extracted with EtOAc (2 x 10 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with EtOAc – hexane (60:40)] afforded as a white foam *(4–bromobenzoyl)methyl cis 3–(N–benzylcarbamoyl)–1,2,2–trimethylcyclopentanecarboxylate* (**320**) (0.59 g, 60%), m.p. 133 – 135°C (from EtOH) (Found: C, 62.25; H, 5.7; N, 3.15. $C_{25}H_{28}BrNO_4$ requires C, 61.7, H, 5.8, N, 2.9%); ν_{max} (KBr) 3370 [C(O) —*NH*], 1730 [*C(O)* —OMe] , and 1645 and

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[bt] Two of the six theoretically non equivalent CH aromatic carbons are superimposed.

1525 cm^{-1} [*C(O)*—NH]; δ_H(300 MHz; $CDCl_3$) 0.93, 1.23, and 1.40 (9H, 3 x s, 6–, 7–, and 8–Me), 1.56, 1.93, 2.22, and 2.43 (4H, 4 x m, 4–CH_2 and 5–CH_2), 2.97 (1H, dd, 3–H), 4.43 (2H, d, NCH_2), 5.27 (2H, dd, OCH_2), 5.83 (1H, s, NH), 7.24 – 7.31 (5H, m, ArH), and 7.68 (4H, dd, ArH); δ_C (75 MHz; $CDCl_3$) 20.94, 21.94, and 22.65 (3 x q, C–6, C–7, and C–8), 23.07 (t, C–4), 32.57 (t, C–5), 43.60 (t, NCH_2), 47.36 (s, C–2), 52.49 (d, C–3), 56.01 (s, C–1), 65.68 (t, OCH_3), 127.48, 127.76, 128.73, 129.22, 132.23 (ArC),[bu] and 173.62 and 175.07 [C(O)O and C(O)N]; *m/z* 485 (M^+,^{79}Br, 0.08%), 288(12), 155(15), 109(27), 106(100), and 91(78).

[bu] Considerable superpositioning of the signals for the aromatic carbons in the ^{13}C spectrum of compound (**320**) occurs.

3.16 Preparation of the Chiral Auxiliaries (328), (329), and (330).

The NaH employed in the alkylation reactions was a 50% dispersion in oil. Prior to all these reactions the dispersion was washed with anhydrous hexane, under an inert atmosphere, to remove the oil.

In some instances the assignment of similar ^{13}C signals within a particular compound were based on comparisons to more comprehensively assigned spectra (*e.g.* with the aid of HETCOR spectra) of analogous compounds.

3.16.1 *Preparation of the trimethyl silyl enol ether of camphor* (331)

A (pre–dried, 4A molecular sieves) solution of (+)–camphor (5.00 g, 33 mmol) in Et_2O (10 ml) was added to a solution of LDA (35 mmol) [prepared from diisopropylamine (3.54 g, 35 mmol) and 1.5 M BuLi (23 ml)] in Et_2O (100 ml) at –78° C. The resulting solution was stirred for 1 h at –78° C and then TMSCl (3.8 g, 35 mmol) was added to the reaction mixture at *ca.* –35° C which was then allowed to warm to room temperature and stirred overnight. The ensuing precipitate was removed by filtration and the filtrate was concentrated by distillation under N_2. Once all the Et_2O had been removed, the residue was vacuum distilled to afford 2–trimethylsiloxy–2–bornene (**331**) (3.74 g, 51%), b.p. 60 – 62° C / 1.5 mmHg (lit.,[280] 74.5 – 75.5° C / 1.9 mmHg); ν_{max} (liquid film) 1620 (C=C), and 1250 cm^{-1} (Si—Me); δ_H(60 MHz; CCl_4) 0.05 (9H, s, 3 x SiMe), 0.55 and 0.68 (9H, 2 x s, 8–, 9–, and 10–Me), 0.80 – 1.80 (4H, m, 5– and 6–CH_2), 1.98 (1H, t, 4–H), and 4.42 (1H, d, 3–H).

3.16.2 *MCPBA oxidation of the trimethyl silyl enol ether of camphor* (331).

Solid 80% MCPBA (2.40 g, 14 mmol) was added to a solution of silyl enol ether (**331**) (2.74 g, 12 mmol) in CH_2Cl_2 (35 ml) at 0° C. The reaction mixture was stirred at room temperature for 5 h and then the CH_2Cl_2 was evaporated *in vacuo*. Hexane (10 ml) was added to the residue and the precipitated solid was removed by filtration. This process was repeated twice more and the combined filtrates were then concentrated *in vacuo*. To a solution of the resulting residue in CH_2Cl_2 (40 ml), TBAF (3.80 g, 12 mmol) was added and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was then extracted with saturated aq. $NaHCO_3$, 1 M HCl, and saturated aq. $NaHCO_3$. The organic layer was separated, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography of the residue [elution with Et_2O – hexane (40:60)] afforded a yellow solid, camphorquinone (**325**) (0.25 g, 12%) m.p. 185 – 191° C (sealed tube, from 10% acetic acid) (lit. [285] 183 – 186° C) and

the lower R_f material as a diastereomeric mixture of *endo*– and *exo*–3–hydroxy–2–bornanone [(**332**) and (**333**)][bv]; δ_H(60 MHz; $CDCl_3$) 0.95 and 1.05 (9H, 2 x s, 8–, 9–, and 10–Me), 1.15 – 2.30 (5H, m, 4–H, 5–, and 6–CH_2), 3.20 (1H, br s, OH), and 3.80 and 4.25 (1H, br s and d respectively, 3–H_{exo} and 3–H_{endo})[bw].

3.16.3 *Oxidation of the potassium enolate of camphor employing 2–(phenylsulphonyl)–3–phenyloxaziridine* (256)

A solution of (+)–camphor (0.89 g, 6 mmol) in anhydrous THF (15 ml) was added, under an inert atmosphere, to a suspension of KHMDS (1.81 g, 9 mmol) in THF (100 ml) at –78° C[bx]. The reaction mixture was allowed to stir for 30

[bv] As both diastereomers were known compounds, they were neither separated nor fully characterized. The structure of the products were merely confirmed by ^1H NMR spectroscopy.

[bw] It was the integral ratios of the 3–H_{exo} and 3–H_{endo} that established the diastereomeric ratio as *ca.* 50:50.

[bx] All tranfers of the pyrophoric KHMDS powder were carried out in a glove bag, which had been thoroughly flushed with nitrogen.

min and then a solution of the sulphonyl oxaziridine (**256**) (2.30 g, 9 mmol) in THF (10 ml) was added to the reaction mixture at –78° C. The resulting mixture was stirred for a further 1 h and the reaction was then quenched by the addition of saturated aq. NH_4Cl (40 ml). The THF was evaporated *in vacuo* and the aqueous residue was extracted with Et_2O (2 x 50 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography [elution with benzene – Et_2O (60:40)] afforded 3–*exo*–hydroxy–2–bornanone (**332**) (0.68 g, 70%), m.p. 206 – 209° C (sealed tube, from hexane) (lit.[281] 209 – 211° C); ν_{max} (KBr) 3450 (OH) and 1735 cm^{-1} (C $=$ O); δ_H(80 MHz; $CDCl_3$) 0.92, 0.94, and 0.99 (9H, 3 x s, 8–, 9–, and 10–Me), 1.30 – 2.10 (5H, m, 4–H, 5–, and 6–CH_2), 3.25 (1H, br s, OH), and 3.75 (1H, br s, 3–H); δ_C(20 MHz; $CDCl_3$) 9.03, 20.08, and 21.04 (C–8, C–9, and C–10), 25.21 (C–6), 28.67 (C–5), 46.80 (C–7), 49.41 (C–4), 57.12 (C–1), 77.37 (C–3), and 220.65 (C–2); *m/z* 168 (M^+, 18%), 125(37), 83(95), and 41(100).

3.16.4 *Preparation of camphorquinone* (325)

SeO_2 (100.00 g, 0.9 mol) and (+)–camphor (80.00 g, 0.53 mol) were mixed in acetic anhydride (80 ml) and the mixture was refluxed for 4 h and then stirred overnight at room temperature.[by] The resultant black selenium powder was removed by filtration and the filtrate was neutralized with 10% aq. NaOH. The yellow precipitate was filtered, washed with water and dried as much as possible. This semi–dry material was dissolved in petroleum ether (80 – 100° C boiling range) and the residual aqueous layer was separated. The organic layer was then concentrated *in vacuo* until crystallization began. The solution was then stored overnight at 10° C to facilitate complete crystallization. Filtration

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[by] The extreme toxicity of SeO_2 necessitates very careful handling of this reagent and the reaction residues.

of the bright yellow needles afforded 2,3–bornanedione (**325**) (65 g, 74%), m.p. 195 – 196° C (lit. [285] 183 – 186° C); $[\alpha]_D^{26}$ –109° (*c* 21.2 in benzene); ν_{max} (KBr) 1770 and 1750 cm^{-1} (C = O); δ_H(60 MHz; $CDCl_3$) 0.95, 1.05, and 1.10 (9H, 3 x s, 8–, 9–, and 10–Me), 1.30 – 2.25 (4H, m, 5–, and 6–CH_2), 2.65 (1H, m, 4–H).

3.16.5 *LAH reduction of camphorquinone (325) to afford the diol (324)* [282]

Solid camphorquinone (10.00 g, 60 mmol) was added to a suspension of LAH (6.00 g, 75 mmol) in anhydrous Et_2O (100 ml) under an inert atmosphere. The reaction mixture was then refluxed for 2.5 h during which time the yellow colour of the initial mixture completely disappeared. H_2O (6 ml), 10% NaOH (6 ml), and H_2O (18 ml) were successively added and the resulting precipitate was filtered. The filtrate was dried ($MgSO_4$) and concentrated *in vacuo*. The solid residue was steam distilled to remove the less volatile 2–*endo*–3–*exo* diol contaminant and the aqueous distillate was subsequently extratced with Et_2O (2 x 100 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallization of the solid residue [petroleum ether (80 – 100° C boiling range)] afforded the 2–*exo*–3–*exo*–dihydroxybornane (**324**) (7.14 g, 70%), $[\alpha]_D^{26}$ –17.8° (*c* 0.8 in EtOH) [lit. [282] $[\alpha]_D^{20}$ –17° (*c* 1 in EtOH), ν_{max} (KBr) 3400 cm^{-1} (OH); δ_H(60 MHz; $CDCl_3$) 0.85, 0.95, and 1.15 (9H, 3 x s, 8–, 9–, and 10–Me), 1.30 – 1.95 (5H, m, 4–H, 5–, and 6–CH_2), 3.05 (2H, br s, 2 x OH), and 3.85 (2H, m, 2– and 3–H).

3.16.6 *LAH reduction of camphoric acid to yield the diol* (**339**).

A solution of (+)–camphoric acid (20.00 g, 0.1 mol) in anhydrous THF (300 ml) was added to a suspension of LAH (12.60 g, 0.33 mol) in THF (200 ml) and the resulting mixture was then refluxed for 4h. H_2O (12 ml), 10% NaOH (12 ml), and H_2O (35 ml) were successively added and the resulting precipitate was filtered. The filtrate was dried ($MgSO_4$) and concentrated *in vacuo* to afford *cis* (+)–1,2,2–trimethyl–1,3–*bis*(hydroxymethyl)cyclopentane (**339**) (16.60 g, 97%), m.p. 135 – 137° C (lit. [311] 135.5 – 136.5° C); $[\alpha]_D^{26}$ +63.9° (*c* 1.3 in EtOH) [lit.,[312] $[\alpha]_D^{25}$ +63.81° (*c* 10 in EtOH)]; ν_{max} (KBr) 3260 cm^{-1} (OH); δ_H(300 MHz; $CDCl_3$)[bz] 0.76, 0.99, and 1.00 (9H, 3 x s, 6–, 7–, and 8–Me), 1.36 (2H, m, 4–H_a and 5–H_a), 1.51 (2H, br s, 2 x OH), 1.58 (1H, m, 5–H_b), 1.94 (1H, m, 4–H_b), 2.07 (1H, m, 3–H), 3.50 and 3.72 (3H, 1 x m and 1 x dd, 2 x CH_2OH); δ_C(75 MHz; $CDCl_3$)[ca] 18.54, 20.45, and 24.20 (C–6, C–7, and C–8), 25.60 (C–4), 33.76 (C–5), 43.96 (C–2), 48.78 (C–1), 50.44 (C–3), 64.90 (C–10), and 69.12 (C–9).

3.16.7 *Preparation of 1–chloro–2–methoxyethane* (335)

Thionyl chloride (98.00 g, 0.82 mol) was added to an ice–cooled solution of 2–methoxyethanol (57.00 g, 0.75 mol) in dimethylaniline (115 ml) and the resulting solution was stirred overnight at room temperature. Dilute HCl was then added to the reaction mixture and this mixture was extracted with Et_2O. The organic layer was separated, dried ($MgSO_4$), and concentrated *in vacuo*. Fractional distillation of the residue afforded 1–chloro–2–methoxyethane (**335**) (49 g, 69%), b.p. 89 – 90° C (lit. [283] 90° C).

3.16.8 *Alkylation of the diol* (324) *employing 1–chloro–2–methoxyethane* (335) *as alkylating agent*

A solution of the diol (**324**) (5.00 g, 30 mmol) in dry DMF (30 ml) was added

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[bz] The assignment of the signals in the ^1H NMR spectrum is based on an analysis of the COSY spectrum. The $H_a - H_b$ notation employed is merely to distinguish the diastereotopic protons of a particular methylene group, and, has no stereochemical significance.

[ca] The assignment of the signals in the ^{13}C spectrum was based on an analysis of the HETCOR spectrum and comparisons with assignments in analogous compounds.

to a suspension of pre–washed NaH (0.78 g, 33 mmol) in DMF (50 ml) and the reaction mixture was stirred for 2 h at room temperature. 1–Chloro–2–methoxyethane (**335**) (3.31 g, 35 mmol) was added to the reaction mixture which was then stirred for a further 5.5 h. The reaction was quenched with H_2O (100 ml) and the resultant mixture was extracted with $CHCl_3$ (2 x 50 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*, after which the excess DMF was removed by vacuum distillation. Flash chromatography [elution with benzene – Et_2O (8:2)] of the residue afforded, as an oil, *2–exo–3–exo–bis(1–methoxyethoxy)bornane* (**326**) (0.22 g, 2%); ν_{max} (liquid film) 2940, 2875, and 1455 cm^{-1}; δ_H(80 MHz; $CDCl_3$) 0.75, 0.88, and 1.11 (9H, 3 x s, 8–, 9–, and 10–Me), 1.60 (5H, m, 4–H, 5–CH_2 and 6–CH_2), 3.38 (6H, s, 2 x OMe), 3.56 (10H, m, 2–H, 3–H, and 4 x OCH_2); δ_C(20 MHz; $CDCl_3$) 11.66, 20.88, and 21.27 (C–8, C–9, and C–10), 24.30 (C–5), 33.89 (C–6), 46.69 (C–7), 48.77 (C–4), 49.33 (C–1), 59.14 (2 x OMe), 69.83, 71.90, and 72.46 (4 x OCH_2), and 86.03 and 89.51 (C–2 and C–3); *m/z* 227 (*M*$^+$, 0.2%), 210(5), 134(8), and 59(100)

and

as a regioisomeric mixture that could not be separated, the monoalkylated products, 2–*exo*–hydroxy–3–*exo*–(1–methoxyethoxy)bornane (**338**) and 3–*exo*–hydroxy–2–*exo*–(1–methoxyethoxy)bornane (**337**) (3.04 g, 44%[cb]); ν_{max} (liquid film) 3590 cm^{-1} (OH); δ_H(80 MHz; $CDCl_3$[cc]) 0.77, 0.93*, and 1.06 (9H, 3 x s, 8–, 9–, and 10–Me), 1.60 (5H, m, 4–H, 5–CH_2 and 6–CH_2), 3.36 (3H, s, OMe), 3.53 (6H, m, 2–H, 3–H, and 2 x OCH_2); δ_C(20 MHz; $CDCl_3$) 11.39*,

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[cb] The quoted yield is the total yield of monoalkylated material. Compounds (**338**) and (**337**) could not be separated and thus neither was fully characterized. However, some spectroscopic data is included to illustrate the isomeric nature of the isolated material.

[cc] For both the the ^1H and ^{13}C NMR spectra only the signals ascribed to the regioisomer present in the higher concentration, as indicated by the intesities of the NMR signals, are quoted. However all the signals which are duplicated due to the second isomer are indicated by an (*).

21.20*, and 21.69* (C–8, C–9, and C–10), 23.93* (C–5), 33.64* (C–6), 46.49 (C–7), 48.94 (C–4), 49.13* (C–1), 58.95* (OMe), 70.38* and 72.33* (2 x OCH_2), and 84.77* and 89.40* (C–2 and C–3); *m/z* 210 (M^+ – H_2O, 23%), 152(36), and 59(100)[cd].

3.16.9 *Alkylation of the diol* (**339**) *employing 1–chloro–2–methoxyethane* (**335**) *as alkylating agent*

A pre–dried (3A molecular sieves) solution of the diol (**339**) (2.40 g, 14 mmol) in dry DMF (15 ml) was added to a suspension of pre–washed NaH (0.36 g, 15 mmol) in DMF (20 ml) and the reaction mixture was stirred for 2.5 h at room temperature. A solution of 1–chloro–2–methoxyethane (**335**) (3.31 g, 35 mmol) in dry DMF (2 ml) was added to the reaction mixture, which was then refluxed for 6 h and subsequently stirred at room temperature overnight. The reaction was quenched with H_2O (50 ml) and the resultant mixture was extracted with Et_2O (2 x 50 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*, after which, the excess DMF was removed by vacumn distillation. Flash chromatography [elution with benzene – Et_2O (7:3)] of the residue afforded, as an oil, *cis–1,3–bis(1–methoxyethoxy)–1,2,2–trimethyl–cyclopentane* (**340**) (0.99 g, 24%); ν_{max} (liquid film) 3040 and 1450 cm^{-1}; δ_H(80 MHz; $CDCl_3$) 0.74, and 0.99 (9H, 2 x s, 6–, 7–, and 8–Me), 1.01 – 1.43 (5H, m, 3–H, 4–CH_2, and 5–CH_2), 3.38 (6H, s, 2 x OMe), and 3.13 – 3.63 (10H,m, 5 x OCH_2), and (2H, d, MeC–O–CH_2); δ_C(20 MHz; $CDCl_3$) 18.51, 21.40, and 23.94 (C–6, C–7, and C–8), 26.34 (C–4), 34.41 (C–5), 44.18 (C–2), 47.58 (C–3), 48.16 (C–1), 59.13 and 59.20 (2 x OMe), and 70.42, 70.99, 72.13, 72.22, 73.97, and 78.08 (6 x OCH_2); *m/z* 229 [M^+ – $(CH_2)_2OMe$, 0.2%], 212(15), 136(66), 123(70), and

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[cd] A GC–MS analysis of this mixture indicated the presence of two components, both having very similar mass spectra. GC–MS of the reaction mixture also indicated the presence of the cyclic ether (**343**); *m/z* 154 (M^+, 18%), 139(16), 122(82), and 107(100).

59(100)

and

as a regioisomeric mixture that could not be separated, the monoalkylated products, 3–hydroxymethanol–1–(1–methoxyethoxy)–1,2,2–trimethyl–cyclopentane (**341**) and 1–hydroxymethanol–3–(1–methoxyethoxy)–1,2,2–trimethyl–cyclopentane (**342**) (0.97 g, 30%[ce]); ν_{max} (liquid film) 3450 cm^{-1} (OH); δ_H(80 MHz; CDCl$_3$[cf]) 0.76*, and 0.99 (9H, 2 x s, 6–, 7–, and 8–Me), 1.32 – 1.50 (5H, m, 3–H, 4–CH$_2$, and 5–CH$_2$), 2.79 (1H, br s, OH) 3.37 (3H, s, OMe), and 3.12 – 3.66 (8H, m, 4 x OCH$_2$); δ_C(20 MHz; CDCl$_3$) 18.25, 20.35*, and 23.81* (C–6, C–7, and C–8), 25.74* (C–4), 33.76 (C–5), 43.77* (C–2), 47.35 (C–3), 48.54* (C–1), 58.82* (C–13), and 64.45, 68.60, 70.12, 70.67, 71.83, 73.59, and 77.77 (OCH$_2$[cg]); m/z 215 (M^+ – CH$_3$, 2%), 200(7), 136(33), 123(58), and 59(100).[ch]

3.16.10 *Raney nickel reduction of camphorquinone* (**325**) *to afford the α–hydroxy ketone* (**332**).

A mixture of activated Raney nickel (3.50 g) and camphorquinone (**325**) in absolute EtOH (200 ml) was stirred at room temperature, under a hydrogen

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[ce] The quoted yield is the total yield of monoalkylated material. Compounds (**341**) and (**342**) could not be separated and thus neither was fully characterized. However, some spectroscopic data is included to illustrate the isomeric nature of the isolated material.

[cf] For both the the ^{1}H and ^{13}C NMR spectra only the signals ascribed to the regioisomer present in the higher concentration, as indicated by the intesities of the NMR signals, are quoted. However all the signals which are duplicated due to the second isomer are indicated by an (*).

[cg] In the case of the CH$_2$O signals all the peaks observed are quoted because the four signals corresponding to the major isomer could not be distinguished.

[ch] A GC–MS analysis of this mixture indicated the presence of two components, both having very similar mass spectra. GC–MS of the reaction mixture also indicated the presence of the cyclic ether (**343**); m/z 154 (M^+, 18%), 139(16), 122(82), and 107(100).

atmosphere (at atmospheric pressure), overnight, during which time *ca.* 0.8 l of hydrogen was taken up by the reaction. The reaction mixture was then filtered through celite and the filtrate was concentrated *in vacuo*. Flash chromatography of the resultant yellow solid [elution with benzene – hexane (7:3)] afforded unreacted camphorquinone (0.41 g) and *exo* 3–hydroxy–2–bornanone (**332**) (4.21 g, 70%), m.p. 206 – 209° C (sealed tube, from hexane) (lit. [285] 209 – 211° C)[ci].

3.16.11 *Alkylation of the α–hydroxy ketone* (332) *with 1–chloro–2–methoxyethane* (335).

A solution of compound (**332**) (4.00 g, 29 mmol) in dry DMF (10 ml) was added to a suspension of pre–washed NaH (0.69 g, 29 mmol) in dry DMF (60 ml) and the resultant mixture was then stirred for 2 h at room temperature. A solution of 1–chloro–2–methoxyethane (**335**) (2.69 g, 29 mmol) in dry DMF (10 ml) was added to the resultant slurry. The reaction mixture was then stirred overnight at room temperature and subsequently refluxed for 2 h. The DMF was evaporated *in vacuo*, H_2O (50 ml) was added to the residue and the mixture was extracted with Et_2O (2 x 50 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Repeated flash chromatography of the multi–component residue [elution with benzene – Et_2O (85:15)] afforded, as an oil *3–exo–(1–methoxyethoxy)–2–bornanone* (**344**) (2.25 g, 43%); ν_{max} (liquid film) 1745 cm^{-1} (C ═ O); δ_H(200 MHz; $CDCl_3$) 0.75, 0.80, and 0.89 (9H, 3 x s, 8–, 9–, and 10–Me), 1.28 – 1.82 (4H, m, 5–, and 6–CH_2), 2.20 (1H, t, 4–H), 3.27 (3H, s, OMe) and 3.29 – 3.82 (5H, m, 3–H and 2 x OCH_2); δ_C(20 MHz; $CDCl_3$) 9.31, 18.91, and 19.75 (C–8, C–9, and C–10), 18.38 (C–5), 31.77 (C–6), 42.78 (C–7), 47.06 (C–4), 58.36 (C–1), 59.05

[ci] The characterization of this compound has been described previously (See Section 3.16.2, p. 314).

(OMe), 69.89 and 71.93 (2 x OCH_2), 81.50 (C–3), and 217.70 (C–2); *m/z* 226 (M^+, 14%), 122(36), 115(100), and 59(65).

3.16.12 *Alkylation of the α–hydroxy ketone* (**332**) *with benzyl bromide.*

A solution of compound (**332**) (6.14 g, 37 mmol) in dry DMF (10 ml) was added to a suspension of pre–washed NaH (1.14 g, 48 mmol) in dry DMF (50 ml) and the resultant mixture was then stirred for 2 h at room temperature. A solution of benzyl bromide (6.84 g, 40 mmol) in dry DMF (15 ml) was added to the resultant slurry. The reaction mixture was then stirred overnight at room temperature. The DMF was evaporated *in vacuo*, H_2O (50 ml) was added to the residue and the mixture was extracted with Et_2O (2 x 50 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Repeated flash chromatography of the multi–component residue [elution with benzene – Et_2O (90:10)] afforded, as an oil 3–*exo*–(benzyloxy)–2–bornanone (**345**) (4.36 g, 46%), ν_{max} (liquid film) 1750 cm^{-1} (C = O); δ_H(60 MHz; $CDCl_3$) 0.62, 0.69, and 0.80 (9H, 3 x s, 8–, 9–, and 10–Me), 1.20 – 2.10 (5H, m, 4–H, 5–, and 6–CH_2), 3.65 (1H, s, 3–H), 4.65 (2H, dd, OCH_2), and 7.19 (5H, s, ArH); δ_C(20 MHz; $CDCl_3$) 9.51, 19.10, and 19.94 (C–8, C–9, and C–10), 18.71 (C–5), 31.97 (C–6), 43.01 (C–7), 47.33 (C–4), 58.49 (C–1), 72.39 (OCH_2), 80.42 (C–3), 127.81 (ArC), 127.91 and 128.47 (2 x ArC), 138.05 (ArC), and 217.39 (C–2); *m/z* 258 (M^+, 0.05%), 152(24), and 91(100).

and

as an oil, *3–benzyl–3–hydroxy–2–bornanone* (**345**) (3.45 g, 36%); ν_{max} (liquid film) 3460 (OH) and 1750 cm^{-1} (C = O); δ_H(200 MHz; $CDCl_3$) 0.96, 0.98, and 1.06 (9H, 3 x s, 8–, 9–, and 10–Me), 1.52 – 1.96 (4H, m, 5– and 6–CH_2), 2.00 (1H, d, 4–H), 2.31 (1H, br s, OH) 2.87 (2H, dd, CH_2), and 7.33 (5H, m, ArH); δ_C(50 MHz; $CDCl_3$) 9.65, 20.63, and 22.73 (C–8, C–9, and C–10), 22.91

(C–5), 29.60 (C–6), 41.65 (*C*–Ph), 46.41 (C–7), 51.90 (C–4), 58.56 (C–1), 78.97 (C–3), 127.15 (ArC), 128.66 and 130.65 (2 X ArC), 136.58 (ArC), and 220.88 (C–2); *m/z* 258 (M^+, 4%), 230(9), 147(84), 91(84), and 84(100).

3.16.13 *L–Selectride reduction of the α–alkoxy ketone* (**344**) *to afford the chiral auxiliary* (**329**)

1 M L–Selectride (10 ml. 10 mmol) was added to a solution of compound (**244**) (1.81 g, 8 mmol) in anhydrous THF (50 ml) at –78°C under an inert atmosphere. The resultant solution was stirred overnight at room temperature and the reaction was then quenched by the successive addition of H_2O (3 ml), EtOH (12 ml), and 3 M NaOH (16 ml) to the ice–cooled reaction mixture, followed by the slow addition of 30% H_2O_2 (12 ml). Solid K_2CO_3 was added to the two phase mixture until saturation of the aqueous layer occurred. The organic layer was separated and the aqueous layer was re–extracted with a 1:1 THF–Et_2O mixture (50 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with benzene – Et_2O (8:2)] afforded *2–exo–hydroxy–3–exo–(1–methoxyethoxy)–bornane* (**329**) (1.15 g, 63%); $\nu_{\max}$ (liquid film) 3490 cm^{-1} (OH); δ_H(200 MHz; $CDCl_3$) 0.79 and 0.81 (9H, 2 x s, 8–, 9–, and 10–Me), 1.08 (1H, m, 6–H_{endo}), 1.31 (1H, m, 5–H_{exo}), 1.65 (2H, m, 5–H_{endo} and 6–H_{exo})[cj], 1.82 (1H, t, 4–H), 2.75 (1H, br s, OH), 3.32 (3H, s, OMe), 3.51 (4H, m, 2 x OCH_2), 3.72 (1H, dd, *J* 9, and 1.5 Hz, 2–H), 3.80 (1H, qd, *J* 9, 3, and 1.5 Hz, 3–H); δ_C(50 MHz; $CDCl_3$) 14.13, 18.29, and 20.05 (C–8, C–9, and C–10), 18.29 (C–5)[ck], 25.60 (C–6), 44.42 (C–7), 48.70 (C–4), 49.52

[cj] The *endo* and *exo* assignments for the 5–CH_2 and 6–CH_2 protons were based on an analysis of the correlations in the COSY and HETCOR spectra.

[ck] Complete superposition of the C–5 signal and one of the terpene methyl signals occurs. However, the DEPT 135 experiment clearly distinguishes the two signals.

(C–1), 59.18 (OMe), 69.68 and 72.02 (2 x OCH_2), 73.84 (C–2), and 76.37 (C–3); *m/z* 210 ($M^+ - H_2O$, 0.2%), 152(43), and 59(100).

3.16.14 *L–Selectride reduction of the α–alkoxy ketone* (**346**) *to afford the chiral auxiliary* (**328**)

1 M L–Selectride (16.5 ml. 17 mmol) was added to a solution of compound (**346**) (3.40 g, 13 mmol) in anhydrous THF (50 ml) at –78° C under an inert atmosphere. The resultant solution was stirred overnight at room temperature and the reaction was then quenched by the successive addition of H_2O (5 ml), EtOH (20 ml), and 3 M NaOH (25 ml) to the ice–cooled reaction mixture, followed by the slow addition of 30% H_2O_2 (20 ml). Solid K_2CO_3 was added to the two phase mixture until saturation of the aqueous layer occurred. The organic layer was separated and the aqueous layer was re–extracted with a 1:1 THF–Et_2O mixture (50 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with benzene – Et_2O (95:5)] afforded 3–*exo*–benzyloxy–2–*exo*–hydroxybornane (**328**) (1.27 g, 38%),[cl] ν_{max} (liquid film) 3550 cm^{-1} (OH); δ_H(200 MHz; $CDCl_3$)[cm] 0.85 and 0.91 (9H, 2 x s, 8–, 9–, and 10–Me), 1.23 (1H, m, 6–H_{endo}), 1.44 (1H, m, 5–H_{exo}), 1.72 (2H, m, 5–H_{endo} and 6–H_{exo}), 1.93 (1H, t, 4–H), 2.75 (1H, br s, OH), 3.82 (1H, dd, *J* 9 and 1.5 Hz, 2–H), 3.97 (1H, qd, *J* 9, 3, and 1.5 Hz, 3–H), 4.50 (2H, dd, OCH_2), and 7.35 (5H, m, ArH); δ_C(50 MHz; $CDCl_3$) 14.14, 18.34, and 20.20 (C–8, C–9, and C–10), 18.53 (C–5), 25.66 (C–6), 44.60 (C–7), 48.38 (C–4), 49.59 (C–1), 72.05 (OCH_2), 74.01 (C–2), and 75.42 (C–3), 128.06 and 128.82 (2 x ArC), 128.16 (ArC), and 138.36 (ArC); *m/z*

[cl] Oppolzer *et al.*[279] have prepared this compound but do not provide any physical data.

[cm] The signal assignments are based on the assignments for compound (**329**), for which two dimensional COSY and HETCOR experiments were obtained.

260 (M^+,0.2%), 169(15), 123(40), and 91(100).

3.16.15 *Monoketalization of camphorquinone* (**325**)

A solution of camphorquinone (**325**) (25.00 g, 0.15 mol), ethylene glycol (18.80 g, 0.303 mol), and *p*–toluenesulphonic acid (1.50 g) in anhydrous benzene (120 ml) was refluxed overnight in a reaction vessel equipped with a Dean and Stark trap. (During this time *ca.* 5 ml of H_2O was collected.) The reaction mixture was washed with 1 M NaOH (100 ml) and H_2O (100 ml). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residual solid was recrystallized from hot EtOH to afford, as transparent needles, 3,3–ethylenedioxy–2–bornanone (**348**) (14.60 g, 46%), m.p. 86 – 88° C (lit. [286] 88° C); $[\alpha]_D^{26}$ +66.6° (*c* 1.1 in EtOH); ν_{max} (KBr) 1740 cm^{-1} (C$=$O); δ_H(60 MHz; $CDCl_3$) 0.91, 1.00, and 1.15 (9H, 3 x s, 8–, 9–, and 10–Me), 1.50 – 2.15 (5H, m, 4–H, 5–, and 6–CH_2), 4.00 – 4.50 (4H, m, OCH_2CH_2O); *m/z* 210(M^+, 0.1%), 182(9), 99(100), and 55(21).

3.16.16 *L–Selectride reduction of the monoketal of camphorquinone* (**348**) *to afford the chiral auxiliary* (**330**)

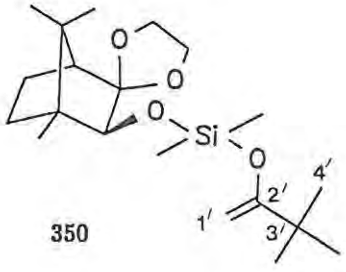
1 M L–Selectride (12 ml. 12 mmol) was added to a solution of compound (**348**) (2.00 g, 10 mmol) in anhydrous THF (50 ml) at –78° C under an inert atmosphere. The resultant solution was stirred overnight at room temperature and the reaction was then quenched by the successive addition of H_2O (3 ml), EtOH (12 ml), and 3 M NaOH (16 ml) to the ice–cooled reaction mixture, followed by the slow addition of 30% H_2O_2 (12 ml). Solid K_2CO_3 was added to the two phase mixture until saturation of the aqueous layer occurred. The organic layer was separated and the aqueous layer was re–extracted with a 1:1 THF–Et_2O mixture (50 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with

benzene – Et_2O (8:2)] afforded 3,3–ethylenedioxy–2–*exo*–hydroxybornane (**330**) (1.19 g, 70%)[279], ν_{max} (liquid film) 3530 cm^{-1} (OH); δ_H(60 MHz; $CDCl_3$) 0.85, 0.90, and 1.15 (9H, 3 x s, 8–, 9–, and 10–Me), 1.10 – 1.90 (5H, m, 4–H, 5–, and 6–CH_2), 2.35 (1H, d, OH), 3.30 (1H, d, 2–H)[cn], and 3.95 (4H, m, OCH_2CH_2O); *m/z* 212(M^+, 7.4%), 197(17), 141(27), and 127(100).

[cn] The doublets at 2.35 and 3.30 ppm are attributed to coupling of the hydroxyl proton with the proton bonded to the adjacent carbon. Addition of D_2O to the NMR solution results in the complete disappearance of the doublet at 2.35 ppm and the collapse of the doublet at 3.30 ppm to a singlet.

3.17 Applications of the camphor – derived chiral auxiliaries .

3.17.1 *Preparation of the pinacolone derived silyl enol ether* (350)



350

A solution of auxiliary (**330**) (2.00 g, 9 mmol) in anhydrous THF (10 ml) was added to a suspension of pre–washed NaH (0.3 g, 13 mmol) in anhydrous THF (75 ml). The reaction mixture was stirred for 6h at room temperature, refluxed for 1 h, and cooled to room temperature again before the addition of the chlorosilane (**168**) (2.70 g, 14mmol). The resulting mixture was stirred overnight at room temperature and then refluxed for 1 h. The THF was evaporated from the reaction mixture *in vacuo* and cold, saturated aq. $NaHCO_3$ (50 ml) was added to the residue. The resultant mixture was extracted with Et_2O (2 x 50 ml) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with hexane – Et_2O (95:5)] afforded, as an oil, *3,3–ethylenedioxy–2–exo–[dimethyl(3,3–dimethylbut–1–en–2–yloxysiloxy)]bornane* (**350**) (1.78 g, 52%), ν_{max} (liquid film) 1630 (C ═C), 1250 [Si —O(C)], and 1060 cm^{-1} (Si —Me); δ_H(200 MHz; $CDCl_3$) 0.18 and 0.19 (6H, 2 x s, 2 xSi —Me), 0.81, 0.83, and 1.16 (9H, 3 x s, 8–, 9–, and 10–Me), 1.04 (9H, s, Bu^t), 1.51 – 1.69 (5H, m, 4–H, 5–, and 6–CH_2), 3.61 (1H, m, 2–H), and 3.85 (4H, m, OCH_2CH_2O), and 4.12 (2H, m, 1′–CH_2); δ_C(50 MHz; $CDCl_3$) –2.51 and –2.41 (SiMe), 11.84, 21.01, and 21.18 (C–8, C–9, C–10), 20.76 (C–5), 28.08 (C–4′), 33.71 (C–6), 36.45 (C–7), 48.06 (C–1), 50.06 (C–3′), 53.02 (C–4), 63.53 and 65.17 (OCH_2CH_2O), 87.01 (C–2), 87.34 (C–1′), 115.95 (C–3), and 166.47 (C–2′);

m/*z* 368(M^+, 0.02%), 353(0.2), 286(0.6), 269(56), 127(91), and 75(100).

3.17.2 *Attempt to prepare a pinacolne derived silyl enol ether from the chiral auxiliary (328)*

A solution of auxiliary (**328**) (0.80 g, 3.1 mmol) in anhydrous DMF (5 ml) was added to a suspension of pre–washed NaH (0.20 g, 4 mmol) in anhydrous DMF (20 ml). The reaction mixture was stirred for 2 h at room temperature and then a solution of the chlorosilane (**168**) (0.89 g, 4.7 mmol) in DMF (2 ml) was added. The resulting darkly coloured reaction mixture was stirred overnight at room temperature and then the DMF was distilled from the reaction mixture *in vacuo* and cold, saturated aq. $NaHCO_3$ (50 ml) was added to the residue. The resultant mixture was extracted with Et_2O (2 x 50 ml) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the multi–component residue [elution with hexane – Et_2O (95:5)] afforded, as an oil, the major component, *[bis(3–exo–benzyloxybornyloxy]dimethylsilane* (**352**) (0.27 g, 15%), δ_H(200 MHz; $CDCl_3$) 0.08 (6H, s, SiMe–), 0.81, 0.82, and 0.90 (18H, 2 x s, 8–, 9–, and 10–Me), 1.17 (2H, m, 6–H_{endo}), 1.39 (2H, m, 5–H_{exo}), 1.75 – 2.15 (4H, m, 5–H_{endo} and 6–H_{exo}), 1.89 (2H, t, 4–H), 3.82 (2H, m, 2–H), 3.97 (2H, m, 3–H), 4.50 (4H, s, OCH_2), and 7.35 (10H, m, ArH); δ_C(50 MHz; $CDCl_3$) 1.37 (SiMe), 17.03, 21.35, and 23.08 (C–8, C–9, and C–10), 21.41 (C–5), 28.80 (C–6), 44.00 (C–7), 48.58 (C–1), 51.32 (C–4), 74.14 (OCH_2), 77.74 (C–2), and 79.02 (C–3),and 130.26, 130.77, 131.22, and 139.54 (ArC); *m*/*z* 260 (M^+,0.1%), 169(17), 123(48), and 91(100).

3.17.3 *Reaction of the chiral silyl enol ether* (**350**) *with benzaldehyde*

The silyl enol ether (**350**) (1.00 g, 3.0 mmol), benzaldehyde (0.30 g, 2.9 mmol) and HCl free $TiCl_4$ (0.55 g, 2.9 mmol) were reacted via Method D as described previously for compound (**164**) (See Section 3.11.1, p. 285). Flash chromatography [elution with benzene–Et_2O (8:2)] resulted in the isolation of the β–hydroxy ketone (**266**) (412 mg, 74%).

The enantiomeric excesses achieved in this reaction were determined as described before.

i) Addition of $Pr(tfc)_3$ (13 mg) to a solution of (**266**) (100 mg) in CCl_4 induced a 16 Hz upfield shift of the tertiary butyl peak while resolving the enantiomeric singlets by 3.3 Hz. Digitisation of two independent data sets gave an average enantiomeric ratio of 63:37.

ii) A 3.3 Hz separation of the singlets of interest is too small for reliable spectrometer integration at 60 MHz. Increasing the amount of chiral shift reagent in the solution to 23 mg superimposed the signal on another peak in the spectrum.

REFERENCES

1. S.G. Davies, J.M. Brown, A.J. Pratt, and G. Fleet, *Chem. Br.*, 1989, 259.
2. J.M. Brown and S.G. Davies, *Nature*, 1989, **342**, 631.
3. For example "Asymmetric Synthesis," ed. J.D. Morrison, Academic Press, Orlando, 1983 – 1985, vol. 1 – 5.
4 L. Pasteur, *Ann.Chim.Physi.*, 1848, **24**, 442. (As cited in ref.7.)
5. L. Addadi, E. Gati, and M.Lahav, *J. Am. Chem. Soc.*, 1981, **103**, 1251.
6. C.H. Soret, *Ztsch. Krystallogr. Mineral*, 1901, **34**, 630. (As cited in ref.23, p. 16.)
7. R.M. Secor, *Chem. Rev.*, 1963, **63**, 297.
8. J. Jacques, A. Collet, and S.H. Wilen, "Enantiomers, Racemates and Resolutions," Wiley (Interscience), New York, 1981.
9. E. Fogassy, A. Lopata, F. Faigl, F. Darvas, M. Acs, and L. Tokes, *Tetrahedron Lett.*, 1980, **21**, 647.
10. E.E. Turner and M.M. Harris, *Quart. Rev.*, 1947, **1**, 299.
11. M.M. Harris, *Prog. Stereochem.*, 1958, **2**, 157. (As cited in ref. 23 p. 4.)
12. J.C. Clark, G.H. Phillips, and M.R. Steer, *J. Chem. Soc. Perkin Trans.* 1, 1976, 475.
13. B.M. Trost and R.F. Hammen, *J. Am. Chem. Soc.*, 1973, **95**, 962.
14. J.P. Greenstein, S.M. Birnbaum, and L. Levintow, *Biochem. Prep.*, 1953, **3**, 84.
15. J. B. Jones, *Tetrahedron*, 1986, **42**, 3351.
16. A. M. Klibanov, *Acc. Chem. Res.*, 1990, **23**, 114.
17. J.H. Russel and H. Hunziker, *Tetrahedron Lett.*, 1969, 4035.

18. R.B. Woodward, K. Heusler, J. Costeli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen, *J. Am. Chem. Soc.*, 1966, **88**, 852.

19. C.W. Scott in "Asymmetric Synthesis" ed. J.D. Morrison, Academic Press, New York, 1984, vol. 4, p.186.

20. F. Johnson, K.G. Paul, D. Favara, R. Ciabatti, and U. Guzzi, *J. Am. Chem. Soc.*, 1982, **104**, 2190.

21. R. Mechoulam, P. Braun, and Y. Gaoni, *J. Am. Chem. Soc.*, 1967, **89**, 4552.

22. R. Rossi and P.A. Salvadori, *Synthesis*, 1979, 209.

23. J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reactions", The American Chemical Society, Washington, 1976.

24. E. Fischer, *Chem. Ber.*, 1894, **27**, 3231.

25. W. Marckwald, *Chem. Ber.*, 1904, **37**, 1368.

26. J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reactions", The American Chemical Society, Washington, 1976, p.5.

27. E. Eliel, *Tetrahedron*, 1974, **30**, 1503.

28. J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reactions", The American Chemical Society, Washington, 1976, p.430.

29. F.R. Japp, *Nature*, 1898, **58**, 482. (As cited in ref. 23 p. 2.)

30. A. M^{c}Kenzie and P.D. Ritchie, *Biochem. Z.*, 1931, **237**, 1.

31. W. Doering and R. W. Young, *J. Am. Chem. Soc.*, 1950, **72**, 631.

32. H.S. Mosher and E. La Combe, *J. Am. Chem. Soc.*, 1950, **72**, 4991.

33. G. Vavon, C. Rivière, and B. Angelo, *Compt. rend.*, **222**, 959, 1946. (As cited in ref. 23 p. 178.)

34. V. Prelog, *Helv. Chim. Acta*, 1953, **36**, 308.

35. D. Cram and F.A. Abd Elhafez, *J. Am. Chem. Soc.*, 1952, **74**, 5828, 5851.

36. M. Cheréśt, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 1968, 2199.

37. N.T. Anh and O. Eisenstein, *Nouv. J. Chim.*, 1977, **1**, 61.

38. D.J. Cram and K.R. Kopecky, *J. Am. Chem. Soc.*, 1959, **81**, 2748.

39. P.C. Bulman Page, D. Westwood, A.M.Z. Slawin and D.J. Williams. *J. Chem. Soc. Perkin Trans 1*, 1989, 1158.

40. J.W. Cornforth, R.H. Cornforth, and K.K. Matthew, *J. Chem. Soc.*, 1959, 112.

41. J. d' Angelo, *Tetrahedron*, 1976, **32**, 2979.

42. D. Caine, "Carbon – Carbon Bond Formation," ed .R.L. Augustine, Dekker, New York, 1979, vol. 1, p.85.

43. D.A. Evans in "Asymmetric Synthesis" ed. J.D. Morrison, Academic Press, New York, 1984, vol. 3, p.29.

44. N.L. Allinger, H.M. Blatter, C.A. Freiberg, and F.M. Karkowski, *J. Am. Chem. Soc.*, 1966, **88**, 2999.

45. G.S. Hammond, *J. Am. Chem. Soc.*, 1955, **77**, 334.

46. H.O. House, B.A. Tefertiller, and H.D. Olmstead, *J. Org. Chem.*, 1968, **33**, 935.

47. M.E. Kuehne, *J. Org. Chem.*, 1970, **35**, 171.

48. H.O. House and T.M. Bare, *J. Org. Chem.*, 1968, **33**, 943.

49. A.P. Krapcho and E.A. Dundulis, *J. Org. Chem.*, 1980, **45**, 3236.

50. D.A. Evans in "Asymmetric Synthesis" ed. J.D. Morrison, Academic Press, New York, 1984, vol. 3, p.31.

51. G. Frater, *Tetrahedron Lett.*, 1981, **22**, 425 and preceeding publications.

52. D. Seebach and D. Wasmuth, *Angew. Chem. Int. Ed. Engl.*, 1981, **20**, 971 and preceeding publications.

53. R. Kane, *Ann. Physik Chem.*, 1838, **44**, 475. (As cited in "Asymetric Synthesis," ed. J.D. Morrison, vol. 3, p. 111.)

54. T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, 1974, **96**, 7503.

55. C.H. Heathcock in "Asymmetric Synthesis" ed. J.D. Morrison, Academic Press, New York, 1984, vol. 3, p.154.

56. H.E. Zimmerman and M.D. Traxler, *J. Am. Chem. Soc.*, 1957, **79**, 1920.

57. M. Stiles, R.R. Winkler, Y. Chang and L. Traynor, *J. Am. Chem. Soc.*, 1964, **86**, 3337.

58. C.H. Heathcock, C.T. Buse, W.A. Kleschick, M.C. Pirrung, J.E. Sohn, and J. Lampe, *J. Org. Chem.*, 1980, **45**, 1066.

59. C.H. Heathcock in "Asymmetric Synthesis" ed. J.D. Morrison, Academic Press, New York, 1984, vol. 3, p.165.

60. S. Masamune, W. Choy, J.S. Petersen, and L.R. Sita, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1.

61. H.C. Brown and B.C. Subba Rao, *J. Am. Chem. Soc.*, 1956, **78**, 2582.

62. H.C. Brown, E.F.Knights and C.G. Scouten, *J. Am. Chem. Soc.*, 1974, **96**, 7765.

63. H.C. Brown and G. Zweifel, *Org. React.*, 1963, **13**, 1.

64. G.M. Cragg, "Organoboranes in Organic Synthesis," Marcel Dekker Inc., New York, 1973.

65. H.C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, New York, 1978, p. 321–325.

66. H.C. Brown, P.K. Jadhav and A.K. Mandal, *Tetrahedron*, 1981, **37**, 3547.

67. H.C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 1961, **83**, 486.

68. H.C. Brown and N.M. Yoon, *Isr. J. Chem.*, 1977, **15**, 12.

69. P.K. Jadhav and H.C. Brown, *J. Org. Chem.*, 1981, **46**, 2988.

70. H.C. Brown and N.M. Yoon, *J. Am. Chem. Soc.*, 1977, **99**, 5514.

71. H. C. Brown and P.K. Jadhav in "Asymmetric Synthesis" ed. J.D. Morrison, Academic Press, New York, 1984, vol. 2, p.28.

72. R. Kiesgen de Richter, M. Bonato, M. Follet, and J–M. Kamenka, *J. Org. Chem.*, 1990, **55**, 2855.

73. H.C. Brown and A.K. Mandal, *J. Org. Chem.*, 1977, **42**, 2996.

74. M.M. Midland and S. Greer, *Synthesis*, 1978, 845.

75. B.M. Mikailov, Yu.N. Bubnov, and V.G. Kiselev, *J. Gen. Chem. USSR* (*Engl. Transl. of Zh. Obshch. Khim.*), 1966, **36**, 65. (As cited in "Assymetric Synthesis," ed. J.D. Morrison, vol. 2 p. 50.)

76. M.M. Midland, S. Greer, A. Tramontano, and S.A. Zderic, *J. Am. Chem. Soc.*, 1979, **101**, 2352.

77. M.M. Midland and A. Tramontano, *J. Org. Chem.*, 1977, **43**, 1470.

78. M.M. Midland and A. Tramontano, *Tetrahedron Lett.*, 1980, **21**, 3549.

79. H.C. Brown and C.G. Pai, *J. Org. Chem.*, 1985, **50**, 1384.

80. H.C. Brown and C.G. Pai, *J. Org. Chem.*, 1982, **47**, 1606.

81. M.M. Midland, J.I. McLouglin, and J. Gabriel, *J. Org. Chem.*, 1989, **54**, 159.

82. O. Červinka. *Collect. Czech. Chem. Commun.*, 1965, **30**, 1684.

83. T. Mukaiyama, M. Asami, J. Hanna, and S. Kobayashi, *Chem. Lett.*, 1977, 783.

84. O. Červinka and O. Belovsky, *Collect. Czech. Chem. Commun.*, 1967, **32**, 3897.

85. R. Noyori, I. Tomino, and M. Nishizawa, *J. Am. Chem. Soc.*, 1979, 101, 5843.

86. J. P. Massé and E. R. Parayre, *J. Chem. Soc., Chem. Commun.*, 1976, 438.

87. J.D. Morrison, E.R. Grandbois, and S.I. Howard, *J. Org. Chem.*, 1980, **45**, 4229.

88. A. Hirao, S. Nakahama, H. Mochizuki, S. Itsuno, and N. Yamazaki, *J. Org. Chem.*, 1980, **45**, 4231.

89. H.C. Brown, S. Krishnamurthy, and J.L. Hubbard, *J. Am. Chem. Soc.*, 1978, **100**, 3343.

90. E.J. Corey, S.M. Albonico, U. Koelliker, T.K. Schaaf, and R.K. Varma, *J. Chem. Soc.*, 1971, **93**, 1491.

91. S. Krishnamurphy, F. Vogel, and H.C. Brown *J. Org. Chem.*, 1977, **42**, 2534.

92. M.M. Midland and A. Kazubski, *J. Org. Chem.*, 1982, **47**, 2814.

93. M.M. Midland and A. Kazubski, *J. Org. Chem.*, 1982, **47**, 2495.

94. A. Feghouli, R. Vanderesse, Y. Fort, and P. Caubère, *J. Chem. Soc., Chem. Commun.*, 1989, 224.

95. V. Grignard, *Ann. chim.*, 1901, **24**, 433. (As cited in ref. 23 p. 177.)

96. J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reactions," The American Chemical Society, Washington, 1976, p.177.

97. M. Falorni, L. Lardicci, G. Uccello–Barretta, and G. Giacomelli, *Gazz. Chim. Ital.*, 1988. **118**, 495.

98. W. French and G.F. Wright, *Can. J. Chem.*, 1964, **42**, 2474.

99. K. Soai and T. Mukaiyama, *Chem. Lett.*, 1978, 491.

100. G. Solladié in "Asymmetric Synthesis," ed. J.D. Morrison, Academic Press, New York, 1984, vol. 2, p.157.

101. D. Seebach, *Chem. Ber.*, 1985, **118**, 3673.

102. Ji–Tao Wang, Xiuju Fan, Xiao Feng, and Yi–Min Qian, *Synthesis*, 1989, 291.

103. P. Duhamel, J.J. Eddine, and J. Valnot, *Tetrahedron Lett.*, 1987, **28**, 3801.

104. N. Oguni and T. Omi, *Tetrahedron Lett.*, 1984, **25**, 2823.

105. E.J. Corey, P–W. Yuen, F.J. Hannon, and D.A. Wierda, *J. Org. Chem.*, 1990, **55**, 784.

106. E.J. Corey, R. Imwinkelried, S. Pikul, and Y.B. Xiang, *J. Am. Chem. Soc.*, 1989, **111**, 5493.

107. R.W. Stevens, N. Iwasawa, and T. Mukaiyama, *Chem. Lett.*, 1982, 1459.

108. N. Iwasawa and T. Mukaiyama, *Chem. Lett.*, 1982, 1441.

109. K. Saigo, M. Osaki, and T. Mukaiyama, *Chem. Lett.*, 1975, 989.

110. M.T Reetz, F. Kunisch, and A. Heitman, *Tetrahedron Lett.*, 1986, **27**, 4721.

111. S. Kobayashi, T. Sano, and T. Mukaiyama, *Chem. Lett.*, 1989, 1319.

112. S. Kobayashi and T. Mukaiyama, *Chem. Lett.*, 1989, 297.

113. T. Katsuki and K.B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974.

114. J.K. Whitesell, *Chem. Rev.*, 1989, **89**, 1581.

115. C.J. Burns, C.A. Martin, and K.B. Sharpless, *J. Org. Chem.*, 1989, **54**, 2826.

116. R.M. Hanson and K.B. Sharpless, *J. Org. Chem.*, 1986, **51**, 1922.

117. J. Halpern in "Asymmetric Synthesis" ed. J.D. Morrison, Academic Press, New York, 1985, vol. 5, p.41.

118. K.E. Koenig in "Asymmetric Synthesis" ed. J.D. Morrison, Academic Press, New York, 1985, vol. 5, p.71.

119. J.A. Osborn, F.H. Jardine, J.F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1966, 1711

120. O. Korpium. R.A. Chickos, and K. Mislow, *J. Am. Chem. Soc.*, 1968, **90**, 4842.

121. H. Wynberg, *Chimia*, 1989, **43**, 150.

122. W.A. Bonner, "Origins of Molecular Chirality," in "Exobiology," ed. C. Ponnamperuma, North Holland Publ., Amsterdam, 1972, chapter 6.

123. M. Calvin, "Chemical Evolution," Oxford University Press, Oxford, 1969.

124. S.F. Mason, *Nature (London)*, 1985, *314*, 400; *Chem. Br.*, 1985, **21**, 538.

125. W.H. Mills, *Chem. Ind. (London)*, 1932, **51**, 750. (As cited in ref. 121.)

126. F.C. Frank, *Biochim. Biophys. Acta*, 1953, **11**, 459.

127. K. Soai, S. Niwa, and H. Hori, *J. Chem. Soc., Chem. Commun.*, 1990, 982.

128. S.G. Davies, *Chem. Br.*, 1989, **25**, 268.

129. F.S. Kipping, *Proc. Chem. Soc.*, 1900, **16**, 226. (As cited in ref. 23, p. 50.)

130. J.B. Cohen and C.E. Whitely, *Proc. Chem. Soc.*, 1900, **16**, 212.

131. A. M^{c}Kenzie, *J. Chem. Soc.*, 1904, **85** 1249.

132. V. Prelog, *Bull. Chim. Fr.*, 1956, 987.

133. V. Prelog, E. Philbin, E.Watanabe, and M. Wilhelm, *Helv. Chim. Acta*, 1956, **39**, 1086.

134. J.K. Whitesell, A. Bhattachara, and K. Henke, *J. Chem. Soc., Chem. Commun.*, 1982, 988.

135. T. Mukaiyama, Y. Sakito, and M. Asami, *Chem. Lett.*, 1253.

136. E.L. Eliel, B. Lohri, and J.K. Koskimies, *J. Am. Chem. Soc.*, 1978, **100**, 1614.

137. D.A. Evans and J.M. Takacs, *Tetrahedron Lett.*, 1980, **21**, 4233.

138. W. Oppolzer and J. Marco–Contelles, *Helv. Chim. Acta*, 1986, **69**, 1699.

139. A.I. Meyers, G. Knaus, and K. Kamata, *J. Am. Chem. Soc.*, 1974, **96**, 268.

140. A.I. Meyers, G. Knaus, K. Kamata, and M.E. Ford, *J. Am. Chem. Soc.*, 1976, **98**, 567.

141. S. Yamada, K. Hiroi, and K. Achiwa, *Tetrahedron Lett.*, 1969, 4233.

142. J.K. Whitesel and S.W. Felman, *J. Org. Chem.*, 1977, **42**, 1663.

143. K. Hiroi and S. Yamada, *Chem. Pharm. Bull.*, 1973. **21**, 54.

144. S. Fioravanti, M. Antonietta Loreta, L. Pellacani, and P.A. Tardella, *J. Chem. Research* (*S*), 1987, 310.

145. D. E. Bergbreiter and M. Newcomb in "Asymmetric Synthesis" ed. J.D. Morrison, Academic Press, New York, 1984, vol. 2, p.248.

146. K.N. Houk, R.W. Stozier, N.G. Rondan, R.R. Fraser, and N. Chuaqui–Offermanns, *J. Am. Chem. Soc.*, 1980, **102**, 1426.

147. D. Mea–Jacheet and A. Horeau, *Bull. Soc. Chim. Fr*, 1968, 4571.

148. A.I. Meyers, D.R. Williams, and M. Druelinger, *J. Am. Chem. Soc.*, 1976, **98**, 3032.

149. A.I. Meyers, D.R. Williams, G.W. Erickson, S. White and M. Druelinger, *J. Am. Chem. Soc.*, 1976, **103**, 3088.

150. E.J. Corey and D. Enders, *Tetrahedron Lett.*, 1976, 3, 11.

151. D. Enders and H. Eichenauer, *Angew. Chem. Int. Ed. Engl.*, 1976, **15**, 549.

152. D. Enders in "Asymmetric Synthesis" ed. J.D. Morrison, Academic Press, New York, 1984, vol. 3, p.278.

153. M.E. Jung, T.J. Shaw, R.R. Fraser, J. Banville, and K. Taymaz, *Tetrahedron Lett.*, 1979, 4149.

154. D.E. Bergbreiter, J. Ludwig, and M. Newcomb, *J. Org. Chem.*, 1980, **45**, 4666.

155. D. Enders and H. Eichenauer, *Tetrahedron Lett.*, 1977, 191.

156. K.G. Davenport, H. Eichenauer, D. Enders, M. Newcomb, and D. Bergbreiter, *J. Am. Chem. Soc.*, 1979, **101**, 5654.

157. D. Enders and V. Bhusan, *Tetrahedron Lett.*, 1988, **29**, 2437.

158. R. Tamura, K. Watabe, H. Katayama, H. Suzuki, and Y. Yamamoto, *J. Org. Chem.*, 1990, **55**, 408.

159. R. Tamura, S. Tamai, H. Katayama, and H. Suzuki, *Tetrahedron Lett.*, 1989, **30**, 3685.

160. I. Fleming, *Pure Appl. Chem.*, 1988, **60**, 71.

161. L.H. Sommer, "Stereochemistry, Mechanisms and Silicon," McGraw–Hill, New York, 1965.

162. R.J.P. Corriu, C. Guérin, and J.J.E. Moreau, *Top. Stereochem.*, 1984, **15**, 43.

163. L.H. Sommer, C.L. Frye, G.A. Parker, and K.W. Michael, *J. Am. Chem. Soc.*, 1964, **86**, 3271.

164. J.F. Klebe and H. Finkbeiner, *J. Am. Chem. Soc.*, 1968, **90**, 7255.

165. R.J.P. Corriu and J.J.E. Moreau, *Bull. Soc. Chim. Fr.*, 1975, 901.

166. W.E. Fristad, T.R. Bailey, L.A. Paquette, R. Gleiter, and M.C. Böhm, *J. Am. Chem. Soc.*, 1979, **101**, 4420.

167. R.G. Daniels and L.A. Paquette, *Organometallics*, 1982, **1**, 1449.

168. S.J. Hathaway and L.A. Paquette, *J. Org. Chem.*, 1983, **48**, 3351.

169. M. Deneux, I.C. Akhrem, D.V. Avetissian, E.I. Myssoff, and M.E. Vol'pin, *Bull. Soc. Chim. Fr.*,1973, 2638.

170. I. Fleming in "Comprehensive Organic Chemistry," ed. D.H.R. Barton and W.D. Ollis, Pergamon Press, Oxford, 1979, vol. 3, p.555.

171. J.L. Fry and M.A. McAdam, *Tetrahedron Lett.*, 1984, **25**, 5859.

172. I. Fleming in "Comprehensive Organic Chemistry," ed. D.H.R. Barton and W.D. Ollis, Pergamon Press, Oxford, 1979, vol. 3, p.558.

173. G.L. Larson, J.A. Prieto, and E. Oritz, *Tetrahedron*, 1988, **44**, 3781.

174. B.F. Bonini, G. Mazzanti, P. Zani, and G. Maccagnani, *J. Chem. Soc., Chem. Commun*, 1988, 365.

175. B.F. Bonini, G. Mazzanti, P. Zani, S. Masiero, and G. Maccagnani, *Tetrahedron Lett.*, 1989, **30**, 2677.

176. A.E. Learned, Ph.D. Thesis, University of Utah, 1987. (As cited in ref. 177.)

177. P.J. Stang and A.E. Learned, *J. Org. Chem.*, 1989, **54**, 1781.

178. I.K. Kusnezowa, K. Rühlmann, and E. Grundemann, *J. Organomet. Chem.*, 1973, **47**, 53.

179. K.K. Andersen, D.M. Gash, and J.D. Robertson in "Asymmetric Synthesis" ed. J.D. Morrison, Academic Press, New York, 1983, vol. 1, chapt.4.

180. V. Schurig "Asymmetric Synthesis" ed. J.D. Morrison, Academic Press, New York, 1983, vol. 1, chapt.5.

181. W.H. Pirkle and J. Finn in "Asymmetric Synthesis" ed. J.D. Morrison, Academic Press, New York, 1983, vol. 1, chapt.6.

182. J.A. Dale, D.L. Dull, and H.S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

183. G. Barth, W. Voeter, H.S. Mosher, E. Bunnenberg, and C. Djerassi, *J. Am. Chem. Soc.*, 1970, **92**, 875.

184. W.H. Pirkle, *J. Am. Chem. Soc.*, 1966, **88**, 1837.

185. K. Mislow and M. Raban, *Top. Stereochem.*, 1967, **8**, 1.

186. C.C. Hinckley, *J. Am. Chem. Soc.*, 1969, **91**, 5160.

187. G.M. Whitesides and D.W. Lewis, *J. Am. Chem. Soc.*, 1970, **92**, 6979.

188. M.D. M^{c}Creary, D.W. Lewis, D.L. Wernick, and G.M. Whitesides, *J. Am. Chem. Soc.*, 1974, **96**, 1038.

189. H.L. Goering, J.N. Eikenberry, and G.S. Koermer, *J. Am. Chem. Soc.*, 1971, **93**, 5913.

190. R.R. Fraser, M.A. Petit, and J.K. Saunders, *J. Chem Soc. Chem. Commun.*, 1971, 1450.

191. T.H. Chan and D. Wang, *Tetrahedron Lett.*, 1983, **24**, 1573.

192. I. Fleming, "Comprehensive Organic Chemistry," ed. D.H.R. Barton and W.D. Ollis, Pergamon Press, Oxford, 1979, Vol. 3, p.568.

193. I. Ojima, T. Kogure, and Y. Nagai, *Chem. Lett.*, 1974, 223.

194. W. Dumont, J.C. Poulin, T.P. Dang, and H.B. Kagan, *J. Am. Chem. Soc.*, 1973, **95**, 8295.

195. K. Tamao, R. Kanatani, and M. Kumada, *Tetrahedron Lett.*, 1884, **25**, 1913.

196. W.P. Weber, "Silicon Reagents for Organic Synthesis," Springer –Verlag, Berlin, 1983, p. 79.

197. K. Tamao, T. Iwahara, R. Kanatani, and M. Kumada, *Tetrahedron Lett.*, 1884, **25**, 1909.

198. K. Tamoa, N. Ishida, T. Tanaka, and M. Kumada, *Organometallics*, 1983, **2**, 1694.

199. L. Cappi, A. Ricci, and M. Taddei, *Tetrahedron Lett.*, 1987, **28**, 965, 969.

200. W. Bernhard, I. Fleming, and D. Waterson, *J. Chem. Soc., Chem. Commun.*, 1984, 28.

201. A. Hosomi and H. Sakurai, *Tetrahedron Lett.*, 1976, 1295.

202. G. Yi, D. Wang, and T.H. Chan, *Youji Huaxue*, 1988, **8**, 115.

203. W.P. Weber, "Silicon Reagents for Organic Synthesis," Springer–Verlag, Berlin, 1983, p. 206 and 228.

204. I. Fleming, Tilden Lecture, 1980.

205. P. Brownbridge, *Synthesis*, 1983, 1 and 85.

206. R.D. Walkup, *Tetrahedron Lett.*, 1987, **28**, 511.

207. French Patent 2,253,751 (1975). (Chemical Abstracts, 1976, **84**: 58761).

208. P.T. Kaye and R.A. Learmonth, *Synth. Commun.*, 1989, **19**, 2337.

209. H.O. House, L.J. Czuba, M. Gall, and H.D. Olmstead, *J. Org. Chem.*, 1969, **48**, 2324.

210. G. Stork and P. Hudrlik, *J. Am. Chem. Soc.*, 1968, **90**, 4462.

211. P. Cazeau, F. Duboudin, F. Moulines, O. Babot, and J. Dunogues, *Tetrahedron*, 1987, **43**, 2075.

212. K. Takai, Y. Kataoka, T. Okazoe, and K. Utimoto, *Tetrahedron Lett.*, 1988, **29**, 1065.

213. S. Ahmad, M. Amin Khan, and J. Iqbal. *Synth. Commun.*, 1988, **18**, 1679.

214 T.H. Chan, Z.Y. Wei, D. Wang, and J.S. Li, *J.Org. Chem.*, 1989, **54**, 528.

215. I. Fleming, "Comprehensive Organic Chemistry," ed. D.H.R. Barton and W.D. Ollis, Pergamon Press, Oxford, 1979, Vol. 3, p.550.

216. A.E. Pierce, "Silylation of Organic Compounds," Pierce Chemical Company, Rockford, Illinois, 1968.

217. D.J. Peterson, *J. Org. Chem.*, 1968, **68**, 780.

218. T.H. Chan, Q.–J. Peng, D. Wang, and J.A. Guo, *J. Chem. Soc., Chem. Commun.*, 1987, 325.

219. W.J. Richter, *J. Organomet. Chem.*, 1979, **169**, 9.

220. H.O. House and V. Kramar, *J. Org. Chem.*, 1963, **28**, 3362.

221. R.B. English, P.T. Kaye, and R.A. Learmonth, Submitted to *Acta Crystallogr. Sect. C.*

222. B.M. Craven and G.T. DeTitta, *J. Chem. Soc., Perkin Trans. 2*, 1976, 814.

223. M.K. Yun, Y.J. Park, W. Shin, and B.M. Craven, *Bull. Korean Chem. Soc.*, 1989, 10, 335.

224. G.M. Sheldrick, *SHELX–76*. Program for crystal structure determination. Univ. of Cambridge, England, 1976.

225. G.M. Sheldrick, *SHELXS–76*. Program for crystal structure determination. Univ. of Cambridge, England, 1986.

226. G. Hagele, D. Wendisch, R. Luckenbach and H. Bechtolsheimer, *Z.Naturforsch.,B*, 1980, *35B*, 1182.

227. S.Seo, Y.Tomita, K.Tori and Y.Yoshimura, *J. Am. Chem. Soc.*, 1978, *100*, 3331.

228. J.Briggs, F.A. Hart, and G.P. Moss, *J. Chem. Soc. Chem Commun.*, 1970, 1506.

229. J.Briggs, F.A. Hart, G.P. Moss, and E.W. Randall, *J. Chem. Soc. Chem. Commun.* 1971, 364.

230. S.P. Sawan, T.L. James, L.D. Gruenke, and J.C. Craig, *J. Magn. Reson*, 1979, **35**, 409.

231. E. Berman, Z. Luz, Y. Mazur, and M. Sheves, *J. Org. Chem.*, 1977, **42**, 3325.

232. P.T. Kaye and R.A. Learmonth, *J. Chromatogr.*, 1990, **503**, 437.

233. R.L. Grob, "Modern Practice of Gas Chromatography," John Wiley and Sons Inc., New York, 1977.

234. J.A. Perry, "Introduction to Analytical Gas Chromatography. History, Principles and Practice," Marcel Dekker Inc., New York, 1981.

235. P.T. Kaye and R.A. Learmonth, *Synth. Commun.*, 1990, **20**, 1333.

236. P.T. Kaye and R.A. Learmonth, *S. Afr. J. Chem.*, In the press.

237. R.D. Walkup and N.U. Obeyesekere, *J. Org. Chem.*, 1988, **53**, 920.

238. G.M. Rubottom, M.A. Vazquez, and D.R. Pelegrina, *Tetrahedron Lett.*, 1974, 4319.

239. A.G. Brook and D.M. Macrae, *J. Organomet. Chem.*, 1974, **77**, C19.

240. A. Hassner, R.H. Reuss, and H.W. Pinnick, *J. Org. Chem.*, 1975, **40**, 1975.

241. G.M. Rubottom, J.M. Gruber, R.K. Boeckman, Jr., M. Ramaiah, and J.B. Medwid, *Tetrahedron Lett.*, 1978, 4603.

242. M.E. Jung and K.T. Hogan, *Tetrahedron Lett.*, 1988, **29**, 6199.

243. P.D. Gardner, *J. Am. Chem. Soc.*, 1956, **78**, 3421.

244. L.A. Paquette, H–S. Lin, and J.C. Gallucci, *Tetrahedron Lett.*, 1987, **28**, 1363.

245. F.A. Davis and A.C. Sheppard, *J. Org. Chem.*, 1987, **52**, 954.

246. H.K. Chenault and S.J. Danishefsky, *J. Org. Chem.*, 1989, **54**, 4249.

247. W. Adam, L. Hadjiarapoglou, and X. Wang, *Tetrahedron Lett.*, 1989, **30**, 649.

248. Y. Watanabe and Y. Ishimura, *J. Am. Chem. Soc.*, 1989, **111**, 410.

249. R.D. Walkup, personal communication.

250. W.E. Kaufmann and E.E.Drenger, *Org. Synth.* 1941, **Coll. Vol. 1**, 258.

251. F.A.J. Meskens, *Synthesis*, 1981, 501.

252. F.A. Davis, J. Lamendola, Jr., U. Nadir, E.W. Kluger, T.C. Sedergran, T.W. Panunto, R. Billmers, R. Jenkins, I.J. Turchi, W.H. Watson, J.S. Chen, and M. Kimura, *J. Am. Chem. Soc.*, 1980, **102**, 2000.

253. F. A. Davis and O.D. Stringer, *J. Org. Chem.*, 1982, **47**, 1774.

254. T.H. Chan, I. Paterson, and J.Pinsonnault, *Tetrahedron Lett.*, 1977, 4183.

255. M.T. Reetz, S. Hüttenhain, P. Walz, and U.Löwe, *Tetrahedron Lett.*, 1979, 4971.

256 L.J. Bellamy, "The Infrared Spectra of Complex Molecules," Chapman and Hall, London, 1975, p. 119.

257. C.H. Heathcock, S.K. Davidsen, K.T. Hug, and L.A. Flippin, *J. Org. Chem.*, 1986, **51**, 3027.

258. C. Gennari, F. Molinari, P. Cozzi, and Oliva, *Tetrahedron Lett.*, 1989, **30**, 5163.

259. H. Wynberg, M.B. Groen, and R.M. Kellogg, *J. Org. Chem.*, 1970, **35**, 2828.

260. S.H. Mashraqui and R.M. Kellogg, *J. Org. Chem.*, 1984, **49**, 2513.

261. M. Taddei, Personal communication.

262. J.G. Smith and G.F. Wright, *J. Org. Chem.*, 1952, **17**, 1116.

263. M. Tanaka and I. Ogata, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1094.

264. H.W. Krause and A. Kinting, *J. Prakt. Chem.*, 1980, **322**, 485.

265. S.C. Watson and J.F. Eastham, *J. Organomet. Chem.*, 1967, **9**, 165.

266. H.H. Zeiss and F.R. Zwanzig, *J. Am. Chem. Soc.*, 1957, **79**, 1733.

267. G.W. Erickson and J.L. Fry, *J. Org. Chem.*, 1987, **52**, 462.

268. W.H. Glaze and C.M. Selman, *J. Org. Chem.*, 1968, **33**, 1987.

269. T.C. Chan and D. Wang, *Tetrahedron Lett.*, 1989, **30**, 3041.

270. T.C. Chan and P. Pellon, *J. Am. Chem. Soc.*, 1989, **111**, 8737.

271. D. Enders, P. Fey, and H. Kipphardt, *Org. Synth.*, 1987, **65**, 1987, 173.

272. C.G. Chavdarian and E. B. Sanders, *Organic Prep. Proced. Int.*, 1981, **13**, 389.

273. F.P. Doyle, M.D. Mehta, G.S. Sach, and J.L. Pearson, *J.Chem. Soc.*, 1958, 4458.

274 M.S. Gibson and R.W. Bradshaw, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 919.

275. K. Saigo, M. Yamamoto, K. Morimura, and H. Nohira, *Chem. Lett.*, 1979, 545.

276. G. Helmchen and R. Schmierer, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 205.

277. K.H. Bell, *Aust. J. Chem.*, 1981, **34**, 665.

278. W. Oppolzer, *Tetrahedron*, 1987, **43**, 1969.

279. W. Oppolzer, C. Chapuis, G. Mao Dao, D. Reichlin, and Thierry Godel, *Tetrahedron Lett.*, 1982, **23**, 4781.

280. G.C. Joshi and L.M. Pande, *Synthesis*, 1975, 451.

281. F. A. Davis, L.C. Vishwakarma, J. M. Billmers, and J. Finn, *J. Org. Chem.*, 1984, **49**, 3243.

282. S.J. Angyal and R.J. Young, *J. Am. Chem. Soc.*, 1959, **81**, 5467.

283. M.Bennett and C.H. Heathcock, *J. Chem. Soc.*, 1929, 270.

284. T.H. Johnson and K.C. Klein, *J. Org. Chem.*, 1979, **44**, 461.

285. B. Pfrunder and Ch. Tamm, *Helv. Chim. Acta*, 1969, **52**, 1630.

286. I. Fleming and R.B. Woodward, *J. Chem. Soc.*, 1968, 1289.

287. D.W. Brown, A.J. Floyd, and M. Sainsbury, "Organic Spectroscopy," Wiley, Chichester, 1988, p.98.

288. W.C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

289. Z.A. Fataftah, M.R. Ibrahim, and M.S. Abu–Agil, *Tetrahedron Lett.*, 1986, **27**, 4067.

290. A. Magata, J. Iyoda, and I. Shiihara, *Kogyo Kagaku Zasshi*, 1966, **69**, 1957. (*Chemical Abstracts*, **68**:69145.)

291. Z. Lasocki and S. Piechucki, *Bull. Acad. Pol. Sci. Ser. Sci. Chim.*, *1974*, **22**, 189. (*Chemical Abstracts*, **81**:90751.)

292. N. Wirth, "Programming in Modula–2," Springer–Verlag, Heidelberg, 1983.

293. J.R. Britton, R.B. Kriegh, and L.W. Rutland, "University Mathematics," Freeman and Company, San Fransisco, 1968, vol.1, p. 568.

294. "Dictionary of Organic Compounds," Eyre and Spottiswoode, London, 1965.

295. Beilstein's "Handbuch der Organischen Chemie," vol.7, p. 160.

296. F.G. Mann and B.C. Saunders, "Practical Organic Chemistry," Longman, London, 1974, 4th edition, p. 247.

297. R. Albrecht, G. Kresze, and B. Mlakar, *Chem. Ber.*, 1964, **97**, 483.

298. M.T. Reetz, W.F. Maier, I. Chatziiosifidis, A. Giannis, H. Heimbach, and U.Löwe, *Chem. Ber.*, 1980, **113**, 3741.

299. Beilstein's "Handbuch der Organischen Chemie," vol.7, p. 338

300. G.A. Hill, C.S. Spear, and J.S. Lachowitz, *J. Am. Chem. Soc.*, 1923, **45**, 1557.

301. H.O. House, D.S. Crumrine, A.Y. Teranishi, and H.D. Olmstead, *J. Am. Chem. Soc.*, 1973, **95**, 3310.

302. I. Fleming and A. Pearce, *J. Chem. Soc.*, *Perkin Trans I,* 1980, 2485.

303. G.W. Erickson, Personal communication.

304. H. Gilman, P.D. Wilkinson, W.P. Fishel, and C.H. Meyers, *J. Am. Chem. Soc.*, 1923, **45**, 150.

305. D. Enders and H. Eichenauer, *Chem. Ber.*, 1979, **112**, 2933.

306. D. Seebach, H.O. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dörr, N.P. DuPreez, V. Ehrig, W. Langer, C. Nussler, H.A. Oei, and N. Schmidt, *Helv. Chim. Acta*, 1977, **60**, 322.

307. W.C. Evans, *J. Chem. Soc.*, 1910, 2337.

308. Beilstein's "Handbuch der Organischen Chemie," vol.5, p. 356.

309. H.R. Ing and R.H.F. Manske, *J. Chem. Soc.*, 1926, 2348.

310. J. McKenna, J.M. Mckenna, A.Tulley, and J. White, *J. Chem. Soc.*, 1965, 1711.

311. G.W. Erickson and J.L. Fry, *J. Org. Chem.*, 1980, **45**, 970.

312. P.Roberts, "Xanadu,Program for Molecular Geometry Calculation," Cambridge University, 1974.

313. F.H. Allen, S.A. Bellard, M.D. Brice, B.A. Cartwright, A. Doubleday, H. Higgs, T.Hunnelink, B.G. Hunnelink–Peters, O. Kennard, W.D.S. Motherwell, J.R. Rodgers, and D.G. Watson, *Acta Crystallogr.*, 1979, *B39*, 2331.

APPENDIX I

TABLE 1 **Crystal Data for (Cholesteryloxy)dimethyl(3,3–dimethylbut–1–en–2–yloxy)silane (194)**

Formula	$C_{35}H_{62}O_2Si$
Molecular mass	542
Space group	C2
F(000)	1212
a (Å)	23.648(8)
b (Å)	8.998(2)
c (Å)	17.118(4)
β (Å)	103.88
V (Å^3)	3536
Z	4
μ (cm^{-1})	0.62
Number of reflections ($1^\circ < \theta < 25^\circ$)	3522
Observed reflections	1765 $\left[I > 6\sigma(I)\right]$
R (unit weights)	0.08
$N_{parameters}$	200

Collection and Reduction of Intensity Data

The crystal used for data collection was grown from hot acetone. It was cut from a transparent needle to final dimensions of 0.45 x 0.30 x 0.20 mm. The initial photography was carried out on a Stoe Darmstadt reciprocal lattice explorer. An oscillation photograph about the axis defined as b^* showed a plane of symmetry indicating monoclinic or higher symmetry. The angle β^* between a^* and c^*, measured on a de Jong–Bouman photograph of the reciprocal lattice plane *h0l*, was less than 90°, confirming that the crystal must be monoclinic.

From de–Jong Bouman and Buerger photographs the general condition, for a reflection *hkl* to have a measurable intensity, that $h + k = 2n$ became apparent. From preliminary calculations of the unit cell dimensions it was established that there were four molecules per unit cell.

The space group **C2** is consistent with the above criteria.

Data were measured on a Enraf Nonius CAD 4 diffractometer at a temperature of 298K using graphite–monochromated Mo $K\alpha$ radiation (λ = 0.7107 Å). The data were corrected for Lorentz polarisation effects and adjusted for absorption.

Structure Solution and Refinement

An attempt to locate the silicon atom by Patterson methods failed. A direct methods strategy was then adopted, making use of the TREF routine from the SHELXS–86 [224] program. By means of a TREF 100 instruction all the non hydrogen atoms were located.

The program SHELX 76 [225] was used for full matrix least squares refinement (data in 2 blocks) and calculations of bond lengths and angles. In the structure refinement only well defined atoms were assigned anisotropic temperature factors. Hydrogens were not refined but included at calculated positions based on the corresponding carbon and oxygen positions in the difference Fourier calculations. Hydrogen atoms bonded to C26 – C29, C31 and C33 – C35 were not located due to the uncertainty of the carbon atom positions.[222,223]

The bonds C25 – C26, C25 – C27, C32 – C33, C32 – C34, and C32 – C35 were constrained to a bond length of 1.54Å. Prior to the final refinement cycle an UNDO –1 instruction was executed to convert the data to the correct enantiomer. The refinement converged with an R factor equal to 0.082.

The program Xanadu [312] was used to calculate the torsion angles in the vicinity of the silyl enol ether functionality (Table 22) and the deviations from the mean plane defined by O2, C30, C31 and C32 (Table 23).

Pluto 78 [313] was used to obtain plots of the molecular struture (Figure 16, p. 111) and packing diagrams (Figure 17, p. 110), viewed from the position of minimum overlap and along the orthogonal Y axis respectively.

The crystal data are recorded in Table 17, the atomic coordinates and equivalent isotropic temperature factors for the non–hydrogen atoms in Table 18, the calculated coordinates and equivalent isotropic temperature factors for the included hydrogen atoms in Table 21, bond lengths and angles for non–hydrogen atoms in Table 19 and anisotropic temperature factors in Table 20.

In all the tables included in this appendix the estimated standard deviation succeeds the entry in parentheses. The carbon, hydrogen, oxygen and silicon atoms are numbered crystallographically. (See Figure 16,).

Observed and calculated structure factors are available from the Department of Chemistry and Biochemistry, Rhodes University, Grahamstown, South Africa.

TABLE 18. Fractional Coordinates ($X10^4$) and Equivalent Isotropic Temperature Factors ($Å^2$, $X10^3$) for (Cholesteryloxy)dimethyl(3,3–dimethylbut–1–en–2–yloxy)silane (194)

	$^{x}/_{a}$	$^{y}/_{b}$	$^{z}/_{c}$	U_{eq}
Si	–580(2)	–4168	–8236(2)	81(1)
O(1)	–751(3)	–2999(10)	–7625(4)	71(2)
C(3)	–1016(4)	–3371(14)	–6970(6)	64(3)
C(2)	–548(5)	–3363(15)	–6203(6)	69(3)
C(1)	–819(4)	–3672(14)	–5490(6)	60(3)
C(4)	–1487(5)	–2268(14)	–6948(6)	64(3)
C(5)	–1747(5)	–2436(12)	–6221(6)	54(3)
C(6)	–2303(4)	–2471(12)	–6281(6)	50(3)
C(7)	–2596(4)	–2573(14)	–5609(5)	60(3)
C(8)	–2182(4)	–2322(13)	–4794(6)	48(2)
C(9)	–1600(4)	–3110(13)	–4746(5)	52(3)
C(10)	–1298(4)	–2540(13)	–5412(5)	54(3)
C(19)	–1029(6)	–981(14)	–5192(7)	78(4)
C(11)	–1194(4)	–3130(16)	–3901(6)	65(3)
C(12)	–1494(4)	–3683(14)	–3252(5)	64(3)
C(13)	–2050(4)	–2771(13)	–3258(6)	53(3)
C(14)	–2441(4)	–2893(13)	–4113(5)	49(2)
C(15)	–3016(4)	–2224(14)	–4035(6)	63(3)
C(16)	–3064(4)	–2802(15)	–3185(6)	67(3)
C(17)	–2475(4)	–3481(13)	–2785(5)	56(3)
C(18)	–1904(5)	–1160(13)	–3006(7)	66(3)
C(20)	–2339(4)	–3320(15)	–1860(5)	68(3)
C(21)	–1726(5)	–3929(18)	–1443(7)	88(4)
C(22)	–2801(5)	–4076(16)	–1548(5)	75(3)

TABLE 18 /Cont.

C(23)	–2780(5)	–3788(18)	–668(6)	92(4)
C(24)	–3330(6)	–4462(17)	–428(7)	94(4)
O(2)	–188(4)	–5422(12)	–7677(5)	109(3)
C(30)	22(8)	–6734(24)	–7858(11)	146(7)
C(31)	69(11)	–7033(34)	–8629(16)	225(11)*
C(32)	133(6)	–7879(17)	–7190(10)	112(5)
C(25)	–3346(6)	–4401(25)	440(8)	171(8)
C(26)	–3899(6)	–5149(20)	582(10)	136(6)*
C(27)	–2963(9)	–3256(23)	995(12)	190(9)*
C(28)	–124(7)	–3069(21)	–8802(9)	126(5)*
C(29)	–1246(7)	–5021(21)	–8899(10)	131(6)*
C(33)	–401(7)	–8010(27)	–6828(10)	168(7)*
C(34)	616(8)	–7177(26)	–6527(11)	177(8)*
C(35)	304(10)	–9448(18)	–7411(13)	192(9)*

* isotropic temperature factor.

$$U_{eq} = {}^{1}\!/_{3} \sum_{i} \sum_{j} \underline{U}_{ij} \, \underline{a}_{i}^{*} \, \underline{a}_{j}^{*} \, (a_{i} . a_{j})$$

TABLE 19. Selected Bond Lengths (Å) and Angles (°) for (Cholesteryloxy)dimethyl(3,3–dimethylbut–1–en–2–yloxy)silane (194)

Si–O(1)	1.602(9)	Si–O(2)	1.619(10)
Si–C28	1.89(2)	Si–C(29)	1.87(2)
O(1)–C(3)	1.450(14)	C(3)–C(2)	1.50(13)
C(3)–C(4)	1.50(2)	C(2)–C(1)	1.53(2)
C(1)–C(10)	1.55(2)	C(4)–C(5)	1.52(2)
C(5)–C(6)	1.293(15)	C(5)–C(10)	1.534(13)
C(6)–C(7)	1.48(2)	C(7)–C(8)	1.518(12)
C(8)–C(9)	1.531(14)	C(8)–C(14)	1.529(15)
C(9)–C(10)	1.570(15)	C(9)–C(11)	1.533(12)
C(10)–C(19)	1.55(2)	C(11)–C(12)	1.539(15)
C(12)–C(13)	1.548(15)	C(13)–C(14)	1.537(12)
C(13)–C(17)	1.569(15)	C(13)–C(18)	1.53(2)
C(14)–C(15)	1.523(15)	C(15)–C(16)	1.57(2)
C(16)–C(17)	1.526(14)	C(17)–C(20)	1.545(13)
C(20)–C(21)	1.553(15)	C(20)–C(22)	1.49(2)
C(22)–C(23)	1.518(14)	C(23)–C(24)	1.58(2)
C(24)–C(25)	1.50(2)	O(2)–C(30)	1.35(2)
C(30)–C(31)	1.38(4)	C(30)–C(32)	1.51(3)
C(32)–C(33)	1.54(2)	C(32)–C(34)	1.54(2)
C(32)–C(35)	1.54(2)	C(25)–C(26)	1.54(2)
C(25)–C(27)	1.54(3)		

O(1)–Si–O(2)	105.7(5)	O(1)–Si–C(28)	104.8(6)
O(2)–Si–C(28)	110.7(6)	O(1)–Si–C(29)	110.9(7)
O(2)–Si–C(29)	110.6(6)	C(28)–Si–C(29)	113.8(7)
Si–O(1)–C(3)	125.3(8)	O(1)–C(3)–C(2)	108.0(9)
O(1)–C(3)–C(4)	109.2(9)	C(2)–C(3)–C(4)	111.8(9)

TABLE 19. /Cont.

C(3)–C(2)–C(1)	109.5(9)	C(2)–C(1)–C(10)	113.7(9)
C(3)–C(4)–C(5)	113.8(9)	C(4)–C(5)–C(6)	122.7(9)
C(4)–C(5)–C(10)	114.5(9)	C(6)–C(5)–C(10)	122.7(10)
C(5)–C(6)–C(7)	126.6(9)	C(6)–C(7)–C(8)	112.7(8)
C(7)–C(8)–C(9)	110.6(9)	C(7)–C(8)–C(14)	111.3(8)
C(9)–C(8)–C(14)	108.8(8)	C(8)–C(9)–C(10)	111.8(8)
C(8)–C(9)–C(11)	114.0(9)	C(10)–C(9)–C(11)	113.4(8)
C(1)–C(10)–C(5)	108.9(8)	C(1)–C(10)–C(9)	108.5(9)
C(5)–C(10)–C(9)	109.7(8)	C(1)–C(10)–C(19)	110.5(9)
C(5)–C(10)–C(19)	108.6(9)	C(9)–C(10)–C(19)	110.6(9)
C(9)–C(11)–C(12)	113.1(8)	C(11)–C(12)–C(13)	111.2(9)
C(12)–C(13)–C(14)	106.5(8)	C(12)–C(13)–C(17)	115.4(9)
C(14)–C(13)–C(17)	98.6(7)	C(12)–C(13)–C(18)	111.5(9)
C(14)–C(13)–C(18)	112.4(9)	C(17)–C(13)–C(18)	111.7(9)
C(8)–C(14)–C(13)	116.3(8)	C(13)–C(14)–C(15)	103.5(8)
C(15)–C(16)–C(17)	106.7(9)	C(13)–C(17)–C(16)	103.5(8)
C(13)–C(17)–C(20)	119.2(8)	C(16)–C(17)–C(20)	111.5(9)
C(17)–C(20)–C(21)	112.4(9)	C(17)–C(20)–C(22)	109.5(8)
C(21)–C(20)–C(22)	110.9(10)	C(20)–C(22)–C(23)	115.2(10)
C(22)–C(23)–C(24)	111.1(9)	C(23)–C(24)–C(25)	117.6(11)
Si–O(2)–C(30)	131.7(10)	O(2)–C(30)–C(31)	121(2)
O(2)–C(30)–C(32)	116(2)	C(31)–C(30)–C(32)	123(2)
C(30)–C(32)–C(33)	110.1(14)	C(30)–C(32)–C(34)	104.0(14)
C(33)–C(32)–C(34)	105.7(14)	C(30)–C(32)–C(35)	117(2)
C(33)–C(32)–C(35)	109(2)	C(34)–C(32)–C(35)	111.4(14)
C(24)–C(25)–C(26)	111.4(12)	C(24)–C(25)–C(27)	119(2)
C(26)–C(25)–C(27)	126(2)		

TABLE 20. Anisotropic Temperature Factors (Å^2, X10^3)

	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
Si	99(3)	88(3)	60(2)	8(2)	28(2)	17(3)
O(1)	89(5)	78(6)	57(4)	8(4)	39(4)	7(5)
C(3)	62(7)	55(7)	74(8)	–1(6)	14(6)	7(7)
C(2)	72(8)	73(9)	62(7)	5(7)	17(6)	4(7)
C(1)	43(6)	77(9)	56(6)	1(6)	5(5)	4(6)
C(4)	73(7)	60(8)	55(7)	7(6)	6(6)	–4(7)
C(5)	68(8)	40(6)	56(7)	–3(5)	16(6)	7(6)
C(6)	50(6)	41(6)	55(7)	1(5)	5(5)	1(6)
C(7)	54(6)	62(8)	56(6)	–4(6)	–1(5)	3(6)
C(8)	50(6)	40(6)	52(6)	–3(5)	6(5)	4(5)
C(9)	57(6)	43(6)	54(6)	–7(5)	11(5)	4(6)
C(10)	63(7)	5(7)	43(6)	0(5)	7(5)	–3(6)
C(19)	97(10)	69(9)	68(8)	–7(7)	22(7)	–23(8)
C(11)	46(6)	91(9)	56(7)	4(7)	6(5)	13(7)
C(12)	66(7)	80(9)	39(5)	8(6)	2(5)	21(7)
C(13)	5(6)	60(8)	48(6)	2(5)	13(5)	–1(6)
C(14)	45(6)	51(7)	50(6)	–7(5)	8(5)	3(6)
C(15)	60(7)	58(8)	68(7)	3(6)	12(6)	9(7)
C(16)	57(7)	74(9)	73(7)	–10(7)	20(6)	–1(7)
C(17)	57(7)	59(7)	55(6)	–4(6)	15(5)	3(6)
C(18)	77(8)	57(8)	62(7)	–10(6)	13(6)	–14(7)
C(20)	76(8)	78(9)	52(6)	3(6)	17(5)	8(7)
C(21)	73(8)	118(12)	72(7)	8(9)	12(6)	6(9)
C(22)	90(8)	91(9)	51(6)	6(7)	29(6)	–11(8)
C(23)	88(8)	123(13)	68(7)	19(8)	22(7)	–1(9)
C(24)	118(11)	91(11)	87(9)	14(8)	49(8)	1(9)
O(2)	127(8)	99(8)	105(7)	25(6)	36(6)	50(7)

TABLE 20. /Cont.

C(30)	168(17)	159(19)	122(14)	3(13)	53(13)	91(15)
C(32)	109(11)	84(11)	159(14)	36(11)	61(11)	30(10)
C(25)	92(10)	352(32)	79(9)	23(16)	39(8)	−52(16)

TABLE 21. Fractional Coordinates ($X10^4$) for Included Hydrogen Atoms at their Calculated Positions for (Cholesteryloxy)dimethyl(3,3–dimethylbut–1–en–2–yloxy)silane (194)

	x/a	y/b	z/c	U
H(3)	–1214(4)	–4459(14)	–7049(6)	87(16)
H(2)	–231(5)	–4215(15)	–6231(6)	115(11)
H(2)	–336(5)	–2291(15)	–6126(6)	115(11)
H(1)	–1011(4)	–4767(14)	–5564(6)	115(11)
H(1)	478(4)	–3638(14)	–4943(6)	115(11)
H(4)	–1306(5)	–1164(14)	–6938(6)	115(11)
H(4)	–1831(5)	–2406(14)	–7486(6)	115(11)
H(6)	–2581(4)	–2421(12)	–6880(6)	45(25)
H(7)	–2935(4)	–1744(14)	–5698(5)	115(11)
H(7)	–2786(4)	–3665(14)	–5616(5)	115(11)
H(8)	–2112(4)	–1138(13)	4724(6)	87(16)
H(9)	–1704(4)	–4266(13)	–4876(5)	87(16)
H(19)	–661(6)	–1123(14)	–4685(7)	85(15)
H(19)	–1350(6)	–282(14)	–5020(7)	85(15)
H(19)	–887(6)	–467(14)	–5682(7)	85(15)
H(11)	–830(4)	–3852(16)	–3907(6)	115(11)
H(11)	–1037(4)	–2015(16)	–3749(6)	115(11)
H(12)	–1611(4)	–4837(14)	–3364(5)	115(11)

TABLE 21. /Cont.

H(12)	–1195(4)	–3577(14)	–2668(5)	115(11)
H(14)	–2498(4)	–4029(13)	–4321(5)	87(16)
H(15)	–3005(4)	–1024(14)	–4054(6)	115(11)
H(15)	–3374(4)	–2628(14)	–4504(6)	115(11)
H(16)	–3402(4)	–3632(15)	–3251(6)	115(11)
H(16)	–3161(4)	–1888(15)	–2830(6)	115(11)
H(17)	–2441(4)	–4674(13)	–2825(5)	87(16)
H(18)	–2294(5)	–518(13)	–3030(7)	85(15)
H(18)	–1666(5)	–683(13)	–3410(7)	85(15)
H(18)	–1634(5)	–1148(13)	–2400(7)	85(15)
H(20)	–2336(4)	–2150(15)	–1719(5)	87(30)
H(21)	–1403(5)	–3335(18)	–1670(7)	101(23)
H(21)	–1664(5)	–5110(18)	–1497(7)	101(23)
H(21)	–1682(5)	–3649(18)	–817(7)	101(23)
H(22)	–3219(5)	–3708(16)	–1901(5)	115(11)
H(22)	–2758(5)	–5259(16)	–1626(5)	115(11)
H(23)	–2391(5)	–4290(18)	–300(6)	115(11)
H(23)	–2770(5)	–2604(18)	–564(6)	115(11)
H(24)	–3345(6)	–5631(17)	–573(7)	115(11)
H(24)	–3710(6)	–3918(17)	–791(7)	115(11)

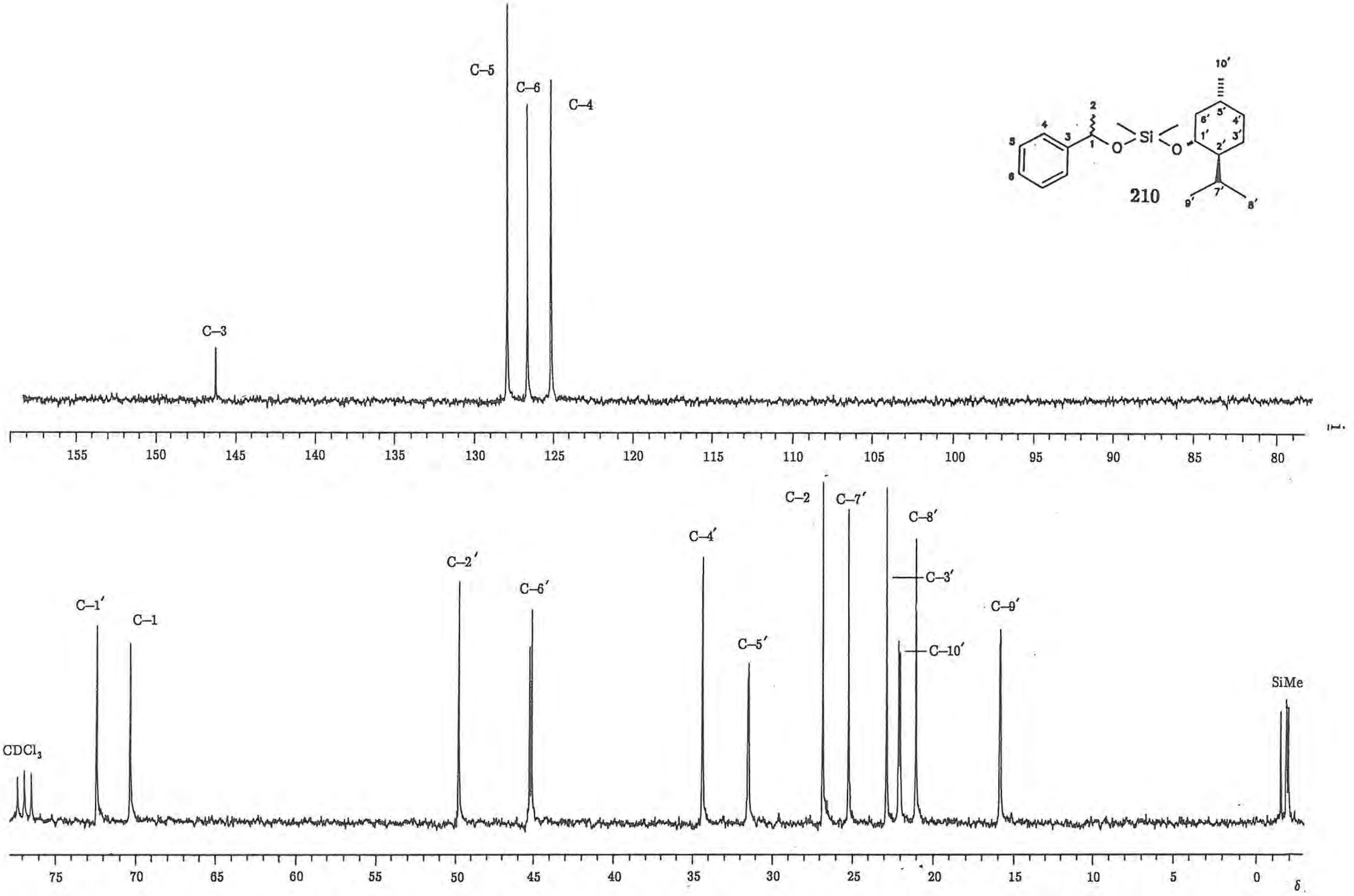
TABLE 22. Torsion Angles in the Vicinity of the Silyl Enol Ether Functionality.

Si	O2	C30	C32	–154.01
Si	O2	C30	C31	19.62
O1	Si	O2	C30	172.09
C29	Si	O2	C30	51.98
C28	Si	O2	C30	–75.02
O2	Si	O1	C3	–52.16
C28	Si	O1	C3	–169.08
C29	Si	O1	C3	67.73

TABLE 23. Deviations from the Mean Plane Defined by O2, C30, C31 and C32.

O2	–0.0118
C30	0.0351
C31	–0.0125
C32	–0.0108

APPENDIX II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C–6
C–4
C–3
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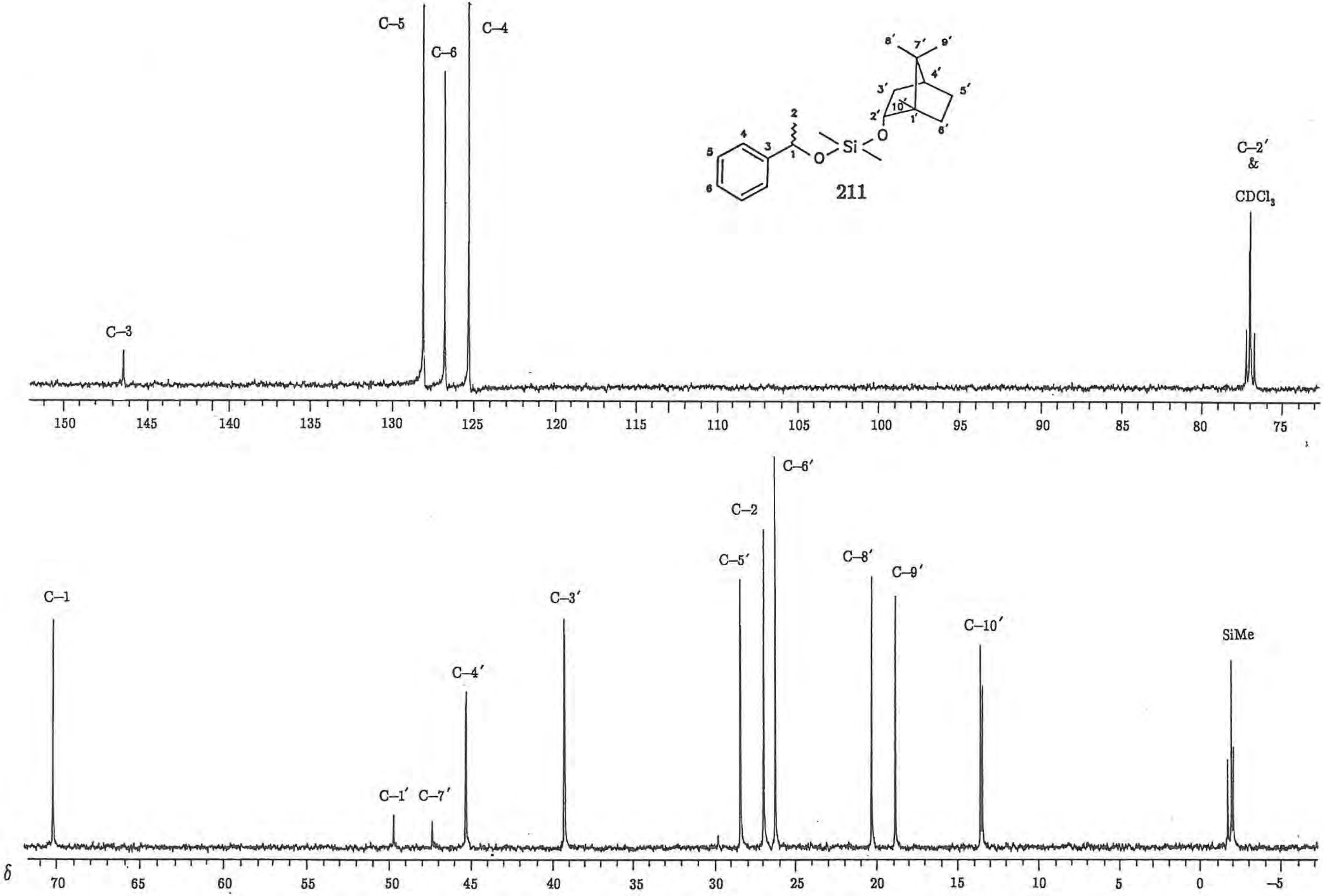
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
210
10′
2
1
3
4
5
6
O
Si
O
1′
2′
3′
4′
5′
6′
7′
8′
9′
CDCl$_3$
C–1′
C–1
C–2′
C–6′
C–4′
C–5′
C–2
C–7′
C–8′
C–3′
C–10′
C–9′
SiMe
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
δ


C–5
C–6
C–4
C–3
C–2′
&
CDCl$_3$
8′
7′
9′
4′
3′
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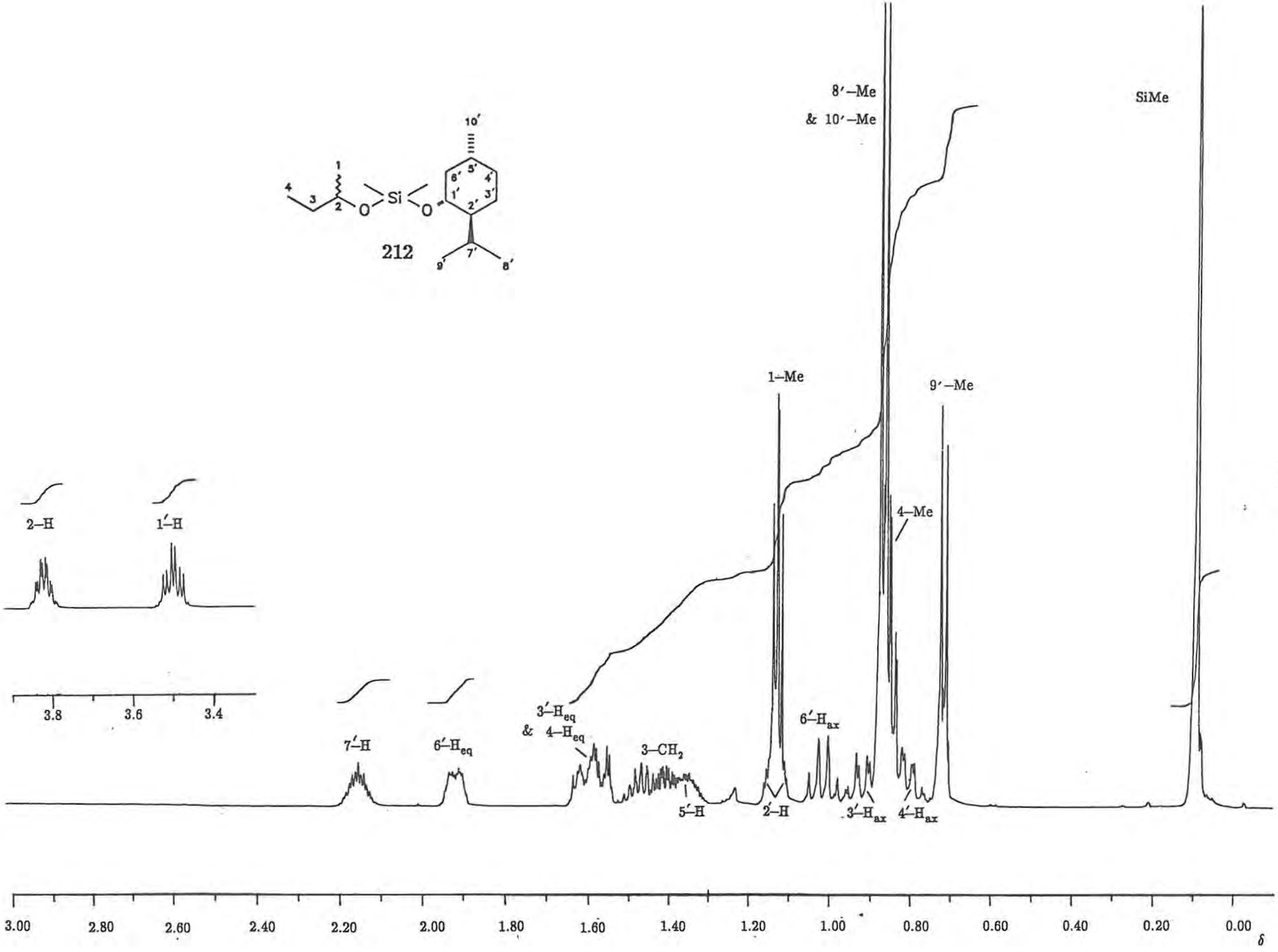
10′
2′
1′
6′
2
4
3
1
5
6
O
Si
O
211
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
C–6′
C–2
C–5′
C–8′
C–9′
C–1
C–3′
C–10′
SiMe
C–4′
C–1′
C–7′
δ
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
–5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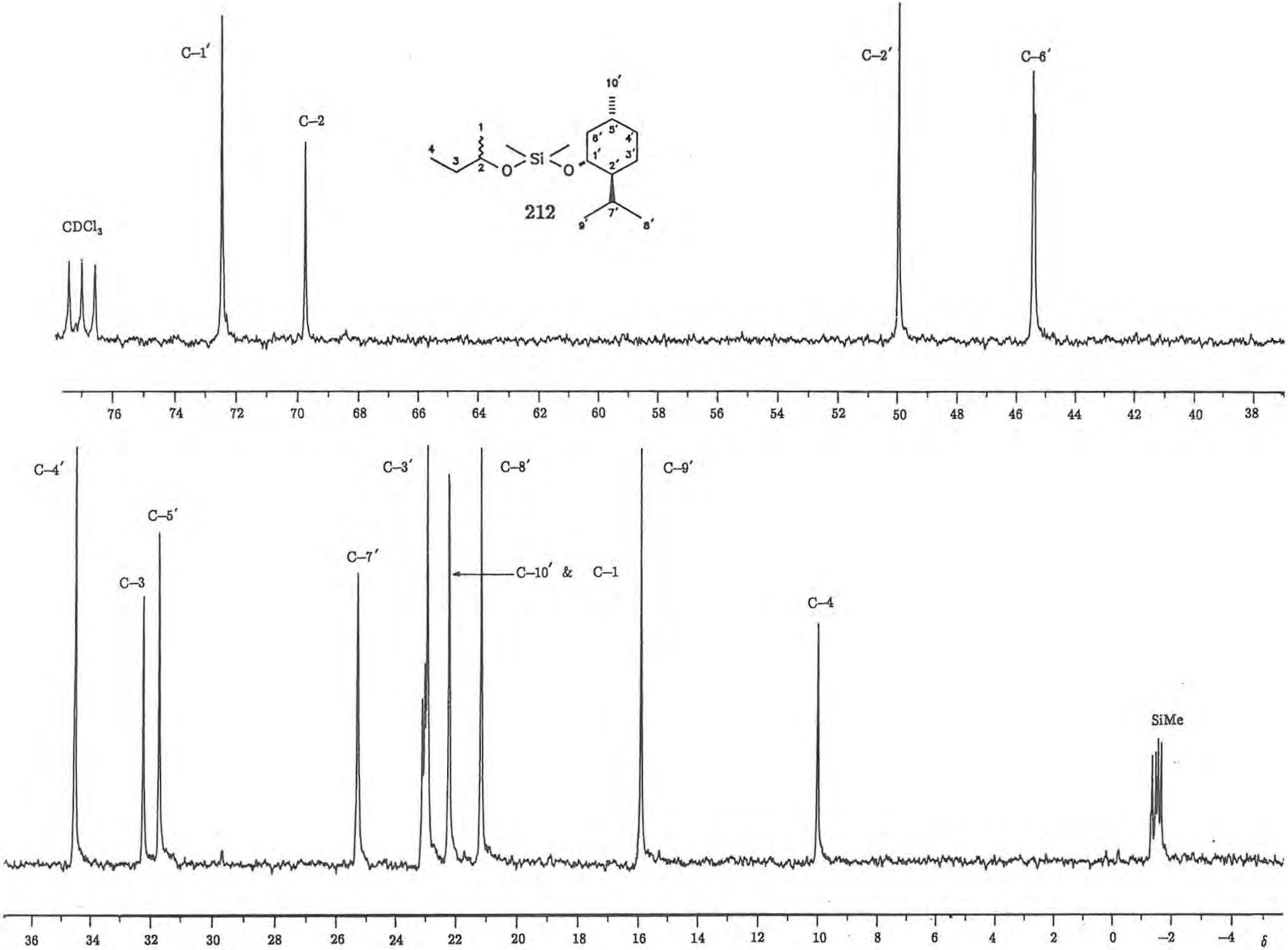
10′
1
4
3
2
O
Si
O
8′
5′
4′
1′
3′
2′
7′
9′
8′
8′–Me
& 10′–Me
SiMe
1–Me
9′–Me
4–Me
2–H
1′–H
3.8
3.6
3.4
7′–H
6′–H_eq
3′–H_eq
& 4–H_eq
3–CH_2
6′–H_ax
5′–H
2′–H
3′–H_ax
4′–H_ax
3.00
2.80
2.60
2.40
2.20
2.00
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
δ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C–1′
C–2
212
C–2′
C–6′
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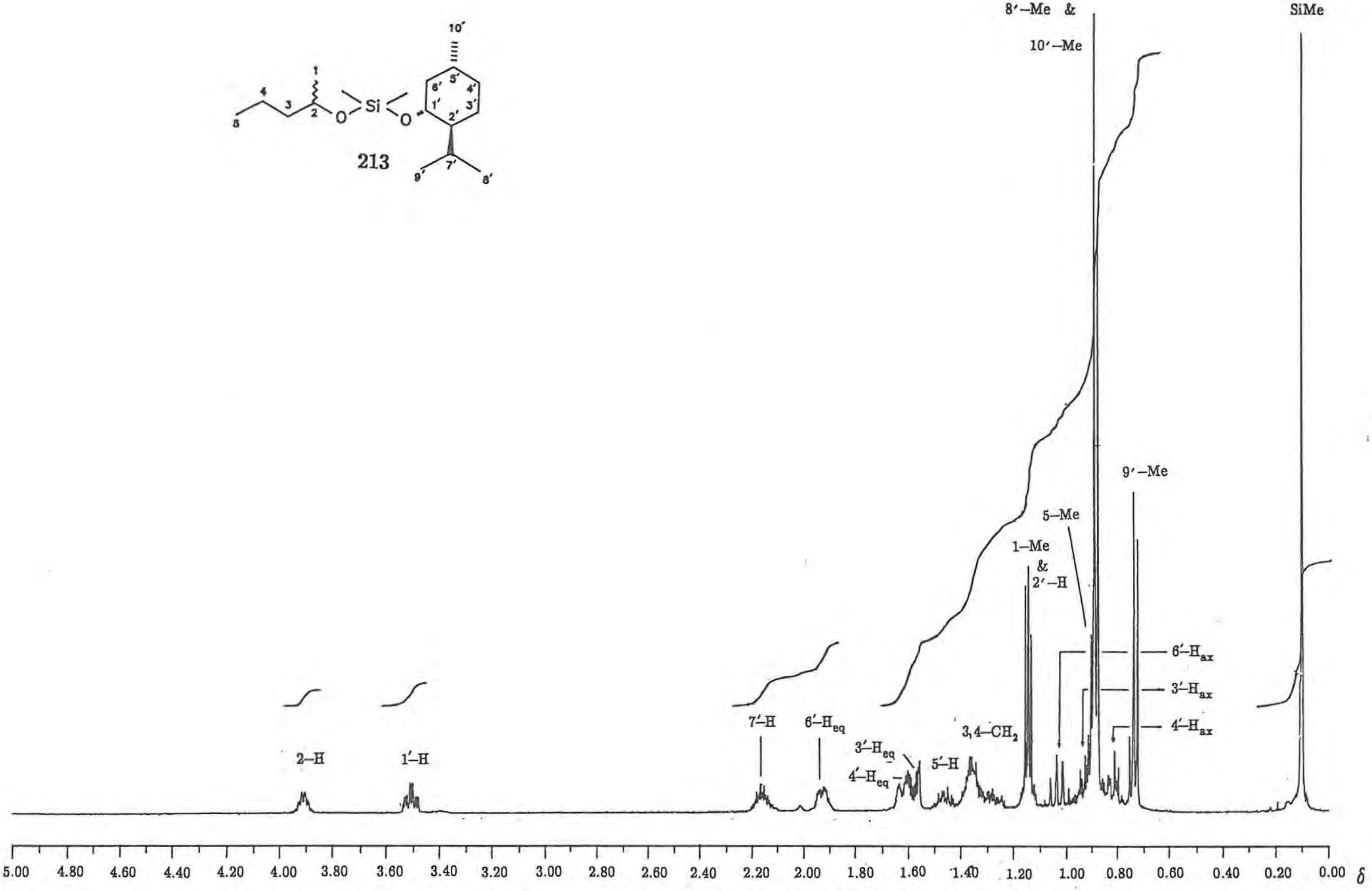
2
3
4
Si
O
10′
5′
4′
6′
3′
1′
2′
7′
9′
8′
76
74
72
70
68
66
64
62
60
58
56
54
52
50
48
46
44
42
40
38
C–4′
C–5′
C–3
C–7′
C–3′
C–10′ & C–1
C–8′
C–9′
C–4
SiMe
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
–2
–4
δ


213
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2
3
4
5
O
Si
O
1′
2′
3′
4′
5′
6′
7′
8′
9′
10′
8′–Me &
10′–Me
SiMe
9′–Me
5–Me
1–Me
&
2′–H
6′–H$_{ax}$
3′–H$_{ax}$
4′–H$_{ax}$
3,4–CH$_2$
5′–H
3′–H$_{eq}$
4′–H$_{eq}$
6′–H$_{eq}$
7′–H
1′–H
2–H
5.00
4.80
4.60
4.40
4.20
4.00
3.80
3.60
3.40
3.20
3.00
2.80
2.60
2.40
2.20
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1.80
1.60
1.40
1.20
1.00
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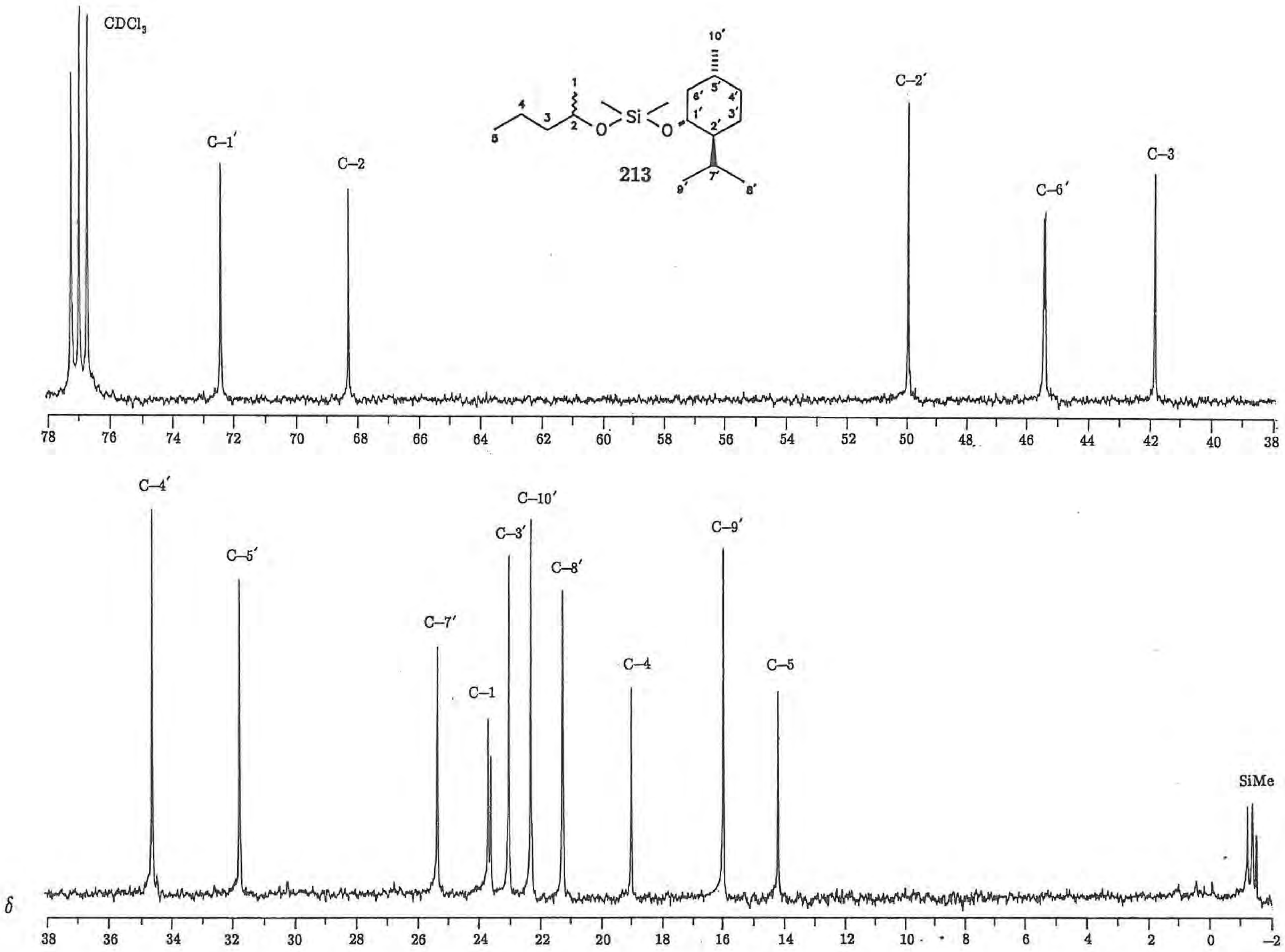
0.60
0.40
0.20
0.00
δ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C–2
213
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4
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Si
O
O
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2′
3′
4′
5′
6′
7′
8′
9′
10′
C–2′
C–6′
C–3
78
76
74
72
70
68
66
64
62
60
58
56
54
52
50
48
46
44
42
40
38
C–4′
C–5′
C–7′
C–1
C–3′
C–10′
C–8′
C–4
C–9′
C–5
SiMe
δ
38
36
34
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22
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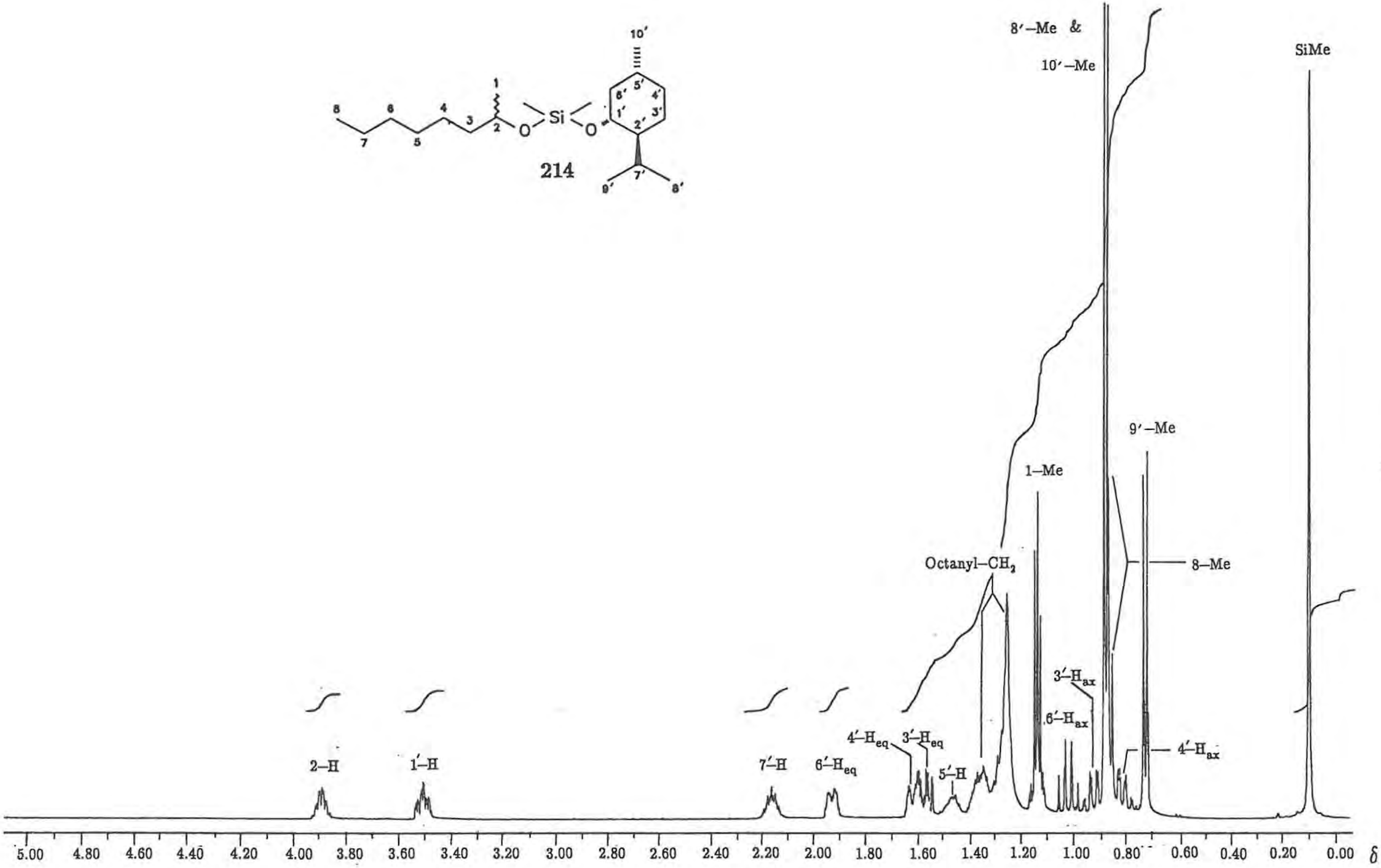
18
16
14
12
10
8
6
4
2
0
–2

VI.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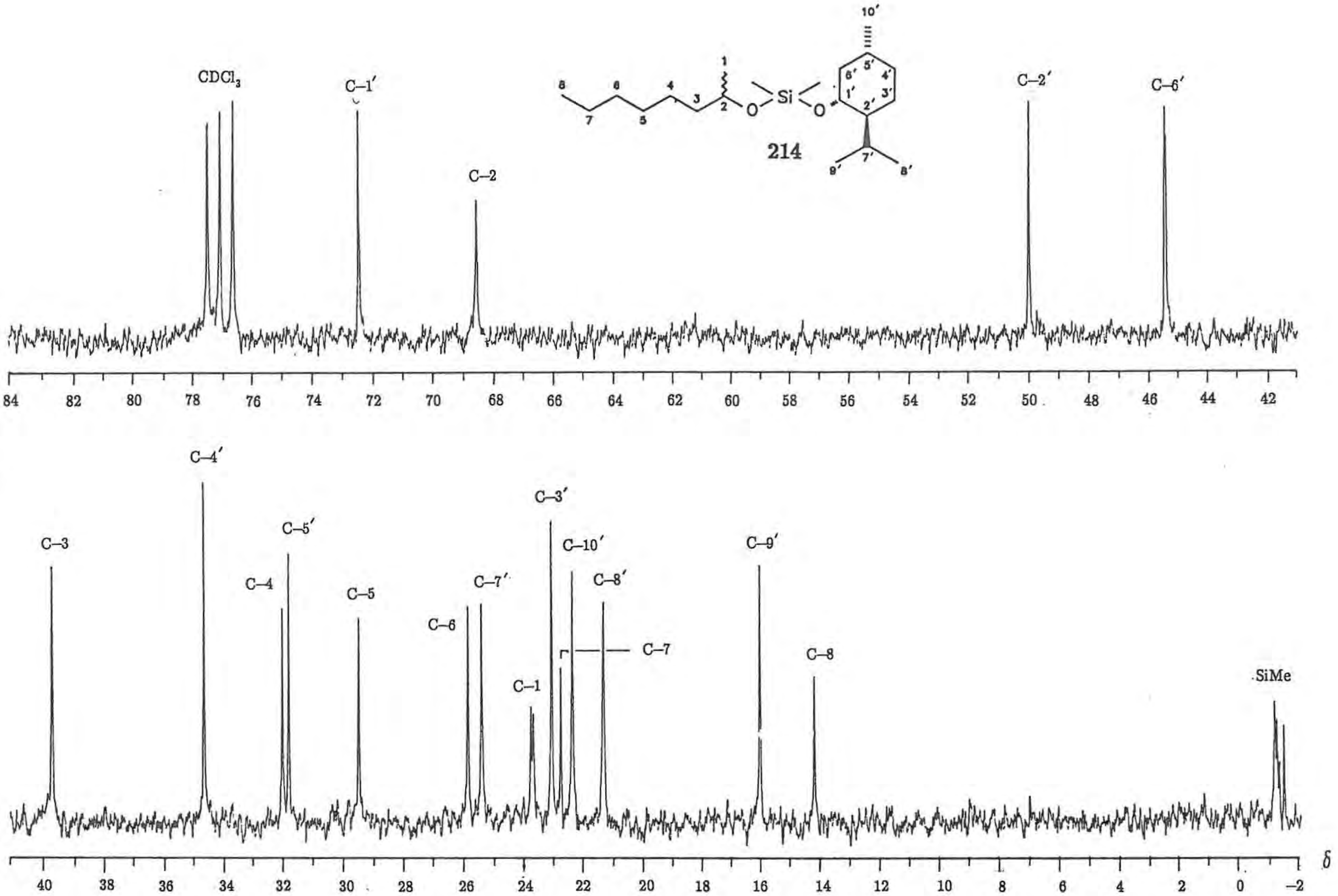
7
8
1'
2'
3'
4'
5'
6'
7'
8'
9'
10'
Si
O
O
8'–Me &
10'–Me
SiMe
9'–Me
1–Me
Octanyl–CH$_2$
8–Me
3'–H$_{ax}$
6'–H$_{ax}$
4'–H$_{ax}$
4'–H$_{eq}$
3'–H$_{eq}$
5'–H
2–H
1'–H
7'–H
6'–H$_{eq}$
5.00
4.80
4.60
4.40
4.20
4.00
3.80
3.60
3.40
3.20
3.00
2.80
2.60
2.40
2.20
2.00
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
δ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6
4
3
2
7
5
Si
O
6′
5′
4′
1′
3′
2′
7′
9′
8′
214
CDCl$_3$
C–1′
C–2
C–2′
C–6′
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
50
48
46
44
42
C–4′
C–3
C–5′
C–4
C–5
C–6
C–7′
C–3′
C–10′
C–8′
C–7
C–1
C–9′
C–8
SiMe
40
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
–2
δ